Enhancing LLM-Based Molecular Captioning with Molecular Fingerprints

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Abstract

The development of large language models (LLMs) has resulted in significant transformations in the field of chemistry, with potential applications in molecular science. Traditionally, the exploration of methods to enhance pre-trained general-purpose LLMs has focused on techniques like supervised fine-tuning (SFT) and retrieval-augmented generation (RAG), to improve model performance and tailor them to specific applications. General purpose extended approaches are being researched, but their adaptation within the chemical domain has not progressed significantly. This study advances the application of LLMs in molecular science by exploring SFT of LLMs, and developing RAG and multimodal models, incorporating molecular embeddings derived from molecular fingerprints and other properties. Experimental results show that a multimodal model with fingerprint inputs achieved the highest MT scores, while RAG with fingerprints excelled in property-specific f1 score. For molecular representation based on SMILES notation, fingerprints effectively capture the structural information of molecular compounds, demonstrating the applicability of LLMs in drug discovery research. Our code is available at https://bitbucket.org/tech-kobo/ellm-mol-cap.

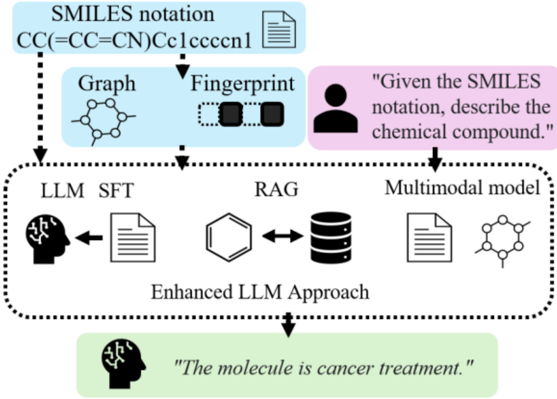

Figure 1: Overview of our molecular captioning task.

1 Introduction

Large language models (LLMs) have recently demonstrated remarkable advancements in the field of natural language processing (NLP), mainly owing to the scaling up of the model parameters and training data sizes (Touvron et al., 2023; Achiam et al., 2023; Anil et al., 2023). Progress in LLMs has achieved state-of-the-art performance across diverse tasks, and also significantly impacted the field of chemistry, with applications rapidly emerging in areas such as drug discovery and domain-specific information retrieval (Zheng et al., 2024; Zhang et al., 2024; Xiao et al., 2024). Molecular captioning is a representative task in chemical application. In this task, a model takes chemical structure information, such as a simplified molecular input line entry system (SMILES) (Weininger, 1988) or molecular graph and generates a textual description of the compound's properties. It enables researchers to understand compound features more easily, accelerating drug discovery. Generally, SMILES, a textual data format, is used as input for this task with LLMs (Edwards et al., 2022).

Improving the accuracy of LLMs for specialized tasks can be classified into two strategies: model-centric improvements and prompt-centric improvements. The model-centric approach focuses on refining the LLM itself, for example through architectural changes, continual pre-training, or supervised fine-tuning (SFT). In particular, SFT is a promising technique because of its relatively low training cost compared with pre-training. The prompt-centric approach focuses on optimizing the input given to the model. This can

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involve techniques like prompt engineering, in-context learning or the use of retrieval-augmented generation (RAG) using text embedding to retrieve and incorporate relevant information from external sources.

Although considerable research has validated these approaches in general tasks (Ovadia et al., 2024), their application to the molecular captioning task remains relatively unexplored. A key challenge in applying LLMs to chemistry is how to represent and input chemical structures for them. This critical question of optimal molecular representation within the LLM framework remains largely unaddressed.

In this study, we investigate the effectiveness of various approaches for improving LLM-based molecular captioning tasks with SMILES notation (Figure 1). The first approach involves the SFT of a closed-source LLM, using SMILES text as the input and the corresponding descriptive text as the ground truth to create a specialized LLM for describing molecular compounds. Closed-source LLMs, which often possess larger model parameters, are hypothesized to achieve more precise inference than fine-tuning open-source LLMs. The second approach employs RAG to leverage the similarity of SMILES strings to retrieve the related compound data. This is intended to allow the LLM to describe molecular compounds that may not have been sufficiently learned or have complex properties not present in the training data. In addition to conventional text embedding-based retrieval for RAG, we incorporate fingerprint-based retrieval using the Tanimoto coefficient (Bajusz et al., 2015) as a similar metric to retrieve structurally similar compounds. The third approach uses multimodal-LLMs with molecular compound embeddings. In multimodal models, the way to embed new modal data is crucial. Here, we compare different types of embeddings: molecular fingerprint, graph neural network embedding, and language model embedding.

Experimental results on a benchmark dataset of molecular compounds show that, among molecular embeddings, the use of molecular fingerprints for RAG and the incorporation of molecular fingerprints as an integrated input for multimodal-LLM yielded the highest accuracy in each approach. Specifically, the latter multimodal model demonstrated the highest performance in this study. This suggests that molecular fingerprints capture molecular property information better than the other two embedding methods, and it is more effective to use a general model with structural information (multimodal) than to improve unimodal model training methods. These findings suggest the potential to support the analysis of molecular compounds and improve the efficiency of drug discovery research.

2 Related Works

2.1 Representation of molecules

There are three types of molecular representation methods that can be converted from SMILES: SMILES itself, Graph, and molecular fingerprint (Table 1). SMILES is a simple notation that represents molecular structures as a single string. It uses element symbols for atoms and symbols for bonds, making it easy to use in machine learning. SMILES embeddings are typically obtained using language models. For SMILES embedding, molecular language models that extend transformer-based models (Vaswani et al., 2017) like T5 (Raffel et al., 2020) or BERT (Devlin et al., 2019) for chemistry, such as molbert or MolT5, are used (Edwards et al., 2022; Fabian et al., 2020; Chithrananda et al., 2020; Ahmad et al., 2022).

Graphs are variable-length data structures capable of representing three-dimensional (3D) structural information. With advancements in deep learning, graph neural network (GNN)-based models (Zhou et al., 2020; Scarselli et al., 2008) are commonly used to generate graph embeddings like MolCLR (Wang et al., 2022).

Molecular fingerprints are vectors, typically binary, that are calculated from SMILES strings using algorithms (Rogers & Hahn, 2010). These vectors store information about the presence or absence of structural features in a compound. Their fixed-length nature allows them to be readily input into general-purpose machine learning models.

From the perspective of chemical structure validity, self-referencing embedded strings (SELFIES) (Krenn et al., 2020) is sometimes used as input for machine learning instead of SMILES. Because LLMs are trained on data crawled from the Web, using the more conventional SMILES as input yields higher accuracy (Guo et al., 2023). Therefore, in this study, we adopt SMILES as the input format for our model.

