Novel compounds targeting InhA for TB therapy

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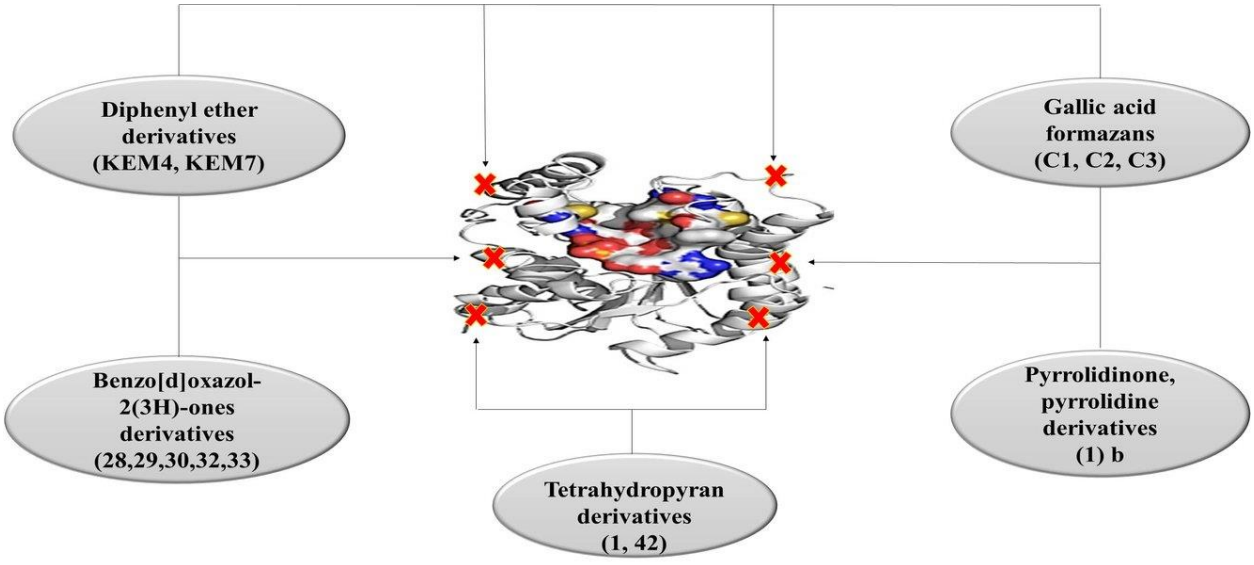
Graphical Abstract



Abstract

Tuberculosis (TB) is described as lethal disease in the world. Resistant to TB drugs is the main reason to have unfavourable outcomes in the treatment of TB. Therefore, new agents to replace existing drugs are urgently needed. Previous reports suggested that InhA inhibitors, an enoyl-ACP-

reductase, might provide auspicious candidates which can be developed into novel antitubercular agents. In this review, we explain the role of InhA in the resistance of isoniazid. Furthermore, five classes of InhA inhibitors, which display novel binding modes and deliver evidence of their prosperous target engagement, have been debated.

Keywords Tuberculosis, Isoniazid resistance, Enoyl ACP reductase, InhA inhibitor, Novel drugs

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), still remains the foremost cause of morbidity and mortality which accounts for nearly 9 million infections and 1.5 million deaths [1, 2]. Short course chemotherapy (SCC), which is considered the back-bone of anti-tubercular chemotherapy, includes not only initial phase for two months but also continuation phase of treatment for four months. The initial phase of anti-tuberculosis treatment consists of isoniazid (INH) rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB), followed by INH and RIF for the continuation phase of four months [3, 4]. However, based on the guidelines of TB treatment, relapses and failures could be reduced by replacement of a regimen including RIF throughout the 2 month period with a regimen based on just 6 months of RIF [5].

Although the most of TB instances are treatable, however, the current complex and long regimen of TB agents can lead to poor adherence with adverse side effects, therefore giving suboptimal therapy responses [4]. Even though many endeavours have been carried out to make the duration of treatment of drug-susceptible TB more shorter and to enhance the outcomes for MDR-TB therapies, the mortality rates are still high [6]. Thus, development of new antitubercular agents, which comprise novel chemical scaffolds with distinctive inhibitory binding modes and new modes of action, are urgently needed [7].

The poorly permeable and very complex cell envelope of mycobacteria are considered as a main barrier in the conveyance of TB agents to their action site. The essential and major components of the mycobacterial cell envelope are a-branched, b-hydroxylated fatty acids with chains of carbon atoms between 60 and 90 in length. Two elongation systems comprise fatty acid synthase type I (FAS-I) and fatty acid synthase type II (FAS-II) control the mycobacterial cell envelope synthesis. FAS-I enzyme is only used by eukaryotic cells to synthesize fatty acids, thus the FAS-II enzymes are viable targets for drug development. InhA, which is an enoyl-acyl carrier protein (ACP)