Supporting Information for

Synthesis of spiropyrazoline oxindoles by a formal [4+1] annulation reaction between 3-bromooxindoles and in situ-derived 1,2-diaza-1,3-dienes

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1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. Flash column chromatography was performed using 200-300 mesh silica gel. \(^1\)H NMR spectra were recorded on 400 or 600 MHz spectrometers. Chemical shifts were reported on the delta (\(\delta\)) scale in parts per million (ppm) relative to the singlet (0 ppm) for tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet), coupling constants (Hz) and integration. \(^{13}\)C NMR spectra were recorded at 100 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to the central line of the triplet at 77.0 ppm for CDCl\(_3\). Mass spectra were measured on a MS spectrometer (EI).
2. Preparation of substrates

2.1 General procedure for the preparation of 3-bromooxindoles

**Step 1:** To a 250 mL 3-necked-round bottom flask equipped with a silicone oil bubbler was added commercially available isatin (7.7 g, 50 mmol) and anhydrous DMF (80 mL). And the mixture was cooled down to 0 °C. To this solution was added NaH (1.32 g, 55 mmol), then CH₃I was added 10 min later (without gas bubbling), and stirred at 0 °C for 15 min. Upon completion of the reaction (monitored by TLC), the mixture was diluted with saturated NH₄Cl solution and extracted with ethyl acetate, the ethyl acetate layer was washed with water and brine. The combined organic layer was then dried over MgSO₄, filtered, and concentrated to yield the crude N-methylindoline-2, 3-dione (7.6 g, 94% yield), which was used directly in the next step. [1]

**Step 2:** The N-methylindoline-2, 3-dione (7.58 g, 47 mmol) was refluxed in NH₂-NH₂·H₂O until the gas evolution stopped. Then the mixture was cooled to room temperature. The crude product was extracted with ethyl acetate. The combined organic layer was then dried over MgSO₄, purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 10:1). 1-Methylindolin-2-one was obtained as a red solid (6.78 g, 98% yield). [2]

**Step 3:** 1-methylindolin-2-one (6.78 g, 46 mmol) and TsOH·H₂O (1.75 g, 9.2 mmol) were dissolved in CH₂Cl₂ (40 mL), Then, the solution of NBS (8.2 g, 46 mmol) in CH₂Cl₂ (260 mL) was added to the mixture dropwisely and the mixture stirred at room temperature. After that, the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 10:1). 3-bromo-1-methylindolin-2-one was obtained as a yellow solid (4.2 g, 18.4 mmol). [3]

The other 3-bromooxindoles were prepared according to the above procedure.

2.2 General procedure for the preparation of α-halo-hydrazones

Ethyl-3-bromo-2-oxopropanoate (5.8 g, 30 mmol) and 2-methoxybenzohydrazide (5.5 g, 33 mmol) was dissolved in MeOH (30 mL), then con. HCl (0.3 mL) was added in 0 °C. The mixture was stirred at room temperature until the large scale of white solid was formed. The crude product was filtered, washed with Et₂O. Then the crude product was recrystallized with MeOH at minus twenty degree for 2 hours. [4][5][6]
References:

3. Optimization studies

3.1 Screening of the N-protecting groups of hydrazones

<table>
<thead>
<tr>
<th>Entry</th>
<th>R$_1$</th>
<th>R$_2$</th>
<th>X</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C$_6$H$_5$CO</td>
<td>C$_6$H$_5$</td>
<td>Cl</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>2-MeOC$_6$H$_4$CO</td>
<td>2,4-ClC$_6$H$_3$</td>
<td>Cl</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>MeCO</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>Br</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>2-MeOC$_6$H$_4$CO</td>
<td>CO$_2$Et</td>
<td>Br</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>Ts</td>
<td>C$_6$H$_5$</td>
<td>Br</td>
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</tr>
<tr>
<td>6</td>
<td>C$_6$H$_5$CO</td>
<td>C$_6$H$_5$</td>
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<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>Boc</td>
<td>C$_6$H$_5$</td>
<td>Br</td>
<td>ND</td>
</tr>
</tbody>
</table>

