List of Abbreviations

Abbreviations	Full Form
AD	Alzheimer’s disease
ATP	Adenosine triphosphate
ADP	Adenosine diphosphate
ADME	Absorption, Distribution, Metabolism, and Excretion
ADT	Agar Diffusion Test
BBB	Blood-Brain Barrier
$CHCl_3$	Chloroform
$CDCl_3$	Deuterated Chloroform
CC_{50}	Cytotoxic concentration required to kill 50% of the population
DL	Druglikeness
DCCD	N, N-Dicyclohexylcarbodiimide
DMF	Dimethylformamide
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
EPS	Extrapyramidal side-effects
EMEM	Eagle's Minimal Essential Medium
Et_2O	Diethyl ether
Et_3N	Triethylamine
FZ	Flumazinil
HTS	High Throughput Screening
HIV	Human Immunodeficiency Virus
HBA	Hydrogen Bond Acceptor
HBD	Hydrogen Bond Donor
HQNO	2-heptyl-4-hydroxyquinoline-N-oxide
IC_{50}	Inhibitory concentration required to kill 50% of the population
IMVs	Inverted Membrane Vesicles
K_2CO_3	Potassium carbonate

KH_2PO_4	Potassium dihydrogen phosphate
KOH	Potassium hydroxide
KI	Potassium iodide
MTT	3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-tetrazolium bromide
MeOH	Methanol
$MgCl_2$	Magnesium chloride
NMR	Nuclear Magnetic Resonance
NaCl	Sodium chloride
ODCB	1-2-dichlorobenzene
PMF	Proton Motive Force
PAMPA	Parallel Artificial Membrane Permeability Assay
PDB	Protein Data Bank
PBL	Porcine Brain Lipid
Pe	Permeability
RMSD	Root Mean Square Deviation
SI	Selectivity Index
SAR	Structure-activity relationship
SEM	Standard Error of the Mean
TGI	Total Growth Inhibition
TLC	Thin-Layer Chromatography
TSA	Total Surface Area
TPSA	Topological Polar Surface Area
THF	Tetrahydrofuran
US-FDA	United States- Food and Drug Administration
UV	Ultraviolet
WHO	World Health Organization
3D	Three-Dimensional
5-HT	5-hydroxytryptamine

List of Symbols

Symbols	Meaning
α	Alpha
β	Beta
δ	Delta
ε	Epsilon
ºC	Degree Celsius
Å	Angstrom
©	Copyright
g	Gram; Gravitational force
mg	Milligram
µg	Micro gram
ng	Nano gram
µM	Micro Mole
mmol	Milli Mole
mL	Milliliter
µL	Microliter
mV	Millivolt
h	Hour
s	Second; Singlet
nm	Nanometer
µm	Micrometer
mm	Millimeter
cm	Centimeter
ppm	Parts per million
rpm	Revolutions per minute
Kcal	Kilocalories
Hz	Hertz
MHz	Megahertz
J	Coupling constant
d	Doublet
m	Multiplet
dd	Doublet of doublet

m/z	Mass to charge ratio
%	Percent
pH	Potential of hydrogen
≤	Less than or equal
<	Less than
>	More than
±	Plus or minus

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Preface

Alzheimer's Disease (AD) is most common neurodegenerative disorder, which accounts for more than 80% of dementia cases worldwide in older people. It is characterized by deposition of amyloid β and neuro-fibrillary tangles. The disease leads to progressive loss of memory, functional ability to learn and is primarily characterized by the progressive loss of memory associated with other cognitive deficits. The global burden on the population suffering from AD was assessed to 44 million in 2015. This number is expected to double by 2030 and triple by 2050, if no effective treatment is in place. In a country like India, where approximately 41 % of the population is in the age group of 25 to 55 years, this needs to be seriously acknowledged and addressed.

Over the last few years, several targets of the disease have been identified. This include, but not limited to, Amyloid-β, Acetylcholinesterase (AChE), Butyrylcholinesterase (BuChE), β-secretase, γ-secretase, β-site APP cleaving enzyme-1 (BACE-1), NMDA receptors, Matrix metalloproteinases (MMPs), Neurofibrillary tangles *etc*.

