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ADVANCES IN TB DRUG DEVELOPMENT: A NOTE ON DERIVATIVES OF ISONIAZID AND PYRAZINAMIDE

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ABSTRACT: Tuberculosis (TB) remains one of the main causes of death from an infectious disease till date. Recent data shows that currently 9.6 million people are infected with TB. Over 95% of TB deaths occur in low- and middle-income countries and it is among the top 5 causes of death for women aged 15 to 44. TB is a leading killer of HIV-positive people and around 1 in 3HIV deaths was due to TB. Furthermore, multidrug-resistant (MDR)-TB and extensively drug-resistant (XDR)-TB is spreading and poses a major threat to progress in global TB control program. The emergence of drug resistant TB strains makes the invention of new molecular scaffold a priority. One of the possible strategies to overcome drug resistance in an economic and simple manner would involve re-engineering and repositioning of some old drugs to obtain derivatives that can work on resistant *TB bacilli*. These may have enhanced bioavailability, be more effective, and serve as cost-effective substitutes, as compared to new drugs identified through conventional methods of drug discovery and development. In view of this, the present review aims to provide a summarizing report on the derivatives of first-line drugs (isoniazid and pyrazinamide) that have the potential to conquer the resistance to the parental drug and could thus serve as effective alternatives.

INTRODUCTION: Tuberculosis (TB) remains one of the main causes of death from an infectious disease. *Mycobacterium tuberculosis* (Mtb), the causative agent of TB was first identified by Robert Koch in 1882, since his discovery till now the global TB epidemic seems unabated [1].

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Members of Mtb complex are responsible for human TB, which includes Mtb itself, *Mycobacterium africanum*, *Mycobacterium bovis*, *Mycobacterium caprae*, *Mycobacterium microti*, *Mycobacterium pinnipedii* and *Mycobacterium canettii*. People with active pulmonary TB are the major cause of infection and most of the people infected with Mtb have it as asymptomatic latent TB infection (LTBI) [2, 3]. TB is spread *via* air from person to person. When people with pulmonary TB cough, sneeze or spit, they thrust the TB germs into the air. People need to breathe in only a few of these germs to become infected.

Around one-third of the world's population has dormant or latent TB, which means people have been infected by TB bacteria but are not ill with the disease and cannot spread the disease. People who are infected with TB bacteria have only 10% lifetime risk of falling ill with TB. TB generally has an effect on adults in their most productive years. Recent data shows that currently 9.6 million people are infected with TB.

Over 95% of TB deaths occur in low and middle-income countries and it is among the top 5 causes of death for women aged 15 to 44. TB is a leading killer of HIV-positive people and around 1 in 3HIV deaths was due to TB. The risk of active TB is also greater in persons suffering from other conditions which suppress the immune system such as malnutrition, diabetes and smoking. Use of tobacco highly increases the risk of TB disease and death. More than 20% of TB cases worldwide are attributed to smoking. Globally around 5% of TB patients develop multidrug-resistant TB (MDR-TB). Instead of all the consequences of this disease the Millennium Development Goal target of stopping and reverse the TB epidemic by 2015 has been met globally. TB occurrence rate has fallen by an average of 1.5% per year since 2000 and is now 18% lower than the level of 2000. The TB death rate has fallen down 47% between 1990 and 2015 [4].

The world's two most heavily populated countries, India and China, are having more than 50% of the world's MDR-TB cases and so these countries are causing a high and increasing TB disease burden [5]. The sheer size of their TB case populations results in the highest estimated numbers of MDR-TB cases (about 100,000 each) emerging annually from these two countries [6].

History of TB Drug Development: Streptomycin, the first antibiotic with proven activity against Mtb, was obtained from *Streptomyces griseus* almost 70 years ago, providing the first hope of a TB-specific therapy [7, 8]. Though little observational studies of streptomycin in human TB were hopeful, doubts remained about its capacity to consistently cure patients after realizing the rapid development of drug resistance when a single drug therapy is used for the treatment of TB. In the 1950s, numerous other TB drugs with diverse mechanisms of action were discovered and developed (**Table 1**), such as *para*-amino salicylic acid, isoniazid, pyrazinamide, cycloserine, kanamycin etc. This paved the way for combination therapy. At that time duration of 18 months or more was used for the treatment plan for TB. The use of rifampicin into treatment plan for TB in the 1960s was a major breakthrough that shortened the treatment duration to 9 months and when course of therapy containing pyrazinamide was used then duration was shortened to 6 months [9].

Standard TB Treatment Regimens: Treatment of drug-susceptible (DS)-TB involves an initial phase of isoniazid, rifampin, pyrazinamide and ethambutol for the first 2 months followed by a continuation phase of isoniazid and a rifamycin for the last 4 months [10]. One point often overlooked regarding existing TB drugs is that the standard four-drug (first-line drugs) combination is relatively inexpensive and works reasonably well in DS-TB patients. The four-drug combination given daily over a period of 6 to 9 months can cure approximately 85% of DS TB patients if the treatment regimen is strictly followed [11]. Although cure rates as high as 95% have been reported, they are not typically observed. If the cure rate is 85%, a follow-up question might be why TB still kills 1.7–1.8 million people every year [12]. The most clear-cut answer is that these drugs are far from ideal. However, the more absolute answer is undoubtedly manifold and related to not only the current treatments but also rooted in socioeconomic factors. The almost universally accepted standard of care that involves long treatment times and multiple-drug combinations in treating TB patients confirms to the fact that the current drugs are not exceedingly efficacious and TB's tendency to develop resistance to any single agent requires the use of combination chemotherapy [13].

MDR-TB is resistant to at least isoniazid and rifampicin, the two most important first-line drugs used in the treatment of TB. This may result from either primary infection with drug-resistant bacteria or may develop in the course of a patient's treatment when non-optimal treatment durations or regimens are used. Cure rates for MDR-TB are lower, typically ranging from 50% to 70%. XDR-TB is resistant to isoniazid and rifampicin as well as any fluoroquinolone and any of the second-line anti-TB injectable drugs (amikacin, kanamycin or

capreomycin). It has very high mortality rates. Usually resistant TB can be cured with long treatments of second-line drugs [10].

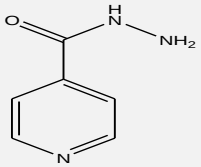
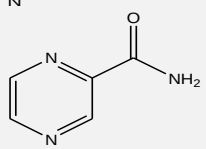
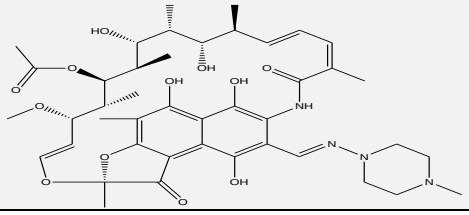
Current Scenario: There is hope that unmet needs for both drug-susceptible TB and MDR-TB are beginning to be addressed by the acceleration in TB drug discovery, development and evaluation in the past decade, particularly for regimens to shorten the duration of treatment and reduce the likelihood of the development of resistance [24]. Much progress has been made in research and development of new drugs for TB over the last decade. Currently ten new or repurposed TB drugs are in clinical trials for the treatment of drug-susceptible, drug-resistant TB or latent TB infection. This includes two Phase III trials examining whether drug-susceptible TB treatment duration can be shortened from the standard 6 months to 4 months by replacing repurposed drugs gatifloxacin or moxifloxacin for ethambutol or isoniazid. One more Phase III trial in progress is using twice-weekly rifapentine with moxifloxacin during the continuation phase for shortening treatment duration [25].