The compound 2 (0.3 mmol) and Na$_2$CO$_3$ (63.59 mg, 0.6 mmol) were dissolved in CH$_2$Cl$_2$ (3 mL), the mixture was stirred for 15 min. Then, compound 1a (45.21 mg, 0.2 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the reaction was purified by flash column chromatography directly, eluting with petroleum ether and ethyl acetate, to afford the corresponding products.

3.2 Screening of base

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na$_2$CO$_3$</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$CO$_3$</td>
<td>4</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>BzOK</td>
<td>96</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>DIPEA</td>
<td>96</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>
The compound \(2a\) (102.95 mg, 0.3 mmol) and base (xx mg, 0.6 mmol) were dissolved in \(\text{CH}_2\text{Cl}_2\) (3 mL), the mixture was stirred for 15 min. Then, compound \(1a\) (45.21 mg, 0.2 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the reaction was purified by flash column chromatography directly, eluting with petroleum ether and ethyl acetate, to afford the corresponding product \(3a\).

### 3.3 Screening of the solvent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{CH}_3\text{CN})</td>
<td>96</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>96</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>4</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>(\text{ClCH}_2\text{CH}_2\text{Cl})</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>(\text{CHCl}_3)</td>
<td>4</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>PhCl</td>
<td>4</td>
<td>80</td>
</tr>
</tbody>
</table>

The compound \(2a\) (102.95 mg, 0.3 mmol) and \(\text{Cs}_2\text{CO}_3\) (195.49 mg, 0.6 mmol) were dissolved in solvent (3 mL), the mixture was stirred for 15 min. Then, compound \(1a\) (45.21 mg, 0.2 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the reaction was purified by flash column chromatography directly, eluting with petroleum ether and ethyl acetate, to afford the corresponding product \(3a\).

### 3.4 Screening of the ratio of base

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base ((\text{eq}))</th>
<th>Time (h)</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>96</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>4</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>4</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>5.0</td>
<td>4</td>
<td>75</td>
</tr>
</tbody>
</table>
The compound 2a (102.95 mg, 0.3 mmol) and Cs₂CO₃ (2.0-5.0 equiv) were dissolved in CH₂Cl₂ (3 mL), the mixture was stirred for 15 min. Then, compound 1a (45.21 mg, 0.2 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the reaction was purified by flash column chromatography directly, eluting with petroleum ether and ethyl acetate, to afford the corresponding product 3a.

3.5 Screening of the ratio of 1a to 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>X/Y</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1.2</td>
<td>4</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>1:1.5</td>
<td>4</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>1:2</td>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>1.2:1</td>
<td>4</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>1.5:1</td>
<td>4</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>2:1</td>
<td>4</td>
<td>62</td>
</tr>
</tbody>
</table>

The compound 2a (Y mmol) and Cs₂CO₃ (195.49 mg, 0.6 mmol) were dissolved in CH₂Cl₂ (3 mL), the mixture was stirred for 15 min. Then, compound 1a (X mmol) was added to the mixture. For entries 1-3, X = 0.2; for entries 4-6, Y = 0.2. Upon the completion of the reaction (monitored by TLC), the crude mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give the desired product 3a as a white solid.

4. Representative procedure for preparation of the products 3

The compound 2a (102.95 mg, 0.3 mmol) and Cs₂CO₃ (195.49 mg, 0.6 mmol) were dissolved in CH₂Cl₂ (3 mL), the mixture was stirred for 15 min. Then, compound 1 (0.2 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give the desired product 3 as a white solid.

