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MOLECULAR GLUE DEGRADERS VERSUS HETEROBIFUNCTIONAL PROTACS: A COMPARATIVE ANALYSIS OF MECHANISM, PHYSICOCHEMICAL SPACE, SELECTIVITY AND CLINICAL PROGRESS

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ABSTRACT

Targeted protein degradation has matured from a laboratory curiosity into a clinically validated therapeutic strategy, and two chemical modalities now define its practice: monovalent molecular glue degraders and heterobifunctional proteolysis-targeting chimeras (PROTACs). Both redirect the cell's own ubiquitin-proteasome system to eliminate a disease-driving protein rather than merely occupy it, yet they arrive at that shared endpoint by opposite chemical logics. A PROTAC tethers a target ligand to an E3 ligase recruiter through a linker and builds a ternary complex from two independent binding events. A molecular glue is a single small molecule that remodels the surface of an E3 ligase so that a new protein-protein interface forms with a neosubstrate that neither partner would otherwise recognise. This review sets the two modalities side by side across four axes that decide their fate in drug development: mechanism and the thermodynamics of induced proximity, physicochemical property space and its consequences for oral drug-likeness, the origins of degradation selectivity, and the state of clinical translation as of 2026, the year the first PROTAC reached the market. The argument advanced here is that glues and PROTACs are not competitors so much as complementary answers to different starting problems, that the boundary between them is becoming porous as cooperative PROTACs behave increasingly like intramolecular glues, and that the central near-term constraint on both is the narrowness of the exploited E3 ligase repertoire rather than any ceiling on target scope.

Keywords: targeted protein degradation; molecular glue; PROTAC; ubiquitin-proteasome system; cereblon; ternary complex; beyond rule of five; drug-likeness.

1. Introduction

For most of the modern era of drug discovery, a protein was considered druggable only if it presented a deep, well-defined pocket into which a small molecule could bind with high affinity and durably suppress function. This occupancy-driven paradigm, the foundation of classical receptor pharmacology, requires sustained target engagement: the drug must remain bound to hold the protein inactive, and the moment it dissociates the pathological process resumes [1]. That requirement excludes a large fraction of the proteome. Transcription factors, scaffolding proteins, and many mutant oncoproteins lack a tractable active site, and by conventional criteria they were labelled undruggable [2].

Targeted protein degradation (TPD) rewrites this premise. Instead of inhibiting a protein, TPD removes it, harnessing the ubiquitin-proteasome system to tag the protein of interest with polyubiquitin and route it to the 26S proteasome for destruction [3]. The pharmacological consequence is a shift from occupancy-driven to event-driven action. Degradation is a catalytic event: a single degrader molecule can trigger the ubiquitination of one target, release, and then promote the destruction of another, so that deep target knockdown becomes achievable at sub-stoichiometric concentrations rather than at the saturating exposures a competitive inhibitor demands [1,4]. Because degradation depends on binding anywhere that positions the target productively rather than on occupying a functional site, proteins without a classical pocket come within reach [2,5].

Three further consequences of the event-driven mode deserve emphasis, because they recur throughout the comparison that follows. First, because the drug removes the protein rather than blocking a site, the pharmacodynamic effect outlasts the pharmacokinetic exposure: recovery of function requires resynthesis of the protein, so a degrader can act longer than its plasma residence would suggest [1]. Second, degradation is indifferent to which face of the protein is engaged, so a ligand that binds an allosteric surface, a shallow groove, or a merely convenient pocket can still drive turnover, which is the structural reason the modality reaches scaffolding and transcription-factor targets at all [2]. Third, because efficacy does not scale with continuous occupancy, a degrader can in principle overcome the resistance that afflicts inhibitors when a target is overexpressed or acquires an active-site mutation, since the drug need not out-compete the target's own biology at equilibrium [10]. These properties are shared by both modalities and set them apart, together, from the inhibitors they aim to displace.

Two chemical strategies dominate the field. The first, the molecular glue degrader, predates the vocabulary of TPD by decades. Thalidomide and its analogues lenalidomide and pomalidomide, the immunomodulatory imide drugs (IMiDs), were in clinical use long before their mechanism was understood to be the drug-dependent recruitment of neosubstrate proteins to the cereblon (CRBN) component of a cullin-RING E3 ligase [6,7]. The second strategy, the PROTAC, was conceived deliberately. In 2001 the Crews

and Deshaies laboratories reported a chimeric molecule that linked a target ligand to a peptide recognised by an E3 ligase complex, and thereby demonstrated that a synthetic bifunctional molecule could redirect the degradation machinery at will [4,8].

