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AI AND DEEP LEARNING IN DRUG DISCOVERY: ADVANCES, BENCHMARKS, AND FUTURE CHALLENGES

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Abstract
Artificial intelligence (AI) and deep learning (DL) are redefining the landscape of modern drug discovery by transforming data-driven prediction, molecular design, and optimization workflows. DL architectures such as convolutional, recurrent, graph-based, and transformer models enable the efficient integration of chemical, biological, and clinical datasets to predict binding interactions, structural conformations, and pharmacokinetic behavior with remarkable accuracy. The incorporation of AlphaFold-like structural predictors, generative adversarial networks (GANs), and reinforcement learning frameworks has accelerated target identification, virtual screening, and de novo compound generation. These developments have significantly reduced the cost and time associated with early-stage drug development while improving hit quality and safety evaluation. However, challenges persist, including limited interpretability, dataset bias, and computational complexity. The review highlights emerging strategies such as explainable AI, multimodal learning, and digital twin modelling to overcome these limitations. Collectively, DL-driven approaches mark a pivotal transition toward predictive, transparent, and sustainable pharmaceutical innovation that bridges computational and experimental discovery.

Keywords Artificial Intelligence (AI); Deep Learning (DL); Drug Discovery; Molecular Design; Virtual Screening; AlphaFold; Generative Adversarial Networks (GANs); Reinforcement Learning; Explainable AI; Multimodal Learning; Digital Twin Modeling; Computational Pharmacology; Predictive Modeling; Structural Bioinformatics; Translational Drug Development.

1. Introduction

Drug discovery represents a complex and multidisciplinary endeavor aimed at identifying and developing novel therapeutic molecules capable of modulating biological targets with precision and safety. Conventional discovery approaches, such as high-throughput screening and structure-based drug design, require extensive time, cost, and experimental resources, with only a small fraction of lead compounds ultimately reaching clinical approval. Despite technological advancements, the

average development cycle for a new drug still exceeds a decade, emphasizing the need for more efficient and predictive strategies[1,2,3].

The emergence of artificial intelligence (AI) and machine learning (ML) has reshaped the landscape of pharmaceutical research. These computational frameworks enable the rapid integration and analysis of vast chemical, biological, and clinical datasets to uncover hidden molecular relationships that traditional methods often overlook. In particular, AI algorithms have demonstrated the ability to predict drug–target interactions, optimize molecular structures, evaluate pharmacokinetic and toxicity properties, and even generate novel chemical scaffolds with desired biological activity[4,5,6].

Among the diverse branches of AI, deep learning (DL) has become especially prominent due to its capacity to model complex nonlinear relationships inherent in biological systems. Architectures such as convolutional neural networks (CNNs), recurrent neural networks (RNNs), graph neural networks (GNNs), and transformer-based large language models (LLMs) have been widely applied to critical stages of drug development, including drug–target interaction (DTI) prediction, binding affinity estimation, virtual screening, and ADMET property assessment. Moreover, generative and structure-aware DL approaches exemplified by AlphaFold2, AlphaFold3, RoseTTAFold, and Chai-1 have enabled unprecedented progress in predicting protein–ligand complexes, facilitating accurate target identification and lead optimization[7,8,9,10].

AI-driven pipelines have proven particularly valuable in addressing complex and multifactorial diseases such as cancer, neurodegenerative disorders, and viral infections. For example, AI frameworks were rapidly deployed during the COVID-19 pandemic to identify antiviral candidates, design peptide inhibitors, and repurpose approved drugs with remarkable speed and accuracy[11,12,13]. By integrating heterogeneous datasets from genomic sequences to structural proteomics, AI systems now support precision medicine through drug repurposing and personalized dosing strategies. Consequently, many pharmaceutical companies have incorporated AI platforms to enhance decision-making, reduce attrition rates, and expedite candidate prioritization.

Despite these successes, the implementation of AI in drug discovery still faces substantial challenges. Key limitations include the scarcity of large, high-quality annotated datasets, the lack of interpretability in deep models, bias propagation, and the computational cost associated with large-scale simulations. Translating in silico predictions into experimentally validated outcomes remains a critical bottleneck, necessitating tighter integration between computational scientists and experimental pharmacologists. Furthermore, the adoption of explainable AI (XAI) and digital twin (DT) technologies is essential to ensure transparency, reproducibility, and regulatory compliance in AI-based predictions[14,15].

This review aims to provide a comprehensive and systematic overview of how AI and DL are transforming the drug discovery paradigm. It synthesizes recent algorithmic advances, benchmark datasets, and evaluation frameworks across key research domains—ranging from target identification and structure prediction to toxicity assessment and dose optimization. Special focus is given to the comparative performance of cutting-edge DL architectures, the integration of large-scale protein language models, and the application of novel paradigms such as XAI and DT in pharmaceutical innovation. In addition, real-world case studies and success stories are discussed to illustrate the tangible impact of AI on accelerating therapeutic development. This schematic presents the end-to-end workflow of an AI-driven drug discovery pipeline, integrating target identification, structure prediction, virtual screening, de novo design, and ADMET assessment. Arrows indicate data flow between experimental and computational modules, illustrating how machine-learning and deep-learning models streamline decision-making and accelerate candidate prioritization **(Fig.1)**.

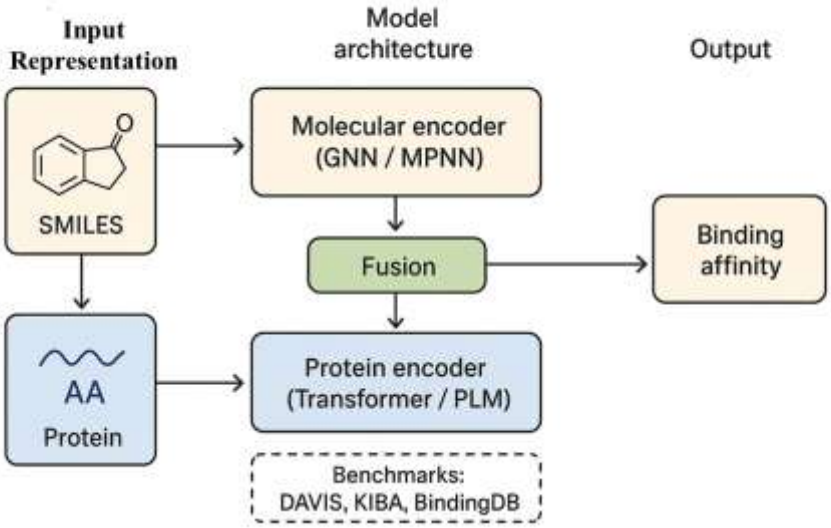

Fig. 1: Workflow of AI-Integrated Drug Discovery Pipeline

Overall, the study underscores that AI-driven deep learning is converting drug discovery from a largely empirical pursuit into a data-driven, predictive science. Through the synthesis of current evidence, methodologies, and practical applications, this review delineates both the breakthroughs achieved and the remaining challenges that will define the next generation of intelligent, model-based pharmaceutical discovery.

