Chapter 3

New Drugs for Treating Tuberculosis in the Clinics and Clinical Trials - An Update

3.1 Drugs in Discovery and Development Stages

Chemotherapy for tuberculosis presents a very unique set of problems to both doctors and patients. The treatment usually involves multidrug therapy with more than 2 drugs for duration of 3 to 18 months. The patient consumes over 300 pills in the course of therapy. If the patient complies, this regimen offers curative therapy. Failure to do so leads to either treatment failure and/or development of drug resistance. Though implementation of DOTS (Directly Observed Treatment Short course) increased the success rate of drug susceptible TB therapy, lack of a good treatment regimen still remained a major barrier to the scale up of access to treatment.[1]

Ideally, every anti TB drug discovery program looks for a molecule with novel mechanism of action so that the molecule can be used against bacteria resistant to existing drugs. Potency and optimal pharmacokinetics are essential for reducing the treatment duration as well as the pill burden. Compounds with selective inhibitory profile, less drug-drug interactions and increased safety window are preferred.[2]

Increase in the involvement of governments and other agencies and increased financial burden of clinical trials made many industries to wean away from this category, which apparently resulted in scarce novel clinical agents for the treatment of multidrug and extensively drug-resistant tuberculosis (MDR/XDRTB). In the year 2000, the Global Alliance for TB Drug Development (GATB) [3] was established with an objective to develop new agents that will shorten the duration of chemotherapy from the current 6–8 months to two months or less, although new drugs with activity against MDR-TB and latent TB are also needed. These efforts resulted in the discovery

of sizeable number of molecules with novel mechanism of action and clinical efficacy in the last decade. They were in various stages of clinical trials and a few potential candidates successfully made it to the market.[4, 5]

Fundamental uncertainties in many aspects of the biology of the organism have substantially hampered the ability to identify critical targets whose inhibition would correlate with sterilising activity. Sterilizing activity refers to the ability of a drug (such as pyrazinamide or rifampicin) to kill those organisms, known as 'persisters', that survive treatment with agents targeting essential processes in dividing bacteria. It is only by discovering new agents with improved sterilising activity that a shorter treatment regimen can be developed.

The past decade has seen intensive efforts to discover and develop new drugs to treat drug-susceptible-, MDR- and XDR-TB, and new combination regimens are also being devised and tested in clinical trials (Fig. 3.1; Table 3.1). New regimens will most likely employ a combination of repurposed drugs and new chemical entities (NCE) and there is a real likelihood that these regimens may contain none of the drugs previously used in TB treatment.

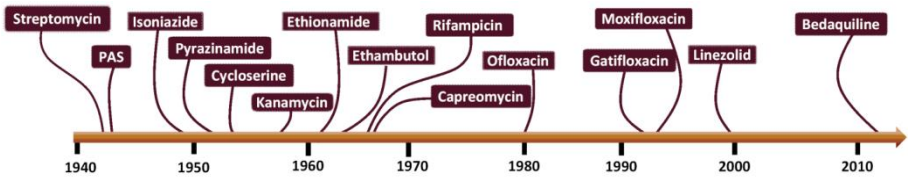


Fig. 3.1 *Timeline scale of anti TB drugs. Bedaquiline (2013) is the only novel drug approved for treating TB after rifampicin (1963).*

Table 3.1 *Global TB Drug Pipeline*.*

Lead Optimization	Early Stage Development	GLP Tox	Phase I	Phase II	Phase III
• Cyclopeptides • Diarylquinoline • DprE inhibitors • InhA inhibitor • LeuRS inhibitor • Macrolide • Mycobacterial gyrase inhibitors • Pyrazinamide analogues • Spectinamides • Translocase-1 inhibitors • Ruthenium complexes	• CPZEN-45 • DC-159a • Q203 • SQ609 • SQ641 • TBI-166	PBTZ169 TBA-354 BTZ043		• AZD5847 • Bedaquiline • Linezolid • PA-824 • Rifapentine • SQ-109 • Sutezolid **Novel regimens#** • J-M-Pa-Z • M-Pa-Z • C-J-Pa-Z • H-R-Z-E-Q-M	• Delaminid • Gatifloxacin • Moxifloxacin • Rifapentine

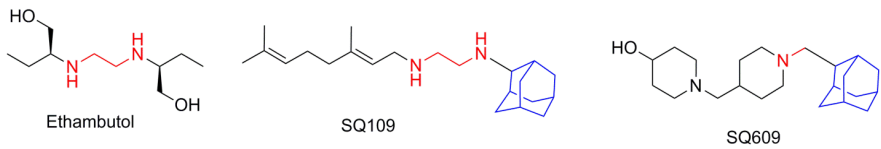
J-Bedaquiline; M-Moxifloxacin; Pa- PA-824; Z- Pyrazinamide; C-Clofazimine; H- Isoniazid; R-Rifampicin; E- Ethambutol; Q- SQ109

* Updated information can be obtained from http://www.newtbdrugs.org/pipeline.php and http://www.newtbdrugs.org/pipeline-discovery.php

3.1.1 Diamines (SQ109)

Ethambutol (EMB) is a very important first line drug for TB therapy. It has a very unusual mycobacterial specific inhibitory activity. But mycobacteria were found to develop resistance to this drug very quickly. Hence, Protopopova and his team working at Sequella Inc., in collaboration with NIH/NIAID prepared a huge combinatorial library of EMB analogues and screened for anti TB activity.[6] Out of 26 active compounds SQ109 exhibited very potent activity in broth micro-dilution assay (MIC = 0.2 mM). SQ109 is currently in Phase IIa trials. Interesting feature of SQ109 is its activity against strains resistant to isoniazid, rifampicin and ethamutol.[7] It has synergistic activity with most of the major front line antiTB agents.[8] This drug has multitarget inhibition which ultimately results

in mycobacterial cell wall damage (Fig. 3.2). In an attempt to define the target of SQ109 and its possible mechanism of action, a proteomic study of the effects of SQ109, EMB and Isoniazid was performed. The effects on ESAT-6/CFP-10 expression were more pronounced for isoniazid and ethambutol but equal for all three compounds in the case of AhpC.[9] Surprisingly SQ109 did not affect *Emb*A and *Emb*B, the target proteins for Ethambutol. The primary target of SQ109 was only recently identified as MmpL3, a transmembrane transporter of trehalosemonomycolate.[10]



Further studies on the ethylenediamine scaffold demonstrated SQ609 to be the most promising compound of this class.[11] It showed good in vitro activity against clinical isolates of *M. tuberculosis*. In a 20-day *M. tuberculosis*-induced weight-lossmouse model, SQ609 successfully restored normal health, improved survival rate and prolonged the therapeutic effect following drug withdrawal for another 10-15 days.

