New Frontiers in the Therapy of Tuberculosis: Fighting with the Global Menace

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Abstract: Tuberculosis has remained an enemy of humankind since its inception. It has affected all facets of human life and remained leading cause of mortality and morbidity despite of availability of effective chemotherapy and BCG vaccine in 21st century. This has exposed the frailties of the current drug armamentarium. No new drug is available acting through novel mechanism of action for last 40 years. This has culminated into resistant strain of TB, MDR-TB and XDR-TB. Concomitant occurrence of TB and HIV presents a lethal combination. The availability of the *M. tuberculosis* genome sequence and mycobacterial genetic tools, such as transposon mutagenesis, gene knockout and gene transfer, greatly facilitate target identification. This review provides a comprehensive literature compilation on the present research paradigm of anti-TB drug discovery including advances in the new structural classes analogs reported in last decade.

Key Words: *Mycobacterium tuberculosis*, antituberculous drugs, resistance, novel targets.

1. INTRODUCTION

Tuberculosis (TB), a contagious infection caused by *Mycobacterium tuberculosis* has troubled humankind since its inception. It has been a leading cause of death throughout the world, mainly in developing and under developed countries. Currently, one third of the world population is latently infected with TB bacteria. There were an estimated 9.2 million new cases of TB reported every year (afflicting mostly the young and productive adults), including 4.1 million new smear-positive cases (44% of the total) and 0.7 million HIV-positive cases (8% of the total) [1]. As resistant strains of *M. tuberculosis* have slowly emerged, treatment failure is too often a fact [2], especially in countries lacking the necessary healthcare system. The emergence of multi-drug resistant TB (MDR-TB) and Extremely Drug Resistant TB (XDR-TB), (first reported in November 2005 [3, 4]) has created new challenges to control and defeat the disease.

From the mid-1990s, this infectious disease was the focus of renewed scientific interest. Regimens were optimized along with the implementation of the directly observed therapy short course (DOTS) initiative [5]. Deciphering of the genome of *M. tuberculosis* provided insights into the mechanisms of action of currently used anti-TB drugs and provided new targets for new drug discovery [6]. Renewed screenings for antimycobacterial substances lead to many growth inhibitors [7, 8]. Extensive listing of the natural products displaying antimycobacterial properties have been reviewed recently [9-13]. Novel drug candidates and the possible biological targets are also published [14-26].

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2. TB THERAPY

In the first half of the 20th century the problem of TB appeared insoluble, the lipid-rich cell wall was believed to make chemotherapy impossible [27]. This situation was further deteriorated when the sulfonamides and penicillin had no useful activity against *M. tuberculosis*. Schatz Waksman's discovery of streptomycin (STM) [28] and Harold Lehman's discovery of *p*-aminosalicylic acid (PAS) in this situation was quite promising [29]. Combined STM and PAS trials proved that combination therapy prevented the emergence of resistance [30]. The subsequent descriptions of isoniazid (INH), pyrazinamide (PZA), rifampin (RIF), ethambutol (EMB), and other drugs gave the medical community the basic tools for TB control. Using these tools many countries have seen the virtual eradication of TB [31] and others have seen a steady decline in the disease until the human immunodeficiency virus (HIV) epidemic caused the number of cases to spiral out of control [32].

Presently used anti-TB drugs can be divided into first-line drugs – INH (**1**), EMB (**2**), PZA (**3**), RIF (**4**), and STM (**5**); and second-line drugs – ethionamide (**6**) (ETA), D-cycloserine (**7**) (DCS), kanamycin (**8**), amikacin (**9**), fluoroquinolones (**10a-b**) (FQs), PAS (**11**), and capreomycin (**12**). Current TB therapy consists of an initial phase of treatment with 4 drugs, INH, RIF, PZA and EMB, for 2 months daily, followed by a continuation phase of treatment with INH and RIF for another 4 months, three times a week [5, 33]. This therapy, also called DOTS (directly observed treatment, short-course), is the best TB therapy and is recommended by WHO for treating every TB patient [5]. DOTS has given a cure rate of up to 95% patient compliance. The WHO has been instrumental in the global fight against TB, including the announcement of TB as a global public health emergency in 1993, implementing the DOTS in 1996, and linking the access to DOTS treatment with basic human rights in 2000.

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Despite the importance of DOTS in the control of TB, there are indications of high incidence of MDR-TB in the area such as in Russian prisons and some African countries where DOTS is failing to control the disease [34, 35]. In view of this, DOTS-Plus (DOTS plus second-line anti-TB drugs) is now recommended for treating MDR-TB and TB in areas with high incidence of MDR-TB [5]. Other drugs like clofazimine and thiacetazone are also considered but their use is the subject of debate [36] and only time and proper observations will provide the necessary data.

The approach to chemotherapy for TB is very different from that for other bacterial infections. The organism has a long generation time and a capacity for dormancy where its low metabolic activity makes it a difficult therapeutic target [37-39]. In addition, *M. tuberculosis* may be located in pulmonary cavities, empyema pus, or solid caseous material, where penetration of antibiotics is difficult or the pH is sufficiently low to inhibit the activity of most antibiotics [40, 41]. Organisms in pulmonary cavities are thought to be multiplying in an aerobic environment and consequently behave in a way that can be mimicked by *in vitro* tests. Organisms located within caseous foci are in a milieu where the low pH is likely to inhibit the activity of agents such as aminoglycosides but provide the conditions necessary for pyrazinamide activity.

The length of the therapy makes patient compliance difficult, which is a frequent source of drug-resistant strains. The need for the lengthy treatment is a consequence of the presence of a population of persistent bacilli that are not effectively eliminated by the current TB drugs. In fact, TB patients following the prescribed anti-TB regimen are rendered

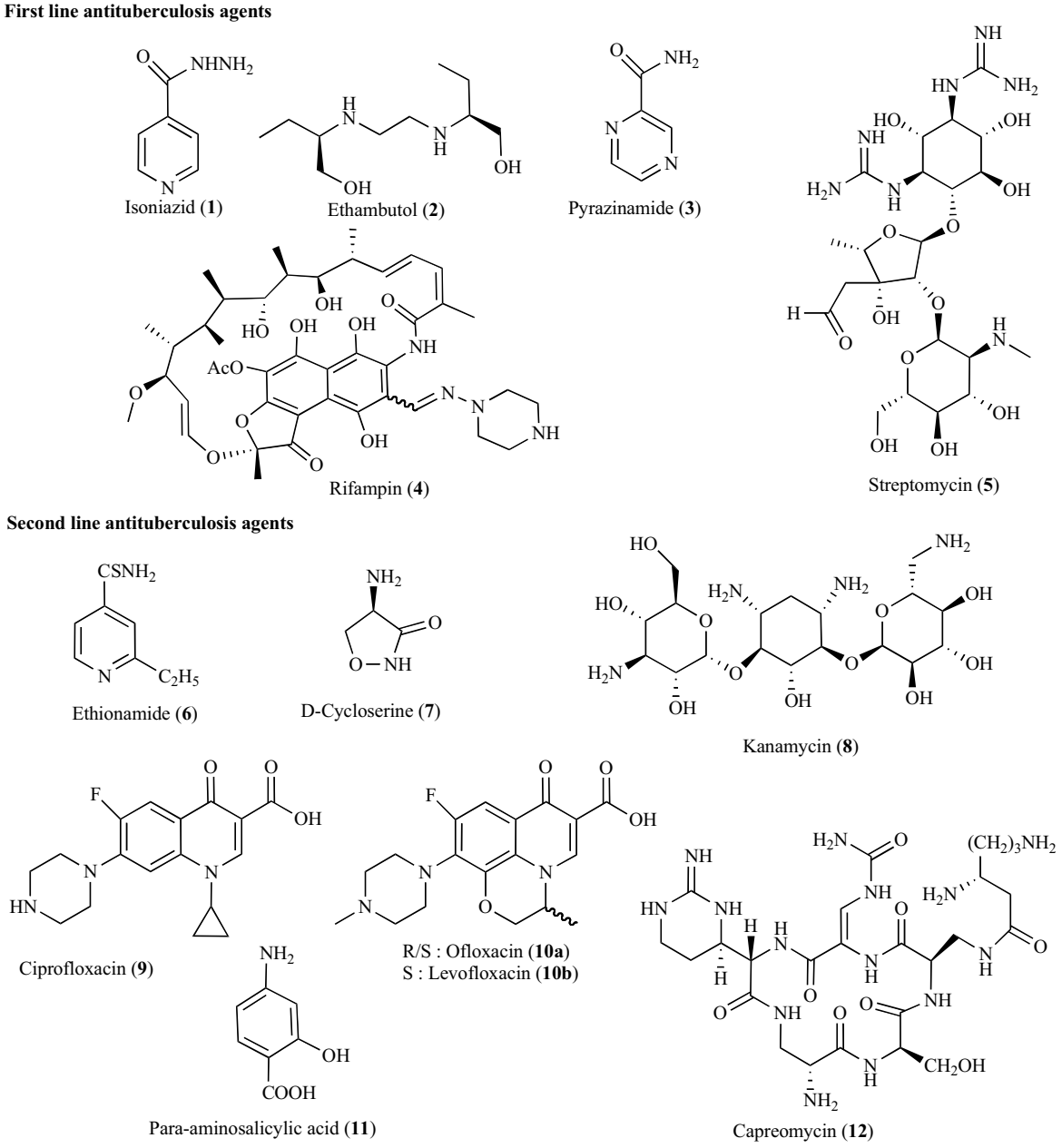


Fig. (1). Current first-line and second-line anti-TB drugs.

Table 1 Commonly Used Anti-TB Drugs and Their Targets

Drug (Year of Discovery)	MIC (μg/mL)	Mechanisms of Action	Targets	Genes Involved in Resistance	Reference
Isoniazid (**1**) (1952)	0.01-0.2	Inhibition of cell wall mycolic acid synthesis and other multiple effects on DNA, lipids, carbohydrates, and NAD metabolism	Multiple targets including acyl carrier protein reductase (InhA), β-keto-acyl synthase (KasA)	*katG* *inhA* *kasA* *ndh*	[15, 19, 44-50]
Ethambutol (**2**) (1961)	1-5	Inhibition of cell wall arabinogalactan synthesis	Arabinosyl transferase	*embCAB*	[19, 48, 51]
Pyrazinamide (**3**) (1952)	20-100 pH 5.5 or 6.0	Disruption of membrane transport and energy depletion	Membrane function and energy metabolism, FAS I	*pncA* *FasI*	[19, 48, 50, 52, 53]
Rifampin (**4**) (1966)	0.05-0.5	Inhibition of RNA synthesis	RNA polymerase β subunit	*rpoB*	[19, 48, 54, 55]
Streptomycin (**5**) (1944)	2-8	Inhibition of protein synthesis	Ribosomal S12 protein and 16S rRNA	*rpsL* *rrs*	[19, 48, 50, 56]
Ethionamide (**6**) (1956)	0.6-2.5	Inhibition of mycolic acid synthesis	Acyl carrier protein reductase (InhA)	*inhA* *etaA/ethA*	[48, 50]
Cycloserine (**7**) (1952)	5-20	Inhibition of peptidoglycan synthesis	D-alanine racemase/synthase	*alrA/dadB* *Ddl*	[19, 57, 58]
Kanamycin (**8**) (1957)	1-8	Inhibition of protein synthesis	16S rRNA	*rrs*	[19, 48, 50, 56]
Quinolones(**9**, **10a-b**) (1963)	0.2-4	Inhibition of DNA synthesis	DNA gyrase	*gyrA* *gyrB*	[19, 48, 55]
PAS (**11**) (1946)	1–8	Inhibition of folic acid and iron metabolism	thymidylate synthase (ThyA)	*thyA*	[59, 60]
Capreomycin (**12**)	4	Inhibition of protein synthesis	16S rRNA, 50S ribosome, rRNA methyltransferase (TlyA)	*rrs*, *tlyA*	[19, 48, 61]
Macrolides	8-16	Inhibition of protein synthesis	50S ribosome	*erm*	[62]

non-infectious after the first two weeks of chemotherapy [42]; the remainder of the 6 month therapy is crucial to eradicate a population of slowly metabolizing persistent bacilli and to allow the host to develop protective immunity to control the residual number of bacilli not killed by the drugs. Current TB drugs are mainly active against growing bacilli, except for RIF and PZA. Therefore, drugs active against slowly growing or non-growing persistent bacilli are thought to be important to achieve a shortened therapy. Side effects, especially hepatotoxicity, is an issue which in some cases forces an untimely treatment termination [43].

