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Anti-tubercular activity of some six membered heterocycle compounds

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ABSTRACT

The effectiveness in TB treatment is difficult because the structural composition of the mycobacterial cell wall is very complicated, which makes many drugs ineffective. Tuberculosis is still one of the most imperative infectious disease worldwide becouse its important reason is drug resistant, persistent or latent tuberculosis and synergism with HIV. Furthermore no any new chemical entity has come. The recently application of modern drug design promise to bring significant development in the fight against TB. In present review we discussed brief introduction of tuberculosis.

Capsule Summary: Anti-tubercular activity of six membered heterocycle compounds is reviewed.

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INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*Mtb*)*;* it is the world's one of common cause of death (Ducati et al., 2006). Aproxymate 2 million people die every year and more than 9 million are getting infected. The present therapy is directly observed treatment short-course (DOTS) and DOTS-Plus (DOTS plus Second-line TB drugs) for Tb and resistnant-TB (Loddenkemper et al., 2002; Perri and Bonora. 2004). The TB has been spreading at a steady rate over the last decade (Bishai and Chaisson, 1997) and the recovery in TB is alarming due to the development of pathogenic synergy with HIV. In the current treatment, 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. These problems are encrage for the development of new anti-TB drug. The MDR-TB strains are resistant to two or more of the five first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin) (Bastian and Colebunders, 1999; Barry et al., 2000). 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 also become ineffective. The development of drug resistance that may become an incurable disease (Asif, 2012a; Asif, 2012b) and provides a strong motivation for the development of effective and affordable (Asif, 2015a-g; Ashraf et al., 2015) anti-TB agents. Approximately 9 million people developing active TB every year and 1.7 million deaths annually, TB is far from under control. Human immunodeficiency virus (HIV) infection dramatically increases the risk of developing active tuberculosis and is driving the TB epidemic in Africa. HIV renders tuberculosis more difficult to diagnose (due to higher incidence of sputum negative disease), and treat (due to interactions and side-effects). The increasing spread of multidrug-resistant TB (MDR-TB) and the recalcitrant nature of persistent infections pose additional challenges to

treatment with currently available anti-TB drugs. The situation is exacerbated by the increasing emergence of extensively drug-resistant (XDR) TB. Resistance to at least two main first-line drugs and additionally to three or more of the six classes of second-line drugs makes this form of TB virtually untreatable with available drugs. Although TB can be cured, current treatment is complex and long lasting, involving four drugs for 2 months and two drugs for at least another 4 months. Directly Observed Therapy (DOT), as promoted by the World Health Organisation (WHO) to improve compliance for the difficult and long-lasting regimen, is demanding for patients, labour intensive for health staff and is compromised in settings where health services are poorly accessible. MDR-TB is even more complex and expensive to treat, and in developing countries treatment is limited to a few projects with limited numbers of patients. After decades of standstill in TB drug development, the drug pipeline has begun to fill up during the last 5 years (Asif, 2012a-c).

Established in 2000, the Global Alliance for TB Drug Development (TB Alliance) has played a critical role in changing the TB research and development (R&D) landscape and is associated with approximately half of all compounds in development. The main criteria established by the TB Alliance to select drug candidates for further development are shortening of the current treatment, activity against MDR-TB and lack of interactions with antiretroviral drugs represent. During the last years, increased public awareness of the lack of R&D for neglected diseases has led at least one pharmaceutical company to establish an institute undertaking R&D activities in tuberculosis on a 'noprofit-no-loss' basis. Other companies have engaged in tuberculosis R&D on for-profit basis, and with some success: three of the six anti-TB candidate drugs currently in clinical trials have been developed by forprofit companies. Major advances have been also made in basic research. Modern molecular and genetic tools have become available for *Mtb* (such as targeted mutagenesis, array-based analysis of mutant libraries, techniques for conditional gene silencing, and global gene expression profiling) and this has led to impressive improvements in the knowledge and understanding of the basic biology and physiology of *Mtb* (Asif, 2012a-c).

CURRENTLY USED ANTITUBERCULAR AGENT

Isoniazid, ethionamide, prothionamide and pyrazinamide

Isoniazid (INH) (1) a potent anti-TB drug with minimal inhibitory concentration (MIC) is 0.05μg/mL. It acts on growing cells and not on resting cells. INH is kill mycobacteria by inhibiting the biosynthesis of mycolic acids, critical component of the cell wall. The 2-Ethyl thioisonicotinamide (ethionamide) (2) and prothionamide (3) have MIC 0.5-2.5μg/mL. The ethionamide also disturbs mycolic acid synthesis in strains resistant to isoniazid, streptomycin and p-amino salicylic acid. Pyrazinamide (4) an analog of nicotinamide is active at a MIC of 6-60μg/mL. Resistance to pyrazinamide develops soon when it is used alone. Its mechanism of action is unknown (Gray. 1997; Janin. 2007; Sunduru et al., 2010).

NEW POTENTIAL ANTI-TUBERCULAR AGENTS

The new potential anti-TB agents have different chemical entities.

Quinolones

Recently, the quinolone drugs; Ofloxacin, Gatifloxacin, Moxifloxacin and Levofloxacin, are serving as second line drugs for TB. In this concern, many researchers optimized the quinolones and evaluated for their anti-TB potency. In this direction, a series of 1-ethyl- and 1-aryl-6-fluoro-1,4-dihydroquinol-4-one derivatives were evaluated for anti-TB and cytotoxic activities. Of these, once derivatives (5) exhibited the preeminent MIC of 1.56μg/mL against *Mtb* H37Rv (MTB) and also a good selectivity index (SI=>40.06). Further, compound 5 also proved to be a potent anti-TB agent with an EC90 value of 5.75μg/ml (Sheu et al., 2003). Similarly, 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 anti-TB agent (6), which showed MIC of 0.09 μM against MTB and MDR-TB respectively. In the in vivo animal model 6 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 (Senthilkumar et al., 2009).

A series of pyridobenzoxazine derivatives by replacement of the *N*-methylpiperazinyl group of Levofloxacin with various basic substituents to investigate anti-TB activities. Among the compounds, compound 7, 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 Levofloxacin. These results suggested that an increase in the lipophilicity of Levofloxacin analogues in part contributed to enhancement of anti-TB activities but that lipophilicity of the compound was not a critical factor affecting the potency (Kawakami et al., 2000). While in the investigation of potency against *M. kansasii* Levofloxacin showed MIC in the range of 0.12-0.25 μg/ml while Moxifloxacin showed the range of MIC=≤0.06-0.12 μg/mL (Alcaide et al., 2004). These results prompted for optimization of other quinolone antibacterials to be investigated as anti-TB agents.

Inspired with the activity profile of quinolones, a series of Lamivudine prodrugs bearing fluoroquinoles (8) and evaluated their efficacy against *Mtb* H37Rv. All the compounds exhibited an inhibition of 92-100% at a concentration of 6.25μg/ml (Sriram et al., 2005). While in ciprofloxacin derivatives, one compound (9) showed in vivo anti-TB activity by reducing the bacterial load in spleen

tissue with 0.76-log10 protections and was considered to be moderately active in reducing bacterial count in spleen (Sriram et al., 2005). In continuation, Gatifloxacin derivatives and found a more potent compound (10) in comparison to compound 9. In the in vivo animal model 10 decreased the bacterial load in lung and spleen tissues with 3.62- and 3.76-log10 protections, respectively (Sriram et al., 2006). 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 (Sriram et al., 2006). Contrarily, 7-(4-(5-amino-1,3,4-thiadiazole-2-sulfonyl))-1-piperazinyl fluoroquinolonic derivatives (211a and 211b), showed moderate anti-TB activity at MIC of 10 µg/mL compared to isoniazid standard (Talatha et al., 2006).

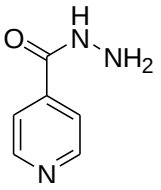
In another approach, 3-unsubstituted 4-hydroxyquinolin-2(1*H*)-one potency against *Mtb* H37Rv, one compound (13) showed moderate activity of MIC 3.125 µg/mL (Arya and Agarwal. 2007). Surprisingly, the series of 1-hydroxy-3-oxo-5,6-dihydro-3*H*-pyrrolo(3,2,1-ij)quinoline-2-carboxylic acid hetarylamides exhibited excellent activity (MIC=0.39-6.25 µg/mL) in comparison to 13. The most active compound 14 showed MIC of 0.39 µg/mL against *Mtb* H37Rv (Ukrainets et al., 2007). Whereas, the effect of nitro substitution on quinoline ring, a series of 2-(sub)-3-fluoro/nitro-5,12-dihydro-5-oxobenzothiazolo (3,2-a)quinoline-6-carboxylic acid derivatives were evaluated for in-vitro and in-vivo anti-TB activities against *Mtb* H37Rv (MTB), MDR-TB, and *M. smegmatis*, and also tested for the ability to inhibit the supercoiling activity of DNA gyrase from *M. smegmatis.* Among the thirty-four compounds, 2-(3-(diethylcarbamoyl)piperidin-1-yl)-)-3-fluoro-5,12-dihydro-5-oxobenzothiazolo(3,2-a)quinoline-6-carboxylic acid (15) 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 15 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 (Dinakaran et al., 2008). In another investigation, 6-nitroquinolone (16) 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 16 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 (Senthilkumar et al., 2009).

In an effort to increase the potency of quinolones, a series of (1,2,3)Triazolo(4,5-h)quinolones were evaluated their anti-TB activity against *Mtb* H37Rv and further 11 clinically isolated strains of *Mtb* endowed with different drug resistance. Among all, compound 17 exhibited best activity against all strains with a MIC of 0.5µg/mL (Carta et al., 2007). Whereas in another series of (1,2,3)Triazolo(4,5-h)quinolones, Compounds 18 and 19 exhibited better potency of MIC in the range 0.125-16.0 µg/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 (Carta et al., 2008).

In the process of investigating novel quinolones as anti-TB agents, many derivatives of quinolones were screened for their in vitro efficacy against MTB and MDR-TB. The most potent (in vitro) compound of the series was screened for in vivo potency too. Compound 20 exhibited MIC99 of 0.19 µM and 0.09 µM against MTB and MDR-TB, respectively and decreased the bacterial load in lung and spleen tissues with 1.91 and 2.91-log10 protections, respectively, in the in vivo animal model at a dose of 50 mg/kg body weight (Dinakaran, et al., 2008). Compound 21 decreased the bacterial load in lung and spleen tissues with 2.54 and 2.92-log10 protections (Senthilkumar et al., 2008), while 22 decreased the bacterial load by 30% and 42%, respectively, at a dose of 50 mg/kg body weight (Dinakaran et al., 2008). In an effort to increase the anti-TB potency of quinolones, 1-(cyclopropyl/2,4-difluorophenyl/tert-butyl)-1,4-dihydro-8-methyl-6-nitro-4-oxo-7-(substituted-secondary-amino) quinoline-3-carboxylic acids. The most active compound (23) of the series showed MIC of 0.42 µM and 0.09 µM against MTB and MDR-TB respectively (Senthilkumar et al., 2009a). While in an another series, 7-(3-(diethylcarbamoyl) piperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (24) exhibited promising MIC of 0.09 µM against MTB and MDR-TB respectively. In the in vivo animal model 24 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 (Senthilkumar et al., 2009b).

With the same motivation, Moxifloxacin and Gatifloxacin derivatives and evaluated against *Mtb* H37Rv (MTB), the most active compound (25) exhibited a MIC of 0.31µg/mL (de Almeida et al., 2007). While in the series of Tetracycline incorporated with quinolones, compound 26 was found to be the most active against MTB with a MIC of 0.2 µg/mL and also nontoxic to the CEM cells until 200 µM (Sriram et al., 2007). Thus, developing quinolones as anti-TB agents is a worthy approach.

New isoniazid derivatives with extended spectra of activity, a series of isonicotinoylhydrazones, isonicotinohydrazides and their cyanoborane adduct were tested for their *in-vitro* anti-TB activities. Among these, isonicotinohydrazide (27) found to be most active, which was able to kill *Mtb* Erdman strain. Compounds 28 showed a MIC of 0.05, 0.1 µg/mL, respectively against *Mtb* H37Rv and Erdman strains (Maccari et al., 2002) and MIC value is <0.025 to <6.25µg/mL. The most potent compound (29) also showed good selectivity index of more than 2000 (Hearn et al., 2009). Two series of 4-thiazolidinone and 2-azitidinone derivatives of INH, compound 30 and 31 having 4-hydroxy-3-methoxyphenyl substituent have shown best activity with a MIC 0.31 µg/mL against *Mtb* H37Rv (Jaju et al., 2009). Benzylsulfanylpyridine-2-carbohydrazides (32) showed moderate activity against *Mtb*, non-tuberculous *Mycobacterium*, and MDR-TB with MIC values in a range of 2 to 125µM/L (Herzigova et al., 2009).