These two lineages, one discovered by fortune and one by design, have converged on the same therapeutic goal while retaining fundamentally different chemistry. A rigorous comparison matters because the choice between them is not academic: it determines the discovery route, the achievable physicochemical profile, the likely selectivity, and ultimately whether a programme yields an oral medicine. This review provides that comparison, organised around mechanism, physicochemical space, selectivity, and clinical progress, and closes by arguing that the more useful framing is convergence rather than rivalry.

2. Scope and evidence base

This is a narrative comparative review synthesising the mechanistic, physicochemical, and drug-development literature on the two degrader modalities, drawn from peer-reviewed journals, primary structural and biophysical studies, and public regulatory records. It deliberately excludes primary human and animal experimental data. No clinical efficacy or safety statistics, patient-level outcomes, or in vivo pharmacokinetic measurements are reported or pooled. Where clinical progress is discussed, it is described in terms of modality validation, development stage, and regulatory milestone, all of which are matters of public record rather than experimental findings. This boundary keeps the analysis focused on the chemical and mechanistic principles that a medicinal chemist or translational scientist would weigh when choosing between the two approaches, and it means the conclusions rest on reproducible molecular reasoning rather than on trial results that lie outside the review's scope.

3. Mechanism: two routes to induced proximity

Both modalities operate by chemically induced proximity, the principle that forcing two proteins together can generate a biological outcome that neither produces alone. In degradation, the induced proximity is between a target and an E3 ubiquitin ligase, and the outcome is target ubiquitination followed by proteasomal turnover [3]. The modalities differ in how they build that proximity.

3.1 The heterobifunctional logic of PROTACs

A PROTAC is a three-part molecule: a ligand for the protein of interest, a ligand that recruits an E3 ligase, and a linker joining them [9]. Neither end needs to inhibit anything. The target ligand must only bind the target somewhere accessible, and the E3 ligand must only engage the ligase. When both ends are occupied simultaneously, a target-PROTAC-E3 ternary complex forms, the ligase positions its ubiquitin-conjugating apparatus against the target, and polyubiquitin chains accumulate [3,9]. The PROTAC is then free to dissociate and act again, which is the structural basis of its catalytic, event-driven behaviour and

its ability to drive knockdown exceeding ninety percent at nanomolar concentrations [10].

This modularity is the PROTAC's defining advantage. Target binding, ligase recruitment, and linker geometry can each be optimised independently, which gives the medicinal chemist a rational, stepwise path from a known target ligand to a degrader [11]. It is also why PROTACs have reached target classes that molecular glues have struggled with, including receptor tyrosine kinases and, increasingly, membrane-associated proteins [11].

The same three-body assembly, however, creates the modality's characteristic liabilities. The productive species is the ternary complex, but at sufficiently high degrader concentration the target and the ligase become saturated in separate binary complexes, one end of each PROTAC engaged and neither bridging the two proteins. Ternary complex formation therefore rises with concentration, peaks, and then falls, which yields the bell-shaped dose response known as the hook effect [12,13]. A drug whose efficacy declines at high dose complicates the definition of a therapeutic window and demands careful pharmacokinetic and pharmacodynamic control in the clinic [14]. The hook effect is more than a laboratory artefact. It is an intrinsic property of any trivalent equilibrium in which a single molecule must simultaneously engage two partners, and its steepness reports on the underlying cooperativity, a point developed below [12].

A second consequence of the bifunctional design is that degradation depends on a longer chain of molecular events than inhibition does. The target must be bound, the ligase must be recruited, the complex must present a surface lysine to the ubiquitin-conjugating enzyme in a geometry the ligase can service, polyubiquitin must be extended to a chain the proteasome recognises, and the tagged protein must be delivered before a deubiquitinating enzyme reverses the mark [3,9]. Each step is a place where an otherwise well-designed molecule can fail, which is why structure-activity relationships for PROTACs are notoriously discontinuous: a change that improves binary affinity can abolish degradation if it perturbs the geometry of ubiquitin transfer [16]. This mechanistic length is the price of the modality's reach.

3.2 Cooperativity as the hidden variable

Whether a PROTAC degrades efficiently is not decided by binary affinities alone. It is governed by the thermodynamic cooperativity of the ternary complex, expressed as the factor alpha, which measures how much the presence of the third body strengthens or weakens the pairwise interactions [15]. Positive cooperativity (alpha greater than one) arises when the linker and the two ligands allow favourable protein-protein contacts to form between target and ligase in the complex; these contacts stabilise the assembly beyond what the ligands alone would predict [16]. Negative cooperativity arises when steric clashes or charge repulsion between target and ligase oppose complex formation [16].

