



Induced Proximity Beyond PROTACs: Computational Discovery of Molecular Glues, Degradation Mechanisms, Ternary Complexes, and Emerging Therapeutic Modalities

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ABSTRACT

Induced proximity has emerged as a transformative strategy in drug discovery, extending far beyond the classical PROTAC paradigm. This review explores computational approaches for the discovery of molecular glues, elucidation of degradation mechanisms, prediction and modeling of ternary complexes, and the development of emerging therapeutic modalities. Molecular glues stabilize protein–protein interactions without the need for a linker, offering new opportunities to degrade previously undruggable targets. Computational methods, including molecular dynamics simulations, docking, machine learning, and artificial intelligence-based platforms, have accelerated the identification of novel glues and the rational design of degraders. Understanding the structural and dynamic features of ternary complexes remains a critical challenge, as cooperativity and interface geometry dictate degradation efficiency and selectivity. Recent advances in cryo-electron microscopy, AlphaFold-based modeling, and free energy calculations have improved the prediction of ternary complex formation. Furthermore, emerging modalities such as lysosome-targeting chimeras, autophagy-based degraders, and antibody-based proximity inducers are expanding the therapeutic landscape. This review highlights integrative computational workflows that bridge chemistry, structural biology, and pharmacology, enabling the discovery of next-generation proximity-inducing agents with improved potency, selectivity, and drug-like properties. The convergence of these technologies promises to reshape the future of targeted protein degradation and induced proximity therapeutics.

Key Words: Induced proximity, Molecular glues, Ternary complexes, Targeted protein degradation, Computational drug discovery, Emerging therapeutic modalities

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INTRODUCTION

Targeted protein degradation established that pharmacology can be generated not only by occupying a functional site but also by recruiting a protein into a new molecular relationship that changes its fate [1]. This principle is broader than proteasomal destruction: chemically induced proximity can redirect interaction networks, enzymatic activities, localization, or protein

stability, depending on the partners and cellular machinery brought together [2]. The resulting drug-discovery problem is therefore intrinsically multicomponent. In a canonical degrader, ligand affinity for a target and an E3 ligase is only part of the mechanism; the induced ternary complex can create additional protein–protein contacts whose cooperativity and geometry alter selectivity, as demonstrated structurally for VHL-recruiting degraders

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[3]. Molecular glues sharpen this conceptual shift because a comparatively small ligand can stabilize or create a protein interface that was absent, transient, or insufficiently populated without the compound [4]. These observations motivate a scoping review centered on what computational methods must represent when pharmacological activity emerges from induced molecular relationships rather than from one ligand–one target binding event. The central question is not whether proximity is universally advantageous, but which structural, chemical, contextual, and evidentiary conditions make a proposed proximity mechanism plausible and experimentally testable. This distinction matters computationally because the relevant object is no longer a single ligand–protein complex: candidate partners, linker or glue chemistry, induced interfaces, conformational states, cellular availability, and downstream machinery can each become limiting. The review consequently treats “proximity” as a mechanistic hypothesis that must be decomposed into testable component relationships rather than as an explanatory label applied after a phenotype has been observed.

Review objectives and questions

This review maps how induced-proximity mechanisms are being discovered, modeled, and validated across molecular glues, bifunctional degraders, noncanonical degradation systems, and emerging proximity-driven modalities. Its first objective is to distinguish the mechanistic variables that are directly supported by structural, biochemical, cellular, proteomic, or computational evidence from variables that remain inferred. The second is to examine how ternary-complex geometry, cooperativity, protein–protein interface remodeling, ligase choice, target accessibility, and conformational dynamics are represented computationally. The third is to identify how molecular-glue discovery has moved from retrospective explanation toward prospective screening, interactome profiling, structure-guided design, and machine-learning-assisted prioritization. The fourth is to assess whether current datasets and benchmarks adequately encode multicomponent biology, negative examples, assay context, and mechanistic validation. Finally, the review asks what evidence distinguishes an induced-proximity mechanism from alternatives such as binary binding, downstream degradation, correlated proteomic change, or structurally plausible but nonproductive association. The synthesis is deliberately evidential rather than effectiveness-oriented: it maps what has been demonstrated, what can be computed, and where the connection between computation and pharmacological consequence remains conditional. Across these questions, particular attention is given to hard cases in which a

plausible ternary structure does not imply activity, a degradation phenotype does not uniquely identify the responsible interface, or an experimentally discovered glue mechanism cannot yet be generalized into a prospective design rule.

