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Synthesis and antimycobacterial activity of 4-[5-(substituted phenyl)-4, 5-dihydro-3-isoxazolyl]-2-methylphenols

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Abstract
Compounds based on the isoxazoline moiety were screened for their antimycobacterial activity *in vitro* against *Mycobacterium tuberculosis* H37R (MTB), and INH (isoniazid) resistant *Mycobacterium tuberculosis* (INHR-MTB) using the agar dilution method and bactec 460. Among the synthesized compounds, 4-[5-(4-bromophenyl)-4,5-dihydro-3-isoxazolyl]-2-methylphenol (**4l**) was found to be the most active agent against MTB and INHR-MTB with minimum inhibitory concentration of 0.62 μM. When compared to INH, compound (**4l**) was 1.12 fold and 3.0 fold more active against MTB and INHR-MTB, respectively.

Keywords: *Isoxazolyl, antimycobacterial agent,* Mycobacterium tuberculosis.

Introduction

Tuberculosis (TB) is a bacterial disease caused by *Mycobacterium tuberculosis*, and occasionally by other species of the *Mycobacterium tuberculosis* complex that includes *Mycobacterium bovis*, *Mycobacterium africanum* and *Mycobacterium canetti*. These organisms are also known as tubercle bacilli or Acid-Fast Bacilli (AFB) [1]. Tuberculosis is by far the most frequently encountered mycobacterial disease in the world. Among infectious diseases, tuberculosis (TB) is the number one killer with over two million casualties annually worldwide. The WHO considers tuberculosis, to be the most dangerous chronic communicable disease in the world [2]. The emergence of AIDS, decline of socioeconomic standards and a reduced emphasis on tuberculosis control programs contribute to the disease's resurgence in industrialized countries [3]. Resistance of *Mycobacterium tuberculosis* strains to anti-mycobacterial agents is an increasing problem worldwide [4–6]. However, powerful new anti-TB drugs with new mechanisms of action have not been developed in the last forty years. In spite of severe toxicity on repeated dosing of isoniazid (INH) it is still considered to be a first line drug for chemotherapy of tuberculosis. The current work describes the synthesis of novel isoxazoline moiety with encouraging anti-mycobacterial activity against *M. tuberculosis* $H_{37}Rv$ and INH resistant *Mycobacterium tuberculosis* (INHR-MTB).

Materials & methods

All chemicals were supplied by E.Merck (Germany) and S.D Fine Chemicals (India). Melting points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked on thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene-ethylformate-formicacid (5:4:1) and benzene (CARE-CARCINOGENIC)-methanol (8:2), the spots were located under iodine vapors or UV light. IR spectrums were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBr Pellets). ^1H – NMR spectra were recorded or a

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Bruker AC 300 MHz spectrometer using TMS as internal standard in DMSO-d_6.

Chemistry

General method for the preparation of compounds ***(3a-m)***

1-(4-hydroxy-3-methyl-phenyl)-3-(substituted phenyl)-2-Propen-1-one. 4-hydroxy-3-methyl acetophenone (1.5017 g, 0.01mmoL) and the appropriate aldehyde (0.01mmoL), were dissolved in ethanol and sodium hydroxide (30%, 5mL) with 10mL of petroleum ether was stirred under room temperature for 4 h. The resulting solution was allowed to stand overnight and then poured into ice-cold water and neutralized with HCl. The solid which separated was filtered off, dried and purified from ethanol.

1-(4′-hydroxy-3′-methyl-phenyl-3-(4″-methoxy phenyl)-2-propen-1-one (3a). IR: (KBr) cm^{-1}: 3200 (OH), 3042 (CH), 1686 (C═O). ***^{1}H NMR (DMSO-d_6 ppm):*** 2.2 (3H,s,CH_3), 3.9 (3H,s, OCH_3),6.8-6.9(1H × 2,d $\mathcal{J}$ = 7.5 Hz, 8.5 Hz, CH═CH), 7.2-7.9 (7H,s, aromatic), 9.2 (1H,s, OH).

1-(4′-hydroxy-3′-methyl-phenyl)-3-(4″-choloro phenyl)-2-propen-1-one (3b). IR: (KBr) cm^{-1}: 3210 (OH), 3030 (CH), 1676 (C═O).***^{1}H NMR (DMSO-d_6 ppm):*** 2.2 (3H,s, CH_3), 6.7-6.8(1H × 2,d $\mathcal{J}$ = 8.34 Hz, 6.79 Hz, CH═CH), 7.7-8.0(7H,m, aromatic), 9.2(1H,s,OH).

