Review Article

Development of structurally diverse antitubercular molecules with pyridazine ring

Abstract

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

Key words:
Antitubercular drugs, mycobacterium, pharmacological activities, pyridazinone

Introduction

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

Pyridazines are diazines containing two nitrogen atoms at adjacent position, in place of two carbon atoms in the benzene ring, in their cyclic structures. Pyridazine and its derivatives are noteworthy for their physiological and biological importance.[6-8] Recently, there have been a subject of intensive research owing to their wide spectrum of pharmacological activities. Differently substituted pyridazines have been found to have potential antibacterial, antifungal, antiviral activities including anti-HIV activities, anticancer, analgesic, anti-inflammatory, anticonvulsant, cardio tonic activity, anti-ulcer, antihypertensive, and anti-asthmatic activities, etc. In view of above facts, there is an ongoing research on pyridazine compounds, particularly in relation to microbial infections.[9-11]

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Tuberculosis an Overview

TB is a chronic infectious disease caused by *mycobacterium* species of the "TB complex", including primarily *M. tuberculosis*, that divides every 16-20 h, an extremely slow rate compared with other bacteria, which usually divide in less than an hour, but *M. bovis*, *M. africanum*, *M. canetti*, and *M. microti* can also cause TB, but these species do not usually infect healthy adults. TB is an air-borne communicable disease caused by transmission of aerosolized droplets of *M. tuberculosis*. The primary source of infection is viable *tubercular bacilli*, expelled in the environment by a patient with active TB.[12] *Mycobacterium* grows slowly under aerobic conditions and is distinguished by acid-fast staining. They are Gram positive, non-motile, rod-shaped, obligate aerobic bacteria that belong to the order actinomycetales, family *Mycobacteriaceae*. Several species, including *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. canetti, M. kansasii*, *M. avium,* and *M. leprae* are intracellular pathogens of higher vertebrates. On the other hand although *M. microti* is not usually pathogenic, it is possible that the prevalence of *M. microti* infections has been underestimated. Other known pathogenic mycobacteria includes *M. leprae*, *M. avium*, and *M. kansasii*. The last two are part of the non-tuberculous *mycobacterium* group. Non-tuberculous *mycobacteria* cause neither TB nor leprosy, but they do cause pulmonary diseases resembling TB.[13-15] TB requires much longer periods of treatment to entirely eliminate mycobacteria from the body. Resistance of *M. tuberculosis* strains to anti-TB agents is an increasing problem worldwide. However, potent new anti-TB drugs with new mechanism of action have not been developed in the last four decades. TB is considered to be the most important chronic communicable disease and about 32% of the world's population is currently infected with TB. The emergence of acquired immunodeficiency syndrome (AIDS), decline of socio-economic standards, and a reduced emphasis on TB control programs contribute to the resurgence of disease. Now, research effort towards the development of novel anti-TB agents is in the direction of discovering new classes of compounds which are structurally different from known anti-TB drugs.[16]

TB is one of the oldest and most pervasive, respiratory transmitted or contagious disease infecting one-third of the world's population, killing 2 to 3 million people each year. According World Health Organization (WHO) report, TB has spread to every corner of the globe. The increase in TB incidence during recent years is largely due to the prevalence of TB in synergy with human immunodeficiency virus (HIV/AIDS) epidemic, which augments the risk of developing the disease 100-fold where 31% of new TB cases were attributable to HIV co-infection and emergence of MDR-TB and extensively drug resistance (XDR-TB) strains. The treatment of MDR-TB and XDR-TB has become a major concern worldwide. However, the total number of new TB cases is still rising slowly. The occurrence of this disease is linked to dense population, poor nutrition, and poor sanitation. Direct observed treatment, short-course (DOTS) strategy, constitutes the cornerstone of the current protocol for control of TB. Despite the success of DOTS strategy, the emergence of MDR-TB strains, recurrently isolated from patient's sputum, darken the future.[17] In addition to this, the increase in *M. tuberculosis* strains resistant to front line anti-TB drugs such as rifampin and INH has further complicated the problem, which clearly indicates the need for more effective drugs for the efficient management of TB. As per WHO reports, approximately 90% of the patients having both TB and HIV died within a few months after clinical symptoms. Therefore, WHO warned the world for "even greater TB-HIV crisis" and called for wide availability of free anti-TB drugs to those living with HIV. As per WHO, HIV is spreading rapidly in India with the largest number of TB cases in the world.[16-18]

Chemotherapy of TB

First line anti-tubercular agents

Chemotherapy of TB mainly depends on first-line anti-TB drugs, which include streptomycin, isoniazid, rifampicin, ethambutol, and pyrazinamide, as they are more effective and less toxic when compared with second-line anti-TB drugs.

