

A REVIEW ON POTENT ANTITUBERCULAR AGENT ISONIAZID AND ITS ANALOGUES

Mohammad Asif

GRD (PG) Institute of Management and Technology, 214-Rajpur Road, Dehradun, 248009, India

Corresponding author*: aasif321@gmail.com

This article is available online at www.ss-journals.com

ABSTRACT:

There has been considerable interest in the development of new anti tubercular agents particularly against multidrug resistance and extensively drug resistant strain of tuberculosis because *mycobacterium* species have developed resistant against currently used drugs. The currently use antitubercular drugs having toxic effect and long period of therapeutic treatment. Therefore, many researchers have synthesized various newer drugs and analogues of currently used drugs for tuberculosis treatment. These observations have been guiding for the development of newer analogues that possess potent antitubercular activity with minimum side effects with effectiveness against multidrug resistant *mycobacterium*, and also in patient co-infected with HIV/AIDS. In this review we are discussed about isoniazid and it analogues as potent antitubercular agents.

Keyword: Antitubercular, multidrug resistance, *mycobacterium*.

1. Introduction

Anti-TB drug treatment started in 1944, when streptomycin and paraaminosalicylic acid were discovered. In 1950, the first trial was performed comparing the efficacy of streptomycin and paraaminosalicylic acid both as monotherapy or combined. The study demonstrated that combined therapy was more effective and resulted in the first multidrug anti-TB treatment that consisted of a long course of both drugs. In 1952, a third drug, isoniazid, was added to the previous combination, greatly improving the efficacy of treatment, but which still had to be administered for 18-24 months. In 1960, ethambutol substituted paraaminosalicylic acid, and the treatment course was reduced to 18 months. In the '70s, with the introduction of rifampicin into the combination, treatment was shortened to just nine months. Finally, in 1980, pyrazinamide was introduced into the anti-TB treatment, which could be reduced further to only six months. Two biological features explain why combined drug therapy is more effective at curing TB than monotherapy. One is that treatment of active TB with a single drug results in the selection of drug resistant bacilli and failure to eliminate the disease. The other is that different populations of tubercle bacilli-each of them showing a distinct pattern of susceptibility for anti-TB drugs-may co-exist in a TB patient. Soon after the introduction of the first anti-TB drugs, drug resistant bacilli started to emerge, but the launch of both combination therapy and new and more effective drugs seemed to be enough to control the disease. In fact, it was thought that TB could be eradicated by the end of 20th century.

However, TB unexpectedly re-emerged in the '80s, and in the following years there was an important increase in the incidence of multiple-, and extensively drug resistant strains. Since 1970, no new drug has been discovered for anti-TB treatment, which today seems insufficient to confront the disease. Fortunately, research efforts have been accomplished and today there is a wide range of new molecules with promising anti-TB activity¹⁻⁵.

According to data from the World Health Organization (WHO), TB has spread to every corner of the globe. As much as one-third of the world's population is currently infected and more than 5000 people die from TB every day. It is estimated that between 2002 and 2020, approximately 1000 million people will be newly infected, over 150 million people will develop diseases and 36 million will die of TB if proper control measures are not established. Tuberculosis (TB) is one of the oldest and most pervasive, respiratory transmitted diseases in history. 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 disease⁶⁻¹⁰. 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 MDR-TB strains, recurrently isolated from patient's sputum, darken the future. 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 and also the emergence of MDR-TB strains¹¹⁻¹⁵. 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 TB¹⁶⁻²⁰. Drug resistance (MDR and XDR) by *M. tuberculosis* is an important obstacle for the treatment and control of TB.

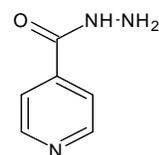
1.2 Multi drugs resistance and extensively drugs resistant TB: Multi drugs resistance (MDR) TB refers to simultaneous resistance to at least two or more of the five first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin). Treatment for MDR-TB is long lasting, less effective, costly, and poorly tolerated²¹⁻²³ (Global Tuberculosis Control: WHO, 2008). Extensively drug resistant (XDR) tuberculosis is resistance to at least isoniazid and rifampicin in addition to any quinolone and at least one injectable second-line agent (capreomycin, amikacin, kanamycin). The principles of treatment for MDR-TB and XDR-TB are the same. 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 options²⁴⁻³⁰. Hence there is an urgent need for novel drugs that are active against resistant strains with shorten duration of therapy.

2. Chemotherapy of Tuberculosis

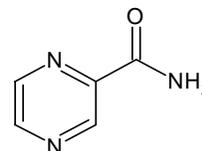
2.1 First line anti-tubercular agents:

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 antitubercular drugs.³¹⁻³³

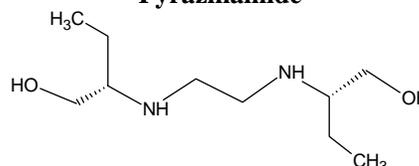
2.2 Second line anti-TB drugs: According to WHO there are six classes of second line drugs that are used in the treatment of tuberculosis. A drug may be classified as a second-line because of one of two possible reasons: it may be less effective than the first-line drugs or it may have toxic side-effects 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.^{34,35}



