# Supporting Information

**Multicomponent Synthesis of Isoindolinones by Rh\(^{\text{III}}\) Relay Catalysis:**

**Synthesis of Pagoclone and Pazinaclone from Benzaldehyde**

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General Information:

$^1$H NMR and $^{13}$C NMR spectra were recorded on BRUKER AVANCE III 600 spectrometer. DMSO-$d_6$ and CDCl$_3$ were used as solvent. Chemical shifts were referenced relative to residual solvent signal (DMSO-$d_6$: $^1$H NMR: $\delta$ 2.50 ppm, $^{13}$C NMR: $\delta$ 39.52 ppm; CDCl$_3$: $^1$H NMR: $\delta$ 7.26 ppm, $^{13}$C NMR: $\delta$ 77.16 ppm). The following abbreviations are used to describe peak patterns where appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants ($J$) are reported in Hertz (Hz). HRMS were performed on AB Sciex LC 30A-Triple TOF 4600 apparatus (ESI). Melting points were measured with micro melting point apparatus.

Unless otherwise noted, materials (1, 2 and 3) obtained from commercial suppliers were used directly without further purification. Amide 7 was prepared in our own way. Amide 11 and olefin 3i were prepared according to the literature.$^{1, 2}$
Scopes of Olefin and Aniline

**olefin:**

- $\text{CO}_2\text{Et}$
- $\text{CO}_2\text{Bu}$
- $\text{CO}_2\text{"Bu}$
- $\text{CN}$

- $3a$
- $3b$
- $3c$
- $3d$

- $3e$
- $3f$
- $3g$
- $3h$

- $3i$
- $3j$

**amide:**

- $2a$
- $2b$
- $2c$

- $2d$
- $2e$
- $2f$
General Procedure for Synthesis of Isoindolinones 4 or 5:

To a 25 mL tube equipped with a magnetic stir bar, 1a (106 mg, 1.0 mmol, 1.0 equiv.), 2a (141 mg, 1.5 mmol, 1.5 equiv.), 3a (200 mg, 2.0 mmol, 2.0 equiv.), [RhCp*Cl₂]₂ (15 mg, 2.5 mol %), Cu(OAc)₂ (362 mg, 2.0 mmol, 2.0 equiv.), CH₃CN (super dry, 10.0 mL) were added under N₂ atmosphere. The sealed tube was stirred at 80 °C for 8-10 h, and then was cooled to room temperature. The solution was diluted with ethyl acetate and transferred to a round bottom flask. Silica was added to the flask, and volatiles were evaporated under vacuum. The purification was performed by flash column chromatography on a silica gel using ethyl acetate/petroleum ether (v/v, 1:5) as the eluent to give isoindolinone products 4a with the yield of 90% (267 mg).

Characterization of Products 4, 5, 6 or 8:

**Ethyl 2-(3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (4a):** 54 mg, 91% yield; White solid; m.p. 123-125 °C; ¹H NMR (CDCl₃, 600 MHz), δ 8.51 (d, J = 8.4 Hz, 1H), 8.37 (dd, J₁ = 4.8 Hz, J₂ = 1.2 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.74-7.70 (m, 1H), 7.57-7.54 (m, 2H), 7.48-7.44 (m, 1H), 7.03 (dd, J₁ = 7.2 Hz, J₂ = 5.4 Hz, 1H), 5.94 (dd, J₁ = 7.8 Hz, J₂ = 3.6 Hz, 1H), 4.07-4.01 (m, 2H), 3.32 (dd, J₁ = 15.6 Hz, J₂ = 3.6 Hz, 1H), 2.76 (dd, J₁ = 16.2 Hz, J₂ = 7.8 Hz, 1H), 1.10 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz), δ170.5, 167.5, 150.8, 147.7, 144.9, 137.9, 132.9, 131.9, 128.7, 124.2, 122.8, 119.5, 115.7, 60.6, 56.5, 38.0, 14.1; HRMS (ESI) (m/z): calcd for C₁₇H₁₇N₂O₃⁺([M+H]⁺), 297.1234; found 297.1242.
Ethyl 2-(6-methyl-3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (4b): 59 mg, 95% yield; Yellow solid; m.p. 89-91°C; \(^1\)H NMR (CDCl\(_3\), 600 MHz), \(\delta\) 8.54 (d, \(J = 8.4\) Hz, 1H), 8.44-8.36 (m, 1H), 7.85-7.70 (m, 2H), 7.39 (s, 1H), 7.31 (d, \(J = 7.2\) Hz, 1H), 7.08-7.04 (m, 1H), 5.93 (dd, \(J_1 = 8.0\) Hz, \(J_2 = 3.6\) Hz, 1H), 4.15-4.04 (m, 2H), 3.33 (dd, \(J_1 = 16.0\) Hz, \(J_2 = 3.6\) Hz, 1H), 2.78 (dd, \(J_1 = 16.0\) Hz, \(J_2 = 8.0\) Hz, 1H), 2.47 (s, 3H), 1.17 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz), \(\delta\) 170.7, 167.7, 151.1, 147.7, 145.4, 143.8, 138.0, 129.8, 129.4, 124.1, 123.3, 119.4, 115.7, 60.7, 56.4, 38.2, 22.2, 14.2; HRMS (ESI) (m/z): calcd for C\(_{18}\)H\(_{19}\)N\(_2\)O\(_3\)\(^+\)([M+H]\(^+\)), 311.1390; found 311.1317.

Ethyl 2-(6-methoxy-3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (4c): 46 mg, 70% yield; Yellow solid; m.p. 116-117 °C; \(^1\)H NMR (CDCl\(_3\), 600 MHz), \(\delta\) 8.51 (d, \(J = 8.4\) Hz, 1H), 8.38 (s, 1H), 7.81 (d, \(J = 8.4\) Hz, 1H), 7.73 (t, \(J = 6.6\) Hz, 1H), 7.05-7.00 (m, 3H), 5.91 (dd, \(J_1 = 7.8\) Hz, \(J_2 = 3.6\) Hz, 1H), 4.25-3.98 (m, 2H), 3.87 (s, 3H), 3.35 (dd, \(J_1 = 16.2\) Hz, \(J_2 = 3.6\) Hz, 1H), 2.72 (dd, \(J_1 = 16.2\) Hz, \(J_2 = 8.4\) Hz, 1H), 1.17 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz), \(\delta\) 170.8, 167.4, 163.9, 151.1, 147.7, 147.5, 138.0, 125.8, 124.5, 119.3, 115.7, 115.5, 107.4, 60.8, 56.3, 55.8, 38.4, 14.2; HRMS (ESI) (m/z): calcd for C\(_{18}\)H\(_{19}\)N\(_2\)O\(_4\)\(^+\)([M+H]\(^+\)), 327.1340; found 327.1348.

