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Synthesis, analgesic and anti-inflammatory activities of some novel pyrazolines derivatives

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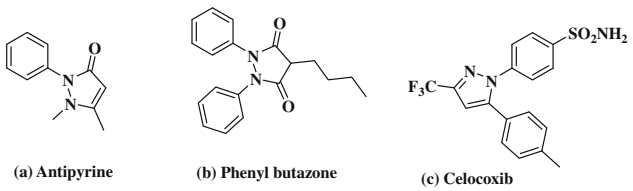
ABSTRACT

In search for a new analgesic and anti-inflammatory agent with improved potency, we designed and synthesized a series of 3,2-(4,5-dihydro-5-(4-morphilinophenyl)-1*H*-pyarazol-3-yl)phenols **6(a–g)** and its *N*-phenylpyrazol-1-carbothioamide **7(a–g)** by Claisan–Schmidt condensation followed by the reaction of hydrazine hydrate. All the synthesized compounds were assayed for their in vivo analgesic and anti-inflammatory activities. All the compounds synthesized showed the potential to demonstrate analgesic and anti-inflammatory activity, of particular interest compounds **6a**, **6b**, **6g**, **7a**, **7d** and **7g** were found comparable to Diclofenac.

Pain is a disagreeable and subjective sensation resulting from a harmful sensorial stimulation that alerts the body about a current or potential damage to its tissues or organs. Despite the painful sensation, which can be efficiently solved by the removal of the main reason, the pain-causing stimulus cannot always be either easily defined or quickly removed. Contemporary analgesics, like opiates and nonsteroidal anti-inflammatory drugs have some limitations in clinical use, such as gastrointestinal (GI) haemorrhage and ulceration, addiction, tolerance especially for opiates.[1] Therefore, medicinal research for the development of safer and more effective anti-inflammatory agents are a great deal of interest for many researchers.

2-Pyrazoline ring system has attracted significant interest in medicinal chemistry over the past few decades. Scaffolds containing the 2-pyrazoline (4,5-dihydropyrazole) heterocyclic have demonstrated a wide range of biological activity viz. anti-inflammatory activity,[2–4] anticancer activity,[5] CB1 receptor antagonism for obesity,[6] antidepressant[7] and antidiabetic.[8]

Literature survey revealed that many pyrazoline derivatives have found their clinical application as NSAIDS. Antipyrine (**a**), 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, was the first pyrazoline derivative used in the treatment of pain and inflammation. Phenyl butazone (**b**) and its potent metabolite celocoxib (**c**), a prototype of pyrazolinedione NSAIDs, are potent anti-inflammatory agents. However their use became restricted due to their GI side effects.[9] Besides these some pyrazoline derivatives (**d**) and (**e**) are also reported in literature as having potent anti-inflammatory activity.[10,11]



N-Functionalized morpholine derivatives exhibit diversified biological activities such as antidiabetic,[12] antiemetic[13,14] platelet aggregation inhibitors[15] inflammatory migraine and asthma.[16] 4-Phenyl morpholine derivatives are reported to possess antimicrobial,[17] anti-inflammatory, central nervous system activities[18] also posses the anti-Alzheimer's diseases activity.[19]

In view of these observations and in continuation of our research programme on the synthesis of five-membered heterocyclic compounds,[20,21] we report herein the synthesis of some new pyrazoline derivatives, which have been found to possess an interesting profile of analgesic and anti-inflammatory activity.

The reaction of morpholine (**2**) with 4-fluorobenzaldehyde (**1**) to gave 4-(morpholin-4-yl)benzaldehyde (**3**) (Scheme 1).[22] (*E*)-1-(2-Hydroxyphenyl)-3-(4-morpholinophenyl)prop-2-en-1-one **5(a–g)**

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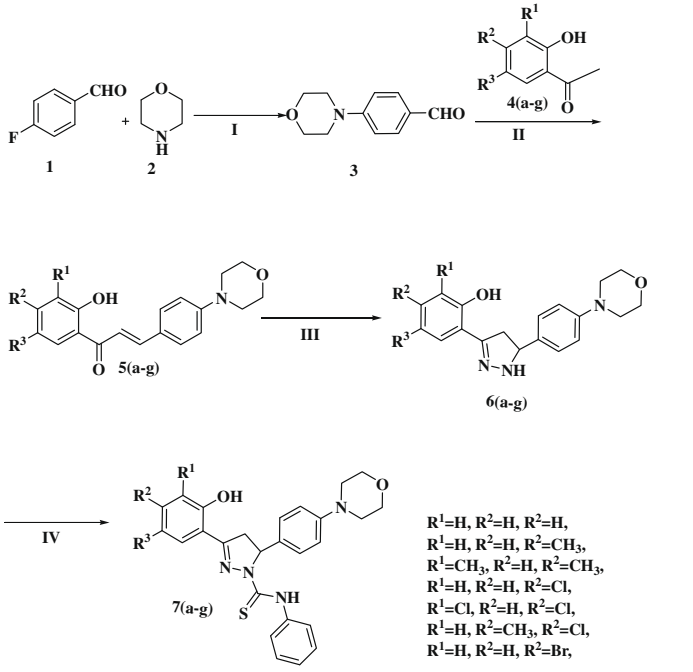

