

Applications of Artificial Intelligence in Discovery and Development of Therapeutics for the Treatment of Alzheimer's Disease



**Thesis submitted in partial fulfilment for the
Award of Degree**

Doctor of Philosophy

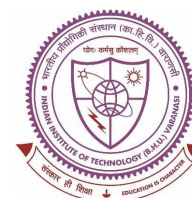
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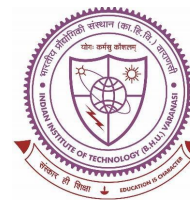
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Table of Contents

1	INTRODUCTION.....	2
1.1	NEURODEGENERATIVE DISORDERS.....	2
1.2	ALZHEIMER’S DISEASE.....	2
1.3	SYMPTOMS OF ALZHEIMER’S DISEASE.....	3
1.4	STAGES OF ALZHEIMER’S DISEASE.....	3
1.5	DIAGNOSIS OF ALZHEIMER’S DISEASE.....	4
1.6	PATHOPHYSIOLOGY OF ALZHEIMER’S DISEASE.....	6
1.7	MANAGEMENT OF ALZHEIMER’S DISEASE.....	9
1.8	ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN DRUG DISCOVERY.....	11
2	OBJECTIVE AND PLAN OF WORK.....	16
2.1	OBJECTIVE.....	16
2.2	PLAN OF WORK.....	16
2.2.1	<i>Classification of BACE-1 inhibitors using machine learning.....</i>	<i>16</i>
2.2.2	<i>Machine learning-based screening of in-house database for BACE-1 inhibitors.....</i>	<i>17</i>
2.2.3	<i>Natural Language Processing (NLP) for deep learning-based prediction of BBB permeability.....</i>	<i>17</i>
2.2.4	<i>Design, synthesis and biological evaluation of N-benzylpiperidines as potential multitargeted ligands for the treatment of Alzheimer’s disease.....</i>	<i>18</i>
	<i>Plan of Work:.....</i>	<i>18</i>
3	CLASSIFICATION OF BACE-1 INHIBITORS USING MACHINE LEARNING METHODS.....	21
3.1	INTRODUCTION.....	21
3.2	COMPUTATIONAL METHOD.....	24
3.2.1	<i>Deriving experimental data for BACE-1 inhibitors.....</i>	<i>24</i>
3.2.2	<i>Ligand pre-treatment and preparation.....</i>	<i>25</i>
3.2.3	<i>Molecular descriptor calculation and feature selection.....</i>	<i>25</i>
3.2.4	<i>BACE-1 inhibitor training and test data sets.....</i>	<i>26</i>
3.2.5	<i>Machine learning classification algorithms.....</i>	<i>26</i>
3.2.6	<i>Validation of performance of the models.....</i>	<i>28</i>

3.2.7	<i>Comparison of the performance of models created on 2D descriptors and fingerprints with 3D descriptors.....</i>	28
3.3	RESULTS AND DISCUSSION.....	29
3.3.1	<i>Chemical space exploration and dataset distribution of BACE-1 inhibitors</i>	29
3.3.2	<i>Feature selection of calculated descriptors.....</i>	29
3.3.3	<i>BACE-1 inhibitor training, validation and test sets</i>	30
3.3.4	<i>Machine learning classification algorithms</i>	33
3.3.5	<i>Prediction of the test set data.....</i>	37
3.3.6	<i>Comparison of the performance of models build on 2D descriptors and fingerprints with 3D descriptors.....</i>	38
3.3.7	<i>Structural diversity of BACE-1 inhibitors</i>	38
3.3.8	<i>k-Means clustering of BACE-1 inhibitors</i>	39
3.3.9	<i>Comparison of performance of classification algorithms and descriptors.....</i>	41
3.3.10	<i>Defining applicability domain of models.....</i>	47
3.4	CONCLUSION	48
4	MACHINE LEARNING BASED SCREENING OF IN-HOUSE DATABASE TO IDENTIFY BACE-1 INHIBITORS.....	51
4.1	INTRODUCTION	51
4.1.1	<i>Sulphonamides as BACE-1 Inhibitors in Human Clinical Trials</i>	51
4.1.2	<i>Machine Learning in drug discovery</i>	53
4.1.3	<i>Machine learning algorithms.....</i>	54
4.2	MATERIALS AND METHODS	55
4.2.1	<i>Dataset Collection</i>	55
4.2.2	<i>Fingerprint Descriptors.....</i>	56
4.2.3	<i>Data Splitting</i>	56
4.2.4	<i>Machine learning classification algorithms</i>	56
4.2.5	<i>Screening Database preparation</i>	58
4.2.6	<i>BACE-1 inhibition assay.....</i>	58
4.2.7	<i>Docking study.....</i>	59
4.3	RESULT AND DISCUSSION	59

