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Research Article

Research Progress in Proteolysis-Targeting Chimeras (PROTACs) Targeting Receptor Tyrosine Kinases

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Abstract

Kinases represent one of the most prominent classes of drug targets in current medicinal chemistry research. They are frequently over expressed in various diseases such as cancer, inflammation, or autoimmune disorders, playing critical roles in their pathophysiology. Since the early 1980s, numerous potent kinase inhibitors have been developed and approved. However, kinase inhibitors often face challenges including drug resistance and off-target effects. To overcome these limitations, novel strategies are required. Since 2013, several research groups have proposed converting potent kinase inhibitors into PROTAC molecules, leveraging cellular machinery to degrade target proteins. Results demonstrate that PROTACs significantly enhance biological effects compared to their parent inhibitors. This review focuses on recent advances in PROTAC technology applied to receptor tyrosine kinases (RTKs), with particular emphasis on compounds reported since 2018.

Keywords: *Receptor tyrosine kinase; Targeted protein degradation; PROTAC; Review*

Kinases are macromolecules involved in signal transduction and pathway regulation within biological systems, primarily functioning through two mechanisms: (1) Catalytic function: transferring phosphate groups from high-energy donor molecules (e.g., ATP) to specific substrates; (2) Non-catalytic functions: such as scaffold roles and allosteric regulation mediated by protein interactions. Protein kinases mainly include receptor tyrosine kinases (RTKs), non-receptor tyrosine kinases (NRTKs), and serine-threonine kinases (STKs), among other families. Dysregulated kinase activity contributes to diseases such as acute myeloid leukemia [1], melanoma [2], breast cancer [3], and prostate cancer, making them hot targets for small-molecule drug discovery. Although existing small-molecule inhibitors [4] have shown significant efficacy in clinical treatments, they possess limitations including lack of selectivity toward highly homologous kinases and the emergence of drug resistance. The rapidly developing technology of Proteolysis-Targeting Chimeras (PROTACs) is considered a promising strategy to overcome these challenges [5]. PROTACs are bifunctional molecules that induce the formation of a complex between the target protein (protein of interest, POI; here, a kinase) and an E3 ubiquitin ligase (UL). This complex mediates polyubiquitination of the POI, leading to its recognition and degradation by the ubiquitin-proteasome system (UPS) (Figure 1). Since 2013, reports on kinase-targeting PROTAC molecules have grown exponentially. This article reviews recent progress in PROTACs targeting protein kinases, which may facilitate the development of novel therapies to overcome drug resistance in cancer treatment.

Receptor tyrosine kinases (RTKs) are cell surface receptors with a similar molecular structure, comprising an extracellular ligand-binding domain, a transmembrane helix, and an intracellular region

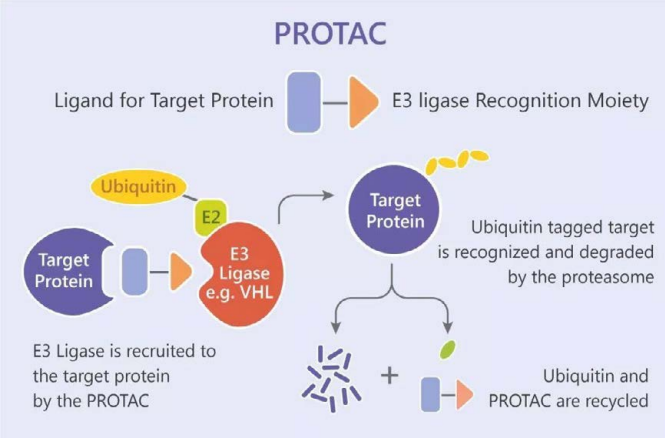

Figure 1: PROTACs induce protein ubiquitination and degradation.

containing a tyrosine kinase domain. Genetic mutations can alter RTK activity, expression levels, cellular distribution, and regulation, potentially leading to cancers, diabetes, inflammation, and severe bone or vascular diseases. Recently, FMS-like tyrosine kinase 3 (FLT3) [6], tropomyosin receptor kinase C (TrkC) [7], anaplastic lymphoma kinase (ALK) [8,9], and epidermal growth factor receptor (EGFR) [10] have been reported to be degraded by their corresponding PROTAC molecules. Their structures are shown in Figure 2, and biological activities are summarized in Table 1.

