National Autonomous University of Mexico
School of Chemistry

Design of Potential DNA Methyltransferase 1 Inhibitors Using Generative Models

QFB. Erik Daniel Díaz Dionisio

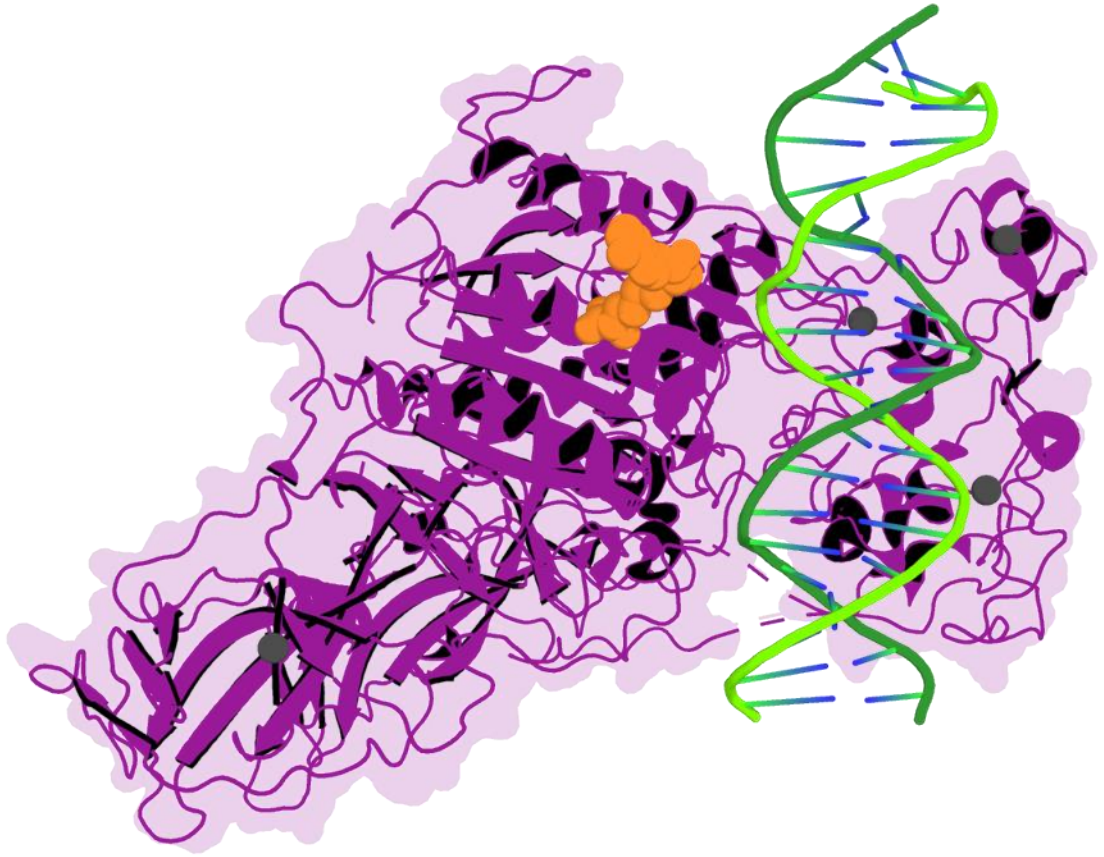
Tutor: Dr. José Luis Medina Franco

Laboratory 117, F building, School of Chemistry, UNAM

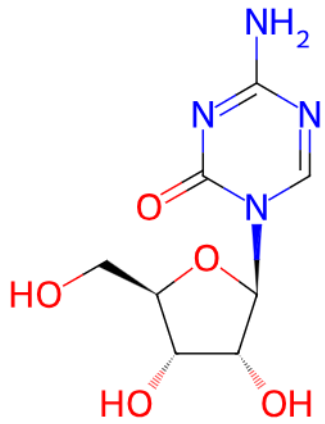
October 2026

DNMT1 as a Target for Epigenetic Drug Discovery

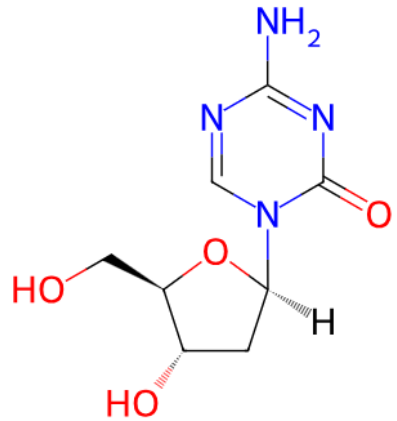
