Novel Compounds and Drugs and Recent Patents in Treating Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis

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Abstract: A number of recent studies revealed that successful treatment of the patients with MDR/XDR- TB was not achieved due to high resistant rates to many second-line drugs such as kanamycin and prothionamide including poor adherence of the lengthy treatment. Many new drugs and compounds such as benzothiazinones, meropenem, PA-824, isoflavonoids, rhein, PNU-100480, TMC207, SQ109, OPC-67683, AZD5847, and linezolid are currently in development pipeline. According to very few patents in new compounds and drugs against MDR/XDR-*Mycobacterium tuberculosis* bacilli have been currently introduced, so inventors must be encouraged to contribute to this area worldwide.

Keywords: Multidrug, extensively-drug, resistant, tuberculosis, compounds, novel, patents.

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is defined as TB demonstrating resistance to at least isoniazid and rifampicin. It has become a major health threat in some parts of the world. Isoniazid and rifampicin are the two principal drugs of anti-TB chemotherapy. The World Health Organization (WHO) globally estimates that 50 million people are infected with MDR-TB [1]. In 1943,para-aminosalicylic acid (PAS) and streptomycin were the first two drugs introduced and they initiated the development of anti-TB treatment regimens [2]. Since then PAS and isoniazid were combined with streptomycin because streptomycin monotherapy frequently resulted in treatment failure [3]. Unfortunately, TB patient care was shifted to outpatient setting in the late 1960s because spreading of TB was not thought to be a public hazard which contributed to poor patient compliance, relapse, treatment failure and secondary or acquired drug resistance [3]. In the situations of an insufficient number of active antimicrobials in a treatment regimen, suboptimal dosage, omission of one or more of the prescribed antimicrobials, poor drug intestinal absorption and interrupted drug ingestion [4] and monotherapy [5] may contribute to MDR-TB. It is clear that MDR-TB treatment needs to be standardized where possible once it has developed into a worldwide epidemiological crisis [6]. No controlled trials or formal observational studies have been conducted rigorously to compare the various treatment drugs and regimens because of the substantial differences among many cases and should group them into homogeneous groups in addition to a great deal of MDR- TB expert opinion. These serious problems lead to the debating around the number of drugs used for MDR-TB in recent years [7-10]. Caminero concluded the main goals in developing recommendations that: 1) the use of three effective second-line drugs could be sufficient (natural resistant mutants per drug > 1X 10^5) from a bacteriological point of view; 2) in the field, some drugs often have compromised efficacy or very weak action; 3) for this reason, under National Tuberculosis Program (NTP) conditions, a second-line drugs regimen should include at least four drugs [11] and 4) occasionally, when several drugs exhibit compromised efficacy or very weak action, it may be justified to prescribe more than four drugs [12]. The WHO recommended streptomycin, kanamycin and capreomycin as the injectable second-line drugs and ofloxacin, levofloxacin, moxifloxacin, ethionamide, cycloserine and PAS as the oral second-line drugs for the treatment of at least six months and until sputum smears and cultures are continuously negative with at least five drugs and inclusion of an injectable drug in the initial phase of treatment and 12-18 months of four oral drugs in the continuation phase [6]. Some experts classified amikacin as an injectable drug and clarithromycin, rifabutin, moxifloxacin, gatifloxacin, ciprofloxacin, thiacetazone, clofazimine, and co-amoxiclav as the additional oral second-line drugs. In MDR-TB patients with human immunodeficiency virus (HIV)- infection/acquired immunodeficiency syndrome (AIDS), the WHO recommended co-trimoxazoleprophylaxis on the first day of MDR-TB treatment and started azidothymidine+lamivudine+efavirenz as the preferred antiretroviral therapy regimen as soon as MDR-TB treatment was tolerated [6]. Genetic sites for anti-TB compound resistance are cornerstones for the development of new compounds against drug-resistant TB bacilli where some drugs share common genetic sites (Table 1). Some

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Table 1. Known genetic sites for anti-TB drug resistance.

Drug	Target	Gene	Reference
Isoniazid	Catalase-peroxidase	*katG*	13
	N-acetyltransferase 2	*nat*	14
	Alkylhydroperoxidase	*ahpC/oxyR*	15, 16, 17
	Nicotinamide Adenine Dinucleotide Hydrate dehydrogenase	*ndh*	18
Isoniazid-ethionamide	Mycolic acid synthesis EnoylAcyl Carrier Protein reductase	*inhA*	13, 19
Rifamycins (Rifampicin, Rifabutin, Rifapentine)	β subunit RNA polymerase	*rpoB*	13, 19, 20, 21
Pyrazinamide	Nicotinamidase/Pyrazinamidase	*pncA*	19
Ethambutol	Arabinosyltransferase	*embA*	19, 22
		embB	
		embC	
Streptomycin	Ribosomal S12 protein	*rpsL*	13, 19
	16S rRNA	*rrs*	13, 19
	rRNAmethyltransferase (G527 in 530 loop)	*gidB*	19
	Aminoglycoside phosphotransferase	*strA*	22
Quinolones	DNA gyrase subunit A	*gyrA*	13, 19
	DNA gyrase subunit B	*gryB*	19
Amikacin	16S rRNA	*rrs*	19, 23-26
Kanamycin	16S rRNA	*rrs*	19, 23-26
		eis	23, 24, 26, 27
Capreomycin	2′-O-methyltransferase	*tylA*	19, 23, 25
	16S rRNA	*rrs*	23, 25, 26
Para-aminosalicylic acid	Thymidylate synthase	*thyA*	19
SQ109	Mycobacterial membrane protein, large 3	*mmpL3*	28
Delamanid (OPC-67683)	Deazflavin-dependent nitroreductase/F420reductase, protein synthesis, Mycolic acid biosynthesis	*ddn*	29-31
PA-824	Glucose-6-phosphate dehydrogenase	*fgd1*	32, 33
		ddn	
Ethionamide	Flavinmonooxygenase	*etaA/ethA*	19, 34
	Transcriptional repressor	*ethR*	
	Enoyl-Acyl Carrier Protein reductase	*inhA*	

Table (1) Cont...

Oxazolidinones (Linezolid, Sutezolid (PNU-100480), AZD5847)	23S rRNA	*cfr*	35
Bedaquiline (TMC207)	Subunit C of Adenosine triphosphate synthase	*atpE*	36, 37
Carbapenems	β-lactamase, Transpeptidase	*blaC*	37-39
Benzothiazinones	Decaprenylphosphoryl-β-D-ribose-2′-epimerase 1	*dprE1*	40, 41
Cycloserine	D-alanine racemase	*alrA*	34, 37, 42
	D-alanine-D-alanine ligase	*ddl*	
Clofazimine	Interleukin-2 luciferase	*qacA/B*	43, 44

previous studies revealed the lowest percentage of uses of clofazimine (Table **2**) which correlated to its lowest percentage of TB bacilli resistance (Table **6**) while some drugs did not. The information of MDR/XDR-TB mentioned above including increased total anti-TB drug-resistant TB is very important for investigators and drug companies to invest in novel anti-TB compounds development for solving the global crisis of current anti- MDR-TB and anti-extensively drug-resistant TB (XDR-TB, TB that develops resistance to at least isoniazid and rifampicin as well as to any quinolone drug and at least one of the second-line anti-TB injectable drug: kanamycin, capreomycin, or amikacin, WHO Global Task Force on XDR-TB, October, 2006) drug resistance and their adverse side effects (Tables **3**, **6**). Presently, moxifloxacin seems to be the most promising drug in the treatment of XDR-TB (Table **5**).

