Some recent approaches in the design of synthetic anti-tubercular agents containing five membered heterocycles rings

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ABSTRACT

The valuable treatment of tuberculosis is difficult, due to the complicated or unusual structure and chemical composition of the mycobacterial cell wall. These complex properties of cell wall make many antibiotics and currently used drugs ineffective and hinder the entry of drugs into the mycobacterium cells. Tuberculosis is still one of the most crucial infectious disease worldwide. The most important complication in the treatment of tuberculosis is drug resistant multidrug (MDR-TB) and extensive drug resistant tuberculosis (XDR-TB), persistent infection or latent-TB and synergism of TB with Human Immuno deficiency Virus (HIV). New chemical entities are required for the MDR-TB and XDR-TB. Furthermore not any new chemical entity has come in last 40 years for potent and effective antitubercular drug against resistant strain. Currently available data from the recently developed antitubercular drugs which containing five membered heterocyclic ring system. The modern drug design promises to bring significant development for effectiveness against tuberculosis. In present review we discussed brief introdution of recently developed antitubercular agents containing five membered heterocyclic rings in their structures.

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease caused by mycobacterium species, including primarily M. tuberculosis, that divides every 16 to 20 hours, an extremely slow rate compared with other bacteria, which usually divide in less than an hour, but also M. bovis and M. africanum, M. canetti, and M. microti can also cause TB, but these species do not usually infect healthy adults. Tuberculosis, an airborne communicable disease caused by transmission of aerosolized droplets of M. tuberculosis. The primary source of infection is viable tubercular bacilli, expelled in the environment by a patient with active TB. Mycobacterium grows slowly under aerobic conditions and is distinguished by acid-fast staining. They are Gram positive, non-motile, rod-shaped, obligate aerobic bacteria that belong to the order actinomycetales, family Mycobacteriaceae. Several species, including M. tuberculosis, M. bovis, M. africanum, M. microti, M. canetti, M. kansasii, M. avium, and M. leprae, are intracellular pathogens of higher vertebrates. On the other hand although M. microti is not usually pathogenic, it is possible that the prevalence of M. microti infections has been under estimated. Other Known pathogenic mycobacteria include M. leprae, M. avium and M.
kansasii. The last two are part of the non tuberculous mycobacterium (NTM) group. Non tuberculous mycobacteria cause neither TB nor leprosy, but they do cause pulmonary diseases resembling TB. TB requires much longer periods of treatment to entirely eliminate mycobacteria from the body\textsuperscript{[6-10]}.

Tuberculosis an overview

Tuberculosis (TB) is one of the oldest and most pervasive, respiratory transmitted or contagious disease infecting one-third of the world’s population and killing between 2 and 3 million people each year. According World Health Organization (WHO) report, TB has spread to every corner of the globe. The increase in TB incidence during recent years is largely due to the prevalence of TB is synergy with Human Immunodeficiency Virus (HIV/AIDS) epidemic, which augments the risk of developing the disease 100-fold\textsuperscript{[11-14]} where 31\% of new TB cases were attributable to HIV co-infection and emergence of MDR-TB and extensively drug resistance (XDR-TB) strains. The treatment of MDR-TB and XDR-TB has become a major concern worldwide. However, the total number of new TB cases is still rising slowly. The occurrence of this disease is linked to dense population, poor nutrition, and poor sanitation\textsuperscript{[15-17]}. Observed Treatment, short-course (DOTS) strategy, constitutes the cornerstone of the current protocol for control of TB. Despite the success of DOTS strategy, the emergence of MDR-TB strains, recurrently isolated from patient’s sputum, darken the future. In addition to this, the increase in M. tuberculosis strains resistant to front line anti-TB drugs such as rifampin and INH has further complicated the problem, which clearly indicates the need for more effective drugs for the efficient management of TB. As per WHO reports, approximately 90\% of the patients having both TB and HIV died within a few months after clinical symptoms. Therefore, WHO warned the world for “even greater TB-HIV crisis” and called for wide availability of free anti-TB drugs to those living with HIV. As per WHO, HIV is spreading rapidly in India with the largest number of TB cases in the world\textsuperscript{[18,19]}, due to XDR-TB and MDR-TB which prompt us for the development of new anti-TB drugs. Even though the fact that it is treatable and avoidable, the TB has been spreading at a secure rate\textsuperscript{[20]}.

Tuberculosis-HIV combination

The current estimations reveal that one-third of the 42 million people living with HIV/AIDS worldwide are co-infected with tuberculosis (TB). As per WHO reports, approximately 90\% of the patients having both TB and HIV died within a few months after clinical symptoms. Therefore, WHO warned the world for “even greater TB-HIV crisis” and called for wide availability of free anti-TB drugs to those living with HIV. As per WHO, HIV is spreading rapidly in India with the...
largest number of TB cases in the World\textsuperscript{[28-30]}. 

Drug-resistant tuberculosis

Drug resistance displayed by \textit{M. tuberculosis} is an important obstacle for the treatment and control of TB. This resistance has traditionally been attributed to the unusual multi-layer cell envelope and active multidrug efflux pumps. Recent insights into mechanisms that neutralize the toxicity of antibiotics in the cytoplasm have revealed other systems that function in synergy with the permeability barrier and efflux systems to provide natural resistance. Drugs inhibiting these intrinsic systems would enable many antibiotics, which are already available but have not been used for TB, to gain new activities against \textit{M. tuberculosis}\textsuperscript{[31,32]}. 

Multi drugs resistant-tuberculosis

Multi-drug-resistance (MDR) TB refers to simultaneous resistance to at least two or more of the five first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin). Multi-drug-resistance arises from sharing of genes between different species or genera, generally mediated by small pieces of extra-chromosomal DNA, known as transposons or plasmids. Treatment for multi-drug-resistance tuberculosis is long lasting, less effective, costly, and poorly tolerated\textsuperscript{[33-35]}. 

Extensively-drug-resistance tuberculosis

Extensively-drug-resistant (XDR) tuberculosis, by definition, is the resistance to at least isoniazid and rifampicin, in addition to any quinolone and at least one injectable second-line agent (any fluoroquinolone, capreomycin, amikacin, kanamycin). The principles of treatment for MDR-TB and XDR-TB are the same. The main difference is that XDR-TB is associated with a much higher mortality rate than MDR-TB, because of the reduced number of effective treatment options. Hence, there is an urgent need for novel drugs that are active against \textit{M. tuberculosis} in order to shorten the duration of tuberculosis therapy\textsuperscript{[33-35]}. 

Currently clinically used 5-membered Heterocyclic antitubercular drugs

(a) Cycloserine and terizidone

Cycloserine and Terizidone is the main synthetic anti-TB drugs that contained 5-membered heterocyclic ring for treatment of TB. D-Cycloserine or D-4-Amino-3-isoxazolidone (1) is a structural analog of the amino acid D-serine. It is active at a concentration of 5-20\,\mu\text{g}/mL and is destroyed by acidic and neutral pH. It blocks the synthesis of peptidoglycan that is an important component of the cell wall, by inhibiting the enzymes D-alanine racemase and D-alanyl alanine synthetase. Whereas a bicyclosperine derivative terizidone, (2) is least tolerable second-line anti-TB drugs\textsuperscript{[5,8]}. 

(b) Currently synthesized potential anti-tubercular agents

The newly potential anti-TB agents with 5-membered heterocyclic compounds are classified on the basis of their chemical entities.

Hetero atoms containing antitubercular agents

(a) \textit{N}-heteroatom containing pyrrole and pyrrolidine derivatives

The LBK-611 (3a) is an antiTB agent. A series of LBK-611 (3a) derivatives were introducing benzimidazoles and benzoxazoles moiety at 2-position and peptides at N-1 position. The Compounds (3b) and (3c) have shown potent IC\textsubscript{50} of 0.010, 0.013\,\mu\text{M} respectively against TB strain. The MIC values of 0.1\,\mu\text{g}/mL and 0.15\,\mu\text{g}/mL against TB-H37Rv in comparison to LBK-611. These compounds also showed promising MIC value 0.03 and 0.06\,\mu\text{g}/mL, respectively against MDR-TB strains\textsuperscript{[36]}. Compound (4) with semi-rigid ethambutol framework being the part of pyrrolidine with \textit{cis} configuration has shown modest growth inhibition at concentrations of over 60\,\mu\text{g}/mL, 30 times less potent than EMB, while by pyrrolidine with \textit{trans}-semi-rigidified EMB framework was found to be inactive against \textit{Mtb}\textsuperscript{[37]}. 