The concomitant resurgence of TB with the MDR- or XDR-TB and HIV/AIDS pandemic has exposed the frailties of the current drug armamentarium. There is now recognition that new drugs to treat TB are urgently required, especially for shortening the treatment regimen and to have better tolerability and improved pharmacokinetic properties so that intermittent chemotherapy can be made feasible. It is more desirable that the new class of agents should possibly act on novel targets through mechanism of actions different from those of the existing drugs.

3. NEWER ANTIMYCOBACTERIAL AGENTS

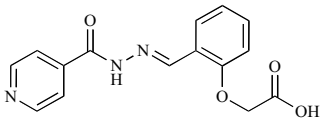
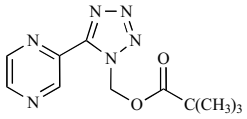
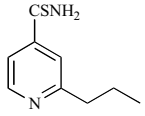
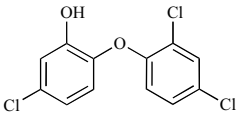
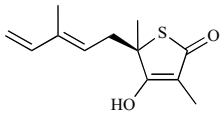
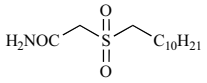
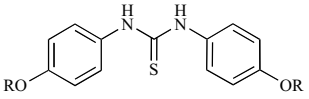
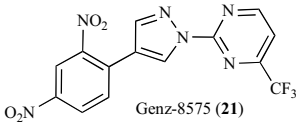
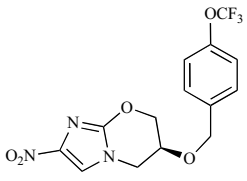
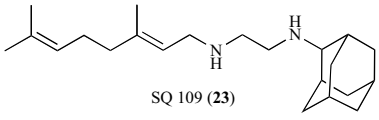
The determination of the biochemical processes targeted by anti-TB drugs is still undergoing and has been reviewed in the recent past (Table **1**) [15, 19, 63]. This is one of the many fascinating facets of this field that many anti-TB drugs have been used for decades with little or no knowledge of their mechanism of action. This 'deorphaning' of anti-TB drugs is today of prime importance, as it can lead to the identification of already validated biological targets of *M. tuberculosis*. These targets can then be used for the search of better inhibitors. The structural similarity of certain new antimycobacterial candidates may be extrapolated further to suggest a biochemical target but this argument will require a great deal of basic research.

3.1. Novel Antimycobacterial Compounds with Known Mode of Action

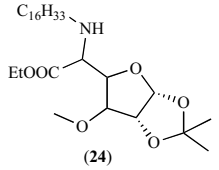
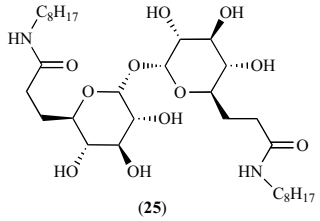
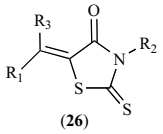
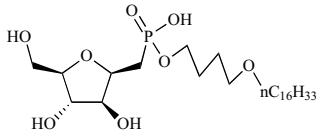
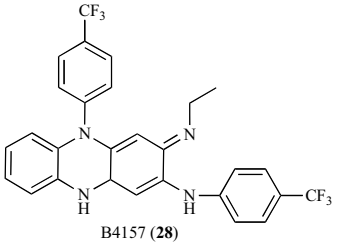
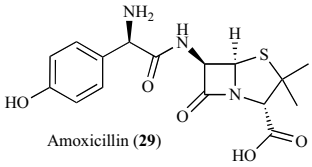
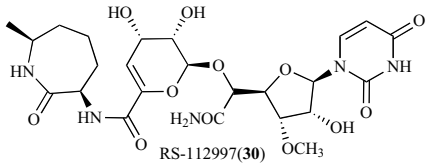
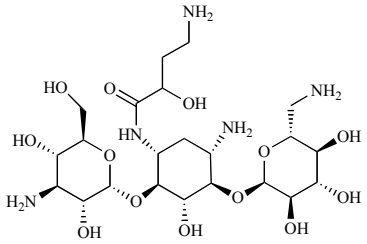
3.1.1. Inhibitors of Fatty Acid Biosynthesis

Mycobacteria produce a wide array of complex fatty acids, such as mycocerosic acid and mycolic acids, not found in mammalian cells. Mycobacteria possess accessory fatty

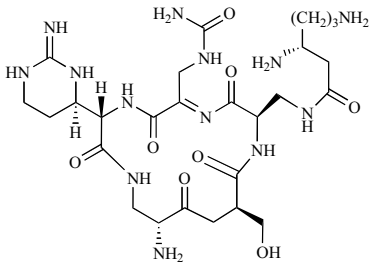
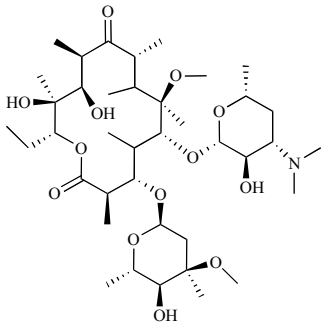
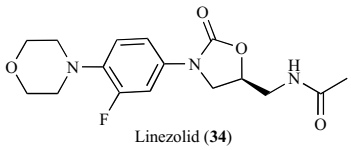
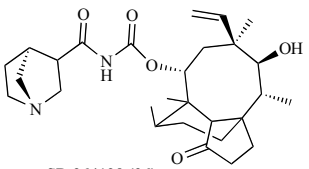
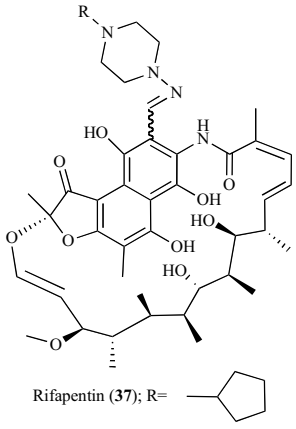
Table 2. Mechanism Based Classification of Novel Anti-TB Agents

Class	Representative Structure	Mechanism (Target)
1. Inhibitors of fatty acid biosynthesis		
(a) Isoniazid analogues	 Aconiazide (**14**)	Inhibition of mycolic acid biosynthesis (NADH-dependent KatG and InhA)
(b)Pyrazinamide analogues	 (**15**)	Inhibition of fatty acid biosynthesis
(c) Thioamides	 Prothionamide(**16**)	Inhibition of fatty acid biosynthesis
(d) Diaryl ethers	 Triclosan (**17**)	Inhibition of fatty acid biosynthesis (FabI/ InhA)
(e) Thiolactones	 Thiolactomycin (**18**)	Inhibition of fatty acid condensation (FAS II)
(f) Alkyl sulfonylcarboxamides	 FAS 20013 (**19**)	Inhibition of lipid biosynthesis (β-ketoacyl synthase) and vital energy pathways (ATP synthase)
(g) Diaryl urea/thiourea	 Isoxyl R= $-(CH_2)_2CH(CH_3)_2$ (**20**)	Inhibition of DesA3(Δ9-desaturase)
(h) Pyrazoles	 Genz-8575 (**21**)	Inhibition of mycolic acid biosynthesis (InhA)
(i) Nitroimidazopyrans	 PA-824 (**22**)	Inhibition of cell wall mycolic acid biosynthesis
2. Arabinogalactan and peptidogalactan biosynthesis inhibitors		
(a) Ethylenediamines	 SQ 109 (**23**)	Inhibition of cell wall biosynthesis

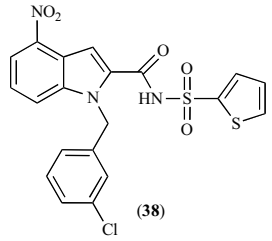
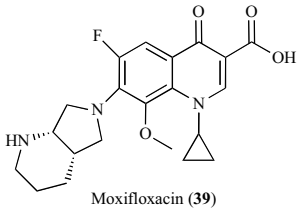
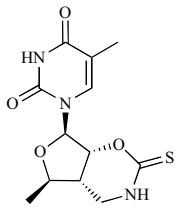
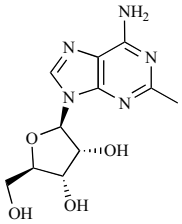
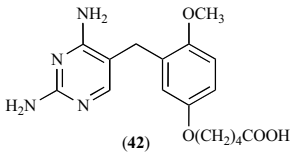
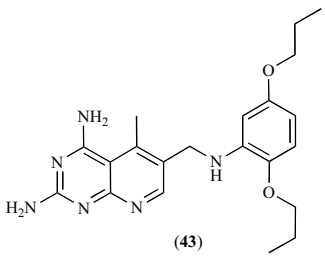
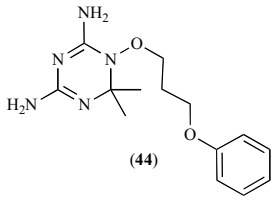
(Table 2. Contd….)

