Studies with Azoles and Benzoazoles: A Novel Simple Approach for Synthesis of 3-Functionally Substituted 3-Acylindoles

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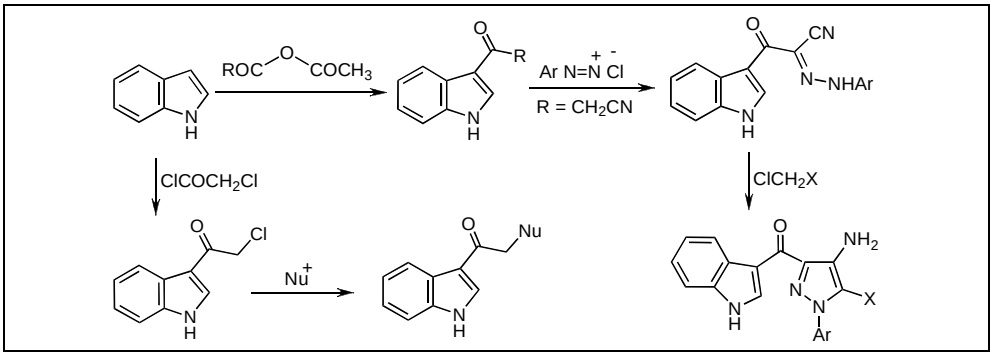

3-Substituted acylindoles **8** are obtained *via* refluxing carboxylic acids with indole in acetic anhydride solutions. The formed 3-substituted acylindole **8a** is readily converted into 4-aminopyrazol-3-ylindoles **20**, and into **22**. Indole reacts with chloroacetyl chloride to yield: 3-chloroacetylindole **9** which could also be utilized for synthesis of a number of 3-substituted indoles.

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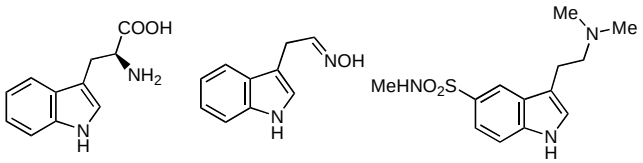
3-Substituted indoles are important heterocycles both in nature as well as pharmaceuticals [1,2]. For example tryptophane **1** and indole-3-acetaldoxime **2** participate in vital biological processes [3] while sumatriptan **3** is used for migraine treatment [4]. Fortunately 3-substituted indoles can be readily obtained by reacting indole with electrophiles under mild conditions. Thus indole readily couples at C-3 with aromatic diazonium salts [5], while C-3 acylation is conducted with acid chlorides in pyridine [6], N-acylation of indoles is generally conducted in the presence of bases [7]. In conjunction to our interest [8] in utilizing functionally susbstituted heteroaromatic ketones as precursors to functionally substituted heteroaromatics, a recent report [9] on synthesis of 3-indolyl-3-oxopropanenitrile **8a** *via* refluxing indole with acetic anhydride and cyanoacetic acid has attracted our attention as it represents a new general synthetic route to functionally substituted acylindoles that seemed interesting as precursors to other 3-substituted indoles. We were further stimulated to utilize **8a** as precursors to heteroaromatics by Slatt *et al*. report on the utility of **8a** for synthesis of substituted indoles and heteroaryl indoles [10]. That would be of interest for biological activity evaluation. It has been found that refluxing indole **7** with organic acids **4a-e**, which were preheated at 85°C for 10 minutes with acetic anhydride affords **8a-e** in excellent yields. We believe that initially the organic acid is converted into the organic acid anhydride **5** or at least the



