Review Article

Recent Advances in Tuberculosis Drug Development

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ABSTRACT

The emergence of drug-resistant tuberculosis is a growing disease worldwide. The lack of safe and effective drugs, together with the frequent development of adverse drug reactions could result in worse condition. Therefore, new drugs able to booster the current tuberculosis treatment regimen are urgently required. Novel drugs that are effective and safe against *Mycobacterium tuberculosis* are required to reduce the number of drugs and the duration of treatment in both drug-susceptible tuberculosis and multi-drug-resistant tuberculosis. Due to increased number of multidrug-resistant and extensively drug-resistant strains and the ineffectiveness of the current treatment against latent tuberculosis are challenges to be overcome in future. The scenario of drug discovery becomes upsetting when it is considered that the number of new drugs does not increase proportionally to the emergence of drug resistance. In this review, we will demonstrate the recent advances in anti-tubercular drug discovery, centre of attention on the research of compounds with potent anti-tuberculosis activity against multidrug-resistant tuberculosis strains. Although, the best treatment regimen for achieving better results and preventing adverse drug reactions remains yet to be determined, with safety concerns regarding cardiac events due to QT prolongation still to be addressed. Therefore a simple and short treatment with higher efficacy, and lesser adverse drug reactions and drug-drug interaction is expected for patients with multidrug-resistant and extensively drug-resistant tuberculosis.

Keywords: Tuberculosis, Multidrug-Resistant, Anti-tubercular Agents, Bedaquiline, OPC-67683.s

INTRODUCTION

Tuberculosis is the leading infectious cause of death worldwide, with 9·6 million cases and 1·5 million deaths reported in 2014. WHO estimates 480 000 cases were multidrug resistant (MDR). Less number[less than half] of patients who entered into treatment for MDR tuberculosis successfully completed that treatment, mainly due to high mortality and loss to follow-up. These in turn illustrate weaknesses in current treatment regimens and national tuberculosis programmes, coupled with operational treatment challenges. Several new or repurposed antimicrobial drugs are in advanced trial stages for MDR tuberculosis, and two new antimicrobial drug candidates are in early-stage trials. Several clinical trials to reduce the duration of therapy in MDR and drug-susceptible tuberculosis are going on. A wide range of candidate host-directed therapies are being developed to accelerate eradication of infection, prevent new drug resistance, and prevent permanent lung injury. We assess risks associated with evaluation of new treatment regimens, and highlight opportunities to advance tuberculosis research generally through regulatory innovation in MDR tuberculosis. Progress in tuberculosis-specific biomarkers (including culture conversion, PET and CT imaging, and gene expression profiles) can support this innovation. *Mycobacterium tuberculosis*, the causative organism agent for tuberculosis was identified in 1882 by Robert Koch, but since yet there is no single drug available for the proper treatment of tuberculosis[1,2]. Tuberculosis is the world's second common cause of death from infectious diseases, after AIDS. In 1993, after 111 years of Robert Koch's discovery of *M. tuberculosis*, the World Health Organization (WHO) declares TB as "a global emergency''. TB kills 5000 people every day that means one person at every 20 seconds. According to the WHO, 2 million people die every year & at least 9 million are getting infected[3]. All countries are affected, but 85% of cases found only in Africa & Asia sub-continents due to irresponsiveness about the health[4]. Most TB cases are found in poor countries due to less health care access, as well as high exposure to unhealthy & crowded living, malnutrition, HIV infection[4]. The first drug regimen which used for treatment of tuberculosis is streptomycin, which leads to streptomycin resistance, comes in the market in the era of 1940s[5]. In between 1940 & 1980, so many drugs come in to market like Isoniazid, p-Amino salicylic acid (PAS), Ethambutol, and Rifampicin & Ofloxacin[5]. The last drug with a new mechanism of action approved for the treatment of tuberculosis is Rifampicin in 1963[5], so it is not wrong to say that from last 50 years there is no molecule get approval as drug regimen for the treatment of TB. Despite advances in TB chemotherapy, DOT's therapy and BCG vaccine, TB remains a significant infectious disease spreads through the air[2,6]. *M. tuberculosis* is an obligate aerobic bacillum that divides at an extremely slow rate & it is clear that monotherapy with any agent led to be development of resistance and clinical failure in two or five months. So, TB chemotherapy & DOT's therapy involves the administration of multiple drugs since late 1960s[6].

Present therapy for Tuberculosis

In 1943, Anti-TB research resulted in discovery of Streptomycin, during this era other agents like *para*-Aminosalicylic acid (1948), Isoniazid (1952), Pyrazinamide (1954), Cycloserine (1955), Kanamycin (1957), Ethionamide (1960), Ethambutol (1962) & Rifampicin (1963)[5]. Grosset & Mitchison postulated that some drugs have excellent bactericidal activity but poor sterilising activity, whereas others possess potent sterilising activity but less bactericidal. So, no single drug can give effective treatment, multidrug therapy required[5].