Second line anti-TB drugs

There are six classes of second line anti-TB drugs for the treatment of TB.[19] A drug may be classified as a second-line because of one of two possible reasons: It may be less effective than the first-line drugs or it may have toxic side-effects. These comprise different classes, namely, aminoglycosides (amikacin, kanamycin), polypeptides (capreomycin, viomycin), fluoroquinolones (ciprofloxacin, moxifloxacin, etc.), thioamides (ethionamides, prothioamide), cycloserine, and *p*-aminosalicylic acid.[16]

Toxic effects of current therapy

The currently available first line anti-TB drugs are showing serious side effects like severe damage to the eighth cranial nerve, inducing irreversible impairment of auditory function, hypersensitivity reactions (streptomycin), hepatotoxicity which may lead to drug-associated hepatitis (isoniazid, pyrazinamide, and rifampicin (rifampicin, rifabutin, rifapentine)), and thrombocytopenic purpura (rifampicin).[3,20] Second line anti-TB drugs are more toxic than first-line drugs, amikacin and kanamycin causes kidney damage as well as hearing loss, viomycin and capreomycin causes nephrotoxicity and eighth cranial nerve toxicity. Fluoroquinolones are increasingly contra-indicated in patients due to growing prevalence of antibiotic resistance. Ethionamide and prothionamide (analogs of isoniazid) cause git disorders (anorexia, salivation, nausea, abdominal pain, and diarrhea), diverse mental disturbances (depression, anxiety psychosis, dizziness, drowsiness, and headache), and hypersensitivity. Cycloserine causes mainly centre nervous system manifestations such as headache, irritability, depression, and convulsions. *p*-Amino salicyclic acid causes gastrointestinal tract problems including anorexia, nausea,

epigastric pain, abdominal distress, diarrhea, peptic ulcers, and hypersensitivity reactions.[16,17]

Drug-resistant TB

Drug resistant *M. tuberculosis* is an important obstacle for the treatment and control of TB. This resistance has usually been attributed to the unusual multi-layer cell envelope and active multi-drug efflux pumps. Recent investigations about mechanisms that neutralize the toxicity of antibiotics in the cytoplasm have revealed other systems that function in synergy with the permeability barrier and efflux systems to provide natural resistance. Drugs inhibiting these intrinsic systems would enable many antibiotics, which are already available but have not been used for TB, to gain new activities against *M. tuberculosis*.[16-18,21]

Multidrug-resistant TB

Multi-drugs resistance (MDR) TB refers to simultaneous resistance to at least two or more of the five first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin). MDR arises from sharing of genes between different species or genera, generally mediated by small pieces of extra-chromosomal deoxyribonucleic acid (DNA) known as transposons or plasmids. Treatment for multidrug-resistant TB is long-lasting, less effective, costly, and poorly tolerated.[16-18,21]

Extensively drug resistant TB

XDR TB by definition is resistance to at least isoniazid and rifampicin in addition to any quinolone and at least one injectable second-line agent (capreomycin, amikacin, kanamycin). The principles of treatment for MDR-TB and XDR-TB are the same. The main difference is that XDR-TB is associated with a much higher mortality rate than MDR-TB, because of reduced number of effective treatment options. Hence there is an urgent need for novel drugs that are active against *M. tuberculosis* to shorten the duration of TB therapy.[16-18,21]