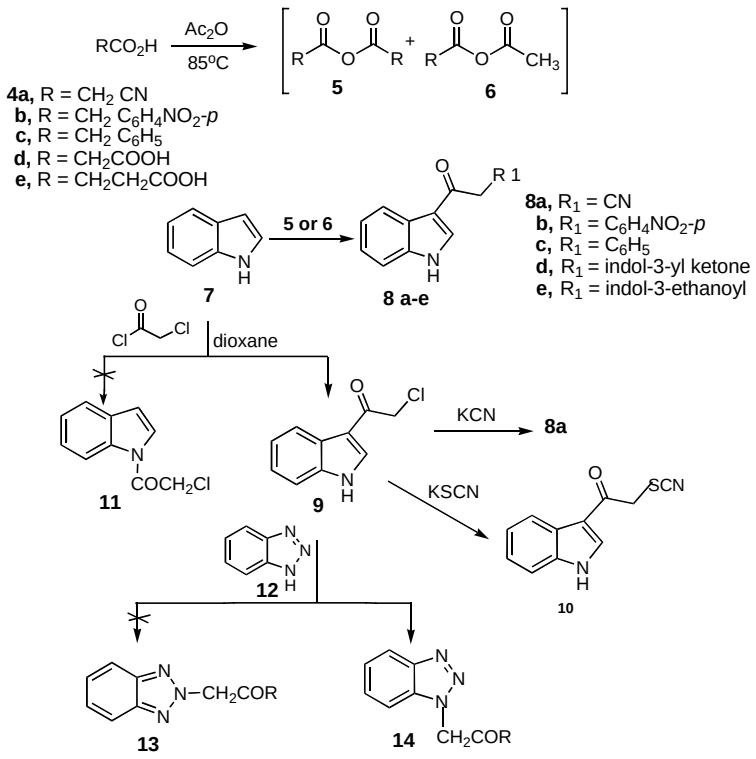
1 **2** **3**

mixed anhydride **6**. This, being more electrophillic than acetic anhydride, reacts with indole to yield the functionally substituted acyl derivatives **8a-e**. It is of value to report that compound **8d** existed as indicated from ^{1}H nmr as an equilibrium mixture of both keto and enol form as expected for 1,3 diketone. On the other hand mixing indole **7** with chloroacetyl chloride in dioxane afforded the chloroacetylindole **9**, hence, the utility of Lewis acid catalyst to promote activity as recently reported seemed to be of no value [11]. The chloroacetyl-indole **9** could be readily converted into **8a** on treatment with potassium cyanide and into **10** on treatment with ammonium thiocyanate. 3-Chloroacetylindole has recently claimed to be formed from reaction with zinc salt of indole with chloroacetyl chloride in presence of $ZnCl_2$ [12]. However the product reported in literature is most likely an N-acetyl indole **11** as it is different in every respect from our product whose spectral data confirm that it is 3-chloroacetylindole **9** (Scheme 1). Treatment of **9** with benzotriazole **12** in toluene/triethylamine afforded a

product that was formulated as **14** rather **13** based on ^{1}H nmr which revealed non identity of all four benzotriazolyl protons. Compound **13** is symmetrical and should have shown only two signals for these protons (Scheme 1).

Compound **8a** condensed with DMFDMA to yield: enaminonitrile **21** which reacted with ethyl thioglycolate and with ethyl glycinate in ethanol / potassium carbonate solution to yield: **22**. Trials to effect cyclisation of **22** into

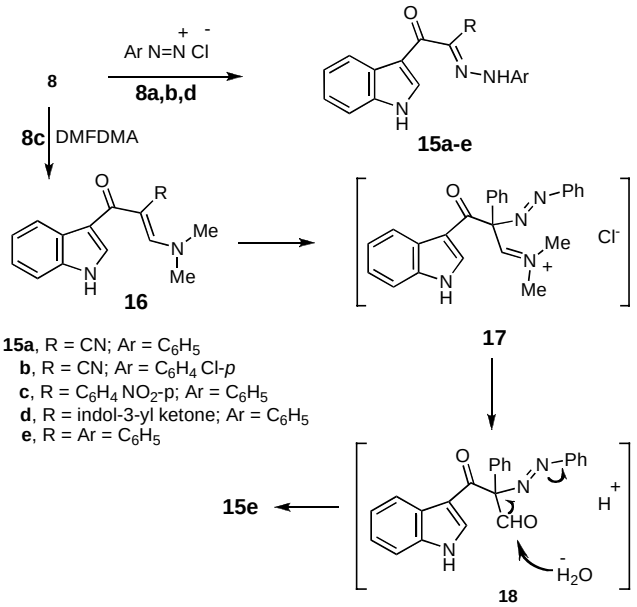
Scheme 1



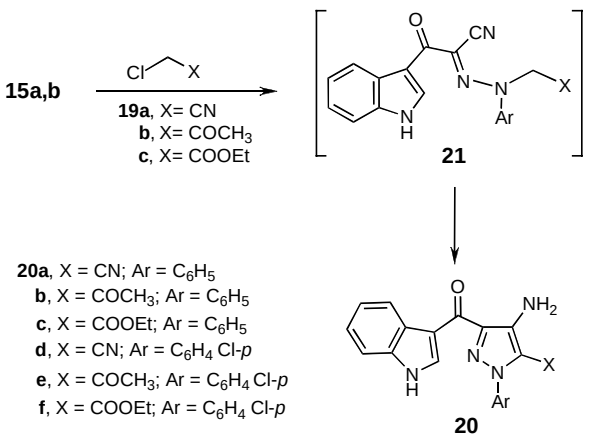
Compounds **8a,b,d** coupled readily with aryldiazonium chlorides to yield the arylhydrazones **15a-d** in excellent yields while compounds **8c,e** failed to couple under similar conditions. However when **8c** was converted into the enamine **16** *via* refluxing **8c** with DMFDMA and the product was then coupled with benzendiazonium chloride, the phenylhydrazone **15e** was formed. It is believed that, as a result of nitrogen lone pair donation to enamine β-carbon, the latter becomes sufficiently nucleophilic and intermediate diazonium salt **17** is initially formed. This then readily hydrolyses into the azo derivative **18** that then undergo Japp-Klingmann cleavage [8] to yield **15e** (Scheme 2).

A novel route to 4-aminopyrazolecarboxylic acids with indolyl substituent at C-3 which can be useful for synthesis of pharmaceutically interesting condensed pyrazoles could be developed. Thus reacting **15a,b** with chloroacetonitrile **19a**, chloroacetone **19b** and ethyl chloroacetate **19c** in triethylamine solution has afforded **20a-f** in excellent yields. Intermediacy of **21** is most likely (Scheme 3).