Two different series of spiro-compounds, first series, 1-methyl-4-(2,4-dichlorophenyl) pyrrolo (spiro[2.3”]oxindole)spiro[3.3’]-1’-methylpiperidin-4’-one (5) has shown activity with a MIC of 1.76 and 0.88\,\mu\text{M} against MTB and MDR-TB respectively\textsuperscript{[38]}. While another series, compound (6) showed increased
potency with MIC value of 0.40 µg/mL against TB and was 4 and 15.6 times more potent than EMB and pyrazinamide, respectively.\(^{39}\) The pyrrolidine containing bis-heterocyclic libraries, bis-cyclic guanidine derivative (7) showed most excellent potency with a MIC of 3.9 µg/mL against TB and found to be less toxic with an IC50 of 39.48 µg/mL.\(^{40}\)

A series of N-substituted-2-pyrrolidine-3-carboxamides as are potent InhA inhibitors. Among all, the racemic compound (8) has shown inhibition of IC50 140 nM, while one of its enantiomeric molecule showed inhibition of IC50 62 nM against InhA of \(Mtb\) H37Rv.\(^{41}\) The tetramic acid (N-substituted-2,4-pyrrolidone) molecules with structural similarity to the antibiotic reutericyclin (9) were exhibited antibacterial activity. Many of them have shown promising activity against Gram-positive bacteria and two compounds (9a) and (9b) showed moderate activity of MIC 12.5 µg/mL against \(Mtb\) H37Rv.\(^{42}\)

A pyrrole derivative BM 212 (10), showed very good \textit{in vitro} activity of MIC 0.7 µg/mL against \(M.\) \textit{tuberculosis}. A series was developed by the variation of N-1, C-3 and C-5 positions. Among these, compound (11) showed potent inhibition of MIC 0.4 µg/mL against \(Mtb\).\(^{43}\) While compounds (12)\(^{44}\) and (13)\(^{45}\) showed comparable MIC of 1 µg/mL. Surprisingly, substitution of 4-isopropylbenzene at C-5 position (14) has increased the potency with a MIC of 0.25 µg/mL, which is equal to that of INH.\(^{46}\) While by replacing 4-isopropylbenzene with 4-methylbenzene (15)\(^{47}\) at C-5 position of compound (14) showed decreased potency of MIC 0.4 µg/mL but lowered the toxicity. On the basis of above activity, introducing an ethyl group at position-2 of the pyrrole nucleus by keeping both N-1 and C-5 phenyl rings, the same substituents that gave the best results in
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terms of activity in previous 2-methyl derivatives. Among them, 1-(4-fluorophenyl)-2-ethyl-3-(thiomorpholin-4-yl) methyl-5-(4-methylphenyl)-1H-pyrrole (16) proved to be particularly active, with a MIC 0.25μg/mL, which is better than or comparable to the reference drugs[48]. Compounds (11-16) were also active against resistant \( Mtb \) strains. A similar series of pyrrole derivatives obtained by the variation of N-1, C-2, C-3 and C-4 positions, compound (17) was found to be most potent with a MIC of 0.5μg/mL[49]. By variation of simple pyrrole at N-1 position, a series of N-(4-substituted) benzoic acid hydrazide analogs and some derived oxadiazole, triazole and pyrrole have been synthesized. Oxadiazole-2-thiol derivative (18) has shown moderate activity with a MIC 16μg/mL[50].

(b) O and S-containing furan and thiophene derivatives

The nitrofuranylamide (19) with an IC50 12μg/mL and also showed good anti-TB activity with a MIC of 1.6μg/mL. With this interest, a series of 5-nitrofuranylamides (NFAs), 5-sulfinylfuranylamides and 5-sulfonylfuranylamides, among all, compound (20) has shown great potency against \( Mtb \) with MIC of 0.1 μg/mL and IC50 115μM/mL. This may be due to the influence of 4-methoxybenzylamide at 2-position of furan ring. While by replacing 2-position with 3,4-methoxybenzylamide (21), led to drop off in the anti-TB activity of MIC 0.2μg/mL and IC50 23μM/mL[51].

The efficacy of anti-TB activity of NFAs (22-26) against TB complex[52] and the NFAs were significantly active against \( Mtb \) complex[52,53]. Compound (22) showed preeminent inhibition of MIC 0.006mg/L against \( Mtb \) UT30 (streptomycin resistant at 4mg/L). Whereas compound (23) showed same potency against \( Mtb \) UT18 and \( M. bovis \) BCG. Compound (24) showed the best potency of all, against \( M. bovis \) BCG with a MIC of 0.0008 mg/L and also showed the same potency against both the \( Mtb \) UT15 and UT18. Similarly, Compound (25) showed the same potency against \( Mtb \) UT18 but shown increased potency of MIC of 0.0004 mg/L against \( Mtb \) UT15. Compound (26) showed the best potency against \( M. bovis \) BCG with a MIC of 0.0015 mg/L. These NFAs have shown MIC in the range of 0.012-0.006mg/L in broth assay, 0.012-0.0015 mg/L in agar assay and 0.85- 0.17 in low-oxygen recovery assay (LORA) against \( Mtb \) H37Rv.

A series of di-cationic 2,5-bis (4-guanidinophenyl) furans, 2,5-bis[4-(alkyl/arylimino) amino phenyl]furans were showed activity against \( Mtb \). The the DNA binding affinities are highly dependent on structure and are significantly affected by substituents both on the phenyl rings of the 2,5 diphenyl furan nucleus and on the cationic centers. Three dicationic compounds (27), (28), and (29) were exhibited MIC = 1μg/mL[54].

A series of 2,3,4-pentanetrione, 3-[4-{[(5 nitro-2 furyl/pyridyl substituted phenyl) methylene] hydrazino carbonyl} phenyl] hydrazones. In these compounds (30) was the most promising compound showed MIC and ED value of 3.13μg/mL and 0.32μg/mL, respectively. Other compound with minor modifications showed less activity. The best activity was shown by (31) having MIC...
of 6.25μg/mL[55]. A number of 5-nitrofuran-2-yl derivatives, pyridyl derivative (32) has shown best potency with a MIC 0.22μM and was 3 times more active than INH and equally active as RIF in log-phase culture of Mtb H37Rv. In starved Mtb H37Rv, it also inhibited with a MIC of 13.9μM and was found to be 50 times more active than INH and slightly more active than RIF[56].

A series of substituted benzoic acid-[(5-nitrothiophen-2-yl)-methylene]-hydrazides were tested against Mtb. The compound (33) of the series was found most active, having a MIC of 2μg/mL[57]. While in the series of N-(aryl)-2-thiophen-2-ylacetamides, compound (34) showed MIC of 25μg/mL and also non-toxic against murine macrophage cells even at the concentration of 100μg/mL[58].

Synthesized Thiolactomycin (TLM) analogues with biphenyl-based 5-substituents, was found to have excellent in-vitro inhibitory activity against Mtb. In particular, 5-(4’-benzylxy-biphen-4-ylmethyl)-4-hydroxy-3,5- dimethyl-5H-thiophen-2-one (35) exhibited approximately a 4-fold (IC50=17μM) increased potency compared to TLM[59]. Whereas in TLM series with
acetylene based side chains, 5-[3-(4-acetyl-phenyl)-prop-2-ynyl]-4-hydroxy-3,5-dimethyl-5H-thiophen-2-one (36) showed more than an 18-fold (IC50=4 μM) increased potency, compared to TLM\(^{[60]}\). Another series, 5-(4-methoxycarbonyl-biphenyl-4-ylmethyl)-4-hydroxy-3,5-dimethyl-5H-thiophen-2-one (37) gave an IC50 value of 3 μM compared to the TLM (75 μM)\(^{[61]}\). The new TLM series was identifying most potent TLM derivative (38) with a MIC of 1 μg/mL against \(Mtb\) H37Rv. This derivative also exhibited activity against resistant strains of \(Mtb\)\(^{[62]}\). In a different advance, a series of 2-amino-5-arylthiophene[2,3-b]thiophenes exhibited \textit{in-vitro} activity against \(Mtb\) H37Rv and MDR-TB strains. Among all, ethyl 2-amino-5-(1-naphthyl) thieno[2,3-b] thiophene-3-carboxylate (39) was found to be the most active compound with MIC of 1.1 μM against \(Mtb\) and MDR-TB strain\(^{[63]}\).

(c) Two nitrogen hetero compounds-pyrazole and pyrazoline derivatives

A series of both pyrazoles and pyrazolones with the basis obtained from the 5-hydroxy-pyrazole, as an inhibitor of \(Mtb\). Out of both the series, 5-hydroxy-pyrazole derivatives (40a) and (40b) have shown MIC of 6.25 μg/mL\(^{[64]}\) and (40c) exhibited most improved potency of MIC 4 μg/mL against \(Mtb\)\(^{[65]}\). In continuation, novel rigid pyrazolone derivatives, two compounds (40d) and (40e) have shown potency similar to that of (40c)\(^{[66]}\).

