Supporting Information

Biocatalytic one-pot three-component synthesis of 3,3'-disubstituted oxindoles and spirooxindole pyrans using α-amylase from hog pancreas

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1 General information

Reactions were monitored by thin-layer chromatography (TLC) on silica gel precoated glass plates (GF254 silica gel plates) from Haiyang chemical industry Co Ltd, Qingdao, China. Flash column chromatography was performed using silica gel (100–200 mesh) from Haiyang chemical industry Co Ltd, Qingdao, China. Melting points were taken on a YuHua X-4 apparatus and were uncorrected. Organic solutions were concentrated under reduced pressure on rotary evaporator. $^1$H (600 and 300 MHz) NMR, as well as $^{13}$C (150 and 75 MHz) NMR spectra were recorded in d$_6$-DMSO on Bruker-AM 300 (300 MHz) or Bruker Ascend 600 (600 MHz) (Bruker BioSpin AG Ltd., Beijing, China). Chemical shifts were reported in ppm from TMS with the solvent resonance as the internal standard and coupling constants ($J$) in Hz. HRMS were recorded on a Varian 7.0T FTICR-MS spectrometer. X-ray crystal structures were tested in Agilent SuperNova X-ray single-crystal diffractometer. Purity of new products is measured by Shimadzu LC-20AT HPLC with Daicel AD-H chiral column or ELITE Hypersil NH$_2$ column.

2 Materials

$\alpha$-Amylase from hog pancreas, EC Number 3.2.1.1, CAS number: 9000-90-2, powder, ~50 U/mg, product number: 10080, 1 U will liberate 1.0 mg of maltose from starch in 3 minutes at pH 6.9 at 20 °C), was purchased from Sigma-Aldrich.

$\alpha$-Amylase from Aspergillus oryzae, EC Number 3.2.1.1, CAS number: 9001-19-8, powder, ~30 U/mg, Product number: 10065-10G, 1 U will liberate 1.0 mg of maltose from starch in 3 minutes at pH 6.9 at 20 °C), was purchased from Sigma-Aldrich.

$\alpha$-Amylase from Bacillus Subtilis, EC Number 3.2.1.1, powder, ~4 U/mg, 1 U will liberate 1.0 mg of maltose from starch in 3 minutes at pH 6.9 at 20 °C), was purchased from Shanghai kayon Biological Technology Co., Ltd, China.

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification.

3 Comparison of different forms of $\alpha$-amylase for the catalysis on the three-component reaction

In our initial study, to find out an enzyme for the reaction, we have screened several enzymes
which included three α-amylases (α-amylase from hog pancreas, α-amylase from *Aspergillus oryzae*, and α-amylase from *Bacillus Subtilis*). Only the reaction with α-amylase from hog pancreas gave the product in a good yield of 55%. The other two α-amylases gave low yields of 7% and 2%. Thus, α-amylase from hog pancreas was selected as the catalyst for the investigation in this study. The results were represented in **S-Table 1**.

**S-Table 1.** Comparison of different forms of α-amylase for the catalysis on the three-component reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-amylase</th>
<th>Time [d]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>α-amylase from hog pancreas</td>
<td>2</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>α-amylase from <em>Aspergillus oryzae</em></td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>α-amylase from <em>Bacillus Subtilis</em></td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: Reaction conditions: isatin (0.25 mmol), malononitrile (0.25 mmol), acetone (2.5 mmol), α-amylase (30 mg), ethanol (0.90 mL), and deionized water (0.10 mL) at 25 ºC.

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4 **Optimization of reaction conditions**

The influence of the amounts of acetone on the yield of α-amylase-catalyzed reaction was investigated (**S-Table 2**). Initially the yield of the product increased with increasing the amount of acetone (**S-Table 2**, entries 1-6). After acetone reached 30 equivalents (the molar ratio of isatin/malononitrile/acetone = 1:1:30), continuous increase in the amount of acetone did not have an obvious effect on the yield (**S-Table 2**, entries 7 and 8). Thus, we choose 30 equivalents of acetone as the best molar ratio of substrates for the further studies.

