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Synthesis, characterisation and pharmacological activities of 1-acetyl/propyl-3-aryl-5-(5-aryloxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-pyrazolines

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ABSTRACT

Aseries of 1-acetyl/propyl-3-aryl-5-(5-aryloxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-pyrazolines were synthesized in one step by condensing suitably substituted propenones, hydrazine and acetic/propionic acid. The newly synthesized compounds were screened for their analgesic and anti-inflammatory activity and most of the compounds showed significant activity comparable with that of the standard drug.

Keywords: 5-Aryloxypyrazoles, pyrazolines, propenones, analgesic activity, anti-inflammatory activity.

INTRODUCTION

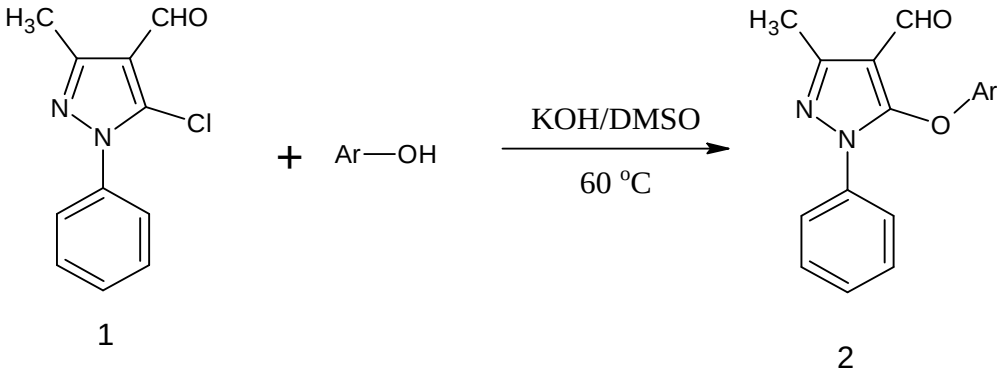
Pyrazoles are a class of heterocyclic compounds containing the 1,2-diazole systems[1]. Many derivatives of pyrazole derivatives are found to exhibit various pharmacological activities such as antimicrobial[2], anti-inflammatory[3], analgesic[4], antitubercular[5], anti-tumour[6], selective COX-2 inhibitor[7] and anticancer activity[8]. Pyrazolines are also well known for their applications in the pharmacological field like anti-oxidant[9], antiamoebic[10], anti-microbial[11] properties etc. Similarly, 5-hydroxy or 5-aryloxy pyrazoles are also reported to exhibit wide-ranging biological activities such as insecticidal[12], potent inhibitors of HMG-CoA reductase[13], anti-tumour properties[14] etc. Prompted by these observations and in continuation of our research on biologically potential pyrazole moiety[15-18], we herein report the synthesis and pharmacological activity of a series of 1-acetyl/propyl-3-aryl-5-(5-aryloxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-pyrazolines **4**.

RESULTS AND DISCUSSION

2.1 Chemistry

The synthesis of until now unreported title compounds was done as shown in **Scheme-1-3.** 5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-carboxaldehyde **1** was prepared in accordance with the literature procedure[16]. Nucleophilic substitution of compound **1** with phenol/2-naphthol in

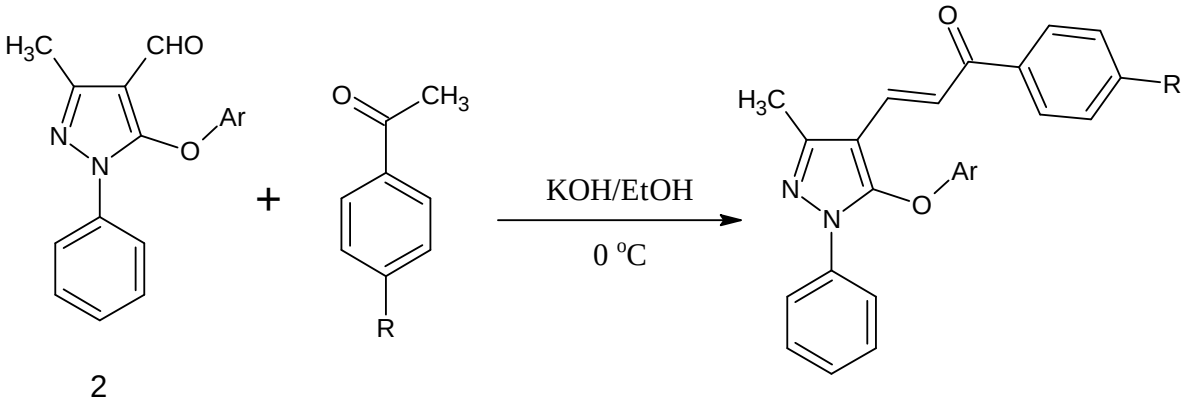
DMSO medium in presence of potassium hydroxide as catalyst at 60^{0}C, gave 5-aryloxy-3-methyl-1-phenyl-1*H*-pyrazol-4-carboxaldehyde **2. Scheme-1**.