4.3.1	<i>Machine learning models</i>	59
4.3.2	<i>Performance of ML models on validation set</i>	60
4.3.3	<i>Screening of in-house library</i>	61
4.3.4	<i>In-vitro BACE-1 inhibitory activity</i>	64
4.3.5	<i>Docking study</i>	65
4.4	CONCLUSION	66
5	NATURAL-LANGUAGE PROCESSING (NLP) BASED FEATURE EXTRACTION TECHNIQUE IN DEEP-LEARNING MODEL TO PREDICT THE BLOOD-BRAIN- BARRIER PERMEABILITY OF MOLECULES	69
5.1	INTRODUCTION	69
5.2	METHODS	72
5.2.1	<i>Dataset</i>	72
5.2.2	<i>Features extractions</i>	72
5.2.3	<i>Neural Network Architecture</i>	74
5.2.4	<i>Model parameters</i>	76
5.2.5	<i>Evaluating the performance of DL models</i>	77
5.3	RESULT AND DISCUSSION	78
5.4	CONCLUSION	84
6	DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF N- BENZYLPIPERIDINES AS POTENTIAL MULTITARGETED LIGANDS FOR THE TREATMENT OF ALZHEIMER'S DISEASE	87
6.1	INTRODUCTION	87
6.2	DESIGN ASPECTS	89
6.3	MATERIAL AND METHODS	90
6.3.1	<i>Docking studies</i>	90
6.3.2	<i>Molecular property and toxicity prediction</i>	91
6.3.3	<i>In silico ADME property analysis</i>	91
6.3.4	<i>Synthesis and Characterization</i>	92
6.3.5	<i>In vitro studies</i>	114
6.3.6	<i>In vivo evaluation of compounds</i>	119
6.4	RESULTS AND DISCUSSION	123

6.4.1	<i>Rationale of drug design & in-silico optimization</i>	123
6.4.2	<i>Chemistry</i>	125
6.4.3	<i>Docking studies</i>	125
6.4.4	<i>Molecular property and toxicity prediction</i>	127
6.4.5	<i>In silico ADME prediction analysis</i>	127
6.4.6	<i>In-Vitro evaluation</i>	130
6.4.7	<i>In-Vivo evaluation</i>	138
6.5	CONCLUSIONS.....	145
7	SUMMARY AND CONCLUSION	148
8	REFERENCES	152

List of Figures

Figure 1.1 Stages of Alzheimer's disease	4
Figure 1.2 Metabolism of APP by secretases	8
Figure 1.3 Chemical structures of FDA approved drug for the treatment of AD	9
Figure 1.4 Flowchart summarizing the applications of AI in drug discovery.....	13
Figure 3.1 Pair plot of BACE-1 inhibitor dataset. The diagonal represents the frequency of distribution. (MW=Molecular weight, TPSA=Total Polar Surface Area, nRot=Number of rotatable bond)	30
Figure 3.2 Pearson correlation coefficient of calculated descriptors after performing feature selection.....	31
Figure 3.3 Data distribution for (A) complete BACE-1 dataset and (B) Chemical space of training, validation and test set as represented by PCA plot.....	33
Figure 3.4 Frequency distribution histogram of Tanimoto similarity coefficient for pair of BACE-1 inhibitor based on MACCS fingerprints.	38
Figure 3.5 Clustering of compounds in 11-subsets along with their centroids (represented by ★). t-SNE1 and t-SNE2 are the two dimensions reduced from 166 dimensions of MACCS fingerprints.....	40
Figure 3.6 Central compounds and their corresponding activities in the eleven subsets	43
Figure 3.7 Receiver operating characteristics (ROC) curves of models build on (A) Mordred, (B) KRFP fingerprints, (C) MACCS fingerprints and (D) Pubchem fingerprints datasets.....	45
Figure 3.8 KRFP fingerprints (A) beneficial and (B) adversely affecting the BACE-1 inhibitory activity obtained from RF classifier	46
Figure 3.9 Pubchem fingerprints (A) beneficial and (B) adversely affecting the BACE-1 inhibitory activity obtained from RF classifier	47

