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Review

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Exploiting targeted degradation of cyclins and cyclin-dependent kinases for cancer therapeutics: a review

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Abstract: Cancer is characterized by abnormal cell proliferation. Cyclins and cyclin-dependent kinases (CDKs) have been recognized as essential regulators of the intricate cell cycle, orchestrating DNA replication, transcription, RNA splicing, and protein synthesis. Dysregulation of the CDK pathway is prevalent in the development and progression of human cancers, rendering cyclins and CDKs attractive therapeutic targets. Several CDK4/6 inhibitors have demonstrated promising anti-cancer efficacy and have been successfully translated into clinical use, fueling the development of CDK-targeted therapies. With this enthusiasm for finding novel CDK-targeting anti-cancer agents, there have also been exciting advances in the field of targeted protein degradation through innovative strategies, such as using proteolysis-targeting chimera, HSP90-mediated targeting chimera, hydrophobic tag-based protein degradation, and molecular glue. With a focus on the translational potential of cyclin- and CDK-targeting strategies in cancer, this review presents the fundamental roles of cyclins and CDKs in cancer. Furthermore, it summarizes current strategies for the proteasome-dependent targeted degradation of cyclins and CDKs, detailing the underlying mechanisms of action for each approach. A comprehensive overview of the structure and activity of existing CDK degraders is also provided. By examining the structure-activity relationships, target profiles and biological effects of reported cyclin/CDK degraders, this review provides a valuable reference for both CDK pathway-targeted biomedical research and cancer therapeutics.

Key words: Cyclin-dependent kinase (CDK); Cyclin; Protein degrader; Targeted protein degradation

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1 Introduction

Cancer is characterized by uncontrolled cell expansion, during which cell cycle control is inevitably reconfigured. Cell cycle progression is a sophisticated process governed by mitotic signals and cell cycle machineries that involve cyclins and cyclin-dependent kinases (CDKs). Human CDKs are a family of 21 serine/threonine protein kinases that usually dimerize with partner subunits known as cyclins to phosphorylate downstream substrates(Satyanarayana & Kaldis, 2009; Wood & Endicott, 2018). In the human genome, over 30 cyclins have been reported based on the presence of cyclin box domains (CBDs), which are critical for CDK binding and share a high homology in sequence including a conservative Lys-Glu pair (Quandt et al., 2020). Accumulating evidence indicates that cyclins and CDKs also play diverse roles in cell cycle/proliferation, transcription, RNA processing, DNA replication, DNA repair, transcription, RNA splicing, RNA polyadenylation, and signal transduction (J. Chou et al., 2020; Hydbring et al., 2016; Kciuk et al., 2022; Parua & Fisher, 2020; Petroni et al., 2020). Indeed, CDKs and cyclins are frequently dysregulated in human cancer. High-throughput genetic screening assays have also suggested most CDKs and cyclins are functional prerequisites of cell viability in cancer. Therefore, targeting CDKs and cyclins for cancer treatment has been a long-standing strategy in pharmaceutical development (Vervoort et al., 2022).

Thus far, tremendous efforts have been made to develop CDK-targeted agents, with numerous CDK inhibitors reported to date. The first breakthrough of CDK-targeted drugs stems from the investigation of palbociclib, a dual inhibitor of CDK4 and CDK6, in treating hormone receptor-positive, HER2-negative advanced or metastatic breast cancer. Following palbociclib, additional CDK4/6 inhibitors including ribociclib, abemaciclib and trilaciclib have been approved for targeted cancer therapy (Morrison et al., 2024). In contrast, the clinical translation of early generations of CDK inhibitors such as flavopiridol, roscovitine, dinaciclib and SNS-032 were hindered by treatment-associated toxicities and the lack of selectivity. Nevertheless, the success of CDK4/6 inhibitors stimulated further research into other CDK-targeted agents with improved specificity.

Along with the pursuit of innovative CDK-targeted agents, several technical routes have been attempted including competitive inhibitors, allosteric inhibitors, covalent inhibitors and chemically induced protein degradation *via* proteolysis-targeting chimeras (PROTACs), heat shock protein 90 (HSP90)-mediated targeting chimeras (HEMTACs), hydrophobic tagging (HyT) degraders, as well as molecular glues. In parallel to small molecule inhibitors, the chemical degradation of CDKs or cyclins emerges as an active area and a promising direction for developing new-modality anti-cancer drugs (L. Wang et al., 2023; B. Yu et al., 2022). This article mainly reviews the latest progress in CDK degraders and their efficacy, with an intention to provide state of the art understanding of this field.

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2 Function of cyclins and CDKs in cancer

CDKs can be generally divided into three major classes (Table S1): cell cycle-regulatory CDKs (including CDK1, CDK2, CDK3, CDK4, and CDK6), transcription-associated CDKs (CDK7, CDK8, CDK9, CDK10, CDK11, CDK12, CDK13, and CDK19) and atypical CDKs (CDK5, CDK14, CDK15, CDK16, CDK17, CDK18, and CDK20). Cyclins can be grouped in a similar fashion: canonical (cell cycle-regulatory) cyclins, transcription-associated cyclins and atypical cyclins (Quandt et al., 2020; L. Wang et al., 2023). Although such classification scheme may be oversimplified, it highlights the key cellular functions of CDKs and the associated cyclins. In fact, cyclins and CDKs are widely involved in DNA replication, transcription, RNA processing, signaling transduction, and immune modulation (J. Chou et al., 2020; Kciuk et al., 2022). The functions of nearly half of CDKs, especially atypical CDKs, remain to be further characterized. Several cyclins (namely Cyclin G2, Cyclin J Like, Cyclin O, Cyclin P, Cyclin Pas1, and Cyclin N-Terminal Domain Containing 1) remain orphans, as their interactive CDKs have not been well established.

Cell cycle-regulatory cyclins and CDKs orchestrate the temporal order of cell cycle events, especially DNA replication and mitotic progression. Among cell cycle-regulatory cyclins and CDKs, CDK4, CDK6, and D-type cyclins are hyperactivated across a wide spectrum of human cancers via amplification, mutation and translocation. CDK4 and CDK6, which share similar structures and functions, are key regulators of the restriction point (also known as R point) in the G1 phase. The CDK4/Cyclin D and CDK6/Cyclin D complexes

phosphorylate pocket proteins (i.e., pRb, p107 and p130) and subsequently prevent them from binding with E2F transcription factors. The CDK6/Cyclin I complex was recently identified to also negatively regulate pRb (Quandt et al., 2023). The release of E2F proteins allows the transcription of E-type cyclins, DNA replication factors and many other targets required for the initiation of DNA synthesis and entry into the S phase. Beyond the R point, loss of CDK4/6 activity in the later stages of interphase also causes cell cycle exit due to compromised CDK2 activity and pRb phosphorylation (Cornwell et al., 2023). Similarly, the inhibitory phosphorylation of CDK1 and CDK4/6 by stress-activated protein kinases during the G2 phase triggers exit of cell cycle after DNA replication (McKenney et al., 2024). However, when recovering from the stress, some cells can re-start cell cycle, initiate a second round of DNA replication and progress through mitotic cell division, producing daughter cells with doubled genome. CDK6 maintains the status of normal mesenchymal stem cells, hematopoietic stem cells and leukemic stem cells (A. J. Hu et al., 2023; Z. Li et al., 2021; Scheicher et al., 2015). As a result of CDK4/6 inhibition, the cell cycle can be arrested and cancer cells switch fate into apoptosis, quiescence or senescence. Importantly, recent studies have revealed various immune modulatory effects of CDK4/6 blockage (Bai et al., 2023; H. Fan et al., 2023; Goel et al., 2017; Nayyar et al., 2024; Schaer et al., 2018; Scirocchi et al., 2022). On the one hand, inhibition of CDK4/6 increased DNA damage and expression of endogenous retroviral elements as well as immune regulators including intercellular adhesion molecule-1 (ICAM1) and genes related to the cGAS-STING1 signaling pathway, interferon response, tumor antigen presentation, and immune cell interaction. On the other hand, blockage of CDK4/6 supported the maintenance and infiltration of $CD8^+$ T cells at the expense of regulatory T cells, thereby inducing a T cell inflamed tumor microenvironment that favors cytotoxic T-cell-mediated clearance of cancer cells and boosts the anti-cancer efficacy of immune checkpoint inhibitors. Of note, the successful development of CDK4/6 inhibitors such as palbociclib further validates the significance of these kinases in cancer biology (Morrison et al., 2024).

Transcription-associated CDKs regulate gene transcription and transcription-coupled RNA processing by phosphorylating the hepta-repeats YSPTSPS within the carboxy-terminal domain (CTD) of the DNA-directed RNA polymerase II (RNA Pol II) subunit RPB1(Parua & Fisher, 2020; Asghar et al., 2015; Zaborowska et al., 2016; Dieci, 2021). CDK7, CDK9, CDK12, and CDK13 represent a subset of members with prominent activities in transcriptional regulation, attracting much interest in drug development. The excessive expression of CDK7 has been reported in many cancer types including triple-negative breast cancer, lung cancer and MYCN-driven neuroblastoma (Y. Wang et al., 2015; J. Wang et al., 2020; Christensen et al., 2014; Chipumuro et al., 2014). CDK7 functions in a complex with Cyclin H and MAT1 to form CDK-activating kinase (CAK) that activates other cell cycle CDKs (e.g., CDK1, CDK2, CDK4 and CDK6) via T-loop phosphorylation (Glover-Cutter et al., 2009; Goel et al., 2022; Schachter & Fisher, 2013). CDK7/Cyclin H is part of the TFIIH module within the RNA Pol II holoenzyme and phosphorylates RPB1 CTD at Ser5 and Ser7 sites during transcriptional initiation. Upon pause release, CDK7/Cyclin H phosphorylates CDK9 to promote transcription elongation. Moreover, CDK7 maintains the cancer-biased transcriptional output of super-enhancer targets that are often associated with cell identity, metabolism, pathobiology, and oncogenic factors (Yao et al., 2023). The inhibition of CDK7 induces transcription dysregulation and genome instability, helps to trigger anti-tumor immunity and overcome drug resistance (H. Zhang et al., 2020; Rusan et al., 2018). Currently, CDK7-selective inhibitors are under active investigation in clinical trials; the progress regarding SY-5609 and samuraciclib is encouraging (Marineau et al., 2022). CDK9 and Cyclin T form a heterodimeric kinase complex termed Positive-Transcription Elongation Factor-b (P-TEFb) where Cyclin T serves as a regulatory subunit for CDK9 (Baumli et al., 2008). P-TEFb activity is restricted by the 7SK small nuclear ribonucleoprotein (7SK snRNP) complex, which includes 7SK RNA, HEXIMI1/2 and LARP7, MEPCE and other regulatory proteins. Activation of P-TEFb requires the dissociation of 7SK snRNP and phosphorylation of CDK9 at the Thr186 residue on its T-loop (e.g., by the CAK complex) (Mbonye et al., 2013). Subsequent interaction of P-TEFb with either BRD4 or AFF1/4 proteins directs the complex to permissive gene promoters and phosphorylates RPB1 CTD at Ser2 and other transcription factors (e.g., androgen receptor at Ser81) (Gordon et al., 2010; K. Zhou et al., 2022). Eventually, P-TEFb facilitates the pause release of RNA Pol II, promoting the transcription machinery for productive elongation (Filippakopoulos et al., 2012). Interfering with CDK9 activity not only induces defective transcription elongation but also impairs the process of RNA splicing and epigenetic silencing of endogenous retrovirus genes (H. Zhang et al., 2018; L. Xiao et al., 2023). Hence, CDK9 emerges as a hot therapeutic target in cancer. The clinical evaluation of CDK9-specific inhibitors (e.g., BAY1251152, GFH009, KB-0742 and

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Zortiraciclib) is ongoing. Zortiraciclib has been granted Orphan Drug Designation for the treatment of glioblastoma by the FDA (J. Wu et al., 2021). Of note, the $CDK9^{L156F}$ mutant confers resistance to various CDK9-targeted agents (C. Hu et al., 2023). CDK12 and CDK13, both partnering with Cyclin K, are crucial for proper transcriptional elongation and RNA processing. Both of them phosphorylate RPB1 CTD at the Ser2 residue, which is implicated in transition from transcription initiation to elongation and subsequent recruitment of RNA processing factors. Alternatively, CDK12 was recently identified to be a bona fide kinase of LEO1 (Ser608), which is a subunit of the polymerase-associated factor 1 complex (PAF1C) for processive transcription elongation (M. Qiu et al., 2023). Other known substrates of CDK12 and CDK13 include splicing factors and components of the spliceosome, as well as the cleavage and polyadenylation specificity factor complex. CDK12 and CDK13 share some overlapping functions in RNA Pol II processivity and transcription elongation (Z. Fan et al., 2020). The single inhibition of either CDK12 or CDK13 elicited transcriptional programs associated with DNA damage response (DDR) and genome stability (Bösken et al., 2014; Tien et al., 2017) but had limited impacts on cell viability. On the contrary, dual inhibition was barely tolerable by cells as a result of defective transcriptional homeostasis, especially in the aspect of alternative polyadenylation, intragenic premature termination and aberrant co-transcriptional splicing (Z. Fang et al., 2017; L. Cheng et al., 2022; Magnuson et al., 2022). Dysregulation of CDK12 results in compromised HR repair, rendering cells more susceptible to DNA-damaging agents and genomically unstable (Dubbury et al., 2018; Iniguez et al., 2018; Krajewska et al., 2019; Quereda et al., 2019). The CDK12 gene is recurrently mutated and dysregulated in several types of cancers, especially high-grade ovarian adenocarcinoma (Cancer Genome Atlas Research Network, 2011). CDK12-deficient cancers often exhibit a BRCAness phenotype, demonstrating increased responsiveness to PARP inhibitors and immune therapy (Choi et al., 2020; Schweizer et al., 2020). Similarly, CDK12/13 inhibitors were shown to elicit a BRCAness phenotype and synergize with PARP inhibitors (Quereda et al., 2019). Agents targeting either CDK12/13 or Cyclin K are under active development and marching towards early phase clinical trials (e.g., CT7439 and CTX-439), providing a new strategy for cancer treatment.

