

# Bridging the Biophysical Gap: Holistic Environmental Awareness for 3D Linker Design

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## Abstract

3D molecular linker design is a critical task in structure-based drug discovery, which requires the precise synthesis of chemical bridges to connect fragments within the constrained environment of a protein binding pocket. Existing methods often suffer from environmental blindness, treating the inter-fragment space as a vacuum and yielding candidates with poor binding affinity or severe steric clashes. To address this, we propose LinkerBridge, an equivariant framework that unifies biochemical semantics with physical constraints through two innovations: a Contextual Interaction-Aware Representation module that internalizes pre-existing biochemical semantics, and a Differentiable Physical Guidance mechanism derived from Van der Waals potentials to steer generation away from collision zones. Extensive evaluations on ZINC, GEOM, and BindingMOAD benchmarks, as well as Hsp90 and JNK3 case studies, demonstrate that LinkerBridge significantly outperforms state-of-the-art methods in real-world drug discovery.

## 1 Introduction

Structure-based drug design (SBDD) is fundamental for modern pharmaceutical research, enabling the precise design of ligands that specifically bind to protein pockets to modulate biological pathways. Within this paradigm, 3D molecular linker design [Bancet *et al.*, 2020] has emerged as a key challenge, particularly for fragment-based drug discovery (FBDD) [Erlanson *et al.*, 2016] and the engineering of proteolysis targeting chimeras (PROTACs) [Békés *et al.*, 2022; Bai *et al.*, 2021; Farnaby *et al.*, 2019]. Unlike de novo generation [Lin *et al.*, 2025; Zhou *et al.*, 2024], it involves synthesizing a chemical bridge to connect pharmacophoric fragments while strictly maintaining their fixed 3D coordinates and bioactive poses. This makes linker design a highly constrained optimization problem within a rigid and sterically crowded microenvironment (Figure 1a). As shown in Figure

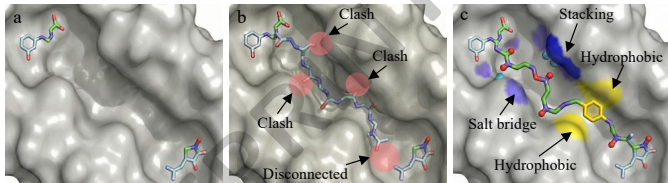


Figure 1: Illustration of difficulties in molecular linker design. (a) Input molecular fragments. (b) Failure Case: Failing to link molecular fragments and exhibiting clashes with pocket. (c) Success Case.

1c, a valid linker must transcend simple geometric connectivity to function as a biochemical conduit, ensuring that its structure and composition satisfy the chemical complementarity and biological activity dictated by the surrounding environment.

Although with great ability to generate molecules, diffusion models show critical issues when applied to linker design: lacking holistic environmental awareness. Specifically, they regard the space between the segments as a vacuum environment and rely solely on coordinate-based point cloud data, ignoring the complex biochemical and physical interactions between the segments. This kind of environmental blindness is fatal to the design of linkers. First, without perceiving pre-existing environmental semantics (e.g., hydrogen bonding or  $\pi$ -stacking), the model lacks the contextual guidance to rationally orchestrate the identity and spatial arrangement of atoms for effective molecular recognition. Some autoregressive methods [Zhung *et al.*, 2024] have attempted to utilize interaction information during the generation process, however, the interaction labels used in training and inference have a significant gap: the interactions used during training are obtained from real protein-ligand complexes, but during inference, only the protein pocket is used to predict the possible interactions. This disparity often leads to the biochemical information obtained by the model unable to effectively guide the generation process. Second, there are strict spatial constraints in protein-molecular fragments complex structure. However, most diffusion models [Peng *et al.*, 2023; Guan *et al.*, 2023] focus on point-wise denoising, that is, considering each atom separately, concentrating on minimizing the loss based on coordinates, while ignoring the surrounding

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neighborhood and boundary information. This loss calculation method leads to the generated linker violating the spatial steric hindrance principle. Coupled with the essence of diffusion random denoising, the generated linker will have severe steric hindrance conflicts with the surrounding environment (Figure 1b), resulting in the generated linker being physically invalid.

To address these issues, we transform the substructure synthesis problem into a context-aware navigation task and propose LinkerBridge (Figure 2), which integrates biochemical semantics and physical constraints into an equivariant diffusion model. First, we identify the non-covalent interactions in protein-fragment or fragment-fragment pairs, and then incorporate them into the diffusion model. By pre-injecting the interaction information, the model is able to perceive the complete biochemical landscape before denoising, thereby being guided to complete and adapt this existing biochemical template during the generation process, ensuring that the linker structure is compatible with the functional requirements of the surrounding context. Furthermore, to prevent space conflicts in highly constrained environment during the linker generation process, we introduce a differentiable physical loss based on van der Waals potential. Specifically, we regard the crowded environment as a differentiable energy surface. At each step of the denoising trajectory, we inject an energy-based gradient to guide the atoms away from the high-energy collision regions and ensure that the synthesized bridges strictly follow the spatial exclusion principle. Through comprehensive experiments in linker design tasks and case studies, LinkerBridge demonstrates superior performance compared to existing approaches.

