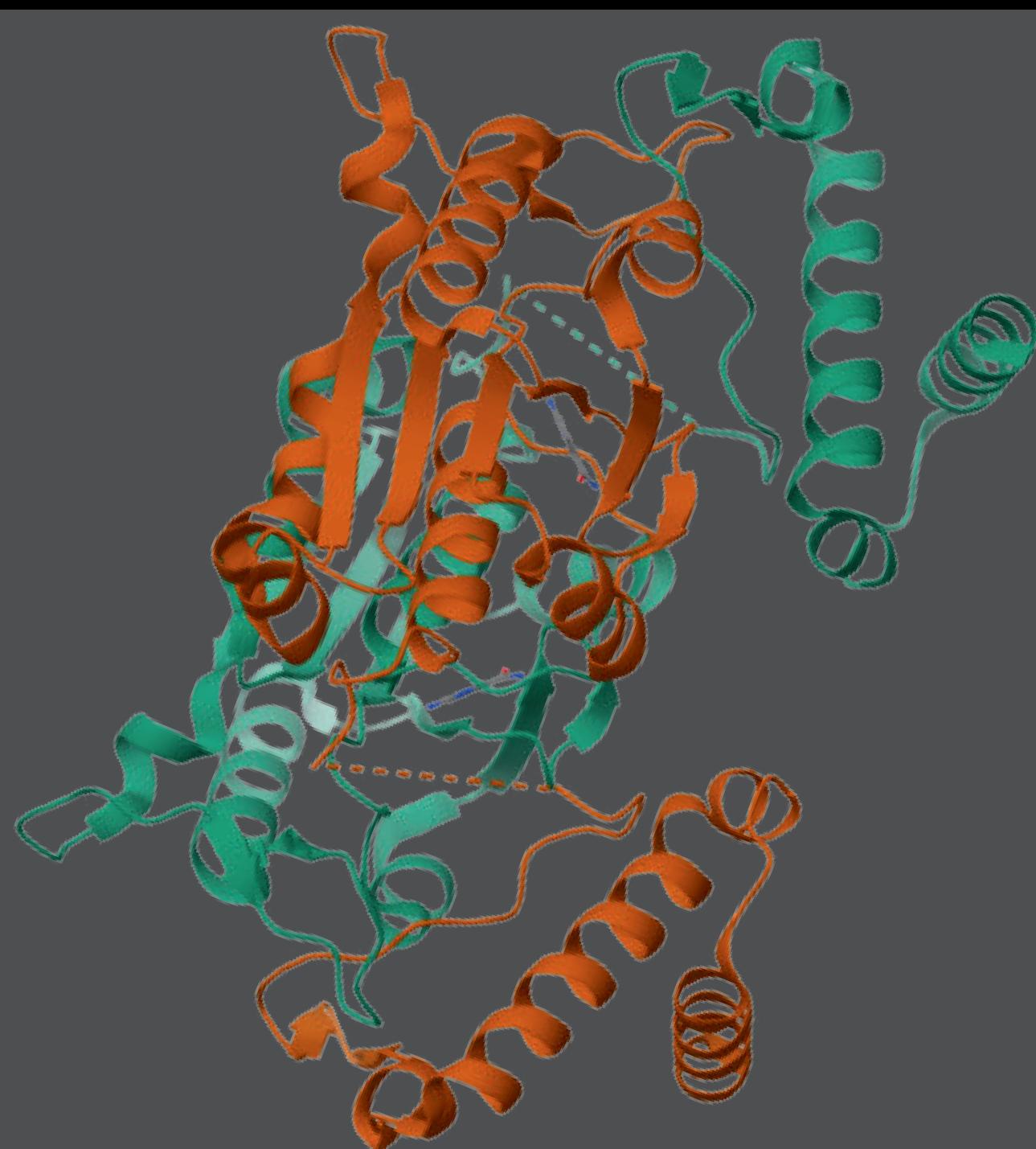


Designing a TrmD inhibitor

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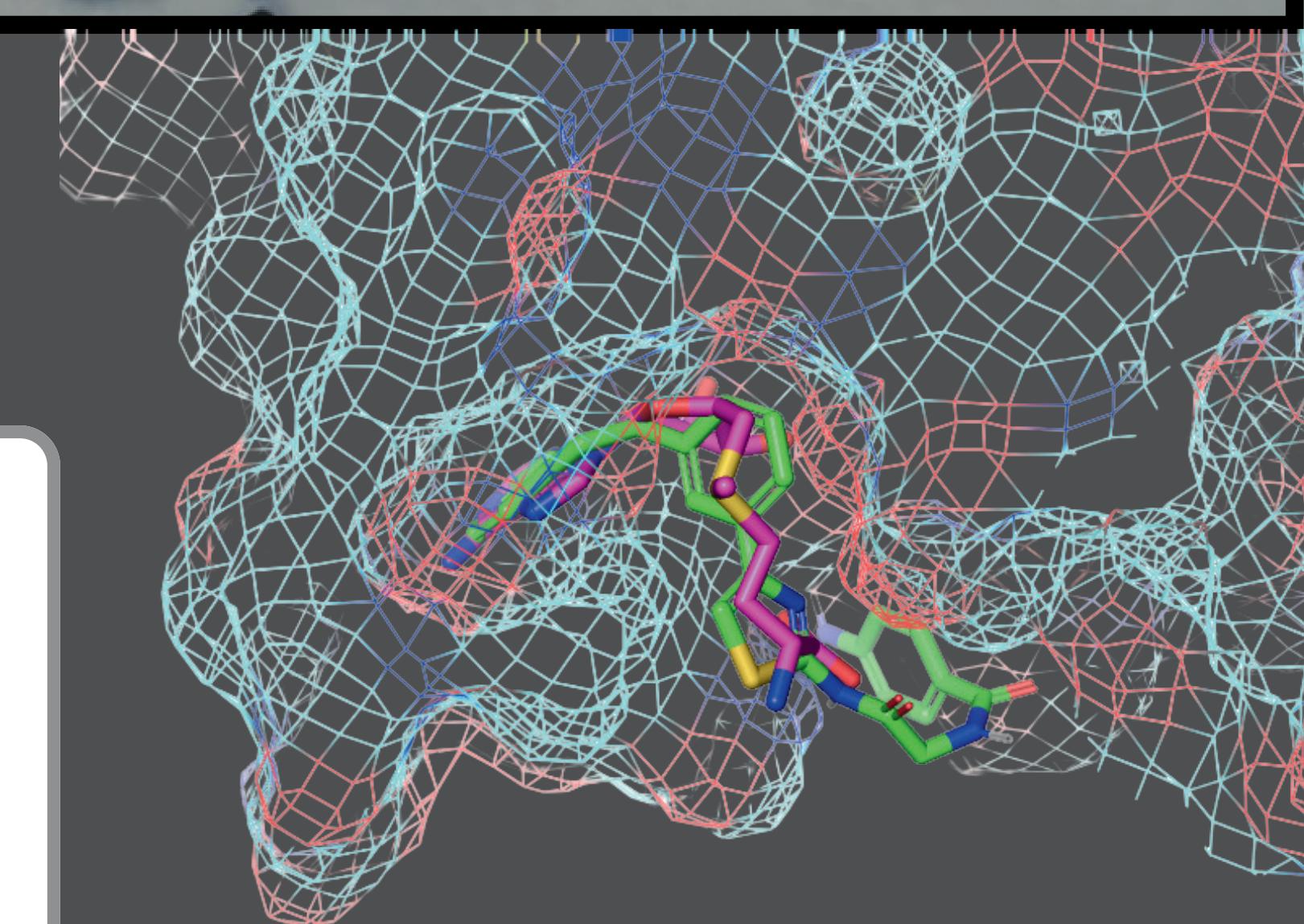
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INTRODUCTION

The bacterial tRNA-(N1G37) methyltransferase (TrmD) is an essential enzyme in many pathogens, making it a promising target for novel antimicrobial agents. This study employed a comprehensive computational approach to identify and design potential TrmD inhibitors.



METHODOLOGY

- Selection and superimposition of TrmD structures - *P. aeruginosa*, *M. abscessus*, *A. baumannii*.
- Selection of ligands - 59 known ligands crystallised with chosen TrmD and 16 from different publications.
- Filtration of PubChem compound database and search for similar SMILES structures using LINGOSIM method.
- Compound generation - leveraging Variational Autoencoder (VAE) from Keras' API.
- Molecular docking - AutoDock VINA.

