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Synthesis and pharmacological study of 1-acetyl/propyl-3-aryl-5-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-pyrazoline

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ABSTRACT

A series of 1-acetyl/propyl-3-aryl-5-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-pyrazolines were synthesized in one step by condensing suitably substituted propenones, hydrazine and acetic/propionic acid. The newly synthesized pyrazolines were characterized by analytical and spectral data. The new compounds were screened for analgesic and anti-inflammatory activity and most of them showed good activity comparable with that of standard drugs Pentazocin and Diclofinac sodium respectively.

1. Introduction

Pyrazoles are novel class of heterocyclic compounds possessing wide variety of application in the agrochemical and pharmaceutical industries [1]. Derivatives of pyrazoles are found to show good antibacterial [2], anti-inflammatory [3], analgesic [4], anti-cancer, radioprotective [5], anti-convulsant [6] and anti-depressant activity [7]. Pyrazolines are well known and important nitrogen containing five membered heterocyclic compounds. Several pyrazoline derivatives have been found to possess considerable biological activities which stimulated research activities in this field [8–12]. After the pioneer work of Fischer and Knovenagal in the late nineteenth century [13], the reaction of α,β-unsaturated aldehyde and ketones with hydrazines became one of the most popular method for the preparation of 2-pyrazolines. In view of these observations and in continuation of our search for biologically active pyrazole derivatives [14–16], we herein report the synthesis and pharmacological activity of a series of 1-acetyl/propyl-3-aryl-5-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-pyrazolines **3**.

2. Results and discussion

2.1. Chemistry

The synthesis of hitherto unreported title compounds was prepared as outlined in Scheme 1. 1-Phenyl-5-chloro-3-methyl-1*H*-pyrazole-4-carboxaldehyde **1** was prepared according to the literature method [14]. The 3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-(aryl)-2-propen-1-one **2** was prepared by the reaction of aldehyde **1** with appropriately substituted acetophenones in ethanol medium employing alcoholic potassium hydroxide as the catalyst at 0–5 °C (Table 1). When these propenones **2** were treated with hydrazine hydrate in acetic acid/propionic acid under reflux gave 1-acetyl/propyl-3-aryl-5-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-pyrazolines **3**. The structures of the newly synthesized compounds have been established on the basis of spectral and analytical data.

In the IR spectra of compounds **3a**–**m** the carbonyl absorption bands were observed in the region of 1710–1725 cm^{-1}. The C–H stretching band was seen around 2925–3025 cm^{-1} whereas the –C=N stretching was observed around 1587–1610 cm^{-1}. In the ^1H NMR spectra of these compounds the chiral CH proton appeared as doublet of a doublet, while the pro-chiral methylene protons appeared as two distinct doublet of a doublet there by indicating the magnetic non-equivalency of the two protons.

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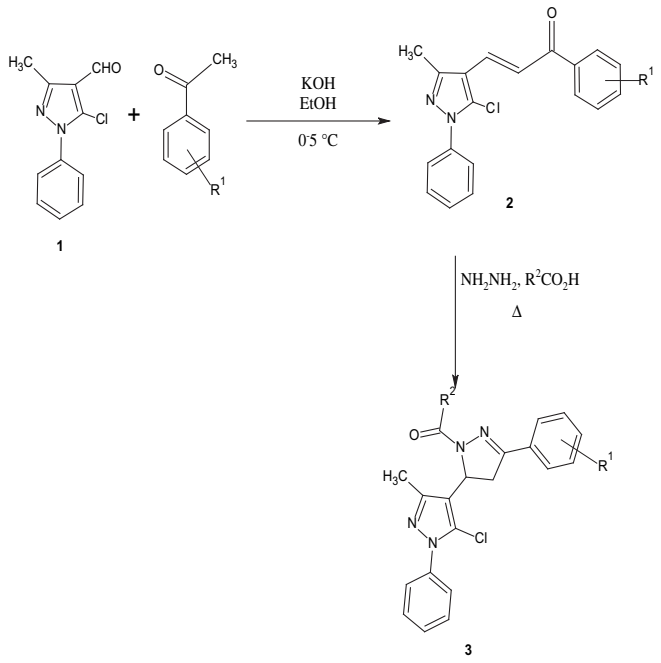

Scheme 1. Synthesis of pyrazolines.

Table 1
Characterization data of 3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-(substituted aryl)-2-propen-1-one **2**.

