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# Recent advances in the design and synthesis of Heterocycles as anti-tubercular agents

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## Abstract

Due to the unusual structure and chemical composition of the mycobacterial cell wall, effective TB treatment is difficult, which makes many antibiotics ineffective and hinders the entry of drugs. With approximately 33% of infection, tuberculosis is still the second most imperative infectious disease worldwide. The most important reason for this is drug resistant TB (MDR, XDR), persistent infection (latent TB) and synergism of TB with HIV; furthermore no any new chemical entity has come in picture in last 40 years. New data available from the recently sequenced genome of the mycobacterium and the application of methods of modern drug design promise to bring significant development in the fight against this disease. In present review we discussed brief introduction of tuberculosis followed

**Keywords:**

XDR-TB: Extensively drug-resistant tuberculosis, a form of TB caused by the most effective anti-TB drugs resistant bacteria.

G+C Gram-positive bacteria: guanine-cytosine content is the percentage of nitrogenous bases on DNA molecule.

Aminoglycoside: A molecule or a portion of a molecule composed of amino group and sugar group.

Macrolide antibiotics: A group of drugs (mainly antibiotics) whose activity is due to the presence of large macrocyclic lactone ring.

Serum half life: Calculated duration of time for a serum level of a compound to be reduced to half its initial value.

CFU: colony-forming unit, measure of viable bacterial or fungal numbers

NIAID: National Institute of Allergy and Infectious Diseases established The Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) in 1994.

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## Introduction

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* it is the worldôs second common cause of death from infectious diseases, after AIDS [1]. According to the World Health Organization (WHO), 2 million people die every year and at least 9 million are getting infected, which provides a pool for the development of new active form of tuberculosis [301]. The present chemotherapy DOTS (directly observed treatment short-course) for TB and DOTS-Plus (DOTS plus Second-line TB drugs) for MDR-TB has a cure rate of up to 95% if patient given compliance [2,3]. Despite the fact that it is treatable and preventable, the disease has been spreading at a steady rate over the past decade [4]. Furthermore, the resurgence in TB is alarming due to the development of pathogenic synergy with HIV. TB commonly has a much earlier onset in AIDS patients than other opportunistic pathogens and is oftentimes hard to detect by standard techniques such as a positive tuberculin skin test that relies on a potent immune reaction which is not possible in immunocompromised patients. The overall incidence of TB in HIV positive patients is 50 times that of the rate for HIV negative individuals [5-7]. In addition, the emergence of multi drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) as a consequence of lengthy treatment, makes patient compliance difficult. The term MDR-TB is used to describe strains that are resistant to two or more of the five first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin) [8,9]. MDR-TB takes longer to treat with second-line drugs (DOT-Plus), which are more expensive and have more side-effects. XDR-TB will develop when these second-line drugs are mismanaged and therefore also become ineffective [302]. This development of drug resistance in the population has increased concern that TB may once again become an incurable disease. Especially, in developing countries, the prevalence of XDR-TB is increasing as a consequence of poor financial resources [10] and thus

provides a strong motivation for the development of effective and affordable antitubercular agents.

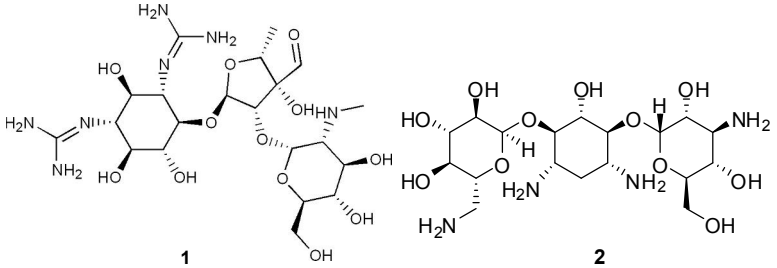
## Present chemoptherapy of Tuberculosis

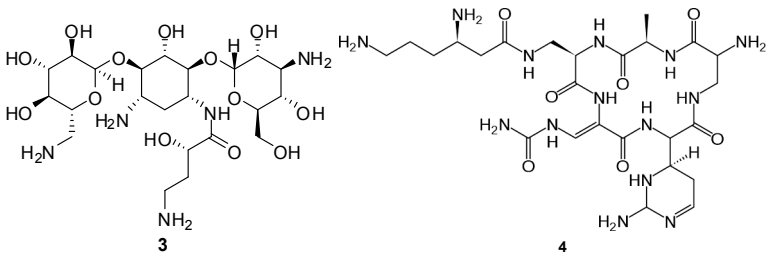
Chemotherapy of TB started in 1940s. In 1943, anti-TB research resulted in discovery of the active anti-TB agent, streptomycin. From that time, a number of agents have been discovered and introduced in anti-TB chemotherapy, including *para*-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cycloserine (1955), ethionamide (1956), rifampin (1963) and ethambutol (1962). The majority of these drugs were discovered through broad screening and very little optimization was undertaken with less regard to the targets of drug action, since the biochemical tools for these studies were not as sophisticated as they are now. The lack of understanding of drug action was compounded by a profound ignorance of the biochemistry of the *M. tuberculosis* bacillus [303,11]. The current short-course TB therapy used to treat drug-susceptible MTB consists of 2 monthsô treatment with four so-called first-line drugs including rifampin (RIF), isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB), followed by 4 monthsô treatment with RIF and INH. Infection by MDR-TB strains requires treatment with second-line drugs such as kanamycin, amikacin, capreomycin, *p*-aminosalicylate (PAS), fluoroquinolones (levofloxacin, gatifloxacin and moxifloxacin), ethionamide (ETH), and cycloserine where treatments often extend for as long 2 years [12-14].

### Aminoglycosides

Streptomycin (**1**) an aminoglycoside, was the first really effective drug against TB isolated from *Streptomyces griseus* and consists of three structural components, streptidine, streptose, and *N*-methyl-L- glucosamine. It is poorly absorbed from the gastrointestinal tract, hence administered intramuscularly and very occasionally by intrathecal route. It penetrates the inner membrane of *M. tuberculosis* and binds to the 30S subunit of the ribosome. Due to many toxic manifestations on the peripheral and central nervous system at higher doses and hypersensitivity reactions, it is not a drug of popular choice.

Aminoglycosides, kanamycin (**2**), amikacin (**3**) and capreomycin (**4**) are complex organic molecules derived from the G+C Gram-positive bacteria *Streptomyces* and used as second-line anti-TB drugs. They work by binding to the bacterial 30S ribosomal subunit, causing misreading of mRNA and leave the bacterium unable to synthesize proteins vital to its growth. These drugs have adverse side effects, such as kidney damage and hearing loss [12-14].





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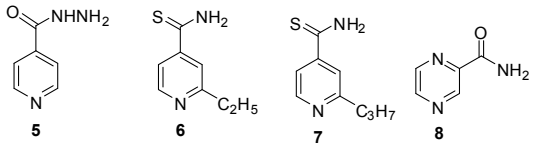
**Isoniazid, Ethionamide, Prothionamide, Pyrazinamide and Isoxyl.**

Isoniazid (INH) (**5**), a derivative of nicotinic acid is a potent antitubercular agent. The minimal inhibitory concentration (MIC) is of the order of 0.05 ε g/mL. It acts on growing cells and not on resting cells. INH is believed to kill mycobacteria by inhibiting the biosynthesis of mycolic acids, critical component of the cell wall.



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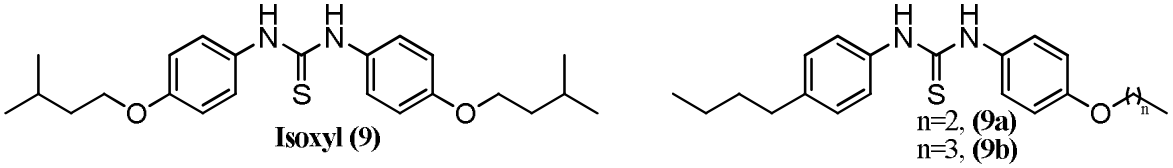
2-Ethyl thioisonicotinamide (ethionamide) (**6**) and prothionamide (**7**) are active at a minimal inhibition concentration of 0.5-2.5 ε g/mL. Recent studies indicate that ethionamide also disturbs mycolic acid synthesis in strains resistant to isoniazid, streptomycin and p-amino salicylic acid. Pyrazinamide (**8**) is a synthetic pyrazine analog of nicotinamide. It is active at a MIC of 6-60 ε g/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. [12-14].

Isoxyl/thiocarlide **(9)** is a thiocarboxyl-containing antitubercular drug and has been used clinically in past. Recently it has been observed that compound has cross resistance with ethionamide and thiacetazone. The biological targets of **(9)** was confirmed as DesA3, a D9-desaturase responsible for the synthesis of oleic acid from stearoyl-CoA

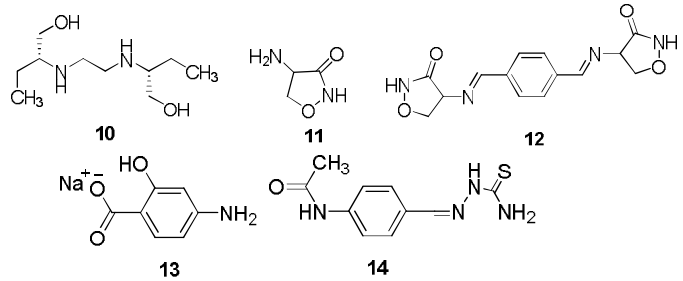



Bhowruth et al synthesized symmetrical and unsymmetrical analogues of the isoxyl and screened them against *Mycobacterium tuberculosis* H37Rv and *Mycobacterium bovis* BCG. In particular, compounds **(9a)** (p-n-butylphenyl)-3-(4-propoxy-phenyl) thiourea and **(9b)** 1-(p-n-butylphenyl)-3-(4-n-butoxy-phenyl) thiourea showed an approximate 10-fold increase in in vitro potency compared to isoxyl [15]. Such analogues of isoxyl may give a new impetus for the development new prototypes as antitubercular agents.

**Ethambutol, Cycloserine, Terizidone, *p*-aminosalicylic acid and Thiacetazone**

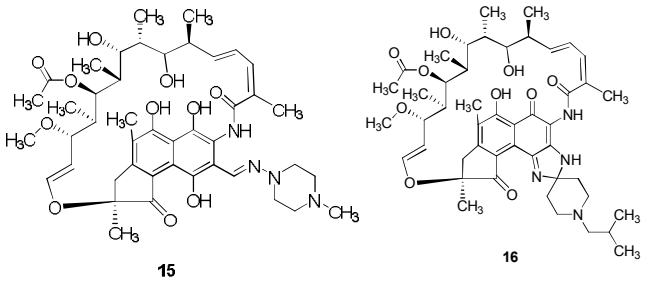
Dextro isomer of *N,N*ô-bis-(1-hydroxy-2-butyl)ethylenediamine (Ethambutol) **(10)** is one out of the four main drugs for treatment of tuberculosis. The meso isomer is less active whereas the levo isomer is almost inactive. It is also active in organisms resistant to streptomycin and isoniazid, but is always used in combination. It is active at a dose of 0.95-7.5 ε g/mL. Resistance to ethambutol develops slowly.

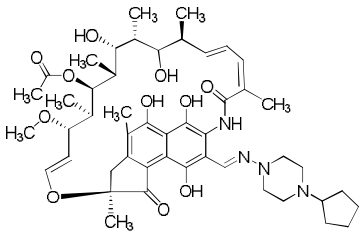
D-Cycloserine (D-4-Amino-3-isoxazolidone) (**11**) is a structural analog of the amino acid D-serine. It is active at a concentration of 5-20 ε g/mL and is destroyed by acidic and neutral pH. Strains resistant to other antimycobacterial drugs have the same sensitivity to cycloserine. It blocks the synthesis of peptidoglycan, an important component of the cell wall, by inhibiting the enzymes D-alanine racemase and D-alaninyl alanine synthetase. Whereas a bicycloserine derivatives (terizidone, **12**), *p*-aminosalicylic acid (**13**) and thioacetzone (**14**) are least tolerable second-line antitubercular drugs [12-14].




**Rifamycins: Rifampicin, Rifabutin and Rifapentine**

The rifamycin and semi-synthetic rifamycins belong to a novel class of macrolide antibiotics that feature a propionate-derived chain bridging a tricyclic naphthalene core. They inhibit prokaryotic DNA-dependent RNA polymerase, an enzyme necessary for RNA synthesis. Inhibition is due to the formation of a stable non-covalent complex between the antibiotic and the enzyme. Rifamycins cause inhibition of bacterial RNA synthesis and have no effect on mammalian enzymes. The mechanism of the action of the rifampicin/rifampin (**15**) is similar to that of rifamycin. Rifabutin (**16**) has activity spectrum similar to rifampicin, but appears to possess incomplete cross-resistance with rifampicin *in vitro*. Rifapentine (**17**) is an analogue of rifampicin in which a cyclopentyl group substitutes for a methyl group on the piperazine ring. It is more lipophilic and has a serum half life about five times longer than rifampicin [12-14].





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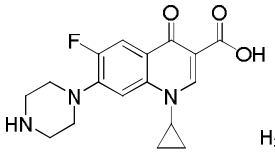
To avoid rapid development of resistance, RMP is recommended in combination with other first-line agents either isoniazid or ethambutol. RMP is effective against *M. tuberculosis* with MIC ranging from 0.1 to 0.2 µg/mL. RMP was modified with several analogs and among them one compound KRM-1648, was found to be more potent than Rifampicin[12-14].

### Fluoroquinolones

Fluoroquinolones (FQ) such as ciprofloxacin (**18**), ofloxacin (**19**) and moxifloxacin (MXF, **20**) are second line drugs used in combination with first line drugs to treat MDR-TB. MIC of these fluoroquinolones range from 0.12 to 2 εg/mL. Levofloxacin (**21**), 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, **22**) and MXF are new fluoroquinolone DNA gyrase inhibitors that offer advantages over ofloxacin and ciprofloxacin. These new FQs **20** and **22**, 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 [12-14].



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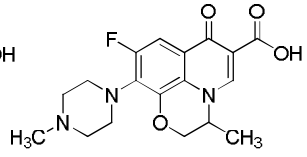

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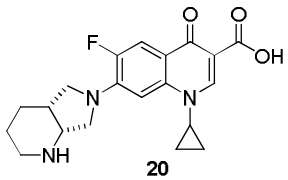

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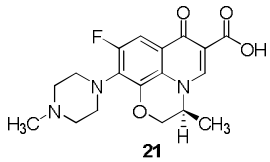

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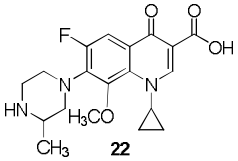

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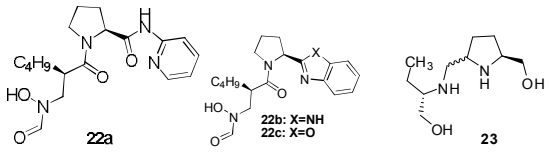
## New Potential Anti-Tubercular Agents

The new potential antitubercular agents are classified on the basis of their chemical entities.

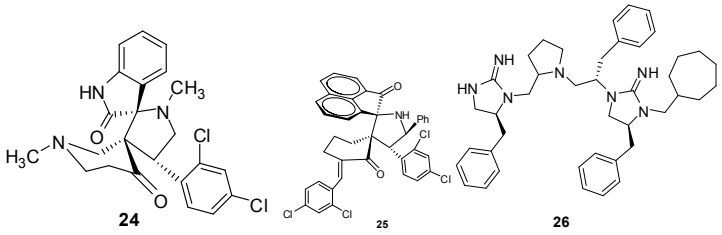
### Pyrrole and Pyrrolidine Derivatives

Peptide deformylase (PDF) is a key enzyme, that deformylates the *N*-formylmethionine of newly synthesized polypeptides, a key step in protein maturation. It is also identified as a validating target after the identification of LBK-611 as an antimycobacterial agent. In this perception, a series of LBK-611 (**22a**) derivatives were synthesized by introducing benzimidazoles and benzoxazoles moieties at 2-position and peptides at N-1 position. Among all, Compounds **22b** and **22c** have shown more potent $IC_{50}$ of 0.010, 0.013 µM

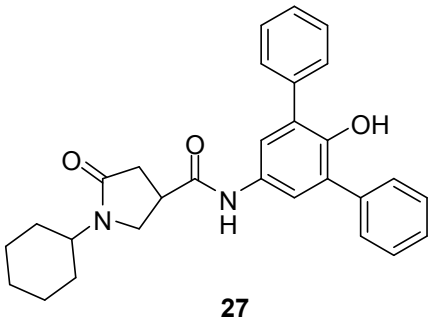
respectively against MTB PDF enzyme and MIC of 0.1 µg/mL and 0.15 µg/mL against MTB H37Rv in comparison to LBK-611. These compounds also showed promising activity of MIC 0.03, 0.06 µg/mL, respectively against MTB MDR strain [16]. In a different approach, three conformationally constrained ethambutol (**10**) analogues having basic skeleton of pyrrolidine and bipyrrolidine were synthesized. Among three, one compound **23** with semi-rigidified EMB skeleton being the part of pyrrolidine with *cis* configuration has shown modest growth inhibition at concentrations of over 60 µg/mL, which is 30 fold less than EMB, while bypyrrolidine and *trans*-semi-rigidified EMB skeleton was found to be inactive against *M. tuberculosis* [17].



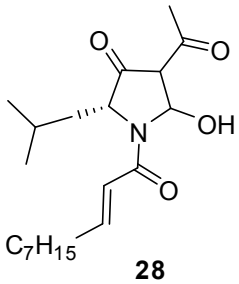

In search of novel heterocycles with antitubercular activity, Perumal group synthesized two different series of spiro-compounds. In the first series, 1-methyl-4-(2,4-dichlorophenyl)pyrrolo(spiro[2.3ò]oxindole)spiro[3.3ô]-1ô-methylpiperidin-4ô-one (**24**) has shown best activity with a MIC of 1.76 and 0.88 ε M against MTB and MDR-TB respectively [18]. While in an another series, compound **25** showed increased potency with MIC value of 0.40 ε g/mL against MTB and was 4 and 15.6 times more potent than ethambutol and pyrazinamide, respectively [19]. In a different approach, Nefzi et al. synthesized pyrrolidine containing bis-heterocyclic libraries. Among all, bis-cyclic guanidine derivative (**26**) showed preeminent potency with a MIC of 3.9 ε g/mL against MTB and found to be less toxic with an $IC_{50}$ of 39.48 ε g/mL [20].



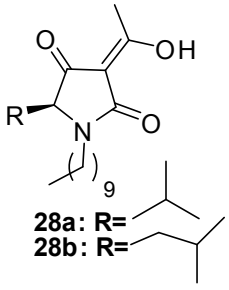

InhA, the enoyl acyl carrier protein reductase (ENR) from *M. tuberculosis*, is one of the key enzymes involved in the mycobacterial fatty acid elongation cycle and has been validated as an effective antitubercular target. A series of N-substituted-2-pyrrolidine-3- carboxamides were synthesized as potent InhA inhibitors. Among all, the racemic compound **27** has shown inhibition of $IC_{50}$ 140 nM, while one of its enantiomeric excess molecules showed inhibition of $IC_{50}$ 62 nM against InhA of *M. tuberculosis* H37Rv [21]. In order to expand the structure-activity relationship of tetramic acid (N-substituted-2,4-pyrrolidone) molecules with structural similarity to the antibiotic reutericyclin (**28**) were synthesized and screened for their antibacterial activity. Many of them have shown promising potency against Gram-positive bacteria and two compounds **28a** and **28b** showed moderate activity of MIC 12.5 ε g/mL against *M. tuberculosis* H37Rv [22].




**27**



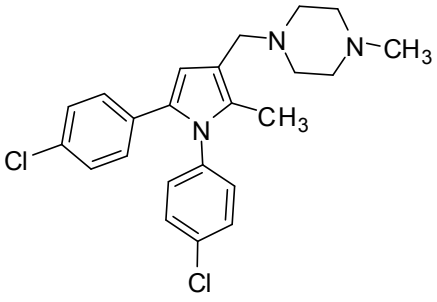

**28**




**28a: R=**
**28b: R=**

A pyrrole derivative BM 212 **(29),** which arose the interest with its very good *in vitro* activity of MIC 0.7 ε g/mL against *M. tuberculosis*, has been studied for its SAR thoroughly**.** Prompted by these results, a series was developed by the variation of N-1, C-3 and C-5 positions. Among all, compound **30** showed potent inhibition of MIC 0.4 ε g/mL against *M. tuberculosis* and also the protection index (PI) of 20 which is more than that of BM 212 (PI: 5.6) [23]. While compounds **31** [24] and **32** [25] showed comparable MIC of 1 ε g/mL with an improved PI of 32. Surprisingly, substitution of 4-isopropylbenzene at C-5 position and 4-fluorobenzene at N-1 position (**33**) has increased the potency with a MIC of 0.25 ε g/mL and enhancement in PI value of 128, which is equal to that of isoniazid (INH) [26]. While by replacing 4-isopropylbenzene with 4-methylbenzene (**34**) [27] at C-5 position of compound **33** showed decreased potency of MIC 0.4 ε g/mL but lowered the toxicity. This made the molecule a promising lead with a protection index of 160, which is greater than the antitubercular drugs (isoniazid, streptomycin). On the basis of above activity, the same group enlarged the SAR by 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 terms of activity in previous 2-methyl derivatives. Among them, 1-(4-fluorophenyl)-2-ethyl-3-(thiomorpholin-4-yl)methyl-5-(4-methylphenyl)-1*H*-pyrrole (**35**) proved to be particularly active, with a MIC 0.25 ε g/mL and a protection index of > 512, which is better than or comparable to those of reference compounds [28]. All the above compounds (**30-35**) were also active against resistant *M. tuberculosis* strains.

In a very similar series of pyrrole derivatives obtained by the variation of N-1, C-2, C-3 and C-4 positions, compound **36** was found to be most potent with a MIC of 0.5 ε g/mL [29]. 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 (**37)** has shown moderate activity with a MIC 16 ε g/mL [30].



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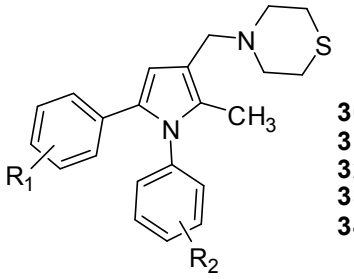
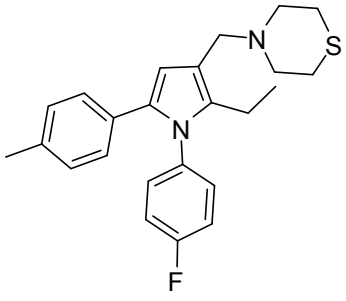


**30: $R_1$=H, $R_2$=4-F**
**31: $R_1$=H, $R_2$=H**
**32: $R_1$=2-F, $R_2$=2-F**
**33: $R_1$=*i*-$C_3H_7$, $R_2$=4-F**
**34: $R_1$=4-$CH_3$, $R_2$=4-F**



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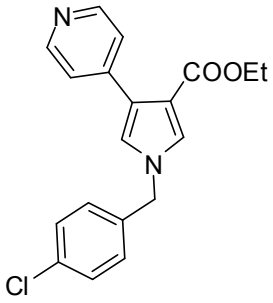

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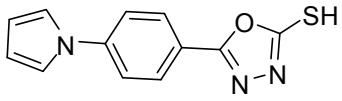
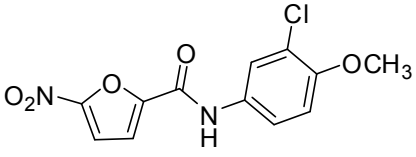


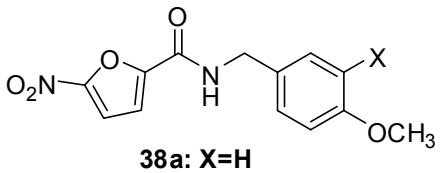
**37**

**Furan and Thiophene derivatives**

Galactofuranose is an essential component of the mycobacterial cell wall and not found in human; UDP-galactofuranose is biosynthesized from UDP-galactopyranose using the enzyme UDP-galactose mutase (Glf). In the course of the screening of different molecules, nitrofuranylamide (**38**) was discovered as an inhibitor of Glf with an $IC_{50}$ 12 µg/mL and also showed good activity against whole cells with a MIC of 1.6 µg/mL. With this interest, Tangallapally et al. synthesized a series of 5-nitrofuranylamides (NFAs), 5-sulfinylfuranylamides and 5-sulfonylfuranylamides. Among all, compound **38a** has shown great potency against *M. tuberculosis* with MIC of 0.1 µg/mL and also shown best selectivity index (SI) of 163.6, even though it is a moderate inhibitor of the enzyme Glf with an $IC_{50}$ 115 µM/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 (**38b**), led to drop off in the antitubercular activity of MIC 0.2 µg/mL but increased the inhibition against Glf with an $IC_{50}$ 23 µM/mL. Compound **38a** also shown in vivo potency by reducing CFU in mice lungs by 1.5 log with the control, at a dose of 300mg/kg which is equal to levofloxacin administered at 100 mg/kg [31].



