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Visible light mediated aerobic oxidative hydroxylation of 2-oxindole-3-carboxylate esters: an alternative approach to 3-hydroxy-2-oxindoles

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Abstract: A convenient aerobic oxidative hydroxylation of 3-substituted oxindoles under mild reaction conditions is described herein. This process was accomplished by the activation of molecular oxygen in the air in the presence of a photocatalyst under the irradiation of visible light. The desired product was delivered in up to 89% yield without the addition of base or stoichiometric oxidant.

Keywords: Visible light, Photocatalysis, Oxindole, Aerobic oxidation

Introduction

The 3-substituted-3-hydroxy-2-oxindole framework is a privileged motif that is abundant in naturally occurring alkaloids and biologically active products [1-2]. For instance, Convolutamydine A, which is isolated from the marine bryozoan *Amathia convolute*, was found to be a potent inhibitor in the differentiation of HL-60 human promyelocytic leukaemia cells [3]. Discovered in *Hibiscus moscheutos* L methyl 2-(3-hydroxy-2-oxoindolin-3-yl)acetate acted as an anti-oxidant [4]. (*R*)-(+)-3-cyanomethyl-3-hydroxyoxindole from *Rheum maximowiczii* Losinsk (Polygonaceae) exhibited activation/inhibition of specific cytokines [5]. 3-Substituted-3-hydroxy-2-oxindoles also act as synthetic precursors in some significant transformations [6-9]. Consequently, their construction is of interest to organic chemists. Previously, several elegant methodologies were applied to build 3-substituted-3-hydroxy-2-oxindoles [10-12]. Transition metal catalyzed intramolecular cyclization of α-keto aromatic amides was reported to synthesize these versatile building blocks [13-15], and direct addition to isatin derivatives was also an efficient approach [16-27]. Moreover, straightforward hydroxylation of 3-substituted-2-oxindoles was also accomplished [28-33]. However, milder, greener, and more efficient methods to change the substituent pattern of C-3 on oxindole rings are still pursued.

Recently, many outstanding groups have sought to make use of light as a clean and abundant source of energy for chemical transformations [34-39]. Many reactions were carried out in the presence of oxygen under mild conditions. Furthermore, as an ideal oxidant molecular oxygen has already participated in the construction of a series of structurally diverse skeletons through photocatalysis [34-40]. For instance, Córdova accomplished the α-hydroxylation of ketones and aldehydes through the utilization of molecular oxygen by photocatalysis [41-42]. In 2012, Meng and co-works documented a hydroxylation of β-oxo esters catalyzed by a phase transfer catalyst and tetraphenylporphine under the irradiation of a 100W halogen lamp, in which singlet oxygen took part [43]. Recently, Xiao's group designed and synthesized a new bifunctional visible light photocatalyst and used it in the asymmetric aerobic oxidation of β-ketoesters [44]. As we continue to be interested in photochemistry, in this communication, we developed an α-hydroxylation of 3-carboxylate oxindole derivatives by means of photocatalysis under mild conditions. The reaction was carried out in air under the irradiation of a household light bulb. Compared with previous work, this work eliminates the need for addition of base and stoichiometric oxidant. We intended this work to further extend the scope of our previously developed research [45].

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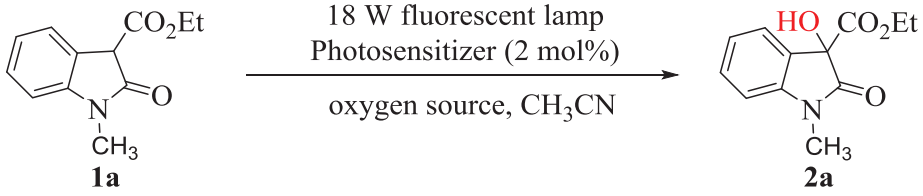
Results and discussion