## 2 Related Work

**Diffusion Models in Drug Discovery.** The diffusion model has emerged as a crucial paradigm for 3D molecular tasks in recent years, with its applications spanning various fields such as molecule generation [Hoogetboom *et al.*, 2022; Vignac *et al.*, 2022], conformational generation [Shi *et al.*, 2021; Jing *et al.*, 2022; Xu *et al.*, 2022], and protein-ligand docking [Corso *et al.*, 2022]. Furthermore, the diffusion framework has successfully expanded to areas such as structure-based drug design [Schneuing *et al.*, 2024; Guan *et al.*, 2023; Peng *et al.*, 2023], protein design [Watson *et al.*, 2022; Ingraham *et al.*, 2023; Luo *et al.*, 2022], prediction of protein-ligand complexes [Qiao *et al.*, 2022], and generation of antibody CDRs. These methods typically generate molecular structures under the constraints of complex 3D environments (such as protein pockets or binding sites), and often employ conditional adjustment mechanisms similar to image restoration [Sohl-Dickstein *et al.*, 2015; Lugmayr *et al.*, 2022] to maintain the consistency of the structural context. Although these advancements demonstrate the powerful generative capabilities of diffusion models, there remains a challenge in adapting them to the highly constrained requirements of linker design.

**Molecular Linker Design.** Molecular linker design has

been widely used in the fragment-based drug discovery community. The early learning-based linker design methods [Yang *et al.*, 2020; Imrie *et al.*, 2021; Sheng and Zhang, 2013] mainly employ Transformer-based or autoregressive models on SMILES [Weininger, 1988], such as DeLinker [Imrie *et al.*, 2020] and 3DLinker [Huang *et al.*, 2022]. However, these methods are difficult to achieve E(3) symmetry and are insufficient in their ability to handle large molecular fragments [Elesedy and Zaidi, 2021; Rath and Condurache, 2022] and multiple fragments. To solve this problem, DiffLinker introduces the equivariant diffusion framework, which can connect any number of segments in a single step. Nevertheless, DiffLinker [Igashov *et al.*, 2024] regards the space between fragments as a vacuum environment, lacking interactive perception of the surrounding biochemical landscape, and the generated linker is prone to physical inconsistencies in crowded spaces, resulting in the generated linker being unable to meet the key recognition patterns or causing serious spatial conflicts. The LinkerBridge proposed in this work further integrates context interaction perception and physical guidance mechanisms, thus balancing biological relevance and structural feasibility.

## 3 Method

### 3.1 Equivariant 3D Conditional Diffusion Model

We adopt the E(3) equivariant 3D conditional diffusion model [Sohl-Dickstein *et al.*, 2015] as the backbone. Our model takes the structural context  $u$  as input and generates  $M$  atoms to bridge the given fragment, thereby forming a complete connected molecule. The context  $u$  is represented in the form of a 3D atomic point cloud and can include protein-fragment complexes or only the fragment itself.

#### Joint Diffusion of Continuous and Discrete States

The molecule is represented by the coordinates of its  $M$  atoms  $r \in \mathbb{R}^{M \times 3}$  and the corresponding one-hot encoded atomic types  $h \in \mathbb{R}^{M \times n_f}$ . To handle the discrete characteristics of atomic types within the Gaussian diffusion framework, the model elevates  $h$  to the continuous space by adding Gaussian noise [Hoogetboom *et al.*, 2022]. The joint forward diffusion process  $q(z_t|x)$  for  $t = 1, \dots, T$  is defined as follows:

$$q(z_t|x) = \mathcal{N}(z_t; \alpha_t x, \sigma_t^2 I) \quad (1)$$

where  $z_t = [z_t^r, z_t^h]$ . Due to the properties of Gaussian noise, the intermediate state  $z_t$  can be sampled directly from the original data  $x$  at any time step  $t$ :

$$z_t = \alpha_t x + \sigma_t \epsilon, \quad \epsilon \sim \mathcal{N}(0, I) \quad (2)$$

The generative reverse process  $p(z_{t-1}|z_t, u)$  is modeled as a Markov chain approximating the true denoising transfer:

$$p(z_{t-1}|z_t, u) = \mathcal{N}(z_{t-1}; \mu_\theta(z_t, u, t), \zeta_t^2 I) \quad (3)$$

The neural network  $\varphi_\theta$  is trained to predict the added noise  $\hat{\epsilon}_t$  [Ho *et al.*, 2020]. The estimated data  $\hat{x}$  and the mean of the reverse transition  $\mu_\theta$  are derived as:

$$\hat{x} = \frac{1}{\alpha_t} (z_t - \sigma_t \varphi_\theta(z_t, u, t)) \quad (4)$$

$$\mu_t(x, z_t) = \frac{\bar{\alpha}_t \sigma_{t-1}^2}{\sigma_t^2} z_t + \frac{\alpha_s \bar{\sigma}_t^2}{\sigma_t^2} \hat{x} \quad (5)$$

