Microwave-assisted Synthesis of Novel 3,4-Bis-chalcone-*N*-arylpyrazoles and Their Anti-inflammatory Activity

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A series of 3,4-bis-chalcone-*N*-arylpyrazoles **3a-h** was prepared conveniently from diacetyl pyrazoles **2a,b**. All reactions were carried out under conventional thermal heating and/or microwave irradiation. The structure of the latter functionally pyrazoles was confirmed under the bases of their IR, mass, ^{1}H NMR and ^{13}C NMR. The X-ray diffraction of compound **3e** not only confirmed the chemical structure of **3a-h**, but also showed the *E* configuration of their chalcone moieties. Treatment of compound **3e** with phenyl hydrazine in presence of acetic acid afforded the tri-pyrazle **4**. The anti-inflammatory activity of the newly synthesized compounds was investigated. Some of these compounds showed a moderate activity when compared with indomethacin as a reference drug. The combination between chalcone and pyrazole moieties revealed a variable effect in anti-inflammatory activity.

Keywords: Microwave-Assisted synthesis; *N*-arylpyrazoles; Bis-chalcones; Anti-inflammatory activity.

INTRODUCTION

NSAIDs (Non-steroidal anti-inflammatory drugs) remain among the most widely prescribed drugs worldwide.[1,2] *N*-arylpyrazoles were found to be a main pharmacophore in many NSAIDs[3-7] such as the famous anti-inflammatory drugs Celecoxib and SC-558.[8,9]

On the other hand, Chalcone derivatives have a variety of pharmacological activities such as anti-inflammatory, analgesic and antipyretic activities.[10,11] Furthermore, some chalcones were observed to be excellent anti-inflammatory agents.[12]

The main method for the synthesis of chalcones is the classical Claisen-Schmidt condensation in the presence of aqueous alkaline bases. They are obtained also *via* the Wittig reaction, by the Friedel-Crafts acylation with cinnamoyl chloride, or photo-Fries rearrangement of phenyl cinnamates. Microwave synthesis offered advantages over conventional heating, due to rapid reaction and improvement in yields, in the synthesis of chalcones.[13,14]

The combination of both previous active moieties, pyarazole and chalcone, may provide a synergistic effect to improve the anti-inflammatory activity. These predictions encouraged us to synthesize hybrid compounds containing *N*-arylpyrazole combined with chalcone scaffold. Based on the previous findings and in continuation of our interest in the synthesis of bioactive heterocycles including pyrazoles,[15-25] we are dealing in this study with the synthesis of the title compounds using microwave irradiation to evaluate their anti-inflammatory activity.

RESULTS AND DISCUSSION

Pyrazoles **2a,b** were synthesized by the reaction of pentan-2,4-dione with the appropriate 2-oxo-*N*′-arylpropanehydrazonoyl chloride **1a,b** at room temperature in ethanolic sodium ethoxide.[26] Although the pyrazoles **2** have been known for more than three decades[26] there is no any studies for their reactivity except their reaction with hydrazine hydrate to afford pyrazolo[3,4-*d*]pyridazine de-

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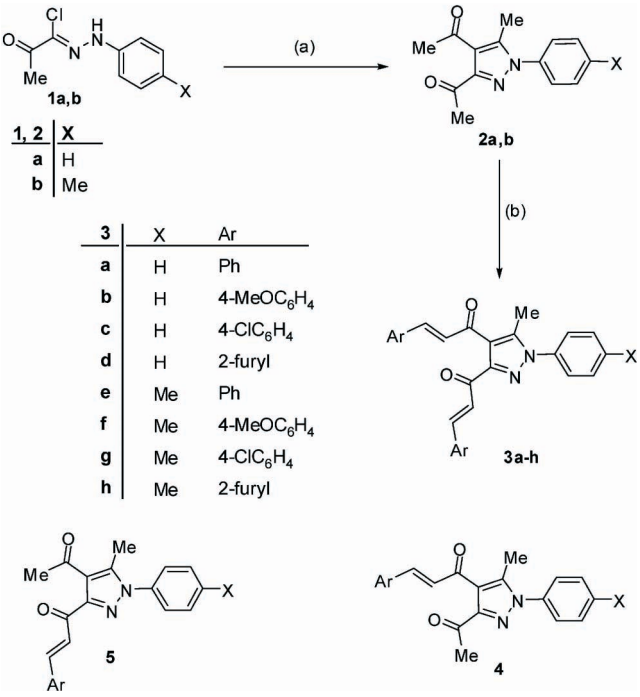
rivatives.[27]