Class	Representative Structure	Mechanism (Target)
(b) D-Cycloserine analogues	 (**24**)	Inhibition of biosynthesis of UDP-muramyl pentapeptide (D-alanine racemase and the D-alanine-D-alanine ligase)
(c) Trehalose analogues	 (**25**)	Inhibition of mycolic acid biosynthesis (mycolyl transferases, antigen 85 complex)
(d) Rhodamines	 (**26**)	Inhibition of rhamnose incorporation into the mycobacterial cell wall (RmlA to RmlD)
(e) Arabinose analogues	 (**27**)	Inhibition of arabinose incorporation into the mycobacterial cell wall (arabinofuranosyl transferases)
(f) Riminophenazines	 B4157 (**28**)	Generalized membrane disruption
(g) β-Lactam antibiotics	 Amoxicillin (**29**)	Inhibition of peptidoglycan biosynthesis
(h) Capuramycin analogues	 RS-112997(**30**)	Inhibition of muramyl-pentapeptide incorporation in peptidoglycan (translocase I)
3. Protein synthesis inhibitors		
(a) Aminoglycoside antibiotics	 Amikacin (**31**)	Inhibition of protein synthesis (16S rRNA and ribosomal S12 protein)

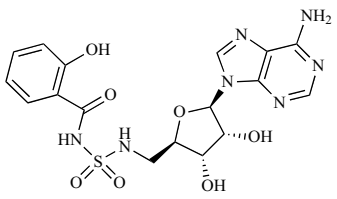
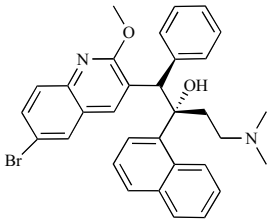
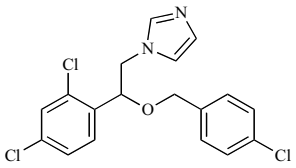
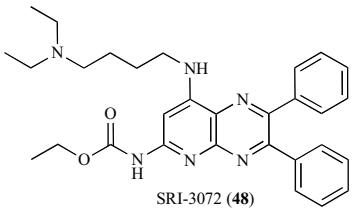
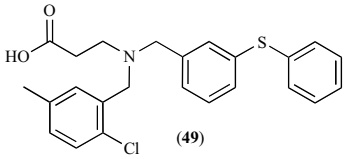
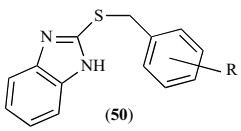
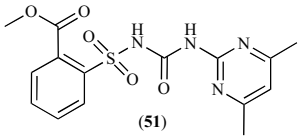
(Table 2. Contd….)

Class	Representative Structure	Mechanism (Target)
(b) Cyclic peptides	 Capreomycin (**32**)	Inhibition of protein synthesis (30S ribosomal subunit)
(c) Macrolide antibiotics	 Clarithromycin (**33**)	Inhibition of protein synthesis (50S ribosomal subunit)
(d) Oxazolidinones	 Linezolid (**34**)	Inhibition of protein synthesis (50S ribosomal subunit)
(e) Thiazole-peptide antibiotics (Nocaithiacins)	BMS-249524(**35**)	Inhibition of protein synthesis (50S ribosomal subunit)
(f) Pleuromutilin analogues	 SB-264128 (**36**)	Inhibition of protein synthesis (23S ribosomal subunit), peptidyl transferase centre of 50S ribosomal subunit
4. Nucleic acid biosynthesis inhibitors		
(a) Rifamycins	 Rifapentin (**37**); R=	Inhibition of bacterial RNA synthesis (β-subunit of the DNA dependent RNA polymerase)

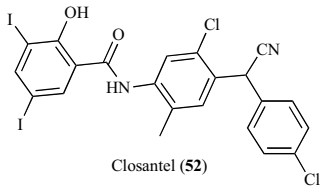
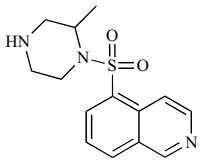
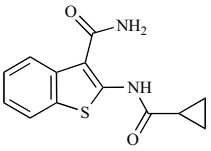
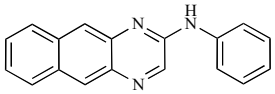
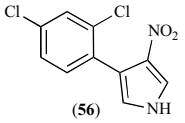
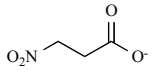
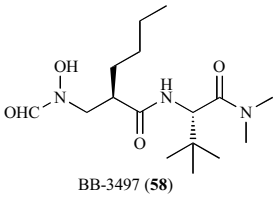
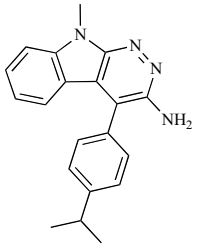
(Table 2. Contd….)

Class	Representative Structure	Mechanism (Target)
(b) Indolecarboxylic acids	 (**38**)	Inhibition of bacterial RNA synthesis (β-subunit of the DNA dependent RNA polymerase)
(c) Fluoroquinolones	 Moxifloxacin (**39**)	Inhibition of DNA synthesis (ATP-dependent DNA gyrase or topoisomerase II/IV)
(d) Pyrimidine nucleoside analogues	 (**40**)	Inhibition of nucleoside monophosphate kinases (thymidine kinases)
(e) Purine nucleoside analogues	 (**41**)	Inhibition of nucleoside monophosphate kinases (adenosine kinases)
5. Dihydrofolate reductase (DHFR) inhibitors		
(a) Diaminopyrimidines	 (**42**)	Inhibition of DHFR
(b) Deazapteridines/ pteridines	 (**43**)	Inhibition of DHFR
(c) Triazines	 (**44**)	Inhibition of DHFR

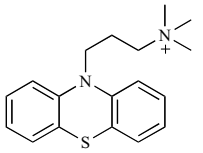
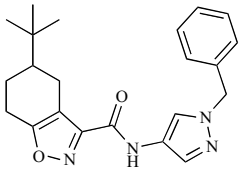
(Table 2. Contd….)

Class	Representative Structure	Mechanism (Target)
6. Inhibitors of siderophore biosynthesis		
(a) Salicylamide analogues	 (**45**)	Inhibition of mycobactin biosynthesis
7. Inhibitors of proton pump		
(a) Diarylquinolines	 TMC 207 (**46**)	Inhibition of mycobacterial proton pump $F_0F_1H^+$ATPase (AtpE, component of ATP synthase)
8. Inhibitors of cytochrome P450 enzyme system		
(a) Azoles	 Econazole (**47**)	Inhibition of mycobacterial cytochrome P450 monooxygenases (14-α-sterol demethylase or CYP1)
9. Tubulin polymerization inhibitors		
(a) Deazapteridines	 SRI-3072 (**48**)	Inhibition of tubulin polymerization (FtsZ proteins)
(b) Thioethers	 (**49**)	Inhibition of mycobacterial cytokinesis
(c) Benzimidazoles	 (**50**)	Inhibition of FtsZ protein polymerization
10. Inhibitors of branched chain amino acid biosynthesis		
(a) Sulfometuron methyl	 (**51**)	Inhibition of branched chain amino acid biosynthesis (acetolactate synthase)

(Table 2. Contd….)

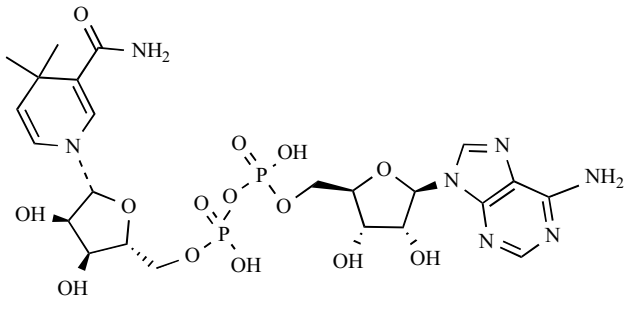
Class	Representative Structure	Mechanism (Target)
11. Signal transduction inhibitors		
(a) Salicylanilides	 Closantel (**52**)	Inhibition of mycobacterial two component signal transduction system (histidine kinases)
(b) Isoquinoline sulfonamides	 (**53**)	Inhibition of mycobacterial signal transduction mechanism (PknA to PknL)
(c) Benzothiophenes	 AX-20017 (**54**)	Inhibition of mycobacterial signal transduction mechanism (PknG)
(d) Benzoquinoxalines	 (**55**)	Inhibition of mycobacterial signal transduction mechanism (PknB, PknG, PknH)
(e) Nitropyrroles	 (**56**)	Inhibition of mycobacterial signal transduction (protein kinase III)
12. Miscellaneous Mechanism Based Inhibitors		
(a) Isocitrate Lyase (ICL) Inhibitors	 3-Nitropropionate (**57**)	Inhibition of glyoxylate shunt (ICL)
(b) Peptide Deformylase (PDF) Inhibitors	 BB-3497 (**58**)	Inhibition of peptide growth
(c) Pyridazinoindoles	 (**59**)	Inhibition of monoamino oxidase (MAO)

(Table 2. Contd….)

Class	Representative Structure	Mechanism (Target)
(d) Phenothiazines	 (**60**)	Inhibition of type II NADH:menaquinone oxidoreuctase
(e) Pentothenate Synthatase (PS) inhibitors	 (**61**)	Fatty acid metabolism, cell signaling and synthesis of polyketides and nonribosomal peptides (PS)

acid synthase (FAS I and II) enzymes with specialized substrate and product specificities and are considered as attractive targets for TB drug development. Kas is responsible for the fatty acid synthesis, and catalyzes the most mechanistically complex sequence of FAS reactions. The mycolic acids, which are covalently linked to arabinogalactan, are components of the complex and thick mycobacterial envelope. The FAS I is a single large multifunctional enzyme which produces C16 and C24/26 fatty acids in four steps and FAS II will then elongate these acids to lengths as long as C56.

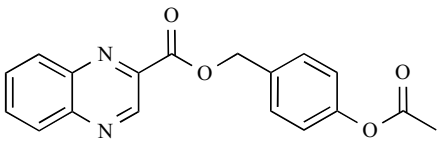
Few synthetic analogues of NAD bearing a double substitution on the nicotinamide moiety such as (**13**) have actually been patented for their antimycobacterial properties and further work along this line has been initiated [64-67]. Moreover, two other NADH-using enzymes of mycobacteria: MabA [68] and DHFR [69] are also inhibited by some of these INH-NAD adducts. Many other analogues featuring the structure of INH have been synthesized and this is still the subject of research [70-78]. A critical review of such approaches has been published recently [79]. A database search of INH-containing structures comes out with more than 3000 compounds, about 2000 of them being hydrazones. Along with aroylhydrazides (**14**) recently reported [80], the preclinical and clinical development of such INH analogues will require a very substantial benefit when compared to INH itself.



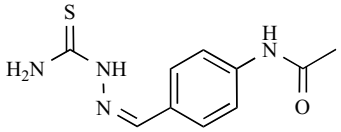
(**13**)

Fig. (2).

Structure activity relationship (SAR) studies have been reported for 5-chloropyrazinamide [81], esters of POA [82, 83] or related derivatives [84, 85]. In another approach, the carboxylic moiety of POA was replaced by isosters of a carboxylic group as for the tetrazole-containing prodrug (**15**) [86, 87]. The quinoxaline prodrug (**15a**) and its pyrazine homologue were also reported to be active on *M. tuberculosis* growth [88]. The very recent report describing the effect of pyrazinoic acid on replicating bacilli and palmitic acid biosynthesis guarantees further mechanistic studies [89].



(**15a**)



(**16a**)

Fig. (3).

Thioamide class of antimycobacterial drugs includes ETA (**6**), prothionamide (**16**) and thioacetazone (**16a**) which are the part of second-line anti-TB agents but suffer from high levels of toxicity. It is confirmed that these compounds are prodrugs and they are oxidized by EthA which can also be mutated in some resistant strains [90-92]. Triclosan (**17**) is a large spectrum inhibitor of the FabI (an NADH-dependent enoyl-acyl carrier protein reductase), including, although with lesser strength, the FabI/InhA of *M. tuberculosis* [93-95]. The X-ray structures obtained further demonstrated that the inhibition takes place *via* the occurrence of a ternary complex between FabI, NAD and triclosan [96-100]. This finding triggered syntheses of structural analogues of triclosan focused on *M. tuberculosis* enoyl-acyl carrier protein reductases [100, 101].

