

Text-Guided Multi-Property Molecular Optimization with a Diffusion Language Model

Yida Xiong

yidaxiong@whu.edu.cn
School of Computer Science, Wuhan
University, Wuhan, China

Kun Li

li_kun@whu.edu.cn
School of Computer Science, Wuhan
University, Wuhan, China

Jiameng Chen

jiameng.chen@whu.edu.cn
School of Computer Science, Wuhan
University, Wuhan, China

Hongzhi Zhang

zhanghongzhi@whu.edu.cn
School of Computer Science, Wuhan
University, Wuhan, China

Di Lin*

lindi1015@163.com
Engineering Research Center for Big
Data Application in Private Health
Medicine of Fujian Universities,
Putian University, Putian, China

Yan Che*

ptucy07@126.com
Engineering Research Center for Big
Data Application in Private Health
Medicine of Fujian Universities,
Putian University, Putian, China

Wenbin Hu*

hwb@whu.edu.cn
School of Computer Science, Wuhan
University, Wuhan, China

ABSTRACT

Molecular optimization (MO) is a crucial stage in drug discovery in which task-oriented generated molecules are optimized to meet practical industrial requirements. Existing mainstream MO approaches primarily utilize external property predictors to guide iterative property optimization. However, learning all molecular samples in the vast chemical space is unrealistic for predictors. As a result, errors and noise are inevitably introduced during property prediction due to the nature of approximation. This leads to discrepancy accumulation, generalization reduction and suboptimal molecular candidates. In this paper, we propose a text-guided multi-property molecular optimization method utilizing **transformer-based diffusion language model (TransDLM)**. TransDLM leverages standardized chemical nomenclature as semantic representations of molecules and implicitly embeds property requirements into textual descriptions, thereby mitigating error propagation during diffusion process. By fusing physically and chemically detailed textual semantics with specialized molecular representations, TransDLM effectively integrates diverse information sources to guide precise optimization, which enhances the model’s ability to balance structural retention and property enhancement. Additionally, the success of a case study further demonstrates TransDLM’s ability to solve practical problems. Experimentally, our approach surpasses

state-of-the-art methods in maintaining molecular structural similarity and enhancing chemical properties on the benchmark dataset. The code is available at: <https://github.com/Cello2195/TransDLM>.

KEYWORDS

Drug Discovery, Multi-Property Molecular Optimization, Diffusion Language Model, Text Guidance

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1 INTRODUCTION

Molecule generation has made significant strides with the rapid advancement of generative models, especially conditional generative models [17, 26]. These models have demonstrated promising results during tasks such as drug response prediction (DRP) and drug–target binding affinity (DTA) [18, 27]. Although the molecules generated for specific tasks possess relevant properties, they are still insufficient for application to industrial production. As a result, optimizing generated molecules has become a crucial task, drawing the attention of scientists seeking to improve their usability. However, improving the desired drug candidate properties while retaining the original structural scaffolds is challenging. Moreover, the complexity of enormous chemical space highlights the substantial quantity of molecular candidates. Consequently, traditional molecular optimization (MO) methods primarily depend on the experience, knowledge and intuition of chemists, thus resulting in time-consuming manual labor and reducing the likelihood of finding ideal molecules within a limited time.

*Corresponding author

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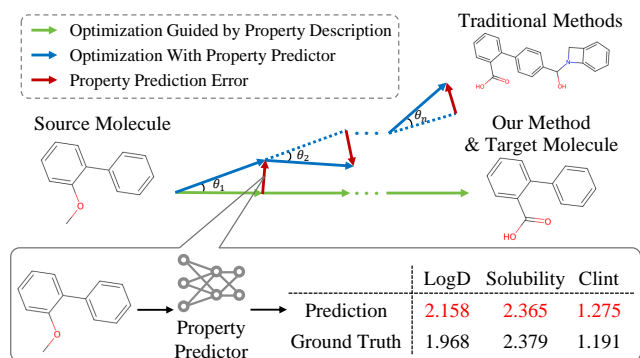


Figure 1: Overall comparison between traditional molecular optimization and text-guided molecular optimization with a diffusion language model. During property prediction, the propagation and accumulation of errors drastically disrupts the optimization process.

To address these challenges, early computational approaches using deep learning generated computational strategies to accelerate the traditional MO paradigm [31, 48]. These deep learning methods mainly learned from Simplified Molecular Input Line Entry System (SMILES), graphs and three-dimensional (3D) structures [4, 55, 56, 59]. To generate molecules with desired properties, conditional generative models [34, 38, 41] have been adopted as auxiliary controllers for the generative process. However, most of these models concentrate on generating molecules from scratch and optimizing them according to specific rules, thereby neglecting the priority of core scaffold retention during molecular optimization. Consequently, molecules optimized through these methods fail to meet the industrial demands, which requires slight changes to the molecular architecture and substantial increases in the desired properties.

Other widely adopted approaches include guided search-based methods, which aim to find target molecules by exploring compounds’ chemical or latent spaces derived from encoder–decoder models. First, latent space search involves encoding a source molecule into a low-dimensional representation, and exploring its adjacent area to find embeddings that meet the specified constraints [31, 33, 61]. Then, these embeddings are decoded into the chemical space, and a property predictor is used to guide the search process. In contrast, chemical space search methods operate directly within the high-dimensional and discrete chemical space to find molecules that meet given constraints. Various advanced optimization techniques, including reinforcement learning and genetic algorithms, have been applied to this search method.

Despite their proven success, a significant limitation of these guided search-based methods lies in their reliance on external property predictors to iteratively optimize molecular properties. As shown in Fig. 1, external predictors, though effective for estimating target properties, inherently introduce errors and noise due to the nature of approximation. Typically, these methods are trained on finite, often biased datasets and may lack complete generalization in novel chemical spaces, resulting in inaccurate property predictions

during the search process. This discrepancy can accumulate over iterations, leading to suboptimal molecular candidates or failure to meet the intended constraints. Moreover, the noise generated by these predictors may cause the search process to deviate from the optimal regions in the chemical or latent spaces, further reducing MO efficiency and effectiveness.

