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Pyrazole-Embedded Pyridazine and Phthalazinedione Hybrids: Synthesis, Characterization and Anti-Inflammatory Potential

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The synthesis of heterocycles incorporating bridgehead nitrogen, particularly pyridazine and phthalazinedione derivatives, has garnered significant interest due to their wide-ranging applications in various pharmacological fields. Recognizing the importance of eco-friendly protocols, this work reports a novel green synthetic route for the preparation of pyridazine and phthalazinedione derivatives featuring a pyrazole moiety. In this synthetic route, a one-pot multi-component reaction was performed using 3-methyl-1-phenyl-1H-pyrazol-5(4*H*)-one (**1**), various substituted aldehydes (**2**), hydrazine hydrate (**3**) and different anhydrides (**4**–**6**). The synthesized compounds were characterized and screened for their anti-inflammatory activity. Most of the compounds showed good anti-inflammatory activity.

Keywords: Pyridazine, Phthalazinedione, PEG-400, Anti-inflammatory activity.

INTRODUCTION

Multi-component reactions (MCRs) have become indispensable tools in organic and medicinal chemistry due to their exceptional efficiency and atom economy, enabling the rapid construction of structurally complex target molecules in a single synthetic operation from three or more reactants [1,2]. These reactions not only streamline synthetic routes by reducing the number of purification steps but also enhance overall yield and sustainability compared to the traditional stepwise syntheses. Consequently, the strategic design and application of MCRs for the synthesis of diverse compound libraries, particularly those with significant biological activity, have garnered substantial attention, driving advancements in drug discovery and development [3-7].

Among heterocyclic compounds, great focus has been directed towards bridgehead nitrogen containing heterocycles especially those containing hydrazine group such as pyridazine and phthalazine. They possess pharmacological and biological activities such as herbicides, insecticides, fungicides, *etc*. [8,9]. Phthalazine-triones are another category of bridge-head hydrazine-containing heterocycles which are bioisostere of indoles and have been widely used in the medicinal chemistry [10]. In fact, compounds containing pyrazole moiety are known to shows variety of biological activities, such as high binding affinity for the estrogen receptor [11], inhibition of protein-kinase C-β, 175-HT2 and 5-HT3 receptor antagonism [12], human immuno deficiency virus (HIV) protease inhibition [13] and antitumor activity [14].

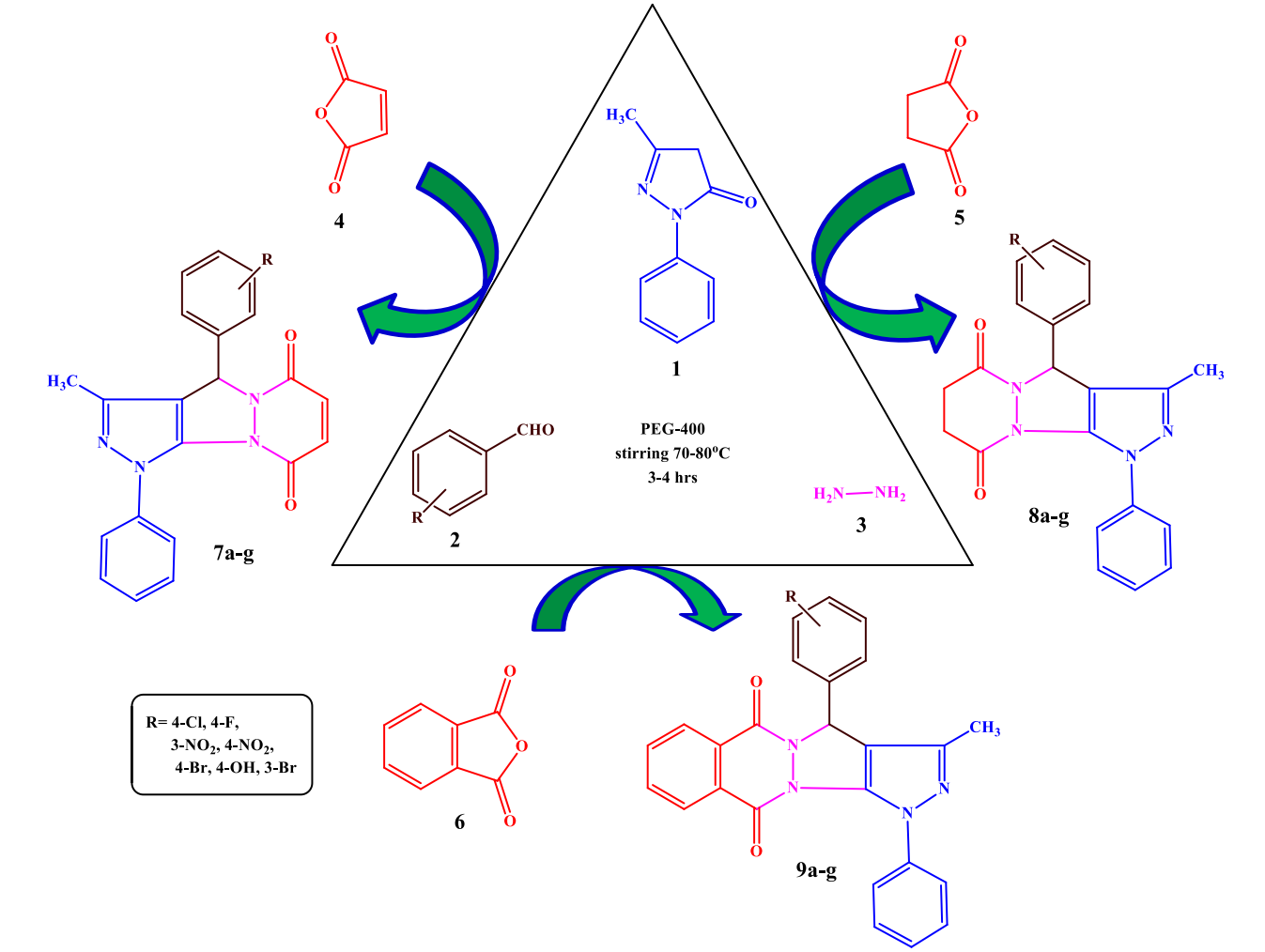
Different catalysts such as supported polyphosphoric acid [15], dodecylphosphonic acid [16], $Ce(SO_4)_2$ [17], modified PEG-600 [18], heteropolyacids [19], trimethylsilyl chloride [20], $Mg(HSO_4)_2$ [21], cyanuric chloride [22] and Brønsted acidic ionic liquid N,N-diethyl-N-sulfoethanammonium chloride ($[Et_3N–SO_3H]Cl$) have been reported for the preparation of these compounds. The afford methods are suffers from one or more drawbacks such as prolonged reaction time, use of strong acidic conditions, use of hazardous catalyst, low yield and purity of compounds. Herein, we report an efficient, catalyst free, PEG-400 mediated synthesis of new pyridazine and phthalazinedione derivatives containing pyrazole moiety *via* four component reactions (MCRs). The newly synthesized compounds were screened for their anti-inflammatory potential by *in vitro* assay.

