Novel candidates in the clinical development pipeline for TB drug development and their Synthetic Approaches

Amit Kumar[a], Bidhu Bhusan Karkara[a,b], Gautam Panda[a]*

[a] Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow 226031, UP, India.

[b] Department of Pharmaceutical Science, Vignan's Foundation for Science, Technology and Research University, Guntur 522213, AP, India[1]

E-mail: gautam.panda@gmail.com, gautam_panda@cdri.res.in; Phone: 915222772450, ext 4659, Fax: 915222771941

[1] Current Address

Abstract

Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis* (Mtb) and one of the deadliest infectious diseases in the world. Mtb has the ability to become dormant within the host and to develop resistance. Hence, new antitubercular agents are required to overcome problems in the treatment of multidrug resistant-Tb (MDR-Tb) and extensively drug resistant-Tb (XDR-Tb) along with shortening the treatment time. Several efforts are being made to develop very effective new drugs for Tb, within the pharmaceutical industry, the academia, and through public private partnerships. This review will address the anti-tubercular activities, biological target, mode of action, synthetic approaches and thoughtful concept for the development of several new drugs currently in the clinical trial pipeline (up to October 2019) for tuberculosis. The aim of this review may be very useful in scheming new chemical entities (NCEs) for Mtb.

Keywords: *Mycobacterium tuberculosis* (MTb), MDR-Tb, XDR-Tb, Bedaquiline, Delamanid, Pretomanid.

1. Introduction:

Tuberculosis remains a very big problem because it is one of the top 10 causes of death globally and is the leading cause of death from a single infectious agent (ranking above HIV/AIDS). According to global tuberculosis report 2020 by WHO, globally about 10 million people develop tuberculosis in 2019. HIV is important driver of tuberculosis epidemic. The peoples living with HIV are being at high risk of developing tuberculosis disease and dying from it. In addition to this, the big challenge is drug resistance counting half million cases per year and high

mortality among those cases [1]. The report also highlighted an estimated 1.2 million TB deaths among HIV-negative people in 2019 (a reduction from 1.7 million in 2000), and an additional 208 000 deaths among HIV-positive people (a reduction from 678 000 in 2000). The numbers in Tb cases and deaths are declining very slowley [2] which may be the effect of the growing interest in tuberculosis and control of its spreading in the recent years worldwide [3]. The TB strategies of WHO are in planned way to reduce more global burden of Mtb by reducing incidence and Tb death by 2035 [4]. The one forth population of the world has been affected with MTB. However, the strong immunity is capable to clear the MTb infection but the challenges arise in the patients with HIV infection and/or diabetes mellitus which suffer with immunocompromised condition. This global Tb control can be accomplished by the development rapid and accurate diagnostic tools especially for latent Tb infaction (LTBI) and drug-resistant Tb. For the treatment of latent Tb, the mycobacterial Rv3097c-encoded lipase LipY is considered as one of the important target. This enzyme is involved in the hydrolysis of triacylglycerol stored in lipid inclusion bodies for the survival of dormant mycobacteria. The overexpression of Rv3097c-encoded lipase (LipY) enzyme increases the virulence of *Mycobacterium tuberculosis* resulting more mortality and bacterial load in lungs with worsening lung morphology and pathology as compared to H37Rv [5]. However, orlistat and saxena *et. al.* [6] reported 4-hydroxy quinoline based small molecules have shown good inhibitory activity against LipY enzyme. Hence, these molecules have opened the door for the discovery of drugs against latent Tb. Moreover, the development of new Tb vaccines which can efficient in pre- and post-exposure of the Tb infection is also the way to control more new Tb cases [7].The current short-course anti-tubercular therapy needs a minimum of six months of treatment consisting of two months of intensive phase of treatment with the first-line drugs including isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB), followed by another four months of therapy with INH and RIF alone. Mostly it has been found that Tb infects the persons of poor health, sanitation and immunity particularly weaker section of the society. So DOTS must be continued in the TB infected patients without any dose interruption. Dose interruption produces MDR-TB [8]. World Health Organization (WHO) has recommended the composition of regimens for longer MDR or rifampicin-resistant tuberculosis [9]. According to that drugs have been categorized into three groups; Group A: levofloxacin/moxifloxacin, bedaquiline, linezolid. Group B: clofazimine, cycloserine/terizidone. Group C: ethambutol, delamanid, pyrazinamide, imipenem–cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, *p*-aminosalicylic acid. For the treatment, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. WHO has also recommended a shorter all-oral bedaquiline-containing regimen for multidrug- or rifampicin-resistant tuberculosis . According to that A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is

recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with secondline TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. The prior mode of treatment of relapsed and interrupted Tb (MDR-Tb) would be the use of drugs that act with novel mode of action like Bedaquiline (in phase III). In the field of new anti-tubercular drug discovery, some molecules (figure-I) have shown significant outcomes against *Mycobacterium tuberculosis*. In this context, Brodin et. al. [10] identified dinitrobenzamide derivatives (DNB) as Decaprenyl-Phosphoribose 2′ Epimerase inhibitors for intracellular mycobacterial strain through High Content Screening. Among them, DNB1 showed prominent activity against *M. tuberculosis* and also for extensively drug resistant (XDR) strains. DNB derivatives inhibited the decaprenyl-phospho-arabinose synthesis catalyzed by the decaprenyl-phosphoribose 2′ epimerase DprE1/DprE. Thus, formation of lipoarabinomannan and arabinogalactan was inhibited. This new target opened the door for fighting against emerging XDR-Tb. Additionally, new generation of quinolone derivative, TBK 613 was also showing promising anti-tubercular activity [11] with possible efficacy against fluoroquinolone-resistant strains [12]. Another molecule of quinolone family, DC-159a was DNA gyrase A inhibitor that demonstrated dose dependent bactericidal activity and the MIC_{90} was found to be 8 times lower than MFX (moxifloxacin) [13]. Bogatcheva et.al. [14] reported the identification of SQ609 as a lead compound from a library of dipiperidines. Dipeperidine ring containing, SQ609 was also very effective against MTb infected macrophages [15]. Prolonged therapeutic effect and prevention of weight loss were main advantages of SQ609. Analogues of capuramycin, SQ641 inhibited the biosynthesis of peptidoglycan (PG) by blocking the translocase I (TL1) enzyme [16,17,18] and found potent anti-tubercular agent. SQ641 was synergistic with ethambutol (EMB) and additive with isoniazid (INH) [19,20,21]. New isoniazid derivative, LL-3858 (INH-pyrrole hybrid) has shown bactericidal activity against both drug sensitive and multidrug resistant Tb [22]. A novel oxazolidinone, AZD5847 (Posizolid), exhibited improved *in vitro* bactericidal activity against both extracellular and intracellular *M. tuberculosis* compared to that of linezolid. Moreover, AZD5847 demonstrated the additive effect when tested along with a variety of conventional TB agents that has shown AZD5847 may function well in combination therapies. Like, linezolid, AZD5847 caused impairment of the mycobacterial 50S ribosomal subunit [23]. AZD5847 has completed phase II studies in December 24, 2013 [24]. However, Development of Posizolid (AZD 5847) for the treatment of tuberculosis has been discontinued (AstraZeneca's pipeline, February 2016) [25].

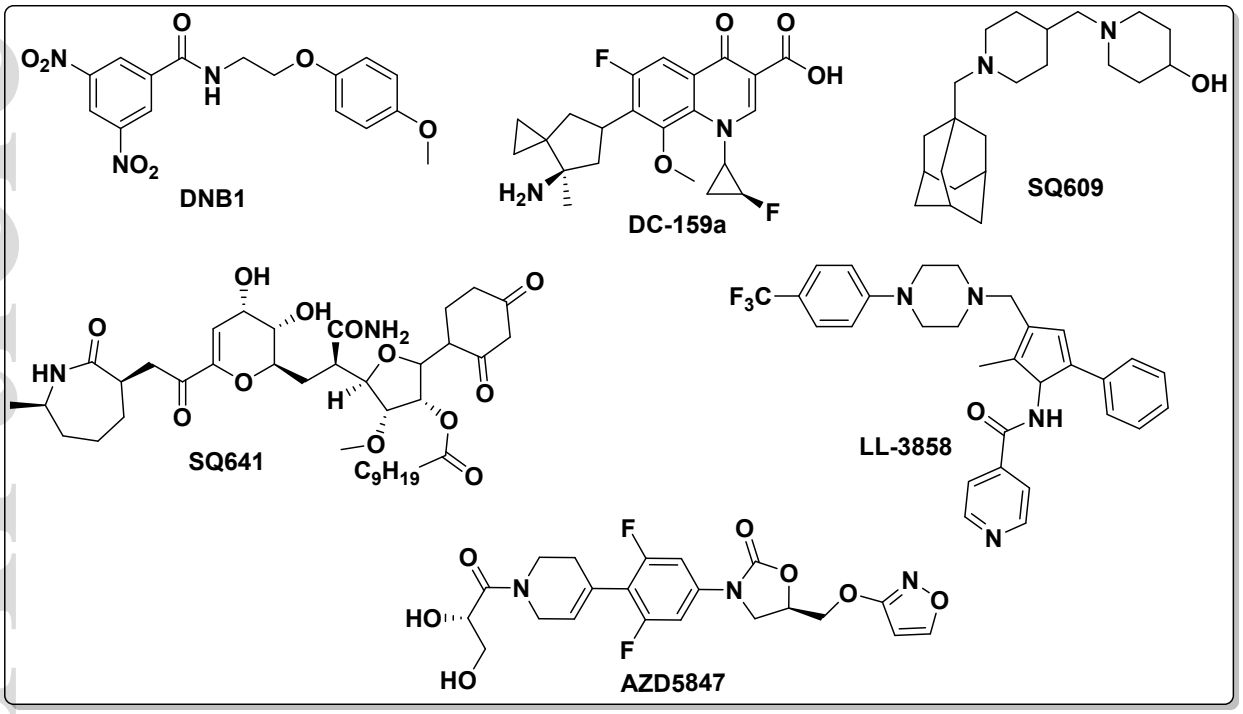


Figure I: Sructures of DNB1, DC-159a, SQ609, SQ641, LL-3858 and AZD5847.

Our research group is consistently working in the area of development of new anti-tubercular agents [26,27,28,29,30,31]. Because of our constant efforts, we have reported CDRI S006-830 as lead molecule for Mtb [32]. The purpose of this review is to focus on the synthesis, biological target existing clinical evidence as well as completed and ongoing clinical trials for various drugs in pipeline for development for treatment of Mtb. Drug candidates with the strongest evidence have been included in this review with a focus on the mechanism of action pertaining to the disease process.

Over the past decade, there has been a conscious and concerted effort to fill the Tb-drug pipeline with new target/inhibitor pairs. In this review, we will provide an update on the progress of anti-tubercular drugs. All drugs with details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical and ongoing projects without a lead compound series identified: https://www.newtbdrugs.org/pipeline/discovery (up to October 2019) have been included. This review categorizes the various anti-Tb candidate drug molecules according to their perceived state of development for the Tb indication **(A) Discovery (B) Preclinical development; a. Early stage of development:** GSK3011724A/GSK724 **(**DG167**)**, GSK839, CPZEN-45, Spectinamide-1810, TB-47. **b. GMP & GLP-Compliant Preclinical Toxicology Studies:** GSK-286 (GSK 2556286), Sanfetrinem, TBAJ-587, TBAJ-876, **(C) Clinical development; a. Phase I:** TBI-223, SPR720, BTZ-043, TBA-7371, PBTZ-169, TBI-166. **b. Phase II:** GSK-656, OPC-167832, Telacebec (Q203), Delpazolid, Sutezolid, SQ-109. **c. Phase III:** Bedaquiline, Pretomanid (PA-824), Delamanid.

2. TB drug development and their Synthetic Approach

2.1. Discovery

In recent years, persistent efforts in this direction have led to several lead molecules progressing to clinical trials which exhibited promising activities against drug-sensitive and drug-resistant strains of the causative organism Mtb. For example, a library of *trans* 6-methoxy-1,1-dimethyl-2-phenyl-3-aryl-2,3-dihydro-1H-inden-4- yloxy alkyl amines was showing prominent antimycobacterial activity against drug sensitive and multidrug resistant strains of *Mycobacterium tuberculosis* with MIC between 1.56 and 6.25 µg/ml [33]. Additionally, modified analogues of the antiprotozoal drug Nitazoxanide (NTZ) were exhibited potent inhibitors of Mtb H37Rv strain with an excellent ability to avoid resistance [34]. Moreover, novel substituted 4-arylthiazoles were also reported as potent anti-tuberculosis agents particularly for the treatment of multi-drug resistant Tuberculosis (MDR-Tb) and extensively drug resistant tuberculosis (XDR-Tb) [35]. Many new anti-tubercular agents have been identified through phenotypic screens. Many promising chemotypes/ inhibitors and enzyme targets have been identified that may be very useful in discovery of lead compounds with great potencies against MTb [36]. The availability of molecules with whole-cell activity discovered by high-throughput screening (HTS) [37,38,39,40,41,42,43] combined with powerful chemical genetic, 'omics' and imaging technologies to get the (MOA) [44,45] and the target identification along with validation, have created a rich resource for priming the pipeline with hits and/or new targets.

2.1.1. Indazole sulfonamides

β-ketoacyl synthase, KasA, was identified as the target of an indazole sulphonamide.

2.1.2. Squaramide based compounds

It inhibits the ATP synthase with good efficacy in the mouse model of TB infection are in the lead optimization phase [46].

2.1.3. Diarylthiazoles

It is an antimycobacterial scaffold potentially targeting PrrB-PrrA two-component system. PrrBA is a conserved, essential regulatory mechanism in Mtb and has been shown to have a role in virulence and metabolic adaptation to stress [47].

2.1.4. DprE1 Inhibitors

Benzothiazinone (BTZ) compounds act by covalently binding the active site of decaprenylphosphoryl-β-D-ribose 2epimerase (DprE). DprE1, in connection with DprE2, epimerizes decaprenylphosphoryl ribose to decaprenylphosphoryl arabinose in an essential step of arabinogalactan and lipoarabinomannan biosynthesis [48].

2.1.5. Direct InhA Inhibitors

InhA gene is essential for the biosynthesis of mycolic acid. Mycolic acid is the one of the part of mycobacterial cell wall. Isoniazid inhibits this InhA gene to suppress the mycolic acid biosynthesis. However Isoniazid itself needs activation by KatG catalase. In case of isoniazid resistance, this KatG gets mutations leading to the inability to activate the drug. The new goal could be development of new compounds that compounds that are capable to reach

the same clinical efficacy as isoniazid through bypassing the requirement of KatG activation and directly inhibiting InhA. The thiadiazoles series was identified by GSK under the TB Alliance partnership. Currently, a thiadiazole (GSK-693) is being used to deepen the knowledge of direct InhA inhibitors in combination.

2.1.6. Mtb energy metabolism

The generation of ATP is crucial for *mycobacterium tuberculosis* to get energy which is accomplished through respiration by the electron transport chain (ETC) and ATP synthesis (oxidative phosphorylation). Hence, energy metabolism of Mtb could be good targets for the development of new Mtb drugs. Bedaquiline (BDQ) is an anti-TB drug targeting the Mtb F1FO ATP synthase [49]. Despite a very good efficacy for the treatment of MDR-Tb and XDR-Tb, clinical resistance has already been observed after three years of market approval [50,51]. Moreover, an undesirable toxicity profile, like phospholipidosis and cardiovascular risks stop a global use of the drug, and is restricted to treatment of the most difficult Tb cases. High lipophilicity (clogP =7.25) and cationic, amphiphilic properties of bedaquiline were found to main reasons of tissue accumulation causes the toxicity. Conformationally-constrained and bisquinoline (replacing a phenyl substituent of TMC207 with a quinoline moiety) analogs of TMC207/bedaquiline have been reported to gain insight into the molecular determinants of the activity of TMC207. However, drug rigidity of lateral chain resulted in a decrease in activity but bisquinolines demonstrated potent antitubercular activity in *in vitro* experiments and also in *in vivo* mouse model of the disease [52]. Additionally, a novel series of aryl sulfonamide derivatives of amodiaquine [53,54] have been investigated for selective mycobacterial ATP synthase inhibitory activity against both replicating and non-replicating *M. tuberculosis* resulted in ATPase inhibitory activities (IC50) of these compounds range between 0.36 and 5.45 μM [55,]. Moreover, Very recently reported of 3,5-dialkoxypyridine analogues (DARQ) of BDQ, TBAJ-876 and TBAJ-587 have less lipophilic along with higher clearance that showed lower cardio-toxic potential [56].

2.1.7. MmpL inhibitors

Mycobacterial membrane protein large (MmpL) belonging to the RND (resistance-nodulation-division) family of transporters have been discovered whose primary function includes metabolite transport across the cytoplasmic membrane. MmpL3 is essential and an emerging new target for Tb drug discovery.

2.1.8. Macrolides

Macrolides are antibiotics used for bacterial infections. Macrolides exhibited the inhibition of protein synthesis in the bacteria. Macrolide molecules could show improve potency and pharmacokinetics for the treatment of Tb [57].

2.1.9. Mycobacterial Gyrase Inhibitors

DNA gyrase, a type II topoisomerase introduces negative supercoiling of DNA in the bacteria. DNA gyrase has major role in DNA replication for its survival. Moreover, DNA gyrase also helps in relaxation, cleavage and

catenation activities. Hence, Inhibitors **[**58,59**]** of DNA gyrase could be targeted for developing potential new anti-Tb drugs [60].

2.1.10. Arylsulfonamides

Sulfone and indoline-5-sulfonamides [61] have been shown to inhibit tryptophan synthase allosterically by binding to the α/β-subunit interface of this enzyme.

2.1.11. Inhibitors of MmpL3- MmpL3

It is promiscuous cell wall target. MmpL3 serves as the flippase for transport of mycolic acids across the inner membrane [62] and has the attractive feature of being a highly vulnerable target in-vivo [63].

2.1.12. PKS13

It catalyses the final step in Mycolic Acid biosynthesis. The druggability of Pks13 was confirmed by demonstrating that it is the target of the benzofuran, TAM1 [64] and a series of thiophene (TP) compounds [65]. Optimization of TAM1 led to the development of TAM16, which inhibits the thioesterase activity of PKS13.

2.2. Preclinical Development

2.2.1. Early stage of development

2.2.1.1. Indazole sulfonamide GSK-724 (DG167)

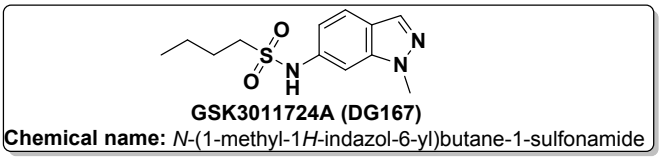
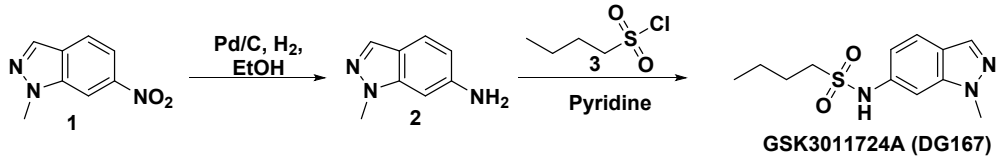


Figure 1. GSK3011724A (DG167).

GSK3011724A/GSK724 **(**DG167**) 1,** a derivative of indazole sulfonamide is undergoing early stage development of preclinical studies **(Figure 1).** It is being developed by GlaxoSmithKline and Rutgers, the State University of New Jersey [66]. GSK3011724A is a small molecule actve against *Mycobacterium tuberculosis* and identified from the aforementioned 228 phenotypic screening hits [67]. Abrahams et al identified the KasA as the cellular target of GSK3011724A in *Mycobacterium tuberculosis* [68]. The *β*-ketoacyl-ACP synthases (KasA) is an essential component of fatty acid synthase-II (FAS-II) system. Fatty acid synthase-II (FAS-II) system is responsible of synthesis of mycolic acids of cell wall of *Mycobacterium tuberculosis.* Kumar. P. et. al. described GSK3011724A as a binary inhibitor of *β*-ketoacyl-ACP synthases (KasA) in *Mycobacterium tuberculosis*. DG167 possessed potent whole-cell activity against *M. tuberculosis*, with a MIC of 0.39 μM [69]. It also demonstrated synergistic lethality in combination with INH and a transcriptional pattern consistent with bactericidality and loss of persisters [70]. Freundlich et al. [71] reported synthetic procedure as illustrated in **scheme 1.** 1-methyl-6-nitro-1H-indazole **1** was reduced to 1-methyl-1H-indazol-6-amine **2** in presence Pd/C and H_2 in ethanol solvent. Finally, 1-methyl-1H-indazol-6-amine 2 was reacted with butane-1-sulfonyl chloride **3** in pyridine environment to furnish DG167.



Scheme 1. Synthetic approach for synthesis of GSK3011724A (DG167).

