



Artificial Intelligence at Cryo-EM–Medicinal Chemistry Interface: Structural Resolution in Drug Discovery

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ABSTRACT

Cryo-electron microscopy (cryo-EM) is increasingly moving from a structural-rescue technique toward a source of medicinal-chemistry information, while artificial intelligence (AI) is changing how density maps are interpreted, atomic models are built, conformational states are reconstructed, and ligand hypotheses are generated. The critical question is therefore no longer whether higher-resolution cryo-EM can support drug discovery, but which chemically consequential inferences become defensible at each evidential level.

A bounded integrative review was conducted across peer-reviewed Q1 literature published from 2017 through 2026. Search and citation-chaining procedures identified 56 records; after duplicate removal and screening, 44 full texts were assessed and 36 studies were included. Evidence was extracted at claim level across reconstruction, validation, ligand placement, conformational heterogeneity, structure prediction, structure-guided medicinal chemistry, and simulation. The literature shows rapid improvement in AI-assisted map-to-model workflows and a growing ability to obtain ligand-relevant structures for difficult targets. However, global resolution, local resolvability, atomic-model correctness, ligand identity, pose confidence, pocket-state assignment, and pharmacological meaning remain distinct inferential layers. The review therefore proposes an evidence-preserving interpretation in which increasing structural resolution expands the set of tractable medicinal-chemistry questions without automatically increasing confidence in every downstream chemical claim. AI and cryo-EM are becoming mutually reinforcing components of modern structure-enabled discovery, but their value depends on local validation, explicit uncertainty, experimentally grounded state interpretation, and orthogonal testing. The principal limitation is that prospective, multi-target validation of fully integrated workflows remains limited.

Key Words: *Cryo-electron microscopy, Artificial intelligence, Medicinal chemistry, Ligand placement, Conformational heterogeneity, Structure-based drug design*

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INTRODUCTION

Cryo-EM has shifted from being mainly a route to structures that were difficult to obtain by crystallography toward a platform that can contribute directly to drug-discovery decisions, particularly for large complexes, membrane proteins, and conformationally heterogeneous

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targets. Its importance is nevertheless conditional: sample preparation, particle behavior, local resolution, model interpretation, and throughput still constrain what can be inferred from a reconstruction [1]. The consequence for medicinal chemistry is not a simple replacement of one structural technology by another, but a change in the range

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of experimentally accessible starting states from which chemical hypotheses can be generated.

Early discussion of fragment-based discovery already anticipated this change by showing that cryo-EM could enter workflows traditionally dominated by crystallographic fragment structures, provided that occupancy and local ligand density were sufficiently informative [2]. More recent examples sharpen the point. High-resolution analysis of human CDK-activating kinase produced structural detail suitable for structure-based design in a defined kinase complex [3], while higher-throughput cryo-EM of TRPML1 enabled comparative interpretation across multiple modulators of a lysosomal membrane channel [4]. These studies do not establish that cryo-EM is uniformly chemically actionable. They instead show that resolution and throughput are beginning to alter when medicinal chemists can obtain experimentally grounded structural hypotheses.

The central argument of this review is therefore deliberately narrower than a technology-progress narrative. Increasing resolution changes the medicinal-chemistry interface only when added image information survives model building, local validation, ligand interpretation, and state assignment. AI can accelerate several of these steps, but it can also make structurally plausible outputs appear more certain than the experimental evidence warrants. The relevant unit of progress is thus not resolution alone, but the conversion of experimental density into bounded chemical information.

Review purpose and questions

This integrative review examines how AI and improving cryo-EM resolution jointly change the information available for structure-enabled medicinal chemistry. The primary purpose is to connect evidence that is often discussed separately: automated reconstruction and atomic model building, local map–model validation, ligand identification and pose refinement, continuous conformational heterogeneity, structure prediction, structure-guided chemical iteration, and molecular simulation. The review asks where these components genuinely reinforce one another and where combining them risks compounding uncertainty.

Four questions organize the synthesis. First, what additional chemical claims become supportable as cryo-EM maps become more locally informative, and which claims remain underdetermined despite high nominal resolution? Second, how should AI-generated protein models, ligand poses, and conformational representations be conditioned by experimental density rather than treated as parallel sources of truth? Third, when does conformational heterogeneity become useful medicinal-chemistry information rather than an attractive but weakly

validated description of structural variability? Fourth, what evidence is required before a cryo-EM–AI workflow can support iterative design rather than retrospective structural rationalization?