2. Current Landscape of AI and Deep Learning Applications in Drug Discovery

The past decade has witnessed a transformative shift in the field of pharmaceutical research, driven by the integration of artificial intelligence (AI) and deep learning (DL) into the drug discovery process[16]. These technologies have transitioned from exploratory computational tools to essential components of modern pharmaceutical innovation. Traditional in silico techniques, such as quantitative structure activity relationship (QSAR) modelling, molecular docking, and pharmacophore mapping, provided early predictive frameworks but were limited by linear assumptions, manual feature engineering, and restricted scalability. In contrast, DL models autonomously learn hierarchical representations of chemical and biological data, including molecular graphs, SMILES strings, and protein sequences, thereby enabling accurate prediction of complex molecular behaviours[17,18,19].

2.1. Deep Learning for Drug–Target Interaction Prediction

Predicting drug–target interactions (DTIs) remains central to early-stage drug discovery. Classical kernel-based and matrix-factorization methods have gradually been supplanted by deep architectures capable of modelling nonlinear dependencies between small molecules and macromolecular targets. Graph neural networks (GNNs) and transformer-based architectures have emerged as dominant approaches, integrating topological, physicochemical, and sequence-level features to improve binding-affinity prediction. Architecture of deep-learning models used for drug–target interaction (DTI) prediction[20,21]. The figure depicts typical input representations (SMILES strings and protein sequences) processed through CNN, GNN, or Transformer layers to yield binding-affinity outputs. Attention mechanisms and feature-fusion modules enhance interpretability and accuracy **(Fig.2)**.

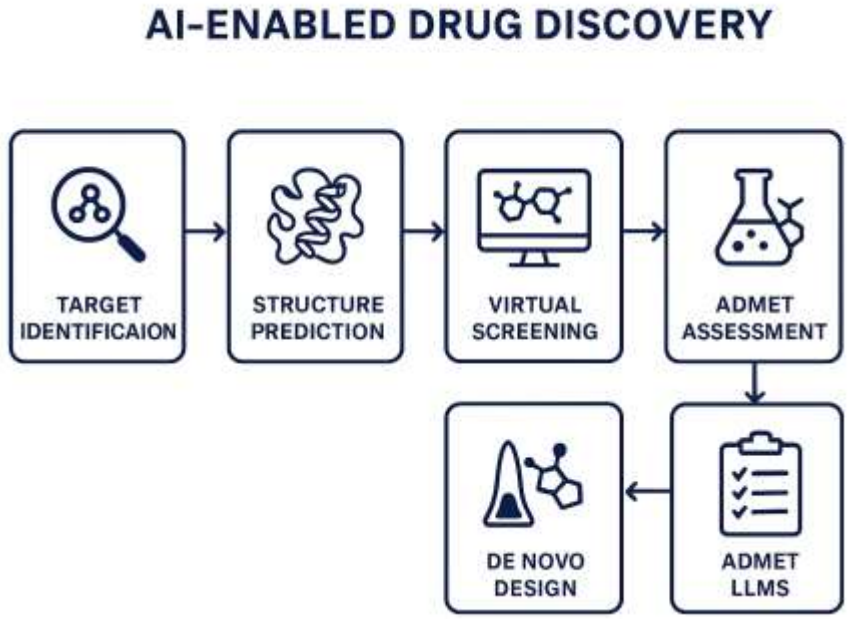

Fig. 2: Deep Learning Framework for Drug–Target Interaction Prediction

Benchmark models such as DeepDTA, GraphDTA, and TransformerCPI have demonstrated superior performance on datasets including DAVIS and KIBA by employing attention mechanisms that highlight key residues and substructures governing molecular binding. Recent innovations combine protein language models (PLMs), for example, ESMFold and Chai-1, with DL frameworks to capture context-dependent sequence information and improve DTI prediction accuracy[23,24].

2.2. Structural Biology and Protein–Ligand Modeling

Breakthroughs in protein structure prediction have revolutionized the modeling of drug–target complexes. AlphaFold2 (AF2) and AlphaFold3 (AF3) achieved near-experimental precision in predicting tertiary and quaternary protein structures, fundamentally reshaping computational structural biology[24]. Comparative studies revealed that AF2 successfully docked over 90 % of peptide ligands to G protein-coupled receptors (GPCRs), outperforming prior template-based algorithms such as RoseTTAFold All-Atom[25]. A comparative benchmarking of DL-based protein–ligand modelling frameworks on GPCR–peptide datasets is presented in **Table 1**, emphasizing the trade-offs between accuracy, recall, and computational efficiency. Comparison of Structural Accuracy Among DL-Based Protein Modelling Tools. Benchmark comparison of AlphaFold 2, AlphaFold 3, RoseTTAFold All-Atom, and Chai-1 for GPCR–peptide complex modeling. Bar graphs display mean DockQ, ligand recall, AUC, and runtime, emphasizing trade-offs between structural accuracy and computational efficiency in deep-learning-based protein modelling **(Fig.3)**.

