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Dual Inhibition of AChE and Amyloid-β Aggregation by 3-Vinyl-Quinoxalin-2(1*H*)-one Derivatives for Alzheimer's Therapy

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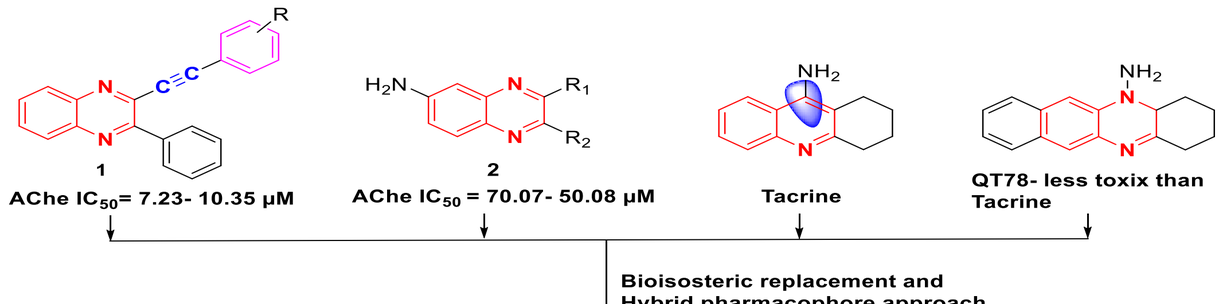
INTRODUCTION

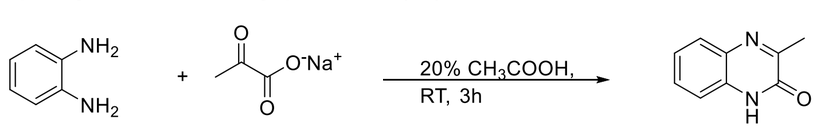
Alzheimer's disease (AD) is the most common neurodegenerative disorder, marked by progressive memory loss, cognitive decline, and behavioral changes. Acetylcholine (ACh) depletion and the aggregation of amyloid-beta (Aβ) plaques are key pathological hallmarks of AD. Current therapies, such as acetylcholinesterase (AChE) inhibitors (donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine, provide only symptomatic relief without halting disease progression. Therefore, developing dual-acting agents that inhibit AChE and prevent Aβ aggregation is of great therapeutic interest. This research aims to design, synthesize, and evaluate novel 3-vinylquinoxalin-2(1H)-one derivatives as potential dual inhibitors capable of blocking AChE activity and preventing Aβ aggregation to slow or prevent disease progression. In this study, compounds were synthesized and biologically screened, among which MHA-2 and MHA-15 showed potent AChE inhibition with low micromolar IC_{50} values and strong suppression of Aβ aggregation. Molecular docking, PAMPA-BBB, and fluorescence assays confirmed their enzyme binding, favorable blood–brain barrier permeability, and anti-aggregation potential. These findings highlight MHA-2 and MHA-15 as promising lead scaffolds for Alzheimer's disease therapy.

METHOD



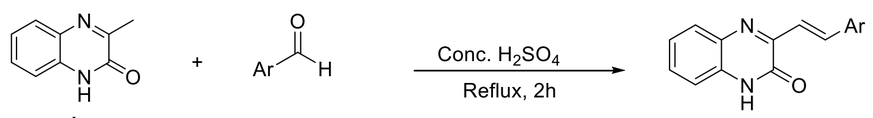
Synthesis of 3-vinylquinoxalin-2(1*H*)-one derivatives

