

One-pot, regioselective synthesis of functionalized indole derivatives: a three-component domino reaction of arylamine, arylglyoxal, and 4-hydroxycoumarin or 4-hydroxy-6-methyl-2-pyrone

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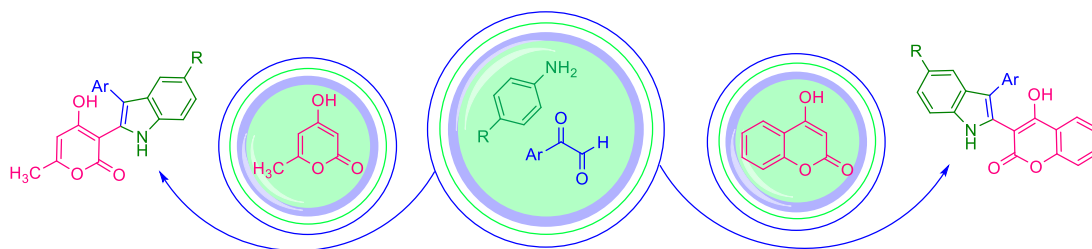
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Abstract

A metal free, one-pot tandem synthetic routes for functionalized indole derivatives has been established. An efficient three-component reaction was designed with incorporation of Knoevenagel condensation followed by inter-, and intramolecular nucleophilic addition reaction in one-pot under mild condition. The structural diversities of the synthesized compounds have been confirmed spectroscopically, by IR, ^1H - and ^{13}C NMR, and elemental analyses which agree with the proposed structures.



Keywords: Arylamine, Arylglyoxal, 4-Hydroxycoumarin, 4-Hydroxy-6-methyl-2-pyrone, Functionalized indole derivatives

Introduction

The indole motifs are one of the most important and abundant nitrogen-containing heterocyclic compounds found in important natural products, various functional molecules, and pharmaceuticals.¹ Indole analogs are very interesting to organic and medicinal chemists due to their biological activities, such as, anti-inflammatory **A**,² antimicrobial **B**,³ antioxidant **C**,⁴ and antibacterial **D** activity (Figure 1).⁵

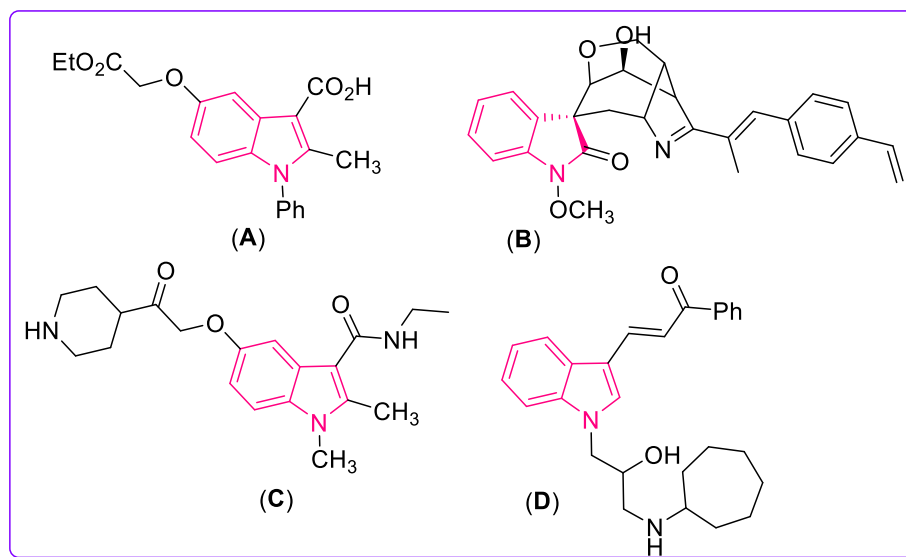


Figure 1. Selected bioactive molecules indoles.

In addition, many indole derivatives have exhibited high cytotoxic activity against breast, esophageal, colonic, lung, and stomach tumor cell lines.^{6,7} Moreover, indole cores can be found in the structure of different drugs such as sumatriptan,⁸ reserpine,⁹ and lotronex.¹⁰ On the other hand, among indole and its structural analogs, especially indolyl chromene and indolyl pyran derivatives, are found in a large number of pharmacological activities, such as antibacterial **E**,¹¹ antimicrobial **F**,^{12,13} anticancer **G**,¹⁴ antioxidant **H**,^{15,16} and antifungal **I** activities (Figure 2).¹⁷

