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Peer Review

Review of: "Unified Guidance for Geometry-Conditioned Molecular Generation"

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This paper introduces a framework (UniGuide) that applies self-guidance techniques to an unconditional molecular diffusion model to flexibly incorporate three-dimensional geometric constraints. Rather than training specialized, condition-specific models, the authors propose a single unconditional diffusion model that can be guided via a "condition map" at inference time. This condition map transforms arbitrary geometric inputs—whether these are protein binding sites, partial scaffolds, or molecular surfaces—into a suitable target representation for self-guidance. In this way, UniGuide can be used in multiple drug discovery tasks, e.g., structure-based, ligand-based, and fragment-based design, under one unified framework. The authors demonstrate that UniGuide is both versatile and performant, matching or surpassing specialized baselines on a variety of benchmarks.

The conditional 3D molecular generation problem is highly relevant in computational drug discovery, especially when bridging purely geometry-based considerations and the demand for novel chemical structures. The authors clearly illustrate why training separate task-specific diffusion models is restrictive and how self-guidance via condition maps can simplify workflows. The idea that a single unconditional model can flexibly adapt to new conditions without retraining is well-motivated. Also, the study performs quantitative comparisons on multiple datasets, addressing ligand-based, structure-based, and fragment-based design; and the considered metrics cover fundamental chemical and pharmacological properties.

On the other hand, although the authors address core tasks in small-molecule drug discovery, there is limited discussion of important property-based/activity-based constraints (e.g., ADMET). The paper focuses mainly on shape or structural guidance; in real-world drug design, additional biochemical or

 doi.org/10.32388/N75WYW

functional data would often be crucial. Moreover, from my understanding, UniGuide is restricted to geometric conditions, as the method cannot directly incorporate global scalar properties. This means combining property-driven generation with geometry-based tasks might require further expansions of the method.

In summary, the material presented in this study justifies the acceptance of the manuscript.

Declarations

Potential competing interests: No potential competing interests to declare.