Cooperativity has direct design consequences. Studies dissecting BTK degradation showed that short linkers imposed steric clashes and negative

cooperativity, and that extending the linker relieved those clashes and restored potent degradation [15]. Work on VHL-recruiting degraders of SMARCA2 and BRD4 established that ternary complex binding affinity and cooperativity correlate with both degradation potency and initial degradation rate, and that the buried surface area at the induced interface tracks with measured affinity, which offers a predictive framework for design [16]. Crucially, a highly cooperative PROTAC forms a stable, long-lived ternary complex whose maximal effect spans a wider concentration window, so the hook effect is blunted or abolished [13,17]. Cooperativity, in other words, is the parameter that converts a bifunctional molecule from a passive tether into something that actively favours the productive complex.

3.3 The monovalent logic of molecular glues

A molecular glue degrader dispenses with the linker and the target ligand entirely. It is a single low-molecular-weight compound that binds one protein, most often the E3 ligase, and in doing so reshapes that protein's surface to create a novel interface complementary to a neosubstrate [5,7]. The glue does not need a pre-existing pocket on the target. It exploits or induces a protein-protein interaction that does not occur in the drug's absence, gluing together two proteins that are otherwise strangers [6]. The paradigm case is the IMiD-CRBN system: lenalidomide binds cereblon and remodels its surface so that zinc-finger transcription factors such as IKZF1 (Ikaros) and IKZF3 (Aiolos) are recruited, ubiquitinated, and degraded, and the loss of these factors underlies the drugs' activity in multiple myeloma [6,18].

Because a glue is essentially a small molecule with an unusual mechanism, it inherits the favourable properties of small molecules: modest size, good membrane permeability, and the potential for oral bioavailability [5,19]. It also inherits a simpler pharmacology. Because a glue engages only one protein directly, it has no linker to optimise, no two-sided affinity to balance, and, importantly, no hook effect, since there is no competing binary equilibrium to saturate [5,19]. The structure-activity relationships of glues are correspondingly more tractable than those of PROTACs, which is a practical advantage that is easy to overlook when attention fixes on the discovery problem [19].

The trade-off historically has been that discovery problem. Where a PROTAC can be designed from a known target ligand, a glue must be found. The founding glues were discovered serendipitously, their mechanism understood only in retrospect, and extending glue discovery to a predefined target of choice remains the central difficulty of the approach [7,11]. The obstacle is fundamental rather than incidental: a glue must simultaneously satisfy a binding surface on the ligase and induce complementarity to a neosubstrate that presents an appropriate degron, and there is no guarantee that any small molecule exists to bridge a given target-ligase pair [7]. That difficulty is now being eroded by systematic phenotypic screening across cancer cell-line panels, structure-based design against known ligase surfaces, and mechanism-informed

library construction that biases compounds toward the degron-presenting chemotypes, which together are converting glue discovery from accident into a more deliberate enterprise [19,20].

Figure 1 summarises the two mechanisms side by side, and Table 1 sets out the head-to-head comparison that the remainder of this review develops.

