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An Insight Into Antitubercular Activity Associated With 1,3,4-Thiadiazoles

Archana Gautam*, Monika Tyagi

**Department of Chemistry, S.G.T.B. Khalsa College, University of Delhi, Delhi 110007, India.*
Department of Chemistry, Monad University, Hapur, UP., India.
E-mail address: gautamarchana98@gmail.com (A. Gautam), mnk02tyg@yahoo.co.in (M. Tyagi)
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Abstract: WHO has declared Tuberculosis (TB) as a "global public health emergency" and the world's most deadly epidemics. Despite of the advancements in medication, tuberculosis remain a major public health issue with a leading cause of death by bacterial infection worldwide, as more and more bacteria become resistant to antibiotics used in the therapy. Consequently the exploration for new promising drugs to fight against drug resistance and to control the disease is a prime concern of scientists. In an effort to discover new and effective chemotherapeutic agent for the treatment of TB, the anti mycobacterial activities of **1,3,4-thiadiazole and its derivatives** have been reported. Thiadiazoles belong to the class of nitrogen–sulfur heterocycles with considerable applications in pharmaceutical chemistry. Thiadiazoles and its analogs are found to be well known antimicrobial agents due to the presence of toxophoric moiety, which exhibits a broad spectrum of biological activities.

Keywords: 1,3,4-thiadiazole, antitubercular activity, mycobacterium, minimum inhibitory concentration, MDR-TB.

Introduction

Nitrogen containing heterocyclic compounds have drawn huge attention in the field of research because of their wide range of applications and functionality as biologically active compounds. They act as antimicrobial, antifungal, antiviral, antiinflammatory, analgesic, antiepileptic, antihypertensive, antimalarial, antioxidants, antihistaminic, antianxiety, antidepressant and antitubercular agents **[1-3].** Tuberculosis is one of the major global health threat worldwide. According to Global Tuberculosis Report from WHO, 10 million new TB cases and 1.5 million deaths were estimated in 2018 **[4].** Most significantly, one third of the world's population is infected with latent infection, out of which 5-10% can develop active TB in their life **[5].** Tuberculosis, also termed as 'white plaque'**[6].** It is an infectious wave caused by

miscellaneous species of mycobacteria, jointly termed the *tubercle bacilli* **[7],** including *Mycobacterium tuberculosis, M. bovis, M. africanum*, *M. caprae, M. microti, M. pinnipedii* and *M. canettii* **[8]**. It typically attacks on the lungs (known as pulmonary tuberculosis) but can also carry out to other organs (known as extra-pulmonary tuberculosis). WHO has approved a contemporary program [DOTS] for the treatment of TB which is a combination of isoniazide, rifampicin, ethambutol, and pyrazinamide for 6 months. Miserably, first line treatment can fail due to poor obedience leading to the emergence of multidrug resistance [MDR]**.** Also, the complex structural characteristics of the mycobacterial cell wall, the long treatment duration, multi-resistance and extensive drug resistance developed by the pathogen cause the recurrence of the infection. As a result, the treatment of the disease becomes difficult. In addition, the occurrence of TB in synergy with AIDS boost up the possibility of infection many times **[9].** That is why the successive death rate shoot up by 12% in the past two decades **[10].** Consequently, there is need to find out new anti-TB drugs with better activity and shorter duration therapy to control this alarming disease. Azole derivatives have shown interesting anti-TB and antimicrobial activity, inhibiting the growth of bacteria by blocking lipid biosynthesis. Thiadiazoles belong to the class of nitrogen–sulfur heterocycles with extensive applications as biologically active molecules and useful intermediates in medicinal chemistry. Thiadiazole exist in four different isomeric forms namely 1,2,3-thiadizole; 1,2,4-thiadizole; 1,2,5-thiadizole and 1,34-thiadizole **(Fig. 1).** Among the different isomers of thiadiazole, 1,3,4-thiadiazole derivatives are extensively studied due to broad spectrum pharmacological activities. In this article we are focusing on the progress made in the development of novel type of compounds based on 1,3,4-thiadiazole as recently evolved effective anti-tubercular agents. 1,3,4-thiadiazole moiety is one of the most significant five membered heterocycles with unique place in the field of medicinal chemistry **[11]** and its various derivatives having wide range of properties **[12, 13].**

