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ChemBERTa-3: An Open Source Training Framework for Chemical Foundation Models

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The rapid advancement of machine learning in computational chemistry has opened new doors for designing molecules, predicting molecular properties, and discovering novel materials. However, building scalable and robust models for molecular machine learning remains a significant challenge due to the vast size and complexity of chemical space. Recent advances in chemical foundation models hold considerable promise for addressing these challenges, but such models remain difficult to train and are often fully or partially proprietary. For this reason, we introduce ChemBERTa-3, an open source training and benchmarking framework designed to train and fine-tune large-scale chemical foundation models. ChemBERTa-3 provides: (i) unified, reproducible infrastructure for model pretraining and fine-tuning, (ii) systematic benchmarking tooling to evaluate proposed chemical foundation model architectures on tasks from the MoleculeNet suite, and (iii) fully open release of model weights, training configurations, and deployment workflows. Our experiments demonstrate that although both graph-based and transformer-based architectures perform well at small scale, transformer-based models are considerably easier to scale. We also discuss how to overcome the numerous challenges that arise when attempting to reproducibly construct large chemical foundation models, ranging from subtle benchmarking issues to training instabilities. We test ChemBERTa-3 infrastructure in both an AWS-based Ray deployment and in an on-premise high-performance computing cluster to verify the reproducibility of the framework and results. We anticipate that ChemBERTa-3 will serve as a foundational building block for next-generation chemical foundation models and for the broader project of creating open source LLMs for scientific applications. In support of reproducible and extensible science, we have open sourced all ChemBERTa3 models and our Ray cluster configurations.

1 Introduction

Drug discovery is a complex and time-intensive process that involves identifying potential therapeutic compounds and evaluating their biological efficacy. Molecular property prediction models have had a significant impact in the drug discovery process, since predicted properties are central to evaluating, selecting, and generating candidate molecules[1]. In recent years, deep learning has been widely used for molecular property prediction. A range of architectures including graph neural networks and transformer-based architectures, alongside methodologies such as pretraining, contrastive learning, multi-task learning, and transfer learning, have all been used to enhance predictive accuracy and generalization[2,1]. Large pre-trained transformer architectures, also known as chemical foundation models, have risen to particular prominence in recent years due to their potential to learn basic chemistry directly from large unlabeled compound databases[3–9].

Despite rapid progress in the development of chemical foundation models, there has been little systematic comparison of how different pretraining methodologies perform across diverse model architectures. Most existing studies focus on individual model classes, offering only a limited perspective on their strengths. This results in a narrow or incomplete understanding of how different models perform and compare across various contexts. One con-

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tributing factor to this lack of benchmarking is the substantial infrastructure required to pretrain and evaluate chemical foundation models at scale. Even with the availability of large-scale chemical datasets [10], the process of pre-training these models remains computationally intensive, and requires both scalable hardware and software infrastructure. These challenges have made large-scale reproducible benchmarking difficult.

In previous work, we introduced and open-sourced ChemBERTa [3] and ChemBERTa-2 [4], BERT-like transformer models designed to learn molecular fingerprints through semi-supervised pretraining. ChemBERTa was trained on a dataset of 10 million compounds, leveraging masked-language modeling (MLM) to extract meaningful molecular representations [11]. ChemBERTa-2 further explored the scaling hypothesis—that pretraining on larger datasets enhances downstream performance—by employing both MLM and multi-task regression (MTR) over a significantly larger corpus of 77 million SMILES strings. The associated pretrained models were open sourced and have been widely used [12,13] (with over 700 citations for ChemBERTa and 200 citations for ChemBERTa-2 at time of writing). In past work, we have also introduced MoleculeNet [14], a widely used benchmarking framework for molecular property prediction (cited over three thousand times at time of writing). All these works (ChemBERTa, ChemBERTa-2, and MoleculeNet) have been released as part of the open source DeepChem ecosystem [15] which has built a broadly used open-source framework (over six thousand stars on Github) for drug discovery, materials science, and biology.

Recent work, such as MegaMolBART [6] and Chemformer [7], has introduced transformer-based models trained on significantly more data than ChemBERTa and ChemBERTa-2 for molecular property prediction. However, in some cases, models have not been fully open sourced and remain hard to use and reproduce. For example, while MoLFormer [5] has demonstrated strong performance and conducted extensive benchmarking, the largest state-of-art MoLFormer models have not been open sourced. Furthermore, benchmarking was not performed in a unified fashion: comparisons between MoLFormer and other models relied primarily on results reported from prior studies and employed a differing dataset splitting strategy from past studies, making reported comparisons not fully accurate (as we will discuss in more detail later in this work).

To address these limitations, we introduce the ChemBERTa-3 framework, an open source extensible platform for training and benchmarking chemical foundation models. ChemBERTa-3 is fully integrated into the DeepChem library and ecosystem and is able to leverage the extensive collection of models and benchmarking infrastructure available in DeepChem [15]. To scale data-parallel training to multiple GPUs, ChemBERTa-3 leverages Ray's distributed training infrastructure [16] and provides tooling specifically designed for efficient pretraining and fine-tuning of large-scale chemical foundation models. This integration supports both transformer-based and graph-based pretraining, allowing users to seamlessly pretrain and fine-tune models within DeepChem's modular ecosystem. We also introduce benchmarking guidelines and scripts to benchmark proposed chemical foundation model architecture using datasets from the MoleculeNet suite [14].

As our first core contribution, we leverage the ChemBERTa-3 framework to compare and contrast several model architectures and their associated pretraining methods by systematically benchmarking. In particular we investigate how transformer-based methods compare to graph-based methods. Our experiments indicate that while graph-based models and pretraining methodologies perform comparably to transformer-based models at small scale, transformer-based approaches are considerably easier to scale to large datasets. Our results suggest that further investment in scaling graph-based pretraining infrastructure may be worthwhile.

As our second core contribution, we use ChemBERTa-3 infrastructure to train fully open-source MoLFormer architecture models on the Zinc20 dataset. We find that reproducing reported past MoLFormer results is highly challenging due to several subtleties in both benchmarking and model training. In particular, we find that MoLFormer's scaffold splitting algorithm is not equivalent to the MoleculeNet/DeepChem scaffold splitting algorithm, making earlier reported comparisons between MoLFormer and ChemBERTa/ChemBERTa-2 models inaccurate. To prevent such issues from arising in future work, ChemBERTa-3 proposes a standard benchmarking process for chemical foundation models using the MoleculeNet suite, ensuring consistent evaluation protocols and enabling more reliable comparisons across different model architectures. This benchmarking infrastructure is easily extensible to new datasets, ensuring that the methodology can remain relevant over time.

To test reproducibility, we train two separate large MoLFormer models on Zinc20, using both an AWS-based Ray deployment and on-premise high-performance computing infrastructure. We find that both models are directly comparable, and demonstrate that ChemBERTa-3 infrastructure can be meaningfully deployed in very different computing contexts. In service of open science, we open source the AWS-trained models (along with other small models). We also open source all training code and configurations used for these experiments.

Finally, our last core contribution in this work is a series of improvements and extensions to the open source DeepChem library and ecosystem to facilitate foundation model development. We introduce a new class into DeepChem, *ModularTorchModel*, that streamlines the process of pretraining and fine-tuning models. We also integrate several new model architectures into DeepChem (discussed in section 3.2), along with support for training transformer models from the HuggingFace library. These updates make DeepChem significantly more useful for foundation model research. The released ChemBERTa-3 training and benchmarking framework is powered by these underlying improvements to the DeepChem library and ecosystem.

We anticipate that ChemBERTa-3 will provide foundational infrastructure for designing and training next-generation chemical foundation models by facilitating both pre-training and benchmarking of new large chemical foundation models. We also anticipate that the lessons shared here, alongside the open-source infrastructure, will serve as a basis for facilitating the construction of both scientific foundation models in other domains [17,18] and for the construction of open source LLMs for scientific work.

2 Related Work

The field of drug discovery has witnessed significant advancements through the application of machine learning techniques[19]. Traditional approaches often relied on handcrafted features and shallow learning models, which limited their ability to capture complex relationships within molecular data. The advent of deep learning has transformed this landscape, enabling the development of more sophisticated models that leverage large datasets to learn sophisticated representations of the structure of chemical space. A broad range of different approaches have been proposed in recent years for molecular property prediction:

Graph-based architectures. Graph Neural Networks learn directly from molecular graphs (atoms as nodes, bonds as edges) and naturally capture structural features of compounds. Message Passing Neural Networks (MPNNs)[20] are a variant of graph convolutional networks that propagate messages between neighboring atoms across molecular graphs to construct informative graph representations. Directed MPNN (D-MPNN)[21], a variant of MPNN popularized by the Chemprop library, differs primarily by associating messages with directed bonds rather than atoms, thereby preventing redundant cyclic message paths (totters) and leading to less noisy, more informative molecular embeddings.

Researchers have explored several unsupervised pre-training methods for GNNs to improve generalization further, enabling these models to learn from unlabeled data before fine-tuning on labeled samples. Infograph [22] maximizes the mutual information between the graph-level representation and the representations of substructures of different scales. Infomax3D [23] improves GNNs for molecular property prediction by leveraging 3D molecular data during pre-training. It maximizes the mutual information (MI) between learned 3D representations and 2D molecular graphs, enabling GNNs to infer implicit 3D geometric information from 2D data.

Transformer architectures. While transformers are designed for efficient processing of large-scale NLP corpora, they also prove highly effective in capturing intricate structural and semantic patterns from large, unlabeled molecular datasets. Our preceding work introduced ChemBERTa [3] and ChemBERTa-2[4] based on the RoBERTa[24] transformer implementation in HuggingFace. Chemformer[7] is based on BART[25] architecture. However, these models were trained on relatively smaller datasets. Larger models like MegaMolBART from NVIDIA trained on approximately 1.45 Billion molecules, and MoLFormer [5], trained on 1.1 Billion chemicals[26], have recently become popular. While MoLFormer has shown promising results, only a model version pre-trained on a smaller dataset of 100M molecules has been open sourced. This dataset combines 10% of Zinc and 10% of PubChem molecules used for MoLFormer-XL training, the best model of the MoLFormer suite. (This full model remains close sourced.)

Graph transformer architectures. GROVER [27] leverages self-supervised learning at the node, edge, and graph levels to capture structural and semantic information from unlabeled molecular data. Instead of predicting node or edge types in isolation, it masks local subgraphs and infers contextual properties, reducing ambiguity. GROVER integrates Message Passing Networks within a Transformer-style architecture to encode this complex information effectively.

Efforts to combine GNNs and transformers aim to provide a comprehensive molecular representation, capturing both the molecular structure and the interactions and characteristics of individual atoms[28].

Pretraining methodologies. In transformer-based models, the masked language modeling (MLM) pretraining task, commonly used for BERT-style architectures, is used to predict masked tokens in SMILES sequences [11]. MLM masks 15% of the tokens in each input string and trains the model to correctly identify them. Multitask regression (MTR) pretraining is used to learn to predict multiple molecular properties simultaneously. For graph neural networks, learning to predict masked atom types or bond connections enables the GNN to capture structural patterns in a molecule's topology, much like MLM does for sequences[29]. Mutual information maximization (e.g., InfoGraph and Infomax3D) aligns local substructure embeddings with global molecular embeddings, often leveraging 2D or 3D data to enrich the learned representation without explicit labels [22].

Evaluating different models and pre-training methodologies requires robust and standardized benchmarks to ensure meaningful comparisons and reproducibility. The MoleculeNet[14] benchmark suite is a widely used collection of datasets for this purpose, aggregating data on properties like solubility, toxicity, and bioactivity from multiple public sources. While MoleculeNet has drawn criticism for data curation issues[30], it provides considerable ease-of-use and standardized reproducible protocols which make it a powerful tool for directly comparing different models and pretraining methodologies. Despite the variety of available models and pretraining methodologies, it remains unclear which approach is most effective across different model architectures. Recognizing this gap, our work evaluates multiple architectures and pretraining methodologies on MoleculeNet benchmarks.