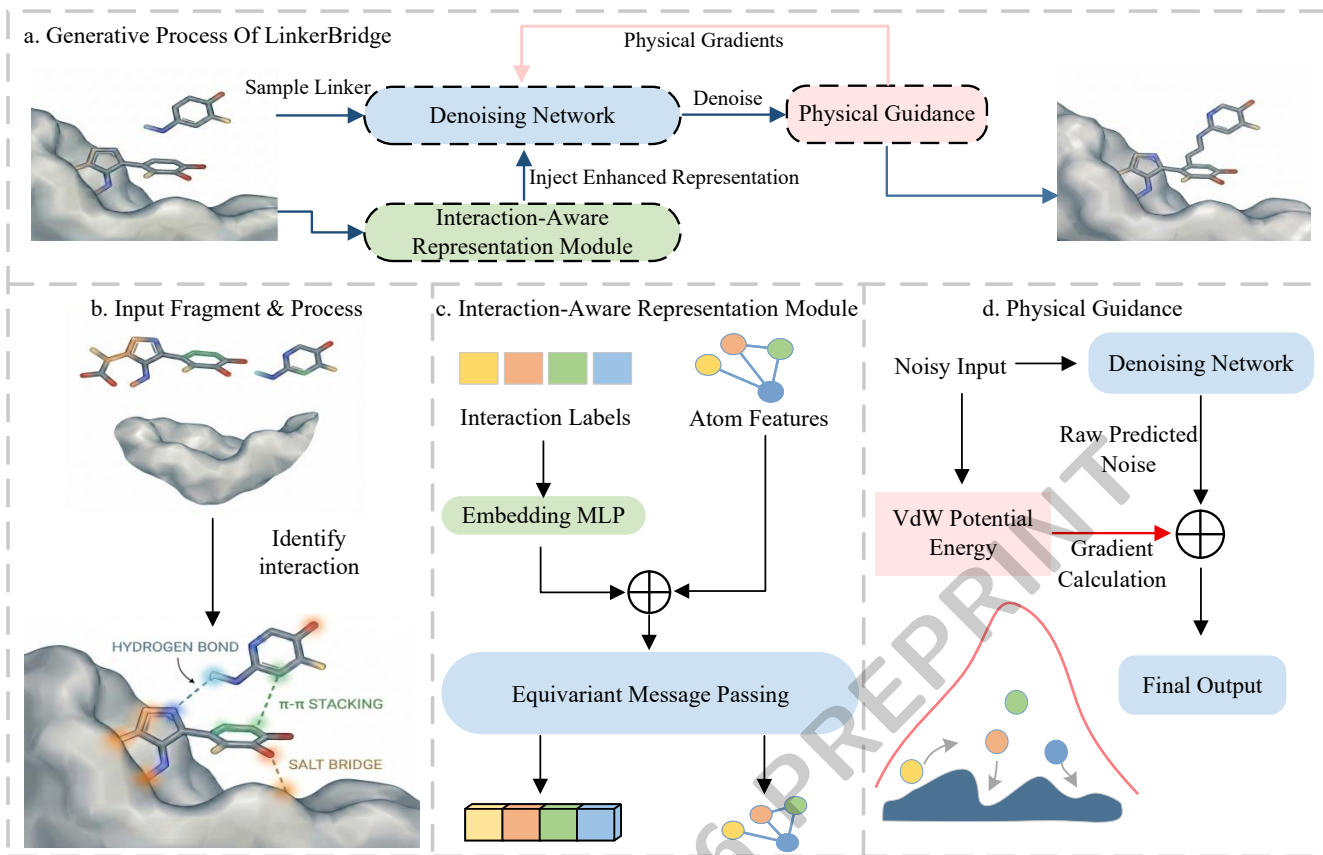


Figure 2: Overview of the LinkerBridge Framework (a) Generative process: Illustrates how the denoising network integrates enhanced representations and physical guidance to sample the connection elements. (b) Input preprocessing step: Identify the interactions (hydrogen bonds,  $\pi-\pi$  stacking, salt bridges) between the fixed fragments and the protein pockets. (c) Interaction-Aware Representation Module: Inject interaction information into the message passing process to update the atomic features and coordinates. (d) Physical guidance: Calculate the van der Waals potential to guide the denoising trajectory and avoid conflicts.

### E(3)-Equivariant Graph Neural Network

To ensure that the generation process is independent of the global orientation and position of the molecules, the denoising function  $\varphi_\theta$  must satisfy  $E(3)$ -equivariance. We adopt the equivariant graph neural network (EGNN) [Garcia Satorras *et al.*, 2021] to construct the model, where the connected linker atoms  $z_t$  and the context  $u$  form a fully connected graph. Each layer of the network executes the following message passing update:

$$m_{ij} = \phi_e(h_i^l, h_j^l, \|r_i^l - r_j^l\|^2, t) \quad (6)$$

where the message  $m_{ij}$  depends on the scalar features and invariant distances. The coordinate displacement is only applied to the connected linker atoms with noise, while keeping the context coordinates fixed:

$$\Delta r_i = \begin{cases} \sum_{j \neq i} (r_i^l - r_j^l) \phi_{vel}(m_{ij}) & \text{if } i \in \text{linker} \\ 0 & \text{if } i \in \text{context} \end{cases} \quad (7)$$

The feature is updated as follows:

$$h_i^{l+1} = \phi_h(h_i^l, \sum_{j \neq i} m_{ij}) \quad (8)$$

To maintain translational invariance, the model centers the data around an anchor point or the centroid of the entire context  $f(u)$  before sampling the initial noise.

