Synthesis of some new indole derivatives containing pyrazoles with potential antitumor activity

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Abstract

A series of new [1-(4-methoxybenzyl)indol-3-yl](1*H*-pyrazol-1-yl)methanones, 1-(1-(4-methoxybenzyl)-1*H*-indole-3-carbonyl)-3-subsituted-1*H*-pyrazol-5(4H)-ones have been developed using the 1-(4-methoxybenzyl)-1*H*-indole-3-carbohydrazide **1** as a key intermediate. The target compounds were tested *in-vitro* for tumor cell-growth inhibition.

Keywords: Indoles, pyrazoles, pyrazolones, antitumor activity

Introduction

Indole nucleus is frequently found in medicinal chemistry and is considered as "privileged scaffolds".[1] Therefore, the synthesis and selective functionalization of indoles have been the focus of active research over the years.[2–4] Indole derivatives constitute an important class of therapeutic agents in medicinal chemistry including anticancer,[5] antioxidant,[6] antirheumatoidal and anti-HIV[7,8] and also play a vital role in the immune system.[9,10] Many indole derivatives are considered as the most potent scavenger of free radicals.[11] Artificial receptors for biologically active molecules have attracted attention from the view point of molecular recognition.[12]

In addition, it was reported that various 3-substituted indoles had been used as starting materials for the synthesis of a number of alkaloids, agrochemicals, pharmaceuticals and perfumes.[13]

On the other hand, over the past two decades, pyrazole-containing compounds have received considerable attention owing to their diverse chemotherapeutic potentials including versatile antineoplastic activities. Literature survey revealed that some pyrazoles have been implemented as antileukemic,[14-16] antitumor[17-20] and anti-proliferative[21,22] agents, beside their capability to exert remarkable anticancer effects through inhibiting different types of enzymes that play important roles in cell division.[23-25] We have recently reported synthesis and antitumor activity of

some indole derivatives containing 1,3,4-oxadiazole and 1,2,4-triazole **A**, and discovered that some of the analogs are potent and selective against various cancer cell lines.[26] Combination of the pyrazole moiety with the indole nucleus may enhance these activities. In view of these previous findings, intriguing cytotoxicity of various indolyl azoles and in continuation of our interest in the functionalization of indoles **(A, B, C** and **D**),[29,30] and in the development of new synthetic methods,[26–31] we report herein on the synthesis of some new indole derivatives containing pyrazoles with potential antitumor activity.