3 Methods

3.1 Base Framework: DeepChem

DeepChem[15] is an open source Python library for machine learning and deep learning on molecular, biological and quantum datasets. It is built on top of PyTorch[31], and other popular ML frameworks such as Scikit-learn[32] and XGBoost[33]. It offers tools to streamline model development, training, and evaluation. DeepChem simplifies the application, benchmarking, and deployment of machine learning models by providing easy-to-use model export and deployment APIs, making it easier to use ML in both research and production environments. In addition to its core functionality, DeepChem has been extended and integrated into multiple larger frameworks, such as the ATOM Modeling Pipeline (AMPL)[34], which combines a diverse array of ML and molecular featurization tools for drug discovery. We have extended DeepChem to support both graph-based and transformer-based architectures and pretraining methodologies, making it a versatile tool for future benchmarking efforts.

3.2 Contributions to DeepChem

We added several new pieces of infrastructure to DeepChem to support the ChemBERTa-3 framework and model pre-training.

ModularTorchModel. The *ModularTorchModel* class is designed to simplify the process of building, pretraining, and fine-tuning both transformer and graph-based models. It allows users to define their model components as modular building blocks that can be easily connected to construct complex architectures. Unlike conventional DeepChem models such as *TorchModel* that compute loss solely from the final output, *ModularTorchModel* enables loss computation from intermediate network values, offering greater flexibility in optimization. While it integrates with HuggingFace for transformer-based pretraining, *ModularTorchModel* also fully supports custom graph pretraining implementations. Fig. 5 shows an example usage that illustrates the build, pre-training, and fine-tuning of a model using ModularTorchModel.

The existing *TorchModel* class in DeepChem provides an interface for training PyTorch models using DeepChem datasets. As shown in Fig. 1, the *ModularTorchModel* class is built upon the *TorchModel* class to provide flexibility in defining individual model components and their respective losses, which aids in fine-tuning specific components of the model for downstream tasks.

HuggingFace Deepchem Wrapper. The HuggingFaceModel class in DeepChem acts as a wrapper to integrate HuggingFace[35] models from the 'transformers' library into the DeepChem framework. This allows users to train, predict, and evaluate HuggingFace models using DeepChem's API, enabling direct comparisons between models from the two ecosystems. The wrapper also has a 'tokenizer' which tokenizes raw SMILES strings into tokens to be used by downstream models, leveraging the efficient tokenization and data handling utilities from the 'transformers' library, such as random masking of tokens for masked language model training.

RDKitConformer Featurizer. The *RDKitConformerFeaturizer* was added to DeepChem to generate 3D molecular representations for use in the *InfoMax3DModular* model. The conformer featurizer is an adaptation from RDKit[36], which featurizes an RDKit mol object as a *GraphData* object with 3D coordinates. The ETKDGv2[37] algorithm is used to generate 3D coordinates for the molecule. It is a conformation generation methodology that combines experimental torsion-angle preferences with knowledge-based terms and distance geometry to generate accurate 3D molecular structures.

ChemBERTa.[3] The original ChemBERTa model was pretrained using Masked Language Modeling (MLM). ChemBERTa-2 extended this approach by adding multitask regression (MTR) pretraining on a larger dataset. At its core, Chemberta uses a byte-pair encoding (BPE) tokenizer, trained on the PubChem10M dataset to get 60k tokens per SMILES.

For MTR, the *RDKitDescriptorFeaturizer* in DeepChem was used to compute a set of 200 molecular properties for each compound in our training dataset. Because these tasks have very different scales and ranges, the labels are mean-normalized for each task before training.

While ChemBERTa and ChemBERTa-2 primarily released pretrained models via HuggingFace, ChemBERTa-3 (discussed in detail in section 3.3) also has a released standalone github repository, fully integrated into the DeepChem ecosystem, that allows researchers to easily pretrain and fine-tune models themselves. ChemBERTa-3 also releases trained models on HuggingFace for ease of access.

InfoGraph.[22] The DeepChem implementation of *InfographModel* learns graph representations through unsupervised contrastive learning by maximizing the mutual information between global graph embeddings and substructure embeddings. It is built upon the *ModularTorchModel* class to facilitate transfer learning. The model randomly samples pairs of graphs and substructures, and then maximizes their mutual information by minimizing their distance in a learned embedding space. The model can be used for downstream tasks such as graph classification and molecular property prediction. It utilizes the *MolGraphConvFeaturizer* in DeepChem for data preprocessing, and the pre-trained model can be fine-tuned on both regression and classification datasets.

GROVER.[27] GROVER implementation in DeepChem utilizes the newly introduced *GroverFeaturizer*, which processes molecules from SMILES strings or RDKit objects to generate a molecular graph for message passing, functional group features for pretraining, and additional features for fine-tuning. Users can also specify an additional featurizer to extract extra molecular properties, enhancing transfer learning capabilities. As a *ModularTorchModel*, *GROVERModel* supports flexible fine-tuning and transfer learning.

Infomax3d.[23] *InfoMax3DModular*, implemented in DeepChem, is a *ModularTorchModel* that uses a 2D model (PNA) and a 3D model (Net3D) to maximize the mutual information between their representations, enabling the 2D model to be used for downstream tasks without requiring 3D coordinates. As mentioned before, it utilizes the *RDKitConformerFeaturizer*, which converts RDKit molecular structures into GraphData objects with 3D coordinates stored in the *node_pos_features* attribute. The ETKDGv2 [38] algorithm is employed to generate these 3D conformers.

In our benchmark, we use *InfoMax3DModular* to compare the impact of incorporating 3D structural data versus relying solely on 2D representations, helping us evaluate the significance of 3D information in molecular property prediction tasks.

MoLFormer.[5] The DeepChem implementation of MolFormer uses the HuggingFace DeepChem Wrapper to wrap the 'ibm/MoLFormer-XL-both-10pct' pre-trained model readily available in the HuggingFace transformers library. It uses the 'ibm/MoLFormer-XL-both-10pct' tokenizer.

DMPNN.[21] DMPNN (Directed Message Passing Neural Network) implementation of DeepChem consists of a message-passing phase, where an encoder updates atom hidden states based on neighbor information, and a read-out phase, where a feed-forward network predicts molecular properties. The *DMPNNFeaturizer* in DeepChem extracts rich molecular representations for the DMPNN by encoding both atoms (nodes) and bonds

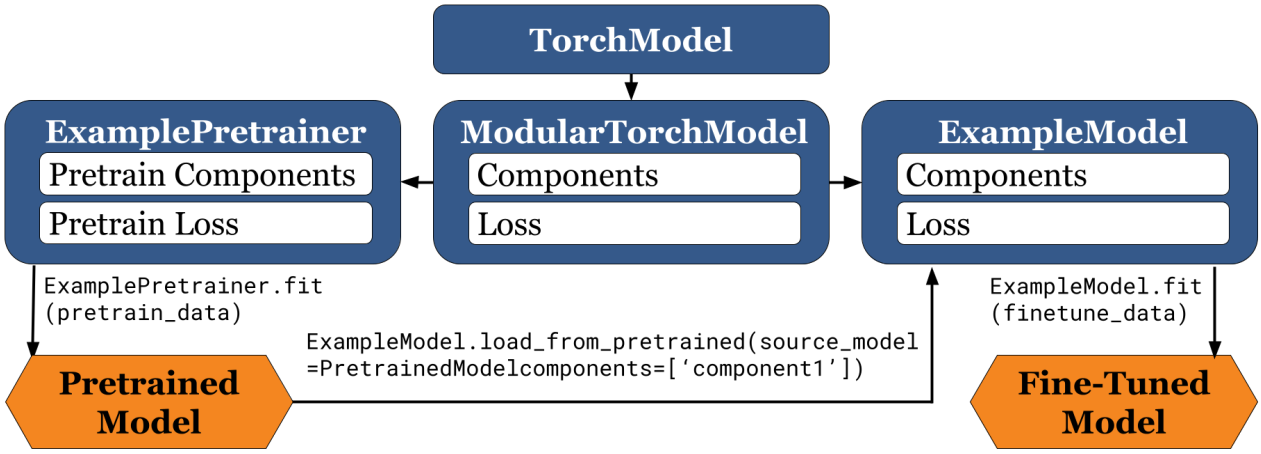

Fig. 1 Schematic representation of the ModularTorchModel framework in DeepChem, demonstrating its workflow for pretraining and fine-tuning tasks. The ModularTorchModel extends the existing TorchModel class.

(edges). Atom features (length 133) include properties like atomic number, degree, charge, chirality, hybridization, and aromaticity, while bond features (length 14) capture bond type, ring membership, conjugation, and stereo configuration. The DMPNN implementation in DeepChem is based on the Chemprop library but is adapted to interoperate with the DeepChem ecosystem [21].

Figure 2 illustrates overall architectures of each model. Table 1 provides a comparison of model architectures, feature / tokenization strategies, types of featurization, pretraining methods, and the corresponding DeepChem class implementations used in this study.

3.3 The ChemBERTa-3 Framework

The ChemBERTa-3 infrastructure is designed as a scalable and extensible framework integrated within the open source DeepChem ecosystem. It allows efficient pretraining and fine-tuning of large-scale chemical foundation models, leveraging DeepChem's extensive molecular machine learning utilities. To effectively handle large datasets and distributed training, we connected ChemBERTa-3 with Ray, an open source framework designed to simplify scaling AI and Python applications, particularly in machine learning [16]. Ray provides a compute layer for parallel processing, enabling users to run distributed tasks. The ChemBERTa-3 Ray infrastructure is illustrated in Fig. 3.

As part of this integration, we built a pipeline where *RayDataset* is implemented as a subclass of the DeepChem *Dataset* superclass, by combining Ray's *ray.data.Dataset* with DeepChem's data handling utilities. This allows datasets to be modified using DeepChem featurizers, stored efficiently as NPZ files using *_RayDcDatasink*, and iterated over using *iterbatches()* for training. This approach enables scalable data handling while maintaining compatibility with DeepChem's modeling APIs.

The distributed data parallel (DDP) strategy is employed to efficiently scale the LLM pretraining on multiple GPUs and machines. It synchronizes gradients and model parameters, ensuring that all processes remain in sync. Each process maintains its copy of the model and performs forward and backward passes independently. During backpropagation, DDP registers an 'autograd hook' that triggers gradient synchronization, ensuring consistency across all replicas before updating the model. This setup ensures efficient resource utilization and enhances scalability, making it easier to explore and optimize new molecules, materials, and designs.

The ChemBERTa-3 platform provides a unified benchmarking framework for evaluating various models, including MoLFormer, ChemBERTa, Infograph, Infomax3D, GROVER, DMPNN, Random Forest (RF), and Graph Convolutional Networks (GCN). It standardizes scaffold split analysis, model training, and evaluation, ensuring fair comparisons and reproducible results. By integrating diverse architectures within a consistent pipeline, our platform facilitates rigorous benchmarking, enabling researchers to assess model performance comprehensively and develop more effective molecular modeling approaches.

3.4 AWS Deployment of ChemBERTa3 on Prithvi

To efficiently pre-train and fine-tune ChemBERTa-3 models at scale, we leverage Prithvi, an open-core commercial suite built on top of DeepChem. Prithvi provides tools for fine-tuning and deploying scientific foundation models. In this work, we use it primarily as a testing environment for ChemBERTa-3 pretraining and evaluation.

We run training on AWS spot instances to reduce computational costs. Although these instances can be preempted at any time, frequent checkpointing allows us to resume from the most recent stable state. Over multiple runs, the cost savings from spot instances typically outweigh the overhead of handling potential interruptions.