2.2.1.2. Tetrazole benzene sulfonamide (GSK839)

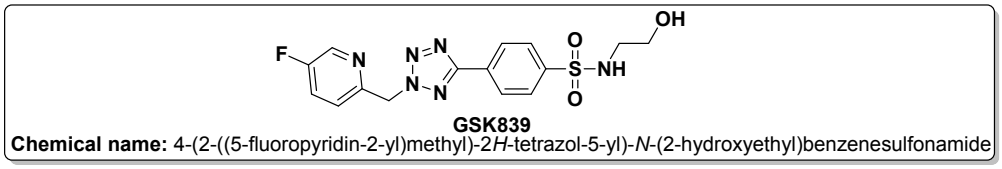
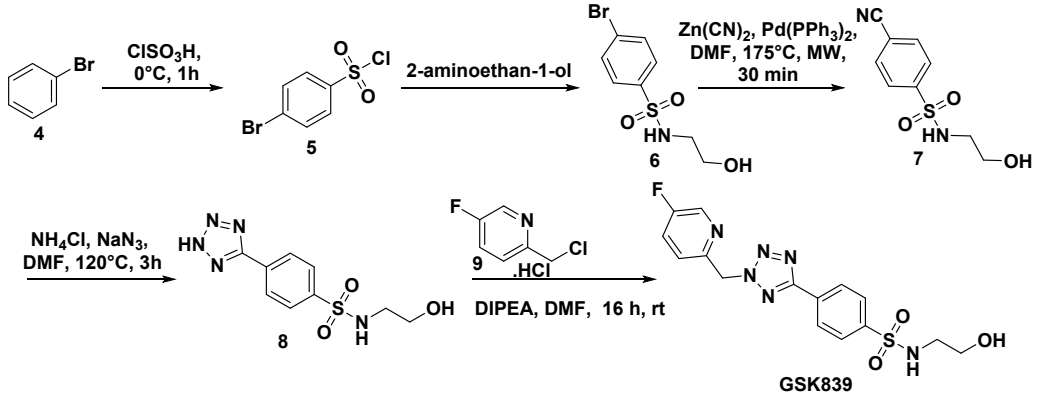


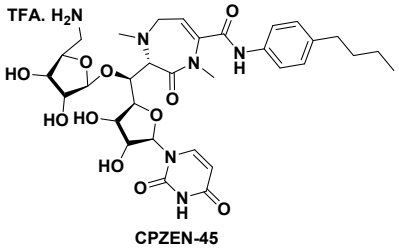
Figure 2. GSK839

GSK839 is a preclinical candidate for Tuberculosis treatment that was identified through a Wellcome Trust sponsored programme. GSK839 is from tetrazole class of molecules which exhibited the selective inhibition of tryptophan synthase of MTb and its MIC value was found to be in the ranges from 0.07 to 0.16 μM. **(Figure 2)**. The whole process for synthesis of GSK-839 was reported by Gallarado et al. [72] as shown in **scheme 2**. Bromobenzene **4** on chlorosulfonation with chlorosulfonic acid provided bromobenzene sulfonyl chloride **5**. Bromobenzene sulfonyl chloride **5** and2-aminoethanol were coupled together to afford bromohydroxyethyl benzene sulfonamide **6**. Palladium catalysed cyanation reaction of bromohydroxyethyl benzene sulfonamide **6** with the help of Zn $(CN)_2$ under microwave irradiation afforded nitrile compound **7**. In the next step, cycloaddition of nitrile with NaN_3 and NH_4Cl produced 1-H tetrazole **8**. This 1-H tetrazole **8** on alkylation with HCl salt of 2-(chloromethyl)-5-fluoropyridine **9** in DMF as solvent and DIPEA as base afforded the final product GSK839.



Scheme 2. Synthesis of GSK839.

2.2.1.3. CPZEN-45

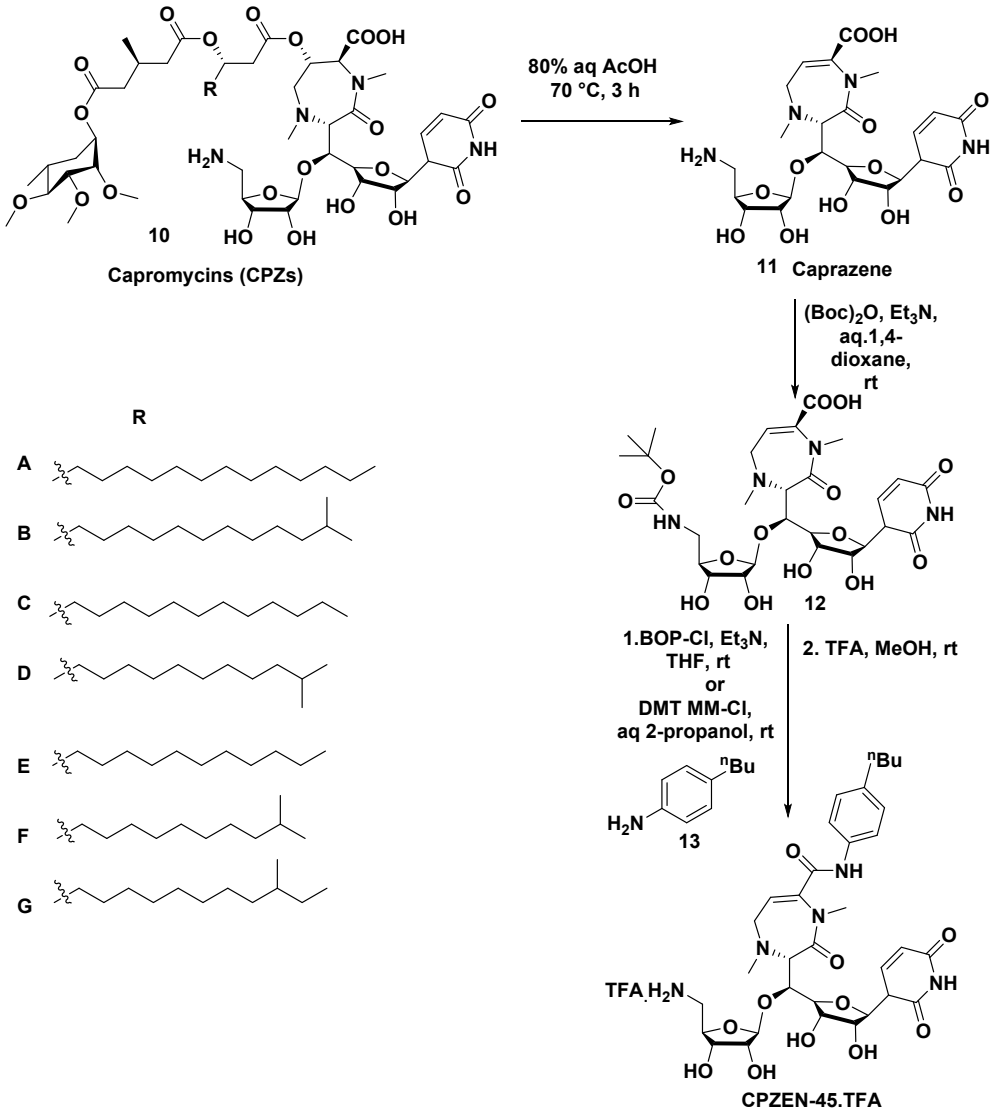


CPZEN-45

Chemical name: (*S*)-2-((S)-(((2*S*,3*S*,4*R*,5*R*)-5-(aminomethyl)-3,4-dihydroxytetrahydrofuran-2-yl)oxy)((2*S*,3*R*,4*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)-*N*-(4-butylphenyl)-1,4-dimethyl-3-oxo-2,3,4,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide. TFA

Figure 3. CPZEN-45.

A nucleosidic antibiotic, CPZEN-45 as trifluoroacetate salt is a preclinical candidate drug for MTb (**Figure 3)**. Its water solubility is about >10 mg/mL in salt form. Basically, it was a caprazamycin obtained from Streptomyces sp. which was first described in 2003 by investigators at the Microbial Chemistry Research Foundation (MCRF) and Meiji Seika Kaisa, Ltd of Japan.

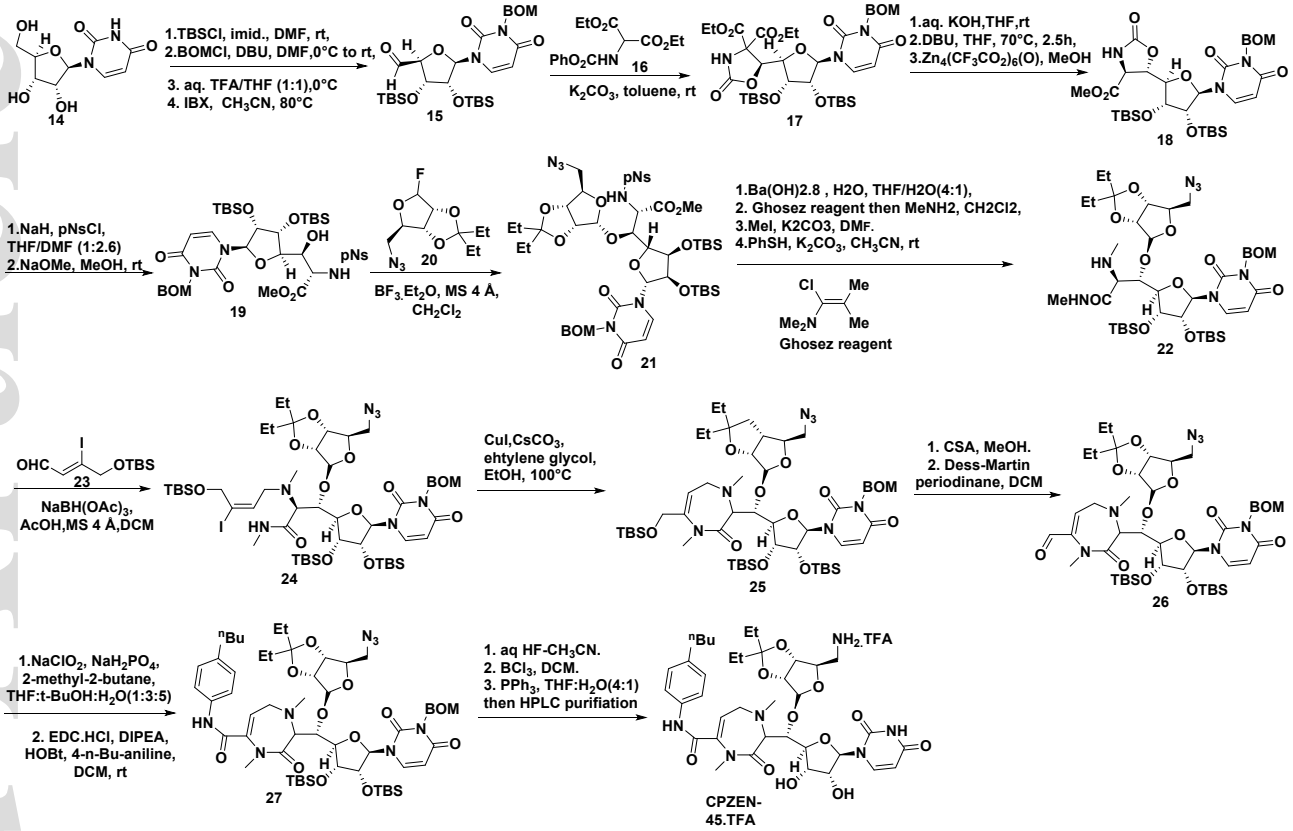


Scheme 3. Synthesis of CPZEN-45.TFA.

Subsequently, semi-synthetic construction of CPZEN-45 was reported in U.S. patent application US2006/017819 (which includes CPZEN-45 - designated compound II-4) and in a presentation at the 235th American Chemical Society National Meeting (2008) during which the structure of CPZEN-45 was first discussed in a public venue. However, CPZEN-45 as potent anti-Mycobacterium tuberculosis (Mtb) agent was described by Takahashi Y.et al in year 2013 [73]. CPZEN-45 showed MIC_{50} against $H_{37}Rv$ strain of *Mycobacterium tuberculosis* (Mtb) and against a multidrug resistant (MDR) strain of Mtb about 1.56 µg/mL and 6.25 µg/mL respectively. CPZEN-45 exhibited the inhibition of the first Step in Synthesis of the mycobacterial cell wall core, catalyzed by the GlcNAc-1-phosphate Transferase WecA [74]. CPZEN-45 was found to active against both replicating and non-replicating Mtb *in vitro*. Additionally, acute tuberculosis (Tb) can be treated with CPZEN-45 as it has shown

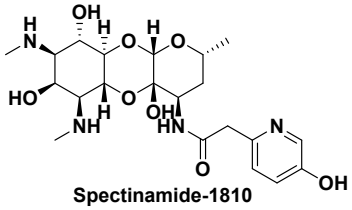
efficacy against both drug sensitive and extremely drug resistant (XDR) Mtb in a mouse model of acute tuberculosis (Tb). CPZEN-45 in combination with other antitubercular drugs showed improved efficacy with drug sensitive Mtb. Data generated by NIAID using the gamma interferon gene-disrupted (GKO) mouse model of acute tuberculosis in which infection was achieved by aerosol exposure to Mtb (Erdman) provided efficacy of CPZEN-45 with 1-1.5 log cfu reduction in lungs of infected mice [75].

Takahashi et. al. also reported the synthesis of **CPZEN-45.** Different caprazamycins (CPZs) **10** were converted to caprazene **11**, subsequently treatment with $(Boc)_2O$ in the presence of triethylamine gave N-Boc derivative **12**. Then intermediate **12** was condensed with 4-butylaniline **13** in presence of bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOP-Cl) or 4-(4, 6-dimethoxy-1, 3, 5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM-Cl) followed by Boc deprotection afforded final CPZEN-45(**scheme 3**). Takemoto et al. [76] also reported the synthesis of CPZEN-45 as illustrated in **scheme 4**. At first uridine **14** was converted to trisilylated uridine followed by N-3-BOM protection. The trisilylated uridine selectively 5′-O-desilylated to gave alcohol. This alcohol was oxidized with IBX to give protected uridine 5′-aldehydes **15**. The aldol reaction of aldehyde **15** with diethyl 2-((phenoxycarbonyl)amino) malonate **16** gave the oxazolidinone **17** as a single isomer. The oxazolidinone **17** was converted into the β-hydroxy amino acid derivatives **19** via the *trans*-oxazolidinone **18** through sequential decarboxylation, *trans* esterification and oxazolidinone ring-opening reactions. The next step was glycosylation of the β-hydroxy amino acid derivatives **19** with (3aR,4R,6aR)-4-(azidomethyl)-2,2-diethyl-6-fluorotetrahydrofuro[3,4-d][1,3]dioxole **20** using Ichikawa and Matsuda's procedure. The resulting compound **21** was subsequently converted to a secondary amine **22** via the formation of an amide using Ghosez's reagent, followed by N-methylation and the removal of the p-nosyl group. The reductive amination of the secondary amine **22** with α, β-unsaturated aldehyde **23** gave the cyclized product **24**. This cyclized product **24** was reacted with CuI (1.0 equiv) and ethylene glycol in ethanol at 100°C to produce important the cyclization precursor **25**. In the next step, selective deporotection ofTBS group followed by oxidation with dess-martine reagent was take place to provide intermediate **26**. Intermediate **26** was further oxidized and underwent acid amine coupling to furnish intermediate **27**.This protected CPZEN-45 **27** on reaction with aq. HF followed by BCl_3 allowed a successful removal of the TBS, BOM, and acetal protecting groups. Then subsequent reduction of the azide with PPh3 followed by HPLC purification provided CPZEN-45.



Scheme 4. Synthesis of CPZEN-45.TFA.

2.2.1.4. Spectinamide-1810



Spectinamide-1810

Chemical name: 2-(5-hydroxypyridin-2-yl)-*N*-((2*R*,4*R*,4a*S*,5a*R*,6*S*,7*S*,8*R*,9*S*,9a*R*,10a*S*)-4a,7,9-trihydroxy-2-methyl-6,8-bis(methylamino)decahydro-2*H*-benzo[*b*]pyrano[2,3-*e*][1,4]dioxin-4-yl)acetamide

Figure 4. Spectinamide-1810.

Spectinamide-1810, a derivative of spectinomycin, undergoing in preclinical studies and devolving by Microbiotix, Inc. (**Figure 4)**. Spectinomycin is a potent bacterial protein synthesis inhibitor and poor anti-mycobacterial activity limits its clinical application for treating tuberculosis **(Figure 5)**. Lee et al. [77] reported structure-based design of a new semi-synthetic series of spectinomycin analogs with selective ribosomal inhibition and narrow-spectrum antitubercular activity. The anti-tubercular activity of spectinamideswas associated with both ribosomal affinity and ability to overcome intrinsic efflux mediated by the *Mycobacterium tuberculosis* Rv1258c efflux pump [78]. These spectinamides reduced lung mycobacterial burden and increased survival in multiple

murine infection models. Additionally, spectinamides showed good activity against both MDR-Tb and XDR-Tb along with lack of cross resistance with existing tuberculosis therapeutics as observed in-vitro studies. Finally, Spectinamide-1810 was selected (the MIC value was found to be 1.6µg/mL against H37Rv strain of *Mycobacterium tuberculosis*) for preclinical studies in early 2017 because of its excellent safety profile (Maximum tolerated dose of 500 mg/kg by IV infusion) and its efficacy in multiple murine models of TB infection. Additionally, it maintained the activity against MDR and XDR strains of Tb. Spetinamide 1810 also showed the synergistic effect with Rifampicin-Pyrazinamide combinations in murine models of Tb infection.

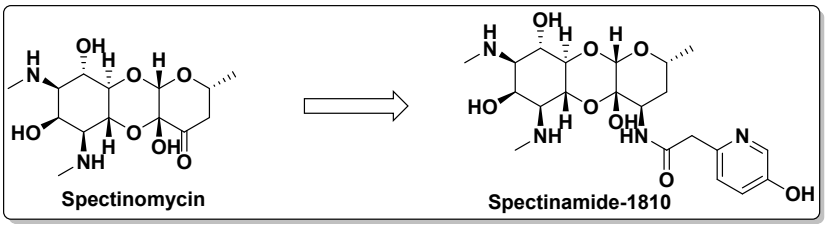
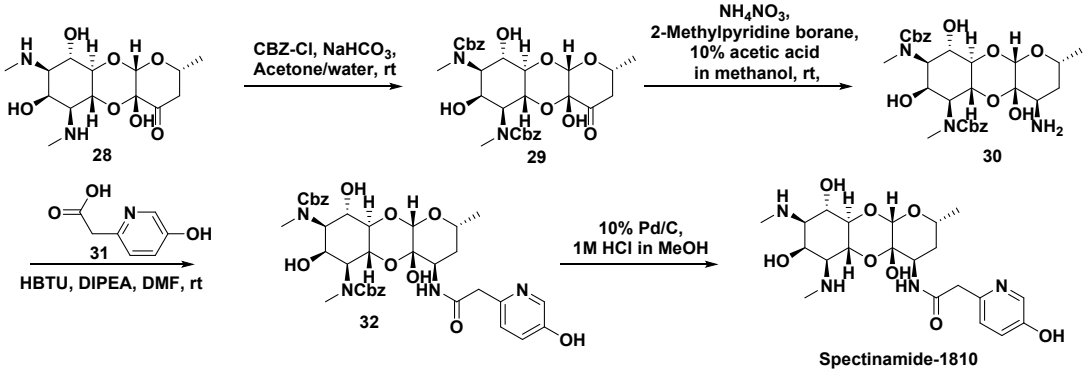


Figure 5. Spectinomycin as lead molecule for Spectinamide-1810.

Spectinamide-1810 was synthesized in a rapid four-step protocol from spectinomycin **28** using the general procedure reported by Lee et al. (**scheme 5**). The two secondary amine of spectinomycin **28** were protected cbz with the help of Cbz-Cl to furnish **29**. Primary Amine containing intermediate **30** was synthesized from **29** by reductive amination using NH_4NO_3, 2-Methylpyridine borane and 10% acetic acid in methanol. The compound **32** was obtained by acid-amine coupling of intermediate **30** with the help of 2-(5-hydroxypyridin-2-yl) acetic acid **31**. The subsequent deprotection of Cbz on **32** with the help of Pd/C, H_2 in methanolic HCl for 2h provided the final Spectinamide-1810.



Scheme 5. Synthesis of Spectinamide-1810.