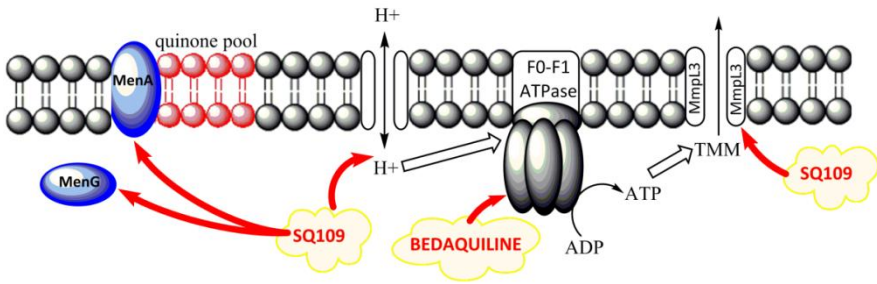
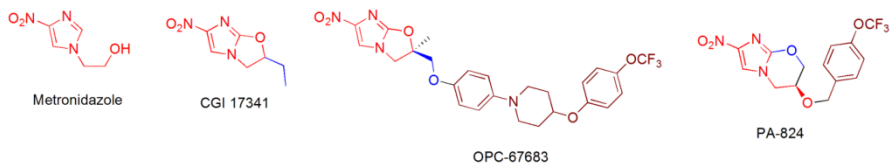


Fig. 3.2 *Mechanism of action of SQ109 and Bedaquiline.*

3.1.2 Nitroimidazofurans and Nitroimidazopyrans



The nitroheterocyclic compounds like nitroimidazoles, nitrofurans and nitrothiazoles are a very important class of antibacterial agents extremely useful to treat infections due to anaerobic bacteria and protozoa. Azomycin (2-nitroimidazole), a relatively rare antibiotic produced by *Nocardiamesenterica* [12] and *Streptomyces eurocidicus*.[13] Inspired by its novel mechanism and activity against pathogenic microbes, scientists at Rhone-Poulenc synthesized more potent and less toxic 5-nitroimidazole derivatives. One of their compounds, registered by the name metronidazole, eventually became a very important antimicrobial agent.[14, 15]

These are prodrugs and activated by metabolism and were shown to exert antibacterial activity via multiple mechanisms. In the bacteria, low-redox-potential electron transfer enzymes like Pyruvate: ferredoxin-oxidoreductase normally generates adenosine triphosphate (ATP) via oxidative decarboxylation of pyruvate (Fig. 3.3). The nitro group present in metronidazole acts as an electron trap, retaining the electrons that will be generally transferred to hydrogen ions in the cycle and produce a reactive anion; while the metronidazole stays in the cellular environment. Reduction of metronidazole generates a concentration gradient that drives uptake of more drug and encourages the formation of intermediate compounds and free radicals that are toxic to the cell. These reactive intermediates interact with nuclear material resulting in disruption of DNA and inhibition of nucleic acid/protein synthesis. These compounds doesn’t react with mitochondria containing pyruvate reductase rich cells like

aerobic microbes and human cells, hence show very good safety index.[16-18]

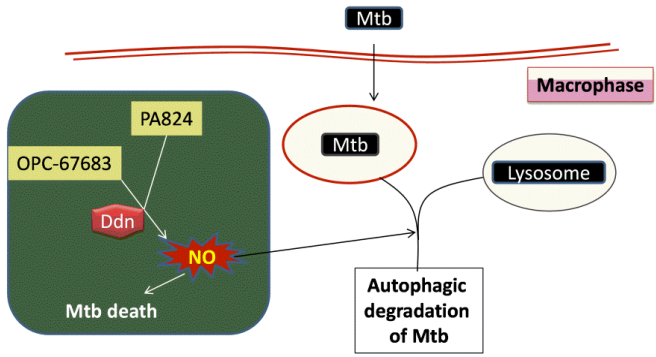


Fig. 3.3 *Mechanism of action of PA824 and Delaminid (OPC-67683).*

In pulmonary tuberculosis, oxygen concentrations are low inside granulomas and these structures are thought to contain an anaerobic environment. It is hypothesized that the Mtb residing in tubercles especially in metabolically inactive and latent forms behave in the same way as anaerobic microbes and hence the nitroimidazoles may be useful in treating tuberculosis. The promising *in vitro* anti TB results obtained for these compounds inspired many to synthesize nitroheterocycles and often succeeded in this approach.[19-21]

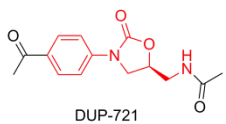
OPC-67683 (Delaminid, Deltyba®) a nitroimidazooxazole derivative recently received conditional approval in April 2014 by European Medical Agency for treating MDR-TB.[22] This drug is in its advanced phase II clinical trials in US. It has a mechanism similar to metronidazole and gets activated by the enzyme deazaflavin dependent nitroreductase (Rv3547). This results in a reactive intermediate metabolite, formed between delamanid and its desnitro-imidazooxazole derivative, which is considered to play a vital role in the inhibition of methoxymycolic acid and ketomycolic acid production. This compound showed significant selective toxicity to *Mycobacterium* and free from mutagenic problems common to nitroimidazoles. Apart from gastric disturbances,

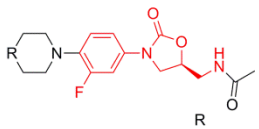
this drug suffers from cardiac side effects like prolongation of QT interval and patients need monitoring for cardiac arrhythmias.

