**Paper 1:**

**Title:** The Rise of Deep Learning in Drug Discovery  
**Link (DOI):** https://doi.org/10.1016/j.drudis.2018.01.039  
**Authors:** Hongming Chen et al.  
**Published in:** Drug Discovery Today, Volume 23, Issue 6, June 2018

**Dataset:**

* **Multiple datasets mentioned** including:
  + **Tox21** (toxicology)
  + **ChEMBL**, **LINCS**, **BindingDB**, **ZINC**
  + MoleculeNet (benchmark suite for ML in drug discovery)

### Methodology or Models Used:

* Explored and reviewed multiple deep learning models applied in drug discovery:
  + **Graph Convolutional Networks (GCNs)**
  + **Multitask Deep Neural Networks (DNNs)**
  + **Convolutional Neural Networks (CNNs)**
  + **Recurrent Neural Networks (RNNs)**
  + **Variational Autoencoders (VAEs)**
  + **Generative Adversarial Networks (GANs)**
  + **Reinforcement Learning (RL)** based SMILES generation

**Novelty:**

* **Comprehensive review of DL applications across the full drug discovery pipeline**, from:
  + **Bioactivity prediction**
  + **De novo molecular design**
  + **Synthesis prediction**
  + **Ligand–protein interaction scoring**
  + **Biological image analysis**
* Highlights **automatic feature extraction** from chemical structures via GCNs and SMILES-based models, bypassing manual descriptors.
* Emphasizes **task-specific neural fingerprints** and the rise of **representation learning**.

**Accuracy / Performance:**

* **GCN-based models** achieved **ROC-AUC ~0.83** on **Tox21** (cited work by Duvenaud et al. and others)
* **Multitask DNNs** outperformed single-task models and traditional ML in bioactivity predictions.
  + Example: DNNs won the **Tox21 challenge**.
  + **BACE inhibitor model** achieved classification accuracy of **0.82**

**Evaluation Metrics Used:**

* **ROC-AUC**
* **Precision**, **Recall**
* **BEDROC** (for ranking tasks)
* **Standard Error**, **Accuracy**
* **Boltzmann-enhanced metrics**

**Paper 2:**

**Title:** Deep Learning in Drug Discovery: An Integrative Review and Future Challenges  
**Link (DOI):** https://doi.org/10.1007/s10462-022-10306-1  
**Authors:** Heba Askr et al.  
**Published in:** *Artificial Intelligence Review*, 2023, Volume 56, Pages 5975–6037

**Dataset:**

* Reviewed use of **benchmark datasets** like:
  + **Tox21**, **ChEMBL**, **BindingDB**, **LINCS**, **PubChem**, **ZINC**
  + Also discussed **MoleculeNet**, **DrugBank**, and **L1000** (transcriptomic data)
* Used for tasks like drug–target interaction prediction, drug sensitivity, and drug–drug interaction analysis.

**Methodology or Models Used:**

* Extensive survey of **deep learning models** in drug discovery, including:
  + **Graph Neural Networks (GNNs)** / **GCNs**
  + **CNNs**, **RNNs**, **LSTMs**
  + **GANs** for molecule generation
  + **Autoencoders (VAEs, DAEs)**
  + **Transformer-based architectures**
  + **Deep Matrix Factorization**, **Deep Collaborative Filtering**
* Also discusses **multimodal learning** and **self-attention-based models**

**Novelty:**

* **First large-scale integrative review** covering 300+ papers across:
  + **Drug–Target Interactions (DTIs)**
  + **Drug–Drug Similarity (DDIs)**
  + **Drug Sensitivity and Response**
  + **Adverse Drug Reactions**
  + **Drug Dose Optimization**
  + **Digital Twins (DT)** and **Explainable AI (XAI)** in drug discovery
* Proposes a **unified classification** of DL applications in drug development stages.

**Accuracy / Performance:**

* Highlights models like:
  + **DeepDTA**, **DeepCPI**, **DeepProfile**, **DrVAE**, **DeepGRMF**, **GNNs**
* Example cited:
  + GCN models achieved **ROC-AUC ~0.83** on **Tox21** dataset.
  + **DeepDDI** achieved **accuracy between 84.8–93.2%** in DDI prediction tasks.
  + **DeepProfile** successfully disentangled gene expression profiles for disease classification.

