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SYNTHESIS AND ANTI-HIV ACTIVITY OF N^1-NICOTINOYL--3-(4'-HYDROXY-3'-METHYLPHENYL)-5-[SUBSTITUTED PHENYL]--2-PYRAZOLINES

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Abstract: A series of N^1-nicotinoyl-3-(4'-hydroxy-3'-methylphenyl)-5-(substituted phenyl)-2-pyrazolines were synthesized by the reaction between isoniazid (INH) and chalcones and were tested for their *in vitro* anti-HIV activity. Among them, compound **(c)** showed a promising anti-HIV activity *in vitro* against used strains (IIIB, ROD), with IC_{50} of both IIIB 5.7 μM and ROD 7.0 μM.

Keywords: pyrazoline, anti-HIV

HIV is the most significant risk factor for many opportunistic infections such as hepatitis, tuberculosis, CNS disorder, CVS diseases and bacterial infections. Acquired immunodeficiency syndrome (AIDS) is also caused by the human immunodeficiency virus (HIV)(1), which results in a serious infection. Without treatment, most people are expected to die from this infection. Once infected with HIV the person carries the virus in the body and remains infectious to others for the rest of life. However, recent treatment advances mean that in treated patients the virus level can be reduced but these treatments need to be maintained and there is not as yet a total cure for HIV. In November 2005, UNAIDS/WHO announced that there were 40.3 million people living with HIV infection worldwide. The vast majority of them live in resource poor (developing) countries. After a quarter century of political denial and social stigma of stunning scientific breakthroughs, bitter policy battles and inadequate prevention campaigns, HIV/AIDS continues to spread rapidly throughout much of the world, particularly in developing nations. To date, some 30 million people worldwide have already died of AIDS (2). The HIV infection, which targets the monocytes expressing surface CD4 receptors, eventually produces profound defects in cell-mediated immunity (3). Anti-AIDS therapy is actually based on the three classes of anti-HIV drugs, the nucleoside reverse transcriptase inhibitors, the non- nucleoside reverse transcriptase inhibitors and protease inhibitors. Rapid development of drug resistance, lower efficacy and more toxicity problems make urgent to develop new anti-HIV agents effective against resistant mutants, with higher efficacy and deprived of side effects. Recently, we reported pyrazoline derivatives having good antitubercular activity (4). In this paper, we wish to report the anti-HIV activity of novel pyrazoline derivatives.

EXPERIMENTAL

All chemicals were supplied by E. Merck (Darmstadt, 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 by thin layer chromatography (TLC) on silica gel G plates, with 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. The IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBr pellets).The ^{1}H-NMR spectra were recorded or a Bruker AC 300

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MHz spectrometer using TMS as an internal standard in DMSO-d_6/ $CDCl_3$ The mass spectra under electron impact conditions (EIMS) were recorded at 70 eV ionizing voltage with a VG ProSpec instrument and are presented as *m*/*z*.

General method

1-(4'-Hydroxy-3'-methylphenyl) -3-(substituted) phenyl-2-propen-1-ones (**C_{I-XI}**)

The compounds 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

IR (KBr, cm^{-1}) 3200 (OH), 3042 (CH), 1686 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s, CH_3), 3.9 (3H, s, OCH_3), 6.8-6.9(1H × 2, dd *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''-choloro-phenyl)-2-propen-1-one

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, dd *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''-dimethyl-aminophenyl)-2-propen-1-one

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, dd *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'-methylphenyl)-3-phenyl-2-propen-1-one

IR (KBr, cm^{-1}) 3210 (OH), 3042 (CH), 1680 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, 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

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

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-furfuryl-2-propen-1-one

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).

1-(4'-Hydroxy-3'-methylphenyl)-3-(4''-fluorophenyl)-2-propen-1-one

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

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

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

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).

General method

Synthesis of 5-(4'-hydroxy-3'-methylphenyl)-5-(substituted phenyl)-4,5-dihydro-1*H*-1-pyrazolyl-4-pyridylmethanone derivatives (**a-k**)

To the solution of 0.002 mol of the appropriate **C_{I-XI}** derivative in 15 mL of glacial acetic acid 0.002 mol of isoniazid was added and the reaction mixture was refluxed for 12 h and cooled. An excess of the

solvent was removed under reduced pressure and the reaction mixture was cooled and poured onto crushed ice (20 g). The product so obtained was filtered, washed with water and recrystallized from methanol.