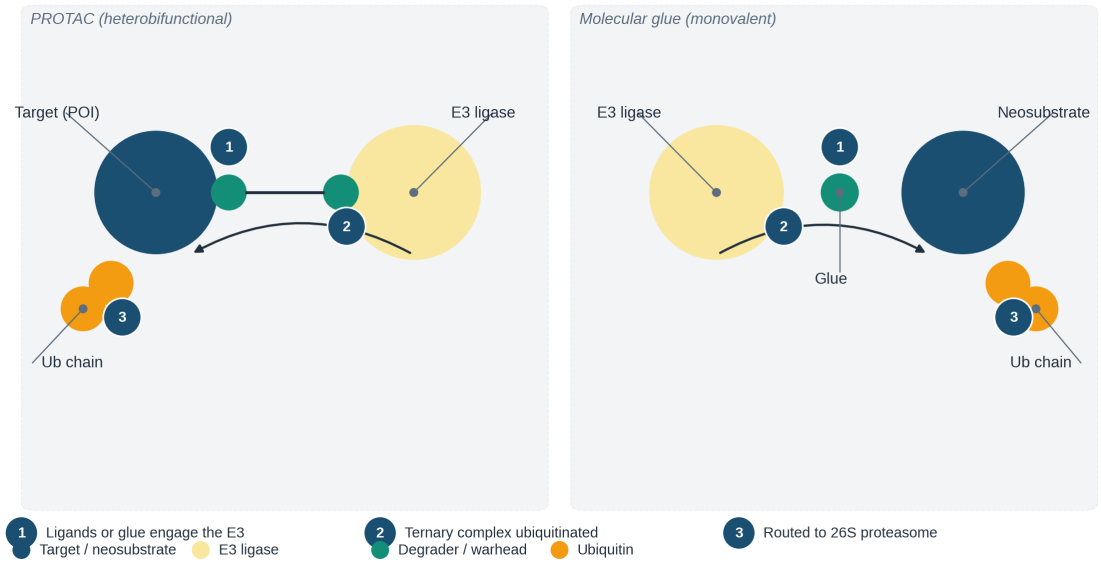

Figure 1

Figure 1. Two routes to induced proximity. A heterobifunctional PROTAC (left) carries two ligands joined by a linker: one warhead binds the target protein of interest and the other recruits an E3 ubiquitin ligase, so that a target-PROTAC-E3 ternary complex assembles from two independent binding events, the target is polyubiquitinated, and the degrader is released to act again.

Table 1. Head-to-head comparison of molecular glue degraders and heterobifunctional PROTACs.

Attribute	Molecular glue degrader	Heterobifunctional PROTAC
Architecture	Single monovalent small molecule	Two ligands joined by a linker
Target ligand required	No	Yes
Binding events to form complex	One (glue to E3)	Two (target and E3)
Typical molecular weight	Small, near rule of five	~700 to 1200 Da, beyond rule of five
Oral drug-likeness	Generally favourable	Achievable but demanding
Hook effect	Absent	Characteristic liability
Design route	Discovery (screen or find)	Rational, modular from a known ligand
Basis of selectivity	Induced degron complementarity	Warhead, ligase, linker, cooperativity
Catalytic, event-driven action	Yes	Yes
Founding clinical validation	IMiDs (thalidomide lineage)	Vepdegestrant, approved 2026

4. Physicochemical space and the problem of drug-likeness

If mechanism is where the two modalities differ in concept, physicochemical property space is where that difference becomes a practical fate. It is here that the choice between a glue and a PROTAC most often decides whether a programme can deliver an oral drug.

4.1 PROTACs and the beyond-rule-of-five regime

Lipinski's rule of five codified the property ranges associated with orally absorbed small molecules: molecular weight below 500, calculated logP below 5, no more than five hydrogen bond donors, and no more than ten acceptors [21]. A PROTAC, by construction, carries two ligands and a linker, and the sum routinely breaches these limits. Clinical and preclinical PROTACs typically fall between roughly 700 and 1200 Da, with elevated lipophilicity, large polar surface area, high hydrogen bond donor and acceptor counts, and many rotatable bonds [21,22]. This places them firmly in the beyond-rule-of-five (bRo5) chemical space [23]. The consequences are predictable: poor passive permeability, limited aqueous solubility, and metabolic and pharmacokinetic liabilities that together threaten oral absorption [21,22].

Yet the picture is not one of simple failure, because the bRo5 space is not empty of oral drugs. Analyses of oral PROTACs suggest that the modality tolerates a broader envelope than rule-of-five compounds for several properties, including molecular weight, polarity, lipophilicity, and hydrogen bond acceptor count, provided one property is held in check [24]. Using solvent-exposed hydrogen bond descriptors, one influential analysis derived an upper limit of roughly two solvent-exposed donors for oral PROTACs in apolar environments, and singled out exposed donor count as the property that must be controlled even when others are relaxed [24]. The choice of E3 ligase compounds this: CRBN-recruiting PROTACs, which use a comparatively small ligand, tend toward more oral drug-like weights than VHL-recruiting PROTACs, and the clinical PROTACs advanced by the oral route have overwhelmingly been CRBN-based [22,25].

The mechanism that rescues permeability in this regime is molecular chameleonicity. Large, flexible bRo5 molecules can adopt different conformations in different environments, folding to form intramolecular hydrogen bonds that shield polar groups and reduce effective polar surface area in the lipid bilayer, then unfolding to expose those groups in aqueous compartments [23,26]. A PROTAC that behaves as a chameleon can therefore be more permeable than its static descriptors predict, which is why in vitro permeability data must be applied cautiously to this class and why NMR conformational analysis has become part of the medicinal chemist's toolkit for oral degraders [24,26]. The design of oral PROTACs, in short, is the deliberate engineering of environment-responsive conformational behaviour, a discipline that did not exist for classical drugs.

The practical corollary is that the familiar screening cascade of small-molecule discovery does not transfer cleanly to this class. Aqueous solubility is frequently poor, so formulation strategies developed for other bRo5 molecules, including amorphous solid dispersions and other enabling formulations, are often required to translate intrinsic activity into oral exposure [21]. Passive permeability assays can underestimate the true absorption of a chameleonic degrader, and metabolic stability must be assessed against a molecule large enough to present many potential sites of oxidation [22,26]. None of these obstacles is prohibitive, as the clinical PROTACs now in late-stage development and the first approval attest, but each adds cost and time that a glue programme largely avoids. The property gap is therefore not only a matter of descriptors on a page; it is a difference in the effort required to reach an oral medicine.

