ejpmr, 2019,6(3), 288-297

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW ON NOVEL APROACHES FOR THE TREATMENT OF TUBERCULOSIS

Prince Srajal[1]*, Shalini Kesharwani[1], Vidyakant Kushwaha[2], Vivek Dwivedi[2], Shahnawaz Sameem[2], Suresh Kumar Nair[3]

[1]Shri Ram Group of Institute Jabalpur, MP.
[2]Chandra Shekhar Singh College of Pharmacy Kaushambi, UP.
[3]Shambhu Nath Institute of Pharmacy Allahabad, UP.

***Corresponding Author: Prince Srajal**
Shri Ram Group of Institute Jabalpur, MP.

Article Received on 14/01/2019 **Article Revised on 03/02/2019** **Article Accepted on 24/02/2019**

ABSTRACT

Tuberculosis (TB) is an infectious disease, caused by Mycobacterium tuberculosis (Mtb). Approximately one third population of the world is infected by M. tuberculosis. M. tuberculosis was first identified by Robert Koch in 1882. Although TB usually affects the lungs but it also affects other organ such as kidneys, spine and brain. The major symptoms of TB are persistent cough with or without expectorant, loss of appetite, intermittent fever, weight loss, chest pain and haemoptysis. More complicated and common Mtb infection is coinfection with HIV due to drug-drug interaction. Currently the drugs that are used for the treatment of TB include rifampin, isoniazid, pyrazinamide, ethambutol and streptomycin. These drugs associated with one or more limitations like duration, complexity of treatment, adverse reaction, efficacy and toxicity of second line drugs etc. that cause patient compliance. A number of new molecules such as diarylquinaline (TMC-207), oxazolidionones (PNU-100480, linezolid), ethylenediamine (SQ-109), pyrroles (LL-3358) and nitroimidapyran (OPC-67683, PA-824) have exhibited potent anti-bacterial properties *in vitro* and are in various clinical stages of development.

KEYWORDS: diarylquinaline (TMC-207), oxazolidionones (PNU-100480, linezolid), ethylenediamine (SQ-109).

1. INTRODUCTION

Tuberculosis (TB) is an infectious disease, caused by Mycobacterium tuberculosis (Mtb). Approximately one third population of the world is infected by M. tuberculosis.[1] M. tuberculosis was first identified by Robert Koch in 1882. Although TB usually affects the lungs but it also affects other organ such as kidneys, spine and brain. The major symptoms of TB are persistent cough with or without expectorant, loss of appetite, intermittent fever, weight loss, chest pain and haemoptysis.[2] More complicated and common Mtb infection is coinfection with HIV due to drug-drug interaction.[3,4]

The current treatment for TB includes a group of four drugs that are used for two month i.e. Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA) and Ethambutol (EMB). RIF and INH are used for longer continuous phase to eradicate the remaining bacilli that have entered a dormant, slowly replicating latent phase. According to World Health Organization (WHO) globally 3.5% naive infections already expressed resistance to the two most efficacious frontline agents, INH and RIF, and the infection is regarded as multidrug resistant tuberculosis (MDR-TB). Extensively drug-resistant TB is a rare type of drugs-resistant tuberculosis that is resistant to INH, RIF, fluoroquinolone and at least one of three injectable second-line drugs (i.e. amikacine, kanamycin, or capreomycin). The treatment of Mtb requires 6 to 9 month of combination therapy in ideal circumstance.[4] Extensively drug-resistant tuberculosis (XDR-TB) use combination of first line and second line drug, and it is based on the result of drug sensitivity testing(DST).[5]

2. Prevalence

TB is one of the top 10 causes of death worldwide. In 2015, 10.4 million people were suffering from TB which accounted for 1.8 million deaths. More than 60% cases of TB were reported in six countries; with India leading the count, followed by Indonesia, China, Pakistan, Nigeria and South Africa. TB infected approx. 1 million children in 2015 and 1,70,000 children died of TB (excluding children with HIV)..

TB is one of the major causes of deaths in HIV patient. In 2015, 35% of HIV deaths were due to TB. Globally, approx. 0.5 million people developed MDR-TB in 2015. According to WHO 2015 data, approx. 2.2 million cases of TB had been reporting in India. It has been estimated that about 40% of Indian population is infected with TB bacteria, the major of them have latent rather than active TB.

3. Diagnosis

The most frequently use diagnostic method of tuberculosis are tuberculin skin test, sputum test, and chest radiographs etc.[1]

Tuberculin skin test: This test was first described by Robert Koch in 1890. Tuberculin (purified protein derivative, PPD) is a glycerol extract of the tubercle bacillusis. Tuberculin is a precipitate of species-nonspecific molecules derived from filtrates of sterilized, concentrated cultures.[1]

A standard dose of 5 tuberculin units (TU-0.1ml) is injected intradermally and check after 48 to 72 hours. This intradermal injection is termed the Mantoux technique. The reaction is read by measuring the diameter of induration across the forearm in millimeters. If there is no induration, the result should be recorded as "0 mm". Erythema should not be measured.[1]

Sputum test: Sputum smears and cultures should be done for acid-fast bacilli if the patient is producing sputum. The preferred method for this is fluorescence microscopy, which is more sensitive than conventional Ziehl-Neelsen staining. In cases where there is no spontaneous sputum production, a sample can be induced, usually by nebulized inhalation of a saline or saline with bronchodilator solution. A comparative study found that inducing three sputum samples is more sensitive than three gastric washings.[1]

4. Treatment of TB

DOTS (Direct Observed Treatment, Short- term)

The World Health Organization (WHO) promotes another version of DOTS called 'directly observed therapy short course' (DOTS). This is a comprehensive tuberculosis management programme that focuses on low-income countries. DOTS is a five-element strategy for the control of tuberculosis that consists of political commitment, improved laboratory analysis, direct patient observation while swallowing each dose of medication, a drug supply that provides for the correct complete short course anti-tubercular drug combination for free, and a reporting system that documents the progress in curing the patient.

Current treatment of TB

The currently used drugs for the treatment of TB are classified into two categories: first line and second line drugs. The first line drugs have high efficacy and low toxicity a compared to second line drugs. The classification of these drugs has been summarized in following tables.

