NEW INSIGHTS INTO ANTI-TUBERCULAR POTENTIAL OF TRIAZOLE SCAFFOLD

*Rina Das and Dinesh Mehta

Faculty of Pharmaceutical Sciences, Maharishi Markendeshwar University, Mullana, Ambala, 133207. HR, India.

ABSTRACT

TB is a worldwide problem and it is a global health emergency. The current problem of tuberculosis therapy is caused by the improper use of antibiotics in chemotherapy of TB patients which gives rise to multi-drug resistant (MDR) strains. Triazoles are heterocyclic compounds featuring five member ring of two carbon atoms and three nitrogen atoms as part of the aromatic five-member ring and possess almost all types of biological activities. This diversity in the therapeutical response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. Present article is sincere attempt to review chemistry, synthesis, spectral studies of triazoles and to study triazoles synthesized in last few years which have shown potent antitubercular activity.

KEYWORDS: Antitubercular activity, Antitubercular drugs, Triazoles, Tuberculosis (TB).

INTRODUCTION

Tuberculosis (TB) is caused by a bacterium called Mycobacterium tuberculosis (MTB) aerobic bacilli belonging to the family Mycobacteriaceae, first identified in 1882 by Robert Koch. It is a chronic bacterial infection, spread through the air, and, which can mainly attack the lungs, although can affect other organs as well.\textsuperscript{[1-7]} The cell wall of the bacilli has a high lipid content resulting in a high degree of hydrophobicity that resists decolorization by acid alcohol after staining with basic fuchsin.\textsuperscript{[8-9]} For this reason, the organism is often referred to as an “acid-fast” bacillus (AFB). The bacillus thrives in oxygen rich environments, such as the apices of the lung, the renal parenchyma, and the growing ends of bones.\textsuperscript{[9-10]}
Tuberculosis (TB) is caused by Mycobacterium of the “tuberculosis complex”, together with mainly M. tuberculosis (MTB). Other Mycobacterium species such as M. bovis, M. africanum, M. canetti and M. microti can also cause TB. TB is an airborne transmissible infection caused by spreading of aerosolized droplets of MTB.[11] Mycobacteriums belong to the order actinomycetales and family Mycobacteriaceae. Several species, including MTB, M. bovis, M. microti, M. canetti, M. africanum, M. kansasii, M. avium, and M. leprae, are intracellular pathogenic bacteria of higher vertebrates.[12] The MTB complex contains three other TB producing mycobacteriums such as M. bovis, M. africanum and M. microti. The first two mycobacteriums are very rarely cause disease in immune capable people. On the other hand M. microti is not typically pathogenic; the prevalence of M. microti infections has been under estimated.[13, 14] The non tuberculous mycobacterium (NTM) causes neither TB nor leprosy, but cause pulmonary diseases resembling TB. The TB requires longer periods of treatment to entirely eliminate mycobacterium from the body.[15, 16]

The current WHO-approved treatment for TB, known as directly observed therapy short course (DOTS), involves an intensive phase with three or four different drugs viz. isoniazid (INH, 1), rifampin (RIF, 2), pyrazinamide (PZA, 3), and ethambutol (EMB, 4) for a minimum of 6 months.[17]
Most of the drugs in the current tuberculosis regime result from research performed over 50 years ago. There is an urgent need to develop more potent and fast acting anti-TB drugs with new modes of action to overcome the cross-resistance with current drugs and low toxicity profiles that can be tolerated for long treatment periods required for TB chemotherapy. Development of resistance to existing drugs is a constantly growing phenomenon that has concerned researchers throughout the world, and now has reached alarming levels for TB. This combined with the recent decline in the development of new drugs to combat them can be anticipated to lead to infectious diseases lacking ready treatment regimens.

The current TB drugs can be divided into two categories: First-line drugs and Second-line drugs. The first-line drugs include INH (1), RIF (2), PZA, (3), EMB, (4) and Streptomycin (SM, 5). The first-line drugs combine the greatest level of efficacy with an acceptable degree of toxicity. Designed to reduce the bacterial population as rapidly as possible and to prevent the emergence of drug-resistant bacteria. These drugs are best given as combination of preparations unless one of the components cannot be given because of resistance or intolerance.

The second-line drugs include Kanamycin (6), Cycloserine (7), p-aminosalicylic acid (PAS, 8), Ethionamide (9), Prothionamide (10), Thiacetazone (11) and Fluoroquinolones (FQ, 12).
The second-line drugs are potentially nephrotoxic, therefore no two drugs from this group should be employed simultaneously or in combination with streptomycin. They are utilized in cases of resistance, retreatment or intolerance to the first-line drugs. They can also be categorized as either Bacteriostatic which include EMB (4) and PAS (8) or Bactericidal which include INH (1), RIF (2), SM (5) and FQ (12). The mechanisms of action and resistance of TB drugs have been reviewed by Silva and Anisa. These drugs can be grouped as cell wall synthesis inhibitors, nucleic acid synthesis inhibitors, protein synthesis inhibitors, and energy inhibitors.

