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Review Article

# Artificial Intelligence-enhanced Computer-aided Drug Design: Recent Advances, Applications and Challenges

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ABSTRACT

CADD has, for four decades, provided the computational scaffolding on which rational drug discovery is built, encompassing structure-based and ligand-based approaches such as molecular docking, molecular dynamics, pharmacophore modelling, and QSAR analysis. Over the last decade this discipline has been transformed by the infusion of AI, giving rise to what is increasingly termed AI-driven drug design (AIDD). Deep neural networks, generative models, graph neural networks, and transformer-based language models now support nearly every stage of the discovery pipeline, from target identification and highly accurate protein structure prediction, through de novo molecular generation and virtual screening of ultra-large chemical libraries, to the prediction of ADMET properties and the optimisation of clinical trial design. This review synthesises recent advances in AI-enhanced CADD, covering key methodological families (generative adversarial networks, variational autoencoders, diffusion models, graph neural networks, and transformers), landmark applications including AlphaFold and its successors, deep-learning-guided antibiotic and antifibrotic drug discovery, and AI-designed molecules that have advanced into clinical trials. It further examines the persistent challenges that temper enthusiasm for the field — data scarcity and bias, limited model interpretability, poor generalisation beyond training distributions, weak experimental validation, and unresolved regulatory and ethical questions — and outlines emerging directions, including multimodal foundation models, physics-informed learning, and closed-loop autonomous laboratories, that are likely to shape the next generation of AI-enhanced drug discovery.

## Introduction

The discovery of a single new medicine remains one of the most protracted, expensive, and failure-prone endeavours in applied science. Traditional drug discovery pipelines span target identification, hit finding, lead optimisation, preclinical development, and multi-phase clinical trials, a process that typically consumes ten to fifteen years and several billion dollars, with attrition rates exceeding ninety percent between first-in-human dosing and regulatory approval. CADD emerged in the 1980s and 1990s as a rational response to this inefficiency, offering in silico tools SBDD, LBDD, FBDD, molecular docking, molecular dynamics simulation, and QSAR modelling - that allow researchers to predict how a candidate molecule will interact with its biological target before committing resources to synthesis and assay (Mihai and Nitulescu, 2025; Wang *et al.*, 2024).

Over the past decade, the convergence of three trends - the exponential growth of publicly available chemical

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and biological data, the maturation of deep learning architectures, and the availability of large-scale computing infrastructure - has driven a qualitative shift in CADD. AI and its subfields, ML and DL, are now embedded throughout the discovery pipeline, giving rise to AI-driven drug design (AIDD) as an enhanced iteration of classical CADD (Wang *et al*., 2024). Rather than relying solely on physics-based scoring functions and hand-crafted molecular descriptors, AIDD systems learn structure--activity and structure--property relationships directly from data, generate novel chemical matter de novo, and increasingly integrate multi-omics and real-world clinical information into target discovery and prioritisation (Lavecchia *et al*., 2024; Singh *et al*., 2024).

This review aims to provide a comprehensive, evidence-based synthesis of recent advances in AI-enhanced CADD. Section 2 outlines the conceptual and methodological foundations of classical CADD and the AI techniques now layered upon it. Section 3 discusses AI-driven target identification and protein structure prediction, centred on the AlphaFold family of models. Section 4 reviews generative approaches to de novo molecular design. Section 5 provides an overview of AI-driven virtual screening, molecular docking and drug--target interaction prediction. In this section, machine learning applications for ADMET and toxicity prediction are discussed. Section 7 lists representative applications and case studies, such as molecules discovered by AI which have gone into clinical development. The challenges - technical, scientific, regulatory and ethical that still limit the field are discussed critically in Section 8 before emerging directions are discussed in Section 9 and the review concludes in Section 10.

## Materials and Methods

Since this is a review article, there are no original procedures reported here. The evidence was compiled by a narrative synthesis of peer-reviewed and preprint publications in the last five years or so, and a few key methodological studies coming before that but still relevant today (such as the seminal work on SMILES notation, and the transformer architecture). Sources were identified through targeted searches of the primary biomedical and cheminformatics literature and were selected for relevance to the major stages of the AI-driven drug discovery pipeline: target identification, protein structure prediction, de novo molecular generation, virtual screening and docking, ADMET/toxicity prediction, and representative clinical case studies. Findings are synthesised and critically discussed in the Results and Discussion section below.