Table 1: Current Anti-tubercular drugs and their targets[2]

Drugs	MIC (µg/ml)	Mechanisms of action	Targets
Isoniazid	0.01-0.20	Inhibition of cell wall mycolic acid synthesis	Enoyl acyl carrier protein reductase
Rifampin	0.05-0.50	Inhibition of RNA synthesis	RNA polymerase, β subunit
Pyrazinamide	20-100	Depletion of membrane energy	Membrane energy trasferase
Ethambutol	1-5	Inhibition of cell wall arabinogalactan synthesis	Arabinosyl trasferase
Streptomycin	2-8	Inhibition of protein synthesis	Ribosomal S12 protein & 16S rRNA
Kanamycin	1-8	Inhibition of protein synthesis	16S rRNA
Ehtionamide	0.6-2.5	Inhibition of mycolic acid synthesis	Acyl carrier protein reductase
PAS	1-8	Inhibition of folate pathway & mycobactin synthesis	Thymidylate synthase

Currently, TB chemotherapy involves first-line drugs Isoniazid, Pyrazinamide & Rifampicin for two months, followed by an additional four months of treatment Isoniazid & Rifampicin alone[7]. If this treatment fails due to bacterial drug resistance, or intolerance, second line drugs PAS, Kanamycin, Fluoroquinolones, Ethionamide are used, which are less effective and produce serious side effects[2]. Problems associated with current TB therapy are mentioned below: 1) Drug resistance, 2) Long duration & more complex therapy leads to produce non-compliance and continuous spread of therapy, 3) Drugs for drug-resistance TB are not available everywhere & require longer use, 4) Poor patient compliance, 5) Co-infection of TB & HIV, 6) Prophylactic therapy of latent TB, 7) Cost of therapy & 8) Treatment of paediatric infection[5-6].Based on prior aim to shorten the duration of period, some affords have been made like WHO recommended DOTS (directly observed treatment, short term) anti-TB therapy involves the administration of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol or Streptomycin, but due to its expensiveness and labour intensity it became a burden on public health programs[3-6].

Multidrug-resistance TB (MDR-TB):

In 2008, an estimated 3,90,000-5,10,000 cases of MDR-TB emerged globally & among all incident TB cases globally, 3.6% are estimated to have MDR-TB. Almost 50% of MDR-TB cases worldwide are estimated to occur in China and India. In May 2009, the World Health Assembly resolution WHA 62.15 urged Member States "to achieve universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis". In this resolution, 20 countries were updating their TB control plans, and after this 7 more countries had shared their plans with WHO. The total cost requires to treat MDR-TB in 2015 will be 16 times higher than that available in 2010. The Global Fund to Fight AIDS, Tuberculosis and Malaria is the single biggest source of external funding for TB control[8].

Multidrug-resistance TB (MDR-TB) is caused by bacteria that are resistant to at least Isoniazid & Rifampicin the most effective anti-TB drugs. MDR results from the either primary infection with resistant bacteria or may develop in the course of patient's treatments[8]. At present, MDR-TB is treated by a combination of 8 to 10 drugs with therapies lasting up to 2 years; which increases poor patient compliance and increase cost of therapy[1].

Extensively drug-resistant TB (XDR-TB)

Extensively drug-resistant TB (XDR-TB) is a form of TB caused by bacteria that are resistant to Isoniazid and Rifampicin as well as any Fluoroquinolones and any of second line anti-TB injectable drugs like Aminoglycosides. So, its treatment is very limited. Thus, the current situation leads the immediate identification of new scaffolds to conduct appropriate clinical trials as to produce effective drugs against MDR-TB and XDR-TB[1].

Drugs under clinical development

Drugs are needed to kill various bacterial subpopulations and prevention of development of resistance that can be altered by other drugs in regimen. Although, the drugs are essential requirement for regimen, high quality drug molecules are needed for proper treatment of TB[5]. Drugs currently evaluated in the clinic have prior aim to shortening the treatment of TB, falls into two categories: 1) those already used in either first or second line TB treatment, 2) those that have completely novel mechanism of action[9]. Twelve compounds are in clinical development for TB- four existing drugs are redeveloped & eight new chemical compounds are specially developed for Tuberculosis[5].

Table 2: Countries and areas reporting data from drug resistance surveys since 2008[8]

Country or area	WHO region	Year	Cases with DST results (H+R)	New cases		Previously treated cases	
				Multidrug resistant		Multidrug resistant	
				Number	%	Number	%
Botswana	African	2008	933	32	3.4% (2.4–4.8)	19	13.1%(8.1 –19.7)
China	Western Pacific	2007	3,037	175	5.7% (4.6–7.1)	226	25.6%(21. 7–30.0)
Mozambiqu e	African	2007	1,102	38	3.5% (2.2–4.8)	3	11.2%(0.0 –25.2)
Myanmar	South-East Asia	2008	1,071	45	4.2% (3.1–5.6)	30	10.0%(6.9 –14.0)

DST = drug susceptibility testing

Table 3: Compounds in clinical development for the treatment of active tuberculosis

