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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 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	Nicastrin
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
$\mathbf{R_f}$	Retention factor
RF	Random forest
Rg	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) is the most common form of dementia causing memory, behaviour and thinking impairment. Eventually, the symptoms become severe and make it difficult for a patient to carry out daily activities. According to the World Health Organization (WHO), one in every 85 individuals will have AD by 2050. The therapeutic targets of the disease include acetylcholinesterase (AChE), butyrylcholinesterase (BChE), β-secretase-1, glycogen synthase kinase 3β, monoamine oxidase B, matrix metalloproteases, N-methyl D-aspartate (NMDA) receptors, tau kinase etc.

Among the targets, inhibition of cholinesterase enzymes is still a major component of anti-AD therapy to provide symptomatic relief. The inhibition of AChE causes improvement in memory and cognition. However, AChE inhibitors produce cholinergic side effects and the therapeutic effect wear-off with the progression of the disease. Alternatively, the presence of a significant level of BChE in the latter stage of the disease and its inhibition causes improvement in memory and thus, makes it an attractive target. Machine learning (ML), structure-based drug design and ligand-based drug design are useful techniques in drug design. The research work presented in the thesis covers three-fold objectives. The first objective of the study is to design selective BChE inhibitors through ML/scaffold hopping. The ligands identified were synthesised, characterised and tested through various *in vitro* and *in vivo* tests. The second objective deals with the identification of the virtual hits and their binding modes. The third objective includes the development of *in silico* tools by using ML techniques for the identification of hits.

The work embodied in this thesis has been presented under the following chapters:

Chapter 1: The chapter provides an introduction to AD and deals with details regarding background, pathophysiology and available therapeutics for the treatment of AD. Further, the various approaches involved in drug design are also described.

Chapter 2: The chapter deals with the literature background related to targets involved in the cholinergic hypothesis. It also includes the field application of ML in drug discovery.

Chapter 3: In this chapter, the objectives of the study and plan of work are incorporated.

Chapter 4: The chapter deals with the development of selective BChE inhibitors using ML. It includes the methodology used for design, synthesis, characterisation, *in vitro*, *in silico* and *in vivo* evaluations of *sulfonamides* of *para-amino benzoic acid*, followed by a discussion.

Chapter 5: The development of selective BChE inhibitors using scaffold hopping is presented in the chapter. It describes the methodology used for design, synthesis, characterisation, *in vitro*, *in silico* and *in vivo* evaluations of *sulfonamides* of *phenylglycine*, followed by results and discussion.

Chapter 6: The chapter deals with *in silico* identification of the potential AChE inhibitors through computational techniques.

Chapter 7: The chapter includes the methodology and results obtained from *in silico* analysis of the binding mode of AVL-3288 with α7-nicotinic acetylcholine receptor.

Chapter 8: The chapter includes the details of the procedure followed and results of the development of the homology model, docking protocol and ML-based scoring function for identification of electric eel's AChE inhibitors.

Chapter 9: In this chapter, the detailed procedure of the development of the homology model, docking protocol and ML-based scoring function for the identification of horse's BChE inhibitors is presented. The chapter also includes results and discussion on the above.

Chapter 10: The chapter deals with the development of ML models for the prediction of inhibitors for the important targets of AD. The ML models are deployed in the form of a web application – AlzLeads.

Chapter 11: This chapter outlines the summary and conclusions of the research work undertaken.

Chapter 12: The references, used to carry out the research work, are presented in the chapter.

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

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CERTIFICATE

It is certified that the work contained in the thesis titled "**Implementation of Computational and Machine learning techniques for the development of *in silico* tools and identification of novel leads for the treatment of Alzheimer's Disease**" by **Mr. Ankit Ganeshpurkar** has been carried out under our supervision and that this work has not been submitted elsewhere for a degree.

It is further certified that the student has fulfilled all the requirements of Comprehensive Examination, Candidacy and SOTA for the award of Ph.D. Degree.

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DECLARATION BY THE CANDIDATE

I, **Ankit Ganeshpurkar**, certify that the work embodied in this Ph.D. thesis is my own bonafide work and carried out by me under the supervision of **Prof. Sushil K. Singh** and co-supervision of **Dr. Ashok Kumar** from **July, 2016 to September, 2021** at the **Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi.** The matter embodied in this Ph.D. thesis has not been submitted for the award of any other degree/diploma. I declare that I have faithfully acknowledged and given credit to the research workers wherever their works have been cited in my work in this thesis. I further declare that I have not willfully copied any other's work, paragraphs, text, data, results, etc. reported in the journals, books, magazines, reports, dissertations, theses, etc., or available at websites and have not included them in this Ph.D. thesis and have not cited as my own work.

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