1 2

Scheme-1

Compound **2** when made to react with suitably substituted acetophenones in alcoholic potassium hydroxide medium at 0^{0}C, underwent Claisen-Schmidt condensation to give 1-substituted aryl-3-(5-aryloxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-propen-1-one **3. Scheme-2. (Table-1).**



2 3

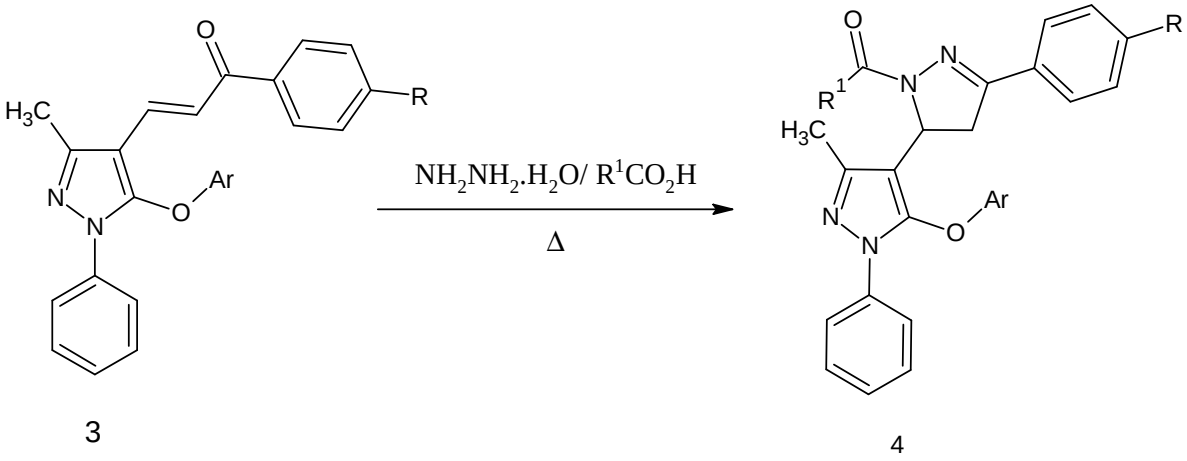
Scheme-2

Table 1: Characterisation data of 3-(5-aryloxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-aryl-2-propen-1-one 3.

Compd. No.	Ar.	R	Mol.Formulae. M.W.	M.P.(^{0}C) Yield(%)	CHN Analysis Found (Calc)		
					C	H	N
3a	Ph	H	$C_{25}H_{20}N_2O_2$ 380	124-126 57	78.88 (78.93)	5.52 (5.30)	7.28 (7.36)
3b	Ph	CH_3	$C_{26}H_{22}N_2O_2$ 394	130-131 57	79.12 (79.16)	5.58 (5.62)	7.24 (7.10)
3c	Ph	Cl	$C_{25}H_{19}ClN_2O_2$ 414.5	109-111 64	72.51 (72.37)	4.70 (4.62)	6.64 (6.75)
3d	2-Naphthyl	H	$C_{29}H_{22}N_2O_2$ 430	139-141 86	80.88 (80.91)	5.22 (5.15)	6.54 (6.51)
3e	2-Naphthyl	CH_3	$C_{30}H_{24}N_2O_2$ 444	158-160 60	81.14 (81.06)	5.46 (5.44)	6.26 (6.30)
3f	2-Naphthyl	Cl	$C_{29}H_{21}ClN_2O_2$ 464.5	139-140 68	74.86 (74.91)	4.52 (4.55)	6.14 (6.03)

Solvent for recrystallisation: EtOH.

These propeonones **3** when treated with hydrazine hydrate in acetic/propionic acid at reflux temperature gave the title compounds 1-acetyl/propyl-3-aryl-5-(5-aryloxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-pyrazolines **4** in one pot reaction. **Scheme-3**.



3 4

Scheme-3

The structures of the newly synthesized compounds have been established on the basis of spectral and analytical data.

In the IR Spectra of the compounds **4a-l** the carbonyl absorption bands were observed in the range of 1650-1670cm^{-1}. The aliphatic C-H stretching were observed in the range of 2924-2975cm^{-1} whereas the –C=N stretching of the ring pyrazole were observed in the range of 1590-1595cm^{-1}. In the ^{1}H NMR spectra of these compounds the chiral proton appeared as doublet of doublet in the range of δ, 5-5.5 and that of the prochiral protons resonated as two distinct doublet of doublet in the range of δ, 3-3.4 & δ, 3.5-3.9 there by indicating the magnetic non-equivalency of these two protons. Similarly the mass spectra of these compounds showed sufficiently intense molecular ion peaks there by indicating the stability of the compounds.

Table 2: Anti-inflammatory activity data of 1-acetyl/propyl-3-aryl-5-(5-aryloxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-pyrazolines 4a-l.

