Review article

The key players in the arsenal of combating TB; reviewing the lead InhA inhibitors

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Abstract:
After decades of decline, tuberculosis (TB) cases are continuously increasing worldwide, mostly in developing countries. Although it has not been regarded as fatal now, the TB situation may become worse with the appearance of multidrug resistant strains (MDR-TB) that do not respond to the most common anti-TB medications, isoniazid and rifampicin. In certain cases, even more severe drug-resistant TB may emerge. Extensively drug-resistant (XDR-TB), is a form of multidrug-resistant TB that also exhibits resistance to other anti-TB agents. The enoyl acyl carrier protein reductase (InhA) enzyme, a crucial regulator of TB mycolic acid biosynthesis, is attracting considerable attention as a druggable molecular target for combating TB and surmounting its resistance mechanisms. The current review covers the currently available anti-TB medications, including the most recently FDA-approved therapy, highlighting their modes of action. In addition, it provides brief structure-activity relationship data and resistance mechanisms halting their efficacy, with a special focus on InhA as an emerging anti-TB target, as well as an overviewing the most promising novel lead inhibitors classified according to their chemical entities.

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1. Introduction

Tuberculosis (TB) is believed to be one of the most infectious diseases caused by *Mycobacterium tuberculosis* (*Mtb*) (1). It has been the main cause of morbidity and mortality for centuries (1). According to the most recent WHO global records, about 1.6 million deaths worldwide were attributed to TB in 2021. Worldwide, TB is the second leading infectious killer after COVID-19 (above AIDS) (2). TB typically attacks the lungs but can also affect other parts of the body. It spreads through the air when people having an active TB infection cough or sneeze (3). The continuously increasing records of the disease especially in developing countries (4), together with the emergence of multi-drug resistant strains (MDR-TB) and the extensively drug-resistant (XDR-TB) TB (5) directed efforts to invest in designing novel inhibitors for targeting the critical TB pathways. The enoyl acyl carrier protein reductase (InhA) enzyme comes at the top of the list as a crucial regulator of TB mycolic acid biosynthesis. Herein, we firstly overviewed the currently available first, second-, and third-line anti-TB medications together with the recently approved FDA treatments, then we reviewed the druggability of InhA as an important molecular target, the structure-activity relationship of its lead inhibitors and the emerging resistance mechanisms.

1.1. Currently available medications for the treatment of tuberculosis.

The drug-susceptible TB cases can be efficiently treated using a combination of three or four medications of the first-line drugs. The currently used regimen involves a two-month course of isoniazid (INH), rifampicin, pyrazinamide, and/or ethambutol, then a four-month course of both isoniazid and rifampicin (6, 7). With the appearance of multidrug-resistant (MDR) as well as extensively drug-resistant (XDR) *Mycobacterium tuberculosis* (*Mtb*) strains, there is a high need to discover novel medications (Fig. 1)(6, 7).

![1. First-line anti-TB medications](1)

- Isoniazid, rifampicin, pyrazinamide and ethambutol.

![2. Second-line anti-TB medications](1)

- Fluoroquinolones and aminoglycosides.

![3. Third-line anti-TB medications](1)

- Bedaquiline and delamanid.

![4. FDA-approved anti-TB combination](1)

- Bedaquiline, pretomanid and linezolid.

![5. Recent advances in TB treatment (Direct InhA Inhibitors)](1)

- Triclosan and its derivatives, triazoles, GEQ analogs, pyrazoles and sulfonamides.

**Fig.1:** Drug development for treatment of TB.

1.1.1. First-line anti-TB medications.

1.1.1.1. Isoniazid (INH).

Isonicotinic acid hydrazide (INH) (Fig. 2) is a famous powerful antitubercular agent. It is a prodrug that must be activated by the bacterial catalase-peroxidase enzyme (KatG) present in *M. tuberculosis*, thus INH oxidation in the presence of NADH leads to covalent INH-NADH adducts formation which are powerful enoyl acyl carrier protein reductase (InhA) inhibitors that is involved in the synthesis of mycolic acids and are thus important for mycobacterial cell wall lipids synthesis (8).

1.1.1.2. Rifampicin (RMP).

RMP (Fig. 2) has a strong bactericidal and sterilizing effect on *M. tuberculosis*. Although RMP is reported to interfere with RNA synthesis via binding to the RNA polymerase β subunit leading to inhibition of this enzyme (9).

