Review Article **Open Access**

Recent Efforts for the Development of Antitubercular Drug Containing Diazine Ring

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Abstract

There has been considerable interest in the development of new molecule with antibacterial activities particularly against tuberclosis because *mycobacterium* species have developed resistant against currently used drugs, their toxic effect and long duration of therapy. The diazine (pyridazine, pyrimidine and piperazine) derivatives possess an important class of compound for new drugs research and development. Therefore, many researchers have synthesized these compounds as target structures and evaluated their antitubercular activity. These observations have been guiding for the development of new molecules that possess potent antitubercular activity with minimum side effects or effective against MDR, XDR *mycobacterium* strains, and also in patient co-infected with HIV/AIDS.

Introduction

Infectious microbial diseases remain a pressing problem worldwide, because microbes have resisted prophylaxis or therapy longer than any other form of life. Infectious diseases have increased dramatically in recent years. In spite of many significant progres in antibacterial therapy, the widespread use and misuse of antibiotics have caused the emergence of resistance to antibiotics, which is a serious threat for the therapy. In particular, the emergence of multidrug resistant (MDR) bacteria has become a serious problem in the treatment of bacterial diseases. Variuos infections are more common because of their causing agents or microbes have a tendency to develop new strains under any circumstances and developing resistance against the available drugs. In addition to the development of new and effective antibacterial agents against MDR bacteria, recently attention has focused on the treatment of tuberculosis (TB) [1-4]. Although, there is an increasing resistance to antimicrobial drugs [5], to overcome the development of drug resistance necessary to synthesize a new class of drugs that possessing different chemical properties. Therefore, the development of new drugs to deal with bacterial resistant has become one of the most important areas of research today. Therefore, recent efforts have been directed toward exploring new, potent anti-TB agents with low toxicity profiles when compared with currently used anti-TB drugs [6-9]. Based on this finding, new anti-TB agents having the pyridazine system have been studied. However, some pyridazine or phthalazine compounds have been reported to have anti-TB activity [10,11].

Diazines are (pyridazines, pyrimidine and piperazine) containing two nitrogen atoms at 1,2 position, 1-3 position and 1,4 position in their cyclic structures respectively. The structures of diazines are prepared by replacing two carbon atoms to two nitrogen atoms in the benzene ring at their respective positions. Diazines and its derivatives are noteworthy for their physiological and biological importance [12-14]. Recently diazine derivatives have been a subject of intensive research owing to their wide spectrum of pharmacological activities. Differently substituted diazines have been found to have potential antibacterial, antifungal and antiviral including anti-HIV activities, anticancer, analgesic, anti-inflammatory, anticonvulsant, cardio tonic, antiulcer, antihypertensive, and antiasthmatic etc activities. In view of above facts and inspired by the research going on diazine compounds, particularly in relation to microbial infections [15-17].

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 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. Observed Treatment, short-course (DOTS) strategy, constitutes the cornerstone of the current protocol for control of TB [18-25]. 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 [26,27].

Drug-Resistant Tuberculosis

Drug resistance *M. tuberculosis* is an important obstacle for the treatment and control of TB. This resistance has usually been recognized to the unusual multi-layer cell envelope and active multidrug efflux pumps. Recent approaches 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

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would enable many antibiotics, which are already available but have not been used for TB, to gain new activities against *M. tuberculosis* [1-3,28-32].

Multi drugs resistance-tuberculosis

Multi drugs 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). MDR 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 multidrug-resistant tuberculosis is long lasting, less effective, costly, and poorly tolerated [1-3,28,32].

## Extensively drug resistant tuberculosis

Extensively drug resistant (XDR) TB by definition is resistance to at least isoniazid and rifampicin in addition to any quinolone and at least one injectable second-line agent (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 reduced number of effective treatment options. Hence there is an urgent need for novel drugs that are active against *M. tuberculosis* in order to shorten the duration of TB therapy [1-3,28,32].

Recently Discovered Antitubercular Agents

The unpleasant side effects, relatively long duration of treatment and non-compliance to treatment regimen are drawbacks of current TB therapy. Such non-adherence with the course of treatment leads to treatment failure and the development of drug resistance. The goal now is to develop anti-TB drugs in a cost-effective manner, which efficaciously treats infectious MDR/XDR-TB strains and latent infections with shortened treatment periods as well as reduced frequency of dosage [1-3,28,32].

Antitubercular Activity of Pyridazines

As series of 6-substituted-3(2*H*)-pyridazinone-2-acetyl-2-(substituted/nonsubstituted acetophenone) hydrazone derivatives 1a-l were teseted for *in-vitro* anti-TB activities against *Mtb* H37Rv. Among the target compounds, 1b and 1f exhibited the best anti-TB activity, with a MIC value of 5 μg/mL [33].
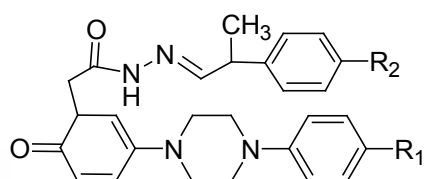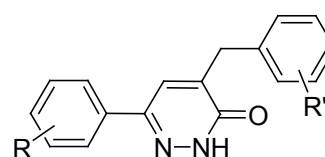

Compounds 1a-l

1a-1d R_1=H, 1e-1h R_1=F, 1i-1l R_1=Cl

1a, 1e and 1i R_2=H; 1b, 1f, and 1j R_2=Br

1c, 1g and 1k R_2=Cl; 1d, 1h and 1l R_2=F

Compounds 2a-h and 3a-h

2a-2h R=*p*-Cl, 3a-3h R=p-CH$_3$; 2a and 3a R'=H;

2b and 3b R'=*p*-Cl; 2c and 3c R'=*p*-NO$_2$; 2d and 3d R'=*p*-OH;

2e and 3e R'=*p*-CH$_3$; 2f and 3f R'=*p*-OCH$_3$,

2g and 3g R'=*p*-OH, *m*-OCH$_3$; 2h and 3h R'=*p*-F

Two series of pyridazinone derivatives (19-34) were evaluated for anti-TB activities against *Mtb* H37Rv strain. The compound 2g, 5-(4-hydroxy-3-methoxybenzyl)-3-(4-chloro-phenyl)-1,6-dihydro-6-pyridazinone emerged as a lead compound with good anti-TB activity. Four more compounds, (2c, 2d, 3c, 3g 21, 22, 29 and 33) were significant in their anti-TB action [10]. Some 3(2*H*)-pyridazinone and 1(2*H*)-phthalazinone derivatives (4a-e, 5a-e and 6a-e) were evaluated for their anti-TB activity against *Mtb* H37Rv at 20 μg/mL concentration. The results showed that compound 6e had the highest antimycobacterial activity [34].
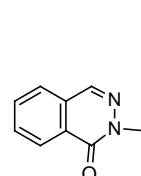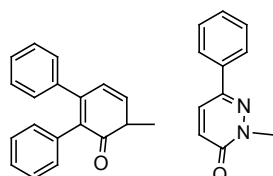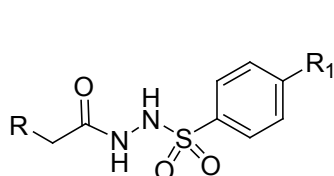

Componds 4a-e, 5a-e and 6a-e   **4** R=   ,   **5** R=   ,   **6** R=

a R_1=H; b R_1=CH$_3$; c R_1=Cl; d R_1=OCH$_3$; e R_1=NHCOCH$_3$

A series of 6-substituted phenyl-2-(3i-substituted phenyl pyridazin-6i-yl)-2,3,4,5-tetrahydropyridazin-3-ones (7a-e, 8a-d, 9a-c, 10 a-c and 11a-e) were investigated for their *in vitro* anti-TB activities. All the compounds (7a-e, 8a-d, 9a-c, 10 a-c and 11a-e) were screened against *Mtb* H37Rv at concentration of 6.25 μg/mL. The results indicated that the all compounds have mild to potent activities with reference to their appropriate reference standards [35].
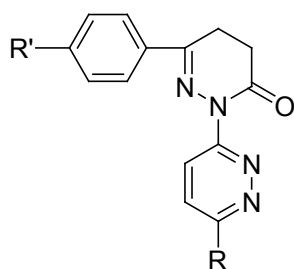
Compounds 7a-e, 8a-d, 9a-c, 10a-c and 11a-e

7a-e R=C₆H₅; 8a-d R=p-CH₃-C₆H₅; 9a-c R=3,5-(CH₃)₂-C₆H₅; 10a-c R=C₁₁H₉O; 11a-e R=-C₆H₄-C₆H₅

7a, 8a, 9a, 10a, 11a R'=H; 7b, 8b, 10b, 11b R'=3,5-(CH₃)₂; 9b R'=4-Cl; 11b R'=p-CH₃; 7c R'=4-Cl;

8c 7 9c R'=C₆H₅; 10c=4-Cl; 11a R=C₆H₅O; 7d R'=4-Br; 8d R'=4-Br; 11d R'=C₆H₅; 7e R=C₆H₅; 11e R'=4-Cl

