PREFACE

AD is an enormous healthcare challenge of society as a few commercial drugs are available for the treatment, which could extend symptomatic relief rather affecting the progression of the disease. There are several pathophysiological hallmarks of the disease, which include depleted levels of acetylcholine (ACh), accumulation of amyloid-beta (Aβ), dysfunction of *N*-methyl-D-aspartate receptor, abnormally hyperphosphorylation of tau proteins to generate neurofibrillary tangles, neuroinflammation, increased reactive oxygen species production, etc.

Current strategies to treat AD encompass the use of FDA approved medications like cholinesterase (ChE) inhibitors (donepezil, rivastigmine, and galantamine) and 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 multifunctional inhibitors has been adopted recently, which involves targeting of 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, the design and development of multifunctional ligands could prove beneficial for successful mitigation of disease progression rather than providing symptomatic relief only.

This research work is divided into two parts. In Part-1, where ferulic acid-based hybrids are designed and synthesized (Series I and II), while in Part-2, 2-pyridylpiperazines-based hybrids were designed using the molecular hybridization strategy. The designed series of ligands were evaluated for their multifunctional enzyme inhibitory potential against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), beta secretase-1 (BACE-1), and amyloid-beta (Aβ) inhibitory potential. Compounds were also assessed for their binding capability with the peripheral anionic site (PAS) of AChE by propidium iodide displacement assay, whereas the blood-brain barrier (BBB) penetrability was determined by PAMPA model. The neurotoxic liability of compounds was evaluated for their neuroprotective activity towards SH-SY5Y neuroblastoma cell

lines against Aβ-induced oxidative stress. The neurobehavioral studies in rats were performed to evaluate the effect of compounds in improving the learning and memory. Moreover, a preliminary pharmacokinetic study was performed to ascertain the oral absorption characteristics of lead candidates.

To this date, the research work has led two publications and Indian Patents (filed). 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 basic information along with the historical background, pathophysiological mechanisms, and current therapeutics available for the treatment of AD. A brief discussion of the adopted molecular hybridization approach.

Chapter 2: This chapter focused on a detailed literature survey on cholinesterase (AChE and BChE), BACE-1, and Aβ inhibitory potential of the compounds bearing important pharmacophoric moieties.

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 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 and filed patents.