A Review on Cyclin-dependent kinase 7 (CDK7) Inhibitors as Anticancer Agents

By

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A thesis submitted to the school of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
Brac University
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing my degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled "A Review on Cyclin-dependent kinase 7 (CDK7) Inhibitors as Anticancer Agents" submitted by Rubina Haque Sorno (18346074) of spring, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on December 2023.

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

Cyclin-dependent kinase 7 (CDK7) is a member of CDK family which is involved in cell cycle progression and transcriptional regulation. Therefore, deregulation of CDK7 has been observed in various types of cancer including ovarian cancer and advanced solid tumors. This potentiates CDK7 as a valid therapeutic target for the treatment of cancer. Thus, selective inhibition of CDK7 can lead to the development of new anticancer therapy with less side effects. However, it is very difficult to selectively inhibit CDK7 as the structure of CDK7 is similar with other CDKs along with the conserved ATP binding site. Despite that, several CDK7 selective inhibitors like SY-5609, Q901, XL102, LGR6768 have reached clinical phases. In this review work, we have compiled updated information on the biology and function of CDK7, its involvement in cancer. Furthermore, we have also studied existing inhibitors of CDK7 which are in various phases of preclinical and clinical trials.

Keywords: Cyclin dependent kinase 7; CDK- activating kinase; CDK7 inhibitors; Cell cycle; Advanced solid tumors; Cancer.

Dedication

This review work is dedicated to all cancer patients.

Acknowledgement

I would like to thank Almighty Allah, the most merciful and benefactor, for granting me life with infinite blessings. All praises to him for giving me patience and strength to continue my journey to complete this project. I also want to thank my supervisor, Dr. Nishat Zareen Khair, Assistant Professor, School of Pharmacy, Brac University, for guiding me on this project. All thanks to her for providing feedback with patience and compassion. I am grateful to her for continuous support, time, and motivation since day one throughout the process.

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List of Acronyms

CDK	Cyclin Dependent Kinase
CAK	Cyclin Activating Kinase
TNBC	Triple-Negative Breast Cancer
CRPC	Castration-Resistant Prostate Cancer
SCLC	Small Cell Lung Cancer
mCRPC	metastatic castration-resistant prostate cancer
HR+/HER2− BC	Hormone Receptor Positive/HER2 Negative Breast Cancer
DYRK1A	dual specificity tyrosine phosphorylation regulated kinase 1A
cryo-EM	Cryogenic electron microscopy
NPC	nasopharyngeal carcinoma
CLL	Chronic lymphocytic leukemia
ALL	Acute lymphoblastic leukemia
MM	Malignant melanoma
AML	Acute myeloid leukemia
MCL	medial collateral ligament
NSCLC	Non-small cell lung cancer

Chapter 1: Introduction

1.1 Background

In the intricate orchestra of cellular processes, Cyclin-dependent kinase 7 (CDK7) takes center stage as a pivotal director. Its partnership with cyclin proteins ensures the symphony of cell growth and division by orchestrating the progression of cells through various phases. Nonetheless, this coordination is not risk-free. When discord arises in this cellular composition, cancer can develop and spread.

CDK7, a versatile protein kinase, functions as the regulator of cellular processes. This particular entity is a part of a kinase family that is cyclin-dependent in nature, which is widely recognized for its significant involvement in regulating the progression of the cell cycle (Satyanarayana & Kaldis, 2009). The participation of CDK7 in the advancement of the cellular cycle is contingent upon its function within the CDK-activating kinase (CAK) complex, which consists of Cyclin H as well. The primary function of this complex is to modulate the activity of other cyclin-dependent kinases (CDKs), particularly CDK1 along with CDK2, through the process of phosphorylation, therefore facilitating their activation(Malumbres, 2014).

Aside from, CDK7s role in the cell cycle, it also functions as a component of the Transcription Factor II H (TFIIH) (Akhtar et al., 2009). The job of CDK7 is to facilitate the enzymatic process of phosphorylating the C-terminal domain of RNA polymerase II (RNAPII). The initiation event serves as the commencement of the transcriptional synthesis, facilitating the expression of genes and the synthesis of proteins **(Figure 1)**. CDK7, following its task, undertakes the responsibility of directing the performance of gene expression.

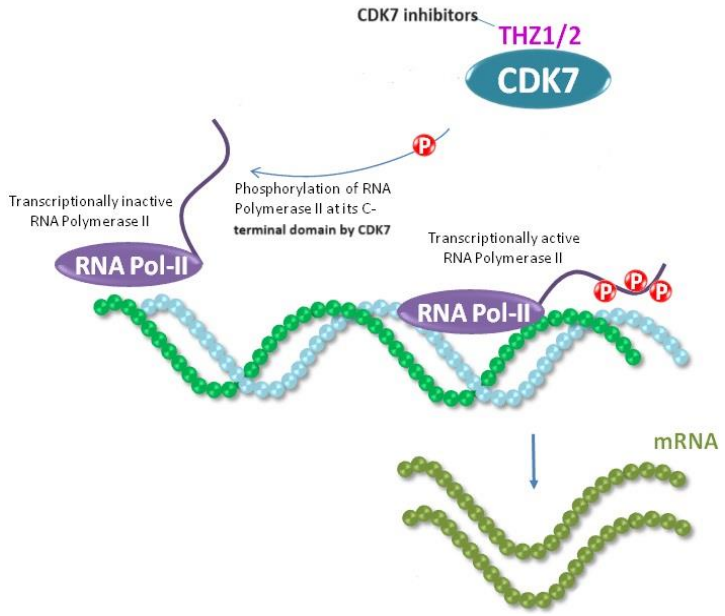


Figure 1: CDK7 act as a regulator of RNA polymerase II enzyme in mRNA formation. (Ocana & Pandiella, n.d.)

Cyclins, appropriately named after their periodic fluctuation in concentration during the progression of the cell cycle, serve as the interactive counterparts of cyclin-dependent kinases (CDKs). Various kinds of cyclins, such as Cyclin D, Cyclin E, and Cyclin A, play an indispensable part in managing the cell cycle by facilitating the passage of cells through distinct stages. Each cyclin possesses a distinct function, facilitating the seamless progression of the cell from one phase to the next. An illustration of cyclins may be observed in the interaction between Cyclin D and CDK4/CDK6, which plays an essential role in propelling the cycle of cells through the G1 phase. Similarly, Cyclin A is implicated in facilitating the transition from the S phase to the G2 phase(Malumbres, 2014).

In the realm of cancer, the intricate coordination between CDK7 and cyclins may be disoriented. The relationship between CDK7, cyclins, and cancer is a complex aspect characterized by many intricacies. In the context of cancer cells, this orchestration can get disrupted. The abnormal upregulation or heightened functionality of CDK7 can induce cells to enter a continuous state of proliferation, hence promoting the formation and progression of

neoplastic growths. This phenomenon might potentially arise due to the cellular incapacity to effectively control cyclin-CDK complexes(Asghar et al., 2015a).

Abnormal CDK7 function has been detected in plenty of cancer categories, such as breast cancer(B. Li et al., 2017), lungcancer (Tsang et al., 2019), and ovarian malignancies(Z. Zhang et al., 2017a). The dysregulation mentioned in the statement portrays a significant role in the uncontrolled development and multiplication of cancer cells, which is a characteristic feature of malignancy. In addition, the activity of CDK7 extends beyond the regulation of the cell cycle. It exerts an impact on transcriptional processes through the phosphorylation of RNA polymerase II. This phosphorylation event can result in the upregulation of oncogenes and the downregulation of tumor suppressor genes(Vervoort et al., 2022).

Scientists have discovered a class of chemicals referred to as CDK7 inhibitors due to the significant role that CDK7 plays in cancer. These chemicals function as CDK7 specific inhibitors by binding to the active site of CDK7 and suppressing its catalytic activity. By employing this approach, they effectively impede the advancement of the cellular cycle and interfere with the transcriptional apparatus, resulting in the suppression of abnormal signals associated with malignant proliferation.