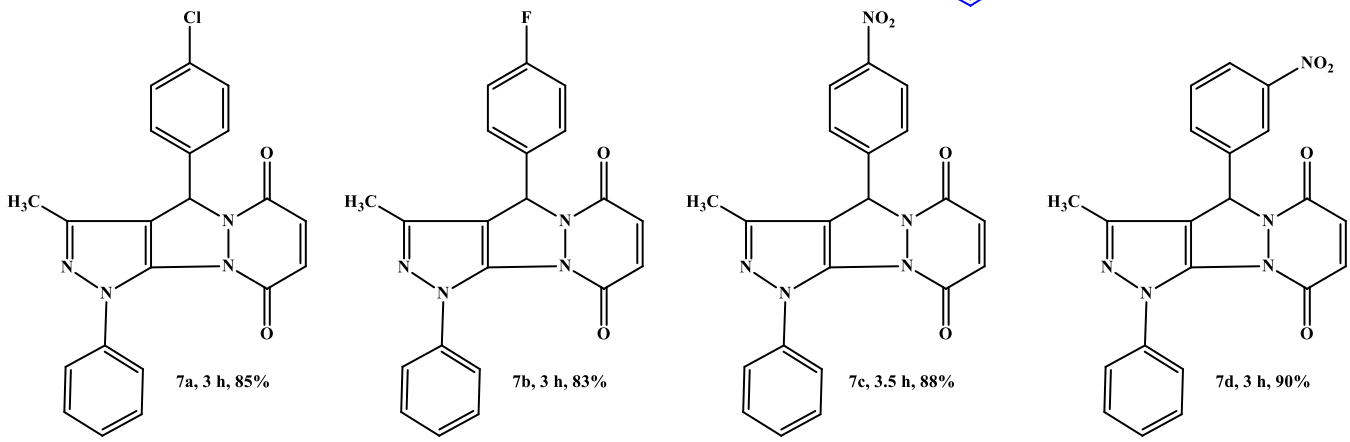
EXPERIMENTAL

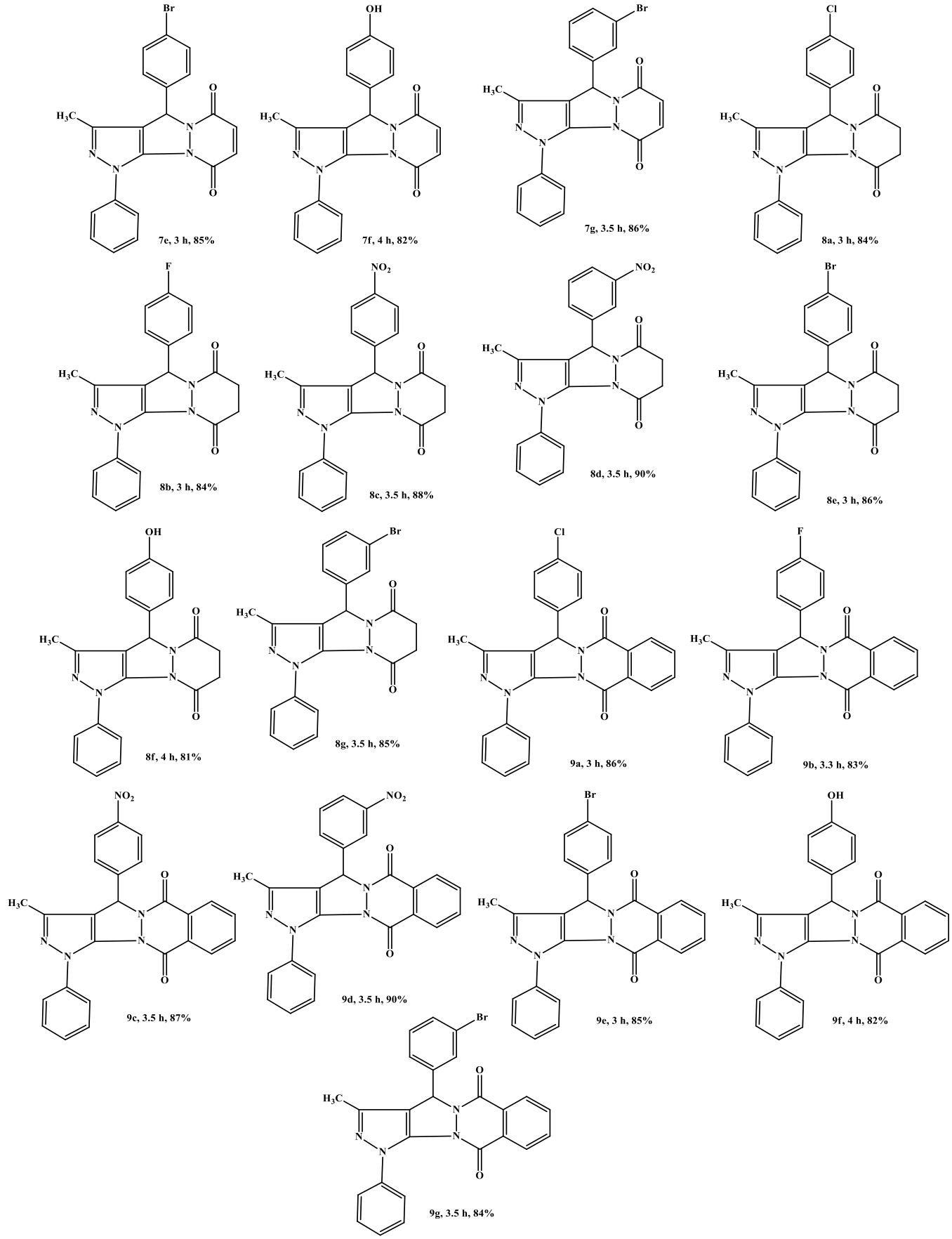
Melting points were determined by open capillary method and were uncorrected. The chemicals and solvents used were of laboratory grade and were purified prior to use. Completion