5. Gram-scale reaction
The compound 2a (2.06 g, 6.0 mmol) and Cs₂CO₃ (3.91 g, 12 mmol) were dissolved in CH₂Cl₂ (50 mL), the mixture was stirred for 15 min. Then, compound 1a (0.9 g, 4.0 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give the desired product 3a (3.4 mmol, 1.39 g) as a white solid in 85% yield.

6. Optimization studies of one-pot, three-component reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X/Y/Z</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.65:1.5:1.0</td>
<td>4+12</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>2.2:2.0:1.0</td>
<td>4+12</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>3.3:3.0:1.0</td>
<td>4+12</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>5.5:5.0:1.0</td>
<td>4+12</td>
<td>83</td>
</tr>
</tbody>
</table>

The compound 4a (X mmol) and compound 5a (Y mmol) were dissolved in CH₂Cl₂ (3 mL), the mixture was stirred for 4 hours. Then, compound 1a (60.99 mg, 0.2 mmol) and Cs₂CO₃ (195.49 mg, 0.6 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the crude mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give the desired product 3f as a white solid.

7. One-pot, two step procedure for preparation of the spirooxindoles 3.

The compound 4 (128.71 mg, 0.66 mmol) and compound 5 (99.71 mg, 0.6 mmol) were dissolved in CH₂Cl₂ (3 mL), the mixture was stirred for 4 hours. Then, compound 1 (60.99 mg, 0.2 mmol) and Cs₂CO₃
(195.49 mg, 0.6 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the crude mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give the desired product 3 as a white solid.

8. Synthetic conversion of product 3f.

The compound 3g (518.3 mg, 1.07 mmol) was dissolved in MeOH (20 mL) and a 15% KOH (aq) solution (210.43 mg, 5.26 mmol) was added. The reaction was stirred at room temperature for 2 h and concentrated to provide a residue which was reconstituted in water and acidified using 1 N HCl until pH 1 was achieved. The solid formed was filtered and washed with water to provide the acid which was dried, dissolved in DMF (10 mL), and heated to 170 °C for 4 h in a microwave reactor. DMF was removed and the crude product was purified by column chromatograph to provide 6 as a white solid.

9. Spectral data of products

**Ethyl 2-(2-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate (3a)**

- White solid; 90% yield in 4 h; 86% yield in 4+12 h. mp 188-190 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.38 (1 H, d, $J = 4.0$ Hz), 7.34 (1 H, d, $J = 8.0$ Hz), 7.31 (1 H, s), 7.21 (1 H, d, $J = 7.5$ Hz), 7.07 (1 H, t, $J = 7.6$ Hz), 6.94 (1 H, d, $J = 8.0$ Hz), 6.90 (1 H, d, $J = 8.0$ Hz), 6.86 (1 H, s), 4.30 (2 H, q, $J = 7.1$ Hz), 3.82 (3 H, s), 3.33 (1 H, d, $J = 20.0$ Hz), 3.31 (3 H, s), 1.31 (3 H, t, $J = 7.1$ Hz).
- $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 173.3, 165.9, 160.7, 156.6, 145.1, 143.4, 132.5, 131.6, 129.8, 129.0, 125.6, 123.1, 122.2, 120.0, 111.3, 108.4, 77.3, 77.0, 76.7, 68.4, 61.9, 55.8, 44.3, 26.8, 14.1; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm$^{-1}$; HRMS (ESI) for C$_{22}$H$_{21}$N$_3$O$_5$ [M+H]$^+$: calcd 408.1554, found 408.1554.