Thiolactomycin (TLM, **18**) is a natural product isolated from *Nocardia spp*. which belongs to a family of thiolactone containing antibiotics. This compound acts by inhibiting the condensing FAS II enzymes (FabH, KasA and KasB in the case of *M. tuberculosis* [102, 103]). The cyclic β-carbonyl structure of TLM was suggested to mimic the thiomalonate portion of the malonyl-acyl carrier protein [104]. A number of thiolactomycin analogues have been synthesized and screened against mycobacteria with varied level of potency [105-107].

The alkyl sulfonylcarboxamides class of compounds was originally designed to inhibit Kas of mycobacteria by mimicking the putative tetrahedral transition state arising from the condensation reaction [108, 109]. A related compound is considered for preclinical trials under the name FAS20013 (**19**) and is very effective in killing MDR-TB organisms. Isoxyl/thiocarlide (**20**), another thiourea containing anti-TB drug, has been used clinically in the past [110-112] before being supplanted by better drugs. Recent studies demonstrated that one of the biological targets of isoxyl is DesA3, a Δ9-desaturase responsible for the synthesis of oleic acid from stearoyl-CoA [113]. Based on the oxidation products of isoxyl, certain compounds, like dicyclohexylcarbodiimide (**20a**), were reported inhibiting several enzymes involved in cation transport [114]. Other remotely related hydrophobic carbodiimides like this compound were reported to inhibit bacterial membrane ATPase [115]. Analogues of isoxyl with a better antimycobacterial activity have also been reported [116].

High-throughput screening (HTS) of a structurally diverse library of compounds showed that indole-5-amides, 4-aryl-substituted piperazines, and various pyrazole derivatives provided useful core templates that display good InhA inhibition [96]. A second more focused library yielded Genz-8575 (**21**), a potent InhA inhibitor (91% inhibition at 40 μM) with potent activity (MIC 2.5 μg/mL) against H37Rv.

The mechanisms of action of nitroimidazole containing PA-824 (**22**) and OPC-67683 (**22a**) have not been reported [117] yet but an enzyme involved in mycolate biosynthesis at the stage of methoxy and the ketomycolic acid syntheses has been proposed as its biological target. A bioreductive activation of the nitroimidazooxazine-bearing PA-824 by a combination of the low redox potential F420-dependent glucose 6-phosphate dehydrogenase and one of the previously unstudied protein (Rv3547) acting as the electron transfer mediator has been suggested [118, 119].

3.1.2. Arabinogalactan and Peptidoglycan Biosynthesis Inhibitors

A central feature of mycobacterial envelop is a polysaccharide made up of arabinose and galactose (arabinogalactan) which acts as the intermediate binding scaffold between the many types of mycolic acids and the inner peptidoglycan. The arabinogalactan component of the cell wall is essential for its integrity, and any disruption to it is lethal for mycobacteria. The galactose residues are present in the unusual furanose conformation, which is not found in human. The arabinogalactan is attached to peptidoglycan *via* a short disaccharide linker, which contains a rhamnosyl residue, another sugar not found in human. This complex cell wall structure of *M. tuberculosis* contributes to its defense against foreign bodies and offers new targets for development of drugs against TB.

An inhibitor of the biosynthesis of the glycoside of mycobacterial envelope, as exemplified by EMB (**2**), turns out to be an excellent anti-TB drug. Simple ethylenediamines,

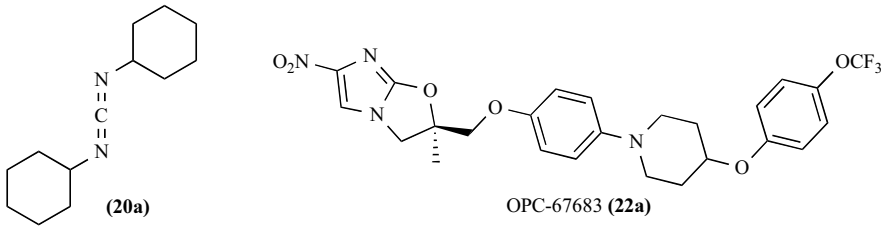


Fig. (4).

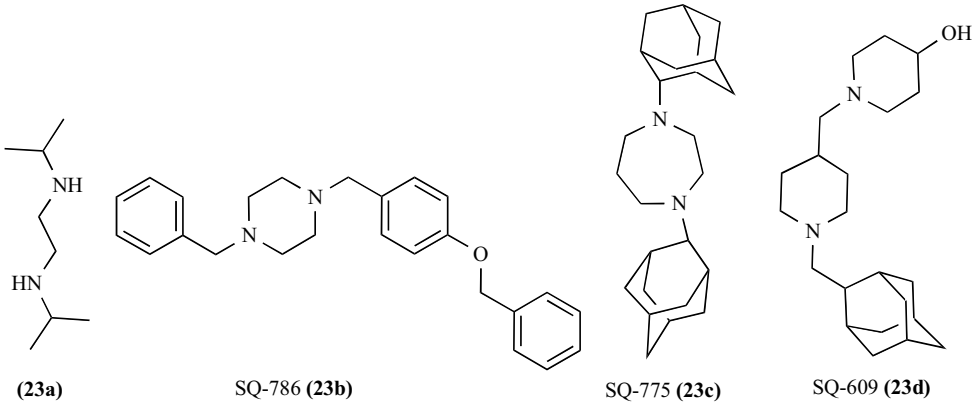


Fig. (5).

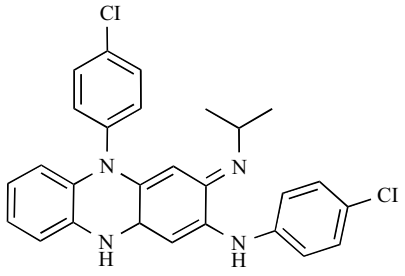
such as (**23a**) [120] or unsaturated analogs [121] are effective inhibitors of mycobacterial growth. Thus, using a modern medicinal chemistry approach, the synthesis of chemical libraries was undertaken featuring a central 1,2-ethylenediamine component [122-124]. Out of the more than 100,000 plus compounds prepared, the remarkable SQ 109 (**23**) and other analogues were as active as EMB. For instance, piperazine (SQ-786**, 23b**) or homopiperazine (SQ 775**, 23c**) containing compounds were noted for their effect on *M. tuberculosis* [124]. Dipiperidine SQ-609 (**23d**) is a novel compound structurally unrelated to existing anti-TB drugs that kills *M. tuberculosis* by interfering cell wall biosynthesis.

D-Alanine racemase is a cytoplasmic enzyme responsible for the conversion of L-alanine to D-alanine, a key building block in peptidoglycan biosynthesis. Contrary to series of alanine analogs which are inhibitors of MurC, DCS analogues (**24**) was found to inhibit the D-alanine racemase and the D-alanine: D-alanine ligase necessary for the synthesis of UDP-muramyl pentapeptide [125-127]. Upon the basis of these observations, it was envisaged that inhibitors of D-alanine racemase and D-alanine:D-alanine ligase can turn out as good antimycobacterial agents by interfering in the glycosyltransferase activity of *M. tuberculosis* [128-130].

The trehalose dimycolate (TDM), also named cord factor, are amongst the 'extractable' cell wall components of the bacteria. These trehalose esters were the focus of many studies because of their strong effect on host immune response [131]. A trehalose analog, 6-azido-6-deoxytrehalose, inhibits mycolyltransferase activity of all three members of the Ag85 complex (Ag85A to Ag85C) *in vitro*, as well as growth of *Mycobacterium aurum*, indicating the importance of TDM for maintaining the integrity of the mycobacterium cell wall [132]. Several other structural analogues were thus prepared and evaluated for their antimycobacterial activity [133-135]. The highly water-insoluble inverse bisamide (**25**) featuring C8 side chains much shorter than the C70–C90 branched mycolic acid, or sulfonamide derivatives (**25a**) [133] turned out to be quite effective on *Mycobacterium smegmatis* growth on a diffusion assay [135].

Four enzymes (RmlA to RmlD) catalyzing the biosynthesis of deoxythymidine-diphosphate-rhamnose, which is the cofactor for providing rhamnose into mycobacterial cell wall, were the focus of a screening of potential inhibitors. The rhodamines (**26**) were found to inhibit this synthetic pathway as well as *M. tuberculosis* growth [136]. This structural motif is very similar to that used in the 4-thiazolidinones, putative diphosphate surrogates that affect sugar nucleotide biosynthesis during peptidoglycan synthesis [137]. Moreover, related antibacterial rhodamines are class C β-lactamase inhibitors [138]. Modest antimycobacterial thiazolidinones, such as (**26a**), targeting the same synthetic path are reported [139].

The interruption of the arabinogalactan biosynthesis pathway, and in particular, development of novel and selective inhibitors of arabinosyltransferases which catalyze the biosynthetic pathway, is considered as an attractive strategy for development of new anti-TB drugs. Attempts were made to prepare compounds featuring an arabinogalactan skeleton which would inhibit a glycosyl transferase activity [140-144]. Certain azaribose [145] and galactofuranosyl analogues [146] were also reported to inhibit the mycobacterial growth. The arabinosyltransferases, which incorporate arabinose into the mycobacterial cell wall, use the decaprenol-phosphoarabinose as a cofactor and thus its phosphonate (**27**), phosphinic and sulfone analogs were prepared as inhibitors of mycobacterial growth [147, 148].

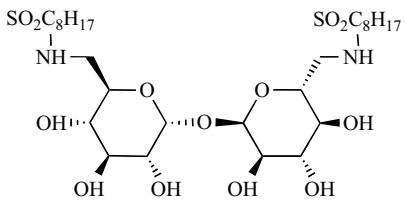


Clofazimine (**28a**)

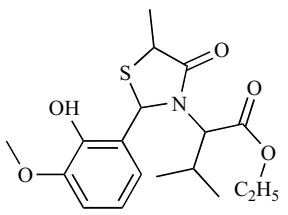
Fig. (7).

Clofazimine is a riminophenazine derivative originally developed in the 1950s from components in lichens active against *M. tuberculosis* [149] and a 'generalized membrane-disrupting effect' [150] has been suggested as its mechanism of action. Few structural alterations of this antimycobacterial compound, such as tetramethylpiperidinophenazines or TMP-phenazines (B4157**, 28**) have been reported recently [151, 152] but exact molecular target still remains a matter of research. Clofazimine (**28a**) and other riminophenazines are reviewed by some authors [153].