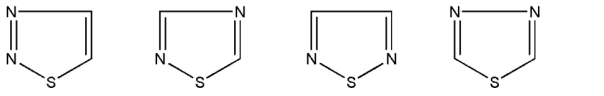
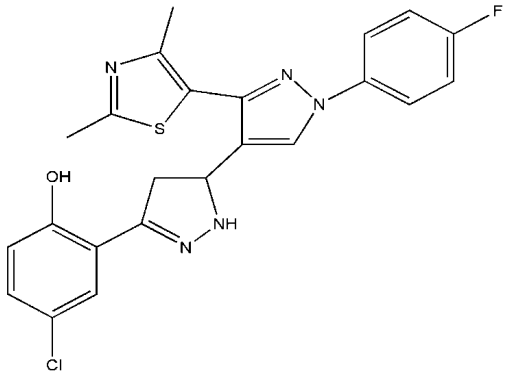


Fig. 1: Isomers of thiadizole ring

Antitubercular activity associated with 1,3,4-thiadiazole and its derivatives

Kerru N. et. al.,**[14]** have reported the recent advances in novel nitrogen-containing heterocycles and their distinct biological activities. The studies are focused on the use of nitrogen-based moieties in drug design and development of different competents against various diseases. Further, it is highlighted on the recent progress of different N-containing heterocyclic structures (four, five and six-membered rings) due to their potential medicinal importance. Pyrazole-linked thiazole hybrid, substituted with a meta-chloro group on the phenyl ring is found to exhibit the most significant M. tubercular activity with MIC values of 1.16 µM against D-MTB and 0.72 µM against D-BCG **(Fig. 2).**



MIC : 0.72 µM against D-BCG

Fig. 2: The antitubercular activity of the most active thiazole-pyrazole hybrid

Aziz H.A. et. al.,**[15]** have synthesized new nitric oxide (NO) donating fluoroquinolones/ nitrate ester hybrids and characterized them by various spectroscopic and analytical tools. Evaluation of antitubercular activity has shown that most of tested compounds exhibit comparable or higher activity than the parent fluoroquinolones. Some compounds are found to possess better activity than ciprofloxacin. From newly synthesized compounds, not a single compound is found to be superior than the parent fluoroquinolones in terms of DNA cleavage stimulation in mycobacteria.

Sych I.V. et. al.,**[16]** have synthesized different products using 2-amino-5-alkyl-1,3,4-thiadiazoles as initial compound **(Fig. 3[a-e])** and screened various derivatives of nitrogen-containing heterocyclic systems 2N (R)-5R1-1,3,4-thiadiazol-2-yl-arylsulfonamides and N-(diethylsulfamoyl)-N-(5-ethyl-1,3,4-thiadiazol-2-yl)benzamides. Further, the acylation of 5-ethylsulfanyl-1,3,4-thiadiazole-2-amine by heteryl-substituted acid chloride is allowed to obtain two cycles of 1,3,4-thiadiazole. From the studies, the compound 4-butoxy-N-{5-[({[5- (ethylsulfanyl)-1,3,4-thiadiazol-2-yl] carbomoyl} methyl) sulfanyl] -1,3,4-thiadiazol-2-yl} benzamide is found to possess high antimicrobial activity.

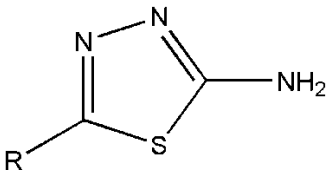


Fig. 3: 2-amino-5-alkyl-1,3,4-thiadiazoles and its derivatives exhibiting antitubercular activity

Compound	R
3(a)	C_3H_7
3(b)	Sec. butyl
3(c)	i- C_3H_7
3(d)	C_2H_5
3(e)	C_2H_5S

Serban G. et. al.,**[17]** have studied 1,3,4-Thiadiazole and some of its derivatives because of their promising antimicrobial activities. Many of the reported derivatives of 2-amino-1,3,4-thiadiazole **(Fig.4)** can be considered as lead compounds for the synthesis of drugs and many of them are confirmed to possess high antimicrobial activity in comparison to standard drugs.