4.2 Molecular glues within reach of the rule of five

Molecular glues occupy a very different position. Being monovalent and small, they largely sit within or close to rule-of-five space and behave, from a formulation and absorption standpoint, like conventional small molecules [5,19]. The IMiD scaffolds and their next-generation successors are compact, and their smaller size confers the high cell permeability and oral bioavailability that PROTACs must fight for [5]. This is the single most consequential practical advantage of the glue approach: the modality begins where PROTACs are trying to arrive.

The contrast is illustrated by an idea that has circulated in the field, that developing potent glues is one route to reducing degrader molecular weight and pulling the chemistry back toward rule-of-five compliance [25]. Figure 2 places the two modalities in property space against the classical small-molecule envelope, and makes explicit the gap that PROTAC design must bridge and that glue design largely sidesteps.

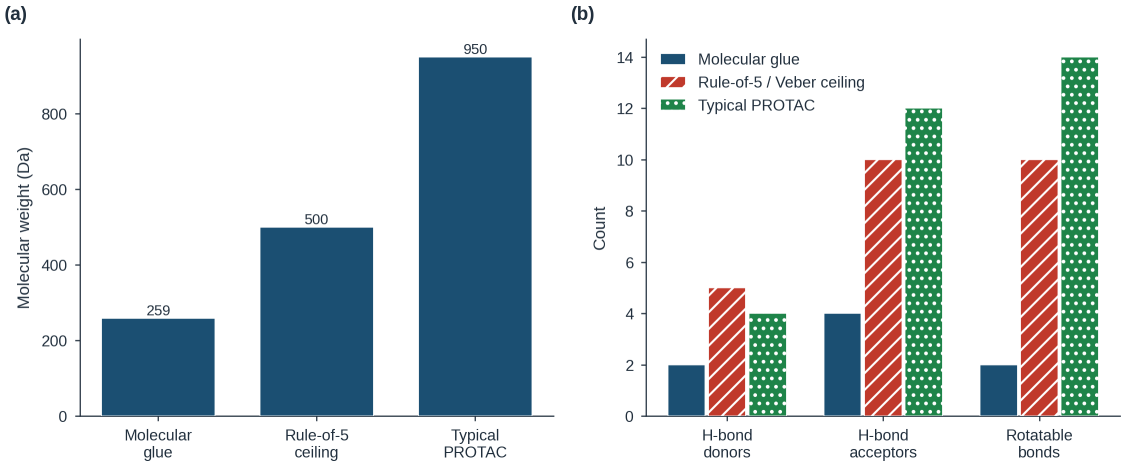

Figure 2

Figure 2. Representative physicochemical property space of the two modalities against the rule-of-five envelope. (a) Molecular weight in daltons for a representative cereblon molecular glue (lenalidomide, 259

Da), the Lipinski rule-of-five ceiling (500 Da), and a typical PROTAC (midpoint of the 700 to 1200 Da range, ~950 Da). (b) Count descriptors, hydrogen bond donors, hydrogen bond acceptors and rotatable bonds, for the same molecular glue, the rule-of-five and Veber ceilings, and a typical PROTAC. Bars are distinguished by both colour and fill pattern so the comparison survives greyscale printing. Values are representative figures extracted from the cited literature and reference compounds, not measured dispersions, so no error bars are shown [6,18,21,22,24].

The glue's physicochemical head start does not make it the better modality in every case, because it is bought at the price of discovery difficulty and, as Section 5 argues, at some cost in the predictability of selectivity. But when an oral medicine is the goal and a glue can be found, the property arithmetic favours the glue.

5. Selectivity: where degradation outperforms and where it surprises

Selectivity is the axis on which TPD makes its most counterintuitive claim, and it is also where the two modalities diverge in how their specificity is determined and controlled.

5.1 Degradation selectivity can exceed binding selectivity

A degrader's specificity is not simply the specificity of its warhead. For a PROTAC, productive degradation requires that the target, once bound, can be positioned to form a stable, cooperative ternary complex with the ligase, and only proteins that satisfy this geometric and thermodynamic requirement are efficiently ubiquitinated [27]. The result is that degradation selectivity can substantially exceed the binding selectivity of the target ligand alone. A promiscuous kinase inhibitor, repurposed as the target end of a PROTAC, can yield a degrader that eliminates only a subset of the kinases the parent inhibitor binds, because only some of those kinases form a productive complex with the chosen ligase [9]. Selectivity is thus shaped by at least four overlapping filters: warhead binding, ligase recruitment, linker geometry, and the cooperativity of the induced interface [9]. This multi-layered specificity is a genuine and sometimes underappreciated advantage of the bifunctional design, and it has been exploited to distinguish between closely related paralogues. Degraders differing only in the target ligand have been shown to select between CDK4 and CDK6, two kinases so similar that selective inhibition is notoriously hard [27].

