

## A new synthetic approach to oxindoles (1,3-dihydro-2H-indol-2-ones) by reductive dephosphorylation with hydroiodic acid of 3-(diethylphosphoryloxy)-oxindoles, derived from isatins (1H-Indole-2,3-diones)

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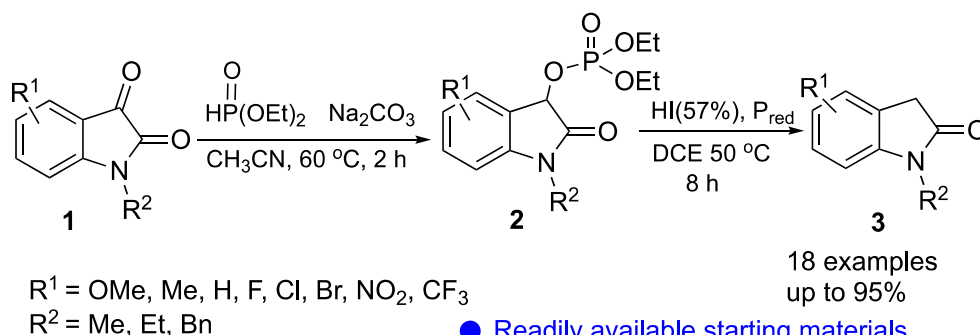
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### Abstract

A novel method for the synthesis of 3-unsubstituted oxindoles by the reductive dephosphorylation of 3-(diethylphosphoryloxy)oxindoles with hydroiodic acid was developed. This synthetic strategy involved a two-step procedure including a phospho-Brook rearrangement of isatins with diethyl phosphite and a reductive dephosphorylation of the phosphorylated oxindoles.

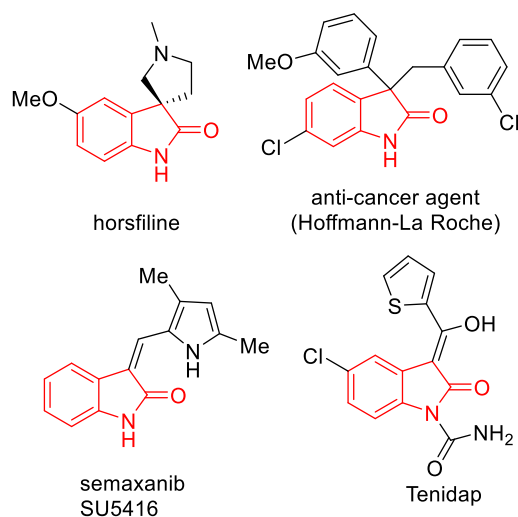


- Readily available starting materials
- Wide substrate scope
- Mild reaction condition

