Full Paper

# Synthesis of Some Chalcones and Pyrazolines Carrying Morpholinophenyl Moiety as Potential Anti-Inflammatory Agents

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Chalcones of **2a–f** and their corresponding products, pyrazolines **3a–f**, were synthesized and evaluated for their anti-inflammatory activity against carrageenan edema in albino rats at a dose of 10 mg/kg. All the compounds of this series showed promising anti-inflammatory activity. The most active compounds of this series, **2a**, **2b**, and **2d**, were found to be most potent. They showed higher percentage of inhibition of edema than the standard drug indomethacin.

**Keywords:** Anti-inflammatory activity / Chalcones / Pyrazolines

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## Introduction

Most currently used non steroidal anti-inflammatory drugs (NSAIDs) have limitations in their therapeutic use since they cause gastrointestinal and renal side effects that are inseparable from their pharmacological activities. Therefore, development of novel compounds having anti-inflammatory activity with an improved safety profile is a great deal of interest to many researchers.

Chalcones are α,β-unsaturated ketones and they are widespread in the plant kingdom. It is well known that the majority of natural or synthetic chalcones are highly biologically active with great pharmaceutical and medicinal applications. For a structurally simple group of compounds, chalcones have been shown to display a diverse array of biological activities among with antimalarial [1, 2], antimicrobial [3–5], anticancer [6, 7], antioxidant [8], antiallergic [9], antihyperglycemic [10], and anti-inflammatory [11, 12] activities.

Moreover, chalcones are useful synthons in the synthesis of a large number of bioactive molecules such as pyrazolines that are well known nitrogen containing heterocyclic compounds. Considerable interest has been focused on the pyrazoline structure which is known to possess a broad spectrum of biological activities such as antiamoebic [13, 14], antimicrobial [15], monoamine oxidase inhibitors [16], antimycobacterial [17, 18], antidepressant [19, 20], anticonvulsant [21], and anti-inflammatory [22, 23] activities.

It is pertinent to mention that 4-phenylmorpholine derivatives have been reported to show anti-inflammatory [24, 25] and antimicrobial [26, 27] activities.

Therefore, both the chalcones and the pyrazolines possess worthy and imperative bioactivities which render them useful substances in drug research. In this study, based on the above findings, our aim was to synthesize a new series of chalcones and pyrazoline derivatives carrying a morpholinophenyl moiety and to investigate their possible anti-inflammatory activities.

## Results and discussion

### Chemistry

The synthesis of the target compounds was accomplished according to the reaction sequence illustrated in Scheme 1.

Chalcones **2a–f** were synthesized by a base catalyzed Claisen-Schmidt condensation reaction [28, 29] of 1-(4-morpholinophenyl)ethanone with appropriate aldehydes. The reaction between the newly synthesized chalcones **2a–f** with hydrazine hydrate in ethanol [30] led to a synthesis of novel pyrazoline derivatives **3a–f**. All synthesized compounds were

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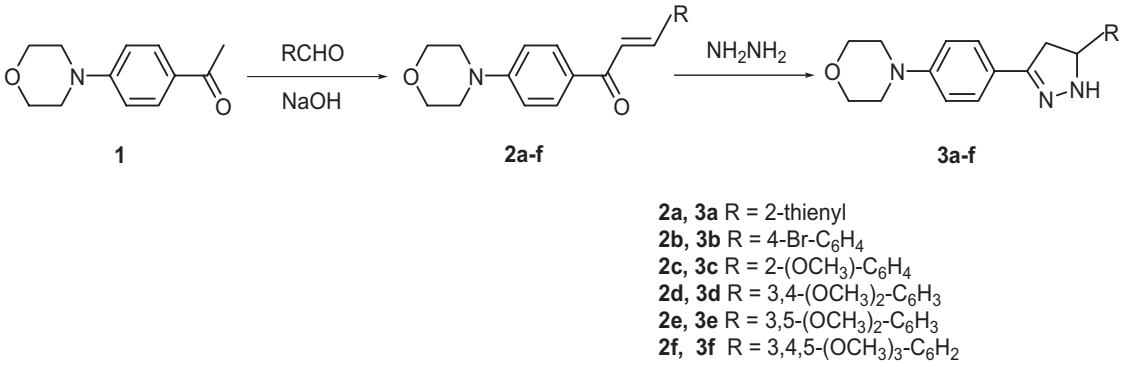