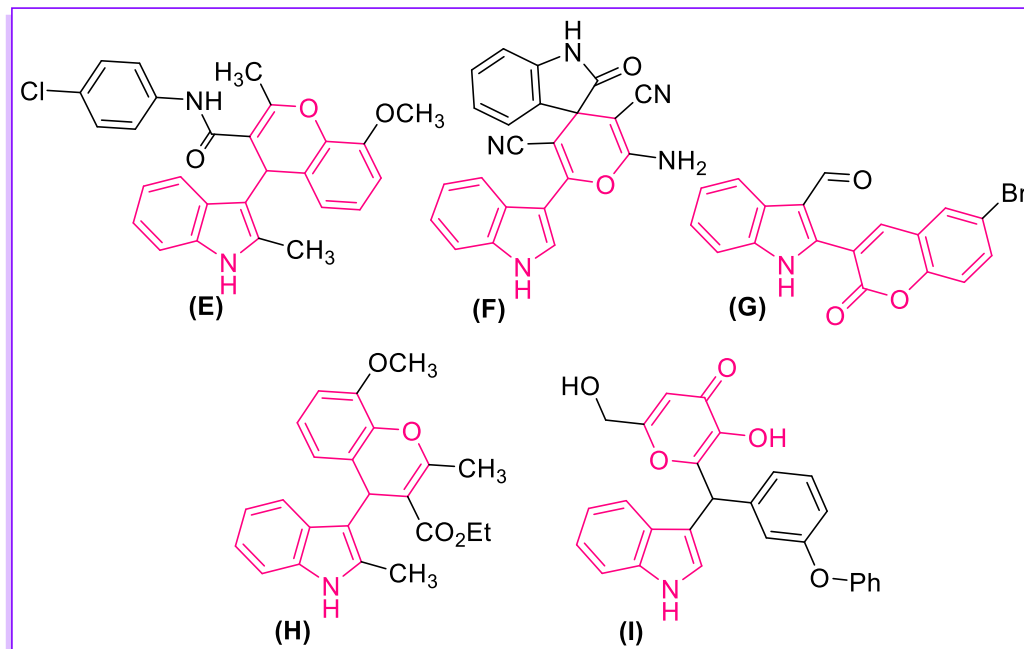
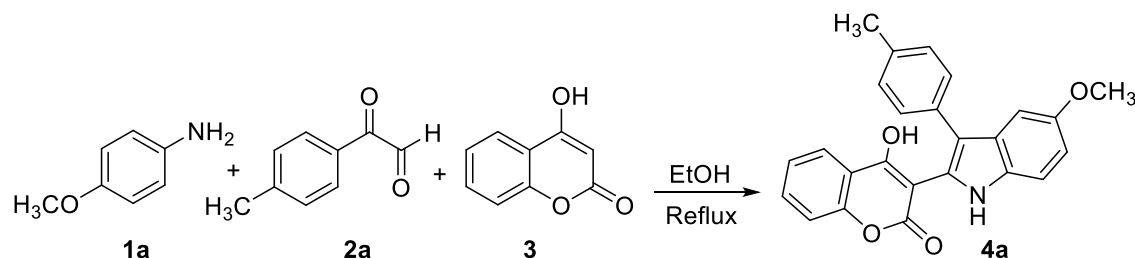


Figure 2. Selected examples of bioactive indolyl chromene and indolyl pyran derivatives.

Therefore, studies on strategies for the synthesis of indole derivatives have received high importance in organic synthesis. In this regard, there are many traditional methods for the preparation of indole derivatives including Fischer reaction,^{18,19} Bischler reaction,²⁰ Reissert reaction,²¹ Bartoli reaction,²² and Leimgruber-Batcho reaction.²³ Recently, new strategies have been developed for the synthesis of indole derivatives; these include: various metal-catalyzed,²⁴⁻²⁹ multi-component method,³⁰ cyclization reaction,³¹ Wittig reactions,³² and various other methods.³³⁻³⁶ Most of these protocols appear to suffer from some drawbacks such as tedious experimental procedures, difficult reaction conditions, multiple synthetic steps, low yields, and usage of expensive catalysts and reagents. Therefore, the development of more economic, convenient and efficient approaches to the regioselective synthesis of substituted indoles under mild conditions is still an attractive proposition. In continuation of our previous works on the application of arylglyoxal in synthesis of heterocyclic compounds,^{37,38} we herein report new synthetic strategy for the domino arylamine, arylglyoxal, and 4-hydroxycoumarin or 4-hydroxy-6-methyl-2-pyrone yielding the synthesis of functionalized indole derivatives with high yields.

Results and Discussion

To find the optimized conditions, we studied the synthesis of 4-hydroxy-3-(5-methoxy-3-(*p*-tolyl)-1H-indol-2-yl)-2H-chromen-2-one **4a** via the three-component reaction of 4-methoxyaniline **1a**, 4-methylphenylglyoxal **2a**, and 4-hydroxycoumarin **3** under a variety of conditions (Table 1).

Table 1. Optimization of the reaction conditions

Entry	Solvent	Temp. ^a	mmol of 1a:2a:3	Yield (%) ^b
1	DMF	r.t.	1:1:1	N.R.
2	CH ₂ Cl ₂	r.t.	1:1:1	N.R.
3	H ₂ O	r.t.	1:1:1	N.R.
4	EtOH	r.t.	1:1:1	21
5	DMF	Reflux	1:1:1	Trace
6	CH ₂ Cl ₂	Reflux	1:1:1	Trace
7	H ₂ O	Reflux	1:1:1	Trace
8	EtOH	Reflux	1:1:1	77
9	EtOH	Reflux	1.0:1.5:1.5	72
10	EtOH	Reflux	1.5:1.0:1.5	69
11	EtOH	Reflux	1.5:1.5:1.0	85
12	EtOH	Reflux ^c	1.5:1.5:1.0	85

^a Reaction conditions: solvent was 15 mL, reaction time was 10 h.

