An overview on Benzothiazinone analogs as Antitubercular Drugs

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ABSTRACT
The reappearance of tuberculosis and the rush of multidrug-resistant clinical isolates of Mycobacterium tuberculosis have reaffirmed tuberculosis as a key public health concern. Describe findings on the pharmacological status of Benzothiazinones as new agents that are being developed as antitubercular drugs. Benzothiazinones act by targeting the enzymes responsible for the formation of arabinans that are essential parts of the cell wall. In view of their novel mechanism of action, these drugs appear promising as anti-TB drugs and considered to be promising candidates for future development.

Keywords: Mycobacterium tuberculosis, tuberculosis, promising drugs, anti-TB therapy

INTRODUCTION
The recent rise in tuberculosis (TB) cases, due in particular to the increased incidence of Mycobacterium tuberculosis infections in HIV-infected individuals, has prompted a vigorous search for new drugs for the treatment of this disease. Increased infection with the M. avium complex (MAC) is also contributing to the morbidity and mortality in AIDS patients. In this context, it is important to consider that the most urgent goal of chemotherapy of TB and MAC infections should be the development of highly active and low-cost drugs that can be used not only in industrialized countries, but also in developing countries in which TB and disseminated MAC infections are now rapidly increasing [1-3]. The progressive immunological deterioration seen in AIDS is often accompanied by opportunistic infections including tuberculosis (M. tuberculosis) and non-tuberculosis (M. avium) mycobacterial diseases. Treatment of these infections, along with other opportunistic infections that cause the majority of all AIDS-related deaths, is often complicated by patient intolerance of the drugs employed or pathogen resistance to conventional drug therapy. The main drugs currently used to treat TB are Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin, and for most of them, the mechanism of action is known. Nearly 19% of TB isolates in a hospital were resistant to Isoniazid and Rifampicin, the two most common antitubercular agents. In general, the resistance to INH and Streptomycin is more common than resistance to Rifampicin, Ethambutol and Pyrazinamide. For empiric treatment of all M. tuberculosis infections, even if drug resistance is not suspected, the 4-drugs regimen of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol or Streptomycin is recommended, until susceptibility results become available. Duration of therapy should be at least one year [4,5]. Regarding the strategy of the search for new, effective compounds with a different mode of action is the most challenging, but also the most likely approach for discovering new agents that may shorten the treatment period and provide solutions to both the drug intolerance and drug-resistance problems. Moreover, the strategy related to the genome of M. tuberculosis. This, coupled with the increasing knowledge of various mycobacterial virulence genes, will promote the identification of genes that code for potential new targets [5].

BENZOTHIAZINONES: A new class of drug with antimycobacterial activity, 1,3-benzothiazin-4-one or
benzothiazinone (BTZ), was recently described. The lead compound, 2-[2-S-methyl-1,4-dioxo-8-azaspiro[4,5]dec-8-yl]-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (BTZ043) was found to have activity against \textit{M. tuberculosis}. It was found to be active against drug-susceptible and MDR clinical isolates of \textit{M. tuberculosis}. Structure of BTZ043 is shown in Figure 1.

![Figure 1. Structure of 1,3-benzothiazin-4-one (BTZ043) (1).](image)