PROTACs Degrading FLT3

FLT3 is expressed in hematopoietic stem cells and plays a crucial role in normal hematopoiesis; its dysfunction often leads to blood

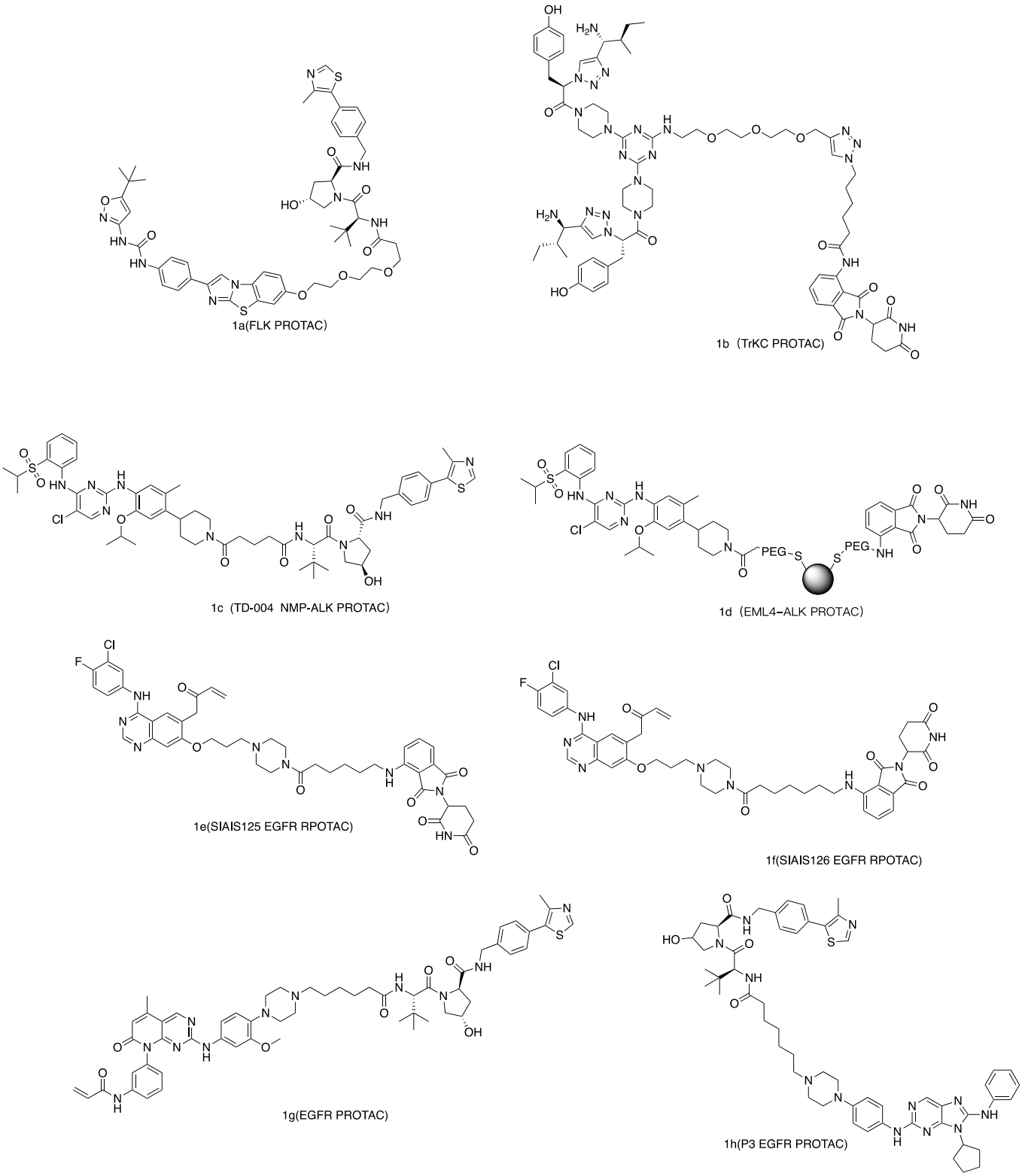

Figure 1: Reported RTKs degrader.

disorders. Acute myeloid leukemia (AML) is a common malignant tumor of the hematopoietic system, with FLT3 gene mutations accounting for 30% of AML cases, among which internal tandem duplication (ITD) mutations are the most common. Patients carrying FLT3-ITD mutations exhibit elevated white blood cell levels and poor prognosis [1,11-13]. Therefore, FLT3/ITD is a promising target for AML treatment, and maximal sustained inhibition of this signaling is crucial for clinical response [11]. Based on this background, numerous PROTACs targeting FLT3 for degradation have emerged. The Burslem group reported a PROTAC 1a [6,11] composed of AC220 [14,15] as

Table 1: Reported RTKs degrader.

Compounds	Target	POI ligand	E3 Ligand	Cells (DC_{50})
1a	FLT3/ITD	AC220	VHL Ligand	MOLM-14 MV4-11[6]
1b	TrKC	IY-IY	Pomalidomide	Hs578t (0.1-1.0 μM) [7]
1c (TD-004)	NMP-ALK	Ceritinib	VHL Ligand	SU-DHL-1 H3122 [8]
1d	EML4-ALK	Ceritinib	Pomalidomide	NCI-H2228 [9]
1e	EGFR	SIAIS092	Pomalidomide	PC9(100 nM) H1975(30-50 nM) [30]
1f	EGFR	SIAIS092	Pomalidomide	PC9(30-100 nM) H1975(<30 nM) [30]
1g	EGFR	XTF-262	VHL Ligand	H1975(5.9±2.1 nM) [28]
1h	EGFR	Ribociclib	VHL Ligand	HCC827(0.51 nM) H1975(126.6 nM) [29]

