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Atom-Based 3D-QSAR Modeling and Molecular Docking of Tadalafil Analogs as Potential Acetylcholinesterase Inhibitors for Alzheimer's Disease.

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INTRODUCTION & AIM

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline, and cholinergic dysfunction. Acetylcholinesterase (AChE) is a key enzyme that hydrolyzes acetylcholine, thereby regulating neurotransmission in the brain. Inhibition of AChE helps restore cholinergic balance and remains a proven therapeutic approach for managing AD symptoms. Existing AChE inhibitors such as donepezil, rivastigmine, and galantamine provide limited efficacy and often cause adverse effects, highlighting the need for new, potent, and safer alternatives. Tadalafil analogs, known for their AChE inhibitory activity, possess structural features that may favor dual inhibition and neuroprotective potential. Computational techniques like 3D-QSAR modeling and molecular docking are powerful tools for understanding structure–activity relationships and for guiding the rational design of novel AChE inhibitors.

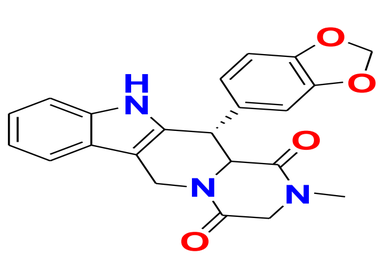

Figure 1: ***structure of Tadalafil***

METHOD

1- Dataset Preparation

A series of 37 tadalafil analogs with reported AChE inhibitory activities were selected from the literature. Biological activities (IC_{50} values) were converted to pIC_{50} (−log IC_{50}).

2-Molecular Docking

Docking studies were conducted using Glide (Schrödinger) to predict the binding mode of each analog in the AChE active site (PDB ID: 4EY7). Glide XP (extra precision) mode was employed to identify key hydrogen bonds, π–π stacking, and hydrophobic interactions. Docking results were used to guide the design of new analogs.

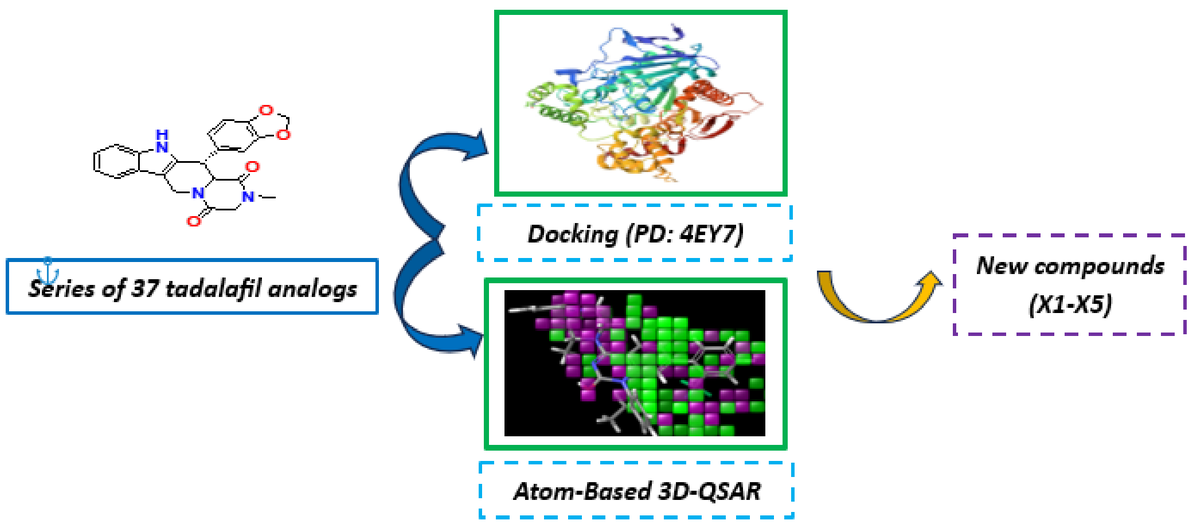

Figure 2: ***Computational design for new selected compounds as potential Acetylcholinesterase Inhibitors.***

3- 3D-QSAR Model

Atom-based 3D-QSAR model was performed using PHASE (Schrödinger). Model performance was evaluated using R^2, Q^2, RMSE, and F-value for internal and external validation.

4- Design of New Compounds

Based on QSAR contour maps and docking insights, five new tadalafil analogs (X1–X5) were proposed. Their predicted pIC_{50} values were estimated using the developed 3D-QSAR model.

