Anti-tubercular Potential of Ethylenediamine Derivatives: A Short Review

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ABSTRACT
Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. Control of TB is complicated by the long-course therapy regimens, the incapability to eliminate latent organisms, and the increasing appearance of multidrug resistant strains of *M. tuberculosis*. New drugs for the prevention of TB are urgently required, including developments of new drug regimens to minimize the emergence of drug resistance, to treat MDR-TB patients and to eliminate the latent bacteria. Recent years, many new structural classes of anti-TB agents are come out, some of which exhibit promising activities against vulnerable and resistant strains of *M. tuberculosis*. In particular, the newly discovered ethylenediamine derivatives with significant anti-TB activity and generated considerable excitement.

Keywords: Ethylenediamines, *Mycobacterium tuberculosis*, drug resistance, drug development

1. INTRODUCTION
Tuberculosis (TB) remains at the beginning of the 21st century the world's leading infectious disease with a global prevalence of more than billion people. One-third of the world's population is currently infected; more than 5000 people die of TB every day. A great number of people are carriers of the latent form that creates dangerous source of illness for the future. The pandemic of AIDS has had a major impact on the worldwide TB problem. Another factor contributing to the rise in TB and responsible for the increased death rate is the emergence of new strains of *Mycobacterium tuberculosis* (*M. tuberculosis*) resistant to some of the current antituberculotic (anti-TB) drugs, so called multidrug resistant TB (MDR-TB). To date, many drugs are available, which are classified into two categories. First line therapy includes five medications: isoniazide (isonicotinic acid hydrazide), pyrazinamide (analog of nicotinamide), ethambutol [(S,S´)-2,2´(ethylenediimino)di-1-butanol], rifampicin (lipophilic ansamycine) and streptomycin (aminocyclitol glycoside). Second line therapy, which is used exceptionally in the cases of drug resistance, includes cycloserine, capreomycin, fluoroquinolones, ethionamide, PAS, thioacetazone, rifabutin, clofazimine and some macrolides (Asif et al., 2014; Asif et al., 2013; Asif et al., 2013; Asif M et al., 2013). The major setback in controlling tuberculosis was the emergence of multidrug resistant tuberculosis (MDR-TB) during 1990-92. Currently, at

least 50 million people are estimated to be affected with MDR-TB. A few MDR strains of *M. tuberculosis* were found to be resistant to many first line agents as well as some of the second line drugs (Belanger, et al., 1996). Moreover, the high rate of coinfection with human immunodeficiency virus (HIV) presented a challenge to the existing chemotherapies. One of the limitations of currently available drugs is their inability to act on latent bacilli. People carrying latent infection are at a risk of reactivation and this is one of the major barriers in controlling tuberculosis. Therefore, there is an urgent need to develop novel drugs that can act against both actively growing and dormant bacteria. The efforts for drug development, has been involved in developing public-private partnerships to bring out new, faster-acting and affordable drugs against tuberculosis. Rational development of a new antitubercular agent requires the exploration of new means to understand the genetics and physiology of *M. tuberculosis*. In this regard, availability of the genome sequence of *M. tuberculosis* and powerful genetic tools for manipulating mycobacteria have provided valuable information about the potential targets (Asif. 2013; Asif. 2012). This review exclusively focuses on mycobacterial targets that have been patent protected from all over the world in the last ten years. The potential drug targets compiled in this review are likely to lead to new medication that should facilitate in controlling the spread of TB.

2. CURRENT THERAPY OF TB

Chemotherapy of TB started in 1940s. In 1943, anti-TB research resulted in discovery of the active anti-TB agent, streptomycin (SM). From that time, various agents have been discovered and introduced in anti-TB agent, including *para*-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cycloserine (1955), ethionamide (1956), rifampin (1963) and ethambutol (1962). The most of these drugs were discovered through broad screening and very little optimization was undertaken with less regard to the targets of drug action. The lack of perceptive of drug action was compounded by a profound ignorance of the biochemistry of the *Mtb* bacillus (Cole and Alzari. 2007; Dye. 2006; Janin. 2007). The current short-course TB therapy used to treat drug-susceptible MTB consists of 2 months' treatment with four so-called first-line drugs including rifampin (RIF), isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB), followed by 4 months' treatment with RIF and INH. Infection by MDR-TB strains requires treatment with second-line drugs such as kanamycin, amikacin, capreomycin, *p*-aminosalicylate (PAS), fluoroquinolones (FQs) (levofloxacin, gatifloxacin and moxifloxacin), ethionamide (ETH), and cycloserine where treatments often extend for as long 2 years (Zhang et al., 2006; Zhang. 2005).

