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Catalyst-Free α-Alkylation-α-Hydroxylation of Oxindole with Alcohols

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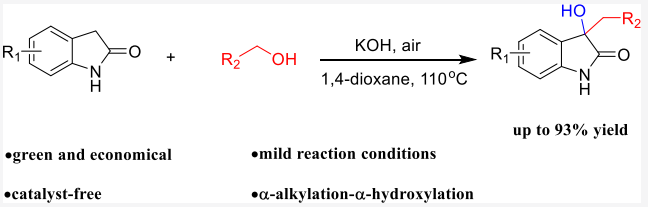
ABSTRACT: 3-Alkyl-3-hydroxyoxindoles, a subclass of oxindole products, have antioxidant, neuroprotective, anticancer, and anti-HIV activities. In this study, a green and economical protocol for the synthesis of 3-alkyl-3-hydroxyoxindoles is developed for the first time via α-alkylation-α-hydroxylation of oxindole with benzyl alcohols without using any transition-metal catalysts in yields of 29−93%.



INTRODUCTION

Natural oxindole products present diverse chemical and biological properties and can be widely used in pharmaceutical agents.[1] 3-Alkyl-3-hydroxyoxindoles and 3-aryl-3-hydroxyoxindoles belong to a subclass of oxindole products (Figure 1).

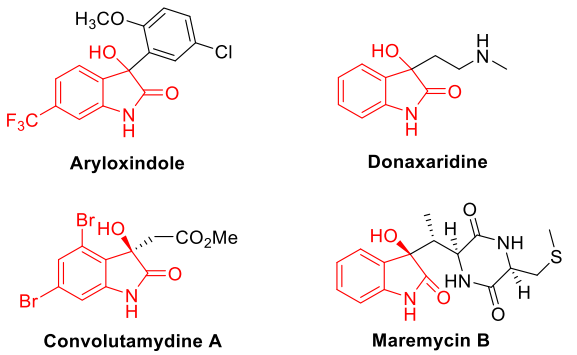


Figure 1. Natural bioactive oxindole products.

These natural compounds have various biological activities,[2] such as antioxidant, neuroprotective, anticancer, and anti-HIV activities. 3-Alkyl/aryl-3-hydroxyoxindole products are important intermediates for the synthesis of complex compounds as well. Consequently, a number of synthetic strategies have been developed for the synthesis of this class of heterocycle.[3] The traditional synthetic method of 3-substituted-3-hydroxyoxindoles is a nucleophilic addition to isatins[4] including aldol reaction and metal-mediated alkylation of isatins and so on. Hayashi's group reported the aldol reaction of isatins with aldehydes using proline as the additive, while the reaction needs further reduction to afford 3-alkyl/aryl-3-hydroxyoxindoles. As to the metal-mediated alkylation of isatins,[5] Grignard-type and Barbier-type reactions are among the most fundamental reactions. Feringa[6] and co-workers developed Rh-catalyzed 1,2-addition of boronic acids to isatins to obtain various 3-aryl-3-hydroxyoxindole. However, the disadvantage of this method is the use of metal catalysts and the formation of metal byproducts. An alternative method to synthesize the target compounds is electrophilic oxidation of 3-alkyl- or 3-aryl-2-oxindoles,[7] which undergoes the process of cyclization and rearrangement. Du[8] and co-workers reported phenyliodine bis(trifluoroacetate) (PIFA) oxidation of anilide derivatives for the synthesis of 3-hydroxy-2-oxindole without using any metal catalysts; besides, this method can be used for the synthesis of spirooxindoles.

Recently, alcohols have been effectively used as versatile alkylating reagents[9−12] in several borrowing hydrogen concepts because of their environmentally benign properties, the only byproduct of this transformation being water. Gnanaprakasam[11]and co-workers reported the direct synthesis of 3-alkyl/aryl-3-hydroxyoxindoles from 2-oxindoles using alcohols as alkylating reagents and metal as catalysts. Xu's group[12] reported the alkylation of ketones with alcohols. Dehydrative α-alkylation reactions of ketones with alcohols are now realized under simple, practical, and green conditions without using external catalysts.[12] However, novel green methods for the synthesis of 3-alkyl/aryl-3-hydroxyoxindoles from 2-oxindoles without using any transition metal catalyst are greatly demanded and highly challenged. Herein, we report a potassium hydroxide-mediated C3-alkylation and C3-hydroxylation of 2-oxindoles with alcohols in simple conditions (Scheme 1).

