Design, synthesis and evaluation of novel heterocyclic compounds as Antitubercular agents

Kalicharan Sharma
Department of Pharmaceutical Chemistry,
Delhi Pharmaceutical Sciences and research university, New Delhi-110017
sharmakcpt@gmail.com

Abstract:

Why my work is important

Tuberculosis is an infectious disease that affects millions of population every year. *Mtb* DHFR is a validated target that is vital for nucleic acids biosynthesis and therefore DNA formation and cell replication. There are no selective *Mtb* DHFR inhibitors available against this target till date.

What the specific objectives of my work are

To identify novel *Mtb* DHFR inhibitors through molecular modelling and virtual screening of various public domain and in-house databases. Synthesis of selected hits and their analogues and their anti-tubercular activity

A brief explanation of the methods I have used

Mtb DHFR contains 159 amino acid residues compared with 187 for the human DHFR with active site on C-terminal side of the sheet. Structural comparison of these complexes revealed that there is 74% similarity between the proteins, such a high similarity the active site environments of the two proteins from host and pathogen contain interesting differences. We have performed virtual screening against *Mtb* DHFR and *h* DHFR by taking public domain and in house databases and selection of molecules has been done on the basis of selective binding interaction to *Mtb* DHFR. The hits identified (17) were synthesized in lab and characterized by ^{1}H NMR, LCMS and IR. The compounds were screened for their antitubercular activity at TAACF, NIAD USA.

A succinct statement of the results and my conclusions:

The main objective of the present study was to identify the drug like molecules as selective inhibitors for *Mtb* DHFR by using Virtual Screening. The compounds were found to have inhibitory activity in range of (30- 100) μM. All compounds presented low cytotoxicity, with less than 15% of cell death at 100 M. Therefore, the structure-based drug deigning provided useful information required for proper understanding of the important structural and binding features for designing novel *Mtb* DHFR inhibitors.