A series of 5-{3i-oxo-6i-(substituted aryl)-2i,3i,4i,5i-tetrahydropyridazin-2i-ylmethyl}-2-substituted 1,3,4-oxadiazole (12a-e, 13a-e and 14a-e) were screened for anti-TB activity at concentration of 6.25 μg/mL. All the synthesized compounds were screened against *Mtb* H37Rv comparable with that of standard drugs. The results indicated that the all compounds have mild to potent anti-TB activities [35].
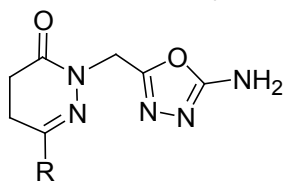

Compound 12a-e, 13a-e, 14a-e

12a, 13a and 14a R=C₆H₅; 12b, 13b and 14b R=3,4-(CH₃)-C₆H₃⁻; 12c, 13c and 14c R=4-CH₃-C₆H₄⁻; 12d, 13d and 14d R=4-C₆H₅O-C₆H₄⁻; 12e, 13e and 14e R=4-Cl-C₆H₄⁻

A series of alkyl 1-heteroaryl-1*H*-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)-1*H*-1,2,3-triazole-4-carboxylate (15) with a MIC of 3.13 μg/mL [36]. In search of potential anti-TB agents, pyridazinoindole analogues and screened them for inhibition of the growth of *Mtb*. The most active compound (16) exhibited a MIC50 of 1.42 μg/mL against *Mtb* H37Rv [37]. 1,2,3,4-tetrahydro-6-substituted-2,5,7-trimethyl-6H-pyrrolo[3,4-d]pyridazin-1,4-ones displayed moderate activity against *Mtb*. On the basis of these findings, we will synthesize new pyridazine derivatives in order to investigate their anti-TB activities.
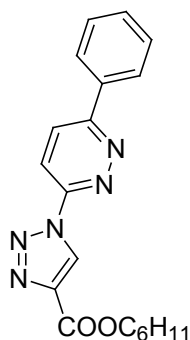

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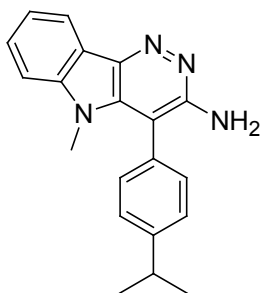
16

In-vitro anti-TB activities of 6-substituted-3(2*H*)-pyridazinone-2-acetyl-2-(substituted/ nonsubstituted acetophenone) hydrazone derivatives 1a-l, compound 1b and 1f exhibited the best activity, with a MIC value of 5 μg/mL [33]. Compounds 1a, 1d and 1e showed MIC value 20 μg/mL and Compounds 1g, 1h, 1i and 1l did not shown any MIC Value. In series (2a-h and 3a-h), compound 2g, 5-(4-hydroxy-3-methoxybenzyl)-3-(4-chloro-phenyl)-1,6-dihydro-6-pyridazinone showed highest anti-TB activity. Compounds, (2c, 2d, 3c, and 3g) were showed significant activity. Compounds 2e showed maxium MIC value 12.5 μg/mL and compound 2e showed lowest MIC value 100 μg/mL. Compounds 2c and 2d showed MIC value 25 μg/mL and compounds 3c and 3g showed MIC value 25 μg/mL [10]. Some pyridazinone or phthalazinone compounds (4a-e, 5a-e and 6a-e) were showed active against *Mtb* H37Rv. Compounds 4e and 5b showed 92.56 and 97.97 percentage resistance. Compound 4c, 6c and 6e showed 47.29, 47.97 and 43.24 respectively at a concentration of 20 μg/mL [33]. A series of 6-substituted phenyl-2-(3'-substituted phenyl pyridazin-6'-yl)-2,3,4,5-tetrahydropyridazin-3-ones (7a-e, 8a-d, 9a-c, 10 a-c and 11a-e) [38] and a other series of 5-{3'-oxo-6'-(substituted aryl)-2',3',4',5'-tetrahydropyridazin-2'-ylmethyl}-2-substituted 1,3,4-oxadiazole (12a-e, 13a-e and 14a-e) [34], the results indicated that the compounds (7a-e, 8a-d, 9a-c, 10 a-c and 11a-e) have mild to potent activities. Compounds 7b, 8b, 9a and 9b showed good percentage inhibition 89, 92, 89 and 95 respectively against tuberculosis at 6.25 μg/mL concentration. Compounds 10c, 11a, 11c, 11d and 11e showed weak percentage inhibition 32,

38, 34, 39 and 40 respectively against tuberculosis at 6.25 μg/mL concentration. Compounds 12e, 13a, 13e 14a and 14e showed good percentage inhibition 84, 88, 87, 91 and 89 respectively against tuberculosis at 6.25 μg/mL concentration. Compounds 12d, 13b, 13d and 14d showed weak percentage inhibition 48, 48, 45 and 49 respectively against tuberculosis at 6.25 μg/mL concentration. All compounds (7a-e, 8a-d, 9a-c, 10a-c and 11a-e) showed the percentage inhibition ranging from 32 to 95% inhibition and compounds (12a-e, 13a-e and 14a-e) were showed the percentage of inhibition ranging from 48 to 91% inhibition against *Mtb* H37 Rv comparable with those of standard rifampicin and isoniazid. The results indicate that the pyridazine with chloro group and dimethyl group showed comparable activity with the reference drugs. Compound 15 and 16 showed MIC value 3.13 μg/mL [35] and MIC$_{50}$ value 1.42 μg/mL against *Mtb* H37Rv respectively [36].

## Piperazine and Pyrazine Derivatives

Pyrazinamide (17) is a synthetic pyrazine analog of nicotinamide. It is active at a MIC of 6-60 μg/mL. Resistance to pyrazinamide develops soon when it is used alone. Its mechanism of action is unknown but it appears to require activation via pyrazinamidases in the organism [39,40]. Since the discovery of pyrazinamide, several derivatives containing pyrazine nucleus have been tested for their activity against *Mtb*. These pyrazine derivatives substituted with oxadiazole, and oxathiazoline [40]. The derivatized isosteres were expected to be biotransformed by esterases to the active species after penetration of the mycobacterial cell wall. The most active compound of the series 18 exhibited a MIC of 4.5 μg/mL in comparison to 49 μg/mL for pyrazinamide. With the same concept, a series of ring substituted (E)-3-Phenyl-1-(2 pyrazinyl)-2-propen-1-ones were screened for their efficacy against *Mtb* H37Rv. Among all, compound 19 showed an inhibition of 94% at 12.5 μg/mL [41]. While in a series of pyrazine derivatives, two compound (140a and 20b) have shown equal potency of MIC 6.25 μg/mL against *Mtb* H37Rv [42]. Compound 20b also showed MIC of <0.25 μg/mL against *Mtb* H37Ra.
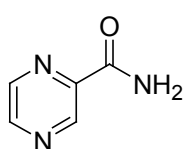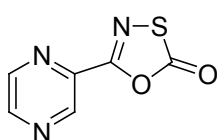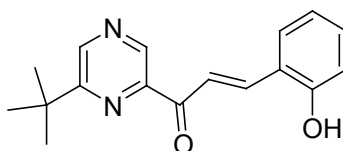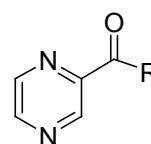
| 17 | 18 | 19 | 20a: R=4-nitrobenzyloxy |
| | | | 20b: R=4-acetoxybenzyloxy |

On the basis of ethionamide, a series of 5-Alkyl-6-(alkyl/aryl sulfanyl) pyrazine-2-carbothioamide, compound (21) showed 91% inhibition at a MIC <6.25 μg/mL. The activity increased with increasing molecular weight of the alkyl sulfanyl group in the 6-position of the pyrazine ring. Thioamides exhibited higher activity than the corresponding amides [43]. While, S methyl-2-(amino(6-chloropyrazin-2-yl)methylene) hydrazine carbodithioate (22) exhibited moderate potency of MIC 32 μg/mL among simple pyrazine hybrids against *Mtb* sensitive and wild strains [44].