Table 1. Benchmark of DL Models on GPCR–Peptide Dataset

S No	Model	Template Usage	Mean DockQ	Ligand Recall (%)	AUC	Runtime (s/prediction)
1	AF2	Yes	0.86	58	0.92	144
2	AF3	Yes	0.82	52	0.89	18
3	Chai-1	No	0.76	48	0.84	50
4	RF-AA	Yes	0.64	35	0.72	120
5	Peptriever	No	0.55	25	0.69	5
6	NeuralPLexer	No	0.02	5	0.50	10

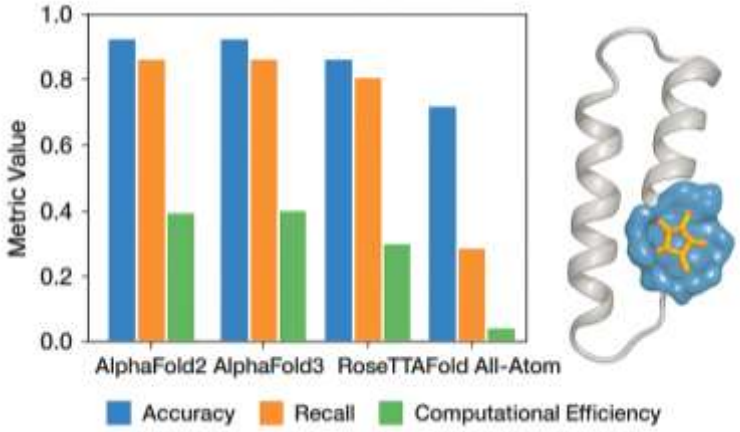

Fig. 3: Comparison of Structural Accuracy Among DL-Based Protein Modeling Tools

Benchmarking analyses of AF2, AF3, Chai-1, and RoseTTAFold have clarified the trade-offs between predictive fidelity and computational efficiency. AF2 consistently achieved the highest docking accuracy, whereas AF3 provided faster runtimes suitable for high-throughput virtual screening. Chai-1, which operates without multiple-sequence alignments (MSAs), achieved an optimal balance between computational speed and structural quality[21]. Collectively, these findings underscore the transformative potential of DL-based structure prediction tools in molecular docking and lead optimization. **Table 2** illustrates the impact of different rescoring strategies on AlphaFold-based predictions, demonstrating how post-processing methods enhance ranking accuracy and statistical significance.

Table 2. Effect of Rescoring Methods on AF2/AF3 Performance

S No	Rescoring Method	Model	Ranking Improvement (%)	p-Value (Wilcoxon Test)	Remarks
1	AFM-LIS	AF2	+23	0.0018	Statistically significant
2	AFM-LIS	AF3	+10	0.075	Moderate effect
3	RIA (SC Metric)	AF3	+4	0.25	Minimal improvement
4	DL-GNN	AF2	+3	0.32	Not significant

2.3. AI in Virtual Screening and De Novo Drug Design

AI-driven virtual screening (VS) and de novo molecular design have redefined early-stage compound discovery by replacing exhaustive experimental screening with predictive, data-driven prioritization[26]. Generative DL models, including variational autoencoders (VAEs), generative adversarial networks (GANs), and reinforcement-learning frameworks, can design novel chemical entities that satisfy predefined pharmacological constraints while maintaining synthetic feasibility[27]. Systems such as *MolGAN*, *REINVENT*, and *GENTRL* have successfully generated bioactive scaffolds for kinase inhibitors, GPCR modulators, and antiviral compounds[27]. The integration of quantum machine learning and diffusion-based molecular generators has further enhanced chemical diversity and docking precision by modelling quantum-level interactions. These advances have shortened the traditional discovery timeline from several years to a few months and enabled rapid iteration cycles between computational prediction and laboratory synthesis. Generative-model pipeline illustrating variational autoencoders (VAEs), generative adversarial networks (GANs), and reinforcement-learning (RL) frameworks for de novo compound design. The flow diagram highlights how reinforcement learning iteratively optimizes molecular properties to satisfy pharmacological and synthetic constraints **(Fig.4)**.

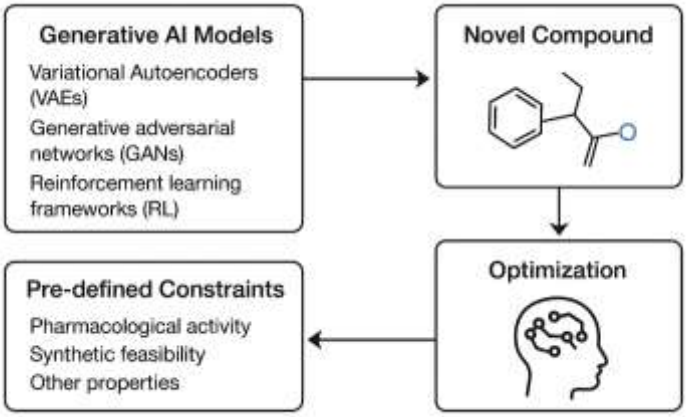

Fig. 4: AI in Virtual Screening and De Novo Drug Design

2.4. ADMET and Toxicity Prediction

Prediction of absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties remains critical for ensuring clinical success. Traditional rule-based approaches, such as Lipinski's Rule of Five, offer limited insight into complex pharmacokinetic behaviour[28]. DL architectures trained on multidimensional pharmacokinetic datasets now provide far greater predictive precision, integrating chemical descriptors, transcriptomic data, and in vitro bioassay outputs. **Table.3** provides an integrated overview of major deep learning frameworks utilized across different stages of drug discovery, highlighting representative algorithms, datasets, and key outcomes. Flowchart summarizing deep-learning models for ADMET (absorption, distribution, metabolism, excretion, and toxicity) prediction. It integrates molecular descriptors, transcriptomic inputs, and explainable-AI visualization to forecast pharmacokinetic behaviour and toxicity risk. Arrows denote data integration from chemical, omics, and in vitro sources **(Fig.5)**.

