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A Review of Antimycobacterial Drugs in Development

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Abstract: The needs of newly developed antitubercular agents are required for the control of tuberculosis in the present time. In the discovery of new antitubercular drugs, the emergence of multidrug-resistant (MDR) and extensively drug resistant (XDR) strains of *Mycobacterium tuberculosis* (Mtb) has encouraged the researchers to intensify the efforts to discover novel antitubercular drugs. These novel drugs will predominantly target the persistent state of *mycobacterium* strains, which are resistant to conventional drugs including non resistant *mycobacterium* strains. In the last three to four decades no new effective drug has been developed for the treatment of resistant tuberculosis. However, in recent years, the research and development programs for the control of TB, there is a lot works is going on to enhancement of the anti-TB activity of new drugs particularly against resistant *mycobacterium* strains. Simultaneously, practical usefulness of some new targets is being identified and validated for the treatment of TB. Some compounds are presently in clinical trials, while others are being investigated in an attempt to explore new compounds for the target based treatment. The present review provides an overview of the new anti-TB agents with different molecular structures that are being clinically used and advanced stages of preclinical as well as clinical stages and also attempted to highlight the efforts that are being made in the development of new drug molecules as lead anti-TB agents.

Keywords: Chemotherapeutic drugs, Mycobacterium species, multidrug-resistant, extensively drug resistant.

INTRODUCTION

Tuberculosis is caused by *Mycobacterium* species. Among all *Mycobacterium* species, *M. tuberculosis* is one of the leading causative agents of tuberculosis (TB). Tuberculosis is responsible for the morbidity and mortality of a large number of population worldwide. Moreover, the opportunistic more TB infection is due to AIDs and emergence of multi drug resistant (MDR-TB) and extensive drug resistant (XDR-TB) strains of *Mycobacterium* species that has made increased and effective antitubercular strategies for the development of newer and novel anti-TB agents [1-3]. Traditionally, current therapy has relied completely on a limited number of first line anti-TB drugs and some second line anti-TB drugs such as isoniazid, rifampicin, ethambutal, streptomycin (first line drugs) and ethionamide, pyrazinamide, fluoroquinolones (second line drugs), etc [4,5]. However, almost all these drugs have different adverse effects with varying quantity. These adverse effects and other treatments related problems are mainly as prolonged treatment periods, toxicities, ineffectiveness against resistant strains etc. This finding motivates the scientists and researchers for the development of new molecules having novel or new chemical prototypes and modification in the currently used drugs (analogs of anti-B drugs) being capable of rapid anti-TB action with short duration of therapy, reduced toxicities and enhanced activity against MDR-TB and XDR-TB strains and latent *Mycobacterium* strains for the control of TB [6-10].

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Development of New Drugs for TB Chemotherapy

The tuberculosis (TB) is more difficult to diagnose due to higher incidence of negative sputum tests. Treatment of TB is also difficult due to drug interaction and side-effects of the currently used therapy. The increasing spread of multidrug resistant (MDR-TB) and extensive drug resistant (XDR-TB) TB that possesses additional challenges to treatment with currently used anti-TB drugs. The situation is mainly exacerbated by the increasing emergence of XDR-TB [11,12]. Although TB can be cured but current treatment is very complex with high doses of drugs, multidrug and long lasting time period. Directly Observed Therapy (DOT) short course was promoted by the World Health Organization (WHO) to improve compliance for the difficult and long-lasting therapy regimen for TB treatment [13]. MDR and XDR-TB are more complex and expensive to the treatment of tuberculosis [14,15]. During the last few years increased awareness for neglected TB and new research activities for development of new anti-TB agents. In current research and development, the molecular and genetic tools will become available for TB treatment and led to impressive improvements in the knowledge and understanding of the basic physiology of *M. tuberculosis*. There are a sufficient number of promising compounds for the effective treatment (mainly in combination therapy) to be developed [16,17] for the resistant strains and reduced the time duration of treatment. Furthermore, many compounds are either derivatives of existing drugs or those molecules that target the same cellular processes as currently used drugs. Whilst these derivatives are far quicker to develop, may be subject to cross-resistance for example, isoniazid, rifamycin and quinolone derivatives, etc [18]. The advanced knowledge of

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Mycobacterium metabolism and physiology that needs to be translated into validated targets which can be used for screening of newly developed anti-TB compounds.

For the MDR-TB and XDR-TB treatment, it is crucial that the new or novel molecules that act through novel mechanisms which are able to target new molecular targets, in order to avoid cross-resistance, which are mostly caused with currently used anti-TB drugs. There are a few new and promising compounds in the clinical trials for the development of new and effective ant-TB drugs that have been shown to be active against MDR-TB and XDR-TB strains with potential activity in human patients. The current therapies have some problems that are even more acute in the case of XDR-TB because XDR-TB is more rapidly fatal and most patients will die before the results of their diagnosis. There is an urgent need for new anti-TB drugs, in order to speed up the development of more effective drugs that accelerate their efficacy and effectiveness to the patients [19,20]. The combination of MDR-TB and XDR-TB with HIV infection leads patients to develop a highly aggressive form of TB that causes death in a very short period [21-23]. The emergence and rapid spread of MDR-TB and XDR-TB in high HIV prevalence represent a major threat to human health globally.

Need of New Antitubercular Drugs

According to the Guidelines for Tuberculosis drug development [24,25], new therapies for the control of TB should offer at least one of the following three improvements over the currently existing drug regimens:

- Shorten the total time period of treatment and/or significantly reduce the number of doses or amount of drug or drugs which needed to be taken under direct observed therapy short course (DOTs),
- Improve the treatment against MDR-TB, XDR-TB,
- Should be more effective in the treatment of latent TB infections,
- Lack of liver enzyme induction and inhibition to avoid interactions with antiretroviral agents, are the main criteria is using to select drugs that should be pursued for further research and development.

ANTITUBERCULAR DRUGS WITH NEW AND DIFFERENT PHARMACOPHORE

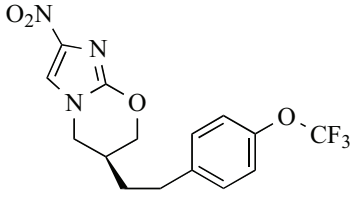
In the development of new anti-TB drug with short time period treatment, TB Alliance is working on both identifying individual novel drug molecules and developing new drug combination therapies. Indeed, the conventional approaches to new drug development procedures, require to substitution in currently used anti-TB drug singularly, only after each new drug has been approved for the TB therapy. In order to analyze useful group of drugs currently in two main categories: Novel molecules and molecules originating from families of currently used drugs, where innovative chemistry is used to optimize the therapeutic effects of new anti-TB drug molecules.

Nitroimidazopyrans and Nitroimidaoxazoles Analogs

In this series, the lead compounds are CGI 17341 and PA824/PA1343. The target enzyme has been identified for both compounds and involved in cell wall synthesis [26] and also caused reductive activation. Further various efforts to try and identify more efficacious molecules. However, there are two major areas of concern that need to be addressed-possible mutagenicity that resulting from the presence of a nitro group, and the opportunity for the development of new drug resistance therapy. Mutagenicity prompted by the fact that the nitroimidazoles induce a high rate of mutation. Furthermore, the obligate activating enzyme, using a flavin co-factor, is not essential for the survival of mycobacterium [27], leading to suspicions that might caused the emergence of drug-resistant strains. Since the drugs will inevitably be used in combination therapy, still needing consideration that should not be too pessimistic.

