



# Mini review on Ethambutol and its some analogues as antitubercular agents

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## ARTICLE INFO

### Article history:

Received: 23 September 2012;

Received in revised form:

20 November 2012;

Accepted: 29 November 2012;

### Keywords

Antitubercular,  
Ethambutol,  
Analogues,  
*Mycobacterium*.

## ABSTRACT

Tuberculosis caused by *Mycobacterium tuberculosis* and has increased dramatically in recent years because of their tendency to develop new strains under any circumstances and developing resistance against the available drugs. In spite of many significant advances in tuberculosis chemotherapy, the widespread use and misuse caused the emergence of bacterial resistance to drugs. In particular, the emergence of multidrug resistant and extensive drug resistance strains, which is a serious threat to public health. Therefore, recently attention has focused on the treatment of tuberculosis to against resistant *mycobacterium* species has become one of the most important areas. Therefore, in this article efforts have been directed toward exploring potential of ethambutol and its analogues as antitubercular agents. Although, there is an increasing resistance to antimicrobial drugs, to overcome the development of drug resistance it is necessary to synthesize new derivatives of antibacterial agent ethambutol.

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## Introduction

Tuberculosis (TB) is one of the oldest and most pervasive, respiratory transmitted diseases in history. According World Health Organization (WHO) report, TB has spread to every corner of the globe. As much as one-third of the world's population is currently infected, more than any other infectious disease.<sup>1-4</sup> It was estimated that nearly 1 billion more people will be infected with TB in the next 20 years.<sup>5-9</sup> Direct Observed Treatment, short-course (DOTS) strategy, constitutes the cornerstone of the current protocol for control of TB. However, the three key drugs, isoniazide, pyrazinamide and rifampicin, used in the regimen are potentially hepatotoxic and may lead to drug associated hepatitis. Despite the undoubted success of DOTS strategy, the emergence of multidrug resistant (MDR-TB) and extensive drug resistance (XDR-TB) strains, recurrently isolated from patient's sputum, darken the future.<sup>10-14</sup> The increase in TB incidence during recent years is largely due to the prevalence of TB is synergy with Human Immunodeficiency Virus (HIV) epidemic, which augments the risk of developing the disease 100-fold and also the emergence of MDR-TB strains. In addition to this, the increase in *M. tuberculosis* strains resistant to front line anti-TB drugs such as rifampin and isoniazid has further complicated the problem, which clearly indicates the need for more effective drugs for the efficient management of TB.<sup>15-20</sup>

## Chemotherapy of Tuberculosis

Chemotherapy of TB are mainly depends on first-line antitubercular drugs, which include streptomycin, isoniazid, rifampicin, ethambutol and pyrazinamide, they more effective and less toxic as compare to second-line anti-TB drugs (Kamal et al, 2008). There are six classes of second line drugs that are used in the treatment of tuberculosis. A drug may be classified as a second-line because of one of two possible reasons: it may be less effective than the first-line drugs or it may have toxic side-effects or. These comprise of different classes namely, aminoglycosides (amikacin, kanamycin), polypeptides (capreomycin, viomycin), fluoroquinolones (ciprofloxacin,

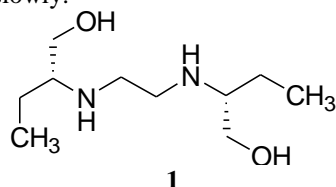
moxifloxacin, etc), thioamides: (ethionamides, prothioamide), cycloserine and *p*-aminosalicylic acid.<sup>21-25</sup>

**Toxic Effects of Currently Used Antitubercular Drugs:** The currently available key medications (first line) used in the regimen are show serious side effects like severe damage to the eighth cranial nerve, inducing irreversible impairment of auditory function, hypersensitivity reactions (streptomycin), potentially hepatotoxic and may lead to drug associated hepatitis (isoniazide, pyrazinamide and rifampicin (rifampicin, rifabutin, rifapentine) and thrombocytopenic purpura (rifampicin). Second line anti-TB drugs are more toxic than first line drugs, amikacin and kanamycin causes kidney damage as well as hearing loss, viomycin and capreomycin causes nephrotoxicity and eighth cranial nerve toxicity. Fluoroquinolones (ciprofloxacin, moxifloxacin, ofloxacin (levofloxacin, the chiral form of ofloxacin is more effective), gatifloxacin, trovafloxacin, enoxifloxacin and sparfloxacin etc). Fluoroquinolones are increasingly contraindicated for patients due to growing prevalence of antibiotic resistance. Ethionamid and prothionamide (structural analogues of isoniazid) causes adverse effects are gastro-intestinal tract disorders (anorexia, salivation, nausea, abdominal pain, and diarrhea), mental disturbances (depression, anxiety, psychosis, dizziness, drowsiness, and headache) and hypersensitivity (Stahlmann and Lode.1999). Cycloserine causes side effects of this drug are mainly CNS manifestations such as headache, irritability, depression, convulsions. Para amino salicylic acid causes gastro-intestinal tract problems including anorexia, nausea, epigastric pain, abdominal distress, diarrhea, ulcers and hypersensitivity.<sup>26-30</sup>

