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Beyond Kinase Inhibition: From Catalytic Blockade to Control of Protein Fate

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Abstract: Kinase inhibitors are a cornerstone of modern drug discovery, with more than 100 approved compounds which have had a transformative impact in precision oncology and inflammatory disease. Their success has rested largely on small-molecule control of catalytic activity through ATP-site engagement; a framework that leaves important biology unaddressed, including non-catalytic kinase functions, resistance driven by active-site mutation, and the limits of selectivity imposed by pocket conservation. Against this backdrop, the observation that kinase inhibitors can reduce target protein abundance has gained new mechanistic depth. Chaperone deprivation, supercharging of native degradation circuits, and context-dependent mutant-selective depletion mark distinct routes through which inhibitor binding can intersect with cellular proteostasis. The kinase inhibitor CR8 extends this logic into chemically encoded degradation: CR8 acts as a molecular glue degrader by creating, within the ligand-bound kinase complex, a composite surface that directly recruits a ubiquitin ligase, resulting in cyclin K degradation. Thalidomide analogues can degrade kinases through scaffolds that do not bind the kinase in isolation: ligase-binding compounds that recruit neosubstrate kinases through recognition of structural surface degrons. Deliberately engineered PROTACs encode ligase-target proximity through heterobifunctional architecture to convert kinase binders into degraders. Beyond degradation, induced-proximity mechanisms – from the clinically established rapamycin to bifunctional molecules that redirect kinase activity or restrict inhibition to tumour cells – show how small molecules can reshape kinase interaction states rather than simply block active sites. Together, these examples define an expanding pharmacological vocabulary for kinase drug discovery: one that asks not only whether a molecule inhibits its target kinase, but how ligand binding rewires protein stability, interactions, localisation, and function.

Keywords: Kinase inhibitors · Molecular glues · PROTACs · Targeted protein degradation

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1. Kinase Inhibitors: Mechanisms and Limitations

Protein kinases catalyse the transfer of the γ-phosphate of adenosine triphosphate (ATP) to serine, threonine, or tyrosine residues on substrate proteins, a reaction that underlies virtually every aspect of cellular signal transduction. Their frequent dysregulation across cancer, inflammatory, cardiovascular, and neurological disease has made kinases one of the most intensively pursued target classes in drug discovery, and sustained investment over four decades has produced a detailed structural and mechanistic understanding of the kinase domain that now underpins rational inhibitor design.[1]

Small-molecule kinase inhibitors can be broadly classified by their binding mode (reviewed in Ref. [2]). Briefly, type I inhibitors engage the active Asp–Phe–Gly (DFG)-in conformation of the kinase, competing directly with ATP at the hinge region of the catalytic cleft. Type II inhibitors instead stabilise the inactive DFG-out conformation, extending into an adjacent hydrophobic pocket that is absent in the active state. Covalent inhibitors add a further dimension by appending electrophilic warheads to engage active-site cysteines or lysines irreversibly, an approach that has proven successful for targeting epidermal growth factor receptors (EGFRs) or Bruton's tyrosine kinase (BTK).[3] Allosteric inhibitors represent a mechanistically distinct category: rather than competing with ATP, they bind regulatory surfaces outside the catalytic cleft – such as the mitogen-activated protein kinase (MEK) allosteric pocket or the myristoyl-binding site of the constitutively active fusion kinase Breakpoint Cluster-Abelson (BCR-ABL) – and modulate activity through conformational rather than competitive mechanisms.[2] Because these sites are structurally less conserved than the ATP pocket, such inhibitors may achieve superior selectivity, though identifying druggable allosteric pockets remains non-trivial.

The approval of imatinib for BCR-ABL-driven chronic myeloid leukaemia in 2001 became a defining demonstration of precision oncology: a rationally designed small molecule that stabilises

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an inactive conformation of an oncogenic kinase, transforming a disease once associated with limited survival into one in which many patients who achieve durable molecular responses can approach near-normal life expectancy.[4] This clinical success catalysed broad investment in kinase drug discovery, which has since yielded more than 100 approved compounds spanning oncology, autoimmunity, and rare disease.[5]