The complex interaction among CDK7, cyclins, and cancer exemplifies the varied character of cellular regulation that coordinates the destiny of the cell. The occurrence of underperformance among CDK7 and cyclins might have severe ramifications, hence playing a role in the onset and advancement of cancer.

The comprehension of the intricacies associated with this molecular phenomenon not only represents a scholarly endeavor but also exhibits potential for the advancement of precise therapeutic interventions. The exploration of CDK7 inhibitors as possible anticancer drugs is focused on their disruption of CDK7's involvement in both cell cycle control and transcription.

Through the suppression(Chipumuro et al., n.d.) of this conductor and the restoration of cellular symphony, researchers endeavor to provide renewed optimism in the ongoing battle against cancer. The ongoing exploration of CDK7, cyclins, and their association with cancer remains a subject of interest, as each new finding contributes valuable insights towards the development of improved cancer therapies.

1.2 Structure of CDK7

The inactive form of CDK2 structure was used as a reference to aid in the determination of the structure of CDK7(Lolli et al., 2004). CDK7 is a protein that comes from the cyclin-dependent kinase family and contains numerous structural domains. The protein structure consists of two lobes, namely the C-terminal lobe (residues 97-311) (Diab et al., 2020) and the N-terminal lobe (residues 13-96) (Z. M. Li et al., 2022a). The N-terminal lobe is mostly constructed of β sheets (Liang et al., 2021) along with a single α helix, whereas the C-terminal lobe is predominately made up of α helices. These lobes exhibit a characteristic kinase fold and are connected by a flexible linker region, as seen in **Figure 2**. The ATP-binding region is situated within the N-terminal lobe (Schneider, 2004)N-terminal lobe, while the C-terminal lobe contains the catalytic kinase area. The catalytic domain incorporates many essential structural elements, including the substrate-binding site, the ATP-binding site, and the activation loop. The ATP-binding region (Feher & Lawson, 2009) facilitates the binding of CDK7 to ATP and the subsequent hydrolysis of ATP, so providing the necessary energy for the activation of kinase activity. The activation loop exerts a fundamental role in regulating kinase activity and undergoes conformational changes upon phosphorylation. The substrate-binding site is responsible for the recognition and binding of certain proteins, such as RNA polymerase II and transcription factors.(Thomas & Chiang, 2006).

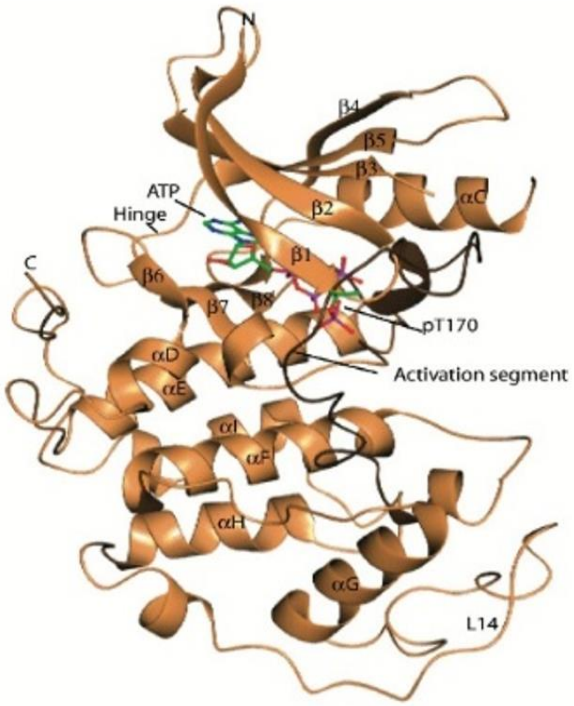


Figure 2: CDK7/ATP Complex Crystal Structure (UIA2). A diagrammatic representation of CDK7, accompanied by annotations denoting its secondary structural constituents. ATP binding occurs at the N- and C-terminal lobes. The activation segment employs darker shade of color (Lolli et al., 2004).

1.3 Function and role of CDK7

CDK7 functions as a transcription kinase in conjunction with CDKs 8, 9, 12, 13, and 19 (Henry et al., 2018). The CDK- activating kinase complex which is responsible for the phosphorylation of other CDKs and a constituent of the transcription factor IIH complex (TFIIH), which stands composed *via* seven subunits and is known for its high degree of conservation (Rimel & Taatjes, 2018). The phosphorylation of the C-terminal domain (CTD) a distinguished major subunit of RNA polymerase II (RNA pol II) using this intricate mechanism initiates transcription (**Figure 3A**). The regulation of gene transcription during phase separation is mediated by CDK7. The carboxy-terminal domain (CTD) of RNA polymerase II (RNAP II) is characterized by its chaotic nature and low complexity, leading to its tendency to form clusters

in hubs (Lu et al. 2018, 2019). It is reported that the unphosphorylated C-terminal domain (CTD) of RNA polymerase II (RNAP II) experiences phase separation through hydrophobic interactions. Conversely, phosphorylation of the CTD through CDK7 facilitates its inclusion into phase-separated droplets formed over cyclin T1 and the histidine-rich domain, primarily *via* electrostatic interactions (Boehning et al., 2018; Lu et al., 2018, 2019). Studies suggest that phosphorylation serves to liberate RNA polymerase II (RNAP II) from the central hub, so initiating the process of transcription elongation.

In addition to its contribution in transcription, CDK7 also shows a crucial role in regulating cell cycle progression through its cyclin-dependent kinase-activating kinase (CAK) activity, as seen in **Figure 3B**. Prior studies asserted the contribution of CDK7 in the phosphorylation of CDK4 and 6, which in turn phosphorylates the retinoblastoma (Rb) protein to facilitate G1 advancement. CDK7 also plays a function in facilitating the development from G1 to S phase by phosphorylating CDK2, and in regulating the transition from G2 to M phase by phosphorylating CDK1 (Larochelle et al., 2007; Schachter et al., 2013). The process of CDK7 phosphorylation seems to regulate the sequential pairing of cyclins and the advancement of the cell cycle.

One example of CDK7's phosphorylation activity is its ability to phosphorylate CDK2 in its monomeric form. However, when CDK7 forms a complex compound with cyclin H affects the phosphorylation of CDK1. During the cell cycle, CDK2 would be given priority over CDK1 in its binding to cyclin A. While the phosphorylation of both CDK1and 2 by CDK7 is absolutely necessary for activation, it is important for both the activation and sustenance of CDK4 and 6 activities. During the passage from G_0 to G_1 period of the cell cycle, there is an observed promotion of CDK7 phosphorylation, which subsequently causes the activation of CDK4. This suggests the existence of a currently unidentified kinase that activates CDK7 during the initial stages of the cell cycle (Schachter et al., 2013; Schachter & Fisher, 2013b).

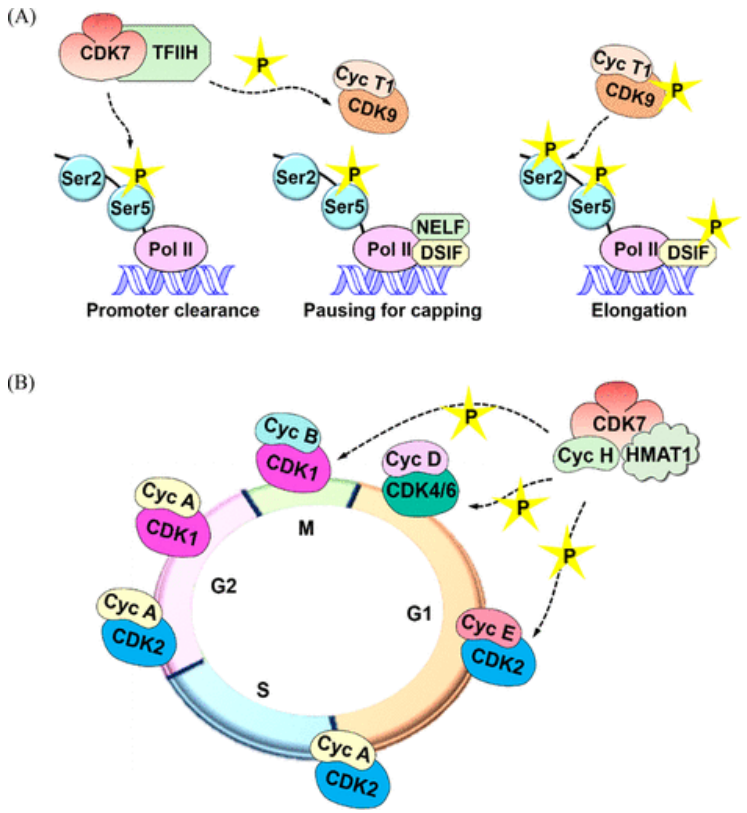


Figure 3: CDK7 functions in mRNA transcription (A) and cell cycle progression (B). (A) CDK7, a component of TFIIH, phosphorylates Ser5 at RNAP II's CTD to commence transcription, and its effect on CDK9 phosphorylation relieves the pause and promotes productive elongation. (B) CDK7 phosphorylates CDK1,2,4,6 to regulate cell cycle succession as an essential component of CAK (Diab et al., 2020)