Microwave irradiation has been used for a rapid and efficient synthesis of the novel bis-chalcones **3a-h**. Thus, pyrazoles **2a,b** were reacted with a series of aldehydes in 10% aqueous sodium hydroxide under microwave irradiation (100W, 60 °C) for 4 min to give the bis-chalcone **3a-h** in good yields (70-93%) (Scheme I). On the other hand, bis-chalcones **3a-h** were prepared conventionally at room temperature for 12 h (Scheme I). The obtained results of microwave irradiation synthesis were compared with the conventional method (Table 1).

Scheme I



1, 2	X
a	H
b	Me

3	X	Ar
a	H	Ph
b	H	4-MeOC$_6$H$_4$
c	H	4-ClC$_6$H$_4$
d	H	2-furyl
e	Me	Ph
f	Me	4-MeOC$_6$H$_4$
g	Me	4-ClC$_6$H$_4$
h	Me	2-furyl

Reagents and conditions: (a), $(CH_3CO)_2CH_2$, EtONa/EtOH; (b), 2ArCHO, EtOH, 10% NaOH, r.t., stirring, 12 h (for thermal heating) or 2ArCHO, EtOH, 10% NaOH, 60 °C, 100 W, 4 min (for microwave irradiation).

The IR spectra of **3a-h** showed the appearance of carbonyl function absorption bands in the region 1670-1655 cm^{-1}. The ^{1}H NMR spectra of **3a-h** displayed the two signals of *E* olefinic protons besides the aromatic protons. However, we confirmed the latter *E*-configuration structure by the X-ray single crystal of compound **3e** (Fig. 1). The mass spectra of **3a-h** revealed, in each case, a peak corresponding to the molecular ion. However, all attempts to isolate any of mono chalcones **4** or **5** were failed.

Table 1. Reaction time and yield of conventionally and microwave-assisted synthesis

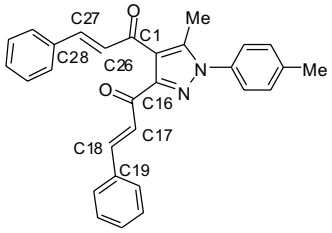
Comp.	Conventionally synthesis		MW-assisted synthesis	
	Time (h)	yield (%)	Time (min)	Yield (%)
3a-h	12	54-80	4	70-93
6	18	58	7	72

Selected bond distances in compound **3e** and the torsion angle of its chalcone double bonds were given in Table 2. The bond lengths and torsion angles of *E*-configuration of chalcones in **3e** are well within the range that typically reported for similar chalcones.[28]

In an attempt to understand the anti-inflammatory potentiality of **3**, we synthesized tri-pyrazoles **6**. Thus, the treatment of compound **3e** with phenyl hydrazine in refluxing ethanol, in presence of acetic acid, afforded the tri-pyrazle **6** (Scheme II). The ^{1}H NMR spectrum of compound **6** revealed the characteristic signals of pyrazolines protons in the regions δ 3.07-3.09, 3.90-3.94 and 5.40-5.43, respectively. Furthermore, compound **6** was prepared under microwave irradiation (100W, 100 °C) for 7 min to give 72% yield.

The anti-inflammatory activity of the tested compounds, meloxicam and indomethacin, as reference standards, was evaluated. Compounds **2a**, **3a** and **3b** revealed significant activity related to the other tested compounds. On the other hand, compounds **3c-h** and **2b** showed a weak to moderate activity related to the reference drugs while

Table 2. Characteristic bond lengths [Å] and torsion angles [°] of **3e**



bond length [Å]			
C16–C17	1.473	C1–C26	1.466
C17–C18	1.324	C26–C27	1.334
C18–C19	1.463	C27–C28	1.488
torsion angles [°]			
C16–C17–C18–C19		178.96	(*E*)
C1–C26–C27–C28		171.70	(*E*)

