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

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

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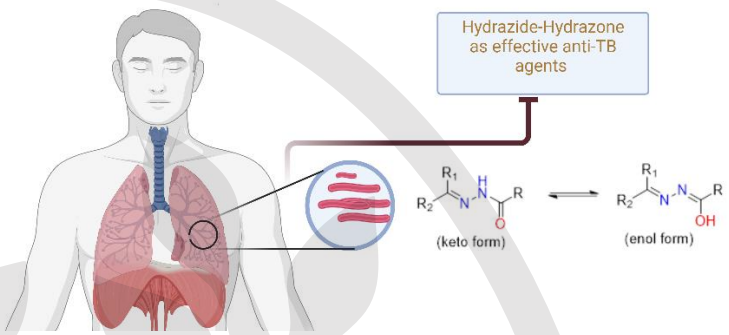
*This article is dedicated to my lovely parents, and my younger brother **Sagar Mali**, who deep-heartedly supported me to achieve my goals*



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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 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.

Key words Hydrazide–hydrazone; 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[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 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.[1,4,5] 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.

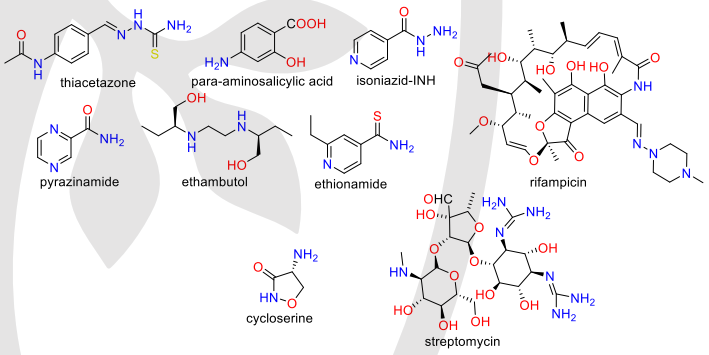

Fig. 1. First-line anti-tubercular drugs, streptomycin, and others used in clinical therapy.

Hydrazones [the active functional group (-C(=O)-NH-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 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** enlist list of drug moieties containing hydrazide-hydrazone core in them.

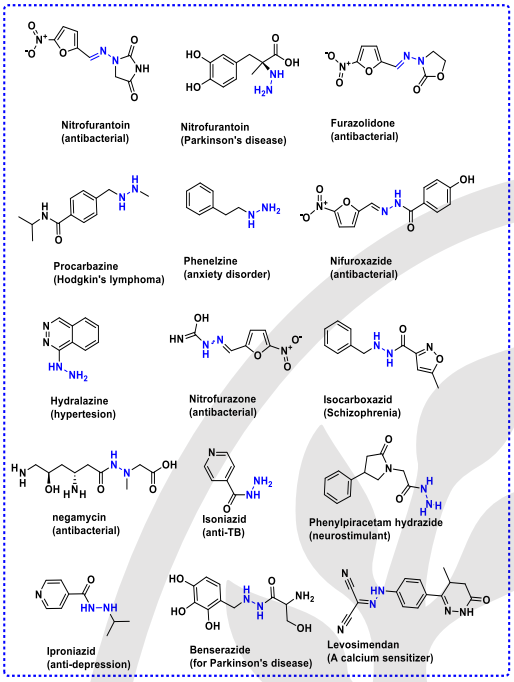

Fig. 2. Marketed drug candidatures based on hydrazide scaffold.

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', 'ScienceDirect', '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*[1b].

Literature Survey

Küçükgüzel *et al*. (1999), studied hydrazones derived from 4-aminobenzoic acid hydrazones (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)**.[2] Their group also reported their pyridylmethyleneamino 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 isonicotinoyl 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.[7] An interesting review[8] on biological activities of hydrazones till year 2007 was published by **Rollas and Kucukguzel**. **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 syntesized 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-quinolinylhydrazones.[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-quinolylhydrazone 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 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. 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 -OCH_3 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^1= H, R^2=4-Cl, 4-F, 3-Cl, 4-OCH_3) resulted inhibitions of all microbial strains of bacteria and fungi. **Pavan *et al.* (2010)**, successfully synthesized some hydrazones based on carbazone 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 '1st 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 antituberculosis 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 -CF_3 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 **Vavríková *et al.* (2011)**.[24]

Thomas *et al.* (2011), tested a series of quinoline-3-carbohydrazides 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 -NO_2 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 carbohydrazides, **Telvekar *et al.* (2012)**, carried out synthesis of benzofuran based carbohydrazides and tested them for their anti-TB activities using REMA assay.[31] Among tested compounds, two benzofuran-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 hydrazones derived from isonicotinic hydrazide and tested against 3 INH-resistant *Mtb* strains.[32] One of compounds **(52)** represented 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 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).[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]

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. 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 same binding site (as PT70 and TCL).