Compd. No	Oedema volume in mL			Percentage reduction (%)		
	30 min	60 min	120 min	30 min	60 min	120 min
Control	0.74	0.75	0.77	-	-	-
Indomethacin	0.24	0.23	0.23	-	-	-
4a	0.45	0.47	0.51	39.19**	37.33**	33.77**
4b	0.39	0.42	0.43	47.29**	44.00**	44.15**
4c	0.66	0.68	0.68	10.81^{ns}	9.33^{ns}	11.68^{ns}
4d	0.41	0.45	0.48	44.59**	40.00**	37.66 **
4e	0.69	0.71	0.72	6.76^{ns}	5.33^{ns}	6.49^{ns}
4f	0.71	0.69	0.71	37.84**	42.16**	31.82**
4g	0.70	0.69	0.71	4.05^{ns}	0.08^{ns}	7.79^{ns}
4h	0.70	0.73	0.71	5.40^{ns}	2.67^{ns}	7.79^{ns}
4i	0.58	0.51	0.49	21.62*	32.00**	36.36**
4j	0.65	0.57	0.54	39.18**	24.00**	29.87**
4k	0.50	0.52	0.54	32.43**	30.66**	29.87**
4l	0.45	0.54	0.57	39.19**	28.00**	25.97**

*Values are expressed as mean, *P<0.05, **P<0.01, ***P<0.001 and ns statistically not significant.*

2.2 Pharmacological activities

The newly synthesized compounds were evaluated for their anti-inflammatory activity using albino rats[19]. The results are summarised in **Table 2**.

These results showed that compounds **4a, 4b, 4d, 4f, 4i, 4j, 4k** & **4l** showed significant anti-inflammatory activity when compared with that of the standard drug. These results indicate that propyl derivatives are more active when compared with that of the acetyl derivatives.

The analgesic activity for the compounds was determined by using Analgesiometer. The results are summarised in **Table 3**.

Table 3: Analgesic activity data of 1-acetyl/propyl-3-aryl-5-(5-aryloxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-pyrazolines 4a-l

Compoond No.	Tail flick latency in sec			
	0 min	30 min	60 min	90 min
Control	3.35 + 0.048	3.225+0.063	3.340+ 0.063	3.350+ 0.06455
Pentazocine	3.19 + 0.12	6.662+0.248**	7.28+ 0.111**	7.550+ 0.0645**
4a	3.25 + 0.063	4.243+0.125*	5.500+ 0.108**	6.125+ 0.085**
4b	3.35 + 0.048	4.725+0.063**	5.300+ 0.108**	5.750+ 0.1190**
4c	3.15+0.1080	3.740+0.048*	4.100+ 0.091*	4.425+ 0.1493*
4d	3.07 + 0.125	4.435+0.108**	5.885+0.063**	6.250+1581**
4e	3.17+0.125	3.575+0.048 ns	3.375+ 0.103 ns	3.400+0.09129 ns
4f	3.4 + 0.1080	3.125+0.063 ns	3.350+ 0.119 ns	3.525+ 0.1109 ns
4g	3.15 + 0.125	3.380+0.082 ns	3.510+ 0.082 ns	3.875+ 0.08539*
4h	3.05 + 0.048	3.300+0.122 ns	3.500+ 0.091 ns	3.870+ 0.1472*
4i	3.22 + 0.103	3.975+0.125*	4.475+ 0.085**	5.000+ 0.09129**
4j	3.3 + 0.048	4.123+0.048*	4.470+0.111**	5.300+ 0.108**
4k	3.35 + 0.12	5.800+0.129**	6.275+ 0.085**	6.775+ 0.06292**
4l	3.15 + 0.125	5.145+0.125**	5.382+0.063**	5.567+ 0.085**

*Values are expressed as mean±SEM, *P<0.05, **P<0.01 , ***P<0.001 and ns statistically not significant.*

These results showed that the compounds **4a, 4b, 4d, 4i, 4j, 4k** & **4l** showed significant analgesic activity and compound **4c** showed moderate activity and compounds **4g** & **4h** showed moderate analgesic activity as the time laps. This result indicated that the presence of 2-naphthyl group in the 5th position of the pyrazole will enhances the activity when compared with that of the phenyl group.

MATERIALS AND METHODS

3.1 General

Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was confirmed by thin layer chromatography using silica gel plates (MERCK) in petroleum ether: ethyl acetate (8.8: 1.2) as mobile phase. ^{1}H NMR spectra were recorded on Bruker Avance-II 400MHz or Bruker DRX 300 300 MHz NMR spectrometer using $CDCl_3$ or DMSO-d_6 as solvent. TMS was used as internal standard. All chemical shift values are expressed in δ scale down field from TMS and proton signals were indicated as s= singlet, d= doublet, dd= doublet of doublet, t= triplet, q= quartet, m= multiplet. The IR spectra were recorded in KBr disc on a Shimadzu-8400 FTIR spectrophotometer. The mass spectra were recorded on a a Micromass Q-Tof Micro LC mass spectrometer or DART-MS on JEOL-Accu TOF JMS-T100LC mass spectrometer having DART source ionization at 350^{0}C with 4 LPM flow of dry Helium gas. CHN analysis was carried out on Elementar Vario-EL III model analyser.

3.2** Synthesis of 5-aryloxy-3-methyl-1-phenyl-1H-pyrazol-4-carboxaldehyde **2:
5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-carboxaldehyde **1** (0.1mol) and phenol/β-naphthol (0.1mol) was dissolved in 10 mL of dimethyl sulfoxide. To this solution 5.6 g (0.1mol) of potassium hydroxide was added. Heated the reaction mixture in an oil bath maintained at 60^0C for 6 hrs. The reaction mixture was cooled to room temperature and added with vigorous stirring to 150 g of crushed ice. Left the content for overnight and filtered the solid separated. Dried and recrystallised from ethanol. Yield and M.P. of these compounds are as follows.