To address the aforementioned MO issues, we explore the utilization of diffusion models in target-oriented MO. Diffusion models [24] have reaped remarkable success in other scientific disciplines, such as computer vision [47], by generating high-quality data through a gradual denoising process that can capture complex distributions [57]. Accordingly, we propose text-guided multi-property molecular optimization with a transformer-based diffusion language model (**TransDLM**). This is a novel approach that leverages a diffusion language model to iteratively yield word vectors of molecular SMILES strings and is guided by language descriptions. Due to SMILES strings’ deficiency in explicit semantic clarity of molecular structures and functional groups, we adopt standardized chemical nomenclature as informatively and intuitively molecular semantic representation. To differentiate generation from scratch, we sample molecular word vectors from the token embeddings of source molecules encoded by a pre-trained language model, which collectively and significantly retains the original molecules’ core scaffolds. Instead of relying on an external property predictor, we encode the molecular structure and property information using a pre-trained language model, implicitly embedding property requirements into textual descriptions, guiding diffusion and mitigating error propagation. This encoded representation serves as a guiding signal during the diffusion process. By embedding the desired molecular properties through the language model, the diffusion process is trained on the molecule’s structure and the specific properties we aim to optimize. Furthermore, we successfully optimized the binding selectivity of xanthine amine congener (XAC) from A_{2A}R to A₁R, which are both adenosine receptors, using TransDLM, indicating its broader applicability in optimizing ligand–receptor interactions in drug discovery. The TransDLM approach’s advantages are as follows:

- Molecules generated by TransDLM retain the core scaffolds of source molecules and structural similarity is ensured while satisfying multiple property requirements.
- Error and noise propagation are reduced by directly training the model on the desired properties during diffusion, thereby improving the reliability of the optimized molecules.
- TransDLM outperforms state-of-the-art methods on the benchmark dataset in optimizing three ADMET¹ properties, *LogD*, *Solubility*, and *Clearance* while maintaining the structural similarity over several metrics. And TransDLM successfully biases XAC’s selectivity preference from A_{2A}R to A₁R.

2 RELATED WORK

This section provides an overview of the research landscape, focusing on different MO approaches and the role of diffusion models in language generation. These advancements establish the conditions for our novel diffusion language model application in the SMILES-based MO field.

¹Absorption, distribution, metabolism, excretion and toxicity

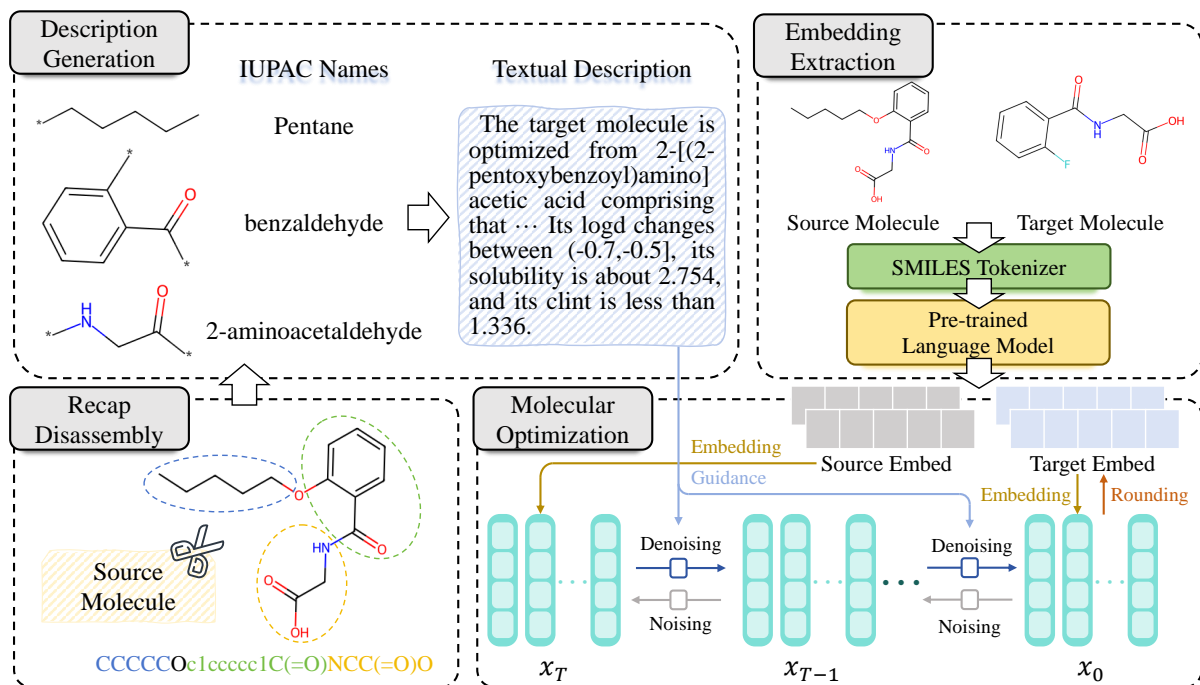


Figure 2: TransDLM framework. First, our optimization method disassembles the source molecules into fragments using the Recap strategy. Then, it generates textual descriptions utilizing IUPAC names, which guide the denoising process. Meanwhile, the source and target molecules are encoded into embeddings through the SMILES tokenizer and a pre-trained language model, which serve as initial and target vectors, respectively.