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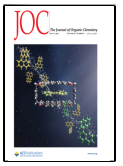

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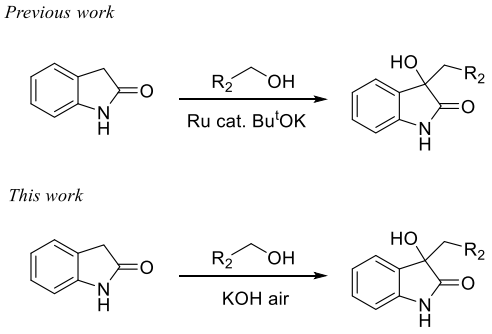
Scheme 1. Synthetic Routes of 3-Alkyl/Aryl-3-Hydroxyoxindoles

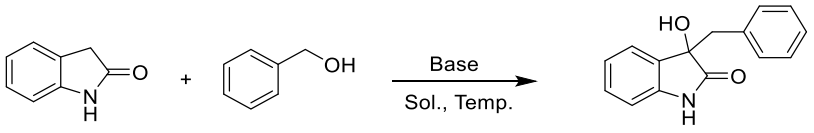


RESULTS AND DISCUSSION

To realize our idea, 2-oxindole **1** and benzyl alcohol **2** were selected as the model substrate (Table 1) in the presence of bases in air. We first screened the effect of solvents on the C-H double functionalization of 2-oxindole. Fortunately, desired product **3a** was obtained in 64% yield in 1,4-dioxane (entry 2). The desired product was obtained in 43 and 31% in toluene and PhCl, respectively, while other solvents were ineffective. Then, we studied different strengths of bases. Strong bases can afford the product in good yields (Table 1, entries 2, 11, 14, and 15) whether it is organic or inorganic bases, and KOH was the best among them. In addition, temperature also played an important role in this reaction, and higher yields were obtained at higher temperatures (Table 1, entries 18−20). Furthermore, this reaction failed to occur when using 1.0 equiv KOH (Table 1, entry 21).

With the optimal conditions in hand, we examined the substrate scope of this reaction (Scheme 2). First, we investigated a broad range of primary benzyl alcohols. Electron-donating substituted benzyl alcohols such as 4-methoxybenzyl alcohol and 4-methylbenzyl alcohol gave moderate yields (**3b, 3h**). When ortho-substituted benzyl alcohols were used, due to steric hindrance, lower yields were obtained (**3g, 3e**). While electron-withdrawing substituted benzyl alcohols and halogen-substituted benzyl alcohols afforded desired products in high yields (**3c, 3d, 3i−3k**). In addition, we also investigated other aromatic heterocyclic alcohols such as 2-thiophene methanol, 2-pyridylmethanol, and 2-furan methanol, and these substrates can all react successfully with 2-oxindole (**3n-3p**). Furthermore, we examined several aliphatic alcohols. When propanol and pentanol were used as substrates, target products were formed with longer reaction times (**3q**), and methanol and ethanol were not effective in this reaction. Unfortunately, when choosing 1-phenylethanol and isopropyl alcohol as substrates, no reaction was detected. We suspected that secondary alcohols were less reactive compared with primary benzyl alcohols. Then, we examined the versatility of 2-oxindole with different substituents, and most of the substrates could provide good yields (**3r−3u**). *N*-

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

entry	solvent	base	atm.	T/°C	yield (%)[b]
1	CH_3CN	KOH	air	110	NR
2	1,4-dioxane	KOH	air	110	64
3	EtOH	KOH	air	110	NR
4	DMF	KOH	air	110	NR
5	DMSO	KOH	air	110	NR
6	THF	KOH	air	110	NR
7	toluene	KOH	air	110	43
8	$CHCl_3$	KOH	air	110	NR
9	THF	KOH	air	110	NR
10	PhCl	KOH	air	110	31
11	1,4-dioxane	NaOH	air	110	50
12	1,4-dioxane	K_2CO_3	air	110	NR
13	1,4-dioxane	Cs_2CO_3	air	110	NR
14	1,4-dioxane	*t*BuOK	air	110	57
15	1,4-dioxane	*t*BuONa	air	110	52
16	1,4-dioxane	DIPEA	air	110	NR
17	1,4-dioxane	Et_3N	air	110	NR
18	1,4-dioxane	KOH	air	100	55
19	1,4-dioxane	KOH	air	90	48
20	1,4-dioxane	KOH	air	80	35
21[c]	1,4-dioxane	KOH	air	110	NR
22	H_2O	KOH	air	110	NR
23	1,4-dioxane	KOH	N_2	110	NR

[a]Reaction conditions: a mixture of **1a** (0.50 mmol), **2a** (0.75 mmol), and base (1.00 mmol) in the solvents (5 mL) was stirred at screening of temperature for 20 h. [b]Isolated yields. [c]**1a** (0.50 mmol), **2a** (0.75 mmol), and KOH (0.50 mmol).