Ar= Ph, Yield: 89%, M.P. 87-89^{0}C. (Lit.[20] 86-89^{0}C).
Ar= β-Naphthyl, Yield: 80%, M.P. 99-101^{0}C. (Li.[20] 100-102^{0}C).

3.3** Synthesis of 1-substituted aryl-3-(5-aryloxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-propen-1-one **3:
The 5-aryloxy-3-methyl-1-phenyl-1*H*-pyrazol-4-carboxaldehyde **2** (0.1mol) and suitably substituted acetophenones (0.1mol) are dissolved in 15mL of ethanol. The reaction mixture was cooled to 0^0C. To this, added ethanolic potassium hydroxide (0.1mol) with care so that the temperature of the reaction mixture was not allowed to rise above 0^0C. Stirred the reaction mixture at this temperature for further 2 hrs. Filtered the solid separated at the suction pump, dried and drained. The recrystallisation was done using ethanol as solvent.

3.4** synthesis of 1-acetyl/propyl-3-aryl-5-(5-aryloxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-pyrazolines **4:
The 3-(5-aryloxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-aryl-2-propen-1-one **3** (0.1mol) and hydrazine hydrate (99%) was taken in 15mL of acetic/propionic acid. Refluxed the reaction mixture with stirring for 4 hrs in an oil bath. Cooled the contents to room temperature and added to 200 g of crushed ice with vigorous stirring. Filtered the solid separated, dried and drained. Recrystallised the compounds from hot ethanol.

The spectral and analytical data of the newly synthesized compounds are given below.

*Compound **4a**:* Ar=Ph, R= H, R^1= CH_3.
Yield: 85%, M.P. 153-154^{0}C.
CHN Analysis: Found (Calc): C: 74.33 (74.29); H: 5.47 (5.54); N: 12.88 (12.84).
^{1}H NMR (300MHz, $CDCl_3$): δ, 1.73 (s, 3H, acyl –CH_3), δ, 2.32 (s, 3H, pyrazole –CH_3), δ, 3.25 (dd, *J*= 5.1Hz & 12.2Hz, 1H, H of –CH_2-), δ, 3.68 (dd, *J*= 12.2Hz & 17.6Hz, 1H, H of –CH_2-), δ, 5.37 (dd, *J*= 5.1Hz & 17.6Hz, 1H, H of –CH-), δ, 6.88-7.58(m, 15H, Ar-H).
Mass: m/z, 437 (M^++1) (M.F.$C_{27}H_{24}N_4O_2$).

*Compound **4b:*** Ar= Ph, R= H, R^1=CH_2CH_3.
Yield: 90%, M.P. 134-136^{0}C.
CHN Analysis: Found (Calc): C: 74.70 (74.65); H: 5.87 (5.82); N: 12.36 (12.44).
IR (KBr): γ_{C-H} 2975.1 7 3045cm^{-1}, $\gamma_{C=O}$ 1653.0cm^{-1}, $\gamma_{C=N}$ 1590.9cm^{-1}, γ_{C-O-C} 1194.0cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$): δ, 1.08 (t, 3H, acyl CH_3), δ, 2.27 (q, 2H, -CH_2-CH_3), δ, 2.44 (s, 3H, pyrazole CH_3), δ, 3.26 (dd, *J*= 5.1Hz & 17.7Hz, 1H, H of –CH_2-), δ, 3.57 (dd, *J*= 12Hz & 17.7Hz, 1H, H of –CH_2-), δ, 5.4 (dd, *J*= 5.1Hz & 12HZ, 1H, -CH-), δ, 6.58-7.6 (m, 15H, Ar-H).
^{13}C NMR (400MHz, DMSO): δ,8.93 (acyl -CH_3), δ, 13.24 (-CH_3 of pyrazole), δ, 27.05 (-CH_2- of propyl), δ, 40.73 (-CH_2- of pyrazoline), δ, 50.49 (-CH- of pyrazoline), δ, 109.73 (C-2 of pyrazole), δ, 114.83-145.04 (12 signals, aromatic carbons of phenyl groups), δ, 147.62 (C-3 of pyrazole), δ, 153.47 (C=N of pyrazoline), δ, 156.16 (C-1 of pyrazole), δ, 171.17 (-CO-).
Mass: m/z, 451 (M^++1) (M.F. $C_{28}H_{26}N_4O_2$).

Compound ***4c*****:** Ar= Ph, R=CH_3, R^1=CH_3.
Yield: 72%, M.P. 128-130^{0}C.
CHN Analysis: Found (Calc): C: 74.58 (74.65); H: 5.75 (5.82); N: 12.50 (12.44).
^{1}H NMR (300MHz, $CDCl_3$): δ, 2.02 (s, 3H, acyl –CH_3), δ, 2.41 (s, 6H, CH_3 of pyrazole and *p*-tolyl), δ, 3.26 (dd, *J*=5.1Hz & 17.4Hz, 1H, H of –CH_2-), δ, 3.57 (dd, *J*= 12.3Hz & 17.4Hz, 1H, H of –CH_2-), δ, 5.37 (dd, *J*=5.1Hz & 12.3Hz, 1H, H of –CH-), δ, 6.62 (d, *J*=8.1Hz, 2H, meta- protons of *p*-tolyl), δ, 7.53 (d, *J*= 7.8Hz, 2H, ortho-protons of *p*-tolyl), δ, 6.92-7.48 (m, 10H, Ar-H).
Mass: m/z, 451 (M^++1) (M.F. $C_{28}H_{26}N_4O_2$).