2.1 Molecular Optimization

Guided Search-Based Methods. Guided search-based methods explore target molecules within the molecules’ chemical or latent space learned through encoder–decoder models using molecular property predictors or statistical models for guidance [25]. For example, Jin et al. [31] introduced a junction tree variational autoencoder (JTVAE), which initially decomposes a molecular graph into a junction tree, and both the junction tree and molecular graph are mapped to latent embeddings. Finally, gradient ascent is used to identify embeddings with enhanced property scores within the latent space. Zhou et al. [62] proposed the MolDQN model, which integrates reinforcement learning with chemical rules to guarantee molecular validity. The model frames molecule modification as a Markov Decision Process (MDP) and uses deep Q-networks [23] to address it. Nevertheless, these guided search-based methods rely on external property predictors to iteratively optimize molecular properties, inevitably introducing errors and noise into the optimization process.

Molecular Mapping-Based Method. Two molecules with moderate structural difference and significant chemical dissimilarities are considered as a matched molecular pair (MMP), where the one with inferior properties is regarded as the source molecule and the other with desired qualities is the target molecule. Molecular

mapping-based method is usually executed using medicinal chemistry transformation rules derived from MMPs, applying the knowledge and expertise of medicinal chemists. For instance, He et al. [21] designed a model based on Seq2Seq architecture to handle property variations between MMPs. The model uses source molecules and property constraints as inputs and is trained to produce target molecules as outputs. Maragakis et al. [40] introduced DESMILES, which utilizes source molecular fingerprints as inputs to generate corresponding SMILES representations. Initially, the transformation from molecular fingerprints to SMILES is pre-trained on a large dataset, and the model is subsequently fine-tuned using the MMPs. Inspired by natural language processing (NLP), Fan et al. [10] developed a semi-supervised approach named BT4MolGen. This method involves training a pseudo-labeled data generation model using MMPs. Then, the generated pseudo-labeled data along with labeled data are employed to train a forward molecular optimization model, addressing the data sparsity issue.

2.2 Language Generation with Diffusion Models

Diffusion models have been extremely successful in generating content in continuous domains, particularly in the images and audio fields [57]. Stable Diffusion [47] and AudioLDM [39] are categorized as diffusion models in continuous domains. They introduced random noises into latent variables based on latent diffusion models

(LDMs) and reverse the process through a series of denoising steps to learn data generation. However, differences in data structure between languages and images exist, since languages are discrete while images exist in continuous domains. In order to tackle this problem, certain approaches retain the discrete nature of text and extend diffusion model to handle discrete data [22, 45]. On the contrary, other methods utilize embedding layers to map the text to a continuous representation domain, thereby preserving the continuous diffusion steps [15, 37, 60]. Our research aligns with the latter strategy, focusing on word vectors and substantially expanding the functionality and feasibility of diffusion models in SMILES-based MO.

3 METHODOLOGY

3.1 Overall Framework

With the solid foundation paved by conditional language generation tasks, exemplified by DiffuSeq [15] and SeqDiffuSeq [60], exploring text-guided MO has become feasible. In this paper, we aim to optimize a molecule until it matches a specified textual description. Formally, let $C = [w_0, w_1, \dots, w_m]$ represent the input description, where w_i is the i -th word in the sequence, and m denotes the text length. Our objective is to develop a model $F(\cdot)$ that takes this text and the original molecule M_0 as input and produces the corresponding molecule as output, which can be mathematically represented as $M = F(M_0, C)$. Overall, our TransDLM is composed of four pivotal processes: embedding, noising, denoising, and rounding. As shown in Fig. 2, these processes work in tandem to produce the desired optimized molecules.

The embedding process begins by treating the text sequence $W = [w_0, w_1, \dots, w_n]$ as an ordered list of words. Each word w_i is mapped using an embedding function, yielding $\text{Emb}(W) = [\text{Emb}(w_0), \text{Emb}(w_1), \dots, \text{Emb}(w_n)] \in \mathbb{R}^{d \times n}$, where n indicates the sequence length and d represents the embedding dimension. Then, the noising process starts with the matrix x_0 , which is sampled from a Gaussian distribution centered at $\text{Emb}(W)$: $x_0 \sim \mathcal{N}(\text{Emb}(W), \sigma_0 \mathbf{I})$.

During the noising process, noise is gradually introduced to x_0 , eventually resulting in pure Gaussian noise $x_T \sim \mathcal{N}(0, \mathbf{I})$, where T is a hyperparameter of total diffusion steps. The transition from x_{t-1} to x_t is defined as follows:

$$q(x_t | x_{t-1}) = \mathcal{N}(x_t; \sqrt{1 - \beta_t} x_{t-1}, \beta_t \mathbf{I}), \quad (1)$$

where β_t is a hyperparameter representing the amount of noise added at diffusion step $t \in (0, T]$.

Next, the denoising process begins with an encoded source molecule, and sequentially samples x_{t-1} from x_t , gradually reconstructing the desired content. Typically, a neural network is trained to predict x_{t-1} given x_t . To improve the accuracy of denoising x_t towards specific word vectors, a neural network $f_\theta(\cdot)$ is trained to predict x_0 directly from x_t . Thus, the denoising transition from x_t to x_{t-1} can be expressed as:

$$p_\theta(x_{t-1} | x_t) = \mathcal{N}(x_{t-1}; \mu_\theta(x_t, t, C), \Sigma_t) \quad (2)$$

$$\mu_\theta(x_t, t, C) = \frac{\sqrt{\bar{\alpha}_{t-1}} \beta_t}{1 - \bar{\alpha}_t} f_\theta(x_t, t, C) + \frac{\sqrt{\bar{\alpha}_t} (1 - \bar{\alpha}_{t-1})}{1 - \bar{\alpha}_t} x_t$$

where $\Sigma_t = \frac{1 - \bar{\alpha}_{t-1}}{1 - \bar{\alpha}_t} \beta_t$ is the covariance matrix, and $\bar{\alpha}_t = \prod_{s=0}^t (1 - \beta_s)$, facilitating the iterative sampling of x_{t-1} from x_t and consequently yielding x_0 .

