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Synthesis of Novel Mannich Bases Containing Pyrazolones and Indole Systems

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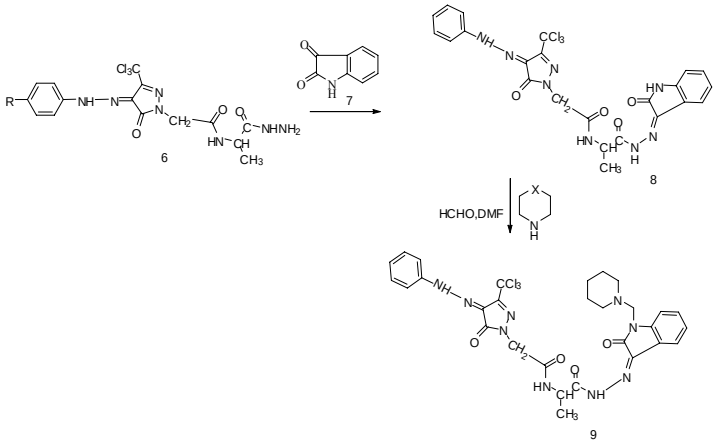
Abstract

Novel mannich bases **9a-h** were synthesized by condensation reaction between 3-Methyl-5-oxo-4-(4'-phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid hydrazide **6** With Isatin **7** 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 **8**, this was subjected to mannich reaction with cyclic secondary amines in the presence of formaldehyde in DMF to give corresponding hydrazide **9** in excellent yields. The structures of these newly synthesized compounds were characterized by ^{1}H-NMR, Mass, IR and elemental analysis.

Graphical Abstract
Synthesis of novel mannich bases containing Pyrazolones and indole systems



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 and used pyrazolones extensively as scaffolds from which novel therapeutic agents are synthesized. 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]

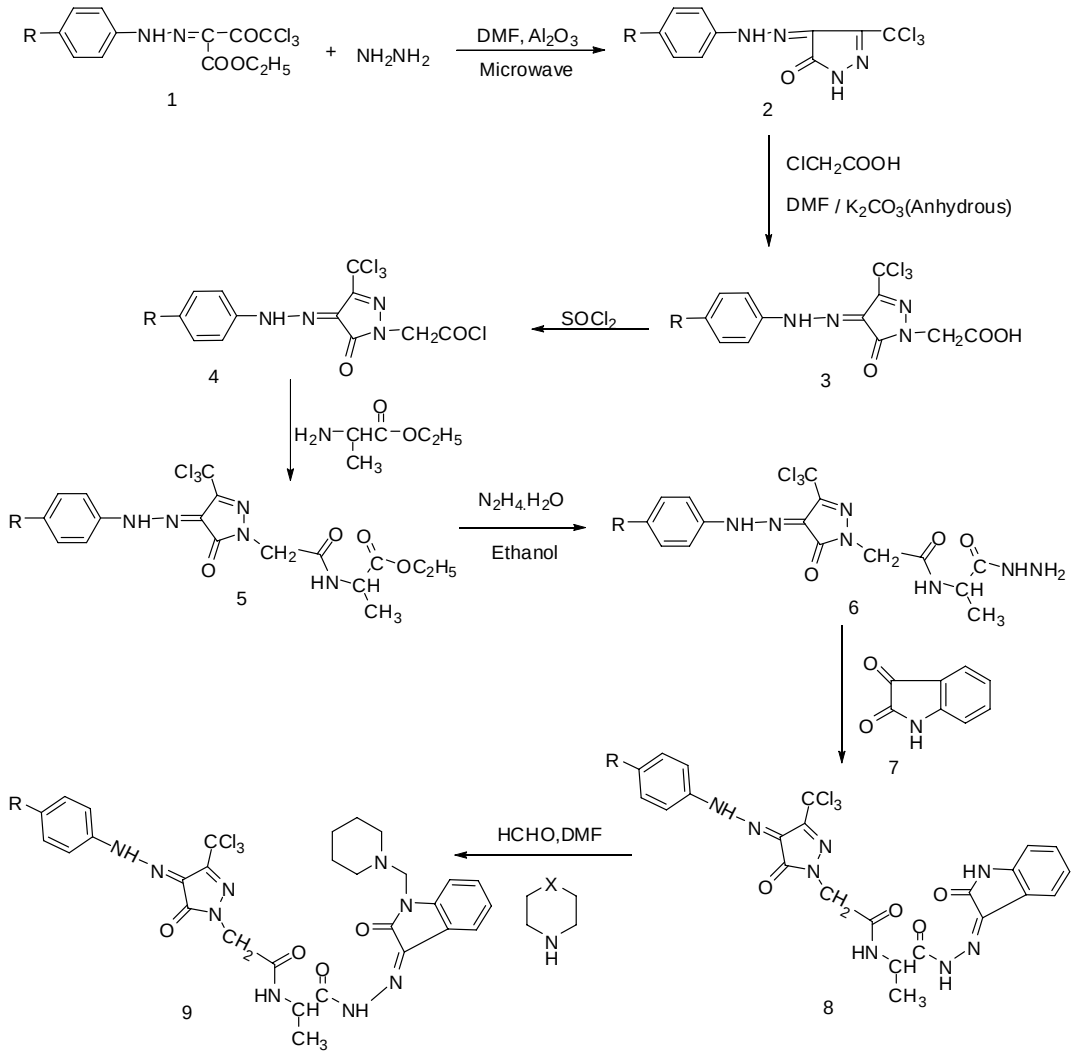
Some substituted pyrazolines and their derivatives are used as antitumor[11] anti bacterial, antifungal, antiviral, anti parasitic, anti-tubercular and insecticidal agents[12-20] some of these compounds have also anti-inflammatory, anti-diabetic, and anesthetic properties[21-23]