3.5 Deploying ChemBERTa3 on HPC Infrastructure

To further verify reproducibility, the software framework was tested on a local HPC cluster using 16 4th generation AMD EPYC nodes, with 4 AMD MI300A APUs per node. The AMPL [34] software environment and the Ray multi-node multi-GPU training framework was used for training new models. The Molformer architecture was selected for comparison with 5 replicate training

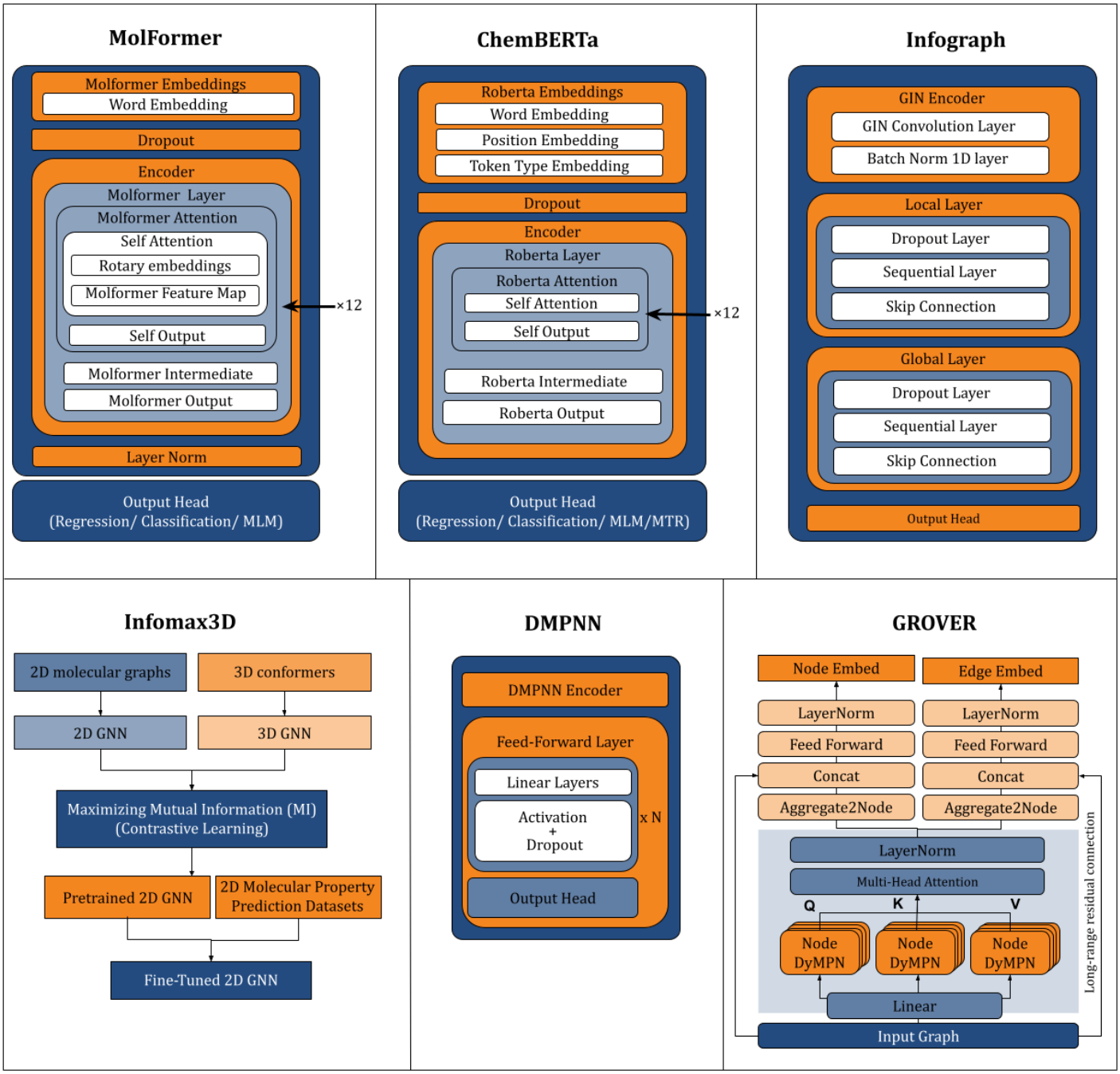

Fig. 2 The figure compares the key components and workflows of model architectures evaluated in this study: MoLFormer, ChemBERTa, InfoGraph, InfoMax3D, DMPNN and GROVER.

Table 1 Comparison of model architectures, featurizer/tokenizer, types of featurization used, and the corresponding pretraining method employed.

Models	Featurizer/Tokenizers	Featurization	Pretraining Method	DeepChem Classname
ChemBERTa-MLM	*Roberta Tokenizer*	SMILES	Masked Language Model	`dc.models.Chemberta`
ChemBERTa-MTR	*RDKitDescriptors*	SMILES	Multi-Task Pretraining	`dc.models.Chemberta`
Infograph	*MolGraphConv*	Graph	Mutual Information Maximization	`dc.models.InfoGraphModel`
Grover	*GroverFeaturizer*	Graph	Self-supervised Message Passing Transformer	`dc.models.GroverModel`
Infomax3D	*RDKitConformer*	Graph	Mutual Information Maximization	`dc.models.InfoMax3DModular`
MoLFormer	*MoLFormer Tokenizer*	SMILES	Masked Language Model	`dc.models.MoLFormer`
DMPNN	*DMPNNFeaturizer*	Graph	-	`dc.models.DMPNNModel`

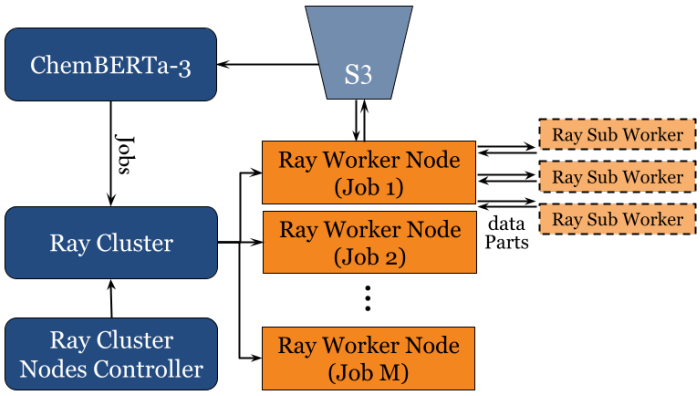

Fig. 3 This figure illustrates the ChemBERTa-3 architecture deployed on Prithvi. The framework utilizes S3 storage service for data access and submits jobs to a Ray Cluster, managed by the Ray Cluster Nodes Controller. The cluster consists of multiple Ray Worker Nodes, each subdividing tasks into Ray Sub Workers for efficient parallel processing. This design leverages Ray's distributed computing capabilities to enable scalable training and evaluation of ChemBERTa-3 models.

runs to measure variability between training runs. After training from scratch with identical conditions to the cloud-based training (including the same 1.1B chemical training set), foundation models were fine-tuned on the labeled tasks to report average accuracy and standard deviation. Each training run took approximately four days. This model is referred to as the Molfomer local HPC trained model (Molformer-LHPC).

4 Datasets

4.1 Pre-training Dataset

ZINC20[39] is a chemical library containing 1.4 billion compounds, 1.3 billion of which are purchasable, sourced from 310 catalogs from 150 companies, specifically designed for virtual screening.

In our work, the model performance is benchmarked across ZINC data sets of varying sizes to understand the impact of the scale of the data on model accuracy and generalization. Additionally, MoLFormer-c3-550M and MoLFormer-c3-1.1B are pretrained on a combination of (50% ZINC20 + 50% Pubchem) and (100% ZINC20 + 100% Pubchem) datasets, respectively. This evaluation highlights the importance of training on large-scale datasets, which tend to improve model performance on downstream tasks, but also provides insights into the diminishing returns of adding more data at certain points.

4.2 Fine-tuning Datasets

The pre-trained models are fine-tuned on various regression and classification tasks from MoleculeNet[14], chosen to cover medicinal chemistry applications, including brain penetrability, toxicity, solubility, and on-target inhibition. The datasets used include BACE, Clearance, Delaney, Lipophilicity, BBBP, ClinTox, HIV, Tox21, and Sider.

4.2.1 Hyperparameter Optimization

We fine-tuned the models for up to 500 epochs with early stopping based on validation loss, exploring train-time hyperparameters like learning rate and batch size. For regression tasks, labels were normalized to zero mean and unit standard deviation.

4.2.2 DeepChem scaffold splits.

DeepChem's implementation of ScaffoldSplitter follows the Bemis-Murcko scaffold-based approach to split molecular datasets[40]. It groups molecules based on their core scaffold structures, ensuring structurally similar compounds remain together. The splitter prioritizes placing larger scaffold groups into the training set before allocating smaller ones to validation and test sets, promoting a more realistic evaluation of model generalization. For benchmarking using DeepChem splits, each dataset was split into 80/10/10 train/validation/test sets using the scaffold splitter. Table 6 compares the performance of models on the classification dataset splits using DeepChem scaffold splitter.

4.2.3 MoLFormer scaffold splits.

To ensure consistency in evaluating our benchmarking platform with MoLFormer, we used the same scaffold splits from the MolFormer manuscript to benchmark models trained using ChemBERTa-3 architecture. Table 2 compares the performance of models on the classification and regression dataset splits provided by MoLFormer. As we discuss in the next section, MoLFormer's scaffold splitting algorithm appears to differ significantly from DeepChem's (The MoLFormer team has open source the splits but not the splitting algorithm for their benchmark datasets so we cannot confirm this directly.)

4.3 Impact of Dataset Splitting on Evaluation Metrics

To better understand the effect of dataset splits on model evaluation, we benchmarked trained models on MoLFormer's provided dataset splits. Additionally, we compared Minimum Tanimoto Distance (MTD) distributions between DeepChem's scaffold split on these same datasets and the MoLFormer's splits to assess structural overlap between training, validation, and test sets.

We find that DeepChem's splits exhibit higher MTD, indicating greater structural dissimilarity between training and test sets, whereas MolFormer's splits have a lower MTD, implying more structural overlap. Consequently, models evaluated on the MolFormer's split may achieve higher ROC AUC scores, likely due to the presence of structurally similar compounds in both training and test sets, which makes the prediction task easier. In contrast, DeepChem scaffold splits provide a more challenging but perhaps more realistic evaluation setting, as they better mimic real-world scenarios where test compounds may belong to novel scaffolds.

To illustrate this difference, we include histograms of the MTD distributions between validation and test sets across multiple classification datasets in Figure 6 (in appendix). These visualizations highlight the variation in scaffold overlap between different splits and provide additional context for interpreting model performance under different evaluation conditions.

These findings emphasize the importance of dataset split selection when benchmarking models. Importantly, papers which use different scaffold splitting algorithms cannot be directly compared! Several past works, including MoLFormer make this (admittedly very subtle) mistake when benchmarking. We hope the ChemBERTa-3 framework can help prevent future issues due to choice of scaffold splitting algorithm.

We note also that while higher evaluation scores may be achieved with lower MTD splits, they do not necessarily reflect better generalization to unseen compounds. By including results from both splits, we provide a comprehensive perspective on model performance across different evaluation settings.

5 Experiments and Results

Pretraining data collection. For the pretraining experiments, GCN, RF, and DMPNN were trained on only the fine-tuning splits for baseline comparisons. InfoGraph, InfoMax3D, and GROVER were pre-trained on only a 250K ZINC dataset and fine-tuned. ChemBERTa and MolFormer models were pre-trained on progressively larger datasets and then finetuned on the fine-tuning splits. ChemBERTa-10M and ChemBERTa-100M were pretrained on 10M and 100M molecules from ZINC20[39], respectively. MolFormer-550M was pretrained on 500M ZINC molecules + 50M PubChem molecules, and MolFormer-1.1B used 1B ZINC molecules + 100M PubChem molecules before fine-tuning. Graph convolutional models were not pretrained on larger datasets due to the relative difficulty of scaling graph-based pretraining. Our results indicate below that transformer-based pretraining is broadly comparable to graph-based pretraining at small scales, but it remains for future-work to test graph-based pretraining at larger scales.