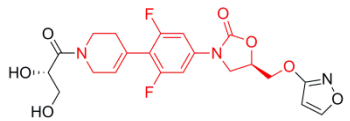
PA-824 (Pretomanid) is a nitroimidazooxazine derivative. This drug in combination with moxifloxacin and pyrazinamide (PaMZ) is advancing to Phase III clinical trials for treating MDR-TB.[22] This is a selective anti-tubercular agent with MIC ranging from 0.015 to 0.25μg/mL and has no appreciable inhibitory activity against Gram+ve or –ve bacteria. PA-824 has activity against drug susceptible, MDR/XDR strains and acts synergistically with other anti TB drugs indicating a novel mechanism for this compound.[23] Similar to delaminid, this drug is also activated by deazaflavin (F420)-dependent nitroreductase and releases reactive nitrogen species, including nitric oxide.

Nitric oxide gas is produced naturally by specific immune cells after they swallow up TB bacteria; this is one way the body fights against TB. But this immune response sometimes might not be sufficient to eliminate an infection. PA-824 mimics the body's natural immune response, but it is more precise and only releases the gas upon entering into the TB bacteria. The released nitric oxide may signify the important effectors of PA-824 killing of *M. tuberculosis* under hypoxic conditions.[25] This also affects the mycobacterial respiratory apparatus and significantly reduces the intracellular ATP levels. This drug also inhibits biosynthesis of essential cell wall lipids ketomycolates from hydroxymycolate and also inhibits protein synthesis but nucleic acid synthesis remained unaffected.[26]

3.1.3 Oxazolidinones







Oxazolidinones, exemplified by Dup - 721, are totally synthetic, orally active antibacterial agents discovered by DuPont. These compounds prevent the initiation of protein synthesis by binding to 23S RNA in the 50S ribosomal subunit of bacteria.[27-33] Linezolid, a first-generation oxazolidinoneandthe only new synthetic antibacterial agent approved after fluoroquinolones, has shown promising results to treat MDR/XDR-TB. However, the noteworthy toxicities, such as peripheral neuropathy and myelo-suppression, could limit the long-term use of this drug.[34]

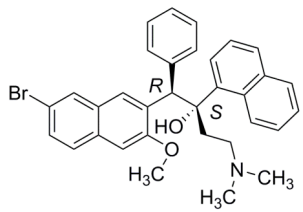
Sutezolide (PNU-100480), a thiomorpholinyl analogue of linezolid was developed recently and found to be more potent than linezolid against *M. tuberculosis* in a murine model.[35] Here, it was found that sutezolid shortens standard treatment by one month, whereas linezolid does not;[36] in the whole blood culture model, the maximal bactericidal activity of sutezolid (-0.42 log/day) is more than twice that of linezolid (-0.16 log/day, P, 0.001).[37] This drug is in later stages of Phase II clinical trials. Combination studies have been performed in whole-blood assays and these showed that sutezolid and TMC207 or SQ109 had additive effects, whereas those including PA-824 were having less than additive or antagonistic effects.[38-40]

AZD5847 is a next generation oxazolidinone developed by AstraZeneca and has recently entered Phase II clinical trials. It is a bactericidal and act synergistically with other anti TB agents.[41] This drug is safer than other

oxazolidines and effective against slow growing and intracellular mycobacteria. Oxazolidines offer promising addition to combination regimes to treat drug resistant TB.

3.1.4 Diarylquinolines (TMC207, SIRTURO^{TM})

Bedaquiline (R207910; SIRTURO^{TM}) a Janssen Pharmaceutica product, is the only novel anti TB drug approved in the last 40 years. It has received conditional approval on 20th December 2013 by European Union for use in adults with drug resistant tuberculosis and marketed by Tibotec and the TB alliance.[42, 43] This drug has extraordinary activity against both drug susceptible and drug-resistant strains of *M. tuberculosis*. It exhibits an impressive MIC value of 30–120 ng/mL, similar to or better than isoniazid and rifampicin. Interestingly, this drug rapidly kills the pathogen *in vitro* at a rate of 3 log orders of CFU (Colony Forming Units)/mL in 12 days.



Bedaquiline (TMC207; SIRTURO™)

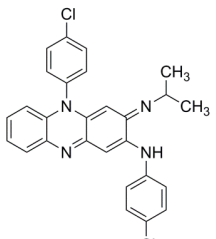
After the drug had been in development for over 6 years and a clinical trial of 47 patients showed that it is effective in the treatment of *M. tuberculosis*.[43] This drug also has shown its efficacy against *Mycobacterium leprae*, the causative agent of leprosy, in a mouse model of the disease.[44] It is found that this drug inhibits the membrane-bound F1-FoATP synthase complex results in depletion of cellular ATP levels and eventual death of the organism. Treatment of whole cells with the drug reduces ATP concentrations even in isolated vesicles.[45, 46] However,

safety concerns of this drug still remain because of an increased risk of death and QT prolongation.[47, 48]

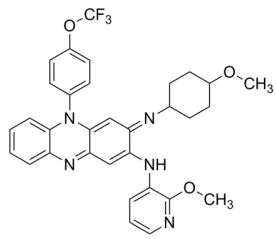
3.2 Preclinical Agents

3.2.1 Clofazimine and its Analogues

Clofazimine (CFM) is one of the oldest drugs synthesized for treating tuberculosis. It has an iminophenazine skeleton and highly lipophilic in nature. Unclear efficacy and unfavourable properties such as accumulation in fat tissues, long half-life and skin discoloration led to its discontinuation as an anti TB agent. But its activity against MDR TB,[49] the intracellular accumulation in mononuclear phagocytic cells, anti-inflammatory activity, a low frequency of drug resistance and slow metabolic elimination rate, made clofazimine an attractive lead molecule for development of newer anti TB agents.[50-52] An observation study done among 206 patients, on the effectiveness of standardized regimens for MDR-TB showed that a clofazimine-containing regimen consisting of gatifloxacin, ethambutol, and pyrazinamide achieved a relapse-free cure rate of 88%.[53]