Nitroimidazole PA-824

Nitroimidazole PA-824 and its analogs are new nitroimidazole derivatives for the treatment of TB. They act by a mechanism dependent on *M. tuberculosis* F420 factor, PA-824 acts mainly by inhibiting the synthesis of cell wall and its components through molecular targets. *In vitro* study, PA-824 exhibited high activity against drug-sensitive and drug-resistant *M. tuberculosis* strains. This indicates that there is no cross-resistance with current clinically used anti-TB drugs. Moreover, PA-824 exhibited *in vitro* bactericidal activities against both replicating and static bacteria [27]. PA-824 is also having bactericidal activity against non replicating bacteria that were as comparable to the rifampicin [28]. Administration of PA-824 at doses ranging from 25 to 100 mg/ml causes reduction in the bacterial burden in spleen and lungs of mice [27]. Although PA-824 was more efficient than isoniazid or moxifloxacin, it was not better than rifampicin and isoniazid combination [29]. In experiments, long-term treatment determines its sterilizing capacity, PA-824 used as mono therapy in mice that led to a decrease bacterial numbers in the lungs than rifampicin or isoniazid monotherapy. The treatment with PA-824, rifampicin or isoniazid, caused complete eradication of the bacteria was not achieved after 12 weeks in any treated mice [28]. When a 6-month treatment therapy containing PA-824, rifampicin, isoniazid and pyrazinmide in combination was tested in mice, any of the PA-824 containing therapy resulted superior to the standard first line drugs that more rapidly reduced the bacterial burden during treatment and lower rates of relapse after treatment [30].



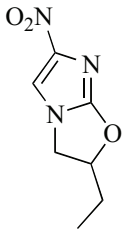
PA-824

Further investigations are necessary to assess the potential of PA-824 to improve treatment of both multi-drug resistant and drug-susceptible tuberculosis. The PA-824 development activities, to maximize the potential of PA824 derivatives by identifying novel and more active compounds with improving properties as a drug. The enzyme dihydrolipoamide cyltransferase (dlaT) is a potential target

for chemotherapy of TB. In *M. tuberculosis* dlaT is a component of two important multi-subunit complexes: pyruvate dehydrogenase, is aenzyme that catalyze the synthesis of Acetyl Coenzyme A, and peroxynitrite reductase, is a defense against oxidative/nitrosative stress conditions [31, 32]. *In vivo* study in mice, the enzyme dlaT has been required for full virulence, while in *in vitro* study mice macrophages can readily kill intracellular *M. tuberculosis* mutants that were lacking dlaT [32]. The identification of newer compounds those are active against specific distinct molecular targets, including inhibitors of DNA gyrase, peptide deformylase (PDF) inhibitors and analogs of quinolone electron transport inhibitors. Bacterial PDF belongs to a subfamily of metalloproteases that catalyze the removal of the N-terminal formyl group from newly synthesized proteins. PDF is essential for bacterial growth but is not required by mammalian cells, is a promising target for the development of new broad-spectrum antibacterial agents. Two PDF inhibitors, VIC-104959 (LBM415) and BB-83698 [33], the PDF inhibitor BB-3497 was found to have potent *in-vitro* anti-TB activity [34]. This suggested that PDF inhibitors can be apply in TB therapy. The inhibition of electron transport can lead to ATP depletion and decline in intracellular redox potential. Recently, anti-TB drugs targeting ATP synthesis (i.e. diarylquinoline) have been particularly effective, even against non-replicating bacteria. Therefore, identification of compounds being able to inhibit the electron transport systems could lead to the development of more effective drugs against both replicating and non-replicating bacteria.

Nitroimidazoles CGI 17341

The Oral treatment with CGI 17341 in tuberculosis infected mice, on days 11 and 12 after infection resulted in an ED_{50} of 7.7 mg/kg and a significant increase in survival time in dose-dependent manner. Unfortunately despite the initial promise of CGI 17341, it's development was terminated due to lack of commercial potential and mutagenicity [26].

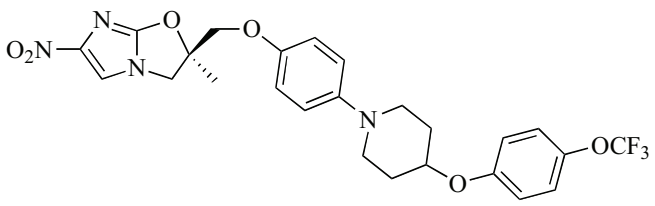


CGI 17341

In preclinical study reported, the Ciba-Geigy 5-nitroimidazole derivative, CGI 17341 showed considerable anti-TB effect. *In vitro* activity, at 0.04 to 0.3 mcg/ml compound inhibited both drug-susceptible and drug resistance strains of *M. tuberculosis*. This compound did not show any cross-resistance with currently clinically used drugs such as isoniazid, rifampicin, streptomycin, ethambutol etc. *In vitro* activity of CGI 17341 was comparable to that of isoniazid and rifampicin but superior to streptomycin, ciprofloxacin, norfloxacin and the oxazolidinone DuP 721. A series of nitroimidazopyrans has been identified for the treatment of TB and related diseases [35]. These compounds did not show mutagenic activity and showed potent bactericidal activity against replicating and static *M. tuberculosis*, including resistant strains [36].

Nitroimidazole OPC-67683

It belongs to a mycolic acid inhibitors, it interferes with the cell wall biosynthesis of the *mycobacterium*. Minimum inhibitory concentration (MICs) was determined by using isolated *M. tuberculosis* strains, including multi-drug resistant strains. *In vitro,* OPC-67683 showed high activity against drug-sensitive and drug-resistant strains having MICs range from 6-24 ng/mL. Cross-resistance was shown with current first-line drugs. Moreover, OPC-67683 showed strong intracellular activity against *M. tuberculosis* H37Rv strain residing within human macrophages and pneumocytes type II. The animal study showed that OPC-67683 is effective against sensitive *M. tuberculosis* H37v and MDR-TB strains *in vivo* from a concentration of 0.03125 mg/body. Furthermore, OPC showed *in vivo* efficacy against sensitive *M. tuberculosis* H37Rv strain, starting form a concentration of 0.00781 mg/body in mice.



OPC-67683

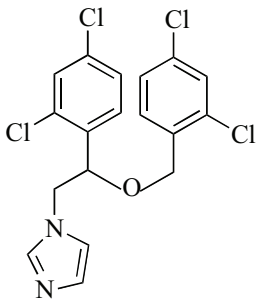
In chronic tuberculosis, OPC-67683 showed a 6-7 fold higher activity compared to first line drugs isoniazid and rifampicin in mice. In combination with currently used anti-TB drugs, no antagonist activity could be observed when OPC-67683 was used *in vivo*. After oral dosing, this compound was relatively well absorbed in animals at 3 mg/kg dose. The bioavailability was 35-60% with a concentration 3-7 times higher in the lung than in the plasma and well distributed in most tissues [37].

Imidazole Analogs

The *in vitro* effect of miconazole was exhibited as antimicrobial properties. From other structural features of azoles are antifungal activities that can be ascertained by screening of the anti-fungal drugs.