Certain β-lactam antibiotics, for instance amoxicillin (**29**), were also tried in the mycobacterial infections owing to their ability to inhibit the transpeptidase that cross-links the peptide side chains making the peptidoglycan. Though the

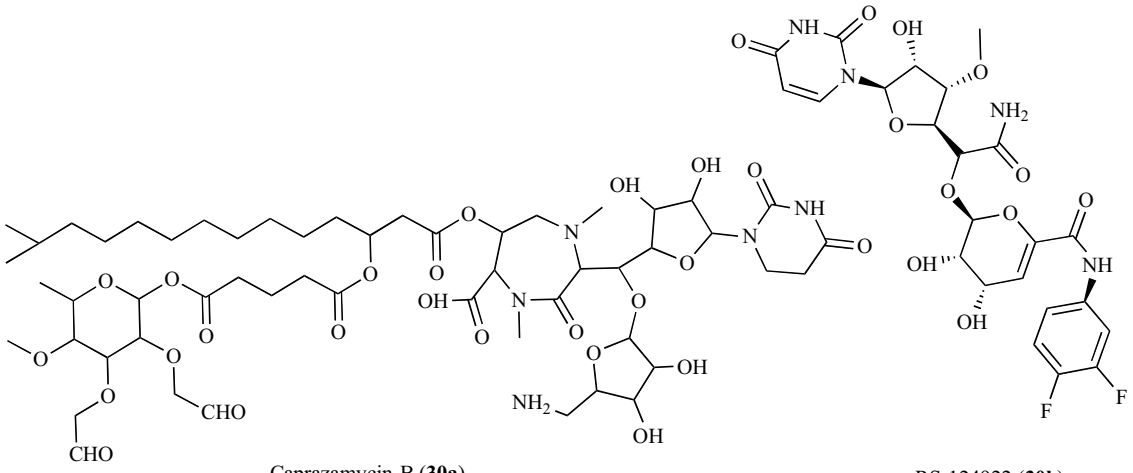


(25a)



(26a)

Fig. (6).



Caprazamycin-B (**30a**) RS-124922 (**30b**)

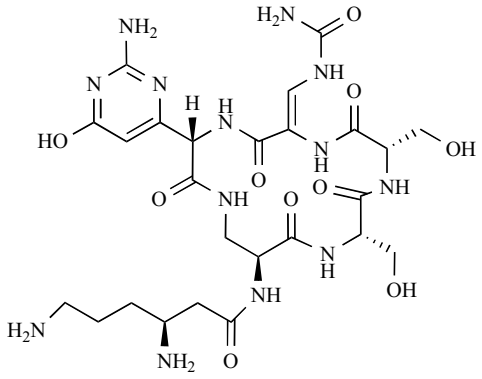
Fig. (8).

activity is too weak, their combination with β-lactamase inhibitors met with some success but still not promising.

The incorporation of UDP-muramyl-pentapeptide into cell wall requires its conversion into an undecaprenyl derivative by corresponding translocase. Inhibition of such translocase was reported for series of natural compounds such as tunicamycin, liposidomycin B, mureidomycin A [154], capuramycins (**30**) [155-157] and caprazamycins (**30a**) [158]. Compound RS-124992 (**30b**) can also be considered as potential antimycobacterials [159, 160].

3.1.3. Protein Synthesis Inhibitors

These inhibitors can be classed in three groups. Series that interact with the 30S subunits make the first group and the second is the inhibitors that interact with the 50S subunit. The last group is made of the compounds that inhibit the function of aminoacyl-tRNA synthetase. Each of the aminoacyl-tRNAs features a specific amino acid which is bound to the ribose of the tRNA stem by a specific aminoacyl-tRNA synthetase [161]. The aminoacyl-tRNAs can then transport and fit the proper amino acids for their incorporation into the nascent peptide by the ribosome machinery.



Viomycin **(32a)**

Fig. (9).

Aminoglycoside antibiotics (e.g. streptomycin, **5**) as well as the cyclic peptides, capreomycin (**32**) and viomycin (**32a**), are targeting the 30S subunit of ribosome and their use can lead to the selection of overlapping cross resistant *M. tuberculosis* strains [162]. Analysis of resistant *M. tuberculosis* strains to the cyclic peptides mentioned above suggests that these compounds bind at the interface between the ribosomal subunits. Contrary to many related macrolides targeting the 50S ribosomal subunit, clarithromycin (**33**) inhibits *M. tuberculosis* growth *in vitro* [163]. The latest generation of macrolides (e.g., telithromycin) was designed to overcome bacterial resistances resulting from methylation of the rRNA.

The oxazolidinone probably represents the most significant recent development in the field of antimicrobials. This class of compounds is amongst the very few antibacterials targeting the 50S ribosomal subunit [164-167]. Linezolid (**34**) represents this class of antibacterials and a very important number of studies were undertaken. [168-180]. According to the publicly available information, the most advanced oxazolidinone in this regard is ranbezolid (RBx 7644, **34a**) [181, 182] which has undergone phase I clinical trials in 2004 [183]. The thiophene analog RBx 8700 (**34b**) had shown even better antimycobacterial activity than ranbezolid [184, 185].

Nocathiacins (**35**), a series of fairly complex thiazol-containing peptides, should also be mentioned here as one of them is about 30 times more active than STM on *M. tuberculosis* growth and strains resistant to them were shown to have mutation on the 50S subunit [186]. Renewed interest in pleuromutilin class of antibiotics (**36**), which targets the 50S ribosome subunit [187-189], can lead to original [190-195] antimycobacterials. Future publications will hopefully report the effect of these pleuromutilins on *M. tuberculosis* growth as other analogues such as (**36a**) were the subjects of a recent patent for their antimycobacterial properties [196].

3.1.4. Inhibitors of Nucleic Acid Synthesis

The rifamycins inhibit bacterial RNA synthesis by binding to the β-subunit of the DNA-dependent polymerase and are the only clinically used antibiotics with this mechanism. Various alterations of the core structure were reviewed recently [197]. As for rifapentin, these modifications were de-

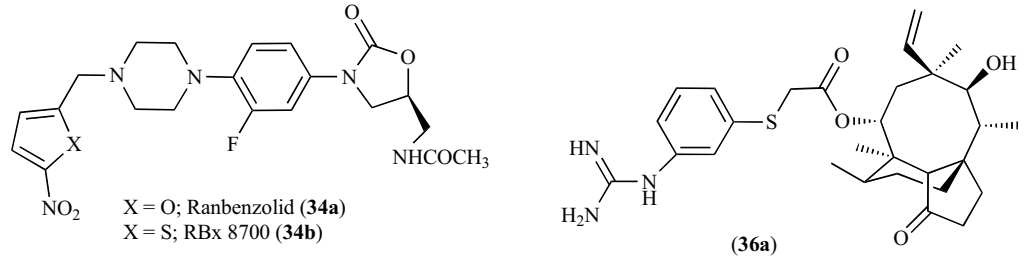


Fig. (10).

signed to obtain compounds with better pharmacokinetics. However, with the exceptions of rifapentin (**37**) and the more recent rifametane (**37a**), which is undergoing phase II clinical trials [197, 198], these analogs do not seem to offer an improvement when compared to RIF. In a completely different approach, a recent patent describes indolecarboxylic acid derivatives (**38**), which turned out to be inhibitors of *M. tuberculosis* RNA polymerase and thus useful for treating TB [199].

In line with expanding indications for the quinolones a number of these compounds have shown promise for the treatment of mycobacterial infections. Ciprofloxacin (**9**), ofloxacin (**10a**) and levofloxacin (**10b**) are finding utility as second line or alternative TB drugs. Several other quinolones like moxifloxacin (**39**) [200, 201], gemifloxacin (**39a**) [202], PD 161148 (**39b**) [203], CS-940 (**39c**) [204] and sitafloxacin (**39d**) [205-207] are also reported. The analogs addressed the side effects, improved the pharmacokinetics, simplified dosing and extended the activity spectrum to many bacteria, including mycobacteria. Several other related compounds showing promising antimycobacterial activity like ABT-255 (**39e**) [208], DC-159a (**39f**) [209], T-3811ME/BMS-284756 or garefloxacin (**39g**) [210] and PGE-9509924 (**39h**) [211] have also been reported.

The thymidine kinase of *M. tuberculosis* sequence is reasonably different (only 22% homology) from the human homologue to represent an original target for the design of anti-TB drugs [212]. Thymidine analogs (**40**) were thus prepared and some turned out to inhibit the *M. tuberculosis* thymidine kinase [213-221]. More recently, benzyl pyrimi-

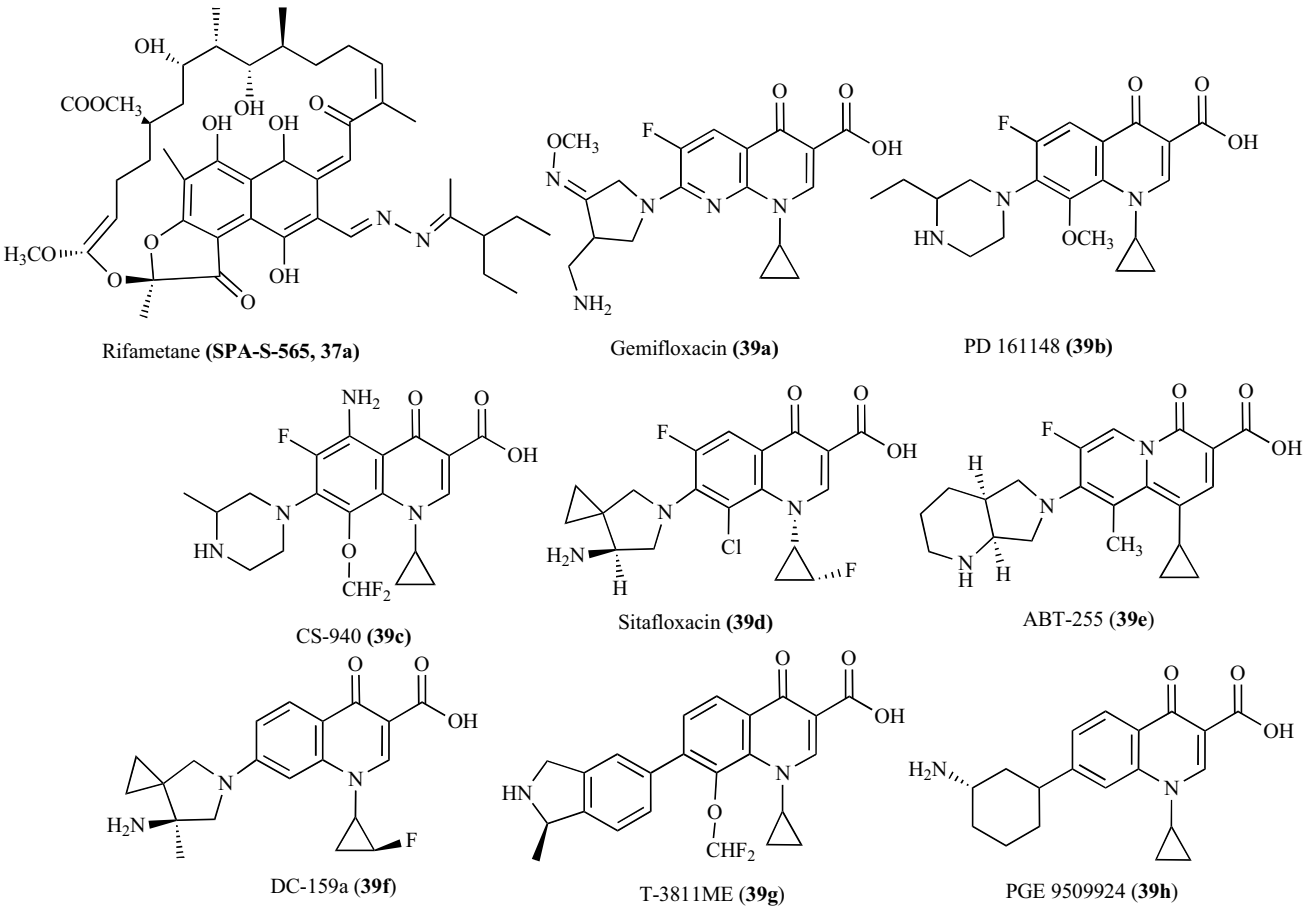
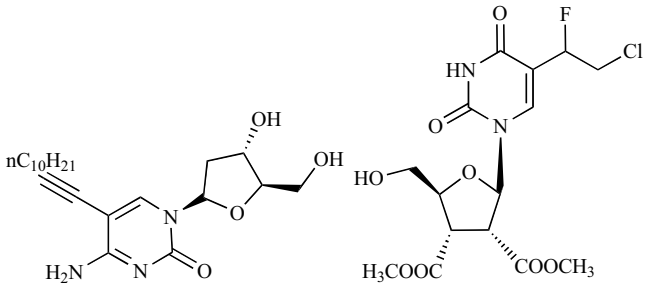


