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Proteolysis-targeting chimeras (PROTACs): a review of their development and potential pharmacological applications

Karrar Najeh Chfat[1,*], Shaker Awad Abdul Hussein[2]

[1]College of Pharmacy, University of Babylon, Hillah, Iraq
[2]Department of Medicinal Chemistry, College of Pharmacy, University of Babylon, Hillah, Iraq

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ABSTRACT

Beyond conventional small-molecule inhibitors, proteolysis-targeting chimeras (PROTACs) represent a novel therapeutic strategy for targeted protein degradation. These heterobifunctional molecules are engineered in order to recruit an E3 ubiquitin ligase to a specific protein of interest, thereby facilitating its ubiquitination and subsequent degradation by the proteasome. This approach has garnered significant attention due to its ability to target proteins traditionally considered "undruggable", including those lacking enzymatic activity or accessible binding pockets. This mini-review outlines the mechanistic basis of PROTACs, key design principles, and recent advances in the field. Particular emphasis is placed on the potential of PROTACs to address persistent challenges in drug discovery, notably the need for selective elimination of pathogenic proteins. The review also explores strategies for optimizing PROTAC-based therapies and discusses current limitations, such as pharmacokinetic constraints and the need for improved E3 ligase engagement. Owing to their distinctive mode of action and expanding therapeutic scope, PROTACs hold promise for transforming the treatment landscape of cancer, neurological disorders, and other diseases driven by aberrant protein expression.

*** CORRESPONDING AUTHOR:**
Karrar Najeh Chfat, College of Pharmacy, University of Babylon, Hillah, Iraq; e-mail: pha482.karrar.najeh@student.uobabylon.edu.iq

1. Introduction

Proteolysis-targeting chimeras (PROTACs) represent a novel therapeutic modality that harnesses the ubiquitin–proteasome system (UPS) in order to selectively mark intracellular proteins for degradation. Physiologically, the UPS eliminates misfolded, mutated, or other-

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wise deleterious proteins from the cellular environment; PROTACs exploit this endogenous degradation machinery so as to direct the removal of specific proteins of interest[1].

Compared to conventional small-molecule inhibitors (SMIs), PROTACs offer several advantages. Firstly, PROTACs can induce the degradation of a wide array of target proteins, often requiring lower concentrations than SMIs to achieve therapeutic efficacy, thereby potentially reducing SMI-associated toxicity. Secondly, PROTACs can engage proteins traditionally considered "undruggable", such as those lacking enzymatic activity or accessible binding pockets. Thirdly, PROTAC-based therapies may overcome drug resistance arising from mutations in the target protein. Fourthly, PROTACs can counteract SMI resistance due to target upregulation by promoting auto-degradation of the target protein itself[2]. Finally, PROTACs may enhance drug selectivity and specificity; for instance, non-selective inhibitors have been converted into selective degraders through PROTAC-mediated targeting, offering promising avenues for the rational design of selective SMIs[3].

The therapeutic potential of PROTACs is particularly compelling in the context of neurodegenerative diseases, where protein-specific degradation is critical. Aging is a major risk factor for these disorders, with Alzheimer disease being the most prevalent. In this condition, aggregation of tau and β-amyloid proteins initiates and sustains neurodegeneration. Parkinson disease, another common neurodegenerative disorder, is associated with the progressive loss of dopaminergic neurons. Huntington disease, although less frequent, belongs to a group of genetically determined disorders characterized by irreversible deposition of misfolded huntingtin protein[4].

Importantly, tumour development is often accompanied by aberrant protein synthesis, providing a rationale for PROTAC-based interventions. Current targets include tumour expansion factors, which can be effectively inhibited *via* PROTAC-mediated degradation. Oncogenes and tumour suppressor genes also represent viable targets, where selective protein degradation may significantly impede tumour progression[5].

2. Strategies of developing PROTACs

The first PROTAC prototype, Protac-1, was introduced in 2001. This molecule validated the concept that engineered compounds could selectively bind and degrade cellular proteins *via* the UPS. Protac-1 was designed to target methionyl aminopeptidase 2; a protein implicated in angiogenesis and various pathophysiological processes, including oncogenesis. In 2003, the same research group developed a PROTAC incorporating oestradiol, an oestrogen derivative, to induce the degradation of oestrogen receptor alpha, which promotes the growth of certain breast carcinoma cells upon oestrogen activation. They also constructed a PROTAC containing dihydrotestosterone in order to target the androgen receptor, which is known to drive proliferation in prostate cancer cell lines following androgen stimulation.

A critical consideration in PROTAC design is the linker connecting the ligand for the protein of interest and the ligand for the E3 ubiquitin ligase. Both linker length and composition are pivotal for ternary complex formation. If the linker is too short, steric hindrance may prevent simultaneous binding to both targets. Conversely, an excessively long linker may impair the spatial proximity required for efficient ubiquitination. Current structural optimization efforts focus on the structure-activity relationship analyses across various linker lengths, typically beginning with longer variants and systematically shortening them until activity is lost[6].