Ethyl 2-(6-(methylthio)-3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (4d): 49 mg, 75% yield; Yellow solid; m.p. 68-70°C; \(^1\)H NMR (CDCl\(_3\), 600 MHz), \(\delta\) 8.51 (d, \(J = 8.0\) Hz, 1H), 8.38 (d, \(J = 3.6\) Hz, 1H), 7.78-7.70 (m, 2H), 7.39 (s, 1H), 7.31 (dd, \(J_1 = 8.4\) Hz, \(J_2 = 1.2\) Hz, 1H), 7.04 (dd, \(J_1 = 6.6\) Hz, \(J_2 = 4.8\) Hz, 1H), 5.92 (dd, \(J_1 = 8.4\) Hz, \(J_2 = 3.6\) Hz, 1H), 5.87 (dd, \(J_1 = 6.6\) Hz, \(J_2 = 4.8\) Hz, 1H), 5.00 (s, 1H), 4.49 (dd, \(J_1 = 11.8\) Hz, \(J_2 = 1.2\) Hz, 1H), 4.42 (dd, \(J_1 = 11.8\) Hz, \(J_2 = 4.8\) Hz, 1H), 3.87 (s, 3H), 3.35 (dd, \(J_1 = 16.2\) Hz, \(J_2 = 8.0\) Hz, 1H), 2.72 (dd, \(J_1 = 16.2\) Hz, \(J_2 = 8.4\) Hz, 1H), 1.17 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz), \(\delta\) 170.8, 167.4, 151.1, 147.7, 147.5, 138.0, 125.8, 124.5, 119.3, 115.7, 115.5, 107.4, 60.8, 56.3, 55.8, 38.4, 14.2; HRMS (ESI) (m/z): calcd for C\(_{18}\)H\(_{19}\)N\(_2\)O\(_4\)\(^+\)([M+H]\(^+\)), 327.1340; found 327.1348.
Hz, 1H), 4.12-4.07 (m, 2H), 3.34 (dd, \(J_1 = 16.2\) Hz, \(J_2 = 3.6\) Hz, 1H), 2.71 (dd, \(J_1 = 16.2\) Hz, \(J_2 = 7.8\) Hz, 1H), 2.52 (s, 3H), 1.16 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz), \(\delta\) 170.7, 167.2, 151.0, 147.8, 145.9, 145.8, 138.0, 128.5, 126.0, 124.4, 119.5, 119.2, 115.7, 60.8, 56.3, 38.2, 15.2, 14.2; HRMS (ESI) (m/z): calcd for C\(_{18}\)H\(_9\)N\(_2\)O\(_3\)S\(^+\)([M+H]\(^+\)), 343.1111; found 343.1122.

**Ethyl 2-(6-fluoro-3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (4e):** 46 mg; 73% yield; White solid; m.p. 106-108 °C; \(^1\)H NMR (CDCl\(_3\), 600 MHz), \(\delta\) 8.47 (d, \(J = 8.4\) Hz, 1H), 8.36 (d, \(J = 4.2\) Hz, 1H), 7.86 (dd, \(J_1 = 7.2\) Hz, \(J_2 = 4.8\) Hz, 1H), 7.75-7.69 (m, 1H), 7.28 (dd, \(J_1 = 7.2\) Hz, \(J_2 = 1.8\) Hz, 1H), 7.16 (td, \(J_1 = 9.0\) Hz, \(J_2 = 2.4\) Hz, 1H), 7.03 (dd, \(J_1 = 7.2\) Hz, \(J_2 = 4.8\) Hz, 1H), 5.92 (dd, \(J_1 = 7.8\) Hz, \(J_2 = 3.0\) Hz, 1H), 4.17-3.91 (m, 2H), 3.35 (dd, \(J_1 = 16.2\) Hz, \(J_2 = 3.0\) Hz, 1H), 2.72 (dd, \(J_1 = 16.8\) Hz, \(J_2 = 8.4\) Hz, 1H), 1.14 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz), \(\delta\) 170.4, 166.4, 165.8 (d, \(J = 252\) Hz), 150.7, 147.8, 147.6 (d, \(J = 10.5\) Hz), 138.0, 128.0, 126.4 (d, \(J = 10.5\) Hz), 119.6, 116.6 (d, \(J = 24\) Hz), 115.5, 110.5 (d, \(J = 25.5\) Hz), 60.8, 56.1 (d, \(J = 3\) Hz), 37.9, 14.1; HRMS (ESI) (m/z): calcd for C\(_{17}\)H\(_6\)FN\(_2\)O\(_3\)\(^+\)([M+H]\(^+\)), 315.1140; found 315.1147.

**Ethyl 2-(6-chloro-3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (4f):** 43 mg; 65% yield; Yellow solid; m.p. 108-110 °C; \(^1\)H NMR (CDCl\(_3\), 600 MHz), \(\delta\) 8.49 (d, \(J = 8.4\) Hz, 1H), 8.39 (d, \(J = 3.6\) Hz, 1H), 7.82 (d, \(J = 7.8\) Hz, 1H), 7.80-7.70 (m, 1H), 7.60 (s, 1H), 7.46 (dd, \(J_1 = 8.4\) Hz, \(J_2 = 1.8\) Hz, 1H), 7.06 (dd, \(J_1 = 6.6\) Hz, \(J_2 = 4.2\) Hz, 1H), 5.93 (dd, \(J_1 = 7.8\) Hz, \(J_2 = 3.0\) Hz, 1H), 4.12-4.08 (m, 2H), 3.35 (dd, \(J_1 = 16.2\) Hz, \(J_2 = 3.6\) Hz, 1H), 2.74 (dd, \(J_1 = 16.2\) Hz, \(J_2 = 8.4\) Hz, 1H), 1.16 (t, \(J = 7.12\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz), \(\delta\) 170.4, 166.5, 150.7, 147.8, 146.6, 139.3, 138.1, 130.5, 129.4, 125.5, 123.5, 119.8, 115.7, 60.9, 56.2, 37.8, 14.1; HRMS (ESI) (m/z): calcd for C\(_{18}\)H\(_9\)N\(_2\)O\(_3\)Cl\(^+\)([M+H]\(^+\)), 363.0820; found 363.0827. 
C_{17}H_{16}ClN_{2}O_{3}\text{/[M+H]}^{+}, 331.0844; found 331.0842.

**Ethyl 2-(6-bromo-3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (4g):** 64 mg; 85% yield; Yellow solid; m.p. 110-112 °C; $^1$H NMR (CDCl$_3$, 600 MHz), δ 8.48 (d, $J = 8.4$ Hz, 1H), 8.39 (dd, $J_1 = 2.8$ Hz, $J_2 = 1.2$ Hz, 1H), 7.79-7.71 (m, 3H), 7.62 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.2$ Hz, 1H), 7.07-7.04 (m, 1H), 5.93 (dd, $J_1 = 8.4$ Hz, $J_2 = 3.6$ Hz, 1H), 4.13-4.06 (m, 2H), 3.34 (dd, $J_1 = 16.2$ Hz, $J_2 = 3.6$ Hz, 1H), 2.74 (dd, $J_1 = 16.2$ Hz, $J_2 = 7.8$ Hz, 1H), 1.16 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz), δ 170.4, 166.6, 150.6, 147.9, 146.8, 138.1, 132.3, 130.9, 127.8, 126.5, 125.7, 119.8, 115.7, 60.9, 56.2, 37.8, 14.2; HRMS (ESI) (m/z): calcd for C$_{17}$H$_{16}$BrN$_2$O$_3$([M+H]$^+$), 375.0339; found 375.0343.