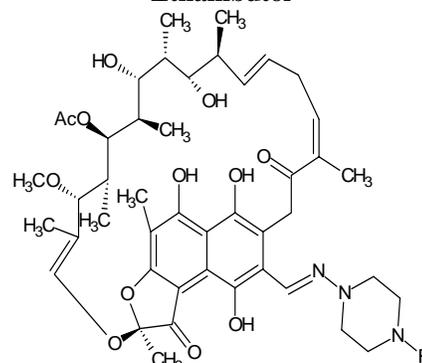
Isoniazid



Pyrazinamide



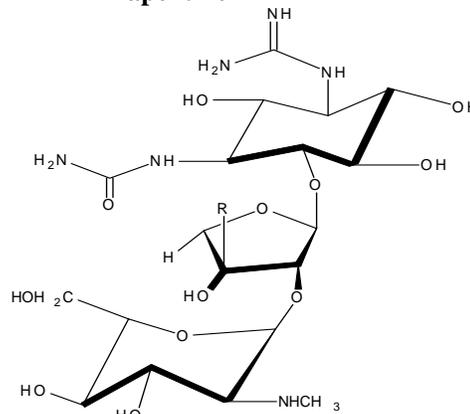
Ethambutol



Rifampicin R = CH₃

Rifabutin R = CH₂CH(CH₃)₂

Rifapentine R =



Streptomycin R = CHO
R = CH₂OH

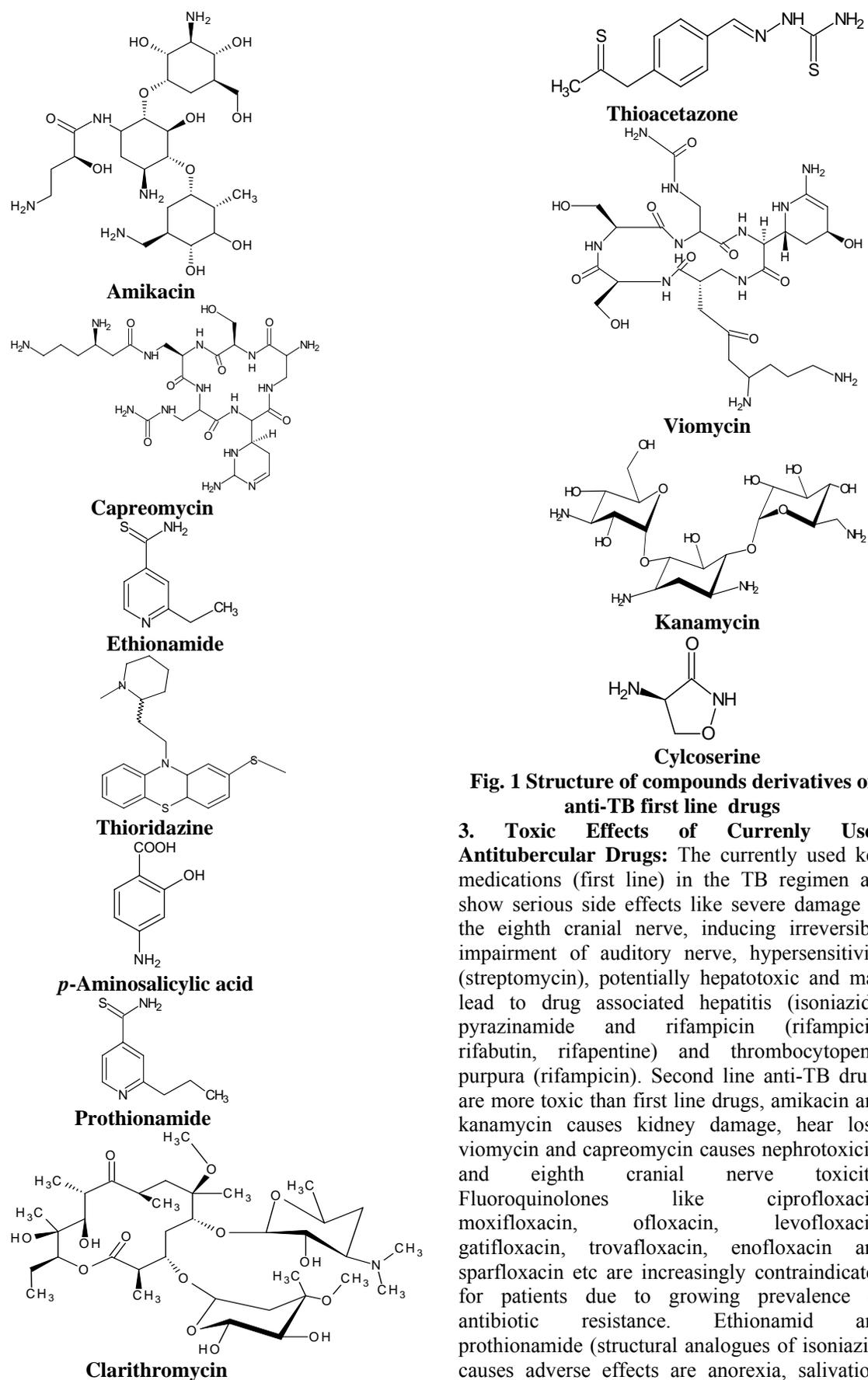


Fig. 1 Structure of compounds derivatives of anti-TB first line drugs

3. Toxic Effects of Currently Used Antitubercular Drugs: The currently used key medications (first line) in the TB regimen are show serious side effects like severe damage to the eighth cranial nerve, inducing irreversible impairment of auditory nerve, hypersensitivity (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, hear loss, viomycin and capreomycin causes nephrotoxicity and eighth cranial nerve toxicity. Fluoroquinolones like ciprofloxacin, moxifloxacin, ofloxacin, levofloxacin, gatifloxacin, trovafloxacin, enofloxacin and sparfloxacin etc are increasingly contraindicated for patients due to growing prevalence of antibiotic resistance. Ethionamid and prothionamide (structural analogues of isoniazid) causes adverse effects are anorexia, salivation,

nausea, abdominal pain, diarrhea, mental disturbances (depression, anxiety, psychosis, dizziness, drowsiness, headache) and hypersensitivity. Cycloserine causes headache, irritability, depression, convulsions. Para amino salicylic acid causes g.i.t. problems including anorexia, nausea, epigastric pain, abdominal distress, diarrhea, ulcers and hypersensitivity³⁵⁻⁴².

3.1 Isoniazid: Isoniazid (isonicotinic acid hydrazide; Nydrazid, Laniazid) is still considered the primary drug for the treatment of tuberculosis. The disease caused by isoniazid-sensitive strains of the tubercle should receive the drug to the patient if they can tolerate it. The discovery of isoniazid was unexpected; in 1945 Chorine reported that nicotinamide possesses tuberculostatic action then examination of the other compounds related to nicotinamide showed that many pyridine derivatives possess tuberculostatic activity; among these were congeners of isonicotinic acid. Because the thiosemicarbazones were known to isoniazidibit *M. tuberculosis*, the thiosemicarbazone of isonicotinaldehyde was synthesized. Isoniazid is the hydrazide of isonicotinic acid. The isopropyl derivative of isoniazid, iproniazid (1-isonicotinyl-2-isopropylhydrazide), also isoniazidibits inhibit the multiplication of the tubercle bacillus. This compound, which is potently isoniazidibits monoamine oxidase, is too toxic for human beings. However, its study led to the use of monoamine oxidase isoniazidibitors for the treatment of depression. Isoniazid is bacteriostatic for resting bacilli, but is bactericidal for rapidly dividing strains. The minimal tuberculostatic concentration is 0.025 to 0.05µg/ml. Isoniazid is highly effective for the treatment of tuberculosis in animals and is strikingly superior to streptomycin. Unlike streptomycin, isoniazid penetrates cells with ease and is just as effective against bacilli growing within cells. Among the various non tuberculous (atypical) mycobacteria, only *M. kansasii* is sometimes susceptible to isoniazid⁴³⁻⁵⁰.

