Sample Efficiency Matters: A Benchmark for Practical Molecular Optimization

Wenhao Gao [*1] **Tianfan Fu** [*2] **Jimeng Sun** [3] **Connor W. Coley** [1 4]

Abstract

Molecular optimization is a fundamental goal in the chemical sciences and is of central interest to drug and material design. In recent years, significant progress has been made in solving challenging problems across various aspects of computational molecular optimizations, emphasizing high validity, diversity, and, most recently, synthesizability. Despite this progress, many papers report results on trivial or self-designed tasks, bringing additional challenges to directly assessing the performance of new methods. Moreover, the sample efficiency of the optimization—the number of molecules evaluated by the oracle—is rarely discussed, despite being an essential consideration for realistic discovery applications. To fill this gap, we have created an open-source benchmark for **p**ractical **m**olecular **o**ptimization, PMO, to facilitate the transparent and reproducible evaluation of algorithmic advances in molecular optimization. This paper thoroughly investigates the performance of 25 molecular design algorithms on 23 tasks with a particular focus on sample efficiency. Our results show that most "state-of-the-art" methods fail to outperform their predecessors under a limited oracle budget allowing 10K queries and that no existing algorithm can efficiently solve certain molecular optimization problems in this setting. We analyze the influence of the optimization algorithm choices, molecular assembly strategies, and oracle landscapes on the optimization performance to inform future algorithm development and benchmarking. PMO provides a standardized experimental setup to comprehensively evaluate and compare new molecule optimization methods with existing ones. All code can be found at https://github.com/wenhao-gao/mol_opt.

1. Introduction

Designing new functional molecules is a constrained multi-objective optimization problem that aims to find molecules with desired properties such as selective inhibition against a disease target, with additional desiderata and constraints to ensure the structures are stable and synthesizable. The importance of molecular design problems has attracted significant efforts to develop systematical molecular design methodologies instead of exhaustive searches, leveraging combinatorial optimization algorithms (Jensen, 2019; Xie et al., 2021), predictive machine learning models (Graff et al., 2021; Gentile et al., 2022), and generative models (Olivecrona et al., 2017; Gómez-Bombarelli et al., 2018). Especially in recent years, we have witnessed significant progress in solving challenging problems across various aspects of computational molecular optimizations, such as achieving high validity (Kusner et al., 2017; Jin et al., 2018; Krenn et al., 2020), diversity (Bengio et al., 2021b), and, most recently, synthesizability (Bradshaw et al., 2020; Gao et al., 2022).

Despite the exciting progress in the field and the abundance of new methods proposed, how these algorithms compare against each other remains unclear. Most method development papers and existing benchmarks such as Guacamol (Brown et al., 2019), Therapeutics Data Commons (TDC) (Huang et al., 2021) and Tripp et al.'s (Tripp et al., 2021) suffer from at least one of three problems: (1) Lack of consideration of the oracle budget: Many papers (Zhou et al., 2019; Nigam et al., 2020; Gottipati et al., 2020) do not report how many times the oracle function is called to achieve the reported results (i.e., how many candidate molecules were evaluated), except in rare cases (Korovina et al., 2020; Fu et al., 2022; Bengio et al., 2021a), despite this range spanning orders of magnitude. As most valuable oracles—experiments or high-accuracy simulations—require substan-

[*]Equal contribution [1]Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139 [2]Department of Computational Science and Engineering, Georgia Institute of Technology, Atlanta, GA 30332 [3]Department of Computer Science, University of Illinois at Urbana-Champaign, Urbana, IL 61801 [4]Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Cambridge, MA 02139. Correspondence to: Connor W. Coley <ccoley@mit.edu>.

2nd AI4Science Workshop at the 39^{th} International Conference on Machine Learning (ICML), 2022.

tial costs, it is vital to identify the desired compound with as few oracle calls as possible. (2) Trivial oracles: Some papers only report results on trivial oracles (Nigam et al., 2020) like quantitative estimate of drug-likeness (QED) (Bickerton et al., 2012) or penalized octanol-water partition coefficient (LogP); other papers even introduce new self-designed tasks (Gottipati et al., 2020; Bengio et al., 2021a), which obfuscates a comparison to prior work. (3) Randomness: Another complication is that many algorithms are not deterministic and exhibit significant run-to-run variation, so reporting results from several independent trials is essential. Besides, all of the existing benchmarks examined no more than five methods due to the significant variation between molecular optimization algorithms. Thus we still lack a unified benchmark to assess which methods are beneficial in a realistic discovery scenario.

This paper presents a new reproducible large-scale experimental study with a sound experimental protocol for molecular design, `PMO`. We have benchmarked 25 methods across 23 various widely-used oracle functions, with each of them tuned and run for multiple independent trials. To consider a combination of optimization ability and sample efficiency, we limit the number of maximum oracle calls up to 10,000 queries and measure model performance with the area under the curve (AUC) of the top-10 average performance versus oracle calls. Our results show that none of the existing molecular optimization algorithms are efficient enough to solve a *de novo* molecular optimization problem within a realistic oracle budget of hundreds of experiments, and "state-of-the-art" methods often fail to outperform their predecessors. We analyze the algorithmic contribution and the influence of oracle landscapes on optimization performance to inform future algorithm development and benchmarking. Our results highlight the necessity of standardized experimental reporting, including independent replicates and extensive hyperparameter tuning. We envision that the `PMO` benchmark will make molecular optimizations more accessible and reproducible, thereby facilitating algorithmic advances and, ultimately, the broader adoption of molecular optimization techniques in experimental drug and materials discovery workflows.

2. Algorithms

A molecular optimization method has two major components: (1) a molecular assembly strategy that defines the chemical space by assembling a digital representation of compounds, and (2) an optimization algorithm that navigates this chemical space. This section will first introduce common strategies to assemble molecules, then introduce the benchmarked molecular optimization methods based on the core optimization algorithms. Table 1 summarizes current molecular design methods categorized based on assembly strategy and optimization method, including but not limited to the methods included in our baseline. We emphasize that our goal is not to make an exhaustive list but to include a group of methods that are representative enough to obtain meaningful conclusions.

2.1. Preliminaries

In this paper, we limit our scope to general-purpose single-objective molecular optimization methods focusing on small organic molecules with scalar properties with some relevance to therapeutic design. Formally, we can formulate such a molecular design problem as an optimization problem:

$$m^* = \arg\max_{m \in \mathcal{Q}} \mathcal{O}(m), \tag{1}$$

where m is a molecular structure, $\mathcal{Q}$ demotes the design space called chemical space that comprises all possible candidate molecules. The size of $\mathcal{Q}$ is impractically large, e.g., 10^{60} (Bohacek et al., 1996). We assume we have access to the ground truth value of a property of interest denoted by $\mathcal{O}(m) : \mathcal{Q} \rightarrow \mathcal{R}$, where an oracle, $\mathcal{O}$, is a black-box function that evaluates certain chemical or biological properties of a molecule m and returns the ground truth property $\mathcal{O}(m)$ as a scalar.

2.2. Molecular assembly strategies

String-based. String-based assembly strategies represent molecules as strings and explore chemical space by modifying strings directly: character-by-character, token-by-token, or through more complex transformations based on a specific grammar. We include two types of string representations: (1) Simplified Molecular-Input Line-Entry System (SMILES) (Weininger, 1988), a linear notation describing the molecular structure using short ASCII strings based on a graph traversal algorithm; (2) SELF-referencIng Embedded Strings (SELFIES) (Krenn et al., 2020), which avoids syntactical invalidity by enforcing the chemical validity rules in a formal grammar table.

Graph-based. Two-dimensional (2D) graphs can intuitively define molecular identities to a first approximation (ignoring stereochemistry): the nodes and edges represent the atoms and bonds. There are two main assembling strategies for molecular graphs: (1) an atom-based assembly strategy (Zhou et al., 2019) that adds or modifies atoms and bonds one at a time, which covers all valid chemical space; (2) a fragment-based assembling strategy (Jin et al., 2018) that summarizes common molecular fragments and operates one fragment at a time. Note that fragment-based strategy could also include atom-level operation.

Synthesis-based. Most of the above assembly strategies can cover a large chemical space, but an eventual goal of molecular design is to physically test the candidate; thus, a

Table 1: Representative molecule generation methods, categorised based on the molecular assembly strategies and the optimization algorithms. Columns are various molecular assembly strategies while rows are different optimization algorithms.

	SMILES	SELFIES	Graph (atom)	Graph (fragment)	Synthesis
GA	SMILES-GA (Brown et al., 2019)	GA+D (Nigam et al., 2020) STONED (Nigam et al., 2021)	-	Graph-GA (Jensen, 2019)	SynNet (Gao et al., 2022)
MCTS	-	-	Graph-MCTS (Jensen, 2019)	-	-
BO	BOSS (Moss et al., 2020)	-	-	GPBO (Tripp et al., 2021)	ChemBO (Korovina et al., 2020)
VAE	SMILES-VAE (Gómez-Bombarelli et al., 2018)	SELFIES-VAE	-	JTVAE (Jin et al., 2018)	DoG-AE (Bradshaw et al., 2020)
GAN	ORGAN (Sanchez-Lengeling et al., 2017)	-	MolGAN (De Cao & Kipf, 2018)	-	-
SBM	-	-	-	GFlowNet(Bengio et al., 2021b) MARS(Xie et al., 2021)	-
HC	SMILES LSTM (Brown et al., 2019)	SELFIES LSTM	-	MIMOSA (Fu et al., 2021)	DoG-Gen (Bradshaw et al., 2020)
RL	REINVENT (Olivecrona et al., 2017)	SELFIES-REINVENT	MolDQN (Zhou et al., 2019) GCPN (You et al., 2018)	RationaleRL(Jin et al., 2020) FREED (Yang et al., 2021)	PGFS (Gottipati et al., 2020) REACTOR (Horwood & Noutahi, 2020)
GRAD	-	Pasithea (Shen et al., 2021)	-	DST (Fu et al., 2022)	-

desideratum is to explore synthesizable candidates only. Designing molecules by assembling synthetic pathways from commercially-available starting materials and reliable chemical transformation adds a constraint of synthesizability to the search space. This class can be divided into template-free (Bradshaw et al., 2020) and template-based (Gao et al., 2022) based on how to define reliable chemical transformations, but we will not distinguish between them in this paper as synthesis-based strategy is relatively less explored in general.

2.3. Optimization algorithms

Screening (a.k.a. virtual screening) involves searching over a pre-enumerated library of molecules exhaustively. We include Screening as a baseline, which randomly samples ZINC 250k (Sterling & Irwin, 2015). Model-based screening (MolPAL) (Graff et al., 2021) instead trains a surrogate model and prioritizes molecules that are scored highly by the surrogate to accelerate screening. We adopt the implementation from the original paper and treat it as a model-based version of screening.

Genetic Algorithm (GA) is a popular heuristic algorithm inspired by natural evolutionary processes. It combines *mutation* and/or *crossover* perturbing a *mating pool* to enable exploration in the design space. We include SMILES GA (Yoshikawa et al., 2018) that defines actions based on SMILES context-free grammar and a modified version of STONED (Nigam et al., 2021) that directly manipulates tokens in SELFIES strings. Unlike the string-based GAs that only have mutation steps, Graph GA (Jensen, 2019) derives crossover rules from graph matching and includes both atom- and fragment-level mutations. Finally, we include SynNet (Gao et al., 2022) as a synthesis-based example that applies a genetic algorithm on binary fingerprints and decodes to synthetic pathways. We adopt the implementation of SMILES GA and Graph GA from Guacamol (Brown et al., 2019), STONED, and SynNet from the original paper. We also include the original implementation of a deep learning enhanced version of SELFIES-based GA from (Nigam et al., 2020) and label it as GA+D.

Monte-Carlo Tree Search (MCTS) locally and randomly searches each branch of the current state (e.g., a molecule or partial molecule) and selects the most promising ones (those with highest property scores) for the next iteration. Graph MCTS (Jensen, 2019) is an MCTS algorithm based on atom-level searching over molecular graphs. We adopt the implementation from Guacamol (Brown et al., 2019).

Bayesian optimization (BO) (Shahriari et al., 2015) is a large class of method that builds a surrogate for the objective function using a Bayesian machine learning technique, such as Gaussian process (GP) regression, then uses an *acquisition function* combining the surrogate and uncertainty to decide where to sample, which is naturally model-based. However, as BO usually leverages a non-parametric model, it scales poorly with sample size and feature dimension (Deisenroth & Ng, 2015). We included a string-based model, BO over String Space (BOSS) (Moss et al., 2020), and a synthesis-based model, ChemBO (Korovina et al., 2020), but do not obtain meaningful results even with early stopping (see Section B.3 for early stopping setting, and

Section B.33 for more analysis). Finally, we adopt Gaussian process Bayesian optimization (GP BO) (Tripp et al., 2021) that optimizes the GP acquisition function with Graph GA methods in an inner loop. The implementation is from the original paper, and we treat it as a model-based version of Graph GA.

Variational autoencoders (VAEs) (Kingma & Welling, 2013) are a class of generative method that maximize a lower bound of the likelihood (evidence lower bound (ELBO)) instead of estimating the likelihood directly. A VAE typically learns to map molecules to and from real space to enable the indirect optimization of molecules by numerically optimizing latent vectors, most commonly with BO. SMILES-VAE (Gómez-Bombarelli et al., 2018) uses a VAE to model molecules represented as SMILES strings, and is implemented in MOSES (Polykovskiy et al., 2020). We adopt the identical architecture to model SELFIES strings and denote it as SELFIES-VAE. JT-VAE (Jin et al., 2018) abstracts a molecular graph into a junction tree (i.e., a cycle-free structure), and design message passing network as the encoder and tree-RNN as the decoder. DoG-AE (Bradshaw et al., 2020) uses Wasserstein autoencoder (WAE) to learn the distribution of synthetic pathways.

Score-based modeling (SBM) formulates the problem of molecule design as a sampling problem where the target distribution is a function of the target property, featured by Markov-chain Monte Carlo (MCMC) methods that construct Markov chains with the desired distribution as their equilibrium distribution. MARkov molecular Sampling (MARS) (Xie et al., 2021) is such an example that leverages a graph neural network to propose action steps adaptively in an MCMC with an annealing scheme. Generative Flow Network (GFlowNet) (Bengio et al., 2021b) views the generative process as a flow network and trains it with a temporal difference-like loss function based on the conservation of flow. By matching the property of interest with the volume of the flow, generation can sample a distribution proportional to the target distribution.

Hill climbing (HC) is an iterative learning method that incorporates the generated high-scored molecules into the training data and fine-tunes the generative model for each iteration. It is a variant of the cross-entropy method (De Boer et al., 2005), and can also be seen as a variant of REINFORCE (Williams, 1992) with a particular reward shaping. We adopt SMILES-LSTM-HC from Guacamol (Brown et al., 2019) that leverages a LSTM to learn the molecular distribution represented in SMILES strings, and modifies it to a SELFIES version denoted as SELFIES-LSTM-HC. MultI-constraint MOlecule SAmpling (MIMOSA) (Fu et al., 2021) leverages a graph neural network to predict the identity of a masked fragment node and trains it with a HC algorithm. DoG-Gen (Bradshaw et al., 2020) instead learn the distribution of synthetic pathways as Directed Acyclic Graph (DAGs) with an RNN generator.

Reinforcement Learning (RL) learns how intelligent agents take actions in an environment to maximize the cumulative reward by transitioning through different states. In molecular design, a state is usually a partially generated molecule; actions are manipulations at the level of graphs or strings; rewards are defined as the generated molecules' property of interest. REINVENT (Olivecrona et al., 2017) adopts a policy-based RL approach to tune RNNs to generate SMILES strings. We adopt the implementation from the original paper, and modify it to generate SELFIES strings, SELFIES-REINVENT. MolDQN (Zhou et al., 2019) uses a deep Q-network to generate molecular graph in an atom-wise manner.

Gradient ascent (GRAD) methods learn to estimate the gradient direction based on the landscape of the molecular property over the chemical space, and back-propagate to optimize the molecules. Pasithea (Shen et al., 2021) exploits an MLP to predict properties from SELFIES strings, and back-propagate to modify tokens. Differentiable scaffolding tree (DST) (Fu et al., 2022) abstracts molecular graphs to scaffolding trees and leverages a graph neural network to estimate the gradient. We adopted the implementation from the original papers and modify them to update the surrogates online as data are acquired.

3. Experiments

3.1. Benchmark setup

This section introduces the setup of `PMO` benchmark. The main idea behind `PMO` is the pursuit of an ideal *de novo* molecular optimization algorithm that exhibits strong optimization ability, sample efficiency, generalizability to various optimization objectives, and robustness to hyperparameter selection and random seeds.

Oracle: To examine the generalizability of methods, we aim to include a broad range of pharmaceutically-relevant oracle functions. Systematic categorization of oracles based on their landscape is still challenging due to the complicated relationship between molecular structure and function. We have included the most commonly used oracles (see a recent discussion of commonly-used oracles in (Tripp et al., 2022)). Several have been described as "trivial", but we assert this is only true when the number of oracle queries is not controlled. In total, `PMO` includes 23 oracle functions: QED (Bickerton et al., 2012), DRD2 (Olivecrona et al., 2017), GSK3β, JNK3 (Li et al., 2018), and 19 oracles from Guacamol (Brown et al., 2019). QED is a relatively simple heuristic function that estimates if a molecule is likely to be a drug based on if it contains some "red flags". DRD2, GSK3β, and JNK3 are machine learning models (support

vector machine (SVM), random forest (RF)) fit to experimental data to predict the bioactivities against their corresponding disease targets. Guacamol oracles are designed to mimic the drug discovery objectives based on multiple considerations, called multi-property objective (MPO), including similarity to target molecules, molecular weights, CLogP, etc. All oracle scores are normalized from 0 to 1, where 1 is optimal. Recently, docking scores that estimate the binding affinity between ligands and proteins have been adopted as oracles (Cieplinski et al., 2020; Huang et al., 2021; García-Ortegón et al., 2021). However, as the simulations are more costly than above ones but are still coarse estimates that do not reflect true bioactivity, we leave it to future work.

Metrics: To consider the optimization ability and sample efficiency simultaneously, we report the area under the curve (AUC) of top-K average property value versus the number of oracle calls (*AUC top-K*) as the primary metric to measure the performance. Unlike using top-K average property, AUC rewards methods that reach high values with fewer oracle calls. We use $K = 10$ in this paper as it is useful to identify a small number of distinct molecular candidates to progress to later stages of development. We limit the number of oracle calls to 10000, though we expect methods to optimize well within hundreds of calls when using experimental evaluations. The reported values of AUCs are min-max scaled to $[0, 1]$.

Data: Whenever a database is required, we use ZINC 250K dataset that contains around 250K molecules sampled from the ZINC database (Sterling & Irwin, 2015) for its pharmaceutical relevance, moderate size, and popularity. Screening and MolPAL search over this database; generative models such as VAEs, LSTMs are pretrained on this database; fragments required for JT-VAE, MIMOSA, DST are extracted from this database.

Other details: We tuned hyperparameters for most methods on the average AUC Top-10 from 3 independent runs of two Guacamol tasks: zaleplon_mpo and perindopril_mpo. Reported results are from 5 independent runs with various random seeds. All data, oracle functions, and metric evaluations are taken from the Therapeutic Data Commons (TDC) (Huang et al., 2021) (`https://tdcommons.ai`) and more details are described in Appendix.

3.2. Results & Analysis

The primary results are summarized in Table 2 and 3. For clarity, we only show the ten best-performing models in the table. We show a selective set of optimization curves in Figure 1. The remaining results are in the Appendix A and D.

Sample efficiency matters. A first observation from the results is that none of the methods can optimize the simple toy objectives within hundreds of oracle calls, except some trivial ones like QED, DRD2, and osimertinib_mpo, which emphasize the need for more efficient molecular optimization algorithms. By comparing the ranking of AUC Top-10 and Top-10, we notice some methods have significantly different relative performances. For example, SMILES LSTM HC, which used to be seen as comparable to Graph GA, actually requires more oracle queries to achieve the same level of performance, while a related algorithm, REINVENT, requires far fewer (see Figure 1). These differences indicate the training algorithm of REINVENT is more efficient than HC, emphasizing the importance of AUC Top-10 as an evaluation metric. In addition, methods that assemble molecules either token-by-token or atom-by-atom from a single start point, such as GA+D, MolDQN, and Graph MCTS, are most data-inefficient. Those methods potentially cover broader chemical space and include many undesired candidates, such as unstable or unsynthesizable ones, which wastes a significant portion of the oracle budget and also imposes a strong requirement on the oracles' quality.

Older algorithms are still powerful. As shown in Table 2 and 3, the best-performing algorithms are REINVENT and Graph GA among all the compared methods, despite both of them being released several years ago. However, we rarely see model development papers list these two methods as baselines. The absence of a thorough benchmark has obfuscated the fact that newer models published in top AI conferences do not seem to offer an improvement in performance by our metrics. Of course, we should acknowledge that some of the methods are developed to solve other problems in molecular optimization, such as strings' validity or synthesizability, and some might have opened new avenues to tackle the problem that could potentially be more efficient when mature. Still, some of the field's efforts and resources might be wasted due to a lack of a thorough and standardized benchmark.

There are no obvious shortcomings of SMILES. SELFIES was designed as a substitute of SMILES to solve the syntactical invalidity problem met in SMILES representation and has been adopted by a number of recent studies. However, our head-to-head comparison of string-based methods, especially the ones leveraging language models, shows that most SELFIES variants cannot outperform their corresponding SMILES-based methods in terms of optimization ability and sample efficiency (Figure 2). We do observe some early methods like the initial version of SMILES VAE (Gómez-Bombarelli et al., 2018) (2016) and ORGAN (Sanchez-Lengeling et al., 2017) (2017) struggle to propose valid SMILES strings, but this is not an issue for more recent methods. We believe this is because current language models are better able to learn the grammar of SMILES strings, which has flattened the advantage of SELFIES. Further, as

Table 2: Performance of ten best performing molecular optimization methods based on mean AUC Top-10. We report the mean and standard deviation of **AUC Top-10** from 5 independent runs. The best model in each task is labeled bold. Full results are in the Appendix A

Method Assembly	REINVENT SMILES	Graph GA Fragments	REINVENT SELFIES SELFIES	GP BO Fragments	STONED SELFIES
albuterol_similarity	0.882± 0.006	0.838± 0.016	0.826± 0.030	**0.898± 0.014**	0.745± 0.076
amlodipine_mpo	0.635± 0.035	**0.661± 0.020**	0.607± 0.014	0.583± 0.044	0.608± 0.046
celecoxib_rediscovery	0.713± 0.067	0.630± 0.097	0.573± 0.043	**0.723± 0.053**	0.382± 0.041
deco_hop	0.666± 0.044	0.619± 0.004	0.631± 0.012	0.629± 0.018	0.611± 0.008
drd2	0.945± 0.007	0.964± 0.012	0.943± 0.005	0.923± 0.017	0.913± 0.020
fexofenadine_mpo	0.784± 0.006	0.760± 0.011	0.741± 0.002	0.722± 0.005	**0.797± 0.016**
gsk3b	**0.865± 0.043**	0.788± 0.070	0.780± 0.037	0.851± 0.041	0.668± 0.049
isomers_c7h8n2o2	0.852± 0.036	0.862± 0.065	0.849± 0.034	0.680± 0.117	0.899± 0.011
isomers_c9h10n2o2pf2cl	0.642± 0.054	0.719± 0.047	0.733± 0.029	0.469± 0.180	0.805± 0.031
jnk3	**0.783± 0.023**	0.553± 0.136	0.631± 0.064	0.564± 0.155	0.523± 0.092
median1	**0.356± 0.009**	0.294± 0.021	0.355± 0.011	0.301± 0.014	0.266± 0.016
median2	0.276± 0.008	0.273± 0.009	0.255± 0.005	**0.297± 0.009**	0.245± 0.032
mestranol_similarity	0.618± 0.048	0.579± 0.022	0.620± 0.029	**0.627± 0.089**	0.609± 0.101
osimertinib_mpo	**0.837± 0.009**	0.831± 0.005	0.820± 0.003	0.787± 0.006	0.822± 0.012
perindopril_mpo	0.537± 0.016	0.538± 0.009	0.517± 0.021	0.493± 0.011	0.488± 0.011
qed	0.941± 0.000	0.940± 0.000	0.940± 0.000	0.937± 0.000	0.941± 0.000
ranolazine_mpo	0.760± 0.009	0.728± 0.012	0.748± 0.018	0.735± 0.013	**0.765± 0.029**
scaffold_hop	**0.560± 0.019**	0.517± 0.007	0.525± 0.013	0.548± 0.019	0.521± 0.034
sitagliptin_mpo	0.021± 0.003	**0.433± 0.075**	0.194± 0.121	0.186± 0.055	0.393± 0.083
thiothixene_rediscovery	0.534± 0.013	0.479± 0.025	0.495± 0.040	**0.559± 0.027**	0.367± 0.027
troglitazone_rediscovery	**0.441± 0.032**	0.390± 0.016	0.348± 0.012	0.410± 0.015	0.320± 0.018
valsartan_smarts	**0.178± 0.358**	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000
zaleplon_mpo	**0.358± 0.062**	0.346± 0.032	0.333± 0.026	0.221± 0.072	0.325± 0.027
Sum	14.196	13.751	13.471	13.156	13.024
Rank	1	2	3	4	5
Method Assembly	LSTM HC SMILES	SMILES GA SMILES	SynNet Synthesis	DoG-Gen Synthesis	DST Fragments
albuterol_similarity	0.719± 0.018	0.661± 0.066	0.584± 0.039	0.676± 0.013	0.619± 0.020
amlodipine_mpo	0.593± 0.016	0.549± 0.009	0.565± 0.007	0.536± 0.003	0.516± 0.007
celecoxib_rediscovery	0.539± 0.018	0.344± 0.027	0.441± 0.027	0.464± 0.009	0.380± 0.006
deco_hop	**0.826± 0.017**	0.611± 0.006	0.613± 0.009	0.800± 0.007	0.608± 0.008
drd2	0.919± 0.015	0.908± 0.019	**0.969± 0.004**	0.948± 0.001	0.820± 0.014
fexofenadine_mpo	0.725± 0.003	0.721± 0.015	0.761± 0.015	0.695± 0.003	0.725± 0.005
gsk3b	0.839± 0.015	0.629± 0.044	0.789± 0.032	0.831± 0.021	0.671± 0.032
isomers_c7h8n2o2	0.485± 0.045	**0.913± 0.021**	0.455± 0.031	0.465± 0.018	0.548± 0.069
isomers_c9h10n2o2pf2cl	0.342± 0.027	**0.860± 0.065**	0.241± 0.064	0.199± 0.016	0.458± 0.063
jnk3	0.661± 0.039	0.316± 0.022	0.630± 0.034	0.595± 0.023	0.556± 0.057
median1	0.255± 0.010	0.192± 0.012	0.218± 0.008	0.217± 0.001	0.232± 0.009
median2	0.248± 0.008	0.198± 0.005	0.235± 0.006	0.212± 0.000	0.185± 0.020
mestranol_similarity	0.526± 0.032	0.469± 0.029	0.399± 0.021	0.437± 0.007	0.450± 0.027
osimertinib_mpo	0.796± 0.002	0.817± 0.011	0.796± 0.003	0.774± 0.002	0.785± 0.004
perindopril_mpo	0.489± 0.007	0.447± 0.013	**0.557± 0.011**	0.474± 0.002	0.462± 0.008
qed	0.939± 0.000	0.940± 0.000	**0.941± 0.000**	0.934± 0.000	0.938± 0.000
ranolazine_mpo	0.714± 0.008	0.699± 0.026	0.741± 0.010	0.711± 0.006	0.632± 0.054
scaffold_hop	0.533± 0.012	0.494± 0.011	0.502± 0.012	0.515± 0.005	0.497± 0.004
sitagliptin_mpo	0.066± 0.019	0.363± 0.057	0.025± 0.014	0.048± 0.008	0.075± 0.032
thiothixene_rediscovery	0.438± 0.008	0.315± 0.017	0.401± 0.019	0.375± 0.004	0.366± 0.006
troglitazone_rediscovery	0.354± 0.016	0.263± 0.024	0.283± 0.008	0.416± 0.019	0.279± 0.019
valsartan_smarts	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000
zaleplon_mpo	0.206± 0.006	0.334± 0.041	0.341± 0.011	0.123± 0.016	0.176± 0.045
Sum	12.223	12.054	11.498	11.456	10.989
Rank	6	7	8	9	10

shown in Appendix D.1, more combinations of SELFIES tokens don't necessarily explore larger chemical space but might map to a small number of valid molecules that can be represented by truncated SELFIES strings, which implies that there are still syntax requirements in generating SELFIES strings to achieve effective exploration.

