Preface

Alzheimer's disease (AD) is a progressive neurodegenerative disorder causing damage to multiple areas of the brain responsible for memory, language, problem solving, and other cognitive skills. The mainstream pathological features simultaneously observed during the progression of the disease, include amyloid β (Aβ) aggregation, neurofibrillary tangle (NFT) deposition, neuroinflammatory cascade, and cholinergic deficits.

According to the amyloid hypothesis, Aβ species are originated from the sequential proteolytic cleavage of the amyloid precursor protein (APP) by β-secretase (BACE1) followed by γ-secretase in the amyloidogenic pathway. Aβ deposits, an extensively studied pathological biomarker, is closely related to AD pathogenesis and indirectly contributes to other toxic entities, which are the major focus of therapeutic and diagnostic developments. The dysfunction of the cholinergic system in the AD is suggested by the well-recognized pathology. The cholinergic hypothesis states that cholinergic neurons are affected in the early stage of the AD with the loss of cholinergic functions involved in the synthesis of ACh resulting into cognitive dysfunctions. Therefore, restoring cholinergic function could help to reduce the severity of cognitive decline. This hypothesis is backed by the observation that cholinesterase inhibitors have demonstrated positive effects on cognition in patients with AD.

The research work presented in the thesis is divided into four parts, first two parts deal with the development of series of theranostic agents and later two deals with development of multi-target-directed ligands (MTDLs) for Alzheimer's disease (AD). The theranostics probes and MTDLs were designed using various design strategies, including scaffold hopping, fragment-based design, hybrid drug design, and lead optimization. The development of theranostics probes that combines both diagnostic and therapeutic capabilities in a single agent is a very potential and attractive approach. The theranostic agents, featuring a rational structural framework that integrates lead therapeutic scaffolds and fluoroprobes with an electron donor–

acceptor architecture, demonstrated promising diagnostic and therapeutic potential. The probe **39** from 1, 3-dimethylbarbituric acid-based series and probe **18** from benzothiazolium based series of theranostic probes, showed the potential for simultaneously detection of the Aβ species, and inhibited the cholinesterase enzymes, the primary targets for the development of therapeutics for AD. Moreover, considering the heterogeneity and complexity of the multifactorial nature of the AD, an innovative strategy to design single chemical entities able to simultaneously modulate more than one target, called "multitarget-directed ligands (MTDLs)" was undertaken. It is a highly promising approach in contrast to "one-molecule, one-target" to improve therapeutic efficacy. The latter two chapters of the thesis demonstrated the development of MTDLs, guided by rational and holistic design approaches. The obtained results of developed MTDLs postulated that potent analogs of *N*-arylpiperazine containing chalcone and pyrazoline scaffolds, specifically lead compounds **41** & **48** respectively, were able to act as multi-modal therapeutic agents for AD.

The organization of the thesis is as follows:

Chapter 1: Introduction section of the thesis mainly describes the introduction of AD, its stages, pathophysiology & hypothesis, diagnostic markers, therapeutic drug targets, and current available clinical drugs for the treatment of AD.

Chapter 2: This chapter focuses on a detailed literature survey on novel strategies of theranostics fluorescent probes including development, recent advancements of multi-target directed ligands (MTDLs) and computer-aided drug discovery.

Chapter 3: This chapter summarizes the major research objectives, the rationale of the design strategies and overall plan of work.

Chapter 4: The chapter deals with the series of 1, 3-dimethylbarbituric acid based novel theranostic agents. The design, synthesis and evaluation against cholinesterase (ChEs) enzymes and detection of Aβ species is presented in detail.

Chapter 5: This chapter describes the development of a series of novel donor−acceptor architecture-type potential benzothiazolium and indolium theranostic agents including design, synthesis, and evaluation for their potential against cholinesterase (ChE) enzymes and detection of Aβ species.

Chapter 6: The chapter includes the design and synthesis of multi-targetable chalcone derivatives bearing *N*-aryl piperazine moiety. All the synthesized compounds were screened for the *in vitro* activity against acetylcholinesterase (AChE), butylcholinesterase (BuChE), β-secretase-1 (BACE-1), and inhibition of amyloid β (Aβ) aggregation.

Chapter 7: This chapter includes lead optimization-based novel multi-targetable series of pyrazoline derivatives. MTDLs were designed by lead optimization of chalcone into pyrazoline scaffold bearing *N*-aryl piperazine moiety, evaluated through *in vitro* and *in-vivo* biological studies.

Chapter 8: This chapter outlines the summary and conclusions of the study.

Chapter 9: This section includes references as a source of information to carry out the research work.

An appendix consisting of the NMR (^{1}H and ^{13}C), Mass spectra and HPLC data/chromatograms of the representative compounds followed by a list of publications produced during the course of Ph.D. are also included.