**Scheme 1.** Synthesis of chalcones **2a–f** and pyrazolines **3a–f.**

characterized by their physical and spectral data (IR, $^1$H-NMR) and confirmed the structures of the novel compounds. The IR spectra of the chalcones showed the characteristic band for conjugated C=O at 1639–1654 cm$^{-1}$. In the $^1$H-NMR spectra of **2a–f**, a pair of the *trans*-olefinic proton doublets appeared at $d = 7.58–7.68$ and $d = 7.79–7.89$ ppm, respectively, with a $J$ value of 14.8–15.6 Hz. IR data of **3a–f** were very informative. The IR spectra of all the pyrazoline products showed disappearance of C=O band of chalcones. A strong band appeared at 1589–1608 cm$^{-1}$ assigned to C=N because of ring closure. Compounds **3a–f** showed an additional sharp band in the region 3325–3395 cm$^{-1}$ due to the NH stretch. Their $^1$H-NMR spectra revealed, in each case, the signals of $CH_2$ protons of the pyrazoline ring in the region 2.77–3.33 and 3.40–3.76 ppm. The CH proton appeared as a multiplet at 4.75–5.40 ppm, while for compounds **3b** and **3c** it appeared as one double doublet at 4.76 and 5.40 ppm, respectively. All the other aromatic and aliphatic protons were observed at the expected regions.

## Anti-inflammatory activity

All the newly synthesized compounds were screened for their anti-inflammatory activities against carrageenan-induced rat's paw edema at 10 mg/kg. The anti-inflammatory properties were compared with that of indomethacin (in a dose of 10 mg/kg) which was used as a reference standard. Chalcones **2a–f**, the first stage compounds, have elicited significant anti-inflammatory activity of varying degree (32.13–65.70%).

Cyclization of these chalcones into their corresponding pyrazolines **3a–f** showed moderate anti-inflammatory activity (13.00–57.76%). In general, they exhibited less degree of inhibition of edema compared to their parent compounds except for compound **3c** (Table 1, Figs. 1 to 3).

**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[c] |
|---|---|---|---|
| Control | 0.55 ± 0.05 | 0.00 | – |
| Indomethacin | 0.23 ± 0.03 | 58.84 | 100.00 |
| **2a** | 0.21[a] ± 0.05 | 62.09 | 105.52 |
| **2b** | 0.19[a] ± 0.03 | 65.70 | 111.66 |
| **2c** | 0.36 ± 0.07 | 34.66 | 58.90 |
| **2d** | 0.22[a] ± 0.03 | 60.65 | 103.07 |
| **2e** | 0.38 ± 0.05 | 32.13 | 54.60 |
| **2f** | 0.28[a] ± 0.05 | 48.74 | 82.82 |
| **3a** | 0.25[a] ± 0.06 | 55.23 | 93.87 |
| **3b** | 0.41 ± 0.08 | 25.63 | 43.56 |
| **3c** | 0.23[a] ± 0.06 | 57.76 | 98.16 |
| **3d** | 0.40 ± 0.03 | 27.44 | 46.63 |
| **3e** | 0.45[a,b] ± 0.07 | 19.13 | 32.52 |
| **3f** | 0.48[a,b] ± 0.05 | 13.00 | 22.09 |

[a] Statistically significant from the control at $p < 0.05$
[b] Statistically significant from the indomethacin at $p < 0.05$
[c] Potency was expressed as % edema inhibition of the tested compounds relative to % edema inhibition of indomethacin (reference standard)