DNA Methyltransferase 1 (DNMT1) **inhibition reactivates** silenced **tumor suppressor genes** via DNA hypomethtlation.



FDA-approved drugs trigger off-target **genotoxicity** through DNA incorporation



Azacitidine

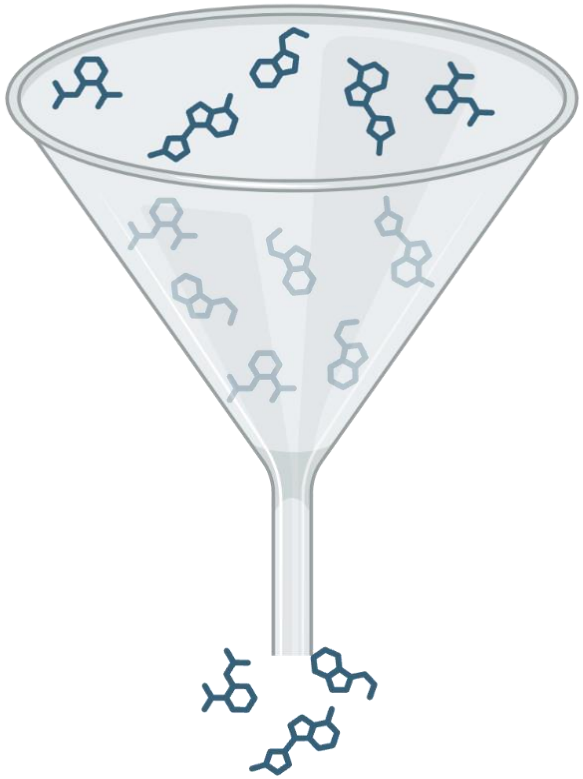


Decitabine

Prado-Romero, D.; *et al.*, *Front. Drug Discov*. 2023, 3, 1261094

DNMT1 current drug design

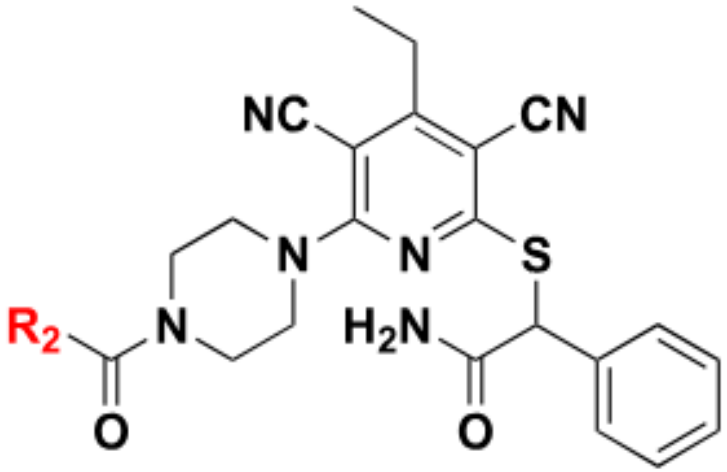
Current DNMT1 **inhibitor identification** is based primarily in **ligand-based strategies** and **virtual screening strategies.**