**Keywords:** 3-Phosphate-substituted oxindoles, hydroiodic acid, reductive dephosphorylation, isatins

## Introduction

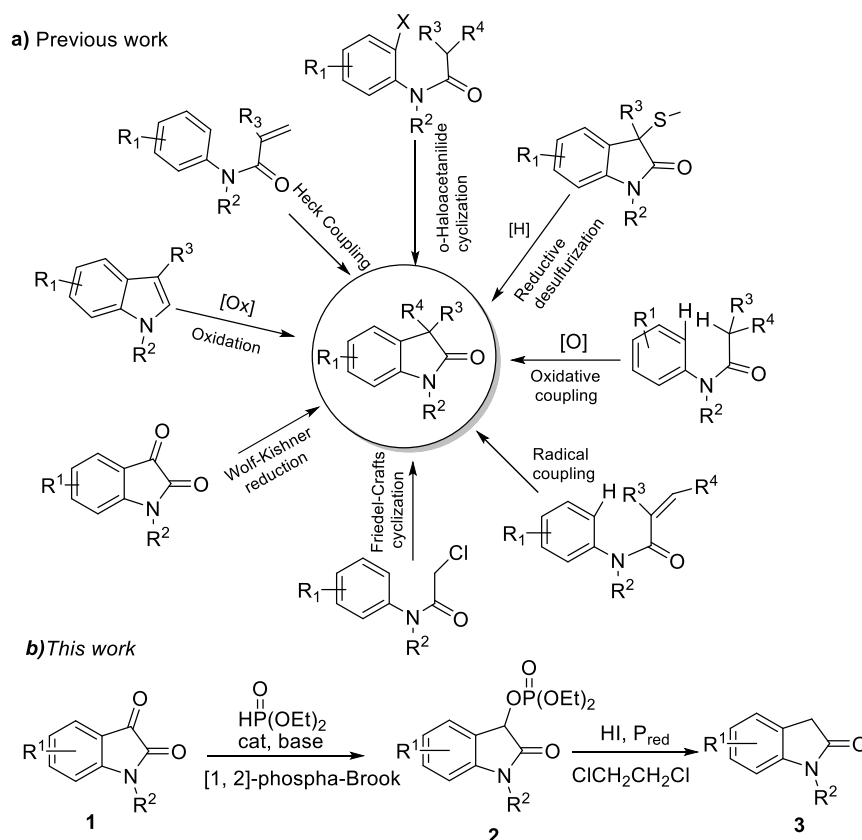
Oxindoles (1,3-dihydro-2*H*-indol-2-ones) are a privileged structural motif, which not only occur widely in bioactive natural products and pharmaceuticals<sup>1-6</sup> but are also used as synthetic intermediates for various organic transformations<sup>7-12</sup> (Figure1). Many synthetic strategies have been established to access this skeleton, including the oxidation of indoles,<sup>13-15</sup> transition metal-catalyzed Heck-type reactions of acrylamides,<sup>16-24</sup> metal-catalyzed cyclization of *o*-haloacetanilides,<sup>25-29</sup> reductive desulfurization of 3-methylthiooxindoles,<sup>30,31</sup> double C–H oxidative coupling of functionalized acetanilides,<sup>32-39</sup> the C–H oxidative radical coupling of acrylanilides,<sup>40-43</sup> and so on (Scheme 1). Regrettably, all of the aforementioned methods inherently require a specifically functionalized precursor such as the presence of an *ortho*-halogen, an amino group and the functionalizations at the pseudobenzyl position. Thus, a laborious synthetic sequence may be required to prepare the appropriate precursors. A classical approach to the oxindole framework that circumvents the need for such functionalization is Wolf–Kishner reduction of the corresponding isatins,<sup>44,45</sup> and intramolecular Friedel–Crafts cyclization of *o*-chloroacetanilides,<sup>46,47</sup> which provide very practical access to 3-unsubstituted oxindoles (Scheme 1(a)). Despite the advantages outlined above, as a versatile intermediate in synthesis, the new synthetic method for 3-unsubstituted oxindoles has scarcely been explored. Accordingly, the development of efficient synthetic method for such a versatile synthon is of great importance.



**Figure 1** Pharmaceutically relevant oxindoles

Recently, our group<sup>48</sup> developed an efficient method for the synthesis of 3-monohalo-oxindoles by the acidolysis of isatin-derived 3-phosphate-substituted oxindoles with haloid acids. In the course of our research, when we attempted the acidic hydrolysis reaction using hydroiodic acid 57% aqueous solution, to our surprise, the reaction delivered the hydrogenolytic reduction of the phosphate, instead of the nucleophilic substitution by iodine anions. Despite the known reduction of benzylic alcohols, aromatic nitro and  $\alpha$ -hydroxy carbonyl compounds by hydriodic acid,<sup>49-51</sup> the hydrogenolytic reduction of phosphates by hydriodic acid as a potential pathway to the preparation of oxindoles remained unexplored. Inspired by the significant finding, and as a part of our long-standing research on the development of new methodologies for the synthesis of the oxindole derivatives,<sup>52-56</sup> we herein propose a new method for the synthesis of 3-unsubstituted oxindoles involving reductive dephosphorylation of phosphates-tethered oxindoles, diethyl 2-oxindolin-3-yl phosphates

**2**, derived from isatins, with hydriodic acid. The diethyl 2-oxoindolin-3-yl phosphates **2** were prepared by employing a base-catalyzed phospho-Brook rearrangement of isatins with diethyl phosphite<sup>57,58</sup> (Scheme 1(b)).



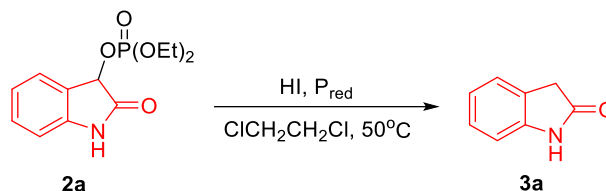
**Scheme 1** Methods for the synthesis of oxindoles