| 21 | 22 | 23 |

24a

24b   **25**   **26: 4S, 11S**   **27**
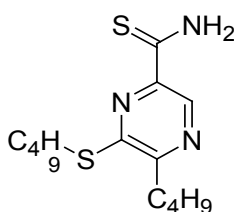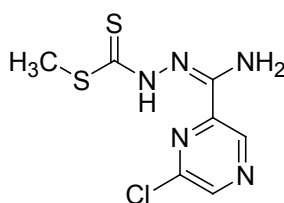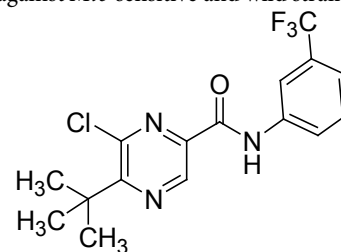
A series of unsubstituted, halogenated and/or alkylated pyrazine-2-carboxylic acid amides connected *via* -CONH- bridge with substituted anilines were screened against *Mtb* H37Rv. Among all, 5-tert-Butyl-6-chloro-N-(3-trifluoromethylphenyl)pyrazine-2-carboxamide (23) has shown the highest activity of MIC 3.13 µg/mL [45]. A number of three hybrids of pyrazine and two of them showed promising anti-TB activity. Compound 24a and 24b showed MIC of 0.78, 0.1 µg/mL respectively, against *Mtb* H37Rv. Compound 24a also showed good activity against atypical strains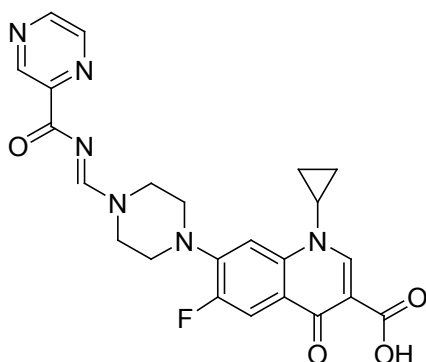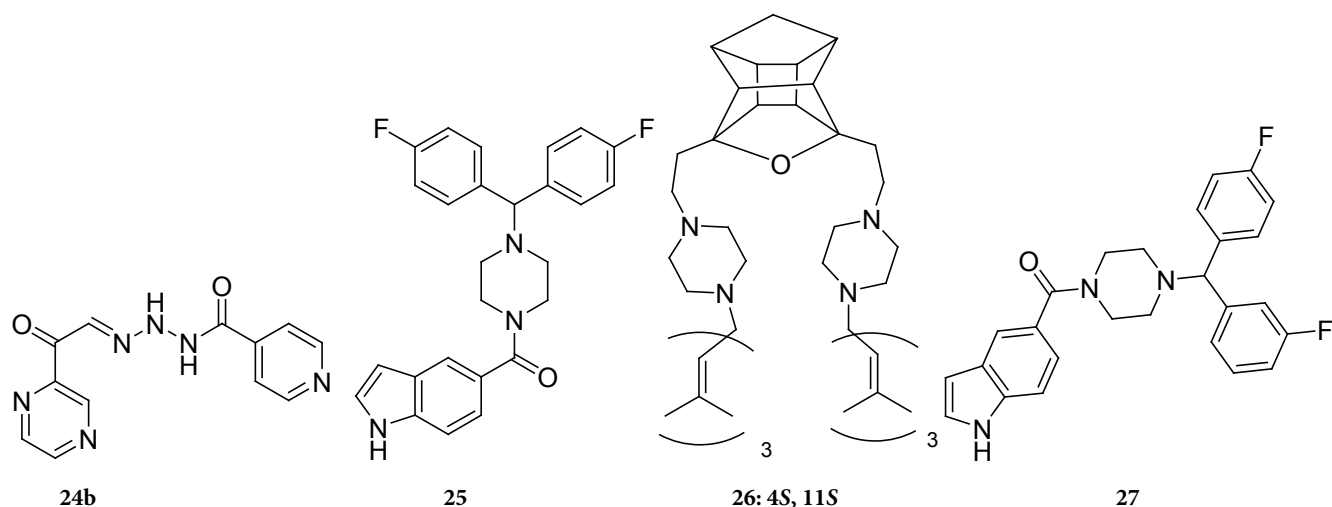 of *Mtb* [46]. In a different approach [47], a series of 1,4-substituted piperazine/homopiperazines, compound 25 showed MIC of 62.5 µM. Similarly, homopiperazine derivatives (26) exhibited more promising activity with MIC 0.78 µg/mL against *Mtb* H37Ra [48]. In a different approach fourteen pentacyclo undecane (PCU) tetra-amine compounds were screened for their *in-vitro* anti-TB activity against *Mtb* H37Rv and XDR strains of *Mtb* 194. The most active compound (27) of the series has shown MIC of 5.04 µM against *Mtb* H37Rv and 1.26 µM against XDR 194 [49].

The new potential anti-TB agents are classified on the basis of their chemical entities. A piperazine derivative BM 212 (28), which arose the interest with its very good *in vitro* activity of MIC 0.7 µg/mL against *Mtb* [50].

28
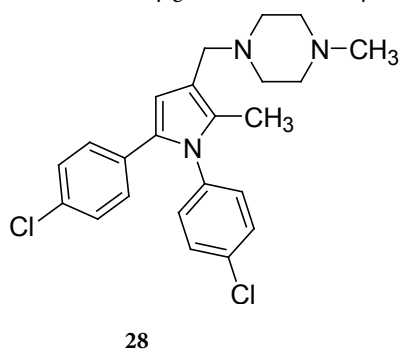
With the same interest, the efficacy of anti-TB, 5-nitrofuranylamides NFAs (29a-e) against TB complex and other clinically relevant non-mycobacterial species [51] and found that the NFAs were significantly active against *Mtb* complex [52-55]. Compound 29a showed preeminent inhibition of MIC 0.006 mg/L against *Mtb* UT30 (streptomycin resistant at 4 mg/L). Whereas, compound 39b shown same potency against *Mtb* UT18 and *M. bovis* BCG. Compound 29d 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 29e showed the same potency against *Mtb* UT18 but shown increased potency of MIC of 0.0004 mg/L against *Mtb* UT15. Compound 29c 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 0.012-0.006 mg/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.

29a   **29b**   **29c**   **29d**

29e   R1=   R2=   R3=
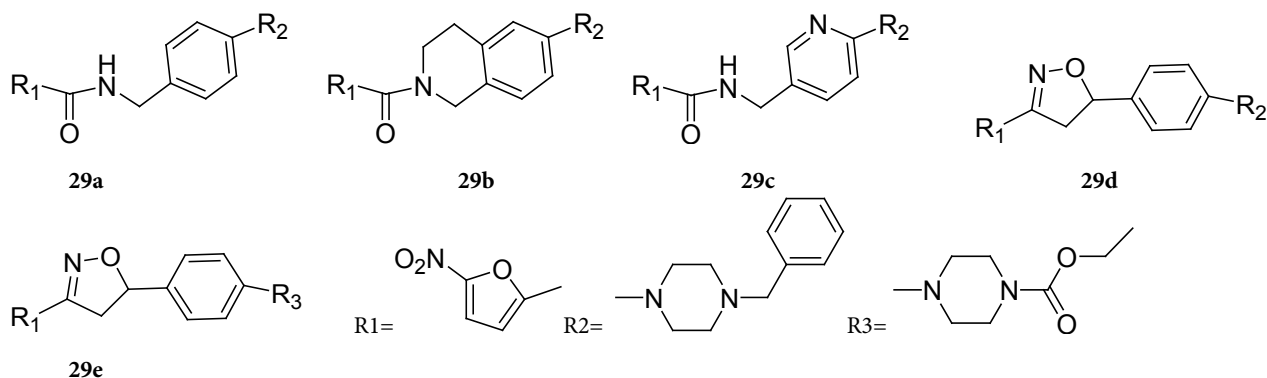
Compound *n*-pentyl 1-(6-phenylpyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (30) with a MIC of 3.13 μg/mL showed significant anti-TB activity against *Mtb* H37Rv [35]. Compound 31 showed great *in vitro* potency of 0.00005 μg/mL. However, their *in-vivo* anti-TB activity was limited by high protein binding and low distribution. This led to the discovery of compound 31b as anti-TB agent, which showed 90% inhibition at a concentration of 1.56 μg/mL [52-55]. A most active molecule 69c has shown a MIC of 0.4 μg/mL against *Mtb* H37Rv [56]. In the same direction a series of isonicotinyl hydrazones and molecule (32) active against *Mtb* H37Rv with a MIC of 0.56 μM, which is more potent than isoniazid (MIC of 2.04 μM) [57].

