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Hydrazide–Hydrazones as Potential Antitubercular Agents: An Overview of the Literature (1999–2023)

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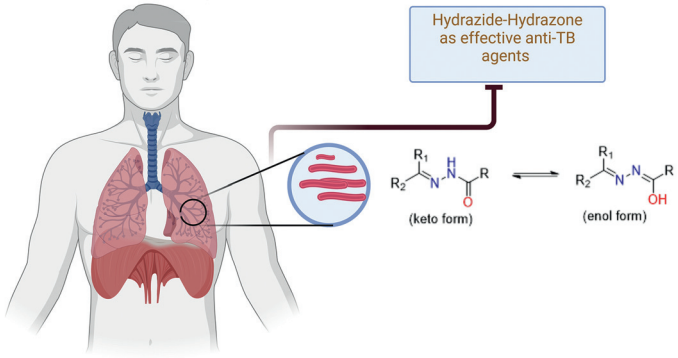
This article is dedicated to my lovely parents, and my younger brother Sagar Mali, who deep-heartedly supported me to achieve my goals.



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Abstract Hydrazide–hydrazone derivatives are prevalent in numerous bioactive compounds, showcasing a diverse array of biological effects including antibacterial, antitubercular, antifungal, anticancer, anti-inflammatory, anticonvulsant, antiviral, and antiprotozoal properties. Consequently, numerous medicinal chemists have undertaken the synthesis of various hydrazide–hydrazones, subjecting them to evaluation for their biological activities. Among these, antituberculosis activity stands out as a recurring focus in the scientific literature. This paper provides a comprehensive overview of research spanning the last 24 years (1999–2023), concentrating on the antituberculosis properties of hydrazide–hydrazone derivatives. The insights presented herein could serve as a valuable roadmap for the development of novel hydrazide–hydrazones with potential antimicrobial efficacy.

Key words hydrazide–hydrazone, antituberculosis, recent advances, tuberculosis

1 Background

In 2023, tuberculosis (TB) continued to pose a significant global health challenge as reported by the World Health Organization (WHO).[1] TB, an infectious disease, is responsible for the deaths of 1.5 million people every year throughout the world.[1,2] TB is caused by the pathogenic bacteria *Mycobacterium tuberculosis*. Despite being a preventable infectious disease, millions of people die every year.[1b] TB has emerged as a major cause of mortality from infectious diseases worldwide, surpassing HIV/AIDS (the human immunodeficiency virus).[1,2] The disease is prevalent in low- and middle-income countries, where more than 95% of TB deaths occur per year.[3] Additionally, TB is a significant contributor to antimicrobial resistance, with roughly 465,000 individuals worldwide developing drug-resistant TB in 2022.[1,4,5] TB is the main cause of HIV deaths and has contributed to anti-TB drug resistance. The WHO estimates that one-quarter of the world's population is infected with TB. As TB bacteria exist in replicating and dormant forms, it is challenging to develop novel anti-TB drugs. Anti-TB agents should act on both forms of the bacterium. Previously, we focused on the development of anti-TB drugs acting on the replicating forms; however, it is also important to develop drugs that act on and inhibit the dormant forms of *Mtb*. With the emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) strains, these infections have been amplified further and have become difficult to cure with conventional anti-TB therapy. Figure 1 illustrates the first-line anti-TB agents known to date.

Hydrazones [the active functional group (-C(=O)-NH-NH_2)] play a crucial role as intermediates in synthesizing diverse heterocyclic compounds, often exhibiting broad biological activities.[1b] These derivatives find extensive utility, serving as chemical preservatives for plants, pharmaceutical agents, key components in polymer manufacturing, adhesives in various industries, and more.[1b] Acid hydrazides and their derivatives are particularly valuable synthons for generating heterocyclic rings with five, six, or seven members, containing one or more heteroatoms. These compounds

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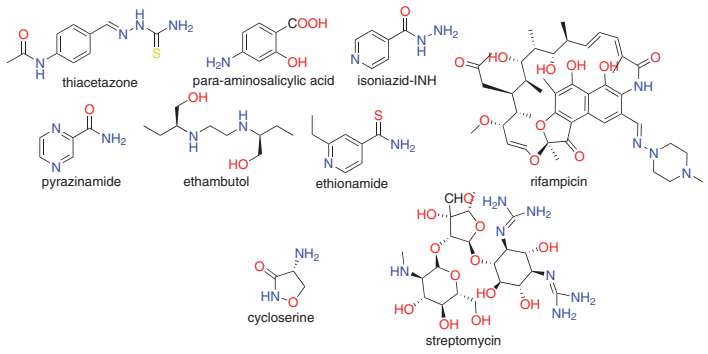

Figure 1 First-line anti-TB drugs, streptomycin, and others used in clinical therapy

have demonstrated notable effectiveness in various applications, including as antibacterial agents, pharmaceuticals, herbicides, antimalarials, antimycobacterial, anticonvulsants, anti-inflammatories, antidepressants, anticancer agents, antimicrobials,[1b] and dyes. Figure 2 lists drug moieties containing a hydrazide-hydrazone core.

2 Methodology and Search Strategy

This review focuses on a specific activity; namely, reported anti-TB agents containing hydrazides. For this, we carried out a literature survey from 1999 to 2024, using keywords such as 'hydrazides', 'hydrazones', 'antitubercular', 'anti-TB'. These keywords were queried using a range of databases such as, 'Scopus', 'PubMed', 'Web of Science', 'ScienceDirect', and 'GoogleScholar'. In total, 63 papers were selected and reviewed for the writing of this review article.