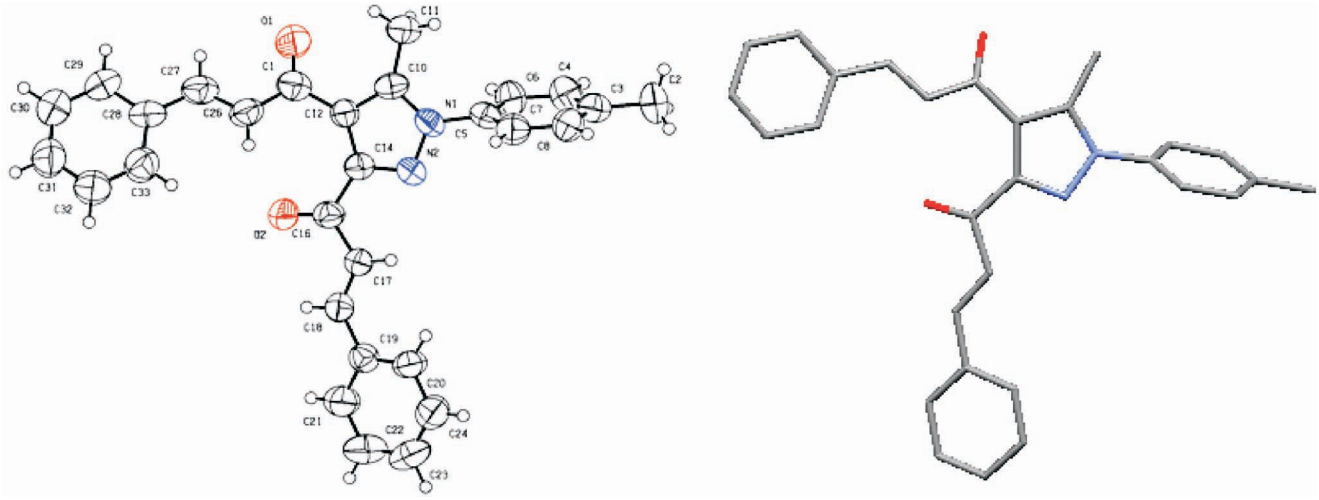
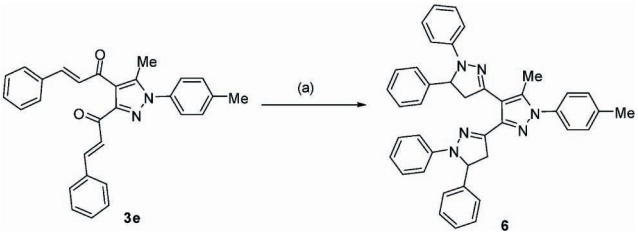


Fig. 1. (a) X-ray structure of **3e**; (b) View of **3e**, hydrogen atoms are omitted for clarity.

Scheme II



Reagents and conditions: (a), $PhNHNH_2$, EtOH/AcOH, reflux 18 h, 58% (for thermal heating) or 100 °C, 100 W, 7 min, 72% (for microwave irradiation).

compound **6** showed no activity as shown in Table 3.

The combination between chalcone moiety and pyrazole ring **2a** was found to increase the activity when compared to **3a** or **3b**. The latter combination slightly decreased the activity in the case of **3c** and **3d**. Similarly, the chalcones **3e**, **3f** and **3g** showed activity higher than the parent pyrazole **2b** while chalcone **3h** revealed slightly lower activity than **2b**. Furthermore, the pyrazoles with *N*-(phenyl)-pyrazoles, have lower anti-inflammatory activity than that of *N*-(4-methylphenyl)pyrazoles. However, compound **3a** was the best among the tested compounds, it reduced the