**Ethyl 2-(6-cyano-3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (4h):** 29 mg; 45% yield; Yellow solid; m.p. 153-155 °C; $^1$H NMR (CDCl$_3$, 600 MHz), δ 8.49 (d, $J = 8.4$ Hz, 1H), 8.42 (dd, $J_1 = 4.8$ Hz, $J_2 = 1.2$ Hz, 1H), 8.00 (d, $J = 4.2$ Hz, 1H), 7.96 (s, 1H), 7.81-7.75 (m, 2H), 7.11 (dd, $J_1 = 6.6$ Hz, $J_2 = 4.8$ Hz, 1H), 6.02 (dd, $J_1 = 8.4$ Hz, $J_2 = 4.8$ Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.40 (dd, $J_1 = 16.2$ Hz, $J_2 = 3.0$ Hz, 1H), 2.77 (dd, $J_1 = 16.2$ Hz, $J_2 = 8.4$ Hz, 1H), 1.16 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz), δ 170.2, 165.6, 150.3 148.0, 145.5, 138.3, 135.9, 132.7, 127.4, 125.1, 120.3, 118.2, 116.2, 115.9, 61.1, 56.5, 37.5, 14.2; HRMS (ESI) (m/z): calcd for C$_{18}$H$_{16}$N$_3$O$_3$([M+H]$^+$), 322.1186; found 322.1200.

**Methyl 3-(2-ethoxy-2-oxoethyl)-1-oxo-2-(pyridin-2-yl)isoindoline-5-carboxylate**
(4i): 58 mg; 82% yield; Yellow solid; m.p. 126-128 °C; ¹H NMR (CDCl₃, 600 MHz), δ 8.49 (d, J = 8.4 Hz, 1H), 8.39 (d, J = 3.6 Hz, 1H), 8.23 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.78-7.71 (m, 1H), 7.08-7.05 (m, 1H), 5.98 (dd, J₁ = 7.8 Hz, J₂ = 3.6 Hz, 1H), 4.07-4.02 (m, 2H), 3.93 (s, 3H), 3.32 (dd, J₁ = 16.2 Hz, J₂ = 3.6 Hz, 1H), 2.86 (dd, J₁ = 16.2 Hz, J₂ = 7.8 Hz, 1H), 1.11 (t, J = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz), δ 170.1, 166.5, 166.2, 150.6, 147.9, 144.8, 138.1, 135.9, 134.2, 130.1, 124.2, 124.2, 119.9, 115.8, 60.8, 56.6, 52.6, 37.7, 14.1; HRMS (ESI) (m/z): calcld for C₁₉H₁₉N₂O₅⁺([M+H]⁺), 355.1289; found 355.1301.

**Ethyl 2-(5-bromo-3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (4j):** 53 mg; 71% yield; Yellow solid; m.p. 74-75 °C; ¹H NMR (CDCl₃, 600 MHz), δ 8.49 (d, J = 8.4 Hz, 1H), 8.40 (d, J = 3.6 Hz, 1H), 8.02 (d, J = 1.8 Hz, 1H), 7.78-7.74 (m, 1H), 7.70 (dd, J₁ = 7.8 Hz, J₂ = 1.8 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.10-7.05 (m, 1H), 5.92 (dd, J₁ = 8.4 Hz, J₂ = 3.6 Hz, 1H), 4.11-4.03 (m, 2H), 3.34 (dd, J₁ = 16.2 Hz, J₂ = 3.6 Hz, 1H), 2.75 (dd, J₁ = 16.2 Hz, J₂ = 7.8 Hz, 1H), 1.15 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz), δ 170.1, 166.1, 150.6, 147.9, 143.7, 138.2, 135.9, 134.0, 127.4, 124.7, 122.8, 119.9, 115.9, 60.9, 56.4, 37.8, 14.2; HRMS (ESI) (m/z): calcld for C₁₇H₁₆BrN₂O₃⁺([M+H]⁺), 375.0339; found 375.0347.

**Ethyl 2-(5-methyl-3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (4k):** 37 mg; 60% yield; White solid; m.p. 95-96 °C; ¹H NMR (CDCl₃, 600 MHz), δ 8.53 (d, J = 8.4 Hz, 1H), 8.42-8.38 (m, 1H), 7.77-7.73 (m, 1H), 7.71 (s, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.41 (dd, J₁ = 7.8 Hz, J₂ = 0.6 Hz, 1H), 7.08-7.04 (m, 1H), 5.93 (dd, J₁ = 8.4 Hz, J₂ = 3.6 Hz, 1H), 4.10-4.06 (m, 2H), 3.33 (dd, J₁ = 16.2 Hz, J₂ = 4.2 Hz, 1H), 2.74 (dd, J₁ = 16.2 Hz, J₂ = 7.8 Hz, 1H), 2.45 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz), δ
Ethyl 2-(4-methyl-3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (4l): 19.5 mg; 31% yield; Yellow solid; m.p. 53-55°C; $^1$H NMR (CDCl$_3$, 600 MHz), $\delta$ 8.55 (d, $J = 7.2$ Hz, 1H), 8.44 (s, 1H), 7.79-7.75 (m, 1H), 7.48 (t, $J = 7.2$ Hz, 1H), 7.40 (d, $J = 7.2$ Hz, 1H), 7.29-7.2 (m, 1H), 7.15-7.00 (m, 1H), 5.95 (dd, $J_1 = 7.2$ Hz, $J_2 = 3.6$ Hz, 1H), 4.18-4.00 (m, 2H), 3.30 (dd, $J_1 = 15.6$ Hz, $J_2 = 3.6$ Hz, 1H), 2.81 (dd, $J_1 = 15.6$ Hz, $J_2 = 7.8$ Hz, 1H), 2.78 (s, 3H), 1.16 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz), $\delta$ 194.6, 170.6, 165.8, 164.0, 150.6, 147.7, 145.6, 138.6, 138.0, 132.7.0, 132.3, 130.3, 129.4, 127.3, 123.9, 119.7, 115.9, 113.9, 60.9, 56.7, 55.6, 38.1, 14.2; HRMS (ESI) (m/z): calcd for C$_{18}$H$_{19}$N$_2$O$_3$([M+H]$^+$), 311.1390; found 311.1389.

Ethyl 2-(4-(4-methoxybenzoyl)-3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (4m): 44 mg; 51% yield; Oil; $^1$H NMR (CDCl$_3$, 600 MHz), $\delta$ 8.40-8.35 (m, 2H), 7.81 (d, $J = 9.0$ Hz, 2H), 7.72-7.62 (m, 3H), 7.43 (d, $J = 7.2$ Hz, 1H), 7.03-7.01 (m, 1H), 6.90 (d, $J = 9.0$ Hz, 2H), 6.05 (dd, $J_1 = 7.8$ Hz, $J_2 = 3.6$ Hz, 1H), 4.15-4.10 (m, 2H), 3.83 (s, 3H), 3.38 (dd, $J_1 = 16.2$ Hz, $J_2 = 3.6$ Hz, 1H), 2.81 (dd, $J_1 = 16.2$ Hz, $J_2 = 7.8$ Hz, 1H), 1.19 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz), $\delta$ 194.6, 170.6, 165.8, 164.0, 150.6, 147.7, 145.6, 138.6, 138.0, 132.7.0, 132.3, 130.3, 129.4, 127.3, 123.9, 119.7, 115.9, 113.9, 60.9, 56.7, 55.6, 38.1, 14.2; HRMS (ESI) (m/z): calcd for C$_{23}$H$_{23}$N$_2$O$_5$([M+H]$^+$), 431.1602; found 431.1615.
Ethyl 2-(7-oxo-6-(pyridin-2-yl)-6,7-dihydro-5H-[1,3]dioxolo[4,5-f]isoindol-5-yl)acetate (4n): 26 mg; 38% yield; Yellow solid; m.p. 96-97°C; 1H NMR (CDCl₃, 600 MHz), δ 8.47 (d, J = 8.4 Hz, 1H), 8.39 (d, J = 3.6 Hz, 1H), 7.77-7.72 (m, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.06 (dd, J₁ = 7.2 Hz, J₂ = 5.4 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 6.12 (d, J = 5.4 Hz, 2H), 5.98-5.93 (m, 1H), 3.94 (dd, J₁ = 7.2 Hz, J₂ = 5.4 Hz, 2H), 3.16 (t, J = 5.4 Hz, 2H), 1.05 (t, J = 7.1 Hz, 3H); 13C NMR (CDCl₃, 150 MHz), δ 169.8, 166.9, 151.8, 147.7, 141.7, 138.0, 127.2, 124.3, 119.6, 119.1, 115.8, 109.5, 102.6, 60.6, 54.4, 36.4, 29.8, 14.1; HRMS (ESI) (m/z): calcld for C₁₈H₁₇N₂O₅⁺([M+H]⁺), 341.1132; found 341.1141.