Concurrent resistance to at least two or more of the five first line anti-TB drugs (INH, RIF, PZA, EBT, and SM) is Multi Drugs Resistance and Extensively Drugs Resistant (MDR-TB and XDR-TB) MTB. MDR-TB treatment is long lasting, less effective, costly, and poorly tolerated. The XDR-TB is resistance to at least INH and RIF in addition to any quinolone and at least one injectable second-line drug (capreomycin, amikacin, and kanamycin). The...
principles of treatment for MDR-TB and XDR-TB are the same but 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 MTB in order to shorten the duration of TB therapy.

This article aims to review the work reported on the synthesis of triazoles with antitubercular activity during past few years. Triazoles are heterocyclic compounds featuring five member ring of two carbon atoms and three nitrogen atoms as part of the aromatic five-member ring. Triazole refers to either one of a pair of isomeric chemical compounds with molecular formula C$_2$H$_3$N$_3$, having a five membered ring of two carbon atoms and three nitrogen atoms. The two isomers (Fig: 13) are.

![Fig 13: Isomers of triazoles.](image)

1,2,3-Triazole is one of a pair of isomeric chemical compounds with molecular formula C$_2$H$_3$N$_3$, called triazoles, which have a five-membered ring of two carbon atoms and three nitrogen atoms. 1, 2, 3-Triazole is a basic aromatic heterocycle.

**Synthetic routes of Triazoles**

Many methods are available to synthesize 1, 2,4-triazole and its derivatives, out of which some are as depicted below.

1. From diacylhydrazide$^{[32]}$

   ![Scheme 1](image)

2. From acyl thiocyanates$^{[33]}$

   ![Scheme 2](image)
3. From Esters\textsuperscript{[34]}

\[
\text{RCOOR} + \text{H}_{2}\text{N-NH}_2 \xrightarrow{\text{H}_2\text{N-NH}_2} \text{R-CONNH}_2
\]

\[
\text{R} - \text{CONHNH}_2 + \text{S} \xrightarrow{\text{K}^+} \text{R-CONHNH}_2\text{-C-S-K}^+
\]

\textbf{Scheme 3}

4. Triazoles may be prepared by heating acid hydrazide with amides e.g. formyl hydrazide and formamide give triazole.\textsuperscript{[35]}

\[
\text{NH}_2 + \text{O= C-NH} \xrightarrow{\text{NH}_2} \text{N} + 2\text{H}_2\text{O}
\]

\textbf{Scheme 4}

5. From condensation of Hydrazide or a mono substituted hydrazine with di-acylamine\textsuperscript{[36]}

Hydrazide or a mono substituted hydrazine is condensed with adi-acylamine in the presence of a weak acid, for example phenyl hydrazine and N-formyl benzamide. Reaction gave 1,5-diphenyl-1,2,4-triazole (Fig. 5) in good yields.

\[
\text{Ph-NH}_2\text{NH}_3 + \text{PhCONHCHO} \xrightarrow{\text{C}_2\text{H}_4\text{OH}} \text{N= C= N= C - H - N+ Ph}
\]

\textbf{Scheme 5}

6. From aminoguanidine and formic acid.\textsuperscript{[37]}

\[
\text{H}_2\text{N-C-NH-NH}_2 + \text{HCOOH} \xrightarrow{\text{H}_2\text{O}} \text{NH}_2\text{C-NHNH-C-H} + \text{H}_2\text{PO}_2
\]

\textbf{Scheme 6}

7. From 1,2,4-oxadiazole\textsuperscript{[38]}

\[
\text{NH}_3 \xrightarrow{} \text{N= C= N= C - H - N+}
\]

\textbf{Scheme 7}
8. By decarboxylation of 1,2,4-triazole -5-carboxylic acid\[39]\n
\[
\begin{array}{c}
\text{COOH} \\
\downarrow \\
\text{NH} \\
\end{array}
\xrightarrow{\text{Scheme 8}}
\begin{array}{c}
\text{NH} \\
\end{array}
\]

9. From 4-amino-1,2,4-triazole\[40]\n
\[
\begin{array}{c}
\text{NH}_2 \\
\text{H}_2\text{PO}_4 \\
\text{H}_2\text{O} \\
\end{array}
\xrightarrow{\text{Scheme 9}}
\begin{array}{c}
\text{NH} \\
\end{array}
\]

10. From 1,3,5- triazines\[41]\n
\[
\begin{array}{c}
\text{NH}_2 \\
\text{H}_2\text{N-NH}_2\cdot\text{HCl} \\
\end{array}
\xrightarrow{\text{Scheme 10}}
\begin{array}{c}
\text{NH} \\
\end{array}
\]

**Biological Activities**

The 1, 2, 4-triazole nucleus has been incorporated into a wide variety of therapeutically important agents. Ribavirin (antiviral),\[42]\ Rizatriptan (antimigraine),\[43]\ Vorozole, Letrozole and Anastrozole (antitumor)\[44]\ are some examples of drugs containing 1, 2, 4-triazole moiety.

