Mini Review Study of Antitubercular Drugs of Nicotinamide, Thioisonicotinamide and Pyrazinamide Derivatives

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Abstract

The tuberculosis is a typically chronic infection caused by Mycobacterium tuberculosis. The progress of effective treatment of tuberculosis (TB) has been recently due to alarm regarding the appearance of vastly drug-resistant TB strains. The efforts that gave rise to current first line and second-line anti-TB drugs in global use today and attempts to summarize ongoing discovery being conducted. The TB has different disease-specific concerns and control that introduce major complexity in drug discovery efforts. In this article a brief discussion about nicotinamide, thioisonicotinamide and pyrazinamide analogues for the better and effect TB treatment particular against resistance mycobacterium strains.

Keywords: Tuberculosis, nicotinamide, pyrazinamide, thioisonicotinamide, resistance

Introduction

Mycobacterium tuberculosis (*Mtb*) is a causative agent of tuberculosis (TB) that has latently infected a third of the world population (Zhang et al, 2006). Infection arises due to aerosol and gulp of air of a few droplets having *Mtb* bacilli is adequate for lung infection (Hassan et al, 2006). After infection, TB occurs in two stages. The first state that can persists for many years in the host and is known as latent TB. The second stage needs only a weaken immune response to become activated (Zhang, 2004), then the bacteria starts replicating and causing typical signs including cough, chest pain, fatigue and mysterious weight loss. If incomplete treated, the disease ultimately terminates in death. The appearance of Human Immunodeficiency Virus (HIV) and the resulting Acquired Immune Deficiency Syndrome (AIDS) epidemic emphasized the significance of reactivation of the disease and its potentially tragic outcome since over 50% of deaths among HIV-infected patients results from co-infection with *Mtb* with the two pathogens inducing each other's replication, thus hastening the subside of the immune system (Cole and Alzari, 2007). The World Health Organization (WHO) estimates that about 2 million deaths occur per year, that there are about 8 million new cases yearly, and that every third person on the earth has been uncovered to or infected by *Mtb* (Dye, 2006).

Though TB can be treated and still cured with therapy, management is extremely lengthy and takes 6-9 months (Blumberg, et al, 2003). In adding to major toxicity, prolonged treatment also causes poor patient agreements, which is a common cause for choice of drug resistant and often fatal multidrug resistant (MDR)-TB (Zang et al, 2006). Presently, TB therapy is made up of a combination of first-line drugs, isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA) and ethambutol (EMB), which are given for six months (Blumberg et al, 2006). If this treatment is not succeed due to bacterial drug resistance or intolerance to one or more drugs, second-line anti-TB drugs are used, like *para*-aminosalicilate (PAS), kanamycin, fluoroquinolones (FQs), capreomycin, ethionamide and cycloserine. These are usually less effective or more toxic with severe side effects (Blumberg et al, 2006). This second-line therapy can also result unsuccessful since MDR-TB strains exhibited resistance to second-line anti-TB drugs that are currently go higher (Zhang and Amzel, 2002). Therapy is also made relatively complex by the existence of metabolically silent, persistent or dormant strain inside host lesions. These are not vulnerable to the anti-TB drugs that generally kill growing but not persistent bacteria (Zhang, 2004). There are several reasons for drug resistance, including instruction of inadequate regimens, an unsure drug supply, and ineffective drugs, time of lengthy treatments is one of the main contributors because some TB patients too early stop their therapy after an initial, rapid heath improvement, thereby supporting the emergence of drug-resistant strains.

Drugs Used to Treat Tuberculosis

Tuberculosis is a major killer disease. The WHO estimates that 1 billion people will be newly infected in the period 2000-2020, resulting in 35 million more deaths. It has become clear that there is an ominous synergy between mycobacteria (*Mtb, M. avium-intercellulare*) and the HIV. In Africa, about 15% of HIV-linked deaths are caused by TB. The TB is out of control in many parts of the world and it is now the world's leading cause of death from a single agent. Against this progressively more troublesomes conditions, the first-line drugs and some second-line anti-TB drugs available and may be used for the treatment of this infections. To reduce the risk of the emergence of resistant organisms, compound drug therapy is used, involving a first initial phase of about 2 months consisting of three drugs used concomitantly: INH, RIF, PZA (plus EMB if the organism is suspected to be resistant) and second, continuation phase, of 4 months, consisting of two drugs: INH and rifampicin; longer-term treatment is needed for patients with meningitis, bone/joint participation or drug-resistant infection (Asif et al., 2013; Asif et al., 2013; Asif et al., 2014).