One recent review article covering recent advancements for hydrazones as anti-TB agents was published in the *Pharmaceuticals*.[1b]

Literature Survey

Küçükgüzel *et al.* (1999), studied hydrazones derived from 4-aminobenzoic acid hydrazones (the diazonium salts) and subsequently tested them for their anti-TB activity against *Mycobacterium fortuitum* ATCC 6841 and *H37Rv* strains.[1,2] Some of compounds (**1**–**3**) were found to be active against *M. fortuitum* ATCC 6841 at an MIC value ≈ 32 µg/mL (Figure 3). Subsequently, Cocco *et al.* (1999), presented the anti-TB activities of some new isonicotinoylhydrazones (**4**).[2] Their group also reported their pyridylmethyleneamino analogues and tested them against a clinically isolated *M. tuberculosis* INH resistant strain. Their results pointed out that there would be an increase in the activity if an amino group was positioned near the C=N bond. Further, Savini *et al.* (2002) demonstrated antimycobacterial activities of novel 4-quinolylhydrazones.[3] They identified two analogues, **5** and **6**, as the most active and evaluated them against both *M. avium* and *M. tuberculosis* strains.[3] Sriram *et al.* (2005) reported the synthesis of newer isonicotinoyl hydrazones and tested them for their antimycobacterial potential.[4] This synthesis was conducted using reactants such as *ortho*-hydroxy acetophenone and INH (isoniazid). The microplate alamar blue assay (MABA) protocol was used to assess the anti-TB activity against *M. tuberculosis H37Rv*. It was also noted that their compounds demonstrated strong antimycobacterial activity of 0.56–4.61 µM.

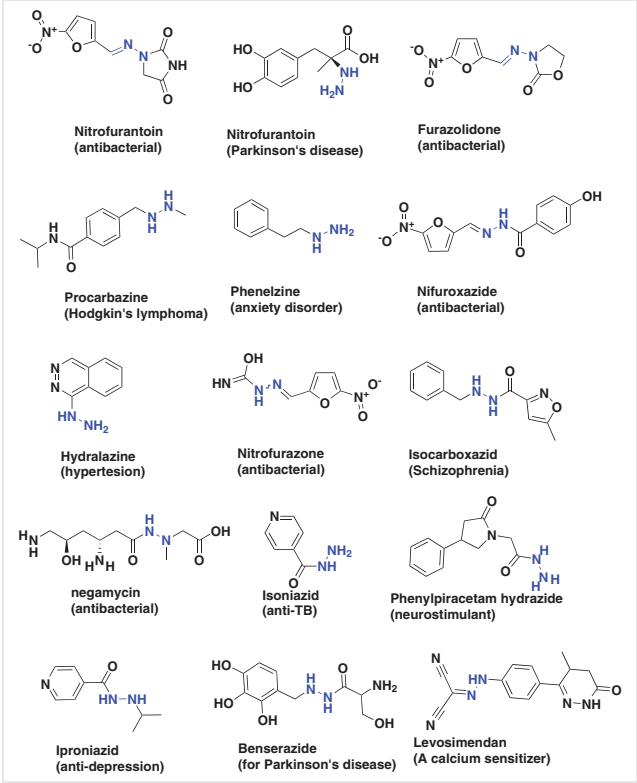

Figure 2 Marketed drug candidatures based on the hydrazide scaffold

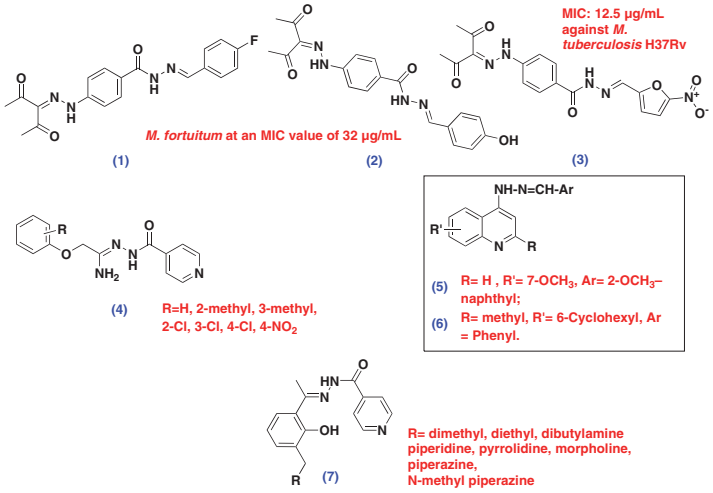

Figure 3

Among their synthesized compounds, compound **7** (with an MIC of 0.56 µM; INH: 2.04 µM) was found to be the most potent analogue.[4]

Sriram *et al.* (2006) designed and synthesized some new thiourea analogues having anti-TB activity (Figure 4).[5] Their anti-TB (*M. tuberculosis H37Rv* and INH resistant- *M. tuberculosis*) evaluation was based on the BACTEC 460 radiometric system. Among all synthesized hydrazones, compound **8** was found to be the most active analogue, with an MIC value of 0.49 µM against both aforesaid strains of *mycobacteria*. In search of potent anti-TB agents, 16 pyrrole enabled hydrazones were synthesized by Bijev (2006).[6] Among their synthesized pyrrole enabled hydrazones, nine compounds (**9**–**16**) exhibited activity against *M. tuberculosis* H37Rv at 6.25 µg/mL. It was also noted that increasing the lipophilicities of the compounds would not always result in increased activity.[6]