On the other hand, we observe a clear advantage of SELFIES-based GA compared to SMILES-based one, which indicates that SELFIES has an advantage over SMILES when we need to design the rules to manipulate the sequence. However, we should note that the comparison is not head-to-head, as GAs' performances highly depend on the mutation and crossover rule design, but not the representation. Graph GA's mutation rules are also encoded in SMARTS strings and operate on SMILES strings, which can also be seen as SMILES modification steps. Overall, when we need to design the generative action manually, the assembly strategy that could derive desired transformation more intuitively should be preferred.

Table 3: The ranking of each methods based on different metrics.

Method	AUC Top-1	AUC Top-10	AUC Top-100	Top-1	Top-10	Top-100	Mean
REINVENT	1	1	1	1	1	1	1
Graph GA	2	2	2	3	2	3	2.33
SELFIES-REINVENT	3	3	4	4	3	2	3.16
SMILES-LSTM-HC	5	6	7	2	4	4	4.66
GP BO	4	4	5	6	5	5	4.83
STONED	6	5	3	7	7	6	5.66
DoG-GEN	7	9	11	5	6	7	7.5
SMILES GA	9	7	6	10	8	8	8
DST	11	10	9	9	10	9	9.66
SynNet	8	8	8	11	11	14	10
SELFIES-LSTM-HC	13	14	13	8	9	11	11.33
MIMOSA	14	12	10	14	12	10	12
MARS	12	11	12	12	13	13	12.16
MolPAL	10	13	15	13	15	16	13.66
GA+D	23	17	14	15	14	12	15.83
DoG-AE	15	15	17	17	17	17	16.33
GFlowNet	20	16	16	19	16	15	17
SELFIES-VAE	16	18	21	16	18	21	18.33
Screening	17	19	19	18	19	19	18.5
SMILES-VAE	18	20	20	20	20	20	19.66
GFlowNet-AL	22	22	18	23	21	18	20.66
Pasithea	19	21	23	21	22	22	21.33
JT-VAE	21	23	22	22	23	23	22.33
Graph MCTS	24	24	24	24	24	24	24
MolDQN	25	25	25	25	25	25	25

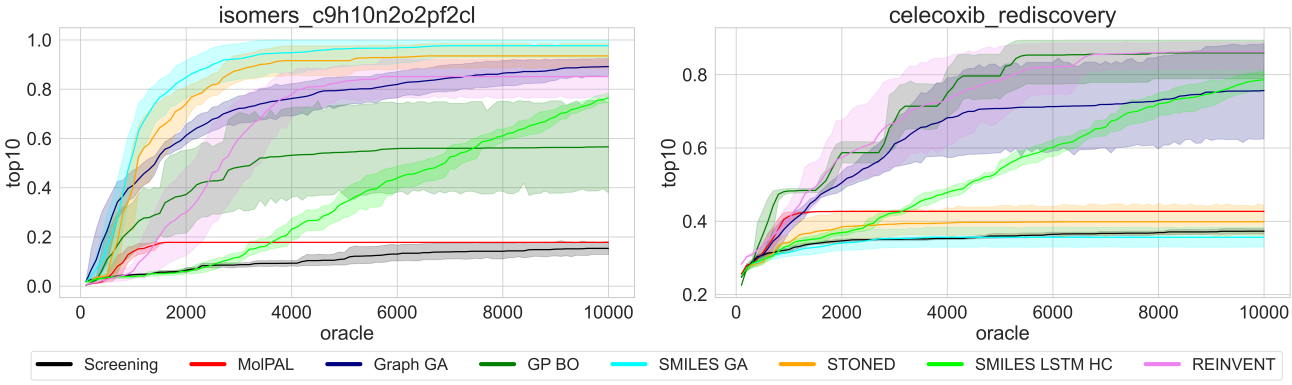

Figure 1: The optimization curves of top-10 average on optimizing isomer_c9h10n2o2pf2cl and celecoxib_rediscovery, as the representation of isomer-type and similarity-type oracles. Only 8 methods are displayed for clarity and full results are in Appendix A.

Model-based methods are potentially more efficient but need careful design. It is widely recognized in the RL community that model-based optimization methods that explicitly leverage a predictive model ("world model") are more sample efficient than the model-free ones (Wang et al., 2019). Our results on MolPAL and screening verify the principle that training a predictive model is beneficial compared to random sampling (see Figure 3). However, the results of Graph GA (model-based variant: GP BO) and GFlowNet (model-based variant: GFlowNet-AL) indicate that simply adding a predictive model might not necessarily be helpful. GP BO outperformed Graph GA in 12 tasks among 23, but Graph GA outperformed GP BO in the summation. GFlowNet outperformed GFlowNet-AL in almost every task. From the step-wise increment behavior (see Figure 1) and hyper-parameter tuning of GP BO (Appendix D.2), we conclude that the performance bottleneck is mainly the quality of the predictive model. Further, GFlowNet-AL adopts a relatively naive model-based strategy that may suppress exploitation, especially when the model is not well-trained. Overall, we observe that model-based optimization algorithms have the potential to be more sample efficient but require careful design of the inner- and outer-loop optimization algorithms so the model does not lead the search astray.

Different types of methods are more suitable for different kinds of landscapes. As shown from Figure 4 and Table 2, we find that there are some clear clusters of oracles based on the relative performance of methods. One clear pattern is that string-based GAs, such as SMILES GA

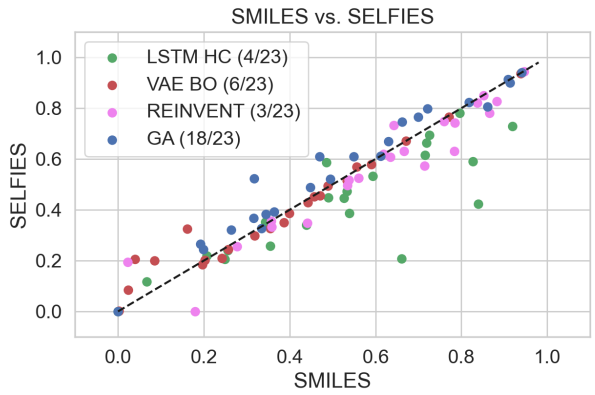

Figure 2: Comparison between SMILES- and SELFIES-based methods. Note GA is not a head-to-head comparison. Each point represents the AUC Top-10 of one task, with x-axis the SMILES variant and y-axis the SELFIES variant of the same method. Colors are labeled by the optimization algorithms. The fractions of the tasks above the parity line are in parentheses.

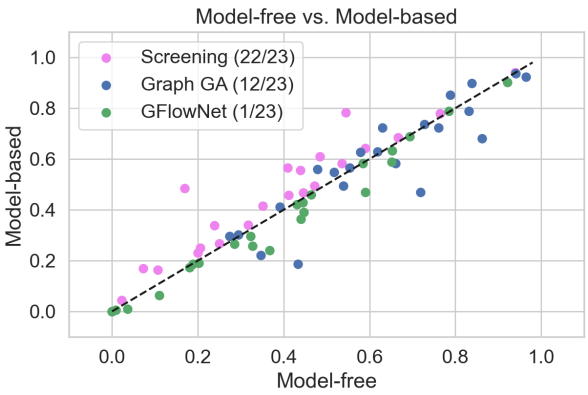

Figure 3: Comparison between model-free and corresponding model-based methods. Each point represents the AUC Top-10 of one task, with x-axis the model-free variant and y-axis the model-based variant of the same method. Colors are labeled by the optimization algorithms. The fractions of the tasks above the parity line are in parentheses.

and STONED, reach superior relative performance in tasks involving isomer functions, including isomer_c7h8n2o2, isomer_c9h10n2o2pf2cl, sitagliptin_mpo, and zaleplon_mpo. Isomer-type oracles are summations of atomic contribution, while all other MPOs are mainly based on similarity measured by fingerprints, and they generally have closer relative performance. Among similarity-based oracles, the ones including logP and TPSA, such as fexofenadine_mpo and osimertinib_mpo, are clustered together against more naive similarities such as the rediscovery and median ones. The machine learning oracles predicting bioactivities belong to the same cluster of similarity-based oracles. While QED is too trivial that almost all methods reach very close values, deco_hop, valsartan_smarts, scaffold_hop that are designed based on whether a molecule contains a substructure have varied performance. The results suggest that different types of landscape are better explored by different kinds of methods, such as string-based GA on isomer-type oracles. It is not evident which type of oracle is closest to a "true" pharmaceutical design objective, which is likely more complex and challenging to optimize; we leave further investigation on oracle landscapes and their influence on optimization to future work.

Hyperparameter reoptimization and multiple runs are required when reporting results. We also observed that the optimal set of hyper-parameters is always not the default ones suggested by a method's original paper (see Appendix D.2). For example, REINVENT's performance is highly dependent on σ; we found the best-performing value to be much larger than the values suggested in the original paper (see Figure 16 and 15) (Olivecrona et al., 2017). We conclude that this is due to unique demands of our setting of limited oracle budget, which was not a goal of the original study, and thus suggest reoptimizing the hyper-parameters whenever the testing environment is changed. Another challenge is the non-determinism of most algorithms. For example, Graph GA suffers from a relatively large variance due to its random-walk-like exploration, as does GP BO. If the oracle were a costly experimental evaluation, we might consider the worst-case performance as an endpoint to reduce the risk rather than the average performance, highlighting the importance of running multiple independent runs and reporting the distribution of outcomes.

4. Conclusions

This paper proposes `PMO`: a standardized molecular design benchmark focusing on sample efficiency as a key impediment to experimental adoption. We conduct a thorough investigation across 25 methods and 23 objectives to determine the current state-of-the-art, investigate problems, and draw insights for future studies. Our primary observations are that (1) methods considered to be strong baselines, like LSTM HC, may be inefficient in data usage; (2) several older methods, like REINVENT and Graph GA, outperform more recent ones; (3) SELFIES does not seem to offer an immediate benefit in optimization performance compared to SMILES except in GA; (4) model-based methods have the potential to be more sample efficient but require careful design of the inner-loop, outer-loop, and the predictive

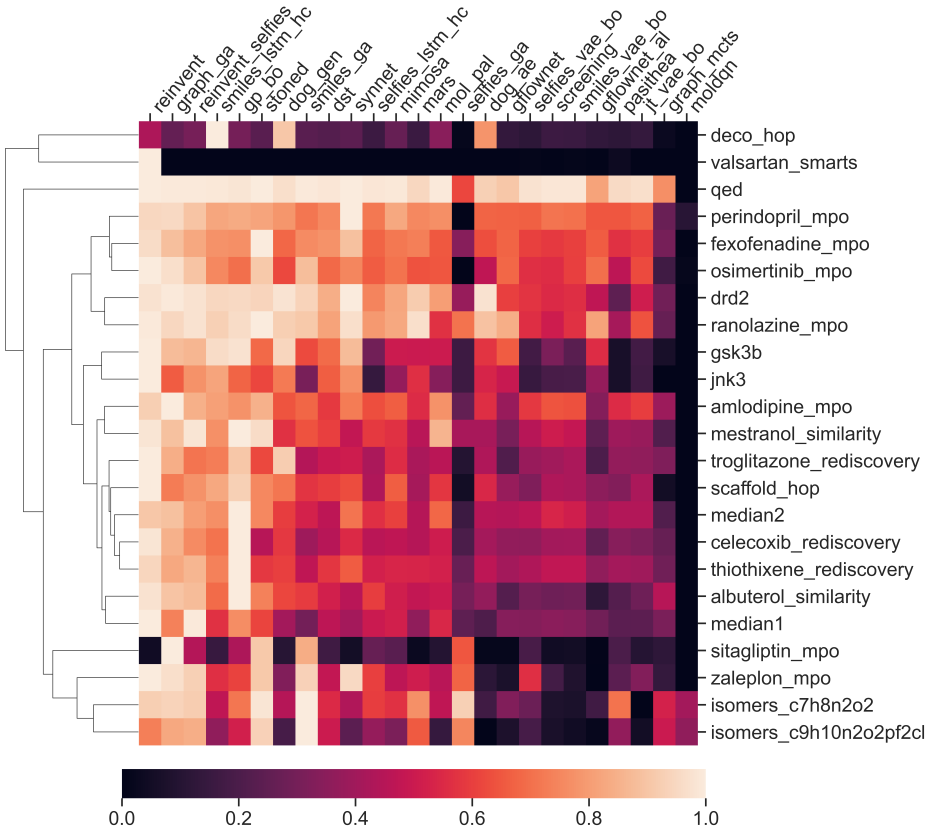

Figure 4: The heatmap and the clustering of oracles based on relative AUC Top-10. Relative AUC Top-10 is computed by normalizing AUC Top-10 values to a range from the lowest and the highest value within the task. The zaleplon_mpo and sitagliptin_mpo are multi-objective versions of isomer functions (Brown et al., 2019), while all other MPOs are based on similarity. Clear patterns emerge between a large cluster of similarity-based oracles, four isomer-based oracles, and other non-clustered ones. Different types of landscape are more suitable for different kinds of methods to explore. The cluster tree was calculated with unweighted pair group method with arithmetic mean (UPGMA) using Euclidean distance.

model; and (5) different optimization algorithms may excel at different tasks, determined by the landscapes of oracle functions; which algorithm to select is still dependent on the use case and the type of tasks.

We acknowledge several limitations of the current study: we cannot exhaustively explore every method and thoroughly tune every hyperparameter, our conclusion might be biased toward similarity-based oracles, and we are not thoroughly investigating other important quantities such as synthesizability (Gao & Coley, 2020) and diversity (Huang et al., 2021). We also emphasize that our experiments consider the number of oracle calls from scratch, i.e., the data used to train the surrogate models in model-based methods are counted in the total budget. If a dataset has been collected previously, it may be prudent to train a surrogate model on this information and use a model-based method as illustrated by Tripp et al. (Tripp et al., 2021). We will support the continued development of this benchmark to minimize the wasted effort caused by non-reproducibility and poor baselines to boost the field's growth toward solving practical molecular design problems.

We would like to conclude with recommendations for subsequent studies: (1) When comparing baselines, it is important to run algorithms under the same oracle budgets; (2) For general-purpose molecular design algorithms, one should test on multiple types of oracles; (3) Conducting multiple independent runs and reporting the distribution of outcomes is critical for non-deterministic methods; (4) Whenever the tasks and testing environment are changed, hyperparameter tuning is necessary.

Software and Data

All code, parameters, and releasable data can be found at https://github.com/wenhao-gao/mol_opt, including instructions in a README file. All results generated in this experiment can be found at https://figshare.com/articles/dataset/Results_for_practival_molecular_optimization_PMO_benchmark/20123453. Appendix B describe the experimental setup, implementation details, datasets used, and hardware configuration.

Acknowledgements

This research was supported by the Office of Naval Research under grant number N00014-21-1-2195 and the Machine Learning for Pharmaceutical Discovery and Synthesis consortium. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the Office of Naval Research. T.F. and J.S. were supported by IQVIA, NSF award SCH-2014438, IIS-1838042, NIH award R01 1R01NS107291-01 and OSF Healthcare. We thank Samuel Goldman and John Bradshaw for commenting on the manuscript.

References

Bengio, E., Jain, M., Korablyov, M., Precup, D., and Bengio, Y. Flow network based generative models for non-iterative diverse candidate generation. *Advances in Neural Information Processing Systems*, 34, 2021a.

Bengio, Y., Deleu, T., Hu, E. J., Lahlou, S., Tiwari, M., and Bengio, E. GFlowNet foundations. *CoRR*, abs/2111.09266, 2021b.

Bickerton, G. R., Paolini, G. V., Besnard, J., Muresan, S., and Hopkins, A. L. Quantifying the chemical beauty of drugs. *Nature chemistry*, 4(2):90, 2012.

Biewald, L. Experiment tracking with weights and biases, 2020. URL https://www.wandb.com/. Software available from wandb.com.

Bohacek, R. S., McMartin, C., and Guida, W. C. The art and practice of structure-based drug design: a molecular modeling perspective. *Medicinal research reviews*, 16(1): 3–50, 1996.

Bradshaw, J., Paige, B., Kusner, M. J., Segler, M., and Hernández-Lobato, J. M. Barking up the right tree: an approach to search over molecule synthesis dags. *Advances in Neural Information Processing Systems*, 33: 6852–6866, 2020.

Brown, N., Fiscato, M., Segler, M. H., and Vaucher, A. C. GuacaMol: benchmarking models for de novo molecular design. *Journal of chemical information and modeling*, 59(3):1096–1108, 2019.

Cieplinski, T., Danel, T., Podlewska, S., and Jastrzebski, S. We should at least be able to design molecules that dock well. *arXiv preprint arXiv:2006.16955*, 2020.

De Boer, P.-T., Kroese, D. P., Mannor, S., and Rubinstein, R. Y. A tutorial on the cross-entropy method. *Annals of operations research*, 134(1):19–67, 2005.

De Cao, N. and Kipf, T. MolGAN: An implicit generative model for small molecular graphs. *arXiv preprint arXiv:1805.11973*, 2018.

Deisenroth, M. and Ng, J. W. Distributed gaussian processes. In *International Conference on Machine Learning*, pp. 1481–1490. PMLR, 2015.

Fu, T., Xiao, C., Li, X., Glass, L. M., and Sun, J. MIMOSA: Multi-constraint molecule sampling for molecule optimization. *AAAI*, 2021.

Fu, T., Gao, W., Xiao, C., Yasonik, J., Coley, C. W., and Sun, J. Differentiable scaffolding tree for molecular optimization. *International Conference on Learning Representations*, 2022.

Gao, W. and Coley, C. W. The synthesizability of molecules proposed by generative models. *Journal of chemical information and modeling*, 60(12):5714–5723, 2020.

Gao, W., Mercado, R., and Coley, C. W. Amortized tree generation for bottom-up synthesis planning and synthesizable molecular design. *International Conference on Learning Representations*, 2022.

García-Ortegón, M., Simm, G. N., Tripp, A. J., Hernández-Lobato, J. M., Bender, A., and Bacallado, S. Dockstring: easy molecular docking yields better benchmarks for ligand design. *arXiv preprint arXiv:2110.15486*, 2021.

Gentile, F., Yaacoub, J. C., Gleave, J., Fernandez, M., Ton, A.-T., Ban, F., Stern, A., and Cherkasov, A. Artificial intelligence–enabled virtual screening of ultra-large chemical libraries with deep docking. *Nature Protocols*, pp. 1–26, 2022.

Gómez-Bombarelli, R., Wei, J. N., Duvenaud, D., Hernández-Lobato, J. M., Sánchez-Lengeling, B., Sheberla, D., Aguilera-Iparraguirre, J., Hirzel, T. D., Adams, R. P., and Aspuru-Guzik, A. Automatic chemical design using a data-driven continuous representation of molecules. *ACS central science*, 2018.

Gottipati, S. K., Sattarov, B., Niu, S., Pathak, Y., Wei, H., Liu, S., Blackburn, S., Thomas, K., Coley, C., Tang, J., et al. Learning to navigate the synthetically accessible chemical space using reinforcement learning. In *International Conference on Machine Learning*, pp. 3668–3679. PMLR, 2020.

Graff, D. E., Shakhnovich, E. I., and Coley, C. W. Accelerating high-throughput virtual screening through molecular pool-based active learning. *Chemical science*, 12(22): 7866–7881, 2021.

Guimaraes, G. L., Sanchez-Lengeling, B., Outeiral, C., Farias, P. L. C., and Aspuru-Guzik, A. Objective-reinforced generative adversarial networks (organ) for sequence generation models. *arXiv preprint arXiv:1705.10843*, 2017.

Horwood, J. and Noutahi, E. Molecular design in synthetically accessible chemical space via deep reinforcement learning. *ACS omega*, 5(51):32984–32994, 2020.

Huang, K., Fu, T., Gao, W., Zhao, Y., Roohani, Y., Leskovec, J., Coley, C. W., Xiao, C., Sun, J., and Zitnik, M. Therapeutics data commons: machine learning datasets and tasks for therapeutics. *NeurIPS Track Datasets and Benchmarks*, 2021.

Jensen, J. H. A graph-based genetic algorithm and generative model/monte carlo tree search for the exploration of chemical space. *Chemical science*, 10(12):3567–3572, 2019.

Jin, W., Barzilay, R., and Jaakkola, T. Junction tree variational autoencoder for molecular graph generation. *ICML*, 2018.

Jin, W., Barzilay, R., and Jaakkola, T. Multi-objective molecule generation using interpretable substructures. In *International Conference on Machine Learning*, pp. 4849–4859. PMLR, 2020.

Kingma, D. P. and Welling, M. Auto-encoding variational bayes. *arXiv preprint arXiv:1312.6114*, 2013.

Korovina, K., Xu, S., Kandasamy, K., Neiswanger, W., Poczos, B., Schneider, J., and Xing, E. ChemBO: Bayesian optimization of small organic molecules with synthesizable recommendations. In *International Conference on Artificial Intelligence and Statistics*, pp. 3393–3403. PMLR, 2020.

Krenn, M., Häse, F., Nigam, A., Friederich, P., and Aspuru-Guzik, A. Self-referencing embedded strings (selfies): A 100% robust molecular string representation. *Machine Learning: Science and Technology*, 1(4):045024, 2020.

Kusner, M. J., Paige, B., and Hernández-Lobato, J. M. Grammar variational autoencoder. In *International Conference on Machine Learning*, pp. 1945–1954. PMLR, 2017.

Li, Y., Tarlow, D., Brockschmidt, M., and Zemel, R. Gated graph sequence neural networks. *arXiv preprint arXiv:1511.05493*, 2015.

Li, Y., Zhang, L., and Liu, Z. Multi-objective de novo drug design with conditional graph generative model. *Journal of cheminformatics*, 10(1):1–24, 2018.

Moss, H., Leslie, D., Beck, D., Gonzalez, J., and Rayson, P. BOSS: Bayesian optimization over string spaces. *Advances in neural information processing systems*, 33: 15476–15486, 2020.

Nigam, A., Friederich, P., Krenn, M., and Aspuru-Guzik, A. Augmenting genetic algorithms with deep neural networks for exploring the chemical space. In *ICLR*, 2020.

Nigam, A., Pollice, R., Krenn, M., dos Passos Gomes, G., and Aspuru-Guzik, A. Beyond generative models: superfast traversal, optimization, novelty, exploration and discovery (STONED) algorithm for molecules using SELFIES. *Chemical science*, 12(20):7079–7090, 2021.

Olivecrona, M., Blaschke, T., Engkvist, O., and Chen, H. Molecular de-novo design through deep reinforcement learning. *Journal of cheminformatics*, 9(1):1–14, 2017.

Polykovskiy, D., Zhebrak, A., Sanchez-Lengeling, B., Golovanov, S., Tatanov, O., Belyaev, S., Kurbanov, R., Artamonov, A., Aladinskiy, V., Veselov, M., et al. Molecular sets (MOSES): a benchmarking platform for molecular generation models. *Frontiers in pharmacology*, 2020.

Sanchez-Lengeling, B., Outeiral, C., Guimaraes, G. L., and Aspuru-Guzik, A. Optimizing distributions over molecular space. an objective-reinforced generative adversarial network for inverse-design chemistry (ORGANIC). 2017.

Schwaller, P., Laino, T., Gaudin, T., Bolgar, P., Hunter, C. A., Bekas, C., and Lee, A. A. Molecular transformer: a model for uncertainty-calibrated chemical reaction prediction. *ACS central science*, 5(9):1572–1583, 2019.

Shahriari, B., Swersky, K., Wang, Z., Adams, R. P., and De Freitas, N. Taking the human out of the loop: A review of bayesian optimization. *Proceedings of the IEEE*, 104 (1):148–175, 2015.

Shen, C., Krenn, M., Eppel, S., and Aspuru-Guzik, A. Deep molecular dreaming: Inverse machine learning for de-novo molecular design and interpretability with surjective representations. *Machine Learning: Science and Technology*, 2021.

Snoek, J., Larochelle, H., and Adams, R. P. Practical bayesian optimization of machine learning algorithms. *Advances in neural information processing systems*, 25, 2012.

Sterling, T. and Irwin, J. J. Zinc 15–ligand discovery for everyone. *Journal of chemical information and modeling*, 55(11):2324–2337, 2015.

Tripp, A., Simm, G. N., and Hernández-Lobato, J. M. A fresh look at de novo molecular design benchmarks. In *NeurIPS 2021 AI for Science Workshop*, 2021.

Tripp, A., Chen, W., and Hernández-Lobato, J. M. An evaluation framework for the objective functions of de novo drug design benchmarks. In *ICLR2022 Machine Learning for Drug Discovery*, 2022.

Wang, T., Bao, X., Clavera, I., Hoang, J., Wen, Y., Langlois, E., Zhang, S., Zhang, G., Abbeel, P., and Ba, J. Benchmarking model-based reinforcement learning. *arXiv preprint arXiv:1907.02057*, 2019.

Weininger, D. Smiles, a chemical language and information system. 1. introduction to methodology and encoding rules. *Journal of chemical information and computer sciences*, 28(1):31–36, 1988.

Williams, R. J. Simple statistical gradient-following algorithms for connectionist reinforcement learning. *Machine learning*, 8(3):229–256, 1992.

Xie, Y., Shi, C., Zhou, H., Yang, Y., Zhang, W., Yu, Y., and Li, L. MARS: Markov molecular sampling for multi-objective drug discovery. In *ICLR*, 2021.

Yang, S., Hwang, D., Lee, S., Ryu, S., and Hwang, S. J. Hit and lead discovery with explorative rl and fragment-based molecule generation. *Advances in Neural Information Processing Systems*, 34, 2021.

Yoshikawa, N., Terayama, K., Sumita, M., Homma, T., Oono, K., and Tsuda, K. Population-based de novo molecule generation, using grammatical evolution. *Chemistry Letters*, 47(11):1431–1434, 2018.