Pahlavani *et al.* (2015), identified and reported hydrazones derived from isonicotinyl hydrazide.[36] 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] **Cihan-Üstündağ *et al.* (2016)**, exploited synthesis of newer indole based hydrazones and tested them for their anticancer 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 antimycobacterial 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 mechanochemical methods by **Oliveira *et* al.**[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 MRC5 human fibroblast cells[44]. In 2018, **Bonnett *et al.*** [45] examined a class of hydrazone 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 IC_{90} values of 22 ± 12 µM and 6.4 ± 2.4 µM, respectively for anaerobic and aerobic settings. **Nogueira *et al.* (2018)**, studied varieties of hydrazone 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 effects 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. [48]

Ghiano *et al.* (2020), 30 tosyl N'-acryl-hydrazones, which subsequently tested against *Mtb* H37Rv strain.[49] It was worthy to note that among all compounds, *E*-isomers represented promising anti-*Mtb* activity (MIC ≤10 µM) **(75-77)**. Authors had 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 antimycobacterial activities (3.125-100 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 highelighted 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 alkyl 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 **Pflégr *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-phenylpicolinimidate.[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 **Briffotaux *et al.* (2022)**, [60] to assess the anti-*Mtb* potentials of hydrazine-hydrazones of adamantine moiety **(94)**. Compounds **(95)** and **(96)** were found to have a 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. 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 antitubercular/ 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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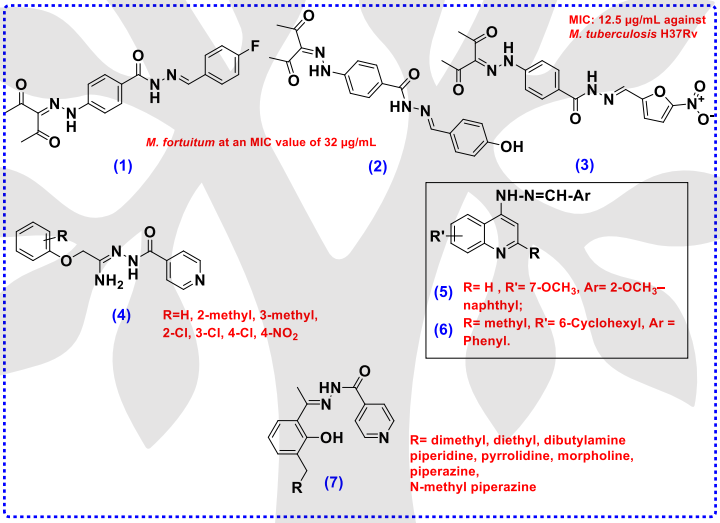
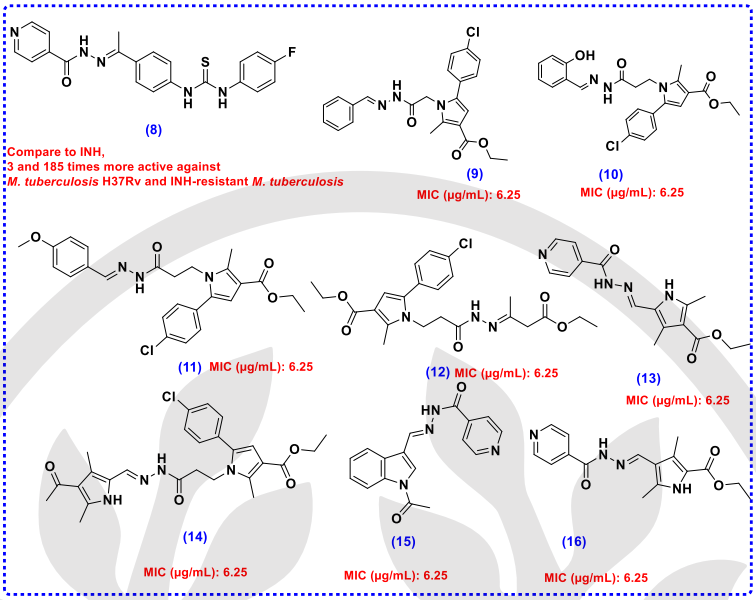
References