 

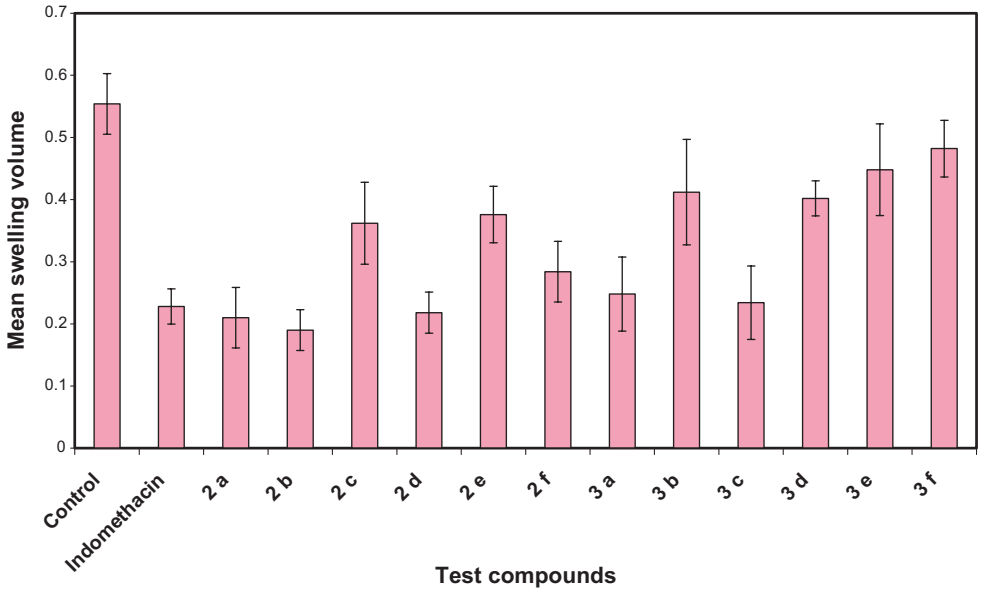


**Figure 1.** Mean edema volume (mL) of the test compounds.

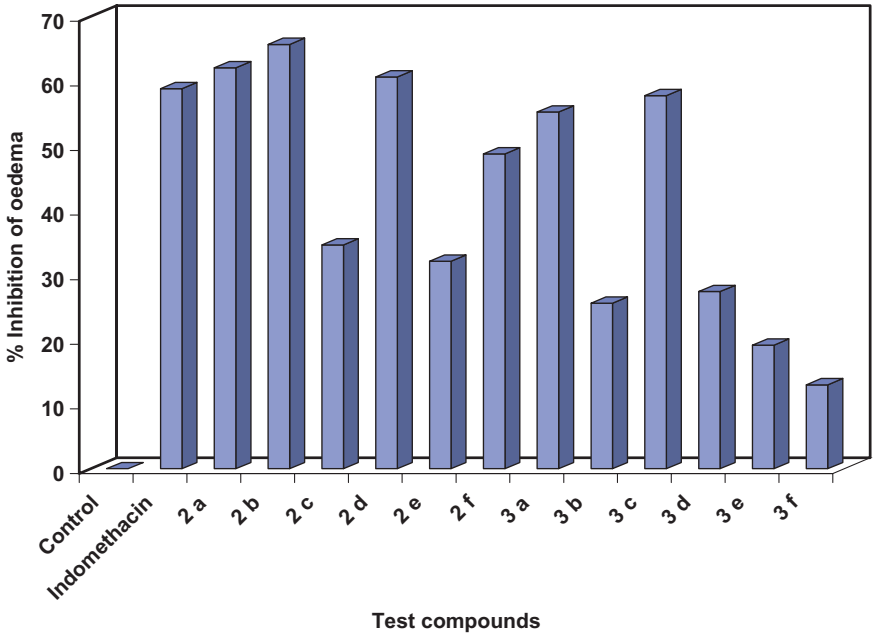


**Figure 2.** % Inhibition of edema for the test compounds.

The presence of 4-bromine (**2b**), or 3,4-dimethoxy groups (**2d**), in the aromatic ring of 3-position of the chalcone nucleus gave rise to an increased anti-inflammatory activity (65.70 or 60.65%, respectively).

