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Synthesis of Novel Pyrazole and Dihydropyrazoles Derivatives as Potential Anti-inflammatory and Analgesic Agents

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Novel dihydropyrazole **5-8**, **10** and pyrazole derivatives **12**, **14**, **15**, **17** were synthesized. The structures of the newly synthesized compounds were elucidated by spectral and elemental analyses. The anti-inflammatory activity of all new compounds was evaluated using the carrageenan-induced rat paw edema test using indomethacin and celecoxib as reference drugs. The most active derivatives as anti-inflammatory agents were accordingly tested for their analgesic activity using the *p*-benzoquinone-induced writhing method in mice and results revealed that these compounds had also good analgesic activity. The ulcerogenic liability of the selected compounds was also evaluated. Results showed that the selected derivatives had anti-inflammatory activity comparable to or slightly lower than the reference drugs, reaching about 82% inhibition with a considerable gastric safety profile.

Key words: Pyrazole, Dihydropyrazole, Anti-inflammatory, Analgesic

INTRODUCTION

Inflammation is the response of the tissue to injury, which is oftenly caused by invading pathogens. Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leucocytes especially granulocytes from the blood into the injured tissue (Jachak, 2006). This process is mediated by the release of histamine, bradykinin and cytokines (inflammatory mediators) such as interleukine-1 (IL-1) and tumor necrosis factor-α (TNF-α) (Black, 2005; Jachak, 2006; Lacerda et al., 2009). These mediators are thought to increase the release of fatty acid precursors of prostaglandins (PGs) and therefore increase the rate of prostaglandin synthesis via the induction of a wide variety of responses including the up regulation of cycloxygenases (COX). COX is the rate limiting enzyme in the arachidonic acid metabolism through catalyzing the biosynthesis of free arachidonic acid to eicosanoids that include prostanoids (prostaglandins, prostacyclins and thromboxanes) and leukotrienes (Jachak, 2006). It exists in two isoforms; namely, COX-1 and COX-2, the constitutive and inducible forms, respectively (Szabó et al., 2008).

Epidemiologic studies support that chronic inflammatory diseases are frequently associated with increased risk of cancers (Coussens and Werb, 2002; Macarthur et al., 2004; Philip et al., 2004), and that the development of cancer from inflammation might be a process driven by inflammatory cells as well as a variety of mediators, including cytokines, chemokines, and enzymes, which altogether establish an inflammatory microenvironment (Coussens and Werb, 2002). Consequently, finding new anti-inflammatory agents represents a concrete strategy in fighting not only different inflammatory diseases but also cancer.

Non-steroidal anti-inflammatory drugs (NSAIDs) are recognized as an important class of therapeutic agents

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for the treatment of acute and chronic inflammation, pain and fever (Kadar, 1998; Laufer and Luik, 2010). Nevertheless, NSAIDs are the most widely used drugs and their long term clinical use is associated with several side effects such as gastrointestinal mucosal damage, bleeding and renal toxicity (Kadar, 1998).

Thus, great efforts had been employed to discover new classes of anti-inflammatory agents with high gastric mucosal tolerance. Interest has been generated in the chemistry and the biological activity particularly the anti-inflammatory potency of pyrazole derivatives as a potential source of new anti-inflammatory and analgesic agents with lower gastrointestinal mucosal toxicity (Satyanarayana and Rao, 1995; Penning et al., 1997; Barsoum et al., 2006; Gökhan-Kelekçi et al., 2007; Szabó et al., 2008). Accordingly, the well known agents containing the pyrazole scaffold such as phenybutazone **I** (Kadar, 1998), various coxibs **IIa-d** (Penning et al., 1997; Szabó et al., 2008), **IIIa**,**b** (Barsoum et al., 2006; Gökhan-Kelekçi et al., 2007), **IV** (Satyanarayana and Rao, 1995), morazone **V** (Reynold, 1993), and famorofazone **VI** (Reynold, 1993) were reported as anti-inflammatory agents with lower GIT toxicity (Fig. 1). In this respect, we aim to design, synthesize and biologically evaluate a number of novel pyrazole derivatives having the general formula A, B, and C (Fig. 2) hoping that they might have potential anti-inflammatory, analgesic activities and devoid of the gastrointestinal side effects.

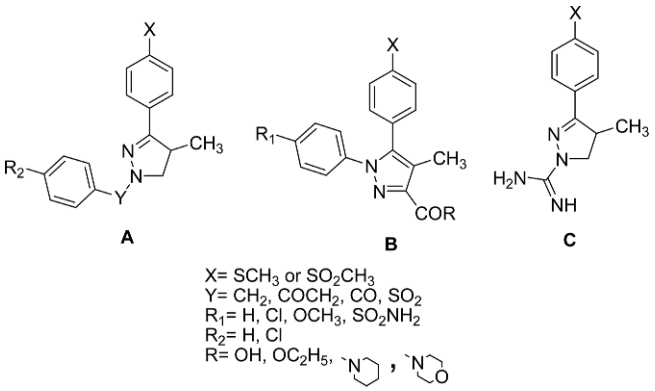


Fig. 2. General structures of the target compounds.

MATERIALS AND METHODS

Chemistry

All the starting materials were purchased from VWR International Merck, Germany or from Sigma-Aldrich and used without further purification. All the reactions were followed by TLC using silica gel F254 plates (Merck) using chloroform: ethyl acetate 6: 4 as an eluting system and were visualized by UV-lamp. Melting points are uncorrected and were carried out

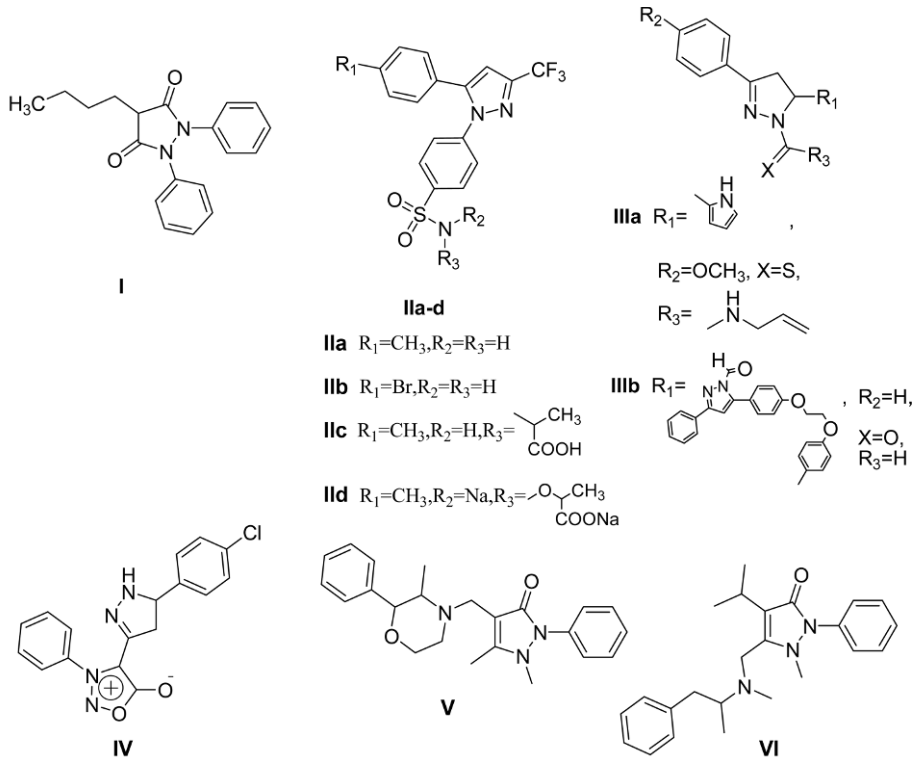


Fig. 1. Structures of pyrazole compounds with anti-inflammatory activity.

by open capillary tube method using IA 9100MK-Digital Melting Point Apparatus. IR spectra were made on Bruker Vector 22 or Jasco FTIR plus 460 and were expressed in wave number (cm^{-1}) using potassium bromide disc. Proton magnetic resonance ^{1}H-NMR and carbon magnetic resonance ^{13}C-NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. The spectra were run at 300 MHz in the specified solvent. Chemical shifts were quoted in δ units, were related to that of the solvents. *J* values are given in Hz. As for the proton magnetic resonance, D_2O was carried out for NH and OH exchangeable protons. Mass spectra were recorded on Finnigan MAT, SSQ 7000 (70 eV) mass spectrometer. All mass spectra were recorded in EI mode unless otherwise stated. Elemental microanalyses were carried out using Heraew and Vario EL III (elementar), CHNS analyzer at the Microanalytical Center, Cairo University. IUPAC chemical nomenclature was assigned using ACDLABS ChemSketch version 12.0. Compounds **2a** (Humphries and Finefield, 2006), **2b** (Burton and Hu, 1948), **9** (Grosscurt et al., 1979; Alberto et al., 1988) and **13** (Organ and Mayer, 2003) were prepared according to the reported method.

General method for preparation of compounds 3a,b

Piperidine (1.2 mL, 12.1 mmol), glacial acetic acid (1.2 mL, 20.8 mmol) and formaline (4 mL, 37% aqueous solution, 53.2 mmol), were successively added to a magnetically stirred solution of the previously prepared propiophenones **2a**,**b** (12.8 mmol) in methanol (50 mL). The reaction mixture was left to stir under reflux for 12 h and then concentrated under *vaccum*. The residue was triturated with water and then extracted with methylene chloride (2 × 30 mL). The organic layer was separated, washed with water (3 × 50 mL), dried over Na_2SO_4, filtered, and evaporated. The product was dried to give yellow oil.

2-Methyl-1-[4-(methylsulfanyl)phenyl]prop-2-en-1-one (3a)

Yellow oil, yield 81%, IR υ_{max}/cm^{-1}: 3100, 3060 (CH aromatic), 2984, 2938, 2885, 2838, 2788 (CH aliphatic), 1666 (C=O). ^{1}H-NMR ($CDCl_3$): δ 2.06 (s, 3H, $C\underline{H}_3$), 2.52 (s, 3H, $SC\underline{H}_3$), 5.56 (d, 1H, $CC\underline{H}_2$, *J* = 1.5 Hz), 5.84 (d, 1H, $CC\underline{H}_2$, *J* = 1.5 Hz), 7.24-7.99 (m, 4H, aromatic H). MS, *m/z* (%): M^+ 192 (0.41%), 98 (100%). Anal. Calcd. for $C_{11}H_{12}OS$ (192.06): C, 68.71; H, 6.29. Found: C, 68.50; H, 6.55.