	Phase 1	Phase 2	Phase 3
Existing drugs redeveloped	-	Linezolid Rifampin	Gatifloxacin Moxifloxacin Rifapentine
New drugs Developed for Tuberculosis	AZD-5847	TMC-207 OPC-67683 PA-823 SQ-109 PNU-100480 LL-3858	-

Fluoroquinolones

Fluoroquinolones are broad-spectrum antibiotics currently used as the second-line drugs to treat tuberculosis primarily in cases involving resistance or intolerance to first-line anti-tuberculosis therapy[2,10]. These Fluoroquinolones have demonstrated, in mouse models as well as in the clinic, marked efficacy against *M. tuberculosis* with safety & tolerability profile[9,11-19]. The new C-8-methoxy-fluoroquinolones like Moxifloxacin (**MXF**) and Gatifloxacin (**GATI**) are more active against *M. tuberculosis* due to its longer half life and have low minimum inhibitory concentrations (MICs) than Levofloxacin, Ciprofloxacin and Ofloxacin[2,10,20-24]. Fluoroquinolones acts via novel mechanism of action, targets DNA gyrase[28-29]. Fluoroquinolones have also been show to penetrate into macrophase and have bactericidal activity there[30-31]. Fluoroquinolones when combined with various first-line anti-tubercular drugs have shown greater reductions in colony forming units (CFUs) of intramacrophase *M. tuberculosis* than the individual alone, indicating that it shows good *in vitro* activity and shows same activity like INH[28,29,32]. As a result, MXF & GATI is currently being evaluated in Phase 3 trails, for investigation of whether treatment of drug-

susceptible tuberculosis can be shortened to 4 months than 6 months by substituting MXF with INH & GATI with Ethambutol[2,5]. An *in vivo* comparison found that GATI, MXF & INH had similar activities against *M. tuberculosis* and treatment studies in mice have shown that MXF is more active & effective than other two[33-35]. MXF has been shown to kill subpopulation of *M. tuberculosis*, that not killed by INH[36]. Of the Fluoroquinolones studied MXF-containing regimens shows bactericidal activity as well as sterilising activity that may allow achieving the goals of shortened therapy from 6 months to 4 months[37].