5-(4'-Hydroxy-3'-methylphenyl)-5-(4''-methoxyphenyl)-4,5-dihydro-1*H*-1-pyrazolyl-4-pyridylmethanone (**a**)

IR (KBr, cm^{-1}) 3210 (OH), 3034 (CH), 1682 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.4 (3H, s, CH_3), 2.3 (2H, s, CH_2), 3.7 (3H, s, OCH_3), 5.78 (1H, s, CH), 6.6-7.3 (7H, m, aromatic), 7.98-8.1 (4H, m, pyridine), 9.2 (1H, s, OH). EIMS (m/z): 388 $(M+1)^+$. Analysis (calc./found): C 71.30/71.31, H 5.46/5.41, N 10.85/10.82.

5-(4'-Chlorophenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolyl-4-pyridylmethanone (**b**)

IR (KBr, cm^{-1}): 3200 (OH), 3040 (CH), 1680 (C=O), 780 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s, CH_3), 2.3 (2H, s, CH_2), 4.1 (1H, s,CH), 6.5-7.3 (7H, m, aromatic), 7.9-8.9 (4H, m, pyridine), 11.49 (1H, s, OH). EIMS (m/z): 392 $(M+1)^+$. Analysis (calc./found): C 67.43/67.51, H 4.63/4.67, N 10.72/10.72.

5-(4'-Dimethylaminophenyl)-3-(4'-hydroxy-3'-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolyl-4-pyridylmethanone (**c**)

IR (KBr, cm^{-1}): 3230 (OH), 3020 (CH), 1676 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.1 (3H, s, CH_3), 2.6 (2H, s, CH_2), 2.9 (6H, s, N-$(CH_3)_2$) 4.1 (1H, s, CH), 6.5-7.5 (7H, m, aromatic), 7.6-8.6 (4H, m, pyridine), 11.2 (1H, s, OH). EIMS (m/z): 400 (M^+). Analysis (calc./found): C 71.98/71.96, H 6.04/6.08, N 13.99/13.93.

3-(4'-Hydroxy-3'-methylphenyl)-5-phenyl-4,5-dihydro-1*H*-1-pyrazolyl-4-pyridylmethanone (**d**)

IR (KBr, cm^{-1}): 3200 (OH), 3040 (CH), 1680 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.1 (3H, s, CH_3), 2.5 (2H, s, CH_2), 4.1 (1H, s, CH), 6.5-7.8 (8H, m, aromatic), 7.9-8.9 (4H, m, pyridine), 11.49 (1H, s, OH). EIMS (m/z): 357 (M^+). Analysis (calc./found): C 73.53/73.50, H 5.36/5.41, N 11.76/11.72.

5-(3',4'-Dimethoxyphenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolyl-4-pyridylmethanone (**e**)

IR (KBr, cm^{-1}): 3220 (OH), 3044 (CH), 1686 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s, CH_3), 2.4 (2H, s, CH_2), 3.8 (6H, s, 2 × OCH_3), 4.1 (1H, s, CH), 6.7-7.3 (6H, m, aromatic), 7.6-7.9 (4H, m, pyridine), 11.90 (1H, s, OH). EIMS (m/z): 418 $(M+1)^+$. Analysis (calc./found): C 69.05/69.08, H 5.55/5.41, N 10.07/10.02.

3-(4'-Hydroxy-3'-methylphenyl)-5-(3'',4'',5''-trimethoxyphenyl)-4,5-dihydro-1*H*-1-pyrazolyl-4-pyridylmethanone (**f**)

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), 2.4 (2H, s, CH_2), 3.8 (9H, s, 3 × OCH_3), 4.1 (1H, s, CH), 6.7-7.5 (5H, m, aromatic), 7.6-7.9 (4H, m, pyridine), 11.84 (1H, s, OH). EIMS (m/z): 448 $(M+1)^+$. Analysis (calc./found): C 67.10/67.51, H 5.63/5.61, N 9.39/9.36.

5-(2'-Furyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolyl-4-pyridyl methanone (**g**)

IR (KBr, cm^{-1}): 3200 (OH), 3040 (CH), 1680 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.0 (3H, s, CH_3), 2.7 (2H, s, CH_2), 5.8 (1H, s, CH), 6.3-6.9 (3H, m, aromatic), 7.4-7.7 (3H, m, furan), 8.7-9.0 (4H, m, pyridine), 10.38 (1H, s, OH). EIMS (m/z): 348 $(M+1)^+$. Analysis (calc./found): C 69.15/69.21, H 4.93/4.86, N 12.10/12.12.