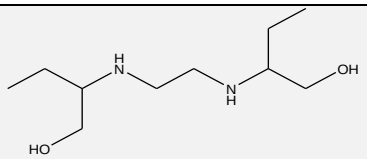
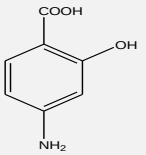
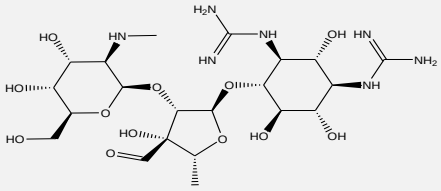
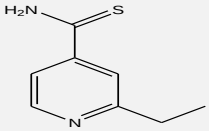
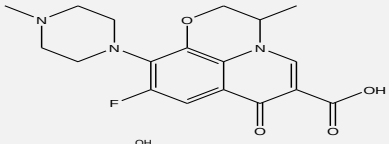
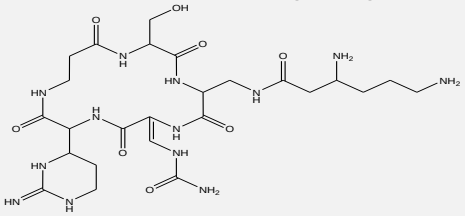
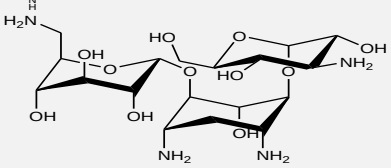
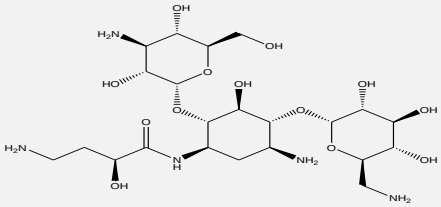
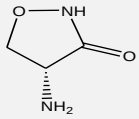
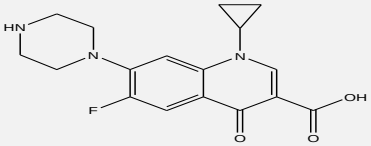
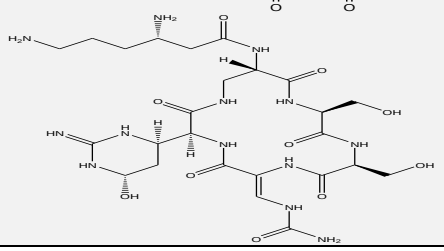
Two new drugs, delamanid, a nitroimidazole derivative that causes intracellular release of lethal reactive nitrogen species and bedaquiline which targets ATP synthesis have been tested in newly diagnosed MDR-TB patients and now these drugs have been approved by stringent regulatory authorities under accelerated or conditional approval procedures for the treatment of MDR-TB as part of combination therapy for adults with pulmonary TB when other alternatives are not available. Other compounds which are being tested for XDR-TB are nitroimidazole derivative and repurposed oxazolidinone linezolid [4].

In spite of some notable progress in TB drug discovery and development, much more is required to meet the big challenges presented by the emergence of all forms of drug-resistant TB as well as the convergence of the TB and HIV epidemics. New drugs in novel combinations require more efficient evaluation for safety, efficacy and shortening treatment duration. New biomarkers are needed to enhance the effectiveness of Phase II and III trials using adaptive designs. Coordination and cooperation among drug developers, national governments, research funders and policy makers is needed for stopping TB plan [4, 25].

One of the possible strategies to overcome drug resistance in an economic and simple manner would involve re-engineering and repositioning of some old drugs to obtain derivatives that can work on resistant TB bacilli. Present review consider the developments made in modification or derivatization of two of the first line drugs, Isoniazid (INH) and pyrazinamide (PZA), for the improved treatment regimen for all forms of TB with the future aspects for further development. Modification of either of these molecules has been a challenge taken up by numerous research groups [26-28].

TABLE 1: STANDARD REGIMEN FOR THE TREATMENT OF TB [14-23]

S. No.	Name	Structure	Target	Mechanism of Action
		First-Line Drugs		
1.	Isoniazid (1952)		Enoyl-[acyl-carrier-protein] reductase	Cell wall (inhibition of InhA)
2.	Pyrazinamide (1954)		S1 component of 30S ribosomal subunit	Multiple (including intracellular acidification, decrease of delta pH)
3.	Rifampin (1963)		RNA polymerase, beta subunit	RNA polymerase

4.	Ethambutol (1961)		Arabinosyl transferases	Cell wall (inhibition of arabinosyl transferase)
		Second-Line Drugs		
5.	Para-amino salicylic acid (1948)		Dihydropteroate synthase	Thymidylate synthase inhibition and interference in iron acquisition
6.	Streptomycin (1944)		S12 and 16S rRNA components of 30S ribosomal subunit	Inhibits protein synthesis
7.	Ethionamide (1961)		Enoyl-[acyl-carrier-protein] reductase	Cell wall biosynthesis (inhibition of InhA)
8.	Ofloxacin (1980)		DNA gyrase and DNA topoisomerase	Inhibits DNA supercoiling
9.	Capreomycin (1963)		Interbridge B2a between 30S and 50S ribosomal subunits	Protein synthesis inhibition (inhibition of translocation)
10.	Kanamycin (1957)		30S ribosomal subunit	Protein synthesis inhibition
11.	Amikacin (1972)		30S ribosomal subunit	Protein synthesis inhibition
12.	Cycloserine (1955)		d-alanine racemase and ligase	Cell wall biosynthesis
13.	Ciprofloxacin		DNA gyrase	DNA synthesis inhibition
14.	Viomycin		Translocation	Protein synthesis inhibition

Isoniazid as Target: The clinical efficacy of INH was discovered in the 1950's and it is undeniable that INH is a magnificent first-line anti-TB drug in TB treatment regimen [28, 29]. INH is specifically highly active against Mtb with a minimum inhibitory concentration (MIC) of 0.05 mg/mL, higher than any other compound used at that time [29]. It is assumed that INH enters Mtb through passive diffusion through the cell-wall and that it is active only against dividing bacteria [30, 31].

The study about mechanism of action of INH was first published in 1970 by Winder and [32] connecting INH with inhibition of mycolic acid biosynthesis. Mycolic acid is a long-chain α-alkyl-β-hydroxy fatty acid; a major component in the cell wall of Mtb. This component plays a vital role in maintaining the integrity of the mycobacterial cell wall [29, 32-34]. In order for INH to be effective against Mtb it needs to be activated by the multifunctional catalase-peroxidase enzyme KatG into a range of activated species, such as an isonicotinoyl radical, that can acylate numerous compounds [35, 36].

The generally accepted mechanism of action of INH postulates that the isonicotinoyl radical binds to the nicotinamide adenine dinucleotide (NADþ) and the resulting adduct inhibits the enoyl-acyl carrier protein (enoyl-ACP) reductase InhA, a NADH-dependent enoyl-ACP reductase of the fattyacid synthase type II system (FASII). This inhibition causes accumulation of long-chain fatty acids, inhibition of mycolic acid biosynthesis and ultimately cell death [29, 37]. However, the burgeoning incidence of INH resistant Mtb strains in the last decades has complicated the TB treatment [5, 38].

The main mechanism of resistance to isoniazid resides in the presence of mutations in the gene encoded for INH activator peroxidase (*katG*), enoyl acyl carrier protein (ACP) reductase (*InhA*), β-ketoacyl ACP synthase (*kasA*), alkyl-hydroperoxide reductase (*ahpC*), NADH dehydrogenase (*ndh*), and also inactivation of INH by *nat*-encoded arylamine *N*-acetyltransferase in its activator, KatG, product of the katG gene [29, 39-45].

However mutations in the katG and inhA gene altogether are responsible for approximately 75% of all cases of Mtb resistance to isoniazid in the clinical setting [46].

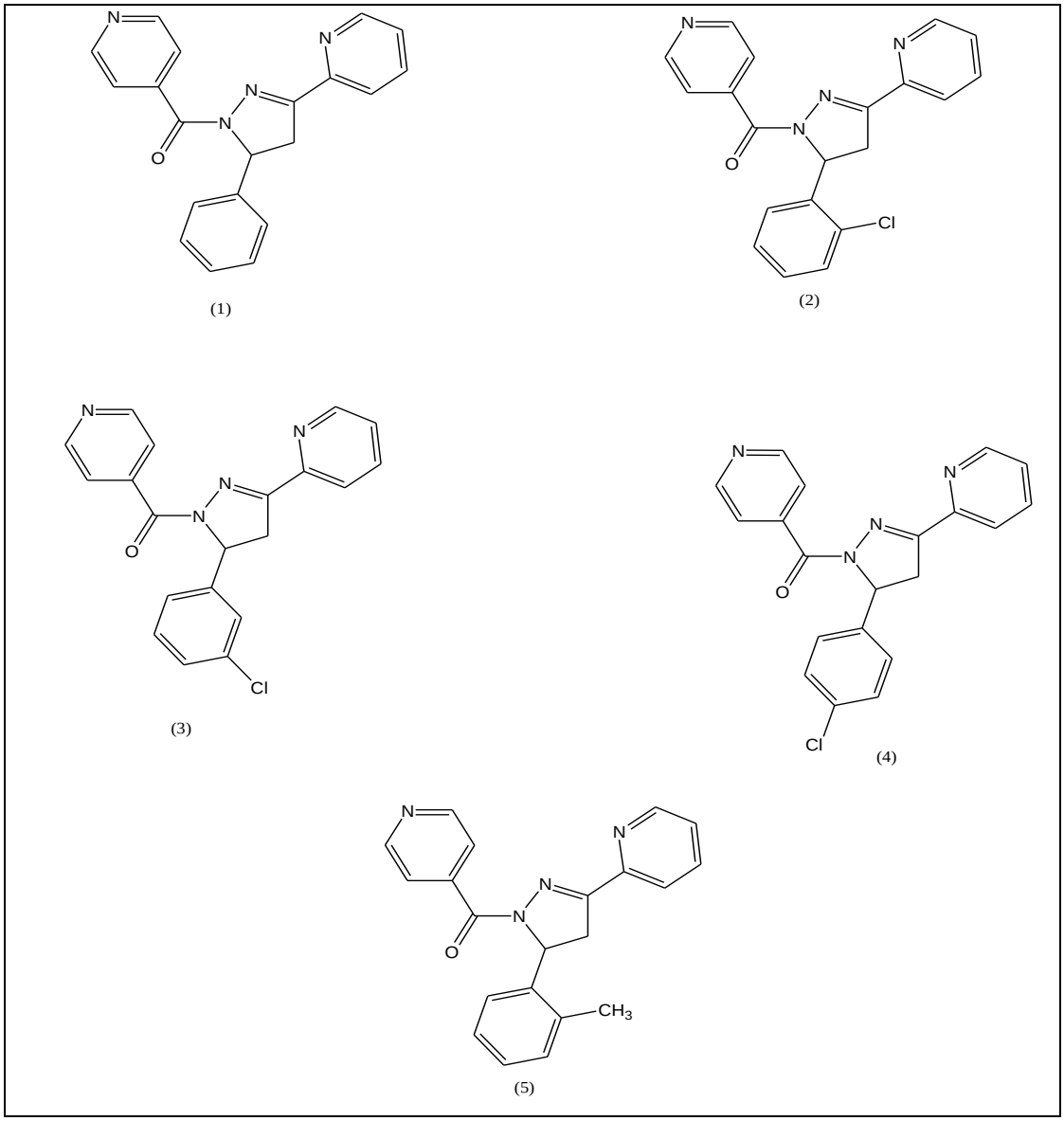
Other studies suggested that the architecture of the cell envelope also contributes to Mtb resistance, whereby, the outer layer of the cell wall hinders the diffusion of chemotherapeutic agents into the cell thus causing resistance by exclusion barrier [47-50]. As mentioned before, isoniazid remains a key component in all multiple drug treatment regimens recommended by the WHO albeit resistant isolates are rapidly generated during monotherapy or inappropriate treatment [51].

