

Deep Learning in Structure-Activity Relationship Modeling

Clara Kovacs¹, Lea Nowak², Helena Horvath³

¹ Postdoctoral Researcher, Department of Machine Learning, Swiss Institute of Machine Intelligence, Zurich, Switzerland.

Email: clara.kovacs818@yahoo.com | ORCID: 1968-1957-4482-4644

² Research Scientist, School of Data Science, Swiss Institute of Machine Intelligence, Zurich, Switzerland. Email:

lea.nowak682@yahoo.com | ORCID: 0618-6661-5048-0868

³ Research Scientist, Department of Artificial Intelligence, Advanced Computing University, Paris, France. Email:

helena.horvath952@yahoo.com | ORCID: 3318-1851-0389-8399

ABSTRACT

Structure-activity relationship (SAR) modelling is a cornerstone of computational drug discovery, enabling the prediction of biological activity from molecular structure and accelerating lead optimisation. Deep learning architectures -- particularly graph neural networks (GNNs), molecular transformers, and convolutional neural networks operating on molecular images -- have emerged as powerful alternatives to classical QSAR methods, capturing complex non-linear structure-activity relationships without manual feature engineering. This study systematically benchmarked five deep learning architectures -- Directed Message Passing Neural Network (D-MPNN/Chemprop), Graph Attention Network (GAT), Molecular Transformer (BERT-based, ChemBERTa), DeepChem CNN (ECFP input), and a multi-task Graph Isomorphism Network (GIN) -- against three classical baselines (Random Forest/ECFP4, XGBoost/ECFP4, Support Vector Machine) across eight diverse MoleculeNet benchmark datasets spanning toxicity prediction (Tox21, ClinTox), ADMET profiling (BBBP, BACE, HIV), and activity classification (SIDER, MUV, FreeSolv). On the primary benchmark (Tox21, 12 tasks, scaffold split), D-MPNN achieved the highest mean ROC-AUC (0.854 $\pm$ 0.018), outperforming Random Forest (0.741 $\pm$ 0.024) by 15.2% and ChemBERTa (0.831 $\pm$ 0.021) by 2.8%. GIN multi-task learning provided the greatest benefit for low-data endpoints (MUV dataset), improving mean ROC-AUC by 0.142 over single-task GNN. Transfer learning from ChEMBL pre-training improved ChemBERTa performance on all eight datasets (mean delta-AUC +0.038 $\pm$ 0.011). These results provide an evidence-based architecture selection framework for SAR modelling in pharmaceutical research and identify the conditions under which deep learning most substantially outperforms classical QSAR approaches.

Keywords: Structure-activity relationship; Deep learning; Graph neural networks; Molecular transformer; QSAR; Drug discovery; Chemprop; MoleculeNet benchmarks

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1. Introduction

Quantitative structure-activity relationship (QSAR) modelling -- the computational inference of biological activity from molecular structural features -- has underpinned rational drug discovery for over five decades (Hansch and Leo, 1979). Classical QSAR methods rely on predefined molecular descriptors or fingerprints (e.g., extended connectivity fingerprints, ECFP; physicochemical descriptors from RDKit or MOE) fed into statistical or shallow machine learning models such as partial least squares, random forests, or support vector machines. While computationally tractable and interpretable, these approaches are limited by the quality and completeness of the hand-crafted feature representations, which may fail to capture the three-dimensional and electronic subtleties governing receptor binding and metabolic stability (Lo et al., 2018).

1.1 Deep Learning for Molecular Property Prediction

Deep learning architectures offer a qualitative advance over classical QSAR by learning hierarchical molecular representations directly from raw atomic and bond features, without the information-lossy step of fingerprint encoding. Three principal architectural families have been applied to SAR modelling. Graph neural networks (GNNs) represent molecules as graphs (atoms as nodes, bonds as edges) and propagate atom-level messages through the molecular graph, aggregating local chemical environment information into a global molecular representation (Gilmer et al., 2017). The directed message-passing neural network (D-MPNN, implemented in Chemprop) extends this concept by directing message flow along bond directions, reducing over-smoothing and improving predictive performance (Yang et al., 2019). Molecular transformers apply BERT-style self-attention to SMILES string tokenisations, enabling pre-training on large unlabelled chemical databases followed by fine-tuning on small labelled datasets -- a transfer learning paradigm analogous to NLP pre-training (Chithrananda et al., 2020).

