# Section-I

Chapter-2
RESEARCH
ENVISAGED

2. RESEARCH ENVISAGED

A comprehensive literature review revealed that Aβ plaque formation can be best targeted by small heterocyclic molecules during the progression of AD. Literature survey also revealed that small heterocyclic molecules help in maintaining acetylcholine levels in brain. Investigation into the cholinergic hypothesis has led to the progress of several fused and non-fused ring systems as cholinesterase inhibitors (ChEIs). The best example, tacrine (**1**), an acridine derivative, was one of the most crucial ChEI developed to treat AD. Recently a guanidine supported ring template (**2**) has been discovered for its capability to inhibit the aggregation of $Aβ_{1–42}$ plaques and it has also revealed dual activity of inhibiting cholinesterase enzymes as well. Keeping in mind the structure of tacrine (tricyclic ring system) and the guanidine supported ring system (**2**) it was planned to synthesize a ring system of type **3** in the Pharmaceutical Chemistry laboratory of the department and to assess the derivatives against cholinesterase enzymes and Aβ aggregation.
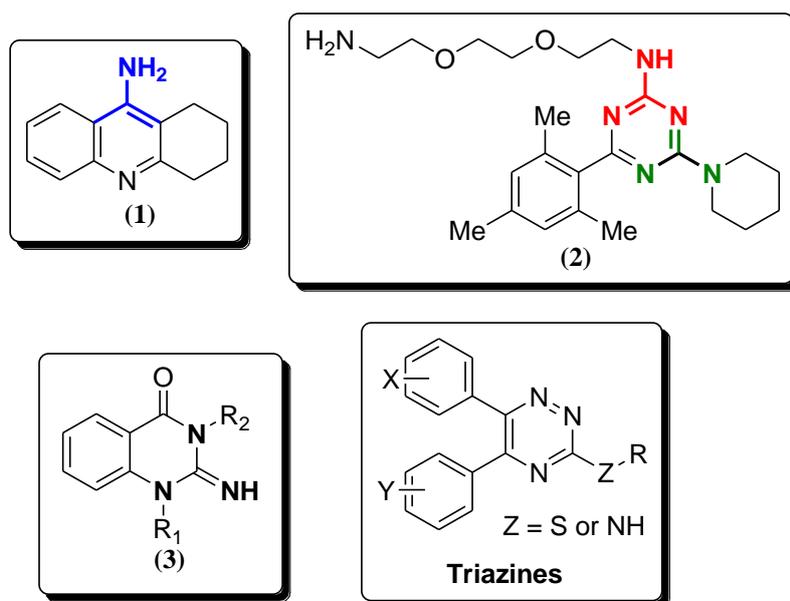
Second series of triazines was designed and synthesized on the basis of some previous reports. Triazine moieties have been widely studied due to their occurrence in natural antibiotics like reurhycin, toxoflavin and fervenulin [60]. The neuropharmacological perspective of triazines [61] is broadening gradually due to their potent antidepressant [62], antiepileptic [63] and anti-anxiety [64] effects, and particularly in neurodegenerative diseases like AD as neuroprotective agents [65]. Some of the diaryl derivatives were reported to be potent neuroprotective agents against hydrogen peroxide induced oxidative stress in differentiated rat pheochromocytoma (PC12) cell line with a marked reduction in caspase-3 activation [66]. Some *sym*-triazines with acetylcholine-like substituents acting as multitarget

modulators in AD have been recently reported as promising candidates against AD [67, 68]. The compounds so synthesized in the Pharmaceutical Chemistry laboratory were planned to be evaluated for their anticholinesterase and anti Aβ aggregation profile keeping the following objectives in mind:

1. To assess the cholinesterase activity of the synthesized compounds using standard cholinesterase inhibition assay described by Ellman.

2. To assess anti Aβ aggregation profile of the compounds selected in the previous assay using thioflavin T (ThT) assay.

3. To evaluate the safety profile of the potent compounds selected in preliminary screening.

4. To evaluate the antiamnesic and antioxidant profile of the selected compounds using scopolamine induced amnesic mice model.

5. To assess the antioxidant, antiapoptotic and reactive oxygen species (ROS) scavenging property of the selected compounds using primary rat hippocampal neuronal culture.

6. To assess the selected compounds for their neuroprotective property using Aβ induced Alzheimer's like rat model.

7. To assess their neuroprotective potential using immunofluorescence technique for Aβ, caspase and fluoro-jade c.

8. To confirm the neuroprotective potentials of the selected compounds by estimation of various protein markers using Western blot technique.

9. To elucidate the mechanistic pathway involved behind the neuroprotective role of the compounds by estimation of certain protein markers using immunofluorescence and Western blot techniques.