30

31a: R=

31b: R= COOC₂H₅

31c

32
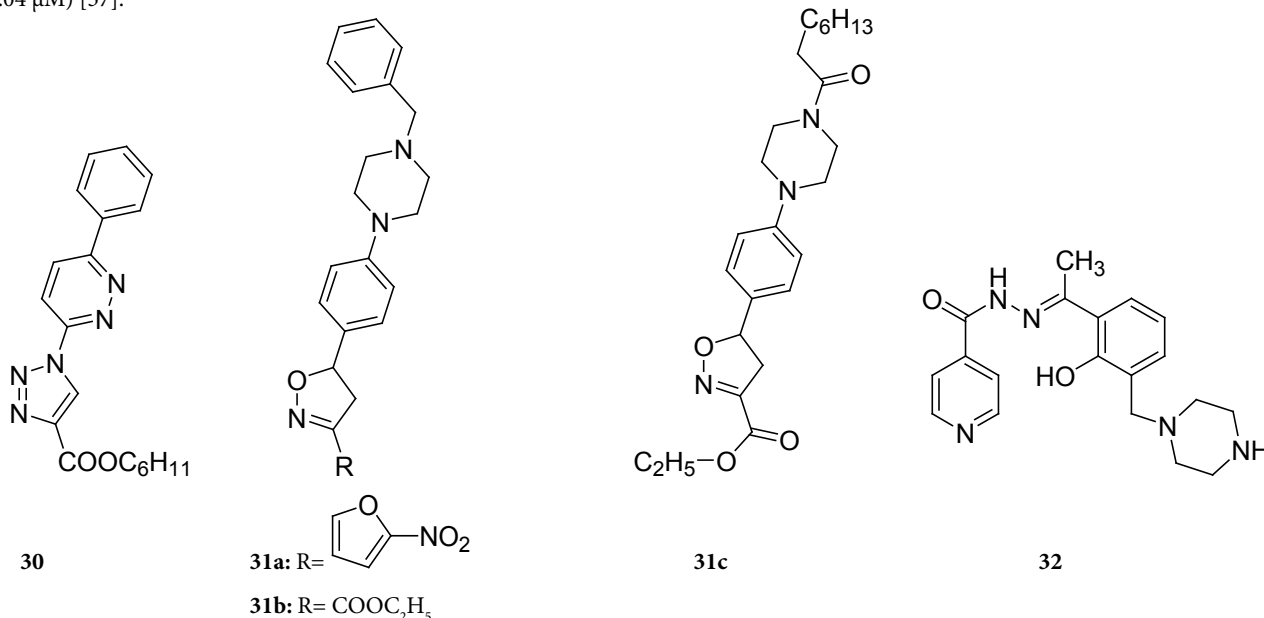
Fluoroquinolones (FQ) such as ciprofloxacin (33) and ofloxacin (34) are second line anti-TB drugs used in combination with first line anti-TB drugs to treat MDR-TB. MIC value of these fluoroquinolones ranged from 0.12 to 2 μg/mL. Levofloxacin (35), levoisomer of ofloxacin is twice as active as the parent drug. They cause side effects as gastrointestinal reactions, central nervous system disturbances, and skin reactions. While, gatifloxacin (GAT, 36) and moxifloxacin (MXF) are new fluoroquinolone DNA gyrase inhibitors that offer advantages over ofloxacin and ciprofloxacin. These new FQs 36, currently in phase III, are the most advanced anti-TB compounds in clinical development showing promise to be the first new anti-TB drugs in nearly 30 years [39].

33

34

35

36
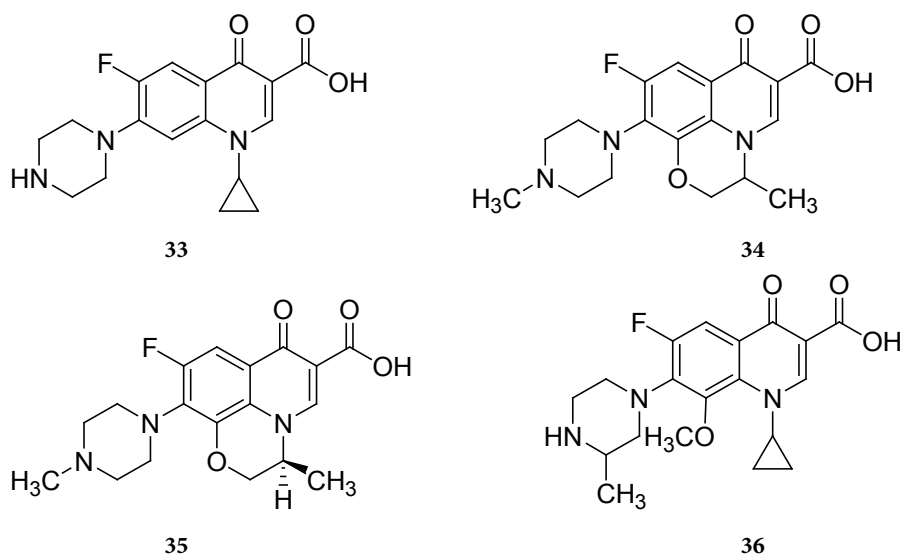
Pyrimidine Derivatives

The antifolates are much importance as they target the enzyme dihydrofolate reductase (DHFR). Most of the antifolates have selectivity toward the pathogen DHFR rather than the host DHFR, as safe target for the development of anti-infective agents. In this concern, a number of compounds with substituted pyrimidines were evaluated their potency against *Mtb* H37Rv. Among them, compounds (37a-f) showed *in-vitro* activity in the range of MIC 25-50 μg/mL [58]. In continuation, a number of trisubstituted pyrimidines, compounds (38) have shown anti-TB potency with a MIC in the range of 12.5-25 μg/mL [59]. To further increase the activity of pyrimidines, synthesized other trisubstituted pyrimidines (39) [60], where the activity profile was remained same as 138. Whereas, chloro-pyrimidines were found to be highly active against *Mtb*. Compounds (140 a-d) were found to be active at a MIC of 0.78 μg/mL. These compounds were further screened against virulent strain (*Mtb* H37Rv) and no change

in their MIC profile was observed [61]. While, in a series of anilino pyrimidines tested against *Mtb* H37Ra, the most potent activity was shown by the compound 41 having a MIC of 3.12 µg/mL [62].

37 a-f, **38 and 39,** **40 a-d** **41**
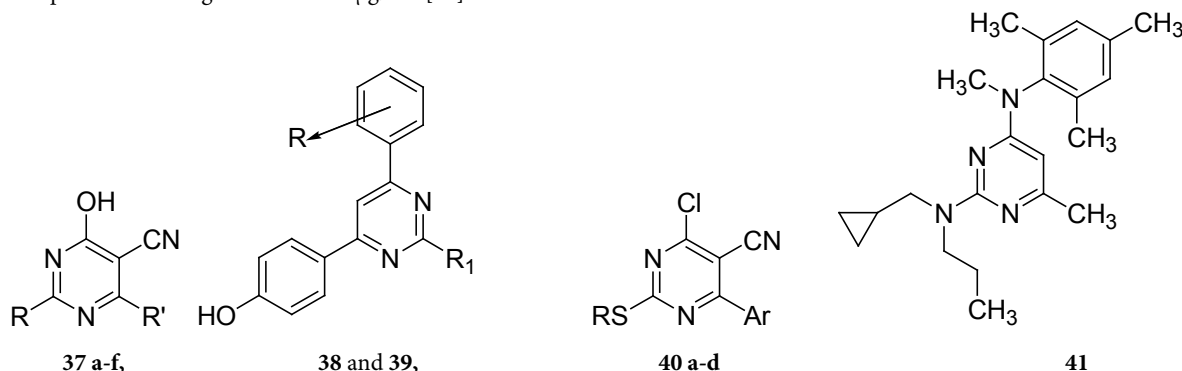
a: R=*N*-phenylpiperazine, R'=4-fluorobenzene

b: R=c-heptylamine, R'=4-methylbenzene

c: R=Octylamine, R'=3-pyridine

d: R=*n*-propylamine, R'=3-pyridine

e: R=4-(2- aminoethyl)morpholine, R'=3-pyridine

f: R=Octylamine, R'=4-methoxybenzene

a: R=n-C_3H_7, Ar=2-Theinyl

b: R=4-Cl $C_6H_4CH_2$, Ar=2-Theinyl

c: R=C_3H_7, Ar=3-F C_6H_4

d: R=n-C_3H_7, Ar=2-Furyl

In a different approach, novel imidazo [1, 2-*c*] pyrimidine derivatives, one compound (42) has shown promising MIC of 2 µg/mL against *Mtb* H37Rv on day 14 and 21, which is equal to that of standard amikacin [63]. A series of *N*-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxamides were evaluated for their anti-TB activity against *Mtb* H37Rv. Among all, two compounds with 2,3-dimethylphenyl (43a) and 3,4-dimethyl (43b) carbamoyl side chain, respectively, showed 65% and 63% inhibition [64].

