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Design and Evaluation of Piperidine-Based Inhibitors targeting Alzheimer's Disease

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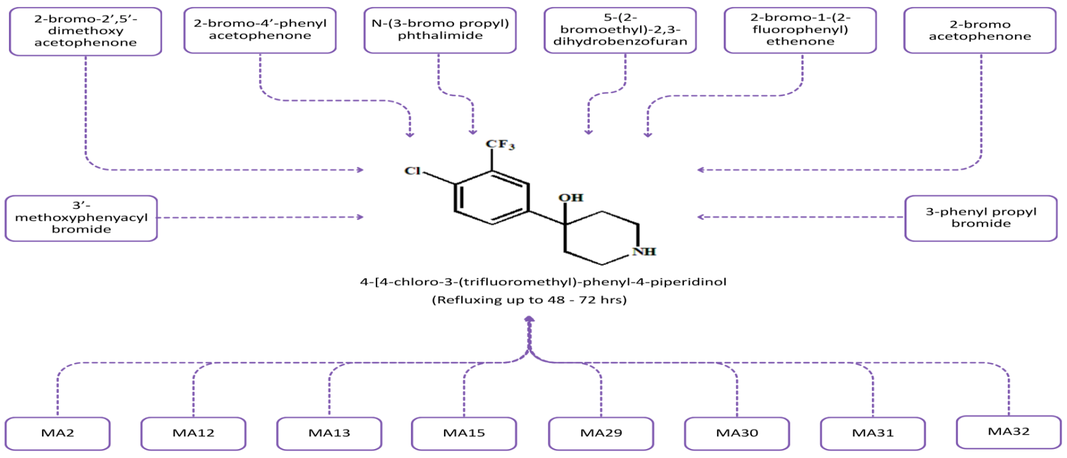
INTRODUCTION & AIM

Alzheimer's Disease (AD) is a degenerative neurological condition marked by a gradual loss of cognitive abilities, alterations in personality, and various psychological symptoms. Each year, the number of new AD diagnoses exceeds 10 million worldwide, and this figure is expected to double by 2036, underscoring the growing global health challenge. Among the treatments available, donepezil, a cholinesterase inhibitor approved in the United States in 1996, remains the most widely prescribed medication to alleviate the symptoms of AD. The drug's therapeutic efficacy is largely attributed to its nitrogen-containing heterocyclic ring known as piperidine, a structural motif frequently incorporated into a variety of compounds designed to target AD. This distinctive piperidine scaffold has become a pivotal focus in ongoing research aimed at developing novel derivatives with enhanced efficacy and safety profiles for Alzheimer's therapy. The aim of present study is to focus on designing and synthesizing novel piperidine derivatives, identifying lead compounds with improved cholinesterase inhibition and reduced side effects, analyzing protein-ligand interactions to establish structure-activity relationships (SAR), and exploring the anti-Alzheimer potential of these new compounds for therapeutic development.

METHOD

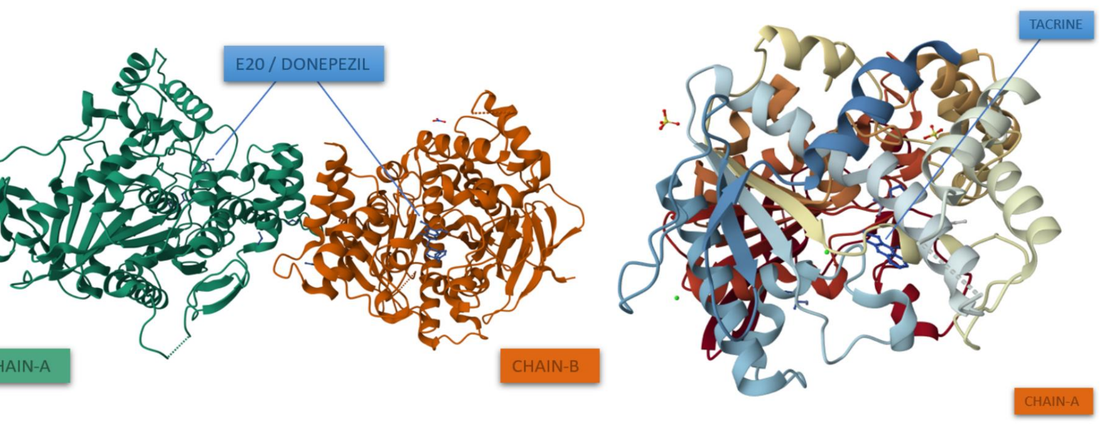
PHASE I : SYNTHESIS & CHARACTERIZATION

Derivatives of 4-[4-chloro-3-(trifluoromethyl)-phenyl-4-piperidinol were synthesized and characterized via spectral analysis.