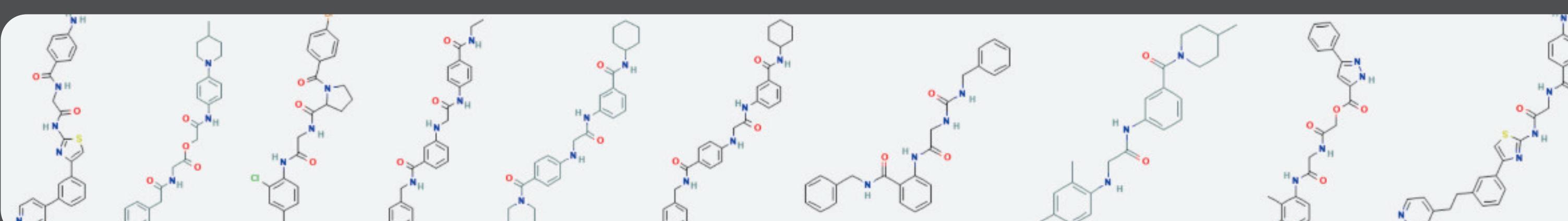
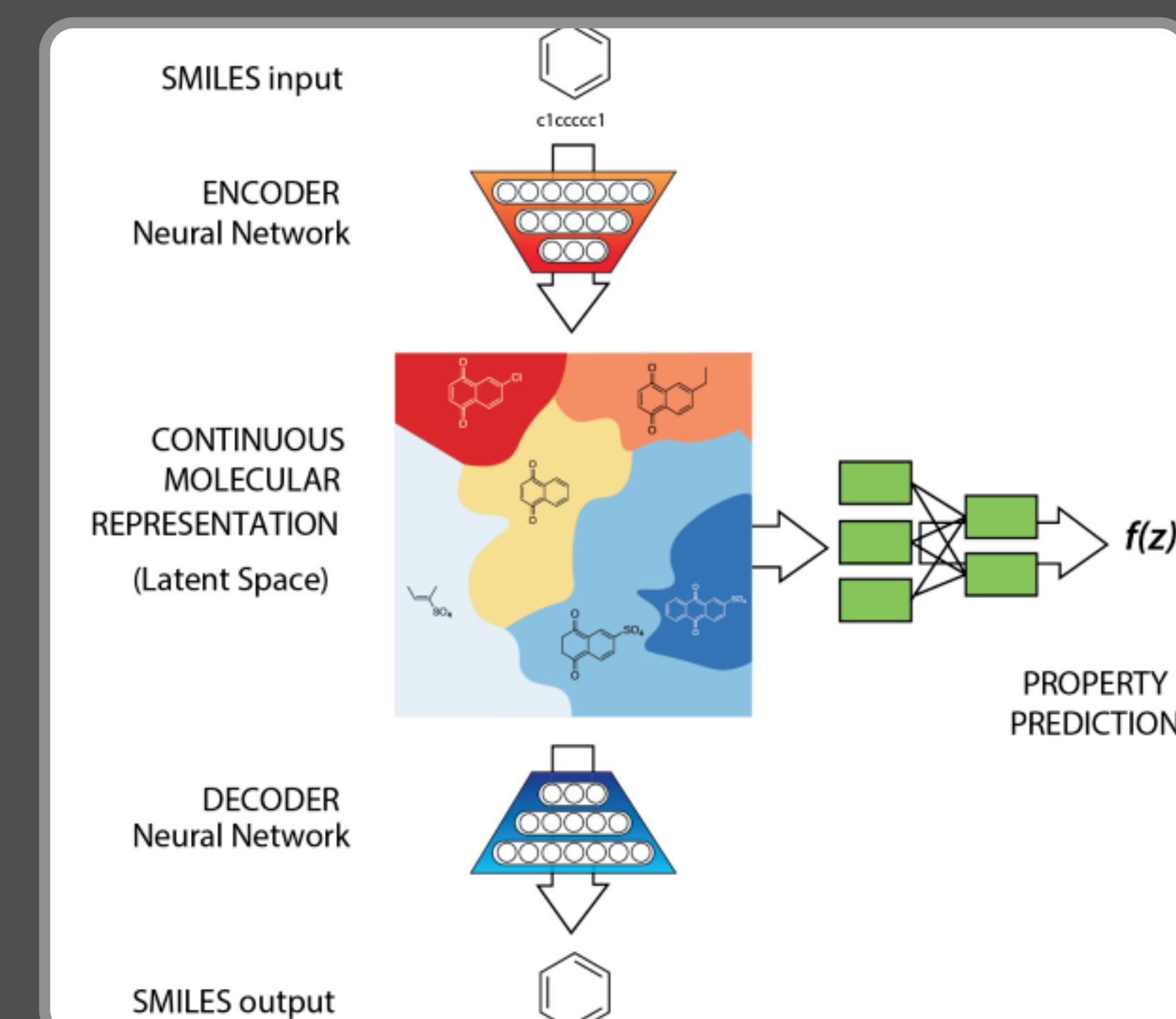