Bacterial Resistance: When tubercles are grown *in vitro* in increasing concentrations of isoniazid, mutants are readily selected that are resistant to the drug. However, cross-resistance between isoniazid and other anti-TB drugs (except structurally related like ethionamide) does not occur. The most common mechanism of isoniazid resistance is mutations in catalase-peroxidase (*katg*) that decrease its activity, preventing conversion of the isoniazid to its active metabolite. Another mechanism of resistance is related to a mutation in the mycobacterial

isoniazida and *KasA* genes involved in mycolic acid biosynthesis. Mutations in NADH dehydrogenase (*ndh*) also confer isoniazid resistance. Isoniazid-resistant strains of *M. tuberculosis* appear to be less virulent in animal models. The incidence of primary resistance to isoniazid until recently had been fairly stable at 2% to 5% of isolates of *M. tuberculosis*.⁵²⁻⁶⁰

Mechanism of Action: Isoniazid is a prodrug; mycobacterial catalase-peroxidase converts isoniazid into an active metabolite. A primary action of isoniazid is to isoniazidibit the biosynthesis of mycolic acids, branched lipids that are attached to a unique polysaccharide, arabino galactan, to form part of the mycobacterial cell wall. The mechanism of action is complex, with resistance mapping to mutations in at least five different genes (*katG*, *isoniazida*, *ahpC*, *kasA*, and *ndh*). The predominance of evidence points to *isoniazida* as the primary drug target. Indeed, the catalase-peroxidase-activated isoniazid, but not the prodrug, binds to the *isoniazida* gene product enoyl-ACP reductase of fatty acid synthase II, which converts unsaturated fatty acids to saturated fatty acids in the mycolic acid biosynthetic pathway. Mycolic acids are unique to mycobacteria, explaining the high degree of selectivity of the antimicrobial activity of isoniazid. Mutations of the *katG* gene that result in an inactive catalase-peroxidase cause high-level isoniazid resistance, since the prodrug cannot be activated by the catalase-peroxidase. Isoniazid also isoniazidibits mycobacterial catalase-peroxidase (the isoniazid-activating enzyme), which may increase the possibility of damage to mycobacteria from reactive oxygen species.⁶⁰⁻⁶³ The main excretory products in humans result from enzymatic acetylation (acetylisoniazid) and enzymatic hydrolysis (isonicotinic acid). Small quantities of an isonicotinic acid conjugate (probably isonicotinyl glycine), one or more isonicotinyl hydrazones, and traces of *N*-methylisoniazid also are detectable in the urine. The rate of acetylation significantly alters the concentrations of the drug that are achieved in plasma and its half-life in the circulation. The half-life of the drug may be prolonged by hepatic insufficiency. The frequency of each acetylation phenotype is dependent upon race but is not influenced by sex or age. Since high acetyltransferase activity (fast acetylation) is isoniaziderited as an autosomal dominant trait, "fast acetylators" of isoniazid are either heterozygous or homozygous. Because isoniazid is relatively nontoxic, a sufficient amount of drug can be administered to fast

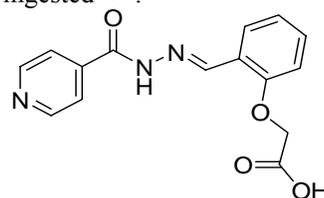
acetylators to achieve a therapeutic effect equal to that seen in slow acetylators. A dosage reduction is recommended for slow acetylators with hepatic failure. The clearance of isoniazid is dependent only to a small degree on the status of renal function, but patients who are slow inactivators of the drug may accumulate toxic concentrations if their renal function is impaired.⁶⁴⁻⁶⁶

Uses: Isoniazid is still the most important anti-TB drug worldwide for all types of TB. Toxic effects can be minimized by prophylactic therapy with *pyridoxine* (vitamin B6) and careful examination of the patient. For treatment of active infections, the drug must be used concurrently with another agent, although it is used alone for prophylaxis. The commonly used total daily dose of isoniazid is 5 mg/kg, with a maximum of 300 mg. Isoniazid usually is given orally in a single daily dose but may be given in two divided doses. Although doses of 10 to 20 mg/kg, with a maximum of 600 mg, occasionally are used in severely ill patients, there is no evidence that this regimen is more effective. Children should receive 10 to 20 mg/kg per day (300 mg maximum). Isoniazid may be used as intermittent therapy for TB; after a minimum of 2 months of daily therapy with isoniazid, rifampin, and pyrazinamide, for sensitive strains of *M. tuberculosis*, patients may be treated with twice-weekly doses of isoniazid (15 mg/kg orally) plus rifampin (10 mg/kg, up to 600 mg per dose) for 4 months. Pyridoxine (10 to 50 mg per day) should be administered with isoniazid to minimize the risks of peripheral neuropathy and CNS toxicity in the elderly, pregnant women, HIV-infected individuals, diabetics, alcoholics, and uremics.⁶⁷⁻⁷¹

Adverse Effects: The incidence of adverse reactions to isoniazid was estimated to be 5.4%, the most prominent of these reactions were rash (2%), fever (1.2%), jaundice (0.6%), and peripheral neuritis (0.2%). Hypersensitivity to isoniazid may result in fever, skin eruptions, hepatitis, purpuric, and urticaria. Hematological reactions also may occur such as agranulocytosis, eosinophilia, thrombocytopenia, anemia. Arthritic symptoms like back pain, arthralgia of the knees, elbows, and wrists have been attributed. If pyridoxine is not given concurrently, peripheral neuritis is the most common reaction to isoniazid and occurs in about 2% of patients receiving 5 mg/kg of the drug daily. Higher doses may result in peripheral neuritis in 10% to 20% of patients. The prophylactic administration of pyridoxine prevents the development not only of peripheral neuritis, but also of most other CNS disorders, even when therapy lasts as long as 2 years.