Miconazole

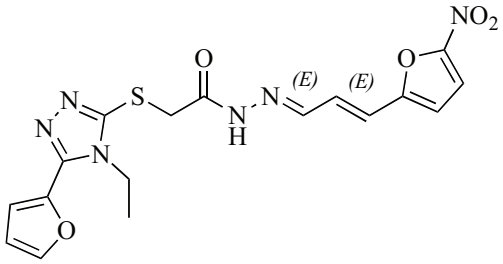
Miconazole is a well known antifungal drug which has been reported as anti-TB activity, *in vitro* study showed that MIC value is 2mcg/ml against *M. tuberculosis* H37Ra. The compound is inhibiting replicating bacteria and has some effect on stationary phase of bacilli [38]. Unfortunately, miconazole is not active in oral dose and hence little interest for progressing further for a TB indication. However, many 2nd and 3rd generation anti-fungal azoles are clinically used by the oral route, including fluconazole which is much used in AIDS patients [39].



Miconazole

1,2,4-Triazoles

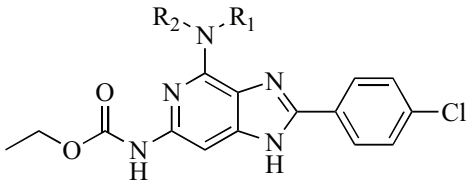
Various 1,2,4-triazoles have been evaluated against *M. tuberculosis* H37Rv. Compound (**1**) exhibited MIC value 6.25 mcg/ml, gave 61% inhibition [40]. Various other close analogs were found inactive.



(**1**)

Imidazo(4,5-c)pyridines

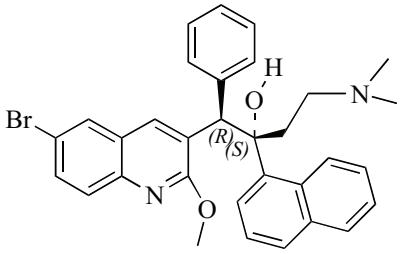
In a series of imidazo(4,5-c)pyridine compounds, one compound (**2**) where in formula (R1, R2 undisclosed), inhibited *M. tuberculosis* H37Rv and other strains with MICs in the range 0.25-2.5mcg/ml. Imidazo (4,5-c)pyridines were prepared as antimitotic agents for cancer treatment but these compounds have less cytotoxic effect then they were selected and found to have anti-TB activity [40].



(**2**) R1 and R2 are various alkyl groups

Diarylquinolines

Diarylquinolines (DARQs) are structurally different from fluoroquinolones and other quinolone derivatives. The DARQ R207910 is a new class of antitubercular compounds and has a MIC value equal to or lower than reference drugs. It has specificity towards mycobacterium including atypical species, important in humans such as MAC, *M. kansai*, *M. fortium* and *M. abscessus* [41]. This anti-TB specific spectrum differs from isoniazid, which has very poor activity against MAC. The clinical use of this will be highly targeted in the mycobacterial therapy, particularly targeting the proton (H^+) pump of adenosine triphosphate (ATP) synthase [42].



DARQ R207910

DRQ TMC207

Diarylquinoline TMC207 is an extremely promising anti-TB agent. Approximately 20 compounds of the diarylquinoline series have been shown to have MIC below 0.5 μg/ml against *M. tuberculosis* H37Rv and *in vivo* antimicrobial activity was confirmed by three compounds [42]. The most active compound is TMC207. The target and mechanism of diarylquinoline TMC207 are different from other anti-TB agents implying low probability of cross-resistance with existing-TB drugs. Diarylquinoline TMC207 is able to inhibit bacterial growth when tested on MDR-TB isolates and act by inhibiting the ATP synthase [42,43], leading to ATP depletion and pH imbalance.

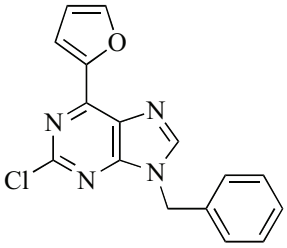
This anti-TB compound has potent bactericidal activity in the non established infection in murine mice model, matching or exceeding that of isoniazid. Moreover, diarylquinoline TMC207 has potent late bactericidal activity in murine TB model. Substitution of rifampicin, isoniazid or pyrazinamide with diarylquinoline TMC207 increased activity. Diarylquinoline TMC207 has also been tested in various combinations with the second line drugs amikacin, pyrazinamide, moxifloxacin and ethionamide in infected mice with the drugs susceptible (MDR) virulent *M. tuberculosis* strain H37Rv. Diarylquinoline containing drug regimen was more active than the current recommended regimen for MDR-TB amikacin-pyrazinamide-moxifloxacin and ethionamide. These are all attributes that are valuable for the treatment of chronic infections and may also be important for the development of simpler dosing regimens [42].

Purine Analouges

9-Benzylpurine derivatives, with different substituent at 2, 6 and/or 8 position, have been shown to possess high anti-tubercular activity. One of the compound of this class carrying trans-styryl or aryl substituent at 6 position and generally chlorine at 2-position tends to increase the activity and has MIC of 0.78mg/mL *in vitro* [44]. 6-arylpurines [45] and 9-sulphonylated or sulphenylated-6-mercaptopurines have shown anti-TB activity [46].

Benzylpurines

The 9-benzylpurine derivative, 2-chloro-4(2-furanyl)-9-benzylpurine exhibited potent anti-TB against *M. tuberculosis* H37Rv *in vitro* with a MIC value of 0.78 mcg/ml [44]. It also exhibited low cytotoxicity towards VERO cells (IC_{50} value-8.1 mcg/ml)–selectivity index (MIC/IC_{50}) of 10.4.

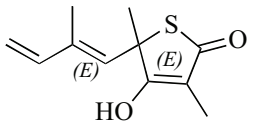


2-Chloro-6(2-furanyl)-9-benzylpurine

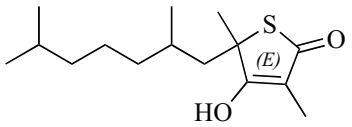
Thiolactomycin Analogs

Thiolactone containg antibiotic (5*R*)-thiolactomycin (TLM) is a naturally occurring and exhibited potent *in-vivo* antimicrobial activity against broad spectrum pathogenic bacteria, and *Mycobacterium* stains [47,48]. TLM inhibited bacterial and plant type-II fatty acid synthases (FAS-II) but not mammalian or yeast type-I fatty acid synthases (FAS-I) [49]. It inhibited both β-ketoacyl-ACP synthase I, II and III and acetyl coenzyme A (CoA): ACP transacylase activities *in-vivo* and *in-vitro* in *Escherichia coli* [50,51].

