A Main Results

A.1 AUC Top-10 Table

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	REINVENT	Graph GA	REINVENT SELFIES	GP BO	STONED
Assembly	SMILES	Fragments	SELFIES	Fragments	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	LSTM HC	SMILES GA	SynNet	DoG-Gen	DST
Assembly	SMILES	SMILES	Synthesis	Synthesis	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	MARS	MIMOSA	MolPal	LSTM HC SELFIES	DoG-AE
Assembly	Fragments	Fragments	-	SELFIES	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	GFlowNet	GA+D	VAE BO SELFIES	Screening	VAE BO SMILES
Assembly	Fragments	SELFIES	SELFIES	-	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

A.2 Optimization Curves

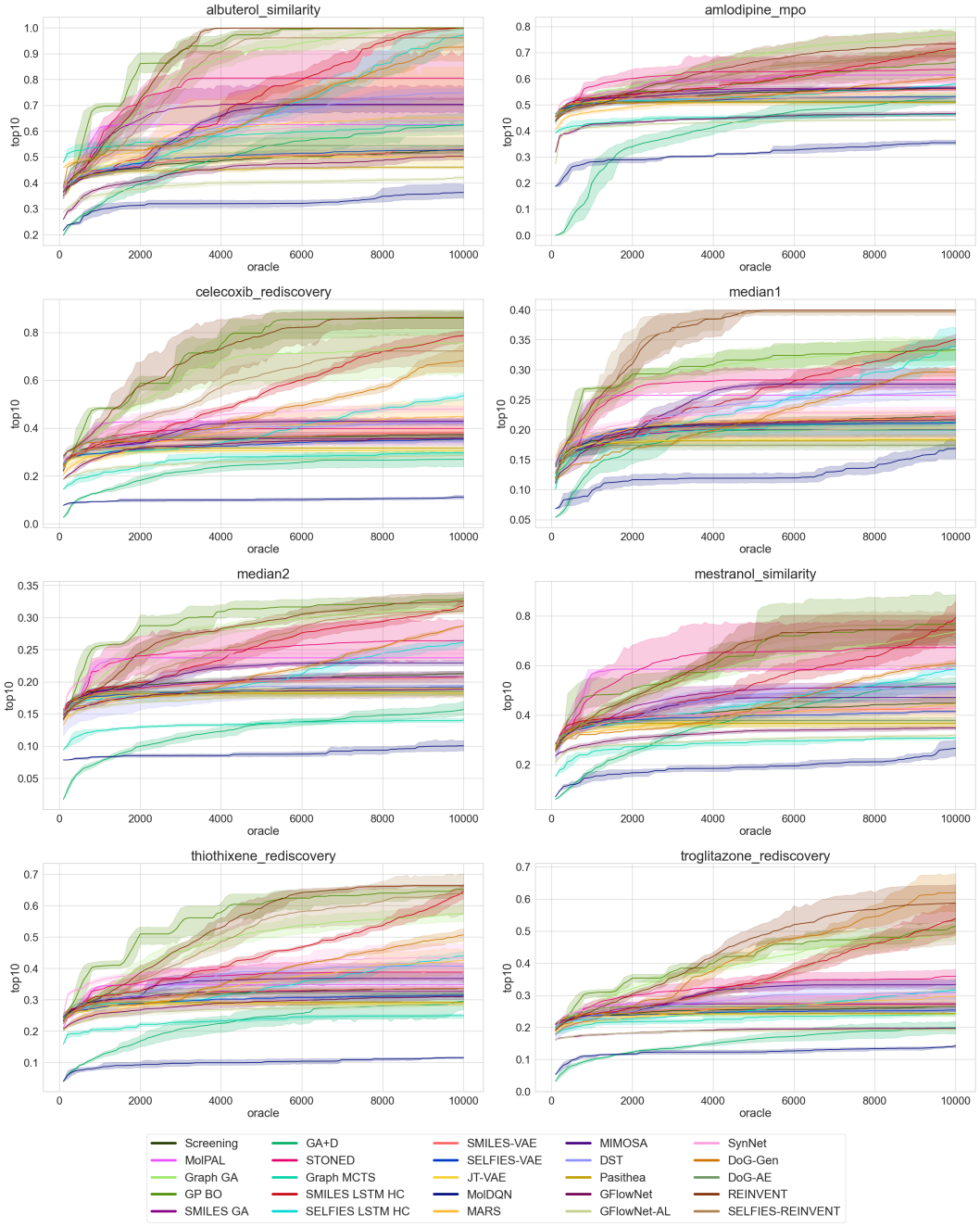

Figure 4: The optimization curves of top-10 average on optimizing similarity-based oracles.

