## Preface

Alzheimer's disease (AD) represents the predominant form of dementia, constituting a significant and escalating global health challenge, particularly among aging populations. Clinically, AD manifests as progressive cognitive deterioration, memory impairment, and behavioral disturbances, ultimately leading to complete loss of functional independence. Pathologically, the disease is defined by two hallmark features: (i) the accumulation of extracellular amyloid-beta (Aβ) plaques, and (ii) intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. These pathological aggregates collectively disrupt synaptic integrity, induce chronic neuroinflammation, and precipitate neuronal apoptosis. Despite decades of extensive research, the precise etiological mechanisms underlying AD remain incompletely elucidated, involving a complex interplay of genetic predisposition (e.g., *APOEε4* allele), environmental influences, and dysregulated biochemical pathways. The persistent absence of effective disease-modifying therapeutics underscores the critical need for innovative pharmacological strategies targeting the multifactorial pathogenesis of AD.

To address the challenges of AD, this thesis explores three research strategies: targeting neuroinflammation through Computer-aided drug design (CADD), applying artificial intelligence (AI) and machine learning (ML) to accelerate drug discovery, and developing multi-target-directed ligands (MTDLs) to simultaneously modulate multiple pathological pathways in AD.

The work embodied in this thesis has been presented under the following chapters:

**Chapter 1:** The chapter provides a comprehensive introduction of AD and the various approaches involved in drug design and discovery are briefly discussed.

**Chapter 2:** The chapter deals with an exhaustive literature review on the importance and applications of CADD, ML, and MTDL approaches in AD research.

**Chapter 3:** In this chapter, the objectives of the study and plan of work are mentioned.

**Chapter 4:** The chapter details the structure-based and ligand-based drug design approaches employed to identify novel small-molecule inhibitors of DAPK1. Several coumarin-based scaffolds were identified as potential DAPK1 inhibitors with favourable pharmacokinetic and safety profiles.

**Chapter 5:** The chapter presents the structure-guided identification of coumarin derivatives as inhibitors of the NLRP3 inflammasome. A comprehensive virtual screening of coumarin libraries, followed by ADMET filtering and binding affinity analysis, led to the selection of promising NLRP3-targeted compounds with predicted blood-brain barrier permeability and low toxicity.

**Chapter 6:** The chapter describes the development of ensemble ML models for the prediction of COX-1 and COX-2 inhibitory activity. The developed models, implemented within an open-source, code-free computational platform, demonstrated high predictive performance and facilitate the efficient identification of selective anti-inflammatory agents with reduced off-target effects.

**Chapter 7:** The chapter describes the design, synthesis, and biological evaluation of a series of biphenyl sulfonamide derivatives developed as MTDLs for AD.

**Chapter 8:** The chapter outlines the design, synthesis, and evaluation of a series of 4-(phenylsulfonamido)benzamide derivatives as MTDLs for AD.

**Chapter 9:** The chapter outlines the summary and conclusions of the research work.

**Chapter 10:** The references used to carry out the research work are presented here.

The references used to carry out the research work, an appendix of additional supporting information, the spectral data of representative compounds, and a list of publications during the course of the Ph.D. are included.