2013-14

Rajnibhai V. Patel
PharmInnova Award
Best M. Pharm Thesis

WINNER

Winner

Mr. Dhagash Vora

Research Guide

Dr. C S Ramaa

Subject:
Pharmaceutical Chemistry

Thesis Title :
Study on new chemical entities of Therapeutic Potential

College:
Bharati Vidyapeeth's College of Pharmacy, Mumbai

Anti-tubercular drug with novel chemical structure

Outcome of Research:

Multi drug-resistance forms of Tuberculosis (TB) are one of the biggest challenges facing effective TB management therapy. In view of the worldwide spread of multidrug-resistant forms of TB, there is an urgent need to discover anti-tubercular agents with novel structure. This study aimed and successfully systhesized a new molecule in the triazole series of AntiTB drugs, which inhibits a vital bacterial metabolizing enzyme (InhA). The molecular docking studies (computational simulation of a ligand binding to a receptor) confirmed the anticipated interactions. The investigators have claimed that this work could lead the way in bridging the gap of 40 years in first-line TB therapy.

ABSTRACT

In view of the worldwide spread of multidrug-resistant, extensively drug-resistant and totally drug-resistant forms of tuberculosis, there is an urgent need to discover anti-tubercular agents with novel structure. InhA, the enoyl acyl carrier protein reductase from Mycobacterium tuberculosis (Mtb), is one of the key enzymes involved in the mycobacterial fatty acid elongation cycle of cell wall synthesis and has been validated as an effective anti-mycobacterial target. We hereby report the discovery of a series of 1,2,4-triazole-5-thiones as a novel class of potent InhA inhibitors. These direct InhA inhibitors require no mycobacterial enzymatic activation and thus circumvent the resistance mechanism to anti-tubercular prodrug such as isoniazid that is most commonly observed in drug-resistant clinical isolates. The 1,2,4-triazole-5-thione compounds were rationally designed and molecular similarity studies were performed. Based on the results of similarity studies, they were synthesized and spectral characterization using IR, 1H NMR and 13C NMR spectroscopies confirmed their structures. Biological evaluation was performed using resazurin microtiter assay on Mtb H37Rv strain followed by InhA enzyme inhibition studies. The most active compound in the series exhibited Mtb H37Rv MIC of 0.19 µg/ml and InhA IC50 of 90 nM. Molecular docking, pharmacophore generation and 3D-QSAR studies were performed on our compounds.