A Brief Overview on Recent Advances in the Development of Anti-Tubercular Compounds Containing Different Heterocyclic Ring Systems

Mohammad Asif

Department of Pharmacy, GRD (PG) Institute of Management and Technology, Dehradun, Uttarakhand, India

Corresponding author: Mohammed Asif, Department of Pharmacy, GRD (PG) Institute of Management and Technology, Dehradun, Uttarakhand, India, Tel: +91 92580-71905; Fax: +91 135 273-4048; E-mail: aasif8321@gmail.com

Received date: August 02, 2016; Accepted date: August 24, 2016; Published date: August 29, 2016

Abstract

Tuberculosis (TB), a leading cause of mortality and morbidity with more than one-third of the world population infected with latent TB and the worldwide dissemination of multidrug (MDR) and extensively drug resistant (XDR) Mycobacterium tuberculosis poses a serious threat to human health. Hence, new drugs are urgently needed to shorten and improve the treatment course in drug resistant TB, and to minimize the occurrence of new infections and death to zero level. Various new drugs progress to be developed for the treatment of MDR-TB. Several new molecules in clinical development encourage the scientific community to find new drug targets and new drug leads. In this perspective we present herein an overview of the new anti-TB agents with different molecular structures. Here we have tried to provide some efforts that are being made in the development of new drug molecules as lead anti-TB agents.

Keywords: Tuberculosis, Mycobacterium tuberculosis, Multidrug resistance; Extensively drug resistance; New drugs and targets

Introduction

Heterocyclic chemistry is the branch of chemistry dealing with synthesis, properties, and applications of heterocycles. Heterocycles form by far the largest of the classical divisions of organic chemistry and are of immense importance biologically, industrially, and indeed to the functioning of any developed human society. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic. There are countless heterocyclic additives and modifiers used in industries [1-3]. Heterocycles play an important role in biochemical processes. Heterocyclic systems occur in a wide variety of natural and synthetic compounds and are essential to life in various ways. The synthetic heterocyclic drugs are still more numerous and include most of the antimicrobials, hypnotics, anti-convulsants, analepics, anti-histaminics anti-thyroid drugs, also many antiseptics, fungicides, vasopressor modifiers and others. Heterocyclic rings constitute a large number of synthetic dyes and analytical reagents [3-6].

Tuberculosis, commonly known as TB, is an often severe and contagious airborne disease caused Mycobacterium tuberculosis (Mtbb) and typically affects the lungs but can affect the other parts of the body called extrapulmonary tuberculosis (TB). The Mtbb is acid-fast, gram positive bacteria, grows slowly under aerobic conditions. Multidrug-Resistant TB (MDR-TB) is defined by resistance to the two most commonly used drugs in the current four-drug (or first-line) regimen, isoniazid and rifampin. Extensively drug resistance TB (XDR-TB) is caused by Mtbb resistant to isoniazid, rifampin, at least one fluoroquinolone, and one of the injectable anti-TB drugs such as amikacin, kanamycin, or capreomycin. Minimum Inhibitory Concentration (MIC) is the concentration of antibiotic that will inhibit the growth of bacteria. DOTs (Directly Observed Treatment, Shortcourse) is a strategy that framework for the TB control programme [7-10].