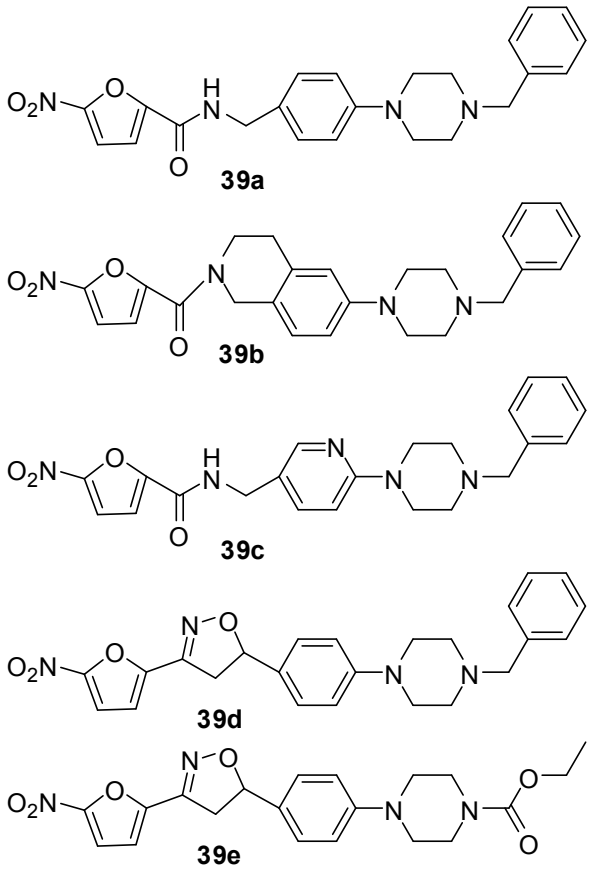
**38**



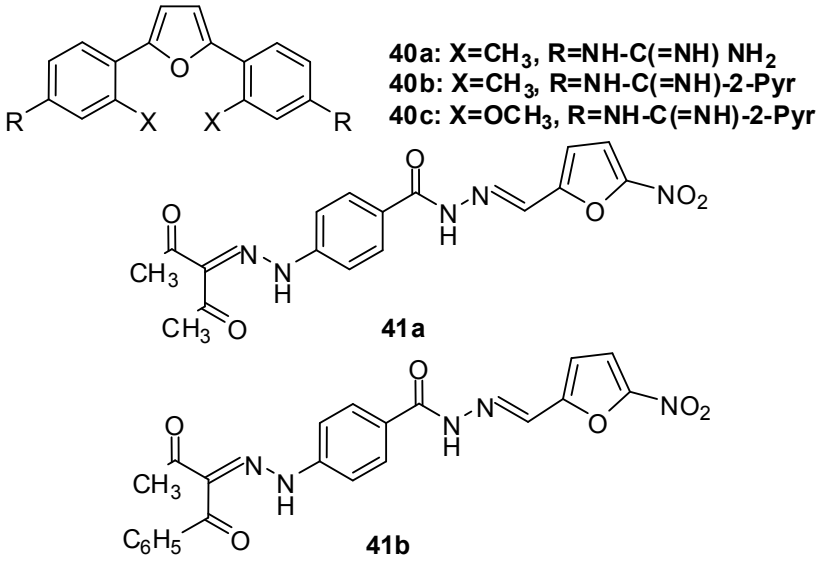
**38a: X=H**
**38b: X=$OCH_3$**

With the same interest, Hurdle et al. investigated [32] the efficacy of antitubercular NFAs (**39a-e**) established by Tangallapally et al. against TB complex and

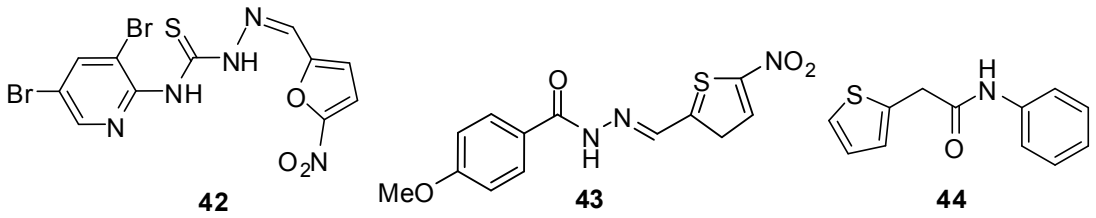
other clinically relevant non-mycobacterial species and found that the NFAs were significantly active against *M. tuberculosis* complex [33-35]. Compound **39a** showed preeminent inhibition of MIC 0.006 mg/L against *M. tuberculosis* UT30 (streptomycin-resistant at 4 mg/L). Whereas, compound **39b** showed same potency against *M. tuberculosis* UT18 and *M. bovis* BCG. Compound **39d** 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 *M. tuberculosis* UT15 and UT18. Similarly, Compound **39e** showed the same potency against *M. tuberculosis* UT18 but shown increased potency of MIC of 0.0004 mg/L against *M. tuberculosis* UT15. Compound **39c** 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 *M. tuberculosis* H37Rv.




A series of dicationic 2,5-bis(4-guanidinophenyl)furans, 2,5-bis[4-(alkyl/arylimino) aminophenyl]furans were synthesized and evaluated against *M. tuberculosis*. The studies showed that 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. Of these three novel dicationic compounds **40a**, **40b** and **40c** exhibited MIC Ò1 ε g/mL [36].

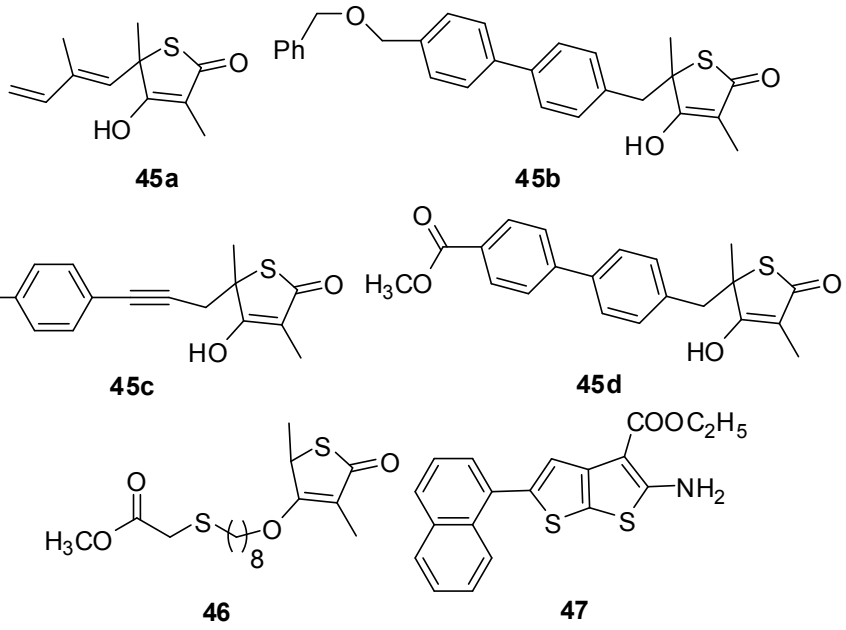



Rollas group synthesized a series of 2,3,4 pentanetrione 3-[4-[{(5 nitro-/2furyl/ pyridyl substituted phenyl) methylene}hydrazino carbonyl} phenyl] hydrazones. Of these compounds **41a** was the most promising derivative showing an inhibition of 95% and a MIC and ED value of 3.13 ε g/mL and 0.32 ε g/mL respectively. In a further effort to improve the activity same group synthesized a series with very minor modifications but the activity was decreased. The best activity was shown by **41b** having 95% inhibition and a MIC of 6.25ε g/mL [37]. Sriram et al. synthesized a number of eighteen hybrid, 5-nitrofuran-2-yl derivatives obtained by reacting 5-nitro-2-furfural with various (sub)-phenyl/pyridyl thiosemicarbazide using microwave irradiation. Of these hybrids, pyridyl derivative (**42**) has shown best potency with a MIC 0.22 ε M and was 3 times more active than standard INH and equally active as RIF in log-phase culture of *Mycobacterium tuberculosis* H37Rv. In starved *M. tuberculosis* H37Rv, it also inhibited with a MIC of 13.9 ε M and was found to be 50 times more active than INH and slightly more active than RIF [38].




A series of substituted benzoic acid-[(5-nitro-thiophen-2-yl)-methylene]-hydrazides were synthesized and tested against *M. tuberculosis*. The most active compound of the series was **(43)** having a MIC of 2 ε g/mL. Topliss approach indicated that more potent compound will be obtained with derivatives having substituents that show electron donor capacity (ů < 0) and hydrophilic character [39]. While in the series

of N-(aryl)-2-thiophen-2-ylacetamides, compound **44** showed MIC of 25 ε g/mL and also nontoxic against murine macrophage cells even at the concentration of 100 ε g/mL [40].



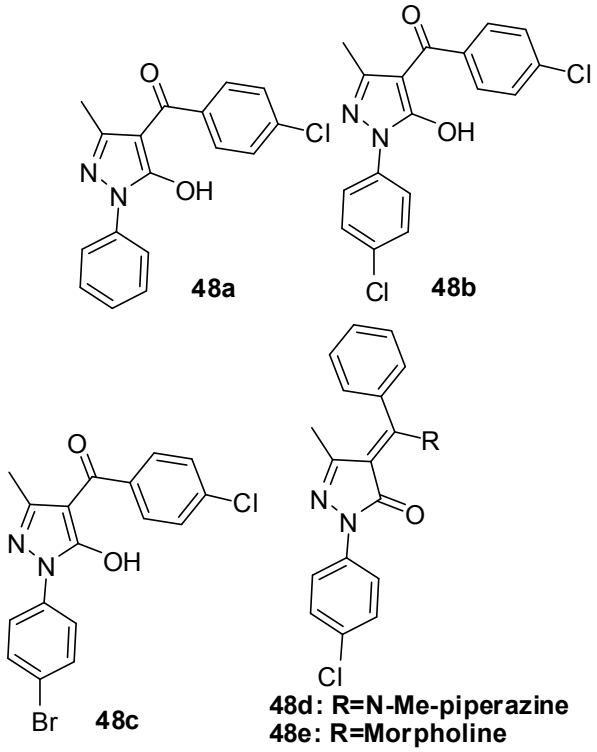

**45a** **45b** **45c** **45d** **46** **47**

Thiolactomycin (TLM) (**45a**) is a thiolactone antibiotic isolated from a soil *Nocardia* spp. TLM exhibits potent in vivo activity against many pathogenic bacteria, including Gram-negative and Gram-positive bacteria and *M. tuberculosis*. It inhibits *M. tuberculosis* FAS-II through inhibition of ß-ketoacyl-ACP synthase condensing enzymes, mtFabH and KasA, in vitro and in vivo leading to inhibition of cell wall mycolic acid biosynthesis and to cell death. In this concept, Besra group, initially synthesized TLM analogues with biphenyl-based 5-substituents and found to have excellent in vitro inhibitory activity against the recombinant *Mycobacterium tuberculosis* ß-ketoacyl-ACP synthase mtFabH condensing enzyme. In particular, 5-(4ô-benzyloxy-biphen-4-ylmethyl)-4-hydroxy-3,5-dimethyl-5*H*-thiophen-2-one (**45b**) exhibited approximately a 4-fold ($IC_{50}$=17 µM) increased potency compared to TLM [41]. Whereas in a series of TLM with acetylene-based side chains, 5-[3-(4-acetyl-phenyl)-prop-2-ynyl]-4-hydroxy-3,5-dimethyl-5*H*-thiophen-2-one (**45c**) exhibited more than an 18-fold ($IC_{50}$=4 µM) increased potency, compared to thiolactomycin against same enzyme [42]. While in another series, 5-(4-methoxycarbonyl-biphenyl-4-ylmethyl)-4-hydroxy-3,5-dimethyl-5*H*-thiophen-2-one (**45d**) gave an $IC_{50}$ value of 3 µM compared to the parent drug TLM (75 µM) against mtFabH [43]. The biological analysis of this library reaffirms the requirement for a linear $\pi$-rich system containing hydrogen bond accepting substituents attached to the *para*-position of the C5 biphenyl analogue to generate compounds with enhanced activity. In the same direction, Kamal et al. synthesized new TLM series, where he succeeded in identifying most potent thiolactomycin derivative (**46**) with a MIC of 1 µg/mL against *M. tuberculosis* H37Rv. This derivative also exhibited potency against resistant strains of mycobacteria [44]. In a different approach, Perumal et al. synthesized a series of novel 2-amino-5-arylthieno[2,3-*b*]thiophenes and evaluated for their in vitro activity against *Mycobacterium tuberculosis* H37Rv (MTB) and multi-drug resistant *M. tuberculosis*

(MDR-TB). Among all, ethyl 2-amino-5-(1-naphthyl) thieno [2, 3-*b*] thiophene-3-carboxylate (**47**) was found to be the most active compound with MIC of 1.1 ε M against MTB and MDR-TB [45].

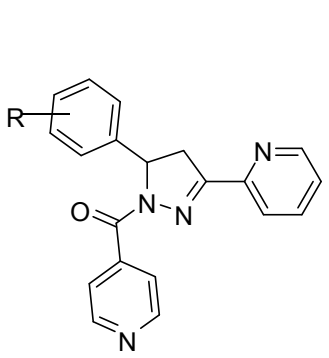
**Pyrazole and Pyrazoline Derivatives**

Castagnolo et al. synthesized a series of both pyrazoles and pyrazolones with the basis obtained from the 5-hydroxy-pyrazole, which was identified by the same group from computational studies as an inhibitor of *M. tuberculosis*. Out of both the series, 5-hydroxy-pyrazole derivatives **48a** and **48b** have shown MIC of 6.25 ε g/mL [46] and **48c** showed best and improved potency of MIC 4 ε g/mL against *M. tuberculosis* [47]. In continuation, the same group also synthesized novel rigid pyrazolone derivatives. Among them, two compounds (**48d** and 4**8e**) have shown potency similar to that of **48c** [48]**.**

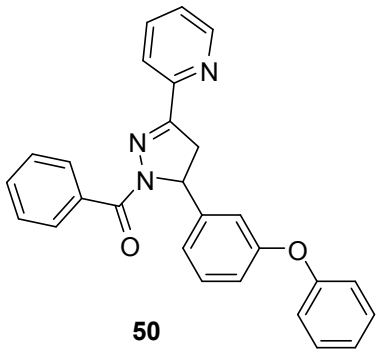



A series of 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazole derivatives have been synthesized with the aim of evaluating their antimycobacterial activity toward a strain of *M. tuberculosis* H37Rv and a strain of *M. tuberculosis* H4, isolated from human bronchial aspirates. Of these derivatives, compounds **49a-e** has shown equal potency against the above strains with a MIC of 8 ε g/mL. The SAR of these molecules confirmed that the substituents on the phenyl residue at the 5-position on the cycle do not exert any important modulatory role on the activity, while the presence of the 2-pyridinyl residue at 3-position on the pyrazoline cycle exerted an important role on the activity of these molecules [49]. With the same inspiration of substituent variation at pyrazole ring, a series of 4-[2-(substitutedphenyl)-3-phenyl-2,3-dihydro-1*H*-5-pyrazolyl]-2-methylphenol derivatives (Ali et al.) and 2-[5-(3-Phenoxyphenyl)-4,5-dihydro-

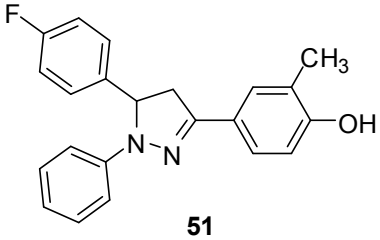
1(benzoyl)-pyrazol-3-yl] pyridine (Kini et al.) (**50**) [50] were synthesized. Among Ali et al. series, compound bearing a 4-fluorophenyl radical at 5-position of the pyrazoline nucleus (**51**), was found to be the most active with a MIC of 0.62 εg/mL against INH-resistant *M. tuberculosis* H37Rv [51], while compound **50** exhibited 100% inhibition at 1 εg/mL against *M. tuberculosis* H37Rv.



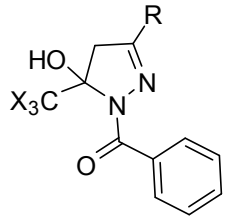
**49a: R=H**
**49b: R=2-Cl**
**49c: R=3-Cl**
**49d: R=4-Cl**
**49e: R=2-$CH_3$**



**50**

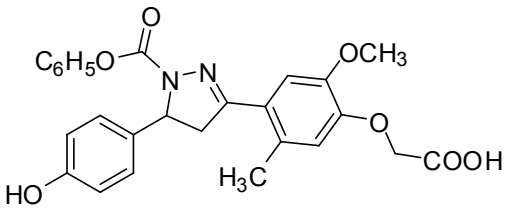


**51**

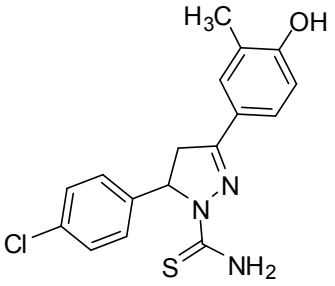


**52a: X=F, R=H**
**52b: X=F, R=4-MePh**
**52c: X=F, R=2-furyl**

Mycolic acids are the essential components of the mycobacterial cell wall and INH inhibits enzyme InhA (enoyl-acyl carrier protein reductase) responsible for the synthesis of mycolic acids. The present resistance against INH is associated mostly with mutations or deletions in *katG* that block the activation step of the drug and the promoter and coding region of *inhA* responsible for encoding the target for INH action. In this perception, a series of 3-substituted-5-hydroxy-5-trifluoro [chloro] methyl-1*H*-1-isonicotinoyl-4,5-dihydropyrazoles were synthesized and their in vitro antimicrobial activity was tested against INH-susceptible *M. tuberculosis* H37Rv, INH-resistant clinical *M. tuberculosis* isolates and non-tuberculous mycobacteria. Of these hybrid derivatives, compound **52a** exhibited best potency against INH-susceptible *M. tuberculosis* H37Rv and INH-resistance strain RGH102 with a MIC of 0.77, 24.13 µM respectively. Whereas, compound **52b** showed good inhibition against INH-resistance strains RGH101& RGH104 with a MIC of 8.94 µM and 4.47 µM respectively. Compound **52c** showed best potency against INH-resistance strain RGH103 with a MIC of 19.23 µM. In addition, compound **52a** also exhibited potency against non-tubercular mycobacteria. It was also observed that the trifluoromethyl-substituted pyrazoles were more active than the respective trichloromethyl-substituted pyrazoles [52].

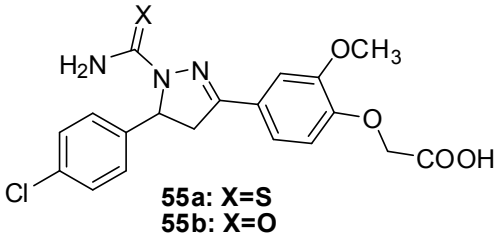


**53**

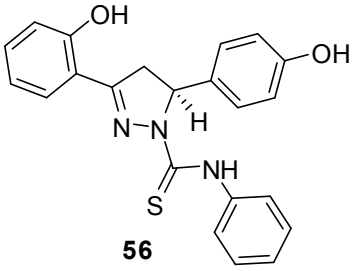


**54**

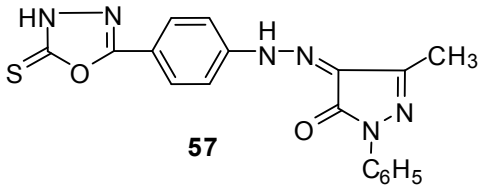
In a further effort to increase the activity, Yar group synthesized a series of 3-phenoxy acetic acid pyrazoline derivatives, which initiated the optimization due to the identification of compound **53** with a MIC of 0.10 µg/mL and 0.64 µg/mL respectively against INH-sensitive and resistant strains of *M. tuberculosis* [53]. In continuation, a series of amino-5-[(substituted)phenyl]-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethiones were synthesized. Among them, compound **54** has shown equal potency of 0.43 µM against both INH-sensitive/resistant strains of *M. tuberculosis* [54]. Similarly, a series of 2-{4-[1-carboxamide/carbothioamide-5-(substitutedphenyl)-4,5-dihydro-1*H*-3-pyrazolyl]-2-methoxyphenoxy}acetic acid derivatives were synthesized. The carbothioamide derivative (**55a**) and carboxamide derivative (**55b**) have shown improved activity of 0.06 µg/mL and 0.13 µg/mL respectively, against the both INH-sensitive and resistant strains of *M. tuberculosis* [55].



**55a: X=S**
**55b: X=O**



**56**

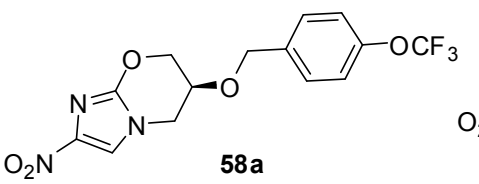


**57**

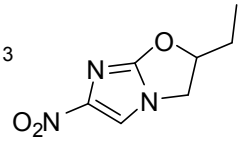
A series of small molecules having similar structure of *M. tuberculosis* (MTB) siderophores (mycobactins, carboxymycobactins) have been synthesized to target the inhibition of the iron scarcity-induction and siderophore-mediated iron-scavenging systems of *M. tuberculosis*. These compounds were evaluated as antituberculars 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 antimicrobial agent (**56**) was identified, which showed MIC of 12.5 µM on average, whose ratio is equal to that of rifampicin (RIF) [56]. In a series of 4-arylhydrazono-2-pyrazoline-5-ones [57], the best activity was exhibited by compound **57** having >90% inhibition and a MIC >12.5 ε g/mL.

**Imidazole, Imidazo-oxazine, Imidazo-pyrimidine and Imidazo-piperazine derivatives**

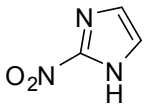
The search for new drugs for TB led to the identification of nitroimidazopyran:PA-824 (**58a**) and CGI-17341 (**58b**) as promising antitubercular agents, which has novel mode of actions to show efficacy against resistant *Mycobacterium*. In this concern, 2-nitroimidazole, 4-nitroimidazole and 1,2-dimethyl-5-nitroimidazole were screened against actively replicating *Mycobacterium bovis* BCG and *Mycobacterium tuberculosis* H37Ra. Among three compounds, 2-nitroimidazole (**58c**) showed preeminent efficacy of 0.226 ε g/mL against the above strains and also found active against *M. tuberculosis* in the intracellular environment of the human monocytic cell line THP-1, with a reduction in viability of bacilli by 2.5 log after 144h of incubation at a concentration of 0.113 µg/mL. While, at five-fold higher concentration (0.565 µg/mL) of 2-nitroimidazole sterilised the macrophages of intracellular pathogens within 192h, without affecting the host [58]. Li et al, synthesized two diastereomers of 7-methyl-nitroimidazo-oxazine. Determination of the crystal structure of the 7-(*S*)-methyl derivative (**59a**, *cis*) revealed that the benzylic side chain remained pseudoaxial while the 7-(*R*)-methyl derivative (**59b**, *trans*) adopted the desired pseudoequatorial conformation. Both derivatives displayed similar activities against *Mycobacterium tuberculosis* (MIC=0.2-0.4 µM), but neither showed improved aqueous solubility, suggesting that inherent lattice stability is not likely to be a major factor in limiting solubility. Conformational analysis revealed that all three (**58a**, **59a** and **59b**) compounds have similar energetically accessible conformations in solution. Additionally, these results suggest that the nitroreductase that initially recognizes PA-824 is somewhat insensitive to substitutions at the 7-position [59].



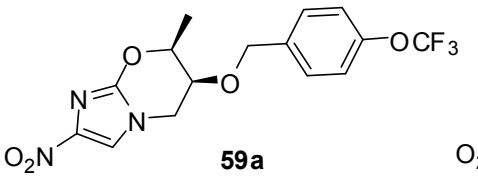

**58a**



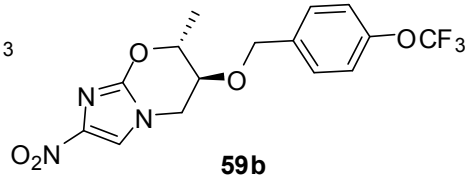

**58b**




**58c**

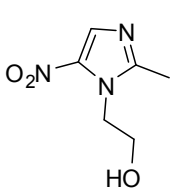



**59a**

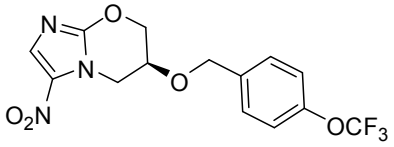



**59b**

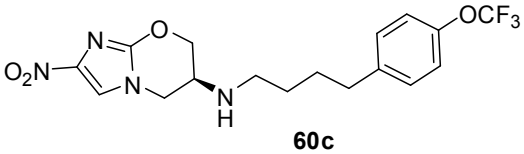
With this motivation, Kim et al. explored the importance of structure activity relationship of PA-824 (**58a**) along with Metronidazole (Mtz) (**60a**). All the synthesized molecules were screened for their activity against aerobic and anaerobic *M. tuberculosis* H37Rv. The first investigation didnôt provide him the molecule with an improved activity. Among all, compound **60b** showed promising aerobic inhibition of 99% at 4-8 µM and anaerobic inhibition of 90% at 31.25 µM, 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 [60]. While in second investigation, Kim et al. was successful in obtaining the molecules which have shown more potency of aerobic & anaerobic inhibition in comparison to parent molecule PA-824. Among all, compound **60c** exhibited aerobic 99% inhibition at 0.039 µM and compound **60d** showed 90% anaerobic inhibition at 1.56-3.13 µM [61].



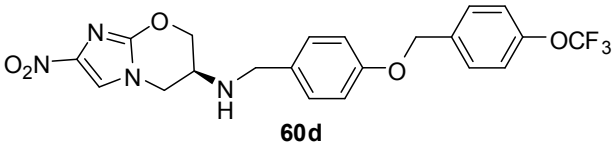
**60a**



**60b**

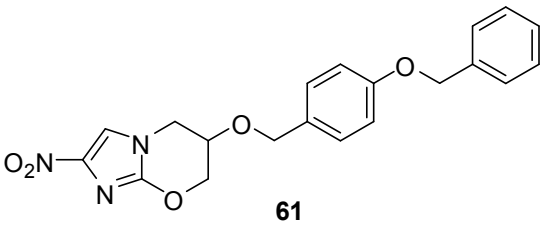


**60c**

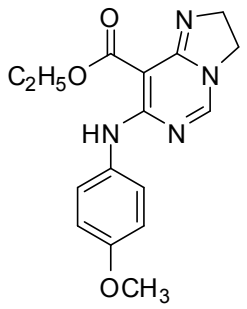


**60d**

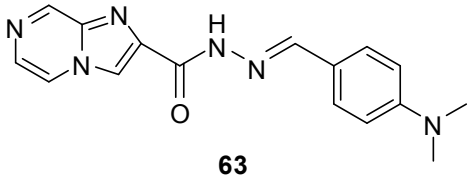
In the same direction, Thompson et al. synthesized analogues of 2-nitroimidazooxazines. Among them, compound **61** has shown best activity with a MIC of 0.11 and 2.7 ε g/mL against *Mycobacterium tuberculosis* in aerobic and anaerobic conditions respectively [62]. In a different approach, Chhabria et al. synthesized novel imidazo [1, 2-*c*] pyrimidines. Of these derivatives, one compound (**62**) has shown promising MIC of 2 ε g/mL against *M. tuberculosis* H37Rv on day 14 and 21, which is equal to that of standard amikacin [63]. Ozdemir et al. synthesized hydrazide derivatives of imidazo [1, 2-a] pyrazine. Among all, compound **63** showed moderate activity with 86% inhibition at 6.25 ε g/mL [64].