Table 3. Summary of Deep Learning Applications in Drug Discovery

	Application	DL Algorithm	Key Example	Dataset Used	Key Output
	Drug–Target Interaction	GNN, Transformer	DeepDTA, GraphDTA	BindingDB	Binding affinity
	De Novo Drug Design	RNN, GAN	MolGAN, REINVENT	ZINC	Novel molecules
	Toxicity Prediction	CNN, DNN	DeepTox	Tox21	Toxicity level
	ADMET Estimation	MLP, XGBoost	ADMET-AI	PubChem	Pharmacokinetic profiles

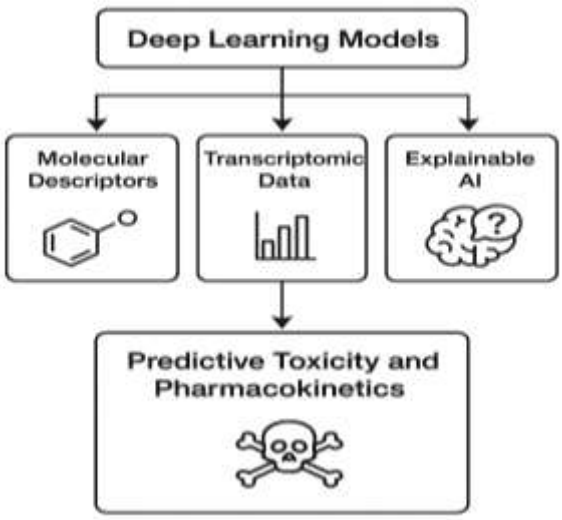

Fig. 5: AI-Based ADMET Prediction Workflow

Ensemble and multitask learning strategies enhance generalization across chemical classes and biological systems. In parallel, explainable AI (XAI) techniques such as attention visualization, Shapley additive explanations (SHAP), and layer-wise relevance propagation (LRP) are increasingly employed to interpret model predictions, identifying substructures responsible for toxicity or poor bioavailability. The inclusion of interpretability frameworks strengthens the credibility of AI-based ADMET models in regulatory and medicinal chemistry applications[29,30].

2.5. Emerging Trends: Explainable AI and Digital Twins

Emerging technologies such as explainable AI (XAI) and digital twins (DTs) are shaping the next generation of intelligent drug discovery systems. XAI enhances transparency by providing interpretable rationales for model decisions, thereby facilitating regulatory acceptance and ethical deployment of AI in pharmaceutical research. DTs' virtual biological replicas that emulate patient-specific physiological and pharmacological responses are enabling personalized drug design, safety prediction, and dosage optimization in silico[31,32].

Simultaneously, standardized benchmarking initiatives have become critical for evaluating algorithmic robustness and reproducibility. Datasets such as PINDER (Protein Interaction Dataset and Evaluation Resource) and LEADS-PEP provide open, curated resources for testing peptide-docking and interaction-prediction performance. Such collaborative efforts between academia and industry are essential to bridge computational predictions with empirical validation and to accelerate translational adoption of AI technologies in pharmaceutical pipelines[32].

Collectively, these developments illustrate how deep learning has reshaped nearly every stage of the drug discovery pipeline from virtual screening and structure prediction to toxicity assessment and precision medicine. While remarkable progress has been achieved, integrating AI into standardized pharmaceutical workflows still requires overcoming challenges in data quality, model interpretability, and regulatory validation. Continuous benchmarking, transparent data sharing, and the synergistic application of XAI and DT technologies are expected to propel the next phase of fully data-driven, intelligent drug discovery.

3. Deep Learning Techniques and Architectures in Drug Discovery

Deep learning (DL) encompasses a diverse family of neural network architectures capable of capturing nonlinear, high-dimensional relationships within biological and chemical data. Each architecture type, ranging from convolutional and recurrent networks to graph-based and transformer models, offers distinct strengths for different stages of the drug discovery process. These models can be applied to predict molecular properties, identify binding interactions, optimize pharmacokinetic parameters, and design novel drug-like compounds[7]. Overview of four principal deep-learning architectures, CNN, RNN, GNN, and Transformer, applied in drug discovery. Each subpanel summarizes its computational principle and representative applications, such as molecular property prediction, sequence modelling, topology learning, and large-scale molecular generation **(Fig.6)**.

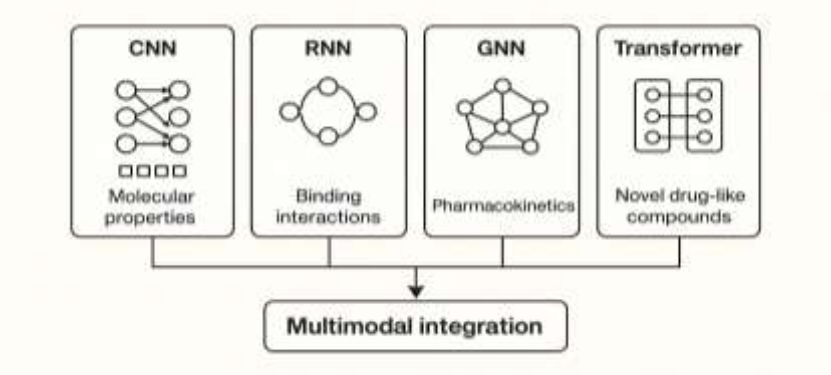

Fig. 6: Representative Deep Learning Architectures Used in Drug Discovery

3.1. Convolutional Neural Networks (CNNs)

Convolutional neural networks (CNNs) have played a pioneering role in the application of DL to chemoinformatics and bioinformatics. Initially designed for image recognition, CNNs have been adapted to analyze spatial and structural representations of molecules and proteins by treating molecular graphs, contact maps, and 3D conformations as **Fig 3.**

In drug discovery, CNNs are used to predict binding affinities, bioactivity, and toxicity by automatically detecting spatial features within molecular structures. They are particularly effective for structure-based virtual screening, where the protein–ligand binding pocket is represented as a voxelized 3D grid. Notable examples include AtomNet, which pioneered CNN-based prediction of small-molecule binding affinities, and DeepBind, which applies similar principles to protein–DNA and protein–RNA interaction prediction[33,34].

Recent enhancements integrate attention mechanisms and residual architectures (ResNet-CNNs) to capture long-range interactions within macromolecular systems. CNN-based methods continue to serve as the foundation for multi-modal AI systems that integrate sequence, structure, and image-derived data to enhance predictive accuracy.

3.2. Recurrent Neural Networks (RNNs) and Sequence Modelling

Recurrent neural networks (RNNs) and their variants, such as long short-term memory (LSTM) and gated recurrent unit (GRU) models, are designed to handle sequential data and have been widely adopted for molecular sequence analysis. They are particularly effective in processing SMILES strings, protein sequences, and gene expression profiles, enabling the modelling of temporal or sequential dependencies among molecular features[35,36].

