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Hydrazide–hydrazones as potential antitubercular agents: overview of the literature (1999-2023)

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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 undertake 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 scientific literature. This paper provides a comprehensive overview of research spanning the last twenty-four 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.

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Hydrazide–hydrazones as potential antitubercular agents: overview of the literature (1999-2023)

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Abstract Hydrazide–hydrazones are prevalent in numerous bioactive compounds, showcasing a diverse array of biological effects including antibacterial, antitubercular, antifungal, antitumor, anti-inflammatory, antimicrobial, antiviral, and antiprotozoal properties. Consequently, numerous medicinal chemists undertake 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 scientific literature. This paper provides a comprehensive overview of research spanning the last twenty-four years (1999-2023), concentrating on the antituberculosis properties of hydrazide–hydrazones derivatives. The insights presented herein could serve as a valuable roadmap for the development of novel hydrazide–hydrazones with potential antimicrobial efficacy.

Keywords Hydrazide–hydrazones; Anti-TB; 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 (tuberculosis), an infectious disease is responsible for deaths of 1.5 million people every year throughout the world.1,2 TB is caused by pathogenic bacteria called "Mycobacterium tuberculosis". Despite being a preventable infectious disease, millions of people die every year.16 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 occurred in the same year.3 Additionally, TB is a significant contributor to antimicrobial resistance, with roughly 465,000 individuals worldwide developing drug-resistant TB in 2022.1,45 TB is the main cause of HIV deaths and is being contributed to anti-Tb drug resistance. WHO estimates the presence of one-quarter of the world's population infected with TB. As TB bacteria exist in the replicating and dormant forms, it becomes challenging to develop a novel anti-TB drug. Anti-Tb agents should act on both forms of the bacterium. Previously, we were just focusing on the developments of anti-TB drugs acting on the replicating forms, whilst it is also important to develop drugs acting and inhibiting 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 became difficult to cure with the conventional anti-TB therapy.

Figure 1 illustrates the first-line anti-TB agents known so far.

Fig. 1. First-line anti-tubercular drugs, streptomycin, and others used in clinical therapy.

Hydrazones [the active functional group (-C(-)=O-NH-NH2)] play a crucial role as intermediates in synthesizing diverse heterocyclic compounds, often exhibiting broad biological activities.16 These derivatives find extensive utility, serving as chemical preservatives for plants, pharmaceutical agents, key components in polymer manufacturing, adhesives in various industries, and more.16 Acid hydrazides and their derivatives are particularly valuable synths for generating heterocyclic rings with five, six, or seven members, containing one or more heteroatoms. These compounds have demonstrated notable effectiveness in various applications, including as antibacterial agents, pharmaceuticals, herbicides, antimalarials, antimycobacterial, anticonvulsants, anti-inflammatory, antidepressants, anticancer agents, antimicrobials16, and dyes.

Figure 2 enlist list of drug moieties containing hydrazide-hydrazine core in them.
2. Methodology and Search Strategy

This review in particular focuses on specific activity, i.e., as anti-TB reported for hydrazides. For this, we carried out literature survey from 1999 to 2024, using the keywords, 'Hydrazides'; 'hydrazones'; 'Antitubercular'; 'Anti-TB', etc. These keywords were queried using the varieties of databases such as, 'Scopus', 'PubMed', 'Web of Science', 'Science Direct', 'GoogleScholar', etc. In total, 63 papers were selected and reviewed for the writing of review article.

One recent review article covering a recent advancement for hydrazones as anti-TB was published in the Pharmaceuticals.10

Literature Survey

Küçükgüzel et al. (1999), studied hydrazones derived from 4-aminobenzoic acid hydrazides (the diazonium salts) and subsequently tested 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. Subsequently, Cocco et al. (1999), presented anti-TB activities of some new isonicotinoylhydrazones (4). Their group also reported their pyridinemethylneamino analogues and tested against a clinically isolated M. tuberculosis INH resistant strain. Their results were pointed out the fact that there would be increase in the activity if we place amino group near to C=N bond. Further, Savini et al. (2002) in their study demonstrated antimycobacterial activities of novel 4-quinolylhydrazones. They identified two analogues (5, 6) as most active and evaluated against both M. avium and M. tuberculosis strains.3 Sriram et al. (2005), reported the synthesis of newer isonicotinyl hydrazones and tested for their antimycobacterial potentials.4 This synthesis was conducted using reactants such as ortho-hydroxy acetophenone and INH (isoniazid). The MABA (Microplate Alamar Blue assay) protocol was used in order to assess the anti-TB activity against M. tuberculosis H37Rv. It was also noted that their compounds demonstrated strong antimycobacterial activity ranging from 0.56-4.61 μM. Among their synthesized compounds, compound (7) (an MIC of 0.56 μM; INH: 2.04 μM) found to be most potent analogue.4

