March 2025

1 To Reviewer J9jx

We sincerely thank you for your time and efforts in reviewing our paper, as well as for your valuable and insightful feedback. In the following, we provide a detailed supplementary experiment table. **We have tested the baseline method you mentioned on CBGBench** (**Table 1-3**). **Tables 4 and 5 validate the effect of force-guiding under lower error conditions.**

VFDiff (prior) refers to the generated results of our proposed model, where the number of ligand atoms is sampled from a statistical distribution based on the protein pocket size. This setting is consistent with TargetDiff's strategy, and all baselines and datasets in the original paper follow this sampling method.

VFDiff (ref), on the other hand, generates ligands with the same number of atoms as the reference ligand. This is also the atom count sampling method used for all diffusion-based models in the table below.

Table 1: Results of interaction and clash analysis. The best experimental results are **bolded**, while the 2nd and 3rd best results are underlined.

Methods	**Vina Score**		**Vina Min**		**Vina Dock**				**Clash**	
	$E_{\text{vina}}\downarrow$	IMP% $\uparrow$	$E_{\text{vina}}\downarrow$	IMP% $\uparrow$	$E_{\text{vina}}\downarrow$	IMP% $\uparrow$	MPBG% $\uparrow$	LBE $\uparrow$	$\text{Ratio}_{cca}\downarrow$	$\text{Ratio}_{cm}\downarrow$
LIGAN	<u>-6.47</u>	<u>62.13</u>	<u>-7.14</u>	70.18	-7.70	**72.71**	4.22	0.3897	**0.0096**	**0.0718**
3DSBDD	-	3.99	-3.75	17.98	-6.45	31.46	9.18	0.3839	0.2482	0.8683
GRAPHBP	-	0.00	-	1.67	-4.57	10.86	-30.03	0.3200	0.8634	0.9974
POCKET2MOL	-5.23	31.06	-6.03	38.04	-7.05	48.07	-0.17	**0.4115**	0.0576	0.4499
TARGETDIFF	-5.71	38.21	-6.43	47.09	-7.41	51.99	5.38	0.3537	0.0483	0.4920
DIFFSBDD	-	12.67	-2.15	22.24	-5.53	29.76	-23.51	0.2920	0.1083	0.6578
DIFFBP	-	8.60	-	19.68	-7.34	49.24	6.23	0.3481	0.0449	0.4077
FLAG	-	0.04	-	3.44	-3.65	11.78	-47.64	0.3319	0.6777	0.9769
D3FG	-	3.70	-2.59	11.13	-6.78	28.99	-8.85	0.4009	0.2155	0.8571
DECOMPDIFF	-5.18	19.66	-6.04	34.84	-1.59	-7.10	48.31	0.3460	0.0462	0.5248
MOLCRAFT	-6.15	54.25	-6.89	56.43	-7.79	56.22	8.38	0.3638	0.0264	0.2691
VOXBIND	<u>-6.16</u>	41.80	-6.82	50.02	-7.68	52.91	9.89	0.3588	<u>0.0103</u>	<u>0.1890</u>
VFDiff(prior)	**-7.26**	**68.04**	**-8.02**	<u>72.02</u>	**-8.71**	71.79	**23.25**	0.3670	0.0289	0.4183
VFDiff(ref)	-5.95	<u>63.46</u>	<u>-7.02</u>	**72.08**	-	-	-	-	<u>0.0246</u>	<u>0.3480</u>

Table 2: Results of substructure analysis.

Methods	**Atom type**		**Ring type**		**Functional Group**	
	JSD_{at}	MAE_{at}	JSD_{rt}	MAE_{rt}	JSD_{fg}	MAE_{fg}
LIGAN	0.1167	0.8680	0.3163	0.2701	0.2468	0.0378
3DSBDD	0.0860	0.8444	0.3188	0.2457	0.2682	0.0494
GRAPHBP	0.1642	1.2266	0.5061	0.4382	0.6259	0.0705
POCKET2MOL	0.0916	1.0497	0.3550	0.3545	0.2961	0.0622
TARGETDIFF	0.0533	**0.2399**	0.2345	0.1559	0.2876	0.0441
DIFFSBDD	0.0529	0.6316	0.3853	0.3437	0.5520	0.0710
DIFFBP	0.2591	1.5491	0.4531	0.4068	0.5346	0.0670
FLAG	0.1032	1.7665	0.2432	0.3370	0.3634	0.0666
D3FG	0.0644	0.8154	**0.1869**	0.2204	0.2511	0.0516
DECOMPDIFF	**0.0431**	0.3197	0.2431	0.2006	0.1916	**0.0318**
MOLCRAFT	0.0490	0.3208	0.2469	**0.0264**	0.1196	0.0477
VOXBIND	0.0942	0.3564	0.2401	0.0301	**0.1053**	0.0761
VFDiff(prior)	0.0991	0.7189	0.2456	0.1493	0.2583	0.0447
VFDiff(ref)	0.0856	0.4387	0.2395	0.1465	0.2547	0.0441

Table 3: Results of chemical property.