of the reaction was monitored by thin-layer chromategraphy on precoated sheets of silica gel-G (Merck, Germany) using UV lamp for detection. IR spectra were recorded (in KBr pallets) on Shimadzu spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded (in DMSO-d_6) on Bruker Avance-400 MHz spectrometer using TMS as an internal standard. The mass spectrum was recorded on EI-Shimadzu-GC-MS spectrometer.

General procedure for synthesis of phthalazinedione and pyridazine derivatives (7a-g, 8a-g and 9a-g): A mixture 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1**) (1 mmol), substituted aldehyde (**2**) (1 mmol), hydrazine hydrate (**3**) (1 mmol) and acid anhydride (**4-6**) (1 mmol) was taken in 100 mL RBF containing 10 mL of PEG-400. The reaction mixture was stirred at 70-80 ºC for appropriate time, after completion of reaction (monitored by TLC) the reaction mixture was cool to room temperature and diluted with ice-cold water (about 100 mL). Solid separates out, isolated by simple filtration, dried and recrystallized with appropriate solvent to yield pure product **7a-g**, **8a-g** and **9a-g** (**Scheme-I**).







Scheme-I: Synthetic route of pyridazine and phthalazinedione derivatives (**7a-g/8a-g/9a-g**)

4-(4-Chlorophenyl)-3-methyl-1-phenylpyrazolo[3′,4′:3,4]pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (7a): m.p.: 151-153 ºC; yield: 85%; IR (KBr, ν_{max}, cm^{-1}): 3087 (Ar-CH), 2962 (aliphatic-CH), 1669 (C=O), 1627 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.31-7.41 (m, 11H, Ar-H), 6.17 (s, 1H, C-H), 2.88 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 165.15, 160.22, 140.74, 133.24, 132.36, 130.80, 130.09, 129.42, 128.96, 128.41, 127.56, 126.39, 101.85, 18.26; EIMS: 390 [M+]; Elemental analysis: Calcd. (found) % for $C_{21}H_{15}N_4O_2Cl$; C, 64.54 (64.56); H, 3.87 (3.84); N, 14.34 (14.37).

4-(4-Fluorophenyl)-3-methyl-1-phenylpyrazolo[3′,4′:3,4]pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (7b): m.p.: 137-139 ºC; yield: 83%; IR (KBr, ν_{max}, cm^{-1}): 3078 (Ar-CH), 2960 (aliphatic-CH), 1670 (C=O), 1608 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.20-7.25 (m, 11H, Ar-H), 5.93 (s, 1H, C-H), 2.93 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 167.48, 158.79, 142.36, 131.11, 130.75, 129.96, 129.45, 129.33, 129.04, 128.68, 128.05, 127.56, 103.87, 13.74; EIMS: 373 [M+]; Elemental analysis: Calcd. (found) % for $C_{21}H_{15}N_4O_2F$; C, 67.37 (67.35); H, 4.04 (4.08); N, 14.97 (14.94).

3-Methyl-4-(4-nitrophenyl)-1-phenylpyrazolo[3′,4′:3,4]-pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (7c): m.p.: 163-165 ºC; yield: 88%; IR (KBr, ν_{max}, cm^{-1}): 3058 (Ar-CH), 2974 (aliphatic-CH), 1671 (C=O), 1619 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.51-7.57 (m, 11H, Ar-H), 6.32 (s, 1H, C-H), 2.67 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 164.91, 161.27, 142.34, 131.67, 131.21, 130.98, 130.56, 130.03, 129.84, 129.32, 128.44, 128.19, 127.33, 127.52, 102.37, 11.98; EIMS: 401 [M+]; Elemental analysis: Calcd. (found) % for $C_{21}H_{15}N_5O_4$; C, 62.84 (62.87); H, 3.77 (3.74); N, 17.45 (17.47).