Imramovský *et al.* (2007) proposed a new way to design and synthesize newer anti-TB analogues (**17**) by connecting standard drugs such as ETH (ethambutol) and (CPX) ciprofloxacin (Figure 5).[7] An interesting review on the biological activities of hydrazones up to 2007 was published by Rollas and Kucukguzel.[8] Joshi *et al.* (2008) screened a series of hydrazides originating from heterocyclic ring systems such as oxadiazoles and triazoles. The antimycobacterial activity was conducted using the standard broth dilution assay against *M. tuberculosis H37Rv*. Compounds **18**–**21** displayed good antimycobacterial activities with MIC values of 31.25 µg/mL.[9]

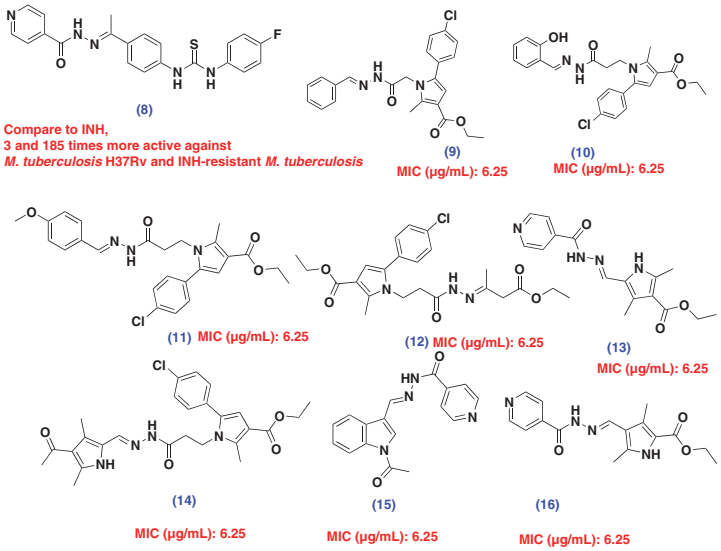

Figure 4

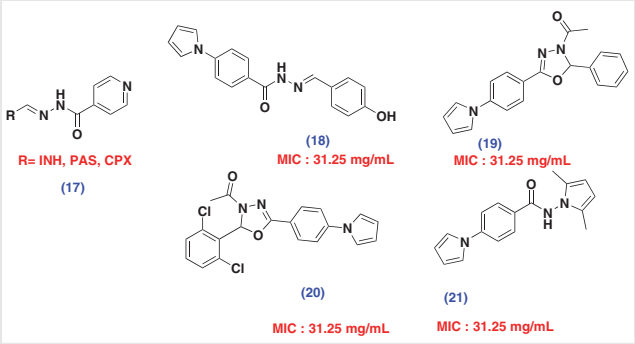

Figure 5

Raparti *et al.* (2009) exploited the synthesis of some newer benzohydrazides analogues wherein they further evaluated all compounds for their anti-TB activity using the luciferase reporter phages (LRP) (Figure 6).[10] Moreover, they also studied quantitative structure–activity relationship (2D-QSAR) analysis to see how physicochemical properties corresponded with the observed biological activity. Two compounds, **22** and **23**, were found to be most potent against *M. tuberculosis* H37Rv.

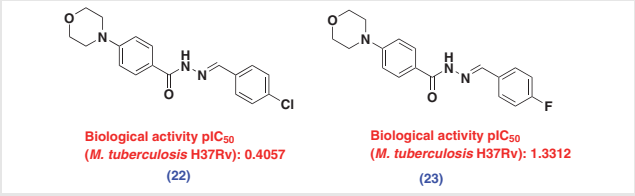

Figure 6

In another attempt, Kaymakcioglu *et al.* (2009) screened a set of hydrazones synthesized from 4-fluorobenzoic acid hydrazide against *M. tuberculosis* H37Rv (Figure 7).[11] As per their results, compound **24** demonstrated the highest inhibitory activity. The most potent analogue had 85% inhibition and contained a 2,6-dichlorophenyl group. Candéa *et al.* (2009) reported 21 analogues obtained from 7-chloro-4-quinolinylhydrazones.[12] It was found that three compounds from this series (**25**–**27**) had lower cytotoxic profiles with good MIC values at 2.5 μg/mL compared to standard anti-TB drugs such as rifampicin (2.0 μg/mL) and ETH (3.12 μg/mL).[12] A series of compounds bearing a 4-quinolylhydrazone moiety was reported by Gemma *et al.* (2009), and these were tested for antitubercular activity at 6.25 μg/mL concentration.[13] It was noted that many of their compounds, such as **28**, showed 100% inhibitory activity at 6.25 μg/mL concentration against *M. tuberculosis*. Some indole-based hydrazones (**29**) were synthesized and investigated by Sonar and Crooks (2009).[14] They examined a range of hydrazone and 3-nitrovinyl analogues derived from indole-3-carboxaldehydes and related compounds for their ability to inhibit *Mycobacterium tuberculosis* H37RV. Screening was conducted using the microplate alamar blue assay (MABA) in BACTEC 12B medium. Several compounds exhibited significant inhibitory activity against *M. tuberculosis* in initial screening assays, demonstrating potency at a concentration of 6.25 μg/mL.

