

MARS: MARKOV MOLECULAR SAMPLING FOR MULTI-OBJECTIVE DRUG DISCOVERY

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ABSTRACT

Searching for novel molecules with desired chemical properties is crucial in drug discovery. Existing work focuses on developing deep generative models to generate either sequences or chemical molecular graphs. However, it remains a great challenge to find novel and diverse compounds satisfying many properties. In this paper, we propose MARS, a method for multi-objective drug molecule discovery. MARS is based on the idea of generating the chemical candidates by iterative editing fragments of molecular graphs. To search for the best candidates, it employs an annealing scheme together with Markov chain Monte Carlo sampling (MCMC) on molecules. To further improve sample efficiency, MARS is equipped with a graph neural network (GNN) as the proposal for candidate edits on molecules, while the GNN is trained on-the-fly utilizing the sample paths in MCMC. Our experiments show that MARS achieves state-of-the-art performance in various multi-objective settings where molecular bio-activity, drug-likeness, and synthesizability are simultaneously considered. **In the most challenging setting where four objectives – bio-activities to two different targets, drug-likeness and synthesizability – are simultaneously considered, our method outperforms the state-of-the-art significantly in a comprehensive evaluation.**

1 INTRODUCTION

Drug discovery aims to find chemical compounds with certain target properties, such as high drug-likeness (QED) (Bickerton et al., 2012). The same problem is referred to as molecular design, molecular generation, or molecular search. The size of drug-like chemical space is enormous, approximate 10^{33} for realistic drugs that could ever be synthesized (Polishchuk et al., 2013). Therefore it is very challenging to search for a high-quality molecule from such a vast space — enumeration would take almost forever. Finding the right candidates targeting specific proteins for a particular disease even further complicates the problem.

Instead of enumerating and search from the immense chemical space, recent work utilizes deep generative models to directly generate candidate molecules (Schwalbe-Koda & Gómez-Bombarelli, 2020; Guo & Zhao, 2020). **However, most prior work focuses on generating molecules concerning a single property such as drug-likeness (QED) or octanol-water partition coefficient (logP) (Jin et al., 2018; You et al., 2018; Popova et al., 2019; Shi et al., 2020; Zang & Wang, 2020).** While in practical settings, typical drug discovery requires consideration of multiple properties jointly (Nicolaou et al., 2012). For example, to find drug-like molecules with high synthesizability and sufficient biological activity against the target protein. Naturally, multi-objective molecule design is much more challenging than the single-objective scenario (Jin et al., 2020).

This paper studies the problem of multi-objective molecule design for drug discovery. An ideal solution should be efficient and meet the following criteria. C1: It should satisfy multiple properties with high scores; C2: It should produce diverse and novel molecules; C3: It does not rely on either expert annotated or wet experimental data collected from a biochemistry lab (since it requires tremendous effort). Existing molecule generation approaches do not meet all these criteria. These methods belong to three categories: generating candidates from a learned continuous latent space (Gómez-Bombarelli et al., 2018; Jin et al., 2018), through reinforcement learning (You et al., 2018), and using an encoder-decoder translation approach (Jin et al., 2019b). Current state-of-the-art multi-objective molecular generation is a rationale-based method (Jin et al., 2020). In this approach, the authors

propose to build molecules by composing multiple extracted rationales, and the model can generate compounds that are simultaneously active to multiple biological targets. However, such an approach will result in quite complex molecules when we have too many objectives. This is because different objectives correspond to different rationales, and including all these rationales could lead to large molecules, which may be less drug-like and hard to be synthesized practically.

In this paper, we propose MARKov molecular Sampling (MARS), a simple yet flexible method for drug discovery. The basic idea is to start from an initial molecule and keep generating candidate molecules by modifying fragments of molecular graph from the prior step. It meets all the criteria C1-3. We formulate the molecular design as an iterative editing procedure with its total objective includes multiple property scores (C1). MARS employs the annealed Markov chain Monte Carlo sampling to search for optimal chemical compounds, which allows for exploration of chemicals with novel and different fragments (C2). The proposal to modify molecular fragments is carefully designed using Graph Neural Networks (GNNs). We used message passing neural networks (MPNNs) in practice (Gilmer et al., 2017), but other GNNs can fit the framework as well. Furthermore, MARS utilizes the sample paths generated on-the-fly to train the proposal network adaptively. Therefore it does not rely on external annotated data (C3). With such an adaptive learnable proposal, it keeps improving the generation quality throughout the process.

We evaluate our proposed method and several other baselines on a variety of multi-objective generation settings. Experiments show that MARS achieves state-of-the-art performance on five out of six tasks in terms of a comprehensive evaluation consisting of the success rate, novelty, and diversity of the generated molecules. **Notably, in the most challenging setting where four objectives – bio-activities to two different targets, drug-likeness and synthesizability – are simultaneously considered, our method outperforms the state-of-the-art significantly in a comprehensive evaluation.**

Our contributions are as follows:

- We present a generic formulation of molecular design using Markov sampling, which can easily accommodate multiple objectives.
- We develop an adaptive fragment-editing proposal based on GNN that is learnable on the fly with only samples self-generated and efficient in exploring the chemical space.
- Experiments verifies our proposed MARS framework can find novel and diverse bioactive molecules that are both drug-like and highly synthesizable.

2 RELATED WORK

Molecular generation. Recent years have witnessed the great success of applying deep generative models and molecular graph representation learning in drug discovery (Schwalbe-Koda & Gómez-Bombarelli, 2020; Guo & Zhao, 2020). In the sense of property optimization, existing approaches can be roughly divided into three categories. The first one lying in these approaches optimize molecular properties in the continuous latent space with continuous optimization algorithms like Bayesian optimization (BO) (Gómez-Bombarelli et al., 2018; Jin et al., 2018; Winter et al., 2019). These methods rely heavily on the quality of latent representations, which imposes huge challenges to the encoders when there are multiple properties to consider. Unlike the first one, other work (Cao & Kipf, 2018; Popova et al., 2018; You et al., 2018; Popova et al., 2019; Shi et al., 2020) proposes to employ reinforcement learning (RL) to optimize desired objectives directly in the explicit chemical space. However, the models are usually hard to train due to the high variance of RL. To alleviate this, the translation-based approaches sidestep RL by training models with pre-constructed molecular pairs (Jin et al., 2019b;a). Although simple, such methods require many high-quality labeled data, making them impractical in scenarios where the data is limited.

In addition to these, some methods are proposed recently to address the multi-objective molecule generation problem. For example, Li et al. (2018) proposes to use a conditional generative model to incorporate several objectives flexibly, while Lim et al. (2020) leverages molecular scaffolds to control the properties of generated molecules better. Among them, the current state-of-the-art approach is a rationale-based method proposed by Jin et al. (2020). In this method, the authors propose to build molecules by assembling extracted rationales. Despite its great success in generating compounds simultaneously active to multiple biological targets, the combination of rationales might hinder the synthesizability and drug-likeness of produced molecules, as they tend to be large as the

number of objectives grows. In contrast, our MARS framework turns the generation problem into a sampling procedure, which serves as an alternative way compared with deep generative models, and can efficiently discover bio-active molecules that are both drug-like and highly synthesizable.