In the target-conditioned scenario, protein pockets are represented by atomic point clouds and integrated into a fixed context  $u$ . We extend the node features by adding binary indicator tags to distinguish between ligand atoms and protein atoms. Considering that the atomic density in the protein receptor is high, to maintain computational efficiency, we convert the fully connected graph used in the original task to a distance-aware graph construction method. Specifically, connection edges are assigned based on a  $4\text{\AA}$  distance cutoff value to balance the increase in the number of nodes while retaining the local structural information necessary for spatial compatibility and binding affinity.

### 3.2 Contextual Interaction-Aware Representation Module

To address the interaction blindness problem in coordinate-based geometric encoding, we introduce a contextual interaction-aware representation integration module. This module is based on a core principle: molecular recognition

is mainly driven by specific physical and chemical patterns rather than merely spatial information. By explicitly characterizing and representing the pre-existing interatomic relationships, we transform the generation process from a point cloud filling task based on vacuum assumptions to a context-guided synthesis process driven by surrounding chemical environment information.

### General Interaction Featurization

For each atom  $i$  within the molecular complex (including fragment atoms and the available protein pocket atoms), we define an interaction vector  $v_i^{int} \in \mathbb{R}^4$ . This vector serves as a high-level descriptor for local chemical information, specifically encoding four basic types of non-covalent interactions: hydrogen bonds, salt bridges, hydrophobic contacts, and  $\pi$ - $\pi$  stacking.

In the target conditioned scenario, these features act as biochemical templates, enabling the model to perceive the specific recognition preferences of the receptor (for example, the donor sites that require hydrogen bond donors). To ensure the generalization ability of the framework in non-target design scenarios, we also apply this featurization as a structural supplement for fragment-fragment relationships. The key point is that for the linker atoms in the denoising process, the interactions  $v_i^{int}$  are set to zero vectors. This ensures that the model does not rely on the actual linker interaction during training but instead optimizes the chemical complementarity adaptively based on fixed environmental cues.

### Integration into Equivariant Dynamics

To integrate this biochemical context information with the geometric features  $h_i$  in the  $E(3)$ -equivariant framework, we employ a multi-stage integration mechanism. Firstly, the original interaction vectors are mapped to a high-dimensional latent space through a dedicated interaction embedding layer:

$$e_i^{int} = \text{SiLU}(W_{int}v_i^{int} + b_{int}) \quad (9)$$

where the SiLU (Sigmoid Linear Unit) activation function is used to ensure the smoothness of the gradient flow.

To integrate this chemical context information with the geometric features  $h_i$  derived from the diffusion process, we adopt a splicing embedding mechanism:

$$\tilde{h}_i = \text{LayerNorm}(W_{comb}[h_i \parallel e_i^{int}] + b_{comb}) \quad (10)$$

where  $\parallel$  represents the vector concatenation operation. This enhanced feature  $\tilde{h}_i$  will be used as the input for the subsequent equivariant message passing layer (such as EGNN). By directly embedding such biochemical prior information into the latent state, this architecture ensures that each step of message passing and coordinate update can effectively perceive the surrounding biochemical environment. This mechanism transforms the denoised trajectory from a random walk in the coordinate space into a guided navigation process. Compared to the traditional framework that only relies on spatial geometry, LinkerBridge can thus synthesize molecules with better binding affinity and conformational stability.

### 3.3 Physical Constraint Guidance Based On VdW Force Loss

To ensure the structural integrity and physical validity of the generated molecules, we integrate basic physical chemistry

principles into the diffusion process. This method is specifically designed to strictly follow the volume exclusion principle in environments with crowded spaces between fragments.

### Formulation of the Van der Waals Potential

An effective 3D linker must navigate through a highly crowded space while avoiding spatial conflicts with predefined segments or rigid protein boundaries. We employ a differentiable potential function based on van der Waals (VdW) interactions to model these spatial constraints. For each predicted linker atom  $i \in \mathcal{M}$  and each context atom  $j \in \mathcal{U}$  (including fragment atoms and receptor atoms), we define the potential energy according to the repulsion term of the Lennard-Jones model:

$$\mathcal{L}_{VdW}(r) = \sum_{i=1}^M \sum_{j=1}^N \max \left( 0, \epsilon \left[ \left( \frac{\sigma_{ij}}{d_{ij}} \right)^{12} - 2 \left( \frac{\sigma_{ij}}{d_{ij}} \right)^6 \right] \right) \quad (11)$$

where  $d_{ij} = \|\hat{r}_i - r_j\|$  represents the Euclidean distance between the predicted linker coordinates  $\hat{r}_i$  and the fixed context atom coordinates  $r_j$ . Parameter  $\sigma_{ij}$  denotes the equilibrium distance, and its value is the sum of the van der Waals radii of the corresponding atomic types. By applying the  $\max(0, \cdot)$  operator, this loss function serves as a differentiable energy barrier: it only penalizes configurations that fall within the repulsion interval ( $d_{ij} < \sigma_{ij}$ ), thereby imposing a high energy penalty for spatial conflicts, while remaining neutral at the equilibrium distance or greater.