5-(4'-Fluorophenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolyl-4-pyridylmethanone (**h**)

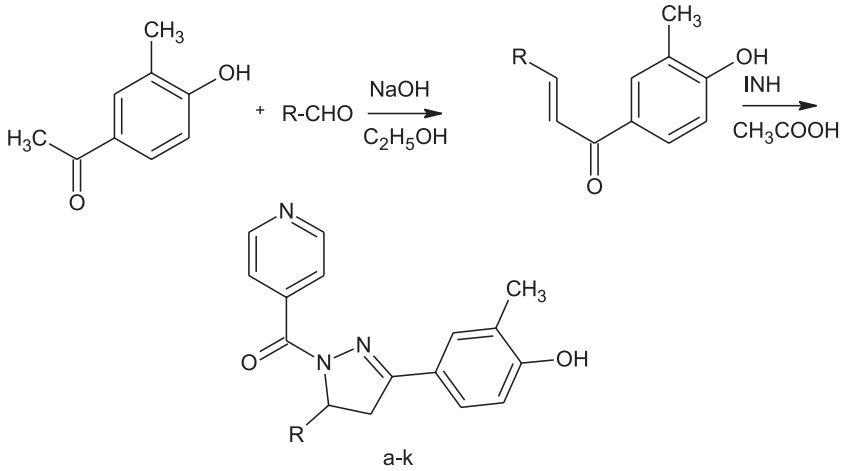
IR (KBr, cm^{-1}): 3200 (OH), 3040 (CH), 1680 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s, CH_3), 2.3 (2H, s, CH_2), 4.1 (1H, s, CH), 6.5-7.3 (7H, m, aromatic), 7.9-8.9 (4H, m, pyridine), 11.49 (1H, s, OH). EIMS (m/z): 376 $(M+1)^+$. Analysis (calc./found): C 70.39/70.41, H 4.83/4.81, N 11.19/11.72.

5-(2'-Chlorophenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolyl-4-pyridylmethanone (**i**)

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), 2.9 (2H, s, CH_2), 4.0 (1H, s, CH), 6.9-7.3 (7H, m, aromatic),7.5-8.2 (4H, m, pyridine), 8.8 (1H, s, OH). EIMS (m/z): 392 $(M+1)^+$. Analysis (calc./found): C 67.43/67.51, H 4.63/4.61, N 10.72/10.73.

5-(2',6'-Dichlorophenyl)-3-(4''-hydroxy-3''-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolyl-4-pyridylmethanone (**j**)

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), 2.5 (2H, s, CH_2), 4.4 (1H, s, CH), 6.5-7.3 (6H, m, aromatic), 7.9-8.4 (4H, m, pyridine), 11.49



Scheme 1. Synthesis of N[1]-nicotinoyl-3-(4'-hydroxy-3'-methylphenyl)-5-(substituted phenyl)-2-pyrazolines.

(1H, s, OH). EIMS (m/z): 427 $(M+1)^+$. Analysis (calc./found): C 61.98/61.96, H 4.02/4.08, N 9.86/9.84.

3-(4'-Hydroxy-3'-methylphenyl)-5-(3''-nitrophenyl)-4,5-dihydro-1*H*-1-pyrazolyl-4-pyridylmethanone (**k**)

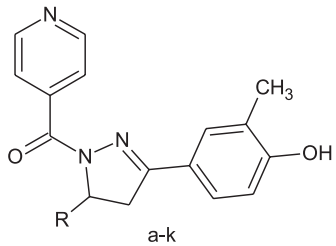
IR (KBr, cm^{-1}): 3240 (OH), 3042 (CH), 1678 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (3H, s, CH_3), 2.5 (2H, s, CH_2), 4.4 (1H, s, CH), 6.5-7.3 (6H, m, aromatic), 7.9-8.4 (4H, m, pyridine), 10.49 (1H, s, OH). EISMS (m/z): 402 (M^+). Analysis (calc./found): C 65.67/65.69, H 4.51/4.53, N 13.92/13.82.

Microbiology

Compounds

Test compounds were dissolved in DMSO at an initial concentration of 200 μM and then were serially diluted in culture medium.

Table. 1 Physical properties of the synthesized N[1]-nicotinoyl-3-(4'-hydroxy-3'-methylphenyl)-5-(substituted phenyl)-2-pyrazolines.



Compound	**R**	Yield (%)	M.p. (°C)	Mol. Formula	Mol. Wt.
a	4-Methoxyphenyl-	72	119	$C_{23}H_{21}N_3O_3$	387.4
b	4-Chlorophenyl-	78	166	$C_{22}H_{18}ClN_3O_2$	391.8
c	4-Dimethylaminophenyl-	66	110	$C_{24}H_{24}N_4O_2$	400.47
d	Phenyl-	80	140	$C_{22}H_{19}N_3O_2$	357.4
e	3,4-Dimethoxyphenyl-	82	138	$C_{24}H_{23}N_3O_4$	417.4
f	3,4,5-Trimethoxyphenyl-	86	186	$C_{25}H_{25}N_3O_5$	447.4
g	Furyl-	94	152	$C_{20}H_{17}N_3O_3$	347.3
h	4-Fluorophenyl-	86	146	$C_{22}H_{18}FN_3O_2$	375.3
i	2-Chlorophenyl-	80	194	$C_{22}H_{18}ClN_3O_2$	391.8
j	2,6-Dichlorophenyl-	78	212	$C_{22}H_{17}Cl_2N_3O_2$	426.2
k	3-Nitrophenyl-	65	112	$C_{22}H_{18}N_4O_4$	402.4

Recrystallization: Ethanol

Table. 2 Anti-HIV activity of the synthesized N[1]-nicotinoyl-3-(4'-hydroxy-3'-methylphenyl)-5-(substituted phenyl)-2-pyrazolines against MT-4 cell line.