Virtual screening

Structure activity analysis

Fragment-based design

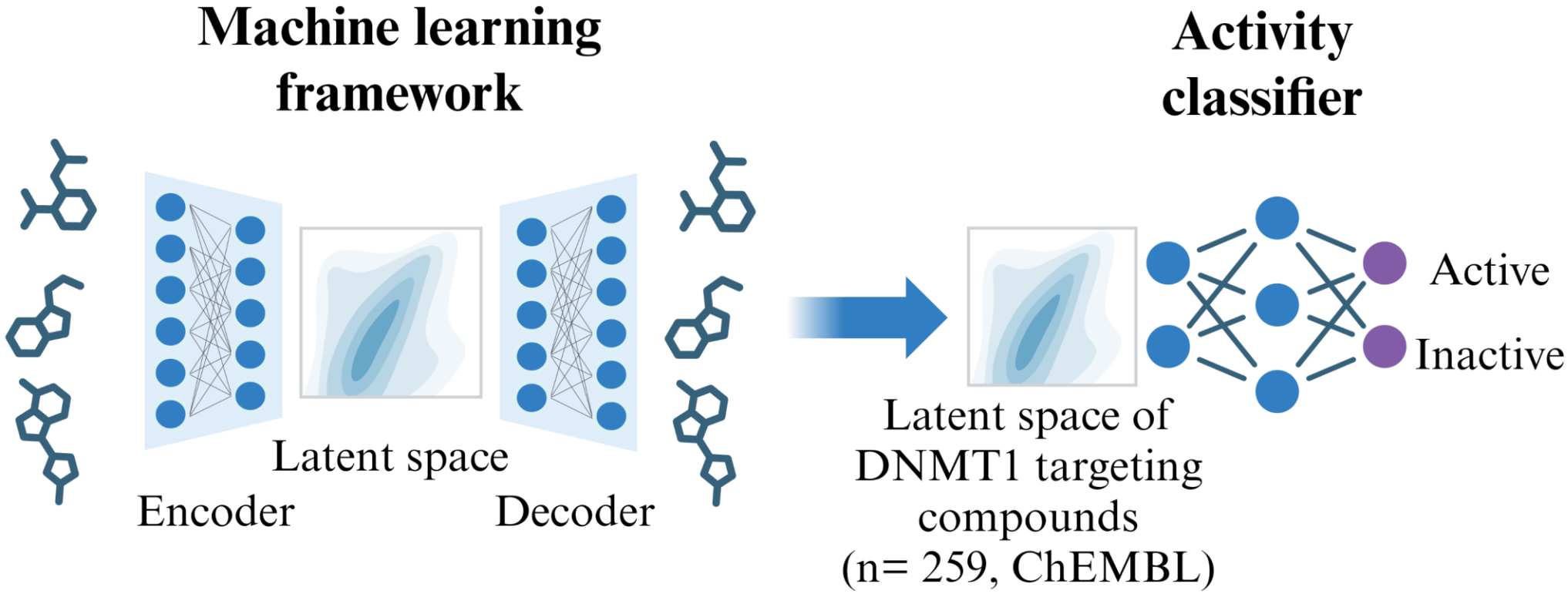


GSK3685032
Analogue

Prado-Romero, D.; Medina-Franco, J.L. *ACS Omega*, 2021, 6, 22478-22486

Expanding the Chemical Space for DNMT1 Inhibitor Discovery

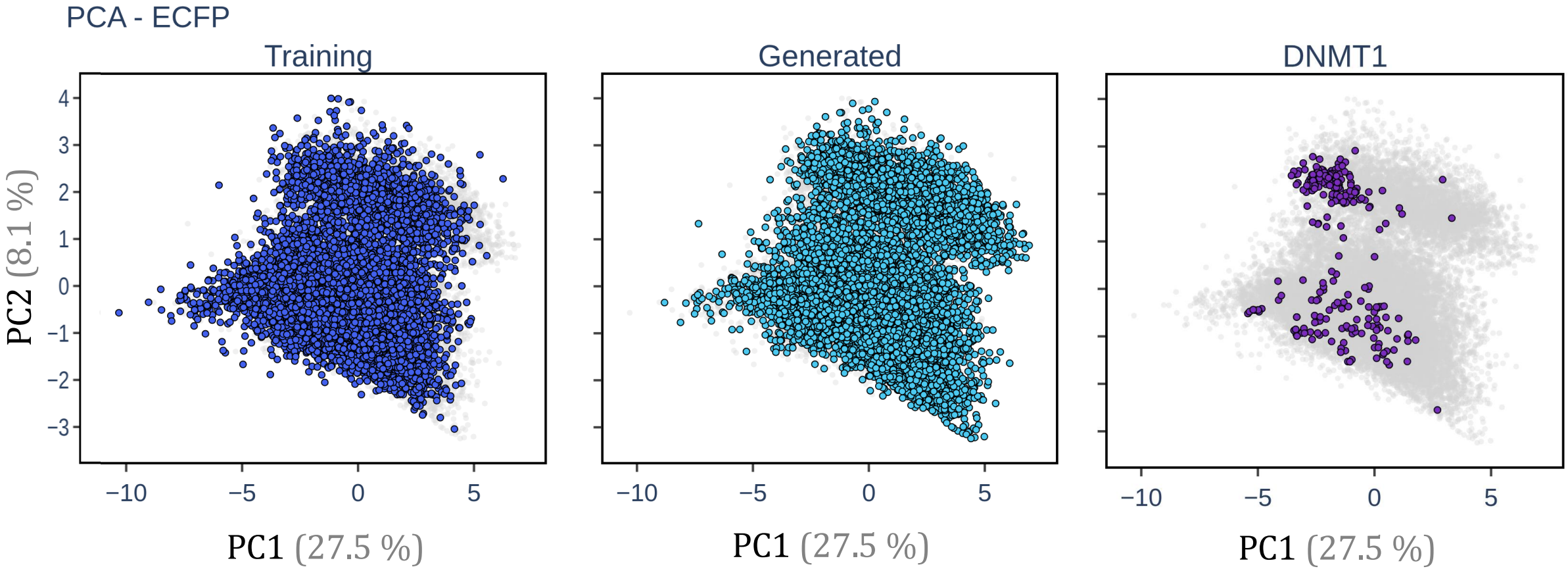
Generative models enable the **exploration of uncharted chemical space** while preserving desirable molecular properties. Variational Autoencoders (VAEs) allows **continuous latent-space sampling**



