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ARTICLE

1,3-Oxazole-isoniazid hybrids: Synthesis, antitubercular activity, and their docking studies

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Abstract

A series of novel *N*′-([2-aryl-5-methyl-1,3-oxazole-4-yl]methylene)isonicotino/nicotino hydrazides **10a-l** were prepared by the condensation reaction of 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes **8a-f** with the corresponding isonicotino/nicotino hydrazides **9a/9b**. The structures of the new compounds were elucidated by various spectroanalytical techniques, including IR, ^{1}H NMR, ^{13}C NMR, elemental (C,H,N), and mass analysis. All the newly prepared INH-1,3-oxazole hybrids were evaluated for their *in vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Rv. Among all the synthesized hybrids, compounds **10c** and **10i** derivatives displayed highest antitubercular activity with minimal inhibitory concentration 1.56 μg/mL. Further, molecular docking studies against the InhA enzyme were carried out to understand the interactions between potent hybrids and the target enzyme. Thus, these kind hybrids have the potentiality for the discovery of new antitubercular agents for deployment in the control and eradication of tuberculosis.

1 | INTRODUCTION

Tuberculosis (TB) is one of the deadly diseases and remains a foremost global health problem as it is still a leading killer in the world.[1,2] Approximately 100 million people are affected with TB every year. TB accounts for nearly 3 million deaths worldwide annually.[3] The development of drug-resistant TB, multidrug-resistant TB, and total drug resistance increases the challenges in the elimination of TB worldwide.[2] It has been reported that a few bacterial strains have developed drug resistance to as many as nine drugs.[4] Natural products are extremely useful templates for the development of a number of the new drug molecules[5] and they have received immense attention as potential anti-TB agents.[6,7] Various natural products have been reported to show resistant against strains of *Mycobacterium tuberculosis*.[8–10] No new anti-TB drugs have been developed in the TB therapy in the course of the past few years, creating an urgent need of design and developing of new drugs and strategies for an effective TB treatment.

Nitrogen-containing heterocycles constitute a major part of natural products[6] and possess a wide range of applications in medicinal chemistry.[11,12] Isoniazid (INH) is isonicotinic acid hydrazide, which is a widely employed first-line drug used for the treatment of TB[13,14] for more than 60 years and it still rests one of the furthermost effective anti-TB drug agents. INH and its derivatives, the *N*-containing heterocyclic hydrazide and derivatives, have added importance in medicinal chemistry due to their variety of biological activities such as antimycobacterial,[15] antibacterial,[16] antivirus,[17] antifungal,[18] antitumor,[19] and analgesic[20] activities. Among the numerous activities, the anti-TB activity is significant and due to that, it is currently used in the treatment of TB. Within the last few years, syntheses of several derivatives of INH have been reported and some of them display excellent in vitro antimycobacterial activity.[21,22] On the other hand, compounds possessing oxazoles have also displayed promising anti-TB activity.[23]

Hydrazones showed diverse biological activities not only because of hydrazone linkage but also due to various

heterocyclic moieties brought together either from hydrazine, hydrazide or from a carbonyl compound. Hydrazones have been studied widely for a variety of biological activities including antimycobacterial,[24] antimalarial,[25] antibacterial,[26] antidepressant,[27] anticonvulsant,[28] anti-inflammatory,[29] analgesic,[25] and antitumor[30] activities. Due to broad biological activities of hydrazones, various types of hydrazides and hydrazones have attracted continuous interest in the medicinal field; among them, INH hydrazone derivatives exhibit excellent anti-TB activity[15,26] (Figure 1).

In recent times, the amalgamation of biologically active molecules has been one of the most modern topics in the field of medicinal chemistry. It is assumed that the combination of two or more bioactive heterocycles in a single molecule may not only synergize their biological potency but may also improve their ability to act upon more than one biological target. As per the reports, a large number of scaffolds with the incorporation of two molecular entities on a single frame, with varied biological profiles, display unusual enhanced biological properties.[31]

Keeping this in mind, we have designed and synthesized target molecules (**10a-l**) based on the concept of molecular hybridization, which makes it possible to bring together biologically potent entities, that is, INH-oxazole, into a single molecular framework Figure 2. All new INH-oxazole hybrids were characterized using various spectroanalytical techniques and were evaluated for their in vitro antitubercular activity against *M. tuberculosis* H37Rv. Further, molecular docking study was carried out to understand the interactions between synthesized molecules and InhA enzyme.

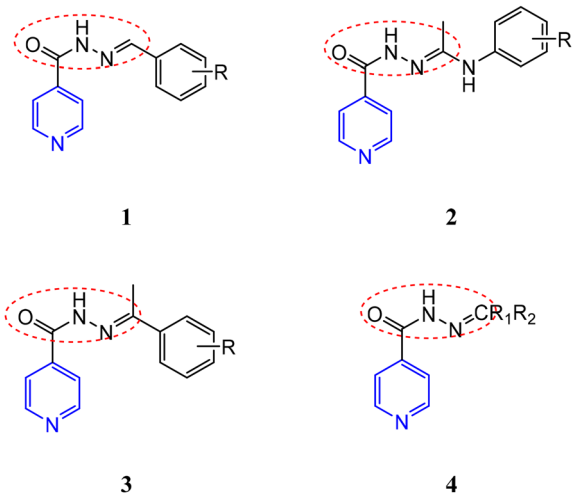


FIGURE 1 Isoniazid-based hydrazone derivatives as antituberculosis agents

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The synthesis of the final 1,3-oxazole-INH hybrids is as depicted in Scheme 1. The synthesis was started with the preparation of six 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes **23a-e**. Consequently, 4-substituted benzaldehydes **5a-f** were reacted with diaceyl monoxime in glacial acetic acid to give 2-aryl-4,5-dimethyl-1,3-oxazole-3-oxides **6a-f**,[32] which were further converted to 2-aryl-4-(chloromethyl)-5-methyl-1,3-oxazoles **7a-f** on heating with $POCl_3$ in dichloroethane.[32] The 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes **8a-f** were obtained by reacting 2-aryl-4-(chloromethyl)-5-methyl-1,3-oxazoles **7** with bis-TBAC (Bis-Tetrabutylammonium dichromate) in chloroform[33] (Scheme 1). Some oxazolyl carbaldehydes **8a-f** are reported using some other synthetic route with no physical or spectral data available.[34,35] Further employing these oxazolyl carbaldehydes, *N*′-([2-Aryl-5-methyl-1,3-oxazolyl] methylene) isonicotino/nicotino-hydrazides **10a-l** were