Similarly to some other candidates in the pipeline that were chemically tailored from drugs to which Mtb was already resistant, departing from isoniazid might also bring new insights into the development of new antitubercular agents. Hence enhancing the biological response of INH against Mtb by augmenting the hydrophilic INH with a hydrophobic/lipophilic side chain and/or circumvent resistance phenomena continues to be an interesting scientific challenge [48-50, 52].

In an effort to overcome resistance and enhancing INH activity, scientists have derivatized isoniazid in different ways. In present study, we have made an attempt to collect and compile various derivatives of isoniazid along with their reported biological activities. Different derivatives of 5-aryl-1-isonicotinoyl-3- (pyridin-2-yl)-4,5-dihydro-1H-pyrazole derivatives were synthesized and evaluated for anti-tubercular activity.

The compounds(5-phenyl-3-(pyridin-2-yl)-4,5-dihydropyrazol-1-yl) (pyridin-4-yl) methanone (1), (5- (2-chlorophenyl) -3- (pyridin-2-yl)- 4,5-dihydropyrazol-1-yl) (pyridin-4-yl) methanone (2), (5- (3-chlorophenyl)-3 - (pyridin-2-yl) -4,5-dihydro pyrazol-1-yl) (pyridin-4-yl)methanone (3), (5- (4-chlorophenyl)-3 -(pyridin-2-yl) - 4, 5-dihydro pyrazol-1-yl) (pyridin-4-yl) methanone (4) and (3-(pyridin-2-yl)-5-o-tolyl - 4, 5 - dihydropyrazol-1-yl) (pyridin-4-yl) methanone (5) were found active anti-mycobacterial agents with MIC of 8 µg/ml against human-pathogenic strain of Mtb [53].

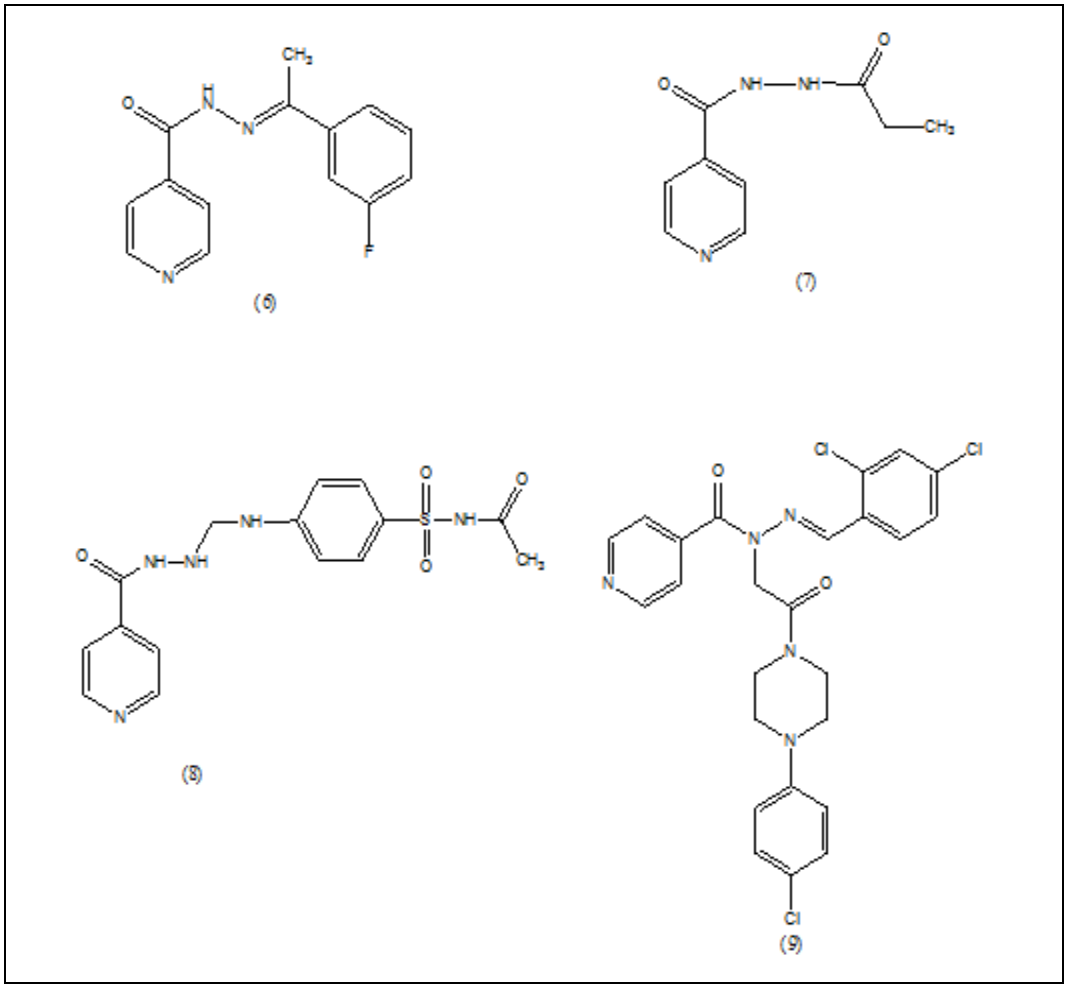
Various isonicotinohydrazides and their cyanoborane adducts were synthesized and evaluated for their *in vitro* anti-mycobacterial activities. Most of the tested compounds displayed moderate to high activity against Mtb H37Rv, with MICs ranging from 0.2 to 12.5µg/ml.



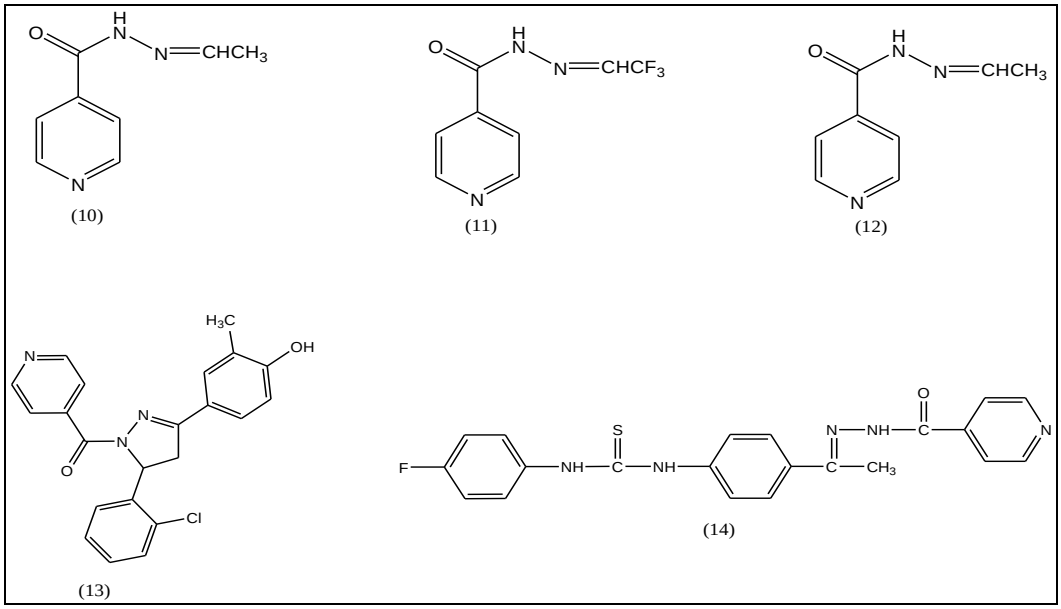
The compound (E)- N'- (1- (3- fluorophenyl) ethylidene) isonicotinohydrazide (6) was the most effective one among the synthesized compounds with MIC value 0.05 µg/ml [54].