Posaconazole, Fluconazole and Itraconazole,\[45,46]\ that are efficient antifungal drugs used in current treatment. A number of biological activity such as antibacterial antifung\[47,48]\ anti-inflammatory, analgesic\[49]\ anticonvulsant,\[50]\ anticancer\[51,52]\ antitumor,\[53,54]\ antiviral,\[55]\ antileishmanial,\[56]\ potassium channel activators,\[57]\ antiplatelet\[58]\ and anti-oxidant\[59]\ have been associated with N- substituted triazole attached with different hetrocyclic nuclei.

In the design of new bioactive agents, the development of hybrid molecules through the combination of different pharmacophores in the same structure may lead to compounds having more efficiency in biological activity. Systematic structural modifications of the amide-1,2,3-triazole leads to develop of bioisosteric relationship in the molecule.\[60]\ It has
been noticed continuously over the years that interesting biological activities were associated with triazole derivatives.

**Some Biologically Active Triazole Derivatives**

Amitrole[^61] (Fig: 14) (3-amino-1H-1,2,4-triazole) is used as a herbicide and also to defoliate cotton plants before mechanical harvesting

![Fig: 14]

The clinically useful derivatives of 1,2,3-triazole includes Tazobactam[^62] (Fig: 15) which is used in combination with β-lactam antibiotics as antibacterial and Fig:14[^63] (Fig:16) used as an anticonvulsant.

![Fig: 15](Fig: 16)

The derivatives of 1,2,4- triazole of therapeutic importance includes Rizatriptan[^64] Trazodone[^65] (Fig:18) an antidepressant, Dapiprazole[^66] (Fig:19) a miotic agent, Ribavirin[^67] (Fig:20) an antiviral agent, Israpafam[^68] (Fig:21) an antiasthmatic, Lotrifin[^69] (Fig:22) an abortifacient and Rilmazafone[^70] (Fig:23) a potent sedative and hypnotic agent.

![Fig: 17](Fig: 18)
Some derivatives of 1H-1,2,4-triazole are also found to be useful as potent antiestrogens, major examples of which are Anastrozole\textsuperscript{[71]} (Fig:24), vorozole\textsuperscript{[72]} (Fig:25) and letrozole\textsuperscript{[73]} (Fig:26).
Antifungal activity exhibited by many potent antifungal agents is attributed to the presence of triazole ring system. Major examples of triazole containing antifungal agents include Fluconazole\(^{74}\) (Fig:27), Voriconazole\(^{75}\) (Fig:28) and Itraconazole\(^{76}\) (Fig:29).
The triazole ring has been fused at 1,2-position of 1,4-benzodiazepines to give Estrazolam\cite{77} (Fig:30) and Triazolam\cite{78} (Fig:31) the potent hypnotic agents and Alprazolam\cite{79} (Fig:32) a potent antipsychotic agent.

\[
\begin{align*}
  &R=H,X=Cl,Y=H \\
  &R=CH_3,X=Cl,Y=Cl \\
  &R=CH_3,X=Cl,Y=H
\end{align*}
\]

A brief review of triazoles associated with antimycobacterial activity is presented below.

Sanna et al.\cite{80} synthesized a series of 3-aryl substituted-2-(1H(2H)-benzotriazol-1(2)-yl)acrylonitriles for a preliminary \textit{invitro} evaluation of antitubercular activity. They reported that several compounds showed interesting activity in the preliminary screening with a percent growth inhibition of \textit{Mycobacterium tuberculosis} between 40 and 99% at the concentration of 12.5 µg/mL. The most effective derivatives were also tested \textit{in vitro} against \textit{M. avium}.

Klimesova et al.\cite{81} evaluated a series of 3-benzylsulfanyl derivatives of 1,2,4-triazole and 4-methyl-1,2,4-triazole for their \textit{invitro} antimycobacterial activity against \textit{Mycobacterium tuberculosis}, \textit{M. avium}, and two strains of \textit{M. kansasii}. The activities were expressed as minimum inhibitory concentrations. The compounds exhibited only a moderate or slight antimycobacterial activity with MICs falling into a range of 32> 1000 µmol/L. The most active substances bear two nitro groups or a thioamide group on the benzyl moiety. As regards to cytotoxicity effect, the evaluated compounds could be considered as moderately toxic.