Romanelli, V.; *et al*. *ACS Omega* 2024, 9, 43963-43976

Generated Chemical Space covers DNMT1 molecules

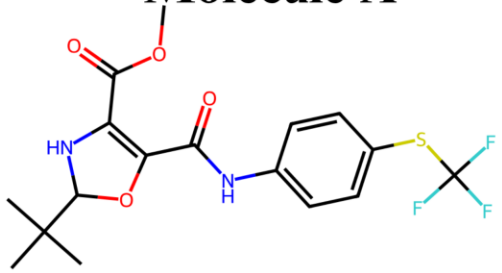
Validity: 100.0 % | **Unicity:** 97.0 % | **Novelty:** 100.0 %



Trustworthiness: 0.848 **Correlation:** 0.880

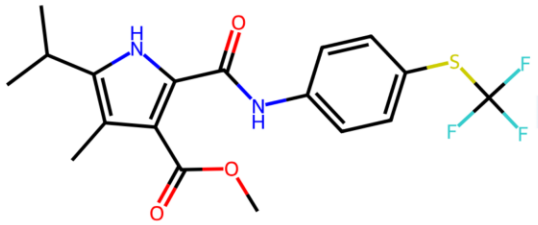
Latent Space Interpolation Show Chemical Pathway

Molecule A



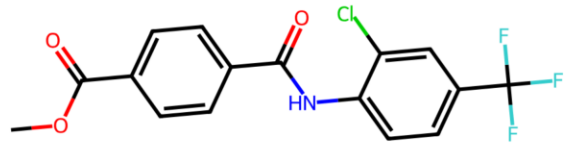
Similarity to A: 1.00
Similarity to B: 0.10

Step 1



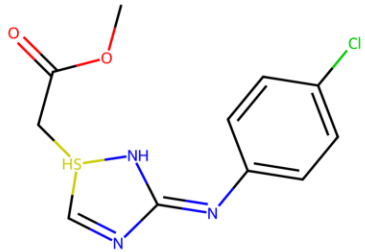
Similarity to A: 0.50
Similarity to B: 0.10

