3. Rationale, Objective and Plan of Work

3.1. Rationale and objective

Our inability to control TB stems from the failure of BCG vaccines. The development of resistance to antibiotics is also one of the factors. The present-day treatment regimen is lengthy and takes 6 to 24 months to complete. The treatment is toxic and also complicated due to different combinations of drugs. The drugs used for the treatment of resistant TB are extremely toxic and also expensive. There is also an issue of incompatibility with certain antiviral drugs used in the treatment of HIV and TB co-infections. Therefore, fast-acting, less toxic, cost effective, and more compatible drugs are absolute need of the hour. Phenothiazine class of drugs *viz*. chlorpromazine, trifluoperazine and thioridazine were reported for potent antitubercular activity but cognitive side effects limited their use in the treatment of TB [142-144]. In the present study, I aimed to introduce definite modifications in chlorpromazine to increase the anti-TB activity with concurrent reduction of unwanted effects. The approach is to remove/modify the pharmacophore/linker/tailing-group(s) of chlorpromazine, essential in exerting antipsychotic activity. We designed a total of 550 molecules by altering the pharmacophore, connector, as well as the tailing groups. Phenothiazine pharmacophore was retained in one series of molecules and was modified to biphenyl and carbazole in the other two series. The alkyl connector was modified to an acyl connector. The tailing group was also modified by introducing different electron donating/withdrawing-substituted phenyl amines/ phenyl piperazines and cyclic amines (**Figure 3-1**). We also found reports for biphenyl compounds [145], carbazole alkaloids [146] and synthetic carbazole derivatives [96] exerting inhibition against *Mtb* H37Rv, *S. aureus* and *E. coli*.