## Results and Discussion

### Conceptual Foundations: From CADD to AI-Driven Drug Design

#### *Classical Computer-Aided Drug Design*

Classical CADD is broadly divided into structure-based and ligand-based methodologies. Structure-based drug design relies on the three-dimensional structure of a therapeutic target, typically obtained through X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, or cryo-electron microscopy, to guide molecular docking and structure-based virtual screening. Ligand-based drug design is used when the target structure is unavailable and instead exploits the properties of known active compounds through pharmacophore modelling and QSAR analysis. Fragment-based drug design complements both approaches by screening small, low-molecular-weight fragments and elaborating them into higher-affinity leads (Mihai and Nitulescu, 2025; Wang *et al*., 2024). These methods substantially narrowed the chemical space that must be explored experimentally, but they remained constrained by the accuracy of physics-based scoring functions, the scarcity of experimentally resolved structures, and the combinatorial size of drug-like chemical space, conservatively estimated at 10^60 molecules.

Table 1 compares the three principal classical CADD strategies introduced in Section 2.1, which continue to underpin AI-enhanced pipelines discussed throughout this review.

**Table 1:** Comparison of Classical Computer-Aided Drug Design Strategies

| *Strategy* | *Structural basis* | *Core techniques* | *Principal limitation* |
|---|---|---|---|
| structure-based drug design (SBDD) | Three-dimensional target structure from X-ray crystallography, NMR spectroscopy, or cryo-electron microscopy | Molecular docking, structure-based virtual screening | Constrained by the availability of experimentally resolved structures and the accuracy of physics-based scoring functions |
| Ligand-based drug design (LBDD) | Properties of known active compounds, used when the target structure is unavailable | Pharmacophore modelling, QSAR analysis | Predictive power limited by the quality and chemical diversity of known ligand data |
| Fragment-based drug design (FBDD) | Small, low-molecular-weight chemical fragments | Fragment screening and stepwise elaboration into higher-affinity leads | Fragments require extensive optimisation and elaboration to reach drug-like potency |

### The Rise of Artificial Intelligence in Drug Design

AI-driven drug design extends CADD by embedding statistical learning throughout the pipeline. Supervised learning models — random forests, support vector machines, gradient-boosted trees, and increasingly deep neural networks — are trained on curated bioactivity databases such as ChEMBL and PubChem to predict binding affinity, potency, and physicochemical properties directly from molecular structure. Unsupervised and self-supervised techniques train low-dimensional, latent chemical representations that can be queried, extrapolated, or fine-tuned for properties. In addition to this, molecules can be represented natively as graphs of atoms and bonds, which can be used to build a molecule graph across which information is processed using GNNs (Chithrananda *et al*., 2020; Ahmad *et al*., 2022), and transformer-based architectures, first developed for NLP, can be adapted to process molecular strings like SMILES as a chemical language, allowing for large-scale self-supervised pretraining on tens of millions of molecules (Vaswani *et al*., 2017). In drug design, AI has been shown to make remarkable progress in various stages of the process, including target identification, hit generation, lead optimisation, and ADMET prediction (Singh *et al*., 2024; Zheng *et al*., 2023).

### Molecular and Protein Representation Learning

A prerequisite for applying deep learning to chemistry is an effective numerical representation of molecules and proteins. SMILES, introduced by Weininger in 1988, encodes a molecular graph as a linear text string and remains the most widely used representation for language-model-based approaches (Weininger, 1988). Building on the transformer architecture of Vaswani *et al*. (Vaswani *et al*., 2017), models such as ChemBERTa and ChemBERTa-2 apply masked-language modelling and multi-task regression to SMILES corpora of up to 77 million compounds, producing molecular embeddings that transfer well to downstream property-prediction tasks with limited labelled data (Ahmad *et al*., 2022; Barranco-Altirriba *et al*., 2024). Analogous protein language models, such as the Evolutionary Scale Modeling (ESM) family, learn amino-acid sequence representations that capture evolutionary and structural information without explicit structural supervision (Lin *et al*., 2023), complementing structure-prediction networks such as AlphaFold discussed in Section 3.

