INNOVATIVE EXPLORATION OF VEGFR-2 INHIBITORS IN CHEMICAL SPACE WITH GRADIENT ASCENT AND JUNCTION TREE VARIATIONAL AUTOENCODER

Gia-Bao Truong[1], Tieu-Long Phan[1], The-Chuong Trinh[1], Hoang-Son Lai Le[1], Van-Thinh To[1], Thanh-An Pham[1] , Phuoc-Chung Van Nguyen[1] , and Tuyen Ngoc Truong[1]

[1]*Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City, 41-43 Dinh Tien Hoang street, Ho Chi Minh city, Vietnam.*

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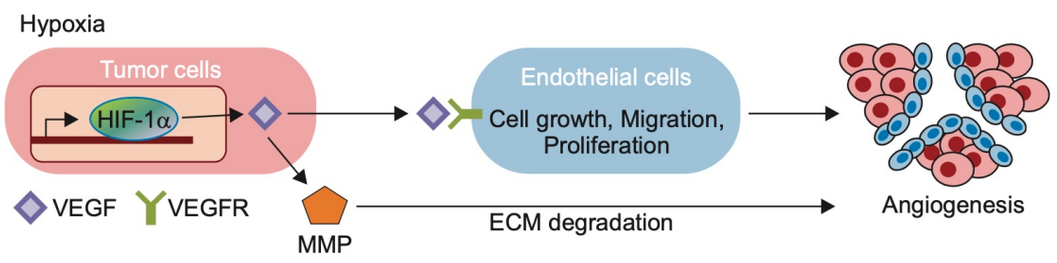
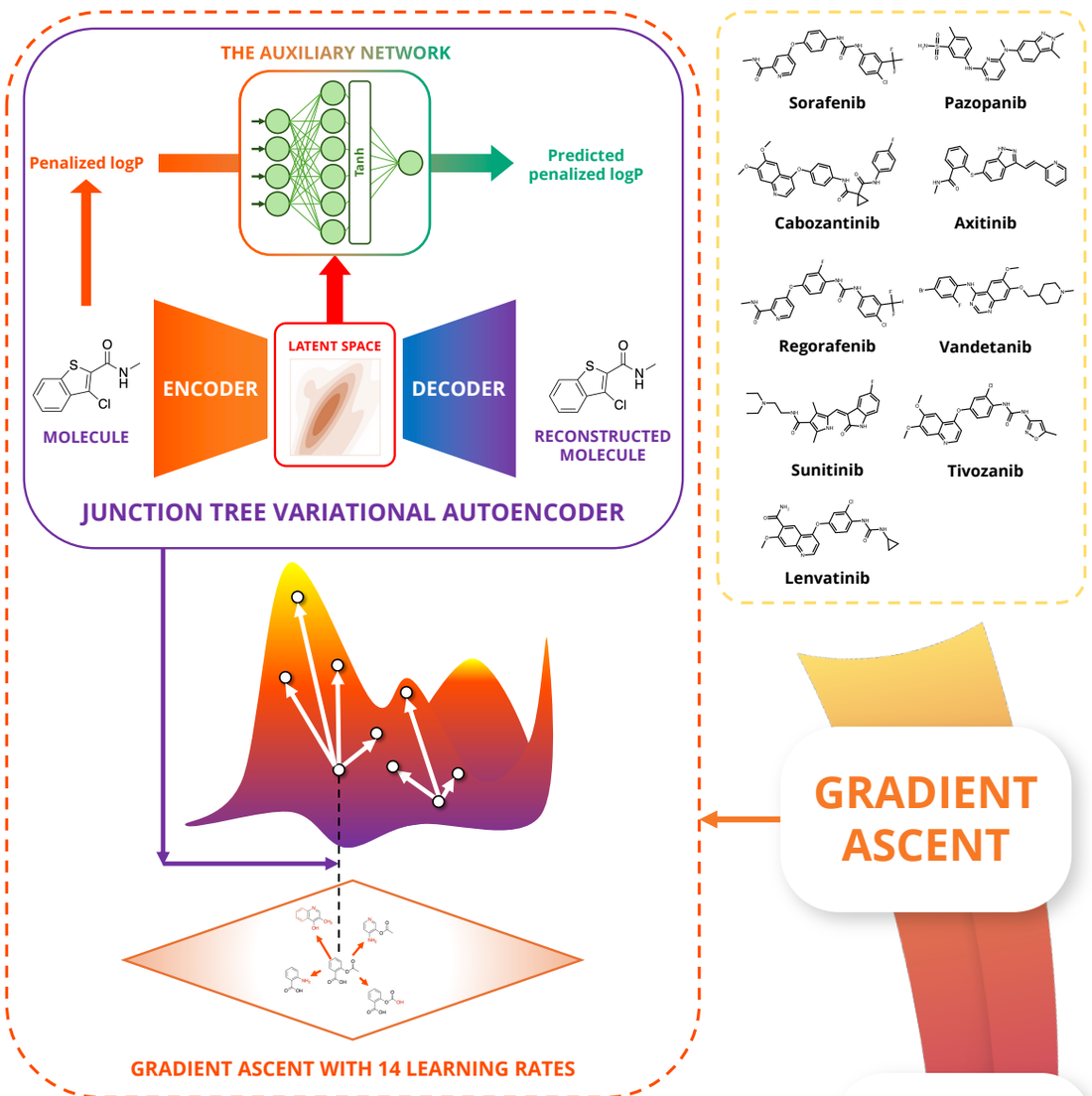
1 BACKGROUND AND OBJECTIVES