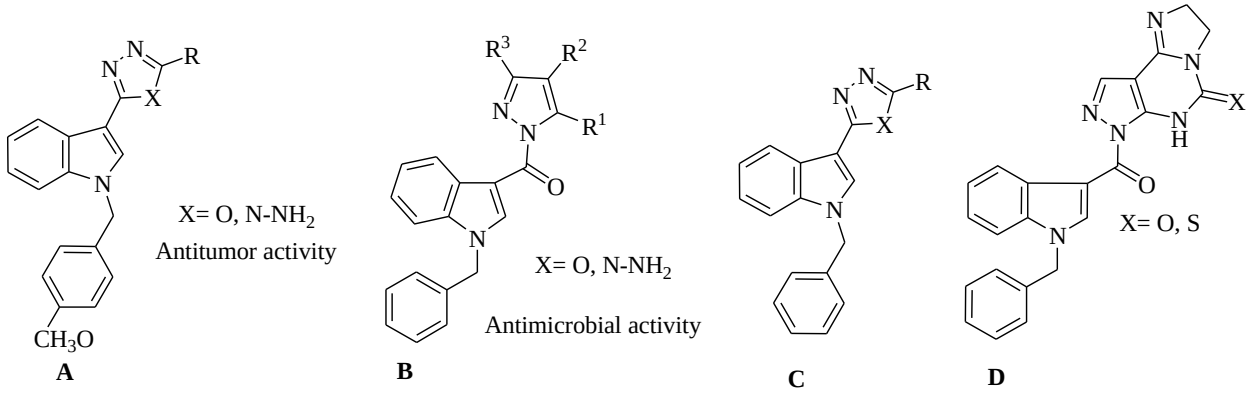


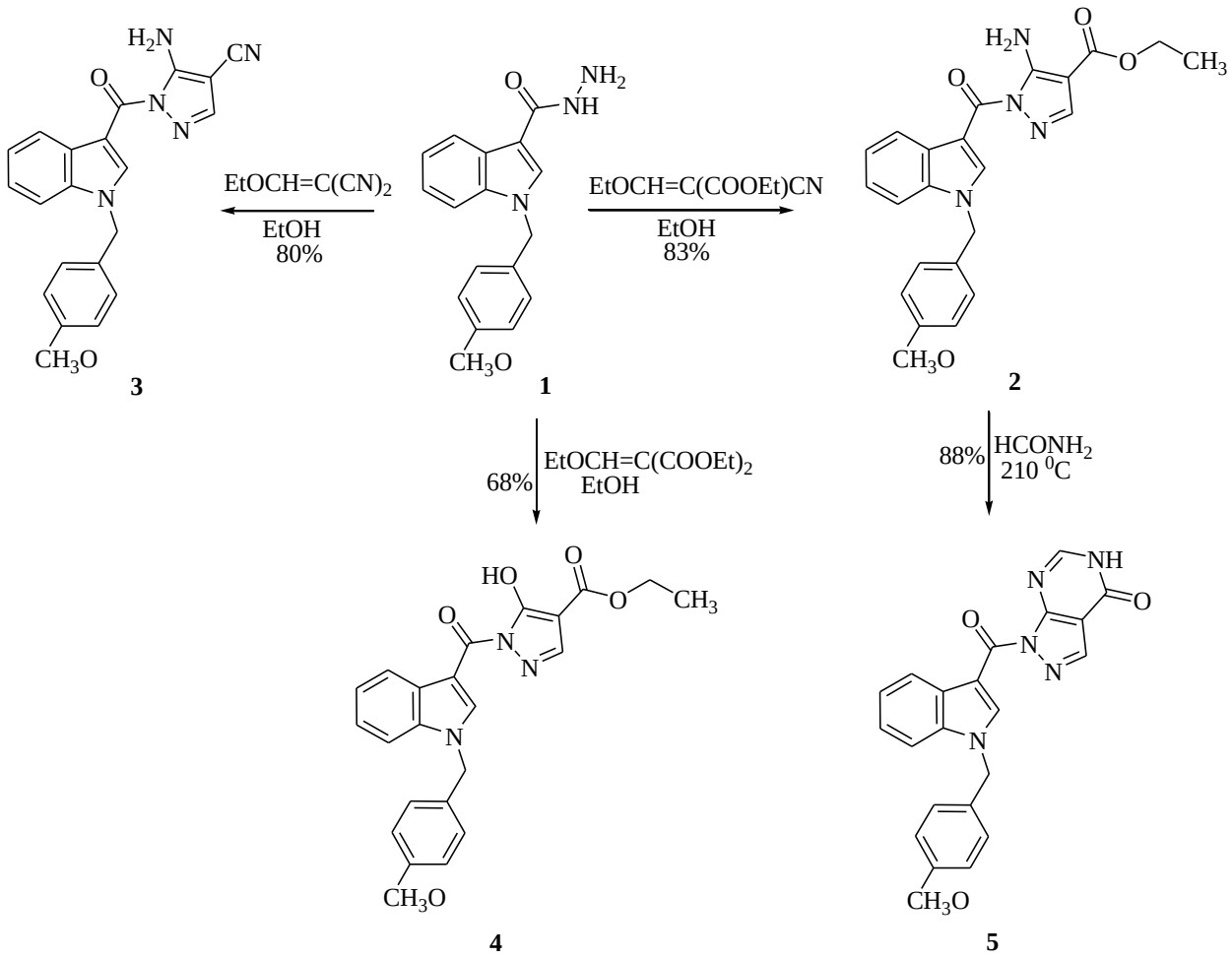
Figure 1

Results and Discussion

The easily accessible 1-(4-methoxybenzyl)-1*H*-indole-3-carbohydrazide **1**[26] was chosen as starting material of the synthesis of the new pyrazole derivatives as well as pyrazolone derivatives. Thus, treatment of carbohydrazide **1** with ethyl ethoxymethylenecyanoacetate or ethoxymethylenemalononitrile in absolute ethanol resulted in the formation of the corresponding ethyl 5-amino-1-(1-(4-methoxybenzyl)-1*H*-indole-3-carbonyl)-1*H*-pyrazole-4-carboxylate **2** and 5-Amino-1-(1-(4-methoxybenzyl)-1*H*-indole-3-carbonyl)-1*H*-pyrazole-4-carbonitrile **3** respectively**.** Analogously, when **1** was allowed to react with diethyl ethoxymethylenemalonate in refluxing absolute ethanol, the expected ethyl 5-hydroxy-1-(1-(4-methoxybenzyl)-1*H*-indole-3-carbonyl)-1*H*-pyrazole-4-carboxylate analog **4** was obtained (Scheme 1).

