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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and anti-inflammatory activity of 1-acetyl/propanoyl-5-aryl-3-(4-morpholinophenyl)-4,5-dihydro-1*H*-pyrazole derivatives

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Abstract A series of novel pyrazoline derivatives containing 4-morpholinophenyl moiety were synthesized to investigate their potential anti-inflammatory activity. The chemical structures of the compounds were elucidated by spectral data and element analyses. The test compounds in the series exhibited different levels of anti-inflammatory activities when compared with reference drug indomethacin.

Keywords Synthesis · Pyrazolines · Anti-inflammatory activity

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs), alleviate pain by counteracting the cyclooxygenase (COX) enzyme. On its own, COX enzyme synthesizes prostaglandins, creating inflammation. Over all, the NSAIDs prevent the prostaglandins ever from being synthesized, reducing or eliminating the pain. Therefore, studies for discovering and developing new anti-inflammatory drugs with greater effectiveness are still preferable. 2-Pyrazolines have been gaining prominence because their derivatives have been found to possess wide spectrum of biological activities, such as antimalarial (Acharya *et al.*, 2010), antimicrobial (Padmavathi *et al.*, 2008; Abdel-Wahab *et al.*, 2009; Dawane *et al.*, 2010), antidepressant (Can *et al.*, 2009; Kaplancikli *et al.*, 2010), anticonvulsant (Özdemir *et al.*, 2007), antihypertensive (Turan-Zitouni et al. 1984), antioxidant (Jeong *et al.*, 2004), anticancer (Shaharyar *et al.*, 2010; Congiu *et al.*, 2010; Liu *et al.*, 2010) and anti-inflammatory (Bansal *et al.*, 2001; Shoman *et al.*, 2009; Barsoum and Girgis, 2009; Chandra *et al.*, 2010) activities.

In addition, 4-phenylmorpholine derivatives have been reported to show quite interesting anti-inflammatory (Verma *et al.*, 1984; Joshi *et al.*, 2010) and antimicrobial (Panneerselvam *et al.*, 2005, 2009) activities.

In our previous study, 5-aryl-3-(4-morpholinophenyl)-4,5-dihydro-1*H*-pyrazoles **A** (Fig. 1) were synthesized and reported to have significant anti-inflammatory activity (Khalil, 2011). As part of our continuous efforts in this area, and in order to better understand the role of *N*-1 substituent for anti-inflammatory activity, a series of some new 1-acetyl/propanoyl-5-aryl-3-(4-morpholinophenyl)-4,5-dihydro-1*H*-pyrazole derivatives have been synthesized with no changes in position-5 of the pyrazoline ring compared to the previous unsubstituted *N*-1 series; **A** (Fig. 1).

Results and discussion

Chemistry

The synthesis of hitherto unreported title compounds was prepared as outlined in Scheme 1.

The key intermediates, chalcones, **1a–f** were previously prepared (Khalil, 2011). Reactions of **1a–f** with hydrazine hydrate in hot acetic acid or propionic acid afforded the corresponding pyrazolines **2a–f** and **3a–f** in yields (56–86%).

In the IR spectra of compounds **2a–f** and **3a–f**, the carbonyl absorption bands were observed in the region of 1700–1739 cm^{-1}. The C=N stretching was observed around 1600–1608 cm^{-1} because of the ring closure.