Scheme 2



Scheme 3



23 under variety of conditions failed. In protic medium **22** decomposed into **8a** and in aprotic medium **22** was recovered unrecated (Scheme 4).

are reported in δ units (ppm). Mass spectra were measured at 70 eV using shimadzu GCms-QP 1000 EX spectrometer. Microanalyses were performed on a LECO CHNS-932 Elemental Analyzer.

General procedures for preparation of compounds 8a-e. ***Method a*: For synthesis of 8a-e.** A solution of the appropriate carboxylic acids **4a-e** (10 mmol) in acetic anhydride (10 mL, 100 mmol) was heated at 85°C for 10 min. then indole **7** (10 mmol) was added to the reaction mixture and heating was continuing under reflux for further 30 min. The reaction mixture was left to cool and poured onto cooled water. The solid product so formed was collected by filtration, crystallized from the appropriate solvent and identified as **8a-e.**

***Method b*: Alternative method for synthesis of (8a).** To a warmed solution of **9** (1.00 g, 5 mmol) in benzene (10 mL) were added 6 mmol of sodium cyanide solution in water (10 mL). The reaction mixture was stirred at 50°C (bath temperature) for 1 hr then the aqueous layer was separated and poured onto acidified cooled water. The product so formed was collected by filtration, dried and identified as **8a**.

3-(1*H*-Indol-3-yl)-3-oxopropanenitrile (8a). Crystallized from acetic acid as creamy white crystals, yield: 1.75 g (95%), mp 240 °C(Lit[9].m.p 241 °C); ir (KBr): 3220.9 (NH), 2252 (CN),

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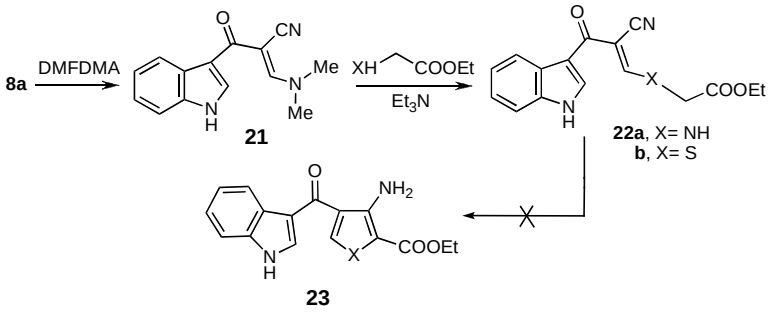

CONCLUSION

In conclusion, organic acids in presence of acetic anhydride can readily acylate indole regioselectively at C-3. The formed acyl derivative is the one derived from the most electrophilic center in the mixed acid anhydride, this procedure is thus useful substitute for acylation by acid chlorides in pyridine solution. Moreover chloroacetyl chloride directly acylate indole at C-3 to give 3-Chloro-acetylindole. The readily obtainable 3-functionally substituted indoles have been shown to be excellent precursors to biologically interesting azolylindoles that are otherwise not readily obtainable.

EXPERIMENTAL

General Remarks. All melting points are uncorrected. ir spectra were recorded in KBr pellets with Satellite 2000 spectrophotometer. ^{1}H nmr and ^{13}C nmr spectra were recorded on a Bruker AC-300 300 MHz spectrometer in DMSO-d6 and $CDCl_3$ as solvents and Tms as internal standard; chemical shifts

1638 cm^{-1} (CO). ^{1}H nmr (DMSO-d6): δ 4.48 (s, 2H, CH_2), 7.23-7.25 (m, 2H, indole H-5 and 6), 7.51 (d, 1H, *J* = 8.4 Hz, indole H-4), 8.13 (d, 1H, *J* = 8.4 Hz, indole H-7), 8.36 (d, 1H, *J* = 2.4 Hz, indole H-2), and 12.15 ppm (br, 1H, NH); ms (EI): m/z (%) 144 (100), 184 (M^+, 31.93), 185 (M^++1, 4.6). *Anal.* Calcd. for $C_{11}H_8N_2O$ (184.19): C, 71.73; H, 4.36; N, 15.21. Found: C, 71.48; H, 4.11; N, 15.02

1-(1*H*-Indol-3-yl)-2-(4-nitrophenyl)ethanone (8b) Crystallized from ethanol as yellow crystals, yield: 2.1 g (75%), mp 212 °C; ir (KBr): 3265 (NH), 1675 (CO), 1626 cm^{-1}(C=C); ^{1}H nmr (DMSO-d6): δ 4.37 (s, 2H, CH_2), 7.16-7.25 (m, 2H, indole H-5 and 6), 7.52 (d, 1H, *J* = 7.5 Hz, indole H-4), 7.60 (d, 2H, *J* = 8.5 Hz, Ar-H), 8.15 (d, 2H, *J* = 8.5 Hz, Ar-H), 8.22 (d, 1H, *J* = 7.5 Hz, indole H-7), 8.56 (d, 1H, *J* = 2.4 Hz, indole H-2) and 12.09 ppm (br, 1H, NH); ^{13}C nmr (DMSO-d6): δ 45.32 (CH_2), 112.26, 116.08, 121.41, 121.99, 123.06, 123.20, 125.60, 130.83, 134.85, 136.88, 144.61, 146.21 (Ar-C) and 191.21 (CO). ms (EI): m/z (%) 144 (100), 280 (M^+, 4.63), 281 (M^++1, 0.91). *Anal.* Calcd. for $C_{16}H_{12}N_2O_3$ (280.28): C, 68.56; H, 4.32; N, 9.99. Found: C, 68.46; H, 4.12; N, 9.73.