## Results and Discussion

The unexpected finding detailed above prompted us to further investigate the reaction, choosing diethyl (2-oxoindolin-3-yl) phosphate **2a** as model substrates under various conditions. Initially, we attempted the reductive dephosphorylation of diethyl (2-oxoindolin-3-yl) phosphate **2a** with hydroiodic acid (57%, 3 equiv.) in CH<sub>3</sub>CN at 50 °C (Table 1, entry 1), but the desired product **3a** was obtained in only 31% yield. To improve the yield of product **3a**, a series of solvents including MeOH, THF, toluene, DCE, 1,4-dioxane and DCM were screened (Table 1, entries 2-7), and dichloroethane was found to be superior (entry 6 vs entries 1-5,7), giving rise to a slightly higher yield (60%) of **3a**. After a solvent screen, we switched to the amount of hydroiodic acid, which was increased from 3 to 5 equiv., improving the yield to 75% after 8 hours (Table 1 entry 8), but further increasing relative loading led to almost an equal result (Table 1, entry 9). Considering the details of the HI reduction reaction, iodine, generated possibly by the oxidation of the iodide (I<sup>-</sup>), might be recycled by the reduction with red phosphorus, regenerating hydriodic acid. We then sought to examine the effects of the added red phosphorus as a reducing agent on the reductive dephosphorylation. With the use of added red phosphorus as a reducing agent, the yield of the desired product **3a** markedly increased to 88% (Table 1, entry 10). Increasing the P<sub>red</sub> amount to the molar ratio of 0.4/2.5 mmol did not further improve the yield of **3a** (Table 1, entry 11). Next, both prolongation (10 h) and shortening (6 h) of the reaction time did not give a satisfactory yield of oxindole **3a** (Table 1, entries 12,13). Finally, attempts to vary the reaction temperature,

lowering the temperature to 30 °C gave 67% yield of **3a** (Table 1, entry 14), whereas raising the temperature to 70 °C provided product **3a** in 64% yield (Table 1, entry 15). Considering all of reaction parameters, the optimal reaction conditions were chosen as summarized in Table 1, entry 10.

**Table 1.** Optimization studies<sup>a</sup>



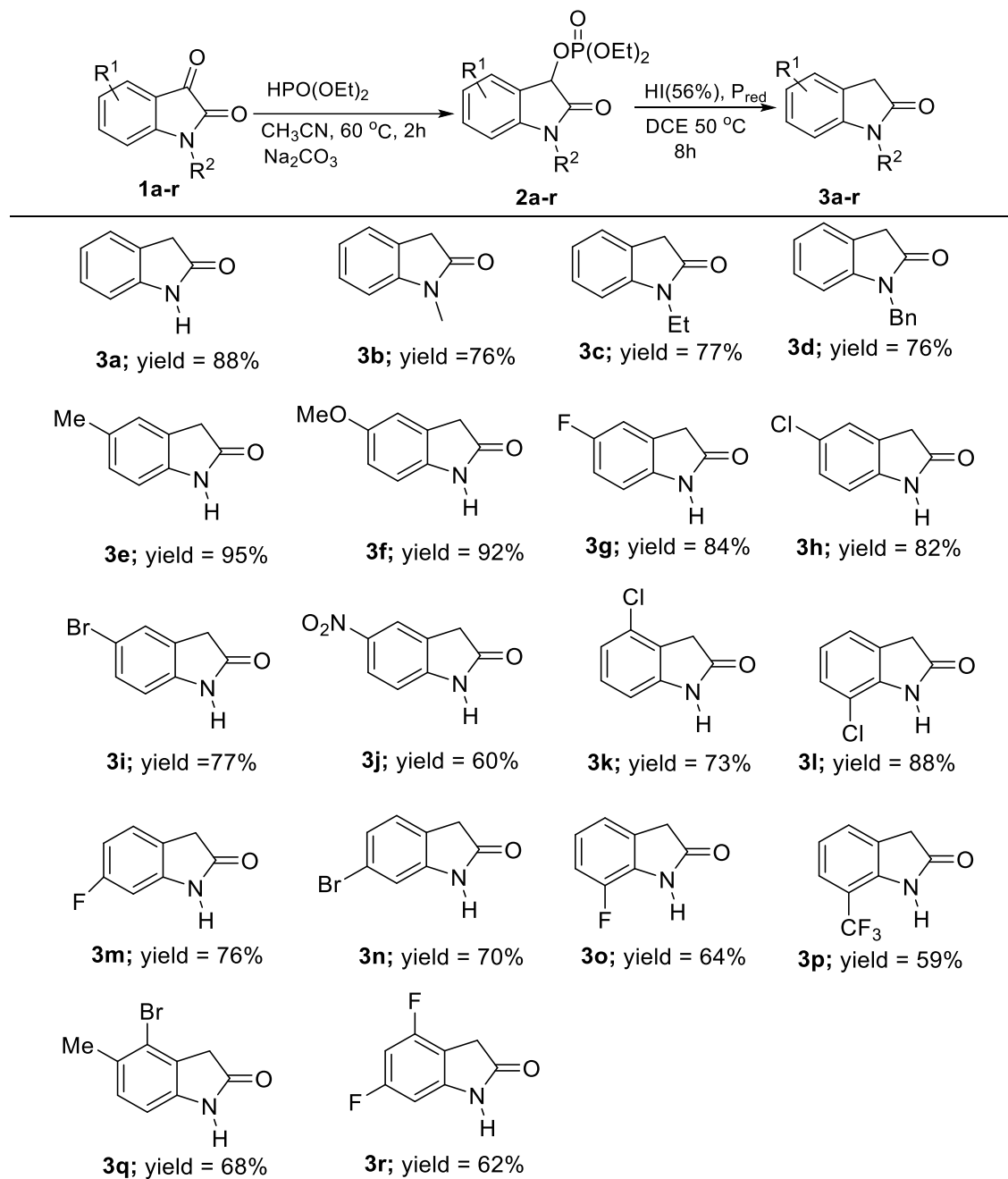
Entry	Additive (x mmol)	Solvent	HI (y equiv.)	Temp (°C)	Time (h)	Yield <sup>b</sup> (%)
1	None	CH <sub>3</sub> CN	3	50	8	31
2	None	MeOH	3	50	8	57
3	None	THF	3	50	8	33
4	None	Toluene	3	50	8	55
5	None	DCM	3	50	8	45
6	None	DCE	3	50	8	60
7	None	1,4-dioxane	3	50	8	35
8	None	DCE	5	50	8	75
9	None	DCE	7	50	8	74
10	P <sub>red</sub> (0.2)	DCE	5	50	8	88
11	P <sub>red</sub> (0.4)	DCE	5	50	8	88
12	P <sub>red</sub> (0.2)	DCE	5	50	10	85
13	P <sub>red</sub> (0.2)	DCE	5	50	6	76
14	P <sub>red</sub> (0.2)	DCE	5	30	8	67
15	P <sub>red</sub> (0.2)	DCE	5	70	8	64

