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Review Article

Recent Advancement in the Development of Newer Antitubercular Agents: A Review

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ABSTRACT

WHO estimates one third of world's population has latent tuberculosis (TB) which indicates that people have been infected by *Mycobacterium tuberculosis* but are not yet ill with disease and cannot transmit the disease and 10% of those infected are prone to develop active tubercular infection in their life.) In 2011, TB alone remained one of the most important cause of death from infectious disease worldwide. The effective treatments of TB with the frontline drugs requires several months of chemotherapy to eliminate the persistent bacteria. The widespread non compliance in prescribing antitubercular drugs has contributed to the emergence of multidrug-resistant (MDR), and extensively drug resistant (XRD) tuberculosis. Nearly 1.3 million multi/extensively drug resistant TB (M/XRD-TB) cases will need to be treated by 2015. In spite of tremendous advances in technology no new drugs have been introduced since the discovery of rifampin. The drugs such as TMC207, PA-824, OPC-67683, SQ109, Linezolid, and PNU-100480 are still in the phase 2 clinical trials and BDM31343, DNB1, and BTZ043 are the new chemical entities. Bedaquiline (TMC207) is expected to enter phase 3 clinical trials to provide early access to patients with XRD and Pre-XRD-TB, and now Food and Drug Administration (FDA) approved it to treat MDR-TB but the drug has severe heart problem. It is the first drug with a new mechanism of action for TB in more than 40 years and the first and only one specifically indicated for MDR-TB. Efforts are still eagerly awaited to develop novel, fast acting and safer antimycobacterial agents to treat TB in order to win the battle against this millenary scourge. The present review briefly deals with the recent advancement in the development of newer antitubercular agent.

Keywords: Antitubercular agents; Tuberculosis; Tubercular vaccines

1. INTRODUCTION

Tuberculosis (TB) is a dreadful disease caused by *Mycobacterium tuberculosis* (MTB) and members of the *Mycobacterium tuberculosis* complex, which includes *Mycobacterium tuberculosis* itself, *Mycobacterium africanum*, *Mycobacterium bovis*,

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Mycobacterium caprae, *Mycobacterium microti*, *Mycobacterium pinnipedii* and *Mycobacterium canettii* and is one of the most important health problems worldwide.

TB treatment is challenging, needs accurate diagnosis, screening for drug-resistance and the administration of effective treatment regimens for at least 6 months through directly observed therapy (DOT) and follow-up support. TB can be differentiated as pulmonary (affecting lung) or extra pulmonary (affecting other sites). The drug resistant TB is further divided into multi drug resistant (MDR) TB (resistant to isoniazid and rifampicin) and extensively drug resistant (XDR) TB (resistant either to quinolones or to any one of kanamycin, capreomycin, or amikacin). As per WHO global tuberculosis report 2013, there were an estimated 8.6 million cases of TB and 1.3 million died from the disease, almost one million deaths occurred among people who were HIV-negative and 0.32 million among HIV-positive individuals. Among these deaths, there were an estimated 0.17 million from MDR TB. Compared with 0.45 million incident cases of MDR TB, approximately 1.3 million lives have been saved between 2005 and end of 2011 by implementing collaborative TB/HIV activities and 48% of the HIV positive TB patients were started on antiretroviral treatment (ART) [1]. Nearly 10% of infected people developed active TB in their life [2]. Researchers from Stanford University revealed that the MTB can persist in hostile intracellular environment escaping immune cells and drug treatment. They also isolated MTB from bone marrow derived CD271+/CD45-mesenchymal stem cell [3]. Tubercular bacteria are spread all the way through the air by active TB patients and commonly affecting the lungs. The directly observed treatment short-course (DOTS) and a multidrug therapy program developed and executed by World Health Organization (WHO), is one of the most efficient tools against the global plague with great success rate in 2010. The increasing problem of MDR-TB has focused attention on developing new drugs that are not only active against drug resistant TB, but also shorten the lengthy therapy [4-6]. Unfortunately, the first-line treatment can fail due to deprived compliance and leads to the emergence of MDR-TB. Today we have more number of antitubercular agents in preclinical and clinical development than during the last four decades. In this article we describe not only the chemical entities currently in the clinical trials but also the new vaccines in the developmental pipeline as well as the new diagnostic test either endorsed by WHO or commercialized.

