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ABSTRACT

Tuberculosis (TB) is a communicable airborne infectious disease caused by the *Mycobacterium tuberculosis* (MTB) that primarily affects the lungs, and can disseminate to other parts of the body. MTB is one of the most dangerous pathogens, killing about 1.4 million people annually worldwide. Although the standard treatment of TB is comprised of four anti-TB drugs, the emergence of multidrug-resistant (MDR) and extensive drug-resistant (XDR) strains in the recent past and associated side effects have affected the tailor-made regimens. Notably, existing therapies approved by the World Health Organisation (WHO) can only treat less than 50% of drug-resistant TB. Therefore, an expeditious pace in the TB research is highly needed in search of effective, affordable, least toxic novel drugs with shorter regimens to reach the goals viz. 2020 milestones End TB strategy set by the WHO. Currently, twenty-three drug-like molecules are under investigation in different stages of clinical trials. These newer agents are expected to be effective against the resistant strains. This article summarizes the properties, merits, demerits, and the probability of their success as novel potential therapeutic agents.

1. Introduction

Tuberculosis (TB) is a communicable airborne infectious disease caused by *Mycobacterium tuberculosis* (MTB) that primarily affects the lungs (pulmonary TB) but can disseminate to other sites (extrapulmonary TB) [1]. Globally, about 10 million people are infected with TB each year, and it is estimated that approximately 1.7 billion people are infected or are at risk of developing TB [1]. Based on clinical and epidemiology, population with TB infection are classified into three types: 1) latent TB infection (LTBI), which is symptomless and non-communicable; 2) active TB, which is symptomatic, communicable and molecular diagnostics can be performed; 3) subclinical TB, which is symptomless and communicable [2]. The standard treatment for MTB patients comprises four first-line anti-TB drugs, viz. Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA), and Ethambutol (EMB). The drug-resistant TB like multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), and totally drug-resistant TB (TDR-TB) made these drugs regimen ineffective [3]. After prolonged negligence, in

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1993, World Health Organisation (WHO) declared TB as a global health emergency and led to reinvigoration and re-appraisal of several TB control strategies [4].

In 1948, the first clinical trial on the treatment of TB was registered [5]. Subsequently, within a decade, several novel anti-TB drugs were entered into clinical trials, with the advent of resistant strains [3,6]. To achieve the Millennium Development Goals (2000–2015) set by the Union Nations (UN), strategies like Directly Observed Treatment Short course or DOTS (2000–2005) and Stop TB (2006–2015) were implemented by the WHO. This was followed by the End TB strategy (2016–2035) under Sustainable Development Goals set by the UN, mainly aiming to complete global eradication of TB. Unfortunately, in 2016, approximately 600,000 new cases of rifampicin-resistant TB (RIF^R-TB) were reported, of which 490,000 cases were MDR-TB 'resistant to at least isoniazid and rifampicin.' About 6% of the MDR-TB cases were termed as XDR-TB, as these exhibited additional resistance towards fluoroquinolones as well as at least 1 s-line injectable [1,7].

The current treatment of drug-susceptible TB (DS-TB) generally includes a six-month regimen comprising of INH, RIF, PZA, and EMB for initial two-months; followed by subsequent administration of INH and RIF for another four-months [8]. Whereas, the treatment of LTBI includes 6 months of INH monotherapy recommended for both children and adults in countries with low and high TB incidence. However, other alternative treatment regimens to INH monotherapy are also recommended by WHO, these are (i) newly recommended preventive treatment consisting of 3 months daily combination therapy with INH and RIF for children and adolescents (<15 years) in high TB burden countries; (ii) newly recommended preventive treatment comprising of 3 months weekly combination therapy with INH and rifapentine for children and adults in high TB burden countries; and (iii) the current recommendation, 9 months INH monotherapy, or 3–4 months RIF monotherapy, or 3–4 months INH and RIF combination, or 3 months weekly regimen of INH and rifapentine in TB low burden countries [9,10]. The treatment for RIF-susceptible and isoniazid-resistant TB (INH^R-TB) includes 6 months regimen with RIF, PZA, EMB, and levofloxacin. The composition of longer MDR-TB and RIF^R-TB regimen consists of all three drugs of Group A (i.e. levofloxacin/moxifloxacin, bedaquiline, and linezolid) combined with at least one Group B drug (i.e. clofazimine or cycloserine/terizidone). The treatment duration of longer MDR-TB may vary (9–20 months) based on the patient's response and selection of drugs. Therefore, a shorter regimen (9–12 months) may be used in case of no previous exposure to the second-line drugs (not more than one month) or exclusion of resistance to second-line drugs and fluoroquinolones [11]. Moreover, WHO approved therapies can only treat less than 50% of MDR-TB and 30% of XDR-TB [6,12].

The recent "*Global Tuberculosis Report 2019,*" published by the WHO, clearly states that most of the high TB burden countries and many WHO regions are off the track to achieve 2020 milestones of End TB strategy. The underreporting, under-diagnosis, the mismatch between estimated incidence and enrolment cases, and problems in 'cascade of care' for TB accounts for this gap including the continuous emergence of drug resistance towards anti-TB drugs [7,13]. Therefore, the research focussing on TB resistance must consider the following perspectives: (i) from the programmatic stance, the strategies should implement appropriate drug use and achieve higher adherence to the tailor-made regimens; and (ii) from clinical stance, the strategies should improvise the surveillance and monitoring methods of drug resistance, and also validate the use of existing or newer drugs or regimens [14]. The duration and drug regimen complexity itself remains the major challenges in the TB treatment, as it not only affects the tailor-made regimen adherence but also affects toxic adverse effects (mainly DR-TB regimens) and paediatric treatments [1,15]. Moreover, the coexistence of HIV with TB further contributes to drug-drug interactions between an anti-TB agent and antiretroviral therapies. The cumulative drug toxicities of combined therapies also amplify the risk of the patients towards the development of immune reconstitution inflammatory syndrome (IRIS). Therefore, an expeditious pace in the TB research is highly needed in search of effective, affordable, least toxic or nontoxic novel drugs probably with shorter regimens to reach the goals established by the WHO. Importantly, "intensified research and innovation"- the third pillar of End TB strategy must be brought into action, to overcome the existing bottlenecks with aggression.

Although bedaquiline and delamanid have been approved by many countries, these drugs possess serious adverse effects and are used only when there is no other choice of treatment for patients with MDR-TB [16]. Various strategies are being used to develop novel anti-TB drugs like- 1) new drugs targeting novel targets and acting by different mechanisms, Ex: diarylquinoline; 2) usage of existing antibiotics for the treatment of TB (e.g. ciprofloxacin); and 3) modification of existing drugs or synthesis of new compounds with better efficacy against TB [17,18].

The emergence of new drug regimens for the treatment of TB emulates a major role in reducing the rates of occurrence and death. It is an essential step to reach worldwide goals marked by WHO [19]. In continuation to our interest [20–24] in search of novel anti-TB drugs, we discuss the merits and limitations of various drug-like candidates that have entered in clinical trials, thereby facilitating the researchers involved in this field to learn from the current research in designing innovative strategies for the discovery and development of better anti-TB drugs.