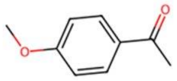
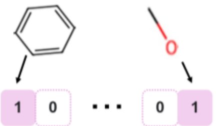
	Image	Feature	Convert method	Encoding Method
SMILES	COc1ccc(C(C)=O)cc1	Variable-length text	-	Molecular Language Model (molt5-large is used in this study)
Graph		Graph including node and edge	Rule based	Graph Neural Network (MolCLR is used in this study)
Molecular fingerprint		Fixed-length vector	Rule based (ECFP is used in this study)	-

Table 1: Three types of molecular representation. The right column represents the conversion methods from SMILES to their respective representation and the creation of embedding vectors employed in this study.

2.2 Molecule-text multimodality

nach0 (Livne et al., 2024), a T5-based model trained to acquire molecular chemistry knowledge, enables multimodal reasoning by distinguishing between SMILES and natural language text tokens. Furthermore, research has been conducted on models that perform contrastive learning after encoding chemical structures and text to solve downstream tasks such as property prediction (Su et al., 2022; Liu et al., 2023; Luo et al., 2023) , and on models that have been extended to include images as input (Liu et al., 2024). As an extension of LLMs, models that perform multimodal reasoning by adding molecular graphs as inputs to accurately capture the structural information of molecular compounds are also being developed (Liu et al., 2023; Cao et al., 2023). Conversely, multimodal models using molecular fingerprints, as well as comparative studies of these, have not been conducted.

3 Problem Settings

This study assumes two tasks using SMILES notations of molecular compounds. The first is the molecular captioning task, which involves explaining the properties of a molecular compound from its SMILES notation. For this task, it is desirable to appropriately describe the properties of the molecular compounds represented by the SMILES. The second task is the molecular property prediction, and its experimental results are presented in detail in the Appendix as part of additional validation.

We assumed that only SMILES is given as the data for molecular compounds, and cases in which molecular structure information is provided as data are not assumed. The molecular embedding models used are detailed in Table 1. RDKit was used for the transformation from SMILES to graph and molecular fingerprints. Extended-Connectivity Fingerprints 4 (ECFP4) was adopted as the algorithm for the transformation to molecular fingerprints. Furthermore, molt5-large was used for SMILES embeddings, and MolCLR was used for graph embeddings.

4 Proposed Methods

We propose three approaches for predicting the properties of molecular compounds based on their SMILES text (Figure 2).

4.1 First Approach: SFT

In our first approach, we perform SFT on a closed-source LLM to specialize in generating descriptive text from SMILES notation. Although open-source LLMs offer greater parameter customization flexibility, they typically have fewer parameters than their closed-source counterparts. Because models with larger parameter counts generally demonstrate superior text generation capabilities, we selected a closed-source LLM for this task, using molecular SMILES strings as inputs and corresponding descriptive texts as outputs for the training process.

4.2 Second Approach: RAG

In the second approach, which uses RAG, a dataset of pairs of training molecule SMILES texts and their corresponding descriptive texts is stored in a database in advance. The molecule that was most similar to the input molecule was retrieved from the database. To prevent data leakage during the search, the SMILES stored in the database are not used in the test data. In this study, we performed similarity searches for similar molecular compounds via following retrievers:

- Similarity between molecular fingerprints and molecular captions via CLIP

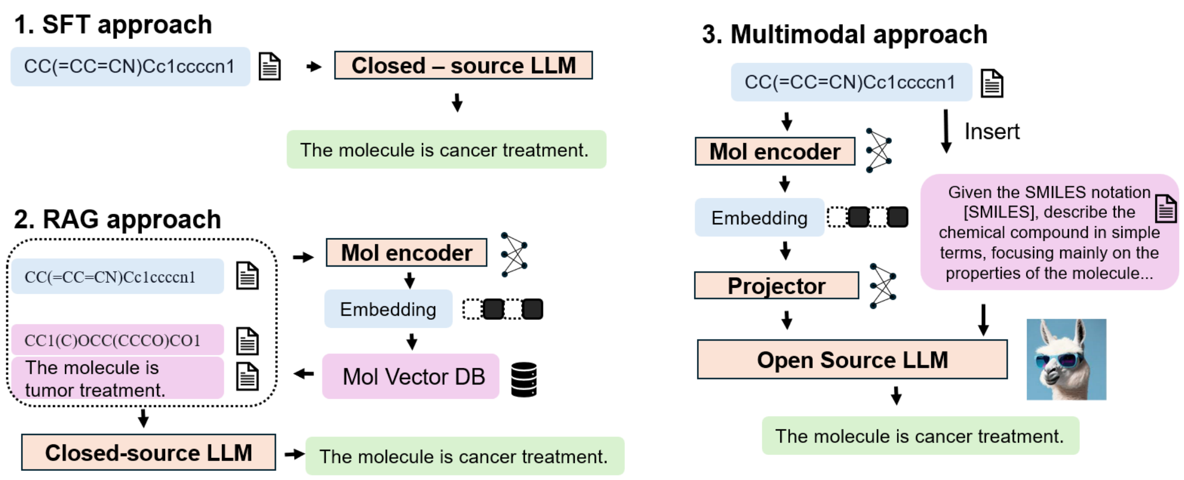

1. SFT approach
CC(=CC=CN)Cc1cccn1
Closed – source LLM
The molecule is cancer treatment.
2. RAG approach
CC(=CC=CN)Cc1ccccn1
CC1(C)OCC(CCCO)CO1
The molecule is tumor treatment.
Mol encoder
Embedding
Mol Vector DB
Closed-source LLM
The molecule is cancer treatment.
3. Multimodal approach
CC(=CC=CN)Cc1ccccn1
Insert
Mol encoder
Embedding
Projector
Given the SMILES notation [SMILES], describe the chemical compound in simple terms, focusing mainly on the properties of the molecule...
Open Source LLM
The molecule is cancer treatment.

Figure 2: Details of our three approaches. Embeddings are created using three patterns: SMILES + MolT5, Graph + MolCLR, and Molecular fingerprint.

Dataset name	L+M-24			ChEBI-20		
	train	valid	test	train	valid	test
Number of samples	101491	25373	33696	23760	5941	3297
Average SMILES sequence length	108.5	105.4	105.4	77.2	76.6	74.4
Average number of caption text words	30.3	30.4	29.5	43.3	43.7	43.9

Table 2: Dataset overview.

- Cosine similarity of embeddings of SMILES by MolT5
- The cosine similarity of GNN embeddings for graph-represented molecules.
- Tanimoto coefficient of molecular fingerprints

The Tanimoto coefficient is most suitable for similarity comparison of molecules converted to fingerprints (Bajusz et al., 2015). In this study, we provided the top five SMILES and caption pairs obtained through a similarity search of LLM and instructed it to generate an appropriate caption for the input SMILES.