**S-Table 2** Influence of the amounts of acetone on the α-amylase-catalyzed three-component reaction

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4 **Optimization of reaction conditions**

The influence of the amounts of acetone on the yield of α-amylase-catalyzed reaction was investigated (**S-Table 2**). Initially the yield of the product increased with increasing the amount of acetone (**S-Table 2**, entries 1-6). After acetone reached 30 equivalents (the molar ratio of isatin/malononitrile/acetone = 1:1:30), continuous increase in the amount of acetone did not have an obvious effect on the yield (**S-Table 2**, entries 7 and 8). Thus, we choose 30 equivalents of acetone as the best molar ratio of substrates for the further studies.

**S-Table 2** Influence of the amounts of acetone on the α-amylase-catalyzed three-component reaction
Temperature has a significant effect on enzyme stability and activity. It is crucial to confirm the optimal temperature for this α-amylase catalyzed reaction. Thus, the effect of temperature on the product yield was investigated (S- Figure 1). The reaction proceeded faster at higher temperatures than at room temperature but afforded lower yield, due to the formation of some side products. So 25 ºC was selected as the optimal temperature for the reaction.
The reactions were carried out with isatin (0.25 mmol), malononitrile (0.25 mmol) and acetone (7.5 mmol) in the presence of α-amylase (738 U) in ethanol (0.90 mL) and deionized water (0.10 mL) for 2 d. Yield of the isolated product.

The influence of enzyme loading on the α-amylase catalyzed three-component reaction was also surveyed (S-Table 3). When 49 U of α-amylase was used, the model reaction only gave the product in a low yield of 25% (S-Table 3, entry 1). Increasing the enzyme loading from 49 U to 246 U led to an obvious increase in yield (S-Table 3, entries 1-5). Further increasing the enzyme loading hardly improved the results. Thus we chose 246 U as the optimal enzyme loading for the three-component reaction.

S-Table 3 Effect of enzyme loading on the α-amylase-catalyzed three-component reaction  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enzyme loading (U)</th>
<th>Yield [%] b</th>
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</tr>
<tr>
<td>4a</td>
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</table>

S-Figure 1 Influence of temperature on the α-amylase-catalyzed reaction
Reaction conditions: isatin (0.25 mmol), malononitrile (0.25 mmol), acetone (7.5 mmol), ethanol (0.90 mL), and deionized water (0.10 mL) at 25 ºC for 2 d.

Yield of the isolated product.

The effect of water content in the system on the reaction yield was also investigated (S-Figure 2). The water content [water/(water+ethanol), in vol.] (%) has been screened from 0 to 60%. The increase of water content from 0 to 10% led to a slight rise in the yield (from 70% to 74%). However, further increasing the water content caused a decrease in yield. Thus we chose a water content of 10% as the optimal condition for the next investigation.

S-Figure 2 Influence of water content on the α-amylase-catalyzed three-component reaction.

The reactions were carried out with isatin (0.25 mmol), malononitrile (0.25 mmol) and acetone (7.5 mmol) in the presence of α-amylase (246 U) in ethanol and deionized water (ethanol + deionized water = 1.0 mL) at 25 ºC for 2 d.
d. Yield of the isolated product.

In order to investigate the relationship between time and yield, we tested the time course of the $\alpha$-amylase-catalyzed model three-component reaction (S-Figure 3). The product yield increased obviously within the first 24 hours, and after that the yield almost kept constant.

![Graph showing the relationship between time and yield]

S-Figure 3 Time course of the $\alpha$-amylase-catalyzed three-component reaction.

The reactions were carried out with isatin (0.25 mmol), malononitrile (0.25 mmol) and acetone (7.5 mmol) in the presence of $\alpha$-amylase (246 U) in ethanol (0.90 mL) and deionized water (0.10 mL) at 25 ºC for 6-72 h. Yield of the isolated product.

5 Crystallographic data

X-ray crystal structure analysis of 6d

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<tr>
<th>Crystal</th>
<th>6d</th>
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Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC: 1053771. Copy of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

**X-ray crystal structure analysis of 11b**

<table>
<thead>
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<th>Property</th>
<th>Value</th>
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</table>

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6 Enzymatic assay of α-amylase

Unit definition (U mg⁻¹), One unit will liberate 1.0 mg of maltose from starch in 3 minutes at pH 6.9 at 20 °C.