2. Anti-TB agents in clinical trials

The global scenario of TB treatment has dramatically evolved in the past decades. Several newer and repurposed drugs are under clinical trials, and a couple of novel drugs have been recently approved by regulatory authorities. Various classes of anti-TB agents that entered the clinical trials successfully have been summarized in Table 1. Broadly they include the derivatives of oxazolidinone, nitroimidazole, benzothiazinone, diarylquinoline, riminophenazine, ethylenediamine, azaindole, imidazopyridine, nitrothiazole, dihydrocarbostyril, rifamycin, fluoroquinolone, benzimidazoles, and oxaboroles (Figs. 1–14). Detailed descriptions of the individual drug are given in the following subsections.

2.1. Oxazolidinones

Oxazolidinones are held as the only important category of antibiotics used against contaminations caused by gram-positive pathogens [25]. They mainly act by inhibiting the synthesis of proteins. It binds to the 50s ribosomal subunit of 23s RNA and blocks the attachment of transfer RNA [26]. From this class, maximum number of candidates have entered the clinical trials. They are linezolid, sutezolid, posizolid, delpazolid, TBI223 and Contezolid (Fig. 1).

Linezolid (**1**) is the primary representative of this category and has shown excellent potency against drug-resistant gram-positive pulmonary pathogens, including MDR-TB [27,28]. Linezolid blocks the synthesis of ribosomal protein at the early stage by inhibiting the initiation of complex formation and thus lacks cross-resistance to existing pathogens. It has shown low rates of emergence to resistant mutant genes, and excellent oral and parenteral bioavailability [28,29]. Linezolid possesses robust effectiveness in treating MDR-TB and paved the way for further oxazolidinones for the treatment of MDR-TB [27,30–33]. Clinical experience with linezolid in TB is scary, as toxicity is a major concern for a drug that has to be used for a longer time. Linezolid of dose 600 mg bis-in-die in adults is safe and generally well accepted by patients [34]. Linezolid therapy is restricted to less than 14 days in general as it may cause serious side effects like myelotoxicity, cytopenia, neuropathies, rhabdomyolysis, and lactic acidosis, etc. [35]. Thus, its use is very much limited.

Sutezolid (**2**) is a thio-analogue of linezolid [36] in which morpholinyl oxygen has been replaced by thiol group. It acts by limiting the

Table 1
Anti-tubercular agents under clinical trials.

Chemical Class	Drug	Mode of Action	Clinical Trial Phase and Identifier	Sponsor
Oxazolidinones	Delpazolid (LCB01-0371)	Inhibits protein synthesis	Phase 2, NCT02836483	LegoChem Biosciences
	Sutezolid (PNU100480)	Inhibits protein synthesis	Phase 2a, NCT01225640	Sequella, Inc.
	Linezolid	Inhibits protein synthesis	Phase 3, NCT03086486	Global Alliance for TB Drug Development
	AZD5847	Inhibits protein synthesis	Phase 2, NCT01516203	National Institute of Allergy and Infectious Diseases
	TBI223	Inhibits protein synthesis	Phase 1, NCT03758612	Global Alliance for TB Drug Development
	Contezolid	Inhibits protein synthesis	Phase 2, NCT03747497	MicuRx
Nitroimidazoles	Delamanid	Forms NO species	Phase 2, NCT00685360	Otsuka Pharmaceutical Development & Commercialization
	Pretomanid	Forms NO species	Phase 2, NCT02256696	Johns Hopkins University
	TBA354	Forms NO species	Phase 2/3, NCT04081077	Medecins Sans Frontieres and Collaborators
Benzthiazinone	BTZ043	Inhibits arabinogalactan synthesis	Phase 1b/2a, NCT04044001	University of Munich
	PBTZ169 (Macozinone)	Inhibits arabinogalactan synthesis	Phase 2 (terminated), NCT03334734 Phase 1, NCT03423030	Nearmedic Plus LLC Innovative Medicines for Tuberculosis
Diarylquinolones	Bedaquiline	Binds to ATP synthase & inhibits respiration	Phase 2/3, NCT02589782 Phase 3, NCT02754765	Médecins Sans Frontières and Collaborators Médecins Sans Frontières
Riminophenazines	Clofazimine	DNA binding leading to cell cycle disruption	Phase 2, NCT01691534 Phase 2, NCT04311502	Global Alliance for TB Drug Development National Institute of Allergy and Infectious Diseases
	TBI166	DNA binding leading to cell cycle disruption	Phase 1a, ChiCTR1800018780	Institute of Materia Medica, CAMS & PUMC
Ethylenediamine	SQ109	Inhibits cell wall synthesis	Phase 2, NCT01218217	University of Munich
Azaindole	TBA7371	Inhibits arabinogalactan synthesis	Phase 2, NCT04176250 (Halted temporarily due to COVID-19)	Bill & Melinda Gates Medical Research Institute
Imidazopyridine	Telacebac (Q203)	Binds to QcrB subunit of cytochrome bc1 & inhibits respiration	Phase 2, NCT03563599	Qurient Co., Ltd.
Nitrothiazole	Nitazoxanide	Disrupts membrane potential & pH homeostasis	Phase 2, NCT02684240	Weill Medical College of Cornell University
Dihydrocarbostyril	OPC167832	Inhibits arabinogalactan synthesis	Phase 1/2, NCT03678688	Otsuka Pharmaceutical Development & Commercialization, Inc.
Rifamycins	Rifapentine	Inhibit DNA-dependent RNA polymerase activity	Phase 2, NCT00814671	Johns Hopkins University
Fluoroquinolones	Levofloxacin	Inhibits DNA replication	Phase 4, NCT00495339	Sanofi-Aventis
Benzimidazoles	SPR720	Inhibits bacterial DNA synthesis (GyrB)	Phase 1, NCT03796910	Spero Therapeutics
Oxaboroles	GSK070	Inhibits Leucyl-tRNA synthetase	Phase 2, NCT03557281	GlaxoSmithKline

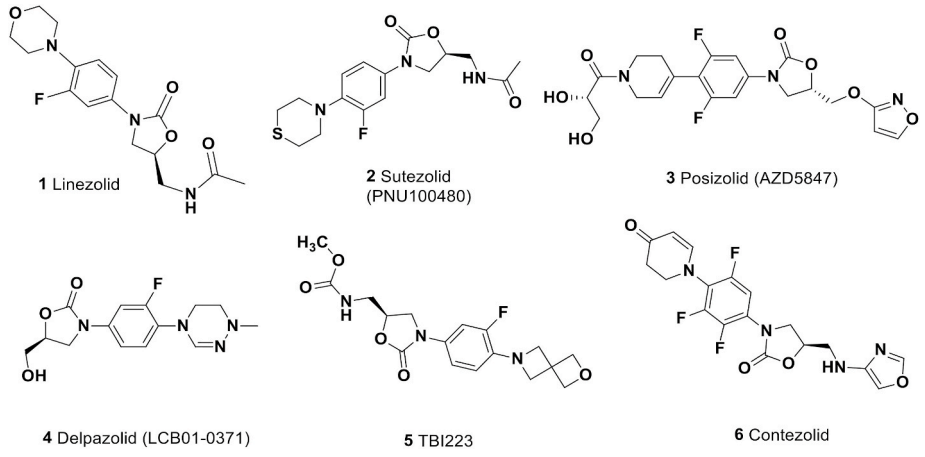


Fig. 1. Chemical structures of oxazolidinone derivatives.

protein synthesis of bacteria by blocking a new component that inhibits the design of complex formation initially [36,37]. *In vitro* and *in vivo* studies demonstrated greater antimicrobial activity and a safety profile for sutezolid. In fact, it was better than linezolid [38,39]. Sutezolid is very much tolerated at doses of 600 mg for 28 days and 1200 mg up to 14 days in adults. However, the early clinical data was not shared by Pfizer and Sequella companies (either publicly or directly). This was an obstacle for further development of this drug in spite of its better results, leading to the repetition of early research by interested parties like TB alliance. As sutezolid is still in the beginning phases of development, it is not suitable for patients and requires advanced and supporting studies before use for the treatment of TB [40].

