A Survey of Large Language Models for Text-Guided Molecular Discovery: from Molecule Generation to Optimization

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Abstract

Large language models (LLMs) are introducing a paradigm shift in molecular discovery by enabling text-guided interaction with chemical spaces through natural language and symbolic notations, with emerging extensions to incorporate multi-modal inputs. To advance this emerging field, this survey provides an up-to-date and forward-looking review of the emerging use of LLMs for two central tasks: molecule generation and molecule optimization. We organize our survey around four fundamental challenges that have emerged as critical evaluation dimensions in recent studies: ensuring validity, enhancing synthesizability, achieving precise property control, and maximizing diversity. Based on this, we systematically analyze how current LLM learning paradigms are applied to tackle each challenge, revealing the distinct capabilities and inherent limitations of each approach. In addition, we include the commonly used datasets and evaluation protocols aligned with these challenges. We conclude by discussing future directions, positioning this survey as a resource for researchers working at the intersection of LLMs and molecular science. A continuously updated reading list is available at `https://anonymous.4open.science/r/LLM-Centric-Molecular-Discovery`.

1 Introduction

Molecular design and optimization are fundamental to multiple scientific disciplines, including drug discovery (Zheng et al., 2024), materials science (Grandi et al., 2025), and synthetic chemistry (Lu et al., 2024; Wang et al., 2025). However, these tasks present significant challenges due to the vast and complex chemical spaces that must be navigated to discover novel compounds with desirable properties while maintaining chemical validity and structural plausibility (Zheng et al., 2024; Yu et al., 2025). Over the years, a range of computational approaches has been developed to achieve these goals, from Variational Autoencoders (Gómez-Bombarelli et al., 2018) and Generative Adversarial Networks (De Cao and Kipf, 2018) to Transformers (Edwards et al., 2022). Despite significant progress, these methods often struggle with generating high-quality, diverse, and synthesizable molecules (Ramos et al., 2025; Sun et al., 2025).

More recently, large language models (LLMs) have emerged as particularly powerful tools for tackling these challenges, drawing increasing research attention (Zheng et al., 2024). These foundation models, characterized by billions of parameters, exhibit emergent capabilities such as advanced reasoning, instruction following, and in-context learning, enabled by extensive pre-training on diverse datasets (Brown et al., 2020; Wei et al., 2022a). Thus, LLMs can leverage their extensive pre-training knowledge to generalize across chemical problems and can be further adapted to specialized tasks through fine-tuning. These unique capabilities have established LLMs as a powerful new paradigm for exploring chemical space and accelerating molecular discovery.

Despite the growing interest in applying LLMs to molecular discovery tasks, existing literature reviews fail to provide a comprehensive analysis of this specific intersection. Most earlier surveys (Cheng et al., 2021; Zeng et al., 2022; Tang et al., 2024; Yang et al., 2024a) focus broadly on general deep generative AI approaches rather than specifically examining LLMs' unique contributions. Other reviews that do mention LLMs (Ramos et al., 2025; Zhang et al., 2025; Guo et al., 2025; AbuNasser, 2024; Janakarajan et al., 2024; Liao et al., 2024) either primarily focus on the general chemical domain or include smaller language models ($<$ 1B parameters) that lack the emergent capabilities of the LLMs central to this survey.

Our survey addresses this critical gap by providing the first overview specifically focused on LLMs in molecular discovery, with particular emphasis on two central tasks: **molecule generation** and **molecule optimization**. We focus on foundation-scale models (>1B parameters) and adopt a multi-dimensional assessment framework based on recent benchmarking studies (Brown et al., 2019; Polykovskiy et al., 2020; Thomas et al., 2024). We organize our survey around four fundamental challenges: **validity** (whether molecules are chemically feasible), **synthesizability** (whether they can be practically synthesized), **property control** (whether they meet desired objectives), and **diversity** (whether they explore chemical space broadly). Unlike prior surveys that categorize studies based on model architectures (AbuNasser, 2024; Janakarajan et al., 2024), we introduce a taxonomy centered on learning paradigms—distinguishing between approaches *without LLM tuning* (Zero-Shot Prompting and In-Context Learning) and those *with LLM tuning* (Supervised Fine-Tuning and Preference Tuning), as illustrated in Fig. 1. To summarize, our main contributions are as follows:

- We introduce a new taxonomy based on learning paradigms, revealing how different approaches address the four fundamental chemical challenges and their respective limitations.
- We provide a systematic summary of commonly used datasets, benchmarks, and evaluation metrics, offering a comprehensive reference for researchers in the field.
- We identify critical challenges and outline promising future research directions to further advance this rapidly evolving domain of LLM-centric molecular discovery.

2 Preliminaries

2.1 Large Language Models

LLMs distinguish themselves from earlier Pre-trained Language Models (PLMs) like BERT (Devlin et al., 2019) primarily through their massive scale—billions versus millions of parameters—and the resultant emergent capabilities (Zhao et al., 2023; Yang et al., 2023). Pre-trained on vast text corpora using autoregressive objectives, LLMs exhibit capabilities such as in-context learning (Brown et al., 2020), chain-of-thought reasoning (Wei et al., 2022b), and powerful zero-shot generalization that are not consistently observed in smaller models (Wei et al., 2022a). These emergent capabilities make LLMs uniquely suited for complex chemical applications like molecule generation and optimization tasks central to this survey.

2.2 Problem Definition and Scope

This survey focuses on LLM-centric approaches to molecular discovery, with two key inclusion criteria: (1) models must have at least **1B parameters** to ensure emergent capabilities, and (2) LLMs must serve as **molecular generators** rather than auxiliary components like feature extraction (Liu et al., 2023) or control (Liu et al., 2024a). Under this scope, we examine two central tasks:

Problem Definition 1 (LLM-centric Molecule Generation). *This task leverages LLMs for the de novo design of novel molecular structures based on specified input instructions.*

Problem Definition 2 (LLM-centric Molecule Optimization). *This task leverages LLMs to modify or edit a given input molecule, aiming to enhance one or more of its properties while often preserving essential structural characteristics.*

As illustrated in Fig. 2, for both tasks, the input prompt provided to the LLM typically comprises three key components: (1) **Instruction** ($\mathcal{I}$): A textual component that defines the primary guidance and objectives of the task. (2) **Few-Shot Examples** (E_{fs}) (Optional): A small set of input-output examples relevant to the task, provided to facilitate in-context learning. (3) **Property Constraints** ($\mathcal{C}_p$) (Optional): Explicit desired values, ranges, or thresholds for specific molecular properties.

2.3 Challenges in Molecular Discovery

Based on recent research studies and established evaluation practices (Brown et al., 2019; Polykovskiy et al., 2020; Thomas et al., 2024), we identify four fundamental challenges that comprehensively capture the unique requirements of molecular discovery. These challenges form a multi-dimensional framework for evaluating LLM-based approaches, as they collectively represent the critical aspects that distinguish chemical generation from general text generation:

- **Validity:** Generated molecules must adhere to fundamental chemical rules (e.g., valency) to be structurally meaningful. Unlike grammatically incorrect sentences, an invalid molecule is physically impossible and unusable (Jin et al., 2018).

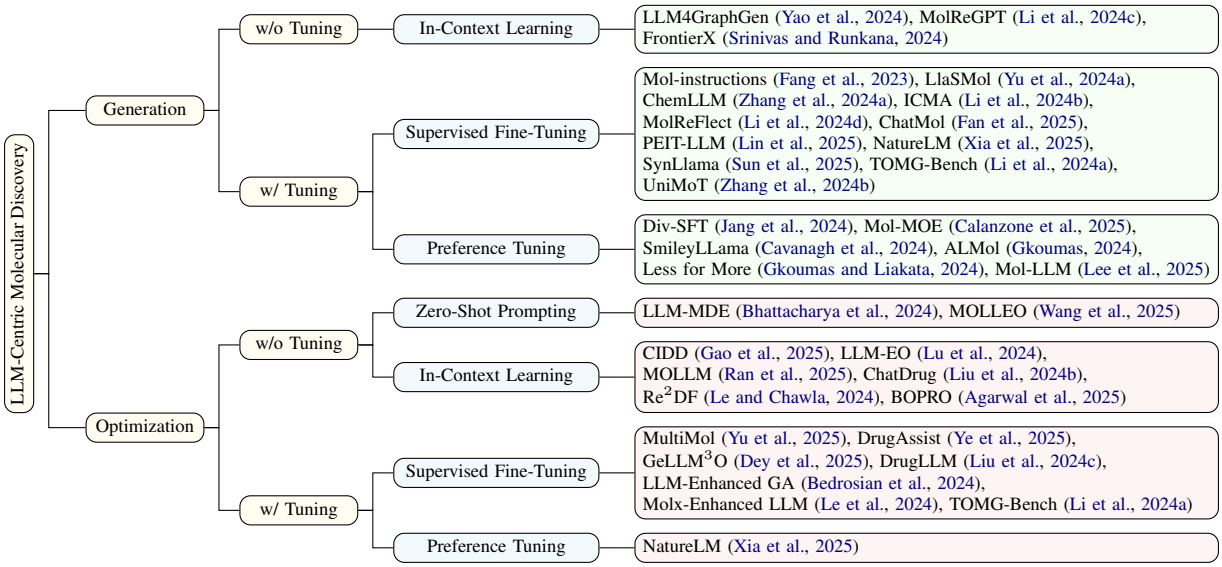

Figure 1: A Taxonomy of LLM-Centric Molecular Discovery.

- **Synthesizability:** A valid molecule must also be practically synthesizable. This requires considering the feasibility and complexity, as a theoretically valid structure may be impossible to create in a lab (Gao and Coley, 2020).
- **Property Control:** The design process must precisely steer molecules toward desired properties, often requiring the simultaneous optimization of multiple, competing objectives (You et al., 2018).
- **Diversity:** To effectively explore the vast chemical space, generated molecules must be structurally diverse, avoiding minor variations of known compounds (Zhavoronkov et al., 2019).

These challenges are interconnected and often conflicting (Gao and Coley, 2020), forming a comprehensive evaluation framework that tests multiple dimensions of LLMs' capabilities in molecular discovery. Throughout this survey, we systematically analyze how different learning paradigms address these competing objectives, revealing their respective strengths and limitations in tackling the full spectrum of molecular design requirements.

2.4 Learning Paradigms

The application of LLMs to molecular discovery tasks, as depicted in the taxonomy in Fig. 2, can be broadly categorized based on whether the model's parameters are updated for the specific task. This distinction defines two primary learning paradigms:

Without LLM Tuning: These methods utilize pre-trained LLMs directly, guiding their behavior solely through the input prompt $\mathcal{I}$ without modifying the model's weights. This paradigm primarily encompasses strategies like *Zero-Shot Prompting*, where the LLM operates based on instructions alone, and *In-Context Learning (ICL)*, where few-shot examples provided within the prompt guide the model's responses. These approaches avoid computational training but rely heavily on the LLM's inherent capabilities and effective prompt engineering.

With LLM Tuning: These methods involve adapting the pre-trained LLM by further training and updating its parameters to specialize it for molecular tasks or align its outputs with desired objectives. This typically includes *Supervised Fine-Tuning (SFT)*, where the model learns from labeled task-specific datasets, and subsequent *Preference Tuning* (or Alignment), where the model is refined based on feedback. While tuning can significantly enhance performance, it requires curated data and computational resources.

3 Molecule Generation

Molecule generation, the computational creation of novel molecular structures, is a cornerstone of modern drug discovery and materials science (Elton et al., 2019). This section reviews recent advances in LLM-centric molecule generation, analyzing how different learning paradigms address the four fundamental challenges while creating molecules from scratch.

