**Triazole: A Promising Antituburcular Agent**

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**Abstract**

Tuberculosis is a contagious disease with comparatively high mortality worldwide. The statistics shows that around three million people throughout the world die annually from tuberculosis and there are around eight million new cases each year, out of which developing countries showed major share. Therefore, the discovery and development of effective antituberculosis drugs with novel mechanism of action have become an insistent task for infectious diseases research programs. The literature reveals that, heterocyclic moieties have drawn attention of the chemists, pharmacologists, microbiologists and other researchers owing to its indomitable biological potential as antiinfective agents. Among hetrocyclic compounds, triazole (1,2,3-triazole/1,2,4-triazole) nucleus is one of the most important and well known heterocycles, which is a common and integral feature of a variety of natural products and medicinal agents. Triazole core is considered as a privileged structure in medicinal chemistry, are widely used as “parental” compounds to synthesize molecules with medical benefits, especially with infection related activities. In the present review, we have collated published reports on this versatile core to provide an insight so that its complete therapeutic potential can be utilized for the treatment of tuberculosis. This review also explores triazole as a potential targeted core moiety against tuberculosis and various research ongoing worldwide. It is hoped that, this review will be helpful for new thoughts in the quest for rational designs of more active and less toxic triazole-based anti-tuberculosis drugs.

**Keywords:** Triazole; Synthesis; Anti-tubercular; Tubercle Bacillus; *Mycobacterium tuberculosis*; Medicinal chemistry

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**Running title: Triazole-based Anti-tuburcular Agents**

**Introduction**

Tuberculosis (TB), a bacterial infection caused by *Mycobacterium tuberculosis* (*MTB*), is one of the leading causes of death in the world due to a single infectious disease, which is second only to human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) [1]. *MTB* is an obligate, intracellular, non-motile bacillus that primarily infects humans. The bacterium is also known for its lipid-rich cell wall, which is impermeable to most dyes. *MTB* also divides at an incredibly slow pace, taking 15 to 20 hours [2]. Mycobacteria can be classified into non-pathogenic organisms, such as *Mycobacterium smegmatis,* which is fast growing and most often used as a laboratory model for *MTB* research, and pathogenic organisms, which cause diseases in humans and animals, such as *MTB* and *Mycobacterium bovis* [3]. *MTB* is generally transmitted *via* the inhalation of respiratory droplets, and grows best in the oxygen-rich tissues of the lung [4]. Within the lung, this is typically phagocytosed by alveolar macrophages, predominantly *via* the human macrophage mannose receptor in addition to complement receptors [5]. Following phagocytosis, *MTB* generally remains within the phagosome, preventing its maturation and acidification in order to avoid being destroyed [6], but it has also been observed residing in the cytoplasm [7].

TB has been one of the deadliest diseases over the past few decades affecting nearly one-third of the world’s population [8] with new infection occurring at 1% of population each year [9]. According to world health organization (WHO) studies, in 2012, there were 8.8 million new cases of TB (13% co-infected with HIV) and 1.4 million people died from TB including one million HIV negative people [10]. The estimated 8.8 million new cases every year correspond to 52,000 deaths per week or more than 7,000 each day [11, 12]. These number shows ever, are only a partial depiction of the global TB threat. More than 80% of TB patients are in the economically productive age of 15-49 years, which results in tremendous economic and social problems. It was estimated that nearly 1 billion more people will be infected with TB in the next 20 years. About 15% of that group (150 million) will exhibit symptoms of the disease, and about 3.6% (36 million) will die from TB if new disease prevention and treatment measures are not developed [13]. There were around 1.3 million TB-related deaths worldwide. Over 95% of TB deaths occur in low- and middle-income countries, and it is among the top three causes of death for women aged 15 to 44. In 2012, an estimated 530000 children became ill with TB and 74000 HIV-negative children died of TB [14]. These data facilitated chemists and biologist to discovery of novel drug targets, assisted the understanding of the biological phenomenon of *MTB*. Currently, the six to nine month multidrug protocol used in the treatment of TB is highly effective with drug-susceptible TB, but poor patient compliance promotes development of drug resistance [15]. Although, the existing method of curing is very effective against TB, the length of treatment, the toxicity and the potential for drug-drug interactions are factors that highlight the need for new anti-TB drugs [16, 17]. In addition, *MTB* is resistant to some of the first and second line drugs [18]. Therefore, effective new drugs [19] and strategies [20] are essential to treat the TB bacilli.