1-(4′-hydroxy-3-methyl-phenyl)-3-(4″-dimethyl amino phenyl)-2-propen-1-one* (3c). *IR: (KBr) cm^{-1}: 3200 (OH), 3040 (CH), 1680 (C═O). ***^{1}H NMR (DMSO-d_6 ppm):*** 2.2(3H,s,CH_3), 2.83(6H,s, N (CH_3 × 2), 6.8-6.9(1H × 2,d $\mathcal{J}$ = 7.61 Hz, 7.63 Hz, CH═CH), 7.6-8.1(7H,m, aromatic), 9.2 (1H,s, OH).

1-(4′-hydroxy-3′-methyl-phenyl)-3-phenyl-2-propen-1-one (3d). IR: (KBr) cm^{-1}: 3210 (OH), 1680 (C═O), 3042 (CH). ***^{1}H NMR (DMSO-d_6 ppm):*** 2.2(3H,s,CH_3), 6.8-7.4(1H × 2,d $\mathcal{J}$ = 8.28 Hz, 6.70 Hz, CH═CH), 7.7-8.2(8H,m, aromatic), 9.2 (1H,s, OH).

1-(4′-hydroxy-3′-methyl-phenyl)-3-(3″,4″-dimethoxy phenyl)-2-propen-1-one (3e). IR: (KBr) cm^{-1}: 3232(OH), 3046 (CH), 1680 (C═O). ***^{1}H NMR (DMSO-d6) ppm:*** 2.2(3H,s, CH_3), 3.9(6H,s, OCH_3 × 2), 6.9-7.3(1H × 2,d $\mathcal{J}$ = 7.45 Hz,, 7.29 Hz, CH═CH), 7.6-8.1(6H,m, aromatic), 9.2 (1H,s, OH).

1-(4′-hydroxy-3′-methyl-phenyl)-3-(3″,4″,5″ trimethoxy0 phenyl)-2-propen-1-one (3f). IR: (KBr) cm^{-1}: 3220(OH), 3036 (CH), 1686 (C═O). ***^{1}H NMR (DMSO-d_6 ppm):*** 2.2(3H,s,CH_3), 3.9 (9H,s,OCH_3 × 3), 6.9-7.5(1H × 2,d $\mathcal{J}$ = 7.55 Hz, 7.27 Hz, CH═CH), 7.7-8.1 (5H,m, aromatic), 9.2 (1H,s, OH).

1-(4′-hydroxy-3′-methyl-phenyl)-3-(4″-fluoro phenyl)-2-propen-1-one (3g). IR: (KBr) cm^{-1}: 3200 (OH), 3040 (CH), 1680 (C═O). ***^{1}H NMR (DMSO-d_6 ppm):*** 2.2 (3H,s,CH_3), 7.7-8.2(7H,m, aromatic), 6.9-7.5 (1H × 2,d $\mathcal{J}$ = 7.24 Hz,7.29 Hz, —CH═CH), 9.2 (1H,s, OH).

1-(4′-hydroxy-3′-methyl-phenyl)-3-(2″-chloro phenyl)-2-propen-1-one (3h). IR: (KBr) cm^{-1}: 3200 (OH), 3042(CH), 1684 (C═O). ***^{1}H NMR (DMSO-d_6 ppm):*** 2.2 (3H,s, CH_3), 7.6-8.0(7H,m, aromatic), 6.9-7.5 (1H × 2,d $\mathcal{J}$ = 8.35 Hz, 3.63 Hz, —CH═CH), 9.2 (1H,s,OH).

1-(4′-hydroxy-3′-methyl-phenyl)-3-(2″,6″ dichloro phenyl)-2-propen-1-one (3i). IR: (KBr) cm^{-1}: 3210 (OH), 3040 (CH), 1670 (C═O). ***^{1}H NMR (DMSO-d_6 ppm):*** 2.2 (3H,s, CH_3), 7.7-8.0 (6H,m, aromatic), 6.9-7.5(1H × 2,d $\mathcal{J}$ = 5.41 Hz, 15.68 Hz, CH═CH), 9.2 (1H,s, OH).