Step 2



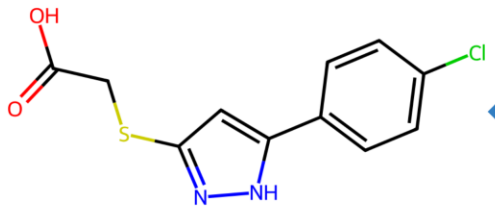
Similarity to A: 0.25
Similarity to B: 0.12

Step 3



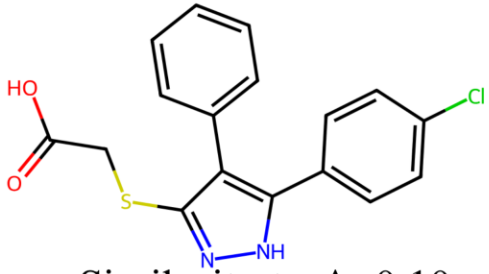
Similarity to A: 0.14
Similarity to B: 0.22

Step 4



Similarity to A: 0.11
Similarity to B: 0.52

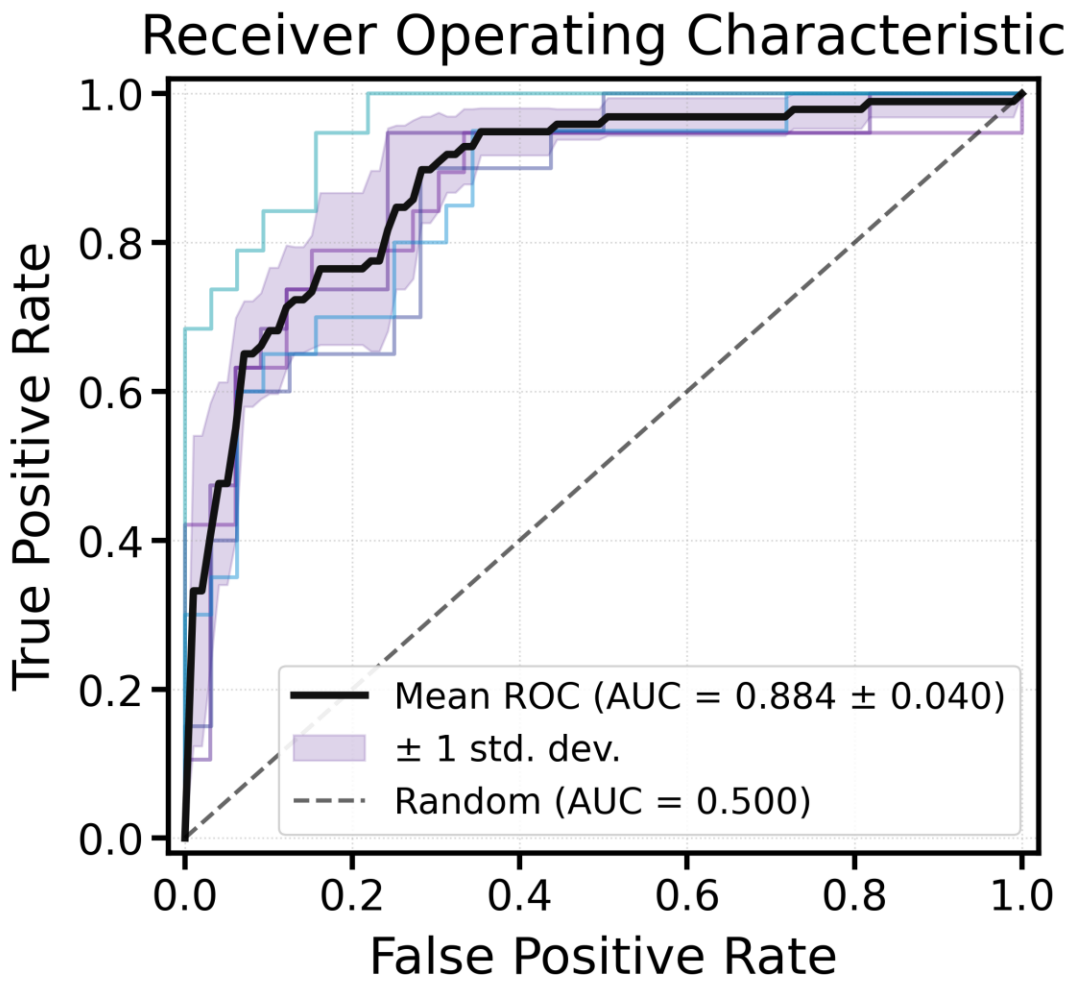
Molecule B

