Abstract

Mycobacterium tuberculosis, the fatal agent to humans is estimated to claim two million deaths annually. Even though the existing drugs are remarkable in controlling the disease to a certain extent, but they still suffer from several shortcomings. The drug discovery efforts are progressively becoming rational, focused at various enzymes and identification of appropriate targets is becoming a fundamental pre-requisite. In the present study, we paid attention on achieving promising anti-tubercular agents based on reported and promising anti-tubercular leads. Utilizing the medicinal chemistry tools of structure based drug design and molecular hybridization/scaffold hopping; we designed and synthesized the compounds. All synthesized novel compounds were characterized by spectral data (IR, NMR and MS), elemental analysis and few compounds were confirmed by single crystal XRD and screened for anti- mycobacterial activity.

In **chapter 3**, twenty six novel 1-((1-(substituted)-1*H*-1,2,3-triazol-4-yl)methyl)-*N*,3-diphenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*c*]pyridine-5(4*H*)-carboxamide derivatives were synthesized and evaluated for their antimycobacterial activity against MTB $H_{37}Rv$ strain and pantothenate synthetase enzyme inhibition was also done. Among the synthesized compounds, **7d** exhibited good activity with MTB MIC 24.72 μM and better MTB PS inhibition with IC_{50} 1.01±0.32 μM. The most active compound **7d** showed SI value 13.76.

In **chapter 4**, we designed 9*H*-fluorenone linked 1,2,3-triazoles based on reported InhA inhibitors of 9*H*-fluorenone analogues and anti-TB agents of 1,2,3-triazoles. In this chapter, fifty compounds were synthesized and evaluated for their antimycobacterial activity against three strains MTB $H_{37}Rv$, MTB *Spec.* 192 and MTB *Spec.* 210. Among the synthesized compounds, 15 whose activities were ≤ 50 μg/mL were screened for the InhA activity. Amongst 15 compounds, **17f** & **17p** showed >73% of InhA inhibition at 50 μM. Compounds **17p** showed good MTB activity with MIC 52.35 μM against MTB $H_{37}Rv$. Most active compounds did not exhibit cytotoxicity against HEK 293 cell line at 50 μM.

In **chapter 5**, a series of thirty six substituted sulfonamide tetrazole derivatives were designed based on the reported MTB inhibitors of 1,2,4, triazoles, tetrazole and sulfonamide analogues using molecular hybridization strategy. The compounds were synthesized over seven steps and evaluated for their anti-tubercular activity. Among the tested compounds, **26c** emerged as a prospective candidate by inhibiting the MTB $H_{37}Rv$ strain at concentration 0.78 μg/mL. In addition, all the active compounds with MIC ≤ 6.25 μg/mL were subjected to cytotoxic studies against CHO-K1 cell lines at concentration 100 μM and the selectivity index values for most of the compounds is >12 indicating suitability of compounds in an endeavour to attain lead molecule for further drug development.

In **chapter 6**, 6-chloro, 6,7-dichloro and 2-methyl-3-(((1-(substitutedphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide derivatives were designed by the approaching molecular hybridization based on the reported MTB inhibitors of 1,4-di-*N*-oxide-quinoxaline and 1,2,3 triazole analogues. Thirty one compounds were synthesized and evaluated for their anti-tubercular activity against three different strains MTB $H_{37}Rv$, MTB *Spec.* 192 and MTB *Spec.* 210. Among the synthesized compounds, **36a** and **37d** showed excellent MTB MIC of 30.35, 47.60 μM and respectively. Cytotoxicity of **36a, 36e, 36i, 36l, 37b, 37c** & **37d** was determined against HEK 293 cell line. The most active compounds did not show toxic nature.

With new anti-TB agents desperately needed, we believe that the present class of triazole based inhibitors reported in this work would be an interesting potential lead to be worked for rational drug design against MTB from pharmaceutical point of view.