

ScaffoldGPT: A Scaffold-based GPT Model for Drug Optimization

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Abstract

Drug optimization has become increasingly crucial in light of fast-mutating virus strains and drug-resistant cancer cells. Nevertheless, it remains challenging as it necessitates retaining the beneficial properties of the original drug while simultaneously enhancing desired attributes beyond its scope. In this work, we aim to tackle this challenge by introducing SCAFFOLDGPT, a novel Generative Pretrained Transformer (GPT) designed for drug optimization based on molecular scaffolds. Our work comprises three key components: (1) A three-stage drug optimization approach that integrates pretraining, finetuning, and decoding optimization. (2) A novel two-phase incremental pre-training strategy for scaffold-based drug optimization. (3) A token-level decoding optimization strategy, TOP-N, that enabling controlled, reward-guided generation using the pretrained or finetuned GPT. We demonstrate via a comprehensive evaluation on COVID and cancer benchmarks that SCAFFOLDGPT outperforms the competing baselines in drug optimization benchmarks, while excelling in preserving original functional scaffold and enhancing desired properties.

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1. Introduction

The rise of rapidly mutating virus strains (Hadj Hassine, 2022), exemplified by those related to SARS-CoV-2 (Yuki et al., 2020), along with drug-resistant cancer cells (Mansoori et al., 2017), has heightened the urgency and interest in accelerating the development of effective treatments. However, traditional De Novo drug discovery processes are prohibitively expensive, often costing from hundreds of millions to billions of dollars (Dickson and Gagnon, 2009), due to their extensive and resource-demanding nature. Despite considerable efforts, the success rate of drug discovery remains low, with many candidates failing early in the development process. This has led to an increased focus on drug repurposing, which leverages existing FDA-approved drugs for new therapeutic uses rather than creating new drugs from scratch. While drug repurposing has seen some success (Pushpakom et al., 2019), its effectiveness is often constrained because drugs are typically developed with a high specificity for a particular disease.

Drug optimization seeks to overcome the limitations inherent in both De Novo drug discovery and drug repurposing by enhancing an existing FDA-approved drug. Drug optimization is becoming an increasingly vital field, yet it remains relatively underexplored compared to drug discovery and repurposing efforts. DrugImprover (Liu et al., 2023a) has started to clearly define the drug optimization problem by using Tanimoto similarity. Additionally, the DrugImprover framework contributes to the drug optimization domain in three key aspects: a detailed workflow for drug optimization, an Advantage-alignment Policy Optimization (APO) reinforcement learning (RL) algorithm to enhance the multi-objective generative model for drug optimization, and an extensive dataset featuring 1 million ligands and their OEDOCK scores for five proteins related to human cancer cells and 24 high-affinity binding sites on the SARS-CoV-2 protein 3CLPro (PDB ID: 7BQY). The DrugImprover framework features a pretrained generative model that is subsequently refined using the APO reinforcement learning algorithm to ensure the molecules produced align with new objectives. Although DrugImprover has demonstrated encouraging outcomes, its effectiveness is limited due to its dependence on the less complex LSTM network architecture, which might lead to limited scalability and capacity, contextual understanding.

On the other hand, generative pretrained language models have shown exceptional performance in diverse areas, from natural language understanding and generation exemplified by ChatGPT (Wu et al., 2023; Ouyang et al., 2022), to text-to-video conversion as seen in SORA (Liu et al., 2024d), and in programming and code generation through platforms like PG-TD (Zhang et al., 2023a) and Copilot (Nguyen and Nadi, 2022). Nevertheless, in the field of drug discovery, tools such as DrugGPT (Li et al., 2023), ChatDrug (Liu et al., 2024a) and ChemGPT (Frey et al., 2023), despite making some initial strides, have not yet achieved performance on par with their counterparts in other domains. The field of drug discovery remains in expectation of breakthroughs similar to the ones achieved by LMs in other domains.

Several challenges have hindered the impact of Language Models (LMs) on drug design: Firstly, the molecules created need to satisfy multiple criteria such as solubility and synthesizability, and must also secure a high docking score against a specific target site (Liu et al., 2024b). However, existing drug discovery LMs generally only undergo pretraining with molecules and do not focus on enhancing multiple attributes simultaneously. Secondly,

given that drugs sharing similar chemical structures tend to exhibit comparable biological or chemical effects (Bender and Glen, 2004), it is crucial to optimize the drug while preserving the beneficial chemical structure of the original molecule. Lastly, the current methodologies in drug discovery LMs primarily focus on maximizing likelihood during the decoding phase, rather than customizing the optimization process to meet specific goals.

REINVENT 4 (He et al., 2021, 2022; Loeffler et al., 2024) achieves the state of art performance in LM-based drug optimization by using the Transformer model and conducting experiments with randomly selected ligand pairs that maintain constrained Tanimoto Similarity. While this method successfully produces ligands with high Tanimoto Similarity, it encounters difficulties in consistently improving the properties of the original drug and tends to simply maximize the likelihood of molecule generation.

Generalizable Insights about Machine Learning in the Context of Healthcare

In this work, we propose SCAFFOLDGPT, a novel scaffold-based GPT with three-stage optimization process for drug optimization. This optimization process is designed to enhance existing drugs to rapidly evolving virus variants and cancer cells, overcoming the limitation of earlier drug optimization efforts. The contributions of SCAFFOLDGPT are summarized as follows:

- A novel framework for drug optimization using GPT, featuring a three-step optimization process, the first of its kind to the best of our knowledge. The underlying motivation is that each stage is complementary to each other, enhances the performance of the preceding one. Furthermore, we have conducted ablation studies to illustrate the performance gains achieved at each step.
- A scaffolds-based GPT with a novel two-phase incremental pre-training specifically designed for drug optimization. The motivation for incremental training is to conduct local optimization before embarking on global optimization by breaking down the whole training corpus into knowledge pieces in an incremental order. We also conducted an ablation study in table 3 to demonstrate the effectiveness of the incremental training.
- A novel token-level decoding optimization strategy, TOP-N, utilizes pretrained GPT to enable controlled, reward-guided generation that aligns with targeted objectives.
- Through extensive experiments and ablation studies on real-world viral and cancer-related benchmarks, we demonstrate that SCAFFOLDGPT outperforms the competing baselines and reliably improves upon existing molecules/drugs in terms of desired targeted objectives while preserving original scaffold, resulting in superior drug candidates.

2. Related Work

2.1. Reinforcement Learning and Finetuning

Reinforcement learning (Tan et al., 2022a; Liu et al., 2023c,b) has become a fundamental strategy in drug design (Born et al., 2021; Guimaraes et al., 2017; Neil et al., 2018; Olivecrona et al., 2017; Popova et al., 2018; Ståhl et al., 2019; Tan et al., 2022b; Wang et al., 2022a; Zhang et al., 2023b; Zhou et al., 2019), focusing on optimizing rewards that aggregate predicted property scores from various pharmaceutical predictors. Traditional reinforcement learning methods in drug discovery often neglected molecular structure constraints, leading

to significant structural changes and unsynthesizable compounds. Our research differs by refining existing drugs to enhance their attributes without redesigning them from scratch and using reinforcement learning to improve a pre-trained language model generator, rather than starting a new. We also incorporate methods like Advantage-aligned Policy Optimization (APO) (Liu et al., 2023a), which assigns rewards based on advantage preference over the original molecule, to fine-tune a Transformer model, ensuring it aligns with multiple pharmaceutical objectives while preserving molecular structure. This approach, which includes controllable decoding, refines the model beyond traditional reinforcement learning fine-tuning stages.