Clofazimine

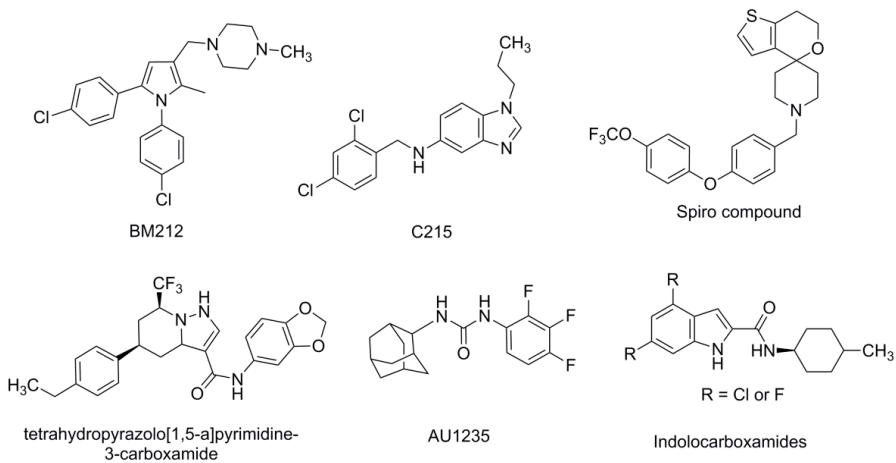


TBI-166

In a recent murine study, a CFM-containing regimen resulted in a reduced bacillary load after 2 months of treatment and negative conversion after 5 months of treatment.[54] CFM is currently used for treating MDR and XDR

patients when other choices are not available.[55] A lead optimization effort gave an important preclinical candidate TBI-166 with greater safety profile and the retained antimycobacterial activity. The mechanism of action of this compound class is still unclear but a recent study suggests that CFM is reduced by the mycobacterial enzyme NADH-quinoneoxidoreductase typeII (NDH-2) and then, spontaneous reoxydation of the reduced CFM by oxygen, is likely to produce reactive-oxygen species (ROS), probably O_2-Clofazimine reduction involves nitrogen groups on the phenazine ring together with the imino substituent and the high levels of ROS generation may provide intracellular concentrations needed for cell death.[56] It has also been suggested that CFM may act bybinding both the guanine base of DNAand stimulating phospholipase A2, which could explain its anti-inflammatory and immune-stimulating properties.

3.2.2 Diarylpyrrole Derivatives



BM212 is a novel diarylpyrrole antitubercular agent. This molecule has excellent *invitro* inhibitory profile against several clinically important mycobacteria including drug resistant and intracellular Mtb. This has an added

activity against several species of yeasts, including *Candida albicans* and *Cryptococcus neoformans.*[57] The later property is of immense use for treating immune compromised or HIV co-infected TB patients, where incidence of opportunistic infections caused by *Candida* sp. is common. Preliminary studies have confirmed that BM212 is a potent inhibitor of MmpL3.[58] MmpL3 is a putative membrane protein belonging to the RND protein family of multidrug resistance pumps that mediate the transport of a diverse array of ionic or neutral compounds as well as heavy metals and fatty acids.[59] It is surprising to notice structurally diverse group of compounds including SQ109[10], C215[65], tetrahydropyrazolo [1, 5-a] pyrimidine-3-carboxamides, [66] some indolcarboxamides [67] and AU1235 [68] showed significant anti-tubercular activity and target primarily MmpL3. These results clearly indicate that MmpL3 is a very susceptible target amenable to drug design.

3.2.3 BTZ043 and its Analogues

BTZ043 is a member of novel benzothiazinine class of antitubercular agents discovered in the year 2009.[69, 70] This compound showed an extraordinary MIC of 1ng/mL against Mtb, several folds better than existing drugs. This enzyme produces the sole source of the D-arabinose required for biosynthesis of the key cell wall components arabinogalactan and lipoarabinomannan. BTZ043 serves as a suicide substrate (Fig. 3.4) for the reduced form of decaprenyl-phosphoribose 2′-oxidase (DprE1). BTZ043 undergoes nitro reduction to yield a nitroso species that specifically attacks the thiol side chain of the active site cysteine residue Cys387 of DprE1, thereby forming semimercaptal covalent adduct and irreversibly inactivates the enzyme.[74]

Very recently, a second generation of 2-piperazino-benzothiazinones (PBTZs) were synthesized in order to improve pharmacological properties.[75] Among

several synthesized compounds, alkyl-PTBZs were found to be more active *in vitro* than BTZ043 and displayed MIC values against *M. tuberculosis* H37Rv rangingfrom 0.00019 to 0.00075 mg/mL. PTBZ169 proved to be the most active one and has many superior features thatmake it the preferred compound in BTZ series for clinical development

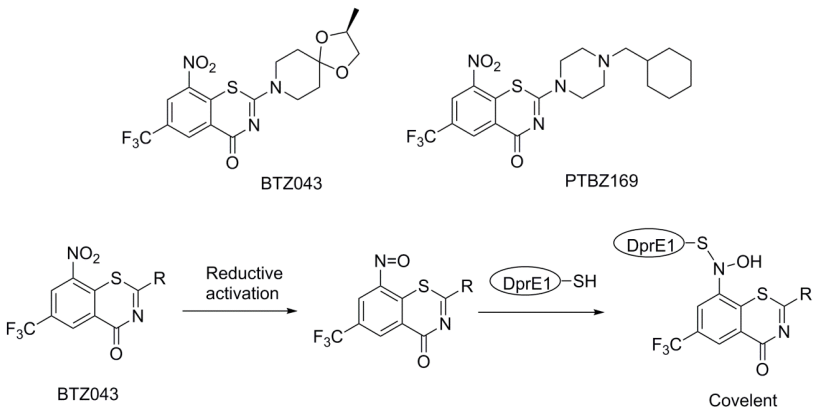
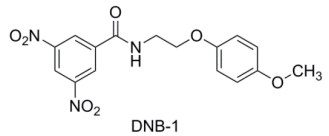
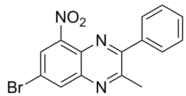