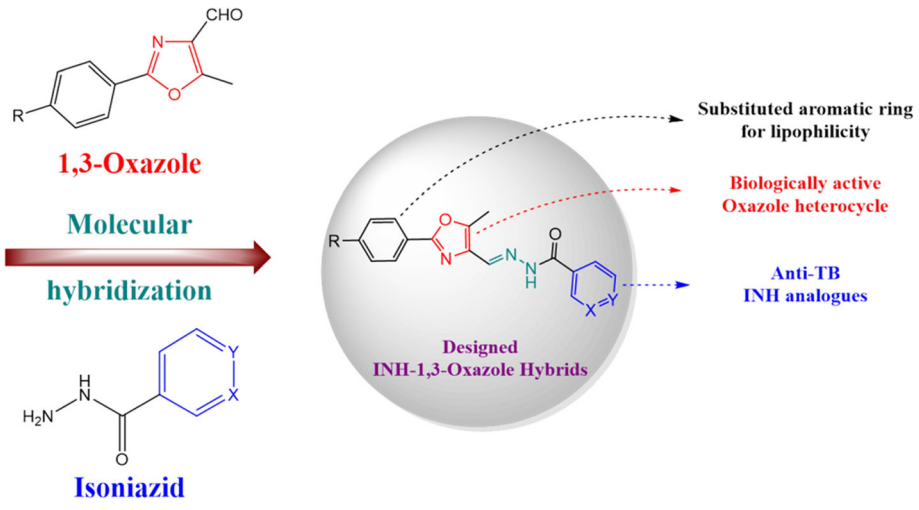
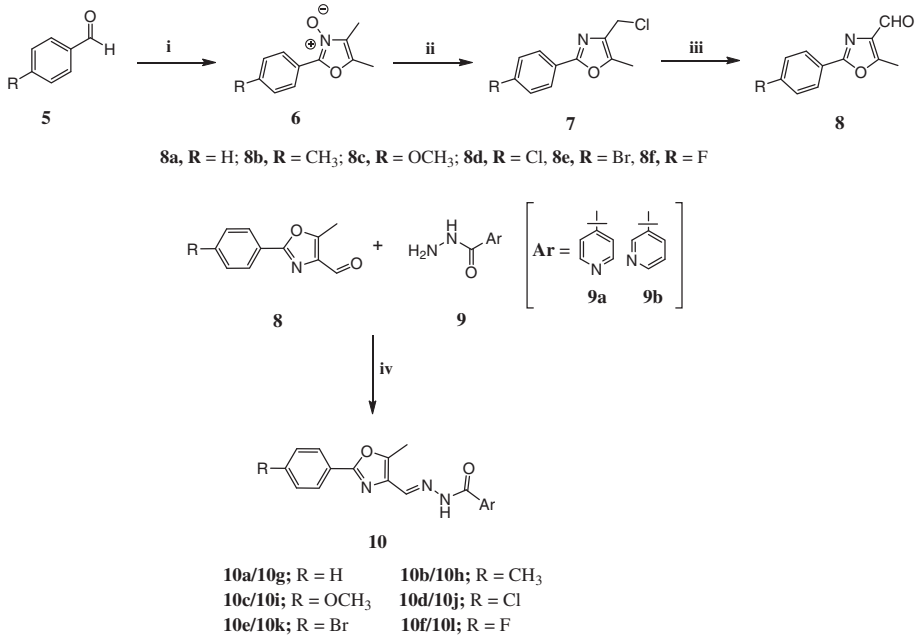


FIGURE 2 Design strategy for the synthesis of hydrazone linked isoniazid-1,3-oxazole hybrids via molecular hybridization approach

SCHEME 1 Synthesis of 1,3-oxazole-isoniazid hybrids



Reagents and conditions: i) Diacetyl monoxime, AcOH, HCl (g), 3h ii) $POCl_3$, 1,2-dichloroethane, 6h iii) Bis-TBAC, $CHCl_3$, 2h, iv) EtOH, AcOH, 80 °C, 3-4 h.

synthesized by condensation[36] of 2-aryl-5-methyl-1,-3-oxazole-4-carbaldehydes **8a-f** with the corresponding isonicotino/nicotino hydrazides **9a/9b** in ethanol using acetic acid as a catalyst to afford the final new INH-1,-3-oxazole hybrids **10a-l**. All the synthesized aryl oxazolyl carbaldehydes **8(a-f)** and 1,3-oxazole-INH hybrids **10(a-l)** were characterized by various spectro-analytical techniques.

The IR spectra of 1,3-oxazole-INH hybrids **10(a-l)** showed the typical N—H stretching bands in between 3295 and 3200 cm^{-1}. A strong band of C═O stretching was observed at ~1695 cm^{-1}. The 1,3-oxazole-INH hybrids **10 (a-f)** showed characteristic ^1H NMR signals with distinct chemical shifts for different kinds of protons. The methyl protons were observed at δ 2.6 ppm for all the 12 compounds. The methylene proton on the imine linkage (—N═CH—) was observed as singlet between δ 7.4 and 7.5 ppm, and N—H proton of the hydrazine group was observed most downfield between δ 12.0 and 14.0 ppm as a singlet. The aromatic proton of pyridine ring was observed as a doublet between δ 8.8 and 7.9 ppm with coupling constant J = 6.0 Hz while the other aromatic protons were observed as a doublet at δ 7.5 and 8.0 ppm, respectively, with coupling constant J = 8.0 Hz. The ^{13}C NMR spectra of hybrids **10(a-f)** showed methyl carbon on oxazole ring signal at δ 11.4 ppm and the signal at δ 162 ppm is observed for the carbonyl carbon (—C═O). The imine carbon (—C═N) is observed at δ 150.7 ppm for hybrid compounds.