2-Methyl-1-[4-(methylsulfonyl)phenyl]prop-2-en-1-one (3b)

Yellow oil, yield 70%, IR υ_{max}/cm^{-1}: 3040, 3030 (CH aromatic), 2931, 2856 (CH aliphatic), 1686 (C=O), 1311, 1151 (SO_2). ^{1}H-NMR ($CDCl_3$): δ 2.03 (s, 3H, $C\underline{H}_3$), 3.00 (s, 3H, $SO_2C\underline{H}_3$), 5.25 (d, 1H, $CC\underline{H}_2$, *J* = 1.5 Hz), 5.34 (d, 1H, $CC\underline{H}_2$, *J* = 1.5 Hz), 7.10-8.22 (m, 4H, aromatic H). MS, *m/z* (%): M^+ 224 (100%). Anal. Calcd. for $C_{11}H_{12}O_3S$ (224.05): C, 58.91; H, 5.39. Found: C, 58.40; H, 5.33.

General method for preparation of compounds 4a,b

A solution of the previously synthesized enones **3a**,**b** (5.2 mmol), hydrazine hydrate (24.6 mL) in absolute ethanol (20 mL) was refluxed for 3 h under dry nitrogen. After cooling of the reaction mixture to room temperature, it was concentrated to half its volume and ice water was added to the mixture. For compound **4a**, the precipitate formed was dried off, washed with water (2 × 30 mL) and dried to give white needle crystals. As for compound **4b**, extraction was performed with methylene chloride (3 × 50 mL) and the organic layer was dried over anhydrous sodium sulfate to give the products **4a**,**b**, respectively.

4-Methyl-3-[4-(methylsulfanyl)phenyl]-4,5-dihydro-1*H*-pyrazole (4a)

White needle crystals, m.p. 110-112ºC, yield 75%, IR υ_{max}/cm^{-1}: 3341 (NH), 3065 (CH aromatic), 2966, 2922, 2862 (CH aliphatic). ^{1}H-NMR ($CDCl_3$): δ 1.09 (d, 3H, $CHC\underline{H}_3$, *J* = 6.6 Hz), 1.12-1.17 (m, 1H, $C\underline{H}CH_3$), 2.51 (s, 3H, $SC\underline{H}_3$), 2.56 (d, 2H, $CHC\underline{H}_2$, *J* = 6.9 Hz), 5.39 (s, 1H, pyrazole NH, (D_2O exch.)), 7.21-7.85 (m, 4H, aromatic H). ^{13}C-NMR ($CDCl_3$): 9.70 ($CH\underline{C}H_3$), 14.31 (SCH_3), 18.13 ($\underline{C}HCH_3$), 21.58 ($CH\underline{C}H_2$), 125.76, 126.21, 127.09, 127.77, 135.08 and 138.44 (C aromatic), 150.94 (C=N olefinic). MS, *m/z* (%): M^+ 206 (90), 205 (100%). Anal. Calcd. for $C_{11}H_{14}N_2S$ (206.09): C, 64.04; H, 6.84; N, 13.58. Found: C, 64.09; H, 6.64; N, 13.80.

4-Methyl-3-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1*H*-pyrazole (4b)

Yellow oil, yield 61%, IR υ_{max}/cm^{-1}: 3354 (NH), 3061, 3003 (CH aromatic), 2966, 2927, 2872 (CH aliphatic), 1350, 1149 (SO_2). ^{1}H-NMR ($CDCl_3$): δ 1.05 (d, 3H, $CHC\underline{H}_3$, *J* = 6.6 Hz), 1.18-1.33 (m, 1H, $C\underline{H}CH_3$), 3.03 (s, 3H, $SO_2C\underline{H}_3$), 3.15 (d, 2H, $CHC\underline{H}_2$, *J* = 6.9 Hz), 5.25 (s, 1H, pyrazole NH, (D_2O exch.)), 7.26-8.11 (m, 4H, aromatic H). MS, *m/z* (%): M^+ 238 (100). Anal. Calcd. for $C_{11}H_{14}N_2O_2S$ (238.08): C, 55.44; H, 5.92; N, 11.76. Found: C, 55.70; H, 5.69; N, 11.48.

General method for preparation of compounds 5a-d

The appropriate benzyl chloride (4.9 mmol) was

added to a stirred solution of 3,4-disubstituted 4,5-dihydro-1*H*-pyrazole **4a**,**b** (4.9 mmol) in absolute ethanol (80 mL) and anhydrous potassium carbonate (0.25 gm, 1.76 mmol). The reaction mixture was heated under reflux for 15 h on a water bath. The solvent was evaporated under reduced pressure and then extracted with methylene chloride (2 × 30 mL). The organic layer was washed with water (2 × 30 mL) and dried over anhydrous sodium sulfate to give yellow oil.

1-Benzyl-4-methyl-3-[4-(methylsulfanyl)phenyl]-4,5-dihydro-1*H*-pyrazole (5a)

Yellow oil, yield 55%, IR υ_{max}/cm^{-1}: 3067, 3050, 3022 (CH aromatic), 2968, 2920, 2873 (CH aliphatic).^{1}H NMR ($CDCl_3$): δ 1.16 (d, 3H, CHC$\underline{H}_3$, *J* = 6.6 Hz), 1.18-1.29 (m, 1H, C$\underline{H}$CH$_3$), 2.50 (s, 3H, SC$\underline{H}_3$), 2.61 (d, 2H, CHC$\underline{H}_2$, *J* = 6.9 Hz), 2.70 (s, 2H, C$\underline{H}_2$), 7.21-7.95 (m, 9H, aromatic H). MS, *m/z* (%): M^+ 296 (41.5), 91 (100%). Anal. Calcd. for $C_{18}H_{20}N_2S$ (296.13): C, 72.93; H, 6.80; N, 9.45. Found: C, 73.06; H, 6.59; N, 9.69.

1-Benzyl-4-methyl-3-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1*H*-pyrazole (5b)

Yellow oil, yield 56%, IR υ_{max}/cm^{-1}: 3068 (CH aromatic), 2970, 2925 (CH aliphatic), 1303, 1147 (SO_2). ^{1}H-NMR ($CDCl_3$): δ 1.15 (d, 3H, CHC$\underline{H}_3$, *J* = 6.6 Hz), 1.20-1.34 (m, 1H, C$\underline{H}$CH$_3$), 2.62 (d, 2H, CHC$\underline{H}_2$, *J* = 6.9 Hz), 3.01 (s, 3H, $SO_2C\underline{H}_3$), 3.07 (s, 2H, C$\underline{H}_2$), 7.26-7.95 (m, 9H, aromatic H). MS, *m/z* (%): M^+ 328 (5.09), 91 (100%). Anal. Calcd. for $C_{18}H_{20}N_2O_2S$ (328.12): C, 65.83; H, 6.14; N, 8.53. Found: C, 65.60; H, 5.91; N, 8.19.

1-(4-Chlorobenzyl)-4-methyl-3-[4-(methylsulfanyl) phenyl]-4,5-dihydro-1*H*-pyrazole (5c)

Yellow oil, yield 43%, IR υ_{max}/cm^{-1}: 3090, 3070 (CH aromatic), 2928, 2850 (CH aliphatic), 1090 (Cl). ^{1}H NMR ($CDCl_3$): δ 1.19 (d, 3H, CHC$\underline{H}_3$, *J* = 6.6 Hz), 1.21-1.29 (m, 1H, C$\underline{H}$CH$_3$), 2.52 (s, 3H, SC$\underline{H}_3$), 2.55 (d, 2H, CHC$\underline{H}_2$, *J* = 6.9 Hz), 2.77 (s, 2H, C$\underline{H}_2$), 7.24-7.41 (m, 8H, aromatic H). MS, *m/z* (%): M^+ 330 (42.29), $[M+2]^+$ 332 (15.01), 98 (100%). Anal. Calcd. for $C_{18}H_{19}ClN_2S$ (330.87): C, 65.34; H, 5.79; N, 8.47. Found: C, 65.60; H, 5.49; N, 8.36.

1-(4-Chlorobenzyl)-4-methyl-3-[4-(methylsulfonyl) phenyl]-4,5-dihydro-1*H*-pyrazole (5d)

Yellow oil, yield 39.5%, IR υ_{max}/cm^{-1}: 3088, 3040 (CH aromatic), 2927, 2869 (CH aliphatic), 1350, 1145 (SO_2), 1089 (Cl). ^{1}H-NMR ($CDCl_3$): δ 1.21 (d, 3H, CHC$\underline{H}_3$, *J* = 6.6 Hz), 1.23-1.27 (m, 1H, C$\underline{H}$CH$_3$), 2.62 (d, 2H, CHC$\underline{H}_2$, *J* = 6.9 Hz), 3.05 (s, 3H, $SO_2C\underline{H}_3$), 3.11 (s, 2H, C$\underline{H}_2$), 7.27-8.01 (m, 8H, aromatic H). MS, *m/z* (%): M^+ 362 (40.82), $[M+2]^+$ 364 (12.63), 125 (100%). Anal. Calcd. for $C_{18}H_{19}ClN_2O_2S$ (362.09): C, 59.58; H, 5.28; N, 7.72. Found: C, 59.88; H, 5.49; N, 7.58.

General method for preparation of compounds 6a-d

The appropriate phenacyl bromide (4.9 mmol) was added to a stirred solution of 3,4-disubstituted 4,5-dihydro-1*H*-pyrazole **4a**,**b** (4.9 mmol) in absolute ethanol (80 mL) and anhydrous potassium carbonate (0.25 gm, 1.76 mmol). The reaction mixture was heated under reflux for 15 h on a water bath. The solvent was evaporated under reduced pressure and then extracted with methylene chloride (2 × 30 mL). The organic layer was washed with water (2 × 30 mL) and dried over anhydrous sodium sulfate to give yellow oil.

2-{4-Methyl-3-[4-(methylsulfanyl)phenyl]-4,5-dihydro-1*H*-pyrazol-1-yl}-1-phenylethanone (6a)

Yellow oil, yield 50%, IR υ_{max}/cm^{-1}: 3088, 3060 (CH aromatic), 2971, 2830 (CH aliphatic), 1692 (C=O). ^{1}H-NMR ($CDCl_3$): δ 1.18 (d, 3H, CHC$\underline{H}_3$, *J* = 6.6 Hz), 1.24-1.27 (m, 1H, C$\underline{H}$CH$_3$), 2.50 (s, 3H, SC$\underline{H}_3$), 2.61 (d, 2H, CHC$\underline{H}_2$, *J* = 6.9 Hz), 3.45 (s, 2H, COC$\underline{H}_2$), 7.26-8.01 (m, 9H, aromatic H). MS, *m/z* (%): $[M-1]^+$ 323, 105 (100%). Anal. Calcd. for $C_{19}H_{20}N_2OS$ (324.13): C, 70.34; H, 6.21; N, 8.63. Found: C, 70.25; H, 5.95; N, 8.28.