You, J., Liu, B., Ying, Z., Pande, V., and Leskovec, J. Graph convolutional policy network for goal-directed molecular graph generation. *Advances in neural information processing systems*, 31, 2018.

Zhou, Z., Kearnes, S., Li, L., Zare, R. N., and Riley, P. Optimization of molecules via deep reinforcement learning. *Scientific reports*, 9(1):1–10, 2019.

A. Main Results

A.1. AUC Top-10 Table

A.2. Optimization Curves

A.3. Synthesizability

We computed the SA_Score of Top-100 molecules from each run and visualized the values in the Figure 10. Though SA_Score is not a great metric, we could see that synthesis-based methods have consistently lower SA_Score in all tasks.

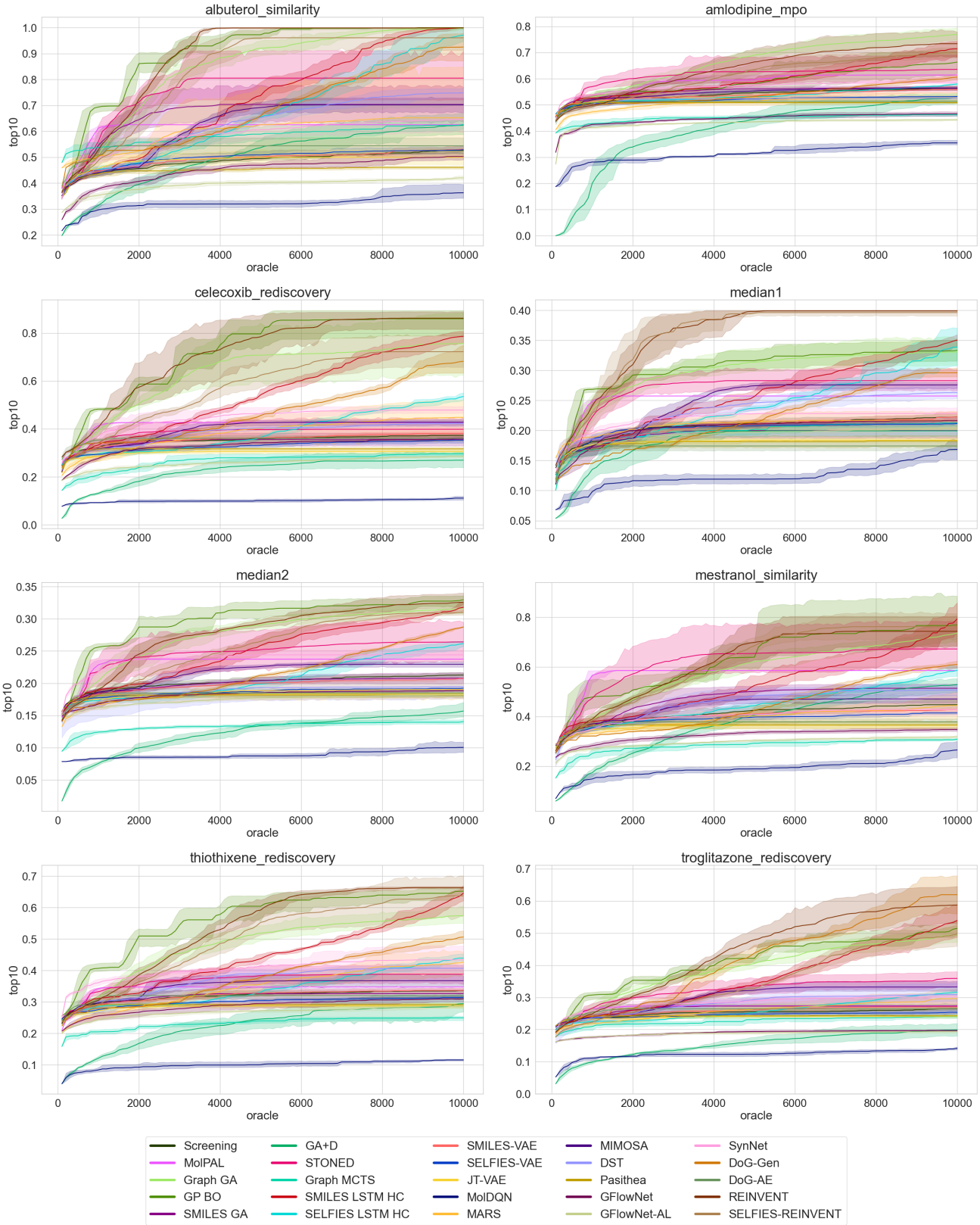

Figure 5: The optimization curves of top-10 average on optimizing similarity-based oracles.

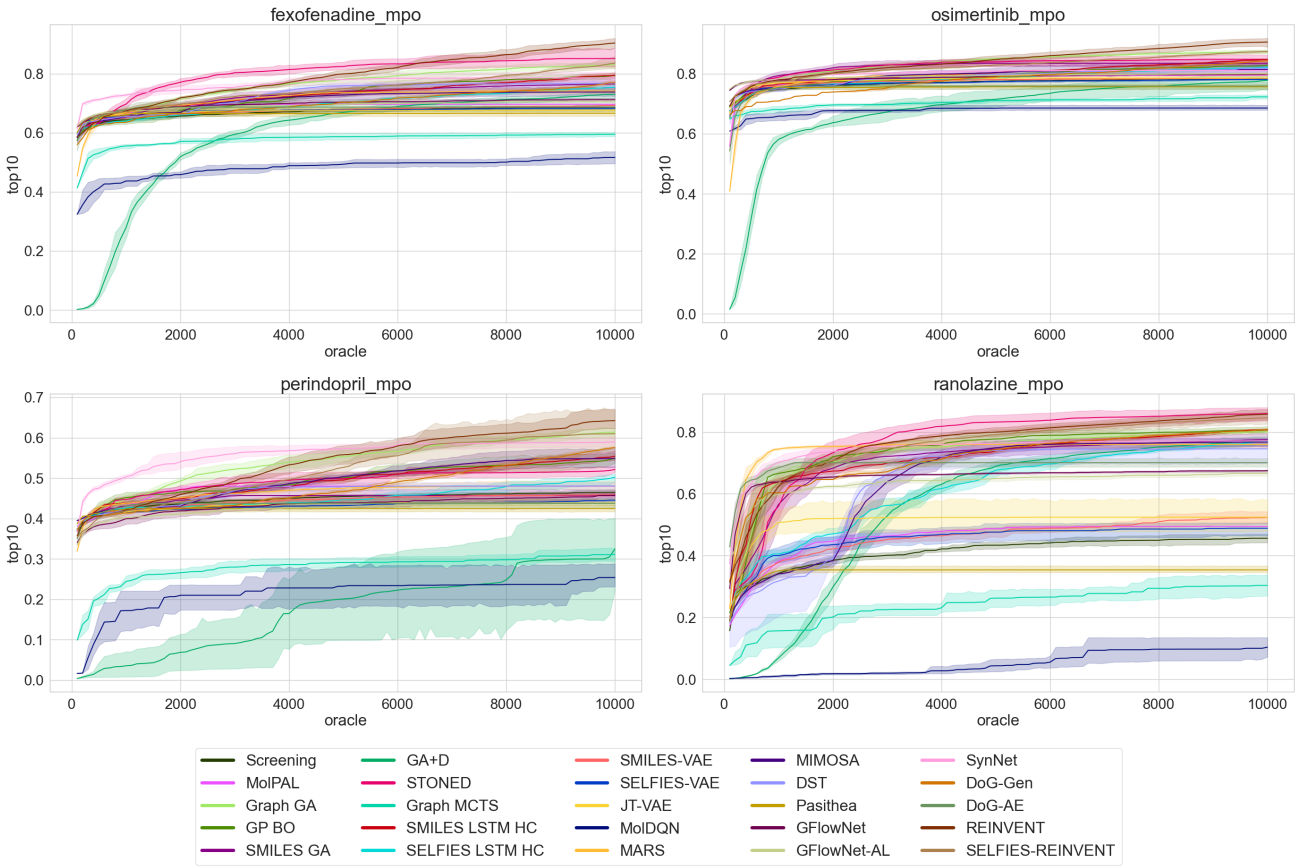

Figure 6: The optimization curves of top-10 average on optimizing similarity-based MPO oracles.

A.4. Diversity

We computed the diversity of the Top-100 molecules from each run and visualized the values in the Figure 11. The diversity is defined as the averaged internal distance within a batch of molecules, measured by Tanimoto similarity. We could see a general trend that the stronger a model is in optimization, the less diverse the results are. The methods with higher diversity would have an advantage, especially when the oracles have non-ignorable noise.

B. Implementation Details

In this section, we elaborate the implementation details for each method. We summarize some shared properties of all the methods in Table 7.

B.1. Hyperparameter setup

We have "hparams_default.yaml" and "hparams_tune.yaml" file for each method in their folders, where "hparams_default.yaml" specify the default setup and "hparams_tune.yaml" specify several possible choices of hyperparameter for tuning.

B.2. Shared Setup: dataset

To avoid the bias introduced by different dataset, e.g., ZINC, ChemBL, for all the methods, we use ZINC to (i) train/pretrain the model; (ii) provide initial molecule set and (iii) extract vocabulary set.

B.3. Shared Setup: Early Stop

We utilize early stop strategies to save computational cost for iterative learning methods, e.g., BO, HC, GA based methods.

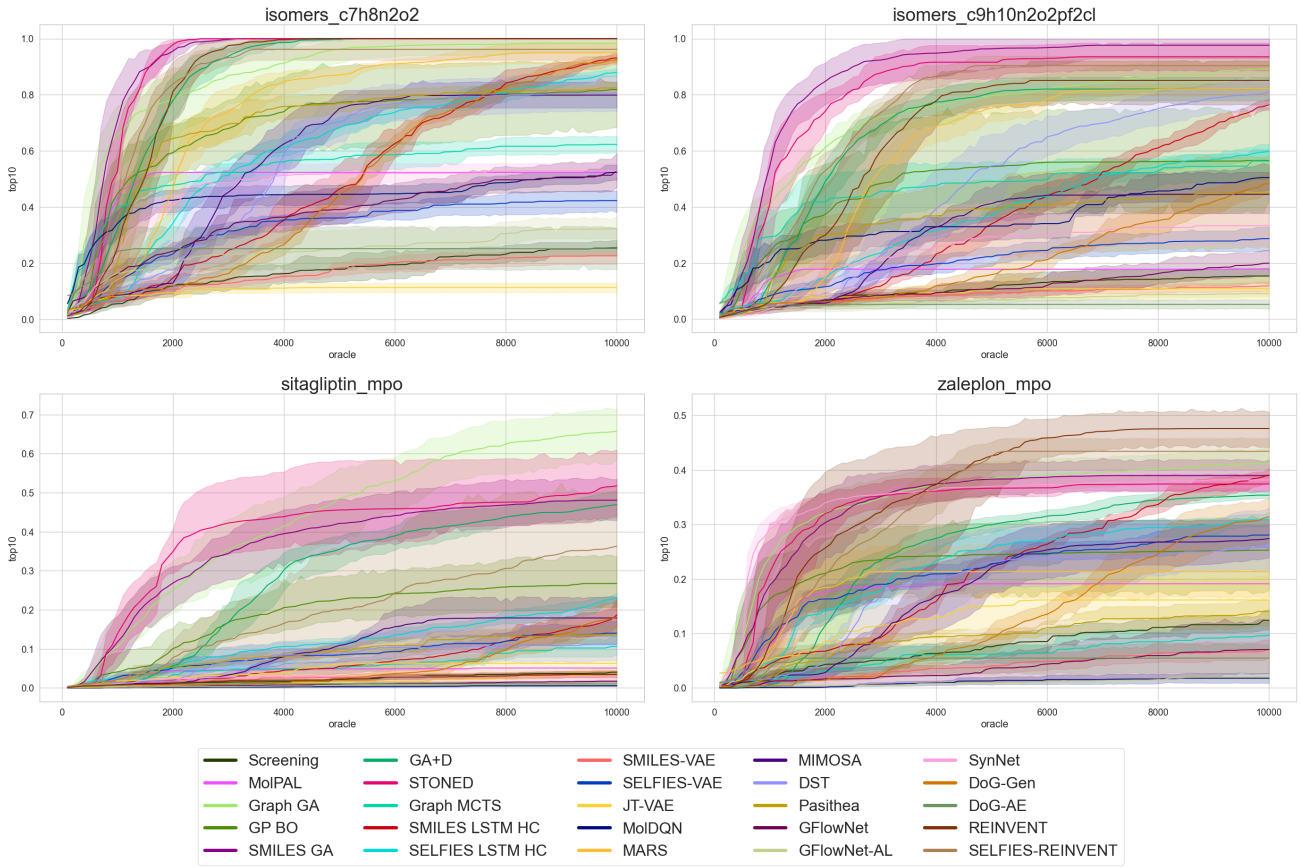

Figure 7: The optimization curves of top-10 average on optimizing isomer-based oracles.

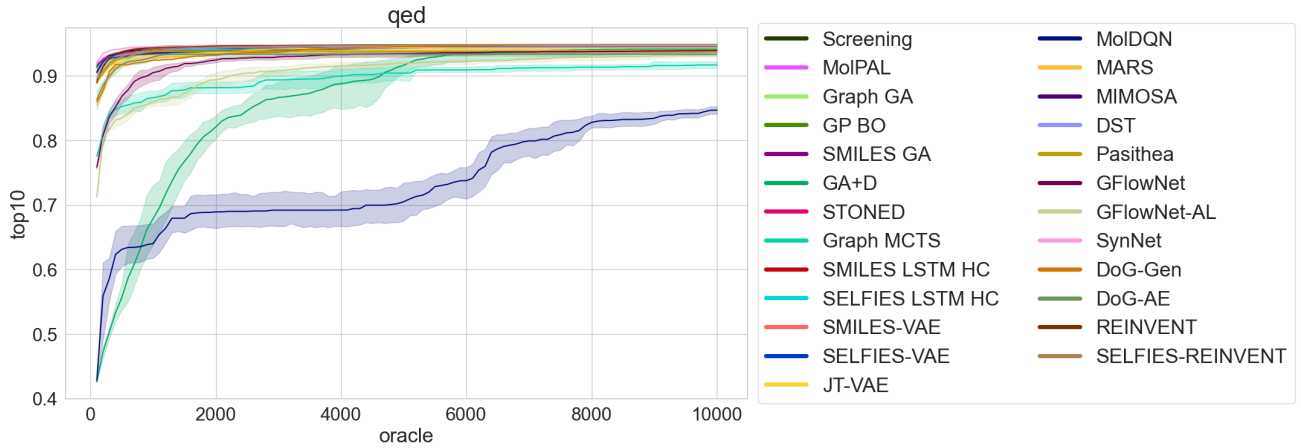

Figure 8: The optimization curves of top-10 average on optimizing QED.

The default patience is set to 5. That is, when the performance does not improve for 5 iteration (generation), we would terminate the process earlier. The methods that uses early stop strategy are ChemBO, DoG-AE, DST, Graph-GA, JTVAE, MIMOSA, RationaleRL, REINVENT, REINVENT-SELFIES, Screening, SELFIES-LSTM-HC, SELFIES-VAE, SMILES-LSTM-HC, SMILES-GA, SMILES-VAE.

B.4. Shared Setup: Bayesian optimization for all VAEs

We unify the implementation of Bayesian optimization for all VAE based methods for fair comparison, including JTVAE, SElFIES-VAE, SMILES-VAE, DoG-AE. Specifically, it is implemented by the python package "botorch". Bayesian optimization usually leverages non-parametric model, the model size will increase as more training data

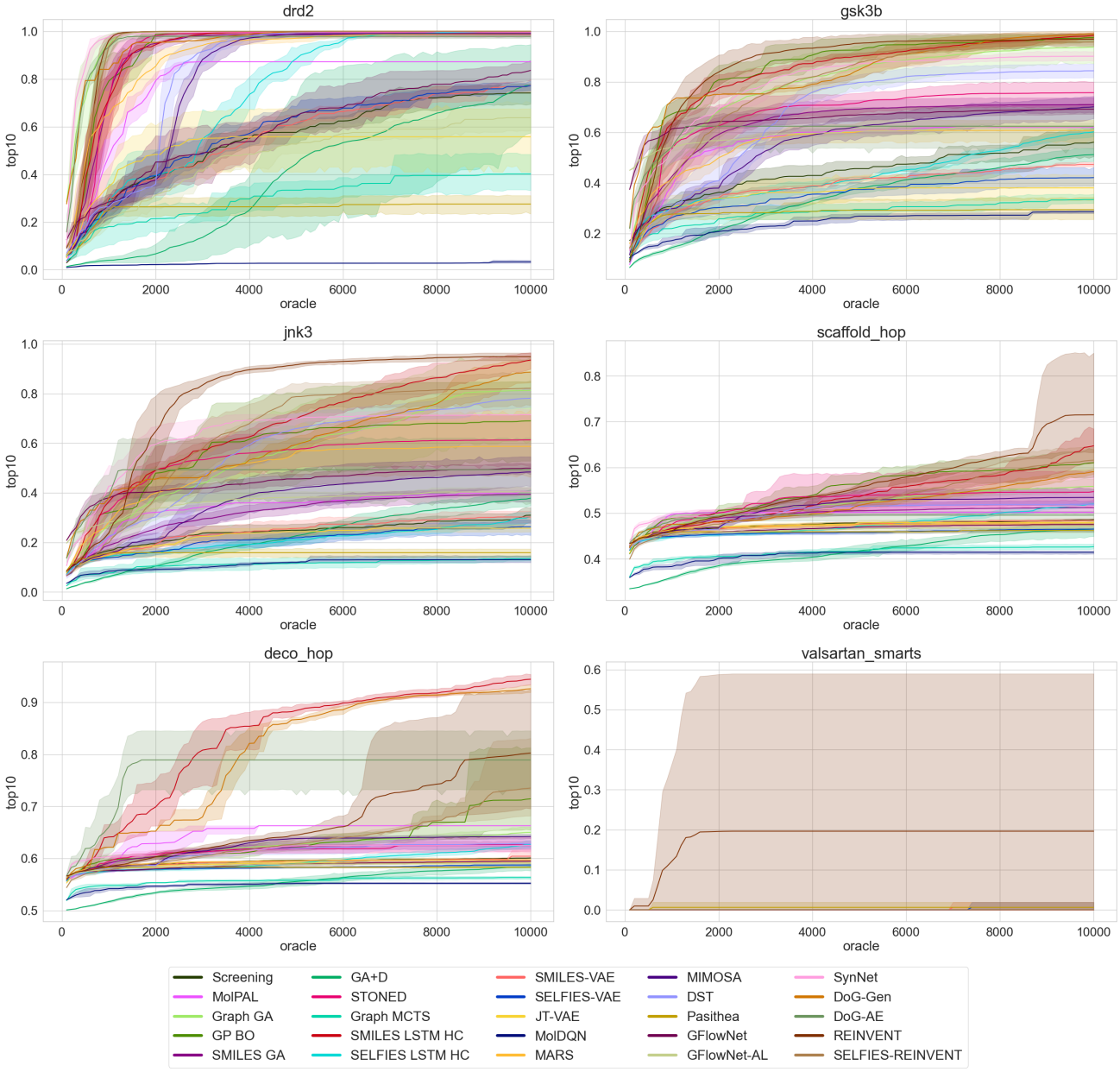

Figure 9: The optimization curves of top-10 average on optimizing SMARTS-based oracles and machine learning oracle.

come in. Worth to mention that due to the non-parametric essence, Bayesian optimization methods **scales poorly with the data size**, the run process is notoriously and intolerably slow even dealing 1k training data, so we choose to terminate the process earlier. For all the VAE+BO methods, we pretrain the VAE model, provided the pretrained model so that users can start from BO process.

B.5. Shared Setup: Pretraining

Pretraining strategy has demonstrated its effectiveness in enhancing the optimization in many approaches, including VAE and HC methods. We pretrain the models on ZINC database, and the pretrained models are available in our repository. Worth to mention that the pretraining process does not require oracle calls.

B.6. Shared Setup: PyTorch based

We want to build a unified software environment to standardize the molecule optimization process and all the methods uses PyTorch to build neural network models.

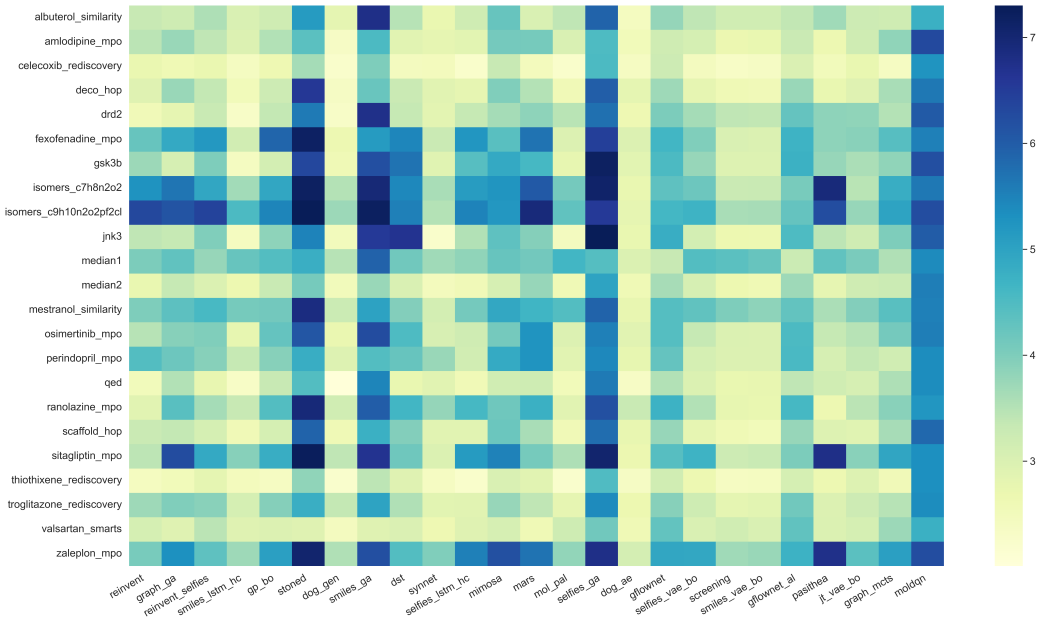

Figure 10: The heat map of SA_Score (the lower the better) calculated from the Top-100 molecules from each method, averaged from all runs.

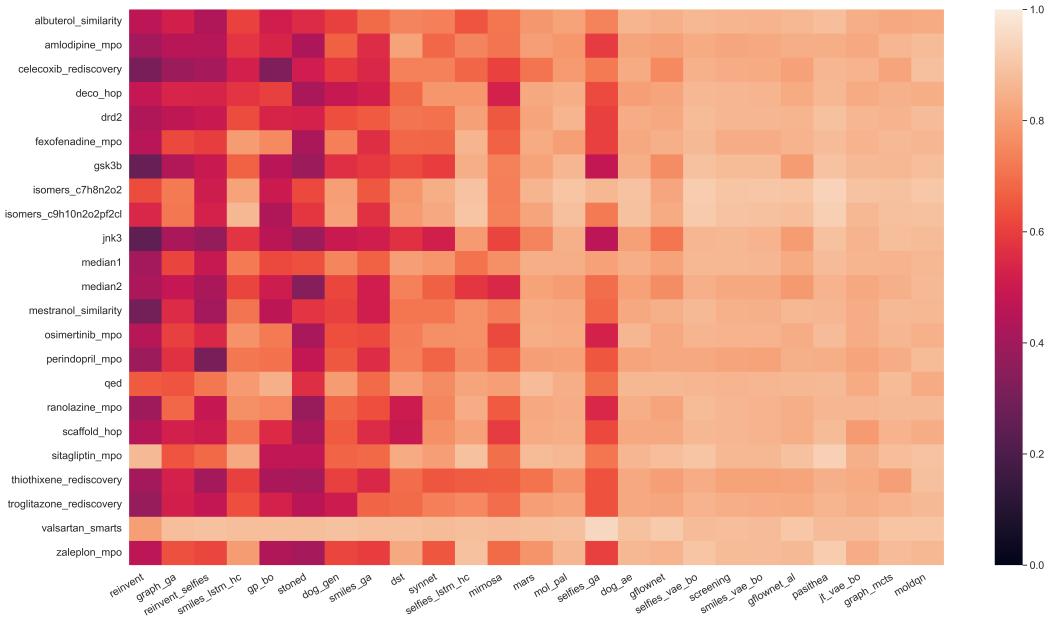

Figure 11: The heat map of diversity (the higher the better) calculated from the Top-100 molecules from each method, averaged from all runs.

B.7. Action space manipulation

There are several types of state-action space: (1) *auto-regressive* (AR): growing the molecule via adding a building bloack each step, conditioned on the partially generated one, e.g, RL method; (2) *one-hot*: constructing or modifying the molecule as a whole, e.g., VAE based method, gradient ascent method (DST, Pasithea); (3) *cross*: maintain a population of molecules and exchange the structural information between molecules. This kind of action space is only used by GA based methods. The action space for all methods are available in Table 7.

B.8. Screening

Screening searches over the molecule database (ZINC in this paper) sequentially via randomly selecting the molecules and evaluating their properties. It does not involve learning process.

B.9. MolPAL

MolPal (Graff et al., 2021) is a machine learning enhanced version of screening (Section B.8). Specifically, it train a machine learning model to predict the molecular property and prioritize the molecule with higher predicted scores in ZINC to replace the random search in screening. Concretely, it firstly trains a molecular property predictor, which is a two-layer message-passing neural network, the hidden dimension is 300, activation function is ReLU. When training the message passing network, the initial training size is set to 500. Then during screening process, it updates the message passing network in online manner with batch size 100. It uses an Adam optimizer with an initial learning rate of 1e-4.

B.10. SMILES-VAE

SMILES-VAE (Gómez-Bombarelli et al., 2018) first trains string based VAE model on ZINC database. Both the encoder and decoder use single-directional GRU as neural architecture. For encoder GRU, the hidden dimension is 256, number of layers is 1, dropout rate is set to 0.5. The VAE latent variable's dimension is 128. The decoder GRU has three layers, dropout rate is 0, hidden dimension is 512. Optimizer is Adam with initial learning rate 3e-4. Gradient is clipped to 50 during training. The batch size is 512. The training and validation data is all the molecules in ZINC database. After training the VAE, it uses Bayesian optimization (BO) to explore the continuous latent variable space, the BO setup has been described in Section B.4. The pretrained SMILES-VAE model is available in the repository.

B.11. SELFIES-VAE

It shares the same setup (neural architecture and learning process) with SMILES-VAE (Gómez-Bombarelli et al., 2018) (Section B.10), except the vocabulary.

B.12. DST

Differentiable Scaffolding Tree (DST) (Fu et al., 2022) utilize graph convolutional network (GCN) as property predictor. In GCN, the number of layer is 3, the hidden dimension and input embedding dimension are both 100. ReLU is used as activation function in hidden layers. DST leverages GA-like process, generate offspring based on a population of molecule candidates in each iteration, and select the promising ones from the offspring set and save them in the population for the next iteration. In each iteration, the population size is set to 50. When generating the offspring pool, it used determinant point process (DPP) to enhance the diversity of the population, where λ controls the weight of diversity compared with fitness. It is set to 2. The pool size is set to 500, which means in each iteration, we generate at most 500 offspring. $\epsilon = 0.7$ controls the probability threshold to add a substructure from the current now. $k = 5$ represent the maximal number of substructures that are sampled from a single branch during expansion. The substructure can be either a single ring or an atom. The vocabulary set contains 82 most frequent substructures in ZINC databases, whose frequencies are greater than 1,000. In the inner loop, when optimize DST for each single molecule, we use Adam optimizer with initial learning rate 1e-3 and the maximal iteration number is set to 5K, with early stop strategy. During the optimization process, we use the new labelled molecules to update the GCN in online manner.