2.2. Planning with GPT Models

Several studies have leveraged planning algorithms to enhance text outputs for a variety of NLP tasks. These include approaches like beam search optimization, machine translation improvements (Scialom et al., 2021; Leblond et al., 2021; Chaffin et al., 2021). The PG-TD (Zhang et al., 2023a) method is tailored for code generation using a singular reward function, whereas ERP (Liu et al., 2024c) introduces a novel concept by considering the certainty of each generated token along with an e -step forward entropy measurement to gauge potential outcomes. It has been shown that ERP effectively balances exploration and exploitation within molecular structures, leading to the discovery of high-reward molecules. Unlike previous studies that focus solely on planning with pre-trained language models, our approach incorporates a novel decoding optimization as a critical final step in the algorithm. Moreover, our focus is on optimizing an existing drug rather than creating a De Novo one from the ground up.

2.3. Drug Optimization

Recent drug optimization efforts have focused primarily on a limited array of drug properties while often disregarding the docking score, an essential metric for evaluating structural compatibility with a target (Zhou et al., 2019; Erikawa et al., 2021). DrugEx v3 (Liu et al., 2023d) seeks to resolve this deficiency by using 3D molecular graphs that encapsulate more comprehensive data such as chemical valence rules. Nevertheless, this method’s complexity poses challenges in generating molecules that closely resemble the originals. The resulting lower similarity could account for the diminished efficacy of graph-based methods, as deviations from the original molecular structures result in the loss of vital chemical properties. Conversely, our approach manages to preserve a decent level of similarity.

Diffusion-based efforts (Alakhdar et al., 2024; Morehead and Cheng, 2024) either focus on De Novo drug discovery while neglecting the essential similarity to the original molecule, or overlook the docking score towards a binding target. Molsearch (Sun et al., 2022) is a Monte Carlo tree search (MCTS)-driven approach for molecular generation and optimization, and MIMOSA (Fu et al., 2021) is a GNN sampling-based method leveraging graph-based molecular optimization. DrugImprover (Liu et al., 2023a) effectively begins to redefine the drug optimization challenge by employing reinforcement learning with a mix of multiple objectives as rewards. Still, it employs an LSTM in its generative model, which faces limitations in scalability, capacity, and understanding context. In contrast, our method applies a Transformer as the primary generative model, enhanced further with

Advantage-aligned Policy Optimization (APO) for exploratory purposes and an optimized decoder for superior performance.

2.4. Language Models for Drug Discovery

Large language models like MolGPT (Bagal et al., 2021) and ChemGPT (Frey et al., 2023) have been utilized in molecule generation and drug discovery (Bagal et al., 2021; Rothchild et al., 2021; Wang et al., 2022b), using formats like SMILES (Weininger, 1988) and SELFIES (Krenn et al., 2020) to standardize molecular representation. These models have shown promise in drug design, outperforming traditional methods in some predictive capacities. However, as noted by Murakumo et al. (2023), using pre-trained language models typically results in minor molecular modifications and serves primarily supportive roles in the design process. We adopt the SMILES format and combine the strengths of GPTs with reinforcement learning. Unlike previous efforts that relied solely on LLMs, our approach uses RL fine-tuning to align with multiple pharmaceutical objectives and employs controlled decoding to guide the GPT model in generating more effective molecular structures.

Further developments include transformer-based models like REINVENT 4 (He et al., 2021, 2022; Loeffler et al., 2024), which mostly focuses on pretraining. While pretraining helps in generating molecules similar to those in the training dataset, it also inherently restricts the exploration scope due to biases in the training data. REINVENT4 uses the original molecule as input, generates molecules that are very similar to the original ones. This likely contributes to its relatively poor performance in other metrics, as the generated molecules exhibit minimal changes in chemical properties. In contrast, our proposed method, which uses SMILES and scaffolds as prompts, achieves a well-balanced trade-off between diversity and similarity in the generated and original molecules, potentially leading to improved performance.

3. Preliminaries

In the following sections, we detail MDP, Language Model (LM) and drug discovery, complete with their mathematical notations, and integrate them within the framework of Markov decision processes.

Markov decision processes. Let us define a finite-horizon Markov decision process (MDP) (Puterman, 2014) $\mathcal{M}_0 = \langle \mathcal{S}, \mathcal{A}, T, \mathcal{P}, R \rangle$. In this context, \mathcal{S} represents a finite set of states, while \mathcal{A} comprises a finite set of actions. The term T denotes the planning horizon. The function \mathcal{P} , defined as $\mathcal{P} : \mathcal{S} \times \mathcal{A} \rightarrow \mathcal{S}'$, describes the deterministic transition dynamics that combine a state s with an action a , with an episode concluding once the agent executes the termination action. Additionally, the reward function $R : \mathcal{S} \times \mathcal{A} \rightarrow \mathbb{R}$ assigns scores exclusively to complete molecules, assigning a reward of 0 to partial molecules. The effectiveness of a policy can be evaluated using the Q -value function, denoted as $Q^\pi : \mathcal{S} \times \mathcal{A} \rightarrow \mathbb{R}$, and defined by the following equation: $Q^\pi(s, a) := \mathbb{E}^\pi \left[\sum_{t=0}^T R(s_t, a_t) \mid s_0 = s, a_0 = a \right]$, where the expectation is based on the trajectory determined by the policy π . The associated value function is given by: $V^\pi(s) := \mathbb{E}_{a \sim \pi(\cdot|s)} [Q^\pi(s, a)]$.

LM. We define the state space \mathcal{S} as the set of all possible molecule, where each molecule is represented as a state s that includes a start token [BOS], a molecule with

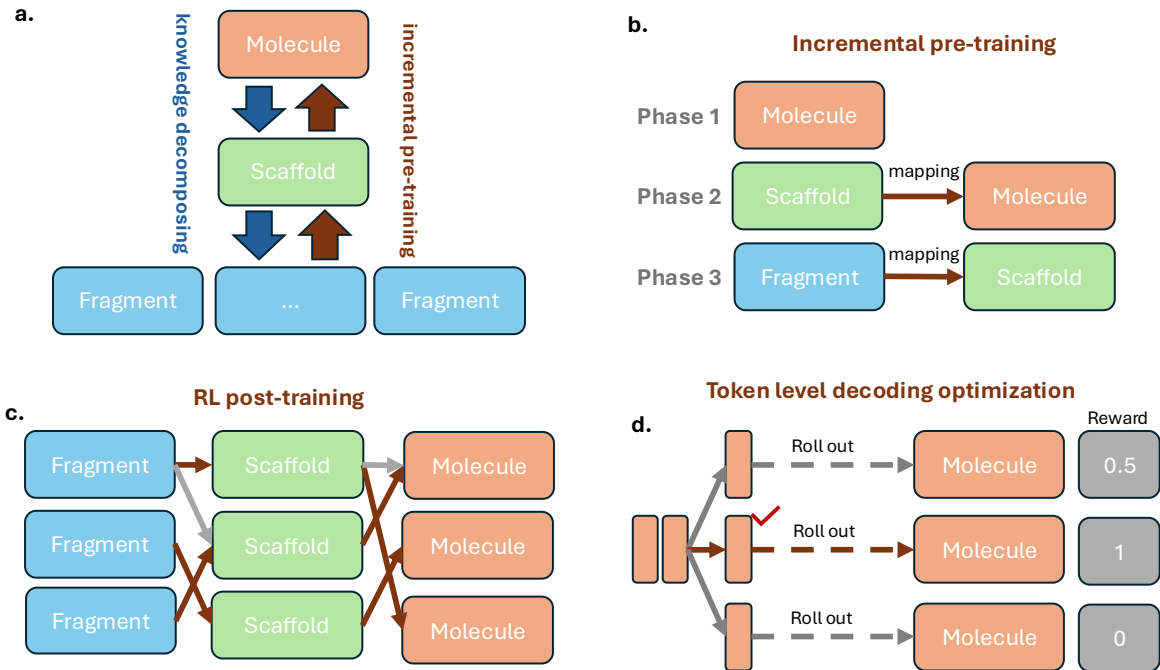


Figure 1: Overview of SCAFFOLDGPT. (a) SCAFFOLDGPT decomposes molecular knowledge top-down into fragments and then reconstructs it bottom-up through linking. (b) In Stage 1, it proposes an incremental pretraining strategy. (c) In Stage 2, it undergoes reinforcement learning-based post-training. (d) In Stage 3, it introduces a token-level controllable decoding optimization approach. SCAFFOLDGPT is the first to introduce a three-stage optimization framework, where each stage complements the others.