Posizolid or AZD5847 (**3**) is another oxazolidinone derivative identified by AstraZeneca company and intended to act on gram-positive pathogens [41]. It has shown outstanding anti-TB activity against various clinical isolates of MTB. Compared to linezolid, it has exhibited improved extracellular and intracellular activity. Recently, a Phase 2a study assessed its pharmacokinetics and early bactericidal activity at

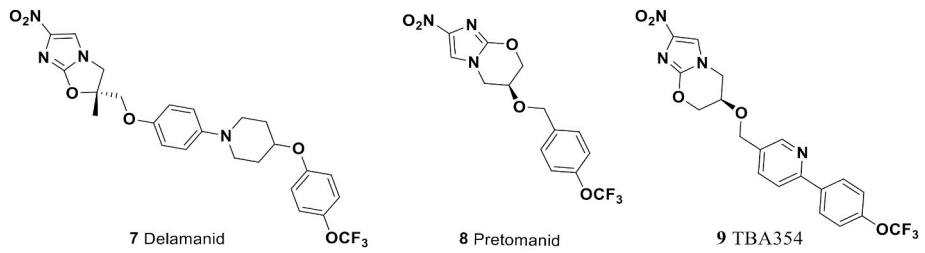


Fig. 2. Chemical structures of nitroimidazole derivatives.

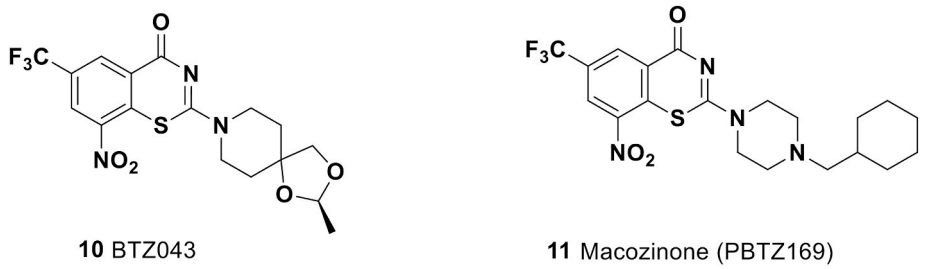


Fig. 3. Chemical structures of benzothiazinone derivatives.

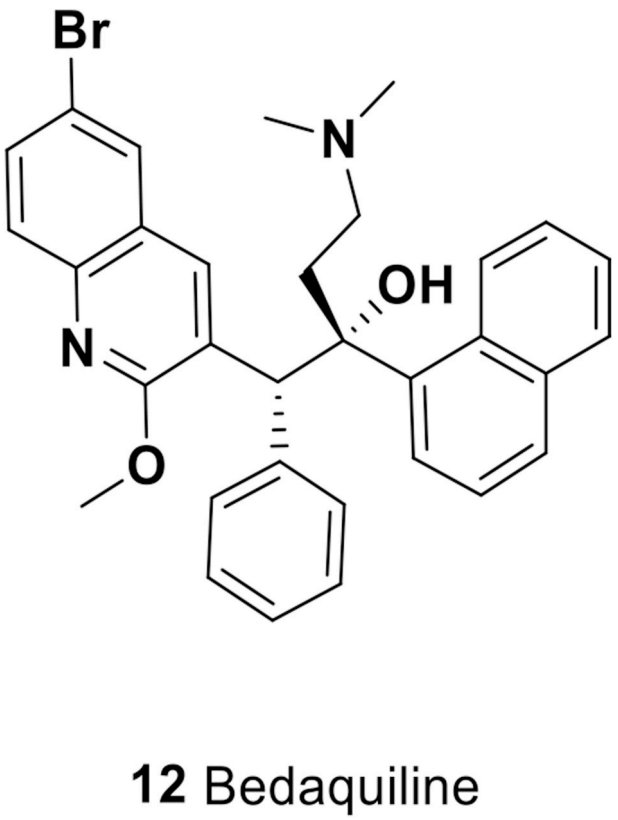


Fig. 4. Chemical structure of a diarylquinolone derivative (Bedaquiline).

several doses and schedules in patients with drug susceptible TB (ClinicalTrials.gov identifier NCT01516203). However, it has shown less favourable PK/PD than other oxazolidinones [42] and found to be associated with serious hepatic and haematological toxicities [43].

Delpazolid or LCB01-0371 (**4**) is a second-generation oxazolidinone derivative which is currently under clinical development. Although its antibacterial property is similar to other oxazolidinones, it is having comparatively better safety profile. In July 2017, US-FDA granted orphan drug status to this molecule for TB treatment and designated it as Qualified Infectious Disease Product (QIDP) in Sep 2017. It has bacteriostatic activity against nearly all Gram-positive bacteria, including MDR-TB. It has finished phase 1 clinical trial investigating the safety and tolerability of its intravenous dosage [44]. A randomized, open, active-controlled, interventional, exploratory, phase 2 trial determining the Early Bacterial Activity (EBA), safety and pharmacokinetics (PK) of oral LCB01-0371 in adult patients with smear-positive pulmonary TB has been completed in July 2019, but the results are not updated yet (ClinicalTrials.gov identifier NCT02836483**).**

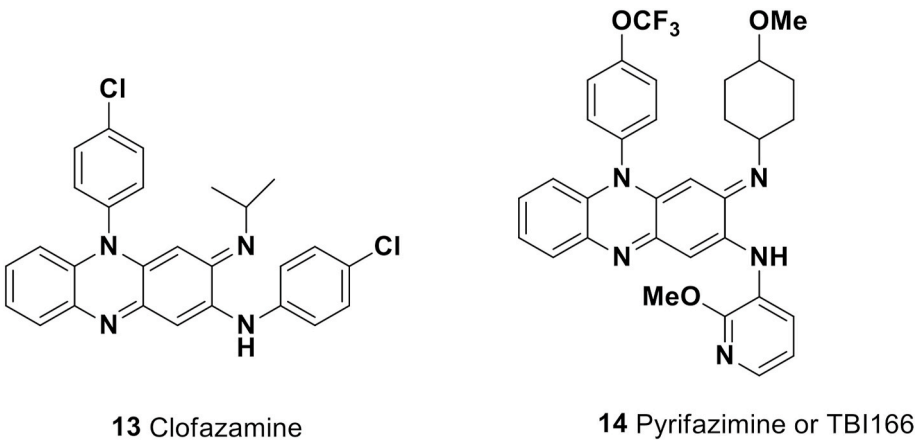
TBI223 (**5**) is another drug in oxazolidinone class undergoing phase 1 trial for TB since Jan 2019. (ClinicalTrials.gov identifier NCT03758612). It is a placebo-controlled, randomized, single ascending dose (SAD) study conducted to evaluate the safety, tolerability, and pharmacokinetics. It exhibited improved stability in microsomes and hepatocytes from five different species tested, as well as a high oral bioavailability with a moderate clearance of 6.6 mL/min/Kg at 800 mg oral dose. It displayed activity in both drug sensitive and resistant MTB, including clinical strains, and no bone marrow toxicity at the therapeutic dose.