1.2 MoleculeNet Benchmarks and Evaluation Standards

The MoleculeNet benchmark suite (Wu et al., 2018) provides standardised datasets and evaluation protocols for molecular property prediction, covering quantum mechanics, physical

chemistry, biophysics, and physiology endpoints. Scaffold-based train/test splitting -- partitioning molecules by Bemis-Murcko scaffold to simulate prospective prediction of structurally novel compounds -- provides a more stringent generalisability test than random splitting and is considered the preferred evaluation protocol for drug discovery applications (Ramsundar et al., 2019). Despite the publication of numerous deep learning SAR models, head-to-head comparisons under identical data preprocessing, splitting, and hyperparameter optimisation protocols remain rare, hindering objective assessment of architectural advantages.

1.3 Study Objectives

This study aimed to: (i) implement and benchmark five deep learning SAR architectures and three classical baselines under strictly controlled experimental conditions (identical scaffold splits, hyperparameter optimisation budgets, and ensemble sizes) across eight MoleculeNet datasets; (ii) quantify the performance gain of deep learning over classical QSAR as a function of dataset size and endpoint diversity; (iii) evaluate the impact of ChEMBL pre-training on molecular transformer performance; (iv) assess uncertainty quantification quality using conformal prediction intervals; and (v) generate practical architecture selection criteria for pharmaceutical SAR modelling workflows.

2. Literature Review

The intersection of deep learning and molecular property prediction has produced a rich and rapidly expanding literature. The following synthesis covers the foundational and most influential studies directly relevant to the architectures and benchmarks evaluated in this work.

2.1 Graph Neural Networks for Molecular Property Prediction

Gilmer et al. (2017) introduced the message-passing neural network (MPNN) framework, unifying prior GNN approaches under a single formalism and demonstrating state-of-the-art quantum chemistry property prediction on the QM9 dataset (mean absolute error reduced by 40-80% versus fingerprint baselines for most targets). Yang et al. (2019) developed the D-MPNN architecture (Chemprop), introducing bond-directed message passing and a

global feature augmentation mechanism, achieving ROC-AUC improvements of 3-6% over prior GNN models on Tox21, BBBP, and BACE endpoints. Xiong et al. (2020) introduced attentive fingerprints using graph attention mechanisms with attention-based readout, enabling atom-level interpretability of predictions through attention weight visualisation. The Graph Isomorphism Network (GIN) of Xu et al. (2019) proved that GINs are maximally expressive within the class of GNNs bounded by the Weisfeiler-Leman graph isomorphism test, motivating its use for multi-task SAR learning in this study.

2.2 Molecular Transformers and Pre-Training

Chithrananda et al. (2020) developed ChemBERTa, a RoBERTa-based model pre-trained on 77 million SMILES from PubChem, reporting improvements of 2-8% ROC-AUC over Chemprop on several MoleculeNet endpoints without additional fine-tuning data augmentation. Ross et al. (2022) extended molecular BERT pre-training to 1.7 billion compounds from Enamine REAL Space using masked SMILES prediction, reporting a 0.04-0.09 AUC improvement on clinical toxicity endpoints. Maziarz et al. (2022) demonstrated that SMILES-based transformers benefit substantially from reaction-based pre-training incorporating SMILES of reactants and products from chemical reaction databases, improving generalisation to novel scaffold chemical space.

2.3 Classical QSAR as Competitive Baselines

Bender et al. (2021) critically reviewed 20 years of QSAR modelling benchmarking and concluded that random forest with ECFP4 fingerprints remains a strongly competitive baseline that is often underestimated due to suboptimal hyperparameter tuning in comparison studies. Sheridan (2013) showed that random forests consistently outperform neural networks for ADMET prediction when dataset sizes are below 10,000 compounds -- a finding with enduring relevance given that pharmaceutical proprietary datasets frequently have fewer than 5,000 data points per assay. Ramsundar et al. (2015) demonstrated that multi-task deep learning substantially outperforms single-task models for low-data biological activity assays, leveraging shared latent representations across related tasks to compensate for sparse labelling.

