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SYNTHESIS AND *IN-VITRO* ANTIMYCOBACTERIAL ACTIVITY OF AMINO-5-[(SUBSTITUTED) PHENYL]-3-(4-HYDROXY-3-METHYLPHENYL)-4,5-DIHYDRO-1*H*-1-PYRAZOLYLMETHANETHIONE

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Abstract: A series of amino-5-[(substituted) phenyl]-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione were synthesized by the reaction between thiosemicarbazide and chalcones and were tested for their antimycobacterial activity *in vitro* against *Mycobacterium tuberculosis* $H_{37}R_v$ and INH resistant *Mycobacterium tuberculosis* using bactec method. Among the synthesized compounds, compound (**4b**), amino-5-(4-chlorophenyl)-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione was found to be the most active agent against *Mycobacterium tuberculosis* $H37_{Rv}$ (MTB) and INH resistant *Mycobacterium tuberculosis* (INHR-MTB) with minimum inhibitory concentration of 0.43 μM . When compared to INH- compound (**4b**) was found to be 1.62 fold and 26.41 fold more active against MTB and INHR-MTB, respectively.

Keywords: antimycobacterial, pyrazoline

Mycobacterium tuberculosis is the primary cause of mortality due to an infectious disease in the world today. Mycobacteria are ubiquitous organisms that are becoming increasingly important intracellular pathogen that establishes an infection in oxygen-rich macrophage of the lung (1). 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 (2). Resistance of *Mycobacterium tuberculosis* strains to anti-mycobacterial agents is an increasing problem worldwide (3-5). However, powerful new anti-TB drugs with new mechanism 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 a first line drug for chemotherapy of tuberculosis (6). Literature survey reveals that pyrazoline derivatives are active against many *Mycobacterias* (7-10). The current work describes the synthesis of novel pyrazoline moiety with encouraging antimycobacterial activity against *M. tuberculosis* H_{37}Rv.

EXPERIMENTAL

All chemicals were supplied by E. Merck (Germany) and S.D. Fine Chemicals (India). Melting points were determined by the open tube capillary method and are uncorrected. Purity of the compounds was checked using thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene-ethyl formate-formic acid (5:4:1, v/v/v) and benzene-methanol (8:2, v/v) The spots were located under iodine vapors and UV light. IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBr pellets). ^{1}H-NMR spectra were recorded or a Bruker AC 300 MHz spectrometer using TMS as an internal standard in DMSO-d_6/ $CDCl_3$ and mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing voltage with a VG Prospec instrument and are presented as *m*/*z*.

General procedure for synthesis of 1-(4'-hydroxy-3'-methylphenyl)-3-(substituted phenyl) 2-propen-1-one (**3a-k**)

1-(4'-Hydroxy-3'-methylphenyl)-3-(substituted phenyl) 2-propen-1-one derivatives were synthesized by condensing 4-hydroxy-3-methylacetophenone with appropriate aromatic aldehydes according to Claisen-Schmidt condensation.

1-(4'-Hydroxy-3'-methylphenyl-3-(4''-methoxyphenyl)-2-propen-1-one (**3a**)

IR (KBr, cm^{-1}): 3200 (OH), 3042 (CH), 1686 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s,

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CH_3), 3.9 (3H, s, OCH_3), 6.8-6.9 (1H × 2, d *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'-methylphenyl)-3-(4''-cholorophenyl)-2-propen-1-one (**3b**)

IR (KBr, cm^{-1}): 3210 (OH), 3030 (CH), 1676 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s, CH_3), 6.7-6.8 (1H × 2, d *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-methylphenyl)-3-(4''-dimethylaminophenyl)-2-propen-1-one (**3c**)

IR (KBr, cm^{-1}): 3200 (OH), 3040 (CH), 1680 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s, CH_3), 2.83 (6H, s, N (CH_3 × 2), 6.8-6.9 (1H × 2, d *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, δ, ppm): 2.2 (3 H, s, CH_3), 6.8-7.4 (1H × 2,d *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'-methylphenyl)-3-(3'',4''-dimethoxyphenyl)-2-propen-1-one (**3e**)

