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SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF NOVEL PYRAZOLE DERIVATIVES

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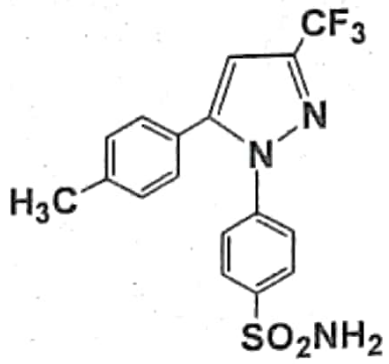
ABSTRACT

The key intermediate ,5-(p-chlorophenyl)-1H-pyrazole-3-carboxylic acid hydrazide *(3)*,was used for the synthesis of some new hydrazones *8a-g* as well as some five membered heterocyclic derivatives such as pyrazoles *10, 11a,b, 12*, pyrrole *13*, 1,3,4-oxadiazole *15*, 1,2,4-triazole *17* and 1,3,4-thiadiazole *19*. Identification of the new compounds was substantiated by spectral data and elemental analysis .Compound 6f which has a sulfadiazine moiety linked to the pyrazole showed a powerful anti-inflammatory activity than diclofenac sodium.

INTRODUCTION

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are known to block the formation of prostaglandins, which are responsible for inflammation symptoms, and have analgesic, antipyretic and anti-inflammatory activities[1]. However, prolonged treatment with NSAIDs, often leads to many side effects such as significant gastrointestinal irritation and the formation of gastrointestinal ulcers[2]. Therefore, in the last few years, synthesis of new selective anti-inflammatory agents was the main aim of many chemists. Among these selective anti-inflammatory compounds, Celecoxib (celebrix®) which has been utilized for treatment of acute pain,osteoarthritis and rheumatic arthritis[3]. Based on these considerations, it deemed of interest to synthesize new pyrazole compounds to explore their anti-inflammatory activities.



(Celecoxib)

EXPERIMENTAL

Melting points: uncorrected, SMP_2 melting point apparatus; Microanalysis: Microanalytical Center, Cairo, Egypt; IR spectra (KBR): Shimadzu IR 435; ^{1}HNMR spectra [DMSO(d_6)] Jeol FX 90 Q 90 MHz.

Synthesis of the compounds:

The intermediate Ethyl 3-(p-chlorobenzoyl) pyruvate *(1)* was prepared according to a reported procedure[12].

Ethyl 5-(p-chlorophenyl)-1H-pyrazole-3-carboxylate (2):

To a solution of *1* (1.0 gm; 0.004 mole) in dichloromethane (20 ml),was added hydrazine hydrate (0.20 ml; 0.004 mole) at 0°C. The reaction mixture was stirred at room temperature overnight and then heated under reflux for 10 hours. The solvent was evaporated and the solid obtained was crystallized from ethanol to give compound *2* yield (65%), m.p 160-162°C; IR (cm^1): 3294 (NH), 3089 (Ar-H), 2934,2905 (C-H, aliphatic), 1697 (C=O). ^{1}HNMR (δppm): 1.3 (t,3H,CH_3), 4.3 (q,2H,CH_2), 7.2(s,1H, C-H pyrazole), 7.4-7.8 (m,4H,Ar-H), 14.6(s,1H,NH, D_2O exchangeable). Microanalysis: $C_{12}H_{11}ClN_2O_2$ (250.5); Calcd.: %C, 57.48; %H, 4.40; %N, 11.17; Found: %C, 57.51; %H, 4.60; %N, 11.37.

5-(p-Chlorophenyl)-1H-pyrazole-3-carboxylic acid hydrazide (3):

Method A: A solution of *1* (2.5 gm; 0.01 mole) and hydrazine hydrate (1.0 ml; 0.02 mole) in absolute ethanol (50 ml) was heated under reflux for 4 hours. The solid that separated after cooling was filtered, dried and crystallized from acetic acid to give compound *3*, yield (66%), m.p > 340°C; IR(cm^{-1}): 3384, 3321, 3245, 3150 (NH), 3109 (Ar-H), 1653 (C=O). ^{1}HNMR(δppm): 4.48 (s,2H,NH_2, D_2O exchangeable), 7.1(s,1H,C-H pyrazole), 7.50 (d,2H,Ar-H), 7.8 (d,2H,Ar-H), 9.8 (s,1H,NH, D_2O exchangeable), 13.68 (s,1H,NH, D_2O exchangeable). Microanalysis: $C_{10}H_9ClN_5O$ (236.5); Calcd.: %C, 50.7; %H, 3.8; %N, 23.67; Found: %C, 50.7; %H, 4.2; %N, 23.28.

Method B: A solution of *2* (2.5 gm; 0.01 mole) and hydrazine hydrate (0.5 ml; 0.01 mole) in absolute ethanol (50 ml) was heated under reflux for 10h. The solvent was evaporated and the separated solid was crystallized from acetic acid to give compound *3*, yield (60%), m.p > 340°C.

5-(p-Chlorophenyl)-1H- pyrazole-3-carboxylic acid (4):

To the ester 2 (0.5 gm; 0.002 mol) was added 8% aqueous solution of NaOH (10 ml), and the mixture was heated under reflux for 2 hours. The mixture was cooled, acidified with conc. hydrochloric acid, and the resulting solid was filtered, washed with water and dried, the obtained solid was crystallized from ethanol to give 4, yield (60%), m.p > 340°C; IR (cm^{-1}): 3272 (NH), 3023 (Ar-H), 1690 (C=O), 1600 (C=N). Microanalysis: $C_{10}H_7ClN_2O_2$ (222.5); Calcd.: %C, 53.93; %H, 3.14; %N, 12.58; Found: %C, 53.50; %H, 3.58; %N, 12.29.

5-(p-Chlorophenyl)-1H- pyrazole-3-carboxylic acid chloride (5):

A suspension of *4* (1.0gm; 0.005 mol) and phosphorous oxychloride (20 ml) was heated at 100 °C for 2h. and the solution was allowed to cool. The excess phosphorous oxychloride was distilled off under reduced pressure and the residual yellow fluid was poured into ice and sodium carbonate to give yellow solid of 5 which filtered, dried and crystallized from DMSO to give compound *5*, yield (70%), m.p > 340°C; IR (cm^{-1}): 3112 (NH), 1727 (C=O). ^{1}HNMR (δppm): 7.2 (s, 1H, C-H, pyrazole), 7.5 (d, 2H, Ar-H), 7.8 (d, 2H, Ar-H), 13.9 (s, 1H, NH, D_2O exchangeable). Microanalysis: $C_{10}H_6Cl_2N_2O$ (241); Calcd.: %C, 49.80; %H, 2.48; %N, 11.61; Found: %C, 50.00; %H, 2.14; %N, 11.26

5-(p-Chlorophenyl)-1H-pyrazole-3-N-substitutedcarboxamides (6a-f):

Method A: Compound *5* (0.48 gm; 0.002 mol) and the appropriate liquid amine (5 ml) were heated at 150 °C for 1h. The mixture was cooled, diluted with ethanol and poured into water. The obtained solid was filtered off, dried and crystallized from aqueous DMF to give *6a-d*. (See table 1)

Method B: To a solution of *5* (0.48 gm; 0.002 mol) in DMF (20 ml), 4-amino antipyrine or sulfadiazine (0.002 mol) and K_2CO_3 (0.56 gm; 0.004 mol) were added. The reaction mixture was heated under reflux for the appropriate time, cooled, diluted with water and the precipitated solid was filtered off, dried and crystallized from aqueous DMF to give *6e* and *6f*. (See table 1).