Protocol and prisma-scr reporting framework

The review was designed as a scoping review and reported using PRISMA-ScR-compatible principles for transparent eligibility, evidence selection, charting, and synthesis [5]. Searches were completed on 11 August 2026 and were structured to capture induced-proximity mechanisms, molecular glues, targeted degradation, ternary-complex modeling, cooperativity, interface remodeling, ligase and target discovery, computational screening, generative design, machine learning, data resources, and emerging non-degradative modalities. The protocol did not seek to estimate a pooled treatment effect, compare clinical effectiveness, or perform a formal meta-analysis. Instead, eligible studies were charted according to the mechanistic and computational questions needed to reconstruct how proximity-based pharmacology is represented and validated. A finite screening ledger was maintained from candidate identification through de-duplication, title/abstract screening, full-text assessment, exclusion, and final inclusion. Because unrestricted web and publisher searches do not provide reproducible database-native hit counts comparable with direct exports from bibliographic databases, only records that entered the verified review ledger were used in the selection accounting. This preserves auditable arithmetic without implying exhaustive capture of every potentially relevant publication. The final synthesis therefore reports the reviewed evidence base transparently while acknowledging that it is a structured map of eligible literature rather than a claim of complete census coverage. PRISMA-ScR was used for reporting transparency rather than as a surrogate for methodological quality: study designs were retained according to their relevance to the mapped questions, and interpretation was bounded by the type of evidence each design could actually provide.

Eligibility criteria

Articles were eligible when they were peer-reviewed journal publications from 2017–2026, carried a verifiable DOI, appeared in a journal with Q1 status in a relevant subject category or latest verifiable completed ranking, and directly informed at least one review domain. Eligible contributions included primary structural, biochemical, cellular, chemoproteomic, medicinal-chemistry, computational, machine-learning, database, and mechanistic studies, together with methodologically necessary reviews and reporting guidance. Sources were

excluded when they were outside the date range, non-journal or non-peer-reviewed items, duplicate versions, lacked DOI verification, could not satisfy the journal-quartile constraint, or were only tangentially related. Relevance required an identifiable role in a manuscript claim, methodological decision, mechanism, boundary condition, validation requirement, or evidence gap; topical mention alone was insufficient. Primary studies were favored for direct mechanistic or computational claims; reviews were retained for necessary field-level scope or classification. Journal quartile was an eligibility constraint, not evidence of individual-study validity.

Information sources and search strategy

Evidence was identified through PubMed/MEDLINE, targeted searching of publisher and journal platforms, backward and forward citation chaining, and DOI-level verification. Search blocks combined terms for induced proximity, chemically induced proximity, PROTACs, targeted protein degradation, molecular glues, ternary complexes, cooperativity, E3 ligases, protein–protein interfaces, docking, molecular dynamics, ensemble modeling, machine learning, databases, negative examples, DUBTACs, phosphorylation-inducing chimeras, RIPTACs, extracellular degradation, and related synonyms. Searches were broadened when a mechanistic or computational domain was underrepresented and narrowed when retrieval became dominated by adjacent pharmacology. Selection emphasized evidence fit over recency alone, while retaining older studies when they provided indispensable structural, methodological, or mechanistic foundations that newer papers did not replace. Search refinement also used opposing and boundary terms—such as nonproductive complex, uncertainty, negative examples, selectivity, validation, and alternative mechanism—to reduce a discovery-only bias and to capture literature useful for interpreting failure rather than only successful proximity systems.