Anti-TB Drugs

To avoid appearance of resistant strains, compound therapy is used, e.g. three drugs initially, then two drugs later.

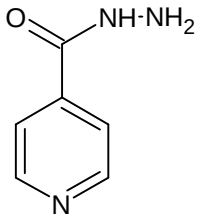
First-Line Drugs

- **Isoniazid** kills actively growing mycobacteria within host cells; mechanism of action unknown. Given orally it penetrates necrotic lesions, also the cebrospinal fluid (CSF). 'Slow acetylators' respond well. It has low toxicity. Pyridoxine deficiency increases risk of neurotoxicity. No cross-resistance with other agents.
- Rifampicin is a potent, orally active drug that inhibits mycobacterial RNA polymerase. It penetrates CSF. Unwanted effects are infrequent (serious liver damage occurred). It induces hepatic drug-metabolising enzymes. Resistance can develop rapidly.
- Ethambutol inhibits growth of mycobacteria by unknown mechanism. It is given orally and can penetrate CSF. Unwanted effects are uncommon; optic neuritis can occur. Resistance can emerge rapidly.
- **Pyrazinamide** is tuberculostatic against intracellular mycobacteria by an unknown mechanism. Given orally, it penetrates CSF. Resistance can develop rapidly. Unwanted effects: increased plasma urate, liver toxicity with high doses.

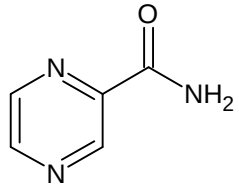
Second-Line Drugs

- Capreomycin is given intramuscularly. Unwanted effects include damage to kidney and to 8th nerve.
- Cycloserine is broad spectrum. It inhibits an early stage of peptidoglycan synthesis. Given orally it penetrates the CSF. Unwanted effects affect mostly CNS.
- Streptomycin, an aminoglycoside antibiotic, acts by inhibiting bacterial protein synthesis. It is given intramuscularly. Unwanted effects are ototoxicity (mainly vestibular) and nephrotoxicity. Infrequently used now.

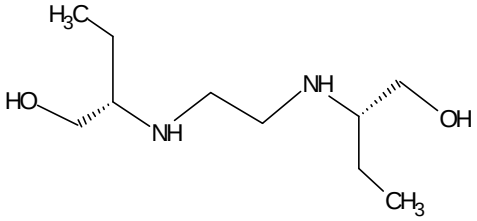
Unwanted effects are kidney damage and injury to the eighth nerve with deafness and ataxia. The drug should not be given at the same time as streptomycin or other drugs that may damage the eighth nerve.