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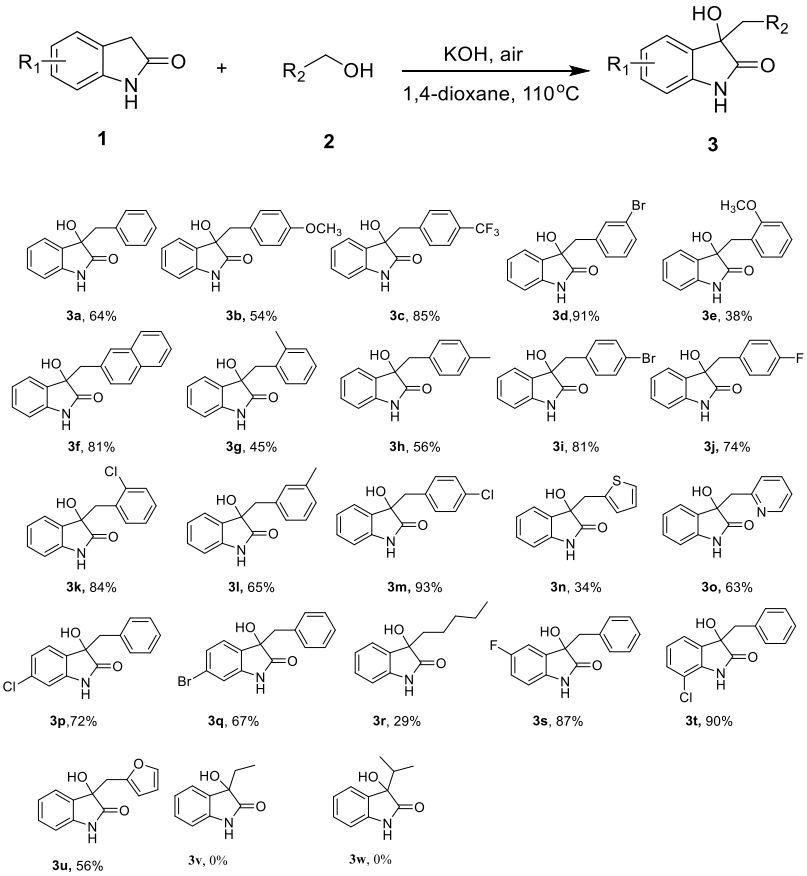
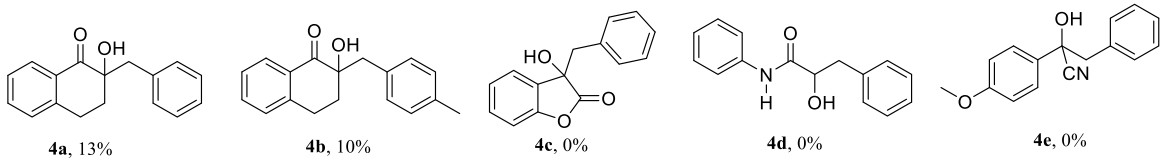
Scheme 2. Scope of Substrates[ab]



[a]Reaction conditions: a mixture of **1** (0.50 mmol), **2** (0.75 mmol), and KOH (1.00 mmol) in the solvents (5 mL) was stirred 110 °C for 20 h. [b]Isolated yields.

Scheme 3. Scope of Other Substrates



protected 2-oxindole only gave trace products. Additionally, we examined other substrate scope of this reaction. (Scheme 3). Unfortunately, ketones yielded lower yields and produced more other compounds, possibly due to their multiple reactive sites. Benzofuran-2(3*H*)-one, amides, and nitrile compounds did not produce target products.

We propose the reaction mechanism shown in Scheme 4. As shown in Scheme 4, we hypothesize that alcohol **2** will be oxidized to aldehyde **3** through Meerwein−Pondorf−Verley−Oppenauer type (MPV-O type) and then condensed with **1** to obtain intermediate **4**, and then, it will be reduced with alcohol **2** through MPV-O type to obtain alkylated 2-oxindole **5**, thus regenerating aldehydes for the catalytic cycle. Next, compound **5** undergoes base-mediated deprotonation to give enolate **6** and then reacts with air to generate compound **7** that may abstract a proton from **5** to form **8**, which is subsequently cleaved by reductant enolate **6** to give the expected product **9**.

CONCLUSIONS

In conclusion, we have developed a transition-metal-free, efficient method for α-C-H hydroxylation and α-C-H alkylation of various oxindoles and alcohols using inexpensive KOH as a base and environmentally benign atmospheric air as an oxidant. This methodology delivers a broad array of substrates and provides an alternate route for the synthesis of 3-alkyl/aryl-3-hydroxyoxindoles. The mechanistic study is in progress in our laboratory.

EXPERIMENTAL SECTION

General Methods. Commercial reagents were purchased from TCI, Acros, Accela, and Adamas, and used without further purification unless otherwise stated. Solvents, unless otherwise specified, were of reagent grade and distilled once prior to use. ^{1}H and ^{13}CNMR spectra were recorded on Bruke Avance-400 (400 MHz), and tetramethylsilane (TMS) was used as a reference. Chromatography was carried out with silica gel (300−400 mesh) using mixtures of petroleum ether (b.p. 60−90 °C) and ethyl acetate

