

DESIGN AND EVALUATION OF NITROGEN CONTAINING HETEROCYCLIC DERIVATIVES FOR THE MANAGEMENT OF COGNITIVE DEFICITS IN NEUROLOGICAL DISORDERS

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Introduction

- Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive impairment, and behavioral decline. Multiple pathological mechanisms, including amyloid- β aggregation, tau hyperphosphorylation, oxidative stress, and synaptic dysfunction, contribute to disease progression.
- Glycogen synthase kinase-3 β (GSK-3 β) is a key regulator of tau phosphorylation and represents an attractive therapeutic target for AD. Due to their favorable pharmacological properties and blood-brain barrier permeability, indole-based heterocyclic compounds have emerged as promising candidates for developing multitarget anti-Alzheimer agents.

Aim and Objectives

Aim

The aim of the study is to design and evaluate indole based heterocyclic derivatives for the management of cognitive deficits in neurological disorders.

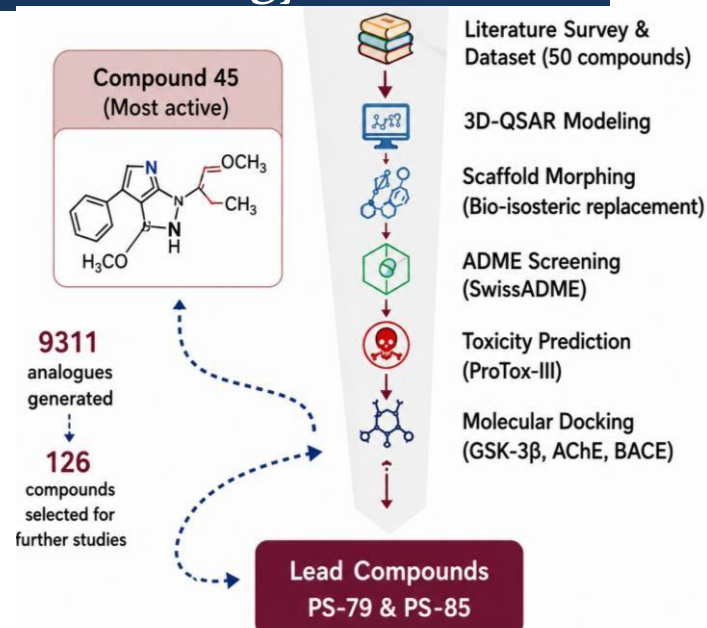
Objectives

- To generate a 3D- QSAR model of indole derivative binding to GSK-3 β target enzyme.
- To design and screen varied compounds using 3D- QSAR.
- To assess ADMET characteristics and drug- likeness.
- To validate the novel designed indole derivatives using molecular docking studies.

Conclusion

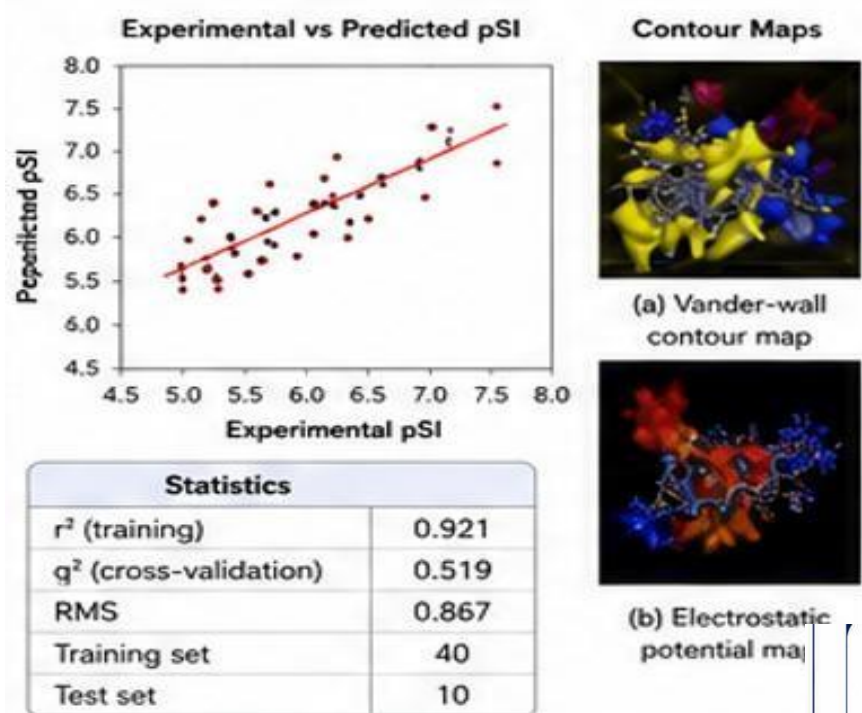
- An integrated computational drug discovery strategy successfully identified novel indole-based heterocyclic derivatives targeting GSK-3 β .
- The developed 3D-QSAR model guided lead optimization through bio-isosteric replacement. Subsequent ADME, toxicity, and molecular docking studies identified **PS-79** and **PS-85** as promising lead compounds exhibiting favorable pharmacokinetic properties, acceptable safety profiles, and strong multitarget binding against GSK-3 β , AChE, and BACE.