**Ethyl 2-(2-methoxybenzoyl)-1,5-dimethyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate (3b)**

- White solid; 67% yield in 4 h, mp 198-200 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.39 (1 H, d, $J = 8.0$ Hz), 7.34 (1 H, dd, $J = 7.5$, 1.8 Hz), 7.26 (2 H, s), 6.94 (1 H, d, $J = 8.0$ Hz), 6.92 (1 H, s) 6.89 (1 H, d, $J = 8.0$ Hz), 4.29 (2 H, q, $J = 6.9$ Hz), 3.81 (3 H, s), 3.66 (1 H, d, $J = 16.0$ Hz), 3.64 (3 H, s), 3.29 (1 H, d, $J = 16.0$ Hz), 2.29 (3 H, s), 1.33 (3 H, t, $J = 7.1$ Hz).
- $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 174.2, 166.2, 160.9, 156.9, 145.2, 138.5, 135.5, 134.5, 131.9, 131.8, 129.3, 123.3, 122.4, 120.3, 111.4, 102.6, 77.3, 77.0, 76.7, 68.1, 62.0, 55.8, 44.7, 30.3, 20.5, 14.0; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm$^{-1}$; HRMS (ESI) for C$_{23}$H$_{23}$N$_3$O$_5$ [M+H]$^+$: calcd 422.1710, found 422.1720.

**Ethyl 5-methoxy-2-(2-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate (3c)**

- White solid; 70% yield in 4 h, mp 217-219 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.39 – 7.35 (1 H, m), 7.31 (1 H, dd, $J = 7.5$, 1.5 Hz), 7.23 (1 H, s), 7.06 (1 H, s), 6.93 (1 H, t, $J = 8.0$ Hz), 6.90 (1 H, d, $J = 12.0$ Hz), 6.81 (1 H, s), 4.29 (2 H, q, $J = 7.0$ Hz), 3.84 (3 H, s), 3.81 (3 H, s), 3.65 (1 H, d, $J = 20.0$ Hz), 3.33 (1 H, d, $J = 20.0$ Hz), 3.26 (3 H, t, $J = 7.1$ Hz).
Ethyl-2-(2-methoxybenzoyl)-1-methyl-2-oxo-5-(trifluoromethoxy)-2,4-dihydropyrido[indoline-3,3-pyrazole]-5-carboxylate(3d)

white solid; 82% yield in 4 h, mp 218-220 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.40 (1 H, t, $J = 11.2$ Hz), 7.33 (1 H, d, $J = 7.5$ Hz), 7.23 (1 H, d, $J = 6.2$ Hz), 7.12 (1 H, s), 6.96 (1 H, t, $J = 7.5$ Hz), 6.92 (1 H, d, $J = 8.4$ Hz), 6.88 (1 H, d, $J = 8.5$ Hz), 4.31 (2 H, q, $J = 8.1$ Hz), 3.82 (3 H, s), 3.71 (1 H, d, $J = 16.0$ Hz), 3.37 (1 H, d, $J = 16.0$ Hz), 3.32 (3 H, s), 1.32 (3 H, t, $J = 7.1$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): 173.6, 166.3, 160.8, 156.8, 145.4, 142.3, 131.9, 129.8, 129.1, 120.2, 120.0 (q, $J_{C,F} = 222.0$ Hz), 111.4, 109.2, 77.3, 77. 0, 76.7, 68.2, 62.0, 55.6, 44.2, 26.9, 14.0. $^{19}$F NMR (376 MHz, CDCl$_3$): δ = -60.1; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm$^{-1}$; HRMS (ESI) for C$_{23}$H$_{20}$F$_3$N$_3$O$_6$ [M+H]$^+$: calecd 492.1377, found 492.1375.

Ethyl 5-fluoro-2-(2-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydropyrido[indoline-3,3-pyrazole]-5-carboxylate(3e)

