Chapter 3
Objective and plan of work

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3.1. Objective

AD is a neurodegenerative disease that progresses into loss of the memory, cognition and thinking ability of a patient. The effects of disease lead to difficulty in performing activities of daily living and make the patient dependent on the caregiver. The treatment of the patient with an AChE inhibitor provides relief in the early stage of the disease, but with the progression of the disease or on late diagnosis, the therapeutic effect is diminished. The level of BChE is much higher than AChE in the later stage of the disease, thus signifying it an attractive target. Further, the selective BChE inhibitors are devoid of the cholinergic adverse effect as produced by AChE inhibitors. In recent decades, the advancement in computational techniques has afforded in successful identification of lead compounds. SBDD is one of the most acclaimed strategies. However, with advancement and expansion in the application of artificial intelligence, ML is gaining popularity to identify inhibitors. The ML-based prediction models are quite robust and provide insight into the approach to inhibitor design. The objective of the present study is in three -folds. It includes the identification and development of anti-AD leads and the development of *in silico* tools through computational and ML-based techniques (**Figure 3.1**).

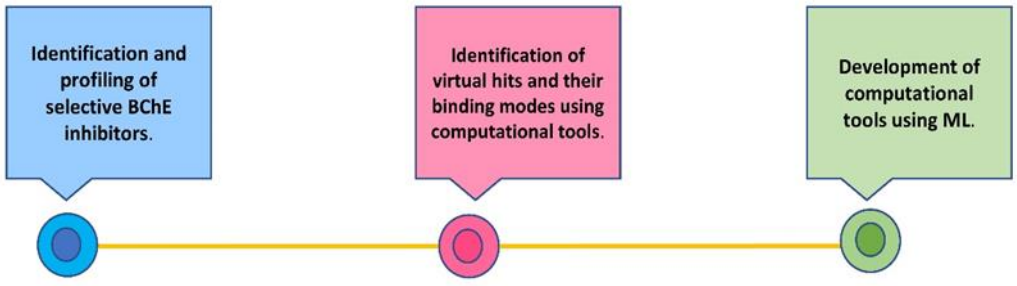

Figure 3.1 Objective of the research work.

3.2. Plan of work

1: Identification and profiling of selective BChE inhibitors

- Identification of BChE inhibitors through ML model/ scaffold hopping.
- Synthesis and characterization of synthesised derivatives by FTIR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.
- *In vitro* evaluation against AChE, BChE and enzyme kinetic studies.
- *In vitro* blood-brain barrier permeation assay (PAMPA).
- *In vitro* cell viability assay.
- *In silico* analysis of compounds by QSAR, docking and molecular dynamics.
- *In vivo* evaluation of compounds against scopolamine-induced amnesia in rats using various behaviour and neurochemical parameters.

2: Identification of virtual hits and binding mode using computational tools

2.1: Identification of virtual hits as AChE inhibitors using SBDD

- Development of structure-based pharmacophore model and screening of chemical database.
- Application of descriptor-based filters.
- Virtual screening and precision docking for identification of hits.
- Virtual alanine scanning and free binding energy calculations of screened compounds.
- Molecular dynamics for identification of suitable inhibitors.

2.2: Identification of binding mode of a compound

- Molecular docking for identification of suitable binding site.
- Virtual alanine scanning and free binding energy calculations.

- Molecular dynamics for identification of stable binding pose of a ligand with protein.

3: Development of computational tools with ML

3.1: Development of docking protocol and ML-based SF

- Development and validation of protein model for electric eel's AChE/Horse BChE.
- Development and validation of docking protocol using Autodock-4.2.6
- Validation of Autodock SF.
- Development and validation of ML-based SF.

3.2: Development of ML-based web application for prediction of anti-AD leads.

- Procurement of inhibitor datasets for various targets involved in AD.
- Development and validation of ML models on the various datasets.
- Deployment of selected ML models as a web application.

The details of the various aspects of the above studies are presented in the following chapters of the thesis.