Compound 6a: IR(cm^{-1}): 3402, 3128 (NH),3001 (Ar-H), 2933,2853 (C-H, aliphatic), 1642 (C=O). **^{1}HNMR(δppm):** 1.1-1.8 (m,10H,cyclohexyl), 3.7 (s,1H NH, D_2O exchangeable), 7.5-7.8 (m,5H,Ar-H), 13.6 (s,1H,NH pyrazole, D_2O exchangeable).

Compound 6d: IR(cm^{-1}): 3285,3235 (NH), 3029 (Ar-H), 2936,2856 (C-H, aliphatic), 1645 (C=O).

Compound 6e: IR (cm^{-1}): 3365, 3143 (NH), 3091, 3057 (Ar-H), 2971, 2931 (C-H, aliphatic), 1689 (C=O). ^{1}HNMR(δppm): 2.2 (s,3H,CH_3), 3.1 (s,3H,N-CH_3), 7.2(s,1H C-H pyrazole), 7.3-7.8(m,9H,Ar-H), 9.2(s,1H,NH amide, D_2O exchangeable), 13.8 (s,1H,NH pyrazole, D_2O exchangeable).

Compound 6f: IR (cm^{-1}): 3387, 3127 (NH), 3070, 3057 (Ar-H), 1681 (C=O).

2-[5-(p-Chlorophenyl)–1H-pyrazol-3-yl]-1H-benzimidazole (7):

To a solution of *5* (0.48 gm. 0.002 mol) in DMF (20 ml), o-phenylenediamine (0.4 gm; 0.002 mol) and K_2CO_3 (0.56 gm; 0.004 mol) were added. The mixture was heated under reflux for 24 h. then cooled. After dilution with water, the precipitated solid was filtered off,dried and crystallized from aqueous DMF to give compound *7*, yield (66%), m.p 253-255°C; IR (cm^{-1}): 3371,3207(NH), 3066,3008 (Ar-H), 1605(C=N). ^{1}HNMR(δppm): 7.3 (s,1H,C-H pyrazole), 7.5 (d,2H,Ar-H),7.8 (d,2H,Ar-H),7.9 (d,2H,Ar-H),8.3 (d,2H,Ar-H), 12.0 (s,1H,NH benzimidazole, D_2O exchangeable), 13.8 (s,1H,NH pyrazole, D_2O exchangeable). Microanalysis: $C_{16}H_{11}ClN_4$ (294.5); Calcd.: %C, 65.19; %H, 3.73; %N, 19.01; Found: %C, 65.02; %H, 3.68; %N, 18.80.

3-Arylidenehydrazinocarbonyl-5-(p-chlorophenyl)-1H-pyrazole (8a-g):

To a solution of the hydrazide *3* (0.002 mole) in ethanol (10 ml) and few drops acetic acid, the appropriate aldehyde or ketone (0.002 mole) was added. The reaction mixture was heated under reflux for 1h.then cooled. The separated solid was filtered off, washed with ethanol and crystallized from acetic acid. (See table 2)

Compound 8a: IR(cm^{-1}): 3319, 3214 (NH), 3110,3005 (Ar-H), 1675 (C=O).

Compound 8d: IR(cm^{-1}): 3235, 3141 (NH), 3084 (Ar-H), 1680 (C=O).

Compound 8f: IR(cm^{-1}): 3355,3218 (NH), 3008 (Ar-H),2977 (C-H, aliphatic), 1680 (C=O).

Compound 8g: ^{1}HNMR(δppm): 2.4 (s,3H,CH_3), 3.8 (s,3H,CH_3), 6.9 (d, 2H, Ar-H), 7.5 (s,1H,C-H pyrazole), 7.80-7.87 (m,6H, Ar-H), 10.25 (s,1H,CONH, D_2O exchangeable), 13.9 (s,1H,NH, D_2O exchangeable).

5-(p-chlorophenyl)-3-[(ethoxycarbonyl-2-propylidene)hydrazinocarbonyl]-1H-pyrazole (9):

A mixture of hydrazide 3 (0.60 gm; 0.0025mol) and ethyl acetoacetate (5 ml) was heated under reflux for 5 hours. The reaction mixture was diluted with pet.ether (bp 60-80°C) and the resultant solid was filtered, dried and crystallized from acetic acid to give compound 9, yield (86%), m.p 188-190°C; IR(cm^{-1}): 3381, 3268, (NH), 3111 (Ar-H), 1727 (C=O), 1630 (C=O). ^{1}HNMR(δppm): 1.1 (t,3H,CH_3), 2.0 (s,3H,CH_3), 2.4 (q,2H, CH_2), 4.1 (dd,2H,CH_2), 7.52 (s,1H,C-H pyrazole), 7.54 (d, 2H,Ar-H), 7.8(d,2H,Ar-H), 10.2 (s,1H,NH, D_2O exchangeable), 13.9 (s,1H,NH, D_2O exchangeable). Microanalysis: $C_{16}H_{17}ClN_4O_3$ (348.5); Calcd.: %C, 55.1;%H, 4.87;%N, 16.10; Found: %C, 55.6;%H, 5.10;%N, 16.62.

5-(p-Chlorophenyl)-3-[(3-methyl-5-oxo-4,5-dihydropyrazol-1-yl)-carbonyl]-1H-pyrazole (10):

Method A: A solution of *9* (0.5gm; 0.0015 mol) in 2M sodium hydroxide (10 ml) was heated under reflux for 5 h. After cooling, the mixture was diluted with water then neutralized with concentrated hydrochloric acid and the obtained precipitate was filtered off,washed with water and crystallized from acetic acid to give *10*, yield (63%), m.p >340°C; IR (cm^{-1}): 3214 (NH), 3008 (Ar-H), 1697,1670 (2C=O). ^{1}HNMR (δppm): 1.0 (s,3H,CH_3), 6.9 (d,2H,Ar-H), 7.11-7.18 (dd,2H,CH_2 pyrazole), 7.5-7.8 (m,5H,Ar-H), 12.2 (s,1H, NH, D_2O exchangeable). Microanalysis: $C_{14}H_{11}ClN_4O_2$ (302.5); Calcd.: %C, 55.50; %H, 3.60; %N, 18.51; Found: %C, 56.03; %H, 3.27; %N, 18.93.

Method B: To a solution of the hydrazide *3* (0.60 gm; 0.0025 mol) in 2M sodium hydroxide (10ml) was added ethyl acetoacetate (0.3 gm; 0.0025 mol) and the reaction mixture was heated under reflux for 10h. The reaction mixture was cooled, diluted with water and neutralized with hydrochloric acid. The separated solid was filtered off,dried and crystallized from acetic acid to give *10*, yield (60%), m.p >340°C.

5-(p-Chlorophenyl)-3-[(3-methyl-5-substitutedpyrazol-1-yl)-carbonyl]-1H-pyrazole (11a, b):

Method A: (for 11a): A mixture of the carboxylic acid hydrazide *3* (0.60 gm; 0.0025mol) and acetylacetone (5 ml) was heated under reflux for 5 h. The reaction mixture was diluted with pet.ether (bp 60-80°C) and the resultant solid was filtered off and crystallized from acetic acid to give compound *11a*, yield (75%), m.p 280-282°C.

