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Iodine-catalyzed efficient synthesis of azaarene substituted 3-hydroxy-2-oxindole derivatives through sp^3 C–H functionalization

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ABSTRACT

Iodine-catalyzed benzylic sp^3 C–H bond functionalization of lutidines or picolines to isatins is described. This synthetic method provides a rapid entry towards biologically interesting 3-azaarene substituted 3-hydroxy-2-oxindole derivatives.

1. Introduction

The development of a new methodology for the direct functionalization of relatively unreactive C–H bonds has become a major topic of research.[1] The recent rapid growth of this area is not surprising, since such methodology facilitates the direct formation of C–C and C–Z bonds (*Z*=O, N, B, Si, etc.) without utilizing prefunctionalized C–X bonds (*X*=halogen, OTf, etc.). Among them, sp^3 C–H bond activation[2] adjacent to nitrogen followed by C–C bond forming reactions of azaarenes provide[3,4] straightforward access to useful building blocks for the design and synthesis of biologically active compounds.

Molecules bearing 3-substituted 3-hydroxy-2-oxindoles are found widely in nature and pharmaceutical materials (Fig. 1).[5] These compounds have a variety of potent biological and pharmaceutical activities, such as anticancer, anti-HIV, antioxidant and neuroprotective properties.[6] Interestingly, the biological effects of these compounds are known to vary with the substituent at the C3 position of oxindoles.[6e] Their wide range of biological activities has promoted research into the development of convenient and efficient syntheses of 3-substituted 3-hydroxy-2-oxindoles. The synthetic routes for the preparation of 3-aryl or 3-alkyl substituted 3-hydroxy-2-oxindoles have already been developed by several groups.[7] However, few synthetic approaches for 3-azaarene-substituted 3-hydroxy-2-oxindole derivatives are known.[3,4]

Recently, a methodology for azaarene-substituted 3-hydroxy-2-oxindole derivatives has been reported by trifluoromethanesulfonic acid-catalyzed sp^3 C–H functionalization.[8] Although one synthetic method has been described, there is still a demand for general and facile synthetic methods that can efficiently provide various azaarene substituents on the 3-position of the 2-oxindole ring using mild catalysts. Among these, we think molecular iodine[9] is a viable alternative, and may be a promising catalyst for the synthesis of azaarene-substituted 3-hydroxy-2-oxindole derivatives due to its high tolerance to air and moisture, low-cost, easy availability, sustainability, non-toxicity, and high catalytic activity. In the related work, the synthesis of new class of alkyl azaarene pyridinium zwitterions by iodine-mediated sp^3 C–H functionalization has been recently described.[10] We report herein on the iodine-catalyzed reaction of isatins with lutidines or picolines to afford a variety of azaarene-substituted 3-hydroxy-2-oxindole derivatives (Scheme 1).

2. Results and discussion

Reaction of 1-methylisatin (**1a**, 1.0 mmol) with 2,6-lutidine (**2a**, 2.5 mmol) was first examined in the presence of 10 or 20 mol % of I_2 as a catalyst in several solvents (Table 1). Across the range of solvents tested, the best yield (80%) was obtained in the presence of 20 mol % of iodine and in refluxing dioxane for 8 h. The product **3a** was determined by analysis of spectral data and compared directly with the reported data.[8]

To explore the generality and scope of this transformation, additional reactions of several isatins with lutidines or picolines were