Finally, the rounding process converts the embedding vectors back into the target molecule’s SMILES string. During this process, each column vector x_0 is matched to the word with an embedding that has the closest L-2 distance. As a result, the combined denoising and rounding processes effectively transform any initial distribution into a coherent SMILES string output.

3.2 Description Generator

Molecular Structure Feature. Molecular structure feature effectively enhances insights into molecules and model performance in specific tasks [7, 11, 54]. Among them, fragment-based molecular structure feature has garnered substantial attention from researchers [16, 58]. Accordingly, we disassemble molecules using Recap [36], which cleaves the structures into fragments based on retrosynthetic chemistry. Once key fragments are recognized as essential for chemical reactivity by Recap, they can easily be divided into latent blocks for optimization. After molecular disassembly, we concentrate on how the fragments connect with each other. RDKit² is an open-source Python software package providing chemical information. We use its built-in functions to determine the binding sites and connection modes between fragments.

IUPAC Nomenclature in Organic Chemistry. The international union of pure and applied chemistry (IUPAC) [29] nomenclature system provides standardized naming conventions for chemical compounds, which is crucial for avoiding ambiguities arising from common or trivial names. This is particularly crucial in organic chemistry, where compound complexity can make identification challenging. When optimizing molecules guided by textual descriptions, we use the IUPAC names instead of SMILES strings to represent fragments, simultaneously complementing IUPAC information of the source molecules as molecular semantic representations. As shown in Fig. 3, on the one hand, IUPAC names provide a detailed and hierarchical description of a molecule’s structure, including functional groups, stereochemistry, branching, and chain length. This level of granularity can potentially enhance the precision of the generative process, especially when targeting specific chemical properties or structures. On the other hand, IUPAC nomenclature conventions provide more semantic information compared to SMILES. This is because they are more structured and descriptive than SMILES strings which feature a linear text format merely based on connectivity. The rich semantic details allow IUPAC names to convey more precise chemical information, making them more interpretable and suitable for language models that benefit from understanding chemical semantics.

Textual Description Generation. In addition to physical structure information, we consider the desired optimized chemical properties. Specifically, the original numerical property values and the changes between MMPs are supplemented into one textual description. Utilizing the above tools, we generate a textual description saturated with detailed molecular structure and rich semantic information. The grammatical template for textual description is as below:

²<https://www.rdkit.org>

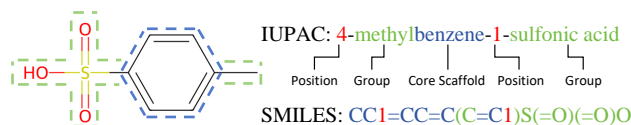


Figure 3: An example of IUPAC name vs. SMILES. The IUPAC name provides clearer semantics by specifying functional groups and their positions, while SMILES focuses on structure without conveying the same intuitive meaning.

The target molecule is optimized from [IUPAC name of source molecule] comprising that [IUPAC name of fragment 1] and [IUPAC name of fragment 2] links via a [bond type] bond, ... Its [property 1] [change verb + value/range], [property 2] [change verb + value/range] ...

For instance, the target molecule C#CCOC(=O)c1ccccc1O can be described as: *The target molecule is optimized from ethyl 2-hydroxybenzoate comprising that ethanol and 2-hydroxybenzaldehyde links via a O C SINGLE bond. Its logd changes between (0.3, 0.5], its solubility is about 2.442, and its clint is less than 1.904.*

3.3 SMILES Tokenizer

Inspired by Gong et al. [14] who considered the fact that tokenizing every single character of a SMILES string destroys the uniformity between multi-character units, we employ the same strategy to retain the semantic groups in SMILES strings. For instance, [CH3-] is a negatively charged methyl group rather than a sequence assembled by unrelated characters, such as [C], and H. With all the semantic groups together forming our vocabulary, TransDLM is capable of encoding any SMILES string semantically and integrally, like CC([Si]=O)C[CH3-] being encoded as [[SOS],C,C,([Si]=O),C,[CH3-],[EOS],[PAD],...,[PAD]]. And we pad each sequence to the maximum length n .

Following tokenization, the resulting tokenized molecule M is prepared for the embedding process, yielding x_0 through sampling from the distribution $x_0 \sim \mathcal{N}(\text{Emb}(M), \sigma_0 \mathbf{I})$.

3.4 Text-Guided Molecular Optimization

Unlike traditional diffusion models that sample from pure noise [37, 47], we propose a novel generation strategy for TransDLM, which samples from an encoded source molecule SMILES string, as mentioned in Chapter 3.3. Our approach effectively addresses the uncertainty and infeasibility of previous MO methods and adjusts the orientation to the desired optimized molecules.

For the purpose of converting textual description into machine-readable language, a pre-trained language model is utilized to map the text sequence C to its latent embeddings $C \in \mathbb{R}^{d_1 \times m}$, where d_1 represents the embedding dimension of the language model output. Our model is based on transformer backbone, which functions as $f_\theta(\cdot)$ in Eq. 2. Considering the current diffusion state x_t , time step t , and text embeddings C , the initial state x_0 is predicted as $\hat{x}_0 = f_\theta(x_t, t, C)$. Given that self-attention mechanism is disordered, the transformer architecture does not inherently have the location information. Hence, the transformer loses the input’s sequential information. As a result, we adopt a position encoding strategy [53]

in the first layer $z_t^{(0)}$ to enable our model to recognize the position of each element in the input sequence, defined as:

$$z_t^{(0)} = \text{PosEmb} + W_{in}x_t + \text{TimeEmb}(t), \quad (3)$$

where PosEmb is the positional embedding, $\text{TimeEmb}(\cdot)$ is an operation to embed the time step t into a high-dimensional vector, $W_{in} \in \mathbb{R}^{d_2 \times d}$, $z_t^{(0)} \in \mathbb{R}^{d_2 \times n}$, and d_2 is the dimension for transformer.