A series of 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1\(H\)-pyrazole derivatives evaluated for their anti-TB activity toward \(Mtb\) H37Rv and \(Mtb\) H4 strains. In this series, compounds (41a-e) has shown equal potency against the above strains with a MIC of 8 μg/mL. The presence of the 2-pyridinyl residue at 3-position on the pyrazoline cycle exerted an important role on the activity of these molecules\(^{[67]}\) and substituent variation at pyrazole ring, a series of 4-[2-(substitutedphenyl)-3-phenyl-2,3-dihydro-1\(H\)-5-pyrazolyl]-2-methylphenol and 2-[5-(3-Phenoxyphenyl)-4,5-dihydro1(benzoyl)-pyrazol-3-yl] pyridine (42) derivatives\(^{[68]}\), compound bearing a 4-fluorophenyl radical at 5-position of the pyrazoline nucleus (43), was found to be the most active with a...
MIC of 0.62µg/mL against INH resistant *Mtb* H37Rv\(^{[69]}\), while compound (42) exhibited 100% inhibition at 1 µg/mL against *Mtb* H37Rv.

A series of 3-substituted-5-hydroxy-5-trifluoro [chloro] methyl-1H-1- isonicotinoyl-4,5-dihydro pyrazoles were exhibited *in-vitro* antimicrobial activity as well as ant-TB activity against INH-susceptible *Mtb* H37Rv. Of these derivatives, compound (44a) exhibited best potency against INH-susceptible *Mtb* H37Rv and INH-resistance strain RGH102 with a MIC of 0.77 µM, 24.13 µM, respectively. In addition, compound (44a) also exhibited potency against non-tubercular mycobacterial, whereas compound (44b) exhibited good inhibition against INH-resistance strains RGH101 & RGH104 with a MIC of 8.94µM and 4.47µM, respectively. Compound (44c) showed best potency against INH-resistance strain RGH103 with a MIC of 19.23µM. The trifluoromethyl-substituted pyrazoles were more active than the respective trichloromethyl-substituted pyrazoles\(^{[70]}\).

The effort to increase the activity, a series of 3-phenoxy acetic acid pyrazoline derivatives, compound (45) with a MIC of 0.10µg/mL and 0.64µg/mL, respectively against INH-sensitive and *Mtb* resistant strains\(^{[71]}\). In continuation, a series of amino-5- [(substituted)phenyl]-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1H-1-pyrazolylmethanethiones, among them, compound (46) has shown equal potency of 0.43 µg/mL against both INH-sensitive and *Mtb* resistant strains\(^{[72]}\). Similarly, a series of 2-[4-[1-carboxamide/carbothioamide-5-(substituted phenyl)-4,5-dihydro-1H-3-pyrazolyl]-2-methoxy phenoxy] acetic acid derivatives, carbothioamide derivative (47a) and carboxamide derivative (47b) have exhibited improved activity of 0.06µg/mL and 0.13µg/mL, respectively, against the both INH-sensitive and *Mtb* resistant strains\(^{[73]}\).

A series of small molecules having similar structure of *Mtb* (MTB) siderophores (mycobactins, carboxymycobactins) have been targeted the inhibition of the iron scarcity-induction and siderophore-mediated iron-scavenging systems of *Mtb*. These compounds showed anti-TB against *Mtb* under iron-limiting conditions (GAST-D), which mimic the iron scarcity, these pathogens encounter and must adapt to in the host, and under standard iron-rich conditions (GAST-D-Fe) for comparison. New anti-TB agent (48) showed MIC of 12.5µM on average, whose ratio is equal to that of RIF\(^{[74]}\). In 4-arylhydrazono-2-pyrazoline-5-one derivatives\(^{[75]}\), the best activity was exhibited by compound (49) having >90% inhibition and a MIC >12.5µg/mL.

(d) Imidazole, oxazine, pyrimidine and piperazine derivatives

The search for new anti-TB drugs led to the identi-
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fication of nitroimidazopyran, PA-824 (49) and CGI-17341 (50) as promising anti-TB compounds, with novel mode of actions and showed efficacy against resistant *Mtb* strains. In this apprehension, 2-nitroimidazole, 4-nitroimidazole and 1,2-dimethyl-5-nitroimidazole were tested against replicating *M. bovis* BCG and *Mtb* H37Ra. Among these compounds, 2-nitroimidazole (51) showed greatest efficacy of 0.226\(\mu\)g/mL\[^{76}\]. The two diastereomers of 7-methyl-nitroimidazo-oxazine, 7-(S)-methyl derivative (52), (cis) and 7-(R)-methyl derivative (53), (trans) derivatives displayed similar activities against *Mtb* (MIC=0.2-0.4\(\mu\)M). Conformational analysis revealed that all three (49), (52) and (53) compounds have similar energetically accessible conformations in solution. The results suggest that the nitroreductase that initially recognizes PA-824 is somewhat insensitive to substitutions at the 7-position\[^{77}\].

The importance of SAR of PA-824 (49) along with Metronidazole (Mtz) (60a), all the molecules (54a-d) were exhibited activity against aerobic and anaerobic *Mtb* H37Rv. Among all, compound 54b showed promising aerobic inhibition of 99% at 4-8\(\mu\)M and anaerobic inhibition of 90% at 31.25\(\mu\)M, which are less than that of PA-824. The SAR of these molecules confirmed that, the structural requirements for aerobic and anaerobic activity for the 4- and 5-nitroimidazoles are fundamentally different\[^{78}\]. While the molecules which have shown more potency of aerobic & anaerobic inhibition in comparison to parent molecule PA-824, compound (54c) exhibited aerobic 99% inhibition at 0.039\(\mu\)M and compound (54d) showed 90% anaerobic inhibition at 1.56-3.13\(\mu\)M\[^{79}\].

Analogues of 2-nitroimidazo-oxazines, compound (55) has shown best activity with a MIC of 0.11 and 2.7\(\mu\)g/mL against *Mtb* in aerobic and anaerobic conditions respectively\[^{80}\]. In a different approach, imidazo[1,2-c] pyrimidine derivatives, one compound (56) has shown promising MIC of 2\(\mu\)g/mL against *Mtb* H37Rv on day 14 and 21, which is equal to that of amikacin\[^{81}\]. Hydrazide derivatives of imidazo [1,2-a] pyrazine, compound (57) showed moderate activity with 86% inhibition at 6.25\(\mu\)g/mL\[^{82}\].

A series of bis-imidazole derivatives have been screened for their anti-TB activity against *Mtb* H37Rv. In this series, three compounds (58a), (58b) and (58c) have exhibited moderate potency of MIC 8\(\mu\)g/mL\[^{83}\].
While in an imidazole & bis-imidazole series provided the molecules which were active against avirulent strain Mtb H37Ra and the virulent strain Mtb H37Rv. Compound (59a) showed highest potency with MIC of 12.5 μg/mL against Mtb H37Ra and compound (59b) exhibited MIC of 6.25 μg/mL against Mtb H37Rv\(^{[84]}\).

(e) Oxazole, isoxazole and thiazole derivatives

A series of 4-(5-cyclobutyloxazol-2-yl) thiosemicarbazones were exhibited preliminary in-vitro and in-vivo activity against Mtb H37Rv (MTB) and MDR-TB. Among them, (4-bromophenyl) (phenyl)methanone N-(5-cyclobutyl-1,3-oxazol-2-yl)-thiosemicarbazone (60a) was found to be the highly active compound in-vitro with MIC of 0.05 μg/mL against MTB and MDR-TB. In the in-vivo study, compound (60a) decreased the bacterial load in lung and spleen tissues with 2.1 and 3.72 log 10 protections, respectively at 50 mg/kg body weight dose, which is better than that of gatifloxacin and comparable to INH\(^{[85]}\). While, to optimize the series, a number of 1-(5-cyclobutyl-1,3-oxazol-2-yl)-3-(sub)-phenyl/pyridylthioureas were evaluated for their efficacy. Among these, compound (60b) showed highest in-vitro potency of MIC 0.14 μg/mL against MTB and MDR-TB strains. In the in-vivo activity, compound (66b) decreased the Mtb load in lung and spleen tissues with 2.8 and 3.94 log10 reductions respectively at 25 mg/kg, which is equal to that of INH\(^{[86]}\).

The oxazolidinones, linezolid (61) represent a new class of antibacterial agent. These compounds have been shown to inhibit translation at the initiation phase of protein synthesis in bacteria. The efforts to increase the...
potency led to the identification of PNU-100480, thiomorpholine analogue of linezolid (61) which showed an interesting anti-TB activity. For increase the anti-TB activity of oxazolidinones, 3-(1H-pyrrol-1-yl)-2-oxazolidinone analogues of PNU-100480 were evaluated as potent anti-TB agents. Among all, compound (62) showed 90% inhibition at 5.8μM concentration, which is comparable to PNU-100480 and INH\(^{[87]}\). While, oxazolidinone derivatives with benzotriazole as pendant and one compound showed greater potency in the range of 2-4 μg/mL against S. aureus, E. faecalis and E. faecium and moderate potency of >32 μg/mL against \(Mtb\)^{[88]}.