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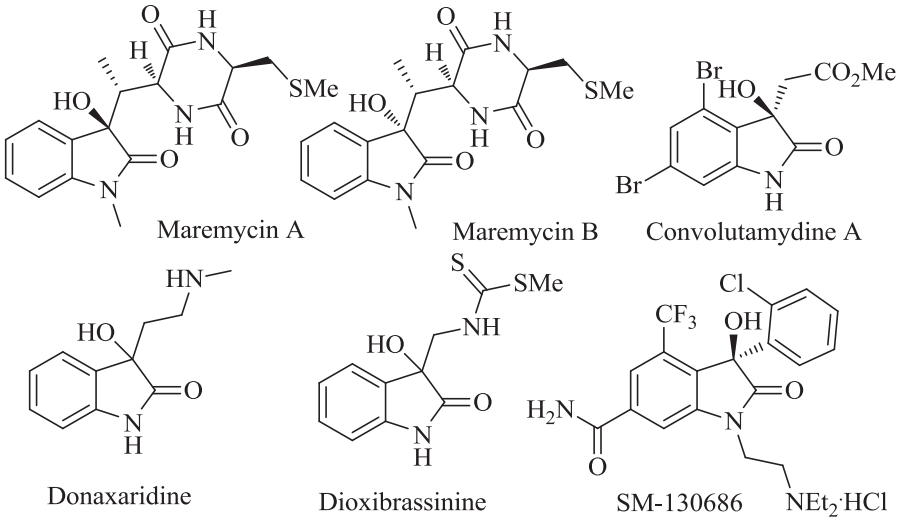
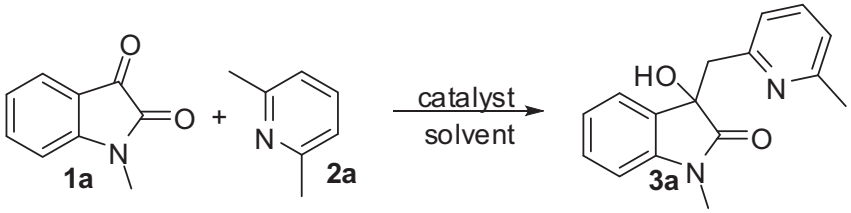


Fig. 1. Selected naturally occurring and pharmaceutical molecules with 3-subsituted 3-hydroxy–oxindoles.

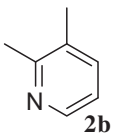
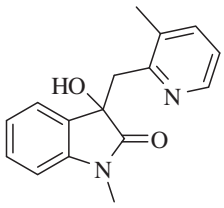
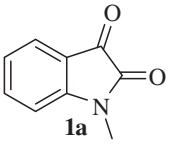
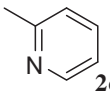
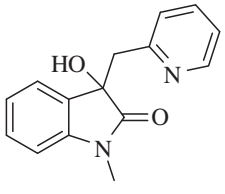
Table 1
Reaction of 1-methylisatin (**1a**) with 2,6-lutidine (**2a**) in the presence of iodine in solvents



Entry	Catalyst	Solvent	Condition	Yield (%)
1	I_2 (20 mol %)	THF	Reflux, 12 h	45
5	I_2 (20 mol %)	Acetonitrile	Reflux, 12 h	10
3	I_2 (20 mol %)	Toluene	Reflux, 10 h	52
4	I_2 (20 mol %)	Dioxane	Reflux, 8 h	80
5	I_2 (10 mol %)	Dioxane	Reflux, 8 h	67

performed under the optimized reaction conditions. The results are summarized in Table 2. Treatment of 1-methylisatin (**1a**) with 2,3-lutidine (**2b**), 2-picoline (**2c**) or 4-picoline (**2d**) in the presence of 20 mol % iodine in refluxing dioxane for 8 h afforded desired products **3b**–**3d** in 80, 70, and 64% yield, respectively (entries 1–3, Table 2). Similarly, reactions of 1-phenylisatin (**1b**) with 2,6-lutidine (**2a**) or 2-picoline (**2c**) gave products **3e** and **3f** in 71 and 62% yield (entries 4–5). Other reactions of isatins without methyl or phenyl substituents on the nitrogen atom were also successful. For example, treatment of isatin (**1c**) with 2,3-lutidine (**2b**) gave the desired

Table 2
Additional reactions of isatins with lutidines or picolines in the presence of 20 mol % of iodine

Entry	Isatins	Lutidines/Picolines	Time (h)	Product	Yield (%)
1			8	 **3b**	80
2			8	 **3c**	70

(*continued on next page*)

Table 2 (*continued*)