For the compounds, **10(g-l**) pyridine ring carbon was observed at δ 148 ppm. The rest of the aromatic carbon signals were similar to the structures of the corresponding hybrid compounds and are found in between δ 124 and 159 ppm. All the synthesized aryl oxazolyl carbaldehydes **8 (a-f)** and hybrids **10(a-l)** were analyzed with the help of Shimadzu, GC-MS QP-2010 Plus mass spectrometer. The molecular ion peaks of all the compounds were observed as $(M + H)^+$ and were found to be in accordance with the expected mass values.

2.2 | Antitubercular activity study

All the new 1,3-oxazole-INH hybrid compounds **10**(**a-l**) were evaluated for their antitubercular activity against *M. tuberculosis* H37Rv strain. The minimal inhibitory concentration (MIC) was evaluated for all compounds, which were measured as the minimum concentration of tested compound required to inhibit the bacterial growth completely. The MIC values (μg/mL) of all the newly synthesized compounds **10a-l** and three antitubercular drugs (INH, Rifampicin, Ethambutol) as a standard were determined in triplicate and are as presented in Table 1.

All newly synthesized compounds showed antitubercular activity against MTB with MICs ranged between 1.56 and 25 μg/mL. Among all the tested compounds, **10c** and **10i** displayed a potent antitubercular activity with MIC value of 1.56 μg/mL, two compounds **10b** and **10h** inhibited MTB with MIC value of 6.25 μg/mL, and compound 10a showed MIC value of 12.5 μg/mL. Two compounds **10g** and **10a** inhibited MTB at MIC

TABLE 1 Lipscomb's parameters, binding affinity, and antitubercular activity (% inhibition) of INH-1,3-oxazole hybrids

ID	—R	Log *P*	Molar refractivity	H-bond donor	H-bond acceptors	MIC (μg/mL)
10a	—H	−2.602	58.605	0	2	12.5
10b	$-CH_3$	−1.921	61.907	0	2	6.25
10c	$-OCH_3$	−1.603	64.737	0	3	**1.56**
10d	—Cl	−1.518	64.815	0	2	25
10e	—Br	−0.699	71.313	0	3	>25
10f	—F	−1.432	61.404	0	2	>25
10g	—H	−2.813	59.656	0	2	25
10h	$-CH_3$	−2.811	64.434	0	2	6.25
10i	$-OCH_3$	−1.852	66.766	0	3	**1.56**
10j	—Cl	−1.627	64.970	0	2	>25
10k	—Br	−2.047	70.118	0	2	25
10l	—F	−0.681	63.095	0	2	>25
INH	—	—	—	—	—	0.1
Rifampicin	—	—	—	—	—	0.2
Ethambutol	—	—	—	—	—	3.13

Abbreviations: INH, isoniazid; MIC, minimal inhibitory concentration.
Bold values in Table 1 corresponding to the compounds showed the highest activity among all synthesized compounds.

value of 25 μg/mL and other four compounds **10e**, **10f**, **10j**, **10l** inhibited MTB with MIC at >25 μg/mL. When compared with the first-line antitubercular drug, Ethambutol (MIC 3.13 μg/mL) two compounds **10c** and **10i** were found to show potent activity (MIC 1.56 μg/mL) as compared to the standard drug Ethambutol. All the other compounds showed moderate activity when compared with other anti-TB drugs, INH (MIC 0.1 μg/mL) and rifampicin (MIC 0.2 μg/mL).

According to the results obtained in in vitro screening, the structural correlations of all newly prepared compounds with respect to their antitubercular potency revealed that compounds bearing methoxy (**10c** and **10i**) and methyl (**10b** and **10h**) groups on phenyl ring attached to the oxazole scaffold displayed better activity compared to other compounds. Compounds with no substitution on phenyl ring (**10a** and **10g**) showed lesser activity than compounds **10c** and **10i** but higher than those compounds substituted with electron withdrawing groups (**10d, 10e, 10f, 10j, 10k, 10l**). Finally, we have concluded that the presence of methyl and methoxy groups on phenyl ring attached to the oxazole moiety appeared to be important for observed activity.

The safety profile of antitubercular active 1,3-oxazole-INH hybrids with MIC ≤12.5 μg/mL were evaluated by testing in vitro cytotoxicity for Human Embryonic Kidney (HEK-293T) cells employing 3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Percentage cell viability of five hybrid analogs at 50 μg/mL concentration are as presented in Figure 3. The results

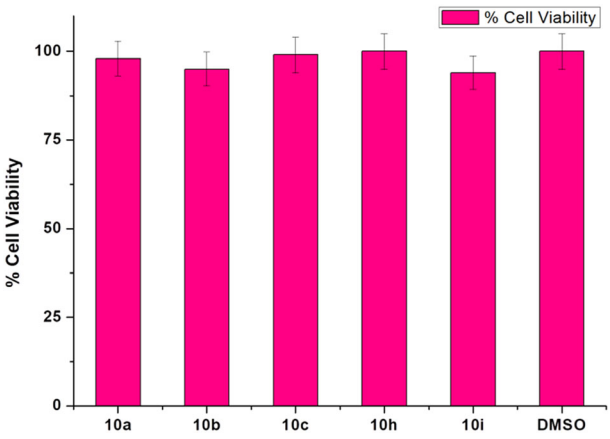


FIGURE 3 Percentage cell viability of 1,3-oxazole-isoniazid hybrids on HEK-293T cells

showed that the potent hybrid analogs **10c** and **10i** did not display noteworthy changes in cytotoxicity as compared to vehicle (DMSO) treatment and can be studied further for mechanistic evaluation.

2.3 | Molecular docking study

Molecular docking studies were performed on all new 1,3-oxazole-INH hybrids **10a-l** of the series with the enzyme, InhA. Docking simulation was done with the aid of Schrödinger Maestro-11.5. The protein structures obtained from the protein data bank (**PDB code: 1P44**)

were initially subjected to various processes such as removal of water molecules and removal of heteroatoms, using the Protein Preparation Wizard of Schrödinger 2015. All the compounds (ligands) were filtered by specifying options for screening like remove molecules that have a molecular weight of greater than 650 remove molecules with too many H-bond acceptor and donor atoms acceptor groups >3, Donor groups >3, Energy minimization was done by choosing a Ligprep (OPLS) module of Schrodinger. The extent of the interactions of the docking study was observed based on the docking score, hydrogen bonding, π-H and π-π interactions of the ligands with the protein. The docking score of the compounds is in the range −7.73 to −9.37 (Table 2). Along with other types of interactions, one or more hydrogen bonding were observed by the interactions of the compounds with the amino acid residues of InhA.