Table 2. Drugs used in treating MDR-TB [45].

Drug	% of Usage
Cycloserine	75.6
Para-aminosalicylic acid	60.7
Thioamides	60.6
Ofloxacin	52.5
Capreomycin	42.2
Kanamycin	42.1
Pyrazinamide	39.9
Augmentin	32.3
Ethambutol	31.9
Ciprofloxacin	26.3
Streptomycin	15.8
Thioacetazone	15.7
Clarithromycin	11.6
Levofloxacin	3.0
Sparfloxacin	1.3
Clofazimine	1.2

Drugs Used in MDR-TB Treatment Regimens

A previous study in Russian Federation (Tomsk Oblast), Peru (Lima), the Philippines (Manila), Latvia and Estonia showed the frequency of anti-TB drugs used in the treatment of MDR-TB as shown in Table **2** [45].

Adverse Side-effects of the Second-line Drugs in Treating of MDR-TB

A previous study by collecting data from directly observed treatment, short course (DOTS)-Plus sites in the Russian Federation (Tomsk Oblast), the Philippines (Manila), Peru (Lima), Latvia and Estonia revealed frequency of adverse events from suspected second-line agents as shown in Table **3** [46].

NEW-DRUG DEVELOPMENT PIPELINE

1. Fluoroquinolones

Moxifloxacin and gatifloxacin are both 8-methoxyquinolones which are the two most advanced anti-TB compounds used in phase III clinical trials [37]. Moxifloxacin demonstrates MIC of 0.5 μg/mL [31] while the MIC of gatifloxacin is 1 μg/mL [47]. They are currently preferred-cornerstone anti-TB agents for MDR-TB chemotherapy without cross-resistance with existing anti-TB compounds [48]. They had been used in replacement of isoniazid by moxifloxacin or gatifloxacin in the first-line regimens which showed the greatest benefit in murine model [48]. The OFLOTUB consortium reported the replacement of ethambutol by moxifloxacin 400 mg or gatifloxacin 400 mg in the first-line regimens with more rapid clearance of TB bacilli in sputum compared to ofloxacin [48]. The earliest sputum culture conversion was demonstrated at week 2 of the treatment course

Table 3. Adverse side-effects of the second-line drugs [46].

Adverse side-effect	Drug	% of Event
Nausea/Vomiting	Fluoroquinolone, Para-aminosalicylic acid, Thioamides	32.8
Diarrhea	Para-aminosalicylic acid, Thioamides	21.1
Arthralgia	Aminoglycosides, Cycloserine, Fluoroquinolone, Thioamides	16.4
Dizziness/Vertigo	Aminoglycosides, Capreomycin, Cycloserine, Fluoroquinolone	14.3
Hearing disturbance	Aminoglycosides, Capreomycin, Thioamides	12
Headache	Cycloserine, Fluoroquinolone	11.7
Sleep disturbances	Cycloserine, Fluoroquinolone	11.6
Electrolyte disturbance	Capreomycin, Thioamides	11.5
Abdominal pain	Para-aminosalicylic acid, Thioamides	10.8
Anorexia	Para-aminosalicylic acid, Thioamides	9.2
Gastritis	Para-aminosalicylic acid, Thioamides	8.6
Peripheral neuropathy	Aminoglycosides, Cycloserine, Thioamides	7.9
Depression	Cycloserine	6.2
Tinnitus	Aminoglycosides, Capreomycin, Cycloserine	5.1
Allergic reaction	Fluoroquinolone	5.1
Rash	Fluoroquinolone, Para-aminosalicylic acid	4.6
Visual disturbances	Cycloserine, Thioamides	4.4

Table (3) Cont..

Seizures	Cycloserine	4.0
Hypothyroidism	Para-aminosalicylic acid, Thioamides	3.5
Psychosis	Cycloserine	3.4
Hepatitis	Thioamides	2.2
Renal failure/Nephrotoxicity	Aminoglycosides, Capreomycin	1.2

found by the investigators from the Johns Hopkins University [48]. Quinolone resistance has been fairly shown in some parts of the world such as India [37]. Moxifloxacin and gatifloxacin were both approved by the United States FDA in 1999 [49]. Chemical structures of moxifloxacin and gatifloxacin are shown below (Figs. **1**, **2**).

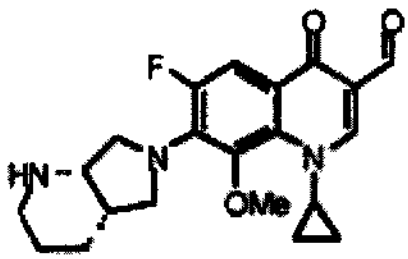

Fig. (1). Moxifloxacin
Source: Slepikas *et al.* Medicina *(Kaunas)* 2011

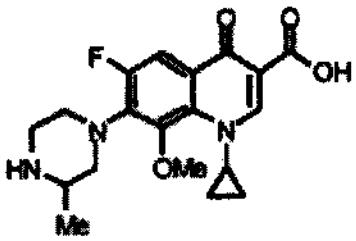

Fig. (2). Gatifloxacin
Source: Slepikas *et al.* Medicina *(Kaunas)* 2011

Patents Claimed

Current patents are claiming a crystalline form (monohydrate) of moxifloxacin which is due to run until 2016 [50-53]. Such patents have been granted in many countries including South Africa, Ukraine, China and Russia for combating the MDR-TB [50]. The US Patent Application Number 10/573329 [54] by Cosme also recently described a crystalline form of gatifloxacin for treating MDR-TB.

2. Carbapenems

There was a study of intravenous- imipenem combination therapy in patients with MDR-TB but its personal contribution was not measured [48]. Meropenem may be more effective than imipenem [48]. It functions as almost like a β-lactamase inhibitor rather than a substrate [55, 56]. A previous study revealed that meropenem was more consistently active than imipenem in the presence of clavulanate (MIC_{90}: 10 μg/mL for imipenem vs 0.94 μg/mL for meropenem) [48]. Evaluation of the efficacy of meropenem/clavulante in the treatment of MDR/XDR-TB patients is underway [48]. There are major disadvantages for clinical use of meropenem in the field because of the need for multiple daily intravenous doses for maximal efficacy [52]. Sulopenem (ClinicalTrials.gov identifier: NCT00797108), faropenem, and ertapenem have not described their activity against *Mycobacterium tuberculosis* [48]. Chemical structure of meropenem is shown below (Fig. **3**).