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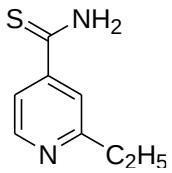

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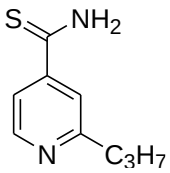

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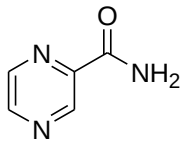

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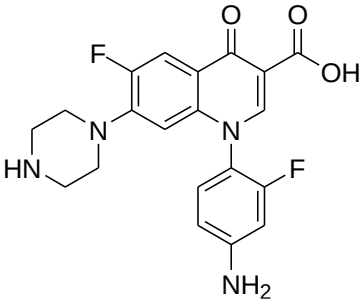

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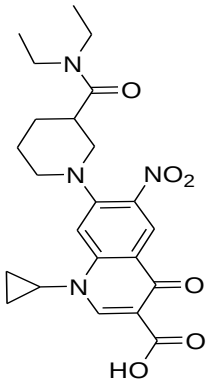

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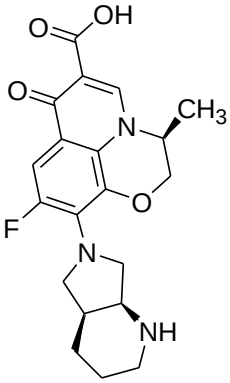

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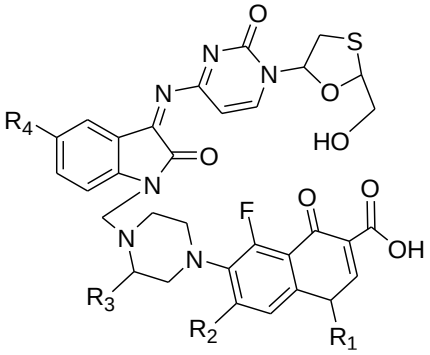
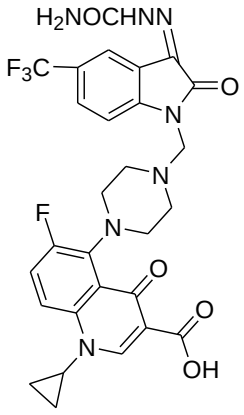


8 R_1= ethyl, cyclopropyl

R_2=H,OCH_3 R_3=H, CH_3 R_4=H,Cl,F



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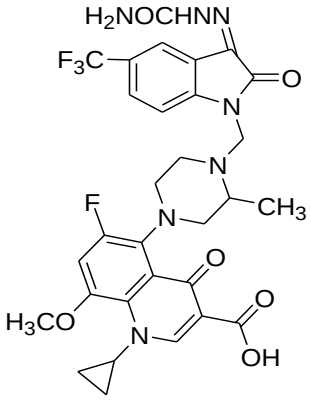

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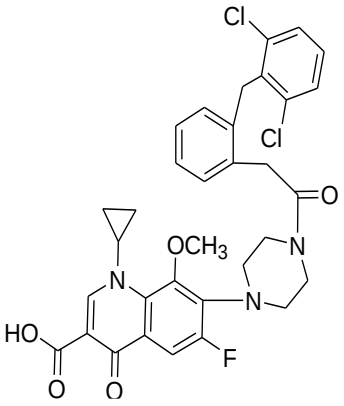

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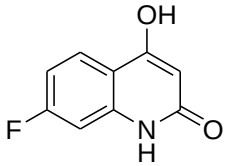
12a: R=ethyl 12b: R=cyclopropyl



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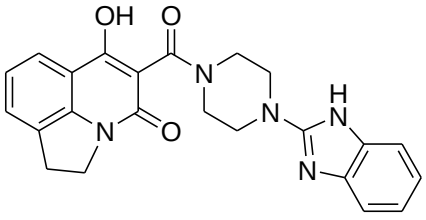

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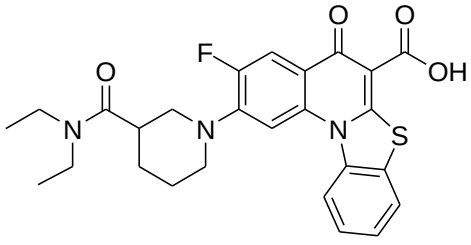

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The 1,4-dihydropyridines recently been shown to possess anti-TB activity. Dihydropyridine derivative 33 was found to be most potent showing 87% inhibition respectively at a concentration of 12.5µg/mL (Gaveriya et al., 2001). While, presence of imidazole group at 4-position and amide group at 3,5-position (34) increased the activity up to 1 µg/mL against *Mtb*. Compound 35 increase the anti-TB activity (Kharkar et al., 2002). Compound 36 showed best potency with a MIC 1

μM/mL against *Mtb* H37Rv, which is equal to that of INH (Khoshneviszadeh et al., 2009). 1,4-dihydropyridine3,5-dicarboxamide derivatives and most active compound (37) of the series showed equal potency similar to that of 36 (Fassihi et al., 2009).

Rifabutin (RBT) analogues, compound 38 displayed good potency of MIC <0.013μg/mL against *Mtb* H37Rv, while compound 39 showed potency of MIC 0.08 μM against non-replicating *Mtb* strains (Figueiredo et al., 2009).

The BM 212 (40) with very good *in vitro* activity of MIC 0.7μg/mL and compound 41 showed potent inhibition of MIC 0.4 μg/mL against *Mtb* (Biava et al., 2003). While compounds 42 (Biava et al., 2004) and 43 (Biava et al., 2005) showed comparable MIC of 1μg/mL. Surprisingly, compound 44 has increased the potency with a MIC of 0.25μg/mL, equal to isoniazid (INH) (Biava et al., 2008). Compound 45 (Biava et al., 2006) showed decreased potency of MIC 0.4μg/mL but lowered the toxicity. This made the molecule a promising lead with a protection index of 160, which is greater than INH and streptomycin. The compound 1-(4-fluorophenyl)-2-ethyl-3-(thiomorpholin-4-yl)methyl-5-(4-methylphenyl)-1*H*-pyrrole (46) is particularly active, with a MIC 0.25 μg/mL (Biava et al., 2009). All the compounds (41-46) were also active against resistant *M. tuberculosis* strains. Compound 47 was found to be most potent with a MIC of 0.5μg/mL (Ragno et al., 2000).

The anti-TB efficacy of compounds (48a-e) was against TB complex and other non-mycobacterial species. The compounds were significantly active against *Mtb* complex. Compound 48a showed preeminent inhibition of MIC 0.006 mg/L against *M. tuberculosis* UT30 (streptomycin resistant at 4 mg/L). Whereas, compound 48b showed same potency against *Mtb* UT18 and *M. bovis* BCG. Compound 48d showed the best potency of all, against *M. bovis* BCG with a MIC of 0.0008 mg/L and also showed the same potency against both the *Mtb* UT15 and UT18. Similarly, Compound 39e showed the same potency against *Mtb* UT18 but shown increased potency of MIC of 0.0004 mg/L against *Mtb* UT15. Compound 48c 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 against *Mtb* H37Rv (Hurdle et al., 2008; Tangallapally et al., 2006; Tangallapally et al., 2007; Tangallapally et al., 2005).

A pyridyl derivative (49) has shown potency with a MIC 0.22 μM and was 3 times more active than standard INH and equally active as RIF in *Mtb* H37Rv. In starved *Mtb* H37Rv, it also inhibited with a MIC of 13.9 μM and was found to be 50 times more active than INH and slightly more active than RIF (Sriram et al., 2009). A series of 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazole derivatives have anti-TB activity toward *Mtb* H37Rv and *Mtb* H4. Compounds 50a-e has shown equal potency against above strains with a MIC of 8μg/mL (Mamolo et al., 2001). A series of 4-(2-(substitutedphenyl)-3-phenyl-2,3-dihydro-1*H*-5-pyrazolyl)-2-methylphenol derivatives and 2-(5-(3-Phenoxyphenyl)-4,5-dihydro (benzoyl)-pyrazol-3-yl) pyridine (51) also exhibited good anti-TB activity(Kini et al., 2009).

The search for new anti-TB drugs, compound PA-824 (52) as promising anti-TB agents, which has novel mode of actions and efficacy against resistant *Mtb* (Khan et al., 2008). The two diastereomers of 7-methyl-nitroimidazo-oxazine, 7-(*S*)-methyl derivative (53a, *cis*) and the 7-(*R*)-methyl derivative (53b, *trans*) displayed similar activities against *Mtb* with MIC=0.2-0.4μM (Li et al., 2008). The PA-824 (52) along with Metronidazole (54a) showed anti-TB effect. Compound 54b 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 (Kim et al., 2009). These molecules have shown more potency of aerobic & anaerobic inhibition than parent molecule PA-824. Among all, compound 54b exhibited aerobic 99% inhibition at 0.039 μM and compound 54c showed 90% anaerobic inhibition at 1.56-3.13 μM (Kim et al., 2009). Analogues of 2-nitroimidazooxazines, compound 55 has shown best activity with a MIC of 0.11 and 2.7μg/mL against *Mtb* in aerobic and anaerobic conditions respectively (Thompson et al., 2009). A imidazo (1,2-*c*) pyrimidine derivatives, compound (56) has shown promising MIC of 2μg/mL against *Mtb* H37Rv, which is equal to amikacin (Chhabria et al., 2009). The hydrazide derivatives of imidazo (1, 2-a) pyrazine, compound 57 showed moderate activity with 86% inhibition at 6.25 μg/mL (Ozdemir et al., 2009).

A series of 4-(5-cyclobutyloxazol-2-yl) thiosemicarbazones were exhibited *in-vitro* and *in-vivo* activity against *Mtb* H37Rv and MDR-TB (Sriram et al., 2007). The oxazolidinones linezolid (58) is a synthetic antibacterial agent, which are active against variety Gram-positive organisms. These compounds inhibit translation at the initiation phase of protein synthesis in bacteria. The compound PNU-100480 and thiomorpholine analogue of linezolid (59) showed an interesting anti-TB activity. With this interest, anti-TB activity of oxazolidinones, 3-(1*H*-pyrrol-1-yl)-2-oxazolidinone analogues of PNU-100480 showed anti-TB activity. A series of nitrofuranyl isoxazolines with increased proteolytic stability over nitrofuranyl amides showed anti-TB activity against *Mtb*. Compound 60a showed *in-* high *vitro* potency of 0.00005μg/mL. However, their *in-vivo* activity was limited by high protein binding and poor distribution. Consequently, a series of non-nitrofuran containing isoxazolines had residual anti-TB activity. This led to the discovery of novel isoxazoline 60b as anti-TB agent, which showed 90% inhibition at a concentration of 1.56μg/mL (Tangallapally et al., 2007). A active molecule 60c has shown a MIC of 0.4 μg/mL against *Mtb* H37Rv (Rakesh, et al., 2009).

The 5-((*E*)-2- arylethenyl)-3-isoxazolecarboxylic acid alkyl ester derivatives were found as promising anti-TB agents. Among all, 5-((*E*)-2-(3,5-Dichloro-4-pyridinyl)ethenyl)-3-isoxazolecarboxylic acid ethyl ester (61a) has shown preeminent activity with a MIC 0.59 μM in MABA assay, whereas compound 5-((*E*)-2-(6-methoxy-4-

quinolinyl)ethenyl)-3-isoxazolecarboxylic acid butyl ester (61b) showed the activity against *Mtb* H37Rv with a MIC 1.8 μM. Both compound showed almost equal potency with standard drugs INH, RMP in terms of activity and cytotoxicity (Pieroni et al., 2009). While in an another series, (*R*)-methyl 2-(5-((2-methylbenzo(d)thiazol-5-yloxy)methyl)isoxazole-3-carboxamido)-2-phenylacetate (62) has shown less activity with a MIC 1.4 μM in MABA assay (Huang et al., 2009) in comparison to compound 61a. A series of alkyl 1-heteroaryl-1*H*-1, 2, 3-triazole-4-carboxylates were exhibited anti-TB activity against *Mtb* H37Rv. Among all, the best potency was shown by *n*-pentyl 1-(6-phenylpyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (63) with a MIC of 3.13μg/mL (Japelj et al., 2005).

The discovery of anti-TB drug INH of pyridine skeleton prompted the research on piperidine (hexahydropyridine). In this perception, a series of 1-piperidino-3-arylthioureas were evaluated for their anti-TB activity. Compound 64 has shown best potency of MIC 8μg/mL against the strain 303 (Hearn et al., 2005). A series of 2-Substituted derivatives of diphenylpyraline and their 1-phenyl and 1-phenethyl analogues were evaluated against *Mtb* H37Rv as well as their cytotoxicity against human cells (HEK-293). Among all, compound 65 showed an inhibition of 75% at a concentration of 6.25μg/mL against *Mtb* H37Rv and also found to be least toxic of the series (Weis et al., 2008).

The 2-substituted derivatives of diphenylpyralines (65), bamipine (66a) and their 1-phenyl analogues exhibited anti-TB activities. Of these, compound 66b showed best potency of MIC 6.25μg/mL (Weis et al., 2008). Where as, piperidinol analogs were exihited anti-TB activity against *Mtb* H37Rv. Among all, the good potency was shown by compound 67 with a MIC 1.4 μg/mL and therapeutic index of 13.3 (Sun et al., 2009). The dipiperidine derivatives were discovered as novel anti-TB agents with a hit molecule 68, 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 IC50 162 μM against HepG2 cells (Bogatcheva et al., 2010).

