Structure-based Drug Design Benchmark: Do 3D Methods Really Dominate?

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Abstract

Currently, the field of structure-based drug design is dominated by three main types of algorithms: search-based algorithms, deep generative models, and reinforcement learning. While existing works have typically focused on comparing models within a single algorithmic category, cross-algorithm comparisons remain scarce. In this paper, to fill the gap, we establish a benchmark to evaluate the performance of sixteen models across these different algorithmic foundations by assessing the pharmaceutical properties of the generated molecules and their docking affinities with specified target proteins. We highlight the unique advantages of each algorithmic approach and offer recommendations for the design of future SBDD models. We emphasize that 1D/2D ligand-centric drug design methods can be used in SBDD by treating the docking function as a black-box oracle, which is typically neglected. The empirical results show that 1D/2D methods achieve competitive performance compared with 3D-based methods that use the 3D structure of the target protein explicitly. Also, AutoGrow4, a 2D molecular graph-based genetic algorithm, 034 dominates SBDD in terms of optimization ability. 035

1. Introduction

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Novel types of safe and effective drugs are needed to meet 039 the medical needs of billions worldwide and improve the quality of human life. The process of discovering a new 041 drug candidate and developing it into an approved drug for clinical use is known as drug discovery (Sinha & Vohora, 043 2018). This complex process is fundamental to the development of new therapies that can manage, cure, or alleviate 045 the symptoms of various health conditions. 046

047 Structure-based drug design (SBDD) (Bohacek et al., 1996) 048 represents a core strategy within the drug discovery process, 049 which utilizes the three-dimensional (3D) structures of pro-050 teins associated with diseases to develop drug candidates, 051 serving as a fundamental method to expedite the drug dis-052 covery process through physical simulation and data-driven 053 modeling. Based on the lock and key model (Tripathi & 054

Bankaitis, 2017), molecules that bind more effectively to a disease target tend to inhibit their abnormal activity or modulate their function in a way that contributes to disease treatment, a phenomenon that has been confirmed through experimental studies (Honarparvar et al., 2014; Blundell, 1996; Lu et al., 2022).

Currently, three main algorithmic approaches dominate the drug design field (Brown et al., 2019; Gao et al., 2022; Du et al., 2022): search-based algorithms like genetic algorithms (GA) (Jensen, 2019; Spiegel & Durrant, 2020; Tripp & Hernández-Lobato, 2023; Fu et al., 2022a), deep generative models (a.k.a. generative model) like variational autoencoder (VAE) (Gómez-Bombarelli et al., 2018) and autoregressive models (Luo et al., 2021; Peng et al., 2022; Zhang et al., 2023), and reinforcement learning (RL) models (Olivecrona et al., 2017; Zhou et al., 2018). Also, there is a trend that represents the target protein in 3D format (Zhang et al., 2023; Luo et al., 2021; Fu et al., 2022a; Peng et al., 2022). These models are often regarded as state-of-the-art due to the high validity, diversity, and synthesizability of their generated molecules. However, comparisons among these models remain unclear for several reasons. Firstly, current benchmarks or survey papers tend to compare models within the same algorithmic category, with a particular focus on deep generative models (Du et al., 2022). Secondly, most existing benchmarks emphasize the properties of the molecules themselves, neglecting the evaluation of protein-ligand interactions, which are crucial for real-world applications (Brown et al., 2019; Gao et al., 2022).

To fill this blank, this paper curates a comprehensive benchmark that encompasses sixteen models spanning all three algorithmic approaches. We assess their generated molecules not only through typical heuristic molecular property oracles but also by evaluating docking scores that reflect the quality of interactions between molecules and target proteins (associated to disease). Our analysis of the top-1/10/50/100scores from each oracle reveals that search-based algorithms, particularly genetic algorithms, generally outperform others. Also, explicit utilization of 3D structure of the target protein has not shown significant improvement compared to 2D methods. While there are some drawbacks in certain aspects, these could potentially be mitigated by integrating other algorithmic strategies.

Table 1. Representative structure-based drug design methods, categorized based on the molecular assembly strategies and the optimization algorithms. Columns are various molecular assembly strategies while rows are different optimization algorithms.

	1D SMILES/SELFIES	2D molecular graph	3D structure-based
Genetic Algorithm (GA)	SMILES-GA (Yoshikawa et al., 2018)	AutoGrow4 (Spiegel & Durrant, 2020), graph GA (Jensen, 2019)	-
Hill Climbing	SMILES-LSMT-HC (Brown et al., 2019)	MIMOSA (Fu et al., 2021)	-
Reinforcement Learning (RL)	REINVENT (Olivecrona et al., 2017)	MolDQN (Zhou et al., 2018)	-
Gradient Ascent (GRAD)	Pasithea (Shen et al., 2021)	DST (Fu et al., 2022b)	
Generative Models	SMILES/SELFIES-VAE- BO (Gómez-Bombarelli et al., 2018)	-	3DSBDD(Luo et al., 2021), Pocket2mol(Peng et al., 2022), PocketFlow(Jiang et al., 2024), ResGen(Zhang et al., 2023)

2. Related Work

There has been significant progress in benchmarking efforts for drug design evaluation (Brown et al., 2019; Tripp et al., 2021; Huang et al., 2021; Gao et al., 2022; Polykovskiy et al., 2020; Harris et al., 2023). Specifically, Guacamol (Brown et al., 2019) encompasses five molecule design algorithms, develops twenty novel objective functions, and assesses their performance comprehensively. Molecular Sets (MOSES) (Polykovskiy et al., 2020) concentrates on five generative-based models (recurrent neural network (RNN), Adversarial Auto-Encoder (AAE) (Makhzani et al., 2015), Variational Auto-Encoder (VAE) (Gómez-Bombarelli et al., 2018)), introducing eleven oracles that primarily evaluate the novelty and uniqueness of the generated molecules. Practical Molecule Optimization (PMO) (Gao et al., 2022) offers a benchmark for twenty-five molecule design models across twenty-three objectives, providing a broad evaluation landscape. POSECHECK (Harris et al., 2023) assesses five generative-based models by employing four physical oracles to gauge the quality of proteinligand interactions, contributing to the nuanced understanding of model efficacy in simulating realistic biochemical interactions. Recently, (Tripp & Hernández-Lobato, 2023) designed a simple genetic algorithm on molecules based on (Jensen, 2019) and compared it with several other molecule generation algorithms. The results show that genetic algorithms perform at least as well as many more complicated methods in the unconditional molecule generation task.

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 1D Molecule Design Methods 1D molecule design methods use Simplified Molecular-Input Line-Entry System (SMILES) (Weininger, 1988) or SELF-referencing Embedded Strings (SELFIES) (Krenn et al., 2020) strings as the representation of molecules. Most 1D methods produce molecule strings in an autoregressive manner. In this paper, we discuss several methods that were developed to produce molecule strings, either SMILES or SELFIES strings, including REINVENT (Olivecrona et al., 2017), SMILES and SELFIES VAE (Gómez-Bombarelli et al., 2018), SMILES GA (Yoshikawa et al., 2018), SMILES-LSTM-HC (Brown et al., 2019), and Pasithea (Shen et al., 2021). Although SELFIES string has the advantage of enforcing chemical validity rules compared to SMILES, through thorough empirical studies, (Gao et al., 2022) showed that SELFIES string-based methods do not demonstrate superiority over SMILES string-based ones.

2D Molecule Design Methods Compared to 1D molecule design methods, representing molecules using 2D molecular graphs is a more sophisticated approach. molecular 2D representation, graphs are used to depict molecules, where edges represent chemical bonds and nodes represent atoms. There are two main strategies for constructing these graphs: atom-based and fragment-based. Atom-based methods operate on one atom or bond at a time, searching the entire chemical space. On the other hand, fragment-based methods summarize common molecular fragments and operate on one fragment at a time, which can be more efficient. In this paper, we discuss several methods belonging to this category: MolDON (Zhou et al., 2018), which uses an atom-based strategy, and Graph GA (Jiang et al., 2024), Multi-constraint Molecule Sampling (MIMOSA) (Fu et al., 2021), Differentiable Scaffolding Tree (DST) (Fu et al., 2022b), and AutoGrow4 (Spiegel & Durrant, 2020), which use fragment-based strategies.

3D Molecule Design Methods Both 1D and 2D molecule design methods are ligand-centric, focusing primarily on designing the molecule itself. In structure-based drug design, as pointed out in (Huang et al., 2021), these models take the

docking function as a black box, which inputs a molecule 111 and outputs the binding affinity score. However, these mod-112 els fail to incorporate target protein structure information 113 and consequently suffer from high computational time (to 114 find binding pose). In contrast, 3D structure-based drug 115 design methods take the three-dimensional geometry of the 116 target protein as input and directly generate pocket-aware 117 molecules in the pocket of target protein. In this paper, we 118 cover four cutting-edge structure-based drug design meth-119 ods: PocketFlow (Jiang et al., 2024), 3DSBDD (Luo et al., 120 2021), Pocket2mol (Peng et al., 2022), and ResGen (Zhang 121 et al., 2023).

3. Models

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In this paper, the models we select for evaluation are based
on one or a combination of the following algorithms. For
ease of comparison, we categorize all the methods based on
optimization algorithm and molecular assembly strategy in
Table 1.

130 Screening: Screening (high-throughput screening) is a tra-131 ditional drug design approach that searches over a library 132 of molecules. However, it is only able to search the known 133 drug molecular space, but is not able to explore unknown 134 chemical space and identify novel/unknown molecules. The 135 known chemical space ($< 10^{15}$) is only taking a tiny fraction 136 of the whole drug-like molecular space (around 10^{60}) (Bo-137 hacek et al., 1996). In our evaluation, we use screening as 138 a baseline method, which randomly searches ZINC 250k 139 library (Irwin et al., 2012). 140

Genetic Algorithm (GA): Inspired by natural selection, 141 genetic algorithm is a combinatorial optimization method 142 that evolves solutions to problems over many generations. 143 Specifically, in each generation, GA will perform crossover 144 and mutation over a set of candidates to produce a pool of 145 offspring and keep the top-k offspring for the next generation, imitating the natural selection process. In our evalua-147 tion, we choose three GA models: SMILES GA (Yoshikawa 148 et al., 2018) that performs GA over SMILES string-based 149 space, Graph GA (Jiang et al., 2024) that searches over 150 atom- and fragment-level by designing their crossover and 151 mutation rules on graph matching and AutoGrow4 (Spiegel 152 & Durrant, 2020) which introduce another procedure called 153 elitism that filtering the candidates by pre-defined rules. 154

Variational Auto-Encoder (VAE): The aim of variational 155 autoencoder is to generate new data that is similar to train-156 ing data. In the molecule generation area, VAE learns a 157 bidirectional map between molecule space and continuous 158 latent space and optimizes the latent space. VAE itself 159 generated diverse molecules that are learned from the train-160 ing set. After training VAE, Bayesian optimization (BO) 161 is used to navigate latent space efficiently, identify desir-162 able molecules, and conduct molecule optimization. In our 163

evaluation, we select two VAE-based models: SMILES-VAE-BO (Gómez-Bombarelli et al., 2018) uses SMILES string as the input to the VAE model, and SELFIES-VAE-BO uses the same algorithm but uses SELFIES string as the molecular representation.

Auto-regressive: An auto-regressive model is a type of statistical model that is based on the idea that past values in the series can be used to predict future values. In molecule generation, an auto-regressive model would typically take the generated atom sequence as input and predict which atom would be the next. In our evaluation, we choose four auto-regressive models: PocketFlow (Jiang et al., 2024) is an autoregressive flow-based generative model. 3DSBDD (Luo et al., 2021) based on conventional Markov Chain Monte Carlo (MCMC) algorithms and Pocket2mol (Peng et al., 2022) choose graph neural networks (GNN) as the backbone. Inspired by Pocket2mol, ResGen (Zhang et al., 2023) used a hierarchical autoregression, which consists of a global autoregression for learning protein-ligand interactions and atomic component autoregression for learning each atom's topology and geometry distributions. Also, note that these models use 3D representations of target proteins.

Hill Climbing (HC): Hill Climbing (HC) is an optimization algorithm that belongs to the family of local search techniques (Selman & Gomes, 2006). It is used to find the best solution to a problem among a set of possible solutions. In molecular design, Hill Climbing would tune the generative model with the reference of generated high-scored molecules. In our evaluation, we adopt two HC models: SMILES-LSTM-HC (Brown et al., 2019) uses an LSTM model to generate molecules and uses the HC technique to fine-tune it. MultI-constraint MOlecule SAmpling (MI-MOSA) (Fu et al., 2021) uses a graph neural network instead and incorporates it with HC.

Gradient Ascent (GRAD): Similar to gradient descent, gradient ascent also estimates the gradient direction but chooses the maximum direction. In molecular design, the GRAD method is often used in molecular property function to optimize molecular generation. In our evaluation, we choose two GRAD-based models: Pasithea (Shen et al., 2021) uses SELFIES as input and applies GRAD on an MLP-based molecular property prediction model. Differentiable Scaffolding Tree (DST) (Fu et al., 2022b) uses differentiable molecular graph as input and uses a graph neural network to estimate objective and the corresponding gradient.

Reinforcement Learning (RL): In molecular generation context, a reinforcement learning model would take a partially-generated molecule (either sequence or molecular graph) as state; action is how to add a token or atom to the sequence or molecular graph respectively; and reward is the property score of current molecular sequence. In our evaluation, we test on two RL-based models: REIN-VENT (Olivecrona et al., 2017) is a policy-gradient method that uses RNN to generate molecules and MolDQN (Zhou

et al., 2018) uses a deep Q-network to generate moleculargraph.

All the methods used in this paper are summarized in Table 1for ease of comparison.

4. Experiments

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172 In this section, we demonstrate the experimental results. 173 We start with the description of experimental setup. Then, 174 we present and analyze the experimental results, including 175 protein-ligand bindings, pharmaceutical properties of gener-176 ated molecules (e.g., drug-likeness and synthetic accessibil-177 ity), and other qualities of generated molecules (e.g., diver-178 sity, validity). The relevant code is available in https:// 179 github.com/zkysfls/2024-sbdd-benchmark. 180

4.1. Experimental Setup

183 4.1.1. ORACLE

184 In drug discovery, we need to evaluate the pharmaceuti-185 cal properties of the generated molecules, such as binding 186 affinity to certain target proteins, drug-likeness, synthetic ac-187 cessibility, and solubility, etc. These property evaluators are 188 also known as oracle. In this section, we introduce the oracle 189 we chose to evaluate these models. All our oracle functions 190 come from Therapeutic Data Commons (TDC) (Huang et al., 191 $2022; 2021)^1$.

Docking Score: Molecular docking is a measurement of 193 free energy exchange between a ligand and a target protein during the binding process. A lower docking score 195 means the ligand would have a higher potential to pose 196 higher bioactivity with a given target. Compared with 197 other heuristic oracles, such as QED (quantitative estimate of drug-likeness), and LogP (Octanol-water partition co-199 efficient), docking reflects the binding affinities between 200 drug molecule and target (Graff et al., 2021). Our experiments use TDC.Docking oracle function, which is based on AutoDock Vina (Eberhardt et al., 2021) to test with these models. We chose seven representative and diverse target 204 proteins in the TDC docking benchmark, which are selected from CrossDock (Francoeur et al., 2020b). The PDBIDs 206 are liep, 3eml, 3ny8, 4rlu, 4unn, 5mo4, 7111. These crystallography structures are across different fields, including 208 virology, immunology, and oncology (Huang et al., 2022; 209 2021; Lu et al., 2019). They cover various kinds of dis-210 eases such as chronic myelogenous leukemia, tuberculosis, 211 SARS-COVID-2, etc. They represent a breadth of function-212 ality, from viral replication mechanisms to cellular signaling 213 pathways and immune responses. 214

Heuristic Oracles: Although heuristic oracles are consid ered to be "trivial" and too easily optimized, we still incorpo-

218 219 rate some of them into our evaluation metrics for comprehensive analysis. In our experiments, we utilize Quantitative Estimate of Drug-likeness (QED), SA, and LogP as our heuristic oracles. QED evaluates a molecule's drug-likeness on a scale from 0 to 1, where 0 indicates minimal druglikeness and 1 signifies maximum drug-likeness, aligning closely with the physicochemical properties of successful drugs. SA, or Synthetic Accessibility, assesses the ease of synthesizing a molecule, with scores ranging from 1 to 10; a lower score suggests easier synthesis. LogP measures a compound's preference for a lipophilic (oil-like) phase over a hydrophilic (water-like) phase, essentially indicating its solubility in water, where the optimal range depends on the type of drug. But mostly the value should be between 0 and 5 (Krenn et al., 2020).

Molecule Generation Oracles: While docking score oracles and heuristic oracles focus on evaluating individual molecules, molecule generation oracles assess the quality of all generated molecules as a whole. In our experiments, we choose three metrics to evaluate the generated molecules of each model: diversity, validity, and uniqueness. Diversity is measured by the average pairwise Tanimoto distance between the Morgan fingerprints (Benhenda, 2017). Validity is determined by checking atoms' valency and the consistency of bonds in aromatic rings using RDKit's molecular structure parser (Polykovskiy et al., 2020). Uniqueness is measured by the frequency at which a model generates duplicated molecules, with lower values indicating more frequent duplicates (Polykovskiy et al., 2020).

4.1.2. MODEL SETUP

For each model, we generate 1,000 molecules for each given target protein, and each molecule is evaluated by the TDC oracle functions (Huang et al., 2021; 2022). Each experiment is run on one OSC Ascend node (Center, 1987) for 96 hours, which is the maximum time allowed for a single experiment, and we only run each model once. Five models (3DSBDD, PocketFlow, Pocket2mol, ResGen, and AutoGrow4) first generate a certain number of molecules within the given time, and then we run oracle functions on each molecule. All the other models come from the PMO benchmark (Gao et al., 2022), and our experiment follows its setting, where each molecule is first generated, then the oracle function is used to calculate the score, and then the model moves on to generate the second molecule. None of the tested models have prior knowledge of these oracle functions. Among all the models, five of them manage to generate and have been evaluated by the oracle for 1,000 or more molecules within the given time across all target proteins (AutoGrow4, PocketFlow, DST, MIMOSA, and Screening); other models do not generate enough molecules or have not been evaluated for enough molecules within the given 96 hours, mostly because the docking oracle function is time-consuming. The

¹https://tdcommons.ai/functions/oracles/



Figure 1. The bar chart of average generated molecules that are calculated by our selected oracles for each model across all target proteins under given time. 1D methods are colored red, blue is used to indicate 2D methods, and green represents 3D methods.

VAE models and REINVENT only generate 200 and 100 molecules, respectively, because we observe that when they generate more than this number of molecules, the models crash. Figure 1 shows the average number of molecules that has been generated and successfully evaluated by oracle functions within experiment time.

4.2. Experimental Results

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4.2.1. RESULTS OF BINDING AFFINITIES

Overall Performance: Overall, search-based algorithms (including Screening, Genetic Algorithm [GA], Hill Climbing [HC], and Gradient-based methods [GRAD]) demonstrate superior performance compared to generative models (like VAE and Auto-regressive) and reinforcement learningbased algorithms. Although generative models have good performance on Top-1 docking score (Table 3), search-based algorithms take advantages on Top-10/50/100 docking score, as shown in Table 2 to 5.

Search-based Algorithms: Among all the search-based algorithms, AutoGrow4 exhibits the best performance. This superiority is not only reflected in its consistently highest scores in the Top 1/10/50/100 categories but also in the outstanding docking scores of the majority of its generated molecules compared to other methods across every target protein, as indicated by Table 3 to 5. We believe that the elitism procedure incorporated in AutoGrow4 enhances its performance by providing better candidates for crossover

and mutation. While other search-based methods also perform well overall, no single algorithm category within this group distinctly outperforms the others. It appears that neither the format of the input (such as SMILES/SELFIES or scaffold graph) nor the specific algorithm employed has a significant impact on performance.

Generative Models: In our experiments, we evaluated two categories of generative models: Variational Autoencoders (VAEs) and Auto-regressive models. Firstly, two VAE-based models, SMILES-VAE-BO and SELFIES-VAE-BO, demonstrated consistent performance across all target proteins, with most of their generated molecules achieving docking scores between -6 and -9. However, only a few molecules from these models exceeded a -10 score, and neither model showed a distinct advantage over the other.

Regarding the autoregressive models, among the four models we evaluated, Pocket2Mol demonstrates the best overall performance. This is not only because it achieves the highest scores in Top-1, Top-10, Top-50, and Top-100 rankings but also because its average top docking score remains above -10 across all these rankings. For the remaining models, Res-Gen ranks second, followed by PocketFlow and 3DSBDD. We also noticed that some of our selected target pockets appeared in Crossdeck (Francoeur et al., 2020a), which is the dataset that our selected autoregressive models used for training and evaluation. However, our experimental results show that these autoregressive models do not always have advantages compared to other models. For example, in target 3EML, AutoGrow4 has the best performance across Top Table 2. The average of each model's Top-10 Docking score for each target protein.