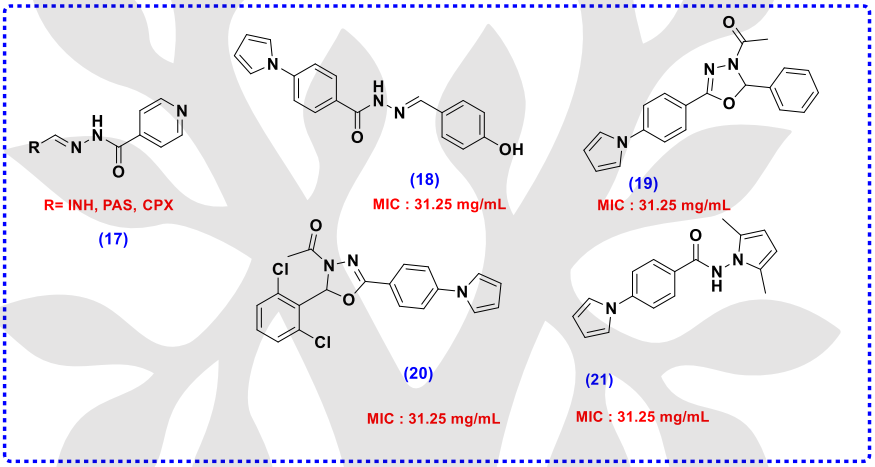
(1) (a) Küçükgüzela, S.G.; Rollas, S.; Küçükgüzel, I.; Kiraz, M. *Eur. J. Med. Chem.* **1999**, *34*, 1093; (b) Teneva, Y.; Simeonova, R.; Valcheva, V. Angelova, V.T. *Pharmaceuticals*, **2023**, *16*, 484.
(2) Cocco, M.T.; Congiu, C.; Onnis, V.; Pusceddu, M.C.; Schivo, M.L.; Logu, A. D. *Eur. J. Med. Chem*. **1999**, *34*, 1071.
(3) Savini, L.; Chiasserini, L.; Gaeta, A.; Pellerano, C. *Bioorg. Med. Chem. Lett.* **2002**, *10*, 2193.
(4) Sriram, D.; Yogeeswari, P.; Madhu, K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4502.
(5) Sriram, D.; Yogeeswari, P.; Madhu, K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 876.
(6) Bijev, A. *Lett. Drug Des. Discov*. **2006**, *3*, 506.
(7) Imramovsky, A.; Polanc, S.; Vinsova, J.; Kocevar, M.; Jampılek, J.; Reckova, Z. Kaustova J. *Bioorg. Med. Chem*. **2007**, 17, 2551.
(8) Rollas, S.; Kucukguzel, S.G. *Molecules*, **2007**, *12*, 1910.
(9) Joshi, S.D.; Vagdevi, H.M.; Vaidya, V.P.; Gadaginamath, G.S. *Eur. J. Med. Chem.* **2008**, *43*, 1989.
(10) Raparti, V.; Chitre, T.; Bothara, K.; Kumar, V.; Dangre, S.; Khachane, C. Gore S.; Deshmane B. *Eur. J. Med. Chem*. **2009**, *45*, 3954.
(11) Kaymakcioglu, B.K.; Oruç-Emre, E.; Unsalan, S.; Rollas, S. *Med. Chem. Res.* **2009**, *18*, 277.
(12) Candéa, A.L.P.; Ferreira, M.D.L.; Pais, K.C.; Cardoso, L.N.D.; Kaiser, C.R.; Henriques, M.G.M.O.; Lourenco, M.C.S.; Bezerra, F.A.F.M.; Souza, M.V.N.de. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6272.
(13) Gemma, S.; Savini, L.; Altarelli, M.; Tripaldi, P.; Chiasserini, L.; Coccone, S.S. Kumar, V.; Camodeca, C.; Campiani, G.; Novellino, E.; Clarizio, S.; Delogu, G.; Butini, S. *Bioorg. Med. Chem*. **2009**, *17*, 6063.
(14) Sonar, V.N.; Crooks, P.A. *J. Enzyme Inhib. Med. Chem*. **2009**, *24*, 117.
(15) Raja, A.S.; Agarwal, A.K.; Mahajan, N.; Pandey, S.N.; Ananthan S. *Indian J. Chem. B*. **2010**, *49*, 1384.
(16) Sankar, C.; Pandiarajan, K. *Eur. J. Med. Chem*. **2010**, 45, 5480.
(17) Pavan, F.R.; Maia, P.I.D.; Leite, S.R.A.; Deflon, V.M.; Batista, A.A.; Franzblau, S.G. Leite C.Q.F. *Eur. J. Med. Chem.* **2010**, *45*, 1898.
(18) Eswaran, S.; Adhikari, A.V.; Pal, N.K.; Chowdhury, I.H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1040.
(19) Eswaran, S.; Adhikari, A.V.; Pal, N.K.; Chowdhury, I.H.; Pal, N.K.; Thomas, K.D. *Eur. J. Med. Chem*. **2010**, *42*, 3374.
(20) Bijev, A.; Georgieva, M. *Lett. Drug Des. Discov*. **2010**, *7*, 430.
(21) Sriram, D.; Yogeeswari, P; Vyas, D.R.K.; Senthilkumar, P.; Bhat, P.; Srividya, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4313.
(22) Vavríková, E.; Polanc, S.; Kocevar, M.; Horváti, K.; Bosze, S.; Stolaríková, J. Vavrova, K.; Vinsova, J. *Eur. J. Med. Chem.* **2011**, *46*, 4937.
(23) Pinheiro, A.C.; Kaiser, C.R.; Nogueira, T.C.M.; Carvalhoa, S.A.; da Silva, E.F.; Feitosa, L.D.O. et al. *Med. Chem.* **2011**, *7*, 611.
(24) Vavríková, E.; Polanc, S.; Kocevar, M.; Kosmrlj, J.; Horváti, K.; Bosze, S. *Eur. J. Med. Chem.* **2011**, *46*, 5902.
(25) Thomas, K.D.; Adhikari, A.V.; Telkar, S.; Chowdhury, I.H.; Mahmood, R.; Pal, N.K. Row, G.; Sumesh, E. *Eur. J. Med. Chem*. **2011**, *46*, 5283.
(26) Utku, S.; Gokce, M.; Aslan, G.; Bayram, G.; Ulger, M.; Emekdas G. et al. *Turk. J. Chem*. **2011**, *35*, 331.
(27) Almasirad, A.; Sadar, S.S.; Shafiee, A. *Iran. J. Pharm. Res.* **2011**, *10*, 727.
(28) Singh, M.; Raghvan, V. *Int. J. Pharm Pharm Sci*. **2011**, *3*, 26.
(29) Verma G, Marella A, Shaquiquzzaman M, Akhtar M, Ali MR, Alam MM. *J. Pharm. Bioall. Sci.* **2011**, *6*, 69.
(30) Sharma. S.; Sharma, P.K.; Kumar, N.; Dudhe H. *Biomed. Pharmacother*. **2011**,*65*, 244.
(31) Telvekar, V.N.; Belubbi, A.; Bairwa, V.K.; Satardekar, K. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2343.
(32) Coelho, TS; Cantos, JB; Bispo, MLF; Gonçalves, RSB; Lima, CHS; da Silva PEA; Souza M. *Infect. Dis. Rep.* **2012**, *4*, e13.
(33) Cihan-Üstündağ, G; Çapan, G. *Mol Divers* **2012**, *16*, 525.
(34) Naveen Kumar, H.S.; Parumasivam, T.; Ibrahim, P.; Asmawi, M.Z.; Sadikun, A. *Med. Chem. Res*. **2014**, *23*, 1267-1277.
(35) More, U.A.; Joshi, S.D.; Aminabhavi, T.M.; Gadad, A.K.; Nadagouda, M.N.; Kulkarni, V.H. *Eur. J. Med. Chem.* **2014**, *71*, 199.
(36) Pahlavani, E.; Kargar, H.; Rad, N.S. *Zahedan J. Res. Med. Sci*. **2015**, *17*, e1010.
(37) Unissa, AN; Hanna, LE; Swaminatha, S. *Chem Biol Drug Des*. **2016**, *87*, 537.
(38) John, S.F., Aniemeke, E., Ha, N.P., Chong, C.R., Gu, P., Zhou, J., Zhang, Y., Graviss, E.A., Liu, J.O., Olaleye, O.A. *Tuberculosis* **2016**, *101*, S73-S77.
(39) Cihan-Üstünda˘ g, G.; ¸Satana, D.; Özhan, G.; Çapan, G. *J. Enzym. Inhib. Med. Chem.* **2016**, *31*, 369.
(40) Velezheva, V; Brennan, P; Ivanov, P; Koronienko, A; Lyubimov, S; Kazarian, K; Nikonenko, B; Majorov, K; Apt, A. *Bioorg Med Chem Lett.* **2016**, *26*, 978.
(41) Angelova, V.T.; Valcheva, V.; Vassilev, N.G.; Buyukliev, R.; Momekov, G.; Dimitrov, I.; Saso, L.; Djukic, M.; Shivachev, B. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 223.
(42) Angelova, V.T.; Valcheva, V.; Pencheva, T.; Voynikov, Y.; Vassilev, N.; Mihaylova, R.; Momekov, G.; Shivachev, B. *Bioorganic Med. Chem*. Lett. **2017**, *27*, 2996.
(43) Concha, C.; Quintana, C.; Klahn, A.H.; Artigas, V.; Fuentealba, M.; Biot, C.; Halloum, I.; Kremer, L.; López, R.; Romanos, J.; et al. *Polyhedron* **2017**, *131*, 40.
(44) Oliveira, P.F.M.; Guidetti, B.; Chamayou, A.; André-Barrès, C.; Madacki, J.; Korduláková, J.; Mori, G.; Orena, B.S.; Chiarelli, L.R.; Pasca, M.R.; et al. *Molecules* **2017**, *22*, 1457.
(45) Bonnett, S.A.; Dennison, D.; Files, M.; Bajpai, A.; Parish, T. *PLoS ONE* **2018**, *13*, e0198059.
(46) Nogueira, T.; Cruz, L.; Lourenço, M.; Souza, M. *Lett. Drug Des. Discov.* **2018**, *15*, 792.
(47) Angelova, V.T.; Pencheva, T.; Vassilev, N.; Simeonova, R.; Momekov, G.; Valcheva, V. *Med. Chem. Res.* **2019**, *28*, 485.
(48) Sampiron, E.G.; Costacurta, G.F.; Baldin, V.P.; Almeida, A.L.; Ieque, A.L.; Santos, N.C.; Alves-Olher, V.G.; Vandresen, F.; Gimenes, A.C.; Siqueira, V.L.; et al. *Future Microbiol.* **2019**, *14*, 981.
(49) Ghiano, D.G.; Recio-Balsells, A.; Bortolotti, A.; Defelipe, L.A.; Turjanski, A.; Morbidoni, H.R.; Labadie, G.R. *Eur. J. Med. Chem.* **2020**, *208*, 112699.
(50) Hassan, N.W.; Saudi, M.N.; Abdel-Ghany, Y.S.; Ismail, A.; Elzahhar, P.A.; Sriram, D.; Nassra, R.; Abdel-Aziz, M.M.; El-Hawash, S.A. *Bioorg. Chem.* **2020**, *96*, 103610.
(51) G, S.T.; Subramanian, S.; Eswaran, S. *Heterocycl. Commun*. **2020**, 26, 137.
(52) Desale, V.J.; Mali, S.N.; Chaudhari, H.K.; Mali, M.C.; Thorat, B.R.; Yamgar, R.S. *Curr comp drug des*. **2020**, *16*, 618.
(53) Thorat, B.R.; Rani, D.; Yamgar, R.S.; Mali, S.N. *Combinatorial Chemistry & High Throughput Screening* **2020**, *23*, 392.
(54) Padmini, T.; Bhikshapathi, D.; Suresh, K.; Kulkarni, R.; Kamal, B.R. *Med. Chem.* **2021**, *17*, 344.
(55) de Faria, C.F.; Moreira, T.; Lopes, P.; Costa, H.; Krewall, J.R.; Barton, C.M.; Santos, S.; Goodwin, D.; Machado, D.; Viveiros, M., *Biomed. Pharm.* **2021**, *144*, 112362.
(56) Karunanidhi, S.; Chandrasekaran, B.; Karpoormath, R.; Patel, H.M.; Kayamba, F.; Merugu, S.R.; Kumar, V.; Dhawan, S.; Kushwaha, B.; Mahlalela, M.C. *Bioorg. Chem*. **2021**, *115*, 105133.