42 **43a** **43b**

44 **45**
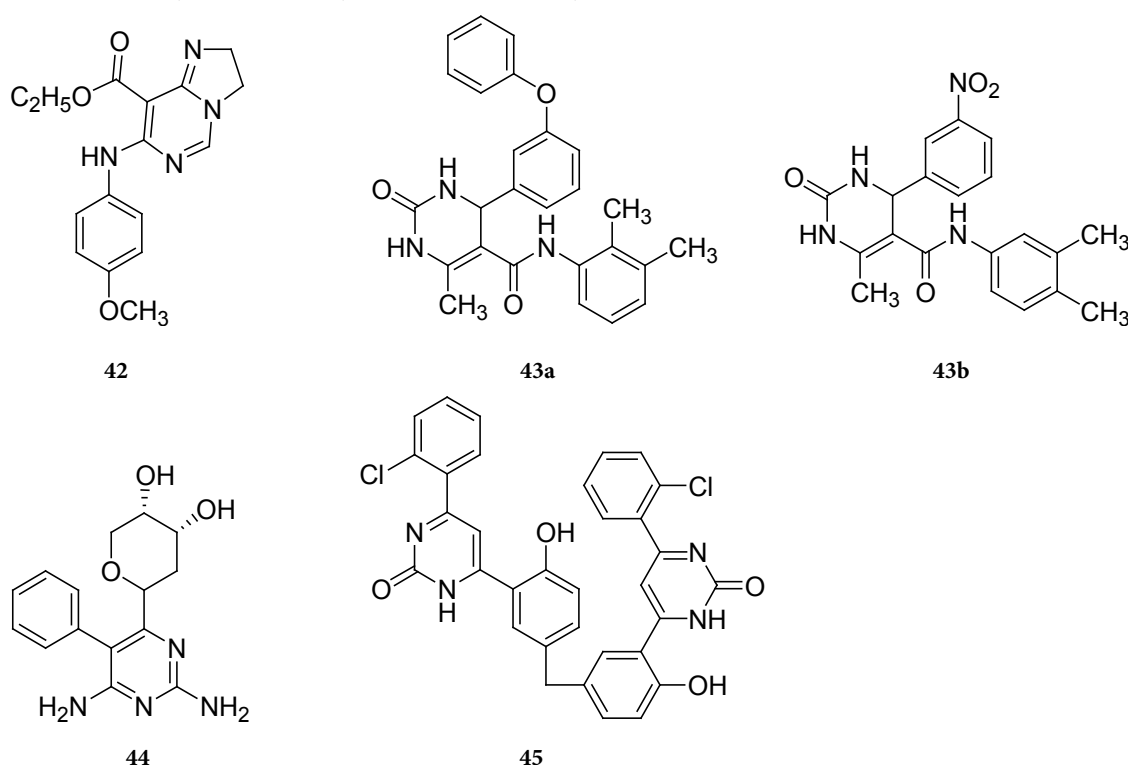
In this perception, a series of pyrimidine-2,4-diamines, these compounds also carried aryl substituents at the 5-position. Preliminary assay of the abilities of these compounds to inhibit the growth of TB5 *Saccharomyces cerevisiae* carrying the DHFR genes from *Mtb*, human and yeast indicated that 5-phenyl-6-((3R,4S)-3,4,5-trihydroxypentyl) pyrimidine-2,4-diamine (44) selectively inhibited *Mtb* DHFR and had little effect on the human or yeast enzymes [65]. Whereas, in a series of methylene-bis-pyrimidinones and methylene-bis-mercapto-pyrimidines, pyrimidinone derivative (45) shown best potency of 0.1 µg/mL while mercapto-pyrimidines showed moderate activity [66].

Syntheses of 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, transstyryl or aryl substituents at the 6th position and generally chlorine at the 2nd position. The most active compounds 46 showed a MIC of 3.13 and 0.78 μg/mL respectively, against *Mtb* H37Rv and also a selectivity index (SI) of 2.7 and 10.4 [67]. In continuation, a series of 6-arylpurines having a variety of substituents in the 9 position and were screened against *Mtb* H37Rv [68]. Eleven analogues of 9-sulphonated/sulphenylated 6-mercaptopurines [69] and out of them six exhibited MIC in the range of 0.39-0.78 μg/mL. The most potent compound (47) (MIC=0.39 μg/mL) also exhibited good activity against several DR strains of *Mtb*.

46 **47** **48** **49**
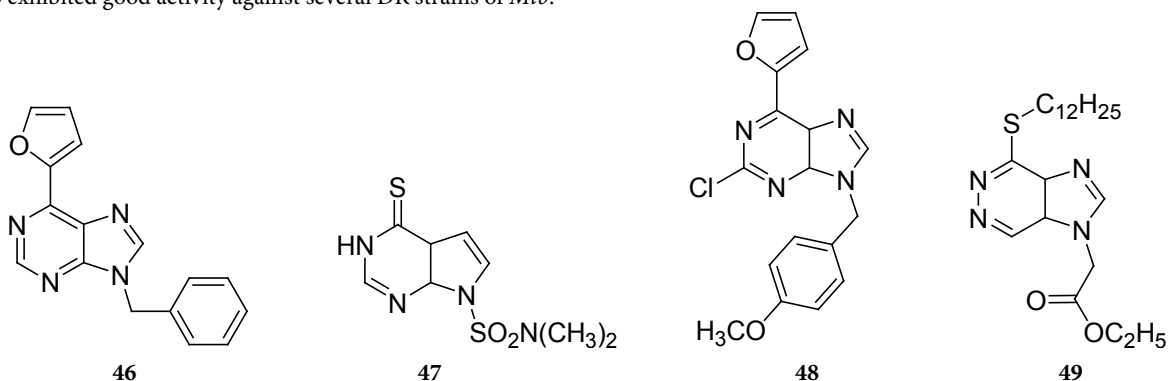
Inspired by the above results, a series of 9-aryl-, 9- arylsulfonyl- and 9-benzyl-6-(2-furyl)purines were screened for their anti-TB activity against *Mtb* H37Rv. Among all, 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (48) exhibited best potency of MIC 0.39 μg/mL and also low toxicity against mammalian cells and activity inside macrophages [70,71]. Purine derivatives 9-(ethylcarboxymethyl)-6-(dodecylthio)-9*H*-purine (49) were showed MIC value of 0.78 μg/mL [72]. In the analogues of agelasine E (50), one derivative (51) showed promising activity with MIC of 1.56 μg/mL against *Mtb* H37Rv [70,71]. The 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 (52, MIC=0.20 μg/mL) [73] of above all series. The purine derivatives and found a more potent molecule (53) of above all series, which has shown an IC90 of <0.20 μg/mL against *Mtb* H37Rv [74].

50 **51** **52** **53**
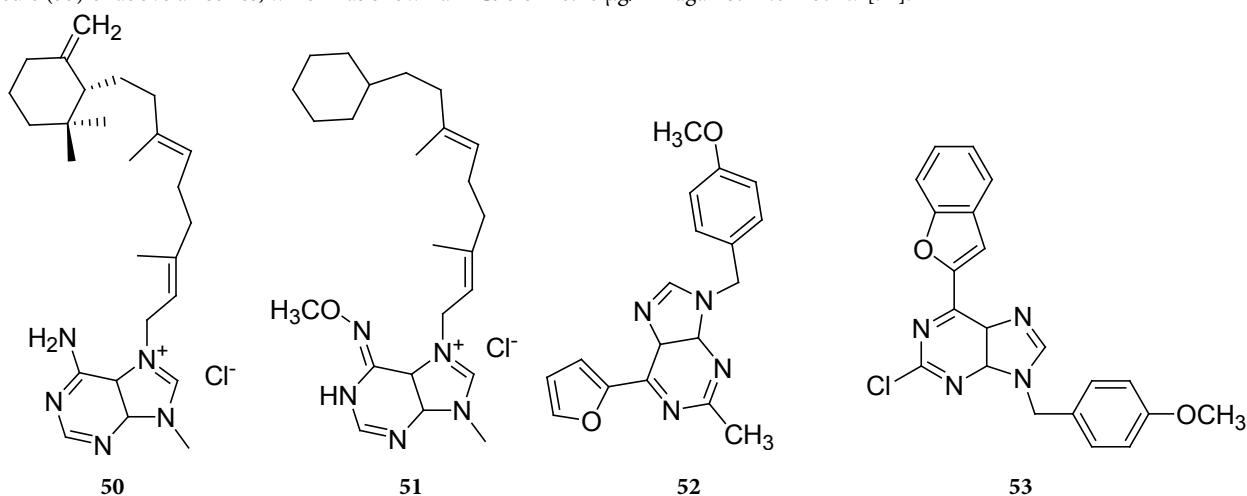
In search of new anti-TB purine type analogues, a series of 1-[1-(4-hydroxybutyl)-1,2,3-triazol-(4 and 5)-ylmethyl]-1*H* pyrazolo[3,4-d] pyrimidines and all of them were inactive but one compound (54) has shown MIC of 12.5 μg/mL [75]. In continuation, a series of di/trisubstituted pyrazolo[3,4-d]pyrimidines (55,56) were observed 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, is carried out. These compounds showed significant anti-TB activity (MICs down to ≤2 μg/mL). Among all, one compound (57) has shown MIC=0.5-1 μg/mL against *Mtb* H37Rv [76].