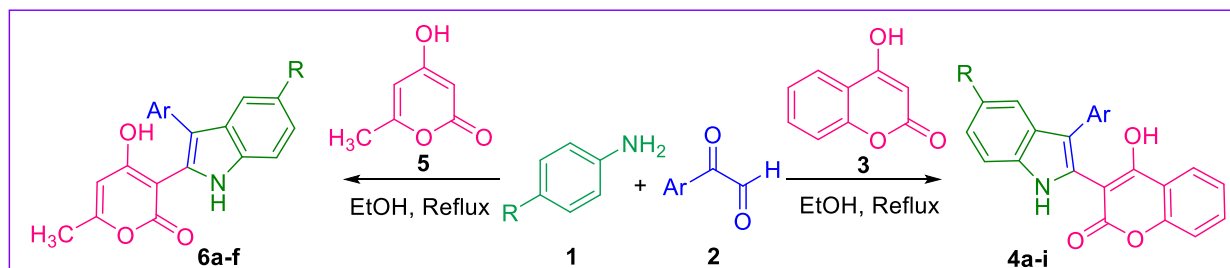
^b Isolated yields.

^c Reaction time was 24 h.

The optimization of the reaction conditions, including the solvent, temperature, and the equivalents of starting materials were investigated. First, various solvents were examined (Table 1, entries 1–4), and ethanol was found to be the preeminent solvent for this reaction. Then, we examined the influence of different temperatures on this reaction. When the reaction was carried out for 10 h. at room temperature, the product formed in 21% yield, but under reflux conditions at the same time, the product was formed in 77% yield (Table 1, entries 4 and 8). Finally, we observed that the amount of starting materials also have important influence on the reaction (Table 1, entries 8–11). A larger amount of 4-methoxyaniline **1a**, and 4-methylphenylglyoxal **2a** (for example, 1.5 mmol) in ethanol at reflux temperature resulted in a higher yield, 85% (Table 1, entry 11). Also, increasing the reaction time in ethanol under reflux condition did not improve the yield (Table 1, entry 12). This series of experiments reveal that the optimal results were obtained when the reaction of 4-methylphenylglyoxal **2a** (1.5 mmol) was conducted with 4-methoxyaniline **1a** (1.5 mmol), and 4-hydroxycoumarin **3** (1.0 mmol) in ethanol under reflux conditions. These optimized reaction conditions (Table 1, entry 11) were then used to synthesize and explore the scope of this novel transformation with various arylamine, arylglyoxal, and 1,3-dicarbonyl compounds such as 4-hydroxycoumarin and 4-hydroxy-6-methyl-2-pyrone, to give two series of 4-hydroxy-3-(3-aryl-1H-indol-2-yl)-2H-pyran-2-ones **4a-i** and 4-hydroxy-3-(3-aryl-1H-indol-2-yl)-2H-chromen-2-ones **6a-f** in good yields (Table 2).

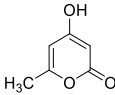
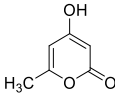
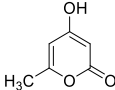
As can be seen from Table 2, the nature of the arylamine, the arylglyoxal, and the 1,3-dicarbonyl compounds was important. When the arylamine derivatives especially with electron-donating groups, the arylglyoxal derivatives with electron-withdrawing groups, and the 1,3-dicarbonyl compounds such as 4-hydroxycoumarin were employed, a higher yield was achieved.

Table 2. Synthesis of 4-hydroxy-3-(3-aryl-1H-indol-2-yl)-2H-pyran-2-ones and 4-hydroxy-3-(3-aryl-1H-indol-2-yl)-2H-chromen-2-ones



Entry	Product ^a	R	Ar	3 or 5	Yield (%) ^b
1	4a	OCH ₃	4-CH ₃ C ₆ H ₄		85
2	4b	OCH ₃	4-ClC ₆ H ₄		93
3	4c	OCH ₃	4-BrC ₆ H ₄		91
4	4d	OCH ₃	4-FC ₆ H ₄		94
5	4e	Cl	4-OCH ₃ C ₆ H ₄		79
6	4f	Br	4-OCH ₃ C ₆ H ₄		78
7	4g	Br	4-NO ₂ C ₆ H ₄		80
8	4h	CH ₃	3,4-(OCH ₃) ₂ C ₆ H ₃		82
9	4i	Cl	2-CH ₃ C ₆ H ₄		78
10	6a	CH ₃	4-CH ₃ C ₆ H ₄		59
11	6b	CH ₃	4-ClC ₆ H ₄		62
12	6c	OCH ₃	4-ClC ₆ H ₄		68