## AI-Driven Target Identification and Protein Structure Prediction

### Target Discovery and Prioritisation

Before any molecule can be designed, a druggable biological target must be identified and validated. AI platforms increasingly integrate multi-omics datasets (transcriptomics, proteomics, and metabolomics), biological network analysis, causal inference, and text mining of the scientific and patent literature to prioritise candidate targets. Insilico Medicine's PandaOmics platform, for example, integrates omics and clinical data with natural-language-processing-based literature analysis and novelty scoring to nominate targets; this pipeline identified TNIK as a high-priority target for idiopathic pulmonary fibrosis IPF, a nomination subsequently validated through preclinical and clinical studies discussed in Section 7 (Zhavoronkov *et al*., 2024).

### AlphaFold and the Protein Structure Prediction Revolution

Arguably the single most consequential AI advance for structural biology and SBDD has been the emergence of highly accurate deep-learning-based protein structure prediction. DeepMind's AlphaFold2, described by Jumper *et al*. in Nature in 2021, achieved prediction accuracy competitive with experimental methods at the CASP14, a result recognised as Nature's Method of the Year for 2021 (Jumper *et al*., 2021; Paiardini, 2023). AlphaFold2 and the independently developed RoseTTAFold democratised access to protein structural models for the majority of the human proteome, alleviating a long-standing bottleneck in structure-based drug discovery, where only a small fraction of known proteins had experimentally resolved structures (Paiardini, 2023; Advances in AI for Protein Structure Prediction, 2023).

Subsequent developments have extended structure prediction beyond single protein chains. AlphaFold3, reported by Abramson *et al*. in 2024, unified prediction of proteins, nucleic acids, small-molecule ligands, ions, and post-translationally modified residues within a single diffusion-based architecture, substantially improving the modelling of protein--ligand and protein--nucleic-acid complexes relevant to drug design (Abramson *et al*., 2024). Complementary efforts, including Meta AI's ESMFold, which predicts atomic-level protein structure directly from a protein language model without an explicit multiple-sequence-alignment step (Lin *et al*., 2023), and open-source and commercial diffusion-based successors such as Boltz-1 and Boltz-2, have further expanded the accessibility and speed of structure prediction for binding-affinity estimation (Wohlwend *et al*., 2024). Independent evaluations emphasise that AlphaFold-generated models are best regarded as valuable, high-confidence hypotheses that accelerate — but do not fully replace — experimental structure determination, particularly for flexible regions, allosteric states, and induced-fit binding phenomena central to drug design (Terwilliger *et al*., 2024).

### Structure-Enabled Drug Discovery

The practical value of AI-predicted structures for drug discovery has been demonstrated in structure-based campaigns that combine AlphaFold models with generative

chemistry platforms to identify first-in-class inhibitors for previously intractable or poorly characterised targets, including a reported rapid-discovery campaign for a cyclin-dependent kinase 20 (CDK20) inhibitor in hepatocellular carcinoma that combined AlphaFold-predicted structures with the PandaOmics and Chemistry42 platforms (AlphaFold Accelerates AI-Powered Drug Discovery, 2022). More broadly, AI-enabled virtual screening frameworks such as Deep Docking use trained deep neural networks to estimate docking scores for ultra-large virtual libraries after explicitly docking only a small, representative subset of compounds, reducing the computational cost of screening billion-compound libraries by orders of magnitude while preserving enrichment of true binders (Gentile *et al*., 2022).

### Generative Approaches to De Novo Molecular Design

De novo molecular design seeks to generate novel chemical structures with desired biological and physicochemical properties, rather than screening pre-existing compound libraries. DGMs have become the dominant paradigm for this task, spanning recurrent neural networks, VAEs, GANs, normalising flows, and, most recently, diffusion models (Lavecchia *et al*., 2024; Relevant Applications of GANs in Drug Design, 2020).