3.1 Molecule Generation without Tuning

3.1.1 In-Context Learning

Property Control: Since *Zero-Shot Prompting* is challenging for general-purpose LLMs due to their lack of specialized chemical knowledge, most

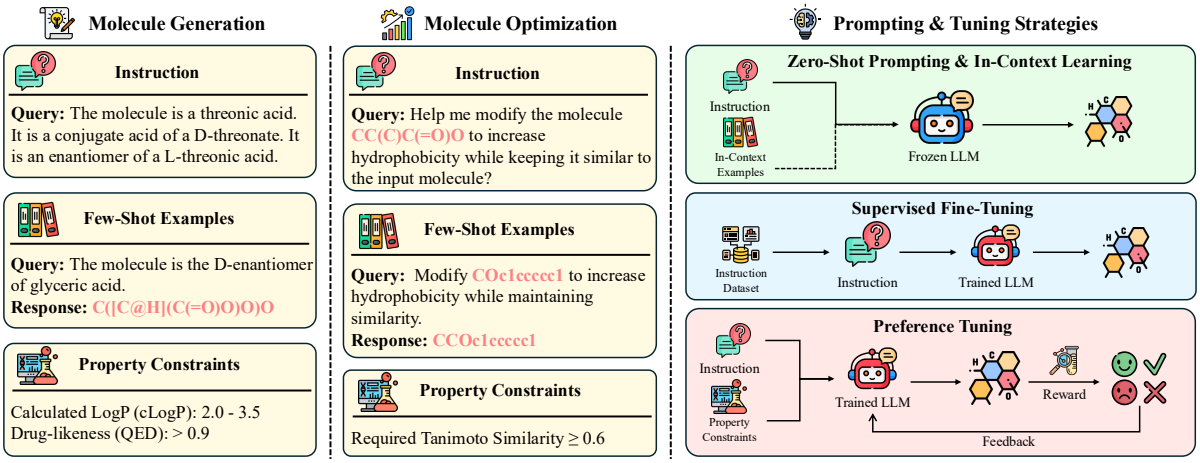

Figure 2: **Overview of LLM-Centric Molecular Discovery.** ***Left:*** Typical input components (Instruction, Few-Shot Examples, Property Constraints) for molecule generation and optimization. ***Right:*** Core learning paradigms for applying LLMs to *Zero-Shot Prompting & In-Context Learning*, *Supervised Fine-Tuning* and *Preference Tuning*.

successful applications in this paradigm rely on In-Context Learning (ICL). This approach primarily addresses the challenge of Property Control by providing high-quality examples to guide generation. For instance, FrontierX (Srinivas and Runkana, 2024) uses knowledge-augmented prompts for text-to-SMILES translation, LLM4GraphGen (Yao et al., 2024) employs text-to-graph generation with intermediate representations, and MolReGPT (Li et al., 2024c) retrieves molecule-caption pairs to create more effective contexts.

In summary, ICL excels at providing guidance for property control. However, it struggles with validity, synthesizability, and diversity—limitations stemming from its reliance on pattern matching rather than learning chemical principles.

3.2 Molecule Generation with Tuning

3.2.1 Supervised Fine-Tuning

While non-tuning methods leverage pre-trained knowledge, their capabilities are often limited for specialized generation tasks. SFT addresses this by adapting a pre-trained LLM on labeled datasets, typically pairs of textual instructions and target molecular representations. This approach moves beyond the capabilities of smaller models like MolGPT (Bagal et al., 2021) and MolT5 (Edwards et al., 2022) by harnessing the power of large foundation models.

Validity: SFT is the primary paradigm for instilling foundational chemical knowledge into LLMs, making it highly effective for ensuring validity. By fine-tuning on millions of valid molecular structures, the LLM learns the complex "grammar" of chemical representations like SMILES. This foundational training is the focus of several large-scale instruction-tuning efforts, such as *LlaSMol* (Yu et al., 2024a) with its SMolInstruct dataset, *ChemLLM* (Zhang et al., 2024a) with ChemData, Mol-Instructions (Fang et al., 2023), and the OpenMolIns dataset from *TOMG-Bench* (Li et al., 2024a). To further improve structural understanding, multi-modal SFT approaches like *UniMoT* (Zhang et al., 2024b) incorporate 2D graph information directly into the training process by converting molecular graphs into discrete "molecule tokens," enhancing the model's ability to generate valid and complex molecules.

Property Control: SFT enables LLMs to learn the intricate mapping between desired properties and molecular structures. This is where instruction tuning truly shines. For instance, *ChatMol* (Fan et al., 2025) directly tackles the need for precise numerical control by introducing a numerical enhancement technique that converts property values into dedicated embeddings to improve the model's fidelity to specific quantitative property values. Addressing the need for multi-property optimization, *PEIT-LLM* (Lin et al., 2025) proposes a two-step framework to fine-tune LLMs for multi-constraint generation. To improve the quality of guidance during training, other innovative strategies integrate retrieval directly into the fine-tuning process. *ICMA* (Li et al., 2024b) and *MolReFlect* (Li et al., 2024d), for example, propose In-Context Molecule Tuning (ICMT), which fine-tunes the LLM using relevant retrieved examples to better align outputs with complex instructions.

Synthesizability: SFT is beginning to address synthesizability. *SynLlama* (Sun et al., 2025) was

developed to specifically tackle synthetic feasibility by fine-tuning the model to generate not just molecules, but also complete synthetic pathways.

In summary, SFT excels at validity through extensive training on chemical structures, provides strong property control via instruction tuning, and shows emerging capabilities in synthesizability assessment. However, its reliance on training data distributions limits diversity, often causing mode collapse where models generate variations of known scaffolds.

3.2.2 Preference Tuning

Following SFT, which teaches models to mimic static datasets, Preference Tuning techniques offer further refinement by employing feedback-driven learning to shape LLM outputs towards desired characteristics. This is achieved either through RL-based methods (Sutton et al., 1998) that optimize a policy against a reward signal, or offline methods like Direct Preference Optimization (DPO) that learn from "chosen" vs. "rejected" pairs.

Diversity: Preference Tuning directly addresses the primary limitation of SFT by excelling at enhancing diversity. By explicitly rewarding novel and varied molecular structures, it encourages exploration of underrepresented chemical spaces. *Div-SFT* (Jang et al., 2024), for example, employs RL with a reward function specifically designed to maximize structural diversity, effectively mitigating SFT's tendency toward mode collapse.

Property Control: Preference-based methods also significantly improve multi-property optimization. *SmileyLlama* (Cavanagh et al., 2024) utilizes DPO to improve adherence to property constraints by learning from preferences between correct and incorrect molecules. *Mol-MoE* (Calanzone et al., 2025) uses a preference objective to train a Mixture-of-Experts router, enabling specialization for different property requirements. (Gkoumas, 2024; Gkoumas and Liakata, 2024) refine molecule quality using Contrastive Preference Optimization (CPO).

Validity: Beyond text-based approaches, preference tuning can enhance validity by improving how models utilize structural information. *Mol-LLM* (Lee et al., 2025) addresses the "graph bypass phenomenon" where models ignore 2D structural inputs. Through Molecular Structure Preference Optimization (MolPO), it trains the model to distinguish between correct and perturbed molecular graphs, forcing deeper engagement with structural information and thereby improving the validity.

In summary, Preference Tuning excels at diversity by explicitly rewarding novelty, provides refined multi-property control through comparative learning, and can enhance validity in multi-modal settings. However, it offers no direct improvement to synthesizability and requires substantial effort to obtain high-quality preference data or design appropriate reward functions.

4 Molecule Optimization

Molecule optimization is the task of refining molecular structures to improve one or more desired properties, such as solubility, binding affinity, or synthetic accessibility. Unlike molecule generation, optimization starts with an initial molecule and proposes targeted structural modifications to achieve specific goals. This section summarizes LLM-centric molecule optimization methods, analyzing how different learning paradigms address the four fundamental challenges in this more constrained but equally important task.

4.1 Molecule Optimization without Tuning

4.1.1 Zero-Shot Prompting

Property Control: Zero-Shot Prompting leverages the pre-trained knowledge of LLMs to perform edits based on natural language instructions alone. This paradigm enables flexible property modification through natural language specifications. For example, *LLM-MDE* (Bhattacharya et al., 2024) uses detailed prompts to specify desired property changes and structural constraints, enabling controlled modifications. *MOLLEO* (Wang et al., 2025) integrates LLMs into evolutionary frameworks, using prompt-based sampling to perform mutations and crossovers.

In summary, zero-shot prompting excels at expressing diverse optimization goals flexibly, but its reliance on general pre-trained knowledge results in limited precision for property control and poor performance on validity and synthesizability.

4.1.2 In-Context Learning

Property Control: ICL enhances property control by providing examples of successful molecular edits within the prompt. This allows the LLM to learn optimization patterns from context. *CIDD* (Gao et al., 2025) implements a multi-step pipeline of

interaction analysis, design, and reflection, feeding previous designs back into the context. *LLM-EO* (Lu et al., 2024) and *MOLLM* (Ran et al., 2025) integrate LLMs into evolutionary algorithms, where historical data from previous generations serves as in-context examples. *BOPRO* (Agarwal et al., 2025) combines ICL with Bayesian optimization for more sophisticated example selection.

Validity: To improve validity, retrieval-augmented methods enhance example quality. *ChatDrug* (Liu et al., 2024b) retrieves structurally similar molecules to inform proposals, while *Re^{2}DF* (Le and Chawla, 2024) incorporates validity feedback from RDKit (Landrum et al., 2013) directly into the prompt to guide the model toward valid outputs.

In summary, ICL offers more guided and iterative control than zero-shot methods through example-based learning, improving both property control and validity. However, its effectiveness depends heavily on example quality, and it still provides limited solutions for ensuring synthesizability or enhancing diversity.

4.2 Molecule Optimization with Tuning

4.2.1 Supervised Fine-Tuning

SFT adapts pre-trained LLMs for molecule optimization by training them on curated datasets of input molecules paired with their corresponding optimized outputs. This supervision allows the model to learn how to perform controlled structural edits based on specific objectives.

Property Control: While smaller Transformer-based chemical language models have shown potential for optimization tasks (Ross et al., 2022, 2024; Wu et al., 2024b; Dai et al., 2025; Liu et al., 2025b), foundation-scale LLMs enable more advanced capabilities through SFT. By training on instruction datasets, models learn precise single- and multi-property optimization. *DrugAssist* (Ye et al., 2025) fine-tunes LLaMA-2-7B-Chat on the MolOpt-Instructions dataset for single/dual-property tasks. *GeLLM^{3}O* (Dey et al., 2025) extends this to multi-property optimization with strong out-of-distribution generalization. *Multi-Mol* (Yu et al., 2025) employs a collaborative framework where a fine-tuned worker generates candidates and a research agent (GPT-4o) ranks them using literature-derived knowledge. *DrugLLM* (Liu et al., 2024c) introduces group-based molecular representation (GMR) to better align structure and semantics for controlled modifications.

Diversity: SFT enables population-based optimization that balances property improvement with diversity. *LLM-Enhanced GA* (Bedrosian et al., 2024) replaces traditional genetic operators with prompt-based sampling from high-performing molecules, incorporating explicit oracle modeling through SFT when performance stagnates to progressively refine understanding of the property landscape.

Validity: Multi-modal SFT approaches enhance validity by incorporating richer structural information (Zhang et al., 2024c; Lin et al., 2024; Nakamura et al., 2025). *Molx-Enhanced LLM* (Le et al., 2024) integrates SMILES, 2D graphs, and fingerprints into a unified embedding. Through fine-tuning the multi-modal MolX module, the model captures both global topology and local substructures essential for chemically valid modifications.

In summary, SFT excels at precise property control through explicit instruction-based training and shows promise for diversity in population-based frameworks. Multi-modal SFT further enhances validity by leveraging structural information. However, its effectiveness remains tied to training data quality, with limited inherent capabilities for assessing synthesizability.

4.2.2 Preference Tuning

Preference Tuning refines tuned LLMs by aligning them with task-specific goals or preferences (Park et al., 2025; Chen et al., 2025). While RL-based alignment techniques built on smaller Transformer architectures have shown promise (Liu et al., 2025a,c), the application of offline preference methods to large foundation models has enabled more scalable optimization.