Compound	III_B strain			ROD strain		
	IC_{50} (μM)	CC_{50} (μM)	% protection	IC_{50} (μM)	CC_{50} (μM)	% protection
a	>125	125	24	>125	125	13
b	>36.1	36.1	42	>1.36	1.36	30
c	5.7	57.8	102	7.0	72.2	93
d	>10.97	10.97	13	>10.76	10.76	08
e	>13.83	11.83	24	>11.81	1.25	34
f	>66.20	66.20	26	>66.20	66.20	23
g	6.8	66.20	86	7.4	66.20	74
h	>67.97	67.97	08	>11.54	11.54	17
i	>53.20	53.20	24	>53.20	53.20	20
j	>13.83	13.83	24	>13.83	13.83	32
k	>10.97	10.76	40	>10.97	10.76	27
Nevirapine	0.10	0.10	98	0.10	0.10	94

Cells

MT-4 cells [grown in RPMI 1640 containing 10% fetal calf serum (FCS), 100 UI/mL penicillin G and100 mg/mL streptomycin] were used for cytotoxicity and anti-HIV assays. Cell cultures were checked periodically for the absence of mycoplasma contamination with a MycoTect Kit (Gibco).

Cytotoxicity and anti-HIV assays

Activity against the HIV-1 and HIV-II (HIV-1, IIIB strain, HIV-II ROD strain obtained from supernatants of persistently infected H9/IIIB cells) multiplication in acutely infected cells was based on inhibition of virus-induced cytopathogenicity in MT-4 cells. Briefly, 50 mL of RPMI 10% FCS containing 1×10^4 cells were added to each well of flat-bottomed microtiter trays containing 50 mL of medium and serial dilutions of test compounds. 20 mL of an HIV-1 suspension containing 100 CCID50 were then added. After a 4-day incubation at 37°C, the number of viable cells was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method. Cytotoxicity of compounds, based on the viability of mock infected cells was monitored by the MTT method (5).

RESULTS and DISCUSSION

Chemistry

N[1]-Nicotinoyl-3-(4'-hydroxy-3'-methylphenyl)-5-(substituted phenyl)-2-pyrazolines **a-k** described in this study are shown in Table 1 and 2, and a reaction sequence for the preparation is outlined in Scheme 1. The required chalcones were prepared by reacting 4-hydroxy-3-methylacetophenone with appropriate aldehyde in the presence of base by conventional Claisen-Schmidt condensation. The reaction between chalcone and isonicotinyl hydrazide in ethanolic solution in the presence of glacial acetic acid (reaction time varied from 8-14 h) afforded pyrazolines **a-k** in 65-94% yield after recrystallization with methanol. 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. The elemental analysis results were within ± 0.4% of theoretical values.

Anti-HIV activity

The synthesized compounds (**a-k**) were tested for their inhibitory effect on the replication oh HIV-I and HIV-II in MT-4 cell line. The results are summarized in Table 2 and compared with standard drug – nevirapine. Among eleven compounds, compound (**c**) and (**g**) were found to be the most active against replication of HIV-I and HIV-II with IC_{50} of both IIIB, ROD 5.7 μM, 7.0 μM and 6.8 μM, 7.4 μM, respectively, and their selective index (SI = CC_{50}/IC_{50}) was found to be more than 10 with maximum protection of both IIIB, ROD 74-102% in two independent experiments. When compared with the reference standard, nevirapine, (IC_{50} = 0.1 μM) the synthesized compounds were less active (**b** and **j**) and showed maximum protection of 24-42% with SI of > 2 but below their toxicity threshold. The loss of activity might be due to degeneration/rapid metabolism in the culture condition used in the screening procedure.

CONCLUSION

Among the investigated derivatives compound **(c)** showed a promising anti-HIV activity *in vitro* against used (IIIB, ROD) strains. Further, it is conceived that derivatives showing anti-HIV activity can be further modified to become better anti-HIV chemotherapeutic agents. Further studies to acquire more information about quantitative structure-activity relationships (QSAR) are in progress in our laboratory.

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