BiScale-GTR: Fragment-Aware graph Transformers for Multi-Scale Molecular Representation Learning

Anonymous authors
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Abstract

Graph Transformers have recently attracted attention for molecular property prediction by combining the inductive biases of graph neural networks (GNNs) with the global receptive field of Transformers. However, many existing hybrid architectures remain GNN-dominated, causing the resulting representations to remain heavily shaped by local message passing. Moreover, most existing methods operate at only a single structural granularity, limiting their ability to capture molecular patterns that span multiple molecular scales. We introduce BiScale-GTR, a unified framework for self-supervised molecular representation learning that combines chemically grounded fragment tokenization with adaptive multi-scale reasoning. Our method improves graph Byte Pair Encoding (BPE) tokenization to produce consistent, chemically valid, and high-coverage fragment tokens, which are used as fragment-level inputs to a parallel GNN–Transformer architecture. Architecturally, atom-level representations learned by a GNN are pooled into fragment-level embeddings and fused with fragment token embeddings before Transformer reasoning, enabling the model to jointly capture local chemical environments, substructure-level motifs, and long-range molecular dependencies. Experiments on MoleculeNet, PharmaBench, and the Long Range Graph Benchmark (LRGB) demonstrate state-of-the-art performance across both classification and regression tasks. Attribution analysis further shows that BiScale-GTR highlights chemically meaningful functional motifs, providing interpretable links between molecular structure and predicted properties. *Code will be released upon acceptance.*

1 Introduction

Predicting molecular properties is a fundamental yet challenging task in drug discovery and materials science. With the availability of large-scale chemical datasets, machine learning models have achieved strong performance in molecular property prediction (Fooladi et al., 2025). Graph Neural Networks (GNNs) are widely used in this setting (Gilmer et al., 2017; Xu et al., 2018; Kipf & Welling, 2016) because molecules can naturally be represented as graphs, where atoms correspond to nodes and chemical bonds correspond to edges. However, long-range reasoning in GNNs relies on stacking multiple message-passing layers. As depth increases, node representations can become increasingly indistinguishable (over-smoothing), while information from distant nodes may be compressed into limited representations (over-squashing) (Alon & Yahav, 2021). This limitation is particularly problematic in molecular graphs, where accurate property prediction can depend on interactions between distant functional groups (Yang et al., 2019).

To address these limitations, recent work has explored Transformer-based architectures for molecular representation learning. Through self-attention, Transformers enable direct interactions between distant atoms, making them well suited for capturing global dependencies. Models such as Graphormer (Ying et al., 2021), MAT (Maziarka et al., 2024), and MolFormer (Ross et al., 2022) demonstrate the promise of this paradigm. However, although these models improve long-range dependency modeling, structural information is incorporated only implicitly through attention biases such as positional encodings, hop-distance embeddings, or edge-aware features (Rampášek et al., 2022; Maziarka et al., 2024). Although these mechanisms introduce structural biases, they do not explicitly propagate information through iterative message passing as in GNNs. As a result, structural reasoning is only indirectly captured through attention biases rather than explicitly

constrained by molecular graph topology. This motivates hybrid architectures that combine GNN-based local structural encoding with Transformer-based global reasoning.

Existing GNN–Transformer hybrids generally follow three integration strategies: sequential, alternating, and parallel architectures (Min et al., 2022). Sequential and alternating designs apply Transformer attention on representations already shaped by message passing, which may still limit the modeling of long-range dependencies. Parallel architectures instead process molecular representations through GNN and Transformer modules simultaneously, allowing local structural encoding and global attention to be learned independently before fusion. A common limitation of existing hybrids is that they operate solely on atom-level representations in both branches (Rong et al., 2020; Mu et al., 2025; Rampášek et al., 2022). While atom-level modeling preserves fine-grained chemical details, many molecular properties are governed by interactions between higher-level structural motifs such as functional groups and substructures (Schaeffer, 2008). Atom-level modeling requires implicit inference of higher-level structures, which can hinder efficient and interpretable long-range reasoning. Conversely, representations based solely on fragment tokens may obscure local electronic environments that are crucial for modeling detailed chemical reactivity (Jinsong et al., 2024). These observations suggest that effective molecular representation learning requires reasoning across both structural granularity.

To address the limitations of purely atom-level modeling, fragment-level representations provide a natural mechanism for constructing higher-level structural units. However, effective fragment tokenization remains challenging. Existing approaches either rely on predefined fragmentation rules (Lewell et al., 1998; Degen et al., 2008) or graph decomposition strategies (Wang et al., 2025; Kashima et al., 2003), which often produce molecule-specific fragments without a shared vocabulary across molecules. More recent data-driven methods attempt to construct fragment vocabularies from large molecular corpora using BPE-style merging (Luong & Singh, 2023; Samanta et al., 2025). While these approaches enable adaptive discovery of recurring substructures, they still face challenges in maintaining consistent fragment identities, preserving chemical validity during merging, and handling unseen fragments during inference.

Inspired by parallel hybrid GNN–Transformer architectures, we propose **BiScale-GTR**, a novel fragment-aware molecular representation framework that introduces explicit multi-scale representations. BiScale-GTR first encodes atom-level structural information using a GNN and then aggregates these representations into fragment-level tokens that serve as inputs to Transformer layers, enabling global reasoning over higher-level molecular structures while preserving fine-grained local chemical information. To support this representation, we introduce a graph-based BPE tokenizer tailored to molecular graphs, which ensures consistent fragment identification through Weisfeiler–Lehman (WL) hashing (Weisfeiler & Leman, 1968), filters chemically invalid fragments, and supports recursive decomposition of unseen fragments during inference. By combining atom-level structural encoding with fragment-level reasoning, BiScale-GTR captures both local chemical environments and long-range molecular dependencies. The overall framework is illustrated in Fig. 1. Our contributions are summarized as follows:

- We propose BiScale-GTR, a hybrid molecular representation framework that jointly models atom-level and fragment-level structures by integrating GNN-based local encoding with Transformer-based global reasoning.
- We introduce a graph-based BPE tokenizer for molecular fragment extraction that incorporates WL-hash–based fragment canonicalization, chemical validity filtering, and a reversible out-of-vocabulary (OOV) decomposition mechanism.
- The model provides chemically meaningful fragment-level interpretability, allowing predictions to be explained in terms of molecular substructures.
- Extensive experiments demonstrate that BiScale-GTR achieves state-of-the-art performance on multiple benchmarks, including MoleculeNet, PharmaBench, and LRGB.

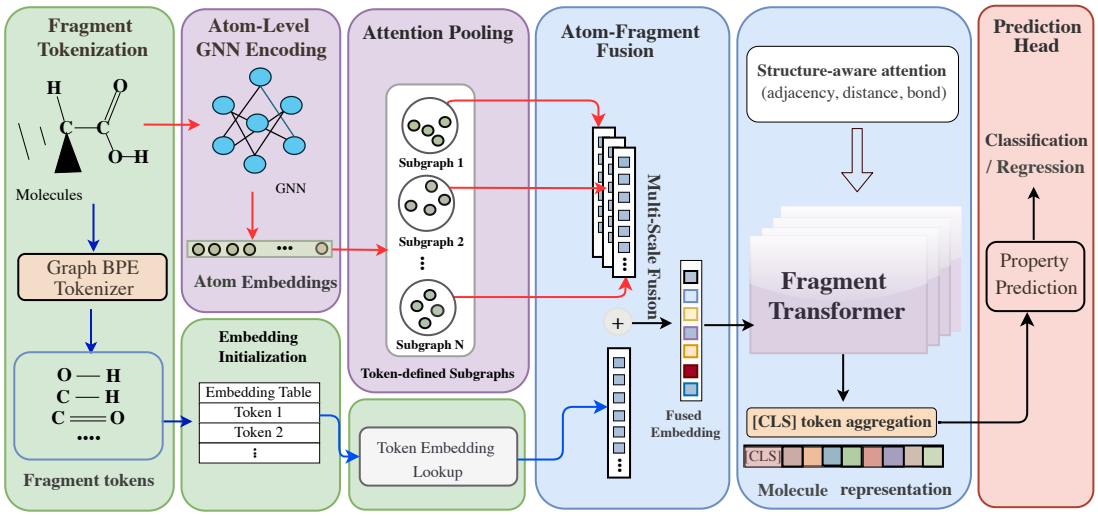


Figure 1: BiScale-GTR combines atom-level GNN encoding and fragment-level token representations. Multi-scale fusion integrates atom and fragment embeddings, which are modeled by a structure-aware fragment Transformer for molecular property prediction.

2 Related works

2.1 Graph Neural Networks for Molecular Representation Learning

Graph Neural Networks (GNNs) have become a standard approach for molecular representation learning, where molecules are modeled as graphs with atoms as nodes and chemical bonds as edges. Early molecular GNN models follow the Message Passing Neural Network (MPNN) framework (Gilmer et al., 2017), where node representations are iteratively updated through message exchange along chemical bonds. Various architectures have been proposed within this paradigm, including graph convolutional and attention-based models (Kipf & Welling, 2016; Veličković et al., 2017; Xu et al., 2018). These models aggregate information from neighboring atoms to learn local chemical representations and obtain graph-level embeddings through different readout operations.

Recent work has further improved molecular representation learning through large-scale self-supervised pre-training. Methods such as GraphMVP (Liu et al., 2021), GraphMAE (Hou et al., 2022), and Mole-BERT (Xia et al., 2023) introduce objectives including masked node prediction, contrastive learning, and graph reconstruction to enhance representation quality. While these approaches improve downstream performance, they still rely on message passing as the core modeling mechanism. Consequently, the locality of message passing remains a fundamental limitation when modeling long-range structural dependencies in molecular graphs.