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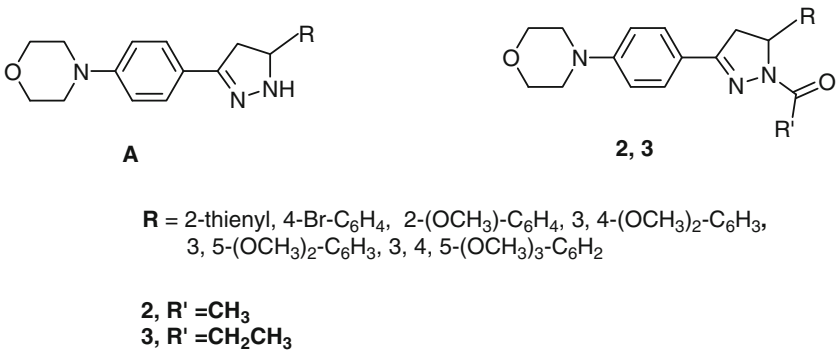
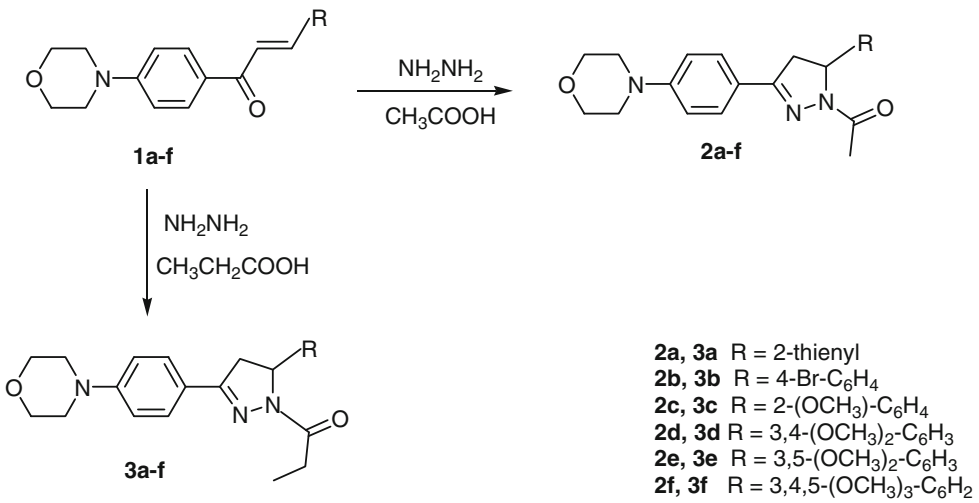
Fig. 1 General formula of derivatives **A**, **2** and **3**



Scheme 1 Synthesis of compounds **2a–f** and **3a–f**



^{1}H NMR spectra of **2a–f** and **3a–f** revealed the signals of CH_2 protons of the pyrazoline ring as a double doublet in the regions of 2.32–3.27 and 3.62–3.80 ppm, while CH proton appeared at 5.40–5.78 ppm.

In addition, ^{1}H NMR spectra of **2a–f** indicated the presence of an *N*-acetyl group as a singlet signal between $\delta = 2.21$ and 2.30 ppm. On the other hand, a triplet (around 1.06 ppm) and a quartet (approximately 2.7 ppm) signals belonging to an *N*-propanoyl unit were assigned in the ^{1}H NMR spectra of **3a–f**. ^{13}C-NMR chemical shift values of the carbon atoms at 39.5 (C-4), 54.1–54.7 (C-5), and about 152.0 or 152.9 ppm (C-3) corroborate the 2-pyrazoline character deduced from the ^{1}H- NMR data. The presence of an *N*-acetyl group was also confirmed by the ^{13}C- chemical shifts of these two carbon atoms detected at about 21 (CH_3) and 166.3–174.4 (C=O) ppm. In addition, *N*-propanoyl groups have also been observed at 8.5–9.2 (CH_3) and at about 26 (CH_2) ppm.

Anti-inflammatory activity

All the newly synthesized pyrazoline derivatives were screened for their anti-inflammatory activities. All the compounds have shown anti-inflammatory activity ranging from 1.08 to 31.05% at the dose of 10 mg/kg given in Table 1. Indomethacin, which is one of the most potent anti-inflammatory agents, was used as the reference drug in a dose of 10 mg/kg. The anti-inflammatory activity of compounds **2a–f** having 1-*N*-acetyl group and **3a–f** with 1-*N*-propanoyl substituent were 3.61–31.05%, and 1.08–31.05% respectively.

Among the compounds **2a–f**, compound **2c**, in which phenyl ring was substituted with a methoxy group at position-2 exhibited 31.05% protection against carrageenan-induced edema. A similar behavior could be observed in the case of compound **3d**, bearing a 3,4-dimethoxyphenyl moiety in position-5 of the pyrazoline. The rest of the pyrazoline derivatives showed weak anti-inflammatory activity.