3-Methyl-4-(3-nitrophenyl)-1-phenylpyrazolo[3′,4′:3,4]-pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (7d): m.p.: 156-158 ºC; yield: 90%; IR (KBr, ν_{max}, cm^{-1}): 3076 (Ar-CH), 2985 (aliphatic-CH), 1662 (C=O), 1609 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.42-7.38 (m, 11H, Ar-H), 6.17 (s, 1H, C-H), 2.86 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 166.13, 162.39, 148.65, 146.78, 145.08, 140.52, 130.42, 130.22, 129.35, 128.78, 126.11, 120.52, 118.20, 104.34, 16.42; EIMS: 401 [M+]; Elemental analysis: Calcd. (found) % for $C_{21}H_{15}N_5O_4$; C, 62.84 (62.81); H, 3.77 (3.79); N, 17.45 (17.49).

4-(4-Bromophenyl)-3-methyl-1-phenylpyrazolo[3′,4′:3,4]pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (7e): m.p.: 144-146 ºC; yield: 85%; IR (KBr, ν_{max}, cm^{-1}): 3119 (Ar-CH), 2961 (aliphatic-CH), 1678 (C=O), 1622 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.30-7.24 (m, 11H, Ar-H), 6.24 (s, 1H, C-H), 2.69 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 169.82, 162.76, 147.34, 145.12, 144.64, 139.50, 131.46, 129.71, 127.60, 126.46, 119.39, 118.33, 100.87, 15.03; EIMS: 434 [M+2]; Elemental analysis: Calcd. (found) % for $C_{21}H_{15}BrN_4O_2$; C, 57.95 (57.99); H, 3.47 (3.51); N, 12.87 (12.90).

4-(4-Hydroxyphenyl)-3-methyl-1-phenylpyrazolo[3′,4′:3,4]pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (7f): m.p.: 149-151 ºC; yield: 82%; IR (KBr, ν_{max}, cm^{-1}): 3080 (Ar-CH), 2956 (aliphatic-CH), 1659 (C=O), 1600 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.22-7.13 (m, 11H, Ar-H), 5.89 (s, 1H, C-H), 2.82 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 166.79, 160.51, 145.83, 143.72, 142.34, 137.65, 130.18, 128.67, 126.40, 122.98, 118.58, 116.03, 99.71, 11.96; EIMS: 372 [M+]; Elemental analysis: Calcd. (found) % for $C_{21}H_{16}N_4O_3$; C, 67.73 (67.76); H, 4.33 (4.36); N, 15.05 (15.01).

4-(3-Bromophenyl)-3-methyl-1-phenylpyrazolo[3′,4′:3,4]pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (7g): m.p.: 153-155 ºC; yield: 86%; IR (KBr, ν_{max}, cm^{-1}): 3091 (Ar-CH), 2969 (aliphatic-CH), 1668 (C=O), 1616 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.41-7.38 (m, 11H, Ar-H), 6.31 (s, 1H, C-H), 2.72 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 170.36, 164.45, 149.75, 147.59, 146.30, 140.12, 133.78, 131.23, 130.48, 129.80, 128.62, 126.24, 120.57, 118.49, 104.07, 17.68; EIMS: 434 [M+2]; Elemental analysis: Calcd. (found) % for $C_{21}H_{15}BrN_4O_2$; C, 57.95 (57.91); H, 3.47 (3.44); N, 12.87 (12.85).

4-(4-Chlorophenyl)-3-methyl-1-phenyl-7,8-dihydropyrazolo[3′,4′:3,4]pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (8a): m.p.: 161-163 ºC; yield: 86%; IR (KBr, ν_{max}, cm^{-1}): 3082 (Ar-CH), 2974 (aliphatic-CH), 1661 (C=O), 1607 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 7.21-7.87 (m, 9H, Ar-H), 4.91 (s, 1H, C-H), 2.52 (t, 2H, CH_2), 2.24-2.33 (t, 2H, CH_2), 1.61 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 160.62, 156.84, 146.19, 141.23, 137.35, 130.52, 130.08, 129.13, 128.89, 127.99, 125.57, 120.52, 104.39, 32.50, 11.63; EIMS: 392 [M+]; Elemental analysis: Calcd. (found) % for $C_{21}H_{17}ClN_4O_2$; C, 64.21 (64.24); H, 4.36 (4.33); N, 14.26 (14.25).

4-(4-Fluorophenyl)-3-methyl-1-phenyl-7,8-dihydropyrazolo[3′,4′:3,4]pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (8b): m.p.: 153-155 ºC; yield: 84%; IR (KBr, ν_{max}, cm^{-1}): 3046 (Ar-CH), 2969 (aliphatic-CH), 1668 (C=O), 1621 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 7.37-7.55 (m, 9H, Ar-H), 5.23 (S, 1H, C-H), 2.39-2.05 (m, 4H, CH_2), 1.87 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 167.25, 163.66, 158.35, 148.42, 145.81, 140.62, 138.26, 130.34, 129.55, 128.07, 126.36, 124.13, 118.48, 94.73, 29.57, 13.14; EIMS: 376 [M+]; Elemental analysis: Calcd. (found) % for $C_{21}H_{17}N_4O_2F$; C, 67.01 (67.03); H, 4.55 (4.51); N, 14.89 (14.91).

3-Methyl-4-(4-nitrophenyl)-1-phenyl-7,8-dihydropyrazolo[3′,4′:3,4]pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (8c): m.p.: 168-170 ºC; yield: 88%; IR (KBr, ν_{max}, cm^{-1}): 3112 (Ar-CH), 2998 (aliphatic-CH), 1678 (C=O), 1619 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.21-7.69 (m, 9H, Ar-H), 6.16 (S, 1H, C-H), 2.61-2.49 (m, 4H, CH_2), 1.92 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 170.36, 167.27, 160.46, 151.78, 149.96, 142.07, 140.27, 130.95, 129.14, 128.82, 127.67, 119.88, 103.43, 31.37, 18.56; EIMS: 403 [M+]; Elemental analysis: Calcd. (found) % for $C_{21}H_{17}N_5O_4$; C, 62.53 (62.55); H, 4.25 (4.27); N, 17.36 (17.39).