2.2.1.5. TB-47

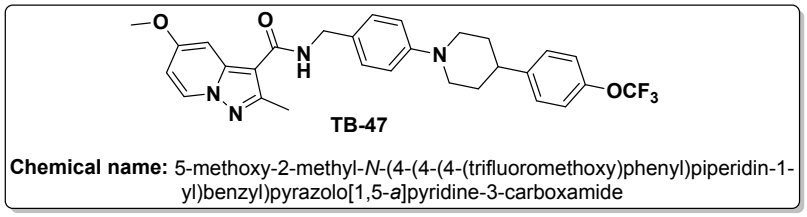
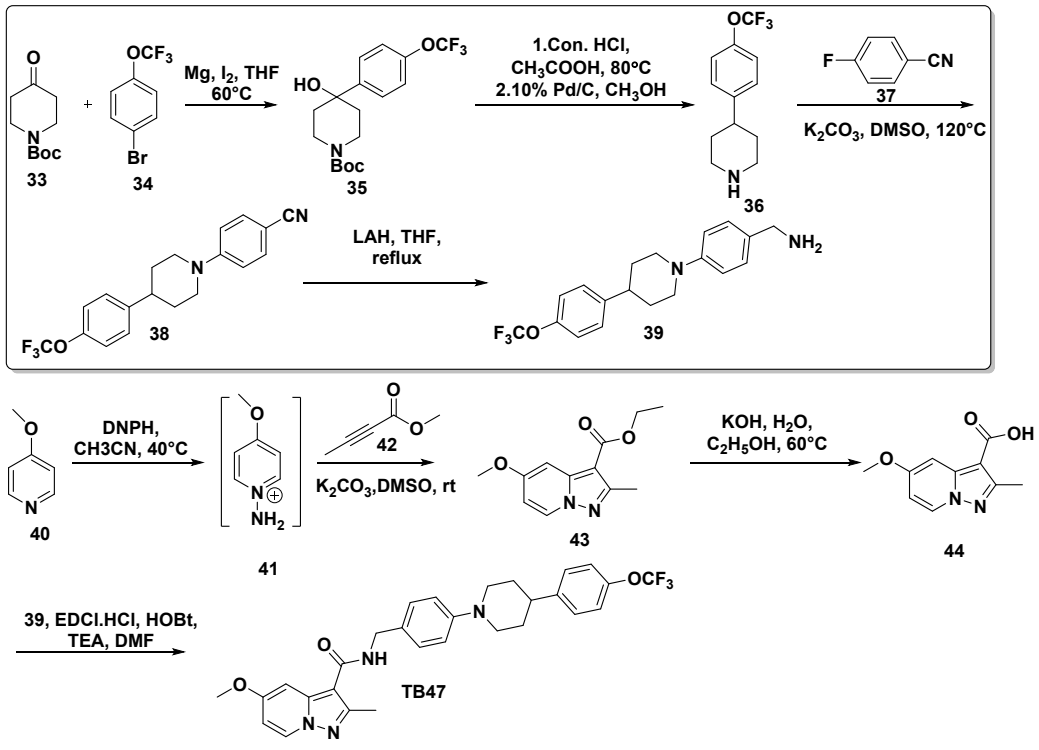


Figure 6. TB-47.

TB47, a pyrazolo[1,5-a]pyridine-3-carboxamide derivative, developing by Guangzhou Egg Biotechnology Co., Ltd. for *Mycobacterium tuberculosis* (**Figure 6).** Tang et al. [79] reported a series of pyrazolo[1,5-a]pyridine-3-carboxamide derivatives as new anti- *Mycobacterium tuberculosis* (Mtb) agents. Among the series, TB-47 was found to be very effective with MIC 0.006 μg/mL and 0.003 μg/mL for $H_{37}Rv$ and $H_{37}Ra$ strain respectively of *Mycobacterium tuberculosis.* As bacterial burden in an auto luminescent H37Ra infected mouse model was reduced by TB-47, suggesting it is promising potential to be a lead compound for future anti-tubercular drug discovery.

Lu et al. [80] identified the menaquinol oxidation site of the mycobacterial QcrB as target of TB47 and proved that pyrazolopyridine carboxyamides are potent novel scaffolds as QcrB inhibitors. TB47 exhibited the inhibition of oxygen consumption with deletion of cytochrome *bd* (alternative oxidase). Additionally, TB47 also causes metabolic stress which was proved with accumulation of steps in TCA cycle and pentose phosphate pathway that are linked to reducing-equivalents. Moreover, TB47 was powerfully synergistic in combination of rifampicin and pyrazinamide.



Scheme 6. Synthesis of TB-47.

Lu et al. also reported the synthesis of TB47 as shown in **scheme 6**. TB47 was synthesized through an EDCl-mediated amidation of primary amine **39** and carboxylic acid **44**. The key intermediate amine **39** was synthesized using *tert*-butyl 4-oxopiperidine-1-carboxylate **33** and 1-bromo-4-(trifluoromethoxy) benzene **34** under Grignard reaction, followed by elimination, reduction and deprotection using Pd/C followed by nucleophilic attack of 4-(4-(trifluoromethoxy)phenyl)piperidine on 4-fluorobenzonitrile and reduction reaction for amine precursor. Another key intermediate carboxylic acid **44** was obtained from 4-methoxypyridine **40** by N-amination with DNPH to get **41**, followed by cycloaddition reaction with methyl but-2-ynoate **42** to get **43** and finally hydrolysis reaction for acid precursor.

2.2.2. GMP/GLP Tox. (GMP & GLP-Compliant Preclinical Toxicology Studies)

2.2.2.1. GSK-286

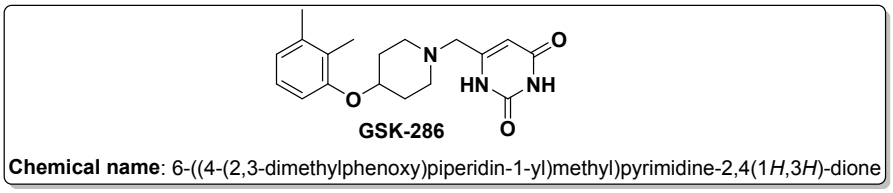
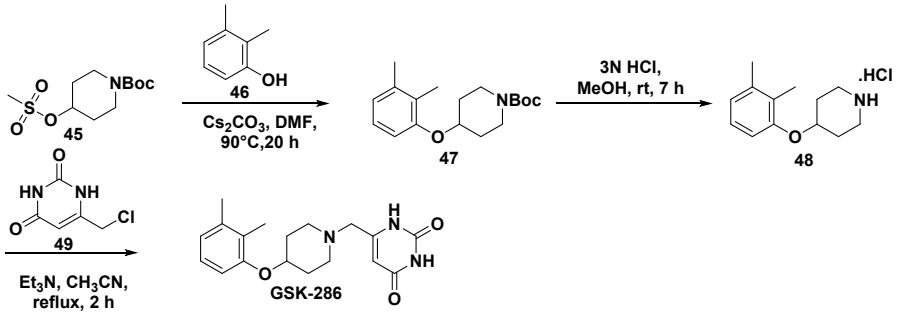


Figure 7. GSK-286.

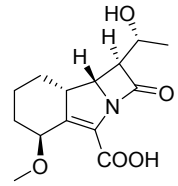
GSK-286 (GSK 2556286) is being developed by GlaxoSmithKline, TB Drug Accelerator, Bill & Melinda Gates Foundation (**Figure 7**). It is currently in GMP/GLP Tox. studies. It is a new chemical entity belongs to chemical class of Piperidinylpyrimidines with a novel mechanism of action related to cholesterol catabolism. GSK-286 selectively killed intracellular Mtb withMIC H37Rv > 10 uM and it was showing intramacrophage activity with MIC < 0.1 uM. Its human study as clinical candidate was planed 2Q2019 [81].

Ballell et.al. [82] reported the synthesis of GSK-286 as illustrated in **scheme 7**. GSK-286 was synthesized by nucleophilic attack of 2,3-dimethylphenol **46** on Boc protected 4-((methylsulfonyl)oxy)piperidine **45** to form Boc protected 2,3-dimethylphenoxy)piperidine **47**. GSK-286 precursor **48** was obtained by Boc deprotection in acidic medium which was reacted with 6-(chloromethyl)pyrimidine-2,4(1H,3H)-dione **49** in presence of triethyl amine and acetonitrile at reflux condition to afford GSK-286.



Scheme 7. Synthesis of GSK-286.

2.2.2.2. Sanfetrinem

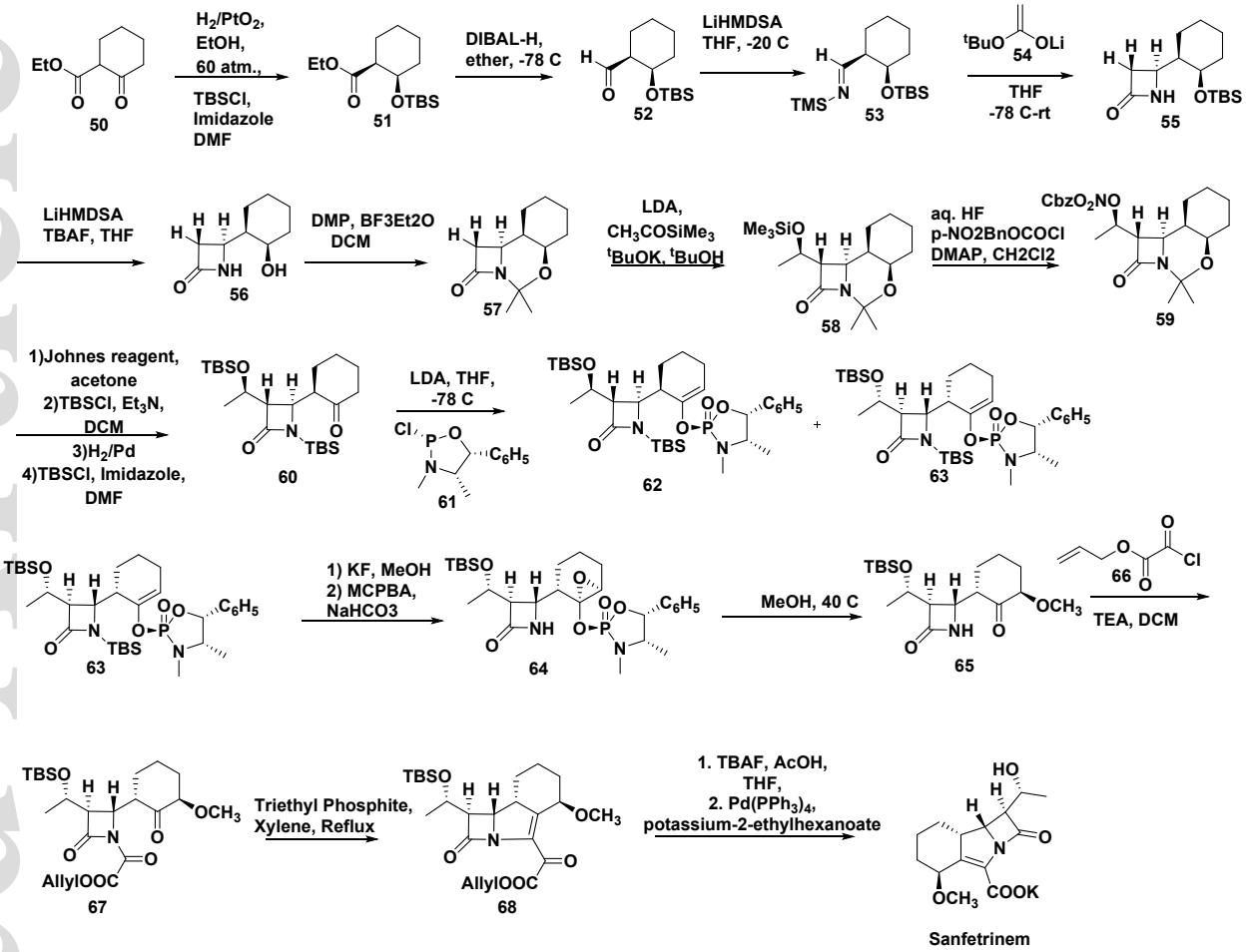


Sanfetrinem

Chemical name: (1*S*,5*S*,8a*S*,8b*R*)-1-((*R*)-1-hydroxyethyl)-5-methoxy-2-oxo-1,2,5,6,7,8,8a,8b-octahydroazeto[2,1-*a*]isoindole-4-carboxylic acid

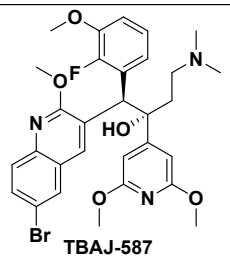
Figure 8. Sanfetrinem.

Sanfetrinem cilexetil, a novel tricyclic β-lactum compound, is the oral prodrug of sanfetrinem and is being developed by GSK in the 1994 (**Figure 8).** A Phase 2a clinical study is being planned for 1Q2021. Panunzio et.al. [83] reported the synthesis of Sanfetrinem as depicted in **scheme 8**. 2-ethoxycarbonyl-cyclohexanone **50** on reduction of ketone followed by TBS protection gave **51**, then ester was reduced to aldehyde **52** with the help of DIBAL-*H* reagent that subsequently converted to imine **53**. This imine on reaction with the lithium enolate of *t*-butyl acetate **54** afforded the azetidinone **55**. TBS protection was removed to obtain hydroxy-azetidinone **56** which then converted to the acetonide derivative **57** by treatment with DMP in the presence of a catalytic $BF3(Et_2O)$.Then, TMS protected hydroxyethyl side chain was introduced on intermediate **57** to avail intermediate **58**.. TMS-group of the hydroxy ethyl side chain removed to give the free hydroxy group which was then protected by the more stable *p*-nitro benzyloxycarbonyl group **59**. The racemic azetidinone **60** was obtained by Jones oxidation of **59** followed by protection of amine group by TBS and deprotection of *p*-NO2-Cbz group followed by TBS protection of hydroxyl group. The racemic azetidinone **60** on reaction with LDA and dialkyl phosphochlorydrate **61** furnished the corresponding diastereomeric enol phosphates **62** and **63**. The phosphoenolates **62** and **63** were isolated by flash chromatography. Phosphoenolate **63** was selectively N-deprotected and treated with *m*-CPBA to obtain epoxide **64**. The epoxide ring was opened by methanol to afford **65**. Acylation on **65** with allyl oxalyl chloride **66** and triethylamine provided allyl oxo acetate **67**. Sanfetrinem precursor **68** was obtained by refluxing the allyl oxo acetate **67** in anhydrous xylene in the presence of an excess of triethyl phosphate. Final compound Sanfetrinem was obtained by silyl protection and deallyation using TBAF, acetic acid and palladium catalyst sequentially [84].



Scheme 8. Synthesis of Sanfetrinem.

2.2.2.3. TBAJ-587 (Diarylquinoline)

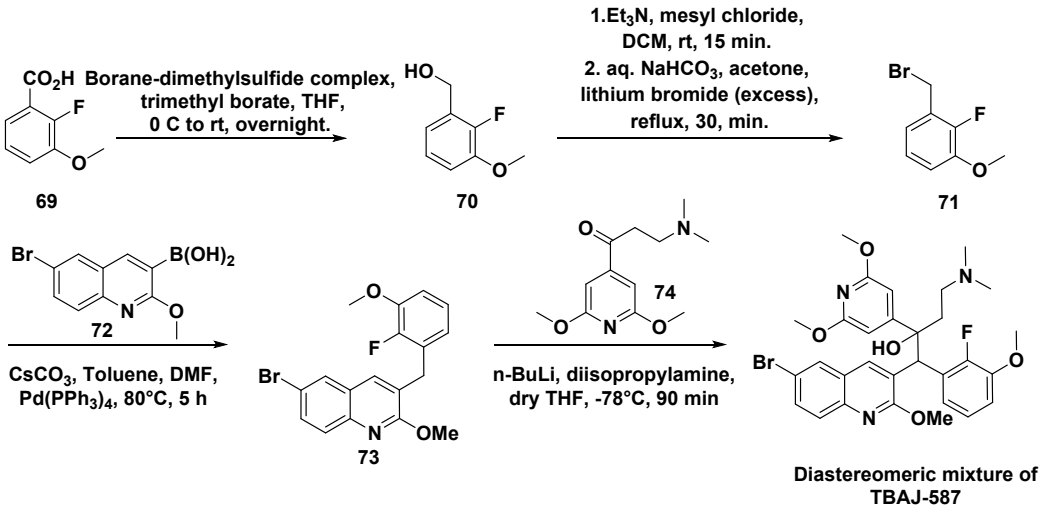


Chemical name: (1S,2S)-1-(6-bromo-2-methoxyquinolin-3-yl)-2-(2,6-dimethoxypyridin-4-yl)-4-(dimethylamino)-1-(2-fluoro-3-methoxyphenyl)butan-2-ol

Figure 9. TBAJ-587.

TBAJ-587 is new diarylquinoline derivative and currently undergoing in GMP & GLP-Compliant Preclinical Toxicology Studies **(Figure 9)**. This is developing by TB Alliance, University of Auckland, Merck & CO.,Inc. Sutherland et al. [85] identified this molecule by inspiring with encouraging result of drug Bedaquiline. However, Bedaquiline shows some limitations like prolongation of the QT interval which comes from inhibition of

potassium channel protein hERG in heart. High Lipophilicity of Bedaquiline increases terminal half-life resulting in accumulation in tissues. TBAJ-587, a diarylquinoline was found to be as potent as bedaquiline against *Mycobacterium tuberculosis*, with lower lipophilicity, higher clearance, and lower risk for QT prolongation. For the development of TBAJ-587, the C-unit naphthalene of bedaquiline was replaced by a 3,5- dimethoxy-4-pyridyl and B-unit phenyl ring was substituted with 2-F, 3-OMe substituents resulted in a significant reduction in clogP (reduction in lipophilicity) from 7.25 for BDQ to 5.8 for TBAJ-587 with MIC_{90} =0.006 µg/mL [minimum inhibitory concentration for 90% inhibition of growth of *M.tb* strain H37Rv, determined under aerobic (replicating; MABA)]. These changes demonstrated TBAJ-587 as more potent *in vitro* and *in vivo* anti-tubercular agent, with greatly attenuated hERG blockade. TBAJ-587 inhibited ATP synthase of *Mycobacterium tuberculosis* like Bedaquiline. Moreover, TBAJ-587 exhibited hERG IC_{50} of 13 µM as compared to 1.6 µM for bedaquiline. Taken together, a higher IC50 against hERG along with a lower efficacious exposure may predict a lower risk of QTc prolongation.



Scheme 9. Synthesis of TBAJ-587**.**

Sutherland et al also reported the synthesis of TBAJ-587 (**scheme 9)**. It was prepared by LDA mediated coupling of Pyridyl quinoline **73** with 1-(2,6-dimethoxypyridin-4-yl)-3(dimethylamino) propan-1-one (Mannich base) **74**. Pyridyl quinoline **73** was prepared from 3-fluoro-4-methoxybenzoic acid **69.** In the very first step, compound **69** reduced to get intermediate **70.** Then intermediate **70** underwent bromination reaction to produce **71.** And then Suzuki coupling with Boronic acid intermediate **72** with compound **71** was take place to furnish Pyridyl quinoline **73**.

2.2.2.4. TBAJ-876

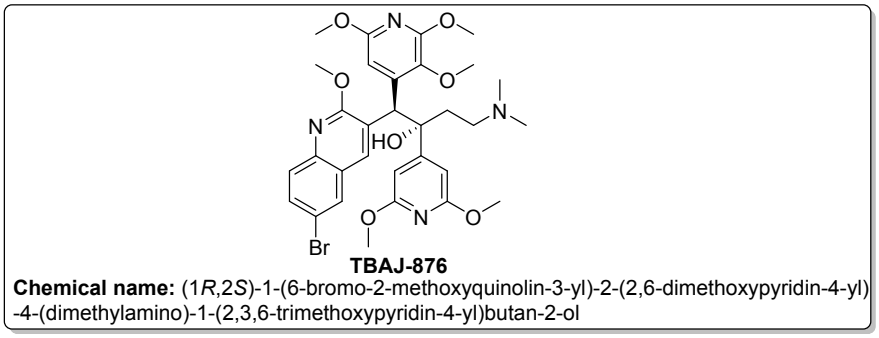
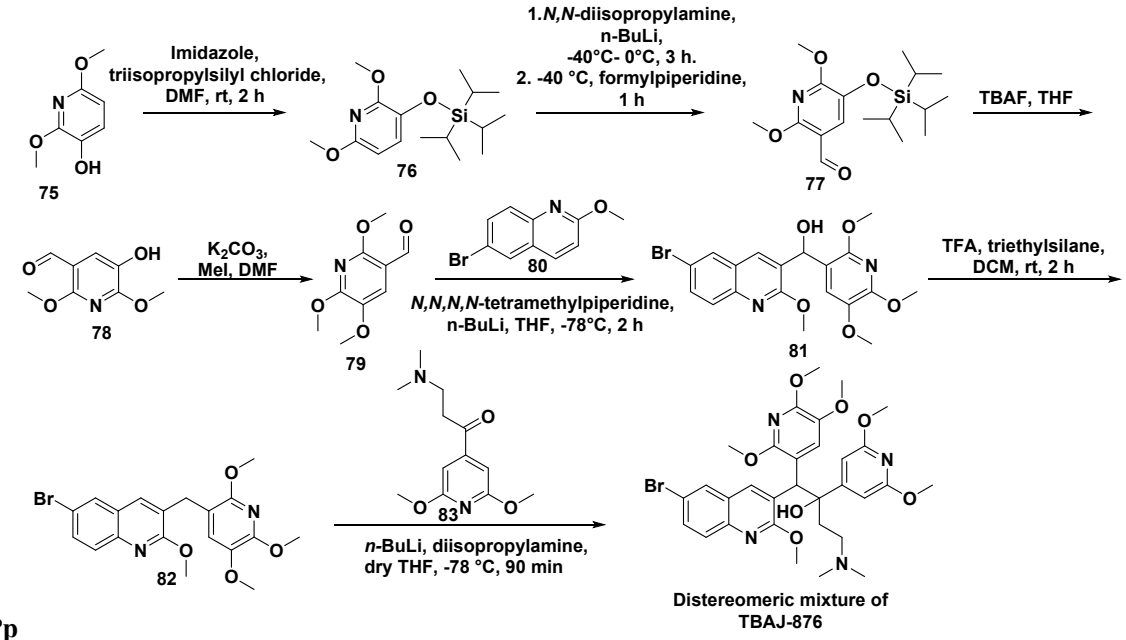


Figure 10. TBAJ-876.

