4-(4-Bromophenyl)-4-piperidinol Derivatives as a Multifactorial anti-Alzheimer agent: Synthesis, *Invitro*, and *In-silico* based Studies

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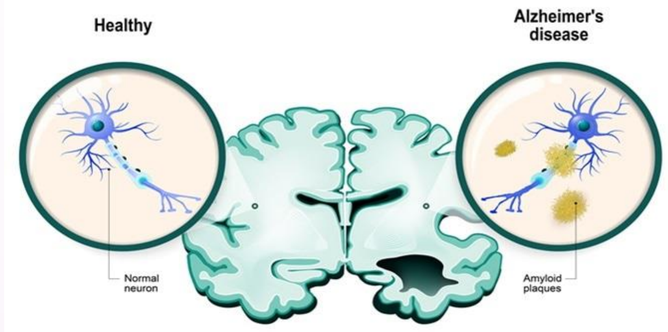
ABSTRACT

4-(4-bromophenyl)-4-piperidinol derivatives were synthesized and evaluated as multifactorial agents for the treatment of Alzheimer's disease (AD). Among all the analogues, AB11 and AB14 showed the best activity against acetylcholinesterase (AChE) with IC_{50} = 0.029µM and 0.038µM respectively. Both compounds also acted as a good antioxidant agents (IC_{50} = 26.38µM for AB11 and 23.99µM for AB14) while AB11 is the only molecule that displayed moderate inhibition of amyloid beta (Aβ) (43.25% at 500µM). AB11 and AB14 were found selective against monoamine oxidase-B (MAO-B) with IC_{50} values of 866µM and 763µM, respectively. AB10, AB17 and AB70 exhibited activity against both MAO-A and MAO-B and showed inhibitory potential against acetylcholinesterase, moreover, all analogues can disassemble the well-structured Aβ fibril. Molecular modeling of selected compounds displayed interactions with the active site of human MAO-B and AChE enzyme. The results suggested that AB11 is a promising multi-target hit that can be optimized further as a successful drug molecule for the treatment of AD.



INTRODUCTION

Alzheimer's disease is characterized by loss of memory, cognitive impairment, and behavioral abnormalities and is the most common cause of dementia. The pathophysiology of AD is not fully elucidated, but the current evidence suggests that

- A decrease in levels of acetylcholine.
- Abnormal accumulation of amyloid-β (Aβ).
- Accumulation of tau protein in the form of neurofibrillary tangles (NFTs).
- Oxidative stress leads to the neuronal damage.

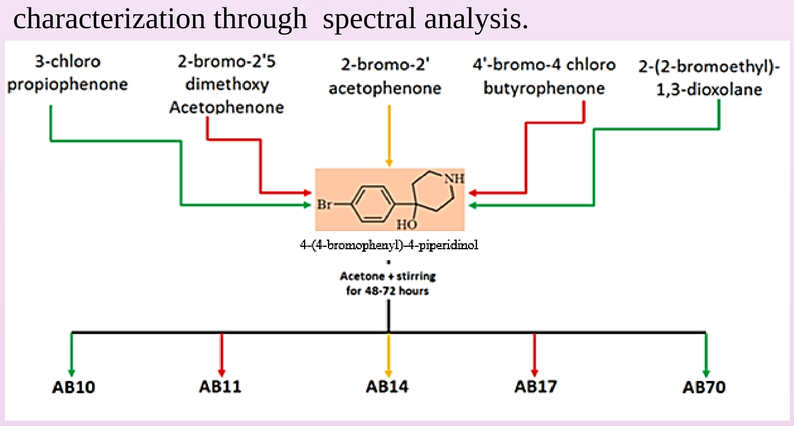
The "multi-target-directed ligands" (MTDLs) strategy, is found to be favorable for the development of drugs with at least two integral bioactivities for the treatment AD because of the pathological intricacy of AD.

METHODOLOGY

Study is based on 3 phases:

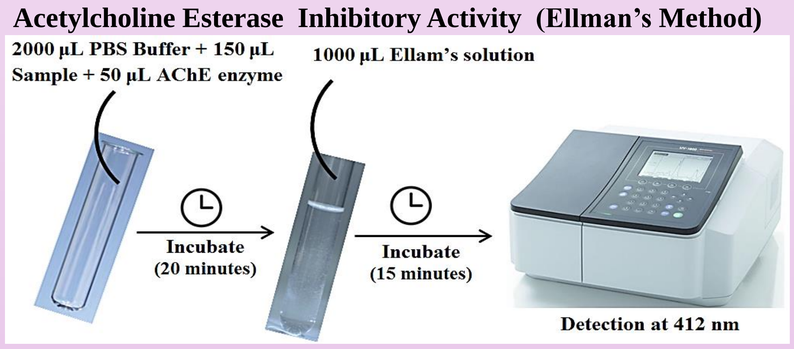
1. Synthesis

Synthesis of 4-(4-bromophenyl)-4-piperidinol Derivatives and characterization through spectral analysis.