Initially, the 3-substituted-2-oxindole (**1a**) was chosen as the model substrate and the reaction was first studied in the presence of commonly used photosensitizers. As shown in Table 1, all of the photocatalysts tested could successfully give the desired product in moderate yields in the presence of an O_2 balloon under the irradiation of visible light (entries 1-4). Among them $[Ir(ppy)_2(dtbbpy)]PF_6$ proved to be the most promising for further optimization. To our delight, changing the oxygen source from an O_2 balloon to atmospheric air did not significantly affect the hydroxylation efficiency (entry 2 vs entry 5). The desired product was still obtained in 70% yield. Control experiments showed that photocatalyst, visible light and O_2 were indispensable for this transformation. No product was afforded when the reaction was conducted in the absence of any of these three parameters (entries 6-8). Subsequently, a variety of solvents were examined, and the choice of the reaction media was found to be essential for the hydroxylation. When using $[Ir(ppy)_2(dtbbpy)]PF_6$, polar solvents such as DMF, DMSO, and MeOH showed relatively low compatibility compared with MeCN, giving the product in yields ranging from 40%-64% (entries 9-11). Only a trace amount of **2a** was detected when less polar solvents were employed (entries 12-14). Fortunately, we found that CF_3CH_2OH markedly improved the yield of this process to 88% (entry 15). Moreover, a shorter reaction time was observed when using silica gel as an additive (entry 16), possibly because the substrate was activated by H-bonding and/or the solubility of molecular oxygen was increased [46-47].

With the optimized conditions in hand, the study was then focused on extending the substrate scope. The electronic effect on the benzene ring of the oxindole moiety was first examined (Table 2, entries a-f). In general, substrates bearing an electron-withdrawing group provided better results than substrates with electron-donating groups. Specifically, when an electron-donating group such as methoxy (**1c**) was installed on the benzene ring, the reaction proceeded sluggishly, and the desired

Table 1 Screening the reaction conditions and control experiment[a]

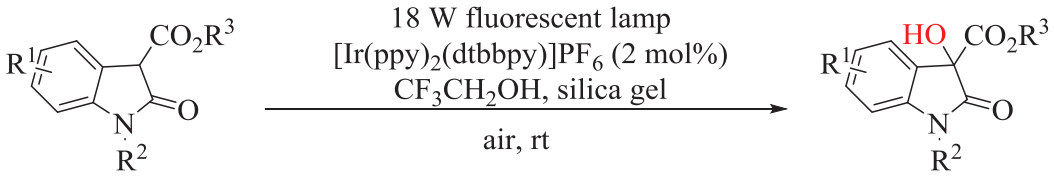


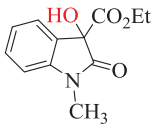
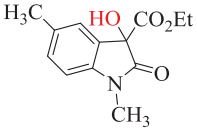
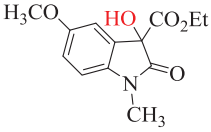
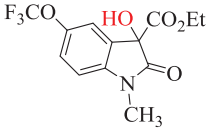
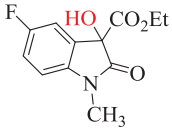
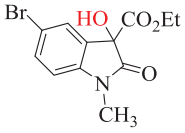
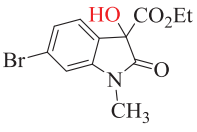
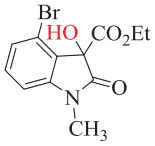
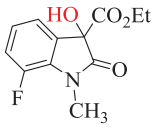
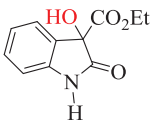
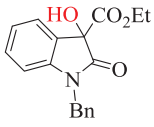
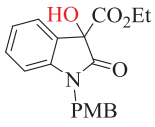
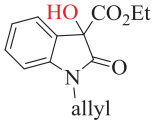
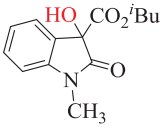
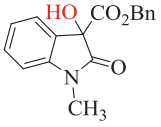
1a **2a**