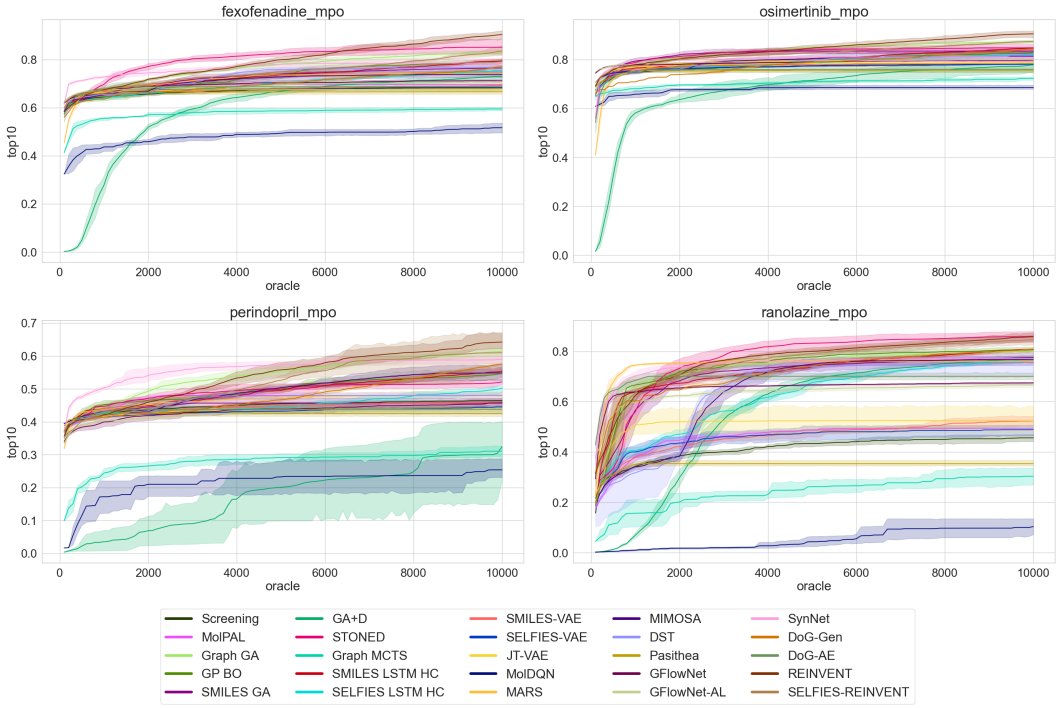

Figure 5: The optimization curves of top-10 average on optimizing similarity-based MPO oracles.

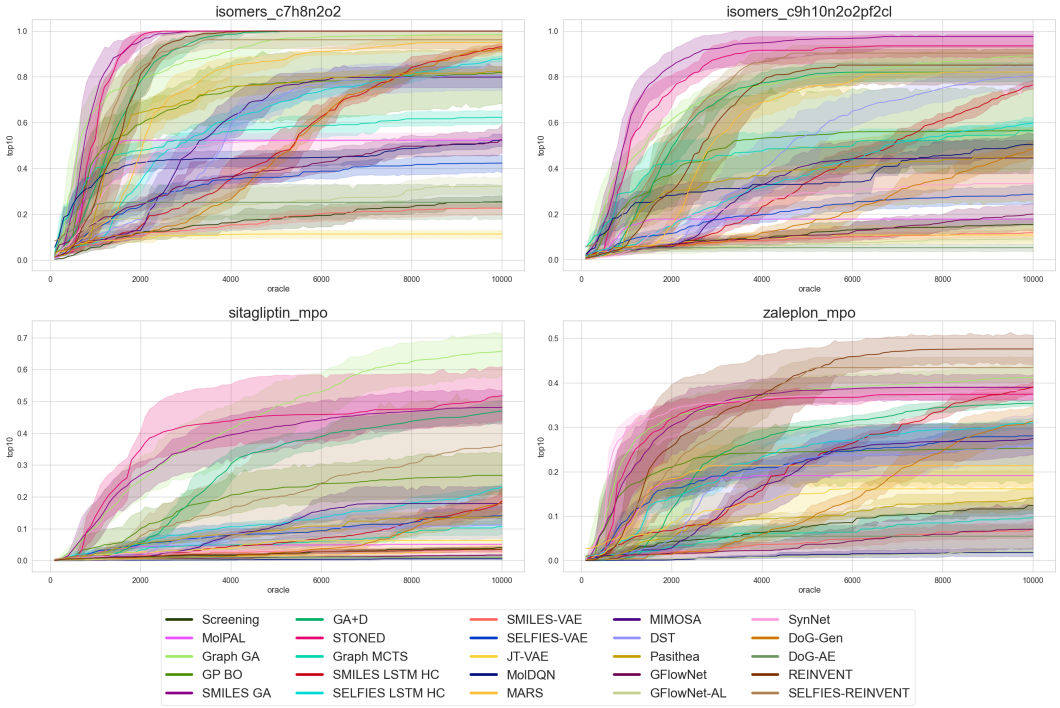

Figure 6: The optimization curves of top-10 average on optimizing isomer-based oracles.

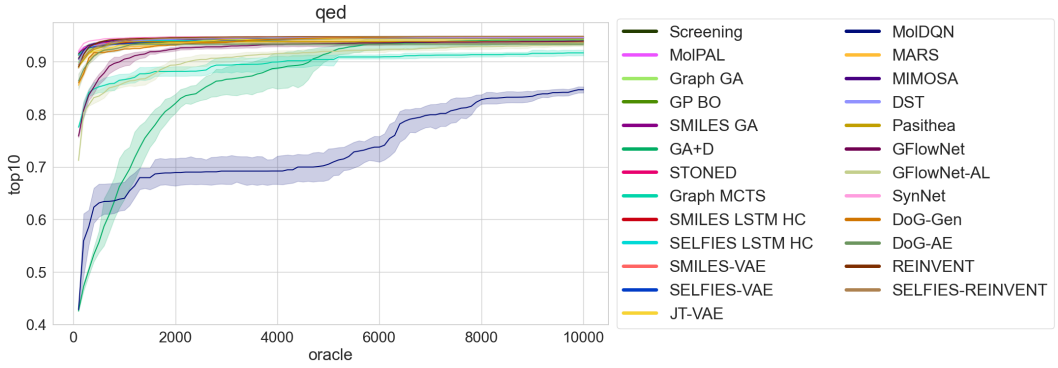

Figure 7: The optimization curves of top-10 average on optimizing QED.