1.1.1.3. Pyrazinamide (PZA).

PZA (Fig. 2) is a prodrug requiring activation by the pyrazinamidase/nicotinamidase enzyme of *M. tuberculosis* to pyrazinoic acid. PZA exhibits several effects on *M.
tuberculosis through inhibiting the synthesis of pantothenate and co-enzyme A, in addition to interfering with membrane energy production.  

1.1.1.4. Ethambutol (EMB).  
EMB (Fig. 2) inhibits the arabinosyl transferase enzyme (encoded by embB), interfering with the cell wall arabinogalactan biosynthesis. When arabinogalactan synthesis is disrupted, mycolic acids can’t be transferred into the cell wall and the cell wall becomes more permeable.  

1.1.2. Second-line anti-TB medications.  
1.1.2.1. Fluoroquinolones.  
Fluoroquinolones such as ciprofloxacin and levofloxacin (Fig. 3) have been found to inhibit the topoisomerase II (DNA gyrase) that catalyzes the DNA supercoiling.  

1.1.2.2. Aminoglycosides.  
Aminoglycosides such as kanamycin and amikacin (Fig. 3) can inhibit protein synthesis by alteration at the 16S rRNA level.
1.1.3. Third-line anti-TB medications.

1.1.3.1. Bedaquiline.
Bedaquiline (Fig. 4) is the first member of a new class of drugs called diarylquinolines, which possess a novel mechanism of action. It inhibits the mycobacterial ATP synthase. Preclinical and clinical studies have shown that Bedaquiline has a potent activity against growing and non-growing mycobacterial populations, it is also active against MDR-TB strains (15).

1.1.3.2. Delamanid.
Delamanid (Fig. 4) is the first member of the dihydro-nitroimidazooxazole family to enter clinical trials. It is used along with other anti-tuberculosis medications for active multidrug-resistant tuberculosis. This drug works by inhibiting the mycolic acids production thus destabilizing the bacterial cell wall. Delamanid is a pro-drug that needs to be activated by the deazaflavin dependent nitroreductase enzyme. A reactive intermediate metabolite, formed between delamanid and desnitro-imidazooxazole derivative, is known to play a critical role in mycolic acid biosynthesis inhibition (16).

1.1.4. Recently FDA-approved anti-TB combination.
In 2019, The U.S. Food and Drug Administration (FDA) approved Pretomanid Tablets in combination with bedaquiline and linezolid (Fig. 5) for the treatment of highly resistant TB of the lungs (17). Clinical studies revealed that the regimen of bedaquiline–pretomanid–linezolid showed 90% activity against highly drug-resistant TB. However, the adverse effects due to linezolid dose were unacceptable. The proper linezolid dose and the treatment duration were investigated in order to lower toxic effects while maintaining anti-TB potency, where linezolid is used for 26 weeks at a dose of 600 mg according to the general risk/benefit ratio favored regimen (18).

Fig. 4: Third line antitubercular agents.

Fig. 5: Recent FDA anti-TB combination.
2. Resistance to the currently available anti-TB medications and their limitations.

*Mycobacterium tuberculosis* has been the leading global cause of human lethal infections and accounts lately for the greatest number of drug-resistant diseases by a single bacterial pathogen. Molecular mechanisms of drug resistance have been elucidated for the currently available medications. The two main resistance mechanisms are the mutation of certain drug-activating enzymes to prevent antitubercular drug activation or the alteration of the essential protein targets preventing the drug binding. Studying the drug resistance mechanisms in *Mycobacterium tuberculosis* could facilitate the development of novel anti-TB drugs (5). Moreover, Adverse effects are very common during the treatment of tuberculosis using the currently available medications. The most common drug-related adverse effects of anti-TB medications are listed in Table 1 (16, 19-21).