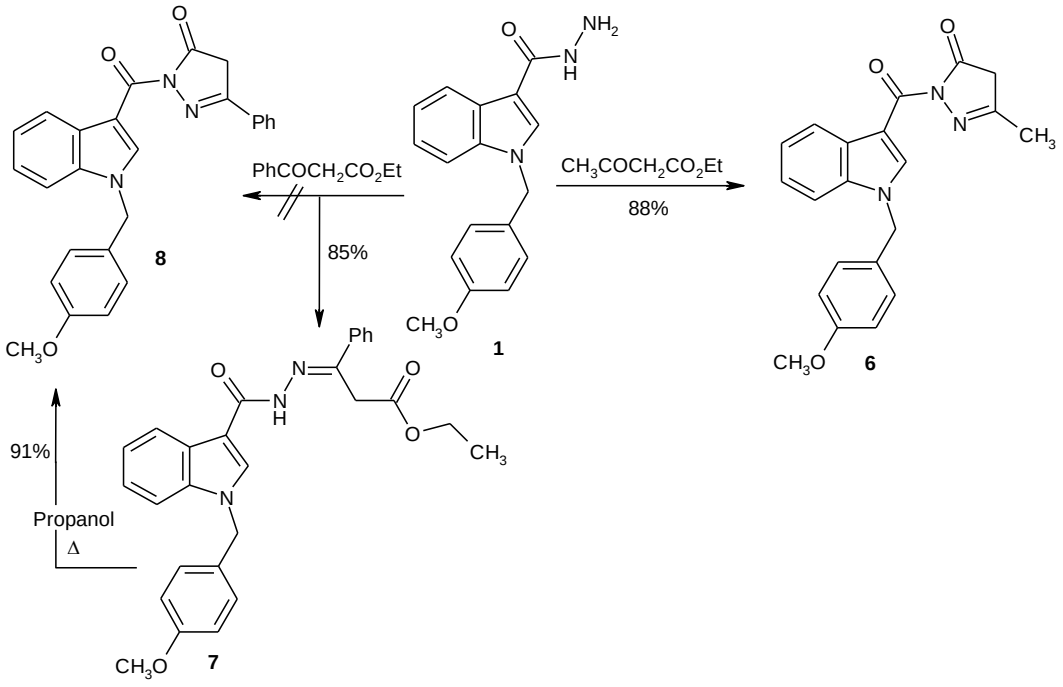
The structures of compounds **2, 3** and **4** were confirmed by their spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS) together with elemental analyses. The IR spectrum of compounds **2, 3** and **4** reveals the absence of characteristic absorption bands due to carbohydrazide $NHNH_2$ function and showed new characteristic bands atd C≡N an$_2$ due to NH $^{1-}$3420, 3320, 3150 and 2220 cm $\bar{\nu}$ respectively. The ^{1}H NMR spectrum of compound **2** expectedly shows characteristic signals near δ 4.31, 1.37 assignable to CH_2 and CH_3 respectively and at δ 10.75 assignable to OH. Further confirmation was achieved by the ^{13}C NMR spectrum which showed signals at δ 49.35, 55.09 and 116.67 due to OCH_3, CH_2 and C≡N respectively. Chemical confirmation for the amino ester

2 was achieved by boiling with formamide at 210 ºC, the pyrazolo[3,4-*d*]pyrimidinone **5** resulted. The formation of the pyrimidinone **5** is clearly evidenced by disappearance of the characteristic bands which belongs NH_2 and ester groups and showed new characteristic absorption bands atdue to NH and C=O respectively. $^{1-}$3300 and 1670 cm $\bar{\nu}$



Scheme 1

Treatment of the acid hydrazide **1** with ethyl acetoactetate led to the formation of the corresponding methyl-1*H*-pyrazol-5(4*H*)-one **6** in good yield, whereas when it was allowed to react with ethyl benzoylacetate under the same conditions, the open structure was obtained. The later compound could be cyclized via its boiling with high boiling point solvent (propanol) to afford the corresponding 1*H*-pyrazol-5(4*H*)-one **8** in good yield (Scheme 2).

