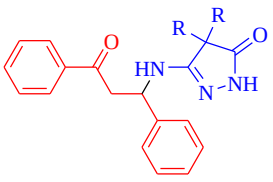
6. Conclusion

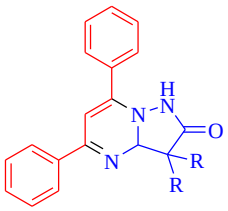
Tuberculosis (TB) is an air-borne, communicable disease that generally affects lungs and respiratory system. The causative organism *Mycobacterium Tuberculosis* (*Mtb*) was the leading cause of mortality until the COVID-19. The prevalence of TB of in South-east Asian countries is major health concern. The disease is curable with more than two dozen of drugs available for the treatment of TB. Yet there are challenges in controlling TB due to several factors such as development of resistance, patient incompliance, long duration of treatment, serious side effects of the existing drugs.

There are numerous targets for development of anti-mycobacterial agents. One of the most talked-about targets at the moment is DprE1. This enzyme is crucial for biosynthesis of arabinogalactan layer of mycobacterial cell wall. It is responsible for synthesis of DPA. A lot of research is going on the enzyme DprE1. Currently there are four DprE1 inhibitors present in the clinical trials as anti-TB agents.

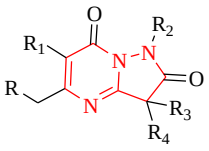
There is a vast literature available on DprE1 about the physiology, crystal structure, and inhibitors of the enzyme. A thorough literature survey encouraged us to perform pharmacophore modelling to search for common structural features present in the reported DprE1 inhibitors. As a result, a pharmacophore model having AHRR (Hydrogen bond acceptor, Hydrophobic group and aromatic rings) having four feature was developed. With an aim to identify some non-reported scaffold as DprE1 inhibitors, Virtual screening was performed on Asinex database. Results of virtual screening provided eight leads out of which two were pyrazolopyrimidines. These pyrazolopyrimidine hits were optimized to get a lead molecule (**Formula III**).



Formula I



FormulaII



Formula III

Hybrid approach has been one of the widely used techniques to develop new drugs. Thus, with an aim to explore some of the reported but not explored scaffolds such as pyrazole and chalcones were fused together via hybrid approach to get some novel compounds (**Formula I** and **Formula II**).

Current work discloses design, synthesis, in silico studies and biological study of novel anti-TB agents. Synthesis of the compounds was done by adopting five general synthetic schemes. Compounds with **Formula III** were synthesized using **Scheme 1-3**, while hybrid compounds with **Formula I** and **Formula II** were synthesized by using **Scheme 5** and **Scheme 6**.

The synthesized compounds were evaluated for their anti-TB activity by using MABA assay. It was noteworthy, that some compounds of were exhibiting excellent MIC value of 1.2 µg/mL.

Overall, pyrazolopyrimidine derivative (**109**, **118**, **130**, **132**, **144** and **145**) showed noticeable inhibition of *Mycobacterium Bovis* (BCG). Wherein compound (**118 and 132**) demonstrated MIC value of 1.2 µg/mL. Four hybrid compounds (**213**, **214**, **216** and **220**) exhibited good inhibition of *Mycobacterium Bovis* (BCG). Wherein. Wherein compound (**216**) demonstrated MIC value of 1.2 µg/mL.

Results of docking studies indicated that anti-TB activity of the synthesized compounds could be a result of binding to the enzyme DprE1. Most of the compounds showed binding affinity similar to the standard compounds while some of the derivatives demonstrated better binding affinity than the standard compound. This was further supported by molecular dynamics simulations studies, that resulted in the stable complex formation of the compound (**118**) and the enzyme. ADMET predictions of the synthesized compounds indicated towards the drug-likeness of the compounds, with a few exceptions. Genotoxicity predictions by Nexus Derrek indicated that a majority of compounds are non-mutagenic.