Compd.	R^1	Yield (%)	M.P. (°C)	CHN analysis		
				Found (Calc)		
				C	H	N
2a	H	84	61–64	70.66 (70.70)	4.74 (4.68)	8.61 (8.68)
2b	4-CH_3	78	69–70	71.36 (71.32)	5.12 (5.09)	8.29 (8.32)
2c	4-OCH_3	81	113–115	68.11 (68.09)	4.80 (4.86)	7.96 (7.94)
2d	3-NO_2	97	176–180	65.10 (65.05)	3.80 (3.84)	11.41 (11.43)
2e	4-Cl	86	156–162	63.84 (63.88)	3.92 (3.95)	7.86 (7.84)
2f	4-Br	98	149–152	56.85 (56.81)	3.53 (3.51)	5.93 (6.97)
2g	4-NO_2	98	172–176	65.08 (65.05)	3.82 (3.84)	11.46 (11.43)

Solvent for recrystallization: EtOH.

2.2. Pharmacological activities

The newly synthesized compounds were evaluated for their anti-inflammatory activity using albino rats [17]. The results are summarized in Table 2. Anti-inflammatory results showed that compounds **3b**, **3d**, **3e**, **3i**, **3k** and **3m** showed significant activity comparable with that of the standard drug. The activity was significant at the beginning but as the elapse of time the activity was not very significant.

The analgesic activity for the compounds was determined by tail immersion method [18]. The results are summarized in Table 3. Compounds **3b**, **3d**, **3f**, **3g**, **3j**, **3l** and **3m** showed activity comparable with that of the standard after 30 min of treatment. However at a longer duration of time the activity of the drugs are not so significant except **3g** which contain an electron withdrawing nitro group at the para-position.

3. Conclusion

A series of acetyl/propyl pyrazolines carrying a pyrazole moiety have been synthesized in good yield and screened for their anti-inflammatory and analgesic activity. The results indicated that compounds bearing electron withdrawing nitro group in the aryl moiety showed the highest analgesic activity.

4. Experimental section

4.1. General

Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds were confirmed by thin layer chromatography using silica gel plates in petroleum ether:ethyl acetate(9.2:0.8) system as mobile phase. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-II 400 MHz NMR spectrometer using $CDCl_3$/DMSO-d_6 as solvent. TMS was employed as internal standard. Chemical shift values are expressed in δ scale down field from TMS. The IR spectra were obtained in KBr disc on a Shimadzu-8400 FTIR spectrophotometer. The mass spectra were recorded on a Waters Micromass Q-Tof Micro LC mass spectrometer. CHN analysis was carried on a Elementar Vario-El-III model analyzer.

Table 2
Anti-inflammatory activity data of 1-acetyl/propyl-3-aryl-5-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-pyrazolene **3**.

Compd.	Change in paw volume (in mL) after (±SE[a])				
	30 min	60 min	90 min	120 min	150 min
3a	–	–	–	–	–
3b	$0.0667 \pm 0.033^{**}$	$0.1 \pm 0.0577^{**}$	$0.0667 \pm 0.033^{**}$	$0.033 \pm 0.033^{**}$	$0.0667 \pm 0.033^{**}$
3c	$0.0 \pm 0.0^{**}$	$0.0 \pm 0.0^{**}$	$0.1 \pm 0.0^{**}$	$0.0667 \pm 0.033^{**}$	$0.1 \pm 0.0^{**}$
3d	$0.0667 \pm 0.033^{**}$	$0.0667 \pm 0.033^{**}$	$0.033 \pm 0.033^{**}$	$0.0667 \pm 0.033^{**}$	$0.133 \pm 0.033^{**}$
3e	$0.033 \pm 0.033^{**}$	$0.0667 \pm 0.033^{**}$	$0.033 \pm 0.0333^{**}$	$0.0667 \pm 0.033^{**}$	$0.0667 \pm 0.033^{**}$
3f	$0.1 \pm 0.0^{**}$	$0.033 \pm 0.033^{**}$	$0.033 \pm 0.033^{**}$	$0.1667 \pm 0.033^{**}$	0.3 ± 0.0^{ns}
3g	$0.1 \pm 0.0^{**}$	$0.0667 \pm 0.033^{**}$	$0.06 \pm 0.033^{**}$	$0.0667 \pm 0.033^{**}$	$0.1667 \pm 0.033^{**}$
3h	0.2667 ± 0.033^{ns}	0.333 ± 0.033^{ns}	0.433 ± 0.033^{ns}	0.367 ± 0.033^{ns}	0.3667 ± 0.033^{ns}
3i	$0.0667 \pm 0.033^{**}$	$0.133 \pm 0.033^{**}$	$0.133 \pm 0.033^{**}$	0.300 ± 0.0577^{ns}	0.300 ± 0.0577^{ns}
3j	$0.1667 \pm 0.033^{**}$	$0.1667 \pm 0.033^{**}$	$0.133 \pm 0.033^{**}$	$0.1667 \pm 0.033^{**}$	$0.200 \pm 0.0577^{**}$
3k	$0.033 \pm 0.033^{**}$	$0.033 \pm 0.033^{**}$	$0.033 \pm 0.033^{**}$	$0.1 \pm 0.0^{**}$	$0.1 \pm 0.0^{**}$
3l	$0.1667 \pm 0.033^{**}$	$0.133 \pm 0.033^{**}$	$0.2 \pm 0.0^{**}$	0.2667 ± 0.033^{ns}	0.2667 ± 0.033^{ns}
3m	$0.0667 \pm 0.033^{**}$	$0.0667 \pm 0.033^{**}$	$0.033 \pm 0.033^{**}$	$0.0 \pm 0.0^{**}$	$0.033 \pm 0.033^{**}$
Control	0.333 ± 0.033	0.333 ± 0.033	0.3667 ± 0.033	0.367 ± 0.033	0.3667 ± 0.033
Standard (diclofinac sodium)	$0.033 \pm 0.033^{**}$	$0.033 \pm 0.033^{**}$	$0.033 \pm 0.033^{**}$	$0.033 \pm 0.033^{**}$	$0.033 \pm 0.033^{**}$