SMILES (Weininger, 1988) representation string, and a termination action [EOS]. We define the set of complete molecules as

$$\mathcal{V}_T := \{[\text{BOS}] \circ \mathbf{v} \circ [\text{EOS}] \mid \mathbf{v} \in \mathcal{V}^*\}, \quad (1)$$

where $\mathcal{V}_t \subseteq \mathcal{S}_t|_{t \in [T]}$ represents the hypothesis space at step t (sequence length t), \mathcal{V}^* represents the Kleene closure of Transformer’s vocabulary \mathcal{V} , with $\mathcal{V} := \mathcal{A}$, and \circ indicating string concatenation. Each action $a \in \mathcal{A}$ is represented as token $y \in \mathcal{V}$. In this work, we train a GPT policy π_θ to acquire prior knowledge for generating valid molecules based on a given set of molecules \mathcal{B} . We define the generator policy π_θ , with learned weights θ , as the product of probability distributions: $\pi_\theta(\mathbf{y}|\mathbf{x}) = \prod_{t=1}^{|\mathbf{y}|} \pi_\theta(y_t|\mathbf{x}, \mathbf{y}_{<t})$, where $\pi_\theta(\cdot|\mathbf{x}, \mathbf{y}_{<t})$ is a distribution, \mathbf{x} is an input sequence, and $\mathbf{y}_{<1} = y_0 := [\text{BOS}]$. The decoding process in text generation involves identifying the most likely hypothesis by optimizing the objective: $\mathbf{y}^* = \arg \max_{\mathbf{y} \in \mathcal{V}_T} \log \pi_\theta(\mathbf{y}|\mathbf{x})$.

Drug Optimization. Given an initial drug candidate $X = (x_1, \dots, x_T)$ and a drug optimization policy π_θ , the goal in drug optimization is to find the optimal policy π_{θ^*} that maximize the following objective:

$$\pi_{\theta^*} = \arg \max_{\pi_\theta} \mathbb{E}_{X \sim d_0} [R(Y) - R(X) | \theta, X], \quad (2)$$

Algorithm 1 SCAFFOLDGPT

Require: GPT-based generator policy π_θ ; critics \mathbf{C} .

- 1: Initialize π_θ with GPT2-like Transformer with random weight θ .
 \triangleright /* Stage 1: Pre-training GPT-based generator */
 - 2: Build the training corpus $C_{\text{Phase 1}}$ (4), $C_{\text{Phase 2}}$ (5).
 - 3: Pre-train BPE tokenizer and π_θ on $C_{\text{Phase 1}}$ via CLM objective (3).
 - 4: Pre-train π_θ on $C_{\text{Phase 2}}$.
 \triangleright /* Stage 2: APO fine-tuning */
 - 5: **for** $n = 1, \dots, N$ **do**
 - 6: $s_0 \sim \rho_0$, where $\rho_0 \in \Delta(\mathcal{B})$.
 - 7: Generate $Y_{1:T} = (y_1, \dots, y_T) \sim \pi_\theta(\cdot | S)$.
 - 8: Compute advantage preference R^{AP} by (10)(11).
 - 9: Update generator θ via policy gradient by (12).
 - 10: **end for**
 \triangleright /* Stage 3: Token-level Decoding Optimization */
 - 11: Optimize the generation of π_θ via TOP-N (13) decoding strategy.
-

where $Y = \pi_\theta(\cdot | X)$, $Y_{1:T} = (y_1, \dots, y_t, \dots, y_T)$, $y_t \in \mathcal{V}$.

Limitation of previous works: DrugImprover, which utilizes LSTM networks, has limitations in scalability, capacity, and contextual understanding, especially when compared to versions that use GPT Models. The current state of the art, REINVENT 4, employs the Transformer architecture; however, it mainly focuses on pretraining with constrained similarity, which restricts its capability to explore molecular spaces that might offer high rewards beyond its training set. In this work, we address these limitations by proposing SCAFFOLDGPT.

4. The ScaffoldGPT Algorithm

Stage 1. Pretrain a GPT generator. Let us note the GPT generator policy as π_θ , which computes the probability p of the occurrence of the t^{th} token in a target molecule Y . It takes into account all preceding tokens $\mathbf{y}_{<t} = [y_1, \dots, y_{t-1}]$ in the target, as well as the scaffold compound S , which is noted as $\pi_\theta(y_t | \mathbf{y}_{<t}, S) = p(y_t | \mathbf{y}_{<t}, S)$. The parameters θ of the generator policy π_θ are trained using the training corpus set through the minimization of the negative log-likelihood (NLL) for the complete SMILES strings across the entire set. This process is described as follows:

$$NLL = -\log P(Y|S) = -\sum_{t=1}^T \log P(y_t | y_{t-1}, \dots, y_1, S) = -\sum_{t=1}^T \log \pi_\theta(y_t | y_{1:t-1}, S), \quad (3)$$

where T signifies the total number of tokens related to Y . The NLL quantifies the probability of converting a specific scaffold into a designated target molecule.

In this project, we employ pre-training to harness large quantities of unlabeled text to construct a basic foundation model of language understanding. This foundation model can subsequently be fine-tuned and tailored to meet various specialized goals. In this work,

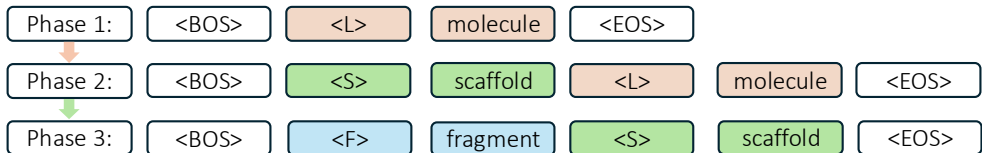


Figure 2: Two-phase incremental training of SCAFFOLDGPT. The first phase concentrates on recognizing the molecule, while the second phase builds connections between its scaffold and the original molecule. This process can be extended into a three-phase pretraining framework by establishing connections among the molecule’s fragments, scaffold, and original molecule.

we propose a novel framework for pre-training a Transformer and linking scaffolds with complete molecules, based on a SMILES (Simplified Molecular Input Line Entry System) (Weininger, 1988) string representation of the molecule. Here, we define \mathcal{S} as the scaffold space and \mathcal{Y} as the target molecule space. With $\mathcal{P} = \{(s, y) | s, y \in \mathcal{S} \times \mathcal{Y}\}$, we denote the set of scaffold and molecular pairs from \mathcal{S} and \mathcal{Y} . In this notation, s represents the scaffold of the target molecule, and y is the corresponding target molecule. We initially pre-trained our tokenizer using the Byte Pair Encoding (BPE) method (Gage, 1994; Sennrich et al., 2015). Building on the pre-trained BPE tokenizer, we propose a two-phase incremental training approach, as illustrated in Fig. 2, to notably enhance the model’s ability to improve the validity of inferring the target molecule from its scaffold.