Raja *et al.* (2010) intended to exploit antimycobacterial activities of diphenyl hydrazones and semicarbazones (Figure 8). The agar double dilution (ADD) method was employed to assess the anti-TB activities of said compounds. Compound **30** depicted 80% inhibition (MIC >6.25 mg/mL) against *M. tuberculosis* H37Rv strain.[15]

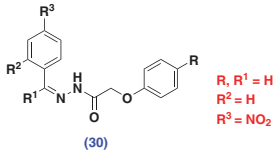

Figure 8

Sankar and Pandiarajan (2010) attempted the synthesis of new isonicotinoylhydrazones.[16] Some of their compounds having a -OCH_3 group in *meta*-position of the aromatic ring demonstrated good antimycobacterial activity compared with standard drug INH as tested by the lucifer-

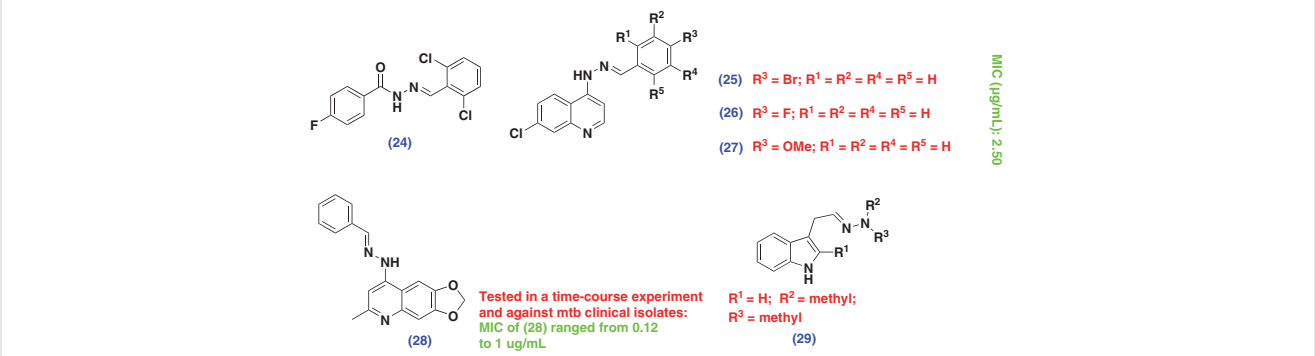

Figure 7

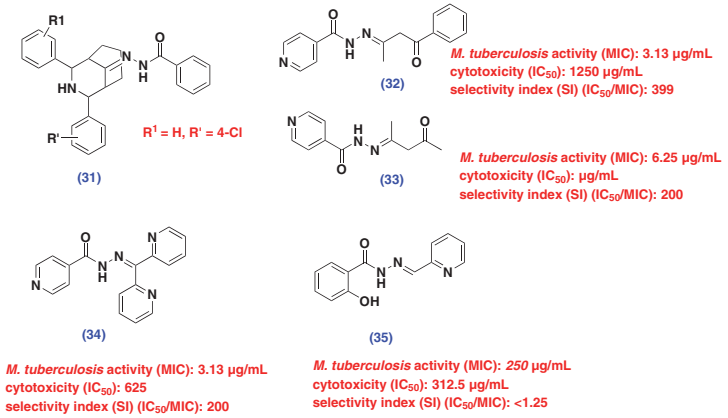

Figure 9

ase reporter phage (LRP) assay (Figure 9). Among the synthesized compounds, four compounds (**31**; R^1 = H, R^2 = 4-Cl, 4-F, 3-Cl, 4-OCH_3) exhibited inhibition of all microbial strains of bacteria and fungi. Pavan *et al.* (2010) successfully synthesized hydrazones based on a carbazone moiety such as thiosemicarbazone.[17] In-vitro cytotoxicities on J774 cells were also reported in the study. Hydrazide/hydrazones **32**–**35** were identified as best in-vitro candidates against *M. tuberculosis* and showed results comparable to those of the standard '1st line' or/and '2nd line' anti-TB drugs, when the authors carried anti-TB activity tests using the resazurin microtiter assay (REMA).[17] Their results suggested that compounds with higher lipophilicity had maximum activity. Furthermore, it was also identified that replacing the sulfur in the thiosemicarbazone with an oxygen atom, resulted in decreased anti-TB activity.[17]

Eswaran and colleagues conducted a study in which they synthesized quinoline-clubbed analogs (compound **36**) and assessed their *in vitro* antituberculosis activity against three distinct strains of *Mycobacterium* (Figure 10).[18] They used the standard MDA method (broth microdilution) to test against *Mycobacterium*. Their analysis revealed that the introduction of a -CF_3 at position 8 substantially increased the biological activity, wherein analogues with a -F substituent resulted in reduced activity. Furthermore, in the same year, the authors also evaluated a newer set of quinoline-based hydrazones (**37**) by adapting a multistep synthesis protocol.[19] Within the series, it was observed that at the R1 position, the incorporation of an imidazole or 4-methyl imidazole moiety resulted in enhanced anti-TB activity. Bijev and Georgieva (2010) analyzed antimycobacterial potentials of some pyrrole-based hydrazones and subsequently evaluated their various physicochemical parameters such as Log P, MW, and molar refractivity.[20] It was also found that compounds with moderate molecular surface would likely result in enhanced anti-TB activity. Their findings suggested that the compounds with moderate molecular surfaces exhibited the highest level of activity. This conclusion was supported by the analysis of different physicochemical molecular descriptors. Another study by Sriram *et al.* (2010) described anti-TB activities of some furoic acid hydrazones tested using the ICL assay (*M. tuberculosis* isocitrate lyase). The active compound **38** exhibited potent activity for ICL inhibition at 10 µM.[21]