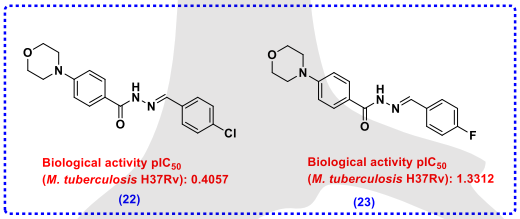
(57) Pflégr, V.; Horváth, L.; Stola˘ríková, J.; Pál, A.; Korduláková, J.; B˝osze, S.; Vinšová, J.; Krátký, M. *Eur. J. Med. Chem.* **2021**, *223*, 113668.
(58) Thorat, B.R.; Mali, S.N.; Rani, D.; Yamgar, R.S. *Curr. Comput.-Aided Drug Des.* **2021**, *17*, 294.
(59) Gobis, K.; Szczesio, M.; Olczak, A.; Korona-Głowniak, I.; Augustynowicz-Kope´c, E.; Mazernt-Politowicz, I.; Ziembicka, D.; Główka, M.L. *Materials* **2022**, *15*, 3085.
(60) Briffotaux, J.; Xu, Y.; Huang, W.; Hui, Z.; Wang, X.; Gicquel, B.; Liu, S. A. *Molecules* **2022**, *27*, 7130.
(61) Akki, M.; Reddy, D.S.; Katagi, K.S.; Kumar, A.; Devarajegowda, H.C.; Kumari, M.S.; Babagond, V.; Joshi, S.D. *ChemistrySelect* **2022**, *7*, e202203260.
(62) Abdelhamid, E.; Mahfouz, N.; Omar, F.; Ibrahim, Y.; Abouwarda, A. SSRN Electron. J. **2022**.
(63) Lone, M.; Mubarak, M.; Nabi, S.; Amin, S.; Nabi, S.; Kantroo, H.; Samim, M.; Shafi, S.; Ahmad, S.; Ahmad, Z.; et al. *Med. Chem. Res.* **2023**, 32, 808.
(64) Mali, S. N.; Pandey, A.; Thorat, B. R.; Lai, C. H. *Struct. Chem.* **2022**, 33, 679.
(65) Mali, S.N., Thorat, B.R., Gupta, D.R., Pandey, A., *Engineering proceedings*, **2021**, *11*, 21.
(66) Popiołek, Ł. *Med. Chem. Res.* **2017**, *26*, 287-301.
(67) Murugappan, S.; Dastari, S.; Jungare, K.; Barve, N.M.; Shankaraiah, N. *J Mol Struct* **2024**, 138012.
(68) Narang, R.; Narasimhan, B.; Sharma, S. *Curr med chem* **2012**, *19*(4), 569-612.
(69) Verma, G.; Marella, A.; Shaquiquzzaman, M.; Akhtar, M.; Ali, M.R.; Alam, M.M. *J Pharmacy and Bioallied Sci* **2014**, *6*, 69-80.
(70) Rollas, S.; Güniz Küçükgüzel, Ş. *Molecules* **2007**, *12*, 1910-1939.
(71) Raj, V. *EC Pharm Sci* **2016**, *2*, 278-306.
(72) Angelova, V.; Karabeliov, V.; Andreeva-Gateva, P.A.; Tchekalarova, J. *Drug dev res* **2016**, *77*, 379-392.
(73) de Oliveira Carneiro Brum, J.; França, T.C.; LaPlante, S.R.; Villar, J.D.F. *Mini-Rev. Med. Chem.* **2020**, *20*, 342-368.
(74) Shakdofa, M.M.; Shtaiwi, M.H.; Morsy, N.; Abdel-rassel, T. *Main Group Chem* **2014**, *13*, 187-218.
(75) Mandewale, M.C.; Patil, U.C.; Shedge, S.V.; Dappadwad, U.R.; Yamgar, R.S. *Beni-Suef univ. j. basic appl. sci.* **2017**, *6*, 354-361.
(76) Popiołek, Ł. *Int J Mol Sci* **2021**, *22*, 9389.