Ethyl 2-(5,6,7-trimethoxy-3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (4o): 25 mg; 32% yield; Oil; 1H NMR (CDCl₃, 600 MHz), δ 8.46 (d, J = 8.4 Hz, 1H), 8.40 (s, 1H), 7.77-7.74 (m, 1H), 7.18 (s, 1H), 7.06 (dd, J₁ = 6.6 Hz, J₂ = 5.4 Hz,1H), 5.89 (t, J = 4.2 Hz, 1H), 4.03 (s, 3H), 3.93 (s, 3H), 3.93 (s, 3H), 3.86 (dd, J₁ = 7.2 Hz, J₂ = 6.0 Hz, 2H), 3.31 (dd, J₁ = 15.0 Hz, J₂ = 4.8 Hz, 1H), 3.12 (dd, J₁ = 15.0 Hz, J₂ = 3.6 Hz, 1H), 0.98 (t, J = 7.2 Hz, 3H); 13C NMR (CDCl₃, 150 MHz), δ 170.0, 167.4, 155.4, 151.0, 148.5, 147.7, 146.0, 138.1, 129.4, 127.6, 119.6, 115.9, 101.8, 61.2, 61.0, 60.3, 56.5, 55.2, 35.9, 14.1; HRMS (ESI) (m/z): calcld for C₂₀H₂₅N₂O₆⁺([M+H]⁺), 387.1551; found 387.1559.

Ethyl 2-(1-oxo-2-(pyridin-2-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-3-yl)acetate (4p): 23.6 mg; 40% yield; Brown solid; m.p. 96-98°C; 1H NMR (CDCl₃, 600 MHz), δ
9.02 (s, 1H), 8.85 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 8.43 (d, J = 4.2 Hz, 1H), 7.85-7.74 (m, 2H), 7.12 (dd, J1 = 6.6 Hz, J2 = 4.8 Hz, 1H), 6.10 (dd, J1 = 7.8 Hz, J2 = 3.0 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.44 (dd, J1 = 16.2 Hz, J2 = 3.0 Hz, 1H), 2.76 (dd, J1 = 16.8 Hz, J2 = 8.4 Hz, 1H), 1.16 (t, J = 7.2 Hz, 3H); 13C NMR (CDCl3, 150 MHz), δ 170.2, 165.9, 150.3, 149.9, 148.1, 145.7, 139.6, 138.3, 120.4, 116.1, 61.1, 56.0, 37.6, 14.2; HRMS (ESI) (m/z): calcd for C16H16N2O3+([M+H]+), 298.1186; found 298.1195.

Ethyl 2-(3-oxo-2-(pyridin-2-yl)-2,3-dihydro-1H-benzo[f]isooindol-1-yl)acetate (4q):
45 mg; 65% yield; Yellow solid; m.p. 106-107 °C; 1H NMR (CDCl3, 600 MHz), δ 8.62 (d, J = 8.4 Hz, 1H), 8.45 (s, 2H), 8.01 (s, 2H), 7.92 (d, J = 7.8 Hz, 1H), 7.80-7.75 (m, 1H), 7.60-7.52 (m, 2H), 7.08 (dd, J1 = 6.6 Hz, J2 = 3.6 Hz, 1H), 6.14 (dd, J1 = 7.2 Hz, J2 = 3.0 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.42 (dd, J1 = 16.2 Hz, J2 = 3.6 Hz, 1H), 2.86 (dd, J1 = 16.2 Hz, J2 = 7.8 Hz, 1H), 1.14 (t, J = 7.2 Hz, 3H); 13C NMR (CDCl3, 150 MHz), δ 170.8, 167.5, 151.0, 147.9, 139.7, 138.1, 136.0, 133.2, 130.0, 129.7, 128.4, 128.1, 126.6, 124.9, 121.9, 119.8, 116.1, 60.8, 56.5, 38.7, 14.2; HRMS (ESI) (m/z): calcd for C21H19N2O3+([M+H]+), 347.1390; found 347.1400.

Diethyl 2,2’-(3,7-dioxo-2,6-dihydropyridin-2-yl)-1,2,3,5,6,7-hexahydropyrrolo[3, 4-f]isooindole-1,5-diyldiacetate (4r): 31 mg; 30% yield; Grey solid; m.p. 201-203 °C; 1H NMR (CDCl3, 600 MHz), δ 8.53 (d, J = 8.4 Hz, 2H), 8.44 (d, J = 3.6 Hz, 2H), 8.12 (s, 2H), 7.81-7.76 (m, 2H), 7.10 (dd, J1 = 6.6 Hz, J2 = 4.8 Hz, 2H), 6.07 (dd, J1 = 7.8 Hz, J2 = 3.6 Hz, 2H), 4.11 (q, J = 7.1 Hz, 4H), 3.38 (dd, J1 = 16.2 Hz, J2 = 3.6 Hz, 2H), 2.87 (dd, J1 = 16.2 Hz, J2 = 7.8 Hz, 2H), 1.17 (t, J = 7.2 Hz, 6H); 13C NMR (CDCl3, 150 MHz), δ 170.2, 166.5, 150.6, 148.0, 145.5, 145.2, 136.4, 120.1, 119.1, 116.0, 61.0, 56.7, 37.9, 14.2; HRMS (ESI) (m/z): calcd for C28H27N4O6+([M+H]+), 515.1925; found
Tert-butyl 2-(3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (5a): 41.1 mg; 64% yield; Yellow solid; m.p. 109-111 °C; $^1$H NMR (CDCl$_3$, 600 MHz), $\delta$ 8.52 (d, $J = 7.8$ Hz, 1H), 8.42 (s, 1H), 7.90 (d, $J = 7.8$ Hz, 1H), 7.77-7.73 (m, 1H), 7.62-7.58 (m, 2H), 7.51-7.47 (m, 1H), 7.06 (dd, $J_1 = 6.6$ Hz, $J_2 = 5.4$ Hz, 1H), 5.91 (dd, $J_1 = 7.2$ Hz, $J_2 = 3.6$ Hz, 1H), 3.18 (dd, $J_1 = 15.6$ Hz, $J_2 = 3.6$ Hz, 1H), 2.89 (dd, $J_1 = 15.6$ Hz, $J_2 = 7.2$ Hz, 1H), 1.23 (s, 9H); $^{13}$C NMR (CDCl$_3$, 150 MHz), $\delta$ 169.5, 167.7, 150.9, 147.9, 144.9, 138.0, 132.8, 132.2, 128.7, 124.2, 123.0, 119.6, 116.0, 81.0, 56.8, 38.7, 27.9; HRMS (ESI) ($m$/z): calcd for C$_{19}$H$_{21}$N$_2$O$_3$+([M+H]$^+$), 325.1547; found 325.1554.