A series of 2,6-diarylpiperidin-4-ones and tetrahydropyridin-4-ol based benzimidazole and *o*-arylsulfonyl derivatives exhibited anti-TB activity. Among all, three compounds (69a, 69b and 69c) have shown equal potency of MIC 16μg/mL against *Mtb* H37Rv, which are one-fold more potent than of the standard RIF drug (Aridoss et al., 2008). In 3,5-bis(benzylidene)-4-piperidone (70) was found active with a MIC of 0.2 μg/mL and also found non toxic in mice (Das et al., 2008). In an effort to increase the potency of piperidones, a series of spiro-piperidin-4-ones were evaluated for their anti-TB activity. Among all, compound 71 showed promising *in-vitro* potency of MIC 0.07μg/mL and 0.16μg/mL against *Mtb* and MDR-TB respectively. Compound 71 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 (Kumar et al., 2008). A series of *N*-Alkyl-1,2-dihydro-2-thioxo-3-pyridinecarbothioamides were exhibited anti-TB activity against *Mtb* and MAC strains. Among all, compound 72 showed good potency of MIC 0.5μg/mL against *Mtb* H37Rv and 2-4μg/mL against MAC strains (Pagani et al., 2000). While, the series of 2-pyridine carboxamidrazones (73) were showed MIC50 in the range of 160-16μg/L against *M. avium* strains (Banfi et al., 2001).

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 *Mtb*. In this view, a series of 1,4-dihydropyridine-3,5-dicarbamoyl derivatives with lipophilic groups (74) were showed activity against *Mtb* H37Rv, most compound showed 90% inhibition at 2.5 μg/mL (Desai et al., 2001). 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 exhibited activity against *Mtb* H37Rv. Among all, 1,3,4-oxathiazoline-2-one derivative (75) showed best activity with MIC of 4.5 μg/mL (Gezginci et al., 2001).

A series of heterocyclic chalcones, compound 76 has shown MIC of 6.8μg/mL against *Mtb* H37Rv (Lin et al., 2002). A series of substituted *N*-pyridinylsalicylamides (77) were exhibited *in-vitro* anti-TB activity against *M. avium* and two strains of *M. kansasii* (Waisser et al., 2004). In the same direction, a series of isonicotinylhydrazones and found a molecule (78) active against *Mtb* H37Rv with a MIC of 0.56 μM, which is more potent than INH (MIC of 2.04 μM) (Sriram et al., 2005). Another series and found a new derivative (79) more active than the former molecule (78). It showed equal MIC of 0.49 μM against *Mtb* H37Rv and INH-resistant *Mtb* strains (Sriram et al., 2006). A series of trans-cinnamic acid derivatives of isonicotinic acid (80), showed moderate in vitro activity of MIC 3.12 μg/mL against *Mtb* strain (Carvalho et al., 2008). Whereas, compounds 81a and 81b of the isonicotinic acid derivatives developed and showed equal potency of MIC 0.39 μg/mL against *Mtb* H37Rv and have selectivity index (SI) of >160, which is comparable to INH and better than ciprofloxacin (Imramovsky et al., 2007). A number of (E)-*N*′-(monosubstitutedbenzylidene) isonicotinohydrazide derivatives exhibited *in-vitro* anti-TB activity against *Mtb* H37Rv. Five compounds (82a-e) have shown significant MIC in the range of 0.31-0.62 μg/mL in comparision with INH and RIF (Lourenco et al., 2008). Whereas, hybrid of isonicotinic hydrazone of pyrrole (83) showed best potency of MIC ≤0.1 μg/mL against *Mtb* H37Rv and also has good selectivity index (Bijev. 2006).

Compounds (84a-f) showed in vitro anti-TB activity in the range of MIC 25-50 μg/mL (Kumar et al., 2002). In continuation, a number of compounds (85) have shown anti-TB potency with a MIC in the range of 12.5-25 μg/mL (Agarwal et al., 2005a). To further increase the activity, trisubstituted compound (86) (Agarwal et al., 2005b), where the activity was same as compound 85. Where as, chloro derivatives were found to be highly active against *Mtb*. Compounds (87a-d) were found to be active at a MIC of 0.78μg/mL (Agarwal et al., 2002). While, in a series of anilino pyrimidines against *Mtb* H37Ra, the most potent activity was

shown by the compound 88 having a MIC of 3.12μg/mL (Morgan et al., 2003).

A series of *N*-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5- carboxamides were shown anti-TB activity against *Mtb* H37Rv. Two compounds with 2,3-dimethylphenyl (89a) and 3,4-dimethyl (89b) carbamoyl side chain, respectively, showed 65% and 63% inhibition (Virsodia et al., 2008). 5-phenyl-6-((3R,4S)-3,4,5-trihydroxypentyl)pyrimidine-2,4-diamine (90) selectively inhibited *Mtb* DHFR (El-Hamamsy et al., 2007). Whereas, in a series of methylene-bis-pyrimidinones and methylene-bis-mercapto pyrimidines, pyrimidinone derivative (91) shown best potency of 0.1μg/mL while mercapto pyrimidines showed moderate activity (Nagaraj et al., 2007).

Several derivatives of pyrazine nucleus have shown activity against *Mtb.* Pyrazine derivatives substituted with 1,2,4-oxadiazole-5-ones, 1,2,4-oxadiazole-5-thiones and 1,3,4-oxathiazoline-2-ones (Gezginci et al., 2001). The most active compound of the series 92 exhibited a MIC of 4.5μg/mL in comparison to 49μg/mL for pyrazinamide. A series of ring substituted (E)-3-Phenyl-1-(2 pyrazinyl)-2-propen-1-ones were shohn efficacy against *Mtb* H37Rv. Among all, compound 93 showed an inhibition of 94% at 12.5μg/mL (Opletalova et al., 2002). While, in a series of pyrazine derivatives, two compound (94a and 94b) have shown equal potency of MIC 6.25 μg/mL against *Mtb* H37Rv (Seitz et al., 2002). Compound 94b also showed MIC of <0.25 μg/mL against *Mtb* H37Ra.

On the basis of ethionamide, a series of 5-Alkyl-6-(alkyl/aryl sulfanyl) pyrazine-2-carbothioamide, compounds inhibited the growth in the range of 61-91%. Compound (95) showed 91% inhibition at a MIC <6.25 μg/mL(Krinkova et al., 2002). While, S-methyl-2-(amino(6-chloropyrazin-2-yl)methylene)hydrazinecarbodithioate (96) exhibited moderate potency of MIC 32 μg/mL among simple pyrazine hybrids, against *Mtb* sensitive and wild strains (Foks et al., 2004).

A series of unsubstituted, halogenated and/or alkylated pyrazine-2-carboxylic acid amides connected *via* -CONH- bridge with substituted anilines shown activity against *Mtb* H37Rv. Among all, 5-tert-Butyl-6-chloro-N-(3-trifluoromethylphenyl)pyrazine-2-carboxamide (97) has shown the highest activity of MIC 3.13 μg/mL (Dolezal et al., 2008). Compound 98a and 98b showed MIC of 0.78, 0.1 μg/mL respectively, against *Mtb* H37Rv. Compound 98a also showed good activity against atypical strains of *Mtb*(127). In a different approach, A series of 1,4-substituted piperazine/homopiperazines. Compound 99 showed MIC of 62.5 μM, homopiperazine derivatives (100a and 100b) showed preeminent MIC of 1.56 μM against *Mtb* H37Rv. Compounds 100a and 100b also exhibited good selectivity index of 84.6 and 46 respectively (He et al., 2007; Bogatcheva et al., 2006). Homopiperazine compounds (101a and 101b) with a more promising activity of MIC 0.78μg/mL against *Mtb* H37Ra (Zhang et al., 2009). In a different approach pentacycloundecane (PCU) tetra-amine compounds were shown *in-vitro* anti-TB activity against H37Rv and XDR strains of *Mtb* 194. The most active compound (102) of the series has shown MIC of 5.04 μM against *Mtb* H37Rv and 1.26 μM against XDR-TB (Onajole et al., 2009).

A series of carbamate derivatives of 1,2-oxazine were shown *in-vitro* anti-TB activity against *Mtb* and *M. lufu* species. Among all compounds, the maximum anti-TB activity was observed for 4,5-dimethyl-2-(*p*-methoxycarbonylamino)phenyl-3,6-dihydro-1,2-oxazine (103) (Velikorodov et al., 2006). In a series of 5,6 dihydro-4H-1,3 thiazine derivatives were shown activity against *Mtb* H37Rv, 5-hydroxy-3-phenyl-4-aza-2-thiabicyclo(3.3.1)none-3-ene (104) showed 97% inhibition at a concentration of 6.25μg/mL (Koketsu et al., 2002). A series of α-methylene-γ-butyrolactones based on the natural product protolichesterinic acid (105) were shown potency against *M. bovis* BCG. Compound 105 was sowed improved activity with MICs in the range of 6.25-12.5 μg/mL (Hughes et al., 2005). Several structural analogues of the polyketide passifloricin lactone (106) were shown acivity against *Mtb* H37Rv (Cardona et al., 2006). Of these, compound 106 exhibited an inhibition percentage higher than 97% at 128μg/mL, while passifloricin A reached 82.9%. Additionally, it has shown best MIC of 17.31μg/mL, which is better than passifloricin A (29.4μg/mL). Peptide deformylase (PDF) is a key enzyme, that deformylates the *N*-formylmethionine, polypeptides, a key step in protein maturation. It is a validating target as an anti-TB agent. In this view, a series of LBK-611 (107) derivatives were showed anti-TB activity (Faugeroux et al., 2007).

The purine analogues possessing anti-TB activity have been pursued with great interest. In this perception, 9-benzylpurines with a variety of substituents at 2, 6 or 8 positions were found as good anti-TB agents. High activity was exhibited by 9-benzylpurines carrying a phenyl ethynyl, transstyryl or aryl substituents at the 6th position and generally chlorine at the 2nd position. The most active compounds 108a and 108b showed a MIC of 3.13 and 0.78 μg/mL respectively, against *Mtb* H37Rv and also a selectivity index (SI) of 2.7 and 10.4 (Bakkestuen et al., 2000). In continuation, a series of 6-arylpurines having a variety of substituents in the 9 position were screened against *Mtb* H37Rv. The most active compound of the series was again found to be same 9-benzyl-2-chloro-6-(2-furyl)purine (108b) having a MIC of 0.78 μg/mL. This compound exhibited relatively low cytotoxicity and it was also active against several singly drug-resistant strains of *Mtb* (Gundersen et al., 2002). Eleven analogues of 9- sulphonated/sulphenylated 6-mercaptopurines (Scozzafava et al., 2001) and out of them six exhibited MIC in the range of 0.39-0.78 μg/mL. The most potent compound (109) (MIC=0.39 μg/mL) also exhibited good activity against MDR strains of *Mtb*.

Inspired by the above results, a series of 9-aryl-, 9-arylsulfonyl- and 9-benzyl-6-(2-furyl)purines and screened for their anti-TB activity against *M. tuberculosis* H37Rv. Among all, 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (110) exhibited best potency of MIC 0.39 μg/mL and also low toxicity against mammalian cells and activity

inside macrophages (Bakkestuen et al., 2005). In a purine derivatives, 9-(ethylcarboxymethyl)-6-(dodecylthio)-9*H*-purine (111) showed MIC of 0.78 μg/mL (Pathak et al., 2004). In the analogues of agelasine E (112a), one derivative (112b) showed promising activity with MIC of 1.56 μg/mL against *Mtb* H37Rv (Bakkestuen et al., 2005). After the keen observation of SAR of above molecules, 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 (113, MIC=0.20 μg/mL) (Braendvang et al., 2007) of above all series. The purine derivatives, found a more potent molecule (1114) of above all series, which has shown an IC90 of <0.20 μg/mL against *Mtb* H37Rv (Braendvang et al., 2009).

In search of new anti-TB purine type analogues, a series of 1-(1-(4-hydroxybutyl)-1,2,3-triazol-(4 and 5)-ylmethyl)-1*H* pyrazolo(3,4-d)pyrimidines and all of them were inactive but one compound (115) has shown MIC of 12.5 μg/mL (Moukha-Chafiq et al., 2001; Moukha-Chafiq et al., 2002; Moukha-Chafiq et al., 2007.

In continuation, a series of di/trisubstituted pyrazolo(3,4-d)pyrimidines (116, 117) and observed no significant anti-TB activity at concentrations up to 6.25 μg/mL. A series of *N*,*S*-bis-alkylated thiopyrazolo(3,4-d)pyrimidines, based on sequential *S*- then *N*-alkylation, is carried out. These compounds showed significant anti-TB activity (MICs down to ≤2 μg/mL) and their potential as significant drug-like leads is substantiated through cytotoxicity evaluation and in silico profiling. Among all, one compound (118) has shown MIC=0.5-1 μg/mL against *Mtb* H37Rv (Ballell et al., 2007). A homologous series of three pyrazolopyrimidine analogues (119a-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 *Mtb* with inhibition constants in the low nanomolar to subnanomolar range. Molecular modeling of one of the homologues bound to *Mtb* lumazine synthase suggests that both the hypothetical intermediate in the lumazine synthase-catalyzed reaction pathway and the metabolically stable analogues bind similarly (Zhang et al., 2007). In a series of Thieno(2,3-d)pyrimidin-4-one, two compounds (120a and 120b) have shown moderate potency of 5μM/L against *Mtb* and *M. avium*, which is equal to that of rifampicin (Chambhare et al., 2003).