1-(1*H*-Indol-3-yl)-2-phenylethanone (8c) Crystallized from ethanol as pale yellow crystals, yield: 1.7 g (72%), mp 197 °C; ir (KBr): 3173 (NH), 1674 cm^{-1} (CO); ms (EI): m/z (%) 144

(100), 235 (M^+, 4.9), 236 (M^++1, 1.32). *Anal.* Calcd. for $C_{16}H_{13}NO$ (235.28): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.14; H, 5.60; N, 6.20.

1,3-Di-1*H*-indol-3-ylpropane-1,3-dione (8d) Crystallized from dioxan as yellow crystals, yield, 2.5 g (83%), mp 152 °C; ir (KBr): 3233 (NH), 1701 (CO), 1625 cm^{-1}(C=C); ^1H nmr (DMSO-d6): δ 4.76 and 5.04 (two s, CH_2 keto form and CH enol form), 6.73-8.60 (complex m, Ar-H of keto form and enol form), 10.87 (br, OH enolic) and 11.95-12.20 ppm (br, NH keto form and enol form). Extra carbons for the presence of keto enol tautomerism ^{13}C nmr (DMSO-d6): δ 44.98 (CH_2), 108.62, 109.10, 109.36, 112.38, 116.04, 121.08, 121.27, 121.67, 123.40, 123.99, 124.88, 125.41, 126.12, 126.95, 127.23, 127.35, 128.88, 130.53, 135.11, 135.68, 136.15, 136.81, 162.34 and 165.75 (Ar - C and CO carbons); ms (EI): m/z (%) 89(100), 302 (M^+, 7.62), 303 (M^++1, 2.18). *Anal.* Calcd. for $C_{19}H_{14}N_2O_2$ (302.33): C, 75.48; H, 4.67; N, 9.27. Found: C, 75.22; H, 4.31; N, 9.10.

1,4-Di-1*H*-indol-3ylbutane-1,4-dione (8e) crystallized from dioxane as pale yellow crystals, yield: 1.75 g (55 %), m p 233 °C; ir (KBr) 3281 (NH), 1705 (CO), 1597 cm^{-1} (C=C); ms (EI): m/z (%)144 (100), 316 (M^+,26%). *Anal.* Calcd. for $C_{20}H_{16}N_2O_2$ (316.35): C, 75.93; H, 5.10; N, 8.86. Found: C, 75.40; H, 5.50; N, 8.70.

2-(1*H*-Indol-3-yl)-2-oxoethyl thiocyanate (10). To a warmed solution of 9 (1.00 g, 5 mmol) in acetonitrile (10 mL) were added ammonium thiocyanate (0.5 g, 6 mmol). The reaction mixture was stirred at 50°C (bath temperature) for 1 hr then the reaction mixture was poured onto ice cooled water. The product so formed was collected by filtration. Crystallized from ethanol as faint pink crystals, yield: 2.1 g (98 %), mp 126 °C; ir (KBr): 3210 (NH), 2157 (SCN), 1696 cm^{-1} (CO); ^1H nmr (DMSO-d6) : δ 4.48 (s, 2H, CH_2), 7.20-7.28 (m, 2H, indole H-5 and 6), 7.50 (d, 1H, *J* = 8.7 Hz, indole H-4), 8.13 (d, 1H, *J* = 8.7 Hz, indole H-7), 8.37 (d, 1H, *J* = 3 Hz, indole H-2), and 12.16 ppm (br, 1H, NH); ms (EI): m/z (%): 117 (100), 216 (M^+, 71.6%), 217 (M^++1, 10.42), 218 (M^++2, 4,56). *Anal.* Calcd. for $C_{11}H_8N_2OS$ (216.26): C, 61.09; H, 3.73; N, 12.95; S, 14.83. Found: C, 61.00; H, 3.55; N, 12.95; S, 14.76.

2-Chloro-1-(1*H*-indol-3-yl)ethanone (9). A mixture of 5 (1.2 g, 10 mmol) and chloroacetyl chloride (1.15 g, 10 mmol) in dioxane (20 mL) was refluxed for 45 min. The mixture was allowed to cool to r.t. then poured onto cooled water. The obtained solid was collected by filtration and crystallized from methanol as pale pink crystals, yield: 1.8 g (93 %), mp 105 °C; ir (KBr): 3118 (NH), 1707 (CO), 1610 cm^{-1} (C=C); ^1H nmr ($CDCL_3$): δ 4.59 (s, 2H, CH_2), 6.72 (d, 1H, *J* = 3.4 Hz, indole H-2), 7.27-7.44 (m, 3H, indole H-5, 6 and NH proton), 7.60 (d, 1H, *J* = 8.1 Hz, indole H-4), 8.44 ppm (d, 1H, *J* = 8.1 Hz, indole H-7); ms (EI): m/z (%) 193 (M^+, 100), 194 (M^++1, 10.9), 195 (M^++2, 26.1). *Anal.* Calcd. for $C_{10}H_8ClNO$ (193.63): C, 62.03; H, 4.16; Cl, 18.31; N, 7.23. Found: C, 62.20; H, 4.30; Cl, 18.18; N, 7.15.