3-Methyl-4-(3-nitrophenyl)-1-phenyl-7,8-dihydropyrazolo[3′,4′:3,4]pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (8d): m.p.: 160-162 ºC; yield: 90%; IR (KBr, ν_{max}, cm^{-1}): 3083 (Ar-CH), 2972 (aliphatic-CH), 1666 (C=O), 1597 (C=N);

^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.34-7.82 (m, 9H, Ar-H), 6.28 (s, 1H, C-H), 2.44-2.31 (m, 4H, CH_2), 1.79 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 167.75, 164.86, 150.91, 149.21, 148.33, 146.57, 144.75, 141.39, 133.42, 128.67, 126.38, 124.18, 101.54, 28.71, 16.34; EIMS: 403 [M+]; Elemental analysis: Calcd. (found) % for $C_{21}H_{17}N_5O_4$; C, 62.53 (62.49); H, 4.25 (4.21); N, 17.36 (17.33).

4-(4-Bromophenyl)-3-methyl-1-phenyl-7,8-dihydropyrazolo[3′,4′:3,4]pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (8e): m.p.: 157-159 ºC; yield: 86%; IR (KBr, ν_{max}, cm^{-1}): 3081 (Ar-CH), 2990 (aliphatic-CH), 1680 (C=O), 1625 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 7.98-7.84 (m, 9H, Ar-H), 5.99 (S, 1H, C-H), 2.84-2.78 (m, 4H, CH_2), 1.84 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 166.87, 163.76, 148.14, 146.36, 142.48, 132.57, 129.69, 127.18, 125.43, 121.26, 102.52, 25.73, 11.98; EIMS: 436 [M+]; Elemental analysis: Calcd. (found) % for $C_{21}H_{17}BrN_4O_2$; C, 57.68 (57.66); H, 3.92 (3.95); N, 12.81 (12.84).

4-(4-Hydroxyphenyl)-3-methyl-1-phenyl-7,8-dihydropyrazolo[3′,4′:3,4]pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (8f): m.p.: 172-174 ºC; yield: 81%; IR (KBr, ν_{max}, cm^{-1}): 3065 (Ar-CH), 2971 (aliphatic-CH), 1662 (C=O), 1614 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.32-7.94 (m, 9H, Ar-H), 6.23 (S, 1H, C-H), 2.76-2.65 (m, 4H, CH_2), 1.96 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 169.19, 166.34, 155.28, 149.72, 147.84, 140.38, 136.57, 129.24, 128.96, 127.68, 126.25, 124.17, 97.68, 28.29, 12.76; EIMS: 374 [M+]; Elemental analysis: Calcd. (found) % for $C_{21}H_{18}N_4O_3$; C, 67.37 (67.40); H, 4.85 (4.88); N, 14.96 (14.99).

4-(3-Bromophenyl)-3-methyl-1-phenyl-7,8-dihydropyrazolo[3′,4′:3,4]pyrazolo[1,2-*a*]pyridazine-6,9(1*H*,4*H*)-dione (8g): m.p.: 161-163 ºC; yield: 85%; IR (KBr, ν_{max}, cm^{-1}): 3088 (Ar-CH), 2994 (aliphatic-CH), 1673 (C=O), 1627 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.11-7.62 (m, 9H, Ar-H), 6.18 (S, 1H, C-H), 2.53-2.46 (m, 4H, CH_2), 1.79 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 165.78, 162.52, 148.17, 145.46, 143.87, 140.58, 132.13, 128.97, 126.87, 122.27, 103.14, 25.68, 15.13; EIMS: 437 [M+]; Elemental analysis: Calcd. (found) % for $C_{21}H_{17}BrN_4O_2$; C, 57.68 (57.70); H, 3.92 (3.90); N, 12.81 (12.79).

4-(4-Chlorophenyl)-3-methyl-1-phenylpyrazolo[3′,4′:3,4]pyrazolo[1,2-*b*]phthalazine-6,11(1*H*,4*H*)-dione (9a): m.p.: 173-175 ºC; yield: 86%; IR (KBr, ν_{max}, cm^{-1}): 3123 (Ar-CH), 2977 (aliphatic-CH), 1660 (C=O), 1607 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 7.89-7.20 (m, 13H, Ar-H), 4.92 (s, 1H, C-H), 1.52 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 161.02, 146.59, 145.71, 132.55, 131.81, 130.96, 128.41, 126.39, 126.23, 108.26, 12.91; EIMS: 440 [M+]; Elemental analysis: Calcd. (found) % for $C_{25}H_{17}N_4O_2Cl$; C, 68.11 (68.15); H, 3.89 (3.85); N, 12.71 (12.75).

4-(4-Fluorophenyl)-3-methyl-1-phenylpyrazolo[3′,4′:3,4]pyrazolo[1,2-*b*]phthalazine-6,11(1*H*,4*H*)-dione (9b): m.p.: 147-149 ºC; yield: 83%; IR (KBr, ν_{max}, cm^{-1}): 3067 (Ar-CH), 2951 (aliphatic-CH), 1661 (C=O), 1627 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 7.97-7.24 (m, 13H, Ar-H), 5.49 (s, 1H, C-H), 1.64 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 163.54, 158.35, 148.74, 146.61, 140.24, 138.27, 133.34, 130.46, 129.51, 128.73, 127.57, 126.40, 118.22, 102.31, 15.27; EIMS: 424 [M+]; Elemental analysis: Calcd. (found) % for $C_{25}H_{17}FN_4O_2$; C, 70.75 (70.79); H, 4.04 (4.07); N, 13.20 (13.22).