TABLE 2 Docking results of the active 1,3-oxazole-INH hybrids on InhA

ID	Docking score	Glide energy	Amino acids interacted with ligands
INH	−13.10	−53.78	Tyr 158, Met 199, Gly 96
10c	−9.37	−49.30	Tyr 158
10i	−8.96	−50.42	Tyr 158
10h	−8.58	−45.88	Tyr 158,Gly 96
10b	−8.27	−50.52	Tyr 158, Met 199
10a	−7.73	−42.27	Tyr 158

Abbreviation: INH, isoniazid.

From the results of the docking, the highest docking score was observed for the compound **10c** (−9.37). The docking score of the two active TB compounds of the series namely **10i** and **10h** was found to be −8.96 and −8.57 with H-bond interaction between Tyr 158 and oxygen atom of the carbonyl group. Compound **10d** also showed π-π interactions with amino acid residue Tyr 158. It is interesting to note that all five (**10a**, **10b**, **10c, 10h, 10i**) and the reference ligand showed similar interactions in to the active site of target enzyme. The greater inhibitory activity of compound **10c** and **10i** with methoxy substitutions and compounds **10b** and **10h** with methyl substitutions on the phenyl ring compared with other analogs could be justified based on the docking results as compounds showed higher docking score than that of other hybrid compounds. Docking pose of the two compounds **10a** and **10b** in the active pocket of InhA is as shown in Figure 4.

3 | EXPERIMENTAL SECTION

3.1 | General Chemistry

The chemicals were used as received without further purification. Organic solvents were purified by distillation prior to use. Column chromatography was carried out using silica gel (60-120 mesh). Thin-layer chromatography was performed on the precoated silica gel 60 F_{254} aluminium sheets. Melting points are determined in open capillary and are uncorrected. FT-IR spectra were recorded on Bruker Alpha FTIR spectrometer between 4000 and 400 cm^{-1} in solid state as KBr discs. The NMR

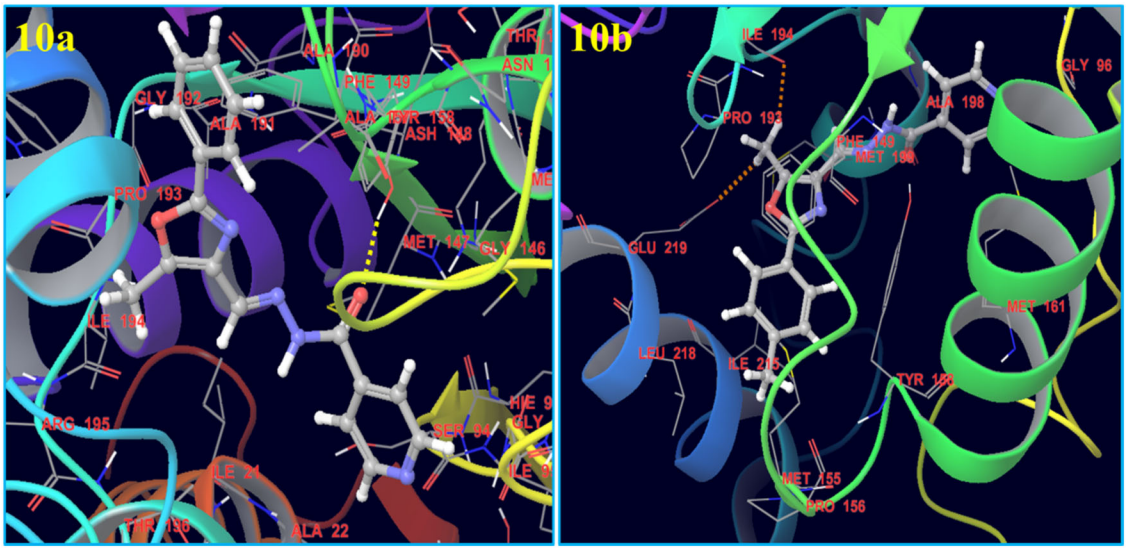


FIGURE 4 Docking pose of the compounds **10a** and **10b** in the active pocket of InhA. Yellow dotted line shows hydrogen binding and blue dotted line represents the hydrophobic interactions

spectra were recorded on 400 MHz Bruker Avance-III instrument and chemical shifts are given in parts per million. In the NMR data for ^{19}F decoupled ^{1}H NMR experiments, the data for the affected signals only are included. ^{19}F chemical shift values are of ^{1}H decoupled ^{19}F signals. Thermo Fischer elemental analyzer was used for elemental analysis. Mass spectra were recorded on Shimadzu, GC-MS QP-2010 Plus mass spectrometer.

3.2 | General Procedure For The Synthesis of 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes, 8a-f

2-Aryl-5-methyl-1,3-oxazole-4-carbaldehydes **8a-f** were prepared from 4-substituted aldehydes and diacetyl monoxime. To an ice-cold mixture of 4-substituted aldehydes **5** (1 eq) and diacetyl monoxime (1 eq) in acetic acid (3-fold), dry HCl gas was passed for 3 hours at 0°C. The reaction mixture was then diluted with diethyl ether (6-fold). Separated solid was filtered, washed with diethyl ether, and dried under vacuum to obtain 2-aryl-4,5-dimethyloxazole 3-oxide **6** as white solids. To an ice-cold suspension of 2-aryl-4,5-dimethyl-1,3-oxazole-3-oxides **6** (1 eq) in dichloro ethane (DCE) (5-fold) was added $POCl_3$ (1.1 eq) dropwise over a period of 2 hours at 10°C. The reaction mixture was slowly heated to 60°C and stirred at that temperature for 3 hours. The reaction mixture was cooled to room temperature, poured into ice cold water, and extracted with DCE. The combined organic extracts were washed with water, dried over $CaCl_2$, and concentrated under vacuum to furnish 2-aryl-4-(chloromethyl)-5-methyl-1,3-oxazoles **7** in excellent yields. A homogeneous solution of the 2-aryl-4-(chloromethyl)-5-methyl-1,3-oxazoles **7** (1 eq) and bis-tetrabutyl ammonium dichromate (0.6 eq) in chloroform (7.5 mL) was heated under reflux for 2 hours. The crude product was filtered through silica gel to eliminate the chromium salt. The silica was than washed with diethyl ether (100 mL). Evaporation of the combined organic layers afforded pure 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes **8a-f**.