Another diaryquinoline molecule, TBAJ-876 has also been entered into GMP & GLP-Compliant Preclinical Toxicology Studies for treatment of MTb **(Figure 10)**. This candidate drug is developing by TB Alliance, University of Auckland, Merck & CO.Inc. TBAJ-876 was identified from same series of TBAJ-587 reported by Sutherland et al. with same concept like lowering of lipophilicity and increasing the rate of clearance. Chemically, for TBAJ-876, C-unit naphthalene of Bedaquiline was replaced by a 3,5-dimethoxy-4-pyridyl and B-unit phenyl ring was substituted with 4-aza, 2,3,5triOMe substituents. These chemical modifications resulted MIC_{90} = 0.004 µg/mL [minimum inhibitory concentration for 90% inhibition of growth of *M.tb* strain H37Rv, determined under aerobic (replicating; MABA)] of quinoline based molecule TBAJ-876. In terms of hERG channel inhibition, this next generation ATP synthase inhibitor was superior with greater IC_{50} > 30 µM, in comparison to BDQ (1.6 µM) and TBAJ 587. In animal studies, TBAJ 876 showed better efficacies than either BDQ or TBAJ 587.



Pp

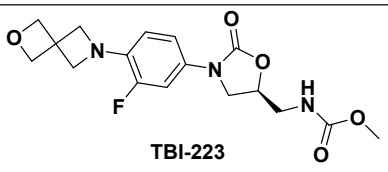
Scheme 10. Synthesis of TBAJ-876.

Sutherland et. al. also reported the synthesis of TBAJ-876 (**scheme 10)**. It was synthesized by LDA mediated coupling of Pyridyl quinoline **82** with 1-(2,6-dimethoxypyridin-4-yl)-3(dimethylamino) propan-1-one (Mannich base) **83**. Pyridyl quinoline **82** was synthesized from intermediate **81** by dehydroxylation reaction with the help of TFA, triethylsilane and DCM as solvent. Intermediate **81** was synthesized by ortholithiation of methoxy quinoline **80** followed by quenching with 2,5,6-trimethoxynicotinaldehyde **79** (compound 79 prepared from 2,6-dimethoxypyridin-3-ol **75** by silyl protection to get **76**, formylation to get **77**, deslilylation to get **78** and *O*-methylation of compound **78).**

2.3. . Clinical Development

2.3.1. Phase-I

2.3.1.1. TBI-223

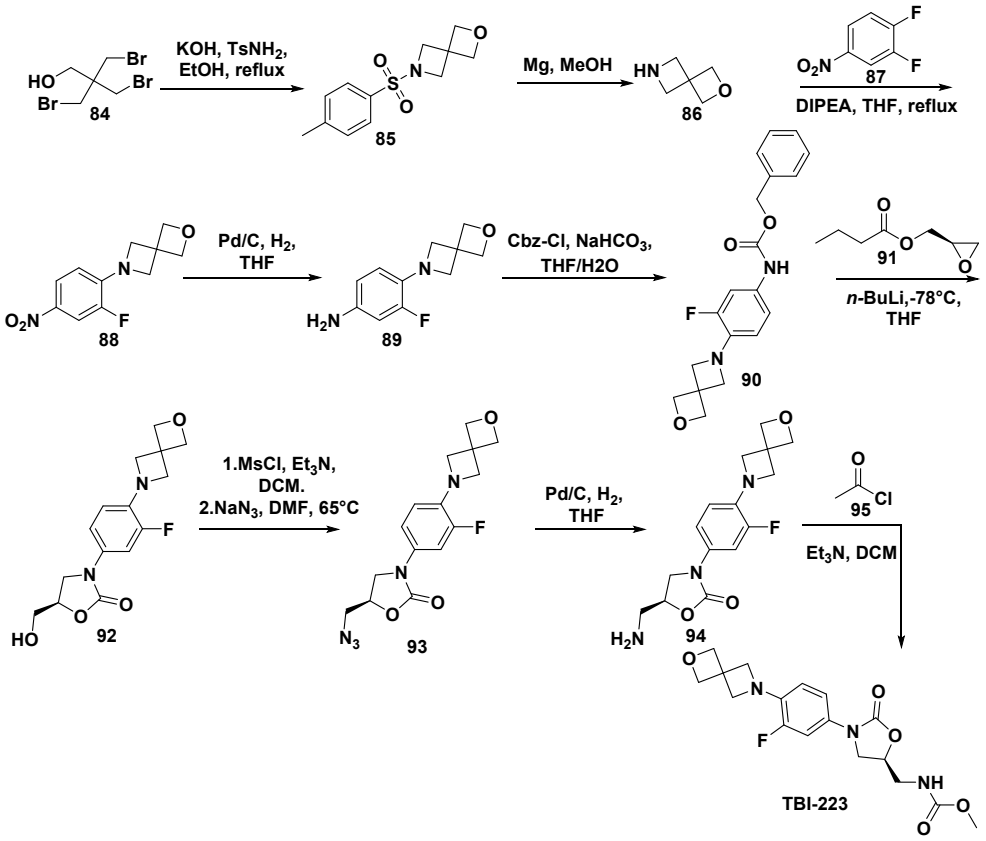


TBI-223

Chemical name: methyl (S)-((3-(3-fluoro-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)carbamate

Figure 11. TBI-223.

The Phase Ia of TBI-223 began on January 16, 2019 for the treatment of MTb. The combined medicinal chemistry work of the Global TB Alliance and Institute of Materia Medica lead to identifing the TBI-223 **(Figure 11)**. Chemically, it is substituted phenyl oxazolidinone derivative. The development of TBI-223 was based on oxazolidinone scaffold containing effective approved drugs like Linazolid. Linazoid was exhibited *in-vitro* bacteriostatic activity against *Mycobacterium Tuberculosis* including MDR and XDR strains. However, Linezolid showed modest activity in murine model of tuberculosis.



Scheme 11. Synthesis of TBI-233.

The bone marrow toxicity was common side effect of Oxazolidinones (like Linazolide) which is associated with inhibition of mitochondrial protein synthesis (MPS). For the treatment of Mtb, High dose of oxazolidinones was required as high rate of clearance occurred. To improve the safety and minimizing the dose, new oxazolidinone derivative, TBI-223 was identified by Cooper, C. B. et al which targeted the protein synthesis. The MIC of TBI-233 against H37Rv stain was found to be in range between 0.8-2.6 µg/mL along with IC_{50} MPS inhibition 38->100 [86]. Additionally, Bone marrow toxicity was absent in a 14-day dog toxicity study of TBI-223 at the highest dose of 150 mg/Kg QD tested (AUC of 789 µg·hr/mL). TBI-223 was found to be safer as compare to Linezolid [87] for Tb therapy and is currently in preclinical development [88]. Cooper et al. [89] reported the synthesis of TBI-223 (**scheme 11)**. 3-Bromo-2,2-bis(bromomethyl)propan-1-ol **84** was refluxed with KOH, $TsNH_2$ to afford tosyl protected spiro compound **85**. In the next step, tosyl group was deprotected to get **86** followed by reaction with 3,4-difluoronitrobenzene **87** provided **88** and subsequent reduction of **88** with the help of Pd/C, H_2 in THF solvent furnished amine **89**. Reaction of amine **89** with Cbz-Cl offered the Cbz protection of free amine to furnish compound **90.** The synthesis of key intermediate **92** i.e. the formation of oxazolidinone ring with defined stereochemistry at the A-ring C-5 position was accomplished by using *n*-butyllithium and (*R*)-(-)-glycidyl butyrate **91** on Cbz protected amine **90**. Derivatization of the alcohol **92** to the mesylate intermediate, followed by

nucleophilic displacement of the mesyl group in the presence of NaN_3 in DMF gave the azide **93**. Hydrogenation of the azide **93** over Pd/C (10%), H_2 in THF at room temperature afforded the amino derivative **94.** The compound **94** was reacted with acetyl chloride **95** to give TBI-223.

2.3.1.2. SPR720/VXc-486

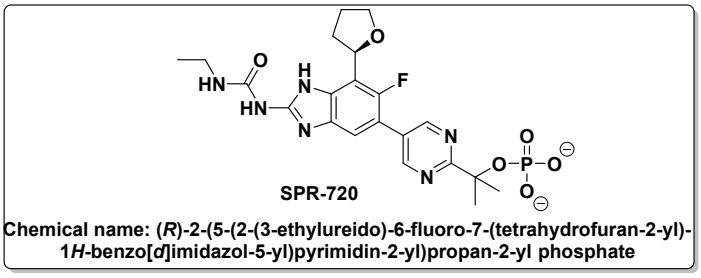
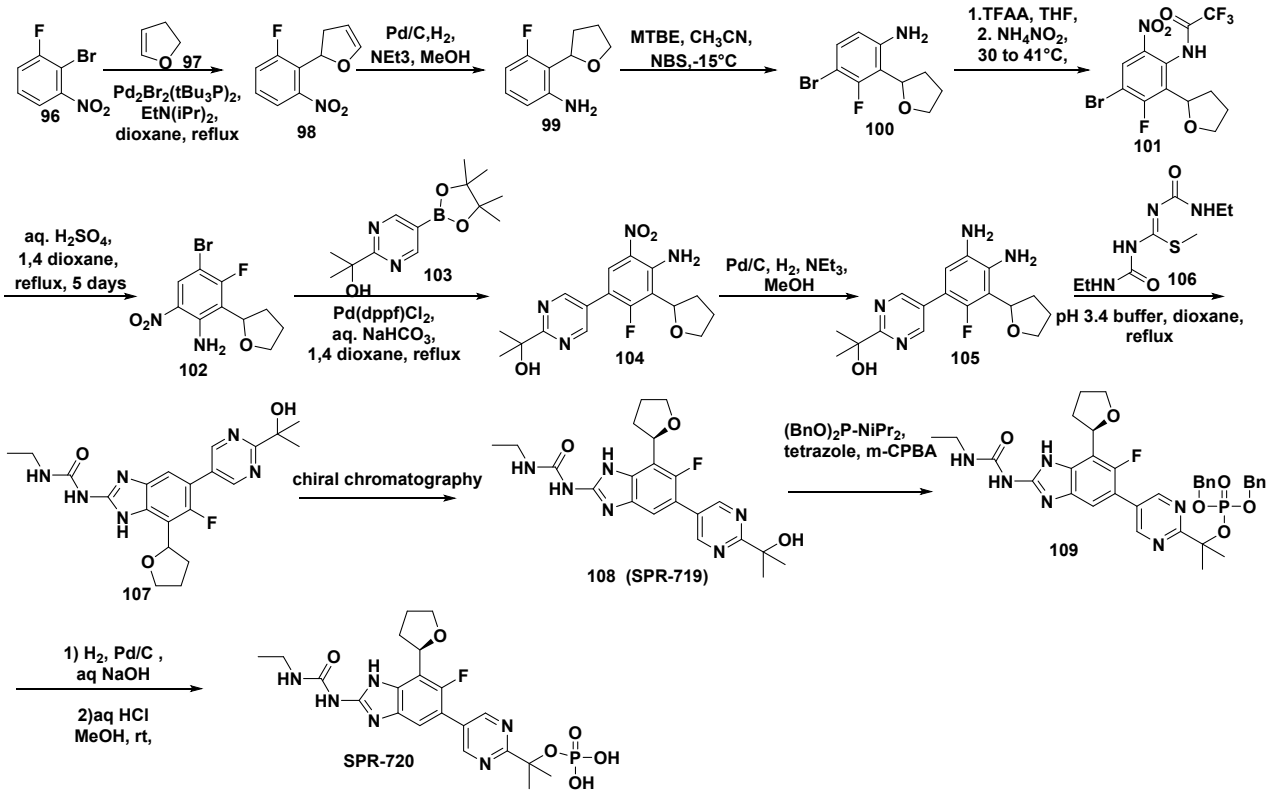


Figure 12. SPR-720.

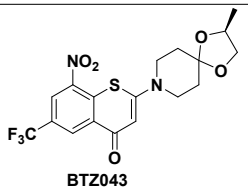
SPR-720/Vxc-486 is belongs to chemical class ethyl urea benzimidazole. It is an active phosphate prodrug of the active parent SPR719 [90]. This compound is being developed by Vertex Pharmaceuticals. It is currently investigated to treat both MTb and non-tuberculous mycobacteria (NTM). It's Phase I clinical study (NCT03796910) is sponsored by Spero Therapeutics, LLC) [91] **(Figure 12)**. SPR720 was a dual inhibitor of bacterial DNA gyrase and topoisomerase IV [92]. In vivo combination of SPR720 with RIF and Pyrazinamide (PZA) showed comparable efficacy to MOX/RIF/PZA regimen.



Scheme 12. Synthesis of SPR-720.

Macikenas et al. [93] reported the synthesis of SPR720 as given in **scheme 12**. In the very first step palladium catalysed reaction of 2-Bromo-1-fluoro-3-nitro-benzene **96** and 2,3-dihydrofuran **97** provided **98.** This compound **98** was subsequently reduced to compound **99**. Compound **99** on subsequent bromination and nitration followed by deacylation gave compound **102**.The coupling of **102** and **103** under Miyaura-Suzuki reaction condition afforded nitroaniline **104**. Reductive hydrogenation of nitroaniline **104** followed by condensation with reagent **106** afforded compound **107** which on chiral chromatography afforded intermediate **108** (SPR-719). Compound **108** reacted with dibenzyl diisopropyl phosphoramidite in presence of tetrazole and the resulting phosphite ester intermediate was oxidized in situ to provide the dibenzylphosphate derivative **109**. Hydrogenolysis of the benzyl groups in the presence of sodium hydroxide gave the disodium salt of the phosphate ester SPR-720.

2.3.1.3. BTZ-043

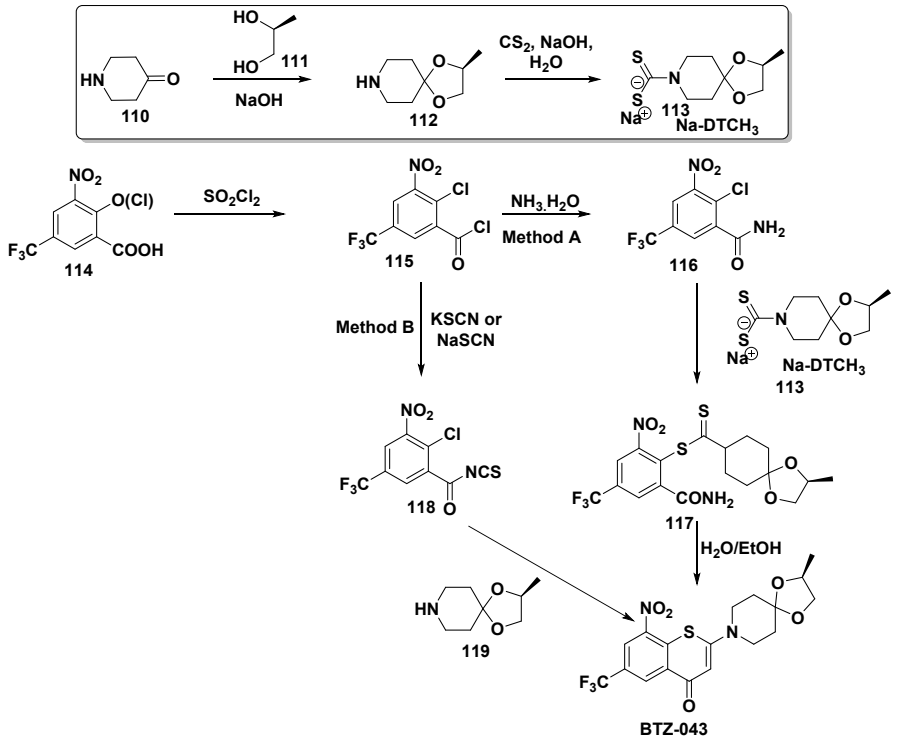


BTZ043

Chemical name: (*S*)-2-(2-methyl-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-8-nitro-6-(trifluoromethyl)-4*H*-thiochromen-4-one

Figure 13. BTZ-043.

University of Munich, Hans-Knoll Institute, Jena, German Center for Infection Research (DZIF), European and Developing Countries Clinical Trials Partnership (EDCTP) Radboud University is developing the BTZ-043 as Anti-tubercular drug which is currently in Phase I trial as per recent report [94] **(Figure 13)**. In 2009, Makarov et al. [95] reported the synthesis and biological evaluation of 1,3- benzothiazin-4-ones (BTZs) which were a new class of antimycobacterial agents that killed *Mycobacterium tuberculosis*.



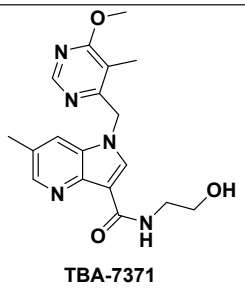
Scheme 13. Synthesis of BTZ-043.

BTZ-043 was found to inhibit the enzyme decaprenylphosphoryl-β-D-ribose 2′oxidase (DprE1) as a major BTZ target. DprE1 enzyme is responsible for the formation of decaprenylphosphoryl arabinose that is required for the synthesis of the cell-wall arabinans. The inhibition of this enzyme leads to provoking cell lysis and bacterial death. The minimal inhibitory concentration (MIC) of BTZ-043 against *M. tuberculosis* H37Rv and *Mycobacterium smegmatis* were found to be 1 ng/ml (2.3 nM) and 4 ng/ml (9.2 nM), respectively.

The synthesis of BTZ-043 was illustrated in **scheme 13** [96]. 2-hydroxy-3-nitro-5-(trifluoromethyl)benzoic acid or 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid **114** was treated with thionyl chloride to give acid chloride **115**. From acid chloride **115**, the synthesis of BTZ043 was reported in two methods. In method A, the acid chloride **115** was reacted with ammonia water to furnish amidic intermediate **116** which further reacted with Na-$DTCH_3$ **113** to give dithiocarbamate as intermediate **117**. Finally, Dithiocarbamate **117** was cyclized to BTZ043 in presence of ethanol/water. In method B, the acid chloride **115** was treated with thiocyanate salt to make 2-chloro-3-nitro-5-

(trifluoromethyl)benzoyl isothiocyanate **118** that was further treated with (*S*)-2-methyl-1,4-dioxa-8-azaspiro[4.5]decane **119** to avail BTZ-043.

2.3.1.4. TBA-7371

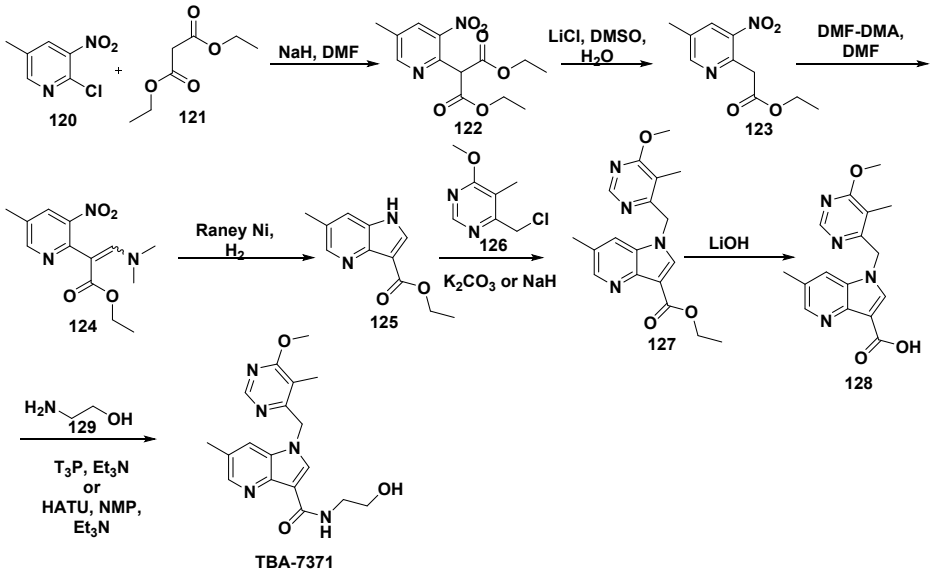


TBA-7371

Chemical name*: N*-(2-hydroxyethyl)-1-((6-methoxy-5-methylpyrimidin-4-yl)methyl)-6-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-3-carboxamide

Figure 14. TBA-7371.