Compound ***4d:*** Ar= Ph, R= CH_3, R^1=CH_2CH_3.
Yield: 67%, M.P. 132-134^{0}C.
CHN Analysis: Found (Calc): C: 74.92 (74.98); H: 6.12 (6.08); N: 12.10 (12.06).
^{1}H NMR (400MHz, DMSO-d_6): δ, 0.932 (t, 3H, propyl –CH_3), δ, 2.16 (q, 2H, propyl-CH_2-), δ, 2.29 (s, 3H, *p*-tolyl-CH_3), δ, 2.501 (s, 3H, pyrazole-CH_3), δ, 3.27 (dd, *J*= 5.2Hz & 18Hz, 1H, H of –CH_2-), δ, 3.68 (dd, *J*= 2.4Hz & 18Hz, 1H, H of –CH_2-), δ, 5.33 (dd, *J*= 5.2Hz & 12.4Hz, 1H, H of –CH-), δ, 6.58 (d, *J*= 8.4Hz, 2H, meta-protons of *p*-tolyl), δ, 7.33 (d, *J*= 8.0Hz, 2H, ortho-protons of *p*-tolyl), δ, 6.94-7.52 (m, 10H, Ar-H).
Mass: m/z, 465 (M^++1) (M.F. $C_{28}H_{26}N_4O_2$).

Compound ***4e*****:** Ar= Ph, R= Cl, R^1= CH_3.
Yield: 86%, M.P. 128-129^{0}C.
CHN Analysis: Found (Calc): C: 68.92 (68.86); H: 4.96 (4.92); N: 11.84 (11.90).
^{1}H NMR(400MHz, DMSO-d_6): δ, 1.94 (s, 3H, acyl –CH_3), δ, 2.29 (s, 3H, pyrazole –CH_3), δ, 3.26 (dd, *J*= 5.2Hz & 17.6Hz, 1H, H of –CH_2-), δ, 3.70 (dd, *J*= 12.4Hz & 17.6Hz, 1H, H of –CH_2-), δ, 5.37 (dd, *J*= 5.2Hz & 12.4Hz, 1H, H of –CH-), δ, 6.58 (d, *J*= 8.4Hz, 2H, ortho-protons of *p*-chlorophenyl), δ, 7.58 (d, *J*= 8.4Hz, 2H, meta-protons of *p*-chlorophenyl),
δ, 6.94-7.51 (m, 10H, Ar-H).
Mass: m/z, 471/473 (M^++1)/(M^++3) (3:1) (M.F. $C_{27}H_{23}ClN_4O_2$).

Compound ***4f:*** Ar= Ph, R= Cl, R^1= CH_2CH_3.
Yield: 95%, M.P. 133-135^{0}C.
CHN Analysis: Found (Calc): C: 69.43 (69.34); H: 5.14 (5.20); N: 11.50 (11.55).
IR (KBr): γ_{C-H} 2971.1cm^{-1}, $\gamma_{C=O}$ 1656.5cm^{-1}, $\gamma_{C=N}$ 1590.9cm^{-1}, γ_{C-O-C} 1195.1cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$): δ, 1.06 (t, 3H, propyl –CH_3), δ, 2.24 (q, 2H, propyl –CH_2-), δ, 2.45 (s, 3H, pyrazole –CH_3), δ, 3.26 (dd, *J*=4.8Hz & 17.7Hz, 1H, H of –CH_2-), δ, 3.55 (dd, *J*= 12.6Hz & 17.7Hz, 1H, H of –CH_2-), δ, 5.42 (dd, *J*= 4.8Hz & 12.6Hz, 1H, H of –CH-), δ, 6.56
(d, *J*=8Hz, 2H, ortho-protons of *p*-chlorophenyl), δ, 7.35 (d, *J*= 8Hz, 2H, meta-protons of *p*-chlorophenyl), δ, 6.90-7.68 (m, 10H, Ar-H).
^{13}C NMR (400MHz, DMSO): δ, 8.46 (-CH_3 of propyl), δ, 12.75 (-CH_3 of pyrazole), δ, 26.51 (-CH_2- of propyl), δ, 40.22 (-CH_2- of pyrazoline), δ, 50.18 (-CH- of pyrazoline), δ, 109.24 (C-2 of pyrazole), δ, 114.28-144.48 (12 signals, aromatic carbons of phenyl and *p*-chlorophenyl), δ, 147.15 (C-3 of pyrazole), δ, 152.03 (-C=N of pyrazoline), δ, 155.64 (C-1 of pyrazole), δ, 170.53 (-CO-).
Mass: m/z, 485/487 (3:1) (M^++1)/(M^++3) (M.F. $C_{28}H_{25}ClN_4O_2$).

Compound ***4g:*** Ar= 2-Naphthyl, R= H, R^1= CH_3.
Yield: 90%, M.P. 87-89^{0}C.
CHN Analysis: Found (Calc): C: 76.48 (76.52); H: 5.42 (5.39); N: 11.44 (11.51).
IR (KBr): γ_{C-H} 2925.2cm^{-1} & 3057.6cm^{-1}, $\gamma_{C=O}$ 1654.9cm^{-1}, $\gamma_{C=N}$ 1591.2cm^{-1}, γ_{C-O-O} 1206.5cm^{-1}.