Zahajska et al.\cite{82} prepared a set of four types of benzazoles, 1,2,4-triazole, and pyridine-2-carbonitrile/-2-carbothioamide substituted with 1-naphthylmethylsulfanyl or pyridylmethylsulfanyl to modify the structure of benzylsulfanyl derivatives. The compounds were evaluated for \textit{in vitro} antimycobacterial activity against \textit{Mycobacterium tuberculosis}, \textit{M. avium}, and two strains of \textit{M. kansasii}. The MIC values were in the range of 2 to >1000mol/L. Introduction of a pyridyl moiety into the molecule generally decreased the activity. A naphthyl moiety did not affect the activity when substituted with a phenyl ring.
The most active substances were 4-(3-pyridylmethylsulfanyl)pyridine-2-carbothioamide (MIC = 2 - >62.5 mol/L) and 4-(1-naphthylmethylsulfanyl)pyridine-2-carbothioamide (MIC = 2 - >32 mol/L).

Kaplancikli et al. [83] synthesized new 3-alkylsulfanyl-1,2,4-triazole derivatives (Fig. 33) and evaluated them for antitubercular activity by broth microdilution assay, the Microplate Alamar Blue Assay, in BACTEC 12B medium using BACTEC 460 Radiometric System against *Mycobacterium tuberculosis* H37Rv (ATCC 27294) at 6.25 µg/ml and the tested compounds showed considerable inhibition ranging from 58-84%.

Costa et al. [84] described the synthesis, *in vitro* anti-*Mycobacterium tuberculosis* profile, and the SAR study of new N-substitutedphenyl-1,2,3-triazole-4-carbaldehydes (Fig. 34). Two compounds screened for the inhibitory activity against *Mycobacterium tuberculosis* H37Rv were able to inhibit the growth of the mycobacterium. Interestingly, these compounds exhibited the best inhibition with MIC values of 2.5 µg/mL, similar to pharmaceuticals currently used in the treatment of tuberculosis. Their SAR study indicated the importance of the hydrogen bond acceptor subunit, the position in the aromatic ring, the planarity of triazole and phenyl rings in these compounds, and a correlation between the uniform highest occupied molecular orbital (HOMO) coefficient distribution and the anti-tubercular activity. The significant activity of two compounds pointed them as promising lead molecules for further synthetic and biological exploration.
Banfi et al.\(^{[85]}\) investigated different series of imidazole and triazole derivatives having an azomethine linkage to pyridine-2-carboxamidohydrazone to develop new antimycobacterial and antifungal drugs. MICs of the compounds were evaluated by reference assay and as well as employing recently developed Microdilution Resazurin Assay (MRA). It was found that halogenated derivatives showed good activity; most of the compounds had inhibitory action against *Mycobacterium tuberculosis* reference and clinical strains, with MICs in the range 4-64 mg/L. Molecular modeling investigations showed that the active new compounds may interact at the new potent site of mycobacterial cytochrome P450-dependentsterol-14α-demethylease and that the calculated binding free energy values are in agreement with the corresponding MIC values.

In 2007 Shiradkar M et al.\(^{[86]}\) synthesized a series of N-\{4-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-1,3-thiazol-2-yl\}-2-substituted-amides (Fig:35) in good yields. The compounds were screened for antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain by broth micro dilution assay method. The in vitro antitubercular activity reports of tested compounds against M. tuberculosis strain H37Rv showed moderate to better activity.
Mahendra Ramesh Shiradkar et al.\cite{87} reported the synthesis of various derivatives of N-{4-[(4-amino-5-sulphanyl-4H-1,2,4-triazol-3-yl)methyl]-1,3-thiazol-2-yl}-2-substituted amides (Fig:36) and tested for antibacterial and antitubercular potency. Compound 5a with R=NHCOCH$_2$Cl and Ar = 4Cl-C$_6$H$_4$ showed good antitubercular activity.

\[
\text{Fig: 36}
\]

Mahendra Shiradkar et al.\cite{88} synthesized analogues of thiazolyl triazoles (Fig:37) and tested for their antimycobacterial and antimicrobial activities. Compound with R= NHCOCH$_2$Cl showed good antitubercular activity.

\[
\text{Fig: 37}
\]

Carta et al.\cite{89} studied activity of 3-methyl-9-substituted-6-oxo-6,9-dihydro-3H-[1,2,3]-triazolo[4,5-h]quinolone carboxylic acids(Fig. 38) and their esters as a new class of antiinfective agents against MDR *Mycobacterium tuberculosis*. In antitubercular screening against H37Rv and clinically isolated strains of *M.tuberculosis* several derivatives showed MIC$_{90}$ in the range 0.5-3.2µg/mL. Preliminary SAR studies suggested that in general the presence of an alkyl substituent on triazole nucleus was more favorable than propenyl or benzyl groups for better antitubercular activity. One compound showed no cytotoxicity and proved to be the most potent derivative exhibiting MIC$_{90}$=0.5 µg/mL against all strains of *M. tuberculosis* and infected human macrophages (J774-A1) tested.