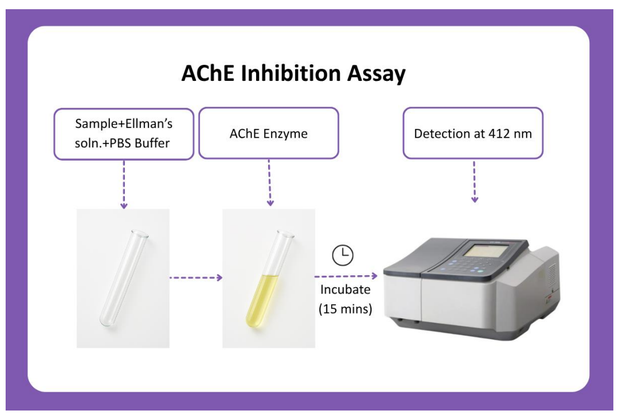
PHASE II : INSILICO EVALUATION

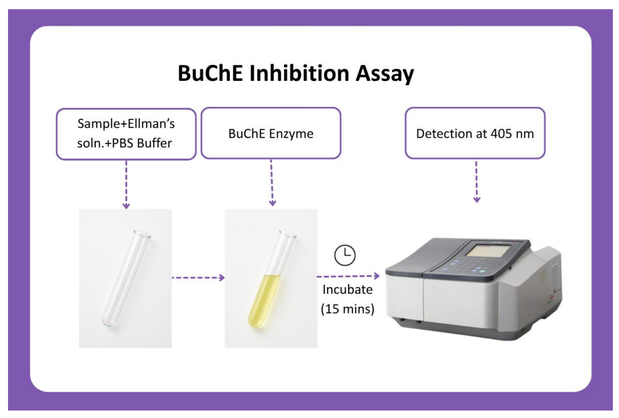
Molecular interactions of all the derivatives were evaluated against human recombinant AChE (PDB ID: 4EY7) and human recombinant BuChE (PDB ID: 4BDS) using Molecular Operating Environment (MOE Version 2018.01) software for potential inhibitory activity.



PHASE III : INVITRO EVALUATION

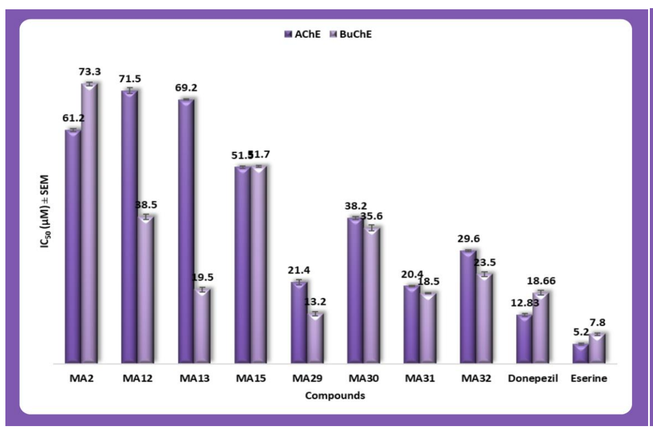
The assessment of cholinesterase (AChE/BuChE) inhibition potential of synthesized compounds were carried out by applying Ellman's method.