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 8 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 9a-h respectively.

The IR spectrum of **9** revealed the appearance of bands characteristics of 3301 (NH), 1608 (C = N), 1622 (pyrazoline C = O), 1792 (Indole C = O), and 3102 (N – NH). The appearance of a signal at δ4.38 due to (N – CH_2- N), 3.52 (t, 4H, CH_2-O-CH_2), 2.15-2.19 (t, 4H, CH_2-N-CH_2), 4.31 (s, 2H, –N–CH_2–N–), conformed the formation of Mannich bases.

Scheme-1



1a- 9a R = H

1b- 9b R = 4-CH_3

1c -9c R = 4-OCH_3

1d-9d R = 4-OC_2H_5 9a R=H, X=CH_2

1e-9e R =4- Cl 9g R=H, X=O

1f-9f R=4-Br 9h R=H, X=N-CH_3

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 JOEL AL300 spectrometers. Proton chemical shifts are relative to tetramethylsilane as internal standard and expressed in ppm.

Ethyl 4,4,4-trichloro-3-oxo-2-(2-phenyl hydrazono) butanoate (1) was prepared by the procedure described by H.M.W.Alborsky, M.E.Baum[24]

4-(4-sudtituted aryl hydrazono)-5-trichloromethyl-2, 4-dihydro-pyrazol-3-one (2)
A mixture of **(1)** and hydrazine hydrate and Dimethyl formamide (10 drops) was subjected to microwave irradiation at 150W intermittently at 30 seconds 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. With an yield of 85%.

2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetic acid (3)
A mixture of **(2)**, 2-chloroacetic acid, anhydrous K_2CO_3 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 2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetic acid **(3)**. Yield 71%, m.p.: 181^{0}C; ^{1}H-NMR (400 MHz,DMSO-d_6δppm): 3.65(s,2H,N CH_2CO), 10.56 (s, H, Ar-NH), 12.68 (s,1H,COOH) 6.81 -7.88 (m, 5H, for C_6H_5 phenyl group);^{13}C-NMR (400 MHz,DMSO-d_6δppm): 51.7 (CH_2), 116-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 149 (CCl_3 - C), 168.4 (Acid C=O); IR (KBr): $\overline{\nu}$ = 1600, 3120,2967,1682,1617 cm^{-1} and these are due to C = N, NH, acid carbonyl and cyclic carbonyl in five membered hetero cyclic ring respectively Anal. Calcd. for $C_{12}H_9Cl_3N_4O_3$ (363.58); C, 39.64; H, 2.50; N, 15.41; found (%); C: 38.23, H: 3.13, N: 22.31.