**61**

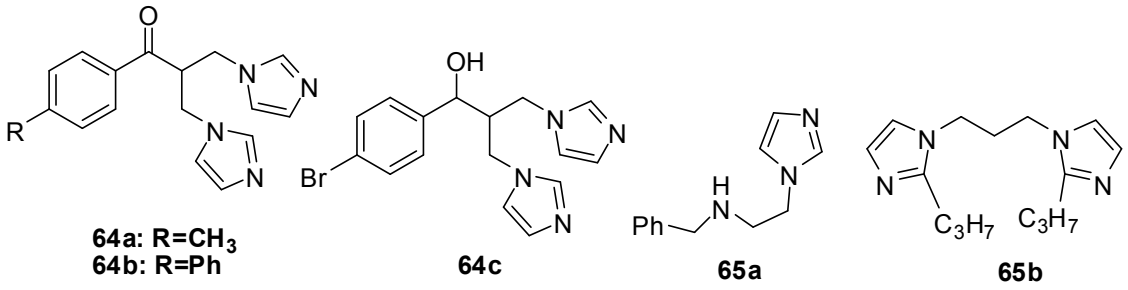


**62**



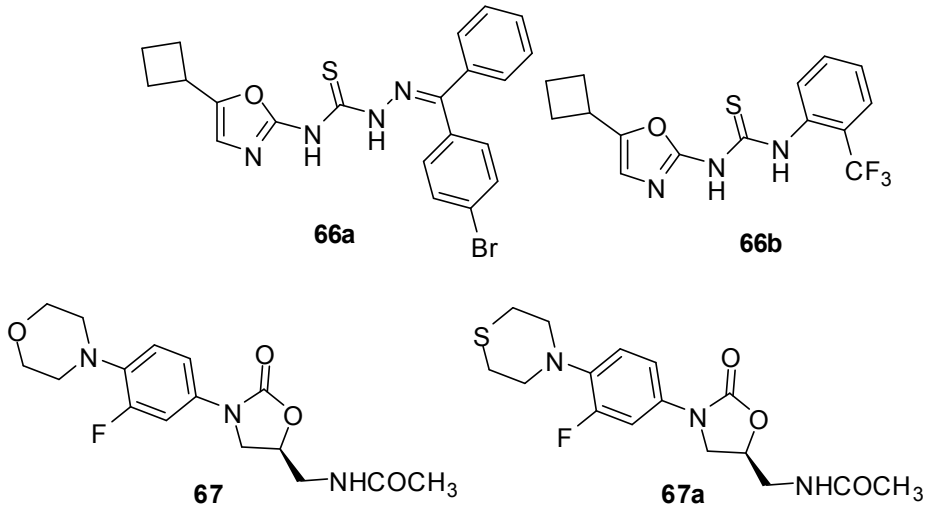
**63**

A series of new bis-imidazole derivatives have been synthesized and screened for their antimycobacterial activity against *M. tuberculosis* H37Rv. Of these, three compounds **64a**, **64b** and **64c** have shown moderate potency of MIC 8 µg/mL [65]. While in an imidazole & bis-imidazole series developed for pharmacophore optimization by J. Pandey et al. provided the molecules which were active against avirulent strain *M. tuberculosis* H37Ra and the virulent strain *M. tuberculosis* H37Rv. Compound **65a** showed best potency of all with MIC of 12.5 µg/mL against *M. tuberculosis* H37Ra and compound **65b** showed MIC of 6.25 µg/mL against *M. tuberculosis* H37Rv [66].



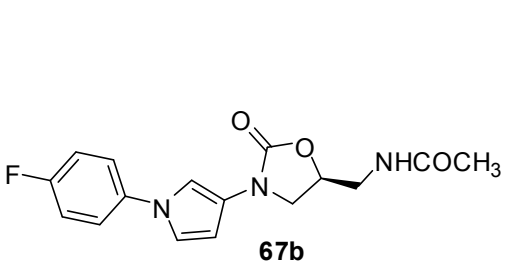

**Oxazole, Isoxazole and Thiazole derivatives**

Sriram et al. synthesized a series of 4-(5-cyclobutyloxazol-2-yl)thiosemicarbazones and evaluated for preliminary in vitro and in vivo activity against *Mycobacterium tuberculosis* H37Rv (MTB) and multidrugresistant *Mycobacterium tuberculosis* (MDR-TB). Among them, (4-bromophenyl)(phenyl)methanone *N*-(5-cyclobutyl-1,3-oxazol-2-yl)-thiosemicarbazone (**66a**) was found to be the most active compound in vitro with MIC of 0.05 µg/mL against MTB and MDR-TB. In the in vivo animal model **66a** 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 isoniazid (INH) [67]. While, in the continuation to optimize the above series, a number of fifteen 1-(5-cyclobutyl-1,3-oxazol-2-yl)-3-(sub)-phenyl/pyridylthioureas were synthesized and evaluated for their efficacy. Among all, compound **66b** showed best in vitro potency of MIC 0.14 µg/mL against MTB and MDR-TB strains. In the in vivo animal model, compound **66b** decreased the *Mycobacterium* 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 [68].

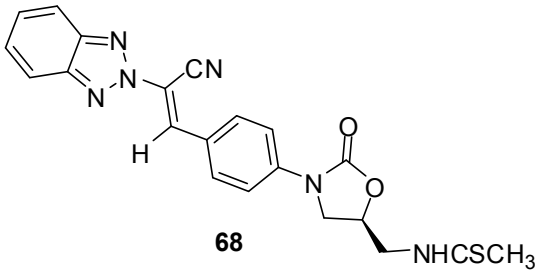



The oxazolidinones, linezolid (**67**) represent a new class of totally synthetic antibacterial agent, active against a variety of clinically important susceptible and resistant Gram-positive organisms. These compounds have been shown to inhibit translation at the initiation phase of protein synthesis in bacteria. Further efforts to increase the potency led to the identification of PNU-100480, thiomorpholine analogue of

linezolid (**67a**) which showed an interesting antimycobacterial activity. With this interest and to increase the antimycobacterial activity of oxazolidinones, Mai et al. synthesized 3-(1*H*-pyrrol-1-yl)-2-oxazolidinone analogues of PNU-100480 and evaluated their potency as an antitubercular agents. Among all, compound **67b** showed 90% inhibition at 5.8 µM concentration, which is comparable to PNU-100480 and INH [69]. While, Das et al. synthesized novel oxazolidinone derivatives with benzotriazole as pendant and one compound **68** showed best 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 *Mycobacterium* [70].



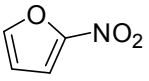

**67b**



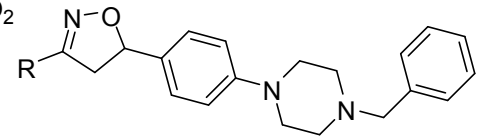

**68**

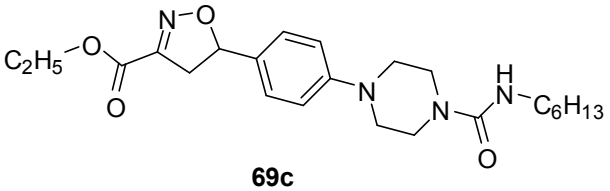
A series of nitrofuranyl isoxazolines with increased proteolytic stability over nitrofuranyl amides were synthesized and screened for their antitubercular activity against *M. tuberculosis*. Among all, compound **69a** showed great in vitro potency of 0.00005 µg/mL. However, their in vivo activity was limited by high protein binding and poor distribution. Consequently, a series of non-nitrofuran containing isoxazolines were prepared to determine if the core had residual anti-tuberculosis activity. This led to the discovery of novel isoxazoline **69b** as anti-tuberculosis agent, which showed 90% inhibition at a concentration of 1.56 µg/mL [71]. With the same inspiration, the same group synthesized 3,5-disubstituted isoxazolines and studied their SAR. The group was successful in generating a most active molecule **69c** has shown a MIC of 0.4 ε g/mL against *M. tuberculosis* H37Rv [72]. Similarly, Kini et al. synthesized a number of three isoxazole derivatives and all the three compounds (**70a**, **70b** and **70c**) have shown 100% inhibition at 1 µg/mL [73].

**69a: R=**

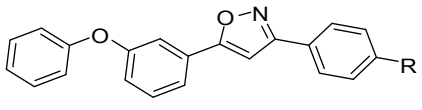



**69b: R= $CO_2C_2H_5$**



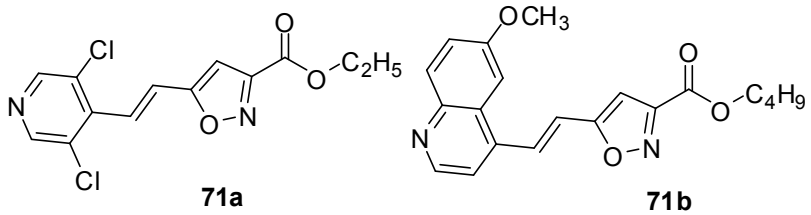




**69c**

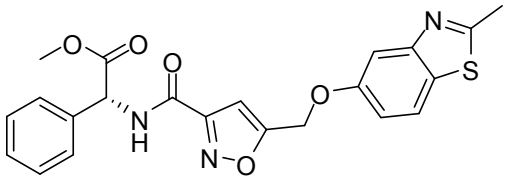



**70a: R=H**
**70b: R=Cl**
**70c: R=$OCH_3$**

In the same direction, Kozikowski group explored the SAR of 5-[(*E*)-2-arylethenyl]-3-isoxazolecarboxylic acid alkyl ester derivatives and found them as a promising antitubercular agents. Among all, 5-[(*E*)-2-(3,5-Dichloro-4-pyridinyl)ethenyl]-3-isoxazolecarboxylic acid ethyl ester (**71a**) has shown preeminent activity with a MIC 0.59 ε M in MABA assay, whereas compound 5-[(*E*)-2-(6-methoxy-4-quinolinyl)ethenyl]-3-isoxazolecarboxylic acid butyl ester (**71b**) showed the best activity against *M. tuberculosis* H37Rv with a MIC1.8 ε M in LORA assay. Both these molecules showed almost equal potency with standard drugs (INH, RMP) in terms of activity and cytotoxicity [74]. While in an another series developed by the same group, (*R*)-methyl 2-(5-((2-methylbenzo[d]thiazol-5-yloxy)methyl)isoxazole-3-carboxamido)-2-phenylacetate (**72**) has shown less activity with a MIC 1.4 ε M in MABA assay [75] in comparison to compound **71a**.

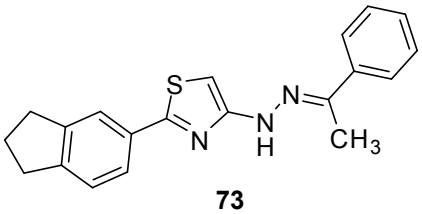


**71a** **71b**

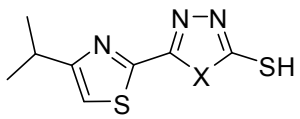


**72**

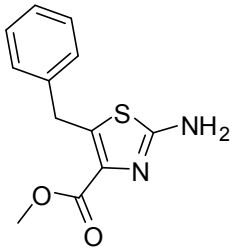
A series of thiazolylhydrazone derivatives were synthesized and evaluated for their antitubercular potency and cytotoxicity. Among all, compound **73** showed best inhibition of 89% at a concentration of >6.25 μg/mL and also found less toxic with an $IC_{50}$ of 200 μg/mL [76]. Whereas in a series of 4-isopropylthiazole hydrazide analogues, two compounds (**74a** and **74b**) have shown better activity with Ò99% inhibition at a concentration of 8 ε g/mL against *M. tuberculosis* H37Rv [77]. While with a motivation to generate the novel compounds that can mimic the mode of action of thiolactomycin, Coxon group identified 2-Aminothiazole-4-Carboxylate derivatives as antitubercular agents. Particularly, methyl 2-amino-5-benzylthiazole-4-carboxylate (**75**) exhibited excellent activity with MIC 0.06 ε g/ml against *M. tuberculosis* H37Rv in comparison to thiolactomycin [78]. In the same direction, de Carvalho et al. identified Nitazoxanide (NTZ, **76**), 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 ε 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 $\log_{10}$ CFUs in 4 days at a concentration of 50 ε g/mL [79].



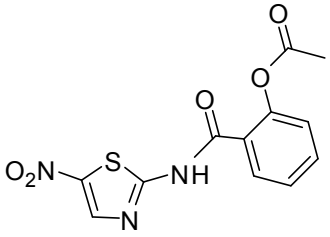
**73**



**74a: X=O**
**74b: X=NNH$_2$**



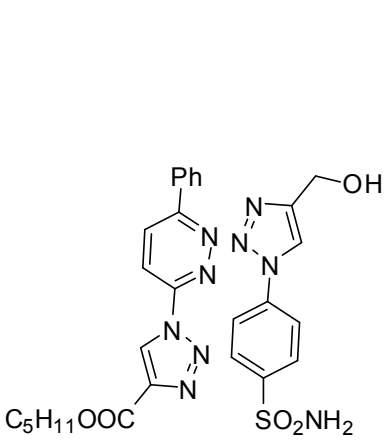
**75**



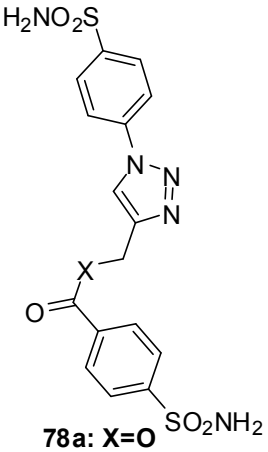
**76**

**Triazole, Oxadiazole and Thiadiazole derivatives**

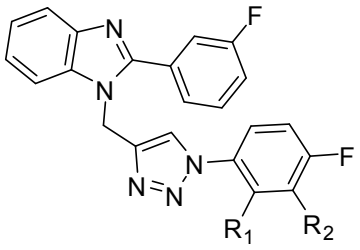
A series of alkyl 1-heteroaryl-1*H*-1, 2, 3-triazole-4-carboxylates were synthesized and tested for their antimycobacterial activity against *M. tuberculosis* H37Rv. Among all, the best potency was shown by *n*-pentyl 1-(6-phenylpyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (**77**) with a minimum inhibitory concentration of 3.13 ε g/mL [80]. While in search of novel chemical entities with antimycobacterial potency, Wilkinson et al. [81] synthesized a number of two bis-arylsulfonamides (**78a** and **78b**) with the interest gained from the antimycobacterial triazole-based sulfonamide (**78**). Compound **78a** and **78b** showed an inhibition of 92% and 50% respectively at a concentration of 100 ε g/mL.



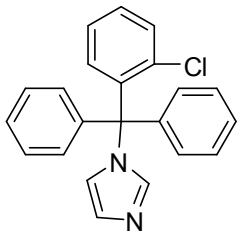
**77** **78**



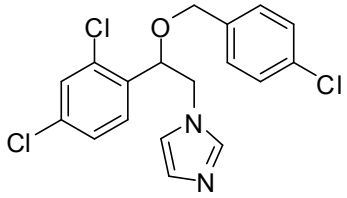
**78a: X=O**
**78b: X=NH**



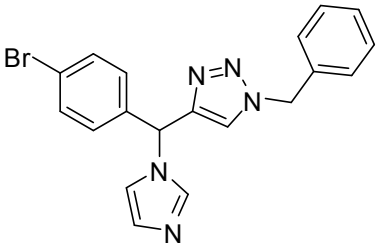
**79a: R$_1$= H, R$_2$=F**
**79b: R$_1$= F, R$_2$=H**



**80a**

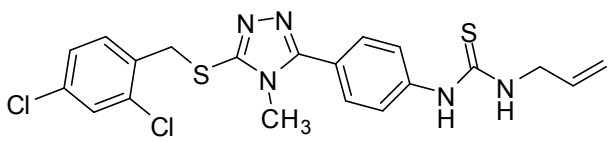


**80b**

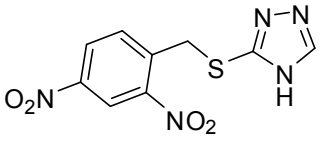


**80c**

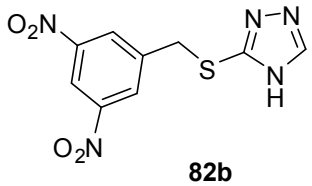
A series of clubbed [1,2,3] triazoles with fluoro-benzimidazole were synthesized as an antitubercular agents, based on the available key factors; such as, over 10% of newly registered pharmaceutical drugs and some 40% of newly registered agrochemicals contain one or more fluorine atoms, reported promising biological activity of fluorine containing benzimidazoles and also the azoles, in particular, [1,2,3] triazole are among the various heterocycles that have broad pharmaceutical and medicinal applications. Of these, two compounds (**79a** and **79b**) have shown almost equal MIC of 0.34 ε M and 0.32 ε M respectively, against *M. tuberculosis* H37Rv [82]. Similarly, Castagnolo et al. focussed the attention on the synthesis and preliminary biological evaluation against *M. tuberculosis* of novel polycyclic azole analogues which resemble the classical antifungal/antibacterial azole drugs, Clotrimazole (**80a**) and Econazole (**80b**). His focus was successful in identifying a potent molecule (**80c**), which is enantiomerically pure (R configuration) and has better antimycobacterial profile in comparison to Clotrimazole. Compound **80c** exhibited a MIC of 16 ε g/mL against *M. tuberculosis* H37Rv, while its enantiomer (S configuration) showed decreased potency, confirming the importance of synthesizing enantiomerically pure compounds due to the different interactions of single enantiomers with chiral biological systems [83].



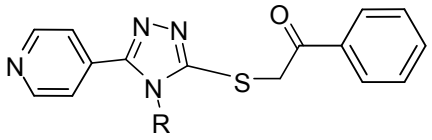
**81**



**82a**

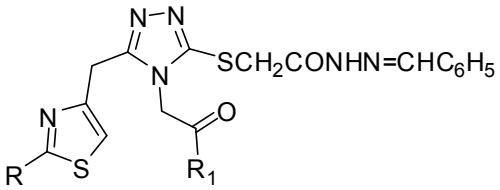


**82b**

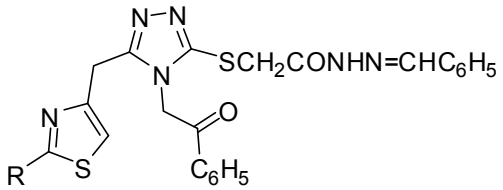


**83**

Keeping in view of azoles and their biological importance, I. Kucukguzel et al. synthesized a series of *N*-alkyl/aryl-*N'*-[4-(4-alkyl/aryl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione-5-yl)phenyl]thioureas and three *S*-alkylated representatives of the former, *N*-alkyl/aryl-*N'*-[4-(3-aralkylthio-4-alkyl/aryl-4*H*-1,2,4-triazole-5-yl)phenyl] thioureas. Among all, *S*-alkylated derivative (**81**) showed the best potency of MIC 6.25 ε g/mL against *M. tuberculosis* H37Rv [84]. With the similar type of modifications, Klimesova et al. synthesized a series of 3-benzylsulfanyl derivatives of 1,2,4-triazole and *S*-substituted-1,2,4-triazoles and evaluated for in vitro antimycobacterial activity against *Mycobacterium tuberculosis, M. avium*, and two strains of *M. kansasii*. Among all, two compounds (**82a** and **82b**) showed moderate potency of MIC 32 ε M/L and 62.5 ε M/L respectively, against *M. tuberculosis* H37Rv on day 14. And also compound **82b** exhibited moderate potency against other strains [85]. While, in a almost similar series 2-(4-substituted-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-ylthio)-1-phenylethanone, all the compounds (**83**) exhibited less than 90% inhibition at a concentration of 6.25 ε g/mL [86].

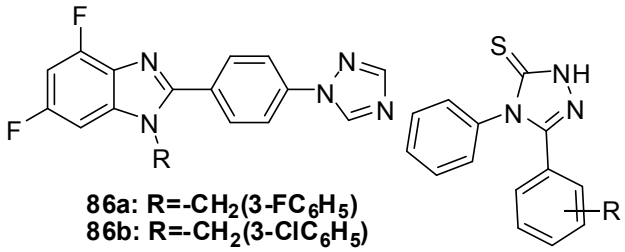


**84a: R=NHCOC$_6$H$_5$, R$_1$=-3-NO$_2$-C$_6$H$_4$**
**84b: R=NHCOCH$_3$, R$_1$=-3-NO$_2$-C$_6$H$_4$**



**85a: R=NHCOC$_6$H$_5$,**
**85b: R=NHCOCH$_2$Cl**

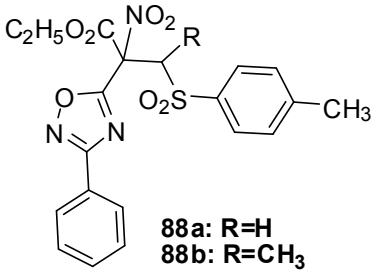
A number of eighty-five 3, 4, 5-substituted-1,2,4-triazole derivatives were synthesized and evaluated for their antitubercular activity against *M. tuberculosis* H37Rv. Among all, two compounds **84a** and **84b** have shown the best potency of MIC 0.39 ε M and 0.79 ε M respectively [87]. In continuation, the same group optimized the above series and found two more compounds (**85a**, **85b**) having same activity profile of MIC 0.39 ε M and 0.79 ε M respectively against *M. tuberculosis* H37Rv [88].



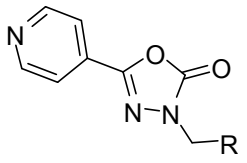
**86a: R=-CH$_2$(3-FC$_6$H$_5$)**
**86b: R=-CH$_2$(3-ClC$_6$H$_5$)**

**87a: R=*o*-phenoxy**
**87b: R=*m*-phenoxy**
**87c: R=*p*-phenoxy**

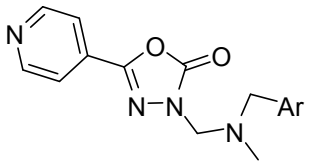
A series of novel 2-[4-(1*H*-[1,2,4]-triazol-1-yl)phenyl]-1-substituted-4,6-difluoro-1*H*-benzo[*d*]imidazole derivatives were synthesized and evaluated for their antitubercular efficacy against *M. tuberculosis* H37Rv. Among all, two derivatives **86a** and **86b** have shown preeminent potency of MIC 0.36 ε g/mL and 0.58 ε g/mL respectively [89]. While a number of three, 3,4-substituted-1*H*-1,2,4-triazole-5(4*H*)-thiones were synthesized by Kini et al. and all (**87a**, **87b** and **87c**) have shown a surprising 100% inhibition at 1 ε g/mL [50].