2-{4-Methyl-3-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1*H*-pyrazol-1-yl}-1-phenylethanone (6b)

Yellow oil, yield 51%, IR υ_{max}/cm^{-1}: 3080, 3040 (CH aromatic), 2971, 2830 (CH aliphatic), 1692 (C=O), 1306, 1148 (SO_2). ^{1}H NMR ($CDCl_3$): δ 1.17 (d, 3H, CHC$\underline{H}_3$, *J* = 6.6 Hz), 1.20-1.25 (m, 1H, C$\underline{H}$CH$_3$), 3.00 (s, 3H, $SO_2C\underline{H}_3$), 3.06 (d, 2H, CHC$\underline{H}_2$, *J* = 6.9 Hz), 3.42 (s, 2H, COC$\underline{H}_2$), 7.26-7.94 (m, 9H, aromatic H). Anal. Calcd. for $C_{19}H_{20}N_2O_3S$ (356.12): C, 64.02 ; H, 5.66; N, 7.86. Found: C, 64.16; H, 5.50; N, 7.66.

1-(4-Chlorophenyl)-2-{4-methyl-3-[4-(methylsulfanyl)phenyl]-4,5-dihydro-1*H*-pyrazol-1-yl}ethanone (6c)

Yellow oil, yield 51%, IR υ_{max}/cm^{-1}: 3066, 3050 (CH aromatic), 2971, 2928 (CH aliphatic), 1692 (C=O), 1091 (Cl). ^{1}H NMR ($CDCl_3$): δ 1.19 (d, 3H, CHC$\underline{H}_3$, *J* = 6.6 Hz), 1.22-1.34 (m, 1H, C$\underline{H}$CH$_3$), 2.50 (s, 3H, SC$\underline{H}_3$), 2.75 (d, 2H, CHC$\underline{H}_2$, *J* = 6.9 Hz), 3.14 (s, 2H, COC$\underline{H}_2$), 7.26-7.89 (m, 8H, aromatic H). MS, *m/z* (%): M^+ 358 (0.63), M+2 360 (0.23), 204 (100%). Anal. Calcd. for $C_{19}H_{19}ClN_2OS$ (358.08): C, 63.59; H, 5.34; N, 7.81. Found: C, 63.41; H, 5.53; N, 7.63.

1-(4-Chlorophenyl)-2-{4-methyl-3-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1*H*-pyrazol-1-yl}ethanone (6d)

Yellow oil, yield 48%, IR υ_{max}/cm^{-1}: 3088, 3040 (CH aromatic), 2971, 2928 (CH aliphatic), 1688 (C=O), 1344, 1146 (SO_2), 1011 (Cl). ^{1}H-NMR ($CDCl_3$): δ 1.18 (d, 3H, CHC$\underline{H}_3$, *J* = 6.6 Hz), 1.20-1.33 (m, 1H, C$\underline{H}$CH$_3$), 3.03 (s, 3H, $SO_2C\underline{H}_3$), 3.09 (d, 2H, CHC$\underline{H}_2$, *J* = 6.9 Hz), 3.98 (s, 2H, COC$\underline{H}_2$), 7.25-7.97 (m, 8H, aromatic H). MS, *m/z* (%): M+1 391 (13.89%), 139 (100%). Anal. Calcd. for $C_{19}H_{19}ClN_2O_3S$ (390.08): C, 58.38; H, 4.90; N, 7.17. Found: C, 58.58; H, 5.21; N, 7.34.

General method for preparation of compounds 7a-d

The appropriate benzoylchloride (4.9 mmol) was added to a stirred solution of 3,4-disubstituted 4,5-dihydro-1*H*-pyrazole **4a**, **b** (4.9 mmol) in absolute ethanol (80 mL) and anhydrous potassium carbonate (0.25 gm, 1.76 mmol). The reaction mixture was heated under reflux for 15 h on a water bath. The solvent was evaporated under reduced pressure and then extracted with methylene chloride (2 × 30 mL). The organic layer was washed with water (2 × 30 mL) and dried over anhydrous sodium sulfate to give yellow oil.

{4-Methyl-3-[4-(methylsulfanyl)phenyl]-4,5-dihydro-1*H*-pyrazol-1-yl}(phenyl)methanone (7a)

Yellow oil, yield 53%, IR υ_{max}/cm^{-1}: 3070, 3055 (CH aromatic), 2971, 2923 (CH aliphatic), 1687 (C=O). ^{1}H-NMR ($CDCl_3$): δ 1.18 (d, 3H, CHC$\underline{H}_3$, *J* = 6.6 Hz), 1.20-1.36 (m, 1H, C$\underline{H}$CH$_3$), 2.50 (s, 3H, SC$\underline{H}_3$), 3.44 (d, 2H, CHC$\underline{H}_2$, *J* = 6.9 Hz), 7.23-7.99 (m, 9H, aromatic H). MS, *m/z* (%): M^+ 310 (10.67), 193 (100%). Anal. Calcd. for $C_{18}H_{18}N_2OS$ (310.41): C, 69.65; H, 5.84; N, 9.02. Found: C, 69.69; H, 5.78; N, 8.83.

{4-Methyl-3-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1*H*-pyrazol-1yl}(phenyl)methanone (7b)

Yellow oil, yield 54%, IR υ_{max}/cm^{-1}: 3080, 3024 (CH aromatic), 2968, 2919 (CH aliphatic), 1692 (C=O), 1310, 1146 (SO_2). ^{1}H-NMR ($CDCl_3$): δ 1.17 (d, 3H, CHC$\underline{H}_3$, *J* = 6.6 Hz), 1.23-1.27 (m, 1H, C$\underline{H}$CH$_3$), 3.05 (s, 3H, $SO_2C\underline{H}_3$), 3.92 (d, 2H, CHC$\underline{H}_2$, *J* = 6.9 Hz), 7.27-8.11 (m, 9H, aromatic H). MS, *m/z* (%): M^+ 342 (6.07), 105 (100%). Anal. Calcd. for $C_{18}H_{18}N_2O_3S$ (342.10): C, 63.14; H, 5.30; N, 8.18. Found: C, 63.00; H, 5.21; N, 8.50.

(4-Chlorophenyl){4-methyl-3-[4-(methylsulfanyl)phenyl]-4,5-dihydro-1*H*-pyrazol-1-yl}methanone (7c)

Yellow oil, yield 40%, IR υ_{max}/cm^{-1}: 3070, 3045 (CH aromatic), 2967, 2922 (CH aliphatic), 1692 (C=O), 1091 (Cl). ^{1}H-NMR ($CDCl_3$): δ 1.16 (d, 3H, CHC$\underline{H}_3$, *J* = 6.6 Hz), 1.29-1.36 (m, 1H, C$\underline{H}$CH$_3$), 2.50 (s, 3H, SC$\underline{H}_3$), 3.92 (d, 2H, CHC$\underline{H}_2$, *J* = 6.9 Hz), 7.24-7.97 (m, 8H, aromatic H). MS, *m/z* (%): M^+ 344 (22.67), M+2 346 (7.02), 139 (100%). Anal. Calcd. for $C_{18}H_{17}ClN_2OS$ (344.08): C, 62.69; H, 4.97; N, 8.12. Found: C, 62.45; H, 4.90; N, 7.94.

(4-Chlorophenyl){4-methyl-3-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1*H*-pyrazol-1-yl}methanone (7d)

Yellow oil, yield 44%, IR υ_{max}/cm^{-1}: 3094, 3070 (CH aromatic), 2998, 2976, 2916 (CH aliphatic), 1689 (C=O), 1311, 1145 (SO_2), 1088 (Cl). ^{1}H-NMR ($CDCl_3$): δ 1.14 (d, 3H, CHC$\underline{H}_3$, *J* = 7.2 Hz), 1.24-1.27 (m, 1H, C$\underline{H}$CH$_3$), 3.06 (s, 3H, $SO_2C\underline{H}_3$), 3.86 (d, 2H, CHC$\underline{H}_2$, *J* = 6.9 Hz), 7.52-8.01 (m, 8H, aromatic H). ^{13}C-NMR (DMSO-d_6): δ 9.70 (CH$\underline{C}$H$_3$), 37.44 ($\underline{C}$HCH$_3$), 43.36 (SO_2CH_3), 53.48 (CH$\underline{C}$H$_2$), 120.73, 127.27, 127.45, 127.67, 127.85, 128.59, 128.92, 131.34, 132.75, 134.89, 135.65 and 141.57 (C aromatic), 159.95 (C=N olefinic), 164.88 (C=O). MS, *m/z* (%): M^+ 376 (12.02), M+2 378 (11.17), 139 (100%). Anal. Calcd. for $C_{18}H_{17}ClN_2O_3S$ (376.06): C, 57.37; H, 4.55; N, 7.43. Found: C, 57.21; H, 4.85; N, 7.66.

General method for preparation of compounds 8a,b

4-Chlorosulfonyl chloride (1.03 gm, 4.9 mmol) was added to a stirred solution of 3,4-disubstituted 4,5-dihydro-1*H*-pyrazole **4a**,**b** (4.9 mmol) in absolute ethanol (80 mL) and anhydrous potassium carbonate (0.25 gm, 1.76 mmol). The reaction mixture was heated under reflux for 15 h on a water bath. The solvent was evaporated under reduced pressure and then extracted with methylene chloride (2 × 30 mL). The organic layer was washed with water (2 × 30 mL) and dried over anhydrous sodium sulfate. The organic layer was concentrated under *vacuum* to give solid, which was re-crystallized from ethanol to give the products **8a**,**b**, respectively.

1-[(4-Chlorophenyl)sulfonyl]-4-methyl-3-[4-(methylsulfanyl)phenyl]-4,5-dihydro-1*H*-pyrazole (8a)

Yellow crystals, m.p. 65-68°C, yield 43%, IR υ_{max}/cm^{-1}: 3100, 3080 (CH aromatic), 2969, 2927, 2815 (CH aliphatic), 1365, 1157 (SO_2), 1090 (Cl). ^{1}H-NMR ($CDCl_3$): δ 1.16 (d, 3H, CHC$\underline{H}_3$, *J* = 6.6 Hz), 1.21-1.42 (m, 1H, C$\underline{H}$CH$_3$), 2.49 (s, 3H, SC$\underline{H}_3$), 3.06 (d, 2H, CHC$\underline{H}_2$, *J* = 6.9 Hz), 7.20-7.88 (m, 8H, aromatic H). MS, *m/z* (%): M^+ 380 (11.57), 130 (100%). Anal. Calcd. for $C_{17}H_{17}ClN_2O_2S_2$ (380.04): C, 53.60; H, 4.50; N, 7.35. Found: C, 53.81; H, 4.78; N, 7.60.

