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Invited review

SAR analysis of new anti-TB drugs currently in pre-clinical and clinical development

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ABSTRACT

Despite enormous efforts have been made in the hunt for new drugs, tuberculosis (TB) still remains the first bacterial cause of mortality worldwide, causing an estimated 8.6 million new cases and 1.3 million deaths in 2012. Multi-drug resistant-TB strains no longer respond to first-line drugs and are inexorably spreading with an estimated 650 000 cases as well as extensively-drug resistant-TB strains, which are resistant to any fluoroquinolone and at least one of the second-line drugs, with 60 000 cases. Thus the discovery and development of new medicines is a major keystone for tuberculosis treatment and control. After decades of dormancy in the field of TB drug development, recent efforts from various groups have generated a promising TB drug pipeline. Several new therapeutic agents are concurrently studied in clinical trials together with much activity in the hittolead and lead optimization stages. In this article we will review the recent advances in TB drug discovery with a special focus on structure activity relationship studies of the most advanced compound classes.

1. Introduction

Despite enormous efforts have been made in the hunt for new drugs, tuberculosis (TB) still remains the first bacterial cause of mortality worldwide, causing an estimated 8.6 million new cases and 1.3 million deaths in 2012 [1]. The current therapy used for treating drug-susceptible TB consists of a 4-drugs combination of rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB) (Fig. 1) for 2 months followed by RIF and INH for 4 months. Poor patient compliance increases the risk of selection of drug-resistant *Mycobacterium tuberculosis* strains. Multi-drug resistant-TB (MDR-TB) strains no longer respond to first-line drugs and are inexorably spreading with an estimated 650 000 cases as well as extensively-drug resistant-TB (XDR-TB) strains, which are resistant to any fluoroquinolone (FQ) and at least one of the injectable second-line drugs, with 60 000 cases [1]. Thus the discovery and development of new medicines is a major keystone for tuberculosis treatment and control.

After decades of dormancy in the field of TB drug development, recent efforts from various groups have generated a promising TB drug pipeline. Several new therapeutic agents are concurrently studied in clinical trials together with much activity in the hittolead and lead optimization stages [2,3]. Notably, after 40 years a new chemical entity, bedaquiline, has been approved by the U.S. Food and Drug Administration (FDA) with the name Sirturo in 2012, and by the European Medicine Agency (EMA) in 2014 for the treatment of MDR-TB patients [4,5]. Moreover, the EMA approved delamanid with the name of Deltyba, for the treatment of MDR-TB in the European Union (EU), for use in combination with optimized background therapy on April 2014 [6,7]. Because of their potential to induce arrhythmia, it is recommended that both Sirturo and Deltyba are utilized only in patients for whom the other treatments failed [4–7]. Despite that, there is a worrying gap between preclinical development and Phase I clinical trials. This gap needs to be addressed in order to maintain a continuum of clinical activity and

Abbreviations: AADAC, arylacetamide deacetylase; AUC, area under the curve; BTZ, benzothiazinone; CFM, clofazimine; CFU, colony forming units; Cfx, ciprofloxacin; DPA, decaprenylphosphoryl-β-D-arabinose; DprE1, decaprenylphosphoryl-β-D-ribose-2′-epimerase; DPR, decaprenylphosphoryl-β-D-ribose; EBA, early bactericidal activity; ECG, electrocardiogram; EMA, european medicine agency; EMB, ethambutol; EU, european union; FDA, food and drug administration; FQ, fluoroquinolone; Gat, gatifloxacin; INH, isoniazid; IPAs, imidazopiridine amides; Lfx, levofloxacin; LORA, low-oxygen-recovery assay; LTBI, latent tuberculosis infection; MBC_{90}, minimum bactericidal concentration; MDR-TB, multi-drug resistant tuberculosis; Mfx, moxifloxacin; MIC, minimum inhibitory concentration; Ofx, ofloxacin; PBTZs, 2-piperazino-benzothiazinones; PK, pharmacokinetic; PTC, peptidyl trasferase center; PZA, pyrazinamide; QRDR, quinolone-restistance-determining-region; RIF, rifampicin; ROS, reactive-oxygen species; SAR, structure activity relationship; TB, tuberculosis; TDM, trehalose dimycolate; TMM, trehalose monomycolate; WCC_{90}, wayne cidal concentration; WHO, World Health Organization; XDR-TB, as extensively-drug resistant tuberculosis.

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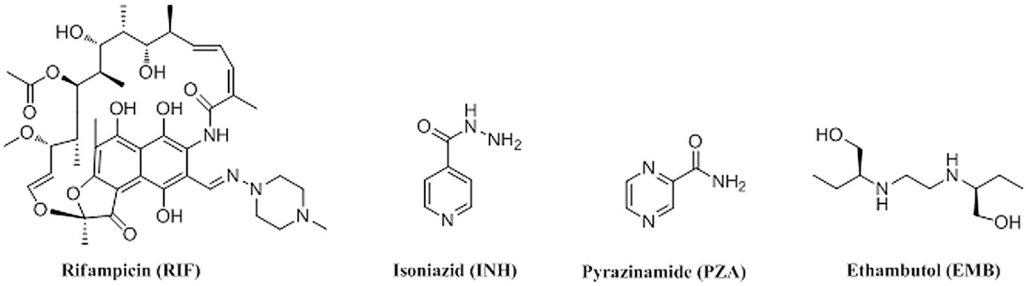

Fig. 1. Chemical structures of RIF, INH, PZA and EMB.

to compensate for possible attrition among the more advanced candidates [2].