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277	MODEL	1 iep	3eml	3ny8	4rlu	4unn	5мо4	7L11
278	3DSBDD	$\textbf{-9.05} \pm 0.38$	$\textbf{-10.02}\pm0.15$	$\textbf{-10.10}\pm0.24$	$\textbf{-9.80} \pm 0.55$	$\textbf{-8.23}\pm0.30$	$\textbf{-8.71} \pm 0.45$	$\textbf{-8.47} \pm 0.18$
270	AUTOGROW4	$\textbf{-13.23}\pm0.11$	$\textbf{-13.03}\pm0.09$	$\textbf{-11.70}\pm0.00$	$\textbf{-11.20}\pm0.00$	$\textbf{-}11.14\pm0.12$	$\textbf{-10.38} \pm 0.27$	$\textbf{-8.84} \pm 0.33$
279	POCKET2MOL	$\textbf{-10.17}\pm0.53$	$\textbf{-12.25}\pm0.27$	$\textbf{-11.89} \pm 0.16$	$\textbf{-10.57} \pm 0.12$	$\textbf{-12.20}\pm0.34$	$\textbf{-10.07}\pm0.62$	$\textbf{-9.74} \pm 0.38$
280	POCKETFLOW	$\textbf{-12.49}\pm0.70$	$\textbf{-9.25}\pm0.29$	-8.56 ± 0.35	-9.65 ± 0.25	-7.90 ± 0.78	$\textbf{-7.80} \pm 0.42$	$\textbf{-8.35} \pm 0.31$
201	RESGEN	-10.97 ± 0.29	$\textbf{-9.25}\pm0.95$	-10.96 ± 0.42	$\textbf{-11.75}\pm0.42$	-9.41 ± 0.23	$\textbf{-10.34} \pm 0.39$	-8.74 ± 0.24
281	DST	-10.95 ± 0.57	-10.67 ± 0.24	-10.54 ± 0.22	-10.88 ± 0.37	-9.71 ± 0.19	$\textbf{-10.03}\pm0.36$	$\textbf{-8.33} \pm 0.41$
282	GRAPH GA	-10.03 ± 0.41	$\textbf{-9.89} \pm 0.25$	-9.94 ± 0.15	$\textbf{-10.22}\pm0.39$	-9.32 ± 0.51	$\textbf{-9.29}\pm0.20$	$\textbf{-7.75} \pm 0.32$
283	MIMOSA	-10.96 ± 0.57	-10.69 ± 0.24	-10.51 ± 0.23	$\textbf{-10.81} \pm 0.39$	$\textbf{-9.66} \pm 0.25$	$\textbf{-10.02}\pm0.36$	-8.33 ± 0.41
200	MolDQN	$\textbf{-6.73} \pm 0.12$	$\textbf{-6.51} \pm 0.15$	-7.09 ± 0.16	$\textbf{-6.79} \pm 0.26$	-5.92 ± 0.26	$\textbf{-6.27} \pm 0.10$	$\textbf{-6.87} \pm 0.20$
284	PASITHEA	-10.86 ± 0.29	-10.31 ± 0.09	-10.69 ± 0.27	-10.92 ± 0.35	-9.69 ± 0.32	-9.77 ± 0.21	-8.06 ± 0.22
285	REINVENT	-9.87 ± 0.31	-9.48 ± 0.39	-9.61 ± 0.36	-9.69 ± 0.29	-8.70 ± 0.25	-8.92 ± 0.38	-7.25 ± 0.21
200	SCREENING	-10.86 ± 0.26	-10.90 ± 0.54	-10.73 ± 0.45	-10.86 ± 0.22	-9.80 ± 0.23	-9.91 ± 0.30	-8.15 ± 0.26
280	SELFIES-VAE-BO	-10.15 ± 0.60	-9.76 ± 0.12	-9.99 ± 0.28	-10.00 ± 0.23	-9.02 ± 0.33	-9.18 ± 0.39	-7.75 ± 0.22
287	SMILES GA	-9.56 ± 0.17	-9.56 ± 0.37	-10.00 ± 0.26	-9.61 ± 0.19	-8.80 ± 0.20	-9.21 ± 0.23	-7.54 ± 0.32
200	SMILES LSTM HC	-10.38 ± 0.21	-10.30 ± 0.15	-10.19 ± 0.12	-10.49 ± 0.49	-9.36 ± 0.17	-9.71 ± 0.43	-7.90 ± 0.26
200	SMILES-VAE-BO	-9.93 ± 0.22	-9.78 ± 0.10	-9.96 ± 0.29	-10.05 ± 0.20	-9.03 ± 0.30	-9.18 ± 0.39	-7.74 ± 0.25
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291 1 to Top 100, while in target 4UNN, Pocket2mol has the 292 advantage.

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293 Reinforcement Learning: We incorporate two reinforcement learning-based models: MolDQN and REINVENT. 295 Overall, REINVENT demonstrates superior performance 296 compared to MolDQN. The majority of molecules gener-297 ated by REINVENT have docking scores around -8, whereas 298 those by MolDON are mostly around -6. This leads us to sus-299 pect that the policy-gradient method might be more suitable 300 than the deep Q-network approach for the task of molecu-301 lar generation. Compared to other models, reinforcement 302 learning models do not exhibit good performance. These 303 two reinforcement learning models have the lowest scores 304 in the docking score oracle. This may suggest that the rein-305 forcement learning algorithm may not have a strong ability 306 to produce molecules with good docking scores. 307

308 **4.2.2. RESULTS OF PHARMACEUTICAL PROPERTIES** 309

310 Then, we report and analyze the pharmaceutical properties 311 of the generated molecules.

SA: Overall, most of the models generate molecules with scores between 1 to 3. Notably, 3DSBDD, MolDQN, and REINVENT produce molecules with scores ranging above 3. Additionally, these models exhibit high variance in their 316 scores. For instance, in the case of 3DSBDD, the lowest score observed is 1, yet it can also generate molecules scoring as high as 8 for a specific target protein.

319 QED: Most of the models generate molecules with scores 320 between 0.8. However, 3DSBDD and REINVENT tend to 321 produce molecules with scores primarily in the range of 322 0.6 to 0.7, while MolDQN's generated molecules hover 323 around 0.4. Overall nearly all models have the same level of 324 performances except reinforcement learning based models 325 which has worse performances.

LogP: Overall, nearly all the models tested produced the majority of their molecules within the 0 to 3 range, which is deemed suitable for a drug, with the exception of MolDQN. The molecules generated by MolDQN often have a LogP score of less than 0 across all target proteins, indicating a high solubility in water. Furthermore, generative models, particularly 3DSBDD, predominantly generate molecules with scores around 0.

4.2.3. MOLECULE GENERATION QUALITY

In the diversity oracle, all models score above 0.8, with one model from each algorithm category exceeding 0.9: Pocket-Flow from generative models, Graph GA from search-based methods, and MolDON from reinforcement learning. This suggests that these three models are particularly effective at generating diverse sets of molecules. In the validity oracle, all models achieve a perfect score of 1, except for 3DS-BDD. Similarly, in the uniqueness oracle, all models score 1, except for 3DSBDD, AutoGrow4, and PocketFlow. It is unclear why these models have lower scores in validity and uniqueness, especially when other models from the same algorithm category perform well. One possible explanation for 3DSBDD's low validity and uniqueness scores could be issues with its molecule generation process, such as producing invalid molecular structures or duplicates. Despite their high diversity scores, AutoGrow4 and PocketFlow's lower uniqueness scores might indicate a tendency to generate similar molecules. Further investigation into the specific architectures and training procedures of these models could provide insights into their divergent performance. It may also be valuable to analyze the trade-offs between diversity, validity, and uniqueness in molecule generation and how different models balance these objectives. Overall, while most models demonstrate strong performance across the three oracles, the lower validity and uniqueness scores of 3DSBDD, AutoGrow4, and PocketFlow highlight the importance of evaluating multiple aspects of generated molecules to assess model performance comprehensively.

Structure-based Drug Design Benchmark: Do 3D Methods Really Dominate?



Figure 2. The heatmap based on the average of each model's Top-10 docking score for each target protein.

4.2.4. Key observations

We summarize the following insightful observations drawn from the experimental results, which benefits design of future SBDD models.

- Most structure-based drug design method uses the 3D structure of the target protein explicitly and grow the drug molecules in the pocket of the target protein. We pinpoint another direction that regards the docking function as a black box and uses 1D/2D ligand-centric methods to produce drug molecules, which is usually neglected by the community. In this paper, we empirically prove that this kind of method would achieve superior performance.
- AutoGrow4, a 2D genetic algorithm, exhibits the best optimization performance in terms of top-K docking scores in most target proteins. Also, it owns desirable synthetic accessibility.
- Generally, 3D SBDD algorithms (using 3D target protein structure explicitly) do not demonstrate significant superiority over 2D methods.
 - No methods can dominate structure-based drug design

in all the evaluation metrics (docking score, SA, QED, diversity, validity, and uniqueness), as shown in Figure 4.

Example of the Generated Molecules Also, we show the 3D poses of molecules that have the best docking score for each target protein in Figure 12 in Appendix. We find that the generated molecules could bind tightly to the pocket of target proteins.

Additional Experimental Results Furthermore, we report the numerical values of top-K docking, QED, SA, LogP score for all the methods across different target proteins in Appendix, as well as their relative ranking on all the metrics.

5. Conclusion and Future Work

Currently, the landscape of structure-based drug design models is vast, featuring various algorithmic backbones, yet comparative analyses across them are scarce. In this study, we design experiments to evaluate the quality of molecules generated by each model. Our experiments extend beyond conventional heuristic oracles related to molecular prop-

Structure-based Drug Design Benchmark: Do 3D Methods Really Dominate?



Figure 3. The bar chart is based on the average of each model's Top-10 docking score. On the left, 1D methods are colored red, blue is used to indicate 2D methods, and green represents 3D methods. On the right, generative models are in blue, search-based methods are in green, and reinforcement learning methods are in red.

402 erties, also examining the affinity between molecules and 403 selected target proteins. Our findings indicate that models 404 based on genetic algorithms exhibit a higher potential for 405 producing molecules that dock effectively with given target 406 proteins. Also, representing target molecules in 3D format 407 does not significantly improve both the molecular quality 408 and blinding affinity. Although we observed that there is 409 no single method that could excel both our two metrics, 410 we suggest that when developing new structure-based drug 411 discovery models in the future, it would be advantageous 412 to integrate genetic algorithms with other computational 413 approaches to enhance both docking scores and molecular 414 properties. 415

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A. Appendix

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Figure 4. The radar chart is based on the ranking of each model's average performance. The outermost circle represents the best ranking for each metric and vice versa. No methods can dominate structure-based drug design in all the evaluation metrics.



Figure 6. Model: AutoGrow4, PDB: 3eml, -13.3



Figure 8. Model: ResGen, PDB: 4rlu, -12.6



Figure 10. Model: Pocket2mol, PDB: 4unn, -

MODEL	1 iep	3eml	3ny8	4RLU
3DSBDD	-10.00	-10.40	-10.60	-11.40
AUTOGROW4	-13.40	-13.30	-11.70	-11.20
POCKET2MOL	-11.50	-12.80	-12.20	-10.70
POCKETFLOW	-13.90	-9.80	-9.20	-10.10
ResGen	-11.60	-10.80	-11.70	-12.60
DST	-12.20	-11.00	-11.00	-11.40
GRAPH GA	-10.80	-10.50	-10.20	-11.10
MIMOSA	-12.20	-11.10	-11.00	-11.40
MOLDQN	-6.90	-6.80	-7.50	-7.50
PASITHEA	-11.60	-10.40	-11.20	-11.60
REINVENT	-10.40	-10.40	-10.30	-10.10
SCREENING	-11.30	-12.20	-11.90	-11.20
SELFIES VAE BO	-11.80	-10.00	-10.70	-10.50
SMILES GA	-9.90	-10.50	-10.60	-9.90
SMILES LSTM HC	-10.70	-10.60	-10.40	-11.30
SMILES-VAE-BO	-10.30	-10.00	-10.70	-10.50
MODEL	4u	NN 5M	104 71	.11
3DSBDD	-8.	90 -9	.80 -8	.80
AUTOGROW4	-11	.20 -1	0.80 -9	.60
POCKET2MOL	-12	.80 -1	1.90 -10).40
PocketFlow	-9.	50 -8	.70 -8	.90
ResGen	-9.	90 -1	1.00 -9	.40
DST	-9.	90 -1	1.00 -9	.30
graph GA	-10	.60 -9	.60 -8	.60
MIMOSA	-10	.00 -1	1.00 -9	.30
molDQN	-6.	40 -6	.50 -7	.20
PASITHEA	-10	.40 -1	0.10 -8	.60
REINVENT	-9.	-9	.60 -7	.70
SCREENING	-10	.30 -1	0.50 -8	.70
SELFIES VAE E	3 0 -9.	-10	0.10 -8	.20
SMILES GA	-9.	30 -9	.60 -8	.10
SMILES LSTM	HC -9.	-10	0.60 -8	.40
SMILES-VAE-E	BO -9.	60 -10	0.10 -8	.20

Table 3. Top 1 Docking score for each target protein.

Table 4. Top 50 Docking score for each target protein.

