SYNTHESIS OF NOVEL MANNICH BASES CONTAINING PYRAZOLONES AND INDOLE SYSTEMS

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Abstract Novel mannich bases 7 a-h were synthesized the condensation reaction between 3-Methyl-5-oxo-4-(4'-phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid hydrazide 4 With Isatin yielded the corresponding [3-Methyl-5-oxo-4-(4'-substituted aryl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid(2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide 6, this was subjected to mannich reaction with cyclic secondary amines in the presence of formaldehyde in DMF to give corresponding hydrazide 7 in excellent yields. The structures of these newly synthesized compounds were characterized by ^{1}H-NMR, Mass, IR and elemental analysis.

Introduction

Heterocyclic compounds represents an important class of biologically active molecules specifically, those containing the pyrazolone nucleus have been shown to posses high biological activities such as tranquillizing, muscle relaxant, psycho analeptic, anticonvulsant, antihypertensive, antidepressant activities. The derivatives of pyrazolone are important class of antipyretic and analgesic Compounds [1-7]

Medicinal chemists have been designed used pyrazolones extensively as scaffolds from which novel therapeutic agents. This heterocyclic ring system is found in a number of compounds showing analgesic morazone[8] immunosuppressant BTS-71412[9] and anti-inflammatory (aspirin–propyphenazone) activity. Numerous methods for general pyrazolone synthesis have been reported[10]

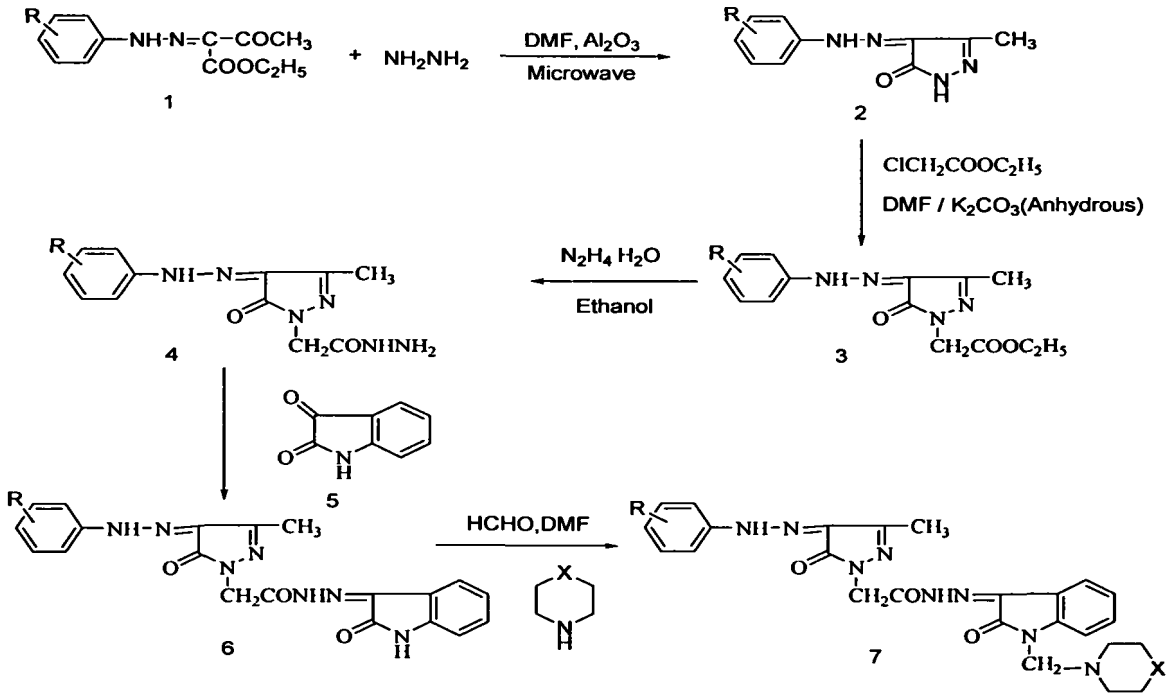
Some substituted pyrazolines and their derivatives are used as antitumor[11] anti bacterial, antifungal, antiviral, anti parasitic, anti-tubercular and insecticidal agents[12-20] some of these compounds have also anti-inflammatory, anti-diabetic, and anesthetic properties[21-23]

Results and Discussion

The development of carbon- nitrogen bond formation was described in all the steps of our synthetic sequence. The advent of microwave synthesis also implemented with the improved yield of 90%. A further step involves simple reaction conditions and good yield procedure. Compound 6 was allowed to undergo the Mannich reaction with different secondary Amines namely piperidine, morpholine and *N*-methyl piprazine and Para formaldehyde in absolute ethanol to give compounds 7 a-c respectively.