## Ethambutol (MYAMBUTOL):

Ethambutol (EMB) is a water-soluble and heat-stable compound. Dextro isomer of *N,N'*-bis-(1-hydroxy-2-butyl) ethylenediamine (EMB) (1) is one out of the four main drugs for treatment of TB. The meso isomer is less active whereas the levo isomer is almost inactive. It is also active in organisms resistant to streptomycin and isoniazid, but is always used in combination. It is active at a dose of 0.95-7.5 µg/mL. In general,

it is well tolerated but has been reported to induce ocular toxicity as a result of depletion of copper and zinc levels. Resistance to EMB develops slowly.<sup>31-36</sup>



EMB is orally active and clinically-used (+) isomer is 16 time more potent than meso isomer and 200 time more potent than (-) isomer. Mycolic acids are covalently bound to peptidoglycan via arabinogalactan. EMB inhibits the polymerization of cell wall arabinan, and results in the accumulation of the lipid carrier decaprenol phosphoarabinose. EMB may interfere with the transfer of arabinose to the cell wall acceptor. EMB is usually bacteriostatic and active only towards actively dividing cells. It is synergistic with rifamycins because EMB enhances intracellular access.<sup>37-40</sup> Nearly all strains of *M. tuberculosis* as well as a number of strains are sensitive to EMB.<sup>41</sup> The sensitivities of other nontuberculous organisms are variable. ETM has no effect on other bacteria. It suppresses the growth of most isoniazid- and streptomycin-resistant mycobacterium. Resistance to ethambutol develops very slowly *in vitro*. Mycobacteria take up ethambutol rapidly when the drug is added to cultures that are in the growth phase. However, growth is not significantly inhibited before about 24 hours. EMB inhibits arabinosyl transferases involved in cell wall biosynthesis. Bacterial resistance to the drug develops *in vivo* via single amino acid mutations in the *embA* gene when ethambutol is given in the absence of other effective agents.<sup>42-45</sup>

Ethambutol has been used in the therapy of TB of various forms when given concurrently with isoniazid. Because of a lower incidence of toxic effects and better acceptance by patients, ethambutol has essentially replaced aminosalicylic acid. The usual adult dose of ethambutol is 15 mg/kg given once a day. Some physicians prefer to treat with 25 mg/kg per day for the first 60 days and then to reduce the dose to 15-25 mg/kg per day. EMB accumulates in patients with impaired renal function, and adjustment of dosage is necessary. EMB is not recommended for children under 5 years of age. Children from ages 6 to 12 years should receive 10 to 15 mg/kg per day. The use of EMB in the chemotherapy of TB is described below.<sup>46-50</sup>

#### Side Effects

The most important side effect is optic neuritis, resulting in decreased visual perception and loss of ability to differentiate red from green. Recovery usually occurs when EMB is withdrawn; the time required is a function of the degree of visual impairment. EMB produces very few untoward reactions like rashes and fever. Other side effects that have been observed are pruritus, joint pain, gastrointestinal upset, abdominal pain, malaise, headache, dizziness, mental confusion, disorientation, and possible hallucinations. Numbness and tingling of the fingers owing to peripheral neuritis are infrequent. Anaphylaxis and leukopenia are rare. Therapy with EMB results in an increased concentration of urate in the blood in about 50% of patients, owing to decreased renal excretion of uric acid. This side effect is possibly enhanced by isoniazid and pyridoxine.<sup>51-53</sup>

#### Compounds Originating from Existing Drug Ethambutol

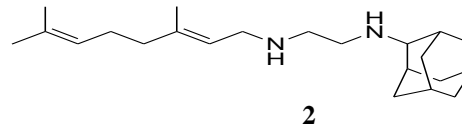
The five first-line drugs for treatment are highly effective and the rate of severe adverse reactions is low and six classes of second line drugs, it may be less effective than the first-line