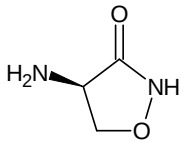
Isoniazid



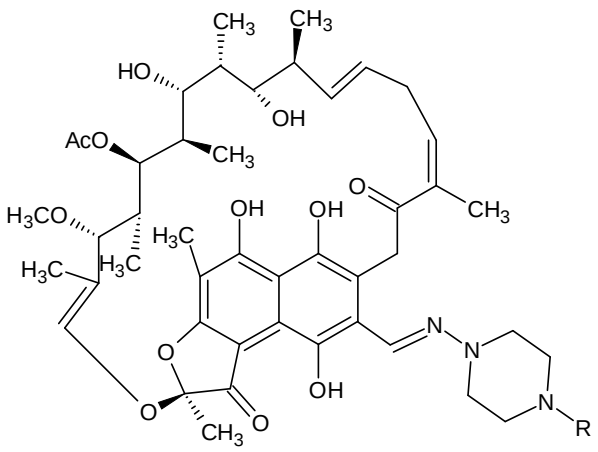
Pyrazinamide

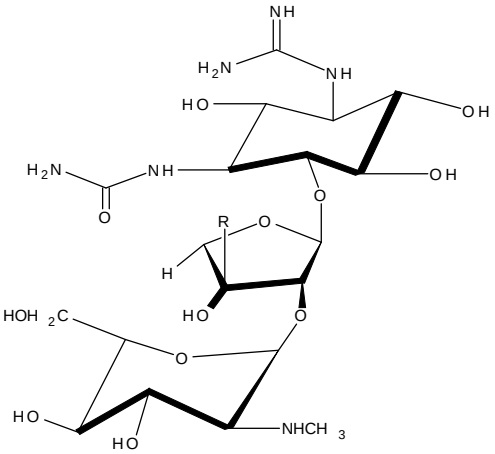


Ethambutol

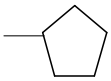


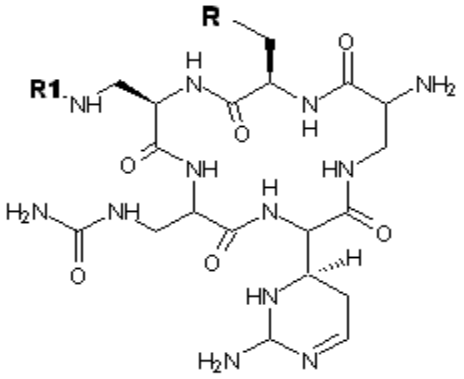
Cylcoserine

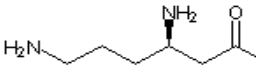




R = CH_3 Rifampicin **R = CHO Streptomycin**
R = $CH_2CH(CH_3)_2$ Rifabutin **R = CH_2OH dihydrostreptomycin**

R =  **Rifapentine**



R=OH; R_1= 

(or β-lysyl)

R=H; R_1= 

(or β-lysyl)

R=OH; R_1=H;
R=H, R_1=H

Capreomycin

Fig. 1: Structures of Different Antitubercular Drugs

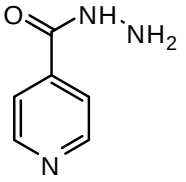
Reasonable Drug Design

One of the design strategies for new anti-TB agents is based on the improvement of analogs of first-line and/or second line anti-TB drugs. The strategies used and explore structure-activity relationships (SAR), which have guided to the development of new anti-TB agents. One difficulty that must be supposed in the design of anti-TB agents is that there is a subpopulation of bacteria in a persistent non replicating condition. This is measured a main causative factor to long anti-TB drug therapy. It is vital to determine if compounds have potential effect against these bacteria at the beginning of design and should also consider the physicochemical properties that directly affect the pharmacodynamics and pharmacokinetics of drugs and also notice the influence of stereoisomers on activity, because individual enantiomers have considerable differences in activity.

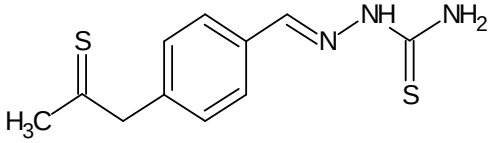
Isoniazid (INH)

The antibacterial activity of INH is limited to mycobacteria and it is bacteriostatic against resting organisms but can kill dividing bacteria. It passes generously into mammalian cells and effective against intracellular organisms. It inhibits the synthesis of mycolic acids, essential ingredient of the cell wall and atypical to mycobacteria. It combines with an enzyme that is exceptionally found in INH sensitive mycobacteria strains, this result in disorganisation of the metabolism of the cell. Resistance can happen and is caused by reduced penetration of the drug. Cross-resistance with other tuberculo-static drugs does not occur.