It has been established that heterocyclic compounds play an important role in designing new class of structural entities for medicinal applications. Among pharmacologically important heterocyclic compounds, triazole and its derivatives are attracted considerable attention in fields, such as medicinal and agrochemical research as well as in the material sciences due to their unique structure and properties [21]. Triazole, also known as pyrrodiazole is one of the classes of organic heterocyclic compounds containing a five membered diunsaturated ring structure composed of three nitrogen atoms and two carbon atoms at non-adjacent positions. This may be of two types, the 1,2,3-triazoles **(1)** and the 1,2,4-triazoles **(3)** (Fig.1). The name triazole was first given by Bladin who described its derivatives in early 1885, although the structures reported slightly incorrect. An alternative name, pyrrodiazole was given by Andreocci in 1889 regarding it as a member of a class of compounds analogous to pyrrole [22, 23].

*Insert Figure 1*

In the recent past, triazole nucleus has gathered an immense attention among chemists as well as biologists as it is one of the key building elements due to their chemotherapeutical values [24, 25]. Triazole and its derivatives are important class of bioactive molecules in the field of drugs and pharmaceuticals. They exhibit significant wide range of pharmacological activities such as anti-microbial [26, 27], anti-inflammatory, anaesthetic [28], analgesic [29], anti-neoplastic [30], anti-convulsant [31], anti-proliferative [32], anti-cancer [33], anti-malarial [34], and anti-viral activities [35]. Also, they show phosphodiesterases enzyme inhibitor [36], hepatitis C [37], β-lactamase inhibitors [38], fungicidal [39], insecticidal [40], and plant growth inhibitor [41] activity and many more. To list a few triazole derivatives, terconazole **(5)**, itraconazole **(6)**, fluconazole **(7)**, bittertanol **(8)**, cyproconazole **(9)** (fungicides), trazodone **(10)** (anti-depressant) and triazolam **(11)** (sedative and hypnotic), which are actively used in pharmacological field (Fig. 2).

*Insert Figure 2*

This broad spectrum of biological and biochemical activities has been further facilitated by the synthetic versatility of trizole, which allows creating a large number of structurally diverse derivatives and this has been reviewed by several authors [42-45]. Among other heterocyclic derivatives, triazole compounds were reported as most promising candidates towards anti-TB activity [46-50]. A spectrum of pharmacological activities exhibited by triazole and its derivatives has been reviewed by many researchers, but, no one review published on 1,2,3 triazole and 1,2,4 triazole (together) as anti-TB agents. It is still a challenge for the pharmaceutical chemist to develop more effective and less toxic agents to treat signs and symptoms of TB disorders. A large amount of effort has been invested in the past decade to develop triazole based compounds as modulator of anti-TB agent, which is active on different clinically approved therapeutic targets showing excellent therapeutic potency. By looking into the importance of this therapeutic area we decided to collect the literature on anti-TB triazole derivatives (from 2000 to date), the indispensable anchor in medicinal chemistry. In this review, it is attempted to shed light and compile published reports on triazole derivatives along with some opinion on different approaches to help the medicinal chemists in designing future generation potent yet safer anti-TB agents.

**1,2,3-Triazole derivatives for treatment of tuberculosis**

Kumar and co-workers reported the synthesis of triazole-isoniazid conjugates and their *in vitro* evaluation as possible anti-TB drugs against *MTB H37Rυ*. The compounds exhibited potent activity against *MTB* strain with minimal inhibitory concentration (MIC99) values ranging from 0.195 to 1.56 μM*.* Compound **(12)** was the most active derivative (MIC99 = 0.195-0.39 μM), being two fold more effective than isoniazid (INH, MIC99 = 0.39 μM) and also tested for its *in vivo* activity, which evidenced mild activity in case of lung as well as spleen. The influence of the compound on the replication of the pathogen was far superior in the case of spleen with compared to the influence on the lung [51]. Menendez and co-workers described synthesis of 1,2,3-triazoles bearing alkyl and aryl/alkyl chain by using click chemistry and examined their anti-TB activity against *MTB H37Rv* strain. Compounds **(13)** and **(14)**, evinced promising inhibition effect with MIC values of 0.50 and 0.25 µg/mL, respectively. Of particular interest, compound **(14)** possessing the best MIC value of 0.6 µM. The length of the alkyl chain is important, which in turn affects the anti-TB activity, the 12-carbon chain derivatives found 8-10 fold more active than 9 and 10-carbon chain [52] (Fig. 3).