The review's proposed contribution is an evidence-preserving interpretation of this interface. It distinguishes experimental observation, computational reconstruction, chemical interpretation, pharmacological testing, and forward-looking design as connected but non-equivalent layers. This distinction is used throughout to prevent improvement in one layer from being mistaken for validation of the next.

Integrative review methodology

A bounded integrative-review design was used because the relevant evidence spans heterogeneous study types that cannot be reduced meaningfully to a single effect estimate or performance metric. Eligible evidence included methodological papers on cryo-EM reconstruction and model building, validation studies, ligand-modeling methods, conformational-heterogeneity approaches, structure-prediction studies, experimentally grounded medicinal-chemistry examples, and simulation methods bearing directly on interpretation of cryo-EM-derived structures. The objective was analytical integration rather than exhaustive systematic-review coverage.

The review process was structured around claim-level relevance. Candidate papers were screened for whether they could support a specific statement about structural inference, chemical interpretation, uncertainty, validation, target tractability, or design iteration. A paper was not retained merely because it mentioned cryo-EM, AI, docking, molecular dynamics, or drug discovery. This approach allowed computational and experimental evidence to be considered together while preserving differences in what each design can establish and the independence of the evidence it contributes.

Critical interpretation emphasized the chain from experimental signal to medicinal-chemistry use. Map reconstruction, atomic modeling, ligand placement, conformational-state estimation, AI prediction, and energetic simulation were therefore treated as linked but distinct inferential operations. Where the literature supported only feasibility, retrospective benchmarking, or target-specific demonstration, the synthesis was kept at that level rather than converted into a claim of general predictive or translational performance. Methodological novelty was likewise separated from demonstrated chemical actionability.

Eligibility criteria

Articles were eligible when they were peer-reviewed journal publications from 2017–2026, had a verifiable

DOI, were published in journals with Q1 status in a relevant category where public verification was available, and contributed directly to at least one review domain. Eligible contributions had to support a specific claim concerning cryo-EM reconstruction, model building, structural validation, ligand placement or identity, conformational heterogeneity, structure prediction, medicinal-chemistry iteration, difficult-target structural access, or molecular simulation.

Records were excluded when they were outside the date window, lacked an eligible publication type or DOI, duplicated another version, were adjacent to the topic without a direct claim role, or would require extrapolation beyond the studied target, chemical space, resolution regime, benchmark, or validation setting. When several papers supported substantially the same methodological claim, preference was given to the most direct and informative evidence rather than to recency alone.

Information sources and search strategy

Literature discovery was performed on 11 August 2026 using targeted PubMed/MEDLINE searches, publisher and journal pages, DOI landing pages, and backward and forward citation chaining from high-fit methodological and validation papers. Search concepts combined cryo-EM with drug discovery and medicinal chemistry; AI, deep learning, transformers, diffusion models, and automated model building; ligand docking, placement, identification, and validation; local map quality and model error; conformational heterogeneity and continuous states; AlphaFold and complex prediction; membrane proteins, GPCRs, and ion channels; and molecular dynamics or free-energy calculations.

The strategy was intentionally broad across evidence types but bounded by the review questions. It was not designed to estimate publication prevalence or claim exhaustive retrieval. Search expansion stopped when additional records largely duplicated already represented methodological roles or lacked a distinct contribution to the planned synthesis.

Evidence selection and critical appraisal

The discovery process captured 56 records. Four duplicate DOI sightings were removed, leaving 52 unique records for screening. Eight were excluded at title or abstract level because they were primarily upstream, adjacent to the medicinal-chemistry interface, or redundant for the intended claim structure. Forty-four full texts were assessed; eight were excluded after full-text review, leaving 36 studies in the integrative synthesis.

Critical appraisal was matched to the claim rather than collapsed into one quality score. For computational methods, emphasis was placed on benchmark design,

comparator choice, input dependence, local-resolution sensitivity, and transferability. For structural and pharmacological studies, appraisal focused on whether chemical conclusions were directly grounded in the observed structure and whether functional evidence was actually measured. Validation papers were assessed for their ability to reveal local errors or competing interpretations that global metrics might miss.