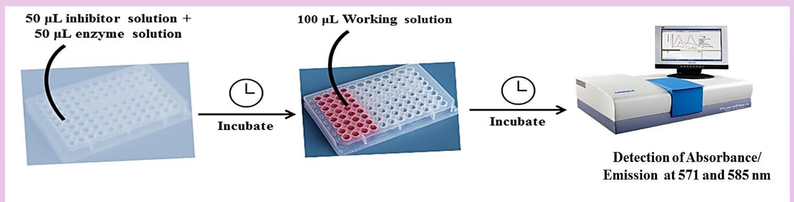


2. *Invitro* (Biological Evaluation)

Acetylcholine Esterase Inhibitory Activity (Ellman's Method)

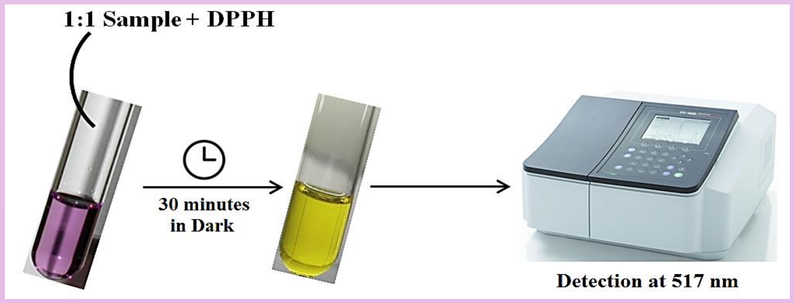


Monoamine Oxidase Inhibitory Activity (Amplex Red Monoamine oxidase kit)

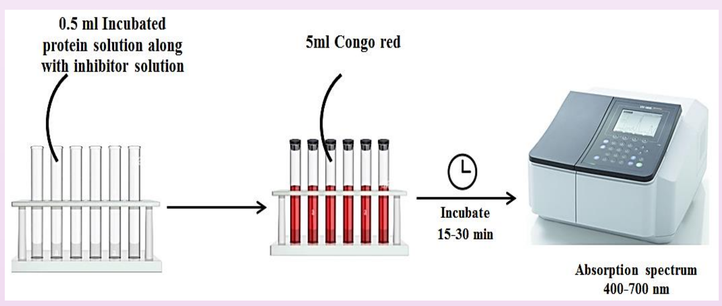


Inhibitor Solution: Standards and Synthesized compounds
Enzyme solution: Synaptosomes obtained from the rat brain were diluted in PBS having a pH of 7.4
Working Solution: Amplex Red reagent , HRP and substrates; tyramine (MAO-A) or benzylamine (MAO-B).