The same structural logic that made imatinib so effective also highlighted two recurring challenges for kinase inhibitors: acquired resistance and kinome-wide promiscuity. Despite transforming the treatment of chronic myeloid leukaemia, imatinib remained vulnerable to resistance-conferring mutations within the BCR-ABL kinase domain, necessitating the development of second-generation inhibitors such as dasatinib and nilotinib, and illustrating a broader challenge faced by many kinase inhibitors in which selective pressure drives the evolution of drug-resistant variants. A second challenge emerges from the highly conserved architecture of the ATP-binding pocket across the approximately 500 human kinases, where inhibitors that achieve potency through hinge engagement tend to do so promiscuously.[6,7] Kinome-wide profiling has shown that most approved inhibitors engage dozens of off-target kinases at pharmacologically relevant concentrations; fostamatinib, a spleen tyrosine kinase (SYK) inhibitor, inhibits more than 120 kinases.[7] Broad target engagement can translate into clinical toxicity, and much structure-guided inhibitor design has focused on exploiting differential features within and adjacent to the ATP pocket to narrow selectivity profiles by leveraging gatekeeper residue identity, back-pocket geometry, and DFG-loop conformation.[2] Yet promiscuity is not uniformly a liability. Co-inhibition of multiple nodes within a signalling network may forestall adaptive resistance, and the multi-target profiles of approved inhibitors may enable repositioning across indications.[7] A recent systematic profiling of approved inhibitors across 758 kinases estimated the druggable kinome at 235 targets rather than the previously assumed 89, suggesting that existing chemical matter accesses considerably more therapeutic space than appreciated.[8] Most approved kinase drugs are therefore best understood as multi-target agents whose full pharmacological profiles reflect the sum of their kinome-wide interactions.

This classical framework, built on occupancy of the ATP pocket and suppression of catalytic output, has been extraordinarily productive – but it has also left important pharmacological territory underexplored. Kinases perform biological functions beyond phosphotransfer that survive catalytic blockade; active-site mutations can erode inhibitor efficacy without eliminating the kinase as a disease driver; and ATP pocket conservation imposes persistent selectivity challenges. Here, we follow a progression from recurring observations that kinase inhibitors can reduce target protein abundance, to deliberate kinase degradation strategies now represented by molecular glue degraders and Proteolysis targeting chimeras (PROTACs) in clinical trials, extending to broader induced-proximity mechanisms that reshape kinase function.[9] This progression reframes kinase pharmacology from a question of target inhibition alone to one of ligand-induced protein state: how small molecules alter kinase stability, interactions, localisation, and downstream function.

2. Inhibitor-induced Kinase Degradation

2.1 *Chaperone Deprivation*

Many kinases depend on the heat shock protein 90 (Hsp90) chaperone for folding and protection from proteasomal clearance. Cdc37 (cell division cycle 37) acts as a kinase-specific co-chaperone, recruiting client kinases to Hsp90 through direct engagement of the kinase N-lobe. Polier *et al.* showed that Cdc37 binding directly antagonizes ATP binding to client kinases, suggesting that the chaperone complex does not merely stabilize kinases but can also regulate access to the active site.[10,11] Conversely, ATP-competitive inhibitors can antagonize Cdc37 recruitment. Vemurafenib and lapatinib, for example, deprived B-Raf and human epidermal growth factor receptor 2 (HER2) of access to the Hsp90–Cdc37 system in cancer cells – without chaperone support, the kinase is thought to be ubiquitylated and degraded.[10] Thus, for Hsp90-dependent kinases, inhibitor binding can couple catalytic-site occupancy to chaperone deprivation and proteasomal clearance, without deliberate degrader design.

2.2 *Supercharging Native Degradation*

Chaperone deprivation does not account for the full spectrum of inhibitor-induced depletion. A systematic dynamic abundance profiling study screening 98 kinases against 1,570 inhibitors identified 160 selective kinase–compound destabilisation events.[12] Hsp90 client kinases were enriched among destabilised targets, but many events fell outside this explanation, pointing to additional routes through which inhibitor binding can accelerate kinase turnover.

Mechanistic dissection of three cases illustrates how varied these routes can be.[12] LYN degradation by SI-3 operated indirectly: SI-3 preferentially inhibited CSK, which normally restrains SRC-family kinases such as LYN through inhibitory phosphorylation, shifting LYN into a hyperactive state recognised and cleared by the ubiquitin ligases CBL and CBLB. Degradation depended on network perturbation rather than direct LYN engagement – the kinase depleted was not the kinase that was principally inhibited. B lymphoid tyrosine kinase (BLK) degradation by TAK285 instead operated through mislocalisation: γ-secretase-mediated loss of BLK's N-terminal myristoyl anchor released the kinase from the cell membrane, triggering cytosolic turnover. Receptor-interacting protein kinase 2 (RIPK2) degradation by RI-4 followed a third route: it induced higher-order RIPK2 assemblies resembling endogenous oligomers formed in response to pathogen-derived stimuli, which were subsequently cleared not by the proteasome but by macroautophagy.

These cases define supercharging as ligand-induced acceleration of native turnover: a kinase is pushed into a hyperactivated, mislocalised, or aberrantly assembled state that endogenous quality-control circuits are primed to clear. The mechanism is not a property of the inhibitor alone but emerges from how drug-induced protein states are interpreted by proteostasis pathways.