The enzymatic assay was conducted according to the literature¹.

7 Characterization data of the products

![Diagram of 4a]
2-(2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile$^{2,3}$

Mp 198-199 °C (lit. 2 199-200 °C), $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 11.02 (s, 1H), 7.51 – 7.18 (m, 2H), 7.14 – 6.75 (m, 2H), 5.54 (s, 1H), 3.62 (d, $J = 18.0$ Hz, 1H), 3.29 (d, $J = 18.0$ Hz, 1H), 2.05 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d6) $\delta$ 204.01, 175.77, 143.42, 130.31, 126.93, 123.77, 122.37, 112.00, 111.64, 110.52, 48.60, 46.04, 30.44, 30.23.

![4b](image)

2-(1-methyl-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile$^{2,3}$

Mp 210-211 °C, $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 7.47 – 7.38 (m, 2H), 7.18 – 7.11 (m, 2H), 5.58 (s, 1H), 3.69 (d, $J = 18.1$ Hz, 1H), 3.32 (s, 1H), 3.21 (s, 3H), 3.15 (d, $J = 6.0$ Hz, 1H), 2.04 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d6) $\delta$ 203.97, 174.17, 144.85, 130.46, 126.19, 123.48, 123.08, 111.87, 111.55, 109.55, 48.22, 46.17, 30.42, 30.15, 26.89.

![4c](image)

2-(4-chloro-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile$^{2,3}$

Mp 206-207 °C (lit. 2 205-206 °C), $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 11.31 (s, 1H), 7.25 (t, $J = 7.9$ Hz, 1H), 7.16 (d, $J = 7.7$ Hz, 1H), 6.95 (d, $J = 7.4$ Hz, 1H), 5.53 (d, $J = 18.1$ Hz, 1H), 3.30 (d, $J = 18.1$ Hz, 1H), 2.08 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d6) $\delta$ 203.81, 174.63, 146.09, 132.55, 126.20, 124.57, 117.92, 111.28, 110.91, 110.14, 50.35, 44.69, 29.93, 28.76.

![4d](image)

2-(4-bromo-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile$^{2,3}$

Mp 197-199 °C (lit. 2 200-201 °C), $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 11.32 (s, 1H), 7.32 (t, $J =
8.0 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 7.7 Hz, 1H), 5.56 (s, 1H), 3.84 (d, J = 18.1 Hz, 1H), 3.33 (d, J = 18.2 Hz, 1H), 2.07 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d6) $\delta$ 203.89, 174.70, 145.80, 132.34, 129.62, 123.06, 122.94, 111.37, 111.02, 109.70, 49.70, 44.72, 29.93, 28.84.

![4e](image)

2-(5-fluoro-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile$^{2,3}$

Mp 204-206 °C (lit. 2 205-206 °C), $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 11.03 (s, 1H), 7.27 (m, 1H), 7.13 (m, 1H), 6.92 (m, 1H), 5.55 (s, 1H), 3.66 (d, J = 18.2 Hz, 1H), 3.30 (d, J = 18.2 Hz, 1H), 2.05 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d6) $\delta$ 204.04, 175.72, 159.74, 156.59, 139.74, 128.61, 128.49, 116.79, 116.49, 112.16, 111.83, 111.74, 111.41, 111.32, 48.99, 45.99, 30.26, 30.06.

![4f](image)

2-(5-chloro-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile$^{2,3}$

Mp 210-211 °C (lit. 2 209-210 °C), $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 11.14 (s, 1H), 7.45 (s, 1H), 7.35 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 5.56 (s, 1H), 3.69 (d, J = 18.3 Hz, 1H), 3.31 (d, J = 18.3 Hz, 1H), 2.05 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d6) $\delta$ 204.13, 175.53, 142.47, 130.18, 129.00, 126.21, 124.23, 111.91, 111.72, 111.39, 48.73, 46.04, 30.23, 30.01.

![4g](image)

2-(5-iodo-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile$^3$

Mp 218-220 °C, $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 11.21 (s, 1H), 7.44 (s, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 5.58 (s, 1H), 3.72 (d, J = 18.2 Hz, 1H), 3.32 (d, J = 18.2 Hz, 1H), 2.04 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d6) $\delta$ 204.19, 175.80, 143.43, 142.69, 128.56, 123.57,
118.02, 111.62, 111.35, 48.81, 45.92, 30.16, 30.02.