Conclusion

A series of acetyl/propanoyl pyrazolines carrying a morpholinophenyl moiety have been synthesized in good yield and screened for their anti-inflammatory activity. The results indicated that compounds **2c** and **3d** showed considerable anti-inflammatory action, reaching about 52.76%

Table 1 Anti-inflammatory activity of the test compounds assessed in comparison to indomethacin as reference

Compound	Mean swelling volume (ml)	% Inhibition of edema	Potency[b]
Control	0.55 ± 0.05	0.00	–
Indomethacin	0.23 ± 0.03	58.84	100.00
2a	0.52 ± 0.08	6.86	11.66
2b	0.49 ± 0.10	11.19	19.02
2c	0.38 ± 0.09	31.05	52.76
2d	0.52 ± 0.10	5.78	9.82
2e	0.48 ± 0.06	13.36	22.70
2f	0.53 ± 0.10	3.61	6.13
3a	0.55 ± 0.13	1.08	1.84
3b	0.45 ± 0.14	18.41	31.29
3c	0.52 ± 0.06	6.14	10.43
3d	0.38 ± 0.06	31.05	52.76
3e	0.47 ± 0.09	15.88	26.99
3f	0.55[a] ± 0.10	1.08	1.84

[a] Statistically significant from the indomethacin at $P < 0.05$

[b] Potency was expressed as % edema inhibition of the tested compounds relative to % edema inhibition of indomethacin "reference standard"

of the action of indomethacin (Table 1, Fig. 2). On the basis of this research, we could show that the anti-inflammatory activity is correlated with *N*-1 substituent; in fact, the elongation of the *N*-1 chain decreased the anti-inflammatory activity, regardless of the nature of other substituents. Therefore, they deserve further attention to develop new leads.

Experimental

Melting points were obtained on a Griffin apparatus and are uncorrected. Microanalyses were carried out at the microanalytical center, Faculty of Science, Cairo University. IR spectra were recorded on a Shimadzu 435 spectrometer, using KBr disks. ^{1}H-NMR and ^{13}CNMRspectra were performed on a Varian Mercury VX-300 MHz NMR Spectrometer using TMS as the internal standard. Mass spectra were recorded using Shimadzu Gas Chromatograph Mass spectrometer-QP 1000 EX (Shimadzu, Kyoto, Japan). Compounds **1a–f** were synthesized and reported (Khalil, 2011) according to known procedures.

General procedure for the synthesis of **2a–f** and **3a–f**

A solution of the appropriate chalcone (0.03 mol) **1a–f**, hydrazine hydrate (0.06 mol) in 15 ml of acetic/propionic acid was heated under reflux for 6 h, then poured onto

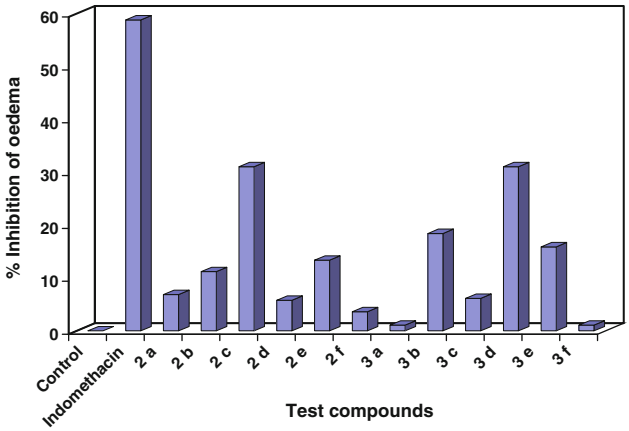


Fig. 2 % Inhibition of edema for the test compounds

crushed ice. The precipitate was separated by filtration, washed with water, and crystallized from ethanol.

1-Acetyl-3-(4-morpholinophenyl)-5-(2-thienyl)-4, 5-dihydro-1*H*-pyrazole (**2a**)