In de novo drug design, RNNs generate valid and synthetically feasible SMILES strings by learning chemical grammar and reaction patterns. The REINVENT and CharRNN frameworks are notable examples that employ reinforcement learning-enhanced RNNs to optimize compounds for activity, solubility, and ADMET characteristics. Although RNNs have been largely superseded by transformer architectures in recent years, they remain valuable for smaller datasets and tasks where sequence continuity plays a dominant role, such as predicting ligand conformational dynamics and temporal drug responses[37,38].

3.3. Graph Neural Networks (GNNs)

Graph neural networks (GNNs) have emerged as a cornerstone of molecular representation learning, as they naturally model the topological structure of molecules and protein–ligand complexes. In GNNs, atoms and amino acids are represented as nodes, while chemical bonds or inter-residue contacts are represented as edges[39].

Frameworks such as GraphDTA, GraphConv, and AttentiveFP have demonstrated superior performance in predicting drug–target interactions, binding affinities, and ADMET properties. By aggregating information from neighboring nodes, GNNs can infer global molecular features and accurately predict physicochemical behavior. Their ability to incorporate both 2D molecular topology and 3D spatial information makes them particularly useful for tasks like virtual screening and fragment-based drug design[40,41].

Recent innovations integrate message-passing neural networks (MPNNs) and graph attention networks (GATs) with protein language embeddings to capture multi-scale molecular contexts. These hybrid systems bridge the gap between sequence-level and structural representations, providing a unified framework for modelling protein–ligand interactions[42].

3.4. Transformer Models and Large Language Models (LLMs)

Transformer-based architectures have revolutionized the landscape of computational biology and chemistry through their ability to capture long-range dependencies and contextual relationships. Introduced initially for natural language processing, transformers have been successfully adapted for protein structure prediction, compound generation, and reaction outcome forecasting.

Large-scale protein language models (PLMs) such as ESMFold, ProtBERT, and Chai-1 utilize billions of parameters trained on evolutionary-scale datasets to learn structural and functional properties directly from amino acid sequences. These models can predict secondary and tertiary structures, estimate binding affinities, and identify novel druggable motifs. In cheminformatics, transformer-based chemistry LLMs (e.g., ChemGPT and MolT5) are being used for reaction prediction, synthetic planning, and molecule generation[43,44].

Compared to CNNs and RNNs, transformer models offer better scalability, faster training convergence, and superior performance in multitask learning. However, they require large training datasets and computational resources, which remain limiting factors for smaller research groups.

3.5. Hybrid and Multimodal Deep Learning Frameworks

Recent trends indicate a convergence of multiple DL paradigms into hybrid and multimodal architectures that combine the strengths of different models. For instance, CNN–GNN hybrids integrate spatial and topological information for protein–ligand docking, whereas transformer-GNN systems utilize attention mechanisms to guide message-passing and enhance contextual learning[45].

These integrated frameworks are especially valuable in multi-omics data fusion, where genomic, proteomic, metabolomic, and chemical datasets must be processed concurrently. Hybrid DL systems also underpin explainable AI (XAI) and digital twin (DT) technologies by providing interpretable models that simulate biological responses under varying physiological conditions[46].

Such multimodal learning strategies represent the current frontier in AI-enabled drug discovery, moving beyond single-task optimization toward comprehensive, systems-level prediction of therapeutic efficacy and safety.

Overall, the evolution of deep learning architectures from CNNs and RNNs to GNNs and transformers reflects the rapid maturation of AI methodologies within pharmaceutical research. Each class of model contributes uniquely to understanding molecular structure activity relationships, predicting pharmacological outcomes, and guiding rational drug design. Future progress lies in the integration of these architectures into unified, explainable frameworks capable of combining sequence, structure, and clinical data into predictive digital twins for truly personalized drug discovery[47].

4. Applications of Deep Learning in Major Drug Discovery Domains

Deep learning (DL) has emerged as a transformative tool in every stage of the modern drug discovery pipeline. Its ability to analyze vast, heterogeneous biological data has enabled more accurate predictions of molecular interactions, efficient screening of drug candidates, and rational optimization of therapeutic efficacy and safety. A Circular schematic illustrating five interconnected domains of deep-learning application—target identification, virtual screening, molecular docking, de novo drug design, and drug repurposing. The arrangement emphasizes the continuum of AI deployment across the drug-discovery pipeline and the feedback between computational prediction and experimental validation **(Fig.7)**.

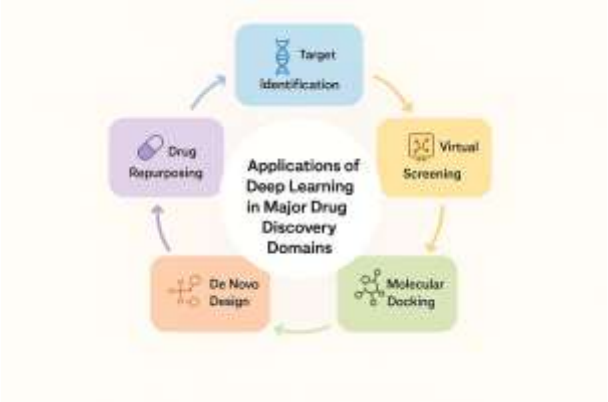

Fig. 7: Applications of Deep Learning in Major Drug Discovery Domains

4.1. Target Identification and Validation

The identification of novel therapeutic targets is a fundamental yet challenging step in drug discovery. Traditional experimental approaches, such as high-throughput screening and proteomic assays, are time-consuming and resource-intensive. DL-based methods have accelerated this process by predicting target–disease associations from genomic, transcriptomic, and proteomic data.

Graph neural networks (GNNs) and transformer models, in particular, can capture complex relationships among genes, proteins, and phenotypic traits. Tools such as DeepTarget and DeepAffinity integrate protein embeddings with disease network data to infer novel target–ligand relationships. Moreover, large-scale protein language models (PLMs) like ESMFold and Chai-1 have enabled the structural characterization of previously unannotated proteins, facilitating target validation at an atomic level[48,49,50].