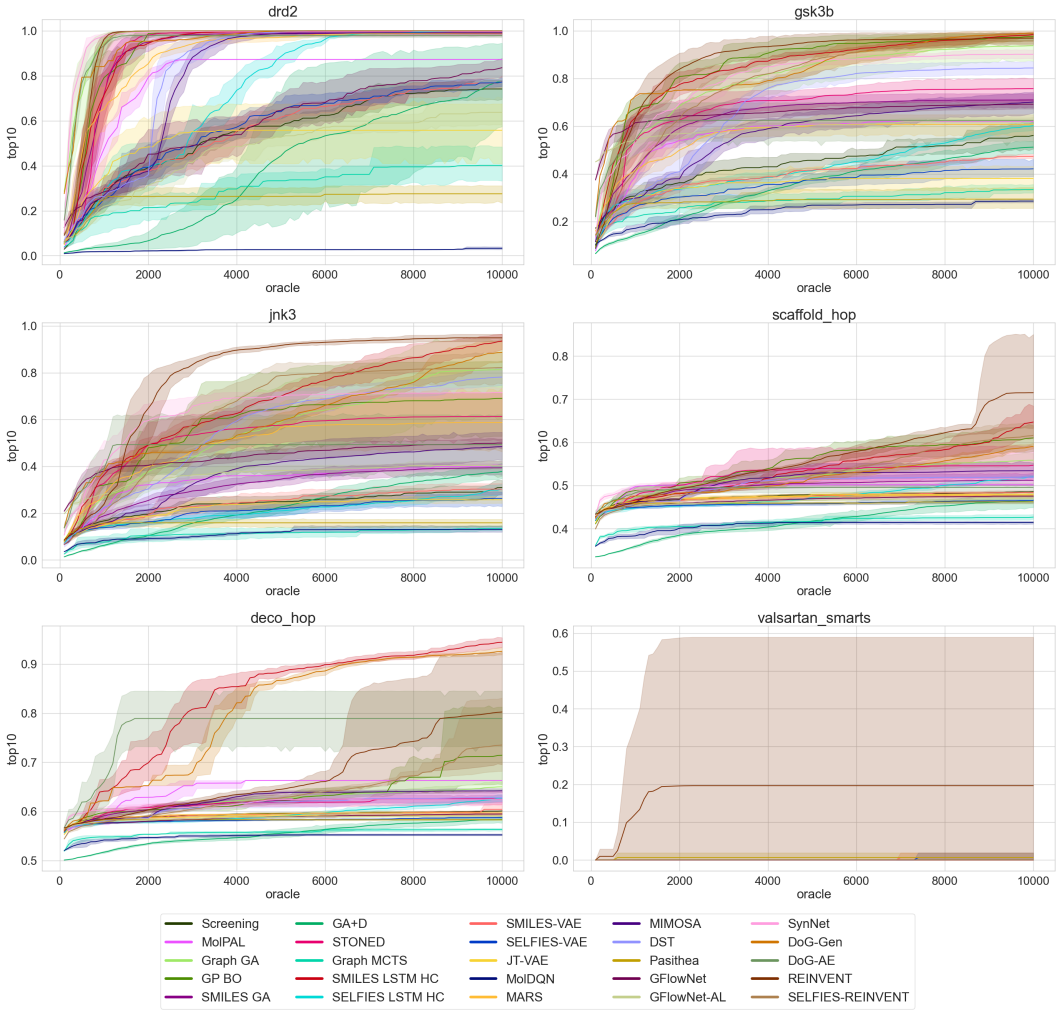

Figure 8: The optimization curves of top-10 average on optimizing SMARTS-based oracles and machine learning oracle.

A.3 Synthesizability

We computed the SA_Score of Top-100 molecules from each run and visualized the values in the Figure 9. Though SA_Score is not a great metric, we could see that synthesis-based methods have consistently lower SA_Score in all tasks.

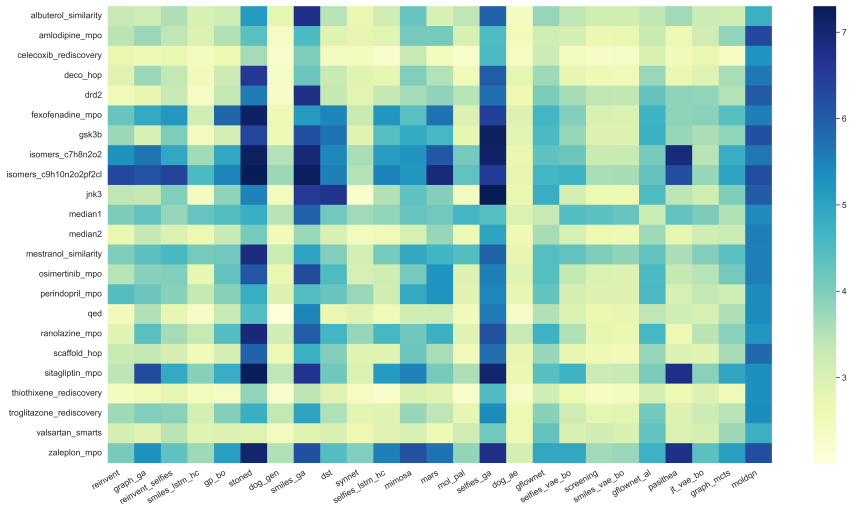

Figure 9: The heat map of SA_Score (the lower the better) calculated from the Top-100 molecules from each method, averaged from all runs.