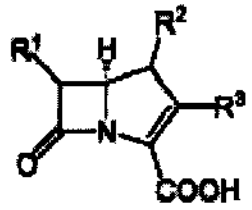

Fig. (3). Chemical structure of Carbapenem Backbone
Source: Dugal *et al.* International Journal of Current Pharmaceutical Research 2011

Patents claimed

The US Patent Application Number 20110190253 [57] by Blanchard recently presented an administering of meropenem or imipenem in conjunction with clavulanic acid to satisfy the need for treating MDR/XDR-TB.

3. PA-824

PA-824 is a nitroimidazole that has sterilizing activity against drug-susceptible and drug-resistant TB and both active and dormant organisms induced in hypoxic condition *in vitro*. The MIC of PA-824 is 0.015-0.25 mg/mL [31]. Studies in healthy subjects with single oral doses of PA-824 showed the maximal blood level approximately 6- to 200-fold higher than MICs found *in vitro* for both drug-susceptible and drug-resistant strains of *Mycobacterium tuberculosis* and reached averaged maximal plasma levels approximately 3 μg/ml (1,500-mg dose) in 4 to 5 hours independently of the dose [58]. PA-824 was well tolerated following oral doses once daily for up to 7 days [58]. The maximum effectiveness of the drug was found at the lowest

dose tested, 200 mg. Its activity was dose-dependent [59]. Studies published in 2011 revealed that PA-824 could be active against TB bacilli in humans in doses as low as 50 or 100 mg/day and postulated that humans require relatively lower doses of the drug than mice because of longer half-life of PA-824 in humans [60]. Currently, PA-824 has already entered phase II clinical trials as part of the first regimen (PA-824/Moxifloxacin/Pyrazinamide) that contains multiple new anti-TB drugs [61-63]. Diacon *et al.* recently concluded that PA-824 bactericidal activity in smear-positive TB patients was over the dose range of 200 to 1,200 mg/day and sustained at least 14 days [64]. Treatment of TB in guinea pigs with dry powder PA-824 aerosols was recently studied and revealed significant reduction in the bacterial burden of lungs and spleen with smaller doses compared with oral doses (eight times the inhaled low dose and four times the inhaled high dose) [65]. The chemical structure of PA-824 is shown below (Fig. **4**).

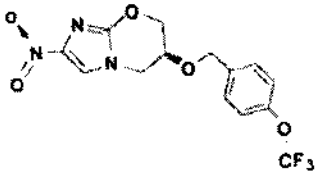

Fig. (4). Chemical structure of PA-824
Source: Bijev A *et al.* Journal of the University of Chemical Technology and Metallurgy 2011

Patents claimed

The US Patent Application Number 2010/043908[66] by Thompson *et al.* recently described new nitroimidaooxazine and nitroimidazooxazole analogs for treating both drug-susceptible and drug-resistant TB.

4. OPC-67683 (Delamanid)

OPC-67683 is a nitroimidazo-oxazole with cross-resistance to PA-824 [67] without cross-resistance to current anti-TB drugs [28, 29]. It is more potent than PA-824 *in vitro* (4-16 times) [34] and *in vivo* with an MIC range of 0.006-0.024 μg/mL and minimal bactericidal dose which resulted in a 2 $\log_{10}$ reduction in CFU of 2.5 mg/kg in mice, compared with 50 mg/kg for PA-824 in a similar model [30]. Combination of OPC-67683 at the minimal bactericidal dose with rifampicin and pyrazinamide resulted in a more rapid achievement of negative cultures in lungs of mice [30]. A phase IIb was underway in MDR-TB patients randomized receiving the regimen with either OPC-67683 at 100 or 200 mg twice daily or placebo (ClinicalTrials.gov identifier: NCT00685360) [23]. OPC-67683 shows rather synergistic effect with the first-line anti-TB drugs and could prove effective in the treatment of MDR/XDR-TB [49]. Desnitroimidazole, one of the major three primary metabolites which were converted by a deazaflavin- dependent nitroreductase of the bacilli in the mouse model experiments, is firstly found in OPC-67683 with intracellularly anaerobic-killing effects on TB bacilli [68]. Formation of desnitroimidazole metabolite generates reactive nitrogen species, including nitric oxide (NO) [68]. The chemical structure of delamanid is shown in Fig. **5**.

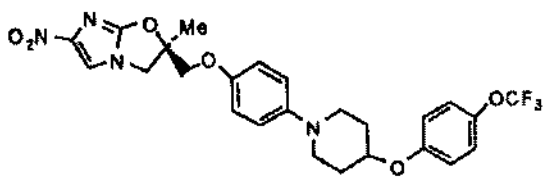

Fig. (5). Chemical structure of OPC-67683
Source: Bijev A *et al.* Journal of the University of Chemical Technology and Metallurgy 2011

PA-824-related Patents Claimed

The US Patent Application Number 20120028973 [69] by Denny *et al.* recently presented a new compound of nitroimidazooxazines with high potency against both hypoxic (latent or persistent) and aerobic (replicating) cultures of *Mycobacterium tuberculosis* and high efficacy in mouse model for use as anti-TB drug and treatment of other bacterial infections.

Oxazolidinones-related Patents Claimed

The US Patent Application Number 20110190199A1 [70] by Brickner *et al.* recently described a compound, (S)---N-[[3[[3-fluoro-4-(4-thiomorpholinyl]-2-oxo-5-oxazolidinyl] me-thyl]acetamide for treating MDR- and latent TB. Its chemical structure is shown in Fig. **6**.

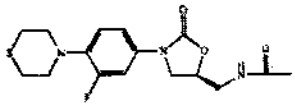

Fig. (6). Compound described by Brickner *et al.*
Source :US Patent Application Number 20110190199A1(**2011**)

5. Linezolid (LZD)

Linezolid is the first oxazolidinone antimicrobial agent [71]. It was first disclosed in the US patent 5,688,792. High maximal serum concentration, MIC_{90} for *Mycobacterium tuberculosis* (0.5-1 mg/L) and excellent penetration into bronchial mucosa and AUC_{24}/MIC of LZD along with the slow growth of *Mycobacterium tuberculosis* contribute to effective daily-half dosage [72]. A previous study on 8 patients with intractable MDR-TB treated with 600 mg once daily and 600 mg twice daily for 2 and 7 weeks then 600 mg once daily of LZD for 3-18 months showed the time to sputum smear and culture conversions of 30-179 days and 25-147 days, respectively [72]. An ongoing phase IIa, randomized, 2-arm, open-label, clinical trial on the treatment of XDR-TBwith LZD has been conducted by the National Masan Tuberculosis Hospital in Masan, South Korea for investigating its effectiveness on XDR-TB treatment. The participants are randomly divided into groups. Group 1 participants are observed for 2 months before starting LZD, while group 2 patients start administering LZD on the first day of attendance. Both groups begin with a 600 mg daily dose of LZD in combination with their existing treatment regimen. After 4 months of treatment or stopping of coughing they are randomly assigned either to take the decreased dose of 300 mg or to continue taking 600 mg of LZD. The primary objective

of this study is to assess the LZD therapy efficacy, measured by sputum culture conversion and the second ones are tolerability and toxicity of prolonged LZD therapy, a potential early LZD toxicity indicator, effects of LZD on mitochondrial function, LZD pharmacokinetic and pharmacodynamics profiles, relapse rate after 12 months of LZD therapy discontinuation, LZD resistance rate, the correlation of whole-blood killing assays with response to LZD therapy, changes in bacterial lipid and immunologic markers, the rate of radiological changes by chest computed tomography, and the changes in pulmonary architecture and cellular activity during LZD therapy by using F-fluoro-2-deoxy-D-glucose-positron emission tomography-computed tomography (FDG-PET-CT)of 20 participants [73].This study has been started since July 2008 and will be completed in January 2015. However, the efficacy of linezolid in treating MDR/XDR-TB must be evaluated when compared to moxifloxacin [74]. The chemical structure of linezolid is shown in Fig. 7.