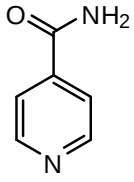
Adverse effects depend on the dosage, the main being allergic skin eruptions and other adverse reactions have been reported are fever, hepatotoxicity, arthritic symptoms, haematological changes and vasculitis. Adverse effects concerning the central or peripheral nervous systems are largely cost of a deficiency of pyridoxine and are general in malnourished patients unless disallowed by use of this drug (Bailey, et al., 1974; Banerjee, et al., 1994; Byrd et al., 1979; Comstock. 1983; Gangadharam. 1986; Garibaldi, et al., 1972). Pyridoxal-hydrazone formation occurs mostly in slow acetylators. The INH may cause haemolytic anaemia in patients with glucose 6-phosphate dehydrogenase deficiency and it reduces the metabolism of the antiepileptic drugs phenytoin, ethosuximide and carbamazepine, resulting in an increase in the plasma level and toxicity of these drugs (Kinzig-Schippers, et al., 2005; McGlynn, et al., 1986; Miesel, et al., 1998; Miller, et al., 1979). Isoniazid or isonicotinic acid hydrazide (**1**) is an analog developed from the anti-TB drug thiacetazone (**2**) which had been used effectively in TB patients in the 1940s but was linked with toxic side effects (Fox. 1952). In an effort to get better thiacetazone (**2**), the phenyl ring was changed with a pyridine ring based on the inspection that nicotinamide (**3**) had a growth inhibitory activity on *Mtb*. The isonicotinaldehyde thiosemicarbazone (**4**) proved to be more active than thiacetazone, which inspired estimation of other intermediates in the synthesis, leading to the discovery of INH the best anti-TB drug developed. Large numbers of INH analogues have been synthesized, but no compound improved on the activity of INH. The N-acetyl-INH, an INH metabolite formed in humans, is inactive, although N-alkyl analogues such as iproniazid (**5**) and hydrazones such as verazide (**6**) exhibit *in vivo* effectiveness although the active metabolite in *Mtb* is INH which is released by in vivo hydrolysis (Kakimoto and Tone. 1965; Fox.1953; Rubbo et al., 1957; Rubbo et al., 1958). The minimum inhibitory concentration (MIC) of INH is 0.2 mM against rapidly growing *Mtb*, with lower activity against slowly growing *Mtb* (Wayne and Sramek 1994). The INH is a prodrug that is activated by the KatG catalase to an isonicotinoyl radical that reacts with nicotinamide-containing substances like NAD (P) to give acyclic isonicotinoyl- NAD(P) adducts and their cyclic hemiamidals. The INH-NAD adduct is a potent inhibitor of the NADH-dependent enoyl-ACP reductase, InhA, involved in mycolic acid synthesis (Vilcheze and Jacobs. 2007; Rozwarski et al., 1998; Rawat et al., 2003). Mutations in katG or inhA give the majority of resistance, but other resistant isolates show mutations at targets that use pyrimidine nucleotides (Argyrou et al., 2006). It is well tolerated although side effects as a result of hepatic enzyme deformities and may cause hepatitis. Also, peripheral neuritis can occur but is easily prevented by the use of pyridoxine (Nolan, et al., 1999; Salpeter, et al., 1997; Snider. 1980; Zhang. 2004).



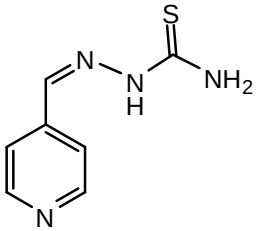
Isoniazid **1**



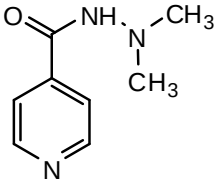
Thioacetazone **2**



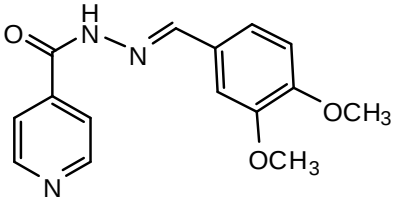
Nicotinamide **3**



Isonictinaldehyde thiosemicarbazone **4**



Iproniazid **5**



Verazide **6**

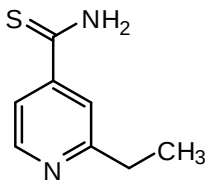
One of the strategies frequently used to develop new drugs is “hybridization”, a method that has been anticipated particularly for new anti-TB drugs. An example is the design of drugs based on INH or PZA, incorporating NR1R2 groups derived from a second anti-TB molecule or possibly other nucleophilic groups to provide anti-TB activity. These could be considered prodrugs because they contain two usual drugs that are bound by a CH fragment. Although the results of activity are very similar to those presented by INH and PZA, the hydrolysis of new compounds ensures prolonged release of the active drugs (Imramovsky et al, 2007). Various compounds derived from INH that include mostly a hydrazine fragment have been determined. Considering the inclusion of an oxadiazole moiety, developed new agents with high anti-TB activity.