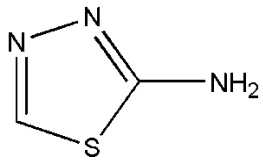


Fig. 4: 2-amino-1,3,4-thiadiazole derivatives exhibiting promising antimicrobial activity

A new *N*-phenyl-*N*′-[4-(5-alkyl/arylamino-1,3,4-thiadiazol-2-yl)phenyl]thiourea, has synthesized and studied by Karakus S. et. al.,**[18] (Fig. 5)** using BACTEC 460 radiometric system (Becton Dickinson, Cockeysville, MD, USA). The *in vitro* activity against *M. tuberculosis* strain H37Rv at 6.25 µg/mL is studied and compared to standard drug, rifampicin. The best inhibitory activity (67%) has shown by the derivative **(5a)** having a cyclohexyl group, while the derivative **(5b)** having a *p*-chlorophenyl group has shown 32% inhibition against *M. tuberculosis*. The other derivatives are found to exhibit low inhibition, 16% for compound **(5c)** and 6% for compound **(5d).**

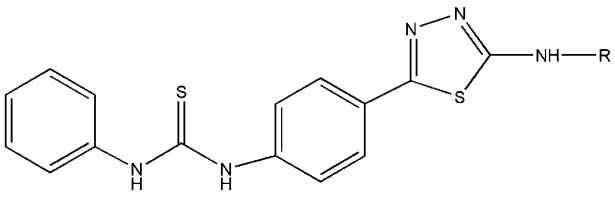


Fig. 5: *N*-phenyl-*N*′-[4-(5-alkyl/arylamino-1,3,4-thiadiazol-2-yl)phenyl]thiourea exhibiting antitubercular activity

Compound	R	Inhib %
5(a)	C_6H_{11}	**67**
5(b)	4-ClC_6H_4	32
5(c)	$CH_2C_6H_5$	16
5(d)	C_2H_5	6

Similarly, 2-amino-5-R-1,3,4-thiadiazole derivatives **(Fig. 6)** have also screened for antitubercular activity. Among the tested compounds, 2-phenylamino-5-(4-fluorophenyl)-1,3,4-thiadiazole **(6e)** has shown the best inhibitory activity (69%), while 2-phenylamino-5-phenyl-1,3,4-thiadiazole **(6a)** has shown 65% inhibitory activity *in vitro* against *M. tuberculosis* H37Rv at a concentration of 6.25 µg/mL. Other derivatives are classified as highly active compounds and can be a good scaffold for further development of new antituberculosis agents.

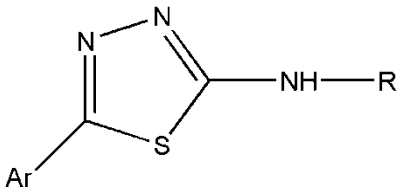
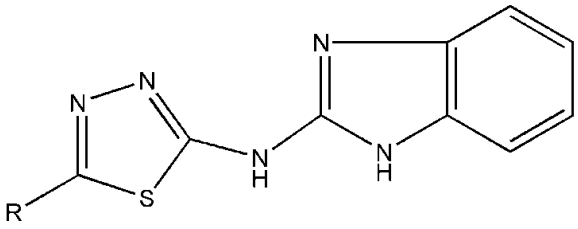


Fig. 6: 2-amino-5-R-1,3,4-thiadiazole derivatives exhibiting promising antitubercular activity

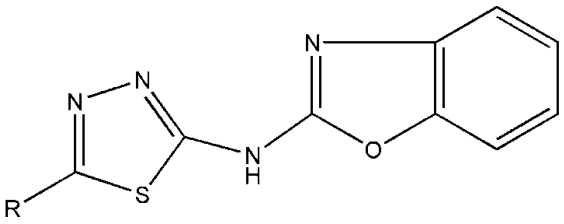
Compound	Ar	R	Inhib %
6(a)	C_6H_5	C_6H_5	65
6(b)	C_6H_5	4-FC_6H_4	50
6(c)	4-ClC_6H_4	C_6H_5	50
6(d)	4-ClC_6H_4	4-FC_6H_4	54
6(e)	4-FC_6H_4	C_6H_5	**69**
6(f)	4-FC_6H_4	4-FC_6H_4	52
6(g)	4-C_5H_4N	4-BrC_6H_4	53
6(h)	4-C_5H_4N	4-FC_6H_4	59