<sup>a</sup>Reaction conditions: **2a** (0.5 mmol), hydroiodic acid (57%) (y equiv.), red phosphorus (x mmol), solvent (2 mL). <sup>b</sup>Isolated yield.

Using the optimal reaction conditions, we prepared a series of substituted diethyl (2-oxoindolin-3-yl) phosphates **2a–r** from various substituted isatins **1a–r** under base-catalyzed phospho-Brook rearrangement conditions for evaluating the substrate **2** scope and limitations (Scheme 2). In general, diethyl (2-oxoindolin-3-yl) phosphates **2** whether bearing electron-withdrawing or electron-donating groups on the aromatic ring, reacted successfully with hydroiodic acid affording the corresponding oxindoles in moderate to good yields (59–95%). More importantly, 2-oxoindolin-3-yl-phosphates **2e**, **2f** bearing electron-donating substituents such as methyl, methoxy were more reactive than those bearing electron-withdrawing groups, **2j**, **2p** such as nitro, trifluoromethyl and gave rise to products **3e**, **3f** in higher yields (95%, 92%) than **3j**, **3p** (60%, 59%). Notably, the position of the fluorine substituent on the phenyl rings of the oxindole moieties had an obvious effect on the reactivity because fluorine substituents at 5,6-positions of the oxindole moieties led to higher yields than

those at 7-position (Scheme 2, **3g**, **3m** vs **3o**), while the effects of the substitution pattern of the chlorine and bromine groups on the reactivity seemingly appear to be small because corresponding products (Scheme 2, **3h**, **3i**, **3k**, **3l**, **3n**) were obtained in similar yields (70 – 88%). The substrates **2q**, **2r** bearing two substituents on the phenyl rings were also examined and afforded products **3** (Scheme 2 **3q**, **3r**) in moderate yields (62–68%). In addition, N-protected 2-oxoindolin-3-yl-phosphates **2** was also found to be suitable for the transformation and gave their respective products **3b-3d** in good yields (76–77%; Scheme 2).