As exemplified by the abovementioned CDKs and cyclins, the current understanding of CDKs and cyclins highlights their importance in diverse aspects of cancer biology. Targeting cyclins and CDKs is likely to have broad impacts on the cell cycle, transcription, DNA replication, RNA processing, signaling transduction, and immune response.

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3 Proteasome-dependent targeted protein degradation technologies for cyclins and CDKs

Targeting CDKs and cyclins represents a promising and feasible strategy for cancer treatment. The majority of efforts have been made to develop CDK inhibitors (Y. Huang et al., 2024). However, due to the high sequence homology and conserved ATP-binding pockets, the design of a conventional inhibitor of a specific CDK has proved challenging. Recent advances in chemically induced protein degradation inspire and stimulate a new direction of drug design. To this end, we next summarize the progress of CDK degraders that mainly employ proteasome-dependent techniques of PROTAC, HEMTACs, hydrophobic tags, and molecular glue (Figs. 1 and 2; Tables. 1 and 2).

PROTACs are chemical degraders that consist of a ligand that binds to a protein of interest (POI), a ligand that recruits an E3 ubiquitin ligase, and a linker that connects the two ligands (Sakamoto et al., 2001). PROTAC induces the formation of a POI-PROTAC-E3 ternary complex, facilitating ubiquitin conjugation to lysine residues on the surface of the POI and subsequent proteasome-dependent degradation (Fig. 1a) (Deshaies, 2015). Bridged PROTAC is a variant of PROTAC, which indirectly recruits POI *via* a bridge protein (BP). Compared with conventional inhibitors that rely on “occupancy-driven” effects (i.e., high affinity and high concentration *in vivo*), PROTACs are based on an “event-driven” mode (Leiser et al., 2014; Dogan et al., 2012). PROTACs possess a catalytic activity where one molecule can induce multiple rounds of POI degradation (Ishida & Ciulli, 2021). Moreover, PROTACs have an advantageous capability which means abolishing both the enzymatic and scaffolding functions of POI via induced protein degradation (Moon & Lee, 2018; X. Huang & Dixit, 2016). Remarkably, PROTACs targeting androgen receptor (ARV-110 and ARV-766), estrogen receptor (ARV-471) and BTK (NX-2127) have entered clinical trials and show promise in treating cancers of interest (Békés et al., 2022; Chirnomas et al., 2023). The preclinical development of CDK-targeted PROTACs is advancing rapidly.

HSP90, a well-established molecular chaperone, has been shown to interact with many E3 ligases and is able to recognize misfolded proteins to accelerate their clearance through the ubiquitin-proteasome pathway. In contrast to the engagement of a selective E3 ligase by PTOTACs, HEMTACs hijack the HSP90 together with various E3 ubiquitin ligases (HSP90/E3 complex) and form a ternary POI-HEMTAC-HSP90/E3 complex to induce targeted protein degradation (Fig. 1b). The structure of a HEMTAC resembles that of a PROTAC except for the HSP90/E3-binding moiety. Such strategy has been applied successfully to degrade BRD4 and CDK4/6 in pre-clinical studies (Kargbo, 2021; Z. Li et al., 2023).

Apart from PROTACs and HEMTACs, hydrophobic tags (HyTs) are heterofunctional molecules that consist of a ligand with binding affinity to a POI, a lipophilic moiety, and a small-molecule linker (Neklesa et al., 2011). HyTs bind to the POI and expose the hydrophobic moiety to the surface of a protein, mimicking the partially denatured state or misfolding of the protein. They then recruit the protein quality control machinery to target the POI for proteasomal degradation (Fig. 1c). Compared with PROTACs, HyTs may be applicable to a broader array of proteins by circumventing the limitation of amenable E3 ligases (Xie et al., 2023).

Molecular glue degraders are small molecules that induce proximity between two intracellular proteins and further the proximity-induced protein degradation (Fig. 2). They typically alter protein-protein interaction surfaces to either create or enhance the interaction affinity. Representative examples include thalidomide, lenalidomide, pomalidomide and other immunomodulatory drugs (IMiDs) which are indicated for multiple myeloma. IMiDs induce the interaction between E3 ligase cereblon (CRBN) and neosubstrates including IKZF1/3 and CK1α (casein kinase 1 alpha 1), and subsequently target them for degradation. Molecular glues are generally smaller in molecular weight and have more favorable physicochemical properties. Until now, the strategy of using molecular glue has been explored mainly to target CDK12 and Cyclin K.

4 Advances in small-molecule degraders of cyclins and CDKs

4.1 CDK2 degradation via PROTACs

PROTACs represent a primary approach for targeted CDK2 degradation (Fig. 3), utilizing CDK2 inhibitors (AT-7519, AT-7519-7, AZD5438, FN-1501, PF-069736, JNJ-7706621/J2, TMX-2039, TAE684) conjugated to either CRBN- or VHL-targeting ligands to recruit E3 ubiquitin ligases (Hati et al., 2021; M. Wu et al., 2024; F. Zhou et al., 2020).

Zhou et al. designed a series of CRBN-dependent PROTACs that connect pomalidomide or 3-hydroxy thalidomide to CDK2 inhibitors AT7519 or FN-1501. In general, FN-1501-based compounds are more potent and effective in inducing the degradation of CDK2 than AT7519-based ones. Of note, CDK9 was identified frequently as another target that was co-depleted with CDK2 by these FN-1501-based PROTACs. Molecule **1** (F3) was one of the leading candidates with desirable activities in human prostate cancer PC-3 cells, where its half-maximal inhibitory concentration (IC_{50}) against cell viability, half-maximal degradation concentration (DC_{50}) against CDK2, DC_{50} against CDK9 was 120 nM, 62 nM and 33 nM, respectively. Mirroring the effect of FN-1501, Molecule **1** impairs cell proliferation and arrested cell cycle in the G2/M phase. Kumarasamy et al. also reported another Pomalidomide and FN-1501 chimera Molecule **2** (FN-pom) that simultaneously depletes CDK2 and Cyclin E1 (Kumarasamy et al., 2023). Through the hybrid design of a pan-CDK inhibitor TMX-2039 and CRBN binder (Teng et al., 2020), Teng et al. developed Molecule **3** (TMX-1160), a PROTAC that turned out to exhibit cell type-dependent target profiles, acting as a multi degrader of CDK2/4/5/6 in Jurkat cells and a dual degrader of CDK2 and CDK5 in OVCAR8 cells. Further optimization of the linker and CDK binding moiety yielded Molecule **4** (TMX-2172), exhibiting enhanced selectivity and degradation efficacy against CDK2/CDK5 in both Jurkat and OVCAR8 cells. Similarly, through the hybrid design of CDK2/4/6 inhibitor PF069736-based PROTACs, Wei et al. developed a CDK2/4/6 degrader Molecule **5** and subsequently converted it into a prodrug Molecule **6** with good oral pharmacokinetic profiles (rat: F = 68%) and anti-melanoma activities *in vivo* (M. Wei et al., 2021). Remarkably, Molecule **7** (CPS2) and Molecule **8** (PROTAC-8) represent two CDK2-selective degraders (F. Zhou et al., 2020; M. Wei et al., 2021). Molecule **7** is a heterobifunctional degrader based on pomalidomide and a JNJ-7706621 derivative J2, and had an impressive selectivity for CDK2 over other CDKs. Although Molecule **7** degraded AURKA as an unintentional target, biologic studies suggested that it induced the differentiation of acute myeloid leukemia (AML) cells and human hematopoietic stem cells without inducing cytotoxicity primarily through CDK2 depletion. Different from

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Molecule **7**, Molecule **8** was developed from the linkage of a VHL binder VH032 and a CDK2 inhibitor AZD5438 (Hati et al., 2021). Despite a good selectivity, Molecule **8** only induces the partial degradation of CDK2.

Interestingly, Huang et al. studied a CRBN-dependent multi-kinase degrader Molecule **9** (TL12-186), which was later shown to exhibit a cell cycle phase-specific activity for protein degradation (L. Wang et al., 2021; Riching et al., 2021). Molecule **9** is able to degrade 16 CDKs including CDK2. While it retains a good binding affinity to CDK2 throughout the cell cycle, it only induces efficient degradation of CDK2 in the G1 or unsynchronized cells. One possible explanation for the reduced efficacy of Molecule **9** in CDK2 degradation in S and G2/M phases is its inability to form a ternary complex with CRBN. It would be interesting to examine whether the pattern of cell cycle-dependent degradation holds true for other CDK degraders.

To date, PROTACs appear as the predominant strategy for achieving targeted proteasomal degradation of CDK2. Notably, a few CDK2-directed PROTACs have demonstrated the ability to degrade CDK2-associated cyclins (e.g., Cyclin E) (Kumarasamy et al., 2023). While CRBN-recruiting CDK2 PROTACs exhibit potent on-target degradation, they frequently deplete unintended kinases (CDK4/5/6/9, AURKA). In contrast, VHL-based CDK2 PROTACs show improved selectivity but reduced maximal degradation efficiency.

4.2 CDK4/6 degradation *via* PROTACs and HEMTACs

PROTACs (including bridged PROTACs) and HEMTACs achieve proteasome-dependent CDK4/6 degradation through bifunctional designs coupling CDK4/6 inhibitors with E3 ligase-recruiting ligands (Fig. 4). HEMTACs substitute the specific E3 ligands with HSP90-recruiting ligands, leveraging chaperone-mediated degradation pathways for selective CDK4/6 degradation.