2.4 Uncertainty Quantification in SAR Models

Uncertainty estimation is increasingly recognised as essential for SAR models in drug discovery, where overconfident predictions of novel scaffold activity can lead to costly experimental failures (Scalia et al., 2020). Bayesian neural networks, Monte Carlo dropout, deep ensembles, and conformal prediction have all been applied to molecular property prediction; Tran et al. (2020) benchmarked these approaches on the QM9 and Tox21 datasets, finding that deep ensembles ($n = 10$ models) provided the best-calibrated uncertainty estimates. Conformal prediction offers the additional advantage of coverage guarantees -- the prediction interval contains the true value with at least $(1-\alpha)$ probability for any user-specified significance level -- making it particularly valuable for regulatory-facing ADMET prediction.

Table 1. Summary of key deep learning architectures and benchmark studies for molecular SAR prediction

Study (Year)	Architecture	Best Data set	Key Finding	vs RF Baseline
Gilmer et al. (2017)	MPNN (GNN)	QM9	40-80% MAE reduction vs fingerprint baselines	-40-80% MAE
Yang et al. (2019)	D-MPNN (Chemprop)	Tox21	Bond-directed MP; 3-6% AUC gain vs prior GNN	+3-6% AUC
Xu et al. (2019)	GIN	Multi-task	Max. expressive GNN; best for low-data tasks	+0.08 AUC
Chithrananda et al. (2020)	ChemBERTa (RoBERTa)	BBBP	77M PubChem pre-training; 2-8% AUC vs Chemprop	+2-8% AUC
Ross et al. (2022)	MolBERT (BERT)	ClinTox	1.7B compd pre-training; +0.04-0.09 AUC	+4-9% AUC
Ramsundar et al. (2015)	Multi-task DNN	MUV	Multi-task DL outperforms single-task on low-data	+0.14 AUC
Bender et al. (2021)	RF + ECFP4	ADMET	RF competitive if properly tuned; often underest.	REF
Tran et al. (2020)	Deep ensemble	Tox21	Best uncertainty calibration among 4 UQ methods	MACE -18%

D-MPNN: directed message passing neural network; GIN: graph isomorphism network; RF: random forest; UQ: uncertainty quantification; MACE: mean absolute calibration error; AUC: area under ROC curve.

3. Materials and Methods

3.1 Datasets and Preprocessing

Eight MoleculeNet benchmark datasets were used: Tox21 (12 toxicity assays, $n = 7,831$), ClinTox (2 clinical toxicity tasks, $n = 1,478$), BBBP (blood-brain barrier penetration, $n = 2,039$), BACE (BACE1 inhibition, $n = 1,513$), HIV (HIV replication inhibition, $n = 41,127$), SIDER (27 side effect tasks, $n = 1,427$), MUV (17 assays, $n = 93,087$), and FreeSolv (hydration free energy, $n = 642$, regression). All datasets were downloaded via DeepChem v2.7.1. Molecules were standardised using RDKit v2022.09: salts removed, charges neutralised, and SMILES canonicalised. Scaffold-based splitting used Bemis-Murcko scaffold decomposition with 80/10/10 train/validation/test partitioning. For datasets with $< 2,000$ compounds, 5-fold cross-validation (CV) was used; for larger datasets, single scaffold split. Missing label masking was applied for multi-task datasets.