54 **55** **56:** X=O, CH$_2$; Y=H, CH$_2$OH R=H, CH$_3$, C$_2$H$_5$
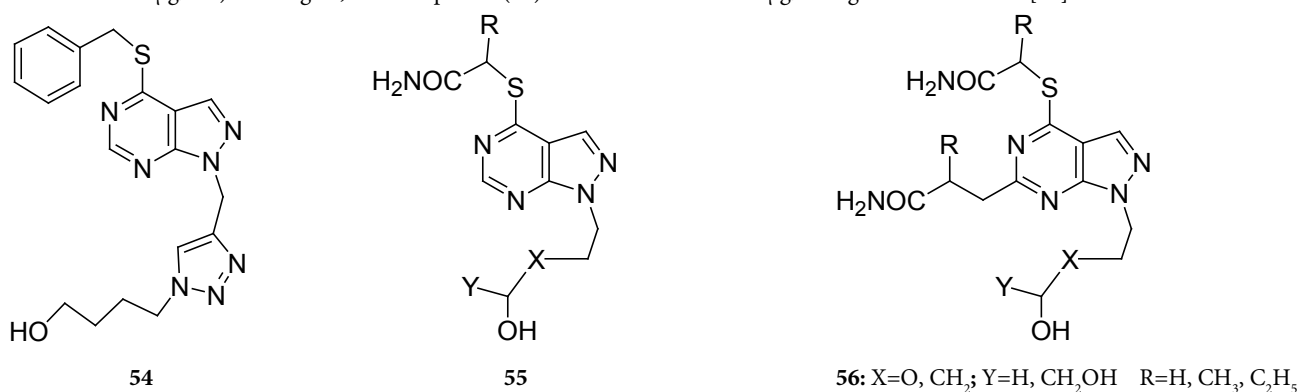
A homologous series of three pyrazolopyrimidine analogues (58a-c) of a hypothetical intermediate in the lumazine synthase-catalyzed reaction and evaluated as lumazine synthase inhibitors. All three compounds were extremely potent inhibitors (Inhibition constant: Ki=15-40 nM) of the lumazine synthases 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 [77]. In a series of Thieno[2,3-d]pyrimidin-4-one, two compounds (59a and 59b) have shown moderate potency of 5 μM/L against *Mtb* and *M. avium*, which is equal to that of rifampicin [78].
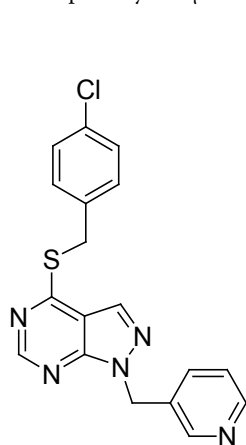
57

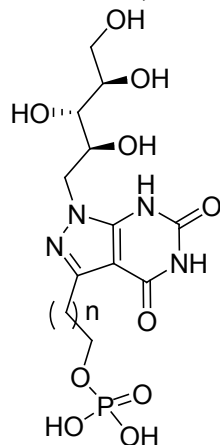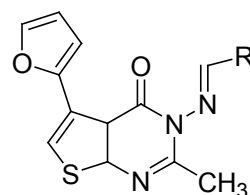**58a:** n=2; **58b:** n=3; **58c:** n=4

**59a:** R=2,4-dichlorophenyl

59b: R=2,4-difluorophenyl

Quinoline and Quinoxaline Derivatives

In this concern, 1-(5-isoquinolinesulfonyl)-2-methylpiperazine (60), a protein kinase inhibitor for its anti-TB profile and found to inhibit the growth of two different mycobacterial strains, the slow-growing *M. bovis* Bacille Calmette Guerin (BCG) and the fast-growing saprophyte *M. smegmatis* mc2 155, in a dose-dependent manner. While screening for the effect of kinase inhibitors on mycobacterial growth, millimolar concentrations of 60 induced a 40% decrease in the growth of *M. bovis* BCG. This 60-induced decrease in growth was shown to involve a 2-log fold decrease in the viable counts of *M. smegmatis* within a 48 h period and a 50% reduction in the number of BCG viable counts within a 10-day period [79].
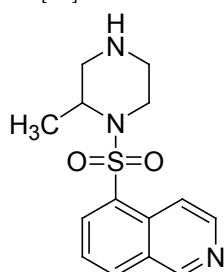
60
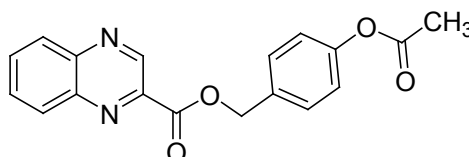
61
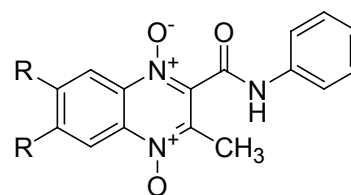
62a: R=Cl   **62b:** R=H

In the series of quinoxaline derivatives, lack of 1,4-dioxide showed reduction in the activity. Most active compound (61) showed MIC of 6.25 μg/mL against *Mtb* H37Rv and 0.5 μg/mL against *Mtb* H37Ra. Which prompted to continue the optimization of quinoxaline 1,4-dioxide [80], a series of quinoxaline-2-carboxamide 1,4-di-*N*-oxide derivatives were evaluated for their *in-vitro* anti-TB activity against *Mtb* H37Rv. Among all, compound 62a exhibited best MIC of 0.78 μM, has a solubility problem, while compound (62b) having MIC of 3.13 μM has a best selectivity index (SI=>40.06). A series of quinoxaline 1,4-di-*N*-oxide derivatives by varying the 2-position and found that 2-methylquinoxaline 1,4-di-*N*-oxides (63a and 63b) were most active of the series with a MIC of 0.39, 0.78 μM respectively and also have better selectivity index (8.46, 20.43). The compound 63b is also active against resistant strains of *Mtb* [81]. In another series, 2-benzyl-3-(methoxycarbonyl) quinoxaline 1,4-dioxide (64) has shown best potency above all, with a MIC=0.10 μg/mL and selectivity index SI=470 [82].
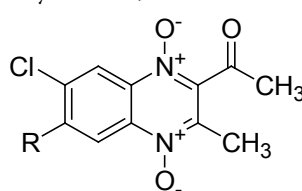
63a: R=Cl   **63b:** R=H
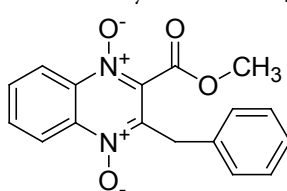
64
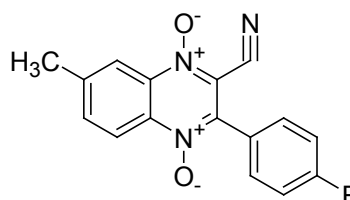
65

A new series of 3-phenylquinoxaline 1,4-di-*N*-oxide having selectivity against *Mtb* have been evaluated. Some compounds showed an MIC value less than 0.2 µg/mL, a value on the order of the MIC of rifampicin. Furthermore, 45% of the evaluated derivatives showed a good *in vitro* activity/toxicity ratio. The most active compound was 7-methyl-3-(4'-fluoro) phenyl quinoxaline-2-carbonitrile 1,4-di-*N*-oxide (65) (MIC <0.2 µg/mL and SI >500) [83]. In conclusion, the potency, low cytotoxicity and selectivity of these compounds make them valid lead compounds for new anti-TB agents. Of these, once derivatives (66) exhibited the preeminent MIC of 1.56 µg/mL against *Mtb* H37Rv (MTB) and also a good selectivity index (SI=>40.06). Further, compound 66 also proved to be a potent anti-TB agent with an EC90 value of 5.75 µg/ml [83].

Recently, A series of pyridobenzoxazine derivative, compound 67, which was a 2,8-diazabicyclo[4.3.0]nonanyl derivative with relatively low lipophilicity, showed the most potent anti-TB against mycobacterial species: the activity was 4- to 32-fold more potent than that of levofloxacin (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 [84]. While in the investigation of potency against *M. kansasii* LVFX showed MIC in the range of 0.12-0.25 µg/ml while Moxifloxacin showed the range of MIC=≤0.06-0.12 µg/mL [85]. These results prompted for optimization of other quinolone antibacterials to be investigated as anti-TB agents.
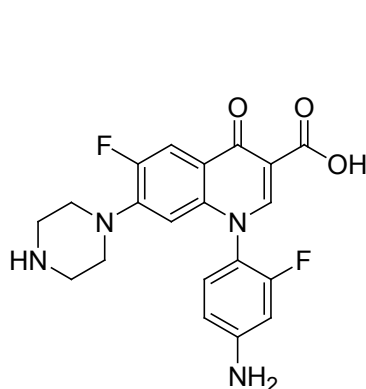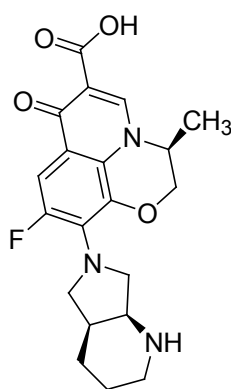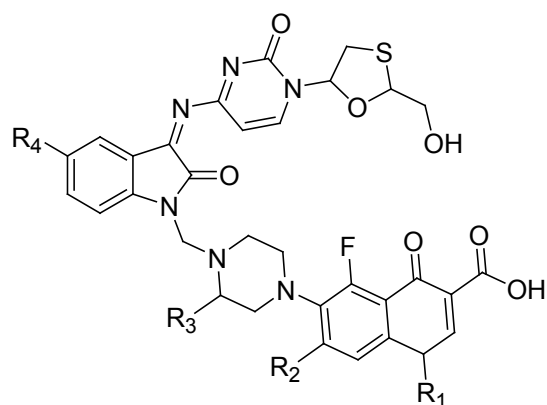
66   **67**   **68** R₁=ethyl, cyclopropyl