white solid; 75% yield in 4 h, mp 180-183 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.40 (1 H, t, $J = 11.6$ Hz), 7.35 (1 H, d, $J = 7.5$ Hz), 7.06 (1 H, t, $J = 8.9$ Hz), 6.99 (1 H, d, $J = 4$ Hz), 6.96 (1 H, t, $J = 4.0$ Hz), 6.92 (1 H, d, $J = 4.0$ Hz), 6.83 – 6.81 (1 H, m), 4.31 (2 H, q, $J = 7.2$ Hz), 3.84 (3 H, s), 3.70 (1 H, d, $J = 16.0$ Hz), 3.36 (1 H, d, $J = 16.0$ Hz), 3.30 (3 H, s), 1.31 (3 H, t, $J = 7.1$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): 173.5, 166.4, 160.9, 159.5 (d, $J_{C,F} = 241.0$ Hz), 156.9, 145.3, 139.7 (d, $J_{C,F} = 2.0$ Hz), 131.9, 129.9 (d, $J_{C,F} = 8.0$ Hz), 129.3, 123.3, 120.3, 116.2 (d, $J_{C,F} = 23.0$ Hz), 111.5, 110.7 (d, $J_{C,F} = 25.0$ Hz), 109.2 (d, $J_{C,F} = 8.0$ Hz), 77.3, 77.0, 76.7, 68.5, 62.0, 55.8, 44.2, 26.9, 14.1. $^{19}$F NMR (376 MHz, CDCl$_3$): δ = -120.7; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm$^{-1}$; HRMS (ESI) for C$_{23}$H$_{20}$FN$_3$O$_6$ [M+H]$^+$: calecd 426.1460, found 426.1474.

Ethyl 5-bromo-2-(2-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydropyrido[indoline-3,3-pyrazole]-5-carboxylate(3f)

white solid; 85% yield in 4 h; 90% yield in 4+12 h, mp 199-201 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.47 (1 H, d, $J = 8.2$ Hz), 7.39 (1 H, t, $J = 8.1$ Hz), 7.34 (2 H, d, $J = 8.5$ Hz), 6.95 (1 H, t, $J = 8.0$ Hz), 6.92 (1 H, d, $J = 8.0$ Hz), 6.77 (1 H, d, $J = 8.3$ Hz), 4.30 (2 H, q, $J = 7.1$ Hz), 3.84 (3 H, s), 3.68 (1 H, d, $J = 12.0$ Hz), 3.36 (1 H, d, $J = 12.0$ Hz), 3.29 (3 H, s), 1.31 (3 H, t, $J = 6.8$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 173.3, 166.4, 160.9, 156.9, 145.4, 142.2, 131.9, 130.1, 129.9, 129.2, 128.5, 123.3, 123.1, 120.3, 111.4, 109.6, 77.3, 77.0, 76.7, 68.3, 62.0, 55.8, 44.2, 26.9, 14.1; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm$^{-1}$; HRMS (ESI) for C$_{23}$H$_{20}$BrN$_3$O$_5$ [M+Na]$^+$: calecd 508.0479, found 508.0494.

Ethyl 6-bromo-2-(2-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydropyrido[indoline-3,3-pyrazole]-5-carboxylate(3g)

white solid; 47% yield in 4 h, mp 188-191 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.43 (1 H, s), 7.38 (1 H, t, $J = 8.0$ Hz), 7.32 – 7.26 (2 H, m), 7.15 (1 H, s), 6.95 (1 H, t, $J = 8.0$ Hz), 6.91 (1 H, d, $J = 8.0$ Hz), 4.31 (2 H, q, $J = 6.9$ Hz), 3.84 (3 H, s), 3.69 (1 H, d, $J = 20.0$ Hz), 3.36 (1 H, d, $J = 20.0$ Hz), 3.28 (3 H, s), 1.32 (3 H, t, $J = 7.1$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 173.0, 166.5, 160.7, 156.8, 145.4, 143.8, 132.0, 129.4, 129.1, 127.4, 126.0, 123.1, 120.3, 117.0, 113.8, 111.4, 77.3, 77.0, 76.7, 67.8, 62.1, 55.8, 44.0, 27.0, 14.0; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm$^{-1}$; HRMS (ESI) for C$_{23}$H$_{20}$BrN$_3$O$_5$ [M]$^+$: calecd 486.0659, found 486.0650.