Butyl 2-(3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate (5b): 51 mg; 78% yield; Yellow solid; m.p. 82-83 °C; $^1$H NMR (CDCl$_3$, 600 MHz), $\delta$ 8.53 (d, $J = 8.4$ Hz, 1H), 8.39 (dd, $J_1 = 4.8$ Hz, $J_2 = 1.2$ Hz, 1H), 7.90 (d, $J = 7.2$ Hz, 1H), 7.77-7.72 (m, 1H), 7.61-7.56 (m, 2H), 7.51-7.47 (m, 1H), 7.07-7.03 (m, 1H), 5.96 (dd, $J_1 = 7.8$ Hz, $J_2 = 3.6$ Hz, 1H), 4.04-3.97 (m, 2H), 3.34 (dd, $J_1 = 16.2$ Hz, $J_2 = 3.6$ Hz, 1H), 2.79 (dd, $J_1 = 16.2$ Hz, $J_2 = 7.8$ Hz, 1H), 1.50-1.44 (m, 2H), 1.26-1.21 (m, 2H), 0.85 (t, $J = 7.8$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz), $\delta$ 170.7, 167.6, 150.9, 147.8, 145.0, 138.0, 132.9, 132.0, 128.7, 124.3, 122.9, 119.6, 115.8, 64.7, 56.6, 38.1, 30.5, 19.1, 13.7; HRMS (ESI) ($m$/z): calcd for C$_{19}$H$_{21}$N$_2$O$_3$+([M+H]$^+$), 325.1547; found 325.1556.

2-(3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetonitrile (5c): 29 mg; 58% yield; White solid; $^1$H NMR (CDCl$_3$, 600 MHz), $\delta$ 8.59 (d, $J = 8.4$ Hz, 1H), 8.39 (dd, $J_1 = 4.8$ Hz, $J_2 = 7.8$ Hz, 1H), 7.90 (d, $J_1 = 7.8$ Hz, 1H), 7.77-7.73 (m, 1H), 7.62-7.58 (m, 2H), 7.51-7.47 (m, 1H), 7.06 (dd, $J_1 = 6.6$ Hz, $J_2 = 5.4$ Hz, 1H), 5.91 (dd, $J_1 = 7.2$ Hz, $J_2 = 3.6$ Hz, 1H), 3.18 (dd, $J_1 = 15.6$ Hz, $J_2 = 3.6$ Hz, 1H), 2.89 (dd, $J_1 = 15.6$ Hz, $J_2 = 7.2$ Hz, 1H), 1.23 (s, 9H); $^{13}$C NMR (CDCl$_3$, 150 MHz), $\delta$ 170.7, 167.6, 150.9, 147.8, 145.0, 138.0, 132.9, 132.0, 128.7, 124.3, 122.9, 119.6, 115.8, 64.7, 56.6, 38.1, 30.5, 19.1, 13.7; HRMS (ESI) ($m$/z): calcd for C$_{19}$H$_{21}$N$_2$O$_3$+([M+H]$^+$), 325.1547; found 325.1556.
= 0.6 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.81-7.75 (m, 1H), 7.75-7.67 (m, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.12-7.09 (m, 1H), 5.77 (dd, J1 = 7.2 Hz, J2 = 3.6 Hz, 1H), 3.43 (dd, J1 = 16.8 Hz, J2 = 3.6 Hz, 1H), 3.22 (dd, J1 = 16.8 Hz, J2 = 3.2 Hz, 1H), 3.43 (dd, J1 = 16.8 Hz, J2 = 3.6 Hz, 1H), 3.22 (dd, J1 = 16.8 Hz, J2 = 3.2 Hz, 1H), 3.52 (dd, J1 = 16.8 Hz, J2 = 3.0 Hz, 1H), 2.65 (dd, J1 = 17.4 Hz, J2 = 3.0 Hz, 1H), 2.47-2.42 (m, 1H), 2.38-2.33 (m, 1H), 1.06 (t, J = 7.2 Hz, 3H); 13C NMR (CDCl3, 150 MHz), δ 209.2, 167.7, 151.0, 147.8, 146.0, 138.0, 133.0, 131.7, 128.6, 124.2, 123.3, 119.6, 115.7, 56.3, 46.2, 36.7, 7.8; HRMS (ESI) (m/z): calcd for C17H17N2O2+[M+H]+, 281.1285; found 281.1291.

N-benzyl-2-(3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetamide (5e): 52 mg; 73% yield; Yellow solid; m.p. 163-164 °C; 1H NMR (CDCl3, 600 MHz), δ 8.46 (d, J = 8.4 Hz, 1H), 8.28 (d, J = 3.6 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.56-7.50 (m, 2H), 7.44 (t, J = 7.2 Hz, 1H), 7.32-7.23 (m, 3H), 7.21 (d, J = 7.2 Hz, 2H), 7.03 (dd, J1 = 6.6 Hz, J2 = 5.4 Hz, 1H), 6.67 (s, 1H), 5.91 (dd, J1 = 8.4 Hz, J2 = 2.4 Hz,
1H), 4.44 (dd, $J_1 = 14.4$ Hz, $J_2 = 5.4$ Hz, 1H), 4.37 (dd, $J_1 = 14.4$ Hz, $J_2 = 5.4$ Hz, 1H), 3.38 (dd, $J_1 = 14.4$ Hz, $J_2 = 3.0$ Hz, 1H), 2.39 (dd, $J_1 = 14.4$ Hz, $J_2 = 9.0$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 150 MHz), $\delta$ 169.9, 167.6, 150.9, 147.7, 145.4, 138.2, 138.1, 133.0, 131.3, 128.7, 128.6, 127.8, 127.5, 124.1, 123.3, 119.6, 115.7, 57.5, 43.6, 40.3; HRMS (ESI) (m/z): calcd for C$_{22}$H$_{20}$N$_3$O$_2$([M+H]$^+$), 358.1520; found 358.1551.

N,N-dimethyl-2-(3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetamide (5f): 35 mg; 60% yield; Yellow solid; m.p. 142-143 °C; $^1$H NMR (CDCl$_3$, 600 MHz), $\delta$ 8.56 (d, $J = 9.0$ Hz, 1H), 8.40 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.2$ Hz, 1H), 7.88 (d, $J = 7.8$ Hz, 1H), 7.76-7.71 (m, 2H), 7.57-7.53 (m, 1H), 7.46 (t, $J = 7.8$ Hz, 1H), 7.05-7.02 (m, 1H), 6.12 (dd, $J_1 = 9.6$ Hz, $J_2 = 3.6$ Hz, 1H), 3.50 (dd, $J_1 = 15.6$ Hz, $J_2 = 1.2$ Hz, 1H), 3.00 (s, 3H), 2.38 (dd, $J_1 = 15.6$ Hz, $J_2 = 10.2$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 150 MHz), $\delta$ 170.2, 167.8, 151.1, 147.9, 146.2, 137.9, 132.9, 131.6, 128.5, 124.1, 124.0, 119.5, 115.6, 57.3, 37.8, 37.3, 35.5; HRMS (ESI) (m/z): calcd for C$_{17}$H$_{18}$N$_3$O$_2$([M+H]$^+$), 296.1394; found 296.1399.