2.3 *Mutant-selective Depletion*

Phosphoinositide 3-kinase alpha (PI3Kα), a crucial lipid kinase and central regulator of cell growth and proliferation, provides a clinically consequential example in which inhibition and degradation are mechanistically intertwined. Inavolisib and taselisib are ATP-competitive PI3Kα inhibitors that also induce preferential degradation of oncogenic mutant p110α – the catalytic subunit encoded by *PIK3CA* – over the wild-type protein, contributing to more durable pathway suppression than catalytic inhibition alone.[13] Inavolisib is now approved for *PIK3CA*-mutant breast cancer, providing a clinically relevant example of kinase inhibition coupled to mutant-selective degradation.

Mutant p110α depletion is not a direct consequence of PI3Kα binding *per se*. Song *et al*. showed that degradation depends on upstream receptor tyrosine kinase activity: in the context of active HER2-family signalling, mutant PI3Kα recruited to receptor complexes at the plasma membrane appears to become selectively susceptible to inhibitor-induced ubiquitin–proteasome clearance.[14] The responsible E3 ligase has not yet been clearly identified.

Mutant-selective PI3Kα depletion thus illustrates how inhibitor-induced degradation can depend on mutation status, upstream signalling context, and subcellular localisation – none of which is encoded in the inhibitor itself. Across chaperone deprivation, supercharging, and mutant-selective depletion, what unifies these

otherwise distinct mechanisms is that the inhibitor does not directly instruct degradation: it perturbs a protein state, and the cell's quality-control systems determine whether and how the target is cleared.

3. CR8-cyclin K: Chemically Encoded Degradation

The cases above share a common feature: degradation is an indirect consequence of inhibitor binding, emerging through cellular circuits that the compound does not deliberately engage. CR8, a 2,6,9-trisubstituted purine derivative of the cyclin-dependent kinase (CDK) inhibitor roscovitine, represents a different situation. The scaffold displayed substantially higher cellular potency than roscovitine despite comparable CDK inhibitory activity – a discrepancy that resisted explanation until we showed that CR8 acts as a molecular glue degrader of cyclin K, the obligate co-activator of CDK12/13.[15,16]

The discovery arose from an unbiased search for molecular glue degraders.[15] CR8 was nominated as a putative degrader through bioinformatic analysis across cancer cell lines, where cytotoxicity correlated with expression of ubiquitin ligase components. Mechanistic follow-up using global proteomics and clustered regularly interspaced short palindromic repeats (CRISPR) knockout screening then revealed rapid and selective loss of cyclin K driven by recruitment of the DDB1–CUL4 ubiquitin ligase complex, leading to cyclin K ubiquitylation and proteasomal degradation.

Structural studies showed that CR8 binds within the ATP pocket of CDK12 while simultaneously engaging DDB1, with the ligand-bound kinase complex contacting DDB1 in a manner reminiscent of canonical substrate receptors, thereby positioning cyclin K for ubiquitylation (Fig. 1a). The roscovitine comparison gave early insight into the chemical basis of this gain-of-function activity: both compounds engage CDK12/13 at the ATP site with similar affinity, yet only CR8 induces cyclin K degradation. The pharmacological distinction lies not in kinase binding but in the ability of the ligand-bound complex to nucleate a degradation-competent interface.

This selectivity is itself instructive. CR8 inhibits multiple CDKs through ATP-site engagement, yet degradation is restricted to cyclin K because only the CDK12/13–cyclin K complex forms a productive ternary complex with DDB1. The compound therefore carries an inherent dual pharmacology – broad CDK inhibition and selective cyclin K degradation – governed by distinct structural determinants: the kinase-binding pharmacophore on one hand, and the compatibility of the ligand-bound complex with the E3 ligase surface on the other. Structural analysis across 29 ternary complex crystal structures showed that chemically diverse CDK12/13 ligands, including previously described inhibitors such as SR-4835 and 919278, support DDB1 recruitment through distinct chemical solutions converging on a shared extended interface.[17–19] CDK12–cyclin K and DDB1 display measurable but weak affinity in the absence of CR8 – interactions in the ~50 μM range that are converted by ligand binding into low-nanomolar ternary complexes – suggesting that the ligand reinforces a pre-existing interface rather than generating protein–protein contacts *de novo*. That such structurally diverse compounds converge on the same degradation outcome demonstrates that degradation selectivity in this system is determined at the level of ternary complex compatibility, not kinase-binding profile alone.