Contezolid or MRX-1 (**6**) was selected for development as it was proposed to have a superior safety profile when compared with linezolid [45]. It exhibited promising *in vitro* and *in vivo* activity against TB [46]. It has completed a phase 2 trial against ABSSSI (ClinicalTrials.gov identifier NCT02269319) using oral dosing. Contezolid acefosamil (MRX-4) the prodrug of contezolid has been evaluated in phase 2 trial for the treatment of ABSSSI in China and USA (ClinicalTrials.gov identifier NCT03747497) using an IV to oral switch route.

2.2. Nitroimidazoles

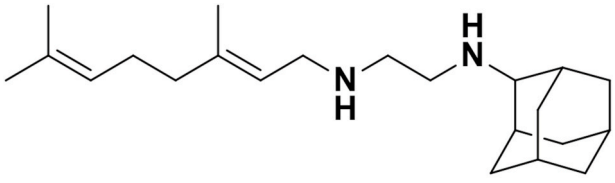
Nitroimidazoles inhibit cell growth by liberating reactive nitrogen species and block the mycolic acid synthesis. Pretomanid, delamanid, and TBA354, are three drugs (Fig. 2) belonging to this class that have entered the clinical trials.

Delamanid (**7**) mainly acts by limiting the components of the mycobacterial cell wall through inhibition of mycolic acid and keto mycolic acid synthesis. It does not restrict alpha-mycolic acid synthesis like isoniazid. It is a prodrug and metabolically stimulated to an active form by mycobacterial f420 coenzyme [47–50]. Delamanid showed *in vitro* efficacy against standardised clinical MTB species and no



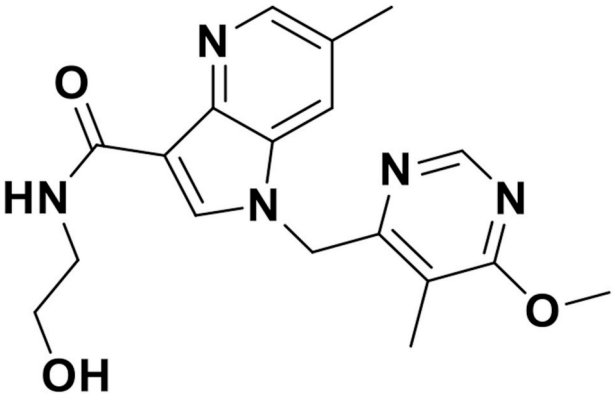
13 Clofazamine **14** Pyrifazimine or TBI166

Fig. 5. Chemical structures of riminophenazines derivatives.



15 SQ109

Fig. 6. Chemical structure of an ethylene diamine derivative (SQ109).



16 TBA7371

Fig. 7. Chemical structure of an azaindole derivative (TBA7371).

cross-resistance with RIF, EMB, INH & streptomycin [47,51,52]. FDA & European medicine agency had approved delamanid to use individually as a component of pulmonary MDR-TB up to 24 weeks but not recommended for the treatment of extrapulmonary TB & meningitis [53]. WHO recently stated the use of delamanid in patients only in case they are immune to all available four first-choice drugs [54]. Delamanid should not be suggested for pregnant women [48]. The reduction of developing fluoroquinolone resistance is possible with delamanid. It shows drug interactions, and it can be beneficial to treat patients with HIV, especially those who are unresponsive to treatment [54,55]. A phase 3 clinical study evaluated the safety and efficacy of the drug at a total daily dose of 200 mg orally for six months in patients with sputum positive pulmonary TB and MDR-TB by planning a multicenter, randomized, double-blind, placebo-controlled parallel-group trial (ClinicalTrials.gov identifier NCT01424670). This drug has been included without FDA approval by the Centre for Disease Control (CDC) funded TB Centre of Excellence (TB-COE) through a compassionate use program for XDR-TB [56].

Pretomanid (**8**) is a bicyclic subsidiary of nitroimidazofuran that has potent anti-TB activity against drug-sensitive and MDR-TB. It is currently undergoing phase 3 clinical trial [57,58]. It is a prodrug and is converted to an active form by nitroreductase enzyme, which hinders the amalgamation of cell wall lipids and proteins [58,59]. Pretomanid mainly inhibits MTB in two ways: 1) as intracellular ATP exhaustion by functioning as a nitric oxide donor and 2) by preventing the synthesis of mycolic acid, the essential component of bacterial cell wall [60,61]. Pretomanid showed antimicrobial activity against both aerobic & anaerobic organisms [61]. The resistance mechanism to pretomanid is mostly related to the loss of glucose-6-phosphate dehydrogenase (FGD1) or the deazaflavin cofactor f420 [62]. Pretomanid in combination with available drugs like bedaquiline & linezolid mentioned as Nix-TB or B-Pa-L, has shown the preliminary results to achieve cure within 6 months of treatments. This resulted in reduction of the number of drugs and an extended length of treatment (18–20 months), which is currently recommended by WHO. The six months period of treatment had led to FDA acceptance of TB alliance to accept pretomanid to research against XDR-TB responsive & non-responsive MDR-TB [63,64]. However, pretomanid in combination with bedaquiline and linezolid includes peripheral neuropathy, acne, anaemia, nausea, vomiting, headache, low blood sugar and diarrhoea. This is the second drug passed under Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) to treat serious or life threatening infections in a limited population of patients with unmet need. Investigations of pretomanid (Nix-TB) are necessary for 1) safety and efficacy, 2) dose optimization & duration of linezolid, 3) comparing delamanid & pretomanid, 4) determination of safety and dose in children [65]. Pretomanid in combination of pyrazinamide and moxifloxacin (PaMZ) were also investigated and a stage 2 trial showed better results with PaMZ regimen and it is currently under phase 3 trial [66]. Another combination of bedaquiline, pretomanid and pyrazinamide (Zenix-TB) has been found to have strong anti-TB activity than standard quadrupole drug regimen [57].

TBA354 (**9**) is another compound of nitroimidazole class designed by Auckland Cancer Society Research Centre (ACSRC) and Maurice Wilkins centre for molecular biodiscovery by collaborating with the University of Illinois and TB Alliance [67]. Its *in vitro* activity was better than pretomanid with potentially superior pharmacokinetic profile and metabolic stability [68]. However, it was withdrawn in 2016 because of side effects revealed in the initial cohort during multiple ascending dose (MAD) studies designed to test the pharmacokinetic tolerability.