Property Control: Preference tuning excels at multi-property optimization through comparative learning. *NatureLM* (Xia et al., 2025) exemplifies this approach by augmenting its post-trained 8B model using Direct Preference Optimization (DPO). Instead of training on absolute labels or scalar rewards, the model learns from 179.5k prompt-response pairs, where each instance contains a "preferred" and "rejected" molecular output for the same optimization goal. By learning from these comparative preferences, NatureLM demonstrates improved alignment across nine pharmacologically relevant properties, showcasing DPO's ability to generalize preference-guided optimiza-

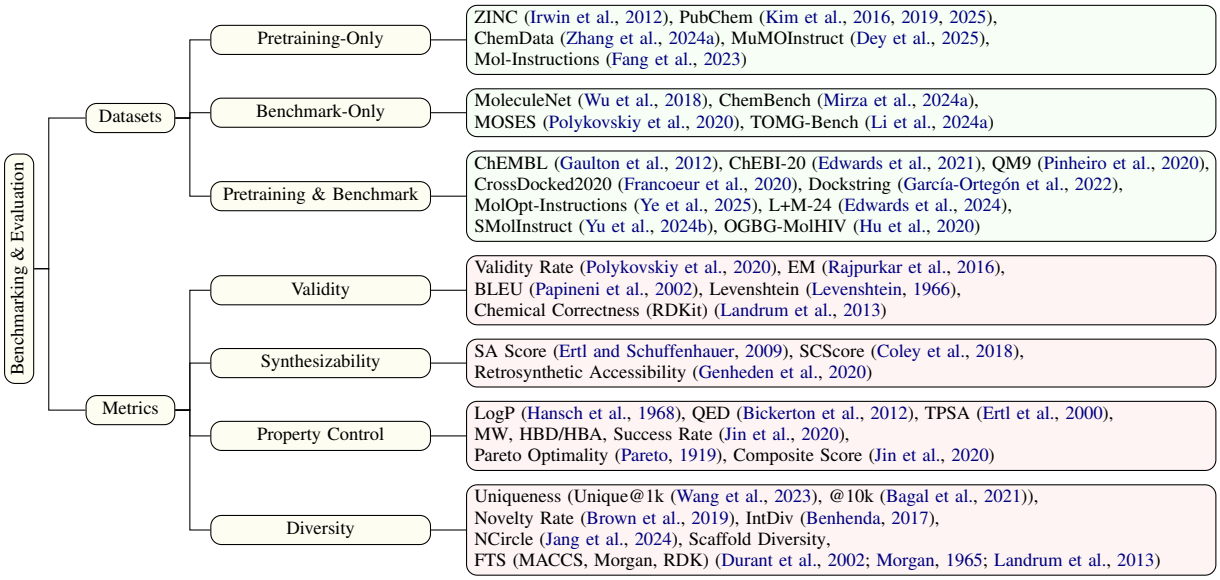

Figure 3: A Taxonomy of Benchmarking & Evaluation in Molecule Discovery.

tion across diverse chemical objectives.

In summary, Preference Tuning, particularly through DPO, provides a powerful and scalable solution for multi-objective property control in optimization tasks. However, it requires significant effort to curate high-quality preference datasets, and its application to other chemical challenges (validity, synthesizability, diversity) remains limited in the optimization domain.

5 Benchmarking and Evaluation

Rigorous benchmarking and comprehensive evaluation are crucial for tracking the progress of LLM-centric molecular discovery. This section provides an overview of the evaluation ecosystem, organized around our four fundamental challenges, with comprehensive details available in the appendices.

5.1 Datasets

Molecular datasets serve distinct purposes in LLM development, ranging from large-scale pretraining to targeted evaluation. **Pretraining-Only Datasets** like ZINC (Irwin et al., 2012) provide vast chemical structures, while instruction collections like ChemData (Zhang et al., 2024a) offer domain-specific knowledge for teaching chemical reasoning. **Benchmark-Only Datasets** include TOMG-Bench (Li et al., 2024a) for text-guided generation and MOSES (Polykovskiy et al., 2020) for distribution learning. **Dual-Purpose Datasets** such as ChEMBL (Gaulton et al., 2012) support both training and evaluation, enabling consistent benchmarking across different stages of model development. See Appendix D for detailed comparisons

5.2 Metrics

Evaluation metrics directly address our four fundamental challenges. **Validity Metrics** include SMILES parsing, uniqueness rates (Unique@1k, Unique@10k), and chemical correctness checks. **Synthesizability Metrics** employ SA Score (Ertl and Schuffenhauer, 2009) and SCScore (Coley et al., 2018) for complexity prediction. **Property Control Metrics** span single-property evaluations (QED (Bickerton et al., 2012), LogP (Hansch et al., 1968), TPSA (Ertl et al., 2000)) and multi-property optimization via success rates and Pareto optimality. **Diversity Metrics** assess chemical space exploration through novelty rate, internal diversity (IntDiv) (Benhenda, 2017), and scaffold analysis. Mathematical definitions and implementation details are provided in Appendix E.

5.3 External Tools

Evaluation requires diverse computational tools that bridge chemistry and machine learning. General cheminformatics relies on RDKit (Landrum et al., 2013) for property calculation and validation, OpenBabel (O'Boyle et al., 2011) for format conversion, and CDK (Willighagen et al., 2017) for Java environments. Synthesizability assessment employs AiZynthFinder (Genheden et al., 2020) and ASKCOS (Coley et al., 2019) for retrosynthetic planning. LLM-specific tools like ChemCrow (M. Bran et al., 2024) integrate language models with chemistry tools. Detailed usage guidelines are in Appendix F.

5.4 Evaluation Frameworks

Standardized frameworks have evolved from classic to LLM-specific approaches. GuacaMol (Brown et al., 2019) pioneered dual evaluation via distribution learning and goal-directed tasks, while MOSES (Polykovskiy et al., 2020) focused on comprehensive distribution metrics. Recent frameworks address modern needs: MolScore (Thomas et al., 2024) unifies previous benchmarks with modular scoring, TDC (Huang et al., 2021) provides continuously updated leaderboards, and LLM-specific benchmarks like TOMG-Bench (Li et al., 2024a) evaluate instruction-following capabilities. However, all frameworks rely on computational validation without experimental verification—a critical limitation discussed in Appendix G.

6 Conclusion and Future Work

This survey presents the first comprehensive review of recent advances in LLM-centric molecular discovery, covering both generation and optimization tasks. We introduced a novel taxonomy that categorizes approaches based on their learning paradigms—distinguishing between methods without LLM tuning (zero-shot prompting and in-context learning) and those with LLM tuning (supervised fine-tuning and preference tuning). Through systematic analysis of how these approaches address four fundamental challenges—validity, synthesizability, property control, and diversity—we uncovered key patterns in the current landscape.

Key Insights: Our analysis reveals that no single approach dominates across all challenges, with each exhibiting distinct trade-offs. Zero-Shot prompting offers unmatched flexibility for diverse tasks but struggles with chemical validity and precise property control. ICL improves guidance through carefully selected examples but remains fundamentally limited by example quality and lacks a systematic understanding of chemical principles. SFT excels at ensuring validity through large-scale chemical training and enables precise property control via instruction tuning, yet often suffers from limited diversity due to mode collapse. Preference tuning emerges as the primary solution for diversity through reward-based exploration while maintaining multi-property optimization capabilities. However, across all methods, synthesizability remains the most poorly addressed challenge—current approaches generate molecules that are computationally valid but often practically impossible to synthesize, representing a critical bottleneck for real-world deployment.

Based on these insights and current limitations, we identify three priority areas for advancing the field:

Prioritizing Synthesizability in Generation: As illustrated in recent analyses (Walters, 2024), current LLMs frequently produce molecules through string manipulation rather than chemical understanding, resulting in theoretically valid but synthetically inaccessible structures. Future work must move beyond post-hoc SA Score filtering to incorporate synthesizability as a primary constraint during generation. This includes: (i) training on datasets of successfully synthesized molecules; (ii) integrating retrosynthetic planning directly into the generation process; (iii) developing reward functions that explicitly penalize synthetic complexity during preference tuning.

Multi-Modal Molecular Understanding: Current LLM approaches predominantly operate on SMILES strings, missing crucial structural information. Future architectures should jointly encode and reason over multiple representations—SMILES strings, 2D molecular graphs, 3D conformations, and quantum chemical properties (Lu et al., 2023; Pirnay et al., 2025). This requires developing unified tokenization schemes that preserve chemical semantics across modalities while enabling efficient transformer processing.

Unified Benchmarks for LLM-Based Molecular Design: Current frameworks like MOSES and GuacaMol were designed for traditional generative models and lack standardization for LLM evaluation. We urgently need a unified benchmark with: (i) standardized train/validation/test splits specifically curated for LLMs, preventing data leakage and ensuring fair comparison across models; (ii) comprehensive evaluation metrics that go beyond traditional measures to include LLM-specific capabilities such as instruction-following accuracy, multi-step reasoning ability, and robustness to representation variations (SMILES, IUPAC, natural language); (iii) a continuously updated leaderboard tracking progress in LLM-based molecular design. Such a unified benchmark would provide the community with a clear view of where we stand and where we need to improve in applying LLMs to molecular discovery.

7 Limitations

This survey deliberately focuses on large language models (>1B parameters) serving as direct molecular generators and optimizers. This narrow scope excludes other important LLM applications in molecular science, including systems where LLMs orchestrate external tools (e.g., retrosynthesis planning, laboratory automation), applications focused on scientific reasoning rather than structure generation (e.g., hypothesis discovery, literature mining), and traditional graph-based generative models or specialized chemical language models below the 1B parameter threshold. This focused scope is necessary for coherent analysis. Our "learning paradigms × four challenges" framework systematically evaluates how training strategies affect molecular generation quality, which requires the LLM to directly produce molecular outputs. As discussed in Appendix A, excluded applications employ LLMs in fundamentally different ways incompatible with our analytical framework. While this limits comprehensive coverage of all LLM applications in chemistry, it enables the deep technical analysis that broader surveys cannot achieve.

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A Scope Definition and Broader Context

The scope of this survey is deliberately focused on methods where Large Language Models (LLMs, with >1B parameters) function as direct **molecular generators and optimizers**. This specific focus is grounded in both the empirical reality of the field and methodological coherence for deep analysis.

A.1 Rationale for Our Focused Scope

Our concentration on generation and optimization tasks is motivated by two fundamental considerations:

1. **Alignment with LLMs' Emergent Capabilities:** LLMs with over 1 billion parameters exhibit unique emergent abilities—in-context learning, instruction following, and compositional reasoning—that are naturally suited for generative tasks. Our systematic review reveals that the vast majority of LLM-based molecular papers concentrate precisely on generation and optimization because these tasks directly leverage what LLMs do best: generate and refine text-based molecular representations. Importantly, generation and optimization are fundamentally similar tasks that both employ LLMs as generators—the primary distinction being whether an initial molecular structure is provided.

2. **Methodological Coherence:** Our central analytical framework—the "learning paradigms × four challenges" taxonomy—systematically evaluates how different training strategies (Zero-Shot Prompting, In-Context Learning, Supervised Fine-Tuning, Preference Tuning) address fundamental molecular design challenges (Validity, Synthesizability, Property Control, Diversity). This analysis is most meaningful when the LLM directly produces the molecular output, allowing us to attribute successes and failures to specific learning paradigm choices. This focused scope enables deep technical analysis within a unified framework, rather than superficial coverage across disparate applications.

A.2 Broader Landscape of LLM Applications in Chemistry

While our survey focuses on LLMs as direct molecular generators, it is important to contextualize this work within the broader landscape of LLM applications in molecular and chemical sciences. We briefly acknowledge two major complementary research directions that, while impactful, utilize LLMs in fundamentally different roles incompatible with our analytical framework:

1. **LLMs as Orchestrators Rather Than Generators:** A significant body of work employs LLMs as intelligent controllers that coordinate specialized external tools rather than directly generating molecular structures. Examples include:

   - Retrosynthesis planning systems like Llamole (Liu et al., 2024a), where LLMs guide search algorithms by coordinating reaction predictors and constraint checkers;
   - Laboratory automation platforms such as ChemCrow (M. Bran et al., 2024), where LLMs orchestrate specialized tools including RDKit, reaction databases, and robotic synthesis platforms;

   In these frameworks, molecular generation or transformation is performed by external specialized models, with the LLM providing high-level planning and tool coordination. Their success cannot be analyzed through our learning paradigm taxonomy (SFT, preference tuning), as the LLM does not directly produce molecular structures.