The indentification of new promising quinoline based anti-TB agents, 2,8-dicyclopentyl-4-methylquinoline (DCMQ, 121) (Jain et al., 2003) and Diarylquinoline (TMC207, 122) (181) have definitely initiated the optimization of quinoline for anti-TB drugs. In this concern, 1-(5-isoquinolinesulfonyl)-2-methylpiperazine (123), a protein kinase inhibitor for its anti-TB profile and found to inhibit the growth of two different mycobacterial strains, the slow-growing *M. bovis* Bacille Calmette Guerin (BCG) and the fast-growing saprophyte *M. smegmatis* mc2 155, in a dose-dependent manner. While screening for the effect of kinase inhibitors on mycobacterial growth, millimolar concentrations of 123 induced a 40% decrease in the growth of *M. bovis* BCG when measured as a function of oxidative phosphorylation. This 123-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 123 induced a significant decrease in the activity of the *M. tuberculosis* protein serine/threonine kinase (PSTK) PknB. The inhibition of mycobacterial growth as well as the inhibition of a representative *Mtb* 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 (Gaurrand et al., 2006; Drews et al., 2001). 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 (124a-c) were having a MIC of 0.78μg/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 (Savini et al., 2002).

Inspired with the activity profile of DCMQ (121), four new series of the ring-substituted quinolinecarbohydrazides were evaluated. 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 μg/mL against *Mtb* H37Rv. The most active compounds were adamantly derivatives (125a and 184b) exhibited MIC of 3.125 μg/mL (Monga et al., 2004). Whereas, a number of thirty-three quinoline derivatives based on TMC207 (122) and found a molecule (126) active with a MIC=3.12 μg/mL (de Souza et al., 2009). With the same interest, 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 (127a-d) showed moderate activity of MIC 6.25 μg/mL against *Mtb* H37Rv (Upadhayaya et al., 2009).

Recently, a series of substituted quinolinyl chalcones and substituted quinolinyl pyrimidines were evaluated for their in vitro anti-TB activity against *Mtb* H37Rv. Chalcone derivatives 128a and 128b have shown antitubercular activity of MIC 3.12 μg/mL and were nontoxic against VERO, MBMDM cell lines (Sharma et al., 2009). The anti-TB potential of NAS-91 (129) and found that NAS-91 has multiple targets, which is particularly desirable for avoiding the emergence of resistant strains of *Mtb*. Therefore, NAS-91 represents a potent pharmacophore and appears to be a promising lead compound for future inhibitor development against TB (Gratraud et al., 2008). The quinoline-3-carbohydrazone derivatives were screened for their anti-TB efficacy. Among all, two compounds (130a and 130b) have

shown promising activity with a MIC 0.625, 2.5 and 1.25μg/mL against *Mtb* H37Rv, *M. smegmatis* and *M. fortuitum* respectively. These compounds have shown almost equal potency similar to that of standard rifampicin (Eswaran et al., 2010). Whereas in the series of 4-quinolylhydrazones, the most active compound (131) displayed an anti-TB activity of MIC 0.6 μM and selectivity index 2.27 (Gemma et al., 2009).

A similar approach, 7-chloro-4-quinolinylhydrazone derivatives and found three molecules (132a-c) with a moderate anti-TB activity with a MIC 2.5μg/mL. These compounds were found to be nontoxic against J774 cell line up to the concentration 100 μg/mL (Candéa et al., 2009). Quinoline derivatives consisting of triazolo, ureido and thioureido substituents at C-6 position, ureido derivative (133a) and triazolo derivative (133b) have shown moderate activity of MIC 3.125 μg/mL against *Mtb* H37Rv (Upadhayaya et al., 2009). A series of amino acid conjugates of 4-(adamantan-1-yl) group containing quinolines. The most active nontoxic compound (134) of the series exhibited increased potency of 1μg/mL against *Mtb* H37Rv and 3.125μg/mL against MDR strain, in comparison to former molecules (133a &133b) (Nayyar et al., 2009). In the same direction of approach, quinoline-based derivatives were evaluated for their anti-TB efficiency. Among all, compound 135 has shown remarkable activity of MIC 0.77 μM against *Mtb* H37Rv and 0.99-1.55 μM against drug-resistant strains (Lilienkampf et al., 2009). In continuation the same group synthesized isoxazole based quinoline derivatives and found a lead molecule 136, which showed MIC of 0.2 μM and 2.6 μM in MABA and LORA assay against *Mtb* H37Rv (Mao et al., 2009). Thus, optimization of quinolines for the development of antit-TB agents is a fruitful approach.

The quinoxaline derivatives show very interesting antimicrobial properties and recently, some researchers have identified the anti-TB 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 (137a and 137b) is favourable for antimicrobial activity. In this context as contribution in the development of quinoxaline derivatives, a number of 36, 6(7)-substituted-3-methyl- or 3-halogenomethyl-2-phenylthio-phenylsulphonyl-chloro-quinoxaline 1,4-dioxides were screened for their in vitro anti-TB acivity. Among all, two compounds 138a and 138b exhibited great potency of MIC 0.39 μg/mL against *Mtb*, which is comparable to Rifampicin (MIC=0.25 μg/mL) (Carta et al., 2002). In another series, four compounds (139a-d) have shown moderate activity of MIC 2 μg/mL (Carta et al., 2004). In the series of quinoxaline derivatives, lack of 1,4-dioxide showed reduction in the activity. Most active compound (140) showed MIC of 6.25μg/mL against MTB H37Rv and 0.5 μg/mL against MTB H37Ra (Seitz et al., 2002). Which prompted to continue the optimization of quinoxaline 1,4-dioxide.

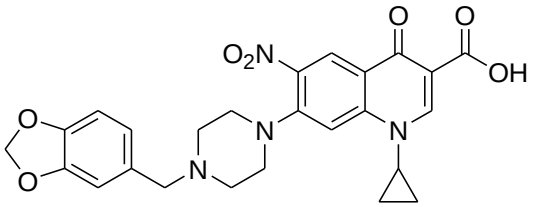
Inspired with the activity profile of 137a and 137b, (Zarranz et al., 2003) a series of quinoxaline-2-carboxamide 1,4-di-*N*-oxide derivatives and evaluated for their in vitro anti-TB activity against *Mtb* H37Rv. Among all, compound 141a exhibited best MIC of 0.78 μM, has a solubility problem, while compound (141b) having MIC of 3.13 μM has a best selectivity index (SI=>40.06). A series of quinoxaline 1,4-di-*N*-oxide derivatives by varying the 2-position and found that 2-methylquinoxaline 1,4-di-*N*-oxides (142a and 142b) 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) (Jaso et al., 2003). Villar et al. also found that the compound 142b is also active against resistant strains of *Mtb* (Villar et al., 2008). In another series, 2-benzyl-3-(methoxycarbonyl)quinoxaline 1,4-dioxide (143) has shown best potency above all, with a MIC=0.10μg/mL and selectivity index SI=470 (Jaso et al., 2005).

A new series of 3-phenylquinoxaline 1,4-di-*N*-oxide having selectivity against *Mtb* have been evaluated. 34 out of the 70 tested compounds showed an MIC value less than 0.2μg/mL, a value on the order of the MIC of rifampicin. Furthermore, 45% of the evaluated derivatives showed a good in vitro activity/toxicity ratio. The most active compound was 7-methyl-3-(4'-fluoro)phenylquinoxaline-2-carbonitrile 1,4-di-*N*-oxide (144) (MIC <0.2 μg/mL and SI >500) (Vicente et al., 2009). In conclusion, the potency, low cytotoxicity and selectivity of these compounds make them valid lead compounds for synthesizing new anti-TB agents.

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 *Mtb*, *M. avium* and *M. intracellulare*. Of these, compound 145 showed best potency of MIC 0.5 μg/mL against MTB H37Rv and 0.5-2 μg/mL against resistant strains. However, the in vivo testing in a mouse model of TB infection did not show significant anti-TB activity, probably because of its poor bioavailability (Kamal et al., 2006). In continuation, 5-nitrofuran, 5-nitrothiophene and arylfuran coupled benzothiadiazines and on evaluation, these compounds exhibited moderate anti-TB activity. The most active compound (146) displayed a MIC of 1 μg/mL against MTB H37Rv (Kamal et al., 2007). With the same inspiration, 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 anti-TB activity. Among all, compound 147 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 (Kumar et al., 2007).

A Series of 9-substituted tetrahydroacridines for their anti-TB activity. These derivatives exhibited promising activity profile, with MIC in the range of 6.25-0.78 μg/mL against *Mtb*. Compound 148a displayed best MIC of 0.78μg/mL against MTB-H37Rv, while compound 148b displayed preeminent activity against MTB-H37Ra with MIC 1.56μg/mL (Tripathi et al., 2006).



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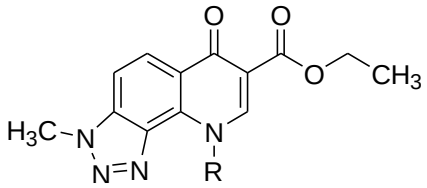
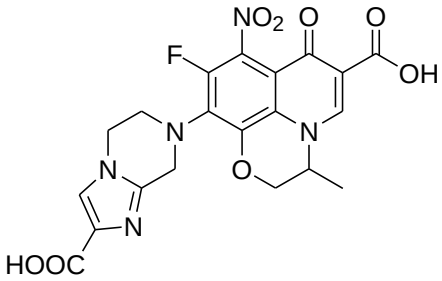


17: R=C_4H_9 18: R=C_2H_5 19: R=$CH_2CH=CH_2$



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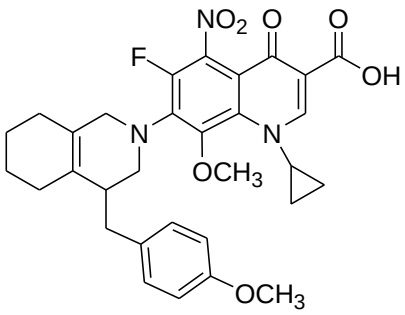

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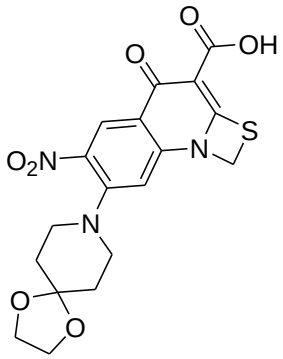

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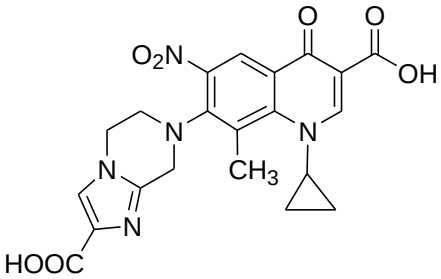

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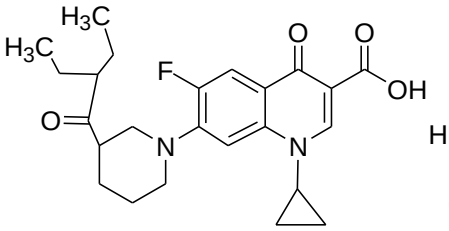

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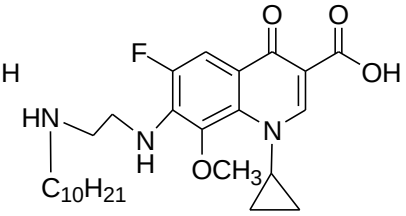

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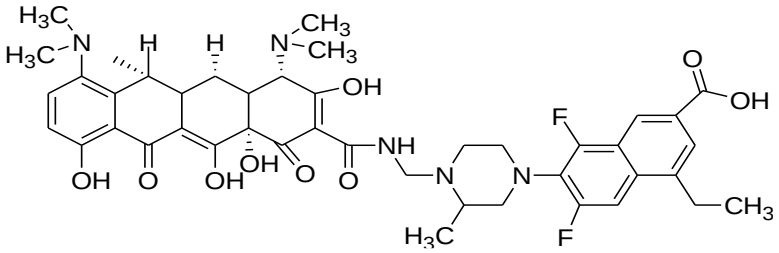

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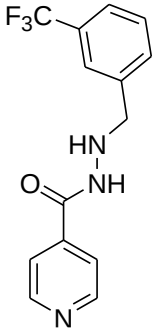

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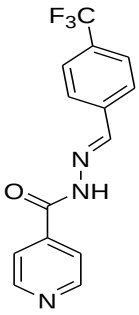

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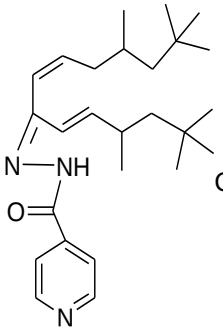

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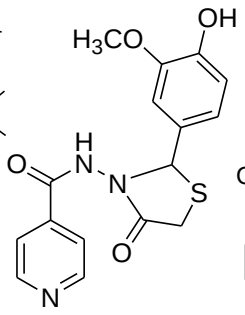

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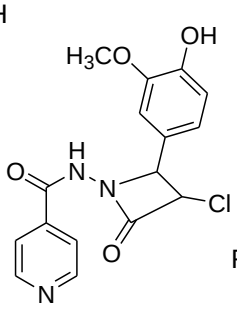

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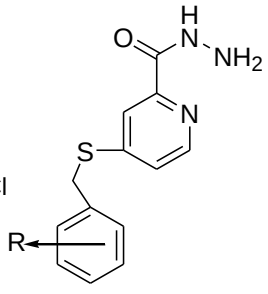

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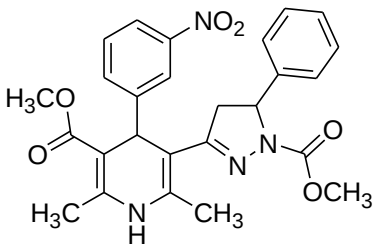