Scheme 1. Reagents and conditions: (I) neat 100 °C; (II) ethanol, KOH at 25 °C; (III) $N_2H_4{\cdot}H_2O$, acetic acid, ethanol, reflux; (IV) phenylisothiocyanate, triethylamine in diethyl ether at 25 °C.

were synthesized by Claisen–Schimdt condensation[23,24] by treating 4-(morpholin-4-yl)benzaldehyde (**3**) with substituted 2-hydroxy acetophenones **4(a–g**) in dilute ethanolic solution of potassium hydroxide at ambient temperature. Further 3,2-(4,5-dihydro-5-(4-morphilinophenyl)-1*H*-pyarazol-3-yl)phenols **6(a–g**)[25] were prepared by reacting (*E*)-1-(2-hydroxyphenyl)-3-(4-morpholinophenyl)prop-2-en-1-one **5(a–g**) with hydrazine hydrate in the presence of acetic acid and ethanol, followed by the reaction of phenylisothiocyanate at room temperature with 3,2-(4,5-dihydro-5-(4-morphilinophenyl)-1*H*-pyarazol-3-yl)phenol **6(a–g**) which gave corresponding 4,5-(dihydro-3(2-hydroxyphenyl)-5-(4-morphinophenyl)-*N*-phenylpyrazol-1-carbothioamide[26,27] **7(a–g**). All the synthesized compounds were characterized by their physical and spectral data (IR, ^{1}H NMR, Mass) and confirmed the structures of novel compounds.

These newly synthesized scaffolds were screened for analgesic and anti-inflammatory activities against mice and rat. Compounds **6b**, **6g**, **7d** and **7g** exhibited equipotent analgesic activity as compared to other tested scaffolds and **6a**, **6g**, **7d** and **7g** shows the good anti-inflammatory activity as compared to other compounds. Compounds **6d**, **6g**, **7d** and **7g** were halogen containing scaffold, so we have confirmed that halogen containing derivatives shows the better activity. We embarked on a hit-to-lead exploration program focus on related scaffolds thus our aim was to explore SAR trends and to find out the lead for further optimization.

The structure of **5d** is interpreted from spectroscopic data. IR spectra of compound **5d** reveals absorption band in the region 3210 cm^{-1} corresponding to –OH stretching of phenolic broad bands because of ring closure. In the ^{1}H NMR spectra of **5d** exhibit each of the olefinic protons as a doublet at d = 6.90–6.93 and 7.89–7.93 regions with a mutual coupling constant value J = 15.24 Hz. These observed coupling constant values indicate the presence of *E,E′*-configuration form the structure, the two triplets at 3.29 and 3.86 of morpholine ring. The phenolic –OH is highly deshielded and appears at 12.97 ppm.

IR spectra of compounds **6c** reveals absorption band in the regions 3428 cm^{-1} corresponding to –OH stretching of phenolic broad bands because of ring closure. The band at 1500–1600 cm^{-1} corresponds to the –C=N stretching. ^{1}H NMR spectra of **6c** reveals the presence of two un-equivalent protons of a methylene group at d = 3.04–3.16 and 3.43–3.49 coupled with each other and in turn with the vicinal methane proton (H-5) at t = 4.80–4.85. It has also been noticed that, the up field shifted proton of methylene residue coupled with the vicinal methane one (H-5) with a coupling constant value J = 8.86–16.48 Hz indicating the presence of *trans*-configuration. In other words, this mentioned proton is located cis to the aryl group attached to the pyrazolines C-5. Also, the coupling constant value between the downfield shifted proton of methylene function and the vicinal methine proton (H-5) J = 8.76–10.6 Hz supports this assumption.

IR spectra of compound **7b** reveals absorption bands in the region 3423 cm^{-1} corresponding to –OH stretching of phenolic broad band because of ring closure. Stretching frequency of –C=S bond

Table 1
Analgesic activity by acetic acid induced writhing response in mice and anti-inflammatory activity of against carrageenan induced rat paw edema model in rats of pyrazoline and its derivatives

