Motivation

Looking into the WHO report-2012, there is no ambiguity that Tuberculosis needs urgent attention from researchers to discover novel antitubercular agents which can combat all forms of TB through a flawless mechanism of action.

From the review of literature, it is clear that the FAS II system involved in the mycolic acid biosynthesis of Mycobacterial cell wall is the most promising target for discovery of new antitubercular agents. Absence of this group of enzymes in human propelled us to choose them as the target for our study. Among the FAS II pool of enzymes, Enoyl acyl carrier protein reductase (ENR) is targeted by Isoniazid. Hence, a lot of study has been done to explore the structural biology of Mtb ENR. In recent times, many reports have been published on the design of novel antitubercular agents targeting Mtb ENR. We also observed that the reported antitubercular agents targeting Mtb ENR lack drug like features and properties. Hence, none of them have reached the clinical trial till date. Thus we took it as a challenge to explore Mycobacterial ENR inhibitors in our antitubercular research programme.

Label extension strategy on antibacterial agent Triclosan (5-chloro-2-(2,4-dichlorophenoxy) phenol) revealed that, it also binds with the Mtb ENR to display MIC at 12.5 µg/mL against *Mycobacterium tuberculosis* H₃₇Rv. Literature reports also suggested that, diphenyl ether analogues unlike Isoniazid does not need any kind activation before binding to the receptor. Hence this class of antitubercular agents is considered to be effective against drug resistant tuberculosis. However, diphenyl ethers can not be administered in vivo for their nonselectivity and high lipophilicity. Low solubility and metabolic instability are also reported to be other major drawbacks of this class of compounds. Although there are many reports published on promising antitubercular activity of diphenyl ether derivatives but to our knowledge improvement of its druggability has so far escaped serious attention from researchers. Our literature survey suggested that intravenous drugs are not the first choice for the treatment of tuberculosis. As orally administered drugs need to have wide spectrum of aqueous solubility, it is a big challenge to decrease the lipophilicity of Diphenyl ether moiety to make them orally bioavailable without compromising their antitubercular potential.

In the course of research aimed at discovery of promising antitubercular agents, novel diphenyl ether derivatives have been synthesized in our lab with significant MIC against *Mycobacterium tuberculosis* H₃₇Rv. Encouraged with our previous experience with diphenyl ether scaffold and subsequent literature reports on antitubercular potential of related compounds, we decided to continue this research work further to develop diphenyl ether
derivatives as third generation antitubercular agents without compromising its safety profile and druggability. Another purpose of this research work is to get relevant information on the structural requirement of diphenyl ether scaffold to improve its antitubercular potential.

**Objectives**

The research program described here, aimed at computer assisted design, synthesis and biological evaluation of novel diphenyl ether based antmycobacterial agents. The specific objectives are illustrated below:

- To design diphenyl ether derivatives using molecular docking technique.
- To synthesize the designed NCEs through facile synthetic route.
- To determine antitubercular activity of the synthesized compounds (MIC) against *Mycobacterium tuberculosis* H37Rv.
- To assess cell cytotoxicity (CC50) and in vitro hepatotoxicity of the compounds.
- To determine the MIC of compounds having Selective index ≥ 10, against Isoniazid resistant and Multi Drug Resistant strain of *Mycobacterium tuberculosis* H37Rv.
- To evaluate the drug like properties of the synthesized compounds.
- To investigate the correlation between drug like properties and molecular docking results of the compounds with their antitubercular activity.

**Major focus**

This thesis places a major focus on

- Designing novel diphenyl ethers which can mimic the binding mode and orientation of Triclosan in InhA protein (Mtb ENR).
- Molecular docking studies against Mtb ENR to provide a rationale for the antitubercular potential of diphenyl ether derivatives.
- Design of diphenyl ether derivatives less lipophilic than Triclosan.
- Estimation of drug-like properties (logP, pKa, % protein binding, stability in Human Liver Microsome, etc.) of promising compounds
- Establishment of Structure Activity Relationships (SAR) and Structure Property Relationships (SPR) of diphenyl ether scaffold.
Chapter-2

Purpose of the work

Research Plan flow chart

First phase

Diphenyl ethers to be designed based on previous reports and through activity landscape. Confirmation of Novelty

Synthesis of designed NCEs through facile synthetic route

Evaluation of Drug likeness

Determination of MIC against *Mycobacterium tuberculosis* H37Rv

Assessment of In Vitro Cytotoxicity (CC₅₀) and Hepatotoxicity (CC₅₀)

Compounds with Selective Index (CC₅₀/MIC) ≥ 10 will be screened for their MIC against MDR and Isoniazid Resistant *Mycobacterium tuberculosis* strains

Second phase

Structural modification of Diphenyl ether moiety based on the SAR of first phase compounds. Generation of diphenyl ether based Chemical Library

Molecular docking and Virtual screening of designed diphenyl ethers

Synthesis of designed NCEs through facile synthetic route

Evaluation of Drug likeness

Compounds with Selective Index (CC₅₀/MIC) ≥ 10 will be screened for their MIC against MDR and Isoniazid Resistant *Mycobacterium tuberculosis* strains

Determination of MIC against *Mycobacterium tuberculosis* H37Rv

Assessment of In Vitro Cytotoxicity (CC₅₀) and Hepatotoxicity (CC₅₀)

Establishment of Structure Activity Relationships (SAR), and Structure Property Relationships (SPR) of the diphenyl ether scaffold.