1-[(4-Chlorophenyl)sulfonyl]-4-methyl-3-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1*H*-pyrazole (8b)
Brown crystals, m.p. 72-75°C, yield 45%, IR υ_{max}/cm^{-1}: 3092, 3070 (CH aromatic), 2971, 2927 (CH aliphatic), 1370, 1340, 1150, 1146 ($2SO_2$), 1088 (Cl). ^{1}H-NMR ($CDCl_3$): δ 1.20 (d, 3H, $CHC\underline{H}_3$, J = 6.6 Hz), 1.24-1.29 (m, 1H, $C\underline{H}CH_3$), 3.03 (s, 3H, $SO_2C\underline{H}_3$), 3.08 (d, 2H, $CHC\underline{H}_2$, J = 6.9 Hz), 7.27-7.97 (m, 8H, aromatic H). Anal. Calcd. for $C_{17}H_{17}ClN_2O_4S_2$ (412.03): C, 49.45; H, 4.15; N, 6.78. Found: C, 49.25; H, 4.44; N, 6.59.

General method for preparation of compounds 10a,b

Methyl carbamimidothioate **9** (1 gm, 5.55 mmol) was added to a magnetically stirred solution of 3,4-disubstituted 4,5-dihydro-1*H*-pyrazole **4a**,**b** (4.83 mmol) in pyridine (10 mL) and left under reflux at 110°C for 1 h. After one night standing at room temperature, diethyl ether was added and the precipitate was collected by filtration and washed with diethyl ether (3 × 20 mL) to afford a brown solid that was dissolved in methanol (20 mL). 2 N sodium hydroxide solution (12 mL) and water (200 mL) were successively added to the previous suspension. The formed precipitate was collected by filtration, washed with diethyl ether (2 × 20 mL) and dried to yield the products **10a**,**b**, respectively.

4-Methyl-3-[4-(methylsulfanyl)phenyl]-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (10a)
Orange powder, m.p. 223-225°C, yields 42%, IR υ_{max}/cm^{-1}: 3300, 3208 (NH, NH_2), 3066 (CH aromatic), 2971, 2921 (CH aliphatic). ^{1}H NMR ($CDCl_3$): δ 1.02 (d, 3H, $CHC\underline{H}_3$, J = 6.1 Hz), 1.16-1.21 (m, 1H, $C\underline{H}CH_3$), 2.49 (s, 3H, $SC\underline{H}_3$), 2.74 (d, 2H, $CHC\underline{H}_2$, J = 6.0 Hz), 7.27-7.79 (m, 4H, aromatic H), 7.82, 8.29 (2s, 3H, N$\underline{H}$ and N$\underline{H}_2$, D_2O exch.). MS, m/z (%): $[M-1]^+$ 247 (28.35%), 157 (100%). Anal. Calcd. for $C_{12}H_{16}N_4S$ (248.11): C, 58.04; H, 6.49; N, 22.56. Found: C, 57.89; H, 6.19; N, 22.90.

4-Methyl-3-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (10b)
Red powder, m.p. 199-201°C, yield 59%, IR υ_{max}/cm^{-1}: 3300, 3222 (NH, NH_2), 3030 (CH aromatic), 2971, 2928 (CH aliphatic), 1330, 1145 (SO_2). ^{1}H-NMR ($CDCl_3$): δ 1.15 (d, 3H, $CHC\underline{H}_3$, J = 6.1 Hz), 1.16-1.34 (m, 1H, $C\underline{H}CH_3$), 3.02 (s, 3H, $SO_2C\underline{H}_3$), 3.09 (d, 2H, $CHC\underline{H}_2$, J = 6.0 Hz), 7.26-8.02 (m, 4H, aromatic H), 8.08, 8.10 (2s, 3H, N$\underline{H}$ and N$\underline{H}_2$, D_2O exch.). ^{13}C-NMR (DMSO-d_6): 9.67 ($C\underline{C}H_3$), 14.55 (SCH_3), 38.22 ($\underline{C}HCH_3$), 43.34 ($CH\underline{C}H_2$), 120.65, 125.39, 125.97, 127.12, 127.76 and 128.56 (C aromatic), 157.87 (C=N olefinic), 168.40 ($NH\underline{C}NH_2$ amidinic). Anal. Calcd. for $C_{12}H_{16}N_4O_2S$ (280.10): C, 51.41; H, 5.75; N, 19.98. Found: C, 51.21; H, 5.91; N, 20.01.

General method for preparation of compounds 11a,b

Sodium hydride (0.614 gm, 25.6 mmol) was added slowly to a stirred solution of the previously synthesized propiophenones, **2a**,**b** (12.8 mmol) in dry toluene (15 mL), at 60°C and the reaction mixture was left to stir for 10 min. Then diethyl oxalate (1.89 mL, 13.95 mmol) was added to the previously stirred solution and the reaction mixture was left for two hours at 60°C. The resulting mixture was acidified with acetic acid (2-5 drops), washed with diethyl ether (30 mL) and the organic layer was extracted with methylene chloride (2 × 30 mL) over anhydrous sodium sulfate. The organic layer was concentrated under *vacuum* to give yellow oil.

Ethyl 2-methyl-3-[4-(methylsulfanyl)phenyl]-3-oxopropanoate (11a)
Yellow oil, yield 61%, IR υ_{max}/cm^{-1}: 3080, 3036 (CH aromatic), 2980, 2926 (CH aliphatic), 1764, 1712, 1695 (C=Os). ^{1}H-NMR ($CDCl_3$): δ 1.18 (t, 3H, $CH_2C\underline{H}_3$, J = 7.2 Hz), 1.34 (d, 3H, $CHC\underline{H}_3$, J = 6.9 Hz), 2.50 (s, 3H, $SC\underline{H}_3$), 4.32 (q, 1H, $C\underline{H}CH_3$, J = 7.2 Hz), 4.37 (q, 2H, $C\underline{H}_2CH_3$, J = 7.2 Hz), 7.22-7.96 (m, 4H, aromatic H). MS, m/z (%): M^+ 280 (3.62), 151 (100%). Anal. Calcd. for $C_{14}H_{16}O_4S$ (280.08): C, 59.98; H, 5.75. Found: C, 59.93; H, 5.87.

Ethyl 2-methyl-3-[4-(methylsulfonyl)phenyl]-3-oxopropanoate (11b)
Yellow oil, yield 50%, IR υ_{max}/cm^{-1}: 3100, 3080 (CH aromatic), 2981, 2927 (CH aliphatic), 1740, 1714, 1693 (C=Os), 1315, 1153, (SO_2). ^{1}H-NMR ($CDCl_3$): δ 1.13 (t, 3H, $CH_2C\underline{H}_3$, J = 6.3 Hz), 1.38 (d, 3H, $CHC\underline{H}_3$, J = 6.9 Hz), 3.00 (s, 3H, $SO_2C\underline{H}_3$), 4.24 (q, 1H, $C\underline{H}CH_3$, J = 7.2 Hz), 4.33 (q, 2H, $C\underline{H}_2CH_3$, J = *7.2* Hz), 7.87-8.18 (m, 4H, aromatic H). MS, m/z (%): M^+ 312 (0.48), 213 (100%). Anal. Calcd. for $C_{14}H_{16}O_6S$ (312.07): C, 53.84; H, 5.16. Found: C, 54.10; H, 5.00.

General method for preparation of compounds 12a-d

Phenyl hydrazine or 4-methoxyphenyl hydrazine (3.6 mmol) was added slowly to a mixture of the previously synthesized butyric acid ethyl ester **11a**,**b** (3.6 mmol) and triethylamine (3-5 drops) in absolute ethanol (20 mL). The reaction mixture was left to stir at reflux for 24 h. It was then cooled, washed with brine and extracted with methylene chloride. The organic

layer was then separated, dried over anhydrous sodium sulfate and evaporated under *vacuum* to give yellow oily products, **12a-d.**

Ethyl 4-methyl-5-[4-(methylsulfanyl)phenyl]-1-phenyl-1*H*-pyrazole-3-carboxylate (12a)
Yellow oil, yield 79%, IR υ_{max}/cm^{-1}: 3080, 3060 (CH aromatic), 2978, 2922 (CH aliphatic), 1709 (C=O). ^{1}H-NMR (DMSO-d_6): δ 1.20 (t, 3H, $CH_2C\underline{H}_3$, J = 7.2 Hz), 1.41 (s, 3H, $CC\underline{H}_3$), 2.52 (s, 3H, $SC\underline{H}_3$), 4.33 (q, 2H, $C\underline{H}_2CH_3$, J = 6.9 Hz), 7.21-7.96 (m, 9H, aromatic H). MS, *m/z* (%): M^+ 352 (2.91), 137 (100%). Anal. Calcd. for $C_{20}H_{20}N_2O_2S$ (352.12): C, 68.16; H, 5.72; N, 7.95. Found: C, 67.89; H, 5.48; N, 7.93.

Ethyl 4-methyl-5-[4-(methylsulfonyl)phenyl]-1-phenyl-1*H*-pyrazole-3-carboxylate (12b)
Yellow oil, yield 72%, IR υ_{max}/cm^{-1}: 3100, 3080 (CH aromatic), 2979, 2927 (CH aliphatic), 1715 (C=O), 1360, 1148, (SO_2). ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, 3H, $CH_2C\underline{H}_3$, J = 7.2 Hz), 1.45 (s, 3H, $CC\underline{H}_3$), 3.04 (s, 3H, $SO_2C\underline{H}_3$), 4.42 (q, 2H, $C\underline{H}_2CH_3$, J = 6.9 Hz), 7.22-8.25 (m, 9H, aromatic H). MS, *m/z* (%): M^+ 384 (0.58), 303 (100%). Anal. Calcd. for $C_{20}H_{20}N_2O_4S$ (384.45): C, 62.48; H, 5.24; N, 7.29. Found: C, 62.42; H, 5.48; N, 7.54.