*Insert Figure3*

Triazole fused spirochromone conjugates were synthesized and screened for their *in vitro* anti-mycobacterial activity against *MTB H37Rv*. Most of the compounds depicted a significant *in vitro* activity against *MTB* with a MIC value in the range, 0.78-6.25 µg/mL. Among them, compound **(15)** found more active having MIC value of 0.78 µg/mL and its potency is better than first line anti-bacterial drug ethambutol (EMB, 1.56 µg/mL). Structure activity relationship (SAR) study revels that, compounds possessing cyclohexyl group at position 2- of the chromone ring favor better activity than piperidinyl moiety and aromatic substitution at position 4- of the triazole is favorable than alkyl substitution [53]. Shanmugavelan and co-workers carriedout the synthesis of 1,2,3-triazole derivatives *via* Huisgen’s 1,3-dipolarcycloaddition between alkyl/arylazides and diethyl/dimethyl acetylene dicarboxylate and screened for their *in vitro* anti-mycobacterial activity against *MTB* in Middlebrook agar medium supplemented with oleic acid-albumin-dextrose-catalase  (OADC) by agar dilution method. Compounds **(16a-c)**, and **(17)** having aromatic substitution evidenced MIC values of 3.13, 1.56, 3.13 and 3.13 µg/mL, respectively. The compound **(16b)**, with MIC 1.56 µg/mL is endowed with maximum potency, being 2.08 times more active than the standard drug EMB (MIC = 3.25 µg/mL) used. The halogen substitution on aromatic ring generally leads to the compounds having better activity in comparison with their counterparts having unsubstituted aromatic ring, and the compounds with alkyl substitution did not display any significant activity [54] (Fig. 4).

*Insert Figure 4*

Kim and co-workers studied 1*H*-1,2,3-triazoles derived from econazole as anti-TB agents. The hydroxy-triazole **(18)** derivative tends to exhibit more activity than ether-triazole derivative **(19)** [55]. The MIC value of **(18)** was as good as econazole (16 µg/mL), which is two-fold more active than econazole, suggesting that this 1,2,3-triazole scaffold could be further optimized to develop *MTB* specific agents. Kamal and co-workers synthesized nitrofuran-triazole conjugates and evaluated their anti-TB activity against *MTB H37Rv*. Compound **(20)** exhibited excellent anti-TB activity with MIC value of 0.25 µg/mL, which found four times more active than the standard anti-TB drug linezolid (1µg/mL) used. The SAR study reveals that, the phenyl ring with electron withdrawing groups like nitro, fluoro, chloro, trifluoromethyl improved the anti-TB activity. The compound with nitro group at *meta* position possesses slightly better activity with compared to its *para* counterpart. Substituents fluoro, trifluoromethyl and hydroxyl at *para* position conferred better activity, among these fluoro substituent (0.25 µg/mL) shows better activity compared with other subtitutents –OH (8µg/mL) and –CF3, while the methoxy substituent derivative did not display any significant effect [56] (Fig. 5).

*Insert Figure 5*

Phenothiazine-triazole hybrids were synthesized using click chemistry and screened for *in vitro* anti-mycobacterial activity against *MTB H37Rv*. Three analogs **(21-23)** found as most potent (MIC= 6.25 µg/mL) anti-TB agents with good selectivity index (SI). SAR study revels that, the increase in inhibition of *MTB* activity is attributed to the increase in alkyl chain length appended to 1,2,3-triazole nucleus. Compounds bearing electron donating (methoxy) group on phenyl ring **(22)** and bearing two fluoro substituents on phenyl ring **(23)** are most active derivatives [57]. Further, the synthesis of 1,2,3-triazole-adamantylacetamidehybrids for anti-TB activity against *MTB H37Rv* is reported. Compound bearing phenanthrene-substitution **(24)** found as the most active moiety inhibiting *MTB* and it is equipotent to anti-TB drug EMB (MIC 3.13 µg/mL) [58]. Jordão and co-workers reported synthesis of 1,2,3-triazole-4-carbohydrazide analogs and tested against *MTB*. The nitrofuran analog **(25)** found as the most potent candidate against the *MTB H37Rv* strain (MIC = 2.5 µg/mL) similar to or better than the current drugs in the market (EMB, MIC = 2 µg/mL). SAR study revels that, the nature of the arylhydrazone moiety found important to improve the biological activity. The presence of the furyl ring, the electronegative group (NO2), the low lipophilicity and small volume groups are important structural features for the anti-TB profile of these compounds [59] (Fig. 6).