Entry	Photosensitizer	Solvent	Oxygen source	Time (h)	Yield %[b]
1	$Ru(bpy)_3Cl_2.6H_2O$	CH_3CN	O_2 balloon	3	68
2	$[Ir(ppy)_2(dtbbpy)]PF_6$	CH_3CN	O_2 balloon	4	72
3	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	CH_3CN	O_2 balloon	3	61
4	Eosin Y	CH_3CN	O_2 balloon	3	69
5	$[Ir(ppy)_2(dtbbpy)]PF_6$	CH_3CN	air	4	70
6	Without photocatalyst	CH_3CN	air	4	0
7[c]	$[Ir(ppy)_2(dtbbpy)]PF_6$	CH_3CN	air	4	0
8[d]	$[Ir(ppy)_2(dtbbpy)]PF_6$	CH_3CN	air	4	0
9	$[Ir(ppy)_2(dtbbpy)]PF_6$	DMF	air	7	44
10	$[Ir(ppy)_2(dtbbpy)]PF_6$	DMSO	air	7	40
11	$[Ir(ppy)_2(dtbbpy)]PF_6$	CH_3OH	air	4	64
12	$[Ir(ppy)_2(dtbbpy)]PF_6$	CH_2Cl_2	air	4	trace
13	$[Ir(ppy)_2(dtbbpy)]PF_6$	THF	air	4	trace
14	$[Ir(ppy)_2(dtbbpy)]PF_6$	Toluene	air	4	trace
15	$[Ir(ppy)_2(dtbbpy)]PF_6$	CF_3CH_2OH	air	12	88
16[e]	$[Ir(ppy)_2(dtbbpy)]PF_6$	CF_3CH_2OH	air	10	88

[a]A mixture of **1a** (0.3 mmol) and photocatalysts (2 mol%) in solvent (3 mL, 0.1 M) were stirred at room temperature under the irradiation of 18 w fluorescent lamp. [b]Isolated yield after column chromatography. [c]Without visible light. [d]Without oxygen. [e]With the addition of silica gel (30 mg per 1 mL solvent). DMF: N,N-Dimethylformamide. DMSO: Dimethyl sulfoxide. THF: Tetrahydrofuran.

Table 2 Substrate scope of the photocatalytic system[a]



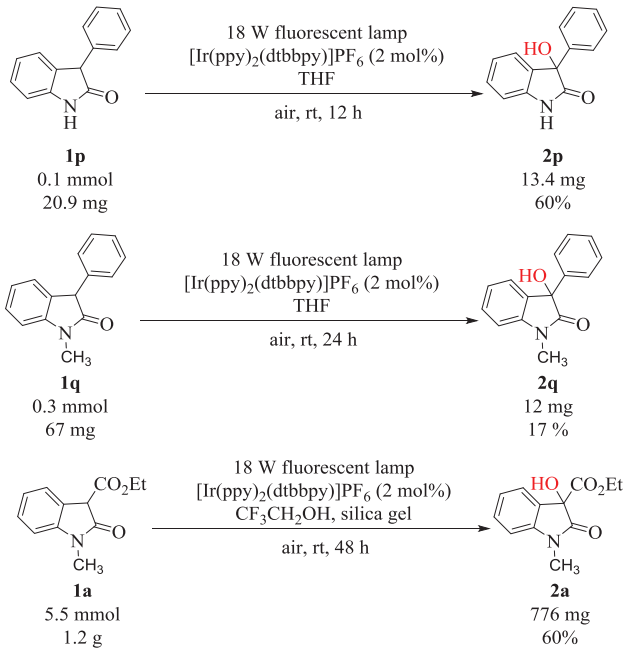
 **2a,** 11 h 88% yield [b]	 **2b,** 48 h 77% yield	 **2c,** 48 h 57% yield	 **2d,** 12 h 89% yield	 **2e,** 18 h 86% yield
 **2f,** 18 h 84% yield	 **2g,** 24 h 20% yield	 **2h,** 72 h 0% yield	 **2i,** 22 h 79% yield	 **2j,** 36 h 82% yield
 **2k,** 33 h 79% yield	 **2l,** 34 h 74% yield	 **2m,** 48 h 39% yield	 **2n,** 48 h 77% yield	 **2o,** 48 h 62% yield

[a]A mixture of **1a-1o** (0.5 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mol%), and silica gel (30 mg per 1 mL solvent) in solvent (5 mL, 0.1 M) were stirred at room temperature under the irradiation of an 18 w fluorescent lamp open to air. [b]Isolated yield after column chromatography.