Several acylated derivatives of isoniazid were synthesized and tested for their anti-mycobacterial activity against Mtb. They found that among these derivatives N'-propionylisonicotinohydrazide (7) closely homologous to the INH metabolite, N2-acetylisoniazid, have MIC values several fold greater than that of INH and thus may serve as significant leads in anti-tubercular drug discovery and in the exploration of the mode of action of INH [55]. Mannich bases with heteroaromatic ring system were synthesized employing mannich reaction of isonicotinyl hydrazide with various sulphonamides / secondary amines. Amongst the synthesized derivatives, compound (8) was the most active one [56].

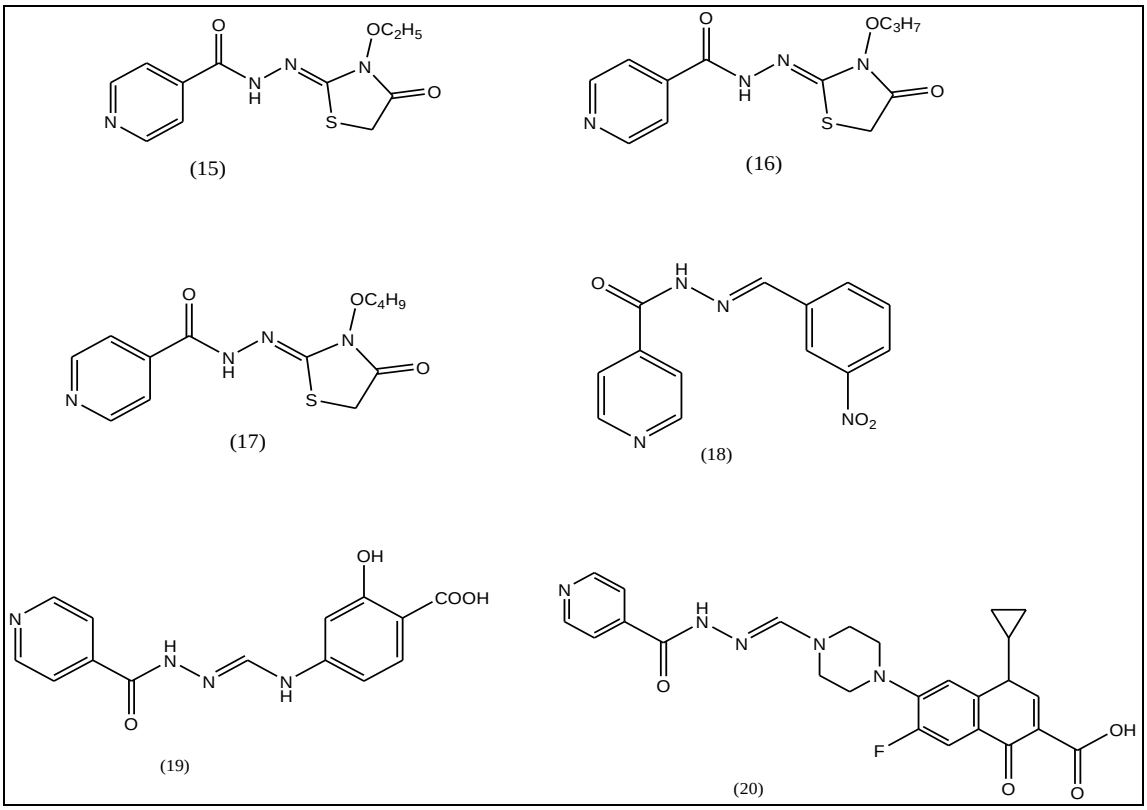
A series of isonicotinic acid N'-arylidene-N-[2-oxo-2-(4-aryl-piperazin-1-yl)-ethyl] - hydrazides as antitubercular agents was designed, synthesized and evaluated for anti-TB activity against Mtb H37Rv and clinical isolates. Some of these compounds showed good potency and there *in vitro* activities against sensitive and resistant strains of Mtb were found to be equivalent or better than isoniazid. The compound (E)-N'-(2,4-dichloro benzylidene)-N-(2-(4-(4 chlorophenyl) piperazin-1-yl) -2-oxoethyl) isonicotino hydrazide (9) was one of the most active derivative synthesized in this series [27].



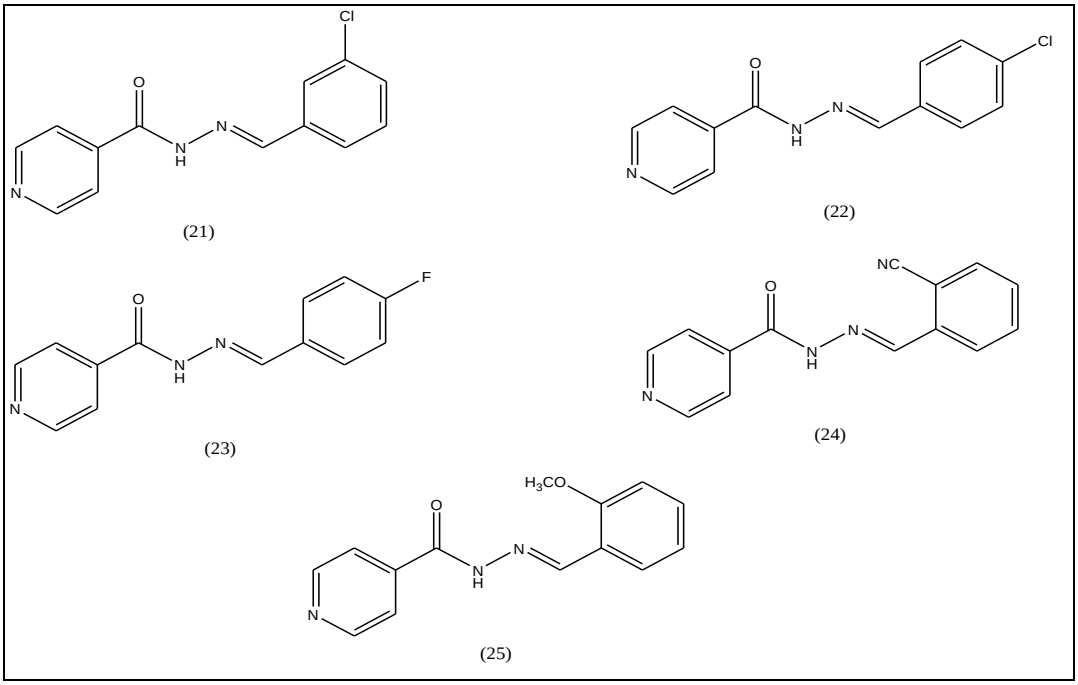
A series of isoniazid-related isonicotinoyl hydrazones (ISNEs), 2'-monosubstituted isonicotinohydrazides and cyanoboranes were evaluated for their *in vitro* anti-myco-bacterial activity. In this study compounds N'-ethylideneisonicotinohydrazide (10), N'-(2, 2, 2-trifluoroethylidene) isonicotinohydrazide (11) and N'-ethylideneisonicotinohydrazide (12) were found to be highly active anti-mycobacterial agents with MIC = 0.025 µg/ml against Mtb H37Rv [57]. A series of N^1-nicotinoyl-3-(4'-hydroxy-3'-methyl- phenyl)- 5 -(substituted phenyl)-2-pyrazolines was synthesized by the reacting INH and chalcones and tested for its *in vitro* anti-mycobacterial activity against Mtb H37Rv and INH-resistant Mtb using the agar dilution method. Out of the synthesized compounds, (5-(2-chlorophenyl)-3-(4-hydroxy –3 -methylphenyl)-4, 5-dihydropyrazol-1-yl)(pyridin-4-yl)methanone (13) was found to be the most active agent against Mtb and INH-resistant Mtb with a minimum inhibitory concentration of 0.26 µM [58]. A series of isonicotinyl hydrazones was synthesized by reacting isonicotinyl hydrazide with 1-(4-acetyl-phenyl)-3-[(4-sub)phenyl]thiourea and tested their anti-mycobacterial activity *in vitro* against Mtb H37Rv and INH-resistant Mtb using the BACTEC radiometric system. Among the synthesized compounds, (E)-N'-(1-(4-(3-(4 fluorophenyl) thioureido) phenyl) ethylidene) isonicotinohydrazide (14) was found to be the most potent compound with a minimum inhibitory concentration of 0.49 µM against Mtb H37Rv and INH-resistant Mtb [59]. A variety of phthalimido [2-aryl-3-(5′-(4″-pyridyl)-1′,3′,4′-thiadiazol-2′-yl) - 4 -oxothiazolidin-5-yl] ethanoates and 3-N-alkoxyphthalimido-2-isonicotinoylhydrazido-1, 3-thiazolidin-4-ones were synthesized using thiosemicarbazide of isoniazid by two alternative pathways. The compounds,(Z)-N'- (3-ethoxy-4-oxothiazolidin – 2 - ylidene) iso nicotine hydrazide (15), (Z)-N'-(4-oxo-3-propoxy thiazolidin-2-ylidene)isonicotinohydrazide (16) and (Z)-N' - (3-butoxy-4-oxothiazolidin-2-ylidene) iso nicotine hydrazide (17) exhibited good antimicrobial activity compared to standard drugs [60].