Incremental pre-training. The rationale for incremental pre-training is to conduct local optimization before embarking on global optimization. Therefore, we divide our training into two phases. In the first phase, we focus on training a GPT exclusively for molecules using Causal Language Modeling (CLM). CLM utilizes an autoregressive method where the model is trained to predict the next token in a sequence by considering only the tokens that precede it. The phase 1 corpus is designed as follows:

$$C_{\text{Phase 1}} = \left\{ [BOS], \langle L \rangle, \underbrace{y_1, \dots, y_T}_{\text{target molecule Y}}, [EOS] \right\}, \langle L \rangle \text{ is the token for ligand.} \quad (4)$$

In the second phase, building upon the success of the GPT model developed in phase 1, which demonstrated high accuracy in molecular generation, we advance the training by focusing on pairs of scaffolds and molecules using CLM. The phase 2 corpus is as follows:

$$C_{\text{Phase 2}} = \left\{ [BOS], \langle S \rangle, \underbrace{s_1, \dots, s_T}_{\text{source scaffold S}}, \langle L \rangle, \underbrace{y_1, \dots, y_T}_{\text{target molecule Y}}, [EOS] \right\}, \langle S \rangle : \text{scaffold.} \quad (5)$$

Consequently, the model can generate the appropriate molecule when given a scaffold as prompt. While this work primarily focuses on scaffolds, the proposed method can be extended to fragments as well. A scaffold represents a complete core structure, while fragments may constitute parts of the scaffold or side chains attached to it. This approach could be further developed into a fragment-based third-phase pre-training strategy, with the phase

3 corpus outlined as follows:

$$C_{\text{Phase 3}} = \left\{ [BOS], \langle F \rangle, \underbrace{f_1, \dots, f_T}_{\text{source fragment F}}, \langle S \rangle, \underbrace{s_1, \dots, s_T}_{\text{source scaffold S}}, [EOS] \right\}, \langle F \rangle : \text{fragment.} \quad (6)$$

As a result, the model can produce a suitable scaffold when provided with a fragment as a prompt, and using the scaffold as the input prompt will generate a complete molecule. However, since a single scaffold can relate to multiple molecules and a fragment can correspond to multiple scaffolds, we further optimize the GPT-based generator policy, π_θ , to focus on specific outcomes by implementing reinforcement learning fine-tuning in the subsequent stage.

Stage 2. RL post-training/finetuning. Fine-tuning a generative model is crucial for producing outcomes that meet specific objectives. In this study, we use the Advantage-alignment Policy Optimization (APO) (Liu et al., 2023a) algorithm to fine-tune the pre-trained GPT-based generator policy π_θ . This approach steers the model from a given scaffold towards the targeted molecule, simultaneously improving multiple properties.

In this work, we adopt the define of reward function from Liu et al. (2024c), and regarded each pharmaceutical property as a critic C and got an ensemble critics \mathbf{C} as follows:

$$[C^{\text{Druglikeness}}, C^{\text{Solubility}}, C^{\text{Synthesizability}}, C^{\text{Docking}}, C^{\text{Tanimoto}}],$$

where each critic $C : Y \rightarrow \mathbb{R}$ acts as a distinct evaluator for a specific pharmaceutical attribute. We built the reward function as follow:

$$R^{\text{norm}}(Y) := R^{\text{norm}}(Y|S) = \lambda \cdot \text{Norm}(C^{\text{Tanimoto}}(S, Y)) + \sum_{i=0}^{|\mathbf{C}|-1} \lambda \cdot \text{Norm}(C_i(Y)) \quad (7)$$

where Norm is employed to standardize diverse attributes to a consistent scale. In this instance, Norm refers to the process of min-max normalization, which is used to adjust the attributes so they fit within the $[0, 1]$ range. We defer the details of critics to §5.1.

In this work, we use BON (Gao et al., 2023) (Best of N) search to estimate the reward for a prompt (partial molecule). BON can be formulated as the following:

$$\text{BON}(\mathbf{y}_{<i}, N, R) |_{S,p,k} = \max_{\mathbf{Y}_j \in \{\mathbf{Y}_1, \dots, \mathbf{Y}_N\}} R(\mathbf{Y}_j), \quad (8)$$

$$\text{where } Y_j = [\mathbf{y}_{<i}, y_i, \dots, y_T]_j, \text{ and } y_i \sim \text{TOP-PK}(\mathbf{y}_{<i}, p, k) |_S.$$

where TOP-PK (Liu et al., 2024c) is defined as follows:

$$\text{TOP-PK}(\mathbf{y}_{<i}, p, k) |_S = \mathcal{A}_{\mathbf{y}_{<i}}, \text{ where } \mathcal{A}_{\mathbf{y}_{<i}} = \{y_1, \dots, y_j\}, y_i \in \mathcal{V}, \quad (9)$$

$$j = \min \left\{ \arg \min_{j'} \sum_{i=1}^{j'} \pi_\theta(y_i | S, \mathbf{y}_{<i}) \geq p, k \right\}, \text{ and } \pi_\theta(y_g | S, \mathbf{y}_{<i}) > \pi_\theta(y_h | S, \mathbf{y}_{<i}), \text{ if } g < h,$$

where $p \in (0, 1]$ represents the maximum cumulative probability, and k denotes the maximum number of candidates for the next tokens.

For each pair consisting of a scaffold and a molecule, we create 8 new molecules from the scaffold using TOP-PK (9) and BON (8) method to select the best one (the one with the highest normalized reward) to serve as the foundation for the final reward calculation.

$$R_c(Y|S) = R^{\text{norm}}(Y)|_S, \quad Y \in \text{BON}(y_0, N, R)|_{S,p,k}. \quad (10)$$

APO makes policy gradient based on the advantage preference (Liu et al., 2023a), which is defined as

$$R^{\text{AP}}(Y_{1:T}, S) = R_c(Y_{1:T}) - R_c(S), \quad (11)$$

and perform APO policy gradient with follows:

$$g = \mathbb{E}_{S \sim \rho_0, Y_{1:T} \sim \pi_\theta(\cdot|S)} [\nabla_\theta \log \pi_\theta(Y_{1:T}|S) \cdot R^{\text{AP}}(S, Y_{1:T})], \quad (12)$$

Stage 3. Token-level Controllable decoding generation. Ultimately, the current GPT-based decoder focuses mainly on maximizing likelihood, neglecting specific metrics of interest. This approach limits its effectiveness in optimizing objectives that diverge from those in its training set, particularly in generating desired molecules. In this study, we introduce controllable decoding after fine-tuning with APO. We present a new approach, TOP-N, to direct the generation process towards enhancements in the optimization objective, as detailed below:

$$\begin{aligned} Y^* &\sim \{[\mathbf{y}_{<i}, y_i, \dots, y_T]\}, \text{ where } y_i \sim \text{TOP-N}(\mathbf{y}_{<i}, p, k, n)|_S \\ \text{TOP-N}(\mathbf{y}_{<i}, p, k, n)|_S &= \mathcal{A}_{\mathbf{y}_{<i}}, \quad \mathcal{A}_{\mathbf{y}_{<i}} = \{y_1, \dots, y_n\}, y_i \in \mathcal{V}, |\mathcal{A}| \leq k, \\ \text{and } R(\text{BON}(\mathbf{y}_{<i} \circ y_g, N, R)|_{S,p,k}) &\geq R(\text{BON}(\mathbf{y}_{<i} \circ y_h, N, R)|_{S,p,k}), \forall g < h, \end{aligned} \quad (13)$$

where $n \leq k$ denotes as top N candidate of next tokens with regard to BON function.

Remark 1 TOP-N differs from TOP-P, TOP-K, and TOP-PK in that it is measured based on maximum reward, whereas the others are measured based on maximum likelihood. TOP-N is also distinct from BON in that BON is optimized at the sequence level, while TOP-N is optimized at the token level.