2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetyl chloride (4)
To a solution of 2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetic acid (**3**). (900 mg) in toluene (30 mL) was added thionyl chloride (0.90 mL) at room temperatures. The resulting solution was heated to reflux for 2 h. Then, it was cooled to room temperature and the excess thionyl chloride and toluene was removed under vacuum. The residue was dissolved one time in toluene and removed again under vacuum to afford 2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetyl chloride **(4)**. Yield 58%, m.p.: 173^{0}C; ^{1}H-NMR (400 MHz,DMSO-d_6δppm): 3.81(s,2H,N CH_2CO), 10.70 (s, H, Ar-NH), 6.78 -7.88 (m, 5H, for C_6H_5 phenyl group) ; ^{13}C-NMR (400 MHz,DMSO-d_6 ppm): 64.5 (CH_2), 116-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (

CCl_3), 145 (CCl_3 - C), 173.5 (Acid Chloride C=O); IR (KBr): $\bar{\nu}$ = 3180,1696,1617,1651 cm^{-1} and these are due to NH, cyclic carbonyl in five membered hetero cyclic ring exo > C = N, acid chloride respectively Anal. Calcd. for $C_{12}H_8Cl_4N_4O_2$ (382.03); C, 37.73; H, 2.11; N, 14.67; found (%); C: 38.23, H: 3.13, N: 22.31.

Ethyl2-(2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamido) propanoate (5)

A solution of acid chloride **(4a-f)** (2.47 mol) in dichloromethane (30 mL) were added DL-Alanine ethyl ester hydrochloride (735 mg, 2.5 mol) and diisopropylethylamine (1.3 mL, 7.5 mol) at 0°C. Then, the solution warmed to room temperature and it was stirred overnight. Then, it was diluted with water (50 mL) and dichloromethane (50 mL). The two layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layer was washed with brine solution and dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration of the solvent gave the crude residue which was purified by using column chromatography to give ethyl 2-(2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl) acetamido) propanoate **(5a-f)** (1.5 g) as a colorless oil. Yield 65%, m.p.: 184^0C; ^{1}H-NMR (400 MHz,DMSO-d_6,δppm) : 1.25-1.28 (d,3H, CH_2CH_3), 2.12-2.15(t,3H,$CHCH_3$), 3.51(s,2H, NCH_2),4.22-4.27(q,2H OCH_2) 5.18-5.25(q,1H,CH CH_3), 10.72 (s, H, CONH), 12.58 (s, H, Ar-NH), 6.82 -7.94 (m, 5H, for C_6H_5 of phenyl group); ^{13}C-NMR (400 MHz,DMSO-d_6,δppm): 64.5 (CH_2), 116-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHNH$_2$), 168 (C=ONH), 49(CHC=O), 17.3(CH_3CH), 65(CH_2C=O) 14(CH_2CH_3); IR (KBr): $\bar{\nu}$ = 3164, 3120, 1592, 1617, 1689, 1732 cm^{-1} and these are due to >NH, CO-NH exo > C = N, cyclic carbonyl in five membered heterocyclic ring, carbonyl group, ester carbonyl group respectively ; Anal. Calcd. for $C_{17}H_{18}Cl_3N_5O_4$ (462.71); C, 44.13; H, 3.92; N, 15.14; found (%); C: 44.20, H: 4.21, N: 22.31.