Many research groups have independently explored strategies of CRBN-dependent degradation of CDK4/6 *via* conjugating a CRBN binder to CDK4/6 inhibitors including palbociclib, ribociclib, abemacicilib and YY173 (He et al., 2024; Jiang et al., 2019; Zhao & Burgess, 2019). Zhao and Burgess connected pomalidomide to either palbociclib or ribociclib, so as to develop dual degraders of CDK4/6 including Molecule **10** (pal-pom) and rib-pom (Zhao & Burgess, 2019). The assembly of Molecule **10** with photosensitizer Chlorin e6 into nanoparticles potentiated the development of photodynamic combination therapy (T. Wang et al., 2023). Jiang and colleagues also reported a series of CDK4/6 degraders derived from palbociclib, ribociclib and abemacicilib (Jiang et al., 2019). Among those, abemacicilib-based Molecule **11** (BSJ-01-184) demonstrated dual degradation activities towards CDK6 and CDK4, while palbociclib-based Molecule **12** (BSJ-02-162) and ribociclib-based Molecule **13** (BSJ-01-152) showed a CDK6-biased and CDK4-biased activity, respectively. Using a similar strategy, Rana et al. also found a series of PROTACs that degrades CDK6 preferentially in pancreatic cancer cells *via* phthalimide-conjugation to palbociclib (Rana et al., 2019). Molecule **14** (PROTAC 6) with a longer linker exhibited the strongest CDK6-proteolytic efficacy. Similarly, palbociclib/thalidomide-based CDK6 degrader Molecule **15** (YX-2-107) showed good anti-tumor effects on Philadelphia-positive acute lymphoblastic leukemia (De Dominici et al., 2020). Wu et al. developed a CDK4/6 degrader Molecule **16** (MS140), which is a palbociclib/pomalidomide chimera with a short linker (X. Wu et al., 2021). Molecule **16** suppressed the pRb-E2F pathway and limited the E2F output and cell growth in sensitive cells. Su et al. compared the applicability of various E3 ligase moieties (i.e., pomalidomide for CRBN, VH032 for VHL, Nutlin-3b for MDM2, bestatin for cIAP1) for CDK4/6 degraders (Su et al., 2019). PROTACs based on CRBN were able to degrade CDK6 with high efficiency; among those, Molecule **17** (CP-10) exerted potent and selective activity against CDK6 with a DC_{50} of 2.1 nM. Of note, IKZF1 and IKZF3 are targets of IMiDs and the above-mentioned IMiD-based PROTACs (Lu et al., 2014). Since DKY709 is an alternative IMiD that targets IKZF2 instead of IKZF1/3, palbociclib-DKY709 chimeras, such as Molecule **18** (ALV-07-082-03), have been developed as potent CDK4/CDK6/IKZF2 triple degraders (Verano et al., 2022). The co-depletion of CDK4/6 and IKZF not only conferred enhanced anti-proliferative activity against cancer cells (e.g., mantle cell lymphoma cells) but also caused unwanted side effects in normal cells. Through optimization of the linker design, Brand et al. converted a palbociclib/phthalimide-based CDK6 and IKZF1/3 dual degrader Molecule **19** (YKL-06-102) into Molecule **20** (BSJ-03-123), which achieved the potent, fast and selective degradation of CDK6, meanwhile it left IKZF1/3 unaffected (Brand et al., 2019). Similarly, Molecule **21** (BSJ-03-204) was identified as a palbociclib/phthalimide-based CDK4/6 dual degrader without IKZF1/3 activity (Jiang et al., 2019). It seems that palbociclib-based CRBN-dependent PROTACs exhibit preferential CDK6 degradation

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selectivity over CDK4 (Anderson et al., 2020). In addition to the usage of known CDK4/6 inhibitors as substrate recruiting moieties, Gan et al. developed Molecule **22** (6a) with CDK1, CDK4 and GRP94 degradation activities through hybrid design of thalidomide and a natural, promiscuous compound celastrol (Gan et al., 2024).

Alternative E3 ligases have been tested for the induced degradation of CDK4/6. Failed attempts have been reported to develop MDM2-based CDK4/6. However, encouraging findings were obtained from CDK4/6 PROTACs dependent on DCAF16, VHL and cIAP1 (baculoviral IAP repeat containing 2). Recently, Pu et al. designed a series DCAF16-based CDK4/6 degraders that combine Palbociclib and DCAF16 E3 ligase ligand KB02 with various linkers (Pu et al., 2023). Despite the relatively high DC_{50} values (CDK4: 6.5 μM; CDK6: 8 μM), Molecule **23** (A4) represents a leading DCAF16-dependent CDK4/6 PROTAC with anti-breast cancer activities both *in vitro* and *in vivo*. Steinebach et al. showed that VHL and cIAP1-based targeted degradation of CDK4/6 is indeed feasible in cancer (Steinebach et al., 2020). Representative VHL-based selective CDK6 degraders include Molecule **24** and Molecule **25**. cIAP1-based Molecule **26** caused the concurrent degradation of CDK4/6 and IAPs (inhibitor of apoptosis proteins) at a concentration of 1 μM, yielding a synergistic anti-proliferative effect on cancer cells. Of note, several palbociclib-based VHL-dependent PROTACs including Molecule **27** (MS28) effectively degrade Cyclin D1 prior to CDK4/6 (T. Wang et al., 2023), mitigating the pRb-E2F pathway and the proliferation and clonogenicity of non-small cell lung cancer cells. Molecule **27** represents the first-in-class degrader of Cyclin D1 working through formation of the Cyclin D1-CDK6-PROTAC-VHL quaternary complex. Further investigation revealed that Molecule **27** simultaneously degrades Cyclin D3 but not Cyclin D2 or other cyclins. As inspired by MS28, "bridged PROTAC" emerges as a new strategy to degrade protein's binding partner (Fig. 1a).

The potential mechanisms of resistance to CDK4/6 inhibitors have been thoroughly reviewed (Steinebach et al., 2020). RB1 loss and hyper-activation of CDK2, Cyclin E and INK4 proteins have been associated with CDK4/6 inhibitor resistance (Xu et al., 2021; Condorelli et al., 2018; Q. Li et al., 2022). The application of a CDK2/Cyclin E PROTAC Molecule **2** synergized with CDK4/6 PROTACs against p16/INK4A-proficient cancer cells (Kumarasamy et al., 2023). The recent development of YY173/pomalidomide-based CDK2/4/6 PROTAC may be beneficial to overcome resistance to CDK4/6 inhibitors (He et al., 2024). Wu et al. also reported that CDK6 is a thermostable, weak HSP90-client, with lower affinity for either inhibitors or degraders of CDK4/6 in cells resistant to CDK4/6-targeted agents (X. Wu et al., 2021). In line with the relevance of HSP90's affinity to drug response, a new approach termed HSP90-mediated targeting chimeras (HEMTACs) was devised by connecting palbociclib with the HSP90 ligand BIIB021 via a flexible linker (Z. Li et al., 2023). In the presence of HEMTACs, HSP90/E3, HEMTAC and CDK4/6 form ternary complexes that prime ubiquitin transfer and proteasomal degradation of CDK4/6. Molecule **28** (HEMTAC 26) was showcased as a good example, exhibiting desirable degradation efficiency and anti-tumor activity. Hence, HEMTACs provide a valuable strategy to cause the degradation of weak- or non-HSP90 client proteins.

PROTAC and HEMTAC studies have evaluated a number of E3 ligases for degrading CDK4/6. Remarkably, "bridged PROTAC" represents a promising strategy for developing cyclin degraders. Thus far, the effective degradation of CDK4/6 has been achieved using CRBN, VHL, cIAP1, DCAF16, and HSP90-recruiting E3 ligases (HEMTACs), whereas MDM2-based approaches remain unsuccessful. Notably, CRBN-recruiting PROTACs frequently cause the co-depletion of IKZF proteins that comprise the major source of toxicity in normal cells. While CDK4/6 share functional redundancy, lineage-associated dependency on each isoform has been recognized. For example, $HER2^+$ breast cancer and prostate cancer exhibit CDK4-dependence (Z. Zhang et al., 2022), whereas hematopoietic cells reply primarily on CDK6 (Maurer et al., 2021). Although CDK4-selective agents may offer a path to circumvent the hematologic toxicities associated with dual CDK4/6 inhibitors (Palmer et al., 2025), achieving selective inhibition remains very challenging due to the highly homologous ATP-binding pockets of CDK4 and CDK6. Encouragingly, through PROTAC optimization, researchers have developed degraders achieving CDK4-specific, CDK6-specific or dual-targeted degradation. These isoform-selective degraders represent valuable tools for dissecting CDK4/6 biology and advancing precision cancer therapy.

4.3 CDK8/19 degradation *via* PROTACs

CDK8 and CDK19 are closely related CDKs that function as key regulatory components within the Mediator complex. PROTAC technology has demonstrated feasibility in transforming CDK8/19 inhibitors into

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either CDK8-selective degraders or CDK8/19/Cyclin C triple degraders (Fig. 5).

In 2018, Hatcher and colleagues developed JH-VIII-49, a CDK8/19 inhibitor analogous to Cortistatin A (Hatcher et al., 2018). The conjugation of JH-VIII-49 and Pomalidomide *via* a polyethylene glycol (PEG) linker further yielded a CDK8-selective PROTAC Molecule **29** (JH-XI-10-02). Another CDK8-selective degrader, Molecule **30** (YKL-06-101), was synthesized by linking mTOR/CDK8 inhibitor THZ4-55 with thalidomide (Menzl et al., 2019). While retaining the function to inhibit mTOR, Molecule **30** acts as a CDK8 degrader without altering levels of CDK19, Cyclin C, MED12, and MED13. Interestingly, CDK8-dependent transcriptional changes impaired the mTOR pathway in Philadelphia-positive acute lymphoblastic leukemia cells, whereas CDK8 kinase inhibitors showed minimal effects. In this scenario, simultaneous CDK8 depletion and mTOR inhibition by Molecule **30** induced the apoptosis of leukemic cells. Chen et al. developed a CDK8/19 PROTAC named Molecule **31** (SNX7886) (Chen et al., 2023) on the basis of the hybridization of pomalidomide and a CDK8/19 inhibitor BI1347. Molecule **31** degraded CDK8 by up to 90% and CDK19 by up to 80% at 30 nM, with concurrent depletion of Cyclin C.

Collectively, the abovementioned findings for CDK8/19 PROTACs suggest the feasibility of developing CRBN-based CDK8 degraders and CDK8/19/Cyclin C degraders. However, CDK19-selective degraders remain unavailable to date. Besides, information on anti-cancer activities that can be attributed to on-targeted effects of CDK8/19 PROTACs remains limited.

4.4 CDK7 degradation *via* PROTACs

CDK7-targeting PROTACs have been developed via the conjugation of CDK7 inhibitors (i.e., YKL-5-167, and A86) to either VHL- or CRBN-targeting ligands. Ji et al. recently reported a series of CDK7 PROTACs that connect the selective CDK7 inhibitor YKL-5-167 analogues to either VHL or CRBN recruiters (Fig. 5) (Ji et al., 2024). A VHL-based CDK7 PROTAC Molecule **32** (JWZ-5-13) induced the near-complete degradation of CDK7 with low nanomolar efficacy in various cancer cell lines. Of note, the CDK7 interacting partners Cyclin H and MAT1 that form the CAK complex could be depleted simultaneously, while other CDKs were barely affected. Molecule **32** exhibited an improved anti-proliferative capability over the CDK7 inhibitor YKL-5-167. Moreover, it was well-tolerated by the mice and exhibited half-lives ($T_{1/2}$) of 3.76 h and 2.82 h via intravenous and intraperitoneal injection, respectively. However, CRBN-based compounds were not able to induce the complete degradation of CDK7, as Molecule **33** that exhibited the best activity only achieved nearly 50% reduction. These data suggest that induced degradation of CDK7 may be more permissive to VHL than CRBN. Nevertheless, Wang et al. developed a CRBN-based multiple-target degrader Molecule **34** (PROTAC 13i), which elicited efficient degradation of CK1α, CDK7 and CDK9 (K. Wang et al., 2024). It also induced p53 and exerted anti-AML potentials at the expense of the transcriptional downregulation of survival genes (e.g., MDM2, MYC, BCL2, and MCL1) and cytokine genes. Altogether, CDK7-targeting PROTACs demonstrate the potential to deplete the CAK complex, thereby indirectly regulating downstream CDK activities. Unlike most CDKs that are generally more vulnerable to CRBN-based degraders, CDK7 displays preferential degradation via VHL-recruiting PROTAC. This ligase-selective vulnerability presents a compelling model for probing structural determinants governing productive E3 ligase engagement.

4.5 CDK9 degradation *via* PROTACs and HyTs

The widespread dysregulation and critical roles of CDK9 in oncogenic transcription stimulate the development of CDK9 degraders. To date, a number of structurally diverse PROTACs and HyTs with CDK9-proteolytic activities have been developed (Fig. 5). These CDK9 degraders exhibit robust target degradation and potent anti-proliferative activities across a wide spectrum of cancers.