Due to the substitution in 5-position on the oxadiazole ring, the compounds obtained showed high lipophilicity, this lipophilicity could facilitate passage of these compounds through the *Mtb* bacterial membrane (Navarrete-Vazquez et al, 2007). Structural modification of the hydrazide moiety on INH provided lipophilic adaptations of the drug that blocked the N-acetylation process, obtained high levels of *in vitro* activity against *Mtb* and macrophages infected, as well as low toxicity (Hearn et al, 2009). Another strategy in drug design is the formation of molecules that mimic the natural substrate of an enzyme. A new series of bi-substrate-type inhibitors based on a covalent linked between molecules mimicking the INH substrate and the NAD cofactor that could provide compounds with a high affinity and selectivity for the INH catalytic site. In these compounds, incorporating a lipophilic component into the nicotinamide hemiamidal framework provides more active compounds (Delaine et al, 2010).

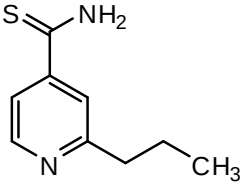
Thioisonicotinamide and Thiosemicarbazone Compounds

The thioisonicotinamide compounds, ethionamide (**7**) and prothionamide (**8**) were exposed during efforts to progress on the *Mtb* inhibitory activity of nicotinamide. Thioisonicotinamide (**9**) exhibited improved *in vivo* activity than *in vitro* activity (Rist et al., 1959) which encouraged further studies on this series resulting in the examination that 2-alkyl derivatives were more active than the nicotinamide with 2-ethyl and 2-propyl derivatives displaying the best activity. Ethionamide (**7**) is a prodrug that is activated by S-oxidation by a monoxygenase (EtaA) to a 4-pyridylmethane radical intermediate that, like to the active radical produced from INH by KatG, reacts with NAD(P) to form a tight binding inhibitor of InhA (Wang et al., 2007; DeBarber et al., 2000). The sulfoxide, the main metabolite formed in humans and is active against *Mtb*. The thioisonicotinamides have unlikable GIT side effects. Thiacetazone (**2**) was prepared to have anti-TB activity in the 1940s and was used as an anti-TB agent despite its toxic side effects (Tiitinen. 1969; Vannelli, et al., 2002

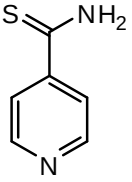
Halsey, et al., 1998; Domagk. 1950; Behnisch et al., 1950). Thiacetazone, like to the thioisonicotinamides, is activated by EthA resulting in a reactive intermediate that inhibits mycolic acid oxygenation as well as cyclopropanation (Alahari et al., 2007; Alahari et al., 2009). Thiacetazone causes GIT disturbances and, particularly in HIV-infected patients, can cause severe life-threatening skin reactions known as Stevens–Johnson syndrome (Lawn et al., 1999).