Table 2. Continued

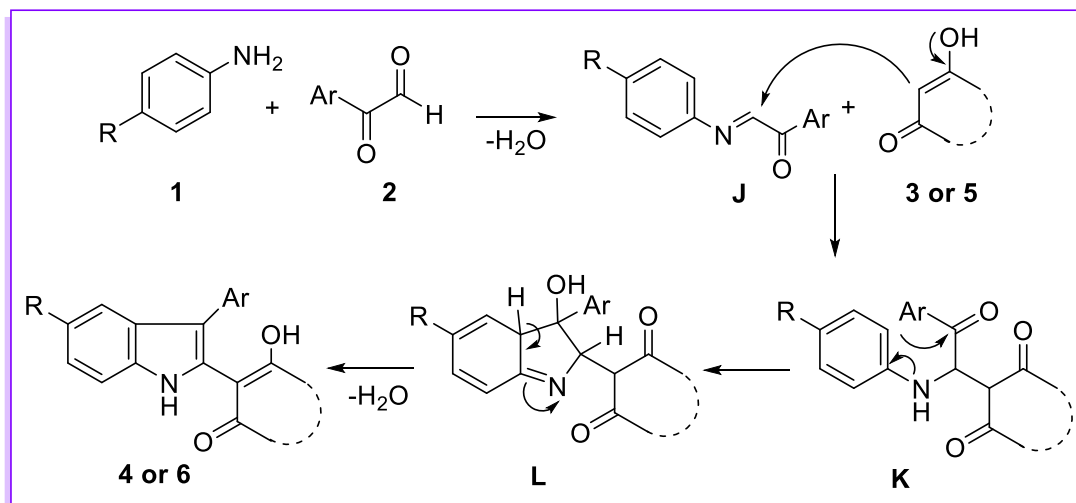
Entry	Product ^a	R	Ar	3 or 5	Yield (%) ^b
13	6d	CH ₃	4-NO ₂ C ₆ H ₄		64
14	6e	CH ₃	4-OCH ₃ C ₆ H ₄		55
15	6f	Cl	2-CH ₃ C ₆ H ₄		58

^a Reaction conditions: **1** (1.5 mmol), **2** (1.5 mmol), **3** or **5** (1.0 mmol); solvent volume 15.0 mL and reaction time was 10 h.

^b Isolated yields.

All the synthesized compounds were unknown, and were characterized by ¹H and ¹³C NMR, IR, CHN analysis and melting points. For instance, the ¹H NMR spectrum of the compound **4a** consisted of one singlet at $\delta = 2.65$ ppm for the three hydrogens of the methyl group. A singlet that integrated for three protons was observed at $\delta = 3.33$ ppm for the methoxy protons. The aromatic protons resonated in the region $\delta = 6.29$ – 7.49 ppm, and a broad singlet that integrated for one hydrogen was observed at $\delta = 9.71$ ppm for the hydroxyl proton. A broad singlet at $\delta = 10.52$ ppm for the proton of the nitrogen group. The ¹³C NMR spectrum of compound **4a** exhibited 23 distinct signals in agreement with the proposed structure. Partial assignments of these resonances for the other products are given in the experimental section.

Based on our experimental results and literature reports, we proposed a possible mechanism for the formation of 4-hydroxy-3-(3-aryl-1H-indol-2-yl)-2H-pyran-2-ones **4** and 4-hydroxy-3-(3-aryl-1H-indol-2-yl)-2H-chromen-2-ones **6** as shown in Scheme 1. Firstly, intermediate **J** is formed through Knoevenagel condensation of the arylamine **1** to the arylglyoxal **2**. Then, this intermediate is converted into intermediate **K** through an intermolecular nucleophilic addition reaction, which subsequently undergoes an intramolecular nucleophilic addition reaction to form intermediate **L**. In the last step, intermediate **L** afforded the desired products **4** and **6** in good yield with removal of H₂O and [1,3-H] shift.



Scheme 1. The proposed mechanism for formation of 4-hydroxy-3-(3-aryl-1H-indol-2-yl)-2H-pyran-2-ones and 4-hydroxy-3-(3-aryl-1H-indol-2-yl)-2H-chromen-2-ones.

Conclusions

In summary, we have reported the development of a facile synthesis of functionalized indol derivatives using a one-pot, three-component process through Knoevenagel condensation followed by inter-, and intramolecular nucleophilic addition reaction. Using this method, we were able to assemble a wide range of indol derivatives with good to excellent yields in a single step. The salient feature of our protocol is high atom-economy, operational simplicity, easy work-up, and easily available precursors.

Experimental Section

General. All chemicals were purchased from Aldrich and Merck with high-grade quality, and used without any purification. All melting points were obtained by Barnstead Electrothermal 9200 apparatus and are uncorrected. The reactions were monitored by TLC and all yields refer to isolated products. NMR spectra were obtained on a Varian 500 MHz spectrometer (^1H NMR at 500 MHz, ^{13}C NMR at 125 MHz) in DMSO using TMS as an internal standard. Infrared spectra were recorded on a Bruker FT-IR Equinax-55 spectrophotometer in KBr with absorption in cm^{-1} . Elemental analyses were performed using a Carlo Erba EA 1108 instrument. All products were characterized by their spectral and physical data.