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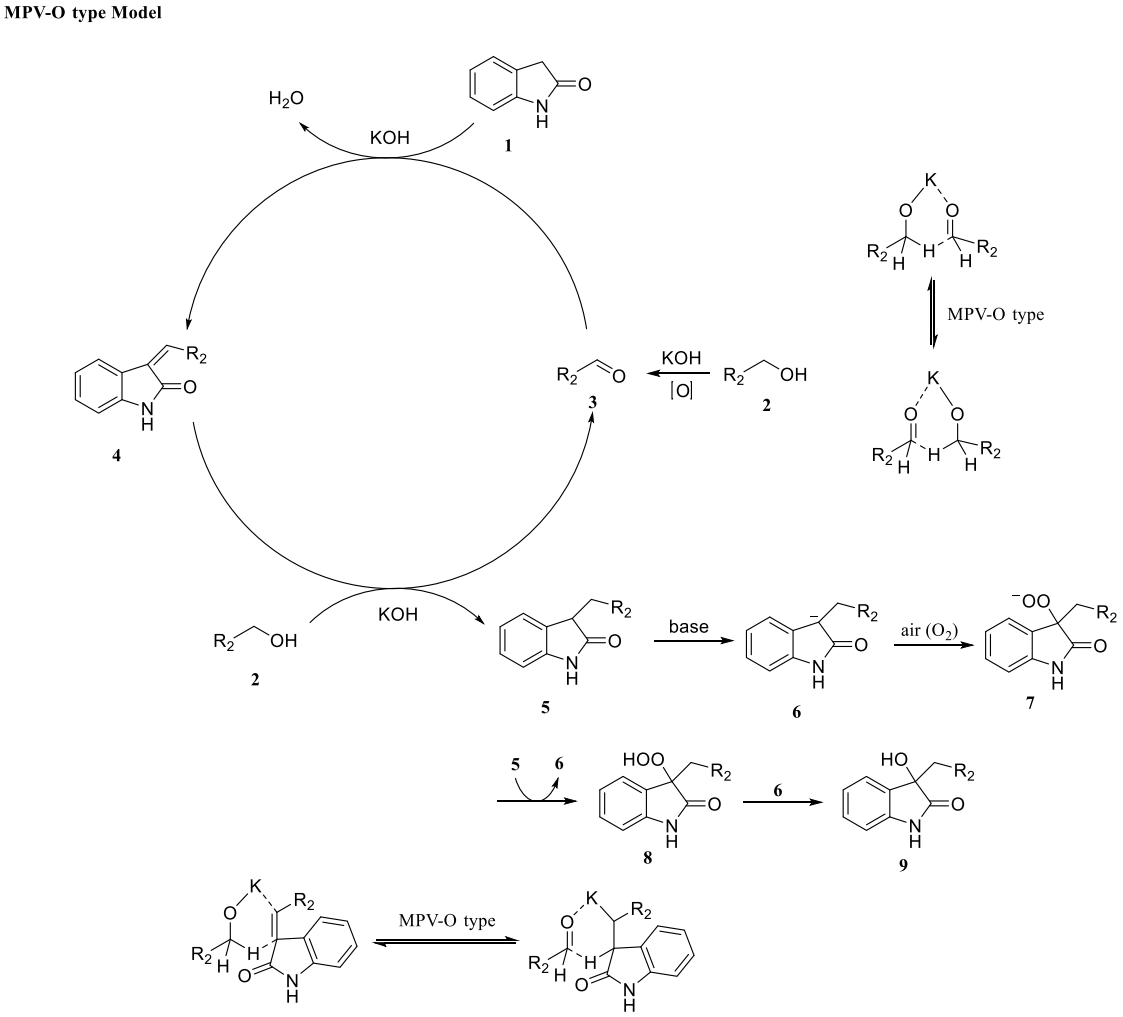
Scheme 4. Proposed Reaction Mechanism[10,12,13]



as eluents. High-resolution mas spectrometry (HRMS) was carried out on Micromass GCTTM gas chromatograph mass spectrometer.

General Procedure for Synthesis of 3a–4b. A mixture of **1** (0.50 mmol, 1.00 equiv), **2** (0.75 mmol, 1.50 equiv), KOH (1.00 mmol, 2.00 equiv) in 1,4-dioxane (5 mL) was stirred at 110 °C under oil bath for 20 h. After the reaction completed, the mixture was filtered and the filtrate was washed by CH_2Cl_2 and water. The organic phase was dried over anhydrous magnesium sulfate and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (Petroleum ether/EtOAc = 10:1) to obtain **3a-4b**.

*Synthesis of 3-Benzyl-3-Hydroxyindolin-2-One (**3a**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3a**; **3a** was isolated as a white solid (77 mg, 64% yield); Mp.122-124 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.06 (s, 1H), 7.12 (d, J = 7.5 Hz, 2H), 7.10–7.06 (m, 3H), 6.95–6.86 (m, 3H), 6.61 (d, J = 7.5 Hz, 1H), 6.14 (s, 1H), 3.17 (d, J = 12.6 Hz, 1H), 3.01 (d, J = 12.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 179.2, 142.1, 135.5, 131.4, 130.6, 129.3, 127.9, 126.8, 125.0, 121.7, 109.7, 77.1, 43.9. This compound was known: Chaudhari, M. B.; Sutar, Y.; Malpathak, S.; Hazra, A.; Gnanaprakasam, B. *Org. Lett.* **2017**, *19*, 3628–3631.

*Synthesis of 3-Hydroxy-3-(4-Methoxybenzyl)Indolin-2-One (**3b**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3b**; **3b** was isolated as a yellow solid (73 mg, 54% yield); Mp.122-124 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.03 (s, 1H), 7.1–7.08 (m, 2H), 6.91 (m, 1H), 6.83–6.77 (m, 2H), 6.66–6.63 (m, 2H), 6.61(d, J = 7.5 Hz, 1H), 6.07 (s, 1H), 3.63 (s, 3H), 3.09 (d, J = 12.8 Hz, 1H), 2.94 (d, J = 12.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.8, 157.7, 141.6, 131.1, 131.0, 128.8, 126.8, 124.5, 121.2, 112.9, 109.2, 76.6, 54.8, 42.5. This compound was known: Chaudhari, M. B.; Sutar, Y.; Malpathak, S.; Hazra, A.; Gnanaprakasam, B. *Org. Lett.* **2017**, *19*, 3628–3631.