Other hybrids containing the 1,3,4-thiadiazole ring, benzimidazole **(Fig. 7**), benzoxazole **(Fig. 8**), and benzothiazole **(Fig. 9**) have also screened for *in vitro* antitubercular activity against *M. tuberculosis* H37Rv strain using the Microplate Alamar Blue Assay (MABA). The compounds indicating 90% inhibition in preliminary screening have further analysed to determine the MIC. All the compounds are found to exhibit inhibitory activity against *M. tuberculosis* with a rate of inhibition between 53% to 95% at a concentration of 6.25 µg/mL. Among all thiadiazole derivatives, the benzoxazole derivative **(8)** have shown the best inhibitory activity 93% for **8(a)** and 95% for **8(b)**, whereas the benzimidazole derivatives **(7)** have shown the moderate inhibitory activity 77% for **7(a)** and 74% for **7(b) [19].**



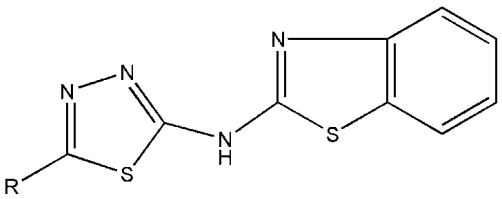
R = Benzyl (a), 3-pyridyl (b)

Fig. 7: benzimidazole derivative of 1,3,4-thiadiazole



R = Benzyl (a), 3-pyridyl (b)

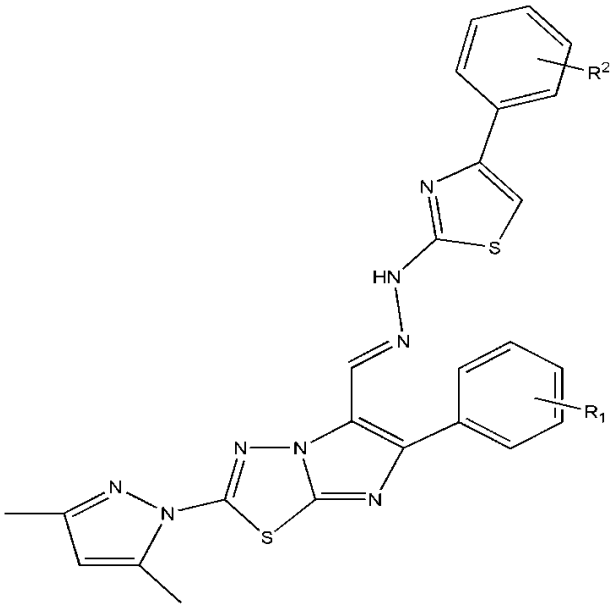
Fig. 8: benzoxazole derivative of 1,3,4-thiadiazole



R = Benzyl (a), 3-pyridyl (b)

Fig. 9: benzothiazol derivative of 1,3,4-thiadiazole

Syed M.A. et al., **[20],** have synthesized and tested imidazo[1,3,4]thiadiazole derivatives **(Fig. 10)** for anti-TB activity. Among all the tested compounds, the compounds with methoxy/ nitro substitution at 4th position of phenyl ring, at 4th position of thiazole ring of the condensed imidazo[1,3,4]-thiadiazoles moiety and also nitro or chloro or methoxy substitution at the 4th position of the phenyl ring and at 6th position of the condensed imidazothiadiazole moiety have shown significant anti-tubercular activity (1.6 to 6.25 mcg/ml) against *Mycobacterium tuberculosis H37Rv* strain and Streptomycin (6.25 mcg/mL), Ciprofloxacin (3.125 mcg/mL) along with pyrazinamide (3.25 mcg/mL) as standard.



