Preface

Alzheimer's Disease (AD) is an age-related neurodegenerative disorder that accounts for over 80% of dementia cases in older adults worldwide. It is characterized by the low level of acetylcholine (Ach), an Increase in oxidative stress, accumulation of metals, deposition of amyloid-beta (Aβ) plaques, and neurofibrillary tangles, leading to the progressive loss of memory and cognitive functions. Despite decades of research on the etiology of the disease and substantial efforts by the pharmaceutical industry to develop effective therapies, no treatment has been found to cure AD or significantly inhibit its progression. Currently, four drugs—donepezil, galantamine, rivastigmine (acting on the cholinergic pathway), and memantine (acting on the NMDA receptor) are approved by the USFDA. Aducanumab and Lecanemab are monoclonal antibodies (MABs) recently approved for treating AD. These drugs target amyloid-beta (Aβ) plaques, which are believed to play a central role in the pathophysiology of AD. As we know, AD is a multifactorial disease; therefore, targeting the single drugs is insufficient for comprehensive treatment. Although combination therapies offer dosing flexibility, they pose considerable challenges, such as the risk of drug-drug interactions, complicated treatment protocols, and lower patient compliance. The development of multiple drugs substantially increases research and development costs. In the case of AD therapies, which encompass both preclinical studies and clinical trials, these costs frequently surpass $2 billion, primarily due to the high attrition rates associated with drug development. In contrast, multifunctional ligands offer a more efficient therapeutic strategy by targeting multiple pathological pathways simultaneously, reducing the need for multiple agents. This approach not only simplifies clinical trial design and regulatory approval processes but also holds the potential to lower overall development costs, providing a more holistic solution to the multifactorial nature of AD.

The present study is divided into six chapters:

Chapter 1: This chapter overviews Alzheimer's disease, including its pathophysiology and the current treatments.

Chapter 2: This chapter presents a comprehensive review of the existing literature related to the relevant research.

Chapter 3: This chapter outlines the research work's hypothesis, rationale, and detailed plan.

Chapter 4: This chapter discusses the rationale for synthesizing and evaluating novel ferulic acid derivatives, specifically glycine/piperazine amide/benzylpiperazine/tryptamine derivatives. The designed molecules were synthesized and subjected to *in-vitro* enzyme inhibition studies. The potent molecules identified from these studies were further investigated for enzyme kinetics, antioxidant activity, metal chelation, Aβ modulation, and neuroprotection. Lead compounds were then selected for *in-vivo* studies in AD animal models to evaluate their effects on working memory and learning.

Chapter 5: This chapter details the general synthetic procedures used for the targeted compounds and their subsequent biological evaluation.

Chapter 6: This chapter provides the final summary and conclusions drawn from the research.