2.2 Graph Transformers for Molecular Representation Learning

Graph Transformers extend the self-attention mechanism to graph-structured data, enabling direct interactions between distant nodes and facilitating long-range dependency modeling. Since Transformers were originally designed for sequential inputs, additional structural encodings are typically introduced to incorporate graph topology into the attention mechanism. For example, Graphormer (Ying et al., 2021) integrates structural encodings such as node centrality, shortest-path distance, and edge features as attention biases, allowing the Transformer to better capture graph structure. Beyond purely Transformer-based models, recent work (Rampášek et al., 2022; Chen et al., 2022) have explored hybrid architectures that combine GNN message passing with Transformer attention to leverage their complementary strengths. GNNs effectively capture local structural patterns through neighborhood aggregation, while Transformers provide a

global receptive field through self-attention. Existing hybrid architectures generally follow three integration strategies: sequential, interleaved, and parallel designs.

Sequential architectures apply Transformer layers on top of GNN encoders to model long-range interactions over GNN-derived representations. Examples include GraphTrans (Wu et al., 2021) and GROVER (Rong et al., 2020). However, because the Transformer operates on representations already shaped by message passing, the expressiveness of the attention module may still be limited by the locality of the underlying GNN representations. Interleaved architectures alternate between GNN and Transformer layers so that local message passing and global attention can be refined iteratively. For instance, TransGNN (Zhang et al., 2024) alternates Transformer and GNN modules, where Transformer layers capture long-range dependencies while GNN layers propagate topology-aware messages along graph edges. Although this iterative design allows the model to progressively integrate structural and contextual information, it increases architectural complexity and may make the relative contributions of local and global interactions harder to interpret. Parallel architectures compute GNN-based message passing and Transformer attention simultaneously and fuse their outputs. Representative examples include GraphGPS (Rampášek et al., 2022) and EHDGT (Mu et al., 2025), which combine local message passing with global attention to jointly model structural information across graphs. Inspired by this line of work, we develop a hybrid GNN–Transformer architecture in which atom-level representations produced by a GNN are fused into fragment-level Transformer tokens, enabling the Transformer to perform reasoning over fragment representations enriched with local structural information.

2.3 Fragment-based Molecular Representation

Fragment-based representations aim to capture meaningful molecular substructures that influence chemical properties. Early approaches include descriptor-based fingerprints such as ECFP (Rogers & Hahn, 2010), MACCS keys (Durant et al., 2002), and PubChem fingerprints (Bolton et al., 2008). Rule-based methods such as RECAP (Lewell et al., 1998) and BRICS (Degen et al., 2008) further decompose molecules into interpretable building blocks using predefined chemical rules. While computationally efficient and chemically meaningful, these approaches rely on manually designed templates or rules and therefore cannot adapt to unseen structural patterns or novel motifs.

Graph-based methods provide another strategy for deriving molecular fragments directly from graph topology. For example, random-walk–based methods (Kashima et al., 2003) capture structural patterns through node co-occurrence along graph walks, primarily modeling local connectivity. More recently, FragFormer (Wang et al., 2025) introduces the DOVE fragmentation strategy, which generates overlapping fragments through k-degree graph decomposition. Although these approaches can adapt to new structural patterns, the resulting fragments are often molecule-specific and do not form a shared fragment vocabulary across molecules, limiting the reuse of learned motifs in token-based models. In contrast, vocabulary learning methods aim to construct reusable fragment tokens from large molecular corpora. GraphFP (Luong & Singh, 2023) derives fragments through principal subgraph mining by iteratively expanding frequent subgraphs in the dataset. Similarly, FragmentNet (Samanta et al., 2025) adopts a graph-based BPE procedure that iteratively merges frequently occurring substructures to form adaptive fragment tokens. Compared with rule-based fragmentation, BPE-style methods can automatically discover recurring structural motifs from large molecular corpora. In this work, we refine graph-based BPE by using WL hashing to canonicalize fragments, applying chemical validity filtering, and introducing a merge-tree–based fallback mechanism for robust tokenization.

3 Methods

In this section, we present BiScale-GTR, a self-supervised learning framework for molecular representation learning. We first introduce a BPE-based fragmentation strategy to construct chemically meaningful fragment tokens from molecular graphs. Next, we describe the BiScale-GTR architecture, which integrates an atom-level GNN with a fragment-level Transformer to jointly capture local chemical structures and long-range molecular dependencies. Finally, we present the self-supervised pretraining objectives and the fine-tuning procedure used for downstream molecular property prediction tasks.

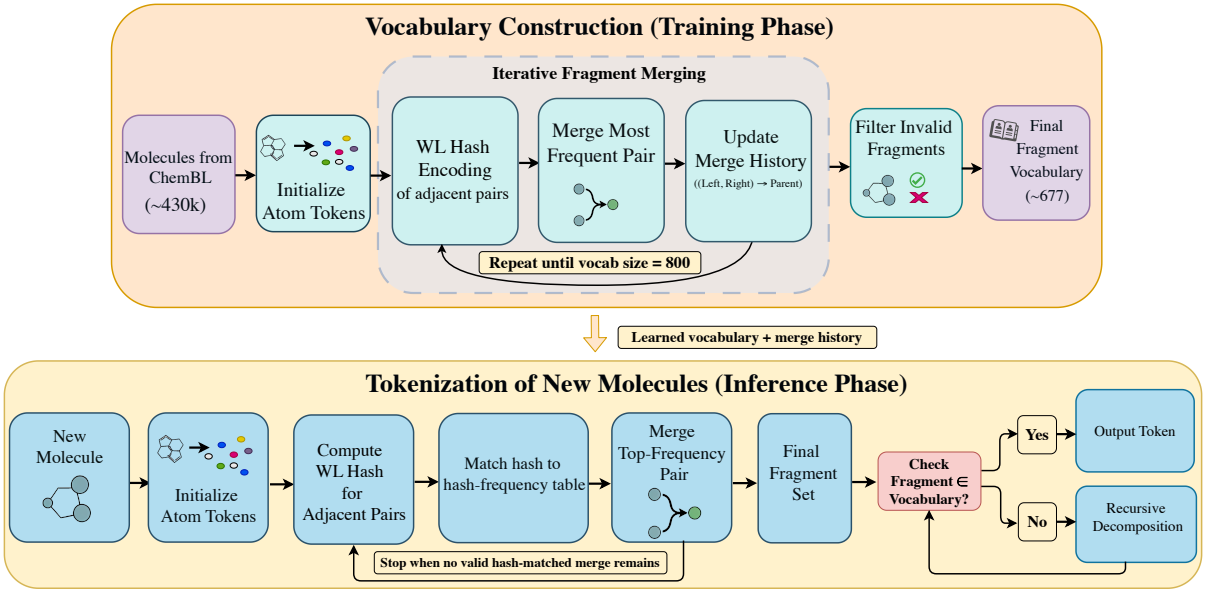


Figure 2: Overview of Graph BPE vocabulary construction and tokenization.

3.1 Fragment Token Construction

Motivated by the success of subword tokenization methods such as BPE in natural language processing (Shibata et al., 1999), we adapt an iterative merge-based procedure to molecular graphs to learn a fragment vocabulary. We construct the vocabulary from a processed subset of approximately 430K molecules from ChEMBL (Mayr et al., 2018), after removing duplicate molecules and invalid SMILES. Merging operates on induced subgraphs extracted from RDKit molecular structures. To ensure consistent fragment identification, we use WL graph hashing, where node labels encode atomic number and aromaticity and edge labels encode bond types. WL hashing maps isomorphic subgraphs to the same permutation-invariant identifier, enabling consistent fragment matching across molecules. The overall vocabulary construction and tokenization pipeline is illustrated in Fig. 2.

3.1.1 Fragment Vocabulary Construction

Each molecule is initialized at the atom level. At every iteration, candidate merges are enumerated between adjacent fragments to form larger induced subgraphs. For each candidate fragment, a WL hash is computed and used to aggregate fragment frequencies across the corpus. The fragment hash with the highest corpus frequency is then selected and merged across all molecules. The corresponding merge operations are recorded during vocabulary construction to form the merge history used for later recursive decomposition. The overall vocabulary construction procedure is summarized in Algorithm 1. Using this procedure, we construct an initial fragment vocabulary of 800 entries, following prior work showing that this size provides strong downstream performance while maintaining compact fragment graphs (Luong & Singh, 2023).

3.1.2 Fragment Validity Filtering

To prevent the fragment vocabulary from containing chemically implausible tokens, each candidate fragment is subjected to a set of chemical sanity checks. Specifically, we verify that the fragment forms a single connected component, satisfies relaxed valence constraints, and preserves aromatic ring integrity. In addition, we avoid fragments that break common functional groups by matching candidate fragments against a library of functional-group SMARTS patterns. Fragments that fail these checks are removed from the vocabulary. Starting from the initial vocabulary of 800 fragments, this filtering step eliminates chemically invalid motifs,

Algorithm 1: Hash-Guided Graph BPE Vocabulary Construction

Input: Molecular corpus $\mathcal{C}$, target vocabulary size V
Output: Fragment vocabulary $\mathcal{V}$, merge history $\mathcal{T}$
Initialize $\mathcal{V}$ with atom tokens;
Initialize hash set $\mathcal{H}$ for fragments in $\mathcal{V}$;
Initialize merge history $\mathcal{T} \leftarrow \emptyset$;
for *each molecule* $M \in \mathcal{C}$ **do**
  Initialize the fragment partition of M as individual atoms;
while $|\mathcal{V}| < V$ **do**
  Initialize frequency table $F \leftarrow \emptyset$;
  for *each molecule* $M \in \mathcal{C}$ **do**
    Enumerate all adjacent fragment pairs in M;
    for *each adjacent pair producing merged fragment* f **do**
      Compute WL hash $h(f)$;
      Increment $F[h(f)]$;
  Select the hash h^* with the highest frequency in F;
  for *each molecule* $M \in \mathcal{C}$ **do**
    Merge each adjacent fragment pair in M whose merged fragment hashes to h^*;
  Extract a representative merged fragment f^* corresponding to h^*;
  if $h(f^*) \notin \mathcal{H}$ **then**
    Add fragment f^* to vocabulary $\mathcal{V}$;
    Add $h(f^*)$ to hash set $\mathcal{H}$;
  Record merge rule $(f_a, f_b) \rightarrow f^*$ in $\mathcal{T}$;
Apply chemical validity filtering to $\mathcal{V}$;
return $\mathcal{V}, \mathcal{T}$;

resulting in a final vocabulary of 677 valid fragments. Additional statistics of the learned fragment vocabulary, including fragment frequency coverage and fragment size distributions, are provided in Appendix A.4.