[Image of structure 5f]

2-(3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetamide (5g): 33 mg; 62% yield; Yellow solid; m.p. 203-205 °C; $^1$H NMR (DMSO, 600 MHz), $\delta$ 8.51-8.46 (m, 1H), 8.39 (d, $J = 8.4$ Hz, 1H), 7.92-7.89 (m, 1H), 7.81 (d, $J = 7.2$ Hz, 1H), 7.72-7.65 (m, 2H), 7.56 (t, $J = 7.2$ Hz, 1H), 7.33 (s, 1H), 7.22-7.19 (m, 1H), 6.96 (s, 1H), 5.89 (dd, $J_1 = 9.0$ Hz, $J_2 = 3.6$ Hz, 1H), 3.18 (dd, $J_1 = 14.4$ Hz, $J_2 = 3.0$ Hz, 1H), 2.33 (dd, $J_1 = 15.0$ Hz, $J_2 = 9.0$ Hz, 1H); $^{13}$C NMR (DMSO, 150 MHz), $\delta$ 171.3, 166.9, 150.5, 148.2, 145.6, 138.3,
133.1, 131.2, 128.7, 123.7, 123.5, 119.9, 115.4, 56.7, 38.0; HRMS (ESI) (m/z): calcd for C_{15}H_{14}N_{3}O_{2}^+([M+H]^+), 268.1081; found 268.1078.

**Ethyl 2-(2-(5-methylpyridin-2-yl)-3-oxoisoindolin-1-yl)acetate (5h):** 57 mg, 92% yield; Yellow solid; m.p. 71-72°C; $^1$H NMR (CDCl$_3$, 600 MHz), $\delta$ 8.39 (d, $J = 9.0$ Hz, 1H), 8.21 (s, 1H), 7.89 (d, $J = 7.2$ Hz, 1H), 7.60-7.54 (m, 3H), 7.50-7.45 (m, 1H), 5.93 (dd, $J_1 = 7.8$ Hz, $J_2 = 3.6$ Hz, 1H), 4.09-4.02 (m, 2H), 3.30 (dd, $J_1 = 15.6$ Hz, $J_2 = 3.6$ Hz, 1H), 2.75 (dd, $J_1 = 16.2$ Hz, $J_2 = 8.4$ Hz, 1H), 2.30 (s, 3H), 1.12 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz), $\delta$ 170.6, 167.4, 148.7, 147.7, 144.9, 138.7, 132.7, 132.1, 129.0, 128.7, 124.2, 122.8, 115.4, 60.7, 56.6, 38.1, 17.9, 14.1; HRMS (ESI) (m/z): calcd for C$_{18}$H$_{19}$N$_2$O$_3$^+([M+H]^+), 311.1390; found 311.1397.

**Ethyl 2-(2-(5-chloropyridin-2-yl)-3-oxoisoindolin-1-yl)acetate (5i):** 44 mg, 67% yield; Yellow solid; m.p. 67-68°C; $^1$H NMR (CDCl$_3$, 600 MHz), $\delta$ 8.55 (d, $J = 9.0$ Hz, 1H), 8.34 (d, $J = 2.4$ Hz, 1H), 7.89 (d, $J = 7.8$ Hz, 1H), 7.71 (dd, $J_1 = 9.0$ Hz, $J_2 = 3.0$ Hz, 1H), 7.61-7.56 (m, 2H), 7.50 (t, $J = 7.2$ Hz, 1H), 5.89 (dd, $J_1 = 7.8$ Hz, $J_2 = 3.0$ Hz, 1H), 4.09-4.04 (m, 2H), 3.30 (dd, $J_1 = 16.2$ Hz, $J_2 = 3.6$ Hz, 1H), 2.78 (dd, $J_1 = 15.6$ Hz, $J_2 = 7.8$ Hz, 1H), 1.13 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz), $\delta$ 170.4, 167.6, 149.2, 146.3, 144.9, 137.9, 133.2, 131.6, 128.9, 126.9, 124.4, 122.9, 116.3, 60.8, 56.7, 38.0, 14.2; HRMS (ESI) (m/z): calcd for C$_{17}$H$_{16}$ClN$_2$O$_3$^+([M+H]^+), 331.0844; found 331.0845.
**Ethyl 2-(2-(4-cyanopyridin-2-yl)-3-oxoisodolin-1-yl)acetate (5j):** 19.1 mg; 30% yield; Yellow solid; m.p. 145-146°C; \(^1^H\) NMR (CDCl\(_3\), 600 MHz), \(\delta\) 8.92 (s, 1H), 8.55 (d, \(J = 4.8\) Hz, 1H), 7.91 (d, \(J = 7.8\) Hz, 1H), 7.64 (t, \(J = 7.2\) Hz, 1H), 7.58 (d, \(J = 7.2\) Hz, 1H), 7.52 (t, \(J = 7.2\) Hz, 1H), 7.26 (d, \(J = 4.8\) Hz, 1H), 5.91 (dd, \(J_1 = 7.8\) Hz, \(J_2 = 3.6\) Hz, 1H), 4.10-4.02 (m, 2H), 3.30 (dd, \(J_1 = 15.6\) Hz, \(J_2 = 3.0\) Hz, 1H), 2.83 (dd, \(J_1 = 16.2\) Hz, \(J_2 = 7.8\) Hz, 1H), 1.13 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz), \(\delta\) 170.2, 167.9, 151.7, 148.9, 144.9, 133.6, 131.1, 129.1, 124.6, 123.0, 122.2, 120.4, 117.4, 116.7, 60.9, 56.8, 37.8, 14.1; HRMS (ESI) \((m/z)\): calcld for C\(_{18}\)H\(_{16}\)N\(_3\)O\(_3\)\([\text{M+H]}^+\), 322.1186; found 322.1188.

![5k](image)

**Ethyl 2-(2-(7-chloro-1,8-naphthyridin-2-yl)-3-oxoisodolin-1-yl)acetate (5k):** 21 mg; 28% yield; Yellow solid; m.p. 155-156°C; \(^1^H\) NMR (CDCl\(_3\), 600 MHz), \(\delta\) 8.96 (d, \(J = 9.0\) Hz, 1H), 8.24 (d, \(J = 8.4\) Hz, 1H), 8.12 (d, \(J = 8.4\) Hz, 1H), 7.96 (d, \(J = 7.2\) Hz, 1H), 7.68-7.63 (m, 2H), 7.55 (t, \(J = 7.8\) Hz, 1H), 7.44 (d, \(J = 8.4\) Hz, 1H), 6.18 (t, \(J = 4.8\) Hz, 1H), 4.01-3.92 (m, 2H), 3.36 (dd, \(J_1 = 5.4\) Hz, \(J_2 = 2.4\) Hz, 2H), 1.03 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz), \(\delta\) 169.9, 168.5, 154.5, 154.2, 154.0, 144.9, 139.1, 138.7, 133.7, 131.6, 129.0, 124.6, 123.1, 122.3, 119.2, 116.6, 60.7, 57.1, 37.5, 14.1; HRMS (ESI) \((m/z)\): calcld for C\(_{20}\)H\(_{17}\)ClN\(_3\)O\(_3\)\([\text{M+H]}^+\), 382.0953; found 381.0952.