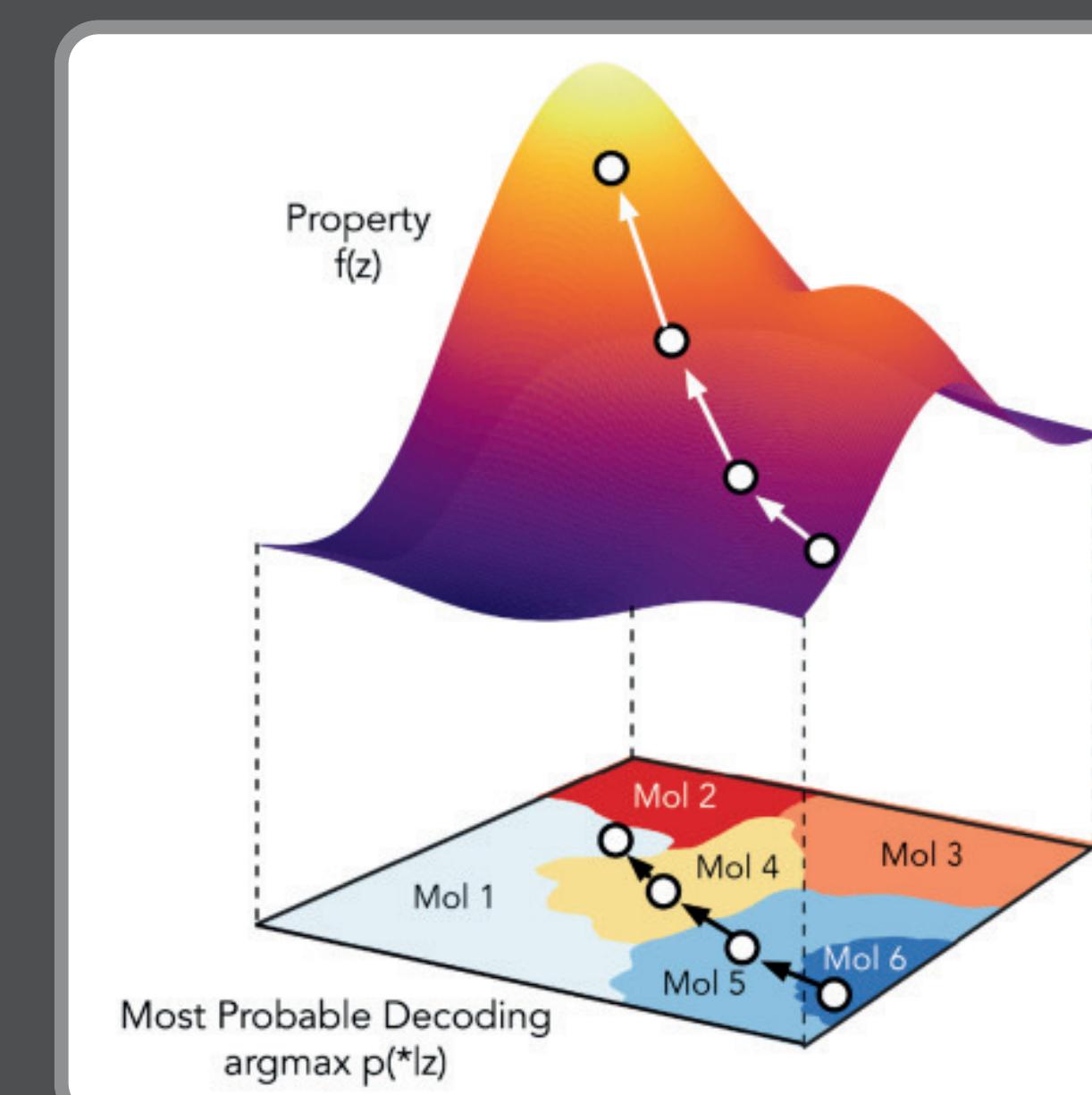