Available molecular targets

The anti-TB drugs are known to target the biosynthetic pathways that involve the production of macromolecules like proteins, nucleic acids, or cell-wall components. In selecting targets for anti-TB agents, it is valuable to avoid targets that are close to the counterparts in mammalian cells. The new targets should be specific to *mycobacterium* to limit the resistance factors from other bacteria. New drugs must act on a target essential for bacterial survival and active against *mycobacterium* both inside and outside the patient cells during infection. The serious efforts of researchers are to develop anti-TB agents based on inhibition of protein synthesis. Many of the inhibitors of protein synthesis like tetracycline, chloramphenicol, and macrolides do not show activity against *M. tuberculosis*, this showed that the ribosome may not be an efficient target for novel anti-TB drugs. Aminoglycoside and streptomycin which are being used for treatment of TB disrupt bacterial protein synthesis. However, mutation altering the 16s ribosomal sub-unit in RNA, results in drug resistance to *M. tuberculosis*.[16-19,21]

A detailed study of enzymes involved in tetrahydrofolate biosynthesis may lead to a design of new and effective anti-TB drugs. The anti-TB drug *p*-amino salicylic acid act on the tetrahydrofolate pathway as well as salicylate-dependent biosynthesis of mycobactins, required for iron transport. Sulphonamides inhibit biosynthesis of tetrahydrofolic acid and block the production of purine and pyrimidine bases of nucleic acid in microbes. A type II topoisomerase, DNA gyrase, involved in ATP-dependent negative supercoiling of double-stranded DNA, ATP-independent relaxation of negatively supercoiled DNA is a potential target for development of potent anti-TB drugs. Recently, gyr A and gyr B have been cloned from *M. tuberculosis* and *M. smegmatis*. Any drug acting against gyr B would be specific to Mycobacteria. Inhibition of its activity prevents supercoiling, as subsequent process such as replication and transcription are topologically dependent on DNA. Nucleotide biosynthesis has been reported to be a good target particularly for TB in HIV cases. In this regard, thymidine monophosphate kinase (dTMKase) has been suggested as target to develop new anti-TB agents for the treatment of MDR-TB and TB in HIV-infected patients. This enzyme is an essential enzyme of nucleotide metabolism that catalyzes the reversible phosphorylation of thymidine monophosphate (dTMP) to thymidine diphosphate (dTDP). This has led to the design of more potent nucleoside analogs to develop new anti-TB agents.[20-28] Based on recent advances in ultra structure and biochemistry, the three basic structural components of the *M. tuberculosis* cell, the cell wall, the plasma membrane, and the capsule have been identified as the important target to develop new anti-TB drugs. The two-layered cell wall in *mycobacterium* is very complex and poorly permeable. The peptidoglycan, the arabinogalactan (AG), and the mycolic acids are the main structural components of the *M. tuberculosis* cell wall. Beyond the membrane peptidoglycan (PG) layer is covalently linked to AG, which in turn, is attached to large mycolic acids with their long meromycolate and short α-chains. These three constitute the cell wall core, the mycolyl arabinogalactan–peptidoglycan (mAGP) complex. Moreover, D-amino acids are important constituents of the mycobacterial cell wall. A cytoplasmic enzyme D-alanine racemase is required in the initial step of peptidoglycan biosynthesis to convert natural L- to D-alanine and has been identified as a novel target for anti-TB drug development. The ability of *M. tuberculosis* has been attributed to its robust cell wall that comprises complex glycolipids including mAGP and lipoarabinomannan (LAM). LAM facilitates the entry of bacterium into macrophages, prevents macrophage activation, and protects *M. tuberculosis* from damage by superoxide and hydroxyl radicals. Many other extractable lipids including glycolipids (glycopeptididolipids (GPL);

lipo-oligosachharide (LOS)), phenolic glycolipids (PGL), and other classes of free lipids (sulpholipids (SL); phthiocerol dimycocerosate (PDM)) are very important in pathogenesis and survival of *M. tuberculosis* in the host macrophages.[29-34]

Recently discovered antitubercular agents

The unpleasant side effects, relatively long duration of treatment, and non-compliance to treatment regimen are drawbacks of current TB therapy. Such non-adherence with the course of treatment leads to treatment failure and the development of drug resistance. The goal now is to develop anti-TB drugs in a cost-effective manner, which efficaciously treats infectious MDR/XDR-TB strains and latent infections with shortened treatment periods as well as reduced frequency of dosage.[16-18,21]