<table>
<thead>
<tr>
<th>Active compound</th>
<th>R</th>
<th>Ar</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>-NHCOCH$_2$Cl</td>
<td>4Cl-C$_6$H$_5$</td>
</tr>
</tbody>
</table>
A series of 4-arylidenamino-4H-1,2,4-triazole-3-thiol derivatives were synthesized and evaluated by Ozdemir et al.\cite{90} for antituberculosis activity against *Mycobacterium tuberculosis* H37Rv (ATCC 27294), using the BACTEC 460 radiometric system and BACTEC 12B medium. One compound showed significant activity at 6.25 µg/mL with a 87% inhibition.

BiswaJit Kumar Singh and coworkers\cite{91} prepared 5-Azido-5-deoxy-xylo-, ribo-, and arabinofuranoses by the reaction of the respective 5-O-(methanesulfonyl) or p-toluenesulfonyl derivatives with NaN₃ in DMF. The intermediate 5-azido-5-deoxy glycofuranoses on 1,3-cycloaddition with different alkynes in the presence of CuSO₄ and sodium ascorbate gave the corresponding sugar triazoles (Fig : 39) in very good yields. The synthesized sugar triazoles were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv, where one of the compounds displayed mild antitubercular activity in vitro with MIC 12.5 µg/mL.

A series of novel N-alkyl/aryl-N’-[4-(4-alkyl/aryl-2,4-dihydro-3H-1,2,4-triazole-3-thione-5-yl)phenyl]thioureas and three S-alkylated representatives of the former, N-alkyl/aryl-N’-[4-(3-aralkylthio-4-alkyl/aryl-4H-1,2,4-triazole-5-yl)phenyl]thioureas was studied by Kucukguzel et al for antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv.
as well as *Mycobacterium fortuitum* ATCC 6841 which is a rapid growing opportunistic pathogen.\(^{[92]}\) Some compounds were found to possess the same MIC value as that of tobramycin against *M. fortuitum* ATCC 6841 whereas other compounds had positive response against *M. tuberculosis* H37Rv at varying degrees. One compound was identified as the most potent derivative of the series with an MIC value of 6.25 µg/mL and selectivity index of 1.6.\(^{[92]}\) Further, they designed a series of novel 5-[(4-aminophenoxy)methyl]-4-alkyl/aryl-2,4-dihydro-3H-1,2,4-triazole-3-thiones and several related thioureas, N-alkyl/aryl-N'-[4-[(4-alkyl/aryl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methoxy]phenyl]thioureas (Fig. 40) for evaluation of their antimycobacterial potency. All compounds were evaluated *in vitro* for antimycobacterial against *Mycobacterium tuberculosis* H37Rv. One compound was the most active compound with 79% inhibition against *M. tuberculosis* H37Rv.

![Fig 40](image-url)

A novel series of 4-pyrrol-1-yl benzoic acid hydrazide analogs, derived 5-substituted-2-thiol-1,3,4-oxadiazoles, 5-substituted-4-amino-1,2,4-triazolin-3-thione (Fig. 41) and 2,5-dimethylpyrroles were designed and synthesized in good yields by Joshi et al.\(^{[93]}\) Compounds were evaluated for their preliminary *in vitro* antibacterial activity against some Gram-positive and Gram negative bacteria and for antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain by broth dilution assay method. Some compounds exhibited very good antibacterial and antitubercular activities.

![Fig 41](image-url)
Singh et al.\textsuperscript{[94]} reported preparation of 5-azido-5-deoxy-xylo-, ribo-, and arabinofuranoses and their intermediate 5-azido-5-deoxyglycofuranoses which on 1,3-cycloaddition with different alkyne safforded the corresponding sugar triazoles in very good yields. The synthesized sugar triazoles were evaluated for their antitubercular activity against \textit{Mycobacterium tuberculosis} H37Rv, where one of the compounds displayed mild antitubercular activity \textit{in vitro} with MIC 12.5 µg/mL.