1-(1*H*-Indol-3-ylacetyl)-2*H*-1,2,3-benzotrizole (14). A mixture of 9 (1.93 g, 10 mmol), benzotriazole (1.2 g, 10 mmol) and triethylamine (2 mL, 20 mmol) in toluene (15 mL) was refluxed for 2 h. The solvent was removed under vacuum and the remaining residue was triturated with 5% sodium hydroxide. The solid product so formed was collected by filtration and crystallized from ethanol as creamy white solid; yield: 2.1 g (76 %), mp 142 °C; ir (KBr): 3151 (NH), 1701 (CO), 1616 cm^{-1} (C=C); ^1H nmr ($CDCL_3$): δ 6.04 (s, 2H, CH_2), 6.79 (d, 1H, *J* = 3.4 Hz, indole H-2), 7.27-7.64 (m, 7H, 4 Ar-H, indole H-5, 6 and NH proton), 8.13 (d, 1H, *J* = 8.1 Hz, indole H-4) and 8.38 ppm (d, 1H, *J* = 8.1 Hz, indole H-7); ms (EI): m/z (%) 219 (100), 276 (M^+, 57.5), 277 (M^++1, 11.5). *Anal.* Calcd. for $C_{16}H_{12}N_4O$ (276.29): C, 69.55; H, 4.38; N, 20.28. Found: C, 69.82; H, 4.50; N, 20.20.

General method for preparation of compounds 15a-d. To a stirred solution of each of **4a,b,d** (10 mmol) in dioxane (15 mL) containing sodium acetate (10 g) was added the appropriate diazonium salt (prepared from 10 mmol of the appropriate aromatic amine and the appropriate quantities of sodium nitrite and hydrochloric acid). The solid product separated on standing was collected by filtration and crystallized from the appropriate solvent.

3-(1*H*-Indol-3-yl)-3-oxo-2-(phenylhydrazono)propanenitrile (15a) crystallized from dioxane as yellow crystals, yield: 2.2 g (76 %), mp 251 °C; ir (KBr): 3440, 3234 (2 NH), 2214 (CN), 1698 cm^{-1} (CO); ^1H nmr (DMSO-d6): δ 7.11-7.26 (m, 3H, Ar-H), 7.38-8.25 (m, 6H, Ar-H), 8.44 (d, 1H, *J* = 3.3 Hz, indole H-2), 11.92 (br, 1H , indole NH) and 12.04 ppm (br, 1H, hydrazone NH); ms (EI): m/z (%) 144 (100), 288 (M^+, 43.9), 289 (M^++1, 10.3). *Anal.* Calcd. for $C_{17}H_{12}N_4O$ (288.30): C, 70.82; H, 4.20; N, 19.43. Found: C, 70.69; H, 4.01; N, 19.35

2-[(4-Chlorophenyl)hydrazono]-3-(1*H*-indol-3-yl)-3-oxo-propanenitrile (15b) crystallized from DMF, yield: 2.5 g (78%, mp 278-80 °C; ir (KBr): 3233, 3180 (2 NH), 2209 (CN), 1682 cm^{-1} (CO); ^1H nmr (DMSO-d6): δ 7.19-7.25 (m, 2H, Ar-H), 7.38-8.28 (m, 6H, Ar-H), 8.40 (d, 1H, *J* = 3 Hz, indole H-2) 11.94 (br, 1H, indole NH) and 12.05 ppm (br, 1H, hydrazone NH); ^{13}C nmr (DMSO-d6): δ 115.62 (CN), 111.67, 112.31, 117.77, 121.45, 122.06, 123.10, 126.64, 128.14, 129.31, 135.36, 135.99, 141.36 (Ar-C) and 179.79 (CO); ms (EI): m/z (%) 144 (100), 322 (M^+, 47.9), 323 (M^++1, 11.9), 324 (M^++2, 18.22), 325 (M^++3, 4.14). *Anal.* Calcd. for $C_{17}H_{11}ClN_4O$ (322.84): C, 63.26; H, 3.44; Cl, 10.98; N, 17.36. Found: C, 63.00; H, 3.21; Cl, 10.76; N, 17.25.

1-(1*H*-Indol-3yl)-2-(4-nitrophenyl)ethane-1,2-dione(2-phenyl-hydrazone) (15c) crystallized from ethanol as orange crystals, yield: 2.5 g (65%), mp 188-190 °C; ir (KBr): 3170, 3136 (2 NH), 1694 (CO), 1621 cm^{-1} (C=N); ms (EI): m/z (%)144 (100), 384 (M^+, 3.9). *Anal.* Calcd. for $C_{22}H_{16}N_4O_3$ (384.39): C, 68.74; H, 4.20; N, 14.58. Found: C, 68.41; H, 4.60; N, 14.19.