^{1}H NMR (300MHz, $CDCl_3$): δ, 1.62 (s, 3H, acyl –CH_3), δ, 2.44 (s, 3H, pyrazole –CH_3), δ, 3.22 (dd, *J*=5.2Hz & 12.4Hz, 1H, H of –CH_2-), δ, 3.70 (dd, *J*=12.4Hz & 17.7Hz, 1H, H of –CH_2-), δ, 5.37 (dd, *J*= 5.2Hz & 17.7Hz, 1H, H of –CH-), δ, 6.68-7.59 (m, 17H, Ar-H).
^{13}C NMR (400MHz, DMSO): δ, 12.83 (-CH_3 of pyrazole), δ, 21.21 (-CH_3 of acetyl), δ, 40.16 (-CH_2- of pyrazoline), δ, 49.95 (-CH- of pyrazoline), δ, 109.16 (C-2 of pyrazole), δ, 109.25-144.44 (18 signals, aromatic carbons of phenyl and 2-naphthyl), δ, 147.22 (C-3 of pyrazole), δ, 153.36 (-C=N of pyrazoline), δ, 153.51 (C-1 of pyrazole), δ, 167.24 (-CO-).
Mass: m/z, 487 (M^++1) (M.F. $C_{31}H_{26}N_4O_2$).

Compound ***4h:*** Ar= 2-Naphthyl, R= H, R^1= CH_2CH_3.
Yield: 85%, M.P. 76-78^{0}C.
CHN Analysis: Found (Calc): C: 76.70 (76.78); H: 5.58 (5.64); N: 11.26 (11.19).
^{1}H NMR (400MHz, DMSO-d_6): δ, 0.84 (t, 3H, propyl –CH_3), δ, 1.994 (q, 2H, -CH_2- of propyl), δ, 2.34 (s, 3H, pyrazole -CH_3), δ, 3.34 (dd, *J*= 5.2Hz & 18Hz, 1H, H of –CH_2-), δ, 3.71 (dd, *J*= 12.4Hz & 18Hz, 1H, H of –CH_2-), δ, 5.4 (dd, *J*= 5.2Hz & 12.4Hz, 1H, H of –CH-), δ, 6.9-7.79 (m, 17H, Ar-H).
Mass: m/z, 501 (M^++1) (M.F. $C_{32}H_{28}N_4O_2$).

Compound ***4i:*** Ar= 2-Naphthyl, R= CH_3, R^1= CH_3.
Yield: 75%, M.P. 87-89^{0}C.
CHN Analysis: Found (Calc): C: 76.76 (76.78); H: 5.70 (5.64); N: 11.12 (11.19).
^{1}H NMR (300MHz, $CDCl_3$): δ, 1.25 (s, 3H, acyl –CH_3), δ, 2.39 (s, 3H, *p*-tolyl –CH_3), δ, 2.47 (s, 3H, pyrazole –CH_3), δ, 3.30 (dd, *J*=4.5Hz & 16.8Hz, 1H, H of –CH_2-), δ, 3.56 (dd, *J*= 12Hz & 16.8Hz, 1H, H of –CH_2-), δ, 5.43 (dd, *J*= 4.5Hz & 12Hz, 1H, H of –CH-), δ, 6.86-7.72 (m, 16H, Ar-H).
Mass: m/z, 501 (M^++1) (M.F. $C_{32}H_{28}N_4O_2$).

Compound ***4j:*** Ar= 2-Naphthyl, R= CH3, R^1= CH_2CH_3.
Yield: 81%,, M.P. 79-81^{0}C.
CHN Analysis: Found (Calc): C: 77.08 (77.02); H: 5.80 (5.88); N: 10.94 (10.89).
IR (KBr): γ_{C-H} 2924.9cm^{-1} & 3057.2cm^{-1}, $\gamma_{C=O}$ 1655.6cm^{-1}, $\gamma_{C=N}$ 1592.0cm^{-1}, γ_{C-O-C} 1207.9cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$): δ, 1.01 (t, 3H, propyl –CH_3), δ, 2.18 (q, 2H, propyl-CH_2-), δ, 2.30 (s, 3H, *p*-tolyl –CH_3), δ, 2.48 (s, 3H, pyrazole –CH_3), δ, 3.26 (dd, *J*=5.2Hz & 18Hz, 1H, H of –CH_2-), δ, 3.70 (dd, *J*= 12.2Hz & 18HZ, 1H, H of –CH_2-), δ, 5.30 (dd, *J*= 5.2Hz & 12.2Hz, 1H, H of –CH-), δ, 6.6 (d, *J*= 8.4Hz, 2H, meta protons of *p*-tolyl), δ, 7.35 (d, *J*= 8.2 Hz, 2H, ortho protons of *p*-tolyl), δ, 6.9-7.5 (m, 12H, Ar-H).
^{13}C NMR (400MHz, DMSO): δ, 8.22 (-CH_3 of propyl), δ, 12.77 (-CH_3 of pyrazole), δ, 21.04 (-CH_3 of *p*-tolyl), δ, 26.49 (-CH_2- of propyl), δ, 40.24 (-CH_2- of pyrazoline), δ, 49.91 (-CH- of pyrazoline), δ, 109.09 (C-2 of pyrazole), δ, 109.28-144.46 (18 signals, aromatic carbons of phenyl, 2-naphthyl and *p*-tolyl), δ, 147.22 (C-3 of pyrazole), δ, 153.01 (-C=N of pyrazoline), δ, 153.52 (C-1 of pyrazole), δ, 170.70 (-CO-).
Mass: m/z, 515 (M^++1) (M.F. $C_{33}H_{30}N_4O_2$).