### Generative Adversarial Networks

GANs, comprising a generator network that produces candidate molecules and a discriminator network that distinguishes generated from real compounds, were among the earliest deep generative frameworks applied to molecular design. LatentGAN combines an autoencoder with an adversarial network operating in a continuous latent chemical space, generating both random drug-like compounds and target-biased compound sets that occupy chemical space comparable to the training distribution (Prykhodko *et al*., 2019). Reinforcement-learning-augmented GAN variants have been used to bias molecule generation toward specific reward functions such as predicted bioactivity or synthetic accessibility (Lee *et al*., 2021), while graph-transformer-based GAN architectures, such as DrugGEN, incorporate a discriminator trained to distinguish generated molecules from known bioactive ligands of a specific target, directing generation toward target-centric chemical space (DrugGEN, 2023). GAN-based frameworks have also been extended beyond small molecules to de novo peptide and protein design and to dimensionality reduction of single-cell transcriptomic data supporting target discovery (Relevant Applications of GANs in Drug Design, 2020; Zervou *et al*., 2024).

### Variational Autoencoders and Latent-Space Optimisation

VAEs learn a continuous, differentiable latent representation of molecular structure that permits gradient-based or Bayesian optimisation toward target properties, as well as smooth interpolation between chemically distinct compounds. These representations underpin many hybrid architectures, including LatentGAN described above, and remain widely used for property-constrained molecule generation and scaffold hopping.

### Diffusion and Transformer-Based Generative Models

Diffusion models, which generate data by learning to reverse a gradual noising process, have recently been adapted to molecular and biomolecular generation, complementing their prominent role in structure prediction (Section 3.2). In parallel, transformer-based chemical language models pretrained on large SMILES corpora — including ChemBERTa-2, SMILES Transformer, and related architectures — support conditional molecule generation and property-guided fine-tuning, leveraging the same self-attention mechanisms that transformed natural language processing (Ahmad *et al*., 2022; Barranco-Altirriba *et al*., 2024; SMILES Transformer, 2019). Reviews of transformer-based SMILES models catalogue a rapidly growing family of encoder-only, encoder--decoder, and decoder-only architectures now applied to property prediction, reaction prediction, and de novo generation tasks (Mswahili and Jeong, 2024).

### Three-Dimensional and Structure-Aware Generation

A limitation of early string- and graph-based generative models is their neglect of explicit three-dimensional molecular geometry, which governs binding-pocket complementarity. Architectures such as DNMG address this by fusing three-dimensional structural information with GAN-based generation and transfer learning, improving the pharmacophoric and binding-affinity properties of generated molecules relative to two-dimensional baselines (Song *et al*., 2023). Such structure-aware generative approaches are increasingly coupled with structure-prediction pipelines (Section 3) to enable fully in silico, structure-guided de novo design campaigns.

## AI-Accelerated Virtual Screening, Docking, and Drug-Target Interaction Prediction

### Deep Learning for Drug--Target Interaction Prediction

Accurate prediction of DTI and binding affinity is central to both virtual screening and lead optimisation. DeepDTA, introduced by Öztürk *et al*., was among the first deep learning models to predict continuous binding-affinity values directly from raw SMILES strings and protein sequences using convolutional neural networks, outperforming earlier similarity-based and binary-classification approaches on the Davis and KIBA

benchmark datasets (Öztürk *et al*., 2018). This work catalysed a broader family of sequence-based DTI models, including graph-neural-network and attention-based successors, that trade the requirement for a resolved three-dimensional structure for scalability across large chemical and proteomic space (Progress of AI-Driven DTI Prediction, 2025).

## Structure-Based Virtual Screening and Deep Docking

SBVS uses molecular docking to estimate the binding pose and affinity of candidate ligands against a target structure, while LBVS relies on similarity to known actives when structural information is unavailable (AI in Virtual Screening, 2025). The explosive growth of make-on-demand virtual chemical libraries, now exceeding tens of billions of compounds, has outpaced the computational feasibility of exhaustive docking. Deep Docking and related AI-guided approaches address this by training a surrogate deep neural network on the docking scores of a small, randomly sampled subset of a library, then using the trained model to predict scores for the remaining compounds, achieving substantial reductions in computational cost while retaining high hit-enrichment rates for the true top-ranked binders (Gentile *et al*., 2022).

