Preface

Alzheimer's disease (AD) is the most common form of dementia causing memory, behaviour and thinking impairment. Eventually, the symptoms become severe and make it difficult for a patient to carry out daily activities. According to the World Health Organization (WHO), one in every 85 individuals will have AD by 2050. The therapeutic targets of the disease include acetylcholinesterase (AChE), butyrylcholinesterase (BChE), β-secretase-1, glycogen synthase kinase 3β, monoamine oxidase B, matrix metalloproteases, N-methyl D-aspartate (NMDA) receptors, tau kinase etc.

Among the targets, inhibition of cholinesterase enzymes is still a major component of anti-AD therapy to provide symptomatic relief. The inhibition of AChE causes improvement in memory and cognition. However, AChE inhibitors produce cholinergic side effects and the therapeutic effect wear-off with the progression of the disease. Alternatively, the presence of a significant level of BChE in the latter stage of the disease and its inhibition causes improvement in memory and thus, makes it an attractive target. Machine learning (ML), structure-based drug design and ligand-based drug design are useful techniques in drug design. The research work presented in the thesis covers three-fold objectives. The first objective of the study is to design selective BChE inhibitors through ML/scaffold hopping. The ligands identified were synthesised, characterised and tested through various *in vitro* and *in vivo* tests. The second objective deals with the identification of the virtual hits and their binding modes. The third objective includes the development of *in silico* tools by using ML techniques for the identification of hits.

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

Chapter 1: The chapter provides an introduction to AD and deals with details regarding background, pathophysiology and available therapeutics for the treatment of AD. Further, the various approaches involved in drug design are also described.

Chapter 2: The chapter deals with the literature background related to targets involved in the cholinergic hypothesis. It also includes the field application of ML in drug discovery.

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

Chapter 4: The chapter deals with the development of selective BChE inhibitors using ML. It includes the methodology used for design, synthesis, characterisation, *in vitro*, *in silico* and *in vivo* evaluations of *sulfonamides* of *para-amino benzoic acid*, followed by a discussion.

Chapter 5: The development of selective BChE inhibitors using scaffold hopping is presented in the chapter. It describes the methodology used for design, synthesis, characterisation, *in vitro*, *in silico* and *in vivo* evaluations of *sulfonamides* of *phenylglycine*, followed by results and discussion.

Chapter 6: The chapter deals with *in silico* identification of the potential AChE inhibitors through computational techniques.

Chapter 7: The chapter includes the methodology and results obtained from *in silico* analysis of the binding mode of AVL-3288 with α7-nicotinic acetylcholine receptor.

Chapter 8: The chapter includes the details of the procedure followed and results of the development of the homology model, docking protocol and ML-based scoring function for identification of electric eel's AChE inhibitors.

Chapter 9: In this chapter, the detailed procedure of the development of the homology model, docking protocol and ML-based scoring function for the identification of horse's BChE inhibitors is presented. The chapter also includes results and discussion on the above.

Chapter 10: The chapter deals with the development of ML models for the prediction of inhibitors for the important targets of AD. The ML models are deployed in the form of a web application – AlzLeads.

Chapter 11: This chapter outlines the summary and conclusions of the research work undertaken.

Chapter 12: The references, used to carry out the research work, are presented in the chapter.

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