4.3 Third Approach: Multimodal

The third approach involves a multimodal-LLM using molecular fingerprints. This is an extension of the SFT method to the multimodal domain, where the LLM is given a molecular compound's SMILES text and fingerprint, enabling it to obtain structural information from SMILES and describe its properties. We implemented a multimodal LLM that processes instruction text and integrated inputs of SMILES, graph representations, or molecular fingerprints. The input SMILES undergoes a two-step branching process. First, it is converted into a molecular embedding by an encoder model. This embedding is then transformed via a projector into a vector with the same dimensionality as the LLM input and fed into the LLM. The other step involves embedding the SMILES string directly into the prompt as text. Finally, these inputs are integrated, and the LLM generates text. By including graph embeddings or fingerprints as inputs, the LLM is able to generate text while having captured the structural information of the molecular compounds.

5 Experiments and Results

5.1 Dataset

We used the L+M-24 dataset [1] and ChEBI-20 dataset [2] (Table 2). L+M-24 is an open dataset containing SMILES notation text of molecular compounds and text describing their properties. There are 3502 property names. The property can be divided into four categories: Biomedical (=2032), Light and Electricity (=58), Human interaction and Organoleptic (=787), and Agriculture and Industry (=625). This is the most

[1] https://huggingface.co/datasets/language-plus-molecules/LPM-24_train

[2] https://huggingface.co/datasets/liupf/ChEBI-20-MM

common dataset containing pairs of SMILES notations of molecular compounds and text describing their properties in English. ChEBI-20 is a dataset containing pairs of molecular structural information and captions that describe them in natural language text. Whereas L+M-24 focuses on captioning, which explains physical properties, ChEBI-20 focuses on captioning the molecular structure itself. For each dataset, we split the non-test data into training and validation sets with an 8:2 ratio.

5.2 LLMs

For SFT approach, we utilized the custom tuning feature of Vertex AI Studio in a Google Cloud environment and used the gemini-2.5-flash model of the closed-source LLM. Also, we used molt5-large (Edwards et al., 2022), biot5-base (Pei et al., 2023), biot5-plus-base-chebi20 (Pei et al., 2024), Meta-Llama-3-8B (Grattafiori et al., 2024), meditron-7b (Chen et al., 2023), nach0_base (Livne et al., 2024) and ChemLLM-7B-Chat (Zhang et al., 2024) as the SFTs of the open-source LLMs. In addition, during the training of the LLM parameters, we used Lora to achieve lightweight fine-tuning. The computational environment for these experiments was an NVIDIA A100 40GB computer connected to Google Cloud Workstations.

For RAG approach, because large context window is required, we used the same Gemini-2.5-flash. This enables the simultaneous input of multiple SMILES and their caption pairs that are similar to the input molecule's SMILES into the LLM. In the RAG using CLIP, we used a distilbert-base-uncased text encoder for captions to perform lightweight and high-speed training. It is necessary to unify the dimensionality of these embeddings, we added projectors both text encoder and molecular fingerprint with 256 output dimensions for CLIP training.

For multimodal approach, from the perspective of high instruction-following ability and trainable parameters, Meta-Llama-3-8B (Grattafiori et al., 2024) was used as the base model for the multimodal model. The training settings and computational environment for the training were the same as those for the SFT conducted with open-source LLMs. The Projector uses linear transformation and Q-Former which was adopted in MolCA and 3D-MoLM (Liu et al., 2023, Li et al., 2024). The Mol Encoder (MolT5, MolCLR) and Q-Former Projector are pre-trained first. Then, the Mol Encoder, Projector, and LLM are trained simultaneously second. As the dimensionality of the hidden layer embeddings of Meta-Llama-3-8B is 4096, the projector from the Mol Encoder to the LLM has an output dimension of 4096.

5.3 Evaluation Metrics

Following the paper that created the L+M-24 dataset (Edwards et al., 2024), we used two types of evaluation metrics. First, we used property-specific scores that calculate whether the generated text includes property-specific words of molecular compounds. Property-specific scores are calculated by matching tokenized names within the generated captions, specifically using macro-F1, precision, and recall. Second, we employed machine translation (MT) evaluation metrics, which are common in NLP tasks like machine translation and text summarization. For the MT evaluation metrics, we performed evaluations using natural language generation metrics such as BLEU-2/4 (Papineni et al., 2002), METEOR (Banerjee & Lavie, 2005), and ROUGE-1/2/L (Lin, 2004).

Comparing MT evaluation metrics and property-specific scores, MT evaluation metrics are influenced by how grammatically similar they are to the ground-truth text. Therefore, the score may be high even if the characteristics of the molecular compound are not properly expressed. Property-specific scores are more appropriate evaluation metrics for assessing whether the characteristics of molecular compounds have been correctly captured. It was only used with L+M-24 dataset because this metric is used to determine properties (Figure 3).

5.4 Results

We evaluated the performance of our three proposed approaches compared with domain-specific baselines. Figure 3 compares models using overall property-scores on the y-axis and models on the x-axis. Table 3 and Table 4 delineate the model characteristics and MT evaluation metrics for each model, using the L+M-24 dataset and the ChEBI-20 dataset respectively. We compared against MolCLR, in Figure 3, represents a non-LLM, GNN-based predictive model which leverages the three-dimensional structure of molecules. It does not generate captions but predicts the presence of property-related words to calculate property-specific scores. Among the baselines, ChemLLM achieved the highest

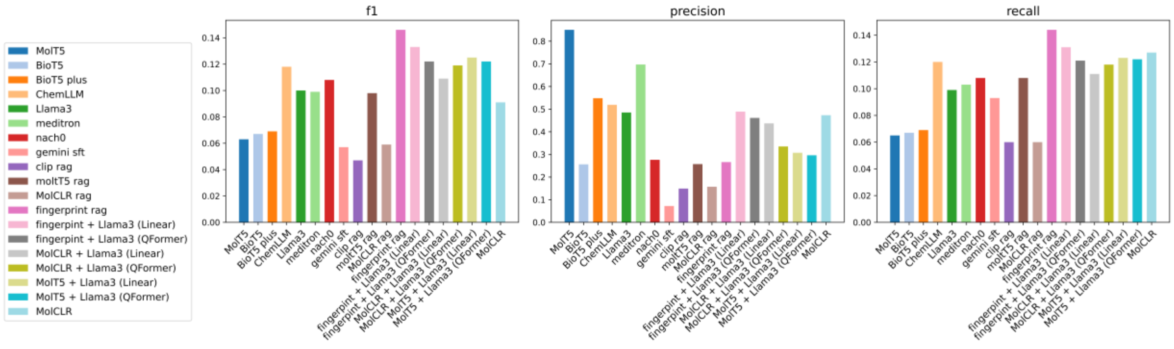


Figure 3: Overall property-specific score for molecular captioning using LLMs on L+M-24 dataset. Evaluation Metrics: macro-F1 score (f1), precision, recall. The model used for verification is the same as the one shown in Table 3.

performance in both MT scores and property-specific f1 score. Furthermore, categorized property-specific score is shown in Appendix A.