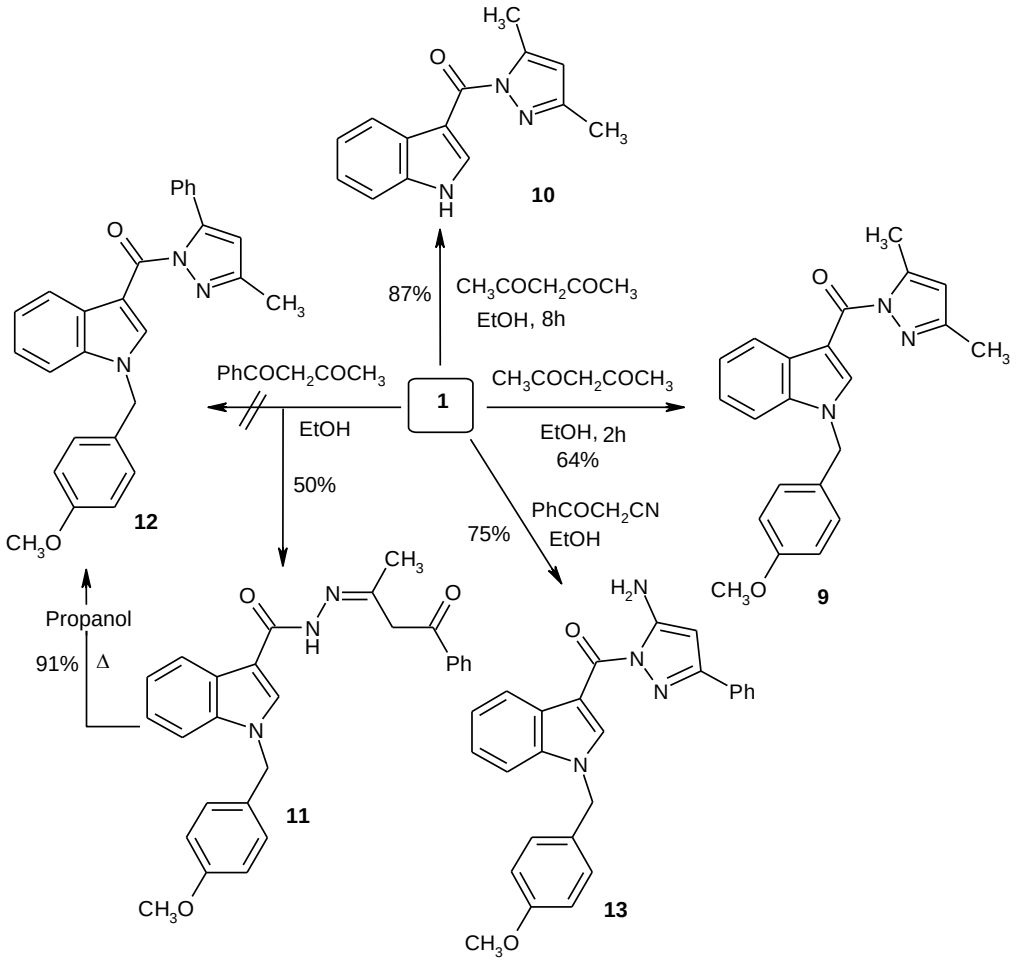


Scheme 2

The formation of compounds **6** and **8** was clearly elucidated by characteristic IR absorption bands of the products at $\bar{\nu}$ 1660 cm^{-1} due to C=O and disappearance the characteristic absorption bands belonging to $NHNH_2$ group. Further elucidation was done by ^1H NMR which showed signals at δ 3.52, 2.35 due to CH_2, CH_3 and 7.65/7.40 due to phenyl protons respectively. The open structure **7** was elucidated by ^{1}HNMR which showed clearly the signals at δ 4.10 and 1.38 due CH_2 and CH_3 respectively.

Interestingly, when the acid hydrazide was allowed to react with acetyl acetone in refluxing ethanol for 2 hours afforded directly the cyclized 3,5-dimethyl pyrazole derivative **9** in 64% yield. Whereas, heating the same acid hydrazide with benzoyl acetone under the same reaction conditions led to the formation the open structure **11**. The later compound was cyclized via its boiling in propanol to afford the corresponding (1-(4-Methoxybenzyl)-*1H*-indol-3-yl)(3-methyl-5-phenyl-*1H*-pyrazol-1-yl)methanone **12** in relatively good yield (Scheme 3).

It is worthy to note that, when the carbohydrazide **1** was allowed to react with acetyl acetone in boiling ethanol for prolonged time, an unexpected debenzylation occurred and the (3,5-dimethyl-1*H*-pyrazol-1-yl)(1*H*-indol-3-yl)methanone **10** was obtained. The debenzylation and the formation of compound **10** was confirmed by ^1H NMR which revealed the disappearance of the methoxy, phenyl and CH_2 signals and showed new signal at δ 10.56 due to NH. Further confirmation for the structure of compound **10** was obtained by MS which showed the $[M]^+$ ion at *m/z* 239 (2%).



Scheme 3

Finally, treatment of the acid hydrazide with benzolyl acetonitrile in boiling ethanol rise to the formation of the corresponding 5-amino-3-phenyl-1*H*-pyrazole **13** in 75% yield. The IR spectrum of compound **13** showed characteristic absorption bands at ν 3450, 3330 due to NH_2.

The biological activity of all synthesized target compounds was tested *in vitro* for antitumor activity using the Alamar Blue assay[32] on a panel of five human tumor cell lines at Zentaris, Germany. The cytotoxicity was evaluated on five different cell lines, cervix cancer (KB/HELA), ovarian carcinoma (SK-OV-3), brain cancer (SF-268), nonsmall-cell lung cancer (NCl-H460), and adenocarcinoma colon cancer (RKOP-27). The first screening was carried out at a predefined concentration of 3.16 µg/ml. If the compound led to more than 50% inhibition at this concentration it was evaluated for EC50 mean values (lM) from at least two experiments on those five different cell lines. It turned out that the amino nitrile **3** showed significant cell-growth inhibitory activity (>50%) at a fixed concentration of 3.16 µg/mL. Subsequent determination of EC50 concentrations from dose-response curves gave valid values for four cell lines (in the case

of NCI H-460, EC50 was above the highest test concentration). The results are summarized in Table 1.