Fig. (11).

dine derivatives devoid of a ribose moiety have been patented for their inhibition of this enzyme [222]. A series of 5-(substituted)alkynylpyrimidines turned out to be of interest and dodecynyl-bearing cytidine analog (**40a**) or the acetylated derivative (**40b**) are amongst the most effective of the series [223, 224]. Purine nucleoside analogs were tested for their activity on *M. tuberculosis* and 2-methyladenosine (**41**) is an inhibitor of its growth [225]. In a more mechanism-focused approach, adenosine analogues were assayed for their inhibition of *M. tuberculosis* adenosine kinase. Further SAR studies of adenosine analogues inhibiting this enzyme have been reported recently [226, 227].



(40a) **(40b)**

Fig. (12).

3.1.5. Dihidrofolate Reductase (DHFR) Inhibitors

DHFR is an important enzyme in the folate cycle which supplies one-carbon units, derived from the action of serine hydroxymethyltransferase [228, 229] on L-serine, for the biosynthesis of deoxythymidine monophosphate (dTMP). Inhibition of the folate cycle leads to interruption of the supply of thymidine and thus to inhibition of DNA biosynthesis and inhibition of proliferation of cells. The research on the three dimensional structure and inhibition of mycobacterial DHFR resulted into several promising compounds with potential antimycobacterial activity [19, 230, 231].

The biological activities of pyrimidine-2,4-diamines have shown that it is not necessary to have the full pteridinediamine structure for inhibition of DHFR. These 'non-classical' inhibitors have advantages in that they are more lipophilic than methotrexate (**42a**), a pteridine DHFR inhibitor that can enter cells by passive diffusion and does not require the folate carrier. Trimethoprim (**42b**), in which the 5-aryl substituent is linked through a methylene bridge to increase flexibility, is cited as an inhibitor of *M. tuberculosis* DHFR and other bacterial DHFRs. It is found less potent (IC_{50} 16.5 μM) and to be only five-fold selective for inhibition of *M. tuberculosis* DHFR versus the human enzyme [232]. Several other diaminopyrimidines (**42**) have been reported recently to inhibit *M. tuberculosis* DHFR [233]. From a series of 2,4-diamino-5-deazapteridine,, SRI-20094 (**43**) displayed potent inhibition of MM6 cells infected with *M. avium* complex strain NJ3440 (MIC = 0.13 μg/mL) with a quite high selectivity of action on mycobacteria versus human DHFR [234, 235]. Few triazines (**44**) were also reported for their inhibition of DHFR and of *in vitro* mycobacterial growth [236].

3.1.6. Inhibitors of Siderophore Biosynthesis

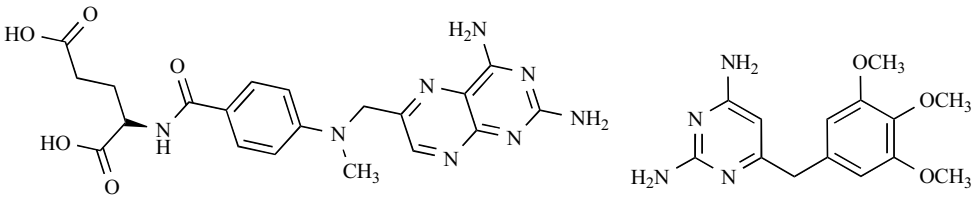
Sequestration of ferric ion from its surrounding milieu is essential for the survival of the many microorganisms including pathogenic *M. tuberculosis.* Microorganisms have evolved ligands known as siderophores with extremely high affinity for the ferric ion that sequesters iron from their vicinity. In mycobacteria, the three types of iron-binding compounds are essentially produced and classified as mycobactins, exochelins and carboxymycobactins. The inhibition of these iron chelating siderophores of *M. tuberculosis* critical for its growth in macrophage and virulence, has been the subject of some studies [237-243]. The closely related compounds such as (**45**) were reported to inhibit the incorporation of salicylic acid in the mycobactin structure by mimicking the normal substrate (the phosphate homologue) [241, 242].

3.1.7. Inhibitors of the Proton Pump

Recently, R207910 (now TMC 207, **46**), a diarylquinoline, has generated great excitement [244, 245]. The compound is extremely potent against a variety of mycobacterial species (MIC, 0.03 to 0.12 μg/mL) and the proton pump $F_0F_1H^+$ATPase was suggested as the biochemical target for *M. tuberculosis*. Remarkably, four additional patents [244, 246-248] and a report [249] are claiming structurally distinct diarylquinoline like (**46a**). Moreover, another patent claimed ATP synthase inhibitors, most of them of a peptidic nature, for the specific treatment of mycobacterial infections [250]. Also of great interest are the facts that the antimalarial mefloquine (**46b**) and some of its derivatives (**46c, 46d**) are active on *M. tuberculosis* growth [251-253].

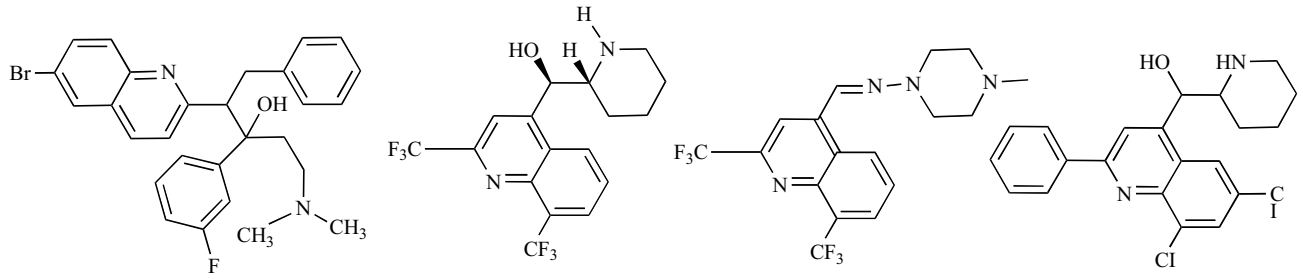
3.1.8. Inhibitors of Cytochrome P450 Enzymes

From the results of the assays of some antifungal and antihelmintic drugs on the growth of *M. tuberculosis* [254] it turned out that the azole class of antifungal, such as econazole (**47**), miconazole (**47a**) or clotrimazole (**47b**) were of interest against mycobacteria [255-257] but lack of oral activity is a serious problem. On the other hand, there are many



Methotrexate **(42a)** Trimethoprim **(42b)**

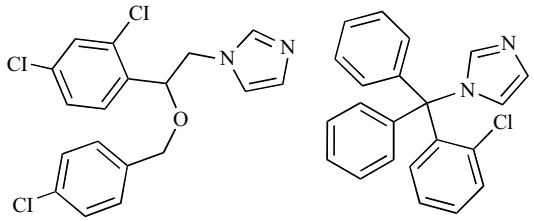
Fig. (13).



(46a) Mefloquine **(46b)** **(46c)** **(46d)**

Fig. (14).

2nd and 3rd generation antifungal azoles which are clinically efficacious by oral route, including the antifungal fluconazole which is much used in AIDS patients. It is likely that their target in mycobacteria is the cytochrome P450 monooxygenase homologue to the eukaryotic 14α-sterol demethylases (CYP51) [255, 256] and that the imidazole moiety is binding the iron of these haem-containing enzymes [258]. Moreover, the recently reported X-ray structure of a *M. tuberculosis* cytochrome P450 CYP121-fluconazole complex will probably lead to specific SAR studies [259].

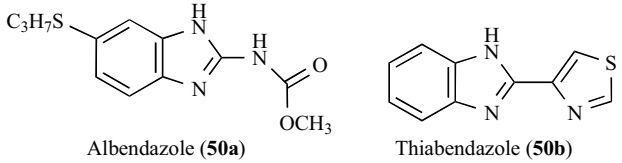


Miconazole **(47a)** Clotrimazole **(47b)**

Fig. (15).

3.1.9. Tubulin Polymerization Inhibitors

The FtsZ protein is the bacterial tubulin polymerase homologue, crucial for cell division [260, 261]. From this, tubulin polymerization inhibitors were tested on mycobacterial growth [262-265] and many inhibitors were designed [266-272]. For instance the deazapteridine derivative SRI-3072 (**48**) [273, 274] was found to affect *M. tuberculosis* growth with a MIC value (0.15 μg/mL) and remarkable selectivity index (SI= 42) [262]. Analogous deazapteridines were reported to inhibit polymerization of mycobacterial FtsZ protein. The antibacterial thioether-bearing compound (**49**) is one of the results of a screening for bacterial cytokinesis inhibitors [271]. Remarkably, a taxane derivative with a similar diphenylthioether moiety was also reported for its inhibition of *M. tuberculosis* growth [275]. The anthelmintic tubulin polymerization inhibitors, albendazole (**50a**) or thiabendazole (**50b**) and related benzimidazoles (**50**), are weakly



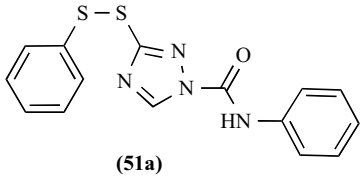
Albendazole (**50a**) Thiabendazole (**50b**)

Fig. (16).

effective on mycobacterial FtsZ polymerization [254, 276]. This fact can be further explored to have better azole inhibitor of tubulin polymerization effective against susceptible and MDR mycobacterial strains.

3.1.10. Inhibitors of Branched-Chain Amino Acid Biosynthesis

The commercially available herbicides, such as sulfometuron methyl (**51**), exhibit an inhibitory activity against acetolactate synthase, an enzyme which catalyses a key step in the branched-chain amino acid biosynthesis [277]. Sulfometuron methyl was found to have a potent effect on mycobacterial growth (MIC 0.3 to 1.8 μg/mL) and displayed good activity in murine model with no over toxicity at 500 mg/kg [278, 279]. Also, the modestly antimycobacterial disulfide (**51a**) is one of the reported inhibitors resulting from the ensuing screening of chemical libraries [280].



