

# A facile one-pot synthesis of novel 1-substituted 2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro-6,6-dimethyl-4H-indol-4-one derivatives

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## Abstract

A green and efficient method for the synthesis of novel 5-(N-substituted indol-2-yl)-8-hydroxyquinolines has been achieved in good to excellent yields by one-pot three-component Domino reaction of 5-chloroacetyl-8-hydroxyquinoline with amines and dimedone using DABCO as a basic catalyst in ethanol under reflux conditions. The products were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, and MS spectra.

**Keywords:** One-pot reactions, quinolines, indol-4-ones, DABCO

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## Introduction

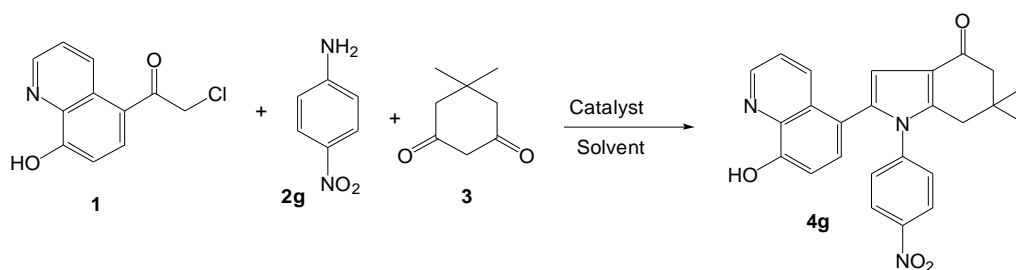
Multi-component reactions have emerged as a valuable tool in the context of modern combinatorial synthesis. Moreover, one-pot multi-component condensation reactions, due to their productivity, facile execution and simple reaction profile, are one of the important strategies in multi-component reactions, which have expanded rapidly in organic chemistry.<sup>1-4</sup> It is found in the recent literature that several indole derivatives are reported to possess a wide variety of biological properties, e.g. CNS depressant,<sup>5</sup> anti-inflammatory and analgesic,<sup>6</sup> antiviral,<sup>7</sup> anthelmintic,<sup>8</sup> antibacterial,<sup>9</sup> anticonvulsant,<sup>10</sup> cardiovascular,<sup>11</sup> and antihypertensive activity.<sup>12</sup>

In recent years, 1,4-diazabicyclo[2.2.2]octane (DABCO) has emerged as a promoter for various organic reactions.<sup>13-17</sup> DABCO is an organic base that can act as a nucleophile. In view of this, and as part of our work on multi-component reactions,<sup>18-22</sup> we here report a simple, practical, and generally three-component reaction for the synthesis of novel indole derivatives by one-pot three-component reaction of 5-chloroacetyl-8-hydroxyquinoline, alkyl-, aryl- and heteroaryl- amines, and dimedone; the reaction is catalyzed by DABCO.

## Results and Discussion

We began our research by essaying the model three-component reaction of 5-chloroacetyl-8-hydroxyquinoline (**1**), *p*-nitroaniline (**2g**) and dimedone (**3**), each in 5 mmol amounts in ethanol under reflux, using 20 mol% DABCO as the base. After 2 h, the cascade reaction provided an excellent (94%) yield of 1-(4-nitrophenyl)-2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro-6,6-dimethyl-4*H*-indol-4-one (**4g**) (Table 1, Entry 6).

**Table 1.** Optimization of the reaction conditions<sup>a</sup>



Entry	Catalyst	Catalyst (mol %)	Solvent	Time (h)	Yield (%) <sup>b</sup>
1	L-proline	20	EtOH	5	15
2	Morpholine	20	EtOH	5	18
3	Piperidine	20	EtOH	5	20
4	Triethylamine	20	EtOH	5	18
5	Imidazole	20	EtOH	5	48
6	DABCO	20	EtOH	2	94
7	DABCO	20	H <sub>2</sub> O	5	40
8	DABCO	20	CH <sub>3</sub> CN	5	40
9	DABCO	20	CH <sub>2</sub> Cl <sub>2</sub>	7	45
10	DABCO	20	THF	7	45
11	DABCO	5	EtOH	5	67
12	DABCO	10	EtOH	5	71
13	DABCO	15	EtOH	4	83
14	DABCO	30	EtOH	5	85
15	DABCO	50	EtOH	5	85