3. ETHAMBUTOL

Ethambutol (Myambutol; ethambutol hydrochloride, EMB, Dextro isomer of *N,N*′-bis-(1-hydroxy-2-butyl)ethylenediamine) (**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. EMB is a water-soluble and heat-stable compound. Approximately all strains of *M. tuberculosis, M. kansasii* and several of strains of MAC are sensitive to EMB (Pablos-Mendez *et al,* 1998). The sensitivities of other nontuberculous organisms are inconsistent. It has no effect on other bacteria. It suppresses the growth of nearly all INH- and streptomycin-resistant tubercle bacilli. Resistance to EMB expanded very slowly *in vitro* and it 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 EMB is given in the nonappearance of other effective drugs (Belanger *et al,* 1996). It is used with remarkable achievement in the therapy of TB of various forms when given along with with isoniazid. Because of a lower occurrence of toxic effects and better receipt by patients, EMB has really replaced aminosalicylic acid. It is used orally in D isomer form. The normal adult dose of EMB is 15-25 mg/kg/day for the first 60 days and then to reduce the dose to 15 mg/kg per day, mainly for those who have received earlier therapy. For children ages 6 to 12 years must receive 10 to 15 mg/kg per day. It collected in patients with impaired renal activity, and alteration of dosage is essential. It is not suggested for children less than 5 years of age, in part because of concern about the capability to test their visual sharpness. The EMB develops resistance slowly. The main side effect is optic neuritis, resulting in decreased visual acuity and loss of ability to differentiate red from green (Kemper, et al., 1992; Shafran, et al., 1996; Bass, et al., 1994). The intensity of the visual trouble is connected to the duration of therapy after the reduced visual acuity first becomes evident and may be unilateral or bilateral. Revival generally occurs when EMB is withdrawn; the time required is a role of the degree of visual impairment. Fewer than 2% patients who received daily doses of 15 mg/kg of EMB had adverse reactions: 0.8% practiced diminished visual acuity, 0.5% had a rash, and 0.3% developed drug fever. Other side effects are pruritus, joint pain, GIT upset, abdominal pain, dizziness, mental confusion, malaise, headache, disorientation, and possible hallucinations. Numbness and tingling of the fingers due to peripheral neuritis are rare. Anaphylaxis and leukopenia are rare. Therapy with EMB results in an raised level of urate in the blood in about 50% of patients, owing to reduced renal excretion of uric acid. This inconvenient effect is possibly raised by isoniazid and pyridoxine (Postlethwaite *et al,* 1972; Mdluli and Spigelman. 2006; Monfeli and Beeson. 2007; Rivers and Mancera. 2008; Sarkar and Suresh. 2011).

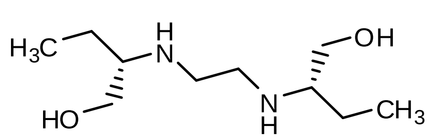
4. ETHYLENEDIAMINE ANALOGUES

The N,N0-diisopropylethylenediamine (**1**) was the first compound in this series developed in early 1950s against MTb. Structural modification of the lead compound led to the discovery of ethambutol (**1**) (Thomas et al., 1961; Shepherd and Wilkinson. 1962; Shepherd et al., 1966; Wilkinson and Shepherd. 1969). Despite its modest potency, EMB is a first-line drug for the treatment of TB.