Heuristic search. Apart from the generative approaches, there is another branch of methods that heuristically explore the molecular space, and is also widely used in molecular property optimization. Among them, the most prevailing ones are evolutionary algorithms (EAs) and genetic algorithms (GAs) (Nicolaou et al., 2012; Devi et al., 2015; Jensen, 2019; Ahn et al., 2020). In Nigam et al. (2020), the authors propose to augment GA by adding an adversarial loss into the fitness evaluation to increase the diversity, and the augmented GA outperforms all other generative models in optimizing logP. Though flexible and straightforward, most GA and EA methods require domain experts to design molecular mutation and crossover rules and might suffer from low search efficiency. Different from these work, MARS is built upon the general MCMC sampling framework in which tons of mathematical tools can be applied, and we also introduce an adaptive proposal based on molecular graph editing actions to improve the sampling efficiency.

3 PROPOSED MARS APPROACH

In this section, we present the MARkov molecular Sampling method (MARS) for multi-objective molecular design. We define a Markov chain on the explicit chemical space and design a kernel to navigation through high probable candidates with acceptance and rejection.

3.1 SAMPLING FROM THE MOLECULAR SPACE

Our proposed MARS framework aims at sampling molecules with desired properties from the chemical space. Specifically, given K properties of interest, the desired molecular distribution can be formulated as a combination of all objectives:

$$\pi(x) = \underbrace{s_1(x) \circ s_2(x) \circ s_3(x) \circ \cdots \circ s_K(x)}_{\text{desired properties}} \quad (1)$$

where x is a molecule in the molecular space \mathcal{X} , $\pi(x)$ is an unnormalized molecular distribution that describes the desired properties, and $s_k(x)$ is a scoring function for the k -th property and the “ \circ ” operator stands for a combination of scores (e.g., summation or multiplication). In practical drug discovery, these terms could be related to the biological activity, drug-likeness, and synthesizability of molecules (Nicolaou et al., 2012), and we can flexibly define them according to our applications. However, as the number of objectives grows, the combined distribution $\pi(x)$ will become more complex and intractable, which makes the sampling non-trivial.

In MARS, we propose to sample molecules from the desired distribution based on Markov chain Monte Carlo (MCMC) methods (Andrieu et al., 2003). Given a desired molecular distribution $\pi(x)$ as the unnormalized target distribution, we define a Markov chain on the explicit chemical space \mathcal{X} (i.e., each state of the Markov chain is a particular molecule) and introduce a proposal distribution $q(x' | x)$ to perform state transitions.

Specifically, as shown in Figure 1, the sampling procedure of MARS starts from an initial molecule $x^{(0)} \in \mathcal{X}$. At each time step t , a molecule candidate $x' \in \mathcal{X}$ will be sampled from the proposal distribution $q(x' | x^{(t-1)})$, where $x^{(t-1)}$ denotes the molecule at time step $t - 1$. Then the proposed candidate x' could be either accepted $x^{(t)} = x'$ or rejected $x^{(t)} = x^{(t-1)}$ according to an acceptance rate $\mathcal{A}(x^{(t-1)}, x') \in [0, 1]$ controlled by the target distribution $\pi(x)$. By repeating this process, a sequence of molecules $\{x^{(t)}\}_{t=0}^{\infty}$ can be generated, and the sequence will converge to the target distribution $\pi(x)$ if the proposal distribution and the acceptance mechanism are specified properly.

For the acceptance rate, it can be generally represented as follow:

$$\mathcal{A}(x, x') = \min \left\{ 1, \frac{\pi^\alpha(x')q(x|x')}{\pi^\alpha(x)q(x'|x)} \right\} \quad (2)$$

where α is a coefficient that varies in different instantiations of MCMC algorithms. Here to find molecules that globally maximize the target distribution, we employ an annealing

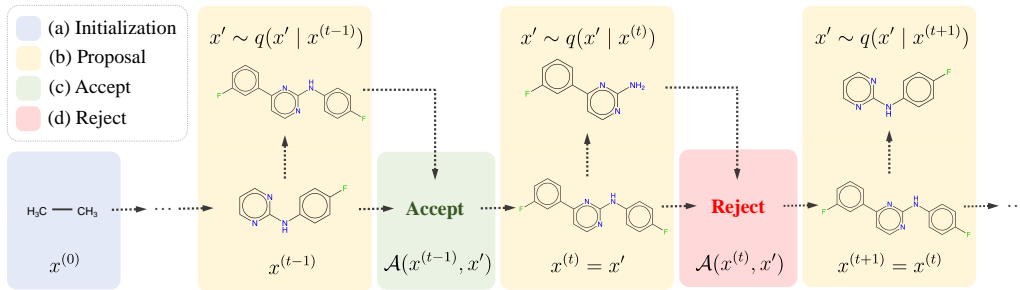


Figure 1: The general architecture of MARS. During the sampling process: (a) starting from an arbitrary initial molecule $x^{(0)}$ from the molecular space \mathcal{X} , (b) we sample a candidate molecule $x' \in \mathcal{X}$ from the proposal distribution $q(x' | x^{(t-1)})$ at each step based on the molecule from the last step $x^{(t-1)}$, (c/d) and then the candidate x' is either accepted or rejected according to an acceptance rate $\mathcal{A}(x^{(t-1)}, x') \in [0, 1]$. By repeating this process, we can generate a sequence of molecules $\{x^{(t)}\}_{t=0}^{\infty}$.

scheme (Laarhoven & Aarts, 1987) where $\alpha = 1/T$ and T is a temperature controlled by a cooling schedule. In addition to this, other instantiations such as Metropolis-Hastings (MH) algorithm (Metropolis et al., 1953) where $\alpha = 1$ are also feasible under our general framework.

As for the proposal distribution $q(x' | x)$, it will greatly influence the sampling performance and should be designed elaborately. In general, it is crucial that the proposal distribution $q(x' | x)$ and the target distribution $\pi(x')$ are as close as possible to ensure high sampling efficiency. So we propose using a proposal distribution $q_{\theta}(x' | x)$ with learnable parameters to capture the desired molecular properties and develop a strategy to train the proposal throughout the sampling process adaptively. The details will be described in the next section.

3.2 ADAPTIVE MOLECULAR GRAPH EDITING PROPOSAL

In this section we will examine in detail our proposed adaptive proposal distribution $q_{\theta}(x' | x)$. In MARS, the proposal distribution is represented with molecular graph editing actions and can be parameterized with MPNNs. To sample molecules with desired properties effectively and efficiently, we also design a strategy to train the networks during sampling in an adaptive manner.

Molecular graph editing actions. To transform a molecule x into another molecule x' , we consider two sets of graph editing actions, i.e., fragment *adding* and *deleting*. These actions are inspired by fragment-based drug design (FBDD) methodology, whose success in drug discovery has been proved in past decades (Kumar et al., 2012). In MARS, we define *fragments* as connected components in molecules separated by single bonds. To reduce the complexity of editing actions, we only consider fragments with a single attachment position. Moreover, we also define a *fragment vocabulary* that contains finite many fragments, and only fragments in the vocabulary are allowed to be added onto a molecule. Examples for fragment adding and deleting actions are shown in Figure 2.