Evidence selection

Candidate records were consolidated by DOI and publication identity before screening. Title and abstract screening evaluated whether each article could contribute to a defined review question concerning mechanism, structural organization, computation, discovery, validation, benchmarking, or modality scope. Full texts were then assessed against the eligibility criteria and coded for the exact claim they could support. Redundant papers were not retained merely because they addressed a fashionable target or method; where several articles supported the same narrow point, preference was given to the source with the strongest direct evidence or the clearest unique role in the planned synthesis. Full-text exclusions

were logged by reason, including evidentiary redundancy and lack of a unique claim after final domain coding. The resulting selection process was intended to maximize interpretability of the evidence map rather than publication volume. No study was excluded because its findings complicated the emerging synthesis.

Data charting and coding

Each included article was charted using a structured extraction scheme covering study purpose, article type, chemical or material class, biological setting, data source, target or assay context, molecular representation, computational or analytical method, comparator, validation design, mechanistic evidence, pharmacological outcome, level of analysis, reported limitations, uncertainty, and transferability boundary. Additional review-specific codes captured induced-proximity modality, ligase or recruiter class, target relationship, ternary-complex logic, interface-remodeling mechanism, computational task, evidence type, and benchmark relevance. Missing information was recorded as not reported or not applicable rather than inferred. For each source, the charting process also specified an exact claim permitted by the evidence and a corresponding claim that would exceed it. This constraint was used to prevent predicted structures, screening associations, degradation phenotypes, or curated database entries from being treated as mechanistic proof without supporting experiments. Coding also distinguished direct evidence from review-level interpretation.

Mapping and synthesis approach

The synthesis used descriptive and relational mapping rather than pooled quantitative analysis. Evidence was first organized by modality and biological consequence, then cross-mapped against the computational problem being solved: partner identification, ternary-complex generation, conformational sampling, cooperativity estimation, interface characterization, molecular-glue discovery, degrader design, activity prediction, or data curation. A second layer classified the evidentiary status of each claim as structural, biochemical, cellular, proteomic, computational, database-derived, or review-level. The review then compared where these layers converge and where they remain disconnected. In particular, structural plausibility was kept separate from productive ubiquitination or functional consequence; computational ranking was separated from experimental validation; and observed degradation or abundance change was not assumed to reveal the responsible proximity mechanism. Original integration introduced by this review is therefore explicitly interpretive. The proposed organizing principle is that induced-proximity computation should be read as a

sequence of linked but non-equivalent inference problems: whether candidate partners can encounter, whether a ligand can stabilize a productive interface with suitable geometry and energetics, and whether that induced state produces the intended biological consequence in the relevant context. Later sections use this structure to map molecular glues, degrader mechanisms, multicomponent models, validation requirements, and benchmarking gaps without converting correlation or computational plausibility into causal certainty. The three inference problems are not assumed to be sequential in practice: discovery may begin from phenotype, structure, chemistry, or interactomics. Their separation is analytical, identifying where one component is directly resolved while another remains uncertain, including non-degradative systems whose consequence is stabilization, phosphorylation, sequestration, relocalization, or extracellular handling.

Evidence-selection results

The verified ledger contained 52 candidate records. Two duplicate DOI or publication-version records were removed, leaving 50 unique records for title and abstract screening. Ten records were excluded, and 40 full texts were sought and assessed; none was unavailable. Six full-text records were excluded: two computational ternary-complex papers were redundant after the final benchmark, dynamics, and ensemble set was established; three molecular-glue studies added no unique role after domain coding; and one secondary structural/computational overview contributed no distinct claim. Thirty-four studies entered the final evidence map. Designs spanned structural

biology, medicinal chemistry, cell biology, proteomics, computation, machine learning, databases, and methodological synthesis. Counts describe the finite verified review ledger rather than unrestricted database-native search yields.

Scope of induced-proximity modalities

The literature supports defining induced proximity by chemically created or stabilized molecular relationships rather than one downstream outcome. Reviews of proximity pharmacology and molecular glues show that bifunctional and monovalent agents can alter interactions through distinct architectures [2, 4, 6]. Intramolecular bivalent glues demonstrate that the boundary between “glue” and “bifunctional degrader” can be mechanistically porous [7]. RIPTACs generate conditional functional consequences without canonical target-to-E3 degradation [8], whereas DUBTACs recruit deubiquitinase activity to stabilize proteins [9]. PHICS compounds redirect kinase proximity to induce phosphorylation [10], and cytokine-receptor-targeting chimeras extend degradation into extracellular space [11]. The review therefore uses a consequence-oriented scope: degradation, stabilization, signaling chemistry, sequestration, and extracellular handling are distinct outputs rather than interchangeable manifestations of one mechanism.