Training MoLFormer on the 1.1B dataset on Prithvi. We utilized 40 T4 GPUs from AWS, which were spot instances chosen to reduce costs. However, these instances are susceptible to preemption, leading to occasional interruptions and necessitating multiple restarts. Each restart involved resuming from the latest checkpoint. Since synchronous training was used, all GPUs needed to resynchronize, further increasing costs in both time and money. To address these challenges, we are exploring the implementation of asynchronous training when restarting from checkpoints. Pretraining the model took approximately 10 days on 40 T4 GPUs.

Experiment Design. We fine-tuned several models including purely supervised baselines, graph-based pre-trained models, and transformer-based pre-trained models on several datasets from MoleculeNet.

For graph-based pretraining, we chose to benchmark GROVER, InfoGraph, and InfoMax3D models. We chose GROVER as it bridges a gap between transformer models and graph models. We chose InfoGraph, to test its mutual-information based pretraining methodology, and InfoMax3D, an extension of InfoGraph captures 3D molecular information, to test the importance of spatial dependencies and conformational variations in pretraining.

For transformer-based pretraining, we trained ChemBERTa and MoLFormer models using the Chemberta-3 harness, lever- aging Ray during pre-training.

The following experiments were conducted:

1. We compare the performance of baseline models, graph-pretrained models and transformer models on a collection of classification and regression datasets drawn from MoleculeNet. The results of this comparison, using MoLFormer splits are presented in Table 2. Results using DeepChem splits are presented in Table 6.

2. The effects of scaling pretraining dataset size on downstream classification fine-tuning tasks for different transformer models are studied. Results are presented in Table 3. For benchmarks that use the standard DeepChem scaffold splits, the full classification scores are reported in 7. We evaluate QM9 on the MolFormer splits; the per-target MAE results are listed in Table 8.

The MoLformer(1.1B)[5] results are directly taken from the MoLFormer paper, trained on ≈1.1 B molecules (100% PubChem + 100% Zinc). Our MoLFormer model, trained using the ChemBERTa3 infrastructure, performs comparably on the three classification datasets (BACE, BBBP, Tox21) but slightly underperforms on other classification and regression tasks, possibly due to insufficient hyperparameter optimization.

6 Discussion and Conclusion

In this paper, we introduced ChemBERTa-3, an open source training framework integrated into DeepChem. The framework supports efficient training of both transformer-based and graph-based models. We benchmarked multiple architectures—including ChemBERTa, MoLFormer, GROVER, InfoGraph, and InfoMax3D—on molecular property prediction tasks from the MoleculeNet dataset. We systematically evaluated several pretraining methodologies to compare their performance across different model types.

Table 2 The table compares baseline models (RF, GCN, DMPNN), graph-pre-training models (Infograph, Infomax3D, Grover) and transformer models (ChemBERTa-MLM-100 M, MoLFormer) on molecular property prediction. The upper block reports ROC-AUC scores (higher is better) for six **classification datasets** (BACE, BBBP, TOX21, HIV, SIDER, CLINTOX) using **MoLFormer scaffold splits**. The lower block reports RMSE (lower is better) for four **regression datasets** (ESOL, Lipophilicity and FreeSolv, and MAE for QM9). c3-MoLFormer is our MoLFormer re-implementation trained with ChemBERTa-3 infrastructure; Infograph/Infomax3D/Grover were pre-trained on 250K SMILES from the ZINC dataset due to scalability issues with larger pretrained datasets. c3-MoLFormer comes close to matching MolFormer paper results on most classification tasks and slightly underperforms MoLFormer on multiple datasets, possibly due to insufficient fine-tuning. NOTE: We performed three runs for each dataset; the "±" shows the range of values and is not a confidence interval. Due to the high expense of running QM9, triplicate runs were not performed for this dataset.

Classification Datasets (Higher is better)

Dataset Tasks	BACE↑ 1	BBBP↑ 1	TOX21↑ 12	HIV↑ 1	SIDER↑ 27	CLINTOX↑ 2
Random Forest	0.884 ± 0.004	0.926 ± 0.002	0.803 ± 0.004	0.829 ± 0.009	0.711 ± 0.004	0.916 ± 0.011
GCN	0.824 ± 0.004	0.898 ± 0.005	0.810 ± 0.004	0.768 ± 0.013	0.603 ± 0.012	0.838 ± 0.068
DMPNN	0.878 ± 0.001	0.930 ± 0.002	0.824 ± 0.002	0.812 ± 0.020	0.633 ± 0.009	0.890 ± 0.001
Infograph-250K	0.840 ± 0.010	0.898 ± 0.013	0.793 ± 0.007	0.785 ± 0.001	0.652 ± 0.016	0.785 ± 0.044
Infomax3D-250K	0.787 ± 0.033	0.904 ± 0.012	0.781 ± 0.003	0.680 ± 0.023	0.575 ± 0.005	0.906 ± 0.006
Grover-250K	0.652 ± 0.321	0.710 ± 0.322	0.789 ± 0.001	0.678 ± 0.243	0.699 ± 0.007	0.882 ± 0.013
Chemberta-MLM-100M	0.859 ± 0.009	0.961 ± 0.003	0.803 ± 0.002	0.789 ± 0.004	0.618 ± 0.018	0.992 ± 0.002
c3-MoLFormer-1.1B	0.848 ± 0.015	0.900 ± 0.015	0.830 ± 0.004	0.715 ± 0.101	0.640 ± 0.008	0.846 ± 0.028
MoLFomer (paper)	**0.882**	0.937	**0.847**	0.822	0.690	0.948

Regression Datasets (Lower is better)

Dataset Tasks	QM9↓ 12	ESOL↓ 1	FREESOLV↓ 1	LIPO↓ 1
Random Forest	14.827	1.154 ± 0.008	2.209 ± 0.028	0.722 ± 0.001
GCN	42.6490	1.219 ± 0.094	4.368 ± 0.269	0.735 ± 0.005
DMPNN	8.9352	0.699 ± 0.022	1.229 ± 0.044	0.577 ± 0.017
Infograph-250K	9.061	0.792 ± 0.044	1.757 ± 0.363	0.697 ± 0.011
Infomax3D-250K	11.6102	0.767 ± 0.057	1.353 ± 0.041	0.569 ± 0.012
Grover-250K	256.7014	3.761 ± 0.079	5.383 ± 0.028	1.082 ± 0.073
Chemberta-MLM-100M	35.2644	0.682 ± 0.089	1.399 ± 0.051	0.615 ± 0.007
c3-MoLFormer-1.1B	4.0019	0.651 ± 0.034	1.052 ± 0.026	0.556 ± 0.004
MoLFomer-1.1B (paper)	1.598	0.279	0.231	0.529

Table 3 This table compares ChemBERTa and MoLFormer models pretrained on ZINC and PubChem datasets of varying sizes on various **classification datasets** and reports ROC AUC scores (Higher is better). We use **MoLFormer scaffold splits**. We have pretrained ChemBERTa models on the ZINC 10M and 100M dataset. Larger pre-training datasets appear to lead to slight improvements in downstream performance, but with diminishing returns. The scaling effect is not consistent; note the Chemberta-MLM-100M model outperforms the scores reported by MoLFormer 1.1B on BBBP and CLINTOX datasets. NOTE: We performed three runs for each dataset; the "±" shows the range of values and is not a confidence interval.

Dataset Tasks	BACE↑ 1	BBBP↑ 1	TOX21↑ 12	HIV↑ 1	SIDER↑ 27	CLINTOX↑ 2
Chemberta-MLM-10M	0.849 ± 0.014	0.956 ± 0.005	0.797 ± 0.009	0.695 ± 0.018	0.611 ± 0.005	0.991 ± 0.001
Chemberta-MLM-100M	0.859 ± 0.009	0.961 ± 0.003	0.803 ± 0.002	0.789 ± 0.004	0.618 ± 0.018	0.992 ± 0.002
c3-MoLFormer-10M	0.829 ± 0.003	0.899 ± 0.006	0.829 ± 0.005	0.747 ± 0.019	0.617 ± 0.011	0.854 ± 0.035
c3-MoLFormer-100M	0.852 ± 0.013	0.899 ± 0.022	0.829 ± 0.006	0.793 ± 0.005	0.625 ± 0.030	0.836 ± 0.029
c3-MoLFormer-550M	0.844 ± 0.015	0.915 ± 0.012	0.840 ± 0.004	0.750 ± 0.062	0.610 ± 0.045	0.839 ± 0.010
c3-MoLFormer-1.1B	0.848 ± 0.015	0.900 ± 0.015	0.830 ± 0.004	0.715 ± 0.101	0.640 ± 0.008	0.846 ± 0.028
MoLFomer (paper)	**0.882**	0.937	**0.847**	**0.822**	**0.690**	0.948

We contributed new tools to DeepChem, including the *ModularTorchModel* class and the *HuggingFaceModel* wrapper to improve model pretraining and fine-tuning. Our experiments identified transformer-based architectures as particularly scalable and effective, especially when trained on large-scale datasets. In the following sections, we discuss various takeaways from our experiments.

6.1 Model Comparisons Are Tricky

The choice of dataset splits is critical when benchmarking models. Scaffold splitting does not necessarily represent a single uniform algorithm; we find in particular that splits used by DeepChem and MoLFormer are not directly comparable. The discrepancy between different scaffold splitting methodologies represents a significant source of complexity and effort in benchmarking. We struggled for several months to reconcile ChemBERTa-3 results with MoLFormer results until we realized that MoLFormer's scaffold splits differed from DeepChem's scaffold splits. To mitigate

these challenges and improve reproducibility, we recommend adopting DeepChem/ChemBERTa-3 as a standardized framework for future benchmarking and model development studies.

As a second consequence, our results show that the improvement of MoLFormer over baseline methods like GCN and DMPNN may be weaker than originally thought. Directly comparing results across papers can lead to misleading comparisons, because different scaffold splits can cause large variations in scores. Our experiments standardize choice of split and subsequently find that baseline methods more closely match reported MoLFormer performance. See Table 2.

6.2 Graph versus Transformer Pretraining

We investigated various graph based pretraining approaches alongside transformer based pretraining approaches. In general, graph based approaches were considerably harder to scale, possibly due to the lower level of community investment in graph-pretraining infrastructure. For example, Grover featurization took up large amounts of disk space (100 GB for a 1M dataset) which made scaling difficult. Other graph models posed other scaling challenges. For this reason, we only pretrained models on graph based approaches on a 250K subset of Zinc20. Broadly, graph-based approaches at this scale appeared broadly comparable to transformer-based approaches (see Table 2). Given the engineering challenges of scaling graph-based approaches, we chose to focus on transformer based approaches for larger pretraining scales in this work. However, the strong performance of graph-based approaches at smaller scales suggests that it may be worth investing in further graph-based training infrastructure since these models may exhibit strong performance at large scales comparable to that of transformer architectures.

6.3 Scaling Challenges

When scaling to larger datasets with a linear learning rate scheduler that includes a warmup phase, configuring the initial learning rate becomes challenging. Setting it too high before the warmup completes often leads to a spike in the loss, causing the model parameters to converge prematurely to a local minimum, as shown in Figure 4. To address this, we opted to restart the training from the most recent stable checkpoint upon spikes, ensuring smoother convergence. We suggest this strategy as a useful stability trick for future efforts.