Ethyl 1-(4-methoxyphenyl)-4-methyl-5-[4-(methylsulfanyl)phenyl]-1*H*-pyrazole-3-carboxylate (12c)
Yellow oil, yield 65%, IR υ_{max}/cm^{-1}: 3080, 3020 (CH aromatic), 3000, 2922, 2880 (CH aliphatic), 1710 (C=O). ^{1}H-NMR (DMSO-d_6): δ 1.19 (t, 3H, $CH_2C\underline{H}_3$, J = 7.2 Hz), 1.42 (s, 3H, $CC\underline{H}_3$), 2.52 (s, 3H, $SC\underline{H}_3$), 3.94 (s, 3H, $OC\underline{H}_3$), 4.36 (q, 2H, $C\underline{H}_2CH_3$, J = 6.9 Hz), 7.22-7.99 (m, 8H, aromatic H). MS, *m/z* (%): M^+ 382 (14.56), 151 (100%). Anal. Calcd. for $C_{21}H_{22}N_2O_3S$ (382.14): C, 65.95; H, 5.80; N, 7.32. Found: C, 66.19; H, 5.75; N, 7.60.

Ethyl 1-(4-methoxyphenyl)-4-methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrazole-3-carboxylate (12d)
Yellow oil, yield 67%, IR υ_{max}/cm^{-1}: 3090, 3040 (CH aromatic), 2998, 2931 (CH aliphatic), 1711 (C=O), 1360, 1144 (SO_2). ^{1}H-NMR (DMSO-d_6): δ 1.11 (t, 3H, $CH_2C\underline{H}_3$, J = 7.2 Hz), 1.45 (s, 3H, $CC\underline{H}_3$), 3.01 (s, 3H, $SO_2C\underline{H}_3$), 3.69 (s, 3H, $OC\underline{H}_3$), 4.39 (q, 2H, $C\underline{H}_2CH_3$, J = 6.9 Hz), 7.25-8.04 (m, 8H, aromatic H). ^{13}C-NMR DMSO-d_6): δ 9.70 ($C\underline{C}H_3$), 13.9 ($\underline{C}H_2CH_3$), 43.11 (SO_2CH_3), 52.11 (OCH_3), 62.22 ($\underline{C}H_2CH_3$), 120.30, 127.28, 127.36, 128.63, 129.98, 134.00, and 152.50 (C aromatic and olefinic), 169.02 (C=O ester). MS, *m/z* (%):$[M+1]^+$ 415 (4.02), 183 (100%). Anal. Calcd. for $C_{21}H_{22}N_2O_5S$ (414.12): C, 60.85; H, 5.35; N, 6.76. Found: C, 60.83; H, 5.59; N, 6.53.

General method for preparation of compounds 14a,b

4-Hydrazino-benzenesulfonamide **13** (0.67 gm, 3.6 mmol) was added slowly to a mixture of the previously synthesized butyric acid ethyl ester **11a**,**b** (3.6 mmol) and triethylamine (3-5 drops) in absolute ethanol (20 mL). The reaction mixture was left to stir at reflux for 24 h. It was then cooled, washed with brine and extracted with methylene chloride. The organic layer was then separated, dried over anhydrous sodium sulfate and evaporated under *vacuum* to give solid products, **14a**,**b** respectively.

Ethyl 4-methyl-5-[4-(methylsulfanyl)phenyl]-1-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylate (14a)
Yellow crystals, m.p. 95-98°C, yield 75%, IR υ_{max}/cm^{-1}: 3320, 3280 (NH_2 stretching), 3065, 3020 (CH aromatic), 2969, 2922 (CH aliphatic), 1709 (C=O), 1368, 1160 (SO_2). ^{1}H NMR (DMSO-d_6): δ 1.08 (t, 3H, $CH_2C\underline{H}_3$, J = 7.2 Hz), 1.96 (s, 3H, $CC\underline{H}_3$), 2.52 (s, 3H, $SC\underline{H}_3$), 4.36 (q, 2H, $C\underline{H}_2CH_3$, J = 7.2 Hz), 7.04-7.84 (m, 8H, aromatic H), 10.08 (s, 2H, NH_2, D_2O exch.). ^{13}C-NMR(DMSO-d_6): δ 9.31 ($C\underline{C}H_3$), 10.60 ($\underline{C}H_2CH_3$), 14.07 (SCH_3), 45.47 ($\underline{C}H_2CH_3$), 123.73, 123.92, 125.50, 125.73, 125.91, 126.08, 127.07, 127.14, 128.83, 129.40, 129.74, 138.00, 146.90, 148.48 and 151.98 (C aromatic and olefinic), 169.02 (C=O ester). MS, *m/z* (%): M^+ 431 (3.34), 163 (100%). Anal. Calcd. for $C_{20}H_{21}N_3O_4S_2$ (431.10): C, 55.67; H, 4.91; N, 9.74. Found: C, 55.71; H, 5.07; N, 9.62.

Ethyl 4-methyl-5-[4-(methylsulfonyl)phenyl]-1–(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylate (14b)
Brown crystals, m.p. 88-91°C, yield 77%, IR υ_{max}/cm^{-1}: 3300, 3258 (NH_2 stretching), 3098, 3066 (CH aromatic), 2974, 2925 (CH aliphatic), 1703 (C=O), 1340, 1140, ($2SO_2$). ^{1}H-NMR (DMSO-d_6): δ 1.08 (t, 3H, $CH_2C\underline{H}_3$, J = 7.2 Hz), 2.08 (s, 3H, $CC\underline{H}_3$), 3.20 (s, 3H, $SO_2C\underline{H}_3$), 4.38 (q, 2H, $C\underline{H}_2CH_3$, J = 7.2 Hz), 7.09-8.07 (m, 8H, aromatic H), 10.08 (s, 2H, NH_2, D_2O exch.). MS, *m/z* (%): $[M+1]^+$ 464 (13.92), 63 (100%). Anal. Calcd. for $C_{20}H_{21}N_3O_6S_2$ (463.09): C, 51.82; H, 4.57; N, 9.07. Found: C, 51.70; H, 4.60; N, 9.00.

General method for preparation of compounds 15a,b

Potassium hydroxide (0.24 g, 4.2 mmol) dissolved in methanol (5 mL) was added to a solution of ethyl 4-methyl-5-[4-(methylsulfanyl)phenyl]-1-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylate **14a** (0.91 g, 2.1 mmol) or ethyl 4-methyl-5-[4-(methylsulfonyl)phenyl]-1--(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylate **14b** (0.97 gm, 2.1 mmol) dissolved in methanol (14 mL).

The reaction mixture was heated to reflux for 3 h, cooled, poured into water and filtered. The filtrate was acidified with 10% HCl, the precipitate separated, washed with water, dried under *vacuum* and extracted with methylene chloride (2 × 50 mL) to give the acid products **15a**,**b**, respectively.

4-Methyl-5-[4-(methylsulfanyl)phenyl]-1-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylic acid (15a)
Yellow oil, yield 59%, IR υ_{max}/cm^{-1}: 3298, 3237 (NH_2), 3080, 3020 (CH aromatic), 2970, 2924 (CH aliphatic), 2790 (OH), 1691 (C=O), 1368, 1151 (SO_2). ^{1}H-NMR (DMSO-d_6): δ 1.23 (s, 3H, CC$\underline{H}_3$), 2.52 (s, 3H, SC$\underline{H}_3$), 7.03-7.97 (m, 8H, aromatic H), 9.79 (s, 1H, COO$\underline{H}$, D_2O exch.), 10.01 (s, 2H, N$\underline{H}_2$, D_2O exch.). MS, *m/z* (%): M^+ 403 (28.04), 349 (100%). Anal. Calcd. for $C_{18}H_{17}N_3O_4S_2$ (403.07): C, 53.58; H, 4.25; N, 10.41. Found: C, 53.60; H, 4.55; N, 10.02.

4-Methyl-5-[4-(methylsulfonyl)phenyl]-1-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylic acid (15b)
Yellow oil, yield 71%, IR υ_{max}/cm^{-1}: 3330, 3220 (NH_2), 3082 (CH aromatic), 2947, 2929 (CH aliphatic), 2795 (OH), 1692 (C=O), 1330, 1141 ($2SO_2$). ^{1}H-NMR (DMSO-d_6): δ 1.23 (s, 3H, CC$\underline{H}_3$), 3.15 (s, 3H, SO_2C$\underline{H}_3$), 7.07-8.06 (m, 8H, aromatic H), 10.15 (s, 1H, COO$\underline{H}$, D_2O exch.), 10.19 (s, 2H, N$\underline{H}_2$, D_2O exch.). MS, *m/z* (%): M^+ 435 (52.53), 77 (100%). Anal. Calcd. for $C_{18}H_{17}N_3O_6S_2$ (435.06): C, 49.65; H, 3.93; N, 9.65. Found: C, 49.95; H, 4.23; N, 10.02.

General method for preparation of compounds 16a,b

The previously synthesized acids **15a**,**b** (1.24 mmol) were suspended in thionyl chloride (5 mL) and heated gently under reflux until a homogenous solution was obtained then for further 45 min. The solutions were then evaporated to dryness under *vacuum* in a water bath to remove excess thionyl chloride. The residues were azeotroped three times with dry benzene (5 mL) each, where the last traces of thiony1 chloride were removed. The residue was then used directly without further purification for the next step.

General method for preparation of compounds 17a-d

The acid chlorides **16a**,**b** (1.21 mmol) were dissolved in dry methylene chloride (5.5 mL) and added dropwise to a solution of triethylamine (2-5 drops) and piperidine or morpholine (1.87 mmol) in methylene chloride (5 mL) maintained at 0°C. The reaction mixture was stirred at room temperature for 8 h after which it was added to brine and extracted with methylene chloride (2 × 30 mL). The organic layer was separated, dried over sodium sulfate and re-crystallised from ethanol to yield the amide products.