It is also obvious that adopting a thienyl function (a bio-isostere of the phenyl group) at the 2-position of the chalcone or the 5-position of the pyrazoline heterocycle seems preferable for obtaining an effective pharmacological agent as exhibited in pairs **2a** or **3a** (65.70 or 55.23%, respectively). On the other hand, compounds **3b**, **3d**, **3e**, and **3f** in the pyrazoline series, when phenyl ring was substituted with 4-bromo, 3,4-dimethoxy, 3,5-dimethoxy or 3,4,5-trimethoxy groups, showed lower degree of anti-inflammatory activity (25.63, 27.44, 19.13, 13.00%, respectively).

 

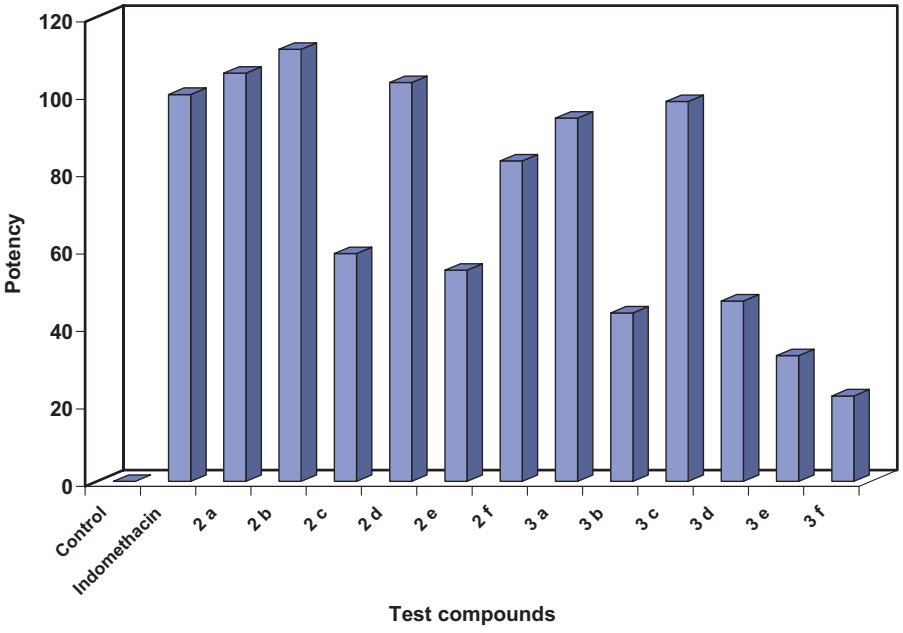


**Figure 3.** Anti-inflammatory activity potency of the test compounds relative to indomethacin which was used as a reference standard.

## Conclusion

The investigation of anti-inflammatory screening data revealed that the entire investigated compounds exhibit considerable anti-inflammatory properties with the percentage inhibition of edema formation ranging from 13.0 to 65.7%, while the reference drug indomethacin showed 58.84% inhibition. All chalcone derivatives, except **2c**, were found to be more potent than their cyclized pyrazolines. Three chalcones **2a**, **2b** and **2d** showed remarkable activities with potency of 105.52, 111.66 and 103.07%, respectively, while two pyrazoline derivatives **3a** and **3c** exhibited comparable activity to indomethacin, although not equal (potency 93.87 and 98.16%, respectively).

Hence, it is concluded that there is ample scope for further study in developing these as good lead compounds.

## 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 discs. $^1$H-NMR spectra were performed on a Joel NMR Varian Gemini 200 MHz Spectrometer and Varian Mercury VX-300 MHz NMR Spectrometer using TMS as the internal standard.