B.13. Pasithea

Pasithea (Shen et al., 2021) is also a gradient ascent method like DST and utilize SELFIES as representation. It differentiate the molecule and back-propagate the gradient of the neural network to update the molecule iteratively. It uses four layer multiple layer perceptron (MLP) as neural model with ReLU function as activation to provide nonlinearity. SELFIES strings are converted into multi-hot vector as the input of the MLP. The hidden dimensions are all set to 500. The output layer is to predict the property, so the output-layer dimension is 1. It first use 800 molecules to train the neural network as predictor and then online update it during the optimization process. The training epoch is set to 5, the optimizer is Adam with initial learning rate 1e-3. During inference, i.e., updating differentiable molecule, Pasithea uses Adam as optimizer with initial learning rate 5e-3, epoch number is 50.

B.14. MolDQN

Molecule Deep Q-Network (MolDQN) (Zhou et al., 2019) formulates molecule optimization as a Markov Decision Process. In each step of a single episode, it add an atom from vocabulary (C, N, O) to any eligible position of the current molecular graph and choose one molecule with highest estimated Q-value for the next step. Q-value is the estimated by deep Q-network. The maximal number of steps in each episode is 40. Each step calls oracle once. The discount factor is 0.9. ϵ controls the weight of exploration and exploitation, we tune the ϵ to make it more exploration at the beginning of learning process and more exploitation at the end (i.e., use up oracle calls). Deep Q-network is a multilayer perceptron (MLP) whose hidden dimensions are 1024, 512, 128, 32, respectively, the output dimension is 1. The input of the Q-network is a 1025-dimensional vector,

which is the concatenation of the molecule feature (1024-bit Morgan fingerprint, with a radius of 2) and the number of left steps. Adam is used as an optimizer with 1e-4 as the initial learning rate. Only rings with a size of 5 and 6 are allowed.

B.15. MIMOSA

Multi-constraint Molecule Sampling (MIMOSA) (Fu et al., 2021) reformulate molecule optimization as a MCMC sampling problem and the property oracles are encoded in the target distribution. We use Adam optimizer with a learning rate of 0.001. In pretraining phase, MIMOSA to set GNNs with 5 layers and 300-dimensional hidden units. MIMOSA randomly masks a single node (a substructure) for each molecule and predict its substructure category based on other feature. The substructure can be either a single ring or an atom. The vocabulary set contains 82 most frequent substructures in ZINC databases, whose frequencies are greater than 1,000, same as DST (Section B.12). Then during inference phase, in each iteration, it samples new molecules via masking one random-selected node (i.e., substructure), and use GNN to predict the substructure's categorical distribution, and flip the node to a new substructures with highest probability. It samples at most 500 molecules and online updates the GNN using the top-300 scored molecules.

B.16. MARS

Markov Molecular Sampling (MARS) (Xie et al., 2021) is based on MCMC sampling. It uses a graph neural network to imitate the MCMC proposal distribution. The GNN is three layer, the dimension of node embedding is 64, the dimension of edge embedding is 128. It uses simulated annealing to sampling and adaptive proposal (online updated) from the target distribution. It collects 1000 frequent fragments as vocabulary. The batch size is set to 128 during training.

B.17. GFlowNet

Generative Flow Network (GFlowNet) is a MCMC sampling method (Bengio et al., 2021b). It predefine 72 basic building blocks as vocabulary set, which are selected from ZINC database. It uses message passing neural network (MPNN) to estimate the flow and takes the atom graph as the input feature. The hidden state dimension and embedding dimension are both set to 256. The number of layer is set to 3. LeadyReLU is used as activation function. ϵ is set to 2e-8, which is defined in Equation 12 in original paper and is used to avoid taking the logarithm of a tiny number. It uses Adam as optimizer with initial learning rate 5e-4, where $\beta_1 = 0.9, \beta_2 = 0.999$. The batch size is set to 4.

B.18. GFlowNet-AL

GFlowNet-AL is a model-based version of GFlowNet that uses predictive model to enhance GFlowNet. GFlowNet-AL share the same setup (neural architecture, learning process) with GFlowNet.

B.19. JTVAE

Junction Tree VAE (JTVAE) (Jin et al., 2018) represent the molecule graph into junction tree, which is cycle-free and easier to generation. JTVAE leverage design message passing network as encoder and tree RNN as decoder. Encoder represent both molecular graph and junction tree into latent variable, decoder first generate junction tree and then reconstruct molecular graph conditioned on the junction tree. The hidden size of message passing network and tree RNN is 450. The dimension of latent variable is 56, where the dimensions of latent variable for both molecular graph and junction tree are 28. The depth of junction tree level message passing network is 20 and the depth of molecular graph-level message passing network is 3. After training the VAE, it uses Bayesian optimization (BO) to explore the continuous latent variable space, the BO setup has been described in Section B.4. The original implementation was based on Python 2, we adapt it to Python 3. Also, we re-implement BO process using BoTorch (Section B.4).

B.20. GP BO

Gaussian Process BO (GP BO) (Tripp et al., 2021) utilizes Gaussian process as the surrogate model and optimize the acquisition function with Graph GA methods internally. We treat it as a model-based version of Graph GA, where we adopt 2-radius 2048 bit molecular fingerprint as molecular feature. In GA, the initial population size is 340; the maximal BO iteration is 10000; BO's batch size is 1180; maximal generations is 60; Size of offspring set is 150; the mutation rate is 0.01; population size is 820. We adopt the implementation from the original paper (Tripp et al., 2021).

B.21. DoG-AE

The autoencoder version of DAGs of molecular graphs (DoG) (Bradshaw et al., 2020) uses autoencoder (AE) to learn the distribution of synthesizable molecules. The dimension of latent variable of autoencoder is 25, for the molecular graph embedder (encoder), the hidden layer size is 80, embedding dimension is 50, number of layer is 4. for DAG embedder, the hidden layer size is 50, number of layer is 7. Decoder is a GRU, whose input size is 50, hidden size 200, num of layers is 3, dropout rate is 0.1. Bayesian optimization is utilized to optimize the continuous latent space. DoG is a basic generator that constructs synthesizable molecules from building blocks via virtual chemical

reactions.

B.22. DoG-Gen

DoG-Gen is the hill climbing[1] version of DoG (Bradshaw et al., 2020). In each iteration, it samples 3,000 molecules and keep 1,000 ones with the best fitness scores for the next iterations. It uses the Molecular Transformer (Schwaller et al., 2019) as a black box oracle for reaction prediction. The molecular transformer is pretrained on USPTO dataset. It uses gated graph neural network (GGNN) (Li et al., 2015) to learn molecular embedding and GRU to generate the molecule.

B.23. SynNet

SynNet (Gao et al., 2022) use GA to manipulate binary molecular fingerprint. It uses MLP as the neural architecture and molecular fingerprint as the input feature of the neural network. It uses 2-radius 4096 bit fingerprint as the input of MLP. During GA-process, the population size is 128, offspring size is 512. mutation probability is set to 0.5. For each element, the number of mutation is set to 24. SynNet consists of four modules, each containing a multi-layer perceptron (MLP), (1.) An Action Type selection neural network that classifies action types among the four possible actions ("Add", "Expand", "Merge", and "End") in building the synthetic tree. The input dimension is 3*4096, the hidden dimension is set to 500, output dimension is 4. (2). A First Reactant selection neural network that predicts an embedding for the first reactant. A candidate molecule is identified for the first reactant through a k-nearest neighbors (k-NN) search from the list of potential building blocks. The input dimension is 3*4096, the hidden dimension is set to 1,200, output dimension is 1. (3). A Reaction selection neural network whose output is a probability distribution over available reaction templates, from which inapplicable reactions are masked (based on reactant 1) and a suitable template is then sampled using a greedy search. The input dimension is 4*4096, the hidden dimension is set to 3000, output dimension is 91. (4). A Second Reactant selection neural network that identifies the second reactant if the sampled template is bi-molecular. The model predicts an embedding for the second reactant, and a candidate is then sampled via a k-NN search from the masked set of building blocks. The input dimension is 4*4096+91, the hidden dimension is set to 3000, output dimension is 1. All the 4 MLP has 5 layers. Adam optimizer is used with initial learning rate 1e-4.

[1] Section 2.3

B.24. REINVENT

REINVENT (Olivecrona et al., 2017) is the top-1 method as shown in Table 2. REINVENT uses SMILES string as representation and recurrent neural network (RNN) as neural model, which contains multiple GRU cells. The embedding dimension of input token is set to 128, the hidden dimensions of all GRU are set to 512. In REINVENT, the whole objective contains (i) prior likelihood to encourage the generated SMILES to be close to training SMILES string and (ii) a reward function for optimization. The σ control the importance of reward function in the whole objective and plays a critical role in optimization performance, as shown in Figure 15 and 16 (σ is sigma). After intensive tuning, σ is set to 500. It is even not found by the original paper, where σ is set to 60. Based on our empirical studies, the selection of σ is vital to the optimization performance. Also, the batch size during the training is set to 64. Adam is used as optimizer with initial learning rate 5e-4. REINVENT is pretrained on ZINC data, the pretrained model is used in two ways: (1) provide a warm start and are finetuned during optimization; (2) evaluate the prior likelihood of the generated SMILES string to measure their SMILES likeness.

B.25. SELFIES-REINVENT

It uses SELFIES string as molecular representation and shares the same setup (neural architecture, learning process) with REINVENT (Olivecrona et al., 2017) (Section B.24), except the vocabulary.

B.26. SMILES-LSTM Hill Climbing (SMILES-LSTM HC)

SMILES-LSTM Hill Climbing (Brown et al., 2019) uses three-layer LSTM as neural model, the hidden size is 512. It pretrains the LSTM using ZINC data. It use Adam as optimizer with initial learning rate 1e-3. During hill climbing, the population size is 100; the epoch is set to 10; batch size is 256; each epoch sample 1024 molecule and keep the best 512 molecules (highest scores) for the next epoch. The maximal length of SMILES is 100.

B.27. SELFIES-LSTM Hill Climbing (SELFIES-LSTM HC)

It uses SELFIES string to represent molecule and shares the same setup (neural architecture, learning process) with SMILES-LSTM Hill Climbing (Brown et al., 2019) (Section B.26), except the vocabulary.

B.28. GA+D (SELFIES-GA)

Genetic Algorithm with Discriminator (GA+D) (Nigam et al., 2020) utilizes SELFIES string to represent molecule

and apply genetic algorithm. It is enhanced by a discriminator neural network. The discriminator neural network is a fully connected neural network with ReLU activation and sigmoid output layer. the number of molecules in the generation (i.e., population) is 300. The patience value is set to 5. beta (β) is the weight of discriminator neural network's score in fitness evaluation, which is used to select most promising molecules in each generation. After empirical studies, we do not find β has positive contribution to the performance. Thus, the default value is set to 0. The maximal generation number is 1000.

B.29. STONED

Superfast Traversal, Optimization, Novelty, Exploration and Discovery (STONED) (Nigam et al., 2021) implements genetic algorithm (only mutation operator, without crossover) on SELFIES string. After tuning, we find when the generation size is set to 500, STONED reached best optimization performance. Like other genetic algorithm, it does not need any learnable parameter, is super-fast and easy to implement.

B.30. SMILES-GA

SMILES-GA (Brown et al., 2019) manipulates SMILES string with only mutation operation. The crossover operation is not conducted because it would lead to poor chemical validity. The population size is set to 100. In each generation, the number of mutated molecule is set to 300. The maximal length of SMILES string is set to 200. Mutation randomly flips a randomly-selected bit in the current SMILES string. The initial population is randomly selected from ZINC. It uses early stop strategy and the patience is set to 5.

B.31. Graph-GA

Graph-GA (Jensen, 2019) manipulates molecular graph with crossover and mutation operators successively. The population size is set to 120. offspring size is set to 70. The mutation rate is set to 0.067. That is, the new child molecule will be mutated with probability 6.7%. The mutation operations includes (1) insert an atom; (2) change bond's order; (3) delete cyclic bond; (4) add ring; (5) delete an atom; (6) change an atom and (7) append an atom.

B.32. Graph-MCTS

Graph level Monte Carlo Tree Search (Graph-MCTS) (Jensen, 2019) manipulate molecular graph using MCTS. Like GA algorithms, it does not involve any learnable parameters. It start from Ethane, whole SMILES string is "CC". During the searching process, it constrains the maximal number of atoms to 60. For each state (molecular graph), the maximal number of children is 5. The root node simulates 22 times. Exploration coefficient balances the weight of exploitation and exploration and is set to 4.3. Larger exploration coefficient indicates more exploration instead of exploitation.

B.33. Methods Not Included

In this section, we describe some other methods that are representative but not included in our benchmark. We also analyze the reasons. These methods contain Bayesian Optimization over String Space (BOSS) (Moss et al., 2020), synthesis-based Bayesian optimization (ChemBO) (Korovina et al., 2020), Objective-Reinforced Generative Adversarial Network (ORGAN) (Guimaraes et al., 2017), Generative Adversarial Network (MolGAN) (De Cao & Kipf, 2018), rationaleRL (Jin et al., 2020). BO based methods (BOSS and ChemBO) are non-parametric methods and use the combination of training data to approximate the landscape. The evaluation of the approximate function relies on the number of training data and the evaluation of kernel function relies on the data's dimension. The optimization process requires intensive evaluation of both approximate function and kernel function, thus BO scales poorly with both data dimension and number and is computationally prohibitive (Snoek et al., 2012). In our experiment, BOSS and ChemBO are only available to generate less than 200 molecules and stop early, which is not comparable with other methods in our benchmark. Thus we decided not to incorporate them. ORGAN uses SMILES as molecular representation and the generated molecules has lower validity ($<1\%$). MolGAN does not achieve comparable optimization performance. RationaleRL requires extracting property-aware rationale as the basic building block, the process relies on Monte Carlo Tree Search and requires intensive oracle calls (more than 10K).

C. Configuration

C.1. Software

We build a unifying conda environment for most of the methods, which relies on the following python packages.

- **Python**. We use Python 3.7.
- **PyTorch** is used to build neural network. We recommend to install PyTorch 1.10.2.
- **PyTDC** (Therapeutic Data Commons) (Huang et al., 2021). TDC provides dataloader for ZINC, evaluator (diversity, novelty, etc) and oracle scoring (all the oracles in this paper).
- **RDKit** is an open-Source cheminformatics software and is used for molecule manipulation. We use RDKit 2020.09.1.0. It can be installed using conda via "conda install -c rdkit rdkit ".
- **wandb** is used to record the learning process. It can be installed using pip. And users need to register a wandb account. It also supports automatic hyperparameter tuning and visualize the results in an intuitive manner.
- **YaML** is used to setup configuration file. It can be installed using pip. We have "hparams_default.yaml" and "hparams_tune.yaml" file.
- **selfies (optional)** is only used for SELFIES related methods. It can be installed using pip.
- **BoTorch (optional)** is a library for Bayesian Optimization built on PyTorch and is only used for BO related methods. It can be installed using pip.

Individual conda environment. The following methods need an individual conda environment.

- **ChemBO** require install our modified dragonfly package and TensorFlow. The modified dragonfly is already in our repository.
- **DoG-AE and DoG-Gen** required installing two individual conda environment following their original instruction in https://github.com/john-bradshaw/synthesis-dags.

C.2. Hardware

We use (i) Intel Xeon E5-2690 machine with 256G RAM and 8 NVIDIA Pascal Titan X GPUs and (ii) Most of the NN based methods require GPU to acclerate learning process.

C.3. License

Our package uses the MIT license. We use ZINC database for all the methods, ZINC is free to use for everyone (Sterling & Irwin, 2015). All the 25 methods' implementation are publicly available at GitHub.

C.4. Run with one-line code

All the methods can be run in one line of code after the setup of conda environment. We provide the pretrained model (if needed) and other necessary data/configuration files.

```
cd mol_opt
python run.py graph_ga
```

```
python run.py dst --task production \
    --n_runs 5 --oracles qed jnk3 drd2
```

```
python run.py graph_ga --task tune \
    --n_runs 30 --smi_file ./data/zinc.txt \
    --wandb offline --max_oracle_calls 10000 \
    --patience 5
```

D. Additional Results

D.1. SELFIES strings collapse

Though most SELFIES strings represent valid molecules, replacing SMILES with SELFIES doesn't necessarily lead to an immediate advantage in molecular optimization. One reason is that different combinations of SELFIES strings could collapse to a single truncated SELFIES strings and don't provide an additional exploration of chemical space. See Figure 12, 13, and 14 for examples. These SELFIES strings were constructed with tokens from the vocabulary of ZINC 250k and converted to SMILES strings using the `decoder` provided in the official Github repository.

D.2. Hyper-parameter Tuning

Most algorithms are sensitive to the choice of hyper-parameters. We tried to tune most algorithms within a reasonably large hyper-parameter space and visualize some of the results here to show how hyper-parameters affect the performance. For each algorithm, the endpoint is a summation of AUC Top-10 of zaleplon_mpo (an isomer-based oracle) and perindopril_mpo (a similarity-based oracle), averaged from 3 runs for each task. We tuned and visualized them with the wandb (Biewald, 2020). The oracles are chosen to discriminate most algorithms and be representative based on preliminary results.

```
SEFLIES: [NH1][=Ring1][#C][#N][C][#C][=O][#C][Branch2][Branch1][C][=O][#C][C]
SMILES: [NH]
```

Figure 12: An example of SELFIES string that is valid but doesn't provide meaningful exploration of chemical space.

```
SEFLIES: [=O][=Ring2][=N][NH1][=Branch1][C][=C][O][=C][-\Ring1][C][#C][#C][=C]
SMILES: O
```

Figure 13: An example of SELFIES string that is valid but doesn't provide meaningful exploration of chemical space.

D.3. Additional Tables

```
SEFLIES: [#C][=O][=C][-/Ring2][#C][C][=C][#N][=Branch2][#C][N][#C][=O][=Ring1]
SMILES: C=O
```

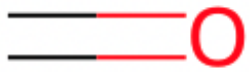

Figure 14: An example of SELFIES string that is valid but doesn't provide meaningful exploration of chemical space.

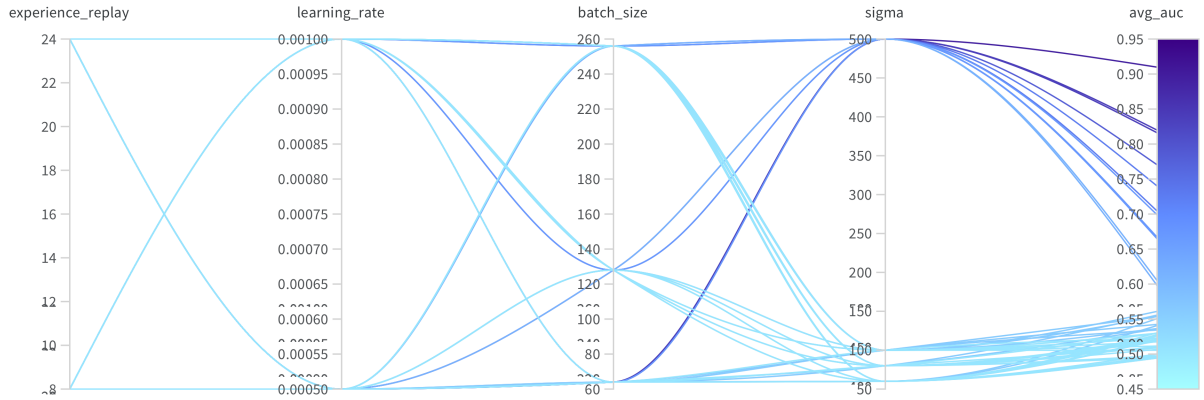

Figure 15: The hyper-parameter tuning result of REINVENT (part 1). We can see that sigma (σ) has large impact on optimization performance, and the optimal value is much larger than the default setting in the original paper (Olivecrona et al., 2017).

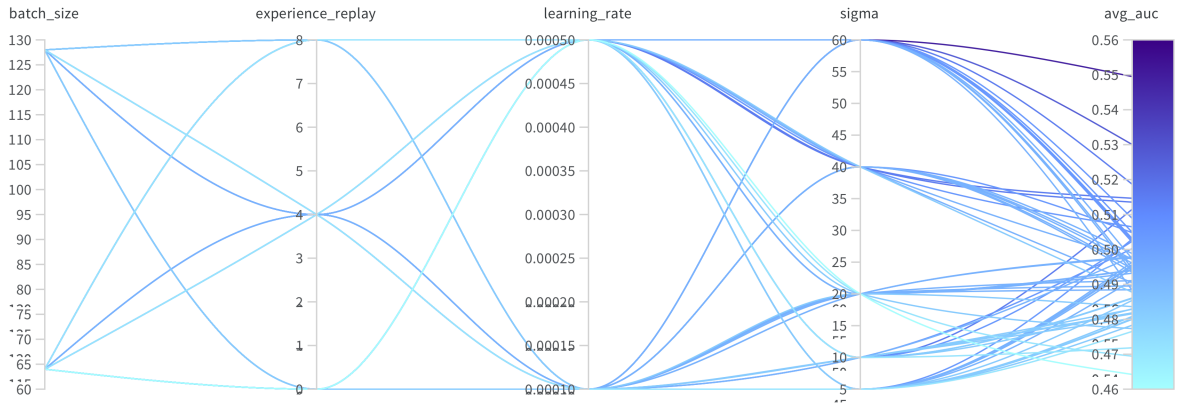

Figure 16: The hyper-parameter tuning result of REINVENT (part 2).

Table 4: We report the mean and standard deviation of AUC Top-10 from 5 independent runs. We ranked the methods by the summation of mean AUC Top-10 of all tasks. (Continued)

Method Assembly	REINVENT SMILES	Graph GA Fragments	REINVENT SELFIES SELFIES	GP BO Fragments	STONED SELFIES
albuterol_similarity	0.882±0.006	0.838±0.016	0.826±0.030	**0.898±0.014**	0.745±0.076
amlodipine_mpo	0.635±0.035	**0.661±0.020**	0.607±0.014	0.583±0.044	0.608±0.046
celecoxib_rediscovery	0.713±0.067	0.630±0.097	0.573±0.043	**0.723±0.053**	0.382±0.041
deco_hop	0.666±0.044	0.619±0.004	0.631±0.012	0.629±0.018	0.611±0.008
drd2	0.945±0.007	0.964±0.012	0.943±0.005	0.923±0.017	0.913±0.020
fexofenadine_mpo	0.784±0.006	0.760±0.011	0.741±0.002	0.722±0.005	**0.797±0.016**
gsk3b	**0.865±0.043**	0.788±0.070	0.780±0.037	0.851±0.041	0.668±0.049
isomers_c7h8n2o2	0.852±0.036	0.862±0.065	0.849±0.034	0.680±0.117	0.899±0.011
isomers_c9h10n2o2pf2cl	0.642±0.054	0.719±0.047	0.733±0.029	0.469±0.180	0.805±0.031
jnk3	**0.783±0.023**	0.553±0.136	0.631±0.064	0.564±0.155	0.523±0.092
median1	**0.356±0.009**	0.294±0.021	0.355±0.011	0.301±0.014	0.266±0.016
median2	0.276±0.008	0.273±0.009	0.255±0.005	**0.297±0.009**	0.245±0.032
mestranol_similarity	0.618±0.048	0.579±0.022	0.620±0.029	**0.627±0.089**	0.609±0.101
osimertinib_mpo	**0.837±0.009**	0.831±0.005	0.820±0.003	0.787±0.006	0.822±0.012
perindopril_mpo	0.537±0.016	0.538±0.009	0.517±0.021	0.493±0.011	0.488±0.011
qed	0.941±0.000	0.940±0.000	0.940±0.000	0.937±0.000	0.941±0.000
ranolazine_mpo	0.760±0.009	0.728±0.012	0.748±0.018	0.735±0.013	**0.765±0.029**
scaffold_hop	**0.560±0.019**	0.517±0.007	0.525±0.013	0.548±0.019	0.521±0.034
sitagliptin_mpo	0.021±0.003	**0.433±0.075**	0.194±0.121	0.186±0.055	0.393±0.083
thiothixene_rediscovery	0.534±0.013	0.479±0.025	0.495±0.040	**0.559±0.027**	0.367±0.027
troglitazone_rediscovery	**0.441±0.032**	0.390±0.016	0.348±0.012	0.410±0.015	0.320±0.018
valsartan_smarts	**0.179±0.358**	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	**0.358±0.062**	0.346±0.032	0.333±0.026	0.221±0.072	0.325±0.027
Sum	14.196	13.751	13.471	13.156	13.024
Rank	1	2	3	4	5

Method Assembly	LSTM HC SMILES	SMILES GA SMILES	SynNet Synthesis	DoG-Gen Synthesis	DST Fragments
albuterol_similarity	0.719±0.018	0.661±0.066	0.584±0.039	0.676±0.013	0.619±0.020
amlodipine_mpo	0.593±0.016	0.549±0.009	0.565±0.007	0.536±0.003	0.516±0.007
celecoxib_rediscovery	0.539±0.018	0.344±0.027	0.441±0.027	0.464±0.009	0.380±0.006
deco_hop	**0.826±0.017**	0.611±0.006	0.613±0.009	0.800±0.007	0.608±0.008
drd2	0.919±0.015	0.908±0.019	**0.969±0.004**	0.948±0.001	0.820±0.014
fexofenadine_mpo	0.725±0.003	0.721±0.015	0.761±0.015	0.695±0.003	0.725±0.005
gsk3b	0.839±0.015	0.629±0.044	0.789±0.032	0.831±0.021	0.671±0.032
isomers_c7h8n2o2	0.485±0.045	**0.913±0.021**	0.455±0.031	0.465±0.018	0.548±0.069
isomers_c9h10n2o2pf2cl	0.342±0.027	**0.860±0.065**	0.241±0.064	0.199±0.016	0.458±0.063
jnk3	0.661±0.039	0.316±0.022	0.630±0.034	0.595±0.023	0.556±0.057
median1	0.255±0.010	0.192±0.012	0.218±0.008	0.217±0.001	0.232±0.009
median2	0.248±0.008	0.198±0.005	0.235±0.006	0.212±0.000	0.185±0.020
mestranol_similarity	0.526±0.032	0.469±0.029	0.399±0.021	0.437±0.007	0.450±0.027
osimertinib_mpo	0.796±0.002	0.817±0.011	0.796±0.003	0.774±0.002	0.785±0.004
perindopril_mpo	0.489±0.007	0.447±0.013	**0.557±0.011**	0.474±0.002	0.462±0.008
qed	0.939±0.000	0.940±0.000	**0.941±0.000**	0.934±0.000	0.938±0.000
ranolazine_mpo	0.714±0.008	0.699±0.026	0.741±0.010	0.711±0.006	0.632±0.054
scaffold_hop	0.533±0.012	0.494±0.011	0.502±0.012	0.515±0.005	0.497±0.004
sitagliptin_mpo	0.066±0.019	0.363±0.057	0.025±0.014	0.048±0.008	0.075±0.032
thiothixene_rediscovery	0.438±0.008	0.315±0.017	0.401±0.019	0.375±0.004	0.366±0.006
troglitazone_rediscovery	0.354±0.016	0.263±0.024	0.283±0.008	0.416±0.019	0.279±0.019
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.206±0.006	0.334±0.041	0.341±0.011	0.123±0.016	0.176±0.045
Sum	12.223	12.054	11.498	11.456	10.989
Rank	6	7	8	9	10