Our proposed closed-source LLM, Gemini (Team Gemini et al., 2023), fine-tuned through SFT (Gemini SFT), did not outperform domain specific language model like ChemLLM, Meditron or nach0 in both MT scores and property-specific scores. The underperformance is likely due to Gemini's lack of specialization in chemical text generation and its inability to effectively distinguish SMILES strings from regular alphabet sequences during tokenization. This suggests that for domain-specific tasks with LLMs, a domain-specific training approach is more vital than model parameter size.

Conversely, the RAG approach, which does not involve SFT, yielded lower scores, failing to fully grasp the characteristics of captioning. Upon examining generated texts, we observed significant variations in grammar and phrasing compared to the ground truth, as well as instances of overly lengthy text. This is likely due to the LLM not having learned the structure of ground truth texts. This issue might be mitigated by adjusting the system prompt to encourage outputs that follow the ground truth text structure. For example, captions in the L+M-24 dataset often begin with "The Molecule is," a pattern not always captured by RAG-generated text. When comparing the property specific score, the molecular fingerprint Tanimoto coefficient-based RAG model (fingerprint-rag) had the highest f1 score among the entire approaches. From the high recall as well, we can see that it most accurately explains the properties of the molecules that should be explained. This suggests that this approach is the most appropriate when we want to generate captions without missing any molecular properties.

Multimodal LLM captioning consistently achieved the highest prediction accuracy overall in MT score across all three approaches. When comparing Llama3 or MolCLR-only models with their Multimodal counterparts, we can confirm an improvement in accuracy. This suggests that, since the information content of SMILES sequences and molecular graphs is equivalent, Llama3 and MolCLR are likely capturing different features of molecules. Moreover, the multimodal model using fingerprint embeddings achieved the highest scores overall, with linear transformation proving to be more suitable as a projector than Q-Former. It's possible that a simpler projection was less prone to overfitting than the more complex Q-Former because molecular fingerprint information is relatively easy to capture. It has higher performance than the combination of Graph encoder and Q-Former Projector adopted in MolCA (Liu et al., 2023).

The superior performance of models that incorporate molecular structure information, either via multimodal methods or molecular fingerprints in RAG, suggests that accurately representing chemical structure is paramount for LLMs. Our results show that correctly encoding chemical structure allows general-purpose LLMs like Llama3 to outperform domain-specific unimodal models in tasks such as molecular captioning. The strong performance of models using molecular fingerprints in both RAG and multimodal settings underscores that text encoder-based representations like those in MolT5 and nach0 may not always fully capture crucial molecular features like the presence of atoms, bonds, and rings. If MolCLR or MolT5 cannot produce embeddings

(a) SFT approach	BLEU-2	BLEU-4	METEOR	ROUGE-1	ROUGE-2	ROUGE-L
MolT5 (baseline)	0.048	0.036	0.310	0.427	0.325	0.402
BioT5 (baseline)	0.047	0.035	0.292	0.407	0.310	0.386
BioT5 plus (baseline)	0.045	0.034	0.279	0.418	0.320	0.393
ChemLLM (baseline)	**0.772**	**0.561**	**0.736**	**0.790**	**0.599**	**0.570**
Meditron (baseline)	0.754	0.545	0.713	0.767	0.580	0.551
nach0 (baseline)	0.756	0.543	0.707	0.745	0.544	0.525
Llama3 (baseline)	0.721	0.521	0.700	0.755	0.565	0.545
Gemini SFT	0.745	0.533	0.694	0.731	0.530	0.512

(b) RAG approach	BLEU-2	BLEU-4	METEOR	ROUGE-1	ROUGE-2	ROUGE-L
CLIP-rag	0.128	0.055	0.248	0.228	0.086	0.165
MolCLR-rag	0.103	0.040	0.224	0.201	0.069	0.149
MolT5-rag	**0.240**	**0.127**	**0.393**	**0.364**	**0.177**	**0.236**
Fingerprint-rag	0.206	0.103	0.368	0.331	0.151	0.219

(c) MM approach	Projector	BLEU-2	BLEU-4	METEOR	ROUGE-1	ROUGE-2	ROUGE-L
MolCLR+Llama3	Linear	0.766	0.552	0.725	0.771	0.573	0.549
MolCLR+Llama3	Q-Former	0.768	0.554	0.730	0.779	0.582	0.557
MolT5+Llama3	Linear	0.727	0.525	0.714	0.770	0.575	0.555
MolT5+Llama3	Q-Former	0.768	0.554	0.732	0.780	0.582	0.558
Fingerprint+Llama3	Linear	**0.776**	**0.560**	**0.738**	**0.785**	**0.587**	**0.563**
Fingerprint+Llama3	Q-Former	0.769	0.554	0.730	0.778	0.580	0.556

Table 3: MT scores for L+M-24 dataset of (a) SFT approach, (b) RAG approach, and (c) multimodal (MM) approach, respectively. The best performing model for each metric is shown in bold.

that adequately capture these structural aspects, the prediction accuracy may suffer. In contrast, molecular fingerprints explicitly represent the local characteristics of molecules, enabling models to easily discern meaningful features.

Based on these findings, the most effective approach depends on the evaluation criteria. While the multimodal model with SFT (Fingerprint+Llama3) achieved the highest scores on some MT evaluation metrics (BLEU-2, METEOR), the fingerprint-rag model achieved the highest property-specific f1 score. Given that property-specific scores are more appropriate for assessing whether molecular characteristics have been correctly captured, the fingerprint-rag approach demonstrates significant effectiveness in accurately describing molecular properties. Furthermore, for low-frequency properties, RAG has been shown to achieve higher accuracy than multimodal model SFT (Appendix C). When computational resources are constrained, RAG offers a viable alternative for generating descriptions based on similar molecules. Across all methods, molecular fingerprint representations, which explicitly encode structural information as vectors, consistently yielded the best results. Examples of the text generated in this experiment are provided in Appendix D.

6 Conclusions

This study explored three enhancement approaches, SFT, RAG, and multimodal LLMs for predicting molecular compound properties from SMILES notation. In the SFT approach, we fine-tuned a closed-source LLM using the Gemini API, and it did not outperform domain specific language model like ChemLLM, Meditron or nach0 in both MT scores and property-specific scores. The RAG-based model exhibited property-specific scores comparable to those achieved by the SFT-trained model. Notably, both RAG and multimodal LLMs demonstrated higher scores when processing molecular fingerprints as input, rather than SMILES or graph representations. Specifically, a multimodal model with fingerprint inputs achieved the highest MT scores and RAG with fingerprints excelled in property-specific f1 score. These findings highlight the potential of LLMs in drug discovery research and suggest their promise for improving the efficiency of future pharmaceutical development.