The first CDK9 PROTAC Molecule **35** was reported by connecting an aminopyrazole analog to thalidomide in 2017 and showed low micromolar activity (Robb et al., 2017). Another aminopyrazole-based Molecule **36** (PROTAC 2) improved CDK9 degradation efficiency with a DC_{50} value of ~150 nM, where shortened linker length had a negative impact on CDK9 degradation (King et al., 2021). In 2018, Olson et al. reported a CDK9 PROTAC Molecule **37** (THAL-SNS-032) through chimeric design of a CDK inhibitor SNS-032 and thalidomide (Olson et al., 2018). Affinity competition assay showed that Molecule **37** degraded CDK9 in a catalytic, sub-stoichiometric fashion. Molecule **37** caused an efficient and selective depletion of CDK9 at a concentration of 250 nM within 2 hours and subsequently induced the loss of Ser2 phosphorylation at RPB1 CTD and sub-

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stantial perturbation of global mRNA biogenesis. As a result, the cancer-associated core regulatory circuitry was disrupted and apoptosis was induced in leukemic cells upon treatment with Molecule **37** (Boyer et al., 2005; Sanda et al., 2012). Wei et al. developed a highly potent and selective CDK9 degrader Molecule **38,** which showed IC_{50} values < 20 nM and strong anti-tumor effect in triple-negative breast cancer models (D. Wei et al., 2021). It had an on-target DC_{50} of < 100 nM, while it showed minimal effects on GSPT1 and other CDK proteins including CDK1, CDK2, CDK4, CDK5, CDK6 and CDK7 at doses up to 500 nM in breast cancer cells. The CDK9 inhibitor BAY-1143572 was also converted successfully into a series of CDK9 PROTACs, among which Molecule **39** (B03) showed enhanced anti-proliferative effect in acute myeloid leukemia cells (X. Qiu et al., 2021). Flavonoid-based CDK9 PROTAC Molecule **40** (CP-07) had a CDK9 DC_{50} of 43 nM in 22RV1 prostate cancer cells and was able to reduce the expression of MCL1 and MYC, cell viability and clonogenicity (T. Wu et al., 2023). AT7519-based CDK9 PROTACs with aminoalkanoic acid linkers such as Molecules **41**~**43** displayed impressive potency in CDK9 degradation and cytotoxicity against acute myeloid leukemia cells (Tokarski et al., 2023). Among those AT7519-based CDK9 PROTACs, compounds with PEG linker were generally less effective. Further exploration of linker length indicated that longer-chain compounds performed better than their shorter-chain analogues.

CRBN-dependent PROTACs with dual activity to degrade CDK9 and other kinases are available from the literature. For example, a Wogonin (natural flavone compound)-based Molecule **44** (PROTAC 11c) could target both CDK9 and CDK7; BPA311-based Molecule **45** (PROTAC 13) could selectively degrade CDK9 and FLT3 in leukemic cells with FLT3-ITD (Řezníčková et al., 2022); Molecule **46** (PROTAC CD-5) exhibited a degradation efficacy against CDK9, CDK1 and KAT6A (Ao et al., 2023).

In parallel to PROTACs, HyT-based small-molecule degraders have been developed by tagging a (-)-methoxyacetyl degron to SNS-032. Molecule **47** (LL-K9-3) and Molecule **48** (LL-CDK9-12) were showcased as two potent CDK9/Cyclin T1-targeted HyTs that could selectively degrade the CDK9/Cyclin T1 heterodimer without affecting other CDKs (J. Li et al., 2022; Lin et al., 2023). While Molecule **47** had off-targets including GSK3α (glycogen synthase kinase 3 alpha), Molecule **48** possessed a more efficient and selective degradation capability, with DC_{50} values of 0.36 μM and 0.68 μM against CDK9 and Cyclin T1, respectively. Both CDK9 HyTs exerted stronger inhibitory effects than SNS-032 on oncogenic transcription programs driven by MYC and androgen receptor in prostate cancer cells (J. Yang et al., 2022; T. Niu et al., 2022).

Altogether, CDK9 represents a highly tractable degradation target for many CDK-targeting PROTACs. CRBN-recruiting warheads are commonly utilized in the CDK9 PROTAC design, where optimizing linker length critically influences degradation efficiency. To date, the known CDK9-selective PROTACs remain limited; however, appending hydrophobic tags to CDK9 inhibitors enables the selective degradation of the CDK9/Cyclin T1 complex. Since CDK9 is a common essential gene for cancer and normal cells, enhancing cancer selectivity is critical for the clinical translation of CDK9-targeting degraders.

4.6 CDK12/13/Cyclin K degradation *via* PROTACs and molecular glues

CDK12 and CDK13 share a high degree of sequence and functional similarity. Both of them interact with Cyclin K. A number of PROTACs successfully degrade CDK12/13, while molecular glues predominantly deplete Cyclin K (Fig. 6). Structurally diverse degraders now enable distinct degradation profiles: CDK12-only, CDK12/13-dual, CDK12/Cyclin K-complex, Cyclin K-only, or CDK12/13/Cyclin K-triple depletion.

Yang and colleagues reported a CRBN-dependent dual CDK12/13 degrader Molecule **49,** which degraded CDK12 (DC_{50}: 2.2 nM), CDK13 (DC_{50}: 2.1 nM) and Cyclin K in MDA-MB-231 breast cancer cells (Yang et al., 2022). In line with the deleterious effect of dual kinase inhibition on cells, Molecule **49** reduced the viability of multiple triple-negative breast cancer cell lines, along with a marked inhibition of DDR gene transcription. Selective CDK12 PROTACs include Molecule **50** (BSJ-4-116) and Molecule **51** (PP-C8) (Y. Liu et al., 2023; Niu et al., 2022). Molecule **50** was the first selective CDK12 degrader developed using fragment of a dual CDK12/13 covalent inhibitor THZ531 as CDK12 binder. It depletes CDK12 in a dose- and a time-dependent manner with any trivial effect on CDK13. In cellular assays, Molecule **50** treatment not only significantly downregulated DDR genes but also overcame resistance to covalent CDK12/13 inhibitors. However, upon chronic exposure, mutations in CDK12 (i.e., I733V and G739S), which impair degrader binding, conferred the acquired resistance to Molecule **50**. Molecule **51** is another PROTAC with the capability to dually degrade both CDK12 (DC_{50}: 416 nM) and Cyclin K (DC_{50}: 412 nM). Both Molecule **50** and Molecule **51** showed a profound

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synthetic lethality with PARP inhibition in preclinical anti-cancer studies.

Molecular glues are best explored in the targeted degradation of Cyclin K, the dimerization partner of CDK12/13. Representative compounds include CR8, DS17/30, Compound 21195, SR-4835, HQ461, NCT02 and dCeMM2/3/4 (Dieter et al., 2021; Houles et al., 2023; Kozicka et al., 2024; Lv et al., 2020; Mayor-Ruiz et al., 2020; Słabicki et al., 2020), all of which act through the engagement of CDK12/13 active sites and DDB1/CUL4/RBX1 E3 ubiquitin ligase. Słabicki et al. identified **Molecule 52** (CR8) as a small-molecule glue that bridges the interaction between CDK12/Cyclin K and DDB1, promoting Cyclin K for ubiquitination and proteasomal degradation. This discovery emerged from correlating drug-sensitivity data for 4,518 clinical/preclinical small molecules with mRNA levels of 499 E3 ligase components across hundreds of human cancer cell lines. A surface-exposed 2-pyridyl moiety of CR8 confers it gluing function. Subsequent structural, biophysical and cellular studies of Molecule **52** derivatives and other Cyclin K molecular glues revealed that simultaneous binding to CDK12 and engagement of DDB1 interfacial residues (in particular Arg928) are essential for glue activity (Kozicka et al., 2024). Through the exploration of Molecule **52** analogues in Cyclin K degradation, Thomas et al. demonstrated that a wide range of modifications to the degradation-inducing group are tolerable as long as the solvent-exposed groups sufficed the interaction between CDK12 and DDB1 (Thomas et al., 2024). The addition of solvent-exposed groups such as pyridine and furan to the core of pan-CDK inhibitors dinaciclib and AT7519 converted them to Cyclin K degraders. Molecule **53** in the dinaciclib series was found to be both an effective CDK12 inhibitor and Cyclin K degrader, while AT7519-based Molecule **54** was a strong Cyclin K degrader but with ∼500-fold weaker CDK12 affinity. Dieter et al. also identified Molecule **55** (NCT02) as a molecular glue degrader of Cyclin K, CDK12 and CDK13 (Dieter et al., 2021). Upon treatment with Molecule **55** in colorectal cancer cells, degradation of Cyclin K occurred before that of CDK12. In line with the preferential growth dependency of TP53-defective colorectal cancer cells on Cyclin K and CDK12, targeted CDK12/Cyclin K degradation by Molecule **55** decreased the corresponding cell expansion both *in vitro* and *in vivo*. Molecule **55** further sensitized patient-derived colorectal cancer spheroids to chemotherapy agents including oxaliplatin and irinotecan. Molecule **56** (SR-4835) and Molecule **57** (DS17) are representatives of CDK12/13-selective inhibitors with concurrent glue activities as Cyclin K degraders. Alterations in the benzimidazole side chain of Molecule **56** decreased cyclin K degradation and cytotoxicity (Houles et al., 2023). Molecule **58** (HQ461) was shown to be a relatively weak glue degrader of Cyclin K with lower inhibitory activities against CDKs (Lv et al., 2020). Structure-activity relationship analysis unveiled a 5-methylthiazol-2-amine moiety as the important pharmacophore of Molecule **58**, and further guided the development of Molecule **59** (HQ005) with an improved potency (Cyclin K DC_{50}: 41 nM). CDK12 mutations in G731R/E and CDK13 mutations in G709R/E conferred Molecule **57** resistance. Through screening a library of approximately 2,000 cytostatic/cytotoxic small molecules against wild-type and UBE2M-mutated near-haploid KBM7 cells, Mayor-Ruiz et al. identified a series of chemical scaffolds that exhibited functional dependence on intact neddylation pathways (Mayor-Ruiz et al., 2020). Subsequent quantitative proteomics analysis indicated that Molecules **60**~**62** (dCeMM2/3/4) profoundly downregulate Cyclin K, whereas they have a milder effect on CDK12/CDK13. On the basis of CRISPR/Cas9 screening assay using a Cullin-RING ubiquitin ligase (CRL)-focused sgRNA library, a number of genes including DDB1, CUL4B, UBE2M, UBE2G1, UBE2Z, and UBA6 were identified to confer cellular sensitivity to Molecules **60**~**62**. These glues also exhibited selective dependence on CUL4B over CUL4A, suggestive of the CRL4B ligase complex-dependent degradation of Cyclin K. Moreover, the engagement of CDK12/13 active site was required for drug-induced degradation of cyclin K via the CRL4B-DDB1 complex, albeit the cellular efficacy of Molecules **60**~**62** appeared to be independent of their weak inhibitory activity against CDK12/13. Acquired resistance to Molecules **60**~**62** emerged from mutations in DDB1, CUL4B, CDK12, and CDK13. A CDK13 (P1043H) mutation outside the kinase domain blunted Cyclin K degradation following treatment with Molecules **60**~**62**. Of note, in spite of the common effect on Cyclin K degradation, Cyclin K molecular glues had distinct target profiles beyond Cyclin K. Through rational design, the independent optimization of CDK inhibition and Cyclin K degradation activities seems feasible, leading to compounds with different target profiles and biologic activities (Thomas et al., 2024).

To sum up, chemically induced degradation of CDK12/13 strongly disrupts DDR gene expression, potentiating synthetic lethality with PARP inhibition. In contrast, Cyclin K molecular glues trigger diverse transcriptomic responses that are different from selective degradation or inhibition of CDK12/13. This variability in target engagement profiles necessitates rigorous characterization and in turn may be beneficial to the devel-

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opment of diverse drugs. Furthermore, developing a CDK13-selective degrader may be helpful to delineate the isoform-specific function between CDK12 and CDK13.

4.7 CDK17 degradation *via* PROTACs

CDK17 is a poorly studied kinase with the highest expression in brain tissue. Although its function remains a mystery, CDK17 was shown as a degradable protein by PROTACs. By employing a chemo-proteomics approach, Donovan et al. found that CDK17 was degraded by 15 different compounds including two potent and selective PROTACs for CDK17 (Donovan et al., 2020). Molecule **63** (DD-03-156; Fig. 5) is the chimeric design of VHL binder and dabrafenib (an inhibitor of $BRAF^{V600E}$ mutant). Interestingly, instead of BRAF, Molecule **63** induced the potent and selective degradation of CDK17 and LIMK2 (Donovan et al., 2020), suggesting that turning an inhibitor with prominent targets into a PROTAC may generate novel, potent and selective degradation events distinct from a warhead inhibitor's primary targets. Meanwhile, the impact of CDK17 degraders on cellular phenotypes remains unclear.

5 Conclusions and future perspectives

As summarized above, cyclins and CDKs are reliable drivers and thus attractive targets in human cancer. The inhibition of cyclins and CDKs impairs diverse oncogenic pathways not limited to cell cycle, transcription, DNA replication, RNA processing, signaling transduction, and immune response. In recent years, encouraging progress has been made in developing CDK and/or cyclin degraders via PROTAC, HEMTAC, HyT, and molecular glue techniques. Chemically induced protein degradation emerges as an innovative and promising strategy to target cyclins and CDKs.

