

## Table of Contents

<b>S. No.</b>	<b>Description</b>	<b>Page No.</b>
a)	LIST OF ABBREVIATIONS	i
b)	LIST OF SYMBOLS	iii
c)	LIST OF TABLES	v
d)	LIST OF FIGURES	vii
e)	PREFACE	xi
<b>1</b>	<b>Chapter 1: Introduction</b>	<b>1</b>
1.1	Neurodegenerative disorders	1
1.1.1	Alzheimer's disease	1
1.1.2	Parkinson's disease (PD)	2
1.1.3	Amyotrophic lateral sclerosis (ALS)	2
1.1.4	Huntington's disease	2
1.1.5	Frontotemporal dementia (FTD)	2
1.2	Pathophysiology of Alzheimer's disease	3
1.2.1	Role of amyloid precursor protein (APP)	3
1.2.2	Role of beta-secretase (BACE)	4
1.2.3	Role of amyloid beta (A $\beta$ )	5
1.2.4	Role of glutamate	5
1.2.5	Acetylcholine	6
1.2.6	Role of NMDA receptor	7
1.2.7	Role of Neuropeptides	8
1.2.8	Neuroprotective role of estrogen in Alzheimer's disease	8
1.3	Stages of Alzheimer's disease	9
1.3.1	Early stage	9
1.3.2	Middle stage	11
1.3.3	Late stage	11
1.4	Treatment of Alzheimer's disease	12
1.4.1	Pharmacological treatment	12
1.4.1.1	Precursors of acetylcholine synthesis	12
1.4.1.2	Acetylcholinesterase (AChE) inhibitors	12
1.4.1.3	NMDA receptor antagonist	13

1.4.1.4	Matrix metalloproteinases (MMP 2 & 9) inhibitors	14
1.4.2	Non-pharmacological therapy for Alzheimer's disease	14
1.4.2.1	Vagus nerve stimulation	15
1.4.2.2	Deep brain stimulation	15
<b>2</b>	<b>Chapter 2: Literature Review</b>	<b>16</b>
2.1	Secretases	16
2.1.1	$\gamma$ - Secretase inhibitors	16
2.1.1.2	$\gamma$ - Secretase modulators (GSMS)	27
2.1.2	$\beta$ -Secretase inhibitor	41
2.1.3	$\alpha$ -Secretase	46
2.1.4	Sirtuins	49
2.1.4.1	SIRT2 inhibitors	51
2.1.4.2	SIRT1 enhancer	53
2.1.5	Caspases	54
2.1.6	Glycogen synthase kinase-3 (GSK3)	55
2.4.1	GSK-3 inhibitors	57
2.2	Tau based therapy: A paradigm shift	57
2.3	Calpains	59
2.4.	Acetylcholinesterase	62
2.4.1	Acetylcholinesterase inhibitors	63
2.5	Noncompetitive N-methyl-D-aspartate antagonists	68
2.6	New mechanistic rationales for drug discovery	68
2.6.1	Autophagy enhancer	68
2.7	Miscellaneous	69
2.7.1	Metal chelators	69
2.7.2	Neurotrophic agents and their mimetics	71
2.7.3	Receptor for advanced glycation end-products (RAGE) inhibitors	73
2.7.4	Phosphodiesterase (PDE) inhibitors	73
2.7.5	Apolipoprotein	74
2.7.6	Biomarkers	75
2.7.7	Non peptidic anti aggregate compounds	76
2.7.8	Hormones	76