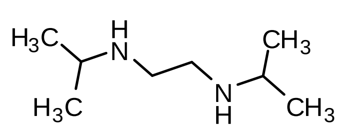
4a. Structure Activity Relationship

Initial studies of structural changes of EMB concluded that the size and nature of the alkyl group on the ethylenediamine nitrogens were critical for activity. The small a-branched alkyl groups were more effective than alkyl chains branched at positions other than that a longer alkyl chain was unfavorable to activity (Shepherd and Wilkinson. 1962). Alterations in the linker region of the molecule were deleterious since any lengthening, incorporation of heteroatoms, or branching of the ethylene from linker led to reduced activity. In addition, aryldiamines and cycloalkylamines were far less effective than the parent compound. The ethylenediamine unit is the minimum pharmacophore required for anti-TB activity. Any change in the basicity of either amino group led to decreased anti-TB activity, with the exception of substitution of the amine with an amide that retained partial activity in some analogs (Hausler et al., 2001). Due to the lack of crystallographic information about the membrane-bound arabinosyltransferase enzyme which is the presume target of EMB (Belanger et al., 1996; Telenti et al., 1997). A library of 63,238 asymmetric diamines was evaluated against *M. tuberculosis* (Lee et al., 2003) of which 25 were either more effective or had comparable activity to the parent compound. The most effective compound, SQ-109 (**3**), was chosen for development based on its activity and pharmacokinetic properties (Fig. 1).

Although it was initially assumed that SQ-109 (**3**) and EMB (**1**) would share the same arabinosyltransferase target, which catalyzes the transfer of arabinosyl residues to the cell wall arabinogalactan polymer, SQ-109 retained potency against EMB resistant strains. In addition, transcriptional profiling studies and analyses of cell wall-linked sugar residues indicated that MTb responds differently to these compounds, suggesting that SQ-109 acts on a different target than EMB (Protopopova et al., 2005; Boshoff et al., 2004). Pharmacokinetic profile of SQ-109 after a single dose shows C max after intravenous and oral use as 1,038 and 135 ng/mL, respectively. The $t_{1/2}$ for the drug after i.v. and oral administration were 3.5 and 5.2 h, respectively. The SQ-109 showed a large volume of distribution into various tissues. SQ-109 levels in most tissues after a single administration were significantly higher than that in blood. The highest level of SQ-109 was present in lung (>MIC), which was at least 120-fold (p.o.) and 180-fold (i.v.) higher than that in plasma with the next ranked tissues being spleen and kidney (Jia et al., 2005; Jia et al., 2006). SQ-109 is highly unstable to human microsomes as evidenced by its oxidation, epoxidation, and N-demethylation and has been shown to have poor oral bioavailability, most probably due to its poor solubility and first pass metabolism (Jia et al., 2005). In a continued effort to enhance the efficacy of SQ-109, carbamate analogs (**4**), which act as prodrugs of the parent compound, have recently been synthesized. Carbamate-based esterasesensitive drug conjugates have been used to create prodrugs of both amines and amidates (Sun et al., 2001; Maryanoff et al., 2006; Burkhart et al., 2006). These carbamates are stable in microsomal assays, but are substrates for plasma esterases. When administered orally, these prodrugs can bypass first pass metabolism in the liver. The bioavailability studies of the new analog **4**, when compared with SQ-109 in a rat model and showed major improvement (Meng et al., 2009). After oral dosing of 13 mg/kg of SQ-109 or **4**, bioavailability of free SQ-109 from pro-SQ-109 **4** was 91.4% compared to 21.9% from SQ-109 (Tuberculosis 2008). The concentration of SQ-109 after oral administration is higher in lungs than in liver, spleen, and plasma (Meng et al., 2009), which may be beneficial for a pathogen predominantly linked with lung disease (Tuberculosis 2008). Amino alcohols that include EMB, which is used for TB treatment, are main class of compounds with various utilities. The 1,2-ethylenediamine moiety is the EMB pharmacophore, possibility due to chelate bond development with divalent metal ions like copper. Based on EMB, a second-line drug has been developed, a agent SQ109 (**3**), which is being tested and exhibits potent activity against *M. tuberculosis*, including MDR-TB strains. Unfortunately, SQ109 has poor bioavailability of about 12% and 3.8% in rats and dogs, respectively. This agent undergoes oxidation, epoxidation and *N*-dealkylation, which cause its low bioavailability, so strategies have been designed to improve its bioavailability and lower first-pass effect. Prodrugs supported on carbamate groups are a good choice for reducing this effect. Developed a new series of analogues based on carbamate prodrugs of SQ109 (**4**) that give good chemical stability as substrates of plasma esterase. The bioavailability of these agents shows a five-fold increase of the SQ109 drug (Meng et al, 2009).



