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Synthesis and anti-inflammatory activity of some novel 3-phenyl-*N*-[3-(4-phenylpiperazin-1*yl*)propyl]-1*H*-pyrazole-5-carboxamide derivatives

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ABSTRACT

A new series of 3-phenyl-*N*-[3-(4-phenylpiperazin-1*yl*)propyl]-1*H*-pyrazole-5-carboxamide derivatives were synthesized and investigated their anti-inflammatory activities using carrageenan-induced rat paw edema model in vivo. All the synthesized compounds were found to be potent anti-inflammatory agents.

Inflammation and different types of arthritis are inflammatory disorders that deal a blow to humanity. Nonsterodial anti-inflammatory drugs (NSAIDs) are one kind of therapeutics, widely used in the world because of their high efficacy in reducing pain and inhibiting inflammation.[1,2] NSAIDs drugs such as ibuprofen, Celecoxib, Cetrizine, Diclofenac (Fig. 1) can inhibit the enzyme cyclooxygenase (COX-1 and COX-2)[3,4], which catalyze the biotransformation of arachidonic acid to prostaglandins (PGs) and to Thromboxane A_2.[5–9] These are the mediators of pain, inflammation, fever, stimulates platelet aggregation and leading to the formation of blood clots.[10–12] Hence, the development and discovery of new reagents that can inhibit the COX-1 and COX-2 activity will be of importance for the controlling inflammation.[13–15]

Many pharmaceuticals are synthetic compounds, and a large number of them are heterocycles. Common examples are the widely used arylpyrazoles in medicinal and pesticide chemistry.[16] Many pyrazole derivatives are known to exhibit a wide range of biological activities such as anti-hyperglycemic, analgesic, anti-inflammatory, anti-pyretic, anti-bacterial, hypoglycemic, sedative–hypnotic activity,[17,18] and anticoagulant activity.[19] Recently, some arylpyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activity.[20] They may prove to be clinically useful compounds and extensive studies have been devoted to arylpyrazole derivatives such as Celecoxib, a well-known COX-2 inhibitor.[21–25]

In our research programme for synthesis of novel and, alternative NSAID with similar or greater efficacy and to minimize the risk of unwanted side effects,[26,27] we have conducted exploratory research.[28] A new series of 3-phenyl-*N*-[3-(4-phenylpiperazin-1*yl*)propyl]-1*H*-pyrazole-5-carboxamide derivatives were synthesized and evaluated their anti-inflammatory activity to inhibit carrageenan-induced paw edema in rats.

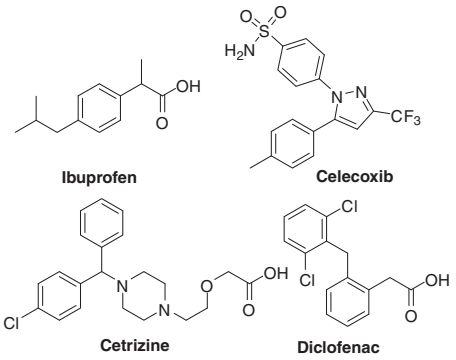

Figure 1. Structure of the nonsterodial anti-inflammatory drugs.