Fig. 3.4 *Mechanism of action of BTZ043.*

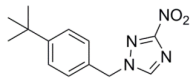
DprE1 is considered a highly vulnerable target[76] since many inhibitors with unrelated chemical structures have been reportedin literature such as dinitrobenzamides (DNB1), benzoxyquinoxalines (VI-9376),[77] and the triazole 377790.[65] To date, all of them target Cys 387 of DprE1. Very recently, series of compounds belonging to azaindoles [78] and benzothiazoles (TCA1) [79] were reported as potent DprE1 inhibitors, which showed significant activity in *in vitro* and mouse models of acute and chronic TB. These compounds have been shown to be non-covalent inhibitors as well as the generated resistors do not show missense mutation in Cys 387, suggesting that their binding mechanism is different from the covalent inhibitors.



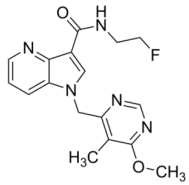
DNB-1



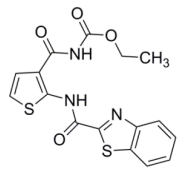
VI-9376



377790



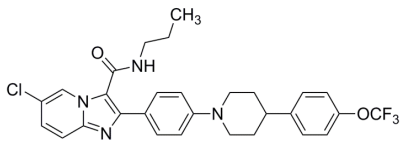
Azaindole



TCA-1

3.2.4 Imidazopyridine Amides

Imidazopyridine amides (IPAs) are a promising class of antitubercular compounds, acting by inhibition the respiratory cytochrome bc1 complex, identified by a phenotypic high-content screening of a commercial chemical libraries of 121156 compounds. A lead optimization campaign led to the optimized Q203.[80] SAR analysis around the 477 synthesized derivatives show that Q203 was active against *M. tuberculosis* H37Rv in the low nanomolar range (MIC50 0.0027 mM) as well as against MDR and XDR M. tuberculosis clinical isolates (MIC90 <0.00043 mM).

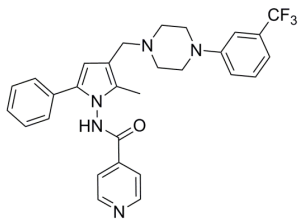


Q203

It also showed safety profile in acute model for toxicity in mice compatible with once-daily dosing. Q203 showed a bioavailability of 90% in mice and a low volume of distribution with a drug concentration in lungs 2 to 3-fold higher than in serum. In an acute mouse model of tuberculosis, it showed a reduction of more than 90% in bacterial load. In a chronic mouse model of tuberculosis

Q203 was slow acting with respect to INH, in fact the reduction of bacterial load was higher in the last 2 weeks. To date, Q203 reduced the formation of lung granulomas lesions.

3.2.5 Sudoterb (Pyrrole, LL-4858)



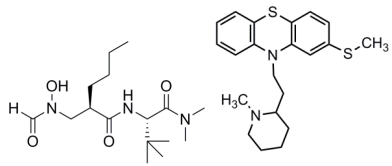
LL-3858 (Sudoterb)

Lupin Ltd., has identified a lead compound, Sudoterb (LL-4858), which has activity against sensitive and resistant strain of *M. tuberculosis*. LL-4858 was reported to have potent anti-TB activity *in vitro* and *in vivo* (mice and guinea pig) studies. LL-4858 had shown *in-vitro* bactericidal activity similar to isoniazid and was synergistic with RMP. The combination of LL-4858 with isoniazid, rifampicin and pyrazinamide led to complete sterilization of sensitive and MDR-TB strains in infected mice within 2 months. In combination with rifampicin and pyrazinamide, LL-4858 also cured TB in all animals after 3 months of treatment. LL-4858 could potentially cut the time of TB treatment to 2 or 3 months.[82, 83] The mechanism of action of this drug is not yet established.

3.2.6 Peptideformylase Inhibitor BB-3497

Bacterial peptide deformylase (PDF) is a metallo-protease that removes the N-terminal formyl group from newly synthesized proteins. Various PDF inhibitors have activity against several pathogens including *E. coli* and *S. aureus in vitro*. Six PDF inhibitors were screened against two isolates of *M. tuberculosis*

and initial testing showed that three compounds, BB-3497, BB-84518 and BB-83698 gave MICs in the range of 0.06–2 μg/mL.[84] These inhibitors were further tested against 17 isolates of *M. tuberculosis* and were found to be the most active with a median MIC of 0.25 μg/mL. Further *in vivo* evaluation is required to fully determine the potency and clinical tests must be carried out whether the drug is toxic or not in human. A recent study suggested that PDF inhibitors had no detectable effect on two different human cell lines *in vitro*.[85]



BB-3497 Thioridazine

3.2.7 Phenothiazines

Phenothiazine based antipsychotics were recently reported to possess clinically useful antitubercular activity against multi-drug/extremely drug resistant tuberculosis.[86, 87] The mechanism proposed for antimycobacterial activity of this drug includes disruption of mycobacterial respiration process most probably via type II NADH: quinone-oxidoreductase inhibition.[88] Another unusual mechanism proposed is the activation of host macrophages to effectively destroy dormant mycobacterium.[89, 90] The later mechanism draws attention of the drug designers as it does not involve biochemistry of the pathogen and hence less chances for development of resistance.[91] The only problem with this therapy is the unwanted CNS activity, neuronal and cardiac toxicity, which makes continuous therapeutic drug monitoring mandatory. Though the efficacy of thioridazine as an alternate treatment for XDR TB was ascertained in one study[92], a comprehensive clinical trial for evaluation of its safety, efficacy and development of an optimized regimen is yet to begin.