Entry	Number of writhings ± SEM	Increase in paw volume ml ± SEM after carrageenan administration			
		2 h	3 h	4 h	24 h
Control	71 ± 3	1.49 ± 0.20	1.64 ± 0.15	1.57 ± 14	1.92 ± 0.12
Diclofenac	08 ± 2	0.18 ± 0.03	0.18 ± 0.015	0.18 ± 0.02	0.03 ± 0.01
6a	11 ± 3	0.73 ± 0.11	0.59 ± 0.12	0.69 ± 0.11	0.68 ± 0.10
6b	10 ± 2	0.87 ± 0. 14	0.85 ± 0.14	0.96 ± 0.10	0.79 ± 0.12
6c	62 ± 3	1.38 ± 0.18	1.57 ± 0.12	1.53 ± 0.18	1.92 ± 0.12
6d	53 ± 4	1.52 ± .0.12	1.60 ± 0.18	1.61 ± 0.12	1.92 ± 0.18
6e	40 ± 1	1.41 ± 0.22	1.46 ± 0.11	1.75 ± 0.15	1.72 ± 0.18
6f	57 ± 3	1.56 ± 0.12	1.62 ± 0.16	163 ± 0.11	193 ± 0.14
6g	15 ± 4	0.86 ± 0.15	0.52 ± 0.14	0.64 ± 0.10	0.98 ± 0.12
7a	12 ± 2	0.82 ± 0.14	0.62 ± 0.18	0.84 ± 0.14	0.94 ± 0.11
7b	46 ± 3	1.52 ± 0.21	1.60 ± 0.12	1.43 ± 0.18	1.92 ± 0.21
7c	38 ± 4	1.41 ± 0.14	1.81 ± 0.16	1.63 ± 0.18	1.73 ± 0.18
7d	09 ± 2	0.64 ± 0.10	0.72 ± 0.14	0.72 ± 0.12	0.86 ± 0.12
7e	47 ± 3	1.49 ± 0.12	1.47 ± 0.13	1.52 ± 0/17	1.92 ± 0.18
7f	65 ± 2	1.42 ± 0.11	1.53 ± 013	1.57 ± 0.16	1.92 ± 0.19
7g	13 ± 3	0.87 ± 0.12	0.69 ± 0.13	0.91 ± 0.17	0.92 ± 0.16

SEM—standard error mean; N = 6.
$^{*}p$ <0.05.
$^{**}p$ <0.01.
$^{***}p$ <0.001.

appears at 1200–1300 cm^{-1}. ^1H NMR spectra of the compound **7b** H_A, H_B and H_X protons of pyrazoline ring were observed as doublet of doublet at 3.12–3.26 (J_{AB}: 17.8 Hz), 3.87–3.90 (J_{AX}: 11.48 Hz) and 6.07–6.11 ppm (J_{BX}: 11.36–11.4 Hz), respectively. An N–H proton of the thiocarbonyl group was observed at 9.4 ppm generally as broad band.

To determine the analgesic activity[28] by using acetic acid induced writhing response in mice.[29] All the compounds were tested with the control sample and reference drug Diclofenac. Analgesic activity was expressed as pain response in the mice as the number of writhing. These compounds inhibited the peripheral pain response in the mice as the number of writhing was found to be less than the control group of vehicle treated animals.

The result is summarized in Table 1 and Figure 1. In tested compounds compound **6a**, **6b**, **6g**, **7a**, **7d** and **7g** were found to be active after comparing with Diclofenac. Compounds **6a**, **6b** and **6g** having pyrazoline derivative and compounds **7a**, **7d** and **7g** having N-substituted pyrazolines were found to be comparable with Diclofenac. 3-(5-Chloro-2-hydroxyphenyl)-4,5-(dihydro-5-(4-morphinophenyl)-*N*-phenylpyrazol-1-carbothio-amide (**7d**) was found to be equipotent with Diclofenac. All data were analyzed by one-way ANOVA test followed by Dunnet's test in the acetic acid induced writhing model.

To determine the anti-inflammatory activity by using carrageenan induced rat paw edema in rats.[30] The effect of synthesized compounds and reference drug on paw edema induced by carrageen have shown in Table 1 and Figure 2. The subplantar injection of carrageenan in control rats induced in increase paw volume over 24 h. The change in paw volume in the rats injected with carrageenan indicates that these four compounds were able to inhibit the change in paw volume at third and fourth hour after the carrageenan injection providing an innuendo towards its probable mechanism of action. Since prostaglandins are secreted at the third and fourth hour after the injection of carrageenan, it may be

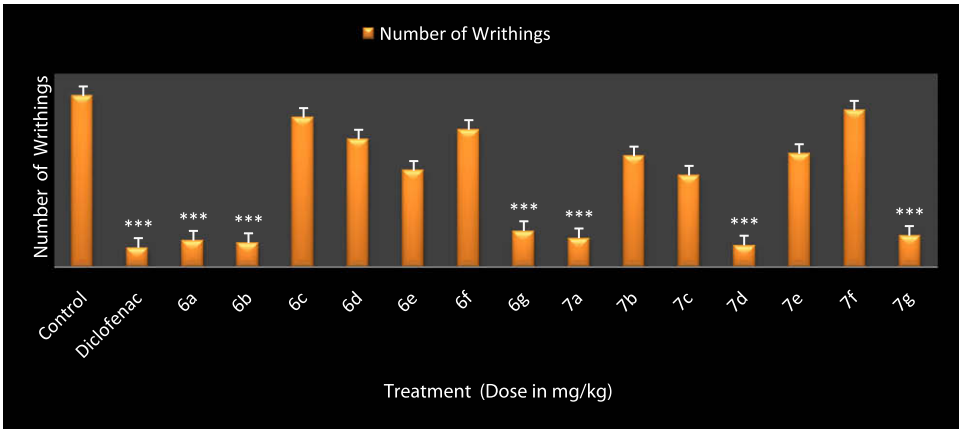

Figure 1. Effect of **6**(**a**–**g**) and **7**(**a**–**h**) on acetic acid induced writhing response in mice. All data were analyzed by one-way ANOVA followed by Dunnet's test in the acetic acid induced writhing model (*p <0.05, **p <0.01, ***p <0.001).