3.1.3 Tokenization of New Molecules

Given the filtered fragment vocabulary and the recorded merge history, tokenization of a new molecule starts from atom-level tokens and iteratively considers adjacent fragment pairs. For each candidate merged fragment, a WL hash is computed and matched against the learned hash-frequency table. At each step, the candidate whose hash matches a learned fragment entry with the highest frequency is merged. This process is repeated until no adjacent pair produces a candidate hash that matches a learned fragment entry. After merging stops, fragments present in the filtered vocabulary are kept as tokens, while fragments not present in the filtered vocabulary are recursively decomposed using the stored BPE merge tree until a valid vocabulary fragment or an atom-level token is reached. If an atom type itself does not exist in the vocabulary, it is mapped to a special ⟨unk⟩ token. This mechanism guarantees deterministic tokenization and full coverage across diverse molecular inputs.

We quantify tokenizer coverage using the fallback rate,

$$r_{\text{fallback}} = \frac{N_{\text{fallback}}}{N_{\text{tokens}}} \tag{1}$$

which measures the fraction of tokens generated through recursive fallback decomposition during tokenization. Across the small-molecule benchmarks, fallback remains limited. For MoleculeNet datasets, fallback rates range from 0.29% to 12.48%, with most datasets lying between 3% and 9%. For PharmaBench datasets, fallback rates are even lower, remaining around 0.6%–1.2%. In contrast, the long-range peptide datasets exhibit a higher fallback rate of approximately 26%, which is expected because the fragment vocabulary is

learned from small-molecule structures in ChEMBL, whereas peptide datasets contain longer chains and substantially different structural patterns. Detailed tokenization statistics for all datasets are provided in Appendix A.3.

3.2 Model Architecture

Let a molecular graph be denoted as $G = (V, E)$, where V denotes the set of atoms and E denotes the set of chemical bonds. Using the fragment vocabulary described in Section 3.1, each molecule is represented as a sequence of fragment tokens $T = \{t_i\}_{i=1}^{m}$. Our framework integrates atom-level structural representations with fragment-level contextual reasoning. The architecture consists of three components: (1) an atom-level graph encoder, (2) atom–fragment alignment and gated fusion, and (3) a fragment-level Transformer with structure-aware attention.

3.2.1 Atom-Level Graph Encoder

We first encode the molecular graph using a Graph Isomorphism Network (GIN) (Xu et al., 2018). Each atom $\mathcal{V}_i$ is represented by a learnable embedding derived from its chemical attributes, including atomic number, chirality, and auxiliary chemical constraints (see Appendix A.5 for details). These features are projected into a d-dimensional embedding space. Bond features are incorporated through edge embeddings that encode bond type and bond direction. These edge representations are injected into the GIN message-passing layers. Atom representations are iteratively updated through stacked GIN message-passing layers:

$$h_i^{(l+1)} = \mathrm{MLP}^{(l)}\left((1+\epsilon)h_i^{(l)} + \sum_{j\in\mathcal{N}(i)} h_j^{(l)}\right) \tag{2}$$

where $\mathcal{N}(i)$ denotes the neighbors of atom i and ϵ is a learnable scalar parameter. After L layers, the encoder produces atom embeddings

$$H^{\text{atom}} = \{h_i\}_{i=1}^{|V|},$$

which capture local chemical environments and bonding patterns. The architecture can operate under two complementary reasoning regimes. In the fragment-centric regime, the GNN operates on isolated fragment subgraphs extracted from the molecular graph, where each fragment is treated as an independent graph. In contrast, in the full-molecule regime, the GNN processes the entire molecular graph, preserving the original connectivity between fragments and enabling message passing across the full structure. In the experimental sections, we denote these two configurations as BiScale-GTR (Fragment) and BiScale-GTR (Molecule), respectively.

3.2.2 Fragment Representation via Atom Pooling

Each fragment F_k corresponds to a set of atoms grouped by graph BPE tokenization. To derive fragment-level features from atom embeddings, we aggregate the atom representations belonging to the same fragment using attention pooling. Given the set of atoms F_k, the fragment representation is computed as

$$h_k^{\text{frag}} = \sum_{i\in F_k} \alpha_i h_i,$$

where the attention weights are

$$\alpha_i = \frac{\exp(w^\top h_i)}{\sum_{j\in F_k}\exp(w^\top h_j)}.$$

This mechanism allows the model to emphasize chemically informative atoms within each fragment.

3.2.3 Atom–Fragment Alignment and Gated Fusion

Fragment tokens represent discrete subgraph patterns drawn from the learned fragment vocabulary, while pooled atom representations capture local structural information. To integrate these complementary signals,

we fuse the pooled atom representations with the fragment token embeddings that initialize the Transformer input. Let $e_k = \text{Embedding}(t_k)$ denote the fragment token embedding and $\tilde{h}_k = W_a h_k^{\text{frag}}$ denote the aligned atom representation projected into the same embedding space. The fusion gate is computed as

$$g_k = \sigma\left(W_g[e_k; \tilde{h}_k]\right), \tag{3}$$

where $[;]$ denotes concatenation. The final fused fragment representation is

$$z_k = (1 - g_k)e_k + g_k\tilde{h}_k. \tag{4}$$

The fused representation z_k is then used as the input to the fragment Transformer. This gating mechanism allows the model to adaptively balance fragment identity information and atom-level structural signals.

3.2.4 Fragment-Level Transformer

Given the fused fragment representations $Z = \{z_k\}_{k=1}^m$, where m denotes the number of fragment tokens in the molecule, we apply a Transformer encoder to model long-range dependencies between fragments. The standard self-attention projections are computed as

$$Q = W_Q Z, \quad K = W_K Z, \quad V = W_V Z.$$

The attention logits incorporate structural biases derived from the fragment graph:

$$A = \text{softmax}\left(\frac{QK^\top}{\sqrt{d}} + B_{\text{graph}}\right).$$

Here B_{graph} injects molecular topology into the attention mechanism and consists of three components:

$$B_{\text{graph}} = B_{\text{adj}} + B_{\text{dist}} + B_{\text{bond}}.$$

Fragment connectivity bias. The adjacency structure of the fragment graph provides a base connectivity signal. Connected fragment pairs receive a learnable bias, while non-connected pairs and diagonal self-attention entries receive a separate learnable bias initialized to zero. This encourages attention to adapt to fragment connectivity during training.

Shortest-path distance bias. To capture longer-range structural relationships, we incorporate shortest-path distance embeddings between fragment pairs. Let d_{ij} denote the shortest-path distance between fragments i and j in the fragment graph. Distances are capped at 8, so all larger distances are mapped to the same bucket. The distance bias is obtained via an embedding lookup:

$$B_{\text{dist}}(i, j) = \text{Embedding}(\min(d_{ij}, 8)),$$

which is added to the attention logits for each attention head.

Bond-type structural bias. For fragment pairs connected through chemical bonds, we additionally encode bond type and bond direction information. Let b_{ij} denote the bond attributes between fragments i and j. The bond bias is computed as

$$B_{\text{bond}}(i, j) = E_{\text{type}}(b_{ij}^{\text{type}}) + E_{\text{dir}}(b_{ij}^{\text{dir}}),$$

where E_{type} and E_{dir} are learnable embeddings for bond type and bond direction. The fused fragment representations are processed by a Transformer encoder to model long-range dependencies between fragments. We prepend a learnable `[CLS]` token to the fragment sequence. The final hidden state of the `[CLS]` token after L Transformer layers is used as the molecule-level representation.

3.3 Training Objectives

During pretraining, we adopt a masked fragment prediction objective similar to masked language modeling (Devlin et al., 2019). A subset of fragment tokens is replaced with a mask token, and the model is trained to predict the original fragment identity based on the surrounding context. Masked positions are sampled using a frequency-aware strategy rather than uniform sampling. Let f_i denote the global frequency of fragment i in the pretraining dataset. The masking weight is defined as $w_i \propto 1/\sqrt{f_i}$. This increases the probability of masking less frequent fragments.

4 Experiments

4.1 Datasets

We evaluate our model on several widely used molecular property prediction benchmarks. For classification tasks, we use datasets from MoleculeNet (Wu et al., 2018). For regression tasks, we evaluate on the PharmaBench ADMET property prediction benchmark (Niu et al., 2024). In addition, we assess the model's ability to capture long-range structural dependencies using the Peptides-func and Peptides-struct datasets from the LRGB (Dwivedi et al., 2022).

MoleculeNet For classification tasks, we evaluate our model on seven biological datasets from the MoleculeNet benchmark. MoleculeNet is a widely used benchmark suite for molecular machine learning that provides standardized datasets, evaluation metrics, and data splits, enabling consistent comparison between models. These datasets cover a diverse set of biochemical and toxicity-related prediction tasks and are commonly used to evaluate the ability of models to learn molecular representations for biological property prediction. We adopt scaffold splitting (Luong & Singh, 2023) to ensure that molecules in the training, validation, and test sets contain distinct molecular scaffolds.