Antitubercular activity of pyridazines

As series of 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(substituted/nonsubstituted acetophenone) hydrazone derivatives 1a-l were tested for *in vitro* anti-TB activities against *M. tuberculosis* H37Rv [Table 1]. Among the target compounds, 1b and 1f exhibited the best anti-TB activity [Table 1], with a minimum inhibitory concentration (MIC) value of 5 μg/ml.[35]

Two series of pyridazinone derivatives (19-34) were evaluated for anti-TB activities against *M. tuberculosis* H37Rv strain [Table 2]. The compound 2g, 5-(4-hydroxy-3-methoxybenzyl)-3-(4-chloro-phenyl)-1,6-dihydro-6-pyridazinone, emerged as a lead compound with good anti-TB activity [Table 2]. Four more compounds, (2c, 2d, 3c, 3g, 21, 22, 29, and 33) were significant in their anti-TB action.[36]

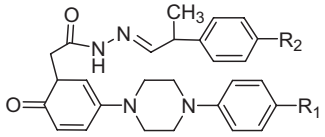
Some 3(2*H*)-pyridazinone and 1(2*H*)-phthalazinone derivatives (4a-e, 5a-e and 6a-e) were evaluated for their anti-TB activity against *M. tuberculosis* H37Rv [Table 3]. The results showed [Table 3] that compound 6e had the highest antimycobacterial activity.[37]

A series of 6-substituted phenyl-2-(3i-substituted phenyl pyridazin-6i-yl)-2,3,4,5-tetrahydropyridazin-3-ones (7a-e, 8a-d, 9a-c, 10 a-c, and 11a-e) were investigated for their *in vitro* anti-TB activities. All the compounds (7a-e, 8a-d, 9a-c, 10 a-c, and 11a-e) were screened against *M. tuberculosis* H37Rv at a concentration of 6.25 μg/ml [Table 4]. The results indicated that the all compounds have mild to potent activities with reference to their appropriate reference standards [Table 4].[38]

A series of 5-(3i-oxo-6i-[substituted aryl]-2',3',4',5'-tetrahydropyridazin-2i-ylmethyl)-2-substituted 1,3,4-oxadiazole (12a-e, 13a-e, and 14a-e) were screened for anti-TB activity at concentration of 6.25 μg/ml. All the synthesized compounds, screened against *M. tuberculosis* H37Rv, were comparable with that of standard drugs [Table 5]. The results indicated that the all compounds had mild to potent anti-TB activities [Table 5].[39]

A series of alkyl 1-heteroaryl-1*H*-1,2,3-triazole-4-carboxylates were tested for their anti-TB activity against *M. tuberculosis* H37Rv. Among all, the best potency was shown by *n*-pentyl 1-(6-phenylpyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (15) with a MIC of 3.13 μg/mL.[40] In search of potential anti-TB agents, pyridazinoindole analogs and screened them for inhibition of the growth of *M. tuberculosis*. The most active compound (16) exhibited a MIC_{50} of 1.42 μg/mL against *M. tuberculosis* H37Rv.[41] 1,2,3,4-tetrahydro-6-substituted-

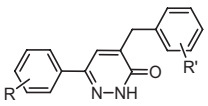
Table 1: Antitubercular activity of 6-substituted-3 (2H)-pyridazinone-2-acetyl-2-(acetophenone) hydrazone derivatives



Compounds 1a-l

Compounds	R_1	R_2	MIC (μg/mL)
1a	H	H	20
1b	H	Br	05
1c	H	Cl	40
1d	H	F	20
1e	F	H	20
1f	F	Br	05
1g	F	Cl	N/A
1h	F	F	N/A
1i	Cl	H	N/A
1j	Cl	Br	40
1k	Cl	Cl	40
1l	Cl	F	N/A
Isoniazid	–	–	0.2
Ethambutol	–	–	01

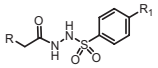
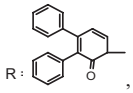
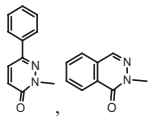
Table 2: Antitubercular activity of 5-(substituted benzyl)-3-aryl-1,6-dihydro-6-pyridazinones



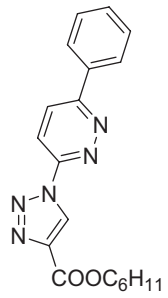
Compounds (2a-h) and (3a-h)