Specifically, given a molecule x with n atoms and m bonds, we choose to add or delete a fragment onto or from this molecule randomly with probability $\frac{1}{2}$ for each set of actions. For the *adding* action, suppose we have a probability distribution over atoms $p_{\text{add}}(u)$ and a probability distribution over fragments in the vocabulary $p_{\text{frag}}(k)$. Here $u \in [n]$ is an indicator of atoms in x and $k \in [V]$ is an indicator of fragments in the vocabulary of size V . We can compute the proposal distribution as follows:

$$q(x'|x) = \frac{1}{2} \cdot p_{\text{add}}(u) \cdot p_{\text{frag}}(k) \quad (3)$$

where x' is the molecule obtained by adding the k -th fragment onto the atom u in molecule x .

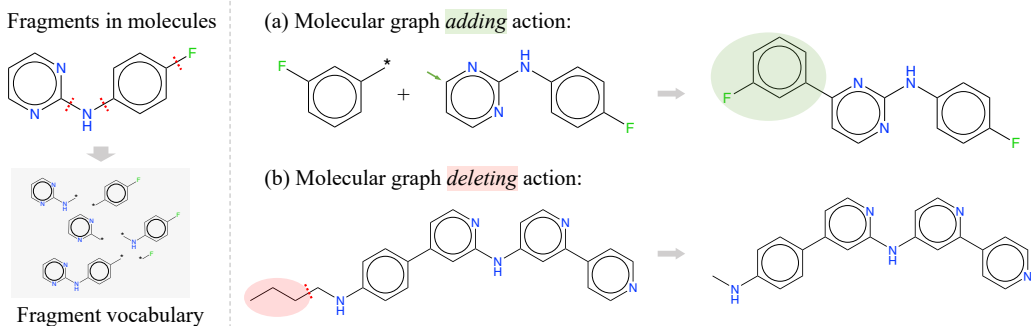


Figure 2: **Left:** Examples of molecular fragments and a fragment vocabulary. Red dashed lines represents cuttable bonds to extract fragments. **Right:** Examples of molecular graph editing actions.

As for the *deleting* action, suppose we have a probability distribution over bonds¹ $p_{\text{del}}(b)$ where $b \in [2m]$ is an indicator of bonds in x . We can compute the proposal distribution as follow:

$$q(x'|x) = \frac{1}{2} \cdot p_{\text{del}}(b) \quad (4)$$

where x' is the molecule obtained by removing bond b and the attached fragment from molecule x .

Parameterizing with MPNNs. To better model the molecular graph editing actions, we propose to use MPNNs to suggest the probability distributions $(p_{\text{add}}, p_{\text{frag}}, p_{\text{del}}) = \mathcal{M}_{\theta}(x)$ where \mathcal{M}_{θ} is a MPNN model specified by parameters θ , which has been proven powerful to predict chemical properties with molecular graphs (Gilmer et al., 2017). **Particularly, given a molecule x , we input the corresponding molecular graph into MPNN to obtain the node hidden representations $\{h_u^{\text{node}} \in \mathbb{R}^d\}_{u=1}^n$ where d is the dimension of the hidden space.** Then we can compute probability distributions as follow:

$$h_b^{\text{edge}} = \text{Concat}(h_v^{\text{node}}, h_w^{\text{node}}) \in \mathbb{R}^{2d} \quad (5)$$

$$h^{\text{graph}} = \text{MaxPooling}(\{h_u^{\text{node}}\}) \in \mathbb{R}^d \quad (6)$$

$$p_{\text{add}} = \text{Softmax}(\{\text{MLP}_{\text{node}}(h_u^{\text{node}})\}) \quad (7)$$

$$p_{\text{frag}} = \text{Softmax}(\text{MLP}_{\text{graph}}(h^{\text{graph}})) \quad (8)$$

$$p_{\text{del}} = \text{Softmax}(\{\text{MLP}_{\text{edge}}(h_b^{\text{edge}})\}) \quad (9)$$

where v, w are atoms connected with bond b , $\{h_b^{\text{edge}}\}_{b=1}^{2m}$ are edge hidden representations, h^{graph} is the graph embedding (Hu et al., 2020), and $\text{MLP}_{\text{node}}, \text{MLP}_{\text{graph}}, \text{MLP}_{\text{edge}}$ are multi-layer perceptrons (MLPs) used in the prediction.

Adaptive training. To capture the desired properties as well as to improve the sampling performance and efficiency, we can train the editing model to increase the probability of suggesting high-quality candidate molecules. Here we propose to train the model on-the-fly during the sampling process in an adaptive manner where the training data is collected from the sampling paths. By doing so, we can bypass the difficulty of lacking training instances that satisfy all property constraints. Particularly, we collect molecule candidates that improve our desired objectives, and train the model \mathcal{M}_{θ} in a maximum likelihood estimation (MLE) manner (i.e. to maximize the probability of producing the collected candidates). So overall, the whole MARS sampling process could be described as Algorithm 1.

Discussion on training and convergence. Compared with standard MCMC algorithms, MARS still falls in the Metropolis-Hastings algorithm with an annealing scheme and an adaptive proposal, which results in inhomogeneous transition kernels. The convergence of annealed MCMC is discussed in Andrieu et al. (2003), and it could be guaranteed by elaborately choosing a temperature

¹Molecular bonds are treated as directed ones to specify the fragments to drop from molecules.

Algorithm 1: MARS.