General procedure for the synthesis of compounds 4a-i. A mixture of arylamine **1** (1.5 mmol) and arylglyoxal **2** (1.5 mmol) was stirred in 15 mL of ethanol at reflux for 2 h. to give iminone. Then, 4-hydroxycoumarin **3** (1.0 mmol) was added, and obtained mixture was refluxed for 8 h. After completion of the reaction, determined by TLC, the solvent was removed under reduced pressure, and the resulting crude product was purified by washing with diethyl ether then, by simple filtration and washing with cold ethyl acetate to give the pure compounds **4a-i** (78–94%).

General procedure for the synthesis of compounds 6a-f.

A mixture of arylamine **1** (1.5 mmol) and arylglyoxal **2** (1.5 mmol) was stirred in 15 mL of ethanol at reflux for 2 h. to give iminone. Then, 4-hydroxy-6-methyl-2-pyrone **5** (1.0 mmol) was added, and obtained mixture was refluxed for 8 h. After completion of the reaction, determined by TLC, the solvent was removed under reduced pressure, and the viscous residue was purified by plate chromatography (20×20 cm) using n-hexane/EtOAc (2:1) as eluent to give the pure compounds **6a-f** (55–68%).

3-(5-Methoxy-3-(p-tolyl)-1H-indol-2-yl)chromane-2,4-dione (4a). White powder; mp 260–263 °C. IR ν/cm^{-1} (KBr): 3026, 1763, 1601, 1444 cm^{-1} . ^1H NMR (500 MHz, DMSO): δ 2.65 (s, 3H, CH_3), 3.33 (s, 3H, OCH_3), 6.29 (s, 1H, ArH), 6.36 (d, J 11.0 Hz, 1H, ArH), 6.69 (d, J 8.0 Hz, 2H, ArH), 6.88 (t, J 7.5 Hz, 1H, ArH), 6.92 (d, J 8.5 Hz, 2H, ArH), 7.08 (d, J 8.0 Hz, 2H, ArH), 7.16 (t, J 7.5 Hz, 1H, ArH), 7.48 (d, J 7.5 Hz, 1H, ArH), 9.71 (s, 1H, OH), 10.52 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 21.1, 60.2, 102.7, 103.5, 116.6, 124.0, 126.8, 127.0, 129.5, 131.8, 132.6, 134.7, 135.1, 137.1, 137.8, 144.6, 145.1, 146.9, 150.2, 154.4, 159.1, 159.2, 171.0 ppm. Anal. Calcd for $\text{C}_{25}\text{H}_{19}\text{NO}_4$ (397.43): C, 75.55; H, 4.82; N, 3.52. Found: C, 75.73; H, 4.86; N, 3.49.

3-(3-(4-Chlorophenyl)-5-methoxy-1H-indol-2-yl)chromane-2,4-dione (4b). White powder; mp 298–301 °C. IR ν/cm^{-1} (KBr): 3311, 1684, 1614, 1485 cm^{-1} . ^1H NMR (500 MHz, DMSO): δ 3.68 (s, 3H, OCH_3), 6.64 (s, 1H, ArH), 6.74 (d, J 6.5 Hz, 1H, ArH), 7.25–7.31 (m, 5H, ArH), 7.52–7.56 (m, 3H, ArH), 7.87 (t, J 7.0 Hz, 1H, ArH), 10.45 (s, 1H, OH), 11.25 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 55.8, 99.5, 101.1, 101.1, 103.0, 112.6, 112.7, 116.6, 124.1, 124.4, 128.6, 129.0, 129.9, 132., 132.30, 132.4, 132.6, 136.5, 153.1, 154.1, 162.2, 162.5 ppm. Anal. Calcd for $\text{C}_{24}\text{H}_{16}\text{ClNO}_4$ (417.85): C, 68.99; H, 3.86; N, 3.35. Found: C, 69.10; H, 3.87; N, 3.39.

3-(3-(4-Bromophenyl)-5-methoxy-1H-indol-2-yl)chromane-2,4-dione (4c). White powder; mp 225–228 °C. IR ν/cm^{-1} (KBr): 3064, 1679, 1631, 1482 cm^{-1} . ^1H NMR (500 MHz, DMSO): δ 3.67 (s, 3H, CH_3), 6.83 (d, J 8.0, 2H, ArH), 7.11 (d, J 6.5 Hz, 2H, ArH), 7.35 (s, 2H, Ar-H), 7.67–7.81 (m, 6H, ArH, OH), 8.04 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 55.8, 96.4, 110.4, 114.8, 117.4, 120.2, 121.5, 124.9, 127.3, 127.4, 128.4, 129.1, 130.0, 130.4, 130.5, 132.7, 134.6, 135.7, 159.7, 176.7, 181.6, 184.8 ppm. Anal. Calcd for $\text{C}_{24}\text{H}_{16}\text{BrNO}_4$ (462.30): C, 62.35; H, 3.49; N, 3.03. Found: C, 62.17; H, 3.45; N, 3.07.