5.2 The structural basis of glue selectivity

For molecular glues, selectivity is written into the induced interface itself. Neosubstrates recruited to CRBN by IMiD-class glues share a structural degron rather than a sequence: a beta-hairpin loop bearing a critical glycine, often within a Cys2His2 zinc-finger domain, that inserts into the composite drug-CRBN surface [18,28]. Proteins presenting this G-loop degron can be recruited; proteins with a clashing residue at the pinnacle position cannot [7]. Selectivity is therefore a property of complementary shape at a small induced interface, and it can be tuned with remarkable precision by minor chemical change to the glue. Lenalidomide and pomalidomide, near-identical in structure, both degrade IKZF1 and IKZF3, yet only lenalidomide degrades casein kinase 1 alpha (CK1alpha), the

neosubstrate that underlies its distinct activity in del(5q) myelodysplastic syndrome [28,29]. Analogues such as CC-885 acquire the ability to recruit the translation termination factor GSPT1, and structure-guided glue design has produced compounds selective for CK1alpha over the IKZF proteins [20,30]. A separate glue chemotype, the aryl sulfonamides including indisulam and E7820, recruits the splicing factors RBM39 and RBM23 to a different substrate receptor, DCAF15, through an entirely distinct alpha-helical degron. Glue selectivity is therefore a general and programmable feature rather than a quirk of one scaffold [30].

5.3 Kinetics, resident time, and the dimension inhibitors lack

Degradation adds a temporal dimension to selectivity that occupancy-driven pharmacology does not possess. Two degraders can reach the same depth of knockdown at equilibrium yet differ in how fast they reach it and how long the effect persists after the drug is cleared, and both parameters follow from the stability and turnover of the ternary complex rather than from binding affinity alone [16]. A degrader that forms a long-lived, cooperative complex tends to degrade quickly and to sustain knockdown, because the target is resynthesised more slowly than it is destroyed; a degrader that forms a transient complex may need continuous high exposure to hold the target down [16,17]. For the medicinal chemist this means that potency, so central to inhibitor design, is an incomplete descriptor of a degrader, and that rate and durability of degradation must be measured directly. It also means that two modalities that look equivalent on a concentration-response curve can behave very differently in a dosing schedule, a consideration that becomes acute in the clinic where intermittent dosing may exploit the durability of a degrader that an inhibitor could not match [10,14].

5.4 The shared liability: off-target neosubstrates and resistance

Both modalities carry selectivity risks that follow directly from their reliance on a small set of E3 ligases. Because CRBN can be induced to recruit many neosubstrates, a CRBN-based degrader of either type can drive unintended degradation of glue-sensitive proteins such as the IKZF factors, SALL4, or GSPT1, an off-target effect that has clinical relevance, including the historical teratogenicity of thalidomide, now understood in part through neosubstrate biology [31]. Resistance is a second shared vulnerability. Because degradation depends on an intact ligase complex, loss-of-function mutations in CRBN or VHL, or in their associated cullin-RING components, can render both PROTACs and glues inactive without any change to the target itself, a mechanism observed when BET-directed PROTACs failed to fully clear tumour cells that subsequently proved to carry ligase-machinery alterations [32]. These liabilities point toward the same solution, discussed in Section 7: expanding the repertoire of exploited E3 ligases.

6. Clinical progress: validation of a modality

The state of clinical translation in 2026 is the clearest evidence that both modalities have crossed from concept to medicine, and it is here that the two lineages show their different maturities. In keeping with this review's scope, what follows describes development stage and regulatory milestone rather than trial outcome data.

6.1 Molecular glues: a long clinical record

Molecular glues, though named late, have the longer clinical history because the IMiDs were established medicines before their mechanism was known. Lenalidomide and pomalidomide are cornerstones of multiple myeloma therapy, and their reclassification as molecular glue degraders retrospectively validated the entire concept of drug-induced neosubstrate degradation [6,7]. That validated scaffold has driven a rational next generation. Purpose-built cereblon modulators, sometimes termed CELMoDs, have been engineered for greater potency and tailored neosubstrate profiles. Iberdomide and mezigdomide, both IKZF1/3-directed CRBN glues designed to overcome resistance to the first-generation IMiDs, have advanced into late-stage development in relapsed or refractory multiple myeloma [33]. Glue-based degraders directed at other neosubstrates and at dual mechanisms, including agents that couple IRAK4 degradation with IMiD-like IKZF degradation, have entered oncology trials, and the discovery pipeline behind them is now deliberate rather than serendipitous [33].

