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IMAGE-BASED CLASSIFICATION MODEL PREDICTING P-GLYCOPROTEIN INHIBITORS

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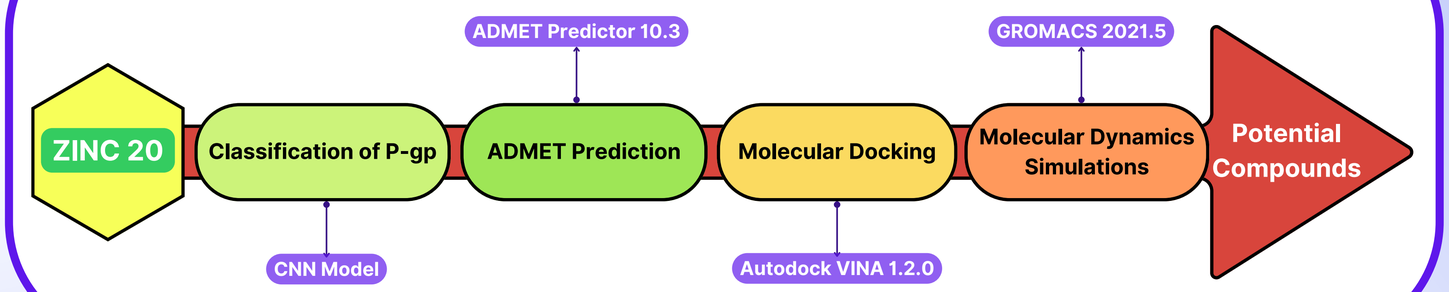
INTRODUCTION

Multidrug resistance (MDR) has been a significant challenge in cancer treatment for decades. P-glycoprotein (P-gp) is a primary active efflux transporter that operates through carrier-mediated mechanisms. It is often overexpressed in cancer cells, significantly influencing drug pharmacokinetics and contributing to drug resistance in anti-tumor therapies. Therefore, P-gp inhibitors lead to an increase in the concentration of anticancer drugs within the cell and cause cell cytotoxicity. This study presents an approach based on convolutional neural networks (CNN) to classify and predict the P-gp inhibitors on the ZINC20 natural database.

MATERIALS AND METHODS



RESULTS

Table 1. Optimizer, Hyperparameters and Evaluation.

Optimizer	Learning rate	Epoch	Fully connected layer	Dropout rate	Accuracy	Precision	Sensitivity	Specificity	F1-score	MCC	AUC
Adam	0.0005	40	1024	0.6	0.79	0.75	0.91	0.65	0.82	0.58	0.86

Table 2. Evaluation results of other databases.

External database	Classification threshold	TP	FP	TN	FN	Accuracy	Precision	Sensitivity	Specificity	F1-score	MCC
This study	Inhibitors: $IC_{50} \leq 15\mu m$ Non-inhibitors: $IC_{50} > 15\mu m$	147	49	91	15	0.79	0.75	0.91	0.65	0.82	0.58
ChEMBL ID (10%)	Inhibitors: $IC_{50} \leq 15\mu m$ Non-inhibitors: $IC_{50} > 15\mu m$	67	14	56	3	0.88	0.83	0.96	0.80	0.89	0.77
GF.Ecker et al.	Inhibitors: $IC_{50} \leq 15\mu m$ Non-inhibitors: $IC_{50} > 100\mu m$	864	220	406	338	0.69	0.80	0.72	0.65	0.76	0.35
B.Zdrazil et al.	Inhibitors: $IC_{50} \leq 15\mu m$ Non-inhibitors: $IC_{50} > 100\mu m$	66	59	57	9	0.64	0.53	0.88	0.49	0.66	0.38

CNN Model

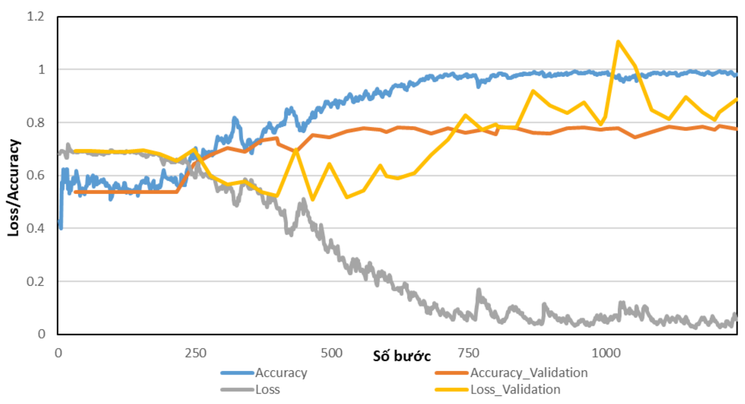


Figure 1. Evaluation graph of deep-learning model.