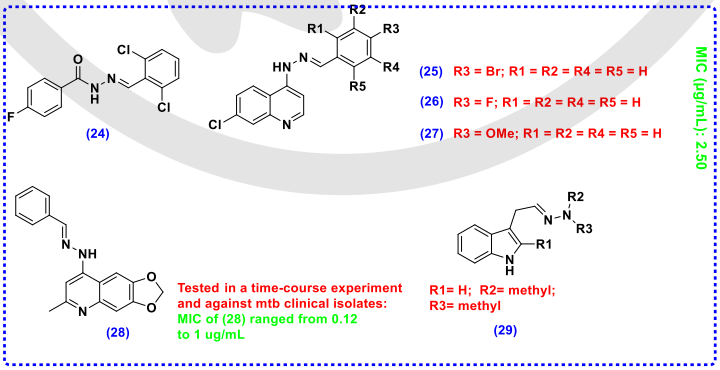
List of Structures to be placed in manuscript

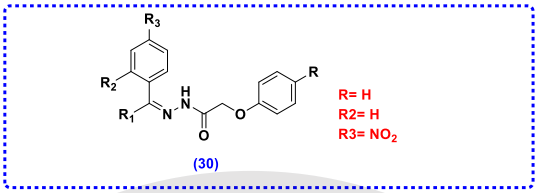












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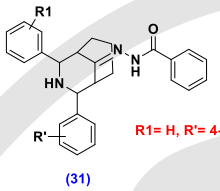

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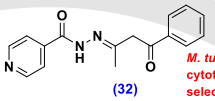
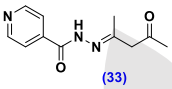


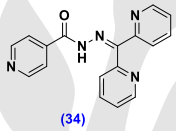
(32)

M. tuberculosis activity (MIC)µg/mL: 3.13,
cytotoxicity (IC_{50}) µg/mL:1250
selectivity index (SI) (IC_{50}/MIC): 399



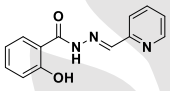
(33)

M. tuberculosis activity (MIC)µg/mL: 6.25,
cytotoxicity (IC_{50}) µg/mL:1250
selectivity index (SI) (IC_{50}/MIC): 200



(34)

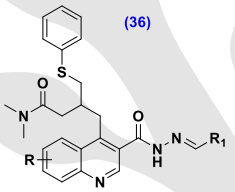
M. tuberculosis activity (MIC)µg/mL: 3.13,
cytotoxicity (IC_{50}) µg/mL:625
selectivity index (SI) (IC_{50}/MIC): 200