A.4 Diversity

We computed the diversity of the Top-100 molecules from each run and visualized the values in the Figure 10. 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.

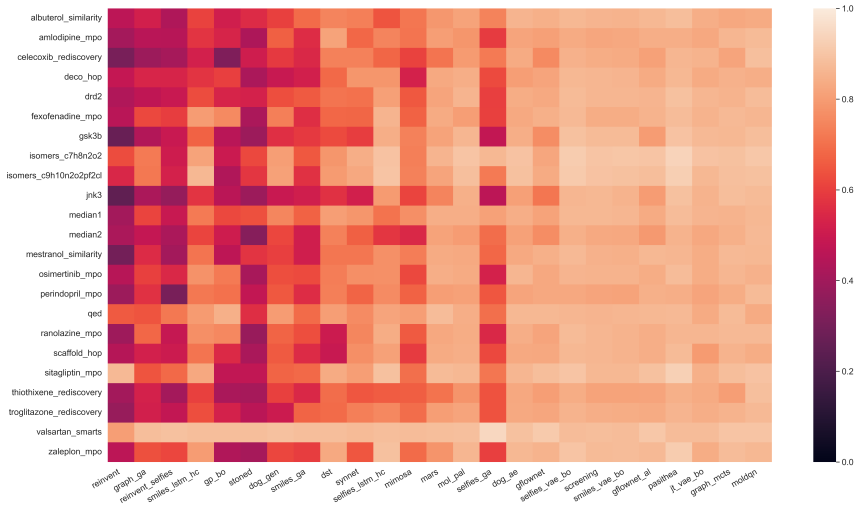

Figure 10: The heat map of diversity (the higher the better) calculated from the Top-100 molecules from each method, averaged from all runs.

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. 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" [52] with an exact Gaussian process model. Note that changing the exact GPs to sparse GPs would help increase the scalability [62], but we found the VAE+BO methods reached at least several thousands oracle calls in most tasks, which is enough for a meaningful comparison. 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 [63] to build neural network models and Adam [64] to train them.

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.

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

B.8 Screening

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

B.9 MolPAL

MolPal [3] 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 [6] 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 [6] (Section B.10), except the vocabulary.

B.12 DST

Differentiable Scaffolding Tree (DST) [20] 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 determinantal 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 [37] 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) [16] 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) [33] 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) [2] 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 [10]. 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) [8] 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) [15] 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. It should be noted that there are other types of fingerprints, such as fragprints [65] and MAP4 [66], and the choice of that could be a major performance determinant. 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 [15].

B.21 DoG-AE

The autoencoder version of DAGs of molecular graphs (DoG) [11] 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[4] version of DoG [11]. 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 [67] as a black box oracle for reaction prediction. The molecular transformer is pretrained on USPTO dataset. It uses gated graph neural network (GGNN) [68] to learn molecular embedding and GRU to generate the molecule.

B.23 SynNet

SynNet [12] 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

[4] Section 2.3

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.

B.24 REINVENT

REINVENT [5] 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 14 and 15 (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 [5] (Section B.24), except the vocabulary.

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

SMILES-LSTM Hill Climbing [13] 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 [13] (Section B.26), except the vocabulary.

B.28 GA+D (SELFIES-GA)

Genetic Algorithm with Discriminator (GA+D) [17] 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) [29] 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 [13] 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 [1] 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) [1] 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) [30], synthesis-based Bayesian optimization (ChemBO) [19], Objective-Reinforced Generative Adversarial Network (ORGAN) [69], Generative Adversarial Network (MolGAN) [32], rationaleRL [34]. 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 [70]. 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. One potential reason is the poor scaling of string subsequence kernels [71]. 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) [14]. 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** [72] 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)** [9] is only used for SELFIES related methods. It can be installed using pip.
- **BoTorch (optional)** [52] 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 [42]. 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 11, 12, and 13 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.

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

Figure 11: 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 12: An example of SELFIES string that is valid but doesn't provide meaningful exploration of chemical space.

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

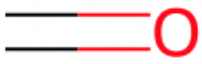

Figure 13: An example of SELFIES string that is valid but doesn't provide meaningful exploration of chemical space.

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 [72]. The oracles are chosen to discriminate most algorithms and be representative based on preliminary results.