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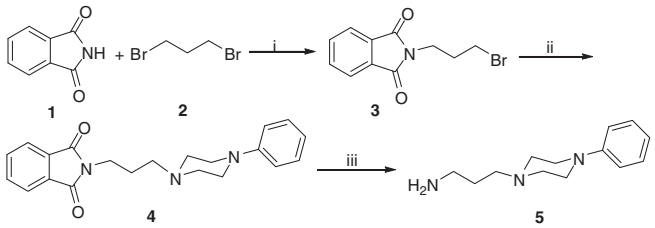
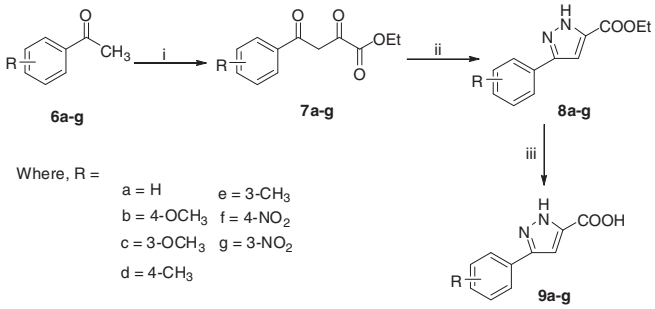
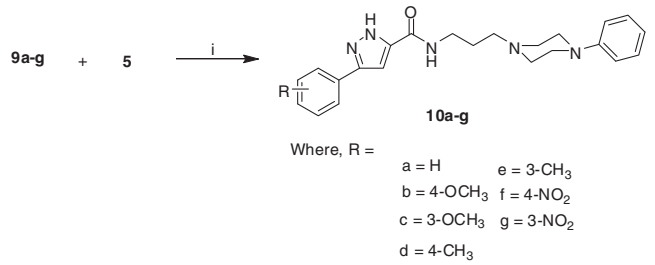


Scheme 1. Reagents and conditions: (i) K_2CO_3, DMF, rt, 3 h, 85%; (ii) *N*-phenylpiprazine, K_2CO_3, DMF, rt, 24 h, 95%; (iii) NH_2NH_2, methanol, rt, 24 h, 72%.



Scheme 2. Reagents and conditions: (i) diethyl oxalate, NaOMe, diethyl ether, rt, 15 h, 73–82%; (ii) NH_2NH_2, AcOH, rt, 12 h, 81–91%; (iii) LiOH, THF, rt, 12 h, 84–97%.



Scheme 3. Reagents and conditions: (i) EDC·HCl, HOBt, DIPEA, CH_2Cl_2, rt, 12 h, 69–81%.

Synthesis of target compounds 3-phenyl-*N*-(3-(4-phenylpiperazin-1*yl*)propyl)-1*H*-pyrazole-5-carboxamide derivatives (**10a–g**) was achieved by the reaction of 3-aryl-1*H*-pyrazole-5-carboxylic acids (**9a–g**) with 3-(4-phenylpiperzin-1-*yl*)propan-1-amine (**5**) in presence of peptide coupling reagents EDC·HCl and HOBt in good to excellent yields (Scheme 3). Compound, 3-(4-phenylpiperzin-1-*yl*)propan-1-amine (**5**) was readily prepared by the reaction of phthalimide (**1**) with 1,3-dibromoporpane (**2**) to give 2-(3-bromopropyl)isoindoline-1,3-dione (**3**) which on reaction with *N*-phenylpiperzine, potassium carbonate in dimethylformamide followed by subsequent deprotection of phthalimide by hydrazine hydrate (Scheme 1). Compounds, ethyl 3-aryl-1*H*-pyrazole-5-carboxylic acids (**9a–g**), were readily prepared by the reaction of various acetophenones (**6a–g**) with diethyl oxalate in sodium methoxide solution to give ethyl 2,4-dioxo-4-arylbutanoate (**7a–g**), which on reaction with hydrazine hydrate in the presence of acetic acid at room temperature, followed by subsequent hydrolysis of ester lithium hydroxide in THF (Scheme 2). All the compounds have been characterized by micro-analytical and spectral data.[28,29]

Anti-inflammatory activity was evaluated using in vivo rat carrageenan-induced foot paw edema model reported previously.[30] A either sex of rats (130–180 g) were fasted with free access to water at least 16 h. The rats were divided in to two groups (Control, test compounds and Standard) of six animals each. Edema was produced by injecting 0.1 mL suspension of 1% carrageenan in the hind paw. One group was kept as control and the animals in other group were treated with the test drug in 1% CMC solution, given orally 1 h before the carrageenan injection. Paw volume of foot was measured by mercury displacement with plethysmometer (UGO BASIL) before and 1, 2, 3, 4 h after carrageenan treatment. The mean increase in paw volume in each group was measured and the percentage was calculated by the following equation: anti-inflammatory activity $(\%) = (1 - D/C) \times 100$, where D represents the difference in paw volume before and after compound was administrated to the rats, and C stands for the difference of volume in the control groups.