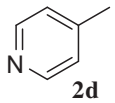
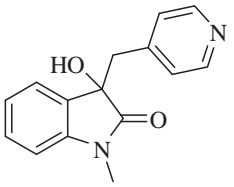
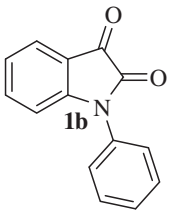
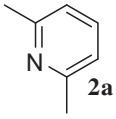
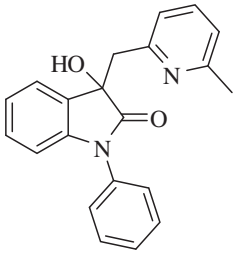
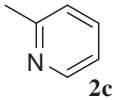
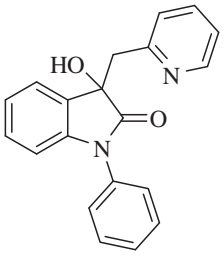
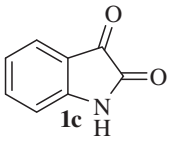
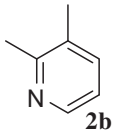
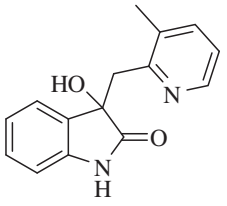
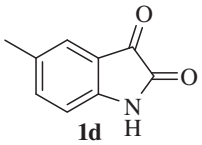
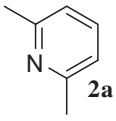
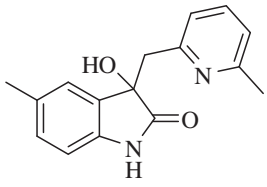
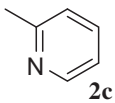
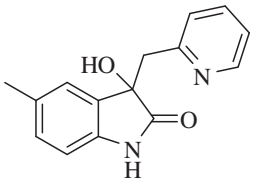
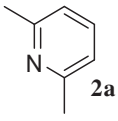
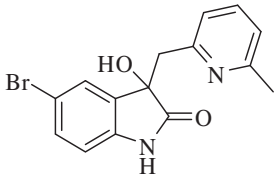
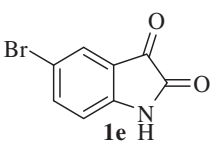
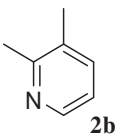
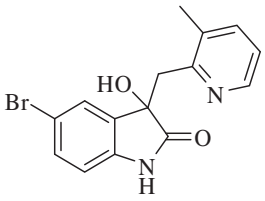
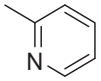
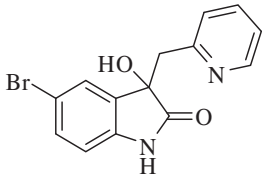
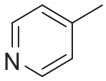
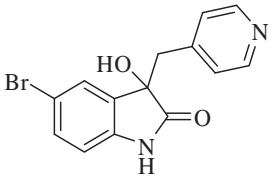
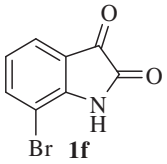
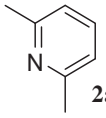
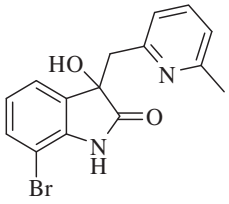
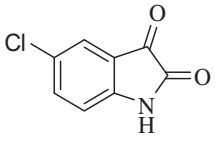
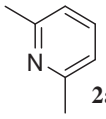
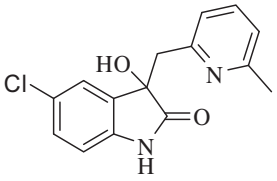
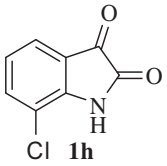
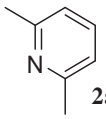
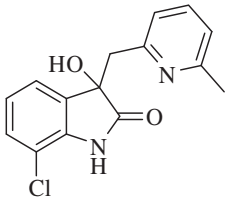
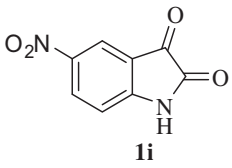
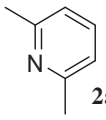
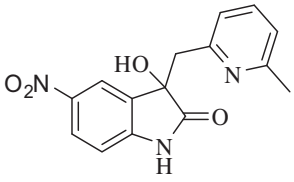
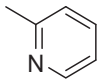
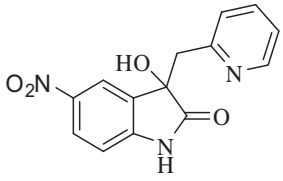
Entry	Isatins	Lutidines/Picolines	Time (h)	Product	Yield (%)
3		 **2d**	8	 **3d**	64
4	 **1b**	 **2a**	8	 **3e**	71
5		 **2c**	8	 **3f**	62
6	 **1c**	 **2b**	8	 **3g**	50
7	 **1d**	 **2a**	8	 **3h**	48
8		 **2c**	8	 **3i**	44
9		 **2a**	8	 **3j**	81
10	 **1e**	 **2b**	8	 **3k**	65