1.4 Activation of CDK7

The activation of CDK7 necessitates the engagement of a must regulatory subunit cyclin H and the phosphorylation of a conserved threonine residue located at position 170 inside its own T loop. Additionally, another phosphorylation is also needed (Ser164) to activate CDK7. Then, activated CDK7 comprises cyclin H, and the RING-finger protein (MAT1) forms the CDK-activating complex (CAK) promoting the advancement of the cell cycle. CDK-activating kinase acting as an essential part of cell cycle helps to activate other kinases. It is commonly believed that CDK1 and CDK2 phosphorylate CDK7 in order to activate and to maintain the trimeric complex, phosphorylation at Thr170 is required (Lolli et al., 2004). According to

recent research (Bisteau et al., 2013; Schachter & Fisher, 2013a, 2013c), these three protein complex functions as a cyclin-activating kinase (CAK). The steps required to initiate phosphorylation were different for each kinase. Phosphorylation of CDK2 occurs prior to cyclin binding, whereas phosphorylation of CDK1 can occur either before or after cyclin binding (**Figure 4**) (Fisher, 2005). Ternary complex phosphorylates cyclin-dependent kinases 1, 2, 4, and 6. This means it plays a role throughout the whole cell cycle and can trigger further cell cycle advancement.

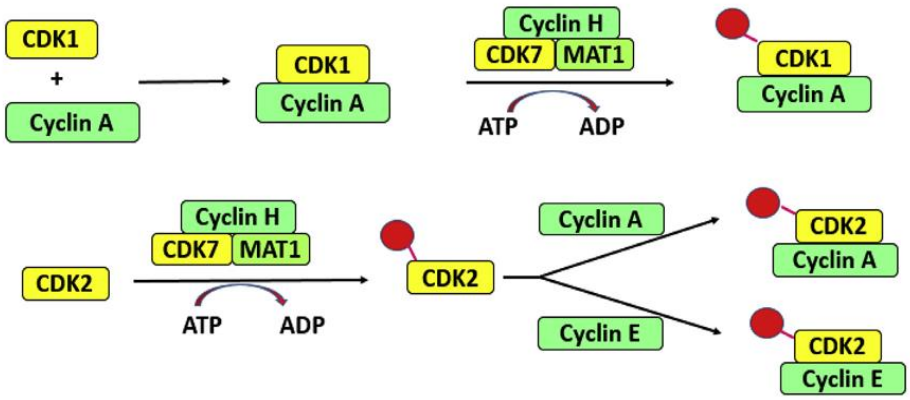


Figure 4: CAK triggers CDK1 and CDK2 in a potentially sequential manner.(Schachter & Fisher, 2013)

1.5 CDK7 as potential drug target

CDK7 functions as the catalytic subunit of CDK-activating kinase (CAK), a protein complex responsible for activating various cyclin-dependent kinases (CDKs) through the phosphorylation of a conserved threonine residue located inside the T loop. The heterotrimeric shape CAK complex is an integral element of TFIIH, a universally conserved transcription factor that governs both cell cycle regulation and transcriptional processes. CDK7 facilitates transcriptional acceleration by phosphorylating RNA polymerase II (Pol II) at effective gene promoters. The disruption of the cell cycle and the occurrence of aberrant transcriptions, which

are mediated by several pathways, have been recognized as the defining characteristic of cancer in a diverse array of malignancies. Furthermore, the clinical findings demonstrate that there is a significant upregulation of CDK7 expression in various malignancies, indicating its potential role in tissue homeostasis. Therefore, CDK7 is regarded as a potentially hazardous therapeutic objective. The efficacy of selective CDK7 inhibitors (CDK7i) as anti-cancer agents has been revealed through recent discoveries. The repurposing of pharmaceuticals for CDK7 kinase treatments is a possible approach for identifying efficacious therapeutic options for extremely challenging cancer types.(Hussain et al., 2023).

1.6 Rationale of the study

The ongoing efforts of scientists in combating cancer have been commendable so far. Nevertheless, it is important to note that none of these attempts has achieved complete eradication of the illness. In recent times, the identification of specific CDK7 inhibitors has paved the way for the precise intervention against malignant cells in many types of cancer. The results indicate that CDK7 is associated with several cancers characterized by diverse pathophysiology and mechanisms. Consequently, efforts to block the activity of CDK7 in malignant cells in respect to fighting cancer might yield a more profound and pivotal outcome. In recent years, there has been a concerted effort by pharmaceutical corporations and university researchers to produce a firmly effective medication for the inhibition of CDK7, with the aim of providing a promising option for cancer therapy. The empirical of this study is to analyze the potential of existing CDK7 inhibitors that are now accessible in various stages of preclinical and clinical trials. In addition, this study will help to inspect the effectiveness and potential of existing CDK7 inhibitors along with updated research information and significant insights.

1.7 Aim and Objectives

Aim:

This review aims to analyze the recent advancement of potential CDK7 inhibitors as a targeted therapy in cancer treatment.

Objectives:

1) To study the anticancer potential of existing CDK7 inhibitors that are in various stages of clinical and preclinical trial.
2) To Provide updated information regarding CDK7 inhibitors as anticancer agent for the treatment of advanced solid tumor.
3) To Study the structure of CDK7 to provide an insight on further initiative to uncover potent and selective CDK7 inhibitors.

Chapter 2: Methodology

The objective of this review paper was to peruse the recent advancements in CDK7 inhibitors as a focused therapeutic approach in the treatment of cancer. The material of the review study was sourced from a diverse range of primary sources, such as Research Gate, Google Scholar, Springer, NCBI, Nature, Elsevier, Science Direct and others. In addition to primary sources, secondary research publications, especially PubMed, are used for the purpose of gathering information. Upon conducting a thorough examination of the articles in question to identify relevant material, a comprehensive framework was produced to present the information in a coherent and organized manner. It was of utmost importance to study the underlying factors contributing to the antitumor effects attributed to CDK7, as well as the potential implications for cancer therapy *via* the inhibition of CDK7. An additional inspection of articles was conducted to highlight the structural and functional aspects of CDK7, along with its correlation to the prognosis of advanced solid tumors such as ovarian cancer, TBNC, endometrial cancer, CRPC, colorectal cancer, HR+/HER2− BC, pancreatic cancer etc. In conclusion, several therapeutic agents exhibiting efficiency in various types of cancer have been identified for the effective eradication of cancer. In addition, extensive effort was given to obtain credible sources, and a precise citation was carefully prepared.