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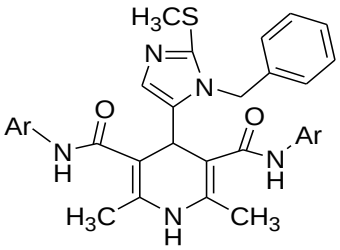
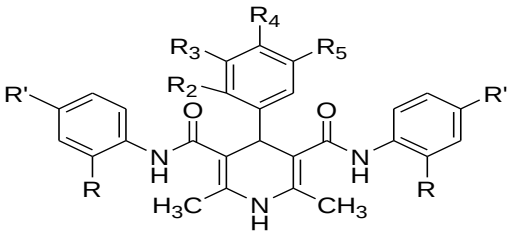


34: Ar=4-chlorophenyl



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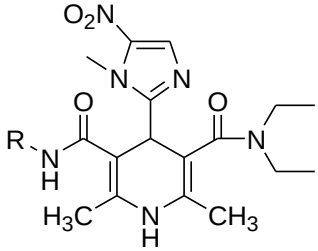
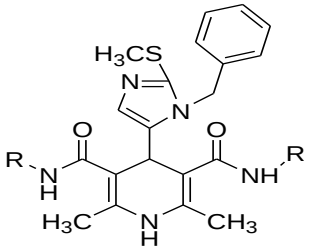
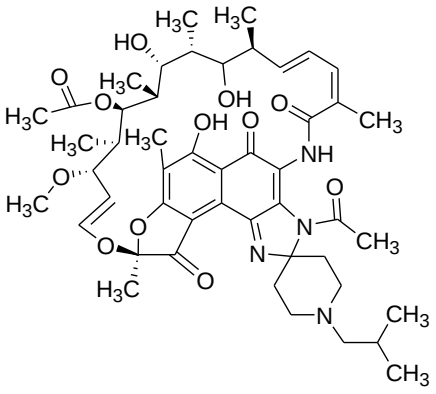


36: R=3-phenylpropyl



37: R=4-chlorophenyl



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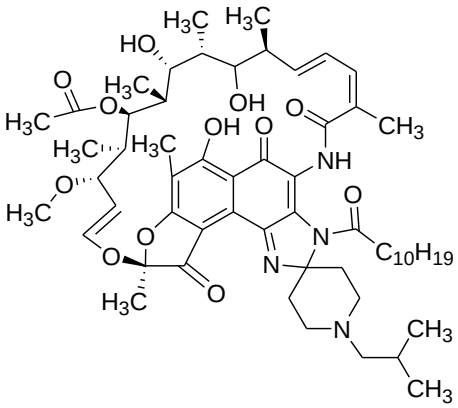

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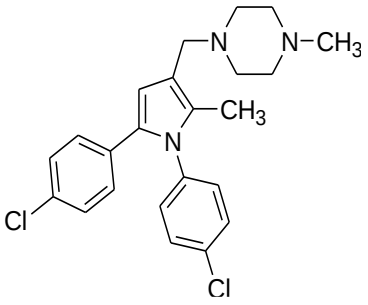

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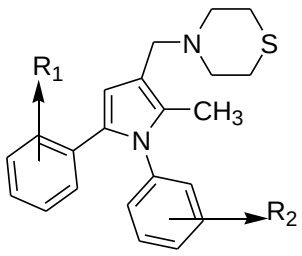


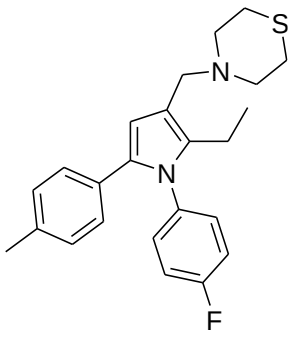
41: R_1=H, R_2=4-F

42: R_1=H, R_2=H

43: R_1=2-F, R_2=2-F

44: R_1=*i* -C_3H_7, R_2=4-F

45: R_1=4-CH_3, R_2=4-F



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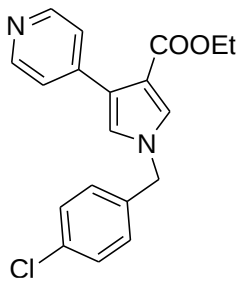

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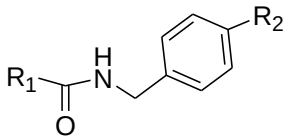
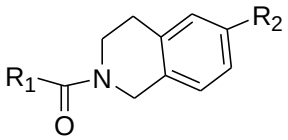
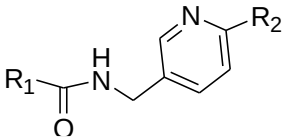


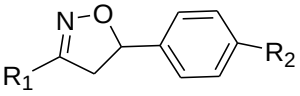
48a



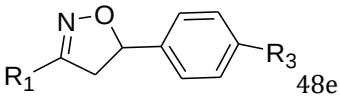
48b



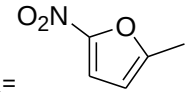
48c

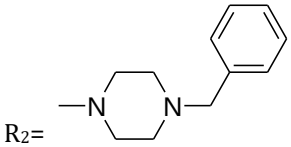


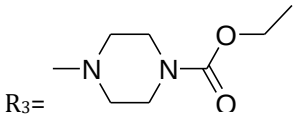
48d

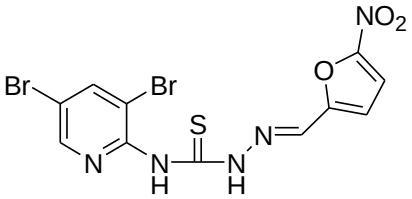


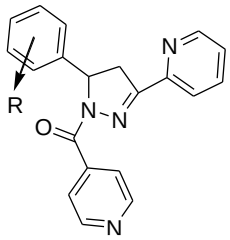
48e

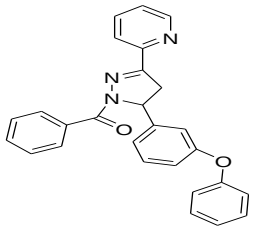








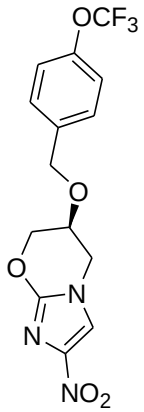




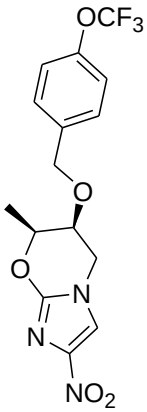
49 50a: R=H 50b: R=2-Cl 51

50c: R=3-Cl 50d: R=4-Cl

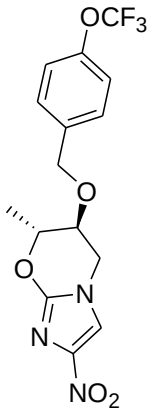
50e: R=2-CH_3



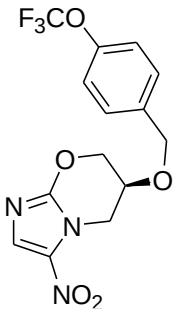
52



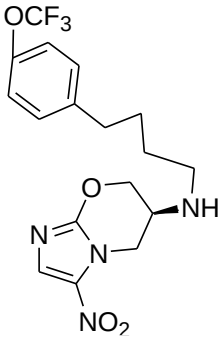
53a



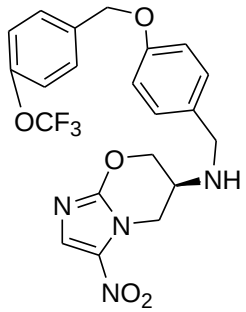
53b



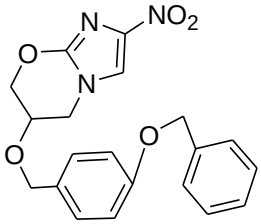
54a



54b



54c



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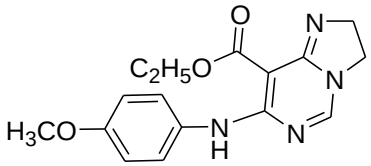

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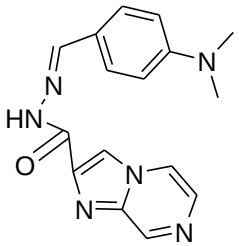

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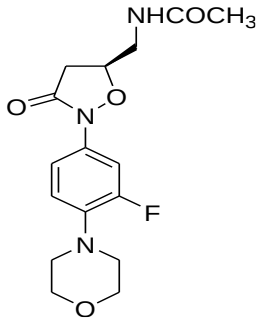

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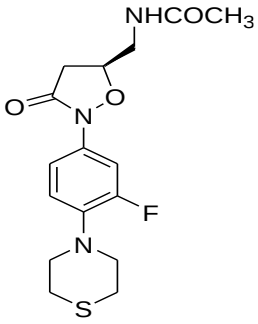

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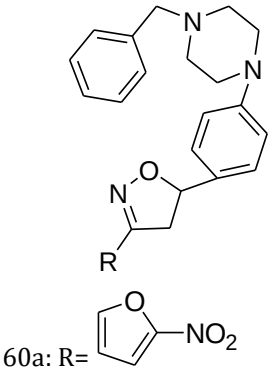
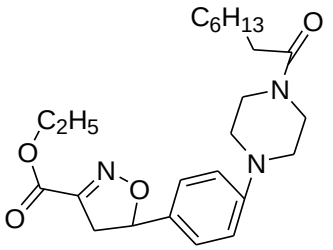
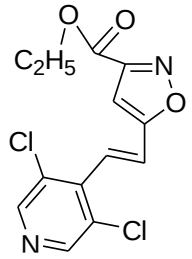


60a: R=

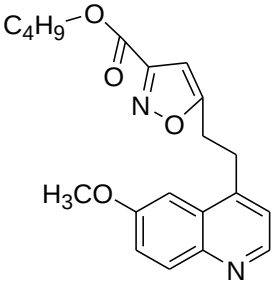
60b: R= $COOC_2H_5$



60c



61a



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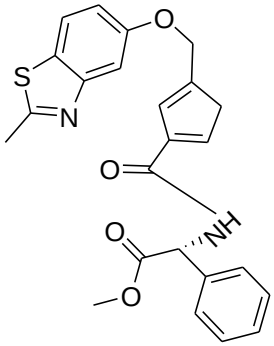

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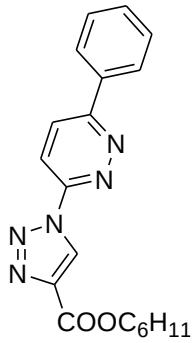

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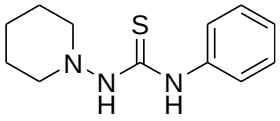

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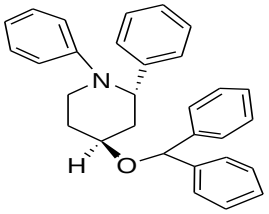

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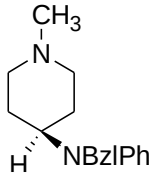
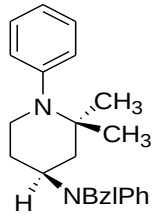
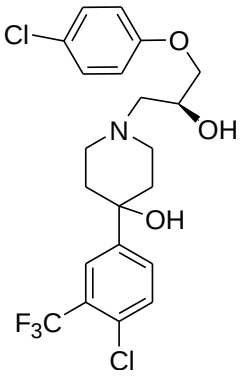


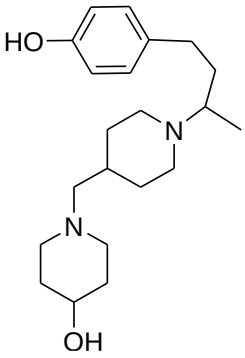
66a



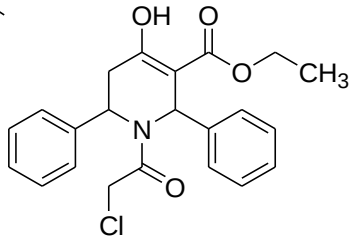
66b



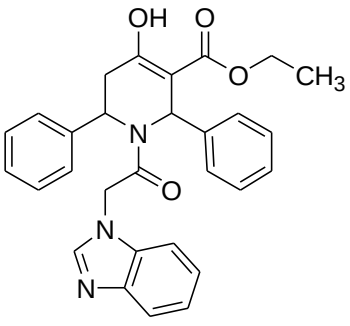
67



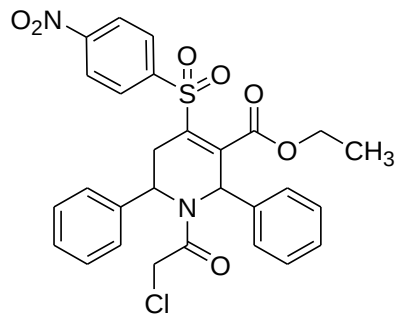
68



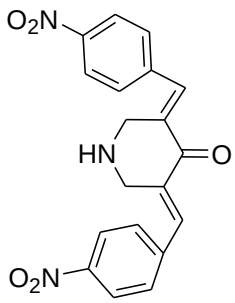
69a



69b



69c



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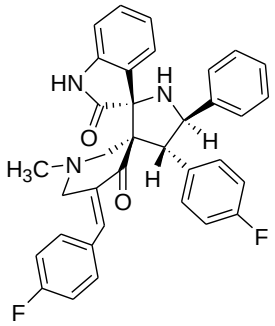
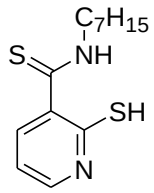