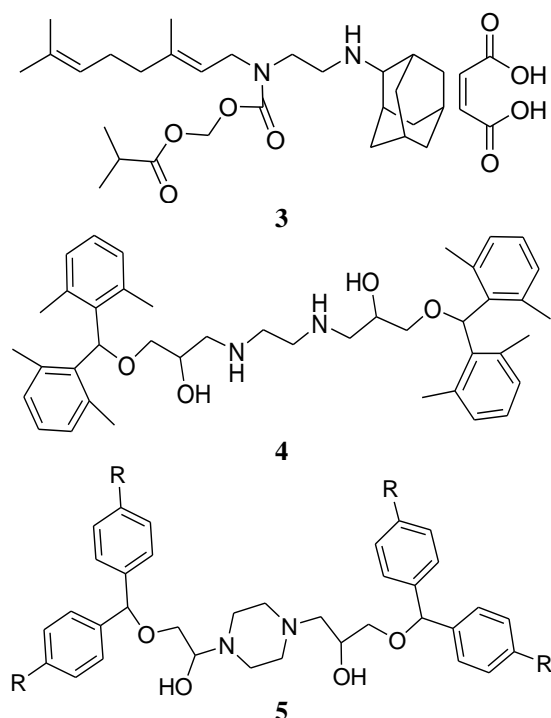
drugs or it may have more toxic side-effects. However, unpleasant side effects, relatively long duration of treatment and non-compliance to treatment regimen are drawbacks. Such non-adherence with the course of treatment leads to treatment failure and the development of drug resistance. The second line drugs used for MDR-TB are more expensive, less effective and more toxic than the five drug standard regimen. The goal now is to develop bactericidal drugs, which efficaciously treats infectious MDR/XDR strains of *M. tuberculosis* and latent infections with shortened treatment periods as well as reduced frequency of dosage. Some of recently discovered first line drug ethambutol analogues as anti-Tb agents are discussed below.<sup>54-59</sup>

#### Ethambutol analogues:

Ethambutol (EMB) is one of the main drugs used in TB-treatment regimens and it has now replaced streptomycin and thiacetazone. EMB interferes with construction of the arabinogalactan layer of the mycobacterial cell wall. The structure of EMB is favourable to the preparation of analogues by combinatorial chemical techniques. Biological screening of EMB analogues has resulted in the identification of various compounds worthy of further evaluation. Of these, few have been tested for TB activity and at least one has been shown to have good oral activity at 10mg/kg comparable with EMB efficacy at 100mg/kg. Cross resistance with the parent drug is unlikely to be a serious consideration. These analogues were tested, like the parent molecule, all appear to have a static rather than a cidal action and are not active against non-mycobacterial microbes. However, unlike EMB they are poor metal ion chelators and consequently are not expected to induce the same ocular toxicities.<sup>60-64</sup>

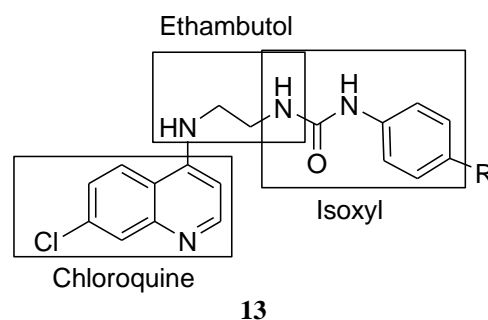
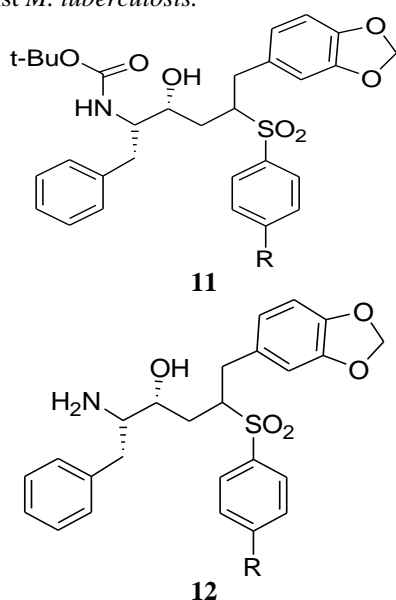
Amino alcohols that include EMB, which is used for pharmacological TB treatment, are an important class of compounds. This compound has been widely studied determining that the 1,2-ethylenediamine moiety is the EMB pharmacophore, possibility due to chelate bond formation with divalent metal ions such as copper. Based on EMB, a second-generation agent has been developed, a compound called SQ109 (2), which is being tested in clinical trials. It is a drug that exhibits potent anti-TB activity against *M. tuberculosis* strains, including multidrug resistant strains (MDR-TB) *in-vitro* and *in-vivo*. Unfortunately, SQ109 has poor bioavailability of only 12% and 3.8% in rats and dogs, respectively. This compound undergoes oxidation, epoxidation and *N*-dealkylation, which cause its low bioavailability; therefore strategies have been designed to improve its bioavailability minimizing this first-pass effect. Prodrugs based on carbamate groups are a good option for reducing this effect. A new series of analogues based on carbamate prodrugs of SQ109 (3) that provide good chemical stability as substrates of plasma esterase. The results of bioavailability of these compounds show a five-fold increase of the SQ109 reference compound.<sup>65</sup> Alternatively, new analogues of S2824 (4), a second-generation compound derived from EMB. The results show that new analogues with a homopiperazine ring (5) have high *in-vitro* activity against both sensitive and MDR-TB strains.<sup>66</sup>