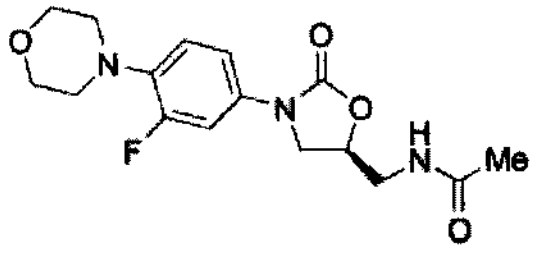

Fig. (7). Chemical structure of Linezolid
Source: Bijev A *et al.* Journal of the University of Chemical Technology and Metallurgy 2011

Patents Claimed

The US patent 7718799 [75] by Rao*et al.* recently presented the invention related to a novel crystalline form of linezolid, to process its preparation and sell it to a pharmaceutical containing it. The present invention is useful as it is effective against *Mycobacterium tuberculosis*.

6. TMC207 (Bedaquiline)

TMC207 (formerly R207910) is a diarylquinoline compound with a new mechanism of action by inhibiting mycobacterial adenosine triphosphate synthase [76, 77]. The MIC of TMC207 ranges from 0.002 to 0.06μg/mL [31]. A recent study by Tasneen *et al.* in a murine model of both drug-susceptible and MDR- or XDR-TB demonstrated that TMC207 plus PZA plus either rifapentine or moxifloxacin was the most effective 3-drug combination regimen compared to other 3-combination regimens (TMC207, PA-824, moxifloxacin, rifapentine, and pyrazinamide) [78]. Diacon *et al.* conducted a previous randomized study among smear-positive pulmonary-TB patients in South Africa with 400 mg, once daily of TMC207 (100-mg tablet) for the 2 weeks and followed by 200 mg, tid for 6 weeks compared to the placebo group as an addition to the MDR-TB treatment regimens. The results showed 11.8 times more rapid sputum culture conversion during 8 weeks (48% for TMC207 vs 9% for placebo group) [79]. The chemical structure of bedaquiline is shown in Fig. **8**.

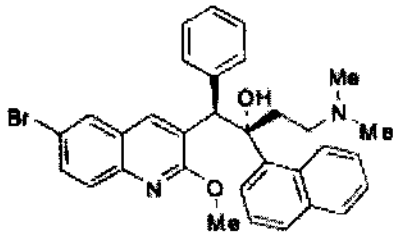

Fig. (8). Chemical structure of Bedaquiline (TM207)
Source: Bijev A *et al.* Journal of the University of Chemical Technology and Metallurgy 2011

Patents Claimed

The US Patent Application Number 20110065723 [80] by Grossman *et al.* recently presented a chemical composition related to a diarylquinoline antibiotic and a rifamycin antibiotic (Timcodar or TIM), n- benzyl-3-(4-chlorophenyl)-2-[methyl-[2-oxo-2(3,4,5-trimoxyphenyl)acetyl]amino]-n-[3-(4-pyridyl)-1-[2-4- pyridyl)ethyl]propyl]propranolamide, useful for the treatment of *Mycobacterium tuberculosis* infection. Its chemical structure is shown in Fig. **9**.

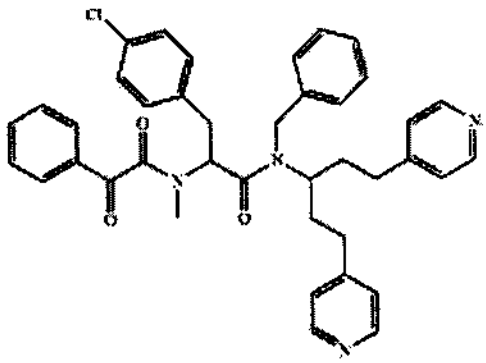

Fig. (9). Compound described by Grossman *et al.*
Source: US Patent Application Number 20110065723 (**2011**)

7. SQ109

SQ109 shows extensive tissue distribution and concentration in animal model that may explain how drug maintains activity in mice while the serum concentrations do not exceed the MIC which is 0.1-0.63 μg/mL [31, 81, 82]. SQ109 was safe and well-tolerated in single doses up to 300 mg [83]. The chemical structure of SQ109 is shown in Fig. **10**.

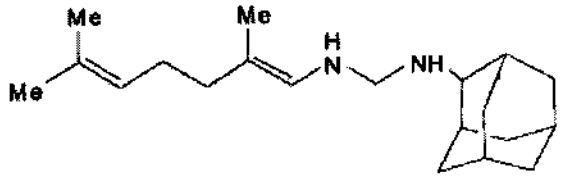

Fig. (10). Chemical structure of SQ109
Source: Bijev A *et al.* Journal of the University of Chemical Technology and Metallurgy 2011

Patents Claimed

The US Patent Application Number 12/255976 [84] by Protopopova *et al.* recently described novel substituted ethylene diamine compound for further comprising current anti-TB drugs. Its chemical structure is shown in Fig. **11**.

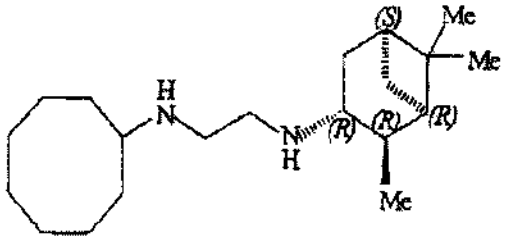

Fig. (11). Compound described by Protopopova *et al.*
Source: US Patent Application Number 12/255976 (**2009**)

8. LL-3858 (Sudoterb or LU-3858)

LL-3858 was discovered in 2004 with reporting of potential killing of both drug-susceptible and drug- resistant *Mycobacterium tuberculosis* bacilli *in vitro* and *in vivo* (murine/mice model) via unknown target and mechanism of action [48, 49]. The MIC_{90} is 0.25 μg/mL [31]. LL-3858 has been claimed to completely sterilize both drug-susceptible and drug- resistant TB bacilli in infected mice within 2 months in combination with isoniazid, rifampicin and pyrazinamide [49]. Currently, there is no more information of LL-3858 progression [85]. The chemical structure of sudoterb is shown in Fig. **12**.