(E)-N-(1-(hydrazinyloxy)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide (6)

A solution of **(5)** (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 **(6)** Yield 64%, m.p. 132^0C; ^{1}H-NMR (400 MHz,DMSO-d_6,δppm): 2.08-2.10 (d,3H, $CHCH_3$), 3.78(s,2H, NCH_2CO), 4.31(s, 2H, NH_2),4.77-4.82(q, H CH_3 CH), 9.72 (s, H, CONH), 11.16 (s, H, NH), 10.75(s, H, Ar-NH), 6.82 -7.98 (m, 5H, for C_6H_5 of phenyl group); ^{13}C-NMR (400 MHz,DMSO-d_6,δppm): 64.5 (CH_2), 116-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHNH2) 168 (C=ONH) 49(CHC=O); IR (KBr): $\bar{\nu}$ = 3420, 3380, 3198, 3132, 3108, 1720, 1680, 1615 and these are due to – NH_2, CO–NH, >NH, Ar-NH exo > C = N, cyclic carbonyl in five membered hetero cyclic ring respectively, Anal. Calcd. for $C_{15}H_{16}Cl_3N_7O_3$ (448.69); C: 40.15, H: 3.59, N: 21.85 found (%); C: 40.17, H: 3.62, N: 21.88.

The required Isatin **7** was prepared by the procedure described by Marvel and Heirs[25]

Synthesis of N-(1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide (8a-f)

Equimolar quantities (0.01 mol) of Isatin (**7**) and the corresponding amino compounds **(6a-f)** were dissolved in warm ethanol (40 mL) containing DMF (0.5 mL). The reaction mixture was refluxed for 1-4 hours and then kept at room temperature overnight. The resulting solid was filtered and washed with ethanol, dried and recrystallized from ethanol to afford compounds **(8a-f).**

N-(1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 8 a: obtained as yellow-orange crystals; Yield 62%, m.p. 216 ^{o}C; ^{1}H-NMR (400 MHz,DMSO-d_6,δppm): 1.67-1.70 (d,3H, CH_3), 3.68(s,2H, NCH_2CO), 4.70-4.81(q,H,CH_3CH) 9.58 (s, H, CONH), 11.08 (s, H, Ar-NH), 12.92 (s, H, CO -NH), 6.78 -8.37 (m, 9H, for C_6H_5 and C_6H_5 of two phenyl groups);^{13}C-NMR: (400 MHz,DMSO-d_6, δppm): 64.5 (CH_2), 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N); IR (KBr disc cm^{-1}) 3302, 3210, 3118, 3080, 1592, 1798, 1738, 1654, 1618 EI ms: m/z: 576.06; Anal.Calcd.for $C_{23}H_{19}Cl_3N_8O_4$ (577.81) C: 47.81; H: 3.31; N: 19.39; Found C: 47.84; H: 3.36; N: 19.42.

N-(1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propan-2-yl)-2-(5-oxo-4-(2-p-tolylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 8b: Yield 65%, m.p. 230 ^{o}C; ^{1}H-NMR (400 MHz,DMSO-d_6, δppm): 3.14 (s, 3H, Ar – CH_3), 1.67-1.70 (d,3H, CH_3), 3.67(s,2H, NCH_2CO), 4.70-4.81((q,H,CH_3CH) 9.57 (s, H, CONH), 11.09 (s, H, Ar-NH), 12.93 (s, H, CO -NH), 6.76 -8.35 (m, 8H, for C_6H_5 and C_6H_5 of two phenyl groups)^{13}C-NMR: (400 MHz,DMSO-d_6, δppm): 64.5 (CH_2), 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N); 21.8(Ar-CH_3) ; IR (KBr disc cm^{-1}) 3302, 3210, 3118, 3080, 1592, 1798, 1738, 1654, 1618;EI ms: m/z: 590.08; Anal.Calcd.for $C_{24}H_{21}Cl_3N_8O_4$ (591.83) C: 48.71; H: 3.58; N: 18.93; Found C: 48.76; H: 3.64; N: 19.00.