R₂=H, OCH₃; R₃=H, CH₃; R₄=H, Cl, F

Inspired with the above activity profile of quinolones, a series of Lamivudine prodrugs bearing fluoroquinoles (68) evaluated their efficacy against *Mtb* H37Rv. All the compounds exhibited an inhibition of 92-100% at a concentration of 6.25 µg/ml [86]. While in ciprofloxacin derivatives, one compound (69) 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 [87]. In continuation, Gatifloxacin derivatives and found a more potent compound (70) in comparison to compound 69. In the *in vivo* animal model 70 decreased the bacterial load in lung and spleen tissues with 3.62- and 3.76-log10 protections, respectively [88]. With this motivation, he was able to find out a most potent molecule (71) 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 [89]. Contrarily, 7-[4-(5-amino-1,3,4 thiadiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolonic derivatives (72a and 72b), showed moderate anti-TB activity at MIC of 10 µg/mL compared to INH standard [90]. The most active compound 73 showed MIC of 0.39 µg/mL against *Mtb* H37Rv [91].
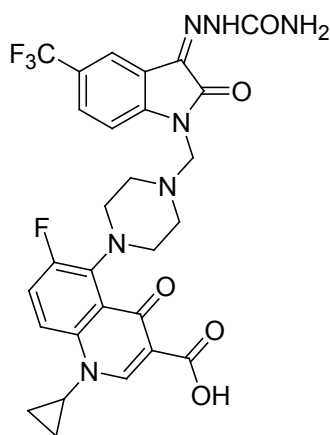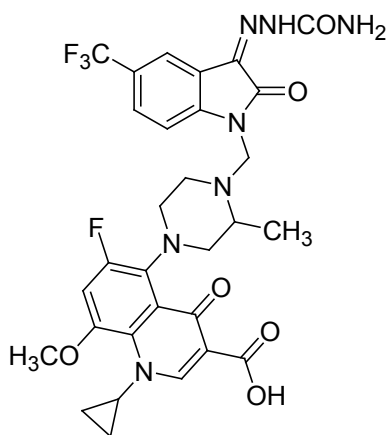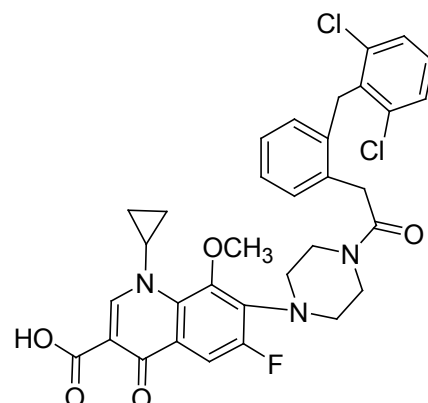
69   **70**   **71**
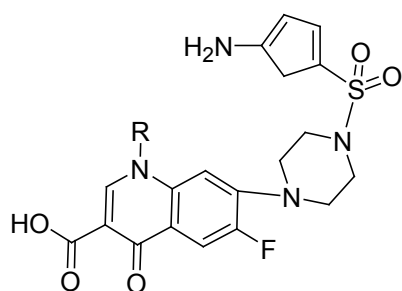
72a: R=ethyl   **72b:** R=cyclopropyl
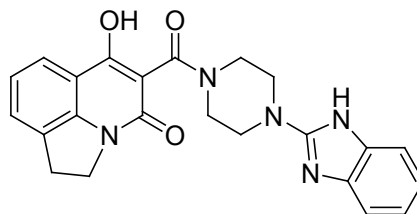
73

In another investigation, 6-nitroquinolone (74) was also found to be the most active compound *in-vitro* with MIC of 0.08 and 0.16 μM against MTB and MDR-TB, respectively. In the *in-vivo* animal model 74 decreased the bacterial load in lung and spleen tissues with 2.78 and 4.15-log 10 protections, respectively, at the dose of 50 mg/kg body weight [92-94].
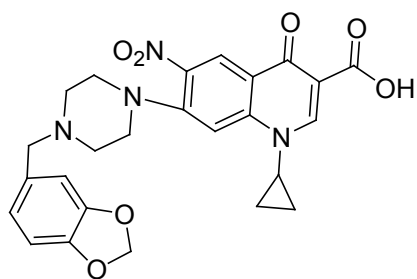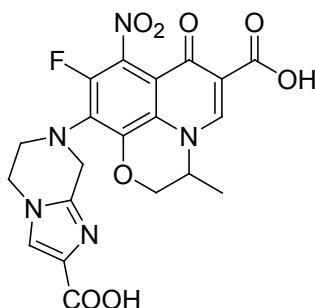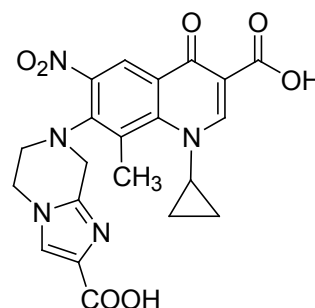
74   **75**   **76**

In the process of investigating novel quinolones as anti-TB agents, many derivatives of quinolones 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 75 exhibited MIC99 of 0.19 μM and 0.09 μM 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* animal model at a dose of 50 mg/kg body weight [95]. In an effort to increase anti-TB potency of quinolones, 1-(cyclo propyl/2,4-difluorophenyl/tert-butyl)-1,4-dihydro-8-methyl-6-nitro-4-oxo-7-(substituted-secondary-amino)quinoline-3-carboxylic acids. The most active compound (76) of the series showed MIC of 0.42 μM and 0.09 μM against MTB and MDR-TB respectively [92].
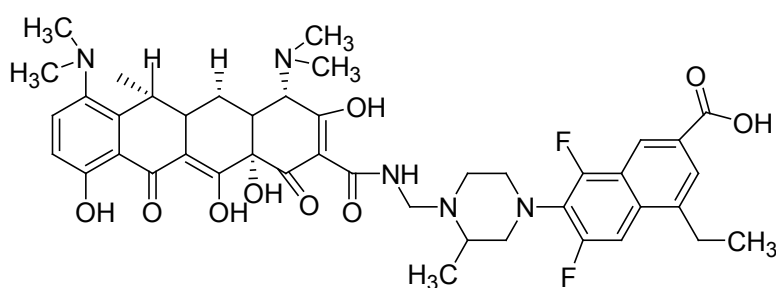
77

While in the series of Tetracycline incorporated with quinolones, compound **77** was found to be the most active against MTB with a MIC of 0.2 μg/mL and also nontoxic to the CEM cells until 200 μM [96]. Thus, developing quinolones as anti-TB agents is a worthy approach.

Compound 78 showed best potency of MIC 0.5 μg/mL against *Mtb* H37Rv and 0.5-2 μg/mL against resistant strains. However, the *in vivo* testing in a mouse model of TB infection did not show significant anti-TB activity, probably because of its poor bioavailability [97]. In continuation, 5-nitrofuran, 5-nitrothiophene and arylfuran coupled benzothiadiazines on evaluation, these compounds exhibited moderate anti-TB activity. The most active compound (79) displayed a MIC of 1 μg/mL against *Mtb* H37Rv [98]. A number of fifteen 2-amino-6-methyl-4-aryl-8-[(E)-arylmethylidene]-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-c]pyridine-3-carbonitriles evaluated for their anti-TB activity. Among all, compound 80 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 [99].