*Insert Figure 6*

Analogues of benzothiazole-1,2,3-triazole conjugates were synthesized and screened for their anti-TB activity against *MTB* strain by broth micro dilution assay method. Compounds **(26a-c)** and **(27)** inhibited the growth of *H37Rv* strain at concentrations of 8 µg/mL. These compounds **(26, 27)** found even active in the concentrations 32-64 µg/mL. From SAR, the 2-mercaptobenzothiazoles conjugated to 1,2,3-triazole ring were more active when compared to the aromatic/aliphatic/cyclic secondary amines attached through an amide linkage. Chloro and nitro substitution **(26a-c)** on aromatic ring displayed potential activity. The bactericidal activities of these compounds demonstrated the utility of sulfur rich benzothiazoles as potent ligands against TB [60]. Naik and co-workers studied the potential of a series of bis-chromenyltriazole hybrids as anti-TB agents against *MTB* using micro plate alamar blue assay (MABA). Compounds **(28a-c)** found highly active with MIC of 6.25 µg/mL, which is comparable with standard drug streptomycin (MIC = 6.25 µg/mL). SAR study reveals that chloro and benzosubstituents on the coumarin ring have had remarkable impact on the anti-TB activity. Thus, these substituents reinforce the anti-TB activity of coumarin-triazole hybrids [61] (Fig. 7).

*Insert Figure 7*

In a contemporary study, benzothiophene, benzofuran and carbazole clubbed 1,2,3-triazoles derivatives are reported to inhibit *MTB*. Compounds with benzothiophene substitution, **(29)** and **(30),** possess the maximum *MTB* inhibitory activity with MIC value of 1.9 μM (0.78 μg/mL) and are 26 times more active than pyrazinamide (PZA, 6.25 μg/mL) and four times more active than EMB (1.56 μg/mL). From SAR, the order of the *MTB* inhibitory activity of the compounds with dibenzo-[b,d]thiophene series showed better activity compared with dibenzo[b,d]furan series and 9-methyl-9*H*-carbazole series [62]. Gallardo and co-workers described the synthesis of 1-alkyl-4-phenyl-[1,2,3]-triazole derivatives as anti-TB agents. Compounds **(31a-g)** displayed the highest activity against *MTB* with MIC of 3.1 μg/mL. The chiral derivatives did not show comparable *in vitro* activity than their racemic counterparts. The phenyl group at position 4 has a strong influence in determining the anti-TB activity [63] (Fig. 8).