**Evaluation Metrics Used:**

* Common metrics covered:
  + **ROC-AUC**
  + **Precision, Recall, F1-Score**
  + **Mean Squared Error (MSE)**
  + **R² Score**
  + **Accuracy**
  + **BEDROC** (for ranking)
  + **RMSE**, **MAE**

**Paper 3:**

**Title:** Deep Learning in Drug Discovery and Medicine: Scratching the Surface  
**Link (DOI):** https://doi.org/10.3390/molecules23092384  
**Authors:** Dibyendu Dana et al.  
**Published in:** *Molecules*, 2018, 23(9), 2384

**Dataset:**

* No single benchmark dataset used, but discussed tools trained on:
  + **Known bioactive molecules**
  + **FDA-approved drug libraries**
  + **ChIP-seq datasets** for genomics
  + **SMILES** strings for molecular generation

**Methodology or Models Used:**

* Broad coverage of **AI and deep learning techniques** in:
  + **De novo molecule generation**
  + **Transfer learning**
  + **Autoencoders (e.g., VAE)**
  + **Generative Adversarial Networks (e.g., ORGAN)**
  + **Recurrent Neural Networks (RNNs)** with **LSTM** for SMILES-based molecule synthesis
  + **DeepSNR** (a CNN + deconvolution network for predicting transcription factor binding sites)

**Novelty:**

* Combines **precision medicine**, **omics**, and **AI models** to propose:
  + Drug design tailored to **individual omics profiles**
  + Use of **signalosome overlap** for patient inclusion in clinical trials (example: ANG3070 for FSGS)
  + **Drug repurposing** via **Erdos Interactomes** based on structural similarity
  + Proposes **future integration** of bio-conjugates and smart drug-delivery systems

**Accuracy / Performance:**

* Focused more on **conceptual frameworks** than specific accuracy numbers
* Cites:
  + **DeepSNR** for high-resolution transcription factor prediction
  + **AI-generated ligands** for retinoid X and PPAR agonists tested with positive results
  + GAN-based ORGAN model capable of generating **FDA-like molecules**
* Acknowledges that **no AI-generated drug** has yet reached market approval at time of writing

**Evaluation Metrics Used:**

* No direct benchmarking or metric tables provided, but references include:
  + **QSAR performance in Merck challenge**
  + **Synthetic accessibility scores (SA scores)**
  + Structural diversity, **logP**, **H-bond donors/acceptors**, etc., for generated compounds

**Paper 4:**

**Title:** Comprehensive Survey of Recent Drug Discovery Using Deep Learning  
**Link (DOI):** https://doi.org/10.3390/ijms22189983  
**Authors:** Jintae Kim, Sera Park, Dongbo Min, Wankyu Kim  
**Published in:** *International Journal of Molecular Sciences*, 2021, Vol. 22, 9983

**Dataset:**

* Discusses widely used **benchmark datasets** in drug discovery, including:
  + **Tox21**, **BindingDB**, **ChEMBL**, **KIBA**, **Davis**, **PubChem**, **DUD-E**, **ZINC**, **MUV**
  + Also highlights **LINCS-L1000**, **CMAP**, **GuacaMol**, and **MOSES** for de novo molecule generation

**Methodology or Models Used:**

* Extensive coverage of **deep learning architectures**:
  + **Multi-Layer Perceptron (MLP)**
  + **Convolutional Neural Networks (CNN)**
  + **Graph Neural Networks (GNN, GCN, GAT, D-MPNN)**
  + **Recurrent Neural Networks (RNN, LSTM, GRU)**
  + **Transformer/BERT/Attention-based models**
  + **Autoencoders (AE, VAE, AAE)**
  + **Generative Adversarial Networks (GAN, ORGAN, MolGAN)**
* Categorized models for:
  + **Drug–Target Interaction (DTI) prediction**
  + **De novo Drug Design** (random, conditional, scaffold-based, genetic algorithm based)

**Novelty:**

* **One of the most comprehensive surveys to date**, providing:
  + Structured classification of DL models across drug discovery stages
  + Insights into **data representation**: SMILES, fingerprints, graphs, voxels
  + New taxonomies for **ligand-based, structure-based, and relationship-based approaches**
  + Discussion on **evaluation challenges** and **dataset bias**
  + Coverage of **conditional latent-space molecule generation**
  + Case studies including **halicin (antibiotic)** found using D-MPNN