Different criteria for developing new anti-tubercular drugs are reported [7–9]. A new antitubercular drug should fulfil a number of factors which are as follows a) fully validated safety profile; b) should provide shorter, safer, more effective and cheaper treatment alternatives for MDR-TB; c) should be able to inhibit new targets so that MDR-TB and XDR-TB can be treated, d) must be compatible with antiretroviral therapy, as many patients are co-infected with HIV; and d) must show no drug interaction with other antitubercular drugs or drug candidates so that a proper regimen comprising at least three active drugs can be constituted.

The past decade has seen an emergence of a promising TB drug discovery (Table 2, 3 and 4). Combining these new drugs with existing TB drugs may provide new regimens that are better tolerated, shorter in duration and with fewer side effects when compared with existing regimens. A number of new therapeutic agents and treatment regimens are under various phases of clinical trials

After several decades of slow progress in antituberculosis drug development, the pipeline has increased in the past 5 years (figure 1).

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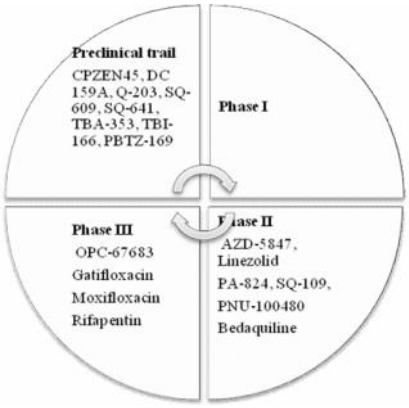

Fig 1: Global pipeline of new antitubercular drug

Progress is being made through repurposing of old drugs, re-engineering of existing antibacterial compounds, and discovery of new compounds. The most rapid progress has been made by researchers repurposing or redosing known antitubercular drugs such as rifamycins (rifampicin, rifapentine), fluoroquinolones (moxifloxacin, gatifloxacin), and rhiminophenazines (clofazimine). These drugs have entered advanced phase 3 studies. There are several candidates in Phase II and Phase III clinical trials (Table 3 and 4) together with a number of drugs in preclinical development. Many of the chemical entities currently in clinical trials are drugs that were developed to treat other infectious diseases (for example, fluoroquinolone, rifamycins, oxazolidinones and rhiminophenazines) and have since been repurposed. Drug candidates such as bedaquiline, PA-824 and OPC67683 that were initially discovered as antimycobacterial agents and have subsequently been developed as potential TB drugs, approved by the FDA for use as part of combination therapy for adults with MDR pulmonary TB

Several additional newer compounds are in preclinical development for TB , including the nitroimidazole TBA 354, the fluoroquinolone DC159a, the dipiperidine SQ609, the capuramycin SQ641, the benzothiazinone BTZ043 and the caprazene nucleoside CPZEN45 (Table 2).

2. CURRENT THERAPY FOR TUBERCULOSIS RECOMMENDED BY WHO

WHO has recommended a combination of isoniazid, rifampin, ethambutol and pyrazinamide (DOTS) for a 6 months therapy. Second-line drugs such as aminoglycosides, capreomycin, cycloserin, *p*-aminosalicylic acid, thioamides and fluoroquinolone has been recommended by WHO for the treatment of MDR-TB, Some of the antitubercular drugs and their mechanism of actions are given in **Table 1** [10-32]. Rifampicin (RIF) is the drug of choice in the TB, which has been modified to rifalazil, rifabutin and rifapentine which enhanced the half-lives and increased *in vitro* potency [33].

3. ADVANCES IN PRECLINICAL DEVELOPEMENT

In this review we have tried to present the latest advances made in antitubercular research since last decade in the development of anti-TB agents in preclinical and clinical trials. The status of new antitubercular drugs and their mechanism of action is shown in Table 2, 3 and 4 [1, 24, 31, 35-54]. Currently there are 8 anti-TB agents in preclinical development and 3 anti-TB agents in Good Laboratory Practice toxicity evaluation [55].