Table 1: Classification of anti-tubercular drugs

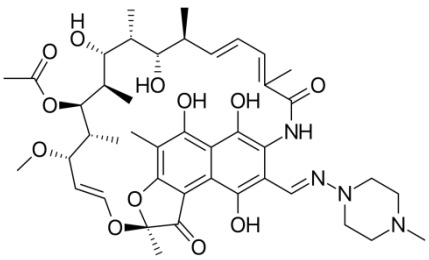
First line drugs	Second line drugs
Isoniazid (INH, H)	Ethionamide (Eto)
Rifampin (R)	Prothionamide (Pto)
Pyrazinamide (Z)	Cycloserine (Cs)
Ethambutol (E)	Terizidone (Trd)
Streptomycin (S)	Para-aminosalicylicacid (PAS)
	Rifabutin
	Thiacetazone (Thz)
	Fluoroquinolones (ofloxacin, moxifloxacin, ciprofloxacin, levofloxacin)
	Injectable drugs (kanamycin, amikacin, capreomycin)

The pharmacodynamics and pharmacokinetics of various currently used anti-tubercular drugs have been summarized in table no 2.

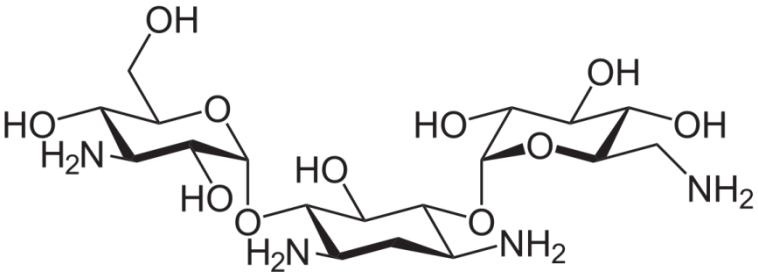
Table 2: Pharmacodynamics and Pharmacokinetics of currently used anti-tubercular drugs.

Drugs	Pharmacodynamics	Pharmacokinetics
Isoniazid	Inhibit mycolic acid biosynthesis Effect on carbohydrate DNA, lipid, NAD metabolism	Well metabolized by Acetylation
Ethambutol	Inhibit biosynthesis of arabinogalactam	Near about ¾ of oral dose is absorbed Less than half is metabolized
Pyrazinamide	Membrane potential disruption	Orally well absorbed Metabolized in liver
Rifampicin	Rifampicin inhibits bacterial DNA-dependent RNA polymerase	Orally well absorbed
Streptomycin	Protein synthesis inhibitor	Poorly absorbed
Amikacin	Inhibit protein synthesis	Eliminated $t_{1/2}$ 2.4 hrs Vd 19.6 L/Kg
Kanamycin	Inhibit protein synthesis	Elimination $t_{1/2}$ 2.4 hrs

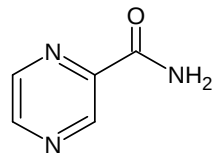
		Vd 19.6 L/Kg
Capreomycin	Inhibit protein synthesis	Peak serum conc. in range of 20-50µg/ml
Streptomycin	Inhibit protein synthesis	Plasma Half life 0.44 hrs Vd 0.47±0.06 L/ Kg
Moxifloxacin	Inhibit DNA gyrase Topoisomerase -IV	Orally well absorbed Absolute bioavailability is 90%
Gatifloxacin	Inhibit DNA gyrase Topoisomerase -IV	Rapid and complete absorption Average bioavailability 96%
Levofloxacin	Inhibit DNA gyrase Topoisomerase -IV	Complete oral absorption Bioavailability is 99%
Ofloxacin	Inhibit DNA gyrase Topoisomerase -IV	Bioavailability 98% Administered orally
Ethionamide	Inhibit mycolic acid biosynthesis	V_d is 3.22 L/Kg
Cycloserine	Inhibit biosynthesis of peptidoglycan.	Well absorbed orally
Clofazimine	Cause cell membrane Distruption	Does not cross the blood brain barrier but can cross placenta Unmetabolized drug excreted in faces
Linezolid	Inhibit protein synthesis	Extensively absorbed after oral dosing Absolute bioavailability is 100%
Thioacetazone	Inhibit methyl transferase in mycolic acid biosynthesis	Well absorbed orally
Clarithromycin	Inhibit protein synthesis	Stable in gastric acid Bioavailability is 37%