Mp: 149–150°C; yield: 62%; IR (cm^{-1}): υ 3082 (arom–H), 2962, 2893, 2835 (aliph–H), 3.27 (dd, 1H, 1710 (C=O), 1600 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.24 (s, 3H, CH_3), 3.27 (dd, 1H, pyrazoline H^4, $J = 16.8, 3.3$ Hz), 3.18 (t, 4H, $N(CH_2)_2$, $J = 3.9$ Hz), 3.72 (t, 4H, $O(CH_2)_2$, $J = 4.5$ Hz), 3.76 (dd, 1H, pyrazoline H^4, $J = 16.2, 11.4$ Hz), 5.78 (dd, 1H, pyrazoline H^5, $J = 11.4, 3.3$ Hz), 6.93 (dd, 1H, thienyl–H, $J = 3.6, 5.1$ Hz), 6.99 (d, 2H, Ar–H, $J = 8.4$ Hz), 7.36 (d, 1H, thienyl–H, $J = 3.9$ Hz), 7.64 (d, 1H, thienyl–H, $J = 5.7$ Hz), 7.99 (d, 2H, Ar–H, $J = 8.7$ Hz). ^{13}CNMR (DMSO-d_6): ∂ 21.6, 39.5, 46.7, 54.5, 65.8, 114.1, 120.9, 124.7, 126.5, 127.7, 130.2, 145.0, 152.2, 154.3, 166.9. Anal. Calcd. for $C_{19}H_{21}N_3O_2S$ (355.45): C, 64.20, H, 5.95, N, 11.82. Found: C, 64.24, H, 6.05, N, 12.15.

1-Acetyl-5-(4-bromophenyl)-3-(4-morpholinophenyl)-4, 5-dihydro-1*H*-pyrazole (**2b**)

Mp: 108–109°C; yield: 70%; IR (cm^{-1}): υ 3039 (arom–H), 2893, 2839(aliph–H), 1701 (C=O), 1608 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.26(s, 3H, CH_3), 3.07 (dd, 1H, pyrazoline H^4, $J = 17.7, 3.3$ Hz), 3.18 (t, 4H, $N(CH_2)_2$, $J = 4.5$ Hz), 3.72 (t, 4H, $O(CH_2)_2$, $J = 4.2$ Hz), 4.12 (m, 1H, pyrazoline H^4), 5.46 (dd, 1H, pyrazoline H^5, $J = 11.4, 3.3$ Hz), 6.97 (d, 2H, Ar–H, $J = 8.1$ Hz), 7.22 (d, 2H, Ar–H, $J = 8.1$ Hz), 7.43 (d, 2H, Ar–H, J = 8.4 Hz), 7.78 (d, 2H, Ar–H, $J = 8.4$ Hz). Anal. Calcd. for $C_{21}H_{22}BrN_3O_2$ (428.31): C, 58.88, H, 5.17, N, 9.81. Found: C, 59.00, H, 5.22, N, 9.95. MS (%, rel int) *m/z* 428.00 (M^+, 26.04).

1-Acetyl-5-(2-methoxyphenyl)-3-(4-morpholinophenyl)-4, 5-dihydro-1*H*-pyrazole (**2c**)

Mp: 107–108°C; yield: 58%; IR (cm^{-1}): υ 3001, 3055 (arom–H), 2976, 2927, 2855 (aliph–H), 1739 (C=O), 1604 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.30(s, 3H, CH_3), 2.90 (dd, 1H, pyrazoline H^4, $J = 17.1$, 4.2 Hz), 3.18 (t, 4H, $N(CH_2)_2$, $J = 4.5$ Hz), 3.72 (t, 4H, $O(CH_2)_2$, $J = 4.2$ Hz), 3.80(dd, 1H, pyrazoline H^4, $J = 17.7$, 10.5 Hz)), 3.90 (s, 3H, OCH_3), 5.62 (dd, 1H, pyrazoline H^5, $J = 11.1$, 4.2 Hz), 6.90 (m, 1H, Ar–H), 7.02 (d, 2H, Ar–H, $J = 8.1$ Hz), 7.21(m, 2H, Ar–H), 7.60 (d, 2H, Ar–H, $J = 8.1$ Hz), 7.80 (m, 1H, Ar–H). Anal. Calcd. for $C_{22}H_{25}N_3O_3$ (379.45): C, 69.63, H, 6.64, N, 11.07. Found: C, 69.49, H, 6.40, N, 11.0. MS (%, rel int) *m/z* 380.00 ($M + 1^+$, 100.00).