3.2.1 | 5-Methyl-2-phenyl-1,3-oxazole-4-carbaldehyde, 8a

Yield = 49%; white solid; M.P. = 88°C; IR (KBr) cm^{-1}: 3064, 2921, 2840, 2741, 1691, 1597, 1129, 1074, 830; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.73 (s, 3H, —CH_3), 7.49 (m, 3H, Ar-H), 8.07 (m, 2H, Ar-H), 10.04 (s, 1H, —CHO); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.8 (—CH_3), 126.3, 126.5, 128.9, 131.0, 135.9, 156.4, 160.4, 185.5 (—C═O). ESI-MS: (m/z) 188.0 $(M + H)^+$ for M = $C_{11}H_9NO_2$.

3.2.2 | 5-Methyl-2-(4-methylphenyl)-1,3-oxazole-4-carbaldehyde, 8b

Yield = 48%; white solid; M.P. = 106°C; IR (KBr) cm^{-1}: 2918, 2861, 2740, 1689, 1596, 1112, 1052, 769; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.41 (s, 3H, —CH_3), 2.73 (s, 3H, —CH_3), 7.28 (d, 2H, J = 8.0 Hz, Ar-H), 7.94 (d, 2H, J = 8.0 Hz, Ar-H), 10.01 (1s, 1H, —CHO); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.7 (—CH_3), 21.5, 123.6, 126.5, 129.6, 135.8, 141.4, 156.3, 160.7, 185.4 (—C═O). ESI-MS: (m/z) 202.0 $(M + H)^+$ for M = $C_{12}H_{11}NO_2$.

3.2.3 | 2-(4-Methoxyphenyl)-5-methyl-1,3-oxazole-4-carbaldehyde, 8c

Yield = 51%; light yellow solid; M.P. = 114°C; IR (KBr) cm^{-1}: 2920, 2839, 1691, 1597, 1441, 1128, 1046, 829; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.73 (s, 3H, —CH_3), 3.71 (s, 3H, —OCH_3), 7.31 (d, 2H, J = 8.0 Hz, Ar-H), 7.86 (d, 2H, J = 8.0 Hz, Ar-H), 10.02 (s, 1H, —CHO); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.7 (—CH_3), 55.8 (—OCH_3), 124.6, 126.5, 128.6, 136.8, 140.4, 155.3, 162.7, 185.6 (—C═O). ESI-MS: (m/z) 218.0 $(M + H)^+$ for M = $C_{12}H_{11}NO_3$.

3.2.4 | 2-(4-Chlorophenyl)-5-methyl-1,3-oxazole-4-carbaldehyde, 8d

Yield = 59%; white solid; M.P. = 109°C; IR (KBr) cm^{-1}: 3071, 2956, 2853, 2746, 1687, 1596, 1066, 1004, 829; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.73 (s, 3H, —CH_3), 7.46 (d, 2H, J = 6.8 Hz, Ar-H), 7.90 (d, 2H, J = 6.8 Hz, Ar-H), 10.02 (s, 1H, —CHO); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.8 (—CH_3), 124.8, 127.3, 127.8, 129.0, 129.2, 135.9, 137.4, 156.7, 159.5, 185.3 (—C═O). ESI-MS: (m/z) 221.95 $(M + H)^+$ for M = $C_{11}H_8ClNO_2$.

3.2.5 | 2-(4-Bromophenyl)-5-methyl-1,3-oxazole-4-carbaldehyde, 8e

Yield = 54%; light yellow solid; M.P. = 128°C; IR (KBr) cm^{-1}: 2956, 2818, 2742, 1687, 1599, 1354, 1064, 1000, 827; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.73 (s, 3H, —CH_3), 7.64 (d, 2H, J = 8.4 Hz, Ar-H), 7.93 (d, 2H, J = 8.4 Hz, Ar-H), 10.02 (s, 1H, —CHO); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.8 (—CH_3), 125.2, 125.6, 127.7, 127.9, 132.0, 132.2, 136.0, 156.7, 159.6, 185.3 (—C═O). ESI-MS: (m/z) 265.90 $(M + H)^+$ for M = $C_{11}H_8BrNO_2$.

3.2.6 | 2-(4-Fluorophenyl)-5-methyl-1,3-oxazole-4-carbaldehyde, 8f

Yield = 50%; light yellow solid; M.P. = 121°C; IR (KBr) cm^{-1}: 3080, 2841, 2740, 1680, 1604, 1506, 1155, 1048, 850; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.73 (s, 3H, —CH_3), 7.18 (m, 2H, Ar-H), 8.15 (m, 2H, Ar-H), 10.02 (s, 1H, —CHO); ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −107.9; ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.8 (—CH_3), 116.2, 116.4, 122.4, 129.20, 129.29, 141.8, 144.4, 162.2, 165.9, 185.9 (—C═O). ESI-MS: (m/z) 206.0 $(M + H)^+$ for M = $C_{11}H_8FNO_2$.

3.3 | General Procedure For The Synthesis of *N′*-([2-aryl-5-methyl-1,3-oxazol-4-yl]methylene)isonicotino/nicotino hydrazides, 10a-l

To a magnetically stirred solution of 2-aryl-5-methyl-1, 3-oxazole-4-carbaldehydes **8a-f** (0.54 mmol, 1 eq) in ethanol, was added an equimolar amount INH **9a/9b** (0.54 mmol, 1 eq) and a few drops of acetic acid as a catalyst. The reaction mixture was refluxed for 3 to 4 hours until the completion of the reaction is observed on TLC. After completion of the reaction, the reaction mixture was poured on crushed ice. The solids precipitated were filtered, washed with ethanol, and recrystallized from ethanol to afford the desired compounds.