Method B (general method): To a solution of compound *3* (0.60 gm; 0.0025 mol) and potassium hydroxide (0.14 gm; 0.0025 mol) in ethanol (20ml), acetylacetone or benzoylacetone (0.0025 mol) was added. The mixture was heated under reflux for 10h. The reaction mixture was cooled, diluted with water and neutralized with hydrochloric acid. The separated solid was filtered off, dried and crystallized from acetic acid to give compound *11a* and *11b*.

Compound 11a: Yield (65%), m.p 280-282°C; IR (cm^{-1}): 3217 (NH), 1687 (C=O). ^{1}HNMR (δppm): 2.52 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 6.3 (s, 1H, pyrazole dimethyl), 7.5 (d, 2H, Ar-H), 7.58 (s, 1H, pyrazole), 7.9 (d, 2H, Ar -H), 14.1(s, 1H, NH, D_2O exchangeable); Microanalysis: $C_{15}H_{13}ClN_4O$ (300.5). Calcd.: C, 59.90; H, 4.30; N, 18.60; Found: C, 59.3; H, 4.0; N, 18.12.

Compound 11b: Yield (60%), m.p 320-322°C; IR (cm^{-1}): 3150 (NH), 1678 (C=O). ^{1}HNMR (δppm): 2.3 (s,3H,CH_3), 7.0 (s, 1H, C=H pyrazole), 7.3 (s,1H, C-H pyrazole), 7.4-7.8 (m, 9H, Ar-H), 10.6 (s,1H, NH, D_2O exchangeable); Microanalysis: $C_{20}H_{15}ClN_4O$ (362.5); Calcd.: C, 66.20; H, 4.13; N, 15.44; Found: C, 66.08; H, 4.13; N, 14.90.

5-(p-Chlorophenyl)-3-[(3-amino-5-oxo-1,5-dihydropyrazol-2-yl)-carbonyl]-1H-pyrazole (12):

To a solution of compound *3* (0.60 gm; 0.0025 mol) and potassium hydroxide (0.14 gm; 0.0025 mol) in ethanol (20ml), ethyl cyanoacetate (0.28 ml;0.0025 mol) was added. The reaction mixture was heated under reflux for 15 h. then cooled. The solid separated after dilution with water and neutralization with hydrochloric acid, was filtered off,dried and crystallized from aqueous DMF to give *12*, yield (60 %), m.p 280-282°C; IR (cm^{-1}): 3273(NH), 3025(C-H aromatic), 1691(C=O). ^{1}HNMR (δppm): 5.9 (s,2H,NH_2, D_2O exchangeable), 7.3-7.8 (m,6H,Ar-H), 13.8,13.9 (s,1H,NH, D_2O exchangeable). Microanalysis: $C_{13}H_{10}ClN_5O_2$ (303.5); Calcd.: %C, 51.40; %H, 3.29; %N, 23.06; Found: %C, 51.73; %H, 3.47; %N, 22.67.

5-(p-Chlorophenyl)-3-[(2,5-dimethylpyrrol-1-yl-amino)carbonyl]-1H-pyrazole (13):

A mixture of the carboxylic acid hydrazide *3* (0.60 gm; 0.0025 mol) and 2,5-hexanedione (0.30 ml; 0.0025 mol) in glacial acetic acid (5 ml)/few drops of DMF was stirred at room temperature overnight. On dilution with water, the separated solid was filtered off, dried and crystallized from acetic acid to give *13*, yield (75%), m.p 295-297°C; IR (cm^{-1}): 3331,3277 (NH), 3069 (Ar-H), 2979,2921 (C-H aliphatic), 1672 (C=O). ^{1}HNMR (δppm): 2.0 (s,6H,$2CH_3$), 5.7 (s,2H,C-H pyrrol), 7.2 (s,1H,C-H pyrazole), 7.5 (d,2H,Ar-H), 7.8 (d,2H,Ar-H), 11.1 (s, 1H, NH amide, D_2O exchangeable), 13.9 (s, 1H, NH, D_2O exchangeable). Microanalysis: $C_{16}H_{15}ClN_4O$ (314.5); Calcd.: %C, 61.04; %H, 4.76; %N, 17.80; Found: %C, 61.50; %H, 4.60; %N, 17.70.

Potassium 3-[5-(p-chlorophenyl)-1H-pyrazole-3-carbonyl]-Dithiocarbazate (14):

Carbon disulfide (1 ml; 0.015 mol) was added dropwise to an ice cooled solution of the hydrazide *3* (0.6 gm; 0.0025 mol) in alcoholic potasium hydroxide (0.14 gm; 0.0025 mol). The mixture was diluted with absolute ethanol (10 ml) and the separated solid was filtered off and washed with ether (20 ml). The product which was obtained in an almost quantitative yield, was used in the next reaction without further purification.

2-[5-(p-Chlorophenyl)-1H-pyrazol-3-yl]-5-mercapto-1,3,4-oxadiazole (15):

Method A: Compound *14* (0.7 gm; 0.002 mol) and 2N potassium hydroxide (20 ml) were heated under reflux for 15h. After cooling, the reaction mixture was diluted with water (10 ml) and neutralized with concentrated hydrochloric acid. The separated solid was filtered off,dried crystallized from aqueous DMF to give compound *15*, yield (65%), m.p. 280-282°C; IR (cm^{-1}): 3229 (NH), 3003 (Ar-H), 2757 (SH). Microanalysis : $C_{11}H_7ClN_4OS$ (278.5); Calcd.: %C, 47.40; %H, 2.51; %N, 20.10; Found: %C, 47.99; %H, 2.80; %N, 20.32.

Method B: A solution of the hydrazide *3* (0.6 gm; 0.0025 mol) in absolute ethanol (10 ml) containing potassium hydroxide (0.14 gm; 0.0025 mol) was heated for 1h. until a clear solution was obtained. The reaction mixture was cooled. Carbon disulfide (1 ml; 0.015 mol) was added dropwise to an ice cooled reaction mixture with stirring. The reaction mixture was heated under reflux for 24 hours. until all hydrogen sulfide has been evolved. Evaporation of solvent, dilution with cold water and acidified with concentrated hydrochloric acid gave a solid which was filtered off, dried and crystallized from aqueous DMF to give *15*, yield (60%), m.p 280-282°C.

3-[5-(p-Chlorophenyl)-1H-pyrazol-3-yl]-4-amino-5-mercapto-1,2,4-triazole (17):

A mixture of compound *14* (0.7 gm; 0.002 mol) and hydrazine hydrate (98%) (0.1 ml; 0.002 mol) in absolute ethanol (10 ml) was heated under reflux for 10h. The reaction mixture was cooled, diluted with cold water (10 ml) and neutralized with hydrochloric acid. The precipitate was filtered off, washed with water dried and crysrallized from dioxane to afford *17*, yield (50%), m.p. 276-278°C; IR (cm^{-1}): 3150,3120 (NH,NH_2), 3003 (Ar-H). ^{1}HNMR(δppm): 5.9 (d,2H,NH_2), 7.3 (s,1H,C-H pyrazole), 7.5 (d,2H,Ar-H), 7.8(d,2H,Ar-H), 13.0(s,1H,SH, D_2O exchangeable), 13.8(s,1H,NH, triazole, D_2O exchangeable), 13.9 (s,1H,NH pyrazole, D_2O exchangeable). Microanalysis: $C_{11}H_9ClN_6S$ (292.5); Calcd.: %C, 45.12; %H, 3.07; %N, 28.71; Found: %C, 45.37; %H, 3.10; %N, 28.32.