1,3-Di-1*H*-Indol-3-ylpropane-1,2,3-trione(2-phenylhydra-zone) (15d) crystallized from ethanol as reddish brown crystals, yield: 3.75 g (92 %), mp 104 °C; ir (KBr): 3173, 3150 (2 NH), 1703 (CO), 1600 cm^{-1} (C=N); ms (EI): m/z (%) 221 (100), 406 (M^+, 1.0), 407 (M^++1, 0.43). *Anal.* Calcd. for $C_{25}H_{18}N_4O_2$ (406.44): C, 73.88; H, 4.46; N, 13.78. Found: 73.60; H, 4.22; N, 13.69.

***E*-1-(1*H*-Indol-3-yl)-2-phenylethane-1,2-dione(2-phenyl-hydrazone) (15e).** To a solution of 16 (5 mmol) in ethanol (20 mL) containing sodium acetate (10 g) was added a solution of phenyl diazonium Chloride (prepared from 5 mmol of aniline and the appropriate amount of hydrochloric acid and sodium nitrite). The solid obtained on standing was collected by filtration and crystallized from ethanol as orange crystals; yield: 1.3 g (77 %), mp 106-08°C; ir (KBr): 3390, 3187 (2 NH), 1681cm^{-1} (CO); ^1H nmr (DMSO-d6): δ 7.23-7.36 (m, 9H, Ar-H), 7.86-8.28 (m, 5H, Ar-H), 8.65 (d, 1H, *J* = 3 Hz, indole H-2), 12.06 (br, 1H, indole NH) and 12.56 ppm (br,1H, hydrazone NH); ms (EI): m/z (%) 144 (100), 339 (M^+, 29.9), 340 (M^++1, 7.5). *Anal.* Calcd. for $C_{22}H_{17}N_3O$ (339.39): C, 77.86; H, 5.05; N, 12.38. Found: C, 77.65; H, 4.90.05; N, 12.13.

3-(Dimethylamino)-1-(1*H*-indol-3-yl)-2-phenylprop-2-en-1-one (16). A mixture of 8c (2.35 g, 10 mmol) and DMFDMA (1.2 g, 10 mmol) in toluene (15 mL) was refluxed for 3 h. The solid product obtained on standing was collected by filtration and crystallized from toluene as yellow crystals; yield: 2.3 g (79 %), mp 200-202 °C; ir (KBr): 3134, (NH), 1604 cm^{-1} (CO). ^1H nmr (DMSO-d6): δ 2.69 (s, 6H, 2 CH_3), 6.84 (d, 1H, *J* = 3 Hz, indole H-2), 7.05-7.36 (m, 8H, Ar-H), 7.46 (s, 1H, olefinicCH), 8.11 (d, 1H, *J* = 8.7 Hz, Ar-H) and 11.30 ppm (br, 1H, NH); ms (EI): m/z (%) 144 (100), 290 (M^+, 50.3), 291 (M^++1, 11.97). *Anal*. Calcd. for $C_{19}H_{18}N_2O$ (290.36): C, 78.59; H, 6.25; N, 9.65. Found: C, 78.30; H, 6.40; N, 9.30.

General method for preparation of compounds 20a-f. To a solution of each of **15a,b** (1.45 g, 5 mmol) in a mixture of DMF (2 mL) and triethylamine (10 mL) was added the appropriate chloro derivative **19a-c** (10 mmol). The reaction mixture was refluxed for 40 min and left to cool to r.t. The obtained residual product was triturated with ethanol to give a solid product that was collected by filtration, washed with water and crystallized from the appropriate solvent.

4-Amino-3-(1*H*-indol-3-ylcarbonyl)-1-phenyl-1*H*-pyrazole-5-carbonitrile (20a) crystallized from ethanol as faint brown crystals, yield: 1.5 g (91 %), m.p. 126-128 °C; ir (KBr): 3474, 3357, 3238 (NH_2 and NH), 2216 (CN), 1630 (CO),1605 cm^{-1} (C=N); ms (EI): m/z (%) 144 (100), 327 (M^+, 23.7), 328 (M^++1, 6.81). *Anal*. Calcd. for $C_{19}H_{13}N_5O$ (327.34): C, 69.71; H, 4.00; N, 21.39. Found: C, 69.56; H, 3.90; N, 21.18.

5-Acetyl-4-Amino-3-(1*H*-indol-3-ylcarbonyl)-1-phenyl-1*H*-pyrazole (20b) crystallized from ethanol as orange crystals, yield: 1.3 g (76%), mp 189°C; ir(KBr): 3416, 3338, 3234 (NH_2 and NH), 1731, 1638 cm^{-1} (2 CO); ms (EI): m/z (%)144 (100), 344 (M^+, 8.85), 345 (M^++1, 2.2). *Anal*. Calcd. for $C_{20}H_{16}N_4O_2$ (344.37): C, 69.76 H, 4.68; N, 16.27, Found: C, 69.53 H, 4.59; N, 15.96.