(a) SFT approach	BLEU-2	BLEU-4	METEOR	ROUGE-1	ROUGE-2	ROUGE-L
MolT5 (baseline)	0.134	0.057	0.185	0.296	0.119	0.234
BioT5 (baseline)	0.230	0.142	0.287	0.344	0.161	0.267
BioT5 plus (baseline)	0.223	0.136	0.249	0.333	0.178	0.280
ChemLLM (baseline)	**0.401**	**0.292**	**0.452**	**0.515**	**0.332**	**0.448**
Meditron (baseline)	0.359	0.244	0.397	0.478	0.289	0.416
nach0 (baseline)	0.381	0.271	0.418	0.501	0.313	0.432
Llama3 (baseline)	0.312	0.193	0.360	0.439	0.238	0.369
Gemini SFT	0.283	0.171	0.363	0.425	0.216	0.345

(b) RAG approach	BLEU-2	BLEU-4	METEOR	ROUGE-1	ROUGE-2	ROUGE-L
CLIP-rag	0.136	0.045	0.188	0.267	0.076	0.188
MolCLR-rag	0.189	0.098	0.250	0.324	0.122	0.230
MolT5-rag	0.175	0.084	0.232	0.310	0.111	0.221
fingerprint-rag	**0.222**	**0.129**	**0.287**	**0.358**	**0.152**	**0.258**

(c) MM approach	Projector	BLEU-2	BLEU-4	METEOR	ROUGE-1	ROUGE-2	ROUGE-L
MolCLR+Llama3	Linear	0.324	0.210	0.369	0.453	0.261	0.389
MolCLR+Llama3	Q-Former	0.397	0.283	0.440	0.511	0.324	0.443
MolT5+Llama3	Linear	0.400	0.285	0.437	0.510	0.323	0.443
MolT5+Llama3	Q-Former	0.404	0.287	0.438	0.513	0.322	0.443
fingerprint+Llama3	Linear	**0.421**	**0.307**	**0.458**	**0.528**	**0.342**	**0.459**
fingerprint+Llama3	Q-Former	0.410	0.294	0.451	0.520	0.331	0.450

Table 4: MT scores for ChEBI-20 dataset of (a) SFT approach, (b) RAG approach, and (c) multimodal (MM) approach, respectively. The best performing model for each metric is shown in bold.

For future research directions, we need to investigate multimodal models that accept 3D structures as input and explore modality extensions, examine molecular captioning that combines SFT and RAG, and explore fine-tuning using SELFIES instead of SMILES. This also includes evaluating the applicability of these technologies to actual drug discovery and other related tasks.

Limitations

A key limitation of this study is its exclusive reliance on 2D molecular representations, as incorporating 3D conformational data presents significant challenges. Generating accurate 3D molecular conformations becomes increasingly challenging and computationally intensive as molecules grow in size, due to the exponential expansion of chemical space (Reymond, 2015). Excluding molecules for which 3D generation failed and using only successfully generated 3D data could bias the dataset toward smaller molecular structures, preventing the model from handling the broader chemical space. Considering the current limitations in accuracy and cost of 3D generation, we focused on 2D representations to prioritize robustness and scalability across diverse and extensive chemical spaces. As a result, our model does not yet fully leverage the potential benefits that 3D information could provide.

References

OpenAI. 2023. Gpt-4 technical report. arXiv preprint arXiv:2303.08774.

Walid Ahmad, Elana Simon, Seyone Chithrananda, Gabriel Grand, and Bharath Ramsundar. 2022. Chemberta-2: Towards chemical foundation models. arXiv preprint arXiv:2209.01712.

Rohan Anil, Andrew M Dai, Orhan Firat, Melvin Johnson, Dmitry Lepikhin, Alexandre Passos, Siamak Shakeri, Emanuel Taropa, Paige Bailey, Zhifeng Chen, and others. 2023. Palm 2 technical report. arXiv preprint arXiv:2305.10403.

David Bajusz, Anita Rácz, and Károly Héberger. 2015. Why is Tanimoto index an appropriate choice for fingerprint-based similarity calculations?. Journal of cheminformatics, volume 7, pages 1-13.

Satanjeev Banerjee and Alon Lavie. 2005. METEOR: An automatic metric for MT evaluation with improved correlation with human judgments. In Proceedings of the acl workshop on intrinsic and extrinsic evaluation measures for machine translation and/or summarization, pages 65–72.

He Cao, Zijing Liu, Xingyu Lu, Yuan Yao, and Yu Li. 2023. Instructmol: Multi-modal integration for building a versatile and reliable molecular assistant in drug discovery. arXiv preprint arXiv:2311.16208.

Zeming Chen, Alejandro Hernández Cano, Angelika Romanou, Antoine Bonnet, Kyle Matoba, Francesco Salvi, Matteo Pagliardini, Simin Fan, Andreas Köpf, Amirkeivan Mohtashami, and others. 2023. Meditron-70b: Scaling medical pretraining for large language models. arXiv preprint arXiv:2311.16079.

Ashok K. Chandra, Dexter C. Kozen, and Larry J. Stockmeyer. 1981. Alternation. Journal of the Association for Computing Machinery, 28(1):114-133.

Seyone Chithrananda, Gabriel Grand, and Bharath Ramsundar. 2020. ChemBERTa: large-scale self-supervised pretraining for molecular property prediction. arXiv preprint arXiv:2010.09885.

Jacob Devlin, Ming-Wei Chang, Kenton Lee, and Kristina Toutanova. 2019.: Pre-training of Deep Bidirectional Transformers for Language Understanding. In Proceedings of the 2019 Conference of the North merican Chapter of the Association for Computational Linguistics: Human Language Technologies, Volume 1 (Long and Short Papers), pages 4171–4186. Association for Computational Linguistics.

Carl Edwards, Tuan Lai, Kevin Ros, Garrett Honke, Kyunghyun Cho, and Heng Ji. 2022. Translation between Molecules and Natural Language. In Proceedings of the 2022 Conference on Empirical Methods in Natural Language Processing, pages 375–413. Association for Computational Linguistics.

Carl Edwards, Qingyun Wang, Lawrence Zhao, and Heng Ji. 2024. L+ M-24: Building a Dataset for Language+ Molecules@ ACL 2024. arXiv preprint arXiv:2403.00791.

Benedek Fabian, Thomas Edlich, Héléna Gaspar, Marwin Segler, Joshua Meyers, Marco Fiscato, and Mohamed Ahmed. 2020. Molecular representation learning with language models and domain-relevant auxiliary tasks. arXiv preprint arXiv:2011.13230.

Team Gemini, Rohan Anil, Sebastian Borgeaud, Jean-Baptiste Alayrac, Jiahui Yu, Radu Soricut, Johan Schalkwyk, Andrew M Dai, Anja Hauth, Katie Millican, and others. 2023. Gemini: a family of highly capable multimodal models. arXiv preprint arXiv:2312.11805.