5.1 Unfilled gaps in CDK and cyclin biology

Many biologic aspects of cyclin and CDKs remain unexplored. For example, functional redundancy and cooperation among CDKs with high homology has not been well addressed. Such situations apply to but are not limited to CDK11A versus CDK11B, CDK4 versus CDK6, CDK8 versus CDK19, CDK12 versus CDK13, as well as CDK7 versus CDK20. Protein degraders, especially PROTACs, usually trigger highly efficient depletion of CDKs or cyclins within hours. Leveraging this advantage, protein degraders of high selectivity serve as valuable tools to elucidate phase-specific roles of CDK/cyclin complexes during cell cycle progression (Fig. 7).

While the non-canonical functions and kinase-independent scaffolding roles of several CDKs have been recognized, their mechanistic underpinnings and biological consequences remain inadequately characterized. This knowledge gap impedes both fundamental understanding and therapeutic exploitation. Furthermore, the functional relevance of cyclins and CDKs to various cancer hallmarks beyond cell cycle biology awaits thorough investigations, especially in the context of cancer signaling transduction, metabolism, epigenetics, immunity, and the microenvironment. It should be also emphasized that CDK/cyclin-targeted cancer therapy influences simultaneously both cancer cells and the non-cancer compartments. The roles of cyclins and CDKs in immune cells and stromal cells are still elusive.

5.2 Advantages of targeted protein degradation over conventional protein inhibition

Rapid advances in targeted protein degradation technologies have yielded diverse therapeutic modalities including PROTAC, HEMTAC, HyT, and molecular glues, all of which hijack the cellular degradation machinery (e.g., the ubiquitin-proteasome system) to eliminate POI. As extensively documented in the literature, targeted protein degradation offers strategic advantages over conventional inhibition through expanded target druggability, catalytic mechanism of action, disruption of scaffolding functions, and reduced susceptibility to resistance (Table 1).

Conventional small-molecule drug design relies on binding to a specific catalytic or allosteric site on a target protein, triggering the so-called occupancy-driven inhibition. However, this occupancy-driven pharmacology usually becomes ineffective in case of proteins either lacking well-defined catalytic pockets (e.g., cyclins, and other CDK partners) or exhibiting highly homologous binding sites (e.g., kinase domains within CDKs). In these scenarios, targeted protein degradation can overcome the limitations by utilizing accessible

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spaces beyond the active sites and an expanded layer of selectivity regulation through substrate permissibility, providing novel chemical tools and therapeutic strategies for protein-based therapy targeting an undruggable or difficult-to-target proteome.

Most proteasome-dependent protein degraders behave catalytically, enabling the ubiquitination of super-stoichiometric target protein pools without occupancy-based equilibrium constraints. The catalytic cycle of PROTACs/molecular glues, operated through dynamic assembly and disassembly of the POI-degrader-E3 complex, permits a single degrader molecule to facilitate multiple rounds of target ubiquitination (X. Wu et al., 2021).

By inducing protein elimination, degraders uniquely abolish all functions of target proteins, including non-catalytic scaffolding roles, while traditional inhibitors usually block specific activities (e.g., enzymatic sites). Evidence from non-CDK/cyclin-targeting PROTACs demonstrated their superior efficacy over parental inhibitors and their ability to overcome acquired resistance (L. Xu et al., 2018). CDK-targeting PROTACs have also shown potential to overcome therapy resistance to CDK inhibitors. For example, CDK2/Cyclin E-targeting PROTAC demonstrated the ability to overcome resistance to CDK4/6 inhibition (Kumarasamy et al., 2023). Similarly, the CDK12 degrader **Molecule 50** treatment achieved robust protein depletion and bypassed cellular resistance to covalent CDK12/13 inhibitors. By degrading entire target proteins, PROTACs can eliminate mutant isoforms or overexpressed proteins evading occupancy-based inhibition including clinically relevant variants (e.g., BTK C481S, BRAF V600E, and KRAS G12V), establishing a new paradigm for precision oncology. Furthermore, some CDK/cyclin-targeting degraders achieve dual or triple depletion of complex subunits. For instance, **Molecule 32** induces the degradation of CAK complex components, while **Molecules 47** and **48** are able to deplete both CDK9 and Cyclin T1. This co-depletion of CDK/cyclin complexes likely raises the genetic barrier for cells to develop resistance-conferring mutations, as the simultaneous acquisition of secondary mutations in both protein subunits (two or more hits) is considered as a low-possibility genetic event.

5.3 Potential of PROTACs to improve selectivity for CDK targets

Lack of selectivity is considered as a critical issue associated with therapeutic toxicity, hindering the clinical translation of many CDK-targeting agents. Due to high sequence homology across CDKs, particularly within conserved ATP-binding pockets, developing isoform-specific CDK inhibitors remain challenging. Indeed, most conventional CDK inhibitors exhibit multi-target activity. For example, SNS-032 inhibits CDK2, CDK7 and CDK9; AT7519 inhibits CDK1, CDK2, CDK4, CDK6, and CDK9; dinaciclib inhibits CDK1, CDK2, CDK4, and CDK9. In contrast to conventional CDK inhibitors, PROTACs operate via an event-driven catalytic mechanism rather than occupancy-driven inhibition. While warhead selectivity influences target engagement, simply repurposing promiscuous CDK inhibitors for PROTAC design often yields non-selective degraders. Notably, a number of CDK PROTACs showing exceptional isoform selectivity have been successfully developed: CDK2-selective CPS2 and PROTAC-8, CDK4-selective BSJ-04-132, CDK6-selective BSJ-03-123 and CP-10, CDK7-selective JWZ-5-13, CDK8-selective JH-XI-10-02, CDK9-selective THAL-SNS-032 and compound C3, and CDK12-selective BSJ-4-116. When compared to inhibitors, PROTACs confer at least three key advantages: (1) access to expanded druggable spaces beyond the active sites; (2) utilization of warheads with moderate affinity yet higher intrinsic specificity; (3) exploitation of ternary complex (POI-PROTAC-E3) conformation-driven substrate permissibility. Accumulating evidence supports that linker length/properties and spatial positioning of vulnerable lysines for ubiquitination are key factors determining substrate permissibility in the ternary complex. To sum up, the above-mentioned mechanisms of PROTACs (i.e., expanded druggable spaces, versatile warhead selection, and the emerging paradigm of substrate permissibility) collectively potentiate the development of degraders with enhanced target selectivity.

5.4 Strategies and challenges in heterofunctional CDK degrader design

The current development of cyclin/CDK degraders is still in its early stages of initial discovery and preclinical investigation. Undoubtedly, improving efficiency and specificity is worthy of further attention. The activity of degraders is greatly influenced by target affinity, warhead physicochemical properties, attachment sites and linker composition/length. More insights are required to elucidate the principles of structure-activity relationships, target engagement, bioavailability, and biologic effects of cyclin/CDK degraders.

In terms of the selection of substrate warheads, the majority of heterofunctional CDK degraders including

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PROTACs, HEMTACs and HyTs were designed based on corresponding inhibitors. Interestingly, reports of CDK PROTACs based on wogonin and celastrol may stimulate the research to expand the pool of warheads to natural products. When it comes to the E3 warheads, in particular for PROTACs, limited choices for E3 ligases and E3 ligase binders appears to be the bottleneck. In fact, CRBN and VHL are employed preferentially by CDK PROTACs. To a lesser extent, cIAP1 and DCAF16 are amenable, while MDM2 had been found inefficient to induce CDK degradation. Therefore, expanding the choices of E3 ligases and new E3 ligase binders would be valuable for PROTAC design.

With regard to designing de novo warheads, fragment-based screening may be used. When high-resolution crystal structures are available, solvent-exposed positions identified from substrate and E3 ligase can serve as candidate attachment sites for new warheads. Insights from explainable artificial intelligent and molecular dynamics simulations may guide the selection of optimal attachment points. Apart from warheads, linkers play a critical role in determining PROTAC physicochemical properties and degradation efficacy. While identifying both substrate and E3 warheads follows established small-molecule discovery principles, linker design presents a unique challenge in PROTAC design due to the structural complexity and dynamic assembly of the POI-PROTAC-E3 ternary complex. Linker length and flexibility dictate the formation of ternary complexes and the subsequent efficiency of POI degradation. Simulation of the binding and dissociation dynamics of VHL-based BRD4 PROTAC MZ1 suggested that appropriate linker orientation is essential for exposing lysine on the surface of target protein (Tang et al., 2023). So far, commonly used PROTAC linkers include PEG and linear alkanes, which are typically synthesized via amidation, esterification, or click chemistry. With the aim to improve overall molecular performance, subsequent linker optimization strategies involve adjusting length, enhancing hydrophobicity/rigidity (e.g., incorporating aryl groups), and reducing molecular twisting (e.g., adding conformation-restricting chains). In fact, early and conventional methods rely on inefficient trial-and-error for PROTAC design. Remarkably, recent efforts in computational approaches (e.g., Generative Pre-trained Transformer, reinforcement learning) demonstrated the potential to aid in linker design. For instance, a recently developed ProLinker-Generator supports rational PROTAC linker design featuring the increased structural diversity and improved control of molecular properties (Luo et al., 2025). After putting warheads and linker together, a functional PROTAC hinges critically on the dynamic assembly and disassembly of the induced POI-PROTAC-E3 ternary complex, posing a challenge given the absence of natural target-E3 interactions. Consequently, developing computational tools to predict the ternary complex structure and stability is very helpful for rational PROTAC design. Advances in molecular docking and simulation, deep learning, protein structure prediction, and artificial intelligence now enable a more precise prediction of ternary complex conformations and expedite PROTAC design (C.-L. Chou et al., 2024; F. Li et al., 2022; Ugurlu et al., 2025; Weng et al., 2021; Zheng et al., 2022). Representative tools include DeepPROTACs (a predictive model for PROTAC degradation capability) (F. Li et al., 2022), PROTAC-RL (a deep reinforcement learning-driven generative model for de novo PROTAC design) (Zheng et al., 2022), and PROTAC-Model (a computational method combining the FRODOCK-based protocol and RosettaDock-based refinement for predict ternary complex modeling) (Weng et al., 2021). Encouragingly, these tools have also demonstrated the potential to address key limitations including linker design, target selectivity and bioavailability, although they have not been tested for CDK PROTACs. The generalizability of these approaches to the rational design of CDK PROTACs merits further investigation.

5.5 Bioavailability challenges for protein degraders

Bioavailability remains a critical challenge for most protein degraders (especially heterofunctional compounds), limiting their therapeutic potential. Hence, technical advances in medicinal chemistry are in great demand to guide optimization and further translation of these classes of degraders into orally bioavailable forms. Drug-like properties of heterofunctional compounds including most PROTACs, HEMTACs and HyTs do not comply with Lipinski's "Rule of Five". In contrast, molecular glues are advantageous due to their smaller molecular weight and more drug-like properties. Since most molecular glues were discovered serendipitously, the rational design of molecular glues would be considered more challenging than that of other entities of protein degraders. Nevertheless, recent practices in the design of Cyclin K glue degraders provide good examples for the development and optimization of compounds with gluing activities.

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5.6 Underdeveloped fields for degraders targeting CDK and cyclin

Based on the literature, heterofunctional degraders mainly target CDKs, while molecular glues predominantly degrade Cyclin K. Unlike conventional small-molecule drugs that modulate predefined binding pockets on target proteins, molecular glues function by rewiring protein-protein interactions through specifically inducing novel ternary complexes between an E3 ligase complex and a neo-substrate. Cullin-RING ubiquitin ligase 4 (CRL4) that comprises CUL4 scaffold protein, E2 enzyme linker protein (e.g., RBX1), substrate adapter protein (e.g., DDB1), and diverse substrate receptors (e.g., DCAF15), is frequently hijacked by molecular glues. With regard to reported Cyclin K glues, most of them contact DDB1 Arg928, a residue essential for complex formation (Kozicka et al., 2024). The central challenge in molecular glue discovery lies in identifying neo-substrates that become susceptible to degradation only upon induced proximity to the hijacked CRL4 complex. Once a neo-substrate is implicated, further optimization of molecular glues may be focused on inducing and stabilizing the novel, ternary complex between an E3 ligase, a neo-substrate, and the molecular glue itself. Until now, few degraders are available for other cyclins and a number of CDKs including CDK1, CDK3, CDK5, CDK10, CDK11, CDK14, CDK15, CDK16, CDK18, and CDK20, while future studies are expected to fill in the blanks. Alternatively, the targeted degradation of other proteins with CDK/cyclin regulatory potential may be an alternative strategy for cancer therapy. Early successes have been achieved for VHL-dependent CDC20 PROTAC CP5V and WEE1 PROTAC MA055 (Aublette et al., 2022; Chi et al., 2019), as well as CRBN-dependent PLK4 PROTAC SP27 (Sun et al., 2023) and AURKA PROTACs (e.g., JB170, dAurA383, SK2188) (Adhikari et al., 2020; F. Liu et al., 2022; Rishfi et al., 2023).