2-(5-nitro-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile

Mp 233-234 °C (lit. 2 233-234 °C), \(^{1}\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) 11.75 (s, 1H), 8.37 (d, \(J = 2.1\) Hz, 1H), 8.27 (dd, \(J = 8.7, 2.2\) Hz, 1H), 7.15 (d, \(J = 8.7\) Hz, 1H), 5.71 (s, 1H), 3.88 (d, \(J = 18.4\) Hz, 1H), 3.41 (d, \(J = 18.5\) Hz, 1H), 2.06 (s, 3H). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\) 204.34, 176.32, 150.00, 142.65, 127.98, 127.57, 120.21, 111.48, 111.18, 110.62, 48.53, 46.28, 29.94, 29.82.

2-(2-oxo-3-(2-oxopropyl)-5-(trifluoromethoxy)indolin-3-yl)malononitrile

Mp 147-149 °C, \(^{1}\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) 11.13 (s, 1H), 7.70 (s, 1H), 7.63 (d, \(J = 8.2\) Hz, 1H), 6.78 (d, \(J = 8.2\) Hz, 1H), 5.54 (s, 1H), 3.68 (d, \(J = 18.3\) Hz, 1H), 3.29 (d, \(J = 18.3\) Hz, 1H), 2.05 (s, 3H). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\) 204.17, 175.26, 143.29, 138.80, 132.22, 129.63, 112.86, 111.75, 111.42, 85.13, 48.45, 46.06, 30.26, 30.04.

2-(5-methyl-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile

Mp 207-208 °C (lit. 2 206-207 °C), \(^{1}\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) 10.89 (s, 1H), 7.18 (s, 1H), 7.09 (d, \(J = 7.9\) Hz, 1H), 6.81 (d, \(J = 7.9\) Hz, 1H), 5.49 (s, 1H), 3.57 (d, \(J = 18.0\) Hz, 1H), 3.25 (d, \(J = 18.1\) Hz, 1H), 2.24 (s, 3H), 2.03 (s, 3H). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\) 203.97, 175.72, 140.97, 131.25, 130.56, 127.02, 124.31, 112.04, 111.66, 110.29, 48.65, 46.07, 30.49, 30.23, 21.15.
2-(5-methoxy-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile$^{2,3}$

Mp 203-204 °C (lit. 202-203 °C), $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 10.81 (s, 1H), 7.01 (s, 1H), 6.84 (s, 2H), 5.50 (s, 1H), 3.69 (s, 1H), 3.60 (d, $J$ = 18.1 Hz, 1H), 3.24 (d, $J$ = 18.1 Hz, 1H), 2.03 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d6) $\delta$ 203.98, 175.57, 155.22, 136.54, 128.18, 114.33, 111.97, 111.62, 111.22, 110.88, 55.76, 48.94, 46.00, 30.46, 30.22.

2-(6-bromo-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile$^3$

Mp 202-204 °C, $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 11.17 (s, 1H), 7.32 (d, $J$ = 8.0 Hz, 1H), 7.23 (d, $J$ = 8.0 Hz, 1H), 7.09 (s, 1H), 5.55 (s, 1H), 3.64 (d, $J$ = 18.2 Hz, 1H), 3.31 (d, $J$ = 18.2 Hz, 1H), 2.04 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d6) $\delta$ 204.10, 175.67, 145.12, 126.35, 125.70, 125.05, 123.11, 113.32, 111.77, 111.42, 48.40, 46.03, 30.12, 30.08.