Aaron Grattafiori, Abhimanyu Dubey, Abhinav Jauhri, Abhinav Pandey, Abhishek Kadian, Ahmad Al-Dahle, Aiesha Letman, Akhil Mathur, Alan Schelten, Alex Vaughan, and others. 2024. The llama 3 herd of models. arXiv preprint arXiv:2407.21783.

Taicheng Guo, Kehan Guo, Bozhao Nan, Zhenwen Liang, Zhichun Guo, Nitesh Chawla, Olaf Wiest, and Xiangliang Zhang. 2023. What can Large Language Models do in chemistry? A comprehensive benchmark on eight tasks. In Advances in Neural Information Processing Systems, volume 36, pages 59662–59688.

Mario Krenn, Florian Häse, AkshatKumar Nigam, Pascal Friederich, and Alan Aspuru-Guzik. 2020. Self-referencing embedded strings (SELFIES): A 100% robust molecular string representation. Machine Learning: Science and Technology, volume 1, number 4, pages 045024.

Sihang Li, Zhiyuan Liu, Yanchen Luo, Xiang Wang, Xiangnan He, Kenji Kawaguchi, Tat-Seng Chua, and Qi Tian. 2024. Towards 3d molecule-text interpretation in language models. arXiv preprint arXiv:2401.13923.

Chin-Yew Lin. 2004. Rouge: A package for automatic evaluation of summaries. In Text summarization branches out, pages 74–81.

Zhiyuan Liu, Sihang Li, Yanchen Luo, Hao Fei, Yixin Cao, Kenji Kawaguchi, Xiang Wang, and Tat-Seng Chua. 2023. MolCA: Molecular Graph-Language Modeling with Cross-Modal Projector and Uni-Modal Adapter. In Proceedings of the 2023 Conference on Empirical Methods in Natural Language Processing, pages 15623–15638.

Pengfei Liu, Yiming Ren, Jun Tao, and Zhixiang Ren. 2024. Git-mol: A multi-modal large language model for molecular science with graph, image, and text. Computers in biology and medicine.

Shengchao Liu, Weili Nie, Chengpeng Wang, Jiarui Lu, Zhuoran Qiao, Ling Liu, Jian Tang, Chaowei Xiao, and Animashree Anandkumar. 2023. Multi-modal molecule structure--text model for text-based retrieval and editing. Nature Machine Intelligence, 1447–1457.

Micha Livne, Zulfat Miftahutdinov, Elena Tutubalina, Maksim Kuznetsov, Daniil Polykovskiy, Annika Brundyn, Aastha Jhunjhunwala, Anthony Costa, Alex Aliper, Alán Aspuru-Guzik, and others. 2024. nach0: Multimodal natural and chemical languages foundation model. Chemical Science, 8380–8389.

Yizhen Luo, Kai Yang, Massimo Hong, Xing Yi Liu, and Zaiqing Nie. 2023. Molfm: A multimodal molecular foundation model. arXiv preprint arXiv:2307.09484.

Oded Ovadia, Menachem Brief, Moshik Mishaeli, and Oren Elisha. 2024. Fine-Tuning or Retrieval? Comparing Knowledge Injection in LLMs. In Proceedings of the 2024 Conference on Empirical Methods in Natural Language Processing, pages 237-250.

Kishore Papineni, Salim Roukos, Todd Ward, and Wei-Jing Zhu. 2002. Bleu: a method for automatic evaluation of machine translation. In Proceedings of the 40th annual meeting of the Association for Computational Linguistics, pages 311–318.

Qizhi Pei, Wei Zhang, Jinhua Zhu, Kehan Wu, Kaiyuan Gao, Lijun Wu, Yingce Xia, and Rui Yan. 2023. BioT5: Enriching Cross-modal Integration in Biology with Chemical Knowledge and Natural Language Associations. In Proceedings of the 2023 Conference on Empirical Methods in Natural Language Processing, pages 1102-1123.

Qizhi Pei, Lijun Wu, Kaiyuan Gao, Xiaozhuan Liang, Yin Fang, Jinhua Zhu, Shufang Xie, Tao Qin, and Rui Yan. 2024. BioT5+: Towards Generalized Biological Understanding with IUPAC Integration and Multi-task Tuning. In Findings of the Association for Computational Linguistics: ACL 2024, pages 1216–1240.

Colin Raffel, Noam Shazeer, Adam Roberts, Katherine Lee, Sharan Narang, Michael Matena, Yanqi Zhou, Wei Li, and Peter J Liu. 2020. Exploring the limits of transfer learning with a unified text-to-text transformer. Journal of machine learning research, volume 21, pages 1–67.

RDKit: Open-source cheminformatics. https://www.rdkit.org

Jean-Louis Reymond. 2015. The Chemical Space Project. Accounts of Chemical Research, volume 48, number 3, pages 722-730.

David Rogers and Mathew Hahn. 2010. Extended-Connectivity Fingerprints. Journal of Chemical Information and Modeling, volume 50, pages 742-754.

Franco Scarselli, Marco Gori, Ah Chung Tsoi, Markus Hagenbuchner, and Gabriele Monfardini. 2008. The graph neural network model. IEEE transactions on neural networks, 19(1):61-80.

Bing Su, Dazhao Du, Zhao Yang, Yujie Zhou, Jiangmeng Li, Anyi Rao, Hao Sun, Zhiwu Lu, and Ji-Rong Wen. 2022. A molecular multimodal foundation model associating molecule graphs with natural language. arXiv preprint arXiv:2209.05481.

Hugo Touvron, Thibaut Lavril, Gautier Izacard, Xavier Martinet, Marie-Anne Lachaux, Timothèe Lacroix, Baptiste Rozière, Naman Goyal, Eric Hambro, Faisal Azhar, and others. 2023. Llama: Open and efficient foundation language models. arXiv preprint arXiv:2302.13971.

Ashish Vaswani, Noam Shazeer, Niki Parmar, Jakob Uszkoreit, Llion Jones, Aidan N Gomez, Łukasz Kaiser, and Illia Polosukhin. 2017. Attention is All you Need. In Advances in Neural Information Processing Systems, volume 30, Curran Associates, Inc.,

David Weininger. 1988. SMILES, a chemical language and information system. 1. Introduction to methodology and encoding rules. Journal of chemical information and computer sciences, volume 28, pages 31–36.

Yuyang Wang, Jianren Wang, Zhonglin Cao, and Amir Barati Farimani. 2022. Molecular contrastive learning of representations via graph neural networks. Nature Machine Intelligence, volume 4, pages 279–287.

Hanguang Xiao, Feizhong Zhou, Xingyue Liu, Tianqi Liu, Zhipeng Li, Xin Liu, and Xiaoxuan Huang. 2024. A comprehensive survey of large language models and multimodal large language models in medicine. arXiv preprint arXiv:2405.08603.

Yanxin Zheng, Wensheng Gan, Zefeng Chen, Zhenlian Qi, Qian Liang, and Philip S Yu. 2024. Large language models for medicine: a survey. International Journal of Machine Learning and Cybernetics, volume 16, pages 1015–1040.