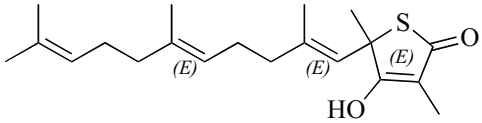
TLM has moderate activity against a broad spectrum of pathogens. Some analogs of TLM have been synthesized and found to have enhanced activity against pathogenic strain of *M. tuberculosis* [52]. TLM analogs act through the inhibition of the mycolate synthase (enzyme for biosynthesis of the cell wall) and inhibited bacterial as well as plant type II fatty acid synthases (FAS-II), which provide essential building blocks for the bacterial cell wall. TLM exert overall effect by inhibition of the β-keto acyl-ACP-synthases (Kas), key condensing enzymes involved in the chain elongation in FAS-II. TLM is of considerable interest because of its selective activity in disrupting essential fatty acid synthesis in bacteria, plants and some protozoa, but not in eukaryotes. This has lead to expectations that inhibitors of the TLM target enzyme, FAS-II, are of potential value in the treatment of malaria [53], trypanosomiasis (sleeping sickness) [54] and various bacterial infections including TB [40]. TLM selectively inhibits the mycobacterial acyl carrier protein-dependent type II fatty acid synthase (FAS-II) but not the multifunctional type I fatty acid synthase (FAS-I) that is present in mammals [55]. They block long-chain mycolate synthesis in a dose-dependent manner. The isoniazid is also disruption of mycolic acid synthesis, but there is no cross-resistance between the two molecules. This is because isoniazid requires activation by a katG catalase-peroxidase enzyme and in many resistant strains of *M. tuberculosis* this enzyme is mutated and unable to convert the drug to its active species [56]. Consequently, TLM is active *in-vitro* against a various strains of *M. tuberculosis*, including MDR, even though at somewhat high concentrations.



Thiolactamycin



(**A**)

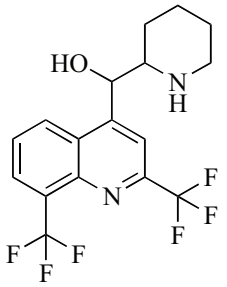


(**B**)

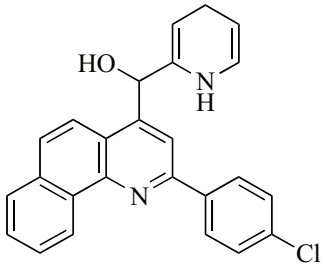
For example, complete inhibition of growth of the virulent strain *M. tuberculosis* Erdmman was 25 mcg/ml. In rodents, TLM is well absorbed orally with an LD50 of 1.689g/kg [48]. It has activity in mice models of bacterial infection, by both the oral and subcutaneous routes, but does not highly potent, with ED50's >70mg/kg [48]. Although, its activity is interesting, but insufficient to further progression of TLM as an anti-TB agents. However, synthetic Analogs as both enantiomerically pure molecules [57] and racemic mixtures, e.g. compounds (**A**) and (**B**), which are reported to have greater activity than the parent in inhibiting *M. tuberculosis* H37Rv *in vitro*.

Mefloquine Analogs

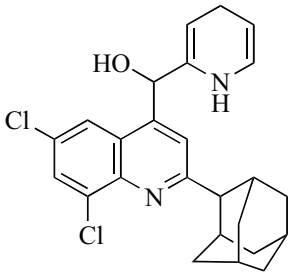
The antimalarial drug mefloquine (4-aminoquinoline methanol), and its several derivatives, exhibited activity against a variety of bacteria including *Mycobacterium* [58]. From a series of quinoline methanols obtained from WRAIR, two compounds, WR-3016 and WR-3017, showed potent inhibitory activity in-vitro against the *M. avium* complex-1 (MAC) assay with MIC_{50} values of 1 and 2 mcg/ml respectively, compared to 16mcg/ml for mefloquine [40]. However, both these two compounds were not as active as the parent molecule in an *in-vivo* MAC assay. Other mefloquine compounds from the WRAIR were also screened [59]. Ideally this should include the two enantiomers of mefloquine and might be worth extending to test, 4-aminoquinoline antimalarials such as chloroquine [60]. There is also interest in the anti-TB properties of the mefloquine analog desbutylhalofantrine (**3**). This compound is under development for its antimalarial properties with the apparent advantage over the parent drug halofantrine of lower cardiotoxicity.



Mefloquine



WR-3016



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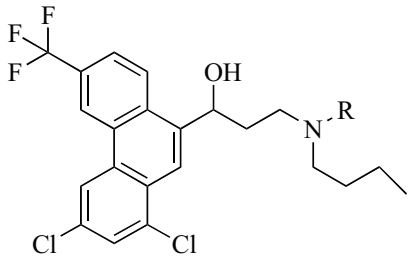
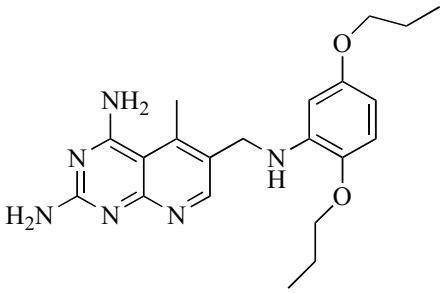


(**3**) R= n-butyl, halofantrine and R= H, desbutylhalofantrine

Deazapteridines

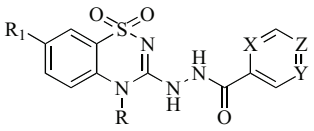
The 2,4-diamino-5-deazapteridine derivatives, SRI-20094 displayed potent inhibition of MM6 cells infected with *M. avium* complex (MAC) strain NJ3440 with an MIC of at most 0.13 mcg/ml. SRI also showed excellent inhibition of dihydrofolate reductase (DHFR) of the MAC, with an IC_{50} value of 1.0 nM as compared to 4100, 1.0 and 1.4 nM for the agents trimethoprim, trimetrexate and piritrexim respectively. It displayed limited inhibition for human DHFR having an IC_{50} value of 7300 nM. SRI-20094 is claimed to be of potential value for the treatment of *M. avium* infections and, in particular, for persons co-infected with HIV. Other close Analogs of this compound have been reported to be highly active against *M. tuberculosis* with MICs of ~0.1mg/l [40]. The tertiary structure of the *M. tuberculosis* enzyme could profitably be used to aid in the identification of TB-specific inhibitors [61]. In addition, the recently developed yeast-based system incorporating the DHFR is a possibility for use in high throughput screening for novel enzyme inhibitors [40].



SRI-20094

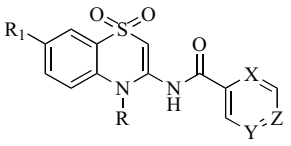
1,2,4-Benzothiadiazines

Sulfonamides are well known antibacterial and a large number of such compounds have been used as antimicrobial agents [62-64]. The compound 1,2,4-benzothiadiazine dioxides have a close relation to sulfonamide and considered as cyclic sulfonamide molecules. These compounds have been possess variety of biological properties, including antimicrobial activity [65,66]. Based on this finding and used to develop new antitubercular agents. The 1,2,4-benzothiadiazine system was explored by incorporating other heterocyclic rings like pyridine and pyrazine moieties (**4** and **5**). Some molecules based on 1,2,4-benzothiadiazine system that exhibited interesting antitubercular activity [67,68].