PharmaBench For regression tasks, we evaluate our model on the PharmaBench ADMET property prediction benchmark (Niu et al., 2024). PharmaBench is a curated benchmark dataset constructed from public bioassay data sources, containing experimentally measured ADMET properties relevant to drug discovery. Compared to earlier ADMET datasets, PharmaBench provides larger and more diverse datasets that better reflect compounds encountered in real-world drug discovery pipelines. We focus on nine regression datasets including CYP2C9, CYP2D6, CYP3A4, HLMC, MLMC, RLMC, LogD, PPB, and Sol. We follow the predefined scaffold split provided by PharmaBench, which partitions each dataset into training and test sets with a ratio of 4:1.

LRGB We further evaluate our model on the peptide datasets from the LRGB, which are designed to assess a model's ability to capture long-range dependencies in molecular graphs. The benchmark includes two peptide datasets derived from 15,535 peptide molecular graphs: Peptides-func, a multi-label graph classification task with 10 functional classes, and Peptides-struct, a graph regression task predicting 5 structural properties derived from peptide 3D structures. Both datasets use the official split provided by LRGB, where the data is divided into 70% training, 15% validation, and 15% test sets. More information regarding the datasets is provided in Appendix A.1.

4.2 Experimental Configurations

During pretraining, 20% of fragment tokens are selected for masking using a frequency-based sampling strategy. The model is optimized using AdamW (Loshchilov & Hutter, 2017) with a learning rate of 4×10^{-4} and a batch size of 256. Pretraining is performed for approximately 503k optimization steps. Atom-level structural representations are computed using a 3-layer GIN. The Transformer encoder consists of 6 layers with hidden dimension $d = 256$, 8 attention heads, and a feed-forward dimension of 1024. Dropout is set to 0.1.

Fine-tuning is also performed using the AdamW optimizer. Batch size and weight decay are selected individually for each benchmark to accommodate differences in dataset size and task characteristics. Detailed

hyperparameter settings for each dataset are provided in Appendix A.2. For classification tasks with significant class imbalance, positive class weighting is applied during training. For the LRGB, models are trained for 200 epochs. For MoleculeNet and PharmaBench, we instead apply early stopping based on the target evaluation metric. The final model is evaluated on the test set using the checkpoint with the highest validation score. All experiments are conducted on a single NVIDIA RTX 4090 GPU. Each experiment is repeated with 10 different random seeds, and we report the mean and standard deviation of the evaluation metrics across runs.

4.3 Baselines

We compare BiScale-GTR with representative models from several major paradigms in molecular representation learning. For the MoleculeNet benchmark, we include self-supervised graph representation learning methods, including GraphMVP (Liu et al., 2021), GraphMAE (Hou et al., 2022), Mole-BERT (Xia et al., 2023), GraphFP (Luong & Singh, 2023), SimSGT (Liu et al., 2023), along with MORE (Son et al., 2025), a multi-level molecular pretraining framework, and GraphGPS+LAC (Yang et al., 2025), a GraphGPS-based architecture with auxiliary learning objectives. For the PharmaBench benchmark, we follow the baselines reported in the original PharmaBench paper (Niu et al., 2024), including classical machine learning models (Random Forest (Rigatti, 2017), XGBoost (Chen & Guestrin, 2016)), graph neural networks (CMPNN (Swanson, 2019), FP-GNN (Cai et al., 2022)), Transformer-based architectures (DHTNN (Song et al., 2023), Transformer-M (Luo et al., 2022)), large-scale pretraining approaches (MPG (Li et al., 2020), KANO (Li et al., 2023)), fragment-based models (FraGAT (Zhang et al., 2021), FragFormer (Wang et al., 2025)), heterogeneous graph models (PharmHGT (Jiang et al., 2023)), and the 3D molecular foundation model Uni-Mol (Zhou et al., 2023). For the long-range molecular datasets, we adopt the baselines reported in the LRGB benchmark, including local message passing GNNs (GCN (Kipf & Welling, 2016), GCNII (Chen et al., 2020), GINE (Hu et al., 2019), GatedGCN (Bresson & Laurent, 2017)) and graph Transformer models with structural encodings, such as LapPE-based Transformers (Dwivedi et al., 2023) and SAN (Kreuzer et al., 2021). We also include fragment-based approaches such as GraphFP and FragFormer for additional comparison.

5 Results and Discussions

We evaluate our model on both classification and regression tasks across multiple molecular benchmarks. Classification results are reported on seven MoleculeNet datasets and long-range graph classification tasks from the LRGB benchmark. Regression performance is evaluated on the PharmaBench benchmarks and long-range peptide datasets.

5.1 Evaluation on MoleculeNet

To study the effect of oversmoothing in graph neural networks, we evaluate two variants of BiScale-GTR that differ in the scope of the GNN encoder. In BiScale-GTR (Fragment), the GNN operates on isolated tokenizer-defined fragment subgraphs. In BiScale-GTR (Molecule), the GNN processes the entire molecular graph before interacting with the Transformer.

Table 1 reports ROC-AUC results on seven MoleculeNet classification benchmarks. Overall, BiScale-GTR (Molecule) achieves the best performance on four out of seven datasets, demonstrating strong performance across diverse molecular property prediction tasks. Of note, MUV and HIV are highly imbalanced datasets with negative-to-positive ratios of approximately 500:1 and 11:1, respectively, and BiScale-GTR (Molecule) achieves the best ROC-AUC on both datasets, indicating that the proposed framework remains robust under severe class imbalance. BiScale-GTR (Fragment) achieves the best performance on BBBP, suggesting that restricting the GNN to fragment-level subgraphs improves the model's ability to distinguish local structural motifs, which are critical for tasks dominated by local reasoning. A similar trend is observed on ToxCast, where the fragment variant outperforms the molecule-level model. In contrast, on most other datasets, including Tox21, MUV, BACE, SIDER, and HIV, the molecule regime performs better, suggesting that access to the full molecular graph enables the model to capture broader structural dependencies and long-range interactions when required.

Compared with recent self-supervised baselines, BiScale-GTR achieves competitive or superior results while maintaining strong data efficiency. In particular, SimSGT shows competitive performance on HIV, MUV, and Tox21 but relies on substantially larger pretraining corpora (2M molecules), whereas our model is pretrained on only 430K molecules. Compared to the GNN-based framework GraphFP, which is pretrained on the same dataset as ours, BiScale-GTR (Molecule) outperforms GraphFP on five out of seven datasets, while BiScale-GTR (Fragment) achieves better performance on BBBP, demonstrating the performance of the proposed Transformer–GNN architecture.

These observations indicate that different datasets may favor either local motif reasoning or global structural reasoning. To better understand the underlying mechanism behind this behavior, we perform a two-regime analysis in Section 5.6.

Table 1: ROC-AUC (%) comparison on MoleculeNet biological classification tasks. Results are reported as mean ± standard deviation when available. Baseline results are taken directly from the corresponding original papers using the same data split protocol. **Bold** indicates the best result and underlined values denote the second-best performance.

Model	**Pretrain Data Size**	**BBBP**	**Tox21**	**MUV**	**BACE**	**ToxCast**	**SIDER**	**HIV**
GraphMVP (Liu et al., 2021)	50k	70.8±0.5	74.9±0.8	77.7±0.6	79.3±1.5	63.1±0.2	60.2±1.1	76.0±0.1
GraphMAE (Hou et al., 2022)	2M	71.2±1.0	75.2±0.9	76.4±2.0	78.2±1.5	63.6±0.3	60.5±1.2	76.8±0.6
Mole-BERT (Xia et al., 2023)	2M	71.9±0.8	**76.8±0.5**	78.9±1.8	80.8±1.4	64.3±0.2	62.8±1.1	78.2±0.8
SimSGT (Liu et al., 2023)	2M	72.2±0.9	76.8±0.9	81.4±1.4	84.3±0.6	**65.9±0.8**	61.7±0.8	78.0±1.9
GraphFP (Luong & Singh, 2023)	430k	72.0±1.7	74.0±0.7	75.4±1.9	80.5±1.8	63.9±0.9	63.6±1.2	78.0±1.5
MORE (Son et al., 2025)	2M	71.9±0.9	75.6±0.5	–	82.8±1.3	64.6±0.6	60.9±0.6	77.0±0.7
GraphGPS+LAC (Yang et al., 2025)	–	73.6	74.0	71.3	82.5	73.7	60.4	77.6
BiScale-GTR (Fragment)	430k	**73.8±0.4**	73.1±0.9	74.7±0.4	83.8±1.2	63.9±0.2	60.1±1.1	77.9±1.1
BiScale-GTR (Molecule)	430k	68.4±0.8	76.1±0.4	**81.6±0.9**	**85.0±1.1**	62.2±0.2	**64.2±0.9**	**79.2±0.6**

5.2 Evaluation on the PharmaBench

We show the results on PharmaBench regression tasks in Table 2. Overall, BiScale-GTR (Molecule) achieves the best performance on five out of nine tasks (CYP2C9, HLMC, MLMC, RLMC and PPB), demonstrating good generalization across diverse ADMET prediction tasks. The model shows particularly strong performance on microsomal clearance prediction tasks (HLMC, MLMC, and RLMC), where it achieves the lowest Root Mean Squared Error (RMSE) among all compared methods. These tasks require modeling complex interactions between multiple molecular substructures that influence metabolic stability. The improved performance suggests that our GNN–Transformer hybrid framework can capture both local chemical environments and broader structural dependencies relevant to metabolic processes. On the remaining datasets, compared to several fragment-aware methods, including GraphFP, FraGAT, PharmHGT, and FragFormer, BiScale-GTR consistently outperforms GraphFP and FraGAT across these tasks, and achieves performance close to the more advanced fragment-based architectures FragFormer and PharmHGT.