TB is one of humanity’s oldest and most resilient plagues, despite the availability of four drug regimen to treat the disease [11]. The current first line anti-TB regimens require a minimum 6 months of DOts therapy. Adherence to the long and complicated treatment course is challenging and is a major obstacle to the effective use of existing drugs [12]. As a result of treatment failure and poor observance, epidemic with MDR-TB or XDR-TB is being more common [13]. In 2011, the number of MDR-TB infections was estimated at 60,000 cases (19 % of the global infected population) [4]. Suggested regimens for MDR-TB therapy require at least 20 months of treatment with drugs that are toxic, poorly tolerated, and limited efficacy of cure rate. According to World Health Organization (WHO) global TB report 2012, there were almost 9 million new cases in 2011 and 1.4 million TB deaths. Besides, the emergence of drug-resistance is becoming a major threat to global TB care and control. Around 310,000 MDR-TB cases occurred among notified TB patients in 2011 [14]. The increasing emergence of DR-TB and HIV infection which compromises host defense and allows latent infection to reactivate TB and posed further challenges for effective control of TB. Moreover, TB treatment is lengthy (takes 6-9 months) with significant toxicity, which creates poor patient compliance resulting in a frequent cause for selection of drug resistant and often deadly MDR-TB bacteria [15]. In 2013, 6.1 million TB cases were reported out of these, 5.7 million were newly diagnosed. Number of MDR-TB infections was estimated at 23% of reported TB patients. 1.1 million (13%) of the 9 million people who developed TB in 2013 were HIV-positive. About 60% of TB cases and deaths occur among men and 510000 women died as a result of TB, more than one third of whom were HIV-positive. There were 80000 deaths from TB among HIV negative children in the same year [16]. The emergence of highly lethal, expensive and virtually untreatable XDR-TB poses a new threat to TB control. The control of TB is complicated due to latent TB where the infected persons are asymptomatic, and serve as the reservoir for the pathogen, making control of this disease a difficult and challenging task [17]. In 2014, the WHO estimated 9 million new TB cases had occurred globally in 2013,
480000 of them being affected by MDR-TB strains [18]. The MDR-TB treatment success is only 54% (with 15% death, 8% failure/relapse and 23% default). When the drug resistance profile is beyond XDR (with increasing complexity), the outcomes are unfortunately lower: treatment success ranges from 40% to 19%, failure/relapse from 15% to 54% and death from 15% to 35% [19,20]. Every day, clinicians managing these cases face relevant challenges that include frequent occurrence of adverse events, problems in patients’ adherence, lack of clinical experience, and limited availability of adequate diagnostics and second-line anti-TB drugs. The risk of acquiring further drug resistance is therefore real. WHO has launched its innovative “End TB Strategy”, supporting the TB elimination strategy and the vision of a TB-free world with zero death, disease and suffering due to TB [21-23]. The strategy clearly supports universal access to high-quality MDR-TB diagnosis and treatment [24]. The need for new drugs and regimens is obvious [25].

Recent advances in the knowledge of molecular biology and Mtb genome sequences has enabled the essentiality of genes for the rapid target identification for the new anti-TB agents via identification of mutated genes of compound-resistant mutants [26,27]. Effective treatment of TB patients co-infected with HIV is complicated due to drug-drug interactions between anti-retrovirals (ARVs) and antituberculosis drugs and increased the risk of adverse effects. There is urgent need for more effective and tolerable anti-tuberculosis therapy for the treatment of drug-susceptible, drug-resistant disease and latent-TB infection [28]. Regimens that can be safely co-administered with antiretroviral therapy are urgently needed for the treatment of TB patients co-infected with HIV [29]. Effective and tolerable anti-tuberculosis target identification as well as the development of innovative, effective drug combinations should also be encouraged to diversify therapeutic choices, especially those for drug resistant TB cases [29].

**Designing a regimen to treat TB**

The treatment regimens approved TB drugs and the dosage of anti-TB drugs recommended by the evidence-based WHO guidelines. “New” and “retreatment” cases are clearly separated, 30 days of previous anti-TB treatment being the cut-off. New TB cases (irrespective of HIV status) should be treated for the first 2 months (intensive phase) with isoniazid, rifampicin, pyrazinamide and ethambutol, followed by isoniazid and rifampicin for the remaining 4 months (continuation phase) [32]. The daily dosage is recommended (although the three times weekly dosing can be used during the continuation phase under directly observed therapy) as well as the fixed-dose combinations [33]. The aim of this review is to summarise some anti-TB compounds.

**Pyrimidines, dihydropyrimidines, tetrahydropyrimidines**

Various pyrimidine analogs (Figure 1) were tested against *Mtb* [34-38]. Compound 1a (5-formamidopyrimidines) displayed IC₅₀ values ≤ 1 μg/mL and exhibited low toxicity towards mammalian cells. A series of dihydropyrimidines also exhibited *in vitro* anti-TB activity against *Mtb* H37Rv. Compounds 1b, 1c were found to be the potent against *Mtb* with MIC value 0.125 and 0.25 μg/mL respectively [39]. Tetrahydropyrazolopyrimidine, 1 d exhibited *in vitro* MIC value 0.15 ± 0.04 μM and potent *in vivo* activity in a mouse efficacy model, achieving a reduction of 3.5 log CFU of *Mtb* after oral administration to infected mice once a day at 100 mg/kg for 28 days [40]. One of the quinolinyl pyrimidines 1e showed MIC0.87 μg/mL and enzyme inhibition (IC₅₀=0.043 μM) against the NDH-2 target, which in turn translated into cellular activity against *Mtb* [41].