3.3.1 | *N′*-([5-methyl-2-phenyl-1,3-oxazol-4-yl]-methylene)-isonicotinohydrazide, 10a

Yield = 0.12 g, 74%; light yellow solid; M.P. = 174°C; IR (KBr) cm^{-1}: 3248, 1690, 1554, 1287, 1218, 846, 687; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.65 (s, 3H, —CH_3), 7.51 (s, 1H, —N═CH—), 7.56 (m, 3H, Ar-H), 7.94 (d, 2H, J = 6.0 Hz, Py-H), 8.02 (d, 2H, J = 7.6 Hz, Ar-H), 8.87 (d, 2H, J = 6.0 Hz, Py-H), 13.88 (s, 1H, —NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 10.9 (—CH_3), 121.3, 124.5, 126.3, 127.7, 131.3, 132.5, 132.6, 1140.7, 150.7, 152.4, 158.8, 162.0 (C═O); ESI-MS: (m/z) 307.11 $(M + H)^+$; Anal. Calc. for $C_{17}H_{14}N_4O_2$; C, 64.23; H, 3.97; N, 3.94; found: C, 63.98; H, 3.75; N, 3.69.

3.3.2 | *N′*-((5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl)-methylene)isonicotino-hydrazide, 10b

Yield = 0.12 g, 79%; light yellow solid; M.P. = 194°C; IR (KBr) cm^{-1}: 3246, 1692, 1500, 1288, 122, 839, 731; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.47 (3H, s, —CH_3), 2.63 (s, 3H, —CH_3), 7.35 (d, 2H, J = 8.0 Hz, Ar-H), 7.49 (s, 1H, —N═CH—), 7.90 (d, 2H, J = 8.4 Hz, Ar-H), 7.94 (d, 2H, J = 6.0 Hz, Py-H), 8.86 (d, 2H, J = 6.0 Hz, Py-H), 13.92 (s, 1H, —NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 10.9 (—CH_3), 21.6 (—CH3), 121.4, 123.0, 126.3, 129.9, 131.1, 133.0, 140.8, 142.2, 150.6, 151.6, 161.9 (C═O); ESI-MS: (m/z) 321.14 $(M + H)^+$. Anal. Calc. for $C_{18}H_{16}N_4O_2$; C, 64.23; H, 3.97; N, 3.94; found: C, 63.98; H, 3.75; N, 3.69.

3.3.3 | *N′*-((2-(4-methoxyphenyl)-5-methyl-1,3-oxazol-4-yl)methylene) isonicotino-hydrazide,10c

Yield = 0.12 g, 79%; light yellow solid; M.P. = 178°C; IR (KBr) cm^{-1}: 3246, 1690, 1525, 1230, 835, 731; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.47 (s, 3H, —CH_3), 3.71 (s, 3H, —OCH_3), 7.34 (d, 2H, J = 8.0 Hz, Ar-H), 7.51 (s, 1H, —N═CH—), 7.92 (d, 2H, J = 8.0 Hz, Ar-H), 7.92 (d, 2H, J = 6.0 Hz, Py-H), 8.86 (d, 2H, J = 6.0 Hz, Py-H), 13.92 (s, 1H, —NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 10.9 (—CH_3), 58.1(—OCH_3), 121.5, 124.0, 125.3, 129.7, 130.1, 132.4, 141.7, 141.3, 151.7, 150.8, 161.8 (C═O); ESI-MS: (m/z) 336.01 $(M + H)^+$; Anal. Calc. for $C_{18}H_{16}N_4O_3$; C, 64.23; H, 3.97; N, 3.94; found: C, 63.98; H, 3.75; N, 3.69.

3.3.4 | *N′*-((2-(4-chlorophenyl)-5-methyl-1,3-oxazol-4-yl)-methylene)-isonicotino-hydrazide,10d

Yield = 0.10 g, 71%; light yellow solid; M.P. = 178°C; IR (KBr) cm^{-1}: 3261, 1695, 1536, 1290, 866, 736; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.65 (s, 3H, —CH_3), 7.49 (s, 1H, —N═CH—), 7.53 (d, 3H, J = 8.8 Hz, Ar-H), 7.91 (d, 2H, J = 4.4 Hz, Py-H), 7.94 (d, 2H, J = 8.8 Hz, Ar-H), 7.95 (s, 1H, —N═CH—), 8.86 (d, 2H, J = 4.4 Hz, Py-H), 13.73 (s, 1H, —NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 10.9 (—CH_3), 121.3, 124.5, 126.3, 127.7, 131.3, 132.5, 132.6, 1140.7, 150.7, 152.4, 158.8, 162.0 (C═O); ESI-MS: (m/z) 341.08 $(M + H)^+$; Anal. Calc. for $C_{17}H_{13}ClN_4O_2$; C, 64.23; H, 3.97; N, 3.94; found: C, 63.98; H, 3.75; N, 3.69.

3.3.5 | *N′*-((2-(4-bromophenyl)-5-methyl-1,3-oxazol-4-yl)-methylene)isonicotino-hydrazide, 10e

Yield = 0.11 g, 78%; light yellow solid; M.P. = 184°C; IR (KBr) cm^{-1}: 3264, 1695, 1535, 1283, 866, 731; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.65 (s, 3H, —CH_3), 7.49 (s, 1H, —N═CH—), 7.69 (d, 2H, J = 8.4 Hz, Ar-H), 7.86 (d,

2H, J = 8.4 Hz, Ar-H), 7.91 (d, 2H, J = 6.0 Hz, Py-H), 8.86 (d, 2H, J = 6.0 Hz, Py-H), 13.72 (s, 1H, —NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 10.9 (—CH_3), 121.3, 124.5, 126.3, 127.7, 131.3, 132.5, 132.6, 1140.7, 150.7, 152.4, 158.8, 162.0 (C=O); ESI-MS: (m/z) 358.03 $(M + H)^+$; Anal. Calc. for $C_{17}H_{13}BrN_4O_2$; C, 64.23; H, 3.97; N, 3.94; found: C, 63.98; H, 3.75; N, 3.69.