### End-to-End Joint Optimization

The objective of the standard diffusion model is to minimize the mean square error between the added noise  $\epsilon$  and the noise predicted by the network  $\varphi_\theta$ :

$$\mathcal{L}_{diff} = \mathbb{E}_{x, \epsilon, t} [\|\epsilon - \varphi_\theta(z_t, u, t)\|^2] \quad (12)$$

Unlike traditional methods that rely on post-processing geometric optimization (often decoupled from the learned generation distribution), we directly integrate the  $\mathcal{L}_{VdW}$  into the training objective. Since the predicted coordinates  $\hat{r}$  are differentiable with respect to the network parameters  $\theta$  through the denoising function, we use a joint loss function to optimize the model:

$$\mathcal{L}_{total} = \mathcal{L}_{diff} + \lambda \mathcal{L}_{VdW} \quad (13)$$

Within this framework,  $\mathcal{L}_{diff}$  ensures that the model captures the chemical distribution of effective molecules, while  $\lambda$  acts as a regularization weight to control the strength of physical constraints. By backpropagating the gradient of the VdW potential energy  $\nabla_{\hat{r}} \mathcal{L}_{VdW}$  to the diffusion network, LinkerBridge can effectively guide its denoising trajectory away from high-energy collision regions. This enables the internalization of physical laws into the model weights, thereby ensuring that the generated linker is not only graphically reasonable but also collision-free and structurally achievable in the crowded microenvironment of the protein pocket.

## 4 Experiments

### 4.1 Experimental Settings

**Datasets.** We conduct a comprehensive evaluation of LinkerBridge on three increasingly complex tasks: (i) Target-free

| Dataset | Method                           | QED $\uparrow$ | SA $\downarrow$ | No. of rings $\uparrow$ | Valid, %    | Unique, %   | Novel, %    | 2DFilters, % | Recovery, % | RMSD $\downarrow$ | SC_RDKit $\uparrow$ |
|---------|----------------------------------|----------------|-----------------|-------------------------|-------------|-------------|-------------|--------------|-------------|-------------------|---------------------|
| ZINC    | Delinker                         | 0.64           | 3.11            | 0.21                    | 98.3        | <u>44.2</u> | <u>47.1</u> | 84.9         | 80.2        | 5.48              | 0.49                |
|         | 3DLinker                         | 0.65           | 3.11            | 0.23                    | <b>99.3</b> | 29.0        | 41.2        | 84.2         | <b>94.0</b> | <b>0.10</b>       | 0.92                |
|         | DiffLinker                       | <u>0.68</u>    | <u>3.03</u>     | <u>0.26</u>             | 97.6        | 22.7        | 32.4        | 85.2         | 83.6        | 0.32              | <u>0.94</u>         |
|         | LinkerBridge(ours)               | <b>0.70</b>    | <b>2.89</b>     | 0.25                    | <u>98.5</u> | 24.4        | 33.1        | <b>86.4</b>  | <u>84.8</u> | <u>0.31</u>       | <b>0.95</b>         |
|         | LinkerBridge(sampled size, ours) | <u>0.68</u>    | 3.14            | <b>0.37</b>             | 93.4        | <b>51.2</b> | <b>47.8</b> | <u>86.1</u>  | 83.3        | 0.33              | 0.92                |
| CASF    | Delinker                         | 0.35           | 4.05            | 0.35                    | <b>95.7</b> | <u>51.6</u> | <u>55.6</u> | 77.3         | <u>52.8</u> | 11.89             | 0.39                |
|         | DiffLinker                       | 0.40           | <u>4.03</u>     | <b>0.38</b>             | 90.2        | 37.3        | 48.4        | 83.5         | 50.2        | <u>0.37</u>       | <u>0.86</u>         |
|         | LinkerBridge(ours)               | <b>0.42</b>    | <b>3.98</b>     | <b>0.38</b>             | <u>91.0</u> | 39.2        | 44.4        | <b>86.1</b>  | <b>52.9</b> | 0.42              | <b>0.87</b>         |
|         | LinkerBridge(sampled size, ours) | <u>0.41</u>    | 4.10            | <u>0.37</u>             | 72.1        | <b>58.2</b> | <b>57.1</b> | <u>85.2</u>  | 51.3        | <b>0.35</b>       | 0.85                |

Table 1: Results on dual-fragment design tasks. The best and second best results are marked by bold and underlined.

dual-fragment linking. Using the ZINC [Su *et al.*, 2018] and CASF [Su *et al.*, 2018] datasets, molecular fragment pairs are generated through non-cyclic bond cleavage, resulting in over 438,000 training samples. (ii) Multi-fragment Connecting. For connection tasks involving three or more segments, the GEOM dataset [Axelrod and Gomez-Bombarelli, 2022] is selected. This dataset was generated based on the MMPA/BRICS rules and contains over 285,000 segment sets. (iii) Target-Conditioned Linker Design. To test the protein-conditioned generation ability, a dataset derived from BindingMOAD [Hu *et al.*, 2005] is used. The binding pocket is defined as a 6Å radius range around the ligand, and the data is classified and numbered according to enzymes. A total of 185,678 training samples are obtained to ensure the evaluation of biological generalization.