### Table 1: Common adverse effects of the currently available anti-TB medications.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Common adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Peripheral neuropathy, and hepatotoxicity</td>
</tr>
<tr>
<td>Rifampicin (high dose)</td>
<td>Renal, hepatic dysfunctions, and convulsions</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Hepatotoxicity, rash, and gout</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuropathy</td>
</tr>
<tr>
<td>Amikacin; Kanamycin</td>
<td>Otitotoxicity, and nephrotoxicity</td>
</tr>
<tr>
<td>Levofloxacin; ciprofloxacin</td>
<td>GI disturbances, tendinitis, and insomnia</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>Disturb the heart and liver function</td>
</tr>
<tr>
<td>Delamanid</td>
<td>Disturb the heart function</td>
</tr>
</tbody>
</table>

3. Enoyl acyl carrier protein reductase (InhA enzyme) as a main target for treating TB.

Mycolic acids are essential components of the unique mycobacterial cell walls, which help to fight against dehydration as well as hydrophobic drugs (22). Two discrete pathways of Fatty Acid Synthase (FAS) systems are involved in mycolic acids biosynthesis; mainly the FASI system (Co-A dependent) and the FASII system (Acyl Carrier Protein dependent).

The FASI pathway involves de novo synthesis of the fatty acids via elongation of the acetyl group by two carbon units giving precursors of 14-26 carbon atoms by using malonyl Co-A and acetyl Co-A. Monofunctional enzymes in the FASII system extend the FASI products to form precursors of mycolic acids. Firstly, the generated precursors of FASI are transformed into β-ketoacyl derivatives through the use of β-ketoacyl-ACP-synthase. In the second step, the product is reduced by β-ketoacyl-ACP-reductase which is subsequently transformed into an unsaturated derivative in the presence of β-hydroxy acyl-ACP-dehydratase. In the final step, the enoyl acyl carrier protein reductase (InhA) catalyzes the fatty acyl substrate reduction to give mycolic acids (23).

Interestingly, the FASII pathway enzymes do not exist in eukaryotes, thereby these enzymes would be safe and attractive clinically validated drug targets. One of these enzymes is InhA (Fig. 6) (24) which is essential for the mycolic wall biosynthesis and the survival of mycobacterial cells. The inhibition of InhA enzyme stops fatty acid elongation in mycolate production leading to cell lysis (25).

![Fig. 6: 3D Representation of InhA enzyme in cartoon view.](image-url)
The InhA active site involves the substrate binding loop (SBL: residues 197-226) as well as the NAD cofactor that interacts with the protein and the acyl substrate (or inhibitors) (26, 27). The InhA inhibitors include prodrugs such as INH which irreversibly interact with NAD forming an adduct (28), direct inhibitors like triazoles, diphenyl ethers, and triclosan involved in reversible binding to the NAD (29-31), or bulky inhibitors displacing the NAD like pyridomycin (32). Literature reports revealed that Tyr158 and Phe149 are the two key amino acids involved in the binding interactions (33).

INH is one of the most effective drugs inhibiting the InhA enzyme. INH is definitely a prodrug that needs to be converted to its active form, the isonicotinoyl radical, via an oxidative activation by the action of KatG enzyme (catalase-peroxidase). The isonicotinoyl radical permanently reacts with NAD cofactor forming an INH-NADH adduct that acts as the real InhA inhibitor (34). The 3D crystal structure of the InhA-isonicotinoyl complex shows that the adduct occupies a hydrophobic pocket (Fig. 7) (24, 35) which was validated as a main site to increase the inhibitory activity (36). Most of the INH resistance is mainly caused by the KatG point mutations rather than InhA itself. The S315 mutation of KatG accounts for about 50–95% of INH-resistant clinical isolates. INH resistance can also occur through mutations in the InhA active site preventing INH-NAD complex binding. While the mutations in the InhA enzyme account for some resistance, the great majority of clinically observed INH resistance is attributed to KatG mutations (37). The INH resistance then directed efforts to discover direct inhibitors that can bypass the essential activation step of INH (38, 39).

Among the introduced direct InhA inhibitors, triclosan (TCS) (Fig. 8) is a broad-spectrum antibacterial agent that was found in many pharmaceutical products. Unfortunately, TCS interferes with the endocrine function especially reproductive hormones which led to its withdrawal (40). TCS directly inhibits the InhA at low concentrations. The presence of three chlorine atoms on the TCS structure increases its lipophilicity while reducing its oral bioavailability leading to limiting its potential as an anti-tubercular medication (41).