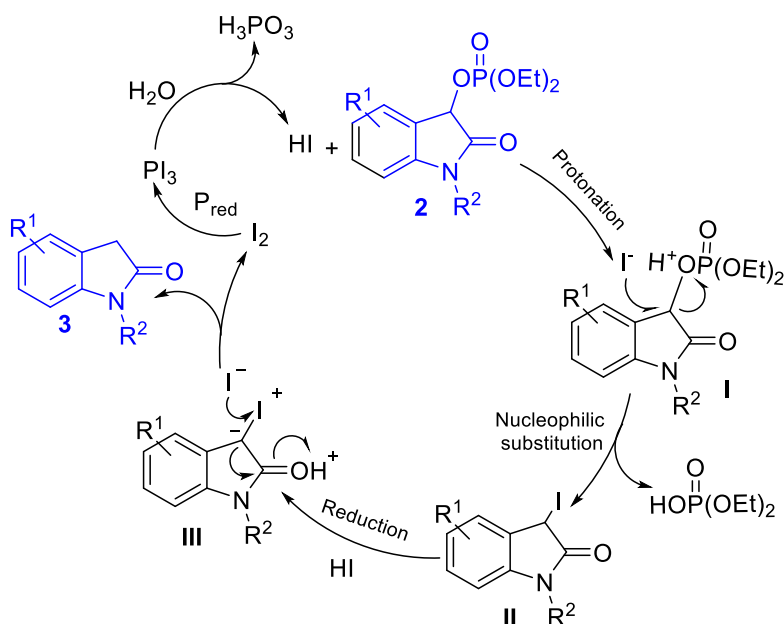
**Scheme 2.** Substrate scope of the reductive dephosphorylation of phosphates **2**<sup>a</sup>



<sup>a</sup>Standard reaction conditions: **2a-2r** (0.5 mmol), hydroiodic acid (2.5 mmol, 5 equiv), red phosphorus (0.2 mmol),  $\text{ClCH}_2\text{CH}_2\text{Cl}$  (2 ml),  $50\text{ }^\circ\text{C}$ , 8 h. Isolated yields are given.

To show the utility of this novel method, we performed a 10 mmol large-scale reaction (Scheme 2, **3a**). This larger-scale reaction took place smoothly to give product **3a** in 88% yield under the standard conditions, which was similar to the result of the small-scale reaction, and column chromatography separation was not usually required. This outcome indicated that the transformation could be applicable for larger-scale synthesis of oxindoles **3**. In addition, the structures of all products **3** were unambiguously assigned by  $^1\text{H}$  and  $^{13}\text{C}$  NMR, and HRMS. Especially, the proton at the C-3-position of oxindoles gave diagnostic singlets (3.38- 3.67Hz) instead of double peaks due to the absence of coupling with phosphorus atoms in their  $^1\text{H}$  NMR spectra. This indicated that the hydrogenolytic reduction of the dephosphorylation with hydroiodic acid had occurred.

A plausible mechanism based on the literature<sup>50,51</sup> is proposed (Scheme 3). Initially, the C–O bond at the C-3 position of the diethyl-(2oxindolin-3-yl) phosphates **2** was activated by the protonation by hydroiodic acid. Subsequently, the phosphate moiety as the leaving group was replaced by iodine ion to form 3-iodoindolin-2-one **II**, which is followed by the hydrogenolytic reduction with hydroiodic acid to provide reduction products, oxindoles **3** and accompanied by the oxidation of  $\text{I}^-$  to  $\text{I}_2$ . Finally, the iodine would be reduced by red phosphorus to phosphorus triiodide, which was hydrolyzed to regenerate hydroiodic acid in the presence of water.



**Scheme 3.** Plausible reaction mechanism

## Conclusions

In conclusion, a new method for the synthesis of 3-unsubstituted oxindoles via reductive dephosphorylation of oxindole-3-phosphates, diethyl (2-oxindolin-3-yl) phosphates, with the hydroiodic acid was developed. The present methodology involves a two-step procedure including the preparation of diethyl (2-oxindolin-3-yl) phosphates *via* a base-catalyzed phospho-Brook rearrangement of isatins with diethyl phosphite and a hydrogenolytic reduction of the phosphorylated oxindoles. This methodology features mild reaction conditions, simple operation, good yields, readily available and inexpensive starting materials, and make this protocol a valuable method for the preparation of various 3-unsubstituted oxindoles in large-scale industrial application.

## Experimental Section

**General.** The reactions were monitored by thin layer chromatography (TLC) using silica gel GF254. All compounds were fully characterized by spectroscopic data. The NMR spectra were recorded on a Bruker Avance III (1H: 400 MHz, <sup>13</sup>C: 100 MHz, <sup>19</sup>F NMR: 377 MHz, <sup>31</sup>P: 162 MHz), chemical shifts ( $\delta$ ) are expressed in ppm, and *J* values are given in Hz. CDCl<sub>3</sub> and DMSO-*d*<sub>6</sub> were used as solvents. High resolution mass spectra (HRMS) were recorded on LCMS-IT-TOF. All chemicals and solvents were used as received without further purification unless otherwise stated. Column chromatography was performed on silica gel (200–300 mesh).