Ethionamide **7**



Protionamide **8**

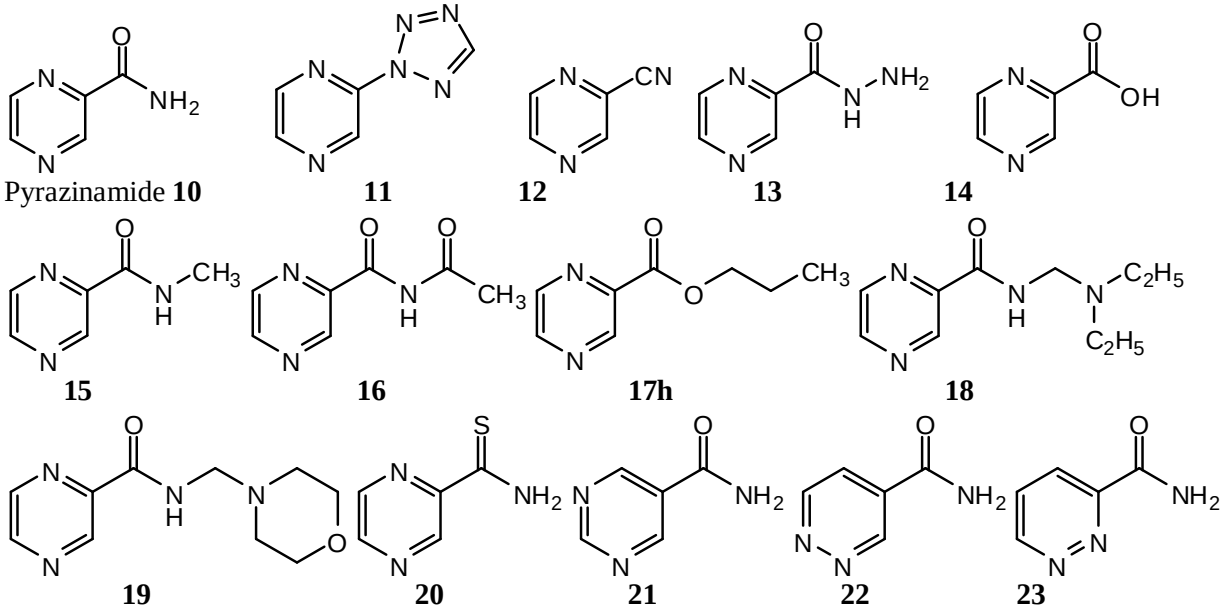


Thioisonicotinamide **9**

Pyrazinamide Analogues

Pyrazinamide (PZA) is inactive at neutral pH but tuberculostatic at acid pH and active against the intracellular organisms in macrophages, since, after phagocytosis, the organisms are contained in phagolysosomes in which the pH is low. Resistance develops rather readily but cross-resistance with INH does not occur. The drug is well absorbed after orally use and is widely distributed, penetrating well into the meninges. It is excreted through the kidney, mainly by glomerular filtration. Adverse effects are gout, linked with high level of plasma urates, GIT upsets, malaise and fever are reported. With the high doses, chances of serious hepatic damage, this is now less expected with lower doses and shorter courses, but nevertheless, liver function should be assessed before treatment. Pyrazinamide (**10**) was developed as anti-TB activity of vitamin B3 (niacin) (Mc Kenzie and Malone 1948). It has no activity against *Mtb* under normal *in vitro* growth circumstances although it has excellent activity in infected animals (Rogers et al., 1952; Kushner et al., 1952). Initial biological studies (Rogers et al., 1952; Kushner et al., 1952; Felder et al., 1962; Chung et al., 2008) performed by in vivo assays of nicotinamide (3c) and PZA analogues in infected mice. The presence of a pyrazine moiety with a carboxamide at the C(2) position was vital for activity. Alteration of the carboxamide to tetrazole, nitrile, hydrazide, or carboxylic acid (**11-14**) leads to entirely inactive agents *in vivo*. Substitutions on the amide nitrogen with either a methyl (**15**) or an acetyl group (**16**) were unfavorable to activity. Pyrazinoic acid (**14**) is considered to be the active metabolite from PZA; hence, various ester derivatives (**17**) were found to be active *in vitro* but inactive *in vivo* possibly due to premature hydrolysis or poor solubility.

However, additional stable aminomethylene prodrugs (**18** and **19**) did not show enhancement in activity apparently because they were not substrates for the amidase. The thioamide (**20**), pyrimidine moiety (**2l**), and pyridazine moiety (**22** and **23**) were inactive or weakly active. Thus, PZA is the minimum pharmacophore; further substitutions on the amide or alteration to the pyrazine moieties are unfavorable to activity. Pyrazinamide possible kills *Mtb* by intracellular acidification following hydrolysis by *Mtb* nicotinamidase/ pyrazinamidase (Scorpio and Zhang. 1996), although inhibition of fatty acid synthase has proposed as a mechanism (Boshoff and Mizrahi 2000; Boshoff et al., 2002; Zimhony et al., 2000). The PZA increases serum uric acid levels thereby causing non gouty arthralgia and, when used in combination with INH and/or RIF, often causes some hepatotoxicity.