The structure–activity relationship (SAR) further showed that because these two activities are governed by distinct structural determinants, they can be decoupled. SR-4835 achieves a narrower kinase inhibition profile than CR8 – selective for CDK12/13 rather than pan-CDK – while retaining cyclin K degradation as a second pharmacological axis.[17,19] HQ461, by contrast, drives cyclin K loss with minimal detectable CDK inhibition, a more purely glue-like mode in which the pharmacological output is

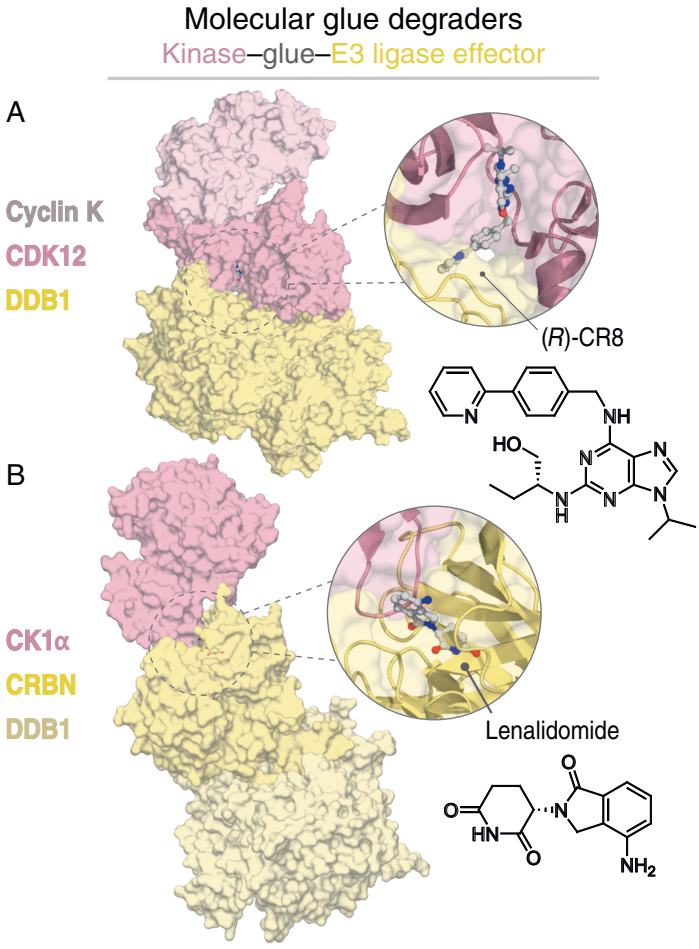

Fig. 1. **Emergent proximity through kinase molecular glue degraders. a**, DDB1–CR8–CDK12–cyclin K (PDB 6TD3); **b**, CRBN–lenalidomide–CK1α (PDB 5FQD). Kinases are shown in pink, E3 ligase effector proteins in yellow, and compounds in grey.

dominated by degradation rather than active-site occupancy.[17,20] More broadly, the CR8–cyclin K system established a design principle with implications beyond this target: solvent-exposed substituents peripheral to the kinase-binding pharmacophore can nucleate or stabilise protein–protein interfaces that redirect target fate – a concept that has since been extended to non-kinase targets including BRD4.[21,22]

Transcriptional profiling supports the idea that cyclin K degradation produces cellular effects distinct from CDK12/13 inhibition and CDK12-directed PROTACs.[23] A related compound, CT7439, is a CDK12/13 inhibitor and cyclin K degrader and is now being tested in early-phase trials in advanced solid tumours in combination with DNA damage-targeting agents (NCT06600789).[23]

4. Thalidomide Analogues as Kinase Degraders

A second class of molecular glue degraders relevant to kinase pharmacology emerged from thalidomide analogues: ligase-binding scaffolds that recruit targets through structural surface degrons, and whose mode of action was, like CR8, discovered *post hoc*.

Thalidomide was introduced in the late 1950s as a sedative and antiemetic, it was withdrawn following recognition of its severe teratogenicity, and subsequently repurposed – first thalidomide itself, then its derivatives lenalidomide and pomalidomide – for haematological malignancies including multiple myeloma.[24] Their molecular mechanism remained unknown until they were shown to bind cereblon (CRBN), the substrate receptor of a cullin-RING E3 ligase, remodelling its substrate-recognition surface to recruit neosubstrates for ubiquitylation and proteasomal degra-

dation (Fig. 1b; further reviewed in Ref. [24]). Crucially, none of these compounds detectably bind their neosubstrates directly – recruitment depends entirely on the compound-remodelled CRBN surface, a defining feature of the molecular glue mechanism.

Kinase degradation by this mechanism emerged from proteomic profiling of lenalidomide-treated cells, which identified casein kinase 1α (CK1α) alongside transcription factors such as IKZF1 and IKZF3 as CRBN neosubstrates.[25] CK1α degradation is thought to contribute to lenalidomide activity in del(5q) myelodysplastic syndrome, where malignant cells are sensitised by partial loss of the CK1α-encoding gene *CSNK1A1*.[25] The discovery that multiple neosubstrates are co-degraded showed that CRBN rewiring could access diverse targets, but also highlighted the challenge of achieving selective degradation profiles.