All the target compounds (**10a–g**) showed potent anti-inflammatory activity (Tables 1 and 2). Four derivatives **10a**, **10e**, **10f**, **10g** were found to be more potent at 3 h (75%, 70%, 76%, and 78%, respectively). These test compounds were treated at a dose of 100 mg/kg ($P < 0.01$ and $P < 0.0001$) to determine the potential-

Table 2
The percentage anti-inflammatory activity of the target compounds against the carrageenan-induced paw edema in rats

Compound	% Activity			
	1 h	2 h	3 h	4 h
Control	–	–	–	–
10a	47.3	55.5	61.9	58.8
10b	55.2	69.4	75.0	70.0
10c	52.6	62.5	65.2	64.4
10d	60.5	55.5	67.3	63.3
10e	60.5	65.2	70.6	70.0
10f	53.9	75.6	76.0	72.2
10g	67.0	75.0	78.0	75.5
Ibuprofen	42.1	55.5	72.8	63.3

Table 1
Anti-inflammatory activity of the target compounds against the carrageenan-induced paw edema in rats

Compound	Dose (mg/kg)	Increase in paw volume[a] (mL)			
		1 h	2 h	3 h	4 h
Control	1% CMC	0.38 ± 0.045	0.72 ± 0.021	0.92 ± 0.056	0.90 ± 0.018
Standard	100	0.22 ± 0.011	0.32 ± 0.010	0.25 ± 0.018	0.33 ± 0.010
10a	100	0.20 ± 0.018	0.32 ± 0.011***	0.35 ± 0.044***	0.37 ± 0.033***
10b	100	0.17 ± 0.011***	0.22 ± 0.011***	0.23 ± 0.040***	0.27 ± 0.011***
10c	100	0.18 ± 0.011***	0.27 ± 0.033***	0.32 ± 0.010***	0.32 ± 0.010***
10d	100	0.15 ± 0.033**	0.32 ± 0.033**	0.30 ± 0.067***	0.33 ± 0.010***
10e	100	0.15 ± 0.022**	0.25 ± 0.022***	0.27 ± 0.033	0.27 ± 0.078***
10f	100	0.17 ± 0.044***	0.17 ± 0.022	0.22 ± 0.067**	0.25 ± 0.055***
10g	100	0.12 ± 0.033***	0.18 ± 0.055***	0.20 ± 0.044**	0.22 ± 0.044***

Standard: ibuprofen, each value is the mean ± SEM for six rats, **$P < 0.01$; ***$P < 0.0001$ compared with control.
[a] Increase in paw volume was calculated as (the volume after carrageen in injection) – (the volume before injection). Data analyzed by one-way ANOVA followed by Student's *t*-test.

ity along with the reference drug ibuprofen. The study of all the derivatives showed anti-inflammatory activity greater than ibuprofen. All the target compounds (**10a–g**) potentially reduced the carrageenan-induced inflammation in rats. The SAR study of the compounds revealed that the substitution of methoxy- and nitro-group on aryl ring had developed the active compounds.

In summary, a new series of pyrazole carboxamides (**10a–g**) were synthesized and has been identified as anti-inflammatory agents. Biological evaluation revealed that the all the target compounds displayed potent anti-inflammatory activity. Therefore, our finding may aid in the strong future potential of new and safe anti-inflammatory agents for the further investigation.