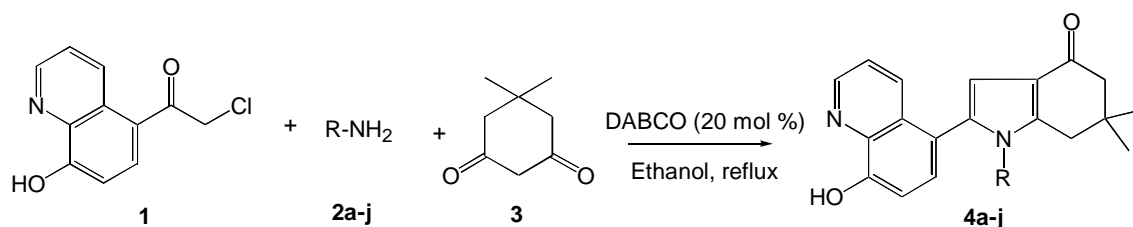
<sup>a</sup> The reaction was performed using **1** (5 mmol), **2g** (5 mmol), **3** (5 mmol) and catalyst (20 mol %) in 15 mL solvent at reflux conditions. <sup>b</sup> isolated yield

To exhibit the merit of the present work of DABCO efficiency in comparison with other catalysts, various catalysts (at 20 mol %) were examined in the model reaction (Table 1, Entry 1-5). The results showed that the nature of the base had a considerable influence on the yield. The reaction was sluggish, with yields below 20%, when L-proline, morpholine and piperidine and triethylamine were used (Table 1, Entries 1-4). Imidazole could also catalyze the reaction, giving the desired product, but in lower yield (Table 1, Entry 5). As shown in Table 1, DABCO can act as an effective catalyst with respect to reaction times and product yield.

To optimize the reaction conditions, the reaction was carried out using different solvents under reflux conditions (Table 1, Entries 6-10) in the presence of DABCO as catalyst. After conducting the reaction in a variety of solvents including ethanol, water, acetonitrile, dichloromethane and tetrahydrofuran, it was concluded that ethanol was the most suitable solvent for this transformation (Table 1, Entry 6). Higher yields were obtained when the reaction was conducted under reflux conditions compared to ambient conditions. After extensive screening of the molar ratio (5, 10, 15, 20, 30 and 50 mol %) of DABCO to the substrates, the results indicated that the amount of 20 mol% promoted the maximum conversion to the product, in a yield of 94%. It was also evident that an increase in the molar ratio above 20 mol % neither increased the yield nor shortened the reaction time.

Next, it was of interest to explore the scope, limitation and generality of compound **4a-j** via one-pot three component reactions of 5-chloroacetyl-8-hydroxyquinoline (**1**) with substituted amines **2a-j** and dimedone (**3**) in refluxing ethanol containing 20 mol % of DABCO as a catalyst (Table 2). Our method could be adapted to the preparation of indoles bearing the following types of substituents at nitrogen: alkyl (Table 2, Entries 1-4), aryl (Table 2, Entries 5-8) and heterocyclic (Table 2, Entries 9, 10). The products were obtained in good to excellent yields (69-94%). The structures of products **4a-j** were consistent with their spectral and elemental analyses. In particular, the IR spectra showed the aliphatic CH stretching bands at 2890-2995  $\text{cm}^{-1}$  as well as the characteristic absorption bands of a conjugated C=O group at 1665-1685  $\text{cm}^{-1}$ . The  $^1\text{H}$  NMR spectrum of **4g** showed the two equivalent methyl groups resonating as a singlet at  $\delta$  0.87, and the methylene protons at C-5 and C-7 showed as two singlets at  $\delta$  1.83 and 2.17 respectively. In addition, a characteristic singlet at 6.50 ppm is ascribed to indole H-3.