Table 5: (Continued)

Method Assembly	MARS Fragments	MIMOSA Fragments	MolPal -	LSTM HC SELFIES SELFIES	DoG-AE Synthesis
albuterol_similarity	0.597±0.124	0.618±0.017	0.609±0.002	0.664±0.030	0.533±0.034
amlodipine_mpo	0.504±0.016	0.543±0.003	0.582±0.008	0.532±0.004	0.507±0.005
celecoxib_rediscovery	0.379±0.060	0.393±0.010	0.415±0.001	0.385±0.008	0.355±0.012
deco_hop	0.589±0.003	0.619±0.003	0.643±0.005	0.590±0.001	0.765±0.055
drd2	0.891±0.020	0.799±0.017	0.783±0.009	0.729±0.034	0.943±0.009
fexofenadine_mpo	0.711±0.006	0.706±0.011	0.685±0.000	0.693±0.004	0.679±0.017
gsk3b	0.552±0.037	0.554±0.042	0.555±0.011	0.423±0.018	0.601±0.091
isomers_c7h8n2o2	0.728±0.027	0.564±0.046	0.484±0.006	0.587±0.031	0.239±0.077
isomers_c9h10n2o2pf2cl	0.581±0.013	0.303±0.046	0.164±0.003	0.352±0.019	0.049±0.015
jnk3	0.489±0.095	0.360±0.063	0.339±0.009	0.207±0.013	0.469±0.138
median1	0.207±0.011	0.243±0.005	0.249±0.001	0.239±0.009	0.171±0.009
median2	0.181±0.011	0.214±0.002	0.230±0.000	0.205±0.005	0.182±0.006
mestranol_similarity	0.388±0.026	0.438±0.015	0.564±0.004	0.446±0.009	0.370±0.014
osimertinib_mpo	0.777±0.006	0.788±0.014	0.779±0.000	0.780±0.005	0.750±0.012
perindopril_mpo	0.462±0.006	0.490±0.011	0.467±0.002	0.448±0.006	0.432±0.013
qed	0.930±0.003	0.939±0.000	0.940±0.000	0.938±0.000	0.926±0.003
ranolazine_mpo	0.740±0.010	0.640±0.015	0.457±0.005	0.614±0.010	0.689±0.015
scaffold_hop	0.469±0.004	0.507±0.015	0.494±0.000	0.472±0.002	0.489±0.010
sitagliptin_mpo	0.016±0.003	0.102±0.023	0.043±0.001	0.116±0.012	0.009±0.005
thiothixene_rediscovery	0.344±0.022	0.347±0.018	0.339±0.001	0.339±0.009	0.314±0.015
troglitazone_rediscovery	0.256±0.016	0.299±0.009	0.268±0.000	0.257±0.002	0.259±0.016
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.187±0.046	0.172±0.036	0.168±0.003	0.218±0.020	0.049±0.027
Sum	10.989	10.651	10.268	10.246	9.790
Rank	11	12	13	14	15

Method Assembly	GFlowNet Fragments	GA+D SELFIES	VAE BO SELFIES SELFIES	Screening -	VAE BO SMILES SMILES
albuterol_similarity	0.447±0.012	0.495±0.025	0.494±0.012	0.483±0.006	0.489±0.007
amlodipine_mpo	0.444±0.004	0.400±0.032	0.516±0.005	0.535±0.001	0.533±0.009
celecoxib_rediscovery	0.327±0.004	0.223±0.025	0.326±0.007	0.351±0.005	0.354±0.002
deco_hop	0.583±0.002	0.550±0.005	0.579±0.001	0.590±0.001	0.589±0.001
drd2	0.590±0.070	0.382±0.205	0.569±0.039	0.545±0.015	0.555±0.043
fexofenadine_mpo	0.693±0.006	0.587±0.007	0.670±0.004	0.666±0.004	0.671±0.003
gsk3b	0.651±0.026	0.342±0.019	0.350±0.034	0.438±0.034	0.386±0.006
isomers_c7h8n2o2	0.366±0.043	0.854±0.015	0.325±0.028	0.168±0.034	0.161±0.017
isomers_c9h10n2o2pf2cl	0.110±0.031	0.657±0.020	0.200±0.030	0.106±0.021	0.084±0.009
jnk3	0.440±0.022	0.219±0.021	0.208±0.022	0.238±0.024	0.241±0.026
median1	0.202±0.004	0.180±0.009	0.201±0.003	0.205±0.005	0.202±0.006
median2	0.180±0.000	0.121±0.005	0.185±0.001	0.200±0.004	0.195±0.001
mestranol_similarity	0.322±0.007	0.371±0.016	0.386±0.009	0.409±0.019	0.399±0.005
osimertinib_mpo	0.784±0.001	0.672±0.027	0.765±0.002	0.764±0.001	0.771±0.002
perindopril_mpo	0.430±0.010	0.172±0.088	0.429±0.003	0.445±0.004	0.442±0.004
qed	0.921±0.004	0.860±0.014	0.936±0.001	0.938±0.000	0.938±0.000
ranolazine_mpo	0.652±0.002	0.555±0.015	0.452±0.025	0.411±0.010	0.457±0.012
scaffold_hop	0.463±0.002	0.413±0.009	0.455±0.004	0.471±0.002	0.470±0.003
sitagliptin_mpo	0.008±0.003	0.281±0.022	0.084±0.015	0.022±0.003	0.023±0.004
thiothixene_rediscovery	0.285±0.012	0.223±0.029	0.297±0.004	0.317±0.003	0.317±0.007
troglitazone_rediscovery	0.188±0.001	0.152±0.013	0.243±0.004	0.249±0.003	0.257±0.003
valsartan_smarts	0.000±0.000	0.000±0.000	0.002±0.003	0.000±0.000	0.002±0.004
zaleplon_mpo	0.035±0.030	0.244±0.015	0.206±0.015	0.072±0.014	0.039±0.012
Sum	9.131	8.964	8.887	8.635	8.587
Rank	16	17	18	19	20

Table 6: (Continued)

Method Assembly	Pasithea SELFIES	GFlowNet-AL Fragments	JT-VAE BO Fragments	Graph MCTS Atoms	MolDQN Atoms
albuterol_similarity	0.447±0.007	0.390±0.008	0.485±0.029	0.580±0.023	0.320±0.015
amlodipine_mpo	0.504±0.003	0.428±0.002	0.519±0.009	0.447±0.008	0.311±0.008
celecoxib_rediscovery	0.312±0.007	0.257±0.003	0.299±0.009	0.264±0.013	0.099±0.005
deco_hop	0.579±0.001	0.583±0.001	0.585±0.002	0.554±0.002	0.546±0.001
drd2	0.255±0.040	0.468±0.046	0.506±0.136	0.300±0.050	0.025±0.001
fexofenadine_mpo	0.660±0.015	0.688±0.002	0.667±0.010	0.574±0.009	0.478±0.012
gsk3b	0.281±0.038	0.588±0.015	0.350±0.051	0.281±0.022	0.241±0.008
isomers_c7h8n2o2	0.673±0.030	0.241±0.055	0.103±0.016	0.530±0.035	0.431±0.035
isomers_c9h10n2o2pf2cl	0.345±0.145	0.064±0.012	0.090±0.035	0.454±0.067	0.342±0.026
jnk3	0.154±0.018	0.362±0.021	0.222±0.009	0.110±0.019	0.111±0.008
median1	0.178±0.009	0.190±0.002	0.179±0.003	0.195±0.005	0.122±0.007
median2	0.179±0.004	0.173±0.001	0.180±0.003	0.132±0.002	0.088±0.003
mestranol_similarity	0.361±0.016	0.295±0.004	0.356±0.013	0.281±0.008	0.188±0.007
osimertinib_mpo	0.749±0.007	0.787±0.003	0.775±0.004	0.700±0.004	0.674±0.006
perindopril_mpo	0.421±0.008	0.421±0.002	0.430±0.009	0.277±0.013	0.213±0.043
qed	0.931±0.002	0.902±0.005	0.934±0.002	0.892±0.006	0.731±0.018
ranolazine_mpo	0.347±0.012	0.632±0.007	0.508±0.055	0.239±0.027	0.051±0.020
scaffold_hop	0.456±0.003	0.460±0.002	0.470±0.005	0.412±0.003	0.405±0.004
sitagliptin_mpo	0.088±0.013	0.006±0.001	0.046±0.027	0.056±0.012	0.003±0.002
thiothixene_rediscovery	0.288±0.006	0.266±0.005	0.282±0.008	0.231±0.004	0.099±0.007
troglitazone_rediscovery	0.240±0.002	0.186±0.003	0.237±0.005	0.224±0.009	0.122±0.004
valsartan_smarts	0.006±0.012	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.091±0.013	0.010±0.001	0.125±0.038	0.058±0.019	0.010±0.005
Sum	8.556	8.406	8.358	7.803	5.620
Rank	21	22	23	24	25

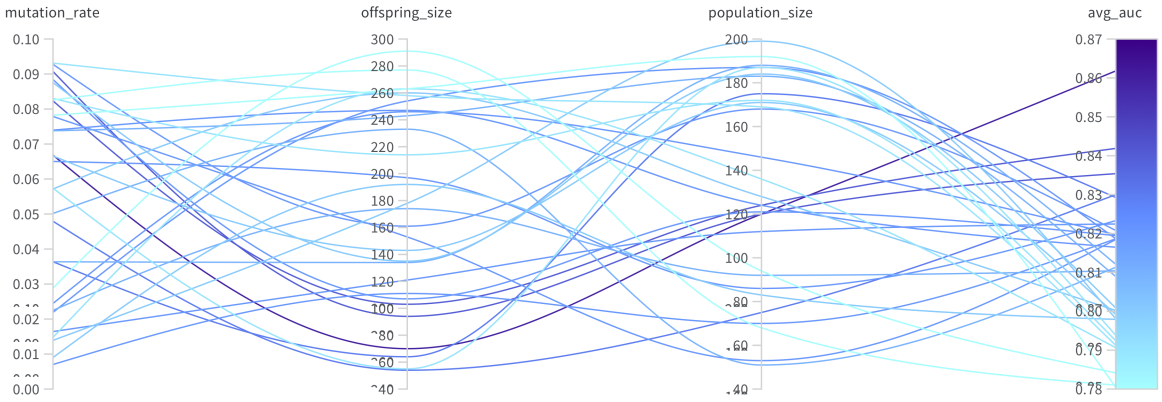

Figure 17: The hyper-parameter tuning result of Gaph GA.

Table 7: The comparison of all the methods. AR represents auto-regressive model. Bayesian optimization usually leverages non-parametric ("non-param" in the column "model size") model, the model size will increase as more training data come in. Run time is the average rough clock time for a single run in our benchmark and do not involve the time for pretraining and data preprocessing.

Categ.	Method	Assemb.	Model	Pretrain	Model Size (M)	Action Space	Type	Run Time (min)
VS	Screening	-	-	N	0	-	model-free	2
	MolPal	-	-	Y	3.2	-	model-based	60
GA	SELFIES-GA	SELFIES	-	N	0	cross	model-free	20
	SMILES-GA	SMILES	-	N	0	cross	model-free	2
	STONED	SELFIES	-	N	0	mutate	model-free	3
	Graph-GA	fragment	-	N	0	cross	model-free	3
	SynNet	synthesis	MLP	Y	2,158	cross	model-free	300
BO	GPBO	fragment	GP	N	non-param	one-hot	model-based	15
VAE+BO	SMILES-VAE	SMILES	RNN	Y	17.9	one-hot	model-based	17
	SELFIES-VAE	SELFIES	RNN	Y	18.7	one-hot	model-based	21
	JTVAE	fragment	GNN& treeRNN	Y	21.8	one-hot	model-based	17
	DoG-AE	synthesis	RNN	Y	8.9	one-hot	model-based	47
HC	SMILES-LSTM-HC	SMILES	RNN	Y	98.9	AR	model-free	3
	SELFIES-LSTM-HC	SELFIES	RNN	Y	30.4	AR	model-free	4
	MIMOSA	fragment	GNN	Y	0.25	one-hot	model-free	10
	DoG-Gen	synthesis	RNN	Y	51.0	AR	model-free	120
RL	REINVENT	SMILES	RNN	Y	16.3	AR	model-free	2
	SELFIES-REINVENT	SELFIES	RNN	Y	16.5	AR	model-free	3
	MolDQN	atom	MLP	N	6.4	AR	model-free	52
SBM	MARS	fragment	GNN	N	16.5	one-hot	model-free	21
	GFlowNet	fragment	GNN	Y	5.7	one-hot	model-free	28
	GFlowNet-AL	fragment	GNN	Y	5.7	one-hot	model-based	29
Gradient	Pasithea	SELFIES	MLP	Y	2.2	one-hot	model-based	46
	DST	fragment	GNN	Y	0.23	one-hot	model-based	300
MCTS	Graph MCTS	atom	-	N	0	one-hot	model-free	2

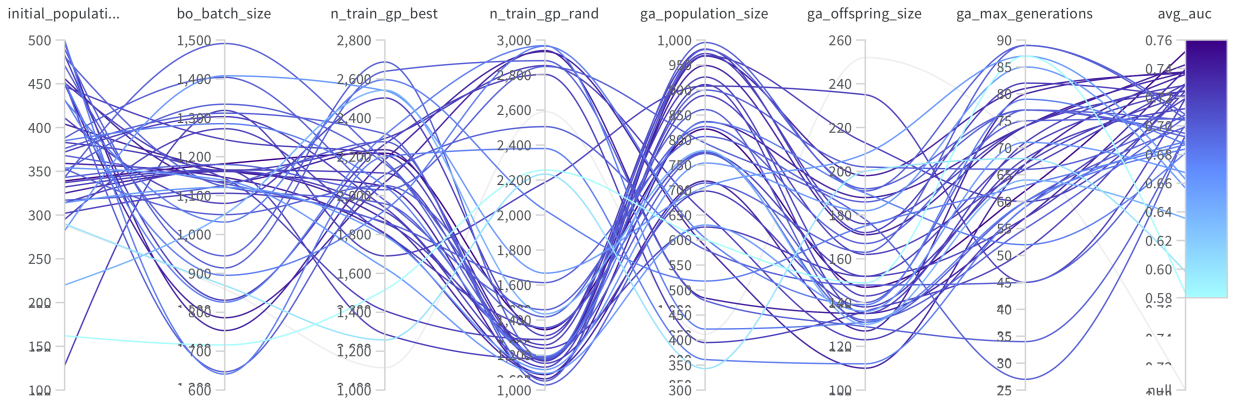

Figure 18: The hyper-parameter tuning result of GP BO.

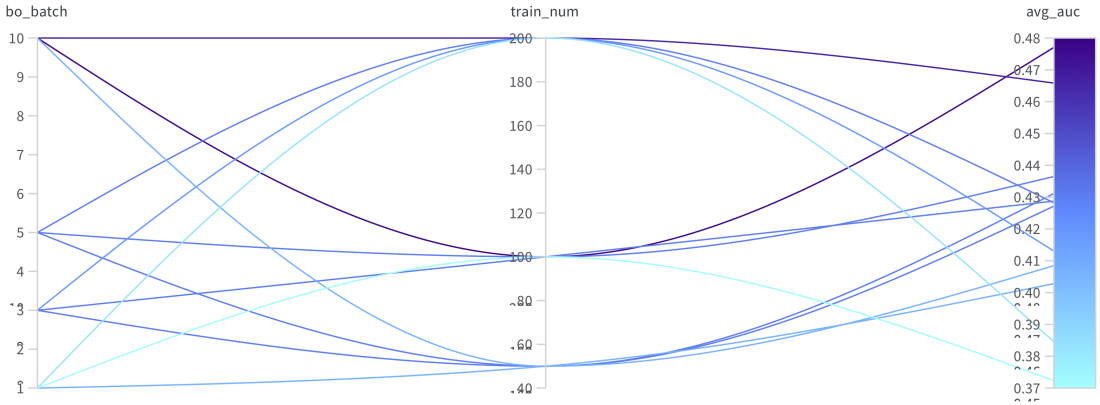

Figure 19: The hyper-parameter tuning result of DoG-AE.

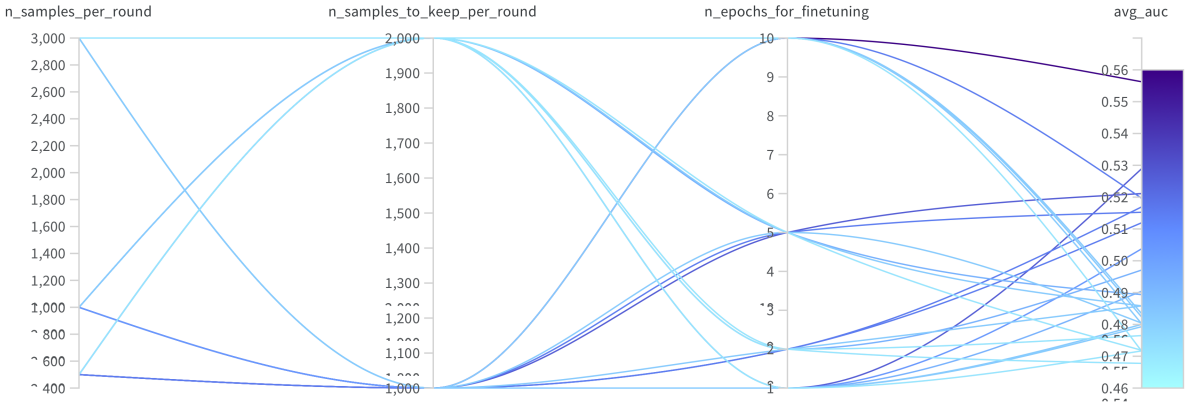

Figure 20: The hyper-parameter tuning result of DoG-Gen.

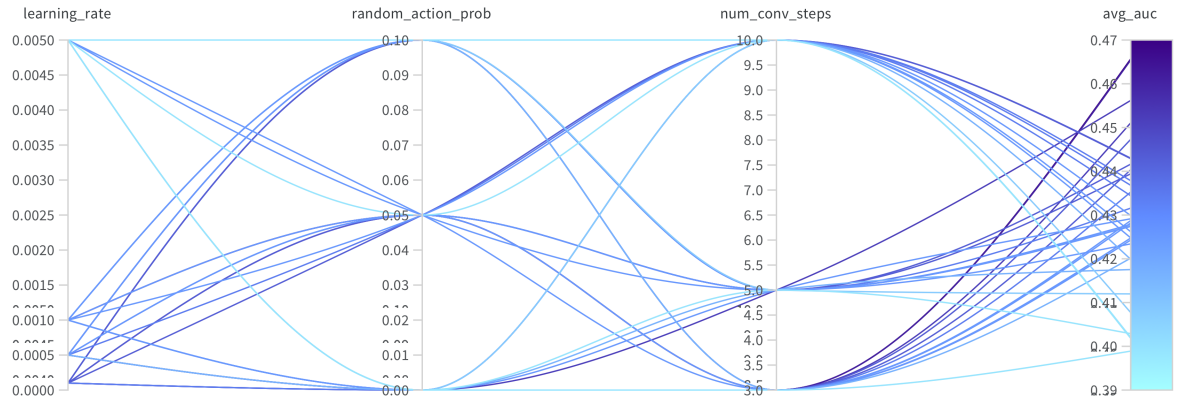

Figure 21: The hyper-parameter tuning result of GFlowNet.

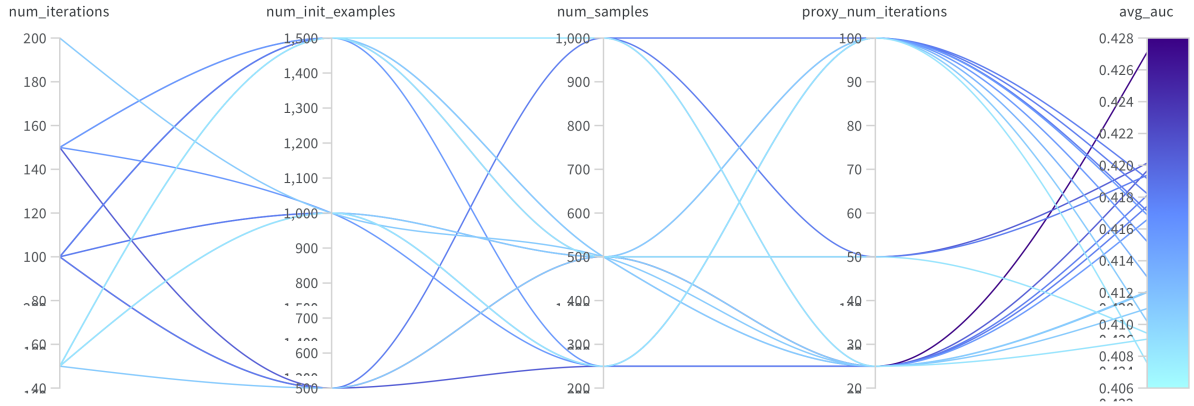

Figure 22: The hyper-parameter tuning result of GFlowNet-AL.

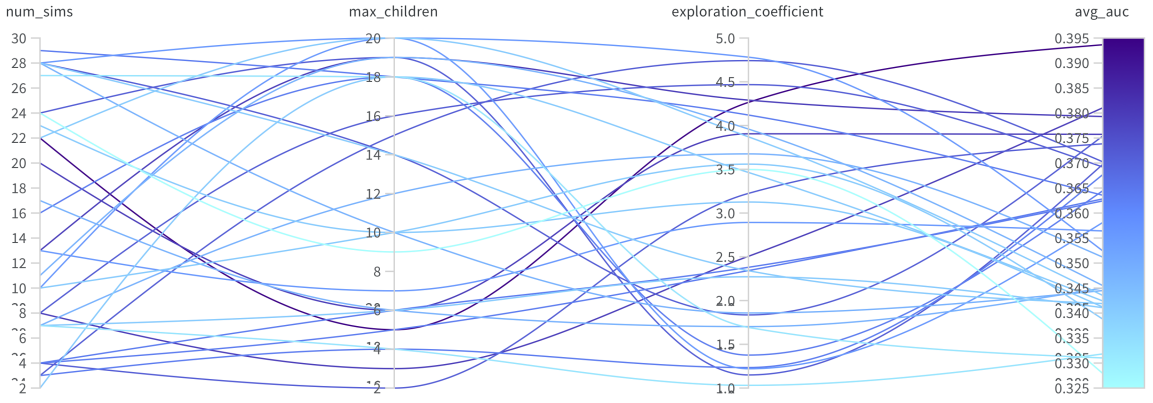

Figure 23: The hyper-parameter tuning result of Graph MCTS.

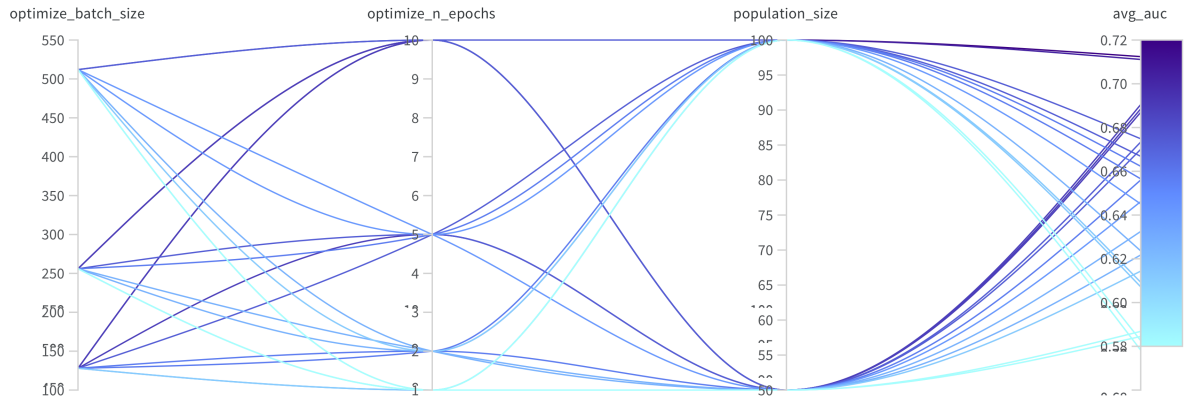

Figure 24: The hyper-parameter tuning result of SMILES LSTM HC.

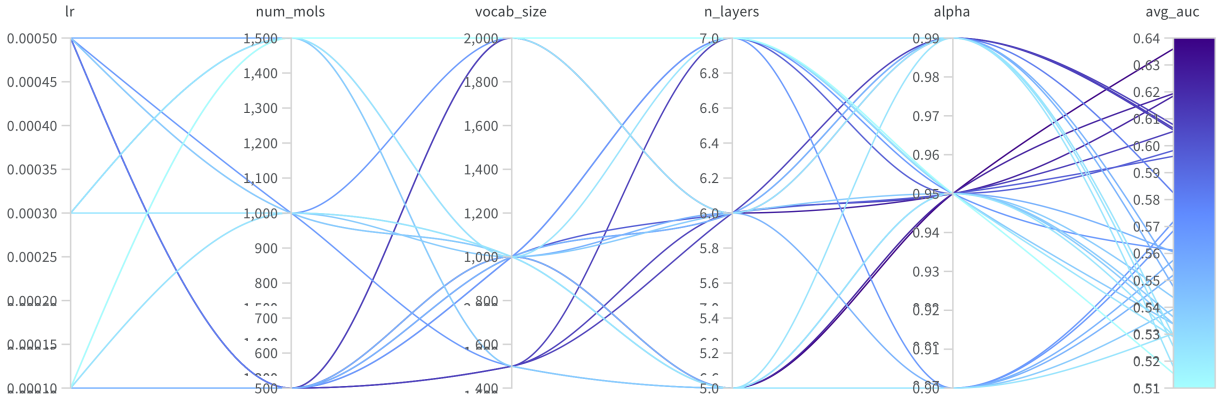

Figure 25: The hyper-parameter tuning result of MARS (part 1).

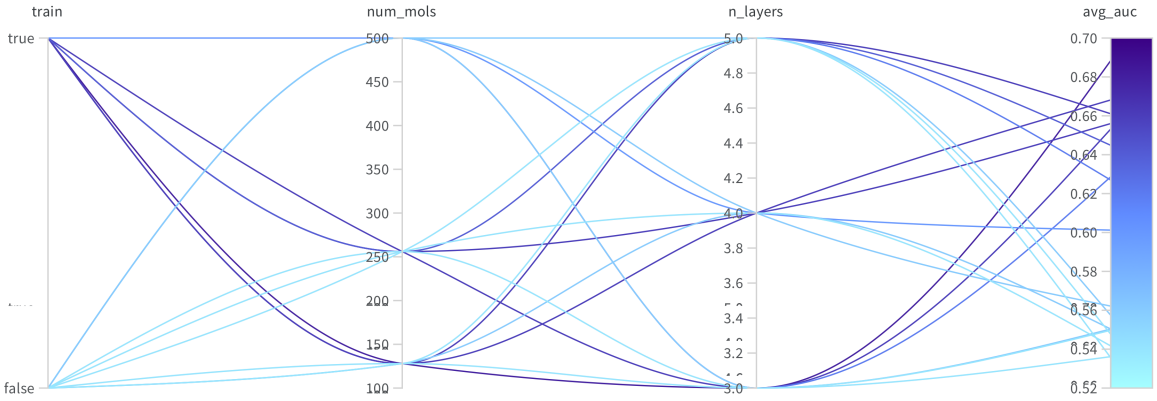

Figure 26: The hyper-parameter tuning result of MARS (part 2).