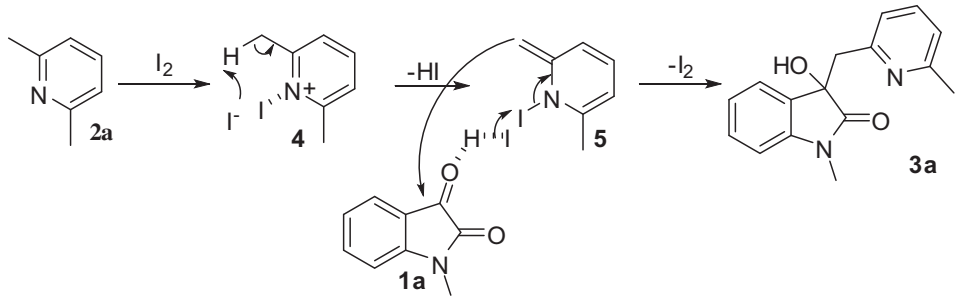
Table 2 (*continued*)

Entry	Isatins	Lutidines/Picolines	Time (h)	Product	Yield (%)
11		 **2c**	8	 **3l**	50
12		 **2d**	8	 **3m**	48
13	 **1f**	 **2a**	8	 **3n**	80
14	 **1g**	 **2a**	8	 **3o**	69
15	 **1h**	 **2a**	8	 **3p**	71
16	 **1i**	 **2a**	8	 **3q**	71
17		 **2c**	8	 **3r**	70

product **3g** in 50% yield (entry 6). Reactions of 5-methylisatin (**1d**) and 2,6-ludine (**2a**) or 2-picoline (**2c**) with electron-donating group on the benzene ring in refluxing dioxane for 8 h produced products **3h**–**3i** in 48 and 44% yield, respectively (entries 7–8). With isatins **1e**–**1i** with electron-withdrawing groups on the benzene ring, the products **3j**–**3r** were also produced in 48–81 % yield (entries 9–17). These reactions provided a rapid route to the synthesis of a variety of azaarene-substituted 3-hydroxy-2-oxindoles derivatives in moderate to good yields.

The formation of **3a** can be explained by the proposed mechanism as shown in Scheme 2. The 2,6-lutidine (**2a**) is first activated by coordination of an iodine catalyst to give *N*-iodopyridinium cation **4**. Importantly, the formation of this type of pyridinium cation by the reaction of pyridine and iodine has been already reported in the literature.[11] Cleavage of the C–H bond of **4** next generates another intermediate **5**, which subsequently undergoes a nucleophilic addition to 1-methylisatin (**1a**) to give product **3a**.

In summary, we have developed a novel iodine-catalyzed coupling reaction of isatins to lutidines or picolines through benzylic sp^3 C–H bond activation of methylpyridines followed by C–C bond formation. This transformation provides a facile and efficient method for the synthesis of 3-azaarenylmethyl-3-hydroxy-2-



Scheme 2.

oxindoles derivatives that are very important in organic and medicinal chemistry. Further studies to expand reactions of iodine-catalyzed benzylic sp^3 C–H functionalization are ongoing in our laboratory.

3. Experimental section

3.1. General

All the experiments were carried out in a nitrogen atmosphere. Merck precoated silica gel plates (Art.5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ and DMSO-d_6 as the solvents. The IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. The HRMS were carried out at the Korea Basic Science Institute.

3.2. General procedure for the preparation of azaarene substituted 3-hydroxy-2-oxindole derivatives (3a–3r)

To a stirred solution of substituted indoline-2,3-diones (1.0 mmol) in dioxane (1 mL) was added lutidines/picolines (2.5 mmol) and Iodine (20 mol %). The resulting mixture was heated at reflux for 8 h. After completion of the reaction, poured EtOAc and then washed with an ice cold saturated aqueous $Na_2S_2O_3$ solution (10 mL×2). Organic layer washed sequentially with brine, ice water and dried over anhydrous $MgSO_4$. Evaporation of the organic solvent afforded the crude products, which was purified by silica gel column chromatography using *n*-hexane/ethyl acetate (4:1–1:1) as eluent to give desired products.

*3.2.1. 3-Hydroxy-1-methyl-3-((6-methylpyridin-2-yl)methyl)indolin-2-one (**3a**).*[8] Yield 80%; a yellow solid; mp 124–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (1H, br s), 7.52 (1H, t, J=7.5 Hz), 7.27–7.21 (1H, m), 7.12 (1H, d, J=7.5 Hz), 6.93–6.74 (4H, m), 3.29 (1H, d, J=15.0 Hz), 3.17 (3H, s), 3.00 (1H, d, J=14.7 Hz), 2.59 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.5, 156.9, 156.7, 142.7, 137.1, 131.0, 129.0, 123.5, 122.4, 121.6, 121.3, 108.0, 75.9, 42.1, 25.9, 24.0; IR (KBr): 3290, 1696, 1613, 1461, 1085, 1009, 755, 664, 600 cm^{-1}.