the warhead, VHL as the E3 ligase ligand, and connected by a PEG linker of appropriate length. This PROTAC exhibited similar cellular inhibitory activity and selectivity to AC220 in vitro but showed 3.5-fold greater inhibition of cell proliferation in MOLM-14 and MV4-11 cell lines and induced better apoptosis in leukemia cells at low doses. 1a induced FLT3-ITD degradation in vivo; in MV4-11 xenograft models, administration at 30 $mg{\cdot}kg^{-1}$ every 24 hours for three days reduced FLT3 levels in tumors by 60%. These results suggest that degradation of FLT3-ITD may provide a useful therapeutic approach for AML.

PROTACs Degrading TrkC

Trk kinases are a family of protein tyrosine kinases with high affinity for neurotrophin (NT) growth factors, which are essential for neuronal differentiation and survival in the peripheral and central nervous systems. TrkC is overexpressed in many human tumors, particularly in neuroblastoma [12], glioblastoma [12], breast cancer [16], and melanoma [2]. Its aberrant activation promotes cell growth and metastasis in certain forms of tumorigenesis [3], making effective reduction of TrkC expression significant for treating these cancers. In 2019, Zhao and Burgess reported the first PROTAC 1b degrading TrkC [7]. This PROTAC uses a bivalent peptide (isoleucine-tyrosine-tyrosine-isoleucine) analog as the warhead, which binds TrkC with submicromolar affinity and facilitates good cellular internalization [17,18]. The warhead is connected to pomalidomide via a PEG linker. 1b degraded TrkC in Hs578t cells at concentrations of 1-10 μM, with a DC_{50} of 0.1-1.0 μM [7]. This PROTAC demonstrates the applicability of the technology to reduce TrkC levels and provides insights for developing more PROTACs, such as those using FDA-approved inhibitors like larotrectinib or entrectinib as warheads [19,20], potentially yielding highly effective molecules.

