

Table of Contents

S. No	Description	Page No.
a)	LIST OF ABBREVIATIONS	i
b)	LIST OF SYMBOLS	v
c)	LIST OF TABLES	vii
d)	LIST OF FIGURES	ix
e)	PREFACE	xi
1	Chapter 1: Introduction	1
1.1	Tuberculosis: An Overview	1
1.2	Geographical Distribution of TB	2
1.3	TB in India	2
1.4	Transmission of TB	3
1.5	Pathogenesis of TB	3
1.6	Latent Tuberculosis	4
1.7	Current TB Therapy	4
1.8	WHO Classification of TB Drugs	6
1.9	Treatment Failure	7
1.9.1	Patients Related Factors	7
1.9.2	Doctors Related Factors	7
1.9.3	Drugs Related Factors	8
1.10	Drug Discovery and Development Pipeline	8
1.10.1	Clinical Development	8
1.10.2	Preclinical Development	8
1.10.3	Lead Optimization	9
1.10.4	Hit to Lead/ Lead Generation	9
2	Chapter 2: Literature Review	11
2.1	Why New Antitubercular Drugs?	11

2.2	Why Phenothiazine Scaffold Against Tuberculosis?	12
2.2.1	Repurposing of Psychotropic Phenothiazine Drugs	13
2.2.2	Phenothiazine Derivatives Possessing Antitubercular Efficacy	14
2.2.3	Structure-activity Relationship of Reported Phenothiazines	17
2.3	Why Carbazole Scaffold Against Tuberculosis?	21
2.3.1	Marketed and Late-Stage Developmental Drugs Containing Carbazole Scaffold	22
2.3.2	Carbazole Alkaloids Possessing Antitubercular Efficacy	23
2.3.3	Synthetic Carbazole Derivatives Possessing Antitubercular Efficacy	24
2.3.4	Structure-activity Relationship of Reported Carbazoles	29
2.4	Essential Components in Respiratory Production of ATP	34
2.4.1	Type-2 NADH Dehydrogenase (NDH-2)	35
2.4.2	ATP Synthase	40
2.5	NDH-2 and ATP Synthase: Vulnerable Targets in Latent TB	42
3	Chapter 3: Rationale, Objective and Plan of Work	43
3.1	Rationale and Objective	43
3.2	Plan of Study	44
4	Chapter 4: Experimental Work	47
4.1	Homology Modeling	47
4.2	Off-target Virtual Screening and Filtering of Designed Molecules	47
4.3	Virtual Screening of ZINC Database Molecules	48
4.4	Superimposition of Protein Structures of NDH-2 From Different Species	48
4.5	Alignment of Amino Acid Sequence of Selected ATP Synthase c-subunits	48
4.6	Extra Precision Molecular Docking	49
4.7	Molecular Property and Toxicity Prediction	49
4.8	Synthesis and Characterization	49
4.8.1	Synthesis of Phenothiazine Derivatives	50

4.8.2	Synthesis of Carbazole Derivatives	52
4.8.3	Synthesis of Biphenyl Derivatives	54
4.9	Biological Profiling	55
4.9.1	Antitubercular Screening	55
4.9.2	Antibacterial Screening	56
4.9.3	Blood Brain Barrier (BBB) Permeability Screening	57
4.9.4	<i>In-vitro</i> Cytotoxicity Screening	58
4.9.5	Type-2 NADH Dehydrogenase (NDH-2) Inhibition Screening	58
4.9.6	Mycobacterial ATP Synthase Inhibition Screening	59
5	Chapter 5: Results and Discussion	61
5.1	Section 1: Preliminary <i>In-silico</i> Studies	61
5.1.1	Off-target Virtual Screening and Filtering of Designed Molecules	61
5.1.2	Preliminary <i>In-silico</i> Study against NDH-2	64
5.1.3	Preliminary <i>In-silico</i> Study against ATP Synthase	66
5.2	Section 2: Molecular Docking, Synthesis, Characterization and Biological Profiling of Phenothiazine derivatives	69
5.2.1	Extra-precision Molecular Docking	69
5.2.2	Molecular Property and Toxicity Prediction	69
5.2.3	Synthesis and Characterization	73
5.2.4	Antitubercular Screening	84
5.2.5	Antibacterial Screening	85
5.2.6	BBB Permeability Screening	85
5.2.7	<i>In-vitro</i> Cytotoxicity Screening	87
5.2.8	NDH-2 Inhibitory Screening	89
5.3	Section 3: Molecular Docking, Synthesis, Characterization and Biological Profiling of Carbazole derivatives	91
5.3.1	Extra-precision Molecular Docking	91
5.3.2	Molecular Property and Toxicity Prediction	91

5.3.3	Synthesis and Characterization	95
5.3.4	Antitubercular Screening	106
5.3.5	Antibacterial Screening	107
5.3.6	BBB Permeability Screening	109
5.3.7	<i>In-vitro</i> Cytotoxicity Screening	109
5.3.8	NDH-2 Inhibitory Screening	111
5.4	Section 4: Molecular Docking, Synthesis, Characterization and Biological Profiling of Biphenyl Derivatives	113
5.4.1	Extra-precision Molecular Docking	113
5.4.2	Molecular Property and Toxicity Prediction	115
5.4.3	Synthesis and Characterization	117
5.4.4	Antitubercular Screening	126
5.4.5	Antibacterial Screening	127
5.4.6	BBB Permeability Screening	129
5.4.7	<i>In-vitro</i> Cytotoxicity Screening	129
5.4.8	NDH-2 Inhibitory Screening	131
5.5	Section 5: ATP Synthase Inhibition Study	133
5.5.1	Extra-precision Molecular Docking	133
5.5.2	<i>In-vitro</i> ATP Synthase Inhibition Assay	135
6	Chapter 6: Summary and Conclusion	137
7	Chapter 7: References	143