## Diffusion-Based and Topological Deep Learning Approaches

In addition to the usual scoring-function-based docking, the denoising diffusion models, originally developed for structure prediction such as AlphaFold3 and the Boltz family, are also being repurposed for competitive docking and pose ranking, sometimes surpassing traditional physics-based docking software on well-characterised targets (Wohlwend *et al*., 2024; AI-Guided Competitive Docking, 2026). One of the methodological innovations that is taking place is topological deep learning (TDL) that uses persistent homology to represent the global, multiscale geometric structure of ligands, protein binding pockets, and protein--ligand interfaces, providing a pathway to better generalisation when predicting DTI, performing virtual screening, and optimising docking scores (Suay-García and Falcó, 2026; Cang and Wei, 2017).

## Practical Considerations and Limitations

Despite these advances, virtual screening performance remains bounded by the accuracy of underlying scoring functions and by dataset biases that can inflate apparent predictive performance in retrospective benchmarks without translating into prospective enrichment of true actives. Reviews of AI-enabled virtual screening emphasise that combining deep learning with virtual screening has measurably increased hit-identification rates against kinases, G-protein-coupled receptors, and proteases, but that false positives and false negatives arising from imperfect docking and scoring remain a critical limitation, motivating growing interest in explainable-AI techniques such as attention visualisation and SHAP to support medicinal-chemist trust and decision-making (AI in Virtual Screening, 2025).

Table 2 summarises the principal AI-accelerated approaches to virtual screening, docking, and drug–target interaction prediction reviewed in Section 5.

## Machine Learning for ADMET and Toxicity Prediction

Poor pharmacokinetics and unanticipated toxicity remain leading causes of clinical-stage drug attrition, making early, accurate prediction of ADMET properties a priority for AI-enhanced CADD (Vemula *et al*., 2023). Machine learning approaches to ADMET prediction have evolved from classical QSPR models using engineered molecular descriptors toward graph neural networks, ensemble learning, and multitask deep learning frameworks capable of jointly predicting dozens of pharmacokinetic and toxicological endpoints from a single molecular

**Table 2:** Comparison of AI-Accelerated Virtual Screening and Docking Approaches

| *Approach* | *Core principle* | *Representative model(s)* | *Reported advantage* |
|---|---|---|---|
| Sequence-based DTI prediction | Predicts binding affinity directly from raw SMILES strings and protein sequences using deep neural networks | DeepDTA and successors | Scalable across large chemical and proteomic space without requiring a resolved 3D structure |
| Surrogate-model virtual screening | Trains a deep neural network on docking scores from a small, randomly sampled subset, then predicts scores for the remaining library | Deep Docking | Reduces computational cost of screening billion-compound libraries by orders of magnitude while preserving hit enrichment |
| Diffusion-based docking | Repurposes denoising diffusion architectures originally developed for structure prediction to rank ligand poses | AlphaFold3, Boltz-1/2 | Competitive with, and in some cases superior to, traditional physics-based docking on well-characterised targets |
| Topological deep learning | Encodes global, multiscale geometric structure of ligands, binding pockets, and interfaces using persistent homology | TDL-based scoring frameworks | Improved generalisation across DTI, screening, and docking benchmarks while addressing dataset bias and leakage |

representation (Fan *et al*., 2025; Venkataraman *et al*., 2025).

Examples of such representative systems are ADMET-AI, a machine learning-generated platform for web-based, instant-access ADMET predictions for large, virtual chemical libraries, bringing together multiple endpoint-specific models under a single interface designed for high throughput generative-chemistry workflows (Swanson *et al*., 2024). Automated machine learning (AutoML) pipelines have also been used for in silico prediction of a range of ADMET properties, where model selection and hyperparameter tuning are both automatic, and predictive accuracy across diverse endpoints is competitive (Employing AutoML Methods, 2025). Domain-specific reviews provide additional evidence of the use of deep learning methods to predict drug metabolism and excretion, with significant advances made recently but also the continued presence of endpoint-specific challenges, such as hepatotoxicity and cardiotoxicity endpoints, where complex and poorly characterised biological mechanisms are involved (Van Tran *et al*., 2023).