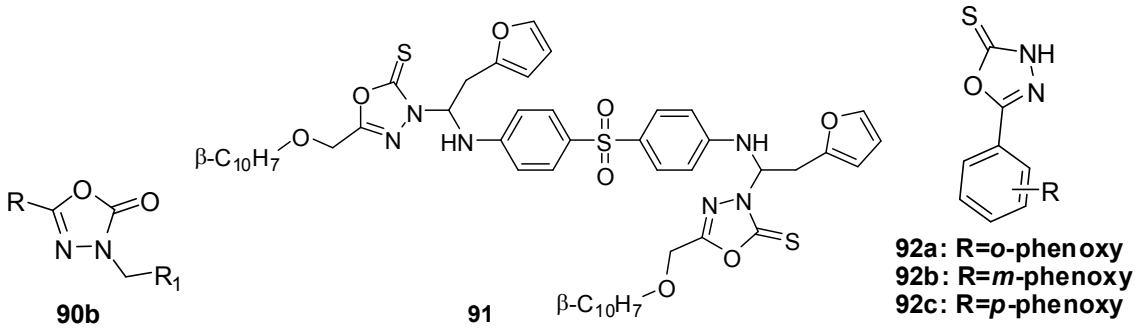
**88a: R=H**
**88b: R=CH$_3$**



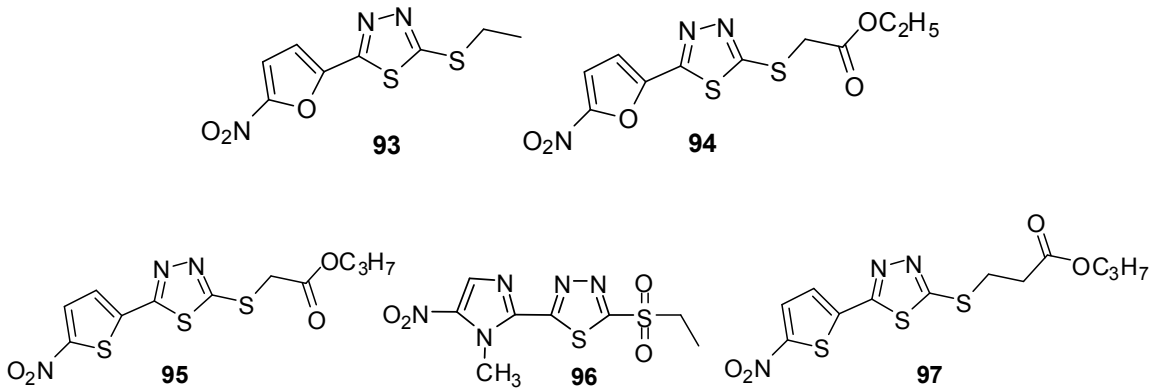
**89a: R=3-methylpiperidine**
**89b: R=tetrahydroisoquinoline**



**90a**

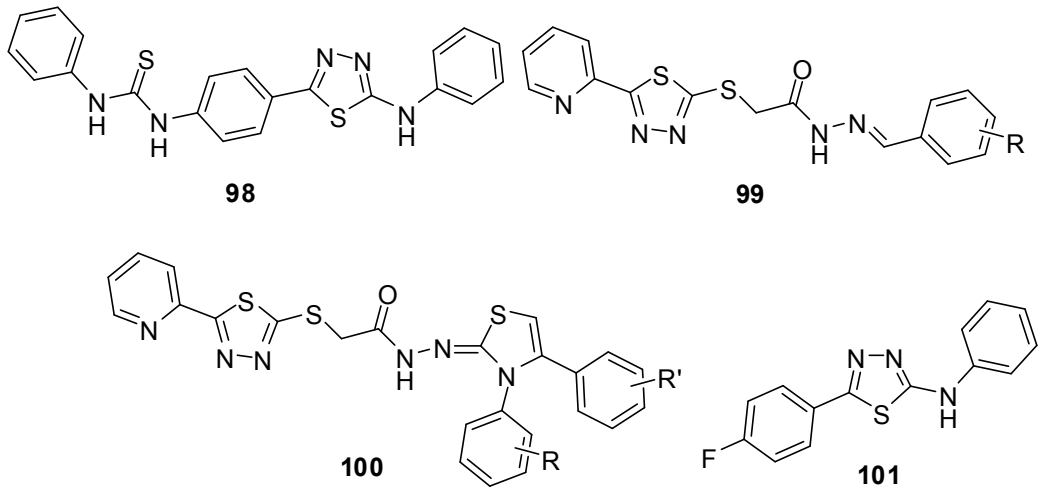



In the search for new compounds possessing antitubercular activity with a low toxicity profile, Tyrkov et al. synthesized a series of substituted 2-nitro-1-(4-tolylsulfonyl)-2-(3-methylphenyl-1,2,4-oxadiazol-5-yl)ethanes and evaluated their antimycobacterial activity with respect to *Mycobacterium lufu* and *Mycobacterium tuberculosis* species. Among all, two compounds **88a** and **88b** exhibited the best minimum bactericidal concentration (MBC), on average of 6.35 ε g/mL and 8.5 ε g/mL respectively against *M. lufu* and *M. tuberculosis* which is comparable to that of isoniazid (INH) [90]. Mamolo et al. synthesized a series of 3*H*-1,3,4-Oxadiazole-2-thione and 3*H*-1,3,4-oxadiazol-2-one derivatives and tested for their in vitro antimycobacterial activity against *M. tuberculosis* H37Rv. Among both the series, oxadiazolone derivatives **89a** and **89b** showed an interesting antimycobacterial activity of MIC 1.25 ε g/mL, while the corresponding thione derivatives showed poor activity [91]. In an effort to increase the potency of oxadiazolones, the same group synthesized 3-[(arylmethylamino)methyl]-5-(pyridin-4-yl)-1,3,4-oxadiazol-2(3*H*)-ones (**90a**) and 3-(2, 3, and 4-methylpiperidin-1-ylmethyl and piperidin-1-ylmethyl)-5-aryl-1,3,4-oxadiazol-2(3H)-ones (**90b**) which have shown poor activity in comparison to former compounds [92]. Surprisingly, the hybrids synthesized by the combination of dapsone and oxadiazole thione, exhibited the promising potency against both *M. tuberculosis* H37Rv (MTB) and INH resistant *M. tuberculosis*. Of these, one compound **91** showed best potency of MIC 0.10 ε M and 1.10 ε M against MTB and INH resistant MTB strains [93]. Similarly, a number of three compounds (**92a**, **92b** and **92c**) synthesized by Kini et al., also showed 100% inhibition at a concentration of 1 ε g/mL against *M. tuberculosis* H37Rv [50].




1, 3, 4 thiadiazoles are well known to exhibit antitubercular activity, so various series were tested against *M. tuberculosis*. Foroumadi et al. [94] synthesized a series of 2-

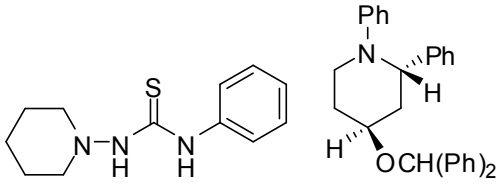
(5-nitro-2-furyl)-1,3,4-thiadiazole-2-sulphide, sulphoxide and sulphones. The most active compound of the series was **93,** which showed a MIC of 0.78 ε g/mL. Cytotoxic effects indicated that this was also the least toxic compound among the series. Whereas, the other series synthesized by the same group exhibited the drop-off in the activity. The compound obtained by the replacement of thioalkyl group with thio-4-ethylaceto group (**94**) exhibited a MIC <6.25 ε g/mL [95], while propyl 2-(5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-ylthio)acetate (**95**) showed MIC of 0.39 g/mL [96]. In another effort to increase the activity, the 5-nitrofuryl was replaced with 1-methyl-5-nitro imidazole [97]. Of this series, the ethyl sulfonyl analogue **(96)** was active with a MIC of 1.56 ε g/mL. Similarly, compound **97** showed the best potency of MIC 1.56 ε g/mL among two series of 2- and 3-[5-(nitroaryl)-1,3,4-thiadiazol-2-ylthio, sulfinyl and sulfonyl propionic acid alkyl esters [98].




Rollas et al. synthesized a series of *N*-Phenyl-*N*-[4-(5-cyclohexylamino-1,3,4-thiazole-2-yl)phenyl]thiourea and the highest activity was exhibited by **98,** which has shown a MIC of 6.25 ε g/mL [99]. While the series synthesized by Mamolo et al., [5-(Pyridin-2-yl)-1,3,4 thiazol-2-yl thio] acetic acid arylidene hydrazides **(99)** showed MIC in the range of 20-80 ε g/mL against *M. tuberculosis* H37Rv [100]. In continuation, the same group synthesized a series of [5-(Pyridin-2-yl)-1,3,4-thiadiazol-2-ylthio]acetic acid (3,4-diaryl-3*H*-thiazol-2-ylidene)-hydrazides (**100**) and found them less active than the former molecules [101]. In search of potent 1,3,4-thiadiazoles, a series of 2,5-disubstituted-1,3,4-thiadiazoles were synthesized and screened for the antituberculosis activity against *Mycobacterium tuberculosis* H37Rv using the BACTEC 460 radiometric system. Among the tested compounds, 2-phenylamino-5-(4-fluorophenyl)-1,3,4-thiadiazole **101** showed the highest inhibitory activity of 69% at a concentration of >6.25 ε L/mL. The relationships between the structures of compounds and their antituberculosis activity were investigated by the Electronic-Topological Method (ETM) and feed forward neural networks (FFNNs) trained with the back-propagation algorithm. As a result of the approach, a system of pharmacophores and anti-pharmacophores has been found that effectively separates compounds of the examination set into groups of active and inactive compounds [102].

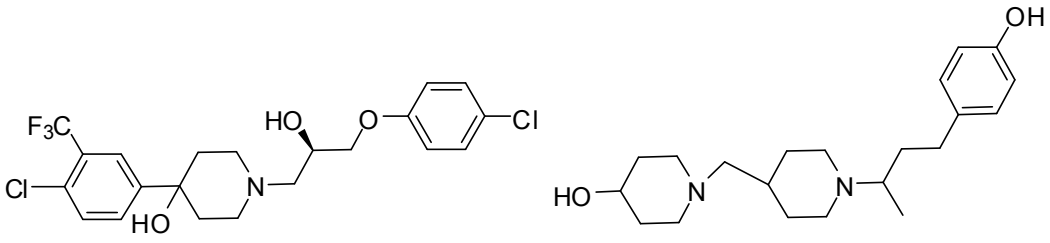
**Piperidine Derivatives**

In spite of the fact that certain heterocyclic compounds have been among the most effective antitubercular medications serving the patients since fifty years and much remained unknown. In addition, the discovery of antitubercular drug isoniazid (INH) of pyridine skeleton prompted the research on piperidine (hexahydropyridine). In this perception, a series of 1-piperidino-3-arylthioureas were synthesized and evaluated for their antitubercular activity. Out of twelve, one compound (**102**) showed the minimum inhibitory concentration (MIC) of 32 ε g/mL against Erdman, a fully drug-susceptible strain of *M. Tuberculosis*. While in a panel of strains of *M. tuberculosis* isolated from the clinic showing resistance to the current frontline medication isoniazid, **102** has shown best potency of MIC 8 ε g/mL against the strain 303 [103]. With the same motivation, Weis et al. synthesized a series of 2-Substituted derivatives of diphenylpyraline and their 1-phenyl and 1-phenethyl analogues and evaluated against *M. tuberculosis* H37Rv as well as their cytotoxicity against human cells (HEK-293). Among all, compound **103** showed an inhibition of 75% at a concentration of 6.25 ε g/mL against *M. tuberculosis* H37Rv and also found to be least toxic of the series [104].

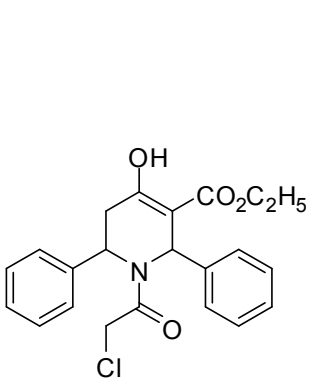



**102** **103** **104a** **104b**

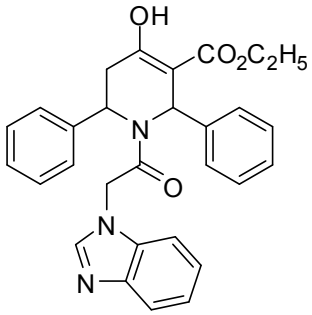
In an effort to increase the potency of above series, the same groups has synthesized 2-substituted derivatives of the antihistaminic agents diphenylpyralines (**103**), bamipine (**104a**) and of their 1-phenyl analogues and tested for their antimycobacterial and $H_1$-antagonistic activities. Of these, compound **104b** showed best potency of MIC 6.25 ε g/mL and showed neglectable $H_1$-antihistaminic activity indicating an alternative mechanism of action of these derivatives [105]. Whereas, Lee group synthesized piperidinol analogs and evaluated for their antimycobacterial activity *M. tuberculosis* H37Rv. Among all, the best potency was shown by compound **105** with a MIC 1.4 ε g/mL and therapeutic index of 13.3 [106]. While Bogatcheva et al. synthesized a combinatorial library of 10,358 compounds on solid support using a pool-and-split technique and tested for their efficacy against *Mycobacterium tuberculosis*. Of this library, dipiperidine derivatives were discovered as novel antitubercular agents with a hit molecule **106,** which showed preeminent activity with a MIC 7.8, 15.65 μM in the broth microdilution and BACTEC assay respectively. This compound is also found to less toxic of all with an $IC_{50}$ 162 μM against HepG2 cells [107].



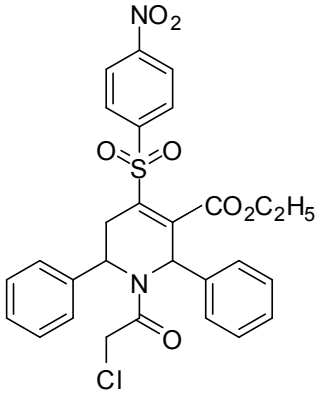

**105** **106**



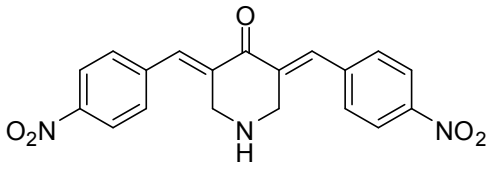

**107a**



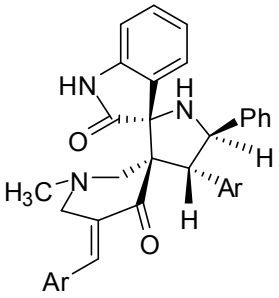

**107b**




**107c**




**108**



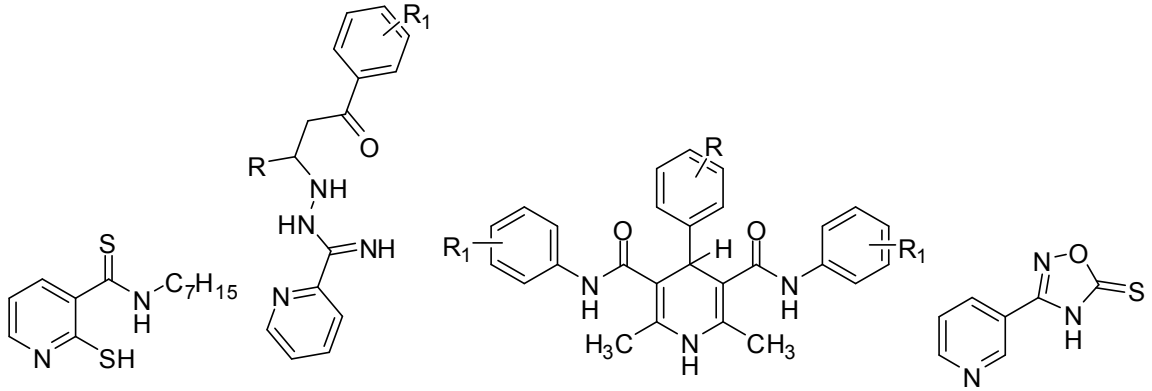

**109: Ar=4-fluorophenyl**

2,6-Disubstitutedpiperidin-4-ones are regarded as an important framework and served as precursors for chiral biologically active natural alkaloids. The biological activities of piperidones were found to be excellent if 2- and/or 6-positions are occupied by aryl groups. In this concern, Aridoss et al. synthesized a series of 2,6-diarylpiperidin-4-ones and tetrahydropyridin-4-ol based benzimidazole and *O*-arylsulfonyl derivatives and screened for their antitubercular activity. Among all, three compounds (**107a**, **107b** and **107c**) have shown equal potency of MIC 16 ε g/mL against *M. tuberculosis* H37Rv, which are one-fold more potent than of the standard rifampicin drug [108]. In 3,5-bis(benzylidene)-4-piperidone (**108**) was found active with a MIC of 0.2 ε g/mL and also found nontoxic in mice [109]. In an effort to increase the potency of piperidones, Kumar et al. synthesized a series of spiro-piperidin-4-ones and evaluated their antimycobacterial activity. Among all, compound **109** showed promising in vitro potency of MIC 0.07 ε g/mL and 0.16 ε g/mL against *M. tuberculosis* and multidrug resistant *M. tuberculosis* respectively. Compound **109** also showed in vivo potency by decreasing the bacterial load in lung and spleen tissues with 1.30 and 3.73-log 10 protections respectively, which is comparable to INH [110].

## Pyridine derivatives

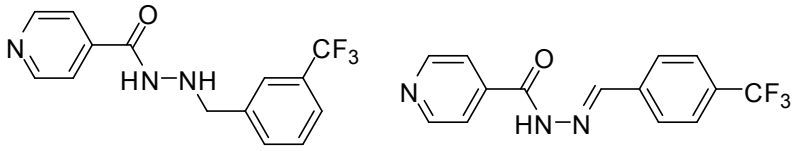
Since the discovery of isoniazid (INH), the pyridine moiety has given much importance for the optimization of antitubercular drugs. In this concern, Pagani et al. synthesized a series of *N*-Alkyl-1,2-dihydro-2-thioxo-3-pyridinecarbothioamides and evaluated their efficacy against *M. tuberculosis* and MAC strains. Among all, compound **110** showed best potency of MIC 0.5 ε g/mL against *M. tuberculosis* H37Rv and 2-4 ε g/mL against

MAC strains [111]. While, the series of 2-pyridinecarboxamidrazones (**111**) synthesized by Banfi et al. [112] showed $MIC_{50}$ in the range of 160-16 ε g/L against *M. avium* strains.



**110** **111** **112** **113**

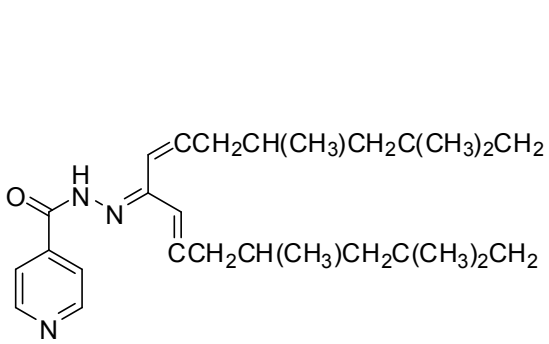
The pyridine derivatives designed as lipophilic precursors were found more active than the unmodified polar isosteres of pyrazinoic acid and nicotinic acid which may be due to better penetration of the compound into the cell wall of *M. tuberculosis*. In this view, a series of 1,4-dihydropyridine-3,5-dicarbamoyl derivatives with lipophilic groups (**112**) were synthesized and on evaluation against *M. tuberculosis* H37Rv, 13 out of 33 derivatives have shown above 90% inhibition at 2.5 ε g/mL. Based on this activity and other physicochemical parameters, it was concluded that the presence of bulkier substituents in the phenyl ring at 4-position of dihydropyridine positively contributes for the activity possibly due to steric interaction in polar space suggesting that the phenyl ring at 4-position may be involved in binding of these molecules with the target [113]. In this direction, Gezginci et al. synthesized 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 and tested against *M. tuberculosis* H37Rv. Among all, 1,3,4-oxathiazoline-2-one derivative (**113**) showed best activity with MIC of 4.5 ε g/mL [114].



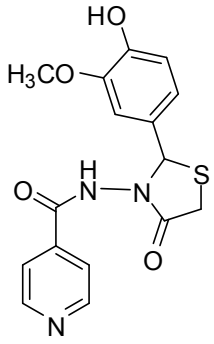
**114a** **114b**

In search of new isoniazid derivatives with extended spectra of activity, a series of isonicotinoylhydrazones, isonicotinohydrazides and their cyanoborane adduct were synthesized and tested for their in vitro antimycobacterial activities. Among these, isonicotinohydrazide (**114a**) found to be most active, which was able to kill *M. tuberculosis* Erdman strain growing within macrophages at a concentration at least 1,250-fold lower than the MIC observed in the culture medium. While, in continuation of optimization didnôt provide the more active molecules compared to former molecule for the same group. Compounds **114b** showed a MIC of 0.05, 0.1 ε g/mL, respectively against *M. tuberculosis* H37Rv and Erdman strains [115]. Whereas Hearn et al. synthesized schiff bases of isoniazid and found them with an antitubercular potency of MIC in the range <0.025 to <6.25 µg/mL. The most potent compound (**115**) also showed good selectivity index of more than 2000 [116]. In a different approach, Jaju et al. synthesized two series of 4-thiazolidinone and 2-azitidinone derivatives of INH. Of both the series compounds **116a** and **116b** having 4-hydroxy-3-methoxyphenyl substituent

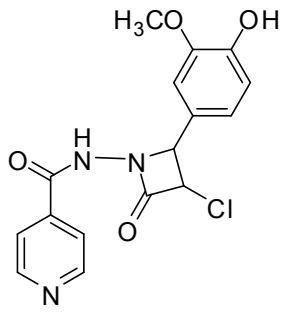
have shown best activity with a MIC 0.31 µg/mL against *M. tuberculosis* H37Rv [117]. Benzylsulfanylpyridine-2-carbohydrazides (**117**) synthesized by Klimesova group showed moderate activity against *Mycobacterium tuberculosis*, non-tuberculous mycobacteria, and multidrug-resistant *M. tuberculosis* with MIC values in a range of 2 to 125 µM/L [118].



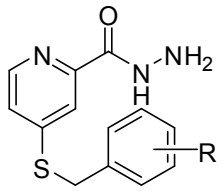
**115**



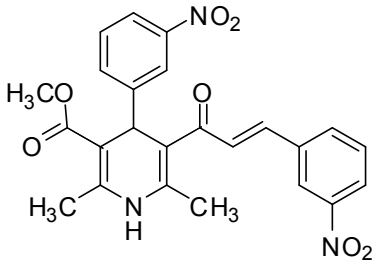
**116a**



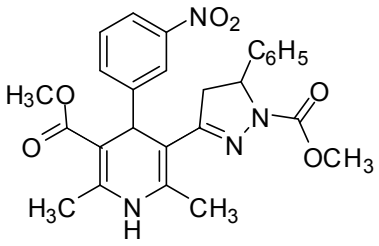
**116b**



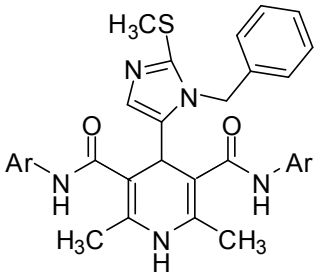
**117**



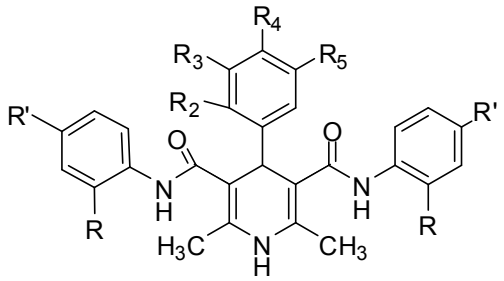
**118a**



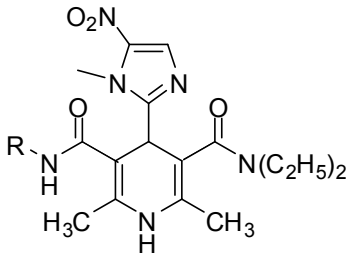
**118b**



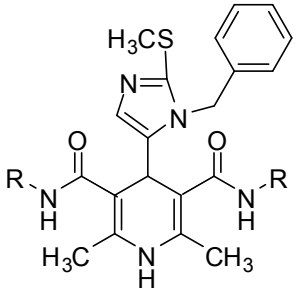
**118c: Ar=4-chlorophenyl**



**119**



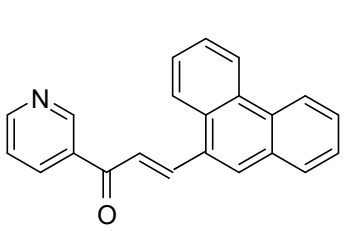
**120: R=3-phenylpropyl**



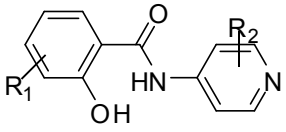
**121: R=4-chlorophenyl**

1,4-dihydropyridines are a well known drug moiety exhibiting mainly calcium channel antagonist activity. This nucleus has recently been shown to possess

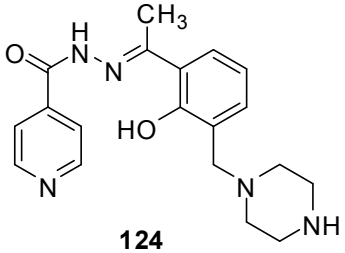
antitubercular activity also. In a series of dihydropyridine derivatives compounds **118a** and **118b** were found to be most potent showing 87% and 85% inhibition respectively at a concentration of 12.5 εg/mL [119]. While, presence of imidazole group at 4-position and amide group at 3,5-position (**118c**) increased the activity up to 1 εg/mL against *M. tuberculosis*. QSAR studies had also been conducted on molecule (**119**) which suggests the presence of electron withdrawing substituents at position 3 and 4 of the 3,5-disubstitutedcarbamoyl phenyl moiety. It also suggests that the groups should be electron withdrawing but with limited steric bulk. There should be increased electron density at position 4 of the 1,4-dihydropyridine ring to increase the antitubercular activity [120]. In the same direction of approach, Khoshneviszadeh et al. synthesized 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 DHP ring. In addition nitroimidazole ring is substitutes at C-4 position. Of these compound **120** showed best potency with a MIC 1 μM/mL against *M. tuberculosis* H37Rv, which is equal to that of INH [121]. Fassihi et al. synthesized 1,4-dihydropyridine3,5-dicarboxamide derivatives and most active compound (**121**) of the series showed equal potency similar to that of **120** [122]**.**




**122**

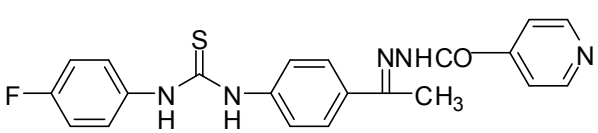



**123**

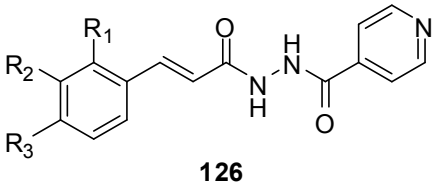



**124**

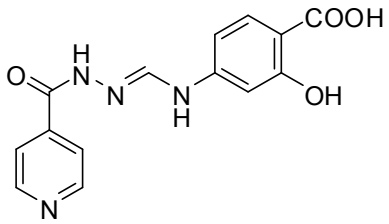
In a series of heterocyclic chalcones, compound **122** has shown MIC of 6.8 εg/mL against *M. tuberculosis* H37Rv [123]. While in search of new potent antitubercular pyridines, Waisser et al. synthesized a series of substituted *N*-pyridinylsalicylamides (**123**) and were evaluated for in vitro antimycobacterial activity against *Mycobacterium avium* and two strains of *Mycobacterium kansasii*. Their moderate activity profile concludes that the 5-chloro-pyridin-2-yl and the substitution of the salicyl moiety by chlorine in position 4 or 5 had the strongest influence on the increase in antimycobacterial activity [124]. In the same direction, Sriram et al. synthesized a series of isonicotinylhydrazones and found a molecule (**124**) active against *M. tuberculosis* H37Rv with a MIC of 0.56 εM, which is more potent than isoniazid (MIC of 2.04 εM) [125].