*Synthesis of 3-Hydroxy-3-(4-(Trifluoromethyl)Benzyl)Indolin-2-One (**3c**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3c**; **3c** was isolated as a yellow solid (131 mg, 85% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.15 (s, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.18–7.13 (m, 3H),7.13–7.10 (m, 1H), 6.93 (m, 1H), 6.66 (d, J = 7.7 Hz, 1H), 6.27 (d, J = 1.3 Hz, 1H), 3.27 (d, J = 12.6 Hz, 1H), 3.10 (d, J = 12.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.5, 141.5, 140.0, 130.9, 130.6, 129.0, 127.1(q, J = 32.7 Hz), 124.5, 124.3(q, J = 270.1 Hz), 124.2(q, J = 3.6 Hz), 121.3, 109.4, 76.3, 43.1. HRMS (EI) m/z calcd for $C_{16}H_{12}F_3NO_2$ (M^+): 307.0820, found: 307.0818.

*Synthesis of 3-(3-Bromobenzyl)-3-Hydroxyindolin-2-One (**3d**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3d**; **3d** was isolated as a yellow solid (144 mg, 91% yield); Mp.135-136 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.18 (s, 1H), 7.33–7.28 (m, 1H), 7.18–7.11 (m, 2H), 7.10 (s, 1H), 7.07 (t, J = 7.9 Hz,1H), 6.96–6.90 (m, 2H), 6.67 (m, 1H), 6.24 (s, 1H), 3.19 (d, J = 12.7 Hz, 1H), 3.01 (d, J = 12.7 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.6, 141.5, 137.9, 132.8, 130.6, 129.5, 129.3, 129.2, 129.0, 124.5, 121.3, 120.7,

https://doi.org/10.1021/acs.joc.1c02185
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109.4, 76.4, 42.8. This compound was known: Wu, Q.; Pan, L.; Du, G. M.; Zhang, C.; Wang, D. W. *Org. Chem. Front.* **2018**, *5*, 2668−2675.

*Synthesis of 3-Hydroxy-3-(2-Methoxybenzyl)Indolin-2-One (**3e**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3e**; **3e** was isolated as a yellow solid (51 mg, 38% yield); Mp.136-137 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.08 (s, 1H), 7.12−7.02 (m, 3H), 6.92 (m, 1H), 6.81 (m, 1H), 6.76−6.70 (m, 2H), 6.59 (d, J = 7.5 Hz, 1H), 6.00 (s, 1H), 3.44 (s, 3H), 3.22 (d, J = 12.9 Hz, 1H), 2.97 (d, J = 12.9 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 179.2, 157.1, 141.4, 131.1, 131.0, 128.4, 127.7, 124.7, 123.3, 120.6, 119.5, 110.4, 108.9, 76.3, 54.7, 35.9. This compound was known: Bisht, G. S.; Chaudhari, M. B.; Gupte, V. S.; Gnanaprakasam, B. *ACS Omega.* **2017**, *2*, 8234−8252.

*Synthesis of 3-Hydroxy-3-(Naphthalen-2-Ylmethyl)Indolin-2-One (**3f**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3f**; **3f** was isolated as a yellow solid (117 mg, 81% yield); Mp.145-146 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.06 (s, 1H), 7.77−7.67 (m, 1H), 7.63−7.60 (m, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 1.6 Hz, 1H), 7.37−7.32 (m, 2H), 7.15 (m, 1H), 7.05 (m, 2H), 6.87 (m, 1H), 6.54 (d, J = 7.6 Hz, 1H), 6.24 (s, 1H), 3.34 (d, J = 12.6 Hz, 1H), 3.19 (d, J = 12.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.8, 141.6, 132.9, 132.5, 131.7, 131.0, 128.9, 128.7, 128.6, 127.4, 127.3, 126.7, 125.8, 125.4, 124.6, 121.3, 109.3, 76.8, 43.7. HRMS (EI) m/z calcd for $C_{19}H_{15}NO_2$ (M^+): 289.1103, found: 289.1100.

*Synthesis of 3-Hydroxy-3-(2-Methylbenzyl)Indolin-2-One (**3g**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3g**; **3g** was isolated as a white solid (57 mg, 45% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.18 (s, 1H), 7.14 (m, 1H), 7.07−7.00 (m, 3H), 6.97−6.94(m, 1H), 6.84 (m, 1H), 6.79 (m, 1H), 6.71 (d, J = 7.6 Hz, 1H), 6.09 (s, 1H), 3.15 (d, J = 13.5 Hz, 1H), 2.97 (d, J = 13.5 Hz, 1H), 1.96 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 179.5, 141.5, 136.9, 133.7, 131.1, 130.8, 129.7, 128.8, 126.4, 124.9, 124.6, 121.0, 109.3, 76.4, 39.5, 19.5. This compound was known: Chaudhari, M. B.; Sutar, Y.; Malpathak, S.; Hazra, A.; Gnanaprakasam, B. *Org. Lett.* **2017**, *19*, 3628−3631.