Step 1: Synthesis of 3-methylquinoxalin-2(1*H*)-one

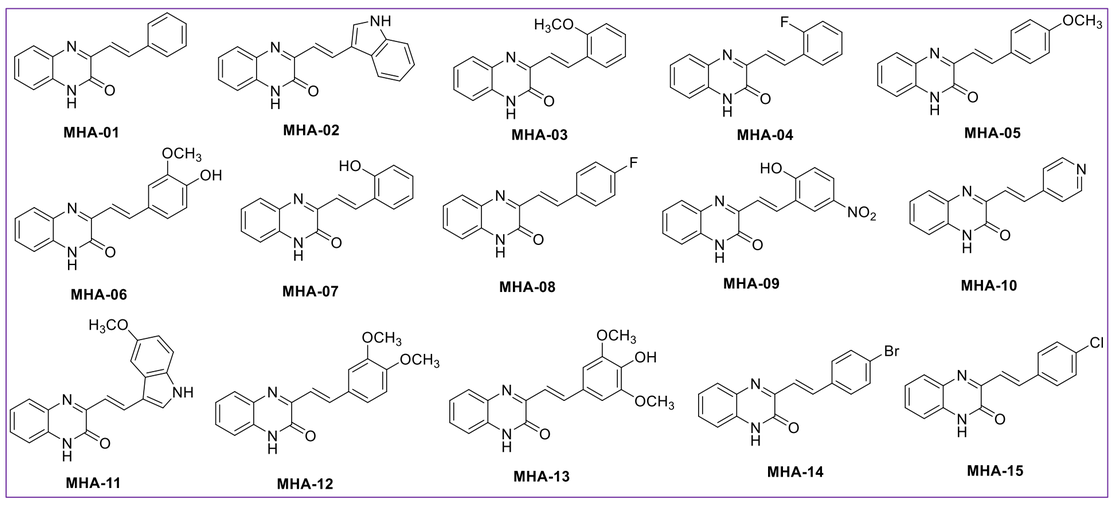


benzene-1,2-diamine sodium 2-oxopropanoate 1

Step 2: Synthesis of 3-styrylquinoxalin-2(1*H*)-ones



1 Ar = Aromatic/ hetaryl aldehydes 3-vinylquinoxalin-2(1*H*)-one derivatives **MHA 01 - 15**



RESULTS & DISCUSSION

Thioflavin-T Assay

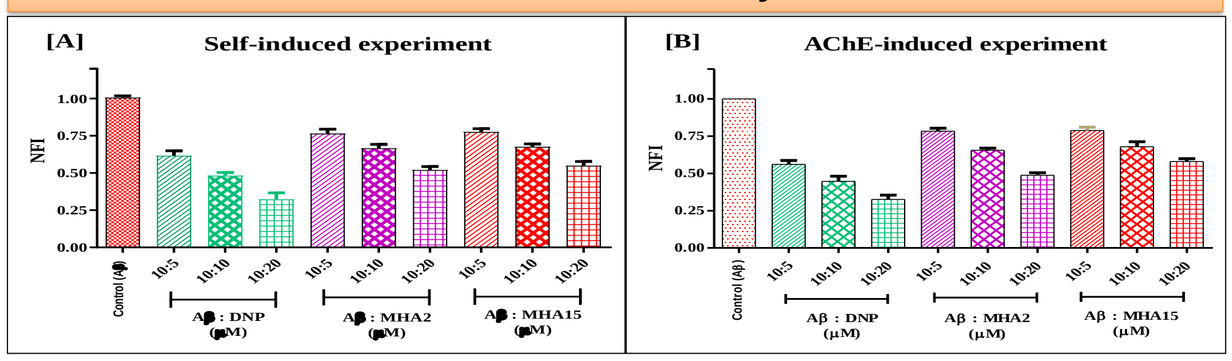


Figure 1: (A) Inhibition of self-induced Aβ1−40 aggregation. (B) AChE-induced Aβ1−40 aggregation by MHA-2, MHA-15, and the reference compound donepezil.

PI displacement Assay

Percentage of PI Displacement from PAS-hAChE.

Comp Code	PI displacement from PAS-hAChE (%)[a]	
	[I] = 10 µM	[I] = 50 µM
MHA-2	12.331 ± 1.124	21.286± 1.016
MHA-15	14.227 ± 0.994	19.256± 1.011
Donepezil	25.311 ± 1.204	42.256 ± 1.136

PAMPA-BBB Assay

Prediction of BBB Permeation of selected ligands.

Comp Code	PAMPA-BBB permeability	
	Pe (exp)	
	(5.8×10^{-6} cm s^{-1})	Prediction
MHA-2	4.981 ± 0.027	CNS±[c]
MHA-15	4.359 ± 0.041	CNS+[c]
Donepezil	5.994 ± 0.038	CNS+[b]

Ellman Assay

Result of hAChE inhibition by compounds

Comp. Code	AChE IC_{50} (µM) ± SEM
MHA-1	2.73 ± 0.041
MHA-3	3.71 ± 0.041
MHA-4	2.6 ± 0.026

Comp. Code	AChE IC_{50} (µM) ± SEM
MHA-2	**1.33 ± 0.023**
MHA-15	**1.94 ±0.042**
Donepezil	0.15 ± 0.01