Methods	**QED**	**LogP**	**SA**	**LPSK**
LIGAN	0.46	**0.56**	**0.66**	4.39
3DSBDD	0.48	0.47	0.63	4.72
GRAPHBP	0.44	**3.29**	0.64	4.73
POCKET2MOL	0.39	**2.39**	0.65	4.58
TARGETDIFF	0.49	**1.13**	0.60	4.57
DIFFSBDD	0.49	**-0.15**	0.34	**4.89**
DIFFBP	0.47	**5.27**	0.59	4.47
FLAG	0.41	0.29	0.58	**4.93**
D3FG	0.49	**1.56**	**0.66**	**4.84**
DECOMPDIFF	0.49	**1.22**	0.66	4.40
MOLCRAFT	0.48	0.87	**0.66**	4.39
VOXBIND	0.54	**2.22**	0.65	4.70
VFDiff(prior)	0.54	**2.31**	0.57	4.68
VFDiff(ref)	**0.55**	**1.87**	0.60	4.75

Table 4: Jensen-Shannon Divergence comparing bond distance distributions between reference molecules and generated molecules.

Bond	liGAN	AR	Pocket2 Mol	Target Diff	Decomp Diff	IP Diff	IR Diff	VF Diff	Approximate force-guiding
C-C	0.601	0.609	0.496	0.369	0.371	0.386	0.439	0.365	**0.318**
C=C	0.665	0.620	0.561	0.505	0.539	0.245	0.272	**0.191**	0.192
C-N	0.634	0.474	0.416	0.363	0.352	0.298	0.302	0.244	**0.243**
C=N	0.749	0.635	0.629	0.550	0.592	0.238	0.255	**0.209**	0.211
C-O	0.656	0.492	0.454	0.421	0.373	0.366	0.371	**0.259**	0.287
C=O	0.661	0.558	0.516	0.461	0.381	**0.353**	0.361	0.377	0.375
C:C	0.497	0.451	0.416	0.263	0.258	0.169	0.214	**0.133**	0.144
C:N	0.638	0.551	0.487	0.235	0.273	**0.128**	0.209	0.158	0.171

Table 5: The effect of energy-planning, force-guiding and position-tuning mechanism. (↑) / (↓) denotes a larger / smaller number is better. The top 2 results are highlighted with bold and underlined text, respectively.

Methods	**Vina Score(↓)**		**Vina Min (↓)**		**Vina Dock (↓)**		**High Affinity(↑)**		**QED(↑)**		**SA(↑)**		**Diversity(↑)**	
	Avg.	Med.	Avg.	Med.	Avg.	Med.	Avg.	Med.	Avg.	Med.	Avg.	Med.	Avg.	Med.
Baseline	-5.23	-6.18	-6.35	-6.81	-7.52	-7.87	56.6%	55.1%	0.47	0.48	0.58	0.58	0.72	0.72
+ Approximated force-guiding	-5.47	-6.28	-6.66	-6.81	-	-	-	-	0.48	0.48	**0.58**	**0.58**	**0.78**	**0.77**
+ energy-planning&force-guiding	-5.80	-6.57	-6.95	-7.03	-7.94	-8.10	61.4%	64.7%	0.47	0.48	0.58	0.57	0.72	0.71
+ position-tuning	-6.93	-7.24	-7.70	-7.68	-8.26	-8.21	68.1%	74.2%	0.54	0.53	0.56	0.57	0.69	0.68
VFDiff	-7.37	-7.75	-8.18	-8.18	**-8.77**	**-8.72**	**69.5%**	**75.5%**	**0.54**	**0.55**	0.57	0.57	0.72	0.71
+ Approximated force-guiding	**-7.48**	**-7.79**	**-8.26**	**-8.26**	-	-	-	-	0.54	0.55	0.56	0.56	0.71	0.71
Reference	-6.36	-6.41	-6.71	-6.49	-7.45	-7.26	-	-	0.48	0.47	0.73	0.74	-	-