Several nicotinic and isoniazid derivatives, most of them containing nitro groups were synthesized and evaluated for their *in vitro* antibacterial activity against Mtb H37Rv using the Alamar Blue susceptibility test. The compound (E)-N'-(3-nitrobenzylidene) isonicotinohydrazide (18) exhibited the best result (1.2 µg/mL) when compared with first line drugs such as isoniazid (INH) and rifampicin (RIP) [61]. Several derivatives were synthesized by linking INH with another conventional drug (morpholine, 2-amino methyl pyridine, benzylamine, PAS, ciprofloxacin) by the CH fragment and evaluated for the activities. The compounds 2-Hydroxy-4-{[(isonicotinoyl hydra zono) methyl] amino}benzoic acid (19) and 1-Cyclopropyl-6-fluoro-7-{4-[(isonicotinoyl hydra zono) methyl] piperazin-1-yl}-4-oxo-1,4-dihydro quinoline-3-carboxylic acid (20) were found to possess higher activity against non-tuberculous strains than INH [62].



A series of 22 (E)-N'-(monosubstituted-benzylidene) isonicotinohydrazide derivatives have been synthesized and evaluated for their *in vitro* antibacterial activity against Mtb $H_{37}Rv$ using Alamar Blue susceptibility test. Compounds, (E)-N'-(3-chlorobenzylidene) isonicotinohydrazide (21), (E)-N'-(4-chloro benzylidene) isonicotin ohydrazide (22), (E)-N'-(4-fluorobenzylidene) isonicotino hydrazide (23), (E)-N'-(2-cyanobenzylidene) isonicotinohydrazide (24) and (E)-N'-(2-methoxybenzylidene) isonicotino hydrazide (25) exhibited a significant activity (0.31-0.62 mg/mL) when compared with first line drugs such as isoniazid and rifampicin [63].



Different amide derivatives of isoniazid have been synthesized and evaluated for their antibacterial activities. The compound N'-(5-(4-bromophenyl)-5-oxopentanoyl) isonicotinohydrazide (26) was found to be effective as antibacterial agent [64].

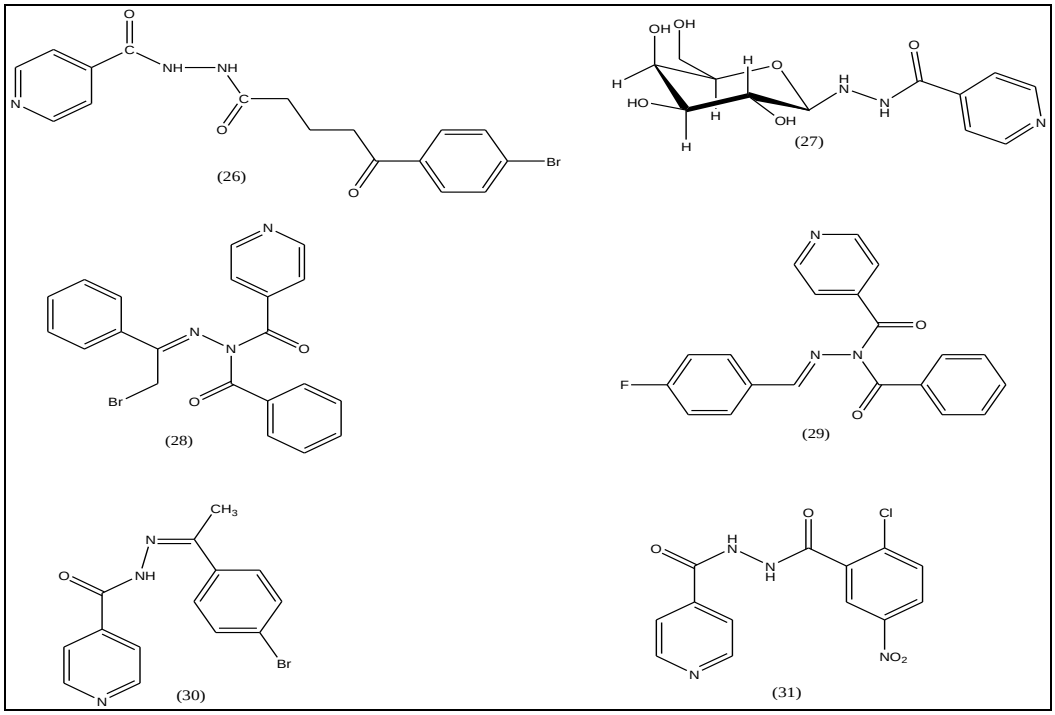
A series of 13 compounds analogous of isoniazid condensed with carbohydrates was synthesized and evaluated for their *in vitro* antibacterial activity against Mtb *H37Rv* using Alamar Blue susceptibility test. The compound N'-((2R, 3S, 4S, 5R)-3,4,5-trihydroxy - 6 - (hydroxyl methyl) - tetrahydro - 2H-pyran – 2 - yl) isonicotin ohydrazide (27) exhibited antitubercular activity (0.31-3.12 µg/mL) when compared with first line drugs such as isoniazid and rifampicin [65].

Some Novel biologically active Isoniazid derivatives substituted with sulphonamides and aldehydes were synthesized and subjected to antimicrobial screening (both *in vitro* and *in vivo*). All the synthesized compounds were docked with DNA GYRASE (Topoisomerase II type).

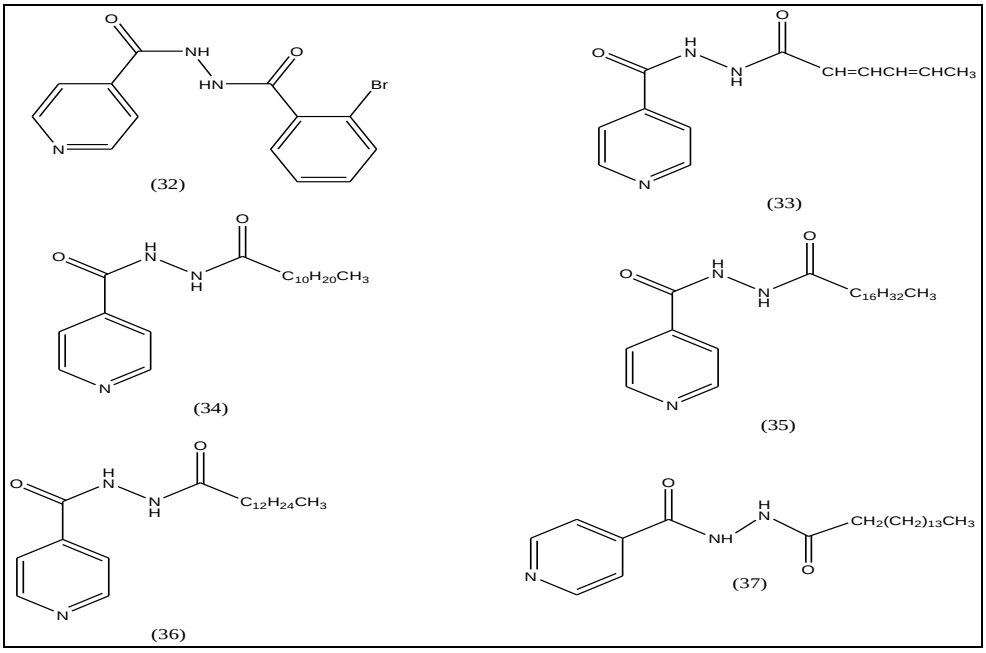
The *in-vivo* antibacterial evaluation revealed that the 2-bromo-1-phenylethylidene (28) and 4-fluorobenzylidene (29) substituted isoniazid derivatives showed very potent activity [66].

A series of isonicotinic acid-1-(substitutedphenyl)-ethylidene/cycloheptylidene hydrazide derivatives was synthesized and tested for their *in vitro* antimycobacterial (against Mtb), antiviral and antibacterial activities. The compound (Z)-N'-(1-(4-bromophenyl)ethylidene)isonicotinohydrazide (30) was found to be more active than isoniazid [67].