Reagents used in synthesis were obtained commercially from Sigma-Aldrich® and Merck®.

### *General procedure for the synthesis of chalcones **(2a–f)***

A mixture of 1-(4-morpholinophenyl)ethanone (0.05 mol), appropriate aromatic aldehyde (0.05 mol) and 10% aqueous sodium hydroxide (10 mL) in ethanol (30 mL) was stirred at room temperature for about 3 h. The resulting solid was filtered off, rinsed with water, dried, and crystallized from ethanol.

### *1-(4-Morpholinophenyl)-3-(2-thienyl)-2-propen-1-one **(2a)***

Mp: 232–233°C; yield: 83%; IR (cm$^{-1}$): $\nu$ 3082 (arom-H), 2962, 2843 (aliph-H), 1643 (C=O); $^1$H-NMR (DMSO-$d_6$): $\delta$ 3.35 (t, 4H, N($CH_2$)$_2$), 3.74 (t, 4H, O($CH_2$)$_2$), 7.07 (d, 2H, Ar-H, $J$ = 8.6 Hz), 7.23 (dd, 1H, thienyl H4, $J$ = 3.4, 4.6 Hz), 7.60 (d, 1H, =CH, $J$ = 14.8 Hz), 7.69 (d, 1H, thienyl H3, $J$ = 3.0 Hz), 7.80 (d, 1H, thienyl H5, $J$ = 5.2 Hz), 7.88 (d, 1H, =CH, $J$ = 15.4 Hz), 8.05 (d, 2H, Ar-H, $J$ = 8.8 Hz). Anal. calcd. for $C_{17}H_{17}NO_2S$ (299.38): C, 68.20, H, 5.72, N, 4.67. Found: C, 68.34, H, 5.81, N, 4.60.

### *3-(4-Bromophenyl)-1-(4-morpholinophenyl)-2-propen-1-one **(2b)***

Mp: 203–204°C; yield: 90%; IR (cm$^{-1}$): $\nu$ 3082 (arom-H), 2965, 2862, 2835 (aliph-H), 1654 (C=O); $^1$H-NMR (DMSO-$d_6$): $\delta$ 3.31 (t, 4H, N($CH_2$)$_2$), 3.77 (t, 4H, O ($CH_2$)$_2$), 7.01 (d, 2H, Ar-H, $J$ = 8.2 Hz), 7.40 (d, 2H, Ar-H, $J$ = 7.4 Hz), 7.54 (d, 2H, Ar-H, $J$ = 7.8 Hz), 7.68 (d, 1H, =CH, $J$ = 15.4 Hz), 7.86 (d, 1H, =CH, $J$ = 15.4 Hz), 8.12 (d, 2H, Ar-H, $J$ = 8.2 Hz). Anal. calcd. for $C_{19}H_{18}BrNO_2$ (372.25): C, 61.30, H, 4.87, N, 3.76. Found: C, 61.18, H, 4.75, N, 3.83.

### *3-(2-Methoxyphenyl)-1-(4-morpholinophenyl)-2-propen-1-one **(2c)***

Mp; 133–134°C; yield: 81%; IR (cm$^{-1}$): $\nu$ 3051 (arom-H), 2962, 2889, 2839 (aliph-H), 1647 (C=O); $^1$H-NMR (DMSO-$d_6$): $\delta$ 3.35 (m,

 

4H, $N(CH_2)_2$), 3.77 (m, 4H, $O(CH_2)_2$), 3.92 (s, 3H, $OCH_3$), 6.98–7.22 (m, 4H, Ar-H), 7.46 (distorted d, 1H, =CH), 7.86–8.10 (m, 5H, Ar-H and =CH). Anal. calcd. for $C_{20}H_{21}NO_3$ (323.38): C, 74.28, H, 6.54, N, 4.33. Found: C, 74.41, H, 6.61, N, 4.32.