TB Alliance, Bill & Melinda Gates Medical Research Institute, Foundation for Neglected Disease Research is developing the TBA-7371 as Anti-Tb drug. It is currently in Phase I clinical trial as per update in 2019 **(Figure 14)**. Chemically, TBA-7371 is 1,4-azaindole which is new class of anti Tb agents. Shirude et al. [97] reported that 1,4-azaindoles non-covalently inhibited decaprenylphosphoryl-β-D-ribose2′-epimerase (DprE1). Designing of 1,4-azaindoles was based on scaffold morphing approach starting with a published anti-Tb, non-DprE1 imidazo-pyridine scaffold [98,99]. TBA-7371 was showing potent Anti-tubercular activity with MIC = 1.56 μM and IC_{50} = 0.010 μM. Shirude et al reported synthesis of TBA-7371 as shown in **scheme 14**. 2-chloro-5-methyl-3-nitropyridine **120** was coupled with diethyl malonate **121** in presence of NaH to provide diester compound **122.** Then, this coupled product **122** was treated with LiCl which furnished the mono-ester **123** that was reacted with DMF-DMA followed by Raney Ni and H_2 to attain the cyclized product **125**. The cyclized product **125** was reacted with 4-(chloromethyl)-6-methoxy-5-methylpyrimidine **126** followed by ester hydrolysis with Lithium hydroxide to achieve corresponding acid **128**. The last step was N- alkylation of acid **128** with 2-aminoethan-1-ol **129** in presence of T_3P, Et_3N or HATU, NMP, Et_3N to get TBA-7371.



Scheme 14. Synthesis of TBA-7371.

2.3.1.5. PBTZ-169:

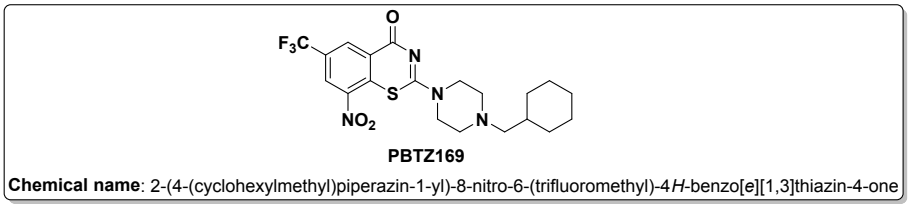
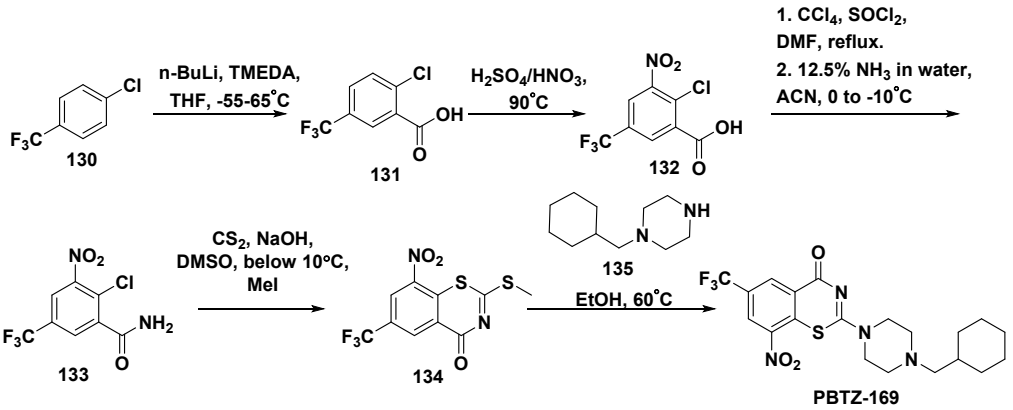


Figure 15. PBTZ169.

PBTZ-169 is Phase I clinical candidate as per update in 2019 with anti-tubercular activity. It is developing by iM4TB- Innovative Medicines for Tuberculosis, Bill and Melinda Gates Foundation **(Figure 15)**. Chemically, it is piperazine-containing benzothiazinone. Makarov et al. [100] reported the innovation of this molecule which was inspired by BTZ043 that kills Mycobacterium tuberculosis by inhibiting the essential flavo-enzyme DprE1, decaprenylphosphoryl- beta-D-ribose 2-epimerase. Like BTZ043, PBTZ169 binds covalently to DprE1. PBTZ169 was sufficiently lipophilic to be highly antimycobacterial with better pharmacodynamic parameters to increase their *in vivo* efficacy. The MIC value against *M. Tuberculosis* was found to be ≤0.19 ng/mL.

Makarov et. al. also synthesized PBTZ-169 as illustrated in **scheme 15**. Synthesis of PBTZ-169 was involved the Carboxylation of 1-chloro-4-(trifluoromethyl)benzene **130** in presence of *n*-BuLi TMEDA to get corresponding acid **131** followed by *m*-nitration in presence of H_2SO_4/HNO_3 at 90°C provided 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid **132**. From acid **132** to corresponding amide **133** formation was take place in presence of CCl_4, $SOCl_2$ followed by 12.5% NH_3 in water. Amidic intermediate **133** was treated with carbon disulfide and NaOH in DMSO followed by reaction with MeI to furnish cyclized product **134** which was alkylated with 1-(cyclohexylmethyl)piperazine **135** to provide PBTZ-169.



Scheme 15. Synthesis of PBTZ-169

2.3.1.6. TBI-166:

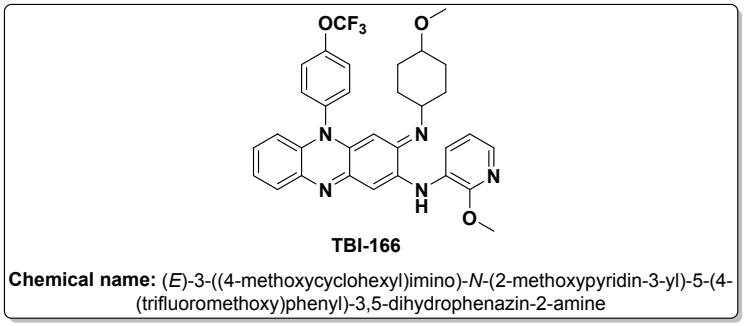
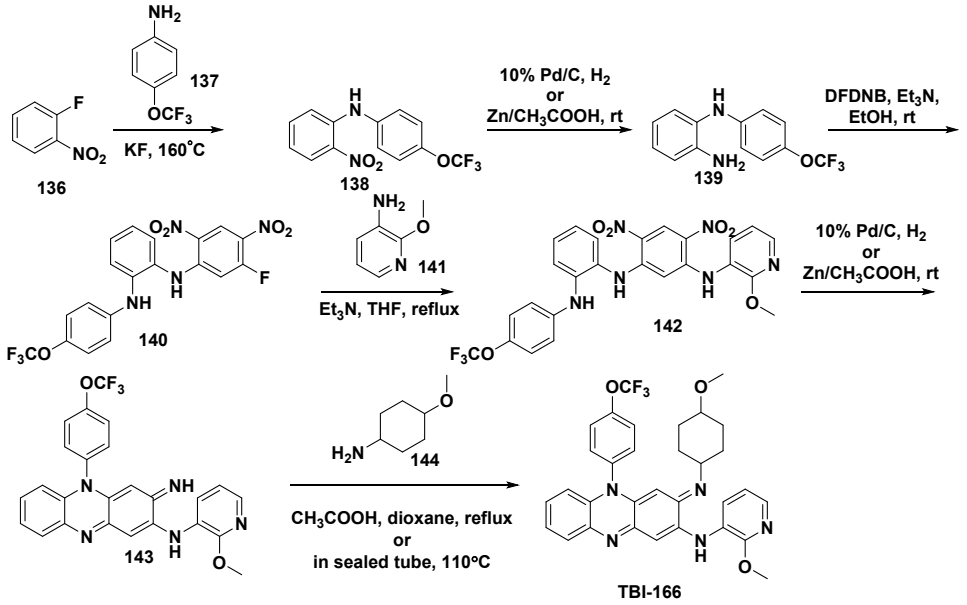


Figure 16. TBI-166.

TBI-166 is riminophenazine based potent anti-tubercular candidate and is in Phase I clinical trial which is developing by Institute of Materia Medica, CAMS & PUMC **(Figure 16)**. This candidate drug is inspired with Clofazimine (CFZ) which is a derivative of the riminophenazine class. Clofazimine (CFZ) has been evaluated in clinical trials for the treatment of multidrug-resistant tuberculosis (MDR-Tb). Because of high lipophilicity, CFZ shows several side effects. Zhang et al. [101] first time introduced TBI-166 molecule in 2012. Zhang et al. reported the design and synthesis of a series of novel riminophenazine analogues bearing a C-2 pyridyl substituent with potent activity against MTb along with improved safety profile by lowering the lipophilicity. Almost, all the compounds were retained the activity against *M. tuberculosis* with MICs of less than 0.03μg/mL and low cytotoxicity with IC_{50} values greater than 64 μg/mL. TBI-166 was showing the MIC 0.016 μg/mL which is much superior as compare to CFZ (MIC = 0.12 μg/mL). Selectivity index (4000) was improved that might be effect of lower lipophilicity (5.40) as compare to selectivity index (572) of CFZ with lipophilicity 6.80.

Zhang et. al. also Synthesized TBI-166 as illustrated in **scheme 16.** Synthesis of TBI-166 involved the nucleophilic substitution reaction on 1-fluoro-2-nitrobenzene **136** with 4-(trifluoromethoxy)aniline **137** in presence of KF in very first step to get compound **138**. Resulting product **138** was treated either with Pd/C, H_2 or with Zn/CH_3COOH at room temperature to reduce nitro group into primary amine **139**. The free amine **139** was coupled

with 1,5 difluoro-2,4-dinitrobenzene (DFDNB) in presence of Et_3N, and EtOH at room temperature to get compound **140**. The flouro group of compound **140** was substituted with 2-methoxypyridin-3-amine **141** in presence of Et_3N as base and THF as solvent at reflux condition to achieve the compound **142**. Compound **142** was cyclized into compound **143** when both the free nitro groups were reduced by either 10% Pd/C, H_2 or Zn/CH_3COOH at room temperature. Finally, 4-methoxycyclohexan-1-amine **144** was reacted with cyclized product **143** to furnish the final desired TBI-166.



Scheme 16. Synthesis of TBI-166.

2.3.2. Phase II

2.3.2.1. GSK656

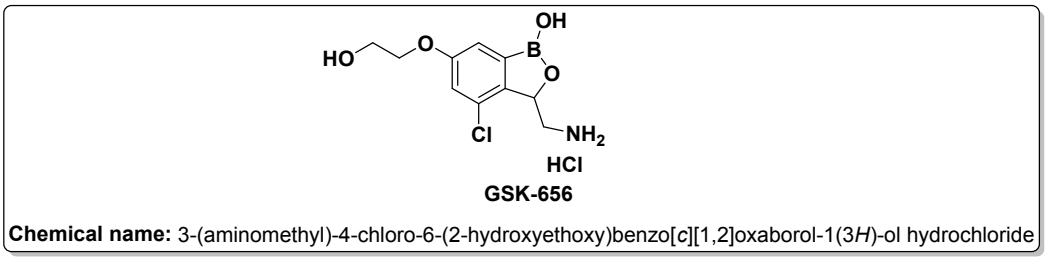
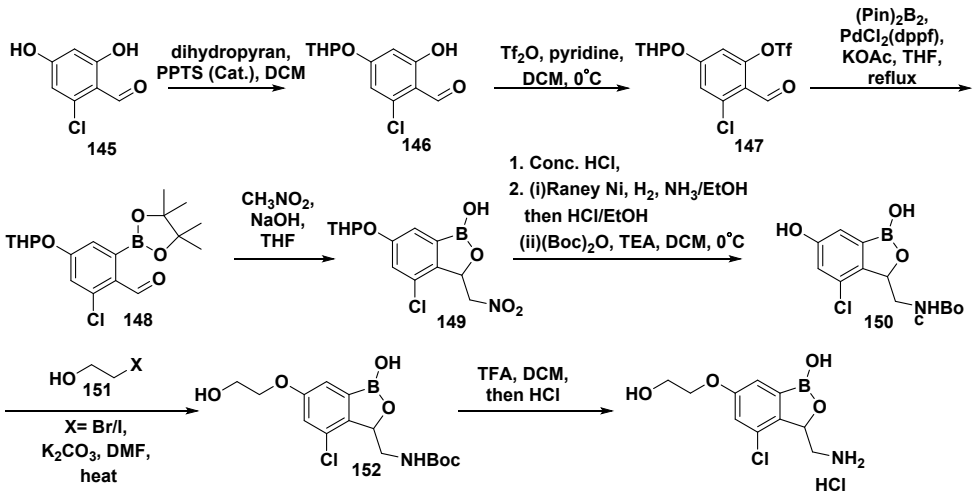


Figure 17. GSK-656.

GSK3036656 (abbreviated as GSK656 or GSK070) is developing by GlaxoSmithKline, European Union Horizon 2020, NIAID, NIH, DHHS as anti-tubercular candidate molecule **(Figure 17)**. As per recent update, this molecule is now in phase II clinical trial. Chemically, GSK-656 is 3-aminomethyl 4-chloro benzoxaborole that was synthesized and evaluated as *Mycobacterium tuberculosis* leucyl-tRNA synthetase (LeuRS) inhibitors by Xianfeng et al. [102] in 2017. GSK-656 molecule was showing excellent antitubercular activity with high selectivity over human mitochondrial and cytoplasmic LeuRS. This molecule has potent inhibition of Mtb LeuRS with IC_{50} = 0.20 μM and *in-vitro* antitubercular activity with MIC = 0.08 μM on Mtb H37Rv. Moreover, the selective was found excellent for the Mtb LeuRS enzyme with IC50 of >300 μM and 132 μM for human mitochondrial LeuRS and human cytoplasmic LeuRS, respectively. Xianfeng et. al. also reported synthesis was discussed in **scheme 17**. The selective THP protection of *pera*-hydroxy group of 2-chloro-4,6-dihydroxybenzaldehyde **145** was take place in very first step to get compound **146**. Resulting product **146** was reacted with Tf_2O in presence of pyridine and DCM to make good leaving group of hydoxyl moiety **147**. Borylation **-** was accomplished on triflate compound **147** with pinacol diborane in the presence of a palladium catalyst to provide compound **148**. Subsequent multistep manipulation of boronate **148** including Henry reaction, nitro reduction, and alkylation with compound **151** provided the 4-Cl compounds **152**. The compound **152** was reacted with TFA to deprotect the Boc group and finally free amino compound was reacted with hydrochloric acid to make hydrochloric salt of GSK-656.



Scheme 17. Synthesis of GSK-656.

2.3.2.2. OPC -167832

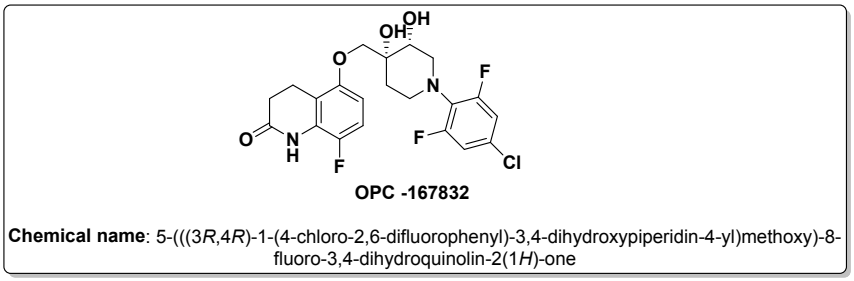
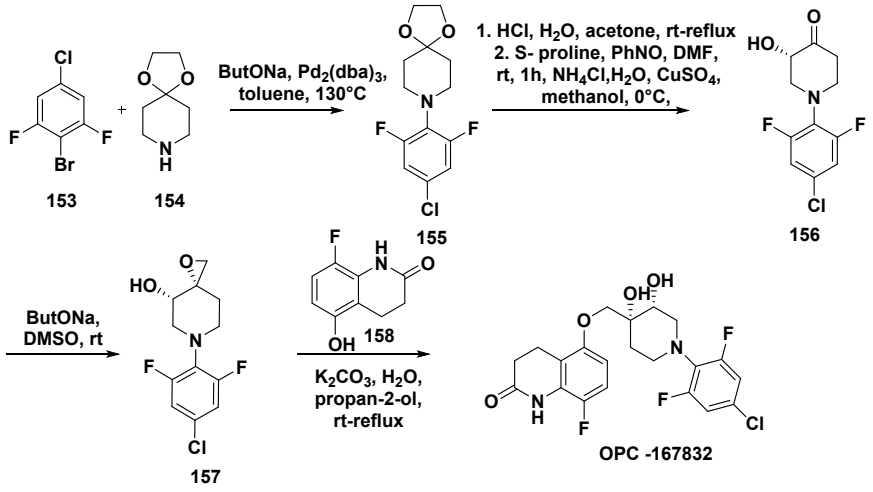


Figure 18. OPC-167832.

OPC-167832, Phase II clinical trial, candidate drug molecule for tuberculosis is developing by Otsuka Pharmaceutical Development & Commercialization, Inc. **(Figure 18)**.



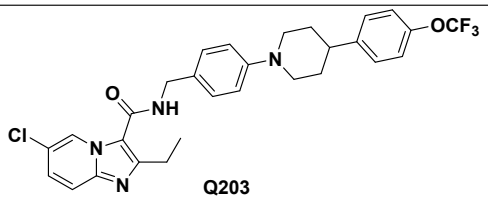
Scheme 18. Synthesis of OPC-167832.

Hariguchi et al. [103] identified OPC- 167832 after screening a library of carbostyrils for anti-tuberculosis activity. OPC- 167832 exhibited with MIC ranged from 0.00024 to 0.002μg/mL for *Mycobacterium tuberculosis*. This molecule was bactericidal (starting at a dose of 0.625 mg/kg) against both growing and intracellular bacilli, and the frequency of spontaneous resistance for *Mycobacterium tuberculosis* H37Rv was less than 1.91×10^{-7}. Decaprenylphosphoryl-β-D-ribose 2'-oxidase (DprE1) was found the target for OPC- 167832. The significant

combination effect of OPC-167832 was also found with delamanid, bedaquiline, or levofloxacin (2-drug combinations).

Hariguchi et al also synthesized OPC-167832 asillustrated in **scheme 18.** 2-bromo-5-chloro-1,3-difluorobenzene **153** and 1,4-dioxa-8-azaspiro[4.5]decane **154** coupled together in Pd mediated reaction to achieve compound **155**. The subsequent two steps involving reaction with HCl followed by reaction with *S*-proline and PhNO accomplished carbonyl compound **156**. The next step was epoxide ring formation in compound **156** in presence of Bu^{t}ONa and DMSO at room temperature that provided compound **157.** Finally, compound **157** reacted with 8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one **158** in presence of K_2CO_3 and propan-2-ol at reflux temperature to give OPC-167832.

2.3.2.3. Telacebec (Q203):



Q203

Chemical name: 6-chloro-2-ethyl-*N*-(4-(4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide

Figure 19. Telacebec (Q203).

In year 2013, Pethe et al. [104] reported the discovery of Q203 as potent clinical candidate for the treatment of tuberculosis **(Figure 19)**. Chemically, Q203 is imidazopyridine amide (IPA) which is developing by Qurient Co.,Ltd,/LLC "Infectex", a Portfolio firm of Maxwell Biotech Venture Fund. Telacebec is currently in Phase II of clinical trial. The identification of this molecule was based on screening of various commercial chemical libraries using a phenotypic high-content screening technology in infected macrophages. Q203 was found to be active with MIC_{50} of 2.7 nM in culture broth medium and at a MIC_{50} of 0.28 nM inside macrophages against the reference strain *M. tuberculosis* H37Rv. Q203 also exhibited activity against the growth of MDR-Tb and XDR-Tb. Q203 has good efficacy at a dose less than 1 mg per kg body weight. Kang et al. [105] reported the optimization of Q203 from lead molecule (**Figure 20**).