2.7.9	Repurposing drugs	77
<b>3</b>	<b>Chapter 3: Objective, Rational and Plan of Work</b>	<b>79</b>
3.1	Objective and rationale	79
3.2	Plan of study	80
<b>4</b>	<b>Chapter 4: Multitargeted Novel Piperazindiones for Management of AD</b>	<b>82</b>
4.1	Experimental work	82
4.1.1	Rationale of drug design & <i>in-silico</i> optimization	82
4.1.2	Virtual screening of commercial and non-commercial databases	82
4.1.3	Extra precision molecular docking	83
4.1.4	Molecular property, BBB permeability and toxicity prediction	83
4.1.5	Synthesis and characterization	83
4.1.5.1	Synthesis of aromatic piperazine derivatives	84
4.1.5.2	Aliphatic piperazine derivatives	85
4.1.5.3	General procedure for the synthesis of substituted sulfonamides using different aminoacids (14-21 and 22-35)	85
4.1.5.4	General procedure for synthesis of 1,4-Bis(substituted-phenylsulfonyl)3, 6 diphenyl/benzyl piperazine-2,5-dione derivatives (36-57 and 62, 63)	87
4.1.6	Biological profiling	100
4.1.6.1	<i>In-vitro</i> AChE and BuChE inhibition assays	100
4.1.6.2	AChE enzyme kinetics	100
4.1.6.3	<i>In-vitro</i> MMP-2 inhibition assay	101
4.1.6.4	MMP-2 enzyme kinetics	102
4.1.6.5	<i>In-vitro</i> blood-brain barrier permeation assay	102
4.1.6.6	MC65 neuroprotection assay	103
4.1.6.7	A $\beta$ <sub>1-42</sub> inhibition assay	103
4.1.6.8	Antioxidant activity (DPPH assay)	104
4.1.6.9	<i>In-vitro</i> metal chelation assay	105
4.1.6.10	Scopolamine induced amnesia model	105
4.1.6.11	Evaluation of memory function; Y-Maze Test	107
4.1.6.12	Passive avoidance test	107
4.1.6.13	Mitochondrial membrane potential	108

4.1.6.14	Neurochemical analysis	109
4.2	Result & discussion	109
4.2.1	Rational of drug design and discovery	109
4.2.2	Chemistry	110
4.2.3	<i>In-vitro</i> biological evaluation	111
4.1.6	Blood-brain barrier permeation assay (PAMPA)	115
4.1.7	Neuroprotection studies	120
4.1.8	AChE-induced A $\beta$ <sub>1-42</sub> aggregation assay	122
4.1.9	Antioxidant activity evaluation	124
4.1.10	<i>In-vitro</i> metal chelation assay	125
4.1.11	Behavioral studies	126
4.1.12	Y-Maze test	129
4.1.13	Passive avoidance test	131
4.1.14	Mitochondrial membrane potential in brain region	132
4.3	Conclusions	134
<b>5</b>	<b>Chapter 5 Biological Profiling of Piperazinediones for the Management of Anxiety associated with AD</b>	<b>136</b>
5.1	Experimental work	136
5.1.1	Background of the proposed study	136
5.1.2	Animals	136
5.1.3	Materials	137
5.1.4	Experimental protocol and drug administration	137
5.1.5	Elevated plus-maze test	138
5.1.6	Open field test	139
5.1.7	Hole board	139
5.1.8	Estimation of serotonin	139
5.1.9	Statistical analysis	140
5.2	Result & discussion	140
5.2.1	Elevated plus-maze test	140
5.2.2	Open field test	142
5.2.3	Hole board	142
5.2.4	Amygdalar monoamines and their metabolites	143
5.2.5	Flumazenil antagonism on anxiolytic activity in EPM	143