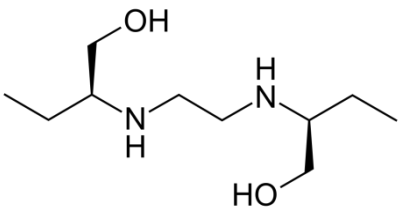
Rifampicin



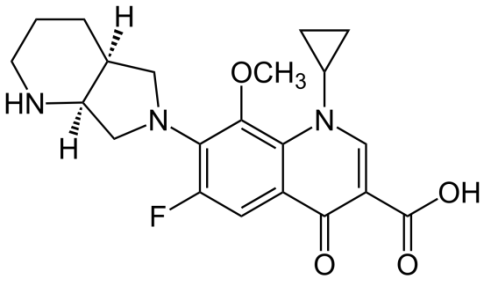
Kanamycin



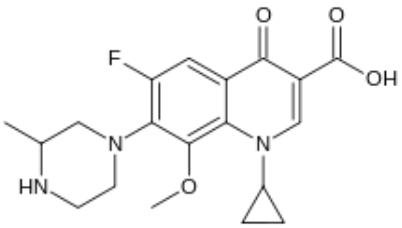
Pyrazinamide



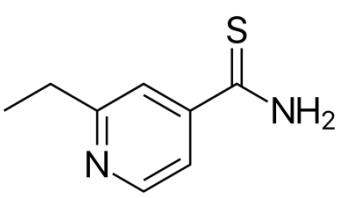
Ethambutol



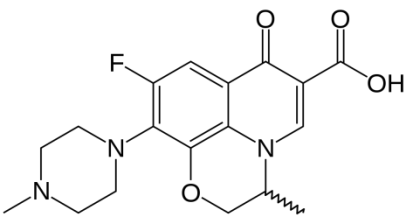
Moxifloxacin



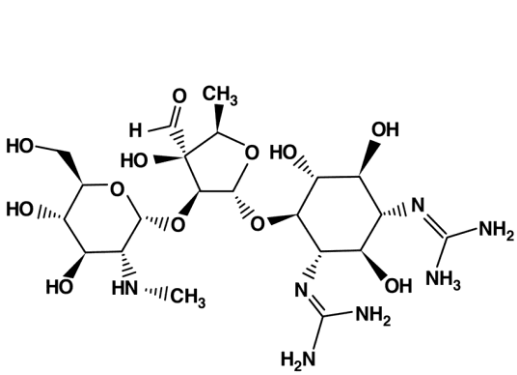
Gatifloxacin



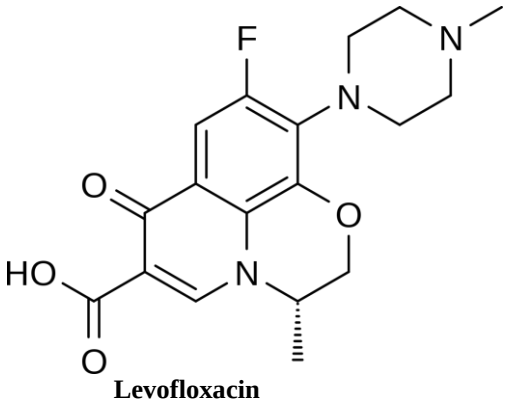
Ethionamide



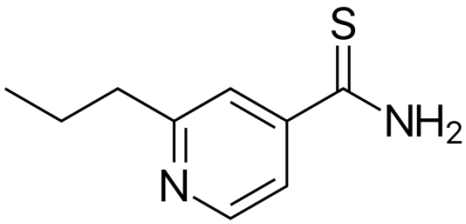
Ofloxacin



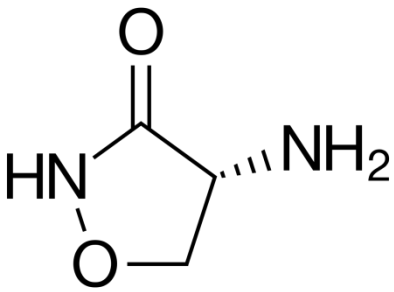
Streptomycin



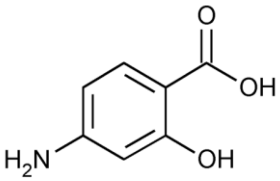
Levofloxacin



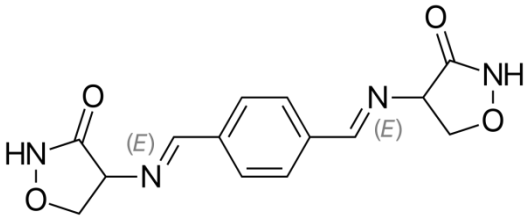
Prothionamide



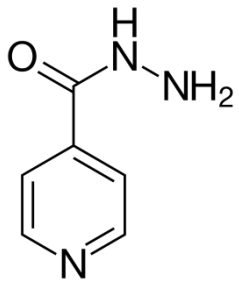
Cycloserine



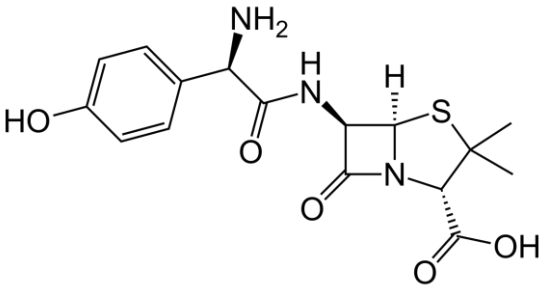
P- Amino salicylic acid



Terizidone



Isoniazid



Amoxicilin

Fig. No. 1: Chemical Structure of various anti-tubercular drugs.

4.3. Limitations of existing therapy

There are several problems associated with the existing drugs that are used for tuberculosis treatment i.e.

- Duration and complexity of treatment result in non-adherence to treatment and it Lead to suboptimal response (failure and relapse), emergence of resistance, and continuous spread of the disease.
- Adverse reaction associated with anti- TB drug.
- Increasing incidence of MDR and XDR-TB.
- Less efficacy and more toxicity of second line drugs.
- Therapeutic complications of TB associated with HIV (toxicity drug interaction.
- i.e. between rifampin and the antiviral protease inhibit and immune reconstitution syndrome).

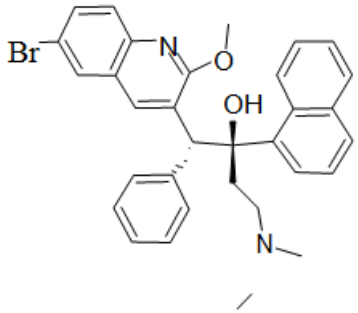
5. New drug for treatment of tubercul0osis

Diarylquinolines

The diarylquinoline R207910 (also known as TMC207) kills mycobacteria by inhibiting ATP synthase and blocking energy production.[19] TMC-207 is highly

potent drug against both drug- susceptible and drug-resistant strains of Mycobacterium. It is a promising candidate for the development of effective once-weekly regimens that may also be capable of shortening the overall duration of treatment of tuberculosis.[20] The anti-bactericidal activity of TMC207 is found to be comparable to INH or RIF.[21,22,19] The most active diarylquinoline (TMC207, also called R 207910, or compound J) is currently being evaluated in phase II clinical trials at a dose of 400 mg/day.

TMC-207 (Bedaquiline)



TMC-207 inhibits mycobacterial ATP synthase enzyme. It has similar activity in susceptible and MDR strains of bacteria. Mycobacteria that are resistant to TMC207 *in vitro* show mutations in the atpE gene, which encodes subunit of ATP synthase. No cross resistance with available drugs is expected since the target of the diarylquinolines differs from that of the currently available anti-TB drugs.[21,23,21]

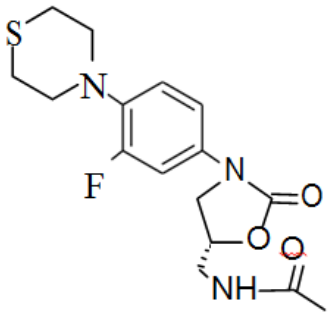
Pharmacokinetic profiles for TMC207 and its active *N*-monodesmethyl metabolite (M2) were determined up to 24 h postdose on day 7. Medication intakes were directly observed once in a day within 30 min after breakfast.[19] The C_{max} is reached after 5 h; the half-life is about 24 h in humans. The pharmacokinetics of TMC207 show linearity with dose. Rifampin reduces plasma TMC207 concentrations by 50%; however, a recent observation in mice showed significant activity of TMC207 even with a 50% reduction in exposure, indicating the relevance of the drug. No drug-drug interactions were observed between TMC207, isoniazid and pyrazinamide.[24,25]

The *in vitro* activity of TMC207 did not increase with increasing drug concentration, suggesting time-dependent rather than concentration-dependent response. The activity of TMC207 is limited to mycobacterial species only. Treatment with various combinations of TMC207 with isoniazid, pyrazinamide and rifampin yielded 100% negative lung cultures in mice after only 2 months of treatment. Replacement of any of the drug in standard regimen with TMC207 improved the bactericidal activity.[26,27] The guinea pig model was used to demonstrate sterilizing activity of TMC207. Almost complete eradication of primary and secondary lung lesions was achieved after 6 weeks of TMC207 monotherapy (15 mg/kg), whereas the standard regimen had limited effect.[28]