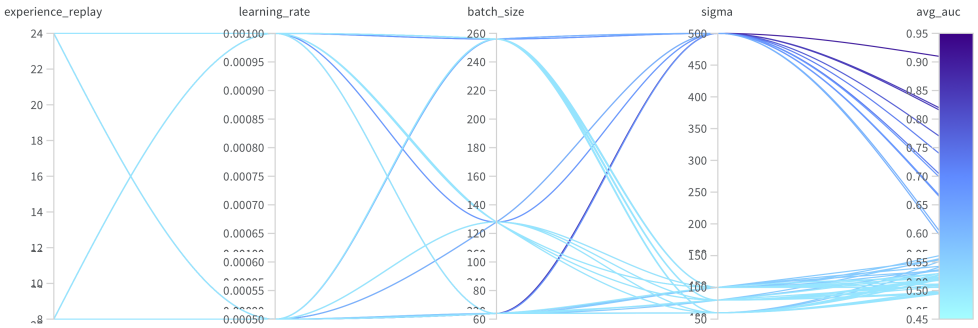

Figure 14: The hyper-parameter tuning result of REINVENT (part 1). We can see that sigma (σ) has large impact on optimization performance, and the optimal value is much larger than the default setting in the original paper [5].

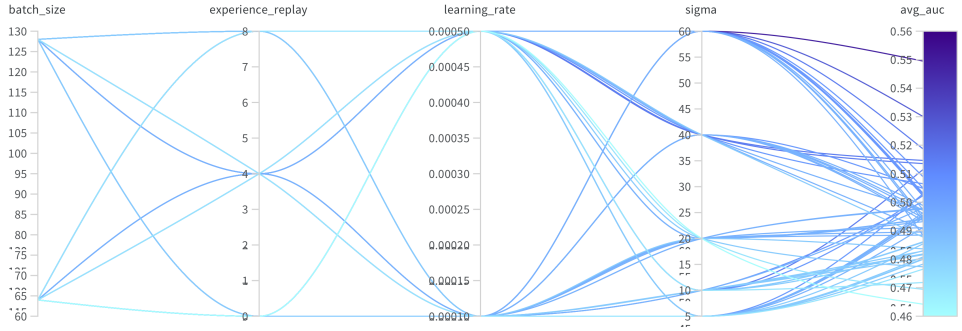

Figure 15: The hyper-parameter tuning result of REINVENT (part 2).

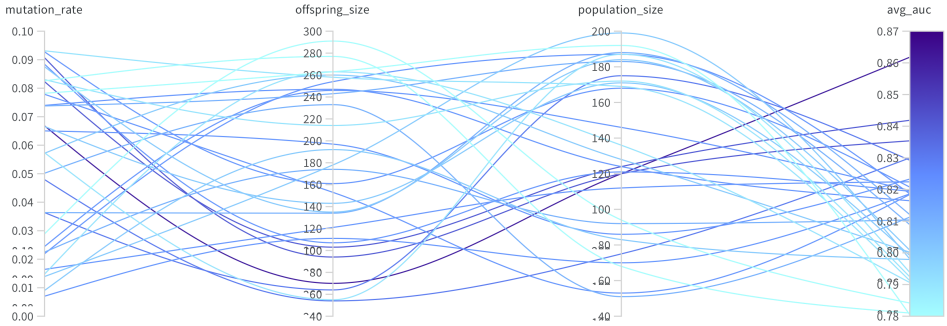

Figure 16: The hyper-parameter tuning result of Gaph GA.

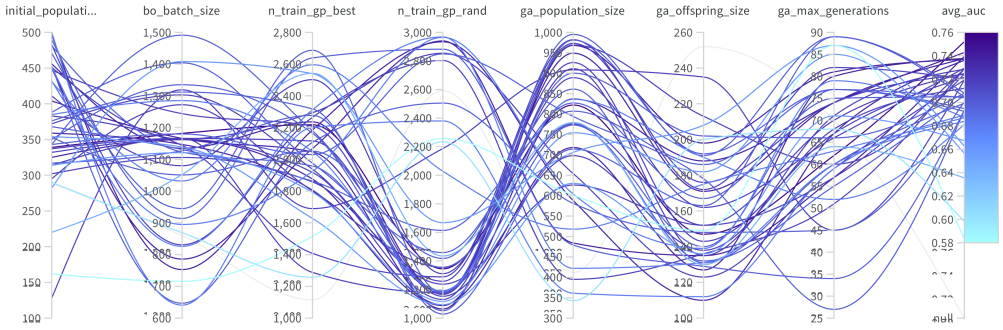

Figure 17: The hyper-parameter tuning result of GP BO.

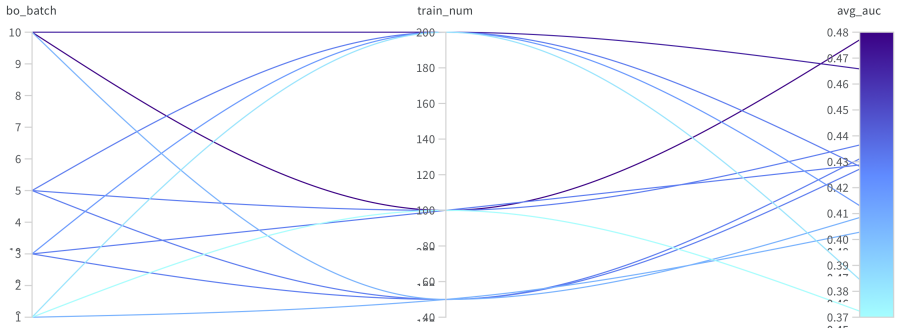

Figure 18: The hyper-parameter tuning result of DoG-AE.