Ethyl 2-{3-[5-(p-chlorophenyl)-1H-pyrazol-3-yl]-6-hydroxy-7H-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazin-7-ylidene}- acetate (18):

A mixture of compound *17* (0.6 gm; 0.002 mol) and diethyl acetylene dicarboxylate (DEAD) (0.34 gm; 0.002 mol) in ethanol (20 ml)/ few drops of acetic acid was heated under reflux for 10h. The solvent was evaporated, diluted with water (10 ml) and the separated yellow solid was filtered off, dried and crystallized from ethanol to afford *18*, yield (40%), m.p 260-262°C; IR (cm^{-1}): 3259 (NH),3003 (Ar-H),2983,2936 (C-H aliphatic), 1735 (C=O), 1609 (C=N). ^{1}HNMR (δppm): 1.3 (s,3H,CH3), 4.3 (q,2H,CH2), 5.9 (d,2H,NH2), 7.2 (s,1H,C-H pyrazole), 7.4 (s,1H,C=H), 7.5 (d,2H,Ar-H), 7.8(d,2H,Ar-H), 14.0 (s,1H,NH, D2O exchangeable). Microanalysis: $C_{17}H_{13}C_lN_6O_3S$ (416.5); Calcd.: %C, 48.97; %H, 3.12; %N, 20.16; Found: %C, 48.73; %H, 3.63; %N, 20.15.

2-[5-(p-Chlorophenyl)-1H-pyrazol-3-yl]-5-mercapto-1,3,4-thiadiazole (19):

To compound *14* (0.7 gm;0.002 mol), ice cold concentrated sulphuric acid (10 ml) was added dropwise while stirring. The reaction mixture was left overnight and then quenched with ice and treated with ammonia solution till neutral to litmus. The separated solid was washed with water, filtered off,dried and crystallized from acetic acid to give *19*, yield (50%), m.p 283-285°C; IR (cm^{-1}): 3198 (NH), 3006 (Ar-H), 1606(C=N). Microanalysis: $C_{11}H_7C_lN_4S_2$ (294.5); Calcd.: %C, 44.80; %H, 2.37; %N, 19.01; Found: %C, 45.21; %H, 2.50; %N, 19.08.

Pharmacological testing:

Anti-inflammatory activity:

The anti-inflammatory activity of the chosen eight tested compounds (**6 e,f - 8c,d,g - 10 and 11a,b**) was carried out on the carragenins-induced inflammed rat paw. 40 Mature male albino rats weighing 150-180 gm were used. They were classified into 10 equal groups each of 4.

Control group (1): Rats were injected with 0.1 ml of 10 % carragenin according to Winter's method[13].

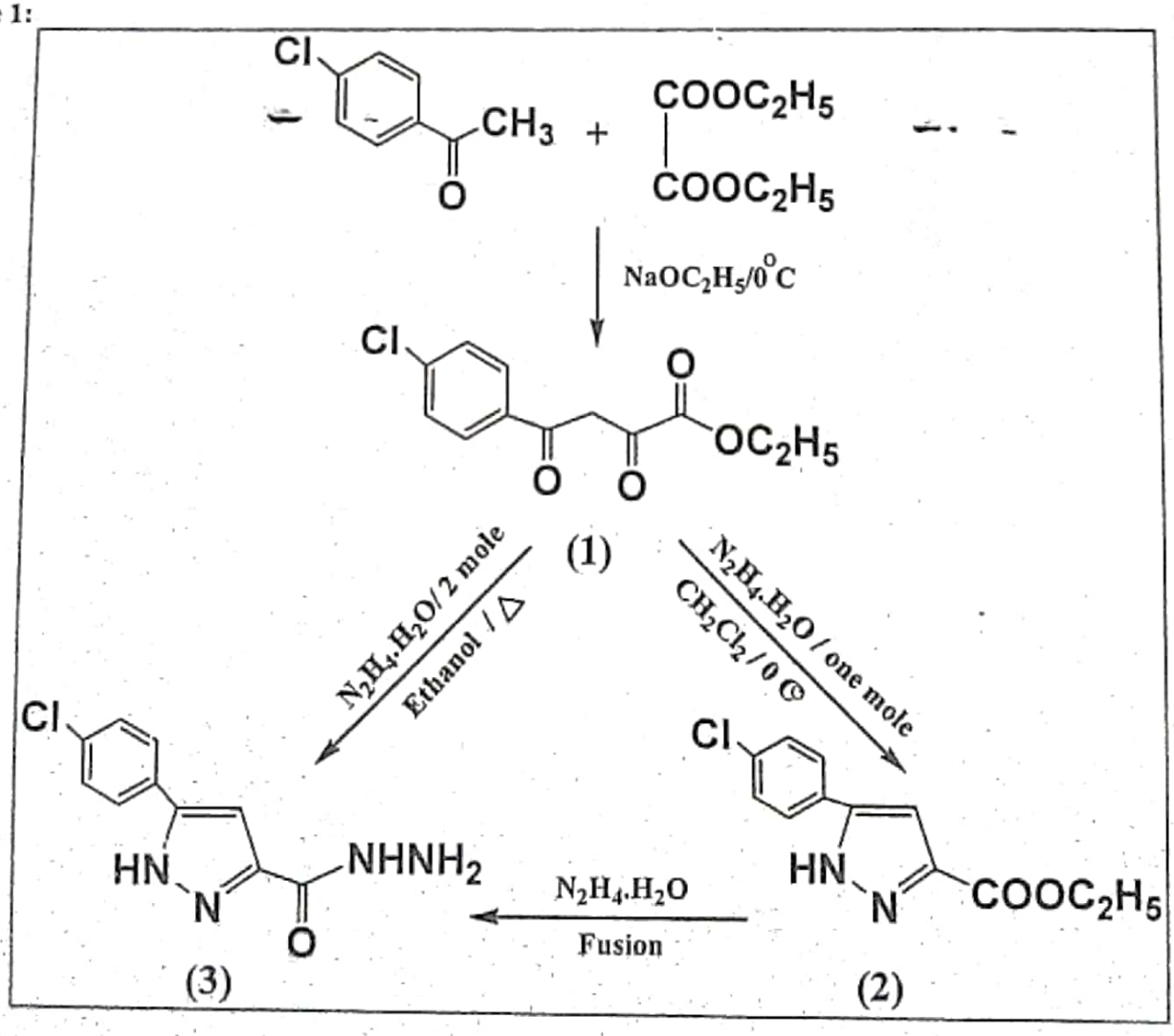
Standard group (2): Rats were injected with Diclofenac sodium intraperitoneal (I/P) at a dose of 0.7 mg/100 gm.

Test groups (from 3 to 10): Rats were injected Intraperitoneal (I/P) with the test compounds in a dose of 0.7 mg/100 gm. The test compounds were dissolved in DMSO and the dose was corrected from a human dose to rat dose according to Paget and Barnes[14]. One hour later, oedema in the rat hind paw was induced in the standard group and test groups with 0.1 ml of 10 % carragenin. The thickness of the rat paw was measured using skin caliber at 1, 2, 3 and 4 hours after carragenin injection to determine the anti-inflammatory effect of Diclofenac sodium as well as the test compounds.