3.3 Conclusions

Uncertain biochemistry, unique cell-wall structure and survival mechanisms, lack of motivation in the pharmaceutical industry and funding agencies probably are responsible for the diminutive proportion of anti TB agents amongst the drugs in clinical trials. TB Alliance, an international organization formed in the year 2000, brought industry, academia, donors and NGOs together to intensify efforts to improve treatment options for tuberculosis. Their concerted efforts resulted in the development of novel drugs Bedaquiline and Pretomanid. These intensified efforts also filled the pipeline with more than 10 new molecules which are in various phases of clinical trials. To expand and encourage the developmental plans of new drugs for TB, government, private and public authorities need to enhance financial support for research at all levels, and adapt regulations to ease the process of evaluation, validation and approval of new drugs without altering the quality of research and life. In addition, there should be an agenda to be implemented by government, public and private agencies i.e on education and awareness, which will contribute to the prevention of TB spread and also development drug resistant MDR or XDR TB.

References

[1] Koul, A.; Arnoult, E.; Lounis, N, *et al*. *Nature* 2011, *469*, 483-490.

[2] Bavesh, D.K.; Petros, C. K.; Tanya, P. and Thomas, D. *Tuberculosis* xxx (2014) 1-6; http://dx.doi.org/10.1016/j.tube.2014.10.003

[3] Global Alliance for TB Drug Development. Tuberculosis. Scientific blueprint fortuberculosis drug development. Tuberculosis (Edinb) 2001; 81 (Suppl. 1): 1-52; www.tballiance.org

[4] Grosset, J. H.; Singer, T. G. and Bishai, W. R. *Int. J. Tuberc. Lung Dis.* 2012, *16*, 1005.

[5] O'Brien, R. J. and Nunn P. P. *Am. J. Respir. Crit. Care Med*. 2001, *163*, 1055.

[6] Lee R. E.; Protopopova, M.; Crooks, E.; Slayden, R. A.; Terrot, M. and Barry, C. E. 3rd, *J. Comb. Chem.* 2003, *5*, 172.

[7] Protopopova, M.; Hanrahan, C.; Nikonenko, B.; Samala, R.; Chen, P.; Gearhart, J.; Einck, L. and Nacy, C. A. *Antimicrob. Chemother*. 2005, *56*, 968.

[8] Chen P.; Gearhart, J.; Protopopova, M.; Einck, L. and Nacy, C. A. *Antimicrob. Chemother*. 2006, *58*, 332.

[9] Boshoff, H. I.; Myers, T. G.; Copp, B. R.; McNeil, M. R.; Wilson, M. A. and Barry, C. E. 3rd., *J. Biol. Chem.* 2004, *279*, 40174.

[10] Tahlan, K.; Wilson, R.; Kastrinsky, D. B.; Arora, K.; Nair, V.; Fischer, E.; Barnes, S. W.; Walker, J. R.; Alland, D.; Barry, C. E. 3rd, *et al*., *Antimicrob. Agents Chemother.* 2012, *56*, 1797.

[11] Bogatcheva, E.; Hanrahan, C.; Nikonenko, B.; de los Santos, G.; Reddy, V.; Chen, P.; Barbos, F.; Einck, L.; Nacy, C. and Protopopova, M. *Bioorg. Med. Chem. Lett*. 2011, *21*, 5353.

[12] Maeda, K.; Osate. T. and Umezawa, H. *J. Antibiot. (Tokyo) Ser.*, 1953, *A 6*, 182.

[13] Osato, T.; Ueda, M.; Fukayama, S.; Yagishita, K.; Okami, Y. and Umezawa, H. *J. Antibiot.* (Tokyo) 1955, *8*, 105.

[14] Cosar, C. and Julou, L. Ann. Inst. Pasteur (Paris), 1959, 96, 238.

[15] Cosar, C.; Crisan, C.; Horclois, R. *et al*., *Arzneimittel. Forsch*. 1966, *16*, 23.

[16] Müller, M. *Biochem. Pharmacol.* 1986, *35*, 37.

[17] Moreno, S. N.; Mason, R. P. and Docampo, R. *J. Biol. Chem*. 1984, *259*, 8252.

[18] Müller, M. *Surgery* 1983, *93*, 165.

[19] Agrawal, K. C.; Bears, K. B. and Sehgal, R. K. *J. Med. Chem.* 1979, *22*, 583.

[20] Nagarjan, K.; Shumker, R. G.; Rajjapa, S.; Shenoy, S. J. and Costa-Perira, R. *Eur. J. Med. Chem*. 1989, *24*, 631.

[21] Wayne, L. G. and Sramek, H. A. *Antimicrob. Agents Chemother*. 1994, *38*, 92054.

[22] Xavier, A. S. and Lakshmanan, M. *J. Pharmacol Pharmacother*. 2014, *5*, 222.

[23] Wayne, L. G. and Sramak, H. A. *Antimicrob. Agents. Chemother.* 1994, *38*, 2054.

[24] Ujjini M.; Helena I. M. B. and C. E. Barry, *Commun. Integr. Biol.* 2009, *2*, 215.

[25] Singh, R.; Manjunatha, U.; Boshoff, H. I.; Ha, Y. H.; Niyomrattanakit, P.; Ledwidge, R.; Dowd, C. S.; Lee, I. Y.; Kim, P.; Zhang, L.; Kang, S.; Keller, T. H.; Jiricek, J. and Barry 3rd, C. E. *Science*, 2008, *322*, 1392.

[26] Stover, C. K.; Warrener, P.; VanDevanter, D. R.; Sherman, D. R., Arain, T. M.; Langhorne, M. H.; Anderson, S. W.; Towell, J. A.; Yuan, Y.; McMurray, D. N.; Kreiswirth, B. N.; Barryk C. E. and Baker, W. R. *Nature*, 2000, *405*, 962.

[27] Eustice, D. C.; Feldman, P. A.; Zajac, I. and Slee, A. M. *J. Antimicrob. Agents. Chemother*., 1988, *32*, 1218.