Apart from proteasome-dependent targeted protein degradation techniques, several lysosome-dependent protein degraders demonstrate feasibility and encouraging efficacy in targeting CDK and cyclin, such as S-indacene-dependent autophagy-targeting chimeras (Zhong et al., 2025), CDK9/Cyclin T1-targeting autophagosome-tethering compounds (ATTECs) (Zeng et al., 2025), and a peptide-based lysosomal degrader of CDK5 (Y.-F. Zhou et al., 2019). For example, AZ-9 was recently developed as a HyT-based autophagy-targeting chimera degrading both CDK9 and Cyclin T1 (Maurer et al., 2021, p. 40487652). Through conjugating the pan-CDK inhibitor AT7519 to S-indacene, AZ-9 recruited ATG101, a component of the autophagy-initiating ULK complex, and activated the autophagy-lysosome pathway. Notably, despite utilizing a multi-CDK inhibitor AT7519 as its 'warhead', AZ-9 exhibited a degradation selectivity profile favoring CDK9/Cyclin T1 over other CDKs. In addition, an anti-cancer drug homoharringtonine was shown to disrupt the interaction between CDK2 and cyclin A and trigger a TRIM21-depdendent autophagic degradation of CDK2 in cancer cells (J. Zhang et al., 2022). It is interesting to note that lysosome-dependent protein degraders preferentially induce the co-depletion of CDK/Cyclin complex. Compared to PROTACs and molecular glues, lysosome-dependent CDK/cyclin degraders operate through a distinct pathway and thus may offer unique opportunities for combination therapy. To date, the development of lysosome-dependent CDK/cyclin degraders is still in its infancy, underscoring the need for further research.

In summary, cyclins and CDKs play critical roles in cancer. Better understanding their mechanism and function will therefore provide important insights for the development of targeted anti-cancer therapy. Cyclin and CDK degraders not only provide novel tools for biomedical research but also represent a bright future in pharmaceutical development.

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Data availability statement

All data supporting the findings of this study are available within the paper.

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Author contributions

Suya ZHENG: Methodology, Visualization, Writing – original draft, Writing – review & editing. Ye CHEN: Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition. Zhipeng ZHU: Methodology, Visualization, Validation, Writing – review & editing. Nan LI: Visualization, Validation, Writing – review & editing. Chunyu HE: Methodology, Visualization, Validation, Writing – review & editing. H. Phillip KOEFFLER: Writing – review & editing, Supervision. Xin HAN: Visualization, Validation, Writing – review & editing, Funding acquisition. Qichun WEI: Writing – review & editing, Funding acquisition, Supervision. Liang XU: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Suya ZHENG, Ye CHEN, Zhipeng ZHU, Nan LI, Chunyu HE, H. Phillip KOEFFLER, Xin HAN, Qichun WEI and Liang XU declare that they have no conflicts of interest.

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Feature	Inhibitors	PROTAC	HEMTAC	Hydrophobic tag	Molecular glue
Molecular feature	Monovalent; smaller molecular weight (usually < 500 Da)	Bivalent/heterofunctional; large molecular weight (usually > 800 Da)	Bivalent/heterofunctional; large molecular weight	Bivalent/heterofunctional; medium molecular weight (variable)	Monovalent; smaller molecular weight (usually < 500 Da)
Reaction process	Stoichiometric	Catalytic	Catalytic	Sometimes catalytic	Catalytic
Active binding site	Required in most cases	Not necessary; expanded to druggable spaces beyond active sites	Not necessary; expanded to druggable spaces beyond active sites	Not necessary; expanded to druggable spaces beyond active sites	Involved in some cases; can be expanded to druggable spaces beyond active sites
Mechanism of action	Reversible, irreversible or competitive inhibition of target activity	Proximity-induced target degradation through the ubiquitin proteasome system after formation of the POI-PROTAC-E3 ligase ternary complex	Proximity-induced target degradation through the ubiquitin proteasome system after formation of a ternary POI-HEMTAC-HSP90/E3 complex	Recruiting the protein quality control machinery to target POI for proteasomal or lysosomal degradation by mimicking the partially denatured state or misfolding of POI	Proximity-induced neo-substrate degradation through the ubiquitin proteasome system after formation of the POI-molecular glue-E3 ligase ternary complex
Potency	Variable	Variable; potential to possess enhanced potency over parental inhibitors	Moderate; lower than PROTACs	Moderate; lower than PROTACs	Variable
Druggable targets	Largely enzymes and proteins containing suitable active sites	Can be proteins with or without active sites (e.g., non-catalytic regulatory subunits, and scaffolding proteins); contain lysine residues susceptible to ubiquitination by specific E3 ligases	Can be proteins with or without active sites; contain lysine residues susceptible to ubiquitination after formation of the ternary complex; contain lysine residues susceptible to ubiquitination by HSP90-associaeted E3 ligases	Can be proteins with or without active sites; contain lysine residues susceptible to ubiquitination by protein quality control machinery	Can be proteins with or without active sites; contain lysine residues susceptible to ubiquitination by specific CRL E3 ligase complexes
Fate of target proteins	Impaired function, protein stabilization (in many cases) or destabilization	Degradation	Degradation	Degradation	Degradation
Permissive CDK/cyclin in the literature	Most CDKs	CDK1/2/4/5/6/7/8/9/12/13/17/19, Cyclin C, Cyclin D1, Cyclin D3, Cyclin E, Cyclin K	CDK4/6	CDK9, Cyclin T1	CDK12/13, Cyclin K
Isoform selectivity	Generally challenging due to high homology among ATP-binding pockets of CDKs; achievable in very limited cases	Potential to enhanced target selectivity after optimization; achievable for several CDKs	Not reported	Not reported	Reported to have variability in target engagement
Drug-like	Relatively good	Hardly meet the Rule of Five;	Similar to PROTACs; limited	Simpler in chemical structure	Relatively good

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properties (bioavailability, hydrophobicity**)**		generally low in oral bioavailability	information of bioavailability	with less hydrogen bond donors/acceptors; more favorable bioavailability than PROTACs	
Developmental status	Several CDK4/6 inhibitors have been successfully translated into clinics; many other inhibitors are under active preclinical and early phase clinical development	Under preclinical development	Under preclinical development	Under preclinical development	Most are under preclinical development; some are in early phase clinical development

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1038 **Table 2 List of molecules introduced in this review**

Name	Category	Targets (CDK/cyclin)	Target binder	E3 ligase binder
Molecule 1 (Compound F3)	PROTAC	CDK2/9	FN-1501	Thalidomide analog
Molecule 2 (FN-pom)	PROTAC	CDK2, Cyclin E1	FN-1501	Thalidomide analog
Molecule 3 (TMX-1160)	PROTAC	CDK2/4/5/6	TMX-2039	Thalidomide analog
Molecule 4 (TMX-2172)	PROTAC	CDK2/5	TMX-2039	Thalidomide analog
Molecule 5	PROTAC	CDK2/4/6	Ribociclib	Thalidomide analog
Molecule 6	PROTAC	CDK2/4/6	Ribociclib	Thalidomide analog
Molecule 7 (CPS2)	PROTAC	CDK2	J2	Thalidomide analog
Molecule 8	PROTAC	CDK2	AZD5438	VH032
Molecule 9 (TL12-186)	PROTAC	Pan-CDK	NVP-TAE 684	Thalidomide analog
Molecule 10	PROTAC	CDK4/6	Palbociclib	Thalidomide analog
Molecule 11 (BSJ-01-84)	PROTAC	CDK4/6	Abemacicilib	Thalidomide analog
Molecule 12 (BSJ-02-162)	PROTAC	CDK4/6	Palbociclib	Thalidomide analog
Molecule 13 (BSJ-01-152)	PROTAC	CDK4/6	Ribociclib	Thalidomide analog
Molecule 14	PROTAC	CDK6	Palbociclib	Thalidomide analog
Molecule 15 (YX-2-107)	PROTAC	CDK6	Palbociclib	Thalidomide analog
Molecule 16 (MS140)	PROTAC	CDK4/6	Palbociclib	Thalidomide analog
Molecule 17 (CP-10)	PROTAC	CDK6	Palbociclib	Thalidomide analog
Molecule 18 (ALV-07-082-03)	PROTAC	CDK4/6	Palbociclib	Thalidomide analog
Molecule 19 (YKL-06-102)	PROTAC	CDK6	Palbociclib	Thalidomide analog
Molecule 20 (BSJ-03-123)	PROTAC	CDK6	Palbociclib	Thalidomide analog
Molecule 21	PROTAC	CDK4/6	Palbociclib	Thalidomide analog
Molecule 22	PROTAC	CDK1/4	Celastrol	Thalidomide analog
Molecule 23	PROTAC	CDK4/6	Palbociclib	KB02
Molecule 24	PROTAC	CDK6	Palbociclib	VH032
Molecule 25	PROTAC	CDK6	Palbociclib	VH032 derivative
Molecule 26	PROTAC	CDK4/6	Palbociclib	Bestatin
Molecule 27 (MS28)	PROTAC	CDK4/6, Cyclin D1/D3	Palbociclib	VH032
Molecule 28	HEMTAC	CDK4/6	Palbociclib	HSP90 ligand BIIB021
Molecule 29 (JH-XI-10-02)	PROTAC	CDK8	JH-VIII-49	Thalidomide analog
Molecule 30 (YKL-06-101)	PROTAC	CDK8	THZ4-55	Thalidomide analog
Molecule 31(SNX7886)	PROTAC	CDK8/19, Cyclin C	BI1347	Thalidomide analog
Molecule 32 (JWZ-5-13)	PROTAC	CDK7, Cyclin H	YKL-5-167	VH032
Molecule 33	PROTAC	CDK7	YKL-5-167	Thalidomide analog
Molecule 34 (PROTAC 13i)	PROTAC	CDK7/9	A86	Thalidomide analog
Molecule 35	PROTAC	CDK9	Aminopyrazole analog	Thalidomide analog
Molecule 36	PROTAC	CDK9	Aminopyrazole analog	Thalidomide analog
Molecule 37 (THAL-SNS-032)	PROTAC	CDK9	SNS-032	Thalidomide analog
Molecule 38	PROTAC	CDK9	Compound **4**	Thalidomide analog
Molecule 39 (B03)	PROTAC	CDK9	BAY-1143572	Thalidomide analog
Molecule 40	PROTAC	CDK9	Flavonoid LWT-111	Thalidomide analog
Molecule 41	PROTAC	CDK9	AT7519	Thalidomide analog

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Molecule 42	PROTAC	CDK9	AT7519	Thalidomide analog
Molecule 43	PROTAC	CDK9	AT7519	Thalidomide analog
Molecule 44	PROTAC	CDK7/9	Wogonin	Thalidomide analog
Molecule 45	PROTAC	CDK9	BPA311	Thalidomide analog
Molecule 46 (CD-5)	PROTAC	CDK1/9	iCDK9	Thalidomide analog
Molecule 47 (LL-K9-3)	HyT	CDK9, Cyclin T1	SNS-032	(-)-menthoxyacetyl moiety
Molecule 48 (LL-CDK9-12)	HyT	CDK9, Cyclin T1	SNS-032	Adamantyl group
Molecule 49	PROTAC	CDK12/13, Cyclin K	Compound **4**	Thalidomide analog
Molecule 50 (BSJ-4-116)	PROTAC	CDK12	THZ531	Thalidomide analog
Molecule 51 (PP-C8)	PROTAC	CDK12, Cyclin K	SR-4835	Thalidomide analog
Molecule 52 (CR8)	Molecular glue	Cyclin K	/	/
Molecule 53	Molecular glue	Cyclin K	Dinaciclib derivative	/
Molecule 54	Molecular glue	Cyclin K	AT7519 derivative	/
Molecule 55 (NCT02)	Molecular glue	CDK12/13, Cyclin K	/	/
Molecule 56 (SR-4835)	Molecular glue	Cyclin K	/	/
Molecule 57 (DS17)	Molecular glue	Cyclin K	/	/
Molecule 58 (HQ461)	Molecular glue	Cyclin K	/	/
Molecule 59 (HQ005)	Molecular glue	Cyclin K	/	/
Molecule 60 (dCeMM2)	Molecular glue	Cyclin K	/	/
Molecule 61 (dCeMM3)	Molecular glue	Cyclin K	/	/
Molecule 62 (dCeMM4)	Molecular glue	Cyclin K	/	/
Molecule 63	PROTAC	CDK17	Dabrafenib	VH032