*Insert Figure 8*

A series of enantiomerically pure azole derivatives bearing an imidazole as well as a triazole moiety were reported as anti-mycobacterial agents. The bromo derivatives **(32)** presented potential activity. One of the two enantiomers, namely ***(R)*-(32)**, with MIC =16 μg/mL evinced very promising anti-mycobacterial activity, showing a biological profile similar to econazole (12.5 μg/mL) and better than clotrimazole (20.4 μg/mL) [64]. Synthesis of glycoconjugates and their utilization with an objective to exert a fine control over a plethora of biological functions has been a key research area in recent times. The synthesis of new sugar-triazoles was reported by Singh *et al.,* The potential anti-TB effects of the synthesized compounds were investigated against virulent strains, *MTB* H37Rα, and *MTB* H37Rυ. Compound **(33)** depicted a moderate anti-TB activity with an MIC value of 12.5 µg/mL, while other compounds possess MIC values >12.5 µg/mL [65]. In a similar study, quinoline coupled 1,2,3-triazoles derivatives were synthesized by ‘click chemistry’ and screened for anti-TB activity against *MTB* by luciferase reporter phage (LRP) assay. Quinoline coupled triazole sugar hybrid, **(34)**, exhibited potent anti-TB activity against *MTB* strain with 76.41 and 78.37% reduction calculated based on percentage reduction in Relative Light Units at concentrations of 5 and 25 µg/mL, respectively. SAR study reveals that the introduction of the phenyl ring at the C-4 position of triazole induced reasonable inhibition against *MTB*. It was apparent that the introduction of bulky and lipophilic substituent such as phenyl exhibits potent inhibition against *MTB*. However, introduction of small hydrophilic substituent such as hydroxyl linked to the C-4 of triazole *via* methylene showed dramatic loss in potent inhibition against *MTB*. Pentoses or hexoses in the chair conformation with 3,4*-trans* diacetyl orientation such as quinoline glycoconjugate of D-galactose **(34)** (3*S*,4*R*), were generally more potent inhibitor than those with corresponding 3,4-*cis-*diacetyl orientation (3S,4S) among the saccharide coupled compounds [66] . Boechat and co-workers carriedout the synthesis of *N*-phenyl-1,2,3-triazole- isonicotinoyl hydrazide derivatives and were evaluated for anti-TB against *MTB H37Rv.* Derivatives of INH, 1*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. Compounds **(35a-c)** showed excellent anti-TB activity, compared with RIF (1 μg/mL). The substituent at the 4-position on the triazole was much more influential on inhibitory ant-TB activity than other positions [67] (Fig. 9).

*Insert Figure 9*

**1,2,3-Triazole: Structural requirements for anti-TB activity**

From the above publish date, it is found that the 1,2,3-triazole at all position with varied substituents has produced potent anti-TB activity. However, 2nd and 3rd position of the nuclei are unsubstituted. The 1-position of 1,2,3-triazole may be unsubstituted or substituents may vary from alkyl and aryl, heterocylcyclic groups. Among them, 1,2,3-triazoles with substituted alkyl chain (with 12- carbon chain), phenyl with halogen, chloro substituents on coumarin, chloro substituted benzothiazole, dibenzo-[b,d]thiophene showed promising activities. The 4- and 5-position of1,2,3-triazole nuclei are more because of the conjugation and substituents may range from functional groups like halogens, alkene linker, glycoconjugates, heteroaryl groups enhance the anti-TB activity ( Fig. 10).

*Insert Figure 10*

**1,2,4-Triazole derivatives for treatment of tuberculosis**

Seelam and co-workers reported the synthesis of 1,2,4-triazole-fused pyrazolo derivatives as anti-mycobacterial agents. The compounds with the electron withdrawing groups (-Cl, -NO2, -Br) have shown high activity against *MTB H37Rv*. Among the synthesized compounds **(36a-c)**, and **(37a-b)** demonstrated good anti-TB activity with MIC value of 3.125 µg/mL [68]. Diphenylamine containing 1,2,4-triazoles were synthesized by Krishna and co-workers as anti-mycobacterial agents. Compounds **(38a-c)** exhibited promising activity against *MTB H37Rv* strain with MIC value of 0.2, 1.6 and 3.125 µM respectively. Compound **(38a)** depicted anti-TB activity (0.2 µM) which is comparable to that of the standard drug INH (< 0.2 µM) and possess benzylidene amino group at position 4- and morpholino methyl group at position 2- of the 1,2,4-triazole ring system. Compounds with substituted phenyl ring at position 4- of the 1,2,4-triazoles confirmed reduced activity with compared to unsubstituted counterparts **(38a)** [69] (Fig. 11).