Isoniazid may precipitate convulsions in patients with seizure disorders, and rarely, in patients with no history of seizures. Optic neuritis and atrophy also have occurred during therapy with the drug. Muscle twitching, dizziness, ataxia, paresthesias, stupor, and toxic encephalopathy that may be fatal are other manifestations of the neurotoxicity of isoniazid. A number of mental abnormalities may appear, including euphoria, transient impairment of memory, separation of ideas and reality, loss of self-control, and florid psychoses. Isoniazid is known to inhibit the parahydroxylation of *phenytoin*, and signs and symptoms of toxicity occur in approximately 27% of patients given both drugs, particularly in those who are slow acetylators.⁷²⁻⁷⁵

Continuation of the drug after symptoms of hepatic dysfunction have appeared tends to increase the severity of damage. The mechanisms responsible for this toxicity are unknown, although acetylhydrazine, which is a metabolite of isoniazid, causes hepatic damage in adults. Hence, patients who are rapid acetylators of isoniazid might be expected to be more likely to develop hepatotoxicity than slow acetylators; whether this is true, however, is unresolved. A contributory role of alcoholic hepatitis has been noted, but chronic carriers of the hepatitis B virus tolerate isoniazid.⁷⁶⁻⁷⁸ Patients receiving isoniazid should be carefully evaluated at monthly intervals for symptoms of hepatitis (anorexia, malaise, fatigue, nausea, and jaundice) and warned to discontinue the drug if such symptoms occur. Among miscellaneous reactions associated with isoniazid therapy are dryness of the mouth, epigastric distress, methemoglobinemia, tinnitus, and urinary retention. In persons predisposed to pyridoxine-deficiency anemia, the administration of isoniazid may result in dramatic anemia, but treatment with large doses of vitamin B₆ gradually returns the blood to normal in such cases. Overdose of isoniazid, as in attempted suicide, may result in nausea, vomiting, dizziness, slurred speech, and visual hallucinations followed by coma, seizures, metabolic acidosis, and hyperglycemia. Pyridoxine is an antidote in this setting; it should be given in a dose that approximates the amount of isoniazid ingested.⁷⁹⁻⁸¹



Aconiazide

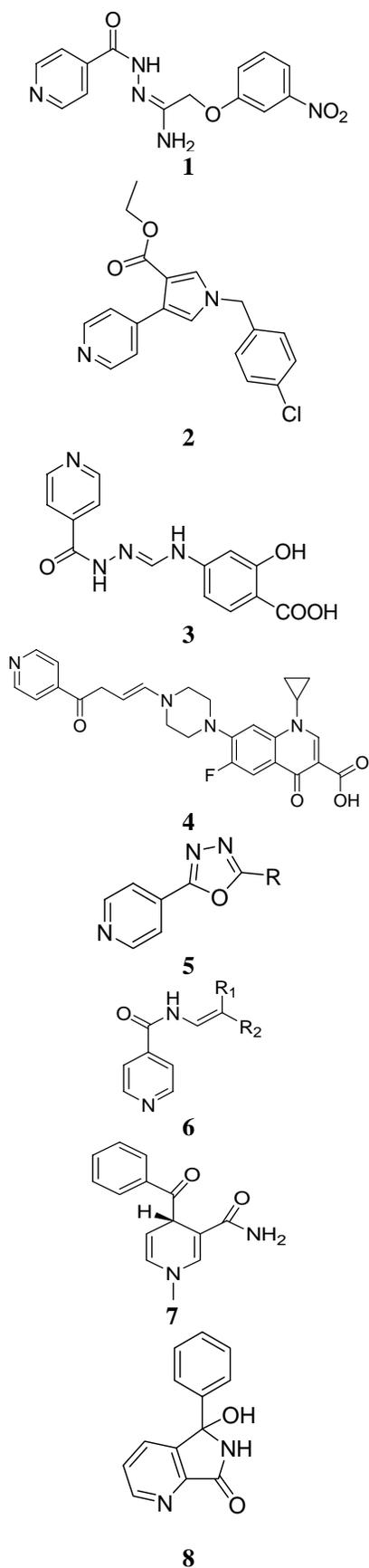


Fig. 2 Structure of Isoniazid analogues (1-8)

4. Isoniazid analogues

Aconiazide: Aconiazide is a pro-drug of isoniazid which was designed to be less toxic than the parent drug. The latter is metabolized to hydrazine and acetyl hydrazine, which have both been implicated in the toxicity of isoniazid. Because aconiazide is converted to isoniazid and 2-formylphenoxyacetic acid, it was expected that the acid would bind to the isoniazid metabolites and so lower toxicity. Aconiazide is indeed less toxic than the parent drug and lacks carcinogenicity. In healthy patients it was found to produce proportionately lower levels of isoniazid in serum than the parent molecule itself.⁸²⁻⁸⁵ Various analogues and derivatives of isoniazid continue to be synthesized, mainly by scientists in academia, and their potential for TB treatment explored, e.g. (1), (2). However, these compounds are likely to be ineffectual against isoniazid-resistant strains of TB either because their activity results from regeneration of this drug or because of close structural similarities. The development of new drugs that has been proposed particularly for new anti-TB drugs, an example is the design of molecules based on isoniazid or pyrazinamide, incorporating NR1R2 groups derived from a second anti-TB molecule or possibly other nucleophilic groups to provide anti-TB activity. With special interest compounds 3 and 4 were obtained. These could be considered prodrugs because they contain two conventional drugs that are bound by a CH fragment. Although the results of activity are very similar to those presented by isoniazid and pyrazinamide, the hydrolysis of new compounds ensures prolonged release of the active drugs.^{86,87} A variety of compounds derived from isoniazid that include mostly a hydrazine fragment have been determined. New agent with high anti-TB activity is compound 5. Due to the substitution in 5-position on the oxadiazole ring, the compounds obtained showed high lipophilicity, hypothesizing that this lipophilicity could facilitate passage of these compounds through the *M. tuberculosis* bacterial membrane.⁸⁸ Also, structural modification of the hydrazide moiety on isoniazid (6) provided lipophilic adaptations of the drug that blocked the N-acetylation process, obtained high levels of *in vitro* activity against *M. tuberculosis* and macrophages infected, as well as low toxicity. Another strategy in drug design is the formation of molecules that mimic the natural substrate of an enzyme. Delaine et al designed a new series of bi-substrate-type isoniazidibitors based on a covalent association between molecules mimicking the isoniazid substrate and

the NAD cofactor that could provide compounds with a high affinity and selectivity for the isoniazid catalytic site (7 and 8). In these compounds, the authors determined that incorporating a lipophilic component into the nicotinamide hemiamidal framework provides more active derivatives.^{89,90}