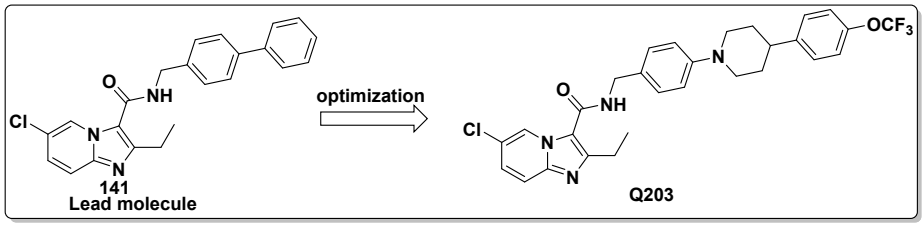
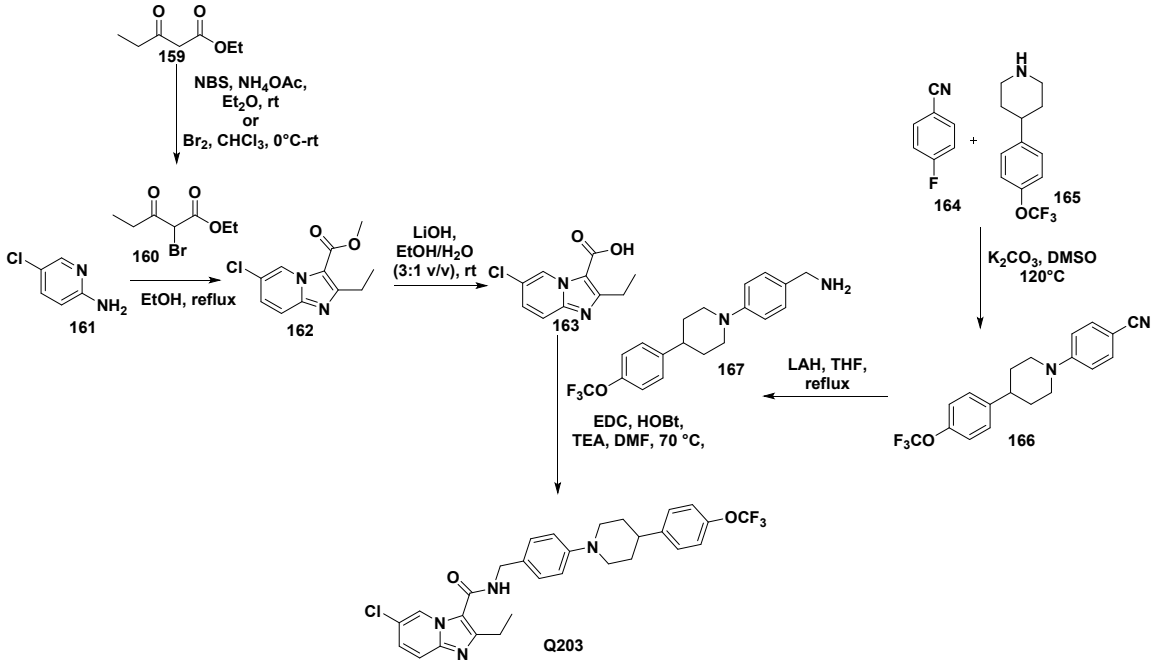


Figure 20. Optomization of lead molecule to Q203.

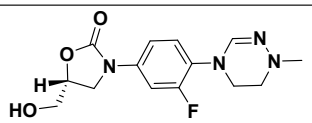
During the optimization, it was observed that amide linker was very essential for the activity. Moreover, Linearity and lipophilicity of the amine element in the IPA series play a critical role in improving *in vitro* and *in vivo* efficacy and pharmacokinetic profile. The mode of action of Q203 was found very exclusive as it inhibited *Mycobacterium tuberculosis* growth by targeting the respiratory cytochrome *bc*1 complex at low concentration. The cytochrome *bc*1 is an essential component of the electron transport chain [106,107] required for ATP synthesis in *M. tuberculosis.* Because of this unique mode of action of Q203, MDR and XDR Tb could be targeted very easily.

Kang et. al. also reported the synthesis of Q203 as discussed in **scheme 19**. First of all, the corresponding acid, 6-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxylic acid **163** was synthesized in several steps including condensation reaction of 5-chloropyridin-2-amine **161** with ethyl 2-bromo-3-oxopentanoate **160** (synthesized from ethyl 3-oxopentanoate **159** by bromination at 2-position) in presence of EtOH at reflux temperature followed by ester hydrolysis with Lithum hydroxide. The another key amine component, (4-(4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)phenyl)methanamine **167** was synthesized in two steps including nucleophilic substitution reaction at 4-fluorobenzonitrile **164** with 4-(4-(trifluoromethoxy)phenyl)piperidine **165** in presence of K_2CO_3 and DMSO at 120°C reflux temperature followed by cyano reduction to amine with LAH in THF solvent at reflux temperature. The final step was acid-amine coupling reaction of synthesized corresponding amine **167** and acid **163** in presence of EDC, HOBt, TEA, and DMF at 70 °C temperature to get Q203.



Scheme 19. Synthesis of Q203.

2.3.2.4. Delpazolid



Delpazolid

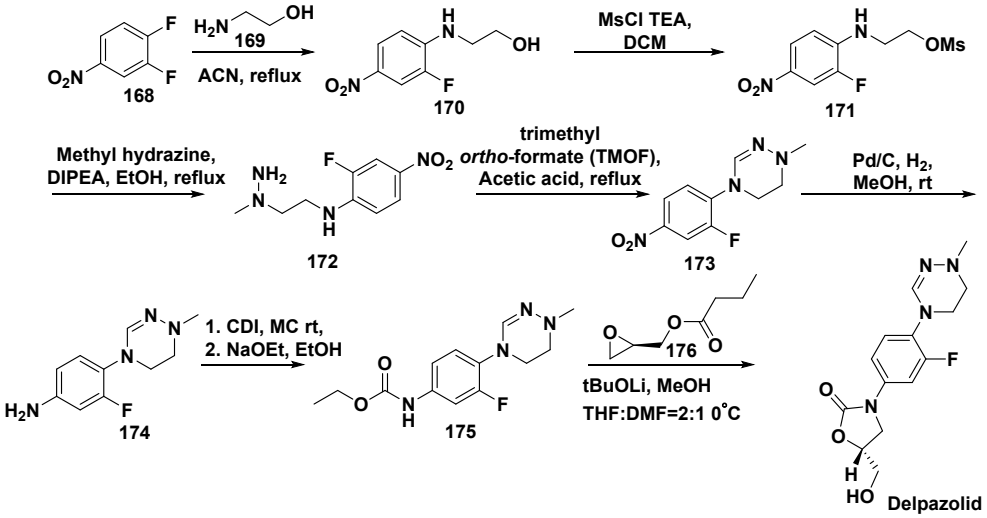
Chemical name: (*R*)-3-(3-fluoro-4-(1-methyl-5,6-dihydro-1,2,4-triazin-4(1*H*)-yl)phenyl)-5-(hydroxymethyl)oxazolidin-2-one

Figure 21. Delpazolid.

LegoChem BioSciences, Inc. (Daejeon, Korea) is developing the delpazolid (LCB01-0371) as anti- tubercular agent. Currently, delpazolid (LCB01-0371) is in Phase II of clinical trial. Chemically, it is novel oxazolidinone with cyclic amidrazone [108] **(Figure 21)**. Linezolid was the first member of the oxazolidinone class approved by the FDA in the United States. Delpazolid improved the minimum bactericidal concentration for *Mycobacterium tuberculosis* H37Rv as well as significantly minimize resistance rates in especially in MDR-Tb isolates, compared with linezolid Therefore, MDR-Tb can be treated with delpazolid. The MIC value for *M. tuberculosis* H37Rv was found to be equal to Linezolid (0.5µg/mL). However, MDR-TB MIC90 of delpazolid (0.5µg/mL) was superior as compare to linezolid (1 µg/mL). Like linezolid, LCB01-0371 also inhibited protein synthesis in *Mycobacterium tuberculosis.* As oxazolidinones [109], delpazolid also inhibited human mitochondrial protein synthesis which could produce myelo suppression [110] after inhibition of mitochondrial protein synthesis. But, it was found that

myelosuppression in delpazolid was less as compare to linezolid because of faster clearance. In delpazolid, the cyclic amidrazone on the side chain was giving hydrophobicity and slightly basic pH similar to that of carboxylate that enhances the solubility and PK profile. Hence, the drug was deposited slowly and rate of excretion become faster resulted as this candidate drug can be administered over the long-term with lower side effects.

The synthesis of Delpazolid was illustrated in **scheme 20** [111]. 1,2-difluoro-4-nitrobenzene **168** was reacted with 2-aminoethan-1-ol **169** in ACN solvent at reflux temperature to give compound **170**. *O*-mesylation of hydroxyl group of compound **170** with MsCl, Et_3N, and DCM was done followed by replacement of mesylate group with methyl hydrazine in presence of DIPEA as base and ethanol as solvent at reflux temperature to provide compound **172**. Reaction of compound **172** with TMOF in presence of Acetic acid at reflux temperature provided compound **173**. The next step was reduction of nitro group of compound **173** in presence of Pd/C, H_2, and methanol at room temperature to achieve the compound **174**. Compound **174** was reacted with CDI followed by NaOEt in ethanol to give carbamate compound **175**. Finally, carbamate compound **175** was reacted with (*R*)-oxiran-2-ylmethyl butyrate **176** to furnish the delpazolid.



Scheme 20. Synthesis of Delazolid.

2.3.2.5. Sutezolid:

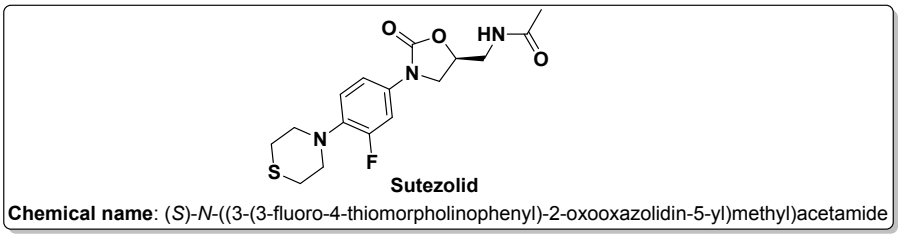


Figure 22. Sutezolid,

Oxazolidinone class of compound shown promising antibacterial activity specially activity against *M. Tuberculosis*. Brickner et. al. [112] reported two new oxazolidinone derivatives U-100592 and U-100766 which were found potent *in vitro* activity against *Mycobacterium tuberculosis.* Inspired from U-100592 and U-100766, Barbachyn et al. [113] identified Sutezolid (PNU/U-100480) with potent anti-mycobacterial activity **(Figure 22)**. Currently, Sutezolid is in phase II clinical trial for treatment tuberculosis. It is developing by Sequella. Inc, TB, Alliance. In 1996, Barbachyn et al. placed thiomorpholine moiety in their course of study at oxazolidinone class and found potent activity against *Mycobacterium tuberculosis* **(Figure 23)**.

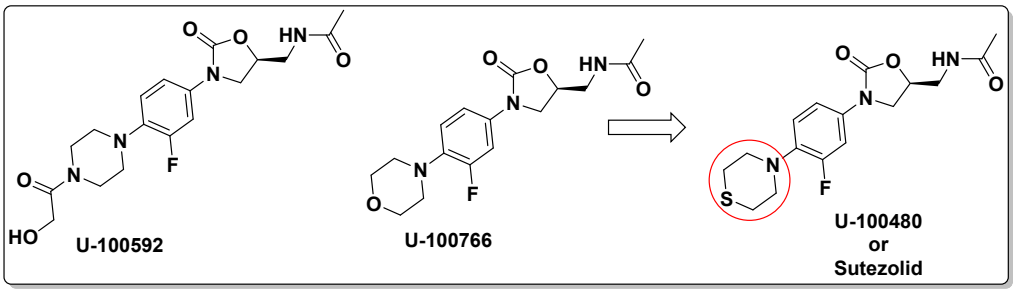
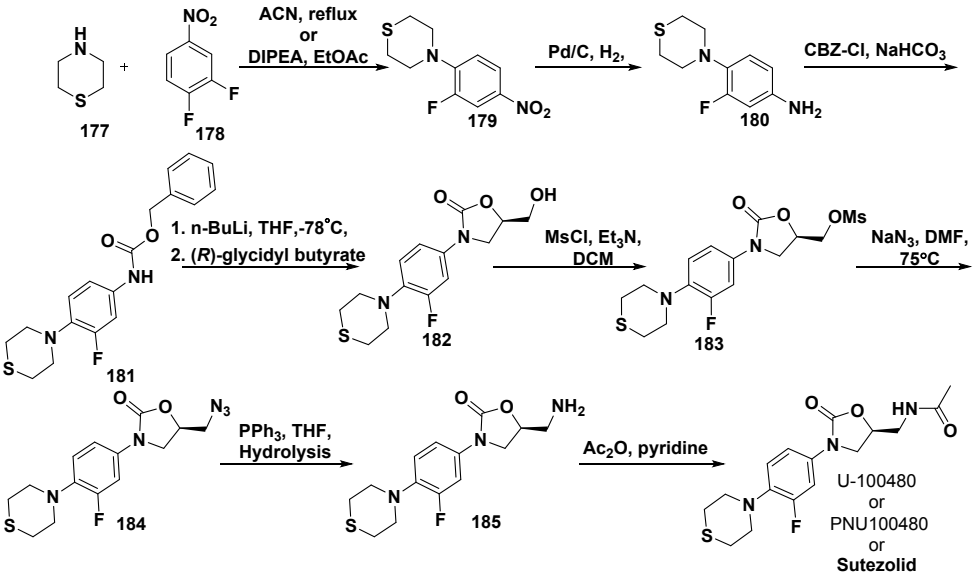


Figure 23. U-100592 and U-100766 as inspirational molecules for Sutezolid.

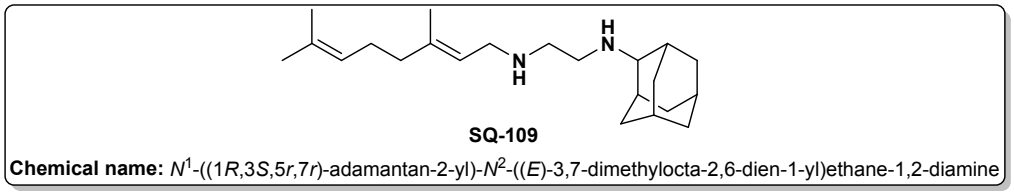
Sutezolid was showing minimum inhibitory concentrations or MIC's ≤0.125 μg/mL and MIC_{90} = 0.50 μg/mL against strain of *Mycobacterium tuberculosis.* The mechanism of action of Sutezolid was found similar to linezolid. Sutezolid attached to the 23S rRNA of the large 50S subunit of ribosome as a result, it inhibited protein biosynthesis of *Mycobacterium tuberculosis.* Metabolism of Sutezolid provided more active sulfoxide metabolite against extracellular TB. However, for the treatment of intracellular Tb in pulmonary Tb infection, the parent molecule, Sutezolid was found to be 17 times more effective than its metabolite [114].



Scheme 21. Synthesis of Sutezolid.

Barbachyn et. al. also synthesized Sutezolid as explained in **scheme 21**. 4-flouro of 1,2-difluoro-4-nitrobenzene **178** was substituted with amino group of thiomorpholine **170** in presence of ACN at reflux temperature or in presence of DIPEA and Ethyl acetate at room temperature in very first step to provide compound **179**. The nitro group of compound **179** was reduced to primary amine group in Pd/C and H_2 to achieve compound **180**. The compound **180** was reacted with Cbz-Cl in presence of $NaHCO_3$ to accomplish compound **181**. Oxazolidinone ring on compound **182** was formed when the compound **181** reacted with (*R*)-glycidyl butyrate in presence of n-BuLi and THF at -78°C. In the next step, *O*-mesylation of free hydroxy group with MsCl, Et_3N, and DCM was take place on compound **182** to provide compound **183**. Mesylate group of compound **183** was replaced with azide group in DMF solvent at 75°C which was reduced to primary amine **185** with the help of PPh_3. Finally, the acylation of compound **185** with the help acetic anhydride and pyridine provided the Sutezolid.

2.3.2.6. SQ-109



SQ-109

Chemical name: N^1-((1*R*,3*S*,5*r*,7*r*)-adamantan-2-yl)-N^2-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)ethane-1,2-diamine

Figure 24. SQ-109.

Sequella, Inc is developing SQ109 as a drug candidate molecule for treatment of *M. Tuberculosis* which has completed Phase IIb clinical trial published in Russia [115] **(Figure 24)**. The development of SQ109 was started in 2003 when Lee et al. [116] reported Ethambutol **(**EMB) inspired 1,2-diamine analogues as potential anti-tubercular preclinical candidates. Chemically, *N*-Geranyl-*N*′-(2-adamantyl)ethane-1,2-diamine (SQ109), the most active compound of diamines series, displayed a 14-35-fold improvement in activity in-vitro against *Mycobacterium tuberculosis* as compared to EMB (**Figure 25)**. In 2005, Protopopova et al. [117] reported the identification of SQ109 as candidate drug for clinical development. SQ109 exhibited selectivity index 16.7 with 99 % inhibition and shown limited *in vitro* and *in vivo* toxicity and was selected for further development. SQ109 inhibited cell wall synthesis by targeting MmpL3 protien in MTb [118,119].It had also shown excellent *in vitro* activity against both drug-sensitive, single-drug-resistant, and MDR *M. tuberculosis* strains (more than 50, including laboratory strains and clinical isolates), with a MIC range of 0.16 to 0.64 µg/ml against all *M. tuberculosis* isolates tested [120]. Moreover, SQ109 by itself at 10 mg/kg of body weight was able to reduce the number of lung CFU by over 1.5 to 2 log10 in a chronic mouse model of Tb that was similar to monotherapy with ethambutol (EMB) at 100 mg/kg. SQ109 was found bactericidal against both MDR-Tb and XDR-Tb causing *M. tuberculosis* strains [121]. However, SQ109 was found to be active against ethambutol-resistant strains which indicated that the mode of action of SQ109 is different from ethambutol.

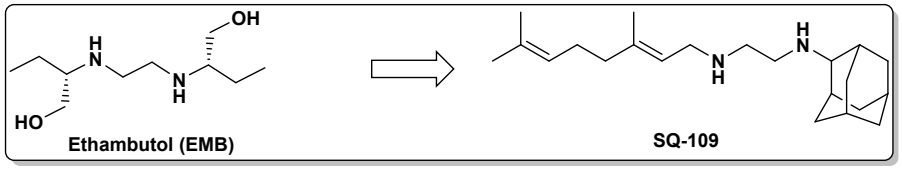
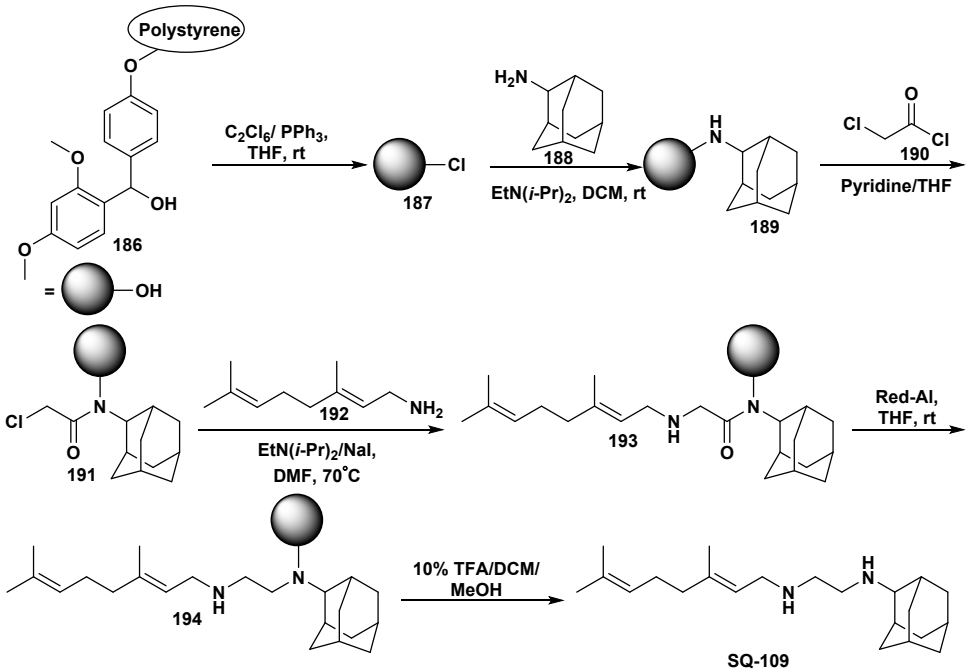


Figure 25. Identifcation of SQ-109 form Ethambutol.