INVESTIGATIONS, RESULTS AND DISCUSSION

The synthesis of the target compounds was carried out according to schemes 1-5.

Scheme 1:



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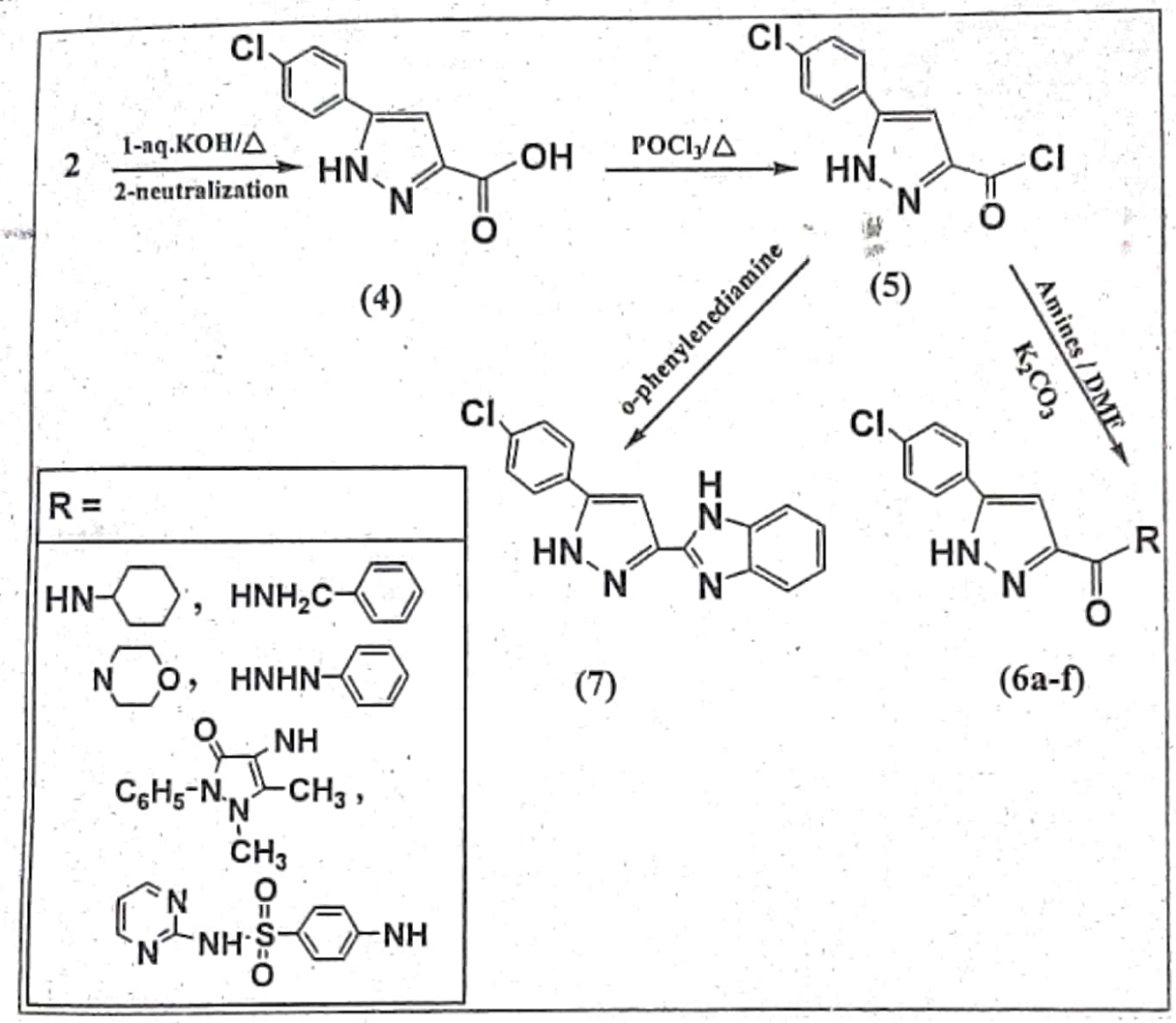
Scheme 2:



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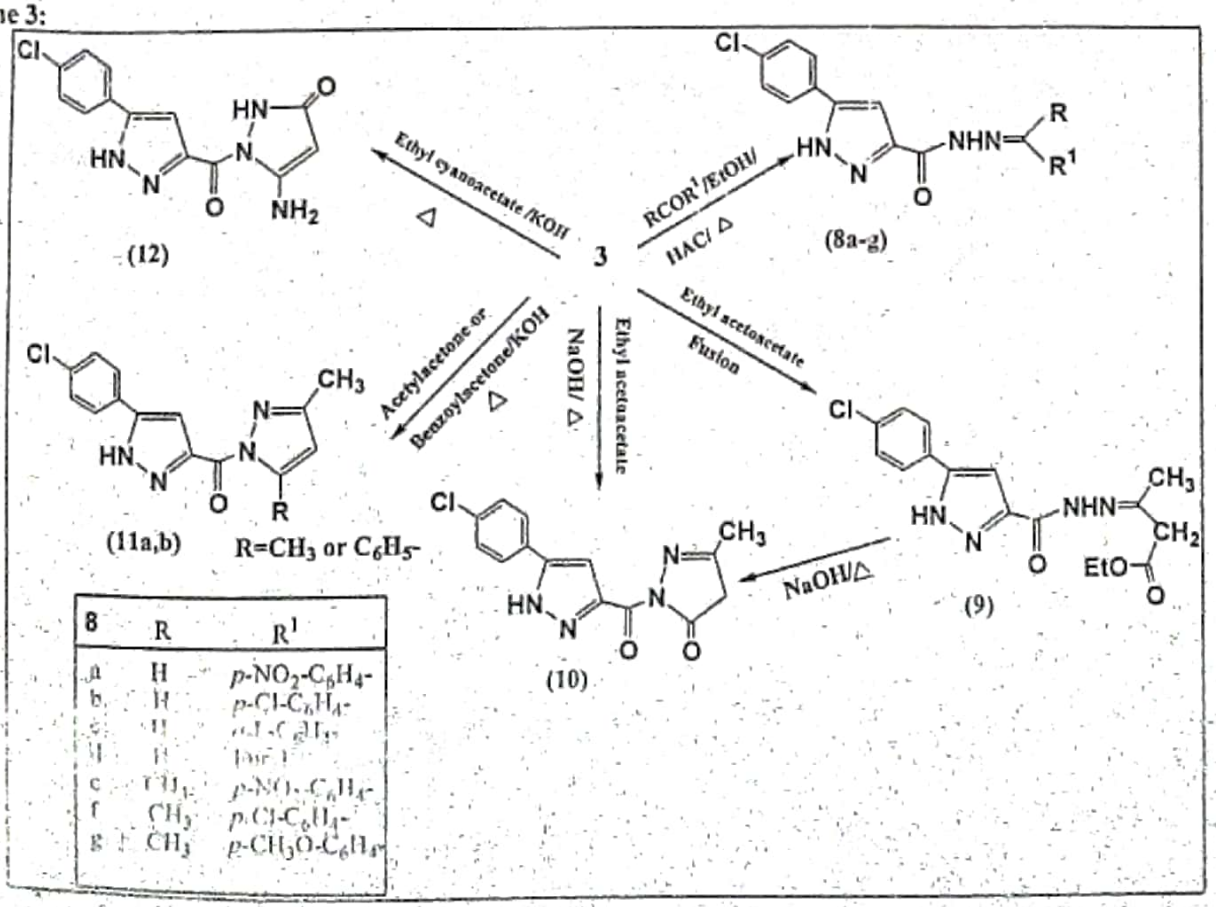
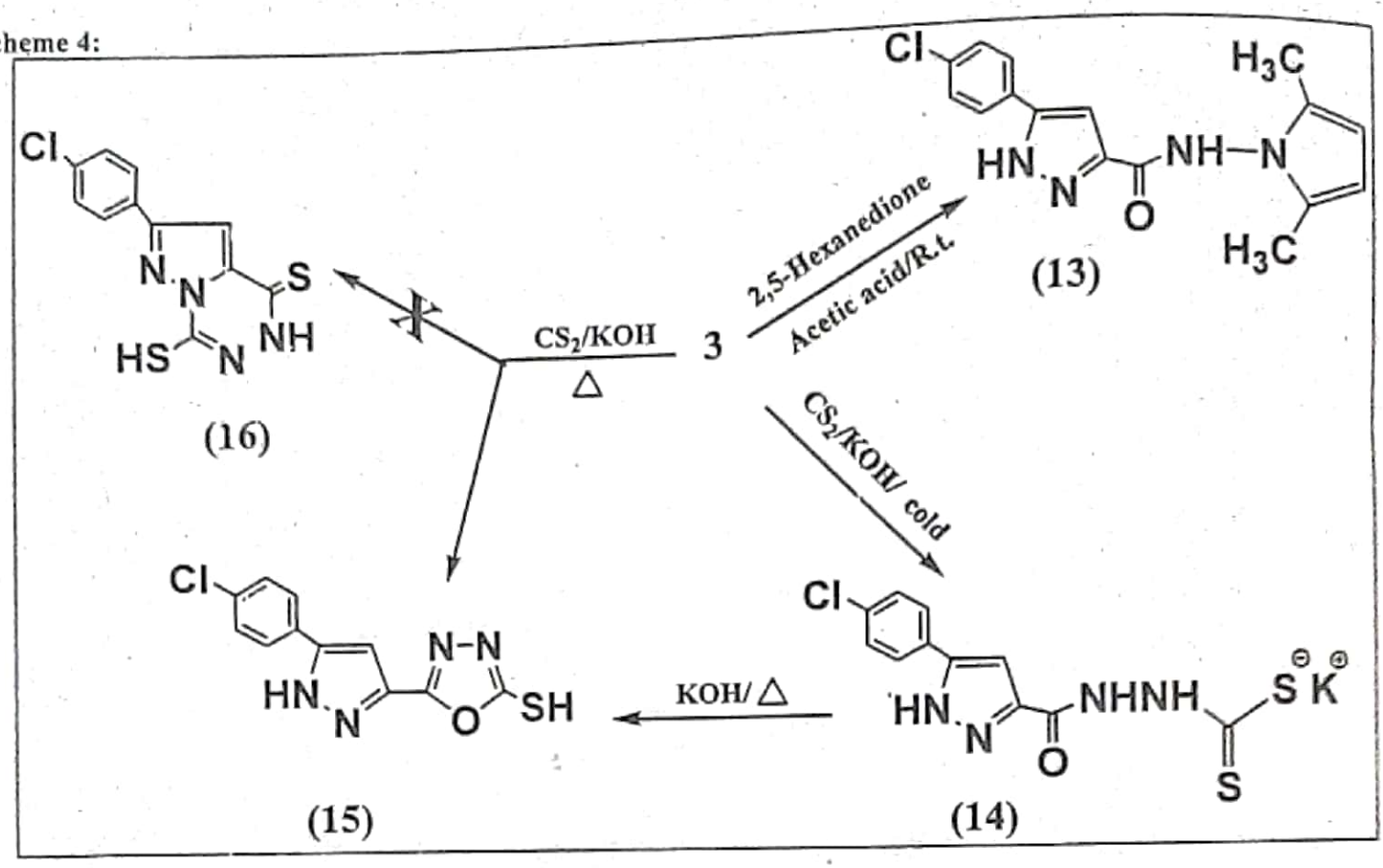
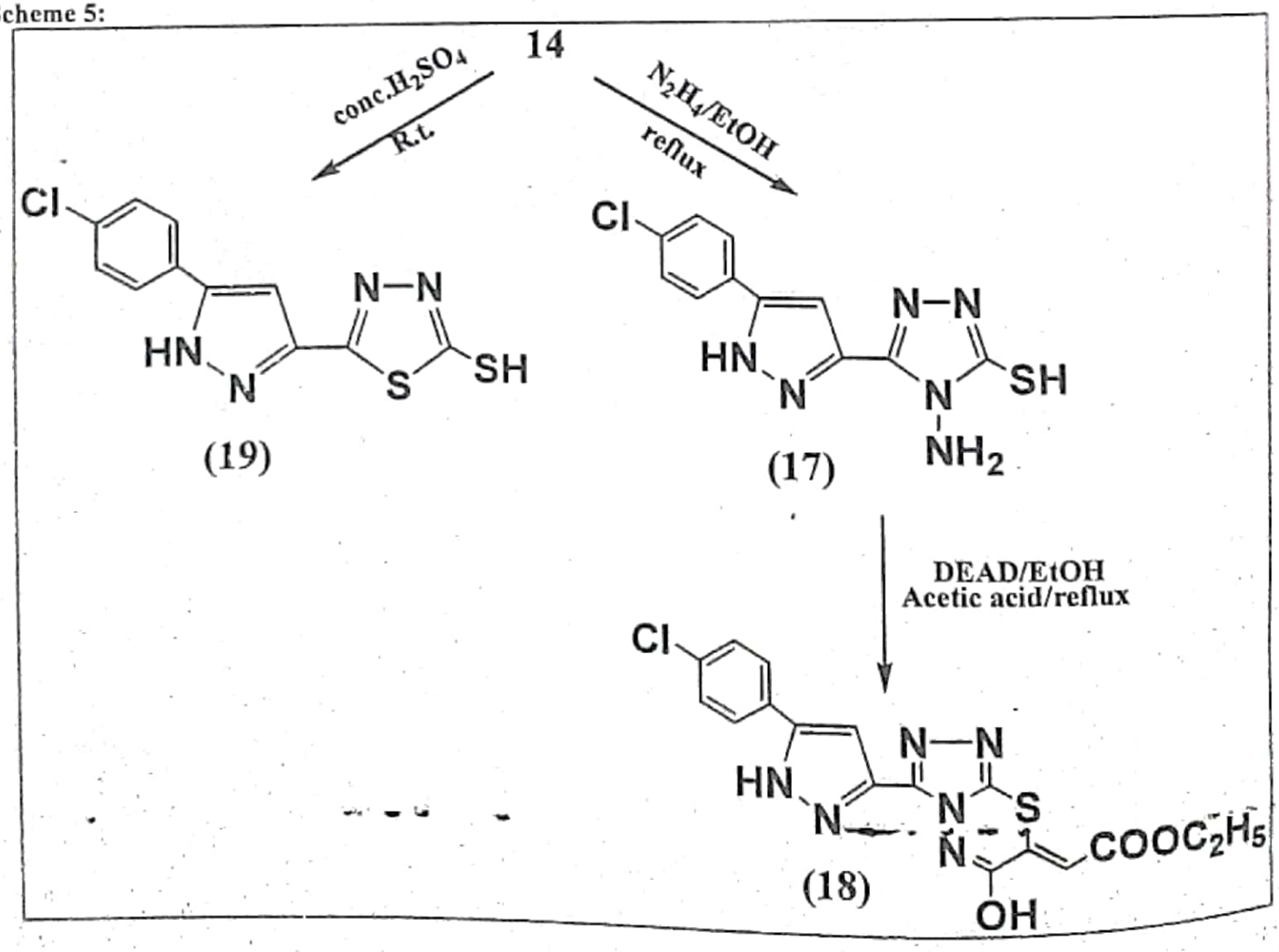