4-[4-Methy1-5-[(4-(methylsulfanyl)phenyl)-3-(piperidine-1-ylcarbonyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (17a)
Red crystals, m.p. 155-158°C, yield 35%, IR υ_{max}/cm^{-1}: 3400, 3300 (NH_2), 3080, 3020 (CH aromatic), 2928, 2848 (CH aliphatic), 1620 (C=O), 1336, 1145 (SO_2). ^{1}H-NMR ($CDCl_3$): δ 1.22-2.03 (m, 6H, 3C$\underline{H}_2$), 2.15 (s, 3H, CC$\underline{H}_3$), 2.50 (s, 3H, SC$\underline{H}_3$), 3.03-3.22 (m, 4H, N(C$\underline{H}_2$)$_2$), 7.26-8.17 (m, 8H, aromatic H), 9.39 (s, 2H, N$\underline{H}_2$, D_2O exch.). ^{13}C-NMR(DMSO-d_6): δ 8.44 (C$\underline{C}$H$_3$), 10.60 ($\underline{C}$H$_2$CH$_3$), 14.20 (SCH$_3$), 21.46, 21.95 and 34.07 (3 piperidine $\underline{C}$H$_2$), 40.94, and 43.52 (2 piperidine $\underline{C}$H$_2$), 125.22, 126.00, 127.34, 128.78, 128.91, 129.57, 130.06, 131.02, 140.88, 142.22, and 149.01 (C aromatic and olefinic), 174.00 (C=O amidic). MS, *m/z* (%): M^+ 470 (35.85), 84 (100%). Anal. Calcd. for $C_{23}H_{26}N_4O_3S_2$ (470.14): C, 58.70; H, 5.57; N, 11.91. Found: C, 58.55; H, 5.29; N, 11.63.

4-[4-Methyl-5-(4-(methylsulfonyl)phenyl-3-(piperidine-1-ylcarbonyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (17b)
Brown crystals, m.p. 152-155°C, yield 49%, IR υ_{max}/cm^{-1} 3308, 3230(NH_2), 3090, 3020 (CH aromatic), 2928 (CH aliphatic), 1639 (C=O), 1335, 1143 ($2SO_2$). ^{1}H-NMR ($CDCl_3$): δ 1.54-1.74 (m, 6H, 3C$\underline{H}_2$), 2.17 (s, 3H, CC$\underline{H}_3$), 3.01(s, 3H, SO_2C$\underline{H}_3$), 3.04-3.20 (m, 4H, N(C$\underline{H}_2$)$_2$), 7.26-8.17 (m, 8H, aromatic H), 9.40 (s, 2H, N$\underline{H}_2$, D_2O exch.). MS, *m/z* (%):$[M+1]^+$ 503 (37.70), 63 (100%). Anal. Calcd. for $C_{23}H_{26}N_4O_5S_2$ (502.61): C, 54.96; H, 5.21; N, 11.15. Found: C, 54.55; H, 4.98; N, 11.13.

4-[4-Methy1-5-[(4-(methylsulfanyl)phenyl)-3-(morpholin-1-ylcarbonyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (17c)
Red crystals, m.p. 166-167°C, yield 40%, IR υ_{max}/cm^{-1}: 3380, 3220 (NH_2), 3090, 3022 (CH aromatic), 2924, 2855 (CH aliphatic), 1620 (C=O), 1336, 1145 (SO_2). ^{1}H-NMR ($CDCl_3$): δ 1.44 (s, 3H, CC$\underline{H}_3$), 2.50 (s, 3H, SC$\underline{H}_3$), 3.03-3.36 (m, 4H, N(C$\underline{H}_2$)$_2$), 3.45-4.01 (m, 4H, O(C$\underline{H}_2$)$_2$), 7.20-8.01 (m, 8H, aromatic H), 10.08 (s, 2H, N$\underline{H}_2$, D_2O exch.). MS, *m/z* (%): M^+ 472.12 (95.96), 108 (100%). Anal. Calcd. for $C_{22}H_{24}N_4O_4S_2$ (472.12): C, 55.91; H, 5.12; N, 11.86. Found: C, 56.19; H, 5.01; N, 11.73.

4-[4-Methyl-5-(4-(methylsulfonyl)phenyl-3-(morpholin-1-ylcarbonyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (17d)
Brown crystals, m.p. 177-180°C, yield 30%, IR $\upsilon_{max}/$

cm^{-1}: 3322, 3262 (NH_2), 3090, 3077 (CH aromatic), 2921, 2853 (CH aliphatic), 1639 (C=O), 1341, 1144 ($2SO_2$). ^{1}H-NMR ($CDCl_3$): δ 1.24 (s, 3H, $CC\underline{H}_3$), 2.84 (s, 3H, $SO_2C\underline{H}_3$), 3.03-3.29 (m, 4H, $N(C\underline{H}_2)_2$), 3.62-3.86 (m, 4H, $O(C\underline{H}_2)_2$), 7.27-8.14 (m, 8H, aromatic H), 10.04 (s, 2H, $N\underline{H}_2$, D_2O exch.). MS, *m/z* (%): M^+ 504 (43.51), 71 (100%). Anal. Calcd. for $C_{22}H_{24}N_4O_6S_2$ (504.11): C, 52.37; H, 4.79; N, 11.10. Found: C, 52.57; H, 4.73; N, 10.92.

Pharmacological screening

The experimental tests on animals have been performed in accordance with the Institutional Ethical Committee approval, Faculty of Pharmacy, Cairo University.

Anti-inflammatory activity

The newly synthesized compounds, indomethacin and celecoxib as reference standards were evaluated for *in vivo* anti-inflammatory activity using the standard acute carrageenan-induced paw edema method in rats (Winter et al., 1962, 1963).

Wister albino rats (obtained from the animal house of Faculty of Pharmacy, Cairo University) of either sex, pregnant female animals were excluded, weighing 120-150 gm were divided into 33 groups of six animals each. The initial hind paw volume of rats was determined volumetrically. Indomethacin and celecoxib (reference standards) and the tested compounds suspended in 2% Tween 80, at a dose of 25 mg/kg body weight, were administered intraperitoneally. The control group received only 2% Tween 80, 1 h before induction of inflammation. One percent solution of carrageenan in saline (0.1 mL/rat) was injected subcutaneously into the right hind paw one hour after the tested compound had been administered intraperitoneally. Paw edema volume was measured after 3 and 4 h using the plethysmometer 7150 (Ugo Basile) and compared with the initial hind paw volume of each rat. Data were collected, checked and revised. Quantitative variables from normal distribution were expressed as means ± S.E. The anti-inflammatory activity was expressed as percentage inhibition of edema volume in treated animals in comparison with the control group (Table I). Statistical differences between the treatments and the control were tested by one-way analysis of variance (ANOVA) followed by Tukey HSD test at a value of $p < 0.05$.

The anti-inflammatory activity was expressed as percentage inhibition of edema and was calculated by the following equation:

$$\% \text{ Inhibition} = 100 \times [Vc - Vt/Vc]$$

Where Vc is the mean of edema volume of rat paw after administration of carrageenan in the positive control group, Vt is the mean of edema volume of rat paw after administration of the tested compounds or the reference drugs.

Analgesic activity

The analgesic effect of the most active anti-inflammatory derivatives **5c**, **12a**, **12c**, **14a**, and **17d** was screened using the reported method of *p*-benzoquinone induced writhing in mice (Okun et al., 1963).

Adult male albino mice weighing 20-25 g were used in this study. The new tested compounds and the reference drugs indomethacin and celecoxib were prepared as a suspension in 2% Tween 80. A sensitivity test was carried out one day before drug administration, where animals were injected intraperitoneally with 0.2-0.25 mL of 0.02% freshly prepared solution of *p*-benzoquinone in distilled water (Kurumbail et al., 1996). Animals showing writhing to *p*-benzoquinone within 30 min were chosen for studying the analgesic activity.

On the next day, mice were divided into eight groups each of 6 animals. The first group received 2% Tween 80 and kept as control while the second and third groups received indomethacin and celecoxib, respectively; in a dose of 25 mg/kg body weight. The rest of the groups received **5c**, **12a**, **12c**, **14a**, and **17d** in the same dose. One hour later, 0.02% solution of *p*-benzoquinone was administered intraperitoneally and the animals were observed for 30 min after injection of the irritant during which the animals showing writhing were counted.

Writhing is defined as stretch, torsion to one side, drawing up of hind leg, retraction of the abdomen, so that the belly of mouse touches the floor. The mice showing any of the previous types of reactions are counted as positive responses. The analgesic activity was expressed as the percentage protection against *p*-benzoquinone induced writhing response in comparison with the control according to the following equation:

$$\% \text{ Protection} = \frac{\text{Number of protected animals} \times 100}{\text{Total number of animals}}$$

Acute ulcerogenicity study

Fifty five adult albino rats of either sex (pregnant female rats were excluded) weighing 120-150 g were used in this study. Animals were divided into 11 groups and received the drug orally. The first group received 2% Tween 80 and kept as control while the second and third groups received indomethacin and celecoxib, respectively; in a dose of 25 mg/kg body

weight. The rest of the groups received **5c**, **8b**, **12a**, **12c**, **14a**, **14b**, **15a**, and **17b** in the same dose. Food was allowed two hours post administration of the drugs. Rats received the given dose orally for three successive days. Two hours following the last dose, rats were scarified; the stomach of each rat was removed, opened along the greater curvature, rinsed with 0.9% sodium chloride (isotonic solution) and the stomach was stretched on a corkboard using pins. Examination for the presence of ulcers and erosions was done using a magnifying lens (10 × s) (Meshali et al., 1983)

The ulcer index was calculated according to the method of Robert et al. (Robert et al., 1968). The degree of ulcerogenic effect was expressed in terms of:

I. Percentage incidence of ulcers in each group of animals divided by 10
II. The average number of ulcers per stomach.
III. The average severity of ulcers by visual observation.

Finally, the ulcer index was expressed as the summation value of the above three items.

Results are tabulated in Table III.

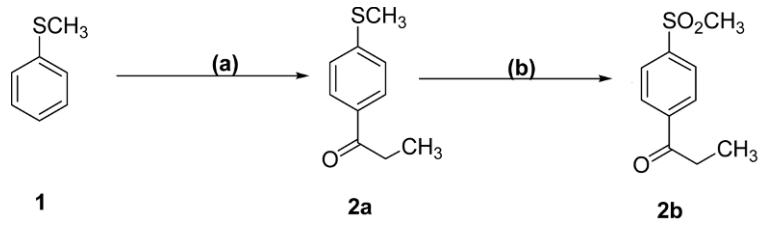
RESULTS AND DISCUSSION

Chemistry

The synthetic pathways applied to obtain target compounds are displayed in Schemes 1-5. As described in Scheme 1, the known 1-[4-(methylsulfonyl)phenyl]propan-1-one intermediate **2b** was prepared according to the previously reported method from thioanisole **1** in two steps (Burton and Hu, 1948; Almirante et al., 1965; Humphries and Finefield, 2006). Compounds **3a**,**b** were synthesized from **2a**,**b** using Mannich reaction/elimination sequence. Cyclocondensation of **3a**,**b** with hydrazine hydrate in absolute ethanol under dry nitrogen, to guarantee a complete cyclocondensation reaction yielded the corresponding pyrazoles **4a**,**b** (Scheme 2).