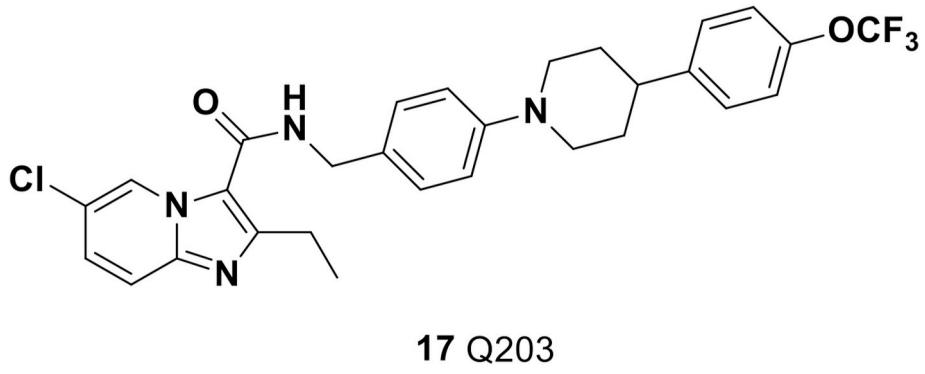


Fig. 8. Chemical structure of an imidazopyridine derivative (Q203).

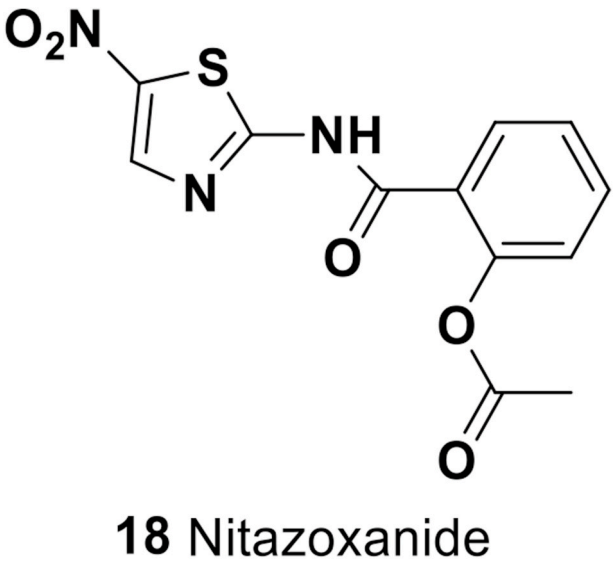


Fig. 9. Chemical structure of a nitrothiazole derivative (nitazoxanidine).

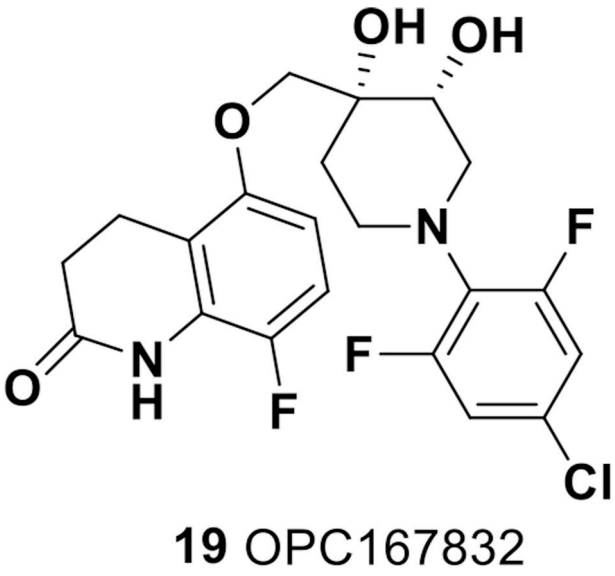


Fig. 10. Chemical structure of a dihydrocarbostyril derivative (OPC167832).

2.3. Benzothiazinones

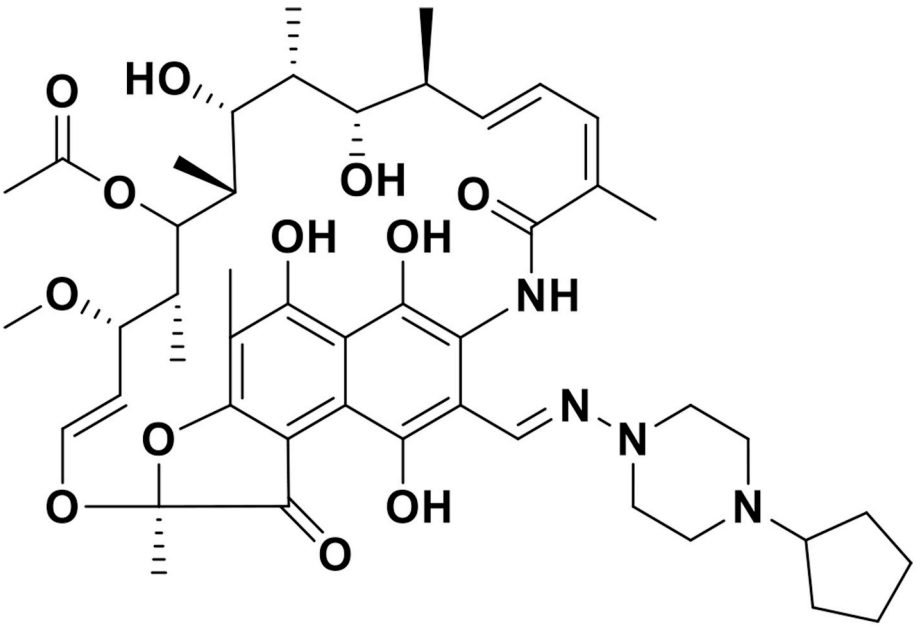
Benzothiazinones are potent anti-TB agents that mainly act by inhibiting decaprenylphosphoryl-β-D-ribose 2^1-epimerase-1 (DprE1) with essential cysteine residue by forming the covalent adduct. Two candidates (BTZ043 and PBTZ169) belonging to this scaffold have entered clinical trials (Fig. 3).

BTZ043 (**10**), a new drug with novel and potent anti-TB activity, is also undergoing clinical trials. BTZ043 is chemically known as 2-(2-methyl-1,4-dioxa-8-azaspiro [4,5]decan-8-yl)-8-nitro-6-(trifluoromethyl)-4*H*-benzo [*E*] [1,3]thiazin-4-one. It has an excellent *in vitro*, *ex vivo,* and *in vivo* activity towards MTB and also potent against drug-sensitive and MDR-TB [69]. Initially, mechanism of action of BTZ043 was considered to be occurring at the cell wall biogenesis level of transcriptome analysis. The drug target was detected at the gene level rv3790 through transcriptome analysis by using *in vitro* mutants that catalyzes the epimerization of Decaprenylphosphoryl Ribose (DPR) to Decaprenylphosphoryl Arabinofuranose (DPA), i.e., the predecessor needed for biosynthesis of the cell wall of bacteria. Recent studies demonstrated that BTZ043 reduces essential nitro group to nitroso derivative via activation in bacteria that can now interact with a cysteine residue in DprE1 and inhibits cell wall synthesis [70–72]. A randomized, double-blind, placebo-controlled SAD study was conducted, and its safety, tolerability, and pharmacokinetics of single doses of BTZ043 were evaluated in healthy volunteers in a study centre at Germany and completed in Mar 2019 (ClinicalTrials.gov identifier NCT03590600). Further in Cape Town, South Africa, Multiple ascending dose (MAD) study of BTZ043 to evaluate safety, tolerability and early bactericidal activity has been conducted from Aug 2019 and currently it is in progress (ClinicalTrials.gov identifier NCT04044001).