5.3 Evaluation on the LRGB Benchmark

We further evaluate BiScale-GTR on the LRGB. As shown in Table 3, BiScale-GTR achieves the best performance on peptides-func, reaching an Average Precision (AP) of 0.6717, outperforming all previous baselines including FragFormer. Although the improvement over FragFormer is modest, it is worth noting that FragFormer relies on a knowledge fusion layer that incorporates handcrafted molecular descriptors. As reported in the FragFormer paper, removing this knowledge fusion module reduces its performance to 0.6571 AP, highlighting the contribution of descriptor-based features. In contrast, BiScale-GTR achieves higher performance using only learned representations derived from the molecular graph and fragment structure. On Peptides-struct, BiScale-GTR achieves an Mean Absolute Error (MAE) of 0.2621, remaining competitive with strong Transformer-based baselines such as SAN and the LapPE-enhanced Transformer. On Peptides-struct, BiScale-GTR achieves a Mean Absolute Error (MAE) of 0.2621, remaining competitive with strong

Table 2: Performance comparison on PharmaBench regression tasks. Results are reported as RMSE (↓). Baseline results are taken directly from PharmaBench paper (Niu et al., 2024)

Model	CYP2C9	CYP2D6	CYP3A4	HLMC	MLMC	RLMC	LogD	PPB	Sol
RF (Rigatti, 2017)	18.471	18.041	16.540	0.813	0.987	0.958	1.249	0.204	0.918
XGBoost (Chen & Guestrin, 2016)	17.582	17.819	16.123	0.647	0.844	0.819	1.071	0.186	0.832
CMPNN (Swanson, 2019)	18.377	19.156	16.701	0.921	1.130	0.939	0.807	0.236	0.858
FPGNN (Cai et al., 2022)	16.933	17.611	15.606	0.604	0.774	0.716	0.838	0.179	0.747
DHTNN (Song et al., 2023)	17.449	17.890	16.156	0.729	0.926	0.915	0.912	0.235	0.828
KANO (Li et al., 2023)	17.350	17.622	15.307	0.554	0.767	0.762	0.766	0.185	0.772
MPG (Li et al., 2020)	17.417	17.527	**14.376**	0.541	0.723	0.685	0.758	0.170	0.758
UniMol (Zhou et al., 2023)	17.774	18.071	15.895	0.613	0.824	0.651	0.745	0.179	**0.707**
Trans-M (Luo et al., 2022)	18.080	17.677	15.867	0.567	0.744	0.677	0.737	0.172	0.834
KP-GPT (Wu et al., 2018)	17.036	16.860	16.379	0.564	0.726	0.881	0.728	0.172	1.221
GraphFP (Luong & Singh, 2023)	17.367	21.183	17.219	0.764	0.878	0.771	0.835	0.208	1.935
FraGAT (Zhang et al., 2021)	17.788	22.503	20.313	0.775	0.849	1.050	0.945	0.220	1.352
PharmHGT (Jiang et al., 2023)	17.490	15.020	16.077	0.544	0.820	0.677	0.676	0.172	0.954
FragFormer (Wang et al., 2025)	16.855	**14.425**	15.894	0.514	0.702	0.596	**0.667**	0.157	0.895
BiScale-GTR (Molecule)	**16.633**	16.901	16.011	**0.501**	**0.696**	**0.571**	0.801	**0.153**	0.977

Transformer-based baselines such as SAN and the LapPE-enhanced Transformer. As Peptides-struct evaluates 3D structural properties of peptides while our model does not incorporate explicit 3D geometric information, this level of performance is reasonable. Overall, these results indicate that combining GNN-based local encoding with fragment-level Transformer reasoning provides an effective mechanism for modeling long-range structural dependencies in peptide graphs.

Table 3: Performance comparison on peptide benchmarks. Average Precision (AP ↑) is reported for Peptides-func and Mean Absolute Error (MAE ↓) for Peptides-struct. Results are shown as mean ± standard deviation. Baseline results are taken directly from the LRGB benchmark

Model	Peptides-func (AP ↑)	Peptides-struct (MAE ↓)
GCN (Kipf & Welling, 2016)	0.5930±0.0023	0.3496±0.0013
GCNII (Chen et al., 2020)	0.5543±0.0078	0.3471±0.0010
GINE (Hu et al., 2019)	0.5498±0.0079	0.3547±0.0045
GatedGCN (Bresson & Laurent, 2017)	0.5864±0.0077	0.3420±0.0013
GatedGCN+RWSE (Dwivedi et al., 2022)	0.6069±0.0035	0.3357±0.0006
Transformer (Vaswani et al., 2017) + LapPE (Dwivedi et al., 2023)	0.6326±0.0126	**0.2529±0.0016**
SAN (Kreuzer et al., 2021) + LapPE	0.6384±0.0121	0.2683±0.0043
SAN + RWSE	0.6439±0.0075	0.2545±0.0012
GraphFP (Luong & Singh, 2023)	0.6267±0.0073	0.3137±0.0019
FragFormer (Wang et al., 2025)	0.6693±0.0154	–
BiScale-GTR (Molecule)	**0.6717±0.0107**	0.2621±0.0022

5.4 Ablation Studies

In this section, we evaluate the impact of key components in BiScale-GTR to understand their contributions to molecular representation learning. All ablation variants are re-pretrained and fine-tuned using the same configurations as the full model. All results are averaged over three runs with different random seeds, and we report the mean and standard deviation.

Component-wise analysis of BiScale-GTR. To investigate the contribution of each component in BiScale-GTR, we conduct architecture ablation studies on MoleculeNet benchmarks, as shown in Table 4. The full model consistently achieves the best performance across all datasets, demonstrating the effectiveness of combining GNN and Transformer representations. Removing the GNN (Transformer-only) leads to a noticeable performance drop on most datasets, particularly on MUV (81.6 vs. 71.6) and BACE (85.0 vs. 65.0), indicating that local structural information captured by the GNN is critical for molecular representation

learning. Conversely, the GNN-only variant performs substantially worse across all tasks, suggesting that relying solely on local message passing is insufficient to capture long-range dependencies and global context. Furthermore, removing the fusion gate also degrades performance compared to the full model, highlighting the importance of adaptive integration between GNN and Transformer features. Overall, these results demonstrate that both the GNN and Transformer components contribute complementary information, and their interaction through the fusion gate is essential for achieving optimal performance.

Table 4: Architecture ablation on MoleculeNet datasets (ROC-AUC %).

Variant	**BBBP**	**Tox21**	**MUV**	**BACE**	**ToxCast**	**SIDER**	**HIV**
Full model (GNN + Transformer)	68.4±0.8	76.1±0.4	81.6±0.9	85.0±1.1	62.2±0.2	64.2±0.9	79.2±0.6
Transformer-only (w/o GNN)	62.8±0.8	73.2±0.5	71.6±0.8	65.0±0.9	61.1±0.7	59.8±0.5	77.1±0.4
GNN-only (w/o Transformer)	58.7±0.3	51.9±0.5	51.8±0.3	59.2±1.1	50.2±0.3	53.3±0.4	51.0±0.5
w/o Fusion Gate	67.4±0.8	75.1±0.6	78.1±0.5	77.0±1.0	60.8±0.3	62.2±1.1	78.4±0.5

Effect of pretraining and masking ratio. We study the impact of pretraining and masking ratio on downstream performance, as shown in Table 5. Removing pretraining leads to a substantial performance drop across all datasets, confirming that the proposed pretraining strategy provides strong initialization and improves generalization.

We further analyze the effect of different masking ratios. A moderate masking ratio of 0.2 consistently achieves the best or near-best performance across most datasets, indicating a good balance between learning informative context and maintaining sufficient input signal. A lower masking ratio (0.1) results in slightly weaker performance, suggesting limited difficulty in the pretraining task, while a higher masking ratio (0.3) leads to performance degradation, likely due to excessive information removal.

Table 5: Effect of pretraining and masking ratio (ROC-AUC %).

Variant	**BBBP**	**Tox21**	**MUV**	**BACE**	**ToxCast**	**SIDER**	**HIV**
w/o pretraining	59.8±0.3	70.5±0.8	59.9±0.6	66.2±1.3	59.8±0.3	59.6±0.7	74.6±0.4
mask ratio = 0.1	69.3±0.5	74.3±0.7	77.9±0.5	83.2±0.8	61.3±0.4	62.1±0.6	77.9±0.3
mask ratio = 0.2 (Full model)	68.4±0.8	76.1±0.4	81.6±0.9	85.0±1.1	62.2±0.2	64.2±0.9	79.2±0.6
mask ratio = 0.3	66.9±0.4	75.2±0.6	76.8±0.6	81.0±1.4	61.9±0.6	62.3±0.4	75.7±0.4

Effect of GNN depth. Deeper GNNs are known to be prone to overfitting and over-smoothing. Since the GNN in our model is intended to provide a complementary structural prior, we adopt a shallow architecture with 3 layers by default. We further evaluate deeper variants with 6 and 8 layers to examine whether a shallow GNN is sufficient and how GNN depth impacts model performance, as shown in Table 6.

The results show that the 3-layer GNN consistently achieves the best performance across most datasets, while increasing depth leads to performance degradation. This drop is particularly significant on BBBP, suggesting that such datasets require sharper representation boundaries. In this case, deeper GNNs may overfit or over-smooth the representations, thereby blurring decision boundaries and degrading performance. Overall, these findings indicate that a shallow GNN is sufficient for capturing local structural information, while deeper architectures may introduce redundant or noisy representations.

Table 6: Effect of GNN depth (ROC-AUC %).