Figure 4.1 Sulphonamides as BACE-1 inhibitors in clinical and pre-clinical studies....	53
Figure 4.2 Top 10 important PubChem fingerprints.....	61
Figure 4.3 2D interaction diagram of (a) compound 28 and (b) compound 37 and 3D interaction diagram of (c) compound 28 and (d) compound 37.	65
Figure 5.1 Basic mechanism involved in the transport of drugs across the BBB.....	70
Figure 5.2 Distribution of dataset into training, validation and test set.....	72
Figure 5.3 Steps of feature extraction from SELFIES	75
Figure 5.4 Neural network architecture of (a) ANN (b) LSTM	77
Figure 5.5 Performance of Model while training: (a) Training loss and validation loss for ANN-5 (b) Training and Validation accuracy for ANN-5 (c) Training loss and validation loss for ANN-7(d) Training and Validation accuracy for ANN-7 (e) Training loss and valid	81
Figure 5.6 ROC curve of models on the test set. (a) ANN-5 (b) ANN-7 (c) ANN-9 (d) ANN-10	82
Figure 6.1 N-benzylpiperidines as AChE and BACE-1 inhibitors.....	90
Figure 6.2 Workflow of molecular generation tool	90
Figure 6.3 Interaction of N-benzylpiperidines with; PAS and CAS site of AChE and BACE-1.	124
Figure 6.4 Reaction scheme (I). TEA/DCM, 1- 5 °C, 1 hr (II). DIPEA/THF, reflux, 24hr	125
Figure 6.5 Lineweaver Burk double reciprocal plot of compounds (a) 72 and (b) 77. Dixon plot for compound (c) 72 and (d) 33 for Ki calculation.....	133
Figure 6.6 2D interaction diagram of ligands with AChE (PDB id- 4ey7). a) Compound 60, b) Compound 64, c) Compound 72, d) Compound 77, e) Compound 80 f) Compound 86.....	134

Figure 6.7 2D interaction diagram of ligands with BACE-1 (PDB id- 6eqm)..... 135

Figure 6.8 Effect of compounds 72 and 77 on A β ₁₋₄₂ aggregation. ^a p<0.05 vs. Control, ^bp<0.05 vs. 72(5 μ M), ^cp<0.05 vs. 72(10 μ M), ^dp<0.05 vs. 72(20 μ M), ^ep<0.05 vs. 77(5 μ M), ^fp<0.05 vs. 77 (10 μ M), ^gp<0.05 vs. 77(20 μ M), ^hp<0.05 vs. DNP(5 μ M), ⁱp<0.05 vs. DNP(10 μ M)..... 138

Figure 6.9 Acute oral toxicity study. Effects of the normal control group (A-D), Compound-72 (E-H) and Compound-77 (I-L) treatment on the Brain, Liver, Heart, and Kidney, respectively..... 140

Figure 6.10 Effect of compounds 72 and 77 on scopolamine-induced cognition and memory impairment. (a) Effect of compounds 72 and 77 on % spontaneous alterations. (b) Effect of compounds 72 and 77 on AChE activity (c) Effect of compounds 72 and 77 on ACh levels. ^ap<0.05 vs. control; ^bp<0.05 vs. SCO; ^cp<0.05 vs. Compound 72 (5 mg/kg); ^dp<0.05 vs. Compound 72 (10 mg/kg); ^ep<0.05 vs. compound 72 (20 mg/kg); ^fp<0.05 vs. Compound 77 (5 mg/kg); ^gp<0.05 vs. Compound 77 (10 mg/kg) One way ANOVA followed by Newman - Keuls posthoc test. [SCO-Scopolamine] 142