1-Acetyl-5-(3,4-dimethoxyphenyl)-3-(4-morpholinophenyl)-4, 5-dihydro-1*H*-pyrazole (**2d**)

Mp: 88–89°C; yield: 59%; IR (cm^{-1}): υ 3001 (arom–H), 2954, 2931, 2835 (aliph–H), 1735 (C=O), 1604 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 2.39 (dd, 1H, pyrazoline H^4, $J = 17.7$, 3.9 Hz), 3.18 (t, 4H, $N(CH_2)_2$, $J = 4.5$ Hz), 3.54 (dd, 1H, pyrazoline H^4, $J = 17.7$, 11.7 Hz), 3.78 (t, 4H, $O(CH_2)_2$, $J = 3.9$ Hz), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.40 (m, 1H, pyrazoline H^5), 6.80 (m, 1H, Ar–H), 7.32 (d, 2H, Ar–H, $J = 9.6$ Hz), 7.48 (m, 1H, Ar–H), 7.60 (d, 2H, Ar–H, $J = 9.6$ Hz), 7.70 (m, 1H, Ar–H). Anal. Calcd. for $C_{23}H_{27}N_3O_4$ (409.47): C, 67.46, H, 6.64, N, 10.26. Found: C, 67.50, H, 6.40, N, 10.42. MS (%, rel int) *m/z* 409.00 (M^+, 28.70), 410.00 ($M + 1^+$, 17.54).

1-Acetyl-5-(3,5-dimethoxyphenyl)-3-(4-morpholinophenyl)-4, 5-dihydro-1*H*-pyrazole (**2e**)

Mp: 101–102°C; yield: 65%; IR (cm^{-1}): υ 3035, 3008 (arom–H), 2966, 2939, 2893, 2835 (aliph–H), 1700 (C=O), 1608 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.28 (s, 3H, CH_3), 3.04 (dd, 1H, pyrazoline H^4, $J = 18$, 4.2 Hz), 3.18 (t, 4H, $N(CH_2)_2$, $J = 3.9$ Hz), 3.73 (t, 4H, $O(CH_2)_2$, $J = 4.5$ Hz), 3.78 (dd, 1H, pyrazoline H^4, $J = 17.4$, 11.1 Hz), 3.79 (s, 6H, 2 × OCH_3), 5.42 (dd, 1H, pyrazoline H^5, $J = 11.1$, 4.2 Hz), 6.29 (s, 2H, Ar–H), 6.37 (s, 1H, Ar–H), 6.97 (d, 2H, Ar–H, $J = 8.7$ Hz), 7.61 (d, 2H, Ar–H, $J = 8.7$ Hz). ^{13}CNMR (DMSO-d_6): ∂ 21.5, 39.5, 47.3, 55.0, 59.0, 65.7, 98.3, 103.2, 114.0, 121.0, 127.6, 144.8, 152.0, 154.0, 160.6, 166.8. Anal. Calcd. for $C_{23}H_{27}N_3O_4$ (409.47): C, 67.46, H, 6.64, N, 10.26. Found: C, 67.49, H, 6.45, N, 10.50.

1-Acetyl-5-(3,4,5-trimethoxyphenyl)-3-(4-morpholinophenyl)-4, 5-dihydro-1*H*-pyrazole (**2f**)

Mp: 148–149°C; yield: 73%; IR (cm^{-1}): υ 3005 (arom–H), 2931, 2855 (aliph–H), 1737 (C=O), 1604 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.29 (s, 3H, CH_3), 3.08 (dd, 1H, pyrazoline H^4, $J = 17.7$, 4.2 Hz), 3.18 (t, 4H, $N(CH_2)_2$, $J = 3.9$ Hz), 3.62 (dd, 1H, pyrazoline H^4, $J = 17.7$, 11.7 Hz), 3.71 (t, 4H, $O(CH_2)_2$, $J = 3.6$ Hz), 3.79 (s, 3H, OCH_3), 3.85 (s, 6H, 2 × OCH_3), 5.41 (dd, 1H, pyrazoline H^5, $J = 11.7$, 4.5 Hz), 6.43 (s, 2H, Ar–H), 6.97 (d, 2H, Ar–H, $J = 8.7$ Hz), 7.62 (d, 2H, Ar–H, $J = 8.4$ Hz). Anal. Calcd. for $C_{24}H_{29}N_3O_5$ (439.50): C, 65.58, H, 6.65, N, 9.56. Found: C, 65.79, H, 6.38, N, 9.35.