2-(4-(2-(4-methoxyphenyl)hydrazono)-5-oxo-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propan-2-yl)acetamide 8c: Yield 64%, m.p. 223 ^{o}C; ^{1}H-NMR (400 MHz,DMSO-d_6, δppm): 3.25 (s, 3H, OCH_3), 1.67-1.70 (d,3H, CH_3), 3.66(s,2H, NCH_2CO), 4.70-4.81 (q,H,CH_3CH) 9.56 (s, H, CONH), 11.07 (s, H, Ar-NH), 12.94 (s, H, CO -NH), 6.77 - 8.36 (m, 8H, for C_6H_5 and C_6H_5 of two phenyl groups) ^{13}C-NMR: (400 MHz,DMSO-d_6, δ ppm): 64.5 (CH_2), 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N); 56(O-CH_3) ; IR (KBr disc cm^{-1}) 3302, 3210, 3118, 3080, 1592, 1798, 1738, 1654, 1618;EI ms: m/z: 606.07; Anal.Calcd.for $C_{24}H_{21}Cl_3N_8O_5$ (607.83) C: 47.42; H: 3.48; N: 18.43; Found C: 47.44; H: 3.52; N: 18.47.

2-(4-(2-(4-ethoxyphenyl)hydrazono)-5-oxo-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propan-2-yl)acetamide 8d: Yield 68%, m.p. 240 ^{o}C; ^{1}H-NMR (400 MHz,DMSO-d_6, ppm): 1.34 (t, 3H, CH_3), 4.12 (q, 2H, O – CH_2), 1.67-1.70 (d,3H, CH_3), 3.65(s,2H, NCH_2CO), 4.70-4.81(q,H,CH_3CH) 9.55 (s, H, CONH), 11.06 (s, H, Ar-NH), 12.92 (s, H, CO -NH), 6.75 -8.34 (m, 8H, for C_6H_5 and C_6H_5 of two phenyl groups);^{13}C-NMR: (400 MHz,DMSO-d_6, δppm): 64.5 (CH_2), 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N); 67 (O-CH_2), 16 (CH_3-CH_2); IR (KBr disc cm^{-1}) 3302, 3210, 3118, 3080, 1592, 1798, 1738, 1654, 1618;EI ms: m/z: 620.09; Anal.Calcd.for $C_{25}H_{23}Cl_3N_8O_5$ (621.86) C: 48.29; H: 3.73; N: 18.02; Found C: 48.32; H: 3.78; N: 18.08.

2-(4-(2-(4-chlorophenyl)hydrazono)-5-oxo-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propan-2-yl)acetamide 8e: Yield 66%, m.p. 225 ^{o}C; ^{1}H-NMR (400 MHz,DMSO-d_6, δppm): 1.67-1.70 (d,3H, CH_3), 3.64(s,2H, NCH_2CO), 4.70-4.81(q,H,CH_3CH) 9.54 (s, H, CONH), 11.05 (s, H, Ar-NH), 12.93 (s, H, CO -NH), 6.74 -8.33 (m, 8H, for C_6H_5 and C_6H_5 of two phenyl groups)^{13}C-NMR: (400 MHz,DMSO-d_6, δppm): 64.5 (CH_2), 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N); IR (KBr disc cm^{-1}) 3302, 3210, 3118, 3080, 1592, 1798, 1738, 1654, 1618; EI ms: m/z: 610.02; Anal.Calcd.for $C_{23}H_{18}Cl_4N_8O_4$ (612.25) C: 45.12; H: 2.96; N: 18.30; Found C: 45.18; H: 3.01; N: 18.36.

2-(4-(2-(4-bromophenyl)hydrazono)-5-oxo-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propan-2-yl)acetamide 8f: Yield 70%, m.p. 230 ^{o}C; ^{1}H-NMR (400 MHz,DMSO-d_6, δppm): 1.67-1.70 (d,3H, CH_3), 3.63(s,2H, NCH_2CO), 4.70-4.81(q,H,CH_3CH) 9.51 (s, H, CONH), 11.04 (s, H, Ar-NH), 12.90 (s, H, CO -NH), 6.73 -8.32 (m, 8H, for C_6H_5 and C_6H_5 of two phenyl groups)^{13}C-NMR: (400 MHz,DMSO-d_6, δppm): 64.5 (CH_2), 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N) ; IR (KBr disc cm^{-1}) 3302, 3210, 3118, 3080, 1592, 1798, 1738, 1654, 1618 EI ms: m/z: 653.97; Anal.Calcd.for $C_{23}H_{18}BrCl_3N_8O_4$ (656.70) C: 42.07; H: 2.76; N: 17.06; Found C: 42.12; H: 2.82; N: 17.08.