Data extraction and integrative synthesis

Data were extracted using a structured claim-oriented framework. For each included article, the review recorded study purpose, design, target or molecular setting, cryo-EM or computational modality, principal method, comparator where applicable, validation strategy, main reported finding, relevant uncertainty, authors' stated or evident scope limits, and the exact manuscript claim that the study could support. Reported quantities were retained only when necessary for a specific synthesis statement; missing values, conditions, or study characteristics were not inferred from adjacent evidence.

The synthesis proceeded in layers. The first concerned conversion of experimental density into protein coordinates through manual, hybrid, or AI-assisted model building. The second addressed whether those coordinates were locally reliable enough to support binding-site interpretation. The third separated ligand identity, pose, geometry, solvent, and interaction claims. A fourth layer considered conformational heterogeneity and whether alternative states materially changed pocket interpretation. Structure prediction and generative complex models were then examined as priors or hypothesis generators rather than experimental observations. Finally, direct medicinal-chemistry examples and molecular simulation were used to assess when structural hypotheses can enter iterative design and how they may be tested.

Cross-study synthesis emphasized correspondence without erasing methodological provenance. Experimental map support, learned structural priors, chemical-energy functions, molecular simulations, and pharmacological assays were therefore not treated as interchangeable confirmation simply because they converged on a compatible structural narrative. The source and independence of each evidential contribution remained part of its interpretation.

This layered synthesis is proposed here as an interpretive device rather than an established hierarchy. Its purpose is to prevent evidence from being upgraded merely because multiple computational stages agree. Agreement can increase coherence without necessarily increasing independence of evidence, particularly when methods share structural priors, training data, starting models, candidate structures, or scoring assumptions. Downstream

medicinal-chemistry confidence must therefore remain conditional on the weakest scientifically consequential inference in the chain.

Characteristics of the included literature

The included literature was methodologically diverse but concentrated around a small number of recurring problems. One cluster addressed AI-assisted map interpretation and atomic model building, including deep-learning, transformer, diffusion, and prediction-integrated approaches. A second focused on validation, especially the distinction between global reconstruction quality and local coordinate support. A third concerned ligand placement and identity, where density-aware docking, chemical-energy terms, explicit solvent treatment, and community challenge data exposed the gap between visually plausible fits and chemically defensible models.

A fourth cluster examined conformational heterogeneity through neural latent-variable, deformation, and continuous-state approaches, with a smaller body of evidence directly linking ligand-bound heterogeneity to molecular dynamics. Structure prediction formed another cluster, progressing from accurate protein models toward broader biomolecular interaction and ligand-specific complex hypotheses. The most direct medicinal-chemistry evidence came from target-specific structural programs involving kinases, ion channels, and GPCRs, where structural information was connected to compound comparison, chemical modification, or functional testing. Molecular simulation added a further interpretive layer by testing structural and energetic consistency under explicit modeling assumptions.

The literature was strongly weighted toward recent methodological development, while earlier studies remained necessary because they established foundational model-building, validation, heterogeneity, and structure-prediction concepts on which newer workflows depend. Across these clusters, the recurring limitation was not

simply technical capability but uncertainty over when local structural confidence can legitimately be transferred into a chemical decision.

From density map to chemically actionable protein model

Turning a cryo-EM map into medicinal-chemistry information requires more than tracing a protein backbone. ModelAngelo showed that automated protein identification and model building can recover substantial atomic structure directly from cryo-EM maps [5], while DeepTracer demonstrated fast de novo deep-learning-based protein modeling [6]. CR-I-TASSER extended this direction by combining learned map interpretation with structural assembly [7], and deep-learning-guided automatic assembly has enabled complex modeling from intermediate-resolution maps [8]. Integration of map evidence with structure-prediction information in DeepMainmast further illustrates how experimentally observed density and learned priors can be combined [9], while Cryo2Struct uses transformer and hidden-Markov-model components for de novo atomic modeling [10].

For medicinal chemistry, however, protein-model completeness is an upstream condition rather than a chemical endpoint. A model can provide a pocket scaffold while leaving side-chain rotamers, local geometry, alternate conformations, solvent, and ligand evidence insufficiently resolved. The proposed distinction is therefore between “model built” and “chemically actionable”: the latter requires local map support, defensible coordinates around the binding site, and uncertainty compatible with the chemical decision being attempted.