Sriram et al. (2006), designed and synthesized some new thiourea analogues having anti-TB activity.5 Their anti-TB (M. tuberculosis H37Rv and INH resistant- M. tuberculosis) evaluation was based on the the BACTEC 460 radiometric system. Among all synthesized hydrazones, compound (8) was found to be 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, 9 compounds (9-16) depicted anti- M. tuberculosis H37Rv activity at 6.25 μg/mL. It was also noted that increasing the lipophilicities of compounds would not always give activities in incremental trends.6

Imramovský et al. (2007), proposed a new way to design and synthesis of newer anti-TB analogues (17) via connecting standard drugs such as ETH (ethambutol), and (CPX) ciprofloxacin, etc. An interesting review6 on biological activities of hydrazones till year 2007 was published by Rollas and Kucükğuzel. Joshi et al. (2008), screened a series varieties of hydrazides originating from heterocyclic ring systems such as oxadiazole, triazole, etc. The antimycobacterial activity was conducted using standard broth dilution assay against M. tuberculosis H37Rv. Compounds (18-21) represented good antimycobacterial activity results at MIC value of 31.25 μg/mL.9 Ruparti et al. (2009), exploited synthesis of some newer benzohydrazides analogues wherein they further evaluated all compounds for their anti-TB activity using the LRP (luciferase reporter phages).10 Moreover, they had also studied 2D-QSAR (Quantitative structure–activity relationship) analysis to see how physicochemical properties were in agreements with an observed biological activity. Two compounds (22, 23) were found to be most potent against M. tuberculosis H37Rv.

In yet another attempt, Kaymakcioglu et al. (2009), screened a set of hydrazones synthesized from 4-fluorobenzoic acid hydrazide against M. tuberculosis H37Rv.11 As per their results, compound (24) demonstrated the highest inhibitory activity. The most potent analogue had 85 % inhibition and contains a 2,6 dichlorophenyl group in it. Candéa et al. (2009) reported various 21 analogues obtained from 7-chloro-4-quinolylhydrazones.12 It was found that three compounds (25-27) from this series had lower cytotoxic profiles with good MIC values at 2.5 μg/mL compared to std anti-TB drugs such as rifampicin (2.0 μg/mL) and ETH (3.12 μg/mL).12 A series of compounds bearing 4-quinolylhydrazide moiety was reported by Gemma et al. (2009), and tested for its’ antitubercular activity at 6.25 μg/mL concentration.13 It was noticed that many of their compounds (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 synthesized and tested a range of hydrazide 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. The ADD (agar double dilution) method was employed in order 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

Sankar and Pandiarajan (2010) attempted synthesis of new isonicotinoylhydrazones.16 Some of their compounds having -OCH3 group in m-positions of aromatic ring demonstrated good antimycobacterial activity than std. drug INH as tested by LRP (luciferase reporter phage) assay. Among all synthesized compounds, four compounds (31) (R= H, R=Cl, 4-Cl, 3-Cl, 3-4-OCH3) resulted inhibitions of all microbial strains of bacteria and fungi. Pavan et al. (2010) successfully synthesized some hydrazones based on carboxane moiety such as thiosemicarbazones, etc.17 This study also reported in-vitro cytotoxicities on J774 cells. Hydrazide/hydrazones (32-35) were identified as best in-vitro candidates against *M. tuberculosis* and showed results comparable with standard ‘14 line’ or/and ‘2nd line’ anti-TB drugs, when authors carried anti-TB activity using REMA assay (the Resazurin Microtiter Assay).17 Their results suggested that compounds with higher lipophilicity had maximum activity. Furthermore, it was also analyzed that replacing ‘Sulphur’ from ‘thiosemicarbazone’ with ‘oxygen’ atom, results 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 anti-tuberculosis activity against three distinct strains of *Mycobacterium*.18 They used the standard MDA method (broth micro dilution) to test against *Mycobacterium*. Their analysis revealed that introduction of a -CF3 at position 8 substantially increased the biological activity, wherein analogue with a -F substituent resulted in decrement in activity. Furthermore, in same year, they had 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 R1 position, if we incorporate an imidazole or 4-methyl imidazole moiety it would result in enhanced anti-TB activity. Bijev and Georgieva (2010), analyzed antimycobacterial potentials of some pyrrole-based hydrazones and subsequently, evaluated for their various physico-chemical parameters such as Log P, MW, molar refractivity, etc.20 It was also found that compounds with moderate molecular surface would likely to 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 physical-chemical molecular descriptors. Another study by Sriram et al. (2010), described anti-TB activities of some furoic acid hydrazones tested using ICL assay (*M. tuberculosis* isocitrate lyase). The active compound (38) represented potent activity for ICL inhibition at 10 μM.21