Ethyl 4-Amino-3-(1*H*-indol-3-ylcarbonyl)-1-phenyl-1*H*-pyrazole-5-carboxylate (20c) crystallized from ethanol as orange crystals yield: 1.4 g (74%), mp 192-194°C; ir(KBr): 3495, 3372, 3266 (NH_2 and NH), 1719, 1636 cm^{-1} (2 CO). ms (EI): m/z (%) 144 (100), 374 (M^+, 25.4) 375 (M^++1, 29.2). *Anal*. Calcd. for $C_{21}H_{18}N_4O_3$ (374.39): C, 67.37 H, 4.85; N, 14.96. Found: C, 67.82; H, 4.40; N, 14.53.

4-Amino-3-(1*H*-indol-3-ylcarbonyl)-1-(4-chlorophenyl)-1*H*-pyrazole-5-carbonitrile (20d) crystallized from ethanol as faint brown crystals; yield: 1.5 g (83 %), mp 252-254; ir (KBr): 3484, 3339, 3235 (NH_2 and NH), 2218 (CN), 1702 cm^{-1} (CO); ^1H nmr (DMSO-d6): δ 6.55 (s, 2H, NH_2), 7.20-7.25 (m, 2H, indole H-5 and 6), 7.52 (d, 1H, *J* = 8.1 Hz, indole H-4), 7.65 (d, 2H, *J* = 9 Hz, Ar-H), 7.84 (d, 2H, *J* = 9 Hz, Ar-H), 8.36 (d, 1H, *J* = 8.1 Hz, indole H-7), 8.79 (1H, *J* = 3 Hz, indole H-2) and 11.99 ppm (br, 1H, NH); ^{13}C nmr (DMSO-d6): δ 114.10 (CN), 98.09, 111.54, 112.34, 117.80, 121.62, 122.06, 123.05, 124.22, 126.53, 129.33, 129.70, 133.25, 135.97, 136.19, 137.22, 137.62, 145.09 (Ar-C) and 181.93 (CO); ms (EI): m/z (%) 144 (100), 361 (M^+, 21.2), 362 (M^++1, 7.24), 363 (M^++2, 7.92), 364 (M^++3, 1.7). *Anal*. Calcd. for $C_{19}H_{12}ClN_5O$ (361.34): C, 63.10; H, 3.32; N, 19.36. Found: C, 63.19; H, 3.45; N, 19.29.

5-Acetyl-4-amino-3-(1H-indol-3-ylcarbonyl)-1-(4-chlorophenyl)-1*H*-pyrazole (20e) crystallized from ethanol as orange crystals yield: 1.4 g (74 %), mp 242-244 °C; ir (KBr): 3421, 3315, 3240 (NH_2 and NH), 1703, 1656 cm^{-1} (2 CO); ^1H nmr (DMSO-d6): δ 2.03 (s, 3H, CH_3), 6.51 (s, 2H, NH_2), 7.19-7.25 (m, 2H, indole H-5 and 6), 7.38-7.68 (m, 5H, 4 Ar-H and indole H-4), 8.40 (d, 1H, *J* = 8.1 Hz, indole H-7), 8.72 (d, 1H, *J* = 3 Hz, indole H-2) and 12.00 ppm (br, 1H, NH); ^{13}C nmr (DMSO-d6): δ 29.64 (CH_3), 111.66, 112.31, 115.59, 117.81, 121.40, 122.07, 123.12, 126.60, 128.13, 129.23, 129.35, 135.42, 135.66, 135.99, 136.12, 141.39, 141.98 (Ar-C), 179.80 and 187.26(2CO); ms (EI): m/z (%) 144 (100), 378 (M^+, 6.33), 379 (M^++1, 2.67), 380 (M^++2, 2.3). *Anal*. Calcd. for $C_{20}H_{15}ClN_4O_2$ (378.5): C, 63.40; H, 3.96; N, 14.80. Found: C, 63.53 H, 3.90; N, 14.60.

Ethyl 4-Amino-3-(1*H*-indol-3-ylcarbonyl)-1-(4-chlorophenyl)-1*H*-pyrazole-5-carboxylate (20f) crystallized from ethanol as orange crystals yield: 1.45 g (71 %), mp 259-260 °C; ir (KBr): 3495, 3478, 3241 (NH_2 and NH), 1716, 1668 cm^{-1} (2 CO); ^1H nmr (DMSO-d6): δ 1.21 (t, 3H, *J* = 7.2 Hz, CH_3CH_2), 4.23 (q, 2H, *J* = 7.2 Hz, CH_3CH_2), 5.34 (s, 2H, NH_2), 7.22-7.32 (m, 2H, indole H-5 and 6), 7.40-7.58 (m, 5H, 4 Ar-H and indole H-4), 8.26 (d, 1H, *J* = 8.4 Hz, indole H-7), 8.42 (d, 1H, *J* = 3 Hz, indole H-2) and 12.10 ppm (br, 1H, NH); ^{13}C nmr (DMSO-d6): δ 47.54 (CH_2), 61.34 (CH_3), 110.71, 111.63, 111.99, 115.19, 115.56, 117.83, 121.41, 122.05, 123.11, 126.62, 128.11, 129.35, 135.40, 135.99, 136.54, 139.07, 141.48 (Ar-C), 168.44 and 179.81(2CO); ms (EI): m/z (%) 144 (100), 408 (M^+, 20.80), 409 (M^++1, 8.75); *Anal*. Calcd. for $C_{21}H_{17}ClN_4O_3$ (408.39): C, 61.68 H, 4.16; N, 13.71. Found: C, 61.70, H, 4.10; N, 13.88.