**Accuracy / Performance:**

* Reports high-performing models like:
  + **GCNs & GATs** achieving **ROC-AUC ~0.83** on **Tox21**
  + **DeepDTA** outperformed traditional ML (KronRLS, SimBoost) on **Davis** and **KIBA**
  + **MolGAN** and **ORGAN** for de novo drug design showed good performance in validity and drug-likeness
  + **D-MPNN** and **Edge Memory Neural Networks (EMNN)** outperformed other models on MUV and other benchmarks

**Evaluation Metrics Used:**

* **Classification Metrics:**
  + ROC-AUC, Accuracy, Precision, Recall, F1-Score, AUPR, Balanced Accuracy, MCC
* **Regression Metrics:**
  + MSE, RMSE, R², Spearman’s ρ, Concordance Index (CI)
* **De novo Design Metrics:**
  + Validity, Novelty, Uniqueness, Diversity

**Paper 5:**

**Title:** Machine Learning in Drug Discovery  
**Link (DOI):** https://doi.org/10.1021/acs.jcim.9b00136  
**Authors:** Günter Klambauer, Sepp Hochreiter, Matthias Rarey  
**Published in:** *Journal of Chemical Information and Modeling*, 2019, Vol. 59, pp. 945–946

**Dataset:**

* Mentions use of large datasets from:
  + **ChEMBL** (for bioactivity prediction)
  + **Industrial ADME datasets**
  + **Toxicity modeling datasets**
* Acknowledges the **lack of reliable large datasets** especially in structure-based design.

**Methodology or Models Used:**

* Focused on the **rise of deep learning** in drug discovery:
  + **Feedforward Deep Neural Networks (DNNs)**
  + **Deep Multitask Networks**
  + **Self-normalizing neural networks**
  + **Decision Trees**
  + **Tree-form ML algorithms**
  + **DeepConfidence framework** for uncertainty estimation
* Application areas include:
  + Bioactivity prediction
  + Toxicity prediction
  + Metabolism site prediction
  + Atom mapping
  + Membrane permeability prediction
  + Structure-based virtual screening

**Novelty:**

* Highlights the **increasing adoption of deep architectures** in cheminformatics.
* Introduces **response maps** for model interpretability (highlighting molecule substructures that impact predictions).
* Emphasizes the need for:
  + Better interpretability of deep models
  + Methods to provide confidence intervals (e.g., **DeepConfidence**)
  + Bias control in chemical datasets (especially in virtual screening)

**Accuracy / Performance:**

* No exact ROC-AUC or precision/recall scores given, but:
  + **Multitask DNNs** were shown to improve performance on ADME and toxicity predictions (as per Wenzel et al. and Sosnin et al.).
  + DeepConfidence improves trustworthiness of DNN predictions.
  + Visual response mapping aids in understanding which molecule parts affect activity prediction.

**Evaluation Metrics Used:**

* Not numerically detailed but references:
  + **Confidence intervals**
  + **Prediction error margins**
  + **Model interpretability metrics**
  + Bias-aware validation for structure-based predictions

**Paper 6:**

**Title:** Machine Learning Methods in Drug Discovery  
**Link (DOI):** https://doi.org/10.3390/molecules25225277  
**Authors:** Lauv Patel, Tripti Shukla, Xiuzhen Huang, David W. Ussery, Shanzhi Wang  
**Published in:** *Molecules*, 2020, Vol. 25, 5277

**Dataset:**

* No specific benchmark dataset was emphasized, but multiple examples included:
  + Datasets from **ZINC**, **ChEMBL**, **DrugBank**, **PubChem**
  + Large volumes of **high-throughput screening data**, **omics**, and **microarray datasets**
  + Cancer drug sensitivity databases, COVID-19 protein targets

**Methodology or Models Used:**

* **Classical ML Algorithms:**
  + Random Forest (RF)
  + Naive Bayes (NB)
  + Support Vector Machines (SVM)
* **Deep Learning Techniques:**
  + Deep Neural Networks (DNNs)
  + Convolutional Neural Networks (CNNs)
  + Recurrent Neural Networks (RNNs), especially for SMILES generation
  + Graph Convolutional Networks (GCNs)
  + Monte Carlo Tree Search (MCTS) with Neural Networks for retrosynthesis planning
* **Use Cases:**
  + Drug–target interaction prediction
  + Compound classification
  + Bioactivity prediction
  + De novo drug generation
  + Retrosynthetic planning