Vavříková et al. (2011), synthesized fluorine-substituted hydrazones active against multi-drug resistant tuberculosis strains.22 From their study, in total of 9 compounds demonstrated good results against MDR-TB (MIC: 0.5 μg/mL). Two compounds, (39) depicted strong activity against *M. kansasii* (MIC: 1–4 μmol/L) with non-cytotoxic profiles. Subsequently, Pinheiro et al. (2011), reported a new set of l-serinyl hydrazones (40) and evaluated them for antitubercular potentials.23 Some INH-hydrazones (41) were also studied by Vavříková et al. (2011).24

Thomas et al. (2011), tested a series of quinoline-3-carboxyhydrazides against *M. tuberculosis* H37Rv.25 Amongst all evaluated analogues, six (42-47) compounds demonstrated promising activity. Authors have also conducted molecular docking analysis and their results suggested that their compounds had interaction with enoyl-ACP reductase.25

Utku et al. (2011) and Almasirad et al. (2011), reported compounds (48) and (49), respectively.26,27 All compounds were tested against *Mtb H37Rv* using the agar proportion method and MABA assay, respectively. In first case, it was found that electron withdrawing groups on aryl (-Ar) moiety had substantial effects on the biological activity, while in second case, an importance of -NO2 group attached to heteroaryl moieties were highlighted. Some other interesting reviews on hydrazones published in year 2011 covered varieties of hydrazones acting as antimycobacterial agents.28,30

In yet another attempt to design and synthesize newer carboxyhydrazides, Telvekar et al. (2012), carried out synthesis of benzofurin based carboxyhydrazides and tested them for their anti-TB activities using REMA assay.13 Among tested compounds, two benzofurin-based compounds (50, 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), studied 23 hydrazines derived from isonicotinic hydrazide and tested against 3 INH-resistant *Mtb* strains.31 One of compounds (52) represented the best activity (MIC=0.98 μg/mL) against *Mtb*.

Cihan-Üstündag and Çapan (2012), screened a set of iodine hydrazides (53-57).31 However, their compounds exhibited lesser 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 against *Mtb H37Rv* and 2 human clinical isolates.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*).35 The compound had a high lipophilicity, as indicated by its Log P value of 8.02, and the estimated LD50 was > 5000 mg/kg BW. Compound (58) was found to be six times more potent than isoniazid.34

In an investigation conducted by More et al. (2014),52 novel pyrrole hydrazine analogues were synthesized to specifically target the critical InhA (enoyl-ACP reductase) enzyme. The authors53 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), which exhibited a MIC of 0.2 μg/mL (4.86 μM) and was found to have same binding site (as P770 and TCI).

Pahlavani et al. (2015), identified and reported hydrazones derived from isonicotinyl hydrazide.54 Analogue (60) showed a strong 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).

A previous literature analysis suggested that many hydrazones reported in year (2016) had quite interesting anti-Mtb activity, especially covered by Unissa et al. (2016)37 and John et al. (2016).38 Ghan-Üstünda et al. (2016), exploited synthesis of newer indole based hydrazones and tested them for their antituberculosis and anti-Mtb activities.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.40 They reported antituberculosis activities on 2 strains of Mtb (H37Rv and CN-40).40 Among examined analogues, compound (65) depicted the best activity (MIC 0.05 μg/ml).40

