<u>PREFACE</u>

Alzheimer's disease (AD) is an enormous healthcare burden caused by loss of neurons and synapses, particularly in neocortex and hippocampus. AD causes substantial structural and functional damage of the brain, which resulted into severe behavioral alterations and cognitive dysfunction. A recent report 2018 from World Health Organization (WHO) accounts for 50 million cases of AD worldwide and this figure is estimated to be tripled by 2050. There are several underlying pathophysiological mechanisms involved in the progressive cognitive deficits of AD such as, decline in acetylcholine (ACh) levels, amyloid beta ($A\beta$) aggregation and deposition, activation of N-methyl-D-aspartate receptor (NMDAR), oxidative stress, tau hyperphosphorylation and generation of neurofibrillary tangles (NFTs), apolipoprotein E4 ($APO\epsilon4$) gene transcription, cyclic-AMP-response element-binding protein (CREB) signaling pathways, etc.

Current treatment strategies for AD encompass the use of FDA approved medications like cholinesterase (ChE) inhibitors (donepezil, rivastigmine, and galantamine) and N-methyl-D-aspartate (NMDA) receptor antagonist (memantine). However, drug therapy for this ailment is still in its infancy and fails to delay the progression of the disease. The new strategy of multi-targeted inhibitors has been adopted recently, which involves targeting multiple enzymes simultaneously with a single molecule. This strategy was built upon the fact that AD is a multifactorial disorder, linked with multiple targets. Thereby, design and development of multitarget-directed ligands could be successful for mitigating the disease progression rather than providing symptomatic relief only.

This research work is divided into two parts. The first part deals with the designing of Series I ligands based upon computational methods, such as pharmacophore modeling, high-throughput virtual screening (HTVS), docking-post processing (DPP), molecular

mechanics generalized Born surface area (MM-GBSA), molecular docking, and dynamics simulations. The designed series of ligands were evaluated for their multitargeted inhibitory potential against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), beta secretase-1 (BACE-1), and Aβ. Compounds were also assessed for their binding capability with peripheral anionic site (PAS) of AChE by propidium iodide displacement assay and blood-brain barrier (BBB) penetrability was predicted by PAMPA model. The neurotoxic liability of compounds was evaluated against SH-SY5Y neuroblastoma cell lines by MTT assay. The neurobehavioral studies in rats were performed to evaluate the effect of compounds in improving the learning and memory. Moreover, pharmacokinetic study was performed to determine the oral absorption characteristics of lead candidates.

The second part of the thesis work involved designing Series II-V compounds using a molecular hybridization approach on the basis of outcomes from Series I. The compounds were evaluated by several *in vitro* and *in vivo* studies to be established as potential multitargeted ligands for the treatment of AD. Additionally, molecular mechanistic analyses were performed by Western-blot and immunohistochemistry.

To this date, the research work has led to the publication of two research papers and two filed Indian Patents. Suggestions and comments on the part of the readers are always welcome.

The work has been presented in this dissertation under the following sections:

Chapter 1: The first chapter offers an introductory section which deals with a basic information along with the historical background, pathophysiological mechanisms involved, and current therapeutics available for the treatment of AD. A brief discussion

about novel strategies adopted for the AD, such as multitargeting, computational methods, and molecular hybridization.

Chapter 2: This chapter focused on detailed literature survey on cholinesterase (AChE and BChE), BACE-1 and Aβ inhibitory potential of the compounds bearing *N*-benzylpiperidines and 1,3,4-oxadiazoles.

Chapter 3: This chapter summarizes the research objectives, the overall rationale for carrying out this investigation and plan of work as embodied in this thesis.

Chapter 4: This chapter describes the experimental procedure used in the synthesis, characterization, protocols for computational studies, and *in vitro* and *in vivo* pharmacological evaluations.

Chapter 5: This chapter covers the results and discussion part of the research work.

Chapter 6: This chapter outlines the summary and conclusion.

Chapter 7: This section includes the references as a source of information to carry out the research work.

Chapter 8: An appendix consisting of the NMR (^{1}H and ^{13}C) and Mass spectra along with HPLC chromatograms of the representative compounds followed by a list of published papers, filed patents, and presentations at international conferences.