3-Methyl-4-(4-nitrophenyl)-1-phenylpyrazolo[3′,4′:3,4]pyrazolo[1,2-b]phthalazine-6,11(1*H*,4*H*)-dione (9c): m.p.: 166-168 ºC; yield: 87%; IR (KBr, ν_{max}, cm^{-1}): 3119 (Ar-CH), 2989 (aliphatic-CH), 1674 (C=O), 1612 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.21-7.48 (m, 13H, Ar-H), 5.87 (s, 1H, C-H), 1.76 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 165.77, 161.82, 149.21, 148.34, 145.49, 139.84, 132.91, 129.62, 128.24, 127.38, 126.76, 125.83, 101.67, 13.97; EIMS: 451 [M+]; Elemental analysis: Calcd. (found) % for $C_{25}H_{17}N_5O_4$; C, 66.51 (66.55); H, 3.80 (3.84); N, 15.51 (15.53).

3-Methyl-4-(3-nitrophenyl)-1-phenylpyrazolo[3′,4′:3,4]pyrazolo[1,2-*b*]phthalazine-6,11(1*H*,4*H*)-dione (9d): m.p.: 155-157 ºC; yield: 90%; IR (KBr, ν_{max}, cm^{-1}): 3098 (Ar-CH), 2990 (aliphatic-CH), 1679 (C=O), 1609 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.47-7.62 (m, 13H, Ar-H), 5.87 (s, 1H, C-H), 1.63 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 162.36, 158.41, 148.74, 147.94, 146.59, 145.18, 140.80, 133.15, 132.27, 129.45, 128.87, 127.73, 126.39, 125.28, 122.04, 103.52, 11.63; EIMS: 451 [M+]; Elemental analysis: Calcd. (found) % for $C_{25}H_{17}N_5O_4$; C, 66.51 (66.53); H, 3.80 (3.82); N, 15.51 (15.54).

4-(4-Bromophenyl)-3-methyl-1-phenylpyrazolo[3′,4′:3,4]pyrazolo[1,2-*b*]phthalazine-6,11(1*H*,4*H*)-dione (9e): m.p.: 154-156 ºC; yield: 85%; IR (KBr, ν_{max}, cm^{-1}): 3046 (Ar-CH), 2961 (aliphatic-CH), 1658 (C=O), 1594 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.17-7.38 (m, 13H, Ar-H), 5.49 (s, 1H, C-H), 1.73 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 160.78, 155.89, 146.13, 143.46, 141.52, 139.26, 132.84, 130.48, 128.11, 126.74, 124.31, 122.78, 101.12, 12.63; EIMS: 484 [M+]; Elemental analysis: Calcd. (found) % for $C_{25}H_{17}BrN_4O_2$; C, 61.87 (61.84); H, 3.53 (3.56); N, 11.54 (11.57).

4-(4-Hydroxyphenyl)-3-methyl-1-phenylpyrazolo[3′,4′:3,4]pyrazolo[1,2-*b*]phthalazine-6,11(1*H*,4*H*)-dione (9f): m.p.: 168-170 ºC; yield: 82%; IR (KBr, ν_{max}, cm^{-1}): 3055 (Ar-CH), 2989 (aliphatic-CH), 1672 (C=O), 1624 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 7.84-7.16 (m, 13H, Ar-H), 5.29 (s, 1H, C-H), 1.62 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 167.85, 163.15, 160.42, 150.43, 148.17, 141.29, 134.37, 132.92, 130.84, 129.41, 128.56, 127.38, 126.98, 123.70, 120.23, 103.49, 13.72; EIMS: 422 [M+]; Elemental analysis: Calcd. (found) % for $C_{25}H_{18}N_4O_3$; C, 71.08 (71.11); H, 4.29 (4.32); N, 13.26 (13.29).

4-(3-Bromophenyl)-3-methyl-1-phenylpyrazolo[3′,4′:3,4]pyrazolo[1,2-*b*]phthalazine-6,11(1*H*,4*H*)-dione (9g): m.p.: 151-153 ºC; yield: 84%; IR (KBr, ν_{max}, cm^{-1}): 3063 (Ar-CH), 2979 (aliphatic-CH), 1668 (C=O), 1615 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ ppm): 8.26-7.30 (m, 13H, Ar-H), 5.57 (s, 1H, C-H), 1.69 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ ppm): 164.19, 158.26, 147.86, 145.74, 143.06, 140.81, 133.58, 132.27, 129.67, 128.48, 127.35, 126.13, 124.31, 123.51, 122.96, 100.75, 15.22; EIMS: 484 [M+]; Elemental analysis: Calcd. (found) % for $C_{25}H_{17}N_4O_2Br$; C, 61.87 (61.85); H, 3.53 (3.50); N, 11.54 (11.56).

***In vitro* anti-inflammatory assay:** The COX- inhibition assay was performed as per the assay protocol instructions of Colorimetric COX (ovine) inhibitor Screening Assay Kit, Cayman Chemical Company, MI, USA. The reaction mixture of 100% initial activity wells contained 160 μL of assay buffer, 150 μL of HAEM and 10 μL of COX enzyme solutions. While the reaction mixture of inhibitor wells was comprised of 150 μL of assay buffer, 10 μL of HAEM and 10 μL of either enzyme COX, 10 μL of test samples (1 mM). The plates were carefully shaken for 5 sec and were incubated for 5 min at 25 ºC. After 5 min incubation, 20 μL of colorimetric substrate solution was added to all the wells, followed by the addition of 20 μL of arachidonic acid to all the wells. The plates were shaken gently for few seconds and again incubated for 5 min at 25 ºC. The absorbance of all the wells was read at 590 nm using Thermo make Automatic Ex-Microplate Reader (M 51118170). Aspirin (1 mM) were tested simultaneously as standard inhibitors. The COX- inhibition activity (%) was calculated using following formula:

$$\text{COX inhibition activity (\%)} = 1 - \frac{T}{C} \times 100$$

where T is the absorbance of inhibitor well at 590 nM, C is the absorbance of 100% initial activity without inhibitor well at 590 nM.