However, the complex models that achieve high performance on retrospective data often struggle to generalise well beyond their training distribution to chemically novel series of molecules away from the observed distribution, properties that are challenging to prove and benchmark for practical use, as evidenced in a recurring theme in the reviewed materials—ADMET-focused reviews (Venkataraman *et al*., 2025; AI in Drug Discovery: A Comprehensive Review, 2025).

## Representative Applications and Case Studies

### AI-Discovered Antibiotics: Halicin

A widely cited proof of concept for AI-driven hit discovery is the identification of halicin. Stokes *et al*. trained a deep neural network to predict antibacterial activity of small molecules from structure alone, using an Escherichia coli growth-inhibition assay as the training signal, and applied the trained model to screen the Drug Repurposing Hub and a library of more than 107 million molecules curated from the ZINC15 database. This screen identified halicin, a compound structurally divergent from known antibiotic classes, which demonstrated bactericidal activity against a broad phylogenetic range of pathogens, including Mycobacterium tuberculosis and carbapenem-resistant Enterobacteriaceae, and successfully treated Clostridioides difficile and pan-resistant Acinetobacter baumannii infections in murine models (Stokes *et al*., 2020). The study illustrated the capacity of deep learning models to identify structurally novel bioactive chemotypes that conventional, similarity-driven screening approaches would be unlikely to prioritise.

### AI-Designed Molecules in Clinical Development: Rentosertib

Perhaps the most extensively documented example of an AI-discovered target and an AI-designed molecule progressing through human clinical trials is rentosertib (formerly ISM001-055 / INS018_055), developed by Insilico Medicine as a potentially first-in-class oral inhibitor of TNIK for idiopathic pulmonary fibrosis. The target was nominated using the PandaOmics platform through integration of multi-omics data, biological network and causal-inference analysis, and literature and patent intelligence, while the molecule itself was designed and optimised using the Chemistry42 generative chemistry platform. The whole research-to-clinic pathway, from the thirteen preclinical experiments to the early clinical trials, was published in Nature Biotechnology (Zhavoronkov *et al*., 2024) and favourable clinical efficacy and safety results were then reported in Nature Medicine (Insilico Medicine, 2025). In 2026, Rentosertib entered a Phase III clinical trial that was also randomised and double-blinded, and placebo-controlled, marking one of the first systematic trials to showcase an end-to-end AI-driven drug discovery process that produced measurable therapeutic benefit in human patients (Bio-IT World, 2026; Insilico Medicine, 2026).

### Balancing Successes with Setbacks

Not every clinical candidate that has been found by AI has been successful. While the AI-driven drug discovery process has made it possible to identify and accelerate the discovery of new small molecule drugs, not every AI discovery path leads into clinical success, as demonstrated by the cancellation of PSP-1181, a serotonin 5-HT1A receptor agonist for OCD co-developed by Exscientia and Sumitomo Dainippon Pharma, which was identified via AI drug design and progressed into Phase I despite a favourable safety profile (AI in Small-Molecule Drug Discovery, 2026). Balanced accounts of AI for small molecule drug discovery highlight that—as is often the case with new technologies—AI can best be thought of as an augmentative technology, one that can help shorten the early stages of discovery and open up new chemical space, but not as a substitute for the breadth of experimental validation and clinical evidence that will ultimately determine whether a small molecule candidate becomes a medicine on the market. (AI in Small-Molecule Drug Discovery, 2026).

### Structural Prediction in Cancer Drug Discovery

The use of AI-driven protein structure prediction has been directly applied in oncology drug discovery. AlphaFold-generated structures of previously unsolved cancer-related targets have facilitated structure-based virtual screening and mechanistic studies of inhibitor interactions, resulting in improvements in experimentally derived structures

and acceleration of hypothesis generation in structurally challenging target classes (Advances in AI for Protein Structure Prediction, 2023).