These approaches are increasingly used to identify druggable pockets, mutational hotspots, and *allosteric sites*, allowing precise modulation of disease-related pathways. Integration of multi-omics DL models further enhances prediction reliability, paving the way for systems-level understanding of disease biology.

4.2. Virtual Screening and Lead Optimization

DL-based virtual screening (VS) has redefined early-stage hit identification by replacing manual docking workflows with end-to-end predictive pipelines. Convolutional neural networks (CNNs) and 3D GNNs analyze protein–ligand complexes in voxelized grids or molecular graphs to estimate binding affinities and prioritize potential leads[51].

For instance, AtomNet, one of the first CNN-driven VS systems, demonstrated high accuracy in predicting bioactive conformations against GPCR and kinase targets. Successor models such as DeepDock and DeepVS incorporate attention mechanisms and multi-task learning to generalize across target families. Similarly, GraphDTA and TransformerCPI employ molecular graph embeddings and protein sequence attention layers to screen large compound libraries with reduced computational cost[52,53].

Beyond screening, DL models contribute to lead optimization by predicting and refining key molecular descriptors such as solubility, lipophilicity, and hydrogen bonding patterns—that correlate with biological activity. Reinforcement learning frameworks (e.g., REINVENT, MolDQN) iteratively modify lead compounds toward desired target profiles, enabling a closed-loop optimization cycle between prediction and synthesis[33].

4.3. Molecular Docking and Binding Affinity Prediction

Molecular docking has traditionally relied on scoring functions and energy minimization algorithms that approximate binding affinity between ligands and targets. DL-based scoring functions now surpass classical approaches by learning directly from experimentally validated binding data[54].

Deep learning models like DeepDocking, DeltaDock, and NeuralDock utilize CNNs and GNNs to capture both spatial and physicochemical features of protein–ligand complexes. They predict binding free energy and pose accuracy with higher consistency than traditional scoring functions such as AutoDock Vina and Glide[55].

Integrating AlphaFold-derived protein conformations with DL docking pipelines has further improved the modeling of flexible or previously uncharacterized targets. Moreover, end-to-end differentiable docking frameworks now allow gradient-based optimization of ligand binding poses, bridging structural biology and cheminformatics in a unified deep learning ecosystem[55].

4.4. De Novo Drug Design and Molecular Generation

Generative AI has opened new frontiers in de novo molecular design, allowing computers to create chemically valid, novel compounds optimized for desired properties. Variational autoencoders (VAEs), generative adversarial networks (GANs), and transformer-based generative models can learn latent molecular representations that encode drug-like features[56].

Frameworks such as GENTRL, MolGAN, and REINVENT integrate reinforcement learning (RL) and property-based reward functions to design molecules with high activity, selectivity, and synthetic accessibility. For example, GENTRL successfully generated DDR1 kinase inhibitors in less than 50 days, demonstrating the potential of AI-driven molecular ideation[38].

Recent diffusion models—like DrugDiff and MolDiffusion—extend this concept by sampling new chemical structures from continuous latent spaces, improving diversity and novelty in generated compounds. Integration of quantum machine learning further enables the simulation of molecular electronic structures and reaction pathways. These approaches drastically reduce discovery time and cost while expanding the accessible chemical space beyond human design capabilities.

4.5. Drug Repurposing and Polypharmacology

AI-driven drug repurposing leverages existing drug data to identify new therapeutic indications, reducing both risk and cost in clinical development. DL models analyze transcriptomic signatures, side-effect profiles, and molecular interactions to uncover cross-disease efficacy.

Graph-based DL frameworks such as DeepDTnet and RepurposeDL predict drug–disease associations by integrating heterogeneous biomedical networks. During the COVID-19 pandemic, DL algorithms rapidly screened thousands of approved drugs, identifying potential antivirals such as remdesivir and baricitinib[57].

In addition, transformer-based PLMs can model polypharmacology the interaction of a single compound with multiple targets, enabling safer and more effective multi-target therapeutics. By predicting shared binding motifs across target families, AI models assist in designing drugs for complex diseases such as cancer and neurodegeneration.

4.6. ADMET Prediction and Toxicology Assessment

Late-stage drug failures often result from poor pharmacokinetics or unexpected toxicity. DL-based ADMET modeling provides an efficient solution by predicting absorption, distribution, metabolism, excretion, and toxicity profiles from molecular structure data[58].

Multi-task learning and ensemble DL approaches enable simultaneous prediction of multiple ADMET parameters, reducing redundancy and enhancing model generalization. Notable models such as DeepADMET, ADMETlab 2.0, and Chemprop employ GNN and transformer architectures to integrate physiochemical, transcriptomic, and metabolic data for robust toxicity assessment[59].

Explainable AI (XAI) techniques now highlight toxic substructures, metabolic liabilities, and bioavailability-limiting features, supporting rational compound design. Integration of ADMET prediction with generative AI pipelines ensures that newly designed molecules maintain both potency and pharmacological safety[60].

The integration of deep learning across the major stages of drug discovery from target identification to ADMET profiling has substantially improved efficiency, accuracy, and scalability. DL models now outperform traditional computational and statistical methods in nearly every subdomain of pharmaceutical research. The convergence of structure-aware modeling, multi-omics integration, and generative design is driving a paradigm shift toward a fully automated, AI-assisted drug discovery ecosystem. As interpretability and data standardization continue to advance, these intelligent systems are poised to transform both preclinical research and precision medicine.

5. Benchmark Datasets and Databases

Robust benchmarking resources are essential for assessing the performance and generalizability of AI and deep learning (DL) models in drug discovery. High-quality datasets enable reproducible comparisons, mitigate overfitting, and ensure fairness in model evaluation. **Table 4** summarizes the major open-access datasets that serve as standardized benchmarks for AI-driven drug discovery, including their domains and data accessibility links.