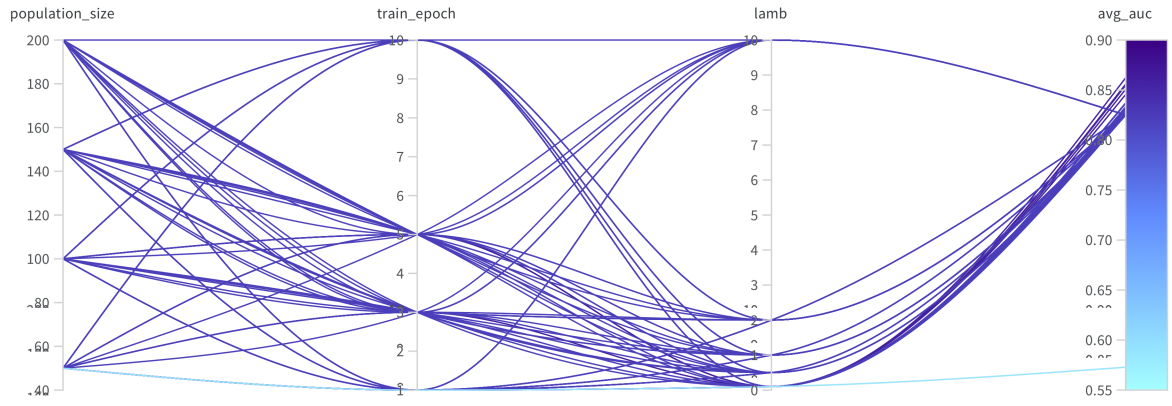

Figure 27: The hyper-parameter tuning result of MIMOSA.

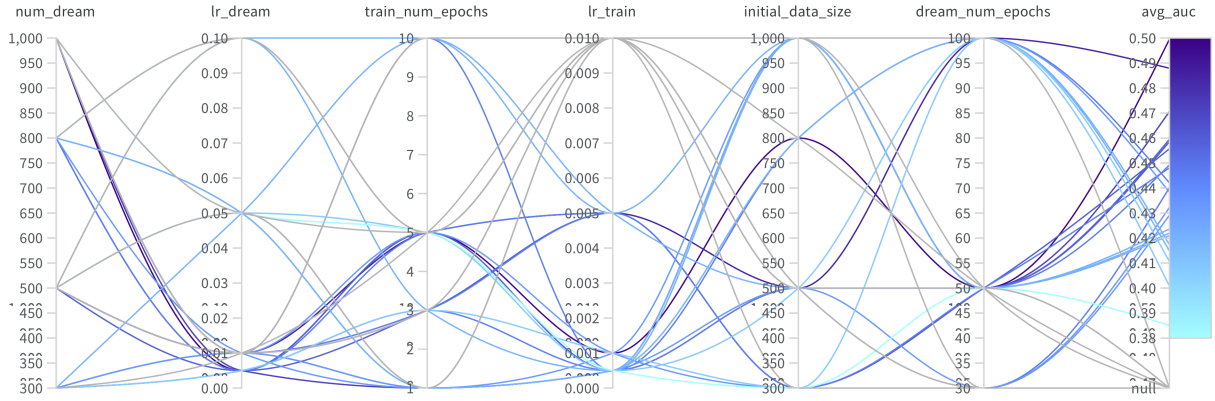

Figure 28: The hyper-parameter tuning result of Pasithea.

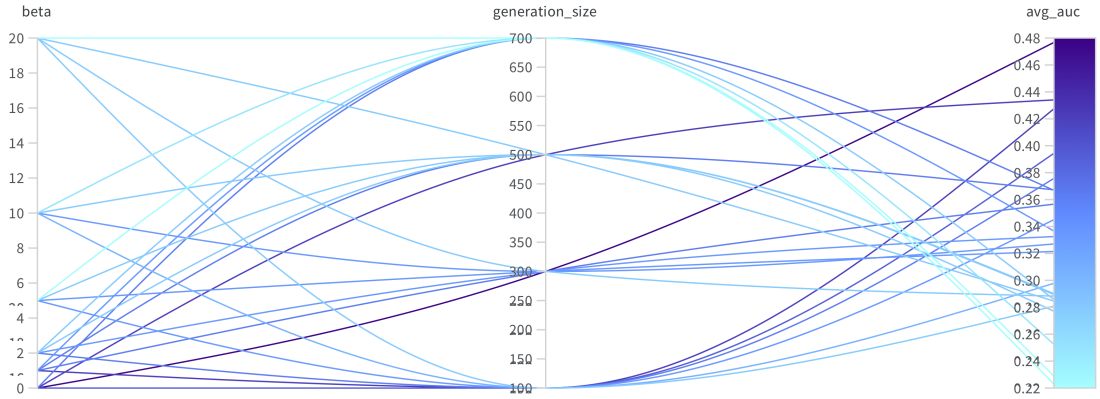

Figure 29: The hyper-parameter tuning result of GA+D.

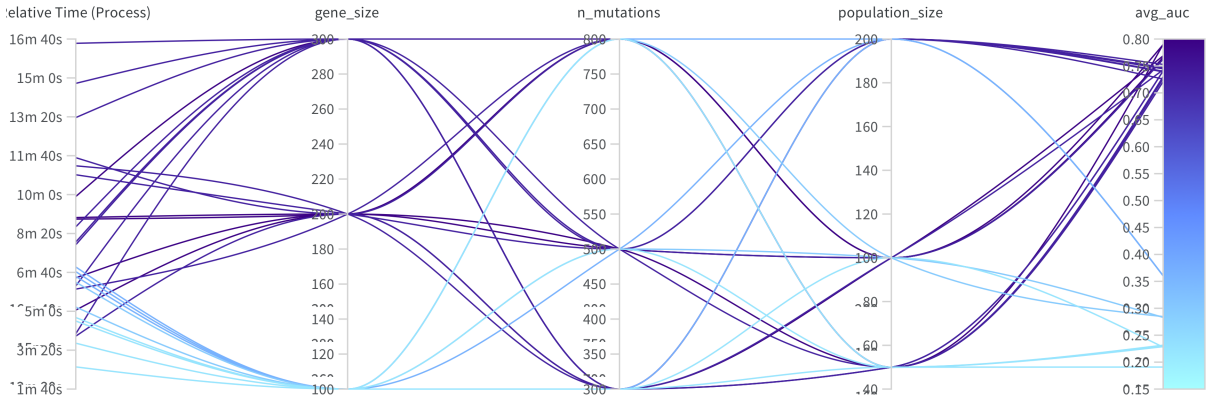

Figure 30: The hyper-parameter tuning result of SMILES GA.

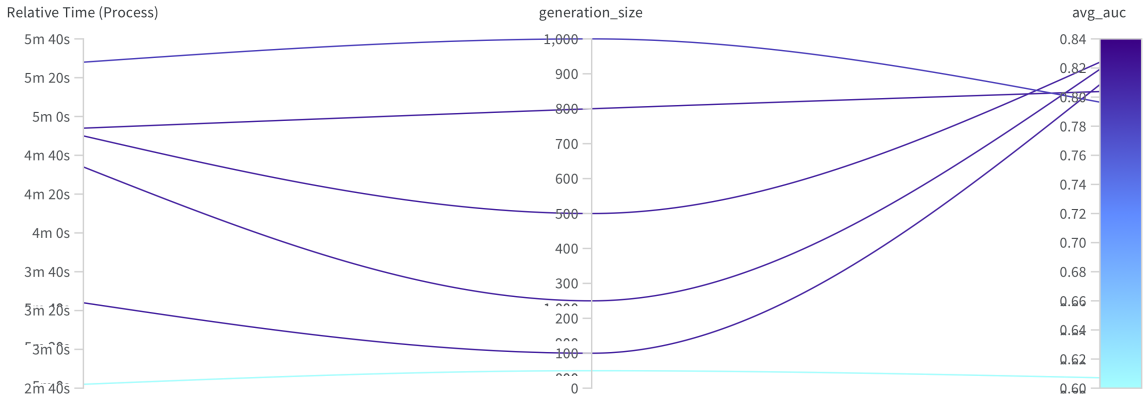

Figure 31: The hyper-parameter tuning result of STONED.

Table 8: The mean and standard deviation of **AUC Top-1** from 5 independent runs. We ranked the methods by the summation of mean **AUC Top-1** of all tasks. (Continued)

Method Assembly	REINVENT SMILES	Graph GA Fragments	REINVENT SELFIES SELFIES	GP BO Fragments	LSTM HC SMILES
albuterol_similarity	0.903±0.003	0.875±0.022	0.853±0.032	**0.922±0.011**	0.798±0.030
amlodipine_mpo	0.652±0.037	**0.685±0.021**	0.626±0.020	0.607±0.044	0.636±0.020
celecoxib_rediscovery	0.801±0.098	0.683±0.122	0.616±0.039	**0.808±0.075**	0.619±0.030
deco_hop	0.679±0.047	0.624±0.005	0.645±0.022	0.645±0.026	**0.888±0.008**
drd2	0.969±0.007	0.992±0.001	0.980±0.003	0.957±0.007	0.957±0.012
fexofenadine_mpo	0.801±0.007	0.774±0.011	0.762±0.004	0.740±0.007	0.753±0.010
gsk3b	0.893±0.044	0.826±0.069	0.823±0.035	0.877±0.040	0.935±0.014
isomers_c7h8n2o2	0.882±0.029	0.899±0.060	0.888±0.033	0.747±0.112	0.615±0.058
isomers_c9h10n2o2pf2cl	0.673±0.059	0.765±0.046	0.780±0.024	0.513±0.172	0.465±0.034
jnk3	**0.813±0.024**	0.597±0.141	0.670±0.069	0.592±0.159	0.787±0.057
median1	0.367±0.009	0.319±0.027	**0.367±0.012**	0.315±0.017	0.298±0.019
median2	0.289±0.009	0.288±0.008	0.269±0.006	**0.309±0.009**	0.276±0.014
mestranol_similarity	0.637±0.048	0.615±0.027	0.646±0.033	0.665±0.082	0.613±0.054
osimertinib_mpo	**0.849±0.010**	0.845±0.006	0.831±0.002	0.803±0.004	0.815±0.003
perindopril_mpo	0.553±0.017	0.559±0.010	0.533±0.022	0.511±0.013	0.514±0.010
qed	**0.943±0.000**	0.942±0.000	0.942±0.000	0.941±0.000	0.942±0.000
ranolazine_mpo	**0.786±0.009**	0.758±0.013	0.777±0.018	0.762±0.013	0.756±0.011
scaffold_hop	0.572±0.021	0.526±0.008	0.540±0.015	0.562±0.023	**0.628±0.058**
sitagliptin_mpo	0.055±0.015	**0.492±0.068**	0.257±0.116	0.237±0.061	0.128±0.030
thiothixene_rediscovery	0.557±0.013	0.506±0.026	0.517±0.046	**0.591±0.026**	0.485±0.015
troglitazone_rediscovery	0.458±0.034	0.410±0.016	0.371±0.014	0.431±0.015	0.405±0.025
valsartan_smarts	**0.187±0.374**	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	**0.383±0.062**	0.366±0.033	0.369±0.020	0.252±0.071	0.286±0.021
Sum	14.711	14.356	14.077	13.798	13.611
Rank	1	2	3	4	5

Method Assembly	STONED SELFIES	DoG-Gen Synthesis	SynNet Synthesis	SMILES GA SMILES	MolPal -
albuterol_similarity	0.755±0.078	0.747±0.014	0.645±0.052	0.679±0.056	0.694±0.003
amlodipine_mpo	0.616±0.048	0.555±0.004	0.580±0.006	0.564±0.004	0.621±0.010
celecoxib_rediscovery	0.388±0.044	0.525±0.012	0.485±0.032	0.350±0.026	0.496±0.002
deco_hop	0.612±0.009	0.874±0.003	0.626±0.011	0.613±0.007	0.804±0.019
drd2	0.933±0.019	**0.992±0.000**	0.983±0.002	0.930±0.017	0.902±0.007
fexofenadine_mpo	**0.803±0.018**	0.730±0.007	0.778±0.017	0.729±0.016	0.704±0.001
gsk3b	0.702±0.055	**0.958±0.007**	0.854±0.044	0.667±0.039	0.776±0.002
isomers_c7h8n2o2	0.913±0.010	0.580±0.034	0.607±0.050	**0.930±0.022**	0.832±0.005
isomers_c9h10n2o2pf2cl	0.822±0.028	0.365±0.031	0.433±0.084	**0.881±0.062**	0.361±0.009
jnk3	0.543±0.093	0.707±0.022	0.722±0.042	0.339±0.025	0.457±0.024
median1	0.281±0.020	0.242±0.003	0.235±0.010	0.204±0.011	0.301±0.000
median2	0.249±0.033	0.229±0.003	0.251±0.007	0.203±0.006	0.266±0.000
mestranol_similarity	0.621±0.103	0.487±0.010	0.424±0.020	0.480±0.029	**0.708±0.006**
osimertinib_mpo	0.827±0.012	0.800±0.004	0.810±0.004	0.823±0.011	0.803±0.001
perindopril_mpo	0.493±0.012	0.505±0.003	**0.579±0.014**	0.453±0.011	0.495±0.003
qed	0.942±0.000	0.939±0.000	0.943±0.000	0.942±0.000	0.942±0.000
ranolazine_mpo	0.783±0.029	0.759±0.010	0.762±0.007	0.719±0.023	0.515±0.007
scaffold_hop	0.524±0.035	0.541±0.005	0.517±0.013	0.498±0.012	0.518±0.001
sitagliptin_mpo	0.406±0.083	0.102±0.019	0.060±0.034	0.396±0.052	0.100±0.013
thiothixene_rediscovery	0.374±0.027	0.411±0.006	0.444±0.029	0.322±0.018	0.356±0.000
troglitazone_rediscovery	0.325±0.018	**0.492±0.025**	0.299±0.006	0.275±0.018	0.290±0.000
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.333±0.026	0.171±0.021	0.376±0.019	0.349±0.042	0.262±0.004
Sum	13.256	12.721	12.425	12.357	12.214
Rank	6	7	8	9	10

Table 9: (Continued)

Method Assembly	DST Fragments	MARS Fragments	LSTM HC SELFIES SELFIES	MIMOSA Fragments	DoG-AE Synthesis
albuterol_similarity	0.671±0.021	0.668±0.121	0.726±0.029	0.649±0.023	0.621±0.045
amlodipine_mpo	0.573±0.047	0.523±0.022	0.569±0.006	0.590±0.009	0.534±0.013
celecoxib_rediscovery	0.422±0.005	0.428±0.049	0.425±0.015	0.420±0.017	0.401±0.024
deco_hop	0.619±0.010	0.597±0.003	0.601±0.004	0.625±0.004	0.841±0.009
drd2	0.886±0.021	0.938±0.014	0.847±0.036	0.879±0.024	0.985±0.003
fexofenadine_mpo	0.741±0.005	0.729±0.007	0.716±0.006	0.721±0.013	0.716±0.041
gsk3b	0.737±0.036	0.628±0.055	0.537±0.040	0.639±0.046	0.754±0.118
isomers_c7h8n2o2	0.664±0.074	0.807±0.048	0.695±0.024	0.635±0.058	0.549±0.187
isomers_c9h10n2o2pf2cl	0.551±0.040	0.640±0.023	0.476±0.039	0.345±0.045	0.134±0.072
jnk3	0.600±0.062	0.548±0.088	0.303±0.053	0.401±0.071	0.539±0.133
median1	0.256±0.017	0.226±0.012	0.268±0.014	0.270±0.005	0.200±0.009
median2	0.194±0.021	0.196±0.009	0.228±0.006	0.227±0.005	0.198±0.008
mestranol_similarity	0.491±0.049	0.430±0.024	0.492±0.014	0.509±0.033	0.429±0.027
osimertinib_mpo	0.799±0.005	0.797±0.007	0.801±0.005	0.801±0.014	0.787±0.024
perindopril_mpo	0.487±0.012	0.475±0.007	0.472±0.006	0.506±0.019	0.459±0.023
qed	0.941±0.000	0.940±0.001	0.942±0.000	0.942±0.000	0.938±0.001
ranolazine_mpo	0.657±0.057	0.763±0.017	0.677±0.014	0.673±0.020	0.735±0.015
scaffold_hop	0.507±0.004	0.482±0.009	0.495±0.007	0.517±0.017	0.519±0.020
sitagliptin_mpo	0.159±0.074	0.040±0.013	0.203±0.025	0.136±0.029	0.037±0.031
thiothixene_rediscovery	0.391±0.011	0.382±0.031	0.370±0.009	0.365±0.017	0.352±0.015
troglitazone_rediscovery	0.295±0.019	0.274±0.019	0.283±0.004	0.314±0.008	0.344±0.052
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.257±0.025	0.291±0.020	0.303±0.027	0.204±0.033	0.145±0.082
Sum	11.911	11.814	11.441	11.378	11.227
Rank	11	12	13	14	15

Method Assembly	VAE BO SELFIES SELFIES	Screening -	VAE BO SMILES SMILES	Pasithea SELFIES	GFlowNet Fragments
albuterol_similarity	0.572±0.043	0.546±0.029	0.563±0.019	0.499±0.005	0.501±0.029
amlodipine_mpo	0.580±0.004	0.580±0.014	0.602±0.032	0.582±2.676	0.467±0.006
celecoxib_rediscovery	0.386±0.022	0.394±0.005	0.406±0.013	0.351±0.010	0.374±0.007
deco_hop	0.590±0.002	0.611±0.002	0.608±0.003	0.603±0.012	0.590±0.001
drd2	0.808±0.055	0.797±0.059	0.818±0.073	0.557±0.087	0.791±0.041
fexofenadine_mpo	0.698±0.006	0.690±0.011	0.699±0.008	0.702±0.039	0.714±0.007
gsk3b	0.506±0.091	0.657±0.078	0.536±0.046	0.401±0.075	0.691±0.033
isomers_c7h8n2o2	0.497±0.052	0.395±0.079	0.332±0.052	0.792±0.057	0.539±0.068
isomers_c9h10n2o2pf2cl	0.367±0.083	0.218±0.047	0.175±0.032	0.499±0.081	0.173±0.046
jnk3	0.341±0.070	0.362±0.063	0.375±0.054	0.206±0.033	0.492±0.024
median1	0.226±0.008	0.249±0.010	0.252±0.035	0.212±0.018	0.224±0.006
median2	0.200±0.001	0.232±0.015	0.211±0.003	0.193±0.006	0.193±0.005
mestranol_similarity	0.495±0.050	0.507±0.121	0.508±0.035	0.446±0.012	0.363±0.017
osimertinib_mpo	0.790±0.003	0.784±0.005	0.792±0.004	0.787±0.008	0.801±0.008
perindopril_mpo	0.458±0.015	0.478±0.018	0.469±0.019	0.445±0.015	0.455±0.008
qed	0.941±0.001	0.942±0.000	0.942±0.000	0.938±0.003	0.939±0.001
ranolazine_mpo	0.534±0.046	0.485±0.026	0.563±0.049	0.437±0.050	0.679±0.004
scaffold_hop	0.474±0.007	0.503±0.004	0.493±0.009	0.493±0.019	0.474±0.003
sitagliptin_mpo	0.173±0.041	0.076±0.023	0.088±0.043	0.176±0.050	0.028±0.012
thiothixene_rediscovery	0.329±0.007	0.350±0.007	0.355±0.017	0.330±0.015	0.312±0.011
troglitazone_rediscovery	0.275±0.023	0.272±0.010	0.286±0.011	0.256±0.007	0.202±0.006
valsartan_smarts	0.017±0.034	0.000±0.000	0.019±0.039	0.060±0.121	0.000±0.000
zaleplon_mpo	0.322±0.033	0.222±0.058	0.094±0.028	0.185±0.033	0.066±0.042
Sum	10.589	10.363	10.197	10.162	10.079
Rank	16	17	18	19	20

Table 10: (Continued)

Method Assembly	JT-VAE BO Fragments	GFlowNet-AL Fragments	GA+D SELFIES	Graph MCTS Atoms	MolDQN Atoms
albuterol_similarity	0.541±0.051	0.440±0.020	0.528±0.029	0.625±0.028	0.348±0.022
amlodipine_mpo	0.582±1.791	0.448±0.007	0.421±0.033	0.472±0.019	0.343±0.013
celecoxib_rediscovery	0.385±0.025	0.289±0.005	0.241±0.023	0.297±0.009	0.114±0.016
deco_hop	0.595±0.003	0.591±0.004	0.553±0.005	0.561±0.003	0.549±0.001
drd2	0.741±0.185	0.716±0.073	0.425±0.207	0.476±0.111	0.030±0.003
fexofenadine_mpo	0.695±0.012	0.713±0.004	0.607±0.008	0.596±0.011	0.498±0.015
gsk3b	0.482±0.054	0.640±0.031	0.363±0.022	0.354±0.032	0.286±0.012
isomers_c7h8n2o2	0.243±0.075	0.450±0.097	0.878±0.012	0.701±0.048	0.594±0.077
isomers_c9h10n2o2pf2cl	0.273±0.121	0.131±0.024	0.681±0.022	0.601±0.066	0.481±0.043
jnk3	0.353±0.063	0.431±0.035	0.234±0.021	0.144±0.031	0.134±0.013
median1	0.209±0.017	0.223±0.001	0.201±0.007	0.234±0.014	0.144±0.013
median2	0.191±0.003	0.182±0.004	0.128±0.005	0.141±0.003	0.094±0.003
mestranol_similarity	0.448±0.055	0.327±0.016	0.396±0.019	0.307±0.007	0.209±0.007
osimertinib_mpo	0.794±0.007	0.803±0.008	0.689±0.029	0.718±0.007	0.689±0.006
perindopril_mpo	0.453±0.012	0.448±0.009	0.187±0.095	0.310±0.023	0.247±0.034
qed	0.940±0.000	0.930±0.004	0.877±0.016	0.913±0.009	0.788±0.030
ranolazine_mpo	0.583±0.039	0.680±0.018	0.575±0.014	0.316±0.051	0.084±0.034
scaffold_hop	0.487±0.006	0.472±0.004	0.417±0.009	0.421±0.004	0.411±0.006
sitagliptin_mpo	0.134±0.070	0.020±0.011	0.311±0.023	0.138±0.047	0.010±0.008
thiothixene_rediscovery	0.311±0.011	0.294±0.012	0.240±0.035	0.249±0.009	0.108±0.011
troglitazone_rediscovery	0.257±0.003	0.201±0.008	0.160±0.013	0.245±0.015	0.135±0.007
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.266±0.047	0.029±0.009	0.263±0.014	0.113±0.035	0.026±0.015
Sum	9.973	9.470	9.387	8.944	6.332
Rank	21	22	23	24	25

Table 11: The mean and standard deviation of **AUC Top-100** from 5 independent runs. We ranked the methods by the summation of mean **AUC Top-100** of all tasks. (Continued)

Method Assembly	REINVENT SMILES	Graph GA Fragments	STONED SELFIES	REINVENT SELFIES SELFIES	GP BO Fragments
albuterol_similarity	**0.842±0.013**	0.759±0.014	0.727±0.070	0.781±0.033	0.839±0.019
amlodipine_mpo	0.608±0.033	**0.622±0.018**	0.593±0.045	0.574±0.009	0.538±0.045
celecoxib_rediscovery	**0.646±0.053**	0.558±0.075	0.366±0.035	0.515±0.044	0.637±0.041
deco_hop	0.649±0.040	0.609±0.004	0.605±0.007	0.610±0.003	0.611±0.014
drd2	0.908±0.007	**0.924±0.020**	0.881±0.026	0.898±0.008	0.870±0.031
fexofenadine_mpo	0.752±0.005	0.731±0.012	**0.777±0.013**	0.705±0.002	0.685±0.005
gsk3b	**0.823±0.042**	0.737±0.072	0.621±0.045	0.711±0.043	0.808±0.046
isomers_c7h8n2o2	0.798±0.043	0.761±0.058	0.864±0.016	0.791±0.023	0.564±0.128
isomers_c9h10n2o2pf2cl	0.590±0.050	0.628±0.048	0.765±0.039	0.656±0.045	0.399±0.184
jnk3	**0.742±0.025**	0.488±0.126	0.481±0.092	0.567±0.057	0.524±0.149
median1	**0.325±0.009**	0.264±0.019	0.244±0.013	0.299±0.012	0.275±0.012
median2	0.258±0.006	0.251±0.011	0.236±0.031	0.232±0.005	**0.275±0.007**
mestranol_similarity	**0.586±0.046**	0.523±0.019	0.577±0.094	0.578±0.026	0.572±0.086
osimertinib_mpo	**0.806±0.008**	0.799±0.004	0.799±0.011	0.791±0.005	0.750±0.010
perindopril_mpo	0.511±0.016	0.503±0.008	0.472±0.011	0.487±0.019	0.460±0.009
qed	0.931±0.000	0.930±0.000	0.930±0.000	0.929±0.000	0.919±0.002
ranolazine_mpo	0.719±0.008	0.670±0.012	**0.738±0.028**	0.695±0.023	0.694±0.016
scaffold_hop	**0.537±0.015**	0.502±0.005	0.512±0.031	0.502±0.011	0.527±0.015
sitagliptin_mpo	0.006±0.000	0.330±0.074	**0.351±0.078**	0.118±0.105	0.117±0.036
thiothixene_rediscovery	0.493±0.013	0.433±0.021	0.352±0.027	0.456±0.033	**0.502±0.023**
troglitazone_rediscovery	**0.411±0.029**	0.358±0.014	0.307±0.018	0.314±0.013	0.379±0.013
valsartan_smarts	**0.168±0.336**	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	**0.325±0.062**	0.305±0.025	0.307±0.027	0.257±0.031	0.165±0.070
Sum	13.445	12.696	12.518	12.475	12.122
Rank	1	2	3	4	5