8	R	R^1
a	H	*p*-NO_2-C_6H_4-
b	H	*p*-Cl-C_6H_4-
c	H	*o*-Cl-C_6H_4-
d	H	Furyl
e	CH_3	*p*-NO_2-C_6H_4-
f	CH_3	*p*-Cl-C_6H_4-
g	CH_3	*p*-CH_3O-C_6H_4-

Scheme 4:



Scheme 5:



The intermediate ethyl 3-(p-chlorobenzoyl) pyruvate *(1)* (Scheme 1) was obtained via the reaction of p-chloroacetophenone and diethyl oxalate in sodium ethoxide. Ethyl 5-(p-chlorophenyl)-1H-pyrazole-3-carboxylate *(2)*, was prepared through the condensation of the 1,3-diketone intermediate *1* with one mole hydrazine hydrate. Key intermediate, 5-(p-chlorophenyl)-1H-pyrazole-3-carboxylic acid hydrazide *(3)*, was obtained via condensation of the intermediate *1* with two moles hydrazine hydrate in ethanol or hydrazinolysis of ethyl pyrazole-3-carboxylate derivative *2*.

The reaction of primary or secondary amines with the ester *2* in order to obtain the amides *6a-f* was failed. This can be explained by weak electrophilicity of the carbonyl carbon as a result of +M effect of both the lone pair of electrons of N-pyrrole like structure and the oxygen atom of the alcohol part of the ester *2*. Instead, the target amides *6a-f* were prepared by heating under reflux the acid chloride *5* with primary or secondary amines in dimethylformamide containing potassium carbonate. The acid chloride *5* was prepared from the corresponding acid *4* using phosphorous oxychloride. The acid *4* was, in turn, obtained by hydrolysis of the ester *2* under basic condition. On the other hand, benzimidazole derivative *(7)* was obtained via the reaction of o-phenylenediamine with the acid chloride *5* in the presence of potassium carbonate in dimethyl formamide adopting Kandemirli method[4] (Scheme 2).

Arylidenes and α-methylarylidenes *8a-g* (Seheme 3) were obtained by heating under reflux the hydrazide *3* and the appropriate aromatic aldehydes or aralkyl ketones in ethanol /acetic acid. Also, fusion of the carboxylic acid hydrazide *3* with ethyl acetoacetate led to the formation of 5-(p-chlorophenyl)-3-[(ethoxycarbonyl-2-propylidene)hydrazinocarbonyl]-1H-pyrazole *(9)* rather than the cyclized product *10*. This result came in accordance to a literature precedence[5]. The cyclized product *10* was obtained by refluxing the hydrazone *9* with aqueous sodium hydroxide or via the reaction of the hydrazide *3* with ethyl acetoacetate in aqueous NaOH[6].

Literature survey revealed that, the reaction of hydrazines and β-dicarbonyl compounds[7] or β-ketonitrile[8] continues to be the method of choice for the synthesis of 3,5-disubstitutedpyrazoles. Thus, the pyrazole derivatives *11 a,b* and *12* (Scheme 3) were obtained via the reaction of the hydrazide *3* with acetylacetone, benzoylacetone or ethyl cyanoacetate in ethanol containing potassium hydroxide under reflux. Compound *11a* was also obtained by fusion of the hydrazide *3* and acetylacetone. The structure of compound *12* came in accordance to the reported data[9]. Furthermore, when 2,5- hexanedione was allowed to react with the hydrazide *3* in acetic acid/ DMF, only the 2,5-dimethylpyrrole derivative *13* was obtained as a sole product (Scheme 4). Cyclocondensation of the hydrazide *3* with carbon disulphide in ethanol containing potassium hydroxide was investigated. The reaction offers the possibility of formation of two products 1,3,4-oxadiazole derivative *15* and/or the pyrazolotriazin-4-one derivative *16*. Although the outstanding feature of the reaction was the good regiochemical control by the formation of a single product, neither elemental analysis nor spectroscopic data could verify the structure of the product. Structure elucidation of *15* was done chemically by an unambiguous synthesis involving cyclic dehydrosulphurization of potassium dithiocarbazate *14* which was obtained via the reaction of the hydrazide *3* with carbon disulphide in a solution of potassium hydroxide in ethanol at room temperature. The product was identical in all aspects (m.p., IR and ^{1}HNMR) with the outcome from the reaction of the hydrazide *3* with carbon disulphide in ethanol containing KOH.

Adopting Reid and Heindel method[10], compound *17* (Scheme 5) was obtained by treating the potassium 3-[5-(p-chlorophenyl)-1H-pyrazol-3-carbonyl]dithio-carbazate *(14)* with hydrazine hydrate in ethanol. In addition, compound *18* was obtained by cyclocondensation of the triazole *17* with diethyl acetylene dicarboxylate in ethanol /acetic acid. This came in accordance to the reported data[11]. On the other hand, cyclodehydration of the potassium dithiocarbazate *14* was achieved by stirring with concentrated sulfuric acid at room temperature to yield the 5-mercapto-1,3,4-thiadiazole derivative *19*.

Table (1): 5-(p-Chlorophenyl)-1H-pyrazole-3-N-substituted carboxamides (6a-f)

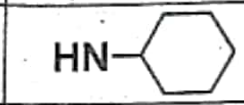
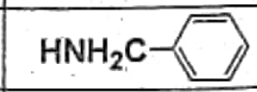
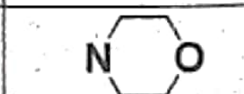
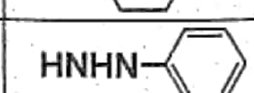
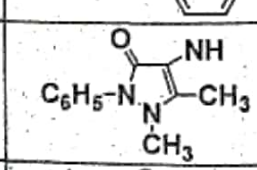
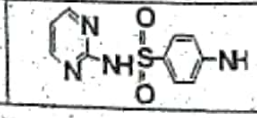
6	R	M.P. °C rea.time/h	Yield %	Molecular Formula (M.W) [M$^+$ m/z]	Analysis% Calcd.	Found
A		287-289	70	$C_{16}H_{14}ClN_3O$ (303.5)	C,63.26 H, 5 93 N,13 83	C,62.75 H, 5.57 N, 14.20
B		297-299	75	$C_{17}H_{14}ClN_3O$ (311.5)	C,65.48 H, 4.49 N,13.48	C,65.43 H, 4.38 N,13.19
C		275-277	65	$C_{14}H_{14}ClN_3O_2$ (291.5)	C,57.63 H, 4.80 N,14.40	C,57.39 H, 4.80 N,15.10
d		> 340	80	$C_{16}H_{13}ClN_4O$ (312.5)	C,61.44 H, 4.16 N,17.92	C,61.50 H, 4.60 N,18.35
e		> 340 (48h)	60	$C_{21}H_{18}ClN_3O_2$ (407.5) M$^+$=408	C,61.84 H, 4.41 N,17.17	C,61.89 H, 4.63 N,17.27
f		>340 (24h)	62	$C_{20}H_{15}ClN_6O_3S$ (454.5)	C,52.80 H, 3.30 N,18.48	C, 52.60 H, 3.66 N,18.03