R1= P-Cl, P-Br, P-OCH_3, P-NO_2, R2= P-Cl, P-Br, P-CH_3, P-OCH_3, P-NO_2, m-NO_2

Fig. 10 Imidazo-thiadiazole derivatives exhibiting antitubercular activity

In view of search for new promising drugs Salim Meeran I. et al., **[21]** have enlightened on the recent reports of the anti-tubercular potency of Schiff bases of 2--amino-5-aryl-1,3,4-thiadiazole derivatives **[Fig. 11(a-j)]** and their metal complexes. These 2-amino-5-aryl-1,3,4-thiadiazole derivatives have screened for anti mycobacterial activity against *M. tuberculosis.* The compounds **11(c), 11(e), 11(f)** and **11(i)** have responded positively at minimum concentration as compared to other compounds **[22].**

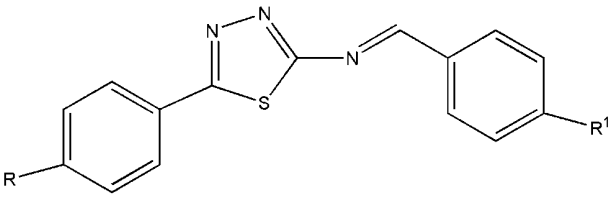
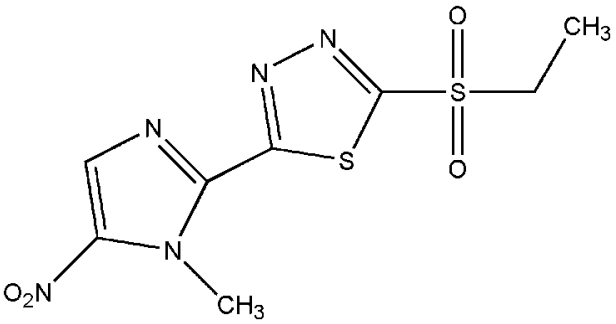


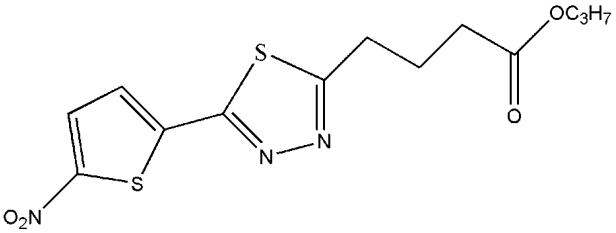
Fig 11: 1,3,4-thiadiazole based Schiff bases exhibiting promising antitubercular activity

Compounds	R	R^1
11(a)	OCH_3	OH
11(b)	OH	OH
11(c)	Cl	OH
11(d)	NO_2	OH
11(e)	$N(CH_3)_2$	OH
11(f)	OCH_3	NO_2
11(g)	OH	NO_2
11(h)	Cl	NO_2
11(i)	NO_2	NO_2
11(j)	$N(CH_3)_2$	NO_2

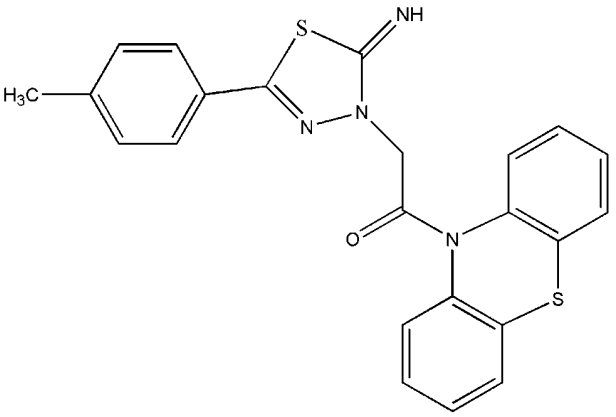
Karakus S. et al., have synthesized 2-(4-aminophenyl)-5-substituted amino-1,3,4-thiadiazoles **[23]** and their coupling products, 2,3,4-pentanetrione-3-[4-(5-alkyl/arylamino-1,3,4-thiadiazole-2-yl)phenyl]hydrazones. The anti tubercular activity of the synthesized compounds has determined *in vitro* using the BACTEC 460 Radiometric System against *Mycobacterium tuberculosis H37Rv* at 6.25 µg/ mL. The anti mycobacterial data of screened compounds have shown that 2-(4-aminophenyl)-5-(4-chlorophenyl)amino-1,3,4-thiadiazole possess highest inhibition. Some representatives of 1,3,4-thiadiazole compounds with promising antituberculosis activity is shown in **Fig. 12**.