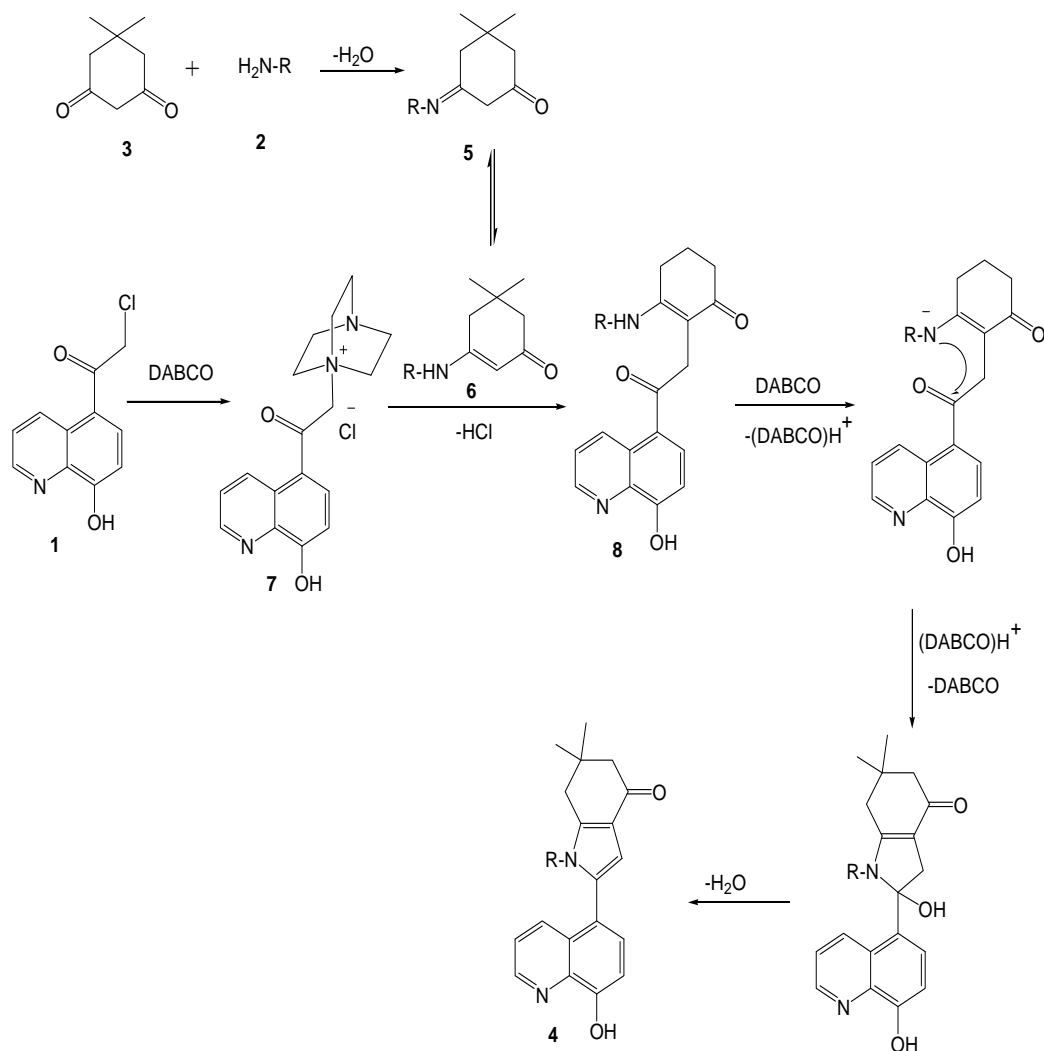
Catalyst reusability is very important for the industrial and economic points of view. The reusability of DABCO was studied for the model reaction in ethanol at reflux. DABCO possesses two important features, being stable in water and not decomposing under aqueous conditions. Once the reaction was complete, the reaction mixture was completely dissolved in dichloromethane and washed with water. The catalyst was recovered from the aqueous layer via evaporation of the water, washed thoroughly with diethyl ether to give reusable catalyst. The recycled catalyst showed no appreciable loss in activity even after the fourth cycle. Listed here are the cycle number and yield of **4g** (%): 1, 95; 2, 92; 3, 92; 4, 90.

**Table 2.** Scope of the reaction using various amines <sup>a</sup>

Entry	Product	R	Time (h)	Yield <sup>b</sup> (%)
1	<b>4a</b>	CH <sub>3</sub>	5	71
2	<b>4b</b>	C <sub>2</sub> H <sub>5</sub>	7	77
3	<b>4c</b>	C <sub>3</sub> H <sub>7</sub>	7	73
4	<b>4d</b>	C <sub>6</sub> H <sub>11</sub>	5	69
5	<b>4e</b>	C <sub>6</sub> H <sub>5</sub>	5	70
6	<b>4f</b>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	12	72
7	<b>4g</b>	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	2	94
8	<b>4h</b>	4-ClC <sub>6</sub> H <sub>4</sub>	5	88
9	<b>4i</b>	2-Pyridyl	7	77
10	<b>4j</b>	3-Pyridyl	7	78

<sup>a</sup> The reaction was performed using **1** (5 mmol), **2a-j** (5 mmol), **3** (5 mmol) and DABCO (20 mol %) in 15 mL ethanol at reflux conditions. <sup>b</sup> isolated yield.