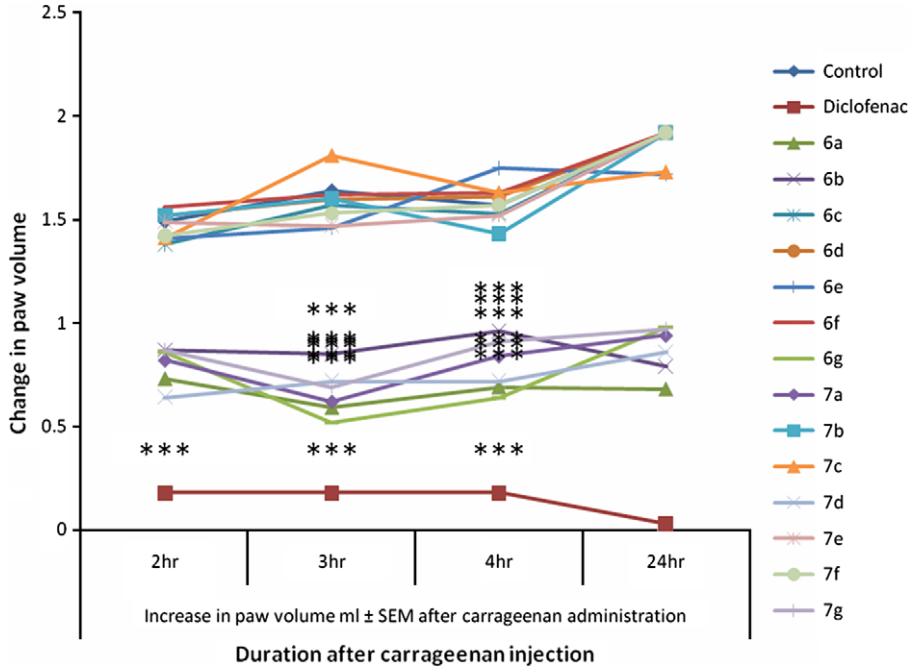

Figure 2. Effect of **6**(**a**–**g**) and **7**(**a**–**g**) on carrageenan induced rat paw edema in rats. All data were analyzed by two-way ANOVA followed by Bonferroni multiple comparison test in the carrageenan induced rat paw edema model (*p <0.05, **p <0.01, ***p <0.001).

postulated that the compounds may act through inhibition of the arachidonic acid pathway. The obtained results were subjected to statistical analysis by two-way ANOVA followed by Bonferroni multiple comparison test in the carrageenan induced rat paw edema model. Results revealed that all the tested compounds showed a variant significant anti-inflammatory activity at the administered dose (1000 mg/kg po) compared to Diclofenac. It is obvious that most of the tested *N*-phenylpyrazol-1-carbothioamide **7a–g** revealed relatively higher activities than their starting pyrazolines **6a–g**.

The results also revealed that in some cases, the presence of the plane pyrazolines and *N*-phenylpyrazol-1-carbothioamide having the anti-inflammatory activity. Also the 2-(4,5-dihydro-5-(4-morphilinophenyl)-1*H*-pyarazol-3-yl)-4-methylphenol and 3-(5-chloro-2-hydroxyphenyl)-4,5-(dihydro-5-(4-morphinophenyl)-*N*-phenylpyrazol-1-carbothioamide having enhance the anti-inflammatory activity. The $\mathbf{R}^3$ of Br having the better activity in pyrazoline and *N*-phenylpyrazol-1-carbothioamide. It is obvious that, there is no direct correlation between enhancement of the anti-inflammatory activity and the presence of electron donating and electron withdrawing group.

We have synthesized a series of morpholine bearing pyrazolines, and *N*-phenylpyrazol-1-carbothioamide. The investigation of analgesic and anti-inflammatory screening data reveals that among the 14 compounds screened six compounds showed good analgesic and anti-inflammatory inhibition almost equivalent to the standard. Hence, it is concluded that there is ample scope for further study in developing these as good lead compounds.