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29. *Spectral data:* Compound **10a**: mp 133–135 °C, 79.8% yield; IR (ν_{max} cm^{-1}, KBr): 3232, 2936, 2874, 1643, 1560, 1244, 1152, 761, 690, ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.77–1.86(m, 2H, CH_2), 2.57–2.69(m, 4H, 2× CH_2), 3.19–3.31(m, 6H, 3× CH_2), 3.46(d, J = 5.52 Hz, 2H, CH_2), 6.76(t, J = 7.36 Hz, 1H, Ar-H), 6.87(d, J = 8.28 Hz, 2H, Ar-H), 6.95(s, 1H, Ar-H), 7.18(t, J = 7.54 Hz, 2H, Ar-H), 7.24–7.43(m, 3H, Ar-H), 7.69(d, J = 8.28 Hz, 2H, Ar-H), 7.94(s, 1H, NH), 13.29(br, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 24.97, 37.17, 47.49, 52.16, 55.80, 95.49, 101.91, 115.38, 119.01, 124.90, 127.46, 128.21, 128.46, 150.15, 161.02; HRMS (ESI$^+$) Calcd for $C_{23}H_{27}N_5O$ [M+H]$^+$: 390.2293. Found: 390.2302. Compound **10b**: mp 207–209 °C, 76.5% yield; IR (ν_{max} cm^{-1}, KBr): 3286, 3225, 2960, 2870, 1642, 1599, 1564, 1510, 1259, 1022, 819, 756, ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.71–1.81(m, 2H, CH_2), 2.39–2.50(m, 2H, CH_2), 3.13–3.24(m, 4H, 2× CH_2), 3.32–3.44(m, 6H, 3× CH_2); 3.83(s, 3H, OCH_3), 6.76–6.84(m, 1H, Ar-H), 6.92–7.01(m, 3H, Ar-H); 7.05(d, J = 7.34 Hz, 2H, Ar-H), 7.24(t, J = 7.34 Hz, 2H, Ar-H), 7.74(d, J = 7.34 Hz, 1H, Ar-H), 8.26(s, 1H, NH), 13.47(br, 1H, NH); HRMS (ESI$^+$) Calcd for $C_{24}H_{29}N_5O_2$ [M+H]$^+$: 420.2399. Found: 420.2408. Compound **10c**: mp 174–176 °C, 72.1% yield; IR (ν_{max} cm^{-1}, KBr): 3293, 3225, 2931, 2829, 1645, 1562, 1497, 1453, 1235, 1041, 754, 688, ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.73–1.86(m, 2H, CH_2), 2.45–2.55(m, 2H, CH_2), 2.55–2.66(m, 4H, 2× CH_2), 3.17–3.28(m, 4H, 2× CH_2), 3.38–3.49(m, Hz, 2H, CH_2), 3.82(s, 3H, OCH_3), 6.75(t, J = 7.17 Hz, 1H, Ar-H), 6.82(s, 1H, Ar-H), 6.86(d, J = 8.30 Hz, 2H, Ar-H), 6.96(s, 1H, Ar-H), 7.17(t, J = 7.83 Hz, 2H, Ar-H), 7.22–7.34(m, 3H, Ar-H), 8.01(s, 1H, NH), 13.36(br, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 26.21, 38.07, 48.61, 53.14, 56.78, 96.11, 102.69, 110.80, 113.95, 116.81, 117.93, 119.23, 129.08, 129.95, 151.19, 159.97; HRMS (ESI$^+$) Calcd for $C_{24}H_{29}N_5O_2$ [M+H]$^+$: 420.2399. Found: 420.2395. Compound **10d**: mp 191–193 °C, 71.7% yield; IR (ν_{max} cm^{-1}, KBr): 3290, 3211, 2925, 1643, 1563, 1504, 1383, 1245, 1155, 817, 756, 690, ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.74–1.86(m, 2H, CH_2), 2.36(s, 3H, CH_3), 2.58–2.69(s, 6H, 3× CH_2), 3.17–3.31(m, 4H, 2× CH_2), 3.36–3.49(m, 2H, CH_2), 6.75(t, J = 7.35 Hz, 1H, Ar-H), 6.83–6.94(m, 