PROTACs Degrading ALK

ALK is part of the insulin receptor family. Although its exact function in mammalian cells is not fully understood, various forms of ALK fusion proteins are known to drive oncogenesis in multiple cancers. For example, the NMP-ALK fusion is commonly found in anaplastic large cell lymphoma (ALCL) [21,22]. Numerous studies indicate that inhibiting ALK activity suppresses the proliferation of cancer cells driven by ALK fusions [23,24]. Thus, developing ALK-targeted PROTACs appears to be a promising approach to enhance the efficacy of approved ALK inhibitors. The Kang group reported a PROTAC TD-004 [8] using ceritinib as the warhead [25] and connected to a VHL ligand via a long linker containing an isopropyl chain and an amide bond. TD-004 degraded approximately 90% of NMP-ALK fusion protein in SU-DHL-1 cells, with IC_{50} values of 58 nM and 180 nM in ALK-positive SU-DHL-1 and H3122 cell lines, respectively, while showing an IC_{50} > 1000 nM in ALK-low A549 cells, indicating significant selectivity [8]. In H3122 xenograft models, daily administration of 58 $mg{\cdot}kg^{-1}$ for 14 days significantly reduced tumor volume without causing notable weight loss. Besides TD-004, Zhang et al. [26] and Powell et al. [27] reported other ceritinib-based PROTACs using pomalidomide as the E3 ligase ligand. These PROTACs differed mainly in linker length and composition, exhibiting stronger anti-proliferative activity in vitro than TD-004 but lacking in vivo validation. These examples illustrate that even with the same warhead, variations in linker length, composition, and E3 ligase ligand can significantly impact PROTAC bioactivity. Besides NMP-ALK, another ALK fusion protein, EML4-ALK, was targeted by a degrader reported by the Liu group. This multivalent PROTAC 2d consists of multiple warheads and E3 ligase ligands attached to gold nanoparticles [9]. Due to the strong affinity of gold nanoparticles for thiols, modified ceritinib and pomalidomide were easily conjugated to the nanoparticle surface to form multivalent PROTACs. Cellular analysis showed that incubation with NCI-H2228 cells for 24 hours reduced EML4-ALK levels by 80%, with prominent anti-proliferative activity (IC_{50} = 4.8 μM), while negligible cytotoxicity was observed in ALK-negative A549 cells. Although in vivo efficacy requires further validation, the multivalency offered by gold nanoparticles provides an effective strategy to bring warheads and E3 ubiquitin ligases into proximity, facilitating ternary complex formation.

PROTACs Degrading EGFR

Activating mutations in EGFR are closely associated with non-small cell lung cancer (NSCLC). However, even with FDA-approved third-generation EGFR-TKIs like osimertinib, resistance eventually develops, reducing therapeutic efficacy. In April 2020, Zhang et al. [28] reported a series of PROTACs selectively targeting mutant EGFR. One of the most potent compounds, 1g, selectively degraded EGFRL858R/T790M with a DC_{50} of 5.9 nM while sparing the wild-type protein. In December of the same year, Zhao et al. [29] reported a series of VHL-based PROTACs, among which compound P3 showed potent anti-proliferative activity in HCC827 and H1975 cells with IC_{50} values of 0.83 nM and 203.01 nM, respectively, and DC_{50} values of 0.51 nM and 126.2 nM for EGFRdel19 and EGFRL858R/T790M, respectively. Besides inhibiting EGFR signaling, P3 significantly induced apoptosis, arrested the cell cycle, and inhibited colony formation. In June 2021, Qu et al. [30] reported SIAIS125 and SIAIS126—two PROTACs composed of the EGFR inhibitor canertinib and pomalidomide connected by linkers of different lengths. These degraders selectively degraded EGFRL858R/T790M in H1975 cells and EGFREx19del in PC9 cells for up to 72 hours, also inducing significant apoptosis, cell cycle arrest, and growth inhibition. They did not degrade the EGFREc19del/T790M mutant in PC9BRca1 cells or wild-type EGFR in A549 lung cancer cells. Since the first report of kinase-targeted PROTACs in 2013, many research groups have proposed converting potent kinase inhibitors into PROTACs. This technology, which