*3.2.2. 3-Hydroxy-1-methyl-3-((3-methylpyridin-2-yl)methyl)indolin-2-one (**3b**).*[8] Yield 80%; a red solid; mp 118–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (1H, d, J=4.8 Hz), 7.41 (1H, d, J=7.8 Hz), 7.19 (1H, td, J=7.8, 1.5 Hz), 7.14 (1H, dd, J=7.5, 4.8 Hz), 6.84–6.71 (3H, m), 3.26 (1H, d, J=15.6 Hz), 3.10 (3H, s), 2.97 (1H, d, J=15.6 Hz), 1.98 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.6, 156.3, 145.1, 142.7, 138.3, 132.3, 131.4, 129.1, 123.6, 122.5, 122.0, 108.1, 75.9, 38.2, 26.0, 18.6; IR (KBr): 3463, 1713, 1619, 1467, 1374, 1241, 1118, 994, 758 cm^{-1}.

*3.2.3. 3-Hydroxy-1-methyl-3-(pyridin-2-ylmethyl)indolin-2-one (**3c**).*[8] Yield 70%; a yellow solid; mp 136–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (1H, d, J=4.8, 0.6 Hz), 7.63 (1H, td, J=7.8, 1.2 Hz), 7.24–7.17 (2H, m), 7.02 (1H, d, J=7.8 Hz), 6.89 (1H, t, J=7.5 Hz), 6.78–6.72 (2H, m), 3.29 (1H, d, J=15.0 Hz), 3.11 (3H, d, J=0.9 Hz), 3.08 (1H, d, J=14.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.6, 157.5, 148.0, 142.8, 137.1, 130.9, 129.2, 124.5, 123.7, 122.6, 122.2, 108.1, 76.1, 42.5, 26.0; IR (KBr): 3317, 2935, 1695, 1608, 1470, 1372, 1237, 1095, 994, 745 cm^{-1}.

*3.2.4. 3-Hydroxy-1-methyl-3-(pyridin-4-ylmethyl)indolin-2-one (**3d**).*[8] Yield 64%; a white solid; mp 199–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (2H, d, J=2.4 Hz), 7.38 (1H, t, J=7.8 Hz), 7.27 (1H, d, J=7.2 Hz), 7.16 (1H, t, J=7.5 Hz), 7.03 (2H, d, J=3.0 Hz), 6.77 (1H, d, J=7.2 Hz), 3.42 (1H, d, J=12.0 Hz), 3.24 (1H, d, J=12.6 Hz), 3.10 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8, 148.0, 143.6, 142.4, 129.1, 128.9, 125.0, 123.6, 122.0, 107.5, 75.8, 43.1, 25.2; IR (KBr): 3087, 1716, 1606, 1474, 1359, 1222, 1074, 1006, 755 cm^{-1}.

*3.2.5. 3-Hydroxy-3-{(6-methylpyridin-2-yl)methyl}-1-phenylindolin-2-one (**3e**).* Yield 71%; a thick syrup; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (1H, br s), 7.44–7.23 (6H, m), 7.09 (1H, td, J=7.2, 0.6 Hz), 7.01 (1H, d, J=7.8 Hz), 6.88–6.76 (3H, m), 6.71 (1H, d, J=7.8 Hz), 3.31 (1H, d, J=14.7 Hz), 3.10 (1H, d, J=14.7 Hz), 2.47 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.0, 157.0, 156.4, 142.6, 137.2, 134.0, 130.7, 129.3, 129.0, 127.7, 126.1, 124.0, 122.9, 121.7, 121.4, 109.3, 76.1, 42.7, 24.1; IR (neat): 3397, 2343, 1728, 1602, 1468, 1373, 1201, 1100, 755 cm^{-1}; HRMS (EI) calculated for $C_{21}H_{18}N_2O_2$: 330.1368, found: 330.1367.