### *3-(3,4-Dimethoxyphenyl)-1-(4-morpholinophenyl)-2-propen-1-one* ***(2d)***

Mp: 168–169°C; yield 54%; IR ($cm^{-1}$): $\nu$ 3005 (arom-H), 2966, 2893, 2835 (aliph-H), 1639 (C=O); $^1$H-NMR (DMSO-$d_6$): $\delta$ 3.31 (t, 4H, $N(CH_2)_2$), 3.74 (t, 4H, $O(CH_2)_2$), 3.81 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 7.00 (d, 1H, Ar-H, $J$ = 8.4 Hz), 7.02 (d, 2H, Ar-H, $J$ = 9.0 Hz), 7.34 (d, 1H, Ar-H, $J$ = 8.7 Hz), 7.50 (s, 1H, Ar-H), 7.61 (d, 1H, =CH, $J$ = 15.6 Hz), 7.79 (d, 1H, =CH, $J$ = 15.3 Hz), 8.06 (d, 2H, Ar-H, $J$ = 9.0 Hz). Anal. calcd. for $C_{21}H_{23}NO_4$ (353.41): C, 71.36, H, 6.55, N, 3.96. Found: C, 71.22, H, 6.41, N, 4.12.

### *3-(3,5-Dimethoxyphenyl)-1-(4-morpholinophenyl)-2-propen-1-one* ***(2e)***

Mp: 180–181°C; yield: 85%; IR ($cm^{-1}$): $\nu$ 3005 (arom-H), 2978, 2943, 2862 (aliph-H), 1651 (C=O); $^1$H-NMR (DMSO-$d_6$): $\delta$ 3.34 (t, 4H, $N(CH_2)_2$), 3.73 (t, 4H, $O(CH_2)_2$), 3.79 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 6.55 (s, 1H, Ar-H), 7.02 (d, 2H, Ar-H, $J$ = 8.7 Hz), 7.03 (s, 2H, Ar-H), 7.58 (d, 1H, =CH, $J$ = 15.6 Hz), 7.89 (d, 1H, =CH, $J$ = 15.6 Hz), 8.07 (d, 2H, Ar-H, $J$ = 9.0 Hz). Anal. calcd. for $C_{21}H_{23}NO_4$ (353.41): C, 71.36, H, 6.55, N, 3.96. Found: C, 71.30, H, 6.48, N, 3.88.

### *3-(3,4,5-Trimethoxyphenyl)-1-(4-morpholinophenyl)-2-propen-1-one* ***(2f)***

Mp: 156–157°C; yield 73%; IR ($cm^{-1}$): $\nu$ 3070, 3005 (arom-H), 2962, 2920, 2897, 2839 (aliph-H), 1654 (C=O); $^1$H-NMR (DMSO-$d_6$): $\delta$ 3.31 (t, 2H, $N(CH_2)_2$), 3.72 (t, 2H, $O(CH_2)_2$), 3.83 (s, 3H, $OCH_3$), 3.86 (s, 6H, 2 × $OCH_3$), 7.02 (d, 2H, Ar-H, $J$ = 9.0 Hz), 7.192 (s, 2H, Ar-H), 7.61 (d, 1H, =CH, $J$ = 15.3 Hz), 7.85 (d, 1H, =CH, $J$ = 15.6 Hz), 8.07 (d, 2H, Ar-H, $J$ = 9.3 Hz). Anal. calcd. for $C_{22}H_{25}NO_5$ (383.43): C, 68.91, H, 6.57, N, 3.65. Found: C, 69.12, H, 6.55, N, 3.60.

### *General Procedure for the synthesis of 5-aryl-3-(4-morpholinophenyl)-4,5-dihydro-1H-pyrazoles (**3a–f**)*

A solution of the appropriate chalcone (0.03 mol) **2a–f** and hydrazine monohydrate (0.06 mol) in ethanol (30 mL) was refluxed for 3 h. The reaction mixture was cooled and kept at 0°C overnight. The resulting solid was crystallized from ethanol.