The IR spectrum of 7 revealed the appearance of bands characteristics of 3195 (NH), 1610 (C = N), 1676 (pyrazoline C = O), 1720 (Indole C = O), and 1654 (C – NH). The appearance of a signal at δ4.5 due to (N – CH_2- N), 3.70 (t, 4H, CH_2-O-CH_2), 2.70 (t, 4H, CH_2-N-CH_2), 4.20 (s, 3H, N-CH_3), conformed the formation of Mannich bases.

Scheme-1



1a, 2a, 3a, 4a, 6a, 7a R = H
1b, 2b, 3b, 4b, 6b, 7b R = 4-CH3
1c, 2c, 3c, 4c, 6c, 7c R = 4-0CH3
1d, 2d, 3d, 4d, 6d, 7d R = 4-0C2H5
1e, 2e, 3e, 4e, 6e, 7e R =4- Cl
1f, 2f, 3f, 4f, 6f, 7f, R=4-Br

7a R=H, X=CH2
7g R=H, X=O
7h R=H, X=N-CH3

General procedures

4-substituted aryl hydrazono acetoacetic ester 1 was prepared by the procedure described by H.M.W.alborsky, M.E.Baum[24]

Condensation of 4-substituted aryl hydrazono acetoacetic ester 1 and hydrazine in the presence of catalytic amount of dimethyl formamide under microwave irradiation afforded Synthesis of 3-methyl-4- (4'-substituted aryl hydrazono)-pyrozoline-5-one 2.

A mixture of 2, anhydrous K_2CO_3, Chloro ethyl acetate and DMF were stirred at room temperature for 8 hours. The reaction mixture was diluted with ice-cold water. The separated solid was identified as 3 this was collected by filtration.

A solution of 3 and hydrazine hydrate in ethanol was refluxed for five hours. The reaction mixture was cooled and poured onto ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford 4.

A mixture of 4 and 5 in 1: 1 ratio when heated in DMF (10 ml) on water bath for 45 minutes yielded a compound was filtered washed with water and recrystallized from ethanol to afford 6, the required Isatin 5 was prepared by the procedure described by Marvel and Heirs[25]

Compounds 6 was subjected to Mannich reaction with cyclic secondary amines (piperidine) / morpholine / N-methyl piperazine) in the presence of formaldehyde in DMF to give [3-Methyl-5-oxo-4- (4'-substituted aryl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro–indol-3-ylidene)- hydrazide 7 in excellent yields.

Experimental

All the chemicals were used as received without further purification. Melting points were measured on a Gallenkamp Electro thermal melting point apparatus and are uncorrected. Reactions were carried out using household micro oven (power consumption 1200 W, microwave frequency 2450 MHz) and monitored by thin layer chromatography (TLC) on silica gel plates (60 F254) visualizing with ultraviolet light or iodine spray. ^{1}H NMR spectra were determined in DMSO-d_6 solution on 400 or 200 MHz AMX Spectrometers. Proton chemical shifts are relative to tetramethylsilane as internal standard and expressed in ppm.

Mixtures of 1 and hydrazine hydrate and dimethyl formamide (10 drops) were subjected to microwave irradiation at 150W intermittently at 30 sec intervals for 2 minutes. After complete conversion as indicated by TLC, the reaction mixture was cooled and treated with cold water. The precipitate 3-methyl 4-(4'-substituted aryl hydrazono) pyrazoline-5-one 2 was filtered and recrystallized from ethanol.

A mixture of [3-methyl-5-oxo-4- (4-substituted aryl hydrazono)-4,5-pyrazoline-5-one 2 (0.02M) anhydrous K_2CO_3 (0.03M) Chloro ethyl acetate (0.02M) and DMF was stirred at room temperature for 8 hours, the reaction mixture was diluted with ice-cold water. The separated solid was identified as 3. This was collected by filtration and recrystallized from ethanol.

A solution of 3 (0.01M) and hydrazine hydrate (0.015M) in ethanol 20 ml was refluxed for 5 hours. The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford 4.

[3-Methyl-5-oxo-4-(aryl hydrazono)-4, 5-dihydro-pyrazol-1-yl]-acetic acid (2-oxo-1,2-dihydro–indol-3- ylidene)-hydrazide 6 a-f.