IR (KBr, cm^{-1}): 3232 (OH), 3046 (CH), 1680 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s, CH_3), 3.9 (6H, s, OCH_3 × 2), 6.9-7.3 (1H × 2, d *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'-methylphenyl)-3-(3'',4'',5''-trimethoxyphenyl)-2-propen-1-one (**3f**)

IR (KBr, cm^{-1}): 3220 (OH), 3036 (CH), 1686 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s, CH_3), 3.9 (9H, s,OCH_3 × 3), 6.9-7.5 (1H × 2, d *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'-methylphenyl)-3-(4''-fluorophenyl)-2-propen-1-one (**3g**)

IR (KBr, cm^{-1}): 3200 (OH), 3040 (CH), 1680 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s, CH_3), 7.7-8.2 (7H, m, aromatic), 6.9-7.5 (1H × 2, d *J* = 7.24 Hz, 7.29 Hz CH=CH), 9.2 (1H, s, OH).

1-(4'-Hydroxy-3'-methylphenyl)-3-(2''-chlorophenyl)-2-propen-1-one (**3h**)

IR (KBr, cm^{-1}): 3200 (OH), 3042 (CH), 1684 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s, CH_3), 7.6-8.0 (7H, m, aromatic), 6.9 -7.5 (1H × 2, d *J* = 8.35 Hz, 3.63 Hz CH=CH), 9.2 (1H, s, OH).

1-(4'-Hydroxy-3'-methylphenyl)-3-(2'',6''-dichlorophenyl)-2-propen-1-one (**3i**)

IR (KBr, cm^{-1}): 3210 (OH), 3040 (CH), 1670 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s, CH_3), 7.7-8.0 (6H, m, aromatic), 6.9 -7.5 (1H × 2, d *J* = 5.41 Hz, 15.68 Hz CH=CH), 9.2 (1H, s, OH).

1-(4'-Hydroxy-3'-methylphenyl)-3-(3'-nitrophenyl)-2-propen-1-one (**3j**)

IR (KBr, cm^{-1}): 3200 (OH), 3040 (CH), 1680 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s, CH_3), 2 7.7-8.2 (7H, m, aromatic), 6.9-7.5 (1H × 2, d *J* = 5.46 Hz, 16.3 Hz CH=CH), 9.2 (1H, s, OH).

1-(4'-Hydroxy-3'-methylphenyl)-3-furfuryl-2-propen-1-one (**3k**)

IR (KBr, cm^{-1}): 3200 (OH), 3040 (CH), 1680 (C=O). ^{1}H-NMR (DMSO-d_6, δ, 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 *J* = 3.0 Hz, 8.36 Hz, CH=CH), 9.2 (1H, s, OH).

General procedure for amino-5-(substituted phenyl)-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethiones **(4a-k)**

To the solution of (0.002 mole) of the appropriate chalcone (**3a-k)** derivative in 15 mL of glacial acetic acid (0.003 mole) of thiosemicabazide was added and the reaction mixture was refluxed for 12 h. The 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**.**

Amino-5-(4'-methoxyphenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione (**4a**)

IR (KBr, cm^{-1}): 3320 (NH_2), 3307 (OH), 1590 (C=N), 1320 (C-N) 1130 (C=S); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.4 (3H, s, CH_3), 2.3 (2H, s, CH_2), 3.8 (3H, s, OCH_3), 4.14 (1H, s, CH), 6.86 (2H, s, NH_2), 7.3-7.8 (7H, m, Ar), 9.1 (1H, s, OH); EI-MS (m/z): 341(M^+); Analysis (calc.) found: C (63.32) 63.30, H (5.61) 5.60, N (12.31) 12.30.

Amino-5-(4'-chlorophenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione (**4b**)

IR (KBr, cm^{-1}): 3320 (NH_2), 3307 (OH), 772 (C-Cl), 1590 (C=N), 1320 (C-N), 1130 (C=S); ^{1}H-

NMR (DMSO-d_6, δ, ppm): 1.4 (3H, s, CH_3), 2.3 (2H, s, CH_2), 3.8 (3H, s, OCH_3), 4.14(1H, s, CH), 6.86 (2H, s, NH_2), 7.3-7.8 (7H, m, Ar), 13.0 (1H, s, OH); EI-MS (m/z): 345(M^+); Analysis (calc.) found: C (59.04) 59.07, H (4.66) 4.60, N (12.15) 12.10.