*3.2.6. 3-Hydroxy-1-phenyl-3-(pyridin-2-ylmethyl)indolin-2-one (**3f**).* Yield 62%; a yellow solid; mp 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (1H, d, J=4.2 Hz), 7.57 (1H, t, J=7.8 Hz), 7.43–7.38 (2H, m), 7.32–7.26 (3H, m), 7.18–7.07 (2H, m), 7.01 (1H, d, J=7.8 Hz), 6.92–6.88 (2H, m), 6.71 (1H, d, J=7.8 Hz), 3.37 (1H, d, J=14.7 Hz), 3.22 (1H, d, J=14.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1, 157.2, 148.1, 142.8, 137.0, 134.1, 130.5, 129.4, 129.1, 127.8, 126.2, 124.6, 124.1, 123.1, 122.2, 109.4, 76.2, 43.2; IR (KBr): 3432, 2340, 1727, 1606, 1490, 1374, 1201, 1102, 755 cm^{-1}; HRMS (EI) calculated for $C_{20}H_{16}N_2O_2$: 316.1212, found: 316.1209.

*3.2.7. 3-Hydroxy-3-((3-methylpyridin-2-yl)methyl)indolin-2-one (**3g**).* Yield 50%; a yellow solid; mp 163–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (1H, br s), 8.42 (1H, d, J=4.8 Hz), 7.48 (1H, d, J=7.8 Hz), 7.18–7.13 (2H, m), 6.86–6.82 (2H, m), 6.78 (1H, d, J=7.5 Hz), 3.34 (1H, d, J=15.3 Hz), 3.09 (1H, d, J=15.3 Hz), 2.05 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.4, 156.2, 145.2, 140.0, 138.5, 132.6, 131.9, 129.1, 124.0, 122.6, 122.2, 110.3, 38.4, 18.7; IR

(KBr): 3378, 3206, 1724, 1620, 1460, 1191, 1116, 1032, 957, 755 cm^{-1}; HRMS (EI) calculated for $C_{15}H_{14}N_2O_2$: 254.1055, found: 254.1054.

*3.2.8. 3-Hydroxy-5-methyl-3-{(6-methylpyridin-2-yl)methyl}indolin-2-one (**3h**).* Yield 48%; a yellow solid; mp 200–203 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 10.03 (1H, s), 7.50 (1H, t, J=7.5 Hz), 7.01–6.89 (3H, m), 6.66 (1H, s), 6.57 (1H, d, J=7.8 Hz), 6.29 (1H, s), 3.23 (1H, d, J=13.2 Hz), 3.09 (1H, d, J=13.2 Hz), 2.29 (3H, s), 2.14 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.6, 156.3, 155.5, 139.1, 136.1, 131.1, 129.5, 128.8, 125.4, 121.1, 120.7, 108.8, 75.6, 44.6, 23.7, 20.6; IR (KBr): 3342, 2966, 2803, 1708, 1595, 1475, 1297, 1147, 1090, 813, 647 cm^{-1}; HRMS (EI) calculated for $C_{16}H_{16}N_2O_2$: 268.1212, found: 268.1213.

*3.2.9. 3-Hydroxy-5-methyl-3-(pyridin-2-ylmethyl)indolin-2-one (**3i**).* Yield 44%; a white solid; mp 212–213 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 10.01 (1H, s), 8.31 (1H, dd, J=5.4, 1.8 Hz), 7.60 (1H, td, J=7.8, 1.2 Hz), 7.14–7.12 (2H, m), 6.90 (1H, dd, J=7.8, 0.9 Hz), 6.71 (1H, s), 6.55 (1H, d, J=7.8 Hz), 6.25 (1H, s), 3.29 (1H, d, J=13.2 Hz), 3.17 (1H, d, J=13.2 Hz), 2.15 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.5, 156.1, 148.3, 139.1, 135.8, 131.0, 129.7, 128.9, 125.2, 124.3, 121.6, 108.9, 75.7, 45.1, 20.6; IR (KBr): 3320, 3016, 2814, 1709, 1488, 1205, 1114, 808, 752, 645 cm^{-1}; FAB-HRMS m/z $(M+H)^+$ calculated for $C_{15}H_{15}N_2O_2$: 255.1134, found: 255.1134.

*3.2.10. 5-Bromo-3-hydroxy-3-{(6-methylpyridin-2-yl)methyl}indolin-2-one (**3j**).* Yield 81%; a white solid; mp 194–196 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 10.28 (1H, s), 7.52 (1H, t, J=7.5 Hz), 7.28 (1H, dd, J=8.1, 1.5 Hz), 7.01–6.96 (3H, m), 6.65 (1H, d, J=8.4 Hz), 6.39 (1H, s), 3.29 (1H, d, J=13.2 Hz), 3.13 (1H, d, J=13.2 Hz), 2.27 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.2, 156.3, 155.0, 141.0, 136.2, 133.5, 131.2, 127.7, 121.2, 120.8, 112.8, 111.0, 75.6, 44.4, 23.6; IR (KBr): 3428, 3174, 2353, 1737, 1628, 1125, 815 cm^{-1}; HRMS (EI) calculated for $C_{15}H_{13}BrN_2O_2$: 332.0160, found: 332.0159.