*Insert Figure 11*

Triazole-cycloalkanols were synthesized and evaluated for anti-TB activity against *MTB H37Rv*. Compounds **(39a-e)** with 5-pyridyl substituent on the alicyclic triazole ring demonstrated excellent anti-TB activity with MIC value in the range 0.59-0.95 µg/mL. Amongst these compounds, unsubstituted five and six membered alicyclic ring containing compounds, **(39a)** and **(39b)**, evinced almost equivalent activity (0.78 and 0.59 µg/mL respectively). Compounds with unsubstituted six membered ring showed slightly better activity than compound with trimethyl substituted six membered rings **(39c)**, and compound with dihydroxyl substituted six membered rings **(39d)** [70]. Patel and co-workers developed the synthesis of benzothiazol-1,2,4-triazole compounds and tested against *MTB H37Rv* by Lowenstein-Jensen (LJ) MIC method. Chloro substituted derivative **(40)** displayed pronounced anti-TB activity with a MIC value of 25 µg/mL). From SAR study, compounds with halogens, nitro, methoxy, and methyl containing 1,2,4-triazoles disclosed good activity against *MTB* [71]. Substituted triazolothiadiazole derivatives were synthesized from phenoxymethyl acids by Hunashal and co-workers. The compounds **(41a-c)** demonstrated good anti-TB activity against *MTB H37Rv* at MIC of 0.50 µg/mL, which is pronounced compared with standard drug RIF and INH which showed MIC of 0.25 µg/mL. The chloro at *ortho* and *para* position of the phenoxymethyl rings increases the anti-TB activity [72] (Fig. 12).

*Insert Figure 12*

Kucukguzel *et al.* reported a series of triazole-thiourea derivatives and tested for anti-mycobacterial activity against *MTB H37Rv* and *M. fortuitum*. Compound **(42)** found as the most potent candidate for this activity with a MIC value of 6.25 µg/mL and selectivity index of 1.6. From SAR studies it evident that the introduction of bulky groups led to a decrease in activity, due to a steric hindrance, which does not allow the compounds to reach with the active site [73]. Kakwani and co-workers reported the synthesis of a series of triazole-cinnamamide derivatives and screened against *MTB H37Rv* using resazurin microtiter assay (REMA) and results were compared with INH (1.8 µM). Compound with 3,4-dimethoxy **(43a)**, nitro substituent at meta position **(43b)** and with furan ring **(43c)**, evidenced promising anti-TB activity with MIC values of 4.6, 9.7 and 4.8 µM, respectively [74] (Fig. 13).

*Insert Figure 13*

Schiff’s base derivatives of triazole-thiazole conjugated compounds were described by Shiradkar *et al.,* as anti-TB agents against *MTB*. Compounds **(44a-b)** have been proven as the most active ones with MIC values of 0.78 and 0.39 µM, respectively [47]. Mundhe and co-workers reported the synthesis of substituted clubbed triazolyl-thiazole derivatives and tested their potential for anti-TB activity. Compound **(45)** (MIC = 0.04 µM) demonstrated potent activity, which is almost equipotent to INH (MIC = 0.03 µM) and without any notable cytotoxicity. By considering the activity of reported molecule that, Lepinski’s rule of five can be bend and molecules which do not obey it, can be treated as drug candidates [75]. 2-Substituted-thiazole clubbed 1,2,4-triazole were synthesized and evaluated for anti-TB activity against *MTB H37Rv* strain by broth dilution assay method. Compounds **(46a-b)** evinced comparatively good activity against all the tested microbial strains and displayed excellent inhibition towards *MTB H37Rv* at MIC 4 µg/mL [76] (Fig. 14).

*Insert Figure 14*

Benzothiazole-triazole-pyridine conjugated analogs reported by Rajani *et al.,* and evidenced for their *in vitro* anti-TB activity against *MTB* H37Rv strain using Lowenstein-Jensen medium. Compound **(47e)** containing 6-methoxybenzothiazole, showed superior activity (50 µg/mL) in the series against *MTB* and compounds **(47a,b)**, (**47d,e)**, and **(47h)** demonstrated good to moderate activity (50-62.5 µg/mL), which is attributed to the presence of 6-flouro, 6-bromo, 6-methyl, 6-methoxy and 4-nitro substituents. However, compound **(47j)** that is having inductively electron withdrawing but mesomerically electron releasing 4-chloro substituent on benzothiazole ring evinced relatively increased activity (25 µg/mL) [48]. Shiradkar and co-workers described the synthesis of trizole clubbed thiazole as anti-TB agents. Screening them *in vitro* for potential anti-mycobacterial activity yielded that the compounds having highly electronegative part at sulfhydryl group as new compounds endowed with anti-TB activity. Specifically, compounds **(48a-c)** shown the best activity, probably due to their ability to increase the penetration in the bacterial cell have [77]. Kaplancikli and co-workers studied alkylsulfanyltriazoles and their function as *in-vitro* anti-mycobacterial agents against *MTB H37Rv* in BACTEC 12B medium using a broth micro dilution assay and MABA, and results were compared with RIF. Compounds **(49a-b)** which are tethered with nitro- and bromophenyl-substitution respectively depicted the highest activity with 84% of inhibition. SAR study reveals that the, substitution on phenyl ring of the alkylsulfanyl moiety, affects the activity [78]. Further, 4-arylidenamino-4*H*-1,2,4-triazole-3-thiol derivatives were synthesized are reported as anti-TB agents. Compound **(50)** appended with nitro-groups and hydroxyl groups on the phenyl substitution showed the highest inhibition (87%) [79] (Fig. 15).