A series of nitrofuranyl isoxazolines with increased proteolytic stability over nitrofuranyl amides were screened for their anti-TB activity against \(Mtb\). Among all, compound (63a) showed great in vitro potency of 0.00005μg/mL. However, their in-vivo activity was restricted by high protein binding and poor distribution. Thus, a series of non-nitrofuran containing isoxazolines were determined if the core had residual anti-TB activity. This led to the discovery of isoxazoline compound (63b) as anti-TB molecule, which showed 90% inhibition at a concentration of 1.56μg/mL^{[89]}. In 3,5-disubstituted isoxazolines and their SAR studied, a most active molecule (63c) has shown a MIC of 0.4μg/mL against \(Mtb\) H37Rv^{[90]}. Similarly, isoxazole derivatives, compounds (64a), (64b) and (64c) have shown 100% inhibition at 1μg/mL^{[91]}.

In the same direction, the SAR of 5-[(E)-2-arylethenyl]-3-isoxazolecarboxylic acid alkyl ester derivatives and found them as a promising anti-TB agents. Among all, 5-[(E)-2-(3,5-Dichloro-4-pyridinyl)ethenyl]-3-isoxazolecarboxylic acid ethyl ester (65a) has shown most excellent activity with a MIC 0.59μM in MABA assay, whereas compound 5-[(E)-2-(6-methoxy-4-quinolinyl)ethenyl]-3-isoxazolecarboxylic acid butyl ester (65b) showed the best activity against \(Mtb\) H37Rv with a MIC1.8μM in LORA assay. Both these molecules showed almost equal potency with standard drugs (INH, RMP) in terms of activity and cytotoxicity^{[92]}. While in another series, (R)-methyl 2-(5-((2-methylbenzo...
[d]thiazol-5-yloxy)methyl)isoxazole-3-carboxamido)-2-phenylacetate (65) has shown less activity with a MIC 1.4\( \mu \)M in MABA assay in comparison to compound (64a).

A series of thiazolylhydrazone derivatives were evaluated for their anti-TB potency and cytotoxicity. Among all, compound (66) showed best inhibition of 89\% at a concentration of >6.25\( \mu \)g/mL and also found less toxic with an IC50 of 200\( \mu \)g/mL. Where as in a series of 4-isopropylthiazole hydrazide analogues, two compounds (67a) and (67b) have shown better activity with 99\% inhibition at a concentration of 8\( \mu \)g/mL against Mtb H37Rv. While with a motivation to generate the novel compounds that can mimic the mode of action, 2-Aminothiazole-4-carboxylate derivatives were evaluated as anti-TB agents. Particularly, methyl 2-amino-5-benzylthiazole-4-carboxylate (68) exhibited outstanding activity with MIC 0.06\( \mu \)g/ml against Mtb H37Rv in comparison to TLM. In the same direction, Nitazoxanide (NTZ), (69), anti-infectious agent used for the treatment of infections caused by the protozoans Giardia and Cryptosporidium as an novel lead compound that kills replicating and nonreplicating M. tuberculosis. It has shown MIC values 16 and 1\( \mu \)g/mL in the presence and absence of bovine serum albumin, respectively. It also showed the activity against Mtb under replicating and nonreplicating conditions by killing 2 log10 CFUs in 4 days at a concentration of 50\( \mu \)g/mL.

A series of alkyl 1-heteroaryl-1H-1,2,3-triazole-4-carboxylates were tested for their anti-TB activity against Mtb H37Rv. Among all, the best potency was shown by n-pentyl 1-(6-phenylpyridazin-3-yl)-1H-1,2,3-triazole-4-carboxylate (70) with a MIC of 3.13 \( \mu \)g/mL. While in search of novel compounds with anti-TB potency, a number of two bis-arylsulfonamides (71a) and (71b) with the interest gained from the anti-TB triazole-based sulfonamide (71). Compound (72a) and (72b) showed an inhibition of 92\% and 50\% respectively at a concentration of 100\( \mu \)g/mL. A series of clubbed [1,2,3] triazoles with fluoro-benzimidazole were exhibited anti-TB activity, based on the some key factors; such as, over 10\% of newly registered drugs and some 40\% of newly registered agrochemicals contain one or more fluorine atoms, reported promising biological activity of fluorine contain-
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ing benzimidazoles and also the azoles. The [1,2,3] triazole derivatives, two compounds (71a) and (72b) have shown almost equal MIC of 0.34 µM and 0.32 µM respectively, against \textit{Mtb} H37Rv\cite{100}.

Similarly, preliminary biological evaluation against \textit{Mtb} of novel polycyclic azole analogues which resemble the classical antifungal/antibacterial azole drugs, Clotrimazole (74a) and Econazole (74b). Compound (74c), which is enantiomerically pure (R configuration) and has better anti-TB profile in comparison to Clotrimazole. Compound (74c) exhibited a MIC of 16µg/mL against \textit{Mtb} H37Rv, while its enantiomer (S configuration) showed decreased potency, confirming the importance of enantiomerically pure compounds due to the different interactions of single enantiomers with chiral biological systems\cite{101}.

Keeping in view of biological importance of azoles, a series of \textit{N}-alkyl/aryl-\textit{N}'-[4-(4-alkyl/aryl-2,4-dihydro -3\textit{H}-1,2,4-triazole-3-thione-5-yl)phenyl]thioureas and three \textit{S}-alkylated, \textit{N}-alkyl/aryl-\textit{N}'-[4-(3-aralkylthio-4-alkyl/aryl-4\textit{H}-1,2,4-triazole-5-yl)phenyl] thioureas. Among all, \textit{S}-alkylated derivative (75) showed the best potency of MIC 6.25 µg/mL against \textit{Mtb} H37Rv\cite{102}. With the similar type of modifications, a series of 3-benzylsulfanyl derivatives of 1,2,4-triazole and \textit{S}-substituted-1,2,4-triazoles and evaluated for \textit{in-vitro} anti-TB activity against \textit{Mtb}, \textit{M. avium}, and two strains of \textit{M. kansasii}. Among all, two compounds (76a) and (76b) showed moderate potency of MIC 32µM/L and 62.5µM/L, respectively, against \textit{Mtb} H37Rv on day 14. Compound (76b) exhibited moderate potency against other strains\cite{103}. While, in a almost similar series 2-(4-substituted-5-(pyridin-4-yl)-4\textit{H}-1,2,4-triazol-3-ylthio)-1-phenylethanones, compounds (77) exhibited less than 90% inhibition at a concentration of 6.25µg/mL\cite{104}.

A number of 3,4,5-substituted-1,2,4-triazole de-
derivatives were evaluated for their anti-TB activity against *Mtb* H37Rv. Among all, two compounds (78a) and (78b) have shown the best potency of MIC 0.39 μM and 0.79 μM, respectively [105] and two more compounds (79a), (79b) having same activity profile of MIC 0.39 μM and 0.79 μM respectively against *Mtb* H37Rv [106].

A series of 2-[4-(1H-[1,2,4]-triazol-1-yl)phenyl]-1-substituted-4,6-difluoro-1H-benzo[d] imidazole derivatives were evaluated for their anti-TB efficacy against *Mtb* H37Rv. Amongst all, two derivatives (80a) and (80b) have shown paramount potency of MIC 0.36 μg/mL and 0.58 μg/mL, respectively [107]. While a number of three, 3,4-substituted-1H-1,2,4-triazole-5(4H)-thione compounds (81a), (81b) and (81c) were shown a surprising 100% inhibition at 1 μg/mL [68].

In the search for new compounds possessing anti-TB activity with a low toxicity report, a series of substituted 2-nitro-1-(4-tolylsulfonyl)-2-(3-methylphenyl-1,2,4-oxadiazol-5-yl)ethanes evaluated their anti-TB activity against to *M. lufu* and *Mtb* species. Amongst all, two compounds (82a) and (82b) exhibited the greater minimum bactericidal concentration (MBC), on average of 6.35 μg/mL and 8.5 μg/mL, respectively against *M. lufu* and *Mtb*, comparable to INH [108]. A series of 3H-1,3,4-Oxadiazole-2-thione and 3H-1,3,4-oxadiazol-2-ones were tested for their in-vitro anti-TB activity against *Mtb* H37Rv. Among both the series, oxadiazolone derivatives (83a) and (83b) showed an interesting anti-TB activity of MIC 1.25 μg/mL, despite the fact that the corresponding thione derivatives showed poor activity [109]. In an effort to increase the
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potency of oxadiazolones, 3-[(arylmethylamino)methyl]-5-(pyridin-4-yl)-1,3,4-oxadiazol-2(3H)-ones (84a) and 3-(2,3, and 4-methylpiperidin-1-ylmethyl and piperidin-1-ylmethyl)-5-aryl-1,3,4-oxadiazol-2(3H)-ones (84b) which showed poor activity in comparison to previous compounds[110]. Unexpectedly, the combination of dapsone and oxadiazole thione, exhibited the promising potency against both Mtb H37Rv (MTB) and INH resistant Mtb. Of these, one compound (85) showed best potency of MIC 0.10 μM and 1.10μM against Mtb and INH resistant Mtb strains[111]. Similarly, three compounds (86a), (86b) and (86c) also showed 100% inhibition at a concentration of 1μg/mL against Mtb H37Rv.

