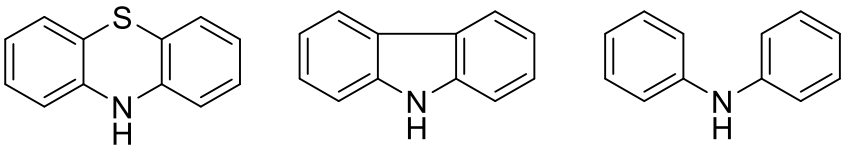
Preface

Tuberculosis (TB) is a curse on human race. It is the most fatal among all infectious diseases of the world. Livelihood of people in India is found to be greatly affected by the deadly disease. The burden of TB continues unabated with emergence of drug resistant cases. It could be due to the limitations associated with the existing drugs. To tackle the menace of this complex disease, development of new medications is extremely needed. There is renewed interest in repurposing the known drugs to treat new indications, due to involvement of less money and time.

Several attempts were made to repurpose the neuroleptic phenothiazine drugs *viz.* chlorpromazine, thioridazine and trifluoperazine to treat TB. Chlorpromazine has been reported for potent antitubercular activity, but the associated antipsychotic activity restricted its clinical use. Novel phenothiazine (i), carbazole (ii) and biphenyl (iii) derivatives having structural similarity with chlorpromazine were designed by removing/ modifying the group/ ring/ pharmacophore essential in producing antipsychotic activity, in an attempt to reduce the associated side effects, while improving the antitubercular activity.



(i) (ii) (iii)

The present study is being divided into seven chapters. Chapter 1 deals global incidence, transmission, and pathogenesis of TB, followed by treatment regimen, treatment failure and drug discovery pipeline against TB. Chapter 2 provides insight on published information related to the work from scholarly articles. It forms the basis of this thesis work. Some literature evidences on phenothiazine drugs and phenothiazine

derivatives as antitubercular leads, carbazole alkaloids and synthetic derivatives as antitubercular leads, components of respiratory chain in *M. tuberculosis*, role of two essential enzymes *viz.* Type-2 NADH dehydrogenase (NDH-2) and ATP synthase in respiratory production of ATP are included. Chapter 3 discusses the hypothesis of the study, and rationale for the design of phenothiazine, carbazole and biphenyl class of compounds for antitubercular activity. It also includes the plan of study that helped to accomplish the research envisaged. Complete experimental procedure of the thesis work is detailed in chapter 4. It elaborates the procedure involved in off-target virtual screening, homology modelling, molecular docking, synthesis, purification, antitubercular, antibacterial, blood-brain barrier permeability, *in-vitro* mammalian cell cytotoxicity, type-2 NADH dehydrogenase and ATP synthase inhibition screenings. Experimental results of the study are presented and discussed in chapter 5 of the thesis. The chapter is further subdivided into 5 sections. The first section encompasses the results of preliminary *in-silico* screening *viz.* off-target virtual screening and filtering, homology modelling, superimposition of proteins and alignment of amino acid sequences. The second section deals with spectral elucidation of synthesized phenothiazine derivatives, and their molecular docking and biological screening results *viz.* antitubercular, antibacterial, blood-brain barrier permeability, *in-vitro* mammalian cell cytotoxicity, and type-2 NADH dehydrogenase inhibition. The section three deals with spectral elucidation of synthesized carbazole derivatives, and their molecular docking and biological screening results *viz.* antitubercular, antibacterial, blood-brain barrier permeability, *in-vitro* mammalian cell cytotoxicity, and type-2 NADH dehydrogenase inhibition. The section four deals with spectral elucidation of synthesized biphenyl derivatives, and their molecular docking and biological screening results *viz.* antitubercular, antibacterial, blood-brain barrier permeability, *in-vitro*

mammalian cell cytotoxicity, and type-2 NADH dehydrogenase inhibition. The final section of chapter 5, includes the results of *in-silico* and *in-vitro* ATP synthase inhibition screening of all phenothiazine, carbazole and biphenyl compounds. A brief summary of salient findings from the research envisaged and scope for further work are included in the penultimate chapter of the thesis. A consolidated list of references cited in the text of the thesis is included in final chapter of the thesis.