*Insert Figure 15*

Recently, Sarkar *et al.* reported propargylated 1,2,4-triazolethiols and their sulphones, corresponding 1,2,3-triazole derivatives as anti-TB agents against *M. bovis*BCG and *MTB H37Rv.* Compounds **(51-58)** found effective against both the stages (active as well as dormant) of the bacilli of *M. bovis* BCG and *M. tuberculosis*. These compounds of the invention are also useful in active as well as dormant phases of mycobacterium [80]. Westwood and co-workers carried out the synthesis of 1,2,4-triazole-3-thione derivatives and tested for tested for inhibitory effects on the growth of *M. bovis* BCG and *MTB H37Rv* as arylamine N-acetyltransferase (NAT) inhibitors. The nat gene and its associated gene cluster are almost identical in sequence in *M. bovis BCG* and *MTB*. The most potent triazole mimics especially compounds **(59a-d)**, the effects of deletion of the nat gene on growth, lipid disruption and intracellular survival. They conclude that screening a chemical library with NAT protein yields compounds that have high potential as anti-TB agents and that the inhibitors will allow further exploration of the biochemical pathway in which NAT is involved [81] (Fig. 16).

*Insert Figure 16*

**1,2,4-Triazole: Structural requirements for anti-TB activity**

From collected literature, 1,2,4-triazole also substituted at all position expect 3rd position, with varied substituents has produced potent anti-TB activity. The 2nd position of 1,2,4-triazole having substituted with morpholino methyl, sulfhydryl group displayed a good anti-TB activity. The 4- and 5-position of 1,2,4-triazole, substituents with benzylidene amino group, 4-pyridyl, dihydroxyl, phenoxymethyl, 3,4-dimethoxy, nitro substituent, furan ring, thiazole enhance the anti-TB activity (Fig. 17)

*Insert Figure 17*

**4. Conclusions and future aspects**

Tubercular infections pose a continuous and serious threat to human health and life in recent years. There has been an increased use of anti-TB agents and has resulted in the development of resistance. This has given rise to search for molecules acting on a novel target or a multi targeted combination therapy. With the increase in the number of new compounds screened against mycobacteria, the opportunity exists to develop a novel drug to cure and complete eradication of TB. Numerous outstanding achievements revealed that triazole-based compounds possess extensively potential anti-TB activity. Information provided in this review article is a result of compilation of the outcomes of research articles reporting anti-TB applications of triazole derivatives. This article is useful for further investigations on this scaffold in order to harness its optimum anti-mycobacterial potential. Moreover, rational design and development of the novel anti-TB agents incorporating this nucleus can help in dealing with escalating problems of the microbial resistance and also to meet the need for an effective anti-microbial therapy for the treatment of various deadly infectious diseases. Further research in this field will bring innovative pharmaceutical developments with a considerable spectrum of use.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

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**Abbreviations**

AIDS, acquired immunodeficiency syndrome; EMB, ethambuthol, GI, growth inhibition; HIV, human immunodeficiency virus, INH, isoniazid, LRP, luciferase reporter phage, MABA, micro plate alamar blue assay; *M. africanum, mycobacterium africanum; M. smegmatis (MS), mycobacterium smegmatis; M. bovis (MB), mycobacterium bovis, M. fortuitum (MF), mycobacterium fortuitum;* MIC, minimal inhibitory concentration; MTB,*mycobacterium* *tuberculosis (M.* *tuberculosis);* NAT, *N*-acetyltransferase inhibitors; PZA, prazinamide; REMA, resazurin microtiter assay; RIF, rifampicin; TB, tubercle bacillus.

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