3-(4-Morpholinophenyl)-1-propanoyl-5-(2-thienyl)-4, 5-dihydro-1*H*-pyrazole (**3a**)

Mp: 122–123°C; yield: 64% IR (cm^{-1}): υ 3078, 3047 (arom–H), 2962, 2916, 2854 (aliph–H), 1732 (C=O), 1604 (C=N); ^{1}HNMR (DMSO-d_6): δ 1.05 (t, 3H, CH_3, $J = 7.5$ Hz), 2.64 (q, 2H, CH_2, $J = 7.5$ Hz), 3.18 (t, 4H, $N(CH_2)_4$, $J = 3.9$ Hz), 3.22 (dd, 1H, pyrazoline H^4, $J = 17.4$, 3.9 Hz), 3.73 (t, 4H, $O(CH_2)_2$, $J = 3.6$ Hz), 4.14 (m, 1H, pyrazoline H^4), 5.78 (dd, 1H, pyrazoline H^5, $J = 11.4$, 3.9 Hz), 6.93 (dd, 1H, thienyl–H, $J = 3.6$, 4.8 Hz), 6.98 (d, 1H, thienyl–H, $J = 3.9$ Hz), 7.36 (d, 1H, thienyl– H, $J = 4.5$ Hz), 7.64 (d, 2H, Ar–H, $J = 8.4$ Hz), 7.98 (d, 2H, Ar–H, $J = 8.4$ Hz). ^{13}CNMR (DMSO-d_6): ∂ 8.5, 26.8, 39.5, 47.3, 54.1, 65.7, 96.0, 113.0, 114.1, 117.3, 120.7, 122.4, 124.5, 127.7, 129.5, 130.2, 133.2, 152.8, 156.4, 159.8, 166.3, 174.4. Anal. Calcd. for $C_{20}H_{23}N_3O_2S$ (369.48): C, 65.01, H, 6.27, N, 11.37. Found: C, 64.85, H, 5.97, N, 11.02. MS (%, rel int) *m/z* 369.00 (M^+, 0.68), 370.00 ($M + 1^+$, 0.43).

5-(4-Bromophenyl)-3-(4-morpholinophenyl)-1-propanoyl-4, 5-dihydro-1*H*-pyrazole (**3b**)

Mp: 177–178°C; yield: 86%; IR (cm^{-1}): υ 3074 (arom–H), 2958, 2893, 2854 (aliph–H), 1732 (C=O), 1604 (C=N); ^{1}HNMR (DMSO-d_6): δ 1.05 (t, 3H, CH_3, $J = 7.2$ Hz), 2.65 (q, 2H, CH_2, $J = 7.2$ Hz), 3.05 (dd, 1H, pyrazoline H^4, $J = 17.7$, 4.5 Hz), 3.19 (t, 4H, $N(CH_2)_2$, $J = 4.5$ Hz), 3.73 (t, 4H, $O(CH_2)_2$, $J = 4.5$ Hz), 3.79 (dd, 1H, pyrazoline H^4, $J = 17.7$, 11.7 Hz), 5.47 (dd, 1H, pyrazoline H^5, $J = 11.7$, 4.5 Hz), 6.97 (d, 2H, Ar–H, $J = 8.7$ Hz), 7.12 (d, 2H, Ar–H, $J = 8.7$ Hz), 7.50 (d, 2H, Ar–H, $J = 8.4$ Hz), 7.61 (d, 2H, Ar–H, $J = 8.7$ Hz). ^{13}CNMR (DMSO-d_6): ∂ 8.9, 26.8, 39.4, 47.4, 58.6, 65.8, 114.1, 127.7, 131.4, 142.0, 168.0. Anal. Calcd. for $C_{22}H_{24}BrN_3O_2$ (442.34): C, 59.73, H, 5.46, N, 9.49. Found: C, 59.79, H, 5.59, N, 9.60. MS (%, rel int) *m/z* 443.00 (M^+, 1.04).

