Review Article

Antitubercular drugs: Advances in nitrogen containing heterocyclic compounds and some other derivatives

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Abstract
Mycobacterial infections are infectious diseases. Control of TB is complicated by difficulties in the long-course chemotherapy treatment, the inability to eliminate latent microbes, and the increasing emergence of multidrug resistant strains of M. tuberculosis. New anti-TB drugs are urgently needed, including developments of short-term treatments to minimize the emergence of drug resistance and new drugs to treat multidrug resistant tuberculosis and to eliminate the latent microbes. Many new structural anti-TB agents exhibited promising activities against susceptible and resistant strains of M. tuberculosis. The diarylquinoline with superior anti-tuberculosis activity and encouraging results of nitroimidazopyrans and oxazolidinones have generated considerable excitement. In this review study the efforts to use of drugs for treatment of tuberculosis.

1. Introduction
Mycobacterium tuberculosis is a causative agent of tuberculosis (TB) that has latently infected a third of the world population. Infection caused via inhalation of few droplets containing M. tuberculosis bacilli [1-3]. After infection, M. tuberculosis pathogenesis takes place in two stages.

• An asymptomatic state that can persist for many years in the host, called latent TB.
• The second stage requires only a weakened immune response to become activated (Zhang, 2004), then the bacteria begins replicating and causing typical symptoms such as cough, chest pain, fatigue and unexplained weight loss. If left untreated, the disease eventually culminates in death.

The appearance of Human Immunodeficiency Virus (HIV) and the Acquired Immune Deficiency Syndrome (AIDS) epidemic emphasized the significance of reactivation of the disease. Over 50% of deaths among HIV infected patient results from co-infection with M. tuberculosis with the two pathogens inducing each other’s replication, thus accelerate the collapse of the immune system. The World Health Organization (WHO) report estimates that close to 2 million deaths occur every year, that there are around 8 million new cases per annum, and that every third person on the earth has been exposed to or infected by M. tuberculosis [4-7]. Even though TB can be treated and even cured with chemotherapy, treatment is lengthy and takes 6-9 months [8]. In addition to lengthy therapy, significant toxicity and poor patient compliance, drug resistant and multidrug resistant TB (MDR-TB) bacteria are seen [1-3]. Currently, TB chemotherapy is made up of first-line drugs isoniazid (INH), Rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB), which are given for six months. If this treatment fails due to bacterial drug resistance or intolerance to one or more drugs, second-line drugs are used (para-aminosalicide (PAS), kanamycin, fluoroquinolones, capreomycin, ethionamide and cycloserine). These are generally less effective or more toxic with severe side effects [8-10]. This second-line treatment can also ineffective since MDR-strains that exhibit resistance to second-line drugs [11]. Treatment is also quite difficult by the presence of metabolically silent, persistent or dormant tubercular bacteria within host lesions. These are not susceptible to the anti-TB drugs that usually kill growing but not persistent bacteria [12]. There are so many reasons for drug resistance, including prescription of inadequate regimens, an uncertain drug supply, ineffective drugs, duration of lengthy treatments is one of the major contributors because some TB patients prematurely stop their therapy after an initial, rapid health improvement, thereby favoring the appearance of drug-resistant strains [5,13].

1.1 Rational drug design
In new pharmacophore groups, one problem that must be considered in the design of anti-TB compounds is that there is a subpopulation of bacteria in a persistent non-replicating state. This is considered a major contributing factor to long drug treatments for TB [14]. For this reason, it is important to determine if compounds have potential activity against these bacteria at the onset of design. The physicochemical properties were also studies that directly affect the pharmacokinetics and pharmacodynamics of drugs. This is the influence of stereoisomers on biological activity, because individual enantiomers have significant differences in activity, although sometimes the activity of some enantiomers cannot be explained.