3-(Dimethylamino-2-(1*H*-indol-3-ylcarbonyl)acrylonitrile (21). A mixture of 8a (0.95 g, 5 mmol), DMFDMA (0.6 mL, 5 mmol) and few drops of DMF in toluene was refluxed for 3 h. The solvent was evaporated under reduced pressure and the remaining residue was crystallized from ethanol as yellow crystals, yield: 0.9 g (75%), mp 186 °C; ir (KBr): 3299 (NH), 2193 (CN), 1630 (CO) cm^{-1}; ^1H nmr (DMSO-d6):δ 3.20 (s, 3H, CH_3), 3.32 (s, 3H, CH_3), 7.13-7.22 (m, 2H, indole H-5 and 6), 7.49 (d, 1H, *J* = 8.7 Hz, indole H-4), 7.99 (s, 1H, olefinic CH), 8.19 (d, 1H, *J* = 8.7 Hz, indole H-7), 8.32 (d, 1H, *J* = 2.5 Hz, indole H-2) and 11.75 ppm (br, 1H, NH); ^{13}C nmr (DMSO-d6): δ 47.42 (CH_3), 77.85 (CH3), 114.87 (CN), 111.97,121.22, 121.83, 121.88, 122.51, 122.57, 126.89, 131.25, 135.95, 158.69 (Ar-C and olefinicC) and 181.87 (CO); ms (EI): m/z (%) 144 (100), 239 (M^+, 31 %), 240 (M^++1, 3.83%). *Anal*. Calcd. for $C_{14}H_{13}N_3O$ (239.27): C, 70.86 H, 5.48; N, 17.56. Found: C, 70.70; H, 5.23; N, 17.78.

General procedure for preparation of compounds 22a-b. A solution of **21** (2.4 g, 10 mmol) in absolute ethanol (50 ml) containing potassium carbonate (3 g), ethyl thioglycolate (1.2 g, 10 mmol), or ethyl glycinate hydrochloride (1.4 g, 10 mmol) was refluxed for 5 h then concentrated upon evaporation to one third its volume. The solid product so formed upon cooling was collected by filtration.

[2-Cyano-3-(1*H*-indol-3-yl)-3-oxo-propenylamino]-acetic acid ethyl ester (22a) crystallized from ethanol as yellow crystals yield: 2.2 g (73%), mp146-148 °C; ir (KBr): 3301, 3149 (2NH), 2198 (CN),1730 (CO ester) and 1637 cm^{-1}(CO); ^1H nmr (DMSO-d6): δ 1.23 (t, 3H, *J* = 7.2 Hz, CH_3CH_2), 4.17 (q, 2H, *J* = 7.2 Hz, CH_3CH_2), 4.27 (d, 2H, *J* = 6 Hz, CH_2NH), 7.14-7.23 (m, 2H, indole H-5 and 6), 7.49 (d, 1H, *J* = 8 Hz, indole H-4), 7.81 (d, 1H, *J* = 13.5 Hz, olefinic CH), 8.26 (d, 1H, *J* = 8 Hz, indole H-7), 8.44 (d, 1H, *J* = 3 Hz, indole H-2), 10.70-10.78 (m, 1H, $NHCH_2$) and 11.85 ppm (br, 1H, indole NH); ms (EI): m/z (%) 144 (100), 297 (M^+, 28.3). *Anal*. Calcd. for $C_{16}H_{15}N_3O_3$ (297.31): C, 64.64; H, 5.09; N, 14.13. Found: C, 64.33; H, 4.95; N, 14.00.

[2-Cyano-3-(1*H*-indol-3-yl)-3-oxo-propenylsulfanyl]-acetic acid ethyl ester (22b) crystallized from ethanol as orange

crystals yield: 2 g (64%), mp 128-130 °C; ir (KBr): 3269 (NH), 2211 (CN), 1732 (CO ester) and 1638 (CO) cm^{-1}; ^1H nmr (DMSO-d6): δ 1.23 (t, 3H, *J* = 7.2 Hz, CH_3CH_2), 4.16 (q, 2H, *J* = 7.2 Hz, CH_3CH_2), 4.22 (s, 2H, CH_2S), 7.20-7.30 (m, 2H, indole H-5 and 6), 7.53 (d, 1H, *J* = 8.7 Hz, indole H-4), 8.14 (d, 1H, *J* = 8.7 Hz, indole H-7), 8.32 (d, 1H, *J* = 3.3 Hz, indole H-2), 8.83 (s, 1H, olefinic CH), and 12.21 ppm (br, 1H, NH); ms (EI): m/z (%) 144 (100), 314 (M^+, 39.06). *Anal.* Calcd. for $C_{16}H_{14}N_2O_3S$ (314.36): C, 61.13 H, 4.49; N, 8.91; S, 10.20. Found: C, 61.01 H, 4.28; N, 8.94; S, 10.00.

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