Lee et. al. also reported synthesis of SQ109 as illustrated in **scheme 22**. In very first step, Rink acid resin (Novabiochem) **186** was converted to the Rink chloride resin **187** upon treatment with triphenylphosphine and hexachloroethane in THF at room temperature. This activated resin **187** was then loaded with an amine (N-1) **188** in the presence of Hu¨nig's base in dichloroethane to provide **189**. Acylation on the resultant resin-bound secondary amine **189** was accomplished using 2-chloroacetyl chloride **190** in the presence of pyridine and THF to provide α-chloro-amide resin **191**. Incorporation of the second nitrogen moiety as a secondary amine into the α-chloro-amide resin **191** was achieved by reaction with (*E*)-3,7-dimethylocta-2,6-dien-1-amine **192** in the presence of Hu¨nig's base in DMF at 70°C in the presence of catalytic sodium iodide [122] to get corresponding aminoethyleneamides molecule **193.** Reduction of the corresponding aminoethyleneamides into corresponding diamines **194** was carried out using the soluble reducing reagent Red-Al at room temperature. Cleavage of the product SQ109 from the resin was achieved with a 10% solution of TFA in dichloromethane (DCM).



Scheme 22. Synthesis of SQ-109.

2.3.3. Phase III

2.3.3.1. Bedaquiline

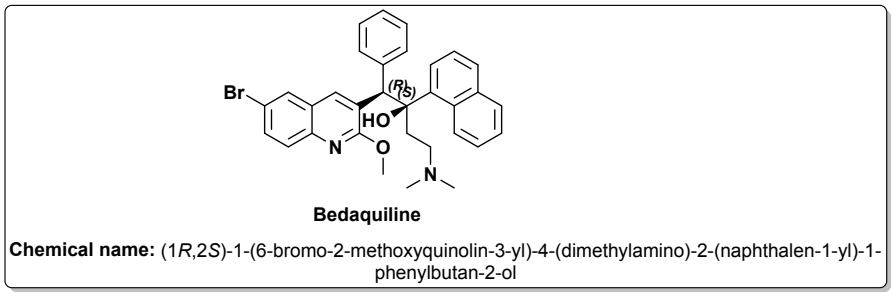


Figure 26. Bedaquiline.

Phase III clinical candidate drug, Bedaquiline was approved by the US Food and Drug Administration (FDA) first time in 40 years on 28 December 2012 to specific use in treatment of resistant tuberculosis (Tb) in combination of other drugs [123,124,125,126] more prevalent in India, China and Eastern Europe [127]. Chemically, Bedaquiline (code name: R207910 or TMC 207) is 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphtalen-1-yl-1-phenyl-butan-2-ol with 1R,2S stereochemistry consisting of diarylquinoline scaffold **(Figure 26)**. TMC207 was found to be very potent against both drug susceptible and drug resistant clinical isolates of *M. tuberculosis* with a MIC range of 0.03-0.12 µg/ml [128]. In ATP synthase pocket of *Mycobacterium Tuberculosis*, Bedaquiline exhibited various type of chemical interaction namely hydrophobic (pi-pi stacking), ionic interaction of positive charged and negative charged of bedaquiline, and also hydrogen bonding **(Figure 27)**.

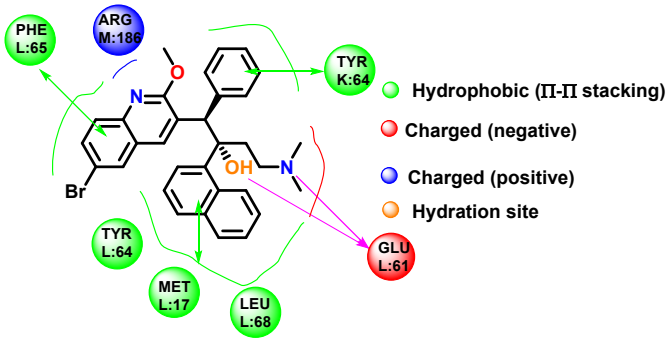


Figure 27. Chemical interaction sits of bedaquiline in pocket of ATP synthase of *Mycobacterium Tuberculosis* [129].

This drug, also be called Sirturo (trade name), was discovered by scientists at Janssen, the pharmaceuticals unit of Johnson and Johnson and transferred to Tibotec Pharmaceuticals for clinical development [130] It was the first in a new class of drugs that aims to treat the drug-resistant strain of the disease. However, WHO had given interim policy guidelines [131] for use of Bedaquiline in MDR-TB. Bedaquiline shows some potential drawbacks like inhibition of the hERG (human Ether-à-go-go-Related Gene; KCNH2) potassium channel [132] (with the concomitant risk of cardiac toxicity), hepatic toxicity [133] and possibly a risk of phospholipidosis [134] (related to its high lipophilicity [calculated clogP of 7.25]) [135]. Bedaquiline targeted the mycobacterial ATP synthase. ATP generation is important for cell survival of both prokaryotic and eukaryotic cells [136]. ATP synthase is made up of

a transmembrane (F0) and a cytoplasmic (F1) domain [137]. Here, Proton flow through the F0 domain leads to a rotation of the c and γ subunits of the F1 domain. This rotation drives ATP synthesis at the $\alpha_3\beta_3$ hexamer [138]. When bedaquiline binds to the site placed between a and c subunits of the F0 domain, near amino acid residue Glu-61 [139] **(Figure 28)** it results in jamming the proton flow and the subsequent conformational changes which finally derives the synthesis of ATP from ADP. Cell death occurs in both replicating and non-replicating mycobacteria by blocking of ATP production and a change in pH homeostasis, making bedaquiline a bactericidal antibiotic [140]. Bedaquiline was found to be very selective towards mycobacterial ATP synthase, compared with the human homologue, despite high similarity in protein sequence [141].

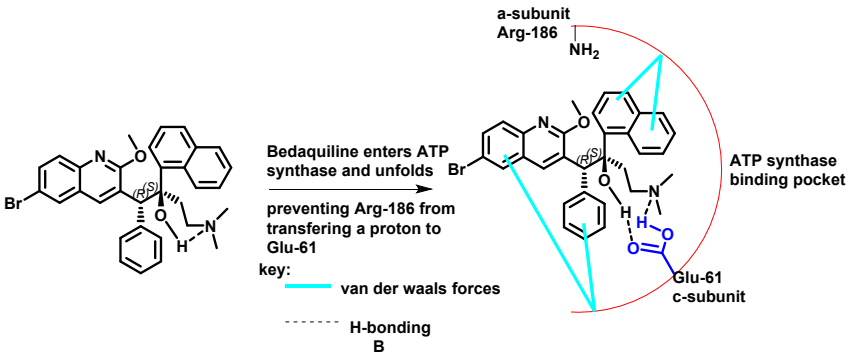
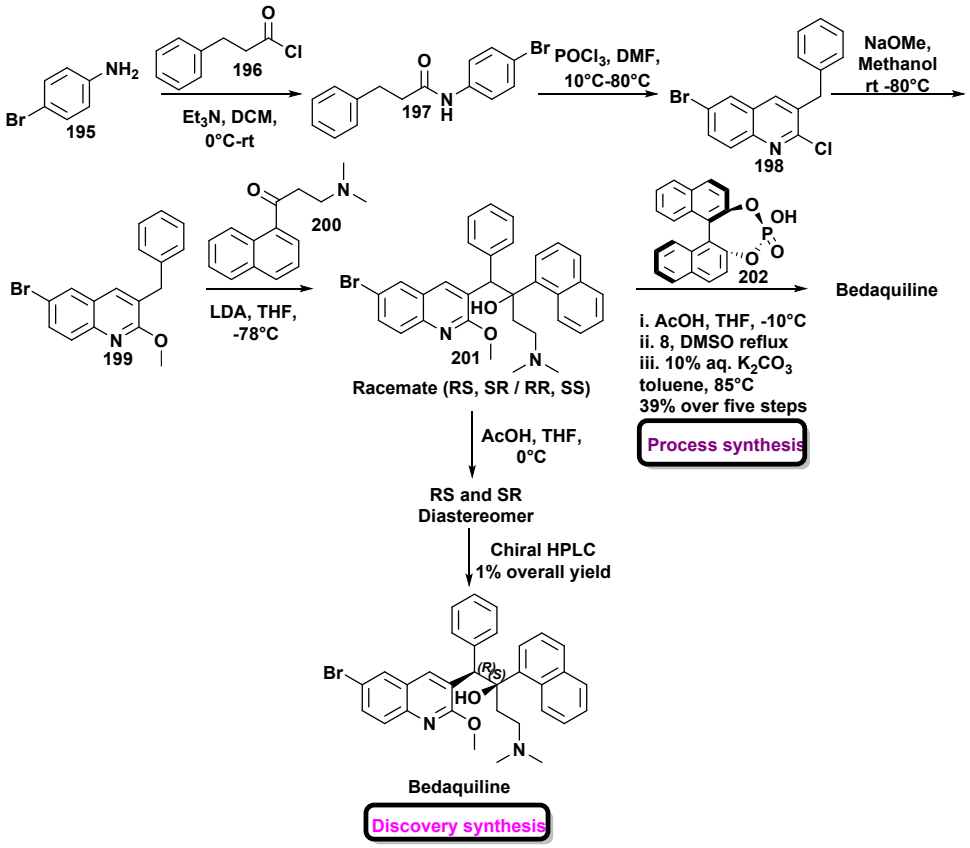


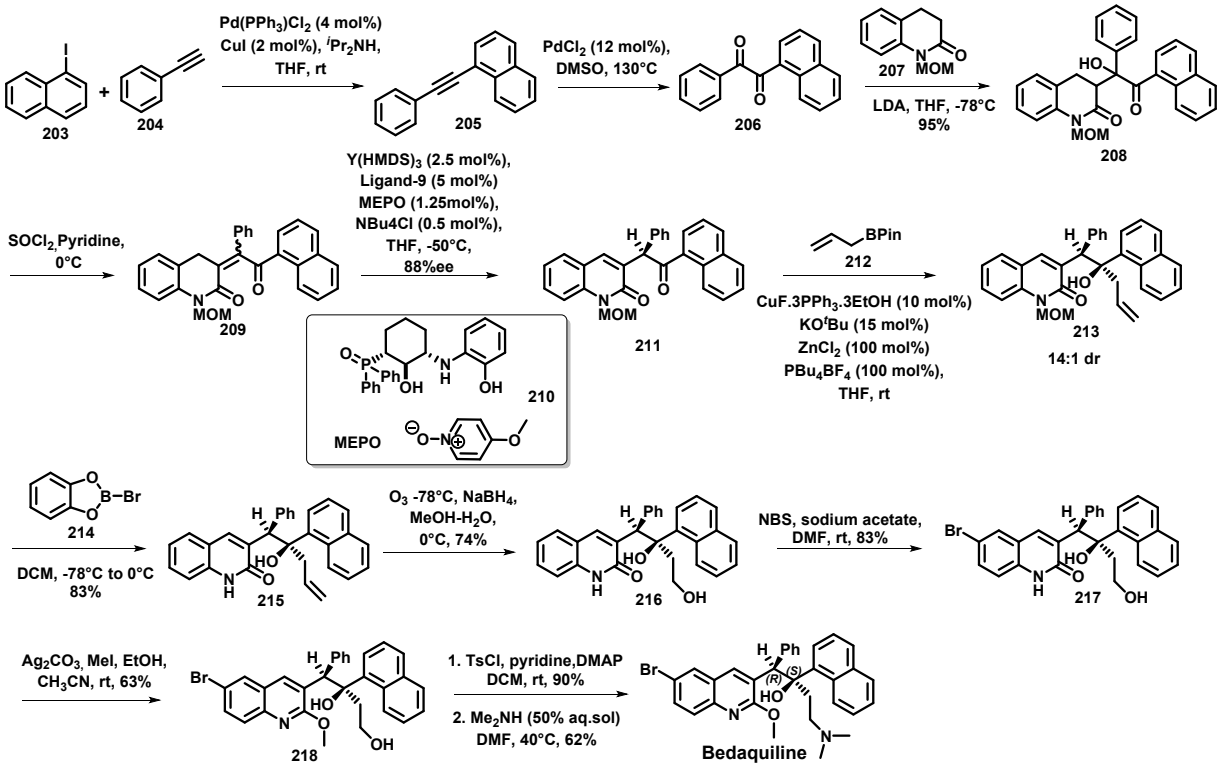
Figure 28. Mechanism of action of bedaquiline: A. binding site of bedaquiline [142]; B. Attachment of bedaquiline with Glu-61 in c-subunit preventing transfer of proton from Arg-186 to Glu-61.

Janssen Synthesis of Bedaquiline [143,144] was discussed in **scheme 23**. 4-bromoaniline **195** was reacted with 3-phenylpropanoyl chloride **196** to give compound **197.** The Vilsmeier- Haack formylation of the corresponding 3-phenylpropanoyl chloride **197** afforded the 2-chloroquinoline intermediate **198**. The 2-chloroquinoline derivative **198** was converted into the desired 2-methoxyquinoline **199** in the presence of sodium methoxide and methanol at 80°C. Finally, metallation of derivative **199** with lithium diisopropylamide at -78°C and the subsequent addition of ketone **200** (prepared by Mannich reaction from acetonaphthone) to the lithio derivative led to a mixture of four isomers **201** with an excellent overall yield (27,5%, 5 steps). In the discovery synthesis, racemate **201** was treated with AcOH in THF solvent to get RS and SR Diastereomer and the final desired isomer was separated with Chiral HPLC. However, Process synthesis, Chiral HPLC in final purification was avoided as racemate **201** was treated acetic acid followed by treatment with chiral phosphoric acid **202** to get bedaquiline.



Scheme 23. Janssen Synthesis of Bedaquiline

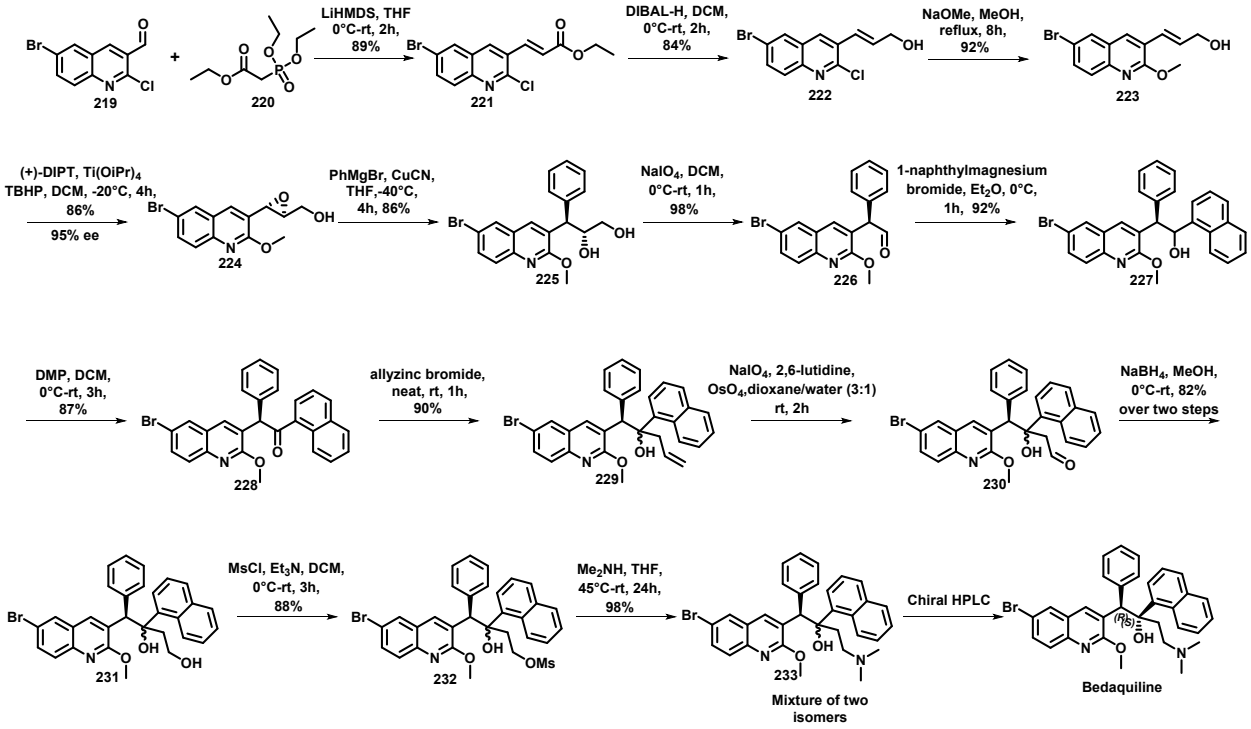
Shibasaki et. al. [145] reported Catalytic Asymmetric Synthesis of R207910 (Bedaquiline) in 2010 based on the development of two novel catalytic transformations that were catalytic enantioselective proton migration and catalytic diastereoselctive allylation as illustrated in **scheme 24**. The very first step was palladium catalyzed Sonogashira reaction between 1-iodonaphthalene **203** and ethynylbenzene **204** to achieved unsymmetrical diarylalkyne derivative **205.** The compound **205** was oxidized into 1, 2 diketone derivative **206** in presence of $PdCl_2$ (12 mol%) and DMSO at 130°C. Compound **208** was synthesized via a site-selective aldol reaction between **206** and **207**. Dehydration reaction with the help of thionyl chloride and pyridine at 0°C on compound **208** provided compound **209.** Catalytic enantioselective proton migration reaction on compound **209** through a chiral metal dienolate generated via deprotonation accomplished ketone intermediate **211**. Diastereoselective construction of the tetrasubstituted carbon **213** through the addition of a carbon nucleophile (allyl boronate **212**) to ketone **211** was achieved in presence of CuF•3PPh3•2EtOH (10 mol %), KO*t*-Bu (15%), $ZnCl_2$ (100 mol %) and PBu_4BF_4 (100 mol %) in THF solvent at room temperature.



Scheme 24. Shibasaki synthesis of bedaquiline

After synthesis of enantiomerically pure key intermediate **213**, the cleaving of *N*-methoxymethyl (MOM) group of was completed in presence *B*-bromocatecholborane **214** in DCM at -78 ºC to get compound **215**. Ozonolysis of allylic group of compound **215** in the reaction with O_3 followed by reductive treatment with the help of sodium borohydride produced diol **216**. Regioselective bromination of **216** with NBS preceded bromo derivative **217** in 83% yield in the presence of buffer NaOAc. Selective *O*-methylation of **217** was found little challenging as the substrate has undesired competitive nucleophilic sites. A combination of Ag_2CO_3 and MeI, produced the desired *O*-methylated product. But, *O*- methylation also occurred at the primary alcohol oxygen atom. This side reaction was effectively suppressed by adding a dummy substrate, EtOH, to the reaction mixture. Thus, the desired product **218** was obtained in 63% yield. Finally, *O*-tosylation with tosylchloride in pyridine atmosphere followed by nucleophilic substitution with Me_2NH (50% aq. Sol.) afforded R207910.

In year 2011, Chandrasekhar et al. [146] reported the practical synthesis of bedaquiline in 10 linear steps starting from a known compound. The synthesis of bedaquiline with name (*S*) R207910 was explained in **scheme 25**.



Scheme 25. Chandrasekhar synthesis of bedaquiline.

The known intermediate 6- bromo-2-chloroquinoline-3-carbaldehyde [147] **219** (prepared from 4-bromo-acetanilide following Vilsmeier–Haack modified protocol) was reacted to lithium enolate of the phosphonate [(OEt)2P(O)CH2CO2Et] **220** under Horner- Wadsworth-Emmons olefination to afford α,β-unsaturated ester **221** in 89% yield with complete *E*-selectivity. The reduction of unsaturated ester of compound **221** with DIBAL-*H* at 0°C accomplished the allyl alcohol **222**. The allylic alcohol **222** was reacted with sodium methoxide to provide 2-methoxy derivative **223**. In the next most important step, the Sharpless asymmetric epoxidation was carried out on 2-methoxy derivative **223** with (+)-DIPT, Ti(O*i*Pr)4, TBHP in DCM solvent at -20°C to afford epoxy alcohol **224** in 86% yield (95% *ee*). Subsequent reaction of the epoxide **224** with PhMgBr in the presence of CuCN furnished diol **225** in yield of 86%. The diol **225** was cleaved oxidatively with the help of $NaIO_4$ impregnated over silica gel to furnish crude aldehyde **226.** Without purification, the aldehyde **226** was subjected to 1-naphthylmagnesium bromide to obtain secondary alcohol **227** as a mixture of isomers. The oxidation of secondary alcohol **227** with Dess-Martin periodinane in DCM solvent afforded the keto derivative **228** in 81% of yield with high enantiomeric purity (95% *ee*). Intestinally, the construction of tetrasubstitute carbon on keto derivative **228** through conventional nucleophiles like allylmagnesium, allylaluminium, allylindium, allylboronate, and allylstannane derivatives was not successful. However, Wang et al. [148] reported allylzinc bromide reaction with carbonyl compound played important role in construction of desired tetrasubstituted carbon. When the keto derivative **228** was treated with allylzinc bromide in THF solvent, inseparable mixture of olefin compound **229** in ratio of 2:3 in favor of unwanted diastereomer was

observed. Additionally, ratio changed to almost equal amounts of diastereomers by using chelating agents $CuBr{\cdot}Me_2S$ in the reaction mixture. Oxidative cleavage of olefin in compound **229** using $OsO_4/NaIO_4$ in presence of 2,6-lutidine afforded aldehyde **230** in mixture of diastereomer. The aldehyde **230** was treated with $NaBH_4$ in methanol at 0°C to obtain the diol **231** in 82% of yield over two steps. Finally, selective *O*-mesylation of one hydroxyl group of compound **231** with the help of MsCl, Et_3N and DCM followed by displacement of the mesylate group in **232** with dimethylamine furnished the mixture of Bedquiline [(2*S*)-R207910] and (2*R*)-R207910 **233** in 79% yield over two steps. The products were separated easily by silica gel chiral chromatography (ethyl acetate:hexane = 1:6).