6.2 PROTACs: from proof of concept to first approval

The PROTAC clinical story is more compressed and, in 2026, more dramatic. The first PROTACs entered human testing only in 2019, with androgen receptor and estrogen receptor degraders providing the proof that these large, bRo5 molecules could be dosed orally and act in patients [2,34]. Development then accelerated across kinases, hormone receptors, anti-apoptotic proteins, and epigenetic and transcriptional regulators. It reached previously intractable targets such as STAT3 and yielded tool compounds against MYC and mutant KRAS [2]. First-to-clinic degraders of STAT3 and of BCL6, the latter an orally bioavailable PROTAC, illustrate how the modularity of the design has been used to attack transcription-factor biology that occupancy-driven chemistry could not [33].

The defining milestone arrived on 1 May 2026, when the United States Food and Drug Administration approved vepdegestrant, an orally bioavailable CRBN-recruiting PROTAC that degrades estrogen receptor alpha, for ESR1-mutated, ER-positive, HER2-negative advanced or metastatic breast cancer following prior endocrine therapy [35,36]. Vepdegestrant is the first PROTAC approved in any indication, and its approval, granted ahead of its scheduled review date with a companion diagnostic, converts the modality from a promising platform into a proven one [36,37]. Behind it, two further PROTACs have reached phase III development, an androgen receptor degrader for metastatic castration-resistant prostate cancer and a BTK

degrader for chronic lymphocytic leukaemia, with a broad field of more than forty degraders in clinical testing across oncology and immunology [38,39]. The trajectory from first-in-human to first approval in roughly seven years is unusually rapid for a new therapeutic class and reflects both the intensity of investment and the strength of the underlying mechanism.

Table 2 summarises representative clinical-stage agents of both modalities by target, recruited ligase, and most advanced development stage.

Table 2. Representative clinical-stage degraders of both modalities. Development stage reflects the most advanced status described in the cited public sources.

Agent	Modality	Target	Ligase	Most advanced stage	Indication
Vepdegestrant (ARV-471)	PROTAC	Estrogen receptor alpha	CRBN	Approved (2026)	ESR1-mutated ER+/HER2- breast cancer
BMS-986365 (CC-94676)	PROTAC	Androgen receptor	CRBN	Phase III	Metastatic castration-resistant prostate cancer
BGB-16673	PROTAC	BTK	CRBN	Phase III	Chronic lymphocytic leukaemia
Lenalidomide	Molecular glue	IKZF1/3	CRBN	Approved (established)	Multiple myeloma
Pomalidomide	Molecular glue	IKZF1/3	CRBN	Approved (established)	Multiple myeloma
Iberdomide (CC-220)	Molecular glue	IKZF1/3	CRBN	Phase III	Multiple myeloma
Mezigdomide (CC-92480)	Molecular glue	IKZF1/3	CRBN	Phase III	Relapsed/refractory multiple myeloma

7. Convergence, the E3 ligase bottleneck, and design implications

The framing of glues against PROTACs, useful for exposition, understates how much the two are converging in practice. The convergence runs in both directions. On the mechanistic side, the most successful PROTACs are precisely those that generate strong positive cooperativity, and a highly cooperative PROTAC works by inducing favourable protein-protein contacts between target and ligase in the ternary complex, which is the very mechanism a molecular glue exploits [16,40]. A cooperative PROTAC is, functionally, a bifunctional molecule that has learned to behave like an intramolecular glue, stabilising a protein-protein interface that would not otherwise exist [40]. On the discovery side, the growth of rational glue design, structure-based and screening-driven, is narrowing the historical gap in tractability that made PROTACs the default choice for a predefined target [19,20]. The two modalities are becoming ends of a continuum rather than rival camps, and a mature degrader programme increasingly evaluates both.