71



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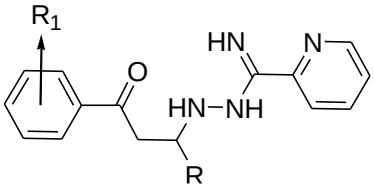
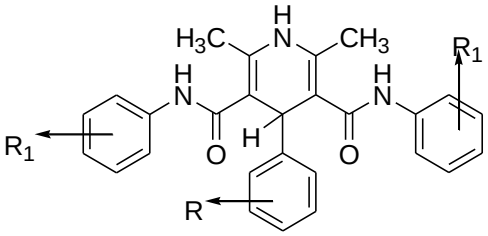
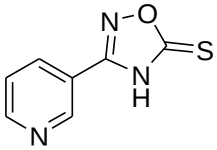


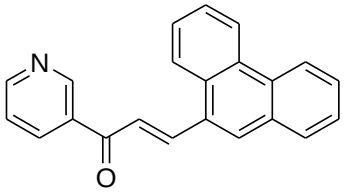
73



74



75



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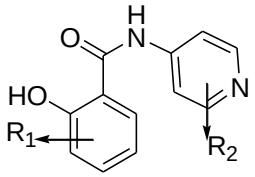

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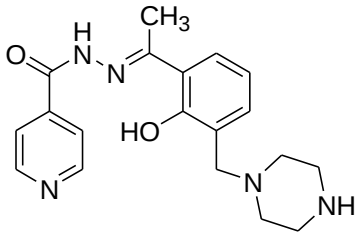

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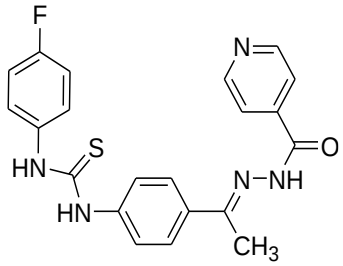
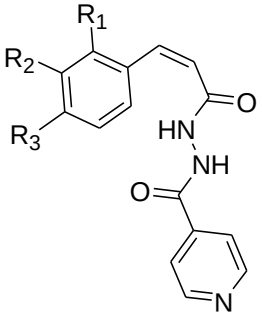


79



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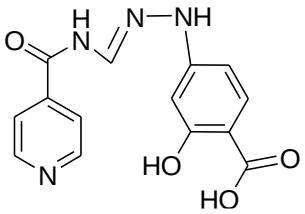
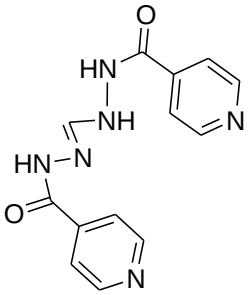
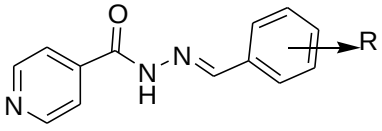
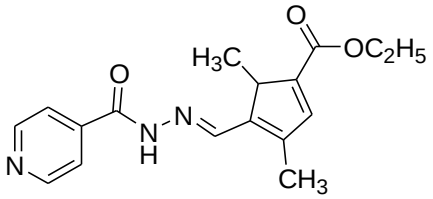


81a

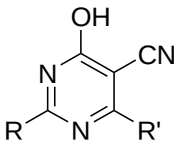


81b

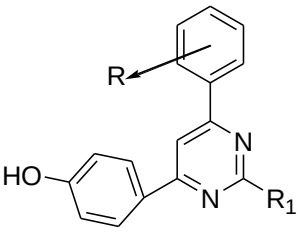




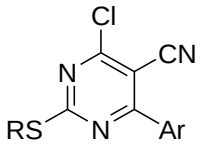
82a: R=3-Cl 82b: R=4-Cl 82c: R=4-F 82d: R=2-CN 82e: R=2-OCH_3 83



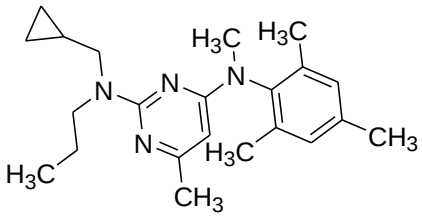
84 a-f,



85 and 86,



87a-d



88

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

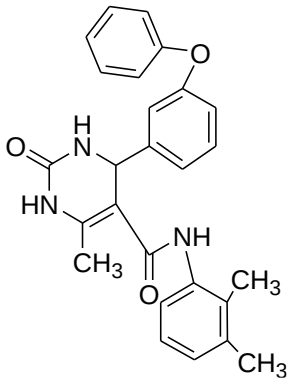
f: R=Octylamine, 130a-f R'=4-methoxybenzene

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

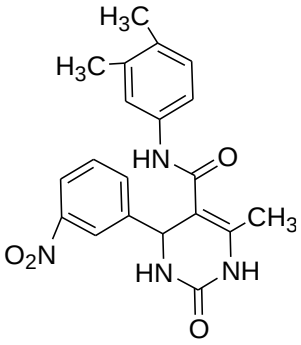
b: R=4-Cl $C_6H_4CH_2$, Ar=2-Theinyl

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

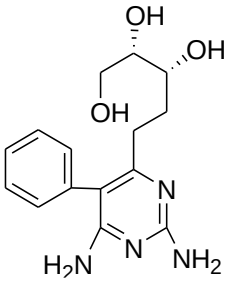
d: R=n-C_3H_7, Ar=2-Furyl



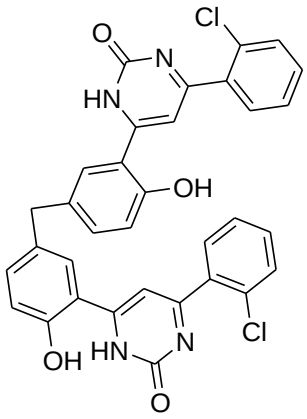
89a



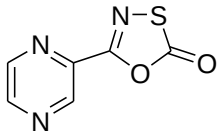
89b



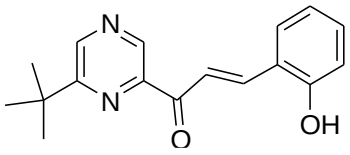
90



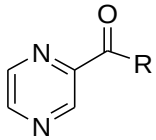
91



92

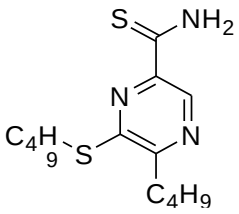


93

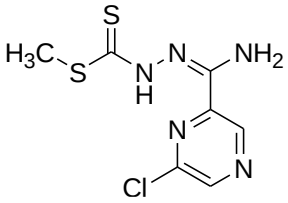


94a: R=4-nitrobenzyloxy

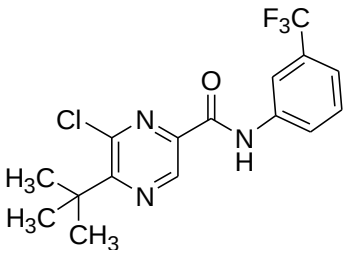
94b: R=4-acetoxybenzyloxy



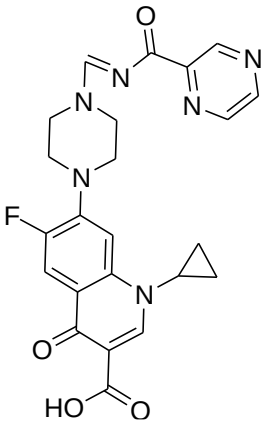
95

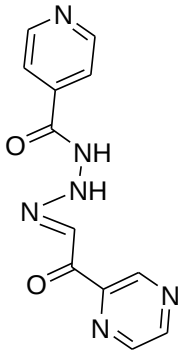


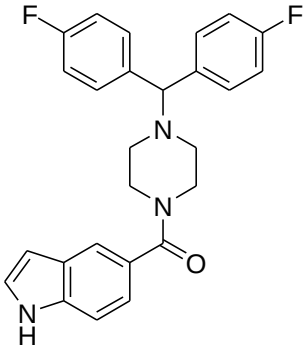
96

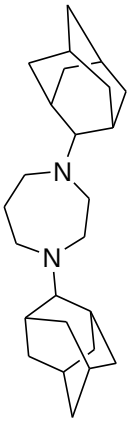


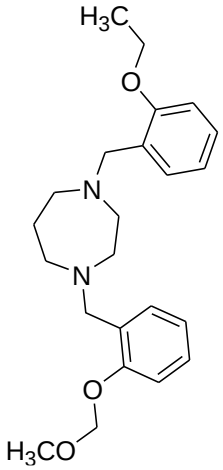
97

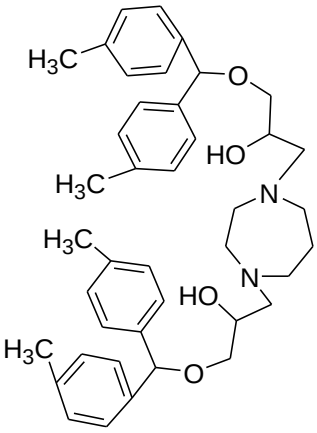

98a

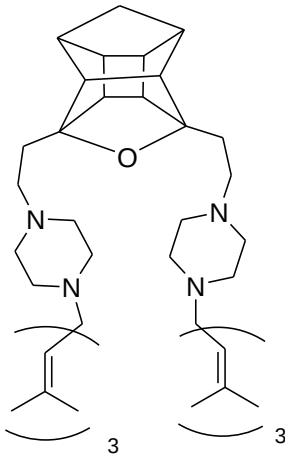

98b

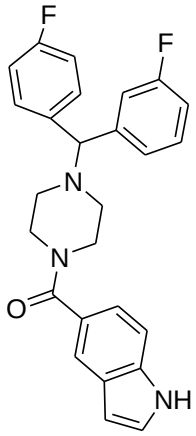

99

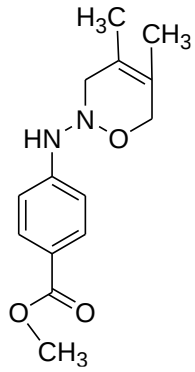

100a

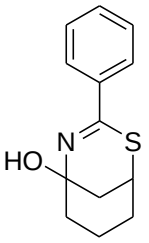

100b


101a: 4*R*,11*R*


101b: 4*S*,11*S*


102


103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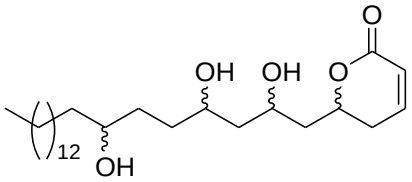
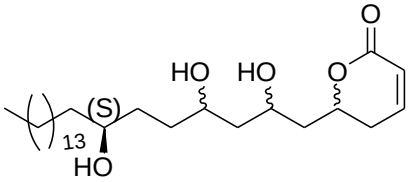
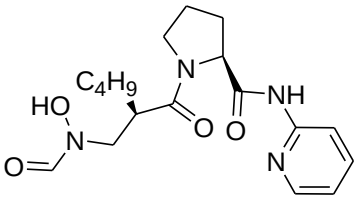
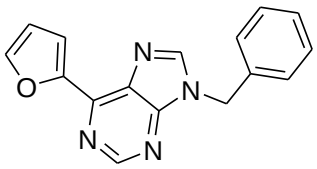
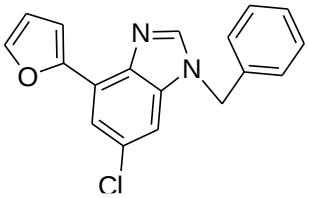
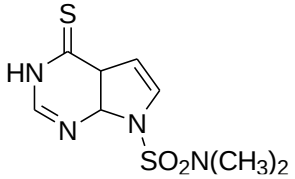

105: 5*R*, 7*S*, 9*S*, 11*S*

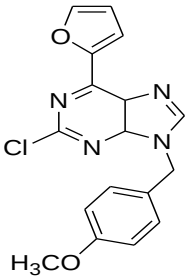

106: 5*R*, 7*S*, 12*S*


107


108a


108b


109



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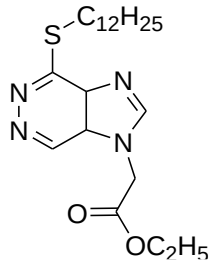

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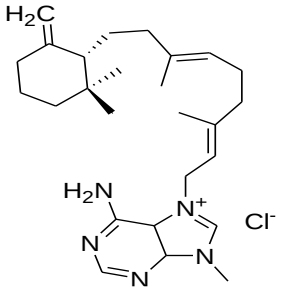
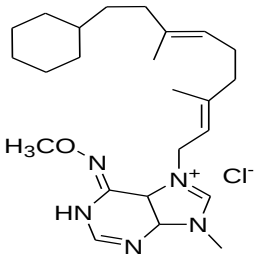
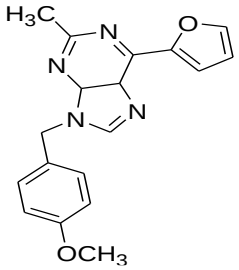