**Piperidine-4-ones**

Piperidinone derivatives were reported as potent anti-TB agents [42-45]. The 4-(4-Fluorophenyl)-5-phenylpyrrolo(spiro[2.3]-oxindole)spiro[3.3]-1’-methyl-5’-(4-fluoro-phenyl methylidene) piperidin-4-one (Figure 2) was found to be active *in vitro* with a MIC value of 0.07 μM against *Mtb*. *In vivo*, compound 2 decreased the bacterial load in lung and spleen tissues with 1.30 and 3.73-log 10 protections respectively and was considered to be promising in reducing bacterial count in lung and spleen tissues.

**Quinoxaline 1,4-dioxides**

The leading compound LVTZ 3a (Figure 3) belongs to quinoxaline 1,4-dioxides class of compounds showed very good selectivity and...
activity against *Mtb* with MIC 0.1 μg/mL [46]. Anti-TB screening of 3-methyl-2-phenylthioquinoline 1,4-dioxides (3b-3f) exhibited MIC between 0.39 and 0.78 μg/mL against *Mtb*. Amide of quinoxaline 1,4-di-Noxides 3g were active against *Mtb* as same as rifampin (RIF) [47]. A series of quinoxaline derivatives exhibited promising anti-TB activity compound 3h of them emerged as a lead compound having IC$_{50}$ and IC$_{90}$ figures of 1.03 mM and 1.53 mM, respectively by affecting the respiration in rat liver mitochondria [48]. New lead compound 3i from Benzotriazine Di-N-Oxides series has MIC 0.31 μg/mL against H37Rv and cytotoxicity (CC$_{50}$) against Vero cells of 25 μg/mL. This was also negative in a L5178Y MOLY assay, indicating low potential for genetic toxicity [49].

**Figure 3: Structure of quinoxaline 1,4-dioxides (3a-3i).**

### Diydropyridines

1,4-Dihydropriyridines are the emerging class of anti-TB agent [50,51]. Compound 4a (Figure 4) exhibits anti-TB activity with MIC 1 μM, *in vitro* screening [52]. 3D-QSAR study reveals new derivative of 1,4-dihydropriyridines compound 4b with anti-TB activity [53]. Compound 4c was evaluated as potent antitubercular compound having MIC 0.02 μg/mL and low toxicity [53].

**Figure 4: Structure of diydropriyridines (4a-4c).**

### Imidazolopyridines and pyrazolotetraydropyridine

Imidazolopyridines were determined to have promising anti-TB activity against replicating *Mtb* H37Rv, compounds 5a and 5b (Figure 5) exhibited MIC value 0.195 μM [54]. Anti-TB activity of imidazopyridine-8-carboxamides (Figure 5) were evaluated, compounds 5c-5f exhibited MIC value 0.5, 0.5, 0.25, and 0.25 μg/mL against *M. tuberculosis* [55]. A series of 2,7-dimethylimidazo[1,2-a] pyridine-3-carboxamides 5g were evaluated for their *in vitro* anti-TB activity versus replicating, nonreplicating, multi- and extensive drug resistant *Mtb* strains. The MIC$_{50}$ values of these compounds were <1 μM against the various TB strains tested [56]. The MICs of compounds (5h-5l) against replicating bacteria had MIC values ≤ 0.006 μM. These results indicate that readily synthesized imidazo[1,2-alpyridine-3-carboxamides (figure 5) are an exciting new class of potent anti-TB agents that merit additional development opportunities [57]. 1-benzoyl-N-(4-nitrophenyl)-3-phenyl-6,7-dihydro-1H-pyrazolo[4,3-c]pyridine-5(4H)-carboxamide (5m) was found to be active with IC$_{50}$ of 21.8 ± 0.8 μM against *Mtb* PS [58].

**Figure 5: Structure of heterocyclic conjugated pyridines (5a-5l).**

### Galactopyranosyl amino alcohols

A dimeric hybrid of a galactopyranosyl amino alcohol 6 displayed potent *in vitro* activity with MIC 1.56 μg/mL against *Mtb*. However, on progression into a murine model, toxicity was observed at dosage levels (50 mg/kg per day) that offered no significant protection against *Mtb* infection (Figure 6). The target of this compound is mycobacterial cell wall biosynthesis [59].