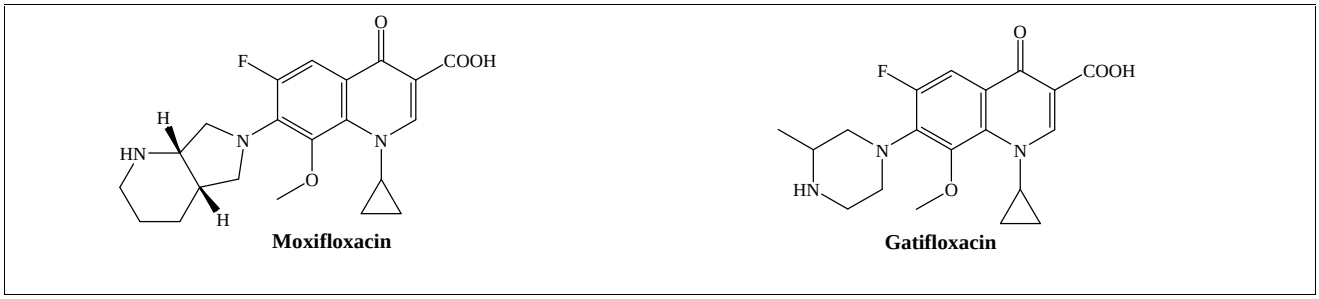

Figure 1: Chemical structure of Moxifloxacin & Gatifloxacin

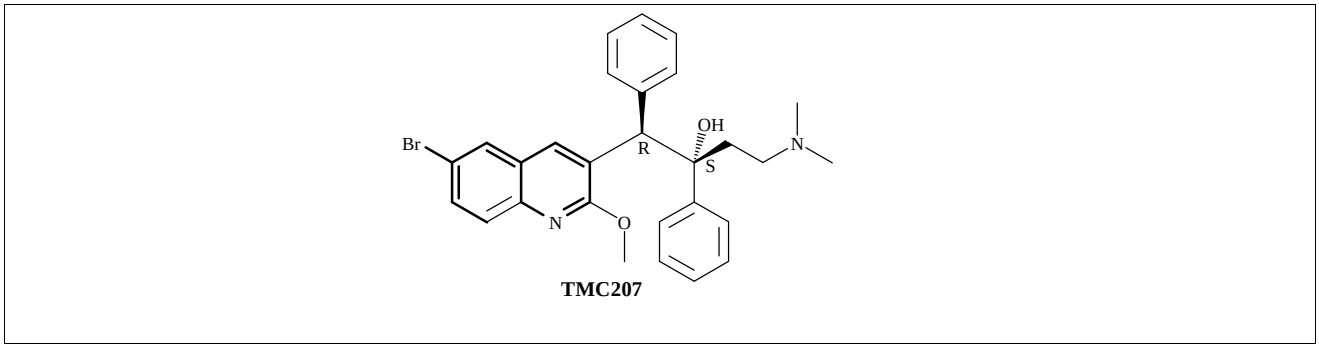

Figure 2: Chemical structure of TMC207

Diarylquinolines

In early 2005, a report from a Johnson and Johnson group in Europe appeared describing the activity of a new class of Diarylquinolines against *M. tuberculosis* and outcome of this report shows that can shorten therapy, has caused a lot of excitement[38]. Diarylquinolines are distinct both in structure and mechanism from fluoroquinolones (which inhibit type II topoisomerases such as DNA gyrase) and quinolines such as mefloquine[39]. Further mechanistic studies have shown that bedaquiline specifically targets the oligomeric subunit-c of mycobacterial ATP synthase[40-43]. Diarylquinolines shows highest activity *in vitro* testing than other class of drugs. One member of the diarylquinoline chemical class is currently in clinical development for TB, TMC207. This compound was discovered from high-throughput screening against *Mycobacterium smegmatis*, by Janssen, a subsidiary of Johnson & Johnson (J&J), and characterized and initially developed by Tibotec, also a J&J subsidiary[38]. The drug acts by inhibiting the F0 subunit of the mycobacterial ATP synthase proton pump, which is a key enzyme for ATP synthesis and membrane-potential generation[44-46]. R207910 or TMC207 was selected as the lead compound in the series after subsequent *in vivo* testing of activity against *M. Tuberculosis*. Recently it has even been shown to have activity against *Mycobacterium leprae*, the causative agent of leprosy, in a mouse model of the disease[45]. In a mouse model of established infection, the combination of TMC-207, RIF, and PYZ was much more efficacious than the standard regimen of INH, RIF, and PYZ. Compared with INH or RIF, TMC-207 showed no early bactericidal activity, this delayed onset of activity could be explained by the time requirement for depleting ATP stocks, and drug accumulation because of the long terminal half-life of TMC-207[47]. TMC207 exhibits excellent activity against drug susceptible, MDR and XDR *M. tuberculosis* strains, with no cross-resistance to current first-line drugs. TMC207 has a potent sterilising ability in guinea pigs, being 100 times more effective than the conventional combination of RIF, INH and PZA[38,44,48]. It is currently being evaluated for safety and efficacy in a Phase II trial placebo-controlled, double-blind, randomised trial. When added to an "optimized background regimen" (OBR) of standard second-line drugs in MDR-TB patients[49]. The most compelling results so far are from a Phase 2, randomized, controlled clinical trial in South Africa of patients diagnosed with MDR-

TB.TMC207 is metabolised by CYP3A4 and, therefore, when it is administered with RIF its levels decrease significantly, making TMC207 likely to be incompatible with anti-retroviral[50].

Rifamycins

Rifamycins class of drugs, specially Rifampicin, is used as key components for the first-line TB treatment; represent the effective agents in killing slowly replicating or "persistent" *M. tuberculosis*[5,9]. Rifamycins act via inhibiting bacterial RNA polymerase and possess sterilising activity[51-54]. Rifapentine was approved by FDA in 1998 and it appears to be safe & well-tolerated at once-weekly dosing but is currently being evaluated in Phase 2 efficacy trials[2,56]. However, rifapentine also induces the expression of P450 enzymes as rifampicin[54]

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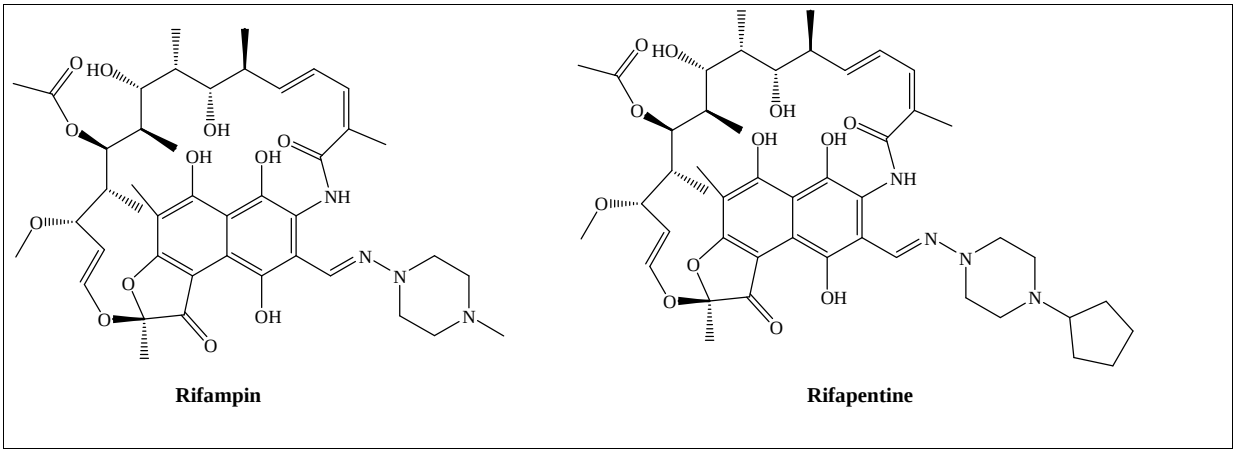