Oxazolidinones

Oxazolidinones are a new class of anti-bacterial protein synthesis inhibitors. The *in vitro* anti- bacterial activities of oxazolidinones against gram-positive organisms, including methicillin- resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumonia*, and multiple drug-resistant enterococci have been reported previously.[29] Linezolid, the only approved drug (by U.S. food and drug administration) in this class, has modest *in vitro* activity against *M. tuberculosis*.[6] It exhibits no cross-resistance with other anti-tubercular drugs.[28] Newly synthesized oxazolidinones were evaluated for their *in vitro* activities against *M. tuberculosis*, and subsequently, a murine model was used to evaluate the *in vivo* activities of the most active compounds.[29] A retrospective assessment in four European countries did not show objective advantages of adding linezolid 600 mg daily to individualized multidrug regimen for treatment of MDR TB/XDR-TB patients due to severe side effects. A reduced dose of 300 mg might retain efficacy while causing fewer side effects. Linezolid 600 mg is presently being tested in a phase IIa trial for treatment of XDR-TB in the Republic of Korea, and the 300 mg dose is under investigation in a phase IIa MDR-TB pilot trial in South Africa.[6]

PNU-100480 (Sutezolid)



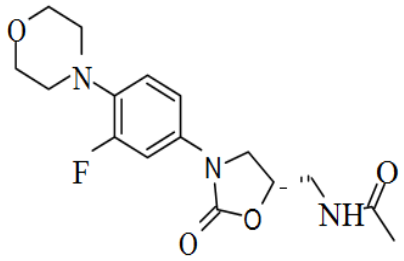
PNU-100480 is a close analogue of linezolid developed by Pfizer, New York, USA, that exhibited slightly better activity *in vitro*.[10] Treatment with PNU-100480, linezolid, and INH reduced the cell counts in spleens and lungs.[29] Recent mouse model studies showed marked improvement of bactericidal activity when PNU-100480 is added to first-line anti-TB drugs or used in combination with moxifloxacin and pyrazinamide. These findings suggest that PNU- 100480 has the potential to significantly shorten therapy for both drug-susceptible and drug- resistant TB. This compound is currently in phase I clinical trials.[6]

PNU-100480 inhibits the initiation of protein synthesis by binding to 23S RNA in the 50S ribosomal subunit of bacteria. Due to its potent action against *M. tuberculosis* in the murine model, it is under investigations in phase I clinical trials in humans, and appeared to be safe and well tolerated.[5,8,30]

Maximal concentrations (C_{max}) of PNU-100480

increased approximately proportionately with the dose, up to 839±386 ng/mL (3.4-fold greater than the minimum inhibitory concentration [MIC]), 1–2 h after receipt of the 1000 mg dose. Cmax values were reduced in comparison to 659±165 ng/mL after the 1500 mg dose, apparently reflecting lower bioavailability and delayed absorption.[31]

Linezolid

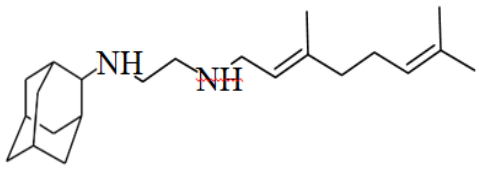


Linezolid is a recently approved anti-tubercular drug belonging to a new class of oxazolidinones. It has shown potent activity against gram-positive bacteria, including resistant staphylococci, enterococci, and pneumococci.[32] Linezolid, a first-generation oxazolidinone, exhibited clinical effectiveness even drug-resistant cases, although the frequency and severity of adverse events (i.e. peripheral neuropathy, optic neuropathy, gastrointestinal disorders and myelosuppression) limit its long-term use. A recent prospective randomized trial enrolling XDR-TB patients failing previous chemotherapy demonstrated the efficacy of a reduced linezolid dosage (300–600 mg per day), confirming previous findings: 87% of all enrolled patients achieved bacteriological conversion within 6 months.[33]

Linezolid is a protein synthesis inhibitor that interacts with domain V of the 23S rRNA which is also the binding site for chloramphenicol, macrolides, and lincosamides, but the lack of cross- resistance between oxazolidinones and other antibiotics supports evidence for a novel mechanism of action.[34,35]

Ethylenediamine

5.3.1 SQ-109



SQ-109 is a derivative of ethambutol that appears to have a different mechanism of action. The substitution of SQ-109 for ethambutol in the standard regimen demonstrated increased efficacy in the mouse model. A phase I single-dose study has been completed and a phase I dose-escalation study is underway.[36]

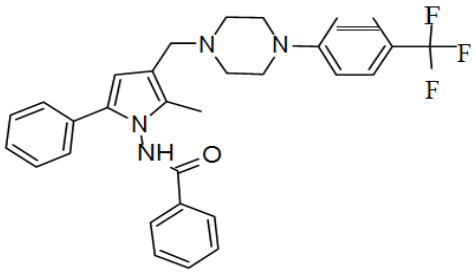
The exact target of SQ-109 is not yet known, however it is assumed that the drug inhibit mycobacterial cell wall synthesis. Since resistance rates to SQ109 are low, it is thought that two mycobacterial gene changes are needed to result in resistance. Therefore, SQ109 may have more than one target in *M. tuberculosis*.[37]

SQ109 undergoes a first-pass metabolism in the liver before it enters the systemic circulation. Liver microsomes convert SQ109 in four predominant metabolites. CYP2D6 and CYP2C19 enzymes are involved in SQ109 metabolism; CYP3A4 has little effect on SQ109. It has been suggested that SQ109 is a prodrug that needs activation by mycobacterial CYP enzymes. Results from a recent drug-drug interaction study in rats suggest that SQ109 induces its own metabolism. SQ109 binding to plasma proteins ranges from 6 to 23% in humans, mice, rats, and dogs. Binding to tissue proteins is higher than that to plasma proteins. SQ109 has a long half-life (61 h) in humans.[37,38]