5.2.6	Flumazenil antagonism on anxiolytic activity in OFT	146
5.2.7	Flumazenil antagonism on anxiolytic activity in hole board	146
5.2.8	Sedative effect of diazepam and compound <b>52</b> in OFT and EPM tests	149
5.3	Discussion	150
5.4	Conclusion	153
<b>6</b>	<b>Chapter 6: Development of Adamantyl Analogy as NMDA Receptor Antagonist for Treatment of AD</b>	<b>154</b>
6.1	Development of adamantly analogous as NMDA receptor antagonist	154
6.2	Rationale of drug design & in-silico optimization	156
6.3	Experimental work	157
6.3.1	Pharmacophore development and virtual screening	157
6.3.2	Drug-likeness, BBB permeability and toxicity filtration	158
6.3.3	Molecular docking	158
6.3.4	Molecular dynamics & simulation	160
6.3.5	Synthesis and characterization	160
6.3.5.1	Synthesis of biphenyl analogues of adamantylamine	161
6.3.5.2	Synthesis of biphenyl analogues of adamantylamine	161
6.3.6	<i>In-vitro</i> MMP-2 inhibition assay	195
6.3.7	Inhibition assay of metal induced A $\beta$ 1-42 aggregation	195
6.3.8	Confocal fluorescence imaging	195
6.3.9	Antioxidant Activity (DPPH assay)	196
6.3.10	MC65 neuroprotection assay	196
6.3.11	Evaluation of Adamantyl analogy on different subtypes of glutamate and glycine mediated NMDA receptors	196
6.4	Result & discussion	197
6.4.1	Pharmacophore development and virtual screening	197
6.4.2	Drug-likeness, ADME and toxicity Prediction	199
6.4.3	Docking studies	199
6.4.4	<i>In-vitro</i> MMP-2 inhibition assay	202
6.4.5	Inhibition assay of metal induced A $\beta$ 1-42 aggregation and confocal fluorescence imaging	203

6.4.6	Antioxidant activity (DPPH assay)	207
6.4.7	Electrophysiological study on oocyte of Xenopus laevis	207
6.4.8	MC65 neuroprotection assay	208
6.4.9	Molecular dynamics simulation	208
6.5	Conclusion	211
<b>7</b>	<b>Chapter 7: Development of Quinoline Analogous as Anti-Alzheimer agent</b>	<b>213</b>
7.1	Development of quinolines as inhibitors of acetylcholinesterase (AChE) and $\beta$ -site APP cleaving enzyme 1 (BACE1)	213
7.2	Experimental work	215
7.2.1	Docking study	215
7.2.2	Synthesis and characterization	215
7.2.2.1	Synthesis of quinolinyl alkyl piperazine derivatives	216
7.2.2.2	Synthesis of quinolinyl piperazine alkyl derivatives	217
7.2.2.3	General procedure for the synthesis of quinolinyl alkyl chloride from 3, 6 and 8 amino quinolines	219
7.2.2.4	General procedure for the synthesis of quinolinyl piperazine	220
7.2.2.5	General procedure for the synthesis of 3/6/8-(piperazin-1-yl) quinoline by using 3, 6 and 8 amino quinolines	220
7.2.2.6	General procedure for the synthesis of quinolinyl piperazine alkyl chloride	220
7.2.2.7	General procedure for the synthesis of aromatic quinolinyl piperazine derivatives	221
7.2.2.8	General procedure for the synthesis of aliphatic quinolinyl piperazine derivatives	221
7.2.3	<i>In-vitro</i> AChE, and BuChE inhibition assays	261
7.2.4	<i>In-vitro</i> $\beta$ -site APP cleaving enzyme 1 (BACE1) inhibition assay	261
7.2.5	PAMPA assay	262
7.2.6	Pharmacokinetic studies	262
7.2.7	Cell line based neuroprotection studies	263
7.3	Results & discussion	263
7.3.1	Docking study	263

7.3.2	<i>In-vitro</i> AChE, and BuChE inhibition assays	266
7.3.3	<i>In-vivo</i> β-site APP cleaving enzyme 1 (BACE1) inhibition assay	266
7.3.4	PAMPA assay	270
7.3.5	ADME prediction	270
7.3.6	Cell line based neuroprotection studies	271
7.4	Conclusion	272
	<b>Summary and Conclusions</b>	<b>273</b>
	<b>Appendix</b>	<b>277</b>
	<b>References</b>	<b>287</b>