3. AIMS AND OBJECTIVES

Alzheimer's disease (AD) is the most common type of dementia that accounts for 60 to 70% of cases of dementia. AD is an overwhelming neurodegenerative disorder characterized by progressive and irreversible decline in cognitive functions.

Acetylcholinesterase (EC: 3.1.1.7), also alternatively known as AChE or acetylhydrolase and is encoded by ACHE gene. It is a hydrolase that hydrolyzes the neurotransmitter acetylcholine. AChE is mainly located at neuromuscular junctions and cholinergic brain synapses, where it performs the role of termination of synaptic transmission. Butyrylcholinestarase (EC: 3.1.1.8), also known as pseudocholinesterase or BuChE or plasma cholinesterase. It is a non-specific cholinesterase which hydrolyses several different choline esters including ACh. BuChE is encoded by BCHE gene. Both of these enzymes belong to carboxylesterase family.

Although these two enzymes are produced from two different genes, the alignment of AChE and BuChE shows more than 50% overall similarity and >65% active site similarity. AChE has two major binding sub-sites, a peripheral anionic site (PAS) and the other a catalytic anionic site (CAS) which is located in the deep gorge of the enzyme structure and is assigned to Ser-His-Glu catalytic triad. 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 that of AChE. Along with the major role of AChE, the importace of BuChE in the pathophysiology of AD has been explained in detail by various groups.

Literature reports and clinical studies as discussed above suggested the importance of AChE and BuChE as major targets in the treatment of Alzhiemer diease. The literature also supports that the tacrine analogs and fused heterocyclic ring systems are more prominent scaffolds towards the inhibition of AChE and BuChE as well as supporting multifunctional activity like BACE1 inhibition, anti-aggregatory activity etc. On the basis of this existing knowledge of enzyme structures as discussed above and from the extensive scaffold database, following five scaffolds were designed and their derivatives were synthesized in respective series as anti-Alzheimer agents.

> ➢ Series I: 10-Substituted benzo[*g*]pteridine-2,4(3*H*,10*H*)-dione.
> ➢ Series II: 3-(Substituted thio)-5*H*-[1,2,4]triazino[5,6-*b*]indole.
> ➢ Series III: 5- Substituted 5*H*-[1,2,4]triazino[5,6-*b*]indole-3-thiol.
> ➢ Series IV: 6-Substituted 6*H*-indolo[2,3-*b*]quinoxaline.
> ➢ Series V: 5-Substituted 5*H*-indolo[2,3-*b*]quinoxaline.

I   II   III

IV   V
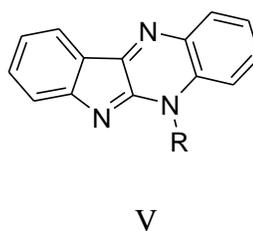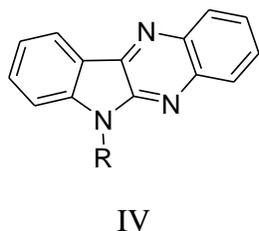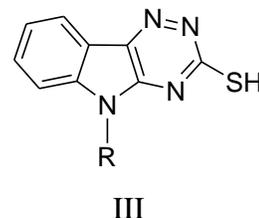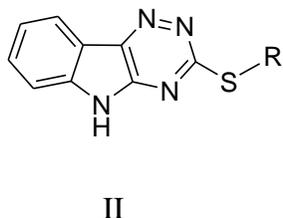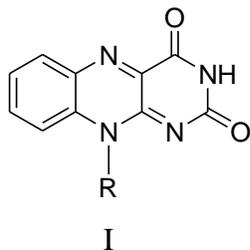
All the synthesized compounds were characterized by different analytical techniques like ¹H-NMR Spectroscopy and mass spectrometry while ¹³C-NMR spectra were obtained only for some representative compounds. Further, it was planned to evaluate the synthesized compounds for their AChE and BuChE inhibition potency.