5. EXPERIMENTS

5.1. Experimental configuration

The language model. We use GPT-2-like Transformers for causal language modeling, employing the standard 11M Drug-like Zinc dataset for training. Entries with empty scaffold SMILES are excluded, and we adopt a 90/10 split for training and validation, respectively. The training process is structured into three phases: pretraining, fine-tuning, and decoding optimization, as outlined in Algorithm SCAFFOLDGPT (See appendix for more details).

Baselines. We compare against baseline models: DrugImprover (Liu et al., 2023a), which utilizes an LSTM-based generator with APO fine-tuning; Molsearch (Sun et al., 2022), a Monte Carlo tree search (MCTS)-driven approach for molecular generation and optimization; MIMOSA (Fu et al., 2021), a sampling-based method leveraging graph-based molecular optimization; and DrugEx v3 (Liu et al., 2023d), which leverages transformer-based reinforcement learning for scaffold-guided drug optimization. Additionally, we incorporate the

model proposed by He et al. (2021, 2022); Loeffler et al. (2024), which trains a transformer to adhere to the Matched Molecular Pair (MMP) guidelines (Kenny and Sadowski, 2005; Tyrchan and Evertsson, 2017). Specifically, given a set $\{\{X, Y, Z\}\}$, where X represents the source molecule, Y denotes the target molecule, and Z signifies the property change between X and Y , the model learns a mapping from $\{X, Z\} \in \mathcal{X} \times \mathcal{Z} \implies Y \in \mathcal{Y}$ during training. Here, $\mathcal{X} \times \mathcal{Z}$ denotes the input space, and \mathcal{Y} denotes the target space. They defined six different types of property changes for Z , including MMP for user-specified alterations, various similarity thresholds, and scaffold-based modifications where molecules share the same scaffold or a generic scaffold. More specifically,

- MMP: there exists user-specified property changes between molecule X and Y .
- Similarity ≥ 0.5 : tanimoto similarity between molecule X and Y is larger than 0.5.
- Similarity $\in [0.5, 0.7)$: the tanimoto similarity of pair (X, Y) is between 0.5 and 0.7.
- Similarity ≥ 0.7 : tanimoto similarity between molecule X and Y is larger than 0.7.
- Scaffold: molecule X and Y share same scaffold.
- Scaffold generic: molecule X and Y share same generic scaffold.

All baseline models are fine-tuned on the cancer and COVID datasets following their respective fine-tuning methods.

Dataset. We employ, from the most recent Cancer and COVID dataset of Liu et al. (2023a), 1 million compounds from the ZINC15 dataset docked to the 3CLPro (PDB ID: 7BQY) protein associated with SARS-CoV-2 and the RTCB (PDB ID: 4DWQ) human cancer protein.

Critics and evaluation metric. In this study, we evaluate the efficacy of SCAFFOLDGPT in generating molecules with desirable attributes within the context of pharmaceutical drug discovery. We leverage the RDKit (Landrum et al.) chemoinformatics package and employ various performance metrics as follows: **Validity** measures if the generated SMILES is valid in syntax. **Druglikeness** measures the likelihood of a molecule being a suitable candidate for drug development. **Solubility** assesses the likelihood of a molecule’s ability to mix with water, commonly referred to as the water-octanol partition coefficient (LogP). **Synthesizability** quantifies the ease (score of 1) or difficulty (score of 10) associated with synthesizing a given molecule (Ertl and Schuffenhauer, 2009). **Docking Score** assesses the drug’s potential to bind and inhibit the target site. To enable efficient computation, we employ a docking surrogate model (See Appendix A.4) to output this score. **Similarity:** We use Tanimoto similarity to evaluate the similarity between original SMILES and generated SMILES. **Average Top 10% Norm Reward** is the average of the normalized reward of the top 10% of molecules based on their average normalized reward. **Average Norm Reward** is the average of the normalized values of the docking score, druglikeness, synthesizability, solubility, and similarity across all valid molecules. This is the most important metric. Evaluations are based on a sample of 1,280 molecules.

Remark 2 *A similarity score that is too high results in low structural diversity, while a score that is too low suggests the molecules have drifted too far from the original. Neither extreme is desirable. Our goal is to achieve a balanced level of similarity with meaningful variation. In this work, the primary optimization objective is the average normalized reward.*