Model	1iep	3emi	<u>-</u>	3ny8	4rlu
3DSBDD	-8.43 ± 0.39	-9.50 ± 0	0.34 -9.1	15 ± 0.61	-9.10 ± 0.10
AUTOGROW4	$\textbf{-12.47} \pm 0.70$	-12.45 \pm	0.36 -11.	04 ± 0.38	-10.92 \pm 0
POCKET2MOL	-9.57 ± 0.40	-11.64 \pm	0.37 -11.	24 ± 0.42	-10.18 ± 0
POCKETFLOW	-11.60 ± 0.57	-8.52 ± 0	0.47 -7.9	97 ± 0.35	-8.96 ± 0.1
RESGEN	$\textbf{-10.36} \pm 0.40$	-7.22 \pm	1.14 -10.	35 ± 0.39	-10.79 ± 0
DST	-10.07 ± 0.55	-10.03 \pm	0.37 -10.	04 ± 0.30	-10.24 ± 0
GRAPH GA	$\textbf{-9.19} \pm 0.53$	-9.19 ± 0	0.43 -9.3	31 ± 0.40	-9.52 ± 0.52
MIMOSA	-10.09 ± 0.55	-10.01 \pm	0.39 -10.	04 ± 0.30	-10.23 ± 0
MolDQN	$\textbf{-6.31} \pm 0.27$	-6.14 ± 0	0.24 -6.3	39 ± 0.49	-6.15 ± 0.11
PASITHEA	$\textbf{-10.10}\pm0.48$	-9.91 ± 0	0.25 -10.	10 ± 0.36	-10.25 ± 0
REINVENT	$\textbf{-8.53}\pm0.81$	-8.55 ± 0	0.58 -8.7	70 ± 0.56	-8.69 ± 0.00
SCREENING	$\textbf{-10.23}\pm0.40$	-10.11 \pm	0.50 -10.	12 ± 0.40	-10.24 ± 0
SELFIES VAE BO	-9.23 ± 0.63	-9.24 ± 0	0.39 -9.3	35 ± 0.42	-9.30 ± 0.1
SMILES GA	-8.90 ± 0.41	-8.65 ± 0	0.53 -9.1	13 ± 0.52	-9.05 ± 0.01
SMILES LSTM HC	-9.61 ± 0.47	-9.80 ± 0	0.33 -9.6	53 ± 0.36	-9.74 ± 0.1
CMILEC WAE DO	0.10 ± 0.40	0 27 1	0.00 0.0		0.21 ± 0
SMILES-VAE-BO	-9.19 ± 0.49	-9.27 ± 0	0.39 -9.3	34 ± 0.41	-9.31 ± 0.4
SMILES-VAE-BU	-9.19 ± 0.49	-9.27 ± 0	0.39 -9.3	34 ± 0.41	-9.31 ± 0.31
Mode	-9.19 ± 0.49 L 4	-9.27 ± 0	0.39 -9.3 5мо4	34 ± 0.41 7L	-9.31 ± 0.31
Mode 3DSBE	L 4 DD -7.45	-9.27 ± 0.000	0.39 -9.3 5мо4 -7.98±0.4	34 ± 0.41 7L 5 -8.08 :	$\frac{-9.31 \pm 0.1}{11}$
Mode 3DSBE AutoGre	-9.19 ± 0.49 L 4 DD -7.45 ow4 -10.8	-9.27 ± 0.00 UNN 5 ± 0.52 9 ± 0.14	<u>5мо4</u> -7.98 ± 0.4 - 10.20 ± 0.1	34 ± 0.41 7L 5 -8.08 = 16 -8.44 =	$ \begin{array}{r} -9.31 \pm 0. \\ \hline 11 \\ \pm 0.25 \\ \pm 0.26 \end{array} $
MODE 3DSBE AUTOGR POCKET2	-9.19 ± 0.49 L 4 DD -7.45 OW4 -10.8 MOL -11.5	-9.27 ± 0 UNN 5 ± 0.52 9 ± 0.14 6 ± 0.40	5M04 -7.98 ± 0.4 -10.20 ± 0.1 -9.55 ± 0.4	34 ± 0.41 7L 5 -8.08 = 16 -8.44 = 0 -9.11 =	$ \begin{array}{r} -9.31 \pm 0. \\ \hline 11 \\ \pm 0.25 \\ \pm 0.26 \\ \pm 0.40 \end{array} $
MODE MODE 3DSBE AUTOGR POCKET2 POCKETF	-9.19 ± 0.49 L 4 DD -7.45 OW4 -10.8 MOL -11.5 LOW -6.91	$ \begin{array}{c} -9.27 \pm 0 \\ \hline \\ 0 \pm 0.52 \\ 9 \pm 0.14 \\ 6 \pm 0.40 \\ \pm 0.63 \\ \end{array} $	$5M04 = -7.98 \pm 0.4$ -7.98 ± 0.4 -10.20 ± 0.1 -9.55 ± 0.4 -7.06 ± 0.4	34 ± 0.41 $7L$ $5 -8.08 \pm$ $16 -8.44 \pm$ $0 -9.11 \pm$ $5 -7.85 \pm$	$ \begin{array}{c} -9.31 \pm 0. \\ \hline 11 \\ \pm 0.25 \\ \pm 0.26 \\ \pm 0.40 \\ \pm 0.31 \\ \end{array} $
MODE MODE 3DSBE AUTOGR POCKET2 POCKETF RESGE	-9.19 ± 0.49 L 4 DD -7.45 OW4 -10.8 MOL -11.5 LOW -6.91 SN -8.63	$ \begin{array}{c} -9.27 \pm 0 \\ \hline \\ 0 \pm 0.52 \\ 9 \pm 0.14 \\ 6 \pm 0.40 \\ \pm 0.63 \\ \pm 0.50 \\ \end{array} $	$5M04 = -7.98 \pm 0.4$ -7.98 ± 0.4 -10.20 ± 0.1 -9.55 ± 0.4 -7.06 ± 0.4 -9.39 ± 0.5	34 ± 0.41 $7L$ $5 -8.08 =$ $16 -8.44 =$ $0 -9.11 =$ $5 -7.85 =$ $6 -8.28 =$	$ \begin{array}{c} -9.31 \pm 0. \\ \hline 11 \\ \pm 0.25 \\ \pm 0.26 \\ \pm 0.40 \\ \pm 0.31 \\ \pm 0.30 \\ \end{array} $
MODE MODE 3DSBE AUTOGR POCKET2 POCKETF RESGE DST	$\begin{array}{c} -9.19 \pm 0.49 \\ \hline \\ L & 4 \\ \hline \\ DD & -7.45 \\ \hline \\ OW4 & -10.8 \\ \hline \\ MOL & -11.5 \\ \hline \\ LOW & -6.91 \\ \hline \\ SN & -8.63 \\ \hline \\ -9.13 \end{array}$	$\begin{array}{c} -9.27 \pm 0 \\ \hline \\$	$\begin{array}{c} \textbf{0.39} & -9.3 \\ \hline \\ \textbf{5} \text{MO4} \\ \hline \\ \textbf{-7.98 \pm 0.4} \\ \textbf{-10.20 \pm 0.1} \\ \textbf{-9.55 \pm 0.4} \\ \textbf{-7.06 \pm 0.4} \\ \textbf{-9.39 \pm 0.5} \\ \textbf{-9.30 \pm 0.4} \end{array}$	34 ± 0.41 $7L$ $5 -8.08 =$ $16 -8.44 =$ $0 -9.11 =$ $5 -7.85 =$ $6 -8.28 =$ $3 -7.81 =$	$ \begin{array}{c} -9.31 \pm 0.2 \\ \hline 11 \\ \pm 0.25 \\ \pm 0.26 \\ \pm 0.40 \\ \pm 0.31 \\ \pm 0.30 \\ \pm 0.35 \\ \end{array} $
MODE 3DSBE AUTOGR POCKET2 POCKETF RESGE DST GRAPH	$\begin{array}{c} -9.19 \pm 0.49 \\ \hline \\ DD & -7.45 \\ 0W4 & -10.8 \\ MOL & -11.5 \\ 1LOW & -6.91 \\ 5N & -8.63 \\ -9.13 \\ GA & -8.43 \end{array}$	$\begin{array}{c} -9.27 \pm 0 \\ \hline \\$	$\begin{array}{c} \textbf{0.39} & \textbf{-9.3} \\ \hline \textbf{5} \textbf{MO4} \\ \hline \textbf{-7.98 \pm 0.4} \\ \textbf{-10.20 \pm 0.1} \\ \textbf{-9.55 \pm 0.4} \\ \textbf{-7.06 \pm 0.4} \\ \textbf{-9.39 \pm 0.5} \\ \textbf{-9.30 \pm 0.4} \\ \textbf{-8.66 \pm 0.4} \end{array}$	34 ± 0.41 $7L$ $5 -8.08 =$ $16 -8.44 =$ $0 -9.11 =$ $5 -7.85 =$ $6 -8.28 =$ $3 -7.81 =$ $1 -7.15 =$	$ \begin{array}{c} -9.31 \pm 0.2 \\ \hline 11 \\ \pm 0.25 \\ \pm 0.26 \\ \pm 0.40 \\ \pm 0.31 \\ \pm 0.30 \\ \pm 0.35 \\ \pm 0.38 \\ \end{array} $
MODE 3DSBE AUTOGR POCKET2 POCKETF RESGE DST GRAPH 0 MIMOS	$\begin{array}{c c} -9.19 \pm 0.49 \\ \hline \\ L & 4 \\ \hline \\ DD & -7.45 \\ \hline \\ OW4 & -10.8 \\ \hline \\ MOL & -11.5 \\ \hline \\ HOW & -6.91 \\ \hline \\ SN & -8.63 \\ \hline \\ -9.13 \\ \hline \\ GA & -8.43 \\ \hline \\ SA & -9.11 \\ \hline \end{array}$	$\begin{array}{c} -9.27 \pm 0 \\ \hline \\$	$\begin{array}{c} \textbf{0.39} & \textbf{-9.3} \\ \hline \textbf{5} \textbf{MO4} \\ \hline \textbf{-7.98 \pm 0.4} \\ \textbf{-10.20 \pm 0.1} \\ \textbf{-9.55 \pm 0.4} \\ \textbf{-7.06 \pm 0.4} \\ \textbf{-9.39 \pm 0.5} \\ \textbf{-9.30 \pm 0.4} \\ \textbf{-8.66 \pm 0.4} \\ \textbf{-9.32 \pm 0.4} \end{array}$	34 ± 0.41 $7L$ $5 -8.08 =$ $16 -8.44 =$ $0 -9.11 =$ $5 -7.85 =$ $6 -8.28 =$ $3 -7.81 =$ $1 -7.15 =$ $1 -7.83 =$	$ \begin{array}{c} -9.31 \pm 0.2 \\ \hline 11 \\ \pm 0.25 \\ \pm 0.26 \\ \pm 0.40 \\ \pm 0.31 \\ \pm 0.30 \\ \pm 0.35 \\ \pm 0.38 \\ \pm 0.35 \\ \end{array} $
MILES-VAE-BO MODE 3DSBE AUTOGR POCKET2 POCKETF RESGE DST GRAPH (MIMOS MOLDO	$\begin{array}{c} -9.19 \pm 0.49 \\ \hline \\ \hline \\ DD & -7.45 \\ 0W4 & -10.8 \\ MOL & -11.5 \\ 1LOW & -6.91 \\ 0W & -6.91 \\ 0W & -8.63 \\ -9.13 \\ 0A & -8.43 \\ 0A & -8.43 \\ 0A & -9.11 \\ 0N & -5.47 \end{array}$	$\begin{array}{c} -9.27 \pm 0 \\ \hline \\$	$\begin{array}{c} \textbf{0.39} \textbf{-9.3}\\ \hline \textbf{5} \text{MO4}\\ \hline \textbf{-7.98 \pm 0.4}\\ \textbf{-10.20 \pm 0.1}\\ \textbf{-9.55 \pm 0.4}\\ \textbf{-7.06 \pm 0.4}\\ \textbf{-9.39 \pm 0.5}\\ \textbf{-9.30 \pm 0.4}\\ \textbf{-8.66 \pm 0.4}\\ \textbf{-9.32 \pm 0.4}\\ \textbf{-5.80 \pm 0.3}\\ \end{array}$	34 ± 0.41 $7L$ $5 -8.08 =$ $16 -8.44 =$ $0 -9.11 =$ $5 -7.85 =$ $6 -8.28 =$ $3 -7.81 =$ $1 -7.15 =$ $1 -7.83 =$ $3 -5.98 =$	$ \begin{array}{c} -9.31 \pm 0.2 \\ \hline 11 \\ \pm 0.25 \\ \pm 0.26 \\ \pm 0.40 \\ \pm 0.31 \\ \pm 0.30 \\ \pm 0.35 \\ \pm 0.38 \\ \pm 0.35 \\ \pm 0.52 \\ \end{array} $
MILES-VAE-BO MODE 3DSBE AUTOGR POCKET2 POCKETF RESGE DST GRAPH (MIMOS MOLDO PASITH	$\begin{array}{c} -9.19 \pm 0.49 \\ \hline \\ 100 & -7.45 \\ 004 & -10.8 \\ 004 & -11.5 \\ 004 & -11.5 \\ 004 & -11.5 \\ 004 & -9.13 \\ 004 & -9.13 \\ 004 & -9.13 \\ 004 & -9.13 \\ 004 & -9.13 \\ 004 & -9.13 \\ 004 & -9.13 \\ 004 & -9.02 \\ 004 $	$\begin{array}{c} -9.27 \pm 0 \\ \hline \\ \text{UNN} \\ \hline \pm 0.52 \\ 9 \pm 0.14 \\ \hline 6 \pm 0.40 \\ \pm 0.63 \\ \pm 0.50 \\ \pm 0.34 \\ \pm 0.34 \\ \pm 0.33 \\ \pm 0.28 \\ \pm 0.41 \end{array}$	$\begin{array}{c} \textbf{0.39} \textbf{-9.3}\\ \hline \textbf{5} \textbf{MO4}\\ \hline \textbf{-7.98 \pm 0.4}\\ \textbf{-10.20 \pm 0.1}\\ \textbf{-9.55 \pm 0.4}\\ \textbf{-7.06 \pm 0.4}\\ \textbf{-9.39 \pm 0.5}\\ \textbf{-9.30 \pm 0.4}\\ \textbf{-8.66 \pm 0.4}\\ \textbf{-9.32 \pm 0.4}\\ \textbf{-5.80 \pm 0.3}\\ \textbf{-9.24 \pm 0.3}\\ \textbf{-9.24 \pm 0.3}\\ \end{array}$	34 ± 0.41 $7L$ $5 -8.08 =$ $16 -8.44 =$ $0 -9.11 =$ $5 -7.85 =$ $6 -8.28 =$ $3 -7.81 =$ $1 -7.15 =$ $1 -7.15 =$ $1 -7.83 =$ $3 -5.98 =$ $3 -7.68 =$	$ \begin{array}{c} -9.31 \pm 0. \\ \hline 11 \\ \pm 0.25 \\ \pm 0.26 \\ \pm 0.40 \\ \pm 0.31 \\ \pm 0.30 \\ \pm 0.35 \\ \pm 0.35 \\ \pm 0.35 \\ \pm 0.52 \\ \pm 0.23 \\ \end{array} $
MILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST GRAPH MIMO3 MoLDO PASITH REINVE	$\begin{array}{c c} -9.19 \pm 0.49 \\ \hline \\ \hline \\ \hline \\ DD & -7.45 \\ 0W4 & -10.8 \\ MOL & -11.5 \\ \hline \\ MOL & -11.5 \\ \hline \\ HOW & -6.91 \\ \hline \\ SN & -8.63 \\ -9.13 \\ \hline \\ SA & -9.13 \\ \hline \\ SA & -9.11 \\ \hline \\ SA & -9.11 \\ \hline \\ SA & -9.12 \\ \hline \\ SA & -9.12 \\ \hline \\ SA & -9.12 \\ \hline \\ SA & -9.13 \\ \hline \\ \\ SA & -9.13 \\ \hline \\ \\ SA & -9.13 \\ \hline \\ \\ \\ SA & -9.13 \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	$\begin{array}{c} -9.27 \pm 0 \\ \hline \\ \text{UNN} \\ \hline \pm 0.52 \\ 9 \pm 0.14 \\ \hline 6 \pm 0.40 \\ \pm 0.63 \\ \pm 0.50 \\ \pm 0.34 \\ \pm 0.54 \\ \pm 0.33 \\ \hline \pm 0.28 \\ \pm 0.41 \\ \pm 0.56 \end{array}$	$\begin{array}{c} \textbf{0.39} \textbf{-9.3}\\ \hline \textbf{5M04}\\ \hline \textbf{-7.98 \pm 0.4}\\ \textbf{-10.20 \pm 0.1}\\ \textbf{-9.55 \pm 0.4}\\ \textbf{-7.06 \pm 0.4}\\ \textbf{-9.39 \pm 0.5}\\ \textbf{-9.30 \pm 0.4}\\ \textbf{-8.66 \pm 0.4}\\ \textbf{-9.32 \pm 0.4}\\ \textbf{-5.80 \pm 0.3}\\ \textbf{-9.24 \pm 0.3}\\ \textbf{-7.98 \pm 0.5}\\ \end{array}$	34 ± 0.41 $7L$ $5 -8.08 = -8.08 = -8.44 = -8.08 = -8.28 = -8.28 = -8.28 = -8.28 = -8.28 = -8.28 = -8.28 = -7.81 = -7.83 = -7.81 = -7.83 = -7.81 = -7.83 = -7.83 = -7.68 = -6.64 = -7.68 = -6.64 = -7.68 = -6.64 = -7.68 = -6.64 = -7.68 = -$	$ \begin{array}{c} -9.31 \pm 0.2 \\ \hline 11 \\ \pm 0.25 \\ \pm 0.26 \\ \pm 0.40 \\ \pm 0.31 \\ \pm 0.30 \\ \pm 0.35 \\ \pm 0.35 \\ \pm 0.35 \\ \pm 0.52 \\ \pm 0.23 \\ \pm 0.40 \\ \end{array} $
MILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST GRAPH MIMO3 MoLDO PASITH REINVE SCREEN	$\begin{array}{c c} -9.19 \pm 0.49 \\ \hline \\ \hline \\ L & 4 \\ \hline \\ DD & -7.45 \\ \hline \\ OW4 & -10.8 \\ \hline \\ MOL & -11.5 \\ \hline \\ ILOW & -6.91 \\ \hline \\ CW & -6.9$	$\begin{array}{c} -9.27 \pm 0 \\ \hline \\ \text{UNN} \\ \hline \pm 0.52 \\ 9 \pm 0.14 \\ \hline 6 \pm 0.40 \\ \pm 0.63 \\ \pm 0.50 \\ \pm 0.34 \\ \pm 0.54 \\ \pm 0.33 \\ \hline \pm 0.28 \\ \pm 0.41 \\ \pm 0.56 \\ \pm 0.38 \end{array}$	$\begin{array}{c} 0.39 & -9.3 \\ \hline \\ 5 \text{MO4} \\ \hline \\ -7.98 \pm 0.4 \\ -10.20 \pm 0.1 \\ -9.55 \pm 0.4 \\ -9.39 \pm 0.5 \\ -9.30 \pm 0.4 \\ -8.66 \pm 0.4 \\ -9.32 \pm 0.4 \\ -5.80 \pm 0.3 \\ -9.24 \pm 0.3 \\ -7.98 \pm 0.5 \\ -9.38 \pm 0.3 \end{array}$	34 ± 0.41 $7L$ $5 -8.08 = -8.44 = -7.85 = -8.28 = -3.28 = -$	$ \begin{array}{c} -9.31 \pm 0. \\ \hline 11 \\ \pm 0.25 \\ \pm 0.26 \\ \pm 0.40 \\ \pm 0.31 \\ \pm 0.30 \\ \pm 0.35 \\ \pm 0.35 \\ \pm 0.35 \\ \pm 0.52 \\ \pm 0.23 \\ \pm 0.40 \\ \pm 0.30 \\ \end{array} $
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST GRAPH MIMO3 MoLDO PASITH REINVE SCREEN SELFIES V	$\begin{array}{c} -9.19 \pm 0.49 \\ \hline \\ 100 & -7.45 \\ 004 & -10.8 \\ 004 & -10.8 \\ 004 & -11.5 \\ 004 & -5.47 \\ 004 & -5.47 \\ 005 & -9.12 \\ 005 & -9.12 \\ 005 & -9.12 \\ 005 & -9.17 \\ 005 $	$\begin{array}{c} -9.27 \pm 0 \\ \hline \\ \text{UNN} \\ \hline \pm 0.52 \\ 9 \pm 0.14 \\ \hline 6 \pm 0.40 \\ \pm 0.63 \\ \pm 0.50 \\ \pm 0.34 \\ \pm 0.54 \\ \pm 0.33 \\ \hline \pm 0.28 \\ \pm 0.41 \\ 0 \pm 0.56 \\ \pm 0.38 \\ \pm 0.44 \end{array}$	$\begin{array}{c} 5\text{MO4} \\ \hline 5\text{MO4} \\ \hline -7.98 \pm 0.4 \\ -10.20 \pm 0.1 \\ -9.55 \pm 0.4 \\ -9.39 \pm 0.5 \\ -9.30 \pm 0.4 \\ -8.66 \pm 0.4 \\ -9.32 \pm 0.4 \\ -5.80 \pm 0.3 \\ -9.24 \pm 0.3 \\ -7.98 \pm 0.5 \\ -9.38 \pm 0.3 \\ -8.59 \pm 0.4 \end{array}$	$\begin{array}{c} 34 \pm 0.41 \\ \hline 7L \\ \hline 5 & -8.08 \\ 16 & -8.44 \\ 5 & -7.85 \\ 6 & -8.28 \\ 3 & -7.81 \\ 1 & -7.15 \\ 1 & -7.15 \\ 1 & -7.83 \\ 3 & -5.98 \\ 3 & -5.98 \\ 3 & -7.68 \\ 8 & -6.64 \\ 4 & -7.67 \\ 0 & -7.15 \\ \end{array}$	$ \begin{array}{c} -9.31 \pm 0. \\ \hline 11 \\ \pm 0.25 \\ \pm 0.26 \\ \pm 0.40 \\ \pm 0.31 \\ \pm 0.30 \\ \pm 0.35 \\ \pm 0.35 \\ \pm 0.35 \\ \pm 0.52 \\ \pm 0.23 \\ \pm 0.40 \\ \pm 0.30 \\ \pm 0.37 \\ \end{array} $
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST GRAPH MIMO3 MoLDO PASITH REINVE SCREEN SELFIES V SMILES	$\begin{array}{c c} -9.19 \pm 0.49 \\ \hline \\ $	$\begin{array}{c} -9.27 \pm 0 \\ \hline \\ \text{UNN} \\ \hline \pm 0.52 \\ 9 \pm 0.14 \\ \hline 6 \pm 0.40 \\ \pm 0.63 \\ \pm 0.50 \\ \pm 0.34 \\ \pm 0.54 \\ \pm 0.33 \\ \hline \pm 0.28 \\ \pm 0.41 \\ \pm 0.56 \\ \pm 0.38 \\ \pm 0.44 \\ \pm 0.35 \end{array}$	$\begin{array}{c} 0.39 & -9.3 \\ \hline \\ 5 \text{MO4} \\ \hline \\ -7.98 \pm 0.4 \\ -10.20 \pm 0.1 \\ -9.55 \pm 0.4 \\ -9.39 \pm 0.5 \\ -9.30 \pm 0.4 \\ -8.66 \pm 0.4 \\ -9.32 \pm 0.4 \\ -5.80 \pm 0.3 \\ -9.24 \pm 0.3 \\ -7.98 \pm 0.5 \\ -9.38 \pm 0.3 \\ -8.59 \pm 0.4 \\ -8.47 \pm 0.4 \end{array}$	$\begin{array}{c} 34 \pm 0.41 \\ \hline 7L \\ \hline 5 & -8.08 \\ 16 & -8.44 \\ 5 & -7.85 \\ 6 & -8.28 \\ 3 & -7.81 \\ 1 & -7.15 \\ 1 & -7.15 \\ 1 & -7.83 \\ 3 & -5.98 \\ 3 & -5.98 \\ 3 & -7.68 \\ 8 & -6.64 \\ 4 & -7.67 \\ 0 & -7.15 \\ 5 & -7.04 \\ \end{array}$	$\begin{array}{c} -9.31 \pm 0. \\ \hline \\ \hline \\ 11 \\ \pm 0.25 \\ \pm 0.26 \\ \pm 0.40 \\ \pm 0.31 \\ \pm 0.30 \\ \pm 0.35 \\ \pm 0.35 \\ \pm 0.35 \\ \pm 0.52 \\ \pm 0.23 \\ \pm 0.40 \\ \pm 0.30 \\ \pm 0.37 \\ \pm 0.30 \end{array}$
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST GRAPH MIMOS MoLDO PASITH REINVE SCREEN SELFIES V SMILES SMILES LS	-9.19 ± 0.49 L 4 DD -7.45 0W4 -10.8 MOL -11.5 LOW -6.91 SN -8.63 -9.13 GA -8.43 SA -9.11 QN -5.47 EA -9.02 ENT -7.89 ING -9.17 AE BO -8.34 GA -8.25 TM HC -8.87	$\begin{array}{c} -9.27 \pm 0 \\ \hline \\ \text{UNN} \\ \hline \pm 0.52 \\ 9 \pm 0.14 \\ \hline 6 \pm 0.40 \\ \pm 0.63 \\ \pm 0.50 \\ \pm 0.34 \\ \pm 0.54 \\ \pm 0.33 \\ \hline \pm 0.28 \\ \pm 0.41 \\ \pm 0.56 \\ \pm 0.38 \\ \pm 0.44 \\ \pm 0.35 \\ \pm 0.31 \end{array}$	$\begin{array}{c} 0.39 & -9.3 \\ \hline \\ 5 \text{MO4} \\ \hline \\ -7.98 \pm 0.4 \\ -10.20 \pm 0.1 \\ -9.55 \pm 0.4 \\ -9.39 \pm 0.5 \\ -9.30 \pm 0.4 \\ -8.66 \pm 0.4 \\ -9.32 \pm 0.4 \\ -5.80 \pm 0.3 \\ -9.24 \pm 0.3 \\ -7.98 \pm 0.5 \\ -9.38 \pm 0.3 \\ -8.59 \pm 0.4 \\ -8.47 \pm 0.4 \\ -9.00 \pm 0.4 \end{array}$	$\begin{array}{c} 34 \pm 0.41 \\ \hline 7L \\ \hline 5 & -8.08 \\ \hline 5 & -8.08 \\ \hline 16 & -8.44 \\ \hline 5 & -7.85 \\ \hline 6 & -8.28 \\ \hline 3 & -7.81 \\ \hline 1 & -7.15 \\ \hline 1 & -7.15 \\ \hline 3 & -5.98 \\ \hline 3 & -5.98 \\ \hline 3 & -5.98 \\ \hline 3 & -7.68 \\ \hline 8 & -6.64 \\ \hline 4 & -7.67 \\ \hline 0 & -7.15 \\ \hline 5 & -7.04 \\ \hline 4 & -7.46 \\ \hline \end{array}$	$\begin{array}{c} -9.31 \pm 0.3\\ \hline \\ \hline \\ 11\\ \pm 0.25\\ \pm 0.26\\ \pm 0.40\\ \pm 0.31\\ \pm 0.30\\ \pm 0.35\\ \pm 0.35\\ \pm 0.35\\ \pm 0.35\\ \pm 0.52\\ \pm 0.23\\ \pm 0.40\\ \pm 0.30\\ \pm 0.37\\ \pm 0.30\\ \pm 0.30\\ \pm 0.27\end{array}$

Table 5. Top 100 Docking score for each target protein.