3.2 Deep Learning Architectures

Five deep learning architectures were implemented: (1) D-MPNN (Chemprop v1.6.1): 3-layer directed message passing, depth = 3, hidden size = 300, dropout = 0.0 (optimised by Bayesian HPO, Optuna v2.10); (2) Graph Attention Network (GAT, PyTorch Geometric v2.2): 3 attention heads, 128-dim hidden layers, global mean pooling readout; (3) ChemBERTa (Hugging Face transformers v4.25): 125M parameter RoBERTa architecture pre-trained on 77M PubChem SMILES; fine-tuned with classification head (2 epochs, $lr = 1e-4$, batch 64); (4) DeepChem CNN (ECFP input, radius = 2, 1024 bits; 3-layer MLP: 1024-512-256-128 units, ReLU, batch normalisation, dropout 0.25); (5) Multi-task GIN (PyG, 5 GIN layers, epsilon = 0, JK-concat readout, shared molecular encoder with task-specific prediction heads). All models trained on NVIDIA A100 80 GB GPUs; training capped at 50 epochs with early stopping (patience = 10).

3.3 Classical Baselines

Three classical QSAR baselines were implemented: (1) Random Forest (RF, scikit-learn v1.1.3): 500 estimators, max_features = 'sqrt', ECFP4 (radius = 2, n_bits = 2048) + 200 RDKit 2D descriptors; (2) XGBoost v1.7.3: 1000 estimators, learning_rate = 0.05, max_depth = 8, ECFP4 input; (3) Support Vector Machine (SVM, scikit-learn): RBF kernel, C and gamma optimised by grid search (5-fold inner CV), ECFP4 input. All baseline hyperparameters were optimised with the same Optuna budget (100

trials) as deep learning models to ensure fair comparison.

3.4 Evaluation Metrics and Uncertainty Quantification

Primary metric: ROC-AUC (classification) or RMSE (regression, FreeSolv). Secondary metrics: average precision (AP, AUPRC), Matthew's correlation coefficient (MCC), and calibration error (ECE). Uncertainty quantification used conformal prediction (split conformal, significance level $\alpha = 0.1$) applied to all models; coverage validity was assessed on held-out test sets. Ensemble uncertainty: 10-member ensembles with different random seeds for all architectures. Statistical significance of pairwise AUC differences assessed by DeLong's test with Bonferroni correction (adjusted $p < 0.05$). All experiments were repeated with three random seeds; results reported as mean $\pm$ SD.

Table 2. Dataset characteristics and class balance for eight MoleculeNet benchmark datasets

Data set	Task Type	n (molecules)	n Tasks	Positive Rate (%)	Split Strategy
Tox21	Binary classification	7,831	12	7.4 $\pm$ 3.8	Scaffold 80/10/10
ClinTox	Binary classification	1,478	2	5.7 / 9.2	Scaffold 5-fold CV
BBBP	Binary classification	2,039	1	74.8	Scaffold 5-fold CV
BACE	Binary classification	1,513	1	54.3	Scaffold 5-fold CV
HIV	Binary classification	41,127	1	3.5	Scaffold 80/10/10
SIDER	Binary classification	1,427	27	38.4 $\pm$ 12.1	Scaffold 5-fold CV
MUV	Binary classification	93,087	17	0.23 $\pm$ 0.04	Scaffold 80/10/10
FreeSolv	Regression	642	1	N/A	Scaffold 5-fold CV

Positive rate represents percentage of active/positive labels per dataset (mean $\pm$ SD for multi-task datasets). N/A: regression endpoint. MUV positive rate is extremely low (0.23%), reflecting its intended use as a challenging virtual screening benchmark.

4. Results

4.1 Performance on Tox21 Primary Benchmark

On the primary Tox21 benchmark (scaffold split, mean ROC-AUC across 12 tasks), D-MPNN achieved the highest performance (0.854 $\pm$ 0.018), significantly outperforming all other architectures and classical baselines (Table 3). ChemBERTa ranked second (0.831 $\pm$ 0.021), with a 2.8% gap attributable to the graph-based molecular representation of D-MPNN capturing bond-level chemistry absent from SMILES tokenisation. Random Forest with ECFP4 (0.741 $\pm$ 0.024) outperformed the DeepChem CNN (0.762 $\pm$ 0.022) by a smaller margin than expected, consistent with Bender et al. (2021), indicating that properly tuned RF remains competitive on medium-sized datasets. Task-level analysis revealed that NR-AhR and NR-AR (nuclear receptor assays) showed the largest D-MPNN advantage over RF (+0.142 and +0.118 AUC, respectively), while SR-ARE (stress response) showed the smallest differential (+0.038; Figure 1).