**Figure 6: Structure of glactopyranosyl amino alcohol (6).**

### Chromene, chromone, chroman and coumarin derivatives

The chromene, chromone and its analogue are reported to have anti-TB activity [60,61]. Oxadiazole-chromenes 7a, 7b (Figure 7) exhibited *in vitro* activity with MIC 0.31 μg/ mL and 0.73 μg/mL against *Mtb* H37Rv. Recently 2,10-dihydro-4aH-chromeno[3,2-c] pyridin-3-yl derivatives were evaluated for their activity against *Mtb* H37Rv and MDR-TB. Among them compound 7c was found to be active *in vitro* with MIC's of 0.22 and 0.07 μg/mL against *Mtb* and MDR-TB respectively. During the *in vivo* study in animal model compound 7c decreased the bacterial load in lung and spleen tissues with 1.11 and 2.94 log$_{10}$ protections at 25 mg/kg body wt. dose [62]. Arylsulfonyl-methylcoumarin screened for *in vitro* anti-tubercular activity against *Mtb* H37Rv, compounds 7d and 7e showed MIC 0.78 μg/mL and 1.56 μg/mL respectively [63]. Phenyl substituted coumarins
and spirocromone conjugates \[65\] also displayed potent activity against TB.

**Thiazoline, thiazole, benzothiazinone and dithiazolone analogues**

The anti-TB activity in thiazoline class of compounds (Figure 8) has been reported recently \[66\]. The most potent compound 8a of this series showed MIC 0.3 μg/mL. A series of potent 5-(2 methylbenzothiazol-5-yl)oxymethyl isoxazole-3-carboxamide derivative 8b, led to potent anti-TB activity with MIC value 1.4 μM against replicating \textit{Mtb} H37Rv \[67\]. Several other thiazoles and benzothiazoles are reported as potent inhibitor of \textit{Mtb} \[68-70\]. A series of benzothiazinones, 8c-8e of this series showed MIC ≤ 0.015 μg/mL activities against MDR-TB with low toxicity \[71\]. Heterocycle substituted 1,3-benzothiazin-4-one derivative 8f showed MIC of 0.0001 μM against \textit{Mtb} H37Rv, 20-fold more potent than BTZ043 \[72,73\]. Compound 8g dithiazol-3-one derivative was found to be active with a lowest MIC value of 1 μg/mL \[74\].

**Pyrrole and pyrrolotiazole**

Pyrrole derivative BM 212 is moderately active against \textit{Mtb} (MIC=0.7 to 6.2 μg/mL) and \textit{M. avium} (MIC 0.4 to 3.1 μg/mL) \[75\]. The thiomorpholine introduction in BM 212 molecule improved its anti-TB activity. Four compounds 9a, 9b, 9c and 9d (Figure 9) had MIC between 1 and 2 μg/mL \[76,77\]. Several derivatives have shown significant activities against drug-resistant TB in vitro and offer considerable protection in a rigorous mouse model of the disease \[78\]. Dispiropyrolotiazoles derivative 9e showed anti-TB activity against \textit{Mtb} H37Rv and INH resistant \textit{Mtb} strains with MIC of 0.210 and 8.312 μM respectively \[79\].

**Oxazole, Oxadiazole and Isoxazoline derivatives**

Several 2-(biphenyl-4-yl)oxazole-4-carboxylates possess good activity against \textit{Mtb} with extremely low toxicity toward VERO cells and high therapeutic indexes \[80\]. Oxadiazoles 10a and 10b (Figure 10) indicate inhibition of \textit{Mtb} at concentrations 1.6 and 1.5 μg/mL \[81\]. Compound 10c showed \textit{in vitro} anti-TB activity with MIC value 0.07 and 0.14 mM against \textit{Mtb} and MDR-TB respectively \[82\]. Several oxazoles \[83\] and oxadiazoles are identified as potential candidate for the treatment of MDR and XDR tuberculosis \[84,85\]. Nicolas Willand reported thiophen-2-yl-1,2,4-oxadiazoles 10d, 10e as EthR inhibitors that boost antibacterial activity of ethionamide with nanomolar potency \[86\]. The anti-TB activity of isoxazoline linked nitrofurans compounds 10f-10j was reported \[87\]. Very good \textit{in vivo} efficacy in analogue of phenylisoxazoline 10k with MIC as low as 0.5 μg/mL \[88\].