Vavříková *et al.* (2011) synthesized fluorine-substituted hydrazones that were active against multi-drug-resistant tuberculosis strains (Figure 11).[22] From their study, a total of nine compounds demonstrated good results against MDR-TB (MIC: 0.5 µg/mL). Two compounds, **39**, exhibited strong activity against *M. kansasii* (MIC: 1–4 µmol/L) with non-cytotoxic profiles. Subsequently, Pinheiro *et al.* (2011)

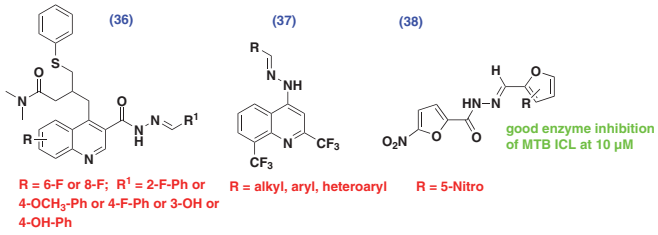

Figure 10

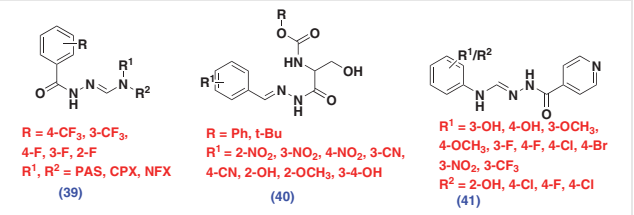

Figure 11

reported a new set of l-serinyl hydrazones **40** and evaluated them for antitubercular potentials.[23] Some INH-hydrazones **41** were also studied by Vavríková *et al.* (2011).[24]

Thomas *et al.* (2011) tested a series of quinoline-3-carbohydrazides against *M. tuberculosis* H37Rv (Figure 12).[25] Amongst the evaluated analogues, six compounds **42**–**47** demonstrated promising activity. The authors also conducted molecular docking analysis and their results suggested that their compounds interacted with enoyl-ACP reductase.[25]

Utku *et al.* (2011) and Almasirad *et al.* (2011), reported compounds **48** and **49**, respectively (Figure 13).[26,27] All compounds were tested against *Mtb* H37Rv using the agar proportion method and MABA assay, respectively. In the first case, it was found that electron-withdrawing groups on the aryl (-Ar) moiety had substantial effects on the biological activity in the second case, the importance of the -NO_2 group attached to the heteroaryl moieties was highlighted. Some other interesting reviews on hydrazones published in that year covered a variety of hydrazones acting as antimycobacterial agents.[28–30]

In another attempt to design and synthesize newer carbohydrazides, Telvekar *et al.* (2012) carried out the synthesis of benzofuran-based carbohydrazides and tested them for their anti-TB activities using the REMA assay (Figure 14).[31] Among the tested compounds, two benzofuran-based compounds, **50** and **51** were found to be most promising and were active against both *Candida albicans* and *Mtb*.

In another study reported by Coelho *et al.* (2012), 23 hydrazones derived from isonicotinic hydrazide were tested against three INH-resistant *Mtb* strains (Figure 15).[32] One of the compounds, **52**, presented the best activity (MIC: 0.98 μg/mL) against *Mtb*. Cihan-Üstündağ and Çapan (2012), screened a set of indole hydrazides **53**–**57**;[33] however, their compounds exhibited lower anti-*Mtb* activity than the control standard (MIC: 0.125 μg/mL).

In their study, Naveen Kumar and colleagues (2014) designed and evaluated InhA inhibitors based on isonicotinic acid hydrazide and evaluated them against *Mtb* H37Rv and two human clinical isolates (Figure 15).[34] Compound **58** showed excellent anti-TB activity, with a MIC of 0.096 μM against the *Mtb* H37Rv strain and 0.049 μM against both human clinical isolates (*Mtb*-1 and *Mtb*-2).[34] The compound had a high lipophilicity, as indicated by its Log *P* value of 8.02, and the estimated LD_{50} was >5000 mg/kg BW. Compound **58** was found to be six times more potent than isoniazid.[34]