Table 2: 3-Arylidenehydrazinocarbonyl-5-(p-chlorophenyl)-1H-pyrazole (8a-g)

8	R	R'	M.P.°C	Yield %	Molecular Formula (M.W)	Analysis% Calcd. Found	
a	H	*p*-$NO_2C_6H_4$	> 340	88	$C_{17}H_{12}ClN_5O_3$ (369.5)	C,55.20 H, 3.24 N,18.9	C,54.99 H,3.4 N,19.2
b	H	*p*-ClC_6H_4	> 340	85	$C_{17}H_{12}Cl_2N_4O$ (359)	C,56.80 H, 3.34 N,15.60	C,56.8 H, 3.36 N,15.61
c	H	*o*-FC_6H_4	294-296	81	$C_{17}H_{12}ClFN_4O$ (342.5)	C,59.56 H, 3.50 N,16.30	C,59.56 H, 3.34 N,16.9
d	H		285-287	89	$C_{15}H_{11}ClN_4O_2$ (314.5)	C,57.23 H, 3.49 N,17.80	C,57.16 H, 3.92 N,17.43
e	CH_3	*p*-$NO_2C_6H_4$	> 340	90	$C_{18}H_{14}ClN_5O_3$ (383.5)	C,56.32 H, 3.65 N,18.25	C,54.96 H, 3.91 N,18.77
f	CH_3	*p*-ClC_6H_4	> 340	85	$C_{18}H_{14}Cl_2N_4O$ (373)	C,57.90 H, 3.75 N,15.01	C,57.78 H, 3.96 N,15.46
g	CH_3	*p*-$CH_3OC_6H_4$	294-296	82	$C_{19}H_{17}ClN_4O_2$ (368.5)	C,61.87 H, 4.61 N,15.19	C,62.48 H, 4.97 N,15.59

Anti-inflammatory activity:

Compounds *(6 e,f - 8c,d,g - 10 and 11a,b)* were evaluated for their anti-inflammatory activity (Table 3). Compound 6f which have a sulfadiazine moiety linked to the pyrazole proved to be more powerful than the standard drug along the entire period of the experiment (4 hours) and this is due to the synergistic effect of both pyrazole and sulfadiazine. Antipyrine substituent in compound *6e* also enhanced the significance as anti-inflammatory. The 3-methyl-5-pyrazolone derivative 10 was more potent than 3-methyl-5-phenylpyrazol-1-yl derivative *11b*, this came in accordance with the reported anti-inflammatory activity of pyrazolones (2). *p*-Flurobenzylidene derivative 8c was the most active among other benzylidenes. Finally, 3,5-dimethylpyrazol-1-yl derivative 11a showed the least anti-inflammatory activity, while the benzylidenes *8d* and *8g* had a non significant activity.

Table 3: The anti-inflammatory activity of the investigated compounds using rat paw

Comp.No.	Initial thickness (mm)	Thickness of rat paw in mm			
		One hour	2 hours	3 hours	4 hours
Control Carragenin	2.125 ± 0.012	4.375 ± 0.037	5.875 ± 0.024	6.375 ± 0.042	7.00 ± 0.035
Standard diclofenac sodium	2.0 ± 0.00	3.75 ± 0.014	3.75 ± 0.014	3.875 ± 0.024	4.125 ± 0.034
6e	2.500 ± 0.028	3.625 ± 0.031	3.625 ± 0.031	4.250 ± 0.025	4.250 ± 0.014
6f	2.250 ± 0.025	3.250 ± 0.014	3.375 ± 0.012	3.75 ± 0.032	3.785 ± 0.034
8c	2.000 ± 0.00	3.625 ± 0.012	4.125 ± 0.012	4.375 ± 0.012	4.625 ± 0.024
8d	2.250 ± 0.011	4.000 ± 0.020	5.700 ± 0.028	6.000 ± 0.030	6.250 ± 0.03
8g	2.500 ± 0.028	3.750 ± 0.014	5.200 ± 0.012	5.700 ± 0.017	6.375 ± 0.012
10	2.500 ± 0.029	3.625 ± 0.024	3.875 ± 0.024	4.250 ± 0.032	4.375 ± 0.03
11a	2.000 ± 0.010	3.750 ± 0.018	4.000 ± 0.020	4.625 ± 0.023	4.750 ± 0.024
11b	2.250 ± 0.025	3.250 ± 0.014	4.000 ± 0.020	4.250 ± 0.014	4.500 ± 0.020

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التشييد و الفعالية المضادة للالتهابات لمشتقات البيرازول الجديدة

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تعتبر حلقة البيرازول حجر الأساس للعديد من المركبات التى لها الكثير من الأهمية البيولوجية و خاصة مضادات الالتهابات الغير ستيرويديه و التى تتميز بأن لها تأثيرفعال و درجة سميه منخفضة .و بناء عليه فقد تم فى هذا البحث تحضير مركب ٥-(٤-كلوروفينيل)- بيرازول-٣- كربوكسيليك هيدرازيد (٣) و الذى استخدم كمركب وسطى لتحضير العديد من المركبات الحلقية الجديدة. و قد تم تحضير العديد من الأميدات (٦) كمضادات للالتهاب من مركب ٥-(٤-كلوروفينيل) بيرازول-٣- حامض الكربوكسيليك عند طريق تفاعل كلوريد الحامض (٥) مع العديد من الأمينات الأولية و الثانوية .

و الجدير بالذكر أن المركب (٦) و الذى يحتوى على مجموعات سلفاديازين و الأنتيبيرين ، وجد له تأثير عالى كمضاد للالتهاب مقارنة بعقار ديكلوفيناك الصوديوم.

و بتفاعل الهيدرازيد مع العديد من الألدهيدات والكيتونات تم الحصول على بعض الهيدرازونات (٨) .و عند تفاعل الهيدرازيد مع أسيتو أسيتات الايثيل تحت ظروف مختلفة تم الحصول على مركبين مختلفين .و كذلك تم الحصول على مشتقات أخرى من البيرازول بتفاعل الهيدرازيد مع الأسيتيل أسيتون و سيانو أسيتات الايثيل.

وقد تم حلقنة الهيدرازيد سالف الذكر الى البيرول (١٣) بتفاعل الأول مع الأسيتونيل أسيتون. بينما عند تفاعل الهيدرازيد مع ثنائى كبريتيد الكربون فى وجود هيدروكسيد البوتاسيوم بالتسخين الى الأوكساديازول (١٥).وكذلك تم الحصول على مركب التريازول امينو ثيول (١٧) بتفاعل مركب بوتاسيوم ثنائى ثيوكربازيت مع الهيدرازين هيدرات و مركب الثياديازول (١٩) مع حامض الكبريتيك المركز فى درجة حرارة الغرفة. ثم بتفاعل مركب التريازول أمينو ثيول مع ثنائى بنزل أسيتيلين ثنائى الكربوكسيلات تم الحصول على مشتق التريازولوثياديازين (١٨).