Table 1. *In-vitro* antitumor activity (% cell-growth inhibition at fixed concentration and EC_{50} values) for synthesized compounds

	Single point					Dose Response				
	KB/HELA	SKOV-3	SF-268	NCI-H46	RKOp27	KB/HELA	SKOV-3	SF-268	NCI-H46	RKOp27
Comp No.	%INH [3.16µg/ml]					EC50 [µg/ml]				
2	-25	-1	5	6	7	-	-	-	-	-
3	52	31	34	51	64	EC50>	-	-	-	-
7	-20	-3	5	-2	4	-	-	-		
9	-2	0	3	4	9					
10	-2	6	7	18	14					
11	2	12	14	41	8					
13	11	7	27	26	25					

KB/HELA: cervical carcinoma; **SK OV-3**: ovarial carcinoma; **SF-268**: CNS cancer; **NCI-H460**: non-small-cell lung cancer; **RKOp27**: colon adenocarcinoma.

Experimental Section

General. Melting points were measured on a Kofler melting point apparatus. IR spectra (KBr pellets) were recorded on a Shimadzu 470 IR-Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Varian Gemini-300 (300 MHz for ^{1}H, and 75 MHz for ^{13}C) or a Varian Inova-500 (500 MHz for ^{1}H, and 125 MHz for ^{13}C) spectrometer at the Chemistry Department, Sogang University, Seoul, Korea. Mass spectra were obtained with a Jeol JMS-600 mass spectrometer. Elemental analyses were carried out using a Perkin-Elmer 240 C Micro analyzer and at the Chemistry Department (Microanalytical Laboratory), Assiut University

Ethyl 5-amino-1-(1-(4-methoxybenzyl)-*1H*-indole-3-carbonyl)-*1H*-pyrazole-4-carboxylate (2). A mixture of **1** (295 mg, 1 mmol) and ethyl ethoxymethylene- cyanoacetate (169 mg, 1 mmol) in ethanol (5 mL) was heated under reflux for 8 h. The progress of the reaction was monitored by HPLC. The solvent was removed under reduced pressure, the residue obtained was collected and recrystallized from ethanol to afford **2** (350 mg, 83%) as buff crystals, mp 135-137 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H, H-2), 8.48 (d, 1H, *J* = 8.70 Hz, H-4), 7.73 (s, 1H, CH pyrazole), 7.26 (m, 5H, H-5,6,7 and NH_2), 7.12 (d, *J* = 8.70 Hz, 2H, ArH), 6.84 (d, *J* =

8.70 Hz, 2H, ArH), 5.34 (s, 2H, CH_2 benzyl), 4.31 (q, *J* = 7.10 Hz, 2H, $C\underline{H}_2CH_3$), 3.77 (s, 3H, OCH_3), 1.37 (t, *J* = 7.10 Hz, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$): 165.83, 164.32, 159.53, 157.62, 154.68, 142.41, 139.80, 136.21, 129.08, 128.39, 127.77, 123.62, 123.00, 122.45, 114.45, 110.71, 107.15, 103.12, 94.41, 59.85, 55.42, 50.75, 14.69; IR (KBr, cm^{-1})3420, 3320, $\bar{\nu}$ 3150 (NH_2), 2950 (CH aliph.), 1725, 1690 (CO), 1620 (C=N). Anal. Calcd. for $C_{23}H_{22}N_4O_4$: C, 66.02; H, 5.30; N, 13.39. Found: C, 66.05; H, 5.27; N, 13.47.

5-Amino-1-(1-(4-methoxybenzyl)-1*H*-indole-3-carbonyl)-1*H*-pyrazole-4-carbonitrile (3). A mixture of **1** (295 mg, 1 mmol) and ethoxymethylene malononitrile (122 mg, 1 mmol) in ethanol (5 mL) was heated under reflux for 8 h. The progress of the reaction was monitored by HPLC. The solvent was removed under reduced pressure and the precipitate obtained was filtered off and recrystallized from ethanol to give **3** (200 mg, 80%) as white crystals, mp 204-206 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.99 (s, 1H, H-2), 8.29 (m, 1H, H-4), 8.05 (sb, 2H, NH_2), 7.98 (s, 1H, CH pyrazole), 7.62 (m, 1H, H-7), 7.27 (m, 4H, H-5,6 and 2H ArH), 6.87 (d, *J* = 8.70 Hz, 2H ArH), 5.52 (s, 2H, CH_2 benzyl), 3.69 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) 164.07, 158.84, 155.55, 143.56, 140.13, 135.75, 128.81, 128.66, 128.25, 127.34, 126.46, 123.32, 122.67, 121.43, 116.67, 114.12, 111.64, 105.55, 72.49, 55.09, 49.35; IR (KBr, cm^{-1}) ν 3400, 3300 (NH_2), 2950 (CH aliph.), 2220 (C≡N), 1660 (C=N). Anal. Calcd. for $C_{21}H_{17}N_5O_2$: C, 67.91; H, 4.61; N, 18.86. Found: C, 67.94; H, 4.57; N, 18.78.