The MIC of SQ109 ranged from 0.16 to 0.64 mg/liter in susceptible and drug resistant Mtb isolates, including ethambutol-resistant strains. SQ109 also exhibits bactericidal activity within macrophages. Its activity is concentration dependent.[38,37] Synergistic activity was shown *in vitro* between SQ109, isoniazid and especially rifampin. Synergy was even present in rifampin- resistant strains. Streptomycin had an additive effect on SQ109 activity; ethambutol and pyrazinamide had no effect on the activity of SQ109.[39] Four weeks of monotherapy with SQ109 (0.1 to 25 mg/kg) in mice resulted in a reduction of mycobacterial load in spleen and lungs that was comparable to the effect of treatment with ethambutol (100 mg/kg) but less than that of treatment with isoniazid (25 mg/kg).[38,40]

Pyrroles

5.4.1 LL3858



During the search of compounds with activity against mycobacteria and fungi, several pyrrole derivatives have been developed. LL3858 is being investigated in phase I clinical trials. A fixed-dose combination called LL3848, containing LL3858 and the standard, first-line anti-TB drugs, is also being developed.[40]

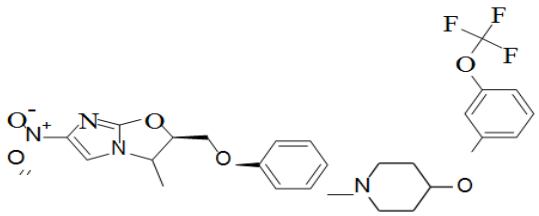
The mycobacterial target of LL3858 is not yet known. Since LL3858 is active against *M. tuberculosis* strains that are resistant to available anti-TB drugs, the target probably differs from that of currently used drugs. No data about the pharmacokinetics of LL3858 in humans

are available yet.[41] The MIC90 of LL3858 for Mtb is 0.25 µg/ml. LL3858 exhibits concentration- dependent activity.[42] LL3858 (12.5 mg/kg) reduced the mycobacterial load in mice to a greater extent than isoniazid. Regimens of 8 weeks of LL3858, isoniazid, and rifampin with or without pyrazinamide sterilized lungs and spleens in 50% of mice. When the treatment period was extended to 12 weeks, complete sterilization of the target organs was achieved in all the mice.[42]

5.3 Nitroimidazopyrans

Nitroimidazopyrans have been derived from the bicyclic nitroimidazofurans and its structure resembles that of metronidazole. Nitroimidazopyrans exhibits anti-cancer and anti-tubercular properties. PA-824 and OPC-67683 both belongs to nitroimidazopyrans and currently being investigated in clinical trials.[43,44,45]

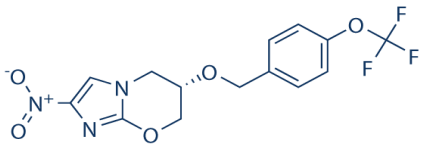
5.5.1 OPC-67683



OPC-67683 is an inhibitor of mycolic acid biosynthesis.[28] OPC-67683 is a prodrug and has to be activated by *M. tuberculosis* to produce its activity. Mutations in the mycobacterial Rv3547 gene found in OPC-67683 resistant *M. tuberculosis* strains suggest that this gene codes for the key enzyme in activating OPC-67683 (as well as PA-824).[10]

OPC-67683 exhibits concentration-dependent activity against intracellular *M. tuberculosis*. OPC-67683 showed better *in vitro* intracellular activity than that of isoniazid and PA-824 and as good as that of rifampin. It exhibited higher sterilizing activity than that of isoniazid and same to that of rifampin in an *in vitro* model of drug-tolerant *M. tuberculosis*, representing semi- dormant bacilli. No antagonism of OPC-67683 with rifampin, isoniazid, ethambutol, and streptomycin was shown *in vitro*. In mice, a regimen of OPC-67683 (2.5 mg/kg), rifampin (5 mg/kg), and pyrazinamide (100 mg/kg) achieved faster eradication of bacilli than the standard RHZE regimen (5, 10, 100, and 100 mg/kg, respectively). Whereas no mycobacterial colonies were detected after 4 months of treatment with the OPC- 67683-containing regimen, colonies were still detected after 6 months of treatment with the standard regimen.[42]

5.5.2 PA-824



PA-824 is found in the form of prodrug and activated by mycobacterial glucose-6-phosphate dehydrogenase (FDG1) or its cofactor, coenzyme F420, into an active form.[16,43] Activated PA- 824 inhibits the synthesis of proteins and cell wall lipids. The mechanism of cell killing by these prodrugs is complex. Treatment with PA-824 or OPC-67683 disrupts the formation of mycolic acids, major constituents of the cell envelope of Mtb. PA-824 is active in susceptible and resistant *M. tuberculosis* strains. It have not any cross-resistance with standard anti-TB drugs.[44] Mutations in the mycobacterial genes fbiA, fbiB, and fbiC cause to impaired coenzyme F420 synthesis and therefore resistance to PA-824.[46,10] Mutations in the Rv3547 gene, encoding a protein with unknown function, have been described in PA-824 resistant strains. Complementing these mutants with intact Rv3547 fully restored the ability of the mutants to metabolize PA-824. This suggests mediation of a highly specific protein, next to FGD1 and coenzyme F420, in PA-824 activity.[47]

Serum PA-824 concentrations in mice are not influenced by co-administration of rifampin, isoniazid, and pyrazinamide in various combinations, and PA-824 does not influence concentrations of the latter drugs in serum.[13] PA-824 is currently being investigated in phase I clinical trial. Studies in healthy volunteers showed a half-life of about 18 h and a time to reach Cmax of 4 to 5 h. About 65% of PA-824 is excreted in urine and 26% in feces.[47]

In vitro studies showed MICs of PA-824 against fully susceptible and MDR strains ranging from 0.015 to 0.25 µg/ml. PA-824 activity is concentration dependent.[26,44,48] The bactericidal activity of PA-824 (dose 25 to 50 mg/kg) was comparable to that of isoniazid (dose 25 mg/kg) in mice and guinea pigs and to those of rifampin (dose 20 mg/kg) and moxifloxacin (dose 100 mg/kg) in mice.[49] PA-824 showed greater activity than isoniazid and moxifloxacin *in vitro* and in mice and comparable activity to combination therapy with rifampin and isoniazid.[50] PA-824 (100 mg/kg) has been incorporated in the standard regimen in mice to evaluate its potential to shorten treatment duration. Only the regimen in which isoniazid was replaced with PA-824 achieved faster lung culture conversion and a lower CFU count after 2 months of treatment than the standard regimen. However, relapse rates were the same in these regimens. The sterilizing activity of a regimen containing PA-824 (dose100 mg/kg), moxifloxacin(dose 100 mg/kg), and pyrazinamide (dose 150 mg/kg) was recently found to be better than that of rifampin (dose 10mg/kg), isoniazid (dose 25mg/kg), and pyrazinamide (dose 150 mg/kg) in mice, indicating thatPA-824 could be incorporated in a rifampin-free regimen to treat MDR TB.PA-824 (dose 100 mg/kg) was highly active in a mouse model for latent TB when combined with moxifloxacin(dose 100 mg/kg). An extended EBA study in humans with daily PA-824 doses of 200 to 1,200 mg over 14 days is ongoing in South Africa. Results are

expected soon.[8,51]

Table 3: New drugs in clinical development.