Synthesis of N-(1-oxo-1-((Z)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 9 a-h.

A mixture of 8 (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 9 a the reaction procedure leading to 9a was then extended to the syntheses of 9g, 9h and the Spectral data of the compounds (9 a–h) are listed.

N-(1-oxo-1-((Z)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene) hydrazinyl)propan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 9 a: obtained as yellow-orange crystals; Yield 68%, m.p. 158 ^{o}C; ^{1}H-NMR (400 MHz,DMSO-d_6, δppm): 1.18–2.01 (d,3H,CH_3) 2.32-2.58 [m, 6H $(CH_2)_3$ of piperidine ring], 2.15-2.19 (t, 4H, –CH_2–N–CH_2 of piperidine ring), 3.92 (s, 2H, N–CH_2–CO,4.38 (s,2H, –N–CH_2–N–),4.92-5.02(q,1H, CH_3 CH), 9.54 (s, 1H, CONH), 13.01 (s, 1H, Ar – NH), 11.20 (s, 1H, CONH), 6.65 – 8.18 (m, 9H, for C_6H_5 and C_6H_4 of two phenyl groups); ^{13}C-NMR: (400 MHz,DMSO-d_6, δppm): 64.5 (CH_2), 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N) 71 (NCH_2N), 24-52$(CH_2)_3$ of piperidine ring ;IR (KBr disc cm^{-1}) 3195, 1720, 1610, 1676, 1654; EI ms: m/z: 673.15; Anal.Calcd.for $C_{29}H_{30}Cl_3N_9O_4$ (674.97) C: 51.60; H: 4.48; N: 18.68; Found C: 51.62; H: 4.52; N: 18.71

N-(1-oxo-1-((Z)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene) hydrazinyl)propan-2-yl)-2-(5-oxo-4-(2-p-tolylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 9 b : obtained orange crystals; Yield 71 %, m.p. 162 ^{o}C ; ^{1}H-NMR (400 MHz,DMSO-d_6, δppm): 3.21 (s,3H, Ar –CH_3) **,** 1.16–2.00 (d,3H,CH_3) 2.30-2.56 [m, 6H $(CH_2)_3$ of piperidine ring], 2.16-2.20 (t, 4H, –CH_2–N–CH_2 of piperidine ring), 3.91 (s, 2H, N–CH_2–CO,4.37(s,2H, –N–CH_2–N–),4.93-5.03(q,1H, CH_3 CH), 9.52 (s, 1H, CONH), 13.00(s, 1H, Ar – NH), 11.21 (s, 1H, CONH), 6.66 – 8.19 (m, 8H, for C_6H_5 and C_6H_4 of two phenyl groups); ^{13}C-NMR: (400 MHz,DMSO-d_6, δppm): 64.5 (CH_2), 21.8(Ar-CH_3) 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N) 71 (NCH_2N), 24-52$(CH_2)_3$ of piperidine ring ; IR (KBr disc cm^{-1}) 3170, 1715, 1616, 1674, 1674; EI ms: m/z: 687.16; Anal.Calcd.for $C_{30}H_{32}Cl_3N_9O_4$ (688.99) C: 52.30; H: 4.68; N: 1830; Found C: 52.34; H: 4.72; N: 18.36.

2-(4-(2-(4-methoxyphenyl)hydrazono)-5-oxo-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-oxo-1-((Z)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-yl)acetamide 9 c : obtained as yellow crystals; Yield 65%, m.p. 164 ^{o}C; ^{1}H-NMR (400 MHz,DMSO-d_6, δppm): 3.84 (s, 3H, O-CH_3), 1.20–2.03 (d,3H,CH_3) 2.31-2.57 [m, 6H $(CH_2)_3$ of piperidine ring], 2.14-2.18 (t, 4H, –CH_2–N–CH_2 of piperidine ring), 3.90 (s, 2H, N–CH_2–CO,4.36 (s,2H, –N–CH_2–N–),4.94-5.03(q,1H, CH_3 CH), 9.53 (s, 1H, CONH), 13.03 (s, 1H, Ar – NH), 11.23 (s, 1H, CONH), 6.67 – 8.20 (m, 8H, for C_6H_5 and C_6H_4 of two phenyl groups); ^{13}C-NMR: (400 MHz,DMSO-d_6, δppm): 64.5 (CH_2), 56(O-CH_3) 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N) 71 (NCH_2N), 24-52$(CH_2)_3$ of piperidine ring ;IR (KBr disc cm^{-1}) 3120, 1680, 1610, 1680, 1654; EI ms: m/z: 703.16; Anal.Calcd.for $C_{30}H_{33}Cl_3N_9O_5$ (704.99) C: 51.11; H: 4.58; N: 17.88; Found C: 51.14; H: 4.62; N: 17.91.