Figure 1 makes the review boundary auditable by showing how the finite ledger moved from identification through de-duplication, screening, full-text assessment, and final inclusion, with exclusions retained as explicit side branches.

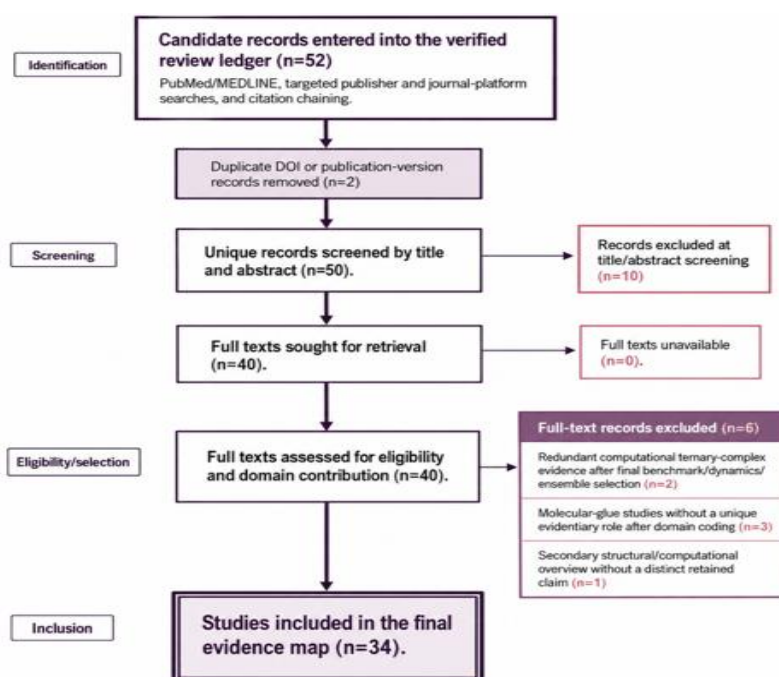


Figure 1. Auditable selection flow for the induced-proximity scoping review

Table 1 organizes how this scope was translated into review-selection categories while keeping distinct biological consequences analytically separate

Table 1. Review-selection map for induced-proximity modality evidence

Evidence stratum	Included mechanistic focus	Selection value	Principal boundary
Degrader-centered	E3 recruitment, ternary recognition, ubiquitination	Establishes canonical proximity logic	Degradation does not define all modalities
Molecular-glue	Ligand-created or stabilized protein interfaces	Tests monovalent interface remodeling	Glue behavior is system-dependent
Stabilization	Deubiquitinase recruitment and increased target persistence	Captures reversed abundance control	Stabilization is not degradation failure
Signaling chemistry	Proximity-driven phosphorylation or related chemistry	Extends proximity to catalytic rewiring	Modification requires pathway-specific validation
Conditional function	Sequestration or state-dependent functional proximity	Captures noncanonical pharmacology	Functional readout may not reveal structure
Extracellular	Receptor-mediated handling of extracellular proteins	Extends compartmental scope	Cellular uptake and receptor context constrain transfer

From bifunctional degraders to molecular glues

Bifunctional degraders provide an explicit bridge between target and recruiter, whereas molecular glues often create or strengthen an interface without a long linker. Yet the distinction is not simply molecular size. Cereblon studies showed that ligand-induced binding plasticity can determine which neosubstrate surfaces become compatible with the ligase [12]. Computationally, bifunctional systems specify two binding events and ask whether a productive higher-order arrangement can form, whereas glue discovery may begin without a known second partner or interface. This shifts emphasis toward surface complementarity, ligand-induced interface emergence, proteomic partner discovery, and context-sensitive recognition. Molecular glues are therefore not treated here as merely “linkerless PROTACs.”