2. **LLMs for Scientific Discovery Beyond Molecular Generation:** Another research direction employs LLMs for high-level reasoning and knowledge discovery tasks rather than concrete molecular design:

   - Hypothesis generation frameworks like MOOSE-Chem (Yang et al., 2024b, 2025) and ChemReasoner (Sprueill et al., 2024), using LLMs to discover chemistry hypotheses by searching conceptual spaces;

   These methods leverage LLMs' reasoning and natural language understanding capabilities but produce textual hypotheses, research plans, or structured knowledge—not molecular representations (SMILES, graphs).

By maintaining our focused scope on LLMs as direct molecular generators, this survey provides coherent, systematic analysis of how LLMs perform as a new class of generative models for molecular design. Our "learning paradigms × four challenges" framework reveals actionable patterns (e.g., SFT

excels at validity but limits diversity; Preference Tuning enhances exploration) that would be obscured in surveys mixing fundamentally different LLM usage paradigms. This deep technical analysis guides researchers developing the next generation of LLM-based molecular design systems, while acknowledging the valuable complementary roles LLMs play across the broader chemical sciences

B LLMs versus Traditional Generative Models

To contextualize LLM-based approaches, we provide a high-level comparison with traditional generative models—graph neural networks (GNNs), variational autoencoders (VAEs), normalizing flows, and diffusion models—highlighting fundamental architectural differences and their implications.

B.1 Key Architectural Distinctions and Trade-offs

Representation and Inductive Biases. Traditional graph-based methods (JT-VAE (Jin et al., 2018), MoFlow (Zang and Wang, 2020), DiGress (Vignac et al., 2022)) explicitly model molecular topology with nodes (atoms) and edges (bonds), enabling direct encoding of chemical constraints (valency rules, 3D geometry) and hierarchical generation through chemically meaningful substructures. This native graph representation achieves near-perfect structural validity by construction but limits flexibility—novel molecular motifs outside training distribution are difficult to generate.

In contrast, LLMs treat molecules as sequential text (SMILES), leveraging pre-trained language understanding but losing native graph structure. Chemical validity must be learned from data rather than architecturally enforced, leading to higher error rates without fine-tuning.

Learning Paradigms and Generalization. The most distinctive advantage of LLMs is their diverse learning modalities. Traditional methods require substantial task-specific training—graph diffusion models need thousands to millions of molecules for distribution learning, though specialized techniques offer exceptions (REINVENT's transfer learning (Loeffler et al., 2024)).

LLMs uniquely offer: (1) *zero-shot and few-shot learning* through in-context learning, enabling novel tasks without retraining; (2) *natural language control* for intuitive specifications ("generate antibiotics with low toxicity"); (3) *instruction following* for flexible task adaptation. These capabilities are architecturally impossible for traditional models, representing a qualitative rather than merely quantitative difference. The trade-off: LLMs require more parameters (>1B vs. typically <100M) and computational resources.

Interpretability and Chemical Intuition. Traditional methods often embed chemical knowledge architecturally—JT-VAE's latent space corresponds to substructure combinations enabling interpretable scaffold-based design; autoregressive graph models expose sequential generation decisions. LLMs operate as black boxes where understanding *why* certain molecules are generated is challenging, though chain-of-thought prompting can provide textual reasoning. Attention visualization offers limited chemical insight compared to graph methods' mechanistic transparency.

Performance Landscape. Benchmarking studies (Brown et al., 2019; Polykovskiy et al., 2020; Weng et al., 2024) reveal nuanced patterns. Graph methods excel at distribution learning and validity by construction, while LLMs (with fine-tuning) achieve comparable validity but show advantages in diversity and exploration. Critically, RediscMol (Weng et al., 2024) found high benchmark performance doesn't guarantee biological relevance—simple models often outperform complex architectures on generating active molecules. Both paradigms struggle with synthesizability, suggesting this challenge transcends architectural choices.

B.2 Practical Guidance

When to use LLMs: Natural language control desired; zero/few-shot generalization needed; integration with text-based workflows (literature mining, planning); exploratory generation prioritized.

When to use traditional methods: Structural validity must be guaranteed; 3D geometry essential (structure-based design); limited computational resources; narrow, well-defined optimization with established datasets.

Emerging direction: Hybrid approaches combining LLM planning with graph-based structural generation (e.g., Llamole (Liu et al., 2024a)) leverage complementary strengths, representing a promising frontier as the field matures.

The key insight: LLMs introduce qualitatively different capabilities (language interfaces, zero-shot adaptation) rather than universal performance improvements. Our survey's detailed learning paradigm analysis reveals how to harness these capabilities while navigating persistent challenges shared across all architectures.

C Data Modalities for Molecular LLMs

LLMs used for molecular generation and optimization interface with structured molecular data in various modalities. Each modality offers distinct structural or physicochemical information, with different implications for model performance and capabilities. As shown in Fig. 4, commonly used molecular representations can be categorized into the following three formats:

- **1D Sequence Representations** (S): These are linear string encodings of molecular structures. Common formats include:
  - *SMILES* (Simplified Molecular Input Line Entry System) (Weininger, 1988): Most widely used due to direct compatibility with LLM tokenizers, but sensitive to representation choices (canonical vs. randomized)
  - *SELFIES* (Self-Referencing Embedded Strings) (Krenn et al., 2020): Guarantees validity through constrained grammar but at the cost of longer sequences
  - *IUPAC nomenclature* (Favre and Powell, 2014): Systematic chemical names used as auxiliary representations

  Advantages: Direct LLM compatibility, compact representation, human-readable
  Limitations: Loss of spatial information, multiple valid representations for same molecule, difficulty capturing stereochemistry

- **2D Graph Representations** (G): A molecule is represented as a graph $G = (V, E)$, where nodes $v \in V$ correspond to atoms and edges $e \in E$ correspond to chemical bonds. Node and edge features encode atom types, bond orders, aromaticity, and other topological attributes.
  - Integration approaches include: hybrid LLM-GNN architectures (e.g., UniMoT (Zhang et al., 2024b)), graph serialization methods, and cross-attention mechanisms (e.g., MvMRL)
  - Recent work shows significant improvement in molecular discovery when combining graphs with SMILES (Zhang et al., 2024b)

  Advantages: Captures topological connectivity, invariant to atom ordering, explicit bond information
  Limitations: Requires specialized architectures, computational overhead, potential "graph bypass phenomenon" where LLMs ignore structural information (Lee et al., 2025)

- **3D Geometric Representations** (X): These representations capture atomic coordinates in three-dimensional space. Formally, $X = \{(a_i, \vec{r}_i)\}_{i=1}^{N}$, where a_i denotes the atomic species and $\vec{r}_i \in \mathbb{R}^3$ specifies the Cartesian coordinates of atom i.
  - Critical for: stereochemistry determination, conformational analysis, binding affinity prediction
  - Integration methods: learned 3D embeddings, auxiliary conformer generation models (e.g., RDKit), geometric deep learning approaches

  Advantages: Captures spatial relationships, essential for stereochemistry, enables interaction modeling
  Limitations: High computational cost, multiple conformers per molecule, challenging to tokenize for LLMs

D Datasets

Datasets are crucial resources for advancing LLM-centric molecule design, serving extensively in both the training and evaluation phases of model development. Table 1 provides a comprehensive summary of commonly utilized molecule datasets, detailing their key features. For each dataset listed, the table specifies its **Last Update** year, approximate **Scale** (number of entries), whether it includes natural language **Instruction** components, and its suitability for **Pretraining** LLMs or as a **Benchmark** for evaluation. Furthermore, the table indicates the types of **Molecule Representations** available within each dataset, such as SMILES, IUPAC names, ready-to-dock formats (**Dock**), graph structures (**Graph**), 3D coordinates (**3D**), or formal chemical ontologies (**Ontology**). Finally, it highlights whether a dataset supports **Generation** or **Optimization** tasks, lists **Other Tasks** it is commonly used for (e.g., property prediction, transla-

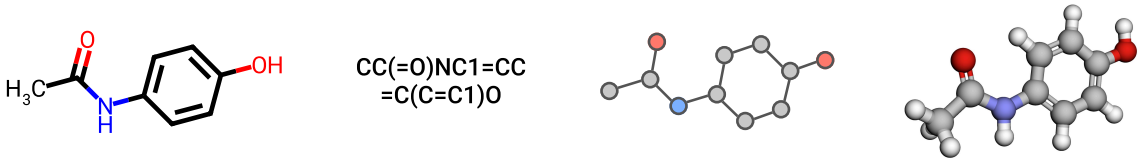

Figure 4: **Illustration of an example molecule and its representation in different data modalities.** From left to right following the 2D chemical structure diagram: its 1D SMILES string representation, a simplified 2D graph view, and its 3D ball-and-stick model.

tion), and provides a **Link** to access the resource.

The subsequent subsections categorize these datasets based on their primary application focus, aligning with the classification used in Section 5 of the main text.

D.1 Pretraining-Only Datasets

Pretraining-only datasets typically contain diverse molecular structures and associated property information, designed to support broad generalization capabilities when pretraining LLMs for downstream tasks. These datasets generally do not include explicit natural language instructions or task-specific labels for direct supervised learning of specific generation or optimization objectives.

- **ZINC:** ZINC (Irwin et al., 2012) is a public and comprehensive database containing over 20 million commercially available molecules presented in biologically relevant representations. These molecules can be downloaded in popular ready-to-dock formats and various subsets, making ZINC widely used for distribution learning-based and goal-oriented molecule generation tasks.
- **PubChem:** PubChem (Kim et al., 2016, 2019, 2025) serves as a vast public chemical information repository, holding over 750 million records. It covers a wide array of data, including chemical structures, identifiers, bioactivity outcomes, genes, proteins, and patents, and is organized into three interlinked databases: Substance (contributed chemical information), Compound (standardized unique structures), and BioAssay (biological experiment details).
- **ChemData:** ChemData (Zhang et al., 2024a) is a large-scale dataset specifically curated for fine-tuning chemical LLMs, containing 7 million instruction query-response pairs. Derived from various online structural datasets like PubChem and ChEMBL, it encompasses a broad range of chemical domain knowledge and is frequently used for tasks in molecule understanding, chemical process reasoning, and other domain-specific applications.
- **Mol-Instructions:** Mol-Instructions (Fang et al., 2023) is a large-scale, diverse, and high-quality dataset designed for the biomolecular domain, featuring over 2 million carefully curated biomolecular instructions. It is structured around three core components: molecule-oriented instructions (148.4K across six tasks focusing on properties, reactions, and design), protein-oriented instructions (505K samples across five task categories related to protein structure, function, and design), and biomolecular text instructions (53K for bioinformatics and chemoinformatics NLP tasks like information extraction and question answering).
- **MuMOInstruct:** MuMOInstruct (Dey et al., 2025) is presented as the first high-quality instruction-tuning dataset focused on complex, multi-property molecular optimization tasks. Unlike datasets such as MolOpt-Instruction (Ye et al., 2025) that primarily target single- or dual-property tasks, MuMOInstruct emphasizes tasks involving at least three properties, facilitating the evaluation of LLMs in both in-domain and out-of-domain settings.

D.2 Benchmark-Only Datasets

Benchmark-only datasets are specifically curated for the evaluation of models, particularly in generative molecular tasks. These datasets often feature structured input-output pairs, such as instruction-molecule pairings, and are typically smaller in scale, manually verified, and tailored to specific evaluative purposes.

- **MoleculeNet:** A large-scale benchmark compendium, MoleculeNet (Wu et al., 2018) is derived from multiple public databases. It comprises 17 curated datasets with over 700,000 compounds, represented textually (e.g., SMILES) and in 3D formats. Covering a wide array of

Table 1: Summary of commonly used molecule datasets and their features. **Dock** denotes the "ready-to-dock" format; **Ontology** denotes the structured representation of the molecule; **Captioning** denotes molecule captioning task; **Docking** denotes molecule docking (a way to find correct molecule binds for proteins); **Translation** denotes the translation from textual knowledge to molecular features; **Conversion** denotes the translation between different representations of a molecule's identity; **Prediction** denotes property prediction, forward reaction prediction and retrosynthesis tasks; **QM** denotes hybrid quantum mechanics.