MIC : 1.56 µg/mL (lit.7)



MIC : 1.56 µg/mL (lit.8)



MIC : 0.8 µg/mL (lit.9)

Fig. 12 1,3,4-thiadiazole derivatives with promising activity against *Mycobacterium tuberculosis H37Rv.*

Aminabhavi T.M. et al., **[24],** have presented the anti tubercular activity of compounds based on substituted 1,3,4-thiadiazole **due to the presence of toxophoric moiety [25]. The Pyrolyl aryloxy thiadiazole derivatives have reported with promising anti-tubercular activities [25-29].**

Syed M.A. et al.,**[30],** have synthesized 6-(4-substituted aryl)-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)imidazo[2,1-*b*][1,3,4]thiadiazole **(Fig. 13)** and its derivatives to analyse for antitubercular activity against Mycobacterium tuberculosis of H37Rv strain in BACTEC**[31]** medium using a broth micro dilution assay. The compounds have shown promising anti tubercular activity. Streptomycin and pyrazinamide (the MIC 7.5mcg/ml) are used as standard drugs.

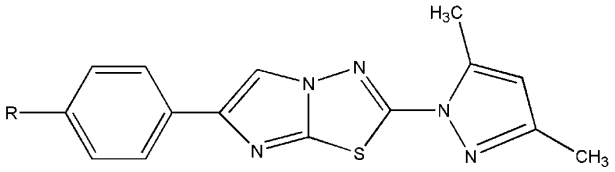


Fig. 13: The 6-(4-substituted aryl)-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)imidazo[2,1-*b*] [1,3,4]thiadiazole and its derivatives exhibiting antitubercular activity

Novli M.N et al., have synthesized a series of imidazo-1, 3, 4-thiadiazole derivatives **(Fig. 14)** and the synthesized compounds have screened *in vitro* for anti tubercular activity against M. tuberculosis H37RV strain by using Alamar Blue susceptibility test. Among the tested compounds, 2-(1-methylimidazol-2-yl)-6-(4-nitrophenyl) imidazo-1, 3, 4-thiadiazole has found to possess the highest inhibitory activity with MIC of 3.14µg/ml as compared to other compound **[32].**

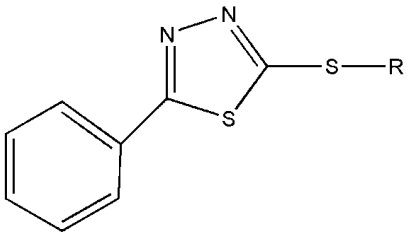


Fig. 14: substituted 1, 3, 4-thiadiazole derivative exhibiting antitubercular activity

Palkar M.B et al., have synthetized and screened a series of 2-substituted-5,6-diaryl substituted imidazo-1, 3, 4-thiadiazoles **(Fig. 15)** for anti

tubercular activity against M. tuberculosis H37RVstrain by Microplate Alamar Blue Assay (MABA) method using Isoniazid as the standard drug**[33].**

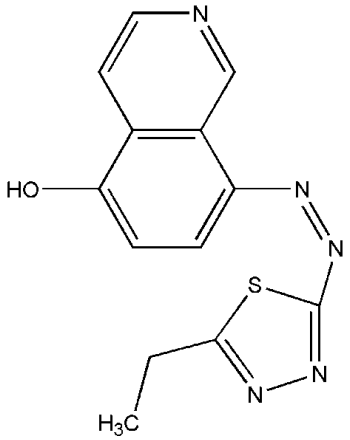


Fig. 15: 2-substituted-5,6-diaryl substituted imidazo-1, 3, 4-thiadiazoles exhibiting antitubercular activity

Shiradhkar M. et al., have synthesized and analysed a series of substituted triazolo-1, 3, 4-thiadiazoles **(Fig. 16)** for anti tubercular activity against M. tuberculosis H37RV. More than 95% inhibition is revealed by compairing the final data of MIC with the standard drug Rifampicin at a concentration of 0.03µg/ml. Nitro phenyl derivatives are found to possess maximum activity against M. tuberculosis among the analysed compounds**[34].**