A plausible mechanism to rationalize the formation indole derivatives **4** is outlined in Scheme 1. It can be presumed that initially dimedone **3** undergoes a reaction with amine **2** to form the cyclic  $\beta$ -imino-ketone **5**, which is in equilibrium with its enaminoketone tautomer **6**. The quaternization reaction of the substrate **1** with DABCO generates the quaternary salt **7**, which subsequently reacts with **6** to form the intermediate **8**, which is the suggested precursor to the final product **4**.



**Scheme 1.** Mechanistic pathway for the synthesis of compounds 4.

## Conclusions

We have developed a concise and a convenient new strategy for the synthesis of novel substituted 1,5,6,7-tetrahydroindol-4-one derivatives in good to excellent yields from 5-chloroacetyl-8-quinolinol, substituted amines and dimedone using 20 mol% DABCO as a catalyst. This reaction has the prominent advantages of easy operation, convergence and broad scope of applicability.

## Experimental Section

**General.** Melting points were measured by a Gallenkamp melting point apparatus. IR spectra were recorded on a Pye-Unicam SP 3-100 spectrophotometer using the KBr Wafer technique. <sup>1</sup>H

NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer and on GNM-LA (400 MHz) in DMSO- $d_6$  as a solvent and TMS as internal standard. Chemical shifts are expressed in ppm.  $^{13}\text{C}$  NMR spectra were measured on a Varian EM-200, 50 MHz spectrometer. Mass spectra were determined on a JEOL JMS-600 spectrometer. Elemental analyses were carried out in the Microanalytical Unit at Assiut University (Egypt). The results were found to be in good agreement ( $\pm 0.4\%$ ) with the calculated values. Compound **1** was prepared according to a literature procedure.<sup>23</sup>

**General procedure for the synthesis of 1-substituted-2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro-6,6-dimethyl-4H-indol-4-ones (4a-j)**

A mixture of 5-chloroacetyl-8-hydroxyquinoline (5 mmol), substituted amines (5 mmol), dimedone (5 mmol) and DABCO (20 mol %) in ethanol (10 mL) was refluxed for the period of time indicated below. The progress of the reaction was monitored by TLC. After cooling, the solid obtained was filtered off, washed with distilled water ( $3 \times 10$  mL) for removal of the catalyst and extracted with dichloromethane. The extract was filtered and concentrated under reduced pressure. The corresponding pure product was obtained by recrystallization procedure in dioxane.

**1,6,6-Trimethyl-2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro-4H-indol-4-one (4a).** Yellow crystals, m.p. 187–189 °C; IR (KBr):  $\nu_{\text{max}}$  3070, 2950, 2850 1665, 1630, 1611, 1574, 1538, 1511, 1439, 1380, 1040, 863, 822, 786  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$ : 0.88 (s, 6H, 2CH<sub>3</sub>), 1.80 (s, 2H, CH<sub>2</sub>), 2.15 (s, 2H, CH<sub>2</sub>), 3.25 (s, 3H, CH<sub>3</sub>), 6.65 (s, 1H, indole-H-3), 6.85–8.75 (m, 6H, ArH);  $^{13}\text{C}$  NMR  $\delta$ : 25.4 (2C), 26.6, 31.3, 44.3, 52.3 (2C), 105.6, 114.3, 115.7, 118.5, 120.4, 122.5, 124.3, 127.2, 129.3, 134.6, 139.6, 150.5, 157.9, 195.4. Mass spectrum,  $m/z$ : 320.09 (45%) [ $\text{M}^+$ ]. Anal. Calcd. for C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>: C 74.98, H 6.29, N 8.74; found C 75.21, H 6.58, N 8.06%.