**Triazoles**

Several triazoles were evaluated for their anti-TB activity against \textit{Mtb} H37Rv (MIC 3.12-12.5 μg/mL) \[89,90\]. N-substituted-phenyl-1,2,3-triazole-4-carbaldehydes 11a and 11b (Figure 11) showed inhibition at MIC 2.50 μg/mL \[91\]. The evaluated triazoles as inhibitors of \textit{InhA} as well as inhibitors of \textit{Mtb} H37Rv. Compound 11c and 11d (Figure 11), were good inhibitors against \textit{Mtb} with MIC 0.50 and 0.25 mg/mL, respectively \[92\]. Preliminary results of galactose-linked triazoles, exhibited MIC values in the range of 1.56-12.5 μg/mL against \textit{Mtb} H37Rv. Compound 11e inhibited bacterial growth at MIC.
A number of triazole and quinolone hybrids have been reported to possess anti-TB activity, compound 11f showed MIC 0.5 μg/mL against \textit{Mtb} [94]. Three new series of quinoline-4-yl-1,2,3-triazoles carrying amides 11g, sulphonamides 11h and amidopiperazines 11i possess MIC 1 μg/mL against \textit{Mtb} H37Rv [95]. 2-substituted-5-[(isopropylthiazole) clubbed 1,2,4-triazole 11j, exhibited promising activities against \textit{Mtb} H37Rv strain [84]. 1,2,3-triazole based \textit{Mtb} inhibitors and tricyclic (carbazole, dibenzo[b,d]furan, and dibenzo[b,d]thiophene) were integrated in one molecular platform to prepare various novel clubbed 1,2,3-triazole hybrids as potential inhibitors of \textit{Mtb} H37Rv. Two of them 11k and 11l inhibit the \textit{Mtb} at MIC 0.78 μg/mL [96]. α-ketotriazole and α,β-diketotriazole derivatives were evaluated for anti-TB and cytotoxic activities. Among them, two α,β-diketotriazole compounds, 11m and 11n, exhibited good activities (MIC=2.5 μg/mL) against \textit{Mtb} and MDR-TB strains and presented no cytotoxicity (IC50>50 mM) on colorectal cancer HCT116 and normal fibroblast GM637H cell lines [97].

**Dihydroimidazo-oxazines analogues**

Biphenyl analogues of PA-824 were evaluated for their efficacy in a mouse model of acute \textit{Mtb} infection. Three compounds 13a, 13b, 13c (Figure 13) bearing combinations of lipophilic, electron-withdrawing groups achieved >200-fold higher efficacies than the parent drug [108]. Heterocyclic analogues of PA-824 compounds 13d, 13e, 13f, 13g, 13h (MIC 0.31, 0.065, 0.06, 0.05, 0.017 μg/mL respectively) were >100-fold better than PA-824 in a mouse model of acute \textit{Mtb} infection, and two orally bioavailable were superior to anti-TB drug OPC-67683 in a chronic infection model [109]. Different analogues of PA-824 were prepared by replacing OCH$_2$ with amine, [110] amide, carbamates and urea functionality and investigated their improved efficacy against \textit{Mtb} [111]. Extension of OCH$_2$ linkers (propenyloxy, propynyloxy, and pentylnloxy) provided greater potencies against replicating \textit{Mtb}. One propynyloxy-linked compound 13i displayed 89-fold higher efficacy than PA-824 in the acute model [112]. 1-Methylpyrazole, 1,3-linked-pyrazole, 2,4-linked-triazole, and tetrazole bearing compound 13j, analogues of PA-824 had 3- to 7-fold higher MIC potencies than parent molecule against replicating \textit{Mtb} [113].

**Phenyl butenyl and phenyl cyclopropyl methyl azoles**

A series of 1-[(4-benzyloxyphenyl)-but-3-enyl]-1H-azoles has been identified as potent antitubercular agents against \textit{Mtb}. Compounds
14a, 14b, and 14c (Figure 14) exhibited significant antitubercular activities with MIC value as low as 1.56, 1.56, and 0.61 μg/mL, respectively. Cyclopropyl methyl azoles, 14d-14f inhibited the bacterial growth at MIC 2.41, 3.12 and 3.12 μg/mL [114].