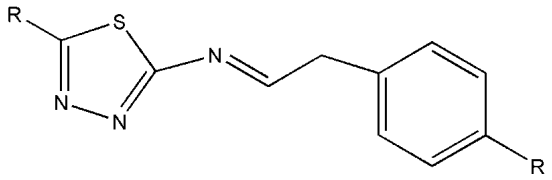
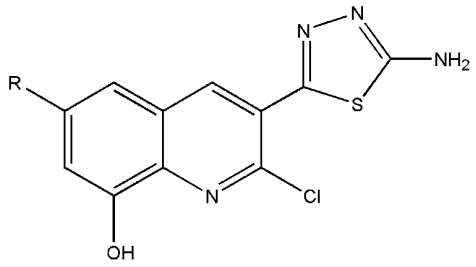


Fig. 16: substituted 1, 3, 4-thiadiazoles exhibiting antitubercular activity

Chitra et al., have synthesized a 3-heteroarylthioquinoline derivatives of 1,3,4-thiadiazole **(Fig. 17)** and screened for anti tubercular activity *in vitro* against H37Rv by agar-dilution method. The anti tubercular activity is found to be considerably affected by various substituent like 2-methyl-1, 3, 4-thiadiazole, benzothiazole and 2-phenyl-2H-tetrazole at the 3-position of quinoline ring. Further, it is supported by the fact that no significant activity is shown by the compounds with no substitution. Compounds 1**7(a)** and **17(b)** with chloro- and bromo-substituted aromatic ring are found to be more active (MIC = 3.2–3.5 µg/ml)**[35].**



R = Cl (a), Br (b)

Fig. 17: 3-heteroarylthioquinoline derivatives of 1,3,4-thiadiazole exhibiting antitubercular activity

Gadad A.K. et al., have synthesized aryl-methylimidazo-1, 3, 4-thiadiazole derivatives **(Fig. 18)** and screened *in vitro* for anti tuberculosis activity against M. tuberculosis against H37RV strain by radiometric BACTEC and broth dilution method. 4-flouro phenyl derivative is found to possess maximum inhibition at a concentration of 6.25µg/ml. All the synthesized compounds are found to be less active as compared to standard drug Isoniazid **[36].**

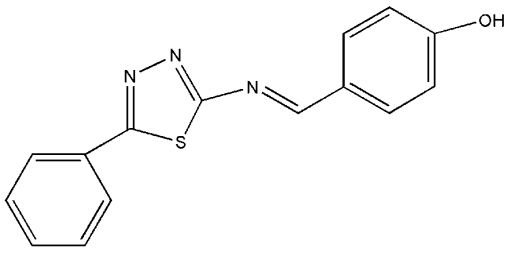


Fig. 18: aryl-methylimidazo-1, 3, 4-thiadiazole derivatives exhibiting antitubercular activity

Conclusion

The nitrogen containing heterocyclic compounds have high degree of structural diversity which is useful to discover new therapeutic agents with wide range of biological applications. A large amount of work has been reported on N-heterocyclic framework in medicinal chemistry. The devastating advantages of nitrogen-containing drugs in the medicinal field is because of their easy preparation, low toxicity, less adverse effects, high bio-availability, lower drug resistance, good bio-compatibility etc., which promotes further research and development in pharmaceutical chemistry. The discovery and development of new antitubercular agents with promising activity against the drug resistant mycobacterial strains has become a need of today. The compounds containing thiadiazole ring shows various biological activities such as antimicrobial, antifungal, antiinflammatory, antianxiety, antidepressant and antitubercular activities. Among the different isomers of thiadiazole, 1,3,4-thiadiazole derivatives are extensively studied due to broad spectrum of pharmacological activities. Although only a few pharmacological effects exhibited by 1,3,4-thiadiazole derivatives are currently in clinical use, the substitution at thiadiazole ring is a demanding approach to achieve agents with better potency and less toxicity, retaining enough scope for future.

Abbreviation

TB – Tuberculosis, MDR - Multi Drug Resistant, WHO - World Health Organization, DOTS - Directly Observed Treatment Short-Course, MDR-TB - Multi Drug Resistant-TB, AIDS - Acquired Immuno Deficiency Syndrome, MABA - Microplate Alamar Blue Assay, MIC - Minimum Inhibitory Concentration, D-MTB - Detection of Mycobacterium tuberculosis, D-BCG - Detection of Bacille Calmette Guerin, DNA - Deoxyribonucleic acid, H37Rv - Mycobacterium tuberculosis strain where R stands for rough morphology and v stands for virulent.

Conflicts of interest statement

The authors report no conflicts of interest in this work.

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