Datasets	Last Update	Scale	Instruction	Pretraining	Benchmark	Molecule Representations						Generation	Optimization	Other Tasks	Link
						SMILES	IUPAC	Dock	Graph	3D	Ontology				
PubChem (Kim et al., 2016, 2019, 2025)	2025	119M	✗	✓	✗	✓	✓	✗	✓	✓	✓	✓	✗	Property Prediction & Biology Domain	Link
ChEMBL (Gaulton et al., 2012)	2024	>20M	✗	✓	✓	✓	✓	✗	✓	✗	✗	✓	✓	Prediction & ML Benchmark	Link
CrossDocked2020 (Francoeur et al., 2020)	2024	22.5M	✗	✓	✓	✓	✗	✓	✗	✓	✗	✗	✓	Docking Datasets	Link
ZINC (Irwin et al., 2012)	2023	>980M	✗	✓	✗	✓	✓	✓	✓	✓	✗	✓	✓	Ligand Discovery	Link
Dockstring (García-Ortegón et al., 2022)	2022	>260k	✗	✓	✓	✓	✗	✓	✓	✓	✗	✓	✓	Virtual Screening	Link
ChEBI-20 (Edwards et al., 2021)	2021	33k	✗	✓	✓	✓	✓	✗	✓	✗	✓	✓	✗	Translation & Classification & Captioning	Link
OGBG-MolHIV (Hu et al., 2020)	2020	∼41k	✗	✓	✓	✓	✗	✗	✓	✗	✗	✓	✗	Graph Property Prediction	Link
MOSES (Polykovskiy et al., 2020)	2020	∼1.9M	✗	✗	✓	✓	✗	✗	✗	✗	✗	✓	✗	De novo Design	Link
MoleculeNet (Wu et al., 2018)	2019	700k	✗	✗	✓	✓	✗	✗	✓	✓	✗	✓	✓	ML Benchmark	Link
QM9 (Pinheiro et al., 2020)	2014	134k	✗	✓	✓	✓	✗	✗	✓	✓	✗	✓	✓	Hybrid QM/ML Modeling	Link
TOMG-Bench (Li et al., 2024a)	2025	5k	✓	✗	✓	✓	✗	✗	✓	✓	✓	✓	✓	Molecule Editing	Link
MuMOInstruct (Dey et al., 2025)	2025	873k	✓	✓	✗	✓	✗	✗	✗	✗	✗	✗	✓	—	Link
ChemData (Zhang et al., 2024a)	2024	7M	✓	✓	✗	✓	✗	✓	✗	✗	✗	✓	✓	Conversion & Prediction & Reaction	Link
ChemBench (Mirza et al., 2024a)	2024	4k	✓	✗	✓	✓	✗	✗	✗	✗	✗	✓	✓	Reaction Benchmark & Virtual Screening	Link
Mol-Instructions (Fang et al., 2023)	2024	2M	✓	✓	✗	✓	✗	✗	✗	✗	✗	✓	✓	Translation, Retrosynthesis	Link
MolOpt-Instructions (Ye et al., 2025)	2024	1M	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗	✓	—	Link
L+M-24 (Edwards et al., 2024)	2024	148k	✓	✓	✓	✓	✗	✗	✓	✗	✗	✓	✗	Captioning	Link
SMolInstruct (Yu et al., 2024b)	2024	3.3M	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✗	Captioning & Prediction	Link

properties categorized into quantum mechanics, physical chemistry, biophysics, and physiology, it serves as a standard for evaluating molecular property prediction models.

- **ChemBench:** ChemBench (Mirza et al., 2024a) offers a comprehensive framework for benchmarking the chemical knowledge and reasoning abilities of LLMs. It consists of thousands of manually curated question-answer pairs from diverse sources, focusing on three core aspects: Calculation, Reasoning, and Knowledge.
- **TOMG-Bench:** As the first benchmark dedicated to the open-domain molecule generation capabilities of LLMs, TOMG-Bench (Text-based Open Molecule Generation Benchmark) (Li et al., 2024a) contains 45,000 samples. It is structured around three primary tasks: molecule editing (MolEdit), molecule optimization (MolOpt), and customized molecule generation (MolCustom).
- **MOSES:** MOSES (Molecular Sets) (Polykovskiy et al., 2020) is a task-specific resource designed for both training and benchmarking molecule generation models in drug discovery. Containing approximately 1.9 million molecules in SMILES format derived from the ZINC Clean Leads dataset, it also furnishes training, testing, and scaffold-split subsets, along with built-in evaluation metrics.

D.3 Datasets for Pretraining & Benchmark Applications

A distinct category of datasets offers the flexibility to be used for both pretraining LLMs and for subsequent benchmarking. These resources often combine substantial scale with features amenable to diverse evaluation scenarios.

- **ChEMBL:** ChEMBL (Gaulton et al., 2012) is a manually curated, open-access database focusing on drug-like bioactive molecules. It houses 5.4 million bioactivity measurements for over 1 million compounds and 5,200 protein targets, effectively integrating chemical, bioactivity, and genomic data to support drug discovery and the translation of genomic insights into therapeutics.

- **ChEBI-20:** ChEBI-20 (Edwards et al., 2021), derived from the ChEBI database, is a freely available, manually curated dictionary of molecular entities concentrated on small chemical compounds. It includes over 20,000 molecules represented by SMILES strings, natural language descriptions, and ontology terms, widely employed in molecule generation and instruction-based tasks requiring chemical understanding.

- **CrossDocked2020:** CrossDocked2020 (Francoeur et al., 2020) is a large-scale dataset specifically geared towards structure-based drug design (SBDD). It features over 22 million 3D docked poses of protein-ligand pairs, making it a valuable resource for tasks like pocket-conditioned 3D molecule generation.

- **Dockstring:** Dockstring (García-Ortegón et al., 2022) provides a large-scale, well-curated dataset for molecular docking. It encompasses an extensive collection of docking scores and poses for more than 260,000 ligands against 58 medically relevant targets, and includes pharmaceutically relevant benchmark tasks such as virtual screening and the *de novo* design of selective kinase inhibitors.

- **QM9:** QM9(The Quantum Mechanics 9) dataset (Pinheiro et al., 2020) is a public quantum chemistry resource containing approximately 134,000 small organic molecules (composed of H, C, N, O, F; up to nine non-hydrogen atoms). It provides SMILES representations, 3D geometries, and quantum chemical properties, widely utilized for training and evaluating molecular property prediction models.

- **SMolInstruct:** SMolInstruct (Yu et al., 2024b) is a large-scale, comprehensive, and high-quality dataset for instruction tuning LLMs in chemistry. It consists of 3.3 million language-molecule pairs and 1.6 million distinct molecules, covering four types of molecular representations and 14 different tasks, with molecules represented in SMILES or SELFIES format.

- **OGBG-MolHIV:** OGBG-MolHIV (Hu et al., 2020), part of the Open Graph Benchmark, is an open-access, task-specific dataset for binary molecular property prediction, specifically for classifying HIV inhibition. It contains 41,127 unique molecules in graph format, where nodes (atoms) have 9 numerical features and edges (bonds) have 3-dimensional features (type, stereochemistry, conjugation). It is derived from MoleculeNet and preprocessed using RDKit.

Molecule Discovery

Molecule Generation

Query: Build a molecule that meets the requirement: The molecule is a phenolate anion obtained by deprotonation of the 7-hydroxy group of noreugenin. It is the major microspecies at pH 7.3 (according to Marvin v 6.2.0.). It has a role as a plant metabolite. It is a conjugate base of a noreugenin.
Response: Here is a potential molecule:
CC1=CC(=O)C2=C([O-])C=C(O)C=C2O

Molecule Optimization

Query: Help me increase the water solubility value of the molecule Cc1cc(C(COCc2ccccc2)sc(C)(C)C)sn1
Response: Here is a potential molecule:
Cc1cc(C(N)COCc2ccccc2)sn1

Figure 5: Visualization of the Instruction dataset of molecule generation and optimization task.

- **MolOpt-Instructions:** MolOpt-Instructions (Ye et al., 2025) is an instruction-based dataset tailored for molecule optimization, containing over 1 million molecule-molecule pairs. It was constructed by selecting molecules from ZINC and using MMPDB to generate and filter for highly similar pairs, covering six molecular properties including solubility, BBBP, and hERG inhibition.

- **L+M-24:** L+M-24 (Language + Molecules 24 Tasks) (Edwards et al., 2024) is a large-scale, multi-task instruction dataset designed to leverage the benefits of natural language (compositionality, functionality, abstraction) in molecule design. Derived from PubChem and other sources, it contains over 148,000 language-molecule pairs spanning 24 distinct molecule design tasks across various application domains.

E Evaluation Metrics

Evaluation metrics for LLM-centric molecular discovery are organized around the four fundamental challenges identified in our survey. Each category of metrics addresses specific aspects of molecular generation and optimization quality, reflecting the unique requirements of chemical tasks compared to general text generation.

E.1 Validity Metrics

Validity metrics assess whether generated molecules adhere to fundamental chemical rules and structural constraints. Unlike grammatically

incorrect text, invalid molecules are physically impossible and unusable.

- **Validity Rate** (Polykovskiy et al., 2020): Fraction of generated molecules that are chemically valid (parsable by RDKit). High validity rates (>90%) indicate successful learning of chemical grammar.
- **Exact Match (EM)** (Rajpurkar et al., 2016): Measures perfect sequence matching between generated and target molecules. Critical for tasks requiring precise molecular replication.
- **BLEU Score** (Papineni et al., 2002): Adapted from NLP, measures n-gram overlap between generated and reference SMILES. Higher scores indicate better sequence-level fidelity.
- **Levenshtein Distance** (Levenshtein, 1966): Minimum edit distance between molecular strings. Lower values indicate closer structural similarity.
- **Chemical Correctness** (Landrum et al., 2013): RDKit-based validation checking valency rules, ring systems, and aromatic systems. Essential for filtering chemically impossible structures.

Performance Benchmarks: State-of-the-art LLMs achieve 85-95% validity on standard benchmarks, with multi-modal approaches reaching 95-99%. However, validity alone is insufficient—many valid molecules are practically useless.

E.2 Synthesizability Metrics

Synthesizability metrics evaluate whether valid molecules can be practically synthesized in a laboratory setting. This addresses the critical gap between theoretical validity and practical utility.

- **SA Score** (Ertl and Schuffenhauer, 2009): Synthetic Accessibility score (1-10 scale, lower is better) based on molecular complexity and fragment contributions. Molecules with SA > 6 are typically considered difficult to synthesize.
- **SCScore** (Coley et al., 2018): Synthetic Complexity score learned from reaction databases. More accurate than SA Score but computationally intensive.
- **Retrosynthetic Accessibility** (Genheden et al., 2020): Evaluates synthesizability through automated retrosynthetic planning. Molecules with viable synthetic routes are considered accessible.

Current Limitations: Most LLM-generated molecules have poor synthesizability (average SA Score > 4.5), highlighting a major gap in current approaches. Only specialized models like SynLlama directly address this challenge.

E.3 Property Control Metrics

Property control metrics assess the model's ability to generate molecules with desired physicochemical or biological properties, often requiring multi-objective optimization.

E.3.1 Single-Property Metrics

- **LogP** (Hansch et al., 1968): Octanol-water partition coefficient, indicating hydrophobicity. Target ranges vary by application (e.g., -0.4 to 5.6 for oral drugs).
- **QED** (Bickerton et al., 2012): Quantitative Estimate of Drug-likeness (0-1 scale). Combines multiple properties; scores > 0.67 indicate drug-like molecules.
- **TPSA** (Ertl et al., 2000): Topological Polar Surface Area. Values < 140 Ự correlate with oral bioavailability.
- **Molecular Weight (MW)**, **HBD/HBA**: Basic descriptors for drug-likeness (Lipinski's Rule of Five).