**Metrics.** We conduct a systematic assessment of the generation quality from three core dimensions. First, we evaluate generation quality using standard metrics, including the validity, uniqueness, and novelty of the generated molecules, along with a chemical practicality score: Quantitative Estimate of Drug-likeness (QED) [Bickerton *et al.*, 2012] and the Synthetic Accessibility score (SA) [Ertl and Schuffenhauer, 2009]. The structural fidelity is measured by the following indicators: the recovery rate of the real molecule, the root mean square deviation of atomic coordinates, and the RDKit conformational comparison score  $SC_{RDKit}$  [Putta *et al.*, 2005] that integrates geometric and chemical similarity. Second, to verify the validity of the physical constraints in the model, we introduced the van der Waals conflict index. This index is based on the van der Waals radii of atoms and quantifies the degree of spatial conflict between the generated linker and the protein-fragment environment. Third, for the protein-conditioned generation tasks, the predicted binding affinity is further evaluated using the docking score of AutoDock Vina [Trott and Olson, 2010].

**Baselines.** In our experiment, we compare LinkerBridge with the sota linker design frameworks, which include the autoregressive model DeLinker [Imrie *et al.*, 2020] and 3DLinker [Huang *et al.*, 2022], as well as DiffLinker based on equivariant diffusion model [Igashov *et al.*, 2024]. For the multi-fragment connection task on the GEOM dataset, we adjust the autoregressive baseline model to enable it to handle multi-segment scenarios through the iterative connection of fragments. According to the standard experimental procedure, the 3D conformation generated by DeLinker is ini-

tially produced by the pre-trained ConfVAE model [Xu *et al.*, 2021], and then further optimized by the MMFF force field relaxation [Halgren, 1996] to obtain a more reasonable spatial structure.

## 4.2 Results on Fragment Pairs

In the fragment-pairs connection task, we evaluate LinkerBridge on the ZINC and CASF benchmarks that focus on the dual-fragment design task. As shown in Table 1, LinkerBridge outperforms the current optimal benchmark models in terms of chemical quality and structural fidelity. On the ZINC dataset, LinkerBridge achieves excellent drug similarity (QED: 0.70) and synthetic accessibility (SA: 2.89) scores, while maintaining 98.5% effectiveness through the built-in chemical constraints. It is worth noting that LinkerBridge demonstrates high robustness across different datasets: it achieves the best RDKit conformational alignment score (ZINC: 0.95; CASF: 0.87), with an atomic coordinate root mean square deviation of only 0.31 Å.

## 4.3 Results on Multiple Fragments and Pockets

To further evaluate the performance of LinkerBridge in complex scenarios, we conduct a comprehensive test on multi-segment connecting and target conditioning tasks.

### Multi-Fragment Linking on GEOM

As shown in Table 2, LinkerBridge demonstrates significant advantages in the one-shot generation task of multi-fragment systems. Under the same complex scenarios, the autoregressive baseline models (such as DeLinker and 3DLinker) fail to generate effective molecules (with effectiveness  $\leq 17\%$ ) or restore the reference structure, while LinkerBridge maintains high effectiveness (93.7%) and achieves an excellent recovery rate of 87.1%. Compared with DiffLinker, our model also performs better in terms of drug similarity (QED 0.51) and geometric fidelity (SC\_RDKit 0.93). These results indicate that the interaction-aware representation method adopted by our model can effectively capture the long-range spatial and electronic correlation information required for simultaneously connecting three or more pharmacophores.

### Target-Conditioned Design on BindingMOAD

In the target-conditioned task on the BindingMOAD dataset (Table 2), LinkerBridge outperforms DiffLinker in almost all evaluation metrics by integrating the interaction awareness

| Dataset     | Method                           | QED $\uparrow$ | SA $\downarrow$ | No. of rings $\uparrow$ | Valid, %    | Unique, %   | Novel, %    | 2DFilters, %  | Recovery, % | RMSD $\downarrow$ | SC_RDKit $\uparrow$ |
|-------------|----------------------------------|----------------|-----------------|-------------------------|-------------|-------------|-------------|---------------|-------------|-------------------|---------------------|
| GEOM        | Delinker                         | <b>0.76</b>    | 3.59            | 0.00                    | 0.1         | <b>74.5</b> | —           | <b>100.00</b> | 0.0         | —                 | 0.42                |
|             | 3DLinker                         | 0.36           | 3.56            | 0.00                    | 16.3        | <u>73.7</u> | —           | <u>94.10</u>  | 0.0         | —                 | 0.72                |
|             | DiffLinker                       | 0.49           | <u>3.02</u>     | 0.79                    | <u>93.4</u> | 33.9        | 68.3        | 49.70         | <u>85.2</u> | 0.12              | <u>0.92</u>         |
|             | LinkerBridge(ours)               | <u>0.51</u>    | <b>2.98</b>     | <u>0.81</u>             | <b>93.7</b> | 32.9        | <u>68.4</u> | 49.50         | <b>87.1</b> | <u>0.11</u>       | <b>0.93</b>         |
|             | LinkerBridge(sampled size, ours) | 0.50           | 3.23            | <b>0.83</b>             | 90.4        | 65.5        | <b>76.8</b> | 58.1          | 68.2        | <b>0.09</b>       | 0.88                |
| BindingMOAD | DiffLinker                       | 0.45           | 3.89            | 1.06                    | <b>88.7</b> | 62.5        | 73.1        | 60.1          | 37.3        | 0.78              | 0.78                |
|             | LinkerBridge(ours)               | <b>0.52</b>    | <b>3.69</b>     | <b>1.10</b>             | 84.1        | <b>65.3</b> | <b>73.5</b> | <b>61.2</b>   | <b>37.5</b> | <b>0.72</b>       | <b>0.80</b>         |

Table 2: Results on Multi-Fragment Linking and Pockets. The best and second best results are marked by bold and underlined.