6.4 Handling Numerical Issues in Training

During the training process of the model, numerical instability was occasionally encountered, manifesting as NaN values in the loss. This issue was attributed to gradient explosion and sensitivity to the learning rate. To address this, a two-phase training strategy was implemented. Initially, the model was pre-trained on a smaller dataset with a very low learning rate to stabilize the initial weights and establish a robust starting point. Subsequently, training was conducted on the larger dataset with the actual learning rate, leveraging the pre-trained weights. Through this approach, instability was mitigated, convergence was improved, and resource utilization was made more efficient.

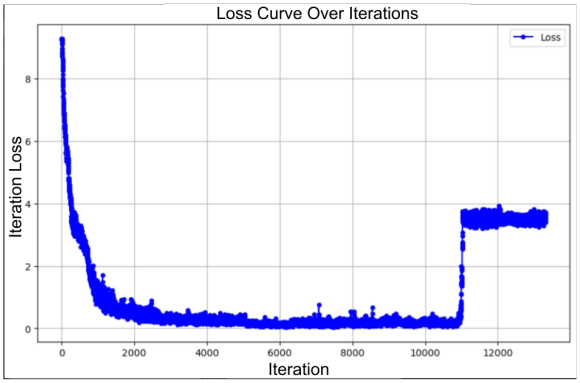

Fig. 4 This graph depicts the loss curve over training iterations, highlighting a sudden spike in loss that occurred during a training run. Such anomalies often arise from high learning rates or data irregularities, particularly when using a linear learning rate scheduler with a warmup phase. To mitigate this issue, checkpointing at regular intervals and restarting from the last stable checkpoint were used to recover from spikes.

6.5 Difficulty of Hyperparameter Optimization

We found that several models were very difficult to tune and required extensive hyperparameter optimization. For example, c3-MoLFormer required considerable tuning before it approached earlier reported MoLFormer results. Given the limitations of our compute budget, it is possible c3-MoLFormer and other models may perform better with additional optimization. We open source all our code and models in the hopes that community feedback and efforts will be able to correct any potential optimization issues despite our best-faith efforts. We list all best hyperparameters in Tables 9, 10, 11, 12, 13, 14, 15and 16, and list costs for all model training in Table 5.

6.5.1 Training Stability and Variance.

In our evaluation of large-scale models such as MoLFormer, we observed notable variance in performance across runs, even under identical hyperparameters and data splits. This instability persisted despite controlled training conditions and is likely attributable to the sensitivity of large models to initialization and other stochastic factors. To account for this, we ran all benchmark experiments using three different random seeds per configuration. We report the mean and standard deviation across these runs to provide a more reliable estimate of model performance and highlight the reproducibility challenges inherent in training large models.

6.6 Open source and Reproducibility

As part of this work, we are open-sourcing the ChemBERTa-3 framework into the DeepChem ecosystem at https://github.com/deepforestsci/chemberta3 *, which includes our top-performing c3-MoLFormer-1.1B model. To ensure transparency and reproducibility, we will publicly release all datasets, model configurations, and evaluation metrics.

* The repository will be made public once the paper review process is completed.

Pre-training datasets and DeepChem splits for fine-tuning on downstream tasks are available in the ChemBERTa-3 repository, while MoLFormer-specific fine-tuning splits can be found at https://github.com/IBM/molformer.

6.7 Future Work

Due to the rapid growth in the chemical foundation model literature, we have not been able to benchmark every notable chemical foundation model release on the ChemBERTa-3 framework. Notably, ChemFormer and MegaMolBART remain to be added to benchmarks. We hope that our open release will incentivize broader community adoption, especially of our standardized benchmarking pipeline, and also incentivize open source community contributions for new chemical foundation models.

6.8 Ethics

While these models are made openly available to advance research and innovation, it is important to acknowledge potential misuse. Specifically, the ability to design molecules with high precision could be exploited to create harmful or dangerous substances. Researchers are encouraged to adhere to ethical guidelines to mitigate such risks.

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Contributions

RS – Main contributor on DeepChem implementations for ChemBERTa and MolFormer. Contributor on Grover implementation for DeepChem. Lead contributor to ChemBERTa3 repo. Contributor on Ray infrastructure in ChemBERTa3 repo. Led experimental execution. Contributed to writing and figures. RI – Literature review. Main contributor on writing and editing of manuscript. Design and iteration on figures. AAB – Contributor to Ray infrastructure in ChemBERTa3 repo. Main contributor on DeepChem DMPNN implementation. Contributed to experimental execution. Contributed to writing and figures. CJA – Conducted computational experiments on local HPC platforms. SH – Evaluated training data splits and experimental results. TD – Main contributor on the DeepChem implementations for ModularTorchModel, InfoGraph, Infomax3d, and RdkitConformerFeaturizer. AT – Main contributor to Grover implementation in DeepChem. Contributed to experiments and ray infrastructure in ChemBERTa3. SS – Contributed to HuggingFace infrastructure in DeepChem. Contributed to writing and editing. SC - Contributed to HuggingFace infrastructure in DeepChem. WA - Contributed to experimental design. Main contributor for dataset processing and gathering. DJ - Development of foundation model training and evaluation infrastructure on local HPC. KM – Helped plan experiments and prepared local HPC environment for testing and evaluation. HK - Evaluated experimental results. AB - Contributed to experimental evaluation and design. SVS - Contributed to experimental design. Contributed to writing and editing. VV - Co-designed study and evaluated computational experiments. JEA – Co-designed study, evaluated computational experiments and contributed to writing manuscript. BR – Co-designed study, designed and evaluated computational experiments, designed and evaluated visualizations, led DeepChem architecture design for new models, reviewed all DeepChem and ChemBERTa3 code and designed tests, and contributed to writing manuscript.

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7 Appendix

7.1 Hyperparameter Tuning and Benchmarking of LLM's

Grid hyperparameter search is employed to tune pre-trained models on fine-tuning datasets. We use DeepChem's *'GridHyperparamOpt'* class, which performs an exhaustive search over a specified hyperparameter space. This approach iteratively evaluates all parameter combinations without parallelization, allowing flexible optimization of selected parameters. In our experiments, we found that batch sizes of 32 work best for the downstream tasks.

A hyperparameter sweep was performed for the fine-tuning strategy using grid search and we randomly picked 18 different variations for each task. The complete search space is listed in Table 4. The best model with the lowest validation loss was picked for further analysis.

Table 4 Different Values of the hyperparameters.

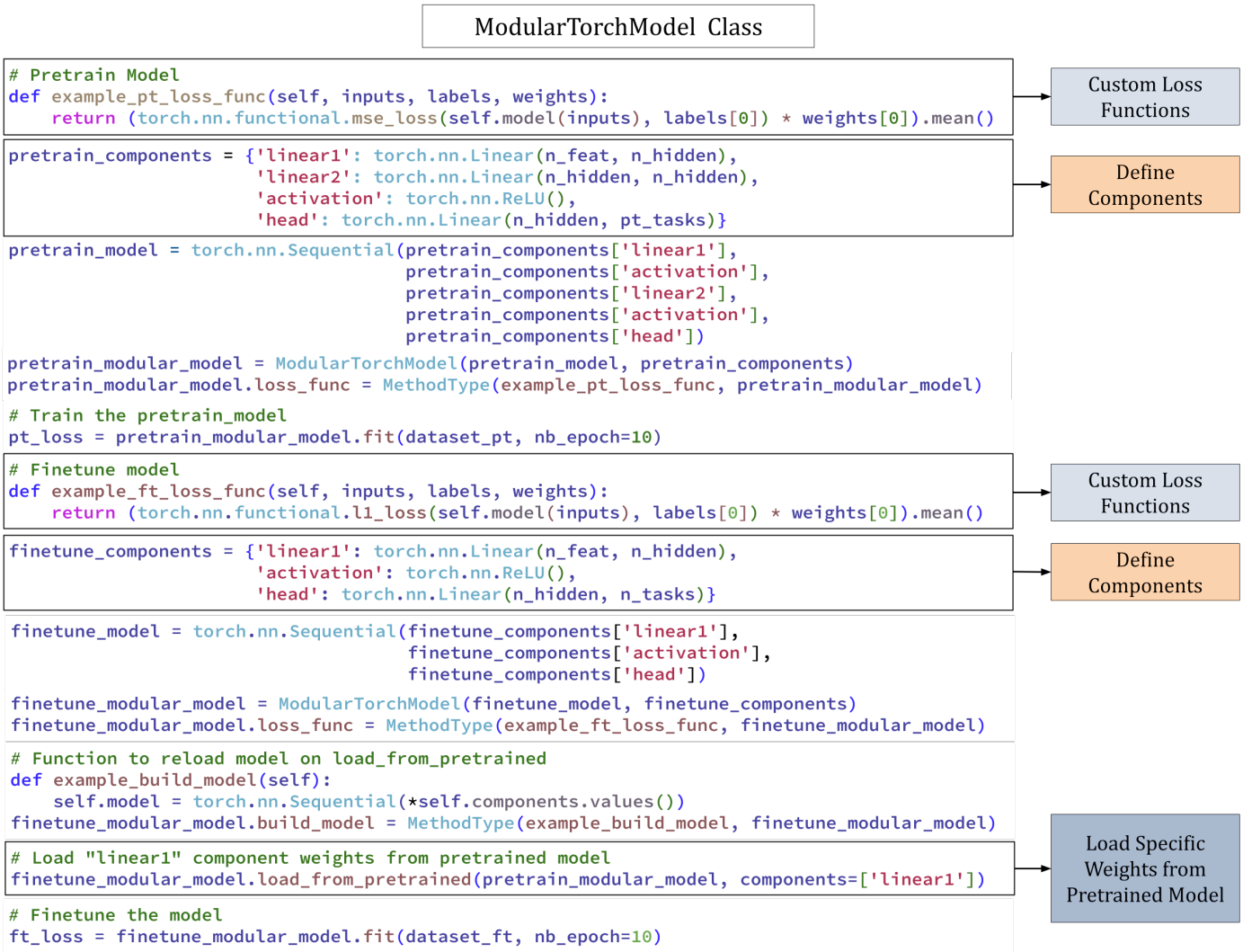
Hyperparameter	Values
Learning Rate	0.0001, 0.00003
Batch Size	16, 32, 64
Epochs	10, 100, 500

7.2 Costs of Model Pre-training and Benchmarking

Training and benchmarking large-scale model architectures, is both computationally expensive and time-consuming. These costs present a significant challenge to reproducibility, as rerunning experiments or comparing models under consistent settings requires substantial GPU resources. Even after pretraining, fine-tuning and evaluating across multiple tasks can be resource-intensive, making it difficult to perform large-scale, systematic benchmarks. Table 5 summarizes the costs of pretraining MolFormer models using AWS T4 GPU instances. Benchmarking took around 287 GPU hours. We have used T4 (1 GPU, g4dn.2xlarge) spot instance for benchmarking.

Table 5 MoLFormer model pre-training and benchmarking costs.