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22. *Synthesis of 4-(morpholin-4-yl)benzaldehyde* (**3**)*:* The mixture of 4-fluorobenzaldehyde (0.8113 mol) was refluxed at 120 °C in the appropriate amount of the morpholine; the progress of the reaction was monitor by TLC. After completion of the reaction, the reaction mass was poured on ice cold water (50 ml) to give white solid, which was filtered, dried and recrystallized in ethanol give the pure solid; yield: 78% (white solid); mp 132–133 °C; FTIR (KBr) cm^{-1}: 3050 (Ar C–H); 2980 (aldehyde stretching –CHO); 1695 (CH=O); 1153 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 3.42 (t, 4H, CH_2); 3.92 (t, 4H, CH_2); 6.78 (dd, 2H, Ar-H); 7.52 (dd, 2H, Ar-H); ES-MI (*m*/*z*) 192 (M^+).
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24. *Synthesis of substituted (E)-1-(2-hydroxyphenyl)-3-(4-morpholinophenyl)prop-2-en-1-one:* Aqueous KOH (1.23 g, 0.0022 mol) was added to a suspension of 1-(2-hydroxyphenyl)ethanone **4**(**a**–**g**) (1 g, 0.0037 mol) and 4-(morpholin-4-yl)benzaldehyde **3** (1.44 g, 0.0037 mol) in 10 ml ethanol. The mixture was stirred at 25 °C temperature for overnight and further the mixture was poured into water and acidified with HCl (2 M) till, pH 4. The solid product separated out was filtered off and recrystallized from ethanol. Compound **5a**: yield: 67% (yellow solid); mp 117–118 °C; FTIR (KBr) cm^{-1}: 3233 (Ar-OH); 1688 (–CO–); 1211 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 2.32 (s, 3H); 3.30 (t, 4H, CH_2); 3.88 (t, 4H, CH_2); 6.89 (dd, *J* = 5.6 Hz, 3H, Ar-H); 7.305 (dd, *J* = 2, 1H, Ar-H); 7.52 (d, *J* = 15.4 Hz, 1H, olefinic); 7.62 (d, *J* = 8.4 Hz, 2H, Ar-H); 7.68 (s, 1H, Ar-H); 7.90 (d, *J* = 15.6 Hz, 1H, olefinic); 12.84 (s, 1H, Ar-OH); ES-MI (*m*/*z*) 324 (M^+). Compound **5d**: yield: 65% (yellow solid); mp 110–111 °C; FTIR (KBr) cm^{-1}: 3210 (Ar-OH); 1680 (–CO–); 763 (Ar-Cl); 1143 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 3.29 (t, 4H, CH_2); 3.86 (t, 4H, CH_2); 6.90 (d, *J* = 2.54 and 11.44 Hz, 2H, Ar-H); 6.98 (d, *J* = 8.92 and 18.88 Hz, 1H, olefinic); 7.42 (t, *J* = 2.04 and 8.44 Hz, 2H, Ar-H); 7.63 (d, *J* = 2.72 and 9.88 Hz, 2H, Ar-H); 7.86 (d, *J* = 2.56, 1H, Ar-H); 7.93 (d, *J* = 15.24 Hz, 1H, olefinic); 12.97 (s, 1H, Ar-OH); ES-MI (*m*/*z*) 342 (M^+).
25. Synthesis of substituted 3,2-(4,5-dihydro-5-(4-morphilinophenyl)-1*H*-pyarazol-3-yl)phenol: (0.1 g, 0.00028 mol) of chalcones **5**(**a**–**g**) was dissolved in 5 ml of ethanol. To this reaction mixture, (0.1 ml, 0.0031 mol) of hydrazine hydrate was added. The reaction mass was heated at reflux for 3 h and then 1 ml gl. acetic acid was added and heating was continued further for 2 h. After completion of reaction (monitor by TLC), reaction mixture was cooled to room temperature. At the end 10 ml cold water was slowly added to the flask and the separated product was filtered off and washed with cold water for several times. The final compound was recrystallized from ethanol. Compound **6a**: yield: 78% (white solid); mp 143–144 °C. FTIR (KBr) cm^{-1}: 3387 (Ar-OH); 1530, 1480 (C=N); 1209 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 3.22 (dd, *J* = 9.2 and 15.8 Hz, 1H, CH_2 pyrazoline); 3.12 (t, 4H, CH_2); 3.49 (dd, *J* = 9.2 and 15.8 Hz, 1H, CH_2 pyrazoline); 3.76 (t, 4H, CH_2); 4.62 (t, *J* = 2.8 and 11.2 Hz, 1H, C_5H); 6.27 (br s, 1H, NH); 7.10 (d, *J* = 12.1 Hz, 2H, Ar-H); 7.21 (d, *J* = 9.8 Hz, 1H, Ar-H); 7.32 (d, *J* = 2.8 Hz, 1H, Ar-H); 7.42 (t, *J* = 2.8 and 9.2 Hz, 2H, Ar-H); 7.42 (s, 1H, Ar-H); 11.00 (s, 1H, Ar-OH); ES-MI (*m*/*z*) 324 (M+1). Compound **6b**: yield: 78% (white solid); mp 92–93 °C; FTIR (KBr) cm^{-1}: 3387 (Ar-OH); 1567, 1509 (C=N); 1132 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 2.33 (s, 3H); 3.07 (dd, *J* = 8.32 and 16.48 Hz, 1H, CH_2 pyrazoline); 3.15 (t, 4H, CH_2); 3.52 (dd, *J* = 10.8 and 16.4 Hz, 1H, CH_2 pyrazoline); 3.86 (t, 4H, CH_2); 4.82 (t, *J* = 8.4 and 10.4 Hz, 1H, C_5H); 5.86 (br s, 1H, NH); 6.70 (d, *J* = 8.0 Hz, 1H, Ar-H); 6.86 (s, 1H, Ar-H); 6.88 (d, *J* = 8.4 Hz, 2H, Ar-H); 7.02 (d, *J* = 8.0 Hz, 1H, Ar-H); 7.33 (t, *J* = 3.2 and 8.8 Hz, 2H, Ar-H); 10.98 (s, 1H, Ar-OH); ES-MI (*m*/*z*) 338 (M^+). Compound **6c**: yield: 80% (white solid); mp 98–99 °C; FTIR (KBr) cm^{-1}: 3428 (OH); 1543, 1505 (C=N); 1220 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 2.33 (s, 6H); 3.04 (dd, *J* = 8.32 and 16.48 Hz, 1H, CH_2 pyrazoline); 3.16 (t, 4H, CH_2); 3.43 (dd, *J* = 8.32 and 16.48 Hz, 1H, CH_2 pyrazoline); 3.87 (t, 4H, CH_2); 4.85 (t, *J* = 8.86 and 18.88 Hz, 1H, C_5H); 5.94 (br s, 1H, NH); 6.90 (t, *J* = 8.6 and 12.84 Hz, 3H, Ar-H); 7.25 (d, *J* = 1.36 and 10.08 Hz, 3H, Ar-H); 10.89 (s, 1H, Ar-OH); ES-MI (*m*/*z*) 371 (M^+). Compound **6d**: yield: 78% (white solid); mp 107–109 °C; FTIR (KBr) cm^{-1}:

3430 (Ar-OH); 1570, 1512 (C=N); 778 (Ar-Cl); 1165 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 3.12 (dd, J = 10.8 and 16.8 Hz, 1H, CH_2 pyrazoline); 3.16 (t, 4H, CH_2); 3.44 (dd, J = 10.8 and 16.8 Hz, 1H, CH_2 pyrazoline); 3.84 (t, 4H, CH_2); 4.87 (t, J = 2.4 and 10.8 Hz, 1H, C_5H); 5.97 (br s, 1H, NH); 6.83 (d, J = 11.6 Hz, 2H, Ar-H); 6.94 (d, J = 9.2 Hz, 1H, Ar-H); 7.17 (d, J = 2.4 Hz, 1H, Ar-H); 7.19 (t, J = 2.8 and 9.2 Hz, 2H, Ar-H); 6.86 (s, 1H, Ar-H); 11.00 (s, 1H, Ar-OH); ES-MI (m/z) 358 (M^+) 360 (M+2). Compound **6e**: yield: 78% (white solid); mp 124–125 °C; FTIR (KBr) cm^{-1}: 3450 (Ar-OH); 1544 (C=N); 787 (Ar-Cl); 1298 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 3.18 (dd, J = 8.2 and 16.3 Hz, 1H, CH_2 pyrazoline); 3.25 (t, 4H, CH_2); 3.48 (dd, J = 10.2 and 15.9 Hz, 1H, CH_2 pyrazoline); 3.76 (t, 4H, CH_2); 4.72 (t, J = 2.6 and 10.2 Hz, 1H, C_5H); 6.21 (br s, 1H, NH); 6.90 (d, J = 10.8 Hz, 1H, Ar-H); 7.02 (d, J = 9.6 Hz, 1H, Ar-H); 7.12 (d, J = 2.6 Hz, 1H, Ar-H); 7.25 (t, J = 2.3 and 8.5 Hz, 1H, Ar-H); 7.86 (s, 1H, Ar-H); 10.67 (s, 1H, Ar-OH); ES-MI (m/z) 392 (M^+) 394 (M+2). Compound **6f**: yield: 82% (white solid); mp 135–136 °C; FTIR (KBr) cm^{-1}: 3456 (Ar-OH); 1544 (C=N); 1338 (C–O–C); 762 (Ar-Cl); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 1.95 (s, 3H, Ar-CH_3); 3.12 (dd, J = 7.65 and 15.98 Hz, 1H, CH_2 pyrazoline); 3.34 (t, 4H, CH_2); 3.54 (dd, J = 10.56 and 15.93 Hz, 1H, CH_2 pyrazoline); 3.84 (t, 4H, CH_2); 4.85 (t, J = 3.12 and 10.56 Hz, 1H, C_5H); 6.1 (br s, 1H, NH); 7.05 (d, J = 10.22 Hz, 1H, Ar-H); 7.14 (d, J = 1.12 Hz, 1H, Ar-H); 7. 20 (d, J = 3.25 Hz, 1H, Ar-H); 7.30 (t, J = 2.42 and 9.12, Hz, 1H, Ar-H); 7.92 (s, 1H, Ar-H); 11.24 (s, 1H, Ar-OH); ES-MI (m/z) 372 (M^+) 374 (M+2). Compound **6g**: yield: 75% (white solid); mp 146–147 °C; FTIR (KBr) cm^{-1}: 3469 (Ar-OH); 1580 (C=N); 1342 (C–O–C); 794 (Ar-Cl); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 3.22 (t, 4H, CH_2); 3.29 (dd, J = 3.45 and 16.29 Hz, 1H, CH_2 pyrazoline); 3.72 (t, 4H, CH_2); 4.15 (dd, J = 10.22 and 16.29 Hz, 1H, CH_2 pyrazoline); 4.54 (t, J = 7.86 and 10.46 Hz, 1H, C_5H); 6.65 (br s, 1H, NH); 7.10 (d, J = 10.21 Hz, 1H, Ar-H); 7.20 (d, J = 2.23 Hz, 1H, Ar-H); 7. 34 (d, J = 3.40 Hz, 1H, Ar-H); 7.49 (t, J = 2.46, 2H, Ar-H); 7.87 (s, 1H, Ar-H); 12.30 (s, 1H, Ar-OH); ES-MI (m/z) 402 (M^+) 404 (M+2).

