

Chapters	Page
No.	
1 Introduction.....	1
1.1 Alzheimer's disease	1
1.2 Statistics of AD	3
1.3 Pathophysiology of AD.....	3
1.3.1 Role of acetyl and butyrylcholines in AD.....	3
1.3.2 Role of Oxidative Stress in AD	5
1.3.3 Role of Metals in AD.....	6
1.3.4 Role of amyloid beta (A β) and tau proteins in AD.....	8
1.3.5 Role of β -secretase (BACE) in AD.....	9
1.3.6 Role of NLRP3 Inflammasome in AD.....	11
1.4 Current Drug Targets for AD	12
1.4.1 Cholinesterase enzymes as target in AD treatment.....	13
1.4.2 NMDA receptor in AD	15
1.4.3 Monoclonal antibodies targeting Amyloid beta (A β aggregates).....	16
2 Literature Review.....	21
2.1 Current treatments of AD.....	21
2.1.1 Cholinesterase inhibitors.....	21
2.1.2 NMDA receptor antagonist.....	23
2.2 Antioxidant therapy for the treatment of AD	23
2.3 Metal (iron) chelators in a clinical trial for the treatment of AD	25
2.4 Monoclonal antibodies in AD treatment	27
2.5 Role of ferulic acid in AD treatment	27
2.5.1 Ferulic acid in AD: <i>In-vitro</i> studies	28
2.5.2 Ferulic acid in AD: <i>In-vivo</i> studies	29
2.5.3 FA in clinical trials.....	30
2.6 Ferulic acid hybrids with their neuroprotective effects.....	31

3	Objective, Rationale, and Plan of Work	55
3.1	Objective and Rationale	56
3.2	Plan of Work	59
3.3	Synthetic Scheme derivatives for the synthesis of ferulic acid derivatives	60
4	Results and Discussion	67
4.1	Rational behind the design of FA hybrid analogs	67
4.2	Chemistry involved in the first series (novel ferulic acid) derivatives	69
4.3	Biological evaluation of the first series (novel ferulic acid) derivatives.....	69
4.3.1	<i>In-vitro</i> inhibition studies of <i>hAChE</i> and <i>eqBChE</i>	69
4.3.2	Enzyme kinetics studies with compound 12o	74
4.3.3	In-silico study with lead compound 12o	76
4.3.3.1	Molecular docking studies with 12o	69
4.3.3.2	Molecular dynamics studies with lead molecule 12o	72
4.3.4	<i>In-vitro</i> -antioxidant property evaluation of 12o	81
4.3.5	Measurement of propidium iodide displacement from the peripheral	84
4.3.6	<i>In-vitro</i> blood-brain barrier permeation assay:	85
4.3.7	Evaluation of metal-chelating properties of 12o	86
4.3.8	Modulation of self and metal-induced A β_{1-42} aggregation by 12o	88
4.3.9	Cell based study on PC12	89
4.3.9.1	Cell cytotoxicity assessment of 12o against PC12	82
4.3.9.2	Assessment of neuroprotective activity against H ₂ O ₂ -induced oxidative.....	84
4.3.10	Evaluation of lead compounds against NLRP3 inflammasome	92
4.3.10.1	Evaluation of 12o against ROS and mitochondrial membrane potential....	85
4.3.10.2	Evaluate 12o against NLRP3 inflammasome and NF- κ B expression.....	88
4.3.11	Evaluation of 12o in transgenic <i>Drosophila</i> model of AD.	98
4.3.11.1	Therapeutic effects of 12o and DPZ on OregonR+ an AD model of <i>Drosophila</i>	