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1 Set initial molecules  $\{x_i^{(0)}\}_{i=1}^N$  and initialize the molecular graph editing model  $\mathcal{M}_\theta$ ;
2 Create an empty editing model training dataset  $\mathcal{D} = \{\}$ ;
3 for  $t = 1, 2, \dots, N$  do
4   for  $i = 1, 2, \dots, N$  do
5     Compute probability distributions  $(p_{\text{add}}, p_{\text{frag}}, p_{\text{del}}) = \mathcal{M}_\theta(x_i^{(t-1)})$  as Equations 7-9;
6     Sample a candidate molecule  $x'$  from the proposal distribution  $q(x' | x_i^{(t-1)})$  defined with
       probability distributions  $p_{\text{add}}, p_{\text{frag}}, p_{\text{del}}$  as Equations 3-4;
7     if  $u < \mathcal{A}(x_i^{(t-1)}, x')$  where  $u \sim \mathcal{U}_{[0,1]}$  then
8       | Accept the candidate molecule  $x_i^{(t)} = x'$ ;
9     else
10      | Refuse the candidate molecule  $x_i^{(t)} = x^{(t-1)}$ ;
11    end
12    if The candidate improves the objectives, i.e.  $\pi(x') > \pi(x_i^{(t-1)})$  then
13      | Adding the editing record  $(x_i^{(t-1)}, x')$  into the dataset  $\mathcal{D}$ ;
14    end
15  end
16  Update the molecular editing model  $\mathcal{M}_\theta$  with the current dataset  $\mathcal{D}$  in a MLE manner;
17 end

```

cooling schedule. The convergence of inhomogeneity is discussed in Rosenthal (2011). According to the diminishing adaptation condition, we can ensure the convergence of inhomogeneous MCMC by making the difference of proposals in consecutive iterations diminish to zero. This is easily satisfied in MARS by using an optimizer (e.g., Adam) whose learning rate will shrink to zero eventually. By combining these two results, it yields the convergence of inhomogeneous annealed MCMC.

4 EXPERIMENTS

4.1 EXPERIMENT SETUP

Biological objectives. Following Jin et al. (2020), we consider the following two properties as the biological activity objectives, where the predictive model for each property is a random forest that takes Morgan fingerprint features (Rogers & Hahn, 2010) as input, and the positive threshold is set as $\delta = 0.5$ (Jin et al., 2020; Li et al., 2018).

- GSK3 β : Inhibition against glycogen synthase kinase-3 β .
- JNK3: Inhibition against c-Jun N-terminal kinase-3.

Multi-objective generation. To evaluate the effectiveness of the proposed method for multi-objective drug design, we also consider the following more challenging objective combinations:

- GSK3 β +JNK3: Jointly inhibiting GSK3 β and JNK3. The combination may provide potential benefits for the treatment of Alzheimer’s disease reported by Li et al. (2018).
- GSK3 β /JNK3+QED+SA: Inhibiting GSK3 β or JNK3 while being drug-like and synthetically accessible. Following Jin et al. (2020), we adopt QED (Bickerton et al., 2012) and synthetic accessibility (SA) (Ertl & Schuffenhauer, 2009) to quantify the last two properties. In particular, we require QED ≥ 0.6 and SA ≥ 0.67 .²
- GSK3 β +JNK3+QED+SA: Jointly inhibiting GSK3 β and JNK3 while being drug-like and synthetically accessible, which are quantified by QED and SA respectively.

Baselines. We compare MARS with the following baselines for molecular property optimization. **GCPN** (You et al., 2018) leverages RL to generate molecules atom by atom, and the adversarial loss is incorporated in the objective to generate more realistic molecules. **JT-VAE** (Jin et al., 2018) is a VAE-based approach that firstly generates junction trees and then assembles them into molecules. It