Variant	**BBBP**	**Tox21**	**MUV**	**BACE**	**ToxCast**	**SIDER**	**HIV**
3-layer GNN (Full model)	68.4±0.8	76.1±0.4	81.6±0.9	85.0±1.1	62.2±0.2	64.2±0.9	79.2±0.6
6-layer GNN	62.9±0.9	76.2±0.3	78.2±0.7	81.7±0.8	61.3±0.3	59.8±0.6	79.1±0.4
8-layer GNN	60.2±0.7	75.3±0.6	77.8±0.8	79.1±0.9	61.1±0.5	59.6±0.4	78.3±0.7

Additional ablation results evaluating the impact of tokenization refinements, including chemical validity filtering and the fallback mechanism, are provided in Appendix A.4.2 .

5.5 Model Analysis and Interpretability

To interpret the fragment-level reasoning behavior of BiScale-GTR, we analyze model predictions using attention-based attribution and embedding visualization techniques.

5.5.1 Fidelity evaluation and visualization

We estimate fragment-level importance using the attention rollout method (Abnar & Zuidema, 2020), which aggregates attention weights across Transformer layers to approximate each token's contribution to the final prediction. Since the Transformer operates on fragment tokens, the resulting attribution scores naturally correspond to fragment-level structural units. Detailed descriptions of the rollout procedure are provided in Appendix A.6. To evaluate the faithfulness of these attribution scores, we perform a fidelity test based on fragment removal. Fragments are ranked by their attribution scores, and the top-ranked fragments are removed from the input molecule. We then measure the change in the model prediction, where a larger decrease indicates higher attribution faithfulness. For visualization, fragment importance scores are mapped back to their corresponding atoms within the fragment to highlight important substructures on the molecular graph.

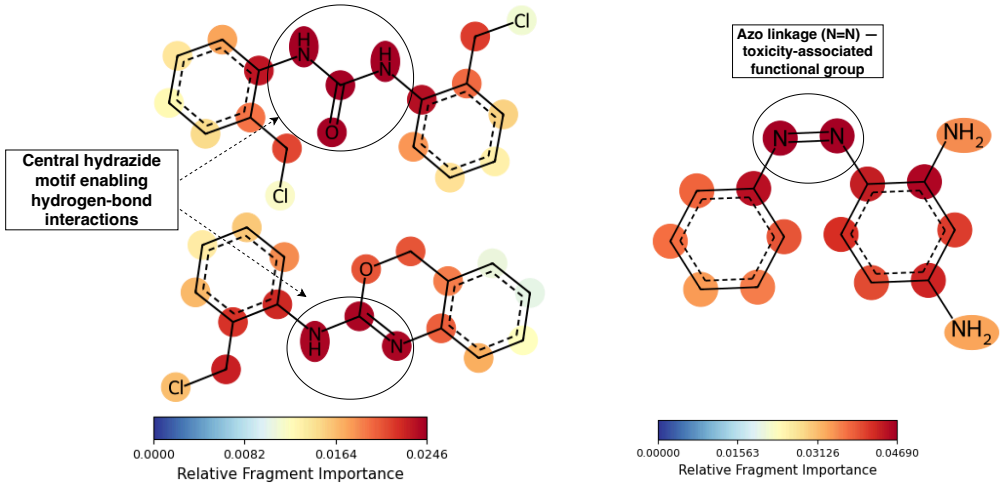
Faithfulness evaluation. We evaluate attribution faithfulness on four representative MoleculeNet datasets: HIV, Tox21, BACE, and BBBP. For HIV, Tox21, and BACE, we use BiScale-GTR (Molecule), which achieves stronger predictive performance on these datasets. For BBBP, we instead use BiScale-GTR (Fragment), since it performs better on this task. As shown in Table 7, removing the top-3 most important fragments consistently leads to a noticeably larger drop in ROC-AUC (Δ_{top}) than removing the bottom-3 fragments (Δ_{bottom}). For example, on HIV and BACE, Δ_{top} exceeds 0.28, while Δ_{bottom} remains close to 0.10, resulting in large gaps of 0.187 and 0.186, respectively. A similar trend is observed on Tox21, although with smaller magnitude. BBBP shows the same overall pattern, with a particularly large gap between Δ_{top} and Δ_{bottom}.

These results indicate that the fragments identified as important by the model are indeed critical for prediction, as their removal significantly degrades performance. In contrast, removing low-importance fragments has a much smaller effect, further validating the selectivity of the attribution method.

Table 7: Faithfulness evaluation via fragment masking. Δ_{top} measures the ROC-AUC drop (%) after removing top-3 most important fragments, while Δ_{bottom} measures drop (%) after removing bottom-3 fragments.

Dataset	Metric	Δ_{top}	Δ_{bottom}	Gap ($\Delta_{\text{top}} - \Delta_{\text{bottom}}$)
HIV	ROC-AUC ↓	28.9	10.2	18.7
Tox21	ROC-AUC ↓	11.1	4.1	7.0
BACE	ROC-AUC ↓	29.8	11.2	18.6
BBBP	ROC-AUC ↓	37.9	10	27.9

Visualization. Figure 3 presents fragment-level attribution visualizations on representative molecules from the HIV and Tox21 datasets. These datasets are chosen as representative benchmarks because they include compounds with known functional groups associated with biological activity , making them suitable for assessing whether the model captures chemically meaningful substructures. The visualization shows that the proposed attention rollout method successfully highlights chemically meaningful substructures. For example, in the HIV dataset, the model assigns high importance to central hydrazide motifs associated with hydrogen-bond interactions, which are known to contribute to binding affinity (Zhao et al., 2003). In Tox21, the model emphasizes azo linkages (–N=N–), a functional group commonly associated with toxicity (Feng et al., 2012). These results demonstrate that the model not only achieves strong predictive performance but also captures relevant functional groups aligned with known chemical and biological mechanisms, supporting the interpretability and reliability of the learned fragment representations.



(a) HIV

(b) Tox21

Figure 3: Fragment-level attention attribution on representative molecules from the HIV and Tox21 datasets. The model highlights chemically meaningful motifs such as aromatic rings and functional linkers, indicating that the learned attention focuses on substructures relevant for biological activity.

5.5.2 Fragment embedding analysis

To further analyze the learned fragment representations, we visualize fragment embeddings using t-SNE. Figure 4 presents the two-dimensional t-SNE projection of the fragment embeddings. The displayed clusters arise from the t-SNE layout, while the color assigned to each fragment corresponds to its cluster membership derived from ECFP fingerprints, which capture underlying structural similarity between fragments.

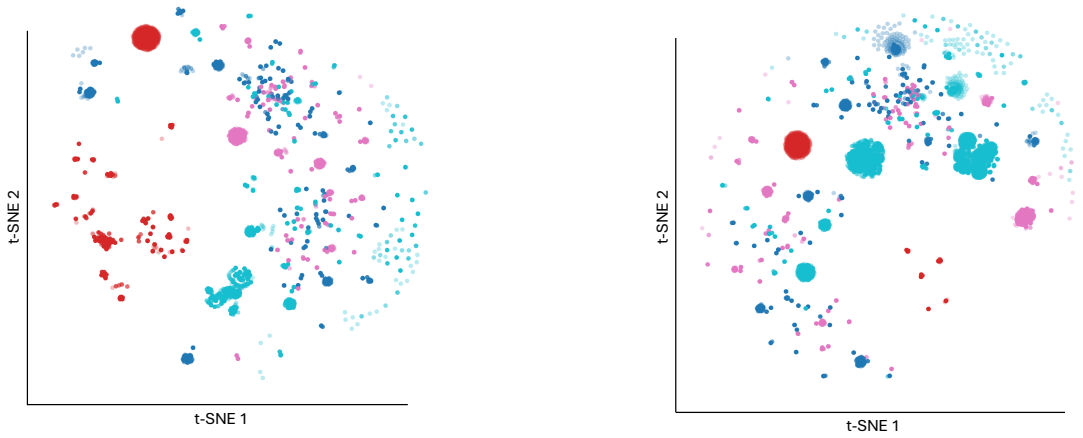
As shown in Figure 4(a), the Transformer without GNN produces fragment embeddings that are relatively dispersed, with weaker separation between clusters corresponding to different chemical substructures. Although some local grouping is observable, there is significant overlap between clusters, indicating limited alignment between the learned representations and chemical similarity.

In contrast, Figure 4(b) demonstrates that incorporating the GNN leads to more structured and compact clusters. Fragments with similar chemical features are more tightly grouped, and distinct clusters are better separated in the embedding space. This improved organization suggests that the model more effectively captures chemically meaningful relationships between fragments.

These observations are consistent with the higher normalized mutual information (NMI) score (see Appendix A.7 achieved by the Transformer with GNN, indicating stronger agreement between learned representations and fingerprint-based structural similarity. Overall, the results suggest that the GNN component enhances the Transformer's ability to encode structural information within its fragment-level embedding space.

5.6 Two-Regime Analysis

To better understand why BiScale-GTR (Fragment) performs better on BBBP while BiScale-GTR (Molecule) is stronger on most other datasets, we analyze both the geometry of the learned token space and the concentration of fragment-level evidence. For the token-space analysis, we collect the final contextualized token representations on the BBBP test set, group them by token identity, and compute two statistics: (1) within-token spread, defined as the mean cosine distance from token occurrences to their centroid, and (2) centroid separation, defined as the mean pairwise cosine distance between token centroids. Lower within-token spread and higher centroid separation indicate a sharper and more discriminative token space.



(a) **Transformer without GNN** (NMI = 0.7009) (b) **Transformer with GNN** (NMI = 0.7678)

Figure 4: t-SNE visualization of fragment embeddings colored by clusters derived from ECFP fingerprints, reflecting structural similarity between fragments. A higher NMI score indicates stronger agreement between the learned fragment representations and the fingerprint-based structural similarity.