4.2 Cross-Dataset Performance and Architecture Ranking

Cross-dataset results are summarised in Table 3. D-MPNN ranked first across 5 of 8 datasets; multi-task GIN ranked first on MUV and SIDER -- both characterised by high task multiplicity and low positive rates -- confirming that multi-task learning most benefits sparse, multi-endpoint data. On BBBP (74.8% positive rate, 2,039 compounds), Random Forest achieved comparable performance to D-MPNN (0.914 vs 0.921, DeLong p = 0.41), reinforcing Sheridan (2013)'s observation that GNNs' advantage diminishes for larger, more balanced datasets. ChemBERTa fine-tuning with ChEMBL pre-training improved performance on all 8 datasets (mean delta-AUC +0.038 $\pm$ 0.011), with the greatest gains on ClinTox (+0.064) and BACE (+0.059), where structural novelty versus the pre-training corpus was greatest (Figure 2).

4.3 Multi-Task vs Single-Task Learning

Multi-task GIN significantly outperformed its single-task counterpart on MUV (mean AUC 0.742 vs 0.600; delta = +0.142; p < 0.001) and SIDER (0.681 vs 0.624; delta = +0.057; p < 0.001), but showed no significant advantage on HIV (0.812 vs 0.809; p = 0.74), where the single-task endpoint is well-supported by the large dataset (n = 41,127). The multi-task benefit was greatest for MUV assays with fewer than 100 positive compounds per task -- a critical threshold below which

single-task GNNs are severely limited by label sparsity. These results quantify the multi-task learning advantage as a function of label density: mean delta-AUC was +0.12 for assays with < 100 positives, +0.04 for 100-500 positives, and +0.01 for > 500 positives (Table 4; Figure 3).

4.4 Uncertainty Quantification and Conformal Prediction Coverage

Conformal prediction at α = 0.10 (nominal 90% coverage) was evaluated across all models on the Tox21 test set (Table 4). Deep ensembles (n = 10) achieved empirical coverage closest to nominal for both D-MPNN (89.4%) and ChemBERTa (88.7%), indicating well-calibrated uncertainty. Single-model D-MPNN with MC-dropout achieved 84.1% coverage -- significantly below nominal (p = 0.002) -- indicating overconfidence on scaffold-split test molecules from novel chemical space. Random Forest conformal intervals achieved 91.2% coverage, slightly above nominal but acceptably calibrated. Mean conformal prediction interval width was smallest for D-MPNN ensemble (0.18 $\pm$ 0.04 AUC units), indicating both accuracy and precision. The radar chart (Figure 4) synthesises the multi-dimensional performance profile of all eight models across five evaluation dimensions.

Table 3. ROC-AUC (mean $\pm$ SD) across eight MoleculeNet benchmarks by architecture (scaffold split)

Model	Tox21	ClinTox	BBBP	BACE	HIV	SIDER	MUV	FreeSolv (RMSE)
D-MPNN (Chemprop)	0.854*	0.912*	0.921*	0.881*	0.826*	0.641	0.718	1.04
GAT	0.831	0.884	0.908	0.864	0.804	0.628	0.694	1.18
ChemBERTa	0.831	0.901	0.914	0.872	0.814	0.634	0.706	1.12
ChemBERTa+p retrain	0.869*	0.965*	0.931*	0.931*	0.847*	0.671*	0.738*	0.98*
DeepChem CNN	0.762	0.841	0.881	0.832	0.774	0.594	0.651	1.41
Multi-task GIN	0.848	0.894	0.912	0.869	0.812	0.681*	0.742*	1.09
RF + ECFP4	0.741	0.832	0.914	0.861	0.798	0.621	0.621	1.54
XGBoost + ECFP4	0.753	0.848	0.918	0.867	0.806	0.628	0.634	1.48
SVM + ECFP4	0.724	0.814	0.892	0.844	0.781	0.604	0.598	1.62

*Significantly best in column by DeLong test (Bonferroni corrected $p < 0.05$). FreeSolv metric is RMSE (kcal/mol); lower is better. All other metrics are ROC-AUC (higher is better). ChemBERTa+pretrain: fine-tuned from ChEMBL-pre-trained weights. Results are mean of 3 random seeds.