Structure	Compounds	R	R'	MIC (μg/mL)
	2a	4-Cl	H	50
	2b	4-Cl	4-Cl	50
	2c	4-Cl	4-NO_2	25
	2d	4-Cl	4-OH	25
	2e	4-Cl	4-CH_3	100
	2f	4-Cl	4-OCH_3	50
	2g	4-Cl	4-OH, 4-OCH_3	12.5
	2h	4-Cl	4-F	50
	3a	4-CH_3	H	50
	3b	4-CH_3	4-Cl	50
	3c	4-CH_3	4-NO_2	25
	3d	4-CH_3	4-OH	50
	3e	4-CH_3	4-CH_3	50
	3f	4-CH_3	4-OCH_3	50
	3g	4-CH_3	4-OH, 4-OCH_3	25
	3h	4-CH_3	4-F	50
Reference drug	Streptomycin	–	–	10

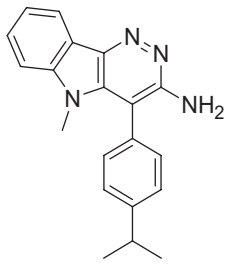
Table 3: Antitubercular activity of benzenesulfonohydrazide bearing 3 (2*H*)-pyridazinone or 1 (2*H*)- phthalazinone rings

Structure	Compounds	R1	Concentration (μg/mL)	Resistance %
	4a	H	20	52.70
	4b	CH_3	20	62.83
	4c	Cl	20	47.29
	4d	OCH_3	20	82.43
Componds 4a-e, 5a-e and 6a-e	4e	$NHCOCH_3$	20	92.56
	5a	H	20	60.81
	5b	CH_3	20	97.97
	5c	Cl	20	72.29
	5d	OCH_3	20	64.84
	5e	$NHCOCH_3$	20	81.08
	6a	H	20	74.32
	6b	CH_3	20	75.67
	6c	Cl	20	47.97
	6d	OCH_3	20	74.32
	6e	$NHCOCH_3$	20	43.24
Reference drugs	Isiniazid	–	0.2	–
	Isiniazid	–	1.0	–
	Rifampicin	–	1.0	–

2,5,7-trimethyl-6H-pyrrolo [3,4-d] pyridazin-1,4-ones displayed moderate activity against *M. tuberculosis*. On the basis of these findings, we will synthesize new pyridazine derivatives to investigate their anti-TB activities.



15



16

In vitro anti-TB activities of 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(substituted/non-substituted acetophenone) hydrazone derivatives 1a-l, compound 1b and 1f exhibited the best activity, with a MIC value of 5 μg/ml.[35] Compounds 1a, 1d, and 1e showed MIC value of 20 μg/ml and Compounds 1g, 1h, 1i, and 1l did not show any MIC Value. In series (2a-h and 3a-h), compound 2g, 5-(4-hydroxy-3-methoxybenzyl)-3-(4-chloro-phenyl)-

Table 4: Antitubercular activity of 6-substituted phenyl-2-(3′-substituted phenyl pyridazin-6′-yl)-tetrahydropyridazin-3-ones