Figure 6.11 Protective effect of compounds 72, 77, and donepezil on A β ₁₋₄₂-induced memory deficits analyzed by the Morris water maze test. (a) Escape latency during the training trials in the MWM tests; (b) time spent in the platform quadrant in the probe trial ^ap< 0.05 vs. control and ^bp < 0.05 vs. A β ₁₋₄₂. One-way ANOVA followed by Newman - Keuls posthoc test..... 144

List of Tables

Table 1.1 FDA-approved medications to treat AD.....	10
Table 3.1 Clinical drug candidates as BACE-1 inhibitors.....	23
Table 3.2 Pearson correlation coefficient between selected molecular properties and BACE-1 inhibition.....	32
Table 3.3 Parameters and performance of classification model built by NB classifier.	34
Table 3.4 Parameters and performance of classification model built by kNN classifier	35
Table 3.5 Parameters and performance of classification model built by SVM classifier	36
Table 3.6 Parameters and performance of classification model built by RF classifier ..	36
Table 3.7 Parameters and performance of classification model built by XGB classifier	37
Table 3.8 Performance of 20 classification models on test set.....	39
Table 3.9 Top ten features from Mordred dataset with their feature importance values from RF classifier	44
Table 3.10 Top ten features from MACCS dataset with their feature importance values from RF classifier	45
Table 4.1 Performance of classification models on the training set	62
Table 4.2 Performance of classification models on the test set	62
Table 4.3 Performance of ML models on validation set.....	63
Table 4.4 Summary of reported properties for identified hits	64
Table 4.5 Summary of in-vitro and docking result of ligands with BACE-1 (PDB ID- 6EQM)	64
Table 5.1 Summary of the architecture of ANN model.....	78
Table 5.2 Summary of the architecture of LSTM Model	78

Table 5.3 Summary of the performance of ANN models on the Training set and Validation set.....	80
Table 5.4 Summary of the performance of LSTM models on the Training set and Validation set.....	80
Table 5.5 Summary of performance on the test set.....	80
Table 5.6 Accuracy of the TEMPO model and our best ANN-10 model	83
Table 5.7 Accuracy of BBB-score model and our best ANN-10 model.....	83
Table 6.1 Summary of docking studies of designed compounds with AChE and BACE-1	126
Table 6.2 Physicochemical properties and predicted toxicities of synthesized compounds	128
Table 6.3 <i>In-silico</i> ADME properties.....	129
Table 6.4 Inhibitory potencies of compounds against eeAChE, eqBuChE and hBCAE-1	130
Table 6.5 Propidium iodide displacement assay.	136
Table 6.6 Permeability P_e (10^{-6} cm s ⁻¹) data for selected potent compounds from the PAMPA-BBB assay along with their BBB Penetration prediction.	137
Table 6.7 Effect of Single-Dose Oral Administration of Compound 72 and Compound 77	139
Table 6.8 Effect of Oral Administration of Compound 72 and 77	139

List of abbreviations

Abbreviation	Full Form
3D	Three dimensional
ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
AI	Artificial intelligence
Aβ	Amyloid- β
APP	Amyloid precursor protein
AS	Anionic site
ATP	Adenosine triphosphate
AUC	Area under the curve
BBB	Blood-brain barrier permeability
BChE	Butyrylcholinesterase
BLAST	Basic local alignment search tool
CaMKII	Ca ⁺² /calmodulin dependent protein kinase II
CAT	Catalase
ChAT	Choline acetyl transferase
ChE	Cholinesterase
CNN	Convolutional neural network
CNS	Central nervous system
CT	Computed tomography
DNP	Donepezil
EAAT2	Excitatory amino acid transporter 2
EC	Enzyme classification
FN	False negative
FP	False positive
GAFF	Generalised amber force field
GSK3	Glycogen synthase kinase-3
iGluRs	ligand-gated ionotropic glutamate receptors
JNK3	c-Jun N-terminal kinase 3
KNN	K-nearest neighbors
LBDD	Ligand based drug design
LDA	Linear discriminant analysis
LGA	Lamarckian Genetic Algorithm
LR	Logistic regression
MACCS	Molecular access system
MD	Molecular dynamics
MEKK	Mitogen-activated Protein/ERK Kinase Kinases
ML	Machine learning
MLP	Multi-layer perceptron
MRI	Magnetic resonance imaging
MSME	Mini-Mental state exam
Nct	Nicestrin
NFT	Neurofibrillary tangle
NMDA	N-methyl D-aspartate
PAC	Passive-aggressive classifier