Ethyl 5-hydroxy-1-(1-(4-methoxybenzyl)-1*H*-indole-3-carbonyl)-1*H*-pyrazole-4-carboxylate (4). An equimolar mixture of 1 (295 mg, 1 mmol), diethyl ethoxymethylene- malonate (225 mg, 1 mmol) in absolute ethanol (10 mL) was refluxed for 10 h. The reaction mixture was concentrated in vacuo, and allowed to attain room temperature. The separated solid product was collected by filtration and recrystallized from ethanol to afford **4** (370 mg, 88%) as buff crystals mp 145-147 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.75 (s, 1H, OH), 8.97 (s, 1H, H-2), 8.50 (d, 1H, *J* = 8.70 Hz, H-4), 7.76 (s, 1H, CH pyrazole), 7.29 (m, 3H, H-5,6,7), 7.15 (d, *J* = 8.70 Hz, 2H, ArH), 6.87 (d, *J* = 8.70 Hz, 2H, ArH), 5.34 (s, 2H, CH_2 benzyl), 4.35 (q, *J* = 7.10 Hz, 2H, $C\underline{H}_2CH_3$), 3.75 (s, 3H, OCH_3), 1.34 (t, *J* = 7.10 Hz, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$): 166.84, 162.35, 158.55, 157.15, 155.65, 143.44, 138.76, 135.29, 129.38, 128.39, 127.67, 124.12, 123.20, 122.15, 115.45, 111.71, 108.15, 102.12, 96.41, 60.85, 55.42, 51.75, 14.69; IR (KBr, cm^{-1}) ν 3460-2720 (OH), 2950 (CH aliph.), 1725, 1690 (CO), 1620 (C=N). Anal. Calcd. for $C_{23}H_{21}N_3O_5$: C, 65.86; H, 5.05; N, 10.02. Found: C, 65.78; H, 5.15; N, 9.95

1-(1-(4-Methoxybenzyl)-1*H*-indole-3-carbonyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (5). A suspension of **2** (418 mg, 1 mmol) and formamide (5 mL) was heated under reflux at 210 ^{0}C for about 5 h. After cooling, the solvent was removed under reduced pressure and the residue obtained was triturated with water. The solid product formed was filtered off, air dried and recrystallized from ethanol to afford **5** (272 mg, 68%) as brown crystals, mp 186-188 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15 (s, 1H, H-2), 8.12 (d, *J* = 7.5 Hz, 1H, H-4), 8.03 (sb, 1H, NH), 7.98 (s, 1H, CH pyrazole), 7.95 (s, 1H, CH pyrimidine), 7.52 (d, *J* = 7.80 Hz, 1H, H-7), 7.16 (m, 4H, indole-H5,6, ArH), 6.88 (m, 2H, ArH), 5.36 (s, 2H, CH_2 benzyl), 3.70 (s, 3H,

OCH_3). IR (KBr, cm^{-1}) ν 3300 (NH), 1670 (CO). Anal. Calcd. for $C_{22}H_{17}N_5O_3$: C, 66.16; H, 4.29; N, 17.53. Found: C, 66.07; H, 4.23; N, 17.44.

1-(1-(4-Methoxybenzyl)-1*H*-indole-3-carbonyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (6). A mixture of **1** (295 mg, 1 mmol) and ethyl acetoacetate (5 mL) was heated under reflux for about 8 h. The progress of the reaction was monitored by HPLC. The excess of the solvent was removed under reduced pressure and the residue obtained was collected and recrystallized from ethanol to give **6** (320 mg, 88%) as buff crystals, mp 145-147 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (s, 1H, H-2), 7.58 (d, J_{4-5} = 8.10 Hz, 1H, H-4), 7.37 (m, 4H, H-5,6 and 2H ArH), 6.97 (d, J = 8.70 Hz, 2H ArH), 5.61 (s, 2H, CH_2 benzyl), 3.70 (s, 3H, OCH_3), 3.52 (s, 2H, CH_2 pyrazolone), 2.35 (s, 3H, CH_3); IR (KBr, cm^{-1}) ν 1660 (C=O). Anal. Calcd. for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.68; H, 5.22; N, 11.52.