D.3 Additional Tables

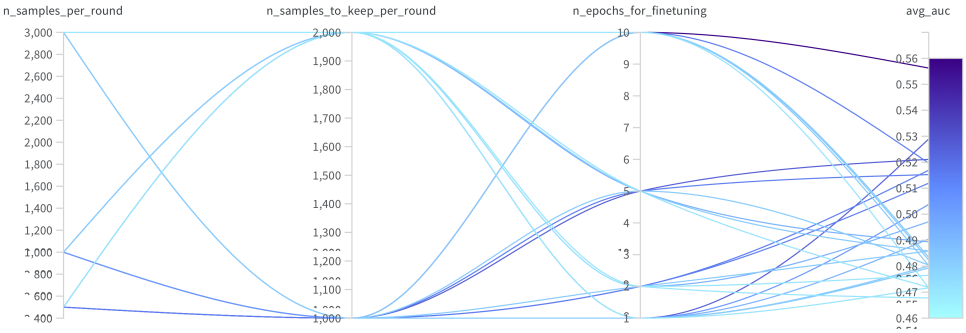

Figure 19: The hyper-parameter tuning result of DoG-Gen.

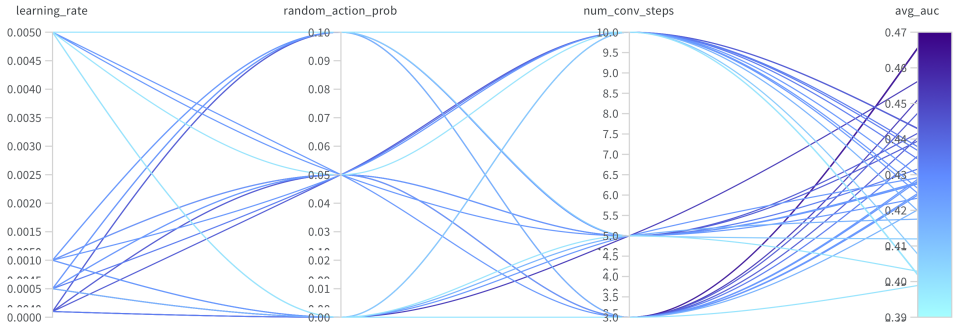

Figure 20: The hyper-parameter tuning result of GFlowNet.

D.4 Distribution of ZINC 250k's properties

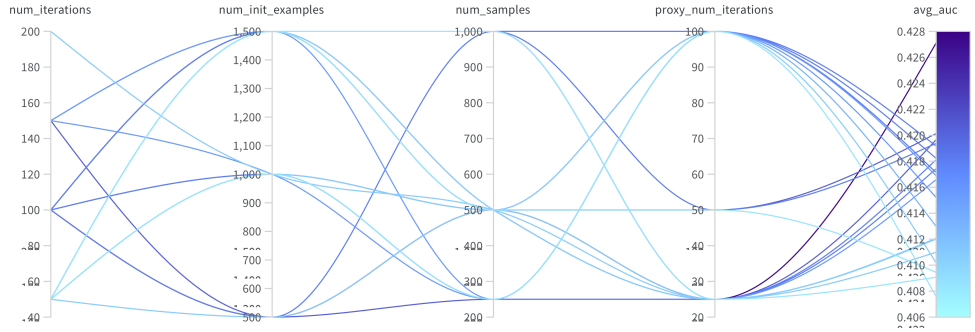

Figure 21: The hyper-parameter tuning result of GFlowNet-AL.

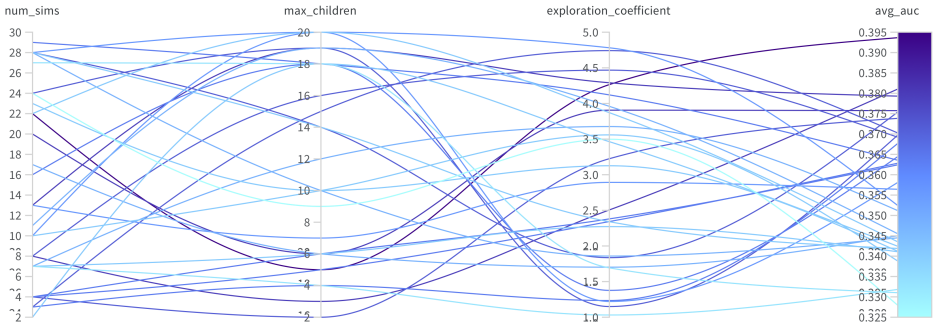

Figure 22: The hyper-parameter tuning result of Graph MCTS.

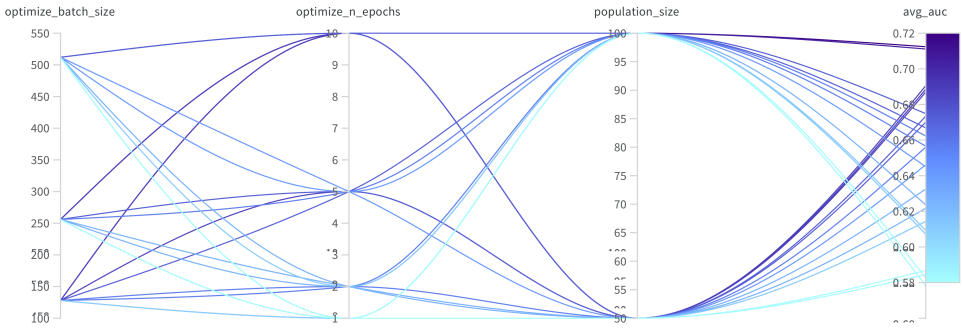

Figure 23: The hyper-parameter tuning result of SMILES LSTM HC.