5. Discussion:

Tuberculosis (TB) is one of the oldest and most pervasive diseases in history. The Directly 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 success of DOTS strategy, the emergence of multi drug resistant strains (MDR-TB), prevalence of TB is synergy with Human Immunodeficiency Virus (HIV) epidemic where 31% of new TB cases were attributable to HIV co-infection. From the chemotherapeutic point of view, there are two sources of new chemical entities. A new 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.⁹¹⁻⁹⁵ 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, where innovative chemistry is used to optimise the compounds. Isoniazid is bacteriostatic against resting cells and bactericidal against dividing organisms. isoniazid is a near ideal antibiotic and very selective. Isoniazid is inexpensive, good oral availability and low toxicity. Isoniazid inhibits mycolic acid biosynthesis and targets the enoyl-acyl carrier protein reductase enzyme (IsoniazidA) involved in mycolic acid synthesis⁷⁶, Isoniazid inactivation of IhhA requires metabolic activation Isoniazid develops quickly resistance in monotherapy and seldom cross-resistance with other antiTB agents. It is also formulated in combinations, isoniazid and rifampin (Rifamate) and isoniazid, rifampin, and pyrazinamide (Rifater)^{27,82}.

In view of the persistent drug-resistant TB problem of currently used anti-TB agents, it is important that new anti-TB drugs should address different targets, as those of currently used drugs including the shortening of TB therapy. The unique structure of the mycobacterial cell wall

makes it a useful target for drug development and studies can be directed to specific sites like cell wall biosynthetic pathways⁸⁵. The identification of novel target sites will also be needed to circumvent the problems associated with the increasing occurrence of multi-drug resistant strains^{39,92,50}. 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*^{77,8,97}.

Conclusion:

In spite of the availability of some chemotherapeutic drugs, TB remains a leading infectious disease worldwide mainly due to the lack of new drugs, particularly for effective against the MDR and XDR, and patients co-infected with HIV/AIDS. Therefore, there is an urgent need of new anti-TB drugs with lesser side-effects, improved therapeutic properties to be effective against MDR and XDR-TB strains and reduce the overall duration of therapy. In view of above facts and inspired by the research going on new derivatives, particularly in relation to microbial infections specially against mycobacterium, different new drugs will be synthesized in the future for development of new and more effective drug molecule. From the chemotherapeutic point of view, there are two sources of new chemical entities. Development of new therapeutic 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 compounds are presently in clinical development, while others are being investigated pre-clinically in an attempt to explore new molecules for the treatment of TB. Simultaneously some new targets are being identified and validated for their practical usefulness. The present review provides an overview of the isoniazid and its some analogues against pathogenic *mycobacterium*.

References

1. Zierski, M. & Bek, E. Side effects of drug regimens used in short-course chemotherapy for pulmonary tuberculosis. *Tubercle*, 1980, 61(1), pp.41-49.
2. World Health Organization (WHO). Treatment of tuberculosis: guidelines for national programmes. 3rd edition. 2003. Geneva. Tuberculosis Coalition for Technical Assistance (TCTA). International Standards for Tuberculosis Care (ISTC). The Hague:

- Tuberculosis Coalition for Technical Assistance, 2006.
3. World Health Organization. Strategic framework to decrease the burden of TB/HIV documents WHO/CDS/TB. 2002; 296, WHO/HIVAIDS/2002, 2. Geneva, Switzerland: World Health Organization.
 4. Centers for Disease Control and Prevention. Adverse drug reactions among children treated for tuberculosis. *M.M.W.R. Morb. Mortal. Wkly. Rep.*, 1980, 29:589-591.
 5. Centers for Disease Control and Prevention. Tuberculosis elimination revisited: obstacles, opportunities, and a renewed commitment. Advisory Council for the Elimination of Tuberculosis (ACET). *M.M.W.R. Morb. Mortal. Wkly. Rep.*, 1999, 48:1-13.
 6. Okada M, Kobayashi K. Recent progress in mycobacteriology, *Kekkaku* (Japanese Journal), 2007, 82(10): 783-799.
 7. Center for Disease Control. "Emergence of Mycobacterium tuberculosis with Extensive Resistance to Second-Line Drugs—Worldwide, 2000–2004". 2006, 55: 301–305.
 8. Cole, ST., and Alzari PM. Towards new tuberculosis drugs. *Biochemical Society Transactions*, 2007, 35(5), pp. 1321-1324. ISSN: 0300-5127.
 9. Dye C. 2006. Global epidemiology of tuberculosis. *Lancet*, 367(9514), 2006, pp.938-40.
 10. Global Alliance for TBdrug development. Tuberculosis. Scientific blueprint for tuberculosis drug development. *Tuberculosis* (Edinb), 2001, 81 Suppl 1, 1-52.
 11. Global Tuberculosis Control: Surveillance, Planning, Financing WHO Report, 2008; 51-54.
 12. *Global Tuberculosis Control: WHO Report* 2010. pp.1–42, WHO Press, ISBN 978-92-4-156406-9.
 13. Gomez, J. E., and McKinney, J. D. M. tuberculosis persistence, latency, and drug tolerance. *Tuberculosis* (Edinb), 2004, 84, 29-44.
 14. Dony JF, Ahmad J, Khen TY. Epidemiology of tuberculosis and leprosy, Sabah, Malaysia. *Tuberculosis*. 2004, 84: 8-18.
 15. Elsayed KA, Bartyzel P, Shen XY, Perry TL, Zjawiony JK, Hamann MT. Marine natural products as antituberculosis agents, *Tetrahedron*. 2000, 56: 949-953.
 16. Espinal MA. The global situation of MDR-TB. *Tuberculosis*. 2003, 83: 44-51.
 17. WHO (2005). Global tuberculosis control-surveillance, planning, financing (Geneva: World Health Organization).
 18. World Health Organisation, Tuberculosis, Fact Sheet No. 104, 2007. <http://www.who.int/mediacentre/factsheets/who104/en/index.html/>.
 19. Zhang, Y. Persistent and dormant tubercle bacilli and latent tuberculosis. *Frontiers Bioscience*, 1(9), 2004, pp. 1136-1156.
 20. D'Oca, Cda R., Coelho, T., Marisoniazido, TG., Hack, CR., Duarte, Rda C., da Silva, PA., D'Oca, MG. Synthesis and antituberculosis activity of new fatty acid amides. *Bioorganic & Med Chem Lett*, 20(17), 2010, pp. 5255-5257.
 21. Barry CE, Slayden RA, Sampson AE, Lee RE. Use of genomics and combinatorial chemistry in the development of new antimycobacterial drugs. *Biochemistry and Pharmacology*. 2000, 59: 221-231.
 22. Ginsburg, A. S., Sun, R., Calamita, H., Scott, C. P., Bishai, W. R., Grosset, J. H. Emergence of fluoroquinolone resistance in Mycobacterium tuberculosis during continuously dosed moxifloxacin monotherapy in a mouse model. *Antimicrob Agents Chemother*, 2005, 49, 3977-3979.
 23. Glickman, S. W., Rasiel, E. B., Hamilton, C. D., Kubataev, A., and Schulman, K. A. Medicine. A portfolio model of drug development for tuberculosis. *Science*, 2006, 311, 1246-1247.
 24. Mitchison, D. A. The action of antituberculosis drugs in short-course chemotherapy. *Tubercle*, 1985, 66(3), pp.219-225.
 25. Monfeli, RR., Beeson, C. Targeting iron acquisition by *Mycobacterium tuberculosis*. *Infectious Disorders- Drug Targets*, 7(3), 2007, pp. 213-220.
 26. Nahid P, Pai M, Hopewell PC. Advances in the diagnosis and treatment of tuberculosis. *Proc Am Thorac Soc*, 2006; 3: 103-10.
 27. Smith, C. V., Huang, C. C., Miczak, A., Russell, D. G., Sacchetti, J. C., and Honer zu Bentrup, K. Biochemical and structural studies of malate synthase from *Mycobacterium tuberculosis*. *J Biol Chem*, 2003, 278, 1735-1743.
 28. Teodori, E.; Dei, S.; Scapecchi, S.; Gualtieri, F. The medicinal chemistry of multidrug resistance (MDR) reversing drugs. *Il Farmaco*. 2000, 57, 385–415.
 29. Russell, D. G. Mycobacterium tuberculosis: here today, and here tomorrow. *Nat Rev Mol Cell Biol*, 2001, 2, 569-577.
 30. Smith, C. V.; Sharma, V.; Sacchetti, J. C. TB drug discovery: Addressing issues of persistence and resistance. *Tuberculosis*. 2004, 84, 45–55.
 31. Kamal A, Azeza S, Malik MS, Shaik AA, Rao MV. Efforts Towards the Development of New Antitubercular Agents: Potential for Thiolactomycin Based Compounds. *J Pharm Pharmaceut Sci*, 2008, 11 (2): 56s-80s.
 32. Kamal A, Babu AH, Ramana AV, Sisoniazida R, Yadav JS, Arora SK. Antitubercular agents. Part I: Synthesis of phthalimido- and naphthalimidolinked phenazines as new