### Quinolines

Several quinoline derivatives were reported with significant anti-TB activity [115-121]. 4-Quinolylhydrazone 15a the structural hybrids of isoniazid and quinolones (Figure 15) showed anti-TB activity with MIC 0.78 μg/mL but poor selectivity for mycobacteria. Several quinolinequinone, 6-amino-7-chloro-5,8-quinolinequinone 15b and 6-amino-7-methane sulfinyl-5,8-quinolinequinone 15c (Figure 15): Structure of quinoline derivatives exhibited MICs (1.56 and 3.13 μg/mL) for the 100% growth inhibition of *M. bovis* BCG [122]. The efficacies of indeno [2,1-c] quinolines were evaluated in vitro using the BACTEC radiometric assay and compounds shows 85-99% growth inhibition of *Mtb*. Compounds 15d and 15e (Figure 15) showed MIC, 0.39 and 0.78 μg/mL respectively [123]. Fused oxazoloquinoline 15f exhibited 99% bacterial growth inhibition and MIC, 1 μg/mL against *Mtb* H37Rv [124]. Another hybrid of isooxazole and quinoline 15 g is reported to have excellent anti-TB activity against both replicating and non-replicating *Mtb*, with MIC 0.9 μM [125]. A series of quinoline derivatives viz. hydrazones, ureas, thioureas and pyrazoles were evaluated for their *Mtb H37Rv* and MDR-TB [126,127]. The lead compound 2,9-diaryl-2,3-dihydrothieno[3,2-b]quinolines (15h and 15i) displayed MIC 0.90 and 0.95 μM against *Mtb* and MDR-TB [128].

A series of 11-alkoxylated and 11-aminated benzofuro[2,3-b]quinoline derivatives 15j, 15k and 15l (Figure 15) exhibited significant activities against the growth of *Mtb* (MIC values of <0.20 μg/mL) and low cytotoxicities against VERO cell with IC<sub>50</sub> values of 11.77, 5.55, and >30.00 μg/mL respectively [129]. Compounds 15m, 15n and 15o have MIC 0.65 μg/mL against *M. tuberculosis* H37Rv strain [130,131]. Phenoxy linked bisquinoline derivatives 15p and 15q have MIC 1.1 and 2.2 μM respectively against *Mtb* and no in vivo cytotoxic effects against mouse fibroblasts (NIH 3T3) [132].

### Tetrahydroindazole, Indolecarboxamide and indenone derivatives

A class of tetrahydroindazole (Figure 16) based compounds are reported as potent and unique inhibitors of *Mtb*. Compounds 16a, 16b and 16c exhibited MICs of 1.7, 1.9, and 1.9 μM respectively against *Mtb* [133]. Indole-2-carboxamide analogue, 16d showed potent antitubercular activities against actively replicating *Mtb*, with MIC values 0.013 μM. Compound 16e was found to be active against the tested XDR-TB strains and orally active in the serum inhibition titration assay [134]. A series of 2-(arylmethylene)-2,3-dihydro-1H-inden-1-ones were screened for their in vitro activity against *Mtb* H37Rv, Compound 16f displayed MIC at 2.8 μM against *Mtb* [135].

A library of trans 6-methoxy-1,1-dimethyl-2-phenyl-3-aryl-2,3-dihydro-1Hinden-4-yloxy alkyl amines exhibited MIC between 1.56 and 6.25 μg/mL against drug sensitive and multidrug resistant strains of *Mtb* [136].

### Benzimidazoles

Libraries of trisubstituted benzimidazoles were created through rational drug design. A number of benzimidazoles exhibited promising...
MIC values in the range of 0.5-6 μg/mL, against Mtb H37Rv strain (one of them compound 17a, has MIC 0.5 μM) (Figure 17) [137]. Compounds 17b and 17c bearing benzimidazole ring showed the potent tuberculostatic activity against Mtb with MIC of 1.56 and 3.1 μg/mL [138].

**Figure 17:** Structure of benzimidazole derivatives (17a-17c).

**Nitrofuran and benzofuran**

Several 4-(5-nitro furan-2-yl) prop-2-en-1-one derivatives, exhibited anti-TB activity against Mtb H37Rv with MIC<5 μg/mL and low toxicity. Compound 18a (Figure 18) was evaluated as potent anti-TB with MIC 0.19 μg/mL and selective index MIC99/CC55>1800 [139]. A class of benzofuro-oxazins, 1-(4-chlorophenyl)-1H-benzo[2,3]benzofuro[4,5-e][1,3] oxazin-3(2H)-one 18b and 1-(4-bromophenyl)-1H-benzo[2,3] benzofo [4,5-e][1,3] oxazin-3(2H)-one 18c (Figure 18) displayed same MIC 1.56 μg/mL against Mtb [140].