**1-Ethyl-2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro--6,6-dimethyl-4H-indol-4-one (4b).** Yellow crystals, m.p. 209–211 °C; IR (KBr):  $\nu_{\text{max}}$  3090, 2957, 2880, 1669, 1628, 1592, 1546, 1513, 1440, 1300, 1035, 921, 834, 815, 779, 727  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$ : 1.02 (s, 6H, 2CH<sub>3</sub>), 1.55 (t,  $J$  7.5 Hz, 3H, CH<sub>3</sub>), 1.95 (s, 2H, CH<sub>2</sub>), 2.20 (s, 2H, CH<sub>2</sub>), 3.75 (q, 2H,  $J$  7.5 Hz CH<sub>2</sub>), 6.60 (s, 1H, indole-H-3), 6.90–8.85 (m, 6H, ArH). Mass spectrum,  $m/z$ : 334.17(52%) [ $\text{M}^+$ ]. Anal. Calcd. for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: C 75.42, H 6.63, N 8.38 ; found: C 75.71, H 6.98, N 8.59%.

**1-Propyl-2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro-6,6-dimethyl-4H-indol-4-one (4c).** Pale yellow crystals, m.p. 167–169 °C; IR (KBr):  $\nu_{\text{max}}$  3065, 2955, 2895, 1680, 1620, 1612, 1539, 1455, 1422, 1336, 1009, 830, 776, 744, 679  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$ : 0.95 (t,  $J$  7.5 Hz, 3H, CH<sub>3</sub>), 1.20 (s, 6H, 2CH<sub>3</sub>), 1.60 (m, 3H, CH<sub>3</sub>), 1.80 (s, 2H, CH<sub>2</sub>), 2.15 (s, 2H, CH<sub>2</sub>), 3.40 (t,  $J$  7.5 Hz, 2H, CH<sub>2</sub>), 6.60 (s, 1H, indole-H-3), 6.99–8.80 (m, 6H, ArH). Mass spectrum,  $m/z$ : 348.11 (35%) [ $\text{M}^+$ ]. Anal. Calcd. for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: C 75.83, H 6.94, N 8.04, found: C 76.19; H 7.22; N 8.33%.

**1-Cyclohexyl-2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro-6,6-dimethyl-4H-indol-4-one (4d).** Pale yellow crystals, m.p. 220–222 °C. IR (KBr):  $\nu_{\text{max}}$  3009, 2970, 2890, 1680, 1625, 1609, 1584, 1526, 1497, 1451, 1424, 1376, 1089, 1045, 873, 851, 809, 768  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$ : 0.99 (m, 2H, CH<sub>2</sub>), 1.15 (s, 6H, 2CH<sub>3</sub>), 1.45 (m, 4H, 2CH<sub>2</sub>), 1.66 (m, 4H, 2CH<sub>2</sub>), 1.77 (s, 2H, CH<sub>2</sub>), 2.08

(s, 2H, CH<sub>2</sub>), 3.55 (m, 1H, N-CH), 6.50 (s, 1H, indole-H-3), 6.95–8.80 (m, 6H, ArH); Anal. Calcd. for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>: C 77.29, H 7.26, N 7.21; found: C 77.43, H 7.51, N 7.62%.

**1-Phenyl-2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro-6,6-dimethyl-4H-indol-4-one (4e).** Light yellow crystals, m.p. 155–157 °C; IR (KBr): 3015, 2975, 2899, 1670, 1627, 1581, 1535, 1411, 1195, 1018, 756 cm<sup>-1</sup>; <sup>1</sup>H NMR δ: 1.10 (s, 6H, 2CH<sub>3</sub>), 1.60 (s, 2H, CH<sub>2</sub>), 2.30 (s, 2H, CH<sub>2</sub>), 6.55 (s, 1H, indole-H-3), 6.99–8.70 (m, 11H, ArH); Anal. Calcd. for C<sub>25</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: C 78.51, H 5.80, N 7.32; found: C 78.25, H 6.11, N 7.03%.

**1-(4-Methoxyphenyl)-2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro-6,6-dimethyl-4H-indol-4-one (4f).** Yellow crystals, m.p. 245–247 °C; IR (KBr):  $\nu_{\max}$  3020, 2985, 2897, 1685, 1630, 1605, 1598, 1479, 1412, 1309, 1209, 1065, 972 cm<sup>-1</sup>; <sup>1</sup>H NMR δ: 1.15 (s, 6H, 2CH<sub>3</sub>), 1.55 (s, 2H, CH<sub>2</sub>), 2.35 (s, 2H, CH<sub>2</sub>), 3.35 (s, 3H, OCH<sub>3</sub>), 6.60 (s, 1H, indole-H-3), 6.88–8.80 (m, 10H, ArH). Mass spectrum, *m/z*: 412.38 (31%) [M<sup>+</sup>]. Anal. Calcd. for C<sub>26</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>: C 75.71, H 5.86, N 6.79; found: C 76.05, H 6.24, N 6.55%.