For all other comparisons $P > 0.05$.
$P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.
[a] ±Standard error.

Table 3
Analgesic activity data of 1-acetyl/propyl-3-aryl-5-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-pyrazolene **3**.

Compd.	Before treatment	After 30 min of treatment	After 60 min of treatment	After 90 min of treatment
3a	–	–	–	–
3b	2.300 ± 0.1155	3.300 ± 0.1155**	4.567 ± 0.08819***	5.467 ± 0.08819***
3c	1.867 ± 0.03333	2.900 ± 0.05774***	3.700 ± 0.05774***	4.333 ± 0.1764**
3d	3.000 ± 0.05773	3.700 ± 0.05774**	4.733 ± 0.08819***	4.833 ± 0.1202**
3e	2.200 ± 0.1000	2.500 ± 0.05773*	3.067 ± 0.08819*	4.200 ± 0.1528**
3f	2.533 ± 0.03333	3.967 ± 0.03333**	4.733 ± 0.2186**	4.833 ± 0.5239*
3g	2.533 ± 0.03333	3.467 ± 0.08819**	4.767 ± 0.1453**	5.267 ± 0.2028**
3h	1.33 ± 0.08819	2.333 ± 0.03333**	2.700 ± 0.1155	3.633 ± 0.08819***
3i	1.767 ± 0.08819	2.900 ± 0.05774**	3.733 ± 0.1202**	4.600 ± 0.05773**
3j	2.300 ± 0.05774	4.667 ± 0.08819**	4.633 ± 0.08819***	4.400 ± 0.05773***
3k	2.000 ± 0.05774	2.767 ± 0.1202**	3.067 ± 0.08819**	4.333 ± 0.2186**
3l	2.133 ± 0.08819	3.800 ± 0.1155***	4.167 ± 0.08819**	4.500 ± 0.1732**
3m	1.833 ± 0.03333	3.100 ± 0.05774**	3.533 ± 0.08819***	3.933 ± 0.2333**
Standard (pentazocin)	2.367 ± 0.06667	2.900 ± 0.05774*	5.600 ± 0.05773***	6.400 ± 0.05773***

For all other comparisons $P > 0.05$.
$P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

*4.2. Synthesis of 3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(aryl)-2-propen-1-one **2***

1-Phenyl-5-chloro-3-methyl-1*H*-pyrazole-4-carboxaldehyde **1** (2.2 g, 0.01 mol) was dissolved in 25 mL of ethanol. To this solution suitably substituted acetophenones (0.1 mol) were added and the reaction mixture was cooled to 0 °C by means of ice-salt mixture. To the cold reaction mixture ethanolic potassium hydroxide (0.4 mol) was added slowly by maintaining the temperature at 0–5 °C. Stirred the reaction mixture at this temperature for further 2 h. Filtered the solid precipitated and washed with cold ethanol and dried.