As shown in Table 8, BiScale-GTR (Fragment) produces a substantially sharper token space than BiScale-GTR (Molecule), with both lower within-token spread and higher centroid separation. This suggests that encoding each tokenizer-defined fragment with a local fragment GNN preserves more discriminative subgraph semantics, whereas full-molecule message passing tends to smooth token representations by mixing information from the broader molecular context.

To compare fragment importance concentration across datasets with different baseline performance, we report the relative top-3 drop as

$$\text{Relative drop} = \frac{\Delta_{\text{top}}}{\text{original ROC-AUC}} \times 100\% \tag{5}$$

and visualize the results in Fig. 5. BBBP exhibits the largest relative ROC-AUC drop after removing the top-3 attributed fragments, indicating that its predictions are more strongly driven by a small number of highly important local motifs. Taken together, these results suggest that BBBP is a motif-driven task that benefits from a model capable of preserving sharper local token distinctions, which helps explain the advantage of BiScale-GTR (Fragment) on this dataset.

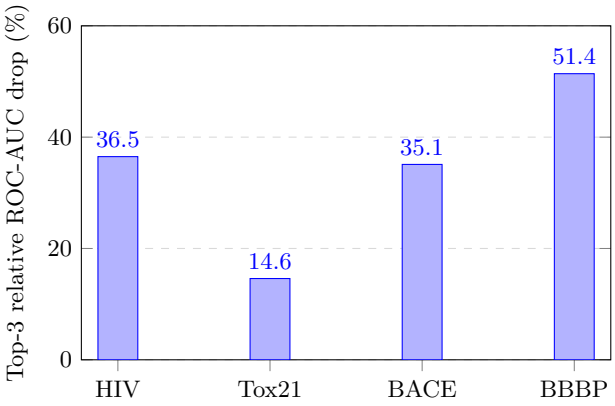


Figure 5: Top-3 relative ROC-AUC drop across datasets, computed using Eq. 5

Table 8: Token-space analysis on the BBBP test set. We report the average within-token spread and average centroid separation of the final contextualized token representations. Lower within-token spread and higher centroid separation indicate a sharper and more discriminative token space.

Model	Within-token spread (↓)	Centroid separation (↑)
BiScale-GTR (Molecule)	0.3627	0.4052
BiScale-GTR (Fragment)	**0.2595**	**0.5549**

6 Conclusions

In this work, we propose BiScale-GTR, a multi-scale molecular representation framework that integrates atom-level message passing with fragment-level Transformer reasoning. A key component of our approach is Graph-BPE tokenization, a data-driven fragment vocabulary learning strategy that constructs chemically meaningful substructures through iterative graph merging while preserving structural validity and enabling robust fallback for unseen motifs. Built on this tokenization scheme, BiScale-GTR combines fragment-level representations with atom-level structural information through gated fusion and structure-aware attention biases, enabling the model to capture both fine-grained chemical environments and higher-level molecular patterns within a unified architecture. Extensive experiments across multiple molecular benchmarks demonstrate strong performance across diverse molecular property prediction tasks. These results highlight the importance of jointly modeling atom- and fragment-level representations, suggesting that multi-scale structural reasoning provides an effective inductive bias for molecular learning.

Recent studies (Feng et al., 2024; Gasteiger et al., 2020; Morehead & Cheng, 2024) suggest that incorporating 3D molecular conformations can further enhance molecular representation learning, particularly for tasks requiring precise geometric modeling such as quantum chemical property prediction. However, leveraging 3D information introduces practical challenges, including the limited availability of high-quality structures and the need for reliable conformation generation. In this work, we therefore focus on 2D molecular graphs to study fragment-aware multi-scale representation learning under a widely accessible setting.

Several opportunities remain for future exploration. First, our Graph-BPE tokenization method learns chemically meaningful fragment vocabularies that may facilitate large-scale molecular language modeling. Furthermore, the proposed multi-scale architecture naturally accommodates additional structural levels, making it well suited for incorporating 3D geometric information as molecular datasets and conformation generation methods continue to advance. We hope this work motivates further research on fragment-aware and multi-scale molecular representations, advancing the development of more expressive molecular learning frameworks.

Acknowledgments

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A Appendix

A.1 Dataset Profiles

Dataset statistics and profiles used in our experiments are summarized in Tables 9, 10, and 11.

Table 9: Dataset profiles for PharmaBench benchmarks.

Dataset	Size	Task Type	Description
CYP2C9	999	Regression	Binding affinity to CYP2C9
CYP2D6	1,214	Regression	Binding affinity to CYP2D6
CYP3A4	1,980	Regression	Binding affinity to CYP3A4
HLMC	2,286	Regression	Human liver microsomal clearance
MLMC	1,403	Regression	Mouse liver microsomal clearance
RLMC	1,129	Regression	Rat liver microsomal clearance
LogD	13,068	Regression	PH-adjusted lipophilicity
PPB	1,262	Regression	Plasma protein binding percentage
Sol	11,701	Regression	Water solubility

Table 10: Dataset profiles for MoleculeNet classification benchmarks. Pos:Neg ratios indicate approximate class imbalance in each dataset.

Dataset	Size	Tasks	Pos : Neg Ratio	Description
BBBP	2,039	1	$\sim$0.8 : 1	Blood-brain barrier permeability
Tox21	7,831	12	varies 1–5 : 1	Toxicity on 12 biological targets
ToxCast	8,575	617	widely variable	High-throughput toxicity screening
SIDER	1,427	27	1–15 : 1	Adverse drug reactions
MUV	93,087	17	$>$500 : 1	Virtual screening validation
HIV	41,127	1	$\approx$11 : 1	HIV replication inhibition
BACE	1,513	1	$\sim$2 : 1	β-secretase 1 inhibition

Table 11: The classification and regression tasks in the LRGB benchmark.

	Peptides-func	Peptides-struct
Number of Graphs	15,535	15,535
Number of Tasks	1	5
Number of Classes	10	–
Task Type	Multi-label classification	Multi-label regression
Description	Peptides-func predicts peptide biological activities such as antibacterial and antiviral functions. Peptides-struct predicts global structural properties derived from peptide 3D conformations, including descriptors such as length and sphericity.	

A.2 Fine-tuning Configuration

Two-stage fine-tuning strategy. To stabilize the adaptation of pretrained molecular representations to downstream tasks, we adopt a two-stage fine-tuning strategy. In the first stage, the pretrained backbone is frozen and only the task-specific prediction head is optimized for a small number of epochs. This warm-up stage allows the classification or regression head to adapt to the downstream task without perturbing the pretrained representations. After the warm-up stage, selected components of the backbone are unfrozen and the model is jointly optimized. Specifically, we unfreeze the fragment attention pooling layer, the atom–fragment alignment module, the fusion gate, and the last few Transformer layers. Earlier layers of the backbone remain frozen to preserve general molecular representations learned during pretraining. Separate learning rates are used for the backbone and the task-specific head during this stage, with a smaller learning rate applied to the backbone parameters.

Optimization settings. All models are optimized using AdamW with different weight decay based on the benchmark characteristics. For MoleculeNet benchmarks, we use a batch size of 64 and a dropout rate of 0.1 or 0.2 (0.2 for MUV and HIV) depending on the susceptibility of each dataset to overfitting. For the PharmaBench benchmarks, we adopt a larger batch size and a learning-rate scheduler to stabilize training. For LRGB, a dropout rate of 0.05 is used based on validation performance. The complete optimization configurations for each benchmark are provided in Table 12. For benchmarks with severe class imbalance (e.g., MUV), we compute task-specific positive class weights using the ratio between negative and positive samples in the training split and apply them in the binary cross-entropy loss.

A.3 Tokenizer Coverage Across Datasets.

Table 13 reports tokenizer statistics across all downstream datasets, including the fallback rate and the UNK rate. The fallback rate measures the proportion of tokens generated through recursive decomposition when a fragment does not directly appear in the learned vocabulary, while the UNK rate indicates the fraction of tokens mapped to the `[UNK]` symbol. Across the MoleculeNet benchmarks, fallback rates remain relatively low, typically ranging between 0.3% and 12.5%, indicating that most molecular fragments can be directly represented by the learned fragment vocabulary. The UNK rate is consistently near zero,

Table 12: Fine-tuning hyperparameters for different benchmark groups. LR denotes learning rate.

Benchmark	Batch Size	Weight Decay	Dropout	Head LR	Backbone LR	Scheduler (factor, patience)
MoleculeNet	64	5×10^{-5}	0.10, 0.20	2×10^{-4}	5×10^{-5}	None
PharmaBench	256	1×10^{-5}	0.10	1×10^{-3}	1×10^{-3}	Plateau (0.8, 6)
Long-range Peptides	128	1×10^{-5}	0.05	3×10^{-4}	2×10^{-4}	Plateau (0.5, 20)

demonstrating that the tokenization scheme provides nearly complete coverage for small-molecule datasets. For the PharmaBench benchmarks, fallback rates are even lower, generally around 0.5%–1.5%, reflecting strong compatibility between the learned vocabulary and the chemical space represented in these datasets. UNK rates remain negligible across all tasks, suggesting that the vocabulary effectively captures the majority of recurring molecular substructures. In contrast, the long-range peptide dataset exhibits a substantially higher fallback rate (26.97%). This is expected because the fragment vocabulary is constructed primarily from small-molecule structures in ChEMBL, whereas peptide datasets contain larger and structurally distinct motifs that are less frequently observed in the training corpus. Despite this distribution shift, the UNK rate remains zero, indicating that recursive decomposition successfully resolves unseen fragments into known substructures.