Models	Cost ($)	Date Trained	Time Taken (hours)	AWS Region	Instance Configuration	Instance Type
MoLFormer 1.1B	4000	2025-01-16	260	us-east-2	g4dn.12xlarge	Spot
MoLFormer 550M	2400	2024-12-02	150	us-east-2	g4dn.12xlarge	Spot
MoLFormer 250M	1000	2024-11-18	70	us-east-2	g4dn.12xlarge	Spot
Benchmarking	150	2025-04-01	200	us-east-2	g4dn.2xlarge	Dedicated




```python
# Pretrain Model
def example_pt_loss_func(self, inputs, labels, weights):
    return (torch.nn.functional.mse_loss(self.model(inputs), labels[0]) * weights[0]).mean()

pretrain_components = {'linear1': torch.nn.Linear(n_feat, n_hidden),
                       'linear2': torch.nn.Linear(n_hidden, n_hidden),
                       'activation': torch.nn.ReLU(),
                       'head': torch.nn.Linear(n_hidden, pt_tasks)}

pretrain_model = torch.nn.Sequential(pretrain_components['linear1'],
                                     pretrain_components['activation'],
                                     pretrain_components['linear2'],
                                     pretrain_components['activation'],
                                     pretrain_components['head'])

pretrain_modular_model = ModularTorchModel(pretrain_model, pretrain_components)
pretrain_modular_model.loss_func = MethodType(example_pt_loss_func, pretrain_modular_model)

# Train the pretrain_model
pt_loss = pretrain_modular_model.fit(dataset_pt, nb_epoch=10)

# Finetune model
def example_ft_loss_func(self, inputs, labels, weights):
    return (torch.nn.functional.l1_loss(self.model(inputs), labels[0]) * weights[0]).mean()

finetune_components = {'linear1': torch.nn.Linear(n_feat, n_hidden),
                       'activation': torch.nn.ReLU(),
                       'head': torch.nn.Linear(n_hidden, n_tasks)}

finetune_model = torch.nn.Sequential(finetune_components['linear1'],
                                     finetune_components['activation'],
                                     finetune_components['head'])

finetune_modular_model = ModularTorchModel(finetune_model, finetune_components)
finetune_modular_model.loss_func = MethodType(example_ft_loss_func, finetune_modular_model)

# Function to reload model on load_from_pretrained
def example_build_model(self):
    self.model = torch.nn.Sequential(*self.components.values())
finetune_modular_model.build_model = MethodType(example_build_model, finetune_modular_model)

# Load "linear1" component weights from pretrained model
finetune_modular_model.load_from_pretrained(pretrain_modular_model, components=['linear1'])

# Finetune the model
ft_loss = finetune_modular_model.fit(dataset_ft, nb_epoch=10)
```

Fig. 5 Example code illustrating the build, pre-training, and fine-tuning of a model using *ModularTorchModel* in DeepChem.

Table 6 The tables compare different baseline models (RF, GCN, DMPNN, Infograph, Infomax3D, and Grover) to the transformer architecture models, ChemBERTa and MoLFormer, on various **classification datasets**, in block 1 and **regression datasets**, in block 2 and repost ROC-AUC scores (Higher is better) and RMSE (Lower is better) respectively. We used the **DeepChem scaffold splitter** to split the datasets provided by MoleculeNet. Here, c3-MoLFormer indicates that the MoLFormer model is trained using Chemberta3 infrastructure and MoLFormer-LHPC is trained using the HPC clusters.

Classification Datasets (Higher is better)

Dataset Tasks	BACE ↑ 1	BBBP ↑ 1	TOX21 ↑ 12	HIV ↑ 1	SIDER ↑ 27	CLINTOX ↑ 2
Random Forest	0.866 ± 0.004	0.694 ± 0.013	0.674 ± 0.007	0.794 ± 0.007	0.630 ± 0.002	0.689 ± 0.011
GCN	0.778 ± 0.008	0.642 ± 0.011	0.710 ± 0.005	0.759 ± 0.007	0.613 ± 0.010	0.870 ± 0.020
DMPNN	0.626 ± 0.004	0.661 ± 0.001	0.706 ± 0.001	0.752 ± 0.007	0.524 ± 0.029	0.642 ± 0.005
Infograph-250K	0.739 ± 0.019	0.639 ± 0.054	0.684 ± 0.010	0.755 ± 0.007	0.627 ± 0.010	0.845 ± 0.004
Infomax3D-250K	0.658 ± 0.008	0.624 ± 0.020	0.645 ± 0.006	0.704 ± 0.056	0.588 ± 0.010	0.860 ± 0.023
Grover-250K	0.825 ± 0.006	0.674 ± 0.006	0.692 ± 0.003	0.759 ± 0.002	0.619 ± 0.010	0.642 ± 0.020
ChemBERTa-MLM-100M	0.781 ± 0.019	0.700 ± 0.027	0.718 ± 0.011	0.740 ± 0.013	0.611 ± 0.002	0.979 ± 0.022
c3-MoLFormer-1.1B	0.819 ± 0.018	0.735 ± 0.019	0.723 ± 0.012	0.762 ± 0.005	0.618 ± 0.005	0.839 ± 0.013
MoLFormer-LHPC	0.887 ± 0.004	0.908 ± 0.013	0.791 ± 0.014	0.750 ± 0.003	0.622 ± 0.007	0.993 ± 0.004

Regression Datasets (Lower is better)

Dataset	ESOL↓	FREESOLV ↓	LIPO ↓	BACE ↓	CLEARANCE ↓
Random Forest	1.697 ± 0.005	1.138 ± 0.017	0.963 ± 0.003	1.249 ± 0.011	51.683 ± 0.402
GCN	1.002 ± 0.034	0.624 ± 0.031	0.879 ± 0.071	1.259 ± 0.028	54.599 ± 1.984
DMPNN	1.068 ± 0.033	0.596 ± 0.033	0.690 ± 0.015	1.146 ± 0.100	50.974 ± 0.542
Infograph-250K	1.410 ± 0.196	0.988 ± 0.063	0.898 ± 0.012	1.440 ± 0.137	92.646 ± 22.630
Infomax3D-250K	1.467 ± 0.013	0.623 ± 0.024	0.787 ± 0.022	1.440 ± 0.174	58.270 ± 0.642
Grover-250K	1.845 ± 0.037	1.038 ± 0.008	0.816 ± 0.027	1.563 ± 0.058	64.452 ± 0.287
ChemBERTa-MLM-100M	0.920 ± 0.011	0.536 ± 0.016	0.758 ± 0.013	1.011 ± 0.038	51.582 ± 3.079
c3-MoLFormer-1.1B	0.829 ± 0.019	0.572 ± 0.023	0.728 ± 0.016	1.094 ± 0.126	52.058 ± 2.767
MoLFormer-LHPC	0.848 ± 0.031	0.683 ± 0.040	0.895 ± 0.080	1.201 ± 0.100	45.74 ± 2.637

Table 7 This table compares the ChemBERTa and MoLFormer models pretrained on ZINC and PubChem datasets of varying sizes on various **classification datasets** and reports ROC AUC scores (Higher is better). We used **DeepChem scaffold splits** and pretrained ChemBERTa models on the ZINC 10M and 100M dataset.

Dataset Tasks	BACE ↑ 1	BBBP↑ 1	TOX21↑ 12	HIV↑ 1	SIDER↑ 27	CLINTOX↑ 2
ChemBERTa-MLM-10M	0.773 ± 0.010	0.715 ± 0.006	0.713 ± 0.014	0.725 ± 0.017	0.616 ± 0.010	0.983 ± 0.010
ChemBERTa-MLM-100M	0.781 ± 0.019	0.700 ± 0.027	0.718 ± 0.011	0.747 ± 0.009	0.629 ± 0.023	0.979 ± 0.022
c3-MoLFormer-10M	0.776 ± 0.031	0.715 ± 0.021	0.718 ± 0.003	0.711 ± 0.014	0.618 ± 0.005	0.847 ± 0.024
c3-MoLFormer-100M	0.809 ± 0.019	0.730 ± 0.016	0.729 ± 0.005	0.747 ± 0.017	0.631 ± 0.009	0.854 ± 0.036
c3-MoLFormer-550M	0.812 ± 0.017	0.742 ± 0.020	0.726 ± 0.002	0.659 ± 0.140	0.594 ± 0.007	0.856 ± 0.020
c3-MoLFormer-1.1B	0.819 ± 0.018	0.735 ± 0.019	0.723 ± 0.012	0.762 ± 0.005	0.618 ± 0.005	0.839 ± 0.013
MoLFormer-LHPC	0.887 ± 0.004	0.908 ± 0.013	0.791 ± 0.014	0.750 ± 0.003	0.622 ± 0.007	0.993 ± 0.004

Table 8 This table compares the baseline models(RF, GCN, DMPNN), graph-pre-trained models (Infograph, Infomax3D, Grover) and transformer models (ChemBERTa-MLM-100 M, MoLFormer) on the QM9 dataset using the **MolFormer scaffold splits**. We report MAE (↓) for **regression tasks** (lower is better). We did not conduct triplicate runs or hyperparameter optimization for the QM9 dataset splits due to their substantial size, extended computational time required, and limited available resources.

Measure	MoLForm (paper) 1.1B	c3-MoLForm 1.1B	GCN	Infograph 250K	DMPNN	Infomax3D 250K	Grover 250K	Chemberta 100M	RF
alpha	0.3327	0.6776	3.9494	0.6734	1.9431	2.4708	66.4236	1.2493	3.9187
cv	0.1447	0.6872	2.1584	0.5082	0.8730	0.9473	40.9454	0.3762	1.5656
G	0.3362	7.1345	17.1677	3.3537	11.3968	13.1874	506.3905	3.8939	18.4361
gap	0.0038	0.0070	0.0125	0.0112	0.0066	0.0072	0.0829	0.00959	0.0079
H	0.2522	0.3900	256.2621	4.4229	11.1296	13.8275	453.8291	3.8955	18.3009
homo	0.0029	0.0039	0.0085	0.0096	0.0048	0.0040	0.0101	0.0075	0.0066
lumo	0.0027	0.0057	0.0086	0.0138	0.0047	0.0047	0.0898	0.00649	0.0071
mu	0.3616	0.6231	0.5910	0.5950	0.5079	0.4893	0.8779	0.7633	0.5595
r2	17.0620	26.2624	177.5807	83.6650	64.7802	81.4212	1210.7322	355.1189	98.4651
u0	0.3211	5.1925	25.2800	9.1437	6.1491	13.6337	605.3215	54.9064	18.3840
U	0.2522	7.0372	28.764	6.3261	10.4231	13.3267	213.4233	2.9415	18.2680
ZPVE	0.0003	0.0017	0.0053	0.0048	0.0036	0.0028	0.2906	0.004	0.0100

Table 9 Best hyperparameters for c3-Molformer model. "Class." and "Reg." in Dataset Type column refers to classification and regression respectively. NOTE: We performed three runs for each dataset; the "±" shows the range of values and is not a confidence interval.

Model	Dataset	Dataset Type	No. of Tasks	Best Parameters			Score (RMSE/ROC AUC)
				Learning Rate	Batch Size	Epochs	
c3-MolFormer	BACE	Class.	1	3.00E-05	32	100	0.848 ± 0.015
	BBBP	Class.	1	3.00E-05	32	150	0.900 ± 0.015
	TOX21	Class.	12	3.00E-05	32	50	0.830 ± 0.004
	HIV	Class.	1	3.00E-05	32	50	0.715 ± 0.101
	SIDER	Class.	27	1.00E-06	16	213	0.640 ± 0.008
	CLINTOX	Class.	2	2.00E-05	32	100	0.846 ± 0.028
	ESOL	Reg.	1	3.00E-05	128	200	0.651 ± 0.034
	FREESOLV	Reg.	1	3.00E-05	128	150	1.052 ± 0.026
	LIPO	Reg.	1	3.00E-05	32	150	0.556 ± 0.004

Table 10 Best hyperparameters for DMPNN model. The score column reports RMSE for regression and ROC AUC for classification tasks. NOTE: We performed three runs for each dataset; the "±" shows the range of values and is not a confidence interval.