[28] Hutchinson, D. K.; Barbachyn, M. R.; Brickner, S. J.; Buysse, J. M.; Demyan, W.; Ford, C. W.; Garmon, S. A.; Glickman, S.; Grega, K. C.; Hendges, S. K.; Kilburn, J. O.; Manninen, P. R.; Reid, R. J.; Toops, D. S.; Ulanowicz, D. A. and Zurenko, G. E., "Piperazinyloxazolidinones: Structure activity relationships of a new class of oxazolidinone antibacterial agents", Abstracts of paper, 35th Interscience Conference on Antimicrobial agents and chemotherapy. San Francisco, CA, September 1995. Washington DC: *American Society for Microbiology;* 1995. Abstract no. F207.

[29] Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W. and Zurenko, G. E, *J. Med. Chem*., 1996, *39*, 673.

[30] Leonard, N. J. and Johnson, C. R., *J. Org. Chem*., 1962, *27*, 282.

[31] Tucker, J. A.; Allwine, D. A.; Grega, K. C.; Barbachyn, M. R.; Klock, J. L.; Adamski, I.; Brickner, S. J.; Hutchinson, D. K.; Ford, C. W.; Zurenko, G. E.; Conradi, A.; Buston, P. S. and Jensen, R. M., *J. Med. Chem.*, 1998, *41*, 3727.

[32] Barbachyn, M. R.; Hutchinson, D. K.; Brickner, S. J.; Cynamon, M. H.; Kilburn, O.; Klemens, S. P.; Glickman, S. E.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W. and Zurenko, G. E., *J. Med. Chem.*, 1996, *39*, 680.

[33] Zamkoff, J. P.; Cline, K.; Klemens, S. P. and Cynamon, M. H., "Activity of

U-100480, an oxazolidinone, against *M. avium* complex (MAC) infection in beige mice", Abstracts of papers, 35th Interscience Conference on antimicrobial agents and chemotherapy, San Francisco, CA, September 1995, Washington DC: *American Society for microbiology;* 1995, Abstract no. F229.

[34] Fortun, J. *et al*. *Antimicrob. Chemother*., 2005, *56*, 180.

[35] Williams, K. N.; Stover C. K.; Zhu T, *et al. Antimicrob. Agents Chemother*., 2009, *53*, 1314.

[36] Williams, K. N.; Brickner, S. J.; Stover, C. K.; Zhu, T.; Ogden, A.; *et al*. *Am. J. Respir. Crit Care Med.*, 2009, 180, 371.

[37] Wallis, R. S.; Jakubiec, W.; Kumar, V.; Bedarida, G.; Silvia, A. *et al*. *Antimicrob. Agents Chemother.*, 2011, *55*, 567.

[38] Wallis, R. S. *et al. Antimicrob. Agents Chemother.*, 2010, *55*, 567.

[39] Wallis, R. S. *et al*. *J. Infect. Dis.*, 2010, *202*, 745.

[40] Wallis, R. S. *et al. PLoS ONE*, 2012, *7*, e30479.

[41] Reele, S. *et al.* A 14-day multiple ascending dose study: AZD5847 is well tolerated at predicted exposure for treatment of tuberculosis (TB) (Abstract A1-1735). 51st Annual Interscience Conference on Antimicrobial Agents and Chemotherapy [online].

[42] Andries, K.; Verhasselt, P.; Guillemont, J.; Gohlmann, H. W.; Neefs, J. M.; Winkler, H.; Van Gestel, J.; Timmerman, P.; Zhu, M. and Lee, E. *Science*, 2005, *307*, 223.

[43] Diacon, A. H. *et al*., *N. Engl. J. Med*., 2009, *360*, 2397.

[44] Matteelli, A.; Carvalho, A. C.; Dooley, K. E. and Kritski, A. *Future Microbiol*., 2010, *5*, 849.

[45] Huitric, E.; Verhasselt, P.; Koul, A.; Andries, K.; Hoffner, S. and Andersson, D. I. *Antimicrob Agents Chemother*., 2010, *54*, 1022.

[46] Koul, A.; Dendouga, N.; Vergauwen, K.; Molenberghs, B.; Vranckx, L.; Willebrords, R.; Ristic, Z.; Lill, H.; Dorange, I. and Guillemont, J. *Nat. Chem. Biol*., 2007, *3*, 323.

[47] World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva, Switzerland: World Health Organization; 2013.

[48] Mase, S.; Chorba, T.; Lobue, P. and Castro, K. Provisional CDC guidelines for the use and safety monitoring of bedaquilinefumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. *MMWR Recomm Rep* 2013; *62*:1.

[49] Morten, B. and Lise-Lotte, G. *Bioorganic & Medicinal Chemistry*, 2005, *13*, 6360.

[50] Field, S. K. and Cowie, R. L. *Chest*, 2003, *124*, 1482.

[51] Reddy, V. M.; Srinivasan, S. and Gangadharam, P. R. *Tuber. Lung. Dis*. 1994, *75*, 208.

[52] Reddy, V. M.; Nadadhur, G.; Daneluzzi, D.; O'Sullivan, J. F. and Gangadharam, P. R. *Antimicrob. Agents. Chemother.*, 1996, *40*, 633.

[53] Van Deun, A.; Maug, A. K.; Salim, M. A. et al. *Am. J. Respir. Crit. Care Med*., 2010, *182*, 684.

[54] Grosset, J. H.; Tyagi, S.; Almeida, D. V. et al. *Am. J. Respir. Crit. Care Med*., 2013, *188*, 608.

[55] Dooley, K. E.; Obuku, E. A.; Durakovic, N.; Belitsky, V.; Mitnick, C. and Nuermberger, E. L. *J. Infect. Dis*. 2013, *207*, 1352.

[56] Cholo, M. C.; Steel, H. C.; Fourie, P. B.; Germishuizen, W. A. and Anderson, R. *Antimicrob. Chemother.* doi:10.1093/jac/dkr444.

[57] Deidda, D.; Lampis, G.; Fioravanti, R.; Biava, M.; Cesare Porretta G.; Zanetti, S. and Pompei, R. *Antimicrob. Agents Chemother*., 1998, *42*, 3035.

[58] Valentina La Rosa *et. al*, *Antimicrob. Agents Chemother*., 2012, *56*, 324.

[59] Poole, K. *Ann. Med*. 2007, *39*, 162.