Figure 3: Chemical structure of Rifampin & Rifapentine

In clinical phase studies, combination of rifapentine and isoniazid given once a week in continuation phase of treatment compared with rifampicin & isoniazid twice a week especially in patients with HIV coresistance. RLZ is also new semi-synthetic rifamycin derivative with a long half-life and active against *M. tuberculosis, M. avium, Chalmydia trachomatis, Chalmydia pneumonia* and *Helicobacter pyroli*[57]. RLZ is more active than RIF or rifabutin in mice and safe at low doses, but at a dose of >100 mg produced flu-like symptoms and decrease in WBCs and platelets counts. However, still now no information is available for clinical trials of RLZ for treatment of TB[58].

Nitroimidazole

M. tuberculosis has an amazing ability to persist in human host & current TB drugs are active against replicating bacteria but not against non-replicating bacteria[59-60]. This drawback leads to create current interest in developing new TB drugs which target non-replicating bacteria, as a bicyclic nitroimidazole PA-824 & OPC-67683 are developed, and these nitroimidazoles are active against drug-susceptible & drug-resistant TB[59,61-62]. Two novel compounds PA-824 & OPC-67683 are currently being evaluated in Phase 2 clinical trial development: PA-824 is from nitroimidazo-oxazine class, developed by Global Alliance for TB Drug Development & OPC-67683 is from nitro-imidazo-oxazole class, developed by Otsuka Pharmaceuticals & both are prodrugs and act via novel mechanism of action[56,62]. The mechanism of action of both drugs is two-fold, as they inhibit *M. tuberculosis* cell wall lipid & protein synthesis[62].

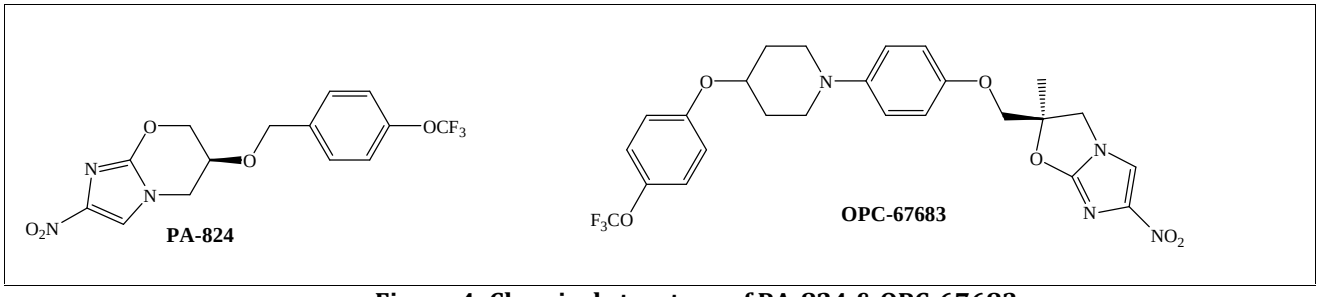

Figure 4: Chemical structure of PA-824 & OPC-67683

These compounds shows their anti-mycobacterial activity through bioreduction of the nitroimidazole pharmacophore means nitro groups under bioreduction forms nitrous oxide species that likely reacts with variety of intracellular targets, is responsible for anti-mycobacterial activity & this

process is mediated by two deazaflavin-dependant enzymes[63-65]. Nitroimidazole possess bactericidal activity and active against replicating & non-replicating bacteria, indicates its potential in shortening treatment and in management of latent infection[59]. PA-824 acts as "suicide bomb" releasing toxic NO and NO possibly reacts with cytochromes/cytochrome oxidase to interfere with electron flow and ATP homeostasis under non-replicating conditions[59,66-67]. NO is known to have multiple targets including DNA as well as mycobacterial enzymes including ATP synthase, PKs 13, RpoB[68-69]. A combination of OPC-67683 with RIF and PAZ for 2 months followed by combination with RIF for further 2 months eliminates all lung bacilli load within 3 months, thus suggesting that OPC-67683 has a powerful sterilising activity and shortens the duration of therapy[6].

Oxazolidinones

Oxazolidinones were first identified in 1950s as antidepressant monoamine oxidase inhibitors and later sold to Pharmacia Upjohn, have a broad spectrum of activity aerobic & variety of gram-positive bacteria including *M. tuberculosis*[70]. These compounds exert their antimicrobial activity by inhibiting protein synthesis by binding to 23s r RNA of 50s & 70s ribosomal complex[54,71]. Linezolid, approved by US-FDA in April, 2000 (for the treatment of skin infection like pneumonia) has low *in vitro* activity against *M. tuberculosis* and also active against broad range of gram-positive bacteria (*staphylococcus aureus*). It is being evaluated in Phase 2 clinical trials developed by Upjohn[72].