1,3,4-thiadiazoles are well known to exhibit anti-TB activity, so a variety of series were tested against Mtb. A series of 2-(5-nitro-2-furyl)-1,3,4-thiadiazole-2-sulphide, sulphoxide and sulphones[112] showed anti-TB activity. The most active compound of the series was (87), which showed a MIC of 0.78μg/mL and least toxic compound among the series. Whereas, other series, compound obtained by the replacement of thioalkyl group with thio-4-ethylaceto group (88) exhibited a MIC <6.25μg/mL[113], while propyl 2-(5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-ylthio)acetate (89) showed MIC of 0.39g/mL[114]. In another effort to increase the activity, the 5-nitrofuryl was replaced with 1-methyl-5-nitro imidazole[115]. Of this series, the ethyl sulfonyl analogue (90) was active with a MIC of 1.56μg/mL. In the same way, compound (91) showed the greatest potency of MIC 1.56μg/mL among two series of 2- and 3-[5-(nitroaryl)-1,3,4-thiadiazol-2-yl thio, sulfanyl and sulfonyl propionic acid alkyl esters[116].

A series of N-Phenyl-N-[4-(5-cyclohexylamino-1,3,4-thiazone-2-yl)phenyl]thiourea, the highest activity was exhibited by compound (92), which has shown MIC of 6.25μg/mL[117]. While other series, [5-(Pyridin-2-yl)-1,3,4 thiazol-2-yl thio] acetic acid arylidene hydrazides, compound (93) showed MIC in the range of 20-80 μg/mL against Mtb H37Rv[118]. In continuation, the same group series of [5-(Pyridin-2-yl)-1,3,4-thiadiazol-2-ylthio]acetic acid (3,4-diaryl-3H-thiazol-2-ylidene)-hydrazides (94) and found them less active than the former molecules[119]. In search of potent 1,3,4-
thiadiazoles, a series of 2,5-disubstituted-1,3,4-thiadiazoles were screened for the anti-TB activity against *Mtb* H37Rv using the BACTEC-460 radiometric system. Among the tested compounds, 2-phenylamino-5-(4-fluorophenyl)-1,3,4-thiadiazole (95) showed the MIC activity of 69% at a concentration of >6.25 Î¼g/mL.[120]

2,6-Disubstituted piperidin-4-ones are considered as an important structure. The biological activities of piperidones were found to be outstanding if 2- and/or 6-positions are engaged by aryl groups. In this concern, a series of 2,6-diarylpiperidin-4-ones and tetrahydropyridin-4-ol based benzimidazole and O-arylsulfonyl derivatives were screened for their anti-TB activity. Compounds (96) have shown equal potency of MIC 16Î¼g/mL against *Mtb* H37Rv, which are one-fold more potent than Rif.[121] In an effort to increase the potency of piperidones, a series of spiro-piperidin-4-ones were evaluated. Among all, compound (97) showed promising *in-vitro* potency of MIC 0.07Î¼g/mL and 0.16Î¼g/mL against *Mtb* s and MDR-TB respectively. Compound (97) also showed *in-vivo* effectiveness by reducing the bacterial load in lung and spleen tissues with 1.30 and 3.73-log 10 protections respectively, which is comparable to INH.[122] In this trend, a series of pyridines substituted with 1,2,4-oxadiazole-5-ones, 1,2,4-oxadiazole-5-thiones and 1,3,4-oxathiazoline-2-ones were tested against *Mtb* H37Rv. Among all, 1,3,4-oxathiazoline-2-one derivative (98) showed finest activity with MIC of 4.5 Î¼g/mL.[123] Other two series of 4-thiazolidinone and 2-azetidinone derivatives of INH, compound (99) having 4-hydroxy-3-methoxyphenyl substituent have shown greatest activity with a MIC 0.31Î¼g/mL against *Mtb* H37Rv.[124]

A series of dihydropyridine derivatives, compound (100a) was found to be most potent showing 87% and 85% inhibition respectively, at a concentration of 12.5Î¼g/mL.[125] While, presence of imidazole group at 4-position and amide group at 3,5-position (100b) increased the activity up to 1Î¼g/mL against *Mtb*. In the same trend, new derivatives of 1,4-dihydropyridines in which different alkyl and aryl esters and diethylcarbamoyl are substituted in C-3 and C-5 of the dihydropyridine ring. In addition nitroimidazole ring is substituted at C-4 position, compound (101) was showed best potency with a MIC 1Î¼M/mL against *Mtb* H37Rv, which is equal to INH.[126] Other 1,4-dihydropyridine3,5-dicarboxamide compounds, in this series, most active compound (102) showed equal potency similar to that of compound (101).[127] Several derivatives containing pyrazine nucleus have been tested for their anti-TB activity against *Mtb*. The pyrazine derivatives substituted with 1,2,4-oxadiazole-5-ones, 1,2,4-oxadiazole-5-thiones and 1,3,4-oxathiazoline-2-ones were showed anti-TB activity. The most active compound of the series (102) exhibited a MIC of 4.5Î¼g/mL in comparison to 49Î¼g/mL for pyrazine...
namide. With the same conception, a series of ring substituted (E)-3-Phenyl-1-(2 pyrazinyl)-2-propen-1-ones were screened for their efficacy against \textit{Mtb} H37Rv. In a different approach, a series of 1,4-substituted piperazine/homopiperazines, compound (103) showed MIC of 62.5\,\mu\text{M}\textsuperscript{118,119}. In a different approach, some pentacycloundecane (PCU) tetra-amine compounds were screened their \textit{in-vitro} anti-TB activity against H37Rv and XDR strains of \textit{Mtb} (194). The most active compound (104) of the series has shown MIC of 5.04\,\mu\text{M} against \textit{Mtb} H37Rv and 1.26\,\mu\text{M} against XDR (194)\textsuperscript{119,120}.

A series of \(\alpha\)-methylene-\(\gamma\)-butyrolactones supported on the natural compound protolichesterinic acid (105) were evaluated for their potency against \textit{M. bovis} BCG. Compounds (105a-d) bearing an allylamide group at the C-4 position showed enhanced activity with MICs in the series of 6.25-12.5\,\mu\text{g/mL}\textsuperscript{121}. In the same way, several structural analogues of the polyketide passifloricin lactone (152) were screened against \textit{Mtb} H37Rv\textsuperscript{112}. Of these, compound (152a) displayed an inhibition percentage higher than 97\% at 128\,\mu\text{g/mL}, while passifloricin A reached 82.9\%. Moreover, it has shown best MIC of 17.31\,\mu\text{g/mL}, which is better than passifloricin A (29.4\,\mu\text{g/mL}).

Indole derivatives have shown interesting biological properties. Hence, for the purpose of obtaining new and more potent anti-TB agents that can improve the current anti-TB therapy. Some spirooxindole derivatives were evaluated as anti-TB agents. Among all, two compounds (106a) and (106b) showed preeminent MIC of 0.05\,\mu\text{g/mL} against \textit{Mtb} H37Rv, which is comparable to INH and RIF\textsuperscript{133}. With the same motivation, a series of hydrazine and 3-nitrovinyl analogs of indole-3-carboxaldehydes, compound (107), exhibited 91\% inhibition at <6.25\,\mu\text{g/mL} against \textit{Mtb} H37Rv and has a good selectivity index (SI) of >1.6\textsuperscript{134}. While \(N\)-Hydroxythiosemicarbazides (108a) and (108b) showed poor potency of MIC 62.04\,\mu\text{M} and 24.58\,\mu\text{M}, respectively\textsuperscript{135}. Indole derivative (109) showed moderate activity of MIC 2\,\mu\text{g/mL} against \textit{Mtb} H37Rv\textsuperscript{136}. A series
of 2-(hydrazinocarbonyl)-3-aryl-1H-indole-5-sulfonamides were evaluated as inhibitors of two β-carbonic anhydrases (CAs, EC) from *Mtb*, Rv1284 and Rv3273. The whole series (110) showed outstanding nanomolar inhibitory activity. The activity profile confirmed that the Rv1284 and Rv3273 have potential for developing anti-TB agents with an alternate mechanism of action[136].

(e) Benzofused compounds-benzimidazole, benzoxazole, benzothiazole and benzothiothiole derivatives

Benzimidazoles and their broad spectrum of activities (antibacterial, antifungal, antihelminthic, antiparasitic and promising anti-TB activity). With this motivation, a series of 2-alkylsulfanyl benzimidazoles were tested against *Mtb*. The values of MIC were within the range 4-125 μM/L in comparison to INH having a MIC of 4 μM/L. The most active compounds of the series were (111a) and (111b), exhibited a MIC of 4 μM/L[137].