Ethyl-2-(2-methoxybenzoyl)-1-methyl-2-oxo-7-(trifluoromethyl)-2,4-dihydropyrido[indoline-3,3-pyrazole]-5-carboxylate(3h)
Ethyl 1-benzyl-2-(2-methoxybenzoyl)-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate (3i)

white solid; 69% yield in 4 h, mp 195-197 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.61 (1 H, d, J = 8.1 Hz), 7.32 – 7.12 (3 H, m), 7.14 (1 H, t, J = 7.8 Hz), 6.94 - 6.89 (2 H, m), 4.30 (2 H, q, J = 6.7 Hz), 3.82 (3 H, s), 3.77 (1 H, d, J = 20.0 Hz), 3.51 (3 H, s), 3.42 (1 H, d, J = 20.0 Hz), 1.31 (3 H, t, J = 7.1 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 174.7, 166.2, 160.9, 157.0, 145.2, 141.7, 131.4, 129.3, 127.8, 127.8, 125.8, 125.5 (q, J$_{C,F}$ = 284.0 Hz), 123.1, 122.7, 120.4, 77.3, 77.0, 76.7, 66.9, 62.0, 55.9, 44.7, 29.6, 29.5, 14.1. $^{19}$F NMR (376 MHz, CDCl$_3$): δ = -55.2; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm$^{-1}$; HRMS (ESI) for C$_{23}$H$_{26}$F$_3$N$_3$O$_5$ [M+H]$^+$: calc 476.1428, found 476.1444.

Ethyl 2-(2-methoxybenzoyl)-2-oxo-1-phenyl-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3j)

white solid; 66% yield in 4 h, mp 225-227 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.59 (4 H, d, J = 4.3 Hz), 7.50 – 7.47 (1 H, m), 7.44-7.41 (2 H, t, J = 7.0 Hz), 7.34 (2 H, t, J = 7.0 Hz), 7.17 (1 H, t, J = 7.5 Hz), 7.01 (1 H, t, J = 8.0 Hz), 6.98 (1 H, d, J = 8.0 Hz), 6.86 (1 H, d, J = 7.8 Hz), 4.37 (2 H, q, J = 7.6 Hz), 3.89 (1 H, d, J = 20.0 Hz), 3.88 (3 H, s), 3.55 (1 H, d, J = 20.0 Hz), 1.37 (3 H, t, J = 7.1 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 173.3, 166.4, 161.1, 156.9, 145.4, 144.0, 134.3, 131.8, 129.9, 129.6, 129.3, 128.4, 126.9, 123.7, 123.5, 122.8, 120.3, 111.5, 109.8, 77.3, 77.0, 76.7, 68.2, 62.0, 55.8, 44.5, 42.9, 14.1; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm$^{-1}$; HRMS (ESI) for C$_{28}$H$_{33}$N$_5$O$_5$ [M+H]$^+$: calc 484.1867, found 484.1883.

Ethyl 2-(2-methoxybenzoyl)-1-(4-methoxybenzyl)-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3k)

white solid; 60% yield in 4 h, mp 230-232 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.43 – 7.39 (1 H, m), 7.38-7.37 (1 H, m), 7.36 (1 H, s), 7.34 (2 H, t, J = 4.0 Hz), 7.31 (1 H, dd, J = 8.3, 2.0 Hz), 7.23 (1 H, s), 6.99 (1 H, t, J = 7.5 Hz), 6.94 (1 H, d, J = 8.3 Hz), 6.88 (2 H, d, J = 8.7 Hz), 6.56 (1 H, d, J = 8.3 Hz), 5.08 (1 H, m), 4.80 (1 H, d, J = 15.7 Hz), 4.32 (2 H, q, J = 7.2 Hz), 3.86 (3 H, s), 3.75 (3 H, s), 3.74 (1 H, d, J = 20.0 Hz), 3.40 (1 H, d, J = 20.0 Hz), 1.32 (3 H, t, J = 7.1 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 173.3, 166.5, 160.8, 159.1, 156.8, 145.3, 141.6, 132.5, 131.9, 130.6, 129.1, 128.5, 126.5, 125.8, 123.5, 123.2, 115.8, 114.2, 111.4, 77.3, 77.0, 76.7, 68.3, 62.0, 55.8, 55.2, 44.8, 44.0, 14.1; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm$^{-1}$; HRMS (ESI) for C$_{29}$H$_{37}$N$_5$O$_6$ [M+H]$^+$: calc 514.1977, found 514.1979.