### General procedure for preparation of targeted molecules

To a 10 mL screw-cap glass vial, diethyl (2-oxoindolin-3-yl) phosphate **2** (0.5 mmol), concentrated hydroiodic acid (0.35 mL, 57%, 2.5 mmol), red phosphorus (0.0062 mg, 0.2 mmol), and ClCH<sub>2</sub>CH<sub>2</sub>Cl (2 mL) were added. The reaction mixture was stirred at 50 °C in a preheated oil bath until the completion of reaction after 8 h. The solvent was evaporated under vacuum and the residue mixture was directly purified by flash column chromatography on silica gel to get the product **3**.

**Indolin-2-one (3a).** White solid; mp: 116-117 °C (58.6 mg, 88%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.42 (s, 1H), 7.13 (d, *J* 7.3 Hz, 2H), 6.93 (t, *J* 7.5 Hz, 1H), 6.83 (d, *J* 7.8 Hz, 1H), 3.46 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  178.6, 142.8, 128.0, 125.4, 124.6, 122.4, 110.0, 36.5. **HRMS (ESI):** *m/z* calcd for C<sub>8</sub>H<sub>7</sub>NO [M-H]<sup>+</sup>: 132.0455; found: 132.0445.

**1-Methylindolin-2-one (3b).** Yellow solid; mp: 78-79 °C (55.9 mg, 76%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.15 (m, 2H), 6.93 (t, *J* 7.5 Hz, 1H), 6.70 (d, *J* 7.8 Hz, 1H), 3.38 (s, 2H), 3.09 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  175.0, 145.1, 127.8, 124.4, 124.2, 122.3, 108.0, 35.6, 26.1. **HRMS (ESI):** *m/z* calcd for C<sub>9</sub>H<sub>9</sub>NO [M+H]<sup>+</sup>: 148.0757; found: 148.0755.

**1-Ethylindolin-2-one (3c).** White solid; mp: 100-101 °C (62.1 mg, 77%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.16 (m, 2H), 6.93 (t, *J* 7.9 Hz, 1H), 6.75 (d, *J* 7.8 Hz, 1H), 3.67 (q, *J* 7.2 Hz, 2H), 3.40 (s, 2H), 1.17 (t, *J* 7.2 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.7, 144.3, 127.8, 124.7, 124.5, 122.1, 108.2, 35.8, 34.6, 12.7. **HRMS (ESI):** *m/z* calcd for C<sub>10</sub>H<sub>11</sub>NO [M+H]<sup>+</sup>: 162.0913; found: 162.0911.

**1-Benzylindolin-2-one (3d).** Yellow oil (84.7 mg, 76%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.16 (m, 6H), 7.02 (t, *J* 7.7 Hz, 1H), 6.86 (t, *J* 7.4 Hz, 1H), 6.59 (d, *J* 7.8 Hz, 1H), 4.77 (s, 2H), 3.46 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  175.1, 144.2, 135.9, 128.7 (2C), 127.7, 127.5, 127.3 (2C), 124.4, 124.3, 122.3, 109.0, 43.6, 35.7. **HRMS (ESI):** *m/z* calcd for C<sub>15</sub>H<sub>13</sub>NO [M+H]<sup>+</sup>: 224.1070; found: 224.1068.

**3,5-Dichloroindolin-2-one (3e).** White solid; mp: 164-165 °C (69.9 mg, 95%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  10.26 (s, 1H), 6.96 (m, 2H), 6.69 (d, *J* 7.8 Hz, 1H), 3.43 (s, 2H), 2.22 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  176.4, 141.2, 130.0, 127.7, 125.9, 125.1, 108.9, 35.8, 20.7. **HRMS (ESI):** *m/z* calcd for C<sub>9</sub>H<sub>9</sub>NO [M-H]<sup>+</sup>: 146.0611; found: 146.0600.

**5-Methoxyindolin-2-one (3f).** Brown solid; mp: 138-139 °C (75.1 mg, 92%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  10.18 (s, 1H), 6.85 (s, 1H), 6.71 (s, 2H), 3.68 (s, 3H), 3.42 (s, 2H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  176.2, 154.6, 137.0, 127.1, 112.2, 111.5, 109.3, 55.4, 36.2. **HRMS (ESI):** *m/z* calcd for C<sub>9</sub>H<sub>9</sub>NO<sub>2</sub> [M-H]<sup>+</sup>: 162.0561; found: 162.0551.