In view of the good activity of (111a), the benzene ring of benzimidazole was further substituted by methyl group at the 5-position. The most active compound (112) showed same potency of MIC 4 μM/L[138]. In another effort, a series of substituted 2-polyfluoroalkyl and 2-nitrobenzylsulphanyl benzimidazoles were evaluated for their activity against four *Mtb* strains. Among all, sulphanyl benzimidazoles (113) exhibited preeminent potency of MIC in the range 2-32 μM/L against *Mtb*. While MIC values against *M. kansasi* and *M. avium* exceeded that of INH. 3,5-dinitro compounds were several times more effective against *Mtb* and *M. kansasi* than the respective isomeric 2,4-dinitro derivatives[139].

Benzoxazoles, recently have been identified for their anti-TB activity. With this interest, a number of 2-substituted 5,7- di-tert-butylbenzoxazoles were evaluated for their anti-TB activity. Of these, 5,7-ditert-butyl-2-styrylbenzoxazole (113) showed MIC of 3.13 μg/mL against *Mtb* H37Rv and also found least toxic of this series[140]. In the similar way, a series of 2-benzylsulfanyl derivatives of benzoxazole and benzothiazole were evaluated for their in-vitro anti-TB activity against *Mtb* and non-tuberculous strains. The substances bearing two nitro groups (114a-d) or a thioamide group (114e-h) exhibited appreciable anti-TB activity of MIC in the range 2-8 μM/L against *Mtb* and also exhibited great activity against non-tuberculous strains. The most active compounds were evaluated as moderately cytotoxic[141]. In a
series of (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl) methyl N,N-disubstituted dithiocarbamates and (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)methyl O-alkyl dithiocarbonates, three compounds (115a-c) showed equal potency of MIC 0.78µg/mL against \textit{Mtb} H37Rv\textsuperscript{[142]}. While benzoxathiolone derivatives (116a-c) exhibited poor activity of MIC 50µg/mL\textsuperscript{[143]}. A series of 3-arylsubstituted-2-[1\textit{H} (2\textit{H}) benzotriazol-1 (2)-yl] acrylonitriles (117a) and (117b) showed 98, 99% inhibition and a MIC of 6.25µg/mL and 12.5µg/mL, respectively against \textit{Mtb}\textsuperscript{[144]}. A diverse variety of substitutions were made in the benzene ring and also their attachment to the benzotriazole ring (118) was varied. Some compounds of this series showed moderate activity whereas the majority of them showed no activity. The replacement of electron withdrawing substituent in the C-4 of the phenyl ring with two or more electron releasing substituents or with cyclohexyl or larger aromatic rings produced a strong reduction in activity in spite of the increased lipophilic character\textsuperscript{[145]}. Limited work has been done to explore the potency of purine analogues as anti-TB agents. Active compounds in these series may target new biochemical mechanisms, potentially allowing treatment of MDRTB. Recently, purine analogues possessing anti-TB activity have been pursued with great interest. In this perception, 9-benzylpurines with a variety of substituents at 2, 6 or 8 positions were found as good anti-TB agents. High activity was exhibited by 9-benzylpurines carrying a phenyl ethynyl, transseryl or aryl substituents at the 6th position and generally chlorine at the 2nd position. The most active compounds (119a) and (119b) showed a MIC of 3.13 and 0.78 µg/mL respectively, against \textit{Mtb} H37Rv and also a selectivity index (SI) of 2.7 and 10.4\textsuperscript{[146]}. In continuation, a series of 6-arylpurines having a variety of substituents in the 9 position were screened against \textit{Mtb} H37Rv. The most active compound of the series was again found to be same 9-benzyl-2-chloro-6-(2-furyl)purine (119b) having a MIC of 0.78µg/mL. This compound exhibited relatively low cytotoxicity and it was also active against several SDR strains of \textit{Mtb}\textsuperscript{[147]}. Some analogues of 9- sulphonated/sulphenylated 6-mercaptopurines\textsuperscript{[148]} and few of them exhibited MIC in the range of 0.39-0.78µg/mL. The most potent compound (120) (MIC=0.39 µg/mL) also exhibited good activity against several drug resistant strains.

A series of 9-aryl-, 9-arylsulfonyl- and 9-benzyl-6-(2-furyl)purines were screened for their anti-TB activity against \textit{Mtb} H37Rv. Among all, 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9\textit{H}-purine (121) exhibited best potency of MIC 0.39µg/mL and also low toxicity against mammalian cells and activity inside macrophages\textsuperscript{[149]}. A purine derivative 9-(ethylcarboxymethyl)-6-(dodecylthio)-9\textit{H}-purine (122) was showed MIC of 0.78µg/mL\textsuperscript{[150]}. Analogues of agelasine E (123), one derivative (123a) showed promising activity with MIC of 1.56µg/mL against \textit{Mtb} H37Rv\textsuperscript{[151]}. Other 6-(2-furyl)-9-(p-methoxybenzyl) purines carrying a variety of substituents in the 2- or 8-position and was successful in identifying a more potent molecule (124), (MIC=0.20µg/mL) of above all series. The purine derivatives and found a more potent molecule (125) of above all series, which...
In search of new anti-TB purine type analogues, a series of 1-[1-(4-hydroxybutyl)-1,2,3-triazol-(4 and 5)-

has shown an IC90 of <0.20μg/mL against *Mtb* H37Rv[153].
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ylmethyl]-1H pyrazolo[3,4-d]pyrimidines and all of them were inactive but one compound (126) has shown MIC of 12.5 μg/mL\[154-156\].

In continuation, a series of di/trisubstituted pyrazolo[3,4-d]pyrimidines (127), (128) were observed and have no significant anti-TB activity at concentrations up to 6.25 μg/mL. A series of N,S-bis-alkylated thiopyrazolo[3,4-d]pyrimidines, based on sequential S-then N-alkylation, these compounds showed significant anti-TB activity (MICs down to =2 μg/mL) and their potential as significant drug-like leads is authenticated through cytotoxicity evaluation. Among all, one compound (129) has shown MIC=0.5-1 μg/mL against \(Mtb\) H37Rv\[157\]. A homologous series of three pyrazolopyrimidine analogues (130a-c) were evaluated as lumazine synthase inhibitors. All three compounds were extremely potent inhibitors (Inhibition constant: \(K_i=15-40\) nM) of the lumazine synthases of \(Mtb\) with inhibition constants in the low nanomolar to subnanomolar range. Molecular modeling of one of the homologues bound to \(Mtb\) lumazine synthase suggests that both the hypothetical intermediate in the lumazine synthase-catalyzed reaction pathway and the metabolically stable analogues bind similarly\[158\]. In a series of Thieno[2,3-d]pyrimidin-4-one, two compounds (131a) and (131b) have shown moderate potency of 5 μM/L against \(Mtb\) and \(M. avium\), which is equal to that of RIF\[159\].

In search of novel potent quinoline derivatives, quinoline derivatives consisting of triazolo, ureido and thioureido substituents at C-6 position, Of these, triazolo derivative (132b) have shown moderate activity of MIC 3.125 μg/mL against \(Mtb\) H37Rv\[160,161\]. In the same direction, quinoline-based derivatives were evaluated for their anti-TB efficiency. Among all, compound (133) has shown remarkable activity of MIC 0.77 μM against \(Mtb\) H37Rv and 0.99-1.55 μM against MDR-TB strains\[162\]. In continuation, isoxazole based quinoline derivatives were found a lead molecule (134), which showed MIC of 0.2 μM and 2.6 μM in MABA and LORA assay against \(Mtb\) H37Rv\[163\]. Thus, optimization of quinolines for the development of anti-TB agents is a fruitful approach.

Recently, new quinolone antibacterial agents were observed for their potency against certain types of mycobacterial species in in-vitro and in-vivo tests. With this motivation, a series of pyridobenzoxazine derivatives by replacement of the N-methylpiperazinyl group...
of Levofloxacin (LVFX) (135) with various basic substituents. Among these compounds, compound (136), which was a 2,8-diazabicyclo[4.3.0]nonanyl derivative with relatively low lipophilicity, showed the most potent activity against mycobacterial species: the activity was 4- to 32-fold more potent than that of LVFX. These results suggested that an increase in the lipophilicity of LVFX analogues in part contributed to enhancement of anti-TB activities but that lipophilicity of the compound was not a critical factor affecting the potency[164]. While in the investigation of potency against M. kansasii LVFX showed MIC in the range of 0.12-0.25 µg/ml while Moxifloxacin (137) showed the range of MIC==0.06-0.12 µg/mL[165]. These results prompted for optimization of other quinoline antibacterials to be investigated as anti-TB.