Table 3 summarises representative AI methodologies mapped onto the principal stages of the CADD pipeline discussed above.

## Challenges and Limitations

Despite significant technological development, AI-enhanced CADD faces a series of interconnected scientific, technical, regulatory, and ethical constraints that dampen unequivocal confidence about the speed of translation from computer prediction to authorized medications.

## Data Quality, Scarcity, and Bias

The quality of AI models is entirely based on the data used to train them. Bioactivity and ADMET databases are frequently tiny, domain-specific, and sparse over the target classes and chemical scaffolds. For instance, data on kinase inhibitors are quite abundant, but other target families are significantly underrepresented (AI in Drug Discovery: A Comprehensive Review, 2025). Label noise arising from differences in experimental protocol across labs overlaps with true biological variation . Models trained on data from one lab are often severely impaired when tested on data generated elsewhere, hampering cross-study generalization (AI in Drug Discovery and Development, 2025). Many solutions are presented and widely evaluated to overcome data scarcity such as transfer learning, active learning, one-shot learning, multitask learning, data augmentation and federated learning on institutional datasets. However, none of these can completely overcome the basic lack of high-quality, standardized biological data (Data-Centric Challenges in AI for Drug Discovery, 2024).

## The Interpretability and 'Black-Box' Problem

Deep neural networks and particularly large graph neural networks and transformer-based architectures are often black-box predictive engines that produce accurate results but lack clear mechanistic interpretability. This opacity limits trust between medicinal chemists and is a substantive barrier to regulatory acceptance, since regulatory agencies require a defensible rationale for safety- and efficacy-relevant predictions (AI in Drug Discovery: A Comprehensive Review, 2025; Gangwal *et al*., 2024). Explainability techniques such as SHapley Additive exPlanations (SHAP), Local Interpretable Model-agnostic Explanations (LIME) and transformer attention visualization offer some insight into model reasoning, however their outputs are often still difficult for domain experts to translate into actionable mechanistic understanding, particularly for endpoints such as toxicity and pharmacokinetics where the causal biological relationships are the key focus (AI in Drug Discovery: A Comprehensive Review, 2025).

## Generalisation, Benchmarking, and Prospective Validation

AI models fine-tuned on historical benchmarks often exhibit significantly inferior performance in forward-looking, real-world discovery initiatives, a variance stemming from impractical benchmark design, dataset contamination between training and testing segments, and erroneous performance assessments due to insufficient uncertainty quantification (AI in Drug Discovery and Development, 2025). Suay-García and Falcó similarly observe that evaluation challenges, including dataset bias and information leakage, persistently undermine trust in the reported efficacy of DTI prediction, virtual screening, and docking-score benchmarks, highlighting the necessity for standardized, leakage-conscious benchmarks and an increased focus on prospective, wet-laboratory validation of computational forecasts (Suay-García and Falcó, 2026).

## Biological Complexity and Multimodal Data Integration

Current AI systems often oversimplify the complex, context-dependent biological mechanisms involved in human disease biology. Due to interoperability issues,

**Table 3:** Summary of Major AI Methodologies Applied Across the CADD Pipeline

| *Pipeline stage* | *Representative AI methods* | *Illustrative tools / Models* | *Key reference(s)* |
|---|---|---|---|
| Target identification | Multi-omics integration, NLP-based literature mining, causal inference | PandaOmics | (Zhavoronkov *et al*., 2024) |
| Protein structure prediction | Deep learning (attention/diffusion-based) | AlphaFold2, AlphaFold3, ESMFold, Boltz-1/2 | (Jumper *et al*., 2021; Abramson *et al*., 2024; Lin *et al*., 2023; Wohlwend *et al*., 2024) |
| De novo molecular design | GANs, VAEs, diffusion models, transformers | LatentGAN, DrugGEN, DNMG, ChemBERTa-2 | (Prykhodko *et al*., 2019; DrugGEN, 2023; Song *et al*., 2023; Barranco-Altirriba *et al*., 2024) |
| Virtual screening & docking | Surrogate DNNs, graph neural networks, topological deep learning | Deep Docking, TDL-based scoring | (Gentile *et al*., 2022; Suay-García and Falcó, 2026) |
| Drug-target interaction | CNN/graph-based sequence models | DeepDTA and successors | (Öztürk *et al*., 2018) |
| ADMET / toxicity prediction | Multitask deep learning, ensemble & AutoML methods | ADMET-AI, AutoML pipelines | (Swanson *et al*., 2024; Employing AutoML Methods, 2025) |