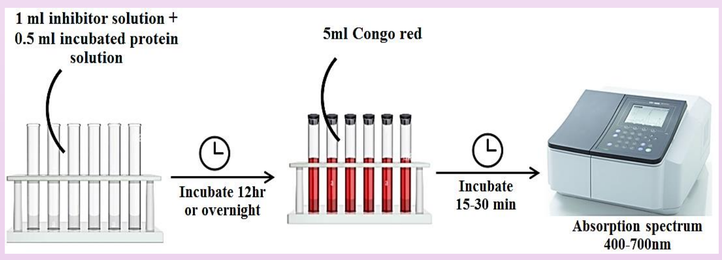
Antioxidant Activity



Amyloid Aggregation

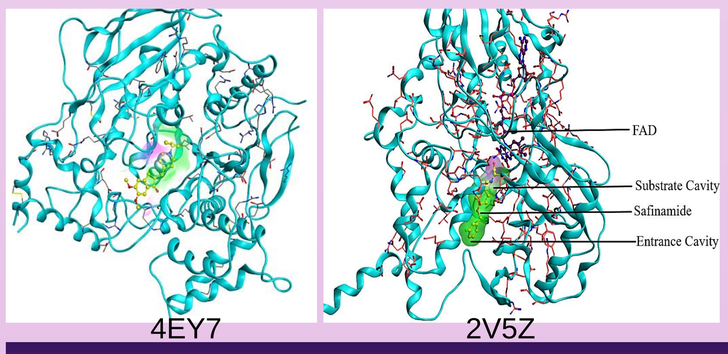


Amyloid Disaggregation



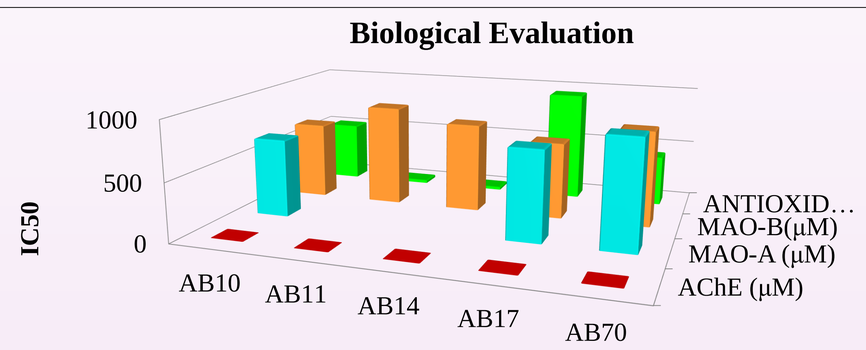
3. Molecular Modelling

Molecular modelling of, AB11 and AB14 against human recombinant acetylcholinesterase (PDB ID:4EY7), and human recombinant monoamine oxidase-B (PDB ID: 2V5Z), were carried out to evaluate the ligand-protein interactions using molecular operating environment (MOE 2014) software.



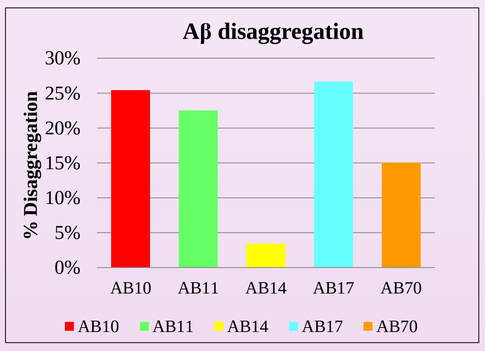
RESULTS

Biological Evaluation

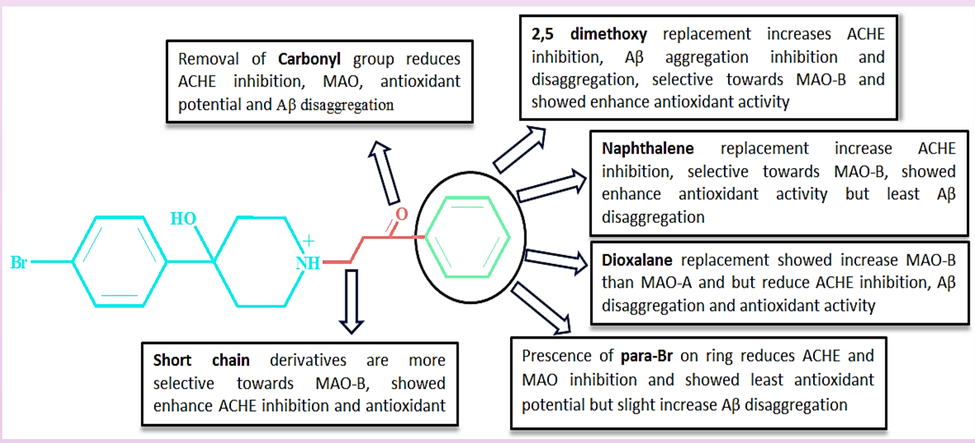


	AB10	AB11	AB14	AB17	AB70
AChE (µM)	0.049	0.029	0.038	0.054	0.056
MAO-A (µM)	673	-	-	769	923
MAO-B(µM)	662	866	763	657	817
ANTIOXIDANT (µM)	520	26.38	23.99	949.72	432.88

Compounds	Aβ disaggregation %	Aβ inhibition %
AB10	25.40%	-
AB11	22.51%	43.25%
AB14	3.38%	-
AB17	26.63%	-
AB70	15%	-



Structure Activity Relationship



CONCLUSION

Among the analogues, **AB11** was found to be more potent than donepezil and gave moderate inhibitory potency towards self-induced Aβ aggregation as well as dissolved the amyloid aggregates, and act as a potent antioxidant agent which was also evident by molecular modeling Thus AB11 can be endowed as a multifunctional agent for the development of new lead molecules as an anti- AD agent.

REFERENCES

1. Association, A. s. (2019). 2019 Alzheimer's disease facts and figures. *Alzheimer's & Dementia, 15*(3), 321-387.
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