A other series of Lamivudine prodrugs bearing fluoroquinoles (138) were evaluated for their efficacy against Mtb H37Rv. All the compounds exhibited an inhibition of 92-100% at a concentration of 6.25µg/ml[166]. While in ciprofloxacin derivatives, one compound (139) showed in-vivo anti-TB activity by reducing the bacterial load in spleen tissue with 0.76-log10 protections and was considered to be moderately active in reducing bacterial count in spleen[167]. In continuation, Gatifloxacin (140) derivatives was found more potent compound (141) in comparison to compound (139). In the in-vivo model compound (141) decreased the bacterial load in lung and spleen tissues with 3.62- and 3.76-log10 protections, respectively[168]. With this motivation, he was able to find out a most potent molecule (142) which decreased the bacterial load in lung and spleen tissues with 2.42- and 3.66-log10 protections, respectively, at 25 mg/kg body weight[169]. Contrarily, 7-[4-(5-amino-1,3,4 thiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolonic derivatives (143a) and (143b), showed moderate anti-TB activity at MIC of 10 µg/mL compared to INH[170].

In another approach, 3-unsubstituted 4-hydroxyquinolin-2(1H)-one were exhibited potency against Mtb H37Rv. One compound (144) showed moderate activity of MIC 3.125µg/mL[171]. Surprisingly, the series of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo [3,2,1-ij]quinoline-2-carboxylic acid hetarylamides exhibited excellent activity (MIC=0.39-6.25µg/mL) in comparison to (144). The most active compound (145) showed MIC of 0.39 µg/mL against Mtb H37Rv[172].

The effect of nitro substitution on quinoline ring, in that direction, a series of 2-(sub)-3-fluoro/nitro-5,12-dihydro-5-oxobenzothiazolo[3,2-a]quinoline-6-carboxylic acid derivatives were evaluated for in-vitro and in-vivo anti-TB activities against Mtb H37Rv (MTB), MDR-TB, and M. smegmatis (MC2), and also tested for the ability to inhibit the supercoiling.
activity of DNA gyrase from *M. smegmatis*. Among the thirty-four compounds, 2-(3-(diethylcarbamoyl)piperidin-1-yl)-3-fluoro-5,12-dihydro-5-oxobenzothiazolo[3,2-a]quinoline-6-carboxylic acid (146) was found to be the most active compound with MIC of 0.18 and 0.08 \(\mu M\) against MTB and MDR-TB, respectively. In the *in-vivo* model compound (146) decreased the bacterial load in lung and spleen tissues with 2.78 and 3.12-log10 protections, respectively, at the dose of 50mg/kg body weight\[^{173}\]. In another investigation, 6-nitroquinolone (147) was also found to be the most active compound in vitro with MIC of 0.08 and 0.16 \(\mu M\) against MTB and MDR-TB, respectively. In the *in-vivo* model compound 147 decreased the bacterial load in lung and spleen tissues with 2.78 and 4.15-log 10 protections, respectively, at the dose of 50mg/kg body weight\[^{174}\].

In an effort to increase the potency of quinolones, Carta et al. synthesized a series of [1,2,3]Triazolo[4,5-h]quinolones and evaluated their antitubercular activity against *Mtb* H37Rv and further 11 clinically isolated strains of *Mtb* endowed with different drug resistance. Among all, compound (148) exhibited best activity against all strains with a MIC of 0.5 \(\mu g/mL\)\[^{175}\]. Whereas in another series of [1,2,3]Triazolo[4,5-h]quinolones synthesized by the same group, Compounds (149a) and (149b) exhibited better potency of MIC in the range 0.125-16.0 \(\mu g/mL\) against H37Rv and 11 clinical isolates of MDR-TB. These results showed that [1,2,3]-triazolo[4,5-h]quinolones were endowed with an excellent activity against MDR-TB strains with no cytotoxicity\[^{176}\].

In the process of investigating novel quinolones as anti-TB agents, many derivatives of quinolones were screened for their *in-vitro* efficacy against MTB and MDR-TB. The most potent (*in-vitro*) compound of the series was screened for *in-vivo* potency too. Compound (150) exhibited MIC99 of 0.19\(\mu M\) and 0.09\(\mu M\) against MTB and MDR-TB, respectively and decreased the bacterial load in lung and spleen tissues with 1.91 and 2.91-log10 protections, respectively, in the *in-vivo* model at a dose of 50mg/kg body weight\[^{177}\]. Compound (151) decreased the bacterial load in lung and spleen tissues with 2.54 and 2.92-log10 protections\[^{178}\], while (152) decreased the bacterial load by 30% and 42%, respectively, at a dose of 50 mg/kg body weight\[^{179}\]. In an effort to increase the anti-TB potency of quinolones, 1-(cyclopropyl/2,4-difluorophenyl/tert-butyl)-1,4-dihydro-8-methyl-6-nitro-4-oxo-7-(substit-
tuted-secondary-amino)quinoline-3-carboxylic acids. The most active compound (153) of the series showed MIC of 0.42 μM and 0.09 μM against MTB and MDR-TB respectively\[180\]. While in another series, 7-(3-(diethyl carbamoyl)piperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (154) exhibited promising MIC of 0.09 μM against MTB and MDR-TB respectively. In the \textit{in-vivo} model compound (154) also decreased the mycobacterial load in lung and spleen tissues with 2.53- and 4.88-log10 protections respectively at a dose of 50 mg/kg body weight\[181\]. With the same motivation, Moxifloxacin and Gatifloxacin derivatives were evaluated against \textit{Mtb} H37Rv (MTB). The most active compound (155) exhibited a MIC of 0.31 μg/mL\[182\].

**e) Benzothiadiazine, pyranopyridine phenazine derivatives**

In an effort to develop new and more effective anti-TB agents, a series of benzothiadiazine 1,1-dioxide derivatives were tested \textit{in-vitro} against \textit{Mtb}, \textit{M. avium} and \textit{M. intracellulare}. Of these, compound (158) showed most excellent potency of MIC 0.5 μg/mL against MTB H37Rv and 0.5-2 μg/mL against MDR-TB strains. However, the \textit{in-vivo} activity model of TB-infection did not show significant anti-TB activity, probably due to its poor bioavailability\[183\]. In continuation, 5-nitrofuran, 5-nitrothiophene and arylfuran coupled benzothiadiazines were exhibited anti-TB activity. These compounds exhibited moderate anti-TB activity. The most active compound (159) showed MIC of 1 μg/mL against MTB H37Rv\[184\]. With the same stimulation, a number of fifteen 2-amino-6-methyl-4-aryl-8-[(E)-arylmethylidene]-5,6,7,8-tetrahydro-4\textit{H}-pyrano[3,2-c]pyridine-3-carbonitriles were evaluated for anti-TB activity. Among all, compound (160) was found to be the most potent compound (MIC: 0.43 μM) against MTB and MDR-TB, being 100 times more active than INH against MDR-TB\[185\].
Clofazimine is a fat-soluble riminophenazine dye used in combination with RIF and dapsone as multidrug therapy (MDT) for the therapy of leprosy. It has been used in combination with other anti-TB drugs to treat *M. avium* infections in AIDS patients and *M. avium* para tuberculosis infection in Crohn’s disease patients. On this basis and to minimize the side-effects and to improve the anti-TB activity of Clofazimine, 3-(2,4-dichloroanilino)-10-(2,4-dichlorophenyl)-2,10-dihydro -2-(2,2,6,6-tetramethylpiperid-4-ylimino)phenazine (B4128), which posses similar mode of action of Clofazimine, with the same motivation, a series of phthalimido- and naphthalimido-linked phenazines, two compounds (162a) and (162b) with a potency of MIC 1 µg/mL against *Mtb* H37Rv. These compounds also exhibited potency against MDR-TB strains[187]. Most interestingly, this series was found to be nontoxic[188], authenticate them as future anti-TB drugs.

In search of potential anti-TB agents, pyrazidinoindole analogues were screened for inhibition of the growth of *Mtb*. The most active compound (163) exhibited a MIC50 of 1.42 µg/mL against *Mtb* H37Rv[189]. In the series (2-aryl-3,4-dihydro-2H-thieno[3,2-b]indoles), compound (164) was found to be the most active compound with MIC of 0.4 µg/mL against MTB and MDR-TB[190].

With the same enthusiasm, a series of pyrrolo[1,2-a] quinoxaline-2- or -4-carboxylic acid hydrazides and compound (165) showed an interesting anti-TB activity at 6.25µg/mL against *Mtb* H37Rv, with a 100 % inhibition[191]. Compound (166) was inhibited 80% at a concentration of 6.25µM[192]. While, Enamine-containing analogues of heteroaryl quinones were showed promising anti-TB activity with a MIC in the range 0.25-0.1 µg/mL against *Mtb* H37Rv. The best selectivity index (SI=15.1) was displayed by the molecule (167) with a MIC 0.39µg/mL[193].

So, for the development of a new class of anti-TB agents in order to fight resistance and shorten the duration of therapy, in this concern, a series of 3,3-dimethyl-3Hbenzofuro[3,2-f][1]benzopyran and 1,2-dihydro-3,3-dimethyl-3Hbenzofuro[3,2-f][11]benzopyran were displayed significant anti-TB activities when tested against...
Mtb H37Rv and Beijing strains, with MIC99 in the range of 1-10μg/ml. The most active compound (168a) exhibited a MIC99 of 5μg/ml and 1μg/ml, respectively against Mtb H37Rv and M. smegmatis[194]. In an effort to increase the potency, another series was found to be the dropoff in the activity. The most active compound (169) exhibited MIC95 8μg/ml against Mtb H37Rv[195].