Despite decades of study on the etiology of disease and also significant efforts by pharmaceutical industry to develop therapies, there is no effective treatment available to cure AD or to inhibit significantly its progression. However, there are four drugs viz. donepezil, galantamine, and rivastigmine, approved by USFDA, acting on cholinergic pathway and recently (2003) approved drug Memantine acting on NMDA receptor.

Considering the complex and multifactorial nature of disease, development of multifunctional ligands was considered a better option.

The present study is being divided into eight chapters. Chapter 1 deals with different types of neurodegenerative disorders, pathophysiology of AD and available treatments.

Chapter 2 provides insight in the literature reports related to the work from scholarly articles which forms the basis of the study. The section summarizes drugable targets for the treatment of AD and agonists or antagonists developed in the recent times. The mechanism of action of inhibitors and the molecular features of the receptors are also discussed in detail. The structural requirements for the agonistic or antagonistic action are explained along with structure-activity relationship (SAR) of the molecules. Chapter 3 includes the hypothesis of the study, and rationale of the work. It also incorporates the plan of study that helped to accomplish the research envisaged.

Chapter 4 deals with the rationale for syntheses of novel piperazinediones, obtained from *in-silico* studies and data mining. The development of pharmacophore was based on the hybrid drug design considering donepezil and PQ912, a chemical moiety in phase II of clinical trial. The designed hybrid pharmacophore was used for extensive data mining by using zinc and asinex databank which yielded over thousand compounds having desired pharmacophoric pattern. These data were further subjected to different filters viz. docking, *in-silico* BBB permeability and finally toxicity filter. The fully optimized molecules thus obtained were promoted to synthesis, *in-vitro* enzyme assays and *in-vivo* studies.. The potent molecules obtained from *in-vitro* study were further investigated for neuroprotection ability in MC 65 cells and antioxidant assay. Most potent compounds were selected for *in-vivo* studies in AD animal models to evaluate the working memory and learning response.

A few, piperazinediones developed also showed anxiolytic property which was further assessed and constitute chapter 5 *i.e.* biological profiling of piperazinediones for the management of anxiety associated with AD. In this, behavioral study on animal model was performed which was followed by estimation of neurotransmitter level in brain.

The detailed mode of action of compounds was also assessed by Flumazenil antagonism on anxiolytic activity of compound.

In the next chapter (Chapter 6), synthesis of adamantly analogous as NMDA antagonists is includes. Memantine, an approved NMDA antagonist, was retained in the final structure and further optimization was done using the fragments of hits obtained from virtual screening. Triazole moiety, reported to exhibit neuroprotective effect was incorporated in some of the compounds. The synthesized compounds were subjected to *in-vitro* MMP-2 inhibition assay, inhibition assay of metal-induced $A\beta_{1-42}$ aggregation, confocal fluorescence imaging, antioxidant activity (DPPH assay), MC65 neuroprotection assay, and electrophysiology on different glutamate and glycine-mediated NMDA receptors and results were analyzed.

Another series of novel compounds synthesized, are presented in chapter 7. This includes quinoline analogues as potent inhibitors of AChE, BuChE, and BACE-1. Fragments from different bioactive molecules *viz* donepezil, LY2811376, MK-8631 were taken and docked against AChE, BACE1. These fragments were further developed by fragment-based techniques. Quinolines, found to be active against AChE and $A\beta_{1-42}$ in our earlier study and piperazines, reported in many CNS active drugs were used as fragments. The later is also reported to improve the water solubility of small synthetic molecules without altering its BBB permeability. Linkers, substituted cyclohexane-1-amine or substituted benzyl-1-amine towards different amino acid residues were used to increase the approach of the tail group. The synthesized compounds were screened for *in-vitro* AChE, and BuChE inhibition, BACE1 inhibition, neuroprotection on MC65 cell lines, PAMPA assay, and pharmacokinetic studies on male Wistar rats.

The summary and conclusions of the study are included in chapter 8, which is followed by appendix and references.