3H, Ar-H), 7.11–7.24(m, 3H, Ar-H), 7.58(d, J = 7.93 Hz, 2H, Ar-H), 7.90(d, J = 6.98 Hz, 1H, Ar-H), 7.99(s, 1H, NH), 13.22(s, 1H, NH); HRMS (ESI$^+$) Calcd for $C_{24}H_{29}N_5O$ [M+H]$^+$: 404.2450. Found: 404.2469. Compound **10e**: mp 116–118 °C, 74% yield; IR (ν_{max} cm^{-1}, KBr): 3298, 3236, 2927, 2872, 1643, 1556, 1497, 1384, 1243, 1150, 1002, 757, 689, ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.71–1.85(m, 2H, CH_2), 2.38(s, 3H, CH_3), 2.47–2.54(m, 2H, CH_2), 3.2(s, 4H, CH_2), 2.55–2.65(m, 4H, 2× CH_2), 3.30–3.38(m, 4H, 2× CH_2), 3.36–3.46(m, 2H, CH_2), 6.75(t, J = 7.17 Hz, 1H, Ar-H), 6.87(d, J = 7.93 Hz, 2H, Ar-H), 6.95(s, 1H, Ar-H), 7.10(d, J = 7.36 Hz, 1H, Ar-H), 7.17(t, J = 7.83 Hz, 2H, Ar-H), 7.25(t, J = 7.45 Hz, 1H, Ar-H), 7.49(d, J = 7.93 Hz, 1H, Ar-H), 7.54(s, 1H, Ar-H), 8.07(s, 1H, NH), 13.35(s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 20.95, 25.59, 37.42, 47.94, 52.51, 56.06, 95.51, 101.89, 115.21, 118.65, 122.13, 125.61, 128.25, 128.49, 137.59, 150.56, 160.76; HRMS (ESI$^+$) Calcd for $C_{24}H_{29}N_5O$ [M+H]$^+$: 404.2450. Found: 404.2442. Compound **10f**: mp 201–203 °C, 73.7% yield; IR (ν_{max} cm^{-1}, KBr): 3190, 2945, 2825, 1647, 1600, 1513, 1342, 1236, 1114, 854, 754, 690, ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.74–1.88(m, 2H, CH_2), 2.47–2.68(m, 6H, 3× CH_2), 3.15–3.30(m, 4H, 2× CH_2), 3.36–3.51(s, 2H, CH_2), 6.77(t, J = 7.17 Hz, 1H, Ar-H), 6.87(d, J = 8.12 Hz, 2H, Ar-H), 7.14–7.25(m, 3H, Ar-H), 7.89–8.02(m, 2H, Ar-H), 8.11–8.27(m, 2H, Ar-H), 8.41(s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 25.35, 37.60, 48.01, 52.50, 56.15, 95.42, 115.09, 118.63, 123.49, 125.38, 128.38, 146.23, 150.48; HRMS (ESI$^+$) Calcd for $C_{23}H_{26}N_6O_3$ [M+H]$^+$: 435.2144. Found: 453.2139. Compound **10g**: mp 174–176 °C, 70.7% yield; IR (ν_{max} cm^{-1}, KBr): 3239, 3143, 2941, 2820, 1649, 1532, 1347, 1235, 1146, 743, 693, ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.74–1.87(m, 2H, CH_2), 2.57–2.68(m, 6H, 3× CH_2), 3.11–3.29(m, 4H, 2× CH_2), 3.35–3.48(m, 2H, CH_2), 6.75(t, J = 7.26 Hz, 1H, Ar-H), 6.87(d, J = 7.93 Hz, 2H, Ar-H), 7.18(t, J = 7.83 Hz, 2H, Ar-H), 7.54–7.55(m, 2H, Ar-H), 8.00(s, 1H, Ar-H), 8.14(d, J = 7.74 Hz, 2H, Ar-H), 8.64(s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 25.59, 37.39, 48.03, 52.49, 55.90, 95.44, 115.14, 118.61, 119.25, 121.63, 128.40, 129.55, 130.83, 148.02, 150.55; HRMS (ESI$^+$) Calcd for $C_{23}H_{26}N_6O_3$ [M+H]$^+$: 435.2144. Found: 453.2134.
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