PBTZ169 (**11**) also acts by forming an adduct with cysteine residue and inhibits DprE1 synthesis. PBTZ169 is more potent and not a stereoselective compound, which leads to a cheaper synthesis process [73]. Due to chemically reactive metabolites formation, it results in the development of idiosyncratic toxicity, which is a risk factor in developing benzothiazinones [74]. A Phase 1 clinical study in Switzerland investigating single ascending doses of a new bio-enhanced formulation of PBTZ169 and plans to include 32 healthy male volunteers in four investigation panels got completed in April 2018 (ClinicalTrials.gov identifier NCT03423030). In 2017, a phase 2a EBA study (monotherapy for 14 days) was started in DS-TB patients in Russia and Belarus. It was completed in February 2018 with 16 enrolled patients (ClinicalTrials.gov identifier NCT03334734).

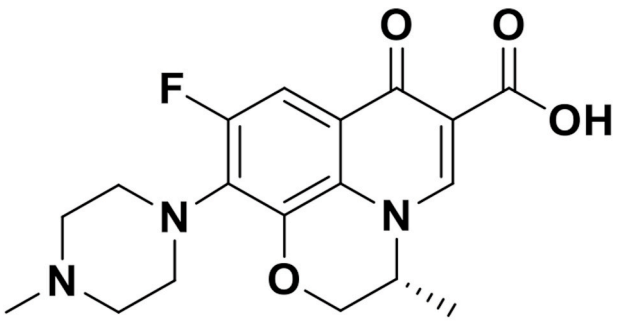
2.4. Diarylquinolones

Diarylquinolones are one of the novel anti-TB agents with most advanced series. These contain new anti-TB medications with progressed sequence [75]. *In vivo* testing against MTB encountered bedaquiline (**12**) as the most potent molecule [47]. Bedaquiline (Fig. 4) has



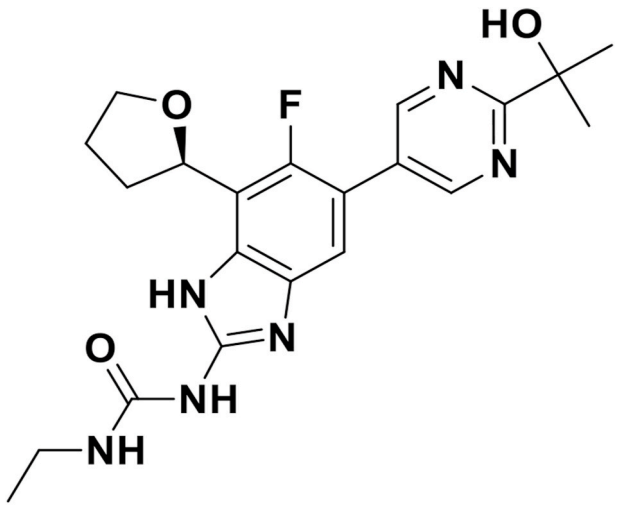
20 Rifapentine

Fig. 11. Chemical structure of a rifamycin derivative (rifapentine).



21 Levofloxacin

Fig. 12. Chemical structure of a fluoroquinolone derivative (levofloxacin).



22 SPR720

Fig. 13. Chemical structure of a benzimidazole derivative (SPR720).

exhibited very good activity against drug-sensitive, MDR-TB & XDR-TB. It has not shown cross-resistance towards first-line drugs [76]. Compared to susceptible MTB isolates, mutant drug-resistant strains possessed a greater activity indicating its unique mechanism of action. Bedaquiline incompatibility with antiretroviral therapy was observed when co-administered. It was attributed to its significant metastasis by the CPY3A4 enzyme [77]. Bedaquiline is a highly lipophilic drug that shows pharmacokinetic drug-drug interactions with RIF due to its metabolism [78]. Bedaquiline has more potency. It has only one or two similarities between mycobacterial and human protein encoded by atpE gene. Bedaquiline codes only C subunit of mycobacterium membrane-bound ATP synthase [79]. By virtue of the development of drug-resistant mutants, it was exposed that the rotor ring from the organisms F0F1 ATP synthase was the target and particularly binding with the C subunit [76]. MTB tolerates in a non-replicating state utilizing an ATP pool that is used to retain an energized membrane produced from the F0F1 ATP synthase. Bedaquiline on co-administration with PZA for 60 days lead to complete eradication of MTB from lungs indicating its synergistic effect [75]. Bedaquiline usage with alternate drugs like fluoroquinolones, macrolides, clofazimine or other drugs which inhibit CYP3A4 must be carefully combined as it has been linked with QT prolongation, a black box warning [80,81]. It was the first approved drug for MDR-TB treatment by US-FDA in 40 years. It granted accelerated approval to Johnson & Johnson's on Dec 2012 [82].

2.5. *Riminophenazines*

Riminophenazines (Fig. 5) are used in treating the patients with

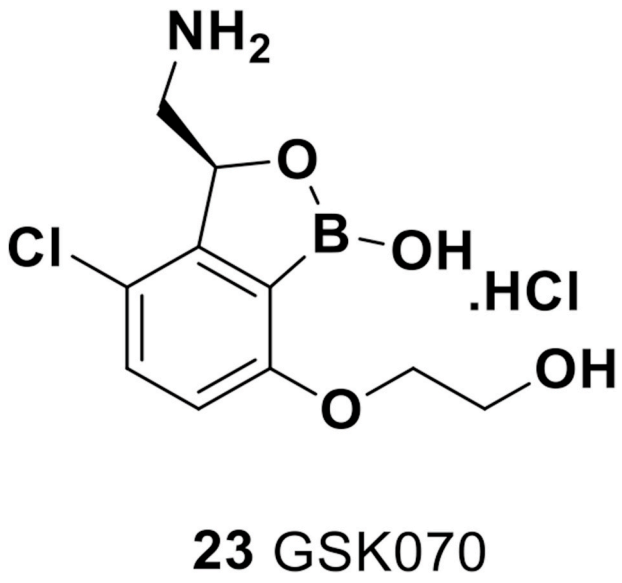


Fig. 14. Chemical structure of an oxaborole derivative (GSK070).