(35)

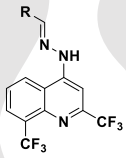
M. tuberculosis activity (MIC)µg/mL: =250,
cytotoxicity (IC_{50}) µg/mL:312.5
selectivity index (SI) (IC_{50}/MIC): <1.25

(36)



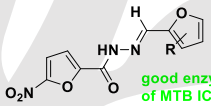
R= 6-F or 8-F; R1= 2-F-Ph or 4-OCH_3-Ph or 4-F-Ph or 3-OH or 4-OH-Ph

(37)



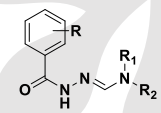
R= alkyl, aryl, heteroaryl

(38)



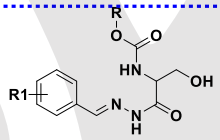
R= 5-Nitro

good enzyme inhibition of MTB ICL at 10 µM



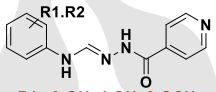
R= 4-CF_3, 3-CF_3, 4-F, 3-F, 2-F
R1, R2= PAS, CPX, NFX

(39)



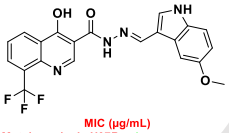
R= Ph; t-Butyl
R1=2-NO_2, 3-NO_2, 4-NO_2, 3-CN, 4-CN, 2-OH, 2-OCH_3, 3-4-OH

(40)



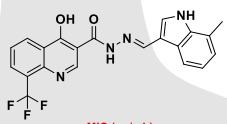
R1= 3-OH, 4-OH, 3-OCH_3, 4-OCH_3, 3-F, 4-F, 4-Cl, 4-Br 3-NO_2, 3-CF_3, R2= 2-OH, 4-Cl, 4-F, 4-Cl

(41)



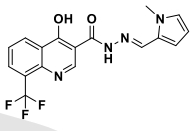
MIC (µg/mL)
M. tuberculosis H37Rv.:1
M. smegmatis (ATCC 19420):10
M. fortuitum (ATCC 19542).:10

(42)



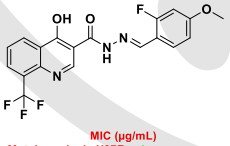
MIC (µg/mL)
M. tuberculosis H37Rv.:1
M. smegmatis (ATCC 19420):1
M. fortuitum (ATCC 19542).:10

(43)



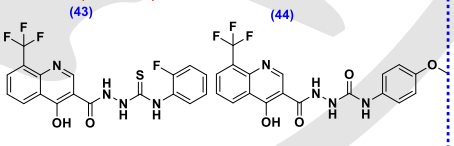
MIC (µg/mL)
M. tuberculosis H37Rv.:1
M. smegmatis (ATCC 19420):1
M. fortuitum (ATCC 19542).:10

(44)



MIC (µg/mL)
M. tuberculosis H37Rv.:1
M. smegmatis (ATCC 19420):10
M. fortuitum (ATCC 19542).:10

(45)