Traditional small-molecule PROTACs often exhibit poor pharmacokinetic profiles and lack cell or tissue selectivity, potentially leading to systemic toxicity. Recent advances in ligand modification have yielded tumour-targeted PROTACs, including conjugates with folate, antibodies, and aptamers. These modified PROTACs demonstrate enhanced tumour accumulation, improved antitumor efficacy *in vivo*, and increased cellular uptake.

2.1. Aptamer-based PROTACs

Aptamers are single-stranded DNA or RNA oligonucleotides comprising fewer than 100 nucleotides.

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They exhibit high affinity and specificity, low toxicity, superior tissue penetration, ease of chemical synthesis, and notable stability, making them attractive candidates for targeted PROTAC delivery.

2.2. Pre-PROTACs

Pre-PROTACs are pharmacologically redesigned agents that become activated upon specific molecular triggers within designated signalling pathways. These constructs aim at reducing systemic toxicity while preserving therapeutic potency. Reactive oxygen species play a key role in modulating the activation cascades of these compounds[7].

2.3. Reactive-triggered (RT)-PROTACs

RT-PROTACs are designed to mitigate systemic toxicity associated with conventional PROTACs, by minimizing off-target protein degradation[8].

2.4. POLY-PROTACs

POLY-PROTAC 13 comprises a ligand for von Hippel–Lindau and a ligand for bromodomain-containing protein 4, connected *via* tunable linkers. Its advantages include: (i) activation by multiple stimuli, leading to enhanced tumour accumulation, improved protein degradation, and deeper tumour penetration; (ii) tumour-specific delivery; and (iii) compatibility with photodynamic therapy[9].

3. Conclusion

PROTACs have emerged as a transformative platform within the UPS framework, offering unprecedented precision in protein-selective targeting. Their capacity to dismantle neoplastic processes, circumvent resistance mechanisms, and enhance therapeutic efficacy and specificity positions them as a promising frontier in drug discovery.

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Conflicts of interest

None exist.

ORCIDs

0009-0003-8081-2403 (K.N. Chfat); 0009-0003-6218-4116 (S.A. Abdul Hussein)

References

1. Zou Y., Ma D., Wang Y. The PROTAC technology in drug development. *Cell Biochem. Funct.* 37(1), 21–30, 2019. DOI: 10.1002/cbf.3369
2. Wang C., Zhang Y., Zhang T., Shi L., Geng Z., Xing D. Proteolysis-targeting chimaeras (PROTACs) as pharmacological tools and therapeutic agents: advances and future challenges. *J. Enzyme Inhib. Med. Chem.* 37(1), 1667–1693, 2022. DOI: 10.1080/14756366.2022.2076675
3. Olson C.M., Jiang B., Erb M.A., Liang Y., Doctor Z.M., Zhang Z., *et al.* Pharmacological perturbation of CDK9 using selective CDK9 inhibition or degradation. *Nat. Chem. Biol.* 14(2), 163–170, 2018. DOI: 10.1038/nchembio.2538
4. Zhou K., Zhang L., Liu Y. Application of PROTACs in the pharmaceutical direction. *Int. J. Biol. Life Sci.* 2(2), 45–47, 2023. DOI: 10.54097/ijbls.v2i2.6889
5. Churcher I. Protac-induced protein degradation in drug discovery: breaking the rules or just making new ones? *J. Med. Chem.* 61(2), 444–452, 2018. DOI: 10.1021/acs.jmedchem.7b01272
6. Zagidullin A., Milyukov V., Rizvanov A., Bulatov E. Novel approaches for the rational design of PROTAC linkers. *Explor. Target. Antitumor Ther.* 1(5), 381–390, 2020. DOI: 10.37349/etat.2020.00023
7. Tamatam R., Shin D. Emerging strategies in proteolysis-targeting chimeras (PROTACs): high-

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lights from 2022. *Int. J. Mol. Sci.* 24(6), 5190, 2023. DOI: 10.3390/ijms24065190

8. Yang C., Yang Y., Li Y., Ni Q., Li J. Radiotherapy-triggered proteolysis targeting chimera prodrug activation in tumors. *J. Am. Chem. Soc.* 145(1), 385–391, 2023. DOI: 10.1021/jacs.2c10177
9. Zhang C., He S., Zeng Z., Cheng P., Pu K. Smart nano-PROTACs reprogram tumor microenvironment for activatable photo-metabolic cancer immunotherapy. *Angew. Chem. Int. Ed. Engl.* 61(8), e202114957, 2022. DOI: 10.1002/anie.202114957

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