leprosy. WHO guidelines stated riminophenazines as "core second-line agent," though there are only a few pieces of evidence from trials on its use in TB. *In vitro* and *in vivo* studies of clofazimine (**13**) showed substantial activity towards MDR and XDR-TB [83,84]. Due to its potent activity against MTB, it was used along with other drug regimens in studies for treating MDR-TB. A very low rate of resistance development has been observed [85]. Clofazimine's prolonged use is associated with adverse effects. Clofazimine is bright red in colour with very poor solubility. It's very long half-life causes accumulation of the drug in tissues of patients in high concentrations which leads to consequent side effects, mainly pronounced skin discoloration. TB Alliance, in collaboration with the Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College (IMM, CAMS & PUMC), identified TBI166 or pyrifazimine (**14**), via lead optimization. It is an orally bio-available derivative. This moiety found to possess improved physicochemical and pharmacokinetic properties with no discoloration of the skin. At the same time, it fought TB with efficacy on par with clofazimine [86]. After testing pharmacokinetics, toxicity, and extensive efficacy evaluation, TBI166 was selected as a candidate for preclinical development. China National Science & Technology Major Project Grant and Beijing Municipal Science & Technology Commission Grant, IMM, in collaboration with Beijing Union Second Pharmaceutical Factory completed preclinical development of TBI166 and filed Clinical Trial Application to Chinese FDA in 2015, which was approved in November 2016. The phase 1 clinical trial was started in January 2018 (ChiCTR1800018780). Recently, the TBI166-bedaqualine-LZD regimen combination effect by *in vitro* and *in vivo* methods was carried out. This has shown that TBI166 has synergistic effects in combination with BDQ and LZD. Thus it has been recommended for further testing in phase 2b clinical trial [87].

2.6. Ethylenediamine

The first line drug EMB is an ethane 1,2-diamine that belongs to ethylenediamine class. SQ109 (**15**) is obtained from the pharmacophore of ethambutol belonging to a class of 1,2-ethylene diamine [88].

As ethambutol is the weakest agent in the first-line therapeutics, an initial effort has been made by using a combinatorial chemistry approach that led to the discovery of SQ109 (Fig. 6), an ethambutol analogue with improved activity [89]. The development of SQ109 is based on the results of *in vitro* and *in vivo* tests wherein it was found resistant to wild type MTB along with MDR and XDR-TB. SQ109 showed positive *in vitro* results administered along with sutezolid and bedaquiline [90]. The mechanism of action of SQ109 is associated with MmpL3 inhibition that is different from the ethambutol [89]. SQ109 is with pharmacological properties that do not require mycolic acids for its action on fungi and bacteria, and it does not require cell wall synthesis for its activity against latent cells. Further studies of SQ109 mode of action revealed that activity on the cytoplasmic membrane by further inhibition of menaquinone synthesis, cellular respiration, and ATP synthesis as a part because of dissipation of the proton motive force [91]. Simply SQ109 mode of action can be defined via intrusion in cell wall formation by targeting the mycobacterial transport protein MmpL3 [83,92,93]. SQ109 was used at different doses (maximum of 300 mg/day) with or without RIF for a period of 14 days [94]. In spite of regular effects documented, SQ109 at dispensed doses was found to be safe, secure, and well-tolerated with low to moderate gastrointestinal disorders. SQ109 has sustained activity against ethambutol resistant strains of MTB [92,93]. It is found to be safe and well-tolerated in phase 1 (ClinicalTrials.gov identifier NCT00866190), and two phase 2 clinical studies were conducted in the USA and Africa, respectively [92]. In addition to this, a phase 2b clinical study has been conducted in Russia [95].

2.7. Azaindoles

The 1,4-azaindoles identified by AstraZeneca via scaffold-morphing approach is a class of DprE1 inhibitors. Global TB alliance is now performing advanced research on azaindoles. Azaindoles are the derivatives of imidazopyridine. HTS hit showed good antimycobacterial activity but not bactericidal. Multiple scaffold transformations were conducted to increase or attain bactericidal activity [96,97]. Generally, human phosphodiesterase VI (PDE VI) enzyme is responsible for visual sensitivity that is found in rod & cones of photoreceptor cells of the eye [98]. Developed 1,4-azaindole scaffold to improve bactericidal activity were trailed for structural activity relationship optimizations by shifting the selectivity from PDE VI and thus increasing its metabolic stability [96,97]. Lead molecules obtained from these modifications exhibited a considerable decrease in PDE VI inhibition and maintained a good pharmacokinetic profile by sustaining or increasing the antimycobacterial activity [97]. This class lack cross-resistance with benzothiazones as they display the non-covalent nature of inhibition, although both groups were having the same molecular target. The single point mutation of Cys387 in the target did not show any effect, neither with the binding of 1,4-azaindoles nor with its antimycobacterial activity [96]. TBA7371 (**16**) is an azaindole class of molecules (Fig. 7), entered in the phase 2 clinical trial. It showed its effect by binding to DprE1 and thus inhibiting arabinogalactan synthesis essential for cell wall formation [71]. The possible toxicities or immune conciliated hypersensitivities of covalent DprE1 inhibitors were inhibited non-covalently by TBA7371 [99]. TB Alliance has started a phase 1 partially-blind, placebo-controlled, randomized, combined single ascending dose (SAD) with a food effect cohort and multiple ascending dose (MAD) and a drug-drug interaction study to evaluate safety, tolerability, PK and interactions between TBA7371 with midazolam and bupropion in healthy adult subjects (ClinicalTrials.gov identifier NCT03199339). A phase 2 trial to study an early bactericidal activity of TBA7371 and pharmacokinetics of TBA7371 in adults with rifampin sensitive TB and selective dose regimen for future studies has been started on Jan 6, 2020 (ClinicalTrials.gov identifier NCT04176250).

2.8. Imidazopyridine

Imidazopyridines are another class of drugs with anti-TB activity, and it was chosen because of its potent activity in macrophages and free broth media, and also the first hit was active against clinical MDR-TB isolates. Subsequent to the evaluation of the first hit, through the aid of structure-guided design, 477 analogues were synthesized. From the

synthesized analogues, Q203 (**17**) was sought to have the best activity with a MIC of 2.7 nM in broth media and 0.28 nM inside the macrophages [100]. Q203 is under development by the Qurient pharmaceutical company. The Q203 (Fig. 8) is a novel anti-TB drug of imidazopyridine class that targets the respiratory chain of MTB [83]. Its mechanism of action is associated mainly with the inhibition of the respiratory Cytochrome bc1 complex. In ATP synthesis of a bacterial cell, this complex is a necessary element of the respiratory electron transport chain. Although Q203 has a similar target comparable to bedaquiline, inhibition of ATP synthesis occurs dominantly in aerobic and hypoxic environments [100]. Q203 exhibits restriction towards intracellular and extracellular TB besides duplicating and non-duplicating bacteria [101]. Q203 exhibited a very strong anti-mycobacterial activity towards MTB by surrounding *in vitro* growth limitation against clinical isolates of MDR and XDR-TB strains at less nanomolar drug concentrations along with 100–1000 times more reduction of colony-forming units and a blocking of granuloma formation from mice models [100,102]. A phase 1 study of Q203 to evaluate the safety, tolerability, and pharmacokinetics of multiple doses was carried out in healthy male and female volunteers and found to be safe (ClinicalTrials.gov identifier NCT02858973). A phase 2 study of randomized, double-blind, placebo-controlled, dose-escalation study in healthy male and female volunteers was started on 23rd July 2018 and ended on 9th September 2019 (ClinicalTrials.gov identifier NCT03563599).