The discovery of entirely new and novel compounds remains challenging task for medicinal chemists. A major advancement in the screening efficacy for novel targets was achieved by researchers shifting from single-enzyme targets to phenotypic screening of the whole bacterial cell [8]. Diarylquinolines (bedaquiline) [56], benzothiazines (BTZ-043 and PBTZ-169) [39] and imidazopyridine amide (Q-203) [57] have been identified through whole bacteria cell. Although many novel compounds are in the preclinical development phase, the pipe line for the early clinical development phase is very rare.

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TBA-354, a second-generation nitroimidazole exhibited similar in-vitro anti-tuberculosis activity like delamanid, but shown better activity than PA-824, and slightly improved activity at higher doses in a mouse model of tuberculosis (1000-fold reduction in colony forming unit). Newer nitroimidazoles derivatives have shown major improvement in bioavailability in animals as compared to first generation nitroimidazoles suggesting a longer exposure to the drug than with PA-824 or delamanid [58].

Riminophenazines (clofazimine) has reduced duration of treatment of multidrug-resistant tuberculosis, but coloration of skin due to accumulation of drug in fatty tissue and organs is a major side effect. To avoid this problem, TBI-166 was selected from a series of 69 rhiminophenazine derivatives suggesting that it has retained the similar anti-mycobacterial properties [59].

Q203 is an imidazopyridine moiety containing compound, a new class of drugs [57] that inhibits ATP synthesis more potently than bedaquiline in both aerobic and hypoxic conditions. It has shown tremendous potential against multidrug-resistant and extensively drug resistant strains of *M. tuberculosis* from human beings, and data from animal studies suggest a 100–1000-fold reduction of colony-forming units and a blocking of granuloma formation.

PBTZ-169 and BTZ-043 have benzothiazinone scaffold, currently in late stage clinical development. Both drugs act by inhibiting the enzyme decaprenylphosphoryl-β-D-ribose-2´-epimerase (DprE1) in M. tuberculosis [8]. Inhibition of this enzyme prevents the formation of decaprenyl phosphoryl arabinose (a key precursor in the biosynthesis of the cell wall arabinans), which results in cell lysis and bacterial death [8].

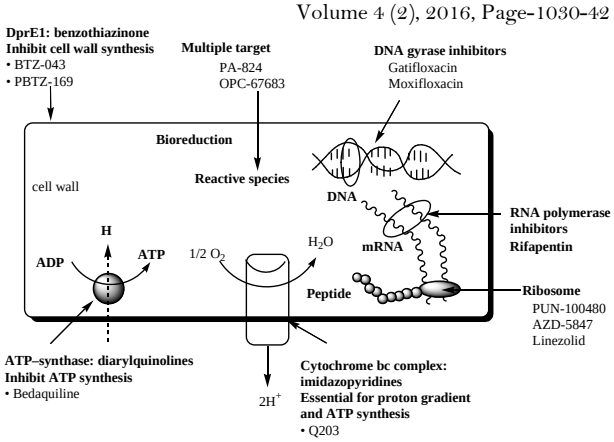

Fig 2: Mechanism of action of the antitubercular agents of newly developed drugs

4. CHEMICAL ALTERATION

Chemical alteration in a molecule (lead or drug), is an important tool for medicinal chemist to modify the pharmaceutical, pharmacokinetic, and pharmacodynamics properties of a drug. The compound SQ109 has been developed by the molecular hybridization of isoprenyl units, ethambutol pharmacophore, and adamantane moiety. The nitroimidazole analogues TBA-354, PA-824, and OPC-67683 were designed by molecular hybridization using nitroimidazole scaffold. Similarly DC-159a, gatifloxacin, and moxifloxacin were derivatized from the parent nalidixic acid using bioisosterism as molecular modification. The oxazolidinone derivatives PNU-100480 and AZD-5847 were developed using linezolid as parent scaffold by bioisosterism molecular modification tool [60]. The antitubercular agents currently in clinical phase of development which were engineered through the existing scaffolds are shown in table 5.