Structural studies provided the mechanistic basis for tuning that selectivity: CRBN engages a β-hairpin G-loop motif on the substrate, a degron whose geometry is compatible with the compound-remodelled CRBN surface.[24,26] This understanding opened several parallel avenues – computational mining of the proteome for degron-presenting targets, derivatisation of existing CRBN binders to tune surface compatibility, and structure-based optimisation informed by a growing body of ternary complex structures. Non-canonical degrons beyond the G-loop have since been identified, further expanding the accessible target space.[27]

Several kinase-directed CRBN glue programmes have now reached clinical development. CC-91633/BMS-986397 was optimised to favour CK1α degradation while reducing IKZF1/3 co-degradation, directly addressing the polypharmacology of the parent compounds.[28] BMS-986463 targets WEE1, a regulator of the G2/M cell-cycle checkpoint, through a glutarimide-based mechanism.[29] MRT-8102 targets NEK7, a kinase whose disease-relevant role in NLRP3 inflammasome activation is primarily scaffolding rather than catalytic – a case where degradation addresses biology that active-site inhibition would leave largely intact.[30] TRI-611, a brain-penetrant ALK degrader, operates through a non-canonical degron distal from the kinase active site, extending the accessible target space beyond G-loop-presenting kinases.[31]

Together, the CR8 and thalidomide analogue examples define two complementary routes to kinase degradation through molecular glue mechanisms: peripheral derivatisation of kinase binders that creates ligase-compatible composite surfaces, and evolution of ligase-binding scaffolds that recognise structural degrons on the target.

5. PROTACs and Related Degrader Modalities

PROTACs approach induced proximity through a modular architecture: a target binder is connected *via* a synthetic linker to an E3 ligase recruiter, physically bringing together the target protein and a ubiquitin ligase (Fig. 2a).[32,33] The heterobifunctional compound promotes the formation of a ternary complex, enabling target ubiquitylation and proteasomal degradation.

The recent approval of vepdegestrant, an estrogen receptor degrader and the first PROTAC drug to receive clinical approval, provides an important translational benchmark for targeted protein degradation, twenty-five years after the PROTAC concept was first introduced.[33,34] It also shows that heterobifunctional degraders can be optimised into orally active medicines despite occupying chemical space beyond the classical Rule of Five: vepdegestrant has a molecular weight of 724 Da and cLogP of 6.8, yet is dosed as a once-daily oral therapy.[35] Kinase-directed degraders are now testing similar principles across oncology, immunology and neurodegeneration. BTK degraders such as bexobrutideg provide clinically advanced kinase examples in B-cell malignancies, including reported activity in cases of central nervous system involvement,[36] while LRRK2 degraders such as ARV-102 test whether this approach can be extended to brain-penetrant degradation of neurodegenerative kinase targets.[37] Together, these examples indicate that oral exposure, systemic target engagement and, in selected cases, brain penetration are achievable for kinase-directed PROTACs.

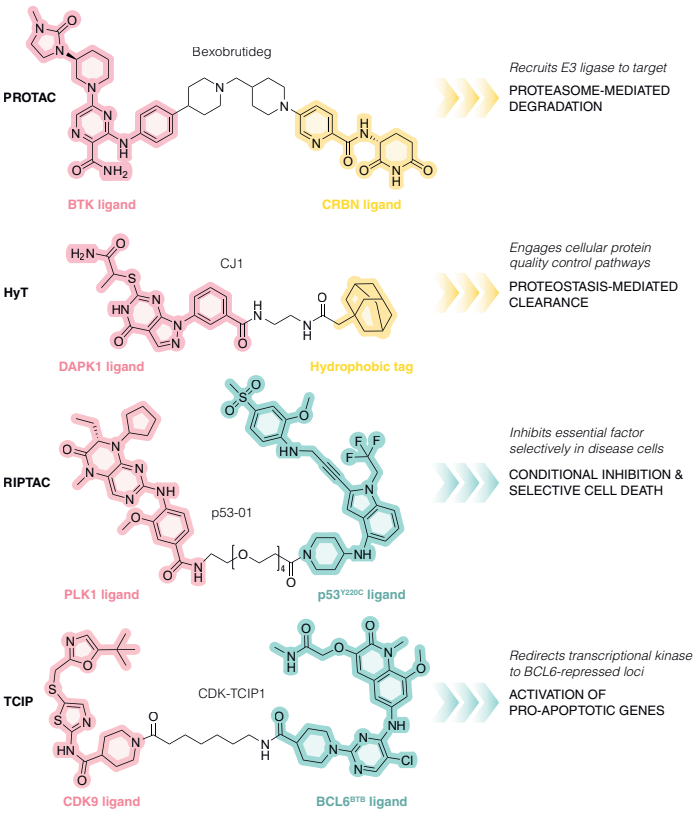

Fig. 2. **Engineered proximity through bifunctional kinase-directed compounds. a**, PROTAC; **b**, Hydrophobic tag; **c**, RIPTAC; d, TCIP. Kinase ligands are shown in pink; recruited effector ligands or tags are shown in yellow or teal.