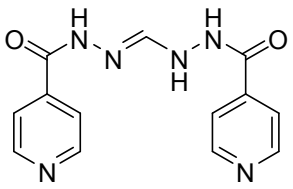

**125**




**126**

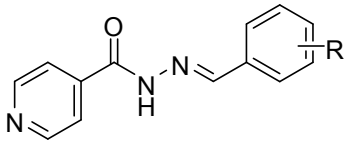


**127a**

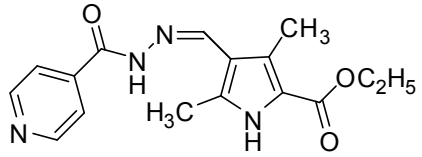


**127b**

In an effort to increase the potency of isonicotinylhydrazones, Sriram et al. synthesized another series and found a new derivative (**125**) more active than the former molecule (**124**). It showed equal MIC of 0.49 ε M against *M. tuberculosis* H37Rv and INH-resistant *M. tuberculosis* strains [126]. A series of trans-cinnamic acid derivatives of isonicotinic acid (**126**), synthesized by Carvalho et al. showed moderate in vitro activity of MIC 3.12 ε g/mL against *M. tuberculosis* strain [127]. Whereas, compounds **127a** and **127b** of the isonicotinic acid derivatives developed by Imramovsky et al., showed equal potency of MIC 0.39 ε g/mL against *M. tuberculosis* H37Rv and have selectivity index (SI) of >160, which is comparable to INH and better than ciprofloxacin [128].



**128a: R=3-Cl**
**128b: R=4-Cl**
**128c: R=4-F**
**128d: R=2-CN**
**128e: R=2-OCH$_3$**



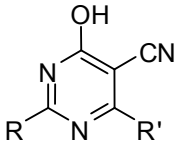
**129**

A number of twenty-two (E)-*N'*-(monosubstituted-benzylidene)isonicotinohydrazide derivatives have been synthesized and evaluated for their in vitro antibacterial activity against *M. tuberculosis* H37Rv. Five compounds (**128a-e**) have shown significant MIC in the range of 0.31-0.62 ε g/mL in comparision with first line drugs such as isoniazid (INH) and rifampicin (RIP) [129]. Whereas, hybrid of isonicotinic hydrazone of pyrrole (**129**) showed best potency of MIC Ò0.1 ε g/mL against *M. tuberculosis* H37Rv and also has good selectivity index [130].

## Pyrimidine Derivatives

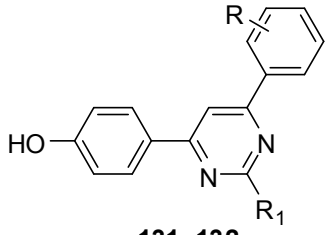
The antifolates were given much importance as they target the enzyme dihydrofolate reductase (DHFR). Most of the antifolates have selectivity toward the pathogen DHFR rather than the host DHFR, making it as safe target for the development of antiinfectious agents. In this concern, Kumar et al. synthesized a number of 80 compounds in a combinatorial library of tetrasubstituted pyrimidines on solid support and evaluated their potency against *M. tuberculosis* H37Rv. Among them, 6 compounds **(130a-f)** showed in vitro activity in the range of MIC 25-50 ε g/mL [131]. In continuation, the same group synthesized a number of thirty trisubstituted pyrimidines and out of them, sixteen compounds (**131**) have shown antitubercular potency with a MIC in the range of 12.5-25 ε g/mL [132]. To further increase the activity of pyrimidines, same group synthesized a small library of trisubstituted pyrimidines (**132**) [133], where the activity profile was remained same as **131**. Whereas, chloropyrimidines synthesized by Agarwal et al. were found to be highly active against *M. tuberculosis*. Four compounds **(133a-d)** were found to be active at a MIC of 0.78 ε g/mL. These compounds were further screened against virulent strain (MTB H37Rv) and no change in their MIC profile was observed [134].

While, in a series of anilino pyrimidines tested against *M. tuberculosis* H37Ra, the most potent activity was shown by the compound **134** having a MIC of 3.12 εg/mL [135].

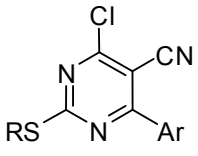


**130a-f**

**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**

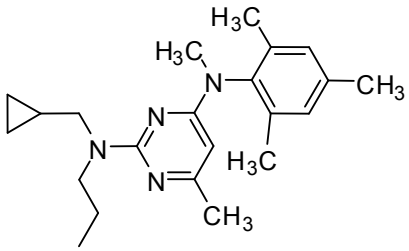


**131, 132**



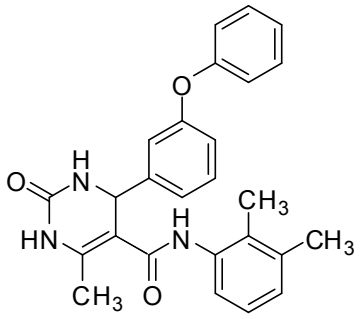
**133a-d**

**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**

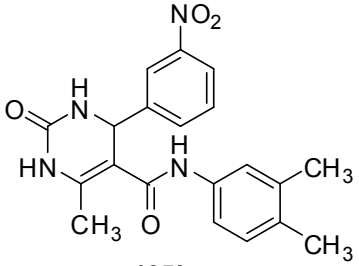


**134**

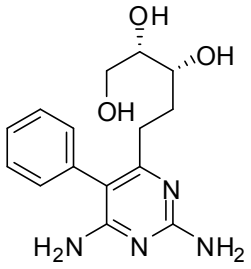
A series of *N*-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamides were synthesized and evaluated for their antitubercular activity against *M. tuberculosis* H37Rv. Among all, two compounds with 2,3-dimethylphenyl (**135a**) and 3,4-dimethyl (**135b**) carbamoyl side chain, respectively, showed 65% and 63% inhibition. The Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA) models generated with the atom-fit alignment were better in terms of the statistical parameters ($r^2$, $q^2$ and $r^2_{pred}$) over the field-fit models. Analysis of the CoMFA and CoMSIA contours provide details on the fine relationship linking structure and activity, and offer clues for structural modifications that can improve the activity [136].



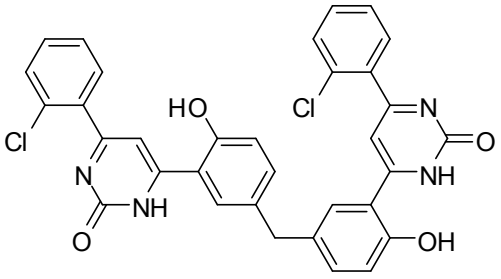
**135a**



**135b**



**136**

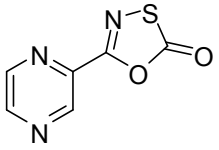


**137**

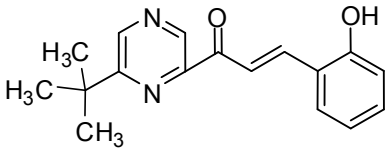
The crystal structure of *M. tuberculosis* DHFR revealed a glycerol tightly bound at the binding site for the substrate dihydrofolate; this glycerol-binding motif is absent from the human enzyme. In this perception, El-Hamamsy et al. synthesized a series of pyrimidine-2,4-diamines, designed with a two-carbon tether between a glycerol-mimicking triol and the 6-position of the heterocycle. These compounds also carried aryl substituents at the 5-position. Their diastereoisomers, analogues lacking two hydroxy groups and analogues lacking the two-carbon spacing linker were also synthesized. Preliminary assay of the abilities of these compounds to inhibit the growth of TB5 *Saccharomyces cerevisiae* carrying the DHFR genes from *M. tuberculosis*, human and yeast indicated that 5-phenyl-6-((3R,4S)-3,4,5-trihydroxypentyl)pyrimidine-2,4-diamine (**136**) selectively inhibited *M. tuberculosis* DHFR and had little effect on the human or yeast enzymes [137]. Whereas, in a series of methylene-bis-pyrimidinones and methylene-bis-mercaptopyrimidines, pyrimidinone derivative (**137**) shown best potency of 0.1 ε g/mL while mercaptopyrimidines showed moderate activity [138].

**Piperazine and Pyrazine derivatives**

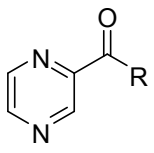
Since the discovery of pyrazinamide, several derivatives containing pyrazine nucleus have been synthesized and tested for their activity against *M. tuberculosis.* On this basis a pyrazine derivatives substituted with 1,2,4-oxadiazole-5-ones, 1,2,4-oxadiazole-5-thiones and 1,3,4-oxathiazoline-2-ones were synthesized [114]. 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 **138** exhibited a MIC of 4.5 ε g/mL in comparison to 49 ε g/mL for pyrazinamide. With the same concept, a series of ring substituted (E)-3-Phenyl-1-(2 pyrazinyl)-2-propen-1-ones were synthesized and screened for their efficacy against *M. tuberculosis* H37Rv. Among all, compound **139** showed an inhibition of 94% at 12.5 ε g/mL [139]. While, in a series of pyrazine derivatives synthesized by Gezginci et al. two compounds (**140a** and **140b**) have shown equal potency of MIC 6.25 ε g/mL against *M. tuberculosis* H37Rv [140]. Compound **140b** also showed MIC of <0.25 ε g/mL against *M. tuberculosis* H37Ra.



**138**

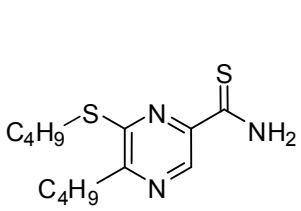


**139**

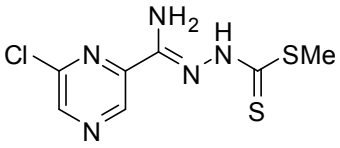


**140a: R=4-nitrobenzyloxy**
**140b: R=4-acetoxybenzyloxy**

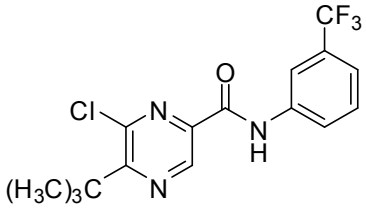
On the basis of ethionamide, Krinkova et al., synthesized a series of 5-Alkyl-6-(alkyl/aryl sulfanyl) pyrazine-2-carbothioamide. Compounds inhibited the growth in the range of 61-91%. Compound **(141)** showed 91% inhibition at a MIC <6.25 εg/mL. Structure activity relationship studies showed that the 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 [141]. While, S-methyl-2-(amino(6-chloropyrazin-2-yl)methylene)hydrazinecarbodithioate (**142**) exhibited moderate potency of MIC 32 εg/mL among simple pyrazine hybrids synthesized by Foks et al., against *M. tuberculosis* sensitive and wild strains [142].




**141**

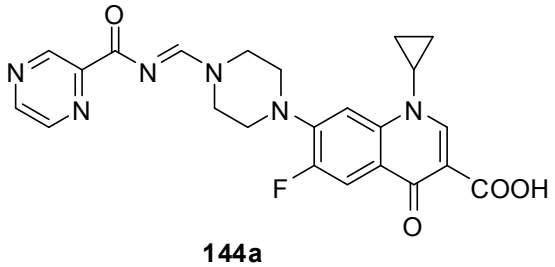



**142**

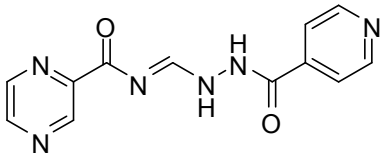



**143**

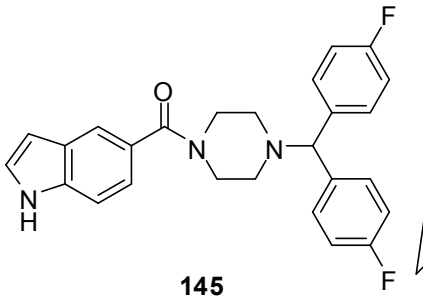
A series of unsubstituted, halogenated and/or alkylated pyrazine-2-carboxylic acid amides connected *via* -CONH- bridge with substituted anilines were synthesized and screened against *M. tuberculosis* H37Rv. Among all, 5-tert-Butyl-6-chloro-N-(3-trifluoromethylphenyl)pyrazine-2-carboxamide (**143**) has shown the highest activity of MIC 3.13 µg/mL [143]. Imramovsky et al. synthesized a number of three hybrids of pyrazine and two of them showed promising antitubercular activity. Compound **144a** and **144b** showed MIC of 0.78, 0.1 µg/mL respectively, against *M. tuberculosis* H37Rv. Compound **144a** also showed good activity against atypical strains of *M. tuberculosis* [127]. In a different approach, He et al. [144] and Bogatcheva et al. [145] synthesized a series of 1,4-substitutedpiperazine/homopiperazines. Compound **145** showed MIC of 62.5 µM, homopiperazine derivatives (**146a** and **146b**) showed preeminent MIC of 1.56 µM against *M. tuberculosis* H37Rv. Compounds **146a** and **146b** also exhibited good selectivity index of 84.6 and 46 respectively. Similarly, Zhang et al. also identified homopiperazine derivatives (**147a** and **147b**) with a more promising activity of MIC 0.78 µg/mL against *M. tuberculosis* H37Ra [146]. In a different approach Onajole et al. synthesized fourteen pentacycloundecane (PCU) tetra-amine compounds and were screened them for their in vitro anti-mycobacterial activity against H37Rv and XDR strains of *M. tuberculosis* 194. The most active compound (**148**) of the series has shown MIC of 5.04 µM against *M. tuberculosis* H37Rv and 1.26 µM against XDR 194 [147].



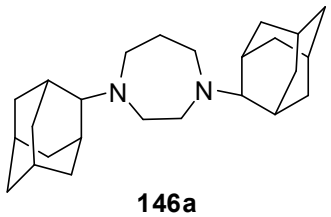

**144a**



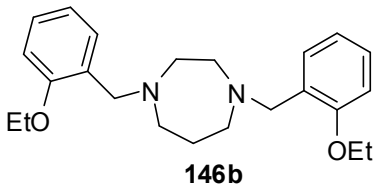

**144b**



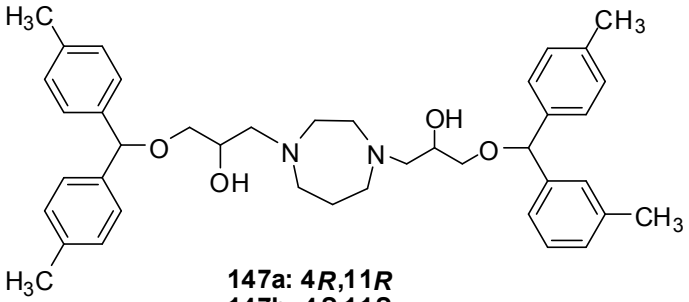

**145**



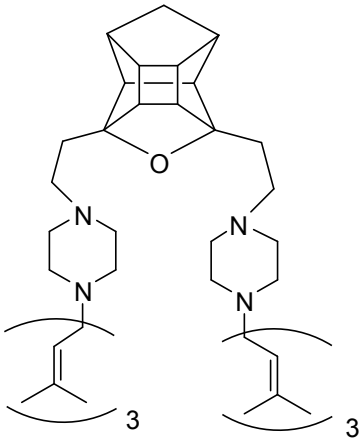

**146a**




**146b**



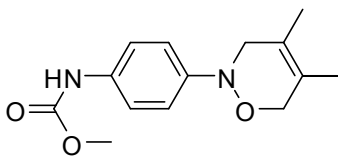

**147a: 4*R*,11*R***
**147b: 4*S*,11*S***



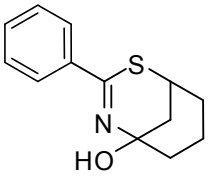

**148**

## Oxazine and Thiazine derivatives

A series of carbamate derivatives of 1,2-oxazine were synthesized and screened for their in vitro antitubercular activity against *Mycobacterium tuberculosis* and *Mycobacterium lufu* species. Among all the tested compounds, the maximum antimycobacterial activity was observed for 4,5-dimethyl-2-( *p*-methoxycarbonylamino)phenyl-3,6-dihydro-1,2-oxazine (**149**) [148]. In a series of 5,6 dihydro-4H-1,3 thiazine derivatives evaluated against *M. tuberculosis* H37Rv, 5-hydroxy-3-phenyl-4-aza-2-thiabicyclo[3.3.1]none-3-ene **(150)** showed 97% inhibition at a concentration of 6.25 ε g/mL [149].




**149**

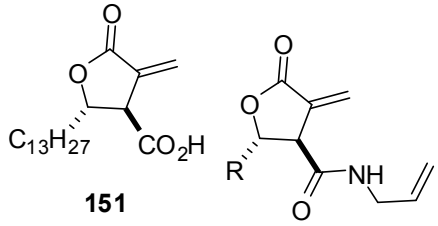


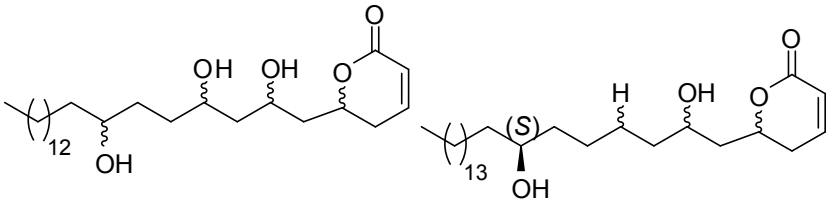

**150**

## Lactones

A series of Ŭ-methylene-ɔ-butyrolactones based on the natural product protolichesterinic acid (**151**) were synthesized and evaluated for their potency against *M. bovis* BCG. Compounds **151a-d** bearing an allylamide group at the C-4 position showed improved activity with MICs in the range of 6.25-12.5 ε g/mL [150]. In the same direction of research, Cardona et al. [151] synthesized several structural analogues of the polyketide passifloricin lactone (**152**) and screened against *M. tuberculosis* H37Rv. Of these, compound **152a** exhibited an inhibition percentage higher than 97% at 128 ε g/mL, while

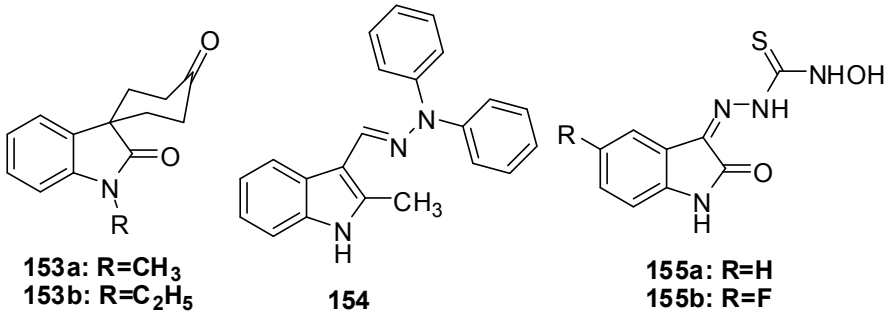
passifloricin A reached 82.9%. Additionally, it has shown best MIC of 17.31 εg/mL, which is better than passifloricin A (29.4 εg/mL).



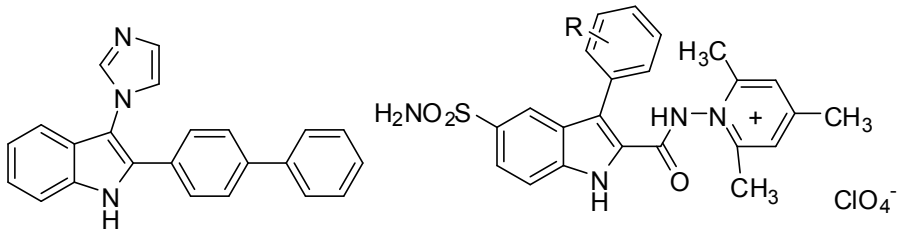

**Indole Derivatives**

Indole derivatives have shown interesting biological properties and some of them are known for their antitubercular activity. Hence, for the purpose of obtaining new and more potent antitubercular compounds that can improve the current chemotherapeutic antituberculosis treatment, Chande et al. have synthesized and evaluated some spiro-oxindole derivatives. Among all, two compounds (**153a** and **153b**) showed best MIC of 0.05 µg/mL against *M. tuberculosis* H37Rv, which is comparable to INH and Rifampacin [152]. With the same inspiration, Sonar et al. synthesized a series of hydrazone and 3-nitrovinyl analogs of indole-3-carboxaldehydes and related compounds and found an active molecule (**154**), which exhibited 91% inhibition at <6.25 µg/mL against *M. tuberculosis* H37Rv and has a good selectivity index (SI) of >1.6 [153]. While *N*-Hydroxythiosemicarbazides (**155a** and **155b**) synthesized by Sriram et al. showed poor potency of MIC 62.04, 24.58 µM respectively [154]. Indole derivative **156** synthesized by Zampieri et al. showed moderate activity of MIC 2 µg/mL against *M. tuberculosis* H37Rv [155].




A series of 2-(hydrazinocarbonyl)-3-aryl-1*H*-indole-5-sulfonamides have been synthesized and were evaluated as inhibitors of two *β*-carbonic anhydrases (CAs, EC) from *Mycobaterium tuberculosis*, Rv1284 and Rv3273. The whole series (**157**) showed excellent nanomolar inhibitory activity, with several subnanomolar inhibitors being

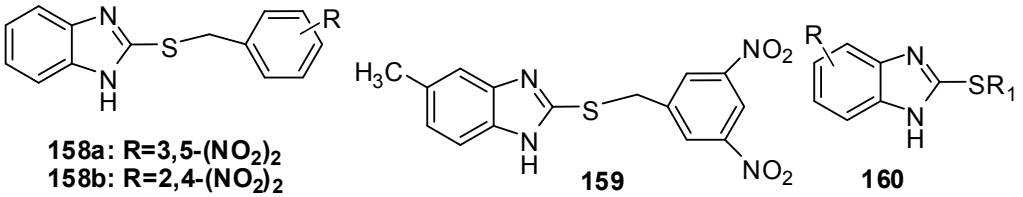
detected. The activity profile confirmed that the Rv1284 and Rv3273 have potential for developing antimycobacterial agents with an alternate mechanism of action [156].



**156** **157**

**Benzimidazole, Benzoxazole, Benzothiazole and Benzoxathiole Derivatives**

A wealth of information is available regarding benzimidazoles and their broad spectrum of activities (antibacterial, antifungal, antihelminthic, antiparasitic and especially a promising tuberculostatic activity). With this motivation, Klimesova et al. synthesized a series of 2-alkylsulfanyl benzimidazoles and tested against *M. tuberculosis*. The values of MIC were within the range 4-125 εM/L in comparison to that of isoniazid having a MIC of 4 εM/L. The most active compounds of the series were **158a** and **158b** exhibited a MIC of 4 εM/L [157]. In view of the good activity of **(158a)**, the benzene ring of benzimidazole was further substituted by methyl group at the 5-position to see the change of activity. The results concluded that substitution at this position did not affect the activity in general. The most active compound **(159)** showed same potency of MIC 4 εM/L [158]. In another effort, Kazimierczuk et al. synthesized a series of substituted 2-polyfluoroalkyl and 2-nitrobenzylsulphanyl benzimidazoles and evaluated for their activity against four *Mycobacterium* strains. Among all, sulphanyl benzimidazoles (**160**) exhibited best potency of MIC in the range 2-32 εM/L against *M. tuberculosis*. While MIC values against *Mycobacterium kansasii* and *Mycobacterium avium* exceeded that of isoniazid. The SAR of this series confirmed that the 3,5-dinitro compounds were several times more effective against *M. tuberculosis* and *M. kansasii* than the respective isomeric 2,4-dinitro derivatives [159].

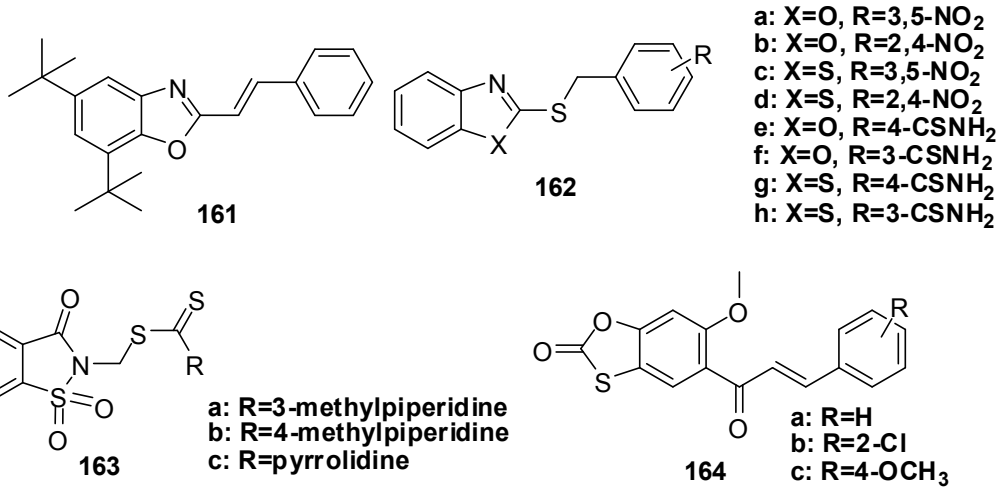


**158a: R=3,5-$(NO_2)_2$**
**158b: R=2,4-$(NO_2)_2$**

**159** **160**

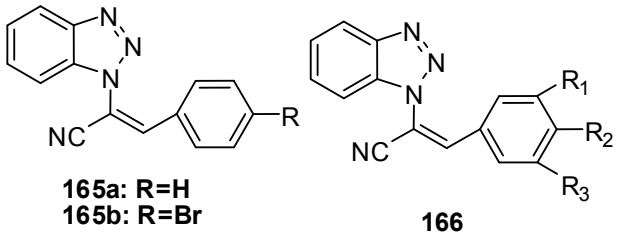
Benzoxazoles can be considered as structural bioisosters of naturally occurring nucleotides such as adenine and guanine, which allow them to interact easily with the biopolymers of a living system. Recently they are also identified for their antitubercular activity. With this interest Vinsova et al. synthesized a number of 30, 2-substituted 5,7-di-tert-butylbenzoxazoles and evaluated for their antitubercular potency. Of these, 5,7-di-tert-butyl-2-styrylbenzoxazole (**161**) showed MIC of 3.13 εg/mL against *M. tuberculosis* H37Rv and also found least toxic of the series [160]. In the similar way, Koci et al. synthesized a series of 2-benzylsulfanyl derivatives of benzoxazole and benzothiazole

and evaluated for their in vitro antimycobacterial activity against *Mycobacterium tuberculosis* and non-tuberculous mycobacteria. The substances bearing two nitro groups (**162a-d**) or a thioamide group (**162e-h**) exhibited appreciable antimycobacterial activity of MIC in the range 2-8 εM/L against *M. tuberculosis* and exhibited great activity particularly against non-tuberculous strains. The most active compounds were subjected to the toxicity assay and were evaluated as moderately cytotoxic [161]. In a series of (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)methyl *N*,*N*-disubstituted dithiocarbamates and (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)methyl *O*-alkyldithiocarbonates, three compounds (**163a-c**) showed equal potency of MIC 0.78 εg/mL against *M. tuberculosis* H37Rv [162]. While, benzoxathiolone derivatives **164a-c** exhibited poor activity of MIC 50 εg/mL [163].