1-(4′-hydroxy-3′-methyl-phenyl)-3-(3′-nitro phenyl)-2-propen-1-one (3j). IR: (KBr) cm^{-1}: 3200 (OH), 3040 (CH), 1680(C═O). ***^{1}H NMR (DMSO-d_6 ppm):*** 2.2 (3H,s, CH_3), 2 7.7-8.2 (7H,m, aromatic), 6.9-7.5 (1H × 2,d $\mathcal{J}$ = 5.46 Hz, 16.3 Hz, CH═CH), 9.2 (1H,s, OH).

1-(4′-hydroxy-3′-methyl-phenyl)-3-furfuryl-2-propen-1-one (3k). IR: (KBr) cm^{-1}: 3200(OH), 3040(CH), 1680(C═O). ^{1}H NMR (DMSO-d_6 ppm): 2.2 (3H,s, CH_3), 7.7-8.2 (6H,m, aromatic), 6.4-7.4 (3H,m, furan), 6.8-6.9 (1H × 2,d $\mathcal{J}$ = 3.0 Hz, 8.36 Hz, CH═CH), 9.2 (1H,s, OH).

1-(4′-hydroxy-3′-methyl-phenyl)-3-(4″-bromo phenyl)-2-propen-1-one (3l). IR: (KBr) cm^{-1}: 3210 (OH), 3030 (CH), 1676 (C═O). ***^{1}H NMR (DMSO-d_6 ppm):*** 2.1(3H,s, CH_3), 6.8-7.1(1H × 2,d $\mathcal{J}$ = 8.23 Hz, 6.72 Hz, CH═CH), 7.7-8.0(7H,m, aromatic), 9.2(1H,s, OH).

1-(4′-hydroxy-3′-methyl-phenyl)-3-(4-hydroxy-3″-methoxyphenyl)-2-propen-1-one (3m). IR: (KBr) cm^{-1}: 3232(OH), 3046 (CH), 1680 (C═O). ***^{1}H NMR (DMSO-d6) ppm:*** 2.2(3H,s, CH_3), 3.9(3H,s, OCH_3), 6.9-7.3(1H × 2,d $\mathcal{J}$ = 7.45 Hz,, 7.29 Hz, CH═CH), 7.6-8.1(6H,m, aromatic), 9.2,9.3 (1H × 2,s, OH).

General method for the preparation of compounds ***(4a-m)***

Synthesis of 4-[5-(substituted phenyl)-4, 5-dihydro-3-isoxazolyl]-2-methylphenol ***(4a-m)***. To the solution of 0.002 moles of the appropriate **(4a-m)** derivatives in 15mL of glacial acetic acid 0.002 moles hydroxylamine HCl was added and the reaction mixture was refluxed for 15 h and cooled. Excess of solvent was removed under reduced pressure and the reaction mixture was cooled, poured onto crushed ice (20 gm).

The product so obtained was filtered, washed with water and recrystallized from methanol.

4-[5-(4-methoxyphenyl)-4,5-dihydro-3-isoxazolyl]-2-methylphenol (4a)*. *IR:(KBr)cm^{-1}: 1628(C=N),1612(C=C); ***^{1}H NMR(DMSO-d_6) ppm:*** 2.34(3H, s, CH_3), 3.56-3.59 (2H, dd, CH_2 J = 6.4 Hz, J = 17 Hz), 3.76(3H, s, OCH_3), 5.78-5.82(1H,t,CH J = 6.4 Hz), 6.78-7.26(7H,m,Ar).

4-[5-(4-chlorophenyl)-4,5-dihydro-3-isoxazolyl]-2-methylphenol (4b)*. *IR:(KBr)cm^{-1}: 1596 (C=N),1600(C=C); ***^{1}H NMR(DMSO-d_6)ppm:*** 2.34(3H, s, CH_3), 3.56-3.59 (2H, dd,CH_2 J = 6.4 Hz, J = 17 Hz), 5.78-5.82(1H,t,CH J = 6.4 Hz),6.78-7.36(7H,m,Ar).

4-[5-(4-dimethylaminophenyl)-4,5-dihydro-3-isoxazolyl]-2-methylphenol (4c)*. *IR:(KBr)cm^{-1}: 1592(C=N),1600(C=C); ***^{1}H NMR(DMSO-d_6) ppm:*** 2.34(3H, s, CH_3), 2.46 (6H,s,$NH_3 \times 2$), 3.56-3.59 (2H, dd, CH_2 J = 6.4 Hz, J = 17 Hz), 5.78-5.82(1H,t,CH J = 6.4 Hz), 6.98-7.6(7H,m,Ar).