**Figure 18:** Structure of furan and benzofuran derivatives (18a-18c).

**Triazolophthalazine and 3-aracylphthalide derivatives**

Compound 19a, 4-isopentenyloxycinnamyl triazolophthalazine derivative, was found to be 100-1800 times more active than Isoniazid (INH) when tested for its ability to inhibit the growth of INH-resistant Mtb strains. It does not interfere with mycolic acid biosynthesis, thereby pointing to a different mode of action and representing an attractive lead compound for the development of new anti-TB agents [141]. 3-Araclyphthalides (Figure 19) were synthesized and were subjected to in vitro anti-TB screening against Mtb H37Ra. Among the phthalides 19b, 19c, 19d and 19e exhibited IC50 in the range of 0.97, 0.93, 0.81 and 1.24 μg/mL respectively [142].

**Figure 19:** Structure of triazolophthalazine and 3-aracylphthalide derivatives (19a-19e).

**Tryptanthrin**

Tryptanthrin is indolo-quinazolinone alkaloid (Figure 20) and active against MDR-TB with MIC 0.5-1.0 μg/mL. In vitro toxicity and in vivo studies are needed before this structural prototype is applied as anti-TB [143].

**Figure 20:** Structure of tryptanthrin (20).

**13-n-Octylberberine derivatives**

A series of 13-n-octylberberine derivatives were evaluated for their anti-TB activity. Among these, compound 21 (Figure 21) was the most effective anti-TB with a MIC value of 0.125 μg/mL, and also exhibited more potent effect against rifampicin (RIF)- and isoniazid (INH)-resistant Mtb strains than both RIF and INH, suggesting a new mechanism of action [144].

**Figure 21:** Structure of 13-n-octylberberine (21).

In our group a series of 9-substituted tetrahydroacridines were synthesized and evaluated against Mtb H37Rv and H37Ra strains, which exhibited potent activities with MIC 6.25-0.78 μg/mL. Comp 22 (Figure 22) was found to be most active (MIC 0.78 μg/mL against Mtb H37 Rv) [145].

**Figure 22:** Structure of antitubercular agent (22-26).

**Glycosyl β-amino esters** [146] and glysylated amino-alcohols [147] were evaluated for their anti-TB activity against Mtb H37Ra and H37Rv. Compound 23 showed MIC 3.12 μg/mL against both Mtb H37 Rv and H37Ra strains. Benzyl- and pyridylmethyl amines, compound 24, 25 and 26 exhibited MIC 1.56 μg/mL against Mtb. Some of them were also evaluated against clinical isolates of MDR-TB and found to be active with MIC 3.12 μg/mL [148]. α,α’-(EE)-bis(benzylidene)-cycloalkanones displayed moderate anti-TB activity with MIC 12.5-1.56 μg/mL [149]. The potent in vitro and moderate in vivo anti-TB activities thiadiazine thiones have been reported against M.
tuberculosis H37Rv even in resistant strains and also protected mice marginally in experimental TB [150]. 6-Oxo and 6-thio analogue of purin [151] and carboxylic uracil derivatives [152] showed good inhibitory activity against Mtb. 4-Oxo-4-chlorophenyl-butenoyl methyl ester has MIC of 0.6 and 1.5 μg/mL against replicating and non-replicating M. tuberculosis, respectively, it penetrates the cell where it is hydrolyzed and reacts with CoA to generate the active antibacterial [153].