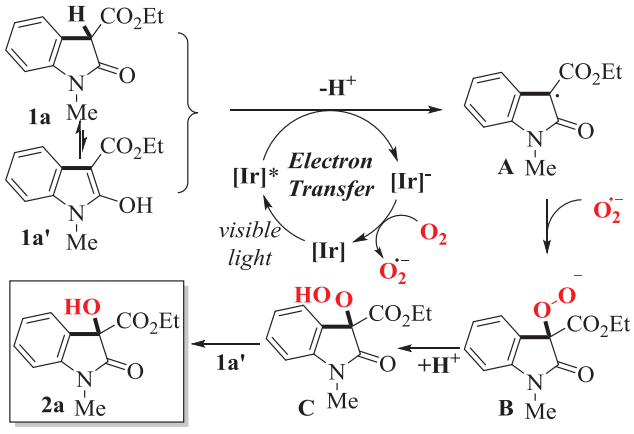
product was delivered in only 57% yield after 2 days. Moreover, the substituted position of the R^1 group had a big influence on the results of the hydroxylation. For example, 6-Br substituted oxindole carboxylate only gave **2g** in 20% yield, while 4-Br substituted oxindole carboxylate (**1h**) did not react upon exposure to the optimized standard conditions, since **1h** exists exclusively in its keto form. However, the 7-F substituted derivative (**1i**) was quite tolerated, and the hydroxylated product **2i** was afforded in a yield of 79%. Gratifyingly, when the N-protecting group was replaced with H, Bn and PMB, the reaction proceeded smoothly and afforded the desired products in moderate to good yields (entries j-l). In the case of **1m**, with an allyl as the protecting group, the product was obtained only in 39% yield. Finally, the ester moiety was also investigated. **1n** and **1o** were not fully hydroxylated even after 2 days. Under the standard reaction conditions, they afforded the products (**2n** and **2o**) in 77% and 62% yields, respectively.

By changing the solvent to THF, the protocol could be extended to the synthesis of 3-hydroxy-3-phenyloxindole (**2p**) and 3-hydroxy-1-methyl-3-phenyloxindole (**2q**) derivatives in 60% and 17% yield, respectively (Scheme 1) [33]. Subsequently, in order to test the application of the protocol we increased the reaction scale to gram scale, as shown in Scheme 1. When the reaction ran on a larger scale, a decrease in reaction efficiency and in yield of the hydroxylated product was observed. After 48 hours the starting material could not be completely transferred to the product, and only 60% of the target molecule was obtained.

A plausible mechanism for this transformation is outlined in Scheme 2. Based on the previous work of Xiao's group, there was an equilibration of the substrate (**1a**) between its keto and enol form [45]. Visible light irradiation of the photocatalyst brought it to its excited state **[Ir]***, and oxidative quenching between **1a'** and **[Ir]*** delivered the radical intermediate **A**. The reduced photocatalyst $[Ir]^-$ underwent a single electron transfer with oxygen to complete the photocatalytic cycle, to obtain an oxygen radical anion. Thereafter, intermediate **A** went through a radical coupling with the oxygen radical anion, giving rise



Scheme 1 Substrate scope extension and large scale reaction



Scheme 2 Proposed mechanism

to the hydroperoxide intermediate **C** through intermediate **B**. Finally, a self-oxidation between **C** and **1a'** furnished the desired product **2a**.

