3. Aim and objectives

Despite its exceptional pharmacological profile, safety and tolerance, donepezil still has some serious issues. Donepezil could be effective for the treatment of early to intermediate stages of AD. It can be useful only to delay the progression of AD or manage the symptoms, it unfortunately failed to terminate or eliminate the cognitive impairments completely. It had been reported that donepezil causes moderate improvements in the quality of life of patients suffering from AD. Moreover, there is no single report available claiming the long-term clinical efficacy and safety of donepezil. Due to its limited potential, use of donepezil becomes inadequate to treat severe and advanced stages of AD. This is the reason why so many efforts have continuously been made by the medicinal chemists involved in AD research to develop novel AChE inhibitors with long-term efficacy and safety.

As the literature survey depicted, a number of new compounds have been designed and developed as multi-target-directed ligands (MTDLs) for the management of AD. These MTDLs have been synthesized either by modifying the central scaffold of the marketed AChEIs or by using their active pharmacophores. A variety of novel donepezil-based MTDLs as multifunctional AChE inhibitors have been reported in the literature which were synthesized by modifying either the 5,6-dimethoxy indanone part or the benzylpiperidine pharmacophore of the donepezil.

Our research group has also been actively involved in the designing and development of various therapeutically active compounds and successfully reported some vicinal diaryl heterocyclic systems as anti-Alzheimer agents. Earlier we have disclosed the anti-Alzheimer activity of compounds (**I**) containing vicinal diaryltriazine scaffold (**Figure 3.1**). Some benzylpiperidine-linked vicinal diarylthiazole derivatives (**II**) as MTDLs for the treatment of AD have also been reported from the lab (**Figure 3.1**). Based on these previous research works, it was planned to explore the structure of vicinal diaryltriazine fused with the substituted benzylpiperidines to develop a novel series of compounds (**III**) as anti-Alzheimer agents (**Figure 3.1**).

There are number of research articles appeared in the literature describing the anti-Alzheimer activity of pyrimidine containing heterocyclic compounds. Pyrimidine itself is a bioactive molecules present in various biologically important natural products. Keeping the significant biological potential of pyrimidine and its derivatives in the mind, it was planned to synthesize some novel vicinal diaryl-substituted pyrimidine derivatives (**IV**) as anti-

Alzheimer agents (**Figure 3.1**). To the best of our knowledge, it is for the first time that these novel vicinal diaryl-substituted pyrimidines would be reported as anti-Alzheimer agents.

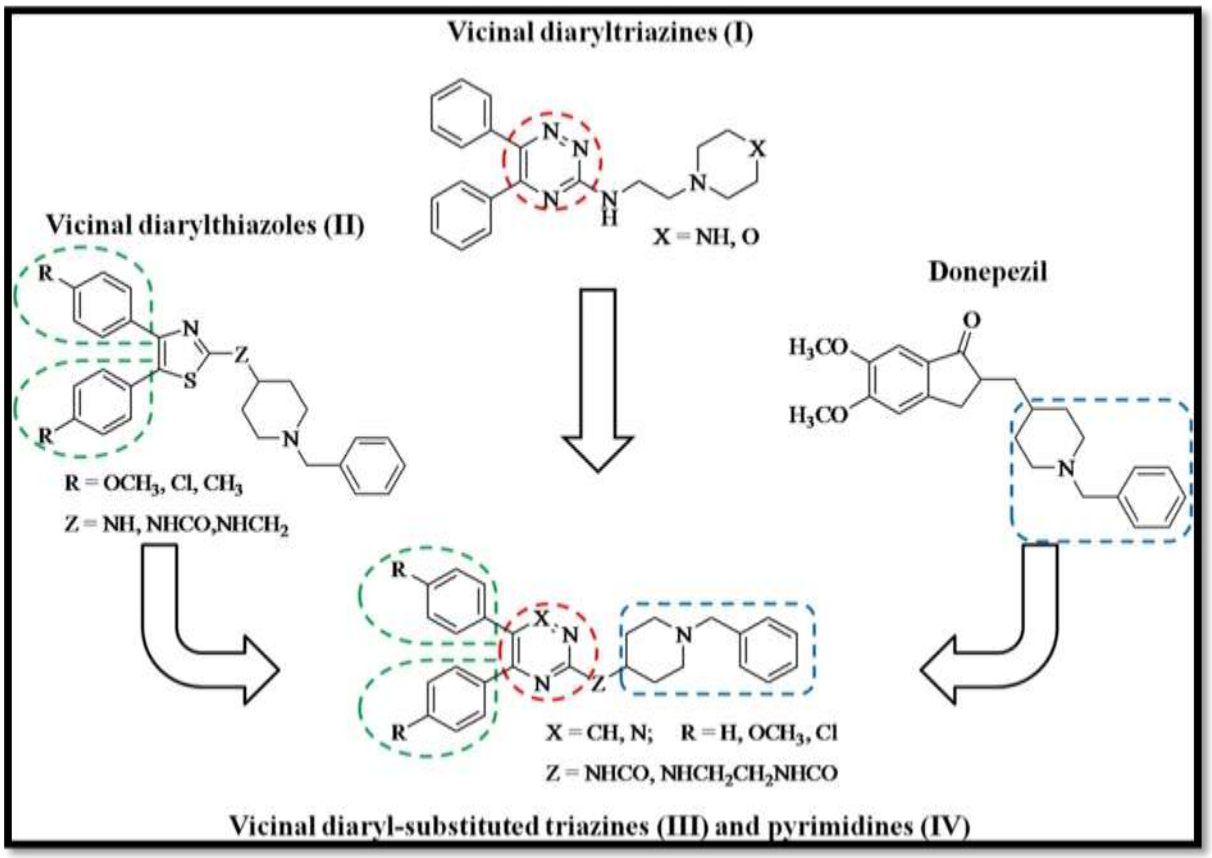

Figure 3.1: Designing of novel vicinal diaryl-substituted triazines (**III**) and pyrimidines (**IV**).

Besides this, we decided to synthesize some donepezil-triazine hybrids (**V**) wherein the 5,6-dimethoxy-indanone of the donepezil have been linked with the vicinal diaryl-substituted triazines as shown in figure 3.2. Further, it was planned to evaluate all the synthesized compounds (**III-V**) for their anti-Alzheimer activity.

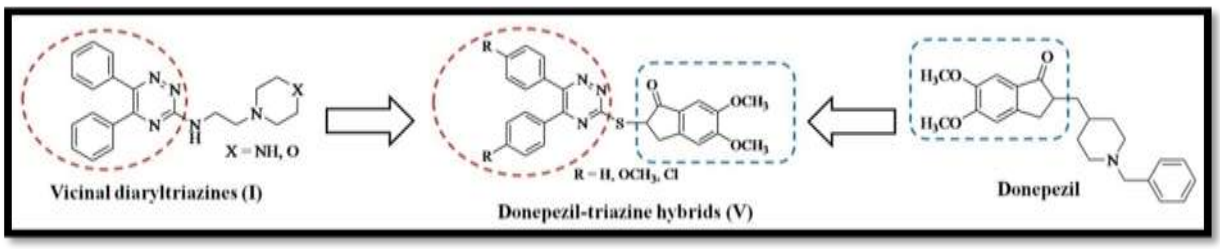

Figure 3.2: Designing of novel donepezil- triazine hybrids (**V**).