Ethyl 3-(2-(1-(4-methoxybenzyl)-1*H*-indole-3-carbonyl)hydrazono)-3-phenyl- propanoate (7). A mixture of **1** (295 mg, 1 mmol) and ethyl benzoylacetate (5 mL) was heated under reflux for about 8 h. The progress of the reaction was monitored by HPLC. The excess of the solvent was removed under reduced pressure and the residue obtained was collected and recrystallized from ethanol to give **7** (360 mg, 85%) as white crystals, mp 156-58 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.59 (s, 1H, NH); 8.35 (s, 1H, H-2), 8.23 (d, J_{4-5} = 7.80 Hz, 1H, H-4), 7.95 (d, J_{7-8} = 7.80 Hz, H-7) 7.62 (m, 3H, ArH), 7.41 (m, 2H, ArH), 7.27 (d, J= 8.10 Hz, 2H ArH), 7.21 (m, 2H, H-5,6 indole), 6.89 (d, J= 8.10 Hz, 2H ArH), 5.43 (s, 2H, CH_2 benzyl), 4.13 (s, 2H, CH_2), 4.10 (q, J= 7.10 Hz, 2H, $C\underline{H}_2CH_3$), 3.70 (s, 3H, OCH_3); 1.38 (t, J= 7.10 Hz, 3H, $CH_2C\underline{H}_3$); IR (KBr, cm^{-1}): ν 3200 (NH), 1730 (CO), 1640 (C=N); Anal. Calcd. for $C_{28}H_{27}N_3O_4$: C, 71.62; H, 5,80; N, 8.95. Found: C, 71.53; H, 5.74; N, 8.86.

1-(1-(4-Methoxybenzyl)-1*H*-indole-3-carbonyl)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (8). A mixture of **6** (469 mg, 1 mmol) in propanol (10 mL) and few drops of acetic acid was boiled under reflux for about 4 h. The reaction was followed up by HPLC. After cooling, the product formed was collected by filtration and recrystallized from ethanol to give **8** (420 mg, 91%) as buff crystals, mp. 306-308 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.67 (d, J_{4-5} = 7.80 Hz, 1H, H-4), 8.40 (s, 1H, H-2), 7.90 (d, J_{7-8} = 7.80 Hz, H-7) 7.65 (m, 3H, ArH), 7.40 (m, 2H, ArH), 7.28 (d, J = 8.10 Hz, 2H ArH), 7.21 (m, 2H, H-5,6 indole), 6.89 (d, J = 8.10 Hz, 2H ArH), 5.53 (s, 2H, CH_2 benzyl), 3.80 (s, 3H, OCH_3), 3.54 (s, 2H, CH_2 pyrazolone); IR (KBr, cm^{-1}): ν 1680 (CO), 1640 (C=N); Anal. Calcd. for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 5.00; N, 9.92; O, 11.33. Found: C, 73.65; H, 4.90; N, 9.86.

(3,5-Dimethyl-1*H*-pyrazol-1-yl)(1-(4-methoxybenzyl)-1*H*-indol-3-yl)methanone (9). A mixture of **1** (295 mg, 1 mmol) and acetylacetone (5 mL) was heated under reflux for about 2 h. The progress of the reaction was monitored by HPLC. The excess of the solvent was removed under reduced pressure and the residue obtained was collected and recrystallized from ethanol to give **9** (230 mg, 64%) as white crystals, mp 252-254 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (s, 1H, H-2), 8.56 (d, J_{4-5} = 8.7 Hz, 1H, H-4), 7.3 (m, 3H, H-5,6,7 indole), 7.14 (d, J = 8.4 Hz, 2H, ArH), 6.87 (d, J = 8.4 Hz, 2H, ArH), 6.05 (s, 1H, CH pyrazole), 5.34 (s, 2H, CH_2 benzyl),

3.78 (s, 3H, OCH_3); 2.33, 2.25 (2s, 2H, $2CH_3$). IR (KBr, cm^{-1}): ν 2920 (aliph. CH) 1670 (CO); Anal. Calcd. for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.47; H, 5.72; N, 11.55.

(3,5-Dimethyl-1*H*-pyrazol-1-yl)(1-(1*H*-indol-3-yl)methanone (10). It was obtained using the same procedure mentioned above but the time of reflux was 8h and the crude product formed was recrystallized from ethanol to give **10** (210 mg, 87%) as white crystals, mp 264-266 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ10.56 (sb, 1H, NH), 9.15 (s, 1H, H-2), 8.25 (d, J_{4-5} = 8.1 Hz, 1H, H-4), 8.01 (d, J_{7-8}= 8.1 Hz, H-7), 7.34 (m, 3H, H-5,6), 7.07 (s, 1H, NH), 6.21 (s, 1H, CH pyrazole), 2.55, 2.26 (2s, 2H, $2CH_3$). IR (KBr, cm^{-1}) ν 2920 (aliph. CH),1670 (CO); Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.19; H, 5.42; N, 17.48; MS *m/z*: 239 (M^+, 2%), 240 (15), 241 (2).