Conclusions

In conclusion, we describe herein a mild photocatalytic system to construct the potentially biologically important molecules 3-ester-3-hydroxy-2-oxindoles in up to 89% yield. Under the irradiation of visible light, the reaction was carried out open to air at room temperature. Moreover, without the addition of base the optimized conditions were suitable for N-allyl protected and N-H free compounds, and the process goes smoothly when enlarged to gram scale. We expect the developed protocol to be useful in the modification of structurally significant chemicals, and further application of this method is ongoing in our laboratory.

Experimental

General procedure for the photocatalytic reaction

To a mixture of ethyl 2-oxoindoline-3-carboxylates **1a-1o** (0.5 mmol) and $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mol%, 9.1 mg) in CF_3CH_2OH (5 mL) was added silica gel (30 mg/mL) at room temperature in a 10 mL round bottom flask. The resulting solution was stirred at a distance of 5 cm from an 18 w fluorescent light bulb until the reaction was determined to be completed by TLC analysis. The crude product was purified by silica gel chromatography.

Characterization Data of the Products

Ethyl 3-hydroxy-1-methyl-2-oxoindoline-3-carboxylate (2a) [10]

White solid; 88% yield; m.p. 137~138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 4.61 (s, 1H), 4.28 – 4.12 (m, 2H), 3.23 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 169.8, 144.6, 130.6, 126.9, 123.7, 123.3, 108.8, 77.3, 63.1, 26.5, 13.8; MS (EI) *m/z*: 235.1.

Ethyl 3-hydroxy-1,5-dimethyl-2-oxoindoline-3-carboxylate (2b) [10]

White solid; 77% yield; m.p. 134~136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 7.2 Hz, 1H), 7.10 (s, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 4.32 (s, 1H), 4.30 – 4.11 (m, 2H), 3.22 (s, 3H), 2.33 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 169.8, 142.0, 132.9, 130.7, 126.8, 124.4, 108.5, 77.4, 63.0, 26.5, 20.9, 13.7; MS (EI) m/z: 249.1.

Ethyl 3-hydroxy-5-methoxy-1-methyl-2-oxoindoline-3-carboxylate (2c)

Light blue solid; 57% yield; m.p. 148~150 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.95 – 6.86 (m, 2H), 6.84 – 6.75 (m, 1H), 4.37 (s, 1H), 4.30 – 4.15 (m, 2H), 3.79 (s, 3H), 3.22 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 172.8, 169.7, 156.3, 137.8, 127.9, 115.2, 11.5, 109.3, 77.6, 63.1, 55.7, 26.6, 13.8; MS (EI) m/z: 265.1; HRMS (ESI): m/z [M + Na^+] calcd for $C_{13}H_{15}NNaO_5$: 288.0848; found: 288.0842.

Ethyl 3-hydroxy-1-methyl-2-oxo-5-(trifluoromethoxy) indoline-3-carboxylate (2d)

White solid; 89% yield; m.p. 77~79 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.27 (s, 1H), 7.18 (s, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 4.45 (s, 1H), 4.28 – 4.17 (m, 2H), 3.25 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 169.1, 145.0, 143.2, 128.3, 123.7, 120.4 (d, *J* = 257.1 Hz), 117.8, 109.4, 77.2, 63.4, 26.7, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -58.34 (s); MS (EI) *m/z*: 319.1; HRMS (EI): m/z [M + NH_4^+] calcd for $C_{13}H_{16}F_3N_2O_5$: 337.1011; found: 337.1007.

Ethyl 5-fluoro-3-hydroxy-1-methyl-2-oxoindoline-3-carboxylate (2e)

Light yellow solid; 86% yield; m.p. 126~128 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.14 – 7.06 (m, 1H), 7.04 (dd, *J* = 7.3, 2.2 Hz, 1H), 6.81 (dd, *J* = 8.5, 3.9 Hz, 1H), 4.46 (s, 1H), 4.29 – 4.18 (m, 2H), 3.23 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9 (s), 169.2 (s), 159.3 (d, *J* = 242.6 Hz), 140.5 (s), 128.3 (d, *J* = 8.6 Hz), 116.8 (d, *J* = 23.5 Hz), 112.0 (d, *J* = 25.4 Hz), 109.4 (d, *J* = 7.9 Hz), 77.4 (s), 63.3 (s), 26.7 (s), 13.8 (s). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –118.95 – –119.07 (m); MS (EI) *m/z*: 253.1; HRMS (EI): m/z [M + H^+] calcd for $C_{12}H_{13}FNO_4$: 254.0829; found: 254.0827.