RESULTS AND DISCUSSION

In this work we reported an efficient, simple and green reaction route for the one-pot synthesis of 4-(substituted phenyl)-3-methyl-1-phenylpyrazolo[3′,4′:3,4]pyrazolo[1,2-*a*]-pyridazine-6,9(1*H*,4*H*)-dione derivatives (**7a-g**) *via* four components coupling of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1**), substituted aldehyde (**2**), hydrazine hydrate (**3**) and maleic/fumaric/phthalic anhydride (**4/5/6**) using PEG-400 as green reaction media with continuous stirring at 70-80 ºC for 3-4 h (**Scheme-I**).

Initially, the four-components reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1**) with equimolar quantity of substituted aldehyde (**2**), hydrazine hydrate (**3**) and maleic anhydride (**4**) was used as model reaction and the reaction was monitored in the absence of solvent and catalyst at room temperature. The reaction did not go to completion even after 24 h of stirring. The same reaction was examined at elevated temperature, the reaction takes place in the forward direction but the yield of the product obtained was low (Table-1, entry 2). Inspired by these results, the model reaction was carried out in the presence of solvent such as ethanol, acetonitrile, THF and toluene. The reaction proceeds successfully but it reaches to about 30-35% yield of the product at higher temperature (Table-1, entry 3-6). In order to modify the reaction path in the light of the Green Chemistry, PEG-400 was used as green reaction media due to its advantages over conventional organic solvents. The results obtained using PEG-400 was superior as compared to the organic solvents (Table-1, entry 7).

With these optimized reaction conditions, the generality of the reaction was tested by using various substituted aldehydes (**2a-g**) and acid anhydrides (**4-6**) such as maleic anhydride (**4**), Phthalic anhydride (**5**) and succinic anhydride (**6**) in the PEG-400 at 70-80 ºC. It was observed that aromatic aldehydes having both electron withdrawing and electron-donating groups participated in the reaction and there was no significant difference in the product yield. However, electron withdrawing substituent's had shorter reaction time. Moreover, use of different acid anhydrides in the reaction has no significant effect in the product yield.

TABLE-1
INFLUENCE OF THE SOLVENT ON THE SYNTHESIS OF (**7d**)

Entry	Solvent	Temp. (ºC)	Time (h)[a]	Yield (%)[b]
1	No solvent	RT	24	0
2	No solvent	>80	>10	34
3	Ethanol	>80	10	62
4	Acetonotrile	80	10	60
5	THF	80	9	65
6	Toluene	>80	8	62
7	PEG-400	80	3	90

[a]Reaction progress monitored by TLC; [b]Yields refer to isolated yield.

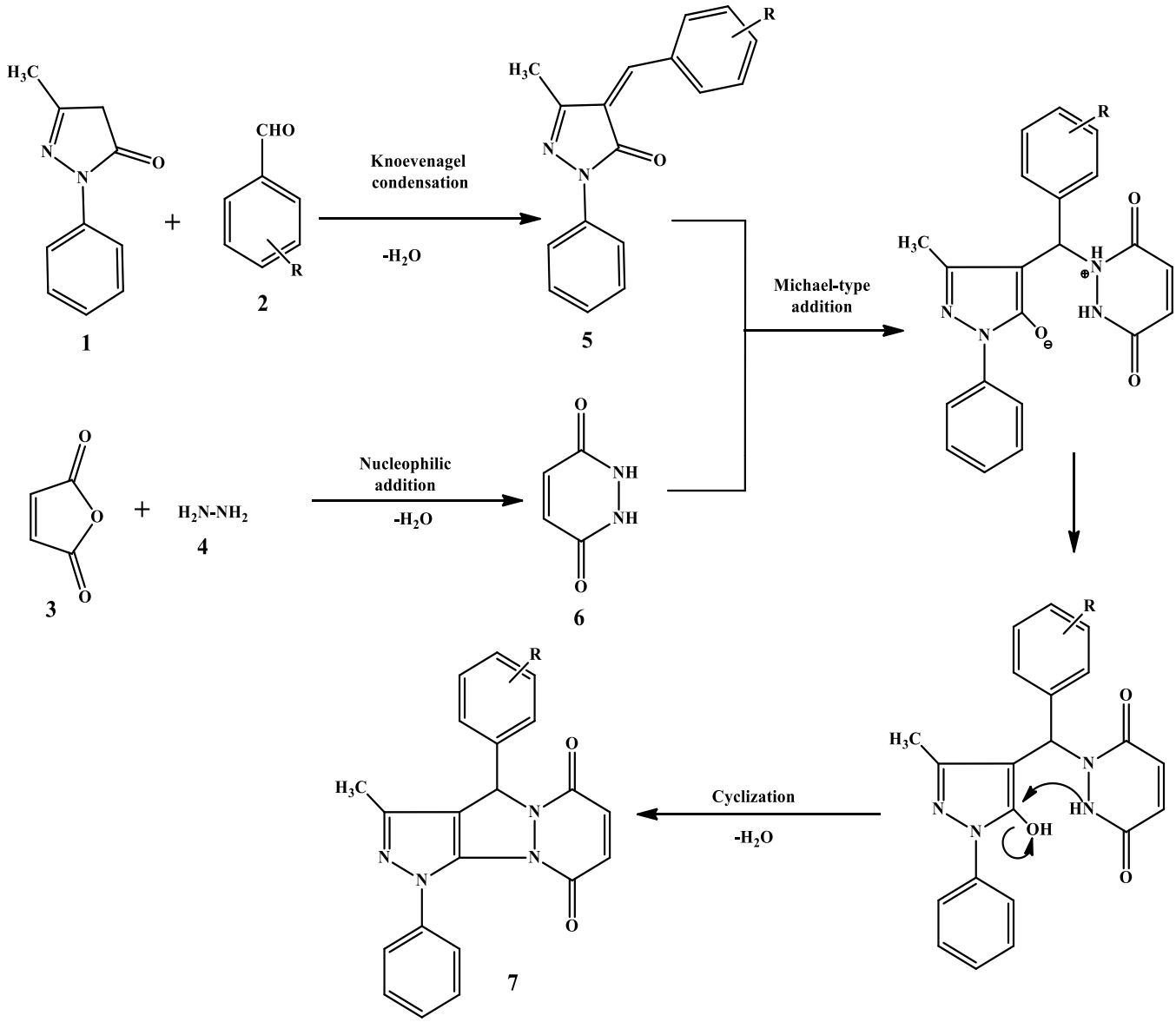
The structures of all the synthesized compounds were established on the basis of IR, NMR and mass spectral analysis. The IR spectrum of compound **7b** shown a band at 1670 cm^{-1} for the α,β-unsaturated carbonyl compound, a band at 1608 cm^{-1} due to presence of C=N. The ^1H NMR of compound **7b** showed characteristic singlet for CH_3 of pyrazole at δ 2.93 ppm, the formation of product was further confirmed due to presence of C-H proton at δ 5.91 ppm and all aromatic protons were observed in their respective aromatic region. The ^{13}C NMR of compound **7b** showed the peaks at δ 13.5 ppm for CH_3 of pyrazole, a peak at δ 108.2 ppm for C-H carbon and δ 167.48 ppm for C=O carbon. Mass spectra of all the compounds gave expected M^+ peak corresponding to their molecular mass. The natural chlorine and bromine ratio were observed whenever present in the compounds.