Figure 5: Chemical structure of Linezolid & PNU-100840

LIN binds to 23s rRNA inhibiting translation in the early phase preventing the proper binding of formyl-methionine t-RNA and also inhibit mammalian mitochondrial protein synthesis[72]. Two recent clinical studies shows that LIN combination with other drugs is effective against MDR-TB but prolonged use of produced significant cumulative toxicity including anemia, peripheral & optic neuropathy and bone marrow suppression, due to this reason, Linezolid has used off-label in combination regimen for MDR-TB[73-74]. Another PUN-100480 (originally U-1004480) molecule developed by Pfizer & being evaluated in Phase 2 clinical trials. In PNU-100480 the morpholino ring of LIN has been replaced by the thiomorpholino group. In mouse model PNU-100480 is more effective than LIN and approached INH. It shows slightly better activity against *M. Tuberculosis in vitro* than LIN[75,76]. A combination of PNU-100480, MXT & Pyrazinamide was more active than standard regimen of Rifampicin, INH, Pyrazinamide, suggest that PNU-100480 has the potential to shorten treatment therapy of MDR-TB & XDR-TB[77,78].

Ethylenediamines

Sequella developed ethambutol derivative, SQ-109 has different modes of action[79]. Ethambutol targets on arabinosyltransferase involved in construction of polymeric cell wall[80-81]. Whereas, SQ-109 may have required another target, related to intracellular targets. But, it seems to function as cell wall synthesis inhibitors[82].

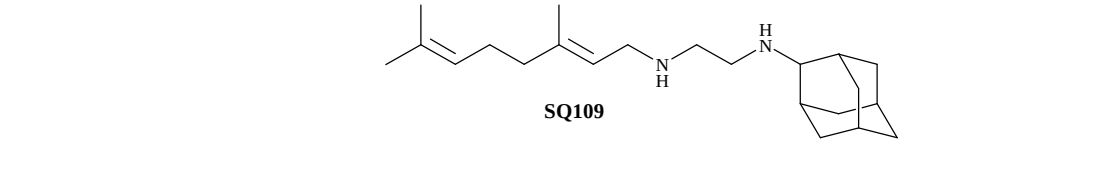

Figure 6: Chemical structure of SQ-109

By using combinatorial approach, a library of 1,2-disubstituted ethylenediamine derivatives are generated. More than 60000 asymmetrically disubstituted ethylenediamines are generated by split and pool strategy. And selective were screened against for in vitro activity and amongst them SQ-109 has been shown to have good selectivity and efficacy in mouse models[83]. It is being evaluated under Phase 2 clinical trials. SQ-109 has synergistic effects both *in vitro* & *in vivo* with major front-line drugs[84-85].

Azole anti-tubercular

The azole anti-tubercular may be regarded as a new class providing truly effective drugs, which is reported to inhibit bacteria by blocking the biosynthesis of

certain bacterial lipids and/or by additional mechanisms[86].

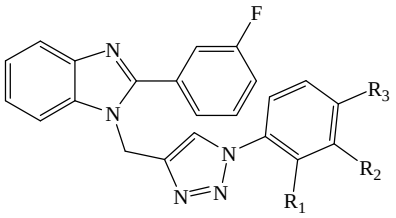

Figure 7: chemical structure of 2-(3-fluoro-phenyl)-1-[1-(substituted-phenyl)-1-H-[1,2,3]-Triazol-4-yl-methyl)-1H-benzo[d] imidazole[87]

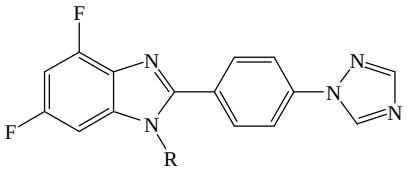

Figure 8: chemical structure of 2-[4-(1*H*-[1,2,4]-triazol-1-yl)phenyl]-1-substituted-4,6-difluoro-1*H*-benzo[*d*] Imidazole[88]

A series of clubbed novel 2-[4-(1*H*-[1,2,4]-triazol-1-yl)phenyl]-1-substituted-4,6-difluoro-1*H*-benzo[*d*]imidazole derivatives were synthesized as an anti-tubercular agent, here specially [1,2,4] triazole is more active than [1,2,3] triazole. Fluorine atoms increases the lipophilicity, hence drug easily can penetrate in to the cell and produce anti-microbial activity[88].

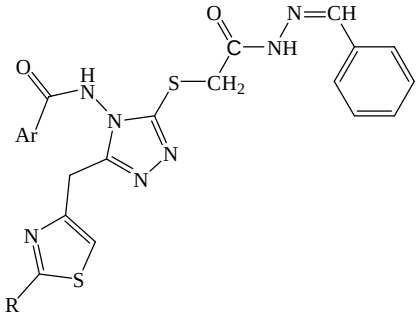

Figure 9: chemical structure of S-derivatives of substituted 1,2,4-triazolyl thiazole[89]

A number of eighty-five S-derivatives of clubbed 1,2,4-triazolyl thiazole derivatives were synthesized and evaluated for their anti-tubercular activity against *M. tuberculosis* H37Rv. These potent derivatives have highly electronegative part at sulfhydryl group. Specifically Schiff bases, probably due to their ability to increase the penetration in the bacterial cell have shown best anti-tubercular activity[89].