The triclosan-InhA crystal structure reveals

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**Fig. 7:** (a) 2D and (b) 3D binding modes of isonicotinoyl-NADH complex inside InhA active site (PDB:1zid).
the engagement of the B-ring with both the Phe149 residue and the NADH cofactor nicotinamide group. H-bonding network was also observed between the TCS hydroxyl group and the ribose 2′-OH group of the NADH as well as the Tyr158 residue. In addition, the ether linkage forms a H-bond with the 2′-hydroxyl group of the ribose (Fig. 8a) (7). Interestingly, the X-ray crystal structure (PDB:1P45) conducted by Kuo et al. (42) declared that two triclosan molecules exist within the InhA active site (Fig. 8b). This occurrence was presumably due to a larger InhA substrate binding loop that can accommodate a bigger substrate. One TCS molecule occupies the same orientation and space as that of the previously shown triclosan-InhA complex. While the second molecule lies close to the first, interacting with the substrate binding loop through Vander Waals interactions (42).

![Fig. 8](image)

**Fig. 8:** (a) Representation of the key interactions of triclosan (red) bound to the InhA binding site & (b) A view of two molecules of triclosan (red) within the active site. NAD+ (magenta) and binding site residues (green).

Most of the InhA binding interactions are formed within the substrate-binding loop which extended from residues 197 to 226. This binding loop was only partially ordered in the subunit containing a single triclosan molecule. The superposition of both subunits of the single-bound versus the double-bound forms demonstrated significant backbone deviations in the substrate-binding loops directly contacting the triclosan molecule. In addition, it was found that the second triclosan molecule stabilized the substrate-binding loop. This may be explained by the *M. tuberculosis* enzyme's specificity to accommodate long fatty acyl substrates (C16 and larger). Interestingly, the mycobacterial InhA enzyme has a special hydrophobic substrate-binding loop (residues 197–226) that is almost ten residues larger than the corresponding *E. coli* binding loop (residues 203–212) (42).

Different classes of direct InhA enzyme inhibitors were identified including TCS and its derivatives (31, 34), triazoles (30, 43), GEQ analogs (44), pyrazoles (33, 45), and sulfonamides (46).

### 3.1. Triclosan analogs.

#### 3.1.1. Expanded triclosan and di-triclosan derivatives.

The two molecules of triclosan unexpectedly found within the active site of mycobacterial InhA enzyme became the strategy basis for the development of larger InhA inhibitors. Thus, expanded triclosan analogs and di-triclosan derivatives I–III were investigated as novel InhA inhibitors and anti-TB agents. These ether-linked derivatives displayed an excellent enzyme inhibitory activity which is comparable with the parent triclosan, while exhibiting moderate to low anti-TB activity. These derivatives provide promising opportunities as leads for additional optimization (7).
A docking study of the di-triclosan derivative III (Fig. 9) revealed that phenyl rings of the docked molecule formed $\pi-\pi$ stacking interaction with both Phe149 and the NAD cofactor. In addition, it displayed a hydrogen bond interaction between the hydroxyl group and the cofactor. Favorable Vander Waals interactions were also observed between the phenyl moiety and amino acids Ile215 and Leu218.

Fig. 9: Representation of the key interactions of compound III (blue) within the InhA binding site. NAD (green) and the binding site residues (brown).

3.1.2. Triclosan-based macrocyclic derivatives.

Based on the unexpected presence of two triclosan molecules at the InhA active site, novel macrocyclic derivatives were also investigated as inhibitors of InhA enzyme. These biaryl ether derivatives IV & V are the first macrocyclic direct InhA inhibitors that can bind to the active site exhibiting promising inhibitory activity. In addition, these macrocyclic compounds demonstrated a good antitubercular potency against *M. tuberculosis* H37Rv strain relative to that of the parent triclosan.

The docking study of compound V showed that this molecule was embedded deeply within the hydrophobic pocket near the cofactor with the bottom OH group directed to the other side away from Tyr158. This OH group displayed strong hydrogen bond interactions with both ribose and phosphate groups of the cofactor.

3.2. 1,4-Disubstituted-1,2,3-triazoles.

1,4-Disubstituted-1,2,3-triazoles are readily accessible via the azide-alkyne cycloaddition, in addition to their excellent stability and biological activity which rendered them promising drug core structures. Thus, the new strategies to synthesize compounds containing fused triazole derivatives are highly desirable.
3.2.1. α-Ketotriazoles and 1,4-dialkyl-substituted triazoles.

α-Ketotriazole derivative VI and 1,4-dialkyl-substituted triazoles VII & VIII were found to exhibit moderate InhA inhibitory activity as well as high antitubercular potency. It was observed that compounds having long alkyl chains showed the highest InhA inhibitory activity among these derivatives. The addition of lipophilic chains could promote more hydrophobic interactions with the enzyme pocket. In addition, this lipophilic chain which mimics the natural InhA substrate led to an increase in the binding affinity toward InhA enzyme (43).