The mechanism suggested for the given reaction is presented in **Scheme-II**. The reaction occurs *via* initial formation of α,β-unsaturated ketone (**5**) by standard Knoevenagel condensation of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1**) and aldehyde (**2**). At the same time formation of an intermediate **6** formed by nucleophilic addition of hydrazine hydrate to maleic anhydride followed by dehydration. Finally, Michael type addition of compounds **5** and **6** followed by cyclization affords the corresponding products.

Anti-inflammatory activity: The synthesized compounds **7a-g**, **8a-g** and **9a-g** were primarily screened for their anti-inflammatory potential. The results of anti-inflammatory screening were determined by *in vitro* COX-I and COX-II assays. Compounds under investigation have inhibited COX-II preferentially and are more selective towards COX-II rather than COX-I. The synthesized compounds are subjected to COX-II inhibition study and results are shown in Fig. 1. The findings revealed that compounds **7c**, **8d** and **9c** showed significant anti-inflammatory activity, with COX-II inhibition ranging from 61.91% to 66.51%. Compounds **7a**, **7d** and **8c** exhibited excellent anti-inflammatory activity, with COX-II inhibition ranging from 52.87% to 55.47%, while the remaining compounds demonstrated good to moderate activity.

Conclusion

In summary, some new pyridazine and phthalazinedione derivatives (**7a-g**, **8a-g** and **9a-g**) containing pyrazole moiety



Scheme-II: Possible mechanism of compounds (**7a-g**)

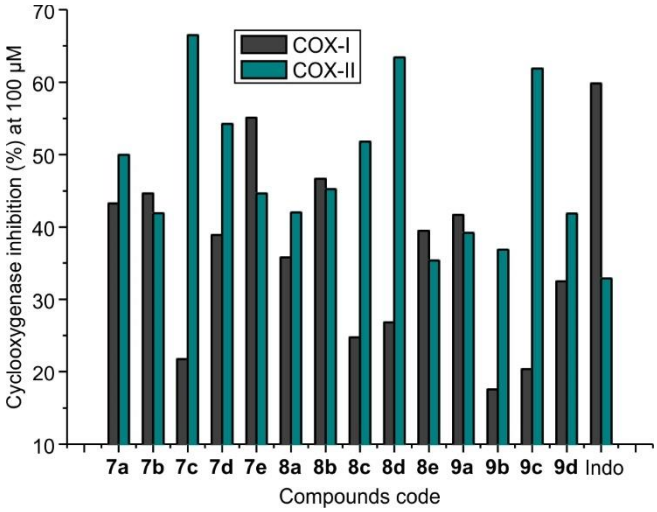


Fig. 1. Anti-inflammatory screening of pyridazine and phthalazinedione derivatives (**7a-g**, **8a-g** and **9a-g**)

were synthesized by one-pot, four-components condensation reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1**), substituted aldehyde (**2**), hydrazine hydrate (**3**) and acid **(**maleic/phthalic/succinic) anhydride (**4-6**) under catalyst-free conditions using PEG-400 as a green reaction media. This protocol offers several key advantages, including a straightforward procedure, clean reaction profile, high yields, simple purification and a rapid reaction rate under ambient conditions. Preliminary anti-inflammatory screening of the synthesized compounds revealed that several exhibit promising activity, underscoring their potential and supporting further exploration in medicinal chemistry

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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