Figure 1 summarizes this evidence-preserving interpretation: map quality, atomic modeling, ligand inference, conformational state, design, and simulation interact, but no downstream layer inherits certainty automatically from an upstream one.

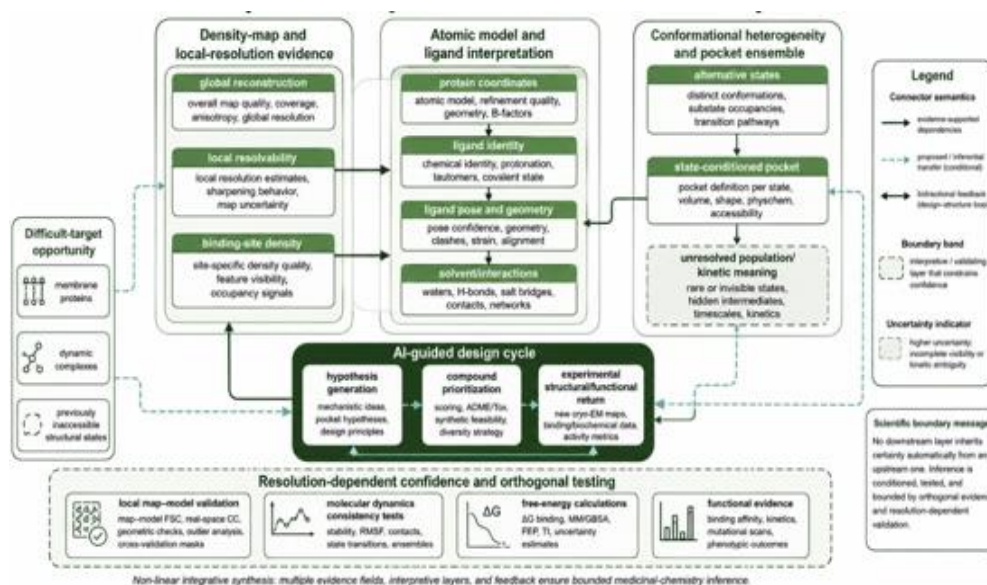


Figure 1. From cryo-EM density to bounded medicinal-chemistry inference

The verified review flow is condensed in **Table 1** to distinguish record handling from scientific synthesis without implying an exhaustive systematic search.

Table 1. Evidence selection and eligibility pathway for the integrative review

Review stage	Records	Decision basis
Records captured	56	Targeted database, journal, DOI-page, and citation-chain discovery
Duplicate DOI sightings removed	4	Duplicate publication identity
Unique records screened	52	Topic, publication, date, and claim-role relevance
Title/abstract exclusions	8	Upstream/adjacent focus or redundant methodological role
Full texts assessed	44	Direct evidence fit and interpretive usefulness
Full-text exclusions	8	Redundant/weaker claim fit, broad adjacent AI/design focus, or superseded ligand-pipeline role
Studies integrated	36	Distinct contribution to the bounded synthesis

What resolution does—and does not—permit

Increasing nominal resolution expands the structural detail potentially available for chemical interpretation, but it does not erase local ambiguity. Cross-modal alignment between maps and protein sequences can reduce assignment uncertainty [11], diffusion-based modeling can extend reconstruction of large complexes [12], and CryoAtom represents a further AI-enabled advance in model building [13]. AlphaFold-conditioned experimental structure determination similarly illustrates how a pretrained structural prior can assist interpretation while the experimental data remain the constraint [14]. Validation evidence sets the boundary. EMDDataResource recommendations show why global resolution cannot substitute for multiple map–model checks [15], and residue-level error detection demonstrates that locally incorrect coordinates can persist within globally plausible models [16]. Q-score provides an atom-level measure of map support, including for small molecules, but does not by itself establish a unique ligand interpretation [17].

Accordingly, nominal resolution, local resolvability, coordinate confidence, and chemical actionability should be treated as separate levels.

AI-assisted map interpretation and atomic model building

AI is most defensible at this interface when it augments reconstruction rather than obscures the provenance of structural information. Integration of DeepTracer with AlphaFold2 illustrates how predicted structure can be brought into model building and refined against cryo-EM evidence [18]. The benefit is faster generation of coherent hypotheses; the risk is that agreement between a prior and an AI-built model may be mistaken for independent experimental confirmation.