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

Mp: 91–92°C; yield: 44% IR ($cm^{-1}$): $\nu$ 3390 (NH), 2958, 2854 (aliph-H), 1597 (C=N); $^1$H-NMR (DMSO-$d_6$): $\delta$ 2.88 (dd, 1H, pyrazoline H4, $J$ = 15.9, 4.8 Hz), 3.11 (t, 4H, $N(CH_2)_4$), 3.62 (dd, 1H, pyrazoline H4, $J$ = 16.0, 11.0 Hz), 3.72 (t, 4H, $O(CH_2)_2$), 5.33 (m, 1H, pyrazoline H5), 5.55 (s, 1H, NH, $D_2O$ exchangeable), 6.93–7.15 (m, 3H, Ar-H, thienyl H4), 7.39 (d, 1H, thienyl H5, $J$ = 4.5 Hz), 7.61 (d, 1H, thienyl H3, $J$ = 2.7 Hz), 7.93 (d, 2H, Ar-H, $J$ = 9.0 Hz). Anal. calcd. for $C_{17}H_{19}N_3OS$ (313.41): C, 65.14, H, 6.11, N, 13.40. Found: C, 65.23, H, 5.98, N, 13.32.

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

Mp: 147–149°C; yield 46%; IR ($cm^{-1}$): $\nu$ 3336 (NH), 2958, 2835 (aliph-H), 1604 (C=N); $^1$H-NMR (DMSO-$d_6$): δ 2.77 (dd, 1H, pyrazoline H4, $J$ = 16.2, 5.7 Hz), 3.14 (t, 4H, $N(CH_2)_2$), 3.40 (dd, 1H, pyrazoline H4, $J$ = 16.2, 10.5 Hz), 3.73 (t, 4H, $O(CH_2)_2$), 4.76 (dd, 1H, pyrazoline H5, $J$ = 10.5, 5.4 Hz), 6.93 (d, 2H, Ar-H, $J$ = 8.4 Hz), 7.33 (d, 2H, Ar-H, $J$ = 8.1 Hz), 7.48 (d, 2H, Ar-H, $J$ = 8.7 Hz), 7.52 (d, 2H, Ar-H, $J$ = 8.7 Hz). Anal. calcd. for $C_{19}H_{20}BrN_3O$ (386.28): C, 59.07, H, 5.21, N, 10.87. Found: C, 59.20, H, 5.00, N, 10.98.

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

Mp: 107–108°C; yield 33%; IR ($cm^{-1}$): $\nu$ 3340 (NH), 2958, 2835 (aliph-H), 1597 (C=N); $^1$H-NMR (DMSO-$d_6$): $\delta$ 3.20 (dd, 1H, pyrazoline H4, $J$ = 17.7, 4.8 Hz), 3.31 (t, 4H, $N(CH_2)_2$), 3.76 (dd, 1H, pyrazoline H4, $J$ = 17.7, 11.7 Hz), 3.87 (t, 4H, $O(CH_2)_2$), 3.94 (s, 3H, $OCH_3$), 5.15 (s, 1H, NH, $D_2O$ exchangeable), 5.40 (dd, 1H, pyrazoline H5, $J$ = 11.7, 4.8 Hz), 7.04 (m, 1H, Ar-H), 7.10 (d, 2H, Ar-H, $J$ = 9.0 Hz), 7.49 (m, 2H, Ar-H), 7.81 (d, 2H, Ar-H, $J$ = 9.0 Hz), 7.87 (m, 1H, Ar-H). Anal. calcd. for $C_{20}H_{23}N_3O_2$ (337.41): C, 71.19, H, 6.87, N, 12.45. Found: C, 71.31, H, 6.91, N, 12.60.