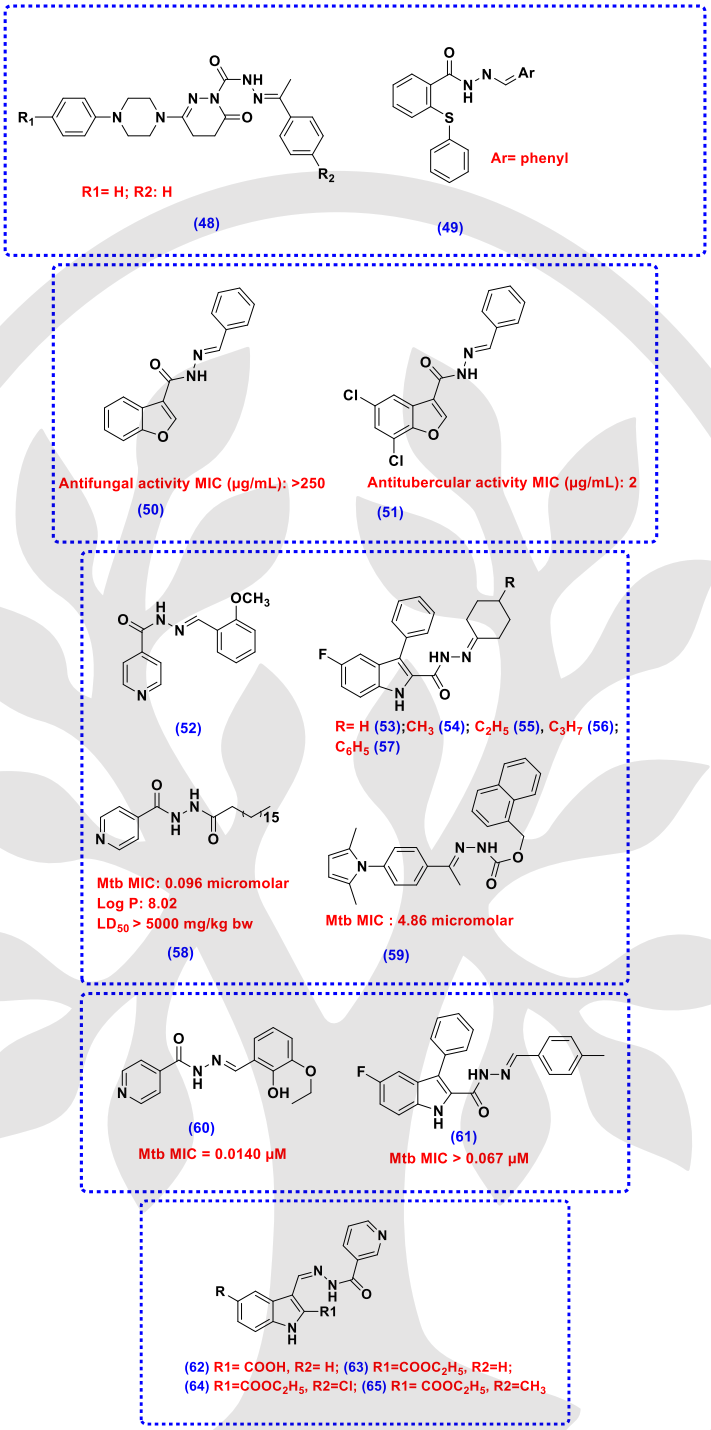


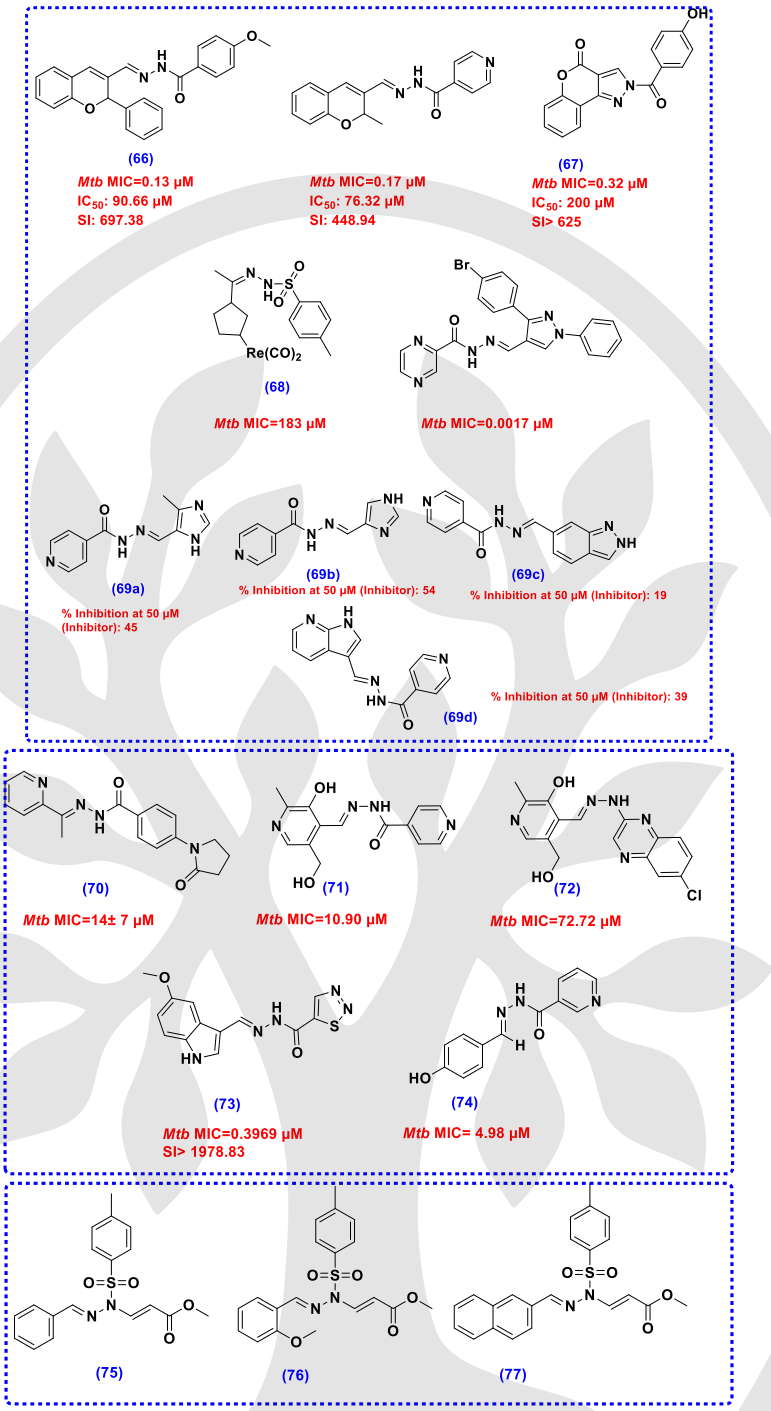
MIC (µg/mL)
M. tuberculosis H37Rv.:1
M. smegmatis (ATCC 19420):10
M. fortuitum (ATCC 19542).:10