Methyl 5-bromo-2-(2-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3l)

white solid; 92% yield in 4+12 h, mp 207-210 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.45 (1 H, d, J = 7.8 Hz), 7.37 (1 H, t, J = 8.0 Hz), 7.31 (2 H, d, J = 11.1 Hz), 6.94 (1 H, t, J = 7.5 Hz), 6.90 (1 H, d, J = 8.4 Hz), 6.76 (1 H, d, J = 8.2 Hz), 3.82 (6 H, s), 3.67 (1 H, d, J = 12.0 Hz), 3.36 (1 H, d, J = 12.0 Hz), 3.27 (3 H, s). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 172.7, 166.0, 160.9, 156.3, 144.8, 142.4, 132.5, 131.5, 130.0, 128.5, 125.5, 123.0, 120.0, 115.3, 111.1, 109.9, 77.3, 77.0, 76.7, 68.0, 55.7, 52.6, 44.1, 26.8; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm$^{-1}$; HRMS (ESI) for C$_{21}$H$_{18}$BrN$_5$O$_5$ [M+H]$^+$: calc 472.0503, found 472.0503.
5-acetyl-5-bromo-2-(2-methoxybenzoyl)-1-methyl-2,4-dihydrospiro[indoline-3,3-pyrazole]-2-one(3m)

white solid; 96% yield in 4+12 h, mp 190-192 ºC. ¹H NMR (400 MHz, CDCl₃): δ = 7.44 (1 H, dd, J = 8.3, 2.0 Hz), 7.41 – 7.37 (1 H, m), 7.32 (1 H, dd, J = 7.5, 1.8 Hz), 7.27 (1 H, d, J = 2.0 Hz), 6.95 (1 H, t, J = 7.5 Hz), 6.89 (1 H, d, J = 8.4 Hz), 6.75 (1 H, d, J = 8.3 Hz), 3.84 (3 H, s), 3.56 (1 H, d, J = 20.0 Hz), 3.31 (1 H, d, J = 20.0 Hz), 3.26 (3 H, s), 2.34 (3 H, s). ¹³C NMR (100 MHz, CDCl₃): δ = 193.4, 172.9, 166.1, 156.4, 151.5, 142.5, 132.6, 131.7, 130.2, 128.8, 125.6, 123.2, 120.1, 115.5, 110.7, 110.0, 77.3, 77.0, 76.7, 68.5, 55.7, 42.7, 27.0, 25.9; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1105 cm⁻¹; HRMS (ESI) for C₂₁H₁₈BrN₃O₄ [M+Na]⁺: calcld 478.0413, found 478.0423.

Ethyl 5-bromo-2-(4-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3n)

white solid; 95% yield in 16 h, mp 227-229 ºC. ¹H NMR (400 MHz, CDCl₃): δ = 7.95 (2 H, d, J = 8.5 Hz), 7.46 (1 H, d, J = 8.4 Hz), 7.31 (1 H, s), 6.90 (2 H, d, J = 8.6 Hz), 6.78 (1 H, d, J = 8.3 Hz), 4.38 (2 H, q, J = 6.9 Hz), 3.84 (3 H, s), 3.66 (1 H, d, J = 16.0 Hz), 3.32 (1 H, d, J = 16.0 Hz), 3.30 (3 H, s), 1.38 (3 H, t, J = 7.0 Hz). ¹³C NMR (100 MHz, CDCl₃): δ = 173.2, 164.8, 162.4, 160.6, 145.3, 142.4, 132.6, 130.7, 125.2, 123.7, 115.6, 113.1, 110.0, 77.3, 77.0, 76.7, 69.3, 62.2, 55.4, 43.4, 27.0, 14.3; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm⁻¹; HRMS (ESI) for C₂₂H₂₀BrN₃O₅ [M+Na]⁺: calcld 508.0479, found 508.0479.