5. TUBERCULOSIS VACCINES IN CLINICAL TRIALS

WHO aims to eradicate TB by 2050, but eradication will be impossible without an effective vaccine [61]. Vaccine provides protective immunity against the acquisition of infection in neonates and infants, and prevents progression from infection to disease or attenuate disease in adults. Vaccines are divided into

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different categories such as recombinant live, viral vectored, recombinant protein or others. BCG (Bacille Calmette Guérin), an attenuated vaccine derived from *Mycobacterium bovis*, is the only licensed TB vaccine, but not recommended in HIV-infected infants [1]. Till now a very substantial research has been carried out over the past decade to develop vaccines against tuberculosis. Existing TV vaccines such as bacille Calmette–Guérin (BCG) is partially effective suggesting an urgent need to develop improved vaccine for tuberculosis. Key components of an ideal TB vaccine include safety and efficacy, effectiveness against pulmonary and MDR-TB, non-interference with other childhood immunizations, easily manufactured formulation on a mass scale which could be stored and administered under feasible conditions.

Currently there are 14 vaccine candidates which have entered clinical trials and over 35 candidates in discovery and preclinical development. *Mycobacterium indicus pranii* [Mw; MIP] and *M. vaccae* are in phase III clinical trial. AdAg85A, MTBVAC, and ID93/GLA-SE, and Dar-901 are in Phase 1 clinical trial while Phase II clinical trial vaccines include H56+IC31, Hybrid 4+IC31/ AERAS-404, VPM 1002, Hybrid-1+IC31, RUTI, MVA85A/AERAS-485, M72+AS01, and AERAS-402/Crucell Ad35. A number of vaccines are also in preclinical studies such as Mtb [Δ*leuCD* Δ*panCD* Δ*secA2*] (rBCG), HBHA (Protein), HG85A, Hsp (DNA) and so forth vaccine etc [62, 63]. Some of the tuberculosis vaccines in clinical trials are given in table 6. For more information on TB vaccines see references [64, 65].

6. CONCLUSION

Tuberculosis remains a major cause of death and morbidity worldwide, and concentrated efforts so far have not adequately controlled the epidemic in many parts of the world, especially in the countries of sub-Saharan Africa and parts of Eastern Europe. There are a number of factors responsible to hamper progress towards achieving control of tuberculosis worldwide. i.e absence of availability of proper diagnostic, long duration of treatment, lack of an effective vaccine, emergence of drug-resistant tuberculosis, and weak health systems in resource-poor developing countries that Despite this, there is growing momentum in basic and applied research activity that is starting to yield new diagnostic, treatment, and prevention methods, and now provide grounds for optimism. There are a number of drugs and new compounds are currently under different phases of preclinical and clinical evaluation for the treatment of TB. As we have seen in this review, not only existing antibiotics are being evaluated, but also new molecules are being discovered and tested. We have an important point to note through this review is that most of these new anti-tuberculosis drugs are also effective against MDR *tuberculosis*. Furthermore, some XDR strains have been tested and a small number of patients have been successfully treated. Caution must be taken to avoid improper use of any new drug; otherwise it will lead to drug resistance. This review presents current clinical trial status of all newer molecules in this article. Some of them may reach the last phases of clinical trial, while others could fail to demonstrate acceptable levels of efficacy and safety. It is evident that appreciable number of newer antitubercular agents has been developed in the last decades than before the last 4 decades with different targets. US FDA has approved TMC207 as a part of combination therapy to treat adults with MDRTB in absence of other alternatives. Furthermore a large number of vaccines are under clinical and preclinical phases of development. The development in the area of newer antitubercular agents and newer vaccines give hope that our vision to eradicate TB might be reached in a few decades.