MODEL	11EP	3eml	3ny	8	4rlu
3DSBDD	-8.01 ± 0.52	-9.15 ± 0.42	$-8.60 \pm$	0.72 -8	$.71 \pm 0.5$
AUTOGROW4	$\textbf{-11.80}\pm0.84$	-12.14 ± 0.40) -10.84 ±	-10	0.73 ± 0.1
POCKET2MOL	$\textbf{-9.36} \pm 0.36$	-11.30 ± 0.44	+ -10.73 ±	-9 -9	$.95 \pm 0.3$
POCKETFLOW	-11.20 ± 0.58	-8.03 ± 0.60	-7.69 \pm	0.38 -8	$.64 \pm 0.4$
ResGen	-10.03 ± 0.44	-6.43 ± 1.14	-10.04 ±	-10	0.27 ± 0.21
DST	-9.72 ± 0.53	-9.74 ± 0.40	-9.77 \pm	0.35 -9	$.91 \pm 0.4$
GRAPH GA	-8.67 ± 0.65	-8.80 ± 0.51	-8.85 \pm	0.55 -9	$.04 \pm 0.0$
MIMOSA	-9.74 ± 0.53	-9.73 ± 0.40	-9.77 \pm	0.35 -9	$.90 \pm 0.4$
MolDQN	$\textbf{-6.03} \pm 0.36$	-5.85 ± 0.36	-5.94 \pm	0.57 -5	$.82 \pm 0.4$
PASITHEA	-9.72 ± 0.52	-9.65 ± 0.32	-9.77 \pm	0.43 -9	$.88 \pm 0.4$
REINVENT	-7.59 ± 1.23	-7.61 ± 1.50	-7.81 \pm	1.16 -7	$.80 \pm 1.$
SCREENING	-9.84 ± 0.50	-9.76 ± 0.51	-9.80 \pm	0.44 -9	$.91 \pm 0.4$
SELFIES VAE BO	-8.64 ± 0.75	-8.75 ± 0.59	-8.86 \pm	0.59 -8	$.87 \pm 0.3$
SMILES GA	-8.50 ± 0.50	-8.23 ± 0.57	-8.74 \pm	0.54 -8	$.77 \pm 0.3$
SMILES LSTM HC	-9.14 ± 0.58	-9.44 ± 0.44	-9.20 \pm	0.52 -9	$.35 \pm 0.3$
	0 (1) 0 (7	0 0	0 0 1		00 1 0
SMILES-VAE-BO	-8.64 ± 0.67	-8.75 ± 0.61	$-8.86 \pm$	0.58 -8	$.88 \pm 0.3$
SMILES-VAE-BO	-8.64 ± 0.67	-8.75 ± 0.61	-8.86 ±	0.58 -8	$.88 \pm 0.3$
SMILES-VAE-BO	-8.64 ± 0.67	-8.75 ± 0.61	-8.86± 5мо4	0.58 -8 7L11	.88 ± 0.:
SMILES-VAE-BO Mode 3DSBE	-8.64 ± 0.67 L 41 DD -6.71	-8.75 ± 0.61 JNN ± 0.86 -7.5	-8.86 ± 5м04 50 ± 0.62	0.58 - 8 7L11 -7.86 ± 0.2	$\frac{.88 \pm 0.3}{29}$
SMILES-VAE-BO Mode 3DSBE AutoGR	$ \begin{array}{c} -8.64 \pm 0.67 \\ \hline L & 41 \\ DD & -6.71 \\ ow4 & -10.81 \\ \end{array} $	$ \begin{array}{r} -8.75 \pm 0.61 \\ \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	$-8.86 \pm$ 5M04 50 ± 0.62 10 ± 0.16	$\begin{array}{c} 0.58 & -8 \\ \hline 7 L11 \\ -7.86 \pm 0.2 \\ -8.32 \pm 0.2 \end{array}$	$\frac{.88 \pm 0.3}{$
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2	-8.64 ± 0.67 L 41 DD -6.71 ow4 -10.83 MOL -11.22	-8.75 ± 0.61 UNN $\pm 0.86 -7.5$ $1 \pm 0.13 -10.$ $2 \pm 0.45 -9.2$	-8.86 ± 5004 50 ± 0.62 10 ± 0.16 20 ± 0.48	0.58 -8 7L11 -7.86 ± 0.2 -8.32 ± 0.2 -8.78 ± 0.4	$.88 \pm 0.3$
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF	-8.64 ± 0.67 L 44 DD -6.71 OW4 -10.8 MOL -11.22 CLOW -6.58	$\begin{array}{c} -8.75 \pm 0.61 \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	$-8.86 \pm 0.500 \pm 0.62$ 500 ± 0.62 10 ± 0.16 20 ± 0.48 70 ± 0.49	$\begin{array}{c} 0.58 & -8 \\ \hline \\ 7L11 \\ -7.86 \pm 0.2 \\ -8.32 \pm 0.2 \\ -8.78 \pm 0.4 \\ -7.62 \pm 0.3 \end{array}$	$.88 \pm 0$
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe	-8.64 ± 0.67 L 44 DD -6.71 OW4 -10.8 MOL -11.22 CLOW -6.58 EN -8.13	-8.75 ± 0.61 UNN $\pm 0.86 -7.5$ $1 \pm 0.13 -10.$ $2 \pm 0.45 -9.2$ $\pm 0.56 -6.7$ $\pm 0.64 -8.8$	-8.86 ± 0.62 55004 50 ± 0.62 10 ± 0.16 20 ± 0.48 70 ± 0.49 88 ± 0.66	$\begin{array}{c} 0.58 & -8 \\ \hline \\ 7L11 \\ -7.86 \pm 0.2 \\ -8.32 \pm 0.2 \\ -8.78 \pm 0.4 \\ -7.62 \pm 0.3 \\ -7.97 \pm 0.3 \end{array}$	
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST	-8.64 ± 0.67 L 44 DD -6.71 OW4 -10.8 MOL -11.22 LOW -6.58 SN -8.13 -8.83	$\begin{array}{c} -8.75 \pm 0.61 \\ \hline \\ \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	-8.86 ± 55004 $\overline{500 \pm 0.62}$ 10 ± 0.16 $\overline{20 \pm 0.48}$ $\overline{20 \pm 0.49}$ $\overline{38 \pm 0.66}$ $\overline{33 \pm 0.41}$	$\begin{array}{c} 0.58 & -8 \\ \hline 7 \text{L11} \\ \hline -7.86 \pm 0.2 \\ -8.32 \pm 0.2 \\ \hline -8.78 \pm 0.4 \\ -7.62 \pm 0.3 \\ -7.97 \pm 0.3 \\ -7.55 \pm 0.3 \end{array}$	
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST GRAPH ($\begin{array}{c c} -8.64 \pm 0.67 \\ \hline \\ L & 41 \\ \hline \\ DD & -6.71 \\ OW4 & -10.8 \\ \hline \\ MOL & -11.22 \\ \hline \\ Clow & -6.58 \\ \hline \\ SN & -8.13 \\ -8.83 \\ \hline \\ GA & -8.03 \\ \end{array}$	$\begin{array}{c} -8.75 \pm 0.61 \\ \hline \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	$-8.86 \pm \frac{1000}{5000}$ 5004 5004 5004 $5000000000000000000000000000000000000$	$\begin{array}{c} 0.58 & -8 \\ \hline 7 \text{L11} \\ \hline -7.86 \pm 0.2 \\ -8.32 \pm 0.2 \\ -8.78 \pm 0.4 \\ -7.62 \pm 0.3 \\ -7.97 \pm 0.3 \\ -7.55 \pm 0.3 \\ -6.87 \pm 0.4 \end{array}$	$ \begin{array}{c} $
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 Pocket5 ResGe DST GRAPH 0 MIMOS	$\begin{array}{c c} -8.64 \pm 0.67 \\ \hline \\ L & 41 \\ \hline \\ DD & -6.71 \\ 0w4 & -10.8 \\ \hline \\ MOL & -11.22 \\ \hline \\ Clow & -6.58 \\ \hline \\ MOL & -8.13 \\ \hline \\ -8.83 \\ GA & -8.03 \\ \hline \\ SA & -8.81 \end{array}$	$\begin{array}{c} -8.75 \pm 0.61 \\ \hline \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	$-8.86 \pm \frac{1000}{5000}$ 5004 60 ± 0.62 10 ± 0.16 60 ± 0.48 60 ± 0.49 88 ± 0.66 63 ± 0.41 22 ± 0.53 85 ± 0.41	$\begin{array}{c} 0.58 & -8 \\ \hline 7 1 \\ -7.86 \pm 0.2 \\ -8.32 \pm 0.2 \\ -8.78 \pm 0.4 \\ -7.62 \pm 0.3 \\ -7.97 \pm 0.3 \\ -7.55 \pm 0.3 \\ -6.87 \pm 0.4 \\ -7.56 \pm 0.3 \end{array}$	$ \begin{array}{c} $
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST GRAPH (MIMOS MOLD(-8.64 ± 0.67 L 44 DD -6.71 0W4 -10.8 MOL -11.22 LOW -6.58 EN -8.13 -8.83 GA -8.03 SA -8.81 QN -5.22	$\begin{array}{c} -8.75 \pm 0.61 \\ \hline \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	$-8.86 \pm \frac{10}{5004}$ $\overline{5004}$ $$	$\begin{array}{c} 0.58 & -8 \\ \hline 7 1 1 \\ \hline -7.86 \pm 0.2 \\ -8.32 \pm 0.2 \\ -8.78 \pm 0.4 \\ -7.62 \pm 0.3 \\ -7.97 \pm 0.3 \\ -7.55 \pm 0.3 \\ -6.87 \pm 0.4 \\ -7.56 \pm 0.3 \\ -5.51 \pm 0.6 \end{array}$	$ \begin{array}{c} .88 \pm 0.: \\ .29 \\ .22 \\ .44 \\ .33 \\ .39 \\ .36 \\ .40 \\ .37 \\ .51 \\ \end{array} $
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST GRAPH (MIMOS MOLDO PASITH	$\begin{array}{c c} -8.64 \pm 0.67 \\ \hline \\ L & 41 \\ \hline \\ DD & -6.71 \\ 0W4 & -10.81 \\ MOL & -11.22 \\ FLOW & -6.58 \\ EN & -8.13 \\ -8.83 \\ GA & -8.81 \\ RSA & -8.81 \\ SA & -8.81 \\ QN & -5.22 \\ EA & -8.72 \\ \end{array}$	$\begin{array}{c} -8.75 \pm 0.61 \\ \hline \\ \hline \\ \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	$-8.86 \pm \frac{10}{5004}$ $\overline{5004}$ $$	$\begin{array}{c} 0.58 & -8 \\ \hline 7 1 1 \\ \hline -7.86 \pm 0.2 \\ -8.32 \pm 0.2 \\ -8.78 \pm 0.4 \\ -7.62 \pm 0.3 \\ -7.97 \pm 0.3 \\ -7.55 \pm 0.3 \\ -7.55 \pm 0.4 \\ -7.56 \pm 0.3 \\ -5.51 \pm 0.6 \\ -7.46 \pm 0.2 \end{array}$	$ \begin{array}{c} .88 \pm 0.3 \\ .29 \\ .22 \\ .44 \\ .33 \\ .39 \\ .36 \\ .40 \\ .37 \\ .51 \\ .29 \\ .29 \\ .37 \\ .51 \\ .29 \\ .37 \\ .51 \\ .29 \\ .37 \\ .51 \\ .29 \\ .37 \\ .51 \\ .29 \\ .37 \\ .51 \\ .29 \\ .37 \\ .3$
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST GRAPHO MIMOS MoLDO PASITH REINVE	$\begin{array}{c c} -8.64 \pm 0.67 \\ \hline \\ L & 41 \\ \hline \\ DD & -6.71 \\ \hline \\ OW4 & -10.81 \\ \hline \\ MOL & -11.22 \\ \hline \\ LOW & -6.58 \\ \hline \\ SI & -8.13 \\ \hline \\ SI & -8.83 \\ \hline \\ SI & -8.83 \\ \hline \\ SA & -8.81 \\ \hline \\ \\ \\ SA & -8.81 \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	$\begin{array}{c} -8.75 \pm 0.61 \\ \hline \\ \hline \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	$\begin{array}{r} -8.86 \pm \\ \hline \\ 5\text{MO4} \\ \hline \hline \\ 60 \pm 0.62 \\ 10 \pm 0.16 \\ 00 \pm 0.48 \\ 00 \pm 0.49 \\ 88 \pm 0.66 \\ 03 \pm 0.41 \\ 22 \pm 0.53 \\ 05 \pm 0.41 \\ 47 \pm 0.40 \\ 04 \pm 0.38 \\ 6 \pm 1.06 \end{array}$	$\begin{array}{c} 0.58 & -8 \\ \hline 7 1 \\ \hline -7.86 \pm 0.2 \\ -8.32 \pm 0.2 \\ -8.78 \pm 0.4 \\ -7.62 \pm 0.3 \\ -7.75 \pm 0.3 \\ -7.75 \pm 0.3 \\ -7.55 \pm 0.3 \\ -5.51 \pm 0.4 \\ -7.56 \pm 0.3 \\ -5.51 \pm 0.4 \\ -7.46 \pm 0.2 \\ -6.06 \pm 0.3 \end{array}$	$ \begin{array}{c} .88 \pm 0.3 \\ .29 \\ .22 \\ .44 \\ .33 \\ .39 \\ .36 \\ .40 \\ .37 \\ .51 \\ .29 \\ .75 \\ .5 $
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST GRAPHO MIMOS MoLDO PASITH REINVE SCREEN	$\begin{array}{c c} -8.64 \pm 0.67 \\ \hline \\ L & 41 \\ \hline \\ DD & -6.71 \\ \hline \\ OW4 & -10.81 \\ \hline \\ MOL & -11.22 \\ \hline \\ ILOW & -6.58 \\ \hline \\ SI & -8.13 \\ \hline \\ SI & -8.83 \\ \hline \\ GA & -8.03 \\ \hline \\ SA & -8.81 \\ \hline \\ QN & -5.22 \\ \hline \\ EA & -8.72 \\ \hline \\ EA & -8.72 \\ \hline \\ ENT & -7.14 \\ \hline \\ ING & -8.85 \end{array}$	$\begin{array}{c} -8.75 \pm 0.61 \\ \hline \\ \hline \\ \text{UNN} \\ \hline \\ \pm 0.86 & -7.5 \\ 1 \pm 0.13 & -10. \\ 2 \pm 0.45 & -9.2 \\ \pm 0.56 & -6.7 \\ \pm 0.56 & -6.7 \\ \pm 0.39 & -9.0 \\ \pm 0.39 & -9.0 \\ \pm 0.33 & -5.4 \\ \pm 0.39 & -9.0 \\ \pm 0.43 & -8.9 \\ \pm 0.97 & -7.1 \\ \pm 0.43 & -9.1 \end{array}$	$\begin{array}{r} -8.86 \pm \\ \hline \\ 5\text{MO4} \\ \hline \\ $	$\begin{array}{c} 0.58 & -8 \\ \hline 7 1 \\ \hline -7.86 \pm 0.2 \\ -8.32 \pm 0.2 \\ -8.78 \pm 0.4 \\ -7.62 \pm 0.3 \\ -7.97 \pm 0.3 \\ -7.55 \pm 0.3 \\ -7.55 \pm 0.3 \\ -5.51 \pm 0.4 \\ -7.56 \pm 0.3 \\ -5.51 \pm 0.4 \\ -7.46 \pm 0.2 \\ -6.06 \pm 0.3 \\ -7.44 \pm 0.3 \end{array}$	$ \begin{array}{c} .88 \pm 0.3 \\ \hline .9 \\ 22 \\ 22 \\ 44 \\ 33 \\ 39 \\ 36 \\ 40 \\ 37 \\ 51 \\ 29 \\ 75 \\ 32 \end{array} $
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST GRAPHO MIMOS MoLDO PASITH REINVE SCREEN SELFIES V	$\begin{array}{c c} -8.64 \pm 0.67 \\ \hline \\ L & 41 \\ \hline \\ DD & -6.71 \\ \hline \\ OW4 & -10.81 \\ \hline \\ MOL & -11.22 \\ \hline \\ ILOW & -6.58 \\ \hline \\ SN & -8.13 \\ \hline \\ SN & -8.83 \\ \hline \\ GA & -8.83 \\ \hline \\ GA & -8.83 \\ \hline \\ SA & -8.81 \\ \hline \\ QN & -5.22 \\ \hline \\ EA & -8.72 \\ \hline \\ EA & -8.72 \\ \hline \\ ENT & -7.14 \\ \hline \\ ING & -8.85 \\ \hline \\ AE BO & -7.93 \end{array}$	$\begin{array}{c} -8.75 \pm 0.61 \\ \hline \\ \hline \\ \text{UNN} \\ \hline \pm 0.86 & -7.5 \\ 1 \pm 0.13 & -10. \\ 2 \pm 0.45 & -9.2 \\ \pm 0.56 & -6.7 \\ \pm 0.56 & -8.2 \\ \pm 0.39 & -9.0 \\ \pm 0.56 & -8.2 \\ \pm 0.39 & -9.0 \\ \pm 0.33 & -5.4 \\ \pm 0.43 & -8.9 \\ \pm 0.97 & -7.1 \\ \pm 0.43 & -9.1 \\ \pm 0.52 & -8.1 \end{array}$	$\begin{array}{r} -8.86 \pm \\ \hline \\ 5\text{MO4} \\ \hline \\ $	$\begin{array}{c} 0.58 & -8 \\ \hline 7 1 \\ \hline -7.86 \pm 0.2 \\ -8.32 \pm 0.2 \\ -8.78 \pm 0.4 \\ -7.62 \pm 0.3 \\ -7.97 \pm 0.3 \\ -7.97 \pm 0.3 \\ -7.55 \pm 0.3 \\ -6.87 \pm 0.4 \\ -7.56 \pm 0.3 \\ -5.51 \pm 0.6 \\ -7.46 \pm 0.2 \\ -6.06 \pm 0.3 \\ -7.44 \pm 0.3 \\ -6.81 \pm 0.4 \end{array}$	$ \begin{array}{c} .88 \pm 0.3 \\ .29 \\ .22 \\ .44 \\ .33 \\ .39 \\ .36 \\ .40 \\ .37 \\ .51 \\ .29 \\ .75 \\ .32 \\ .44 \\ .44 \\ $
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST GRAPHO MIMO2 MoLDO PASITH REINVE SCREEN SELFIES V SMILES	$\begin{array}{c c} -8.64 \pm 0.67 \\ \hline \\ L & 41 \\ \hline \\ DD & -6.71 \\ \hline \\ OW4 & -10.81 \\ \hline \\ MOL & -11.22 \\ \hline \\ CW & -6.58 \\ \hline \\ EN & -8.13 \\ \hline \\ CW & -6.58 \\ \hline \\ EN & -8.83 \\ \hline \\ GA & -8.81 \\ \hline \\ QN & -5.22 \\ \hline \\ EA & -8.72 \\ \hline \\ EA & -8.72 \\ \hline \\ ENT & -7.14 \\ \hline \\ ING & -8.85 \\ \hline \\ AE BO & -7.93 \\ \hline \\ GA & -7.97 \end{array}$	$\begin{array}{c} -8.75 \pm 0.61 \\ \hline \\ \hline \\ \text{UNN} \\ \hline \\ \pm 0.86 & -7.5 \\ 1 \pm 0.13 & -10. \\ 2 \pm 0.45 & -9.2 \\ \pm 0.56 & -6.7 \\ \pm 0.56 & -6.7 \\ \pm 0.39 & -9.0 \\ \pm 0.39 & -9.0 \\ \pm 0.33 & -5.4 \\ \pm 0.39 & -9.1 \\ \pm 0.43 & -8.9 \\ \pm 0.97 & -7.1 \\ \pm 0.43 & -9.1 \\ \pm 0.52 & -8.1 \\ \pm 0.37 & -8.1 \end{array}$	$\begin{array}{r} -8.86 \pm \\ \hline \\ 5M04 \\ \hline \\ $	$\begin{array}{c} 0.58 & -8 \\ \hline 7 \text{L11} \\ \hline -7.86 \pm 0.2 \\ -8.32 \pm 0.2 \\ -8.78 \pm 0.4 \\ -7.62 \pm 0.3 \\ -7.97 \pm 0.3 \\ -7.97 \pm 0.3 \\ -7.55 \pm 0.3 \\ -6.87 \pm 0.4 \\ -7.56 \pm 0.3 \\ -5.51 \pm 0.6 \\ -7.46 \pm 0.2 \\ -6.06 \pm 0.7 \\ -7.44 \pm 0.3 \\ -6.81 \pm 0.4 \\ -6.83 \pm 0.3 \\ \end{array}$	$ \begin{array}{c} $
SMILES-VAE-BO Mode 3DSBE AutoGr Pocket2 PocketF ResGe DST GRAPHO MIMOS MoLDO PASITH REINVE SCREEN SELFIES V SMILES SMILES LS	$\begin{array}{c c} -8.64 \pm 0.67 \\ \hline \\ L & 41 \\ \hline \\ DD & -6.71 \\ \hline \\ OW4 & -10.81 \\ \hline \\ MOL & -11.22 \\ \hline \\ CW & -6.58 \\ \hline \\ EN & -8.13 \\ \hline \\ CW & -6.58 \\ \hline \\ EN & -8.83 \\ \hline \\ GA & -8.03 \\ \hline \\ SA & -8.81 \\ \hline \\ QN & -5.22 \\ \hline \\ EA & -8.72 \\ \hline \\ EA & -8.72 \\ \hline \\ ENT & -7.14 \\ \hline \\ ING & -8.85 \\ \hline \\ AE BO & -7.93 \\ \hline \\ GA & -7.97 \\ \hline \\ TM HC & -8.53 \\ \hline \end{array}$	$\begin{array}{c} -8.75 \pm 0.61 \\ \hline \\ -8.75 \pm 0.61 \\ \hline \\ \pm 0.86 & -7.5 \\ 1 \pm 0.13 & -10. \\ 2 \pm 0.45 & -9.2 \\ \pm 0.56 & -6.7 \\ \pm 0.56 & -8.2 \\ \pm 0.39 & -9.0 \\ \pm 0.39 & -9.0 \\ \pm 0.33 & -5.4 \\ \pm 0.39 & -9.0 \\ \pm 0.43 & -8.9 \\ \pm 0.43 & -8.1 \\ \pm 0.43 & -9.1 \\ \pm 0.52 & -8.1 \\ \pm 0.37 & -8.1 \\ \pm 0.42 & -8.0 \end{array}$	$\begin{array}{r} -8.86 \pm \\ \hline \\ \hline \\ 5M04 \\ \hline \\ $	$\begin{array}{c} 0.58 & -8 \\ \hline 7 \text{L11} \\ \hline -7.86 \pm 0.2 \\ -8.32 \pm 0.2 \\ -8.78 \pm 0.4 \\ -7.62 \pm 0.3 \\ -7.97 \pm 0.3 \\ -7.55 \pm 0.4 \\ -7.55 \pm 0.4 \\ -7.56 \pm 0.4 \\ -7.56 \pm 0.4 \\ -7.46 \pm 0.2 \\ -6.06 \pm 0.7 \\ -7.44 \pm 0.3 \\ -6.81 \pm 0.4 \\ -6.83 \pm 0.3 \\ -7.20 \pm 0.3 \\ -7.20 \pm 0.3 \\ \end{array}$	$ \begin{array}{c} $

MODEL	1 iep	ЗЕМ	L 3N	Y8 4	4rlu
3DSBDD	1.23	2.94	2.0	56	0.60
AUTOGROW4	3.47	2.95	5 2.0	53	2.86
POCKET2MOL	2.32	3.83	4.	14	3.50
POCKETFLOW	6.10	6.10 4.86		57	4.38
ResGen	3.91	10.7	2 5.4	17	3.50
DST	3.72	3.72	3.7	72	3.72
graph GA	3.06	3.32	2. 3.0	57	3.70
MIMOSA	3.72	3.72	3.7	72	3.72
MolDQN	0.36	0.55	0.3	36	0.33
PASITHEA	3.22	3.22	3.2	22	3.22
REINVENT	3.90	3.90) 3.9	90	3.90
SCREENING	3.67	3.67	3.0	57	3.67
SELFIES VAE BO	3.22	3.22	2. 3.2	22	3.22
SMILES GA	3.00	3.00) 3.4	40	3.00
SMILES LSTM HC	6.51	6.51	6.5	51	6.51
SMILES-VAE-BO	3.22	3.22	2 3.2	22	3.22
					_
MODEL	4u	INN	5мо4	7l1	1
3DSBDD	2.	69	2.10	3.30	6
AUTOGROW4	2.	72	2.93	2.8	1
POCKET2MOL	2.	86	3.66	3.92	2
POCKETFLOW	2.	16	2.26	5.2	1
ResGen	3.	40	3.54	3.23	3
DST	3.	72	3.72	3.72	2
graph GA	3.	13	3.01	3.70	6
MIMOSA	3.	72	3.72	3.72	2
molDQN	-0	.26	1.00	0.50	0
PASITHEA	3.	22	3.22	3.22	2
REINVENT	3.	90	3.90	3.90	0
SCREENING	3.	67	3.67	3.6	7
SELFIES VAE BO	O 3.	22	3.22	3.22	2
SMILES GA	3.	40	3.00	3.00	0
SMILES LSTM H	C 6	51	6 51	6.5	1
	U. U.	51	0.51	0.0	1

Table 6. Top 1 LogP score for each target protein.

Table 7. Top 10 LogP score for each target protein.