Amino-5-(4'-dimethylaminophenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione (**4c**)

IR (KBr, cm^{-1}): 3320 (NH_2), 3307 (OH), 1590 (C=N), 1320 (C-N), 1130 (C=S); ^{1}H-NMR (DMSO-d_6, d, ppm): 1.6 (2H, s, CH_2), 2.1 (3H, s, CH_3), 2.3 (6H, s, $N(CH_3)_2$), 4.24 (1H, s, CH), 6.86 (2H, s, NH_2), 7.3-7.8 (7H, m, Ar), 9.1 (1H, s, OH); EI-MS (m/z): 352 $(M-3)^+$; Analysis (calc.) found: C (64.38) 64.34, H (6.26) 6.24, N (15.81) 15.76.

Amino-3-(4'-hydroxy-3'-methylphenyl)-5-phenyl-4,5-dihydro-1*H*-1-pyrazolyl methanethione (**4d**)

IR (KBr, cm^{-1}): 3320 (NH_2), 3307 (OH), 1590 (C=N), 1320 (C-N), 1130 (C=S); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.8 (2H, s, CH_2), 2.3 (3H, s, CH_3), 4.2 (1H, s, CH), 6.6 (2H, s, NH_2), 7.0-7.9 (8H, m, Ar), 9.5 (1H, s, OH); EI-MS (m/z): 311 (M^+); Analysis (calc.) found: C (65.57) 65.50, H (5.50) 5.54, N (13.49) 13.46.

Amino-5-(3',4'- dimethoxyphenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione (**4e**)

IR (KBr, cm^{-1}):3320 (NH_2), 3307 (OH), 1590 (C=N), 1320 (C-N), 1130 (C=S); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.6 (3H, s, CH_3), 2.4 (2H, s, CH_2), 3.8 (6H, s, $OCH_3 \times 2$), 4.24 (1H, s, CH), 6.86 (2H, s, NH_2), 7.3-7.8 (6H, m, Ar), 8.6 (1H, s, OH); EI-MS (m/z): 370 $(M-1)^+$; Analysis (calc.) found: C (61.44) 61.78, H (5.70) 5.72, N (11.31) 11.30.

Amino-5-(3',4',5'-trimethoxyphenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione (**4f**)

IR (KBr, cm^{-1}): 3320 (NH_2), 3307 (OH), 1590 (C=N), 1320 (C-N), 1130 (C=S); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.6 (3H, s, CH_3), 2.3 (2H, s, CH_2), 3.9 (9H, s, $OCH_3 \times 3$), 4.24 (1H, s, CH), 6.86 (2H, s, NH_2), 7.3-7.8 (5H, m, Ar), 9.5 (1H, s, OH); EI-MS (m/z): 402 $(M+1)^+$; Analysis (calc.) found: C (59.83) 59.88, H (5.77) 5.72, N (10.47) 10.42.

Amino-5-(4'-flurophenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione (**4g**)

IR (KBr, cm^{-1}): 3320 (NH_2), 3307 (OH), 1590 (C=N), 1320 (C-N), 1130 (C=S); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.4 (3H, s, CH_3), 2.5 (2H, s, CH_2), 6.86 (2H, s, NH_2), 4.14 (1H, s, CH), 7.3-7.8 (7H, m, Ar), 8.6 (1H, s, OH); EI-MS (m/z): 329 (M^+); Analysis (calc.) found: C (61.99) 61.70, H (4.90) 4.74, N (12.76) 12.70.

Amino-5-(2'-chlorophenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione (**4h**)

IR (KBr, cm^{-1}): 3320 (NH_2), 3307 (OH), 1590 (C=N), 1320 (C-N), 1130 (C=S); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.7 (3H, s, CH_3), 2.5 (2H, s, CH_2), 4.24 (1H, s, CH), 6.08 (2H, s, NH_2), 7.3-8.4 (7H, m, Ar), 11.6 (1H, s, OH); EI-MS (m/z): 345 (M^+); Analysis (calc.) found: C (59.04) 59.0, H (4.66) 4.46,N (12.5) 12.10.