Compound ***4k:*** Ar= 2-Naphthyl, R= Cl, R^1= CH_3.
Yield: 80%, M.P. 85-88^{0}C.
CHN Analysis: Found (Calc): C: 71.52 (71.46); H: 4.80 (4.84); N: 10.74 (10.75).
IR (KBr): γ_{C-H} 2925.5cm^{-1} & 3058.1cm^{-1}, $\gamma_{C=O}$ 1660.4cm^{-1}, $\gamma_{C=N}$ 1593.0cm^{-1}, γ_{C-O-C} 1209.0cm^{-1} (C-O-C str.).

^{1}H NMR (400MHz, DMSO-d_6): δ, 1.85 (s, 3H, acyl -CH_3), δ, 2.33 (s, 3H, pyrazole –CH_3), δ, 3.34 (dd, *J*= 5.0Hz & 17.8Hz, 1H, H of –CH_2-), δ, 3.67 (dd, *J*= 12.4Hz & 17.8Hz, 1H, H of –CH_2-), δ, 5.4 (dd, *J*= 5.0Hz & 12.4Hz, 1H, H of –CH-), δ, 6.93-7.79 (m, 16H, Ar-H).
^{13}C NMR (400MHz, DMSO): δ, 12.80 (-CH_3 of pyrazole), δ, 21.20 (-CH_3 of acetyl), δ, 40.22 (-CH_2- of pyrazoline), δ, 50.15 (-CH- of pyrazoline), δ, 109.03 (C-2 of pyrazoline), δ, 115.99-144.35 (18 signals, aromatic carbons of phenyl, 2-naphthyl and *p*-chlorophenyl), δ, 147.23 (C-3 of pyrazole), δ, 152.20 (-C=N of pyrazoline), δ, 153.52 (C-1 of pyrazole), δ, 167.26 (-CO-).
Mass: m/z, 521/523 (M^++1)/(M^++3) (3:1) (M.F. $C_{31}H_{25}ClN_4O_2$).

Compound ***4l:*** Ar= 2-Naphthyl, R= Cl, R^1= CH_2CH_3.
Yield: 57%, M.P. 80-83^{0}C.
CHN Analysis: Found (Calc): C: 71.80 (71.83); H: 5.14 (5.09); N: 10.42 (10.47).
^{1}H NMR (300MHz, $CDCl_3$): δ, 0.95 (t, 3H, propyl –CH_3), δ, 2.00 (q, 2H, propyl –CH_2-), δ, 2.5 (s, 3H, pyrazole –CH_3), δ, 3.23 (dd, *J*= 4.8Hz & 17.7Hz, 1H, H of –CH_2-), δ, 3.51 (dd, *J*= 12.6Hz & 17.4Hz, 1H, H of –CH_2-), δ, 5.45 (dd, *J*= 4.5Hz & 12.6Hz, 1H, H of –CH-), δ, 6.86 (d, *J*= 8.1Hz, 2H, ortho-protons of *p*-chlorophenyl), δ, 7.56 (d, *J*= 8.4Hz, 2H, meta-protons of *p*-chlorophenyl), δ, 7.09-7.75 (m, 16H, Ar-H).
Mass: m/z, 535/537 (3:1) (M^++1)/(M^++3) (M.F. $C_{32}H_{27}ClN_4O_2$).

3.5 Pharmacological activity

3.5.1 Anti-inflammatory activity of the compound **4**

Healthy albino rats weighing from 150-250 g were selected and kept for 18 hrs pasting. The animals are weighed and divided into control, standard and test groups and each group contained six rats. The rats in the control, standard and test groups were orally treated with suspension of 1 mL of 1% gum acacia (control), 20 mg/kg of Indomethacin (standard) and 20 mg/kg of the test compounds respectively.

After 30 minutes of the drug administration, animals are injected with 0.1 mL of 1% carrageenan in normal saline subcutaneously in to the sub-plantar region of right hind paw of the rats. Paw volumes was measured immediately (0 hr) and after 30 min, 60 min, 90 min, 120 min and 150 min respectively by using Plethysmometer.

The experiments were carried out under normal laboratory conditions. The animals were handled gently to avoid too much of stress on them which could result in an increased adrenal output. A mark was made at the lateral maleous of the left hind paw so that the dipping was done to the same level while measuring the paw volume.

The change in paw volume was compared with that in vehicle treated control animals, percent inhibition of oedema by different compounds compared to the control and the standard compound was calculated using the formula.

$$\text{Percent oedema inhibition} = 100\text{-}[V_{test}/V_{control}]X100$$

Where V_{test} = Volume of paw oedema in test group.
$V_{control}$ = Volume of paw oedema in control group.
The results obtained are given in **Table 2**.