5-(2-Methoxyphenyl)-3-(4-morpholinophenyl)-1-propanoyl-4, 5-dihydro-1*H*-pyrazole (**3c**)

Mp: 79–80°C; yield: 63%; IR (cm^{-1}): υ 3062, 3043 (arom–H), 2962, 2935, 2893 (aliph–H), 1710 (C=O), 1604 (C=N); ^{1}HNMR (DMSO-d_6): δ 1.07 (t, 3H, CH_3, $J = 7.2$ Hz), 2.70 (q, 2H, CH_2, $J = 7.2$ Hz), 2.85 (dd, 1H, pyrazoline H^4, $J = 17.4, 4.5$ Hz), 3.17 (t, 4H, $N(CH_2)_2$, $J = 3.9$ Hz), 3.72 (t, 4H, $O(CH_2)_2$, $J = 3.9$ Hz), 3.80 (m, 1H, pyrazoline H^4), 3.87 (s, 3H, OCH_3), 5.62 (dd, 1H, pyrazoline H^5, $J = 11.1$, 4.5 Hz), 6.91 (m, 1H, Ar–H), 7.08 (d, 2H, Ar–H, $J = 8.1$ Hz), 7.21 (m, 2H, Ar–H), 7.59 (d, 2H, Ar–H, $J = 8.1$ Hz), 7.83 (m, 1H, Ar–H). ^{13}CNMR (DMSO-d_6): ∂ 9.1, 26.8, 39.5, 47.4, 54.7, 55.5, 65.8, 110.5, 111.5, 113.0, 114.1, 120.4, 121.3, 122.0, 124.9, 127.4, 128.4, 129.6, 130.3, 131.7, 136.8, 152.1, 154.4, 155.0, 170.2. Anal. Calcd. for $C_{23}H_{27}N_3O_3$ (393.47): C, 70.20, H, 6.91, N, 10.67. Found: C, 70.15, H, 6.90, N, 10.95.

5-(3,4-Dimethoxyphenyl)-3-(4-morpholinophenyl)-1-propanoyl-4, 5-dihydro-1*H*-pyrazole (**3d**)

Mp: 68–69°C; yield: 56%; IR (cm^{-1}): υ 3051 (arom–H), 2962, 2935, 2835 (aliph–H), 1735 (C=O), 1600 (C=N); ^{1}HNMR (DMSO-d_6): δ 1.06 (m, 3H, CH_3), 2.32 (m, 1H, pyrazoline H^4), 2.69 (q, 2H, CH_2, $J = 7.5$ Hz), 3.18 (t, 4H, $N(CH_2)_2$, $J = 5.1$ Hz), 3.74 (m, 4H, $O(CH_2)_2$, $J = 4.5$ Hz), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.10 (m, 1H, pyrazoline H^4), 5.40 (m, 1H, pyrazoline H^5), 6.80 (m, 1H, Ar–H), 7.35 (m, 2H, Ar–H), 7.49 (m, 1H, Ar–H), 7.61 (d, 2H, Ar–H, $J = 9.3$ Hz), 7.68 (m, 1H, Ar–H). Anal. Calcd. for $C_{24}H_{29}N_3O_4$ (423.50): C, 68.06, H, 6.90, N, 9.92. Found: C, 67.80, H, 6.71, N, 10.02. MS (%, rel int) *m/z* 423.00 (M^+, 1.04).

5-(3,5-Dimethoxyphenyl)-3-(4-morpholinophenyl)-1-propanoyl-4, 5-dihydro-1*H*-pyrazole (**3e**)

Mp: 133–134°C; yield: 62%; IR (cm^{-1}): υ 3005 (arom–H), 2954, 2924, 2850 (aliph–H), 1710 (C=O), 1608 (C=N); ^{1}HNMR (DMSO-d_6): δ 1.06 (t, 3H, CH_3, $J = 7.5$ Hz), 2.69 (q, 2H, CH_2, $J = 7.5$ Hz), 2.96 (m, 1H, pyrazoline H^4), 3.18 (m, 4H, $N(CH_2)_2$, $J = 4.2$ Hz), 3.71 (t, 4H, $O(CH_2)_2$, $J = 3.6$ Hz), 3.79 (s, 6H, 2 × OCH_3), 4.12 (m, 1H, pyrazoline H^4), 5.42 (m, 1H, pyrazoline H^5), 6.26 (s, 1H, Ar–H), 6.36 (s, 2H, Ar–H), 6.97 (d, 2H, Ar–H, $J = 8.1$ Hz), 7.60 (d, 2H, Ar–H, $J = 8.1$ Hz). Anal. Calcd. for $C_{24}H_{29}N_3O_4$ (423.50): C, 68.06, H, 6.90, N, 9.92. Found: C, 67.80, H, 6.63, N, 10.15. MS (%, rel int) *m/z* 423.00 (M^+, 2.06).