Drug	Class	Stage	Mechanism of Action
TMC-207	Diarylquinaline	Phase-II	ATP synthase inhibitor
(Bedaquiline)			
PNU-100480	Oxazolidinones	Phase-I	Protein synthesis inhibitor
Linezolid	Oxazolidinones	Phase-I	Protein synthesis inhibitor
SQ-109	Ethylenediamine	Phase-I	Inhibits mycobacterial cell
			wall synthesis
LL3858	Pyrroles	Phase-I	Not known
OPC-67683	Nitroimidazopyrans	Phase-I/II	Mycolic acid biosynthesis
			inhibitor
PA-824	Nitroimidazopyrans	Phase-II	Inhibits the synthesis of
			protein and cell wall lipids

6. CONCLUSION

TB is one of the major problem in the world. Currently the drugs that are used for the treatment of TB include rifampin, isoniazid, pyrazinamide, ethambutol and streptomycin. These drugs associated with one or more limitations like duration, complexity of treatment, adverse reaction, efficacy and toxicity of second line drugs etc. that cause patient compliance. A number of new molecules such as diarylquinaline (TMC-207), oxazolidionones (PNU-100480, linezolid), ethylenediamine (SQ-109), pyrroles (LL-3358) and nitroimidapyran (OPC-67683, PA-824) have exhibited potent anti-bacterial properties *in vitro* and are in various clinical stages of development.

REFERENCE

1. Caulfield, A. J.; Wengenack, N. L. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases Diagnosis of Active Tuberculosis Disease: From Microscopy to Molecular Techniques. J. Clin. Tuberc. Other Mycobact. Dis, 2016; 4: 33–43.
2. Koul, A. N.; Wagay, H. A.; Rather, A. B.; Dhobi, G. N.; Bhat, F. A.; Bhat, M. R. Demography and Clinical Outcome of Pulmonary Tuberculosis in Kashmir; 2 Year Prospective Study. Egypt. J. Chest Dis. Tuberc, 2016; 65(2): 455–460.
3. Lienhardt, C.; Raviglione, M.; Spigelman, M.; Hafner, R.; Jaramillo, E.; Hoelscher, M.; Zumla, A.; Gheuens, J. New Drugs for the Treatment of Tuberculosis: Needs, Challenges, Promise, and Prospects for the Future, 2012; 1–9.
4. Hoagland, D. T.; Liu, J.; Lee, R. B.; Lee, R. E. New Agents for the Treatment of Drug- Resistant Mycobacterium Tuberculosis. Adv. Drug Deliv. Rev, 2016; 102: 55–72.
5. Ambrosio, L. D.; Centis, R.; Sotgiu, G.; Pontali, E.; Spanevello, A.; Migliori, G. B. New Anti-Tuberculosis Drugs and Regimens: 2015 Update, 2015.
6. Lienhardt, C.; Vernon, A.; Raviglione, M. C. New Drugs and New Regimens for the Treatment of Tuberculosis: Review of the Drug Development Pipeline and Implications for National Programmes, 2010, No. Table 1.
7. Ramaswamy, S. V; Amin, A. G.; Göksel, S.; Stager, C. E.; Dou, S. J.; El Sahly, H.; Moghazeh, S. L.; Kreiswirth, B. N.; Musser, J. M. Molecular Genetic Analysis of Nucleotide Polymorphisms Associated with Ethambutol Resistance in Human Isolates of Mycobacterium Tuberculosis. Antimicrob. Agents Chemother, 2000; 44(2): 326–336.
8. Nuermberger, E.; Tyagi, S.; Tasneen, R.; Williams, K. N.; Almeida, D.; Rosenthal, I.; Grosset, J. H. Powerful Bactericidal and Sterilizing Activity of a Regimen Containing PA-824, Moxifloxacin, and Pyrazinamide in a Murine Model of Tuberculosis. Antimicrob. Agents Chemother, 2008; 52(4): 1522–1524.
9. Weiner, M.; Burman, W.; Luo, C.; Peloquin, C. A.; Engle, M.; Goldberg, S.; Agarwal, V.; Vernon, A. Effects of Rifampin and Multidrug Resistance Gene Polymorphism on Concentrations of Moxifloxacin, 2007; 51(8): 2861–2866.
10. Choi, K.-P.; Bair, T. B.; Bae, Y.-M.; Daniels, L. Use of Transposon Tn, 5367.
11. Mutagenesis and a Nitroimidazopyran- Based Selection System To Demonstrate a Requirement for fbiA and fbiB in Coenzyme F 420 Biosynthesis by Mycobacterium Bovis BCG. J. Bacteriol, 2001; 183(24): 7058–7066.
12. Pletz, M. W. R.; Roux, A. De; Roth, A.; Neumann, K.; Mauch, H.; Lode, H. Early Bactericidal Activity of Moxifloxacin in Treatment of Pulmonary Tuberculosis: A Prospective, Randomized Study, 2004; 48(3): 780–782.
13. Lubasch, A.; Keller, I.; Borner, K.; Koeppe, P. Comparative Pharmacokinetics of Ciprofloxacin, Gatifloxacin, Grepafloxacin, Levofloxacin, Trovafloxacin, and Moxifloxacin after Single Oral Administration in Healthy Volunteers, 2000; 44(10): 2600–2603.
14. Lanoix, J. P.; Betoudji, F.; Nuermbergera, E. Novel Regimens Identified in Mice for Treatment of Latent Tuberculosis Infection in Contacts of Patients with Multidrug- Resistant Tuberculosis. Antimicrob. Agents Chemother, 2014; 58(4): 2316–2321.
15. Shandil, R. K.; Jayaram, R.; Kaur, P.; Gaonkar, S.; Suresh, B. L.; Mahesh, B. N.; Jayashree, R.; Nandi,