Across distinct architectures, automated protein-modeling pipelines combine experimental cryo-EM map evidence with learned structural or sequence priors to construct protein models [5, 9, 12]. The proposed operational rule is therefore to retain map support, prior-derived information, and subsequent validation as separable evidential layers.

Ligand placement under incomplete or ambiguous density
Ligand interpretation is a sharper test of structural actionability because several questions can fail independently. EMERALD combines density and chemical or energetic evaluation for automated ligand structure determination [19]. ChemEM uses cryo-EM information for flexible small-molecule docking [20], whereas GOLEM adds explicit water treatment to cryo-EM-guided docking [21]. The EMDDataResource Ligand Modeling Challenge showed that even near-atomic maps can support competing ligand models and therefore require composite validation rather than visual fit alone [22]. DockEM demonstrates that lower- to medium-resolution density can still constrain docking refinement when combined with physical modeling [23]. Automated small-molecule identification further separates the problem of ligand identity from the problem of obtaining a plausible pose [24], and density-guided molecular-dynamics workflows can refine AI-generated ligand-bound models without making their microstates experimentally observed [25]. Density-aware ligand-placement methods combine local cryo-EM evidence with chemical or physical scoring rather than treating density fit alone as sufficient [20, 21, 23]. For medicinal chemistry, confidence should therefore be reported hierarchically: identity, pose, geometry, solvent, and specific interactions are progressively stronger claims.

Conformational heterogeneity as medicinal chemistry information

Cryo-EM can expose structural variability that a single consensus model suppresses. CryoDRGN reconstructs heterogeneous structural landscapes using neural representations [26], while 3DFlex estimates flexible motion directly from cryo-EM data [27]. DynaMight improves reconstruction by modeling molecular motion [28], and HetSIREN provides another route to heterogeneous reconstruction and disentanglement of conformational states [29]. Continuous-state methods can recover structured conformational variability, but encode motion using different latent representations and assumptions [26, 28, 29]. For medicinal chemistry, these states become informative only when they alter a chemically relevant pocket feature and remain compatible with the underlying

data. A latent coordinate should not be interpreted automatically as a free-energy axis, kinetic pathway, or ligand mechanism.

Pocket definition across cryo-em structural ensembles

The medicinal-chemistry consequence of heterogeneity is that “the binding pocket” may be state-conditioned rather than singular. Comparison of cryo-EM heterogeneity methods with molecular dynamics for ligand-bound TRPV1 demonstrates that the apparent conformational landscape can depend on the method used to reconstruct or sample it [30]. This makes ensemble-aware pocket definition useful but conditional.

The synthesis proposed here is to preserve alternative pocket states when they are supported by density and chemically consequential, rather than forcing them into one optimized coordinate set. Differences in cavity accessibility, side-chain orientation, or local packing can then generate testable chemical hypotheses, while uncertain state populations and transitions remain explicitly unassigned.

AI-guided ligand design from cryo-em structures

Structure prediction expands the hypothesis space available around experimentally derived structures. AlphaFold established highly accurate protein-structure prediction at broad scale [31], and AlphaFold 3 extended prediction to biomolecular interactions that include small molecules [32]. DynamicBind illustrates ligand-specific complex prediction with an equivariant generative approach [33]. These methods can propose conformations or binding hypotheses worth testing, but a predicted complex is not equivalent to cryo-EM evidence of occupancy, a binding measurement, or pharmacological function.

The most defensible integration is therefore asymmetric: prediction can suggest candidate states and poses, whereas cryo-EM can constrain which hypotheses remain compatible with observed density. This preserves the experimental anchor while allowing AI to enlarge the search space.

Figure 2 shows the proposed future-facing workflow in which AI accelerates hypothesis generation, but progression toward medicinal-chemistry decisions requires explicit structural and experimental gates.