The modularity of PROTACs is especially consequential for kinases because kinase inhibitor discovery has generated an unusually large repertoire of chemically tractable ligands. In a PROTAC, these serve as recognition elements that position the kinase in proximity to an E3 ligase, repurposing kinase-binding chemistry from an occupancy-driven mechanism into an event-driven one: the ligand-bound kinase becomes a substrate for ubiquitin-dependent elimination rather than merely an inhibited enzyme.[32] As a result, PROTAC design can extract pharmacological value from kinase ligands whose inhibitory potency, selectivity profile or biological consequence would otherwise be insufficient.

This conceptual shift is especially relevant for pseudokinases and kinase binders with limited functional consequences despite efficient target engagement. Many pseudokinases retain chemically tractable ATP-binding pockets but lack canonical phosphotransferase activity while still playing important regulatory roles in signalling networks.[38] In such cases, active-site occupancy may have limited biological impact, whereas degradation removes the entire regulatory protein. Proof-of-concept degraders of IRAK3 and TRIB2, both signalling regulators, illustrate how pseudokinase ligands can be repurposed to suppress disease-relevant cellular phenotypes through elimination of the target itself.[39,40]

The distinction between binding and degradation has important consequences for selectivity. Many kinase inhibitors have broad target profiles because of the structural conservation of the ATP-binding pocket across the kinome. However, kinase engagement and kinase degradation are not equivalent outcomes. For instance, THAL-SNS-032, derived from the multi-CDK inhibitor

SNS-032, retained nanomolar biochemical activity against several CDKs and showed a kinase-binding profile similar to SNS-032 in cell lysates, yet selectively degraded CDK9 in cells.[41] Similarly, a foretinib-derived PROTAC transformed a highly promiscuous kinase inhibitor (>130 kinase targets) into a degrader with a substantially narrower profile centred on MET/c-Met.[42] Kinome-scale studies extended this principle with a series of kinase degraders built from promiscuous kinase ligands, showing that the identity of the E3 recruiter and linker could redirect which kinases were depleted. Together, these findings illustrate that PROTACs can, in favourable cases, improve kinase-family selectivity relative to the parent inhibitor by converting broad ATP-site engagement into a more restricted degradation profile.

Mechanistically, productive degradation requires more than target engagement alone. The kinase and recruited E3 ligase must form a ternary complex with an orientation compatible with ubiquitin transfer and lysine presentation. In non-kinase PROTAC systems, high-resolution structures have shown directly how target–ligase contacts can support ternary-complex cooperativity and selectivity.[43] For kinase PROTACs, analogous public structures recruiting CRBN or von Hippel-Lindau (VHL) are lacking at the time of writing, so productive target–ligase geometry remains inferred mainly from biochemical and cellular assays, linker dependence and computational modelling.[44,45] Collectively, these studies suggest that kinase degradation depends on steric compatibility, linker architecture and productive presentation of ubiquitin-acceptor lysines, although kinase-specific structural rules remain incompletely defined.

Kinase-targeted PROTACs may also address resistance mechanisms that limit occupancy-driven kinase inhibition, provided that the mutant kinase remains competent for degrader binding and ternary-complex formation. BTK degraders illustrate this for C481 mutations, which reduce the efficacy of covalent BTK inhibitors by preventing irreversible modification of the target cysteine. Because degradation can still proceed through reversible engagement of the mutant kinase, ibrutinib-derived degraders such as MT-802 can degrade BTK^{C481S} despite loss of covalent bond formation.[46] At the same time, resistance studies with BTK degraders show that this advantage depends on the nature of the mutation: variants that compromise target engagement or the induced degradation complex can still reduce degrader activity.

Hydrophobic tagging strategies provide a related but mechanistically less defined route to kinase destabilization. In these systems, bulky hydrophobic groups are appended to kinase binders to promote degradation of the ligand-bound protein, without deliberate recruitment of a defined E3 ligase (Fig. 2b). An early example converted the HER3 pseudokinase ligand TX1–85–1 into an adamantane-tagged derivative, which induced partial HER3 depletion.[47] Compared with PROTACs and molecular glues, however, hydrophobic tagging remains less mechanistically resolved: the relevant quality-control factors, recognition events and determinants of substrate selectivity are still incompletely defined. More recent kinome-scale studies nevertheless suggest that susceptibility to hydrophobic tag-induced destabilization is selective and target-dependent, arguing against a simple model in which hydrophobic tagging passively destabilizes any ligand-bound kinase.[48]

Collectively, these studies add a new dimension to kinase inhibitors when such ligands are considered as degrader starting points. Conversion into a PROTAC can reveal a distinct pharmacological profile in which target depletion, resistance coverage, and degradation selectivity emerge from productive ternary-complex formation and cellular degradability rather than occupancy alone. In this framework, the role of the kinase ligand is no longer simply to inhibit catalysis – the ligand-bound kinase itself becomes a node for new protein interactions and downstream cellular outcomes.