2.3.3.2. Pretomanid:

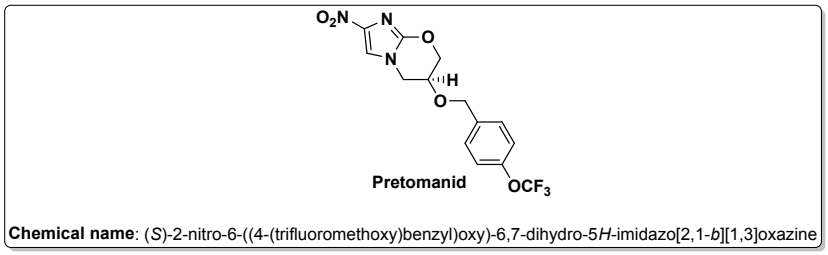
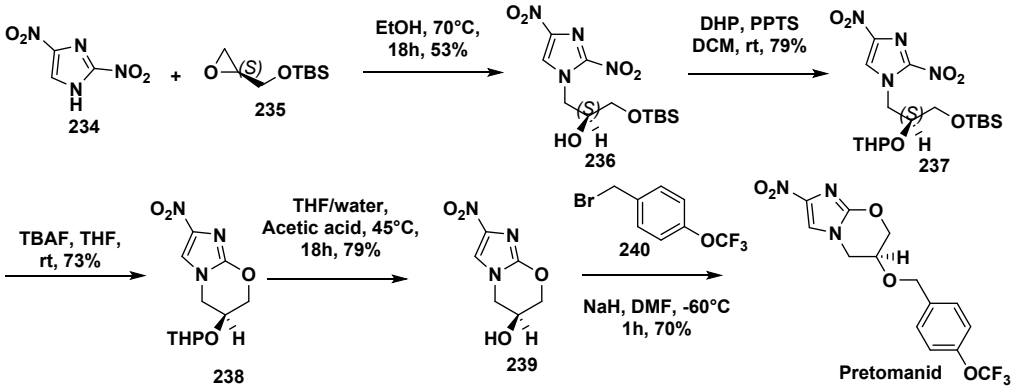


Figure 29. Pretomanid.

Pretomanid also known as PA-824, is currently in Phase III clinical trials and is developing by Novartis (formerly Chiron) and the Global Alliance for TB Drug Development. However, US FDA has approved pretomanid on **14 Aug 2019** as part of combination therapy with bedaquiline and linezolid MDR Tb and XDR Tb [149]. Chemically, Pretomanid is compound of the nitroimidazopyran class **(Figure 29)**.

The story of development of pretomanid was started when Stover et al. [150] reported nitroimidazopyran based PA-824 as candidate drug molecule inspired from CGI 17341 for treatment of tuberculosis in year 2000. Stover et al. described that PA-824 was showing potent bactericidal activity against multi-drugresistant *M. tuberculosis* (MDR-Tb). PA-824 exhibited a sub-micromolar minimal inhibitory concentration (MIC) against a panel of MTB pan-sensitive and rifampin mono-resistant clinical isolates ranged from 0.015 to 0.25 mg/ml. The bicyclic nitroimidazole PA-824 was a pro-drug and exhibited a very complex mechanism of action against both replicating and hypoxic, non-replicating *Mycobacterium tuberculosis*. Stover et al. claimed that PA-824 inhibited oxidation of hydroxymycolates to ketomycolates, a lipid class that makes the mycobacterial pseudo-outer membrane and over one-third of the dry weight of MTb [151].

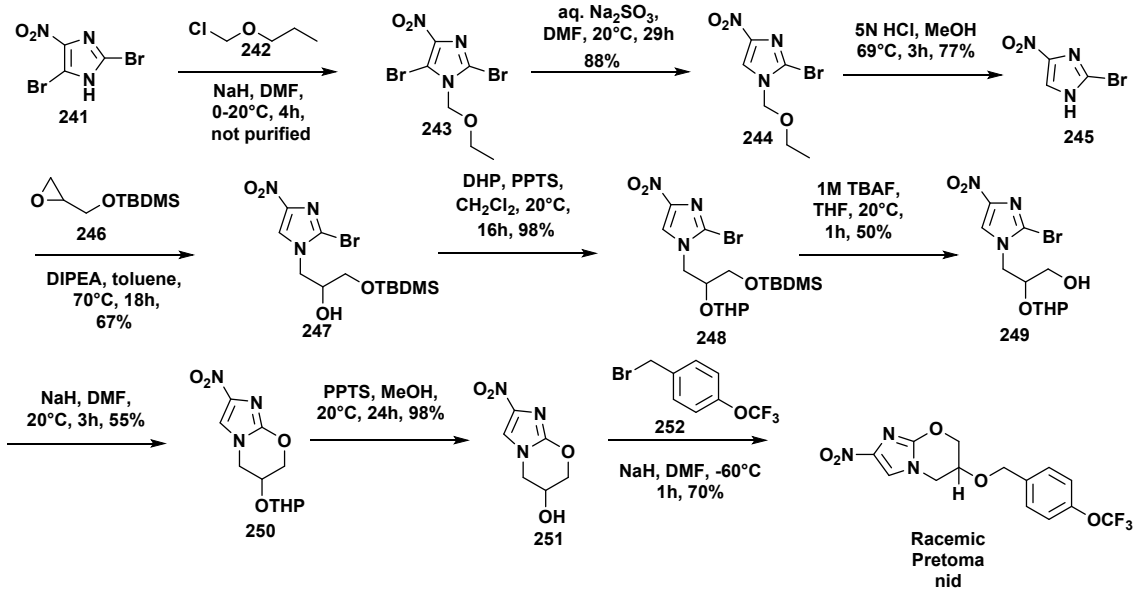


Scheme 26. Synthesis of Pretomanid.

Manjunatha et al. [152] also explained the mechanism of action of pretomaind. Microarray analysis of the mode of action of PA-824 showed that it acts on genes responsive to both cell wall inhibition (like isoniazid) and respiratory poisoning (like cyanide). It is still a puzzle that how aerobic killing mechanism inhibits of cell wall mycolic acid biosynthesis. However, based on the metabolite profiling of PA-824 and various derivatives by Ddn-mediated activation, Singh et al. [153] showed that PA-824 acts directly as an NO donor. In consequence of nitric oxide release was found to be a crucial element of anaerobic activity by PA-824 which gives respiratory poisoning. Under hypoxic non-replicating conditions, the effect of PA-824 on the respiratory complex was responsible for a rapid drop in intracellular ATP levels which is similar to that observed by cyanide treatment.

Synthetic approach [154,155] for synthesis of Pretomanid was illustrated in **scheme 26**. 2,4-dinitroimidazole **234** was reacted with (*S*)-glycidil tributylsilyl ether **235** through epoxide ring opening reaction in presence of EtOH at 70°C to provide the tributylsilyl alcohol containing compound **236.** This tributylsilyl alcohol **236** was converted to its tetrahydropyrane ether protection of only free hydroxyl group with the help of dihydropyrane and pyridinium *p* toluenesulfonate to get **237**. Desilylation of **237** with TBAF under spontaneous cyclisation afforded **238**. The THP deprotection of compound **238** was carried out in acidic conditions to give free hydroxyl compound **239**. Finally, compound **239** was benzylated with **240** in presence of sodium hydride and DMF to accomplished PA-824 in 17% overall yield. The explosive starting material 2,4-dinitroimidazole **234** (mentioned in scheme 26) was avoided in racemic synthesis of pretomanid reported by Thompson et al. [156] as described in **scheme 27**. 2,5-dibromo-4-nitroimidazole **241** was used the starting material which was reacted with 1-(chloromethoxy)propane **242** to give ethoxymethyl protection **243** of secondary amine in presence of sodium hydride as base. Reduction of compound **243** (one bromo elimination) with sodium sulfite provided mono-bromo compound **244**. The cleavage of the ethoxymethyl protecting group with 5N HCl gave **245** in very good overall yield from **244.** TBDMS ether of racemic glycidol **246** was reacted with compound **245** in presence of DIPEA, and toluene to provide 4-nitroimidazole **247**. THP protection of the secondary hydroxyl group in **247** gave compound **248**. Compound **248** was reacted with excess TBAF at room temperature to give the primary alcohol **249**. The

spontaneous cyclization of compound **249** was take place in presence of sodium hydride to furnish the bicyclic product **250**. THP deprotection of **250** in presence of PPTS and methanol provided hydroxyl compound **251**. Finally, compound **251** was benzylated with **252** in presence of sodium hydride and DMF to accomplished PA-824 as racemic mixture.



Scheme 27. Synthesis of racemic Pretomanid.

2.3.3.3. Delamanid:

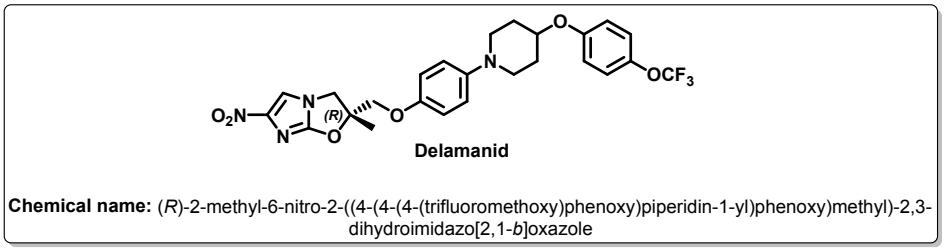


Figure 30. Delamanid.

Phase III candidate drug, Delamanid (formerly called as OPC-67683) is drug candidate for Tb and also known by its trade name of Deltyba. Delamanid comes from nitroimidazoles **(Figure 31)**. Currently, Delamanid is developing by the Otsuka pharmaceutical company as a treatment for MDR Tb. However, Delamanid received its first global approval for the treatment of MDR-TB in the European Union (EU), for use in combination with optimized background therapy [157]. In year 2006, Sasaki et al. [158] identified delamanid (OPC-67683) as effective antitubercular agent for both drug-susceptible and drug-resistant strains of *Mycobacterium tuberculosis.* Delamanid (OPC-67683) exhibited excellent *in-Vitro* activity against both drug-susceptible and drug-resistant strains of *M. tuberculosis* H37Rv (MIC = 0.006 μg/mL). The thoughtful discovery of delamanid was inspired from

Metronidazole (from class of Nitroimidazole) which is widely used for the treatment of anaerobic bacteria and protozoan infections but Metronidazole shown poor potency against *M. tuberculosis* [159]. Furthermore, development of delamanid encouraged by the bicyclic nitroimidazooxazole (CGI 17341) [160] reported by researchers at Ciba-Geigy with antitubercular activity in 1989. However, in further study, CGI 17341 was found mutagenic in nature [161] **(Figure 31)**.

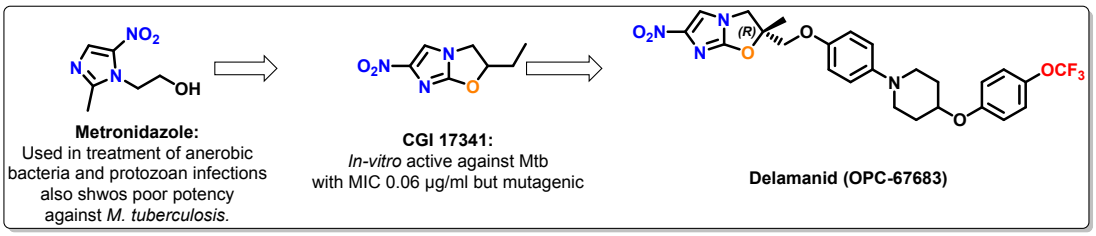
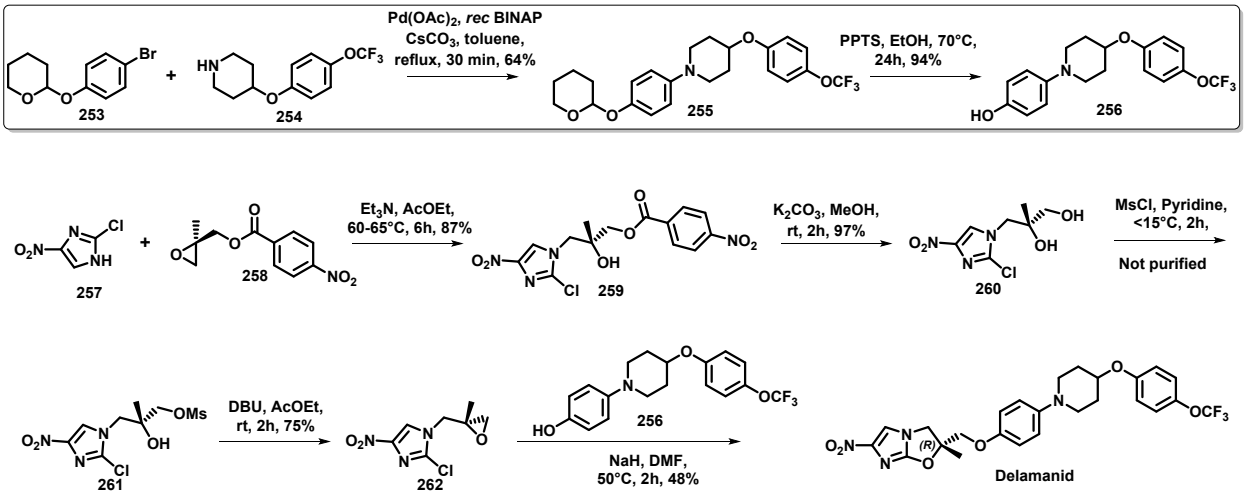


Figure 31. Development of Delamanid.

Later, Bicyclic nitroimidazopyran, (PA-824), was developed by research group at Pathogenesis Corporation that exhibited potent bactericidal activity against MDR-Tb and promising oral activity in animal infection models. Based on all the above facts, 6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole core (found in CGI 17341) was selected because of its inhibitory activity against mycolic acid biosynthesis [162], which plays an important role in mycobacteria [163] and along with change at the 2-position of 6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazoles in order to enhance antituberculosis activity and eliminate mutagenicity which finally led to discovery of delamanid. Delamanid inhibited the mycolic acid synthesis similar to INH with slight change. Delamanid inhibited the synthesis of methoxy and keto mycolic acid but not the synthesis of α-mycolic acid. However, INH inhibited all types of mycolic acid subclasses.

Delamanid required metabolic activation by *M. tuberculosis* in order to show the anti-Tb activity. Rv3547 was found the catalytic enzyme responsible for the metabolism of delamanid. The main metabolite formed in the presence of *M. tuberculosis* was characterized as a non-active desnitro-imidazooxazole [164]. Hence, one can be understand that Rv3547 has a reduction potency of the nitro residue which was an intermediate between OPC-67683 and the desnitro-imidazooxazole and could be the active form. The mechanism of action of metronidazole derivatives against *H. pylori* due to the production of a radical intermediate [165] has been reported. This indicated that a radical intermediate obtained from metabolism of a nitro residue covalently binds to the target molecule. Sasaki et. al. also reported synthesis of delamanid as illustrated in **scheme 28**. 2-chloro-4-nitro-1H-imidazole **257** was reacted with the (*R*)-2-methyl-2,3-epoxypropyl 4-nitrobenzoate **258** [166] in the presence of triethylamine in ethyl acetate to afford **259**. De-esterification of compound **259** with methanol and a catalytic amount of potassium carbonate to provide the 1,2 diol **260**. Selective *O*-mesylation of primary alcohol of compound **260** with methanesulfonyl chloride in pyridine provided the mesylate **261**. The compound **261** was easily converted into the (*R*)-form epoxide **262** with 1,8- diazabicyclo[5.4.0]-7-undecene (DBU) in ethyl acetate at room temperature. Finally,

the target compound delamanid was synthesized by epoxide ring opening reaction of compound **262** with phenolic compounds **256** (prepared from palladium catalysed coupling of bromo-compound **253** and amino compound **254**, followed by THP deprotection in presence of PPTS, and EtOH at 70°C), followed by ring closure in the presence of sodium hydride in *N*,*N*-dimethylformamide.



Scheme 28. Synthesis of Delamanid.

3. Future prospective of tuberculosis & Conclusion

To reduce the global burden of Tb, we have to make certain strategies. We should focus on screening of active Tb infection, control and prevention.. We have to eradicate poverty, improve the health and protection, and strengthen the social sector policies and systems to prevent tuberculosis. In addition to this, we have to do intensified research and innovation to develop new drug molecules and vaccines. Tb prevention step is taken to reduce the risk of Tb infection progressing to Tb disease. Tb preventive treatment should be recommended to the people living with HIV, household contact of confirmed pulmonary Tb cases, clinical risk groups. To reach the target of lowering Tb and to increase the speed at which we are reducing the Tb incidence, new tools are required. Among the new tools visions are on new drugs and treatment regimens for Tb infection. Another avenue in this direction is repurposing of medications already FDA-approved for other indications, when strong experimental evidence exists to justify a potential anti-mycobacterial effect. To make easier and comfortable treatment of Tb, there is need of focused research towards treatment with one drug that should act through multi-target mechanism with short duration of treatment which can also reduce the risk of development of resistant Tb. However, to reduce the toxicity and side effects, the new drug should be specific to protein of mycobacterium. Moreover, looking for the discovery of new drug candidates with novel mechanism of action would help in the treatment of resistant Tb. The current medications available for the treatment of tuberculosis have succeeded in changing this disease in many patients to normal condition. There were various novel Tb drugs in combination trials with one another, or with existing Tb drugs to hit multiple targets in different pathways to kill *mycobacteria tuberculosis.* The various ongoing

Clinical Development work on novel Tb regimen include BPaL (bedaquiline + pretomanid + linezolid) and BPaMZ (Bedaquiline + pretomanid + Moxifloxacin + pyrazinamide). Pretomanid in combination with bedaquiline and linezolid approved by US FDA for treatment of adult patients with extensively drug resistant, treatment-intolerant or nonresponsive multidrug resistant pulmonary Tb [167].

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Biography

Amit kumar received his B. Pharmacy (2012) from Gautam Buddh Technical University (GBTU), Lucknow (India) and Master of Science (Pharm) in Medicinal chemistry (2014) from National Institute of Pharmaceutical Education and Research (NIPER), Raebareli (India). He has also qualified several national level exams like Graduate Pharmacy Aptitude Test (GPAT-2012), NIPER Joint Entrance Examination (NIPER-JEE- 2012), Graduate Aptitude Test Engineering (GATE Chemistry -2014 and 2015) and CSIR- NET-JRF (Chemical Science-2016). He was also former research associate at Jubilant chemsys Ltd. Noida (18 months). He is currently pursuing his Ph.D. with Dr. Gautam Panda at CSIR-Central Drug Research Institute, Lucknow. His current research interest is the design and synthesis of bioactive molecules against *Mycobacterium Tuberculosis* (Mtb).

Dr. Bidhu Bhusan Karkara was born in Koraput district of Odisha. After passing his B.Pharm from Jeypore College of Pharmacy, jeypore in 2010, he completed his M.Pharm from Indira Gandhi Institute of Pharmaceutical Sciences, Bhubaneswar in 2012. He joined Dr. Gautam Panda group in CDRI in 2015 as a Junior Research Fellow (JRF) for pursuing doctoral program and obtained his Ph.D. degree on thesis entitled "**QUEST FOR ANTIMYCOBACTERIAL AGENTS FROM TRISUBSTITUTED METHANES AND NITROGENS**" in 2019. Dr. Bidhu Bhusan Karkara is currently working as Assistant Professor in Vignan's Foundation for Science, Technology and Research University (Deemed to be University) Guntur, Andhra Pradesh.

After receiving B. Sc. and M.Sc. in Chemistry from Calcutta University and Indian Institute of Technology (IIT) Kharagpur respectively, Dr. Gautam Panda had completed Ph.D. in 1999 working with Prof. Goverdhan Mehta at University of Hyderabad, India. He was a visiting fellow at National Chiao Tung Univ., Hsinchu, Taiwan, in the laboratory of Prof. Tse Lok Ho, Taiwan in 1999 before pursuing his postdoctoral work (2000-2001) in the group of Dr. Prabhat Arya, National Research Council, Ottawa, Canada and Prof. Howard Alper, University of Ottawa. Later he has started his own research career at CSIR-Central Drug Research Institute (CDRI), Lucknow in 2002 where currently he is a senior principal scientist and Professor at Academy of Scientific and Innovative Research (AcSIR), New Delhi. He has published over 100 papers and is inventor of three patents.

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