²We rescale SA score into $[0, 1]$ such that molecules with higher scores are more synthetically accessible, and 0.67 is the rescaled threshold corresponding to the one reported in Jin et al. (2020).

performs Bayesian optimization (BO) to guide molecules towards desired properties. **RationaleRL** (Jin et al., 2020) is a state-of-the-art approach for multi-property optimization, which generates molecules from combined rationales. **GA+D** (Nigam et al., 2020) is a heuristic search method that applies the genetic algorithm (GA) to find molecules with high property scores. To increase the diversity of generated molecules, an adversarial loss is incorporated in the fitness evaluation.

Evaluation metrics. Following Jin et al. (2020), we generate $N = 5000$ molecules for each approach and compare the proposed method with the baselines on the following evaluation metrics: **Success rate (SR)** is the percentage of generated molecules that are evaluated as positive on all given objectives; **Novelty (Nov)** is the percentage of generated molecules with similarity less than 0.4 compared to the nearest neighbor x_{SNN} in the training set (Olivecrona et al., 2017): $\text{Nov} = \frac{1}{n} \sum_{x \in \mathcal{G}} \mathbb{1}[\text{sim}(x, x_{\text{SNN}}) < 0.4]$; **Diversity (Div)** measures the diversity of generated molecules, which can be calculated based on pairwise Tanimoto similarity over Morgan fingerprints $\text{sim}(x, x')$ as $\text{Div} = \frac{2}{n(n-1)} \sum_{x \neq x' \in \mathcal{G}} 1 - \text{sim}(x, x')$; **Product (Prod)** is the product of the above three metrics, which is a more comprehensive evaluation of the proposed method. **Intuitively, it can present the percentage of generated molecules that are simultaneously bio-active, novel and diverse, which are essential criteria to be considered in building a suitable drug candidate library in early-stage drug discovery (Huggins et al., 2011).**

Implementation details. For the fragment vocabulary, we extract the top 1000 frequently appearing fragments that contain no more than 10 heavy atoms from the ChEMBL database (Gaulton et al., 2017) by enumerating single bonds to break. As for the sampling process, the unnormalized target distribution is set as $\pi(x) = \sum_k s_k(x)$ where $s_k(x)$ is a scoring function for the above-mentioned properties of interests, the temperature is set as $T = 0.95^{\lfloor t/5 \rfloor}$ and we sample $N = 5000$ molecules at one time. **And sampling paths are all starting with an identical molecule "C-C", which is also adopted by previous graph generation methods for organic molecules (You et al., 2018).** For the MPNN model, it has 6 layers, and the node embedding size is $d = 64$. Moreover, for the model training, we use an Adam optimizer (Kingma & Ba, 2015) to update the model parameters with an initial learning rate set as 3×10^{-4} , the maximum dataset size is limited as $|\mathcal{D}| \leq 50,000$, and at each step, we update the model for no more than 25 times.

4.2 MAIN RESULTS AND ANALYSIS