*4.3. Synthesis of 1-acetyl/propyl-5-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-3-(aryl)-2-pyrazolene **3***

3-(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-(aryl)-2-propen-1-one **2** (0.1 mol) was dissolved in 15 mL of acetic/propionic acid. To this reaction mixture hydrazine hydrate (0.1 mol) was added. The reaction mixture was refluxed to boiling for about 12 h and allowed to cool to room temperature. The cooled reaction mixture was added to 150 g of crushed ice with vigorous stirring. The solution was neutralized with saturated sodium bicarbonate solution and left for 6 h at room temperature. The solid separated was filtered, washed with water and dried. Further purification was done by recrystalization from ethanol.

The spectral and analytical data of the compounds synthesized according to this procedure are given below.

Compound **3a**: $R^1 = H$, $R^2 = -CH_3$, M.P. 55–57 °C, Yield: 78.71%. CHN Analysis: Found (Calc): C: 66.82 (66.58), H: 5.13 (5.05), N: 14.38 (14.79). ^{1}H NMR: 400 MHz, $CDCl_3$: δ, 2.18 (s, 3H, $-CH_3$), δ, 2.27 (s, 3H, CO–CH_3), δ, 3.02–3.08 (dd, $J = 5.3$ Hz & 17.6 Hz, 1H, H of $-CH_2-$), δ, 3.61–3.70 (dd, $J = 12.2$ Hz & 17.6 Hz, 1H, H of $-CH_2-$), δ, 5.47–5.55 (dd, $J = 5.3$ Hz & 12.2 Hz, 1H, H of –CH–), δ, 6.99–7.55 (m, 10H, Ar–H). Mass: *m*/*z*, 379/381 $(M^+ + 1)/(M^+ + 3)$ (M.F. $C_{21}H_{19}ClN_4O$).

Compound **3b**: $R^1 = 4\text{-}CH_3$, $R^2 = -CH_3$, M.P. 79–83 °C, Yield: 80.01%. CHN Analysis: Found (Calc): C: 67.19 (67.26), H: 5.46 (5.39), N: 14.33 (14.26). IR (KBr): $\nu_{C=O}$ 1662 cm^{-1}, $\nu_{C=N}$ 1596 cm^{-1}, ν_{C-H} 3010 cm^{-1}. ^{1}H NMR: 400 MHz, $CDCl_3$: δ, 2.1 (s, 3H, $-CH_3$), δ, 2.24 (s, 3H, $-CH_3$ of p-tolyl), δ, 2.41 (s, 3H, –CO–CH_3), δ, 3.12–3.18 (dd, $J = 5.6$ Hz & 17.7 Hz, 1H, H of $-CH_2-$), δ, 3.68–3.77 (dd, $J = 12.5$ Hz & 17.7 Hz, 1H, H of $-CH_2-$), δ, 5.51–5.60 (dd, $J = 5.6$ Hz & 12.5 Hz, 1H, H of –CH–), δ, 7.12 (d, 2H, p-tolyl), δ, 7.41 (d, 2H, p-tolyl), δ, 7.31–7.61 (m, 5H, Ar–H). Mass: *m*/*z*, 393/395 $(M^+ + 1)/(M^+ + 3)$ (M.F. $C_{22}H_{21}ClN_4O$).

Compound **3c**: $R^1 = 4\text{-}OCH_3$, $R^2 = -CH_3$. M.P. 62–65 °C, Yield: 87.7%. CHN Analysis: Found (Calc): C: 64.77 (64.62), H: 4.95 (5.18), N: 13.65 (13.70). ^{1}H NMR: 400 MHz, $CDCl_3$: δ, 2.3 (s, 3H, CH_3), δ, 2.37 (s, 3H, –CO–CH_3), δ, 3.88 (s, 3H, OCH_3), δ, 3.22–3.28 (dd, $J = 5.4$ Hz & 17.8 Hz, 1H, H of $-CH_2-$), δ, 3.68–3.76 (dd, $J = 12.6$ Hz & 17.8 Hz, 1H, H of $-CH_2-$), δ, 5.57–5.62 (dd, $J = 5.4$ Hz & 12.6 Hz, 1H, –CH–), δ, 6.99 (d, 2H, $J = 8.8$ Hz, p-anisyl) & δ: 7.73 (d, 2H each, $J = 8.8$ Hz, p-anisyl), δ, 7.37–7.55 (m, 5H, Ar–H). ^{13}C NMR: 400 MHz, DMSO: δ, 12.31 (CH_3 of pyrazole), δ, 21.38 (acyl $-CH_3$), δ, 39.77 ($-CH_2-$ of pyrazoline), δ, 50.36 (–CH– of pyrazoline), δ, 54.92 (OCH_3), δ, 113–160.84 (12 signals, aromatic carbons, pyrazole carbon and C-3 of pyrazolin), δ, 167.75 (–CO–). Mass: *m*/*z*, 409/411 $(M^+ + 1)/(M^+ + 3)$ (M.F. $C_{22}H_{21}ClN_4O_2$).