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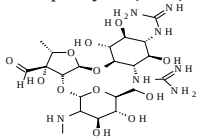
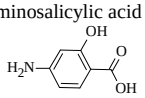
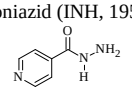
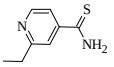
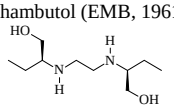
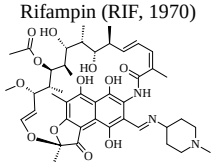
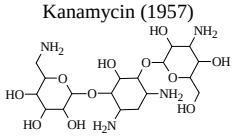
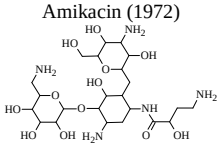
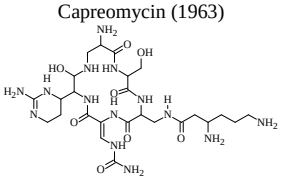
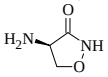
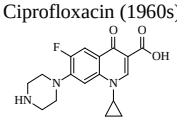
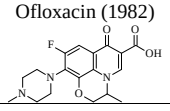
Table 1: Mechanisms of action of antitubercular drugs

Antituberculosis drug	Class	Genes involved in resistance (34)	Mode of action
Streptomycin (1944) 	Aminoglycoside	rpsL, rrs	Interferes with biosynthesis of protein through interaction with the 30S subunit of the ribosome [10-12]
Para-aminosalicylic acid (1946) 	-	thyAc	Still unknown and an area of investigation [13, 14]
Isoniazid (INH, 1952) 	Hydrazide	*katG*, *inhA*	Mycolic acid synthesis inhibitor, one of the essential components of the mycobacterial cell wall [15, 17].
Pyrazinamide (PZA, 1952)	Amide	pncA	interferes release of pyrazinoic acid, which causes intake of proton and dysfunction of the pH balance of mycobacteria. Recently it has been shown that pyrazinoic acid also targets the ribosomal protein S1, an essential protein involved in the ribosome-sparing process of trans-translation [18-21].
Ethionamide (1956) 	Thioamide	inhA, etaA/ethA	inhibits mycolic acids biosynthesis through the inhibition of *InhA* [17].
Ethambutol (EMB, 1961) 	Ethylenediamine	*embCAB*	Mycobacterial cell wall inhibition by specifically targeting the polymerization of arabinogalactane and lipoarabinomannane [22-24].
Rifampin (RIF, 1970) 	Rifamycine	rpoB	Inhibits the mycobacterial RNA synthesis by binding to the β-subunit of the DNA-dependent polymerase [25].
Kanamycin (1957) 	Aminoglycoside	rrs	Target the small subunit 30S of the ribosome [26].
Amikacin (1972) 	Aminoglycoside	rrs	Target the small subunit 30S of the ribosome [26].
Capreomycin (1963) 	Polypeptides	rrs, tlyAb	Target the small subunit 30S of the ribosome [26]
Cycloserin (1952) 	Oxazolidinone		Triggers peptidoglycan synthesis through D-alanine racemase and D-alanine ligase inhibition [27-29].
Ciprofloxacin (1960s) 	Fluoroquinolone	gyrA, gyrB	DNA gyrase inhibitor, which is the sole type II topoisomerase in this organism [30-32].
Ofloxacin (1982) 	Fluoroquinolone	gyrA, gyrB	DNA gyrase inhibitor, which is the sole type II topoisomerase in this organism [30-32].

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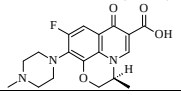
Levofloxacin (1992) 	Fluoroquinolone	gyrA, gyrB	DNA gyrase inhibitor, which is the sole type II topoisomerase in this organism [30-32].