NEW TB DRUGS – TRIALS, BEDAQUILINE, DELAMANID, PRETOMANID (PA-824)

Why are new TB drugs needed?

New TB drugs are needed because of the complexity and toxicity of the current TB drug regimes. There is also the major problem of TB drug resistance. This together with the problem of the interactions of the current TB drugs with the antiretroviral drugs taken by HIV positive people, means that there is an urgent need for new TB drugs. However, what is required of these new TB drugs is considerable as:

New TB drugs need to provide:

- Shorter and simpler, but still affordable, multi drug regimens for drug sensitive TB
- Shorter, more effective , less toxic, and less expensive regimes for drug resistant TB
- Short, simple, easily tolerable and safe regimes for latent TB
- Drugs with few drug-drug interactions, so they can be safely provided for people with HIV.

New TB drugs under development

A drugs "pipeline" in drug development terms, refers to all the drugs at different stages of development. It

also shows how the drugs are progressing down the "pipeline" through the various clinical trial stages etc. At the point at which they exit the "pipeline" they are available for general use.

The pipeline of new drugs for TB under clinical development is not considered to be a very extensive drugs "pipeline" for such a major disease as TB.[4]

The Stop TB Partnership has a Working Group on New TB Drugs, which helps to coordinate, guide, and accelerate the speed of worldwide development of new TB therapies.[5]

TB drug bedaquiline

Bedaquiline is the active substance in the new TB drug Sirturo. Sirturo is available for the treatment of drug resistant TB, when there are an insufficient numbers of other TB drugs available. There is much more about bedaquiline.

The Nitroimidazoles

The Nitroimidazoles are an existing class of drugs known to have antimicrobial activity. Two "next generation" or derivatives of this class of drugs, OPC-67683 (now also known as delamanid) and PA-824 are under development as potential TB drugs.[6]There is much more about delamanid.

TB drug Pretomanid (PA-824)

PA-824 is another nitroimidazo-oxazole currently being developed by the TB Alliance. It also can potentially be used for the treatment of both drug sensitive and drug resistant TB, and it has also shown activity against both latent and active TB.

TB drug TBA-354

In March 2016 it was announced that the TB Alliance had voluntarily halted the clinical development program for TBA-354.[7]

AZD5847

AZD5847 is a potential new TB drug being developed by AstraZeneca. In December 2012 it was announced that the first patient had been enrolled in a Phase 2a trial of the drug in South Africa, to assess the effectiveness of the drug for patients with TB, including patients with HIV and TB coinfection.[8] The study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), which is part of the U.S. National Institutes of Health.

The Fluoroquinolones

Several members of the fluoroquinoles class of drugs are currently already used as second line TB drugs for the treatment of multi drug resistant TB. However, the older drugs such as ofloxacin and levofloxacin are often used rather than the newer fluoroquinolones moxifloxacin and gatifloxacin. Moxifloxacin and gatifloxacin are currently being developed for the treatment of drug sensitive TB. Each of these potential TB drugs is currently undergoing evaluation in a phase 3 trial, to see how effective it is when substituted for either ethambutol or isoniazid, to shorten the treatment of drug sensitive TB from the standard six months to four months. The gatifloxacin trial is being conducted by the Oflotub Consortium and moxifloxacin is being developed by Bayer and the TB Alliance.[9]

The Rifamycins

The Rifamycins are potent inhibitors of mycobacterial activity. Three semi synthetic rifamycins – rifampicin, rifapentine, and rifabutin – have been used for the treatment of various microbial infections. Rifampicin is a key component of first line drug treatment for TB. Rifapentine is attractive as a possible TB drug for shortening treatment, and for intermittent TB drug treatment, and clinical trials are under way to further assess this.[10]

TB drug combinations

What is ideally needed is not just one new TB drug but several which can be used together. In July 2012 it was announced that a phase 2A study had been carried out investigating a number of drug combinations including PA-824 over a 14 day period to assess their suitability for further development. The combination of PA-824 moxifloxacin and pyrazinamide had the greatest early bactericidal activity (EBA).One advantage of this drug combination is that it does not involve either isoniazid or rifampicin. It is therefore suitable for use with patients who are resistant to these drugs. A regimen without rifampicin would greatly simplify the provision of TB treatment alongside HIV antiretroviral therapy.This three drug combination now needs to be further investigated over a longer period of time, taking into account that PA-824 and moxifloxacin all have at least some potential to cause cardiac side effects.[11]

Challenge in TB drug development:

In spite of having effective, safe treatment for tuberculosis, the prevalence, incidence and mortality remain high[90].Current pipeline for the treatment of TB has good enough advance where it was in past 20 years ago but the requirement for the drugs is still not fulfilled. And drugs that are being evaluated in clinical trials have negligible chance to treat MDR-TB, XDR-TB & TDR-TB, unless those agents can be introduced with combination simultaneously. To identify and develop novel drug combinations for MDR-TB & XDR-TB is quite essential. Ideal combination should consist at least 3 drugs, and should be equally against drug susceptible and drug-resistance TB, and produce stable cure in a much shorter period of time than standard regimen[91].