Compound **3d**: $R^1 = 3\text{-}NO_2$, $R^2 = -CH_3$. M.P. 68–71 °C, Yield: 71.35%. CHN Analysis: Found (Calc): C: 59.38 (59.51), H: 4.34 (4.28), N: 16.59 (16.52). IR (KBr): $\nu_{C=O}$ 1660 cm^{-1}, $\nu_{C=N}$ 1598 cm^{-1}, ν_{C-H} 2996 cm^{-1}. ^{1}H NMR: 400 MHz, $CDCl_3$: δ, 2.09 (s, 3H, CH_3), δ, 2.45 (s, 3H, CO–CH_3), δ, 3.35–3.42 (dd, $J = 5.2$ Hz & 17.5 Hz, 1H, H of $-CH_2-$), δ, 3.78–3.85 (dd, $J = 12.4$ Hz & 17.5 Hz, 1H, H of $-CH_2-$), δ, 5.67–5.76 (dd, $J = 5.2$ Hz & 12.4 Hz, 1H, –CH–), δ, 7.41–8.6 (m, 9H, Ar–H). Mass: *m*/*z*, 424/426 $(M^+ + 1)/(M^+ + 3)$ (M.F. $C_{21}H_{18}ClN_5O_3$).

Compound **3e**: $R^1 = 4\text{-}Cl$, $R^2 = -CH_3$. M.P. 117–120 °C, Yield: 70.24%. CHN Analysis: Found (Calc): C: 61.13 (61.03), H: 4.26 (4.39), N: 13.63 (13.56) IR (KBr): ν_{CO} 1672 cm^{-1}, $\nu_{C=N}$ 1600 cm^{-1}, ν_{C-H} 2972 cm^{-1}. ^{1}H NMR: 400 MHz, DMSO-d_6: δ, 2.24 (s, 3H, $-CH_3$), δ, 2.34 (s, 3H, CO–CH_3), δ, 3.23–3.30 (dd, $J = 5.52$ Hz & 17.88 Hz, 1H, H of $-CH_2-$), δ, 3.75–3.83 (dd, $J = 12.5$ Hz & 17.88 Hz, 1H, H of $-CH_2-$), δ, 5.53–5.58 (dd, $J = 5.52$ Hz & 12.5 Hz, 1H, –CH–), δ, 7.37–7.85 (m, 9H, Ar–H). ^{13}C NMR: 400 MHz, DMSO: δ, 12.82 ($-CH_3$ of pyrazole), δ, 21.85 (acyl $-CH_3$), δ, 39.78 ($-CH_2-$ of pyrazoline), δ, 51.20 (–CH– of pyrazoline), δ, 117.38–152.71 (12 signals, aromatic carbons, pyrazole carbons and C-3 of pyrazoline), δ, 168.89 (–CO–). Mass: *m*/*z*, 413/415/417 $(M^+ + 1)/(M^+ + 3)/(M^+ + 5)$ (M.F. $C_{21}H_{18}Cl_2N_4O$).

Compound **3f**: $R^1 = 4\text{-}Br$, $R^2 = -CH_3$. M.P. 110–115 °C, Yield: 89.5%. CHN Analysis: Found (Calc): C: 55.21 (55.1), H: 4.05 (3.96), N: 7.62 (7.75). ^{1}H NMR: 400 MHz, $CDCl_3$: δ, 2.21 (s, 3H, $-CH_3$), δ, 2.55 (s, 3H, –CO–CH_3), δ, 3.20–3.26 (dd, $J = 5.6$ Hz & 18.0 Hz, 1H, H of $-CH_2-$), δ, 3.73–3.8 (dd, $J = 12.6$ Hz & 18.0 Hz, 1H, H of $-CH_2-$), δ, 5.41–5.45 (dd, $J = 5.6$ Hz & 12.6 Hz, 1H, H of –CH–), δ, 7.45–7.56 (m, 5H, Ar–H), δ, 7.59–7.61 (d, $J = 8.0$ Hz, 2H, ortho protons of p-bromophenyl), δ, 7.69–7.71 (d, $J = 8.0$ Hz, 2H, meta protons of p-bromophenyl). Mass: *m*/*z*, 457/459/461 $(M^+ + 1)/(M^+ + 3)/(M^+ + 5)$ (M.F. $C_{21}H_{18}BrClN_4O$).