Figure 1: Identified compounds with highest binding affinity

Best hit

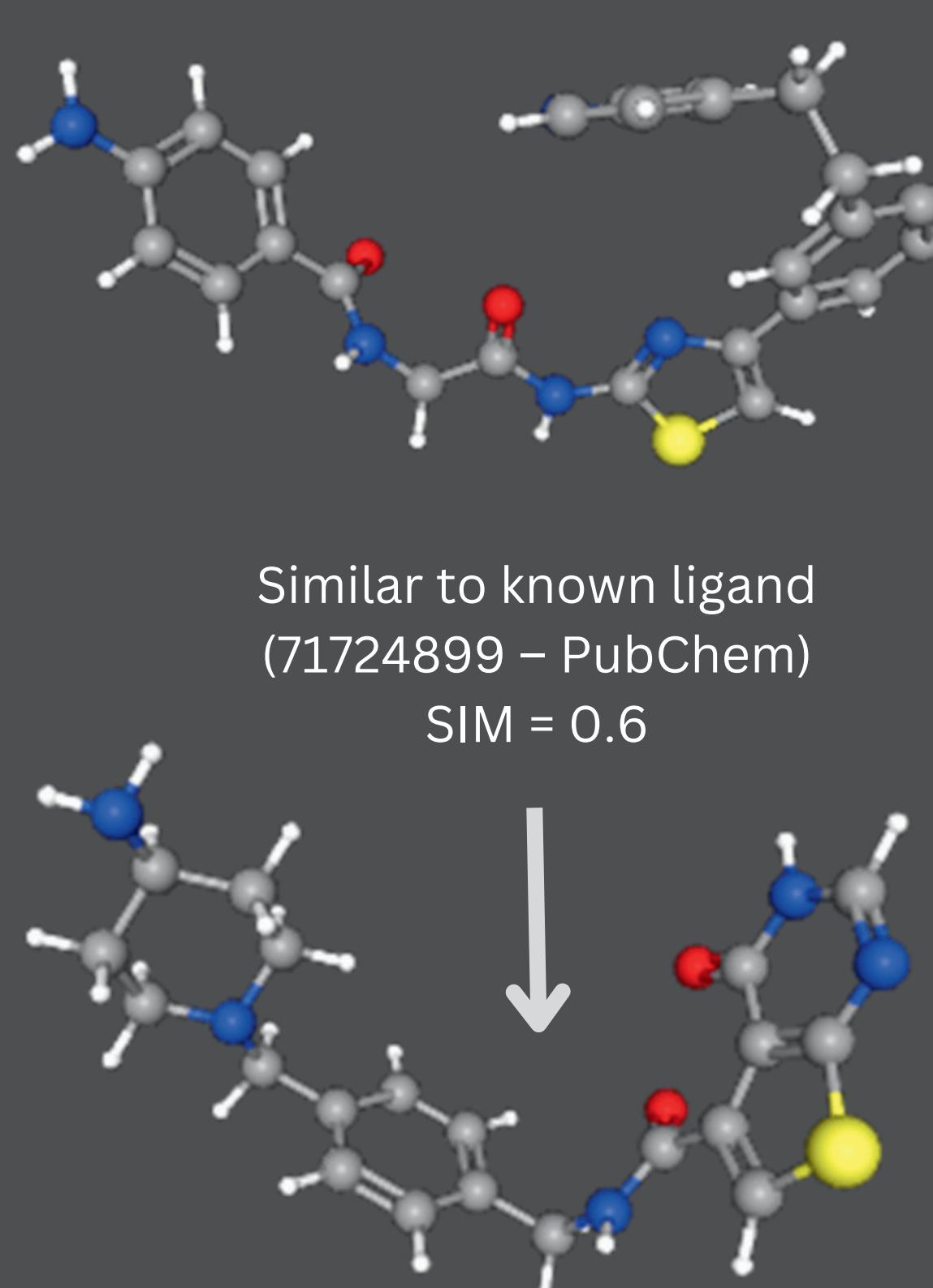


Figure 2: Docked hit and interactions with target protein.

CONCLUSION

Our work highlights critical considerations in inhibitor design, including careful target protein selection, appropriate tool and screening library selection, and parameter optimization. We believe our approach has identified a promising lead compound that warrants further optimization and experimental investigation.

RESULTS

A total of 5000 compounds was selected for docking with AutoDock Vina. A mean value of binding affinity was -7.15 kcal/mol with standard deviation 0.80 and ranging from -4.24 to -9.98 kcal/mol. We identified molecule 155792348 (PubchemID) as our potential lead compound with affinity -9.98 kcal/mol.