2-(4-(2-(4-ethoxyphenyl)hydrazono)-5-oxo-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-oxo-1-((Z)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-yl)acetamide 9 d: obtained as yellow crystals; Yield 69%, m.p. 149 ^{o}C; ^{1}H-NMR (400 MHz,DMSO-d_6, δppm): 1.36(s,3H,CH_3),4.07

(t,2H,O-CH_2),1.34 (t, 3H, CH_3), 4.12 (q, 2H, O – CH_2),1.21–2.04 (d,3H,CH_3) 2.33-2.59 [m, 6H $(CH_2)_3$ of piperidine ring], 2.13-2.18 (t, 4H, –CH_2–N–CH_2 of piperidine ring), 3.89 (s, 2H, N–CH_2–CO,4.37 (s,2H, –N–CH_2–N–),4.95-5.05(q,1H, CH_3 CH), 9.55 (s, 1H, CONH), 13.04 (s, 1H, Ar – NH), 11.22 (s, 1H, CONH), 6.68 – 8.21 (m, 8H, for C_6H_5 and C_6H_4 of two phenyl groups); ^{13}C-NMR: (400 MHz,DMSO-d_6, δppm): 64.5 (CH_2), 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N) 71 (NCH_2N), 24-52$(CH_2)_3$ of piperidine ring,67 (O-CH_2), 16 (CH_3-CH_2) ; IR (KBr disc cm^{-1}) 3175, 1711, 1614, 1674, and 1656; EI ms: m/z: 717.17; Anal.Calcd.for $C_{31}H_{34}Cl_3N_9O_5$ (719.02) C: 51.78; H: 4.77; N: 17.53; Found C: 51.80; H: 4.79; N: 17.58

2-(4-(2-(4-chlorophenyl)hydrazono)-5-oxo-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-oxo-1-((Z)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-yl)acetamide 9 e : obtained as orange crystals; Yield 64%, m.p. 172 ^oC; ^{1}H-NMR (400 MHz,DMSO-d_6, δppm): 1.22–2.06 (d,3H,CH_3) 2.34-2.59 [m, 6H $(CH_2)_3$ of piperidine ring], 2.12-2.16 (t, 4H, –CH_2–N–CH_2 of piperidine ring), 3.94 (s, 2H, N–CH_2–CO,4.39 (s,2H, –N–CH_2–N–),4.96-5.08(q,1H, CH_3 CH), 9.56 (s, 1H, CONH), 13.05 (s, 1H, Ar – NH), 11.24 (s, 1H, CONH), 6.64 – 8.17(m, 8H, for C_6H_5 and C_6H_4 of two phenyl groups); ^{13}C-NMR: (400 MHz,DMSO-d_6, δppm): 64.5 (CH_2), 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N) 71 (NCH_2N), 24-52$(CH_2)_3$ of piperidine ring ; IR (KBr disc cm^{-1}) 3155, 1714, 1616, 1674, 1658; EI ms: m/z: 707.11; Anal.Calcd.for $C_{29}H_{29}Cl_4N_9O_4$ (709.41) C: 49.10; H: 4.12; N: 17.77. Found C: 49.13; H: 4.15; N: 17.79.

