Preface

Alzheimer's disease (AD), a progressive neurodegenerative disorder characterized by inexorable cognitive decline and memory impairment, represents a significant and growing public health concern. While existing interventions primarily focused on mitigating cholinergic dysfunction offer symptomatic relief, they fail to address the underlying pathophysiological processes. Recognizing the limitations of current approaches, researchers are delving into the intricate molecular pathways implicated in AD pathogenesis, paving the way for a paradigm shift towards multi-target-directed therapeutic strategies.

C**hapter 1** initiates a comprehensive exploration of AD, encompassing its background, pathophysiology, and the current therapeutic landscape. Additionally, the various methodologies, such as Artificial intelligence (AI), that are involved in drug discovery and design are detailed.

Chapter 2: In this chapter, the objectives of the study and plan of work are mentioned.

Chapter 3: This chapter utilizes machine learning to predict potential BACE-1 inhibitors for AD. By analyzing molecular properties and applying algorithms like SVM and Random Forest, the chapter identifies promising candidates and key structural features associated with BACE-1 inhibition, contributing to the development of targeted AD treatments.

Chapter 4: This section outlines the development and application of an XGBoost-based machine learning model to screen an in-house database for potential BACE-1 inhibitors, a key target in AD treatment. The model utilizes PubChem fingerprints to identify promising candidates, which are then subjected to experimental validation for their inhibition activity.

Chapter 5: This section explores a novel approach for predicting Blood-Brain-Barrier (BBB) permeability of molecules using Natural Language Processing (NLP) and Deep Learning. It utilizes the B3DB database and extracts features from molecules via SELFIES and N-gram tokenization, converting them into numerical vectors. These features are then fed into various Deep Learning models like ANN and LSTM to predict BBB permeability. The best-performing model achieved high accuracy, suggesting its potential for early screening of drugs targeting the central nervous system.

Chapter 6: This section describes developing and evaluating multi-target directed ligands (MTDLs) based on *N-benzylpiperidines* for AD treatment. Utilizing suitable approaches, promising N-benzylpiperidine scaffolds are identified. Synthesis of derivatives with predicted enhanced multi-target activity against BACE-1, cholinesterases, and amyloid aggregation is followed by *in-vitro* and, for promising candidates, *in-vivo* efficacy evaluation in AD animal models.

Chapter 7: This chapter outlines the summary and conclusions of the research work undertaken.

Chapter 8: The references used to carry out the research work are presented in the chapter.

An appendix of additional supporting information, spectral data of representative compounds, and a list of publications from the course of the Ph.D. are included.