Gill et al.\textsuperscript{[95]} Synthesized a series of novel clubbed [1,2,3] triazoles (Fig. 42) with fluorine benzimidazole series of H37Rv strain inhibitors. As a part of SAR studies, they had incorporated fluoro substituent at positions 2, 3 & 4 in different variations on the phenyl ring attached to triazole nucleus. Replacement of fluoro with trifluoromethyl group resulted in a substantial loss of biological activity. This loss may indicate retardation in the intracellular transport due to highly electronegativity in one region. In case of electron donating groups, like methyl substitutions resulted in loss of activity. The biological data generated revealed that compounds having an electron withdrawing group like fluoro attached to triazole nucleus may prove a template for anti tuberculosis activity for further development. Some of the derivatives are under further evaluation showing better and considerable activity compared to rifampin.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig42.png}
\caption{Fig: 42}
\end{figure}

A series of 1-nitrobenzyloxybenzotriazoles was synthesized and tested against four \textit{Mycobacterium} strains by Augustynowicz-Kopec et al.\textsuperscript{[96]} High antimycobacterial activity, comparable with that of isoniazide, was found for 5,6-dichloro-1-(3,5-dinitrobenzyloxy)-1\textit{H}-benzotriazole (Fig. 43).
Gupte et al.\textsuperscript{[97]} Demonstrated synthesis, biochemical, and biological evaluation of a systematic series of 2-triazole derivatives (Fig. 44) of 5'-O-[N-(salicyl)sulfamoyl]adenosine (Sal-AMS) and described them as inhibitors of aryl acid adenylating enzymes (AAAE) involved in siderophore biosynthesis by \textit{Mycobacterium tuberculosis}. SAR revealed a remarkable ability to tolerate a wide range of substituents at the 4-position of the triazole moiety, and a majority of the compounds possessed subnano molar apparent inhibition constants. However, the \textit{in vitro} potency did not always translate into whole cell biological activity against \textit{M. tuberculosis}, suggesting that intrinsic resistance plays an important role in the observed activities.

Castagnolo et al.\textsuperscript{[98]} Reported a series of novel enantiomerically pureazole derivatives (Fig. 45). The new compounds, bearing an imidazole and a triazole moiety, were evaluated as antimycobacterial agents. One of them proved to have activity against \textit{Mycobacterium tuberculosis} comparable to those of the classical antibacterial/antifungal drugs such as econazole and clotrimazole.
A series of fluorinated 1,2,4-triazolo[1,5-a]pyrimidine-6-carboxylic acid derivatives was designed and synthesized by Abdel-Rahman et al.\textsuperscript{[99]} These compounds were screened against *Mycobacterium tuberculosis* H37Rv strain at 6.25 µg/mL concentration. One compound, the 7-oxo-2-(trifluoromethyl)-4,7-dihydro-1,2,4-triazolo[5,1-a]pyrimidine-6-carboxylic acid (Fig. 46) was found to be a very potent inhibitor, being able to inhibit 92% growth of *M. tuberculosis* H37Rv at 6.25 µg/mL concentration. At the same time, it proved to be nontoxic to mammalian cells (IC50 > 62.5 µg/mL *in vitro*).

Newly 1,2,4 triazoles analogs (Fig: 47) were synthesized by NB Patel et al.\textsuperscript{[100]} and carried in vitro antitubercular activity against Mycobacterium tuberculosis H37Rv strain. Compound 3-(3-pyridyl)-5-(4-methylphenyl)-4-(N-4-chloro-1,3-benzothiazol-2-amino)-4H-1,2,4 triazole showed better antitubercular activity compared to rifampicin.
A series of 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole and 1,3,4-oxadiazole derivatives (Fig:48) were synthesized and were evaluated for their preliminary cytotoxicity, antimicrobial and antitubercular activity against Mycobacterium tuberculosis H37Rv strain by broth dilution assay method. Antimycobacterial activity tested against M. tuberculosis indicated that compounds 4b and 6g exhibited twofold enhanced potency than parent compound and the results indicate that some of them exhibited promising activities and they deserve more consideration as potential antitubercular agents. The tested compounds possessed moderate to good inhibition, compounds 6g and 6i showed comparatively good activity against all tested microbial strains and excellent inhibition towards M. tuberculosis H37Rv at MIC 4 mg/mL.

Different 1,4-Disubstituted -1,2,3-triazoles(Fig:49) were developed by Tripathi and coworkers and were screened for antitubercular activity against Mycobacterium tuberculosis H37Rv and compounds 9,12 and 14 exhibited antitubercular activities with MIC ranging from 12.5 to 3.12 ug/ml.