78   79   80

81   82

83a: n=3 84b: n=4   85a: R=-NH-C$_6$H$_4$-4F   85b: R=-NH-C$_6$H$_4$-3Br
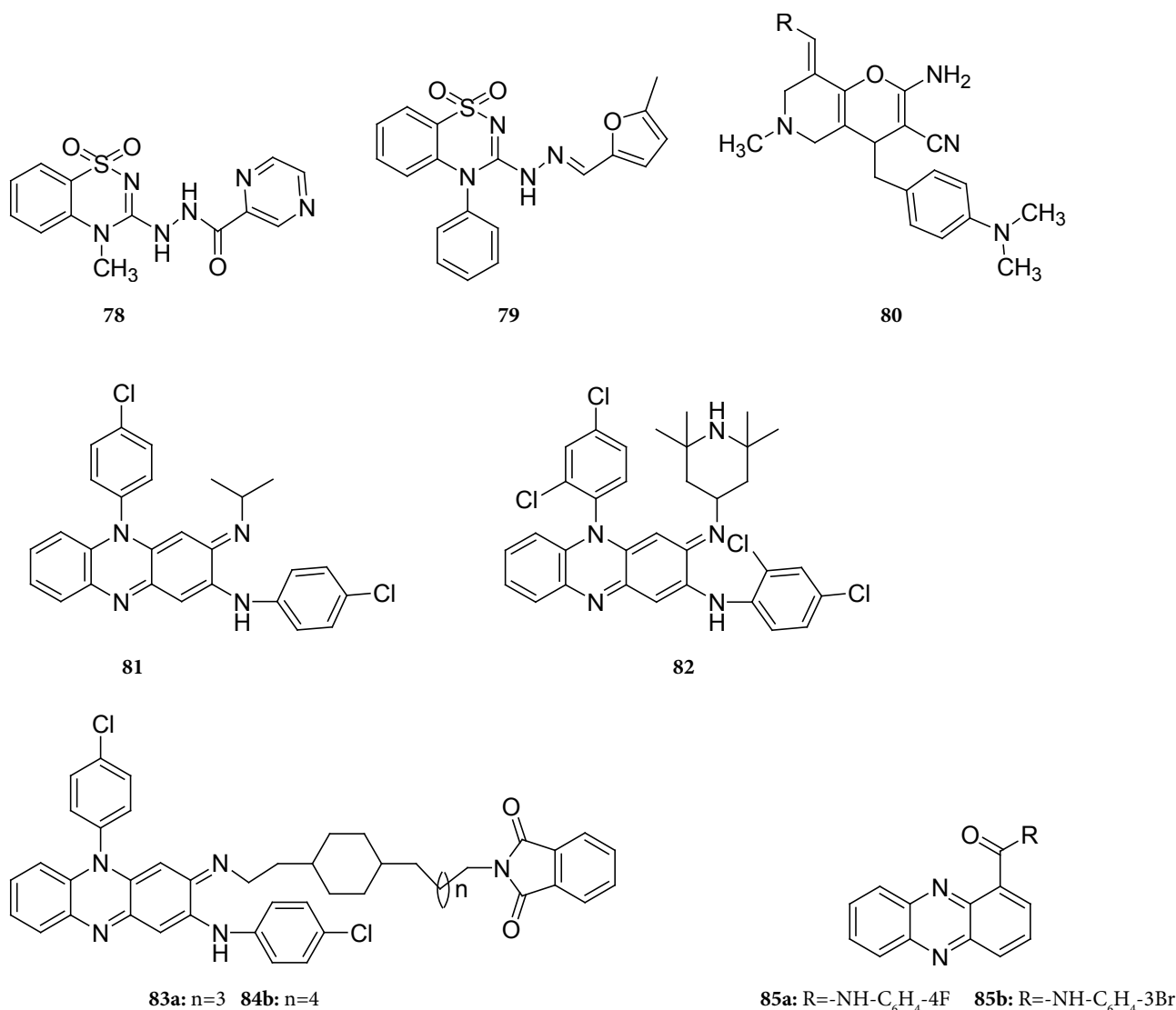
Clofazimine (81) is a fat-soluble riminophenazine dye used in combination with RIF and dapsone as multidrug therapy (MDT) for the treatment of leprosy. It has been used investigationally in combination with other anti-TB drugs to treat *M. avium* infections in AIDS patients and *M. avium* para-TB infection in Crohn's disease patients. On this basis and to minimize the side-effects and to improve the anti-TB activity of Clofazimine [100], 3-(2,4-dichloroanilino)-10-(2,4-dichlorophenyl)-2,10-dihydro-2-(2,2,6,6tetramethyl piperid-4-ylimino) phenazine (B4128) (82) posses a similar mode of action of Clofazimine [101]. With the same motivation, a series of phthalimido- and naphthalimido-linked phenazines were found two compounds (83a and 84b) with a potency of MIC 1 μg/mL against *Mtb* H37Rv. These compounds also exhibited potency against resistant strains of *Mycobacterium* [102]. Whereas in a series of phenazine carboxamides, compounds 85a and 85b showed excellent activity against *Mtb* H37Rv with a MIC of 0.19 μg/L and also against DR strains of *Mtb*. Most interestingly, this series was found to be nontoxic [103], validating them as future anti-TB drugs. While a macrolactone (86) derived from benzo[a]phenazine exhibited best potency against *Mtb* H37Rv with a MIC 0.62 μg/mL, which is better than that of RIF [104]. With the same motivation, a series of pyrrolo[l,2-a] quinoxaline-2- or -4-carboxylic acid hydrazides and one compound (241) showed an interesting activity at 6.25 μg/mL against *Mtb* H37Rv, with a 100 percentage inhibition [105].

86   87
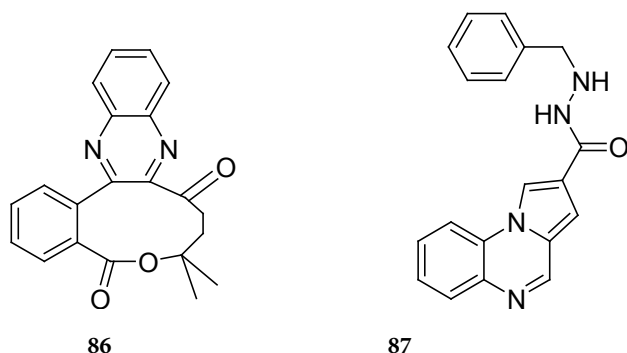
Future Prospectives

Development of new anti-TB drugs is the need to control TB. In the last fourty years no new anti-TB drug has been brought to the market. However, in recent years there is an enhanced activity in the research and development of new anti-TB drugs. Some compounds are presently in clinical development, while others are being investigated pre-clinically in an attempt to explore new anti-TB molecules. This review provides an overview of the pyridazines against *M. tuberclosis* [1-5,30,31].

The unremitting and steady rise in tuberculosis together with the emergence of resistance against traditional antitubercular drug regimen and the pathogenic synergy with HIV has put enormous pressure on public health systems to introduce new treatments. In drug resistant tuberculosis it is important to understand how the resistance emerges. Consequently, great efforts have been made in the area of Mtb genomics, proteomics and target identification via advanced technologies and therefore several welcome developments comes in the light having novel target with newer mode of action. In this concern, some new class of drugs antibiotics is under study and was approved for the treatment of MDR-TB. Remarkably, the mechanisms of action of these new arrivals are well-understood with new and novel target. Also, in the field of clinical 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 [106-109]. Further investment in developing fundamental genetic systems and more accurate models of human disease would significantly facilitate TB drug discovery efforts in the long term, in particular enabling robust validation of novel targets. However, all these possibilities therefore, there is a demand in continuing research in this direction to achieve the goal of eradicating *Mtb* from the world in coming years.

Disscussion

Tuberculosis (TB) is a chronic infectious disease caused by *Mtb*. 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 namely INH, RIF, pyrazinamide, streptomycin and ethambutol followed by second line antiTB drugs namely fluoroquinolones and one of the injectable aminoglycosides. Besides the traditional antitubercular drugs available commercially, several new heterocycles were synthesized in recent past. The new potential antitubercular agents have been classified according to their chemical entities. In an effort to developed new and more effective therapies, molecules that can also effective against MTB and MDR-TB. Natural products play a major role in drug discovery, as a unique source of original structures, which can provide models for future drug design. In the field of antitubercular agents, the lichen dibenzofuran derived secondary metabolite: usnic acid has been shown to display an interesting activity, but its weak potency did not permit its further development as an antimycobacterial drug [26,37,92,110].

In view of the persistent drug-resistant TB problem of currently used anti-TB agents, it is important that new anti-TB molecules or drugs should address different targets, as those of currently used drugs including the shortening of TB therapy. The unique structure of the mycobacterial cell wall makes it a useful target for drug development and studies can be directed to specific sites like cell wall biosynthetic pathways [111,112]. Although one possible long term solution to the problem is a better vaccine, in the short term, the major reliance will be on chemotherapy requiring the development of novel, effective and non-toxic anti-TB agents [113,114]. The identification of novel target sites will also be needed to circumvent the problems associated with the increasing occurrence of MDR-TB and XDR-TB strains. One of these attractive targets for the rational design of new anti-TB agents are the mycolic acids, the major components of the cell wall of *Mtb* [26,115,116].

Conclusion

The difficulty in managing TB includes the prolonged duration of the treatment, the emergence of drug resistance, and coinfection with HIV/AIDS. Tuberculosis control programme requires new drugs that act on novel drug targets to help in combating resistant forms of *Mtb* and reduce the treatment duration. The availability of the various chemotherapeutic agents, TB remains a leading killer worldwide. This is mainly due to the lack of new drugs, particularly for effective treatment against MDR-TB, XDR-TB, and patients co-infected with HIV/AIDS. Therefore, there is an urgent need for the development of new and effective anti-TB drugs particularly against resistant strains with lesser side-effects [117-119]. More importantly, the newly developed drugs are required to reduce the duration of treatment. The newer anti-TB compounds need to be developed on the understanding of the molecular mechanisms of drug action and drug resistance. Focusing on the existing anti-TB targets for drug development may be of limited value because chances of resistance by mutation in the protein target may render the drugs ineffective. Precisely, because of this observed drug–resistance by the bacterium, it is imperative to develop smart new drugs that inhibit novel targets that are structurally and functionally different from those currently known [120]. Medicinal chemists will be interested to working on pyridazine molecules due to their wide range of biological activities pertcularly agaist microbes. In view of above facts and inspired by the research going on pyridazine derivatives, particularly against *mycobacterium*. Different new pyridazines will be synthesized in the future for development of new anti-TB molecules.

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