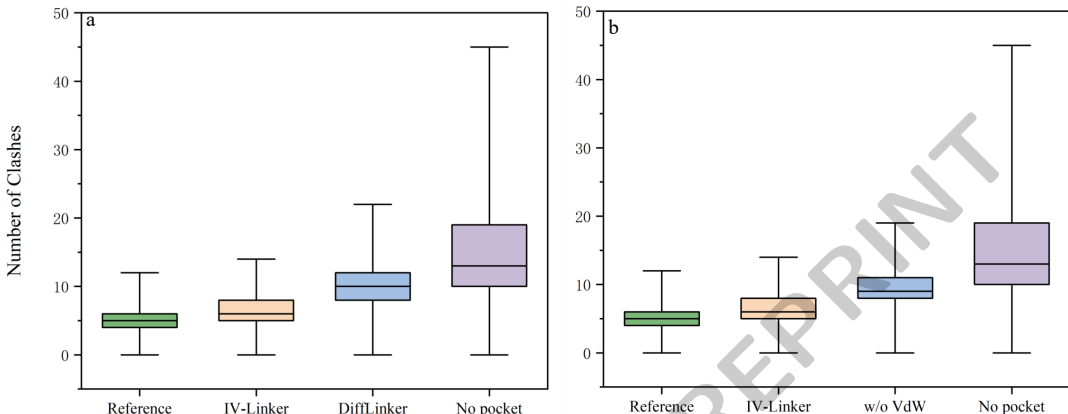


Figure 3: Analysis of steric clash. (a) Comparison between LinkerBridge and other methods. (b) Ablation study on physical constrained loss.

mechanism and the physical guidance strategy. Its drug similarity score (QED: 0.52) and pocket matching performance are excellent. The high uniqueness (65.3%) and structural fidelity (61.2%) further demonstrate that LinkerBridge can effectively screen out candidate molecules that have both physical feasibility and biochemical activity, rather than merely generating graphically reasonable but impractically unfeasible structures.

### Steric Clash Analysis

To assess the structural integrity of the generated linker in the biological environment, we quantify the frequency of spatial conflicts between it and the target protein receptor. As illustrated in Figure 3a, the spatial conflict distribution of the molecules generated by LinkerBridge is highly similar to that of the reference complex, and it shows a significant improvement compared to DiffLinker. The significant reduction in spatial conflicts validates the effectiveness of the differentiable physical guidance module. By directly integrating the potential energy function based on van der Waals forces into the denoising process, LinkerBridge successfully implements the volume exclusion principle, ensuring that the synthesized linker not only aligns with the fragment geometry but also achieves the rationality of the physical structure under the rigid constraints of the protein pocket.

## 4.4 Case Studies

To demonstrate the practical application value of LinkerBridge in diverse drug chemistry workflows, we select two representative tasks for evaluation: fragment-based lead com-

pound optimization for Hsp90, and scaffold hopping design for JNK3 selective inhibitors.

### Fragment Linking for Hsp90

For the ATPase binding pocket of Hsp90 [Barker *et al.*, 2010], this study demonstrates the application value of LinkerBridge in fragment-based lead compound optimization (Figure 4). Our model successfully restores the structure of the reference inhibitor (Figure 4d), and generates a series of candidate molecules with Vina scores comparable to or better than the reference compound (Figure 4f). More importantly, by combining interaction-aware representation with physical guidance, LinkerBridge optimizes the protein-ligand interface and successfully restores the key hydrophobic interactions identified by the PLIP tool [Salentin *et al.*, 2015] (Figure 4e). These results confirm that LinkerBridge can transform isolated active fragments into physically feasible high-affinity lead compounds.

### Scaffold Hopping for Kinase Selectivity (JNK3)

We evaluate the scaffold hopping ability of LinkerBridge at the JNK3 target site, the core challenge of this task is to achieve selective inhibition for the p38 subtype. Starting from the indazole inhibitor fragment (PDB: 3F13), LinkerBridge not only successfully restores the original indazole backbone, but also generates a highly selective aminopyrazole backbone (Figure 5b, e). The high degree of superposition between the generated structure and the experimental crystal conformation (Figure 5c, f) confirms that our model can effectively explore a diverse range of selective chemical spaces.