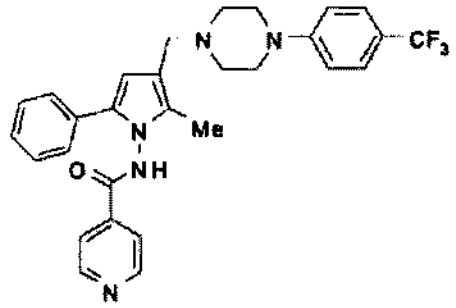

Fig. (12). Chemical structure of Sudoterb (LL-3858)
Source: Bijev A *et al.* Journal of the University of Chemical Technology and Metallurgy 2011

9. PNU-100480 (Sutezolid)

It is classified in oxazolidinones with current investigations in phase I (ClinicalTrials.gov identifier: NCT00990990) and more potent activity against *Mycobacterium tuberculosis* than LZD which is the only currently marketed oxazolidinone [48,86-88]. The $MIC_{90}$of PNU-100480 ranges from 0.0625 to 0.5 μg/mL [31]. Its anti-TB activity was first reported in 1996 [86]. Single doses of 600 and 1,000 mg were well-tolerated and bactericidal drug concentrations were maintained in whole blood samples for 12 and 24 hours post-dose, respectively [89]. A recent study on bactericidal activities of XDR-TB treatment regimens containing sutezolid (PNU-100480), bedaquiline (TMC207), PA-824, SQ109, and pyrazinamide using rapid evaluation in whole blood culture revealed that combinations of sutezolid, SQ109, and bedaquiline were fully additive, whereas those including PA-824 were less than additive and antagonistic in some instances [90]. Wallis *et al.* recently concluded that measurement of sutezolid bactericidal activity against *Mycobacterium tuberculosis* in *ex vivo* whole blood culture was a superior biomarker for efficient dose selection in early development of this drug [91]. The chemical structure of sutezolid is shown in Fig. **13**.

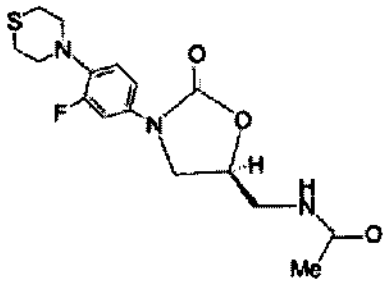

Fig. (13). Chemical structure of PNU100480
Source: Bijev A *et al.* Journal of the University of Chemical Technology and Metallurgy 2011

10. AZD5847

It is another oxazolidinone which has entered Phase I study with an ascending dose study of the pharmacokinetics (PK), safety and tolerability of the compound (ClinicalTrials.gov identifier: NCT01037725) [48]. Its MIC_{90} is 1 μg/mL [31]. Public information of the pre-clinical evaluation of this compound is not available [47]. The chemical structure of AZD5847 is currently not yet available.

Patents Claimed

The US Patent Application Number 20120035219 [92] by Das *et al.* recently described a compound with ring nitrogen (AZD2563) in the additional hetero ring (e.g. oxazole, etc.), (5R)-3-[4-[1-[2S)-2,3- dihydroxypropanoyl]-3,6-dihydro-2H-pyridin-4-yl]-3-,5-difluoro-phenyl]-5-(isoxazol-3-yloxymethyl)oxazolidin-2- one, for the treatment of *Mycobacterium tuberculosis*. The chemical structure of AZD2563 is shown in Fig. **14**.

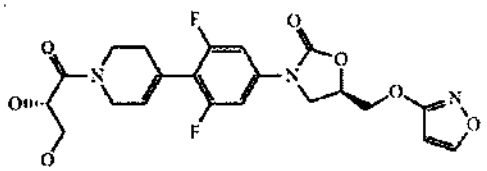

Fig. (14). Compound described by Das *et al.*
Source: US Patent Application Number 20120035219(**2012**)

11. Benzothiazinones (BTZ043)

A new class of anti-TB agent is called benzothiazinones. It inhibits the major target enzyme, decaprenylphosphoryl-β-D-ribose- 2'-epimerase and contributes to cessation of decaprenylphosphoryl arabinose formation which is required for the synthesis of the cell-wall arabinans of *Mycobacterium*

tuberculosis [93]. MIC_s of BTZ043 against 3 strains of *Mycobacterium tuberculosis*, H37Rv, NTB9 and NTB1 are 1, 250 and 10,000 ng/mL, respectively [93]. This most advanced compound is a candidate for inclusion in combination therapies for both MDR/XDR-TB and drug-susceptible TB [93]. The chemical structure of benzothiazinones is shown in Fig. **15**.

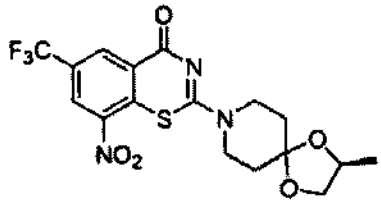

Fig. (15). Chemical structure of Benzothiazinones
Source : Shakya *et al.* Chemotherapeutic strategies and targets against resistant TB. In : Pere-Joan Cardona, Ed. Understanding tuberculosis-new approaches to fight against drug resistance 2012

Patents claimed

The US Patent 7863268 [94] by Makarov *et al.* recently presented the generation of a novel compound of benzothiazin derivatives to combat drug-resistant-TB bacilli including leprosy. Its chemical structure is shown in Fig. **16**.

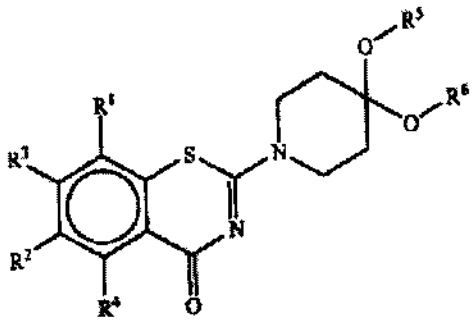

Fig. (16). Chemical structure of Benzothiazin derivatives described by Makarov *et al.*
Source: US Patent 7863268 (2011)

12. Isoflavonoids

Isoflavonoids are a class of flavonoid phenolic compounds (Phytoestrogens). Phytoestrogens are a biologically active compounds in this class, produced by pea family plants. They are converted by intestinal bacteria to compounds with estrogenic activity. One example of this herbs is licorice root (*Glycyrrhiza glabra*). *Glycyrrhiza glabra* in Liquorice has impressive documented uses with identification of potentially healing substances. It is useful for many inflammatory conditions such as TB, emphysema, asthma, bursitis, arthritis, tendinitis, viral infection, gingivitis, prostate enlargement, etc [95]. A previous study demonstrated potential anti-TB bacilli activity of *Glycyrrhiza glabra* fraction with ethyl acetate by MIC range of100-250 μg/mL [96]. The chemical structure of isoflavonoids is shown in Fig. **17**.

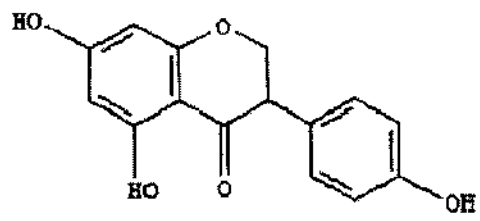

Fig. (17). Chemical structure of Isoflavonoids
Source: http://www.friedli.com/herbs/phytochem/flavonoids.html, accessed on May 7, 2012

Patents Claimed

The US Patent 5399558 [97] by Baker *et al.* summarized that new erythrabyssin II isoflavonoid derivatives can control MDR-TB and gram-positive organisms *in vitro* and *in vivo*.