Method Assembly	SMILES GA SMILES	LSTM HC SMILES	SynNet Synthesis	DST Fragments	MIMOSA Fragments
albuterol_similarity	0.643±0.068	0.602±0.014	0.494±0.026	0.539±0.012	0.566±0.014
amlodipine_mpo	0.534±0.011	0.533±0.010	0.533±0.006	0.469±0.005	0.509±0.004
celecoxib_rediscovery	0.331±0.027	0.448±0.012	0.374±0.023	0.333±0.005	0.353±0.003
deco_hop	0.605±0.006	**0.738±0.019**	0.593±0.005	0.591±0.006	0.605±0.002
drd2	0.875±0.022	0.788±0.017	0.897±0.015	0.738±0.025	0.709±0.021
fexofenadine_mpo	0.700±0.014	0.680±0.003	0.720±0.011	0.690±0.004	0.672±0.009
gsk3b	0.586±0.043	0.670±0.011	0.655±0.039	0.598±0.036	0.475±0.040
isomers_c7h8n2o2	**0.880±0.027**	0.313±0.032	0.167±0.028	0.380±0.083	0.468±0.036
isomers_c9h10n2o2pf2cl	**0.823±0.073**	0.186±0.015	0.053±0.022	0.307±0.084	0.259±0.046
jnk3	0.288±0.022	0.489±0.025	0.466±0.038	0.489±0.059	0.302±0.055
median1	0.185±0.012	0.213±0.007	0.187±0.005	0.193±0.006	0.212±0.004
median2	0.191±0.005	0.217±0.004	0.205±0.003	0.166±0.016	0.195±0.004
mestranol_similarity	0.449±0.028	0.428±0.018	0.352±0.018	0.400±0.016	0.391±0.013
osimertinib_mpo	0.798±0.012	0.749±0.001	0.759±0.002	0.742±0.001	0.750±0.010
perindopril_mpo	0.436±0.013	0.446±0.004	**0.512±0.010**	0.425±0.009	0.458±0.007
qed	**0.932±0.001**	0.923±0.001	0.930±0.001	0.925±0.001	0.925±0.000
ranolazine_mpo	0.670±0.028	0.630±0.012	0.690±0.015	0.579±0.044	0.587±0.015
scaffold_hop	0.487±0.010	0.491±0.004	0.478±0.007	0.480±0.003	0.488±0.009
sitagliptin_mpo	0.307±0.058	0.020±0.006	0.007±0.004	0.017±0.005	0.052±0.012
thiothixene_rediscovery	0.300±0.014	0.377±0.005	0.351±0.012	0.325±0.007	0.316±0.015
troglitazone_rediscovery	0.256±0.024	0.301±0.008	0.254±0.007	0.250±0.020	0.273±0.008
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.310±0.034	0.111±0.005	0.223±0.017	0.089±0.063	0.132±0.038
Sum	11.598	10.365	9.914	9.737	9.708
Rank	6	7	8	9	10

Table 12: (Continued)

Method Assembly	DoG-Gen Synthesis	MARS Fragments	LSTM HC SELFIES SELFIES	GA+D SELFIES	MolPal -
albuterol_similarity	0.578±0.011	0.478±0.121	0.572±0.027	0.448±0.018	0.528±0.002
amlodipine_mpo	0.489±0.003	0.465±0.010	0.485±0.003	0.365±0.029	0.514±0.006
celecoxib_rediscovery	0.387±0.006	0.317±0.056	0.324±0.004	0.200±0.024	0.349±0.002
deco_hop	0.715±0.010	0.577±0.002	0.573±0.001	0.545±0.004	0.585±0.001
drd2	0.740±0.003	0.752±0.019	0.510±0.035	0.314±0.190	0.403±0.009
fexofenadine_mpo	0.640±0.001	0.669±0.003	0.650±0.004	0.553±0.007	0.639±0.002
gsk3b	0.629±0.018	0.463±0.042	0.292±0.003	0.309±0.016	0.319±0.007
isomers_c7h8n2o2	0.305±0.011	0.583±0.025	0.415±0.042	0.799±0.024	0.199±0.003
isomers_c9h10n2o2pf2cl	0.095±0.004	0.471±0.015	0.208±0.007	0.608±0.024	0.071±0.001
jnk3	0.436±0.022	0.386±0.081	0.136±0.003	0.195±0.020	0.200±0.004
median1	0.181±0.000	0.169±0.015	0.200±0.003	0.152±0.006	0.202±0.001
median2	0.188±0.001	0.159±0.012	0.178±0.004	0.111±0.005	0.191±0.000
mestranol_similarity	0.369±0.004	0.323±0.033	0.381±0.006	0.333±0.014	0.433±0.002
osimertinib_mpo	0.706±0.001	0.730±0.006	0.732±0.006	0.645±0.025	0.736±0.003
perindopril_mpo	0.422±0.002	0.432±0.005	0.399±0.003	0.155±0.079	0.423±0.002
qed	0.912±0.000	0.886±0.012	0.920±0.001	0.821±0.013	0.930±0.000
ranolazine_mpo	0.601±0.003	0.684±0.019	0.502±0.007	0.525±0.016	0.357±0.004
scaffold_hop	0.483±0.004	0.450±0.004	0.445±0.001	0.406±0.008	0.461±0.000
sitagliptin_mpo	0.015±0.005	0.004±0.000	0.040±0.002	0.232±0.021	0.014±0.000
thiothixene_rediscovery	0.329±0.003	0.294±0.014	0.294±0.006	0.201±0.024	0.302±0.001
troglitazone_rediscovery	0.331±0.016	0.228±0.013	0.225±0.002	0.139±0.012	0.245±0.000
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.073±0.011	0.082±0.040	0.103±0.010	0.214±0.015	0.046±0.001
Sum	9.635	9.612	8.595	8.280	8.156
Rank	11	12	13	14	15

Method Assembly	GFlowNet Fragments	DoG-AE Synthesis	GFlowNet-AL Fragments	Screening -	VAE BO SMILES SMILES
albuterol_similarity	0.374±0.009	0.423±0.020	0.324±0.002	0.410±0.003	0.412±0.003
amlodipine_mpo	0.398±0.004	0.457±0.004	0.374±0.002	0.477±0.000	0.475±0.002
celecoxib_rediscovery	0.275±0.006	0.282±0.019	0.213±0.002	0.289±0.002	0.291±0.001
deco_hop	0.572±0.002	0.626±0.041	0.570±0.000	0.571±0.000	0.570±0.000
drd2	0.279±0.065	0.543±0.069	0.165±0.010	0.186±0.005	0.187±0.014
fexofenadine_mpo	0.653±0.004	0.618±0.007	0.645±0.002	0.613±0.002	0.616±0.002
gsk3b	0.585±0.022	0.356±0.074	0.504±0.011	0.235±0.008	0.214±0.007
isomers_c7h8n2o2	0.191±0.013	0.052±0.015	0.084±0.018	0.036±0.005	0.039±0.005
isomers_c9h10n2o2pf2cl	0.047±0.012	0.012±0.004	0.021±0.002	0.027±0.002	0.025±0.001
jnk3	0.367±0.022	0.245±0.065	0.272±0.016	0.126±0.005	0.123±0.003
median1	0.165±0.004	0.134±0.006	0.145±0.001	0.161±0.002	0.160±0.001
median2	0.164±0.001	0.156±0.006	0.156±0.001	0.170±0.001	0.169±0.000
mestranol_similarity	0.273±0.006	0.304±0.013	0.246±0.002	0.328±0.005	0.323±0.001
osimertinib_mpo	0.758±0.001	0.661±0.007	0.758±0.001	0.704±0.001	0.712±0.002
perindopril_mpo	0.384±0.012	0.374±0.007	0.375±0.001	0.397±0.002	0.398±0.001
qed	0.861±0.007	0.877±0.004	0.820±0.007	0.922±0.000	0.922±0.000
ranolazine_mpo	0.615±0.004	0.566±0.038	0.543±0.006	0.302±0.003	0.318±0.003
scaffold_hop	0.445±0.001	0.453±0.011	0.442±0.000	0.443±0.000	0.441±0.001
sitagliptin_mpo	0.001±0.000	0.001±0.000	0.001±0.000	0.006±0.000	0.006±0.000
thiothixene_rediscovery	0.246±0.009	0.256±0.012	0.224±0.003	0.272±0.001	0.270±0.002
troglitazone_rediscovery	0.170±0.001	0.207±0.007	0.167±0.000	0.218±0.002	0.220±0.001
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.011±0.013	0.005±0.002	0.002±0.000	0.010±0.002	0.006±0.001
Sum	7.844	7.620	7.060	6.915	6.909
Rank	16	17	18	19	20

Table 13: (Continued)

Method Assembly	VAE BO SELFIES SELFIES	JT-VAE BO Fragments	Pasithea SELFIES	Graph MCTS Atoms	MolDQN Atoms
albuterol_similarity	0.413±0.003	0.412±0.018	0.365±0.004	0.497±0.014	0.273±0.008
amlodipine_mpo	0.465±0.002	0.468±0.007	0.442±0.004	0.385±0.005	0.230±0.011
celecoxib_rediscovery	0.260±0.004	0.240±0.012	0.242±0.005	0.204±0.007	0.080±0.002
deco_hop	0.560±0.001	0.567±0.002	0.558±0.000	0.539±0.001	0.534±0.001
drd2	0.174±0.007	0.170±0.046	0.060±0.010	0.121±0.008	0.018±0.000
fexofenadine_mpo	0.619±0.006	0.616±0.009	0.583±0.011	0.522±0.005	0.431±0.010
gsk3b	0.206±0.006	0.201±0.025	0.141±0.029	0.183±0.008	0.176±0.008
isomers_c7h8n2o2	0.094±0.008	0.025±0.009	0.450±0.021	0.304±0.018	0.269±0.011
isomers_c9h10n2o2pf2cl	0.063±0.004	0.021±0.006	0.193±0.093	0.203±0.044	0.134±0.013
jnk3	0.113±0.002	0.119±0.007	0.076±0.008	0.066±0.005	0.075±0.003
median1	0.159±0.003	0.144±0.006	0.133±0.007	0.143±0.003	0.094±0.003
median2	0.159±0.001	0.159±0.003	0.153±0.002	0.117±0.000	0.072±0.002
mestranol_similarity	0.316±0.001	0.299±0.010	0.274±0.007	0.229±0.006	0.150±0.008
osimertinib_mpo	0.711±0.002	0.727±0.005	0.643±0.019	0.655±0.003	0.636±0.005
perindopril_mpo	0.382±0.002	0.390±0.007	0.364±0.003	0.219±0.005	0.125±0.019
qed	0.914±0.001	0.912±0.004	0.896±0.004	0.832±0.006	0.630±0.006
ranolazine_mpo	0.313±0.019	0.337±0.062	0.211±0.011	0.122±0.010	0.018±0.006
scaffold_hop	0.427±0.002	0.443±0.005	0.424±0.001	0.392±0.002	0.388±0.003
sitagliptin_mpo	0.021±0.003	0.010±0.005	0.026±0.004	0.013±0.002	0.000±0.000
thiothixene_rediscovery	0.252±0.003	0.242±0.007	0.238±0.006	0.193±0.002	0.081±0.004
troglitazone_rediscovery	0.207±0.002	0.206±0.004	0.200±0.002	0.194±0.005	0.101±0.002
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.059±0.004	0.024±0.012	0.027±0.007	0.014±0.005	0.002±0.001
Sum	6.899	6.740	6.712	6.156	4.528
Rank	21	22	23	24	25

Table 14: The mean and standard deviation of **Top-100** from 5 independent runs. We ranked the methods by the summation of mean **Top-100** of all tasks. (Continued)

Method Assembly	REINVENT SMILES	REINVENT SELFIES SELFIES	Graph GA Fragments	LSTM HC SMILES	GP BO Fragments
albuterol_similarity	0.991±0.223	0.948±0.228	0.951±0.190	0.953±0.198	**0.995±0.181**
amlodipine_mpo	0.728±0.114	0.684±0.097	**0.743±0.106**	0.669±0.073	0.638±0.090
celecoxib_rediscovery	**0.821±0.199**	0.684±0.169	0.692±0.168	0.694±0.143	0.802±0.177
deco_hop	0.796±0.104	0.706±0.044	0.642±0.026	**0.921±0.140**	0.698±0.053
drd2	**0.999±0.250**	0.999±0.262	0.999±0.209	0.999±0.312	0.998±0.273
fexofenadine_mpo	**0.892±0.110**	0.818±0.080	0.817±0.089	0.763±0.072	0.774±0.088
gsk3b	**0.965±0.243**	0.934±0.262	0.919±0.226	0.942±0.249	0.957±0.218
isomers_c7h8n2o2	0.986±0.338	0.948±0.301	0.948±0.241	0.848±0.289	0.749±0.264
isomers_c9h10n2o2pf2cl	0.820±0.336	0.865±0.313	0.837±0.227	0.610±0.189	0.538±0.257
jnk3	**0.943±0.295**	0.782±0.268	0.796±0.258	0.851±0.255	0.675±0.244
median1	**0.382±0.080**	0.339±0.070	0.310±0.056	0.315±0.064	0.316±0.052
median2	**0.313±0.055**	0.300±0.056	0.300±0.048	0.290±0.046	0.313±0.046
mestranol_similarity	0.733±0.177	**0.755±0.181**	0.680±0.127	0.652±0.118	0.733±0.168
osimertinib_mpo	**0.896±0.101**	0.865±0.084	0.861±0.098	0.829±0.095	0.812±0.091
perindopril_mpo	**0.635±0.099**	0.608±0.105	0.591±0.078	0.532±0.060	0.523±0.058
qed	**0.948±0.030**	0.947±0.031	0.946±0.028	0.947±0.029	0.943±0.026
ranolazine_mpo	0.848±0.163	0.836±0.170	0.781±0.150	0.783±0.149	0.790±0.147
scaffold_hop	**0.708±0.089**	0.608±0.064	0.550±0.040	0.573±0.046	0.593±0.056
sitagliptin_mpo	0.010±0.003	0.269±0.172	**0.578±0.197**	0.088±0.023	0.195±0.080
thiothixene_rediscovery	**0.644±0.149**	0.616±0.144	0.536±0.099	0.554±0.097	0.613±0.111
troglitazone_rediscovery	**0.570±0.140**	0.469±0.101	0.464±0.083	0.465±0.084	0.482±0.082
valsartan_smarts	**0.194±0.363**	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	**0.463±0.187**	0.384±0.159	0.389±0.105	0.330±0.105	0.216±0.093
Sum	16.297	15.377	15.342	14.621	14.365
Rank	1	2	3	4	5

Method Assembly	STONED SELFIES	DoG-Gen Synthesis	SMILES GA SMILES	DST Fragments	MIMOSA Fragments
albuterol_similarity	0.805±0.163	0.852±0.154	0.698±0.127	0.682±0.117	0.667±0.127
amlodipine_mpo	0.631±0.080	0.583±0.070	0.558±0.048	0.482±0.031	0.550±0.049
celecoxib_rediscovery	0.393±0.062	0.583±0.115	0.349±0.047	0.381±0.056	0.405±0.068
deco_hop	0.626±0.023	0.910±0.140	0.624±0.022	0.613±0.022	0.637±0.029
drd2	0.997±0.274	0.999±0.314	0.986±0.260	0.993±0.377	0.981±0.383
fexofenadine_mpo	0.847±0.100	0.736±0.085	0.756±0.075	0.753±0.083	0.723±0.075
gsk3b	0.733±0.178	0.959±0.251	0.687±0.171	0.821±0.267	0.672±0.207
isomers_c7h8n2o2	0.993±0.280	0.809±0.285	**0.995±0.264**	0.713±0.291	0.732±0.303
isomers_c9h10n2o2pf2cl	0.919±0.271	0.337±0.100	**0.966±0.272**	0.698±0.272	0.413±0.182
jnk3	0.587±0.179	0.802±0.221	0.374±0.094	0.748±0.249	0.457±0.160
median1	0.264±0.045	0.261±0.055	0.198±0.029	0.231±0.037	0.251±0.050
median2	0.260±0.045	0.263±0.038	0.204±0.019	0.178±0.022	0.216±0.025
mestranol_similarity	0.665±0.151	0.552±0.105	0.508±0.085	0.469±0.078	0.443±0.072
osimertinib_mpo	0.847±0.104	0.826±0.123	0.834±0.095	0.802±0.095	0.804±0.092
perindopril_mpo	0.514±0.055	0.546±0.074	0.454±0.041	0.453±0.044	0.530±0.065
qed	0.943±0.025	0.947±0.046	0.946±0.026	0.941±0.026	0.939±0.025
ranolazine_mpo	**0.855±0.190**	0.782±0.170	0.766±0.155	0.730±0.223	0.757±0.222
scaffold_hop	0.545±0.055	0.559±0.044	0.509±0.030	0.512±0.035	0.527±0.040
sitagliptin_mpo	0.482±0.174	0.085±0.025	0.436±0.151	0.027±0.011	0.101±0.044
thiothixene_rediscovery	0.382±0.053	0.463±0.079	0.316±0.033	0.374±0.053	0.348±0.048
troglitazone_rediscovery	0.351±0.052	0.534±0.130	0.270±0.037	0.286±0.044	0.316±0.049
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.369±0.108	0.253±0.090	0.377±0.114	0.156±0.095	0.239±0.108
Sum	14.017	13.653	12.824	12.052	11.717
Rank	6	7	8	9	10

Table 15: (Continued)

Method Assembly	LSTM HC SELFIES SELFIES	GA+D SELFIES	MARS Fragments	SynNet Synthesis	GFlowNet Fragments
albuterol_similarity	0.891±0.173	0.576±0.123	0.554±0.154	0.554±0.065	0.422±0.051
amlodipine_mpo	0.553±0.044	0.513±0.150	0.496±0.063	0.559±0.046	0.439±0.064
celecoxib_rediscovery	0.473±0.082	0.252±0.066	0.394±0.091	0.410±0.052	0.308±0.041
deco_hop	0.610±0.019	0.580±0.024	0.587±0.013	0.603±0.012	0.584±0.009
drd2	0.992±0.371	0.678±0.339	0.959±0.279	0.985±0.201	0.492±0.152
fexofenadine_mpo	0.726±0.069	0.717±0.206	0.717±0.102	0.749±0.057	0.678±0.037
gsk3b	0.503±0.120	0.482±0.130	0.536±0.133	0.797±0.182	0.637±0.076
isomers_c7h8n2o2	0.765±0.259	0.993±0.302	0.845±0.309	0.212±0.067	0.341±0.105
isomers_c9h10n2o2pf2cl	0.436±0.138	0.811±0.286	0.737±0.287	0.079±0.036	0.100±0.032
jnk3	0.216±0.050	0.356±0.109	0.497±0.164	0.563±0.150	0.438±0.077
median1	0.285±0.051	0.171±0.035	0.181±0.026	0.197±0.020	0.186±0.026
median2	0.240±0.032	0.148±0.034	0.169±0.020	0.213±0.016	0.175±0.012
mestranol_similarity	0.520±0.079	0.497±0.131	0.375±0.060	0.385±0.044	0.306±0.034
osimertinib_mpo	0.804±0.092	0.768±0.169	0.776±0.128	0.789±0.079	0.779±0.041
perindopril_mpo	0.469±0.043	0.293±0.137	0.463±0.058	0.546±0.053	0.424±0.054
qed	0.945±0.026	0.928±0.140	0.903±0.038	0.942±0.029	0.913±0.086
ranolazine_mpo	0.724±0.183	0.763±0.264	0.720±0.115	0.744±0.106	0.648±0.090
scaffold_hop	0.495±0.027	0.459±0.038	0.461±0.019	0.489±0.017	0.460±0.014
sitagliptin_mpo	0.101±0.029	0.436±0.165	0.010±0.003	0.008±0.005	0.004±0.001
thiothixene_rediscovery	0.399±0.054	0.271±0.073	0.378±0.060	0.379±0.035	0.268±0.027
troglitazone_rediscovery	0.286±0.033	0.189±0.044	0.264±0.033	0.273±0.023	0.181±0.012
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.213±0.070	0.336±0.124	0.101±0.057	0.280±0.076	0.029±0.019
Sum	11.657	11.230	11.133	10.768	8.824
Rank	11	12	13	14	15

Method Assembly	MolPal -	DoG-AE Synthesis	GFlowNet-AL Fragments	Screening -	VAE BO SMILES SMILES
albuterol_similarity	0.545±0.049	0.434±0.034	0.356±0.032	0.448±0.035	0.452±0.037
amlodipine_mpo	0.554±0.059	0.468±0.040	0.411±0.059	0.505±0.037	0.501±0.033
celecoxib_rediscovery	0.364±0.041	0.288±0.028	0.239±0.025	0.317±0.029	0.324±0.033
deco_hop	0.596±0.015	0.639±0.052	0.580±0.008	0.582±0.010	0.582±0.010
drd2	0.476±0.135	0.589±0.146	0.253±0.065	0.308±0.084	0.319±0.091
fexofenadine_mpo	0.665±0.067	0.634±0.058	0.672±0.036	0.649±0.056	0.649±0.048
gsk3b	0.369±0.083	0.377±0.098	0.555±0.066	0.312±0.064	0.284±0.060
isomers_c7h8n2o2	0.220±0.056	0.055±0.018	0.132±0.038	0.065±0.020	0.067±0.020
isomers_c9h10n2o2pf2cl	0.078±0.019	0.013±0.005	0.033±0.009	0.045±0.013	0.039±0.010
jnk3	0.233±0.053	0.263±0.084	0.324±0.059	0.167±0.034	0.161±0.034
median1	0.210±0.025	0.138±0.014	0.164±0.019	0.181±0.019	0.180±0.020
median2	0.197±0.016	0.159±0.010	0.167±0.011	0.183±0.013	0.181±0.012
mestranol_similarity	0.451±0.053	0.313±0.028	0.272±0.027	0.368±0.036	0.356±0.034
osimertinib_mpo	0.770±0.096	0.687±0.089	0.779±0.041	0.750±0.084	0.753±0.074
perindopril_mpo	0.440±0.039	0.384±0.034	0.404±0.046	0.425±0.035	0.423±0.030
qed	0.944±0.025	0.890±0.036	0.884±0.081	0.939±0.023	0.939±0.025
ranolazine_mpo	0.396±0.071	0.589±0.083	0.617±0.113	0.357±0.061	0.392±0.070
scaffold_hop	0.470±0.017	0.460±0.019	0.454±0.012	0.458±0.015	0.457±0.014
sitagliptin_mpo	0.018±0.004	0.002±0.000	0.001±0.000	0.010±0.003	0.010±0.002
thiothixene_rediscovery	0.311±0.027	0.262±0.019	0.245±0.021	0.295±0.023	0.293±0.022
troglitazone_rediscovery	0.253±0.019	0.211±0.013	0.177±0.011	0.235±0.016	0.236±0.016
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.054±0.015	0.006±0.003	0.004±0.001	0.020±0.006	0.013±0.004
Sum	8.625	7.872	7.735	7.630	7.623
Rank	16	17	18	19	20

Table 16: (Continued)

Method Assembly	VAE BO SELFIES SELFIES	Pasithea SELFIES	JT-VAE BO Fragments	Graph MCTS Atoms	MolDQN Atoms
albuterol_similarity	0.447±0.036	0.379±0.019	0.432±0.036	0.543±0.050	0.329±0.034
amlodipine_mpo	0.489±0.032	0.449±0.024	0.484±0.033	0.425±0.062	0.315±0.068
celecoxib_rediscovery	0.289±0.026	0.247±0.015	0.249±0.021	0.232±0.029	0.093±0.009
deco_hop	0.570±0.008	0.563±0.005	0.575±0.010	0.549±0.008	0.541±0.007
drd2	0.293±0.082	0.065±0.015	0.196±0.068	0.180±0.047	0.023±0.004
fexofenadine_mpo	0.643±0.046	0.596±0.037	0.633±0.045	0.562±0.067	0.482±0.049
gsk3b	0.261±0.051	0.151±0.036	0.223±0.046	0.231±0.042	0.217±0.040
isomers_c7h8n2o2	0.152±0.045	0.638±0.199	0.029±0.012	0.417±0.107	0.366±0.081
isomers_c9h10n2o2pf2cl	0.106±0.030	0.291±0.135	0.026±0.010	0.298±0.089	0.260±0.064
jnk3	0.146±0.029	0.080±0.013	0.139±0.029	0.083±0.017	0.093±0.020
median1	0.174±0.018	0.138±0.012	0.150±0.014	0.164±0.021	0.138±0.021
median2	0.168±0.009	0.156±0.006	0.165±0.009	0.127±0.010	0.084±0.008
mestranol_similarity	0.348±0.032	0.279±0.016	0.312±0.025	0.261±0.034	0.213±0.038
osimertinib_mpo	0.750±0.072	0.662±0.061	0.753±0.072	0.690±0.061	0.650±0.032
perindopril_mpo	0.406±0.027	0.370±0.020	0.404±0.028	0.262±0.048	0.162±0.043
qed	0.935±0.025	0.906±0.020	0.929±0.027	0.875±0.053	0.802±0.113
ranolazine_mpo	0.363±0.066	0.218±0.025	0.362±0.085	0.175±0.041	0.036±0.015
scaffold_hop	0.440±0.011	0.431±0.007	0.454±0.015	0.407±0.013	0.398±0.012
sitagliptin_mpo	0.038±0.011	0.049±0.016	0.014±0.008	0.026±0.008	0.001±0.000
thiothixene_rediscovery	0.271±0.018	0.242±0.011	0.250±0.015	0.217±0.024	0.097±0.014
troglitazone_rediscovery	0.220±0.013	0.204±0.008	0.213±0.012	0.210±0.019	0.121±0.015
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.100±0.030	0.050±0.017	0.034±0.018	0.029±0.010	0.004±0.002
Sum	7.622	7.173	7.037	6.975	5.435
Rank	21	22	23	24	25

Table 17: The mean and standard deviation of **Top-10** from 5 independent runs. We ranked the methods by the summation of mean **Top-10** of all tasks. (Continued)

Method Assembly	REINVENT SMILES	Graph GA Fragments	REINVENT SELFIES SELFIES	LSTM HC SMILES	GP BO Fragments
albuterol_similarity	0.998±0.188	0.997±0.180	0.960±0.194	0.998±0.199	**1.0±0.156**
amlodipine_mpo	0.733±0.095	**0.769±0.088**	0.700±0.076	0.714±0.065	0.663±0.072
celecoxib_rediscovery	**0.861±0.190**	0.756±0.179	0.722±0.155	0.785±0.160	0.859±0.181
deco_hop	0.802±0.107	0.650±0.021	0.735±0.057	**0.944±0.117**	0.714±0.056
drd2	**0.999±0.178**	0.999±0.120	0.999±0.178	0.999±0.203	0.999±0.200
fexofenadine_mpo	**0.903±0.080**	0.830±0.059	0.835±0.051	0.794±0.044	0.793±0.056
gsk3b	0.968±0.195	0.937±0.191	0.956±0.219	0.984±0.171	0.974±0.188
isomers_c7h8n2o2	1.0±0.300	0.984±0.214	0.961±0.243	0.931±0.310	0.818±0.237
isomers_c9h10n2o2pf2cl	0.851±0.318	0.891±0.207	0.903±0.269	0.764±0.249	0.565±0.238
jnk3	**0.948±0.262**	0.812±0.259	0.821±0.247	0.935±0.218	0.689±0.233
median1	**0.399±0.069**	0.330±0.050	0.396±0.072	0.350±0.059	0.333±0.045
median2	0.325±0.049	0.315±0.043	0.309±0.048	0.317±0.046	**0.329±0.039**
mestranol_similarity	0.742±0.154	0.736±0.122	0.761±0.156	**0.792±0.130**	0.768±0.161
osimertinib_mpo	**0.905±0.046**	0.872±0.040	0.873±0.034	0.847±0.033	0.828±0.031
perindopril_mpo	**0.642±0.078**	0.613±0.059	0.609±0.081	0.553±0.042	0.548±0.041
qed	**0.948±0.007**	0.947±0.006	0.948±0.007	0.948±0.005	0.947±0.006
ranolazine_mpo	0.857±0.109	0.801±0.106	0.846±0.121	0.807±0.101	0.807±0.114
scaffold_hop	**0.714±0.089**	0.558±0.034	0.615±0.058	0.647±0.058	0.610±0.054
sitagliptin_mpo	0.034±0.011	**0.657±0.211**	0.362±0.185	0.186±0.055	0.267±0.106
thiothixene_rediscovery	**0.663±0.138**	0.574±0.095	0.637±0.135	0.645±0.104	0.651±0.106
troglitazone_rediscovery	0.587±0.133	0.494±0.081	0.496±0.098	0.539±0.100	0.514±0.081
valsartan_smarts	**0.196±0.376**	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	**0.475±0.172**	0.412±0.096	0.433±0.141	0.390±0.124	0.252±0.093
Sum	16.564	15.946	15.889	15.880	14.940
Rank	1	2	3	4	5