Model	Dataset	Dataset Type	No. of Tasks	Best Parameters				Score
				Batch Size	ffn_dropout_p	enc_dropout_p	Epochs	
DMPNN	BACE	Class.	1	128	0.2	0.2	100	0.878 ±0.001
	BBBP	Class.	1	128	0.2	0.2	100	0.930 ±0.002
	TOX21	Class.	12	128	0.2	0.2	100	0.824 ±0.002
	HIV	Class.	1	128	0.2	0.2	100	0.812 ±0.020
	SIDER	Class.	27	128	0.2	0.2	100	0.633 ±0.009
	CLINTOX	Class.	2	128	0.2	0.2	100	0.890 ±0.001
	ESOL	Reg.	1	64	0.2	0.2	100	0.699 ±0.022
	FREESOLV	Reg.	1	128	0.2	0.2	100	1.229 ±0.044
	LIPO	Reg.	1	128	0.2	0.2	100	0.577 ±0.017

Table 11 Best hyperparameters for Infograph model. "Class." and "Reg. in the dataset type column refer to classification and regression, respectively. `num_features` and `edge_features` represent the number of input node and edge features, respectively. `embedding_dim` is the embedding size, and `num_gc_layers` refers to the number of graph convolutional layers used. *num_features* value for all the datasets was reported to be 30, and *embedding_dim* value for the datasets was reported to be 11. NOTE: We performed three runs for each dataset; the "±" shows the range of values and is not a confidence interval.

Model	Dataset	Dataset Type	No. of Tasks	Best Parameters				Score (RMSE/ROC AUC)
				Learning Rate	Batch Size	num_gc_layers	Epochs	
Infograph	BACE	Class.	1	0.001	128	4	100	0.840 ±0.010
	BBBP	Class.	1	0.001	128	4	100	0.898 ±0.013
	TOX21	Class.	12	0.001	128	4	100	0.793 ±0.007
	HIV	Class.	1	0.001	128	4	100	0.785 ±0.001
	SIDER	Class.	27	0.001	128	4	100	0.652 ±0.016
	CLINTOX	Class.	2	0.001	128	4	100	0.785 ±0.044
	ESOL	Reg.	1	0.001	128	4	100	0.792 ±0.044
	FREESOLV	Reg.	1	0.001	128	4	100	1.757 ± 0.363
	LIPO	Reg.	1	0.001	128	4	100	0.697 ±0.011

Table 12 Best hyperparameters for ChemBerta model. NOTE: We performed three runs for each dataset; the "±" shows the range of values and is not a confidence interval.

Model	Dataset	Dataset Type	No. of Tasks	Best Parameters			Score (RMSE/ROC AUC)
				Learning Rate	Batch Size	Epochs	
ChemBerta	BACE	Class.	1	3.00E-05	32	100	0.859 ± 0.009
	BBBP	Class.	1	3.00E-05	32	100	0.961 ± 0.003
	TOX21	Class.	12	3.00E-05	32	100	0.803 ± 0.002
	HIV	Class.	1	3.00E-05	16	50	0.789 ± 0.004
	SIDER	Class.	27	3.00E-05	16	50	0.618 ± 0.018
	CLINTOX	Class.	2	3.00E-05	32	100	0.992 ± 0.002
	ESOL	Reg.	1	3.00E-05	32	100	0.682 ± 0.089
	FREESOLV	Reg.	1	3.00E-05	128	100	1.399 ± 0.051
	LIPO	Reg.	1	3.00E-05	128	100	0.615 ± 0.007

Table 13 Best hyperparameters for Infomax3D model. The score column reports RMSE for regression and ROC AUC for classification tasks. NOTE: We performed three runs for each dataset; the "±" shows the range of values and is not a confidence interval.

Model	Dataset	Dataset Type	No. of Tasks	Best Parameters					Score
				Learning Rate	Batch Size	hidden_dim	target_dim	Epochs	
Infomax3D	BACE	Class.	1	0.001	64	64	10	100	0.787 ± 0.033
	BBBP	Class.	1	0.001	64	64	10	100	0.904 ± 0.012
	TOX21	Class.	12	0.001	64	64	10	100	0.781 ± 0.003
	HIV	Class.	1	0.001	128	64	10	50	0.680 ± 0.023
	SIDER	Class.	27	0.001	64	64	10	100	0.575 ± 0.005
	CLINTOX	Class.	2	0.001	64	64	10	100	0.906 ± 0.006
	ESOL	Reg.	1	0.001	32	64	10	500	0.767 ± 0.057
	FREESOLV	Reg.	1	0.001	32	64	10	500	1.353 ± 0.041
	LIPO	Reg.	1	0.001	32	64	10	500	0.569 ± 0.012

Table 14 Best hyperparameters for GROVER model. NOTE: We performed three runs for each dataset; the "±" shows the range of values and is not a confidence interval.

Model	Dataset	Dataset Type	No. of Tasks	Best Parameters			Score (RMSE/ROC AUC)
				hidden size	Batch Size	Epochs	
GROVER	BACE	Class.	1	128	128	100	0.652 ±0.321
	BBBP	Class.	1	128	128	500	0.710 ±0.322
	TOX21	Class.	12	128	100	100	0.789 ±0.001
	HIV	Class.	1	128	128	100	0.678 ±0.243
	SIDER	Class.	27	128	100	500	0.699 ± 0.007
	CLINTOX	Class.	2	128	100	500	0.882 ± 0.013
	ESOL	Reg.	1	128	128	100	3.761 ±0.079
	FREESOLV	Reg.	1	128	128	100	5.383 ±0.028
	LIPO	Reg.	1	128	128	500	1.082 ± 0.073

Table 15 Best hyperparameters for GCN model. NOTE: We performed three runs for each dataset; the "±" shows the range of values and is not a confidence interval.

Model	Dataset	Dataset Type	No. of Tasks	Best Parameters			Score (RMSE/ROC AUC)
				hidden size	Batch Size	Epochs	
GCN	BACE	Class.	1	128	128	100	0.824 ± 0.004
	BBBP	Class.	1	128	128	100	0.898 ± 0.005
	TOX21	Class.	12	128	128	100	0.810 ± 0.004
	HIV	Class.	1	128	128	100	0.768 ± 0.013
	SIDER	Class.	27	128	128	100	0.603 ± 0.012
	CLINTOX	Class.	2	128	128	100	0.838 ± 0.068
	ESOL	Reg.	1	128	128	500	1.219 ± 0.094
	FREESOLV	Reg.	1	128	128	500	4.368 ± 0.269
	LIPO	Reg.	1	128	128	100	0.735 ± 0.005

Table 16 Best hyperparameters for Random Forest model. NOTE: We performed three runs for each dataset; the "±" shows the range of values and is not a confidence interval.

Model	Dataset	Dataset Type	No. of Tasks	Best Parameters				Score (RMSE/ROC AUC)
				n-estimators	min samples split	criterion	bootstrap	
RF	BACE	Class.	1	100	20	gini	True	0.884 ±0.004
	BBBP	Class.	1	100	20	gini	True	0.926 ±0.002
	TOX21	Class.	12	100	32	gini	False	0.803 ±0.004
	HIV	Class.	1	100	20	gini	True	0.829 ±0.009
	SIDER	Class.	27	100	32	gini	False	0.711 ±0.004
	CLINTOX	Class.	2	100	16	entropy	False	0.916 ±0.011
	ESOL	Reg.	1	100	2	squared_error	True	1.154 ±0.008
	FREESOLV	Reg.	1	100	2	squared_error	True	2.209 ±0.028
	LIPO	Reg.	1	100	2	squared_error	True	0.722 ±0.001

Table 17 Performance of baseline models (RF, GCN, DMPNN), graph-pre-trained mdels (Infograph, Infomax3D, Grover) and transformer models (ChemBERTa-MLM-100 M, MoLFormer) across three independent runs using **MoLFormer scaffold splits**. For classification tasks (BACE, BBBP, TOX21, HIV, SIDER, CLINTOX) we report ROC AUC score (higher is better); for regression tasks (ESOL, FREESOLV, LIPO) we report RMSE (lower is better). Due to the high expense of running QM9, triplicate runs were not performed for this dataset.

Classification Datasets (Higher is better)

Dataset Tasks	BACE 1↑			BBBP 1↑			TOX21 12↑		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
Random Forest	0.889	0.880	0.883	0.923	0.929	0.926	0.801	0.808	0.799
GCN	0.820	0.821	0.830	0.903	0.891	0.899	0.810	0.815	0.806
DMPNN	0.877	0.879	0.877	0.927	0.931	0.932	0.827	0.825	0.821
Infograph-250K	0.826	0.847	0.847	0.906	0.879	0.908	0.787	0.802	0.788
Infomax3D-250K	0.815	0.806	0.741	0.910	0.887	0.916	0.777	0.784	0.782
Grover-250K	0.883	0.880	0.878	0.937	0.936	0.939	0.788	0.791	0.788
Chemberta-MLM-100M	0.847	0.861	0.869	0.957	0.965	0.960	0.805	0.802	0.802
c3-MoLFormer-1.1B	0.869	0.833	0.843	0.917	0.902	0.881	0.831	0.824	0.835

Classification Datasets (Higher is better)

Dataset Tasks	HIV 1↑			SIDER 27↑			CLINTOX 2↑		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
Random Forest	0.839	0.832	0.817	0.712	0.706	0.716	0.925	0.901	0.924
GCN	0.766	0.754	0.786	0.588	0.618	0.602	0.746	0.863	0.907
DMPNN	0.812	0.836	0.787	0.621	0.643	0.635	0.890	0.889	0.892
Infograph-250K	0.784	0.784	0.787	0.634	0.673	0.651	0.839	0.730	0.786
Infomax3D-250K	0.707	0.684	0.650	0.573	0.570	0.582	0.905	0.899	0.914
Grover-250K	0.849	0.851	0.852	0.690	0.707	0.699	0.883	0.865	0.897
Chemberta-MLM-100M	0.794	0.785	0.789	0.626	0.594	0.636	0.995	0.989	0.992
c3-MoLFormer-1.1B	0.573	0.773	0.799	0.629	0.640	0.650	0.824	0.828	0.886

Regression Datasets (Lower is better)

Dataset Tasks	ESOL 1↓			FREESOLV 1↓			LIPO 1↓		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
Random Forest	1.165	1.147	1.149	2.247	2.183	2.196	0.721	0.719	0.723
GCN	1.103	1.221	1.333	4.463	4.000	4.641	0.741	0.736	0.729
DMPNN	0.669	0.707	0.721	1.213	1.184	1.289	0.568	0.601	0.562
Infograph-250K	0.767	0.756	0.855	1.766	1.308	2.198	0.692	0.688	0.712
Infomax3D-250K	0.847	0.725	0.728	1.304	1.404	1.351	0.552	0.574	0.581
Grover-250K	3.690	3.871	3.723	5.391	5.346	5.410	1.025	1.184	1.036
Chemberta-MLM-100M	0.610	0.808	0.628	1.364	1.472	1.363	0.614	0.606	0.625
c3-MoLFormer-1.1B	0.699	0.622	0.632	1.075	1.065	1.015	0.555	0.553	0.561

Table 18 Performance of ChemBERTa and MoLFormer models, each pretrained on ZINC and PubChem datasets of varying sizes, on **classification datasets**, across three independent runs using **MoLFormer scaffold splits**. ROC-AUC scores (higher is better) is reported for all classification tasks (BACE, BBBP, TOX21, HIV, SIDER, CLINTOX).