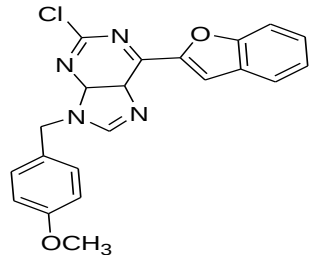
112a



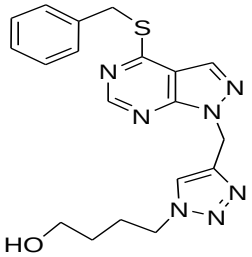
112b



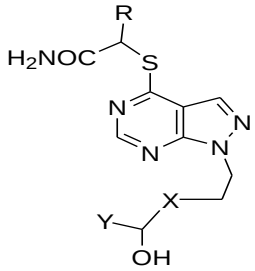
113



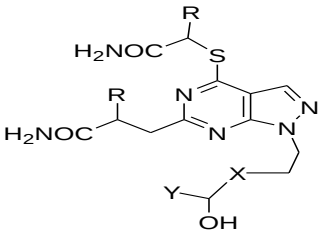
114



115

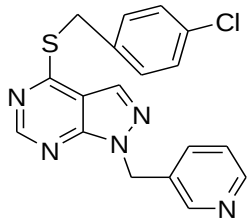


116

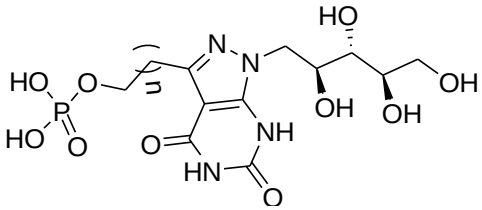


117 X=O,CH_2 Y=H,CH_2OH

R=H, CH_3, C_2H_5

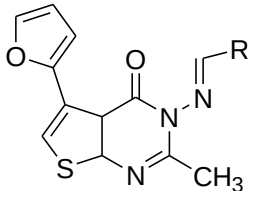


118



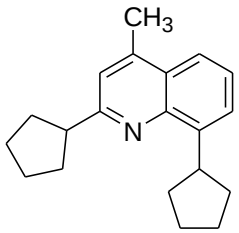
119a:n=2 119b:n=3

119c:n=4;

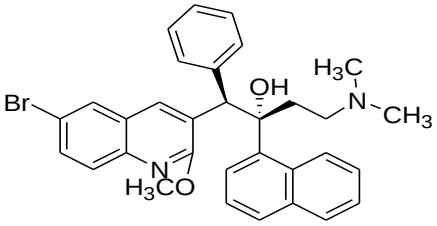


120a: R=2,4-dichlorophenyl

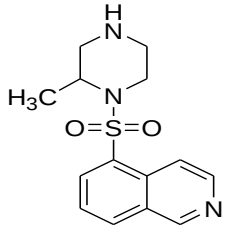
120b: R=2,4-difluorophenyl



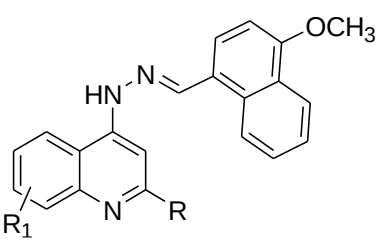
121

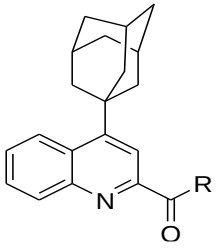


122



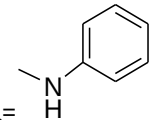
123



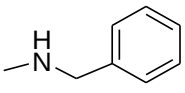


124a: R=H, R_1=7-OCH_3

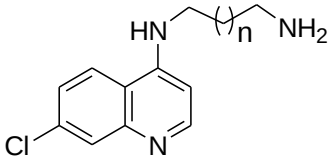
125a: R=



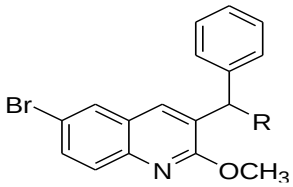
125b: R=



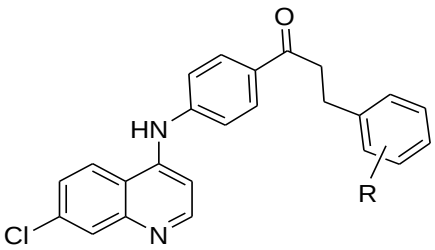
125



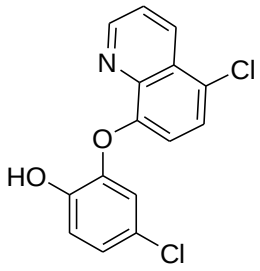
126



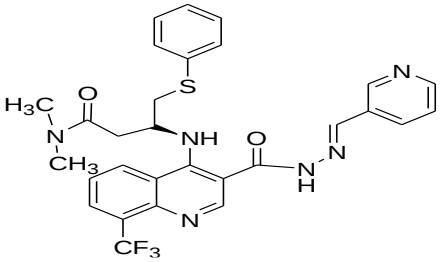
127a: R=Imidazolyl 127b: R=C-(Thiophen-2-yl)-methylamine
127c: R=Pyrazolyl 127d: R=6-Amino-chromen-2-one



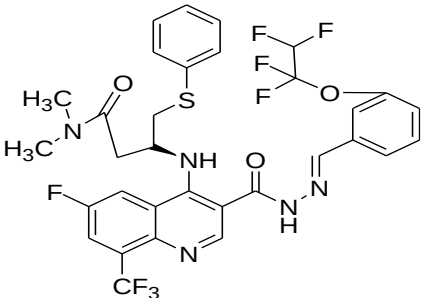
128a: R=2,3-dimethoxy
128b: R=2,5-dimethoxy



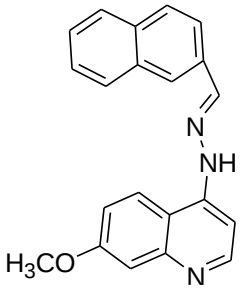
129



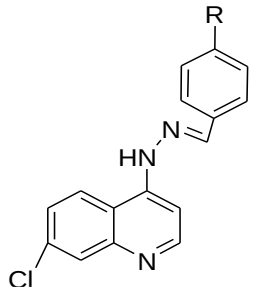
130a



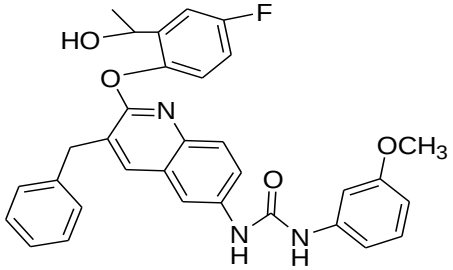
130b



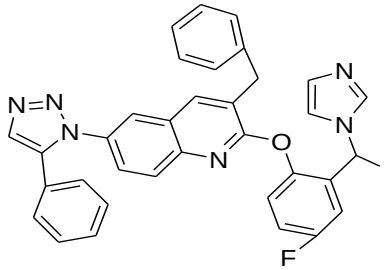
131



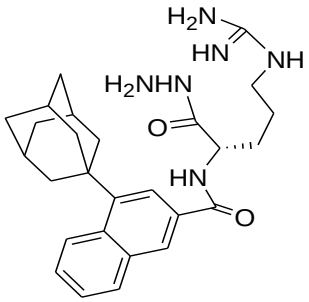
132 a:R=Br b:R=F c:R=OCH_3



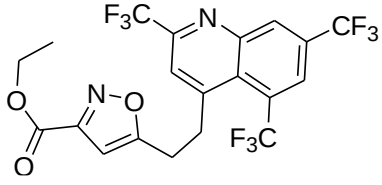
133a

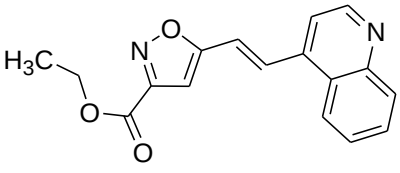


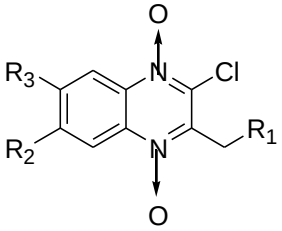
133b



134

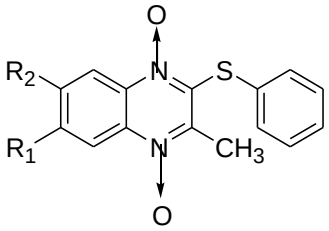






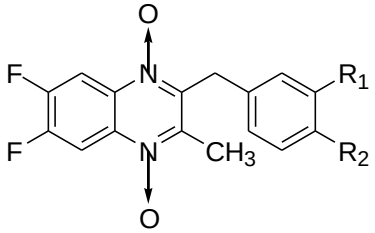
137a:R_1=H

137b:R_1=Br



138a: R_1=H, R_2=Cl

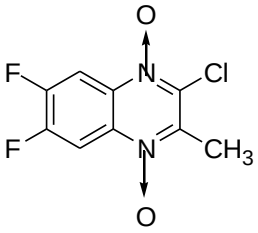
138b: R_1=CF_3, R_2=H



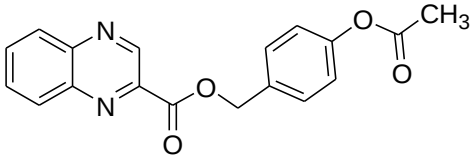
139a: R_1=H, R_2=F

139b: R_1=H, R_2=OCH_3

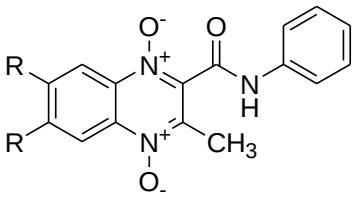
139c: R_1=R_2=OCH_3



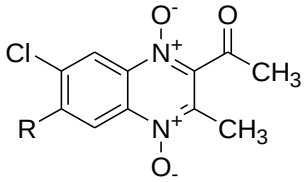
139d



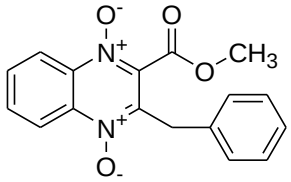
140



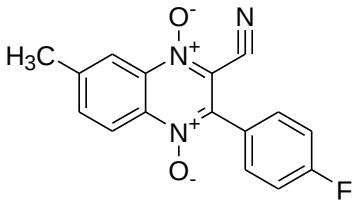
141a:R=Cl 141b: R=H



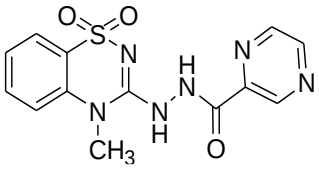
142a: R=Cl 142b: R=H



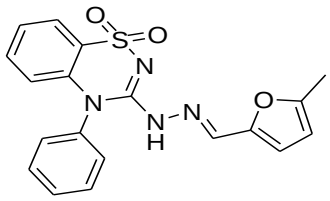
143



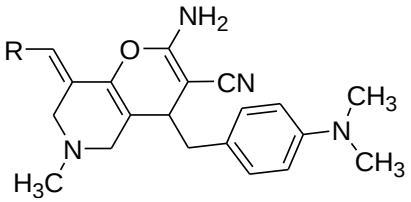
144



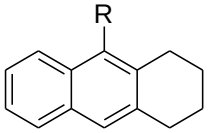
145



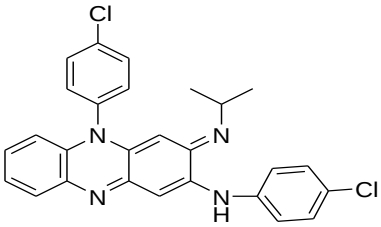
146



147

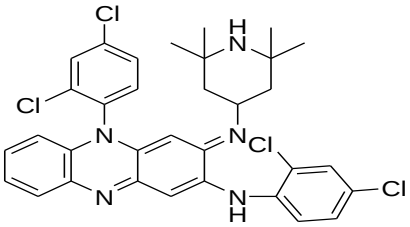


148a: R=-NH-$C_{12}H_{25}$

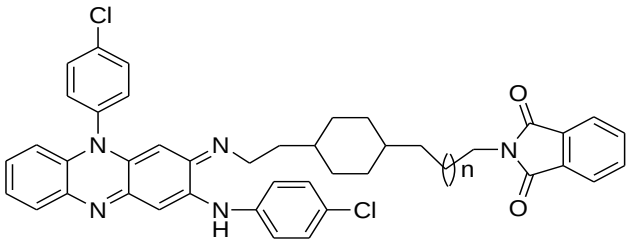


149

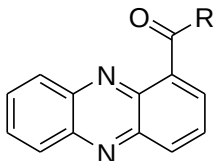
148b: R=-NH-C_8H_{17}



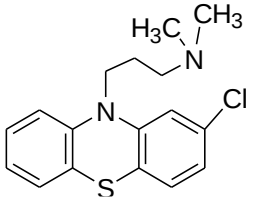
150



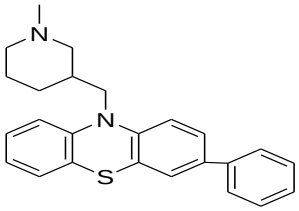
151a: n=3 151b: n=4



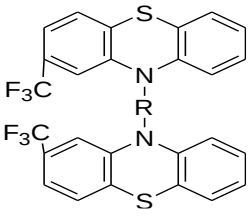
152a: R=-NH-C_6H_4-4F 152b:R=-NH-C_6H_4-3Br