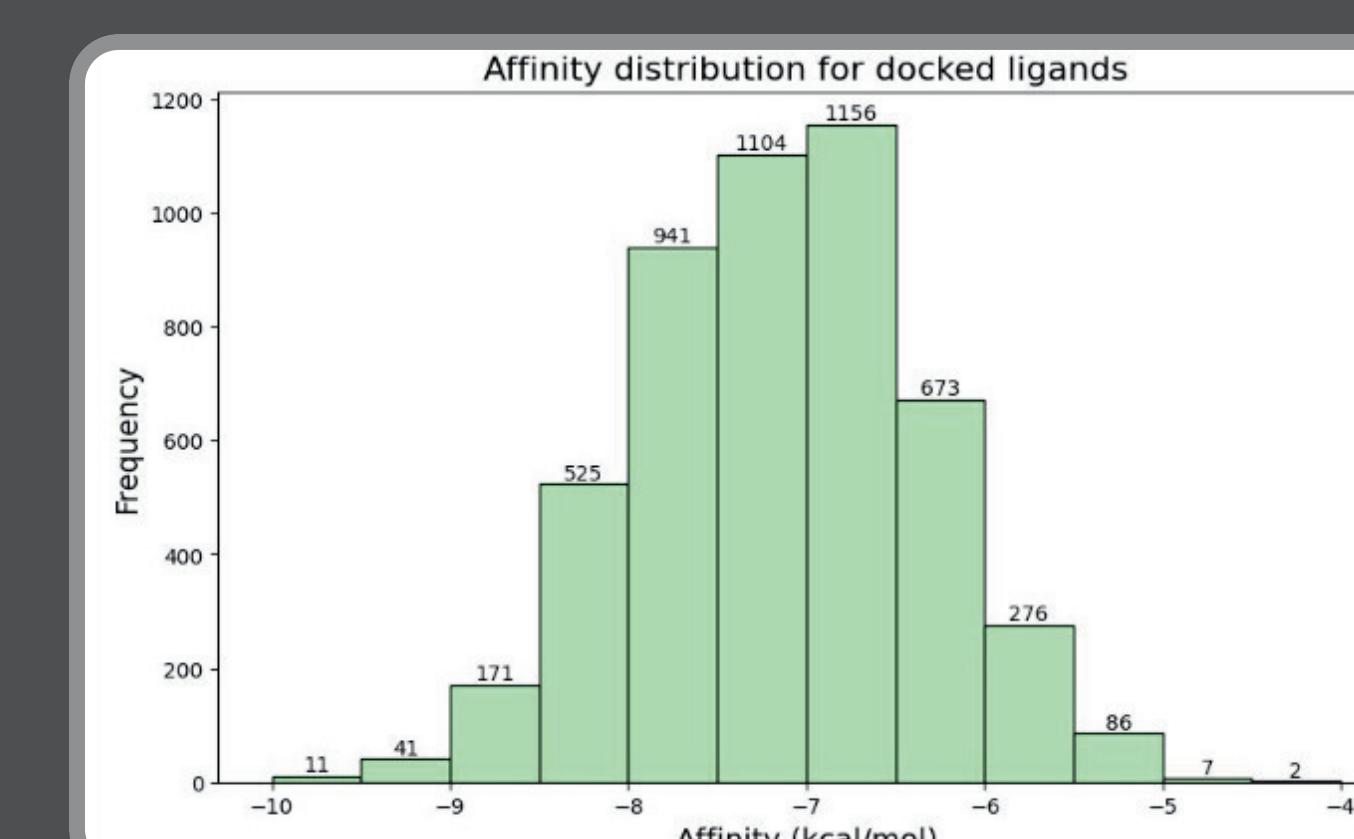


Figure 3: A histogram of affinity distribution for docked molecules.

REFERENCES

- Ya-Ming Hou, Ryuma Matsubara, Ryuichi Takase, Isao Masuda, Joanna I. Sulkowska. TrmD. 89–115 In RNA Modification. Elsevier, 2017.
- Thomas Christian et al., Distinct Origins of tRNA(m1G37) Methyltransferase. *Journal of Molecular Biology* **339** Elsevier BV, 2004.
- Andrew J. Wilkison et al., Evaluating the druggability of TrmD, a potential antibacterial target, through design and microbiological profiling of a series of potent TrmD inhibitors. *Bioorganic & Medicinal Chemistry Letters* **90** Elsevier BV, 2023.
- Wenhe Zhong, et al., Thienopyrimidinone Derivatives That Inhibit Bacterial tRNA (Guanine37-N1)-Methyltransferase (TrmD) by Restructuring the Active Site with a Tyrosine-Flipping Mechanism. *Journal of Medicinal Chemistry* **62** American Chemical Society (ACS), 2019.