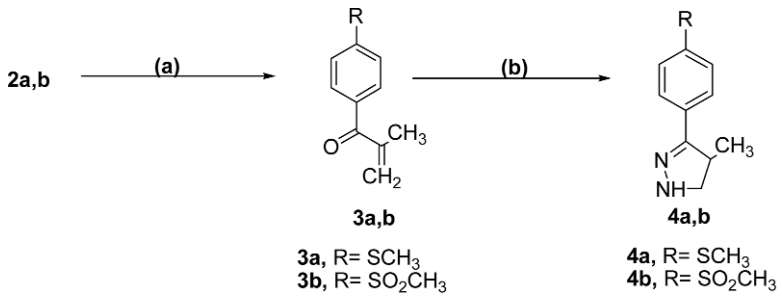
Nucleophilic *N*-alkylation reactions of secondary amines **4a**,**b** with the appropriate aryl halides, unsubstituted phenacyl bromides, unsubstituted benzoyl chlorides and *p*-chlorosulfonyl chloride that contain reasonable leaving groups achieved **5a-d**, **6a-d**, **7a-d**, and **8a**,**b**, respectively. Additionally, amidated products of compounds **4a**,**b** have been achieved through the reaction with the previously prepared methyl carbamimidothioate **9 (**Grosscurt et al., 1979; Alberto et al., 1988) in pyridine to furnish compounds **10a**,**b** (Scheme 3).

On the other hand, the reaction of **2a**,**b** with diethyl oxalate under strong alkaline and dry solvent conditions yielded the ester derivatives **11a**,**b** which were cyclized with unsubstituted phenylhydrazine or the previously synthesized 4-hydrazinylbenzenesulfonamide **13** (Organ and Mayer, 2003) to achieve the pyrazole-3-carboxylic acid ethyl esters **12a-d** and **14a**,**b** (Scheme 4).



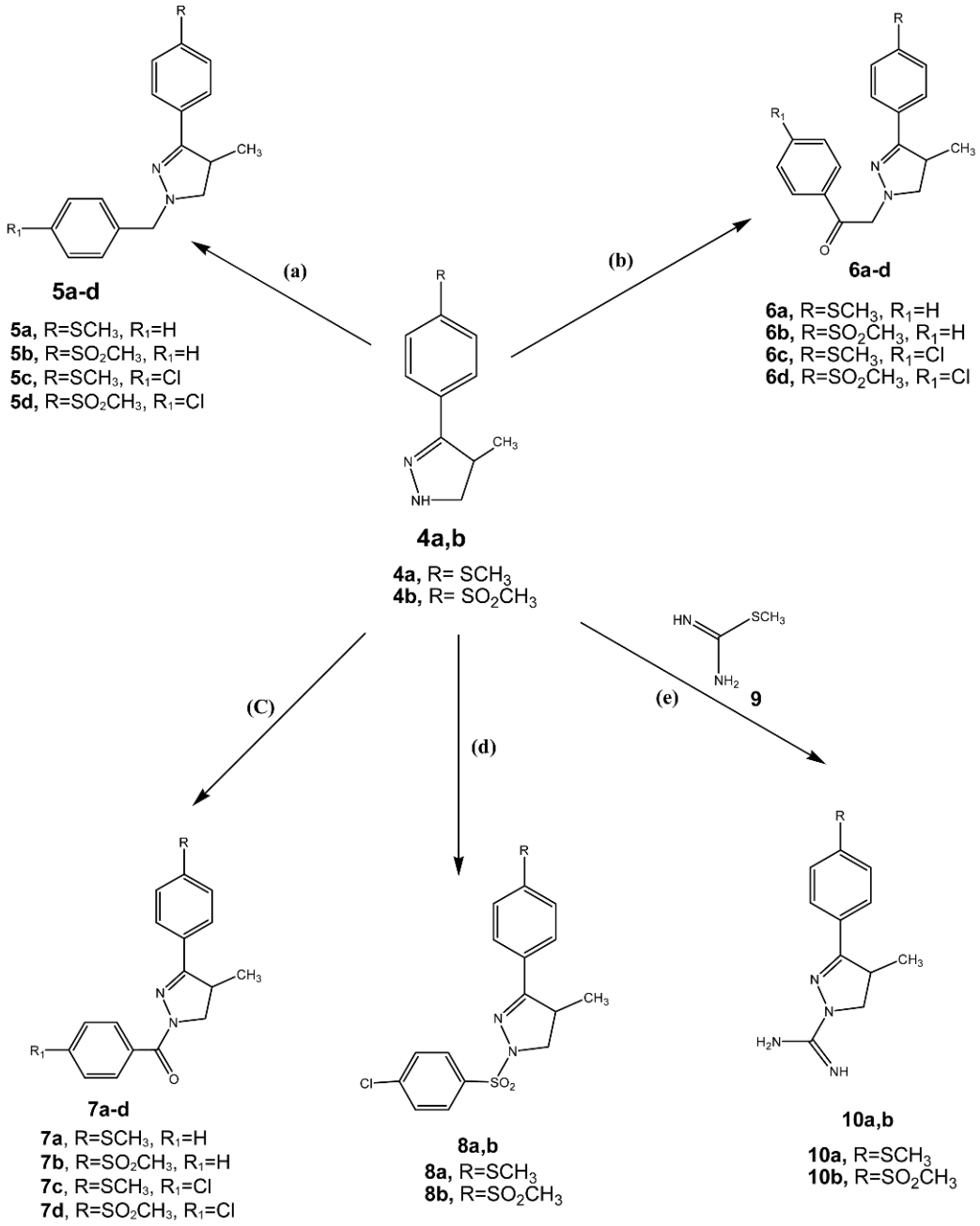
Reagents and conditions: (**a**) Propionyl chloride, $AlCl_3$, dichloromethane, 0-5°C, 16 h; (**b**) 30% Hydrogen peroxide, glacial acetic acid, reflux, 8 h.

Scheme 1. Synthesis of the key intermediates **2a** and **2b**.



Reagents and conditions: (**a**) 37% Aq. formaldehyde, piperidine, glacial acetic acid, reflux, 12 h; (**b**) Hydrazine hydrate, absolute ethanol, reflux, 3 h.

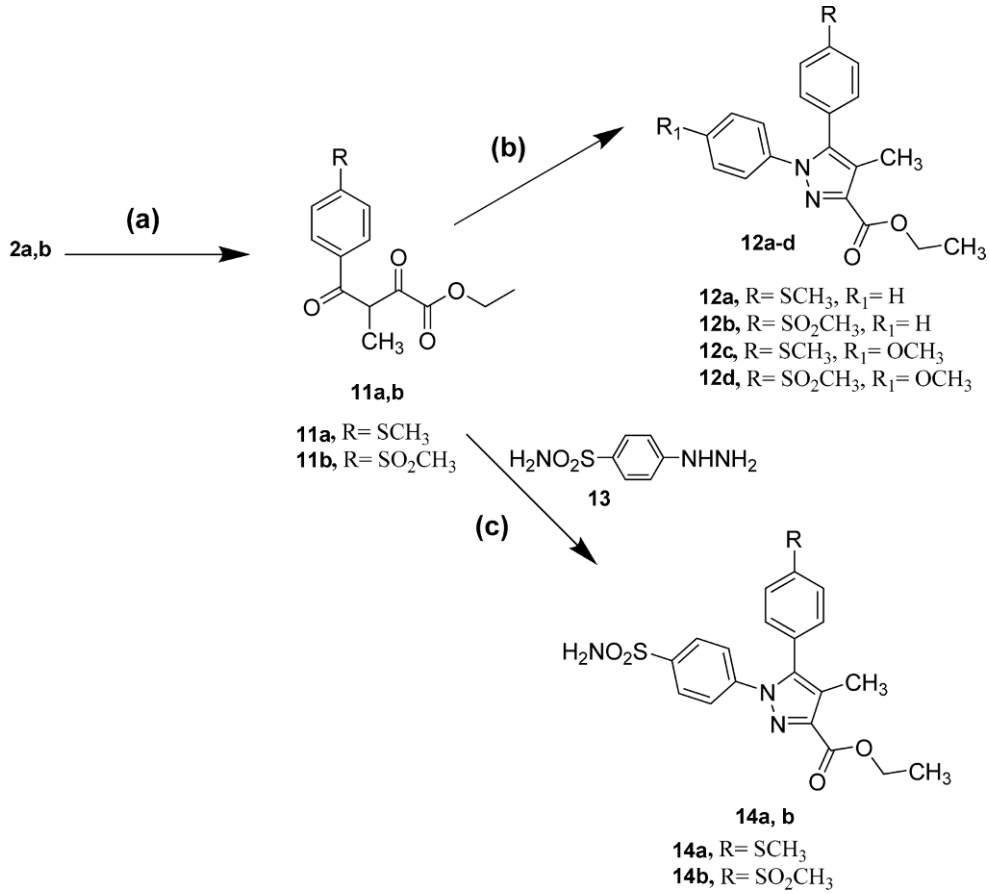
Scheme 2. Synthesis of the key intermediates **3a**,**b** and **4a**,**b**.



Reagents and conditions: (**a**) Benzyl chloride or 4-chlorobenzyl chloride, K_2CO_3, absolute ethanol, reflux, 15 h; (**b**) Phenacyl bromide or 4-chlorophenacyl bromide, K_2CO_3, absolute ethanol, reflux, 15 h; (**c**) Benzoyl chloride or 4-chlorobenzoyl chloride, K_2CO_3, absolute ethanol, reflux, 15 h; (**d**) P-chlorosulfonyl chloride, K_2CO_3, absolute ethanol, reflux, 15 h; (**e**) Pyridine, reflux, 1 h.

Scheme 3. Synthesis of compounds **5a-d**, **6a-d**, **7a-d**, **8a,b**, and **10a**,**b**.

As illustrated in scheme 5, base catalyzed hydrolysis of the previously synthesized ester derivatives **14a**,**b** has been carried out via refluxing them with potassium hydroxide in methanol to produce the expected corresponding free acids **15a**,**b**, respectively. Furthermore, compounds **15a**,**b** reacted with thionyl chloride to yield the unstable acid chloride derivatives **16a**,**b**. These derivatives **16a**,**b** were reacted directly in situ, without further purification with secondary amines, named piperidine or morpholine, in the presence of a catalytic amount of triethylamine to yield the amide derivatives **17a-d**. The structures of the newly synthesized compounds were elucidated by elemental analyses and spectral data [IR, ^{1}H-NMR, ^{13}C-NMR



Reagents and conditions: (**a**) Diethyl oxalate, NaH, dry toluene, 60°C, 2 h; (**b**) Phenylhydrazine or 4-methoxyphenylhydrazine, triethylamine, absolute ethanol, reflux 24 h; (**c**) 4-hydrazinylbenzenesulfonamide, triethylamine, absolute ethanol, reflux 24 h.