3.2.2. Chromone based 1,2,3-triazole derivatives.

Chromone derivatives are frequently found in several therapeutically active medications such as anti-inflammatory and anti-microbial agents (48-50). In addition, 1,2,3-triazole-embedded heterocyclic derivatives displayed various biological activities, especially antimycobacterial activity (51-54). It was reported that chromone-linked 1,2,3-triazole analogs IX-XII showed a high inhibitory efficiency with MIC values ranging from 1.56 to 6.25 μg/ml against the Mycobacterium tuberculosis H37Rv (47). The preliminary structure-activity relationship studies of the chromone-linked triazoles revealed that compounds possessing bulky substituents such as 4-tert-butylphenyl group (compound IX) exhibited excellent antitubercular activity. In addition, the introduction of large aliphatic substituents (mimicking the InhA substrate) potentiated the activity as demonstrated by compounds X & XI (47). Also, it has been reported that combining the diaryl ethers with the chromone-based triazoles to obtain a hybrid structure (compound XII) led to the enhancement of antitubercular potency (30). The docking studies revealed that chromone-based triazoles possessed promising binding scores toward InhA enzyme when compared with the other target proteins. Compound IX formed π–π stacking with Phe149 (Fig. 10) (24). Similarly, compound XI displayed π–π interaction with both Trp222 and Tyr158 amino acids (Fig. 11) (24). These results indicate that π–π interaction could enhance the docking scores (47).

3.2.3. 1-Phenyl-4-substituted-1,2,3-triazole derivatives.

It was observed that the 1-phenyl 1,2,3-triazole analogs XIII-XVI displayed variable inhibitory activities against the Mycobacterium tuberculosis H37Rv strain. The substitution at the 4-position of the triazole ring was found to exhibit a major effect on antitubercular activity. Thus, it could be concluded that the reactivity order...
3.2.4. 1,2,3-Triazole incorporated benzothiazinone derivatives

Benzothiazinone incorporated 1,2,3-triazoles XVII-XIX were found to be promising inhibitors of *Mycobacterium tuberculosis* H37Ra. According to the structure-activity relationship study, the inhibitory activity depends on the type of substituents as well as their position on the phenyl ring. Both compounds XVII (possessing p-F) and XVIII (possessing m-Cl) exhibited moderate antitubercular activities with MIC values 29.24 and 27.34 μg/ml, respectively. Furthermore, changing the substituent position on the phenyl ring greatly affects the antitubercular activity. The introduction of the chloro substituent at the ortho position readily reduces the activity as demonstrated by compound XIX (MIC >30 μg/ml) (56).

3.3. Fluorene derivatives.

Genz-10850 molecule (also called GEQ) and GEQ analogs were identified as very promising InhA inhibitors. Although GEQ is a strong InhA inhibitor, it has a low potency against *M. tuberculosis* due to its limited permeability or the efflux pump’s activation (57). Hence, GEQ was chemically modified to
potentiate its poor biological activity through improving its membrane permeability or inhibiting the efflux pumps \(^{(44)}\). By substituting the phenyl group (compound \(XX\)) with an indole ring, the GEQ activity was significantly increased. In order to guarantee comparable binding interactions with the InhA binding site, the global GEQ scaffold (presence of fluorene moiety and piperidine carboxamide) was retained. In addition, compound \(XXI\), which has an extra hexyloxy group on the fluorene part, exhibited the highest activity against both \(M.\,\text{tuberculosis}\) growth and InhA enzyme. This alkyl group would increase the molecule’s activity and most likely facilitate more hydrophobic contacts with the binding site by somewhat imitating the native substrate. Interestingly, reserpine, verapamil, or carbonyl cyanide \(m\)-chlorophenylhydrazone (CCCP) are efflux pump inhibitors that enhanced the antitubercular activity of Genz-10850 (GEQ) and its derivatives. These findings supported the hypothesis that some efflux pump might be responsible for effluxing GEQ as well as its derivatives out of the mycobacterial cell \(^{(44)}\).

3.4. 1,3-Diphenyl pyrazole derivative.
Pyrazoles and their analogs are regarded as pharmacologically active agents which display nearly all pharmacological actions, they are also documented for their potent antitubercular activity \(^{(58-60)}\). Hence, pyrazoles are a promising choice for synthesizing new antitubercular agents.