3-(3-(4-Fluorophenyl)-5-methoxy-1H-indol-2-yl)chromane-2,4-dione (4d). White powder; mp 162–165 °C. IR ν/cm^{-1} (KBr): 3041, 1634, 1595, 1438 cm^{-1} . ^1H NMR (500 MHz, DMSO): δ 3.67 (s, 3H, CH_3), 6.83 (m, 12H, ArH, OH), 8.06 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz): δ 55.6, 114.6, 115.7, 116.7, 116.8, 117.4, 120.2, 124.9, 126.1, 127.4, 127.5, 127.5, 128.5, 128.5, 131.6, 131.6, 135.6, 154.3, 159.3, 164.7, 168.7, 168.7 ppm. Anal. Calcd for $\text{C}_{24}\text{H}_{16}\text{FNO}_4$ (401.39): C, 71.82; H, 4.02; N, 3.49. Found: C, 71.90; H, 4.05; N, 3.46.

3-(5-Chloro-3-(4-methoxyphenyl)-1H-indol-2-yl)chromane-2,4-dione (4e). White powder; mp 271–274 °C. IR ν/cm^{-1} (KBr): 3324, 1701, 1610, 1468, cm^{-1} . ^1H NMR (500 MHz, DMSO): δ 3.74 (s, 3H, OCH_3), 6.97 (d, J 9Hz, 2H, ArH), 7.11 (d, J 6.5Hz, 1H, ArH), 7.21 (s, 1H, ArH), 7.37 (t, J 7.5Hz, 1H, ArH), 7.43 (d, J 8.5Hz, 2H, ArH), 7.54 (d, J 8.5Hz, 2H, ArH) 7.66 (t, J 8.5Hz, 1H, ArH), 7.90 (d, J 9.0Hz, 1H, ArH), 11.07 (s, 1H, OH), 11.71 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 55.5, 99.1, 101.5, 113.0, 114.6, 116.6, 118.3, 121.5, 124.1, 124.1, 124.3, 125.3, 128.5, 131.0, 132.5, 135.1, 139.0, 153.2, 159.4, 162.2, 162.6, 170.7 ppm.

3-(5-Bromo-3-(4-methoxyphenyl)-1H-indol-2-yl)chromane-2,4-dione (4f). Yellow powder; mp 291–294 °C. IR ν/cm^{-1} (KBr): 3319, 1701, 1610, 1467, 1411, cm^{-1} . ^1H NMR (500 MHz, DMSO): δ 3.73 (s, 3H, CH_3), 6.96 (d, J 8.5Hz, 2H, ArH), 7.21 (d, J 6.5Hz, 1H, ArH) 7.34–7.43 (m, 3H, ArH), 7.42 (d, J 8.5Hz, 1H, ArH), 7.52 (d, J 9.0Hz, 2H, ArH), 7.65 (t, J 8.5Hz, 1H, ArH) 7.89 (d, J 6.5Hz, 1H, ArH) 11.05 (s, 1H, OH), 11.70 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 55.5, 112.0, 113.4, 114.6, 116.6, 116.7, 121.3, 123.9, 124.0, 124.1, 124.2, 125.2, 128.5, 128.6, 131.7, 132.5, 135.3, 138.8, 153.2, 159.4, 162.2, 170.7 ppm.

3-(5-Bromo-3-(4-nitrophenyl)-1H-indol-2-yl)chromane-2,4-dione (4g). White powder; mp 303–306 °C. IR ν/cm^{-1} (KBr): 3087, 1658, 1600, 1493 cm^{-1} . ^1H NMR (500 MHz, DMSO): δ 6.85 (d, J 8.5Hz, 2H, ArH), 7.31–7.48

(m, 5H, OH, ArH), 7.68 (t, *J* 8.5Hz, 1H, ArH), 7.85 (d, *J* 9.0Hz, 1H, ArH), 7.93 (d, *J* 7.5Hz, 1H, ArH), 8.27 (d, *J* 9.0Hz, 2H, ArH), 12.15 (s, 1H, NH) ppm. ¹³C NMR (125 MHz, DMSO): δ 98.5, 105.4, 112.7, 114.1, 116.7, 120.2, 122.3, 124.2, 124.3, 124.5, 125.8, 127.9, 131.1, 132.3, 132.8, 136.0, 139.2, 146.7, 153.3, 162.0, 162.9 ppm. Anal. Calcd for C₂₃H₁₃BrN₂O₅ (477.27): C, 57.88; H, 2.75; N, 5.87. Found: C, 57.79; H, 2.74; N, 5.90.