2. Non fluoroquinolones
A quinoline ring is one of the moieties frequently used in drug design and development. It has been calculated a pharmacophore for the design of anti-TB agents (Fig 1). Diarylquinoline (TMC207) (1), is an adenosine ATP synthase inhibitor that is one of the most important non fluorinated quinoline compound with anti-TB activity. Butanamide is established as an important pharmacophore with good antibacterial activity and the carbonydrase moiety is also known as a pharmacophore group. The design of new quinoline derivatives with active carbonydrase and butanamide moieties in 3 and 4-position, respectively, has been carried out. These compounds shows that the presence of a trifluoromethyl group at 8-position increases activity; however, the fluoro group in 6-position partially decreases activity (2) and these type of compounds were nontoxic [15]. The development of
mefloquine analogs (3) in a series of compounds (4), good anti-TB activity has been recognized to the presence of biologically active heterocyclic groups like pyrazole, imidazole, and indole rings on the quinoline moiety. Compounds with a pyrazole ring have activity against resistant strains, which can be accredited to the presence of electron donating groups that stabilize the pyrazole ring, making the more active entity of quinoline ring [16].

The conformational restriction of the piperidinyl ring of mefloquine through the construction of an oxazolidine ring and different substituents on the phenyl ring (5). Conformational restriction showed that the introduction of an oxazolidine core in the mefloquine moiety improved anti-TB activity. The activity of these compounds is affected by substituents on the aromatic ring bound to C-17 of the oxazolidinyl nucleus. Compounds that show hydroxyl or aliphatic side chain with various degrees of unsaturation, lengths chains, and double bond positions (10). The results showed that increasing the chain length enhances anti-TB activity, showing optimal activity with 14 C atoms. There is an increase of more carbon atoms in the chain, activity decreases dramatically. This behavior has also been described for ciprofloxacin derivatives where lipophilicity could play an important role in anti-TB activity. The saturated aliphatic chain has less activity than unsaturated analogues. The unsaturation of an aliphatic chain is an essential structure for anti-TB activity (Figure 2) [21].

Figure 2: Quinoline and oxazole derivatives as anti-TB agents (7-10).

Phenazine and quinoxaline rings are considered bioisosteres of the quinoline ring. Phenazine derivatives are useful compounds for new anti-TB drug development, particularly Tubercymcin B and Clofazimine (phenazine analogues). Similarly, new compounds that show activity (11) in a concentration range of 0.19 to 3.12 mg/l against tubercular resistant clinical isolates. This series of compounds were ineffective in inhibiting the growth of INH resistant strains. Compounds that had exocyclic groups, which present different lipophilic and electronic properties, but with a size similar to INH, such as phenylamide methyl lipophilic group in 4-position, were the most active. Same group in 3-position is reduced activity 100-fold. Phenazine derivatives having electron withdrawing groups in 2 and 3-position have similar biological activity. The importance of the arylic moiety is a pharmacophore for phenazinecarbamoyl anti-TB compounds. Mechanism of action of phenazine derivatives is still unknown and hypothesized that it could act as a cellular superoxide dismutase inhibitor. The compound Lomofungin (1-carboxy-5-formyl-4,6,8-trihydroxyphenazine) is capable of inhibiting RNA-dependent RNA polymerase, both these options may be possible for mechanisms of action of phenazine derivatives [22].

Quinoxalines compounds have broad spectrum of biological activities. Quinoxaline-N oxide derivatives are known as M. tuberculosis bioreductor agents. Compounds missing N-oxide groups have led to the loss of anti-TB activity. Over 500 derivatives of quinoxaline (12), demonstrating the importance of this group for developing a new class of anti-TB compounds. The quinoxaline compounds have activity on nonreplicating bacteria, which could lead to shorter anti-TB activity[23].

A compound denominated ER-2 is a new derivative of quinolines (13), is a gyrase supercoiling inhibitor and has potency similar to Ciprofloxacin with a MIC of 0.5μg/ml (fig 3) [24].

Figure 3: Structure of phenazine-1-carboxamides, quinoline and quinoxaline derivatives (11-13).