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27. *Synthesis of substituted 4,5-(dihydro-3(2-hydroxyphenyl)-5-(4-morphilino-phenyl)-N-phenylpyrazol-1-carbothioamide* (**7a–g**)*:* (0.20 g, 0.00061 mol) of 3,2-(4,5-dihydro-5-(4-morphilinophenyl)-1*H*-pyarazol-3-yl)phenol **6**(**a–g**) was dissolved in 5 ml of dry diethyl ether. To this reaction mixture, (0.083 g, 0.0061 mol) of phenylisothiocyanate was added and the reaction mass was stirred at 25 ºC temperature and then 4–5 drops of triethylamine was added and stirred further for 4 h after completion of reaction (monitor by TLC). The mixture was evaporated to dryness and the residue was recrystallized from ethyl acetate. Compound **7a**: yield: 72% (white solid); mp 145–146 ºC. FTIR (KBr) cm^{-1}: 3398 (Ar-OH); 2945 (N–H); 1517 (C=N); 1217 (C=S); 1126 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 3.08 (t, 4H, CH_2); 3.12 (dd, J = 2.98 and 16.8 Hz, 1H, CH_2 pyrazoline); 3.91 (t, 4H, CH_2); 3.98 (t, J = 12.18 and 16.23 Hz, 1H, C_5H); 6.23 (dd, J = 2.98 and 16.8 Hz, 1H, CH_2 pyrazoline); 6.92 (t, J = 8.32 Hz, 3H, Ar-H); 7.34 (dd, J = 8.14 and 8.98 Hz, 3H, Ar-H); 7.47 (t, J = 2.11 and 9.23 Hz, 3H, Ar-H); 7.56 (t, J = 8.34 and 11.9 Hz, 2H, Ar-H); 7.97 (d, J = 7.8 Hz, 2H, Ar-H); 9.78 (br s, 1H, NH); 10.34 (s, 1H, Ar-OH); ES-MI (m/z) 458 (M^+). Compound **7b**: yield: 80% (white solid); mp 171–172 °C; FTIR (KBr) cm^{-1}: 3423 (Ar-OH); 2980 (N–H); 1512 (C=N); 1287 (C=S) 1189 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 2.15 (s, 3H); 3.09 (t, 4H, CH_2); 3.22 (dd, J = 8.36 and 17.8 Hz, 1H, CH_2 pyrazoline); 3.79 (t, 4H, CH_2); 3.90 (t, J = 11.48 and 17.8 Hz, 1H, C_5H); 6.11 (dd, J = 8.36 and 17.8 Hz, 1H, CH_2 pyrazoline); 6.82 (t, J = 8.72 Hz, 3H, Ar-H); 7.19 (dd, J = 7.4 and 8.68 Hz, 3H, Ar-H); 7.34 (t, J = 1.8 and 9.2 Hz, 3H, Ar-H); 7.49 (t, J = 7.52 and 12.36 Hz, 2H, Ar-H); 9.45 (br s, 1H, NH); 9.74 (s, 1H, Ar-OH); ES-MI (m/z) 472 (M^+). Compound **7c**: yield: 73% (white solid); mp 154–155 °C. FTIR (KBr) cm^{-1}: 3398 (Ar-OH); 3024 (N–H); 1576 (C=N); 1227 (C=S); 1223 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 2.36 (s, 6H); 3.01 (t, 4H, CH_2); 3.16 (dd, J = 3.48 and 16.6 Hz, 1H, CH_2 pyrazoline); 3.53 (t, 4H, CH_2); 3.82 (t, J = 10.88 and 16.6 Hz, 1H, C_5H); 6.22 (dd, J = 3.86 and 12.46 Hz, 1H, CH_2 pyrazoline); 6.90 (t, J = 8.32 Hz, 2H, Ar-H); 7.04 (d, J = 8.8 Hz, 2H, Ar-H); 7.30 (dd, J = 7.2 and 8.29 Hz, 3H, Ar-H); 7.56 (t, J = 2.2 and 8.9 Hz, 1H, Ar-H); 7.77 (t, J = 7.76 and 11.9 Hz, 2H, Ar-H); 10.23 (br s, 1H, NH); 12.02 (s, 1H, Ar-OH); ES-MI (m/z) 506 (M^+) and 505 (M). Compound **7d**: yield: 75% (white solid); mp 156–157 °C. FTIR (KBr) cm^{-1}: 3354 (Ar-OH); 2987 (N–H); 1533 (C=N); 1227 (C=S); 1139 (C–O–C), ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 3.09 (dd, J = 3.10 and 15.9 Hz, 1H, CH_2 pyrazoline); 3.18 (t, 4H, CH_2); 3.36 (dd, J = 3.10 and 15.9 Hz, 1H, CH_2 pyrazoline); 3.65 (t, 4H, CH_2); 4.12 (t, J = 10.76 and 16.56 Hz, 1H, C_5H); 6.98 (t, J = 8.32 Hz, 2H, Ar-H); 7.12 (d, J = 8.44 Hz, 2H, Ar-H); 7.30 (dd, J = 8.43 and 8.88 Hz, 3H, Ar-H); 7.39 (t, J = 