3-(3(3,4-Dimethoxyphenyl)-5-methyl-1H-indol-2-yl)chromane-2,4-dione (4h). Yellow powder; mp 295–298 °C. IR ν/cm⁻¹ (KBr): 2939, 1692, 1613, 1494 cm⁻¹. ¹H NMR (500 MHz, DMSO): δ 2.33 (s, 3H, CH₃), 3.64 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 6.94-6.98 (m, 3H, ArH), 7.13 (d, *J* 6.5Hz, 1H, ArH), 7.24 (s, 1H, ArH), 7.33 (d, *J* 8.0Hz, 1H, ArH), 7.38 (t, *J* 7.0Hz, 1H, ArH), 7.44 (d, *J* 8.5Hz, 1H, ArH), 7.66 (t, *J* 6.5Hz, 1H, ArH), 7.91 (d, *J* 6.5Hz, 1H, ArH), 11.00 (s, 1H, OH), 11.39 (s, 1H, NH) ppm. ¹³C NMR (125 MHz, DMSO): δ 21.6, 55.6, 55.9, 100.1, 101.2, 110.9, 111.2, 112.4, 116.6, 116.6, 118.7, 119.6, 123.3, 124.0, 124.5, 126.0, 127.9, 130.0, 132.5, 135.0, 137.2, 148.7, 148.9, 153.1, 162.3, 162.4 ppm. Anal. Calcd for C₂₆H₂₁NO₅ (427.46): C, 73.06; H, 4.95; N, 3.28. Found: C, 72.98; H, 4.93; N, 3.31.

3-(5-Chloro-3-(o-tolyl)-1H-indol-2-yl)chromane-2,4-dione (4i). Yellow powder; mp 234–236 °C. IR ν/cm⁻¹ (KBr): 3315, 1715, 1608, 1467, 1411, cm⁻¹. ¹H NMR (500 MHz, DMSO): δ 2.27 (s, 3H, CH₃), 7.02-7.11 (m, 4H, ArH), 7.15 (d, *J* 7.0Hz, 1H, ArH), 7.29 (s, 1H, ArH), 7.31 (d, *J* 8.0Hz, 1H, ArH), 7.40 (t, *J* 7.0Hz, 1H, ArH), 7.49 (d, *J* 8.5Hz, 1H, ArH), 7.71 (t, *J* 7.0Hz, 1H, ArH), 7.85 (d, *J* 6.5Hz, 1H, ArH), 11.03 (s, 1H, OH), 11.47 (s, 1H, NH) ppm. ¹³C NMR (125 MHz, DMSO): δ 20.4, 102.5, 104.7, 110.3, 111.7, 114.4, 116.2, 116.8, 117.3, 119.7, 122.3, 124.2, 124.8, 125.3, 127.6, 131.4, 133.7, 135.2, 138.2, 144.2, 149.6, 157.4, 159.3, 161.6 ppm.

4-Hydroxy-6-methyl-3-(5-methyl-3-(p-tolyl)-1H-indol-2-yl)-2H-pyran-2-one (6a). Yellow powder; mp 188-201 °C. IR ν/cm⁻¹ (KBr): 3411, 3117, 1650, 1442 cm⁻¹. ¹H NMR (500 MHz, DMSO): δ 2.04 (s, 3H, CH₃), 2.10 (s, 3H, CH₃), 2.15 (s, 3H, CH₃), 5.74 (s, 1H, ArH), 6.70 (d, *J* 9.9Hz, 1H, ArH), 6.85 (s, 1H, ArH), 6.90 (d, *J* 7.8Hz, 2H, ArH), 7.05 (d, *J* 8.1Hz, 1H, ArH), 7.26 (d, *J* 5.1Hz, 2H, ArH), 9.22 (s, 1H, OH), 10.11 (s, 1H, NH) ppm. ¹³C NMR (125 MHz, DMSO): δ 19.7, 21.0, 21.3, 100.5, 108.8, 110.8, 119.0, 123.6, 124.9, 126.0, 126.7, 128.2, 128.9, 130.3, 134.6, 136.6, 136.7, 161.0, 164.9, 166.6 ppm. Anal. Calcd for C₂₂H₁₉NO₃ (345.40): C, 76.50; H, 5.54; N, 4.06. Found: C, 76.37; H, 5.51; N, 4.04.

3-(3-(4-Chlorophenyl)-5-methyl-1H-indol-2-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (6b). Yellow powder; mp 254-257 °C. IR ν/cm⁻¹ (KBr): 3397, 3085, 1651, 1445 cm⁻¹. ¹H NMR (500 MHz, DMSO): δ 2.22 (s, 3H, CH₃), 2.32 (s, 3H, CH₃), 6.08 (s, 1H, ArH), 6.92 (s, 1H, ArH), 6.93 (d, *J* 9.0Hz, 1H, ArH), 7.27 (d, *J* 8.5Hz, 1H, ArH), 7.45 (d, *J* 8.5Hz, 2H, ArH), 7.56 (d, *J* 8.5Hz, 2H, ArH), 11.07 (s, 1H, OH), 11.34 (s, 1H, NH) ppm. ¹³C NMR (125 MHz, DMSO): δ 19.9, 21.6, 96.0, 100.8, 104.1, 111.4, 119.5, 123.27, 127.8, 128.4, 128.9, 129.6, 132.0, 132.7, 134.7, 135.0, 161.8, 164.1, 167.7 ppm.