*Synthesis of 3-Hydroxy-3-(4-Methylbenzyl)Indolin-2-One (**3h**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3h**; **3h** was isolated as a white solid (71 mg, 56% yield); Mp.185-188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.03 (s, 1H), 7.15 (m, 1H), 7.10 (m, 1H), 6.94−6.86 (m, 3H), 6.77 (d, J = 7.9 Hz, 2H), 6.60 (d, J = 7.6 Hz, 1H), 6.10 (s, 1H), 3.12 (d, J = 12.6 Hz, 1H), 2.98 (d, J = 12.6 Hz, 1H), 2.16 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.7, 141.6, 135.1, 131.9, 131.0, 129.9, 128.8, 128.1, 124.5, 121.1, 109.2, 76.6, 43.1, 20.5. This compound was known: Chaudhari, M. B.; Sutar, Y.; Malpathak, S.; Hazra, A.; Gnanaprakasam, B. *Org. Lett.* **2017**, *19*, 3628−3631.

*Synthesis of 3-(4-Bromobenzyl)-3-Hydroxyindolin-2-One (**3i**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3i**; **3i** was isolated as a yellow solid (128 mg, 81% yield); Mp.161-162 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.14 (s, 1H), 7.33−7.26 (m, 2H), 7.17−7.11 (m, 2H), 6.95−6.91 (m, 1H), 6.90−6.84 (m, 2H), 6.69−6.64 (m, 1H), 6.22 (s, 1H), 3.16 (d, J = 12.7 Hz, 1H), 3.00 (d, J = 12.7 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.6, 141.5, 134.5, 132.3, 130.7, 130.3, 129.0, 124.5, 121.3, 119.7, 109.4, 76.3, 42.8. This compound was known: Wu, Q.; Pan, L.; Du, G. M.; Zhang, C.; Wang, D. W. *Org. Chem. Front.* **2018**, *5*, 2668−2675.

*Synthesis of 3-(4-Fluorobenzyl)-3-Hydroxyindolin-2-One (**3j**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3j**; **3j** was isolated as a white solid (95 mg, 74% yield); Mp.126-127 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.12 (s, 1H), 7.13 (m, 2H), 6.95 (d, J = 1.2 Hz, 2H), 6.94−6.92 (m, 2H), 6.91 (d, J = 1.0 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 6.19 (s, 1H), 3.18 (d, J = 12.8 Hz, 1H), 3.01 (d, J = 12.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.7, 162.9(d, J = 240.4 Hz), 141.6, 131.8(d, J = 10.6 Hz), 131.2, 130.8, 128.9, 124.5, 121.2, 114.2(d, J = 21.4 Hz), 109.3, 76.5, 42.5. This compound was known: Wu, Q.; Pan, L.; Du, G. M.; Zhang, C.; Wang, D. W. *Org. Chem. Front.* **2018**, *5*, 2668−2675.

*Synthesis of 3-(2-Chlorobenzyl)-3-Hydroxyindolin-2-One (**3k**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3k**; **3k** was isolated as a white solid (115 mg, 84% yield); Mp.168-171 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.28 (s, 1H), 7.39−7.36 (m, 1H), 7.29−7.24 (m, 1H), 7.23−7.17 (m, 2H), 7.13 (m, 1H), 6.85−6.80 (m, 2H), 6.71 (d, J = 7.7 Hz, 1H), 6.22 (s, 1H), 3.32 (d, J = 13.5 Hz, 1H), 3.15 (d, J = 13.5 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 179.0, 141.3, 134.1, 133.1, 132.1, 130.5, 128.9, 128.8, 128.3, 126.3, 124.6, 121.1, 109.3, 75.9, 39.2. This compound was known: Wu, Q.; Pan, L.; Du, G. M.; Zhang, C.; Wang, D. W. *Org. Chem. Front.* **2018**, *5*, 2668−2675.

*Synthesis of 3-Hydroxy-3-(3-Methylbenzyl)Indolin-2-One (**3l**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3l**; **3l** was isolated as a white solid (82 mg, 65% yield); Mp.155-156 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.08 (s, 1H), 7.17−7.08 (m, 2H), 6.97−6.88 (m, 3H), 6.73 (s, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.62 (d, J = 7.6 Hz, 1H), 6.13 (s, 1H), 3.14 (d, J = 12.6 Hz, 1H), 2.98 (d, J = 12.6 Hz, 1H), 2.11 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.8, 141.6, 136.2, 134.9, 131.0, 130.8, 128.8, 127.3, 127.2, 126.9, 124.6, 121.1, 109.2, 76.6, 43.4, 20.9. This compound was known: Chaudhari, M. B.; Sutar, Y.; Malpathak, S.; Hazra, A.; Gnanaprakasam, B. *Org. Lett.* **2017**, *19*, 3628−3631.