Structural logic of ternary complex formation

Ternary-complex structure is not adequately represented by asking whether three components can be docked into one acceptable pose. Experimental ensembles, prediction benchmarking, and dynamic encounter-complex modeling show that conformational states and method dependence matter [13-15]. A predicted complex can be plausible yet fail to reproduce the ensemble governing residence, ubiquitination geometry, or function. Productive modeling should distinguish binary affinity, ternary compatibility, interface contacts, linker strain, conformational entropy, and accessibility of relevant functional surfaces. A single structural score may hide compensating effects. Static structures remain valuable constraints on ensemble hypotheses, but they do not prove that one captured conformation uniquely explains pharmacology.

Cooperativity as a computable property

Cooperativity describes how formation of one interaction changes the favorability of completing the ternary complex. Coarse-grained alchemical approaches show that it can be modeled through free-energy relationships rather than inferred from degradation potency [16]. Its boundary is equally important: cooperativity belongs to a defined molecular system and state, not to efficacy in general. Positive cooperativity can stabilize a ternary complex, while kinetics, concentrations, catalytic turnover, or geometry may still dominate biological outcome. Computational studies should therefore state what cooperativity is estimated, under which assumptions, and against which experimental observable.

Protein-protein interface remodeling

Molecular-glue ternary structures reveal classifiable protein-protein interface patterns [17]. These interfaces are not passive consequences of ligand binding: a compound may fill cavities, reshape complementarity, expose recognition motifs, or stabilize weak contacts. Prospective glue discovery therefore requires protein-surface representations extending beyond residues that contact the ligand to ligand-mediated changes in protein-protein geometry, electrostatics, hydration, and conformational accessibility. Because known structures are selected toward successful and tractable systems, interface descriptors should remain hypotheses about recruitability rather than universal design rules.

Computational discovery of molecular glues

Prospective molecular-glue discovery spans phenotypic screening, chemical profiling, structure-guided design,

interactomics, and computational prioritization [18]. Rational chemical design shows that defined ligand systems can be redirected toward glue-degrader behavior [19], while scalable profiling can connect response to E3-dependent degradation [20]. CK1 α studies illustrate medicinal-chemistry optimization within a defined glue series [21]. Cross-linking proteomics expands observable E3 interactions [22], and direct-to-biology screening can begin from complex reaction mixtures [23]. CRBN interactome mapping exposes additional candidate neosubstrates [24]. Structural cyclin-K studies provide system-specific design principles [25], while G3BP2 degradation demonstrates molecular-surface mimicry as another recruitment logic [26]. Collectively, these studies favor computational workflows integrating chemistry, protein surfaces, partner identity, and orthogonal biology rather than predicting “glueability” from ligand structure alone.

Modeling degrader productive geometry

Computational degrader design increasingly links chemical generation with three-dimensional ternary organization. PROTACable integrates 3D modeling and deep learning to automate elements of de novo design [27], whereas SILCS-xTAC represents ternary complexes as ensembles [28]. These approaches address candidate construction and conformational plausibility, but neither makes productive geometry directly observable. Ranking structural compatibility can omit ubiquitination kinetics, cellular concentrations, proteasome engagement, or target resynthesis. “Productive geometry” is therefore used here as a proposed hypothesis class: a configuration or ensemble whose features make the intended proximity consequence plausible and testable, not one whose score establishes activity.

Table 2 compares the study characteristics defining what current computational approaches can and cannot establish about productive proximity geometry.

Table 2. Study characteristics relevant to computational inference of productive proximity geometry

Evidence class	Primary object	Computational role	Validation anchor	Residual uncertainty
Structure benchmark	Known ternary complexes	Compare pose-generation methods	Experimental structures	Transfer to unseen systems
Dynamic modeling	Encounter-state ensembles	Sample alternative conformations	Structural and trajectory consistency	Which states are productive
Free-energy modeling	Ternary energetics	Estimate cooperative contributions	Biophysical trends	Cellular consequence
Interface analysis	Protein–protein surfaces	Identify contact patterns	Resolved glue complexes	Generality beyond known structures
Integrated design	Degrader chemistry plus 3D context	Generate or prioritize candidates	Computational and experimental follow-up	Prospective domain transfer
Ensemble modeling	Multiple plausible complexes	Preserve heterogeneity	Known ternary structures	Ubiquitination competence