V.; Bharath, S.; Balasubramanian, V. Moxifloxacin, Ofloxacin, Sparfloxacin, and Ciprofloxacin against Mycobacterium Tuberculosis: Evaluation of In Vitro and Pharmacodynamic Indices That Best Predict In Vivo Efficacy, 2007; 51(2): 576–582.
16. Prasad, V.; Singhal, R.; Umer, K. First and Second Line Drug Resistance ¨ ve Pulmonary among Treatment Naı Tuberculosis Patients in a District under Revised National Tuberculosis Control Programme (RNTCP) in New Delhi. J. Epidemiol. Glob. Health, 2015; 5(4): 365–373.
17. Williams, K. N.; Stover, C. K.; Zhu, T.; Tasneen, R.; Tyagi, S.; Grosset, J. H.; Nuermberger, E. Promising Antituberculosis Activity of the Oxazolidinone PNU- 100480 Relative to that of Linezolid in a Murine Model. Antimicrob. Agents Chemother, 2009; 53(4): 1314–1319.
18. Song, T.; Lee, M.; Jeon, H.; Park, Y.; Dodd, L. E.; Dartois, V.; Follman, D.; Wang, J.; Cai, Y.; Goldfeder, L. C.; Olivier, K. N.; Xie, Y.; Via, L. E.; Nae, S.; Barry, C. E.; Chen, R. Y. EBioMedicine Linezolid Trough Concentrations Correlate with Mitochondrial Toxicity-Related Adverse Events in the Treatment of Chronic Extensively Drug-Resistant Tuberculosis. EBIOM, 2015; 2(11): 1627–1633.
19. Chen, T.; Lu, P.; Lin, C.; Lin, W.; Chen, Y. International Journal of Infectious Diseases Fluoroquinolones Are Associated with Delayed Treatment and Resistance in Tuberculosis: A Systematic Review and Meta-Analysis. Int. J. Infect. Dis, 2011; 15(3): e211–e216.
20. Rustomjee, R.; Diacon, A. H.; Allen, J.; Venter, A.; Reddy, C.; Patientia, R. F.; Mthiyane, T. C. P.; Marez, T. De; Heeswijk, R. Van; Kerstens, R.; Koul, A.; Beule, K. De; Donald, P. R.; Mcneeley, D. F. Early Bactericidal Activity and Pharmacokinetics of the Diarylquinoline TMC207 in Treatment of Pulmonary Tuberculosis, 2008; 52(8): 2831–2835.
21. Guillemont, J.; Poncelet, A. R Esearch A Rticle Diarylquinolines, Synthesis Pathways and Quantitative Structure – Activity Relationship Studies Leading to the Discovery of TMC207, 2011; 3: 1345–1360.
22. Petrella, S.; Cambau, E.; Chauffour, A.; Andries, K.; Jarlier, V.; Sougakoff, W.; Curie, M. Genetic Basis for Natural and Acquired Resistance to the Diarylquinoline R207910 in Mycobacteria, 2006; 50(8): 2853–2856.
23. Koul, A.; Arnoult, E.; Lounis, N.; Guillemont, J.; Andries, K. The Challenge of New Drug Discovery for Tuberculosis. Nature, 2011, 469(7331): 483–490.
24. Garcia, B. J.; Loxton, A. G.; Dolganov, G. M.; Van, T. T.; Davis, J. L.; Jong, B. C. De; Voskuil, M. I.; Leach, S. M.; Schoolnik, G. K.; Walzl, G.; Strong, M.; Walter, N. D. Sputum Is a Surrogate for Bronchoalveolar Lavage for Monitoring Mycobacterium Tuberculosis Transcriptional pro Fi Les in TB Patients *. Tuberculosis, 2016; 100: 89– 94.
25. Lounis, N.; Bentoucha, A.; Truffot-pernot, C.; Ji, B.; Brien, R. J. O.; Vernon, A.; Roscigno, G.; Grosset, J. Effectiveness of Once-Weekly Rifapentine and Moxifloxacin Regimens against Mycobacterium Tuberculosis in Mice, 2001; 45(12): 3482–3486.
26. Boogaard, J. Van Den; Kibiki, G. S.; Kisanga, E. R.; Boeree, M. J.; Aarnoutse, R. E. MINIREVIEW New Drugs against Tuberculosis: Problems, Progress, and Evaluation of Agents in Clinical Development, 2009; 53(3): 849–862.
27. Lenaerts, A. J.; Hoff, D.; Aly, S.; Ehlers, S.; Andries, K.; Cantarero, L.; Orme, I. M.; Basaraba, R. J. Location of Persisting Mycobacteria in a Guinea Pig Model of Tuberculosis Revealed by R207910, 2007; 51(9): 3338–3345.
28. Inhibitor, S.; Huitric, E.; Verhasselt, P.; Andries, K.; Hoffner, S. E. In Vitro Antimycobacterial Spectrum of a Diarylquinoline ATP, 2007; 51(11): 4202–4204.
29. Lenaerts, A. J.; Gruppo, V.; Marietta, K. S.; Johnson, C. M.; Driscoll, D. K.; Nicholas, M.; Rose, J. D.; Reynolds, R. C.; Ian, M.; Tompkins, N. M.; Orme, I. M. Preclinical Testing of the Nitroimidazopyran PA-824 for Activity against Mycobacterium Tuberculosis in a Series of In Vitro and In Vivo Models Preclinical Testing of the Nitroimidazopyran PA-824 for Activity against Mycobacterium Tuberculosis in a Series. Antimicrob. Agents Chemother. 2005; 49(6): 2294–2301.
30. Cynamon, M. H.; Klemens, S. P.; Sharpe, C. A.; Chase, S. Activities of Several Novel Oxazolidinones against Mycobacterium Tuberculosis in a Murine Model. Antimicrob. Agents Chemother. 1999; 43(5): 1189–1191.
31. Wallis, R. S. Assessment of Whole Blood Bactericidal Activity in the Evaluation of New TB Drugs Robert S. Wallis, MD, FIDSA In: Donald PR, van Helden (Eds). Antituberculosis Chemotherapy. Progress in Respiratory Research. Basel, Karger, 2011. 2011.
32. Wallis, R. S.; Jakubiec, W. M.; Kumar, V.; Silvia, A. M.; Paige, D.; Dimitrova, D.; Li, X.; Ladutko, L.; Campbell, S.; Friedland, G.; Mitton-fry, M.; Miller, P. F. Pharmacokinetics and Whole-Blood Bactericidal Activity against Mycobacterium Tuberculosis of Single ... Pharmacokinetics and Whole-Blood Bactericidal Activity against Mycobacterium Tuberculosis of Single Doses of PNU-100480 in Healthy Volunteers, 2016; No. September 2010.
33. Alcala, L.; Jesu, M.; Viedma, D. G. De; Díaz-infantes, M.; Marín-arriaza, M.; Bouza, E.; Maran, G. In Vitro Activities of Linezolid against Clinical Isolates of Mycobacterium Tuberculosis That Are Susceptible or Resistant to First-Line Antituberculous Drugs, 2003; 47(1): 416–417.
34. Sotgiu, G.; Alffenaar, J. C.; Centis, R.; Ambrosio, L. D.; Spanevello, A.; Piana, A.; Battista, G. International Journal of Infectious Diseases Therapeutic Drug Monitoring: How to Improve Drug