Molecular Docking

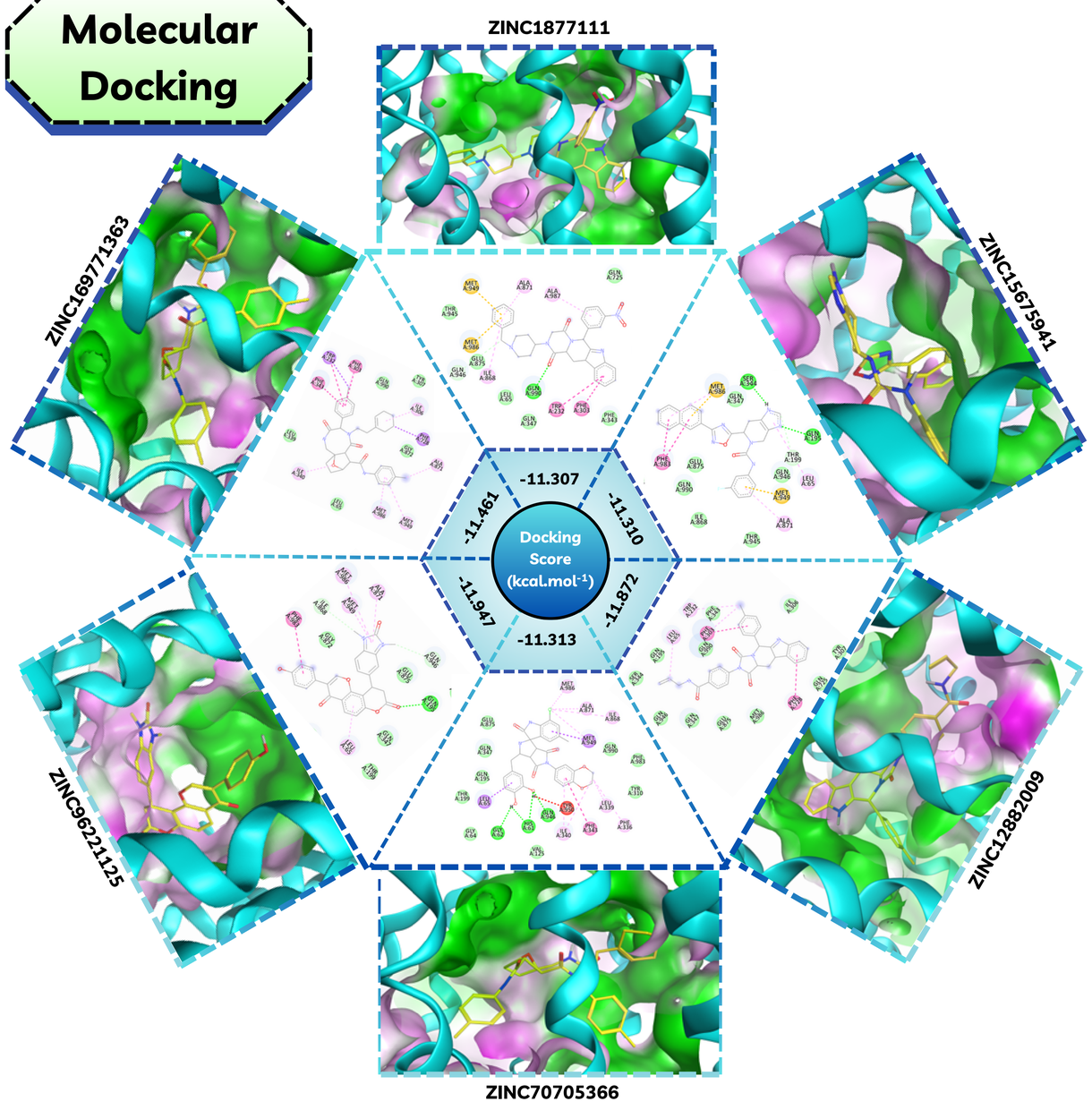
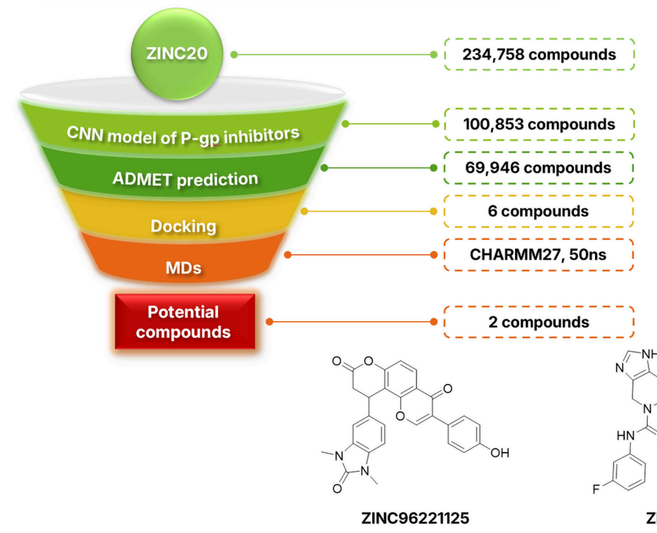


Figure 2. The binding pocket, docking score, and amino acids interaction of 6 potential compounds.