**Benzotriazole Derivatives**

A series of 3-arylsubstituted-2-[1*H*(2*H*)benzotriazol-1(2)-yl]acrylonitriles (**165a** and **165b**) were synthesized and showed 98, 99% inhibition and a MIC of 6.25 εg/mL and 12.5 εg/mL respectively against *M. tuberculosis* [164]. In light of the above results, some minor substitutions were made in the above series. A varied variety of substitutions were made in the benzene ring and also their attachment to the benzotriazole ring **(166)** was varied. Some compounds of this series showed moderate activity whereas most of them showed no activity. The structure activity relationship studies showed that 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 general strong reduction in activity inspite of the increased lipophilic character. This indicates that the steric hindrance as well as the kinds of substituents may play relevant role in activity. Also the 1-Benzotriazole derivatives were more active than 2-isomers. Conversion of the cyano group into carboxamido or carboxylic group also produced loss of activity which indicates that an increase of the hydrophilic properties is not profitable for the activity [165].

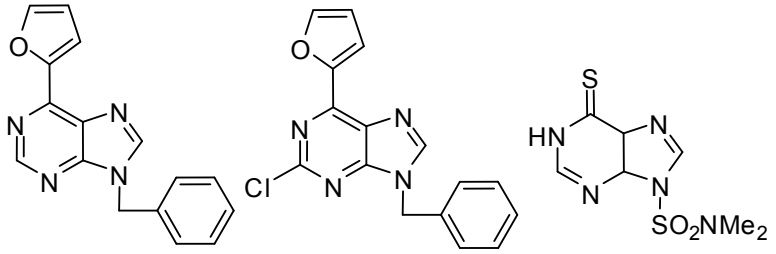



**165a: R=H**
**165b: R=Br**

**166**

**Purine, Pyrazolopyrimidine and Thienopyrimidine Derivatives**

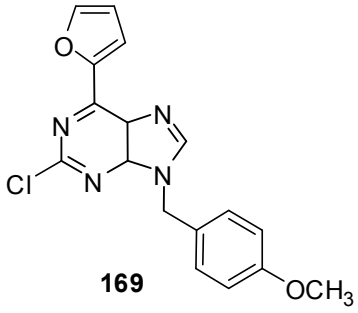
The purine ring system is a key structural element of substrates and ligands of many biosynthetic, regulatory, and signal transduction proteins including cellular kinases, G proteins, and polymerases. Very little work has been done to explore the potency of purine analogues as antitubercular agents due to the fact that purines are not represented in the current clinical antitubercular regimens, suggesting that active compounds in these series may target new biochemical mechanisms, potentially allowing treatment of MDRTB. Recently, syntheses of purine analogues possessing antitubercular activity have been pursued with great interest. In this perception, 9-benzylpurines with a variety of substituents at 2, 6 or 8 positions were synthesized and found as good antimycobacterial agents. High activity was exhibited by 9-benzylpurines carrying a phenyl ethynyl, trans-styryl or aryl substituents at the 6$^{th}$ position and generally chlorine at the 2$^{nd}$ position. The most active compounds **167a** and **167b** showed a MIC of 3.13 and 0.78 ε g/mL respectively, against *M. tuberculosis* H37Rv and also a selectivity index (SI) of 2.7 and 10.4 [166]. In continuation, same group synthesized a series of 6-arylpurines having a variety of substituents in the 9 position and screened against *M. tuberculosis* H37Rv. The most active compound of the series was again found to be same 9-benzyl-2-chloro-6-(2-furyl)purine **(167b)** having a MIC of 0.78 ε g/mL. This compound exhibited relatively low cytotoxicity and it was also active against several singly drug-resistant strains of *M. tuberculosis* [167]. Scozzafava et al. synthesized eleven analogues of 9-sulphonated/sulphenylated 6-mercaptopurines [168] and out of them six exhibited MIC in the range of 0.39-0.78 ε g/mL. The most potent compound **(168)** (MIC=0.39 ε g/mL) also exhibited good activity against several drug resistant strains of *M. tuberculosis*.



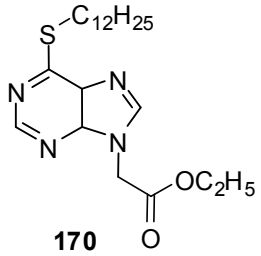

**167a** **167b** **168**

Inspired by the above results, Bakkestuen et al. synthesized a series of 9-aryl-, 9-arylsulfonyl- and 9-benzyl-6-(2-furyl)purines and screened for their antitubercular activity against *M. tuberculosis* H37Rv. Among all, 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (**169**) exhibited best potency of MIC 0.39 ε g/mL and also low toxicity against mammalian cells and activity inside macrophages [169]. In a purine derivatives synthesized by Pathak et. al., 9-(ethylcarboxymethyl)-6-(dodecylthio)-

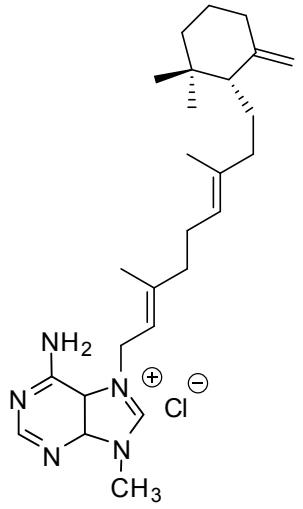
9*H*-purine (**170**) showed MIC of 0.78 ε g/mL [170]. In the analogues of agelasine E (**171**), one derivative (**171a**) showed promising activity with MIC of 1.56 ε g/mL against *M. tuberculosis* H37Rv [171]. After the keen observation of SAR of above molecules, Braendvang et al. synthesized 6-(2-furyl)-9-(p-methoxybenzyl)purines carrying a variety of substituents in the 2- or 8-position and was successful in identifying a more potent molecule (**172**, MIC=0.20 ε g/mL) [172] of above all series. The same group further synthesized the purine derivatives and found a more potent molecule (**173**) of above all series, which has shown an $IC_{90}$ of <0.20 μg/mL against *M. tuberculosis* H37Rv [173].



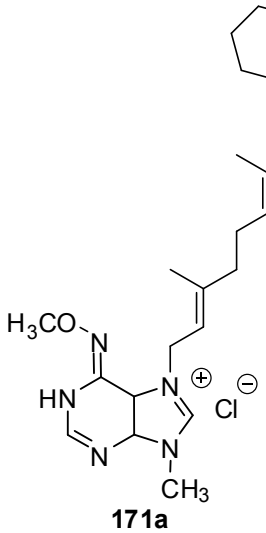

**169**



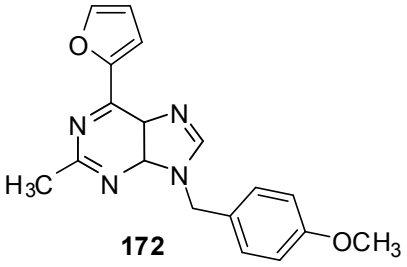

**170**



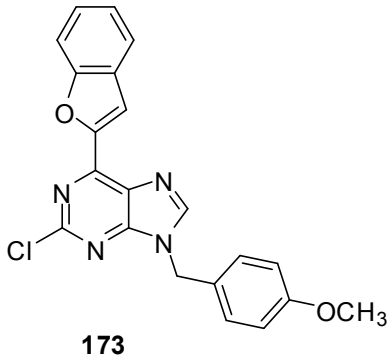

**171**




**171a**



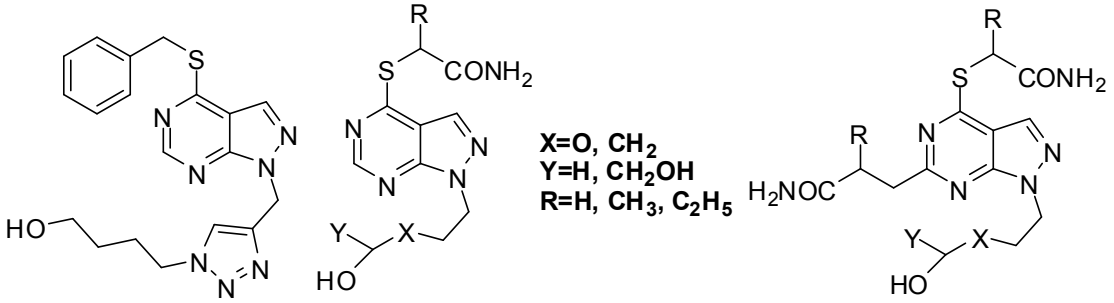

**172**




**173**

In search of new antitubercular purine type analogues, Moukha-Chafiq et al. synthesized a series of 1-[1-(4-hydroxybutyl)-1,2,3-triazol-(4 and 5)-ylmethyl]-1*H*-

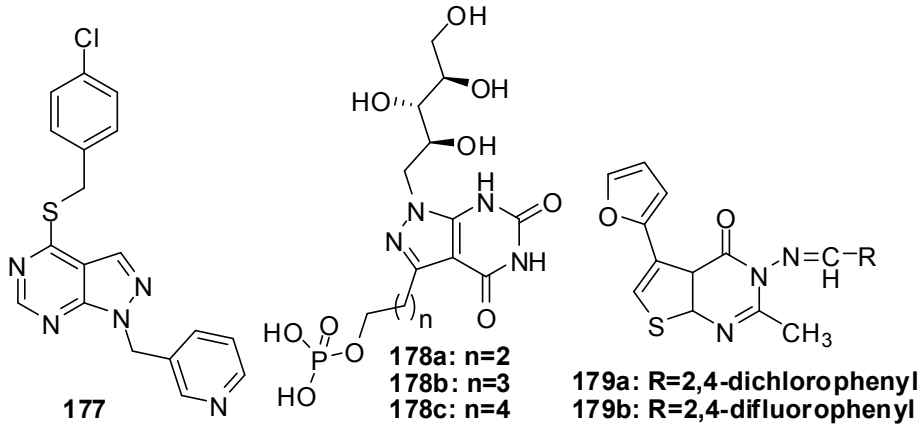
pyrazolo[3,4-d]pyrimidines and all of them were inactive but one compound (**174**) has shown MIC of 12.5 ε g/mL [174]. [175,176].




**174** **175** **176**

In continuation, they synthesized a series of di/trisubstituted pyrazolo[3,4-d]pyrimidines (**175, 176**) and observed no significant antituberculosis activity at concentrations up to 6.25 ε g/mL

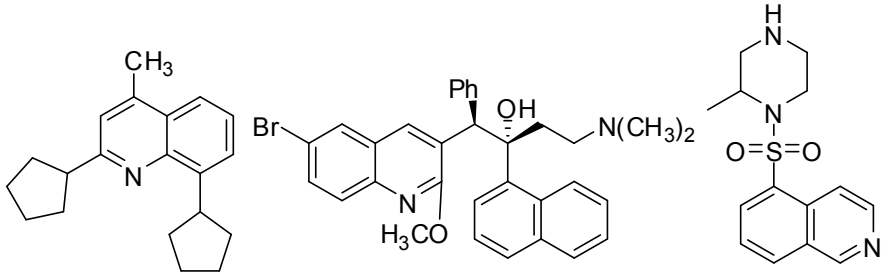
A multiple parallel synthesis of a series of *N*,*S*-bis-alkylated thiopyrazolo[3,4-d]pyrimidines, based on sequential *S*- then *N*-alkylation, is carried out. These compounds showed significant anti-mycobacterial activity (MICs down to Ò2 µg/mL) and their potential as significant drug-like leads is substantiated through cytotoxicity evaluation and in silico profiling. Among all, one compound (**177**) has shown MIC=0.5-1 µg/mL against *M. tuberculosis* H37Rv [177]. Zhang et al. synthesized a homologous series of three pyrazolopyrimidine analogues (**178a-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: $K_i$=15-40 nM) of the lumazine synthases of *Mycobacterium tuberculosis* with inhibition constants in the low nanomolar to subnanomolar range. Molecular modeling of one of the homologues bound to *Mycobacterium tuberculosis* lumazine synthase suggests that both the hypothetical intermediate in the lumazine synthase-catalyzed reaction pathway and the metabolically stable analogues bind similarly [178]. In a series of Thieno[2,3-d]pyrimidin-4-one, two compounds (**179a** and **179b**) have shown moderate potency of 5 µM/L against *M. tuberculosis* and *M. avium*, which is equal to that of rifampicin [179].



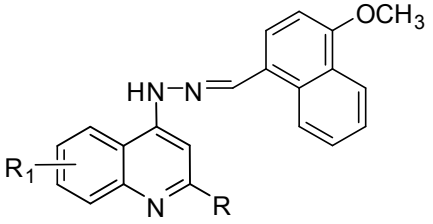

**177**

**Quinoline and Quinoxaline Derivatives**

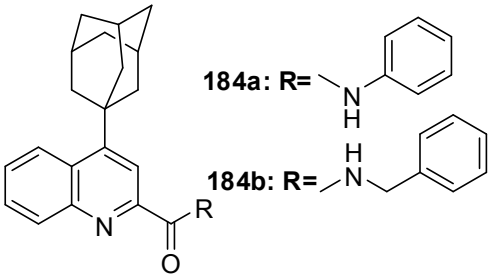
The start point for the preparation of the quinoline derivatives to be evaluated against TB were quinoline based malaria drugs, such as quinine, chloroquine, mefloquine, primaquine, and amodiaquine which possessed moderate biological activity against TB. In adition, indentification of new promising quinoline based antitubercular agents, 2,8-dicyclopentyl-4-methylquinoline (DCMQ, **180**) [180] and Diarylquinoline (TMC207, **181**) [181] have definitely initiated the optimization of quinoline for antitubercular drugs. In this concern, Drews et al. screened 1-(5-isoquinolinesulfonyl)-2-methylpiperazine (**182**), a protein kinase inhibitor for its antitubercular profile and found to inhibit the growth of two different mycobacterial strains, the slow-growing *Mycobacterium bovis* Bacille Calmette Guerin (BCG) and the fast-growing saprophyte *Mycobacterium smegmatis* $mc^2$ 155, in a dose-dependent manner. While screening for the effect of kinase inhibitors on mycobacterial growth, millimolar concentrations of **182** induced a 40% decrease in the growth of *M. bovis* BCG when measured as a function of oxidative phosphorylation. This **182-**induced decrease in growth was shown to involve a 2-log fold decrease in the viable counts of *M. smegmatis* within a 48h period and a 50% reduction in the number of BCG viable counts within a 10-day period. Micromolar concentrations of **182** induced a significant decrease in the activity of the *Mycobacterium tuberculosis* protein serine/threonine kinase (PSTK) PknB. The inhibition of mycobacterial growth as well as the inhibition of a representative *M. tuberculosis* protein serine/threonine kinase PknB suggests that conventional PSTK inhibitors can be used to study the role that the mycobacterial PSTK family plays in controlling bacterial growth [182]. Savini et al. synthesized a series of quinolinyl hydrazones and majority of the tested compounds showed an inhibitory activity between 95 and 100%. The most potent compounds of the series (**183a-c**) were having a MIC of 0.78 εg/mL. Theese results indicated that the activity was significantly affected by substituents both on the quinoline nucleus and hydrazinoic moiety. On quinoline nucleus the most effective substituents resulted were 6-cyclohexyl, 7-methoxy or ethoxy and 7-chloro groups. Similarly, for the hydrazinoic moiety greater effectiveness resulted for *para* and ortho-methoxynaphthyl substituents whereas disubstitution with chlorine resulted in inactive compounds [183].




**180** **181** **182**



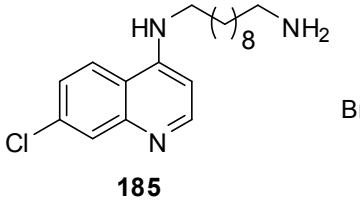
**183a: R=H, $R_1$=7-$OCH_3$**
**183b: R=$CH_3$, $R_1$=6-*n*.$OC_4H_9$**
**183c: R=$CH_3$, $R_1$=7-Cl**



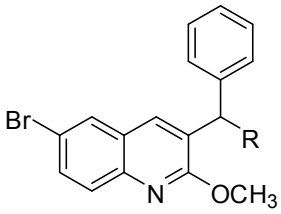
**184a: R=**

**184b: R=**

Inspired with the activity profile of DCMQ (**180**), Monga et al. synthesized four new series of the ring-substituted quinolinecarbohydrazides. Of these 3-quinolinehydrazides and $N^2$-alkyl/$N^2$,$N^2$-dialkyl/$N^2$-aryl-4-(1-adamantyl)-2-quinolinecarboxamides showed moderate activity of MIC in the range of 6.25-3.125 ε g/mL against *M. tuberculosis* H37Rv. The most active compounds were adamantyl derivatives (**184a** and **184b**) exhibited MIC of 3.125 ε g/mL [184]. Whereas, de Souza et al. synthesized a number of thirty-three quinoline derivatives based on TMC207 (**181**) and found a molecule (**185**) active with a MIC=3.12 ε g/mL [185]. With the same interest, Upadhayaya et al. synthesized 3-benzyl-6-bromo-2-methoxy-quinolines and amides of 2-[(6-bromo-2-methoxy-quinolin-3-yl)-phenylmethyl]-malonic acid monomethyl ester. Among all, four compounds (**186a-d**) showed moderate activity of MIC 6.25 ε g/mL against *M. tuberculosis* H37Rv [186].

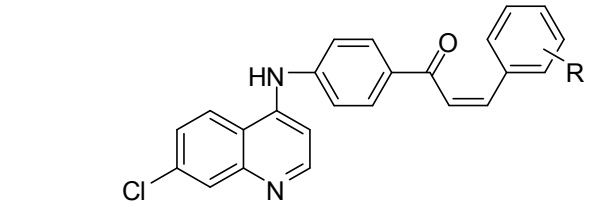


**185**

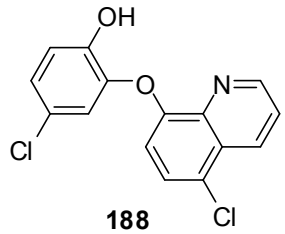


**186a: R= Imidazolyl**
**186b: R=C-(Thiophen-2-yl)-methylamine**
**186c: R=Pyrazolyl**
**186d: R=6-Amino-chromen-2-one**

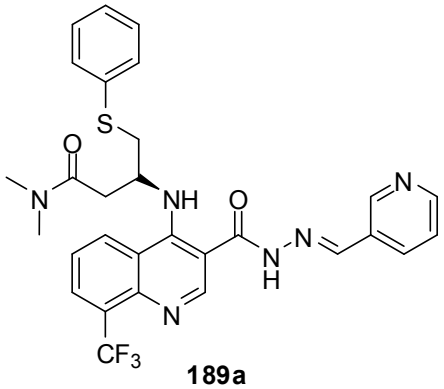
Most recently, Sharma et al. synthesized a series of substituted quinolinyl chalcones and substituted quinolinyl pyrimidines and evaluated for their in vitro antitubercular activity against *Mycobacterium tuberculosis* H37Rv. Among both the series, chalcone derivatives **187a** and **187b** have shown antitubercular activity of MIC 3.12 μg/mL and were nontoxic against VERO, MBMDM cell lines [187]. P. Gratraud evaluated the antimycobacterial potential of NAS-91 (**188**) and found that NAS-91 has multiple targets, which is particularly desirable for avoiding the emergence of resistant strains of *M. tuberculosis*. Therefore, NAS-91 represents a potent pharmacophore and appears to be a promising lead compound for future inhibitor development against tuberculosis [188]. Eswaran et al. synthesized quinoline-3-carbohydrazone derivatives and screened for their antitubercular efficacy. Among all, two compounds (**189a** and **189b**) have shown promising activity with a MIC 0.625, 2.5 and 1.25 μg/mL against *M. tuberculosis* H37Rv, *M. smegmatis* and *M. fortuitum* respectively. These compounds have shown almost equal potency similar to that of standard rifampicin [189]. Whereas in the series of 4-quinolylhydrazones synthesized by gemma et al., the most active compound (**190**) displayed an antitubercular activity of MIC 0.6 μM and selectivity index 2.27 [190].



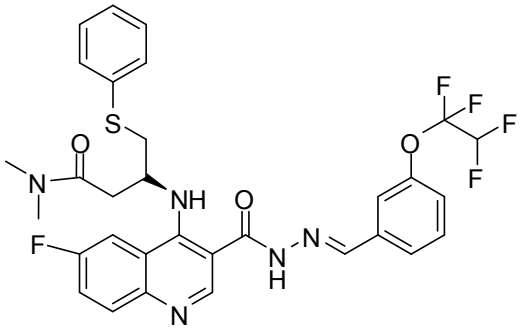
**187a: R=2,3-dimethoxy**
**187b: R=2,5-dimethoxy**



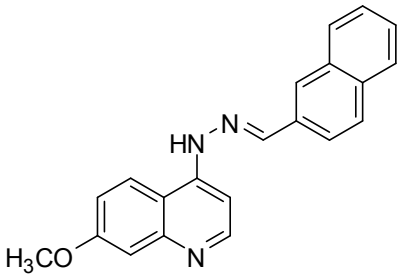
**188**



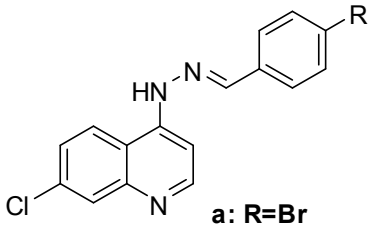
**189a**



**189b**



**190**

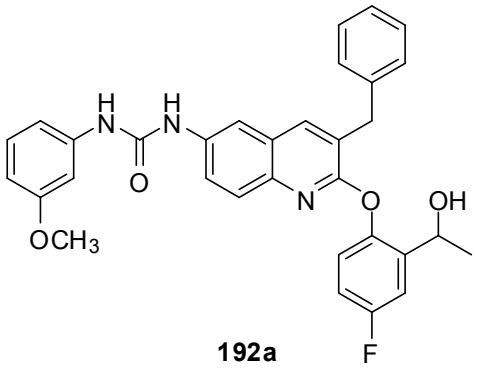


**191**

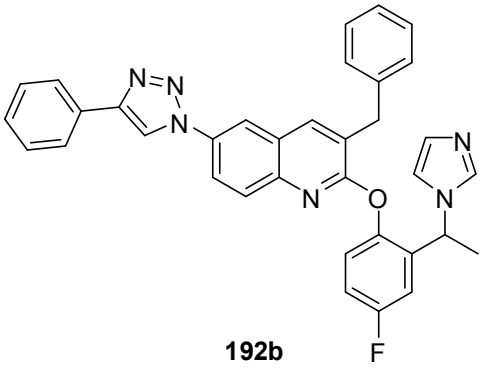
**a: R=Br**
**b: R=F**
**c: R=OCH$_3$**

In a similar approach, Candea et al. synthesized 7-chloro-4-quinolinylhydrazone derivatives and found three molecules (**191a-c**) with a moderate antimycobacterial activity with a MIC 2.5 µg/mL. These compounds were found to be nontoxic against J774 cell line up to the concentration 100 µg/mL [191]. In search of novel potent quinoline derivatives, Upadhayaya et al. synthesized quinoline derivatives consisting of triazolo, ureido and thioureido substituents at C-6 position. Of these, ureido derivative (**192a**) and triazolo derivative (**192b**) have shown moderate activity of MIC 3.125 µg/mL against *M. tuberculosis* H37Rv [192]. With the same motivation Nayyar et al. synthesized a novel series of amino acid conjugates of 4-(adamantan-1-yl) group containing quinolines. The most active nontoxic compound (**193**) of the series exhibited increased potency of 1 µg/mL against *M. tuberculosis* H37Rv and 3.125 µg/mL against drug-resistant strain, in comparison to former molecules (**192a** &**192b**) [193]. In the same direction of approach, Kozikowski group synthesized quinoline-based derivatives and evaluated for their antitubercular efficiency. Among all, compound **194** has shown remarkable activity of MIC 0.77 µM against *M. tuberculosis* H37Rv and 0.99-1.55 µM against drug-resistant strains [194]. In continuation the same group synthesized isoxazole based quinoline derivatives and found a lead molecule **195**, which showed MIC of 0.2 µM and 2.6 µM in MABA and LORA assay against *M. tuberculosis* H37Rv [195]. Thus,

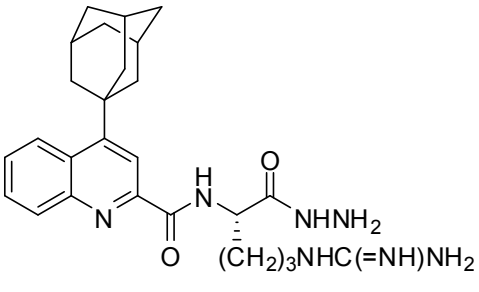
optimization of quinolines for the development of antitubercular agents is a fruitful approach.



