Design and Synthesis of Some Novel Anti-tubercular Agents

Abstract

Tuberculosis (TB) is an infectious disease caused by a deadly pathogen, *Mycobacterium tuberculosis*. Despite being curable. TB is still prevailing in the modern world especially in the Southeast Asian and African continents. The available treatment regimen consists of first line agents namely isoniazid, rifampicin, pyrazinamide, ethambutol and second line agents such as cycloserine, ofloxacin, streptomycin etc. But the disease is as old as human kind, thus there is development of resistance by bacteria towards the anti-TB agents. Specialized agents to treat drug resistant TB such as bedaquiline, delamanid, pretomanid etc are also available. Yet, all these agents are unable to suffice the need of the hour, *i.e.* to eradicate TB. There are many collective reasons that TB is still prevailing, such as development of resistance, inefficacy of the available drugs, long duration of therapy, side-effects of the existing drugs etc. There are various mycobacterial enzymes, that can be targeted for development of new anti-TB agents. DprE1 is the most druggable target at the moment because of its location and essentiality in the cell wall biosynthesis. Aim and objective of this work was to utilize different techniques of drug discovery process such as pharmacophore modelling, virtual screening and hybrid approach for identifying and developing new anti-TB agents. The existing reported DprE1 inhibitors were used to develop a pharmacophore model having four features-AHRR (Hydrogen bond acceptor, hydrophobic group and two aromatic rings). This pharmacophore model was then used to perform virtual screening for identification of newer scaffold as DprE1 inhibitors. Based on the results, pyrazolopyrimidine derivatives were designed, synthesized and evaluated for anti-TB activity by using MABA assay. Hybrid approach was also used to design novel compounds consisting of pyrazoles fused with dihydrochalcones. These compounds were synthesized and evaluated for their anti-TB activity by using MABA assay via Michael-aza addition reaction. Total 89 compounds were synthesized using both the approaches. Out of the synthesized compounds two compounds (**216, 118**) showed most potent activity having MIC value of 1.5 µg/mL with no cytotoxic effect on human lung adenocarcinoma cells. Molecular docking studies, *in silico* ADMET predictions, mutagenicity predictions, molecular dynamic simulations were also carried out to understand the binding pattern and potential to act as drug like properties of the developed compounds. The results of these studies would be helpful to develop novel anti-TB agents acting through DprE1 inhibition.