Compound **3g**: $R^1 = 4\text{-}NO_2$, $R^2 = -CH_3$. M.P. 81–84 °C, Yield: 68.4%. CHN Analysis: Found (Calc): C: 59.37 (59.51), H: 4.36 (4.28), N: 16.55 (16.52). ^{1}H NMR: 400 MHz, DMSO-d_6: δ, 2.26 (s, 3H, $-CH_3$), δ, 2.40 (s, 3H, CO–CH_3), δ, 3.31–3.37 (dd, $J = 5.72$ Hz & 18.04 Hz, 1H, H of $-CH_2-$), δ, 3.80–3.88 (dd, $J = 12.68$ Hz &

18.04 Hz, 1H, H 0f $-CH_2-$), δ, 5.61–5.65 (dd, $J = 5.72$ Hz & 12.68 Hz, 1H, −CH−), δ, 7.49–7.84 (m, 5H, Ar−H), δ, 7.97–7.99 (d, $J = 8.84$ Hz, 2H, ortho protons of p-nitrophenyl), δ, 8.21–8.24 (d, $J = 8.84$ Hz, 2H, meta protons of p-nitrophenyl). ^{13}C NMR: 400 MHz, DMSO: δ, 12.42 (pyrazole $-CH_3$), δ, 21.59 (acyl $-CH_3$), δ, 37.00 (pyrazoline $-CH_2-$), δ, 54.78 (pyrazoline −CH−), δ, 117.59–152.58 (12 signals, aromatic carbons, pyrazoline carbons and C-3 of pyrazoline), δ, 167.82 (−CO−). Mass: *m/z*, 424/426 $(M^+ + 1)/(M^+ + 3)$ (M.F. $C_{21}H_{18}ClN_5O_3$).

Compound **3h**: $R^1 = H$, $R^2 = -CH_2CH_3$. M.P. 40–43 °C, Yield: 87.1%. CHN Analysis: Found (Calc): C: 67.21 (67.26), H: 5.47 (5.39), N: 14.3 (14.26). ^1H NMR: 400 MHz, $CDCl_3$: δ, 1.20 (t, 3H, $-CH_2-CH_3$), δ, 2.21 (s, 3H, $-CH_3$), δ, 2.29 (q, 2H, $-CH_2-CH_3$), δ, 3.04–3.10 (dd, $J = 5.6$ Hz & 17.7 Hz, 1H, H of $-CH_2-$), δ, 3.73–3.81 (dd, $J = 12.7$ Hz & 17.7 Hz, 1H, H of $-CH_2-$), δ, 5.50–5.58 (dd, $J = 12.7$ Hz & 5.6 Hz, 1H, H of −CH−), δ, 6.98–7.53 (m, 10H, Ar−H). Mass: *m/z*, 393/395 $(M^+ + 1)/(M^+ + 3)$ (M.F. $C_{22}H_{21}ClN_4O$).

Compound **3i**: $R^1 = 4-CH_3$, $R^2 = -CH_2CH_3$. M.P. 65–69 °C, Yield: 55.3%. CHN Analysis: Found (Calc): C: 67.85 (67.89), H: 5.77 (5.70), N: 13.71 (13.77). IR (KBr): $\nu_{C=O}$ 1658 cm^{-1}, $\nu_{C=N}$ 1593 cm^{-1}, ν_{C-H} 2988 cm^{-1}. ^1H NMR: 400 MHz, $CDCl_3$: δ, 1.22 (t, 3H, $-CH_2-CH_3$), δ, 2.29 (s, 3H, $-CH_3$), δ, 2.45 (s, 3H, $-CH_3$ of p-tolyl), δ, 2.83 (q, 2H, $-CH_2-CH_3$), δ, 3.21–3.37 (dd, $J = 17.8$ Hz & 5.6 Hz, 1H, H of $-CH_2-$), δ, 3.68–3.76 (dd, $J = 17.8$ Hz & 12.5 Hz, 1H, H of $-CH_2-$), δ, 5.57–5.61 (dd, $J = 12.5$ Hz & 5.6 Hz, 1H, −CH− proton), δ, 7.67–7.69 (d, $J = 8$ Hz, 2H, ortho protons of p-tolyl group), δ, 7.26–7.28 (d, $J = 8$ Hz, 2H, meta protons of p-tolyl group), δ, 7.36–7.55 (m, 5H, Ar−H). ^{13}C NMR: 400 MHz, DMSO: δ, 8.96 ($-CH_3$ of propyl), δ, 12.85 ($-CH_3$ of pyrazole), δ, 21.54 ($-CH_3$ of p-tolyl), δ, 27.49 ($-CH_2-$ of propyl), δ, 39.78 ($-CH_2-$ of pyrazoline), δ, 51.05 (−CH− of pyrazoline), δ, 117.73–153.72 (12 signals, aromatic carbons, pyrazole carbons and C-3 of pyrazoline), δ, 172.35 (−CO−). Mass: *m/z*, 407/409 $(M^+ + 1)/(M^+ + 3)$ (M.F. $C_{23}H_{23}ClN_4O$).