- prototypantitubercular agents. *Bioorg & Med Chem Lett*. 2005, 15: 1923-1926.
33. Kamal A, Reddy KS, Ahmed SK, Khan MNA, Sisoniazida RK, YadavJS, Arora SK. Anti-tubercular agents. Part 3: Benzothiadiazines as a novel scaffold for anti-mycobacterim activiy. *Bioorg & Med Chem*. 2006, 14: 650-658.
 34. Kamal, A., Shett, RVCRCNC., Azeeza, S., Ahmed, SK., Swapna, P., Reddy, AM., Khan, IA., Sharma, S., Abdullah, ST. Anti-tubercular agents. Part 5: Synthesis and biological evaluation of benzothiadiazine 1,1,-dioxide based congeners. *Euro J Med Chem*, 45(10), 2010, pp. 4545-4553.
 35. Aldrich, C. C.; Bosshoff, H. I. & Remmel R. P. Antitubercular agents, In: *Burger's Medicinal Chemistry, Drug Discovery and Development*, vol. 7 *Antiinfectives*, Abraham, Understanding Tuberculosis-D. J. & Rotella, D. P. (Eds.), 7th ed., 2010, pp.713–812, Wiley, ISBN 978-0-470-27815-4, New York.
 36. Da Silva AD, De Almeida MV, De souza MVN, Couri MRC. Biological activity and synthetic methodologies for the preparation of fluoroquinolones, a class of potent antibacterial agents. *Current Med Chem*. 2003; 10: 21-39.
 37. Flynn, J. L., and Chan, J. Tuberculosis: latency and reactivation. *Infect Immun*, 2001, 69, 4195-4201.
 38. Frieden, T. R.; Sterling, T. R.; Munsiff, S. S.; Watt, C. J.; Dye, C. Tuberculosis. *Lancet*. 2003, 362, 887–899.
 39. Garay, S. M. In Tuberculosis, W. N. a. G. Rom, S.M., ed. (Philadelphia: Lippincott Williams & Wilkins), 2004, 345-394.
 40. Grosset, J. H. Treatment of tuberculosis in HIV infection. *Tuber Lung Dis*, 1992, 73, 378-383.
 41. Kaufmann, S. H., Cole, S. T., Mizrahi, V., Rubin, E., and Nathan, C. Mycobacterium tuberculosis and the host response. *J Exp Med*, 2005, 201, 1693-1697.
 42. Rieder HL, Arnadottir T, Trebucq A, Enarson DA. Tuberculosis treatment: dangerous regimens? *Inter J Tuberculosis & Lung Diseases*. 2001, 5: 1–3.
 43. Betts, JC., McLaren, A., Lennon, MG., Kelly, FM., Lukey, PT., Blakemore, SJ., Duncan, K. Signature gene expression profiles discriminate between isoniazid-, thiolactomycin-, and triclosan-treated *Mycobacterium tuberculosis*. *Antimicrobl Agents & Chemother*, 2003, 47(9), pp. 2903-2913.
 44. Brennan, PJ., Crick, DC. The cell-wall core of *Mycobacterium tuberculosis* in the context of drug discovery. *Curr Topics in Med Chem*, 2007, 7(5), pp. 475-88.
 45. Kamal A, Ahmed SK, Reddy KS, Khan MNA, Shetty RVCRCNC, Siddhardha B, Murthy USN, Khan IA, Kumar M, Sharma S, Ram AB. Antitubercular agents. Part IV: Synthesis and antimycobacterial evaluation of nitroheterocyclic-based 1, 2, 4-benzothiadiazines. *Bioorganic and Medicinal Chemistry Letters*. 2007, 17: 5419-5422.
 46. Maccari R, Ottana R, Monforte F, Vigorita MG. In Vitro Antimycobacterial Activities of 2'-Monosubstituted Isonicotinohydrazides and Their Cyanoborane Adducts. *Antimicrob. Agents Chemother*. 2000, 46(2), 294-299.
 47. Marrakchi, H., Lan elle, G., Qu emard, A. Isoniazid A, a target of the antituberculous drug isoniazid, is involved in a mycobacterial fatty acid elongation system, FAS-II. *Microbiology*, 2000, 146(2), 289-296.
 48. McKenzie, D.; Malone, L.; Kushner, S.; Oleson, J. J. & Subbarow, Y. The effect of nicotinic acid amide on experimental tuberculosis of white mice. *J Lab & Clin Med*, 33(10), pp.1249-1253.
 49. Mdluli, K., Spigelman, M. Novel targets for tuberculosis drug discovery. *Current Opinion Pharmacology*, 6(5), 2006, pp. 459-467.
 50. Zhang, Y. The magic bullets and tuberculosis drug targets. *Annu Rev Pharmacol Toxicol*, 2005, 45, 529-564.
 51. Zhang, Y., Amzel, LM. (2002). Tuberculosis drug targets. *Current Drug Targets*, 3(2), 2002, pp. 131-154.
 52. Blanchard, J.S. Molecular mechanisms of drug resistance in *Mycobacterium tuberculosis*. *Annu. Rev. Biochem.*, 1996, 65:215-239.
 53. Banerjee, A., Dubnau, E., Quemard, A., et al. *IsoniazidA*, a gene encoding a target for isoniazid and ethionamide in *Mycobacterium tuberculosis*. *Science*, 1994, 263:227-230.
 54. Banerjee, A., Sugantino, M., Sacchettini, JC., Jacobs, WR. Jr. The *mabA* gene from the *isoniazidA* operon of *Mycobacterium tuberculosis* encodes a 3-ketoacyl reductase that fails to confer isoniazid resistance. *Microbiology*, 144(10), 1998, pp. 2697-2704.
 55. Meisel, P. Arylamine *N*-acetyltransferases and drug response. *Pharmacogenomics*, 2002, 3:349-366.
 56. Zhang, Y. Isoniazid. In, *Tuberculosis*, 2nd ed. (Rom, W.N., and Gray, S.M., eds.) Lippincott, Williams, Wilkins, Philadelphia, 2004, pp. 739-758.
 57. Sarkar, S., Suresh, MR. An overview of tuberculosis chemotherapy - a literature review. *J Pharm and Pharm Sci*, 2011, 14(2), pp. 148-161.
 58. Velayati, A. A.; Masjedi, M. R.; Farnia, P.; Tabarsi, P.; Ghanavi, J.; Ziazarifi, A. H. & Hoffner, S. E. Emergence of new forms of totally drug-resistant tuberculosis bacilli: Super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. *Chest*, 2009, 136(2), pp.420–425.
 59. Vin sova, J. & Kratky, M. Tuberculosis – The development of new MDR-TB drugs, In: *Drug-Resistant Tuberculosis, Causes, Diagnosis and Treatments*, Nguy, S. & K'ung, Z. (Eds.), 2010,