(4)

R= Me, Et, i-Pr, Ph
R1= H, Cl
X=CH, N
Y= CH, N
Z=CH, N, CCl



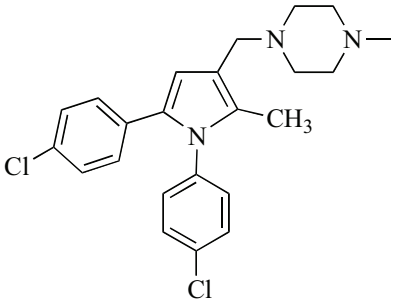
(5)

R= Me, Ph
R_1= H, Cl
X= CH, N
Y=CH, N
Z= CH, N, CCl

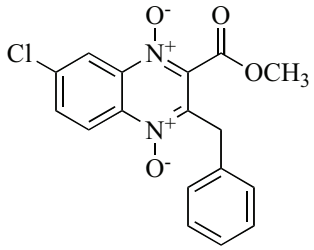
Other Molecules

Several other molecules like pyrroles (**6**), [69] quinoxaline-1,4-dioxides (**7**) [70] and alkylsulfinyl amides (**8**), [71] etc. have also been prepared for their antimycobacterial activity. Some new targeted molecules such as signaling kinase inhibitors have been investigated. The survival of *M. tuberculosis* against the macrophage phagocytosis relies not only on a thick cell wall but also on many mycobacterial kinases and phosphatases which disrupt the host-cell defenses against parasitism [72-74]. Histidine kinase is focus for the specific inhibition of signal transduction system in *mycobacterium* [75-78]. Based on signal transduction system, a series of antimycobacterial salicylanilides and their

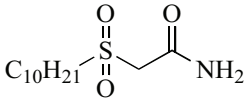
analogs have been reported [79-82]. Inhibition of regulation has been involved in the virulence of *M. tuberculosis* in mice.



Pyrrole (**6**)



Quinoxaline 1,4-dioxide (**7**)

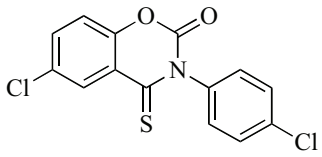


Alkyl sulfinyl amide (**8**) **FAS20013**

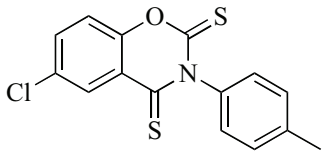
Eleven putative eukaryotic–like protein serine-threonine kinases (Pkn A to L) involved in signal transduction have been identified in *M. tuberculosis* H37Rv genome [83,84]. Based on this kinase inhibition benzothiophenes (specifically inhibits Pkn G) [85, 86] and benzoquinoxalines (inhibitors of Pkn B, Pkn G, and Pkn H) [87-90] have been reported. Hence the research on signaling kinase inhibitors could provide a target oriented lead molecules for the tuberculosis therapy because the persistent drug-resistant TB problem. It is important that new drugs should act on different targets or different mechanisms with the shortening of TB therapy. The unique structure of the mycobacterial cell wall makes it a useful target for drug development that can be directed to specific sites like cell wall biosynthetic pathways [91] e.g. Thiolactomycin, inhibits mycobacterial fatty acid synthase and the elongation steps of mycolic acid biosynthesis [55], with negligible toxicity and this could provide a new class of antibiotics against tuberculosis.

Benzoxazines

A series of 6-chloro-3-phenyl-4-thioxo-2H-1,3-benzoxazine-2(3H)-ones and 6-chloro-3-phenyl-2H-1,3-benzoxazine-2,4(3H)-dithiones compounds (**9**) and (**10**) have potent antimycobacterial activity against *M. tuberculosis* (MIC values 0.5 mcmol/l), *M. avium* (16 and 16 mcmol/l), *M. kansasii* 235/80 (2 and 2 mcmol/l), and *M. kansaii* 6509/96 (1 and 0.5 mcmol/l), compared with MIC values of 4, 500, 8 and 500 mcmol/l for isoniazid after 14 days [40]. However, the presence of the thioamide moiety, it showed some structural similarities to thiacetazone and may cause cross-resistance.



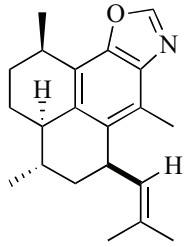
(**9**)



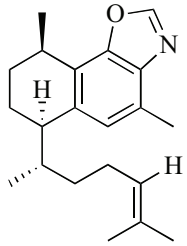
(**10**)

Diterpenoids

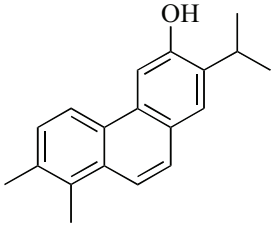
The natural products from the West Indian gorgonian coral *Pseudopterogorgia elisabethae* exhibited anti-tuberculosis activity. It has two novel active diterpenoid alkaloids, pseudopteroxazole and seco-pseudopteroxazole containing the benzoxazole moiety [92]. The pseudopteroxazole was to be a potent inhibitor giving 97% growth inhibition at 12.5mcg/ml while secopseudopteroxazole was somewhat less active against *M. tuberculosis* H37Rv. However, it was noted that various plant-derived diterpenoids have been reported as antitubercular. Some of these, e.g. (**5**), are considerably more active than the marine diterpenoids with MIC of (**11**) vs *M. tuberculosis* H37Rv = 0.46mcg/ml. Although, such compounds are still novel and seem to be structurally more amenable to synthesis of new analogue.



Pseudopteroxazole



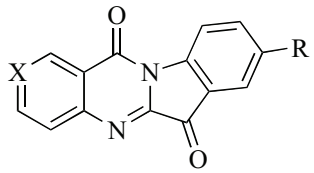
Seco-pseudopteroxazole



(11)

Tryptanthrin Analogs

Tryptanthrin is structurally indoloquinazolinone, this novel alkaloid was first isolated by Chinese scientists, and tested against various strains of *M. tuberculosis* [93] including drug-sensitive strains. The MIC of tryptanthrin was 1.0 mcg/ml compared to 0.03mcg/ml for isoniazid. When tested against MDR-TB strains, whilst tryptanthrin maintained its potency (MICs of 0.5-1mcg/ml), isoniazid had decreased activity with MIC's 4-16mcg/ml. Many Analogs of tryptanthrin have been developed for their potential against tuberculosis. However, it is not been possible to identify a compound that sufficiently efficacious to warrant further progression. For example, PA-505, having potent activity towards *M. tuberculosis* H37Rv in-vitro with MIC 0.015mcg/ml and had only modest effects in the spleen of infected mice when given at 50mg/kg/day orally for ten days against *M. tuberculosis* [93]. There would be insufficient drug concentration to exert a bactericidal effect. Although, the mode of action of the tryptanthrins is not known, from structural considerations they may be DNA intercalators, would raise toxicological issues [93].