The 1,3-benzothiazin-4-ones (BTZ) kills \textit{M. tuberculosis} by blocking arabinan synthesis. The most advanced compound, 1,3-benzothiazin-4-one (BTZ043) (1), was found to be a candidate for inclusion in combination therapies for both drug-sensitive and extensively drug-resistant TB. By transcriptome analysis, the mode of action of BTZ043 was initially spotted at the cell wall biogenesis level. By further genetic analysis, using \textit{in vitro} generated mutants, the target of the drug was identified at the level of the gene rv3790, which together with rv3791 encode proteins that catalyze the epimerization of decaprenylphosphoryl ribose (DPR) to decaprenylphosphoryl arabinose (DPA), a precursor for arabinan synthesis needed for the bacterial cell wall. DprE1 and DprE2 were proposed as names for these two key enzymes. More recent studies have characterized more precisely the mechanism of action of BTZ043 by showing that the drug is activated in the bacteria through reduction of an essential nitro group to a nitroso derivative, which can react with a cysteine residue in DprE1. In studies with \textit{M. smegmatis}, an alternative mechanism of resistance has been suggested. The overexpression of a nitroreductase NfnB led to the inactivation of the drug by reducing an essential nitro group to an amino group. Although \textit{M. tuberculosis} apparently lacks nitroreductases able to reduce the drug, this finding could be important for development of new BTZ analogues with improved activity. A series of piperazine-containing 1,3-benzothiazin-4-ones has been reported. The lead compound PBTZ169 has improved activity, safety and efficacy in animal models and has shown \textit{in vitro} synergy with bedaquiline signaling it as an attractive new compound for further drug development. The nitro-benzothiazinone (BTZ) class was derived from a series of sulfur-containing heterocycles to develop antibacterial and antifungal agent. BTZ-043 (1), the most promising compound among the benzothiazinones, shows high antitubercular activity in vitro, in macrophages, and in the murine model of chronic TB. The sulfur atom and the nitro group at positions 1 and 8, respectively, play a critical role in bactericidal activity. When the nitro is replaced with either an amine or a hydroxylamine at position 8, the resulting analogs show a 500 to 5,000-fold decreased activity. More than 30 different BTZ derivatives showed MICs of less than 116 nM against \textit{M. tuberculosis}. Electron-withdrawing group such as CN, CF₃, and Cl at the R₃ position and 1,4-dioxo-8-azaspiro[4,5]decane groups with methyl substituents at R₂ show promising activity against \textit{M. tuberculosis}. The BTZ class of compounds is thought to inhibit decaprenylphosphoryl-b-D-ribose 20-epimerase, hereby preventing the conversion of decaprenylphosphoryl ribose (DPR) into decaprenylphosphoryl arabinose (DPA), which is a substrate for the arabinosyl transferases of mycobacterial cell wall synthesis. The MIC of BTZ-043 against \textit{M. tuberculosis} H37Rv is 2.3 nM.

![Fig. 2 Structure of BTZ-043 pharmacophore](image)

Despite the 100-fold better \textit{in vitro} activity of BTZ-043 against \textit{M. tuberculosis} than frontline agents such as INH, its \textit{in vivo} effect during treatment of chronically infected mice was comparable to that of INH and RIF. In mice, BTZ-043 has a t1/2 greater than 2 h, a Cmax of 2 mg/mL, and an AUC of 4.6h.mg/ml. It is also relatively stable to degradation by human liver microsomes and shows less than 20% inhibition of various cytochrome P450 enzymes. BTZ-043 showed high activity against clinical isolates of \textit{M. tuberculosis}.

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tuberculosis including multidrug resistant (MDR) and extensive drug resistant (XDR) M. tuberculosis strains [7]. This compound is in preclinical development and will soon enter phase I clinical trials. The 1,3-benzothiazin-4-ones represent a new class of drugs, which have activity against M. tuberculosis [6]. The 1,3-benzothiazin-4-ones are activated in M. tuberculosis by reduction of an essential nitro group to a nitroso derivative, which then specifically reacts with a cysteine residue in the active site of the enzyme decaprenylphosphoryl-β-D-ribose 2′-epimerase (DprE1) [9]. Inhibition of this enzymatic activity abolishes the formation of decaprenylphosphoryl arabinose, a key precursor that is required for the synthesis of the cell-wall arabinans, thus causing bacterial lysis and death [6]. Although spontaneous BTZ-resistant laboratory mutants were found to have a Ser or Gly substitution at codon Cys387 of dprE1, resistance to benzothiazin-4-ones has not been reported in clinical M. tuberculosis isolates [7]. Recently, a novel resistance mechanism to The 1,3-benzothiazin-4-one was described in M. smegmatis involving the overexpression of the nitro-reductase NfnB, which leads to the inactivation of the drug by reduction of a critical nitro-group to an amino-group [10]. However, M. tuberculosis seems to lack nitroreductases able to inactivate 1,3-benzothiazin-4-ones.

DISCUSSION

The strategies followed to generate new TB therapies may involve developing new drugs from existing lead molecules used to treat other bacterial infections. Modifying the existing drugs to improve anti-TB activities and pharmacokinetic properties to make it less susceptible to the known mechanism of resistance. This is the strategy adopted in developing new anti-TB drug analogues. Discovering new drugs either by random screening or if a specific target is known, by a rational design. In this context the strategies led to the identification of drugs, such as new Benzothiazinones, as active agents [13-15]. Since resistance will likely develop upon prolonged treatment, such agents will always be used in conjunction with one (or perhaps more) other anti-TB drugs to which mycobacteria is susceptible.

CONCLUSION

Benzothiazinones have demonstrated in vitro and in vivo activity against M. tuberculosis and they also penetrate human macrophages in which mycobacteria survive and appear to have promising activity against TB. The antibacterial effects of the Benzothiazinones, have been extended to include anti-TB activity. In general, they are used in combination with at least one other drug in order to prevent resistance.

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