- pp.59-141, Nova Science Publishers, ISBN 978-1-60876-055-8, New York
60. Vinšová, J.; Imramovský, A.; Jampílek, J.; Monreal-Férriz, J.; Doležal, M. Recent advances on isoniazide derivatives. *Anti-Infective Agents in Med Chem*, 2008, 7(1), pp.12-31.
 61. Zhang, Y., Post-Martens, K., Denkin, S. New drug candidates and therapeutic targets for tuberculosis therapy. *Drug Discovery Today*, 2006, 11(1), pp. 21-27.
 62. Duncan, K. Identification and validation of novel drug targets in tuberculosis. *Current Pharm Design*, 2004, 10(26), pp. 3185-94.
 63. Jaju S, Palkar M, Maddi V, Ronad P, Mamledesai S, Satyanarayana D, Ghatole M. Synthesis and Antimycobacterial Activity of a Novel Series of Isonicotinylhydrazide Derivatives. *Arch. Pharm. Chem. Life Sci.* 2009, 342(12), 723-731.
 64. Janin YL. Antituberculosis drugs: Ten years of research. *Bioorg. Med. Chem.* 2007, 15 (7), 2479–2513.
 65. Kinzig-Schippers, M., Tomalik-Scharte, D., Jetter, A., et al Should we use *N*-acetyltransferase type 2 genotyping to personalize isoniazid doses? *Antimicrob. Agents Chemother.* 2005, 49: 1733-1738.
 66. Byrd, R.B., Horn, B.R., Solomon, D.A., and Griggs, G.W. Toxic effects of isoniazid in tuberculosis chemoprophylaxis. Role of biochemical monitoring in 1,000 patients. *JAMA*, 1979, 241:1239-1241.
 67. Cauthen, G.M., Kilburn, J.O., Kelly, G.D., and Good, R.C. Resistance to anti-tuberculosis drugs in patients with and without prior treatment: survey of 31 state and large city laboratories, 1982-1986. *Am. Rev. Respir. Dis.*, 1988, 137(suppl): 260.
 68. Delaine, T., Bernades-Genisson, V., Quemard, A., Constant, P., Meunier, B., Bernadou, J. Development of isoniazid-NAD truncated adduct embedding a lipophilic fragment as potential bi-substrate IsoniazidA isoniazidibitorsd and antimycobacterail agents. *Euro J Med Chem*, 2010, 45(10), pp. 4554-4561.
 69. Ducati, R.G., Basso, L.A., Santos, D.S. Mycobacterial shikimate pathway enzymes as targets for drug design. *Current Drug Targets*, 2007, 8(3), pp. 423-35.
 70. Hearn MJ., Cynamon MH., Chen MF., Coppins R., Davis J., Joo-On Kang, H., Noble A., Tu-Sekine B., Terrot MS., Trombino D., Thai M., Webster ER., Wilson, R. Preparation and antitubercular activities in vitro and in vivo of novel Schiff bases of isoniazid. *Eur J Med Chem*, 2009, 44(10), pp. 4169-4178.
 71. Held HR, Landi S. Binding of toxic metabolites of isoniazid by aconiazide. *J Pharm Sci*, 1980, 69(11):1284-1287.
 72. Management of MDR-TB. A field guide, A companion document to Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2008.402, WHO Library Cataloguing-in-Publication Data: World Health Organization, 2009.
 73. McGlynn, K.A., Lustabader, E.D., Sharrar, R.G., Murphy, E.C., and London, W.T. Isoniazid prophylaxis in hepatitis B carriers. *Am. Rev. Respir. Dis.*, 1986, 134:666-668.
 74. Miller, R.R., Porter, J., and Greenblatt, D.J. Clinical importance of the interaction of phenytoin and isoniazid: a report from the Boston Collaborative Drug Surveillance Program. *Chest*, 1979, 75:356-358.
 75. Comstock, G.W. New data on preventive treatment with isoniazid. *Ann. Intern. Med.*, 1983, 98: 663-665.
 76. Johnsson K, Schultz PG. Mechanistic studies of the oxidation of isoniazid by the catalaseperoxidase from *Mycobacteria tuberculosis*. *J Am Chem Soc*, 1994, 116:7425-7426.
 77. Jones, P. B., Parrish, N. M., Houston, T. A., Stapon, A., Bansal, N. P., Dick, J. D., and Townsend, C. A. A new class of antituberculosis agents. *J Med Chem*, 2000, 43, 3304-3314.
 78. Katz, A. H.; Caufield, C. E. Structure-based design approaches to cell wall biosynthesis isoniazidibitors. *Curr. Pharm. Design*. 2003, 9, 857–866.
 79. Bagchi, M.C.; Maiti, B.C.; Mills, D.; Basak, S. C. Usefulness of graphical invariants in quantitative structure-activity correlations of tuberculostatic drugs of the isonicotinic acid hydrazide type. *J. Mol. Model.* 2004, 10, 102–111.
 80. Palomino, J.C., Ramos, D.F., da Silva P.A. New anti-tuberculosis drugs: strategies, sources and new molecules. *Current Med Chem*, 16(15), 2009, pp. 1898-1904.
 81. Pasquato KFM, Ferreira EI. An approach for the rational design of new antitubercular agents. *Current Drug Targets*. 2001, 2: 427-437.
 82. Snider, D.E., Jr. Pyridoxine supplementation during isoniazid therapy. *Tubercle*, 1980, 61:191-196.
 - Somoskovi, A.; Parsons, L. M.; Salfinger, M. The molecular basis of resistance to Isoniazid, Rifampin, and Pyrazinamide in *Mycobacterium tuberculosis*. *Respir. Res.* 2001, 2, 164–168.
 83. McDermott, W. & Tompsett, R. Activation of pyrazinamide and nicotinamide in acidic environment *in vitro*. *American Review of Tuberculosis*, 70,(4), pp.748-754.
 84. Sunduru, N.; Sharma, M.; Chauhan, P.M.S. Recent advances in the design and synthesis of Heterocycles as anti-tubercular agents. *Fut. Med. Chem.*, 2010, 2(9), 1469-1500.
 85. Tomioka H, Namba K. Development of antitubercular drugs: current status and future