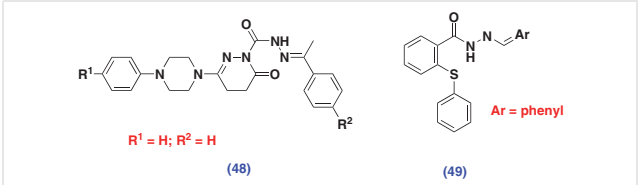

Figure 13

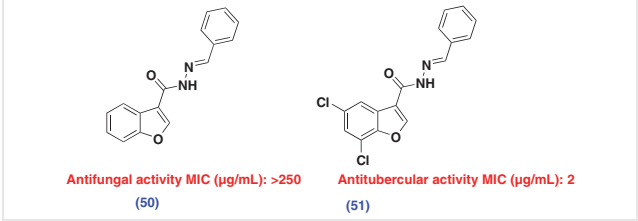

Figure 14

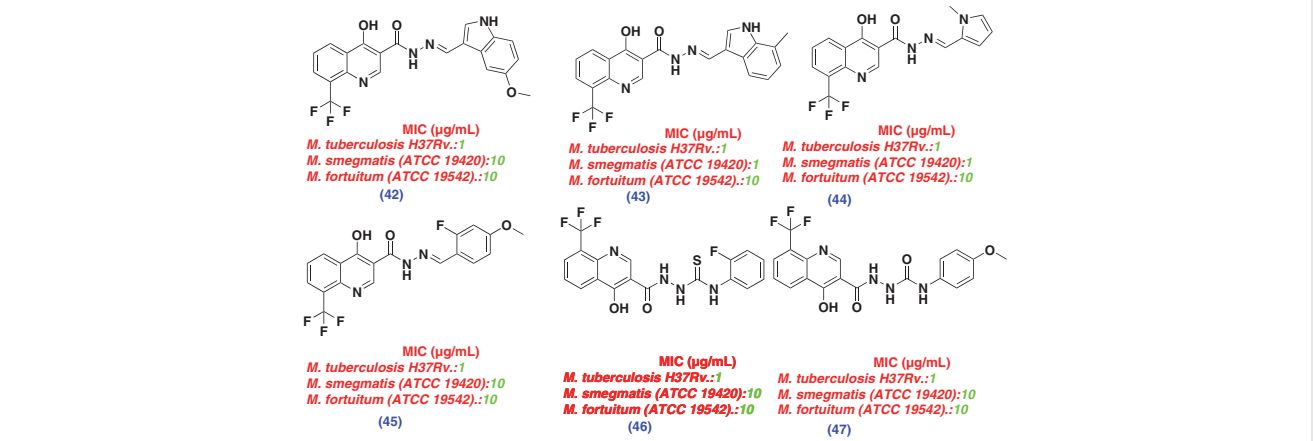

Figure 12

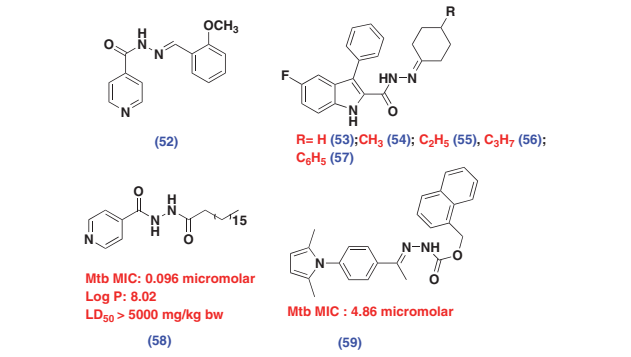

Figure 15

In an investigation conducted by More *et al.* (2014),[35] 52 novel pyrrole hydrazine analogues were synthesized to specifically target the critical InhA (enoyl-ACP reductase) enzyme (Figure 15). The authors[35] proposed, based on the binding model analysis, that the pyrrole hydrazones had H-bonding interactions with the InhA enzyme. The lead compound identified was compound **59**,[35] which exhibited a MIC of 0.2 μg/mL (4.86 μM) and was found to have the same binding site as PT70 and TCL.

Pahlavani *et al.* (2015) identified and reported hydrazones derived from isonicotinyl hydrazide (Figure 16).[36] Analogue **60** showed trong activity against *Mtb* H37Rv with an MIC value of 4 μg/mL. However, the activity of **60** was far less than standard INH (MIC: 0.025 μg/mL).

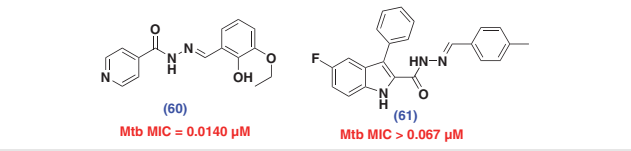

Figure 16

A previous literature analysis suggested that many hydrazones reported in 2016 had quite interesting anti-*Mtb* activity, especially covered by Unissa *et al.* (2016)[37] and John *et al.* (2016).[38] Cihan-Üstündă *et al.* (2016) exploited the synthesis of newer indole-based hydrazones and tested them for their anticancer and anti-*Mtb* activities (Figure 16).[39] Compound **61** exhibited anti-*Mtb* activity with MIC greater than 25 μg/mL (0.067 μM). Velezheva *et al.* (2016) investigated a series of hydrazides-hydrazones derived from indole-pyridine (Figure 17).[40] They reported antimycobacterial activities on two strains of *Mtb* (H37Rv and CN-40).[40]Among examined analogues, compound **65** presented the best activity (MIC: 0.05 μg/mL).[40]

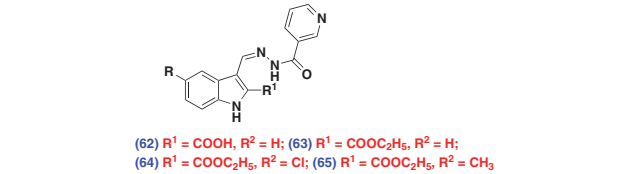

Figure 17

Angelova et al. (2017) reported hydrazide-hydrazones of heterocyclic moieties such as 2*H*-chromene, coumarin, and pyrazol-4(1*H*)-one cores (Figure 18).[41] Overall, 22 compounds were synthesized and tested against *Mtb* H37Rv strain. Compound **66**[41] was observed to have a lower MIC of 0.13 μM, which was surprisingly 11× more potent than standard INH (MIC: 1.45 μM).[41] Additionally, they reported pyrazol-based hydrazones, wherein compound **67** was the most active (MIC: 0.32 μM).[42] Some newer tosyl hydrazones were also investigated by Concha *et al.* (2017).[43] These compounds were submitted for anti-*Mtb* analysis with *Mtb* mc26230 strain. It was found that these tosyl hydrazones **68** (MIC: 183 μM) were less active than the standard drug INH. Isoniazid derivatives with phenolic or heteroaromatic frames were synthesized via mechanochemical methods by Oliveira *et al.*[44] Activity against *M. tuberculosis* was also assessed, highlighting compounds such as phenolic hydrazine **69a** and heteroaromatics **69b–d** as more potent molecules than isoniazid.[44] Selected derivatives, including **69a** and **69d**, exhibited high activity against *M. tuberculosis* MDR clinical isolates, with compound **69d** showing a selectivity index of >1400 on MRC5 human fibroblast cells.[44]

