2. REVIEW OF LITERATURE

In 1907, Dr. Alois Alzheimer, a German scientist, reported a neurodegenerative disease characterized by decreased cognitive ability and severe behavioural abnormalities like disorientation, depression, restlessness, irritability and anxiety, now known as Alzheimer’s disease (AD). The progression rate of AD can vary and the average life expectancy subsequent to diagnosis is approximately three to nine years.\textsuperscript{102}

Literature has supported the role of both the enzymes AChE (E.C. 3.1.1.7) as well as BuChE (E.C. 3.1.1.8) in AD. Literature has supported the evidence of gradual fall in the levels of AChE in the brain of AD patients, while there occurs slight increase in the activity of BuChE as the condition progresses. Further, postmortem tissue analysis of AD patients showed a high level of BuChE in the hallmark lesions of AD. In rats, selective BuChE inhibitor cymserine was found to elevate ACh levels and enhanced long-term CNS potentiation and learning.\textsuperscript{104,105}

Figure 4: Alignment of AChE and BuChE amino acid sequence (catalytic triad marked in red color).
From the literature it was clearly observed that although AChE and BuChE are produced by different genes they are highly homologous with more than 65% similarity in conserved region. AChE has two major binding sub-sites, a peripheral anionic site (PAS) and the other a catalytic anionic site (CAS), located in the deep gorge of the enzyme structure and is assigned to Ser-His-Glu catalytic triad. The gorge is lined by around 14 aromatic amino acids making the active site more hydrophobic, leading to better interaction with hydrophobic substrates. The gorge goes through half way in the enzyme and is roughly 20 Å long. Common to AChE, BuChE also has a catalytic triad consisting of Ser–His–Glu. Majority of the important features of the active site of BuChE like a triad of Ser-His-Glu, a p-cation-binding site, an oxyanion hole, and an acyl-binding pocket are similar to AChE. The acyl binding pocket of BuChE is obviously larger than that of AChE. The active sites of both the enzymes acting as nucleophiles are situated at the base of a cavity to attack the carbonyl group of the substrates.\textsuperscript{109}

There are several molecules under study for AD. In 1993, FDA approved tacrine as the first drug against Alzheimer’s but later on it was discarded because of its hepatotoxicity. Tacrine was a dual acting first approved drug for AD that was marketed under the trade name of Cognex. It inhibits both AChE as well as BuChE enzymes.\textsuperscript{106}

Currently four drugs are approved for Alzheimer’s treatment by FDA and these are discussed below.

Donepezil was approved in 1996 for AD treatment and it is a centrally acting reversible and selective AChE inhibitor. It was developed by developer Eisai and partner Pfizer, and is marketed under the trade name Aricept.\textsuperscript{112}
Rivastigmine\textsuperscript{113} was developed by Marta Weinstock-Rosin of the Pharmacology Department, the Hebrew University of Jerusalem. Then it was sold to Novartis for commercial development. It is a semi-synthetic derivative of physostigmine and it is a dual AChE and BuChE inhibitor.

Galantamine\textsuperscript{113} is an alkaloid used for the treatment of mild to moderate AD. It is competitive and reversible nicotinic AChE inhibitor approved by US FDA in 2001 for the treatment of AD.

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\textbf{Galantamine}

\begin{center}
\includegraphics[width=0.4\textwidth]{memantine}
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\textbf{Memantine}

Memantine\textsuperscript{114} is noncompetitive Glutaminergic NMDA receptor blocker used in AD. It was first synthesized by Eli Lilly in 1968. It is marketed under various trade names like Axura, Akatinol, Namenda etc for the treatment of AD.

Apart from these drugs, recently many research groups have reported diverse scaffolds against AD. These include cholinesterase inhibitors, ChEIs combined with A\textbeta aggregation inhibitors, \beta-secretase inhibitors or multifunctional agents. It is reported that in healthy brain tissue, AChE is the primary enzyme accountable for acetylcholine hydrolysis, while BuChE plays a supportive role whereas in AD, the AChE activity decreases and BuChE shows a progressive and considerable increase in its action. In the following section various recently developed ChEIs with different scaffolds are summarized.

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(1)
The structure of tacrine is widely used as a pharmacophore for the development of agents against AD. Tang et al. reported oxoisoaporphine-tacrine heterodimers causing a combined action on both the sites i.e. CAS and PAS as well as inhibition of Aβ aggregation. The compound (1) reported by this research group showed IC$_{50}$ value on $Ee$AChE = 3.4 nM and $Ee$BuChE 110 nM. The Aβ aggregation inhibition was observed to be 79.8% at 10μM.$^{115}$

Benzothiazole derivatives are used as Alzheimer’s brain imaging agents. The use of benzothiazole moiety connected to tacrine with different linkers as heterodimers are reported to be neuroprotective in nature. The representative compound (2) exhibited $Ee$AChE IC$_{50}$ = 0.57 μM. The Aβ aggregation inhibition was observed to be 61.3% at 50μM.$^{116}$

![Structure of compound (2)](image)

The heterodimers of substituted tacrine with chromone derivatives were reported by Fernandez-Bachiller et al. as potent AChE, BuChE and BACE1 inhibitors. The representative compound (3) showed very good activity against all the three targets. The IC$_{50}$ values against $h$AChE = 8.0 nM, $h$BuChE = 1.5 nM and $h$BACE1 = 2.8 μM was reported for compound (3).$^{117}$