3. Hydrazides/hydrazone derivatives

Hydrazide/hydrazone compounds (Fig 4) have been considered for new anti-TB drug design. An example is diflunisal, which has dual effect acting with antimicrobial and anti-inflammatory activities. In thiazolylhydrazone derivatives have found that...
substitutions on the phenyl ring affect anti-TB activity (14) [25]. A thiazolylhydrazine is compound (15), which has high anti-TB activity with an IC₅₀ of 6.22 μg/ml and low toxicity (CC₅₀> 40 μg/ml), pyridyl moiety plays a direct role related to anti-TB activity [26]. A series of pyridine compounds have potential anti-TB activity (16)[27]. New designs have been made by molecular hybridization of E-dynamic acid and guanylhydrazones. The electronic and steric parameters have an important role in the activity of these compounds on M. tuberculosis (17). They remain the basis of new anti-TB drugs [28].

4. Nitrogen heterocyclic derivatives

Purines (Fig 5) are an important group in the design of anti-TB drugs. In these compounds (18), activity depends on the substituents present in C2, C6 and N9 of the purine ring [29]. In 6,9-disubstituted purine derivatives, activity increases substantially when a Cl atom is presented in the 2-position. Purine derivatives with thienyl substituents exhibited better activity in non-replicating bacteria, although in these compounds a Cl atom in 2-position is not beneficial for activity. The purine N-9 is important for activity, in the case of purine C-8, an atom can be exchanged without losing activity and a change in purine N-7 results in a loss of activity, although there are 7-deazapurines derivatives (19) that could be compared with RIF[30].

Heterocycles, pyrimidines have potential therapeutic applications as anti-TB agents. The design of pyrimidine derivatives is a possible option (20, Figure 6). The substituent nature in 2-position can modulate cytotoxic activity [31]. The thymidine monophosphate kinase of M. tuberculosis (TMPKmt) is a prominent target for the development of anti-TB drugs. TMPK is the last specific enzyme for dTTP synthesis and is a key enzyme in M. tuberculosis metabolism. This enzyme is different from human enzyme analogs (22% homology). TMPK inhibitors have been developed with single or multiple chemical modifications of the pyrimidine moiety and thymidylate sugar. In particular benzyl-thymine derivatives have been remarkable TMPK inhibitors, which has led to the proposal of new modifications such as: chain length in para-position on the benzyl ring, saturation of the alkyl chain, functionalization of the chain group and substitution at 5-position of the core base. This has led to more selective compounds on TMPK that correspond to benzyl-pyrimidines substituted by a chain length of 4 carbons and a terminal carboxylic acid function. Docking of molecule 21 on TMPKmt showed that the hydrogen of the thymine and acid group can interact with Arg95 [32].

Pyridine derivatives have also been illustrated as anti-TB agents, compound 22 (Fig 7), which presents inhibitory activity with an IC₅₀ value of 0.38 μM, its possible mechanism of action is through glutamine synthetase inhibition. This would be the first inhibitor compound not derived from amino acids [33]. Another series of pyridine derivatives were developed, compound 23, a potent anti-TB agent with activity similar to RIF. The results showed that an imidazole group as a substituent is equivalent to a nitro phenyl group, which has been reported in anti-TB agents derived from 1,4-dihydropyridine carboxamides [34].

The thiosemicarbazone derivatives can be used in TB therapy and prophylaxis. The 1H-2-thiosemicarbazoneindolone derivatives indicated that halogenation of R₄, elongation of the alkyl chain in R₂, substitutions of the alkyl chain in R₃ with cyclohexyl or phenyl and the presence of a substituent in R₅, are more efficient for increasing anti-TB activity, while R₃ substitutions with a nitro group produce the most active compounds. The presence of a morpholine ring in Schiff bases substituted in R₄ with a nitro group has a significant impact on anti-TB activity. The results indicated that the elongation of the alkyl chain increases activity. This enhanced activity is related to lipophilicity properties. Also, replacement of the alkyl chain in R₃ and phenyl unsubstituted ciclohexyl has led to more active compounds (27). The absence of substitutions at N₁ on the indole ring and increased lipophilicity appear to be responsible for high activity against M. tuberculosis [36]. The thiosemicarbazone-derived compounds have exhibited important anti-TB activity with an IC₅₀ value of 2.59 μM/ml is compound 28 (Fig 9) [37].