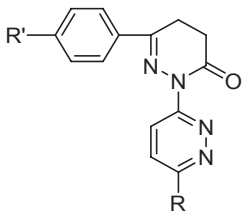
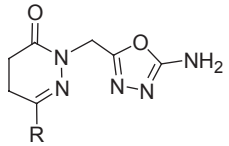
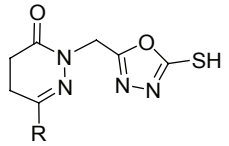
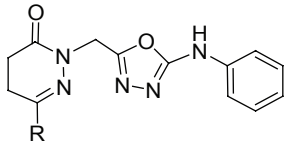
Structure	Compounds	R	R′	Concentration (μg/mL)	Inhibition %
	7a	C_6H_5	H	6.25	48
	7b	C_6H_5	3,5-$(CH_3)_2$	6.25	89
	7c	C_6H_5	4-Cl	6.25	60
	7d	C_6H_5	4-Br	6.25	62
	7e	C_6H_5	C_6H_5	6.25	51
	8a	4-CH_3-C_6H_5	H	6.25	70
	8b	4-CH_3-C_6H_5	3,5-$(CH_3)_2$	6.25	92
	8c	4-CH_3-C_6H_5	C_6H_5	6.25	62
	8d	4-CH_3-C_6H_5	4-Br	6.25	64
Conpounds 7a-e, 8a-d, 9a-c, 10a-c and 11a-e	9a	3,5-$(CH_3)_2$-C_6H_5	H	6.25	89
	9b	3,5-$(CH_3)_2$-C_6H_5	4-Cl	6.25	95
	9c	3,5-$(CH_3)_2$-C_6H_5	C_6H_5	6.25	72
	10a	$C_{11}H_9O$	H	6.25	47
	10b	$C_{11}H_9O$	3,5-$(CH_3)_2$	6.25	54
	10c	$C_{11}H_9O$	4-Cl	6.25	32
	11a	$(C_6H_5)_2$	H	6.25	38
	11b	$(C6H_5)_2$	p-CH_3	6.25	41
	11c	$(C_6H_5)_2$	C_6H_5O	6.25	34
	11d	$(C_6H_5)_2$	C_6H_5	6.25	39
	11e	$(C_6H_5)_2$	4-Cl	6.25	40
Reference drugs	Rifampicin	–	–	0.25	98
	Isoniazid	–	–	0.031	95
	Tobramycin	–	–	10.0	99
	Clarithromycin	–	–	26.0	99
	Ethionamide	–	–	1.17	99
	PAS	–	–	2.31	99
	Ethambutol	–	–	1.17	99
	Gentamycin	–	–	6.0	99
	Doxycyclin	–	–	12.0	99

Table 5: Antitubercular activity of 1,3,4-oxadiazole bearing 3 (2H)-pyridazinone derivatives

Structure	Compounds	R	Concentration (μg/mL)	Inhibition %
	12a	C_6H_5	6.25	86
	12b	3,4-(CH_3)-C_6H_3-	6.25	52
	12c	4-CH_3-C_6H_4-	6.25	56
	12d	4-C_6H_5O-C_6H_4-	6.25	48
	12e	4-Cl-C_6H_4-	6.25	84
Compounds 12a-e	13a	C_6H_5	6.25	88
	13b	3,4-(CH_3)-C_6H_3-	6.25	48
	13c	4-CH_3-C_6H_4-	6.25	51
	13d	4-C_6H_5O-C_6H_4-	6.25	45
	13e	4-Cl-C_6H_4-	6.25	87
	14a	C_6H_5	6.25	91
Compounds 13a-e	14b	3,4-(CH_3)-C_6H_3-	6.25	52
	14c	4-CH_3-C_6H_4-	6.25	55
	14d	4-C_6H_5O-C_6H_4-	6.25	49
	14e	4-Cl-C_6H_4-	6.25	89
	Rifampicin	–	0.25	98
	Isoniazid	–	0.031	95
Compounds 14a-e	Tobramycin	–	10.0	99
Rereference drugs	Clarithromycin	–	26.0	99
	Ethionamide	–	1.17	99
	PAS	–	2.31	99
	Ethambutol	–	1.17	99
	Gentamycin	–	6.0	99
	Doxycyclin	–	12.0	99