2.10 and 8.13 Hz, 2H, Ar-H); 7.67 (t, J = 7.34 and 11.9 Hz, 3H, Ar-H); 10.10 (br s, 1H, NH); 11.56 (s, 1H, Ar-OH); ES-MI (m/z) 494 (M^+) and 496 (M^-). Compound **7e**: yield: 76% (white solid); mp 149–149 °C; FTIR (KBr) cm^{-1}: 3410 (Ar-OH); 2946 (N–H); 1497 (C=N); 1234 (C=S); 1109 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 3.02 (dd, J = 3.12 and 16.13 Hz, 1H, CH_2 pyrazoline); 3.30 (t, 4H, CH_2); 3.52 (dd, J = 3.12 and 16.13 Hz, 1H, CH_2 pyrazoline); 3.61 (t, 4H, CH_2); 3.98 (t, J = 10.67 and 16.32 Hz, 1H, C_5H); 6.78 (t, J = 7.90 Hz, 2H, Ar-H); 6.92 (d, J = 8.54 Hz, 2H, Ar-H); 7.02 (dd, J = 8.2 and 8.80 Hz, 3H, Ar-H); 7.35 (t, J = 2.40 and 8.51 Hz, 2H, Ar-H); 7.73 (t, J = 8.14 and 12.67 Hz, 2H, Ar-H); 9.56 (br s, 1H, NH); 12.23 (s, 1H, Ar-OH); ES-MI (m/z) 527 (M^+) and 529 (M+2). Compound **7f**: yield: 70% (white solid); mp 156–157 °C; FTIR (KBr) cm^{-1}: 3435 (Ar-OH); 2896 (NH); 1523 (C=N); 1215 (C=S); 1123 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 1.82 (s, 3H, Ar-CH_3);3.09 (t, 4H, CH_2); 3.21 (dd, J = 3.23 and 15.97 Hz, 1H, CH_2 pyrazoline); 3.97 (t, 4H, CH_2); 4.03 (dd, J = 3.15 and 16.24 Hz, 1H, CH_2 pyrazoline); 4.28 (t, J = 10.65 and 16.54 Hz, 1H, C_5H); 6.12 (t, J = 7.92 Hz, 2H, Ar-H); 7.22 (d, J = 8.58 Hz, 2H, Ar-H); 7.38 (dd, J = 8.12 and 8.65 Hz, 3H, Ar-H); 7.51 (t, J = 2.21 and 8.87 Hz, 2H, Ar-H); 7.89 (t, J = 8.45 and 12.14 Hz, 2H, Ar-H); 10.54 (br s, 1H, NH); 12.14 (s, 1H, Ar-OH); ES-MI (m/z) 507 (M^+) and 509 (M+2). Compound **7g**: yield: 73% (white solid); mp 164–165 °C; FTIR (KBr) cm^{-1}: 3425 (Ar-OH); 2898 (NH); 1526 (C=N); 1214 (C=S); 1163 (C–O–C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 2.97 (t, 4H, CH_2); 3.13 (dd, J = 3.31 and 16.27 Hz, 1H, CH_2 pyrazoline); 4.06 (t, 4H, CH_2); 4.21 (dd, J = 12.65 and 15.78 Hz, 1H, CH_2 pyrazoline); 4.32 (t, J = 10.25 and 15.86 Hz, 1H, C_5H); 6.21 (t, J = 7.96 Hz, 2H, Ar-H); 7.23 (d, J = 8.65 Hz, 1H, Ar-H); 7.65 (dd, J = 8.25 and 8.75 Hz, 3H, Ar-H); 7.64 (t, J = 2.25 and 8.98 Hz, 2H, Ar-H); 7.98 (t, J = 8.35 and 12.46 Hz, 2H, Ar-H); 10.52 (br s, 1H, NH); 12.35 (s, 1H, Ar-OH); ES-MI (m/z) 537 (M^+) and 539 (M+2).
28. *Pharmacology:* The solvents and chemicals were purchased and used as received. Carrageenan (Sigma, St. Louis, Missouri, USA), acetic acid (S.D. Fine chemicals, Mumbai), Diclofenac sodium (Gift sample from Symed Pharmaceuticals, Hyderabad). Male Wistar rats (200–220 g) and Swiss albino mice (18–22 g) were used for experiments. All animals were maintained in standard laboratory conditions in the animal house at (temperature) 24 ± 1 °C) in a 12-h light:12-h dark cycle. They were fed with laboratory diet and tap water. All experiments were carried out using six animals per group. The compounds were tested for toxicity according to the OECD guidelines and LD_{50} was determined by AOT 425 guideline. The compounds were found to be safe up to a dose of 1000 mg/kg po hence a dose of 30 mg/kg po was selected as the therapeutic dose and all the pre clinical models were performed by administering this dose.
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