13. Rhein

Rhein is a glycoside in *Rheum* species, senna leaves, and in several other species of Cassia [59]. Presently, it is a compound of interest because of its antioxidant, antiangiogenic, antitumor, antiviral, and antifungal effects [98-101]. It has been found that diacerein which is derived from rhein has anti- inflammatory effects and might be used for the treatment of chronic inflammatory diseases or conditions including prevention of tissue or organ transplant rejection [102]. The chemical structure of rhein is shown in Fig. **18**.

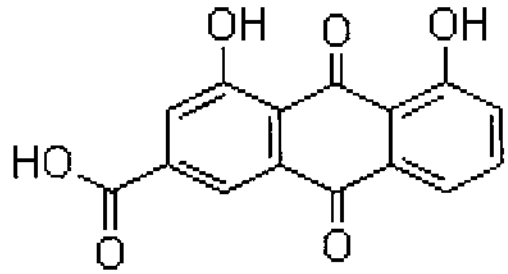

Fig. (18). Chemical structure of Rhein
Source: http://www.chemblink.com/products/478-43-3.htm, accessed on May 7, 2012

Patents Claimed

The US Patent 5652265 [103] by Vittori *et al.* contemplated the use of rhein in the treatment of MDR- TB. It was found to be the most effective agent of the anthraquinone derivatives for mycobacterial treatment. During the chemical production, their intermediate products formed for example, diacetylrhein, aloe-emodin triacetate, and aloe-emodin all of which in *in vitro* tests demonstrated antimycobacterial activity while aloe-emodin had MIC ratio of only 1: 100,000. Rhein was found to be the most effective of the anthraquinone derivatives against mycobacterial organisms. The US Patent 4861599 [104] by Springolo *et al.* recently presented the preparation of rhein derivatives pharmaceutical formulations, especially of diacetyl rhein for permission of a programmed and gradual release of the agent throughout the 24 hour period from the administration of the therapeutic dose.

14. Other Pre-clinical Study Compounds

CPZEN45, a nucleoside antibiotic produced by *Streptomyces* species, was first described in 2003. CPZEN45 (Fig. **19**) has shown activity against XDR-TB in a mouse model [31] with MICs of 2.26 μM for MDR-TB and 9.07 μM for XDR-TB bacilli [31, 105]. The US Patent Application Number 20110237530 by Takahashi *et al.* recently introduced a caprazamycin derivative or CPZEN45 for initiation of a new anti-MDR/XDR-TB compound [106]. A fluoroquinolone derivative, DC159a (Fig. **20**) demonstrated the highest activity against quinolone-resistant MDR-TB with MIC_{90} of 0.06-0.5 mg/L *in vitro* [31, 107]. DC159a revealed 2-3 times more longer mean survival days than levofloxacin, moxifloxacin, rifampicin, and isoniazid and lacked interaction with cytochrome P450 3A4 [31]. SQ609 (Fig. **21**) is the most potent candidate among a new series of potential cell-wall inhibiting dipiperidines (SQ609, SQ614, SQ615) [31, 108]. It demonstrated MIC of 4μg/mL [31] while SQ614 and SQ615 showed MICs of 7.8 μM *in vitro* [109]. Surprisingly, a recent study reported that the MIC of SQ614 was 4 μg/mL [108]. SQ641 is a natural product with acting as a translacase 1 enzyme inhibitor and faster mycobactericidal rate than any existing anti-TB drugs [31]. SQ641 (Fig. **22**) showed MIC ranges of 0.67-1.35 μM for drug-susceptible and 0.081-2.71 μM for drug-resistant TB bacilli [105]. Venkata *et al.* claimed in the US Patent Application Number 12/331929 [110] new capuramycin analogs for treating TB. The invention particularly related to methods and compositions comprising capuramycin and capuramycin analogs in combination with another anti-TB compound. Q201 is an imidazopyridine without much available detail of this compound [31]. SQ73 is another new diamine derivative with MIC range of 6.25-12.5 μM [105]. BDM31343 and DNB1 are other new chemical entities being under development [36]. A Sesqeterpene, Heteronemin which is isolated from a red sea sponge, disclosed activity against *Mycobacterium tuberculosis* H37Rv with MIC of 6.25 μg/mL [111]. Nephalsterol C and Litosterol, (Fig. **23**) compounds of C19 hydroxy steroids which are isolated from a red sea Nephthea sp, had 96% and 90% of inhibitory activity against *Mycobacterium tuberculosis* H37Rv, respectively [111]. A compound isolated from the Sacoglossan mollusk Elysia rufescens, Kahalalides A (Fig. **24**) also had inhibitory activity against *Mycobacterium tuberculosis* H37Rv [111]. Tryptanthrin (PA- 505, Fig. **25**), a potent structurally novel indol-quinazolinone alkaloid, firstly discovered by Chinese scientists was active against MDR-TB bacilli with MIC range of 0.5-1.0 μg/mL [111, 112]. But to date, *in vivo* and *in vitro* data of its toxicity are needed to identify the efficacy in animal models before application in MDR-TB treatment [111, 112]. From its chemical and structural considerations, it will be a DNA intercalator which contributes to its toxicological effects [112]. ATP Synthase Inhibitor FAS20013 (FASgene), Translocase I Inhibitor, InhA Inhibitors, Isocitrate Lyase Inhibitors, and Pleuromutilins (Figs. **26**, **27**) are being evaluated before going into pre-clinical studies [111].

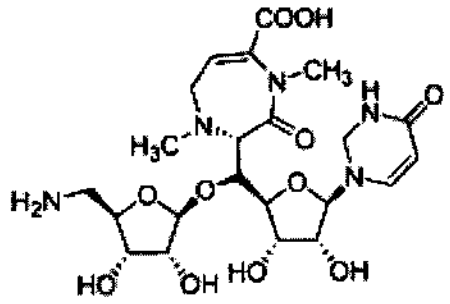

Fig. (19). Chemical structure of CPZEN45
Source: Shakya *et al.* Chemotherapeutic strategies and targets against resistant TB. In : Pere-Joan Cardona, Ed. Understanding tuberculosis-new approaches to fight against drug resistance 2012

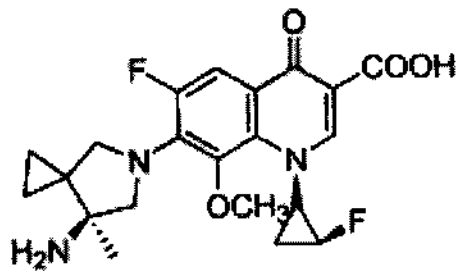

Fig. (20). Chemical structure of DC159a
Source: Shakya *et al.* Chemotherapeutic strategies and targets against resistant TB. In : Pere-Joan Cardona, Ed. Understanding tuberculosis-new approaches to fight against drug resistance 2012