Vascular endothelial growth factor receptor 2 (VEGFR-2) is a tyrosine kinase receptor involved in vasculogenesis and angiogenesis, which can be activated by tumors to form new blood vessels for nutrition delivery and metastasis potential.[1] The Junction Tree Variational Autoencoder (JTVAE) is one of the state-of-the-art generative deep learning models that have been achieving success in *de novo* drug designs by attempting to reconstruct the chemical space.[2,3] Acknowledging the promise of these innovations, we explored the chemical space to identify novel small molecules potentially inhibiting VEGFR-2 using gradient ascent on the JTVAE model.

2 METHODS AND MATERIALS

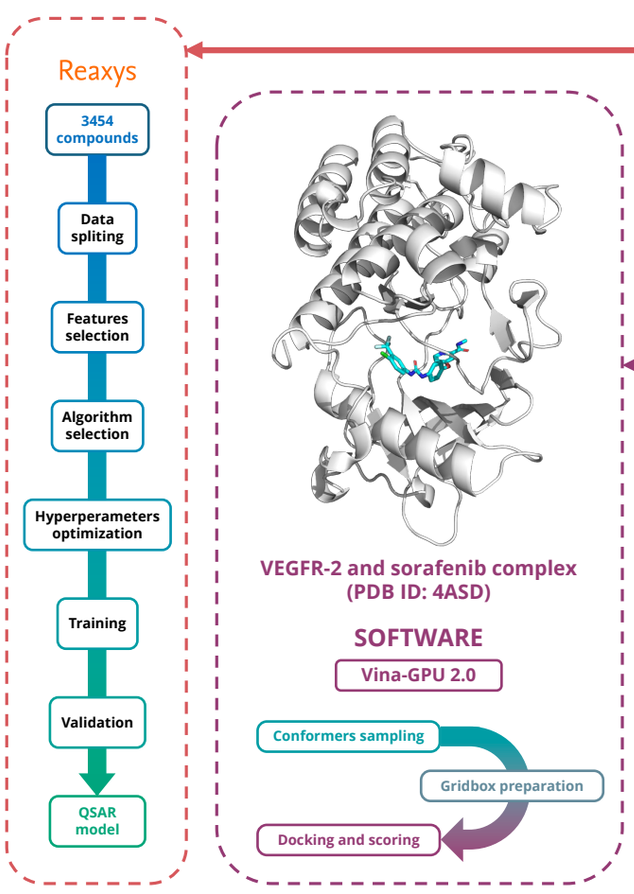


GRADIENT ASCENT

QSAR

MOLECULAR DOCKING

Potential compounds



3 RESULTS

GRADIENT ASCENT

217 compounds were found using gradient ascent.