Kumar et al. studied a series of 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole (Fig. 50) and 1,3,4-oxadiazole derivatives for their antitubercular activity against Mycobacterium tuberculosis H37Rv strain by broth dilution assay method. One compound exhibited promising antitubercular activity with MIC value of 4 µg/mL when compared with standard drug INH having MIC value of 0.25 µg/mL. This result indicates that it deserve more consideration as potential antitubercular agent.
Patel et al. \cite{104} Synthesized 3-(3-pyridyl)-5-(4-methylphenyl)-4-(Nsubstituted-1,3-
benzothiazol-2-amino)-4\textit{H}-1,2,4-triazole analogs (Fig. 51) and evaluated for antitubercular
activity against \textit{Mycobacterium tuberculosis} H37Rv strain using Lowenstein-Jensen medium
and antimicrobial activity against various bacteria and fungi using broth microdilution
method. Some compounds emerged as promising antimicrobials. It was also observed that the
promising antimicrobials have proved to be better antituberculars. One compound showed
better antitubercular activity with MIC value of 25 µg/mL when compared with standard drug
rifampicin having MIC value of 40 µg/mL.

Various 4-substituted N-phenyl-1,2,3-triazole derivatives were synthesized by N Nubia
Boechat(Fig:52) using click chemistry. \cite{105} The derivatives were screened in vitro for
antimicrobial activity against \textit{Mycobacterium tuberculosis} strain H37Rv (ATCC 27294)
using the Alamar Blue susceptibility test. Derivatives of isoniazid (INH), (E)-N0-[(1-aryl)-
1\textit{H}-1,2,3-triazole-4-yl)methylene] isonicotinoyl hydrazides, exhibited significant activity
with MIC values ranging from 2.5 to 0.62 µg/mL. In addition, they displayed low
cytotoxicity against liver cells (hepatoma HepG2) and kidney cells (BGM), thereby providing
a high therapeutic index. The results demonstrated the potential and importance of
developing new INH derivatives to treat mycobacterial infections.
N-substituted-phenylamino-5-methyl-1H-1,2,3-triazole-4-carbohydrazide derivatives were synthesized by Mandal S and coworkers\textsuperscript{[106]} (Fig:53). These derivatives were synthesized in good yields and some of them showed a promising antitubercular profile. The N-acetylhydrazone (NAH) 8n was the most potent against the Mycobacterium tuberculosis H37Rv strain (MIC = 2.5 $\mu$g/mL) similar to or better than the current drugs on the market. The theoretical structure–activity relationship study suggested that the presence of the furyl ring and the electronegative group (NO$_2$) as well as low lipophilicity and small volume group at R position are important structural features for the antitubercular profile of these molecules.

Rapid synthesis of 1,2,3-triazole derivatives (Fig : 54) has been achieved via Huisgen's 1,3-dipolar cycloaddition between alkyl/arylazides and diethyl/dimethyl acetylenedicarboxylate in excellent yields under solvent-free conditions by Shanmugavelan P and coworkers.\textsuperscript{[107]} In vitro antitubercular activity of these triazoles were screened against Mycobacterium tuberculosis H(37)Rv strain. Four of the compounds(2b,2d,2e,3d) showed MIC in the range of 1.56-3.13 $\mu$g/mL proving their potential activity.
Analogues of Gallic acid [3, 4, 5-trihydroxybenzoic acid, C₆H₂(OH)₃ COOH] containing triazole nucleus (Fig: 55) were synthesized. Then all synthesized compounds were subjected to investigation for their antitubercular activity against M.Tuberculosis H37Rv strain using MABA method and Rifampicin as the standard. The results of which showed that among the synthesized compounds few compounds showed equivalent activity as that of standard while remaining compounds found to be less active when compared to standard. Compounds S₂ and S₅ with Ar = -3NO₂ and -4OH showed good antitubercular activity.

Shashikant Patten et al. Synthesised 5-mercapto 1,2,4-triazole derivatives (Fig: 56) and evaluated for antimicrobial, anti-inflammatory, antitubercular activities. Compounds 5g and 5h with Ar = p-NH₂-C₆H₄ showed very good antitubercular activity.
Suhyun Kim and coworkers\textsuperscript{[110]} designed and synthesized 1H-1,2,3-triazoles derived from econazole (Fig : 57). The majority of triazole derivatives have been prepared by microwave-assisted click chemistry. The prepared triazoles had no antifungal activities. However, most of the hydroxy-triazoles (10) turned out to have antitubercular activities. Overall, hydroxy-triazoles 10 were more active than their corresponding ether-triazoles. While the MIC value of hydroxy-triazole 10d was as good as econazole (16 lg/mL), the MIC value of 10a was two-fold more active than econazole, suggesting that this 1H-1,2,3-triazole scaffold could be further optimized to develop Mtb specific agents.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{Compound} & \textbf{R} \\
\hline
10a & n-Bu \\
10d & cyclohexyl \\
\hline
\end{tabular}
\caption{Chemical structures of hydroxy-triazoles (10) and their MIC values.}
\end{table}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{fig57.png}
\caption{Chemical structures of hydroxy-triazoles (10).}
\end{figure}