Model	1iep	3	3eml	3ny	8	41
3DSBDD	0.16 ± 0	.37 1.59	9 ± 0.67	$1.89 \pm$	0.51	-0.18
AUTOGROW4	3.36 ± 0	.05 2.72	2 ± 0.13	$2.63~\pm$	0.00	2.86
POCKET2MOL	2.10 ± 0	.13 3.59	9 ± 0.15	$3.66 \pm$	0.22	3.15
POCKETFLOW	5.81 ± 0	.17 2.21	1 ± 0.92	$2.01 \pm$	0.32	3.79
ResGen	3.58 ± 0	.24 6.62	2 ± 1.55	$4.91 \pm$	0.32	3.05
DST	3.13 ± 0	.21 3.13	3 ± 0.21	$3.13 \pm$	0.21	3.13
GRAPH GA	2.79 ± 0	.20 2.91	1 ± 0.23	$3.14 \pm$	0.28	3.00
MIMOSA	3.13 ± 0	.21 3.13	3 ± 0.21	$3.13 \pm$	0.21	3.13
MOLDQN	-0.75 ± 0	0.49 -0.5	2 ± 0.48	-0.75 \pm	0.50	-0.35
PASITHEA	3.03 ± 0	.09 3.03	3 ± 0.09	$3.03 \pm$	0.09	3.03
REINVENT	2.50 ± 0	.51 2.47	7 ± 0.53	$2.50~\pm$	0.51	2.47
SCREENING	3.30 ± 0	.18 3.30	0 ± 0.18	$3.30 \pm$	0.18	3.30
SELFIES VAE BO	2.68 ± 0	.33 2.68	8 ± 0.33	$2.68 \pm$	0.33	2.68
SMILES GA	2.32 ± 0	.30 2.02	2 ± 0.36	$2.52 \pm$	0.43	2.17
SMILES LSTM HC	4.72 ± 0	.85 4.72	2 ± 0.85	$4.72~\pm$	0.85	4.72
SMILES-VAE-BO	2.68 ± 0	33 269	8 ± 0.33	$2.68 \pm$	0.33	2.68
Shires of the bo			5 ± 0.55	2.00 ±	0.55	2.00
		2.00	5 ± 0.55	2.00 ±	0.55	2.00
MODEL	,	4UNN	<u>5 т 0.55</u> 5м	04	7L	11
Model 3DSBD	D 2	$\frac{4000}{2.02 \pm 0.28}$	5 ± 0.33 5м 3 1.40 ±	04 = 0.39	7L1 2.46 ±	11
Model 3DSBD AutoGro	D 22 Dw4 22	$\frac{4000}{2.02 \pm 0.28}$	5M 5M 5 1.40 ± 5 2.86 ±	04 = 0.39 = 0.06	7L1 2.46 ± 2.77 ±	11 = 0.59 = 0.02
Model 3DSBD AutoGrc Pocket2M	D 2 0w4 2 MOL 2	$\frac{4000}{4000}$ $\frac{2.02 \pm 0.28}{2.68 \pm 0.05}$ $\frac{2.68 \pm 0.05}{2.56 \pm 0.16}$	5M 5M 5 1.40 ± 5 2.86 ± 5 3.23 ±	04 = 0.39 = 0.06 = 0.22	7L1 2.46 ± 2.77 ± 3.46 ±	11 = 0.59 = 0.02 = 0.19
MODEL 3DSBD AUTOGRC POCKET2N POCKETFI	D 2 DW4 2 MOL 2 LOW 1	$\frac{4\text{UNN}}{4\text{UNN}}$ 2.02 ± 0.28 2.68 ± 0.05 2.56 ± 0.16 1.44 ± 0.28	5M 5M 5 1.40 ± 5 2.86 ± 5 3.23 ± 3 1.00 ±	04 = 0.39 = 0.06 = 0.22 = 0.47	7L1 2.46 ± 2.77 ± 3.46 ± 4.79 ±	11 0.59 0.02 0.19 0.26
MODEL 3DSBD AUTOGRC POCKET2M POCKETFI RESGET	D 22 DW4 22 MOL 22 LOW 1 N 22	$\frac{4\text{UNN}}{4\text{UNN}}$ 2.02 ± 0.28 2.68 ± 0.05 2.56 ± 0.16 1.44 ± 0.28 2.19 ± 0.60	5M 5M 5 1.40 ± 5 2.86 ± 5 3.23 ± 3 1.00 ± 0 2.71 ±	04 = 0.39 = 0.06 = 0.22 = 0.47 = 0.49	7L1 2.46 ± 2.77 ± 3.46 ± 4.79 ± 2.74 ±	11 0.59 0.02 0.19 0.26 0.27
MODEL 3DSBD AUTOGRC POCKET2N POCKETFI RESGEI DST	D 2 W4 2 AOL 2 LOW 1 N 2 3	$ \frac{4000}{4000} 400$	5M 5M 5 5 3 1.40 ± 5 2.86 ± 5 3.23 ± 3 1.00 ± 0 2.71 ± 3.13 ±	$\begin{array}{c} 0.00 \pm \\ 0.00 $	$ \begin{array}{r} 7L1 \\ 2.46 \pm \\ 2.77 \pm \\ 3.46 \pm \\ 4.79 \pm \\ 2.74 \pm \\ 3.13 \pm \\ \end{array} $	$\begin{array}{c} 11\\ = 0.59\\ = 0.02\\ = 0.19\\ = 0.26\\ = 0.27\\ = 0.21\\ \end{array}$
MODEL 3DSBD AUTOGRC POCKET2M POCKETFI RESGEI DST GRAPH C	D 2 W4 2 AOL 2 LOW 1 N 2 GA 2	$\frac{4000}{4000}$ $\frac{4000}{2.02 \pm 0.28}$ $\frac{2.02 \pm 0.28}{2.68 \pm 0.05}$ $\frac{2.56 \pm 0.16}{2.56 \pm 0.16}$ $\frac{1.44 \pm 0.28}{2.19 \pm 0.60}$ $\frac{3.13 \pm 0.21}{2.84 \pm 0.19}$	5M 5M 5 1.40 ± 5 2.86 ± 5 3.23 ± 3 1.00 ± 0 2.71 ± 3.13 ± 0 2.71 ±	$\begin{array}{c} 0.00 \pm \\ 0.00 $	$ \begin{array}{r} 7L1 \\ 2.46 \pm \\ 2.77 \pm \\ 3.46 \pm \\ 4.79 \pm \\ 2.74 \pm \\ 3.13 \pm \\ 2.99 \pm \\ \end{array} $	$\begin{array}{c} 2.00 \\ \hline 2.00 \\ \hline 11 \\ \hline 0.59 \\ \hline 0.02 \\ \hline 0.19 \\ \hline 0.26 \\ \hline 0.27 \\ \hline 0.21 \\ \hline 0.29 \end{array}$
MODEL 3DSBD AUTOGRC POCKET2M POCKETFI RESGEJ DST GRAPH C MIMOS	D 2 D 2 W4 2 AOL 2 LOW 1 N 2 GA 2 A 3	$ \frac{4000}{4000} 400$	5M 5M 5 1.40 ± 5 2.86 ± 5 3.23 ± 3 1.00 ± 0 2.71 ± 3.13 ± 0 2.71 ± 3.13 ±	$\begin{array}{c} 2.03 \pm \\ \hline \\ \hline \\ 04 \\ \hline \\ 0.39 \\ \hline \\ 0.06 \\ \hline \\ 0.22 \\ \hline \\ 0.47 \\ \hline \\ 0.49 \\ \hline \\ 0.21 \\ \hline \\ 0.20 \\ \hline \\ 0.21 \end{array}$	7L1 2.46 ± 2.77 ± 3.46 ± 4.79 ± 2.74 ± 3.13 ± 2.99 ± 3.13 ±	2.00 11 2.059 2.02 2
MODEL 3DSBD AUTOGRC POCKET2M POCKETFI RESGEJ DST GRAPH C MIMOS MOLDQ	D 2 W4 2 MOL 2 LOW 1 N 2 GA 2 A 3 N -4	$\frac{4000}{4000}$ $\frac{4000}{4000}$ $\frac{4000}{2.02 \pm 0.28}$ $\frac{2.02 \pm 0.28}{2.68 \pm 0.05}$ $\frac{2.56 \pm 0.16}{2.56 \pm 0.16}$ $\frac{1.44 \pm 0.28}{2.19 \pm 0.60}$ $\frac{3.13 \pm 0.21}{2.84 \pm 0.19}$ $\frac{3.13 \pm 0.21}{0.95 \pm 0.43}$	5M 5M 5 1.40 ± 5 2.86 ± 5 3.23 ± 6 3.23 ± 3 1.00 ± 0 2.71 ± 3.13 ± 0 2.71 ± 3.13 ± 3 -0.12 =	$\begin{array}{c} 2.08 \pm \\ \hline \\ 04 \\ = 0.39 \\ = 0.06 \\ = 0.22 \\ = 0.47 \\ = 0.49 \\ = 0.21 \\ = 0.20 \\ = 0.21 \\ \pm 0.54 \end{array}$	$7L1$ $2.46 \pm 2.77 \pm 3.46 \pm 4.79 \pm 2.74 \pm 3.13 \pm 2.99 \pm 3.13 \pm -0.23 \pm 0.23 \pm $	2.00 11 2.059 2.02 0.19 2.026 2.027 2.021 2.029 2.021 2.029 2.021 2.029
MODEL 3DSBD AUTOGRC POCKET2M POCKETFI RESGEJ DST GRAPH C MIMOS MOLDQ PASITHE	D 2 W4 2 MOL 2 LOW 1 N 2 GA 2 A 3 N -0 GA 3		5M 5M 5 1.40 ± 5 2.86 ± 5 3.23 ± 6 3.23 ± 3 1.00 ± 0 2.71 ± 3.13 ± 0 2.71 ± 3.13 ± 3 -0.12 = 0 3.03 ±	$\begin{array}{c} 2.08 \pm \\ \hline \\ 04 \\ \hline \\ 0.39 \\ \hline \\ 0.06 \\ \hline \\ 0.22 \\ \hline \\ 0.47 \\ \hline \\ 0.49 \\ \hline \\ 0.21 \\ \hline \\ 0.20 \\ \hline \\ 0.21 \\ \hline \\ 0.20 \\ \hline \\ 0.21 \\ \hline \\ 0.54 \\ \hline \\ 0.09 \end{array}$	7L1 2.46 ± 2.77 ± 3.46 ± 4.79 ± 2.74 ± 3.13 ± 2.99 ± 3.13 ± -0.23 ± 3.03 ±	2.00 11 2.059 0.02 0.19 0.26 0.27 0.21 0.29 0.21 0.29 0.21 0.48 0.09
MODEL 3DSBD AUTOGRC POCKET2M POCKETFI RESGEJ DST GRAPH C MIMOS MOLDQ PASITHE REINVE	D 2 W4 2 MOL 2 LOW 1 N 2 GA 2 A 3 N -4 CA 3 CA 3	$\frac{4000}{4000}$ $\frac{4000}{4000}$ $\frac{4000}{2.02 \pm 0.28}$ $\frac{2.02 \pm 0.28}{2.68 \pm 0.05}$ $\frac{2.56 \pm 0.16}{2.56 \pm 0.16}$ $\frac{1.44 \pm 0.28}{2.19 \pm 0.60}$ $\frac{3.13 \pm 0.21}{2.84 \pm 0.19}$ $\frac{3.13 \pm 0.21}{3.03 \pm 0.09}$ $\frac{2.50 \pm 0.51}{2.50 \pm 0.51}$	5 ± 0.33 5M 5 ± 0.33 5M 5 ± 0.33 5 ± 0.12 $5 $	$\begin{array}{c} 2.08 \pm \\ \hline \\ \hline \\ 04 \\ \hline \\ 0.39 \\ \hline \\ 0.06 \\ \hline \\ 0.22 \\ \hline \\ 0.47 \\ \hline \\ 0.49 \\ \hline \\ 0.21 \\ \hline \\ 0.20 \\ \hline \\ 0.21 \\ \hline \\ 0.20 \\ \hline \\ 0.21 \\ \hline \\ 0.54 \\ \hline \\ 0.09 \\ \hline \\ 0.51 \end{array}$	7L1 2.46 ± 2.77 ± 3.46 ± 4.79 ± 2.74 ± 3.13 ± 2.99 ± 3.13 ± -0.23 ± 3.03 ± 2.50 ±	$\begin{array}{c} 2.00 \\ \hline 2.00 \\ \hline 2.00 \\ \hline 11 \\ \hline 2.00 \\ \hline 0.02 \\ $
MODEL 3DSBD AUTOGRC POCKET2M POCKETFI RESGEJ DST GRAPH C MIMOS MOLDQ PASITHE REINVE SCREENII	D 2 W4 2 AOL 2 LOW 1 N 2 GA 2 A 3 N -4 CA 3 CA 3	$\frac{4000}{4000}$ $\frac{4000}{4000}$ $\frac{4000}{2.02 \pm 0.28}$ $\frac{2.02 \pm 0.28}{2.68 \pm 0.05}$ $\frac{2.56 \pm 0.16}{2.56 \pm 0.16}$ $\frac{1.44 \pm 0.28}{2.19 \pm 0.60}$ $\frac{3.13 \pm 0.21}{2.84 \pm 0.19}$ $\frac{3.13 \pm 0.21}{3.13 \pm 0.21}$ $\frac{3.13 \pm 0.21}{0.95 \pm 0.43}$ $\frac{3.03 \pm 0.09}{2.50 \pm 0.51}$ $\frac{3.30 \pm 0.18}{3.30 \pm 0.18}$	5 ± 0.33 $5 m$ 5 ± 0.33 $5 m$ 5 ± 0.33 5 ± 0.12	$\begin{array}{c} 2.08 \pm \\ \hline \\ \hline \\ 04 \\ \hline \\ 0.39 \\ \hline \\ 0.06 \\ \hline \\ 0.22 \\ \hline \\ 0.47 \\ \hline \\ 0.49 \\ \hline \\ 0.21 \\ \hline \\ 0.20 \\ \hline \\ 0.21 \\ \hline \\ 0.20 \\ \hline \\ 0.21 \\ \hline \\ 0.20 \\ \hline \\ 0.51 \\ \hline \\ 0.18 \end{array}$	7L1 2.46 ± 2.77 ± 3.46 ± 4.79 ± 2.74 ± 3.13 ± 2.99 ± 3.13 ± -0.23 ± 3.03 ± 2.50 ± 3.30 ±	$\begin{array}{c} 2.00 \\ \hline 2.00 \\ \hline 2.00 \\ \hline 11 \\ \hline 2.00 \\ \hline 0.02 \\ $
MODEL 3DSBD AUTOGRC POCKET2M POCKETFI RESGEJ DST GRAPH C MIMOS MOLDQ PASITHE REINVE SCREENII SELFIES VA	D 2 W4 2 AOL 2 LOW 1 N 2 GA 2 A 3 N -4 A 3 N -4 A 3 N -4 A 3 N -4 A 3 N A	$\frac{4000}{40000}$ $\frac{4000}{40000}$ $\frac{4000}{2.002 \pm 0.28}$ $\frac{2.02 \pm 0.28}{2.68 \pm 0.05}$ $\frac{2.56 \pm 0.16}{2.56 \pm 0.16}$ $\frac{1.44 \pm 0.28}{2.19 \pm 0.60}$ $\frac{3.13 \pm 0.21}{2.84 \pm 0.19}$ $\frac{3.13 \pm 0.21}{3.13 \pm 0.21}$ $\frac{3.03 \pm 0.19}{2.50 \pm 0.51}$ $\frac{3.03 \pm 0.09}{3.30 \pm 0.18}$ $\frac{2.50 \pm 0.51}{3.30 \pm 0.18}$ $\frac{2.68 \pm 0.33}{2.68 \pm 0.33}$	$5 \pm 0.33 \pm 0.33$ $5 \pm 0.33 \pm 0.33$ $5 \pm 0.33 \pm 0.33$ $5 \pm 0.33 \pm 0.23 \pm 0.12 $	$\begin{array}{c} 0.39 \\ = 0.39 \\ = 0.06 \\ = 0.22 \\ = 0.47 \\ = 0.20 \\ = 0.21 \\ = 0.20 \\ = 0.21 \\ \pm 0.54 \\ = 0.09 \\ = 0.51 \\ = 0.18 \\ = 0.33 \end{array}$	7L1 2.46 ± 2.77 ± 3.46 ± 4.79 ± 2.74 ± 3.13 ± 2.99 ± 3.13 ± -0.23 ± 3.03 ± 2.50 ± 3.30 ± 2.68 ±	$\begin{array}{c} 2.00 \\ \hline 2.00 \\ \hline 2.00 \\ \hline 11 \\ \hline 2.00 \\ \hline 0.02 \\ $
MODEL 3DSBD AUTOGRC POCKET2M POCKETFI RESGEI DST GRAPH C MIMOS MOLDQ PASITHE REINVE SCREENII SELFIES VA SMILES	D 2 W4 2 AOL 2 LOW 1 N 2 GA 2 A 3 N -4 A 3 A 3 A 3 A 3 A 3 A 3 A 3 A 3	$\frac{4000}{4000}$ $\frac{4000}{2.02 \pm 0.28}$ $\frac{2.02 \pm 0.28}{2.68 \pm 0.05}$ $\frac{2.56 \pm 0.16}{2.56 \pm 0.16}$ $\frac{1.44 \pm 0.28}{2.19 \pm 0.60}$ $\frac{3.13 \pm 0.21}{2.84 \pm 0.19}$ $\frac{3.13 \pm 0.21}{3.03 \pm 0.09}$ $\frac{2.50 \pm 0.51}{3.30 \pm 0.18}$ $\frac{2.50 \pm 0.51}{3.30 \pm 0.18}$ $\frac{2.50 \pm 0.51}{3.30 \pm 0.18}$ $\frac{2.58 \pm 0.33}{2.48 \pm 0.44}$	5 ± 0.33 $5 m$ 5 ± 0.33 $5 m$ 5 ± 0.33 5 ± 0.33 5 ± 0.33 5 ± 0.33 5 ± 0.12	$\begin{array}{c} 2.03 \pm \\ \hline \\ \hline \\ 04 \\ \hline \\ = 0.39 \\ = 0.06 \\ = 0.22 \\ = 0.47 \\ = 0.49 \\ = 0.21 \\ = 0.20 \\ = 0.21 \\ \pm 0.54 \\ = 0.09 \\ = 0.51 \\ = 0.18 \\ = 0.33 \\ = 0.30 \end{array}$	7L1 2.46 ± 2.77 ± 3.46 ± 4.79 ± 2.74 ± 3.13 ± 2.99 ± 3.13 ± -0.23 ± 3.03 ± 2.50 ± 3.30 ± 2.68 ± 2.14 ±	$\begin{array}{c} 2.00 \\ \hline 2.00 \\ \hline 2.00 \\ \hline \\ 11 \\ \hline \\ 0.29 \\ \hline 0.26 \\ \hline 0.27 \\ \hline 0.21 \\ \hline 0.29 \\ \hline 0.21 \\ \hline 0.29 \\ \hline 0.21 \\ \hline 0.48 \\ \hline 0.09 \\ \hline 0.51 \\ \hline 0.18 \\ \hline 0.33 \\ \hline 0.34 \\ \hline \end{array}$
MODEL 3DSBD AUTOGRC POCKET2M POCKETFI RESGEI DST GRAPH C MIMOS MOLDQ PASITHE REINVE SCREENII SELFIES VA SMILES SMILES LST	D 2 W4 2 AOL 2 LOW 1 N 2 GA 2 A 3 N -4 CA 3 CA 3	$\begin{array}{r} 4\text{UNN} \\ \hline \\ \hline \\ 4\text{UNN} \\ \hline \\ 2.02 \pm 0.28 \\ 2.68 \pm 0.05 \\ 2.56 \pm 0.16 \\ 1.44 \pm 0.28 \\ 2.19 \pm 0.60 \\ 3.13 \pm 0.21 \\ 2.84 \pm 0.19 \\ 3.13 \pm 0.21 \\ 0.95 \pm 0.43 \\ 3.03 \pm 0.09 \\ 2.50 \pm 0.51 \\ 3.30 \pm 0.18 \\ 2.68 \pm 0.33 \\ 2.48 \pm 0.44 \\ 4.72 \pm 0.85 \end{array}$	$5 \pm 0.33 \pm 0.33$ $5 m$ $5 \pm 0.33 \pm 0.33$ $5 \pm 0.33 \pm 0.33$ $5 \pm 0.33 \pm 0.23 \pm 0.12 \pm$	$\begin{array}{c} 2.03 \pm \\ \hline \\ \hline \\ 04 \\ \hline \\ = 0.39 \\ = 0.06 \\ = 0.22 \\ = 0.47 \\ = 0.49 \\ = 0.21 \\ = 0.20 \\ = 0.21 \\ \pm 0.54 \\ = 0.09 \\ = 0.51 \\ = 0.18 \\ = 0.33 \\ = 0.33 \\ = 0.30 \\ = 0.85 \end{array}$	7L1 2.46 ± 2.77 ± 3.46 ± 4.79 ± 2.74 ± 3.13 ± 2.99 ± 3.13 ± -0.23 ± 3.03 ± 2.50 ± 3.30 ± 2.68 ± 2.14 ± 4.72 ±	$\begin{array}{c} 2.00 \\ \hline 2.00 \\ \hline 2.00 \\ \hline \\ 11 \\ \hline \\ 0.29 \\ \hline 0.26 \\ \hline 0.27 \\ \hline 0.21 \\ \hline 0.29 \\ \hline 0.21 \\ \hline 0.29 \\ \hline 0.21 \\ \hline 0.29 \\ \hline 0.21 \\ \hline 0.48 \\ \hline 0.09 \\ \hline 0.51 \\ \hline 0.18 \\ \hline 0.33 \\ \hline 0.34 \\ \hline 0.85 \\ \hline \end{array}$

Table 8. Top 50 LogP score for each target protein.

MODEL	11	EP	3e	EML	3N	Y8	4rlu
3DSBDD	0.03 =	E 0.18	0.56	± 0.64	0.53 ±	0.78	-2.01 ± 1
AUTOGROW4	2.96 =	± 0.22	2.56 :	± 0.15	2.49 ±	0.13	2.67 ± 0.00
POCKET2MOL	1.80 =	E 0.18	3.12 :	± 0.31	3.20 ±	0.30	2.76 ± 0.12
POCKETFLOW	5.38 =	E 0.29	1.20 :	± 0.70	0.98 ±	0.66	2.19 ± 0.11
ResGen	2.99 =	E 0.37	5.22 :	± 1.02	3.99 ±	0.54	2.20 ± 0.00
DST	2.78 =	± 0.25	2.78 :	± 0.25	2.78 ±	0.25	2.78 ± 0.00
GRAPH GA	2.06 =	±0.42	2.18 :	± 0.44	2.22 ±	0.55	2.18 ± 0.11
MIMOSA	2.78 =	±0.25	2.78 :	± 0.25	2.78 ±	0.25	2.78 ± 0.12
MOLDQN	-1.73 :	± 0.60	-1.51	± 0.59	-1.68 =	± 0.58	-1.20 ± 0
PASITHEA	2.69 =	±0.25	2.69 :	± 0.25	2.69 ±	0.25	2.69 ± 0.00
REINVENT	1.50 =	E 0.65	1.42 :	± 0.69	1.46 ±	0.69	1.46 ± 0.00
SCREENING	2.85 =	E 0.27	2.85 :	± 0.27	2.85 ±	0.27	2.85 ± 0.00
SELFIES VAE BO	1.99 =	±0.42	1.99 :	± 0.42	1.99 ±	0.42	1.99 ± 0.00
SMILES GA	1.72 =	E 0.39	1.25 :	± 0.48	1.81 ±	0.47	1.73 ± 0.00
SMILES LSTM HC	3.51 ±	E 0.77	3.51	± 0.77	3.51 ±	0.77	3.51 ± 0.01
SMILES VAE BO	1.99 =	± 0.42	1.99 :	± 0.42	1.99 ±	0.42	1.99 ± 0.01
Moi	DEL	4u	NN	5M	104	71	L11
3DS	BDD	0.90 =	± 0.77	0.30 =	± 0.58	0.73	± 0.98
AUTO	Grow4	2.63 :	± 0.04	2.70 =	± 0.14	2.40	± 0.31
Pocke	t2mol	2.12 :	± 0.30	2.80 =	± 0.28	2.96	± 0.32
Pocke	tFlow	0.61 :	± 0.53	0.57 :	± 0.31	4.06	± 0.44
Res	Gen	0.81	± 0.91	1.68 =	± 0.62	1.97	± 0.47
DS	ST	2.78 :	± 0.25	2.78 =	± 0.25	2.78	± 0.25
GRAP	'H GA	2.15 :	± 0.44	2.09 =	± 0.37	2.27	± 0.46
MIM	OSA	2.78 :	± 0.25	2.78 =	± 0.25	2.78	± 0.25
MOL	DQN	-1.88	± 0.57	-1.46	± 0.79	-1.34	± 0.66
PASI	ГНЕА	2.69 :	± 0.25	2.69 =	± 0.25	2.69	± 0.25
REIN	VENT	1.47 :	± 0.68	1.48 =	± 0.67	1.49	± 0.66
SCREE	ENING	2.85 :	± 0.27	2.85 =	± 0.27	2.85	± 0.27
SEL FIES	VAE BO	1.99 =	± 0.42	1.99 =	± 0.42	1.99	± 0.42
5 LLI IL5		1 77	+0.46	1 70 -	± 0.40	1.50	± 0.42
SMILI	ES GA	1.//	L 0.40	1.70 -			
SMILI SMILES I	ES GA LSTM HC	1.77 ± 3.51 ±	± 0.40 ± 0.77	3.51	± 0.77	3.51	± 0.77

Table 9. Top 100 LogP score for each target protein.

