Chapter 7

Summary, Conclusion and Future Prospects

7 Summary and Conclusion

Alzheimer's disease (AD) is a multifactorial neurodegeneration that causes dementia and other neuropsychiatric symptoms such as apathy, depression, and shifts in sleep patterns. A significant degeneration of the hippocampus and cerebral cortex results in the loss of short and long-term memory. There are several hypotheses for the neurodegeneration process featuring β-amyloids, tau protein, cholinergic system etc.

The research aimed to explore the potential of AI in various stages of drug discovery for AD treatment. The key findings and conclusions are:

1. Machine learning models were developed for accurate classification of BACE-1 inhibitors, with the best models achieving an F1 score of 0.87. The models identified important structural features and fragments present in active and inactive compounds.
2. An *in-house* database of sulfonamide compounds was screened using a machine learning model, leading to the identification of two potential BACE-1 inhibitors. The IC_{50} value of compound 28 was found to be 0.431 ± 0.06 μM, and compound 37 showed an IC_{50} value of 0.272 ± 0.019 μM. The docking study revealed that compound 37 also showed interactions with the catalytic dyad of BACE-1, i.e., Asp32 and Asp228.
3. A novel approach using NLP and Deep Learning was investigated for predicting BBB permeability, which is crucial for CNS drug development. The accuracy, precision, recall, F1, specificity and AUC of ROC scores were found to be 0.89, 0.91, 0.91, 0.91, 0.85 and 0.90. Thus, the developed model can be used for the early screening of CNS drugs.
4. A series of *N-benzylpiperidine* compounds were designed and evaluated as multi-target directed ligands for AD treatment. Two promising compounds, 72 and 77,

demonstrated good AChE and BACE-1 inhibitory potential, Aβ aggregation inhibition, and cognitive improvement in animal studies without toxicity.

The research highlights the potential of AI techniques in accelerating drug discovery for AD by aiding in the identification of potential inhibitors, predicting BBB permeability, and designing multi-target directed ligands.

Future Prospects:

1. The developed machine learning models can be further improved and expanded to include a larger and more diverse set of BACE-1 inhibitors, potentially leading to the discovery of novel and potent inhibitors.
2. The NLP-based BBB permeability prediction model can be extended to other CNS drugs and combined with other AI techniques for a more comprehensive evaluation of CNS drug candidates.
3. The promising *N-benzylpiperidine* compounds identified in this research can be further optimized and evaluated in pre-clinical studies for their potential as AD therapeutics.
4. The integration of AI techniques with experimental data and expert knowledge can facilitate the design and optimization of multi-target directed ligands for AD and other complex diseases.
5. The application of AI techniques can be expanded to other stages of drug discovery, such as hit-to-lead optimization, ADMET prediction, and clinical trial data analysis, to further accelerate the development of AD therapeutics.

Overall, the research demonstrates the potential of AI in accelerating drug discovery for AD and paves the way for future integration of AI techniques throughout the drug development process.