1,6-dihydro-6-pyridazinone showed the highest anti-TB activity. Compounds 2c, 2d, 3c, and 3g showed significant activity. Compounds 2e showed maximum MIC value of 12.5 μg/ml and compound 2e showed lowest MIC value 100 μg/ml. Compounds 2c and 2d showed MIC value of 25 μg/mL and compounds 3c and 3g showed MIC value of 25 μg/mL.[36] Some pyridazinone or phthalazinone compounds (4a-e, 5a-e, and 6a-e) were active against *M. tuberculosis* H37Rv. Compounds 4e and 5b showed 92.56% and 97.97% resistance, respectively. Compound 4c, 6c, and 6e showed 47.29%, 47.97%, and 43.24% resistance, respectively, at a concentration of 20 μg/mL.[37] In a series of 6-substituted phenyl-2-(3'-substituted phenyl pyridazin-6'-yl)-2,3,4,5-tetrahydropyridazin-3-ones (7a-e, 8a-d, 9a-c, 10 a-c and 11a-e)[38] and a series of 5-{3'-oxo-6'-(substituted aryl)-2',3',4',5'-tetrahydropyridazin-2'-ylmethyl}-2-substituted 1,3,4-oxadiazole (12a-e, 13a-e and 14a-e)[39], the results indicated that the compounds (7a-e, 8a-d, 9a-c, 10 a-c, and 11a-e) have mild to potent activities. Compounds 7b, 8b, 9a, and 9b showed good percentage inhibition 89, 92, 89, and 95, respectively, against TB at 6.25 μg/mL concentration. Compounds 10c, 11a, 11c, 11d, and 11e showed weak percentage inhibition 32, 38, 34, 39, and 40, respectively, against TB at 6.25 μg/mL concentration. Compounds 12e, 13a, 13e, 14a, and 14e showed good percentage inhibition 84, 88, 87, 91, and 89, respectively, against TB at 6.25 μg/mL concentration. Compounds 12d, 13b, 13d, and 14d showed weak percentage inhibition 48, 48, 45, and 49, respectively, against TB at 6.25 μg/mL concentrations. All compounds (7a-e, 8a-d, 9a-c, 10a-c, and 11a-e) showed the percentage inhibition ranging from 32 to 95% and compounds 12a-e, 13a-e, and 14a-e showed percentage inhibition ranging from 48 to 91% against *M. tuberculosis* H37 Rv comparable with those of standard rifampicin and isoniazid. The results indicated that the pyridazine with chloro group and dimethyl group showed comparable activity with the reference drugs. Compound 15 and 16 showed MIC value of 3.13 μg/mL[40] and MIC_{50} value of 1.42 μg/mL against *M. tuberculosis* H37Rv respectively.[41]

Discussion

Development of new anti-TB drugs is the need of the hour to control TB. In the last 40 years, no new anti-TB drug has been brought into the market. However, in recent years there is an enhanced activity in the research and development of new anti-TB drugs. Presently, some compounds are in clinical development, whereas others are being investigated preclinically in an attempt to explore new anti-TB molecules. This review provides an overview of the pyridazines against *M. tuberculosis*. In view of the persistent drug-resistant TB problem of currently used anti-TB agents, it is important that new anti-TB molecules or drugs should address different targets, as those of currently used drugs including the shortening of TB therapy. The unique structure of the mycobacterial cell wall makes it a useful target for drug

development, and studies can be directed to specific sites like cell wall biosynthetic pathways.[40-46] Although one possible long-term solution to the problem is a better vaccine, in the short term, the major reliance will be on chemotherapy requiring the development of novel, effective, and non-toxic anti-TB agents. The identification of novel target sites will also be needed to circumvent the problems associated with the increasing occurrence of MDR-TB and XDR-TB strains.[13,47-50] One of these attractive targets for the rational design of new anti-TB agents are the mycolic acids, the major components of the cell wall of *M. tuberculosis*.

Conclusion

The difficulty in managing TB includes the prolonged duration of the treatment, the emergence of drug resistance, and co-infection with HIV/AIDS. TB control program requires new drugs that act on novel drug targets to help in combating resistant forms of *M. tuberculosis* and reduce the treatment duration. Despite the availability of the various chemotherapeutic agents, TB remains a leading killer worldwide. This is mainly due to the lack of new drugs, particularly, for effective treatment against MDR-TB, XDR-TB, and patients co-infected with HIV/AIDS. Therefore, there is an urgent need for the development of new and effective anti-TB drugs particularly against resistant strains with lesser side-effects.[13,48,49] More importantly, newly developed drugs are required to reduce the duration of treatment. The newer anti-TB compounds need to be developed by understanding the molecular mechanisms of drug action and drug resistance. Focusing on the existing anti-TB targets for drug development may be of limited value because chances of resistance by mutation in the protein target may render the drugs ineffective. Precisely, because of this observed drug resistance by the bacterium, it is necessary to develop new drugs that inhibit novel targets and are structurally and functionally different from those currently known.[50-52] Medicinal chemists will be interested to work on pyridazine molecules due to their wide range of biological activities particularly against microbes. In view of above facts, there is an ongoing research on pyridazine derivatives, particularly against *mycobacterium*. Different new pyridazines will be synthesized in the future for development of new anti-TB molecules.

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