Method Assembly	DoG-Gen Synthesis	STONED SELFIES	SMILES GA SMILES	LSTM HC SELFIES SELFIES	DST Fragments
albuterol_similarity	0.925±0.150	0.805±0.146	0.703±0.109	0.971±0.181	0.748±0.115
amlodipine_mpo	0.605±0.036	0.635±0.062	0.563±0.022	0.579±0.023	0.525±0.015
celecoxib_rediscovery	0.682±0.117	0.398±0.053	0.356±0.035	0.535±0.083	0.422±0.045
deco_hop	0.925±0.122	0.627±0.017	0.624±0.017	0.626±0.016	0.627±0.020
drd2	0.999±0.116	0.997±0.228	0.986±0.208	0.999±0.304	0.998±0.298
fexofenadine_mpo	0.769±0.043	0.851±0.065	0.764±0.044	0.753±0.039	0.767±0.047
gsk3b	**0.989±0.141**	0.756±0.148	0.709±0.138	0.601±0.107	0.843±0.220
isomers_c7h8n2o2	0.923±0.316	1.0±0.255	**1.0±0.229**	0.879±0.264	0.804±0.299
isomers_c9h10n2o2pf2cl	0.483±0.147	0.935±0.254	**0.976±0.243**	0.597±0.185	0.810±0.300
jnk3	0.886±0.179	0.613±0.164	0.393±0.084	0.303±0.053	0.781±0.223
median1	0.296±0.052	0.282±0.039	0.199±0.020	0.338±0.054	0.262±0.031
median2	0.287±0.039	0.264±0.041	0.207±0.013	0.261±0.032	0.194±0.023
mestranol_similarity	0.609±0.102	0.671±0.141	0.513±0.067	0.585±0.075	0.506±0.069
osimertinib_mpo	0.843±0.043	0.848±0.037	0.834±0.032	0.822±0.029	0.817±0.029
perindopril_mpo	0.575±0.052	0.521±0.034	0.456±0.021	0.502±0.028	0.480±0.027
qed	0.948±0.013	0.947±0.005	0.948±0.005	0.947±0.005	0.946±0.006
ranolazine_mpo	0.807±0.090	**0.859±0.149**	0.775±0.118	0.769±0.138	0.745±0.184
scaffold_hop	0.590±0.039	0.546±0.050	0.512±0.023	0.519±0.024	0.519±0.026
sitagliptin_mpo	0.181±0.057	0.517±0.173	0.480±0.150	0.230±0.063	0.111±0.054
thiothixene_rediscovery	0.506±0.080	0.388±0.042	0.326±0.025	0.439±0.054	0.406±0.046
troglitazone_rediscovery	**0.619±0.134**	0.359±0.043	0.272±0.030	0.315±0.031	0.308±0.038
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.314±0.111	0.373±0.100	0.389±0.107	0.310±0.093	0.259±0.105
Sum	14.772	14.201	12.997	12.894	12.889
Rank	6	7	8	9	10

Table 18: (Continued)

Method Assembly	SynNet Synthesis	MIMOSA Fragments	MARS Fragments	GA+D SELFIES	MolPal -
albuterol_similarity	0.646±0.075	0.702±0.112	0.652±0.155	0.623±0.118	0.625±0.046
amlodipine_mpo	0.585±0.023	0.564±0.021	0.526±0.030	0.525±0.136	0.614±0.042
celecoxib_rediscovery	0.478±0.056	0.428±0.050	0.448±0.091	0.269±0.063	0.426±0.033
deco_hop	0.624±0.016	0.641±0.023	0.596±0.007	0.583±0.023	0.662±0.031
drd2	0.998±0.109	0.990±0.301	0.988±0.190	0.772±0.365	0.872±0.200
fexofenadine_mpo	0.785±0.033	0.737±0.038	0.741±0.044	0.729±0.187	0.696±0.018
gsk3b	0.901±0.164	0.700±0.156	0.607±0.105	0.511±0.128	0.619±0.118
isomers_c7h8n2o2	0.529±0.135	0.798±0.294	0.949±0.303	1.0±0.274	0.523±0.115
isomers_c9h10n2o2pf2cl	0.332±0.126	0.444±0.179	0.820±0.304	0.820±0.265	0.177±0.040
jnk3	0.715±0.148	0.483±0.140	0.587±0.166	0.378±0.111	0.404±0.077
median1	0.228±0.019	0.275±0.044	0.216±0.018	0.199±0.036	0.257±0.024
median2	0.244±0.017	0.229±0.019	0.190±0.017	0.156±0.031	0.237±0.017
mestranol_similarity	0.427±0.040	0.470±0.051	0.444±0.053	0.527±0.129	0.585±0.061
osimertinib_mpo	0.810±0.027	0.813±0.030	0.797±0.049	0.777±0.143	0.794±0.029
perindopril_mpo	0.589±0.040	0.548±0.050	0.480±0.025	0.324±0.144	0.480±0.024
qed	0.947±0.003	0.945±0.005	0.938±0.012	0.941±0.118	0.947±0.004
ranolazine_mpo	0.771±0.055	0.767±0.176	0.759±0.068	0.771±0.252	0.494±0.064
scaffold_hop	0.515±0.019	0.534±0.034	0.476±0.009	0.465±0.038	0.501±0.015
sitagliptin_mpo	0.029±0.017	0.179±0.078	0.034±0.011	0.469±0.173	0.051±0.012
thiothixene_rediscovery	0.433±0.042	0.367±0.036	0.426±0.067	0.294±0.072	0.347±0.023
troglitazone_rediscovery	0.303±0.022	0.332±0.041	0.296±0.033	0.198±0.041	0.273±0.013
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.381±0.078	0.274±0.111	0.213±0.074	0.353±0.123	0.191±0.049
Sum	12.279	12.233	12.193	11.696	10.786
Rank	11	12	13	14	15

Method Assembly	GFlowNet Fragments	DoG-AE Synthesis	VAE BO SELFIES SELFIES	Screening -	VAE BO SMILES SMILES
albuterol_similarity	0.502±0.054	0.543±0.043	0.528±0.038	0.526±0.033	0.530±0.035
amlodipine_mpo	0.465±0.024	0.513±0.012	0.531±0.015	0.563±0.024	0.559±0.021
celecoxib_rediscovery	0.359±0.036	0.360±0.018	0.352±0.024	0.372±0.022	0.382±0.027
deco_hop	0.594±0.007	0.789±0.084	0.587±0.004	0.600±0.007	0.604±0.007
drd2	0.836±0.208	0.978±0.122	0.772±0.197	0.741±0.189	0.773±0.193
fexofenadine_mpo	0.711±0.019	0.686±0.023	0.682±0.013	0.686±0.019	0.692±0.016
gsk3b	0.691±0.056	0.624±0.114	0.420±0.078	0.560±0.099	0.473±0.080
isomers_c7h8n2o2	0.530±0.141	0.251±0.088	0.423±0.115	0.254±0.079	0.226±0.064
isomers_c9h10n2o2pf2cl	0.199±0.063	0.052±0.018	0.286±0.086	0.153±0.047	0.118±0.030
jnk3	0.499±0.062	0.492±0.156	0.262±0.054	0.309±0.056	0.302±0.065
median1	0.216±0.022	0.174±0.012	0.211±0.016	0.222±0.018	0.222±0.020
median2	0.188±0.008	0.184±0.009	0.192±0.006	0.212±0.012	0.207±0.010
mestranol_similarity	0.347±0.027	0.378±0.023	0.414±0.029	0.447±0.040	0.427±0.031
osimertinib_mpo	0.798±0.009	0.759±0.028	0.780±0.013	0.783±0.019	0.784±0.014
perindopril_mpo	0.457±0.025	0.437±0.018	0.445±0.011	0.464±0.018	0.458±0.015
qed	0.939±0.027	0.933±0.010	0.945±0.007	0.946±0.004	0.946±0.007
ranolazine_mpo	0.674±0.046	0.700±0.037	0.488±0.061	0.456±0.052	0.523±0.066
scaffold_hop	0.475±0.010	0.495±0.016	0.464±0.007	0.485±0.010	0.483±0.011
sitagliptin_mpo	0.017±0.006	0.010±0.005	0.140±0.044	0.040±0.012	0.034±0.011
thiothixene_rediscovery	0.309±0.026	0.320±0.020	0.314±0.016	0.336±0.019	0.336±0.022
troglitazone_rediscovery	0.196±0.009	0.264±0.020	0.253±0.009	0.264±0.013	0.270±0.013
valsartan_smarts	0.000±0.000	0.000±0.000	0.006±0.007	0.000±0.000	0.006±0.008
zaleplon_mpo	0.070±0.042	0.054±0.032	0.280±0.075	0.124±0.039	0.071±0.024
Sum	10.084	10.007	9.788	9.553	9.435
Rank	16	17	18	19	20

Table 19: (Continued)

Method Assembly	GFlowNet-AL Fragments	Pasithea SELFIES	JT-VAE BO Fragments	Graph MCTS Atoms	MolDQN Atoms
albuterol_similarity	0.420±0.027	0.460±0.020	0.499±0.039	0.626±0.041	0.362±0.034
amlodipine_mpo	0.443±0.020	0.508±0.007	0.526±0.014	0.462±0.017	0.354±0.035
celecoxib_rediscovery	0.285±0.023	0.317±0.014	0.305±0.016	0.296±0.038	0.111±0.008
deco_hop	0.590±0.005	0.583±0.003	0.591±0.006	0.563±0.007	0.552±0.006
drd2	0.637±0.168	0.275±0.060	0.557±0.177	0.401±0.118	0.032±0.005
fexofenadine_mpo	0.706±0.015	0.665±0.017	0.675±0.015	0.594±0.028	0.516±0.038
gsk3b	0.623±0.040	0.293±0.047	0.379±0.074	0.333±0.053	0.285±0.046
isomers_c7h8n2o2	0.322±0.090	0.824±0.233	0.113±0.026	0.623±0.124	0.523±0.088
isomers_c9h10n2o2pf2cl	0.090±0.025	0.448±0.200	0.108±0.046	0.563±0.138	0.504±0.119
jnk3	0.403±0.052	0.158±0.021	0.257±0.048	0.134±0.031	0.130±0.025
median1	0.203±0.015	0.182±0.013	0.183±0.010	0.212±0.021	0.168±0.023
median2	0.182±0.008	0.181±0.005	0.183±0.005	0.140±0.008	0.100±0.007
mestranol_similarity	0.318±0.020	0.365±0.021	0.365±0.022	0.308±0.031	0.265±0.038
osimertinib_mpo	0.800±0.009	0.756±0.013	0.785±0.016	0.722±0.017	0.685±0.017
perindopril_mpo	0.437±0.017	0.424±0.010	0.438±0.014	0.311±0.038	0.253±0.066
qed	0.932±0.034	0.938±0.006	0.943±0.008	0.916±0.025	0.846±0.081
ranolazine_mpo	0.666±0.046	0.354±0.025	0.524±0.074	0.303±0.069	0.104±0.046
scaffold_hop	0.469±0.008	0.462±0.006	0.479±0.012	0.426±0.013	0.414±0.013
sitagliptin_mpo	0.009±0.003	0.137±0.044	0.063±0.037	0.106±0.034	0.005±0.003
thiothixene_rediscovery	0.286±0.018	0.291±0.010	0.287±0.012	0.249±0.020	0.115±0.015
troglitazone_rediscovery	0.193±0.008	0.242±0.005	0.241±0.007	0.240±0.016	0.141±0.014
valsartan_smarts	0.000±0.000	0.006±0.013	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.020±0.006	0.140±0.043	0.161±0.061	0.096±0.034	0.017±0.009
Sum	9.044	9.020	8.671	8.635	6.495
Rank	21	22	23	24	25

Table 20: The mean and standard deviation of **Top-1** from 5 independent runs. We ranked the methods by the summation of mean **Top-1** of all tasks. (Continued)

Method Assembly	REINVENT SMILES	LSTM HC SMILES	Graph GA Fragments	REINVENT SELFIES SELFIES	DoG-Gen Synthesis
albuterol_similarity	1.0±0.166	1.0±0.188	**1.0±0.168**	0.960±0.162	0.978±0.150
amlodipine_mpo	0.735±0.086	0.739±0.063	**0.783±0.078**	0.706±0.068	0.621±0.034
celecoxib_rediscovery	**0.959±0.226**	0.850±0.188	0.810±0.199	0.750±0.146	0.760±0.127
deco_hop	0.805±0.109	**0.955±0.083**	0.654±0.019	0.736±0.069	0.932±0.076
drd2	0.999±0.108	**0.999±0.149**	0.999±0.008	0.999±0.062	0.999±0.003
fexofenadine_mpo	**0.910±0.073**	0.818±0.047	0.845±0.053	0.842±0.044	0.808±0.036
gsk3b	0.972±0.160	**1.0±0.119**	0.946±0.156	0.964±0.187	1.0±0.076
isomers_c7h8n2o2	1.0±0.260	0.971±0.285	**1.0±0.196**	0.961±0.172	0.990±0.324
isomers_c9h10n2o2pf2cl	0.855±0.290	0.832±0.267	0.905±0.190	0.913±0.214	0.624±0.148
jnk3	0.954±0.233	**0.968±0.196**	0.818±0.257	0.838±0.227	0.948±0.146
median1	**0.399±0.058**	0.388±0.064	0.350±0.050	0.399±0.063	0.322±0.053
median2	0.332±0.045	**0.339±0.049**	0.324±0.040	0.313±0.040	0.297±0.040
mestranol_similarity	0.748±0.140	**0.894±0.154**	0.761±0.118	0.761±0.134	0.657±0.106
osimertinib_mpo	**0.909±0.040**	0.859±0.023	0.880±0.029	0.878±0.028	0.850±0.028
perindopril_mpo	**0.644±0.071**	0.568±0.037	0.625±0.054	0.610±0.070	0.587±0.044
qed	**0.948±0.000**	0.948±0.002	0.948±0.001	0.948±0.002	0.948±0.007
ranolazine_mpo	**0.865±0.068**	0.824±0.073	0.810±0.072	0.851±0.095	0.823±0.057
scaffold_hop	0.716±0.088	**0.797±0.136**	0.561±0.031	0.617±0.052	0.621±0.040
sitagliptin_mpo	0.080±0.034	0.262±0.079	**0.689±0.214**	0.409±0.170	0.252±0.099
thiothixene_rediscovery	0.665±0.128	**0.734±0.116**	0.601±0.092	0.642±0.127	0.553±0.087
troglitazone_rediscovery	0.593±0.127	0.587±0.115	0.505±0.079	0.509±0.094	**0.707±0.124**
valsartan_smarts	**0.197±0.382**	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	**0.478±0.150**	0.413±0.126	0.421±0.086	0.441±0.109	0.343±0.111
Sum	16.772	16.754	16.244	16.059	15.633
Rank	1	2	3	4	5

Method Assembly	GP BO Fragments	STONED SELFIES	LSTM HC SELFIES SELFIES	DST Fragments	SMILES GA SMILES
albuterol_similarity	1.0±0.140	0.805±0.136	1.0±0.185	0.792±0.113	0.715±0.095
amlodipine_mpo	0.681±0.067	0.638±0.054	0.600±0.012	0.582±0.054	0.570±0.006
celecoxib_rediscovery	0.946±0.206	0.401±0.051	0.585±0.090	0.459±0.039	0.358±0.031
deco_hop	0.727±0.067	0.627±0.015	0.637±0.018	0.635±0.019	0.624±0.014
drd2	0.999±0.130	0.997±0.182	0.999±0.237	0.999±0.209	0.986±0.161
fexofenadine_mpo	0.805±0.053	0.851±0.058	0.769±0.039	0.778±0.041	0.771±0.041
gsk3b	0.986±0.164	0.766±0.106	0.65±0.074	0.861±0.160	0.722±0.090
isomers_c7h8n2o2	0.858±0.216	1.0±0.234	0.937±0.242	0.836±0.235	1.0±0.204
isomers_c9h10n2o2pf2cl	0.583±0.219	0.935±0.230	0.713±0.210	0.861±0.281	**0.976±0.217**
jnk3	0.698±0.221	0.62±0.150	0.428±0.101	0.789±0.200	0.414±0.080
median1	0.345±0.044	0.295±0.036	0.362±0.058	0.281±0.036	0.207±0.014
median2	0.337±0.033	0.265±0.038	0.274±0.031	0.201±0.024	0.210±0.009
mestranol_similarity	0.796±0.153	0.671±0.132	0.646±0.079	0.529±0.070	0.515±0.057
osimertinib_mpo	0.837±0.020	0.848±0.024	0.832±0.018	0.827±0.018	0.835±0.019
perindopril_mpo	0.562±0.036	0.522±0.027	0.521±0.028	0.502±0.026	0.459±0.014
qed	0.947±0.002	0.947±0.001	0.948±0.001	0.947±0.003	0.948±0.002
ranolazine_mpo	0.817±0.080	0.862±0.113	0.795±0.099	0.752±0.163	0.780±0.082
scaffold_hop	0.619±0.055	0.548±0.047	0.543±0.029	0.521±0.019	0.512±0.020
sitagliptin_mpo	0.318±0.117	0.526±0.169	0.349±0.089	0.205±0.106	0.504±0.145
thiothixene_rediscovery	0.663±0.097	0.390±0.036	0.468±0.057	0.427±0.042	0.329±0.021
troglitazone_rediscovery	0.544±0.083	0.360±0.039	0.344±0.035	0.317±0.034	0.282±0.023
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.269±0.084	0.373±0.088	0.360±0.093	0.344±0.119	0.396±0.097
Sum	15.345	14.257	13.770	13.455	13.123
Rank	6	7	8	9	10

Table 21: (Continued)

Method Assembly	SynNet Synthesis	MARS Fragments	MolPal -	MIMOSA Fragments	GA+D SELFIES
albuterol_similarity	0.697±0.083	0.710±0.149	0.714±0.054	0.720±0.099	0.633±0.109
amlodipine_mpo	0.596±0.020	0.546±0.034	0.651±0.043	0.594±0.009	0.527±0.124
celecoxib_rediscovery	0.525±0.062	0.486±0.082	0.511±0.041	0.438±0.032	0.289±0.060
deco_hop	0.639±0.019	0.603±0.005	0.860±0.102	0.642±0.018	0.584±0.023
drd2	0.999±0.084	0.994±0.141	0.964±0.165	0.993±0.203	0.836±0.374
fexofenadine_mpo	0.797±0.031	0.755±0.034	0.709±0.006	0.743±0.030	0.737±0.174
gsk3b	0.932±0.146	0.683±0.109	0.82±0.128	0.718±0.097	0.534±0.127
isomers_c7h8n2o2	0.685±0.147	0.961±0.260	0.882±0.163	0.804±0.233	1.0±0.254
isomers_c9h10n2o2pf2cl	0.507±0.173	0.864±0.302	0.391±0.091	0.465±0.164	0.820±0.246
jnk3	0.797±0.141	0.646±0.160	0.608±0.117	0.497±0.120	0.392±0.111
median1	0.244±0.019	0.233±0.017	0.309±0.028	0.296±0.039	0.219±0.037
median2	0.259±0.016	0.203±0.015	0.273±0.021	0.238±0.016	0.161±0.028
mestranol_similarity	0.447±0.040	0.481±0.047	0.733±0.081	0.523±0.049	0.543±0.128
osimertinib_mpo	0.821±0.016	0.809±0.021	0.816±0.020	0.817±0.022	0.784±0.129
perindopril_mpo	0.610±0.039	0.488±0.016	0.504±0.020	0.557±0.047	0.337±0.147
qed	0.948±0.001	0.946±0.001	0.948±0.002	0.947±0.002	0.945±0.104
ranolazine_mpo	0.783±0.038	0.776±0.050	0.556±0.064	0.773±0.139	0.775±0.244
scaffold_hop	0.531±0.022	0.489±0.012	0.525±0.016	0.534±0.026	0.467±0.038
sitagliptin_mpo	0.067±0.040	0.083±0.037	0.117±0.030	0.209±0.085	0.482±0.175
thiothixene_rediscovery	0.481±0.057	0.463±0.077	0.361±0.016	0.378±0.029	0.307±0.068
troglitazone_rediscovery	0.326±0.022	0.328±0.040	0.296±0.013	0.341±0.036	0.201±0.039
valsartan_smarts	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.402±0.059	0.296±0.023	0.286±0.064	0.287±0.103	0.359±0.119
Sum	13.105	12.853	12.844	12.524	11.942
Rank	11	12	13	14	15

Method Assembly	VAE BO SELFIES SELFIES	DoG-AE Synthesis	Screening -	GFlowNet Fragments	VAE BO SMILES SMILES
albuterol_similarity	0.594±0.063	0.633±0.054	0.603±0.056	0.550±0.069	0.593±0.048
amlodipine_mpo	0.593±0.022	0.539±0.017	0.613±0.039	0.482±0.016	0.611±0.036
celecoxib_rediscovery	0.391±0.027	0.406±0.027	0.419±0.023	0.409±0.042	0.425±0.026
deco_hop	0.602±0.006	0.862±0.060	0.616±0.003	0.600±0.007	0.666±0.027
drd2	0.940±0.183	0.999±0.059	0.949±0.206	0.951±0.185	0.899±0.164
fexofenadine_mpo	0.707±0.011	0.723±0.045	0.706±0.021	0.727±0.017	0.719±0.016
gsk3b	0.564±0.128	0.778±0.143	0.836±0.185	0.726±0.058	0.606±0.100
isomers_c7h8n2o2	0.605±0.143	0.563±0.200	0.488±0.154	0.693±0.158	0.418±0.109
isomers_c9h10n2o2pf2cl	0.461±0.162	0.140±0.078	0.273±0.075	0.290±0.094	0.209±0.067
jnk3	0.414±0.117	0.554±0.143	0.456±0.100	0.54±0.047	0.432±0.098
median1	0.231±0.017	0.203±0.014	0.271±0.029	0.237±0.019	0.267±0.043
median2	0.206±0.006	0.201±0.010	0.244±0.021	0.198±0.009	0.222±0.011
mestranol_similarity	0.507±0.059	0.436±0.036	0.552±0.143	0.388±0.038	0.523±0.049
osimertinib_mpo	0.802±0.010	0.793±0.026	0.801±0.016	0.817±0.016	0.801±0.010
perindopril_mpo	0.482±0.024	0.464±0.026	0.500±0.028	0.478±0.021	0.484±0.028
qed	0.947±0.003	0.944±0.004	0.947±0.001	0.945±0.005	0.947±0.003
ranolazine_mpo	0.564±0.065	0.744±0.025	0.532±0.059	0.701±0.030	0.598±0.076
scaffold_hop	0.487±0.013	0.526±0.024	0.509±0.006	0.488±0.010	0.504±0.015
sitagliptin_mpo	0.244±0.083	0.039±0.033	0.142±0.060	0.045±0.020	0.114±0.068
thiothixene_rediscovery	0.343±0.016	0.358±0.021	0.362±0.017	0.342±0.030	0.370±0.028
troglitazone_rediscovery	0.287±0.032	0.349±0.056	0.294±0.018	0.211±0.013	0.306±0.024
valsartan_smarts	0.064±0.072	0.000±0.000	0.000±0.000	0.000±0.000	0.064±0.077
zaleplon_mpo	0.379±0.091	0.156±0.093	0.280±0.101	0.118±0.061	0.139±0.046
Sum	11.423	11.418	11.403	10.945	10.926
Rank	16	17	18	19	20

Table 22: (Continued)

Method Assembly	Pasithea SELFIES	JT-VAE BO Fragments	GFlowNet-AL Fragments	Graph MCTS Atoms	MolDQN Atoms
albuterol_similarity	0.507±0.018	0.550±0.057	0.472±0.032	0.686±0.052	0.383±0.038
amlodipine_mpo	0.585±0.0	0.585±0.0	0.466±0.016	0.483±0.024	0.383±0.033
celecoxib_rediscovery	0.355±0.015	0.390±0.031	0.332±0.030	0.329±0.037	0.128±0.019
deco_hop	0.608±0.013	0.600±0.006	0.596±0.006	0.569±0.008	0.554±0.006
drd2	0.592±0.122	0.778±0.215	0.863±0.198	0.586±0.197	0.049±0.012
fexofenadine_mpo	0.707±0.041	0.702±0.016	0.732±0.015	0.611±0.024	0.532±0.039
gsk3b	0.414±0.084	0.511±0.086	0.675±0.052	0.404±0.067	0.344±0.061
isomers_c7h8n2o2	0.902±0.231	0.264±0.099	0.561±0.163	0.783±0.144	0.652±0.126
isomers_c9h10n2o2pf2cl	0.607±0.186	0.307±0.147	0.182±0.061	0.704±0.150	0.583±0.122
jnk3	0.210±0.035	0.404±0.104	0.463±0.060	0.178±0.051	0.152±0.029
median1	0.216±0.021	0.212±0.019	0.229±0.012	0.242±0.023	0.188±0.028
median2	0.194±0.006	0.192±0.003	0.191±0.009	0.148±0.010	0.108±0.009
mestranol_similarity	0.449±0.015	0.454±0.060	0.351±0.024	0.330±0.030	0.294±0.041
osimertinib_mpo	0.792±0.009	0.800±0.011	0.812±0.010	0.738±0.018	0.699±0.018
perindopril_mpo	0.447±0.016	0.463±0.019	0.464±0.020	0.334±0.038	0.282±0.062
qed	0.943±0.005	0.946±0.003	0.944±0.015	0.928±0.019	0.871±0.067
ranolazine_mpo	0.443±0.054	0.587±0.041	0.705±0.034	0.369±0.096	0.171±0.077
scaffold_hop	0.503±0.022	0.496±0.013	0.479±0.009	0.434±0.014	0.421±0.015
sitagliptin_mpo	0.230±0.085	0.169±0.096	0.028±0.017	0.210±0.088	0.015±0.009
thiothixene_rediscovery	0.333±0.016	0.315±0.014	0.319±0.020	0.265±0.022	0.129±0.018
troglitazone_rediscovery	0.258±0.007	0.259±0.003	0.206±0.011	0.267±0.027	0.153±0.016
valsartan_smarts	0.064±0.126	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
zaleplon_mpo	0.243±0.084	0.302±0.089	0.048±0.020	0.166±0.065	0.042±0.024
Sum	10.611	10.296	10.130	9.778	7.143
Rank	21	22	23	24	25