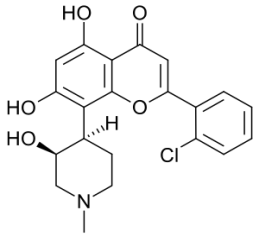
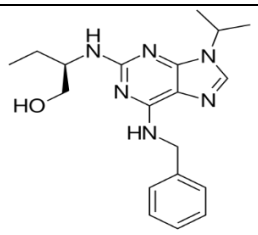
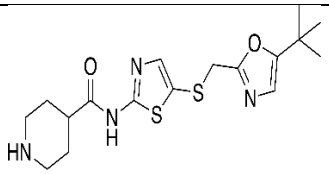
Chapter 3: CDK7 Inhibitors

3.1 CDK7 inhibiting pan-CDK inhibitors

CDK7 inhibitors are set to emerge as a highly promising therapeutic agent for treating cancer in the approaching future. This is due to the constant clinical progress of these inhibitors as well as the increased examination of their target. Pan-CDK inhibitors represent the first generation of CDK inhibitors. As their name suggests, these inhibitors work by preventing the CDK enzyme from doing its job, so stopping the cell cycle and halting cell proliferation. Over the past few decades numerous numbers of CDK7 inhibitors were developed and tested for their drug like characteristics. Some initial pan-CDK inhibitors such as flavopiridol, roscovotine, SNS-032 did express high potency towards CDK7 inhibition. However, they also did show the same or greater level of affinity towards other CDKs. Normal cells are inevitably harmed by the initial generation of pan-CDK inhibitors because of their poor selectivity and high toxicity. Hence, these early pan-CDK inhibitors got eliminated from the race of being potent CDK7 selective inhibitors. On the other hand, one commendable thing that needed to be mentioned about these pan-CDK inhibitors is that they have given rise to many CDK7 selective inhibitors later on(M. Zhang et al., 2021). **Table 1** shows the distinctive characteristics of three highly potent pan-CDK inhibitors.

Table 1: Characteristics of some CDK7 inhibitors with more than one target(Sava et al., 2020)

No. and Name	**Structure**	**IC_{50}(nM)**	**Highest reached clinical trial phase**	**Studies in preclinical models**

1.Alvocidib (flavopiridol)		**CDK7-CycH=~300** CDK9-CycT=6 CDK6-CycD=~100 CDK4-CycD=65 CDK2-CycA=100 CDK1-CycB=41	Phase II	CLL, MM, lymphoma, AML, MCL, ALL
2.Seliciclib (roscovotine)		**CDK7-CycH=490** CDK9-CycT=600 CDK6-CycD1>100,000 CDK4-CycD1>10,000 CDK2-CycE=100 CDK1-CycB=2700	Phase II	Advanced solid tumor, CD, Metastatic breast cancer, NPC, NSCLC
3. SNS-032		**CDK7-CycH=62**. CDK9-CycT=4 CDK6-CycD>1000 CDK4-CycD=92;5 CDK2-CycA=38 CDK1-CycB=480	Phase I	Tumors, CLL, B-lymphoid Malignancies

Alvocidib (flavopiridol): Alvocidib, (**table1, No.1**) also known as flavopiridol, was previously identified as a non-selective inhibitor of cyclin-dependent kinase (CDK) that has been found in recent decades. Initial endeavors to cultivate CDK inhibitors have resulted in limited selectivity, exhibiting activity against many CDKs, frequently including CDK7. Alvocidib (flavopiridol) is a semi-synthetic flavone derivative, has been identified as a potent inhibitor of CDK1, 2, 4, 6, 7, and 9. Notably, it has the distinction of being the initial CDK inhibitor to go into clinical trials. Alvocidib underwent evaluation in over 60 clinical studies spanning the years 2008 to 2014, encompassing a diverse range of tumor types. The majority of studies had little therapeutic efficacy, while some modest responses were found in the context of mantle cell lymphoma along with chronic lymphocytic leukaemia (CLL). The pharmaceutical company Tolero Pharmaceuticals is presently conducting clinical trials to

evaluate the efficacy in respect to cyclin-dependent kinase 9 (CDK9) inhibitor known as alvocidib in the context of treating acute myeloid leukaemia (AML) (Sava et al., 2020).

Seliciclib (roscovitine): Seliciclib (roscovitine) (**table1, No.2**) is a purine-based pan-CDK inhibitor that has been investigated in clinical studies for several tumour types. It has been shown to inhibit CDK1, 2, 5, 7, and 9. However, despite these properties, seliciclib has shown limited efficacy in clinical settings. Roscovitine, is a compound that obtained a patent over two decades ago, continues to undergo human testing using approaches that are not directly associated with the inhibition of cyclin-dependent kinases (CDKs). Both seliciclib and alvocidib have inhibitory effects on CDK7 as well as other CDKs and kinases within the CMGC group, embracing dual specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A) (Teng et al., 2019)

SNS-032: SNS-032 (**table1, No.3**) is a second generation CDK inhibitor that targets multiple CDKs. SNS-032 is based on aminothiazole was developed with the objective of creating CDK inhibitors that exhibit enhanced selectivity for CDK1 and CDK2 (Asghar et al., 2015; Whittaker et al., 2017). This molecule demonstrates strong inhibition towards CDK9, CDK7, and CDK2. SNS-032 has been subjected to clinical trials as a treatment option for advanced lymphoid lymphoma (Tong et al., 2010) and advanced solid tumors(Heath et al., 2008) but limited to Phase I. SNS032 has a higher degree of selectivity compared to Roscovitine and Flavopiridol. The clinical incompetence of these initial CDK inhibitors likely stemmed from their lack of specificity in targeting specific members of the CDK family. It is probable that a narrow therapeutic range exists, accompanied by associated toxicities such as fatigue, gastrointestinal disturbances (namely diarrhea and nausea), and elevated blood glucose levels(Aklilu et al., 2003; Asghar et al., 2015b; Burdette-Radoux et al., 2004; Heath et al., 2008; Le Tourneau et al., 2010). Nevertheless, the broad spectrum of these compounds poses a challenge in identifying between cancerous cells and normal ones(Asghar et al., 2015b). The

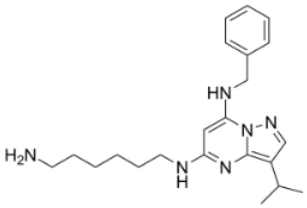
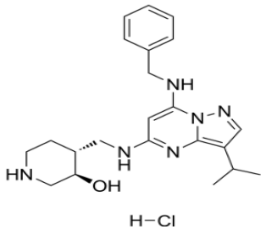
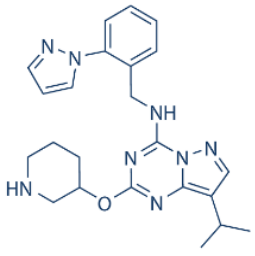
normal functioning of tissues necessitates the involvement of many CDK proteins. Furthermore, it is challenging to determine the suppressed CDKs *in vivo*, and CDKs that are crucial for the underlying mechanism of action due to their lack of specificity. The knowledge insufficiency results in limitations on the ongoing development of these pan-CDK inhibitors as targeted pharmaceutical interventions.

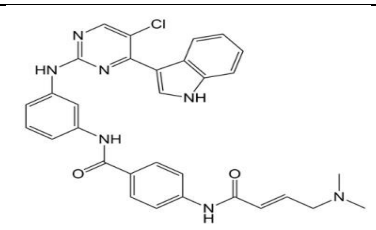
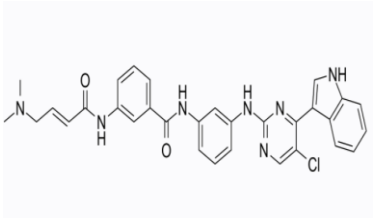
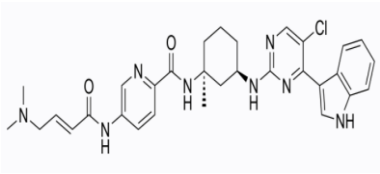
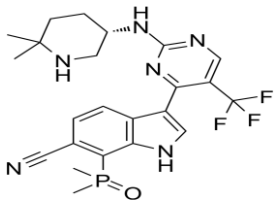
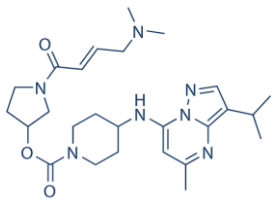
3.2 CDK7 selective inhibitors