3.4.1. Pyrazoloureia derivatives.
Pyrazoloureia conjugates were reported to exhibit promising inhibitory activity against \(Mycobacterium\,\text{tuberculosis}\,H37R\alpha\). The structure-activity relationship study revealed that the basic skeleton 1,3-diphenyl pyrazole scaffold is observed to possess remarkable antitubercular activity via InhA inhibition. Moreover, the substitution of the \(p\)-position of the \(N\)-phenyl urea with an electron-withdrawing group such as halogen or nitro substituent (compounds \(XXII\) & \(XXIII\)) greatly enhanced the antitubercular activity \(^{(33)}\).

3.4.2. Pyrazole embedded pyrazine derivatives.
It was observed that pyrazole-linked pyrazine analogs \(XXIV-XXVI\) showed remarkable antitubercular efficiency with MIC values ranging from 0.78 to 3.12 \(\mu\)g/ml. It was found that the substitution of the phenyl group at C3 of the pyrazole ring with a halogen atom led to prominent improvement in the inhibitory activity as demonstrated by compounds \(XXV\) and \(XXVI\) which displayed the highest potency among this series. This effect was attributed to the increase in lipophilicity of these compounds \(^{(61)}\).

3.4.3. Pyrazole incorporated thiazolo[3,2-\(a\)]pyrimidones derivatives.
1,3-Diphenyl pyrazole derivatives were found to exhibit potential anti-TB efficiency. Regarding the structure-activity relationship study, substitutions at the 1-phenyl group
may not be favorable for the activity. Hence, it should be kept as unsubstituted. Moreover, the position of substituents at the 3-phenyl group significantly affected the antitubercular activity, compound XXVII possessing p-methyl exhibited the least activity among this series, while methyl substitution at the ortho (compound XXVIII) or meta-position (compounds XXIX & XXX) of the 3-phenyl group displayed a favorable effect and a prominent enhancement in the inhibitory activity. In *M. tuberculosis* H37Rv screening, the most active derivative, compound XXIX, exhibited a minimum inhibitory concentration of 1.9 µg/ml. This compound also showed an excellent synergistic effect with the first and second-line medications used in tuberculosis screening (62, 63).

### 3.4.4. pyrazole-linked benzothiazole analogs.

It was reported that pyrazole-linked benzothiazole derivatives possessed excellent antitubercular potency. According to the structure-activity relationship investigation, compounds that have benzothiazole and pyrazole groups linked via hydrazine linkage XXXI & XXXII (MIC values 1.6 µg/ml) displayed the best activity compared with those possessing a carbohydrazide linkage XXXIII (MIC values 25 µg/ml). Regarding the hydrazine-linked derivatives, derivatives having p-CH₃ and p-Cl (compounds XXXI & XXXII, respectively) displayed the best anti-TB activity among this series (45).

### 3.5. Sulfonamide derivatives.

A series of sulfonamides has been developed as novel nanomolar InhA inhibitors via fragment-based design. Sulfonamide derivatives substituted with an aryl group such as tert-butyl phenyl (compound XXXIV) showed low activity against InhA enzyme. Replacing the aryl moiety with heterocyclic rings in compounds XXXV and XXXVI increased the InhA inhibitory activity. Moreover, compound XXXVII having a halogen atom and methyl substituent exhibited the highest activity among all tested derivatives (46).

The first-line anti-TB medication; isoniazid effectively inhibits InhA enzyme which is considered a crucial enzyme in mycolic acid biosynthesis. INH is a prodrug that forms NAD-INH adduct after being activated by the mycobacterial catalase-peroxidase KatG. Despite INH prominence as the most powerful antitubercular agent, mechanistic investigations revealed that KatG mutation is the main cause of INH resistance due to impaired activation. Thus, efforts are directed toward finding inhibitors that can skip the crucial activation step of INH. One of the newly developed direct InhA inhibitors is triclosan which is a broad-spectrum antibiotic with a promising InhA inhibitory profile. However, because of its poor absorption and endocrine toxicity, triclosan can’t be used as an antitubercular drug. Furthermore, different classes of novel antitubercular agents and potential direct InhA inhibitors were developed in order to overcome resistance such as expanded triclosan analogs, 1,2,3-triazoles, fluorene derivatives in addition to pyrazoles.

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