Di Zhang, Wei Liu, Qian Tan, Jingdan Chen, Hang Yan, Yuliang Yan, Jiatong Li, Weiran Huang, Xiangyu Yue, Wanli Ouyang, and others. 2024. Chemllm: A chemical large language model. arXiv preprint arXiv:2402.06852.

Qiang Zhang, Keyang Ding, Tianwen Lyv, Xinda Wang, Qingyu Yin, Yiwen Zhang, Jing Yu, Yuhao Wang, Xiaotong Li, Zhuoyi Xiang, and others. 2024. Scientific large language models: A survey on biological & chemical domains. arXiv preprint arXiv:2401.14656.

Jie Zhou, Ganqu Cui, Shengding Hu, Zhengyan Zhang, Cheng Yang, Zhiyuan Liu, Lifeng Wang, Changcheng Li, and Maosong Sun. 2020. Graph neural networks: A review of methods and applications. AI open, volume 1, pages 57–81.

A Categorized property-specific score

Table 5 displays the categorized property-specific scores from L+M-24 dataset. We observed that biomedical properties were generally easier to predict. While fingerprint-based models generally performed best, the performance differences across representation methods varied more by property category.

B Molecular Property Prediction

Molecular property prediction involves predicting the property labels of a molecular compound using SMILES notation. For this task, accurate prediction

	Biomedical			Human Interaction and Organoleptics			Agriculture and Industry			Light and Electricity		
	p	r	f1	p	r	f1	p	r	f1	p	r	f1
MolT5	0.886	0.200	0.203	**0.990**	0.001	0.001	**0.960**	0.022	0.025	0.564	0.038	0.021
BioT5	0.531	0.201	0.205	0.197	0.002	0.002	0.203	0.021	0.025	0.091	0.045	0.035
BioT5 plus	0.701	0.204	0.210	0.596	0.002	0.004	0.799	0.021	0.025	0.095	0.049	0.036
ChemLLM	0.614	0.276	0.276	0.455	0.064	0.068	0.829	0.061	0.064	0.178	0.079	0.065
Llama3	0.568	0.255	0.259	0.377	0.031	0.037	0.790	0.048	0.051	0.204	0.061	0.052
Meditron	0.868	0.255	0.258	0.413	0.045	0.044	0.914	0.056	0.058	**0.592**	0.058	0.036
nach0	0.536	0.263	0.265	0.315	0.055	0.054	0.190	0.059	0.059	0.064	0.053	0.054
Gemini SFT	0.355	0.256	0.248	0.251	0.033	0.035	0.111	0.057	0.050	0.073	0.050	0.054
CLIP-rag	**0.895**	0.192	0.193	0.158	0.010	0.007	0.102	0.004	0.005	0.000	0.000	0.000
Molt5-rag	0.649	0.211	0.220	0.381	0.058	0.057	0.161	0.024	0.027	0.254	0.054	0.068
MolCLR-rag	0.651	0.219	0.232	0.380	**0.071**	0.065	0.170	0.029	0.031	0.252	0.118	0.129
Fingerprint-rag	0.765	0.234	0.254	0.345	0.070	0.061	0.187	0.028	0.030	0.276	**0.139**	**0.151**
MolCLR + Llama3 (Linear)	0.578	0.277	0.280	0.315	0.062	0.066	0.200	0.055	0.059	0.134	0.097	0.096
MolCLR + Llama3 (Q-Former)	0.565	0.272	0.273	0.427	0.056	0.060	0.234	0.061	0.062	0.113	0.085	0.080
MolT5 + Llama3 (Linear)	0.554	0.268	0.269	0.371	0.052	0.052	0.734	0.059	0.060	0.089	0.067	0.055
MolT5 + Llama3 (Q-Former)	0.560	0.272	0.273	0.286	0.059	0.062	0.222	0.061	0.063	0.116	0.098	0.093
fingerprint + Llama3 (Linear)	0.572	**0.280**	**0.281**	0.484	**0.071**	**0.073**	0.707	**0.063**	**0.064**	0.194	0.111	0.113
fingerprint + Llama3 (Q-Former)	0.547	0.272	0.274	0.431	0.067	0.069	0.733	0.061	0.063	0.135	0.083	0.083

Table 5: Categorized property-specific score from L+M-24 dataset. p is precision, r is recall, f1 is macro-F1 score.

	BBBP	Clintox	HIV	bace
Detail of task	Binary labels of blood-brain barrier penetration (permeability).	Qualitative data of drugs approved by the FDA and those that have failed clinical trials for toxicity reasons.	Experimentally measured abilities to inhibit HIV replication.	Quantitative (IC50) and qualitative (binary label) binding results for a set of inhibitors of human β-secretase 1(BACE-1).
Number of samples	2039	1480	41127	1513
Positive label ratio	0.765	0.936	0.035	0.458
Task Type	Binary Classification	Binary Classification	Binary Classification	Binary Classification

Table 6: Molecule Net dataset overview.

of the property labels of the molecular compound represented by SMILES is desirable. For blood-brain barrier penetration (BBBP) task, the input SMILES is given as text, and if the molecular compound given in SMILES can penetrate the blood–brain barrier, the output will be "Yes", otherwise, it will be "No". In this study, molecular property prediction solves only binary classification tasks, where whether the molecular compound exhibits a certain property is

	BBBP		clintox		HIV		bace	
	ROC	PR	ROC	PR	ROC	PR	ROC	PR
fingerprint + LR	0.910	0.967	0.627	0.952	0.755	0.260	0.904	0.855
fingerprint + XGB	0.929	0.972	0.675	0.956	**0.802**	**0.421**	**0.922**	**0.891**
fingerprint + SVM	0.897	0.964	0.631	0.957	–	-	0.889	0.844
fingerprint + NN	0.917	0.969	0.640	0.960	0.785	0.374	0.903	0.849
MolCLR	0.894	0.958	0.766	0.980	0.773	0.077	0.816	0.752
MoBERT	0.957	0.987	0.998	**1.000**	0.759	0.355	0.863	0.818
MolT5	0.958	0.988	0.996	**1.000**	0.661	0.101	0.626	0.513
nach0	**0.963**	**0.990**	**0.999**	**1.000**	0.785	0.381	0.895	0.857
Llama3	0.812	0.929	0.822	0.984	0.746	0.205	0.720	0.688
fingerprint + Llama3 (Linear)	0.953	0.986	0.981	0.999	0.774	0.341	0.878	0.825

Table 7: ROC-AUC (ROC) and PR-AUC (PR) of molecule property prediction.

represented in a binary format; it does not solve regression tasks. This is because, given that the LLMs output tokens probabilistically in the forward direction, numerical regression tasks are challenging. In contrast, classification tasks are easier to solve because probabilistically outputting tokens is equivalent to multiclass classification.