*3.2.11. 5-Bromo-3-hydroxy-3-{(3-methylpyridin-2-yl)methyl}indolin-2-one (**3k**).* Yield 65%; a yellow solid; mp 208–210 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 10.29 (1H, s), 8.04 (1H, s), 7.46 (1H, d, J=6.9 Hz), 7.28 (1H, d, J=8.1 Hz), 7.15 (1H, s), 7.03 (1H, s), 6.70 (1H, d, J=7.5 Hz), 6.35 (1H, s), 3.47 (1H, d, J=16.5 Hz), 3.25 (1H, d, J=15.0 Hz), 2.24 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.2, 154.9, 145.3, 141.7, 137.2, 134.5, 131.6, 131.1, 126.7, 121.4, 112.4, 111.0, 75.2, 18.4; IR (KBr): 3380, 2937, 2349, 1732, 1616, 1464, 1290, 1204, 1100, 954, 756 cm^{-1}; HRMS (EI) calculated for $C_{15}H_{13}BrN_2O_2$: 332.0160, found: 332.0158.

*3.2.12. 5-Bromo-3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-one (**3l**).* Yield 50%; a yellow solid; mp 215–216 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 8.30 (1H, d, J=3.9 Hz), 7.63 (1H, t, J=8.1 Hz), 7.27 (1H, d, J=7.2 Hz), 7.17–7.11 (2H, m), 7.05 (1H, s), 6.62 (1H, d, J=8.1 Hz), 6.39 (1H, s), 3.34 (1H, d, J=10.5 Hz), 3.21 (1H, d, J=13.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.0, 155.7, 148.3, 140.9, 135.9, 133.4, 131.3, 127.5, 124.3, 121.7, 112.7, 111.2, 75.7, 44.8; IR (KBr): 3344, 2934, 1714, 1473, 1194, 1110, 898, 747 cm^{-1}; HRMS (EI) calculated for $C_{14}H_{11}BrN_2O_2$: 318.0004, found: 318.0002.

*3.2.13. 5-Bromo-3-hydroxy-3-(pyridin-4-ylmethyl)indolin-2-one (**3m**).* Yield 48%; a yellow solid; mp 225–228 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 10.29 (1H, s), 8.33 (2H, s), 7.33 (1H, d, J=8.1 Hz), 7.25 (1H, s), 6.95 (2H, d, J=4.8 Hz), 6.61 (1H, d, J=8.1 Hz), 6.39 (1H, s), 3.23 (1H, d, J=12.3 Hz), 3.01 (1H, d, J=12.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 177.8, 148.7, 143.7, 140.7, 132.9, 131.7, 127.4, 127.3, 125.4, 113.1, 111.4, 76.0, 42.2; IR (KBr): 3352, 2978, 2813, 2708, 1709, 1609, 1465, 1209, 1004, 812, 624 cm^{-1}; HRMS (EI) calculated for $C_{14}H_{11}BrN_2O_2$: 318.0004, found: 318.0002.

*3.2.14. 7-Bromo-3-hydroxy-3-{(6-methylpyridin-2-yl)methyl}indolin-2-one (**3n**).* Yield 80%; a white solid; mp 158–160 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (1H, br s), 7.80 (1H, s), 7.51 (1H, t, J=7.8 Hz), 7.26 (1H, dd, J=8.1, 0.9 Hz), 7.08 (1H, d, J=8.1 Hz), 6.81 (1H, d, J=7.5 Hz), 6.75 (1H, t, J=7.5 Hz), 6.65–6.63 (1H, m), 3.25 (1H, d, J=15.0 Hz), 3.00 (1H, d, J=14.7 Hz), 2.53 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.4, 157.2, 156.3, 139.3, 137.6, 133.0, 131.8, 123.9, 123.0, 122.1, 121.6, 103.1, 77.6, 42.2, 24.1; IR (KBr): 3445, 3154, 1731, 1613, 1464, 1323, 1220, 1119, 784, 729 cm^{-1}; HRMS (EI) calculated for $C_{15}H_{13}BrN_2O_2$: 332.0160, found: 332.0159.