In the standard transformer self-attention mechanism, each token performs attention calculations on others in the same input sequence. Therefore, to improve the multi-modal data processing capability of our model and enhance the positive guidance of textual description to MO, TransDLM uses the cross-attention mechanism to calculate the input sequence with textual description as an additional context. Specifically, our transformer backbone is composed of L layers with a cross-attention block respectively, which incorporates the textual description into the hidden states as follows:

$$\begin{aligned} \text{Attention}(Q, K, V) &= \text{softmax}\left(\frac{QK^T}{\sqrt{d_k}}\right)V, \\ Q &= W_Q^{(i)} z_t^{(i)}, \\ K &= W_K^{(i)} \text{MLP}(C), \\ V &= W_V^{(i)} \text{MLP}(C), \end{aligned} \quad (4)$$

where $W_*^{(i)} \in \mathbb{R}^{d_2 \times d_2}$ represents the learnable parameters in the i -th layer, and $\text{MLP}(\cdot)$ is the multilayer perception.

After completing the above procedures, we obtain the matrix \hat{x}_0 from the initial embedded source molecule, guided by the textual description C . Then, the matrix \hat{x}_0 is prepared for rounding and subsequently transformed into a SMILES string.

3.5 TransDLM Training

During the training process, our methodology mainly maximizes the variational lower bound (VLB) of the marginal likelihood. Moreover, we refine and adapt our approach according to the insights from previous studies [24, 37]. We primarily aim to train $f_\theta(\cdot)$ to progressively reconstruct the desired data x_0 at every time step within the denoising diffusion trajectory, described as:

$$\mathcal{L}_{M,C} = \mathbb{E}_{q(x_{0:T}|M)} \left[\sum_{t=1}^T \|f_\theta(x_t, t, C) - x_0\|^2 - \log p_\theta(M | x_0) \right], \quad (5)$$

where $p_\theta(M | x_0)$ represents the rounding process, featuring a product of the softmax distribution $p_\theta(M | x_0) = \prod_{i=0}^n p(a_i | x_{0[:i]})$.

By iteratively refining the noisy intermediate states to optimized forms, the TransDLM learns to effectively reverse the diffusion process, leveraging underlying data structure and guiding text.

4 THEORETICAL ANALYSIS

This section theoretically demonstrates that text-guided multi-property MO based on diffusion language models is more effective in reducing errors than traditional methods that use external property predictors to constrain optimization.

4.1 Error Propagation in Traditional Methods

Usually, the optimization process of traditional methods involves Z iterations. The estimated property values per round using an external predictor is $\hat{y}_z = y_z + \epsilon_z$, where $\epsilon_z \sim \mathcal{N}(0, \sigma^2)$ is the prediction error. Since the optimization direction is determined by the gradient $\nabla_{\theta} \mathcal{L}(\hat{y}_z)$, the parameters are updated to $\theta_{z+1} = \theta_z - \eta \nabla_{\theta} \mathcal{L}(\hat{y}_z)$. Consequently, the projection of error in the gradient direction is:

$$\Delta_z = \nabla_{\theta} \mathcal{L}(y_z) - \nabla_{\theta} \mathcal{L}(\hat{y}_z) \approx \epsilon_z \cdot \nabla_{\theta}^2 \mathcal{L}(\hat{y}_z). \quad (6)$$

Assuming the upper bound of the spectral radius of the Hessian matrix is H , the cumulative error can be expressed as follows:

$$\mathcal{E}_{\text{trad}} \leq \sum_{z=1}^Z \eta H |\epsilon_z| \sim O(Z \eta H \sigma), \quad (7)$$

which implies that $\mathcal{E}_{\text{trad}}$ will increase linearly with the number of iterations Z , leading to a substantial deviation of the final optimization direction from the theoretically optimal value.

4.2 Error Suppression Mechanism of TransDLM

On the contrary, TransDLM exhibits exceptional error suppression capabilities. The generation distribution at each time step t is given by $\mathcal{N}(\mu_{\theta}(x_t, t, C), \Sigma_t)$, where μ_{θ} is influenced by text condition C , and Σ_t represents a fixed value. The error associated with TransDLM arises from the deviation in predicting x_0 , expressed as $\delta_t = \hat{x}_0^{(t)} - x_0$. Consequently, the discrepancy between the actual generated value x_{t-1} and its ideal counterpart x_{t-1}^* is:

$$\Delta x_{t-1} = \mu_{\theta} - \mu^* = \frac{\sqrt{\alpha_t - 1} \beta_t}{1 - \alpha_t} \delta_t. \quad (8)$$

Notably, as outlined in the diffusion scheduling design [24], the coefficient $\gamma_t = \frac{\sqrt{\alpha_t - 1} \beta_t}{1 - \alpha_t} < 1$, indicating that the propagation of error δ_t is significantly attenuated.

Due to the Markovian nature of the diffusion process [3], x_{t-1} is solely dependent on x_t and the currently predicted value of x_0 . The influence of errors on subsequent steps is expressed as follows:

$$\begin{aligned} \Delta x_{t-1} &\propto \gamma_t \delta_t \\ \Delta x_{t-2} &\propto \gamma_t \gamma_{t-1} \delta_t + \gamma_{t-1} \delta_{t-1} \\ &\dots \end{aligned} \quad (9)$$

As a consequence, the cumulative error of TransDLM is:

$$\mathcal{E}_{\text{ours}} \propto \sum_{t=1}^T \left(\prod_{s=1}^t \gamma_s \right) \delta_t. \quad (10)$$

Due to the exponential decay of $\prod_{s=1}^t \gamma_s$ with respect to t , error propagation is effectively suppressed.