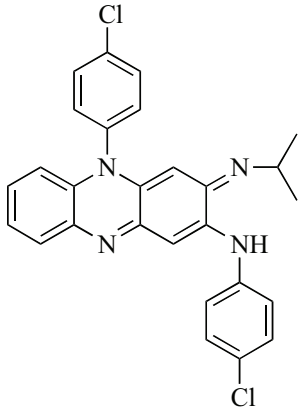


Tryptanthrin R=H, X=CH and PA 505, R=CH $(Me)(CH_2)_5Me$, X=N

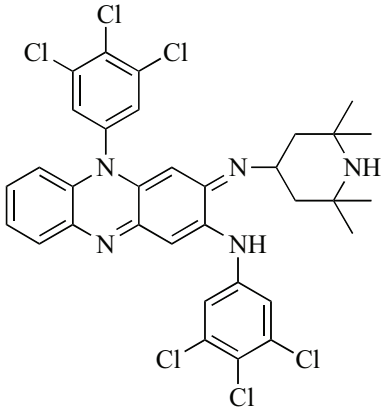
Clofazimine or Tetramethylpiperidino (Tmp) Phenazines Analogs

The tetramethyl piperidine substituted phenazines B4169 and B4128 (TMP phenazines) significantly exhibited activity against *M. tuberculosis*, including MDR strains than clofazimines [94]. The important virtues of tetramethylphenazines are intracellular accumulation in mononuclear phagocytic cells, a low incidence of drug resistance and slow metabolic elimination rate, which make them attractive molecules for the treatment of tuberculosis. Recently, new conjugates of phenazine with phthalimido and naphthalimido moieties have been designed as antitubercular compounds [95]. Some of the compounds in this class of phenazine hybrids have shown promising results in the inhibition of *M. tuberculosis* ATCC 27294. This study showed that there is a potential to design such type of phenazine hybrids for the development of new antitubercular drugs.

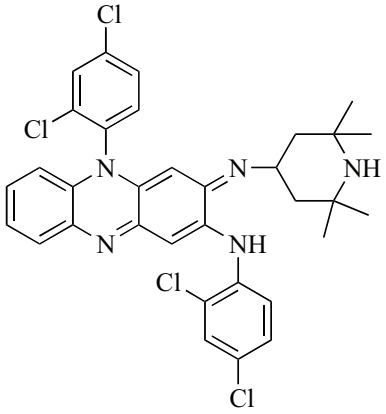
The anti-TB activity of novel tetramethylpiperidinophenazines closely related to the antileprosy drug clofazimine. The intra- and extra-cellular activities of these compounds were compared to clofazimine and rifampicin against *M. tuberculosis* H37Rv (ATCC 27294). One of the phenazines, B4169, potently inhibited the bacterium with an MIC value of 0.015mcg/ml, MIC for clofazimine was 0.06mcg/ml. The compounds were also more active than clofazimine against *M. tuberculosis* isolates including MDR strains. Several phenazines, e.g. B4128, showed significant intracellular activity (~60% inhibition of growth) at 0.001mcg/ml against *M. tuberculosis* and were superior to both clofazimine and rifampicin. Most likely they will suffer from the undesirable property of imparting marked coloration to the skin of patients [40].



Clofazimine



B4169

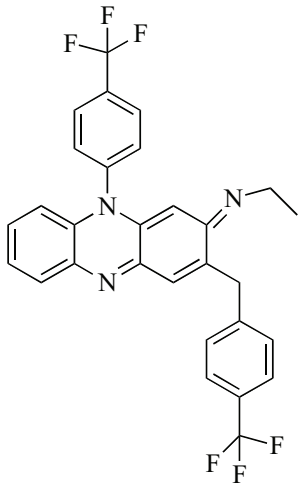


B4128

Phenazine B4157

B4157 is a phenazinamine derivative, closely related to the antileprosy drug clofazimine, which has been investigated as

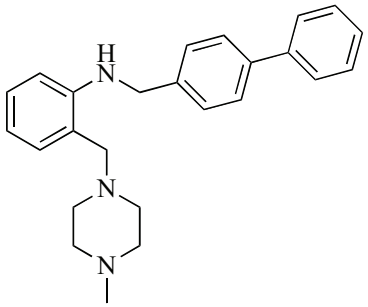
potential antitubercular [96]. *In-vitro*, clofazimine and B4157 were tested against 20 strains of *M. tuberculosis*, including 16 MDR strains, and all were found to be susceptible to B4157 including one which showed moderate resistance to clofazimine. The MICs of B4157 and clofazimine were 0.12 and 1.0 mcg/ml, respectively. However, against *M. tuberculosis* in C57BL at 20 mg/kg in mice, clofazimine was slightly superior to B4157. Both compounds prevented mortality. The animals treated with B4157 showed less pigmentation than those receiving clofazimine [40].



B4157

Toluidine Derivatives

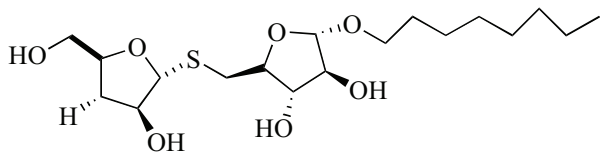
A number of toluidine derivatives have shown interesting *in vitro* activity against *M. tuberculosis* 103471. The compounds (**12**), showed more potent activity having MICs of 4 mcg/ml, MICs of isoniazid, 0.25 mcg/ml, and streptomycin, 0.5 mcg/ml. However, there are concerns that these aromatic amines will undergo rapid metabolic degradation, possibly to toxic metabolites [40].



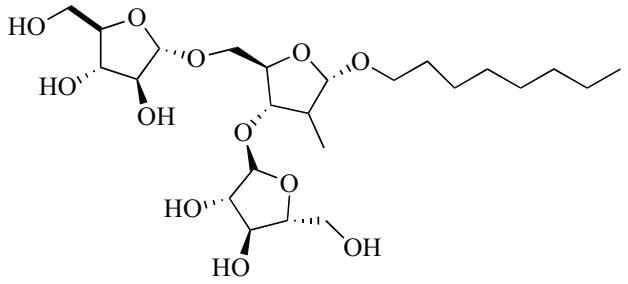
(**12**)

Saccharides

The arabinose disaccharide SR-9581 is active against *M. tuberculosis* strain *in-vitro*, with a MIC value of 4mcg/ml. It decreased the viability of *M. tuberculosis* by 76.1%, 97.8% and 99.9% at 8, 16 and 32 mcg/ml respectively within 3 days. Another saccharide, an arabinofuranoside oligosaccharide (**13**), is a substrate for mycobacterial arabinosyltransferases. Both compounds can be expected to disrupt mycobacterial cell wall synthesis [97, 98].



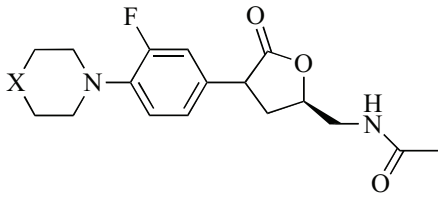
SR-9581



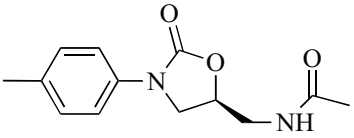
(13)

Oxazolidinones (Linezolid)

Oxazolidinones are broad-spectrum antibiotics and inhibit protein synthesis by binding to the 50S subunit of ribosomes. Oxazolidinones had significant activities against *M. tuberculosis in-vitro* and in mice [99,100]. However, oxazolidinones are less promising due to their toxicity and high price. Similar remarks are applied to this series as to the quinolones. However, far less information is in the public domain as to the likely toxicities of these agents following long-term administration [101-103].