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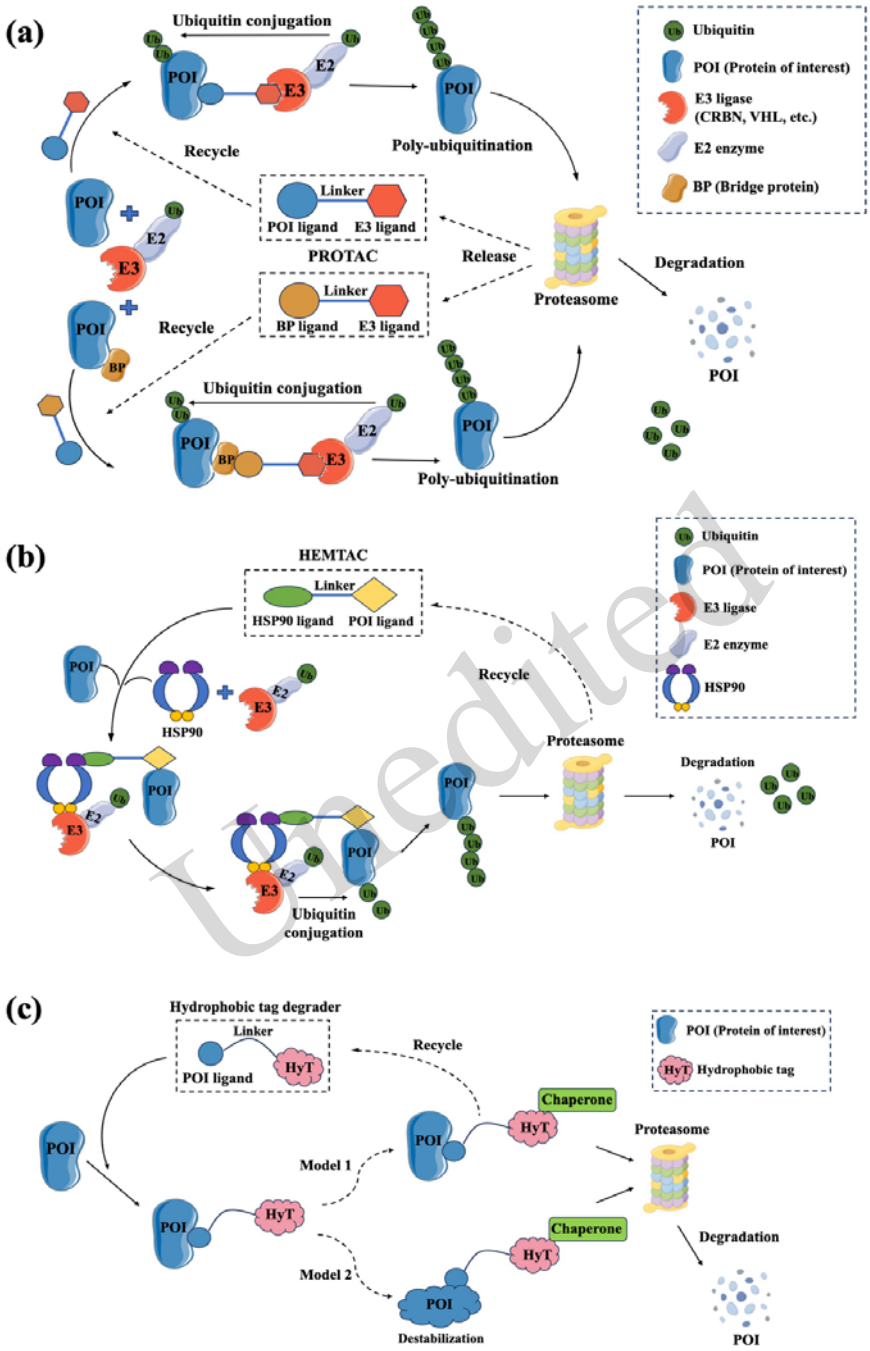

Fig. 1 Working mechanisms of PROTAC, HEMTAC and hydrophobic tag. (a) PROTAC induces proteasome-dependent degradation of the protein of interest (POI) via the formation of the POI-PROTAC-E3 ternary complex, while bridged PROTAC recruits POI indirectly via a POI interacting protein (bridge protein, BP) and degrades POI via the formation of a POI-BP-PROTAC-E3 complex. (b) HEMTAC recruits various E3 ubiquitin ligases via the adaptor protein HSP90 and subsequently forms the POI-HEMTAC-HSP90-E3 complex to induce targeted protein degradation. (c) Hydrophobic tags (HyTs) bind to POI and mimic the partially denatured state or misfolding by exposing the hydrophobic moiety to the protein surface (Model 1). Alternatively, HyTs may destabilize POI by direct interference with protein folding (Model 2). Subsequently, either signals mimicking the abnormal protein folding or failure of chaperones in protein folding activate the protein quality control machinery to target POI for proteasomal degradation.

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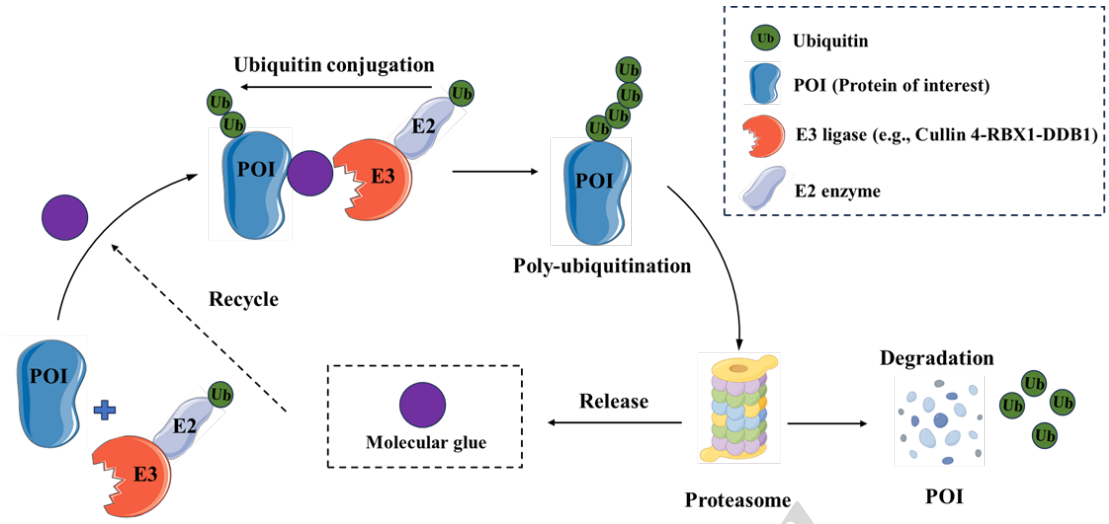

Fig. 2 Working mechanisms of molecular glue degraders. Molecular glue alters protein-protein interaction surfaces between an E3 ligase complex and POI or a complex containing POI, thereby either creating or enhancing the interaction affinity to trigger proximity-induced protein degradation.

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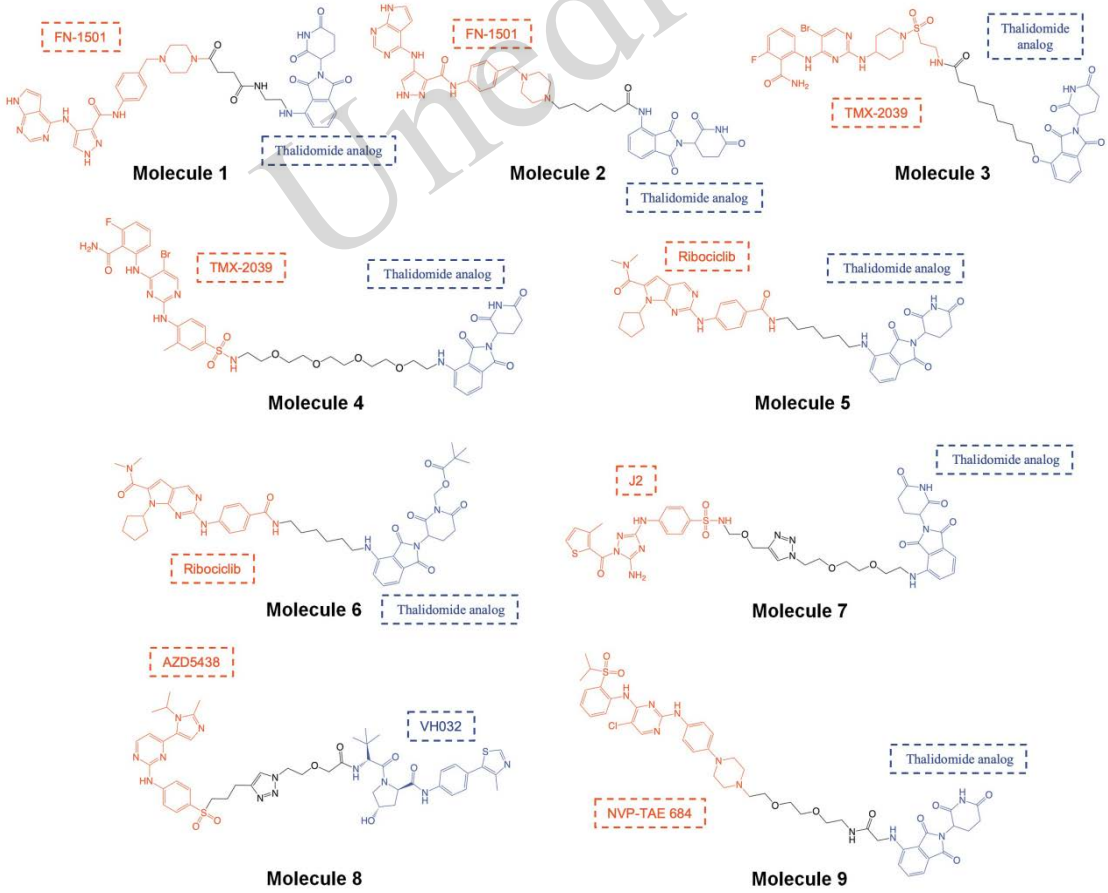

Fig. 3 Molecular structures of selective PROTACs targeting CDK2. Molecule 8 is a VHL-dependent PROTAC, while the rest are CRBN-dependent.