Amino-5-(2',6'-dichlorophenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione (**4i**)

IR (KBr, cm^{-1}): 3320 (NH_2), 3307 (OH), 1590 (C=N), 1320 (C-N), 1130 (C=S); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.8 (3H, s, CH_3), 2.5 (2H, s, CH_2), 4.24 (1H, s, CH), 6.86 (2H, s, NH_2), 7.3-8.4 (6H, s, Ar), 11.7 (1H, s, OH); EI-MS (m/z): 380 (M^+); Analysis (calc.) found: C (59.78) 59.76, H (5.02) 5.14, N (13.94) 13.90.

Amino-5-(3'-nitrophenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione (**4j**)

IR (KBr, cm^{-1}): 3320 (NH_2), 3307 (OH), 1590 (C=N), 1320 (C-N), 1130 (C=S); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.8 (3H, s, CH_3), 2.5 (2H, s, CH_2), 6.86 (2H, s, NH_2), 4.24 (1H, s, CH), 7.3-8.7 (7H, s, Ar), 11.2(1H, s, OH); EI-MS (m/z): 356 (M^+); Analysis (calc.) found: C (53.65) 53.76, H (3.98) 3.63, N (11.05) 11.0.

Amino-5-(2'-furyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione (**4k**)

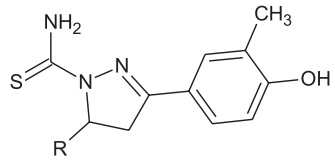
IR (KBr, cm^{-1}): 3320 (NH_2), 3307 (OH), 1590 (C=N), 1320 (C-N), 1130 (C=S); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.6 (3H, s, CH_3), 2.4 (2H, s, CH_2), 4.14 (1H, s, CH), 5.86 (2H, s, NH_2), 6.8-7.2 (3H, m, furan), 7.3-7.8 (3H, m, Ar),11.4 (1H, s, OH); EI-MS (m/z): 300 $(M-1)^+$; Analysis (calc.) found: C (59.78) 59.74, H (5.02) 10.72, N (13.94) 13.92.

Biological evaluation

Antimycobacterial screening

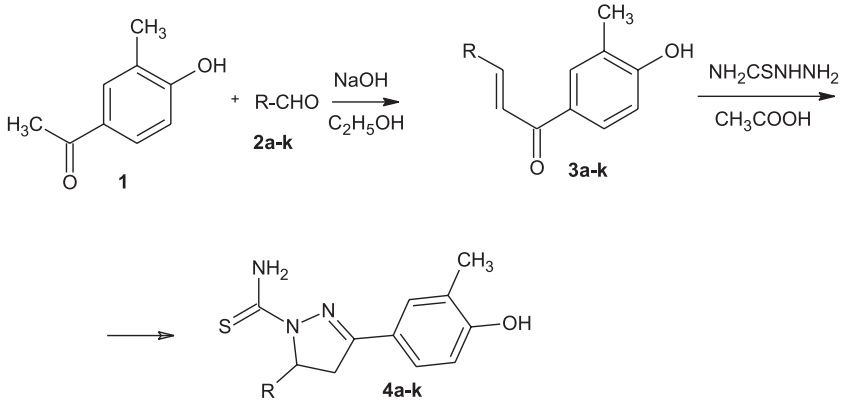
The primary screening was conducted at concentration of 6.25 µg/mL (or molar equivalent of the highest molecular weight compound in a series of

Table. 1 Physical constants and antimycobacterial activity of the synthesized compounds



Compound	R	Yield (%)	M.P (°C)	Molecular formula	Mol. wt.	(MIC) µM	
						MTB[a]	MTB[b]
4a	4-Methoxyphenyl-	74	170	$C_{18}H_{19}O_2N_3S$	341.42	6.25	6.12
4b	4-Chlorophenyl-	80	178	$C_{17}H_{16}ON_3S$ Cl	345.84	0.43	0.43
4c	4-Dimethylaminophenyl-	85	130	$C_{19}H_{22}ON_4S$	354.46	6.32	6.25
4d	Phenyl-	65	105	$C_{17}H_{17}ON_3S$	311.40	5.16	6.25
4e	3,4-Dimethoxyphenyl-	85	85	$C_{19}H_{21}O_3N_3S$	371.45	4.12	6.25
4f	3,4,5-Trimethoxyphenyl-	76	117	$C_{20}H_{23}O_4N_3S$	401.47	5.74	6.12
4g	4-Fluorophenyl-	82	68	$C_{17}H_{16}ON_3S$ F	329.39	1.32	3.92
4h	2-Chlorophenyl-	94	162	$C_{17}H_{16}ON_3S$ Cl	345.84	0.62	4.12
4i	2,6-Dichlorophenyl-	80	141	$C_{17}H_{15}ON_3S$ Cl_2	380.29	0.58	4.10
4j	3-Nitrophenyl-	78	172	$C_{17}H_{16}O_3N_4S$	356.39	6.25	3.12
4k	Furfuryl-	90	144	$C_{15}H_{15}O_2N_3S$	301.36	2.76	2.82
INH	-	-	-	-	-	0.70	11.36