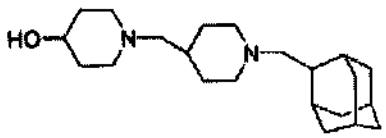

Fig. (21). Chemical structure of SQ609
Source: Shakya *et al.* Chemotherapeutic strategies and targets against resistant TB. In : Pere-Joan Cardona, Ed. Understanding tuberculosis-new approaches to fight against drug resistance 2012

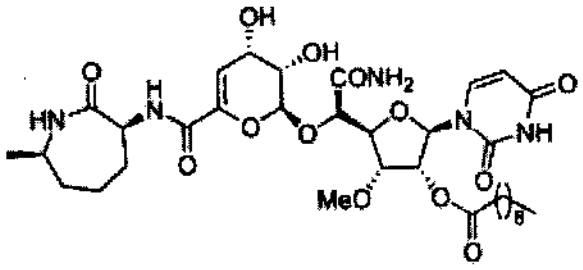

Fig. (22). Chemical structure of SQ641
Source: Shakya *et al.* Chemotherapeutic strategies and targets against resistant TB. In : Pere-Joan Cardona, Ed. Understanding tuberculosis-new approaches to fight against drug resistance 2012

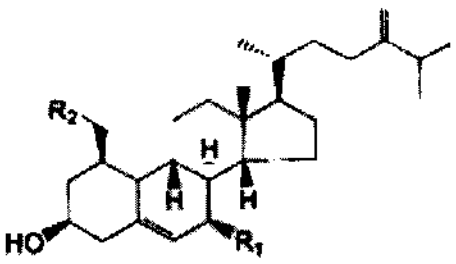

Fig. (23). Litosterol;R1=H,R2=OH;Nephalsterol; R1=OAc,R2=OH
Source: Bijev A *et al.* Journal of the University of Chemical Technology and Metallurgy 2011

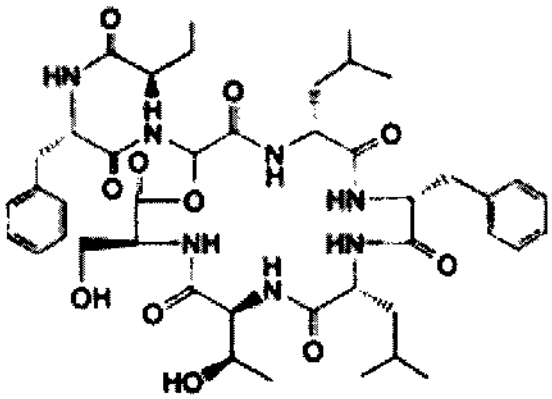

Fig. (24). Kahalalides A
Source: Bijev *et al.* Journal of the University of Chemical Technology and Metallurgy 2011

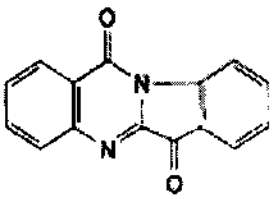

Fig. (25). Tryptanthrin (PA-505)
Source: Bijev *et al.* Journal of the University of Chemical Technology and Metallurgy 2011

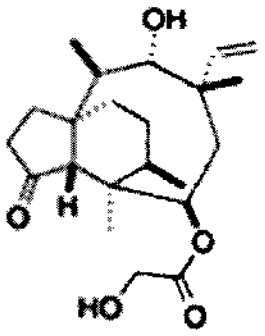

Fig. (26). Pleuromutilins described by Procter DJ
Source: Angew Chem Int Ed. 2009

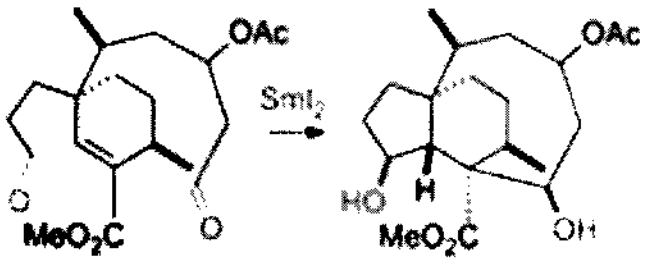

Fig. (27). Pleuromutilin analogs described by Procter DJ
Source: Angew Chem Int Ed. 2009, 48, 9315

Table 4. Anti-TB compound and MIC.

Anti-TB compound	MIC	Reference
Moxifloxacin	0.5 μg/mL	[31]
Gatifloxacin	1 μg/mL	[47]
Carbapenems	0.94 μg/mL (meropenem) 10 μg/mL (imipenem)	[48]
PA-824	0.015-0.25 mg/mL	[31]
Delamanid (OPC-67683)	0.006-0.024 μg/mL	[30]
Linezolid	0.5-1 mg/L	[72]
Bedaquiline (TM207)	0.002-0.06 μg/mL	[31]
SQ109	0.1-0.63 μg/mL	[31]
Sudoterb (LL-3858 or LU-3858)	0.25 μg/mL	[31]
Sutezolid (PNU-100480)	0.0625-0.5 μg/mL	[31]
AZD5847	1 μg/mL	[31]
Benzothiazinones (BTZ043)	1,250-10,000 ng/mL	[93]
Isoflavonoids	100-250 μg/mL	[96]
Rhein	ratio of 1: 100,000 (Aloe-emodin)	[103]
CPZEN45	2.26-9.07 μM	[31]
DC159a	0.06-0.5 mg/L	[31]
SQ609	4 μg/mL	[31]
SQ614	7.8 μM	[109]
SQ615	7.8 μM	[109]
SQ641	0.081-2.71 μM	[105]
SQ73	6.25-12.5 μM	[105]
Heteronemin	6.25 μg/mL	[111]
Trytanthrin (PA-505)	0.5-1.0 μg/mL	[111]

Table 5. The MDR/XDR-TB treatment pipeline-drugs in clinical trials, July 2010 [31, 37,48 , 49, 105, 106, 107, 108,109, 110, 111,113, 114].

Agent	Class	Status
Moxifloxacin	Fluoroquinolone	Phase III
Gatifloxacin	Fluoroquinolone	Phase III
Meropenem	Carbapenem	Phase III
PA-824	Nitroimidazo-oxazine	Phase II
OPC-67683	Nitroimidazo-oxazole	Phase II
Linezolid	Oxazolidinone	Phase II
TMC207	Diarylquinolone	Phases I/II
SQ 109	Diamine	Phases I/II
LL-3858	Pyrrole	Phases I/II
PNU-100480	Oxazolidinone	Phase I
AZD5847	Oxazolidinone	Phase I
CPZEN45	Caprazamycin	Pre-clinical
DC159a	Quinolone	Pre-clinical
SQ609	Dipiperidine	Pre-clinical
SQ614	Dipiperidine	Pre-clinical
SQ615	Dipiperidine	Pre-clinical
SQ641	Capuramycin	Pre-clinical
BTZ043	Benzothiazinone	Pre-clinical
Q201	Imidazopyridine	Pre-clinical
Q73	Diamine	Pre-clinical
Heteronemin	Sesqeterpene (a red sea sponge)	Pre-clinical
Nephalsterol	Marine natural products (C19 hydroxy steroids, a red sea Nephthea sp)	Pre-clinical
Litosterol	Marine natural products (C19 hydroxy steroids, a red sea Nephthea sp)	Pre-clinical
Kahalalides	Marine natural products (Sacoglossan mollusk Elysia rufescens)	Pre-clinical

Recent Patents Claimed

The US Patent Application Number WO2009US0056470 [116] by Zamecnik *et al.* recently provided anti-TB/MDR-TB/XDR-TB compounds comprising an oligonucleotide having a sequence complementary to a translation initiation region of an mRNA encoding a mycolyltransferase of *Mycobacterium tuberculosis*. The US Patent Application Number

Table 6. *In vitro* second-line drug susceptibility testing results [115].