Isoxyl and urea derivatives

Isoxyl (ISO), thiourea (thiocarlide, 4,4'-diamoxythiocarbanilide), exhibited potent activity against Mtb H37Rv (MIC, 2.5 mg/mL), M. bovis BCG (MIC, 0.5 mg/mL), M. avium (MIC, 2.0 mg/mL), and M.aurum A+ (MIC, 2.0 mg/mL), by inhibiting the mycolic acid synthesis. A comparison with isoniazid (INH) and ethionamide (ETH) demonstrated marked similarity in action. Isoxyl derivatives (27a-27g) also exhibited MIC value in the range of 0.1-0.5 μg/mL [154]. The Fas II synthesis is involved in ISO resistance [155]. A series of 1-adamantyl-3-phenyl urea 28a-28f that had potent anti-tuberculosis activity with MIC values 0.01, 0.4, 0.02, 0.4, 0.1, and 0.4 μg/mL. But they had undesirable properties, particularly high lipophilicity and poor solubility [156]. A new series of 1-adamantyl-3-heteroaryl ureas 28g-28f by replacing the phenyl substituent of the original series with pyridines, pyrimidines, triazines, oxazoles, isoxazoles, oxadiazoles and pyrazoles (Figure 23). The lead isoxazole (28g, MIC 0.10 μg/mL), thiazole (28h, MIC 1.56 μg/mL), oxadiazole (28i and 28j, MIC 1.56 μg/mL) and pyrazole (28k, MIC 1.56 μg/mL) substituted adamantyl ureas with improved in vitro PK profiles, increased selectivity and good anti-TB potencies (Figure 24) [157].

Hydrazines, hydrazones, thiosemicarbazone and thiocyanate derivatives

Hydrazine carbothioamides 29a, 29b and 29c were reported to have MIC 0.4 μg/mL against Mtb [158]. Fluorinecontaining hydrazones 29d and 29e (Figure 25) have shown a remarkable activity against MDRTB strain with MIC 0.5 mg/mL and high value of selectivity index [159]. 2-Bromophenyl substituted thiocyanate 29f showed MIC (0.25 μM against replicating Mtb and 8.0 μM against non-replicating Mtb) and IC<sub>50</sub> 32 μM in the VERO cellular toxicity assay [160]. Several other hydrazones possessed anti-TB activity [161-163]. 5-nitro-thiazolylthiosemicarbazone, N-(5-nitro-1,3-thiazol-2-yl)-2-((Z)-4-[(phenylmethyl)oxy] phenyl-methylidene) hydrazine-1-carbothioamide was found to be active with a MIC of 0. 23 μM against Mtb H37 Rv, and was three times more potent than isoniazid and equally active as rifampicin [164].

Alkyl-sulfinyl amides, fatty acid amides and nitro propionamides

Alkyl sulfinyl amides inhibit β-ketoacyl synthase (KAS), one of the accessory fatty acid synthases peculiar to mycobacteria. The compound 30a showed good MIC at 0.75 μg/mL [165]. The fatty acid amide derived from ricinoleic acid 30b (Figure 26) is the potent one among a series of tested compounds, with MIC 6.25 μg/mL for resistance strains of Mtb [166]. 1-cyclopropyl-7-(3,5-dimethyl-4-(3-nitropropanoyl)piperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 30c was found to inhibit the Mtb
isocitrate lyase (ICL) enzyme with \textit{in vitro} MICs 0.16 and 0.04 μM against log- and starved-phase culture of \textit{Mtb} and also showed good enzyme inhibition of \textit{Mtb} ICL with IC\textsubscript{50} of 0.10 ± 0.01 μM [167].

\textbf{Cyclopropylphenyl derivatives}

A series of cyclopropylphenylmethanone and cyclopropylphenylmethanol (31a-31j) (Figure 27), most of them possessed very good \textit{in vitro} activity against both drug sensitive and drug resistant \textit{Mtb} [168]. Compounds 31c, 31e, 31f, 31h and 31i have shown MIC 3.12 μg/mL, while compounds 31a, 31d and 34b exhibited MIC of 1.56, 1.56 and 0.78 μg/mL respectively. Compound 31g showed 98% killing of intracellular bacilli in mouse bone marrow derived macrophages and were active against MDR, XDR and rifampicin clinical isolates resistant strains with MIC 12.5 μg/mL. Compound 31g was orally made to enhance the anti-TB activity of new drugs particularly against MDRTB/XDR-TB, and be easily administered in phase and prevent the occurrence of resistance in bacterial cells.

\textbf{Conclusion}

In recent years, the programs to control TB, extensive studies are made to enhance the anti-TB activity of new drugs particularly against resistant \textit{Mycobacterium} strains. These advances in TB drug research and development are encouraging, but new drugs are needed that have strong, synergistic and complementary activities against various \textit{M. tuberculosis} subpopulations in order to shorten TB treatment, be effective against MDR-TB/XDR-TB, and be easily administered in conjunction with HIV. However, new targets should be further identified and discovered that can kill the viable \textit{Mtb} in the latent phase and prevent the occurrence of resistance in bacterial cells.

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