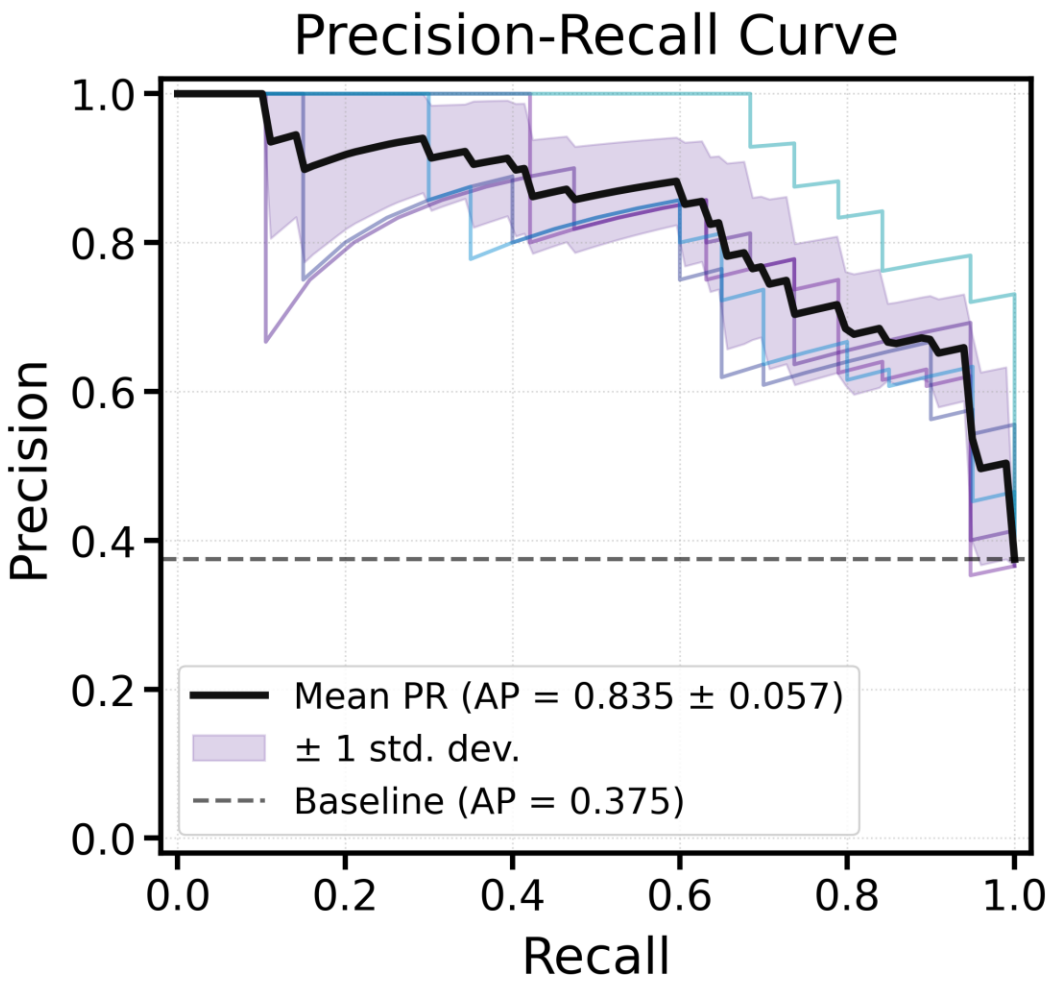


Similarity to A: 0.10
Similarity to B: 1.00

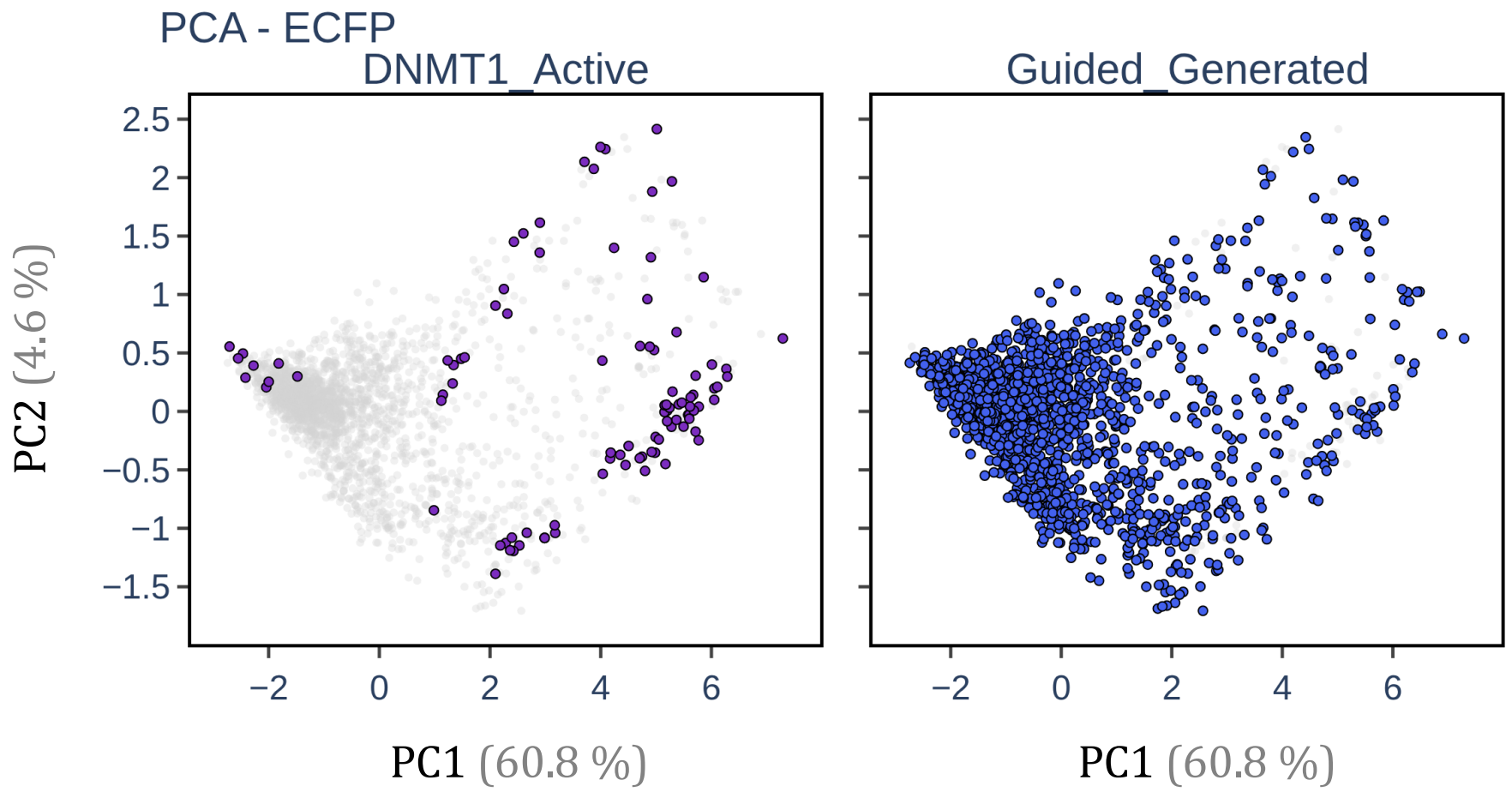
Similarity computed with Tanimoto / ECFP4