Compound **3j**: $R^1 = 4-OCH_3$, $R^2 = -CH_2CH_3$. M.P. 48–51 °C, Yield: 77.46%. CHN Analysis: Found (Calc): C: 65.36 (65.32), H: 5.46 (5.48), N: 13.21 (13.25). IR (KBr): ν_{CO} 1682 cm^{-1}, $\nu_{C=N}$ 1595 cm^{-1}, ν_{C-H} 2982 cm^{-1}. ^1H NMR: 400 MHz, $CDCl_3$: δ, 1.23 (t, 3H, $-CH_2-CH_3$), δ, 2.28 (s, 3H, $-CH_3$), δ, 2.82–2.88 (q, 2H, $-CH_2-CH_3$), δ, 3.89 (s, 3H, $-OCH_3$), δ, 3.21–3.29 (dd, $J = 17.6$ Hz & 7 5.5 Hz, 1H, H of $-CH_2-$), δ, 3.74–3.83 (dd, $J = 17.6$ Hz & 12.6 Hz, 1H, H of $-CH_2-$), δ, 5.59–3.67 (dd, $J = 12.6$ Hz & 5.5 Hz, 1H, −CH− proton), δ, 6.96–6.98 (d, $J = 8.64$ Hz, 2H, ortho protons of p-anisyl), δ, 7.72–7.74 (d, $J = 8.64$ Hz, 2H, meta protons of p-anisyl), δ, 7.36–7.57 (m, 5H, Ar−H). Mass: *m/z*, 423/425 $(M^+ + 1)/(M^+ + 3)$ (M.F. $C_{23}H_{23}ClN_4O_2$).

Compound **3k**: $R^1 = 3-NO_2$, $R^2 = -CH_2CH_3$. M.P. 112–115 °C, Yield: 81.68%. CHN Analysis: Found (Calc): C: 60.28 (60.34), H: 4.67 (4.60), N: 15.91 (15.99). ^1H NMR: 400 MHz, DMSO-d_6: δ, 1.10–1.19 (t, 3H, $-CH_2-CH_3$), δ, 2.26 (s, 3H, $-CH_3$), δ, 2.78–2.83 (q, 2H, $-CH_2-CH_3-$), δ, 3.32–3.38 (dd, $J = 5.7$ Hz & 18.0 Hz, 1H, H of CH_2), δ, 3.84–3.92 (dd, $J = 12.58$ Hz & 18.04 Hz, 1H, H of $-CH_2-$), δ, 5.59–5.64 (dd, $J = 5.7$ Hz & 12.52 Hz, 1H, −CH−), δ, 7.38–7.52 (m, 5H, Ar−H), δ, 7.69–7.74 (t, 1H, 5H of m-nitrophenyl), δ, 8.15–8.17 (d, 1H, 6H of m-nitrophenyl), δ, 8.27–8.29 (d, 1H, 4H of m-nitrophenyl), δ, 8.58 (s, 1H, 2H of m-nitrophenyl). ^{13}C NMR: 400 MHz, DMSO: δ, 8.87 ($-CH_3$ of propyl group), δ, 12.79 ($-CH_3$ of pyrazole), δ, 27.50 ($-CH_2-$ of propyl group), δ, 39.46 ($-CH_2-$ of pyrazoline), δ, 51.63 (−CH− of pyrazoline), δ, 117.31–151.3 (12 signals, aromatic carbons, pyrazole carbons and C-3 of pyrazoline), δ, 172.58 (−CO−). Mass: *m/z*, 438/440 $(M^+ + 1)/(M^+ + 3)$(M.F. $C_{22}H_{20}ClN_5O_3$).