Ethyl 5-bromo-3-hydroxy-1-methyl-2-oxoindoline-3-carboxylate (2f)

White solid; 84% yield; m.p. 150~153 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.54 – 7.49 (m, 1H), 7.40 (s, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 4.38 (s, 1H), 4.31 – 4.16 (m, 2H), 3.22 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 169.1, 143.6, 133.4, 128.7, 127.0, 115.8, 110.3, 77.1, 63.4, 26.7, 13.8; MS (EI) *m/z*: 313.0; HRMS (EI): m/z [M + H^+] calcd for $C_{12}H_{13}BrNO_4$: 314.0028; found: 314.0022.

Ethyl 6-bromo-3-hydroxy-1-methyl-2-oxoindoline-3-carboxylate (2g)

Light blue solid; 20% yield; m.p. 155~156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (s, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.03 (s, 1H), 4.34 (s, 1H), 4.28 – 4.16 (m, 2H), 3.22 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 169.2, 145.8, 126.1, 125.8, 125.0, 124.3, 112.4, 76.9, 63.4, 26.7, 13.8; MS (EI) *m/z*: 313.0; HRMS (EI): m/z [M + H^+] calcd for $C_{12}H_{13}BrNO_4$: 314.0028; found: 314.0024.

Ethyl 7-fluoro-3-hydroxy-1-methyl-2-oxoindoline-3-carboxylate (2i)

White solid; 79% yield; m.p. 118~119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 – 6.98 (m, 3H), 4.38 (s, 1H), 4.34 – 4.15 (m, 2H), 3.45 (s, 3H), 1.18 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7 (s), 169.2 (s), 147.6 (d, *J* = 244.6 Hz), 131.1 (d, *J* = 8.9 Hz), 129.5 (s), 124.0 (d, *J* = 6.1 Hz), 119.6 (s), 118.6 (d, *J* = 19.2 Hz), 77.2 (s), 63.3 (s), 29.1 (s), 13.8 (s); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -135.27 – -135.69 (m); MS (EI) *m/z*: 253.1; HRMS (EI): m/z [M + H^+] calcd for $C_{12}H_{13}FNO_4$: 254.0829; found: 254.0820.

Ethyl 3-hydroxy-2-oxoindoline-3-carboxylate (2j)

White solid; 82% yield; m.p. 147~148 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.47 (s, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.28 (s, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 4.51 (s, 1H), 4.31 – 4.14 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 174.7, 169.3, 142.8, 130.3, 129.2, 123.9, 122.1, 110.2, 77.6, 61.3, 14.0; MS (EI) *m/z*: 221.1; HRMS (EI): m/z [M + H^+] calcd for $C_{11}H_{12}NO_4$: 222.0766; found: 222.0762.

Ethyl 1-benzyl-3-hydroxy-2-oxoindoline-3-carboxylate (2k) [10]

Light blue solid; 79% yield; m.p. 140~143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 – 7.27 (m, 7H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 5.19 (d, *J* = 15.9 Hz, 1H), 4.68 (d, *J* = 16.0 Hz, 1H), 4.39 (s, 1H), 4.36 – 4.26 (m, 1H), 4.24 – 4.08 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 169.7, 143.5, 135.0, 130.5, 128.6, 127.6, 126.9, 123.7, 123.3, 109.8, 77.4, 63.2, 43.7, 13.7; MS (EI) *m/z*: 311.1.