Beyond degradation: stabilization, relocalization, and proximity-driven chemistry

The wider landscape shows why degradation should not be the default endpoint of proximity models. RIPTACs generate state-dependent functional effects [8], DUBTACs recruit deubiquitination to increase stability [9], and PHICS systems redirect phosphorylation [10]. Extracellular chimeras extend proximity-based handling beyond intracellular ubiquitin–proteasome biology [11]. The computational question becomes “what consequence follows when these partners are forced together?” rather than simply “will this target degrade?” Outcome-specific representations may require recruiter activity, compartment, accessibility, competing substrates, and downstream chemistry. Evidence remains modality-specific, so no single architecture can yet be assumed to predict these outcomes.

Representing multicomponent systems for machine learning

DeepPROTACs shows that machine learning can learn degradation-related labels from curated PROTAC data [29]. The broader representational challenge is that induced proximity depends on compound chemistry, target identity, recruited partner, higher-order structure, and assay or cellular context. A ligand-only embedding can therefore absorb correlations caused by recurrent target–ligase pairs or experimental practice. This review proposes multicomponent representations pairing molecular features with target and recruiter descriptors, structural or ensemble information when available, and explicit context metadata. Extrapolation to new ligases, interfaces, modalities, or compartments requires separate validation rather than ordinary random splits.

Datasets, benchmarks, and the scarcity of negative examples

PROTAC-DB 3.0 aggregates PROTAC structures with expanded pharmacokinetic annotation [30], while MGTbind curates molecular-glue compounds and ternary interactions [31]. These resources enable systematic modeling, but a database is not automatically a benchmark. Published records combine heterogeneous assays, targets, ligases, concentrations, time points, and endpoints, and successful compounds are often characterized more deeply than failed hypotheses. “Negative” may mean no degradation in one assay, failed ternary binding, an inactive analog, failed recruitment, or an untested mechanism. Benchmarks should preserve these distinctions and separately evaluate chemical novelty, unseen target–ligase pairs, unseen interfaces, and cross-assay transfer.

A central benchmarking problem is label provenance. Activity labels derived from heterogeneous reports can mix potency, maximal degradation, target abundance, assay duration, and author-defined thresholds. For glues, absence of a reported recruited partner may reflect incomplete mechanistic work rather than true partner independence. Benchmark construction should therefore retain assay provenance and distinguish measured negatives from missing evidence. Without that distinction, apparently large training sets can encode uncertainty as if it were biological ground truth.

Experimental evidence required to establish an induced-proximity mechanism

Mechanistic edge cases show why phenotype alone is insufficient. A degron-mimicking glue can drive CRBN homodimerization and degradation [32]. A DCAF16-recruiting glue can selectively degrade BRD9 through a distinct ligase mechanism [33], while TRIM21-directed chemistry can be elaborated into TRIMTACs acting on protein aggregates [34]. These examples broaden the topologies a mechanistic study must test. This review therefore proposes an evidence hierarchy in which target engagement, higher-order complex formation, interface dependence, functional consequence, perturbational causality, and context dependence are resolved with orthogonal assays when feasible. No layer automatically substitutes for the next.

Mechanistic confirmation should also distinguish necessity from sufficiency. Loss of the recruiter, mutation of a critical interface, competition with a binding ligand, or rescue by pathway perturbation can show that a component is required, but such experiments do not necessarily establish that the observed complex alone explains the phenotype. Conversely, structural observation of a ternary complex demonstrates physical organization without proving that the same state dominates in cells. The strongest evidence therefore triangulates physical interaction, perturbational dependence, and functional consequence while preserving plausible alternative mechanisms.

Table 3 maps the proposed evidence layers needed to distinguish induced-proximity mechanism from association or downstream phenotype.