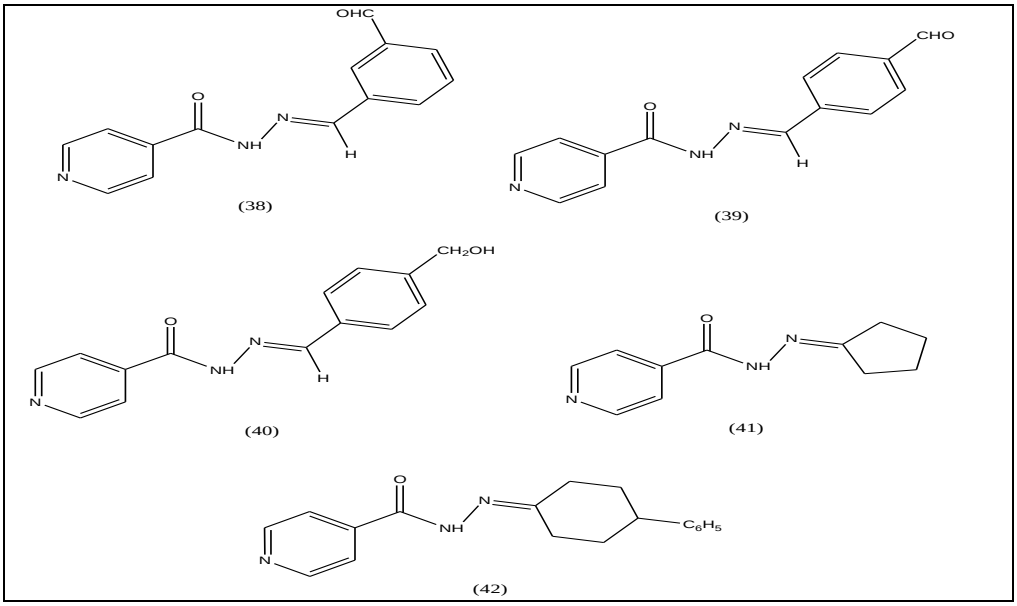
A series of isonicotinic acid hydrazide derivatives was synthesized and evaluated for *in vitro* antimycobacterial activity against Mtb and antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Candida albicans*, and *Aspergillus niger* and the compound N'-(2-chloro-5-nitrobenzoyl) isonicotinohydrazide (31) was found to be effective as antimycobacterial agent than standard drugs [68].



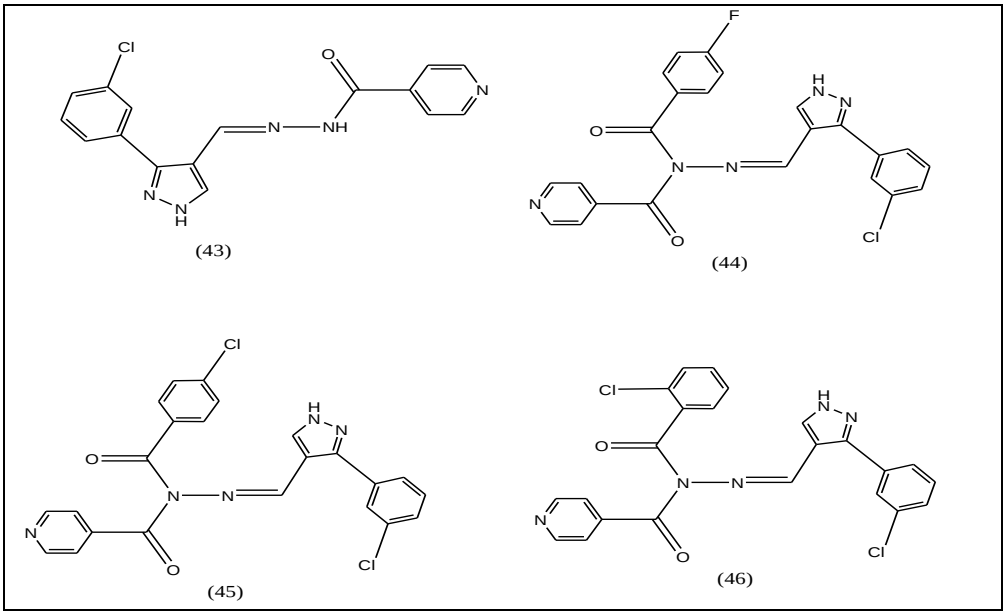
Various isonicotinic acid hydrazide derivatives were synthesized and tested for their *in vitro* antimycobacterial activity against Mtb and the compounds 2-Bromo-benzoic acid N'-(pyridine-4-carbonyl) - hydrazide (32), N'-hexa-2,4-dienoylisonicotinohydrazide (33), N'-dodecanoyl isonicotinohydrazide (34) and N'-stearoyl isonicotinohydrazide (35) were found to be the most effective than the standard drug isoniazid.[69] Several N2-acyl isonicotinic acid hydrazides were synthesized and tested for their *in vitro* antimycobacterial activity against Mtb and the results indicated that the compound N'-stearoylisonicotinohydrazide (36) was more active than the reference compound isoniazid [70]. The hydrophobic isoniazid derivative, 1-isonicotinoyl-2-hexadecanoyl hydrazine (37) was synthesized and evaluated for its MIC on Mtb H37Rv with respect to cell viability, cellular morphology, and acid-fastness properties. The observations were compared to that of INH and the compound was found to be effective at lower MIC (0.0391µg/mL) then INH (0.0781µg/mL) [71].



The QSAR-oriented design, synthesis and *in vitro* antitubercular activity of several potent isoniazid derivatives (isonicotinoyl hydrazones and isonicotinoyl hydrazides) against H37Rv and two resistant Mtb strains was studied. Compounds, (E)-N' - (3-formylbenzylidene) isonicotinohydrazide (38), (E) - N' - (4-formylbenzylidene) isonicotino hydrazide (39), (E)-N'-(4-(hydroxymethyl) benzyli dene) isonicotinohydrazide (40), N'-cyclo penty lideneisonicotinohydrazide (41) and N'-(4-phenylcyclohexylidene) isonicotinohydrazide (42) showed measured activities against H37Rv higher than INH (*i.e.*, MIC < 0.28 mM) [72].



A series of isonicotinohydrazide based pyrazole derivatives was synthesized and screened for *in vitro* antimycobacterial activity against Mtb H37Rv strain. Four compounds N'-((3-(3-chlorophenyl)-1H-pyrazol-4-yl) methylene) isonicotinohydrazide (43), N'-((3-(3-chlorophenyl) - 1H - pyrazol-4-yl) methylene) - N - (4-fluorobenzoyl) isonicotino hydrazide (44), N- (4-chlorobenzoyl) - N' - ((3-(3-chlorophenyl)-1H-pyrazol-4-yl) methylene) iso nicotino hydrazide (45) and N-(2-chlorobenzoyl)-N'-((3-(3-chlorophenyl) -1H-pyrazol -4-yl) methyl ene) isonicotinohydrazide (46) emerged as promising antitubercular agents with MIC of 64.9 µM which is much lower than the MIC of the first line antitubercular drug, ethambutol [80].