RESULTS & DISCUSSION

1- 3D-QSAR analysis:

The constructed 3D-QSAR model demonstrated excellent statistical robustness and predictive accuracy, showing a high correlation for the training set (**R^2 = 0.975, SD = 0.190, F = 464.7, N = 29)** and strong predictive performance for the test **set (Q^2 = 0.809, Pearson(r) = 0.941, RMSE = 0.564 N = 8)** using three PLS factors.

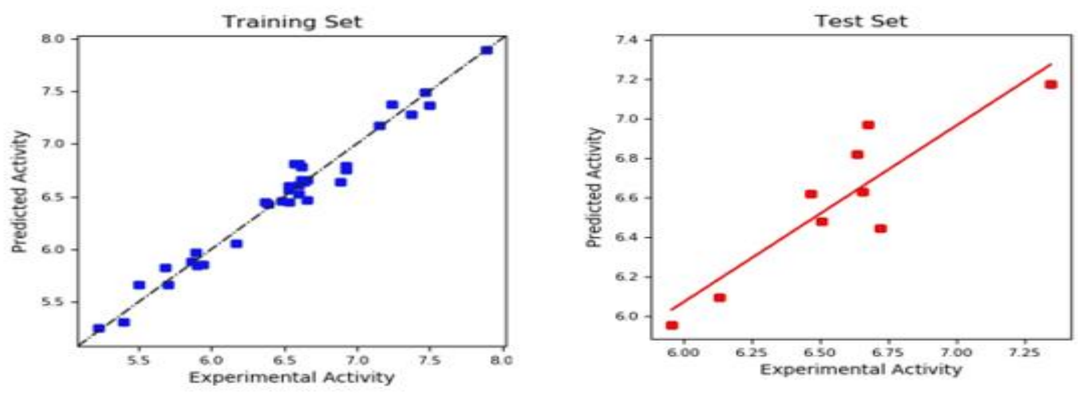

Figure 3: ***Correlation between actual and predicted activity (PIC_{50}) of training and test sets***

2- Moleculer Docking

Five new candidate molecules were proposed, among which compound X1 exhibited the highest predicted inhibitory activity.

Table 1: Docking results of the Five compounds with the predicted activity (pIC_{50}).

Compounds	XPScore	Glide Emodel	pIC_{50}
X1	-11.51	-85.91	8.53
X2	-10.96	-59.63	7.51
X3	-10.94	-84.56	7.47
X4	-8.66	-64.27	5.96
X5	-9.76	-83.06	6.43
Tadalafil	-9.84	-70.15	/

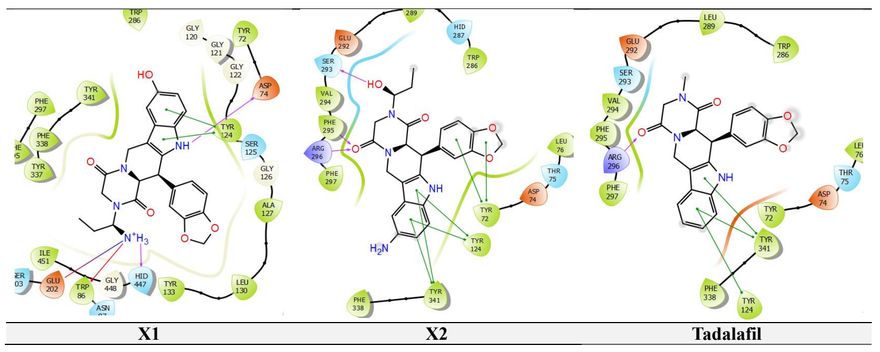

Figure 4. ***Molecular docking and interaction analysis of acetylcholinesterase (AChE) inhibitors Tadalafil and proposed molecules X1–X2.***

CONCLUSION

- A combined 3D-QSAR and molecular docking approach was successfully used to evaluate 37 tadalafil analogs as potential AChE inhibitors for Alzheimer's disease.
- The 3D-QSAR model showed excellent robustness and predictive accuracy, confirming reliable structure–activity relationships.
- Docking studies identified key interactions within the AChE active site responsible for inhibitory potency.
- Five new analogs were designed based on these insights, with compound X1 showing the highest predicted activity.
- This integrated computational strategy provides a powerful framework for designing novel, potent AChE inhibitors as promising anti-Alzheimer's agents.

FUTURE WORK / REFERENCES

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[4] Fei Mao, Huan Wang, Wei Ni, Xinyu Zheng, Manjiong Wang, Keting Bao, Dazheng Ling, Xiaokang Li, Yixiang Xu, Haiyan Zhang, Jian Li. *ACS Chemical Neuroscience.* 2018; **9**(2):328–345.