2-(7-chloro-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile$^2$

Mp 197-199 °C (lit. 200-201 °C), $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 11.47 (s, 1H), 7.36 (t, $J$ = 8.4 Hz, 2H), 7.04 (t, $J$ = 7.9 Hz, 1H), 5.58 (s, 1H), 3.67 (d, $J$ = 18.2 Hz, 1H), 3.35 (d, $J$ = 18.2 Hz, 1H), 2.04 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d6) $\delta$ 204.12, 175.75, 141.24, 130.38, 128.81, 123.70, 122.47, 114.71, 111.72, 111.41, 49.31, 46.23, 30.34, 30.07.
2-(4,6-dibromo-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile

Mp 207-209 °C, $^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.50 (s, 1H), 7.45 (d, J = 1.1 Hz, 1H), 7.12 (d, J = 1.1 Hz, 1H), 5.55 (s, 1H), 3.84 (d, J = 22.0 Hz, 1H), 3.33 (d, J = 18.3 Hz, 1H), 2.09 (s, 3H).
$^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 203.98, 174.61, 147.19, 127.98, 124.25, 118.81, 113.01, 111.17, 110.68, 50.20, 44.74, 29.83, 28.54.

2-(1-methyl-3-(nitromethyl)-2-oxoindolin-3-yl)malononitrile

Mp 162-164 °C, $^1$H NMR (300 MHz, DMSO-d$_6$) δ 7.56 (d, J = 7.3 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.27 – 7.15 (m, 2H), 5.78 (s, 1H), 5.49 (q, J = 14.1 Hz, 2H), 3.24 (s, 3H).
$^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 171.80, 144.65, 131.80, 124.33, 123.83, 122.59, 111.11, 110.70, 110.36, 75.73, 49.69, 28.79, 27.17. HRMS (QFT-ESI): calcd for C$_{13}$H$_9$N$_4$O$_3$ [M-H]$^-$: 369.0680, found 369.0677.

The purity was determined by HPLC on Daicel AD-H chiral column with i-PrOH /Hexane (20:80) as the eluent. Flow: 1.0 mL/min; $\lambda$ = 254 nm: $t_1$ = 12.877 min; $t_2$ = 16.696 min

2-(5-fluoro-3-(nitromethyl)-2-oxoindolin-3-yl)malononitrile

Mp 154-156 °C, $^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.39 (s, 1H), 7.45 (dd, J = 8.1, 2.4 Hz, 1H), 7.25 (td, J = 9.2, 2.5 Hz, 1H), 7.01 (dd, J = 8.6, 4.3 Hz, 1H), 5.74 (s, 1H), 5.48 (dd, J = 39.5, 14.3 Hz, 2H).
$^{13}$C NMR (151 MHz, DMSO-d$_6$) δ 173.43, 159.23, 157.65, 139.80, 124.99, 118.37, 118.22, 112.88, 112.71, 112.50, 112.44, 111.04, 110.57, 75.63, 50.49, 28.71. HRMS (QFT-ESI): calcd for C$_{12}$H$_8$FN$_4$O$_3$ [M-H]$^-$: 273.0430, found 273.0427. The purity was determined by HPLC.
on Daicel AD-H chiral column with i-PrOH /Hexane (8:92) as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t₁ = 48.874 min; t₂ = 55.111 min

![Image](image_url)

**2-(3-(nitromethyl)-2-oxo-5-(trifluoromethoxy)indolin-3-yl)malononitrile**

Mp 130-132 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 11.56 (s, 1H), 7.63 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 5.78 (s, 1H), 5.52 (dd, J = 46.7, 14.3 Hz, 2H). ¹³C NMR (151 MHz, DMSO-d₆) δ 173.51, 143.88, 142.69, 125.05, 121.43, 119.73, 118.80, 112.42, 110.94, 110.50, 75.58, 50.33, 28.61. HRMS (QFT-ESI): calcd for C₁₃H₆F₃N₄O₄ [M-H]⁻: 339.0347, found 339.0345. The purity was determined by HPLC on Daicel AD-H chiral column with i-PrOH /Hexane (10:90) as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t₁ = 14.710 min; t₂ = 16.237 min

![Image](image_url)

**2-(5-methyl-3-(nitromethyl)-2-oxoindolin-3-yl)malononitrile**

Mp 185-187 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 11.24 (s, 1H), 7.32 (s, 1H), 7.18 (d, J = 7.9 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H), 5.70 (s, 1H), 5.50 – 5.33 (m, 2H), 2.26 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 173.38, 140.88, 132.16, 131.95, 124.95, 123.39, 111.25, 111.04, 110.79, 75.82, 50.11, 28.78, 21.08. HRMS (QFT-ESI): calcd for C₁₃H₉N₄O₃ [M-H]⁻: 269.0680, found 369.0678.