Ethyl 2-acetyl-5-bromo-1-methyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3o)

white solid; 90% yield in 4+12 h, mp 201-204 ºC. ¹H NMR (400 MHz, CDCl₃): δ = 7.43 (1 H, d, J = 9.6 Hz), 7.24 (1 H, s), 6.73 (1 H, d, J = 8.3 Hz), 4.37 (2 H, q, J = 7.1 Hz), 3.64 (1 H, d, J = 16.0 Hz), 3.31 (1 H, d, J = 16.0 Hz), 3.24 (3 H, s), 2.35 (3 H, s), 1.38 (3 H, t, J = 7.1 Hz). ¹³C NMR (100 MHz, CDCl₃): δ = 172.8, 168.4, 160.3, 145.0, 142.2, 132.5, 130.3, 125.2, 115.5, 109.9, 77.3, 77.0, 76.7, 67.7, 62.2, 44.3, 26.8, 21.7, 14.2; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm⁻¹; HRMS (ESI) for C₁₆H₁₆BrN₃O₄ [M+H]⁺: calcld 394.0397, found 394.0401.

N-(5-bromo-3-(cyanomethyl)-1-methyl-2-oxindolin-3-yl)-2-methoxybenzamide (6)

white solid, 57% yield in 4 h, mp 194-196 ºC. ¹H NMR (400 MHz, CDCl₃) δ = 9.26 (1 H, s), 8.07 (1 H, d, J = 6.7 Hz), 7.74 (1 H, d, J = 2.0 Hz), 7.57 – 7.52 (2 H, m), 7.08 (2 H, t, J = 7.3 Hz), 6.87 (1 H, d, J = 8.3 Hz), 4.15 (3 H, s), 3.37 (3 H, s), 3.31 (1 H, d, J = 16.0 Hz), 2.72 (1 H, d, J = 16.0 Hz). ¹³C NMR (100 MHz, CDCl₃): δ = 173.1, 164.4, 157.7, 142.2, 134.0, 132.9, 132.2, 129.5, 126.5, 121.3, 119.2, 116.0, 115.0, 111.4, 110.2, 77.2, 77.0, 76.8, 57.8, 56.2, 27.0, 26.2. IR (in KBr): 3437, 2960, 2926, 1732, 1464, 1304, 1252, 1162, 1057 cm⁻¹; HRMS (ESI) for C₁₉H₁₈BrN₃O₅ [M+Na]⁺: calcld 436.0267, found 436.0269.
10. X-ray single crystal structures of 3f and 6
11. Copies of $^1$H NMR, $^{13}$C NMR and $^{19}$F NMR spectra
$^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of 3a
$^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of 3b
$^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of 3c
$^1$H NMR (400 MHz, CDCl$_3$), $^{13}$C NMR (100 MHz, CDCl$_3$) and $^{19}$F NMR (400 MHz, CDCl$_3$) spectra of 3d
$^1$H NMR (400 MHz, CDCl$_3$), $^{13}$C NMR (100 MHz, CDCl$_3$) and $^{19}$F NMR (376MHz, CDCl$_3$) spectra of 3e
$^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of 3f
$^{1}$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of 3g
$^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) and $^{19}$F NMR (376MHz, CDCl$_3$) spectra of 3h
$^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of 3i
$^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of 3k
$^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of 3l
$^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of 3m
$^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of 3n
$^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of 3o
$^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra of 6