Exploring the Chemical Space of HDAC6 Inhibitors: A deep generative study using a Gradient Ascent Algorithm

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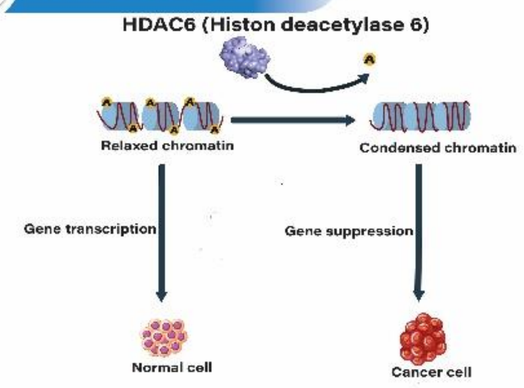
01 Introduction



Background

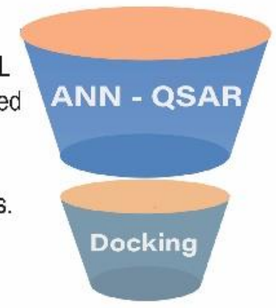
The process of deacetylation, regulated by histone deacetylases (HDACs) plays a pivotal role in cancer occurrence developemnt with HDAC6 being expressed in various tumor tissues. Therefore, HDAC6 inhibitors serve as a profound function in impeding the metastasis of cancer cells

Research goals

- Building JT-VAE model with gradient ascent algorithm
- Building ANN-QSAR model
- Screening potential drug candidates

Workflow

Build models based on ChEMBL dataset. Subsequently, generated compounds from JT-VAE and gradient ascent algorithm were evaluated through these models.



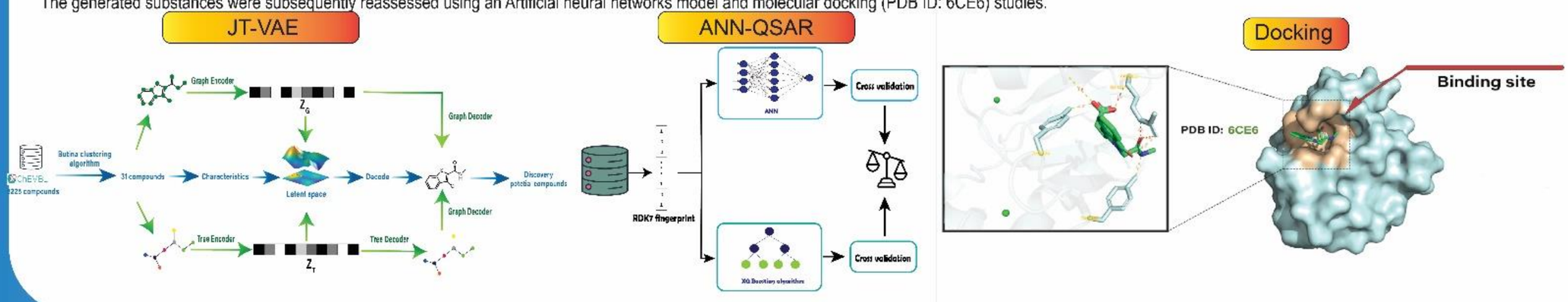
02 Material and methods

2.1. Material

5225 compounds from the ChEMBL database was used to construct JT-VAE model and ANN-QSAR model

2.2. Methods

In the generation stage, a diverse subset of active compounds was identified using the Butina algorithm.These compounds were then subjected to chemical space exploration employing JT-VAE and a gradient ascent algorithm. The generated substances were subsequently reassessed using an Artificial neural networks model and molecular docking (PDB ID: 6CE6) studies.

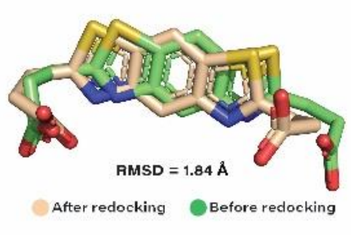


03 Results

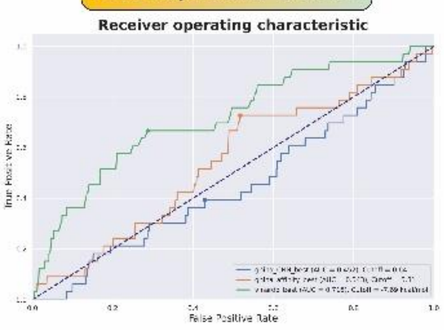
Thirty-one active compounds with a Tanimoto coefficient under 0.35 were identified from 5225 compounds collected from the ChEMBL database. These compounds underwent a chemical exploration stage, resulting in the generation of 303 novel substances. ANN-QSAR model was constructed with external validation yielding an R2 value of 0.596 and an RMSE value of 0.643. A retrospective control protocol was used to determine the scoring function and the cutoff of binding affinity energy, using Deepcoys to generate decoys at a ratio of 1:50 (active:decoys) through deep learning algorithm. Finally, Vinardo was chosen as the preferred scoring function in the GNINA software due to its superior ROC-AUC value of 0.715 when compared to two other scoring functions, and 13 distinguished compounds were identified with a pChEMBL Value threshold above 7 and binding affinity below -7.69 kcal/mol.