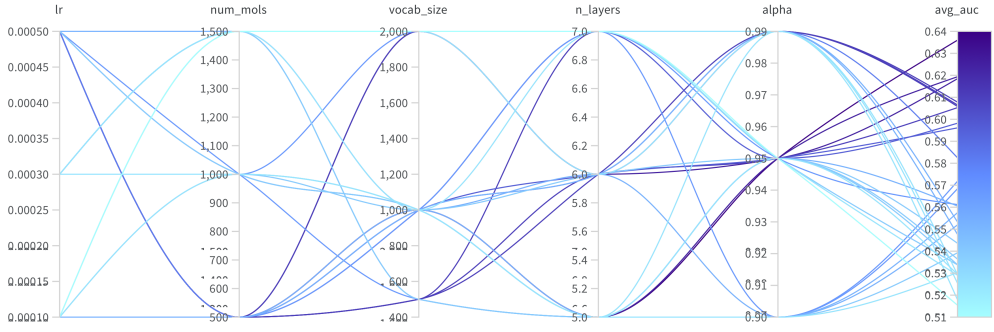

Figure 24: The hyper-parameter tuning result of MARS (part 1).

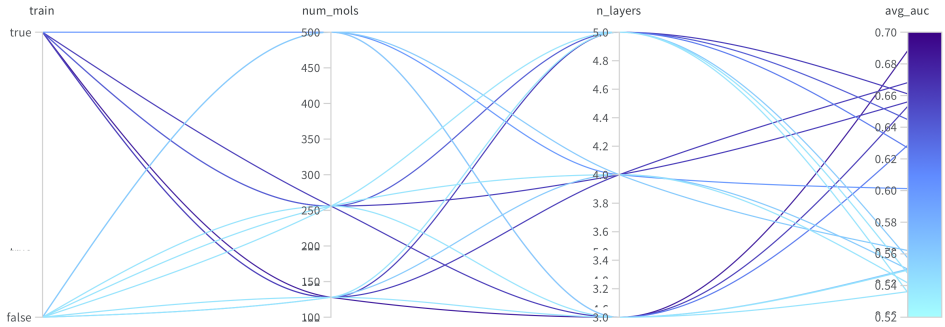

Figure 25: The hyper-parameter tuning result of MARS (part 2).

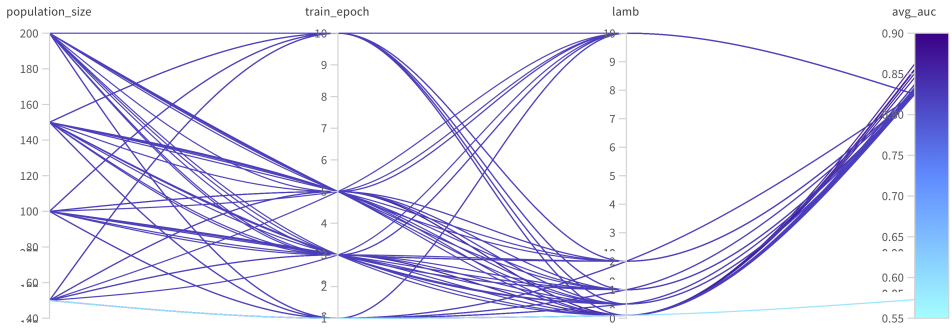

Figure 26: The hyper-parameter tuning result of MIMOSA.

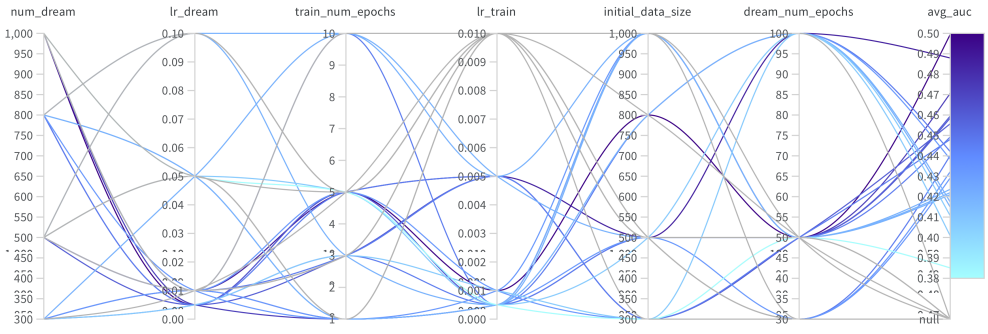

Figure 27: The hyper-parameter tuning result of Pasithea.

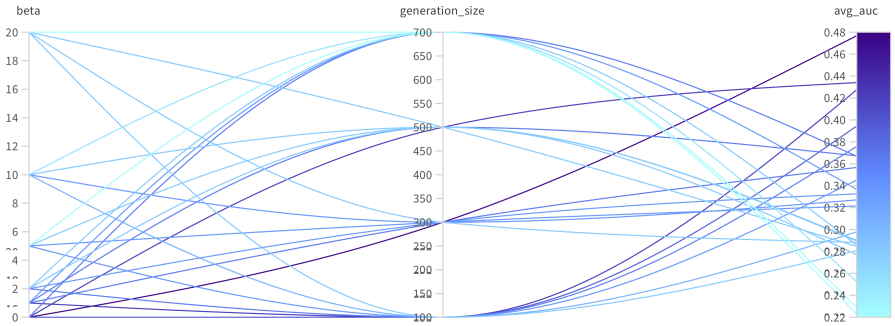

Figure 28: The hyper-parameter tuning result of GA+D.