Dosage and Patient Safety in Tuberculosis Treatment. Int. J. Infect. Dis, 2015; 32: 101–104.
35. Richter, E.; Ru, S.; Hillemann, D. First Linezolid-Resistant Clinical Isolates of Mycobacterium Tuberculosis, 2007; 51(4): 1534–1536.
36. Gentry-nielsen, M. J.; Olsen, K. M.; Preheim, L. C. Pharmacodynamic Activity and Efficacy of Linezolid in a Rat Model of Pneumococcal Pneumonia, 2002; 46(5): 1345– 1351.
37. Chen, P.; Gearhart, J.; Protopopova, M.; Einck, L.; Nacy, C. A. Synergistic Interactions of SQ109, a New Ethylene Diamine, with Front-Line Antitubercular Drugs in Vitro. J. Antimicrob. Chemother, 2006; 58(2): 332–337.
38. Mo, P.; Zhu, Q.; Teter, C.; Yang, R.; Deng, L.; Yan, Y.; Chen, J.; Zeng, J.; Gui, X. International Journal of Infectious Diseases Prevalence, Drug-Induced Hepatotoxicity, and Mortality among Patients Multi-Infected with HIV, Tuberculosis, and Hepatitis Virus. Int. J. Infect. Dis, 2014; 28: 95–100.
39. Jia, L.; Tomaszewski, J. E.; Hanrahan, C.; Coward, L.; Noker, P.; Gorman, G.; Nikonenko, B.; Protopopova, M. Pharmacodynamics and Pharmacokinetics of SQ109, a New Diamine-Based Antitubercular Drug. Br. J. Pharmacol, 2005; 144(1): 80–87.
40. Qian, T.; Fu, S.; Chen, Y.; Chien, S.; Lee, J.; Lin, C. Outbreak of Multidrug-Resistant Tuberculosis in an Aboriginal Family in Eastern Taiwan. Tzu Chi Med. J, 2016; 28(1): 29–32.
41. Nikonenko, B. V.; Protopopova, M.; Samala, R.; Einck, L.; Nacy, C. A. Drug Therapy of Experimental Tuberculosis (TB): Improved Outcome by Combining SQ109, a New Diamine Antibiotic, with Existing TB Drugs. Antimicrob. Agents Chemother, 2007; 51(4): 1563–1565.
42. Van Boogaard, J. Den; Kibiki, G. S.; Kisanga, E. R.; Boeree, M. J.; Aarnoutse, R. E. New Drugs against Tuberculosis: Problems, Progress, and Evaluation of Agents in Clinical Development. Antimicrob. Agents Chemother, 2009; 53(3): 849–862.
43. Papadopoulou, M. V.; Bloomer, W. D.; Rosenzweig, H. S.; Arena, A.; Arrieta, F.; Rebolledo, J. C. J.; Smith, D. K. Nitrotriazole- and Imidazole-Based Amides and Sulfonamides as Antitubercular Agents. Antimicrob. Agents Chemother, 2014; 58(11): 6828–6836.
44. Manjunatha, U. H.; Lahiri, R.; Randhawa, B.; Dowd, C. S.; Krahenbuhl, J. L.; Barry, C. E. Mycobacterium Leprae Is Naturally Resistant to PA-824. Antimicrob. Agents Chemother, 2006; 50(10): 3350–3354.
45. Stover, C. K.; Warrener, P.; Vandevanter, D. R.; Sherman, D. R.; Arain, T. M.; Langhorne, M. H.; Anderson, S. W.; Towell, J. A.; Yuan, Y.; Mcmurray, D. N.; Kreiswirth, B. N.; Barry, C. E.; Baker, W. R. A Small-Molecule Nitroimidazopyran Drug Candidate for the Treatment of Tuberculosis, 2000; 405 (June).
46. Spigelman, M. K. New Tuberculosis Therapeutics: A Growing Pipeline. J. Infect. Dis, 2007; 196(s1): S28–S34.
47. Choi, W. H.; Lee, I. A. SC. Asian Pac. J. Trop. Biomed, 2016.
48. Singh, R.; Manjunatha, U.; Boshoff, H. I. M.; Ha, Y. H.; Niyomrattanakit, P.; Ledwidge, R.; Dowd, C. S.; Lee, I. Y.; Zhang, L.; Kang, S.; Keller, T. H.; Jiricek, J.; Barry, C. E. NIH Public Access, 2009; 322(5906): 1392–1395.
49. Tyagi, P.; Dharmaraja, A. T.; Bhaskar, A.; Chakrapani, H.; Singh, A. Free Radical Biology and Medicine Mycobacterium Tuberculosis Has Diminished Capacity to Counteract Redox Stress Induced by Elevated Levels of Endogenous Superoxide. Free Radic. Biol. Med, 2015; 84: 344–354.
50. Johnson, C. M.; Pandey, R.; Sharma, S.; Khuller, K.; Basaraba, R. J.; Orme, I. M.; Anne, J.; Khuller, G. K.; Lenaerts, A. J. Oral Therapy Using Antituberculosis Drugs in Guinea Pigs Infected with Mycobacterium Tuberculosis Oral Therapy Using Nanoparticle- Encapsulated Antituberculosis Drugs in Guinea Pigs Infected with Mycobacterium Tuberculosis. Antimicrob. Agents Chemother, 2005; 49(10): 4335–4338.
51. Hu, Y.; Coates, A. R. M.; Mitchison, D. A. Sterilizing Activities of Fluoroquinolones against Rifampin-Tolerant Populations of Mycobacterium Tuberculosis, 2003; 47(2): 653–657.
52. Yoshimatsu, T.; Nuermberger, E.; Tyagi, S.; Chaisson, R.; Bishai, W.; Grosset, J. Bactericidal Activity of Increasing Daily and Weekly Doses of Moxifloxacin in Murine Tuberculosis, 2002; 46(6): 1875–1879.
53. Van Niekerk, C.; Ginsberg, A. Assessment of Global Capacity to Conduct Tuberculosis Drug Development Trials: Do We Have What It Takes? Int. J. Tuberc. Lung Dis, 2009; 13(11): 1367–1372.