MODEL	11E	Р	3e	EML	3N	¥8	41
3DSBDD	$0.02 \pm$	0.13	0.28	± 0.53	0.26 ±	0.61	-2.58
AUTOGROW4	$2.83 \pm$	0.21	2.37	± 0.23	2.20 ±	0.33	2.31
POCKET2MOL	$1.61 \pm$	0.24	2.79	± 0.40	2.91 ±	0.37	2.50
PocketFlow	$5.02 \pm$	0.43	0.57	± 0.82	$0.40 \pm$	0.76	1.42
ResGen	$2.65 \pm$	0.44	4.52	± 1.05	3.59 ±	0.56	1.72
DST	$2.51 \pm$	0.32	2.51	± 0.32	2.51 ±	0.32	2.51
GRAPH GA	$1.69 \pm$	0.49	1.78	± 0.52	$1.76 \pm$	0.62	1.76
MIMOSA	$2.51 \pm$	0.32	2.51	± 0.32	2.51 ±	0.32	2.51
MOLDQN	-2.21 \pm	0.66	-1.97	± 0.63	-2.19 =	± 0.67	-1.72
PASITHEA	$2.42 \pm$	0.33	2.42	± 0.33	$2.42 \pm$	0.33	2.42
REINVENT	$0.15 \pm$	1.82	0.02	± 1.89	$0.05 \pm$	1.90	0.07
SCREENING	$2.60 \pm$	0.32	2.60	± 0.32	$2.60 \pm$	0.32	2.60
SELFIES VAE BO	$1.43 \pm$	0.68	1.43	± 0.68	$1.43 \pm$	0.68	1.43
SMILES GA	$1.35 \pm$	0.47	0.80	± 0.57	$1.41 \pm$	0.52	1.35
SMILES LSTM HC	$2.96 \pm$	0.78	2.96	± 0.78	2.96 ±	0.78	2.96
SMILES VAE BO	$1.43 \pm$	0.68	1.43	± 0.68	$1.43 \pm$	0.68	1.43
MOD	EL	4un	NN	5м	04	71	211
3DSB	DD	$0.45 \pm$	0.70	$0.15 \pm$	0.44	-0.05	± 1.22
AUTOG	row4	$2.46 \pm$	0.21	$2.43 \pm$	0.30	2.10	± 0.38
Pocket	2mol	$1.80 \pm$	0.39	$2.53 \pm$	0.35	2.50	± 0.54
Pocket	Flow	$0.04 \pm$	0.69	0.19 ±	0.46	3.56	± 0.62
ResG	EN	$0.00 \pm$	1.05	$1.20 \pm$	0.66	1.48	± 0.61
DS	Г	$2.51 \pm$	0.32	$2.51 \pm$	0.32	2.51	± 0.32
GRAPH	I GA	$1.70 \pm$	0.56	$1.70 \pm$	0.48	1.84	± 0.55
MIMC	SA	$2.51 \pm$	0.32	2.51 ±	0.32	2.51	± 0.32
MOLD	QN	-2.34 ±	= 0.62	-2.07 =	± 0.84	-1.93	± 0.77
PASITI	HEA	$2.42 \pm$	0.33	$2.42 \pm$	0.33	2.42	± 0.33
REINV	ENT	$0.05 \pm$	1.90	$0.08 \pm$	1.89	0.09	± 1.89
SCREEN	NING	$2.60 \pm$	0.32	$2.60 \pm$	0.32	2.60	± 0.32
SELFIES V	/AE BO	$1.43 \pm$	0.68	1.43 ±	0.68	1.43	± 0.68
SMILES	S GA	$1.39 \pm$	0.51	$1.37 \pm$	0.44	1.10	± 0.52
SMILES LS	STM HC	$2.96 \pm$	0.78	$2.96 \pm$	0.78	2.96	± 0.78
			0 (0	1 10	0 (0	1 / 2	1060

MODEL	1 iep	3eml	3NY8	4rlu
3DSBDD	0.81	0.93	0.95	0.85
AUTOGROW4	0.86	0.85	0.92	0.84
POCKET2MOL	0.92	0.91	0.93	0.92
POCKETFLOW	0.92	0.86	0.81	0.88
ResGen	0.92	0.80	0.93	0.94
DST	0.95	0.95	0.95	0.95
GRAPH GA	0.94	0.94	0.94	0.94
MIMOSA	0.95	0.95	0.95	0.95
MOLDQN	0.52	0.65	0.62	0.67
PASITHEA	0.95	0.95	0.95	0.95
REINVENT	0.95	0.95	0.95	0.95
SCREENING	0.95	0.95	0.95	0.95
SELFIES VAE BO	0.94	0.94	0.94	0.94
SMILES GA	0.93	0.93	0.94	0.94
SMILES LSTM HC	0.94	0.94	0.94	0.94
SMILES VAE BO	0.94	0.94	0.94	0.94
Model	40	INN 5	бмо4 7	L11
Model 3DSBDD	4u 0.	INN 5	бмо4 7 0.80 (L11).90
Model 3DSBDD AutoGrow4	4u 0. 0.	INN 5 88 89	бмо4 7 0.80 0 0.87 0	0.90 0.84
Model 3DSBDD AutoGrow4 Pocket2mol	4u 0. 0.	INN 5 88 89 88	бмо4 7 0.80 (0.87 (0.90 (0.90 0.84 0.94
Model 3DSBDD AutoGrow4 Pocket2mol PocketFlow	4u 0. 0. 0. 0. 0. 0.	INN 5 88 89 88 83	5MO4 7 0.80 (0 0.87 (0 0.90 (0 0.80 (0	0.90 0.84 0.94 0.91
Model 3DSBDD AutoGrow4 Pocket2mol PocketFlow ResGen	4u 0. 0. 0. 0. 0. 0. 0.	INN 5 88 89 88 83 93	5M04 7 0.80 0 0.87 0 0.90 0 0.80 0 0.88 0	L11).90).84).94).91).95
Model 3DSBDD AutoGrow4 Pocket2mol PocketFlow ResGen DST	40 0. 0. 0. 0. 0. 0. 0. 0.	INN 5 88 89 88 83 93 93 95	5M04 7 0.80 0 0.87 0 0.90 0 0.88 0 0.88 0 0.95 0	L11).90).84).94).91).95).95
Model 3DSBDD AutoGrow4 Pocket2mol PocketFlow ResGen DST GRAPH GA	4u 0. 0. 0. 0. 0. 0. 0. 0. 0.	INN 5 88 89 88 83 93 93 95 94	5M04 7 0.80 0 0.87 0 0.90 0 0.88 0 0.88 0 0.95 0 0.94 0	0.90 0.84 0.94 0.91 0.95 0.95 0.95
MODEL 3DSBDD AutoGrow4 Pocket2mol PocketFlow ResGen DST GRAPH GA MIMOSA	4u 0. 0. 0. 0. 0. 0. 0. 0. 0. 0.	INN 5 88 89 88 83 93 95 94 95	5M04 7 0.80 0 0.87 0 0.90 0 0.88 0 0.95 0 0.94 0 0.95 0	L11).90).84).94).91).95).95).95).95
MODEL 3DSBDD AutoGrow4 Pocket2mol PocketFlow ResGen DST GRAPH GA MIMOSA MOLDQN	4u 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0.	NN 5 88 89 88 83 93 93 95 94 95 67	5M04 7 0.80 0 0.87 0 0.90 0 0.88 0 0.95 0 0.94 0 0.95 0 0.52 0	L11).90).84).94).91).95).95).95).95).95).70
MODEL 3DSBDD AutoGrow4 Pocket2mol PocketFlow ResGen DST GRAPH GA MIMOSA MOLDQN PASITHEA	4u 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0.	INN 5 88 89 88 83 93 93 94 95 67 95	5M04 7 0.80 0 0.87 0 0.90 0 0.88 0 0.95 0 0.95 0 0.52 0 0.95 0	1.11).90).84).94).91).95).95).95).95).70).95
MODEL 3DSBDD AutoGrow4 Pocket2mol PocketFlow ResGen DST GRAPH GA MIMOSA MOLDQN PASITHEA REINVENT	4u 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0.	INN 5 88 89 88 83 93 93 94 95 67 95 95	6M04 7 0.80 0 0.87 0 0.90 0 0.88 0 0.95 0 0.95 0 0.52 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0	L11).90).84).94).95).95).95).95).95).70).95).95
MODEL 3DSBDD AutoGrow4 Pocket2mol PocketFlow ResGen DST GRAPH GA MIMOSA MOLDQN PASITHEA REINVENT SCREENING	4u 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0.	INN 5 88 89 88 93 93 95 94 95 95 95 95 95 95 95 95 95 95 95 95 95	6M04 7 0.80 0 0.87 0 0.90 0 0.88 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0	L11).90).84).94).95).95).95).95).70).95).95).95).95
MODEL 3DSBDD AUTOGROW4 POCKET2MOL POCKETFLOW RESGEN DST GRAPH GA MIMOSA MOLDQN PASITHEA REINVENT SCREENING SELFIES VAE BO	4u 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0.	INN 5 88 89 88 93 93 95 94 95 95 95 95 95 95 95 95 95 95 95 95 95 94 95	6M04 7 0.80 0 0.87 0 0.90 0 0.88 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.94 0	L11).90).84).94).95).95).95).95).95).95).95).95
MODEL 3DSBDD AUTOGROW4 POCKET2MOL POCKETFLOW RESGEN DST GRAPH GA MIMOSA MOLDQN PASITHEA REINVENT SCREENING SELFIES VAE BO SMILES GA	4u 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0.	NN 5 888 89 88 83 93 95 94 95 94 95 95 95 95 94 93	6M04 7 0.80 0 0.87 0 0.90 0 0.88 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.93 0	L11).90).84).94).95).95).95).95).95).95).95).95
MODEL 3DSBDD AUTOGROW4 POCKET2MOL POCKETFLOW RESGEN DST GRAPH GA MIMOSA MOLDQN PASITHEA REINVENT SCREENING SELFIES VAE BO SMILES GA SMILES LSTM H	4u 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0. 0.	INN 5 88 89 88 83 93 95 94 95 95 95 95 95 95 95 95 95 94 93 93 94	6M04 7 0.80 0 0.87 0 0.90 0 0.88 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.95 0 0.94 0 0.93 0 0.94 0	L11).90).84).94).95).95).95).95).95).95).95).95

Table 10. Top 1 QED score for each target protein.

Table 11. Top 10 QED score for each target protein.

MODEL	1 iep	Зем	L	3ny	8	41
3DSBDD	0.77 ± 0.02	$0.83 \pm$	0.05	$0.88 \pm$	0.03	0.81
AUTOGROW4	0.83 ± 0.01	$0.79 \pm$	0.04	$0.92 \pm$	0.00	0.82
POCKET2MOL	0.90 ± 0.01	$0.89 \pm$	0.01	$0.92 \pm$	0.01	0.90
POCKETFLOW	0.89 ± 0.01	$0.81 \pm$	0.03	$0.77 \pm$	0.03	0.79
RESGEN	0.91 ± 0.01	$0.73 \pm$	0.03	$0.90 \pm$	0.02	0.93
DST	0.94 ± 0.00	$0.94 \pm$	0.00	$0.94 \pm$	0.00	0.94
GRAPH GA	0.93 ± 0.01	$0.93 \pm$	0.01	$0.93 \pm$	0.01	0.92
MIMOSA	0.94 ± 0.00	$0.94 \pm$	0.00	$0.94 \pm$	0.00	0.94
MOLDQN	0.49 ± 0.02	$0.55 \pm$	0.04	$0.51 \pm$	0.05	0.60
PASITHEA	0.94 ± 0.00	$0.94 \pm$	0.00	$0.94 \pm$	0.00	0.94
REINVENT	0.91 ± 0.02	$0.91 \pm$	0.02	$0.91 \pm$	0.02	0.91
SCREENING	$\textbf{0.94} \pm 0.00$	0.94 \pm	0.00	0.94 \pm	0.00	0.94
SELFIES VAE BO	0.91 ± 0.02	$0.91 \pm$	0.02	$0.91 \pm$	0.02	0.91
SMILES GA	0.92 ± 0.01	$0.93 \pm$	0.01	$0.93 \pm$	0.00	0.93
SMILES LSTM HC	0.92 ± 0.01	$0.92 \pm$	0.01	$0.92 \pm$	0.01	0.92
SMILES VAE BO	0.91 ± 0.02	$0.91 \pm$	0.02	$0.91 \pm$	0.02	0.91
Modi	EL 4u	JNN	5мо-	4	7l1	1
3DSB	DD 0.82	± 0.03	0.76 ± 0	0.02	$0.86 \ \pm$	0.02
AutoGi	row4 0.87	± 0.01	0.83 ± 0	0.03	$0.80 \ \pm$	0.02
POCKET	2мог 0.84	± 0.02	0.88 ± 0	0.01	$0.94~\pm$	0.01
POCKET	Flow 0.74	± 0.04	0.74 ± 0	0.03	$0.90 \ \pm$	0.01
ResG	en 0.85	+0.04	0.84 ± 0	0.01	$0.92 \ \pm$	0.02
		± 0.01	0.04 1	0.01		
DST	Г 0.94	± 0.00	$0.04 \pm 0.04 \pm 0.04 \pm 0.000$	0.00	$0.94~\pm$	0.00
DS GRAPH	GA 0.94	$\pm 0.00 \pm 0.00 \pm 0.01$	$0.94 \pm 0.93 \pm 0.93 \pm 0.000$	0.00 0.01	${}^{0.94~\pm}_{0.93~\pm}$	$\begin{array}{c} 0.00\\ 0.01 \end{array}$
DS7 GRAPH MIMO	Г 0.94 GA 0.93 SA 0.94	$\pm 0.00 \\ \pm 0.00 \\ \pm 0.01 \\ \pm 0.00$	0.94 ± 0 0.93 ± 0 0.94 ± 0	0.00 0.01 0.00	$\begin{array}{c} 0.94 \pm \\ 0.93 \pm \\ 0.94 \pm \end{array}$	$\begin{array}{c} 0.00 \\ 0.01 \\ 0.00 \end{array}$
DS GRAPH MIMO MOLD	C 0.94 GA 0.93 SA 0.94 QN 0.57	$\pm 0.01 \\ \pm 0.00 \\ \pm 0.01 \\ \pm 0.00 \\ \pm 0.04$	0.94 ± 0 0.93 ± 0 0.94 ± 0 0.48 ± 0	0.00 0.01 0.00 0.02	$\begin{array}{c} 0.94 \pm \\ 0.93 \pm \\ 0.94 \pm \\ 0.54 \pm \end{array}$	$\begin{array}{c} 0.00 \\ 0.01 \\ 0.00 \\ 0.07 \end{array}$
DS graph mimo mold Pasiti	Г 0.94 GA 0.93 SA 0.94 QN 0.57 HEA 0.94	$\pm 0.01 \\ \pm 0.00 \\ \pm 0.01 \\ \pm 0.00 \\ \pm 0.04 \\ \pm 0.00$	$\begin{array}{c} 0.04 \pm 0 \\ 0.94 \pm 0 \\ 0.93 \pm 0 \\ 0.94 \pm 0 \\ 0.48 \pm 0 \\ 0.94 \pm 0 \end{array}$	0.00 0.01 0.00 0.02 0.00	$\begin{array}{c} 0.94 \pm \\ 0.93 \pm \\ 0.94 \pm \\ 0.54 \pm \\ 0.94 \pm \end{array}$	$\begin{array}{c} 0.00 \\ 0.01 \\ 0.00 \\ 0.07 \\ 0.00 \end{array}$
DS" graph mimo mold Pasith reinvi	Г 0.94 GA 0.93 SA 0.94 QN 0.57 HEA 0.94 ENT 0.91	$\begin{array}{c} \pm 0.00 \\ \pm 0.00 \\ \pm 0.01 \\ \pm 0.00 \\ \pm 0.04 \\ \pm 0.00 \\ \pm 0.02 \end{array}$	$\begin{array}{c} 0.94 \pm 0 \\ 0.94 \pm 0 \\ 0.93 \pm 0 \\ 0.94 \pm 0 \\ 0.94 \pm 0 \\ 0.94 \pm 0 \\ 0.91 \pm 0 \end{array}$	0.00 0.01 0.00 0.02 0.00 0.02	$\begin{array}{c} 0.94 \pm \\ 0.93 \pm \\ 0.94 \pm \\ 0.54 \pm \\ 0.94 \pm \\ 0.91 \pm \end{array}$	$\begin{array}{c} 0.00 \\ 0.01 \\ 0.00 \\ 0.07 \\ 0.00 \\ 0.02 \end{array}$
DS" GRAPH MIMO MOLD PASITH REINVI SCREEN	Г 0.94 GA 0.93 SA 0.94 QN 0.57 HEA 0.94 ENT 0.91 NING 0.94	$\begin{array}{c} \pm 0.00 \\ \pm 0.00 \\ \pm 0.01 \\ \pm 0.00 \\ \pm 0.04 \\ \pm 0.00 \\ \pm 0.02 \\ \pm 0.00 \end{array}$	$\begin{array}{c} 0.94 \pm 0 \\ 0.93 \pm 0 \\ 0.94 \pm 0 \\ 0.94 \pm 0 \\ 0.94 \pm 0 \\ 0.94 \pm 0 \\ 0.91 \pm 0 \\ 0.94 \pm 0 \\ 0.94$	0.00 0.01 0.00 0.02 0.00 0.02 0.00	$\begin{array}{c} 0.94 \pm \\ 0.93 \pm \\ 0.94 \pm \\ 0.54 \pm \\ 0.94 \pm \\ 0.91 \pm \\ \textbf{0.94} \pm \end{array}$	$\begin{array}{c} 0.00\\ 0.01\\ 0.00\\ 0.07\\ 0.00\\ 0.02\\ 0.00 \end{array}$
DS GRAPH MIMO MOLD PASITH REINVI SCREEN SELFIES V	Г 0.94 GA 0.93 SA 0.94 QN 0.57 HEA 0.94 ENT 0.91 NING 0.94 VAE BO 0.91	$\begin{array}{c} \pm 0.00 \\ \pm 0.01 \\ \pm 0.00 \\ \pm 0.04 \\ \pm 0.00 \\ \pm 0.02 \\ \pm 0.00 \\ \pm 0.02 \end{array}$	$\begin{array}{c} 0.04 \pm 0\\ 0.94 \pm 0\\ 0.93 \pm 0\\ 0.94 \pm 0\\ 0.94 \pm 0\\ 0.91 \pm 0\\ 0.94 \pm 0\\ 0.91 \pm 0\\ 0\\ 0.91 \pm 0\\ 0\\ 0.91 \pm 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ $	0.00 0.01 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.02	$\begin{array}{l} 0.94 \pm \\ 0.93 \pm \\ 0.94 \pm \\ 0.54 \pm \\ 0.94 \pm \\ 0.91 \pm \\ 0.91 \pm \\ 0.91 \pm \end{array}$	$\begin{array}{c} 0.00\\ 0.01\\ 0.00\\ 0.07\\ 0.00\\ 0.02\\ 0.00\\ 0.02 \end{array}$
DS GRAPH MIMO MOLD PASITH REINVI SCREEN SELFIES V SMILES	Г 0.94 GA 0.93 SA 0.94 QN 0.57 HEA 0.94 ENT 0.91 NING 0.94 VAE BO 0.91 GA 0.93	$\begin{array}{c} \pm 0.01 \\ \pm 0.00 \\ \pm 0.01 \\ \pm 0.00 \\ \pm 0.04 \\ \pm 0.00 \\ \pm 0.02 \\ \pm 0.00 \\ \pm 0.02 \\ \pm 0.00 \\ \pm 0.02 \end{array}$	$\begin{array}{c} 0.94 \pm 0\\ 0.94 \pm 0\\ 0.93 \pm 0\\ 0.94 \pm 0\\ 0.94 \pm 0\\ 0.91 \pm 0\\ 0.91 \pm 0\\ 0.91 \pm 0\\ 0.91 \pm 0\\ 0.93 \pm 0\end{array}$	0.00 0.01 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.02 0.00	$\begin{array}{l} 0.94 \pm \\ 0.93 \pm \\ 0.94 \pm \\ 0.54 \pm \\ 0.94 \pm \\ 0.91 \pm \\ 0.91 \pm \\ 0.91 \pm \\ 0.92 \pm \end{array}$	$\begin{array}{c} 0.00\\ 0.01\\ 0.00\\ 0.07\\ 0.00\\ 0.02\\ 0.00\\ 0.02\\ 0.01\\ \end{array}$
DS GRAPH MIMO MOLD PASITH REINVI SCREEN SELFIES V SMILES SMILES LS	Г 0.94 GA 0.93 SA 0.94 QN 0.57 HEA 0.94 ENT 0.91 NING 0.94 VAE BO 0.91 GA 0.93 STM HC 0.92	$\begin{array}{c} \pm 0.01 \\ \pm 0.00 \\ \pm 0.01 \\ \pm 0.00 \\ \pm 0.04 \\ \pm 0.00 \\ \pm 0.02 \\ \pm 0.00 \\ \pm 0.02 \\ \pm 0.00 \\ \pm 0.01 \end{array}$	$\begin{array}{c} 0.94 \pm 0 \\ 0.94 \pm 0 \\ 0.93 \pm 0 \\ 0.94 \pm 0 \\ 0.94 \pm 0 \\ 0.91 \pm 0 \\ 0.91 \pm 0 \\ 0.91 \pm 0 \\ 0.91 \pm 0 \\ 0.93 \pm 0 \\ 0.92 \pm 0 \end{array}$	0.00 0.01 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.01	$\begin{array}{l} 0.94 \pm \\ 0.93 \pm \\ 0.94 \pm \\ 0.54 \pm \\ 0.94 \pm \\ 0.91 \pm \\ 0.91 \pm \\ 0.92 \pm \\ 0.92 \pm \end{array}$	$\begin{array}{c} 0.00\\ 0.01\\ 0.00\\ 0.07\\ 0.00\\ 0.02\\ 0.00\\ 0.02\\ 0.01\\ 0.01 \end{array}$

Table 12. Top 50 QED score for each target protein.