Ethambutol (EMB) **1**



N,N'-diisopropylethylenediamine **2**

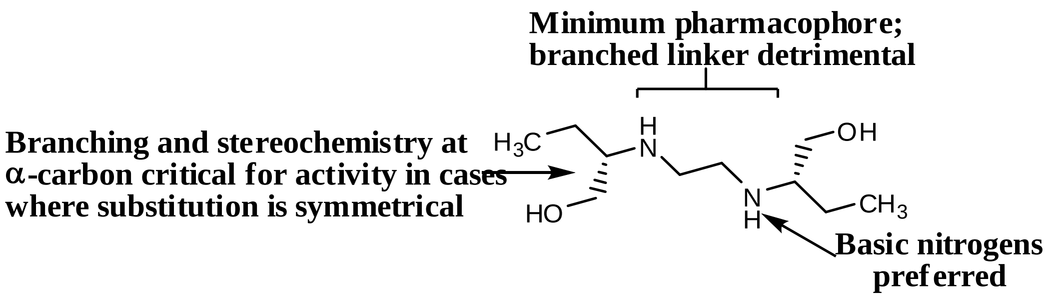
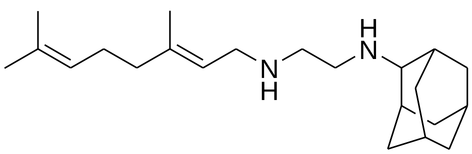
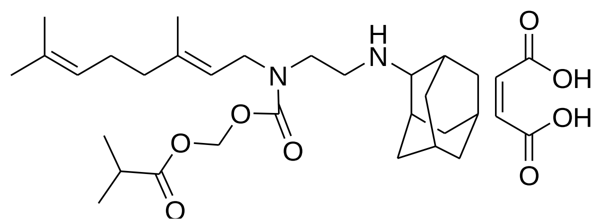


Figure 1

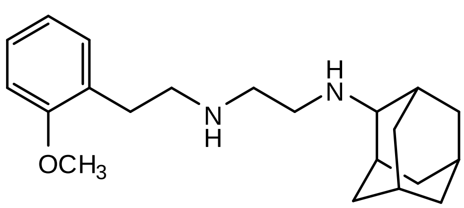
Structure activity relationship of ethylenediamine analogues



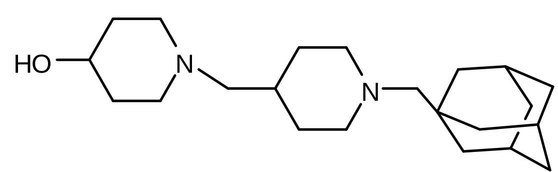
SQ-109 (**3**)



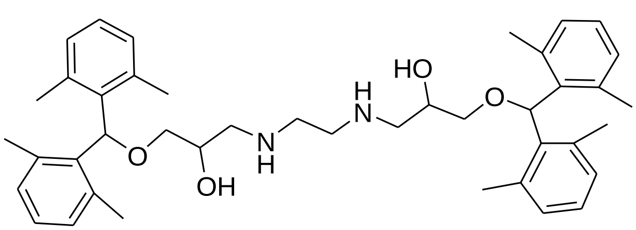
pro-SQ-109 (**4**)



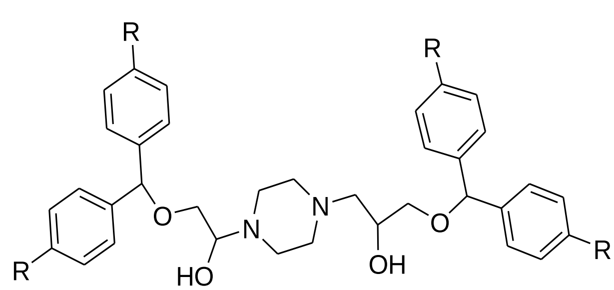
SQ-73 (**5**)



SQ-609 (**6**)