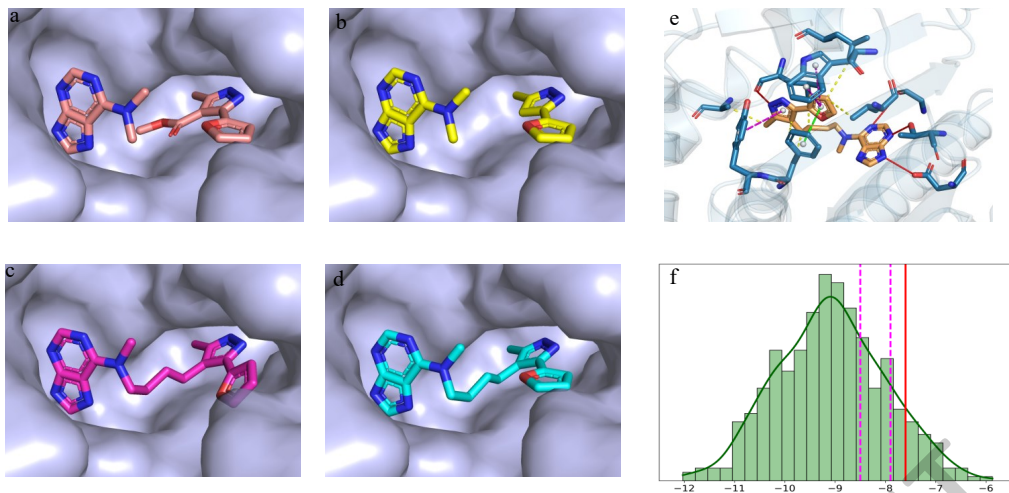


Figure 4: Hsp90 for fragment-based ligand generation. (a) Experimentally identified fragments bound to separate subsites within the ATPase pocket of Hsp90 (PDB code 3HZ1). (b) Starting fragments after removing methyl ester group. (c) Crystal structure of the inhibitor (PDB code 3HZ5). (d) Generated molecule by LinkerBridge. (e) Interactions between the generated molecule and the target. (f) Distributions of vina scores for samples generated by LinkerBridge. The red line indicates the reference and the magenta lines indicate the recovered.

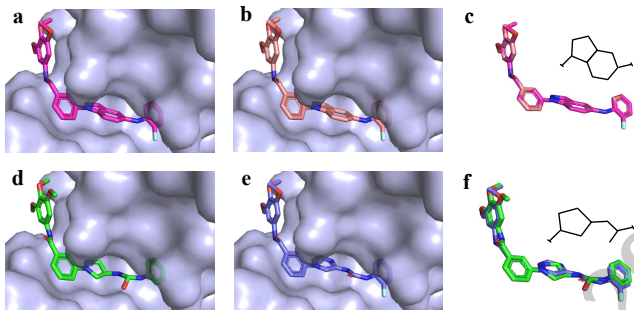


Figure 5: Exploring chemical diversity for improving selectivity of JNK inhibitors. (a) Crystal structures of compounds with indazole. (b) LinkerBridge samples that reproduce indazole. (c) Overlay of real and sampled indazole. (d) Crystal structures of compounds with aminopyrazole. (e) LinkerBridge samples that reproduce aminopyrazole. (f) Overlay of real and sampled aminopyrazole.

#### 4.5 Ablation Study

To assess module necessity, we conduct an ablation study on ZINC (Table 3). The full LinkerBridge outperforms all variants, demonstrating that the combination with biochemical priors and physical constraints is vital for synthesis. Specifically, removing the interaction representation ( $v^{int}$ ) degrades QED from 0.70 to 0.68, highlighting its role in capturing biochemical context for drug-like generation.

The steric clash analysis (Figure 3b) confirms that removing the VdW loss term would significantly increase the median number of conflicts and produce extreme outliers. When LinkerBridge is able to suppress the degree of atomic overlap to the level of the reference complex, the model without VdW terms exhibits severe physical conflicts within the rigid protein pocket. This validates the necessity of the VdW potential energy for enforcing the principle of volume exclusion, it ensures that the generated linker structure is physically feasible,

| Method          | QED $\uparrow$ | SA $\downarrow$ | Valid, %    | Recovery, % | SC_RDKit $\uparrow$ |
|-----------------|----------------|-----------------|-------------|-------------|---------------------|
| LinkerBridge    | <b>0.70</b>    | <b>2.89</b>     | <b>98.5</b> | <b>84.8</b> | <b>0.95</b>         |
| w/o VdW         | 0.69           | 2.94            | 98.1        | 84.1        | 0.94                |
| w/o interaction | 0.68           | 2.98            | 97.9        | 83.9        | 0.94                |

Table 3: Ablation Study on Key Modules Of LinkerBridge.

rather than merely being a geometrically reasonable configuration.

## 5 Conclusion

This study proposes LinkerBridge, a novel equivariant diffusion framework, aiming to overcome the interaction blindness and physical inconsistency problems existing in the design of 3D molecular linker. By introducing a contextual interaction-aware representation module, our model can effectively capture the key biochemical recognition patterns (such as hydrogen bonding and  $\pi$ -stacking interactions) in its surrounding environment. Furthermore, we implement a physical constraint-guided mechanism through a differentiable VdW loss function. This mechanism dynamically adheres to the volume exclusion principle during the denoising process, thereby avoiding spatial conflicts. Experimental results on multiple benchmarks show that LinkerBridge significantly outperforms current methods in generating linkers with high drug similarity, synthetic accessibility, and structural fidelity. Case studies on Hsp90 and JNK3 further validate the practical application value of our model in lead compound optimization and scaffold hopping. By integrating high-fidelity characterization with physical prior knowledge, LinkerBridge bridges the gap between statistical rationality and physical feasibility, providing a powerful tool for structure-based drug discovery research.

## Ethical Statement

There are no ethical issues.

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