The quantitative results are summarized in Table 1 and Table 2. From these tables, we observe that MARS outperforms all the baselines on five out of six tasks in terms of the Prod score. Furthermore, on the most challenging multi-objective optimization task, i.e., GSK3 β +JNK3+QED+SA, it significantly surpasses the best baseline with a 100% improvement for the Prod score.

Table 1: Comparison of different methods on molecular generation with only bio-activity objectives. Results of GA+D are obtained by running its open-source code. Results of other baselines are taken from Jin et al. (2020).

| Method | GSK3 β | | | | JNK3 | | | | GSK3 β + JNK3 | | | |
|-------------|--------------|-------|-------|-------------|--------|-------|-------|-------------|---------------------|-------|-------|-------------|
| | SR | Nov | Div | Prod | SR | Nov | Div | Prod | SR | Nov | Div | Prod |
| GCPN | 42.4% | 11.6% | 0.904 | 0.04 | 32.3% | 4.4% | 0.884 | 0.01 | 3.5% | 8.0% | 0.874 | 0.00 |
| JT-VAE | 32.2% | 11.8% | 0.901 | 0.03 | 23.5% | 2.9% | 0.882 | 0.01 | 3.3% | 7.9% | 0.883 | 0.00 |
| RationaleRL | 100% | 53.4% | 0.888 | 0.47 | 100% | 46.2% | 0.862 | 0.40 | 100% | 97.3% | 0.824 | 0.80 |
| GA+D | 84.6% | 100% | 0.714 | 0.60 | 52.8 % | 98.3% | 0.726 | 0.38 | 84.7% | 100% | 0.424 | 0.36 |
| MARS | 97.8% | 82.1% | 0.828 | 0.66 | 98.1% | 85.4% | 0.774 | 0.65 | 99.2% | 89.6% | 0.734 | 0.65 |

Table 2: Comparison of different methods on molecular generation with bio-activity, QED, and SA objectives. Results of all baselines are obtained by running their open-source codes.

| Method | GSK3 β + QED + SA | | | | JNK3 + QED + SA | | | | GSK3 β + JNK3 + QED + SA | | | |
|-------------|-------------------------|-------------|--------------|-------------|-----------------|-------------|--------------|-------------|--------------------------------|-------------|--------------|-------------|
| | SR | Nov | Div | Prod | SR | Nov | Div | Prod | SR | Nov | Div | Prod |
| GCPN | 0.0% | 0.0% | 0.000 | 0.00 | 0.0% | 0.0% | 0.000 | 0.00 | 0.0% | 0.0% | 0.000 | 0.00 |
| JT-VAE | 9.6% | 95.8% | 0.68 | 0.06 | 21.8% | 100% | 0.600 | 0.13 | 5.4% | 100% | 0.277 | 0.02 |
| RationaleRL | 69.9% | 40.2% | 0.893 | 0.25 | 62.3% | 37.6% | 0.865 | 0.20 | 75.0% | 55.5% | 0.706 | 0.29 |
| GA+D | 89.1% | 100% | 0.682 | 0.61 | 85.7 % | 99.8% | 0.504 | 0.43 | 85.7% | 100% | 0.363 | 0.31 |
| MARS | 99.8% | 89.9% | 0.809 | 0.73 | 88.2% | 83.8% | 0.739 | 0.55 | 91.3% | 91.1% | 0.741 | 0.62 |

Comparing all these methods, the GA+D baseline is most similar to our MARS in terms of the high novelty and Prod score, as both methods focus on molecular space exploration. However, the

diversity score of GA+D drops a lot when optimizing multiple properties simultaneously, as GAs are likely to get trapped in regions of local optima (Paszkowicz, 2009). RationaleRL is a very strong baseline that performs better than MARS in the GSK3 β +JNK3 setting. Nevertheless, when taking the drug-likeness and synthetic accessibility into consideration, their performance falls short of ours and fails to generate novel molecules. The performance of GCPN and JT-VAE remains relatively low in most settings, as they are not tailored for multi-objective property optimization.