Table 2: Pipeline for new antitubercular agents

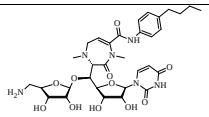
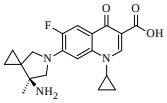
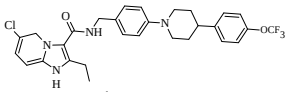
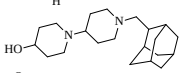
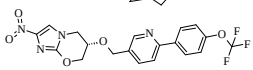
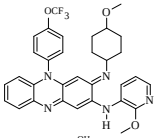
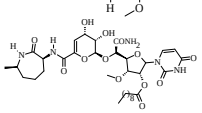
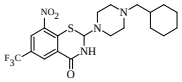
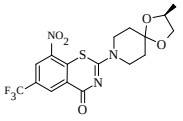
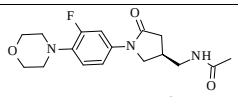
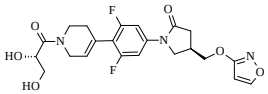
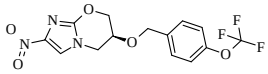
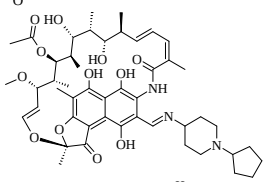
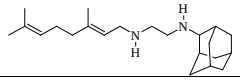
Compounds	Structure	Chemical Class	Developer	Target/Mode of action
Preclinical development				
CPZEN-45		Nucleoside antibiotic	Microbial Chemistry Research Foundation, Tokyo, Japan Lilly TB Drug Discovery Initiative NIAID, IDRI, Lilly	Inhibits a novel target WecA [36]
DC-159a		Fluoroquinolone	Japan Anti-Tuberculosis Association, JATA Daiichi-Sankyo Pharmaceutical Co	Under investigation but as other quinolone derivatives, DC-159a possibly affects GyrA activity [37,38]
Q-203		Imidazopyridine amide	Qurient Co. Ltd	Specifically targets cytochrome bc1 complex of MTB [39]
SQ-609		Dipiperidines	Sequella	Cell wall synthesis inhibitor [40]
TBA-354		Nitroimidazole	TB Alliance	Cell wall lipid and protein synthesis inhibitor [41]
TBI-166		Riminophenazines antibiotics	Institute of Materia Medica, Beijing	Targeting the outer membrane & possibly bacterial respiratory chain and ion transporters [42].
SQ-641		Capuramycins (Semi-synthetic Antibiotic)	Sequella	Translocase 1 (TL-1) enzyme inhibitors [43]
PBTZ 169		Piperazinobenzothiazinone	Innovative Medicines for Tuberculosis (iM4TB), New York	PBTZ169 binds covalently to DprE1, decaprenylphosphoryl-beta-D-ribose 2-epimerase [44a].
BTZ043		Benzothiazinone	New Medicines For Tuberculosis (NM4TB)	Acts by inhibition of decaprenylphosphoryl-b-D-ribose 2′-epimerase enzyme which abolishes the formation of decaprenylphosphoryl arabinose, a key precursor required for the synthesis of the cell-wall arabinans, thus provoking cell lysis and bacterial death [44b]

Table 3: Pipeline of drugs in Phase II

Phase II				
Compounds	**Structure**	**Chemical Class**	**Resistance**	**Target/Mode of action**
Linezolid		Oxazolidinone	rRNA 23S mutations	Protein synthesis inhibitor [45]
AZD-5847		Oxazolidinone	----------	Protein synthesis inhibitor [46]
PA-824		Nitroimidazole	Rv0407, Rv3547, Rv3261 and Rv3262 mutations	Cell wall lipid and protein synthesis inhibitor [47]
Rifapentine		Rifamycin	----------	Inhibits DNA dependent RNA polymerase [24, 48]
SQ-109		Diamine derivatives	Unknown	Cell wall synthesis inhibitor, induces iniBAC operon transcription [50]

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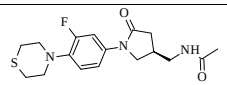
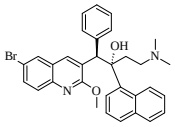
PNU-100480 (Sutezolid)		Oxazolidinone	----------	Protein synthesis inhibitor [51]
Bedaquiline (TMC207) Janssen		Diarylquinoline	atpE mutations	ATP synthase inhibitor [52,53]

Table 4: Pipeline of drugs in Phase III

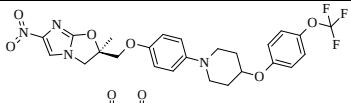
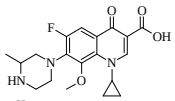
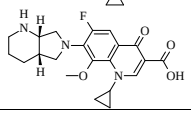
Phase III				
Compounds	**Structure**	**Chemical Class**	**Resistance**	**Target/Mode of action**
OPC-67683 (Delamind)		Nitroimidazole	Rv3547 mutations	Cell wall synthesis inhibitor [54]
Gatifloxacin		Fluoroquinolone	gyrA mutations	Protein synthesis inhibitor (DNA gyrase) [31]
Moxifloxacin		Fluoroquinolone	gyrA mutations	Protein synthesis inhibitor (DNA gyrase) [31]