Compound **3l**: $R^1 = 4-Br$, $R^2 = -CH_2CH_3$. M.P. 71–74 °C, Yield: 77.68%. CHN Analysis: Found (Calc): C: 56.08 (56.01), H: 4.23 (4.27), N: 11.85 (11.88). ^1H NMR: 400 MHz, DMSO-d_6: δ, 1.07–1.16 (t, 3H, $-CH_2-CH_3$), δ, 2.22 (s, 3H, $-CH_3$), δ, 2.71–2.77 (q, 2H, $-CH_2-CH_3-$) δ, 3.22–3.28 (dd, $J = 5.56$ Hz & 18.1 Hz, 1H, H of $-CH_2-$), δ, 3.76–3.83 (dd, $J = 12.6$ Hz & 18.1 Hz, 1H, H of $-CH_2-$), δ, 5.52–5.57 (dd, $J = 5.56$ Hz & 12.6 Hz, 1H, −CH−), δ, 7.45–7.56 (m, 5H, Ar−H), δ, 7.59–7.61 (d, $J = 8.28$ Hz, 2H, ortho protons of p-bromophenyl), δ, 7.69–7.71 (d, $J = 8.28$ Hz, 2H, meta protons of p-bromophenyl). ^{13}C NMR: 400 MHz, DMSO: δ, 8.94 (propyl $-CH_3$), δ, 12.42 (pyrazole $-CH_3$), δ, 26.81 (propyl$-CH_2-$), δ, 38.8 (pyrazoline $-CH_2-$), δ, 50.89 (pyrazoline −CH−), δ, 117.85–153.29 (12 signals, aromatic carbons, pyrazole carbons and C-3 of pyrazoline), δ, 170.79 (−CO−). Mass: *m/z*, 471/473/475 $(M^+ + 1)/(M^+ + 3)/(M^+ + 5)$ (M.F. $C_{22}H_{20}BrClN_4O$).

Compound **3m**: $R^1 = 4-NO_2$, $R^2 = -CH_2CH_3$. M.P. 72–75 °C, Yield: 62.86%. CHN Analysis: Found (Calc): C: 60.31 (60.34), H: 4.55 (4.60), N: 16.05 (15.99). ^1H NMR: 400 MHz, $CDCl_3$: δ, 1.32 (t, 3H, $-CH_2-CH_3$), δ, 2.27 (s, 3H, $-CH_3$), δ, 2.44–2.50 (q, 2H, $-CH_2-CH_3$), δ, 3.33–3.38 (dd, $J = 5.8$ Hz & 18.2 Hz, 1H, H of $-CH_2-$), δ, 3.83–3.91 (dd, $J = 12.7$ Hz & 5.8 Hz, 1H, H of $-CH_2-$), δ, 5.62–5.67 (dd, $J = 5.8$ Hz & 12.7 Hz, 1H, H of −CH−), δ, 7.49–7.84 (m, 5H, Ar−H), δ, 7.98–8.002 (d, $J = 8.8$ Hz, 2H, ortho protons of p-nitrophenyl), δ, 8.23–8.25 (d, $J = 8.8$ Hz, 2H, meta protons of p-nitrophenyl). Mass: *m/z*, 438/440 $(M^+ + 1)/(M^+ + 3)$ (M.F. $C_{22}H_{20}ClN_5O_3$).

4.4. Pharmacological activity

4.4.1. Anti-inflammatory activity of the compound **3**

The healthy albino rats weighing from 150 − 250 g were selected and kept for 18 h fasting. The animals are weighed and devided into control, standard and test groups and each group contained six rats. The rats of the control, standard and test groups were orally treated with suspension of 0.1 mL of 1% gum acacia (control), 10 mg/kg of diclofinac sodium (standard) and 10 mg/kg of the test compounds respectively.

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

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 amount of oedema in the drug treated group was compared in relation to the control group with corresponding time intervals. The results were expressed as change in paw volume of oedema over the untreated control group and were summarized in Table 2.

4.4.2. Analgesic activity of compound **3**

The albino rats weighing about 150–200 g were made into group of six animals and were held in position in a suitable restrainer with the tail extending out. 3–4 cm area of the tail was marked and immersed in the water bath thermostatically maintained at 55 °C. The withdrawal time of the tail from hot water (in seconds) was noted as reaction time, initially as tail flick latency before the administration of any drug and then recorded at 30, 60 and 90 min after the administration of the test compounds and pentazocin. The maximum cut off time for immersion was 30 s to avoid the injury of the tissues of the tail. All the drugs are administered orally in 10 mg/kg body weight in 1% gum acacia. The control animals received the vehicle only. The results of the analgesic activity were summarized in Table 3.

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