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

Mp: 125–126°C; yield 40%; IR ($cm^{-1}$): $\nu$ 3394 (NH), 2931, 2831, 2849 (aliph-H), 1600 (C=N); $^1$H-NMR (DMSO-$d_6$): $\delta$ 3.16 (dd, 1H, pyrazoline H4, $J$ = 17.1, 6.0 Hz), 3.30 (t, 4H, $N(CH_2)_2$), 3.74 (m, 4H, $O(CH_2)_2$), 3.76 (dd, 1H, pyrazoline H4, $J$ = 17.4, 11.1 Hz), 3.83 (s, 3H, $OCH_3$), 3.85 (s, 3H, $OCH_3$), 5.05 (m, 1H, pyrazoline H5), 6.87 (d, 2H, Ar-H, $J$ = 9.0 Hz), 7.06–7.52 (m, 3H, Ar-H), 8.04 (d, 2H, Ar-H, $J$ = 9.0 Hz). Anal. calcd. for $C_{21}H_{25}N_3O_3$ (367.44): C, 68.64, H, 6.85, N, 11.43. Found: C, 68.50, H, 6.73, N, 11.52.

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

Mp: 105–106°C; yield 42%; IR ($cm^{-1}$): $\nu$ 3325 (NH), 2947, 2843 (aliph-H), 1608 (C=N); $^1$H-NMR (DMSO-$d_6$): $\delta$ 3.33 (m, 5H, $N(CH_2)_2$ and pyrazoline H4), 3.72 (t, 4H, $O(CH_2)_2$), 3.76 (d, 1H, pyrazoline H4, $J$ = 16.2, 11.1 Hz), 3.80 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 4.68 (s, 1H, NH, $D_2O$ exchangeable), 5.23 (m, 1H, pyrazoline H5), 6.55 (s, 1H, Ar-H), 6.99 (d, 2H, Ar-H, $J$ = 9.0 Hz), 7.23 (s, 2H, Ar-H), 8.07 (d, 2H, Ar-H, $J$ = 9.0 Hz). Anal. calcd. for $C_{21}H_{25}N_3O_3$ (367.44): C, 68.64, H, 6.85, N, 11.43. Found: C, 68.53, H, 6.70, N, 11.24.

### *5-(3,4,5-Trimethoxyphenyl)-4,5-dihydro-3-(4-morpholinophenyl)-1H-pyrazole* ***(3f)***

Mp: 109–110°C; yield 38%; IR ($cm^{-1}$): $\nu$ 3395 (NH), 2931, 2831 (aliph-H), 1589 (C=N); $^1$H-NMR (DMSO-$d_6$): $\delta$ 3.15 (dd, 1H, pyrazoline H4, $J$ = 16.8, 4.8 Hz), 3.29 (t, 4H, $N(CH_2)_2$), 3.65 (dd, 1H, pyrazoline H4, $J$ = 16.2, 11.1 Hz), 3.72 (t, 4H, $O(CH_2)_2$), 3.82 (s, 3H, $OCH_3$), 3.84 (s, 6H, 2 × $OCH_3$), 4.75 (m, 1H, pyrazoline H5), 6.49 (s, 2H, Ar-H), 6.96 (d, 2H, Ar-H, $J$ = 8.4 Hz), 7.68 (d, 2H, Ar-H, $J$ = 8.4 Hz). Anal. calcd. for $C_{22}H_{27}N_3O_4$ (397.46): C, 66.48, H, 6.84, N, 10.57. Found: C, 66.53, H, 7.01, N, 10.71.

## 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 one week prior 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 to the carrageenan-induced paw edema method [31]. 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 indomethacin one hour 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 one hour prior to carrageenan injection. The paw volume of each rat was measured before 1 h and after 3 h of carrageenan treatment with the help of a Plethysmometer. Quantitative variables from normal distribution were expressed as means ± SE (standard error). The significant difference between groups was tested by using 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, Figs. 1 to 3):

$$\%\,\text{Inhibition of edema} = V_c - V_t / V_c \times 100 \quad (1)$$

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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