[a] *Mycobacterium tuberculosis* $H_{37}R_v$ [b] INH resistant *Mycobacterium tuberculosis*



Scheme 1. Synthesis of amino-5-(substituted phenyl)-3-(4-hydroxy-3-methylphenyl)-4, 5-dihydro-1*H*-1-pyrazolylmethanethiones.

congeners) against *Mycobacterium tuberculosis* $H37_{RV}$ (ATCC27294) in BACTEC 12B medium using the BACTEC 460 radiometric system (11-13).

RESULTS AND DISCUSSION

Chemistry

Amino-5-(substituted phenyl)-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolyl methanethiones, **4a-k**, described in this study are shown in Table 1, and a reaction sequence for their preparation is outlined in Scheme 1. The required chalcones were prepared by reacting 3-methyl-4-hydroxyacetophenone with appropriate aldehyde in a presence of base by conventional Claisen-Schmidt condensation. The reaction between chalcone and thiosemicarbazide in glacial acetic acid (reaction time varied from 4 to 12 h) afforded the title pyrazolines, **4a-k**, in 72 -96% yield after recrystallization from ethanol. The purity of the compounds was checked by TLC and elemental analyses. 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 NH_2, OH, CH, C=O, C=N, C-N and C=S peaks at 3320, 3300, 3040, 1680, 1580 and 1130 cm^{-1}, respectively. In the

^{1}H-NMR spectra, the signals of the respective protons of the prepared title compounds were verified on the basis of their chemical shifts, multiplicities and coupling constants. The spectra showed singlet at δ 2.3 ppm corresponding to C4-methylene group; singlet at δ 3.4 ppm corresponding to methyl group; singlet at δ 4.24 ppm corresponding to C5 proton; singlet at δ 6.86 ppm corresponding to NH_2 group; multiplet at δ 7.3-7.8 ppm for aromatic protons; and singlet at δ 9.5 ppm corresponding to OH proton. The elemental analysis results were within ± 0.4% of the theoretical values.

Antimycobacterial activity

The synthesized compounds (**4a-k**) were tested for their antimycobacterial activity *in vitro* against MTB and INHR-MTB by agar dilution method using BACTEC-460 radiometric system and INH resistant *Mycobacterium tuberculosis* (INHR-MTB) using agar dilution method (11-13) for the determination of minimum inhibitory concentration (MIC). The MIC was defined as the minimum concentration of compound required to inhibit 90% of bacterial growth and MIC values of the compounds are reported in Table 1 with standard drug INH for comparison.

Among the eleven compounds synthesized, five compounds were found to be the most active compounds with minimum inhibitory concentration of less than 1 μM and were more active than INH against MTB. Compounds with halogen substituted phenyl group showed higher activity. Among the synthesized compounds, amino-5-(4-chlorophenyl)-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione (**4b**) was found to be the most active agent against *Mycobacterium tuberculosis* $H37_{Rv}$ (MTB) and INH resistant *Mycobacterium tuberculosis* (INHR-MTB) with minimum inhibitory concentration of 0.43 μM. When compared to INH, compound (**4b)** was found to be 1.62 fold and 26.41 fold more active against MTB and INHR-MTB, respectively, whereas compounds with 2,6-dichlorophenyl (**4h**) and 2-chlorophenyl (**4i**) substituents also were found to be more active than INH against MTB with MIC of 0.58 and 0.62 μM.

Among the newer derivatives, compound **4b** 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. Further studies to acquire more information about structure-activity relationships are in progress in our laboratory.

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