Target	Algorithm	Validity \uparrow	Avg Norm Reward \uparrow^*	Avg Top 10 % Norm Reward \uparrow	Docking \downarrow	Druglikeness \uparrow	Synthesizability \downarrow	Solubility \uparrow	Similarity \uparrow
3CLPro (PDBID: 7BQY)	Original	-	0.533	0.689	-8.698	0.682	3.920	2.471	-
	MMP (Loeffler et al., 2024)	0.995 ± 0.001	0.628 ± 0.001	0.718 ± 0.000	-8.259 ± 0.004	0.691 ± 0.001	2.682 ± 0.004	3.109 ± 0.020	0.862 ± 0.000
	Similarity (≥ 0.5) (Loeffler et al., 2024)	0.995 ± 0.001	0.615 ± 0.000	0.706 ± 0.001	-8.165 ± 0.024	0.697 ± 0.004	2.621 ± 0.006	3.180 ± 0.029	0.782 ± 0.001
	Similarity ($[0.5, 0.7]$) (Loeffler et al., 2024)	0.995 ± 0.001	0.612 ± 0.001	0.701 ± 0.001	-8.187 ± 0.010	0.691 ± 0.001	2.611 ± 0.009	3.240 ± 0.014	0.756 ± 0.003
	Similarity (≥ 0.7) (Loeffler et al., 2024)	0.995 ± 0.001	0.628 ± 0.001	0.718 ± 0.001	-8.214 ± 0.002	0.691 ± 0.002	2.717 ± 0.002	3.080 ± 0.016	0.881 ± 0.002
	Scaffold (Loeffler et al., 2024)	0.995 ± 0.001	0.602 ± 0.001	0.703 ± 0.002	-8.116 ± 0.002	0.695 ± 0.001	2.728 ± 0.008	2.968 ± 0.038	0.776 ± 0.001
	Scaffold Generic (Loeffler et al., 2024)	0.994 ± 0.001	0.617 ± 0.001	0.710 ± 0.002	-8.179 ± 0.012	0.701 ± 0.000	2.645 ± 0.008	3.090 ± 0.029	0.801 ± 0.000
	DrugImprover (Liu et al., 2023a)	0.884 ± 0.005	0.432 ± 0.002	0.493 ± 0.005	-6.726 ± 0.007	0.506 ± 0.002	1.306 ± 0.010	2.057 ± 0.011	0.531 ± 0.002
	Molsearch (Sun et al., 2022)	1.000 ± 0.001	0.616 ± 0.001	0.726 ± 0.002	-8.855 ± 0.040	0.686 ± 0.001	3.105 ± 0.006	2.452 ± 0.008	0.969 ± 0.001
	MIMOSA (Fu et al., 2021)	0.985 ± 0.008	0.622 ± 0.001	0.734 ± 0.002	-8.800 ± 0.015	0.677 ± 0.004	3.105 ± 0.008	2.711 ± 0.010	<u>0.950</u> ± 0.001
	DrugEx v3 (Liu et al., 2023d)	1.000 ± 0.001	0.524 ± 0.001	0.613 ± 0.001	-8.089 ± 0.013	0.583 ± 0.002	3.095 ± 0.005	3.932 ± 0.008	0.495 ± 0.001
	ScaffoldGPT (w/o APO & Top-N)	0.951 ± 0.004	0.587 ± 0.004	0.693 ± 0.004	-8.238 ± 0.101	0.659 ± 0.014	2.865 ± 0.038	2.999 ± 0.163	0.754 ± 0.005
	ScaffoldGPT (w/o Top-N)	0.857 ± 0.061	0.627 ± 0.009	0.717 ± 0.004	-8.583 ± 0.075	0.727 ± 0.019	2.566 ± 0.088	3.388 ± 0.095	0.717 ± 0.028
	ScaffoldGPT (w/o APO)	0.998 ± 0.001	<u>0.666</u> ± 0.000	<u>0.740</u> ± 0.001	<u>-9.312</u> ± 0.018	<u>0.734</u> ± 0.002	2.698 ± 0.006	<u>3.676</u> ± 0.006	0.813 ± 0.002
	ScaffoldGPT	0.944 ± 0.094	0.675 ± 0.031	0.740 ± 0.015	-9.343 ± 0.440	0.746 ± 0.028	<u>2.453</u> ± 0.154	3.913 ± 0.358	0.745 ± 0.032
RTCB (PDBID: 4DWQ)	Original	-	0.536	0.698	-8.572	0.709	3.005	2.299	-
	MMP (Loeffler et al., 2024)	0.998 ± 0.001	0.636 ± 0.000	0.731 ± 0.001	-8.465 ± 0.021	0.709 ± 0.001	2.599 ± 0.004	3.013 ± 0.013	0.845 ± 0.001
	Similarity (≥ 0.5) (Loeffler et al., 2024)	0.999 ± 0.001	0.626 ± 0.000	0.723 ± 0.001	-8.511 ± 0.012	0.713 ± 0.002	2.543 ± 0.002	3.082 ± 0.031	0.760 ± 0.000
	Similarity ($[0.5, 0.7]$) (Loeffler et al., 2024)	0.999 ± 0.001	0.622 ± 0.001	0.718 ± 0.000	-8.486 ± 0.021	0.713 ± 0.003	2.542 ± 0.005	3.101 ± 0.005	0.740 ± 0.001
	Similarity (≥ 0.7) (Loeffler et al., 2024)	0.999 ± 0.001	0.639 ± 0.000	0.734 ± 0.001	-8.496 ± 0.009	0.718 ± 0.001	2.628 ± 0.001	2.868 ± 0.003	0.875 ± 0.002
	Scaffold (Loeffler et al., 2024)	0.998 ± 0.001	0.609 ± 0.001	0.718 ± 0.000	-8.508 ± 0.026	0.711 ± 0.000	2.627 ± 0.002	2.803 ± 0.010	0.735 ± 0.002
	Scaffold Generic (Loeffler et al., 2024)	0.998 ± 0.001	0.625 ± 0.001	0.722 ± 0.000	-8.544 ± 0.009	0.722 ± 0.002	2.551 ± 0.010	2.898 ± 0.005	0.768 ± 0.004
	DrugImprover (Liu et al., 2023a)	0.920 ± 0.008	0.478 ± 0.001	0.618 ± 0.002	-8.701 ± 0.037	0.486 ± 0.002	1.181 ± 0.010	2.026 ± 0.013	0.427 ± 0.001
	Molsearch (Sun et al., 2022)	1.000 ± 0.001	0.625 ± 0.001	0.742 ± 0.001	-8.747 ± 0.009	0.719 ± 0.001	3.012 ± 0.004	2.273 ± 0.005	0.950 ± 0.001
	MIMOSA (Fu et al., 2021)	0.989 ± 0.001	0.631 ± 0.001	0.749 ± 0.001	-8.972 ± 0.011	0.706 ± 0.003	3.080 ± 0.007	2.561 ± 0.008	<u>0.945</u> ± 0.001
	DrugEx v3 (Liu et al., 2023d)	1.000 ± 0.001	0.592 ± 0.001	0.668 ± 0.001	-8.762 ± 0.010	0.583 ± 0.002	<u>2.488</u> ± 0.005	5.827 ± 0.010	0.393 ± 0.001
	ScaffoldGPT (w/o APO & Top-N)	0.956 ± 0.004	0.582 ± 0.007	0.700 ± 0.008	-8.214 ± 0.125	0.686 ± 0.017	2.788 ± 0.056	2.781 ± 0.214	0.707 ± 0.005
	ScaffoldGPT (w/o Top-N)	0.811 ± 0.074	0.639 ± 0.004	0.723 ± 0.005	-8.808 ± 0.071	0.741 ± 0.013	2.521 ± 0.081	3.279 ± 0.067	0.730 ± 0.030
	ScaffoldGPT (w/o APO)	0.997 ± 0.001	<u>0.673</u> ± 0.001	<u>0.755</u> ± 0.001	<u>-9.659</u> ± 0.023	<u>0.764</u> ± 0.001	2.606 ± 0.007	<u>3.481</u> ± 0.027	0.773 ± 0.003
	ScaffoldGPT	0.826 ± 0.100	0.682 ± 0.004	0.756 ± 0.003	-9.757 ± 0.057	0.765 ± 0.013	2.437 ± 0.059	3.582 ± 0.043	0.747 ± 0.026

Table 1: **Main results.** A comparison of eight baselines including Original, six baselines from REINVENT {MMP, Similarity (≥ 0.5), Similarity $\in [0.5, 0.7)$, Similarity ≥ 0.7 , Scaffold, Scaffold Generic}, DrugImprover, Molsearch, MIMOSA and different versions of SCAFFOLDGPT on various objectives based on 3CLPro and RTCB datasets. The top two results are highlighted as **1st** and 2nd. * represents the top-priority target objective. Results are reported for five experimental runs.

5.2. Main results.

Table 1 shows that SCAFFOLDGPT surpasses DrugImprover and six different versions of REINVENT4 in performance measures for both virus-related and cancer-related proteins. Moreover, SCAFFOLDGPT exceeds the performance of all baseline methods and also demonstrates a decent level of Tanimoto similarity to the original drug, indicating that it preserves the advantageous features of the original drugs while improving desired properties.

Several key factors contribute to this superior performance. Although DrugImprover established a strong foundation for the drug optimization field, including a workflow and a reinforcement learning algorithm to align the generative model with multiple pharmaceutical objectives, SCAFFOLDGPT outshines DrugImprover in all benchmarks. This is because SCAFFOLDGPT employs a GPT-2-like Transformer as the basis of its generative model, whereas DrugImprover relies solely on LSTM. Consequently, the GPT-2 Transformer grants SCAFFOLDGPT enhanced scalability, capacity, and contextual understanding compared to DrugImprover.

In contrast to the current state-of-the-art approach, REINVENT4, which pre-trains a Transformer with constraints on Tanimoto similarity, their method falls short in achieving drug optimization as it overlooks the optimization of multiple pharmaceutical properties. Therefore, Table 1 reveals that although REINVENT4 achieved high similarity, the generated molecules often failed to surpass the original ones. SCAFFOLDGPT, on the other hand, employs the APO reinforcement learning algorithm to fine-tune the pre-trained generative model and utilizes the TOP-N decoding optimization strategy. These approaches ensure improvements aligned with multiple pharmaceutical objectives and enable SCAFFOLDGPT

to successfully enhance the original drug across various pharmaceutical properties while maintaining a high Tanimoto similarity.