4.3 Comparative Analysis

For traditional methods, error propagation is characterized as a random walk process. On the contrary, in the TransDLM framework, errors not only accumulate independently due to the fixed covariance matrix Σ_t , but also the series presented in Eq. 10 converge owing to the condition $\gamma_s < 1$. Assuming the variance of single-step

errors for both methods is σ^2 , we can readily derive the total error variance for each approach:

$$\text{Var}(\theta_Z) = \sum_{z=1}^Z \text{Var}(\Delta_z) = Z^2 \eta^2 H^2 \sigma^2 \sim O(Z^2 \sigma^2) \quad (11)$$

$$\text{Var}(x_0) = \sum_{t=1}^T \left(\prod_{s=1}^t \gamma_s \right) \sigma^2 \leq T \sigma^2 \sim O(T \sigma^2) \quad (12)$$

For traditional methods relying on external property predictors, the total variance exhibits a quadratic growth pattern with respect to the number of optimization steps Z . This implies that as the optimization process is extended, error accumulation becomes more pronounced compared to TransDLM, resulting in substantial deviations from the optimal solution. In contrast, TransDLM benefits from an inherent error suppression mechanism within its diffusion framework, which ensures that accumulated errors remain significantly lower than those observed in traditional approaches. The derivation presented above offers robust theoretical evidence that TransDLM effectively mitigates error propagation, thereby ensuring a more stable and reliable multi-property MO process.

5 EXPERIMENTS

5.1 Dataset

Based on our research purpose, our evaluation centers on an MMP dataset [21], which is currently the sole publicly available dataset and includes 198,558 source–target molecule pairs with their ADMET properties. We randomly split the whole dataset into 90% as training and validation, and 10% as test, and further split the former into 90% as training and 10% as validation, with ensuring that the random seed and dataset partitioning for all experiments is consistent.

5.2 Metrics

Following the previous work outlined by Edwards et al. [9], we employed eight metrics to assess the structural construction abilities and six criteria to evaluate property optimization capabilities.

- **SMILES BLEU** [43] score and **Levenshtein** [42] distance. These metrics evaluate the syntactic similarity and the distance between the optimized and target SMILES strings.
- **MACCS** [8], **RDKit** [49], and **Morgan FTSS** [46]. These metrics calculate the average Tanimoto similarity between the fingerprints of the optimized and target molecules.
- **Exact match and Validity**. We measure the proportions of optimized molecules identical to the target molecules and syntactically valid molecules that can be processed by the RDKit [35].
- **FCD** [44] metric. The FCD metric leverages the penultimate layer of a pre-trained network called ChemNet, which incorporates chemical and biological information for more sophisticated comparisons.
- **Accuracy of ADMET property changes**. According to the dataset, the property changes are categorized into *decrease*, *increase*, and *remain*. A property prediction model [30] trained on ADMET properties in the MMP dataset is utilized to predict the optimized molecules' corresponding properties.

Table 1: Optimization results for structural similarity compared with baseline models on the test split of MMP dataset. Bold indicates the best scores.

	BLEU↑	Exact↑	Levenshtein↓	MACCS↑	RDKit↑	Morgan↑	FCD Metric↓	Validity↑
MIMOSA	0.717	0	16.24	0.806	0.788	0.637	0.194	1
Modof	0.25	0.001	38.316	0.752	0.786	0.553	6.615	1
MolSearch	0.522	0.001	27.683	0.678	0.646	0.468	1.355	1
FRATTVAE	0.263	0	36.7	0.459	0.351	0.155	17.972	0.859
DyMol	0.369	0	35.728	0.406	0.365	0.254	5.155	1
TransDLM (Ours)	0.74	0.009	14.838	0.818	0.792	0.665	0.109	0.993

Table 2: Optimization results for ADMET properties compared with baseline models on the test split of MMP dataset. The criterion 'All' indicates the ratio of optimized molecules satisfying all property requirements.

Model	LogD↑	Solubility↑	Clint↑	All↑	HV↑	R2↓
MIMOSA	0.1	0.765	0.755	0.075	0.911	0.141
Modof	0.08	0.615	0.733	0.044	0.908	0.145
MolSearch	0.06	0.706	0.746	0.039	0.923	0.136
FRATTVAE	0.044	0.663	0.745	0.026	0.865	0.214
DyMol	0.041	0.58	0.722	0.023	0.876	0.207
TransDLM (Ours)	0.157	0.783	0.757	0.11	0.929	0.121

Then, the accuracy of property change type between the optimized and source molecules is calculated to convey the model’s optimization ability toward the desired orientation.

- **HV** and **R2** indicator. The hypervolume indicator (HV) [63] measures the volume covered by the Pareto front solutions in the objective space relative to a reference point, while the R2 indicator [2] assesses the Pareto front’s performance under different preference weightings. We use these indicators to determine whether the optimized molecules are a desirable solution set on quantitative estimate of drug-likeness (QED) and synthetic accessibility score (SA).

5.3 Baselines

Five baselines were selected, encompassing autoregressive models, deep generative models and variational autoencoder (VAE) models.

1. **MIMOSA** [13]. This model uses their prediction tools and employs sub-structure operations to generate new molecules.
2. **Modof** [5]. A pipeline of multiple and identical Modof models modify an input molecule at predicted disconnection sites.
3. **MolSearch** [52]. This framework uses a two-stage search strategy to modify molecules based on transformation rules derived from compound libraries.
4. **FRATTVAE** [28]. A fragment tree-transformer based VAE model is trained for the MO task.
5. **DyMol** [51]. This is a divide-and-conquer approach combined with a decomposition strategy for multi-property optimization.

It is worth noting that all competing approaches optimize molecules guided by the external property predictors.

5.4 Experiment Settings

The SMILES vocabulary included 265 tokens, with token embeddings being trainable at $d = 32$. We used a pre-trained SciBERT

model [1] with an embedding dimension of $d_1 = 768$ to encode the textual descriptions. Moreover, the core transformer architecture, $f_\theta(\cdot)$, consists of $L = 12$ layers with a hidden dimension of $d_2 = 1024$. Our TransDLM has around 181 million trainable parameters.