In 2018, Bonnett *et al.*[45] examined a class of hydrazone compounds active against non-replicating *Mtb*. Among the studied compounds, compound **70** exhibited a MIC of 14 ± 7 μM against *Mtb* (Figure 19). The authors also analyzed the same compounds using the low-oxygen-recovery assay (LORA). Compound **70** had IC_{90} values of 22 ± 12 μM and 6.4 ± 2.4 μM, respectively for anaerobic and aerobic conditions. Nogueira *et al.* (2018), studied varieties of hydrazone analogues bearing a vitamin B6 moiety.[46] Compound **71** presented activity at 10.90 μM concentration, wherein compound **72** was found to have a minimum inhibitory concentration value at 72.72 μM.

In another study, Angelova and Simeonova (2019)[47] carried out an extended study on female mice for compound **73** (MIC: 0.3969μM) to establish its effects on various functions of the liver and kidneys (Figure 19). Three doses (100, 200, and 400 mg/kg bw) were administered to mice for a period of two weeks, wherein INH was used as a control. It was noticed that compound **73** did not have any impact when checked against various biochemical parameters. Sampiron *et al.* (2019) evaluated various hydrazones against *Mtb*. Interestingly, analogue **74** had a MIC of 4.98 μM.[48]

Ghiano *et al.* (2020) synthesized 30 tosyl *N′*-acryl-hydrazones, which were subsequently tested against *Mtb* H37Rv strain (Figure 20).[49] Notably, among the tested compounds, *E*-isomers **75–77** presented the most promising anti-*Mtb* activity (MIC ≤10 μM). The authors also carried out molecular docking simulations to establish binding

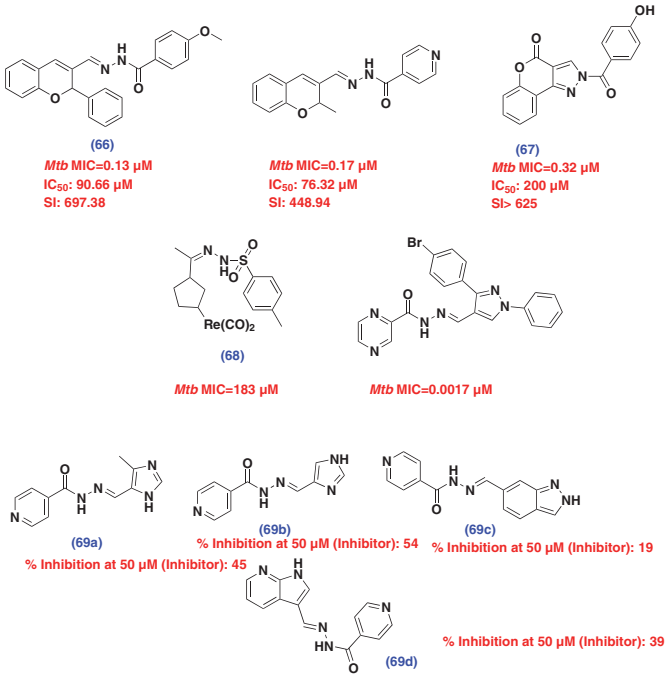

Figure 18

mechanisms underlying the activity. Amino acid residues, Tyr158 and Ile194 were found to be crucial for the biological activity.

Compound **78** reported by Hassan *et al.* (2020), was found to have the lowest MIC value at 0.78 µg/mL (Figure 21).[50] Similarly, compounds (**79–81**) displayed 4 µg/mL MIC (control, RIF: MIC: 3.038 µM) values when tested using the broth microdilution (BMD) method as reported in a study by Sruthi *et al.* (2020).[51]

In 2020, Desale *et al.* attempted to synthesize halogen-containing 2-aryloxyacetohydrazones and tested them for their antimycobacterial activities (3.125–100 µg/mL).[52]All the synthesized compounds were found to have a strong affinity towards enoyl reductase. Compound **82** was obtained as a best-docked candidate with –8.058 kcal/mol docking