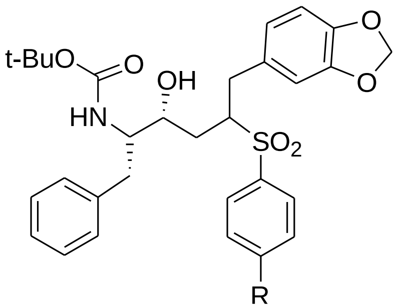
Compound 7



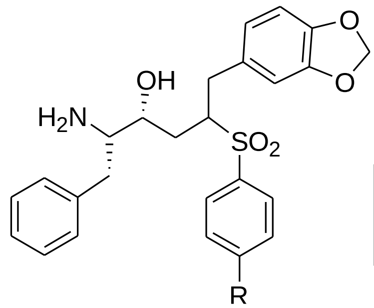
Compound 8

Figure 2

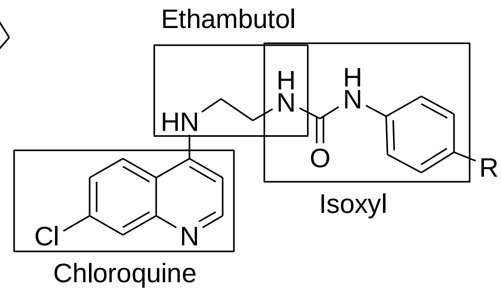
Structure of ethylenediamine and SQ109 analogs



Compound 11



Compound 12



Compound 13

Figure 3

Ethambutol analogues as anti-TB agents

4b. other diamine analogues

Another compound, SQ-73 (**5**), having a moderate MIC at 12.5 mM but a better therapeutic index of 6.4, and exhibited better activity in macrophages. In vivo studies with SQ-73 showed moderate tissue distribution (Protopopova et al., 2005). A structurally related dipiperidine compound was recently reported, with the most active agent from this series exhibiting an MIC of 6.25 mM against *M. tuberculosis* (Protopopova and Bogatcheva. 2003). After optimization and analysis of the dipiperidine library, compound SQ-609 (**96**) was selected as the most promising in the class. This compound has moderate in vitro cytotoxicity in cultured mammalian cells and a appropriate therapeutic window. SQ-609 has shown efficacy against intracellular *M. tuberculosis*, good aqueous solubility and oral bioavailability. In murine studies, SQ-73 (5 mg/kg), SQ-109 (10 mg/kg), and SQ-609 (10 mg/kg) showed activity similar to INH (25 mg/kg) after 3 weeks of treatment (Protopopova and Bogatcheva. 2003). Alternatively, synthesis of new analogues of S2824 (**7**), a second-generation drug derived from EMB. The new analogues with a homopiperazine ring (**8**) have high *in vitro* activity against both sensitive and MDR-TB strains (Zhang et al, 2009).

In the design of new 1,2-diamine derivatives (**9**) compounds with 35 times more activity than EMB have been synthesized. Interestingly, they do not have the same target as EMB. An SAR analysis has determined that the presence of an β-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 hydroxyethylamine signifying a good relationship between both structures (**10**). In a new series of EMB analogs obtained, it was determined that the sulfonamide moiety reduces activity against *M. tuberculosis*, and that the amino alcohol moiety on hidroxy-ethylsulfonamide is crucial for anti-TB activity, where the presence of a carbamate moiety leads to a loss of activity. It has been reported that if compounds lose the basicity of the amino group (**10**), loss of activity (Cunico et al, 2011). Finally, EMB has served as a proposal for tripartite hybridization (chloroquine, isoxyl and EMB) for the development of new anti-TB agents (**11**), which show high activity against *M. tuberculosis* (Nava-Zuazo et al, 2010).

5. DISCUSSION AND CONCLUSION

Tuberculosis is a leading infectious disease worldwide, even though the accessibility of TB therapy, half a year of treatment with multiple drugs is needed. New drug development strategies have permitted the find of new anti-TB drugs. These are increasingly more attention, and various new agents or analogues from existing drugs are investigated. For better understanding of the unique biology of TB, more targets will be authorized, and guide will emerge that will help us reach the aim of more effective agents that permit multiple stages and drug targets to be tackled (Duncan. 2004; Palomino et al., 2009; Shi and Sugawara. 2010). The revival of TB and the surge of MDR-TB have a key public health concern. In this review, some pharmacological statuses of ethylenediamine analogues were discussed and are being developed as anti-TB drugs. Some of these are under clinical investigation, while others are considered to be promising agents for future development and also describe the mechanism of drug resistance in mycobacteria, as well as new potential targets.

Peer-review

External peer-review was done through double-blind method.

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Conflict of Interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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