**Novelty:**

* Reviews and integrates **both traditional ML and modern DL** techniques
* Highlights specific **algorithmic pipelines** for target discovery, lead optimization, and synthesis
* Provides real-world applications like:
  + Discovery of **halicin** (antibacterial) using DNNs
  + Use of **MCTS + NN** for chemical synthesis
  + ML for **COVID-19 drug repurposing**
  + Development of **bioactive bacteriocins** through ML vector models

**Accuracy / Performance:**

* Not always quantitatively detailed, but key findings included:
  + DNN-based models identified novel antibiotics structurally distinct from existing drugs (e.g., **halicin**)
  + SVM models accurately separated active/inactive compounds for disease pathways
  + RF and NB combined improved predictions for **HIV/HCV** QSAR models
  + MCTS-based retrosynthesis solved **>90% of synthetic pathways in 60 seconds**

**Evaluation Metrics Used:**

* Common ML/DL metrics discussed:
  + Accuracy
  + Precision
  + ROC-AUC
  + Recall
  + Confidence intervals
  + Error estimates (e.g., overfitting/underfitting, false positives)

**Paper 7:**

**Title:** Recent Applications of Deep Learning and Machine Intelligence on In Silico Drug **Discovery**: Methods, Tools and Databases  
**Link (DOI):** <https://doi.org/10.1093/bib/bby061>  
**Authors:** Ahmet Sureyya Rifaioglu et al.  
**Published in:** *Briefings in Bioinformatics*, 2019, Volume 20, Issue 5, Pages 1878–1912

**Dataset:**

* Comprehensive mention of benchmark datasets and data repositories:
  + **Tox21**, **DUD-E**, **MUV**, **BindingDB**, **ChEMBL**, **DrugBank**, **PubChem**, **ZINC**, **STITCH**, **MoleculeNet**
  + **Merck Kaggle Challenge dataset**, **Yamanishi dataset**
  + Supports data for DTI, QSAR, toxicity, activity prediction

**Methodology or Models Used:**

* Detailed review of **Machine Learning and Deep Learning** in:
  + **Virtual Screening (VS)** – ligand-based, structure-based, and **proteochemometric modeling (PCM)**
* Key deep learning models include:
  + **Deep Neural Networks (DNNs)**
  + **Autoencoders**, **CNNs**, **RNNs**
  + **DeepDTIs**, **DeepChem**, **DeepConfidence**
  + Hybrid models using both ligand and protein descriptors
* Introduced **PCM** as a third approach to VS combining ligand and target descriptors

**Novelty:**

* One of the most detailed surveys on:
  + Descriptors (compound and protein) for ML modeling
  + Tools, libraries, and software (RDKit, OpenBabel, Dragon, DeepChem, etc.)
  + Extensive database summary with metadata
* Introduced taxonomies for descriptor types and prediction frameworks
* Presented a **pipeline-based view** of VS with ML/DL components

**Accuracy / Performance:**

* No single benchmark model evaluated, but cited:
  + **AtomNet**, **DeepDTIs**, **DeepChem** as high-performing systems
  + **DUD-E and MUV** datasets used for rigorous evaluation
  + Example: DeepDTIs showed improved AUC scores on benchmark datasets (not specific values mentioned here)

**Evaluation Metrics Used:**

* Discussed and recommended metrics:
  + **ROC-AUC**, **Precision**, **Recall**, **Accuracy**, **F1 Score**
  + **Mean Squared Error (MSE)**, **Root Mean Squared Error (RMSE)**
  + **Balanced Accuracy**, **Matthews Correlation Coefficient (MCC)**
  + Evaluation pipelines included cross-validation and train/test splits

**Paper 8:**

**Title**: Structure-Based Drug Discovery with Deep Learning  
**Link**: https://doi.org/10.1002/cbic.202200776  
**Authors**: R. Özçelik, D. van Tilborg, J. Jiménez-Luna, F. Grisoni  
**Published in**: *ChemBioChem*, 2023

**Dataset:**

* **PDB**, **scPDB**, **BioLip**, **PDBbind**, **UniProt**, **AlphaFold**, **Binding MOAD**, **BindingDB**, **KIBA**, **Davis**, etc.
* These datasets cover over 60 million sequences and hundreds of thousands of protein-ligand complexes.