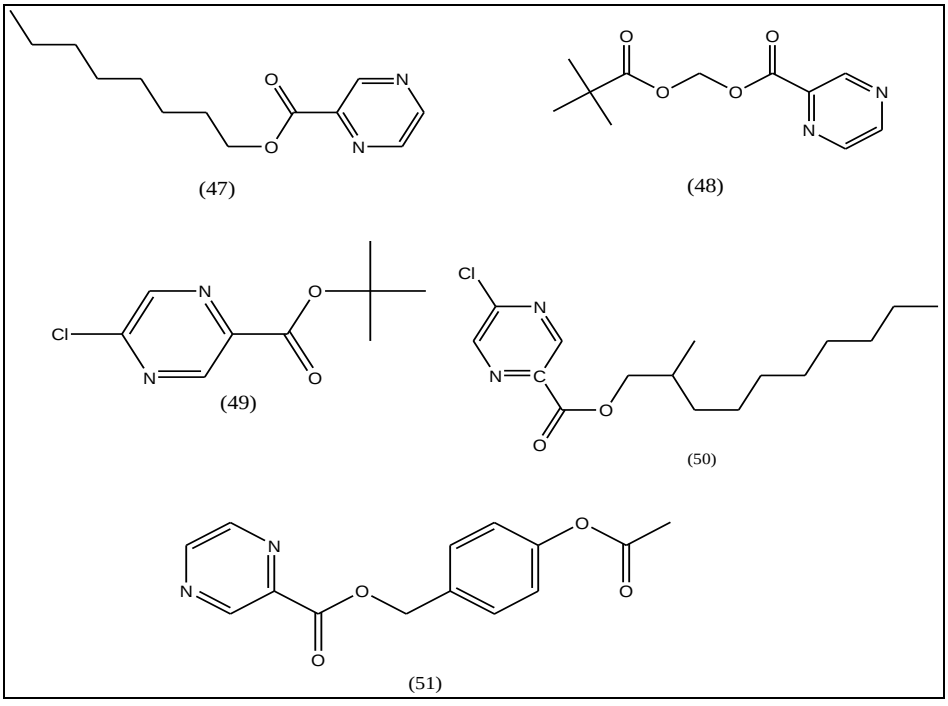


Pyrazinamide as Target: The pyrazine nucleus is an important heteroaromatic class of compounds with a wide range of pharmacological activities such as antibacterial, anti-inflammatory, anticancer, anti-diabetic, and sedative [74]. Another important application of this nucleus is the pyrazinamide (PZA), a first-line antitubercular drug [75, 76] PZA plays a unique role in shortening the TB therapy from the previous 9-12 months to 6 months because it kills a population of semi-dormant bacilli that are not killed by other TB drugs [77]. PZA is considered to be a prodrug of Pyrazinoic Acid (POA), which is believed to be the active inhibitor of Mtb [78]. Experimental evidences suggest that PZA diffuse into Mtb through passive diffusion and after that it is converted in POA by *pncA* gene encoded pyrazinamidase, present in all PZA-sensitive strains of Mtb [43]. It has been shown that acid pH enhances the accumulation of POA in Mtb, which has been shown to have a defective efflux mechanism for POA [79].

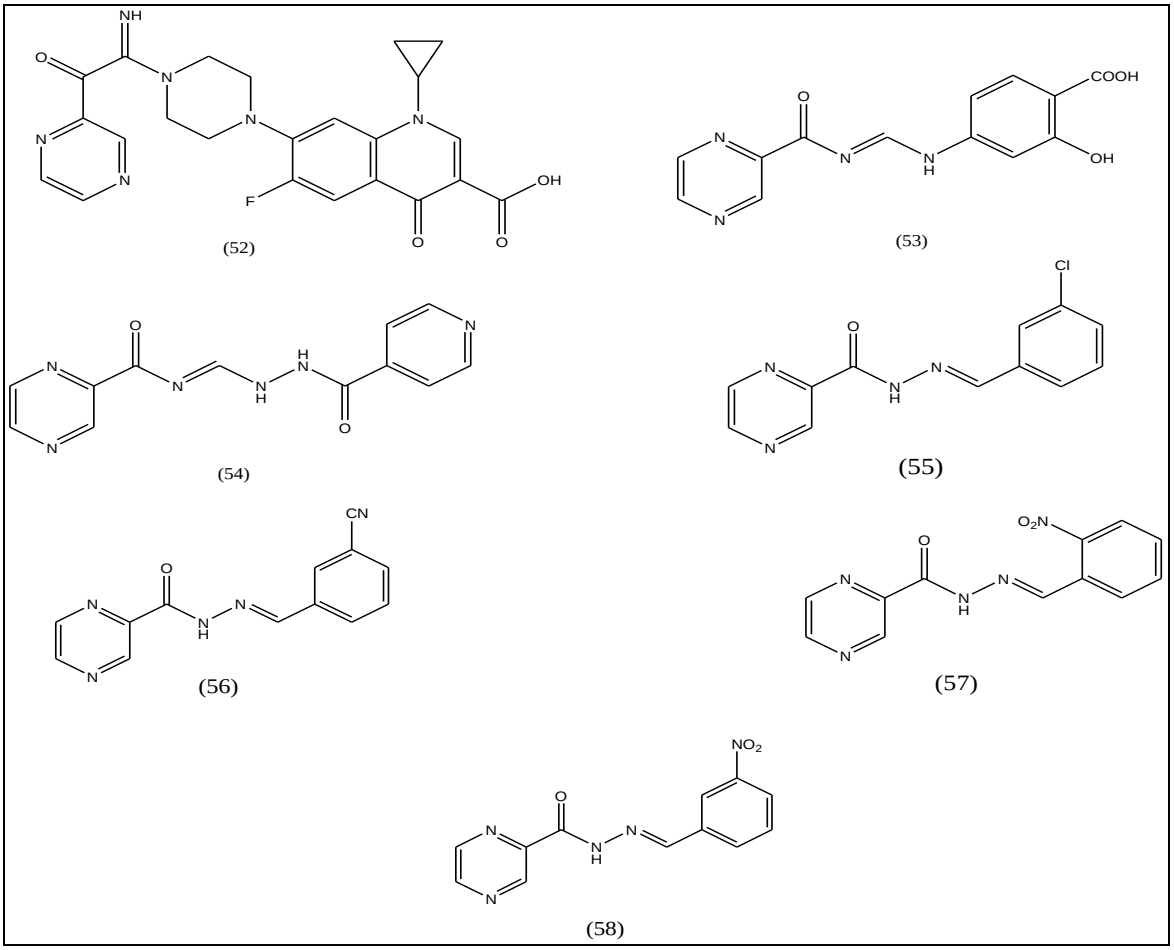
The mechanism of action of PZA is thought to be deactivation of fatty acid synthetase enzyme by its activated form POA, leading to de-energised membrane and ultimately cell death.[80, 81] The major mechanism of PZA resistance in Mtb described in the literature is mutation in its activator gene *pncA* [82-89]. In an effort to overcome resistance and enhancing PZA activity, scientists have derivatized pyrazinamide in different ways. In present study, we have made an attempt to collect and compile various derivatives of pyrazinamide along with their reported biological activities.

Various pyrazinamide analogs were synthesized and assayed there *in vitro* antimycobacterial activities in order to find new drugs which are more active against Mtb than pyrazinamide and also active against *Mycobacterium avium* and *Mycobacterium intracellulare*. Of the synthesized compounds, pyrazinoic acid *n*-octyl ester (47) and pyrazinoic acid pivaloyloxymethyl ester (48) were found potent against mycobacteria in comparison to pyrazinamide [90]. A quantitative structure-activity relationship was developed to understand the relationship between the activities of the pyrazinoic esters with the needed biostability.

This study revealed that *tert*-butyl 5-chloropyrazinoate (49) and 2‘-(2‘-methyldecyl) 5-chloropyrazinoate (50) compounds were 100-fold more active than pyrazinamide against Mtb and possess a serum stability 900-1000 times greater than the lead compound [91]. A series of pyrazine derivatives was synthesized and their activity against Mtb and *Mycobacterium avium* are reported. The 4-acetoxybenzyl ester of pyrazinoic acid (51) showed excellent activity against Mtb (MIC ranges of less than 1-6.25 mg/mL) [92].



The connection of two active molecules across an easily released bridge as a new type of potentially active molecule was studied. The synthesis is based on derivatives of activated pyrazine derivative with ciprofloxacin (52), p-aminosalicylic acid (PAS) (53) and isonicotinic acid (54) The compounds exhibited significant activity [62]. A series of twenty-six N'-[(E)-(monosubstituted-benzylidene)]-2-pyrazinecarbohydrazide (4–29) was synthesized and evaluated for their cell viabilities in non infected and infected macrophages with *Mycobacterium bovis*, *Bacillus Calmette–Guerin* (BCG). The compounds N'-[(E)-(3-chlorophenyl) methylidene] – 2 - pyrazine carbo hydrazide(55), N'-[(E)-(3-cyanophenyl) methyl dene] - 2-pyrazine carbohydrazide (56), N'-[(E)-(2-nitro phenyl) methylidene] – 2 - pyrazinecarbo hydrazide (57) and N'-[(E)-(3-nitrophenyl) methylidene] - 2 – pyrazinecarbohydrazide (58) exhibited a significant activity (50–100 mg/mL) when compared with first line drug pyrazinamide and were not cytotoxic in their respective MIC values [93].