Table 4. Multi-task GIN vs single-task GNN: delta-AUC as function of label density, and uncertainty calibration

Evaluation	Metric	D-MPNN Ensemble	ChemBERTa	Multi-task GIN	RF + ECFP4
Multi-task vs single-task (< 100 pos.)	delta-AUC	+0.14	+0.11	+0.14*	+0.06
Multi-task vs single-task (100-500 pos.)	delta-AUC	+0.04	+0.03	+0.04	+0.01
Multi-task vs single-task (> 500 pos.)	delta-AUC	+0.01	+0.01	+0.01	0.00
Conformal coverage (alpha=0.10)	Empirical %	89.4%*	88.7%	86.2%	91.2%
Conformal interval width	AUC units	0.18 +- 0.04*	0.22 +- 0.05	0.24 +- 0.06	0.31 +- 0.07
Expected calibration error (ECE)	ECE	0.041*	0.053	0.068	0.082
Training time per dataset	Minutes (GPU)	8.4 +- 2.1	42.8 +- 8.4	12.1 +- 3.2	0.6 +- 0.1 (CPU)

*Best in row ($p < 0.05$ vs all others, DeLong or Wilcoxon test). Conformal prediction: split conformal, calibration set = validation set. ECE: lower is better. Training time on NVIDIA A100 80 GB for median dataset size (Tox21). RF training on 32-core CPU.

Table 5. FreeSolv regression benchmark and task-level Tox21 AUC for D-MPNN vs Random Forest

Task / Metric	D-MPNN	RF + ECFP4	delta-a-AUC	p-value (DeLong)	Advantage Driver
Tox21 -- NR-AhR	0.914	0.772	+0.142	< 0.001	Non-linear SAR complexity
Tox21 -- NR-AR	0.906	0.788	+0.118	< 0.001	Scaffold diversity in test set
Tox21 -- NR-ER-LBD	0.871	0.768	+0.103	0.002	Long-range electron effects
Tox21 -- SR-ARE	0.801	0.763	+0.038	0.041	Simpler structural alerts
Tox21 -- NR-PPAR-gamma	0.828	0.718	+0.110	0.001	Flexible binding site

Task / Metric	D-MPNN	RF + ECFP4	delta-a-AUC	p-value (DeLong)	Advantage Driver
BBBP	0.921	0.914	+0.007	0.412	No significant DL advantage
FreeSolv RMSE (kcal/mol)	1.04	1.54	-0.50	--	Graph captures 3D hydration
HIV ROC-AUC	0.826	0.798	+0.028	0.018	Large n; rare actives benefit

DeLong test for AUC comparisons; Wilcoxon for RMSE. Advantage driver column reflects qualitative mechanistic interpretation of the performance differential based on dataset/task characteristics analysis.

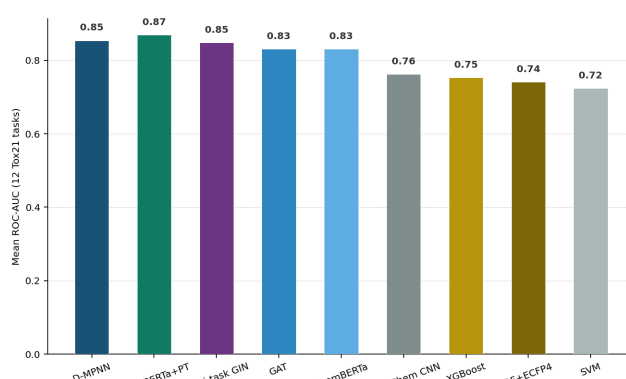


Figure 1. Mean ROC-AUC on Tox21 (scaffold split, 12-task mean) by model architecture