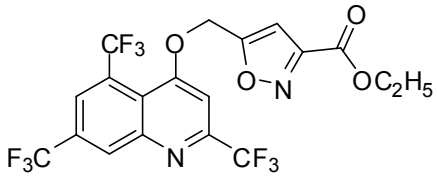
**192a**



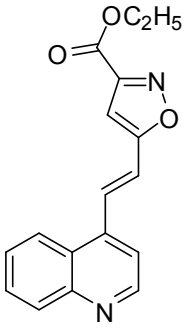
**192b**



**193**

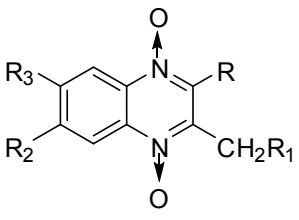


**194**

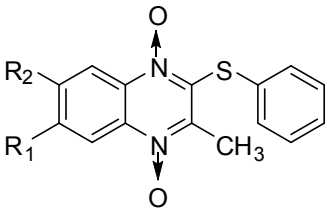


**195**

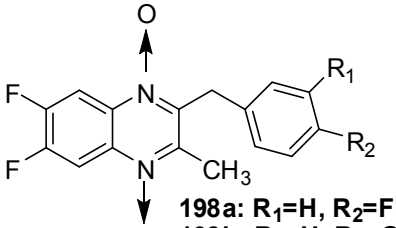
The quinoxaline derivatives show very interesting biological properties (antibacterial, antiviral, anticancer, antifungal, anthelmintic, insecticidal) and recently, some researchers have identified the antimycobacterial activities of various 2-methylquinoxaline 1,4-dioxides, confirming that the presence of a methyl (or halogenomethyl) group at 2(3) position of this ring ( **196a** and **196b**) is favourable for antimicrobial activity. In this context as contribution in the development of quinoxaline derivatives, Carta et al. synthesized a number of 36, 6(7)-substituted-3-methyl- or 3-halogenomethyl-2-phenylthio-phenylsulphonyl-chloro-quinoxaline 1,4-dioxides and screened for their in vitro antimycobacterial acivity. Among all, two compounds **197a** and **197b** exhibited great potency of MIC 0.39 µg/mL against *M. tuberculosis*, which is comparable to Rifampicin (MIC=0.25 µg/mL) [196]. In another series, four compounds (**198a-d**) have shown moderate activity of MIC 2 µg/mL [197]. In the series of quinoxaline derivatives, lack of 1,4-dioxide showed reduction in the activity. Most active compound (**199**) showed MIC of 6.25 µg/mL against MTB H37Rv and 0.5 µg/mL against MTB H37Ra [140]. Which prompted to continue the optimization of quinoxaline 1,4-dioxide.



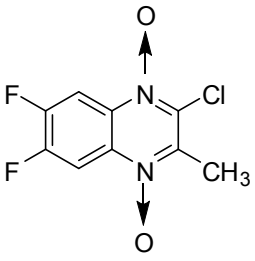
**196a: $R_1$=H**
**196b: $R_1$=Br**



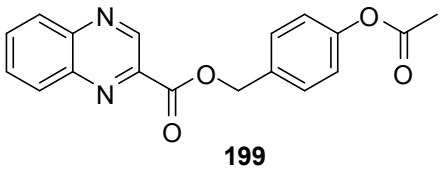
**197a: $R_1$=H, $R_2$=Cl**
**197b: $R_1$=$CF_3$, $R_2$=H**



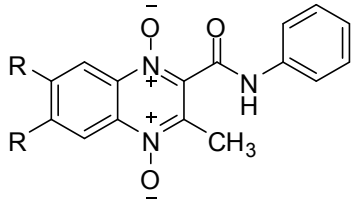
**198a: $R_1$=H, $R_2$=F**
**198b: $R_1$=H, $R_2$=$OCH_3$**
**198c: $R_1$=$R_2$=$OCH_3$**



**198d**

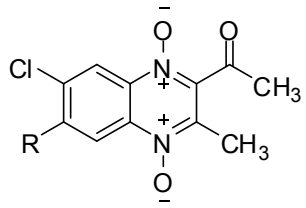


**199**

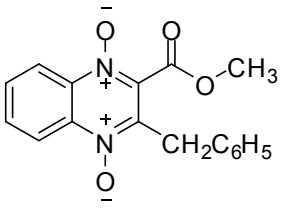


**200a: R=Cl**
**200b: R=H**

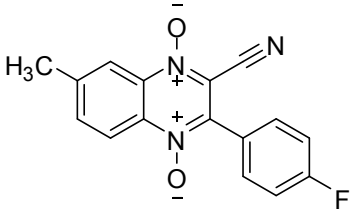
Inspired with the activity profile of **196a** and **b,** Zarranz et al. [198] synthesized a series of quinoxaline-2-carboxamide 1,4-di-*N*-oxide derivatives and evaluated for their in vitro antituberculosis activity against *M. tuberculosis* H37Rv. Among all, compound **200a** exhibited best MIC of 0.78 µM, has a solubility problem, while compound (**200b**) having MIC of 3.13 µM has a best selectivity index (SI=>40.06). Same group also synthesized 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 (**201a** and **201b**) 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) [199]. Villar et al. also found that the compound **201b** is also active against resistant strains of *M. tuberculosis* [200]. In another series, 2-benzyl-3-(methoxycarbonyl)quinoxaline 1,4-dioxide (**202**) has shown best potency above all, with a MIC=0.10 µg/mL and selectivity index SI=470 [201].



**201a: R=Cl**
**201b: R=H**



**202**

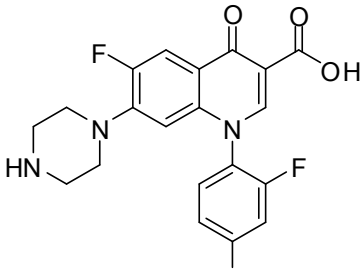


**203**

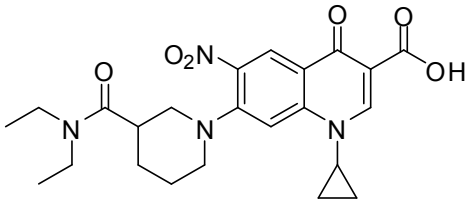
A new series of 3-phenylquinoxaline 1,4-di-*N*-oxide having selectivity against *Mycobacterium tuberculosis* have been prepared and evaluated. 34 out of the 70 tested compounds showed an MIC value less than 0.2 µg/mL, a value on the order of the MIC of rifampicin. Furthermore, 45% of the evaluated derivatives showed a good in vitro activity/toxicity ratio. The most active compound was 7-methyl-3-(4ô-fluoro)phenylquinoxaline-2-carbonitrile 1,4-di-*N*-oxide (**203**) (MIC <0.2 µg/mL and SI >500) [202]. In conclusion, the potency, low cytotoxicity and selectivity of these compounds make them valid lead compounds for synthesizing new antitubercular agents.

**Quinolones**

The introduction of nalidixic acid during 1962 has shown the new avenue for the patients with the bacterial infections. The continuous effort to increase the efficacy against bacteraemia has led to identify new prototype quinolone which is active only against gram-negative bacteria similar to that of nalidixic acid. But the introduction of norfloxacin, a fluoroquinolone derivative during 1980s has changed the landscape of antibacterial chemotherapy being active against both gram-negative and gram-positive bacterial pathogens. Recently, the quinolone drugs; Ofloxacin (**19**), Gatifloxacin (**22**), Moxifloxacin (**20**) and Levofloxacin(**21**), are serving as second line drugs for tuberculosis. In this concern, many researchers optimized the quinolones and evaluated for their antitubercular potency. In this direction, Sheu et al. synthesized a series of 1-ethyl- and 1-aryl-6-fluoro-1,4-dihydroquinol-4-one derivatives and evaluated for antimycobacterial and cytotoxic activities. Of these, once derivatives (**204**) exhibited the preeminent MIC of 1.56 µg/mL against *M. tuberculosis* H37Rv (MTB) and also a good selectivity index (SI=>40.06). Further, compound **204** also proved to be a potent anti-TB agent with an $EC_{90}$ value of 5.75 µg/ml [203]. Similarly, Senthilkumar et al. synthesized a number of fifty-one novel 1-(cyclopropyl/2,4-difluorophenyl/t-butyl)-1,4-dihydro-6-fluoro-7-(sub secondary amino)-4-oxoquinoline-3-carboxylic acids and found a potent antitubercular agent (**205**), which showed MIC of 0.09 µM against MTB and MDR-TB respectively. In the in vivo animal model **205** 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 [204].

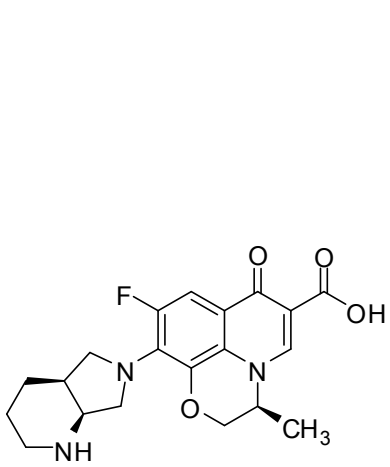



**204**

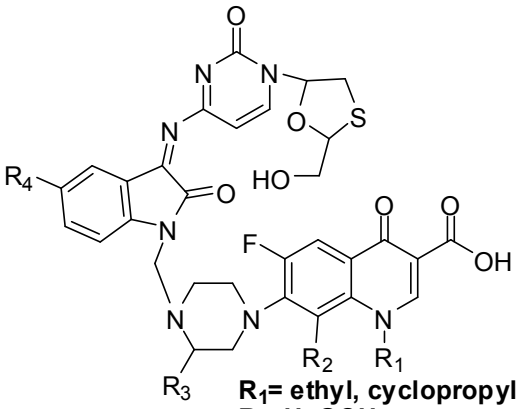



**205**

Recently, new quinolone antibacterial agents were observed for their potency against certain types of mycobacterial species in in vitro tests and in experimental animals. With this motivation, Kawakami et al. synthesized a series of pyridobenzoxazine derivatives by replacement of the *N*-methylpiperazinyl group of Levofloxacin (**21**) with various basic substituents to investigate the structure-activity relationships between antimycobacterial activities and basic substituents at the C-10 position. Among the compounds synthesized, compound **206**, 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 antimycobacterial activities but that lipophilicity of the compound was not a critical factor affecting the potency [205]. While in the investigation of potency against *M. kansasii* LVFX showed MIC in the range of 0.12-0.25 µg/ml while Moxifloxacin (**20**) showed the range of MIC=Ò0.06-0.12 µg/mL [206]. These results prompted for optimization of other quinolone antibacterials to be investigated as antituberculars.



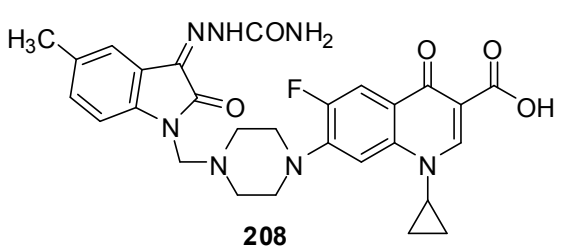
**206**



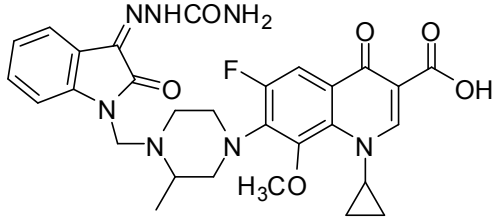
**207**

**$R_1$= ethyl, cyclopropyl**
**$R_2$=H, $OCH_3$**
**$R_3$=H, $CH_3$**
**$R_4$=H, Cl, F**

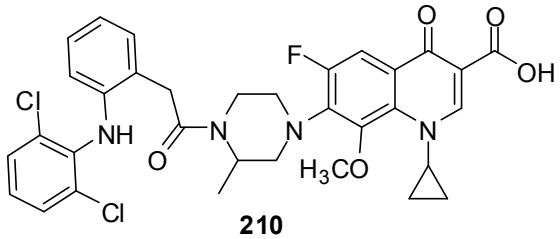
Inspired with the above activity profile of quinolones, Sriram et al. synthesized a series of Lamivudine prodrugs bearing fluoroquinoles (**207**) and evaluated their efficacy against *M. tuberculosis* H37Rv. All the compounds exhibited an inhibition of 92-100% at a concentration of 6.25 µg/ml [207]. While in ciprofloxacin (**19**) derivatives synthesized by the same group, one compound (**208**) showed in vivo antitubercular 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 [208]. In continuation, Sriram et al. synthesized Gatifloxacin (**22**) derivatives and found a more potent compound (**209**) in comparison to compound **208**. In the in vivo animal model **209** decreased the bacterial load in lung and spleen tissues with 3.62- and 3.76-log10 protections, respectively [209]. With this motivation, he was able to find out a most potent molecule (**210**) 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 [210]. Contrarily, 7-[4-(5-amino-1,3,4 thiadiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolonic derivatives (**211a** and **211b**), synthesized by Talath et. al, showed moderate antitubercular activity at MIC of 10 εg/mL compared to isoniazid standard [211].



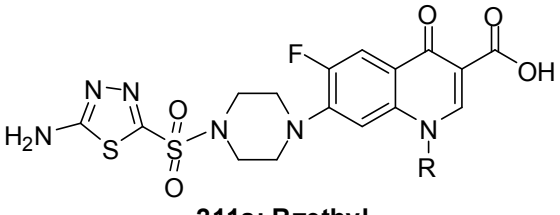
**208**



**209**

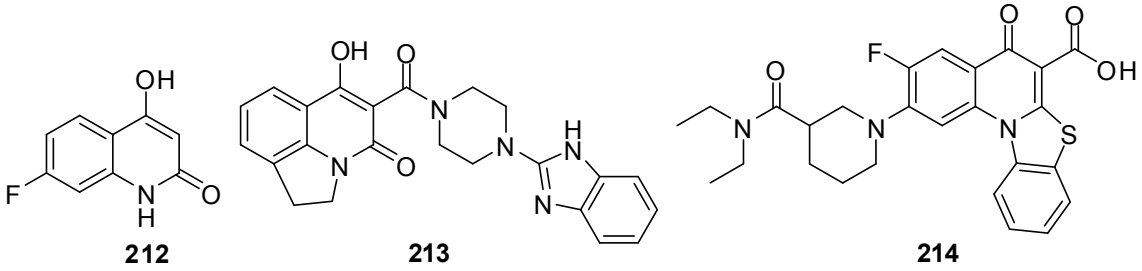


**210**



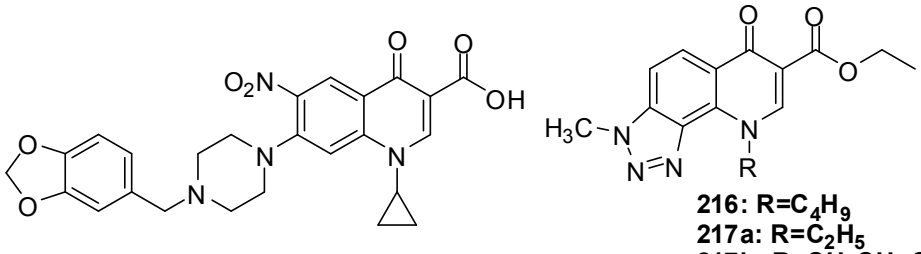
**211a: R=ethyl**
**211b: R=cyclopropyl**

In another approach, Arya et al. investigated 3-unsubstituted 4-hydroxyquinolin-2(1*H*)-one potency against *M. tuberculosis* H37Rv. Among all, one compound (**212**) showed moderate activity of MIC 3.125 εg/mL [212]. Surprisingly, the series of 1-hydroxy-3-oxo-5,6-dihydro-3*H*-pyrrolo[3,2,1-ij]quinoline-2-carboxylic acid hetarylamides exhibited excellent activity (MIC=0.39-6.25 εg/mL) in comparison to **212**. The most active compound **213** showed MIC of 0.39 εg/mL against *M. tuberculosis* H37Rv [213].



**212** **213** **214**

Whereas, Dinakaran et al. investigated the effect of nitro substitution on quinoline ring. In that direction, they synthesized a series of 2-(sub)-3-fluoro/nitro-5,12-dihydro-5-oxobenzothiazolo[3,2-a]quinoline-6-carboxylic acid derivatives and evaluated for in-vitro and in-vivo antimycobacterial activities against *M. tuberculosis* H37Rv (MTB), multi-drug resistant *M. tuberculosis* (MDR-TB), and *Mycobacterium smegmatis* ($MC^2$), and also tested for the ability to inhibit the supercoiling activity of DNA gyrase from *M. smegmatis.* Among the thirty-four synthesized compounds, 2-(3-(diethylcarbamoyl)piperidin-1-yl)-)-3-fluoro-5,12-dihydro-5-oxobenzothiazolo[3,2-a]quinoline-6-carboxylic acid (**214**) was found to be the most active compound with MIC of 0.18 and 0.08 µM against MTB and MDR-TB, respectively. In the in-vivo animal model **214** decreased the bacterial load in lung and spleen tissues with 2.78 and 3.12-log10 protections, respectively, at the dose of 50 mg/kg body weight [214]. In another investigation, 6-nitroquinolone (**215**) 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 **215** 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 [215].

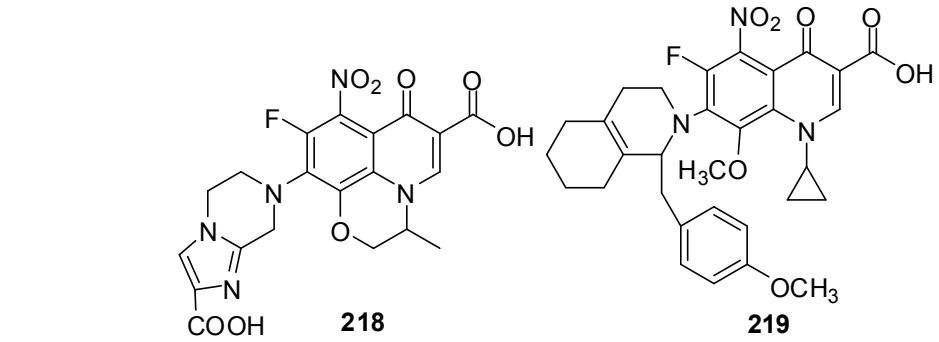


**215**

**216: R=$C_4H_9$**
**217a: R=$C_2H_5$**
**217b: R=$CH_2CH=CH_2$**

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 *M. tuberculosis* H37Rv and further 11 clinically isolated strains of *M. tuberculosis* endowed with different drug resistance. Among all, compound **216** exhibited best activity against all strains with a MIC of 0.5 εg/mL [216]. Whereas in another series of [1,2,3]Triazolo[4,5-h]quinolones synthesized by the same group, Compounds **217a** and **217b** exhibited better potency of MIC in the range 0.125-16.0 εg/mL against H37Rv and

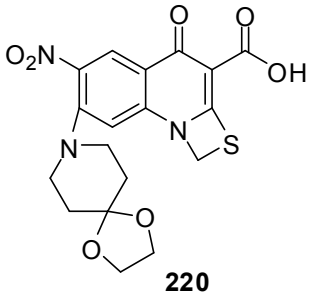
11 clinical isolates of MDR-TB. These results showed that [1,2,3]-triazolo[4,5-*h*]quinolones were endowed with an excellent activity against MDR-TB strains with no cytotoxicity [217].



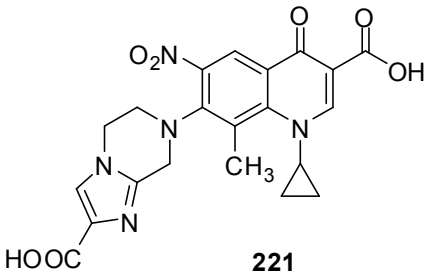
**218**



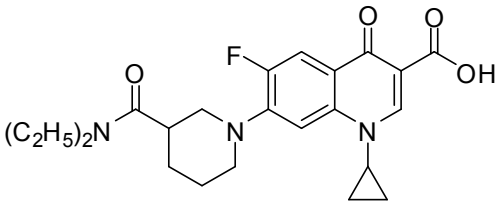
**219**



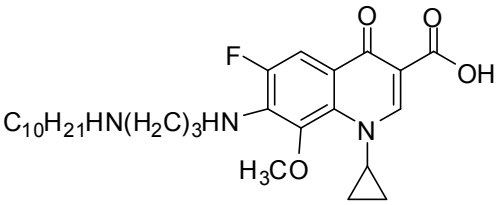
**220**



**221**



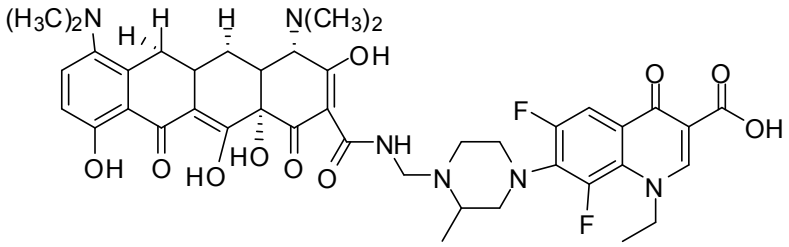
**222**



**223**

In the process of investigating novel quinolones as antimycobacterial agents, Sriram group synthesized many derivatives of quinolones and 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 **218** exhibited $MIC_{99}$ 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 [218]. Compound **219** decreased the bacterial load in lung and spleen tissues with 2.54 and 2.92-log10 protections [219], while **220** decreased the bacterial load by 30% and 42%, respectively, at a dose of 50 mg/kg body weight [220]. In an effort to increase the antitubercular potency of quinolones, synthesized 1-(cyclopropyl/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 (**221**) of the series showed MIC of 0.42 ε M and 0.09 ε M against MTB and MDR-TB respectively [221]. While in an another series, 7-(3-(diethylcarbamoyl)piperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**222**) exhibited promising MIC of 0.09 ε M against MTB and MDR-TB respectively. In the in vivo animal model **222** 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 [222].

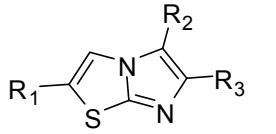


**224**

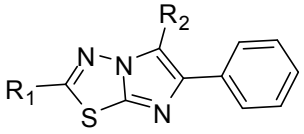
With the same motivation, de Almeida et al. synthesized Moxifloxacin and Gatifloxacin derivatives and evaluated against *M. tuberculosis* H37Rv (MTB). The most active compound (**223**) exhibited a MIC of 0.31 εg/mL [223]. While in the series of Tetracycline incorporated with quinolones, compound **224** was found to be the most active against MTB with a MIC of 0.2 µg/mL and also nontoxic to the CEM cells untill 200 µM [224]. Thus, developing quinolones as antimycobacterial agents is a worthy approach.

**Imidazooxazole, Imidazothiazole and Imidazothiadiazole Derivatives**

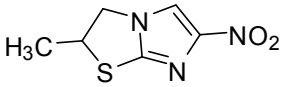
A number of selected imidazo[2,1-*b*]thiazoles entered the screening at the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) and one of these compounds, 2-chloro-6-phenylimidazo[2,1-*b*]thiazole (**225a**) showed antitubercular activity. On this basis, Andreani et al. synthesized new analogues bearing a substituted ring at the 6-position and compounds bearing nitroso group at 5-position. Among all the derivatives screened against *M. tuberculosis* H37Rv, compound **225b** exhibited best activity of MIC 0.39 εg/mL, which is better than that of **225a** and comparable to rifampicin [225]. In a series of 2,6-disubstituted and 2,5,6-trisubstituted imidazo[2,1-b][1,3,4]thiadiazoles, only two compounds (**226a** and **226b**) showed 100% inhibition at a concentration of >6.25 εg/mL [226]. Zwawiak et al. developed a series of 2,3-dihydro-7-nitroimidazo[5,1-b]oxazoles on the basis of PA-824 (**58a**) and CGI-17341 (**58b**)**.** Among all, one compound (**227**) exhibited a moderate activity of MIC 5 εg/mL against *M. tuberculosis* H37Rv [227].



**225a: $R_1$=Cl, $R_2$=H, $R_3$=$C_6H_5$**
**225b: $R_1$=H, $R_2$=NO, $R_3$=4-Cl-$C_6H_5$**



**226a: $R_1$=2-furyl, $R_2$=CHO**
**226b: $R_1$=cyclohexyl, $R_2$=$CH_2OH$**

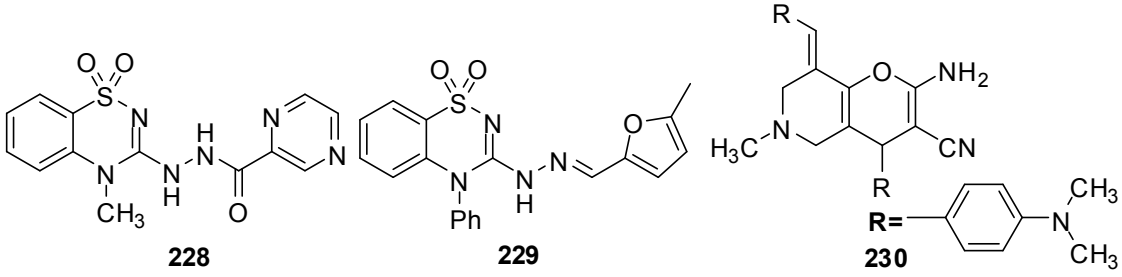


**227**

**Benzothiadiazine and Pyranopyridine Derivatives**

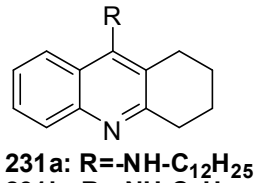
In an effort to develop new and more effective therapies to treat tuberculosis, Kamal et al. synthesized a series of benzothiadiazine 1,1-dioxide derivatives and their in vitro activity was evaluated against *Mycobacterium tuberculosis* (MTB), *M. avium* and *M. intracellulare*. Of these, compound **228** showed best potency of MIC 0.5 εg/mL against MTB H37Rv and 0.5-2 εg/mL against resistant strains. However, the in vivo testing in a mouse model of tuberculosis infection did not show significant anti-tubercular activity, probably because of its poor bioavailability [228]. In continuation, the same group

synthesized 5-nitrofuran, 5-nitrothiophene and arylfuran coupled benzothiadiazines and on evaluation, these compounds exhibited moderate antitubercular activity. The most active compound (**229**) displayed a MIC of 1 ε g/mL against MTB H37Rv [229]. With the same inspiration, Kumar et al. synthesized 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 and evaluated for their antitubercular activity. Among all, compound **230** was found to be the most potent compound (MIC: 0.43 µM) against MTB and MDR-TB, being 100 times more active than isoniazid against MDR-TB [230].