Table 3. Proposed evidence map for establishing an induced-proximity mechanism

Evidence layer	Question resolved	Suitable evidence	Remaining boundary
Partner engagement	Do intended partners bind or encounter?	Binary binding or engagement assays	Does not prove ternary formation
Higher-order complex	Is compound-dependent proximity formed?	Biophysical, structural, proximity assays	Formation may be nonproductive
Interface dependence	Which contacts support the complex?	Structure, mutagenesis, competition	Static interface may miss dynamics
Functional consequence	What changes after proximity?	Degradation, stabilization, modification, localization, phenotype	Readout may be downstream
Perturbational causality	Is recruited machinery required?	Recruiter loss, rescue, resistant mutants	Context-specific alternatives may remain
Transferability	Does mechanism persist across contexts?	Orthogonal models and prospective testing	Does not establish universal applicability

Underexplored modalities and computational gaps

The field remains uneven across recruiters, compartments, mechanisms, and data quality. Extracellular degradation, noncanonical ligases, self-directed ligase mechanisms, stabilization, phosphorylation, and aggregate-directed architectures expand the search space faster than standardized representations are developing. Ligase–target pairing remains difficult because recruitability depends on

surface geometry, localization, expression, competing interactions, and available chemistry. Negative examples are sparse and inconsistent, limiting learning about failure. Priorities therefore include prospective benchmarks with explicit failure labels, interface-aware ensemble models, cross-ligase and cross-target evaluation, and datasets linking structural hypotheses to orthogonal mechanistic

experiments. These are research needs, not evidence that present methods lack utility within validated domains.

RESULTS AND DISCUSSION

Across the evidence, induced proximity is best interpreted as a family of conditional multicomponent mechanisms rather than one technology class. The shared computational challenge is to connect partner availability, induced-interface formation, and biological consequence without assuming success at one level proves the next. Glues make this visible because the relevant partner or interface may emerge only after phenotypic or proteomic discovery, whereas bifunctional degraders provide predefined binding handles but retain conformational and kinetic uncertainty. Structural and computational methods can generate poses, ensembles, energetic hypotheses, interfaces, or candidate molecules; experiments establish whether those hypotheses correspond to mechanism.

The principal synthesis proposed here is an evidence-bounded “encounter–interface–consequence” view. It is not a causal law and does not require discovery to proceed in that order. Instead, it keeps three questions separately auditable. This explains why convincing ternary docking can coexist with poor cellular activity, why degradation may precede identification of its recruiter, and why non-degradative modalities cannot be evaluated using degradation labels alone. The practical implication is to replace searches for one universal proximity score with models whose outputs correspond to explicit mechanistic hypotheses and validated domains.

This separation also changes how failure should be interpreted. A candidate may fail because partners do not colocalize, an interface is unstable, a ternary state forms but is geometrically unproductive, downstream machinery is limiting, or the assay context suppresses the intended consequence. These are scientifically different negatives. Treating them as one class obscures the mechanistic information most useful for model improvement and medicinal-chemistry iteration. Accordingly, computational progress should be judged not only by aggregate predictive performance but also by whether a model identifies the biological reason a proximity hypothesis succeeds or fails under a defined experimental context.

Review limitations

This review maps a rapidly changing literature rather than an exhaustive census. The ledger used PubMed/MEDLINE, targeted publisher and journal-platform searches, and citation chaining; source-specific unrestricted search yields were not reconstructed. Eligibility restrictions may exclude informative work outside the defined publication boundaries. Structural,

biochemical, cellular, proteomic, computational, and database studies also answer different questions and report different endpoints, limiting direct comparison. No effect estimates were pooled. Finally, the encounter–interface–consequence framework and proposed evidence hierarchy are integrative tools derived from the mapped literature; their usefulness requires testing against prospective datasets and mechanistically characterized failures.

CONCLUSION

Induced-proximity discovery now extends beyond canonical PROTAC degradation. Molecular glues, noncanonical degraders, stabilization systems, proximity-driven chemistry, extracellular approaches, and emerging recruiter architectures show that pharmacological consequence depends on multicomponent relationships whose formation and function must be demonstrated rather than assumed. Computational methods can identify partners, generate structures, sample ensembles, estimate cooperativity, prioritize chemistry, and organize data, but prediction and mechanism remain distinct evidentiary layers. The proposed encounter–interface–consequence framework preserves that distinction. Progress will depend on context-aware models, explicit negative evidence, rigorous benchmarks, and orthogonal experiments connecting computational hypotheses to productive biology.

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