4-[5-phenyl-4,5-dihydro-3-isoxazolyl)-2-methyl phenol (4d)*. *IR:(KBr)cm^{-1}: 1596(C=N),1608 (C=C); ***^{1}H NMR(DMSO-d_6)ppm:*** 2.34(3H,s, CH_3),3.56-3.59 (2H, dd, CH_2 J = 6.4 Hz, J = 17 Hz), 5.78-5.82(1H,t,CH J = 6.4 Hz),6.88-7.32(8H,m,Ar).

4-[5-(3,4-dimethoxyphenyl)-4,5-dihydro-3-isoxazolyl]-2-methylphenol (4e)*. *IR:(KBr)cm^{-1}: 1600(C=N),1622(C=C); ***^{1}H NMR(DMSO-d_6) ppm:*** 2.34(3H, s, CH_3), 3.56-3.59 (2H, dd, CH_2 J = 6.4 Hz, J = 17 Hz), 3.76(6H, s, $OCH_3 \times 2$), 5.78-5.82(1H,t,CH J = 6.4 Hz),6.78-7.26(6H,m,Ar).

4-[5-(3, 4, 5-trimethoxyphenyl)-4,5-dihydro-3-isoxazolyl] 2-methyl-phenol (4f)*. *IR:(KBr)cm^{-1}: 1600(C=N),1618(C=C); ***^{1}H NMR(DMSO-d_6) ppm:*** 2.34(3H, s, CH_3), 3.56-3.59 (2H, dd, CH_2 J = 6.4 Hz, J = 17 Hz), 3.76(9H, s, $OCH_3 \times 3$), 5.78-5.82(1H,t,CH J = 6.4 Hz), 6.78-7.26(5H,m,Ar).

4-[5-(4-flourophenyl)-4, 5-dihydro-3-isoxazolyl]-2-methylphenol (4g)*. *IR:(KBr)cm^{-1}: 1600 (C=N),1624(C=C),772(C-Cl); ***^{1}H NMR(DMSO-d_6)ppm:*** 2.34(3H, s, CH_3), 3.56-3.59 (2H, dd, CH_2 J = 6.4 Hz, J = 17 Hz), 5.78-5.82 (1H, t, CH J = 6.4 Hz), 6.78-7.36(7H,m,Ar).

4-[5-(2-chlorophenyl)-4, 5-dihydro-3-isoxazolyl]-2-methylphenol (4h)*. *IR:(KBr)cm^{-1}: 1600 (C=N),1622(C=C),772(C-Cl); ***^{1}H NMR(DMSO-d_6)ppm:*** 2.34(3H, s, CH_3), 3.56-3.59 (2H, dd, CH_2 J = 6.4 Hz, J = 17 Hz), 5.78-5.82 (1H, t, CH J = 6.4 Hz), 6.78-7.36(7H,m,Ar).

4-[5-(2, 6-dichlorophenyl)-4, 5-dihydro-3-isoxazolyl]-2-methylphenol (4i)*. *IR:(KBr)cm^{-1}: 1606(C=N),1618(C=C) 772(C-Cl); ***^{1}H NMR (DMSO-d_6)ppm:*** 2.34(3H, s, CH_3), 3.56-3.59 (2H, dd, CH_2 J = 6.4 Hz, J = 17 Hz), 5.78-5.82(1H,t,CH J = 6.4 Hz), 6.78-7.36(6H,m,Ar).

4-[5-(3-nitrophenyl)-4,5-dihydro-3-isoxazolyl]-2-methyl-phenol (4j)*. *IR:(KBr)cm^{-1}: 1596(C=N),1600(C=C); ***^{1}H NMR(DMSO-d_6)ppm:*** 2.34 (3H,s,CH_3), 3.56-3.59 (2H, dd, CH_2 J = 6.4 Hz, J = 17 Hz), 5.78-5.82(1H,t,CH J = 6 Hz),6.82-8.12(7H,m,Ar).

4-[5-(2-furyl)-4,5-dihydro-3-isoxazolyl]-2-methylphenol (4k)*. *IR:(KBr)cm^{-1}: 1606(C=N), 1612(C=C); ***^{1}H NMR(DMSO-d_6)ppm:*** 2.34(3H, s,CH_3),3.56-3.59 (2H, dd,CH_2 J = 6.4 Hz, J = 17 Hz), 3.92 (3H,s,OCH_3),5.78-5.82(1H,t,CH J = 6.4 Hz),6.82-7.43(3H,m,furan),6.2-6.7(3H,m,Ar).