Problems associated for producing novel regimen:

- Global clinical trial capacity[92,93]
- Clinical trial designs[94]
- Lack predictive biomarkers[95]
- Paediatric studies of novel regimens[96]
- Funding market & high cost of studies[97,98]
- Lack of laboratories in TB-endemic areas
- Lack of clear TB-specific regulatory guidance.

Thus, the current situation leads to identify new scaffold moieties for the bright future in TB at any cost.

Future scope in TB

In the past decade, there are multiple novel TB drugs are in clinical development, so it is historic opportunity to produce potential drug. The Aeras Global TB vaccine Foundation (previously known as Squella foundation) conducted clinical trials for the vaccines, is the more important approach for the future of TB programme[99]. TB Alliance in collaboration with Bayer Healthcare & Johns Hopkins University build up the laboratory for TB drugs development. Interesting thing here is that, the Bill and Melinda Gates Foundation is also sponsors for new TB drugs. Advantage in the case of the TB is that most of the sponsors are working without the expectation of any significant profit. In the bright future for TB, the main ultimate goal is to develop regimen that successfully cure TB in 2 weeks or in less time. But achieving this goal is likely requiring better understanding of mechanisms. WHO approached the Global Plan to stop TB which being tremendous and quite effective in future. As tuberculosis enters a new era, with promising new diagnostic approaches and drugs, WHO role will be crucial[100].

Stop TB Partnership Target.

- Eliminate TB as a public health problem, defined as a incidence of active TB of less than one case per 1 million population per year.
- By 2050: the global incidence of TB disease will be less than 1 case per million populations per year[101].

The Stop TB Strategy has six principal components[101]:

- Pursue high-quality DOTS expansion and enhancement
- Address TB/HIV and MDR-TB and other special challenges
- Contribute to health system strengthening
- Engage all care providers
- Empower people with TB, and communities
- Enable and promote research

The fund required for TO STOP TB PLAN 2011-2015 is US$47 billion for the five year of the plan, of which US$37 billion is for implement and US$10 billion is for Research & Development.

Future novel chemical scaffolds:

Poor efficacy of current TB drugs has been linked to the limited chemical diversity. Most TB drugs and antimicrobials in general do not follow Lipinski's rule of 5, whereas other pharmaceuticals follow this rule[102]. Important fact here that still now no enzyme inhibitor drugs are neither in market nor in clinical trials, which is one of the major drawback for us, which could be good targets. The *M. Tuberculosis* two component systems, sigma factors & virulence factors have been proposed for the future targets. Such efforts are made to evaluate host immunomodulators such as PDE4 inhibitors, interferon ϒ1b, high dose IVIG[103,104].

Table 4: Summary of recently reported targets in M. tuberculosis[105]

	Target	Pathway	Inhibitor
Targeting actively growing Mtb	GlgE	Maltose metabolism	-
	Mycolic acid cyclopropanation	Mycolic acid metabolism	Dioctylamine
	DprE1/DprE2	Cell wall metabolism	Benzothiazinone, dinitrobenzamides
	MshC	Mycothiol ligase	Dequalinium chloride
	HisG	Histidine biosynthesis	Nitrobenzothiazole
	AtpE	ATP synthesis	Diarylquinoline TMC207
	Def	Protein processing	LBK-611
	Methionine Aminopeptidase	Protein processing	2,3-dichloro-1,4-naphthoquinones
Targeting dormant Mtb	Isocitrate lyase	Energy metabolism	-
	Proteasome Complex	Protein processing	Oxathiazol-2-one
	L,D-transpeptidase	Peptidoglycan metabolism	-
	DosR (DevR)	Regulation of dormancy	-
	CarD	Stringent response	-

New molecular biology reagents and genetic tools have been developed and whole genome sequences of *M. tuberculosis* strains are now widely available based on this we can identify new targets in *M. tuberculosis* that might be inhibited to effectively kill the existing strains[105]. Azole antifungals are the potent inhibitors of the cytochrome P450 mono-oxygenase and bacterial growth in mycobacterial. This azole class drugs doesn't follow Lipinski's rule of 5 & they are high molecular weight compounds so the high lipophilicity leads to easily penetration of drug in to the *M.Tuberculosis* cells. May be in future, azole candidates might be comes into the clinical trial phases for TB due to its high potency.

Conclusion

The emergence of MDR/XDR-TB is a growing problem worldwide. Currently, MDR-TB treatment requires the use of many drugs including injectable and a prolonged duration of treatment, causing many side effects. Advances in TB drug development over the past decade are leading to the development of enhanced MDR-TB treatments with simple and short regimens. Before widespread usage of these new drugs, however, many issues must be addressed, including dose optimization, selection of the best regimens with increased efficacy and reduced drug interactions, and various safety concerns. Additionally, efforts must be made to reduce the development of resistance to these valuable new TB drugs during treatment.

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