**Fig 2. Structure of SQ109 and analogs**

In the design of new 1,2-diamine derivatives (6) compounds with 35 times more activity than EMB have been developed. Interestingly, they do not have the same target as EMB. An SAR study has determined that the presence of an  $\alpha$ -hydroxy group on the amine increases anti-TB activity. However, the distance between oxygen and nitrogen atoms in EMB are the same as between both atoms in the hydroxyl-ethylamine signifying a relationship between both structures (7). In a new series of EMB analogs, it was determined that the sulfonamide moiety reduces anti-TB activity against *M. tuberculosis*, and that the amino alcohol moiety on hydroxyethyl sulfonamide is crucial for anti-TB activity, where the presence of a carbamate moiety leads to a loss of activity. It has been reported that compounds lose the basicity of the amino group (7), results in a loss of activity.<sup>67</sup> Finally, EMB has served as a proposal for tripartite hybridization (chloroquine, isoxyl and ethambutol) for the development of new anti-TB agents (8), which exhibit high activity against *M. tuberculosis*.<sup>68</sup>



**Fig. 3 Ethambutol analogs as anti-TB agents**

#### Discussion:

In view of the persistent drug-resistant TB problem of currently used anti-TB agents, it is important that new molecules or drugs should address different targets, as those of currently used drugs including the shortening of TB therapy with negligible toxicity and thus structures based on this new molecule could provide a new chemotherapeutic agent against TB. The unique structure of the mycobacterial cell wall makes it a useful target for drug development. Many unique metabolic processes occur during the biosynthesis of mycobacterial cell wall components. One of these attractive targets for the rational design of new anti-TB agents are the mycolic acids, the major components of the cell wall of *M. tuberculosis*.<sup>69-72</sup> Development of new chemotherapeutic drugs is the need to control TB. However, in recent years there is an enhanced activity in the research and development of new drugs for TB. Some anti-TB drug analogues are presently in clinical development, being investigated pre-clinically in an attempt to explore new drug molecules for the treatment of TB. The identification of novel target sites will also be needed to avoid the problems associated with the increasing occurrence of MDR-TB and XDR-TB strains.<sup>73-76</sup>

A newer and potent TB treatment should offer following three improvements over the existing regimens: shorten the total duration of treatment and/or significantly reduce the number of doses, improve the treatment of MDR-TB and XDR-TB, provide a more effective treatment of latent TB infection. In order to analyse useful to group drug candidates currently in two main categories: 1) Novel chemical entities and 2) Compounds originating from existing families of drugs. Drug resistance by *M. tuberculosis* is an important obstacle for the treatment and control of TB. The main difference is that XDR-TB is associated with a much higher mortality rate than MDR-TB, because of reduced number of effective treatment options.<sup>77-80</sup> Hence there is an urgent need for new drugs that are active against *M. tuberculosis* in order to shorten the duration of TB therapy.

**Conclusion:** In spite of the availability of various chemotherapeutic agents, TB remains a leading infectious killer worldwide. This is mainly due to the lack of new drugs, particularly effective against MDR-TB and XDR-TB, and patients co-infected with HIV/AIDS. Therefore, there is an urgent need for the development of new anti-TB drugs with lesser side-effects, with improved pharmacokinetic properties. In view of above facts and inspired by the research going on new derivatives, particularly in relation to mycobacterium chemotherapy, different new drugs will be synthesized in the future for development of new effective anti-TB molecule.

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