*Synthesis of 3-(4-Chlorobenzyl)-3-Hydroxyindolin-2-One (**3m**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3m**; **3m** was isolated as a white solid (127 mg, 93% yield); Mp.142-143 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.14 (s, 1H), 7.20−7.13 (m, 2H), 7.13 (d, J = 7.5 Hz, 2H), 6.94 (m, 3H), 6.66 (d, J = 7.4 Hz, 1H), 6.23 (s, 1H), 3.18 (d, J = 12.7 Hz, 1H), 3.02 (d, J = 12.7 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.6, 141.5, 134.1, 131.9, 131.2, 130.7, 129.0, 127.4, 124.5, 121.3, 109.4, 76.4, 42.7. This compound was known: Wu, Q.; Pan, L.; Du, G. M.; Zhang, C.; Wang, D. W. *Org. Chem. Front.* **2018**, *5*, 2668−2675.

*Synthesis of 3-Hydroxy-3-(Thiophen-2-Ylmethyl)Indolin-2-One (**3n**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3n**; **3n** was isolated as a white solid (42 mg, 34% yield); Mp.115-116 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.16 (s, 1H), 7.20 (m, 1H), 7.16 (m, 1H), 7.11 (m, 1H), 6.92 (m, 1H), 6.79 (m, 1H), 6.68 (d, J = 7.7 Hz, 1H), 6.58 (m, 1H), 6.23 (s, 1H), 3.34 (d, J = 14.0 Hz, 1H), 3.25 (d, J = 14.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.4, 142.0, 136.6, 130.8, 129.1, 127.1, 126.1, 124.9, 124.4, 121.4, 109.4, 75.9, 37.7. This compound was known: Wu, Q.; Pan, L.; Du, G. M.; Zhang, C.; Wang, D. W. *Org. Chem. Front.* **2018**, *5*, 2668−2675.

*Synthesis of 3-Hydroxy-3-(Pyridin-2-Ylmethyl)Indolin-2-One (**3o**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3o**; **3o** was isolated as a white solid (76 mg, 63% yield); Mp.167-169 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.16 (s, 1H), 8.30 (m, 1H), 7.58 (m, 1H), 7.16−7.06 (m, 3H), 6.93 (m, 1H), 6.83 (m, 1H), 6.66 (d, J = 7.7 Hz, 1H), 6.34 (s, 1H), 3.31 (d, J = 13.1 Hz, 1H), 3.19 (d, J = 13.1 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.5, 156.0, 148.2, 141.6, 135.8, 130.9, 128.7, 124.5, 124.3, 121.6, 121.1, 109.2,

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75.6, 45.1. This compound was known: Yaragorla, S.; Singh, G.; Dada, R. *Tetrahedron Lett.* **2015**, *56*, 5924−5929.

*Synthesis of 3-Benzyl-6-Chloro-3-Hydroxyindolin-2-One (**3p**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3p**; **3p** was isolated as a white solid (98 mg, 72% yield); Mp.119−121 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.27 (s, 1H), 7.14 (s, 1H), 7.13−7.09 (m, 3H), 6.95 (m, 3H), 6.66 (d, J = 1.9 Hz, 1H), 6.29 (s, 1H), 3.20 (d, J = 12.7 Hz, 1H), 3.04 (d, J = 12.7 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.7, 143.1, 134.7, 133.0, 130.1, 129.8, 127.6, 126.4, 126.0, 120.9, 109.4, 76.3, 43.2. This compound was known: Bisht, G. S.; Chaudhari, M. B.; Gupte, V. S.; Gnanaprakasam, B. *ACS Omega* **2017**, *2*, 8234−8252.

*Synthesis of 3-Benzyl-6-Bromo-3-Hydroxyindolin-2-One (**3q**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3q**; **3q** was isolated as a white solid (106 mg, 67% yield); Mp.135-136 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.22 (s, 1H), 7.14−7.10 (m, 3H), 7.09 (d, J = 1.8 Hz, 1H), 7.04 (d, J = 7.9 Hz, 1H), 6.92 (m, 2H), 6.76 (d, J = 1.7 Hz, 1H), 6.24 (s, 1H), 3.17 (d, J = 12.7 Hz, 1H), 3.01 (d, J = 12.7 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.6, 143.3, 134.7, 130.3, 130.1, 127.6, 126.5, 126.4, 123.8, 121.4, 112.1, 76.3, 43.1. HRMS (EI) m/z calcd for $C_{15}H_{12}BrNO_2$ (M^+):319.0031, found: 319.0030.

*Synthesis of 3-Hydroxy-3-Pentylindolin-2-One (**3r**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3r**; **3r** was isolated as a white solid (32 mg, 29% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.21 (s, 1H), 7.24 (m, 1H), 7.19 (m, 1H), 6.96 (m, 1H), 6.80 (d, J = 7.6 Hz, 1H), 5.82 (s, 1H), 1.75 (m, 2H), 1.15 (m, 4H), 1.08−0.84 (m, 2H), 0.86−0.72 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 179.4, 141.7, 132.1, 128.7, 123.7, 121.5, 109.4, 75.6, 37.6, 31.3, 22.3, 21.8, 13.7. This compound was known: Wu, Q.; Pan, L.; Du, G. M.; Zhang, C.; Wang, D. W. *Org. Chem. Front.* **2018**, *5*, 2668−2675.