For the MO task, we used a uniform step-skipping strategy during the denoising process, which reduced the sampling steps from 1,000 to 200. As a result, optimizing a molecule takes approximately 1.02 seconds on an AMD EPYC 7763 (64 cores) @ 2.450GHz CPU and a single NVIDIA A6000 GPU. During training, we set the total diffusion steps to $T = 2000$. The Adam optimizer’s [32] learning rate was $5e^{-5}$, and we included a linear warm-up.

5.5 Overall Performance and Visualization

As shown in Tables 1 and 2, TransDLM mostly outperformed all baseline models across multiple evaluation metrics, demonstrating its superiority in multi-property MO. Although some baselines excelled in validity, they performed poorly in other metrics, which demonstrates limitations. Specifically, TransDLM achieved the best BLEU score and an 11.8% improvement in Levenshtein distance, indicating better alignment with the target molecules’ structures and higher sequence accuracy. Most advantages on FTS criteria further highlighted its ability to capture molecular fingerprints, providing deeper insights into the molecule’s structural information. Notably, we observed a 78% improvement in FCD, which indicates that TransDLM generated molecules with closer distributions to the training data, thereby outperforming other methods. Regarding ADMET properties, drastic *LogD*, *Solubility*, and *Clint* improvements by 57%, 2.4% and 0.3%, resulted in a remarkable 46.7% increase in the ratio of optimized molecules that met all ADMET property criteria. Additionally, TransDLM outperformed all competing methods across HV and R2 indicators on QED and SA, indicating our approach can stably and comprehensively generate high-quality

Table 3: Optimization results for structural similarity compared with ablation studies on the test split of MMP dataset. Additionally, TransDLM_{noise} and TransDLM_{SMILES} respectively denote sampling from pure noise and optimizing guided by SMILES string-based descriptions.

	BLEU↑	Exact↑	Levenshtein↓	MACCS↑	RDKit↑	Morgan↑	FCD Metric↓	Validity↑
TransDLM	0.74	0.009	14.838	0.818	0.792	0.665	0.109	0.993
TransDLM _{noise}	0.694	0.011	16.868	0.779	0.707	0.587	0.211	0.895
TransDLM _{SMILES}	0.537	0.001	21.919	0.628	0.486	0.404	2.353	0.427

Table 4: Optimization results for ADMET properties compared with ablation studies on the test split of MMP dataset.

Model	LogD↑	Solubility↑	Clint↑	All↑	HV↑	R2↓
TransDLM	0.157	0.783	0.757	0.11	0.929	0.121
TransDLM _{noise}	0.16	0.789	0.757	0.108	0.927	0.124
TransDLM _{SMILES}	0.038	0.756	0.753	0.025	0.912	0.127

and practically feasible candidate molecules. These results highlight TransDLM’s advantage in balancing structural fidelity with functional optimization, making it a more effective approach for multi-property MO.

To further validate that TransDLM genuinely satisfies the MO goal of moderate structural disparities [20, 62] and substantial chemical dissimilarities, we visualized some representative results in Fig. 4.

In the first two examples, the two MMPs underwent one atom and one functional group substitution. TransDLM precisely identified the site that needed replacement and carried out structural modifications, fulfilling all ADMET property requirements under the guidance of the textual descriptions. In examples where TransDLM did not fully recognize all modification sites, such as the third example, TransDLM also maintained the core scaffold of the source molecule effectively, fulfilling the requirements of chemical properties without overly modifying the physical structure. In contrast, other methods either significantly disrupted the original molecule’s structure or failed to meet the chemical properties required by MMPs, underscoring their limitations.

5.6 Ablation Study

We performed two ablation studies to validate the effectiveness of the TransDLM strategies, as outlined below:

- During description generation, we substituted IUPAC names with original SMILES strings to demonstrate that the former carry more semantic information.
- During the denoising process, we directly sampled from pure noise instead of the encoded source molecules to validate the latter is efficacious for retaining the scaffolds of source molecules.

As shown in Tables 1 and 2, optimization guided by descriptions made of IUPAC names displayed a better performance than of original SMILES strings. This implies that IUPAC nomenclature conveys more physical and chemical semantics information which benefits text-guided MO. Similarly, though sampling from the encoded source molecules sacrificed few advantages on property criteria, it generated superior outcomes for most structural metrics than

from pure noise, indicating that our sampling strategy optimizes molecules without destroying the original scaffolds.

5.7 Case Study Analysis

In this section, we present the application of TransDLM through a case study involving XAC, a ligand recognized for its dual binding affinity to A₁R and A_{2A}R receptors [6]. The primary objective of this optimization was to modulate the binding affinities of XAC to enhance its selectivity toward the A₁R receptor while reducing its affinity for A_{2A}R. The optimization process entailed optimizing XAC conforming to the specified binding affinity textual description. To validate the effectiveness of the optimization, we utilized Schrödinger³, a professional molecular docking software, to evaluate the docking scores between both the original XAC molecule and its optimized counterpart with the A₁R and A_{2A}R receptors.

We located potential binding sites utilizing Schrödinger’s SiteMap tool [19] with a cubic exploration grid (15 Å × 15 Å × 15 Å) centered on the receptor’s critical functional areas. The XAC was processed through LigPrep, where protonation states were generated at pH 7.0 ± 2.0 using Epik (up to 32 states per ligand) [50]. Molecular docking was subsequently carried out with the Glide module in Maestro [12], and docking scores for each pose were automatically computed to identify the most favorable binding conformations.

The yielded docking scores aligned well with our expectations, as illustrated in Fig. 5. Specifically, the optimized XAC showed a significantly higher docking score for A₁R and a lower one for A_{2A}R compared to the original molecule. This outcome confirms that our optimization successfully achieved the desired preferential binding.

Notably, optimizing the binding affinities between ligands and proteins is entirely an out-of-distribution task with TransDLM trained on MMP dataset. Therefore, it is reasonable to assert that if TransDLM were trained on a broader range of diverse datasets, it could achieve superior optimization results in drug discovery.