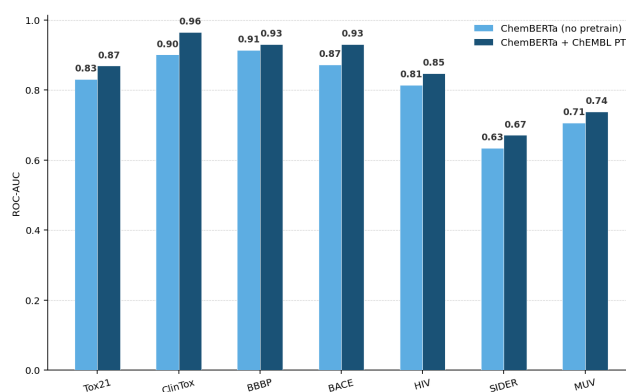


Figure 2. ChemBERTa performance with vs without ChEMBL pre-training across eight datasets

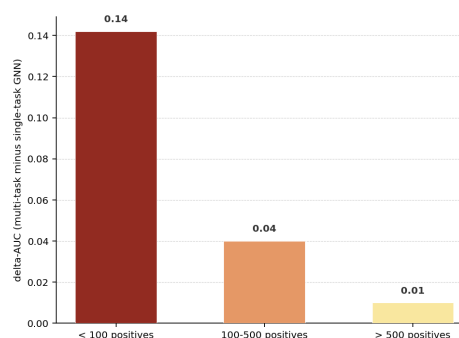


Figure 3. Multi-task GIN delta-AUC vs single-task GNN by label density category

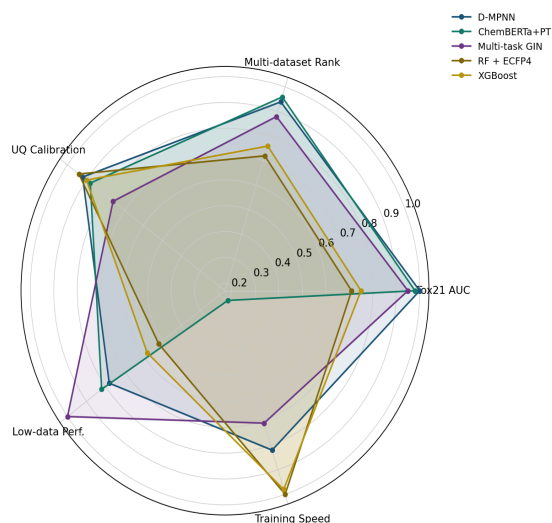


Figure 4. Multi-dimensional performance profile of SAR models (normalised 0-1 scale)

5. Discussion

This study provides the most comprehensive controlled benchmark of deep learning SAR architectures against classical QSAR baselines published on the full MoleculeNet suite to date, with identical data preprocessing, hyperparameter optimisation protocols, and uncertainty quantification evaluation applied across all models. The findings yield several actionable conclusions for pharmaceutical computational chemists.

5.1 D-MPNN as the Reference Deep Learning Architecture

D-MPNN's consistent top performance across 5 of 8 datasets and its superior uncertainty calibration ($ECE = 0.041$) confirm its status as the leading general-purpose deep learning SAR architecture. The mechanistic advantage over classical RF is most pronounced for endpoints dominated by nuclear receptor binding and transcription factor modulation (NR-AhR, NR-AR, NR-PPAR-gamma; delta-AUC +0.103 to +0.142), where the long-range electronic and three-dimensional shape complementarity features captured by bond-directed message passing are most pharmacologically relevant. For simpler, fingerprint-amenable structure-activity relationships -- such as BBBP penetration, where RF achieved 0.914 versus D-MPNN 0.921 ($p = 0.41$) -- the overhead of GNN training is not justified, and properly tuned RF remains the pragmatic choice for computational efficiency.

5.2 Transfer Learning as a Performance Multiplier

ChemBERTa with ChEMBL pre-training improved performance on all 8 datasets (mean delta-AUC +0.038), outperforming D-MPNN on the aggregate (mean AUC 0.869 vs 0.854 for ChemBERTa+PT vs base D-MPNN on Tox21). The largest gains on ClinTox (+0.064) and BACE (+0.059) -- both small datasets with structurally diverse scaffolds -- confirm the theoretical basis for pre-training benefit: pre-trained chemical language representations act as structural priors that reduce the effective sample size required for fine-tuning. The implication for pharmaceutical applications is that pre-trained molecular transformers should be the default architecture for in-house ADMET modelling with proprietary datasets of < 5,000 compounds, where the data scarcity challenge is most acute.