4-[5-(4-bromophenyl)-4,5-dihydro-3-isoxazolyl]-2-methylphenol (4l)*. *IR:(KBr)cm^{-1}: 1602 (C=N),1610(C=C); ***^{1}H NMR(DMSO-d_6)ppm:*** 2.34(3H,s,CH_3), 3.56-3.59 (2H, dd, CH_2 J = 6.4 Hz, J = 17 Hz), 5.78-5.82(1H,t,CH J = 6.4 Hz),6.88-7.32(7H,m,Ar).

4-[5-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-3-isoxazolyl]-2-methylphenol (4m). ***IR:(KBr)cm^{-1}:*** 1600(C=N),1608(C=C);***^{1}H NMR (DMSO-d_6)ppm:*** 2.34(3H,s,CH_3), 3.56-3.59 (2H, dd, CH_2 J = 6.4 Hz, J = 17 Hz), 3.92(3H,s, OCH_3),5.78-5.82(1H,t,CH J = 6.4 Hz),6.82-8.12 (6H,m,Ar), 9.2,9.7 (1H $\times$ 2, s,OH);

Biology

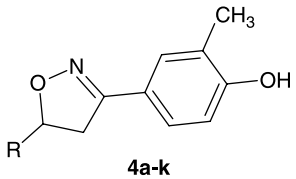
The primary screening was conducted at a concentration of 6.25μg/mL (or molar equivalent of highest molecular weight compound in a series of congeners) against *M. tuberculosis* H37Rv (ATCC27294) and INH resistant *M. tuberculosis* in the agar dilution technique and Bactec 460 [7–8]. Compound demonstrating at least 90% inhibition in the primary screen was re-examined at lower concentration (MIC) in broth micro dilution assay with almar blue. The MIC was defined as the lowest concentration inhibiting ~99% of the innoculum. Concurrent with the determination of MICs, compounds were tested for cytotoxicity (IC_{50}) in VERO at concentration equal to and greater than the MIC for *M. tuberculosis* H37Rv and INH resistant *M. tuberculosis* after 72 h exposure. Viability was assessed on the basis of cellular conversion of MTT in to a formazan product using the promega cell Titer 96 non radioactive cell proliferation assay [9].

Results and discussion

Chemistry

The 4-[5-(substituted phenyl)-4, 5-dihydro-3-isoxazolyl]-2-methylphenols **4a-m** described in this study

Table I. Physical constants and antimycobacterial activity of the synthesized compounds.