Angelova et al. (2017), reported hydrazide-hydrazones of heterocyclic moieties such as 2H-chromene, coumarin and pyrazol-4(1H)-one cores.41 Overall, 22 compounds were synthesized and tested against Mtb H37Rv strain. Compound (66)41 was observed to have lower MIC as of 0.13 μM, which was surprisingly 11 X more potent than std. INH (MIC: 1.45 μM).41 Additionally, they also reported pyrazol-based hydrazones, wherein compound (67) was found be most active (MIC 0.32 μM).42 Some newer tosyl hydrazones were also investigated by Concha et al. (2017).43 These compounds were subjected 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 mecanochemical methods by Oliveira et al. (2017).44 Activity against M. tuberculosis was also assessed, highlighting compounds like phenolic hydrazine (69a) and heteroaromatics (69b), (69c), and (69d) 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 >1400 on MRCS human fibroblast cells.45 In 2018, Bonnett et al.45 examined a class of hydrazones compounds active against non-replicating Mtb. Among studied compounds, compound (70) depicted a MIC of 14 ± 7 μM against Mtb. Authors also analyzed the same compounds using LORA (the low-oxygen-recovery) assay. Compound (70) had IC₅₀ values of 22 ± 12 μM and 6.4 ± 2.4 μM, respectively for anaerobic and aerobic settings. Nogueira et al. (2018), studied varieties of hydrazine analogues bearing vitamin B₆ moiety.46 One compound (71) represented an activity at 10.90 μM concentration, wherein compound (72) found to have a minimum inhibitory concentration value at 72.72 μM.

In another study, Angelova and Simeonova (2019)47 carried out the extended study on female mice for the compound (73) (MIC = 0.3969 μM) to see how it affects on various functions of the liver and kidneys. 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) didn’t show any kind of impact when checked against various biochemical parameters. Sampiron et al. (2019), evaluated various hydrazones against Mtb. Interestingly, analogue (74) showed minimal MIC value at 4.98 μM.41

Ghiano et al. (2020), 30 tosyl N’-acyl-hydrazones, which subsequently tested against Mtb H37Rv strain.48 It was worthy to note that among all compounds, E-isomers represented promising anti-Mtb activity (MIC ≤10 μM) (75-77). Authors also carried out molecular docking simulations to establish binding 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), found to have lowest MIC value at 0.78 μg/ml.50 Similarly, compounds (78-81) displayed 4 μg/ml MIC (control, RIF: MIC= 3.038 μM) values when tested using BMD method (broth microdilution) 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 further for their antituberculosis activities (3125-100 μg/ml).52 All synthesized compounds were found to have strong affinity towards enoyl reductase. Compound (82) was obtained as a best docked candidate with -8.058 kcal/mol docking score. Subsequently, Thorat et al. (2020), designed and prepared 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. 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 importance of H-bonding with key amino acid residues for a target InhA. Further, Faria et al. (2021), conducted synthesis and anti-Mtb activities of alkyI hydrazides and hydrazones.55 Molecules (88) and (89) had an MIC value of 0.3 μM each. They were also found with moderate anti-Mtb activity for 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 Pflegr et al. (2021).57 Thorat et al. (2021), carried out the synthesis of 10 new hydrazones from benzohydrazides. All compounds showed an MIC value in the range of 3.125-50 μg/ml (92) against Mtb H37Rv strain.58

Gobis et al. (2022), examined antimicrobial activities of hydrazones of methyl 4-phenylpyrimidine.59 The lead analogue (93) depicted an MIC value of 0.009 μM against 2 Mtb strains (sensitive and resistant). A whole-cell-based screening was performed by Briffoutaux et al. (2022),60 to assess the anti-Mtb potentials of hydrazine-hydrazones of adamantane moiety (94). Compounds (95) and (96) were found to have a promising anti-Mtb activities as reported by Akhd 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. Compound (97) was found to be active against H37Ra and H37Rv strains with MIC value 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 antibacterial/ antimycobacterial agents. Other potential reviews (from different time periods)65-76 were also found in the literature for various bioactivities of hydrazide-
hydrazone; however, they lack full coverage of articles having anti-TB activity.

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**Conflict of Interest**

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**References**

List of Structures to be placed in manuscript

(1) M. herbicide at an MIC value of 32 μg/mL

(2) M. herbicide at an MIC value of 1.5 μg/mL, against M. aborescens H37Rv

(3) 

(4) Re: diethyl, diethyl 2-methyl, 3-methyl, 2-Cl, 3-Cl, 4-Cl, 4-NO2

(5) R= H, R'= 7-OCH3, Ar= 2-OCH3-naphthyl;
R= dimethyl, R'= 6-Cyclohexyl, Ar= Phenyl

(6) 

(7) Re: dimethyl, diethyl dibutyramine piperidino, pyrrolidine, morpholine, piperazine, N-methyl piperazine
### Biosketches

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