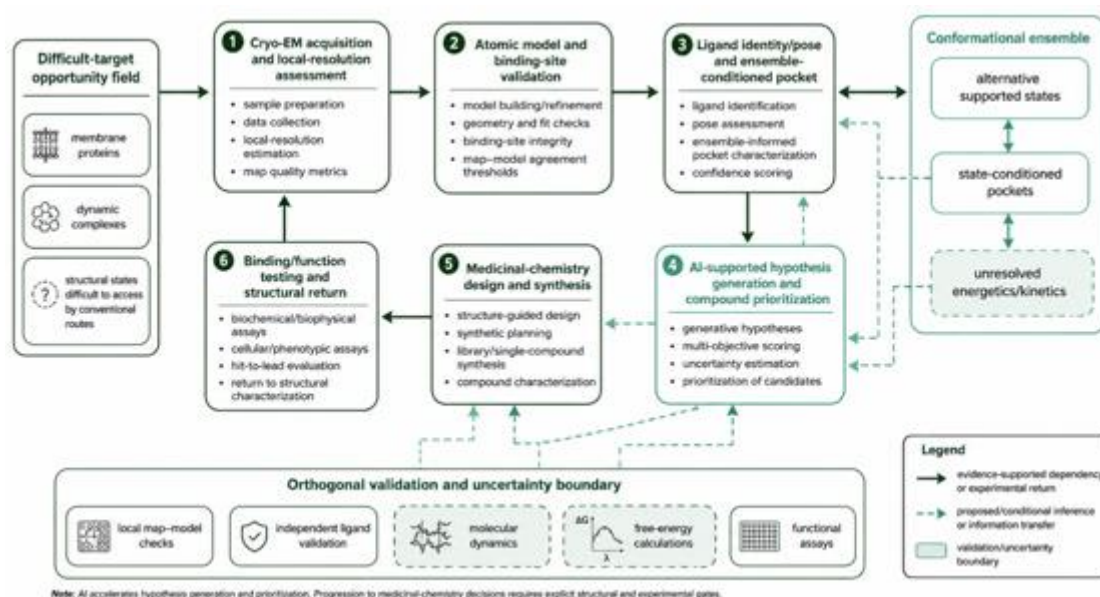


Figure 2. Evidence-gated AI–cryo-EM design cycle for chemically consequential decisions

Table 2 organizes the included evidence domains by the medicinal-chemistry decision each can inform and the boundary that prevents overinterpretation.

Table 2. Evidence domains linking cryo-EM, AI, and medicinal-chemistry decisions

Evidence domain	Principal decision supported	Main boundary
Map-to-model AI	Generate and complete protein hypotheses	Learned prior is not independent map evidence
Local validation	Judge coordinate support near a pocket	Global resolution cannot replace local checks
Ligand modeling	Compare identity and pose hypotheses	Fit does not prove unique identity or interaction
Heterogeneity analysis	Preserve alternative pocket states	Latent states do not establish kinetics or energetics
Structure prediction	Expand candidate complexes and conformations	Prediction does not demonstrate binding or function
Direct design studies	Connect structural hypotheses to chemical modification	Target-specific success does not ensure transferability
MD/free-energy analysis	Test structural and energetic consistency	Simulation cannot retroactively validate uncertain coordinates

Iterative cryo-em–design–synthesis cycles

The strongest evidence for structural actionability comes from cycles in which a structure changes a chemical decision and the resulting compound is experimentally tested. A cryo-EM structure of a small-molecule agonist bound to the delta opioid receptor–Gi complex supported discovery and characterization of a biased compound [34]. In another GPCR system, structure-informed design of allosteric modulators altered G-protein subtype selectivity at NTSR1 [35].

These examples support feasibility of experimentally coupled structure–design iteration in defined systems, not a universal prediction rule. The meaningful closed loop contains structural observation, a chemically explicit intervention, renewed measurement, and functional evaluation; retrospective explanation alone is weaker evidence of design utility.

Membrane proteins and previously difficult drug targets

Membrane proteins illustrate why the interface matters. Higher-throughput structural analysis of TRPML1 showed that cryo-EM can compare multiple modulators within a difficult membrane-protein setting [4], while opioid-receptor and NTSR1 studies connected GPCR structures to chemical and functional experimentation [34, 35]. Cryo-EM therefore increases access to targets and states that can be challenging for conventional structural workflows. Opportunity should not be confused with uniform tractability. Flexibility, compositional heterogeneity, partial ligand occupancy, and state-dependent pockets remain particularly relevant in these systems. Their value for medicinal chemistry depends on whether locally informative structures can be reproduced and tied to orthogonal chemical or functional evidence.