3-(4-Morpholinophenyl)-1-propanoyl-5-(3,4,5-trimethoxy-phenyl)-4, 5-dihydro-1*H*-pyrazole (**3f**)

Mp: 143–144°C; yield: 78%; IR (cm^{-1}): υ 3050 (arom–H), 2962, 2939, 2839 (aliph–H), 1701 (C=O), 1604 (C=N); ^{1}HNMR (DMSO-d_6): δ 1.08 (t, 3H, CH_3, $J = 7.2$ Hz), 2.63 (m, 2H, CH_2), 3.18 (t, 4H, $N(CH_2)_2$, $J = 4.8$ Hz), 3.20 (dd, 1H, pyrazoline H^4, $J = 17.7$, 4.2 Hz), 3.67 (dd, 1H, pyrazoline H^4, $J = 18$, 11.2 Hz), 3.71 (t, 4H, $O(CH_2)_2$, $J = 4.5$ Hz), 3.77 (s, 3H, OCH_3), 3.85 (s, 6H, 2 × OCH_3), 5.40 (m, 1H, pyrazoline H^5), 6.42 (s, 2H, Ar–H), 6.96 (d, 2H, Ar–H, $J = 8.4$ Hz), 7.61 (d, 2H, Ar–H, $J = 8.1$ Hz). ^{13}CNMR (DMSO-d_6): ∂ 9.2, 26.9, 39.5, 47.4, 55.8, 59.2, 59.8, 65.8, 102.3, 114.1, 120.5, 127.7, 138.3, 152.1, 152.9, 154.1, 170.0. Anal. Calcd. for $C_{25}H_{31}N_3O_5$ (453.53): C, 66.20, H, 6.88, N, 9.26. Found: C, 66.39, H, 6.90, N, 9.18. MS (%, rel int) *m/z* 453.00 (M^+, 9.51).

Anti-Inflammatory activity screening

Adult male albino rats (180–200 g) were used. All animals were kept under uniform and controlled conditions of temperature and light/dark (12/12 h) cycles, fed with standard rodent diet and water ad libitum. Animals were allowed to adapt to the laboratory environment for 1 week before to experiments. The experimental tests on animals have been performed in accordance with the Institutional Ethical Committee approval. The anti-inflammatory effect of the newly synthesized compounds was evaluated in correspondence with the carrageenan-induced paw edema method (Winter *et al.*, 1962). Fourteen groups of animals each consisting of five rats weighing 180–200 g were selected. The first group was injected with 0.05 ml of 1% carrageenan in the subplantar tissue of the right hind paw and served as untreated control.

The positive control group was given 10 mg/kg i.p. indomethacin 1 h before carrageenan injection.

The test compounds were suspended in 0.5% carboxymethylcellulose (CMC) and given to the rats at a dose of 10 mg/kg i.p. 1 h before carrageenan injection. The paw volume of each rat was measured before 1 h and after 3 h of carrageenan treatment using Plethysmometer. Quantitative variables from normal distribution were expressed as means ± SE ''standard error''. The significant difference between groups was tested by means of one-way ANOVA, and the chosen level of significance was $P < 0.05$.

The anti-inflammatory activity was expressed as percentage inhibition of edema volume in treated animals in comparison with the control group (Table 1; Fig. 2):

$$\% \text{ Inhibition of edema} = V_c - V_t/V_c \times 100$$

where, V_c and V_t are the volumes of edema for the control and drug-treated animal groups, respectively.

Potency of the tested compounds was calculated relative to indomethacin ''reference standard''-treated group according to the following equation:

$$\text{Potency} = (\%\ \text{edema inhibition of tested compound treated group}) / (\%\ \text{edema inhibition of indomethacin treated group}).$$

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