![5l](image)

**3-(2-oxo-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethyl)-2-(pyridin-2-yl)isoindolin-1-one (5l):** 47 mg; 60% yield; Yellow solid; m.p. 136-138°C; \(^1^H\) NMR (CDCl\(_3\), 600 MHz), \(\delta\) 8.56 (d, \(J = 8.4\) Hz, 1H), 8.39 (dd, \(J_1 = 4.8\) Hz, \(J_2 = 1.2\) Hz, 1H), 7.87 (d, \(J = 7.2\) Hz, 1H), 7.75-7.71 (m, 1H), 7.68 (d, \(J = 7.8\) Hz, 1H), 7.67-7.54 (m, 1H), 7.47 (t, \(J = 7.2\) Hz, 1H), 7.26 (d, \(J = 7.2\) Hz, 1H), 7.05 (d, \(J = 7.2\) Hz, 1H), 6.96 (d, \(J = 7.2\) Hz, 1H), 6.82 (d, \(J = 7.2\) Hz, 1H), 6.78 (d, \(J = 7.2\) Hz, 1H), 3.92 (t, \(J = 7.2\) Hz, 1H), 3.86 (m, 1H), 3.55-3.51 (m, 4H), 3.36-3.32 (m, 4H), 3.28 (s, 3H), 2.33 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz), \(\delta\) 169.9, 168.5, 154.5, 154.2, 154.0, 144.9, 139.1, 138.7, 133.7, 131.6, 129.0, 124.6, 123.1, 122.3, 119.2, 116.6, 60.7, 57.1, 37.5, 14.1; HRMS (ESI) \((m/z)\): calcld for C\(_{20}\)H\(_{17}\)ClN\(_3\)O\(_3\)\([\text{M+H]}^+\), 382.0953; found 381.0952.
= 7.8 Hz, 1H), 7.04 (dd, J₁ = 6.6 Hz, J₂ = 4.8 Hz, 1H), 6.08 (dd, J₁ = 9.6 Hz, J₂ = 3.0 Hz, 1H), 3.95-3.90 (m, 4H), 3.75 (t, J = 6.0 Hz, 2H), 3.53 (dd, J₁ = 15.6 Hz, J₂ = 3.6 Hz, 1H), 3.46-3.43 (m, 2H), 2.40 (dd, J₁ = 15.6 Hz, J₂ = 9.6 Hz, 1H), 1.71-1.67 (m, 2H), 1.58-1.52 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz), δ 168.5, 167.7, 151.1, 147.8, 146.0, 138.0, 133.0, 131.6, 128.6, 124.1, 124.0, 119.5, 115.6, 106.8, 64.5, 57.3, 43.6, 40.0, 37.5, 35.6, 34.9; HRMS (ESI) (m/z): calcd for C₂₂H₂₄N₃O₄([M+H]⁺), 394.1762; found 394.1765.

3-(5-methyl-2-oxohexyl)-2-(pyridin-2-yl)isoindolin-1-one (5m): 20 mg; 31% yield; White solid; m.p. 57-59°C; ¹H NMR (CDCl₃, 600 MHz), δ 8.58 (d, J = 8.4 Hz, 1H), 8.38 (dd, J₁ = 4.8 Hz, J₂ = 1.2 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.78-7.74 (m, 1H), 7.06 (dd, J₁ = 7.2 Hz, J₂ = 5.4 Hz, 1H), 6.05 (dd, J₁ = 8.4 Hz, J₂ = 2.4 Hz, 1H), 3.55 (dd, J₁ = 17.4 Hz, J₂ = 3.0 Hz, 1H), 2.66 (dd, J₁ = 17.4 Hz, J₂ = 9.0 Hz, 1H), 2.44-2.33 (m, 2H), 1.53-1.46 (m, 3H), 0.86 (dd, J₁ = 6.6 Hz, J₂ = 1.2 Hz, 6H); ¹³C NMR (CDCl₃, 150 MHz), δ 209.1, 167.8, 151.1, 147.8, 146.1, 138.1, 133.1, 131.8, 128.6, 124.3, 123.4, 119.6, 115.7, 56.3, 46.6, 41.7, 32.6, 27.8, 22.4, 22.4; HRMS (ESI) (m/z): calcd for C₂₀H₂₃N₂O₂([M+H]⁺), 323.1754; found 323.1754.

2-(7-chloro-1,8-naphthyridin-2-yl)-3-(5-methyl-2-oxohexyl)isoindolin-1-one (6): 12 mg; 15% yield; White solid; m.p. 165-167°C; ¹H NMR (CDCl₃, 600 MHz), δ 8.98 (d, J = 9.0 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.67-7.60 (m, 2H), 7.55-7.50 (m, 1H), 7.43 (d, J = 8.4 Hz, 1H), 6.18 (dd, J₁ = 7.8 Hz, J₂ = 3.0 Hz, 1H), 3.64 (dd, J₁ = 16.8 Hz, J₂ = 3.6 Hz, 1H), 3.09 (dd, J₁ = 17.2 Hz, J₂ = 3.0 Hz, 1H), 2.44-2.33 (m, 2H), 1.53-1.46 (m, 3H), 0.86 (dd, J₁ = 6.6 Hz, J₂ = 1.2 Hz, 6H); ¹³C NMR (CDCl₃, 150 MHz), δ 209.1, 167.8, 151.1, 147.8, 146.1, 138.1, 133.1, 131.8, 128.6, 124.3, 123.4, 119.6, 115.7, 56.3, 46.6, 41.7, 32.6, 27.8, 22.4, 22.4; HRMS (ESI) (m/z): calcd for C₂₀H₂₃N₂O₂([M+H]⁺), 323.1754; found 323.1754.
Hz, J2 = 7.8 Hz, 1H), 2.40-2.31 (m, 2H), 1.46-1.37 (m, 3H), 0.80 (d, J = 6.0 Hz, 6H); 13C NMR (CDCl3, 150 MHz), δ 208.4, 168.6, 154.5, 154.2, 154.0, 146.0, 139.1, 138.7, 133.8, 131.4, 128.8, 124.7, 123.5, 122.3, 119.1, 116.5, 57.0, 45.4, 41.9, 32.4, 27.7, 22.4; HRMS (ESI) (m/z): calcd for C23H23ClN3O2+ ([M+H]+), 408.1474; found 408.1474.

2-(7-chloro-1,8-naphthyridin-2-yl)-3-(2-oxo-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethyl)isoindolin-1-one (8): 19 mg, 20% yield; White solid; m.p. 226-228 oC; 1H NMR (CDCl3, 600 MHz), δ 8.94 (d, J = 9.0 Hz, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 6.09 (dd, J1 = 9.0 Hz, J2 = 3.0 Hz, 1H), 3.97-3.92 (m, 4H), 3.85-3.77 (m, 2H), 3.70 (dd, J1 = 15.0 Hz, J2 = 3.0 Hz, 1H), 3.65-3.56 (m, 2H), 2.74 (dd, J1 = 14.4 Hz, J2 = 9.0 Hz, 1H), 1.71-1.52 (m, 4H); 13C NMR (CDCl3, 150 MHz), δ 168.6, 167.8, 154.3, 154.1, 153.9, 145.7, 139.0, 138.7, 133.6, 131.1, 128.8, 124.5, 123.9, 122.1, 119.0, 116.3, 106.9, 64.5, 57.8, 44.0, 40.0, 36.9, 35.6, 34.9; HRMS (ESI) (m/z): calcd for C25H24ClN4O4+ ([M+H]+), 479.1481; found 479.1482.