4.3.11.2	Effect of 12 on mitochondrial and total cellular ROS and oxidative stress .	92
4.3.12	<i>In-vivo</i> evaluation of 12o	102
4.3.12.1.	<i>In-vivo</i> acute toxicity and hepatotoxicity studies with 12o	95
4.3.12.2.	Assessment of <i>in vivo</i> efficacy of 12o in scopolamine-induced cognitive	96
4.3.13	<i>Ex-vivo</i> estimation of AChE and BChE.....	105
4.4	Rational behind the design of the Second series of FA hybrid analogs.....	109
4.5	Chemistry involved in the second series (ferulic acid-piperazine acetamide)...	112
4.6	Biological evaluation of the second series of compounds	113
4.6.1	<i>In-vitro</i> inhibition studies of <i>h</i> AChE and <i>eq</i> BChE.....	113
4.6.2	Determination of enzyme kinetics of 24a against AChE/BChE.....	117
4.6.3	Determination of antioxidant activity of 24a	118
4.6.4	<i>In-silico</i> studies with compound 24a	120
4.6.4.1	Molecular docking study with 24a	111
4.6.4.2	molecular dynamics studies with 24a	112
4.6.5	Evaluation of PAS binding activity through propidium iodide.....	123
4.6.6	Measurement of metal-chelating properties of 24a	124
4.6.7	Inhibition of self and metal-induced A β ₁₋₄₂ aggregation by 24a	126
4.6.8	Cell cytotoxicity assay of compound 24a on PC12 cells.....	127
4.6.9	Evaluation of <i>In-vitro</i> blood-brain barrier permeability of 24a	128
4.6.10	Evaluation of 24a in NLRP3 Model	129
4.6.10.1	Effect of 24a on proliferation and cytotoxicity caused by LPS and ATP ..	120
4.6.10.2	Effect of 24a on NLRP3 signaling cascade and microglial activation.....	121
4.6.11	Evaluation of compound 24a in transgenic drosophila model of AD.	133
4.6.11.1	Therapeutic efficacy of 24a and DPZ on OregonR+ an AD model.....	123
4.6.11.2	Effect of 24a on mitochondrial, cellular ROS, and oxidative stress	124
4.6.12	<i>In-vivo</i> evaluation of 24a	137
4.6.12.1	Acute toxicity studies of 24a	127
4.6.12.2	Determination of <i>in-vivo</i> efficacy 24a to ameliorate spatial and learning.	128

4.6.13	<i>Ex-Vivo</i> and biochemical Analysis of neurotransmitters.....	140
5	Experimental work.....	145
5.1	Chemistry.....	145
5.1.1	General procedure for the synthesis of intermediate 2a-2c.....	145
5.1.2	Synthesis of intermediate 3a-3c.....	146
5.1.3	Synthesis of intermediate 4a-4c.....	147
5.1.4	General procedure for the synthesis of target compounds 5a-5c.....	148
5.1.5	General procedure for the preparation of intermediate 7a-7b and 10a-10o	149
5.1.6	General procedure for the preparation of intermediate 8a-8b and 11a-11o	150
5.1.7	General procedure for the preparation of targets 9a-9f and 12a- 12o	150
5.1.8	General procedure for the synthesis of 14 and 15.....	162
5.1.9	General procedure for the synthesis of intermediate 17a-17m and 20a-20f	163
5.1.10	General procedure for synthesis target compound 18a-18m and 21a-21f.	164
5.1.11	General procedure for the synthesis of intermediate 23.....	174
5.1.12	General procedure for the synthesis of target compound 24a	174
5.2	Biological Evaluation.....	175
5.2.1	In Vitro cholinesterase enzyme inhibition Assays.....	175
5.2.2	Enzyme kinetic assay of lead compound 12o and 24a	176
5.2.3	Molecular docking studies of 12o , EJMC-4e , 24a and DPZ	176
5.2.4	Molecular dynamics:.....	177
5.2.5	DPPH Assay.....	178
5.2.6	PAS binding assay.....	178
5.2.7	Blood-brain barrier (BBB) permeability assay:.....	179
5.2.8	Metal chelation study with 12o	179
5.2.9	Metal chelation study with 24a	180
5.2.10	A β_{1-42} peptide inhibition studies of compounds 12o and 24a	181

5.2.11	Confocal microscopy of compound 12o	181
5.2.12	Cell culture.....	182
5.2.13	Culture and treatment of cells	183
5.2.14	Fly husbandry and culture.....	185
5.2.15	Biological evaluation using <i>In-vivo</i> animal model	187
6	Summary and Conclusions	195
	References.....	201
	Appendix.....	213
	List of Publications.....	219