E.3.2 Multi-Property Metrics

- **Success Rate** (Jin et al., 2020): Fraction of molecules meeting all specified property constraints. Typical success rates: 60-80% for single properties, 20-40% for multiple properties.
- **Pareto Optimality** (Pareto, 1919): Identifies solutions optimal across multiple objectives. Essential for understanding trade-offs between competing properties.
- **Composite Score** (Jin et al., 2020): Weighted combination of multiple properties. Allows single-objective optimization of multi-property goals.

Benchmarking Insights: Instruction-tuned models show 15-25% improvement in property control over base models. Multi-property optimization remains challenging, with success rates dropping exponentially with constraint count.

E.4 Diversity Metrics

Diversity metrics evaluate the breadth of chemical space explored, preventing mode collapse and encouraging novel discoveries.

- **Uniqueness** (Wang et al., 2023; Bagal et al., 2021): Fraction of non-duplicate valid molecules. Measured at different scales:
  - Unique@1k: Short-term diversity (typical: 95-99%)
  - Unique@10k: Long-term diversity (typical: 85-95%)
- **Novelty Rate** (Brown et al., 2019): Fraction of generated molecules not in training set. Low novelty (<50%) indicates overfitting.
- **Internal Diversity (IntDiv)** (Benhenda, 2017): Average pairwise dissimilarity within generated set:

$$\text{IntDiv}_p(S) = 1 - \left(\frac{1}{|S|^2} \sum_{s_i, s_j \in S} T(s_i, s_j)^p \right)^{\frac{1}{p}}$$

- **NCircle** (Jang et al., 2024): Largest subset with pairwise Tanimoto similarity below threshold. Higher values indicate better structural diversity.
- **Scaffold Diversity**: Number of unique Bemis-Murcko scaffolds. Critical for avoiding "decoration" of known structures.
- **Fingerprint Tanimoto Similarity (FTS)**: Structural similarity using various fingerprints:
  - MACCS keys (Durant et al., 2002): 166-bit structural keys
  - Morgan fingerprints (Morgan, 1965): Circular fingerprints
  - RDKit fingerprints (Landrum et al., 2013): Topological fingerprints

Key Findings: Supervised fine-tuning often reduces diversity (IntDiv drops 20-30%). Preference tuning methods like Div-SFT successfully restore diversity while maintaining other properties.

E.5 Integrated Evaluation Framework

No single metric captures all aspects of molecular quality. We recommend:

1. **Minimum requirements**: Validity > 90%, Uniqueness@1k > 95%
2. **Task-specific priorities**: Weight metrics based on application (e.g., prioritize synthesizability for lead optimization)
3. **Multi-metric reporting**: Always report all four categories to reveal trade-offs
4. **Baseline comparisons**: Compare against both random generation and domain-specific baselines

E.6 Critical Limitations of Current Metrics

While standardized, current evaluation metrics often serve as imperfect proxies for real-world success. Over-reliance on these computational stand-ins can lead to misleading conclusions about a model's practical utility. We highlight three fundamental limitations:

1. Unreliability of Predictors on Novel Molecules Metrics like QED and LogP rely on predictive models (e.g., QSAR) trained on known chemical space. These predictors can fail catastrophically on the novel, out-of-distribution (OOD) molecules that generative models are designed to create (Tossou et al., 2024; Antoniuk et al., 2025). Consequently, a high metric score may reflect a model's ability to exploit predictor inaccuracies rather than generate genuinely superior molecules.

2. Disconnect Between SA Score and Real-World Synthesizability The SA Score is a computationally cheap heuristic that correlates poorly with actual laboratory synthesis success (Walters, 2024). It does not guarantee the existence of a viable synthetic route or account for practical factors like cost and yield. As our own results confirm (Section H), even molecules with good SA scores can be synthetically challenging, making this metric an unreliable guide for practical design.

3. The Fundamental "Proxy Problem" The current evaluation ecosystem incentivizes optimizing for a narrow set of computationally convenient proxies (e.g., QED, SA Score), not the complex, multi-faceted objectives of real-world drug discovery (e.g., metabolic stability, low toxicity). This "proxy problem" rewards models for "passing the test" rather than designing truly viable drug candidates. True progress requires integrating more holistic criteria, such as feedback from retrosynthe-

sis planners (Appendix F) and eventual experimental validation.

F External Tools

The evaluation of molecular generation and optimization models relies on a comprehensive ecosystem of computational tools that bridge chemistry, machine learning, and specialized assessment frameworks. These tools can be categorized into three main groups based on their primary functions.

F.1 General Cheminformatics Libraries

RDKit (Landrum et al., 2013) has become the de facto standard in the field, providing extensive functionality for molecular representation, property calculation, and structure validation. It handles SMILES parsing, canonicalization, and validation; calculates physicochemical properties including logP, molecular weight, TPSA, and hydrogen bond donors/acceptors; generates various molecular fingerprints (Morgan/ECFP, MACCS, RDK topological); performs substructure searching and Bemis-Murcko scaffold extraction; and validates chemical structures including aromatic system detection. Nearly all major benchmarks including MOSES and GuacaMol rely heavily on RDKit for their metric calculations.

OpenBabel (O'Boyle et al., 2011) serves as the "universal translator" of chemical file formats, supporting over 110 formats and providing critical interoperability between different computational chemistry software. While it also offers descriptor calculation and structure manipulation, its primary strength lies in format conversion, accessible through the PyBel Python interface. This capability is essential when integrating diverse chemical data sources or connecting different software tools in evaluation pipelines.

CDK (Chemistry Development Kit) (Willighagen et al., 2017) provides a comprehensive Java-based cheminformatics library with mature graph algorithms for structural analysis and 3D molecular modeling. Its Java foundation makes it particularly suitable for integration into enterprise-level applications, offering robust APIs for custom chemical informatics solutions.

F.2 Synthesizability Assessment Tools

Given that computational validity does not guarantee practical synthesizability, specialized tools have emerged to bridge this critical gap.

AiZynthFinder (Genheden et al., 2020) employs neural network-guided Monte Carlo tree search for retrosynthetic planning. It evaluates synthesizability by attempting to find viable synthetic routes from commercially available starting materials, providing both binary feasibility assessments and synthetic accessibility scores. The tool has become increasingly important as the field recognizes that many computationally valid molecules remain synthetically inaccessible.

ASKCOS (Coley et al., 2019) (Automated System for Knowledge-based Continuous Organic Synthesis) offers a comprehensive platform that integrates multiple machine learning models for forward reaction prediction, retrosynthetic route planning, condition recommendation, and synthetic complexity evaluation. This unified approach provides more reliable synthesizability assessments by considering multiple aspects of the synthetic process simultaneously.

F.3 LLM-Specific Integration Tools

The emergence of LLMs has necessitated new tools that bridge natural language processing with chemical computation.

ChemCrow (M. Bran et al., 2024) represents a paradigm shift by augmenting LLMs with 17 expert-designed chemistry tools. It enables LLMs to execute chemical calculations they cannot perform natively, access real-time chemical databases, perform safety checks on generated molecules, and plan and evaluate synthetic routes. This tool-augmented approach addresses the fundamental limitation that LLMs, while excellent at pattern recognition, lack the ability to perform precise chemical calculations or access up-to-date chemical information.

ChemBench Package (Mirza et al., 2024b) provides a modular, extensible framework specifically designed for benchmarking LLM performance on chemical tasks. It offers standardized evaluation pipelines through automated model querying, answer parsing, and report generation, significantly simplifying the process of evaluating LLMs on chemical reasoning and generation tasks.

G Evaluation Frameworks

The evolution of evaluation frameworks in molecular generation reflects the field's progression from statistical distribution matching to instruction-

following and multi-objective optimization. Each framework addresses specific limitations of its predecessors while introducing new evaluation paradigms.

G.1 Classical Generation Frameworks

MOSES (Molecular Sets) (Polykovskiy et al., 2020) established the foundation for standardized evaluation by providing a carefully filtered dataset of 1.9M drug-like molecules from ZINC, a comprehensive metric suite including validity, uniqueness, novelty, FCD, and fragment/scaffold similarity, baseline implementations of multiple architectures (CharRNN, VAE, AAE, ORGAN, JT-VAE), and standardized train/test splits to ensure fair comparison. MOSES primarily focuses on distribution learning—the ability of models to replicate the statistical properties of the training set. Its key contribution was creating a unified, reproducible testing ground for comparing different generative architectures.

GuacaMol (Brown et al., 2019) significantly expanded the evaluation scope by introducing both distribution learning tasks using KL divergence and Fréchet ChemNet Distance, and goal-directed benchmarks comprising 20 tasks ranging from simple property maximization to complex multi-parameter optimization (MPO). These tasks were specifically designed to mirror real drug discovery scenarios, such as generating molecules similar to celecoxib but with improved properties. This dual approach better reflects the practical needs of molecular design, where both exploration (distribution learning) and exploitation (goal-directed optimization) are crucial.

G.2 Modern Unified Frameworks

MolScore (Thomas et al., 2024) addresses the fragmentation issue in molecular optimization evaluation through its modular architecture supporting over 40 scoring functions, unified interface for diverse molecular optimization algorithms, flexible aggregation methods for multi-objective optimization, and extensive configuration options via JSON/YAML. Its key innovation lies in decoupling scoring from optimization, allowing researchers to mix and match components freely while maintaining consistent evaluation protocols.

TDC (Therapeutics Data Commons) (Huang et al., 2021) takes a community-driven approach by providing 66+ datasets across 22+ therapeutic tasks, continuously updated leaderboards with standardized evaluation protocols, and realistic data splits (scaffold-based, temporal, and combination splits) that better reflect real-world deployment scenarios. The framework's APIs enable easy integration and benchmarking, making it particularly valuable for researchers seeking to evaluate their methods against established baselines on therapeutically relevant tasks.

G.3 LLM-Specific Evaluation Frameworks

The emergence of LLMs necessitated entirely new evaluation paradigms that assess instruction-following and reasoning capabilities rather than just statistical properties.

TOMG-Bench (Li et al., 2024a) pioneered open-domain molecule generation evaluation with three task categories: MolEdit for component manipulation (adding, removing, or replacing functional groups), MolOpt for property optimization (LogP, QED, molecular refractivity), and MolCustom for constrained generation based on specific requirements. The framework provides 45,000 test samples with diverse instructions and employs weighted accuracy metrics that combine task success with chemical similarity or novelty scores. Its automated evaluation system directly assesses whether generated molecules adhere to the given instructions while maintaining chemical validity.

ChemBench (Mirza et al., 2024b) focuses on evaluating chemical reasoning capabilities through a question-answering format covering calculation tasks, chemical reasoning, and factual knowledge. The framework enables direct comparison with human expert performance, includes safety evaluation components to assess potentially harmful outputs, and supports multi-modal queries involving both text and molecular structures. This comprehensive approach reveals that while LLMs can match or exceed human experts on certain knowledge tasks, they still struggle with deep chemical reasoning requiring multi-step inference.

AMORE (Augmented Molecular Retrieval) (Ganeeva et al., 2024) further probes the robustness of chemical language models by assessing if they truly understand the underlying molecular structure rather than memorizing textual patterns. This zero-shot framework evaluates a model's chemical awareness through a retrieval task based on molecular augmentations that preserve chemical identity,

such as canonicalization, explicit hydrogen addition, kekulization, and cycle renumbering. The model is tasked with matching the embedding of an original SMILES string to the embedding of its chemically equivalent but textually different augmentation. Key findings reveal that many LLMs are not robust to these variations, showing significant performance degradation on both the retrieval task and downstream property prediction tasks when presented with augmented inputs. This indicates that models often overfit to specific string representations, highlighting a critical gap in their chemical understanding.

G.4 Recommendations for Framework Selection

For researchers navigating this landscape, framework selection should align with specific evaluation needs. MOSES provides the most standardized comparison for distribution learning tasks. GuacaMol or MolScore offer comprehensive evaluation for goal-directed optimization, with MolScore providing greater flexibility for custom objectives. TDC excels when therapeutic relevance is paramount, offering realistic data splits that better predict real-world performance. For LLM evaluation, TOMG-Bench effectively assesses generation capabilities while ChemBench evaluates reasoning and knowledge. Comprehensive evaluation often requires combining multiple frameworks to capture different aspects of model performance.

