Alzheimer's disease is a progressive neurodegenerative dementia that robs the cognitive abilities and distorts the normal functioning of the brain. Alzheimer's disease has moved from being a rare neurodegenerative disorder to one of the most prevalent threats to the global economy and health. It is now becoming a nightmare spurring fear among older as well as adult populations worldwide. As per the recent reports, the number of victims of this chronic debilitating disorder may escalate to 152 million by the year 2050. The ever-increasing crisis linked with varied risk factors is severely affecting the patients of Alzheimer's disease with massive monetary as well as an emotional burden. The neuro-pathological hallmarks of the disease include compromised levels of acetylcholine (ACh), deposition of amyloid-β, neurofibrillary tangles of hyperphosphorylated τ-protein, oxidative stress, and biometal dyshomeostasis.

Regardless of the substantial advancement in the high-throughput selection techniques and the enormous exertions for drug discovery, numbers of efficacious drugs for Alzheimer's disease have not increased considerably since the last decade. Existing treatment comprises of drugs that typically target the augmentation of cognitive functions or the management of neurological symptoms involving neurotransmitter mechanisms. Approved medications include cholinesterase inhibitors were proved to be unsuccessful in preventing and halting the progression of Alzheimer's disease. The development of disease transforming drugs that decelerate the progression of Alzheimer's disease is still susceptible to skulking complications, inadequate effectiveness in humans. The available single targeted drugs were unable to induce the desired effect due to the multifaceted nature of Alzheimer's disease that necessitates the development of multitargeted therapeutics to slow down the disease progression.

In the first part of the thesis research work, a series of multifunctional molecular hybrids with ferulic acid and 1,3,4-oxadiazole frameworks was designed for the treatment of Alzheimer's disease. Several scaffolds of ferulic acid-based hybrids were reported in the recent past to possess significant anticholinesterase and antioxidant activities. The ferulic acid has been reported to possess several therapeutic benefits such as antioxidant, anti-inflammatory, free radical scavenging activity, and anti-Aβ aggregator. Ferulic acid is considered to be an important pharmacophoric moiety due to its higher therapeutic benefits and lower toxic effects.

On the basis of the above-mentioned literature, we have designed and synthesized a series of ferulic acid-based 1,3,4-oxadiazole hybrids. These hybrids were screened for their inhibitory potential against several targets that includes AChE, BChE, and BACE-1. The results of propidium iodide displacement assay showed significant PAS-AChE binding, with excellent BBB permeability predictions in PAMPA assay by compounds **6j** and **6k**. Both these lead candidates remarkably disassembled Aβ aggregation in self- and AChE-induced experiments. Further, MTT assay of compounds **6j** and **6k** elicited neuroprotective activity in neuroblastoma SH-SY5Y cells against Aβ-induced stress. Compounds **6j** and **6k** elicited amelioration of cognitive dysfunctions in the scopolamine-induced amnesia model performed by Y maze test. The *ex-vivo* studies signified declined hippocampal brain AChE levels and potential antioxidant activity of **6j** and **6k**. The Aβ-induced Alzheimer's disease like-phenotypic ICV rat model improved learning and memory behavior by **6j** in Morris water maze test. The most potent activity of compound **6j** might be attributed to the presence of a strong electron-withdrawing group at the terminal phenyl group, which is extended deep into the CAS-AChE. Also, compound **6j** showed consensual binding interactions with the PAS-AChE and aspartate dyad of BACE-1.

In the second part of thesis research work, we have designed several molecular hybrids of 2-pyridylpiperazine and substituted 5-phenyl-1,3,4-oxadiazoles with significant inhibitory potential against the major targets of AD, i.e., hAChE, hBACE-1, and Aβ. In particular, compounds **12n**, **12o**, **13j**, **13k**, **13n**, and **13o** showed balanced and substantial inhibition of both the target enzymes in two to three digits nanomolar IC_{50} range. These identified potential inhibitors were evaluated for their BBB permeability by PAMPA-BBB assay and propidium iodide displacement capability from PAS-AChE. The results demonstrated that compounds **13n** and **13o** have an excellent prediction of BBB permeability and displaced the propidium iodide significantly from PAS-AChE comparable to donepezil. The PAS-AChE binding of molecules is reported to be associated with aggregation of Aβ; thereby both the potential lead candidates (**13n** and **13o)** were evaluated for their anti-Aβ aggregatory activity in self- and AChE-induced experiments by thioflavin T assay and results suggested that both the compounds have remarkable activity in inhibiting Aβ aggregation. The anti-Aβ aggregatory activity of compound **13o** was also ascertained by morphological characterization of Aβ samples in the presence or absence of inhibitory by AFM. Further, compounds **13n** and **13o** also exhibited neuroprotective activity against Aβ-induced oxidative stress in neuroblastoma SH-SY5Y cell lines. The *in-vivo* behavioral investigations signified that compound **13o** exhibited a higher ability to ameliorate scopolamine- and Aβ-induced cognitive dysfunctions in Y-maze and Morris water maze tests, respectively. Moreover, *ex-vivo* and biochemical analyses of rat hippocampal homogenates showed significant AChE inhibition and antioxidant potential of compound **13o** with excellent oral absorption in the pharmacokinetic experiment. Furthermore, *in-silico* molecular docking and dynamics simulations study affirmed the

consensual binding interactions of compound **13o** to PAS-AChE and aspartate dyad of BACE-1.

Based on overall results, compounds **6j** and **13o** could be considered as remarkable 'lead candidates' with multifunctional activities against AD and can be optimized further for their Western-Blotting and immunohistochemical analysis. Some additional experiments, i.e., metal chelation, ability to prevent NFT formation, and toxicological studies, can also be performed in direction to establish the mechanism of action at a molecular level against AD pathogenesis.