Pyrazinamide (PZA) is indicated for the initial treatment of active TB in adults and children when combined with other anti-TB agents. The PZA is an important sterilising TB drug that helps to shorten the duration of current therapy regimens for TB. It is unique among anti-TB drugs in having no genomic site of action and having greater bactericidal activity as bacillary metabolism slows down; it is amazingly active in human disease. It is an important component in the intensive phase of short-course treatment of TB owing to its sterilising activity, ability to work in acidic environments (in macrophages), and excellent synergy with RIF (Mitchison, 1985; Zhang & Mitchison, 2003). It appears to kill at least 95% of the semi-dormant bacterial population persisting in a low-pH environment since its activity is present only in the acidic environment found in active inflammation (Mitchison, 1985; Heifets et al., 1992). The progress of a new drug with a similar mode of activity might be very rewarding, particularly if there were no need for an acid environment (Aldrich et al., 2010).

Discussion

Isoniazid (INH) (**5**), a derivative of nicotinic acid is a potent anti-TB agent. The MIC is of the order of 0.05µg/ml and acts on growing cells and not on resting cells. The INH is believed to kill mycobacteria by inhibiting the biosynthesis of mycolic acids, critical component of the cell wall. The 2-Ethyl thioisonicotinamide (ethionamide) and prothionamide are active at a MIC of 0.5-2.5 µg/ml. The ethionamide also disturbs mycolic acid synthesis in strains resistant to INH, streptomycin and p-amino salicylic acid. Pyrazinamide is a synthetic pyrazine analog of nicotinamide and is active at a MIC of 6-60 µg/ml. Resistance to PZA develops soon when it is used alone. It appears to require activation via pyrazinamidases in the organism (Gray. 1997; Gutierrez-Lugo and Bewley. 2008; Janin. 2007; Bhowruth et al., 2006). Isoxyl/thiocarlide is a thiocarboxyl-containing anti-TB drug and has been used clinically in past. The compound has cross resistance with ethionamide and thiacetazone, biological targets was confirmed as DesA3, a D9-desaturase responsible for the synthesis of oleic acid from stearoyl-CoA. Unsymmetrical analogues of the isoxyl and screened them against *Mtb* H37Rv and *M. bovis* BCG. The compounds (p-n-butylphenyl)-3-(4-propoxy-phenyl) thiourea and 1-(p-n-butylphenyl)-3-(4-n-butoxy-phenyl) thiourea showed an approximate 10-fold increase in in vitro potency compared to isoxyl (Bhowruth et al., 2006). Such analogues of isoxyl may give a new impetus for the development new prototypes as anti-TB agents.

The constant and steady rise in TB together with the appearance of resistance against traditional anti-TB drug regimen and the pathogenic synergy with HIV has put huge pressure on public health systems to introduce new treatments. In drug resistant TB it is vital to know how the resistance emerges. Therefore, great efforts have been made in the area of *Mtb* genomics, proteomics and target recognition and therefore several developments comes in the light having novel target with newer mode of action. However, there is a demand in continuing research in this direction to achieve the goal of eradicating *Mtb* from the world in coming years (Asif. 2014; Asif. 2013; Asif. 2012; Asif. 2013). Aim for TB drug development to shorten the total duration of effective treatment and/or reduce the number of doses needed to be taken under directly observed treatment, short-course (DOTS) supervision, to improve the treatment of MDR-TB, which cannot be treated with INH and rifampicin and to provide a more effective treatment of latent TB. Genomics, the systematic identification of all of the genes in a cell through deoxyribonucleic acid (DNA) sequencing and bioinformatic analysis, also offers great potential in terms of drug target discovery of new anti-TB drugs, and sequenced genome of *Mtb* should provide a number of new targets for novel drugs (Cole et al., 1998; Vinšová & Krátký, 2011).

Conclusion

Tuberculosis (TB) is a infectious disease caused by *M. tuberculosis*. The term MDR-TB is used to describe strains that are resistant to two or more of the five first-line anti-TB drugs. Treatment of TB comprises five first line anti-TB drugs namely isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol followed by second line anti-TB drugs namely fluoroquinolones and one of the injectable aminoglycosides. Besides the traditional anti-TB drugs available commercially, several new agents were synthesized. The efforts to develop new and more effective therapies, compounds can also effective against *Mtb* and MDR-TB.

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