**1-(4-Nitrophenyl)-2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro-6,6-dimethyl-4H-indol-4-one (4g).** Yellow crystals, m.p. 275–279 °C; IR (KBr):  $\nu_{\max}$  3010, 2980, 2890, 1680, 1635, 1599, 1537, 1463, 1318, 1242, 1066, 955 cm<sup>-1</sup>; <sup>1</sup>H NMR δ: 1.05 (s, 6H, 2CH<sub>3</sub>), 1.48 (s, 2H, CH<sub>2</sub>), 2.40 (s, 2H, CH<sub>2</sub>), 6.58 (s, 1H, indole-H-3), 6.80–8.75 (m, 10H, ArH); <sup>13</sup>C NMR δ: 25.6 (2C), 32.8, 40.1, 53.4 (2C), 108.3, 113.7, 120.4, 121.3, 121.8, 122.3, 123.1, 125.7, 126.4, 132.6, 135.3, 137.5, 139.1, 144.5, 146.8, 151.2, 155.3, 194.9. Mass spectrum, *m/z*: 427.13 (62%) [M<sup>+</sup>]. Anal. Calcd. for C<sub>25</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>: C 70.25, H 4.95, N 9.83; found: C 70.47; H 5.26, N 10.05%.

**1-(4-Chlorophenyl)-2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro-6,6-dimethyl-4H-indol-4-one (4h).** Yellow crystals, m.p. 305–307 °C; IR (KBr):  $\nu_{\max}$  3080, 2980, 2895, 1685, 1630, 1599, 1553, 1427, 1380, 1208, 1049, 845 cm<sup>-1</sup>; <sup>1</sup>H NMR δ: 1.10 (s, 6H, 2CH<sub>3</sub>), 1.40 (s, 2H, CH<sub>2</sub>), 2.60 (s, 2H, CH<sub>2</sub>), 6.65 (s, 1H, indole-H-3), 6.90–8.70 (m, 10H, ArH). Mass spectrum, *m/z*: 416.66 (41%) [M<sup>+</sup>]; Anal. Calcd. for C<sub>25</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>2</sub>: C 72.02, H 5.08, Cl 8.50, N 6.72; found: C 72.39, H 4.75, Cl 8.86, N 6.45%.

**1-(Pyridin-2-yl)-2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro-6,6-dimethyl-4H-indol-4-one (4i).** Light yellow crystals, m.p. 266–268 °C; IR (KBr):  $\nu_{\max}$  3085, 2978, 2880, 1687, 1619, 1603, 1455, 1360, 1512, 1195, 828 cm<sup>-1</sup>; <sup>1</sup>H NMR δ: 0.99 (s, 6H, 2CH<sub>3</sub>), 1.30 (s, 2H, CH<sub>2</sub>), 2.55 (s, 2H, CH<sub>2</sub>), 6.60 (s, 1H, indole-H-3), 6.88–8.79 (m, 10H, ArH); Mass spectrum, *m/z*: 383.51 (45%) [M<sup>+</sup>]; Anal. Calcd. For C<sub>24</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: C 75.18, H 5.52, N 10.96; found: C 74.85, H 5.71, N 10.61%.

**1-(Pyridin-3-yl)-2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro-6,6-dimethyl-4H-indol-4-one (4j).** Yellow crystals, m.p. 213–215 °C. IR (KBr):  $\nu_{\max}$  3100, 2988, 2960, 1685, 1625, 1600, 1524, 1452, 1368, 1259, 977 cm<sup>-1</sup>; <sup>1</sup>H NMR δ: 1.12 (s, 6H, 2CH<sub>3</sub>), 1.35 (s, 2H, CH<sub>2</sub>), 2.48 (s, 2H, CH<sub>2</sub>), 6.55 (s, 1H, indole-H-3), 6.90–8.88 (m, 10H, ArH); Anal. Calcd. For C<sub>24</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: C 75.18, H 5.52, N 10.96; found: C 75.45, H 5.44, N 11.15%.

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