![Structure of compound (3)](image)
Barreiro et al. reported the design and synthesis of a series of selective AChE inhibitors containing azaheterocyclic pyrazolo[4,3-d]pyridine or pyrazolo[3,4-b][1,8]naphthyridine systems as isosteres of the quinoline ring of tacrine. The most active compounds (4 and 5) obtained from this study showed IC$_{50}$ values of 6.0 μM and 6.4 μM respectively against AChE, while, the inhibition of BuChE was found to be poor with the selectivity indices of 5.3 and 20.9 respectively.\textsuperscript{118}

Marco et al. synthesized novel class of tacrine analogs comprising [1,8]naphthyridine (6) as dual cholinesterase inhibitors. Compound (6) was found to be selective AChE inhibitor with IC$_{50}$ value of 52 nM. The aromatic ring of tacrine was replaced with furo-aromatic five membered ring which gave compound (7) with IC$_{50}$ against AChE = 0.377 μM, and BuChE = 100 μM.\textsuperscript{119}

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Savini et al. have reported some novel homo- and hetero- dimers of tacrine (8) (IC$_{50}$: AChE = 1.3 nM and BuChE = 2 nM) and dichlorotacrine (9) analog (IC$_{50}$: AChE = 6 nM and BuChE = 180 nM).\textsuperscript{120}
Heterodimer of tacrine with coumarin was reported by Hamulakova et al. Compound (10) was found to be active against both AChE and BuChE with IC$_{50}$ values of 0.015 µM and 0.32 µM, respectively.$^{121}$

![Chemical structure of compound 10](image)

Ozer et al. developed a new series of compounds based on the structure of donepezil. The representative molecule (11) was found to be active against the cholinesterases as well as against Aβ aggregation. It was found to inhibit hAChE and EqBuChE with IC$_{50}$ of 53.1 µM and 67.3 µM respectively. The Aβ aggregation inhibition was observed to be 80% at 100 µM.$^{122}$

![Chemical structure of compound 11](image)

Catto et al. reported benzo[e][1,2,4]triazin-7(1H)-one derivatives and [1,2,4]triazino[5,6,1-j,k]carbazol-6-one derivatives as ChE and Aβ aggregation inhibitors. Compound (12) was observed to be having balanced activity against EcAChE as well as EqBuChE with IC$_{50}$ value of 1.5 µM and 1.9 µM. Comparatively, compound (13) was observed to be a selective BuChE inhibitor with EqBuChE IC$_{50}$ = 25 nM. Both the compounds showed Aβ aggregation inhibition at IC$_{50}$ 1.4 µM.$^{123}$

![Chemical structures of compounds 12 and 13](image)
Section II

Review of Literature

Karlsson et al. reported the diarylimidazole derivatives as a potential class of selective BuChE and Aβ aggregation inhibitors. The representative compound (14) inhibits hBuChE (IC\(_{50} = 1.11 \mu M\)) and Aβ aggregation (IC\(_{50} = 5.8 \mu M\)).\(^{124}\)

![Diagram of compound 14](image1.png)

Chelerythrine (15) (an isoquinoline alkaloid) was reported to be moderately active AChE/BuChE as well as Aβ aggregation inhibitor by Brunhofer et al. This compound inhibits hAChE and hBuChE with IC\(_{50}\) values of 1.54 μM and 10.34 μM, respectively. Its Aβ aggregation inhibition IC\(_{50}\) value was 4.2 μM.\(^{125}\)

![Diagram of compound 15](image2.png)

Munoz-Torrero group developed hybrid compounds of huprine and tacrine connected by alkyl or alkylamine linkers. These compounds are potential inhibitors of AChE, BuChE and BACE1. The representative compound (16) shows IC\(_{50}\) values of 1.32 nM, 35.1 nM and 4.9 μM against hAChE, hBuChE and BACE1 respectively.\(^{126}\)

![Diagram of compound 16](image3.png)


Mohamed et al. reported the design and synthesis of pyrimidine derivatives as ChEs and BACE1 inhibitors. The representative compound (17) shows IC\textsubscript{50} values of 7.7 μM, 2.5 μM and 0.6 μM against hAChE, EqBuChE and hBACE1, respectively.\textsuperscript{127,128}

![Chemical structure of 18]

By using structure based approach Peng et al. reported a series of benzamide derivatives as ChEIs as well as BACE1 inhibitors. The representative compound (18) exhibited potent activity with IC\textsubscript{50} values of 81 nM, 93 nM and 0.31 μM against hAChE, hBuChE and BACE1, respectively.\textsuperscript{129}

Jiaranaikulwanitch et al. developed a new series of tryptoline and tryptamine triazole derivatives as potential BACE1 and Aβ aggregation inhibitors. The representative compound (19) showed IC\textsubscript{50} values of 20.75 μM against BACE1 and 83.23 μM for anti-aggregation activities.\textsuperscript{130}

![Chemical structures of 19, 20, and 21]

Sinha et al. reported piperazinoethyl and morpholinoethyl substituted triazine derivatives as novel ChEIs. Representative compounds (20, IC\textsubscript{50}= 4.23 μM and 13.3 μM) and (21, IC\textsubscript{50}= 5.79 μM and 163.4 μM) were found to be potent AChE and BuChE inhibitors, respectively.\textsuperscript{131}