Equimolar quantities (0.01 mol) of Isatin 5 and the corresponding amino compound (6 a-f) were dissolved in warm ethanol (40 ml) containing DMF (0.5 ml). The reaction mixture was refluxed for 1-4 hr and then kept at room temperature overnight. The resulting solid was filtered and washed with ethanol, dried and recrystallized from ethanol to afford compounds (6a-f).

[3-Methyl-5-oxo-4- (phenyl-hydrazono)-4, 5-dihydro-pyrazol-1-yl]-acetic acid (2-oxo-1, 2-dihydro-indol-3-ylidene)-hydrazide 6 a: Yield 70%, m.p.214°C; IR (KBr disc cm^{-1})3205,3170,1602,1670 and 1618; ^{1}H-NMR (DMSO-d_6, δppm): 1.1 (*s*, 3H, CH_3) 7.2(*s*, 1H, Ar - NH) 9.7 (*s*, 1H, CONH) 3.9 (*s*, 2H, N-CH_2 - CO) 10.42(*s*, 1H, Indole NH) 6.4- 7.6 (m, 9H, Ar -H); ^{13}C-NMR: (DMSO-d_6, δppm): 18.6, 54.5, 116.3, 117.8, 118.8, 121.7, 124.5, 128.6, 129.4, 131.3, 133, 146.8, 148, and 167.7; EI ms: m/z: 403 Anal.Calcd.for $C_{20}H_{17}N_7O_3$ (403.39) C:59.74; H: 4.43; N: 24.46; Found C: 59.55; H: 4.25; N: 24.31.

[3-Methyl-5-oxo-4-(p-tolyl-hydrazono)-4,5-dihydro-pyrazol-1-yl]-aceticacid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide 6 b: obtained as yellow orange crystals; Yield 70%, m.p. 241°C. IR (KBr disc cm^{-1}) 3180 , 3140 , 1600 , 1674 , 1700 and 1622; ^{1}H-NMR (DMSO-d_6, δppm): 1.14 (s, 3H, CH_3) 2.39(s,3H,Ar-CH_3) 7.4(s, 1H, Ar - NH) 10.2 (s, 1H, CONH) 3.92 (s, 2H, N-CH_2- CO) 10.47 (s, 1H, Indole NH) 6.43-7.62 (m, 8H, Ar -H); EI ms: m/z: 417.1; Anal.Calcd.for $C_{21}H_{19}N_7O_3$ (417.42) C: 60.60; H: 4.77; N: 23.63; Found C: 60.42; H: 4.59; N: 23.49.

{4-[(4-Methoxy-phenyl)-hydrazono]-3-methyl-5-oxo-4,5-dihydro-pyrazol-1-yl}-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide 6 c:

obtained as orange crystals; Yield 70%, m.p. 234 °C; IR (KBr disc cm^{-1}) 3100, 3150, 1505, 1674, 1701 and 1625; ^{1}H-NMR (DMSO-d_6, δppm): 1.12(s, 3H, CH_3) 3.73(s, 3H, OCH3) 7.1 (s, 1H, Ar -NH) 10.35 (s, 1H, CONH) 4.1 (s, 2H, N-CH_2 - CO) 10.46(s, 1H, Indole NH) 6.43-7.58(m, 8H, Ar - H); EI ms: m/z: 433; Anal.Calcd.for $C_{21}H_{19}N_7O_4$ (433.42) C: 58.37; H: 4.32; N: 22.77. Found C: 58.19; H: 4.42; N: 22.62.

{4-[(4-Ethoxy-phenyl)-hydrazono]-3-methyl-5-oxo-4,5-dihydro-pyrazol-1-yl}-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide 6 d: obtained as orange crystals; Yield 75%, m.p. 224 °C; IR (KBr disc cm^{-1}) 3195, 3155, 1604, 1674, 1701 and 1624; ^{1}H-NMR (DMSO-d_6, δppm): 0.98 (s, 3H, CH3) 1.34(t, 3H, CH3) 3.96(q, 2H, O-CH2) 7.18(s, 1H, Ar-NH) 10.21 (s, 1H, CONH) 4.2 (s, 2H, N-CH_2 - CO) 10.47 (s, 1H, Indole NH) 6.43-7.60 (m, 8H, Ar - H); EI ms: m/z: 447.1; Anal.Calcd.for $C_{22}H_{21}N_7O_4$ (447.45) C: 59.23; H: 4.90; N: 22.03; Found C: 59.05; H: 4.73; N: 21.91.