Linezolid (**U-100766**) X=O PNU and **100480** X=S,



DuP 721 R=MeCO and **DuP 105** R=MeSO

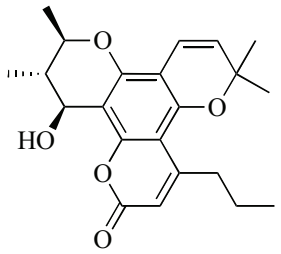
Oxazolidinones PNU 100480 and AZD 2563

The oxazolidinones are a new class of synthetic antimicrobial agents with a unique mechanism in inhibiting protein synthesis [104]. General these compound displayed bacteriostatic activity against many important human pathogens, including MDR strains. One compound, linezolid [105], has reached in the market and other members are in varying stages of development. The oxazolidinones have activity against *M. tuberculosis* with linezolid (U-100766) inhibiting MDR isolates *in-vitro* at 2mcg/ml [100]. Oxazolidinones containing a thiomorpholine moiety in place of the morpholine present in linezolid reported as active against *M. tuberculosis* with MICs of 0.125mcg/ml [106]. One other compound, PNU-100480, was tested in a murine model against ten viable strains of *M. tuberculosis* in comparison to linezolid and

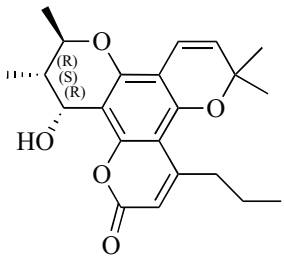
isoniazid. When treatment was started one-day post infection and after four weeks, PNU-100480 proved comparable to isoniazid and more active than linezolid [99]. Further comparisons are warranted with other oxazolidinones, such as the AstraZeneca compound, AZD-2563 which is being useful for the treatment of MDR bacterial infections.

Calanolides

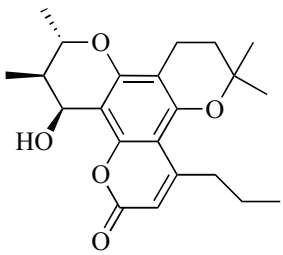
Calanolide A is a naturally occurring pyranocoumarin, with dual activity against TB and HIV infections [107]. The compound is an inhibitor of HIV-1 reverse transcriptase [40] and is in Phase I/II development stage for the HIV indication. It also displayed good *in-vitro* activity towards *M. tuberculosis*. In a preliminary assessment, calanolide A was comparable to the isoniazid and remained effective against rifampin and streptomycin-resistant TB strains. The large-scale synthesis of calanolide A is for reducing the dependency of on the scarce natural resource [107]. Various other Analogs have been obtained either from natural extracts or by synthesis [40] and some compound, e.g. (**14**), have been patented for their antiTB activity [108]. In addition, calanolide B, which unlike calanolide A, is readily available in substantial quantities from natural sources, e.g. from *Calophyllum* seed oil, [109] is claimed to have a similar spectrum of activity to calanolide A against *mycobacterium* and may be a more cost-effective therapy.



Calanolide A



Calanolide B



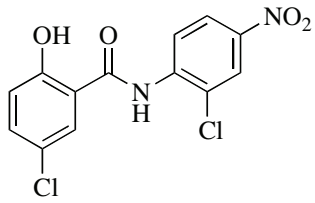
(**14**)

Poloxamer 315 (CRL-1072)

Poloxamer 315 is a methyloxirane surfactant polymer that appears to disrupt the cell membranes of microbes or their intracellular components. The purified polymer has been shown to be active against *M. tuberculosis* and *M. avium* [110,111]. *In-vitro* studies against *M. tuberculosis* showed MIC values of 3.1-6.2mcg/ml while, in macrophage assay, these drop to 0.92 to 1.25mcg/ml. This compound was active against *M. tuberculosis* that resistant to isoniazid, streptomycin and rifampin. *In-vivo*, 2mg/kg/day of CRL315 administered intravenously three times a week, for three weeks allowed survival of *M. tuberculosis*-infected mice and reduced CFU (colony forming unit) counts in lungs and spleens. In an acute toxicity study with CRL315 in mice, the maximum tolerated i.v. dose was 125mg/kg [111]. The pharmacokinetic analysis showed very little of the drug in blood with high concentrations being found in liver, kidney and spleen. In sub chronic toxicology studies, poloxamer CRL315 was non-toxic at doses up to 100 mg/kg/day orally for 28 days [112]. In order to evaluate its true potential and oral activity should be determined in various animal models [40].

Niclosamide

The anthelmintic drug niclosamide showed anti-TB activity *in-vitro* (MIC 0.5-1mcg/ml) against *M. tuberculosis* H37Ra as well as being active against growing cells. It has the interesting property of acting against stationary phase non-replicating bacterial cells. However, niclosamide has been extremely useful for the treatment of human tapeworm infections and not absorbed to any significant extent from the intestine [113]. The pharmacokinetic profile, along with its mutagenic capability, considerably blights the potential of this compound for TB chemotherapy.



Niclosamide

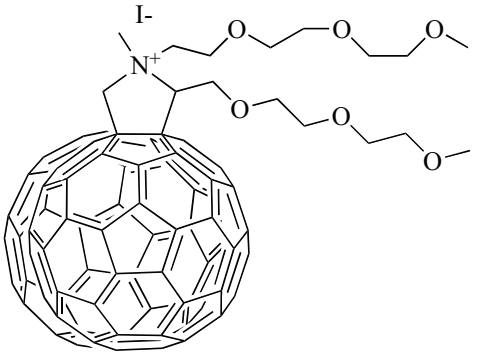
Mikasome

The anti-TB activity of liposome-encapsulated drug, MiKasome, has been found to be effective against *M. avium* strain *in vitro* in animal models [40]. In preclinical studies [112], after 48 hr of delivery to the lungs via liposome, over half of the antibiotic remained in the tissue. The pharmacokinetic data showed that MiKasome produced 7-fold higher peak plasma levels compared to free anti-TB drug (amikacin- an aminoglycoside) administered intravenously. Additionally, the area under curve (AUC) was 150-fold higher with the liposomal material and a single dose of liposomal amikacin produced therapeutic levels of antibiotic for more than 72 hr. In a preliminary study, a TB-patient treated with MiKasome for 49 days exhibited negative culture. Once weekly dosing maintained constant

amikacin dose levels. Phase II studies showed that MiKasome was resolved *M. tuberculosis* infections who had failed conventional therapies.

Fulleropyrrolidines

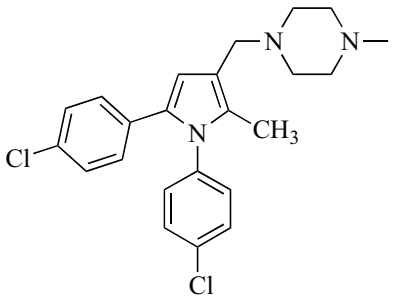
A series of fullerene derivatives, compound (**15**) displayed anti-TB activity that inhibited the growth of *M. tuberculosis* strain H6/99, a human clinical isolate, with a MIC value of 5 mcg/ml. In strain H37Rv with a MIC value of 50mcg/ml [40]. Some fullerene derivatives have also shown *in-vitro* activity against the HIV protease offering the possibility of joint efficacy towards both AIDS and TB. However, the presence of the quartenary nitrogen atom in compound (**15**) suggests that toxicity issues might be a problem.