The purity was determined by HPLC on Daicel AD-H chiral column with i-PrOH /Hexane (20:80) as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t₁ = 6.061 min; t₂ = 7.630 min

![Image](image_url)

**2-(6-bromo-3-(nitromethyl)-2-oxoindolin-3-yl)malononitrile**
Mp 47-49 °C, $^1$H NMR (300 MHz, DMSO-d6) δ 11.52 (s, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.35 (dd, J = 8.1, 1.7 Hz, 1H), 7.16 (d, J = 1.6 Hz, 1H), 5.75 (s, 1H), 5.47 (dd, J = 30.6, 14.2 Hz, 2H). $^{13}$C NMR (75 MHz, DMSO-d6) δ 173.36, 144.94, 126.55, 125.93, 124.56, 122.74, 114.12, 111.05, 110.54, 75.54, 49.86, 28.49. The purity was determined by HPLC on Daicel AD-H chiral column with i-PrOH /Hexane (20:80) as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t₁ = 26.809 min; t₂ = 31.815 min.

![Structure 6f](image)

2-(7-chloro-3-(nitromethyl)-2-oxoindolin-3-yl)malononitrile

Mp 153-155 °C, $^1$H NMR (300 MHz, DMSO-d6) δ 11.84 (s, 1H), 7.49 (dd, J = 7.2, 5.9 Hz, 2H), 7.15 (t, J = 7.9 Hz, 1H), 5.78 (s, 1H), 5.51 (q, J = 14.3 Hz, 2H). $^{13}$C NMR (75 MHz, DMSO-d6) δ 173.49, 141.18, 131.72, 125.22, 124.50, 123.50, 115.40, 111.00, 110.53, 75.69, 50.73, 28.72. HRMS (QFT-ESI): calcd for C$_{12}$H$_6$ClN$_4$O$_3$ [M-H]⁻ : 289.0134, found 289.0135. The purity was determined by HPLC on Daicel AD-H chiral column with i-PrOH /Hexane (20:80) as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t₁ = 14.154 min; t₂ = 24.643 min.

![Structure 8a](image)

2-(3-(1H-indol-3-yl)-2-oxoindolin-3-yl)malononitrile

Brown oil, $^1$H NMR (300 MHz, DMSO-d6) δ 11.45 (s, 1H), 11.24 (s, 1H), 7.43 (t, J = 8.1 Hz, 4H), 7.10 (ddd, J = 22.8, 15.4, 8.0 Hz, 4H), 6.89 (t, J = 7.5 Hz, 1H), 6.30 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-d6) δ 175.08, 142.65, 137.20, 130.91, 128.01, 125.63, 125.08, 124.62, 123.15, 122.28, 119.80, 119.54, 113.01, 112.56, 112.29, 111.15, 108.29, 60.17, 52.86, 30.17, 21.14, 14.46. HRMS (QFT-ESI): calcd for C$_{19}$H$_{11}$N$_4$O [M-H]⁻ : 311.0938, found 311.0935. The purity was determined by HPLC on Elite Hypersil NH$_2$ column with methanol as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t = 6.784 min.
2-(3-(1H-indol-3-yl)-5-iodo-2-oxoindolin-3-yl)malononitrile

Brown oil, $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.47 (s, 1H), 11.41 (s, 1H), 7.76 (d, $J = 8.2$ Hz, 1H), 7.63 (s, 1H), 7.44 (dd, $J = 11.5$, 5.3 Hz, 2H), 7.15 – 7.01 (m, 2H), 6.93 (dd, $J = 12.8$, 7.8 Hz, 2H), 6.35 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 174.47, 142.29, 139.46, 137.12, 133.07, 130.63, 125.55, 124.37, 122.42, 120.01, 119.06, 113.60, 112.72, 112.04, 107.75, 85.90, 52.49, 29.81. HRMS (QFT-ESI): calcd for C$_{19}$H$_{10}$IN$_4$O $[M-H]^-$: 436.9905, found 436.9901. The purity was determined by HPLC on Elite Hypersil NH$_2$ column with methanol as the eluent. Flow: 1.0 mL/min; $\lambda = 254$ nm: $t = 19.035$ min.