CONCLUSION



The *in silico* process, including CNN model application and virtual screening, discovered two potential compounds, **ZINC96221125** and **ZINC15675941**. These compounds have the ability to inhibit P-gp, increasing the bioavailability of anticancer drugs and decreasing the MDR in clinical treatment. These substances required *in vitro* testing in further research to confirm their bioactivity. Furthermore, generating another deep-learning model to classify P-gp substrates and inhibitors should be taken into consideration.

Molecular Dynamics Simulations (MDs)

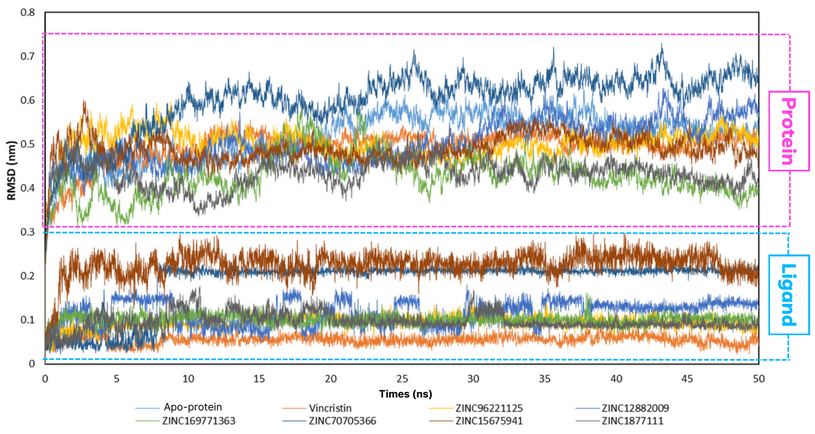


Figure 3. The RMSD value of apo-protein; ligands and protein of ligand in complexes.

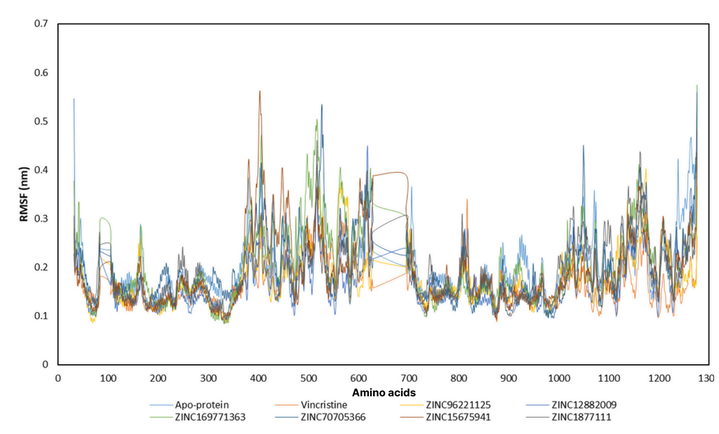


Figure 4. The RMSF value of apo-protein and protein of ligand in complexes.

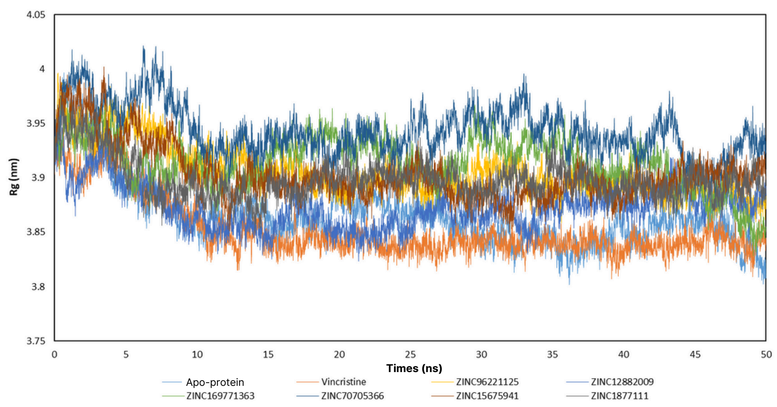


Figure 5. The Rg value of apo-protein and protein of ligand in complexes.

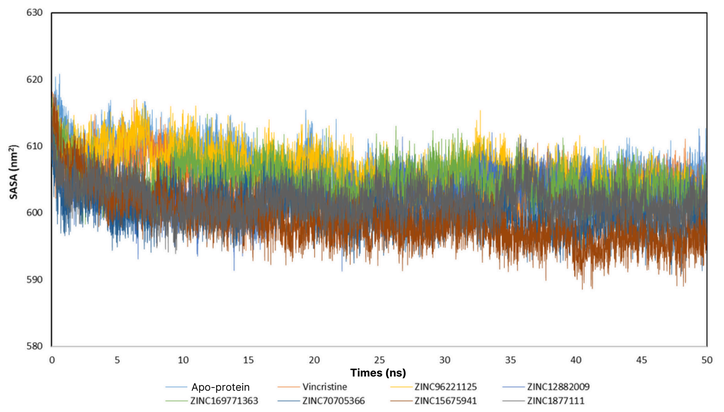


Figure 6. The SASA value of apo-protein and protein of ligand in complexes.

References

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2. Herédi-Szabó K, et al., *Eur. J. Pharm. Sci*., **2013**; *49(4),* 773-781.
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