Methodology workflow



Results

3D-QSAR Modeling



Bio steric Replacements

Top 5 compounds			
S. No.	Compound ID	Structure	Synthetic Accessibility (SA Score)
1	PS-79		2.162
2	PS-85		2.215
3	PS-92		2.183
4	PS-93		2.215
5	PS-94		2.216

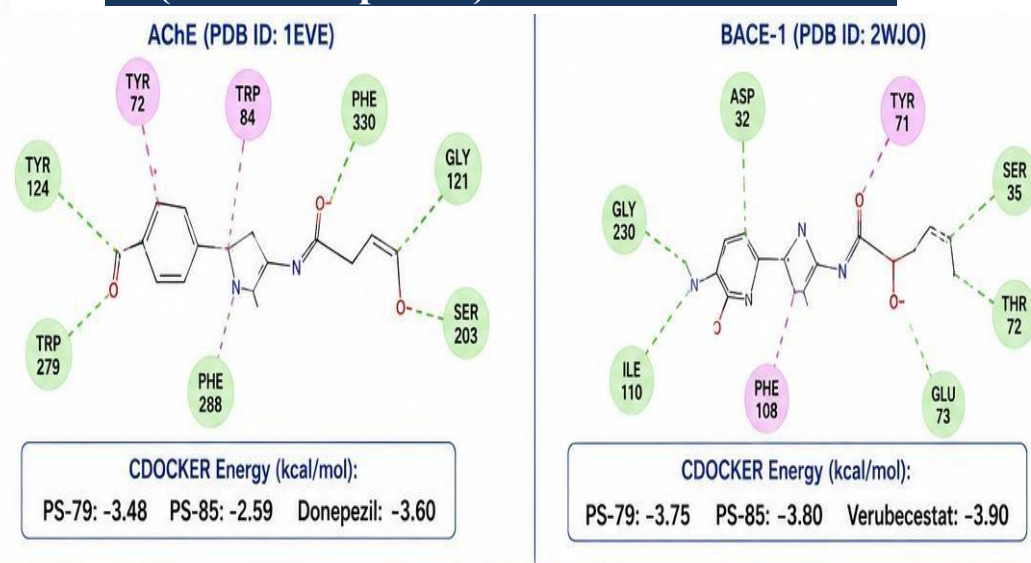
Toxicity Study (Pro Tox 3.0)

Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity	LD ₅₀ (mg/kg)
					>2000 (Relatively Safe)
36/84 Non-toxic	48/84 Carcinogenic (Excluded)	Non-toxic	Non-toxic	Non-toxic	

36 non-carcinogenic and relatively safe compounds selected for docking studies

MW: Molecular Weight; HBA: Hydrogen Bond Acceptors; HBD: Hydrogen Bond Donors; RB: Rotatable Bonds; TPSA: Topological Polar Surface Area; GI: Gastrointestinal; BBB: Blood Brain Barrier

Multi-Target Docking Analysis (Lead Compound)

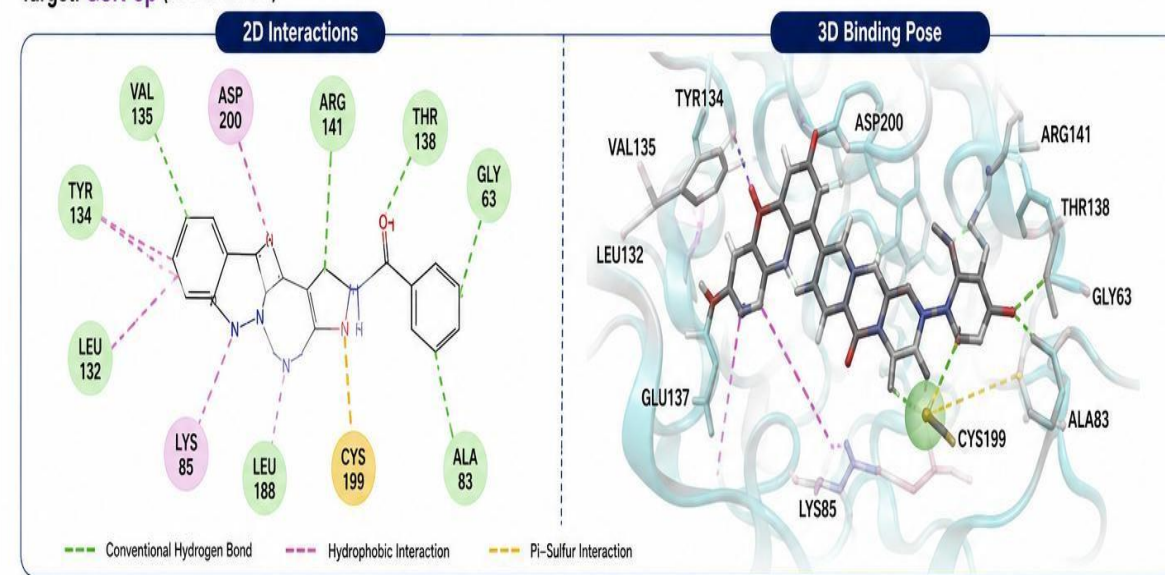


Swiss-ADME Study

S. No.	Compounds ID	MW	Rotatable bonds	H-bond acceptors	H-bond donors	TPSA	I LOGP	Ali Log S	GI absorption	BBB permeation	Lipinski #violations
1	PS-79	308.37	5	2	1	43.26	3.01	-3.42	High	yes	0
2	PS-85	295.33	4	3	1	51.46	2.29	-3.54	High	yes	0
3	Ps93	295.33	4	3	1	51.46	2.29	-3.54	High	yes	0
4	Ps94	308.37	5	2	1	43.26	2.98	-3.42	High	yes	0

Molecular Docking Study

Target: GSK-3 β (PDB ID: 4PTC)



Future Prespective

- Synthesize the lead compounds **PS-79** and **PS-85**.
- Perform **in vitro** GSK-3 β enzyme inhibition studies.
- Evaluate neuroprotective activity in neuronal cell lines.
- Conduct **in vivo** efficacy studies using Alzheimer's disease animal models.
- Optimize pharmacokinetic and safety profiles.
- Explore further multitarget optimization against **GSK-3 β , AChE, and BACE**.
- Validate lead compounds through preclinical studies.