

SC-VAE : Structure-Conditioned Molecular Generation for Target-Specific Drug Discovery

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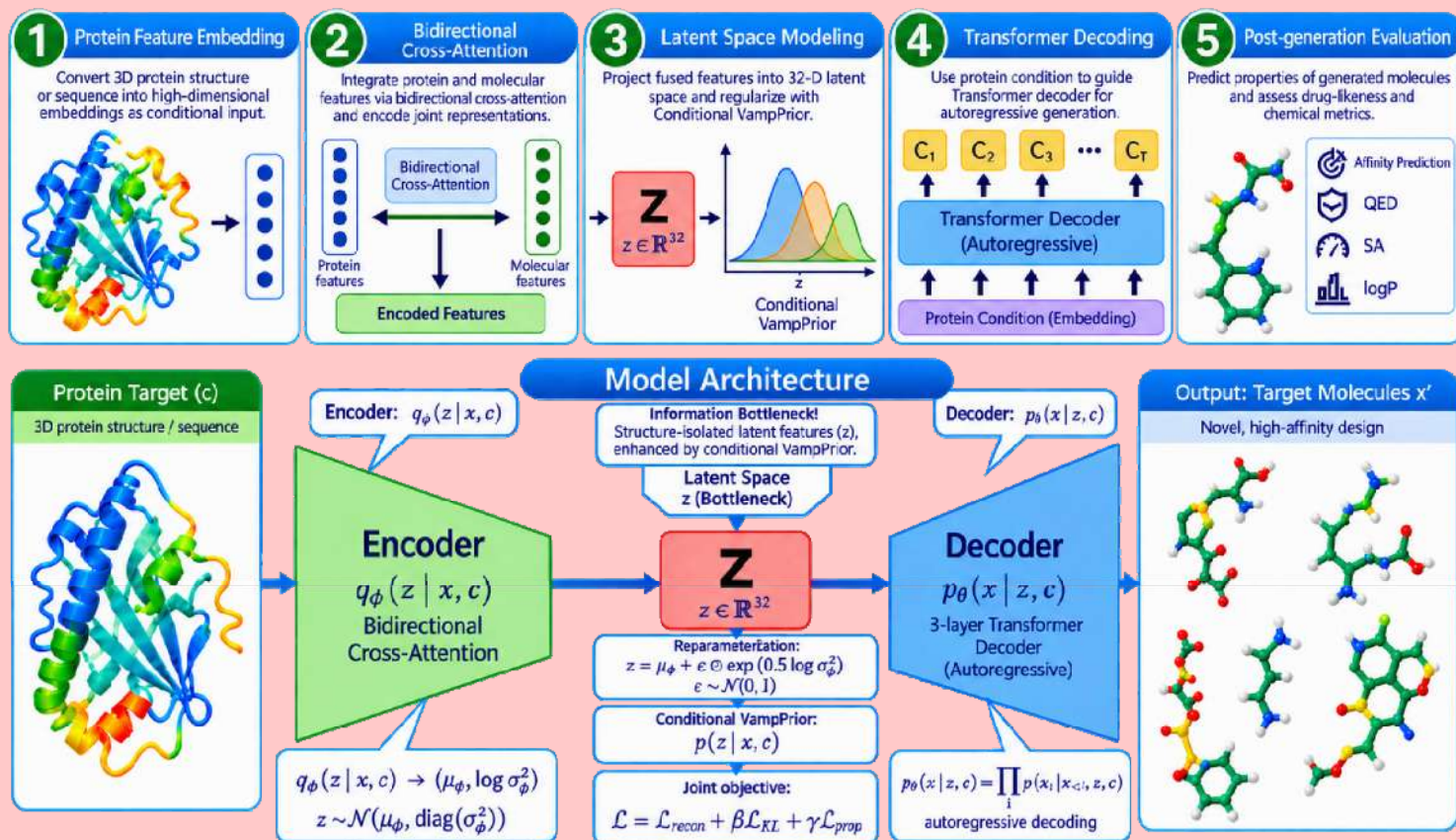
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Abstract

