PREFACE

Alzheimer's disease (AD) is considered to be an enormous healthcare problem caused by the loss of neurons and synapses, particularly in the neocortex and hippocampus. AD results in remarkable structural and functional damage to the brain, which resulted in 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 pathophysiology associated with the progression of cognitive deficits in AD condition that includes, lower acetylcholine (ACh) levels in the synaptic cleft, amyloid beta (Aβ) aggregation and deposition, *N*-methyl-D-aspartate receptor (NMDAR) activation, oxidative stress in response to neuroinflammation, tau hyperphosphorylation that results in generation of neurofibrillary tangles (NFTs), genetic mutation in apolipoprotein E4 (APOε4), etc.

The current treatment strategy for AD involves the use of some FDA-approved drugs which only provide symptomatic relief to the patient. Certain FDA-approved medications such as AChE inhibitors (donepezil, rivastigmine, and galantamine) and NMDA receptor antagonists (memantine) are being used for the treatment of AD. Recently, Aducanumab and Lecanemab (monoclonal antibodies) have been approved by FDA in an accelerated approval pathway as a disease-modifying therapy for AD, though their use is still controversial in AD progression.

This research work in this thesis was divided into two parts; the first part of the thesis describes the design, synthesis, and biological evaluation of a novel series-I **(SD1-17**) compounds against hAChE, hBChE, hBACE-1, and Aβ aggregation inhibitory potentials. A detailed *in vivo* study of the most active compound of the series was also performed in scopolamine and Aβ-induced behavioral rat models of AD following *ex-vivo* biochemical estimation, and histopathological examination of brain tissue slices to

observe any neuronal tissue damage. The *in silico* molecular docking and Molecular dynamic simulation studies were also performed to confirm the ligand-protein complex's stability.

The second part of the thesis demonstrates the successful design and synthesis of a new class of compounds using in silico e-Pharmacophore hypothesis. A novel series II & III were designed as multitarget-directed ligands to discover new agents for Alzheimer's disease treatment. All the compounds were tested for their *in vitro* inhibitory potential against hAChE, hBChE, hBACE-1, and Aβ aggregation. The neurotoxic liabilities of the compounds were also tested against RA/BDNF differentiated SH-SY5Y neuroblastoma cell lines. Both the scopolamine and A*β*-induced mouse models for AD were studied to evaluate the learning and memory behavior improvements after treatment with the most active compounds of the series. E*x vivo* studies of hippocampal and cortex brain homogenates were performed to investigate the oxidative stress biomarker and pro-inflammatory cytokines (TNF-α, and IL-6 mRNA) levels. The histopathological examination was performed to observe neuronal appearance in the hippocampal and cortex region of the brain. Western blot analysis and immunohistochemical analysis were also performed to investigate the A*β*, APP/A*β*, BACE-1, and tau protein molecular expression levels.

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

Chapter 1: This chapter flashes the light on AD, its development & progression, etiology, and various pathophysiology associated with AD. This chapter also deals with the current treatment strategy for AD, a newer designing approach to tackle the disease progression that includes mainly molecular hybridization, and computational methods.

Chapter 2: This chapter describes a detailed literature survey on benzylpiperidines and 1,3,4-oxadiazoles, piperazine, and N-benzylpiperidine derivatives as multitarget directed ligands (AChE, BChE, BACE-1, and Aβ).

Chapter 3: This chapter summarizes the research objectives of the overall study, the rationale for performing different *in vitro* and *in vivo* investigations, and a detailed plan of work that is exemplified 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 overall findings as results and discussion part of the research work.

Chapter 6: Describes the summary and conclusion of the presented work.

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 and presentations at international conferences.