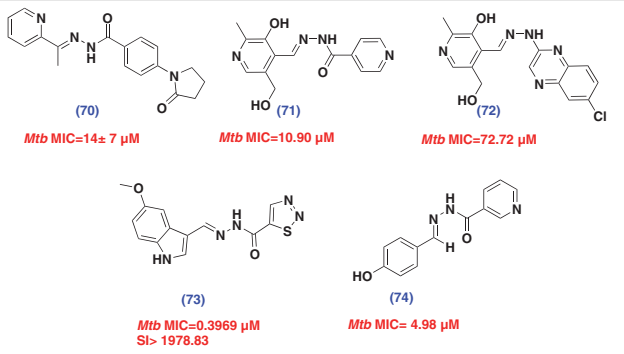

Figure 19

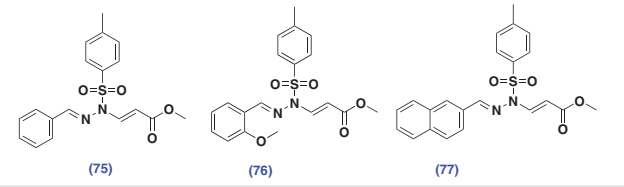

Figure 20

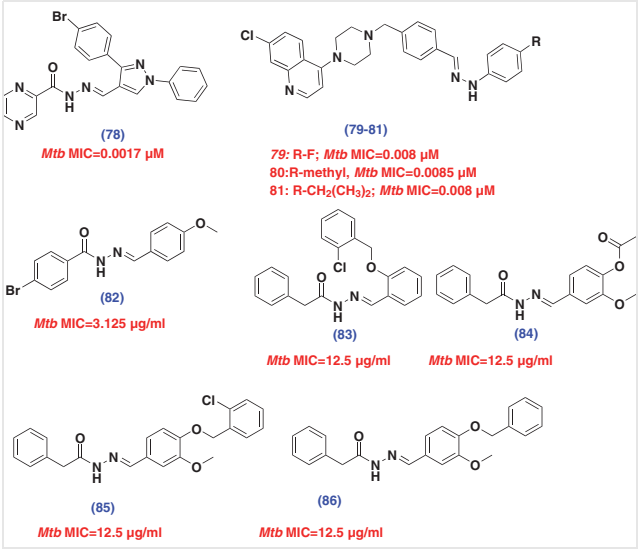

Figure 21

score (Figure 21). Subsequently, Thorat *et al.* (2020) designed and prepared a newer set of hydrazones **83–86** with moderate anti-*Mtb* activity with MIC value of 12.5 μg/mL.[53] Padmini *et al.* (2021) analyzed antitubercular activities of new hydrazones bearing pyrazole acetamide cores (Figure 22). Their results suggested that compound **87** had a promising anti-*Mtb* MIC value of 3.12 μg/mL.[54] Molecular docking analysis with these compounds highlighted the importance of H-bonding with key amino acid residues for a target InhA. Further, Faria *et al.* (2021) conducted the synthesis and examined the anti-*Mtb* activities of alkyl hydrazides and hydrazones.[55] Molecules **88** and **89** both had MIC values of 0.3 μM. They were also found to have moderate anti-*Mtb* activity for the H37RvINH strain with values >128 μM and 128 μM, respectively. A novel isatin hydrazone, **90**, was reported by Karunanidhi *et al.* (2021).[56] Some isonicotinoylhydrazine moieties **91** were reported by Pflégr *et al.* (2021).[57] Thorat *et al.* (2021) carried out the synthesis of 10 new hydrazones from benzohydrazides. All compounds **92** showed MIC values in the range 3.125–50 μg/mL against the *Mtb* H37Rv strain.[58]

Gobis *et al.* (2022) examined antimicrobial activities of hydrazones of methyl 4-phenylpicolinimidate (Figure 23).[59] The lead analogue **93** had an MIC value of 0.009 μM against two *Mtb* strains (sensitive and resistant). A whole-cell-based screening was performed by Briffotaux *et al.* (2022),[60] to assess the anti-*Mtb* potentials of hydrazine-hydrazones bearing an adamantine moiety **94**. Compounds **95** and **96** were found to have promising anti-*Mtb* activities as reported by Akki *et al.* (2022) and Abdelhamid *et al.* (2022), respectively.[61,62] Lone *et al.* (2023) examined hydrazones of butanoic acid **97** for their anti-*Mtb* activity and found that compound **97** was active against H37Ra and H37Rv strains with MIC values of 0.0042 μM each.[63]

Summary

In summary, this article provides an overview of the antitubercular properties of hydrazide-hydrazones reported since 1999. The study highlights the versatility of the hydrazide-hydrazone structure, which can be incorporated into diverse bioactive compounds. Therefore, this review underscores the significance of advancing hydrazide-hydrazones for their potential as antitubercular/antimycobacterial agents. Other potential reviews (from different time periods)[64–76] were also found in the literature for various bioactivities of hydrazide-hydrazone; however, they lack full coverage of articles having anti-TB activity.

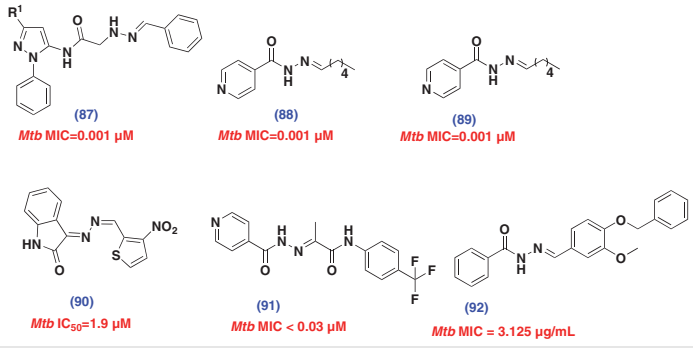

Figure 22

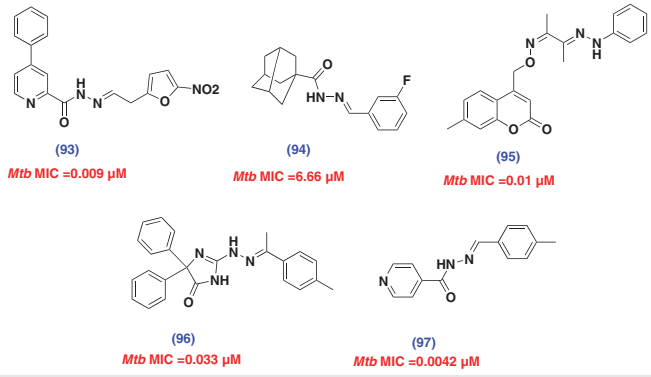

Figure 23

Conflict of Interest

The authors declare no conflict of interest.

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