Docking Studies

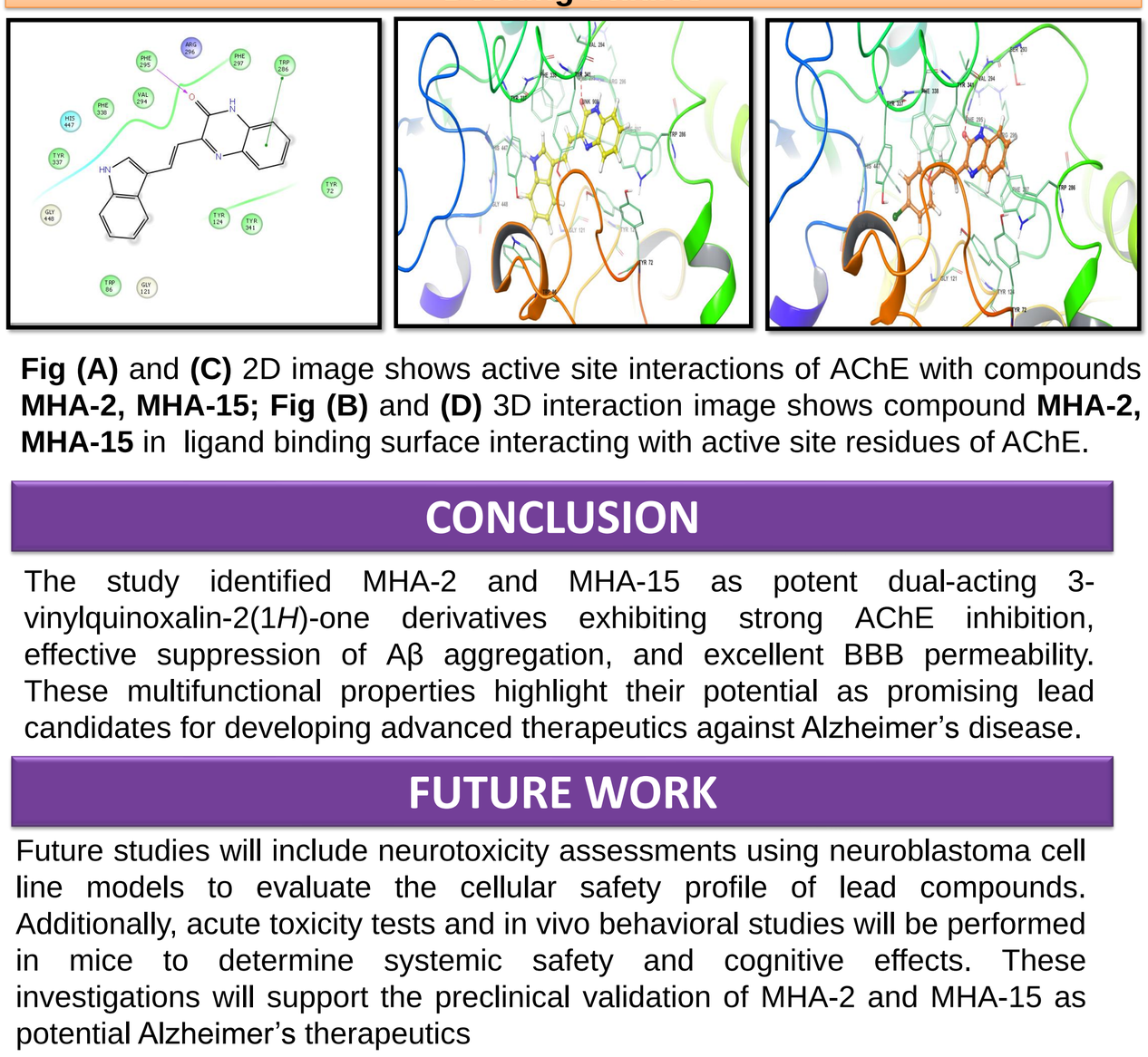


Fig (A) and **(C)** 2D image shows active site interactions of AChE with compounds **MHA-2, MHA-15; Fig (B)** and **(D)** 3D interaction image shows compound **MHA-2, MHA-15** in ligand binding surface interacting with active site residues of AChE.

CONCLUSION

The study identified MHA-2 and MHA-15 as potent dual-acting 3-vinylquinoxalin-2(1*H*)-one derivatives exhibiting strong AChE inhibition, effective suppression of Aβ aggregation, and excellent BBB permeability. These multifunctional properties highlight their potential as promising lead candidates for developing advanced therapeutics against Alzheimer's disease.

FUTURE WORK

Future studies will include neurotoxicity assessments using neuroblastoma cell line models to evaluate the cellular safety profile of lead compounds. Additionally, acute toxicity tests and in vivo behavioral studies will be performed in mice to determine systemic safety and cognitive effects. These investigations will support the preclinical validation of MHA-2 and MHA-15 as potential Alzheimer's therapeutics

References: Singh, M., Karthikeyan, C., Waiker, D.K. et al. 3 Biotech 15, 134 (2025).