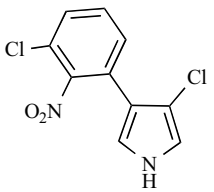
(51a)

Fig. (17).

3.1.11. Signal Transduction Inhibitors

It is likely that the survival of *M. tuberculosis* against the macrophage phagocytosis relies not only on a thick cell wall but also on many of the mycobacterial kinases (or phosphatases) which disrupt the host-cell defence mechanism against such parasitism [281], Concerning the specific inhibition of signal transduction system in mycobacteria, a series of antimycobacterial salicylanilides (**52**) were recently reported [282, 283]. Inhibition of this regulatory system probably remains a worthy research subject since regulation of this type is involved in the virulence of *M. tuberculosis* in mice [284].

Eleven putative eukaryotic-like protein serine-threonine kinases (PknA to L) involved in signal transduction were identified in *M. tuberculosis* H37Rv genome [6, 285-287]. Moreover, the 'generic' kinase inhibitor (**53**) [288] as well as other more complex compounds [289] were shown to inhibit the growth of some mycobacteria. Protein kinase PknG does not have a transmembrane domain and could be a secreted



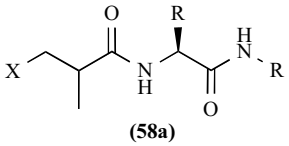
Pyrrolnirtin **(56a)**

Fig. (18).

protein, enabling the mycobacteria survival within the macrophages [290]. This suggestion is probably very important as there would thus be no need for a PknG inhibitor to pass the mycobacterial cell wall to reach this enzyme. Concerning PknG, the specific inhibitor benzothiophene AX-20017 (**54**) was reported to be inactive on the growth of *M. tuberculosis in vitro* but to have a dose dependent inhibition effect on mycobacteria grown inside macrophages [290, 291]. Benzoquinoxalines (**55**) were patented for their inhibition of PknB, PknG and PknH as well as for their effect on mycobacterial growth [292]. A number of pyrroles related to pyrrolnitrin (**56a**), a natural antifungal antibiotic isolated from *Streptomyces pyrrocinia,* were tested against various strains of mycobacteria. The synthesis of a series of analogs was undertaken and the best compound (**56**) showed an MIC value of 1 μg/mL [293]. In an 'opposite' approach, mycobacterial tyrosine phosphatase inhibitors, which are secreted by mycobacteria, have been suggested for the research of new antimycobacterials [281].

3.1.12. Isocitrate Lyase (ICL) Inhibitors

The ICL enzyme has been shown to be essential for long-term persistence of *M. tuberculosis* in mice, but not required for bacilli viability in normal culture or hypoxic conditions [294]. It cleaves isocitrate to succinate and glyoxalate. Survival of *M. tuberculosis* in the adverse *in vivo* environment requires utilization of C_2 substrates (generated by β-oxidation of fatty acids) as the carbon source [294]. McKinney and collaborators have recently shown that inhibition of ICL1 and ICL2, the two isoforms of ICL present in *M. tuberculosis*, blocks growth and survival of *M. tuberculosis* bacteria in macrophages in mice at early and late stage of infection [294]. The absence of ICL orthologs in mammals should facilitate the development of glyoxylate cycle inhibitors (**57**) as new drugs for the treatment for TB. Such a new drug is expected to be able to kill persistent bacteria and therefore have sterilizing activity and shorten treatment time.



(58a)

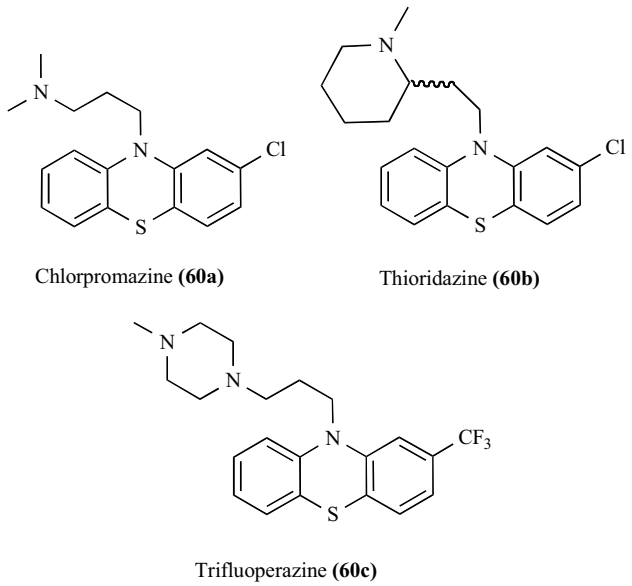
Fig. (19).

3.1.13. Peptide Deformylase Inhibitors (PDF)

PDF is an essential enzyme catalyzing the hydrolytic removal of the N-terminal formyl group from the methionine of nascent ribosome-synthesized polypeptides and inhibitors of PDF were found to be effective on *M. tuberculosis* growth. This result validates this biochemical process as a target for anti-TB drugs [295-297]. PDF is a ferrous metalloprotease enzyme essential for bacterial survival but is not vital to human cells and thus generic PDF inhibitors (**58a**) could prove to be potential antimycobacterial agents [298]. The PDF inhibitor BB-3497 (**58**) has recently been found to be active against *M. tuberculosis* with MIC of 0.06-2 μg/mL [299].

3.1.14. Monoamine Oxidase (MAO) Inhibitors

The correlation between MAO inhibition and anti-TB activity was first reported in the 1960s [299], a concept that was revisited in the recent publication exploring the SAR of pyradazinoindoles against these targets [300]. Few of the compounds were active and compounds with modest (micromolar) levels of MAO inhibition were shown to have potent anti-TB activity (MIC 1.42 μg/mL for **59**).



Chlorpromazine **(60a)** Thioridazine **(60b)**

Trifluoperazine **(60c)**

Fig. (20).

Phenothiazines (**60**) such as chlorpromazine (CPZ, **60a**), thioridazine (**60b**), and trifluroperazine (**60c**) are antipsychotic drugs with anti-TB activity [301]. Phenothiazines are calmodulin antagonists and their antituberculous activity appears to correlate with the presence of a calmodulin-like protein in mycobacteria [302]. Phenothiazines are also active against MDR-TB [303, 304], suggesting that they inhibit a novel target in *M. tuberculosis*. Weak anti-TB activity of phenothiazine derivative was also investigated [305, 306]. However, since these compounds are inhibitors of type II NADH: menaquinone oxidoreductase, further research in this direction may be of interest [307].

3.1.15. Pantothenate Synthetase (PS) Inhibitors

PS catalyzes amide bond formation of pantothenate from D-pantoate and β-alanine accompanied by hydrolysis of Mg^{+2}-ATP into AMP and Mg-PPi. Pantothenate is a key precursor of coenzyme A and acyl carrier protein, essential for many intracellular processes including fatty acid metabolism, cell signaling, and synthesis of polyketides and nonri-

bosomal peptides. Several recent publications explored PS as a potential antimycobacterial target [308-311]. For instance, a series of 5-tert-butyl-N-pyrazol-4-yl-4,5,6,7-tetrahydrobenzo[*d*]isoxazole-3-carboxamide derivatives (**61**) was reported recently as novel potent *M. tuberculosis* PS inhibitors.

3.2. The Enigma of Latent Mycobacteria

M. tuberculosis is the most conspicuous example of an intracellular bacterium that persists for long periods within the host, causing a latent infection, namely a chronic asymptomatic infection without tissue damage. The terms latent, dormant and persister have often been used interchangeably, however, the first and second terms are synonymous to a physiological state of the microbe in individuals identified by a chronic asymptomatic infection without tissue damage and thus did not receive treatment with anti-TB drugs. The third term refers to a specific sub-population of organism in the host selected during the course of the treatment of active TB. The underlying features of this latent or the persister population are: the inability to detect these microbes using conventional culture techniques, the failure of the immune system to eradicate them and the ability of this population to cause active TB in the host. The major limitation in identifying individuals with latent or dormant TB is the lack of a proven diagnostic technique which, in addition to the lack of authenticated *in vitro*, *ex vivo* or disease models in animals, limits the drug discovery specific for the treatment of latent TB. An alternate strategy to identify compounds with potential activity on the latent microbe is to assume identical metabolic states for both the latent and the persister population, though the triggers or signals inducing this state may have been different. The fundamental characteristic of both these physiological states being the 'nonreplicating microbe', compounds cidal on the non-replicating microbe can be expected to be active on both the latent and persister forms of *M. tuberculosis*. Moreover, immunotherapy is an area that merits more consideration than it has previously received, as it could potentially avoid the problem of pathogen resistance.

The prevailing scientific paradigm has been that the intracellular location of *M. tuberculosis* prevents antibodies access. This paradigm was originated from the classical view that a division of roles exists between antibody-mediated and cell-mediated immunity [312]. While antibody-mediated immunity is thought to work against extracellular pathogens exclusively, cell-mediated immunity is thought to be effective against intracellular pathogens exclusively. However, it can be argued that this division of roles is not always applicable. During the initial steps of infection, antibodies alone, or in conjunction with the proper cytokines, may provide important functions, such as prevention of entry of bacteria at mucosal surfaces. In recent years, researchers demonstrated that antibodies can modify various aspects of mycobacterial infection to the benefit of the host [312]. Interest in using antibodies to treat infectious diseases is now being fuelled by the wide dissemination of drug-resistant microorganisms, the emergence of new microorganisms, the relative inefficacy of antimicrobial drugs in immunocompromised hosts and the fact that antibody-based therapies are the only means to provide immediate immunity against biological weapons.

The antibodies can be exploited in two ways in clinical management and control of TB: as serological diagnostic tools; and as active participants in protection. BCG and most vaccine candidates against TB are directed at augmenting cell-mediated immune responses. However, this mechanism of protection is fundamentally different from that of most currently licensed vaccines which protect against a variety of pathogens. The later vaccines confer protection primarily by eliciting protective antibody responses that are thought to eliminate the infectious inoculum [313]. Some of the most successful vaccines currently used in humans against several pathogens are the polysaccharide vaccines. Polysaccharide conjugate vaccines have no potential for virulence and were shown to be effective against several pathogens, including intracellular microorganisms by inducing protective antibodies. The mycobacterial polysaccharides like lipoarabinomannan (LAM) are promoting similar immune response and thus can be useful for developing new vaccines against the persistant organism.

The specific mycobacterial targets for antibody-mediated enhanced interiorization and/or killing are not known, but surface antigens such as LAM or proteins expressed under stress conditions, such as alpha crystallin protein, may be relevant [314]. Lately, their participation in the control of acute infections including *M. tuberculosis* has been explored [314]. In some other experiments, beneficial outcome mediated by antibody was achieved when mAb was administered before or after the infection or antigen exposure. For example mice infected with *M. tuberculosis* Erdman strain that had been pre-incubated with mAb 9d8, survived significantly longer than controls [315]. Murine IgG3 mAbs have been shown to be protective against *M. Tuberculosis*[315]. A new approach toward protection against TB, using passive inoculation with IgA antibodies, was tested in an experimental mouse model of TB lung infection [316]. Intranasal inoculation of mice with an IgA monoclonal antibody against alpha crystalline protein reduced the *M. tuberculosis* colony up to 10-fold [317]. However, the protection was of short duration, probably due to the rapid degradation of the intranasally-applied IgA. Toll-like receptors (TLRs) are one of the families of pattern-recognition receptors to sense a wide range of microorganisms including mycobacteria which induces dendritic cell maturation and cytokine production, resulting in development of adaptive immunity. TLRs are critically involved in the induction of host defense to *M. tuberculosis* [318].