Dataset	**Fallback Rate**	**UNK Rate**
MoleculeNet		
BACE	0.1248	0.0000
BBBP	0.0525	0.0022
Tox21	0.0742	0.0033
ToxCast	0.0867	0.0089
SIDER	0.1153	0.0067
HIV	0.0370	0.0030
MUV	0.0029	0.0000
PharmaBench		
CYP3A4	0.0102	0.0000
CYP2D6	0.0106	0.0000
CYP2C9	0.0057	0.0000
LogD	0.0115	0.0001
MLMC	0.0121	0.0006
PPB	0.0104	0.0004
RLMC	0.0074	0.0001
Sol	0.0645	0.0000
HLMC	0.0145	0.0000
Peptide		
Long-range Peptide	0.2697	0.0000

Table 13: Tokenizer statistics across downstream datasets.

Notes. Fallback rate is defined as $\text{fallback_rate} = \frac{\text{fallback_tokens}}{\text{final_tokens}}$, which measures the fraction of tokens produced through recursive fallback decomposition during tokenization. UNK rate denotes the fraction of tokens mapped to the `[UNK]` symbol.

A.4 Fragment Vocabulary Statistics

To further analyze the properties of the learned fragment vocabulary, we report additional statistics regarding fragment frequency coverage and fragment size distributions. These analyses provide insight into how the vocabulary captures structural patterns in molecular graphs.

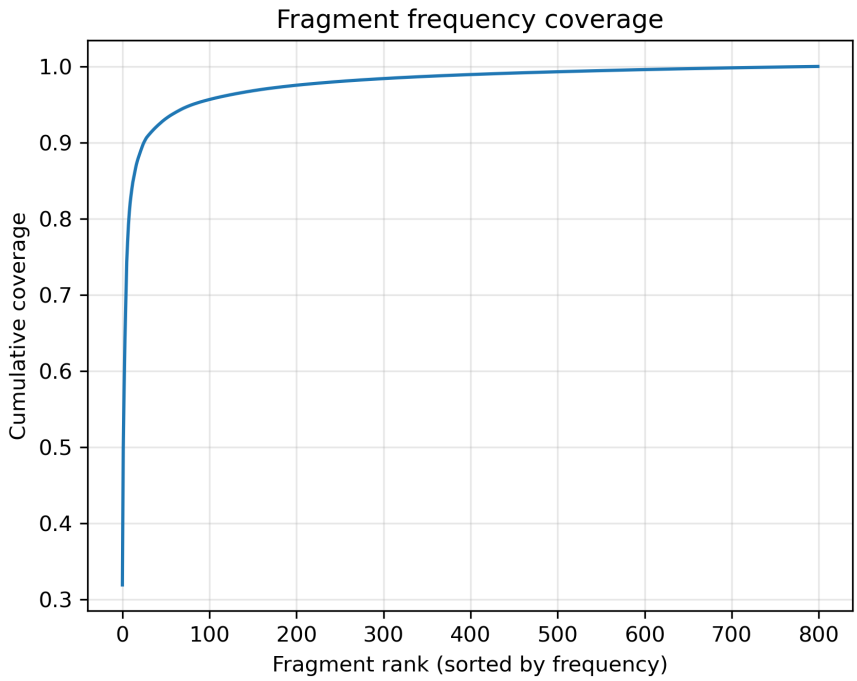

Figure 6: Cumulative coverage of fragment occurrences when fragments are sorted by corpus frequency. A small number of fragments accounts for the majority of occurrences, indicating that the learned vocabulary captures common structural motifs.

A.4.1 Fragment Frequency Coverage

Figure 6 illustrates the cumulative coverage of fragment occurrences when fragments are sorted by decreasing corpus frequency. The distribution is highly skewed: a small number of fragments accounts for the majority of fragment occurrences across the corpus. In particular, the top-ranked fragments rapidly accumulate coverage, while the remaining fragments contribute only marginally. This behavior indicates that the learned vocabulary captures common structural motifs that frequently appear across molecules. Such a distribution is consistent with patterns observed in subword tokenization methods, where token frequencies typically follow a heavy-tailed distribution. The result suggests that a compact vocabulary is sufficient to represent most molecular structures encountered during training.

A.4.2 Fragment Size Distribution

Figure 7 shows the frequency-weighted distribution of fragment sizes measured by the number of atoms contained in each fragment. Most fragments are relatively small, typically containing only 2-3 atoms. Larger fragments appear less frequently but capture recurring higher-order chemical motifs. The predominance of small fragments ensures that tokenization preserves local chemical structure while still allowing the vocabulary to represent meaningful functional groups and substructures. This balance enables the resulting fragment graphs to remain compact while retaining sufficient structural information for downstream learning tasks.

Ablation on Tokenization Refinements. Table 14 evaluates the effect of the proposed tokenization refinements on the LRGB benchmark. Long-range molecules contain diverse structural motifs, leading to more frequent fallback during tokenization. We compare our full tokenizer with a Graph BPE baseline that does not include chemical validity filtering and the OOV fallback decomposition mechanism. As shown in Table 14, incorporating these refinements improves performance on both tasks, increasing ROC-AUC from 0.6321 to 0.6717 on Peptides-func and reducing MAE from 0.2929 to 0.2621 on Peptides-struct. This results highlight the necessity of filtering chemically invalid tokens.

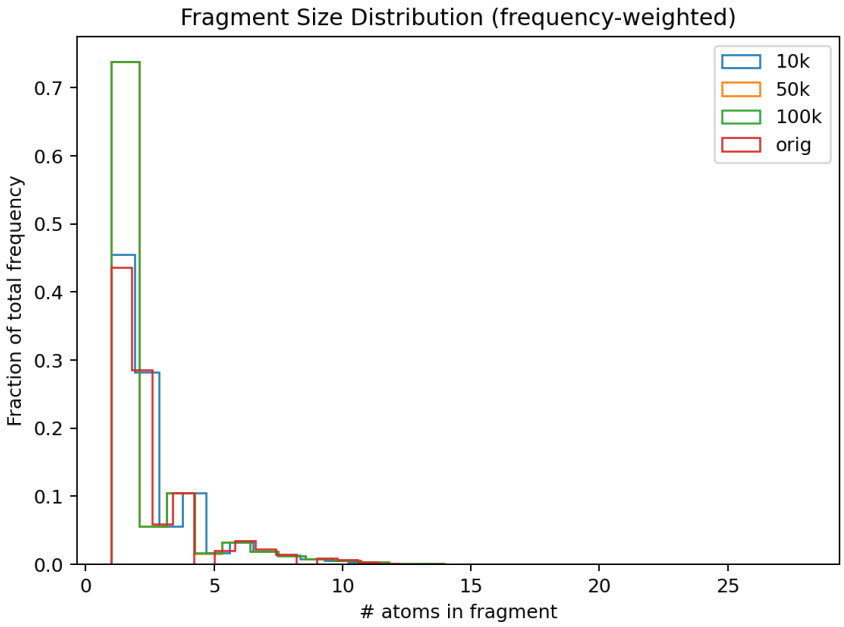

Figure 7: Frequency-weighted distribution of fragment sizes measured by the number of atoms per fragment. Curves correspond to vocabularies learned from different corpus sizes of the same dataset (10k, 50k, 100k molecules), while *orig* denotes the full ChEMBL corpus used for vocabulary construction (430k molecules). Across corpus sizes, most fragments remain small substructures, while larger fragments correspond to recurring chemical motifs captured by the vocabulary.

Table 14: Effect of tokenization refinements on long-range molecular datasets. Removing the validity filtering and OOV fallback mechanisms leads to degraded performance.

Method	Peptides-func (ROC-AUC)	Peptides-struct (MAE)
Graph BPE (without validity/OOV handling)	0.6321	0.2929
Graph BPE (with validity/OOV handling)	0.6717	0.2621

A.5 Atom Features

In addition to standard atom attributes, we incorporate a small set of atom-level constraint features derived from the molecular graph to provide additional chemical context for the GNN encoder. For each atom v_i, we compute a four-dimensional constraint vector based on its bonding configuration and aromaticity. These features are concatenated with the atom embeddings before message passing.

Table 15: Atom-level constraint features used by the GNN encoder.

Feature	**Description**
Max valence	Maximum valence of the atom as determined by RDKit
Bond order sum	Sum of bond orders of all bonds connected to the atom
Remaining valence	Difference between maximum valence and bond order sum
Aromatic indicator	Binary flag indicating whether the atom is aromatic

A.6 Attention Rollout for Fragment Importance

We estimate fragment-level importance using an attention rollout method that aggregates self-attention weights across Transformer layers. For each layer, multi-head attention weights are first averaged across

heads. Residual connections are incorporated by adding the identity matrix followed by row-wise normalization. The overall attention propagation is then computed by recursively multiplying the attention matrices across layers:

$$R = \hat{A}^{(L)} \hat{A}^{(L-1)} \cdots \hat{A}^{(1)}, \tag{6}$$

where $\hat{A}^{(l)}$ denotes the normalized attention matrix at layer l. We use the `[CLS]` token as the global representation, and define the importance of each fragment token i as:

$$s_i = R_{\text{CLS},i}, \tag{7}$$

where s_i denotes the importance score of fragment token i, defined as its contribution to the `[CLS]` representation in the attention rollout matrix. Padding tokens are excluded using the key padding mask. The resulting fragment-level importance scores are mapped back to the atoms within each fragment, enabling visualization on molecular structures.

A.7 Normalized Mutual Information (NMI)

To quantify the alignment between learned fragment embeddings and fingerprint-based structural clusters, we use normalized mutual information (NMI). Given two cluster assignments X and Y, NMI is defined as:

$$\text{NMI}(X, Y) = \frac{2I(X;Y)}{H(X) + H(Y)}, \tag{8}$$

where $I(X;Y)$ denotes the mutual information between X and Y, and $H(\cdot)$ denotes entropy. Higher NMI values indicate stronger agreement between the two clustering.