TB treatment is challenging and new TB drugs should address several factors including: be active against both replicating and non-replicating bacteria, act by a new target or mechanism of action for treating both MDR-TB and XDR-TB patients, be compatible with HIV drugs as many patients are co-infected with HIV; and show no antagonism to other TB drugs or drug candidates so that a regimen comprising at least three active drugs can be constituted [2,3]. The two principal approaches, followed in the recent years for hunting for new anti-TB drugs, have been optimization of known drugs and discovery of new drug candidates. In this article we will review the recent advances in TB drug discovery with a special focus on structure activity relationship (SAR) studies of the most advanced compound classes.

2. Optimization of known drugs

2.1. Rifamycins

Rifamycins (Fig. 2) are a class of antimycobacterial agents related to rifampicin, one of the most used anti-TB drugs. The members of this class share the same mechanism of action, and inhibit transcription by binding β-subunit of bacterial RNA-polymerase [8,9].

Rifamycins scaffold has been extensively investigated and SAR analysis show that (Fig. 2) [10,11]:

- modifications of the hydroxyl groups at both positions 21 and 23 are not tolerated and cause loss of activity;
- C25 deacetylation does not affect activity;
- modifications at naphthalene group are possible but hydroxyl group at position 8 must be retained;
- modifications at position 3 are more tolerated; ring closure at positions 3 and 4 is also possible.

Rifampicin is commonly used in therapy, but it has many disadvantages such as: i) high frequency of resistance, due to a spontaneous mutation in *rpoB* gene that encodes the RNA-polymerase β-subunit region; ii) problematic side effects, especially when it is administered at high doses; iii) drug–drug interaction, because it strongly induces CYP450 enzymes. This is very problematic in HIV-infected patients undergoing antiretroviral therapy [10].

Currently, two other agents are approved by the FDA for TB treatment, rifapentine and rifabutin (Fig. 2).

Rifapentine is a long-lasting semisynthetic rifamycin. It was discovered in the mid-80s and it proved to be more active than rifampicin both *in vitro* and *in vivo* and to have a better pharmacokinetic (PK) profile in mice [12]. Unfortunately, it showed cross-resistance with rifampicin, but its great pharmacokinetic properties could be useful in shortening treatment and reducing therapy costs. In fact, its half-life is much longer than rifampicin (13–14 h and 2–3 h, respectively) and protein binding is higher (97% vs 85%) [13]. As other rifamycins, it is metabolized by a human arylacetamide deacetylase (AADAC), that converts it into 25-O-desacetylrifapentine, its major metabolite, that retains activity [14]. As shown in Phase II and III trials, rifapentine effectiveness was investigated at different stages of the therapy. In a continuation therapy of HIV-uninfected patients, co-administration of rifapentine (600 mg) plus INH (900 mg) once a week proved to be as effective as 600 mg rifampicin and 900 mg INH twice a week [15]. On these grounds, its activity in latent infection was further investigated, and results showed that therapy with once weekly rifapentine plus INH for three months was not less effective than therapy with INH for nine months [16]. Finally, rifampicin was substituted with rifapentine in intensive phase treatment and was administered 5 days weekly for eight weeks, in association with INH, PZA and ETB, but no significant differences with current rifampin therapy were observed in humans in this stage of disease [17]. As rifampicin, rifapentine is not recommended for HIV co-infected patients in concomitance with antiretroviral therapy not only because it strongly induces CYP450 but also because its association with INH in a three-month therapy proved to be less effective than six months INH therapy in adults with HIV co-infection [18].

Rifabutin was approved by the FDA for *M ycobacterium avium* complex treatment. It showed a great micromolar microbicidal activity against both *M. tuberculosis* H37Rv (minimum inhibitory concentration, MIC = 0.015 μg/mL) and *M. avium* (MIC = 0.06 μg/mL), and a larger volume of distribution and a longer half-life than rifampicin [19]. Differently from rifampicin and rifapentine, rifabutin induces CYP450 to a lesser extent [20,21] and is consequently recommended for HIV-co-infected patients [22]. As a consequence, it was introduced in the World Health Organization (WHO) list of essential medicines for TB treatment in patients that received ritonavir therapy [23]. Since rifabutin is a substrate of CYP450, antiretroviral inhibitors and protease inhibitors can affect its metabolism and consequently its recommended dosages for patients who received antiretroviral therapy are lower (150 mg/daily or 300 mg thrice a week vs 300 mg daily in HIV-uninfected patients) [23,24]. As reported in literature, lower and intermittent dosages can result in a sub therapeutic plasma concentration, that can favor drug resistance. Indeed, a very recent trial reported the pharmacokinetic profile of rifabutin when it is administered with lopinavir/ritonavir therapy, and compared 150 mg/daily and thrice a week dosages in Vietnamese patients [25,26]. While any variations in concentration of lopinavir and ritonavir were found at both dosages, significant differences in rifabutin concentration at steady-state were observed. On these grounds, daily dosage might be preferred.