Dataset Tasks	BACE 1↑			BBBP 1↑			TOX21 12↑		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
Chemberta-MLM-10M	0.869	0.839	0.841	0.963	0.952	0.954	0.806	0.785	0.800
Chemberta-MLM-100M	0.847	0.861	0.869	0.957	0.965	0.960	0.805	0.802	0.802
c3-MoLFormer-10M	0.829	0.824	0.832	0.907	0.892	0.899	0.829	0.824	0.836
c3-MoLFormer-100M	0.835	0.856	0.865	0.915	0.916	0.868	0.832	0.835	0.820
c3-MoLFormer-550M	0.843	0.826	0.863	0.899	0.927	0.918	0.838	0.838	0.846
c3-MoLFormer-1.1B	0.869	0.833	0.843	0.917	0.902	0.881	0.831	0.824	0.835

Dataset Tasks	HIV 1↑			SIDER 27↑			CLINTOX 2↑		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
Chemberta-MLM-10M	0.719	0.690	0.676	0.607	0.607	0.618	0.991	0.989	0.992
Chemberta-MLM-100M	0.794	0.785	0.789	0.626	0.594	0.636	0.995	0.989	0.992
c3-MoLFormer-10M	0.754	0.766	0.721	0.605	0.632	0.613	0.807	0.868	0.889
c3-MoLFormer-100M	0.796	0.786	0.797	0.611	0.597	0.667	0.876	0.823	0.810
c3-MoLFormer-550M	0.663	0.782	0.805	0.642	0.643	0.546	0.826	0.845	0.849
c3-MoLFormer-1.1B	0.573	0.773	0.799	0.629	0.640	0.650	0.824	0.828	0.886

Table 19 Performance of baseline models (RF, GCN, DMPNN), graph-pre-trained mdels (Infograph, Infomax3D, Grover) and transformer models (ChemBERTa-MLM-100 M, MoLFormer) across three independent runs using **DeepChem scaffold splits**. For classification tasks (BACE, BBBP, TOX21, HIV and SIDER) we report ROC AUC score (higher is better); for regression tasks (ESOL, FREESOLV, LIPO) we report RMSE (lower is better). Due to the high expense of running QM9, triplicate runs were not performed for this dataset.

Classification Datasets (Higher is better)

Dataset Tasks	BACE 1↑			BBBP 1↑			TOX21 12↑		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
Random Forest	0.870	0.866	0.861	0.702	0.676	0.704	0.675	0.666	0.682
GCN	0.789	0.773	0.771	0.639	0.657	0.630	0.710	0.716	0.704
DMPNN	0.627	0.631	0.621	0.661	0.661	0.663	0.705	0.706	0.706
Infograph-250K	0.739	0.762	0.716	0.705	0.572	0.640	0.692	0.669	0.691
Infomax3D-250K	0.648	0.666	0.660	0.653	0.612	0.608	0.653	0.645	0.639
Grover-250K	0.817	0.825	0.833	0.681	0.668	0.671	0.688	0.696	0.692
ChemBERTa-MLM-100M	0.803	0.756	0.784	0.663	0.728	0.709	0.704	0.721	0.730
c3-MoLFormer-1.1B	0.821	0.839	0.796	0.739	0.709	0.756	0.729	0.707	0.735
MoLFormer-LHPC	0.891	0.881	0.888	0.889	0.914	0.919	0.771	0.800	0.800

Classification Datasets (Higher is better)

Dataset Tasks	HIV 1↑			SIDER 27↑			CLINTOX 2↑		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
Random Forest	0.803	0.793	0.785	0.632	0.628	0.631	0.699	0.674	0.694
GCN	0.752	0.756	0.769	0.617	0.623	0.600	0.866	0.896	0.848
DMPNN	0.759	0.742	0.756	0.539	0.549	0.484	0.648	0.643	0.635
Infograph-250K	0.746	0.763	0.755	0.614	0.639	0.628	0.839	0.849	0.846
Infomax3D-250K	0.742	0.746	0.625	0.596	0.573	0.594	0.892	0.848	0.841
Grover-250K	0.757	0.761	0.761	0.616	0.632	0.609	0.631	0.624	0.670
ChemBERTa-MLM-100M	0.758	0.736	0.727	0.612	0.613	0.609	0.948	0.992	0.996
c3-MoLFormer-1.1B	0.756	0.761	0.768	0.621	0.622	0.611	0.854	0.841	0.823
MoLFormer-LHPC	0.746	0.753	0.751	0.629	0.612	0.623	0.987	0.993	0.997

Regression Datasets (Lower is better)

Dataset Tasks	ESOL 1↓			FREESOLV 1↓			LIPO 1↓		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
Random Forest	1.705	1.692	1.695	1.119	1.134	1.159	0.965	0.959	0.965
GCN	0.954	1.015	1.035	0.662	0.586	0.623	0.806	0.856	0.975
DMPNN	1.069	1.107	1.026	0.570	0.576	0.643	0.682	0.678	0.711
Infograph-250K	1.193	1.668	1.369	0.919	1.071	0.972	0.887	0.916	0.891
Infomax3D-250K	1.462	1.485	1.455	0.615	0.597	0.655	0.757	0.792	0.811
Grover-250K	1.796	1.885	1.853	1.049	1.038	1.028	0.798	0.796	0.855
ChemBERTa-MLM-100M	0.905	0.924	0.932	0.542	0.551	0.514	0.760	0.772	0.742
c3-MoLFormer-1.1B	0.439	0.446	0.392	0.552	0.559	0.604	0.594	0.587	0.597
MoLFormer-LHPC	0.804	0.871	0.869	0.627	0.700	0.720	0.967	0.783	0.933

Regression Datasets (Lower is better)

Dataset Tasks	BACE 1↓			CLEARANCE 1↓		
	Run1	Run2	Run3	Run1	Run2	Run3
Random Forest	1.234	1.251	1.262	51.123	51.876	52.049
GCN	1.225	1.295	1.256	57.149	52.311	54.336
DMPNN	1.073	1.287	1.078	50.438	51.717	50.768
Infograph-250K	1.426	1.281	1.615	124.305	72.759	80.873
Infomax3D-250K	1.685	1.335	1.301	57.658	57.997	59.158
Grover-250K	1.484	1.619	1.585	64.744	64.061	64.551
ChemBERTa-MLM-100M	1.037	0.958	1.039	47.618	52.002	55.126
c3-MoLFormer-1.1B	1.066	1.261	0.956	48.793	51.823	55.559
MoLFormer-LHPC	1.334	1.160	1.10	49.412	43.950	43.852

Table 20 Performance of ChemBERTa and MoLFormer models, each pretrained on ZINC and PubChem datasets of varying sizes, on classification regression datasets, across three independent runs using **DeepChem scaffold splits**. ROC-AUC scores (higher is better) is reported for all classification tasks (BACE, BBBP, TOX21, HIV and SIDER) and RMSE (lower is better) is reported for all regression tasks (ESOL, FREESOLV and LIPO

Classification Datasets (Higher is better)

Dataset Tasks	BACE 1↑			BBBP 1↑			TOX21 12↑		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
ChemBERTa-MLM-10M	0.763	0.770	0.787	0.709	0.724	0.712	0.733	0.704	0.703
ChemBERTa-MLM-100M	0.803	0.756	0.784	0.663	0.728	0.709	0.704	0.721	0.730
c3-MoLFormer-10M	0.738	0.778	0.814	0.701	0.744	0.699	0.722	0.716	0.715
c3-MoLFormer-100M	0.832	0.785	0.813	0.750	0.729	0.711	0.725	0.736	0.728
c3-MoLFormer-550M	0.791	0.812	0.832	0.769	0.721	0.739	0.727	0.729	0.723
c3-MoLFormer-1.1B	0.821	0.839	0.796	0.739	0.709	0.756	0.729	0.707	0.735

Classification Datasets (Higher is better)

Dataset Tasks	HIV 1↑			SIDER 27↑			CLINTOX 2↑		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
ChemBERTa-MLM-10M	0.713	0.713	0.749	0.617	0.626	0.603	0.970	0.993	0.986
ChemBERTa-MLM-100M	0.757	0.736	0.748	0.612	0.613	0.662	0.948	0.992	0.996
c3-MoLFormer-10M	0.717	0.692	0.725	0.623	0.611	0.621	0.880	0.824	0.837
c3-MoLFormer-100M	0.771	0.731	0.741	0.635	0.639	0.618	0.806	0.895	0.860
c3-MoLFormer-550M	0.742	0.748	0.461	0.603	0.592	0.588	0.835	0.853	0.882
c3-MoLFormer-1.1B	0.756	0.761	0.768	0.621	0.622	0.611	0.854	0.841	0.823

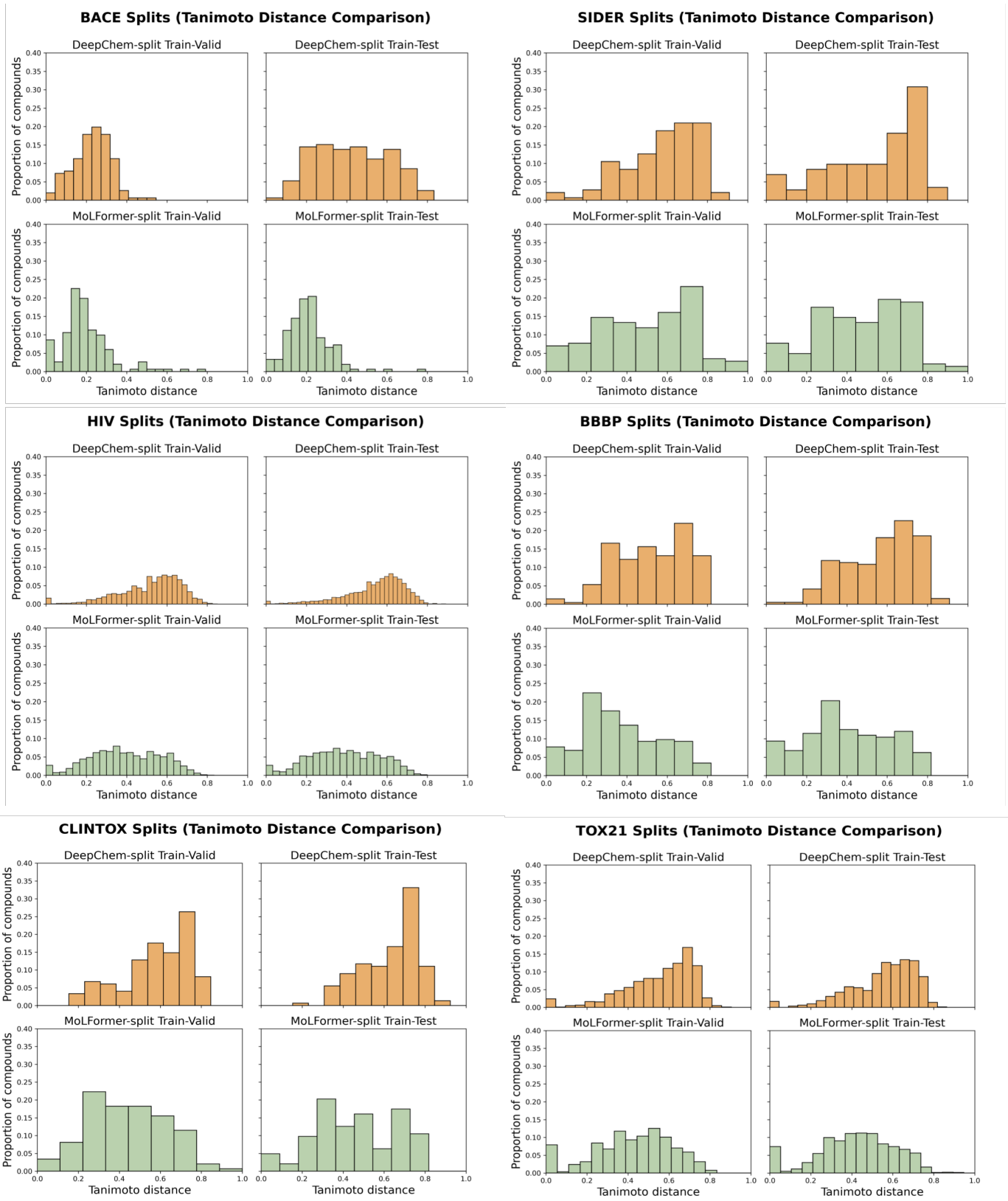


Fig. 6 Histograms of Minimum Tanimoto Distance (MTD) distributions comparing validation and test sets across multiple MoleculeNet classification datasets: BACE, SIDER, HIV, BBBP, CLINTOX and TOX21.

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