6. Induced Proximity Beyond Degradation

The induced-proximity logic underlying molecular glue degraders and PROTACs is not inherently tied to target elimination – the same principle of small-molecule-mediated ternary complex formation can be applied to stabilise signalling assemblies, localise kinase inhibition to specific cellular contexts, or redirect kinase activity toward new substrates.

The conceptual basis for this type of pharmacology is longstanding. Rapamycin and FK506 are macrolide natural products that bind FKBP12; the resulting complexes engage mTOR and calcineurin respectively through composite protein–small molecule interfaces, inhibiting a kinase and a phosphatase without occupying their catalytic sites (Fig. 3a). Both are, in retrospect, among the earliest examples of molecular glue pharmacology, and both reached the clinic as immunosuppressants long before their ternary complex mechanism was understood – an early demonstration that small-molecule-stabilised protein–protein interactions can produce potent and clinically useful biology.

Trametinib, a clinically approved MEK inhibitor, provides a striking example of induced-proximity pharmacology embedded in an approved drug. Structural work from Dar and colleagues showed that trametinib occupies the canonical MEK allosteric site adjacent to ATP but also extends into a sub-pocket, reaching the KSR interaction interface (Fig. 3b).[49] As a result, trametinib stabilizes the KSR–MEK complex while disrupting the related RAF–MEK complex, leveraging interface residues that distinguish these signalling sub-complexes. This insight directly enabled the design of trametiglue, an analogue with enhanced interfacial contacts that limits adaptive resistance by more stably sequestering MEK away from RAF.[49]

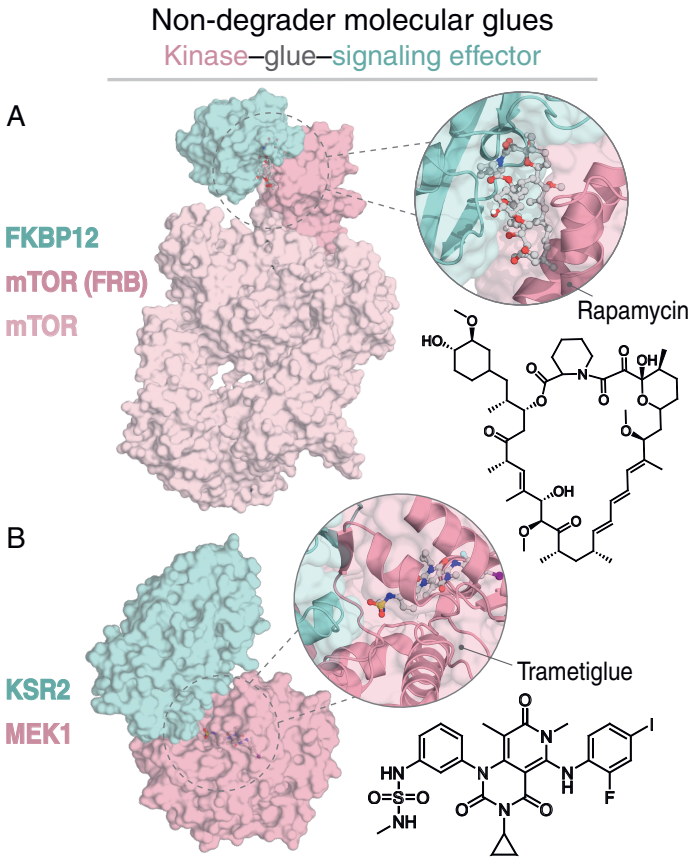

Fig. 3. **Emergent proximity through non-degradative kinase molecular glues. a**, FKBP12–rapamycin–mTOR/FRB (PDB 1FAP, 4JSV). **b**, MEK1–trametiglue–KSR2 (PDB 7JUV). Kinases are shown in pink, effector proteins in teal, and compounds in grey.

Regulated induced proximity targeting chimeras (RIPTACs) offer another way to leverage induced proximity: to make kinase inhibition conditional rather than simply more effective. These bifunctional molecules are designed to bring a disease-enriched protein into proximity with an essential target protein, so that inhibition of the essential target is concentrated in cells carrying the disease marker (Fig. 2c). A recent preclinical example links a ligand for mutant $p53^{Y220C}$ to an inhibitor of the mitotic kinase PLK1, inducing a $p53^{Y220C}$–RIPTAC–PLK1 ternary complex.[50] Rather than broadly inhibiting PLK1 in all proliferating cells, the molecule exploits accumulation of mutant p53 to localize PLK1 inhibition to $p53^{Y220C}$ tumour cells, leading to selective cell death. In this setting, induced proximity specifies the molecular context of inhibition rather than its target.