5.3. Ablation studies.

Model	Diversity \uparrow	Validity \uparrow	Avg Norm Reward \uparrow	Avg Top 10% Norm Reward \uparrow	Docking \downarrow	Druglikeliness \uparrow	Synthesizability \downarrow	Solubility \uparrow	Similarity \uparrow
COVID									
SCAFFOLDGPT (w/o TOP-N) TOP-K	0.988	0.947	0.645	0.727	-8.726	0.760	2.418	3.499	0.697
SCAFFOLDGPT (w/o TOP-N) TOP-P	0.988	0.938	0.642	0.722	-8.653	0.756	2.420	3.505	0.696
SCAFFOLDGPT (w/o TOP-N) TOP-PK	0.989	0.941	0.643	0.724	-8.667	0.759	2.407	3.506	0.692
SCAFFOLDGPT (TOP-N)	0.965	0.944	0.675	0.740	-9.343	0.746	2.453	3.913	0.745
CANCER									
SCAFFOLDGPT (w/o TOP-N) TOP-K	0.912	0.709	0.648	0.728	-8.944	0.756	2.456	3.258	0.730
SCAFFOLDGPT (w/o TOP-N) TOP-P	0.931	0.704	0.645	0.729	-8.907	0.756	2.466	3.226	0.723
SCAFFOLDGPT (w/o TOP-N) TOP-PK	0.926	0.719	0.645	0.727	-8.888	0.757	2.466	3.219	0.725
SCAFFOLDGPT (TOP-N)	0.916	0.826	0.682	0.756	-9.757	0.765	2.437	3.582	0.747

Table 2: Ablation study of TOP-N, TOP-P, TOP-K and TOP-PK sampling strategies. The top result is highlighted as **1st**. * represents the top-priority target objective. Evaluations are based on five random seeds. TOP-N outperforms others in most of the metrics.

We next present ablation studies that underscore the necessity and effectiveness of each component of SCAFFOLDGPT. These components complement each other, substantially enhancing overall performance.

Effectiveness of (two-phase) incremental training. In two-phase incremental pretraining, the intuition behind the first phase lies in training on critical keywords as knowledge pieces, reinforcing the memory of these key terms, particularly in longer sequences. We conducted an ablation study comparing our novel two-phase incremental training with conventional one-phase training in Table 3. To ensure a fair comparison in terms of total training epochs, we trained for 10 epochs in the conventional single-phase setting, and for five epochs per phase in our two-phase setting. The results showed that the two-phase approach improves validity compared to one-phase training, demonstrating the effectiveness of the incremental training method.

1024 SMILES	Details
1024	> 100 length, > 50 scaffold
Validity	
One phase	0.57 \pm 0.010
Two phases	0.68 \pm 0.006

Figure 3: Ablation study of one-phase vs two-phases. Evaluations are based on five random seeds.

Effectiveness of APO Finetuning. SCAFFOLDGPT adopts APO finetuning as the second step, following the completion of pretraining the GPT-based generator. Table 1 demonstrates the effectiveness of APO through two comparisons: SCAFFOLDGPT (w/o APO, TOP-N) vs. SCAFFOLDGPT (w/o TOP-N), which shows that after applying APO finetuning, performance improved on most properties. Additionally, SCAFFOLDGPT vs. SCAFFOLDGPT (w/o APO) validates the importance of the APO component. By applying APO on top of pretraining and TOP-N decoding, performance improved. Both cases demonstrate the effectiveness of APO finetuning. Note that APO may compromise certain reward metrics, such as similarity or validity, if this trade-off leads to improved performance in the target weighted objective.

Effectiveness of Top-N decoding strategy. SCAFFOLDGPT adopts the TOP-N decoding strategy as the final step followed by APO finetuning. Table 1 demonstrates the effectiveness of TOP-N through two comparisons: SCAFFOLDGPT (w/o APO, TOP-N) vs. SCAFFOLDGPT (w/o APO), showing that after applying the TOP-N decoding strategy on


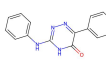




Molecule						
SMILE String	<chem>Cc1ccc(O)c(Nc2nnc(-c3ccccc3)c(=O)[nH]2)c1</chem>		<chem>CCOc1ccc(O)c(Nc2nnc(-c3ccccc3)c(=O)[nH]2)c1</chem>	<chem>Cc1ccc(-c2nnc(Nc3ccc(C(C)C)cc3)[nH]c2=O)cc1</chem>	<chem>COc1ccc(-c2nnc(Nc3ccccc(C)C3)[nH]c2=O)cc1</chem>	<chem>Cc1ccc(-c2nnc(Nc3ccccc(C(C)C)C3)[nH]c2=O)cc1</chem>
Scaffold	<chem>O=c1[nH]c(Nc2ccc(cc2)nnc1-c1ccccc1</chem>		<chem>c1ccc(Nc2nnc(-c3ccccc3)[nH]2)cc1</chem>	same as original	same as original	same as original
Similarity	-		0.878	0.826	0.911	0.866
Docking (↓)	-10.031		-9.258	-11.478 ✓	-11.474 ✓	-11.087 ✓
Druglikeness (↑)	0.646		0.624	0.762 ✓	0.774 ✓	0.762 ✓
Synthesizability (↓)	2.390		2.417	2.298 ✓	2.257 ✓	2.356 ✓
Solubility (↑)	2.590		2.680 ✓	4.007 ✓	2.893 ✓	4.007 ✓
Avg Norm Reward (↑)*	0.618		0.589	0.759 ✓	0.753 ✓	0.754 ✓

Table 3: One optimization example from cancer benchmark. Every generated molecules retains the scaffold, with all desired properties improved compared to the original. * represents the top-priority target objective. ✓ indicates improved property.

top of pretrained GPT, performance improved across most properties. Moreover, SCAFFOLDGPT vs. SCAFFOLDGPT (w/o TOP-N) illustrates that after applying APO on top of pretraining and RL, performance still improves on multiple attributes, surpassing all baselines. Furthermore, by comparing SCAFFOLDGPT (w/o APO) and SCAFFOLDGPT (w/o TOP-N), we observe that applying TOP-N decoding alone enhances performance more than applying APO alone.

Top-N selects a higher-reward alternative missed by Top-K. These two SMILES strings are nearly identical, but TOP-N selects a slightly different generation path—preferring ‘c’ and ‘c1C’ over ‘c(C)c1’—which results in a higher average reward. This demonstrates how TOP-N can identify token-level alternatives that improve the optimization objective while preserving scaffold structure.

Method	Generated SMILES	Avg. Normalized Reward
Top-K	<chem>Cc1ccc(NC(=O)COC(=O)C2C[C@H]3CCCC@HC3=O)c(C)c1</chem>	0.579
Top-N	<chem>Cc1ccccc(NC(=O)COC(=O)C2C[C@H]3CCCC@HC3=O)c1C</chem>	0.614

Table 4: Comparison of generated SMILES and average normalized rewards across methods.

Ablation study of Top-N vs Top-P, Top-K and Top-PK strategies. Following the setup described in §5.1, we perform an ablation study on sampling strategies. When removing TOP-N component, we employ multinomial generation, where multinomial sampling randomly selects the next token from the entire vocabulary based on the model’s probability distribution. In the ablation study detailed in Table 2, we examined TOP-N over TOP-P, TOP-K, and TOP-PK with K=20 and P=0.95. The results indicate that Top-N surpasses the other strategies in most metrics.

Drug optimization illustration. Finally, we provide three examples illustrating the effectiveness of SCAFFOLDGPT in improving upon the original molecule on the cancer benchmark, as shown in Table 3 (Refer to Appendix A.5 for the COVID benchmark). The results in Table 3 demonstrate that the drugs generated by SCAFFOLDGPT outperform the original drugs across all desired properties. Additionally, the comparison figure in Table 3

illustrates that the improved molecules preserve the original drug to a significant extent, with only minor changes highlighted in red. The results indicate that SCAFFOLDGPT effectively optimizes desired properties while preserving the beneficial properties of the original drug.

6. Conclusion

We have introduced SCAFFOLDGPT, a novel framework for drug optimization. This framework incorporates a unique scaffold-based GPT design, a three-stage optimization process, a two-phase incremental pre-training approach, and a novel TOP-N decoding strategy that facilitates controlled reward-guided generation using GPT. To showcase the superior performance of SCAFFOLDGPT, we conduct evaluations on real-world viral and cancer-related datasets to compare it against eight competing baselines. Our results demonstrate that SCAFFOLDGPT surpasses all baselines across the majority of performance metrics, underscoring its efficacy. Our work highlights SCAFFOLDGPT’s effectiveness in drug optimization, as evidenced by enhancements in various pharmaceutical properties. Currently, SCAFFOLDGPT is limited to handling molecules in SMILES format. We are working to expand SCAFFOLDGPT’s capabilities to accommodate a broader range of drug representation formats as a future direction.