2-(4-(2-(4-bromophenyl)hydrazono)-5-oxo-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-oxo-1-((Z)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-yl)acetamide 9 f : obtained as reddish-orange crystals; Yield 71%, m.p. 168 ^oC; ^{1}H-NMR (400 MHz,DMSO-d_6, δppm): 1.21–2.05 (d,3H,CH_3) 2.35-2.61 [m, 6H $(CH_2)_3$ of piperidine ring], 2.14-2.17 (t, 4H, –CH_2–N–CH_2 of piperidine ring), 3.95 (s, 2H, N–CH_2–CO,4.35 (s,2H, –N–CH_2–N–),4.90-5.01(q,1H, CH_3 CH), 9.57 (s, 1H, CONH), 13.06 (s, 1H, Ar – NH), 11.26 (s, 1H, CONH), 6.63 – 8.16 (m, 8H, for C_6H_5 and C_6H_4 of two phenyl groups); ^{13}C-NMR: (400 MHz,DMSO-d_6, δppm): 64.5 (CH_2), 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N) 71 (NCH_2N), 24-52$(CH_2)_3$ of piperidine ring ;IR (KBr disc cm^{-1}) 3170, 1716, 1674, 1614, 1626; EI ms: m/z: 751.06; Anal.Calcd.for $C_{29}H_{29}BrCl_3N_9O_4$ (753.86) C: 46.20; H: 3.88; N: 16.72. Found C: 46.23; H: 3.89; N: 16.78.

N-(1-((Z)-2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 9 g: obtained as orange crystals; Yield 64%, m.p. 159 ^oC; ^{1}H-NMR (400 MHz,DMSO-d_6, δppm): 3.52 (t, 4H, –CH_2–O–CH_2 of morpholine ring)**,** 2.45 (t, 4H, –CH_2–N–CH_2 of morpholine ring), 3.96 (s, 2H, N–CH_2–CO,4.36 (s,2H, –N–CH_2–N–),4.82-5.08(q,1H, CH_3 CH), 9.58(s, 1H, CONH), 13.07 (s, 1H, Ar

– NH), 11.27(s, 1H, CONH), 6.61 – 8.14 (m, 8H, for C_6H_5 and C_6H_4 of two phenyl groups); ^{13}C-NMR: (DMSO-d_6, δppm): 64.5 (CH_2), 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N) 71 (NCH_2N), 51-68$(CH_2)_4$ of piperazine ring; IR (KBr disc cm^{-1}) 3170, 1716, 1674, 1614, 1626; EI ms: m/z: 675.13; Anal.Calcd.for $C_{28}H_{28}Cl_3N_9O_5$ (676.94) C: 49.68; H: 4.17; N: 18.62. Found C: 49.72; H: 4.19; N: 18.66.

N-(1-((Z)-2-(1-((4-methylpiperazin-1-yl)methyl)-2-oxoindolin-3-ylidene)hydrazinyl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 9 h : obtained as yellow-orange crystals; Yield 72%, m.p. 149 ^oC; ^{1}H-NMR (400 MHz,DMSO-d_6, δppm): 2.26 (s, 3H, N–CH_3), 2.47 (t, 4H, –CH_2–N–CH_2 of piperazine ring)3.97 (s, 2H, N–CH_2–CO,4.31 (s,2H, –N–CH_2–N–),4.98-5.09(q,1H, CH_3 CH), 9.50 (s, 1H, CONH), 13.08 (s, 1H, Ar – NH), 11.29 (s, 1H, CONH), 6.62 – 8.15 (m, 9H, for C_6H_5 and C_6H_4 of two phenyl groups); ^{13}C-NMR: (400 MHz,DMSO-d_6, δppm): 64.5 (CH_2), 113-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHN-) 168 (C=ONH) 49(CH C=O) 168 (Isatin C=O), 134 (Isatin C=N) 71 (NCH_2N), 48-51$(CH_2)_4$ of piperazine ring; IR (KBr disc cm^{-1}) 3170, 1716, 1674, 1614, 1626; EI ms: m/z: 688.16; Anal.Calcd.for $C_{29}H_{31}C_{l3}N_{10}O_4$ (689.98) C: 50.48; H: 4.53; N: 20.30; Found C: 50.54; H: 4.55; N: 20.32.

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