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Amino group substitutions by phthalimide ring also lead to a decrease anti-TB activity (34, fig 12). Modifications in the pyridine ring decrease anti-TB activity. The phthalimide group by molecular hybridization did not produce compounds with activity similar to INH; however, it allowed for compounds with MIC values similar to PZA [40].

Figure 12: Phthalimide derivatives as anti-TB agent (34)

The compounds that act as inhibitors of the FAS-II system, diphenyl ether that interact with enzyme-cofactor binary complex, new compounds such as indols, benzofuran and cinnamic acid derivatives have been reported. Development of cinnamic acid derivatives would focus on more specific FAS-II inhibitors. A series of compounds 35 (fig 13) was determined that addition of an alkyl chain increases anti-TB activity. The compound 64 was the most active substance with an MIC of 0.1μg/ml[41]. The amide derivatives of fatty acids have anti-TB activity. These compounds are designed to penetrate bacterial cells, which can be useful for the mechanism of INH resistance, this can be due to factors such as mutations in unknown genes, decreased permeability, or increased efflux [42].

Figure 13: Cinnamic derivatives (35).

5. Other non nitrogen heterocyclic derivatives

The hybrid compound has been used for the design of anti-TB agents such as compound 31 (figure 11), formed from dibenzofuran and 2,2- dimethylpyran subunits. The modifications of benzofurobenzopyran have showed less active compounds such as compound 32, where the furan B ring is replaced by an ether linker, a carbonyl group, a hydroxy methylene or a methylene group. The modifications such as acylation and bromination in 5-position on the C ring have produced inactive compounds. Other derivatives of compound 31, substitutions with a hydroxy, methoxy, or halogen group on benzofurobenzopyran increases anti-TB activity. The hydroxy compounds with good activity also showed cytotoxic activity on VERO cells. Halogenated compounds with a Cl or Br atom in 8, 9 and 11-position, exhibit improved potency than compound 31. The potency was significantly decreased when the A ring was substituted by an electron withdrawing group. The electron donating group substitutions such as hydroxy or methoxy showed significant increase activity (33). All these compounds showed a possible mechanism of action of interaction with lipid biosynthesis of the M. tuberculosis cell wall and act as an epoxy-mycolate synthesis inhibitor [39].

Figure 11: Structure of benzofurobenzopyran as anti-TB agents (31-33).

Other compounds with phthalimide moiety have described as biophor to design new drugs with different biological activities. The hybridization of both phthalimide (thalidomide) and sulfonamide (dapsone) moiety leads to compounds with antileprotic activity. The design of new compounds with anti-TB activity is interesting. A series of derivatives showed that if the pyrimidine ring is substituted in any position or changed by an isosteric, this decreases anti-TB activity.

6. Drugs in clinical trials

The bicyclic nitroimidazofurane derivatives have anti-TB activity, such as CGI-17341, this compound is mutagenic. This has led to the development of PA-824. Its mechanism of action is to inhibit M. tuberculosis cell wall lipids and protein synthesis. It also inhibits replicating bacteria. The derived oxazoles as anti-TB compounds led to the development of OPC-67683, which has excellent activity in sensitive and resistant M. tuberculosis strains. Its mechanism of action involves inhibition of the synthesis of keto-mycolic, and methoxy-mycolic acid, although is possible another possible mechanism of action or interaction with another drug target in M. tuberculosis. The OPC-67683 also acts as a prodrug, since M. tuberculosis metabolizes it and produces as a product desnitro-imidazoazo metabolite. TMC207 is a quinoline derivative with potent anti-TB activity in susceptible, DR and XDR strains. Its mechanism of action involves inhibition of ATP synthase that binds the M. tuberculosis membrane and there is a synergistic effect between TMC207 and PZA. Other very promising compounds anti-TB compounds are LL-3858 and OPC-37306 [43-45].
References