H Quantitative Insights and Benchmark Design

To ground our qualitative analysis in concrete empirical evidence and address the lack of unified evaluation protocols in existing literature, we conducted a systematic benchmark study. This represents an initial attempt to realize the **unified benchmark** proposed in our future directions (Section 6), providing direct, fair comparison across openly available models under controlled conditions.

H.1 Experimental Framework

Model Selection and Scope We selected seven representative open-source LLMs spanning both general-purpose models (`Llama-3.1-8B`, `Qwen2.5-7B`) and task-specific chemical LLMs (`ChemLLM-7B`, `LlaSMol`, `PEIT-LLM`, `DrugAssist`, `GeLLMO`). Importantly, **not all models were designed to evaluate on all tasks**, as some were designed specifically for either generation or optimization. For instance, `LlaSMol` was primarily designed for generation tasks. Our goal was to assess each model within its intended application scope while using a unified evaluation protocol.

Task Design We designed two core evaluation tasks, each with standardized instruction templates to ensure fair comparison:

- **Single Property Optimization:** Given an input molecule, modify it to improve a target property. The instruction explicitly specifies the property to optimize.
- **De Novo Generation:** Generate novel molecules from scratch based on property specifications. For example, the QED task uses the instruction: *"Generate a drug-like molecule with QED (Quantitative Estimate of Drug-likeness) greater than 0.6."*

Each task was evaluated across five pharmacologically relevant properties: QED (drug-likeness), LogP (lipophilicity), JNK3 (kinase inhibition), GSK3β (kinase inhibition), and DRD2 (receptor binding).

Evaluation Metrics To align with our four fundamental challenges, we computed the following metrics for all generated molecules:

- **Validity (Val):** Fraction of outputs that are chemically valid SMILES strings, parsed successfully by RDKit without errors. This directly measures chemical correctness.
- **Property Control (PC):** We evaluate Property Control differently for generation and optimization tasks to reflect their distinct objectives.
  - **For the Generation task,** PC is the success rate of generating molecules that meet predefined property thresholds. We use specific criteria for each property (e.g., QED > 0.6, LogP > 2.0, JNK3 > 0.5) and calculate the fraction of valid molecules that satisfy these constraints.
  - **For the Optimization task,** PC measures the success rate of achieving any positive improvement in the target property. Success is defined as the fraction of valid modified molecules where the property value has changed favorably compared to the input molecule (e.g., $\text{QED}_{\text{new}} > \text{QED}_{\text{old}}$).

Table 2: **Performance Comparison of LLMs for Molecular Optimization.** For each metric, the best performance is in **bold** and the second best is underlined. The arrows (↑, ↓) indicate whether a higher or lower value is better.

Model	QED				LogP				JNK3				GSK3B				DRD2			
	Val↑	PC↑	Syn↓	Div↑	Val↑	PC↑	Syn↓	Div↑	Val↑	PC↑	Syn↓	Div↑	Val↑	PC↑	Syn↓	Div↑	Val↑	PC↑	Syn↓	Div↑
General-purpose LLMs																				
Llama3.1	0.39	0.38	4.71	0.67	0.36	0.35	5.24	0.64	0.30	0.27	5.28	0.62	0.34	0.31	5.20	0.65	0.36	0.34	5.36	0.67
Qwen2.5	0.46	0.39	3.40	0.36	0.43	0.39	3.69	0.33	0.36	0.21	3.41	0.34	0.37	0.28	3.77	0.36	0.36	0.26	3.79	0.34
Task-Specific LLMs																				
ChemLLM	0.50	0.20	3.26	0.40	0.46	0.18	3.50	0.39	0.43	0.09	3.08	0.28	0.41	0.10	3.47	0.33	0.45	0.12	3.59	0.32
LlaSMol	0.68	0.68	3.93	0.67	0.67	0.67	4.00	0.63	0.68	0.64	4.21	0.69	0.67	0.61	4.31	0.68	0.68	0.67	4.32	0.68
PEIT-LLM	0.76	0.76	**2.45**	**0.74**	0.72	0.72	**2.65**	**0.75**	0.72	**0.69**	**2.61**	**0.75**	0.71	**0.69**	**2.73**	**0.75**	0.72	0.72	**2.61**	**0.75**
DrugAssist	**0.85**	**0.84**	3.48	0.22	**0.79**	**0.78**	3.73	0.25	**0.87**	0.66	3.29	0.24	**0.79**	0.68	3.70	0.25	**0.81**	**0.80**	3.73	0.24
GeLLMO	0.80	0.79	2.81	0.46	0.77	0.77	3.10	0.46	0.74	0.62	2.88	0.46	0.68	0.59	3.18	0.46	0.72	0.71	3.28	0.45

* Val: Validity, PC: Property Control, Syn: Synthesizability, Div: Diversity.

Table 3: **Performance Comparison of LLMs for Molecule Generation.** For each metric, the best performance is in **bold** and the second best is underlined. The arrows (↑, ↓) indicate whether a higher or lower value is better.

Model	QED				LogP				JNK3				GSK3B				DRD2			
	Val↑	PC↑	Syn↓	Div↑	Val↑	PC↑	Syn↓	Div↑	Val↑	PC↑	Syn↓	Div↑	Val↑	PC↑	Syn↓	Div↑	Val↑	PC↑	Syn↓	Div↑
General-purpose LLMs																				
Llama3.1	0.56	0.15	3.84	0.81	0.64	0.24	3.31	0.81	0.37	0.03	5.02	0.85	0.35	0.18	4.93	0.83	0.42	0.00	4.14	0.82
Qwen2.5	0.83	0.39	3.46	0.86	0.73	0.27	3.69	0.86	0.64	0.00	3.68	0.84	0.70	0.12	3.75	0.85	0.52	0.01	3.70	**0.86**
Task-Specific LLMs																				
ChemLLM	0.29	0.12	5.18	**0.91**	0.28	0.03	4.22	**0.90**	0.09	0.00	4.58	**0.85**	0.16	0.01	4.84	**0.87**	0.14	0.00	5.19	0.83
LlaSMol	**0.99**	0.57	2.52	0.84	0.96	0.48	2.44	0.86	0.96	**0.10**	2.79	0.82	**0.98**	**0.29**	2.65	0.84	0.99	0.08	2.70	0.82
PEIT-LLM	0.98	0.92	2.63	0.80	**1.00**	0.58	2.64	0.83	0.96	0.01	2.55	0.80	0.97	0.09	2.63	0.81	**1.00**	0.03	2.65	0.81
DrugAssist	0.81	0.00	5.82	0.63	0.68	0.01	5.18	0.72	0.56	0.00	5.84	0.38	0.70	0.00	5.80	0.58	0.61	0.00	5.48	0.30
GeLLMO	0.98	0.74	**1.89**	0.81	0.99	**0.66**	**1.81**	0.82	**0.98**	0.00	**2.08**	0.83	0.93	0.00	**1.82**	0.78	0.98	**0.14**	**2.16**	0.82

* Val: Validity, PC: Property Control, Syn: Synthesizability, Div: Diversity.

De Novo Generation Task Prompt Template

System Message:
You are an expert medicinal chemist specializing in molecular design. You understand how molecular structures affect key properties including drug-likeness, lipophilicity, synthetic accessibility, and biological activities.

Task Instruction:
Design a novel molecule that satisfies the specified property requirements. The molecule should be chemically valid and synthetically accessible.

Property Requirements (task-specific):
- QED: Generate a drug-like molecule with QED > 0.6
- LogP: Generate a lipophilic molecule with LogP > 2.0
- JNK3: Generate a molecule with JNK3 inhibition probability > 0.5
- GSK3β: Generate a molecule with GSK3β inhibition probability > 0.5
- DRD2: Generate a molecule with DRD2 inhibition probability > 0.5

Output Format:
- SFT-Trained Models (*GeLLMO, LlaSMol, PEIT-LLM, DrugAssist*):
  Return SMILES in <SMILES> ... </SMILES> tags
- **General-Purpose Models** (*Llama-3.1, Qwen2.5, ChemLLM*):
  Response only with SMILES, no other text

Example Response (QED task):
SFT Model: <SMILES>CC(C)Cc1ccc(C(=O)O)cc1</SMILES>
General Model: CC(C)Cc1ccc(C(=O)O)cc1

- **Synthesizability (Syn):** Mean SA Score (Ertl and Schuffenhauer, 2009) of all valid molecules, where lower scores indicate easier synthesis. An SA Score below 3.0 is generally considered syn-

Molecular Optimization Task Prompt Template

System Message: You are an expert medicinal chemist specializing in molecular optimization. You understand how structural modifications affect key molecular properties including drug-likeness, lipophilicity, synthetic accessibility, and target inhibition activities.

Task Instruction: Your task is to modify the given molecule to adjust the specified molecular properties while keeping structural changes as minimal as possible. The modified molecule should maintain a structural similarity of at least 0.6 with the original molecule.

Input Parameters:
- Input Molecule: input_smiles
- Requested Modifications: (Select from the options below)

Modification Options (task-specific):
- QED: increase drug-likeness (QED)
- LogP: increase lipophilicity (LogP)
- JNK3: increase JNK3 inhibition probability
- GSK3β: increase GSK3β inhibition probability
- DRD2: increase DRD2 inhibition probability
- SA: decrease synthetic accessibility score (lower is better)

Output Format:
- SFT-Trained Models (*GeLLMO, LlaSMol, etc.*): Return SMILES in <SMILES> ... </SMILES> tags
- **General-Purpose Models** (*Llama-3.1, Qwen2.5, etc.*): Response only with SMILES, no other text

Example Response (LogP task for c1ccccc1):
SFT Model: <SMILES>Cc1ccccc1</SMILES>
General Model: Cc1ccccc1

thetically accessible.

- **Diversity (Div):** Internal diversity computed as $1 -$ mean pairwise Tanimoto similarity using Morgan fingerprints. Higher values indicate greater structural variety within the generated set.

All evaluations used identical random seeds, test sets, and computing infrastructure to eliminate confounding factors.

H.1.1 Key Findings

The comprehensive results, presented in Tables 2 and 3, provide quantitative validation of our qualitative analysis and reveal several critical insights:

1. Empirical Validation of Paradigm Trade-offs Our experiments directly confirm the strengths and limitations:

- **SFT Models Excel at Validity & Property Control:** Task-specific models consistently outperform general-purpose LLMs on these dimensions. In optimization tasks (Table 2), fine-tuned models achieve 68–85% validity versus 36–46% for general models, and property control rates of 0.59–0.84 versus 0.26–0.39.
- **Diversity-Control Trade-off is Observable:** Models optimized aggressively for property control sacrifice diversity. DrugAssist achieves the highest PC (0.78–0.84) but lowest diversity (0.22–0.25), demonstrating mode collapse. Conversely, PEIT-LLM maintains balanced performance with high PC (0.69–0.76) *and* diversity (0.74–0.75) through its multi-constraint training approach, suggesting that careful SFT design can mitigate this trade-off.
- **Synthesizability: The Universal Bottleneck:** This challenge remains poorly addressed across *all* paradigms and models. In de novo generation (Table 3), even the best-performing GeLLMO achieves SA Scores of only 1.81–2.16, while most models produce molecules with SA > 2.5. For optimization tasks, SA Scores range from 2.45 to 5.36, with the majority exceeding 3.0—indicating limited synthetic accessibility. This quantitatively confirms synthesizability as the most critical unsolved challenge.

2. The Transformative Impact of Domain-Specific SFT Comparing general-purpose and specialized models reveals the dramatic benefits of fine-tuning:

- **Optimization Tasks:** General-purpose `Llama-3.1-8B` achieves 0.38 property control on QED, while the fine-tuned `LlaSMol` (built on a similar architecture) reaches 0.68—a **79% relative improvement**. Validity improves from 39% to 68% (+74%).
- **Generation Tasks:** The performance gap is even more pronounced. `Qwen2.5-7B` achieves 0.39 PC on QED generation, while `PEIT-LLM` reaches 0.92—a **136% improvement**. Validity jumps from 0.83 to 0.98 (+18% absolute).
- **Consistency Across Properties:** These improvements are not isolated to specific properties. Across all five evaluated properties, fine-tuned models show 50–150% relative gains in property control and 15–100% gains in validity compared to their general-purpose counterparts.