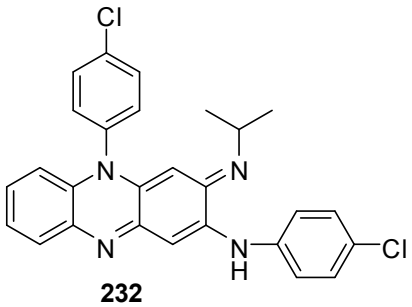


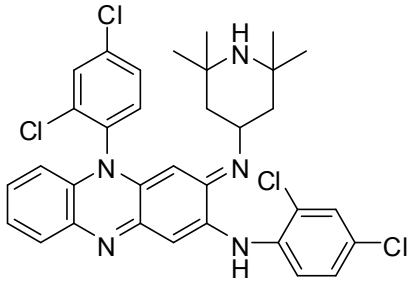

**Acridine, Phenazine and Phenothiazine Derivatives**

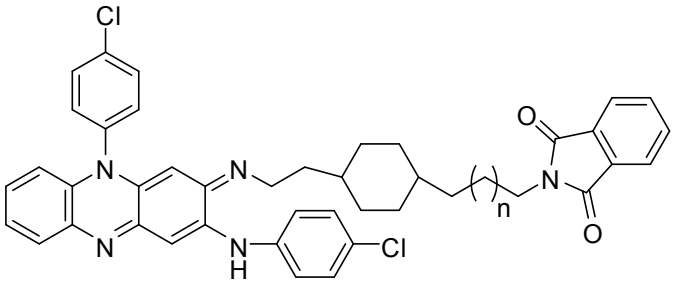
Acridine derivatives have been widely used in malaria chemotherapy and this skeleton is still being explored for better antimalarials. In addition, the antibacterial activities are also known to be associated with many acridine analogues. It has been established that amino acridines having electronic conjugation between the ring nitrogen and the amino group are most active antibacterial agents. It has also been documented that acridines reduce antimycobacterial resistance. In this concern Tripathi et al. synthesized a series of 9-substituted tetrahydroacridines and evaluated for their antitubercular activity. These derivatives exhibited promising activity profile, with MIC in the range of 6.25-0.78 ε g/mL against *M. tuberculosis* (MTB). Compound **231a** displayed best MIC of 0.78 ε g/mL against MTB-H37Rv, while compound **231b** displayed preeminent activity against MTB-H37Ra with MIC 1.56 ε g/mL [231].



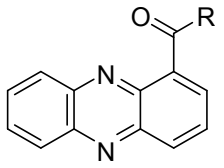

**231a: R=-NH-$C_{12}H_{25}$**
**231b: R=-NH-$C_8H_{17}$**



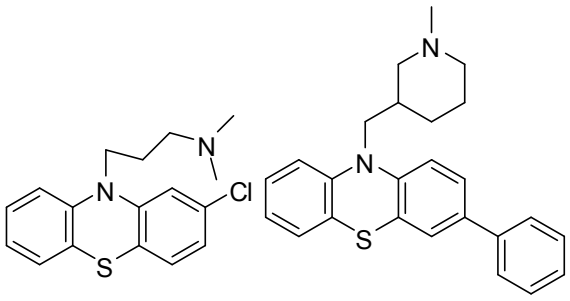


**234a: n=3**
**234b: n=4**



**235a: R=-NH-$C_6H_4$-4F**
**235b: R=-NH-$C_6H_4$-3Br**

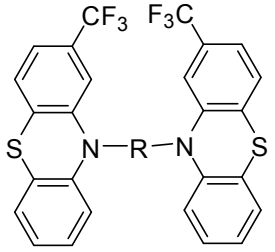
Clofazimine (**232**) is a fat-soluble riminophenazine dye used in combination with rifampicin and dapsone as multidrug therapy (MDT) for the treatment of leprosy. It has been used investigationally in combination with other antimycobacterial drugs to treat *Mycobacterium avium* infections in AIDS patients and *Mycobacterium avium* paratuberculosis infection in Crohn's disease patients. On this basis and to minimize the side-effects and to improve the antimycobacterial activity of Clofazimine, J. F. O'Sullivan group [232] developed 3-(2,4-dichloroanilino)-10-(2,4-dichlorophenyl)-2,10-dihydro-2-(2,2,6,6tetramethylpiperid-4-ylimino)phenazine (B4128) (**233**), which posses a similar mode of action of Clofazimine [233]. With the same motivation, Kamal et al. synthesised a series of phthalimido- and naphthalimido-linked phenazines and found two compounds (**234a** and **234b**) with a potency of MIC 1 µg/mL against *M. tuberculosis* H37Rv. These compounds also exhibited potency against resistant strains of *Mycobacterium* [234]. Whereas in a series of phenazine carboxamides, compounds **235a** and **235b** showed excellent activity against *M. tuberculosis* H37Rv with a MIC of 0.19 µg/L and also against drug-resistant strains of *M. tuberculosis*. Most interestingly, this series was found to be nontoxic [235], validating them as future antitubercular drug candidates.



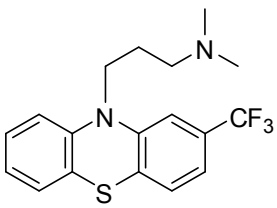
**236a**



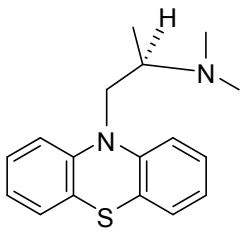
**236b**



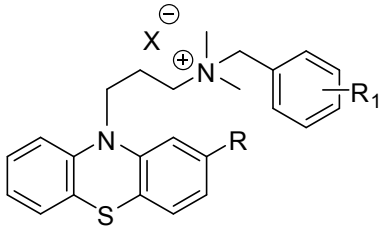
**236c: R=$C_3H_6$**
**236d: R=1,4-$C_6H_4$**



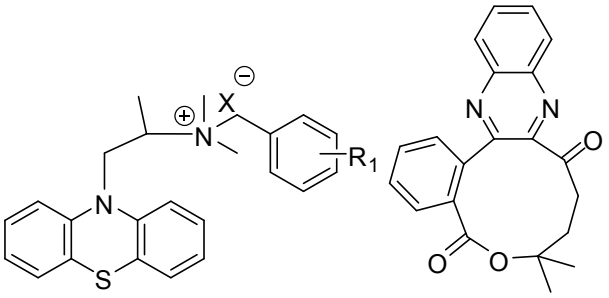
**237a**



**237b**



**237c: R=Cl**
**237d: R=H**
**237e: R=$CF_3$**

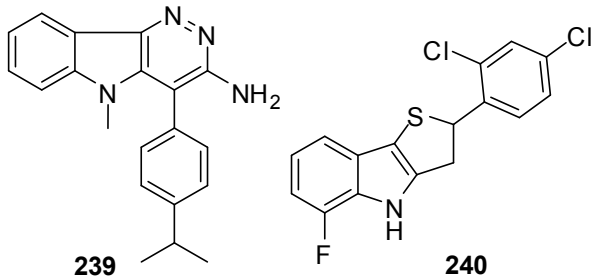



**237f** **238**

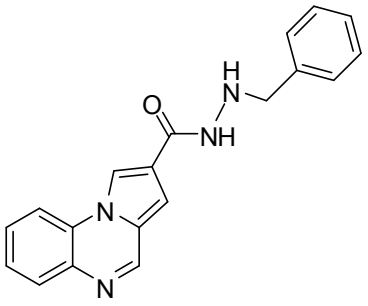
Phenothiazines have been reported for their antitubercular activity for many years, and the phenothiazine drug chlorpromazine (CPZ) (**236a)** is reported to have been successfully used to treat a TB patient. In this concern, a series of psychotropic phenothiazines were synthesized and examined as antitubercular agents against *Mycobacterium tuberculosis* H37Rv. Among all, three compounds (**236b-d**) exhibited promising activity with a mean MIC of 2.13 µg/mL [236]. Whereas quaternized CPZ, trifluprom azine (**237a**) and promethazine (**237b**) derivatives inhibited non-replicating *M. tuberculosis* at concentrations equal to or double their MICs against the actively growing strain. All the active compounds (**237c-f)** were non-toxic toward Vero cells ($IC_{50}$ > 128 µM). Based on SAR it was concluded that the benzyl or substituted benzyl groups, an electron-withdrawing substituent on the phenothiazine ring improved the potency. Commonly the optimum antitubercular structures possessed *N*-(4- or 3-chlorobenzyl) substitution on trifluprom azine [237]. While a macrolactone (**238**) derived from benzo[a]phenazine exhibited best potency against *M. tuberculosis* H37Rv with a MIC 0.62 µg/mL, which is better than that of Rifampacin [238].

**MiscellaneousClasses**

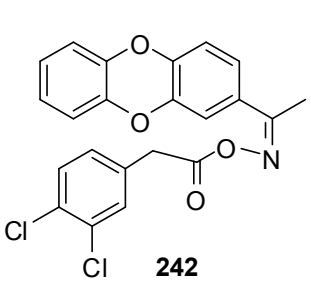
In search of potential antitubercular agents, Velezheva et al. synthesized pyridazinoindole analogues and screened them for inhibition of the growth of *M. tuberculosis*. The most active compound (**239**) exhibited a $MIC_{50}$ of 1.42 µg/mL against *M. tuberculosis* H37Rv (MTB) [239]. In the series (2-aryl-3,4-dihydro-2H-thieno[3,2-b]indoles) synthesized by Karthikeyan et al., compound **240** was found to be the most active compound with MIC of 0.4 ε g/mL against MTB and MDR-TB [240].



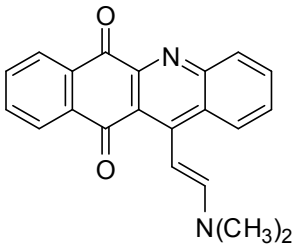

**239** **240**



**241**

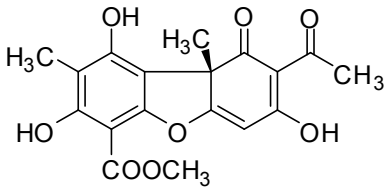


**242**

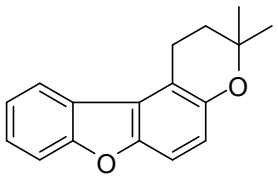


**243**

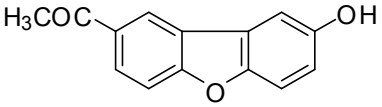
With the same motivation, Guillon et al. synthesized a series of pyrrolo[l,2-a] quinoxaline-2- or -4-carboxylic acid hydrazides and one compound (**241**) showed an interesting activity at 6.25 ε g/mL against *Mycobacterium tuberculosis* H37Rv, with a 100 percentage inhibition [241]. Compound **242** developed by Scozzafava et al. inhibited 80% at a concentration of 6.25 μζ [242]. While, Enamine-containing analogues of heteroarylquinones showed promising activity with a MIC in the range 6.25-0.1 ε g/mL against *Mycobacterium tuberculosis* H37Rv. The best selectivity index (SI=15.1) was displayed by the molecule (**243**) with a MIC 0.39 ε g/mL [243].



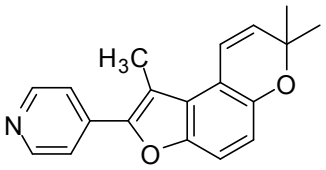
**244**



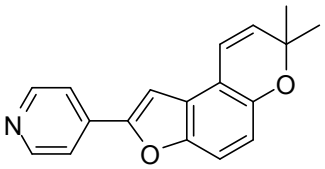
**244a**



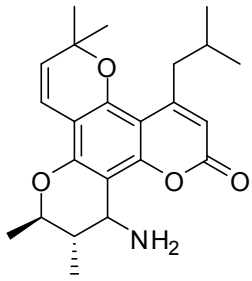
**245**



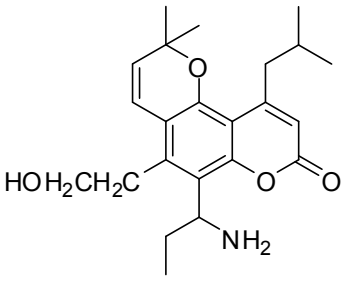
**246**



**247**



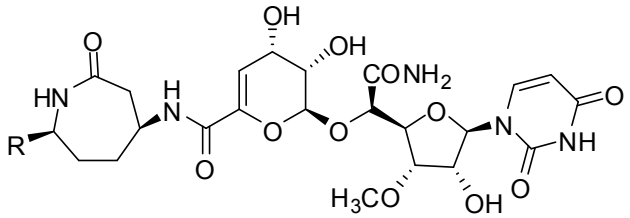
**248a**



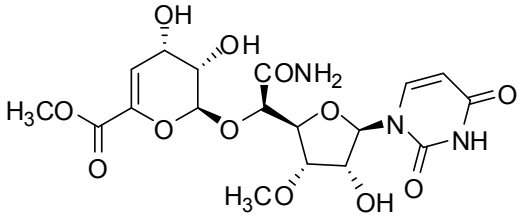
**248b**

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 (**244**) has been shown to display an interesting activity, but its weak potency did not permit its further development as an antimycobacterial drug. Simple dibenzofurans also occur in higher plants, where they often act as antifungal phytoalexins. So, for the development of a new class of antimycobacterial agents in order to fight resistance and

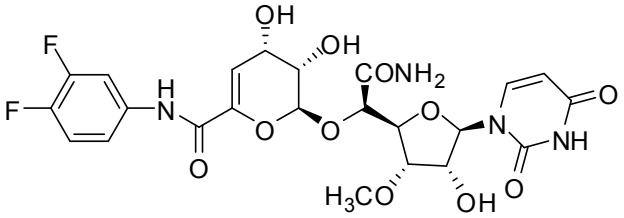
shorten the duration of therapy synthesis of natural product-like hybrids is an efficient route. In this concern, Prado et al. synthesized a series of 3,3-dimethyl-3*H*benzofuro[3,2-*f*][1]benzopyran and 1,2-dihydro-3,3-dimethyl-3*H*benzofuro[3,2-f][1]benzopyran, which displayed significant activities when tested against *Mycobacterium tuberculosis* H37Rv and Beijing strains, with $MIC_{99}$ in the range of 1-10 µg/ml. The most active compound (**244a**) exhibited a $MIC_{99}$ of 5, 1 µg/ml respectively against *M. tuberculosis* H37Rv and *M. smegmatis* [244]. In an effort to increase the potency, the same group synthesized another series, where they found the drop off in the activity. The most active compound (**245**) displayed $MIC_{95}$ 8 µg/ml against *M. tuberculosis* H37Rv [245]. In the next trial, the group was successful in producing molecules **246** and **247** with more potency of $MIC_{95}$ in the range 0.6-2.5 µg/ml against *M. tuberculosis* H37Rv [246, 247]. With the same inspiration, Xu et al. synthesized a series of pyranocoumarin derivatives, and found two compounds (**248a** and **248b**) were bactericidal in their effect on *M. tuberculosis* since their MBC/MIC ratios was 2. These two compounds had a MIC value of 16 µg/mL [248].



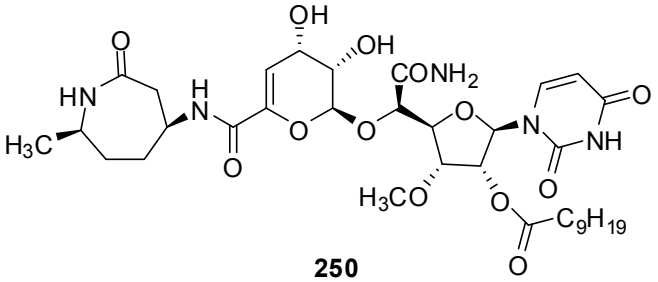
**249a: R=H**
**249b: R=CH$_3$**



**249c**



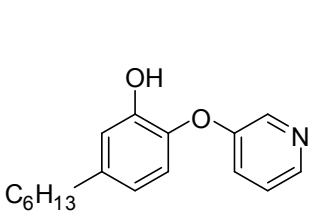
**249d**



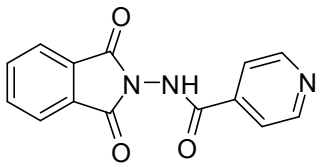
**250**

Translocase I (Mra Y) is one of the enzymes involved in the biosynthesis of peptidoglycan and is a possible target for developing antibiotics. In the course of screening for new antibiotics with translocase I inhibitory activity, Hotoda et al. found the capuramycin (**249a**), with a selective antibacterial activity against mycobacteria along with its methylated derivative, A-500359A (**249b**). In continuation the same group isolated A-500359E (**249c**) lacking the azepan-2-one moiety of capuramycin. So, in an effort to increase the potency of capuramycin skeleton, Hotoda developed the analogues of **249a**, **249c** and tested for their translocase I inhibitory activity and in vitro antimycobacterial activity. It was observed that the aryl analogs were found to be effective substituents for capuramycin analogues. The most active compound (**249d**)

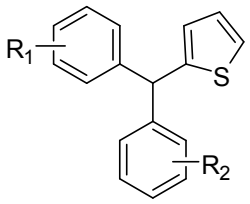
displayed a MIC of 6.25 µg/ml against *M. smegmatis* and translocase I inhibition with an $IC_{50}$ 9 ng/mL. This compound also exhibited good activity profile against resistant strains of *Mycobacterium*, which is better than the both capuramycin and A-500359E [249]. In the next trail, he synthesized the analogues of acylated derivatives of capuramycin and A-500359A and found a most potent molecule (**250**) of all, which displayed a MIC of 6.25 µg/ml against *M. smegmatis* and best potency particularly against resistant strains of *Mycobacterium* [250].



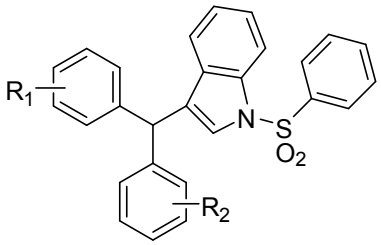

**251**



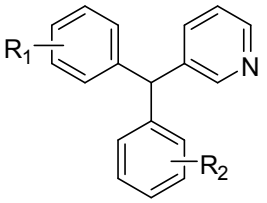

**252**




**253**

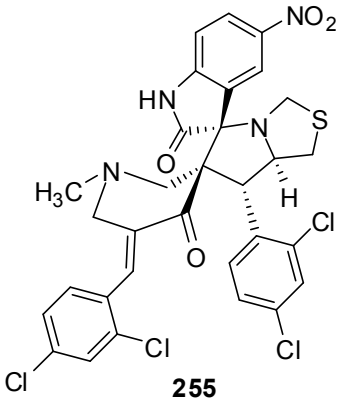



**254a**

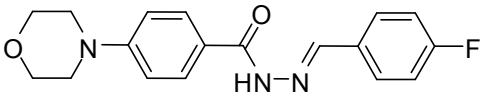



**254b**

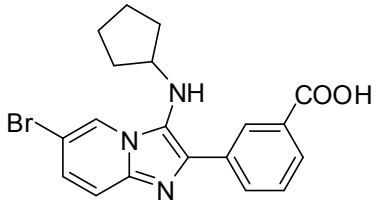
Previous structure-based design studies resulted in the discovery of alkyl substituted diphenyl ether inhibitors of InhA, the enoyl reductase from *Mycobacterium tuberculosis*. However, despite their promising in vitro activity, these compounds have Clog*P* values of over 5. In efforts to reduce the lipophilicity of the compounds, and potentially enhance compound bioavailability, Ende et al. synthesized a series of substituted hetero/aryl ethers and of these, one compound (**251**) exhibited a moderate $MIC_{90}$ 3.13 µg/mL but have improved Clog*P* value [251]. Santos et al. [252] synthesized a series of pthalamide derivatives. The most active compound (**252**) displayed a MIC of 5 µg/mL against *M. tuberculosis* H37Rv and a good selectivity index. While Panda group synthesized two series of thiophene (**253**) and benzopyrrole/pyridine (**254a** and **254b**) triarylmethanes [253, 254]. Thiophene analogues displayed MIC in the range 3.12-12.5 µg/mL and benzopyrrole/pyridine analogues displayed 6.25-25 µg/mL against *M. tuberculosis* H37Rv.



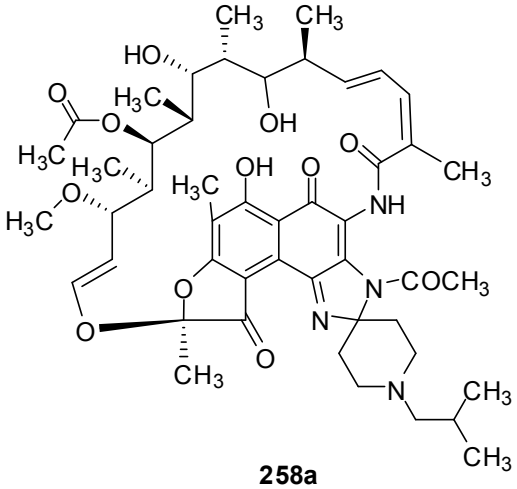
**255**



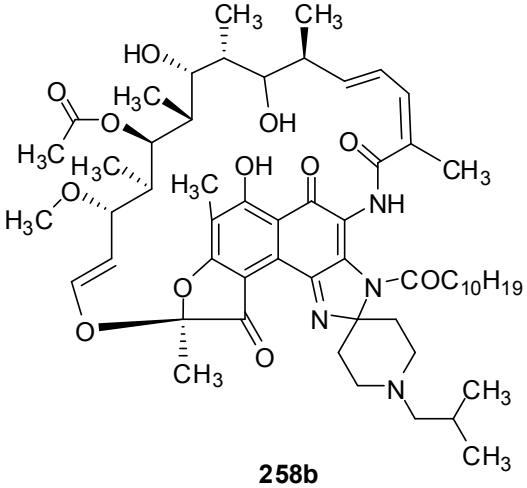
**256**



**257**

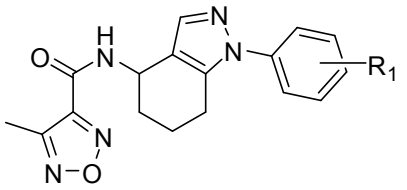


**258a**

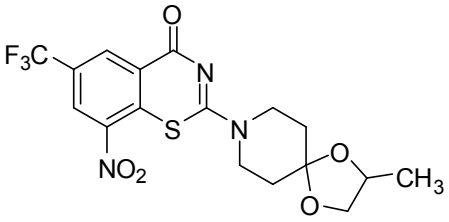


**258b**

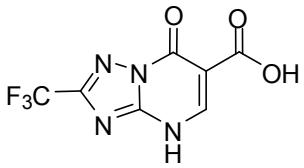
Karthikeyan et al. synthesized a novel series of spiro-pyrrolothiazoles and evaluated for their antitubercular activity. Among all, the best potency was displayed by compound **255** with a MIC of 0.6 ε M against MTB and MDR-TB [255]. Whereas Raparti et al. synthesized novel 4-(morpholin-4-yl)-Nô-(arylidene)benzohydrazide derivatives and found a new hit molecule (**256**) which showed an inhibition of 96.78% at a concentration of 0.05 ε g/mL against *M. tuberculosis* H37Rv. This compound also showed good percentage of inhibition against clinical isolates of drug-resistant strains [256]. Larhed group identified 3-amino-imidazo[1,2-a]pyridines as a novel class of *Mycobacterium tuberculosis* glutamine synthetase inhibitors. The most active compound (**257**) showed an inhibition of $IC_{50}$ = 0.38 ± 0.02 µM [257]. In a different approach, Figueiredo et al. synthesized Rifabutin (RBT) analogues. Among them, compound **258a** displayed good potency of MIC <0.013 ε g/mL against *M. tuberculosis* H37Rv, while compound **258b** showed potency of MIC 0.08 ε M against non-replicating *M. tuberculosis* strains [258].



**259a: $R_1$=4-$C(CH_3)_3$**
**259a: $R_1$=4-$OCF_3$**
**259a: $R_1$=4-$CCF_3$**



**260**



**261**

In search of novel antitubercular agents, Kozikowski group synthesized tetrahydroindazole based compounds and evaluated their efficiency. Among all, three compounds **259a-c** have shown MIC in the range 1.7-1.9 µM against *M. tuberculosis* H37Rv in MABA assay. These compounds also displayed any toxicity against VERO cells up to the concentration 128 µM [259]. Makarov et al. identified 1,3-benzothiazin-4-ones (BTZ) kills *Mycobacterium tuberculosis* by blocking arabinan synthesis. The most advanced compound, BTZ043 (**260**), was found to a candidate for inclusion in combination therapies for both drug-sensitive and extensively drug-resistant TB [260]. Abdel-Rahman et al. synthesized 1,2,4-Triazolo[1,5-a]pyrimidine-6-carboxylic acid derivatives and one compound (**261**) has shown 92% growth inhibition of *M. tuberculosis* H37Rv at 6.25 µg/mL concentration [261].

## High-throughput screening for Antimycobacterials

Besides the discussed traditional methodologies for antitubercular screening, a new High Throughput Screening (HTS) methodology was also developed in recent years. High-throughput screening (HTS) is a method for scientific experimentation especially used in drug discovery. It is the process by which a large number of compounds are screened relatively in a very short time. In antitubercular drug discovery HTS is used to identify drug like small molecule libraries. Through the Molecular Libraries Screening Center Network, the NIAID Tuberculosis Antimicrobial Acquisition and Coordinating Facility, a number of compounds 215,110 and 100,997 compound library was screened in single-dose format against H37Rv at 10 mg/mL, all the relevant results were well documented by Maddry J. A.et al. [262] and Ananthan S et al. [263].

## Future perspective

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, Linezolid a class of oxazolidinone antibiotics is under study and was approved for the treatment of MDR tuberculosis. A remarkable series of diarylquinolines, TMC207, have a very good level of in vitro activity against *M. tuberculosis*. Moreover, further research led to a series of structurally related nitroimidazo [2,1-b]oxazoles that is: OPC-67683 and compound is under the clinical trials since 2004. 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. 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 require R&D 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 *Mycobacterium tuberculosis* from the world in coming years.

## Executive summary

- Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis*. 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 isoniazid, rifampicin, 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 develop 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.
- In order to encourage tuberculosis drug discovery research The Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) Program was established through the NIAID in 1994 to allow researchers access to high quality screening services.

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