Table 4. Common Datasets in AI-Driven Drug Discovery

Dataset	Description	Domain	URL
BindingDB	Protein–ligand binding affinities	DTI	https://bindingdb.org
ChEMBL	Bioactivity data	QSAR	https://www.ebi.ac.uk/chembl
ZINC15	3D molecular structures	Virtual screening	https://zinc15.docking.org
GPCRdb	GPCR–ligand interactions	GPCR prediction	https://gpcrdb.org
Tox21	Toxicology data	Toxicity prediction	https://tripod.nih.gov/tox21

Public repositories such as ChEMBL, BindingDB, DrugBank, PubChem BioAssay, and ZINC remain foundational for molecular property prediction and drug–target interaction (DTI) modeling. ChEMBL, curated by the European Bioinformatics Institute, provides over two million bioactivity records linking compounds to their biological targets. BindingDB and DrugBank further enrich these data with quantitative binding affinities and pharmacological annotations[61,62].

In the domain of structural modeling, GPCRdb, LEADS-PEP, and PINDER (Protein Interaction Dataset and Evaluation Resource) provide standardized benchmarks for receptor–ligand and protein–protein interactions. For generative and de novo design, datasets such as MOSES, GuacaMol, and QM9 support property-based molecular generation and quantum mechanical validation [63.]

Despite their utility, dataset heterogeneity and noise remain major obstacles. Inconsistent assay conditions, duplicate entries, and sparse annotations can propagate bias into AI predictions[64]. Emerging frameworks advocate for FAIR data principles—Findable, Accessible, Interoperable, and Reusable to enhance data traceability. Federated learning and privacy-preserving data integration approaches now allow model training on distributed, confidential datasets, thereby safeguarding proprietary pharmaceutical data. The continued development of curated, domain-specific benchmarks will be crucial for the transparent evaluation of next-generation DL algorithms in drug discovery.

6. Evaluation Metrics and Model Validation

Standardized performance metrics are crucial for ensuring that AI-based predictions are accurate, interpretable, and comparable across studies. Evaluation protocols vary according to the problem domain, ranging from regression of binding affinities to classification of active versus inactive compounds.

For classification tasks, commonly employed metrics include accuracy, precision, recall, F1-score, and area under the receiver operating characteristic (ROC-AUC) curve. In regression problems such as affinity estimation or pharmacokinetic modeling, root mean square error (RMSE) and mean absolute error (MAE) quantify prediction deviations. For structural predictions, DockQ, root mean square deviation (RMSD), and template modeling scores (TM-score) evaluate three-dimensional accuracy[65,66].

Benchmark initiatives like CASP, LEADS-PEP, and PINDER have standardized metrics to compare docking and DTI performance under consistent data conditions. Cross-validation and independent test splits remain indispensable to prevent data leakage, while transfer learning enables performance assessment on underrepresented targets. The inclusion of explainability metrics such as feature importance, stability, and Shapley-based relevance consistency adds interpretability to purely numerical validation[63].

Ultimately, harmonizing evaluation methodologies across academia and industry is imperative for establishing the reproducibility and credibility of AI-driven pipelines in pharmaceutical development.

7. Drug Dose Optimization and Personalized Therapeutics

Beyond drug discovery, DL frameworks are increasingly applied to dose optimization, addressing inter-patient variability and adverse drug responses. Traditional pharmacokinetic/pharmacodynamic (PK/PD) models rely on compartmental approximations, which often fail to capture nonlinear

physiological feedback. In contrast, reinforcement learning (RL) and neural ODE-based systems dynamically infer optimal dosing regimens from temporal clinical data[67].

Recent studies have demonstrated that recurrent neural networks (RNNs) and long short-term memory (LSTM) models can predict individualized dose–response trajectories, improving safety margins in oncology and chronic disease management. The advent of digital twin (DT) frameworks, virtual patient replicas trained on genomic, metabolomic, and real-time physiological data, further enables simulation of pharmacological outcomes before clinical administration[68,69].

AI-driven dose optimization is being explored for chemotherapeutic protocols, antibiotic stewardship, and insulin titration, demonstrating reductions in toxicity and improved therapeutic efficacy. Coupled with Bayesian uncertainty quantification, these approaches can identify confidence intervals for dosing predictions, aligning AI outputs with clinical risk assessment standards.

Nevertheless, large-scale adoption demands regulatory alignment, real-world validation, and transparent model interpretability to ensure safe clinical integration. By combining DL-based prediction with mechanistic PK/PD models, future intelligent dosing systems will enable truly personalized therapeutics.

8. Success Stories and Translational Applications

The translation of AI and DL methodologies from theoretical models to tangible clinical applications marks a defining achievement in modern drug discovery. Notable success stories underscore the accelerating role of AI across the pharmaceutical pipeline[70]. **Table 5** compiles notable real-world examples of AI-enabled drug discovery efforts that have achieved translational success, from target identification to clinical evaluation.

Table 5. Key Success Stories in AI-Driven Drug Discovery

Company / Institute	AI Model Used	Drug Target	Outcome	Year
Insilico Medicine	GNN + RL	Fibrosis (ENPP1)	Entered Phase I	2021
BenevolentAI	Knowledge Graphs	COVID-19 (Baricitinib)	FDA Approved	2020
DeepMind	AlphaFold	Structural Biology	Protein Structure Database	2021
Exscientia	AI-based design	Oncology drug	Phase II Clinical	2023

One of the earliest examples, *In-silico* Medicine's GENTRL platform, generated potent DDR1 kinase inhibitors within 46 days, an unprecedented acceleration compared to traditional timelines. Similarly, Exscientia employed reinforcement-learning frameworks to design the obsessive-compulsive disorder candidate DSP-1181, which advanced to human trials within 12 months. DeepMind's AlphaFold and AlphaFold 2/3 revolutionized structure prediction, enabling accurate modeling of protein–ligand complexes for previously undruggable targets[71,72,73].

Collaborations between academia and the pharmaceutical industry have produced additional breakthroughs. Pfizer, AstraZeneca, and Roche have adopted AI-driven platforms for lead optimization and clinical trial design, integrating graph neural network (GNN)-based toxicity prediction and transformer-based molecule generation. During the COVID-19 pandemic, AI models rapidly screened existing antiviral libraries, identifying repurposed drugs such as baricitinib and remdesivir within weeks[74,75].