A novel series of some 2-(4,5-disubstituted-4,5-dihydro-3H-1,2,4-triazol-3-yl) pyrazine (B1-B9) derivatives (Fig:58) were prepared from N'-substituted pyrazine-2-carbohydrazide by Dighe NS and coworkers.\textsuperscript{[111]} The compounds were evaluated for antibacterial activity, antifungal activity, antitubercular and anti-inflammatory activities. Among the synthesized compounds some compounds found to possess all these activities. Compounds B2, B4, and B7 has showed promising antitubercular activity.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Compound} & \textbf{R} & \textbf{Ar} \\
\hline
B2 & H & \includegraphics[width=0.2\textwidth]{fig58b2.png} \\
B4 & \includegraphics[width=0.2\textwidth]{fig58b4.png} & \includegraphics[width=0.2\textwidth]{fig58b4.png} \\
B7 & \includegraphics[width=0.2\textwidth]{fig58b7.png} & \includegraphics[width=0.2\textwidth]{fig58b7.png} \\
\hline
\end{tabular}
\caption{Chemical structures of 2-(4,5-disubstituted-4,5-dihydro-3H-1,2,4-triazol-3-yl) pyrazine derivatives (B1-B9).}
\end{table}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{fig58.png}
\caption{Chemical structures of 2-(4,5-disubstituted-4,5-dihydro-3H-1,2,4-triazol-3-yl) pyrazine derivatives (B1-B9).}
\end{figure}
CONCLUSION
This review is an attempt to explore the anti-tubercular potential of triazole scaffold in medicinal chemistry and drug development. The plethora of research effort carried out focus that myriad spectrums of promising anti-tubercular activity exhibited by triazole derivatives. Information provided in this manuscript can be found useful for further investigations on this scaffold. Moreover, rational design and development of the novel antitubercular agents incorporating this nucleus can help in dealing with escalating problems of the microbial resistance and also to meet the need for an effective antitubercular therapy for the treatment of MDR tuberculosis.

Various studies suggested that electron donating groups, like methyl substitutions resulted in loss of activity. The biological data generated revealed that compounds having an electron withdrawing group like fluoro attached to triazole nucleus may prove a template for anti tuberculosis activity for further development. It was also suggested that in general the presence of an alkyl substituent on triazole nucleus was more favorable than propenyl or benzyl groups for better antitubercular activity. Studies also indicated that the presence of the furyl ring and the electronegative group (NO$_2$) group present in the molecule are important structural features for the antitubercular profile of the molecules.

SAR studies also revealed a remarkable ability to tolerate a wide range of substituents at the 4-position of the triazole moiety, and a majority of the compounds possessed subnanomolar apparent inhibition constants. However, the in vitro potency did not always translate into whole cell biological activity against M. tuberculosis, suggesting that intrinsic resistance plays an important role in the observed activities. Studies indicated the importance of the hydrogen bond acceptor subunit, the position in the aromatic ring, the planarity of triazole and phenyl rings in these compounds, and a correlation between the uniform HOMO coefficient distribution and the anti-tubercular activity.

The examples used in this manuscript demonstrate the usefulness of triazole derivatives as, thereby confirming that these compounds can still have a place in the tool-kit of the modern medicinal chemist to synthesize novel anti-tubercular drugs.

CONFLICT OF INTEREST
The authors confirm that this article content has no conflicts of interest.
ACKNOWLEDGEMENT
The authors wish to thank Maharishi Markandeshwar University, Mullana, India for all necessary facilities.

REFERENCES
8. Marwick C. Do worldwide outbreaks mean tuberculosis again becomes 'captain of all these men of death'? JAMA, 1992; 257: 1174–75.


34. Reid SJ, Heindel ND. Improved syntheses of 5-substituted-4-amino-3-mercapto-(4H)-1,2,4-triazoles. J. Heterocycl. Chem, 1976; 13: 1925
38. Reid SJ, Heindel ND. Synthesis of 1,2,4-triazole derivatives containing benzothiazoles as pharmacologically active molecule. J. Heterocyclic Chem, 1978; 11: 1547.


58. Ilango K, Valentina P. Synthesis and biological activities of novel 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles. Der Pharma Chemica, 2010; 2 (2): 16.


Das et al. World Journal of Pharmaceutical Research


100. Patel NB, Khan IH, Rajani SD. Pharmacological evaluation and characterizations of newly synthesized 1,2,4-triazoles. European Journal of Medicinal Chemistry, 2010; 45:4293-99.


111. Dighe NS, Saudagar RB, Jain DA. Design, synthesis, antimicrobial and anti-inflammatory activities of some substituted-1,3,4-oxadiazole and substituted-1,2,4-triazoles. Medicinal Chemistry & Drug Discovery, 2012; 2: 17-29.