B.1 Dataset

For molecular property prediction, we used four datasets released by Molecule Net[3], a large-scale benchmark that organizes several public datasets for molecular machine-learning evaluation. All datasets used in this research were for binary classification tasks that express whether a compound exhibits an arbitrary property in a binary format, and datasets for solving regression tasks were not used. To preprocess the datasets, all samples containing SMILES that could not be converted to fingerprint notation via rdkit were removed. Table 6 shows the types of datasets used and their basic statistics.

These datasets were divided into training, validation, and test data in a ratio of 6:2:2. The divided training data were used to train the proposed methods, and the validation data were used to evaluate the checkpoints with the highest accuracy. All the parameters used for the experiments were the same as those used for molecular captioning.

B.2 Results

As a baseline, we converted the SMILES into molecular fingerprints and performed predictions using linear regression (LR), XGBoost (XGB), support vector machine (SVM) and Neural Network (NN).

We also performed classification tasks via transformer encoder models, such as molbert, MolT5, and nach0. This is inputting SMILES directly as text. Furthermore, we performed classification based on LLMs, and by fine-tuning an LLM to ask for either "Yes" or "No," evaluation on the basis of the probability distributions of "Yes" or "No" outputs is possible.

Owing to the API specifications, we did not conduct experiments using closed-source models because it is difficult to output the probability distributions of words. We verified a multimodal model by encoding with MolT5 and a multimodal model via fingerprints. We used the predictions made via fine-tuned Llama3 as the baseline for the LLM SFT.

Tables 7 shows the ROC-AUC and PR-AUC scores for binary classification for each dataset. The prediction model using MolCLR has not achieved accuracy surpassing that of text-based models. As with molecular captioning, this is likely due to the loss of information, such as the representation of isomers in SMILES notation, when it is converted into a molecular graph.

It can also be seen that transformer encoder-based models, such as MolBERT, MolT5, and nach0 (T5 base), are more accurate than the Llama3-based models, including the multimodal model. This is apparent from the fact that transformer decoder models, such as Llama3, are designed with an emphasis on text generation and are not suitable for classification and that Llama3 cannot properly tokenize molecules expressed in

[3] https://moleculenet.org/

SMILES. By contrast, the Llama3 multimodal model, which uses fingerprints, achieved an accuracy similar to that of the other transformer encoder models. This shows that even without properly tokenizing the SMILES, fingerprints contain sufficient molecular information.

C RAG vs. multimodal model SFT

In a general-purpose LLM approach, SFT often requires repeated training to memorize specific information. In contrast, RAG can predict information that is not present in the training data with few-shot learning by externally inserting knowledge into the prompt. To confirm this in our study, we compared fingerprint-rag (our best performing RAG model) with fingerprint + Llama3 (our best performing fine-tuned multimodal model). Figure 4 plots the frequency of property words within the training data against the accuracy of those words appearing in the generated text. The left side of the figure plots words with a training data frequency below 100, while the right-side plots words with a frequency above 100.

As shown in Figure 4, for properties with a limited number of samples in the training data, multimodal models tend to struggle with accurate predictions, while RAG models show higher accuracy. Therefore, the performance of multimodal models relies on high-frequency properties. For instance, properties with a frequency exceeding 10,000, such as "alcohol," "fatty," and "catalyst," achieved accuracy above 99% across all models that underwent supervised fine-tuning, except for MolT5.

Table 8 gives the macroF1 scores of RAGs and multimodal approach for each categorized property. All model's categorized property specific scores are listed in the Appendix. As indicated in Table 8, the performance categorized by different properties generally favors multimodal models. However, for properties related to "Light and electricity" category, RAG approach exhibit better performance. This can be attributed to the relatively low frequency of properties within the "Light and electricity" category, with the maximum frequency being around 500, suggesting that the supervised fine-tuning of multimodal models was not successful for these properties. The study showed similar trends to those seen in general-purpose LLMs, and it is expected that applying RAG to chemistry-specific LLM that have undergone SFT, can lead to the creation of more robust models, even for properties with insufficient sample data.

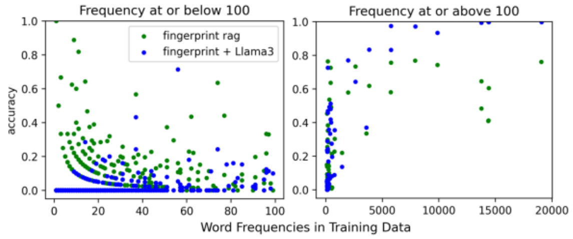


Figure 4: Training data property count and generated text accuracy. Molecular fingerprint is used for both fingerprint-rag and fingerprint + Llama3.

D Output Text

Figure 5 shows the text generated by each molecule captioning method, along with the ground truth. The Gemini SFT and multimodal models exhibited high lexical recall against the ground truth, whereas the fingerprint RAG, which lacks SFT, produced texts with larger word counts and more technical terms. As mentioned in the main text, the RAG performance is attributed to the model itself not having learned vocabulary or phrasing.

	Biomedical	Human Interaction and Organoleptics	Agriculture and Industry	Light and electricity
fingerprint-rag	**0.281**	0.064	0.039	**0.199**
fingerprint + Llama3 (Linear)	**0.281**	**0.073**	**0.064**	0.113

Table 8: Categorized property-specific score (macro-f1) using molecular fingerprints in RAG and multimodal models.

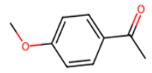
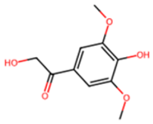
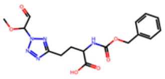
Molecule	Ground Truth	Gemini SFT	Fingerprint-rag	Multimodal Model
 COc1ccc(C(C)=O)cc1	When heated to decomposition it emits acrid smoke and irritating fumes. The molecule has both a Bitter and unpleasant taste and a Pleasant odor.	When heated to decomposition it emits acrid smoke and irritating vapors.	The molecule possesses a pleasant and characteristic aroma, and its structure suggests it may function as a nutrient or energy source.	The molecule is an energy source, energy storage, emulsifier, surfactant, nutrient, membrane stabilizer.
 COc1cc(C(=O)CO)cc(OC)c1O	The molecule is a flavoring agent, savory, meaty, and sulfur.	The molecule is a nutrient.	The molecule is an antioxidant, a nutrient, and potentially functions as an emulsifier, surfactant, and membrane stabilizer.	The molecule is a nutrient.
 COC(C=O)n1nnc(CCC(NC(=O)OCc2ccccc2)C(=O)O)n1	The molecule is an anti-cancer.	The molecule is a cancer treatment.	This is a complex organic molecule containing a tetrazole ring an aldehyde group a carboxylic acid and a benzyloxycarbonyl (Cbz) protected amine. It is a biologically active compound.	The molecule is a anti-inflammatory.

Figure 5: Output caption of models. Molecular fingerprinting is used for multimodal model.