[60] Biava, M.; Fioravanti, R.; Porretta, G. C.; Deidda,; Maullu, C. and Pompei, R. *Bioorg. Med. Chem. Lett*., 1999, *9*, 2983.

[61] Biava, M.; Porretta, G. C.; Deidda, D.; Pompei, R.; Tafi, A. and Manetti, F. *Bioorg. Med. Chem*., 2003, *11*, 515.

[62] Biava, M.; Porretta, G. C.; Deidda, D.; Pompei, R.; Tafi, A. and Manetti, F. *Bioorg. Med. Chem*., 2004, *12*, 1453.

[63] Biava, M.; Porretta, G. C.; Poce, G.; Deidda, D.; Pompei, R.; Tafi, A. and Manetti, F. *Bioorg. Med. Chem*., 2005, *13*, 1221.

[64] Biava, M.; Porretta, G. C.; Poce, G.; Supino, S.; Deidda, D.; Pompei, R.; Molicotti, P.; Manetti, F. andBotta, M. *J. Med. Chem*., 2006, *49*, 4946.

[65] Stanley, S. A.; Grant, S. S.; Kawate, T.; Iwase, N.; Shimizu, M.; Wivagg, C.; Silvis, M.; Kazyanskaya, E.; Aquadro, J.; Golas, A.; Fitzgerald, M.; Dai, H.; Zhang, L. and Hung, T. D. *ACS Chem. Biol*., 2012, *7*, 1377.

[66] Remuinan, M. J. *et al*., *PLoS One*, 2013, *8*, e60933.

[67] S. P. Rao, *et al*., *Sci. Trans. Med*. 2013, *5*, 214ra 168.

[68] A. E. Grzegorzewicz, *et al*., *Nat. Chem. Biol*., 2012, *8*, 334.

[69] Makarov, V. *et al*., *Science*, 2009, *324*, 801.

[70] Makarov, V. *et al*., *EMBO Mol. Med*. 2014, DOI: 10.1002/emmm.201303575.

[71] Sarah M. Batt; Talat Jabeen; Veemal Bhowruth; Lee Quill; Peter A. Lund; Lothar Eggeling; Luke J. Alderwick; Klaus Fütterer and Gurdyal S. Besra. *PNAS*, 2012, *109*, 11354-11359.

[72] Trefzer, C.; Rengifo-Gonzalez, M.; Hinner, M. J.; Schneider, P.; Makarov, V.; Cole, S. T. and Johnsson, K. *J. Am. Chem. Soc*., 2010, *132*, 13663.

[73] Trefzer, C.; Skovierová, H.; Buroni, S.; Bobovská, A.; Nenci, S.; Molteni, E.; Pojer, F.; Pasca, M. R.; Makarov, V.; Cole, S. T.; Riccardi, G.; Mikusova, K. and Johnsson, K. *J. Am. Chem. Soc*., 2012, *134*, 912.

[74] Crellin, P. K.; Brammananth, R. and Coppel, R. L. *PLoS One*, 2011, *6*, e16869.

[75] Makarov, V.; Lechartier, B.; Zhang, M.; Neres, J.; Van der Sar, A. M.; Raadsen, S. A.; Hartkoorn, R. C.; Ryabova, O. B.; Vocat, A.; Decosterd, L. A.; Widmer, N.; Buclin, T.; Bitter, W.; Andries, K.; Pojer, F.; Dyson, P. J. and Cole, S. T. *EMBO Mol. Med*., 2014, *6*, 372.

[76] Zumla, A.; Nahid, P. and Cole, S. T. *Nat. Rev.* 2013, *12*, 388.

[77] Christophe, T. *et. al*., *PLoS Pathog*. 2009, *5*, e1000645.

[78] Magnet, S.; Hartkoorn, R. C.; Szekely, R.; Pat, J.; Triccas, J. A.; Schneider, P.; Szantai-Kis, C.; Orfi, L.; Chambon, M.; Banfi, D.; Bueno, M.; Turcatti, G.; Keri, G. and Cole, S. T. *Tuberc*. Edinb., 2010, *90*, 354.

[79] Shirude, P. S. *et. al*., *J. Med. Chem.*, 2013, *56*, 9701.

[80] F. Wang, *et. al*., *Proc. Natl. Acad. Sci. U. S. A.*, 2013, *110*, 2510.

[81] K. Pethe, *et al*., *Nat. Med.*, 2013, *19*, 1157.

[82] Arora S. K., 45th *ICAAC* (Washington), (2004), Abst. F-1115.

[83] Sinha R. K., 45th *ICAAC* (Washington), (2004), Abst. F-1116.

[84] Cynamon, M. H.; Alvirez-Freites, E. and Yeo, A. E, *Antimicrob. Chemother*., 2004, *53*, 403.

[85] Nguyen, K. T.; Hu, X.; Colton, C.; Chakrabarti, R.; Zhu, M. X. and Pei, D., *Biochemistry*, 2003, *42*, 9952.

[86] Amaral, L.; Viveiros, M.; Molnar, J. and Kristiansen, J. E. *Recent Pat. Antiinfect. Drug. Discov.*, 2011, *6*, 84.

[87] Amaral, L. and Molnar, J. *In Vivo*, 2014, *28*, 267.

[88] Warman, A. J.; Rito, T. S.; Fisher, N. E.; Moss, D. M.; Berry, N. G.; O'Neill, P. M.; Ward, S. A. and Biagini, G. A. *Antimicrob. Chemother*., 2013, *68*, 869.

[89] Martins, M.; Viveiros, M. and Amaral, L. *In Vivo*, 2008, *22*, 69.

[90] Martins, M. *Recent Pat. Antiinfect. Drug Discov.* 2011, *6*, 110.

[91] Anil, K.; Eric, A.; Nacer, L.; Jerome, G. and Koen, A. *Nature* 2011, *469*, 483.

[92] Amaral, L.; Udwadia, Z. F. and van Soolingen, D. *Biochem Pharmacol* 2012, 1:e137. doi:10.4172/2167-0501.1000-1137.