3-(3-(4-Chlorophenyl)-5-methoxy-1H-indol-2-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (6c). Yellow powder; mp 272-275 °C. IR ν/cm⁻¹ (KBr): 3401, 3094, 1649, 1484 cm⁻¹. ¹H NMR (500 MHz, DMSO): δ 2.22 (s, 3H, CH₃), 3.69 (s, 3H, OCH₃), 6.05 (s, 1H, ArH), 6.60 (s, 1H, ArH), 6.74 (d, *J* 9.5Hz, 1H, ArH), 7.27 (d, *J* 8.5Hz, 1H, ArH), 7.42 (d, *J* 8.5Hz, 2H, ArH), 7.55 (d, *J* 8.5Hz, 2H, ArH), 11.25 (s, 1H, NH) ppm. ¹³C NMR (125 MHz, DMSO): δ 19.9, 55.9, 101.7, 112.4, 128.4, 128.9, 129.8, 130.4, 131.7, 131.8, 131.9, 132.0, 132.8, 135.1, 143.7, 145.7, 153.7, 161.7, 163.7 ppm. Anal. Calcd for C₂₁H₁₆ClNO₄ (381.81): C, 66.06; H, 4.22; N, 3.67. Found: C, 66.12; H, 4.22; N, 3.70.

4-Hydroxy-6-methyl-3-(5-methyl-3-(4-nitrophenyl)-1H-indol-2-yl)-2H-pyran-2-one (6d). Yellow powder; mp 285–288 °C. IR ν/cm⁻¹ (KBr): 3413, 3085, 1645, 1469 cm⁻¹. ¹H NMR (500 MHz, DMSO): δ 2.00 (s, 3H, CH₃), 2.29 (s, 3H, CH₃), 5.41 (s, 1H, ArH), 6.88 (d, *J* 8.0Hz, 1H, ArH), 6.94 (s, 1H, ArH), 7.20 (d, *J* 8.0Hz, 1H, ArH), 7.95 (d, *J* 9.0Hz, 2H, ArH), 8.13 (d, *J* 9.0Hz, 2H, ArH), 8.49 (s, 1H, OH) 11.09 (s, 1H, NH) ppm. ¹³C NMR (125 MHz, DMSO): δ 20.0, 29.5, 102.4, 110.9, 123.7, 126.9, 137.9, 149.5, 150.5, 151.6, 153.6, 154.7, 155.2, 155.6, 157.1, 160.9, 161.8, 162.8, 178.2 ppm. Anal. Calcd for C₂₁H₁₆N₂O₅ (376.37): C, 67.02; H, 4.29; N, 7.44. Found: C, 66.91; H, 4.27; N, 7.38.

4-Hydroxy-3-(3-(4-methoxyphenyl)-5-methyl-1H-indol-2-yl)-6-methyl-2H-pyran-2-one (6e). Yellow powder; mp 133-136 °C. IR ν/cm^{-1} (KBr): 3411, 3001, 1657, 1448 cm^{-1} . ^1H NMR (500 MHz, DMSO): δ 2.22 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 6.08 (s, 1H, ArH), 6.88 (d, J 7.0Hz, 1H, ArH), 6.89 (s, 1H, ArH), 6.95 (d, J 8.5Hz, 2H, ArH), 7.25 (d, J 8.5Hz, 1H, ArH), 7.50 (d, J 8.5Hz 2H, , ArH), 11.16 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 19.9, 21.7, 55.5, 96.4, 100.6, 102.3, 111.0, 114.3, 119.0, 122.9, 126.4, 127.5, 128.0, 129.9, 134.8, 136.0, 158.9, 161.5, 164.3, 167.6 ppm. Anal. Calcd for $\text{C}_{22}\text{H}_{19}\text{NO}_4$ (361.40): C, 73.12; H, 5.30; N, 3.88. Found: C, 73.20; H, 5.34; N, 3.86.

4-Hydroxy-6-methyl-3-(5-chloro-3-(o-tolyl)-1H-indol-2-yl)-2H-pyran-2-one (6f). Yellow powder; mp 157-159 °C. IR ν/cm^{-1} (KBr): 3387, 3007, 1655, 1445 cm^{-1} . ^1H NMR (500 MHz, DMSO): δ 2.13 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 5.93 (s, 1H, ArH), 6.63 (d, J 8.5Hz, 1H, ArH), 6.89 (s, 1H, ArH), 6.94-7.05 (m, 3H, ArH), 7.10 (d, J 8.0Hz, 1H, ArH), 7.26 (t, J 7.5Hz, 1H, ArH), 9.73 (s, 1H, OH), 10.84 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 21.1, 22.7, 101.7, 109.4, 117.8, 120.6, 122.5, 124.7, 125.3, 126.8, 127.5, 128.7, 129.9, 131.7, 133.6, 135.7, 136.2, 136.8, 161.6, 165.3, 167.2 ppm.

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