Table 3. Anti-inflammatory results of the tested compounds

Group	Before injection Edema vol.	3 h			6 h		
		Edema vol.	% Edema inhibition	Pot. (%)	Edema vol.	% Edema inhibition	Pot. (%)
Control	0.289 ± 0.018	0.475 ± 0.012	–	0	0.475 ± 0.012	–	0
2a	0.254 ± 0.014	0.383 ± 0.016[a]	30.23	65.98	0.379 ± 0.030[b]	32.43	66.41
2b	0.245 ± 0.010	0.407 ± 0.019	12.49	27.26	0.404 ± 0.015	13.95	28.57
3a	0.319 ± 0.009	0.439 ± 0.013	35.58	77.66	0.433 ± 0.016	38.90	79.67
3b	0.265 ± 0.009	0.389 ± 0.019[a]	32.69	71.35	0.383 ± 0.016[c]	35.92	73.56
3c	0.243 ± 0.006	0.383 ± 0.019[a]	24.37	53.20	0.376 ± 0.019[b]	28.31	57.97
3d	0.253 ± 0.013	0.386 ± 0.023	28.15	61.45	0.385 ± 0.016[a]	28.61	58.60
3e	0.239 ± 0.006	0.371 ± 0.013[b]	28.72	62.69	0.369 ± 0.010[b]	30.16	61.76
3f	0.245 ± 0.010	0.380 ± 0.013[a]	27.43	59.87	0.391 ± 0.015	21.38	43.78
3g	0.256 ± 0.010	0.356 ± 0.026[c]	21.23	46.35	0.405 ± 0.011	25.92	53.08
3h	0.254 ± 0.010	0.422 ± 0.019	9.69	21.14	0.419 ± 0.021	11.33	23.20
6	0.247 ± 0.009	0.452 ± 0.020	0.00	0.00	0.447 ± 0.002	0.00	0.00
Meloxicam	0.279 ± 0.009	0.385 ± 0.017[a]	42.65	93.10	0.375 ± 0.018[b]	48.25	98.82
Indomethacin	0.263 ± 0.016	0.364 ± 0.010[b]	45.81	100	0.358 ± 0.017[c]	48.83	100

The potency (pot.) was calculated compared to the reference drug indomethacin.
Significance levels [a], $P < 0.05$; [b], $P < 0.01$ and [c], $P < 0.001$ as compared with control.

volume of edema by 38.90% after 6 h with 79.67% potency respect to the reference drug indomethacin.

EXPERIMENTAL

Melting points (°C, uncorrected) were determined using a Gallenkamp melting point apparatus. The IR spectra (KBr) were recorded on a PerkinElmer FT/IR spectrometer. The NMR spectra were recorded at 400 MHz on a Jeol spectrometer using tetramethylsilane as an internal standard. ^{1}H and ^{13}C spectra were run at 400 and 100 MHz, respectively. Chemical shift (δ) values are given in parts per million and coupling constants (*J*) in Hertz. The mass spectra were performed using a Varian MAT CH-5 spectrometer (70 eV). Microwave experiments were carried out using a CEM microwave reactor, USA.

Synthesis of bis chalcones 3a-h

Microwave synthesis

To a solution of the appropriate pyrazole **2a,b** (1 mmol) and the appropriate aldehyde (2 mmol) in ethanol (10 mL), 10% aqueous sodium hydroxide (1 mL) was irradiated under microwave irradiation at 100W and 60 °C for 4 min. The reaction mixture was cooled. The resulting solid was filtered off, washed with water, dried and crystallized from EtOH/DMF to afford chalcones **3a-c**.

Conventional synthesis

To a stirred solution of the appropriate pyrazole **2a,b** (10 mmol) and the appropriate aldehyde (20 mmol) in ethanol (30 mL), 10% aqueous sodium hydroxide (10 mL) was added portion-wise at room temperature for 10 min, the reaction mixture was further stirred for 12 h. The resulting solid was filtered off, washed with water, dried and crystallized from EtOH/DMF to afford chalcones **3a-c**.

1,1′-(5-Methyl-1-phenyl-1H-pyrazole-3,4-diyl)bis(3-phenylprop-2-en-1-one) (3a)

Pale yellow crystals, 70% yield; mp 170-172 °C; IR (KBr) ν_{max}/cm^{-1} 1661 (2C=O), 1596 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.38 (s, 3H, -C<u>H</u>$_3$), 7.24-7.84 (m, 19H, ArH); ^{13}C NMR δ 11.98 (-<u>C</u>H$_3$), 122.58, 123.59, 126.23, 128.36, 129.08, 129.29, 129.53, 129.62, 129.84, 130.07, 131.01, 131.39, 134.92, 135.14, 138.72, 142.83, 143.58, 144.47, 149.69, 184.80 (-<u>C</u>=O), 189.07 (-<u>C</u>=O); MS *m/z* (%) 418 (M$^+$, 0.50), 281 (27.90), 207 (100), 73 (43.92). Anal. Calcd for $C_{28}H_{22}N_2O_2$ (418.49): C, 80.36; H, 5.30; N, 6.69. Found: C, 80.56; H, 5.21; N, 6.82.