(**15**)

Pyrrole LL- 3858

Currently limited information on the pyrrole compounds as anti-TB agents. Some pyrrole derivatives were found to be active against *M. tuberculosis* including MDR-TB strains *in-vitro* [69,114]. The pyrrole derivative (LL-3858) showed higher bactericidal activity than Isoniazid when administered as monotherapy in infected mice. In mouse models, 12 weeks treatment with LL-3858 plus isoniazid and rifampicin, or LL-3858 plus isoniazid-rifampicin-pyrazinamide, sterilized the lungs of all TB-infected mice. Experiments conducted in mice and dogs also showed that the compound is well absorbed, with levels in serum above the MIC and high Cmax than isoniazid [40].



Pyrrole LL- 3858

Dipiperidine SQ-609

Dipiperidine SQ-609 is a novel compound and structurally different to existing anti-TB drugs. It kills *M. tuberculosis* by interfering with cell wall biosynthesis. Anti-TB activity has been reported *in-vivo* in mice models [115,116].

Pleuromutilins

The pleuromutilins are a naturally occurring novel class of antibiotic. They act by interfere with protein synthesis by binding to the 23S rRNA and inhibiting the peptide bond formation [117]. Despite the novelty of compounds, the studies have shown that cross-resistance might occur among pleromutilins and oxazolidinones [118]. The pleuromutilins have been shown *in vitro* anti-TB and active against MDR-TB with shorter of the treatment period [119].

ATP Synthase Inhibitor FAS20013

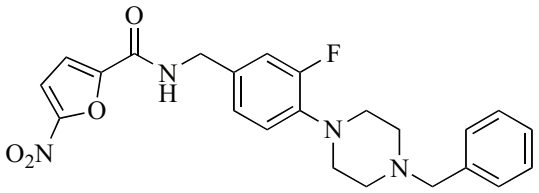
FAS20013 is a novel compound, which belongs to the class of β-sulphonylcarboxamides that kill more organisms in a 4-hour exposure than isoniazid or rifampicin. This compound has been very high bactericidal effect against MDR-TB. The researches indicate that superior effect of FAS20013 compared to current drugs by its ability to "sterilize" TB lesions and kill latent TB strains. Therapeutic evaluation of FAS20013 has shown its effectiveness in mice with no serious side effects and showed up to 100% oral bioavailability and no dose-limiting toxicity has been encountered. This compound is thought to act through inhibition of ATP synthase [71,119,120].

Diamine SQ-109

Diamine SQ-109 has been identified and based on the pharmacophore of ethambutol. This aim was developed as second-generation agent from the first line drug ethambutol. When tested in a low-dose infection model of TB in mice, SQ-109 at 1 mg/kg was as effective as ethambutol at 100mg/kg. However SQ-109 did not show improved effectiveness at higher doses (10mg/kg; 25mg/kg) and was less effective than isoniazid [121]. The SQ-109 is also effective against MDR-TB, including those that are ethambutol-resistant, and that it targets different intracellular target(s) and can be considered as a new TB drug and not simply as an ethambutol analogue.

Nitrofuranylamides

M. tuberculosis is quite susceptible to Nitro containing compounds [38, 122]. Nitrofuranylamide (**16**) was identified in a screening for UDP-Gal mutase inhibition. An expanded set of nitrofuranylamides was synthesized and tested as antimicrobial agent. This led to a number of nitrofuranylamides which active against *M. tuberculosis*. However, further investigation has revealed that the primary target for antimicrobial activity of nitrofuranylamides is not the UDP-Gal mutase. Some nitrofuranyl amide compounds showed significant activity in mouse models for TB infection [123,124].



(16)

Granulysin

Granulysin is an antimicrobial protein prepared by human cytotoxic T-lymphocytes and natural killer cells [125]. This protein has been found to reduce the viability of a broad spectrum of pathogens and parasites *in-vitro*. Furthermore, synthetic 22 and 29 residue peptides of granulysin directly kill extracellular *M. tuberculosis*, and altering the membrane integrity of the *bacillus*. However, difficult barriers exist to produce a therapeutic agent, especially cost and lack of oral bioavailability of peptides.

Stazyme

The stazyme is prepared from *Staphylococcus clavelios* containing several different-sized proteins which cause significant inhibition of mycobacterial growth [126]. At concentrations of 50 and 200 mcg/ml of total protein, stazyme was highly bactericidal against *M. smegmatis*, and bacteriostatic against *M. tuberculosis* and *M. avium*. It was able to break the permeability barrier of *M. avium* isolates and significantly enhancing the activity of other anti-TB drugs. Identification of the mycobacteriolytic determinant in stazyme may be helpful to define novel drug targets.

DISCUSSION

Despite current anti-TB therapy, TB is the one of the most leading infectious diseases all around the world. The main obstacles to control the TB are the HIV/AIDs epidemic that has dramatically increased risk for developing tubercular infection, the increasing resistance against MDR-TB, XDR-TB and the recalcitrance of persistent infections to treat with conventional anti-TB drugs [127-131]. According to mode of action, first and second line anti-TB drugs can be grouped as cell wall inhibitors (isonizide, ethambutol, ethionammide, and cycloserine), nucleic acid synthesis inhibitors (rifampicin, quinolones), protein synthesis inhibitors (streptomycin, kanamycin) and inhibitors of membrane energy metabolism (pyrazinamide). Existing anti-TB drugs are only able to target actively on growing bacteria through the inhibition of cell processes such as cell wall biogenesis and DNA replication. This implies current TB therapy is characterized by an efficient bactericidal activity but has an extremely weak sterilizing activity, as the ability to kill the slowly growing or slowly metabolizing bacteria. The current situation clearly demonstrates the need for a re-evaluation of our approach to treating TB [132]. Drug development for tuberculosis has been at a virtual standstill for decades, but increased awareness and advocacy in recent years have led to new initiatives in TB drug development. This review provides a analysis of anti-TB drugs whether current approaches are likely to provide truly effective new tools to treat TB [133,134]. This article also provides details of various antitubercular agents with different pharmacophores except conventially used drugs with potential anti-TB activity with the specific objective to identify promising candidates for the development of novel drugs for the treatment of tuberculosis.

CONCLUSION

In tuberculosis (TB) therapy, the problem is that *M. tuberculosis* can survive for long period of time in nonreplicative or persistent phase. In this state, *M. tuberculosis* is resistant to conventionally used chemotherapeutic agents. Patient non compliance with the ability of *M. tuberculosis* to enter the persistence state has contributed to the emergence of MDR and XDR strains. The ineffectiveness of current anti-TB drugs against persistent, MDR, and XDR strains of *Mycobacterium* has greatly motivated the search for novel and effective anti-TB therapy. In spite of the BCG vaccine and various anti-TB agents, TB remains a leading infectious disease worldwide. This is mainly due to the lack of new and novel drug molecules, particularly for MDR and XDR strains of *Mycobacterium*. Therefore, there is an urgent need for the development of new anti-TB drugs with low harmful/side-effects, improved pharmacokinetics, reduce treatment duration, effective against pathogenic and resistant strains of *Mycobacterium*. It is also based on the inhibition of bacterial targets, molecular mechanisms of drug actions; need to understand host factors such as immune mechanisms, genetic susceptibility and disease relapse. Further, the molecular mechanisms are being unraveled for the already known and newly discovered active molecules.

CONFLICT OF INTEREST

The author confirm that this article content has no conflicts of interest.

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