Synthesis and Characterization of amide 7 and 11:

\[ \text{N-(7-chloro-1,8-naphthyridin-2-yl)benzamide (7)} \]: To the 7-chloro-1,8-naphthyridin-2-amine (1.79 g, 10 mmol) was added DCM (30 mL) and TEA (1.4 mL, 10 mmol), and
the solution was cooled to 0 °C, benzoic chloride (1.4 g, 10 mmol) was added dropwise over 30 min. Afterwards, the solution was warmed to RT and kept for 5 h. Then it was concentrated and the residue was subject to flash column chromatography on silica gel using ethyl acetate/petroleum ether (v/v, 1:1) as eluent to give amide 7 as a yellow solid (2 g, 70% yield), m.p. 182-184 °C; 1H NMR (CDCl3, 600 MHz), δ 9.20 (s, 1H), 8.69 (d, J = 9.0 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.2 Hz, 2H), 7.36 (d, J = 8.4 Hz, 1H); 13C NMR (CDCl3, 150 MHz), δ 166.2, 154.5, 154.4, 139.4, 138.9, 133.6, 132.8, 129.5, 129.0, 127.4, 122.2, 119.3, 115.5; HRMS (ESI) (m/z): calcd for C15H10ClN3O Na+: [M+Na+]+, 306.0404; found 306.0403.

4-methyl-N-(pyridin-2-yl)benzamide (11): Prepared according to the literature.2 Yellow solid; m.p. 90-92 °C; 1H NMR (CDCl3, 600 MHz), δ 9.33 (s, 1H), 8.39 (d, J = 8.4 Hz, 1H), 8.09 (dd, J1=4.8 Hz, J2=1.2 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.72-7.68 (m, 1H), 7.23 (d, J = 7.8 Hz, 2H), 6.99-6.96 (m, 1H), 2.38 (s, 3H); 13C NMR (CDCl3, 150 MHz), δ 166.1, 151.9, 147.8, 147.8, 142.8, 138.5, 131.6, 129.4, 129.4, 127.4, 119.7, 114.4, 21.5.

**Derivation of isoindolinone 4 to 9 and 10:**

![Derivation of isoindolinone 4 to 9 and 10](image)

2-(2-(pyridin-2-yl)isoindolin-1-yl)ethan-1-ol (9): To a solution of ethyl 2-(3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetate 4a (0.2 mmol, 59.2 mg) in THF (4 mL) at room temperature, was added LiAlH4 (23 mg, 0.6 mmol, 3.0 eq.). The solution was heated to 60 °C for 8 hours. It was quenched with saturated NH4Cl (aq.) solution and the aqueous phase was extracted 3 times with ethyl acetate. The combined organic phases were dried over Na2SO4 and the solvent removed in vacuo. The crude compound was purified by silica gel chromatography (ethyl acetate/petroleum ether, v/v = 1:1 as eluent) to give 9 (40.8 mg, 85%) as a oil, 1H NMR (CDCl3, 600 MHz), δ 8.10 (d, J = 3.6 Hz, 1H), 7.56-
7.49 (m, 1H), 7.33-7.23 (m, 4H), 6.63 (dd, $J_1 = 6.6$ Hz, $J_2 = 5.4$ Hz, 1H), 6.53 (d, $J = 8.0$ Hz, 1H), 5.72-5.65 (m, 1H), 4.77 (dd, $J_1 = 13.8$ Hz, $J_2 = 2.4$ Hz, 1H), 4.62 (d, $J = 13.8$ Hz, 1H), 3.71-3.65 (m, 1H), 3.60-3.54 (m, 1H), 2.28-2.22 (m, 1H), 1.71-1.64 (m, 1H);

$^{13}$C NMR (CDCl$_3$, 150 MHz), $\delta$ 158.0, 147.3, 142.9, 138.0, 136.2, 127.6, 127.3, 122.5, 122.4, 112.6, 107.4, 60.0, 58.8, 54.1, 41.8; HRMS (ESI) ($m/z$): calcd for C$_{15}$H$_{17}$N$_2$O$^+$ ([M+H$^+$]), 241.1336; found 241.1341.

2-(6-methyl-3-oxo-2-(pyridin-2-yl)isoindolin-1-yl)acetic acid (10): To a solution of 4b (62 mg, 0.2 mmol), a mixture of THF (5 mL) and 4 M NaOH aq. (0.25 mL) was added and stirred for 4 h at 60 °C. Aqueous HCl solution (1 M) was added to adjust the pH to 6, and the solution was extracted with ethyl acetate (10 mL * 3). The combined organic layer was washed with brine (10 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo, thereby giving compound 10 (51g, 90%) as a white solid, m.p. 216-218°C; $^1$H NMR (DMSO, 600 MHz), $\delta$ 8.45 (d, $J = 3.6$ Hz, 1H), 8.40 (d, $J = 8.4$ Hz, 1H), 7.91-7.84 (m, 1H), 7.67 (d, $J = 7.8$ Hz, 1H), 7.48 (s, 1H), 7.34 (d, $J = 7.8$ Hz, 1H), 7.17 (dd, $J_1 = 6.6$ Hz, $J_2 = 5.4$ Hz, 1H), 5.76 (dd, $J_1 = 7.2$ Hz, $J_2 = 2.4$ Hz, 1H), 3.23 (dd, $J_1 = 16.2$ Hz, $J_2 = 3.0$ Hz, 1H), 2.80 (dd, $J_1 = 16.2$ Hz, $J_2 = 7.8$ Hz, 1H), 2.42 (s, 3H); $^{13}$C NMR (DMSO, 150 MHz), $\delta$ 171.5, 166.9, 150.6, 147.9, 145.5, 143.4, 138.2, 129.6, 128.9, 123.4, 123.3, 119.6, 115.0, 56.0, 36.8, 21.7; HRMS (ESI) ($m/z$): calcd for C$_{16}$H$_{14}$N$_2$O$_3$Na$^+$ ([M+Na$^+$]), 305.0896; found 305.0895.
Kinetic Isotope Effect Study:

Following general procedure, a 25 mL tube equipped with a magnetic stir bar was added benzaldehyde 1a (21.2 mg, 0.2 mmol, 1.0 equiv.), pyridin-2-amine 2a (28 mg, 0.3 mmol, 1.5 equiv.), [Cp*RhCl$_2$]$_2$ (3 mg, 2.5 mol%), Cu(OAc)$_2$ (0.4 mmol, 2.0 equiv), The sealed tube was evacuated and backfilled with N$_2$. Then 3a (45 µL, 0.04 mmol) and CH$_3$CN (super dry, 2.0 mL) were added to the tube and stirred for 15 min at 80 °C (monitored by TLC). In another reaction vial, [D$_5$]-1a (22 mg, 0.2 mmol) was used instead of 1a. The two reactions were both kept at 80 °C for 15 min. Then they were diluted with EA and combined. Silica gel was added and all the solvent were concentrated under vacuum. The residue was subject to flash chromatography and the value of $K_H/K_D$ was obtained based on $^1$HNMR (CDCl$_3$).
Many Other Control Experiments Carried Out:

Reference:


$^1$H and $^{13}$C NMR spectra of all the products