Docking Results

Redocking

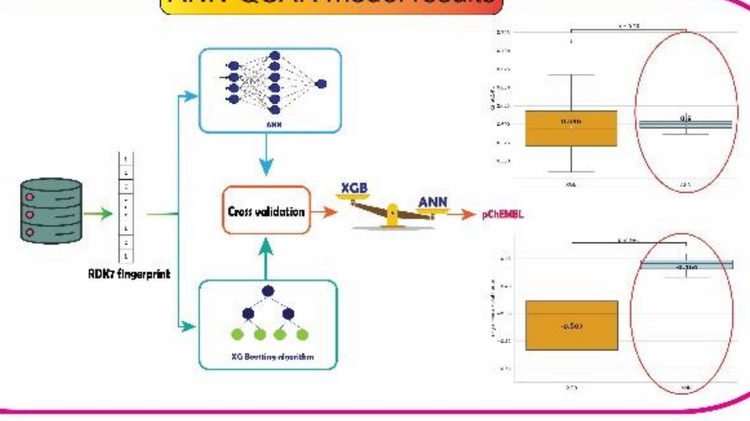


Retrospective Control

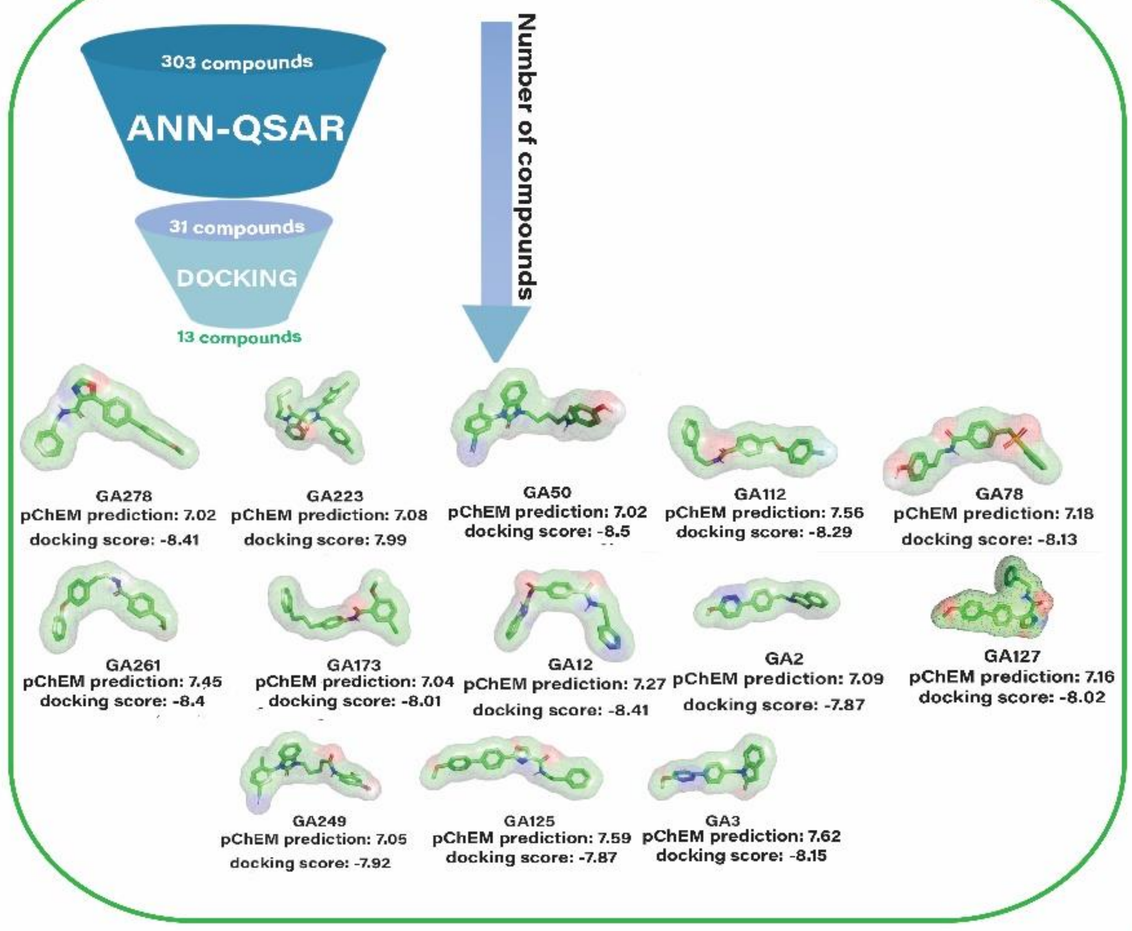


Vinardo was chosen as the preferred scoring function in the GNINA software due to its superior ROC-AUC value of 0.715 when compared to two other scoring functions.

ANN-QSAR model results



Screening results



04 Conclusions

The virtual screening conducted in this study led to the discovery of 13 potential compounds that could inhibit HDAC6 activity in an in vitro assay. This multi-pronged approach efficiently identified potential inhibitors of Histone deacetylase 6, suggesting the following stages involve synthesis and biological testing.

Reference

1. Bi G, Jiang G. The molecular mechanism of HDAC inhibitors in anticancer effects. Cell Mol Immunol. 2006 Aug;3(4):285-90.PMID: 16978537..
2. Takatsuka, H.; Shibata, A.; Umeda, M. Genome Maintenance Mechanisms at the Chromatin Level. Int. J. Mol. Sci. 2021, 22, 10384

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