Visualization. We also use t-SNE (van der Maaten & Hinton, 2008) to visualize the distribution of generated positive molecules with the positive ones in the training set under the GSK3 β +JNK3+QED+SA setting. **In the visualization, we use the ECFP6 fingerprints as suggested in Li et al. (2018).** As shown by Figure 3, most molecules generated by GA+D fall into two massive clusters, which aligns their low diversity. As for RationaleRL, the generated molecules also tend to be clustered, with each cluster standing for a specific combination of rationales. By contrast, the molecules generated by MARS are evenly distributed in the space with a range of novel regions covered, which justifies our high novelty and diversity scores. We further visualize some molecules generated by MARS with high property scores in Figure 4, indicating its ability to generate highly synthesizable drug-like molecules that jointly inhibit GSK3 β and JNK3.

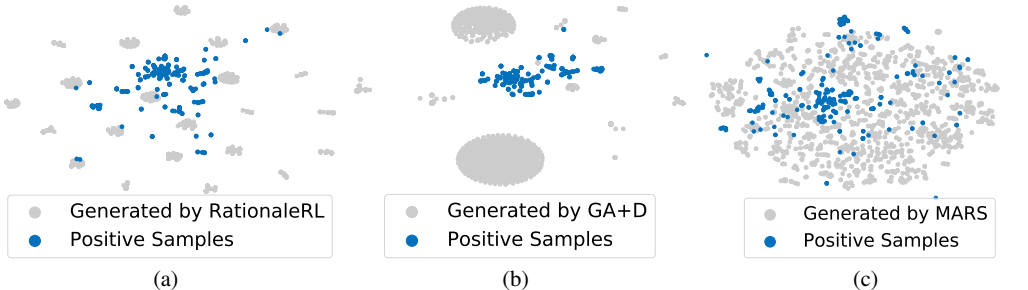


Figure 3: t-SNE visualization of generated molecules (gray) from different models and positive molecules in the training set (blue): (a) RationaleRL; (b) GA+D; (c) The proposed MARS.

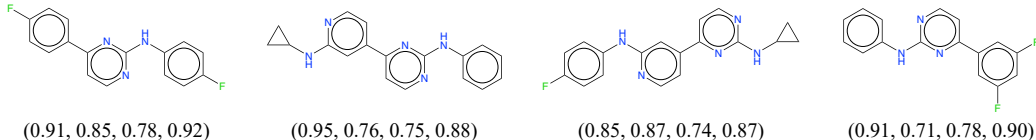


Figure 4: Samples generated by MARS in the GSK3 β +JNK3+QED+SA setting. The numbers in brackets are GSK3 β , JNK3, QED, and SA scores of each molecule respectively.

Running time. In the GSK3 β +JNK3+QED+SA setting, MARS takes roughly $T = 500$ sampling steps and 16 hours in total to converge. The sampling curves are shown in Figure 5. For other baselines, RationaleRL takes 5.7 hours to fine-tune the model, and GA+D takes 278 steps and 2.2h to achieve its best performance. However, one thing should be noted, both RationaleRL and GA+D are greatly accelerated by adopting parallel computation, which is not implemented in MARS yet. We believe MARS will have comparable computation efficiency if the conversions of molecules to graphs and molecular evaluations are computed parallelly. In addition, comparing to the conventional drug discovery process, which usually takes months to years, the time we spent on molecular generation models is ignorable (at most several hours). And in molecular generation, it is more important to well explore the chemical space – find novel and diverse bio-active molecules (Huggins et al., 2011).

4.3 ABLATION STUDY

To justify the contributions of the designed proposal and acceptance strategy, we compare them with some naive ones and summarize the results of different combinations in Table 3. For acceptance strategies, **Annealed** stands for annealed MCMC where the acceptance rate is computed as Equation 2 given $\alpha = 1/T$, **AlwaysAC** stands for always accepting the candidate, i.e., $\mathcal{A}(x, x') \equiv 1$, and **HillClimb** stands for accepting the candidate only when the overall score is improved, i.e., $\mathcal{A}(x, x') = \text{sign}[s(x') > s(x)]$. For proposal strategies, **Random** stands for random proposal

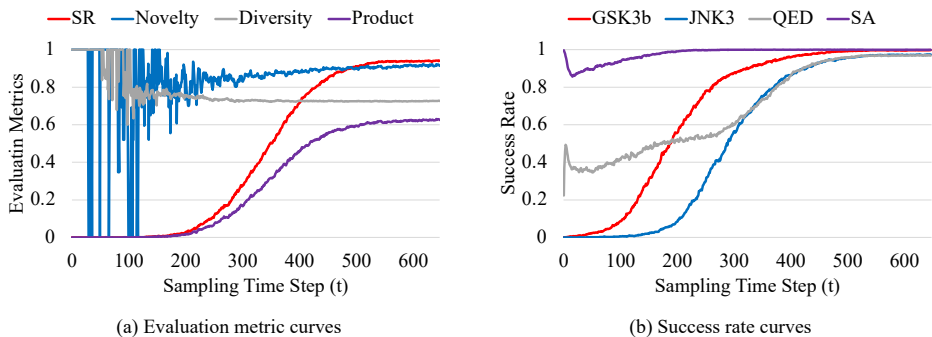


Figure 5: MARS sampling curves of the GSK3 β +JNK3+QED+SA setting: (a) evaluation metric values along sampling time steps; (b) success rate of objectives along sampling time steps.

where we randomly select atoms, bonds, and fragments to edit, and **Adaptive** stands for the adaptive fragment-based graph editing model trained during the sampling process as described in Section 3.2.