**5-Fluoroindolin-2-one (3g).** White solid; mp: 133-134 °C (63.5 mg, 84%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  10.37 (s, 1H), 7.07 (d, *J* 8.5 Hz, 1H), 6.97 (t, *J* 10.5 Hz, 1H), 6.77 (m, 1H), 3.48 (s, 2H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  176.2, 157.8 (d, *J*<sub>FC</sub> 235.6 Hz), 139.9, 127.7, 113.6 (d, *J* 23.2 Hz), 112.2 (d, *J* 24.6 Hz), 109.6 (d, *J* 8.3 Hz), 36.2.

**<sup>19</sup>F NMR** (377 MHz, DMSO-*d*<sub>6</sub>) δ -121.01 (s). **HRMS (ESI)**: *m/z* calcd for C<sub>8</sub>H<sub>6</sub>FNO [M-H]<sup>+</sup>: 150.0361; found: 150.0349.

**5-Chloroindolin-2-one (3h)**. Brown solid; mp: 184-185 °C (68.7 mg, 82%). **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.47 (s, 1H), 7.19 (m, 2H), 6.78 (d, *J* 8.2 Hz, 1H), 3.47 (s, 2H). **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) δ 172.0, 141.9, 132.3, 130.9, 126.0, 122.4, 109.3, 53.5, 21.4. **HRMS (ESI)**: *m/z* calcd for C<sub>8</sub>H<sub>6</sub>ClNO [M-H]<sup>+</sup>: 166.0065; found: 166.0054.

**5-Bromoindolin-2-one (3i)**. Brown solid; mp: 198-199 °C (81.6 mg, 77%). **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.46 (s, 1H), 7.31 (s, 2H), 6.74 (s, 1H), 3.47 (s, 2H). **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) δ 175.9, 130.1, 128.5, 127.2, 112.8, 110.9, 35.8. **HRMS (ESI)**: *m/z* calcd for C<sub>8</sub>H<sub>6</sub>BrNO [M-H]<sup>+</sup>: 209.9560; found: 209.9550.

**5-Nitroindolin-2-one (3j)**. Brown solid; mp: 231-232 °C (53.4 mg, 60%). **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.53 (s, 1H), 7.27 (s, 1H), 7.22 (d, *J* 7.8 Hz, 1H), 6.96 (d, *J* 7.8 Hz, 1H), 3.67 (s, 2H). **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.8, 150.3, 141.8, 127.1, 125.0, 120.1, 109.0, 35.7. **HRMS (ESI)**: *m/z* calcd for C<sub>8</sub>H<sub>6</sub>N<sub>2</sub>O<sub>3</sub> [M-H]<sup>+</sup>: 177.0306; found: 177.0297.

**4-Chloroindolin-2-one (3k)**. Yellow solid; mp: 206-207 °C (61.2 mg, 73%). **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.59 (s, 1H), 7.19 (t, *J* 8.0 Hz, 1H), 6.96 (d, *J* 8.2 Hz, 1H), 6.77 (d, *J* 7.7 Hz, 1H), 3.48 (s, 2H). **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) δ 175.2, 145.1, 129.4, 129.0, 124.2, 121.0, 108.0, 35.3. **HRMS (ESI)**: *m/z* calcd for C<sub>8</sub>H<sub>6</sub>ClNO [M-H]<sup>+</sup>: 166.0065; found: 166.0054.

**7-Chloroindolin-2-one (3l)**. Brown solid; mp: 168-169 °C (73.7 mg, 88%). **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.76 (s, 1H), 7.21 (d, *J* 8.2 Hz, 1H), 7.15 (d, *J* 7.2 Hz, 1H), 6.93 (t, *J* 7.8 Hz, 1H), 3.58 (s, 2H). **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.1, 141.3, 127.7, 127.4, 123.0, 122.4, 113.3, 36.5. **HRMS (ESI)**: *m/z* calcd for C<sub>8</sub>H<sub>6</sub>ClNO [M-H]<sup>+</sup>: 166.0065; found: 166.0055.