AI success is also evident in GPCR–peptide modeling, where AlphaFold 2 (AF2) achieved superior structural accuracy (DockQ $\geq$ 0.86) over AF3 and Chai-1, confirming its predictive reliability for G-protein-coupled receptor complexes. These results, supported by extensive benchmarking datasets such as LEADS-PEP and GPCRdb, demonstrate that structural precision directly enhances true ligand identification and docking fidelity[76].

Collectively, these cases illustrate AI's tangible contribution to modern pharmacology, reducing R&D cycles, lowering attrition rates, and enabling precision-guided therapeutics. The next generation of hybrid AI platforms, combining generative design, quantum simulation, and digital twin validation, promises to further bridge computational prediction and clinical success.

9. Explainable Artificial Intelligence (XAI) in Drug Discovery

Explainability has emerged as a pivotal requirement for the responsible deployment of AI and deep learning (DL) in pharmaceutical research. While black-box models often achieve superior predictive accuracy, their opacity hinders clinical validation, regulatory approval, and scientific interpretability. Explainable AI (XAI) techniques aim to bridge this gap by elucidating how input features influence model outcomes, allowing researchers to interpret decision pathways in terms of chemical or biological relevance[15].

Approaches such as Shapley Additive Explanations (SHAP), Layer-wise Relevance Propagation (LRP), and Integrated Gradients quantify feature contributions in molecular predictions, identifying structural motifs responsible for drug efficacy or toxicity. In graph neural networks (GNNs), attention visualization highlights substructures critical for binding affinity, thereby enhancing chemical insight. Similarly, in protein–ligand docking, saliency mapping helps correlate predicted conformations with experimentally observed residues[77].

The integration of XAI into generative models also promotes transparent compound design. By interpreting latent space dynamics, chemists can understand how specific modifications impact predicted activity or ADMET properties. This level of transparency fosters interdisciplinary collaboration between AI specialists and medicinal chemists, improving trust in computational recommendations. Regulatory agencies increasingly emphasize the need for interpretable models to ensure patient safety and reproducibility. Therefore, incorporating XAI not only strengthens ethical compliance but also accelerates translational acceptance of AI-driven drug discovery frameworks.

10. Digital Twin Frameworks in Drug Discovery and Development

The Digital Twin (DT) paradigm represents an advanced convergence of AI, systems biology, and computational pharmacology. A digital twin is a dynamic, data-driven virtual representation of a biological system, ranging from molecular pathways to entire patient profiles, that evolves in real time based on continuous feedback from experimental or clinical data[78],

In drug discovery, DT models integrate multi-omics datasets, clinical biomarkers, and physiological parameters to simulate patient-specific drug responses. By coupling reinforcement learning (RL) and mechanistic pharmacokinetic/pharmacodynamic (PK/PD) modeling, digital twins can predict optimal dosage strategies and assess potential toxicity prior to human trials[18]. This has shown particular promise in oncology, where DTs can model tumor evolution and treatment resistance, supporting adaptive therapeutic regimens[79].

Moreover, digital twins extend beyond dosing optimization into clinical trial design, enabling synthetic control arms that reduce participant risk and cost. Integration with federated learning infrastructures allows global collaboration while preserving data privacy, ensuring scalable yet secure model refinement.

The DT framework, when paired with explainable AI, offers a powerful route toward personalized medicine, a paradigm shift from population-based to individual-centric treatment strategies. Future advances will depend on standardizing data acquisition protocols, ensuring model interpretability, and validating digital twin predictions against real-world evidence.

11. Open Problems and Future Research Directions

Despite transformative advances, significant open challenges persist in the application of AI and DL to drug discovery. These issues span data representation, algorithmic generalization, computational scalability, and regulatory adaptation.

1. **Data Bias and Representation Gaps:** Biomedical datasets remain biased toward well-studied protein families and disease types, limiting the generalization of trained models. Expanding coverage to rare diseases and neglected pathogens is critical[80,81].
2. **Cross-Domain Integration:** Combining multi-omics, imaging, and clinical data requires harmonized frameworks capable of processing heterogeneous formats. The development of universal biological embeddings could improve model interoperability[82,83].

3. **Scalability and Efficiency:** Large foundation models such as AlphaFold 3 and Chai-1 demand immense computational resources. Research into **model compression**, **low-rank adaptation**, and **quantum-assisted ML** may mitigate these constraints[84].
4. **Explainability and Ethics:** The interpretability of AI decisions remains insufficient for high-stakes clinical use. Establishing ethical AI standards, interpretability audits, and transparent reporting will be vital[85].
5. **Regulatory and Validation Bottlenecks:** Although AI-generated candidates enter clinical trials, formal guidelines for their evaluation remain evolving. Global regulatory harmonization will determine the pace of AI adoption in pharmaceutical pipelines.

Future research will likely emphasize self-supervised learning, foundation models, and quantum-biological simulations to predict molecular behaviour at atomic resolution. Collaboration between computational scientists, medicinal chemists, and clinicians will remain essential to translate algorithmic insights into practical therapeutics. Ultimately, addressing these open challenges will solidify AI's role as a central enabler of precision drug discovery, transforming how molecules are designed, optimized, and delivered.

12. Conclusion

Artificial intelligence and deep learning have reshaped modern drug discovery by streamlining prediction, design, and toxicity assessment processes. Advanced frameworks such as AlphaFold, graph neural networks, and generative algorithms now enable faster and more reliable target identification, molecular screening, and compound creation. However, challenges remain, particularly data imbalance, limited interpretability, and high computational cost. Certain model predictions still fail experimental validation, underscoring the need for closer integration between in silico and laboratory research. For broad industrial adoption, transparent and explainable models, standardized datasets, and clear regulatory pathways are essential. Future development should emphasize hybrid multimodal architectures, digital twin platforms, and quantum-assisted methods to strengthen translation into clinical practice. Overall, deep learning offers a powerful yet evolving route toward faster, safer, and more sustainable pharmaceutical innovation.

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CRediT authorship contribution statement

L. Sowjanya Upadhyayula: Original draft, Methodology, Investigation, Formal analysis, Data curation. **Mallu Mallikarjuna:** Investigation, Formal analysis, Data curation, Review and editing. **GV Ramesh Babu**: Review and editing, Supervision, and Funding.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Ethical Approval

Not applicable

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