3.3.6 | *N′*-((2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl)-methylene) isonicotinohydrazide, 10f

Yield = 0.11 g, 74%; light yellow solid; M.P. = 188°C; IR (KBr) cm^{-1}: 3255, 1694, 1498, 1290, 871, 739; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.65 (s, 3H, —CH_3), 7.24 (d, 2H, J = 8.8 Hz, Ar-H), 7.49 (s, 1H, —N=CH—), 7.91 (d, 1H, J = 6.0 Hz, Py-H), 8.02 (m, 2H, Ar-H), 8.87 (d, 2H, J = 6.0 Hz, Py-H), 13.76 (s, 1H, —NH); ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −106.6; ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 10.9 (—CH_3), 116.6 ($^2J_{CF}$ = 23 Hz), 121.3, 128.5 ($^2J_{CF}$ = 8 Hz), 131.2 ($^3J_{CF}$ = 3 Hz), 132.8, 140.8, 150.7, 162.0 (—C=O); ESI-MS: (m/z) 325.11 $(M + H)^+$; Anal. Calc. for $C_{17}H_{13}FN_4O_2$; C, 64.23; H, 3.97; N, 3.94; found: C, 63.98; H, 3.75; N, 3.69.

3.3.7 | *N′*-([5-methyl-2-phenyl-1,3-oxazol-4-yl]methylene)nicotinohydrazide, 10g

Yield = 0.12 g, 76%; light yellow solid; M.P. = 196°C; IR (KBr) cm^{-1}: 3223, 1655, 1561, 1288, 1194, 874; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.61 (s, 3H, —CH_3 protons), 7.54 (s, 1H, —N=CH—), 7.58 (m, 4H, Ar-H), 7.98 (d, 2H, J = 4.8 Hz, Py-H), 8.25 (d, 1H, J = 8.0 Hz, Ar-H), 8.76 (d, 1H, J = 4.8 Hz, Py-H), 9.04 (d, 1H, J = 2.0 Hz, Py-H), 12.06 (s, 1H, —NH proton); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 11.4 (—CH_3), 124.2, 126.3, 126.7, 129.4, 129.7, 131.3, 132.1, 135.9, 141.1, 148.8, 151.0, 152.8, 159.8, 162.1 (—C=O); ESI-MS: (m/z) 307.12 $(M + H)^+$; Anal. Calc. for $C_{17}H_{14}N_4O_2$; C, 64.23; H, 3.97; N, 3.94; found: C, 63.98; H, 3.75; N, 3.69.

3.3.8 | *N′*-((5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl)-methylene)-nicotinohydrazide, 10h

Yield = 0.12 g, 78%; light yellow solid; M.P. = 178°C; IR (KBr) cm^{-1}: 3218, 1560, 1290, 744, 710; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.47 (s, 3H, —CH_3 protons), 2.63 (s, 3H, —CH_3 protons), 7.48 (s, 1H, —N=CH—), 7.50 (d, 1H, J = 8.0 Hz, Py-H), 7.53 (s, 1H, —CH— proton), 7.70 (d, 2H, J = 8.4 Hz, Ar-H), 7.89 (d, 2H, J = 8.4 Hz, Ar-H), 8.41 (d, 1H, J = 8.0 Hz, Py-H), 8.83 (d, 1H, J = 4.4 Hz, Py-H), 9.29 (s, 1H, Py-H), 13.70 (s, 1H, —NH proton); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.5 (—CH_3), 21.5 (—CH_3), 124.1, 124.2, 126.3, 129.6, 130.2, 132.0, 135.8, 141.1, 141.3, 148.9, 150.4, 152.8, 159.9, 161.9 (—C=O); ESI-MS: (m/z) 321.14 $(M + H)^+$; Anal. Calc. for $C_{18}H_{16}N_4O_2$; C, 64.23; H, 3.97; N, 3.94; found: C, 63.98; H, 3.75; N, 3.69.

3.3.9 | *N′*-((2-(4-methoxyphenyl)-5-methyl-1,3-oxazol-4-yl)methylene) nicotinohydrazide, 10i

Yield = 0.12 g, 78%; light yellow solid; M.P. = 182°C; IR (KBr) cm^{-1}: 3221, 1544, 1275, 836, 721; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.47 (s, 3H, —CH_3 protons), 3.75 (s, 3H, —OCH_3 protons), 7.24 (d, 2H, J = 8.4 Hz, Ar-H), 7.48 (s, 1H, —N=CH—), 7.50 (d, 1H, J = 8.4 Hz, Py-H), 8.04 (d, 2H, J = 8.4 Hz, Ar-H), 8.42 (d, 1H, J = 8.0 Hz, Py-H), 8.84 (d, 1H, J = 3.2 Hz, Py-H), 9.30 (s, 1H, Py-H), 13.72 (s, 1H, —NH proton); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.5 (—CH_3), 55.8 (—OCH_3), 123.1, 124.8, 125.3, 128.7, 131.1, 133.5, 134.8, 140.1, 142.3, 147.5, 151.1, 153.8, 158.6, 161.7 (—C=O); ESI-MS: (m/z) 321.14 $(M + H)^+$; Anal. Calc. for $C_{18}H_{16}N_4O_3$; C, 64.23; H, 3.97; N, 3.94; found: C, 63.98; H, 3.75; N, 3.69.

3.3.10 | *N′*-((2-(4-chlorophenyl)-5-methyl-1,3-oxazol-4-yl)-methylene)-nicotinohydrazide, 10j

Yield = 0.10 g 70%; light yellow solid; M.P. = 194°C; IR (KBr) cm^{-1}: 3295, 1690, 1541, 1289, 845, 734; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.65 (s, 3H, —CH_3 protons), 7.52 (s, 1H, —N=CH—), 7.52 (m, 3H, Ar-H), 7.97 (d, 2H, J = 8.4 Hz, Ar-H), 8.42 (d, 1H, J = 4.0 Hz, Py-H), 8.84 (d, 1H, J = 4.0 Hz, Py-H), 9.30 (s, 1H, Py-H), 13.71 (s, 1H, —NH proton); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.6 (—CH_3), 124.1, 125.6, 128.1, 129.8, 132.3, 135.9, 141.1, 148.9, 150.9, 15.8, 158.8 (—C=O); ESI-MS: (m/z) 341.08 $(M + H)^+$; Anal. Calc. for $C_{17}H_{13}ClN_4O_2$; C, 64.23; H, 3.97; N, 3.94; found: C, 63.98; H, 3.75; N, 3.69.