Mo	DEL	1	IEP		31	EML		3	ny8		4	RLU	
3DS	BDD	0.69	$\pm 0.$	05	0.71	± 0	.07	0.79	$\pm 0.$.05	0.77	± 0.02	
Auto	Grow4	0.78	$\pm 0.$	03	0.73	± 0	.04	0.88	$\pm 0.$	03	0.76	± 0.04	
POCK	et2mol	0.87	$\pm 0.$	02	0.85	± 0	.03	0.88	$\pm 0.$	03	0.87	± 0.02	
Роски	etFlow	0.85	$\pm 0.$	03	0.71	± 0	.06	0.69	$\pm 0.$	04	0.69	± 0.06	
RE	SGEN	0.86	$\pm 0.$	04	0.65	± 0	.05	0.85	$\pm 0.$	03	0.90	± 0.02	
D	ST	0.92	$\pm 0.$	01	0.92	± 0	.01	0.92	$\pm 0.$	01	0.92	± 0.01	
GRA	PH GA	0.89	$\pm 0.$	02	0.89	± 0	.03	0.89	$\pm 0.$	03	0.88	± 0.03	
MIN	IOSA	0.92	$\pm 0.$	01	0.92	± 0	.01	0.92	$\pm 0.$	01	0.92	± 0.01	
MO	LDQN	0.43	$\pm 0.$	03	0.48	± 0	.04	0.44	$\pm 0.$	04	0.49	± 0.06	
PAS	ITHEA	0.92	$\pm 0.$	01	0.92	± 0	.01	0.92	$\pm 0.$	01	0.92	± 0.01	
REIN	IVENT	0.84	$\pm 0.$	05	0.84	± 0	.05	0.84	$\pm 0.$	05	0.84	± 0.05	
SCRE	ENING	0.92	$\pm 0.$	01	0.92	± 0	.01	0.92	$\pm 0.$	01	0.92	± 0.01	
SELFIE	S VAE BO	0.87	$\pm 0.$	03	0.87	± 0	.03	0.87	$\pm 0.$	03	0.87	± 0.03	
SMIL	ES GA	0.87	$\pm 0.$	03	0.87	± 0	.03	0.89	$\pm 0.$	02	0.89	± 0.02	
SMILES	LSTM HC	0.88	$\pm 0.$	03	0.88	± 0	.03	0.88	$\pm 0.$	03	0.88	± 0.03	
SMILES	S VAE BO	0.87	$\pm 0.$	03	0.87	± 0	.03	0.87	$\pm 0.$	03	0.87	± 0.03	
												_	
_	MODEL	,		4un	N		5мс	94		7l1	1	_	
	3DSBD	D	0.	$74 \pm$	0.06	0	.64 ±	0.08	0.	74 ±	0.07		
	AUTOGRO	w4	0.	$86 \pm$	0.01	0	$.75 \pm$	0.05	0.	$74 \pm$	0.04		
	POCKET2N	AOL	0.	$80 \pm$	0.03	0	$.84 \pm$	0.03	0.	$91 \pm$	0.02		
	PocketFi	LOW	0.	$67 \pm$	0.04	0	$.68 \pm$	0.04	0.	$85 \pm$	0.03		
	ResGei	N	0.	$76 \pm$	0.06	0	$.78 \pm$	0.04	0.	$85 \pm$	0.04		
	DST		0.	$92 \pm$	0.01	0	$.92 \pm$	0.01	0.	$92 \pm$	0.01		
	GRAPH C	βA	0.	$89 \pm$	0.03	0	$.89 \pm$	0.02	0.	$89 \pm$	0.03		
	MIMOSA	4	0.	$92 \pm$	0.01	0	$.92 \pm$	0.01	0.	$92 \pm$	0.01		
	MOLDQ	N	0.	$49 \pm$	0.05	0	$.43 \pm$	0.03	0.	$45 \pm$	0.06		
	PASITHE	A	0.	$92 \pm$	0.01	0	$.92 \pm$	0.01	0.	$92 \pm$	0.01		
	REINVEN	ΙT	0.	$83 \pm$	0.06	0	$.83 \pm$	0.05	0.	$83 \pm$	0.05		
	SCREENI	NG	0.	$92 \pm$	0.01	0	.92 \pm	0.01	0.	$92 \pm$	0.01		
	SELFIES VA	E BO	0.	$87 \pm$	0.03	0	$.87 \pm$	0.03	0.	$87 \pm$	0.03		
	SMILES O	βA	0.	$90 \pm$	0.02	0	.89 ±	0.02	0.	$88 \pm$	0.03		
	SMILES LST	м нс	0.	$88 \pm$	0.03	0	$.88 \pm$	0.03	0.	$88 \pm$	0.03		
	SMILES VA	E BO	0	87 +	0.03	0	.87 +	0.03	0.	$87 \pm$	0.03		

Table 13. Top 100 QED score for each target protein.

MODEL	1 iep	31	EML	3ny	8	4rlu
3DSBDD	0.64 ± 0.00	.07 0.65	± 0.08	$0.73 \pm$	0.08	0.75 ± 0.21
AUTOGROW4	0.76 ± 0.12	.03 0.67	± 0.07	$0.84 \pm$	0.05	0.72 ± 0.2
POCKET2MOL	0.85 ± 0.1	.03 0.82	± 0.03	$0.85 \pm$	0.04	0.86 ± 0.1
POCKETFLOW	0.80 ± 0.0	.05 0.65	± 0.07	$0.65 \pm$	0.05	0.64 ± 0.2
RESGEN	0.82 ± 0.1	.05 0.60	± 0.06	$0.83 \pm$	0.04	0.86 ± 0.1
DST	0.91 ± 0.01	.02 0.91	± 0.02	$0.91 \pm$	0.02	0.91 ± 0.2
GRAPH GA	0.85 ± 0.01	.04 0.85	± 0.04	$0.85 \pm$	0.04	0.85 ± 0.000
MIMOSA	0.91 ± 0.01	.02 0.91	± 0.02	$0.91 \pm$	0.02	0.91 ± 0.01
MOLDQN	0.40 ± 0.00	.04 0.44	± 0.05	$0.41 \pm$	0.05	0.45 ± 0.000
PASITHEA	0.90 ± 0.0	.02 0.90	± 0.02	$0.90 \pm$	0.02	0.90 ± 0.0
REINVENT	0.73 ± 0.00	.14 0.73	± 0.14	$0.73 \pm$	0.14	0.73 ± 0.0
SCREENING	0.91 ± 0.01	.02 0.91	± 0.02	$0.91 \pm$	0.02	0.91 ± 0
SELFIES VAE BO	0.83 ± 0.01	.05 0.83	± 0.05	$0.83 \pm$	0.05	0.83 ± 0.000
SMILES GA	0.84 ± 0.1	.04 0.83	± 0.05	$0.86 \pm$	0.04	0.86 ± 0.1
SMILES LSTM HC	0.85 ± 0.1	.04 0.85	± 0.04	$0.85 \pm$	0.04	0.85 ± 0.000
SMILES VAE BO	0.83 ± 0.01	.05 0.83	± 0.05	$0.83~\pm$	0.05	0.83 ± 0.6
Modi	EL	4unn	5мо	4	7l1	1
3DSB	DD 0	$.65 \pm 0.10$	$0.54 \pm$	0.12	$0.66 \pm$	0.10
AutoGi	Row4 0	$.84 \pm 0.02$	$0.71 \pm$	0.06	$0.69 \pm$	0.06
POCKET	2мог 0.	$.77 \pm 0.04$	$0.81 \pm$	0.03	$0.88 \pm$	0.03
POCKET	FLOW 0	$.63 \pm 0.05$	$0.64~\pm$	0.05	$0.82 \pm$	0.04
ResG	EN 0	$.70 \pm 0.07$	$0.75~\pm$	0.05	$0.81 \pm$	0.05
DST	Г О.	$.91 \pm 0.02$	$0.91 \pm$	0.02	$0.91 \pm$	0.02
GRAPH	GA 0	$.85 \pm 0.05$	$0.86 \pm$	0.04	$0.85 \pm$	0.04
MIMO	SA 0	$.91 \pm 0.02$	$0.91 \pm$	0.02	$0.91 \pm$	0.02
MOLD	QN 0	$.44 \pm 0.06$	$0.39 \pm$	0.04	$0.41 \pm$	0.06
PASITI	IEA 0	$.90\pm0.02$	$0.90 \pm$	0.02	$0.90 \pm$	0.02
				0.13	$0.73 \pm$	0.14
REINV	ENT 0	$.73 \pm 0.14$	$0.73 \pm$	0.15		
REINVI SCREEN	ENT O	$.73 \pm 0.14$ $.91 \pm 0.02$	0.73 ± 0.91 ±	0.02	$0.91 \pm$	0.02
REINVI SCREEN SELFIES V	ENT 0 NING 0 AE BO 0	$.73 \pm 0.14$ $.91 \pm 0.02$ $.83 \pm 0.05$	$0.73 \pm $ 0.91 $\pm $ 0.83 $\pm $	0.02 0.05	0.91 ± 0.83 ±	0.02 0.05
REINVI SCREEM SELFIES V SMILES	ENT 0. NING 0. AE BO 0. GA 0.	$\begin{array}{c} .73 \pm 0.14 \\ .91 \pm 0.02 \\ .83 \pm 0.05 \\ .88 \pm 0.03 \end{array}$	$0.73 \pm 0.91 \pm 0.83 \pm 0.86 \pm$	0.02 0.05 0.03	0.91 ± 0.83 ± 0.84 ±	0.02 0.05 0.04
REINVI SCREEN SELFIES V SMILES SMILES LS	ENT 0. IING 0. AE BO 0. GA 0. TM HC 0.	$\begin{array}{c} .73 \pm 0.14 \\ .91 \pm 0.02 \\ .83 \pm 0.05 \\ .88 \pm 0.03 \\ .85 \pm 0.04 \end{array}$	$\begin{array}{c} 0.73 \pm \\ \textbf{0.91} \pm \\ 0.83 \pm \\ 0.86 \pm \\ 0.85 \pm \end{array}$	0.02 0.05 0.03 0.04	0.91 ± 0.83 ± 0.84 ± 0.85 ±	0.02 0.05 0.04 0.04

MODEL	1 iep	Зем	L 3NY	y8 4F	RLU
3DSBDD	1.37	1.00) 1.0	0 1.	.99
AUTOGROW4	1.00	1.00) 1.8	33 1 .	.00
POCKET2MOL	1.05	1.00) 1.9	0 1.	.00
POCKETFLOW	1.00	1.00) 1.0	0 1.	.61
ResGen	1.00	1.00) 1.0	0 1.	.16
DST	1.41	1.4	1 1.4	1 1.	.41
GRAPH GA	1.00	1.00) 1.0	0 1.	.00
MIMOSA	1.41	1.4	1 1.4	1 1.	.41
MOLDQN	1.51	1.65	5 1.5	51 1.	.62
PASITHEA	1.41	1.4	1 1.4	1 1.	.41
REINVENT	1.67	1.67	7 1.6	57 1.	.67
SCREENING	1.51	1.51	l 1.5	51 1.	.51
SELFIES VAE BO	1.75	1.75	5 1.7	5 1.	.75
SMILES GA	1.61	1.61	l 1.6	6 0 1.	.61
SMILES LSTM HC	1.60	1.60) 1.6	6 0 1.	.60
SMILES VAE BO	1.75	1.75	5 1.7	5 1.	.75
					_
MODEL	4u	INN	5мо4	7l11	
3DSBDD	1.	.00	1.00	1.00	_
AUTOGROW4	1.	74	1.00	1.83	
POCKET2MOL	. 1.	.00	1.00	1.00	
PocketFlow	v 1.	11	1.54	1.00	
ResGen	1.	.00	1.00	1.00	
DST	1.	41	1.41	1.41	
GRAPH GA	1.	.00	1.00	1.00	
MIMOSA	1.	41	1.41	1.41	
MOLDQN	1.	98	2.04	1.51	
PASITHEA	1.	41	1.41	1.41	
REINVENT	1.	67	1.67	1.67	
SCREENING	1.	51	1.51	1.51	
SELFIES VAE B	o 1.	75	1.75	1.75	
SMILES GA	1.	60	1.61	1.61	
SMILES LSTM H	IC 1.	60	1.60	1.60	
SMILES VAE BO	o 1.	75	1.75	1.75	

Table 14. Top 1 SA score for each target protein.

Table 15. Top 10 SA score for each target protein.

MODEL	1 iep	3eml	3ny8	4rlu
3DSBDD	2.20 ± 0.38	1.54 ± 0.24	1.52 ± 0.34	2.80 ± 0.60
AUTOGROW4	1.04 ± 0.13	1.74 ± 0.26	1.91 ± 0.04	1.55 ± 0.31
POCKET2MOL	1.36 ± 0.14	$\textbf{1.02} \pm 0.03$	2.07 ± 0.08	$\textbf{1.09} \pm 0.08$
PocketFlow	$\textbf{1.00} \pm 0.00$	1.46 ± 0.19	1.33 ± 0.18	1.61 ± 0.00
ResGen	1.03 ± 0.04	1.08 ± 0.08	$\textbf{1.07} \pm 0.07$	1.40 ± 0.13
DST	1.62 ± 0.09	1.62 ± 0.09	1.62 ± 0.09	1.62 ± 0.09
GRAPH GA	1.37 ± 0.19	1.26 ± 0.17	1.32 ± 0.21	1.13 ± 0.14
MIMOSA	1.62 ± 0.09	1.62 ± 0.09	1.62 ± 0.09	1.62 ± 0.09
MOLDQN	2.53 ± 0.37	2.39 ± 0.36	2.61 ± 0.37	2.46 ± 0.32
PASITHEA	1.67 ± 0.10	1.67 ± 0.10	1.67 ± 0.10	1.67 ± 0.10
REINVENT	1.85 ± 0.08	1.88 ± 0.09	1.86 ± 0.09	1.88 ± 0.09
SCREENING	1.63 ± 0.07	1.63 ± 0.07	1.63 ± 0.07	1.63 ± 0.07
SELFIES VAE BO	1.90 ± 0.06	1.90 ± 0.06	1.90 ± 0.06	1.90 ± 0.06
SMILES GA	1.90 ± 0.11	1.96 ± 0.14	1.86 ± 0.13	1.90 ± 0.11
SMILES LSTM HC	1.77 ± 0.09	1.77 ± 0.09	1.77 ± 0.09	1.77 ± 0.09
SMILES VAE BO	1.90 ± 0.06	1.90 ± 0.06	1.90 ± 0.06	1.90 ± 0.06
MODEL	4unn	5мо4	7L11	
3DSBDD	2.20 ± 0.38	1.54 ± 0.24	1.52 ± 0.34	2.80 ± 0.60
AUTOGROW4	1.04 ± 0.13	1.74 ± 0.26	1.91 ± 0.04	1.55 ± 0.31
POCKET2MOL	1.36 ± 0.14	$\textbf{1.02} \pm 0.03$	2.07 ± 0.08	$\textbf{1.09} \pm 0.08$
POCKETFLOW	$\textbf{1.00} \pm 0.00$	1.46 ± 0.19	1.33 ± 0.18	1.61 ± 0.00
ResGen	1.03 ± 0.04	1.08 ± 0.08	$\textbf{1.07} \pm 0.07$	1.40 ± 0.13
DST	1.62 ± 0.09	1.62 ± 0.09	1.62 ± 0.09	1.62 ± 0.09
GRAPH GA	1.37 ± 0.19	1.26 ± 0.17	1.32 ± 0.21	1.13 ± 0.14
MIMOSA	1.62 ± 0.09	1.62 ± 0.09	1.62 ± 0.09	1.62 ± 0.09
MOLDQN	2.53 ± 0.37	2.39 ± 0.36	2.61 ± 0.37	2.46 ± 0.32
PASITHEA	1.67 ± 0.10	1.67 ± 0.10	1.67 ± 0.10	1.67 ± 0.10
REINVENT	1.85 ± 0.08	1.88 ± 0.09	1.86 ± 0.09	1.88 ± 0.09
SCREENING	1.63 ± 0.07	1.63 ± 0.07	1.63 ± 0.07	1.63 ± 0.07
SELFIES VAE BO	1.90 ± 0.06	1.90 ± 0.06	1.90 ± 0.06	1.90 ± 0.06
SMILES GA	1.90 ± 0.11	1.96 ± 0.14	1.86 ± 0.13	1.90 ± 0.11
SMILES LSTM HC	1.77 ± 0.09	1.77 ± 0.09	1.77 ± 0.09	1.77 ± 0.09
SMILES VAE BO	1.90 ± 0.06	1.90 ± 0.06	1.90 ± 0.06	1.90 ± 0.06

Table 16. Top 50 SA score for each target protein.