*Synthesis of 3-Benzyl-5-Fluoro-3-Hydroxyindolin-2-One (**3s**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3s**; **3s** was isolated as a white solid (112 mg, 87% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.13 (s, 1H), 7.17−7.07 (m, 3H), 7.00 (m, 1H), 6.97−6.91 (m, 3H), 6.61 (m, 1H), 6.31 (s, 1H), 3.21 (d, J = 12.7 Hz, 1H), 3.05 (d, J = 12.7 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.7, 157.71(d, J = 235.2 Hz), 137.7, 134.7, 132.7(d, J = 8.7 Hz), 130.1, 127.5, 126.4, 115.0(d, J = 23.6 Hz), 112.3(d, J = 24.4 Hz), 110.0(d, J = 8.0 Hz), 77.0, 43.2. HRMS (EI) m/z calcd for $C_{15}H_{12}FNO_2$ (M^+):257.0852, found: 257.0854.

*Synthesis of 3-Benzyl-7-Chloro-3-Hydroxyindolin-2-One (**3t**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3t**; **3t** was isolated as a white solid (123 mg, 90% yield); Mp.227-229 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.54 (s, 1H), 7.19 (m, 1H), 7.11 (m, 3H), 7.09 (d, J = 1.1 Hz, 1H), 7.00−6.89 (m, 3H), 6.33 (s, 1H), 3.21 (d, J = 12.7 Hz, 1H), 3.06 (d, J = 12.7 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.7, 139.3, 134.6, 132.9, 130.1, 128.8, 127.6, 126.5, 123.2, 122.6, 113.5, 77.2, 43.3. HRMS (EI) m/z calcd for $C_{15}H_{12}ClNO_2$ (M^+):273.0557, found: 273.0556.

*Synthesis of 3-(Furan-2-Ylmethyl)-3-Hydroxyindolin-2-One (**3u**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **3u**; **3u** was isolated as a white solid (64 mg, 56% yield); Mp.140-142 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.20 (s, 1H), 7.35 (m, 1H), 7.16 (m, 1H), 7.11 (m, 1H), 6.92 (m, 1H), 6.72 (d, J = 7.7 Hz, 1H), 6.22 (m, 1H), 6.19 (s, 1H), 5.79 (m, 1H), 3.22 (d, J = 14.4 Hz, 1H), 3.08 (d, J = 14.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [ppm]: 178.4, 149.8, 141.7, 141.5, 131.0, 129.0, 124.3, 121.4, 110.3, 109.3, 107.4, 74.9, 35.9. This compound was known: Wu, Q.; Pan, L.; Du, G. M.; Zhang, C.; Wang, D. W. *Org. Chem. Front.* **2018**, *5*, 2668−2675.

*Synthesis of 3,4-Dihydro-2-Hydroxy-2-(Phenylmethyl)-1(2H)-Naphthalenone (**4a**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **4a**; **4a** was isolated as a yellow solid (16 mg, 13% yield); Mp. 97-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.03 (d, J = 8.0 Hz, 1H), 7.57 (dt, J = 1.2 Hz, 1H), 7.38 (m, 2H), 7.30 (m, 3H), 7.16 (m, 2H), 4.70 (bs, 1H), 3.28 (m, 1H), 3.07 (m, 1H), 3.00 (d, J = 16 Hz, 1H), 2.93 (d, J = 12 Hz, 1H), 2.29 (m, 1H), 2.21 (m, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ [ppm]: 201.0, 143.3, 135.4, 134.3, 130.5, 129.2, 128.7, 128.2, 128.1, 127.8, 127.2, 127.1, 127.0, 76.2, 42.1, 33.9, 26.5. This compound was known: Chaudhari, M. B.; Sutar, Y.; Malpathak, S.; Hazra, A.; Gnanaprakasam, B. *Org. Lett.* **2017**, *19*, 3628−3631.

*Synthesis of 3,4-Dihydro-2-Hydroxy-2-[(4-Methylphenyl)-Methyl]-1(2H)-Naphthalenone (**4b**).* Following the general procedure, the crude product was purified using silica gel column chromatography (EtOAc/petroleum ether = 1:10) to produce the desired product **4b**; **4b** was isolated as a yellow solid (13 mg, 10% yield); Mp.103−105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.03 (d, J = 8.0 Hz, 1H), 7.57 (dt, J = 1.2 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 3.76 (bs, 1H), 3.27 (m, 1H), 3.04 (m, 1H), 2.97 (d, J = 16 Hz, 1H), 2.89 (d, J = 16 Hz, 1H), 2.32 (s, 3H), 2.22 (m, 2H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ [ppm]: 200.1, 142.33, 135.5, 133.2, 131.3, 129.6, 129.3, 128.2, 128.0, 127.1, 126.2, 75.2, 40.7, 33.0, 25.5, 20.2. This compound was known: Chaudhari, M. B.; Sutar, Y.; Malpathak, S.; Hazra, A.; Gnanaprakasam, B. *Org. Lett.* **2017**, *19*, 3628−3631.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c02185.

^{1}H-NMR, ^{13}C-NMR copies of compounds (**3a**−**4b**), and additional spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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