Drug	% of Resistance
Rifabutin	85
Streptomycin	63
Ethambutol	37
Pyrazinamide	23
Prothionamide	8
Amikacin	5
Para-aminosalicylic acid	5
Ciprofloxacin	4
Cycloserine	1
Clofazimine	0

2008000808801 [117] by Fussenegger *et al.* recently described a pharmaceutical composition called formula 1 which was selected from benzyl acetate, 2-phenyl butyrate, in particular 2-phenylethyl butyrate, A-phenyl-2-butanone, 3-phenylpropyl propionate and another compound of formula 2 selected from ethionamide, -thiourea or thiacetazone, isoxyl,; Λ /'-[/-arabinofuranosyl- Λ and p-(isoamyloxy)phenyl & rsqb which was recently described in the US Patent Application Number WO2008EP0066124 [118]. The chemical structures of compound formula 1 and 2 are shown in Figs. **28** and **29**, respectively.

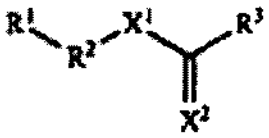

Fig. (28). Compound formula 1 described by Fussenegger *et al.* Source: US Application Number 2008000808801 **(2008)**

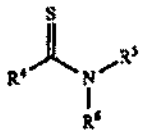

Fig. (29). Compound formula 2 described by Fussenegger *et al.* Source: US Patent Application Number WO2008EP0066124 **(2008)**

CURRENT & FUTURE DEVELOPMENTS

As we mentioned above, only 48-81% of MDR-TB patients were cured [16-18]. The previous studies revealed kanamycin and rifabutin resistances [115,Table **6**] and

percentage of adverse side-effects of numerous second-line drugs [Table **3**, reference 19] are still high and contribute to the needs for new compounds, drugs, regimens, and technologies to combat MDR/XDR-TB. MDR/XDR-TB drugs procured through the Green Light Committee/Global Drug Facilities (GLC/GDF) cost between US$ 4,400 and US$ 9,000 per patient for a standardized 18-24 month- treatment regimen while prices may be higher for drugs purchased outside of the GLC/GDF, this acts as a barrier to treatment scale up [119]. There are few quality-assured producers of the drugs that exist, such as PAS, capreomycin, clofazimine, terizidone, moxifloxacin and prothionamide [119] of which only one quality-assured source exists [120]. There is little information on how the second-line drugs interact with antiretroviral drugs which are used to treat HIV-infected/AIDS patients because today TB co-infected with HIV/AIDS is uncommon to be a priority for developers of antiretrovirals for HIV/AIDS in developed countries [121]. Only two drugs (levofloxacin and amikacin) have been developed as not widely available- pediatric formulations while particularly neglected-childhood MDR-TB cases have been assumed 10-15% of total TB cases each year [122]. The new anti-TB agents- discovery pipeline has considerably grown over the past 5 years with more than 30 discovery and preclinical projects currently being pursued which are derived from two sources, pursuit of specific molecular targets and phenotypic screening [52]. Millions of anti-TB compounds have literally been screened over the past 5 to 10 years. Relative lack of sophisticated medicinal chemistry capability to modify the expensive and time-consuming step is one of the current rate-limiting steps in phenotypic- screening approach [48]. There are various pursuing specific targets within *Mycobacterium tuberculosis* and its genetic sites (Table **1**) such as *Mycobacterium tuberculosis*–specific protease, kinase, etc. The better understanding of the TB-cell death mechanism is one of the advantages of the target-specific discovery programs [48]. Inhalational approaches [123, 124] with nanoparticles such as nanosuspension, nanoemulsion (polymeric and nonpolymeric nanoparticles, polymeric micelles and other self-assembled structures, dendrimers, complexation with cyclodextrin, liposomes and microencapsulation) [125-128] of anti-TB compounds have the possibility to deliver much higher doses of drug to the lung tissues and reduce dosing frequency. The intracellular persistence of the TB organism is the rationale for nanoparticles approaches that has never been well-validated assumption [129] while the exact histological localization of increased delivery of the inhalational approaches is still not clear [48]. Cost of new products always needs to be considered in the aspect of all novel delivery systems as well as new anti-TB compounds such as benzothiazinones introduced by Makarov *et al.* [93], compounds introduced by Zamecnik *et al.* [116] and Fussenegger *et al.* [117, 126], isoflavonoid introduced by Baker *et al.* [97], and rhein introduced by Vittori *et al.* [103] and Springolo *et al.* [104]. Among the TB endemic countries with limited resource, it can be a limiting factor for the feasibility of using some novel delivery methods.

ACKNOWLEDGEMENTS

None declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

AIDS	=	Acquired Immunodeficiency Syndrome
AUC_{24}	=	Concentration-Time Curve-24 hours
AZD	=	AstraZeneca Development Pipeline
BID	=	twice a day
CFU	=	Colony-Forming Unit
CFX	=	Ciprofloxacin
CFZ	=	Clofazimine
DOTS	=	Directly Observed Treatment, Short Course
DNA	=	Deoxyribonucleic Acid
E	=	Ethambutol
Eth	=	Ethionamide
FDA	=	Food and Drugs Administration
FDG-PET-CT	=	F-fluoro-2-deoxy-D-Glucose-Positron Emission Tomography-Computed Tomography
GDF	=	Global Drug Facility
GLC	=	Green Light Committee
HIV	=	Human Immunodeficiency Virus
LL	=	Lupin Limited
LZD	=	Linezolid
MDR-TB	=	Multidrug-Resistant Tuberculosis
MIC_{90}/MIC	=	Minimal Inhibitory Concentration
NO	=	Nitric Oxide
NTP	=	National Tuberculosis Program
OFLOTUB	=	A Multicentre Randomized Control Trial of Ofloxacin-containing Short-course Regimen for the Treatment of Pulmonary Tuberculosis
OPC	=	Nitro-dihydro-imidazooxazole
PA	=	Nitroimidazopyran
PAS	=	Para-aminosalicylic Acid
PK	=	Pharmacokinetics
PNU-100480	=	PF (Pfizer) 02341272-U 100480 or (S)-N-((3-(3-fluoro-4-thiomorphilinophenyl)-2-oxooxazolidine-5-yl)methylacetamide
qd	=	Once a day
rRNA	=	Ribosomal Ribonucleic Acid
SQ	=	Sequella
TB	=	Tuberculosis

tid	=	three times a day
TMC	=	Tibotec Medicinal Compound
VS	=	Versus
WHO	=	World Health Organization
XDR-TB	=	Extensively Drug-Resistant Tuberculosis

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