- prospects, *Kekkaku* (Japanese Journal). 2006, 81 (12): 753-774.
86. Imramovsky, A., Polanc, S., Vinsova, J., kocevar, M., Jampilek, J., Reckova, Z., Kaustova, J. A new modification of anti-tubercular active molecules. *Bioorg & Med Chem*, 2007, 15(7), 2007, pp. 2551-2559.
87. Imramovsky, A., Vinsova, J., Ferriz, JM., Dolezal, R., Jampilek, J., Kaustova, J., Kunc, F. New antitubercotics originated from salicylanilides with promising in vitro activity against atypical mycobacterial strains. *Bioorg & Med Chem*, 2010, 17(10), pp. 3572-3579.
88. Navarrete-Vázquez, G., Molina-Salinas, GM., Duarte-Fajardo, ZV., Vargas-Villarreal, J., Estrada-Soto, S., Gonzalez-Salazar, F., Hernandez-Nuñez, E., Said-Fernández, S. Synthesis and antimycobacterial activity of 4-(5-substituted-1,3,4-oxadiazol-2-yl)pyridines. *Bioorg & Med Chem*, 2007, 15(16), pp. 5502-5508.
89. Shi, R., Sugawara, I. Development of new anti-tuberculosis drug candidates. *The Tohoku J exp med*, 22(2), 2010, pp. 97-106.
90. Shoen, C. M., DeStefano, M. S., and Cynamon, M. H. Durable cure for tuberculosis: rifalazil in combination with isoniazid in a murine model of *Mycobacterium tuberculosis* infection. *Clin Infect Dis*, 2000, 30 Suppl 3, S288-290.
91. Bairwa, R., Kakwani, M., Tawari, NR., Lalchandani, J., Ray, MK., Rajan, MG., Degani, MS. Novel molecular hybrids of cinnamic acids and guanylhydrazones as potential antitubercular agents. *Bioorg & Med Chem Lett*, 2010, 20(5), pp. 1623-1625.
92. Corbett, E. L., Watt, C. J., Walker, N., Maher, D., Williams, B. G., Raviglione, M. C., and Dye, C. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med*, 2003, 163, 1009-1021.
93. Iseman, M.D. Treatment of multidrug-resistant tuberculosis. *N. Engl. J. Med.*, 1993, 329:784-791.
94. Izumizono, Y., Arevalo, S., Koseki, Y., Kuroki, M., Aoki, S. Identification of novel potential antibiotics for tuberculosis by in silico structure-based drug screening. *Eur J Med Chem*, 46(5), 2011, pp. 1849-1856.
95. O'Brien, R. J., and Nunn, P. P. The need for new drugs against tuberculosis. Obstacles, opportunities, and next steps. *Am J Respir Crit Care Med*, 2001, 163, 1055-1058.
96. Oishi H, Noto T, Sasaki H, Suzuki K, Hayashi T, Okazaki H, Ando K, Sawada M. Thiolactomycin, a new antibiotic. I. Taxonomy of the producing organism, fermentation and biological properties. *J Antibio* (Tokyo). 1982, 35: 391-395.
97. Tripathi RP, Tewari N, Dwivedi N, Tiwari VK. Fighting tuberculosis: An old disease with new challenges. *Medicinal Research Reviews*. 2005, 25: 93-131.
98. Wade, M. M. & Zhang, Y. Mechanism of drug resistance in *Mycobacterium tuberculosis*. *Frontiers in Bioscience*, 2004, 9(1), pp.975-994.
99. Asif M. Study of clinically used and recently developed antimycobacterial agents. *Orient Pharm Exp Med*, 2012, 12, 15-34.
100. Asif M, Singh A and Ratnakar L. Antimicrobial Agents: Brief Study of Pyridazine Derivatives against Some Pathogenic Microorganisms. *J Pharm Res*. 2011, 4(3), pp 664-667.
101. Asif M. A Review of Antimycobacterial Drugs in Development. *Mini review in Med Chem.* 2012 May 22. [Epub ahead of print].