{4-[(4-Chloro-phenyl)-hydrazono]-3-methyl-5-oxo-4,5-dihydro-pyrazol-1-yl}-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide 6 e: obtained as reddish-orange crystals; Yield 75%, m.p. 225 °C; IR (KBr disc cm^{-1}) 3175, 3140, 1605, 1674, 1701 and 1624; ^{1}H-NMR (DMSO-d_6, δppm): 1.05(s, 3H, CH3) 6.98(s, 1H, Ar - NH), 10.73 (s, 1H, CONH), 3.7 (s, 2H, N-CH_2 -CO), 10.49(s, 1H, Indole NH), 6.43-7.6 (m, 8H, Ar - H); EI ms: m/z: 437; Anal.Calcd.for $C_{20}H_{16}N_7O_3Cl$ (437.84) C: 55.02; H: 3.84; N: 22.53. Found C: 54.86; H: 3.68; N: 22.39.

{4-[(4-Bromo-phenyl)-hydrazono]-3-methyl-5-oxo-4,5-dihydro-pyrazol-1-yl}-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide 6 f: obtained as orange brown crystals; Yield 80%, m.p. 243 °C; IR (KBr disc cm^{-1}) 3190, 3150, 1605, 1673, 1702 and 1625; ^{1}H-NMR (DMSO-d_6, δppm): 1.05(s, 3H, CH3), 6.98(s, 1H, Ar - NH) 10.83 (s, 1H, CONH) 3.8 (s, 2H, N-CH_2 -CO) 10.47 (s, 1H, Indole NH) 6.3-7.65 (m, 8H, Ar - H); EI ms: m/z: 481; Anal.Calcd.for $C_{20}H_{16}N_7O_3Br$ (482.29) C: 49.99; H: 3.48; N: 20.49. Found C: 49.81; H: 3.34; N: 20.33.

Synthesis of [3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro–indol-3-ylidene)- hydrazide 7 a-h.

A mixture of 6 (0.1 mol), piperidine (0.15 mol) and water (20 ml) was stirred to obtain a clear solution. To this solution, HCHO (0.05mol) and DMF were added in ice-cold condition and stirred for 2 hr in an ice-bath and left overnight at

room temperature. The obtained white solid was isolated and crystallized from ethanol. To give Compound 7 a the reaction procedure leading to 7a was then extended to the syntheses of 7b, 7 c and the Spectral data of the compounds (7 a–h) are listed.

[3-Methyl-5-oxo-4-(phenyl-hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid (2-oxo-1- piperidin-1-ylmethyl-1, 2-dihydro-indol-3-ylidene)-hydrazide 7 a: obtained as yellow-orange crystals; Yield 70%, m.p. 158 °C; IR (KBr disc cm^{-1}) 3195, 1720, 1610, 1676, 1654; ^{1}H-NMR (DMSO-d_6, □ppm): 1.40-1.52 (m, 6H (CH_2)$_3$) 2.56-2.62 (m, 4H, -CH_2-N-CH_2) 4.43 (s, 2H, -N-CH_2-N-) 9.5 (s, -CONH) 7.15 (s, 1H, Ar - NH) 3.95 (s, 2H, N-CH_2-CO) 6.45 - 7.7 (m, 9H, Ar-H); ^{13}C-NMR: (DMSO-d_6, □ppm): 18.8, 25. 6, 26.0, 51, 54.9, 70.9, 115.2, 118,120.1, 123, 124, 129, 131, 146, 162,173; EI ms: m/z: 500; Anal.Calcd.for $C_{26}H_{28}N_8O_3$ (500.55) C: 62.56; H: 5.78; N: 22.58; Found C: 62.39; H: 5.64; N: 22.39.

[3-Methyl-5-oxo-4-(p-tolyl-hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid (2-oxo-1-piperidin-1-ylmethyl-1,2-dihydro-indol-3-ylidene)-hydrazide 7 b : obtained orange crystals; Yield 70 %, m.p. 164 °C ; IR (KBr disc cm^{-1}) 3170, 1715, 1616, 1674, 1674; EI ms: m/z: 514; Anal.Calcd.for $C_{27}H_{30}N_8O_3$ (514.58) C: 63.13; H: 6.00; N: 21.96; Found C: 23.02; H: 5.88; N: 21.78.