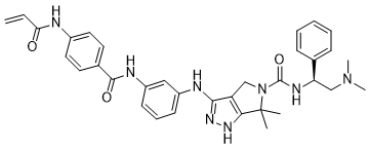
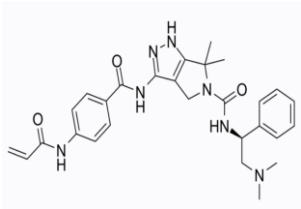
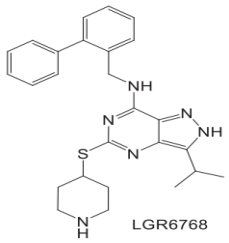
There is a considerable number of small chemical inhibitors that are currently being developed specifically targeting CDK7. CDK7 can be inhibited by a variety of inhibitors, including covalent and noncovalent inhibitors. Covalent inhibitors mainly target cysteine residues for covalent connections in the case of CDK7 due to the nucleophilic nature of the thiol group in the cysteine side chain. Covalent bond formation permanently alters the active site of the enzyme, blocking substrate binding and kinase activity. On the other hand, noncovalent inhibitors, as the name indicates, do not create a permanent covalent link with CDK7. Instead, they rely on reversible interactions including hydrogen bonding, electrostatic interactions, hydrophobic interactions, and van der Waals forces. Noncovalent inhibitors bind to the active or allosteric regions of CDK7 via weak contact.

The pyrazolopyrimidine derivatives BS-181 and ICEC0942, as well as the pyrazolotriazine derivative LDC4297, are noteworthy compounds. Furthermore, ATP-competitive covalent inhibitors of CDK7, such as the pyrimidine-based medicines THZ1 and SY-1365, together with the pyrrolidinopyrazole-based medication YKL-5-124, have been created, targeting the ATP-binding site of CDK7. In addition, there have been various novel covalent inhibitors that specifically target CDK7, including the trisubstituted pyrazolo[4,3-d]pyrimidine derivative LGR6768, along with Q901 and XL102. **Table 2** shows the salient features of the in-development CDK7 specific inhibitors in various stages of clinical and preclinical trials.

Table 2: CDK7 inhibitors at various stages of clinical and preclinical trial. (Sava et al., 2020)

No. and Name	Structure	Types of inhibitors	IC_{50}(nM)	Highest reached clinical trial phase (clinical trial ID)	Studies in preclinical models
1. BS-181(B. Y. Wang et al., 2016)		Non-covalent	**CDK7-CycH-MAT1=21** CDK9-CycT=4200 CDK6-CycD1=47000 CDK4-CycD1=33000 CDK2-CycE=880 CDK1-CycB=8100	Did not enter clinical trial	Gastric cancer, Breast cancer.
2. ICEC0942 (CT7001)(Constantin et al., 2023)		Non-covalent	**CDK7-CycH-MAT1=40** CDK9-CycT1=1200 CDK6-CycD1=34000 CDK4-CycD1=49000 CDK2-CycA1=620 CDK1-CycA1=1800	Phase I/ II; **(NCT03363893)**	Advanced solid malignancies, CRPC, HR + /HER2- BC, TNBC (Kovalová, Baraka, et al., 2023)
3. LDC4297(Kelso et al., 2014)		Non-covalent	**CDK7-CycH-MAT1<5** CDK9-CycT=1711 CDK6-CycD>1000 CDK4-CycD≥1000 CDK2-CycE=6.4 CDK1-CycB=54	Did not enter clinical trial	HCMV, antiviral activity
4. THZ1(Kwiatkowski et al., 2014a)		Covalent	**CDK7-CycH-MAT1=3.2**	Did not enter clinical trials	T-cell acute lymphoblastic leukemia (T-

					ALL), melanoma.
5. THZ2(Huang et al., 2018)		Covalent	**CDK7-CycH=14** CDK9-CycT=194 CDK2-CycA=222 CDK1-CycB=97	Did not enter clinical trials	Gastric cancer, TBNC
6. SY-1365(Hu, Marineau, Rajagopal, et al., 2019a)		Covalent	**CDK7-CycH-MAT1=84** CDK12-CycK=204 CDK9-CycT1=914 CDK2-CycE1=2117	Phase I; **(NCT03134638)** terminated	Ovarian and breast cancer, advanced solid tumor.
7. SY-5609(Marineau et al., 2022)		Non-covalent	**CDK7-CycH-MAT1=0.06** CDK12-CycK=770 CDK2-CycE1=2900 CDK9-CycT1=970	Phase I; **(NCT04247126),** active but not recruiting	Breast cancer, advanced solid tumors, pancreatic cancer, SCLC, (Kovalová, Baraka, et al., 2023)
8. LY3405105		-	**CDK7-CycH-MAT1=92.8** CDK6-CycD1=8079 CDK4-CycD1=2830 CDK2-CycE1=20000 CDK1-CycB1=20000 CDK9-CycT1=6320	Phase I; **(NCT03770494),** terminated	TNBC, soft tissue sarcoma, ovarian cancer, solid tumor, bladder cancer epithelioid sarcoma, (Kovalová,

					Baraka, et al., 2023)
9. YKL-1-116(Kalan et al., 2017a)		Covalent	**CDK7-CycH-MAT1= 2**	Did not enter clinical trial	Ovarian cancer.
10. YKL-5-124(Olson et al., 2019a)		Covalent	CDK2-CycA=1300 CDK9-CycT1=3020 **CDK7-CycH-MAT1=9.7**	Did not enter clinical trials	Small cell lung cancer (SCLC)
11. LGR6768(Kovalová, Havlíček, et al., 2023)		Covalent	**CDK7-CycH=20**	Phase I	Advanced solid tumors, leukemia.
12. Q901(Yu et al., 2022)	structure not disclosed yet	Covalent	**CDK7-CycH= 4**	Phase I/ II; **(NCT05394103)** recruiting	Advanced or metastatic ovarian cancer, Advanced solid tumors, endometrial cancer, CRPC, colorectal cancer, HR+/HER2− BC, pancreatic cancer, SCLC, (Kovalová, Baraka, et al., 2023)

13. XL102 (AUR102)(Satyam et al., 2020a)	structure not disclosed yet	Covalent	**CDK7-CycH= 4**	Phase I; **(NCT04726332)** recruiting	Ovarian cancer, solid tumors, HR + BC, TNBC, mCRPC (Kovalová, Baraka, et al., 2023)

BS-181: BS-181 (**Table 2, No.1**) is the initial occurrence of a CDK7 inhibitor with pronounced selectivity, exhibiting structural resemblances to the broad-spectrum CDK inhibitor roscovitine. The compound has a high degree of selectivity as a CDK7 inhibitor; however, it also demonstrates inhibitory activity against CDK2, albeit to a lower extent. The purported cancer therapeutic target CDK7 was validated by means of BS-181, as it demonstrated a reduction in the phosphorylation of CDK7 targets and hindered the development of tumors in xenografts and cancer cell lines. Despite demonstrating *in vivo* efficacy, the therapeutic potential of BS-181 was limited by its inadequate bioavailability and restricted cell permeability(Diab et al., 2020).

ICEC0942: The development of ICEC0942 (**Table 2, No.2**), the initial orally bioavailable CDK7 inhibitor, was driven by the objective of generating analogues of BS-181 that possess enhanced pharmacological properties while retaining selectivity for CDK7. The growth of MCF7 and HCT116 cell lines was claimed to be inhibited by ICEC0942 in many research articles, which was subsequently renamed as CT7001. Several chemical compounds derived from the same patent had much higher potency against CDK7, while demonstrating comparatively reduced efficacy against the tumor cell lines. The compound ICEC0942 exhibited inhibitory effects on the proliferation as regards diverse cancer cell lines, including ER+ breast cancer xenografts. Furthermore, its favorable characteristics in terms of absorption,

distribution, metabolism, and excretion (ADME) as well as pharmacokinetics (PK) render ICEC0942 a very attractive option for therapeutic intervention. The medication has been granted a license to Carrick Therapeutics and reached Phase I/II clinical studies aimed at advanced level solid malignancies, focusing on distinct groups of patients with breast and prostate cancer. However, the clinical trial has been completed till today's date (Sava et al., 2020).