**Table 4:** Summary of Key Challenges Constraining AI-Enhanced CADD

| *Challenge* | *Core issue* | *Illustrative consequence* |
|---|---|---|
| Data quality, scarcity, and bias | Bioactivity and ADMET datasets are small, unevenly distributed, and affected by inconsistent experimental protocols across laboratories | Degraded cross-study generalisation; models trained at one laboratory often underperform on data generated elsewhere |
| Interpretability ('black-box' problem) | Deep neural networks often yield accurate predictions without transparent, mechanistically interpretable reasoning | Constrains medicinal-chemist trust and poses a barrier to regulatory acceptance, despite partial mitigation from SHAP and LIME |
| Generalisation and benchmarking | Retrospective benchmark performance frequently fails to translate into prospective, real-world discovery campaigns | Performance misestimation arising from dataset leakage and inadequate uncertainty quantification |
| Biological complexity and multimodal integration | Integrating genomic, transcriptomic, proteomic, electronic health record, and biosensor data streams remains technically difficult | Interoperability and privacy constraints limit the extent to which models capture systems-level biological complexity |
| Regulatory, ethical, and IP considerations | Unresolved questions on evaluating AI-generated evidence, apportioning liability, and assigning intellectual property | Complicates independent regulatory assessment of AI-enabled drug discovery claims |

disparate data formats, and patient data privacy restrictions, integrating heterogeneous multimodal data streams—genomic, transcriptomic, proteomic, electronic health record, and real-time biosensor data—remains technically challenging. This limits the degree to which AI models can capture systems-level biological complexity relevant to efficacy and safety prediction (AI in Drug Discovery: A Comprehensive Review, 2025; Gangwal *et al*., 2024).

### Regulatory, Ethical, and Intellectual Property Considerations

The increasing use of AI for target identification and candidate molecule design brings with it regulatory and ethical issues that remain unresolved, including how regulatory agencies should assess the provenance and reliability of evidence generated by AI, how liability should be assigned when AI-informed decisions lead to adverse outcomes, and how intellectual property rights should be assigned to AI-generated chemical matter (Blanco-González *et al*., 2023). Further complicating independent regulatory examination of AI-enabled discovery claims are the variations in reproducibility and benchmarking throughout the academic and commercial AI-drug-discovery literature (Blanco-González *et al*., 2023).
Table 4 consolidates the principal challenges discussed in Section 8 that continue to temper enthusiasm for AI-enhanced CADD.

## Conclusion

Artificial intelligence has made tremendous progress in computer-aided drug design, providing new opportunities to supplement the traditional structure-based and ligand-based approaches with data-driven target identification, near-experimental-accuracy protein structure prediction, generative de novo molecular design, AI-accelerated virtual screening and machine learning-based ADMET prediction. Landmark achievements, spanning from revolutionizing structural biology by AlphaFold, to the discovery of halicin and clinical development of rentosertib, illustrate that AI-augmented CADD can provide real scientific and translational values. Simultaneously, the enduring challenges of data quality and scarcity, model interpretability, generalization beyond training distributions, and regulatory and ethical readiness imply that AI is most realistically viewed, at this stage of maturity, as a potent augmentative technology that accelerates and enriches human-led drug discovery rather than a fully autonomous replacement for experimental validation and clinical evidence generation. Moving forward will require rigorous prospective benchmarking, more standardization and sharing of data, improved interpretability of models and closer integration of computational prediction and experimental validation along the drug discovery pipeline.

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