1,1′-(5-Methyl-1-phenyl-1H-pyrazole-3,4-diyl)bis(3-(4-methoxyphenyl)prop-2-en-1-one) (3b)

Pale yellow crystals, 78% yield; mp 121-125 °C; IR (KBr) ν_{max}/cm^{-1} 1655 (2C=O), 1590 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 3H, -C<u>H</u>$_3$), 3.79 (s, 3H, -OC<u>H</u>$_3$), 3.81 (s, 3H, -OC<u>H</u>$_3$), 6.97-7.12 (m, 5H, ArH), 7.47-7.79 (m, 12H, ArH); ^{13}C NMR δ 11.96 (-<u>C</u>H$_3$), 55.91 (2 -O<u>C</u>H$_3$), 115.02, 115.10, 121.24, 122.68, 126.12, 126.20, 127.55, 127.68, 129.74, 130.05, 130.91, 131.23, 138.79, 142.6, 143.10, 144.44, 149.85, 161.76, 162.06, 184.78 (-<u>C</u>=O), 189.08 (-<u>C</u>=O); MS *m/z* (%) 478 (M$^+$, 0.29), 281 (43.94), 207 (100), 73 (26.87). Anal. Calcd for $C_{30}H_{26}N_2O_4$ (478.54): C, 75.30; H, 5.48; N, 5.85. Found: C, 75.51; H, 5.66; N, 5.98.

1,1′-(5-Methyl-1-phenyl-1H-pyrazole-3,4-diyl)bis(3-(4-chlorophenyl)prop-2-en-1-one) (3c)

White powder, 75% yield; mp 195-197 °C; IR (KBr) ν_{max}/cm^{-1} 1662 (2C=O), 1598 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.38 (s, 3H, C<u>H</u>$_3$), 7.23-7.86 (m, 17H, ArH); MS *m/z* (%) 487 (M$^+$, 0.95), 207 (100). Anal. Calcd for $C_{28}H_{20}Cl_2N_2O_2$ (487.38): C, 69.00; H, 4.14; N, 5.75. Found: C, 69.17; H, 4.35; N, 5.91.

1,1′-(5-Methyl-1-phenyl-1H-pyrazole-3,4-diyl)bis(3-(furan-2-yl)prop-2-en-1-one) (3d)

Beige powder, 70% yield; mp 187-189 °C; IR (KBr) ν_{max}/cm^{-1} 1665, 1654 (2C=O), 1604 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 3H, C<u>H</u>$_3$), 6.66-6.69 (m, 2H, ArH), 6.90 (d, 1H, *J* = 15.88 Hz, ArH), 6.98 (d, 1H, *J* = 3.64 Hz, ArH), 7.08 (d, 1H, *J* = 3.64 Hz, ArH), 7.35 (d, 1H, *J* = 15.88 Hz, ArH), 7.49-7.71 (m, 7H, ArH), 7.88 (d, 2H, *J* = 12.20 Hz, ArH); ^{13}C NMR δ 11.95 (-<u>C</u>H$_3$), 112.54, 113.61, 113.78, 117.43, 118.33, 120.19, 125.15, 126.17, 129.56, 129.84, 129.92, 130.08, 130.65, 146.68, 147.07, 151.32, 151.46, 184.10 (-<u>C</u>=O), 188.25 (-<u>C</u>=O); MS *m/z* (%) 398 (M$^+$, 3.1), 207 (100). Anal. Calcd for $C_{24}H_{18}N_2O_4$ (398.41): C, 72.35; H, 4.55; N, 7.03. Found: C, 72.44; H, 4.72; N, 7.31.