LDC4297: LDC4297 (**Table 2, No.3**) is identified as a molecule based on Pyrazolotriazines, with structural similarities to Roscovitine and Dinaciclib. Various pyrazolotriazines have demonstrated significant potency and selectivity as inhibitors of CDK7. The chemical compound LDC4297 exhibits a significant inhibiting effect on CDK7, with an IC50 value of 0.13nM. Additionally, it displayed inhibitory activity against CDK2 with an IC50 value of 6.4nM. The compound LDC4297 exerts its inhibitory effect on transcription by diminishing the phosphorylation as concerns the C-terminal domain (CTD) at serine 5 and serine 7 residues(Sava et al., 2020).

THZ1 and THZ2: THZ1(**Table 2, No.4**) is the pioneer covalent inhibitor of CDK7 which represents a significant advancement in the realm of irreversible CDK7 targeted therapeutic agents. It has demonstrated potent activity against various cancer types(Christensen et al., 2014; Chipumuro et al., 2014; Kwiatkowski et al., 2014; Z. Zhang et al., 2017). The compound THZ1 exhibited inhibition of CDK7 with an IC_{50} value of 3.2 nM. However, it also displayed inhibitory effects on CDK12 and CDK13, with IC_{50} values of 893 nM and 628 nM, respectively(Olson et al., 2019b). Nevertheless, THZ1 exhibits covalent binding towards CDK12 and CDK13, targeting at Cys1039 and Cys1017 residue, resulting in the inhibition of their enzymatic function (Kwiatkowski et al., 2014b; H. Zhang et al., 2020). The utilization of THZ1 as a means to investigate the function of CDK7 has been extensive (Nilson et al., 2015). Though, recent findings suggest that its effects on transcriptional inhibition and tumor

suppression are dependent not only on the inhibition of CDK7, but also on the inhibition of CDK12 and CDK13 (Olson et al., 2019b). In contrast, THZ1 has established effectiveness in treating malignancies that have developed resistance to conventional therapy. For example, it resulted in a substantial reduction of growth *in vitro* in T47D palbociclib-resistant (PDR) cells of breast cancer(Guarducci et al., 2019).

Figure 5 shows THZ1 bound to the CDK7 binding pockets using selective residues which includes Met94 and Glu95 in the hinge region, Asp155 in the DFG motif residue, as well as Thr96, Asp97, and Gln141 in the ATP-binding site. Through the investigation of the binding mode, it is revealed that the presence of hydrogen bond interactions is a reason for specific residue binding in several regions of CDK7. Additionally, a crucial residue outside the kinase domain, namely Cys312 of CDK7, was also found to be involved in the binding (Kwiatkowski et al., 2014b; H. Zhang et al., 2020).

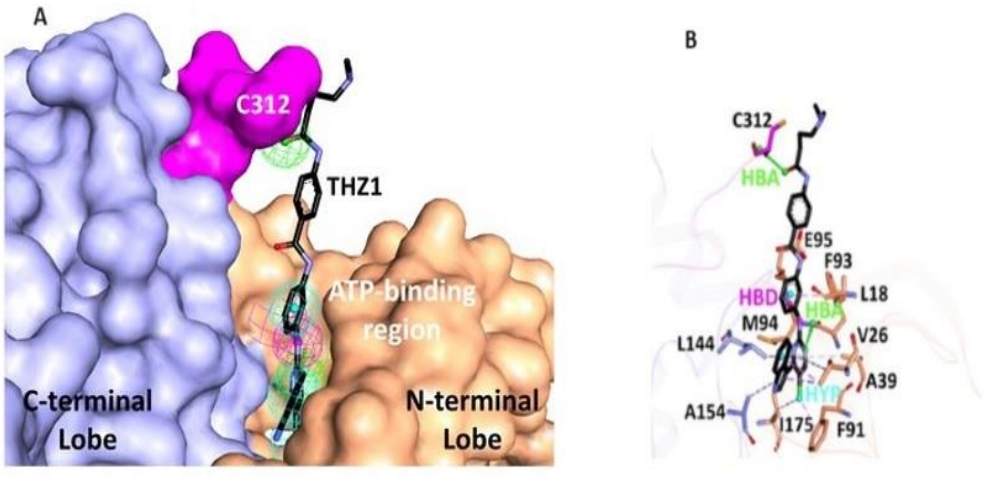


Figure 5: CDK7 in combination with THZ1. (A) A docking structure of CDK7 in combination with THZ1 where CDK7's N and C terminals are depicted in tan and purple, respectively. In addition, the pink area represents part of the protein that is located outside of the kinase domain. Also, the black stick represents THZ1. (B) CDK7's ATP-binding site residues along with Cys312 residue, which is outside of the kinase domain.(Kumar et al., 2021).

A modified version of THZ1, known as THZ2 (**Table 2, No.5**), has been synthesized with changes in the regiochemistry of the acryl amide and improved stability *in vivo* (Y. Wang et al., 2015). Triple-negative breast cancer (TNBC), which is well recognized for its very aggressive characteristics, was confronted by THZ2, a meta-isomer of THZ1 that exhibits CDK7 inhibitory action that is ten times greater in magnitude.

The effectiveness of THZ1 or THZ2 was additionally validated through *in vitro* and/or *in vivo* experiments conducted on many types of malignancies, including hepatocellular, gastric, cervical, pancreatic, colorectal, and non-small-cell lung (NSCL) cancers. The cancer cells of these specific kinds exhibited susceptibility to THZ1 or THZ2, resulting in the activation of apoptosis and/or disruption of cell cycle progression. In general, THZ1 and THZ2 have proved their effectiveness against a range of resistant cancers both in vitro and *in vivo*, without any observable harmful effects on the entire system. Although neither of these interventions advances beyond the preclinical stage(Diab et al., 2020).

SY-1365 and SY-5609: SY-1365 (**Table 2, No.6**), is a CDK7 inhibitor derived from THZ1 developed by Syros Pharmaceuticals in order to enhance the effectiveness, metabolic stability, and specificity of THZ1, as a potential candidate for clinical advancement (Hu, Marineau, Rajagopal, et al., 2019b). The investigational drug SY-1365 has commenced Phase I clinical trials for the management of advanced solid tumors. The trial also includes expansion cohorts that specifically target ovarian cancer along with breast cancer. Yet, Syros Pharmaceuticals has recently made the decision to halt the clinical advancement of SY-1365 and instead focus on the development of a novel CDK7 inhibitor, SY-5609 (**Table 2, No.7**). This new inhibitor is orally accessible and exhibits enhanced selectivity and potency towards CDK7 (Johannessen et al., 2019; Hu, Marineau, Hamman, et al., 2019). SY-5609 has demonstrated antitumor efficacy in preclinical models of ovarian cancer (Johannessen et al., 2019; Hu, Marineau, Hamman, et al., 2019), triple-negative breast cancer (TNBC) (Hu, Marineau, Hamman, et al.,

2019; Johannessen et al., 2019), and estrogen receptor-positive (ER+) breast cancer when used in combination with fulvestrant (Johannessen et al., 2019). Furthermore, durable tumor regressions have been observed, which have been linked to modifications in the retinoblastoma (RB) pathway (Johannessen et al., 2019). The official start of Phase I clinical trial targeting patients suffering from specific advanced solid tumors took place in the initial months of 2020 (Sava et al., 2020).

LY3405105: LY3405105 (**Table 2, No.8,**), a CDK7 inhibitor produced by Eli Lilly, has gone through scientific trials to evaluate its efficacy in treating advanced or metastatic solid cancers. Insufficient data has been presented regarding LY3405105. Currently, the clinical trial of LY3405105 has been terminated due to insufficient efficacy (Sava et al., 2020).

