

Chapter 3

Objective, Rationale and Plan of Work

3. Objectives, Rationale and Plan of Work

Abstract: The objective of the present study is to develop multi modal new chemical entities with the potential to provide symptomatic treatment along with modulation of pathogenic factors such as cholinergic pathways, A β aggregation, excitotoxicity caused by NMDAR and neuroprotection. The development of MTDLs is based on rational and holistic view of target combination, ligand selection, and equilibrium of desired activities to maximize efficacy and safety. Modern drug design approaches *viz.* fragment-based drug design, scaffold hopping and hybrid drug design considering marketed AD drugs; were utilized for ligand design. Three different chemical class of ligands *viz.* spiropyazole, benzo[d]oxazol-5-amine and triazole bridged aryl adamantane were identified and derivatized to three series of molecules by utilizing the synthetic suitability.

3.1 Objective and Rationale

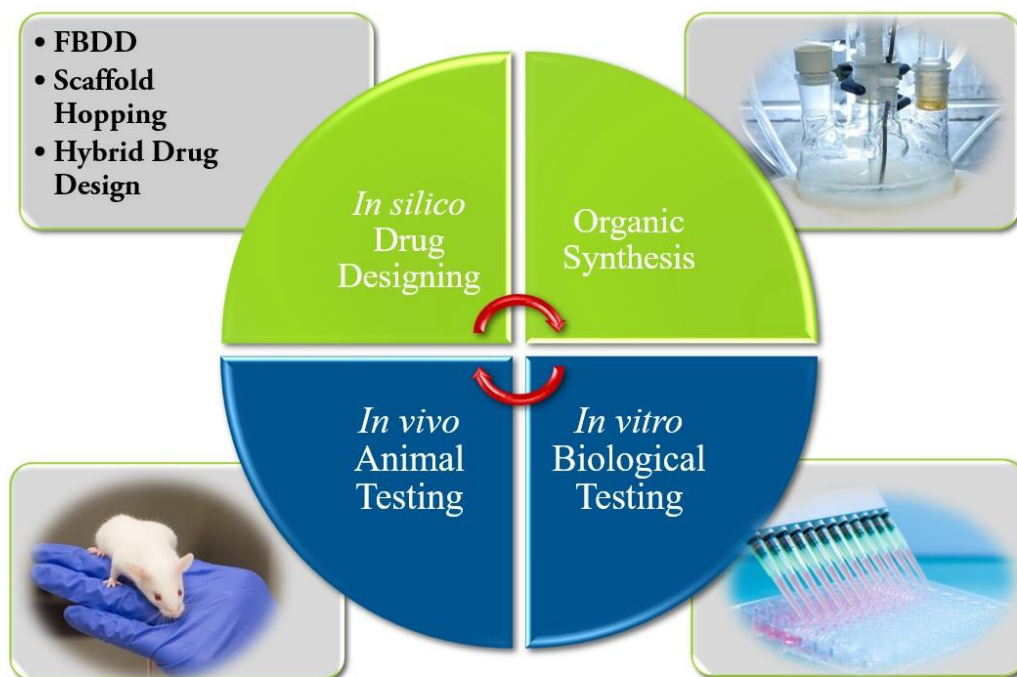


Figure 3.1. Overview of the designed study.

3.2 Plan of Work

It is divided into the following:

- A. Pharmacophore development and fragment-based screening OR scaffold identification.
- B. Derivatization of fragment/scaffold based on synthetic suitability.
- C. Molecular docking and validation.
- D. Synthesis and characterization of synthesized derivatives by Physical and spectral methods *viz.* melting point, TLC, ^1H NMR, ^{13}C NMR and Mass spectrometry.
- E. *In-vitro* cholinesterase (AChE, BuChE) inhibition assays.
- F. Evaluation of triazole bridged aryl adamantane analogs on glutamate- and glycine evoked currents in eight combination (GluN1-1a/GluN2A, GluN1-1b/GluN2A, GluN1-1a/GluN2B, GluN1-1b/GluN2B, GluN1-1a/GluN2C, GluN1-1b/GluN2C, GluN1-1a/GluN2D and GluN1-1b/GluN2D) of receptors.
- G. Selectivity assessment of potent compounds.
- H. *In-vitro* blood-brain barrier permeation assay (PAMPA).
- I. Cell line-based neuroprotection and toxicity studies using MC-65 and SH-SY5Y cell lines.
- J. Self, metal and AChE-induced $\text{A}\beta_{1-42}$ aggregation assay.
- K. *In-vivo* Behavioral studies.
 - a. Scopolamine induced amnesia model.
 - b. $\text{A}\beta_{1-42}$ induced ICV rat model.
- L. Neurochemical level estimation and histology assessment of brain samples.