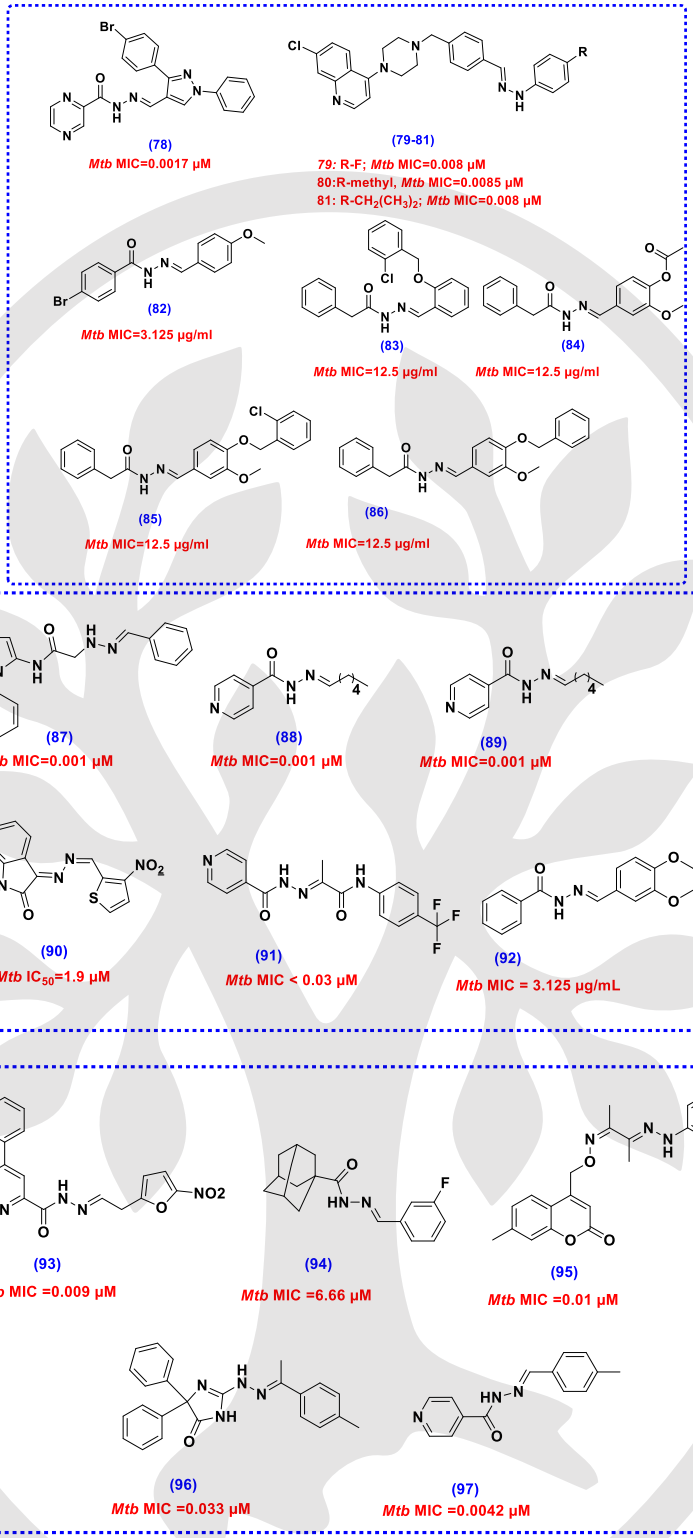
(46)

MIC (µg/mL)
M. tuberculosis H37Rv.:1
M. smegmatis (ATCC 19420):10
M. fortuitum (ATCC 19542).:10

(47)







Biosketches

	Dr. Suraj Mali has a Ph.D. in Pharmacy. He is an Assistant Professor in Pharmaceutical Chemistry at School of Pharmacy, DY Patil University, Navi Mumbai, India. He has an academic background in pharmaceutical science and technology from the Institute of Chemical Technology, Mumbai, India. He serves as a respected reviewer for multiple scientific journals and was designated as a Bentham Science Brand Ambassador for 2019–2020. He has more than **124** international journal publications to his credit (**Scopus H-Index: 26**). He received the Institute of Chemical Technology's (ICT) Masters Best Thesis Aditya Birla Award in 2019. His diverse expertise spans molecular modeling, synthetic chemistry, phytochemistry, pharmacology, and analytics, with a focus on drug design and synthesis. A recent publication in Nature Scientific Reports highlights his work in identifying antimycobacterial agents using computational tools. Dr. Mali was listed among the world's top 2% of scientists by Stanford University, USA, in 2023.
	Dr. Anima Pandey is an Assistant Professor, at Department of Pharmaceutical Sciences & Technology, B.I.T. Mesra, Ranchi, India. She has guided many M. Pharm and Ph.D. candidates in her tenure. Currently, she is senior most faculty of Pharmacognosy and Phytochemistry division at Birla Institute of Technology, Ranchi.
	Dr Umang Shah is an Associate Professor at Department of Pharmaceutical Chemistry and Analysis, Ramanbhai Patel College of Pharmacy, Charotar University of Science & Technology, Charotar University of Science and Technology, CHARUSAT Campus, Off. Nadiad-Petlad Highway Anand, Gujarat, India – 388421. Experienced with a demonstrated history of working in the education management industry. Skilled in Good Laboratory Practice (GLP), Liquid Chromatography-Mass Spectrometry (LC-MS), Pharmaceutical Research, Patent Law, and Nanoparticles. Strong education professional with a Doctor of Philosophy (Ph.D.) focused in Medicinal and Pharmaceutical Chemistry from Ramanbhai Patel College of Pharmacy, CHARUSAT. His area of interest covers Drug Design and Synthesis, Cytotoxicity Assay, and Computational Studies.
	Prof. Rahul Jawarkar has specialization in QSAR, Molecular docking, MD Simulation, MMGBSA study, and QSAR Based virtual screenings. Currently, he has Citations of 845 with h-index: 18. He is currently an Asso. Prof. at Department of Medicinal Chemistry and Drug Discovery, Dr. Rajendra Gode Institute of Pharmacy, University Mardi Road, Amravati, 444603, India.
	Dr. Rakesh Somani, is currently a Professor of Pharmaceutical Chemistry & acting as Principal, at School of Pharmacy, Dr. D. Y. Patil University, Navi Mumbai, India. He has guided many M. Pharm and Ph.D. candidates in his tenure. He is a President of ASSOCIATION OF PHARMACEUTICAL TEACHERS OF INDIA (APTI), Maharashtra, India. Currently, he has H-index of 15 with 821 citations in his GoogleScholar profile. His area of specialization includes various disciplines such as Green Chemistry and environmentally friendly chemical reactions; Microwave Synthesis; Heterocyclic Chemistry in anti-TB, anti-HIV and anti-cancer areas, etc.