In the next trial, compounds (170) and (171) were more potency of MIC95 in the range 0.6-2.5μg/ml against Mtb H37Rv[196,197]. With the same inspiration, a series of pyranocoumarin derivatives, two compounds (172a) and (172b) were bactericidal in their effect on Mtb since their MBC/MIC ratios was 2. These two compounds had a MIC value of 16μg/mL[198].

A series of phthalamide derivatives, the most active compound (173) was displayed a MIC of 5μg/mL against Mtb H37Rv and a good selectivity index[199]. While two series of thiophene (174) and benzopyrrole/pyridine (175a) and (175b) triarylmethanes[200,201], thiophene analogues displayed MIC in the range 3.12-12.5μg/mL and benzopyrrole/pyridine analogues displayed 6.25-25μg/mL against Mtb H37Rv.

A novel series of spiro-pyrrolothiazoles were evaluated for their anti-TB activity. Among all, the best potency was showed by compound (176) with a MIC of 0.6μM against MTB and MDR-TB[202]. 3-amino-
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Imidazo[1,2-a]pyridines as a novel class of Mtb glutamine synthetase inhibitors. The most active compound (177) showed an inhibition of IC50 = 0.38 ± 0.02 μM203. In a different approach, Rifabutin (RBT) analogues, compound (178a) showed good potency of MIC <0.013 μg/mL against Mtb H37Rv, while compound (178b) showed potency of MIC 0.08 μM against non-replicating Mtb strains204.

In search of novel antitubercular agents, tetrahydroindazole based compounds were evaluated for their anti-TB efficiency. Among all, three compounds 179a-c have shown MIC in the range 1.7-1.9 μM against Mtb H37Rv in MABA assay. These compounds also displayed any toxicity against VERO cells up to the concentration 128 μM205. The 1,3-benzothiazin-4-ones (BTZ) kills Mtb by blocking arabinan synthesis. The most advanced compound, BTZ043 (180), was found to be a candidate for inclusion in combination therapies for both MDR-TB and XDR-TB strains206. The 1,2,4-Triazolo[1,5-a]pyrimidine-6-carboxylic acid derivatives, one compound (181) has shown 92% growth inhibition of Mtb H37Rv at 6.25 μg/mL concentration207.

A number of selected imidazo[2,1-b]thiazoles, one of these compounds, 2-chloro-6-phenyl-imidazo[2,1-b]thiazole (155a) showed anti-TB activity. Analogues bearing a substituted ring at the 6-position and compounds bearing nitroso group at 5-position were screened against Mtb H37Rv, compound (155b) exhibited best activity of MIC 0.39 μg/mL, which is better than that of (155a) and comparable to RIF208.

In a series of 2,6-disubstituted and 2,5,6-trisubstituted imidazo[2,1-b][1,3,4]thiadiazoles, only two compounds (156a) and (156b) showed 100% inhibition at a concentration of >6.25 μg/mL209. A series of 2,3-dihydro-7-nitroimidazo[5,1-b]oxazoles on the basis of (PA-824) and (CGI-17341). Among all, one compound (227) exhibited a moderate activity of MIC 5 μg/mL against Mtb H37Rv210.

**DISCUSSION**

Tuberculosis (TB), a highly infectious disease primarily caused by M. tuberculosis, is one of the oldest recorded human afflictions and remains today a leading cause of impoverishment, human suffering and death. The majority of deaths resulting from TB infection occur in poverty stricken regions of the developing world. TB is responsible for the deaths of nearly two million people per year, with approximately one third of the global population infected with the latent form of the disease. While TB in humans is primarily due to infection with M. tuberculosis, several other species of the M. tuberculosis complex, namely M. bovis, M. africanum, M. microti and M. canettii may also cause the disease. Recently two additional species have been suggested as belonging to the M. tuberculosis complex: M. caprae and M. pinnipedi. Mycobacteria possess a unique cell wall of high lipid content, which includes mycolic acids and other glycolipids. Mycolic acids of the mycobacterial cell wall are one of the specific features of bacteria belonging to this genus. However, these fatty acids can also be found in the cell walls of certain genera of aerobic Actinomycetes and in the majority of species of the genus Corynebacterium. This unique cell wall is thought to be responsible for certain features of mycobacteria, including low cell wall permeability and pathogenicity. It is the low permeability of the mycobacterial cell wall which is believed to play a significant role in the antibiotic resistance of M. tuberculosis. TB usually affects the lungs (pulmonary TB) of an infected person, but the disease can also affect other areas of the body including kidneys, bones, joints and lymph nodes (extrapulmonary TB). TB is an airborne disease that spreads much like the common cold, with the circulation of M. tuberculosis-containing aerosols into the air caused by the coughing, sneezing, talk-
ing or spitting of a person with infectious pulmonary TB. Inhalation of only a small number of these TB bacilli by a person will result in their infection with the disease. A person infected with latent TB will exhibit none of the obvious symptoms of TB, which include a fever, fatigue, weight loss, a persistent cough and sputum production which will contain blood at an advanced stage of the disease. While a person with latent TB is not infectious, they may develop the active form of the disease if their immune system is compromised\[211-214\]. It is estimated that one person in every 10 of the two billion people infected worldwide will develop infectious TB. A number of factors have led to the reduction in successful treatment of the disease. These include a lengthy (6-9 months) multi-drug treatment program, the misuse or mismanagement of which can lead to the development of multi or extensive drug resistant TB (MDRTB or XDR-TB) and the co-infection of TB with the human immunodeficiency virus (HIV). As a result of this interaction with HIV, TB has become the leading cause of death among people infected with HIV, while infection with HIV has become the most significant risk factor for a person with latent TB developing the active form of the disease\[215,216\]. Treatment with multiple drug regimens over an extended period of time is necessary in order to minimize the emergence of MDRTB. The long period of treatment is also necessary as a result of the persistence of \( \text{M. tuberculosis} \) in the host during infection. Patient non-compliance, often due to the lengthy treatment period, has led to an increase in MDRTB. MDRTB is defined as tubercule bacilli resistant to at least isoniazid and rifampin (the two most potent antitubercular drugs). Treatment of MDRTB requires up to two years of treatment with second-line antitubercular drugs (for example cycloserine and ethionamide, which have more side effects and are more expensive than the first-line drugs. The development of XDR-TB can then occur when second-line drugs are misused. XDR-TB is defined as TB that is resistant to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin, and amikacin), in addition to isoniazid and rifampin resistance (MDRTB).

**CONCLUSION**

Tuberculosis (TB) is a chronic infectious disease caused by \( \text{Mtb} \) strains. The term MDR-TB is used to describe strains that are resistant to two or more of the five first-line anti-TB drugs. Treatment regimen of tuberculosis comprises five first line antiTB drugs followed by second line antiTB drugs. Besides the traditional antitubercular drugs available commercially, several new heterocycles were synthesized in recent past. The new potential anti-TB agents have been classified according to their chemical entities. In an effort to develop new and more effective therapies, molecules can also effective against MTB and MDR-TB. The World Health Organization (WHO) have implemented a directly observed therapy short course (DOTS) program in an attempt to overcome the problem of patient non-compliance.\[23\] However, this strategy is difficult to carry out in areas most at risk due to the lack of resources and infrastructure required to ensure adequate monitoring of drug administration.\[23\] There is therefore an urgent need to develop new antitubercular drugs with greater potency, requiring shorter duration of treatment. This should result in better patient compliance, which in turn should reduce the development of MDRTB and XDR-TB. Novel antitubercular drugs are also needed to treat the current strains of MDRTB and XDR-TB. Resistance of \( \text{M. tuberculosis} \) strains to anti-TB agents is an increasing problem worldwide. However, potent new anti-TB drugs with new mechanism of action have not been developed in the last four decades. TB is considered to be the most important chronic communicable disease and about 32% of the world’s population is currently infected with TB. The emergence of AIDS, decline of socioeconomic standards and a reduced emphasis on TB control programs contribute to the disease’s resurgence. Now research effort towards the development of novel anti-TB agents is in the direction of discovering new classes of compounds, which are structurally different from known anti-TB drugs. The continuous and sturdy rise in tuberculosis together with the appearance of resistance against conventional anti-TB drug regimen and the pathogenic synergy with HIV has put vast stress on public health systems to introduce new drug management. In drug resistant TB it is important to understand how the resistance appears. Remarkably, the mechanisms of action of these new arrivals are well-understood with new and novel target.
Also, in the field of preclinical research, well-established classes of compounds and molecular targets are still interesting, however, in some of the cases when similar target molecules are present in humans; future development has to ensure a high degree of selectivity. However, all these possibilities require research activities and therefore, there is a demand in continuing research in this direction and more financial assistance from developed nations and industrial houses to achieve the goal of eradicating *Mtb* from the world in coming years.

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