YKL-1-116 and YKL-5-125: The YKL class of CDK7 inhibitors was established by Syrus Pharmaceuticals. YKL 1-116 (**Table 2, No.9,**) is widely recognized as a prominent chemical compound. The compound had a significant inhibitory impact on CDK7, as evidenced by its IC_{50} value of 2nM. The investigation focused exclusively on other cyclin-dependent kinases (CDKs) and did not consider any other kinases in terms of selectivity. The efficacy of YKL-1-116 in combination with other antiproliferative medicines, such as 5-fluorouracil (Kalan et al., 2017b), has been demonstrated. The activities of YKL-5-125 (**Table 2, No.10**) have also been lately disclosed(Olson et al., 2019b). In contrast, to the majority of CDK7 inhibitors, this particular compound exhibits the ability to instigate cell cycle arrest in the G1 phase through inhibition of CDK1 activity. According to the study YKL 5-124 was synthesized through the fusion of the covalent warhead(Olson et al., 2019b) found in THZ1 with the pyrrolidinopyrazole core present in PAK4 inhibitor known as PF-3758309. YKL-5 124, similar to THZ1, forms a covalent bond with Cys312 residue of CDK7, while exhibiting no discernible impact on CDK12 or CDK13.

LGR6768: The compound LGR6768 (**Table 2, No.11**) is a currently developed derivative of trisubstituted pyrazolo[4,3-d]pyrimidine. It has been found to effectively block the activity of CDK7 at nanomolar concentrations. Additionally, LGR6768 exhibits a notable level of selectivity towards the CDK family of proteins. The validation of the specific targeting of CDK7 was accomplished by the use of biochemical kinase profiling as explained by Kavalova, which was further substantiated by structural analysis. LGR6768 had potential antileukemic properties and revealed a reduction in the phosphorylation of substrates associated with CDK7, such as RNA polymerase CTD, CDK2, and CDK1. The examination of the cell cycle indicated an obstruction in the G1 phase subsequent to the administration of therapy. Moreover, increased concentrations resulted in the initiation of apoptosis, which was accompanied by a blockage in the G2/M phase, activation of caspases, cleavage of PARP-1, and synthesis of apoptosis inhibiting proteins (mRNA and protein) has decreased. Additionally, LGR6768 was found to lower the activity of many oncogene factors linked to blood cancers (Kovalová, Havlíček, et al., 2023).

Figure 6 shows the binding poses of LGR6768 at the active sites of CDK7. In order to elucidate the selectivity of LGR6768 towards CDK7, a molecular docking analysis was conducted by Kavalova, whereby LGR6768 was docked into the cryo-EM structure of CDK7 (PDB: 7B5O). The binding posture of the inhibitor in the active site of CDK7, as determined by the Vina scoring function with a calculated ΔG value of -9.4 kcal/mol, exhibits a striking resemblance to that observed in CDK2. Specifically, the pyrazolo[4,3-d]pyrimidine core of the inhibitor establishes direct hydrogen bonding interactions with the amino acid residues Asp92 and Met94. In general, the active site cavity of CDK7 exhibits a greater width and a heightened propensity for potential interactions. One possible explanation for the relaxed conformation of LGR6768 in CDK7 and the deeper positioning of the piperidine moiety to interact with Asp155 could be attributed to this phenomenon. Subsequently, the isopropyl moiety of LGR6768

extends into the hydrophobic pocket of CDK7, establishing interactions with Ala39, Ile75, and the gatekeeper residue Phe91.

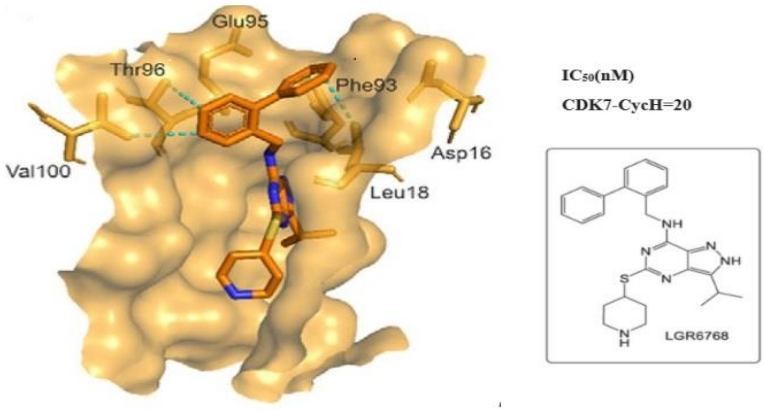


Figure 6: The binding poses of LGR6768 at the active sites of CDK7.(Kovalová, Havlíček, et al., 2023)

Q901: Q901 (**Table 2, No.12**), a CDK7 inhibitor with a significant level of selectivity, was created by Qurient, a firm based in Korea. Q901 inhibited tumor development in an estrogen receptor-positive breast cancer xenograft model by arresting cells in the G1 phase of the cell cycle, as well as in a model of patient-derived xenografts resistant to CDK4/6 inhibitors. Additionally, Q901 exhibited similar inhibitory effects on many types of solid tumors (Yu et al., 2020, 2021). The efficacy of Q901 was assessed across a diverse range of solid tumor cell lines, revealing its enhanced potency in cancer cells with intact TP53 compared to those with TP53 mutations. The possible pharmacodynamic marker, POLR2A, was identified based on its observed dose-response increase in expression following Q901 treatment, as well as its association with the rate of tumor growth inhibition (Yu et al., 2022). The current clinical trial for Q901 involves the administration of intravenous infusions to adult patients suffering from advanced level, solid tumors. Additionally, a cohort expansion (NCT05394103) is being conducted at the indicated phase 2 dose for designated advanced level solid tumors.

XL102: XL102 (**Table 2, No.13**), previously referred to as AUR102, is a strong CDK7 inhibitor that exhibits high selectivity and oral bioavailability (Satyam et al., 2020b). This compound was initially identified by Aurigene and is presently being developed through collaborative endeavors involving Exelixis. The administration of XL102 resulted in apoptosis of diverse cancer cell lines and exhibited a significantly reduced tumor size in numerous xenograft models. XL102 is now being investigated in phase 1 clinical research as a standalone treatment and in conjunction with other therapies for patients who have advanced solid tumors. These cancers include mCRPC (metastatic castration-resistant prostate cancer), HR + BC (hormone receptor-positive breast cancer), TNBC (triple-negative breast cancer) and epithelial ovarian cancer. The specific trial being referred to is QUARTZ-10, which has the clinical trial identifier NCT047263321. The initial findings from the phase of dose-escalation of the trial were found to have reached the maximum concentration (T max) of XL102 in a time frame of 1 to 3 hours and 5 to 9 hours ranging half-life. The administration of XL102 showed well tolerability at the levels that were examined. However, at higher doses, there were instances of treatment-emergent adverse effects. It is important to note that these events were of mild severity and were reversible. At the data cutoff, there were no objective responses observed, and patients who had a stable disease continued to participate in research. The evaluation of XL102 will be extended to include patients in three distinct cohorts: a dose-escalation cohort for a single agent, a dose-escalation cohort for a combination of agents, and a cohort for patients with a specific kind of cancer (Shapiro et al., 2022).

Several CDK7 inhibitors are discussed in this review study, including BS-181, ICEC0942, LDC4297, THZ1, THZ2, SY-1365, SY-5609, LY3405105, YKL-1-116, YKL-5-125, LGR6768, Q901, and XL102. These inhibitors differ in their selectivity and efficacy against CDK7, with some showing encouraging outcomes in preclinical and clinical trials. Notable compounds such as THZ1 and its derivative THZ2 have shown efficacy against resistant

malignancies (Diab et al., 2020), while SY-5609 and XL102 are progressing to clinical trials for possible therapeutic interventions in advanced solid tumors such as breast and ovarian cancer. In conclusion, the encouraging findings from continuing studies on CDK7 inhibitors highlight them as a strong anticancer agent, indicating that it may improve the present scenario of cancer therapies.