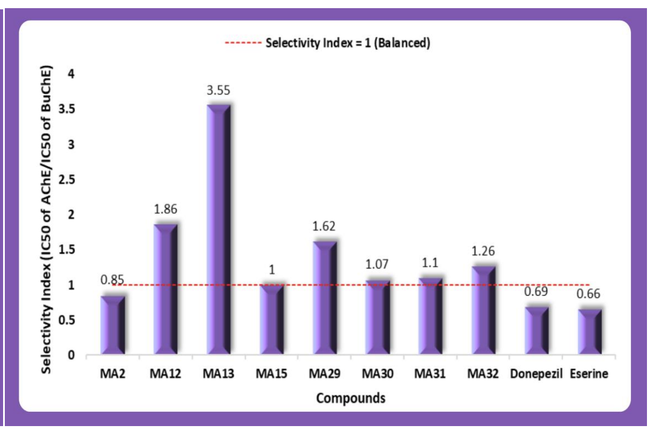




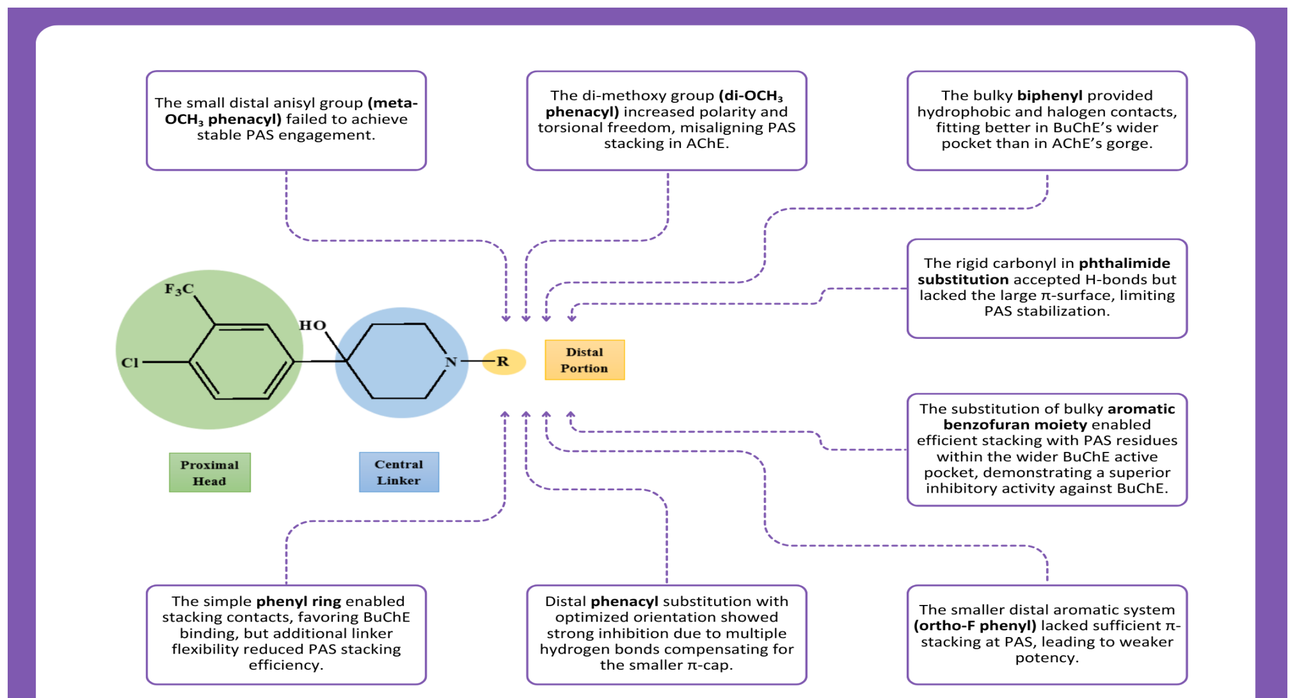
RESULTS & DISCUSSION

Compound	MA2	MA12	MA13	MA15	MA29	MA30	MA31	MA32	Donepezil	Eserine
AChE Inh. IC_{50} (μM)	61.2	71.5	69.2	51.5	21.4	38.2	20.4	29.6	12.83	5.2
BuChE Inh. IC_{50} (μM)	72.3	38.5	19.5	51.7	13.2	35.6	18.5	23.5	18.66	7.8
Selectivity Index (SI)	0.85	1.86	3.55	1.00	1.62	1.07	1.10	1.26	0.69	0.66
Preference	AChE	BuChE	BuChE	Bal.	BuChE	Bal.	Bal.	BuChE	AChE	AChE





SUBSTITUENT-DEPENDENT STRUCTURE ACTIVITY RELATIONSHIP



CONCLUSION

This research utilized computer-aided drug design together with biological evaluation to discover new cholinesterase inhibitors from a set of designed compounds, selecting eight for synthesis and testing. MA29 and MA31 stood out for their potent BuChE inhibition, equaling or surpassing the benchmark donepezil, though their AChE inhibition was somewhat lower. Structure-activity relationship analysis highlighted that variations in the distal portion significantly influenced potency and selectivity, supporting the importance of aromatic systems for effective cholinesterase inhibition.. Continued optimization, molecular validation, toxicity studies, and clinical assessment will be vital to fully establish their therapeutic value.

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