PAINS	Pan-assay interference compounds
PAM	Positive allosteric modulator
PAMPA	Parallel artificial membrane assay
PAS	Peripheral anionic site
PBL	Porcine brain lipid
PLIP	Protein ligand interaction profiler
PS1	Presenilin 1
PS2	Presenilin 2
QDA	quadratic discriminant analysis
QSAR	Quantitative structure-activity relationship
R_f	Retention factor
RF	Random forest
R_g	Radius of gyration
RMSD	Root mean square deviation
RMSF	Root mean square fluctuation
RO5	Lipinski rule of five
ROC	Receiver operation characteristic
ROS	Reactive oxygen species
RT	Room Temperature
SAR	Structure activity relationship
SASA	Solvent accessible surface area
SBDD	Structure-based drug design
SBVS	Structure based virtual screening
SCO	Scopolamine hydrobromide
SEM	Standard error of mean
SF	Scoring function
SOD	Superoxide dismutase
SVC	Support vector classifier
SVM	Support vector machine
SVR	Support vector regression
TI	Thermodynamic integration
TN	True negative
TP	True positive

Preface

Alzheimer's disease (AD), a progressive neurodegenerative disorder characterized by inexorable cognitive decline and memory impairment, represents a significant and growing public health concern. While existing interventions primarily focused on mitigating cholinergic dysfunction offer symptomatic relief, they fail to address the underlying pathophysiological processes. Recognizing the limitations of current approaches, researchers are delving into the intricate molecular pathways implicated in AD pathogenesis, paving the way for a paradigm shift towards multi-target-directed therapeutic strategies.

Chapter 1 initiates a comprehensive exploration of AD, encompassing its background, pathophysiology, and the current therapeutic landscape. Additionally, the various methodologies, such as Artificial intelligence (AI), that are involved in drug discovery and design are detailed.

Chapter 2: In this chapter, the objectives of the study and plan of work are mentioned.

Chapter 3: This chapter utilizes machine learning to predict potential BACE-1 inhibitors for AD. By analyzing molecular properties and applying algorithms like SVM and Random Forest, the chapter identifies promising candidates and key structural features associated with BACE-1 inhibition, contributing to the development of targeted AD treatments.

Chapter 4: This section outlines the development and application of an XGBoost-based machine learning model to screen an in-house database for potential BACE-1 inhibitors, a key target in AD treatment. The model utilizes PubChem fingerprints to identify promising candidates, which are then subjected to experimental validation for their inhibition activity.

Chapter 5: This section explores a novel approach for predicting Blood-Brain-Barrier (BBB) permeability of molecules using Natural Language Processing (NLP) and Deep Learning. It utilizes the B3DB database and extracts features from molecules via SELFIES and N-gram tokenization, converting them into numerical vectors. These features are then fed into various Deep Learning models like ANN and LSTM to predict BBB permeability. The best-performing model achieved high accuracy, suggesting its potential for early screening of drugs targeting the central nervous system.

Chapter 6: This section describes developing and evaluating multi-target directed ligands (MTDLs) based on *N*-benzylpiperidines for AD treatment. Utilizing suitable approaches, promising N-benzylpiperidine scaffolds are identified. Synthesis of derivatives with predicted enhanced multi-target activity against BACE-1, cholinesterases, and amyloid aggregation is followed by *in-vitro* and, for promising candidates, *in-vivo* efficacy evaluation in AD animal models.

Chapter 7: This chapter outlines the summary and conclusions of the research work undertaken.

Chapter 8: The references used to carry out the research work are presented in the chapter.

An appendix of additional supporting information, spectral data of representative compounds, and a list of publications from the course of the Ph.D. are included.