harnesses cellular machinery to degrade proteins, has propelled several compounds to the forefront of drug development, offering advantages for enhancing therapeutic efficacy. PROTACs may yield superior biological outcomes compared to parent inhibitors; for instance, FLT3-PROTACs induce apoptosis more effectively in leukemia cells, and BCR-ABL degraders exhibit longer-lasting inhibition of BCR-ABL and its downstream signaling than dasatinib. PROTACs may achieve higher selectivity than ATP-competitive kinase inhibitors, as seen with CST620 selectively targeting CDK6. They can degrade proteins that have developed resistance to inhibitors due to mutations, such as the aforementioned EGFR degraders. PROTACs can utilize allosteric inhibitors as POI recruiters to enhance selectivity and reduce side effects of parent inhibitors; for example, GMB-475, using GNF-2 as the warhead, degrades the target kinase while abolishing its non-kinase functions (scaffold roles), deepening our understanding of the protein's role in signaling networks. PROTACs can degrade membrane-bound proteins associated with various diseases, such as JAK degraders JP-1 and JP-2. PROTACs synthesized using reversible covalent inhibitors as POI recruiters may retain the reversible covalent binding characteristics of the parent inhibitors, slowing displacement by competitors. Rapid synthesis methods for PROTACs have been reported, reducing the time cost of degrader synthesis and facilitating the design of degraders for other targets.

Compared to small molecules, PROTACs offer numerous advantages. However, developing in vivo effective PROTACs remains a challenge for medicinal chemists. Although PROTACs can be viewed as combinations of POI ligands, linkers, and E3 ubiquitin ligase ligands, the aforementioned reports confirm that random combinations do not yield预设 effects. In the design and synthesis of PROTACs, the choice and structural modification of the POI ligand, the chemical composition and length of the linker, and the selection of the E3 ligase ligand can significantly impact their efficacy. Therefore, in-depth structure-activity relationship studies are necessary to discover the most active structures, which may require considerable time. Another critical challenge is the in vivo evaluation of PROTACs. Their large molecular weight places them outside the realm of traditional small molecules, and the flexibility and chemical composition of the linker make them susceptible to in vivo environmental interference, leading to poor stability, as seen with MT802. However, optimization has yielded PROTACs with improved pharmacokinetic parameters and orally available degraders, addressing stability issues to a great extent. In 2019, the first PROTACs entered clinical trials, and several kinase-targeted candidates are expected to follow soon. To date, the use of thalidomide and its analogs as E3 ligase ligands remains the most common approach. However, these agents can lead to degradation of lymphoid transcription factors like IKZF1 and IKZF3, potentially affecting the hematopoietic system. Moreover, cereblon (CRBN) is not essential in most cancer cell lines, and mutations in this ligase could confer resistance to PROTACs. Thus, the discovery of novel E3 ligase ligands is extremely important. In summary, PROTAC technology is a suitable tool for generating active compounds for treating various diseases. Currently, most reported PROTACs are based on well-established positive compounds and commonly used FDA-approved drugs, somewhat limiting the technology's full potential. This strategy will likely be applied in the coming years to target currently undruggable targets, playing a crucial role in revealing new clinical targets and providing treatments for many diseases. Therefore, although this rapidly growing research field is still in its early stages, it offers encouraging directions for both biological understanding and the future of medicinal chemistry.

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