1-(4-Methoxybenzyl)-*N'*-(4-oxo-4-phenylbutan-2-ylidene)-1*H*-indole-3-carbohydrazide (11). A mixture of **1** (295 mg, 1 mmol) and benzoyl acetone (162 mg, 1 mmol) in ethanol (10 mL) was heated under reflux for about 2 h. The reaction was controlled by HPLC. After cooling, the precipitate formed was filtered off and recrystallized from ethanol/ethyl acetate (1:2) to afford **11** (220 mg, 50%) as pale yellow crystals, mp 262-264 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H, H-2), 8.35 (d, J_{4-5} = 8.1 Hz, 1H, H-4), 7.48 (d, J_{7-8}= 8.1 Hz, H-7), 7.32 (m, 3H, ArH), 7.26 (m, 2H, ArH), 7.17 (d, *J*= 8.1 Hz, 2H ArH), 7.10 (m, 2H, H-5,6), 6.86 (d, *J*= 8.1 Hz, 2H ArH), 5.64 (s, 1H, NH exchangeable with D_2O), 5.32 (s, 2H, CH_2 benzyl), 3.78 (s, 3H, OCH_3); 2.94 (2d, *J* =18.6 Hz, 2H, CH_2), 2.09(s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 197.98, 164.70, 159.87, 159.85, 153.99, 153,96, 145.13, 145.10, 136.68, 136.53, 129.23, 129.14, 128.88, 128.81, 124.65, 123.31, 123.19, 122.31, 119.52, 114.82, 110.52, 108.87, 95.22, 55.86, 53.95, 36.83, 14.69; IR (KBr, cm^{-1}): ν 3300 (NH), 2920 (aliph. CH), 1700 and 1680 (CO); Anal. Calcd. for $C_{27}H_{25}N_3O_3$: C, 73.78; H, 5.73; N, 9.56. Found: C, 73.67; H, 5.62; N, 9.48.

(1-(4-Methoxybenzyl)-*1H*-indol-3-yl)(3-methyl-5-phenyl-*1H*-pyrazol-1-yl)methanone (12). A suspension of **11** (439 mg, 1 mmol) in propanol (10 mL) and few drops of acetic acid was boiled under reflux for about 4 h. The reaction was followed up by HPLC. After cooling, the product formed was collected by filtration and recrystallized from ethanol to give **11** (400 mg, 91%) as buff crystals, mp. 278-280 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H, H-2), 8.33 (d, J_{4-5} = 8.1 Hz, 1H, H-4), 7.50 (d, J_{7-8}= 8.1 Hz, H-7), 7.36 (m, 3H, ArH), 7.28 (m, 2H, ArH), 7.20 (d, *J* = 8.1 Hz, 2H ArH), 7.14 (m, 2H, H-5,6), 6.88 (d, *J*= 8.1 Hz, 2H ArH), 5.52 (s, 2H, CH_2 benzyl), 3.84 (s, 3H, OCH_3); 2.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 165.70, 158.85, 157.80, 152.94, 151,91, 144.13, 143.10, 138.65, 137.52, 130.87, 130.18, 129.10, 128.83, 128.17, 127.97, 126.49, 124.65, 123.26, 122.31, 119.52, 114.82, 110.52, 108.87, 105.22, 55.36, 52.45, 13.65; IR (KBr, cm^{-1}): ν 2920 (aliph. CH), 1680 (CO); Anal. Calcd. for $C_{27}H_{23}N_3O_2$: C, 76.94; H, 5.50; N, 9.97. Found: C, 76.87; H, 5.58; N, 9.88.

(5-Amino-3-phenyl-1*H*-pyrazol-1-yl)(1-(4-methoxybenzyl)-*1H*-indol-3-yl)methanone (13). A mixture of **1** (295 mg, 1 mmol) and benzoyl acetonitrile (145 mg, 1 mmol) in absolute ethanol (10 mL) was heated under reflux for about 6 h. The reaction was controlled by HPLC. After cooling, the precipitate formed was filtered off and recrystallized from ethanol to afford **13** (318 mg, 75%) as pale yellow crystals, mp 221-223 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03

(s, 1H, H-2), 8.36 (d, $J_{4\text{-}5}$ = 7.2 Hz, 1H, H-4), 7.92 (d, $J_{7\text{-}8}$= 7.2 Hz, H-7), 7.76 (d, J = 8.7 Hz, 2H ArH), 7.38 (m, 7H, indole and ArH), 6.98 (d, J= 8.7 Hz, 2H ArH), 5.87 (s, 1H, pyrazole), 5.85 (s, 2H, NH_2), 5.52 (s, 2H, CH_2 benzyl), 3.73 (s, 3H, OCH_3); IR (KBr, cm^{-1}): ν 3450, 3330 (NH_2), 1670 (CO); Anal. Calcd. for $C_{26}H_{22}N_4O_2$: C, 73.92; H, 5.25; N, 13.26. Found: C, 73.87; H, 5.20; N, 13.19.

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