A similar modality extends induced-proximity pharmacology *via* a distinct mechanistic axis by relocalising kinase activity rather than suppressing it. CDK-transcriptional chemical inducers of proximity (CDK-TCIPs) are bifunctional molecules that link a ligand derived from an ATP-competitive CDK9 inhibitor to a binder of BCL6, a transcriptional repressor (Fig. 2d).[51] Rather than globally blocking CDK9 activity, CDK-TCIPs relocalise a fraction of cellular CDK9 to BCL6-bound chromatin. There, CDK9 remains sufficiently active to promote RNA polymerase II phosphorylation and transcriptional elongation at genes normally repressed by BCL6, including pro-apoptotic target genes, leading to selective killing of BCL6-dependent lymphoma cells.[51] Conceptually, kinase inhibitor scaffolds can therefore be repurposed as a recruitment handle: not to switch off CDK9 globally, but to redirect its catalytic output to a therapeutically relevant genomic context.

7. Outlook

The examples discussed here collectively argue that the pharmacological output of a kinase-directed small molecule is not determined solely by what it binds, but by the protein state and interaction landscape that this binding creates. Ligand engagement can alter protein stability, reshape interaction networks, perturb localisation, or promote assembly of higher-order complexes.

Among these modalities, targeted degradation is the most translationally mature, with approved degraders and multiple kinase-directed clinical programmes. Unlike catalytic blockade, it may eliminate scaffolding, regulatory, and non-catalytic kinase functions entirely, and could address resistance where sufficient engagement remains to nucleate productive ternary complexes or trigger destabilisation pathways. Inavolisib further illustrates that oncogenic mutations can confer preferential susceptibility to degradation in ways that depend on target conformation, signalling context, and subcellular localisation.

Several principles have emerged from the degradation literature that are worth consolidating. Degradation introduces a layer of selectivity distinct from inhibitor selectivity: promiscuous kinase binders can yield restricted degradation profiles because selectivity is determined at the level of ternary complex compatibility rather than binary target affinity, as illustrated across PROTACs, molecular glues, and native degradation systems alike. Degradability is not a simple downstream consequence of target engagement – kinome-wide studies show that broad occupancy does not translate into broad degradation, and susceptibility to native inhibitor-induced turnover does not predict PROTAC-mediated depletion, underscoring that each modality faces distinct constraints. Induced-proximity mechanisms can derive selectivity from kinase surfaces beyond the conserved ATP pocket, exploiting structural degrons, composite protein–protein interfaces, and conformational features inaccessible to ATP-competitive inhibition alone. Structural biology has proved essential for converting observations into design principles – most clearly for molecular glues, where ternary complex structures have enabled rational tuning of substrate selectivity – and equivalent structures for kinase PROTACs remain a notable gap whose closure would meaningfully advance rational degrader design.

The non-degradative induced-proximity examples discussed here – conditional kinase inhibition, redirected catalytic activity, stabilised signalling assemblies – are largely at preclinical proof-of-concept stage, but they point toward a broader design space in which small molecules specify not just whether a kinase is active, but where, when, and in what molecular context. How far that space is explored will reflect the development of tools to capture the consequences of induced complex formation with sufficient resolution to guide design, the expanding repertoire of binders to diverse effector proteins, and the creativity applied to combining them.

Several open mechanistic questions remain. Why are certain kinases particularly susceptible to degradation whereas others resist depletion despite efficient binding? To what extent do inhibitors accelerate endogenous turnover mechanisms versus inducing entirely new degradation-competent states? How important are chaperone systems such as Hsp90–Cdc37 in determining kinase degradability across modalities? And more broadly, when is degradation therapeutically advantageous relative to sustained catalytic inhibition, and when might it instead produce undesirable or poorly controlled biology? These questions are especially important because genetic loss, catalytic inhibition, and targeted degradation are not interchangeable perturbations. NEK7, whose role in NLRP3 inflammasome activation is largely scaffolding rather than catalytic, illustrates why protein removal may be preferable to active-site inhibition; cyclin K degradation by CR8, which produces transcriptional consequences distinct from CDK12/13 inhibition despite cyclin K serving as their obligate co-activator, further illustrates that degradation can produce pharmacology distinct from catalytic blockade.[17,27]

For the non-degradative modalities, the questions are more exploratory, reflecting how recently these concepts have emerged. What other kinase–effector combinations are accessible? Can bifunctional architectures be optimised with the rigour now applied to PROTACs? For molecules that redirect transcriptional output, what are the genome-wide consequences and how is the therapeutic window defined? The frameworks to address these questions are still being developed, and their answers will determine whether the conceptual promise of these approaches translates into therapeutic impact.

Taken together, the reviewed examples suggest that the pharmacological vocabulary of kinase drug discovery is expanding beyond occupancy and catalytic output — towards a framework in which ligand binding is evaluated not only by what it inhibits, but by how it shapes the fate of its target, and what new biology that shift unlocks.

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