Chapter 3.3: Challenges

CDK7 is a key regulator of the cell cycle and transcription, making it an appealing target for anticancer drug development. CDK7 inhibitors have demonstrated potential in preclinical and early clinical studies, but their full therapeutic application is contingent upon addressing the current limitations in their selectivity towards CDK7 inhibitors. The structure of CDK7 is quite similar to other CDKs for instance CDK2 has 44% sequence similarity with CDK7 (Lolli et al., 2067). As a result , it is very diffcult to seletively inhibit CDK7 with abundant possibility of inhibiting other necessary cell cycle regulatory kinases.

Inhibition of CDK7 can arrest cell proliferation and has shown promise in preclinical models for various cancer types.Multiple CDK7 inhibitors have been developed, and some have advanced to clinical trials. However, the therapeutic potential of these inhibitors is hindered by issues related to selectivity, pharmacokinetics, and safety profiles. Understanding the precise binding interactions between CDK7 and its inhibitors is challenging due to limitations in crystallography. High-resolution crystal structures are invaluable for elucidating the mode of action of CDK7 inhibitors and for guiding rational drug design. However, obtaining such structures for CDK7 is challenging due to the protein's dynamic nature and a lack of suitable crystallization tools. The accurate prediction of the binding modes of CDK7 inhibitors using molecular docking software is hampered by the absence of high-quality crystal structures. The

future prospects of CDK7 inhibitors rely heavily on overcoming selectivity issues and docking limitations.

Tackling the limitations in understanding CDK7 crystal structures and accurate docking with inhibitors is pivotal for optimizing CDK7 inhibitors' therapeutic potential and selectivity. This will allow the rational design of novel compounds with improved selectivity and pharmacological profiles, potentially leading to more effective cancer therapies. Additionally, it will guide the identification of patient populations who are most likely to benefit from CDK7 inhibitor-based treatments.

Chapter 5: Conclusion

CDK7, a protein belonging to the cyclin-dependent kinase family, causes cancer due to its dysregulation and overexpression. Moreover, the association of CDK7 with various cancer advancements may be the reason for its double role in cell cycle as well as in transcription processes. CDK7 inhibitors have distinctive properties in regulating cellular proliferation, migration, and mitosis, among other processes whereby CDK7 offers in facilitating the accelerated expansion of several cancer types such as ovarian cancer, TNBC, endometrial cancer, CRPC, colorectal cancer, HR+/HER2− BC, pancreatic cancer etc. Furthermore, the upregulation of CDK7 may lead to the dephosphorylation and subsequent suppression of other associated protein kinases, including CDK1, CDK2, CDK4, and CDK6. Moreover, inhibitors that specifically target CDK7 could impede several phases of the cell cycle as well as transcriptional processes. Consequently, there has been a notable focus on CDK7 selective inhibitors in the field of tumor pathology research and the advancement of anticancer therapeutics, with the aim of devising targeted therapies for advanced solid tumors and malignancies. The current findings and research results published by many researchers have clearly indicate that CDK7 selective inhibitors have significant promise in the field of healthcare. The suppression of CDK7 elicits substantial structural alterations and a notable initiation of senescence, hence impeding the progression of cancer.

Chapter 6: Future prospects

Cancer cells often exhibit transcriptional addiction which refers to their significant reliance on the continual generation of short-lived transcripts, as well as their processing and stability (Bradner et al., 2017). This addiction involves transcripts that encode apoptosis inhibiting proteins and transcription factors for oncogene. The co-occurrence of CDK7 overexpression in several cancer types presents an intriguing case for investigating this kinase as a potential therapeutic target. Additionally, this phenomenon serves as a catalyst for the advancement of CDK7 inhibitors as pharmaceutical agents in the field of oncology (Z. M. Li et al., 2022b).

Indeed, the exploration of this potentiality has been undertaken subsequent to the revelation that the first iteration of all-encompassing CDK inhibitors impede the progression of the cell cycle along with substantial inhibitory effects on transcriptional CDKs (tCDKs). While initial inhibitors, frequently shown a deficiency in biochemical selectivity and exhibited associated toxicities, hence it becomes hard to figure out what role tCDKs play in the antitumor reaction, they played a substantial role in advancing our understanding of cancer biology and the actual function of tCDKs (Galbraith et al., 2018). Significant research efforts have made notable progress in addressing challenges pertaining to potency and selectivity, particularly in relation to certain cyclin-dependent kinases (CDKs) such as palbociclib and ribociclib, which specifically target CDK4. Consequently, these compounds have successfully passed through the necessary approval processes and are now recognized as pharmaceutical medications. The aforementioned narratives provide compelling evidence that selectivity may really be achieved even among enzymes that are closely related belonging to the CDK family (Kovalová, Baraka, et al., 2023).

Fortunately, CDK7 is also classified as a kinase for which there have been encouraging advancements in inhibitor development. At least in part, a distinctive cysteine residue like

Val100, Thr96 and Pro310 (Lolli et al., 2067) present on the entrance of the active site of CDK7 structure has facilitated the use of irreversible ligands to target this enzyme. Despite the potential for off-target toxicities associated with reactive functional groups, covalent medicines have shown promise in the advancement of CDK7 inhibitors. Notably, SY-1365 has progressed to clinical trials as the first irreversible inhibitor of CDK7 (Hu, Marineau, Rajagopal, et al., 2019a) with additional candidates like Q901 and XL102 also being explored. The substantial quantity of patents pertaining to irreversible binders that have been issued in the last five years indicates a sustained level of interest in this domain.

Reversible drugs, such as samuraciclib (Therapeutics et al., 2023), SY-5609 (Marineau et al., 2022), and other additional clinical candidates, may be used to achieve selectivity over other cyclin-dependent kinases (CDKs) and different kinases. Over the past half-decade, a substantial number of patent applications have been produced that detail inhibitors lacking a reactive group and functioning as ATP competitors. The anticipated outcomes of clinical investigations aim to address the inquiry of the potential manageability of toxicity associated with covalent compounds, as well as the potential for enhanced safety offered by reversible medications. Nevertheless, the identification of a definitive response may be obscured by several pharmacological factors, such as selectivity, which often influences both the desired target activity and unintended off-target effects and potential toxicity.

However, the genetic silencing of CDK7 demonstrates its dispensability in the context of global transcription and its lack of adverse effects in adult tissues (Ganuza et al., 2012). This discovery presents two noteworthy and partially conflicting implications, suggesting that the potential toxicity level of selective CDK7 inhibitors may be minimal, while also indicating that the inhibition of CDK7 selectively could be counteracted by other kinases, rendering extremely selective compounds ineffective. The second option poses additional inquiries as not all tCDKs, which may possess compensatory functions, are associated with tumor promotion. In

certain circumstances, they may even exhibit contrasting roles, such as CDK8, which also exhibits tumor suppressive properties(Wu et al., 2021). Consequently, deactivating these tCDKs may yield counterproductive outcomes.

Another intriguing aspect of CDK7 regulation is the use of induced protein breakdown. The use of developed proteolysis-targeting chimeras (PROTACs) has the potential to provide insights into potential compensatory mechanisms. Furthermore, the investigation of other potential roles of CDK7 might be facilitated. Certain kinases, including CDK6 and CDK9, have been shown to have noncatalytic functions in addition to their catalytic responsibilities. These kinases participate in regulating the transcription by acting as a protein scaffold, facilitating interactions with other transcription regulators (Kung & Jura, 2016). There is a potential inclination to hypothesize that if CDK7 may likewise be classified within this cohort of multimodal regulators, the elimination of both its degradation and enzymatic activity might result in the complete eradication of all potential activities, hence yielding a more marked impact.

Expanding our learning of CDK7 biology, which may lead to the discovery of genes that are specifically reliant on CDK7 (Kovalová, Baraka, et al., 2023), has the potential to enhance the precision in selecting cancer types and optimize specific therapy approaches. The ongoing interest in effective CDK7 inhibitors persists, and it is anticipated that additional advancements in their development will elucidate the genuine efficacy of this treatment approach.

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