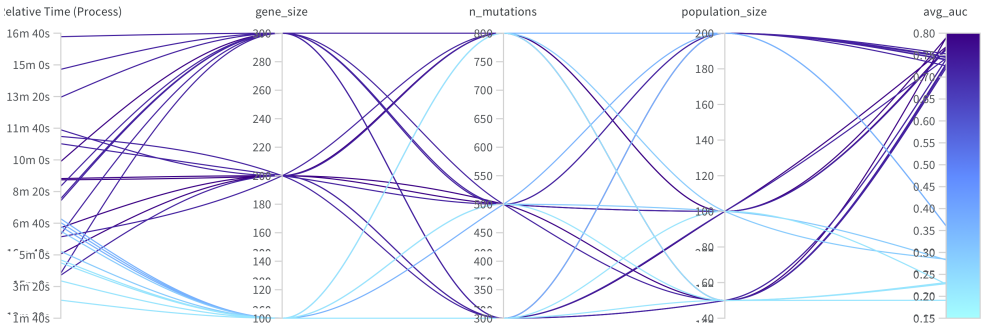

Figure 29: The hyper-parameter tuning result of SMILES GA.

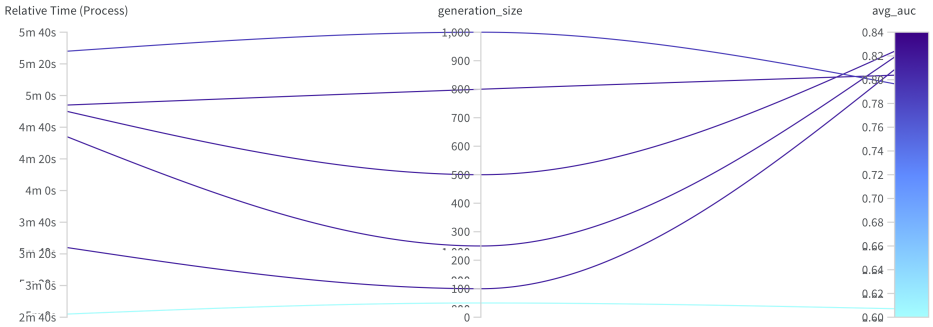

Figure 30: The hyper-parameter tuning result of STONED.

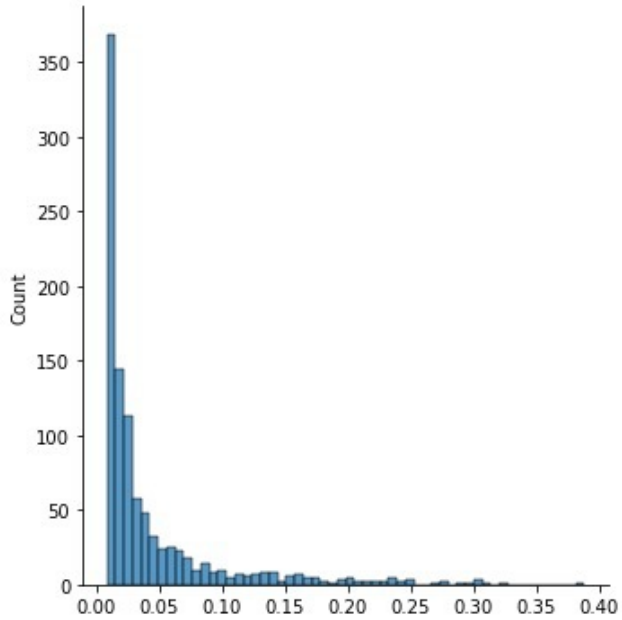

Figure 31: The distribution of Zaleplon MPO values in the ZINC 250k database. We show the values of top 1000 molecules only and all remaining are less than 0.02.

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	REINVENT	Graph GA	REINVENT SELFIES	GP BO	LSTM HC
Assembly	SMILES	Fragments	SELFIES	Fragments	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	STONED	DoG-Gen	SynNet	SMILES GA	MolPal
Assembly	SELFIES	Synthesis	Synthesis	SMILES	-
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	DST	MARS	LSTM HC SELFIES	MIMOSA	DoG-AE
Assembly	Fragments	Fragments	SELFIES	Fragments	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	VAE BO SELFIES	Screening	VAE BO SMILES	Pasithea	GFlowNet
Assembly	SELFIES	-	SMILES	SELFIES	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	REINVENT	Graph GA	REINVENT SELFIES	LSTM HC	GP BO
Assembly	SMILES	Fragments	SELFIES	SMILES	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	DoG-Gen	STONED	SMILES GA	LSTM HC SELFIES	DST
Assembly	Synthesis	SELFIES	SMILES	SELFIES	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	REINVENT	LSTM HC	Graph GA	REINVENT SELFIES	DoG-Gen
Assembly	SMILES	SMILES	Fragments	SELFIES	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	GP BO	STONED	LSTM HC SELFIES	DST	SMILES GA
Assembly	Fragments	SELFIES	SELFIES	Fragments	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