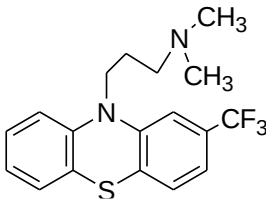
153a



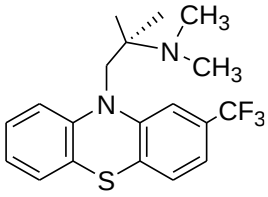
153b



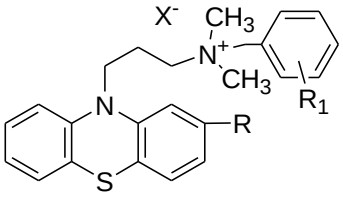
153c: R=C_3H_6 153d: R=1,4-C_6H_4



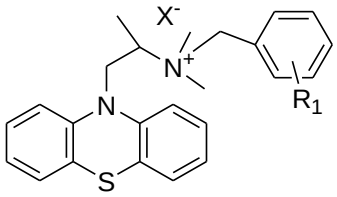
154a



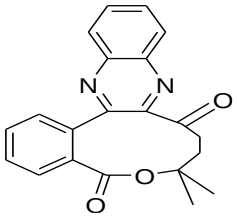
154b



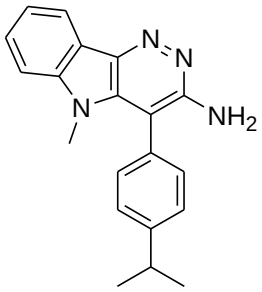
154c:R=Cl 154d:R=H 154e:R=CF_3



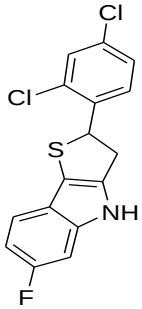
154f



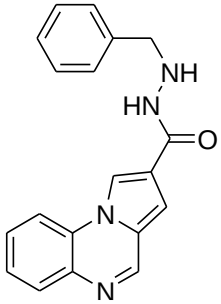
155



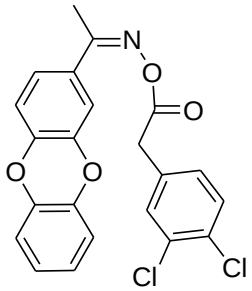
156



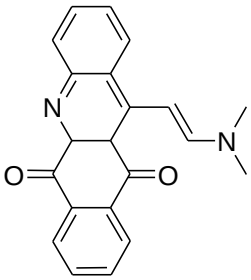
157



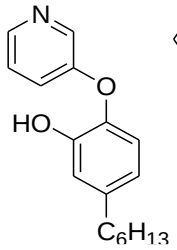
158



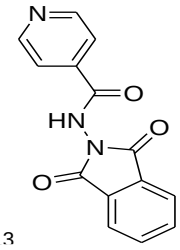
159



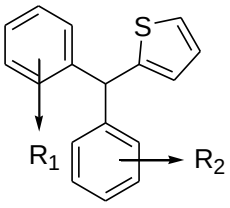
160



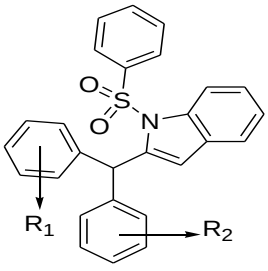
161



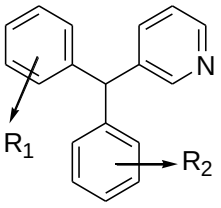
162



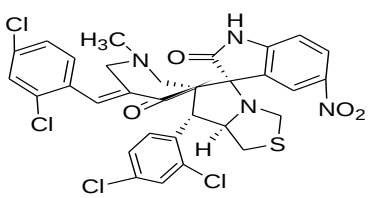
163



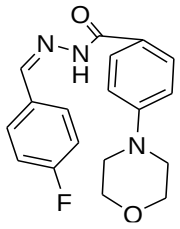
164a



164b



165



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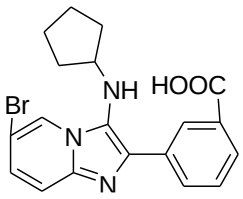
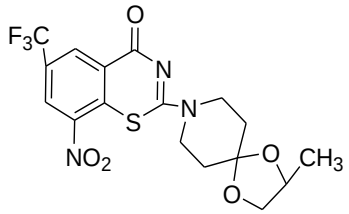


167



168

On this basis and to minimize the side-effects and to improve the anti-TB activity of Clofazimine (149), 3-(2,4-dichloroanilino)-10-(2,4-dichlorophenyl)-2,10-dihydro-2-(2,2,6,6-tetramethyl piperid-4-ylimino)phenazine (B4128) (150), which posses a similar mode of action of Clofazimine (Reddy et al., 1999; Matlola et al., 2001). With the same motivation, a series of phthalimido- and naphthalimido-linked phenazines and found two compounds (151a and 151b) with a potency of MIC 1 µg/mL against *M. tuberculosis* H37Rv. These compounds also exhibited potency against resistant strains of *Mtb* (Kamal et al., 2005). Whereas in a series of phenazine carboxamides, compounds 152a and 152b showed excellent activity against *Mtb* H37Rv with a MIC of 0.19 µg/L and also against drug-resistant strains of *Mtb*. Most interestingly, this series was found to be nontoxic (De Logu et al., 2009), validating them as future anti-TB drug candidates.

Phenothiazines have been reported for their anti-TB activity for many years, and the phenothiazine drug chlorpromazine (CPZ) (153a) is reported to have been successfully used to treat a TB patient. In this concern, a series of psychotropic phenothiazines were examined as anti-TB agents against *Mtb* H37Rv. Among all, three compounds (153b-d) exhibited promising activity with a mean MIC of 2.13µg/mL (Madrid et al., 2007). Whereas quaternized CPZ, triflupromazine (154a) and promethazine (154b) derivatives inhibited non-replicating *Mtb* at concentrations equal to or double their MICs against the actively growing strain. All the active compounds (154c-f) were non-toxic toward Vero cells (IC50 > 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 anti-TB structures possessed *N*-(4- or 3-chlorobenzyl) substitution on triflupromazine (Bate et al., 2007). While a macrolactone (155) derived from benzo(a)phenazine exhibited best potency against *Mtb* H37Rv with a MIC 0.62µg/mL, which is better than that of Rifampacin (Silva et al., 2009).

In search of potential anti-TB agents, pyridazinoindole analogues screened for inhibition of the growth of *Mtb*. The most active compound (156) exhibited a MIC50 of 1.42µg/mL against *Mtb* H37Rv (MTB) (Velezheva et al., 2004). In the series (2-aryl-3,4-dihydro-2H-thieno(3,2-b)indoles), compound 157 was found to be the most active compound with MIC of 0.4 µg/mL against MTB and MDR-TB (Karthikeyan et al., 2009).

With the same motivation, a series of pyrrolo(l,2-a) quinoxaline-2- or -4-carboxylic acid hydrazides and one compound (158) showed an interesting activity at 6.25 µg/mL against *Mtb* H37Rv, with a 100 percentage inhibition (Guillon et al., 2004). Compound 159 inhibited 80% at a concentration of 6.25 µM (Scozzafava et al., 2001). While, Enamine-containing analogues of heteroarylquinones showed promising activity with a MIC in the range 6.25-0.1µg/mL against *Mtb* H37Rv. The best selectivity index (SI=15.1) was displayed by the molecule (160) with a MIC 0.39 µg/mL (Copp et al., 2005).

The structure-based design in the discovery of alkyl substituted diphenyl ether, inhibitors of InhA, the enoyl reductase from *Mtb*. 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, A series of substituted hetero/aryl ethers and of these, one compound (161) exhibited a moderate MIC90 3.13 µg/mL but have improved Clog*P* value (am Ende et al., 2008). A series of pthalamide derivatives, compound (162) displayed a MIC of 5µg/mL against *Mtb* H37Rv and a good selectivity index (Jean et al., 2009). Series of thiophene (163) and benzopyrrole/pyridine (164a and 164b) triarylmethanes (Parai et al., 2008; Panda et al., 2007), thiophene analogues displayed MIC in the range 3.12-12.5 µg/mL and benzopyrrole/pyridine analogues displayed 6.25-25 µg/mL against *Mtb* H37Rv.

A series of spiro-pyrrolothiazoles, the best potency was displayed by compound 165 with a MIC of 0.6µM against *Mtb* and MDR-TB (Karthikeyan et al., 2010). Whereas 4-(morpholin-4-yl)-N'-(arylidene) benzohydrazide derivative (166) which showed an inhibition of 96.78% at a concentration of 0.05 µg/mL against *Mtb* H37Rv. This compound also showed good percentage of inhibition against clinical isolates of MDR strains (Raparti et al., 2009). The 3-amino-imidazo(1,2-a)pyridines as a novel class of *Mtb* glutamine synthetase inhibitors. The compound (167) showed an inhibition of IC50 = 0.38±0.02µM (Odell et al., 2009)

In search of novel anti-TB agents, tetrahydroindazole based compounds and evaluated their efficiency (Guo et al., 2010). The 1,3-benzothiazin-4-ones (BTZ) kills *Mtb* by

blocking arabinan synthesis. The most advanced compound, BTZ043 (168), was found to a candidate for inclusion in combination therapies for both drug-sensitive and extensively drug-resistant TB (Makarov et al., 2009; Abdel-Rahman et al., 2009).

DISCUSSION

Despite these positive changes there are still problems that need to be tackled. A critical question today is whether they are sufficient to bring improved treatment to patients in the next few years. A first challenge concerns the sustainability of the current effort. The next important question is whether there are a sufficient number of promising compounds in the TB pipeline for a broadly effective new treatment combination to be developed. Although different attrition rates might apply, the number of candidate compounds is still small compared to the drug pipelines for diseases of major concern to wealthy countries such as cancer or cardiovascular diseases (and the number of companies engaged in the latter is also greater). Furthermore, many of the compounds in the pipeline are either derivatives of existing compounds or they target the same cellular processes as drugs currently in use. Whilst analogues and derivatives are far quicker to develop, they may be subject to cross-resistance, as has been the case with the new rifamycins and quinolones. Modern technologies and rational approaches to drug design (such as creation of genomic libraries of *Mtb* conditional knock-out mutants for comprehensive target identification and validation, target-based drug discovery, or determination of three dimensional crystal structure of molecular targets) are still weakly implemented in the field of drug discovery for TB. Even the more promising candidate compounds currently in clinical development were identified serendipitously in screenings that were not designed originally for activity against *Mtb*. There is consensus among the TB scientific community that in order to obtain a real breakthrough in TB therapy and drastically shorten treatment there is an urgent need for rational approaches aimed at tackling the problem of mycobacterial persistence. The adaptations that allow *Mtb* is to persist in the host despite a vigorous adaptive immune response likely contribute to the difficulty in curing TB with current chemotherapy. Although drugs currently in the pipeline could significantly shorten treatment, it is likely to remain a matter of months rather than weeks or days. There are two major roadblocks that hamper the implementation of rational drug design in TB drug discovery. The first is the lack of a comprehensive characterization of the fundamental biology of mycobacteria as they persist in human tissues, which prevents the identification and validation of potential targets that are relevant for the survival of the bacteria in vivo. The second is the weak engagement into early-stage drug discovery; as a consequence the advanced knowledge about M. tuberculosis metabolism, physiology and genetics is not being translated into validated targets that can be used for screening of new lead compounds (Asif. 2012a; Asif. 2012b).

As part of the Grand Challenges in Global Health initiative the Gates Foundation is funding research into the molecular pathways of persistence, with the aim of novel target identification. In addition, the Gates Foundation recently announced a new initiative that specifically aims at accelerating drug discovery for tuberculosis. While acknowledging this significant contribution, it is important not to rely exclusively on a single initiative to address a complex scientific problem of such great importance. Much attention must be paid to these critical issues. If faster progress is to be achieved in drug discovery for TB then the advanced knowledge about *Mtb* metabolism and physiology needs to be translated into validated targets that can be used for screening of new lead compounds. A key difficulty lies in securing sustained funding for translational research projects such as target validation and chemical genetics. Rare exceptions are made for occasional grants based on request for application, but generally it is very difficult for academic labs to obtain funds for projects that fall between the areas of basic and applied research. The private sector for its part is reluctant to engage in early stage drug discovery projects; drug development is instead only embarked upon when rigorously validated targets are available or a lead compound has been already identified. Real improvements in TB treatment will require substantial strengthening of early-stage discovery research to identify new compounds and targets (Asif. 2012c; Asif et al., 2011; Asif, et al., 2012; Asif et al., 2013). Without a thriving background of discovery-oriented translational research, which is largely dependent on public funding, drug development is destined to fail in terms of long-term goals for effective TB management. Existing modern technologies need to be urgently and more comprehensively applied to TB if the pipeline for drug R&D is to be filled. The reluctance of the pharmaceutical sector to invest in early-stage discovery research for neglected diseases exacerbates the pressing need to translate basic scientific knowledge into novel targets and fresh approaches towards improved therapies. Without proper public engagement in early stage drug discovery and implementation of rational approaches, progress in innovation will be severely hindered.

Future perspectives

The unremitting and steady rise in TB together with the emergence of resistance against traditional anti-TB drug regimen and the pathogenic synergy with HIV has put enormous pressure on public health systems to introduce new treatments. In MDR-TB, 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. Remarkably, the mechanisms of action of these new drugs are well-

understood with new and novel target. 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.

CONCLUSIONS

Tuberculosis (TB) is a chronic infectious disease caused by *Mtb*. The term MDR-TB is used to describe strains that are resistant to two or more of the five first-line anti-TB drugs. Treatment regimen of TB 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 anti-TB drugs available commercially, several new heterocycles were synthesized in recent past. The new potential anti-TB agents have been classified according to their chemical entities. The new developed and more effective molecules are also effective against MTB and MDR-TB.

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