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Appendix A. Appendix

A.1. Pre-training and finetuning dataset

For pretraining, We used the ZINC dataset, filtering for Standard, In-Stock, and Drug-Like molecules, resulting in approximately 11 million molecules. For preprocessing, we perform a few straightforward steps:

1. We first canonicalize smiles `Chem.MolToSmiles(Chem.MolFromSmiles(mol), True)`.
2. We filter out molecules whose scaffold SMILES is an empty string. These preprocessing steps are also included in the huggingface data repo.

For finetuning, we utilize 1 million compounds from the ZINC15 dataset, docked to the 3CLPro protein (PDB ID: 7BQY) linked to SARS-CoV-2 and the RTCB protein (PDB ID: 4DWQ) associated with human cancer, as sourced from the latest Cancer and COVID dataset by [Liu et al. \(2023a\)](#), across all baselines.

A.2. Generation with finetuned model

The top five epochs with the highest historical average normalized reward (as detailed in Section 5.1) are selected. From these five epochs, the epoch with the highest product of validity and average normalized reward is chosen as the final model for generation.

With this epoch and corresponding weights, we apply the proposed decoding method (as described in section 4) for generation.

A.3. BPE Tokenization

The Byte Pair Encoding (BPE) algorithm involves the following steps:

1. **Initialize the Vocabulary:** Start with a base vocabulary consisting of all individual characters in the text corpus.
2. **Count Frequencies:** Count the frequency of all character pairs in the text.
3. **Merge Most Frequent Pair:** Identify the most frequent pair of characters and merge them into a single token. Add this new token to the vocabulary.
4. **Update Text:** Replace all occurrences of the most frequent pair with the new token in the text.
5. **Repeat:** Repeat the process of counting frequencies, merging pairs, and updating the text until the desired vocabulary size is reached or no more merges are possible.

BPE constructs a robust vocabulary by iteratively merging the most frequent token pairs, effectively capturing common subword units for more efficient and flexible text representation. The resulting vocabulary comprises 3,152 tokens and includes special tokens as well. For instance, the sequence `<L>` is tokenized into three separate tokens: `<`, `L`, and `>`. The tokenizer was trained on 10 million molecules from the ZINC dataset, ensuring comprehensive coverage of chemical elements.

A.4. Surrogate model

The surrogate model ([Vasan et al., 2023](#)) is a simplified variant of a BERT-like transformer, extensively utilized in natural language processing. In this model, tokenized SMILES strings are inputted and then embedded with positional information. The resulting outputs are

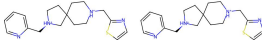
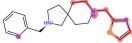
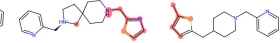
	Original	Scaffold improved 1	improved 2
Molecule			
SMILE String	<chem>c1ccc(C[N@H+]2CCC3(CC[NH+](C4nccs4)CC3)C2)nc1</chem>	<chem>CC1(c2ccccc(C(=O)Nc3ccccc3C)c2)CCCC1</chem>	<chem>Cc1ccc(CC2CCN(Cc3ccccc3)CC2)s1</chem>
Scaffold	<chem>c1ccc(C[N@H+]2CCC3(CC[NH+](C4nccs4)CC3)C2)nc1</chem>	-	-
Docking (↓)	-9.748	-10.184 ✓	-10.187 ✓
Druglikeness (↑)	0.839	0.840 ✓	0.847 ✓
Synthesizability (↓)	5.631	1.983 ✓	2.199 ✓
Solubility (↑)	0.192	5.079 ✓	3.906 ✓
Similarity	-	0.335	0.563
Avg Norm Reward (↑)	0.398	0.688 ✓	0.694 ✓

Table 5: One molecule example from 3CLPro dataset, where scaffold and original are same. In this case the model tries to modify the scaffold, and the generated molecules does not contain scaffold. ✓ indicates improved property.

subsequently fed into a series of five transformer blocks, each comprising a multi-head attention layer (21 heads), a dropout layer, layer normalization with residual connection, and a feedforward network. This feedforward network consists of two dense layers followed by dropout and layer normalization with residual connection. Following the stack of transformer blocks, a final feedforward network is employed to generate the predicted docking score. The validation r^2 values are 0.842 for 3CLPro and 0.73 for the RTCB dataset.

A.5. Drug Optimization illustration on COVID benchmark

This is another example illustrating the effectiveness of SCAFFOLDGPT in enhancing the original molecule on the COVID benchmark. The results in Table 5 show that the drugs generated by SCAFFOLDGPT outperform the original drugs across all desired properties. Even though the original scaffold is altered and not present in the generated molecules, the similarity still demonstrates a decent level.

A.6. Computing infrastructure and wall-time comparison

We trained our docking surrogate models using 4 nodes of the supercomputer where each node contains CPUs (64 cores) and 4 A100 GPU nodes (Facility). The training time for each model was approximately 3 hours.

We conducted other experiments on a cluster that includes CPU nodes (approximately 280 cores) and GPU nodes (approximately 110 Nvidia GPUs, ranging from Titan X to A6000, set up mostly in 4- and 8-GPU configurations).

The pretraining process utilizes 8 GPUs, while APO and generation employs a single GPU. Both processes use either V100 or A100 GPUs. Based on the computing infrastructure, we obtained the wall-time comparison in Table 6 as follows.

A.7. Hyperparameters and architectures

Table 7 and 8 provides a list of hyperparameter settings we used for our experiments.

Methods	Total Run Time
Pretraining	24h
APO	27h
Top-N (One Generation)	17-20s

Table 6: Wall-time comparison between different methods.

For APO finetuning and experimentation, we have two different set of 1280 molecules that were selected from each of the RTCB and 3CLPro datasets, with docking scores ranging from -14 to -6. This range is based on (Liu et al., 2024c).

Moreover, when computing the average normalized reward for the original molecule, in the absence of similarity considerations, we use weights of 0.25 for docking, drug-likeness, synthesizability, and solubility, respectively.

Moreover, when the generated SMILES is invalid, indicating that the reward R_c cannot be calculated, we have two options: either directly subtract the reward of the original SMILES (i.e., $-R_c(X)$), or consider the advantage preference as zero instead.

Parameter	Value
Pretraining	
Learning rate	$5 \times e^{-5}$
Batch size	24
Optimizer	Adam
# of Epochs for Training First Phase	10
# of Epochs for Training Second Phase	10
Model # of Params	124M
Generation	
N (Top-N)	1
K (Number of possible next token)	16
TopK	[10, 15, 20]
TopP	[0.85, 0.9, 0.95]

Table 7: Hyperparameters for pretraining and generation.

Parameter	Value
Shared	
# of Molecules Optimized	1280
Learning rate	1×10^{-4}
Optimizer	Adam
# of Epochs for Training	100
Batch size	64
Best-of-N	[4, 6, 8]
TopK	[10, 15, 20]
TopP	[0.85, 0.9, 0.95]
APO Objective Weight	
Docking Score	0.2
Druglikeness	0.2
Synthesizability	0.2
Solubility	0.2
Tamimoto Similarity	0.2
APO Other	
Fingerprint Size	1024
Normalize Min/Max	$[-10, 10]$
Advantage preference with invalid generated SMILES	
3CLPro	$[0, -R_c(X)]$
RTCB	$[0, -R_c(X)]$

Table 8: Hyperparameters for APO.