2.9. Nitrothiazoles

Nitrothiazoles are the class of antibiotics which act by inhibiting the growth of bacteria and protozoa, including inhibition of MTB. Nitazoxanide (**18**) is a type of nitrothiazole exhibiting wide range of anti-parasitic and antiviral activity discovered in 1980's. Nitazoxanide (Fig. 9) is a nitrothiazolyl-salicylamide derivative. It is now explored as a potential aid in the treatment of TB. It is presently in phase 2 clinical trial. Its mechanism of action is associated with interruption of the membrane potential and pH homeostasis [103]. It is used in a proposed randomized two-arm 14-day, early bactericidal activity study in the treatment of native, and drug-sensitive patients with uncomplicated pulmonary TB (ClinicalTrials.gov identifier NCT0684240).

2.10. Dihydrocarbostyril

Dihydrocarbostyril is another class of drugs exhibiting potent anti-TB activity. Otsuka Company announced the development of a new drug called OPC167832 (**19**) of carbostyril class. The OPC167832 (Fig. 10) mainly acts by binding to DprE1 and inhibiting the arabinogalactan synthesis, an essential enzyme needed for bacterial cell wall biosynthesis of MTB [71]. OPC167832, along with delamanid, has a better activity to standard regimen rifampicin, isoniazid, pyrazinamide, ethambutol (RHZE) [99]. The US-FDA has already approved the investigation of OPC167832 as fast track status, and clinical trials are in progress.

2.11. Rifamycins

Rifamycins are another class of antibiotics that are especially effective against MTB and thus used to treat TB. RIF is the first choice anti-TB drug belonging to the rifamycin category of antibiotics [104]. Rifapentine (**20**) considered as the sister drug of rifampicin, is presently in phase 3 clinical trial and has been tested for the treatment of drug-susceptible TB. Rifapentine (Fig. 11) mainly acts by inhibiting DNA-dependent RNA polymerase activity in sensitive cells. It only inhibits bacterial RNA polymerase but does not interfere with the mammalian enzyme. The purpose of this study (ClinicalTrials.gov identifier NCT00023452) is to determine whether one or two four-month regimens of TB treatment are as effective as a standard six-month regimen for the treatment of pulmonary TB. All three regimens are administered daily, seven days each week, with direct observation of each dose by a health-care worker at least five of the seven days of each week.

2.12. Fluoroquinolones

Fluoroquinolones are a class of bactericidal agents, especially targeting the synthesis of bacterial DNA. Levofloxacin (**21**) as shown in Fig. 12, is a drug belonging to fluoroquinolone that has been tested for its activity towards MTB and MDR-TB. It mainly acts by interacting with DNA gyrase enzyme and suppressing DNA replication [105]. A phase 2 study of levofloxacin with smear and culture-positive pulmonary MDR-TB to determine its dose and exposure that results in a greater reduction of MTB with acceptable tolerability in 100 adults in Peru and South Africa has been conducted (ClinicalTrials.gov identifier NCT01918397).

2.13. Benzimidazoles

Benzimidazoles are the class of drugs with wide biological activities. SPR720 (**22**) is the novel anti-TB drug that belongs to the category of aminobenzimidazole. The SPR720 (Fig. 13) inhibits the DNA gyrase B, which is the topoisomerase, and blocks the replication of DNA. SPR720 inhibits the MDR-TB. It results in anorexia, dizziness, vomiting, and nausea. It is presently under phase 1 clinical trial sponsored by the company Spero therapeutics in collaboration with Bill & Melinda Gates Medical Research Institute. A phase 1 study of randomized, double-blind, placebo-controlled, single, and multiple ascending dose (SAD and MAD) trial is also planned (ClinicalTrials.gov identifier NCT03796910).

2.14. Oxaboroles

GSK070 (**23**), as shown in Fig. 14, is an oxaborole moiety with a new mode of action, is under development for the treatment of TB. It selectively inhibits enzyme Leucyl t-ribose nucleic acid synthetase (LeuRS) and thereby suppresses the protein synthesis in MTB [106]. *In vivo* anti-TB activity of GSK070 has been demonstrated in the standard acute and chronic murine assays. Further, when it was administered in combination with new anti-TB drugs, it was found to be more active than standard care. A phase 2, open-label trial to investigate the early bactericidal activity, safety, and tolerability of GSK070 in participants with drug-sensitive pulmonary TB is also planned [107] (ClinicalTrials.gov identifier NCT03075410).

3. Summary and future perspectives

There is a compelling demand to develop novel anti-TB drug candidates with a novel mode of action against MTB, as TB is becoming a worldwide burden due to the development of resistance to the existing drugs. Drug-resistant TB treatment has expanded significantly over the last years. The diversified categories and systems of operation of the new anti-TB agents have constituted hope that the remarkable correction of DR-TB may be conquered. Based on problems faced due to TB, US-FDA had recently approved drugs like pretomanid (2019), delamanid & bedaquiline (2017) due to their better activity against MDR-TB in a restricted manner. However, delamanid and bedaquiline causes significant adverse effects. Nonetheless, it is anticipated that treatment and survival rate of patients will improve in the near future. Currently, twenty three drug-like molecules are undergoing clinical trials and the success of these molecules might fulfil the future hope of developing a universal new regimen suitable for all types of TB patients, either susceptible or resistant to all the existing anti-TB drugs.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Abbreviations

AIDS	Acquired Immuno-Deficiency Syndrome
CDC	Centers for Disease Control and Prevention
DOTS	Directly Observed Treatment- Short course
DPA	Decaprenylphosphoryl Arabinofuranose
DPR	Decaprenylphosphoryl Ribose
DR-TB	Drug-Resistant Tuberculosis
DS-TB	Drug Susceptible Tuberculosis
EBA	Early Bacterial Activity
EMB	Ethambutol
HIV	Human Immunodeficiency Virus
HR-TB	Isoniazid-Resistant Tuberculosis
IFNγ	Interferon-γ
INH	Isoniazid
IRIS	Immune Reconstitution Inflammatory Syndrome
LPAD	Limited Population Pathway for Antibacterial and Antifungal Drugs
LTBI	Latent Tuberculosis Infection
MAD	Multiple Ascending Dose
MDR-TB	Multi-Drug Resistant Tuberculosis
MTB	*Mycobacterium tuberculosis*
PD	Pharmacodynamics
PDE VI	Phosphodiesterase VI
PK	Pharmacokinetics
PZA	Pyrazinamide
QIDP	Qualified Infectious Disease Product
RIF	Rifampicin
Rpf	Resuscitation-Promoting Factor
RR-TB	Rifampicin-Resistant Tuberculosis
TB	Tuberculosis
TB-COE	Tuberculosis Centre of Excellence
TDR-TB	Totally Drug-Resistant Tuberculosis
TLR9	Toll-Like Receptor 9
TNF	Tumor Necrosis Factor
US-FDA	United States Food and Drug Administration
VEGF-A	Vascular Endothelial Growth Factor A
WHO	World Health Organisation
XDR-TB	Extensively Drug-Resistant Tuberculosis

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