**6-Fluoroindolin-2-one (3m)**. Brown solid; mp: 128-129 °C (57.4 mg, 76%). **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.49 (s, 1H), 7.17 (m, 1H), 6.69 (t, *J* 8.0 Hz, 1H), 6.61 (d, *J* 9.3 Hz, 1H), 3.42 (s, 2H). **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.8, 161.9 (d, *J* 240.5 Hz), 145.1 (d, *J*<sub>F-C</sub> 12.2 Hz), 123.5 (m), 107.1 (d, *J* 22.1 Hz), 97.3 (d, *J* 26.9 Hz), 35.2. **<sup>19</sup>F NMR** (377 MHz, DMSO-*d*<sub>6</sub>) δ -114.14 (s). **HRMS (ESI)**: *m/z* calcd for C<sub>8</sub>H<sub>6</sub>FNO [M-H]<sup>+</sup>: 150.0361; found: 150.0349.

**6-Bromoindolin-2-one (3n)**. Brown solid; mp: 204-205 °C (74.2 mg, 70%). **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.48 (s, 1H), 7.10 (m, 2H), 6.93 (s, 1H), 3.42 (s, 2H). **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.2, 145.4, 126.2, 125.2, 123.6, 119.9, 111.9, 35.4. **HRMS (ESI)**: *m/z* calcd for C<sub>8</sub>H<sub>6</sub>BrNO [M-H]<sup>+</sup>: 209.9560; found: 209.9549.

**7-Fluoroindolin-2-one (3o)**. Yellow solid; mp: 179-180 °C (48.3 mg, 64%). **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.84 (s, 1H), 7.06 (dd, *J* 12.8, 8.7 Hz, 2H), 6.92 (m, 1H), 3.54 (s, 2H). **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.6, 146.6 (d, *J*<sub>F-C</sub> 241.2 Hz), 131.0 (d, *J* 12.0 Hz), 129.4, 122.4, 120.9, 114.9 (d, *J* 17.1 Hz), 36.4. **<sup>19</sup>F NMR** (377 MHz, DMSO-*d*<sub>6</sub>) δ -133.26 (s). **HRMS (ESI)**: *m/z* calcd for C<sub>8</sub>H<sub>6</sub>FNO [M-H]<sup>+</sup>: 150.0361; found: 150.0349.

**3-Chloro-1-methylindolin-2-one (3p)**. Yellow solid; mp: 182-183 °C (59.3 mg, 59%). **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.83 (s, 1H), 7.44 (m, 2H), 7.08 (t, *J* 7.7 Hz, 1H), 3.57 (s, 2H). **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) δ 177.3, 141.3, 128.7, 128.4, 124.2 (d, *J* 4.5 Hz), 124.2 (d, *J*<sub>F-C</sub> 269.8 Hz), 121.6, 110.7 (d, *J* 32.7 Hz), 35.4. **<sup>19</sup>F NMR** (377 MHz, DMSO-*d*<sub>6</sub>) δ -60.17 (s). **HRMS (ESI)**: *m/z* calcd for C<sub>9</sub>H<sub>6</sub>F<sub>3</sub>NO [M-H]<sup>+</sup>: 200.0329; found: 200.0318.

**4-Bromo-5-methylindolin-2-one (3q)**. White solid; mp: 229-230 °C (76.8 mg, 68%). **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.51 (s, 1H), 7.14 (s, 1H), 6.72 (s, 1H), 3.40 (s, 2H), 2.27 (s, 3H). **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) δ 175.0, 142.3, 129.6, 129.2, 126.9, 120.6, 108.2, 37.7, 21.6. **HRMS (ESI)**: *m/z* calcd for C<sub>9</sub>H<sub>8</sub>BrNO [M-H]<sup>+</sup>: 223.9717; found: 223.9708.

**4,6-Difluoroindolin-2-one (3r)**. Yellow solid; mp: 182-183 °C (52.4 mg, 62%). **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.73 (s, 1H), 6.71 (t, *J* 10.9 Hz, 1H), 6.51 (d, *J* 10.7 Hz, 1H), 3.49 (s, 2H). **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) δ 175.8, 162.3 (dd, *J*<sub>F-C</sub> 242.8, 13.2 Hz), 157.4 (dd, *J*<sub>F-C</sub> 245.1, 14.9 Hz), 146.5 (dd, *J* 14.7, 12.5 Hz), 107.4 (dd, *J* 22.0, 3.3



H<sub>z</sub>), 96.2 (m), 94.2 (dd, *J* 27.1, 3.6 Hz), 32.2. <sup>19</sup>F NMR (377 MHz, DMSO-*d*<sub>6</sub>) δ -110.55 (s), -114.53 (s). HRMS (ESI): *m/z* calcd for C<sub>15</sub>H<sub>11</sub>F<sub>2</sub>NO [M-H]<sup>+</sup>: 258.0736; found: 258.0727.

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## Supplementary Material

Supplementary data associated with this article is available in the Supplementary Material

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