Latent Representation Capture Information Associated with DNMT1 Activity





Generated Molecules Allow Chemical Space Exploration in DNMT1 Related Molecules

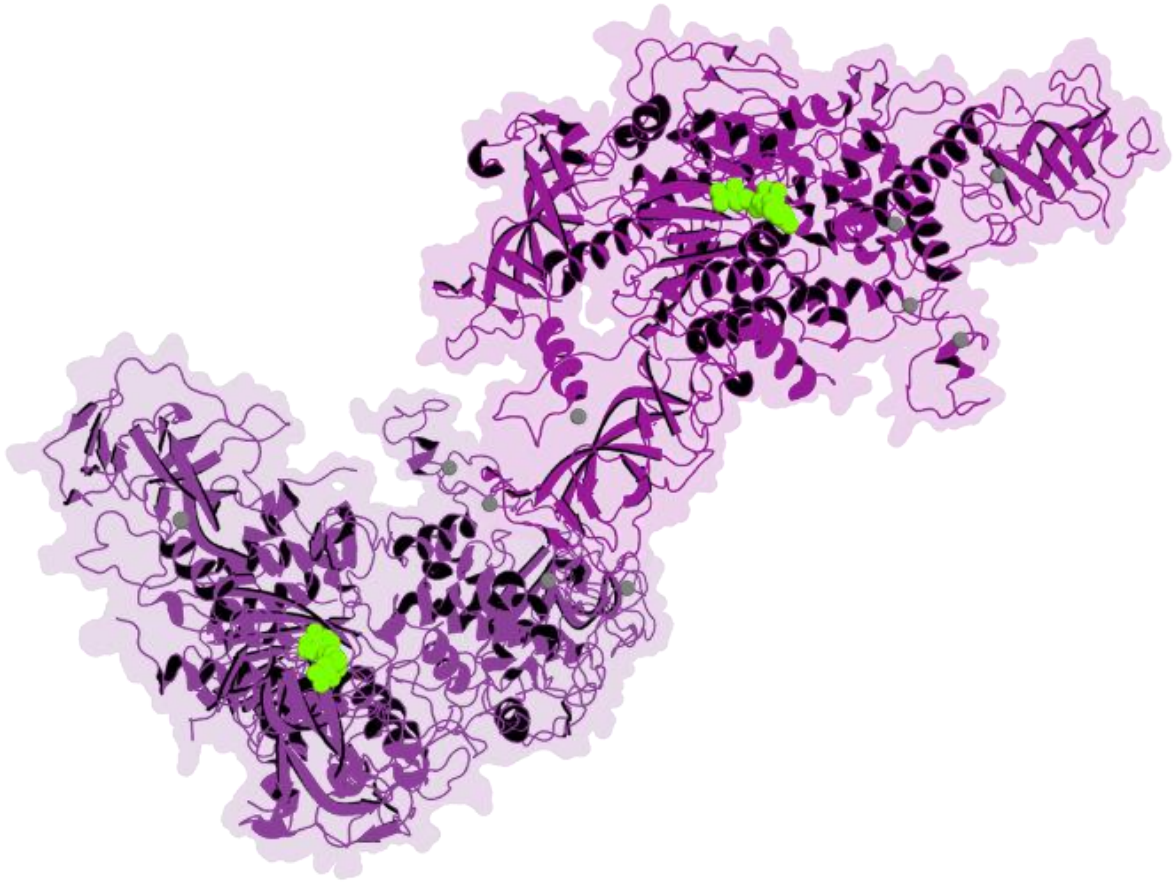


Trustworthiness: 0.886

Correlation: 0.985

Take home message

- Our VAE can **generate molecules** whithin the **same chemical space** of **DNMT1 molecules.**
- **Latent space** capture **information of DNMT1 activity** allowing the training of a classiffier.
- Coupling both models can **guide the sampling** to generate **DNMT1 active molecules.**



Future work

- Consensus Docking for candidate selection.
- Analogue search or candidate synthesis.
- Experimental validation

Acknowledgements



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