{4-[(4-Methoxy-phenyl)-hydrazono]-3-methyl-5-oxo-4,5-dihydro-pyrazol-1-yl}-acetic acid (2-oxo-1-piperidin-1-ylmethyl-1,2-dihydro-indol-3-ylidene)-hydrazide 7 c : obtained as yellow crystals; Yield 70%, m.p. 167 °C; IR (KBr disc cm^{-1}) 3120, 1680, 1610, 1680, 1654; EI ms: m/z: 530.1; Anal.Calcd.for $C_{27}H_{30}N_8O_4$ (530.58) C: 61.27; H: 5.83; N: 21.26; Found C: 61.12; H: 5.70; N: 21.12.

{4-[(4-Ethoxy-phenyl)-hydrazono]-3-methyl-5-oxo-4,5-dihydro-pyrazol-1-yl}-acetic acid(2-oxo-1-piperidin-1-ylmethyl-1,2-dihydro-indol-3-ylidene)-hydrazide 7 d: obtained as yellow crystals; Yield 75%, m.p. 159 °C; IR (KBr disc cm^{-1}) 3175, 1711, 1614, 1674, and 1656; EI ms: m/z: 544; Anal.Calcd.for $C_{28}H_{32}N_8O_4$ (544.60) C: 61.92; H: 6.08; N: 20.72; Found C: 61.75; H: 5.92; N: 20.58.

{4-[(4-Chloro-phenyl)-hydrazono]-3-methyl-5-oxo-4,5-dihydro-pyrazol-1-yl}-acetic acid (2-oxo-1-piperidin-1-ylmethyl-1,2-dihydro-indol-3-ylidene)-hydrazide 7 e : obtained as orange crystals; Yield 75%, m.p. 161 °C; IR (KBr disc cm^{-1}) 3155, 1714, 1616, 1674, 1658; EI ms: m/z: 534; Anal.Calcd.for $C_{26}H_{27}N_8O_3Cl$ (535) C: 58.83; H: 5.24; N: 21.05. Found C: 58.70; H: 5.09; N: 20.94.

{4-[(4-Bromo-phenyl)-hydrazono]-3-methyl-5-oxo-4, 5-dihydro-pyrazol-1-yl}-acetic acid (2-oxo-1-piperidin-1-ylmethyl-1,2-dihydro-indol-3-ylidene)-hydrazide 7 f: obtained as reddish-orange crystals; Yield 80%, m.p. 160 °C; IR (KBr disc cm^{-1}) 3170, 1716, 1674, 1614, 1626; EI ms: m/z: 578; Anal.Calcd.for $C_{26}H_{27}N_8O_3Br$ (579.45) C: 54.02; H: 4.84; N: 19.47. Found C: 53.89; H: 4.70; N: 19.34.

[3-Methyl-5-oxo-4-(phenyl-hydrazono)-4, 5-dihydro-pyrazol-1-yl]-acetic acid (1-morpholin-4-ylmethyl-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide 7 g: obtained as orange crystals; Yield 85%, m.p. 159 °C; IR (KBr disc cm^{-1}) 3193, 1710, 1620, 1681, 1660; ^{1}H-NMR (DMSO-d_6, □ppm): 3.70-3.50 (m, 4H, CH2-O-CH2), 2.70-2.60 (m,4H,CH2-N-CH2), 4.40 (s, 2H, N-CH_2-N-) 4.7 (s, 2H, N-CH_2-CO-) 9.2 (s, 1H, CONH) 7.35 (s, 1H, Ar - NH) 6.4 - 7.62 (m, 9H, Ar - H); EI ms: m/z: 502; Anal.Calcd.for $C_{25}H_{26}N_8O_4$ (502.53) C: 59.90; H: 5.32; N: 22.35. Found C: 59.76; H: 5.17; N: 22.31.

[3-Methyl-5-oxo-4-(phenyl-hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid [1-(4-methyl-piperazin-1-ylmethyl)-2-oxo-1,2-dihydro-indol-3-ylidene]-hydrazide 7 h : obtained as yellow-orange crystals; Yield 80%, m.p. 157 °C; IR (KBr disc cm^{-1}) 3180, 1710, 1617, 1666, 1657; ^{1}H-NMR (DMSO-d_6, □ppm): 2.62-2.71 (m, 4H, CH_2-N-CH_2) 2.93 (s, 3H, N-CH_3) 4.52 (s, 2H, N-CH_2-N-) 4.9 (s, 2H, N-CH_2-CO-) 9.4 (s, 1H, CONH) 7.15 (s, 1H, Ar -NH) 6. 5 - 7.6 (m, 9H, Ar - H); EI ms: m/z: 515; Anal.Calcd.for $C_{26}H_{29}N_9O_3$ (515.57) C: 60.69; H: 5.75; N: 24.58; Found C: 60.58; H: 5.63; N: 24.46.

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