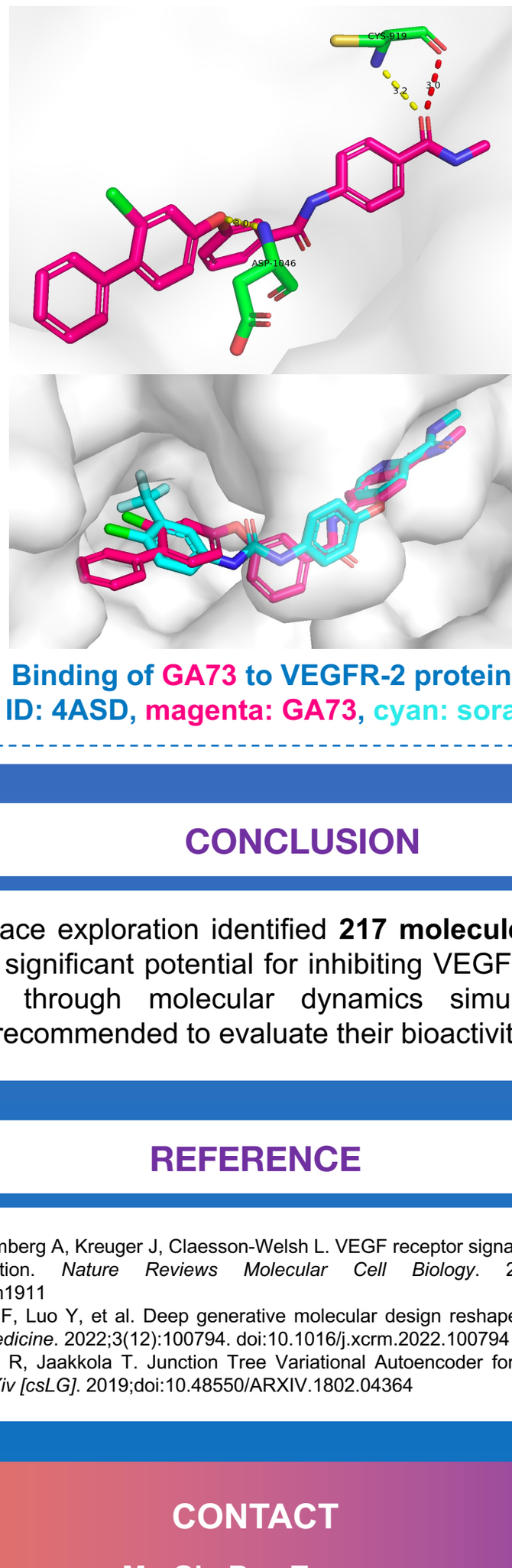
QSAR

FEATURES **RDK7** ALGORITHM **CatBoost**

Validation	R^2
Cross-validation	**0.865 ± 0.034**
External validation	**0.869**

MOLECULAR DOCKING

13 compounds had binding affinities equal to or better than **sorafenib** (≤ -11.20 kcal/mol), with predicted pIC50 values ranging from 5.30 to 6.85. **GA73** was identified as having significant interactions with vital amino acids in the VEGFR-2 protein.



Binding of GA73 to VEGFR-2 protein (PDB ID: 4ASD, magenta: GA73, cyan: sorafenib)

4 CONCLUSION

Chemical space exploration identified **217 molecules**, of which 13 exhibited significant potential for inhibiting VEGFR-2. Further investigation through molecular dynamics simulations and synthesis is recommended to evaluate their bioactivity.

REFERENCE

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CONTACT

Mr. Gia-Bao Truong

Affiliation: Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City, 41-43 Dinh Tien Hoang street, Ho Chi Minh city, Vietnam.

Email: tgbao.d18@ump.edu.vn

Phone: (+84) 949 348 657

Website: github.com/buchijw