Scheme 4. Synthesis of compounds **11a**,**b**, **12a-d**, and **14a**,**b**.

and mass spectra].

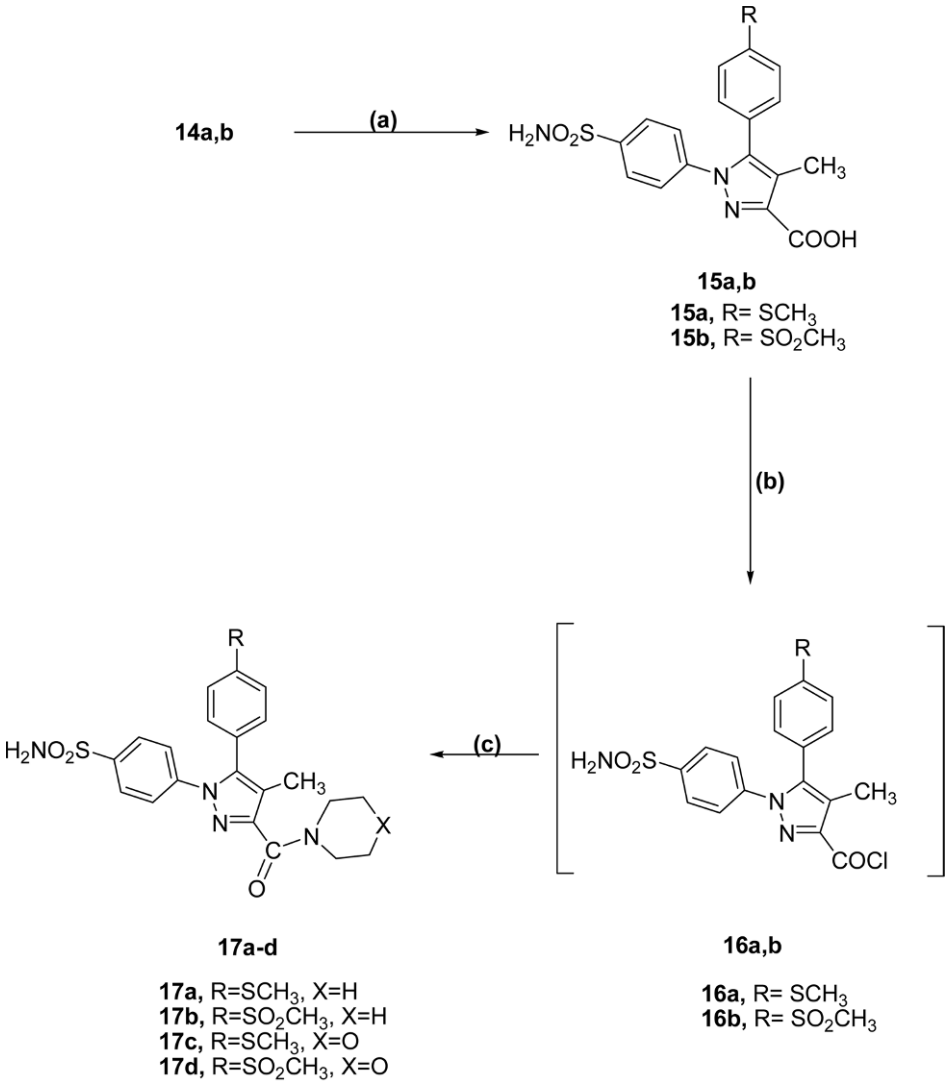
Anti-inflammatory activity

The newly synthesized compounds, indomethacin and celecoxib as reference standards were evaluated for *in vivo* anti-inflammatory activity at a 25 mg/kg body weight single dose using the standard acute carrageenan-induced paw edema method in rats reported by Winter et al. (Winter et al., 1962, 1963). The employed technique is based on the ability of the tested compounds to inhibit the edema produced in the hind paw of the rat after injection of carrageenan.

The inhibitory effect of the tested compounds on the carrageenan induced edema in rats was illustrated in Table I in comparison with indomethacin and celecoxib which were used as reference drugs. From the obtained results, it has been revealed that eleven compounds **5c**, **6c**, **6d**, **8b**, **10b**, **12a**, **12c**, **14a**, **14b**, **17b**, and **17d** showed anti-inflammatory activity comparable to or slightly lower than the reference drugs.

Concerning the dihydropyrazole derivatives **5**, **6**, **8** and **10** it has been noticed that the 4-chlorophenyl compounds **5c**, **6c**, **6d**, and **8b** have shown considerable anti-inflammatory effect compared to their unsubstituted analogues. Moreover, the sulfonyl derivatives **6d**, **8b**, and **10b** have shown more anti-inflammatory effect than their sulfanyl analogues. On the other hand, the reverse was true for the sulfanyl derivatives **5c** and **6c**, which have shown better anti-inflammatory effect than their sulfonyl analogues.

As for the pyrazole derivatives **12**, **14**, **15** and **17**, it has been noticed that the sulfonyl derivatives **14b**, **17b**, and **17d** have shown better anti- inflammatory effect than their sulfanyl analogues. Moreover, the incorporation of the sulfonamide moiety in compounds **14b**, **17b**, and **17d** made a positive impact on the anti-inflammatory activity more than the methoxy moiety and even more than the unsubstituted phenyl analogues, a concept that was derived from one of the used reference drug, celecoxib.



Reagents and conditions: (**a**) KOH, methanol, reflux, 3 h; (**b**) Thionyl chloride, CH_2Cl_2, gentle reflux, 45 min; (**c**) piperidine or morpholine, TEA, CH_2Cl_2, 8 h, R.T.

Scheme 5. Synthesis of compounds **15a**,**b**, **16a**,**b**, and **17a-d.**

Analgesic activity

The analgesic effect of the most active anti-inflammatory derivatives **5c**, **12a**, **12c**, **14a**, and **17d** was screened using the reported method of *p*-benzoquinone induced writhing in mice by Okun et al. (Okun et al., 1963).

The results were recorded in Table II. From the obtained data, it was noticed that all the tested compounds have shown good analgesic activity, equal to or even higher than indomethacin or equal to celecoxib.

Acute ulcerogenicity study

The ulcerogenic liability of compounds **5c**, **7c**, **8b**, **12a**, **12c**, **14a**, **14b**, **15a**, and **17b** as well as indomethacin and celecoxib was evaluated following the reported method by Meshali et al. (Meshali et al., 1983). The ulcer index was calculated according to the method of Robert et al. (Robert et al., 1968).

The results of the ulcer index of the reference drugs and the tested compounds were tabulated in Table III. It was noticed that compounds **5c**, **8b**, **12a**, **12c**, **14a**, and **14b** have shown a considerable gastric safety profile when compared to celecoxib as a reference drug, yet all the tested compounds have shown less gastric ulcer than indomethacin. Furthermore, the sulfanylphenyl pyrazole derivatives with a protective ester side chain **12a**, **12c**, and **14a** have displayed remarkable gastric protection. On the other hand, the sulfanylphenyl pyrazole derivative **15a** has shown the highest ulcer index value, which may be attributed to

Table I. Percentage inhibition of indomethacin, celecoxib and the new pyrazole derivatives on carragenan-induced edema of the hind paw rats (n = 6)

Cpd. No.	Dose mg/kg	% Inhibition	
		3 h	4 h
Control	0	0	0
Indomethacin	25	61.86	63.96[c]
Celecoxib	25	85.06	80.07[c]
4a	25	22.29	30.28
4b	25	41.87	10.19
5a	25	62.05	56.41[b]
5b	25	47.47	42.06[a]
5c	25	89.64	82.26[c]
5d	25	53.43	42.39[a]
6a	25	45.90	40.03[a]
6b	25	65.18	55.86[b]
6c	25	41.93	65.17[c]
6d	25	58.80	70.76[c]
7a	25	27.83	16.76
7b	25	40.72	29.24
7c	25	65.24	55.26[b]
7d	25	39.04	33.30
8a	25	53.31	45.62[a]
8b	25	59.16	76.62[c]
10a	25	41.57	22.67
10b	25	84.22	69.99[c]
12a	25	66.27	65.22[c]
12b	25	38.31	31.76
12c	25	87.65	67.80[c]
12d	25	40.48	39.21
14a	25	78.73	65.22[c]
14b	25	85.36	79.85[c]
15a	25	74.52	63.86[c]
15b	25	61.27	57.01[b]
17a	25	38.92	27.49
17b	25	73.01	73.99[c]
17c	25	41.39	29.08
17d	25	78.13	74.92[c]

Significant at [a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$.

Table II. Analgesic activity of indomethacin, celecoxib and some new pyrazole derivatives in rats

Cpd. No.	Dose mg /kg	No. of animals	No of protected animals	% protection
Control	0	6	0	0
Indomethacin	25	6	1	16.7[b]
Celecoxib	25	6	2	33.3[c]
5c	25	6	2	33.3[c]
12a	25	6	2	33.3[c]
12c	25	6	2	33.3[c]
14a	25	6	1	16.7[b]
17d	25	6	1	16.7[b]

Significant at [b]$p < 0.01$, [c]$p < 0.001$

Table III. Ulcerogenic effect of indomethacin, celecoxib and some new pyrazole derivatives in rats (25 mg/kg b.wt, n = 5)

Cpd. No.	% Incidence divided by 10	Average no. of ulcer	Average severity	Ulcer index
Control	0	0	0	0
Indomethacin	10	5.7	1	16.7
Celecoxib	8	2	1.2	11.2
5c	8	1.8	1	10.8
8b	8	1.8	1.1	10.9
12a	4	0.8	1.3	6.1
12c	4	0.8	1	5.8
14a	6	1.2	1.1	8.3
14b	8	1.8	1.2	11
15a	10	3.6	1.3	14.9
17b	10	3	1.2	14.2

the presence of an acidic carboxylic side chain.

In conclusion, eleven compounds **5c**, **6c**, **6d**, **8b**, **10b**, **12a**, **12c**, **14a**, **14b**, **17b**, and **17d** showed anti-inflammatory activity comparable to or slightly lower than the reference drugs, reaching about 82% inhibition with a considerable gastric safety profile. The compounds that showed significant anti-inflammatory activity possessed also an excellent analgesic activity, especially compounds **5c**, **12a**, **12c**, **14a**, and **17c**.

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