*3.2.15. 5-Chloro-3-hydroxy-3-{(6-methylpyridin-2-yl)methyl}indolin-2-one (**3o**).* Yield 69%; a white solid; mp 191–193 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 10.24 (1H, s), 7.51 (1H, t, J=7.5 Hz), 7.15 (1H, dd, J=8.4, 2.4 Hz), 7.00 (2H, t, J=8.1 Hz), 6.90 (1H, d, J=2.1 Hz), 6.68 (1H, d, J=8.4 Hz), 6.38 (1H, s), 3.29 (1H, d, J=13.5 Hz), 3.14 (1H, d, J=13.5 Hz), 2.26 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.2, 156.3, 155.0, 140.6, 136.2, 133.1, 128.3, 124.8, 121.1, 120.7, 110.4, 75.6, 44.4, 23.6; IR (KBr): 3295, 2965, 2804, 2686, 1711, 1481, 1291, 1166, 1012, 839, 647 cm^{-1}; HRMS (EI) calculated for $C_{15}H_{13}ClN_2O_2$: 288.0666, found: 288.0667.

*3.2.16. 7-Chloro-3-hydroxy-3-{(6-methylpyridin-2-yl)methyl}indolin-2-one (**3p**).* Yield 71%; a white solid; mp 167–169 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.31 (1H, br s), 8.10 (1H, br s), 7.55 (1H, t, J=7.8 Hz), 7.16–7.09 (2H, m), 6.85–6.79 (2H, m), 6.64 (1H, d, J=7.2 Hz), 3.31 (1H, d, J=14.7 Hz), 3.03 (1H, d, J=14.7 Hz), 2.56 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9, 177.8, 157.2, 156.3, 137.7, 137.5, 133.0, 129.0, 123.4, 122.4, 122.0, 121.5, 115.2, 42.1, 24.1; IR (KBr): 3294, 2966, 2804, 2687, 1714, 1468, 1292, 1167, 1104, 846, 647 cm^{-1}; HRMS (EI) calculated for $C_{15}H_{13}ClN_2O_2$: 288.0666, found: 288.0668.

*3.2.17. 3-Hydroxy-3-{(6-methylpyridin-2-yl)methyl}-5-nitroindolin-2-one (**3q**).* Yield 71%; a yellow solid; mp 206–208 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 10.88 (1H, s), 8.11 (1H, dd, J=8.7, 2.4 Hz), 7.82 (1H, d, J=2.4 Hz), 7.51 (1H, t, J=7.8 Hz), 7.00 (2H, t, J=6.0 Hz), 6.89 (1H, d, J=8.7 Hz), 6.53 (1H, s), 3.42 (1H, d, J=13.8 Hz), 3.24 (1H, d, J=13.8 Hz), 2.20 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6): δ 179.0, 156.4, 154.7, 148.6, 141.5, 136.4, 132.2, 126.0, 121.2, 120.9, 120.4, 109.3, 75.1, 44.1, 23.5; IR (KBr): 3298, 2976, 1722, 1616, 1527, 1466, 1335, 1168, 1104, 637 cm^{-1}; HRMS (EI) calculated for $C_{15}H_{13}N_3O_4$: 299.0906, found: 299.0906.

*3.2.18. 3-Hydroxy-5-nitro-3-(pyridin-2-ylmethyl)indolin-2-one (**3r**).* Yield 70%; a yellow solid; mp 221–223 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 10.87 (1H, s), 8,25 (1H, d, J=3.9 Hz), 8.09 (1H, dd, J=8.4, 2.1 Hz), 7.84 (1H, d, J=2.4 Hz), 7.62 (1H, td, J=7.5, 1.8 Hz), 7.19 (1H, d, J=7.8 Hz), 7.14–7.10 (1H, m), 6.86 (1H, d, J=8.7 Hz), 6.57 (1H, s), 3.47 (1H, d, J=13.5 Hz), 3.30 (1H, d, J=13.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.9, 155.3, 148.4, 141.6, 136.1, 132.0, 126.1, 124.4, 121.8, 120.3, 120.2, 109.4, 75.2, 44.6; IR (KBr): 3497, 3393, 1743, 1616, 1482, 1335, 1264, 1199, 1005, 834, 751 cm^{-1}; HRMS (EI) calculated for $C_{14}H_{11}N_3O_4$: 285.0750, found: 285.0748.

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