**Methodology / Models Used:**

* Focuses on **structure-based drug discovery (SBDD)** enhanced by deep learning.
* Used models include:
  + **Graph Neural Networks (GNNs)**
  + **Convolutional Neural Networks (CNNs)**
  + **Recurrent Neural Networks (RNNs)**
  + **Transformers**
  + **Geometric Deep Learning**
  + **Generative Models (e.g., GANs, VAEs, Diffusion Models)**

**Novelty:**

* Comprehensive review of **deep learning applied to SBDD**, rather than ligand-based models.
* Highlights how **protein structure (3D), surface, and sequence** can all be leveraged using different deep learning architectures.
* Discusses **binding site detection**, **drug-target interaction (DTI) prediction**, and **structure-based de novo molecule design**.
* Addresses the gap in **protein-ligand co-structure data availability** and proposes leveraging **AlphaFold** and **geometric deep learning** for enhanced prediction.

**Accuracy / Performance**

* Highlights that models such as **DeepDTA**, **BiteNet**, **OctSurf**, and others achieve **high binding site prediction and DTI performance** on benchmark datasets.
* Emphasizes the importance of **interpretable, robust, and unbiased** model evaluation over raw accuracy alone.

**Evaluation Metrics Discussed:**

* **Binding affinity (Kd, IC50, etc.)**
* **Docking score**
* **Binding site prediction accuracy**
* **ROC-AUC** and **precision/recall** metrics are referenced but not reported for specific models in this review.

### ****Paper 9:****

**Title**: *Deep Docking: A Deep Learning Platform for Augmentation of Structure-Based Drug*   
**Link**: <https://pubs.acs.org/doi/10.1021/acscentsci.0c00229>  
**Authors**: Francesco Gentile et al.  
**Published in**: *ACS Central Science,* American Chemical Society (ACS),May 19,2020

**Dataset:**

* **ZINC15 database** – ~1.36 billion small molecules
* 12 protein targets (e.g., AR, ERα, VEGFR2, GABAA)

**Methodology or Models Used:**

* Introduced **Deep Docking (DD)**: combines QSAR-based deep learning models with traditional docking (FRED).
* Uses **2D molecular fingerprints** (Morgan fingerprints) and iterative learning to predict docking outcomes and filter non-hits.

**Novelty:**

* First platform enabling **billion-scale virtual screening** with high computational efficiency.
* Achieved **up to 100× database reduction** and **6000× enrichment** for high-quality hits.
* Offers a **scalable, target-independent** framework for deep learning–enhanced docking.

**Accuracy:**

* **ROC-AUC up to 0.91** (e.g., for ERα, AR)
* **90% recall** maintained for virtual hits across all 12 targets
* **Enrichment Factor (EF)** up to **6000×** for top-ranked 100 molecules

**Evaluation Metrics:**

* ROC-AUC
* Precision
* Recall
* Enrichment Factor (EF)
* Full Predicted Database Enrichment (FPDE)

**Paper 10:**

**Title**: *Machine Learning in Drug Discovery*  
**Link**: https://doi.org/10.1021/acs.jcim.8b00478  
**Authors**: Sepp Hochreiter, Guenter Klambauer, Matthias Rarey  
**Published in**: *Journal of Chemical Information and Modeling*, American Chemical Society (ACS), August 15, 2018

**Dataset:**

* No specific dataset used (editorial)
* References major ML challenges like:
  + **Merck Molecular Activity Challenge (2013)**
  + **Tox21 Data Challenge (2015)**

**Methodology or Models Used:**

* Discusses a broad range of **machine learning approaches**, with emphasis on **deep learning (DNNs)**
* Highlights challenges in:
  + Molecular representation
  + Handling of 3D structure and conformations
  + Sparse, noisy, and inconsistent experimental data

**Novelty:**

* Emphasizes the growing importance of **ML and DL in drug discovery**
* Stresses the need for **interdisciplinary collaboration** and **curated experimental data**
* Promotes realistic and robust evaluation strategies for model performance

**Accuracy:**

* No model-specific accuracy reported (editorial overview)
* Notes that deep learning models were **top performers** in prominent drug discovery challenges

**Evaluation Metrics:**

* Not explicitly measured
* Focus on the importance of:
  + Reliable validation strategies
  + Real-world performance assessments
  + Interpretability and reproducibility in ML for drug discovery