1,1′-(5-Methyl-1-(4-tolyl)-1H-pyrazole-3,4-diyl)bis(3-phenylprop-2-en-1-one) (3e)

Pale yellow crystals, 88% yield; mp 156-158 °C; IR (KBr) ν_{max}/cm^{-1} 1662 (2C=O), 1598 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 3H, -C<u>H</u>$_3$), 2.43 (s, 3H, -C<u>H</u>$_3$), 7.23-7.83 (m, 18H, ArH); ^{13}C NMR δ 11.95 (-<u>C</u>H$_3$), 21.30 (-*p*-<u>C</u>H$_3$), 122.48, 123.62, 126.04, 128.36, 129.08, 129.27, 129.53, 129.63, 130.45, 131.00, 131.39, 134.92, 135.14, 136.29, 139.57, 142.77, 143.54, 144.41, 149.56, 184.81 (-<u>C</u>=O), 189.07 (-<u>C</u>=O); MS *m/z* (%) 432 (M$^+$, 0.46), 281 (28.18), 207 (100), 73 (52.93). Anal. Calcd for $C_{29}H_{24}N_2O_2$ (432.51): C, 80.53; H, 5.59; N, 6.48. Found: C, 80.71; H, 5.82; N, 6.69.

Crystallographic data for the structure **3e** has been deposited with the Cambridge Crystallographic Data Centre (CCDC) under the number 813247. Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK [Fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk].

1,1′-(5-Methyl-1-(4-tolyl)-1H-pyrazole-3,4-diyl)bis(3-(4-methoxyphenyl)prop-2-en-1-one) (3f)

Pale yellow crystals, 93% yield; mp 146-148 °C; IR (KBr) ν_{max}/cm^{-1} 1664 (2C=O), 1596 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H, -C$\underline{H}_3$), 2.42 (s, 3H, -C$\underline{H}_3$), 3.79 (s, 3H, -OC$\underline{H}_3$), 3.80 (s, 3H, -OC$\underline{H}_3$), 6.96-7.11 (m, 5H, ArH), 7.41-7.78 (m, 11H, ArH); ^{13}C NMR δ 11.93 (-$\underline{C}$H$_3$), 21.29 (-*p*-$\underline{C}$H$_3$), 55.90 (-*p*-O$\underline{C}$H$_3$), 55.94 (-*p*-O$\underline{C}$H$_3$), 115.01, 115.09, 121.28, 122.58, 126.01, 126.12, 127.55, 127.69, 130.42, 130.89, 131.20, 136.36, 139.44, 142.87, 143.07, 144.35, 149.71, 161.75, 162.05, 184.79 (-$\underline{C}$=O), 189.05 (-$\underline{C}$=O); MS *m/z* (%) 492 (M$^+$, 0.52), 281 (26.88), 207 (100), 73 (32.88). Anal. Calcd for $C_{31}H_{28}N_2O_4$ (492.57): C, 75.59; H, 5.73; N, 5.69. Found: C, 75.84; H, 5.95; N, 5.81.

1,1′-(5-Methyl-1-(4-tolyl)-1H-pyrazole-3,4-diyl)bis(3-(4-chlorophenyl)prop-2-en-1-one) (3g)

White powder, 79% yield; mp 221-225 °C; IR (KBr) ν_{max}/cm^{-1} 1670 (2C=O), 1608 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 3H, -C$\underline{H}_3$), 2.43 (s, 3H, -C$\underline{H}_3$), 7.25-7.85 (m, 16H, ArH); MS *m/z* (%) 501 (M$^+$, 1.6), 207 (100). Anal. Calcd for $C_{29}H_{22}Cl_2N_2O_2$ (501.40): C, 69.47; H, 4.42; N, 5.59. Found: C, 69.63; H, 4.65; N, 5.83.