3.5.2 *Analgesic activity of compound* ***4***

All the compounds were tested for their analgesic activity using Analgesiometer. Rats of either sex weighing between 150-200 g were used for the experiment. The animals were weighed and

divided into different groups (control, standard and the test groups) of five rats each. In this method heat is used as a source of pain. Animals were individually placed on an analgesiometer, so that the tail lies over the nichrome wire of instrument without touching it (i.e., about 1/8 inch above the nichrome wire). Cut off time is 10 seconds. The end point of the sensation is when rat lifts its tail (i.e. tail flick). Reaction time is noted at an intervals of 30, 60, 90 min after the administration of drug. Values are expressed as mean±SEM, by one way ANOVA analysis followed by dunnet's-t-test.

CONCLUSION

A series of acetyl/propyl pyrazolines carrying 5-aryloxypyrazole moiety has been synthesized in good yield and screened for their anti-inflammatory and analgesic activity. The results indicated that, presence of aryloxy group in the 5th position will decreases the anti-inflammatory and analgesic activity when compared with that of 5-chloro derivatives of the corresponding pyrazolinopyrazoles which was described in our earlier report[18].

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REFERENCES

[1] Meena V Patel; Randy Bell; Sandra Majest; Rodger Henry and Teodozyj Kolasa *J. Org. Chem*, **2004**, *69*, 7058.
[2] Vinod Kumar; Ranjana Aggarwal; Parikshit Tyagi and Shiv P Singh *Eur. J. Med. Chem*, **2005**, *40(9)*, 922.
[3] Adnan A Bekhit; Hayam M A Ashour; Yasser S Abdel Ghany; Alaa El-Din A Bekhit and Azza Baraka *Eur. J. Med. Chem*, **2008**, *43(3)*, 456.
[4] Sherif A F Rostom; Manal A Shalaby and Maha A El-Demellawy *Eur. J. Med. Chem*, **2003**, *38*, 959.
[5] Subash Velaparthi; Michael Brunsteiner; Reaz Uddin, Baojie Wan; Scott G Franzblau and Pavel A Petukhov *J. Med. Chem*, **2008**, *51*, 1999.
[6] Ahmad M Farag; Abdelrahman S Mayhoub; Saber E Barakat and Ashraf H Bayomi *Bio-Org. & Med. Chem*, **2008**, *16(2)*, 881.
[7] Morshed A Chowdhury; Khaled R A Abdellatif; Ying Dong; Gang Yu; Zhangjian Huang; Moshfiqur Rahman; Dipankar Das; Carlos A Velazquez; Mavanur R Suresh and Edward E Knaus *Bio-Org. & Med. Chem. Lett*, **2010**, *20(4)*, 1324.
[8] Sherif A F Rostom *Bio-Org. & Med. Chem*, **2010**, *18(7)*, 2767.
[9] H Harinadha Babu; C H Sridevi; A Joseph and K K Srinivasan *Indian J. Pharm.Sci*, **2007**, *69(3)*, 470.
[10] Abdul R Bhat; Fareeda Athar and Amir Azam *Eur. J. Med. Chem*, **2009**, *35*, 426.
[11] Bakr F Abdel-Wahab; Hatem A Abdel-Aziz and Essam M Ahmed *Eur. J. Med. Chem*, **2009**, *35(6)*, 2632.
[12] Hong Dai; Hai-Bo Yu; Jian-Bing Liu; Yong-Qiang Li; Xue Qin; Xin Zhang; Zhen-Fang Qin; Ting-Ting Wang and Jian-Xin Fang *Arkivoc*, **2009**, *vii*, 126.
[13] Scott D Larsen; Toni-Jo Poel; Kevin J Filipski; Jeffrey T Kohrt; Jeffrey A Pfefferkorn; Roderick J Sorenson; Bradley D Tait; Valerie Askew; Lisa Dillon; Jeffrey C Hanselman; Gina H

Lu; Andrew Robertson; Catherine Sekerke; Mark C Kowala and Bruce J. Auerbach *Bio-Org. & Med. Chem. Lett*, **2007**, *17(20)*, 5567.
[14] Hyun-Ja Park; Kyung Lee; Su-Jin Park; Bangle Ahn; Jong-Cheol Lee; HeeYeong Cho and Kee-In Lee *Bio-Org. & Med. Chem. Lett*, **2005**, *15(13)*, 3307.
[15] N. Sathish Rai; Balakrishna Kalluraya; B Lingappa; Shalini Shaenoy; Vagdevi G Puranic *Eur.J.Med.Chem*, **2008**, *43*, 1715.
[16] Balakrishna Kalluraya; Prashanth Gunaga and K Ananda *Indian J. Chem*, **1999**, *38B*, 1295.
[17] N Sathish Rai and Balakrishna Kalluraya *Indian J. Chem*, **2007**, *46B*, 375.
[18] K S Girisha; Balakrishna Kalluraya; Vijaya Narayana and Padmashree *Eur. J. Med. Chem*, **2010**, *45(10)*, 4640-4644.
[19] S K Kulakarni. In Hand Book of Experimental Pharmacology, 3rd Ed. Ed. By Vallabha Publications, **1999**, 128.
[20] S Sarenko; L S Efros and Kvitko I Ya *Pharmaceutical Chemistry Journal*, **1970**, *4(9)*, 488.