3.3.11 | *N′*-((2-(4-bromophenyl)-5-methyl-1,3-oxazol-4-yl)-methylene)-nicotinohydrazide, 10k

Yield = 0.11 g, 76%; light yellow solid; M.P. = 202°C; IR (KBr) cm^{-1}: 3218, 1650, 1561, 1220, 846, 709; ^{1}H NMR

(400 MHz, $CDCl_3$, δ ppm): 2.64 (s, 3H, —CH_3), 7.48 (s, 1H, —N═CH—), 7.50 (d, 1H, J = 8.0 Hz, Py-H), 7.53 (s, 1H, —CH— proton), 7.70 (d, 2H, J = 8.4 Hz, Ar-H), 7.89 (d, 2H, J = 8.4 Hz, Ar-H), 8.41 (d, 1H, J = 8.0 Hz, Py-H), 8.83 (d, 1H, J = 4.4 Hz, Py-H), 9.29 (s, 1H, Py-H), 13.70 (s, 1H, —NH proton); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 10.9 (—CH_3), 123.7, 124.5, 126.2, 127.8, 129.4, 131.3, 132.2, 132.6, 135.9, 148.1, 152.0, 158.8, 162.1 (—C═O); ESI-MS: (m/z) 385.03 $(M + H)^+$; Anal. Calc. for $C_{17}H_{13}BrN_4O_2$; C, 64.23; H, 3.97; N, 3.94; found: C, 63.98; H, 3.75; N, 3.69.

3.3.12 | *N′*-((2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl)-methylene)-nicotinohydrazide, 10l

Yield = 0.12 g, 76%; light yellow solid; M.P. = 212°C; IR (KBr) cm^{-1}: 3249, 1692, 1557, 1290, 848, 708; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.64 (s, 3H, —CH_3), 7.24 (d, 2H, J = 8.4 Hz, Ar-H), 7.48 (s, 1H, —N═CH—), 7.50 (d, 1H, J = 8.4 Hz, Py-H), 8.04 (d, 2H, J = 8.4 Hz, Ar-H), 8.42 (d, 1H, J = 8.0 Hz, Py-H), 8.83 (d, 1H, J = 3.2 Hz, Py-H), 9.30 (s, 1H, Py-H),13.72 (s, 1H, —NH proton); ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −106.9; ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.6 (—CH_3), 116.8 ($^2J_{CF}$ = 22 Hz), 124.1, 128.8, 128.9 ($^2J_{CF}$ = 9 Hz), 129.5, 132.2, 135.9, 141.2, 148.9, 152.8, 161.9 (—C═O); ESI-MS: (m/z) 325.12 $(M + H)^+$; Anal. Calc. for $C_{17}H_{13}FN_4O_2$; C, 64.23; H, 3.97; N, 3.94; found: C, 63.98; H, 3.75; N, 3.69.

3.4 | Experimental Procedure For Antitubercular Activity

The preliminary antimycobacterial assessment for the final synthesized compounds was carried out using BACTEC mycobacterial growth indicator tube (MGIT) method. The MGITs containing 4 mL of modified Middle brook 7H9 Broth Base were numbered as per the title compounds to be tasted for antimycobacterial efficacy at various concentrations prepared. The suspension was allowed to sit for 20 minutes and the tubes were centrifuged at 3000 rpm for 15 minutes. After that, prepared suspension of 10^4 to 10^7 CFU/mL of *M. tuberculosis* H37Rv was added in the medium to be incubated and 0.1 mL of egg-based medium (L.J.) was also added. The MGIT tubes were then tightly recapped, mixed well, and incubated into BACTEC MGIT instrument at (37 ± 1)°C until positivity is observed. The readings were measured daily starting from the second day of incubation. Positive cultures were usually detected within 10 days. For reading the actual results, the MGIT tubes were removed from incubator and placed on the UV light next to a positive control tube and an inoculated tube (negative control). Bright fluorescence detected by the corresponding MGIT tube was noticed in the form of bright orange color in the bottom of the tube and also an orange reflection on the meniscus. The primary screening was conducted at concentration of 6.25 μg/mL against *M. tuberculosis* H37Rv in BACTEC MGIT system. If any compound is demonstrating 99% inhibition in the primary screen, it is described as the most potent compound. All the other compounds were re-examined for their actual MIC by using Lowenstein-Jensen MIC method. The highest dilution showing at least 99% inhibition is taken as MIC.

The secondary antimycobacterial screening for test compounds was obtained for *M. tuberculosis* H37Rv, by using L.J. (Lowenstein and Jensen) MIC method. 2-fold serial dilutions (50.0, 25.0, 12.5, 6.25, 3.13, 1.56, and 0.78 μg/mL) of each test compound in DMSO (dimethyl sulfoxide) were added in the liquid L.J. Medium and then media were sterilized by inspissation method. A culture of *M. tuberculosis* H37Rv growing on L.J. medium was harvested in 0.85% saline in bijou bottles. These tubes were then incubated at 37°C for 24 hours followed by streaking of *M. tuberculosis* H37Rv (5×10^4 bacilli per tube). These tubes were then incubated at 37°C ± 1°C. Growth of bacilli was seen after 12 days, 22 days, and finally 28 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with *M. tuberculosis* H37Rv. The concentration at which no development of colonies occurred or <20 colonies was taken as MIC concentration of test compound. INH was used as a reference control against *M. tuberculosis* H37Rv being a standard drug in use.

3.5 | Cytotoxicity Evaluation

Anti-tubercular active compounds with MIC ≤12.5 μg/mL were further examined for cytotoxicity in a HEK-293T cell line at the concentration 50 μg/mL. After 24 hours of exposure, cell viability of HEK-293T cells was evaluated based on cellular conversion of MTT into a formazan product.

4 | CONCLUSION

In this study, we reported the synthesis of *N′*-([2-aryl-5-methyl-1,3-oxazole-4-yl]methylene)isonicotino/nicotino hydrazides **10a-l** by the condensation reaction of 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes **8a-f** with the corresponding isonicotino/nicotino hydrazides **9a/9b**. in vitro antitubercular evaluations and docking studies showed that

the derivative compounds (**10a-l**) exhibited important activity against *M. tuberculosis* H37Rv. Two hybrid compounds **10c** and **10i** displayed the highest inhibition with MIC value of 1.56 μg/mL. Furthermore, the current study showed that the presence of methyl and methoxy groups significantly affected the behavior of INH-1,3-oxazole hybrids as antitubercular agents. Further structural modifications to these derivatives could be used to prepare a library of antitubercular analogs with enhanced activity and selectivity.

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