Chapter Six

Summary

&

Conclusion
6.1 Summary

The present research work has been discussed in required depth in this thesis and is summarized as follows:

1. General introduction: Alzheimer’s disease (AD) is a progressive, neurodegenerative disorder and the characteristic hallmarks of the disease are amyloid (Aβ) peptide deposits in senile plaques and neurofibrillary tangles. Various approaches to confront AD pathogenesis such as cholinergic hypothesis, NMDA receptor modulation, amyloid cascade hypothesis and others along with their therapies were discussed. The amyloid cascade hypothesis explained the role of β- and γ- secretases in the formation of amyloid plaques. β-secretase (BACE1) was identified as one of the main enzyme involved in the cascade of physiological events that lead to Alzheimer’s disease. Over the past decade, many peptidomimetic BACE1 inhibitors were reported which, due to their high molecular weights, had poor ability to cross the blood-brain barrier. Computer aided drug design was found to be a valuable tool for predicting potentially active non-peptide β-secretase inhibitors. Thiadiazole nucleus was found to be present in compounds with biological activities related to the central nervous system (CNS); G-protein coupled receptors, inflammation, cardiovascular system or antibiotic activity. Looking at the usefulness of 1,2,4-thiadiazole as pharmacophore, this newly developed system was explored in the research work and FRET assay was employed for the pharmacological screening.

2. Literature survey: In literature survey, non-peptide compounds which were reported as BACE1 inhibitors, beginning from the first Takeda inhibitors (2001) till 2012, have been discussed. Several strategies of drug discovery were explored in the search for potent BACE1 inhibitors, e.g., substrate-based design, high-throughput screening (HTS) and fragment-based lead generation approaches.

3. Plan & scope of the research work: The overall aim of the research work was to design, understand the intermolecular interactions, synthesize, screen and develop promising non-peptide inhibitors of BACE1. Despite the painstaking efforts put in discovering drug candidates for Alzheimer’s disease, no truly disease modifying agents have been yet made available.
4. Experimental work: The methodology involved in structure-based drug design, synthesis, characterization, in silico ADME studies and pharmacological screening has been mentioned in detail.

5. Results & discussion: The results obtained were discussed with respect to molecular docking, synthesis, computational ADME studies and inhibition studies of the synthesized non-peptide inhibitor compounds of β-secretase.

6. Summary & conclusion: The entire research work has been summarized and conclusions are derived from the research findings.

6.2 Conclusion
In the present research work non-peptide inhibitor compounds of β-secretase have been designed and synthesized. On the basis of encouraging results it can be concluded that of the 3-substituted-1,2,4-thiadiazol-5-amines, the 3-ethylthio and 3-methyl substituted 1,2,4-thiadiazol-5-amines (compound nos. 12 & 17) may serve as promising candidates for further optimization. There is further scope for design of different analogues from these two scaffolds.
In the series of phenyl 1,2,4-thiadiazolyl urea analogues derived from 3-substituted-1,2,4-thiadiazol-5-amine scaffolds, the acetyl and chloro substitutions in the phenyl ring lead to loss of activity while the methylthio, cyano and nitro substituents resulted in moderate activity. There is scope for detailed pharmacological and toxicological studies of these compounds. The Type I biphenyl urea analogues with various substituents interacted and exhibited BACE1 enzyme inhibition but the phenyl 1,2,4-thiadiazolyl urea analogues showed better results in the in silico ADME studies.