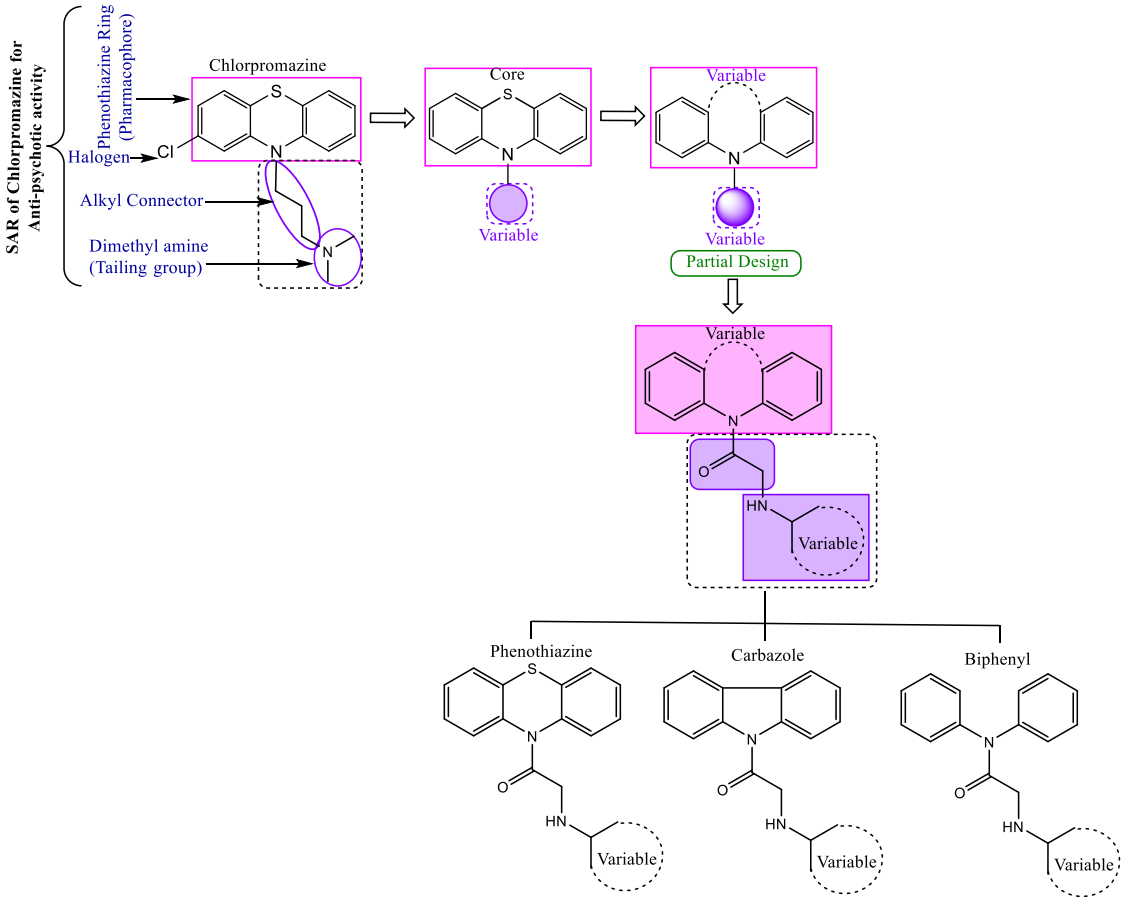

Figure 3-1: Design strategy for phenothiazine, carbazole and biphenyl derivatives

3.2. Plan of Study

The plan of study was as follows:

1. Molecular design and virtual screening of designed molecules
2. Development of designed phenothiazine derivatives as antitubercular agents
   a) Synthesis of substituted-phenyl, substituted-phenyl piperazine and cycloalkane analogues of phenothiazine
   b) Purity assessment of the synthesized phenothiazine derivatives by thin layer chromatography (TLC), melting point and elemental composition analyses
   c) Characterization of the synthesized derivatives by ^{1}H NMR, ^{13}C NMR and Mass spectrometry

d) Biological screening of the synthesized compounds for *in-vitro* antitubercular activity against *Mtb* H37Rv

e) Antibacterial screening of the synthesized compounds against *S. aureus* and *E. coli* to understand the spectrum of activity against *gram*-positive and *gram*-negative organisms

f) Blood brain barrier (BBB) permeability assessment of the developed compounds

g) Cytotoxicity screening of the synthesized compounds against kidney epithelial cells (VERO)

h) Type-2 NADH dehydrogenase (NDH-2) and ATP synthase inhibition screening

3. Development of the designed carbazole derivatives as antitubercular agents

a) Synthesis of substituted-phenyl, substituted-phenyl piperazine and cycloalkane analogues of carbazole

b) Purity assessment of the synthesized carbazole derivatives by TLC, melting point and elemental composition analyses

c) Characterization of the synthesized derivatives by ^{1}H NMR, ^{13}C NMR and Mass spectrometry

d) Biological screening of the synthesized carbazole compounds for *in-vitro* antitubercular activity against *Mtb* H37Rv

e) Antibacterial screening of the synthesized compounds against *S. aureus* and *E. coli* to understand the spectrum of activity against *gram*-positive and *gram*-negative organisms

f) Blood brain barrier (BBB) permeability assessment of the developed compounds

g) Cytotoxicity screening of the synthesized compounds against kidney epithelial cells (VERO)

h) Type-2 NADH dehydrogenase (NDH-2) and ATP synthase inhibition screening

4. Development of the designed biphenyl derivatives as antitubercular agents
   a) Synthesis of substituted-phenyl, substituted-phenyl piperazine and cycloalkane analogues of biphenyl scaffold
   b) Purity assessment of the synthesized biphenyl derivatives by TLC, melting point and elemental composition analyses
   c) Characterization of the synthesized derivatives by ^{1}H NMR, ^{13}C NMR and Mass spectrometry
   d) Biological screening of the synthesized biphenyl compounds for *in-vitro* antitubercular activity against *Mtb* H37Rv
   e) Antibacterial screening of the synthesized compounds against *S. aureus* and *E. coli* to understand the spectrum of activity against *gram*-positive and *gram*-negative organisms
   f) Blood brain barrier (BBB) permeability assessment of the developed compounds
   g) Cytotoxicity screening of the synthesized compounds against kidney epithelial cells (VERO)
   h) Type-2 NADH dehydrogenase (NDH-2) and ATP synthase inhibition screening