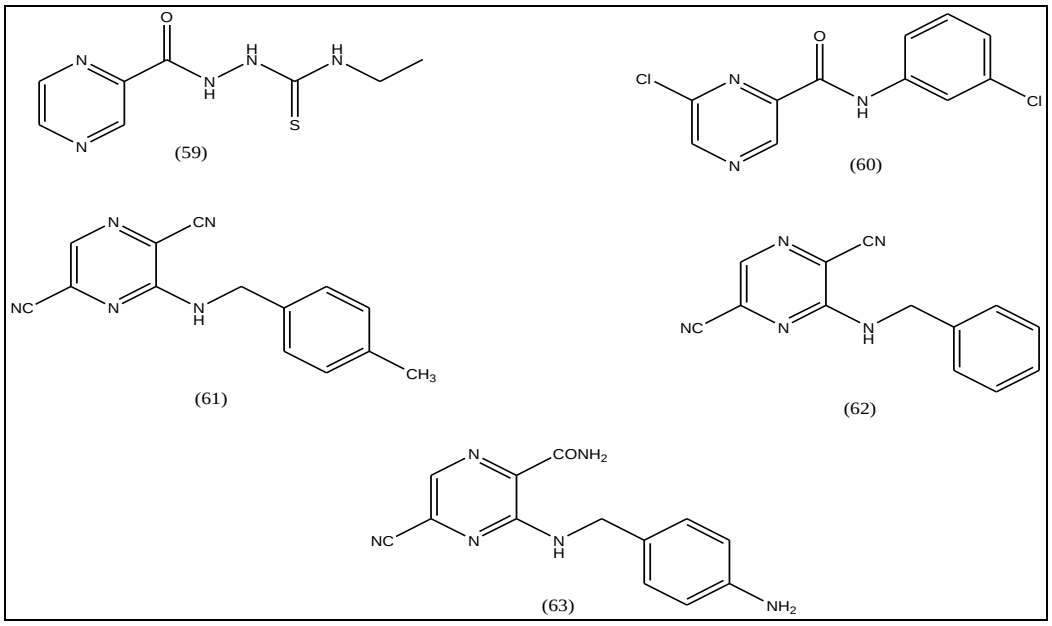


Several pyrazine - 2 - carboxylicacidhydrazide derivatives were synthesized and screened for their activity against Mtb. The results show that pyrazine-2-carboxylic acid hydrazide-hydrazone derivatives were less active than pyrazinamide. In contrast, the N^4-ethyl-N^1-pyrazinoyl-thiosemi carbazide (59) showed the highest activity against Mtb H37Rv (IC90 ¼ 16.87 mg/ mL) [94].

A series of sixteen pyrazinamide analogues with the -CONH- linker connecting the pyrazine and benzene rings was synthesized by the condensation of chlorides of substituted pyrazine carboxylic acids with ring-substituted (chlorine) anilines. The synthesized compounds were characterized and screened for their antimycobacterial activity. 6-Chloro-*N*-(4-chlorophenyl)pyrazine-2-carboxamide (60) manifested the highest activity against Mtb strain H37Rv (65% inhibition at 6.25 μg/mL) [95].

A set of 19 new compounds related to pyrazinamide were synthesized, characterized with analytical data and screened for *in vitro* whole cell antimycobacterial activity against Mtb H37Rv,

Mycobacterium kansasii and two types of *Mycobacterium avium*. The series consisted of 3-(benzylamino)-5-cyanopyrazine - 2 - carboxamides and 3-(benzylamino) pyrazine-2, 5-dicarbonitriles with various substituents on the phenyl ring. Compound 3-(4-methylbenzylamino) pyrazine-2, 5-dicarbonitrile (61) possessed the best antimycobacterial activity against Mtb; 3-(benzylamino)pyrazine - 2, 5 - dicarbonitrile (62) inhibited all of the tested strains and had the broadest activity spectrum; 3-(4-amino benzyl amino)-5-cyanopyrazine – 2 - carboxamide (63) combined good antimycobacterial activity against Mtb with relatively low cytotoxicity (hepato toxicity) [96].

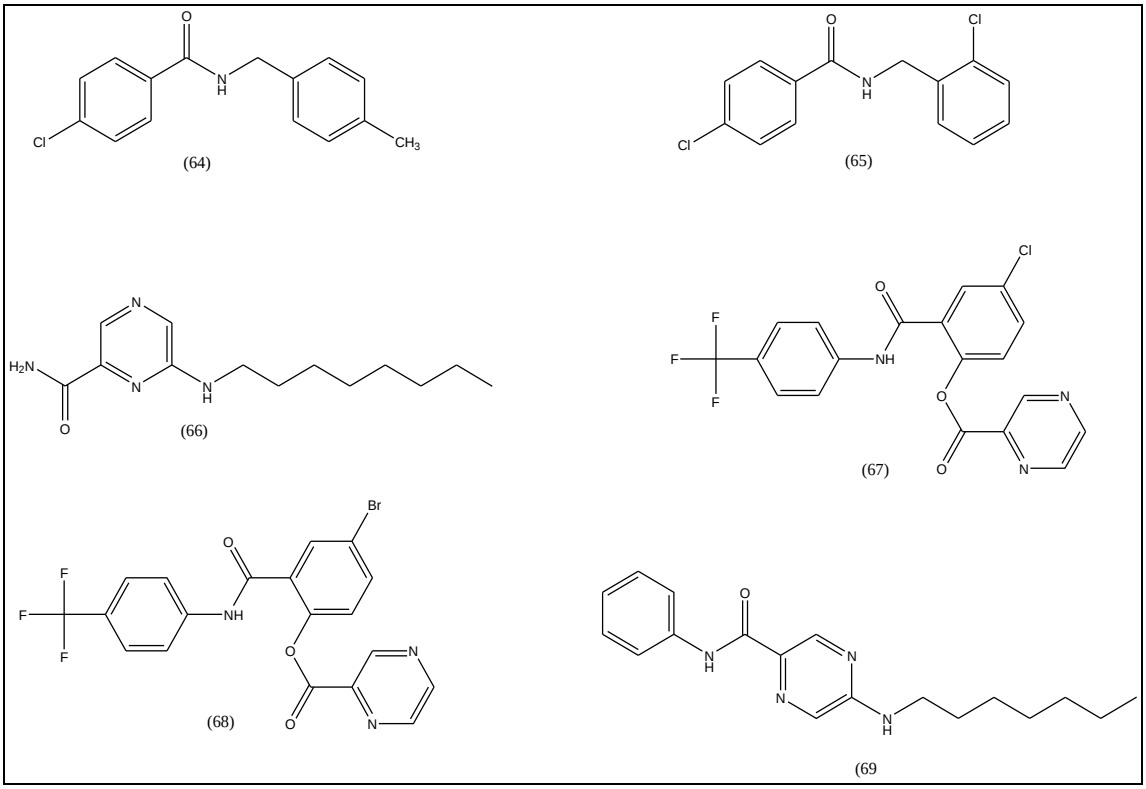


A series of binuclear pyrazinamide analogues containing the –CONH–CH2– bridge, namely on N-benzyl-5-chloropyrazine-2-carboxamides with various substituents on the phenyl ring was designed, synthesized and evaluated for activity against mycobacterial strains (Mtb H37Rv, *Mycobacterium kansasii* and two strains of *Mycobacterium avium*). The Compounds 5-chloro-N-(4-methylbenzyl) pyrazine-2-carboxamide (64) (MIC = 3.13 µg/mL) and 5-chloro-N-(2-chloro benzyl) pyrazine-2-carboxamide (65) (MIC = 6.25 µg/mL) were active against *M. kansasii* [97]. Several pyrazinamide derivatives with alkylamino substitution were designed, synthesized and evaluated for activity against selected mycobacterial, bacterial and fungal strains. 6-Octylamino-pyrazine-2-carboxamide (66) showed the highest activity against Mtb H37Rv (MIC = 1.56 µg/mL), broadest spectrum of activity as well as highest selectivity index (SI) for Mtb H37Rv (SI = 25.8) within all compounds [98].

Mutual prodrugs of both antimycobacterial active salicylanilides and pyrazinoic acid were synthesized and evaluated for *in vitro* antimycobacterial activity, mycobacterial isocitrate lyase inhibition and cytotoxicity. The compound 4-chloro-2-{[4-(trifluoromethyl) phenyl] carbamoyl} phenyl pyrazine-2-carboxylate (67) (MICs 6.025 µmol/l) was found to be the most active compound and 4-bromo-2-{[4-(trifluoromethyl) phenyl] carbamoyl} phenyl pyrazine-2-carboxylate (68) showed the most convenient toxicity profile [99].

A series of 5-alkylamino-N-phenylpyrazine-2-carboxamides derivatives was synthesized and evaluated for antimycobacterial activity and found to possess similar or increased activity against Mtb H37Rv compared to parent 5-chloro-N-phenylpyrazine-2-carboxamide. Importantly, the substitution led to significant decrease of *in vitro* cytotoxicity in HepG2 cell line.

5-Heptylamino-N-phenylpyrazine-2-carboxamide (69) exerted better activity than standard drug pyrazinamide (MIC = 2.5) with significant decrease of *in vitro* cytotoxicity in HepG2 cell line [100].



CONCLUSION: In spite of some notable progress in TB drug discovery, the emergence of all forms of drug-resistant TB as well as the convergence of the TB and HIV epidemics makes the invention of new molecular scaffold a priority. New drugs in novel combinations require more efficient evaluation for safety, efficacy and shortening treatment duration. New biomarkers are needed to enhance the effectiveness of Phase II and III trials using adaptive designs. Coordination and cooperation among drug developers, national governments, research funders and policy makers is needed for improved TB treatment plan. One of the possible strategies to overcome drug resistance in an economic and simple manner would involve re-engineering and repositioning of some old drugs to obtain derivatives that can work on resistant TB bacilli. In present study we attempted to collect and compile various such derivatives of first-line drugs (isoniazid and pyrazinamide) along with their reported biological activities.

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CONFLICT OF INTEREST: The authors report no conflict of interest.

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