Traditional drug discovery faces high costs and failure rates, and while deep learning accelerates 3D binding simulations, current generative AI models often suffer from posterior collapse, yielding chemically invalid molecules with inaccurate affinity scores. To overcome these bottlenecks, we propose a novel Conditional Variational Autoencoder (CVAE) that functions as an "inventor." By integrating a symmetric dual cross-attention fusion module, a dynamic feature bypass mechanism, and multi-task learning across diverse datasets, our model breaks single-source data limitations. It successfully guarantees a 100% chemical validity rate for *de novo* generated structures. By simultaneously predicting thermodynamic affinity and synthetic properties during the generation stage, the framework rigorously screens small molecules, establishing a seamless, fully automated closed-loop from virtual generation to physical validation to revolutionize early-stage drug design.

Framework



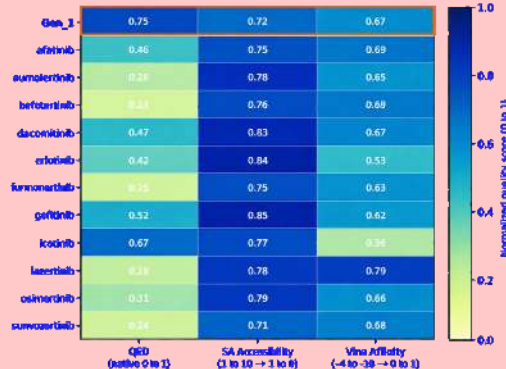
Results

Metric	Pocket2Mol (Mean $\pm$ Std)	TargetDiff (Mean $\pm$ Std)	SC-VAE (Mean $\pm$ Std)
Vina score ($\downarrow$)	-7.169 $\pm$ 1.962	-7.221 $\pm$ 2.132	-7.338 $\pm$ 0.699 ★
QED ($\uparrow$)	0.389 $\pm$ 0.063	0.585 $\pm$ 0.098	0.404 $\pm$ 0.051
SA ($\downarrow$)	3.028 $\pm$ 0.361	3.194 $\pm$ 1.172	4.448 $\pm$ 0.310
Diversity ($\uparrow$)	0.842 $\pm$ 0.005	0.727 $\pm$ 0.161	0.914 $\pm$ 0.007
logP ($-$)	1.116 $\pm$ 0.801	2.029 $\pm$ 1.477	1.026 $\pm$ 0.807
Fragment similarity ($\uparrow$)	0.061 $\pm$ 0.020	0.116 $\pm$ 0.144	0.010 $\pm$ 0.010
Scaffold similarity ($\uparrow$)	0.282 $\pm$ 0.108	0.154 $\pm$ 0.140	0.053 $\pm$ 0.024
Time (s, $\downarrow$)	1962	2558	3

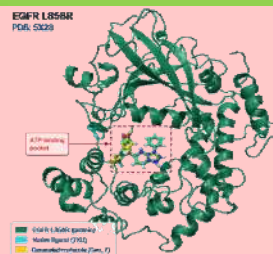
Overall Vina score average = **4.955 $\pm$ 0.51** ★ = top-10

($\uparrow$) Higher is better, ($\downarrow$) Lower is better, (—) Value closer to the desired range is better

Benchmarked on CrossDocked2020 across 100 targets, our model achieves outstanding performance in molecular diversity, and generation efficiency. The lower scaffold similarity and higher SA reflect its distinct capability in true *de novo* scaffold generation.



Using EGFR L858R as a representative lung cancer target, the top AI-generated small-molecule candidate identified through large-scale generation and screening was compared with existing EGFR drugs using normalized chemical metrics.



Conclusion

Our SC-VAE framework delivers record diversity, and 2x faster generation. Validated on EGFR L858R, it yields candidates outperforming current drugs, demonstrating immense potential to accelerate *de novo* precision drug discovery.