3.3. Novel Drug Targets in *M. tuberculosis*

Our knowledge of the tubercle bacillus and its complex interaction with the human host has improved dramatically in recent years, particularly with the determination of its complete genome sequence. New genome-scale tools are being applied to aid in drug target identification, alongside traditional approaches aimed at understanding the basic biology of *M. tuberculosis*. Many potential drug targets have been identified, but very few have been validated by showing that they are essential for growth or survival of the bacterium. In choosing targets for drug development, it is important that the targets should be involved in vital aspects of bacterial growth, metabolism, and viability, survival and

Table 3. Promising Drug Targets of *M. tuberculosis*

Classification	Drug Target (Gene)	Biochemical Process
Cell Envelope	Enoyl-ACP reductase *(inhA)*	Mycolic acid biosynthesis
	β-Ketoacyl-ACP reductase (MabA/FabG1)*	Biosynthesis of long chain fatty acids (precursors of mycolic acid)
	β-Ketoacyl-ACP synthase (*kasAB*, *fabH*)*	Mycolic acid biosynthesis
	EmbC, EmbA, and EmbB	Cell wall arabinogalactan biosynthesis (incorporation of arabinose)
	Polyketide synthase (*pks13*)	Mycolic acid biosynthesis
	S-adenosylmethionine-dependent	Mycolic acid biosynthesis
	methyltransferase (*mmaA4*)	Mycolic acid biosynthesis
	Acyl-coenzyme A carboxylase (*acc*)	Mycolic acid biosynthesis
	Acyl-AMP ligase (*fadD32*)	Mycolic acid biosynthesis
	Glycosyltransferase (*mshA*)	Mycolic acid biosynthesis
	N-acetyl-1-D-*myo*-inosityl-2-amino-2-deoxy-α-D-gluco-pyranoside deacetylase (*mshB*)	Mycolic acid biosynthesis
	L-cysteine:1-d-*myo*-inosityl-1-amino-2-deoxy-α-D-glucopyranoside ligase (*mshC*)	Mycolic acid biosynthesis
	Mycothiol synthase (*mshD*)	Mycolic acid biosynthesis
	Polyprenol monophospho-mannose synthase (*ppm1*)*	LAM synthesis
	Mannosyltransferase (*pimB*, *pimF*)*	LAM synthesis
	Phosphatidylinositol mannosyltransferase (*pimA*)	Phosphatidyl-*myo*-inositol-mannoside synthesis
	Cyclopropane synthase (*pcaA, cmaA,mmaA2*)*	Cyclopropanation at distal position of the mero chain in the α-mycolic acid series
	D-alanine racemase (alrA)	Conversion of L-alanine to D-alanine
	D-alanine:D-alanine ligase	Dimerization of D-alanine into D-alanyl-D-alanine
	dTDP-glucose dehydratase (*rmlB*)	mAGP complex synthesis
	dTDP-keto-deoxyglucose epimerase (*rmlC*)	mAGP complex synthesis
	dTDP-deoxyhexulose reductase (*rmlD*)	mAGP complex synthesis
	Cytochrome P_{450} 14α-sterol demethylase (CYP51)	Oxidative removal of 14α-methyl group of lanosterol for sterol biosynthesis
Cellular Metabolism	Arylamine N-acetyl transferase	Acetyl Co-A dependant conjugation of acetyl group with aromatic amine, hydroxylamine or hydrazine
	Mpa (Rv2115c)	Proteasome-associated protease activity
	Paf (Rv2097c)	Proteasome associated factor
	urvB	Responsible for DNA repair
	fbiC	Synthesis of flavin cofactor
	Acetolactate synthase (ALS) and ketolacid-reducto-isomerase (KARI)	Synthesis of branched chain amino acids like valine, leucine and isoleucine
	Thymidylate synthase	Conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP)
	1,4-dihydroxy-2-naphthoate prenyltransferase (*memA*)	Menaquinone synthesis
	1,4-dihydroxy-2-naphthoyl-coenzyme A synthase (*menB*)	Menaquinone synthesis

(Table 3. Contd….)

Classification	Drug Target (Gene)	Biochemical Process
	Type II NADH:menaquinone oxidoreductase (*ndh*)	Menaquinone synthesis
	Adenosine 5'-phosphosulfate reductase (*cysH*)	Reductive sulfur assimilation
	Dihydropteroate synthase (*folP*)	Folate synthesis
	Dihidrofolate reductase (*dfrA*)	Folate synthesis
	3-Dehydroquinate dehydratase type II (DHQase II)	Dehydration of dehydroquinate to yield dehydroshikimate for the biosynthesis of folate, ubiquinone and aromatic amino acids
	Pantothenate synthetase (*panC*)	Pantothenate synthesis
	Asparate-1-decarboxylase (*panD*)	Pantothenate synthesis
	Adenosine kinase (*Rv2202c*)	AMP synthesis
	ATP synthase (*atpE*)	ATP synthesis
Transcription	SigF, OrfX, and OrfY	Trigger growth arrest and dormancy during active TB
	AlgU	Inhibition of RNA polymerase activity
	RNA Polymerase α-subunit	Inhibition of RNA polymerase activity
	WhiB1, WhiB2, WhiB3 and WhiB4	Sporulation and cell septation
	Thymidylate kinase (*tmk*)	DNA synthesis
	Filamentation temperature-sensitive protein Z (*ftsZ*)	Septum formation
Translation	Isoleucyl tRNA synthase	Transfer of specific amino acid to its corresponding tRNA to form aminoacyl-tRNA
	Methionyl tRNA synthase	Transfer of specific amino acid to its corresponding tRNA to form aminoacyl
	Seryl tRNA synthase	Transfer of specific amino acid to its corresponding tRNA to form aminoacyl
	NusB	Regulation of rRNA biosynthesis
Signal Transduction	Adenylyl cyclases (ACs)	Increase in the level of cAMP leadig to inhibition of phagosome-lysosome fusion
	Protein kinase (Pkn) B, G, H, J	Inhibition of phagosome-lysosome fusion by phosphorylation of host proteins
	Tyrosine phosphatases (MptpA and MptpB)	Inhibition of INF-γ mediated signaling pathways by protein dephosphorylation
	DevR(*devR*)*	Transcriptional response regulator for oxygen limitation and initiation and maintenance of adaptive response to hypoxia
Dormancy and Persistence	Rv2623, Rv2626c, Rv3133c/DosR (*dosR*/*devR*)*	Regulatory protein in hypoxic condition and induction of dormancy (RNI/hypoxic stress)
	Resuscitation Factor (RpfA-E)	Resuscitation of dormant bacilli and stimulation of growth at very low bacilli concentration
	Rv1174c and phospholipids	Resuscitation of dormant bacilli
	Isocitrate lyase (ICL) (*icl1*, *icl2*, *aceA*)*	Conversion of isocitrate to glyoxylate and succinate as C_2 source for bacterial persistence
	Malate synthase (*glcB*)	Supply of two carbon source for energy production during hypoxic conditions

(Table 3. Contd….)

Classification	Drug Target (Gene)	Biochemical Process
Virulence	Antigen 85 complex (Ag85A-C)	Biogenesis of TDM for maintenance of cellular integrity
	Truncated hemoglobin N (trHBN)	Survival of bacilli in hypoxic environment during latency, resistance to ROI/RNI
	Phthiocerol dimycocerosyl transferase (*papA5*)*	Phthiocerol dimycocerosate esters
	Mycobacterial membrane protein large family of proteins (*mmpL7*)*	Phthiocerol dimycocerosate esters
	Sigma factors SigA (RpoV) and SigB	Transcription of essential housekeeping genes in response to environmental signals
	Alkyl hydroperoxide reductase (AhpC)	Resistance to ROI/RNI stress
	AhpD	Antioxidant defense by detoxifying hydroperoxides/ROI and RNI
	SecA (*secA1,secA2*)	Mediator of protein translocation across the cytoplasmic membrane
	Superoxide dismutase (SOD)(*sod*)*	Resistance to ROI/RNI stress
	Dihydrolipoamide acyltransferase (*dlaT*)*	Resistance to ROI/RNI stress
	Dihydrolipoamidedehydrogenase (*lpdC*)*	Resistance to ROI/RNI stress
	Iron-dependent regulator (*ideR*)**	Regulatory protein
	RelA protein (*relA*)*	Stringent response regulatory protein

*Obligatory for bacterial survival and growth in macrophages and animals.

persistence *in vivo*. and persistence *in vivo*. Some of the promising drug targets [13-16, 19, 22] are summarized in the Table **3**.

CONCLUSION

Despite the availability of the BCG vaccine and TB chemotherapy, TB still remains a leading infectious disease responsible for higher morbidity and mortality, especially in Third World countries. Due to concomitant occurrence of resistant strains of *M. tuberculosis* and HIV epidemic treatment failure is too often a fact, especially in countries lacking the necessary health care organization to provide the long and costly treatment adapted to patients. This is a human-generated problem and more fatal than TB itself.

Among the major advances in basic research, molecular and genetic tools have become available for *M. tuberculosis* and include targeted mutagenesis, array-based analysis of mutant libraries, techniques for conditional gene silencing, and global gene expression profiling. This has led to impressive improvements in the knowledge and understanding of the basic biology and physiology of *M. tuberculosis*. Despite these positive changes there are still problems that need to be tackled. There is an urgent need of a sufficient number of promising compounds in the TB pipeline for a broadly effective new treatment combination to be developed. Many of the compounds currently in the pipeline are either derivatives of existing compounds or they target the same cellular processes as drugs currently in use. Whilst analogues and derivatives are far quicker to develop, they may be subject to cross-resistance, as has been the case with the new rifamycins and quinolones. Modern technologies and rational approaches to drug design such as creation of genomic libraries of *M. tuberculosis* conditional knock-out mutants for comprehensive target identification and validation, target-based drug discovery, or determination of three dimensional crystal structures of molecular targets, are still weakly implemented. Even the more promising candidate compounds currently in clinical development were identified serendipitously. There is also an urgent need for rational approaches aimed at tackling the problem of mycobacterial persistence.

The adaptations that allow *M. tuberculosis* to persist in the host despite a vigorous adaptive immune response likely contribute to the difficulty in curing TB with current chemotherapy. Now it is required to develop a drug which should act on different target than those of currently used drugs, which may help to tackle drug resistance. Moreover, it is need of time to discover drugs or combination of drugs which can reduce the time for TB therapy and should destroy the mycobacteria in dormant stage. With the availability of the *M. tuberculosis* genome sequence, the drug development process such as the choice of drug targets will be increasingly dependent on the functional genomics approaches. Moreover, recent developments in mycobacterial molecular genetic tools (transposon mutagenesis, signature-tag mutagenesis and allelic exchange) will facilitate the identification and validation of new drug targets essential for tubercle bacilli not only *in vitro* but also for its survival and persistence *in vivo*.

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