Resolution-dependent sources of false structural confidence

False confidence arises when a high-quality global reconstruction is allowed to license a stronger local

chemical claim. Multi-criterion cryo-EM validation argues against that shortcut [15], while residue-level error detection shows that local coordinate problems can persist inside apparently credible models [16]. Atom-level map support can sharpen this assessment [17], but ligand challenge results still reveal competing interpretations under favorable map conditions [22].

A second source of overconfidence is identity–pose conflation: a density-compatible shape may not uniquely determine which small molecule is present [24]. The practical implication is that uncertainty should propagate forward. Resolution can narrow plausible interpretations, but unresolved protein geometry, ligand identity, occupancy, solvent, or conformational state should remain visible in subsequent design claims.

Integrating cryo-em with molecular dynamics and free-energy methods

Molecular simulation is most useful here as an orthogonal computational test rather than as a repair mechanism that silently upgrades uncertain experimental coordinates. Free-energy calculations can support drug-discovery decisions when sampling, force fields, system setup, and validation are adequately controlled [36]. Comparison of cryo-EM heterogeneity with molecular dynamics in ligand-bound TRPV1 further shows the value of interrogating structural variability across methods [30]. Explicit-water docking likewise illustrates how physical modeling can alter ligand interpretation [21], while ligand-conditioned generative models offer candidate complexes that may seed additional computational testing [33]. The proposed boundary is simple: simulation can test stability, compatibility, or energetic consequences of structural hypotheses, but it cannot retrospectively establish that an ambiguous atom, water, protonation state, or ligand pose was experimentally observed.

Emerging ai–structural biology workflows

The emerging workflow is increasingly hybrid rather than purely predictive. CryoAtom advances AI-assisted experimental model building [13]; AlphaFold-conditioned structure determination explicitly treats a pretrained network as a prior [14]; and DeepTracer–AlphaFold2 integration shows how prediction and map fitting can be combined [18]. Density-guided molecular dynamics of AI-like ligand models extends the same logic downstream into ligand refinement [25], while AlphaFold 3 broadens the range of interaction hypotheses available before or alongside experiment [32].

The opportunity is not to collapse these stages into one confidence score. A more defensible future architecture preserves provenance: experimental density defines observational support; AI supplies structured priors and

candidate interpretations; chemistry constrains ligand plausibility; simulation tests consistency; and assays evaluate biological consequences. Prospective validation should therefore emphasize blinded multi-target tests, local-map-quality stratification, chemically diverse ligands, independent refinement, orthogonal binding or functional measurements, and repeated structure–design–synthesis cycles. These requirements are proposed priorities rather than demonstrated universal standards.

A further reporting implication follows from this evidence-preserving approach. Future studies should distinguish which structural features were directly supported by density, which were supplied or stabilized by learned priors, which ligand features depended on chemical scoring, and which interpretations emerged only after simulation or functional testing. This proposed provenance record would make apparent agreement across methods easier to interpret without assuming that computational convergence constitutes multiple independent observations.

Review limitations and technical boundaries

This review integrates heterogeneous evidence and therefore cannot provide a single quantitative estimate of AI or cryo-EM performance. Validation recommendations identify persistent local-model uncertainties [15], ligand-challenge evidence shows that chemically plausible alternatives can survive structural modeling [22], and comparisons of heterogeneity methods indicate that state representations are method-dependent [30]. Free-energy methods add useful tests but introduce their own sampling and model assumptions [36].

The search was bounded rather than exhaustive, and the evidence base combines methodological benchmarks with target-specific demonstrations. Direct prospective studies connecting AI-assisted cryo-EM interpretation to repeated medicinal-chemistry success remain limited. Accordingly, the proposed framework should be read as an organizing interpretation of current evidence, not as a validated decision algorithm, performance benchmark, or implementation standard.

CONCLUSION

Increasing cryo-EM resolution changes modern drug discovery chiefly by expanding which structural questions can become experimentally tractable, while AI accelerates conversion of those observations into testable models. The central boundary is that resolution, model completeness, ligand plausibility, conformational interpretation, energetic consistency, and pharmacological meaning are not interchangeable forms of confidence. This review therefore positions AI as an inference and hypothesis-

generation layer constrained by experimental density, local validation, chemistry, simulation, and functional testing. The emerging opportunity is a closed, evidence-preserving cycle in which difficult targets and alternative states become accessible without concealing uncertainty. Its value will ultimately depend on prospective chemical iteration and independent validation across diverse targets, ligands, structural qualities, and conformational regimes

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