Table 3: Results of different acceptance strategies and proposal strategies for molecular sampling.

| AC Strategy | Proposal | GSK3 β + JNK3 | | | | GSK3 β + JNK3 + QED + SA | | | |
|-------------|----------|---------------------|-------|-------|------|--------------------------------|-------|-------|------|
| | | SR | Nov | Div | Prod | SR | Nov | Div | Prod |
| Annealed | Random | 40.9% | 94.9% | 0.828 | 0.32 | 25.5% | 80.4% | 0.793 | 0.16 |
| AlwaysAC | Adaptive | 49.1% | 88.4% | 0.742 | 0.32 | 10.1% | 94.6% | 0.716 | 0.07 |
| HillClimb | Adaptive | 53.7% | 96.1% | 0.814 | 0.42 | 51.4% | 86.6% | 0.777 | 0.35 |
| Annealed | Adaptive | 99.2% | 89.6% | 0.734 | 0.65 | 91.3% | 91.1% | 0.741 | 0.62 |

The results in Table 3 indicate that proposals will influence the performance of MARS dramatically (the first and the last row), especially when the number of objectives increases. The proposed adaptive proposal not only outperforms the random proposal but also converges 4.6x faster in practice. By comparing the last three rows, we find the Annealed strategy outperforms the other two strategies by a large margin on both settings, as samples from such strategy are more likely to jump out of local optimums. Another interesting observation is that even with the naive AlwaysAC or heuristic HillClimb strategy, the MARS achieves comparable or even better performance compared to GA+D and RationaleRL in some settings, e.g., HillClimb on GSK3 β +JNK3+QED+SA optimization, which again proves the effectiveness of the proposed proposal.

5 CONCLUSION AND FUTURE WORK

In this paper, we propose a simple yet flexible Markov Molecular Sampling framework (MARS) for multi-objective drug discovery. MARS includes a trainable proposal to modify chemical graph fragments, which is parameterized by a MPNN. Our experiments verify that MARS outperforms prior approaches on five out of six molecule generation tasks, and it is capable of finding novel and diverse bioactive molecules that are both drug-like and highly synthesizable. Future work can include further study of parameterization and training strategy of the molecular-editing proposal.

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Appendix

A PROPERTY SCORE DISTRIBUTIONS OF SAMPLED MOLECULES

The property score distributions of sampled $N = 5000$ molecules of the GSK3 β +JNK3+QED+SA setting are shown in Figure 6.

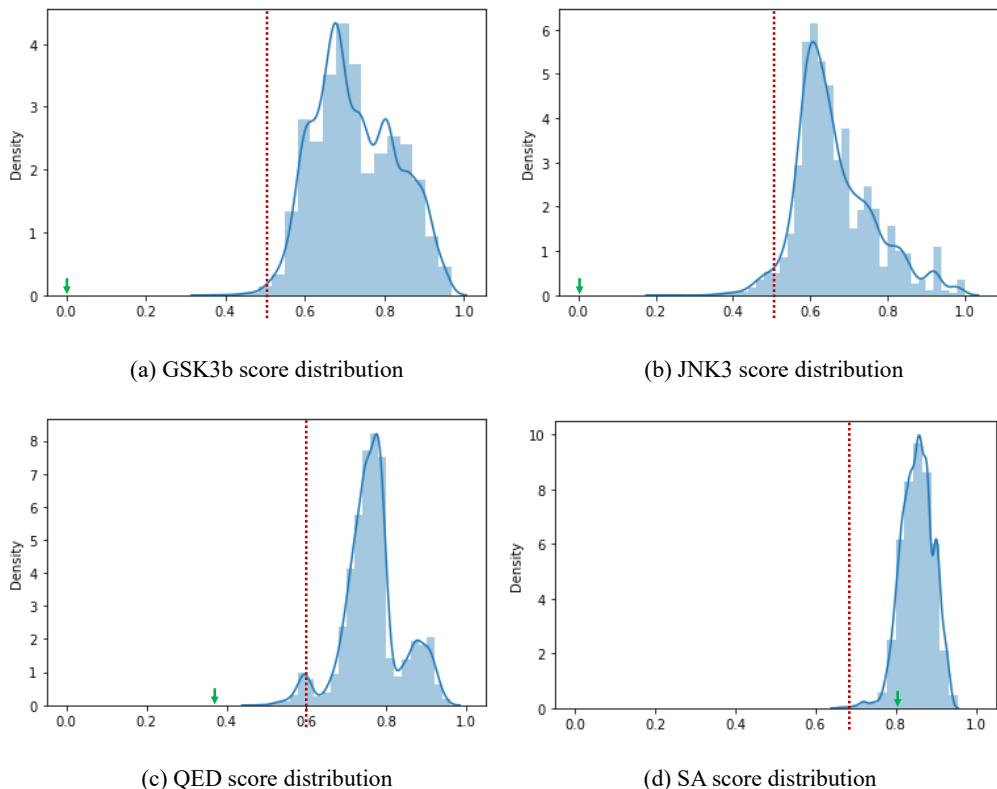


Figure 6: Property score distributions of sampled $N = 5000$ molecules. The dashed red lines stand for success thresholds, and the green arrows stand for the initial scores of the initial molecule "C-C".

B EXAMPLES OF SAMPLED MOLECULES

We also provide some examples of sampled molecules from the GSK3 β +JNK3+QED+SA setting. The numbers under molecule graphs are GSK3 β , JNK3, QED, and SA scores respectively.

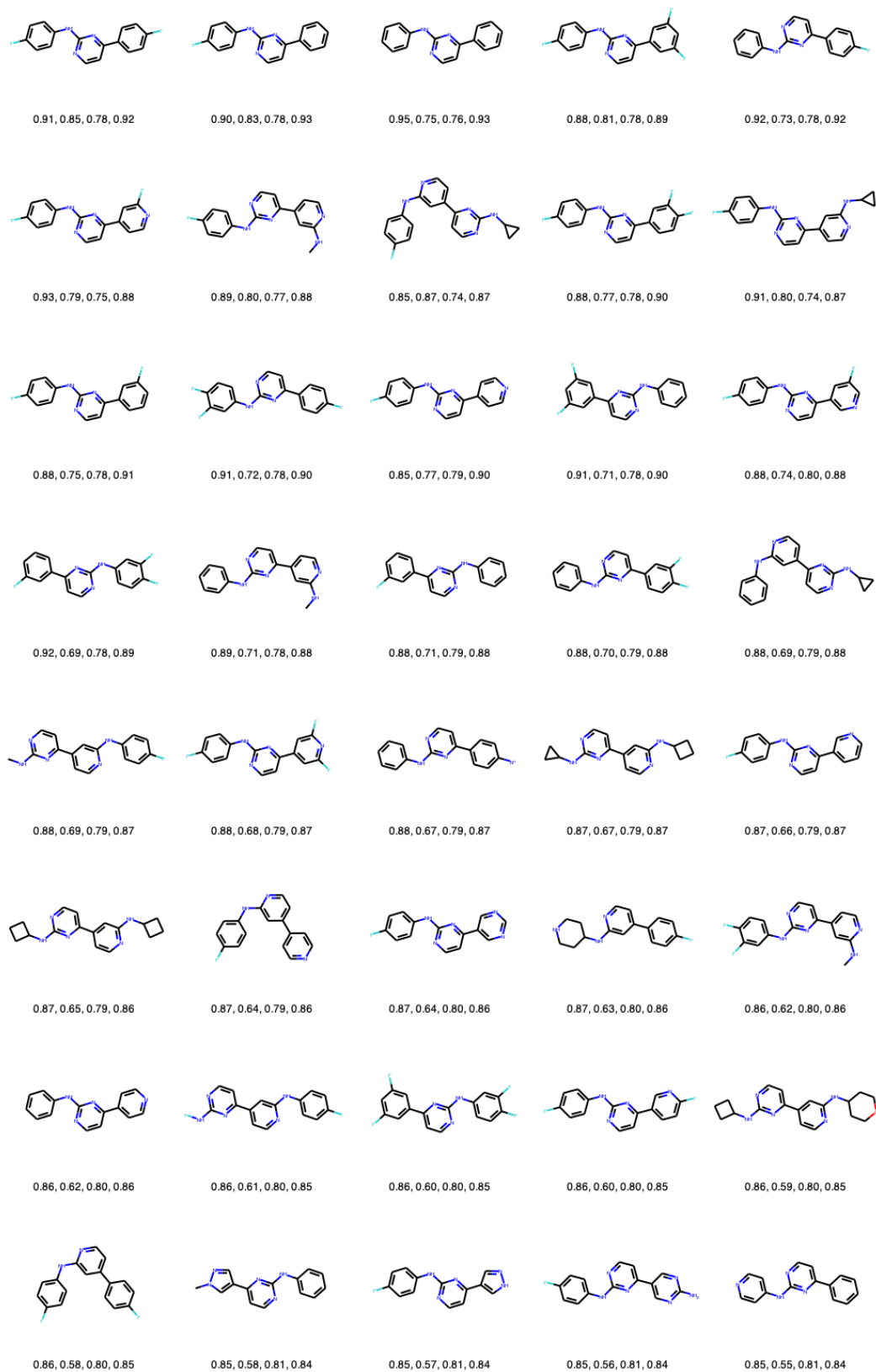
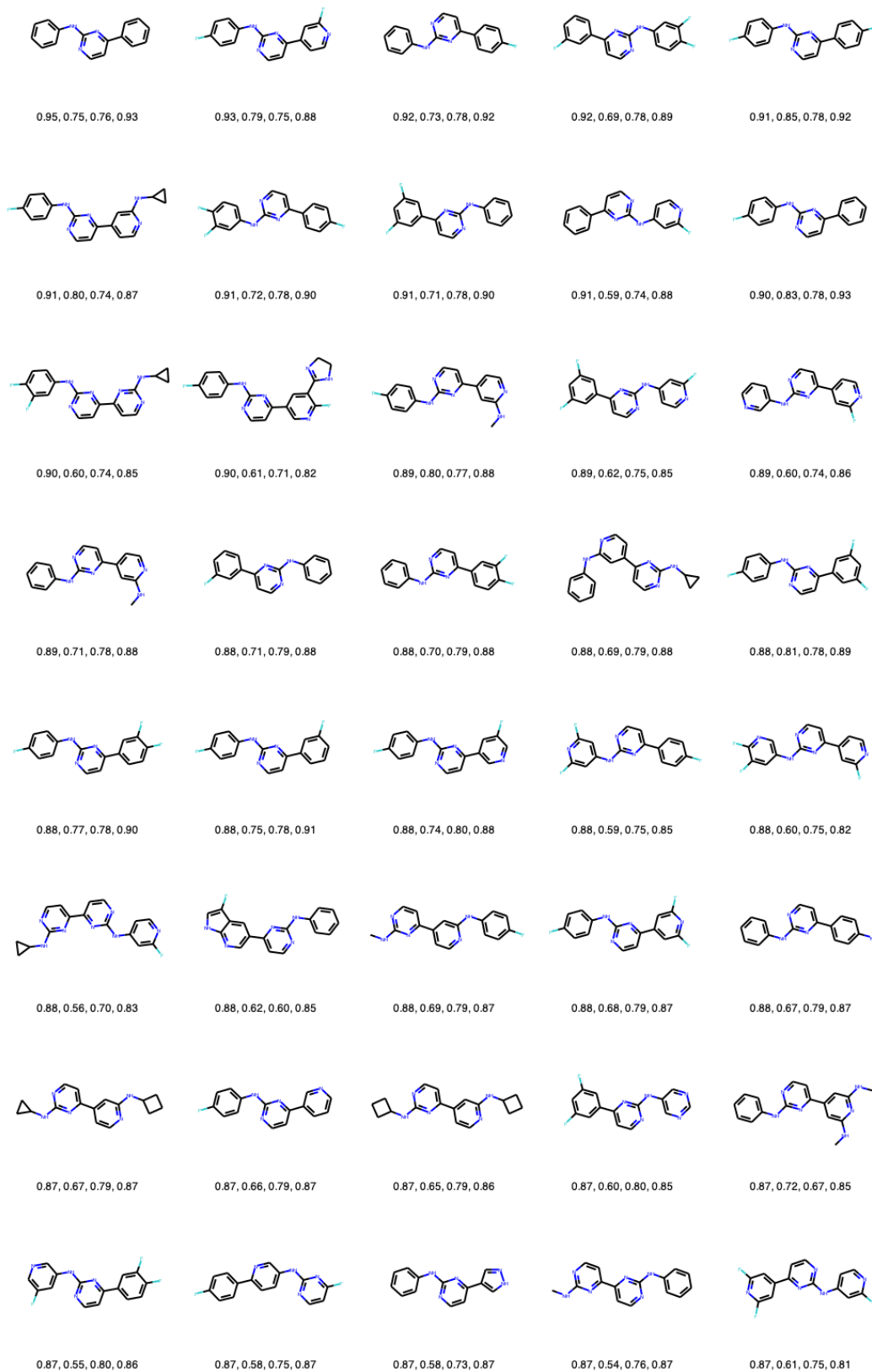


Figure 7: 40 sampled molecules with highest average property scores.

Figure 8: 40 sampled molecules with highest GSK3 β scores.

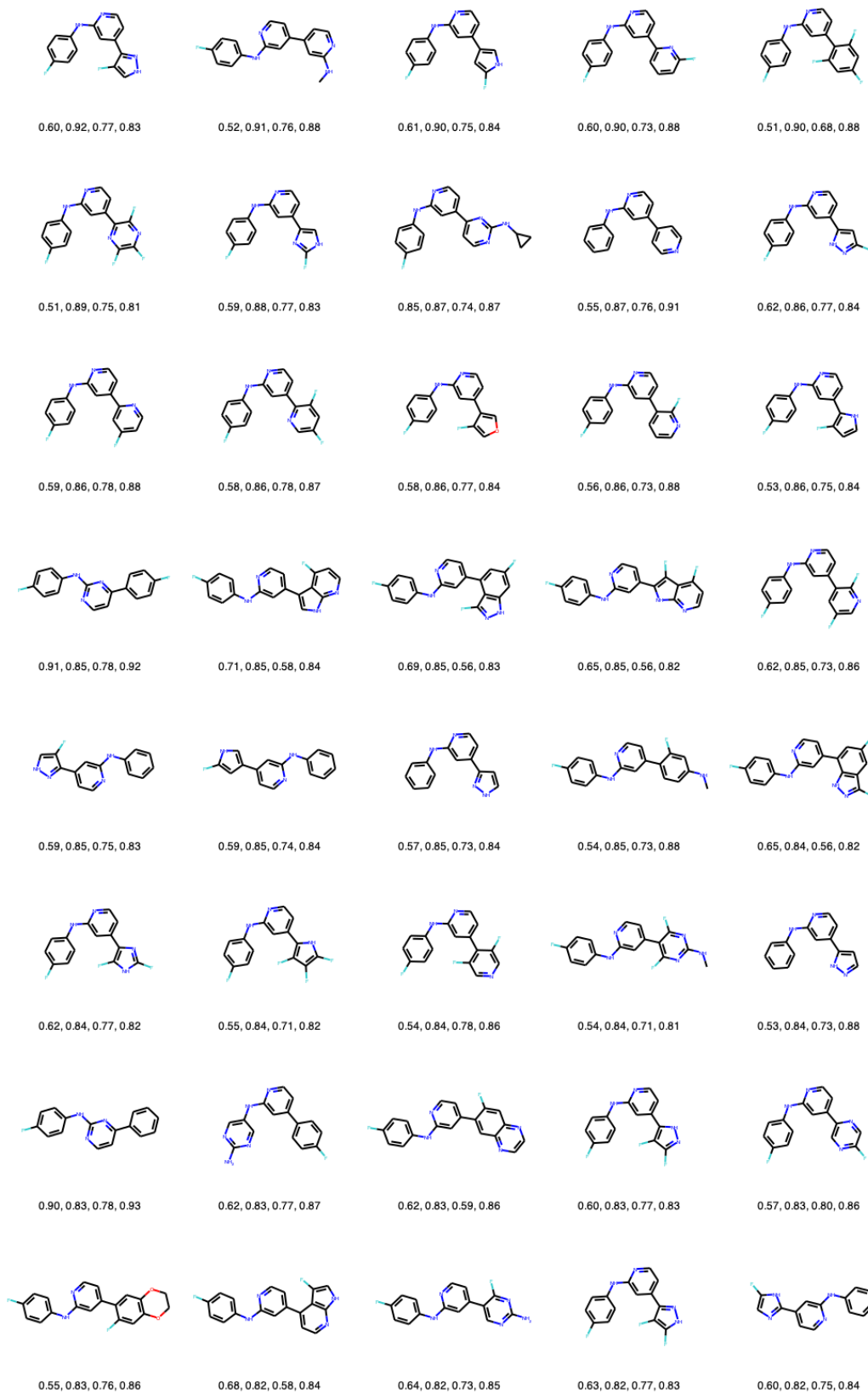


Figure 9: 40 sampled molecules with highest JNK3 scores.

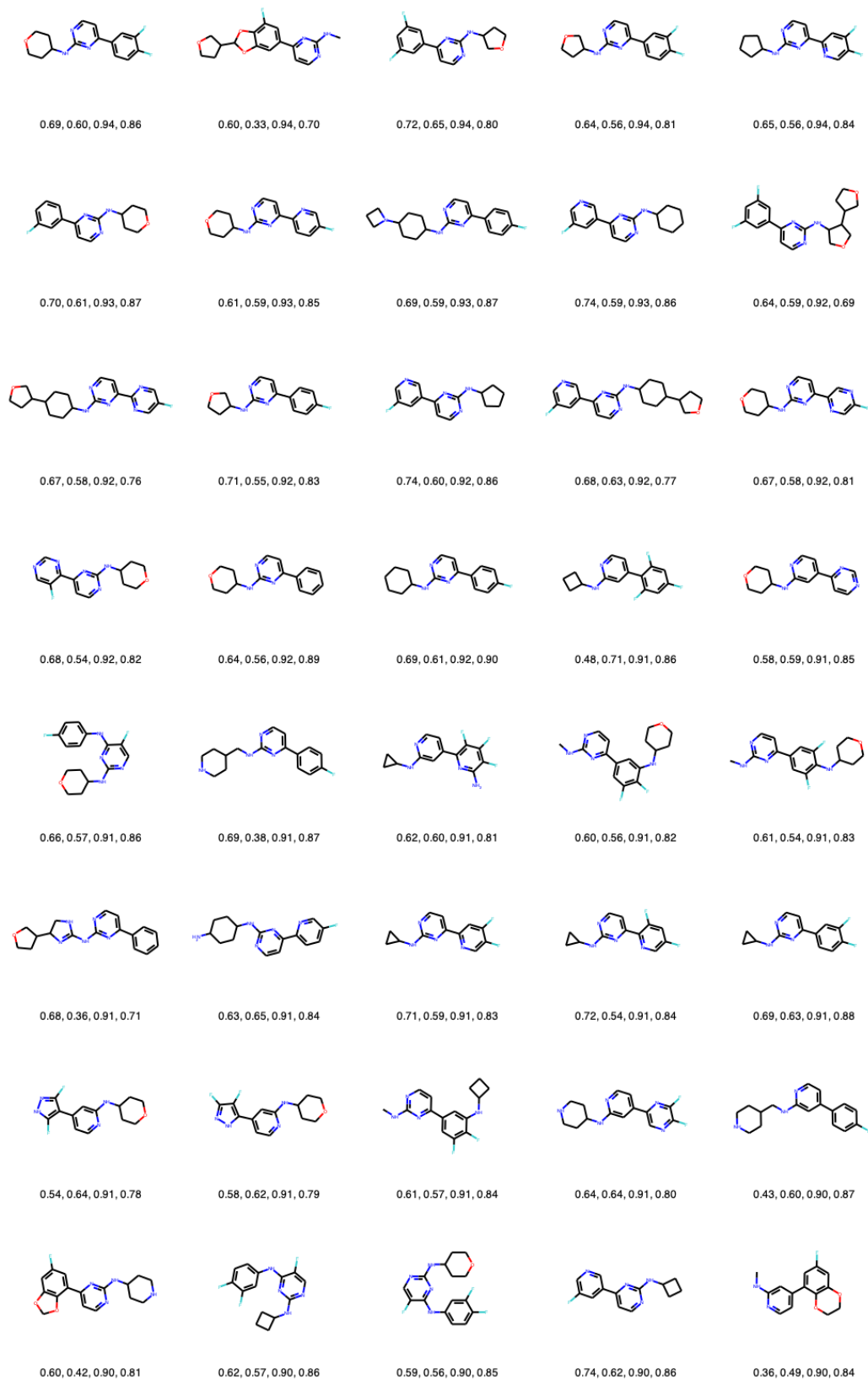


Figure 10: 40 sampled molecules with highest QED scores.



Figure 11: 40 sampled molecules with highest SA scores.