Ethyl 3-hydroxy-1-(4-methoxybenzyl)-2-oxoindoline-3-carboxylate (2l)

Light blue solid; 74% yield; m.p. 131~132 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 3H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 7.9 Hz, 1H), 5.10 (d, *J* = 15.6 Hz, 1H), 4.63

(d, *J* = 15.6 Hz, 1H), 4.37 (s, 1H), 4.34 – 4.27 (m, 1H), 4.22 – 4.12 (m, 1H), 3.78 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 169.7, 158.9, 143.5, 130.4, 128.3, 126.9, 126.9, 123.6, 123.2, 114.0, 109.8, 77.4, 63.1, 55.1, 43.2, 13.7; MS (EI) *m/z*: 341.1; HRMS (ESI): m/z [M + Na^+] calcd for $C_{19}H_{19}NNaO_5$: 364.1161; found: 364.1155.

Ethyl 1-allyl-3-hydroxy-2-oxoindoline-3-carboxylate (2m)

White solid; 39% yield; m.p. 136~137 ° C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 5.90 – 5.80 (m, 1H), 5.29 – 5.18 (m, 2H), 4.49 (d, *J* = 16.8 Hz, 1H), 4.32 – 4.12 (m, 4H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 169.7, 143.6, 130.5, 130.4, 126.8, 123.7, 123.3, 117.1, 109.6, 77.4, 63.2, 42.3, 13.7; MS (EI) *m/z*: 261.1; HRMS (ESI): m/z [M + Na^+] calcd for $C_{14}H_{15}NNaO_4$: 284.0899; found: 284.0893.

Isobutyl 3-hydroxy-1-methyl-2-oxoindoline-3-carboxylate (2n)

Light blue solid; 77% yield; m.p. 70~72 ° C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.38 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 4.32 (s, 1H), 3.94 (p, *J* = 10.5 Hz, 2H), 3.24 (s, 3H), 1.87 – 1.75 (m, 1H), 0.72 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 169.7, 144.4, 130.5, 127.0, 123.6, 123.2, 108.7, 77.4, 72.4, 27.5, 26.5, 18.4; MS (EI) *m/z*: 263.1; HRMS (ESI): m/z [M + Na^+] calcd for $C_{14}H_{17}NNaO_4$: 286.1055; found: 286.1050.

Benzyl 3-hydroxy-1-methyl-2-oxoindoline-3-carboxylate (2o)

Light blue solid; 62% yield; m.p. 116~118 ° C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.38 (t, *J* = 7.7 Hz, 1H), 7.29 – 7.26 (m, 3H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.13 – 7.03 (m, 3H), 6.87 (d, *J* = 7.8 Hz, 1H), 5.19 (q, *J* = 12.5 Hz, 2H), 4.29 (s, 1H), 3.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 169.5, 144.4, 134.6, 130.7, 128.4, 128.2, 127.2, 126.7, 123.8, 123.3, 108.8, 77.5, 68.0, 26.6; MS (ESI) *m/z*: 297.1; HRMS (ESI): m/z [M + Na^+] calcd for $C_{17}H_{15}NNaO_4$: 320.0899; found: 320.0893.

3-Hydroxy-3-phenylindolin-2-one (2p) [33]

White solid; 60% yield; ^{1}H NMR (500 MHz, DMSO-d^6): δ = 10.41 (s, 1H), 7.34 – 7.22 (m, 6H), 7.11 (d, *J* = 7.3 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.67 – 6.61 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d^6): δ = 178.5, 141.9, 141.5, 133.7, 129.2, 128.0, 127.4, 125.4, 124.8, 122.0, 109.8, 77.3.

3-Hydroxy-1-methyl-3-phenylindolin-2-one (2q) [33]

White solid; 17% yield; ^{1}H NMR (500 MHz, DMSO-d^6): δ = 7.35 (t, *J* = 7.7 Hz, 1H), 7.32 – 7.24 (m, 5H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.69 (s, 1H), 3.16 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d^6): δ = 176.7, 143.4, 141.3, 133.0, 129.4, 128.1, 127.5, 125.5, 124.3, 122.7, 108.8, 77.0, 26.1.

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