The constraint that limits both, and that this review identifies as the central near-term bottleneck, is the E3 ligase repertoire. The human genome encodes more than six hundred E3 ubiquitin ligases, yet only about a dozen have been exploited for degradation, and the overwhelming majority of clinical and preclinical degraders of either modality recruit

just two, CRBN and VHL [41,42]. Roughly two percent of the ligase space has been touched [43]. This concentration has real costs. It funnels the off-target and resistance liabilities of Section 5 through a narrow channel, it forecloses the tissue selectivity that a restricted-expression ligase could provide, and it limits the substrate scope reachable by any single ligase surface [42,44]. The response is an active search for new ligases. Screening efforts have converged on a handful of newly tractable candidates, including DCAF16, DCAF11, and FBXO22, and structure-guided and fragment-based campaigns are opening others [43,45]. Ligases with tissue-restricted expression are of particular interest, because a degrader recruited through an E3 confined to a target tissue could deliver on-target degradation while sparing other tissues, which would convert a general liability into a source of therapeutic selectivity [44,46]. Expanding this toolbox, more than any refinement of linker or scaffold, is what would most enlarge what both modalities can do.

For the practising chemist, the comparison yields a usable heuristic. When a good target ligand already exists, a PROTAC offers the more direct and rational starting point, because the design can proceed modularly from that ligand [11]. When conventional ligand discovery has failed, or when an oral small molecule with clean pharmacokinetics is the priority, a molecular glue, if one can be found, offers a physicochemical profile that PROTAC design must labour to approach [11,19]. Neither choice is permanent, and the increasing ease of moving between them is itself the field's most encouraging development.

8. Discussion

The weight of the evidence supports several conclusions and marks clearly where the evidence is still thin. First, both modalities are now validated, glues by a long clinical record extending from the IMiDs to purpose-built cereblon modulators, and PROTACs by the 2026 approval of the first agent of their class [7,36]. The question of whether induced-proximity degradation can yield medicines has been answered affirmatively. Second, the choice between the modalities is best understood as a choice of starting problem rather than a judgement of superiority. The PROTAC's modular, rational assembly and its access to targets that resist glue chemistry are real advantages, and so are the glue's small size, oral drug-likeness, and structurally programmable selectivity [5,9,11]. Third, the mechanistic distinction between them is softening. Cooperativity research shows that the best PROTACs succeed by inducing the same kind of protein-protein interface that defines a glue, and rational glue discovery is closing the tractability gap that once separated the approaches [16,19,40].

Where the evidence remains incomplete, three areas stand out. The determinants of ternary complex cooperativity, though increasingly well characterised for individual systems, are still difficult to predict de novo, which keeps degrader optimisation partly empirical despite advances in structural modelling and buried-

surface-area analysis [16]. The physicochemical rules for oral bRo5 degraders, while sharpening around descriptors such as solvent-exposed hydrogen bond donors and molecular chameleonicity, do not yet constitute a predictive rule set equivalent to the rule of five, so oral PROTAC design remains an expert craft [24,26]. And the narrowness of the E3 ligase repertoire, arguably the single greatest limitation on the whole field, is only beginning to be addressed, with newly tractable ligases identified but few yet advanced toward the clinic [43,44]. Progress on these three fronts, predictive cooperativity, predictive oral drug-likeness, and an expanded ligase toolbox, would do more to enlarge targeted protein degradation than any further proliferation of degraders against already-validated targets.

A final observation concerns strategy. The rapid clinical ascent of PROTACs and the deep clinical roots of glues have created a moment in which both modalities are simultaneously credible, well-resourced, and technically maturing. The most productive posture for the field is not to declare a winner but to treat the two as a coordinated arsenal, selecting between them, and increasingly hybridising their logic, according to the target and the desired drug profile. The porousness of the boundary between them is not a conceptual untidiness to be resolved; it is the practical space in which the next generation of degraders will be designed.

9. Conclusion

Molecular glue degraders and heterobifunctional PROTACs pursue the same therapeutic aim, the catalytic elimination of a disease-driving protein through the ubiquitin-proteasome system, by opposite chemical means. PROTACs build induced proximity from two binding events and a linker, gaining modularity and broad target access at the cost of size, beyond-rule-of-five properties, and the hook effect. Molecular glues induce a single new interface from a small monovalent molecule, gaining oral drug-likeness and structurally encoded selectivity at the cost of discovery difficulty. Their selectivity often exceeds that of their warheads, and in the case of glues it can be tuned to single-residue precision. In 2026 both stand clinically validated, glues through a lineage reaching back to the IMiDs and forward to rationally designed cereblon modulators, and PROTACs through the first regulatory approval of their class. The evidence favours regarding them not as competitors but as complementary and increasingly convergent tools, and it identifies the small number of exploited E3 ligases as the constraint whose loosening would most expand what either can achieve. The decisive advances of the coming decade are likely to come less from new degraders against familiar targets than from predictive models of ternary complex cooperativity and oral drug-likeness, and from an enlarged repertoire of ubiquitin ligases through which proximity can be induced.

Conflicts of interest

The author declares no conflict of interest.

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