

Pharmacology of Antitubercular Drugs: Challenges and Advances

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Abbreviations: TB: Tuberculosis; MTB: *Mycobacterium tuberculosis*; WHO: World Health Organization; MRD-TB: Multidrug-Resistant Tuberculosis; XDR-TB: Extensively Drug-Resistant Tuberculosis; HIV: Human Immunodeficiency Virus; FDA: Food and Drug Administration

Tuberculosis (TB) is a highly prevalent infectious disease caused by *Mycobacterium tuberculosis* (MTB). The World Health Organization (WHO) recently estimated that one-third of the world's population is infected with MTB and that 13.7 million people worldwide have active TB [1]. Long-term therapy consists of four drugs (isoniazid, rifampin, ethambutol, and pyrazinamide), which are administered for 2 months, followed by two drugs (isoniazid and rifampin), which are used in combination for 4 months [2]. Although this treatment regimen has reduced the mortality rate worldwide, the emergence of multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), and TB/HIV co-infection are challenges that need to be overcome [3]. The mechanism involved in drug resistance is still not fully understood, but several factors are involved, including changes in membrane permeability, mutations in or modifications to cellular targets, and increased expression of efflux pumps [4].

In recent years, the number of new drugs approved for treating TB has not increased proportionally to the investment made in this clinical field. Since the discovery of rifampicin in the 1950s, the last drug approved by United States Food and Drug Administration for treating TB was bedaquiline (Sirturo[®]; Janssen Pharmaceuticals Inc./ Johnson & Johnson) in 2012 [5]. Despite the lack of new anti-TB drugs, it is clear from the scientific literature that researchers are still pursuing new potent and safe anti-TB drugs. We recently performed a review of articles published between 2008 and 2013 in several databases, including Science Direct, Medline, Scopus, and EMBASE, to identify novel anti-TB compounds with activity against MTB strain H37Rv, a minimum inhibitory concentration (MIC) of <10 μ M, and a selective index (SI) of >10. The SI was calculated as the median inhibitory concentration (IC₅₀)/MIC. This literature search revealed 110 different chemical scaffolds, but <10% were evaluated against resistant strains [6].

All of the anti-TB compounds reported in the literature were derived from three main sources: 1) natural products, 2) synthetic organic compounds, and 3) synthetic inorganic compounds. In particular, several organic compounds have been obtained using molecular modification strategies [7]. Koul et al. reported that the anti-TB compounds used in clinical trials, including SQ109, PNU-100480, PA-824, and OPC-67683, were derived from known antimicrobial compounds [8]. Our review revealed that fluoroquinolones and quinoxaline derivatives were the most active compounds. The fluoroquinolone derivative 7-(3-(diethylcarbamoyl)piperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid was active against MTB (strain H37Rv) and MDR-TB *in vitro*, with an MIC of 0.09 μ M in both strains. This compound also reduced the mycobacterial load in the lung and spleen of mice *in vivo* [9]. Quinoxaline derivatives were also potent against MTB. The high activities of some quinoxalines, mainly against resistant MTB strains, are well known and their biological effects are

related to an induction of hypoxia, which causes damage to genetic material [8]. Vicente et al. reported that the compound 7-methyl-3-(4'-fluoro)phenylquinoxaline-2-carbonitrile 1,4-di-N-oxide had potent anti-TB effects with an MIC of <0.2 μ g/mL and an SI of >500 [10].

The absence of new drugs to treat latent TB is another challenge that demands investigation. The next milestone for treating TB is to identify new drugs with potent sterilizing activity against replicating and non-replicating strains that can reduce the duration of chemotherapy [11,12]. Additionally, determining the association with other drugs that can decrease or inhibit TB's main drug-resistance mechanisms will improve treatment efficiency and cure rates.

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