Table 5: Development of Antitubercular Drug By Chemical Alteration

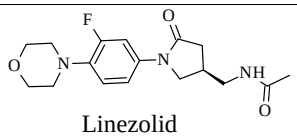
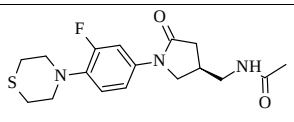
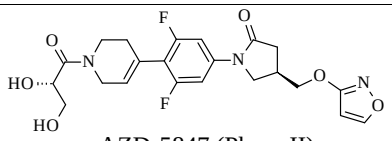
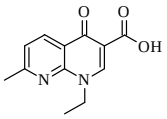
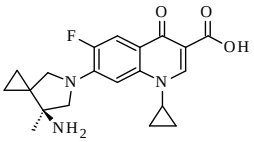
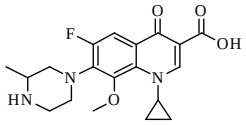
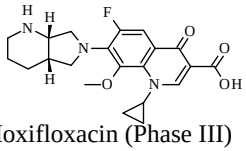
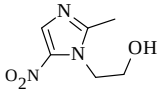
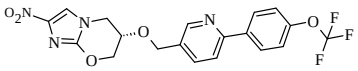
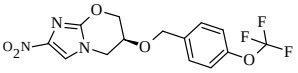
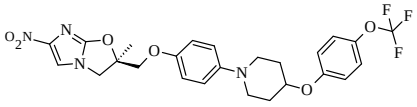
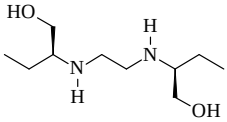
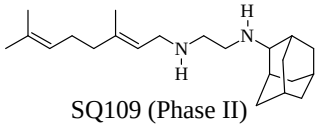
	Parent drug	**Derivatives**	
Oxazolidinone	 Linezolid	 PNU-100480 (Phase II)	 AZD-5847 (Phase II)
Fluoroquinolones	 Nalidixic acid	 DC-159a (Preclinical)	 Gatifloxacin (Phase III)
		 Moxifloxacin (Phase III)	
Nitroimidazole	 Metronidazole	 TBA-354 (Preclinical)	 PA-824 (Phase II)
		 OPC-67683 (Phase III)	
1,2-Ethylenediamine	 Ethambutol	 SQ109 (Phase II)	

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Table 6: The Developmental Pipeline for New Tb Vaccines

Stage of development	Name of the vaccine	Type of vaccine	Indication
Preclinical (GMP)	Mtb [Δ*leuCD* Δ*panCD* Δ*secA2*]	rBCG	Prime
	HBHA	Protein	Prime, Boost, Post infection & Immunotherapy
	HG85A	DNA	Boost & immunotherapy
	Hsp DNA vaccine	DNA	Boost, Post infection & Immunotherapy
Phase I	MTBVAC	rBCG	Prime
	Dar-901	WC *M. Vaccae*	Prime & Boost
	ID93/GLA-SE	Protein/adjuvant	Boost, Post infection & Immunotherapy
	AdAg85A	Viral-vectored	Prime, Boost, Post infection & Immunotherapy
Phase IIa	H56+IC31	Protein/adjuvant	Prime, Boost & Post infection
	Hybrid 4+IC31/ AERAS-404	Protein/adjuvant	Boost
	VPM 1002	rBCG expressing listeriolysin and urease deletion	Prime & Boost
	Hybrid-1+IC31	Protein/adjuvant	Prime, Boost & Post infection
	RUTI	Killed WC or Extract	Boost, Post infection & Immunotherapy
Phase IIb	MVA85A/AERAS-485	Viral-vectored	Boost, Post infection & Immunotherapy
	M72+AS01	Protein/adjuvant	Boost & Post infection
	AERAS-402/Crucell Ad35	Viral-vectored	Boost
Phase III	Mw [*M. indicus pranii* (MIP)]	Killed WC or Extract	Immunotherapy
	M. vaccae	Killed WC or Extract	Boost, Post infection & Immunotherapy

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