MODEL	1 iep	,	3ei	ML	3N	Y8	4
3DSBDD	3.49 ± 0	0.78	2.28 ±	= 0.48	2.95 =	± 1.00	4.06
AUTOGROW4	1.53 ± 0	0.26	2.00 ±	= 0.20	2.07 =	± 0.13	1.93
POCKET2MOL	1.68 ± 0	0.19	1.32 ±	= 0.19	2.30 =	± 0.15	1.30
PocketFlow	1.00 ± 0	0.00	$1.88 \pm$	0.25	1.73 =	± 0.28	1.67
ResGen	1.36 ± 0	0.21	$1.71 \pm$	= 0.41	1.39 :	± 0.21	1.77
DST	1.82 ± 0	0.13	1.82 ±	= 0.13	1.82 =	± 0.13	1.82
GRAPH GA	1.80 ± 0	0.26	$1.77 \pm$	= 0.30	1.83 =	± 0.30	1.65
MIMOSA	1.82 ± 0	0.13	1.82 ±	= 0.13	1.82 =	± 0.13	1.82
MOLDQN	3.11 ± 0	0.42	3.07 ±	= 0.45	3.18 =	± 0.41	2.95
PASITHEA	1.85 ± 0	0.12	1.85 ±	= 0.12	1.85 :	± 0.12	1.85
REINVENT	2.32 ± 0	0.35	2.37 ±	= 0.35	2.35 =	± 0.36	2.38
SCREENING	1.83 ± 0	0.12	1.83 ±	= 0.12	1.83 =	± 0.12	1.83
SELFIES VAE BO	2.15 ± 0	0.18	2.15 ±	= 0.18	2.15 =	± 0.18	2.15
SMILES GA	2.27 ± 0	0.24	2.45 ±	= 0.30	2.24 =	± 0.25	2.23
SMILES LSTM HC	2.00 ± 0	0.14	$2.00 \pm$	= 0.14	2.00 =	± 0.14	2.00
SMILES VAE BO	2.15 ± 0	0.18	2.15 ±	= 0.18	2.15 =	± 0.18	2.15
		4		<i>C</i> -	4	7-	1.1
MODI	EL	401	NN	21	404	/L	.11
3DSB	DD 2	$2.14 \pm$	0.73	3.18	± 0.87	2.52 =	± 0.90
AumoCi	4	1 00 1			1 0 00	206	0 10
AUTOGI	ROW4 2	$2.00 \pm$: 0.14	1.94	± 0.22	2.00 =	± 0.10
POCKET	ROW4 2 2mol 1	2.00 ± 1.60 ±	: 0.14 : 0.17	1.94 1.26	± 0.22 ± 0.14	2.06 ± 1.92 ±	± 0.10 ± 0.26
POCKET	ROW4 2 2MOL 1 FLOW 1	2.00 ± 1.60 ± 1.92 ±	: 0.14 : 0.17 : 0.27	1.94 1.26 1.72	$\pm 0.22 \\ \pm 0.14 \\ \pm 0.15$	1.92 = 1.43 =	± 0.10 ± 0.26 ± 0.20
POCKET POCKET RESG	ROW4 2 2MOL 1 FLOW 1 EN 2	2.00 ± 1.60 ± 1.92 ± 2.34 ±	0.14 0.17 0.27 0.46	1.94 1.26 1.72 1.88	$\pm 0.22 \\ \pm 0.14 \\ \pm 0.15 \\ \pm 0.32$	1.92 = 1.43 = 1.57 =	± 0.10 ± 0.26 ± 0.20 ± 0.31
POCKET POCKET RESG DST	ROW4 2 2MOL 1 FLOW 1 EN 2 F 1	$2.00 \pm$ 1.60 ± 1.92 ± 2.34 ± 1.82 ±	: 0.14 : 0.17 : 0.27 : 0.46 : 0.13	1.94 1.26 1.72 1.88 1.82	$\pm 0.22 \\ \pm 0.14 \\ \pm 0.15 \\ \pm 0.32 \\ \pm 0.13$	1.92 = 1.43 = 1.57 = 1.82 =	± 0.10 ± 0.26 ± 0.20 ± 0.31 ± 0.13
POCKET POCKET RESG DST GRAPH	ROW4 2 2MOL 1 FLOW 1 EN 2 FLOW 1 EN 2 FLOW 1	$2.00 \pm 2.00 \pm 1.60 \pm 1.92 \pm 2.34 \pm 1.82 \pm 1.82 \pm 1.95 \pm $	0.14 0.17 0.27 0.46 0.13 0.37	1.94 1.26 1.72 1.88 1.82 1.76	$\pm 0.22 \\ \pm 0.14 \\ \pm 0.15 \\ \pm 0.32 \\ \pm 0.13 \\ \pm 0.29$	1.92 = 1.43 = 1.57 = 1.82 = 1.79 =	± 0.10 ± 0.26 ± 0.20 ± 0.31 ± 0.13 ± 0.35
POCKET POCKET RESG DS GRAPH MIMO	ROW4 2 2MOL 1 FLOW 1 EN 2 C 1 GA 1 SA 1	$\begin{array}{c} 2.00 \pm \\ 1.60 \pm \\ 1.92 \pm \\ 2.34 \pm \\ 1.82 \pm \\ 1.95 \pm \\ 1.82 \pm \\ 1.82 \pm \end{array}$	0.14 0.17 0.27 0.46 0.13 0.37 0.13	1.94 1.26 1.72 1.88 1.82 1.76 1.82	$\pm 0.22 \\ \pm 0.14 \\ \pm 0.15 \\ \pm 0.32 \\ \pm 0.13 \\ \pm 0.29 \\ \pm 0.13$	2.06 = 1.92 = 1.43 = 1.57 = 1.82 = 1.79 = 1.82 =	$\pm 0.10 \\ \pm 0.26 \\ \pm 0.20 \\ \pm 0.31 \\ \pm 0.13 \\ \pm 0.35 \\ \pm 0.13$
POCKET POCKET RESG DS GRAPH MIMO MOLD	ROW4 2 2MOL 1 FLOW 1 EN 2 GA 1 GA 1 SA 1 QN 2	$2.00 \pm 1.60 \pm 1.92 \pm 2.34 \pm 1.82 \pm 1.95 \pm 1.82 \pm 3.24 \pm 3.24 \pm 1.95$	0.14 0.17 0.27 0.46 0.13 0.37 0.13 0.38	1.94 1.26 1.72 1.88 1.82 1.76 1.82 3.16	$\pm 0.22 \pm 0.14 \pm 0.15 \pm 0.32 \pm 0.13 \pm 0.29 \pm 0.13 \pm 0.36$	2.06 = 1.92 = 1.43 = 1.57 = 1.82 = 1.79 = 1.82 = 3.06 =	± 0.10 ± 0.26 ± 0.20 ± 0.31 ± 0.13 ± 0.35 ± 0.13 ± 0.39
POCKET POCKET POCKET RESG DS GRAPH MIMO MOLD PASITI	ROW4 2 2MOL 1 FLOW 1 EN 2 GA 1 GA 1 SA 1 QN 2 HEA 1	$\pm 2.00 \pm 1.60 \pm 1.92 \pm 1.92 \pm 1.82 \pm 1.82 \pm 1.82 \pm 1.82 \pm 1.82 \pm 3.24 \pm 1.85 $	 0.14 0.17 0.27 0.46 0.13 0.37 0.13 0.38 0.12 	1.94 1.26 1.72 1.88 1.82 1.76 1.82 3.16 1.85	$\begin{array}{c} \pm \ 0.22 \\ \pm \ 0.14 \\ \pm \ 0.15 \\ \pm \ 0.32 \\ \pm \ 0.13 \\ \pm \ 0.29 \\ \pm \ 0.13 \\ \pm \ 0.36 \\ \pm \ 0.12 \end{array}$	2.06 = 1.92 = 1.43 = 1.57 = 1.82 = 1.79 = 1.82 = 3.06 = 1.85 =	$\begin{array}{c} \pm \ 0.10 \\ \pm \ 0.26 \\ \pm \ 0.20 \\ \pm \ 0.31 \\ \pm \ 0.13 \\ \pm \ 0.35 \\ \pm \ 0.13 \\ \pm \ 0.39 \\ \pm \ 0.12 \end{array}$
POCKET POCKET POCKET RESG DS GRAPH MIMO MOLD PASITH REINVI	ROW4 2 2MOL 1 FLOW 1 EN 2 GA 1 GA 1 GA 1 GA 1 GA 1 EN 1 CHOM	$\begin{array}{c} 2.00 \pm \\ 1.60 \pm \\ 1.92 \pm \\ 2.34 \pm \\ 1.82 \pm \\ 1.82 \pm \\ 1.95 \pm \\ 1.82 \pm \\ 3.24 \pm \\ 1.85 \pm \\ 2.37 \pm \end{array}$	0.14 0.17 0.27 0.46 0.13 0.37 0.13 0.38 0.12 0.35	1.94 1.26 1.72 1.88 1.82 1.76 1.82 3.16 1.85 2.36	$\begin{array}{c} \pm \ 0.22 \\ \pm \ 0.14 \\ \pm \ 0.15 \\ \pm \ 0.32 \\ \pm \ 0.13 \\ \pm \ 0.29 \\ \pm \ 0.13 \\ \pm \ 0.36 \\ \pm \ 0.12 \\ \pm \ 0.34 \end{array}$	2.06 = 1.92 = 1.43 = 1.57 = 1.82 = 1.79 = 1.82 = 3.06 = 1.85 = 2.36 =	$\begin{array}{c} \pm \ 0.10 \\ \pm \ 0.26 \\ \pm \ 0.20 \\ \pm \ 0.31 \\ \pm \ 0.13 \\ \pm \ 0.35 \\ \pm \ 0.13 \\ \pm \ 0.39 \\ \pm \ 0.12 \\ \pm \ 0.34 \end{array}$
POCKET POCKET POCKET RESG DS GRAPH MIMO MOLD PASITH REINVI SCREEN	ROW4 2 2MOL 1 FLOW 1 EN 2 GA 1 GA 1 GA 1 GA 1 GA 1 GA 1 GA 1 GA 1	$\begin{array}{c} 2.00 \pm \\ 1.60 \pm \\ 1.92 \pm \\ 2.34 \pm \\ 1.82 \pm \\ 1.82 \pm \\ 1.85 \pm \\ 3.24 \pm \\ 1.85 \pm \\ 2.37 \pm \\ 1.83 \pm \end{array}$	$\begin{array}{c} 0.14\\ 0.17\\ 0.27\\ 0.46\\ 0.13\\ 0.37\\ 0.13\\ 0.38\\ 0.12\\ 0.35\\ 0.12\\ \end{array}$	1.94 1.26 1.72 1.88 1.82 1.76 1.82 3.16 1.85 2.36 1.83	$\begin{array}{c} \pm \ 0.22 \\ \pm \ 0.14 \\ \pm \ 0.15 \\ \pm \ 0.32 \\ \pm \ 0.13 \\ \pm \ 0.29 \\ \pm \ 0.13 \\ \pm \ 0.36 \\ \pm \ 0.12 \\ \pm \ 0.34 \\ \pm \ 0.12 \end{array}$	2.06 = 1.92 = 1.43 = 1.57 = 1.82 = 1.79 = 1.82 = 3.06 = 1.85 = 2.36 = 1.83 =	$\begin{array}{c} \pm \ 0.10 \\ \pm \ 0.26 \\ \pm \ 0.20 \\ \pm \ 0.31 \\ \pm \ 0.13 \\ \pm \ 0.35 \\ \pm \ 0.13 \\ \pm \ 0.39 \\ \pm \ 0.12 \\ \pm \ 0.34 \\ \pm \ 0.12 \end{array}$
AUTOG POCKET POCKET RESG DS GRAPH MIMO MOLD PASITH REINVI SCREEN SELFIES V	ROW4 2 2MOL 1 FLOW 1 EN 2 GA 1 GA 1 GA 1 GA 1 HEA 1 HEA 1 ENT 2 HING 1 /AE BO 2	$\begin{array}{c} 2.00 \pm \\ 1.60 \pm \\ 1.92 \pm \\ 2.34 \pm \\ 1.82 \pm \\ 1.82 \pm \\ 1.82 \pm \\ 3.24 \pm \\ 1.85 \pm \\ 2.37 \pm \\ 1.83 \pm \\ 2.15 \pm \end{array}$	0.14 0.17 0.27 0.46 0.13 0.37 0.13 0.38 0.12 0.35 0.12 0.18	1.94 1.26 1.72 1.88 1.82 1.76 1.82 3.16 1.85 2.36 1.83 2.15	$\begin{array}{c} \pm \ 0.22 \\ \pm \ 0.14 \\ \pm \ 0.15 \\ \pm \ 0.32 \\ \pm \ 0.13 \\ \pm \ 0.29 \\ \pm \ 0.13 \\ \pm \ 0.36 \\ \pm \ 0.12 \\ \pm \ 0.34 \\ \pm \ 0.12 \\ \pm \ 0.18 \end{array}$	2.06 = 1.92 = 1.43 = 1.57 = 1.82 = 1.82 = 1.82 = 2.36 = 1.83 = 2.15 =	$\begin{array}{c} \pm 0.10 \\ \pm 0.26 \\ \pm 0.20 \\ \pm 0.31 \\ \pm 0.13 \\ \pm 0.35 \\ \pm 0.13 \\ \pm 0.13 \\ \pm 0.13 \\ \pm 0.12 \\ \pm 0.34 \\ \pm 0.12 \\ \pm 0.18 \end{array}$
AUTOG POCKET POCKET RESG DS GRAPH MIMO MOLD PASITH REINVI SCREEN SELFIES V SMILES	ROW4 2 2MOL 1 FLOW 1 EN 2 GA 1 GA 1 GA 1 HEA 1 HEA 1 HEA 1 HEA 1 HEA 1 HING 1 VAE BO 2 GA 2	$\begin{array}{c} 2.00 \pm \\ 1.60 \pm \\ 1.92 \pm \\ 2.34 \pm \\ 1.82 \pm \\ 1.82 \pm \\ 1.85 \pm \\ 2.37 \pm \\ 1.83 \pm \\ 2.15 \pm \\ 2.23 \pm \end{array}$	0.14 0.17 0.27 0.46 0.13 0.37 0.13 0.38 0.12 0.35 0.12 0.35 0.12 0.18 0.24	1.94 1.26 1.72 1.88 1.82 1.76 1.82 3.16 1.85 2.36 1.83 2.15 2.30	$\begin{array}{c} \pm \ 0.22 \\ \pm \ 0.14 \\ \pm \ 0.15 \\ \pm \ 0.32 \\ \pm \ 0.13 \\ \pm \ 0.29 \\ \pm \ 0.13 \\ \pm \ 0.29 \\ \pm \ 0.13 \\ \pm \ 0.36 \\ \pm \ 0.12 \\ \pm \ 0.34 \\ \pm \ 0.12 \\ \pm \ 0.18 \\ \pm \ 0.23 \end{array}$	2.06 = 1.92 = 1.43 = 1.57 = 1.82 = 1.82 = 1.82 = 3.06 = 1.85 = 2.36 = 1.83 = 2.15 = 2.39 =	$\begin{array}{c} \pm 0.10 \\ \pm 0.26 \\ \pm 0.20 \\ \pm 0.31 \\ \pm 0.13 \\ \pm 0.13 \\ \pm 0.13 \\ \pm 0.13 \\ \pm 0.12 \\ \pm 0.34 \\ \pm 0.12 \\ \pm 0.18 \\ \pm 0.27 \end{array}$
AUTOGI POCKET POCKET RESG DST GRAPH MIMO MOLD PASITI REINVI SCREEN SELFIES V SMILES LS	ROW4 2 ROW1 1 FLOW 1 EN 2 GA 1 GA 1 QN 1 HEA 1 ENT 2 VAE BO 2 GA 2 GA 2 STM HC 2	$\begin{array}{c} 2.00 \pm \\ 1.60 \pm \\ 1.92 \pm \\ 2.34 \pm \\ 1.82 \pm \\ 1.82 \pm \\ 1.85 \pm \\ 1.85 \pm \\ 2.37 \pm \\ 1.83 \pm \\ 2.15 \pm \\ 2.23 \pm \\ 2.00 \pm \end{array}$	0.14 0.17 0.27 0.46 0.13 0.37 0.13 0.38 0.12 0.35 0.12 0.35 0.12 0.18 0.24	1.94 1.26 1.72 1.88 1.82 1.76 1.82 3.16 1.85 2.36 1.83 2.15 2.30 2.00	$\begin{array}{c} \pm \ 0.22 \\ \pm \ 0.14 \\ \pm \ 0.15 \\ \pm \ 0.32 \\ \pm \ 0.13 \\ \pm \ 0.29 \\ \pm \ 0.13 \\ \pm \ 0.36 \\ \pm \ 0.12 \\ \pm \ 0.34 \\ \pm \ 0.12 \\ \pm \ 0.18 \\ \pm \ 0.23 \\ \pm \ 0.14 \end{array}$	2.06 = 1.92 = 1.43 = 1.57 = 1.82 = 1.82 = 1.82 = 3.06 = 1.85 = 2.36 = 1.83 = 2.15 = 2.39 = 2.00 =	$\begin{array}{c} \pm 0.10 \\ \pm 0.26 \\ \pm 0.20 \\ \pm 0.31 \\ \pm 0.13 \\ \pm 0.13 \\ \pm 0.35 \\ \pm 0.13 \\ \pm 0.39 \\ \pm 0.12 \\ \pm 0.34 \\ \pm 0.12 \\ \pm 0.14 \end{array}$

MODEL	1 iep	3emi	L 3	ny8	4rlu
3DSBDD	4.05 ± 0.79	2.85 ± 0	0.69 3.76	± 1.09	4.46 ± 0.12
AUTOGROW4	1.72 ± 0.28	2.17 ± 0	0.23 2.29	± 0.26	2.11 ± 0.11
POCKET2MOL	1.86 ± 0.23	1.49 ± 0	0.22 2.50	± 0.23	1.44 ± 0.0
POCKETFLOW	$\textbf{1.10}\pm0.16$	2.11 ± 0	0.30 2.06	± 0.40	1.87 ± 0
ResGen	1.64 ± 0.33	2.24 ± 0	0.65 1.66	± 0.32	2.10 ± 0
DST	1.93 ± 0.14	1.93 ± 0	0.14 1.93	± 0.14	1.93 ± 0
GRAPH GA	2.03 ± 0.30	2.02 ± 0	0.33 2.09	± 0.34	1.95 ± 0
MIMOSA	1.93 ± 0.14	1.93 ± 0	0.14 1.93	± 0.14	1.93 ± 0
MOLDQN	3.53 ± 0.52	3.49 ± 0	0.53 3.59	± 0.51	3.30 ± 0
PASITHEA	1.97 ± 0.15	1.97 ± 0	0.15 1.97	± 0.15	1.97 ± 0
REINVENT	2.96 ± 0.80	3.03 ± 0	0.85 3.02	± 0.86	3.03 ± 0
SCREENING	1.94 ± 0.14	1.94 ± 0	0.14 1.94	± 0.14	1.94 ± 0
SELFIES VAE BO	2.42 ± 0.31	2.42 ± 0	0.31 2.42	± 0.31	2.42 ± 0
SMILES GA	2.52 ± 0.31	2.76 ± 0	0.38 2.54	± 0.35	2.51 ± 0
SMILES LSTM HC	2.14 ± 0.18	2.14 ± 0	0.18 2.14	± 0.18	2.14 ± 0
SMILES VAE BO	2.42 ± 0.31	2.42 ± 0	0.31 2.42	± 0.31	2.42 ± 0
MOD	EL 4	UNN	5мо4	7L1	1
3DSB	DD 3.25	± 1.29 4	4.28 ± 1.37	$3.49 \pm$	1.17
AUTOG	ROW4 2.12	± 0.16 2	2.11 ± 0.23	2.19 ± 0	0.16
Pocket	2мог 1.76	± 0.20	1.40 ± 0.18	2.17 ± 0	0.31
Pocket	FLOW 2.20	± 0.35	2.04 ± 0.35	1.67 ± 0	0.28
RESC	Gen 2.70	± 0.49	2.20 ± 0.40	1.97 ± 0	0.47
DS	T 1.93	± 0.14	1.93 ± 0.14	1.93 ± 0	0.14
GRAPH	I GA 2.22	± 0.38	1.99 ± 0.32	2.05 ± 0	0.36
MIMO	osa 1.93	± 0.14	1.93 ± 0.14	$1.93 \pm$	0.14
MOLI	QN 3.60	± 0.45	3.56 ± 0.48	$3.46 \pm$	0.49
PASIT	hea 1.97	± 0.15	1.97 ± 0.15	$1.97 \pm$	0.15
REINV	ENT 3.03	± 0.85 .	3.01 ± 0.84	3.01 ± 0	0.84
SCREE	NING 1.94	± 0.14	1.94 ± 0.14	$1.94 \pm$	0.14
SELFIES	VAE BO 2.42	± 0.31 2	2.42 ± 0.31	2.42 ± 0	0.31
SMILE	s ga 2.49	± 0.32	2.54 ± 0.30	$2.68 \pm$	0.36
DIMILL		1 0 10	14 + 0.10	214 ± 6	0.18
SMILES L	STM HC 2.14	± 0.18 1	2.14 ± 0.18	2.14 ± 1	0.10

Table 17. Top 100 SA score for each target protein.

Table 18. Model Rankings based on QED

MODEL	TOP 1 RANK	TOP 10 RANK	TOP 100 RANK	OVERALL RANK
3DSBDD	13	14	15	14
AUTOGROW4	14	13	12	13
POCKET2MOL	11	11	8	11
POCKETFLOW	15	15	14	15
RESGEN	12	12	11	12
DST	2	2	2	1
GRAPH GA	6	5	6	5
MIMOSA	2	2	2	1
MOLDQN	16	16	16	16
PASITHEA	2	4	4	4
REINVENT	4	10	13	10
SCREENING	5	1	1	3
SELFIES VAE BO	8	8	9	8
SMILES GA	10	6	5	6
SMILES LSTM HC	7	7	7	6
SMILES VAE BO	8	8	9	8

	Table 19. Wodel Kankings based on SA						
MODEL	TOP 1 RANK	TOP 10 RANK	TOP 100 RANK	OVERALL RANK			
3DSBDD	12	6	1	6			
AUTOGROW4	11	9	8	8			
POCKET2MOL	14	14	16	16			
POCKETFLOW	13	13	15	14			
RESGEN	15	16	9	13			
DST	9	11	13	11			
GRAPH GA	16	15	10	14			
MIMOSA	9	11	14	12			
MOLDQN	3	1	2	1			
PASITHEA	9	8	11	8			
REINVENT	4	5	3	5			
SCREENING	7	10	12	10			
SELFIES VAE BO	1	3	5	2			
SMILES GA	5	2	4	4			
SMILES LSTM HC	6	7	7	7			
SMILES VAE BO	1	3	5	2			

Table 19. Model Rankings based on SA

	Table 20. Model Kankings based on docking score								
MODEL	TOP 1 RANK	TOP 10 RANK	TOP 100 RANK	OVERALL RANK					
3DSBDD	12	12	13	12					
AUTOGROW4	2	1	1	1					
POCKET2MOL	1	2	2	2					
POCKETFLOW	11	14	14	13					
ResGen	3	3	7	4					
DST	6	5	4	5					
GRAPH GA	9	9	9	9					
MIMOSA	5	6	5	6					
MOLDQN	16	16	16	16					
PASITHEA	7	7	6	7					
REINVENT	15	15	15	15					
SCREENING	4	4	3	3					
SELFIES VAE BO	10	10	11	10					
SMILES GA	14	13	12	13					
SMILES LSTM HC	8	8	8	8					
SMILES VAE BO	13	11	10	11					

Table 20. Model Rankings based on docking score

1542					
1543	Mol	DEL	DIVERSITY	VALIDITY	UNIQUENESS
1544	3DS	BDD	0.83	0.63	0.63
1545	AUTO	AUTOGROW4		1.00	0.29
1546	Роске	t2mol	0.86	1.00	1.00
1547	Pocke	tFlow	0.90	1.00	0.87
1548	RES	Gen	0.83	1.00	1.00
1540	DS	ST	0.88	1.00	1.00
1549	GRAP	H GA	0.91	1.00	1.00
1550	MIM	OSA	0.88	1.00	1.00
1551	MOL	DQN	0.91	1.00	1.00
1552	PASI	ГНЕА	0.89	1.00	1.00
1553	REIN	VENT	0.88	1.00	1.00
1554	SCREE	ENING	0.88	1.00	1.00
1555	SELFIES	VAE BO	0.88	1.00	1.00
1556	SMILI	ES GA	0.88	1.00	1.00
1550	SMILES	LSIM HC	0.89	1.00	1.00
1557	SMILES	VAE DU	0.88	1.00	1.00
1558	MODEL	DIVEDEIT			
1559	MODEL	DIVERSII	I KANK	VALIDIT I KAN	K UNIQUENESS KAP
1560	3DSBDD	14.0	00	2.00	3.00
1561	AUTOGROW4	13.0	00	1.00	4.00
1562	POCKET2MOL	12.0	00	1.00	1.00
1563	POCKETFLOW	3.0	00	1.00	2.00
1564	RESGEN	15.0	00	1.00	1.00
1504		7.0		1.00	1.00
1363	GRAPH GA	2.0		1.00	1.00
1566	MIMOSA	8.0		1.00	1.00
1567	PASITHEA	1.0		1.00	1.00
1568	I ASII DEA DEINVENT	4.0		1.00	1.00
1569	SCREENING	9.0	00	1.00	1.00
1570	SELFIES VAE BO	6.0	0	1.00	1.00
1571	SMILES GA	11.0	00	1.00	1.00
1571	SMILES LSTM HC	5.0	00	1.00	1.00
1572	SMILES VAE BO	6.0	00	1.00	1.00
1573					

Table 21. Model Rankings based on average Molecule Generation Metrics across all target proteins

Table 22. Number of molecules generated under given 96 hours.

	1	2	2 0	4	4		
MODEL	IIEP	3EML	3NY8	4RLU	4UNN	5M04	7LII
3DSBDD	1002	715	753	826	900	616	589
AUTOGROW4	1429	1438	1319	1272	1552	1496	1301
POCKET2MOL	1038	1020	900	900	841	900	900
POCKETFLOW	1000	1000	1000	1000	1000	1000	1000
ResGen	800	800	800	800	322	369	527
DST	1001	1001	1001	1001	1001	1001	1001
GRAPH GA	700	1001	700	700	300	1001	1001
MIMOSA	1001	1001	1001	1001	1001	1001	1001
MoLDQN	501	501	501	501	501	501	501
PASITHEA	800	1000	800	800	1000	1000	1000
REINVENT	100	100	100	100	100	100	100
SCREENING	1000	1000	1000	1000	1000	1000	1000
SELFIES VAE BO	200	200	200	200	200	200	200
SMILES GA	525	441	615	618	808	710	376
SMILES LSTM HC	501	501	501	501	501	501	501
SMILES VAE BO	200	200	200	200	200	200	200