These results provide quantitative confirmation that domain-specific SFT is **essential** rather than merely beneficial for molecular discovery, transforming baseline capabilities into expert-level performance.

3. Task Difficulty and Model Specialization Cross-task comparisons reveal interesting patterns:

- **Optimization is Easier than Generation:** Models generally achieve higher property control in optimization (0.59–0.84 for top performers) than in generation (0.00–0.92), suggesting that guided modification of existing structures is more tractable than de novo design.
- **Task-Specific Specialization Matters:** `ChemLLM`, despite lower overall performance, achieves the highest diversity in generation tasks (0.83–0.91), indicating it may explore more unusual chemical spaces. However, this comes at the cost of validity (0.09–0.29), highlighting the need for task-appropriate model selection.
- **Generalist vs. Specialist:** General-purpose models show more consistent (but lower) performance across tasks, while specialized models exhibit higher variance, excelling on their target tasks but potentially underperforming outside their training distribution.

4. Model-Specific Insights Our unified framework enables direct comparison of model characteristics:

- `GeLLMO` consistently achieves the best synthesizability (SA Scores 1.81–3.28), validating its multi-property optimization objective with emphasis on synthetic feasibility.
- `PEIT-LLM` demonstrates the most balanced profile, achieving top-3 performance across all four metrics on most tasks, making it suitable for applications requiring simultaneously high validity, property control, and diversity.
- `DrugAssist` specializes in validity and property control at the expense of diversity, potentially useful for targeted optimization where structural novelty is secondary.

H.1.2 Implications

These quantitative results strongly validate our qualitative framework and provide actionable insights:

1. **Paradigm Selection Matters:** No single approach dominates all challenges. Researchers should select paradigms (zero-shot, SFT, preference tuning) based on their specific application requirements—whether prioritizing diversity, control, or synthesizability.
2. **SFT is Non-Negotiable:** For production applications requiring high reliability, domain-specific fine-tuning provides 50–150% performance improvements over general-purpose models. Zero-shot prompting, while convenient, is insufficient for most practical molecular design tasks.
3. **Synthesizability Demands Priority:** The uniformly poor performance across models (SA Scores rarely below 2.0) underscores the urgent need for methods that integrate retrosynthetic planning directly into the generation process, as advocated in Section 6.
4. **Unified Benchmarks are Crucial:** Our framework represents an initial step toward the standardized evaluation infrastructure discussed in Section 6. The dramatic cross-model variations observed here (e.g., 0.09–0.98 validity on generation tasks) highlight why unified, reproducible benchmarks are essential for meaningful progress tracking.

In summary, this quantitative study not only validates our qualitative taxonomy but also provides concrete evidence for the field's current state and future priorities. It demonstrates that while LLMs show promise for molecular discovery, sub-

stantial challenges—particularly in synthesizability—remain unresolved, requiring the paradigm shifts and unified evaluation standards proposed in this survey.

I Distribution Shift and Out-of-Distribution Generalization

A critical challenge in molecular discovery is **distribution shift**, where models trained on known molecules fail to generalize to novel, out-of-distribution (OOD) compounds necessary for true innovation. Recent benchmarks reveal that molecular ML models exhibit OOD errors **3× larger** than in-distribution performance (Antoniuk et al., 2025), with performance degradations of 20-60% in real-world scenarios (Tossou et al., 2024). This problem is a primary cause of "mode collapse" and directly limits the **Diversity** discussed in the main text (Tossou et al., 2024). Effectively navigating this shift is essential for moving beyond rediscovery to genuine design.

To address this, machine learning models have developed distinct strategies. Traditional methods like GNNs and VAEs often focus on learning invariant representations, for instance, through Mixture-of-Experts (MoE) architectures that handle specific data domains (Wu et al., 2024a) or by disentangling molecules into "causal" and "spurious" substructures to improve robustness (Yang et al., 2022). However, these approaches often require substantial data to avoid spurious correlations.

LLMs leverage different learning paradigms with unique advantages. While standard Supervised Fine-Tuning (SFT) can overfit to the training distribution, **Preference Tuning (PT)** directly encourages OOD exploration by explicitly rewarding novelty and diversity, as exemplified by models like `Div-SFT` (Jang et al., 2024). Furthermore, advanced **Instruction Tuning** on complex, multi-property tasks (using datasets like `MuMOInstruct`) enables the model to learn more generalizable chemical reasoning for unseen tasks.

Test-time adaptation represents a particularly promising direction, with methods like TAIP achieving 30% error reduction through self-supervised learning during inference (Kreiman and Krishnapriyan, 2025). Finally, **Agentic frameworks** like `MultiMol` (Liu et al., 2022) contribute by incorporating external, out-of-distribution knowledge from scientific literature to guide the generation process. Together, these LLM-centric techniques represent a key frontier in developing models that can truly innovate, though significant challenges remain in ensuring synthesizability and practical utility of OOD-generated molecules.

J Method Summary

This section provides a consolidated overview of representative LLM-based methods for molecular discovery, as detailed in Table 4. The table organizes these approaches primarily by the two core task categories central to this survey: molecule generation and molecule optimization. Within each task, methods are further sub-categorized by their primary learning Strategy (referred to as "Category" and "Technique" in the table), encompassing approaches without LLM tuning (such as zero-shot prompting and in-context learning) and those with LLM tuning (supervised fine-tuning and preference tuning).

Table 4 details several key aspects for each listed **Method**:

- **Venue**: The publication venue or preprint archive where the method was reported.
- **Input Type**: Specifies the primary format of molecular data and instructions provided to the LLM (e.g., SMILES strings, textual instructions, few-shot examples, or multi-modal inputs like graphs).
- **Base Model**: Indicates the foundational LLM architecture (e.g., GPT-4, LLaMA variants, Mistral) upon which the method is built or applied.
- **Dataset**: Lists the key molecular corpora or benchmarks used for training the model (if applicable) or for its evaluation in the context of the reported work.
- **Repository**: Provides a link to the public code or resource repository, if available.

This structured presentation aims to offer a clear comparative landscape of the current methodologies in the field.

Table 4: Summary of LLM-based methods for molecule generation and optimization. Each row corresponds to a method, organized by **Task** (generation or optimization), and **Technique**. **Input Type** denotes the molecular data format provided to the model. **Base Model** denotes the large language model architecture used. **Dataset** denotes the molecular corpus or benchmark used for training or evaluation.

Task	Category	Technique	Method	Venue	Input Type	Base Model	Dataset	Repository
Molecule Generation	w/o Tuning	ICL	LLM4GraphGen (Yao et al., 2024)	Arxiv	Instruction + Few shot	GPT-4	OGBG-MolHIV	Link
			MolReGPT (Li et al., 2024c)	TKDE	Instruction + Few shot	GPT-3.5-turbo/ GPT-4	ChEBI-20	Link
			FrontierX (Srinivas and Runkana, 2024)	Arxiv	Instruction	GPT-3.5	ChEBI-20	N/A
	w/ Tuning	SFT	Mol-instructions (Fang et al., 2023)	ICLR	Instruction	LLaMA-7B	Mol-Instructions	Link
			LlaSMol (Yu et al., 2024a)	COLM	Instruction	Galactica 6.7B/ LLaMA-2-7B/ Mistral-7B	SMolInstruct	Link
			ChemLLM (Zhang et al., 2024a)	Arxiv	Instruction	InternLM2-7B-Base	ChemData	N/A
			ICMA (Li et al., 2024b)	TKDE	Instruction + Few shot	Mistral-7B	PubChem & ChEBI-20	N/A
			MolReFlect (Li et al., 2024d)	Arxiv	Instruction + Few shot	Mistral-7B	ChEBI-20	Link
			ChatMol (Fan et al., 2025)	Arxiv	Instruction	LLaMA-3-8B	ZINC	Link
			PEIT-LLM (Lin et al., 2025)	Arxiv	Instruction	LLaMA-3.1-8B/ Qwen2.5-7B	ChEBI-20	Link
			NatureLM (Xia et al., 2025)	Arxiv	SMILES + Instruction	NatureLM-8B	ChEMBL & MoleculeNet	Link
			SynLlama (Sun et al., 2025)	Arxiv	Instruction	LLaMA-3.1-8B / LLaMA-3.2-1B	ChEMBL	Link
			TOMG-Bench (Li et al., 2024a)	Arxiv	Instruction	LLaMa-3.1-8B	TOMG-Bench	N/A
			UniMoT (Zhang et al., 2024b)	Arxiv	Instruction	LLaMA-2-7B	Mol-Instructions	Link
		Preference Tuning	Div-SFT (Jang et al., 2024)	Arxiv	Instruction	LLaMA-7B	ChEBI-20	N/A
			Mol-MOE (Calanzone et al., 2025)	Arxiv	Instruction	LLaMA-3.2-1B	ChEMBL & ZINC & MOSES	Link
			SmileyLLama (Cavanagh et al., 2024)	NeurIPS Workshop	Instruction	LLaMA-3.1-8B	ChEMBL	N/A
			ALMol (Gkoumas, 2024)	ACL Workshop	Instruction	Meditron-7B	L+M-24	N/A
			Less for More (Gkoumas and Liakata, 2024)	Arxiv	Instruction	Meditron-7B	L+M-24	N/A
			Mol-LLM (Lee et al., 2025)	Arxiv	Instruction	Mistral-7B	ChEBI-20	N/A
Molecule Optimization	w/o Tuning	Zero-Shot Prompting	LLM-MDE (Bhattacharya et al., 2024)	JCIM	SMILES + Instruction	Claude 3 Opus	ZINC	N/A
			MOLLEO (Wang et al., 2025)	ICLR	SMILES + Instruction	GPT-4	ZINC	Link
		ICL	CIDD (Gao et al., 2025)	Arxiv	SMILES + Interaction report	GPT-4o	CrossDocked2020	N/A
			LLM-EO (Lu et al., 2024)	Arxiv	SMILES + Ligands Pool	Claude 3.5 Sonnet / OpenAI o1-preview	TMC dataset	Link
			MOLLM (Ran et al., 2025)	Arxiv	SMILES + Instruction	GPT-4o	ZINC	N/A
			ChatDrug (Liu et al., 2024b)	ICLR	SMILES + Instruction	Galactica / LLaMA-2 / ChatGPT	ZINC	Link
			Re^{2}DF (Le and Chawla, 2024)	Arxiv	SMILES + Instruction	LLaMA-3.1-8B/ LLaMA-3.1-70B	ZINC	Link
			BOPRO (Agarwal et al., 2025)	ICLR	SMILES + Instruction	Mistral-Large-Instruct-2407	Dockstring	Link
	w/ Tuning	SFT	MultiMol (Yu et al., 2025)	Arxiv	SMILES + Instruction	Qwen2.5-7B / LLaMA-3.1-8B / Galactica 6.7B	PubChem	Link
			DrugAssist (Ye et al., 2025)	Brief Bioinform	SMILES + Instruction	LLaMA-2-7B-Chat	MolOpt-Instructions	Link
			GeLLM^{3}O (Dey et al., 2025)	Arxiv	SMILES + Instruction	Mistral-7B-Instruct / LLaMA-3.1-8B-Instruct	MuMOInstruct	Link
			DrugLLM (Liu et al., 2024c)	Arxiv	Group-based Molecular Representation	LLaMA-2-7B	ZINC & ChEMBL	N/A
			TOMG-Bench (Li et al., 2024a)	Arxiv	Instruction	LLaMa-3.1-8B	TOMG-Bench	N/A
			LLM-Enhanced GA (Bedrosian et al., 2024)	NeurIPS Workshop	JSON Objects	Chemma / Chemlactica	PubChem	Link
			Molx-Enhanced LLM (Le et al., 2024)	Arxiv	SMILES + Graph + Instruction	LLaMA-2-7B	PubChem	N/A
		Preference Tuning	NatureLM (Xia et al., 2025)	Arxiv	SMILES + Instruction	NatureLM-8B	ChEMBL & MoleculeNet	N/A