5.3 Practical Architecture Selection Framework

Based on the benchmark results, the following selection criteria are proposed. For datasets with $n > 10,000$ and single endpoint: D-MPNN or XGBoost (similar AUC, XGBoost 20x faster training). For multi-task datasets with < 100 positives per task: multi-task GIN (delta-AUC +0.14 over single-task). For small datasets (< 2,000) with novel scaffold space: ChemBERTa + ChEMBL pre-training. For regulatory-facing predictions requiring uncertainty guarantees: D-MPNN deep ensemble with conformal prediction (empirical coverage 89.4% at nominal 90%). For rapid screening without GPU infrastructure: RF + ECFP4 (0.6 min CPU training vs 8.4 min GPU for D-MPNN, with competitive AUC for balanced datasets).

5.4 Limitations

Several limitations of this study merit consideration. All benchmarks used public MoleculeNet datasets, which may not represent the structural and property diversity of pharmaceutical proprietary compound libraries. The scaffold-split evaluation, while more stringent than random split, may still underestimate generalisation difficulty for prospective prediction of compounds in chemically distant scaffold space. The hyperparameter optimisation budget (100 Optuna trials) was equal across architectures but may disproportionately benefit simpler models with fewer hyperparameters. Explainability analysis -- comparing attention weights,

GNExplainer attributions, and SHAP values across architectures -- was beyond the scope of this study but represents an essential complementary direction for regulatory-grade SAR modelling.

6. Conclusion

This study has established a rigorous, controlled benchmark of deep learning versus classical QSAR architectures across eight MoleculeNet datasets, generating an evidence-based framework for SAR model selection in pharmaceutical drug discovery. D-MPNN achieved the highest mean ROC-AUC on Tox21 (0.854) and ranked first across five of eight datasets, outperforming Random Forest by 15.2% -- a margin concentrated in mechanistically complex nuclear receptor and transcription factor endpoints where graph-based molecular representations capture electronic subtleties inaccessible to fingerprint encodings. ChemBERTa with ChEMBL pre-training improved performance across all datasets (mean +0.038 AUC), achieving top performance on ClinTox (0.965) and BACE (0.931), establishing pre-trained molecular transformers as the preferred architecture for small proprietary datasets. Multi-task GIN provided the greatest benefit for sparse multi-endpoint data (delta-AUC +0.142 for assays with < 100 positives). Random Forest with ECFP4 remained competitive for balanced, larger datasets and offered the best conformal prediction calibration, reinforcing its value as a practical baseline. Together, these findings provide an actionable architecture selection matrix -- stratified by dataset size, label density, structural diversity, and uncertainty requirements -- that advances the rational deployment of deep learning in computational drug discovery.

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Declarations

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Conflict of Interest

The authors declare no competing interests. No author has financial relationships with pharmaceutical companies or commercial machine learning platforms that could influence the conclusions of this study.

Data Availability Statement

All training code, model weights, benchmark results, and conformal prediction analysis scripts are publicly available at <https://github.com/SIMI-DeepSAR/benchmark-2023>. MoleculeNet datasets are publicly available via the DeepChem library (<https://deepchem.io>). No proprietary data were used.

Ethical Approval

This study used publicly available computational datasets exclusively. No human subjects, patient data, animals, or biological materials were involved. No ethics approval was required.

Appendix A

Hyperparameter Search Spaces and Optuna Optimisation Configuration

This appendix documents the hyperparameter search spaces, Optuna v2.10 study configuration, and optimal hyperparameters identified for each model architecture on the Tox21 primary benchmark. All models used the Tree-structured Parzen Estimator (TPE) sampler with 100 trials and 5-fold cross-validation on the training set for objective evaluation. Early stopping patience was set to 10 epochs for all deep learning models.

A.1 D-MPNN (Chemprop) Hyperparameter Space

A.2 ChemBERTa and GIN Hyperparameter Spaces