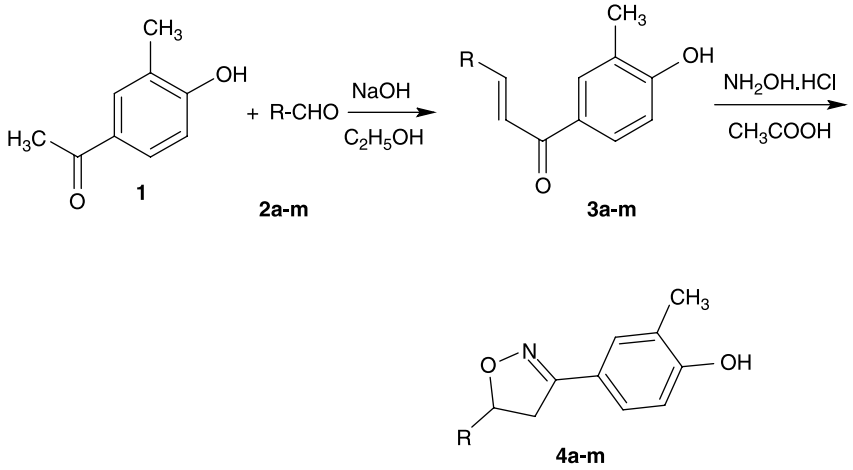


4a-k

Compound	**R**	Yield (%)	M.P (°C)	Cytotoxicity	(MIC) μM MTB[a]	MTB[b]
4a	4-methoxy phenyl-	74	170–72	>62.25	>6.25	>6.25
4b	4-Chloro phenyl-	80	178–80	>62.25	0.83	0.93
4c	4-Dimethylamino phenyl-	85	130–32	>62.25	>6.25	>6.25
4d	Phenyl-	65	105–07	>62.25	>6.25	6.25
4e	3,4-Dimethoxy phenyl-	85	154–57	>62.25	>6.25	>6.25
4f	3,4,5-Trimethoxy phenyl-	76	117–19	>62.25	>6.25	>6.25
4g	4-Fluoro phenyl-	82	126–28	>62.25	1.32	2.92
4h	2-Chloro phenyl-	94	162–64	>62.25	0.72	0.83
4i	2,6-Dichloro phenyl-	80	141–43	>62.25	1.82	2.90
4j	3-Nitro Phenyl-	78	172–74	>62.25	6.25	6.12
4k	Furfuryl-	90	144–46	>62.25	2.76	4.82
4l	4-Bromophenyl	78	152–54	>62.25	0.62	0.62
4m	4-Hydroxy-3-methoxy phenyl	90	144–46	>62.25	>6.25	6.25
INH	–	–	–	>62.25	0.70	1.86

[a] *Mycobacterium tuberculosis* $H_{37}Rv$; [b] INH resistant *Mycobacterium tuberculosis*.

are shown in Table I, and a reaction sequence for the preparation is outlined in Scheme I. The required chalcones were prepared by reacting 3-methyl-4-hydroxy acetophenone with the appropriate aldehyde in the presence of base by a conventional Claisen-Schmidt condensation. Reaction between chalcone with hydroxylamine HCl in glacial acetic acid (reaction time varied from 9-12 h) afforded the titled isoxazolines (**4a-m**) in 76-94% yield after recrystallization and purity was checked by TLC. Both analytical and spectral data (^{1}H-NMR, IR) of all the synthesized compounds were in full agreement with the proposed structures. In general, Infra Red spectra (IR) revealed, OH, CH, C=N peaks at 3300, 3040, 1600, cm^{-1}, respectively. The ^{1}H NMR spectra showed a singlet at δ 2.3 ppm corresponding to the methyl group; double doublet at δ 3.56-3.59 ppm corresponding to the C-4 methylene group; a singlet at δ 3.92 ppm corresponding to the OCH_3 group; double doublet at δ 5.78-5.82 ppm corresponding to C-5 proton; a multiplet at δ 6.82-8.12 ppm for the aromatic protons; and a singlet at δ 9.7 ppm corresponding to the OH proton. The elemental analysis results (not shown) were within ±0.4% of the theoretical values.



Scheme I. Protocol for synthesis of 4-[5-(substituted phenyl)-4, 5-dihydro-3-isoxazolyl]-2-methylphenols.

Antimycobacterial activity

The synthesized compounds **4a-m** was tested for their antimycobacterial activity *in vitro* against MTB and INHR-MTB by using the agar dilution method and bactec 460 for the determination of the Minimum Inhibitory Concentration (MIC). The MIC was defined as the minimum concentration of compound required to inhibit ~99% of bacterial growth and MIC's of the compounds are reported in Table I with the standard drug INH for comparison.

Among the thirteen compounds synthesized, three compounds were found to be most active compounds with MICs of less than 1 μM, against MTB. In general compounds with halogen-substituted phenyl group showed more activity. Among the synthesized compounds, compounds **4l**, 4-[5-(4-bromophenyl)-4,5-dihydro-3-isoxazolyl]-2-methylphenol, was found to be the most active agent against MTB and INHR-MTB with MIC of 0.62 μM. Compounds with a 4-chloro phenyl (**4b**) or 2-chlorophenyl (**4h**) substituent were also found to be active against MTB with MIC of 0.83, and 0.72 μM, respectively. Among these compounds that with the 4- bromophenyl substituent (**4l**) was found to be 1.12-fold and 3.0-fold more active than INH against MTB and INHR-MTB, respectively. However fluorophenyl and nitrophenyl substitutions produced moderate inhibitory activity against MTB and INHR-MTB. On the other hand the analogues with an electron donating group (OCH_3) 4-methoxyphenyl (**4a**), 3′,4′ dimethoxy phenyl (**4e**) and 3′,4′, 5′ trimethoxy phenyl (**4f**) exhibited relatively low inhibitory activity against MTB and INHR-MTB.

Among the newer derivatives, compound **4l** showed a promising activity *in-vitro*. It is conceivable that these derivatives showing antimycobacterial activity can be further modified to exhibit better potency than the standard drugs and further studies are in progress in our laboratory.

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