1,1′-(5-Methyl-1-(4-tolyl)-1H-pyrazole-3,4-diyl)bis(3-(furan-2-yl)prop-2-en-1-one) (3h)

Beige powder, 80% yield; mp 140-142 °C; IR (KBr) ν_{max}/cm^{-1} 1669, 1657 (2C=O), 1600 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H, -C$\underline{H}_3$), 2.43 (s, 3H, -C$\underline{H}_3$), 6.65-6.69 (m, 2H, ArH), 6.90 (d, 1H, *J* = 15.88 Hz, ArH), 6.98 (d, 1H, *J* = 3.68 Hz, ArH), 7.08 (d, 1H, *J* = 3.64 Hz, ArH), 7.34 (d, 1H, *J* = 15.24 Hz, ArH), 7.42-7.63 (m, 6H, ArH), 7.88 (d, 2H, *J* = 13.44 Hz, ArH); ^{13}C NMR δ 11.91 (-$\underline{C}$H$_3$), 21.29, (-$\underline{C}$H$_3$), 113.58, 113.76, 117.38, 118.28, 120.24, 122.25, 125.16, 125.96, 129.47, 130.45, 130.59, 136.28, 139.54, 143.56, 146.65, 147.04, 149.25, 151.33, 151.47, 184.08 (-$\underline{C}$=O), 188.46 (-$\underline{C}$=O); MS *m/z* (%) 412 (M$^+$, 3.6), 207 (100). Anal. Calcd for $C_{25}H_{20}N_2O_4$ (412.44): C, 72.80; H, 4.89; N, 6.79. Found: C, 72.96; H, 4.98; N, 6.87.

Synthesis of 3,3′-(5-Methyl-1-(4-tolyl)-1H-pyrazole-3,4-diyl)bis(1,5-diphenyl-4,5-dihydro-1H-pyrazole) (6)

To a solution of chalcone **3e** (0.43 g, 1 mmol) in absolute ethanol (15 mL), phenyl hydrazine (0.22 g, 2 mmol) and acetic acid (0.5 mL) were added. The reaction mixture was irradiated under microwave irradiation for 7 min at 100W and 60 °C then left to cool and the solid mass separated out was filtered off, washed with ethanol and recrystallized from ethanol to give compound **6** as beige powder in 72% yield. Compound **6** was prepared conventionally by refluxing a mixture of chalcone **3e** (0.43 g, 1 mmol) in absolute ethanol (30 mL), phenyl hydrazine (0.22 g, 2 mmol) and acetic acid (0.5 mL). The reaction mixture was refluxed for 18 h then left to cool and the solid mass separated out was filtered off, washed with ethanol and recrystallized from ethanol to give compound **6** as beige powder in 58% yield; mp 180-182 °C; IR (KBr) ν_{max}/cm^{-1} 1597 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.39 (s, 3H, -C$\underline{H}_3$), 2.54 (s, 3H, -C$\underline{H}_3$), 3.07-3.09 (m, 2H, CH pyrazoles), 3.90-3.94 (m, 2H, CH pyrazoles), 5.40-5.43 (m, 2H, CH pyrazoles), 6.97-7.44 (m, 24H, ArH); MS *m/z* (%) 612 (M$^+$, 100). Anal. Calcd for $C_{41}H_{36}N_6$ (612.76): C, 80.36; H, 5.92; N, 13.71. Found: C, 80.56; H, 6.08; N, 13.94.

Anti-inflammatory activity

Edema was induced in the right hind paw of adult albino 90 rats (120-150 g) by the subcutaneous injection of 0.1 mL 2% carrageenan sodium (Sigma, USA) in water. Both sexes were used but pregnant females were excluded. Each group was composed of 6 animals. The animals were obtained from animal house laboratory of Nile Company, Cairo, Egypt and acclimatized for 1 week in the animal facility that has 12 h light/dark cycles with the temperature controlled at 21-23 °C. The rats were starved for 18 h and water was provided *ad libitum*. The tested compounds, after complete dissolution in EtOH/Tween 80-H_2O (2:2:20 v/v/v), and meloxicam were administered by oral route directly after injection of the carrageenan at a dose of 10 mg/kg. Indomethacin was given by oral route at 5 mg/kg body weight. This dose of indomethacin was considered as a positive control for experiments with any new chemical entity. The volume of the rat's paw was measured 3 and 6 h after injection of carrageenan using Dial micrometer model (120-1206 Baty, Sussex, England). The reported values were expressed as volume of edema at each time interval, percentage inhibition of edema volume at each time with respect to control and potency which was calculated com-

pared to indomethacin.[29] Data of anti-inflammatory study were expressed as value ± SEM in. Differences between vehicle control and treatment groups were tested using one-way ANOVA followed by multiple comparisons by the Bonferroni's test.

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