³<https://www.schrodinger.com>

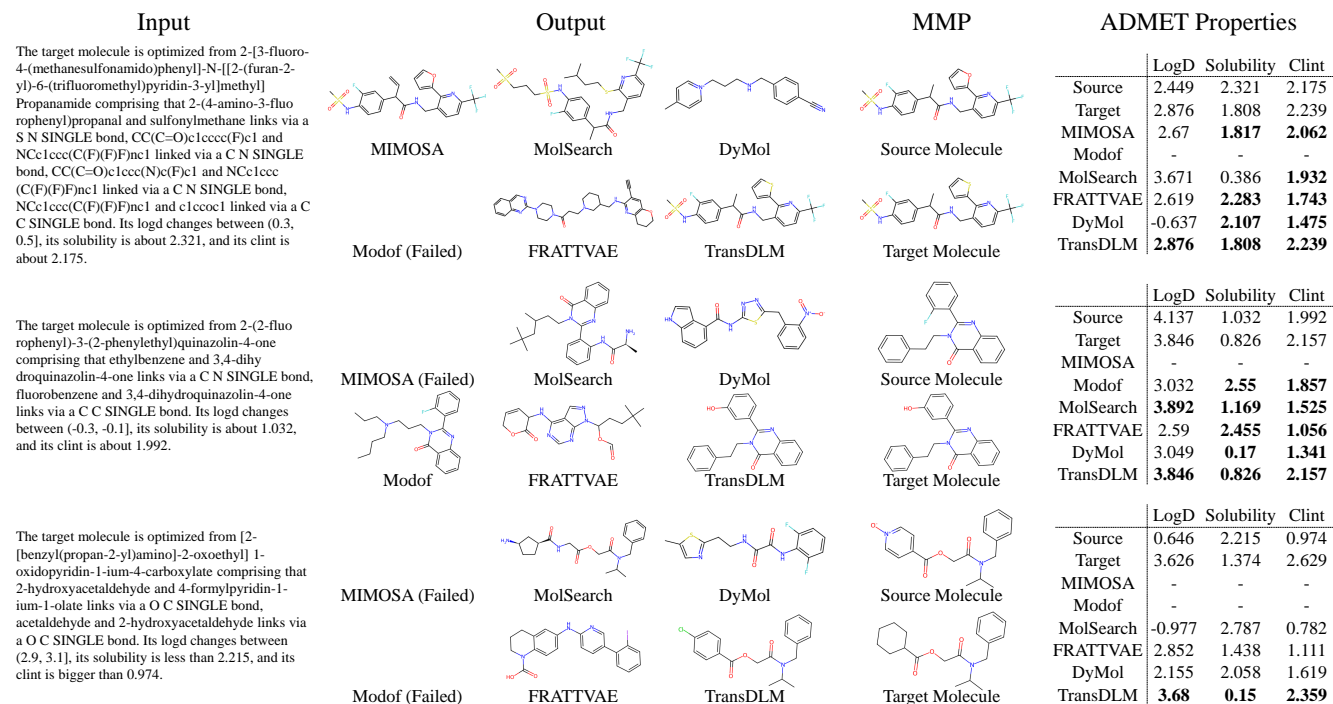


Figure 4: Examples of molecules optimized by different models with the same input textual descriptions. For clearer visualization, the generated SMILES strings are transformed into molecular graphs. Bold indicates that the optimized molecule satisfies the corresponding property requirement.

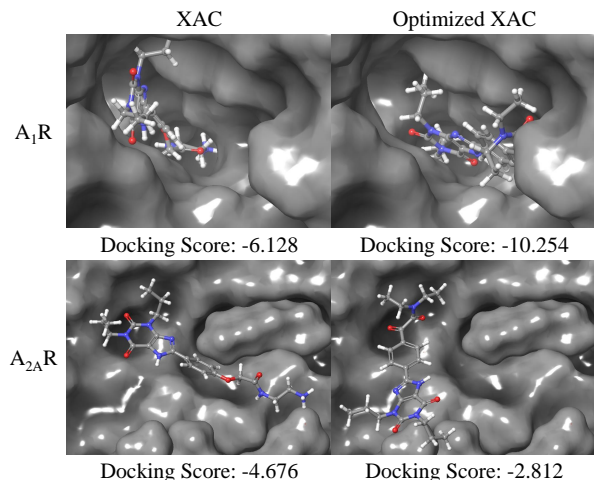


Figure 5: Visualization of XAC and optimized XAC binding to A₁R and A_{2A}R. The lower the docking score, the greater the binding affinity..

6 CONCLUSION

In this paper, we proposed TransDLM, a novel diffusion language model for text-guided MO, which utilizes IUPAC nomenclature for molecular semantic representation and optimizes molecules

guided by physically and chemically detailed textual descriptions. To retain the core scaffolds of source molecules, TransDLM samples from the encoded source molecules. Moreover, instead of relying on an external property predictor, error propagation was greatly mitigated during diffusion process. Additionally, we theoretically demonstrated TransDLM’s effectiveness and performed validation experiments. Notably, TransDLM outperformed other methods on most structural metrics and all ADMET property criteria, demonstrating robust structural construction and property enhancement capabilities. Notably, the successful optimization of XAC using TransDLM underscores its effectiveness in out-of-distribution problems. Furthermore, these achievements occurred without relying on additional data sources or pre-training, underscoring the effectiveness of TransDLM in text-guided multi-property MO.

In future research, TransDLM will be extended to other types of property optimization, such as non-biological properties represented by QED and SA, affinity for specific protein targets, etc. Additionally, we aim to enhance TransDLM’s generalizability by training it on more diverse datasets, including larger and more varied molecular libraries, to improve its performance on out-of-distribution tasks. These advancements will further strengthen TransDLM’s applicability in drug discovery and other chemical engineering domains, paving the way for more efficient and targeted molecular optimization.

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