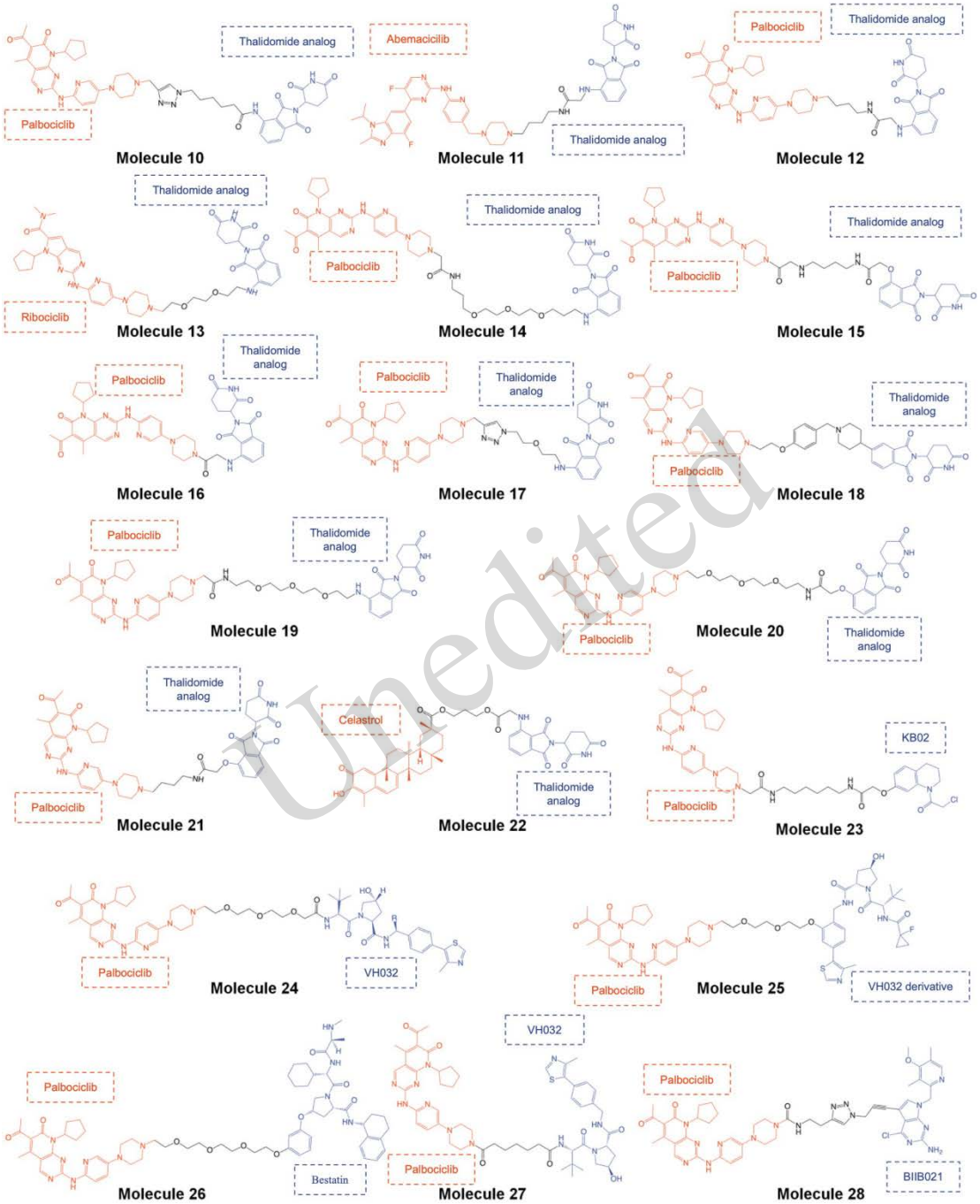

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Fig. 4 Molecular structures of selective PROTACs and HEMTACs targeting CDK4/6. CRBN is frequently hijacked by CDK4/6 PROTACs for protein degradation, while DCAF16 (Molecule 23), VHL (Molecules 24, 25, 27) and cIAP1 (Molecule 26) prove amenable for the design of CDK4/6 PROTACs. Molecule 28 is a HEMTAC targeting CDK4/6.

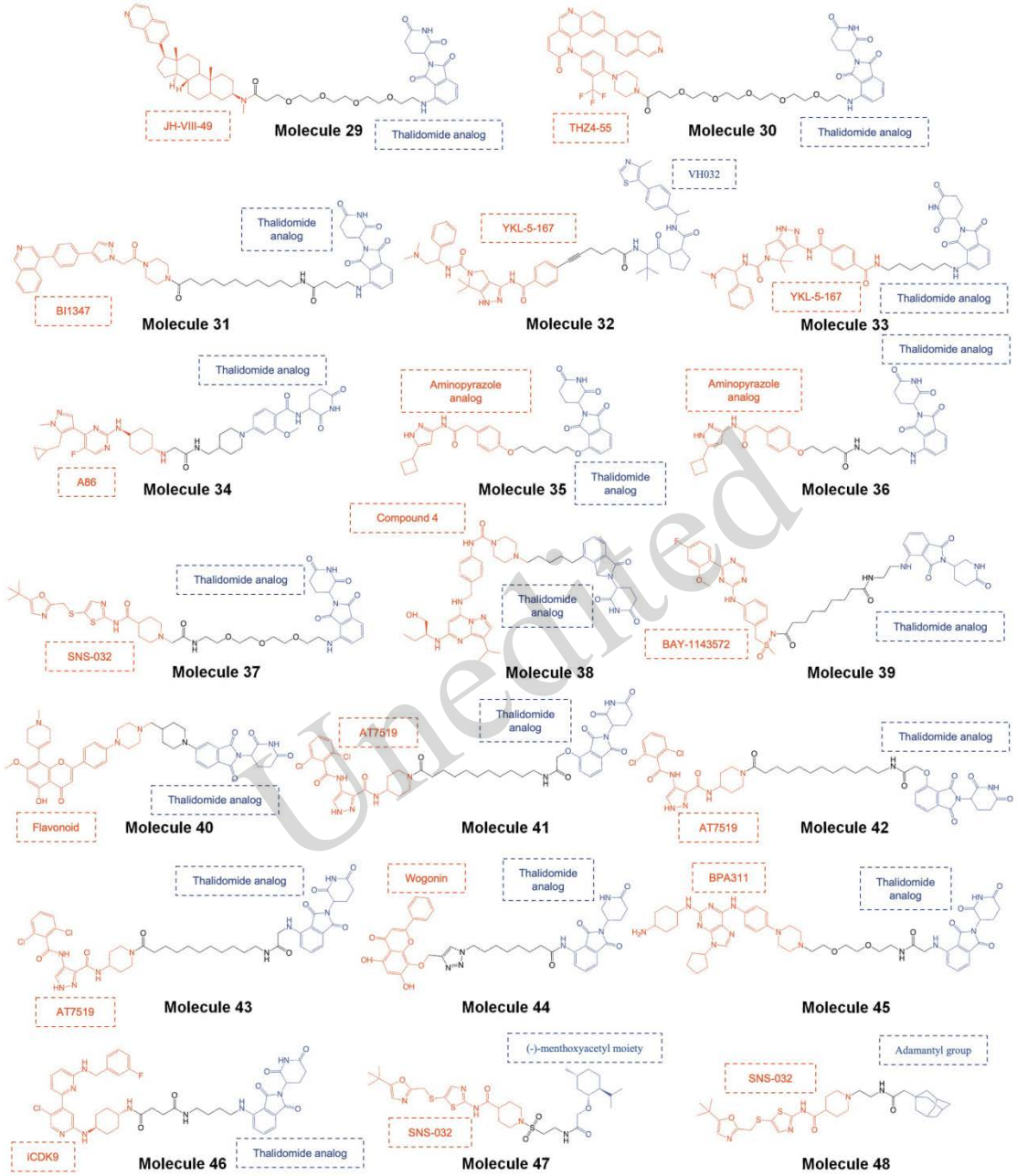

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Fig. 5 Molecular structures of selective degraders against CDK8/19, CDK7, and CDK9/Cyclin T. Molecules 29~31 are CRBN-dependent PROTACs against CDK8/19. Molecule 32 and Molecule 33 are VHL-dependent and CRBN-dependent PROTACs against CDK7, respectively. Molecule 34 is a CRBN-dependent PROTAC of CK1α, CDK7 and CDK9. Molecules 35~46 are CRBN-dependent CDK9 PROTACs. Molecules 47 and 48 are HyTs against CDK9/Cyclin T1 heterodimer.

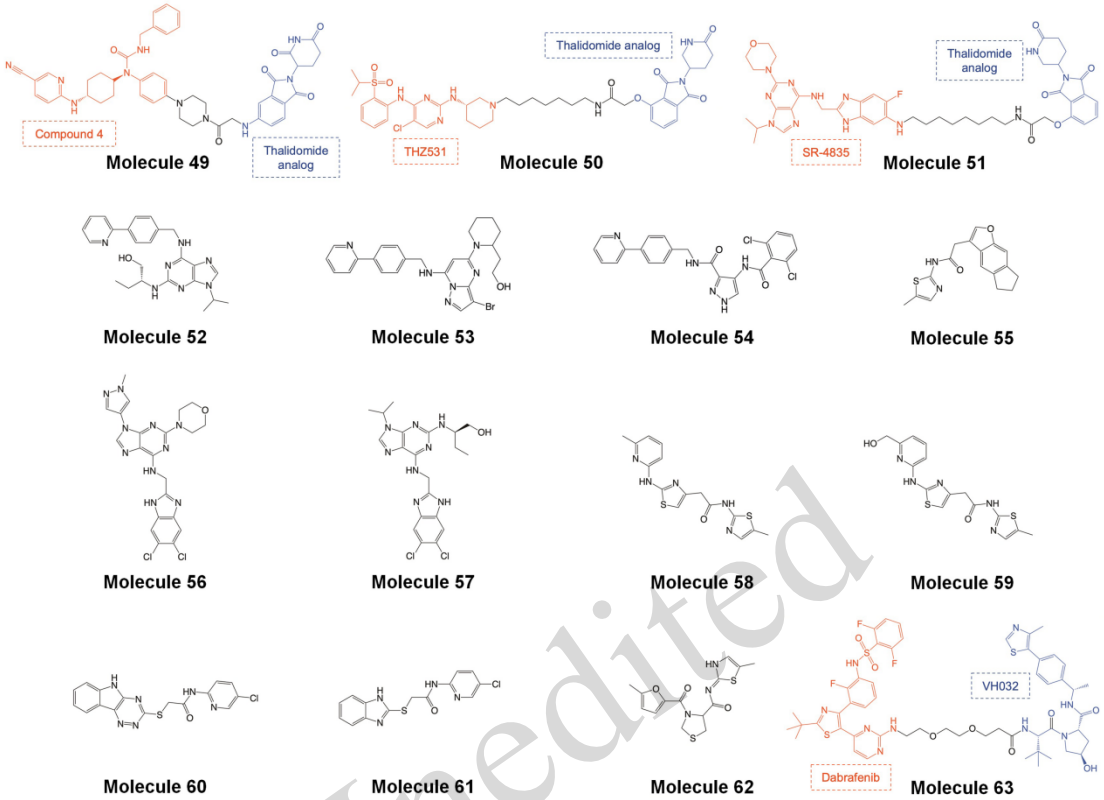

Fig. 6 Molecular structures of selective molecular glue of Cyclin K and PROTACs targeting either CDK12/13 or CDK17. Molecules 49~51 are CRBN-dependent PROTACs against CDK12 and/or CDK13, while molecules 52~62 are molecular glues degraders of Cyclin K. Molecule 63 is a VHL-dependent PROTAC against CDK17.

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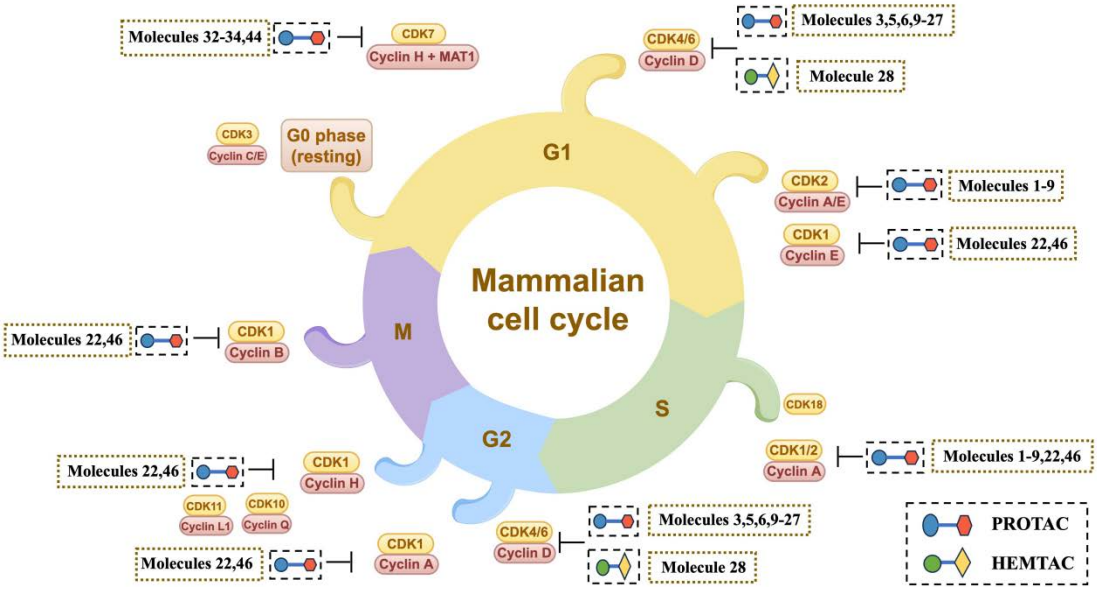

Fig. 7 Cell cycle regulatory CDK/cyclin complexes and their reported degraders.