2-(3-(1H-indol-3-yl)-5-nitro-2-oxoindolin-3-yl)malononitrile

Brown oil, $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 12.03 (s, 1H), 11.56 (s, 1H), 8.39 (dd, $J = 8.7$, 2.2 Hz, 1H), 8.31 (d, $J = 2.1$ Hz, 1H), 7.54 (d, $J = 2.6$ Hz, 1H), 7.45 (d, $J = 8.1$ Hz, 1H), 7.37 – 7.25 (m, 2H), 7.13 (t, $J = 7.5$ Hz, 1H), 6.98 (t, $J = 7.5$ Hz, 1H), 6.53 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 175.44, 148.68, 143.23, 137.30, 128.78, 127.99, 126.14, 124.21, 122.54, 120.70, 120.18, 119.27, 112.82, 112.48, 111.88, 111.60, 106.93, 52.70, 29.72. HRMS (QFT-ESI): calcd for C$_{19}$H$_{10}$N$_5$O$_3$ $[M-H]^-$: 356.0789, found 356.0785. The purity was determined by HPLC on Elite Hypersil NH$_2$ column with methanol as the eluent. Flow: 1.0 mL/min; $\lambda = 254$ nm: $t = 51.267$ min.

2-(3-(1H-indol-3-yl)-2-oxo-5-(trifluoromethoxy)indolin-3-yl)malononitrile
Brown oil, $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.51 (s, 2H), 7.55 – 7.36 (m, 4H), 7.23 (d, J = 8.5 Hz, 1H), 7.10 (dd, J = 14.9, 7.5 Hz, 2H), 6.93 (t, J = 7.5 Hz, 1H), 6.41 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 175.05, 143.93, 143.90, 141.86, 137.19, 129.48, 125.75, 124.40, 124.33, 122.42, 119.96, 119.18, 118.67, 112.71, 112.66, 112.37, 111.98, 107.41, 53.01, 29.94. HRMS (QFT-ESI): calcd for C$_{20}$H$_{10}$F$_3$N$_4$O$_2$ [M-H]$^-$: 395.0761, found 395.0758. The purity was determined by HPLC on Elite Hypersil NH$_2$ column with methanol as the eluent. Flow: 1.0 mL/min; $\lambda$ = 254 nm: t = 18.902 min.

![Image of 2-(7-chloro-3-(1H-indol-3-yl)-2-oxoindolin-3-yl)malononitrile](image)

2-(7-chloro-3-(1H-indol-3-yl)-2-oxoindolin-3-yl)malononitrile

Brown oil, $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.74 (s, 1H), 11.50 (d, J = 1.4 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.42 (dd, J = 6.6, 3.4 Hz, 3H), 7.14 (dt, J = 19.8, 6.8 Hz, 3H), 6.94 (t, J = 7.5 Hz, 1H), 6.38 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 175.04, 140.37, 137.22, 130.95, 129.67, 125.79, 124.58, 128.41, 123.75, 122.41, 120.00, 119.37, 115.39, 112.70, 112.09, 107.61, 60.17, 53.63, 30.10. HRMS (QFT-ESI): calcd for C$_{19}$H$_{10}$ClN$_4$O [M-H]$^-$: 345.0548, found 345.0544. The purity was determined by HPLC on Elite Hypersil NH$_2$ column with methanol as the eluent. Flow: 1.0 mL/min; $\lambda$ = 254 nm: t = 14.718 min.

![Image of 3'-acetyl-6'-amino-2'-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile](image)

3'-acetyl-6'-amino-2'-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile

Mp 243-244 °C (lit. 4 240 °C), $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 10.38 (s, 1H), 7.19 – 7.07 (m, 3H), 7.02 (d, J = 7.2 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 2.27 (s, 3H), 2.07 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 197.89, 178.92, 159.60, 156.61, 142.34, 134.49, 128.89, 123.72, 122.26, 117.96, 115.22, 109.81, 57.02, 49.76, 31.73, 19.76.
3'-acetyl-6'-amino-1,2'-dimethyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile

Mp 248-250 °C (lit. 250-252 °C), \(^1\)H NMR (300 MHz, DMSO-d6) \(\delta\) 7.24 (t, \(J = 7.6\) Hz, 1H), 7.17 (s, 2H), 7.08 (d, \(J = 7.0\) Hz, 1H), 6.98 (t, \(J = 7.9\) Hz, 2H), 3.11 (s, 3H), 2.30 (s, 3H), 2.07 (s, 3H). \(^{13}\)C NMR (75 MHz, DMSO-d6) \(\delta\) 197.15, 176.95, 159.16, 156.81, 143.37, 133.39, 128.57, 122.91, 122.48, 117.36, 114.76, 108.28, 56.27, 48.91, 31.31, 26.33, 19.47.

3'-acetyl-6'-amino-2'-methyl-5-nitro-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile

Mp >300 °C, \(^1\)H NMR (300 MHz, DMSO-d6) \(\delta\) 11.11 (s, 1H), 8.12 (dd, \(J = 8.6, 2.2\) Hz, 1H), 7.93 (d, \(J = 2.0\) Hz, 1H), 7.33 (s, 2H), 6.98 (d, \(J = 8.6\) Hz, 1H), 2.42 (s, 3H), 2.24 (s, 3H). \(^{13}\)C NMR (75 MHz, DMSO-d6) \(\delta\) 197.34, 179.58, 160.12, 159.44, 148.97, 142.68, 136.44, 126.14, 119.00, 117.58, 114.60, 109.78, 55.93, 49.93, 32.00, 20.57.

3'-acetyl-6'-amino-5-chloro-2'-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile

Mp 276 °C, \(^1\)H NMR (300 MHz, DMSO-d6) \(\delta\) 10.80 (s, 1H), 7.20 (d, \(J = 10.7\) Hz, 3H), 7.00 (d, \(J = 7.0\) Hz, 1H), 6.91 (t, \(J = 7.7\) Hz, 1H), 2.33 (s, 3H), 2.16 (s, 3H). \(^{13}\)C NMR (75 MHz, DMSO-d6) \(\delta\) 197.65, 178.94, 159.47, 157.96, 140.17, 136.63, 128.80, 123.47, 122.21, 117.77, 115.10, 113.93, 56.60, 50.66, 31.93, 20.08.
3'-acetyl-6'-amino-5-iodo-2'-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile

Mp >300 °C, 1H NMR (300 MHz, DMSO-d6) δ 10.49 (s, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.32 (s, 1H), 7.19 (s, 2H), 6.63 (d, J = 8.1 Hz, 1H), 2.33 (s, 3H), 2.17 (s, 3H). 13C NMR (75 MHz, DMSO-d6) δ 197.42, 178.44, 159.39, 158.58, 142.14, 137.79, 137.26, 131.68, 117.82, 114.86, 112.24, 84.91, 56.69, 49.82, 31.98, 20.27.

3'-acetyl-6'-amino-2',5-dimethyl-2-methylenespiro[indoline-3,4'-pyran]-5'-carbonitrile

Mp 280-281 °C, 1H NMR (300 MHz, DMSO-d6) δ 10.29 (s, 1H), 7.10 (s, 2H), 6.94 (d, J = 7.7 Hz, 1H), 6.83 (s, 1H), 6.66 (d, J = 7.8 Hz, 1H), 2.27 (s, 3H), 2.20 (s, 3H), 2.07 (s, 3H). 13C NMR (75 MHz, DMSO-d6) δ 197.75, 178.90, 159.52, 156.69, 139.82, 134.70, 131.11, 129.17, 124.26, 118.01, 115.23, 109.58, 57.28, 49.82, 31.70, 21.04, 19.79.

3'-acetyl-6'-amino-5-methoxy-2'-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile

Mp 275-277 °C, 1H NMR (600 MHz, DMSO-d6) δ 10.22 (s, 1H), 7.11 (s, 2H), 6.74 (dt, J = 17.9, 5.4 Hz, 2H), 6.68 (d, J = 2.5 Hz, 1H), 3.68 (s, 3H), 2.29 (s, 3H), 2.11 (s, 3H). 13C NMR (151 MHz, DMSO-d6) δ 197.95, 178.88, 159.67, 156.57, 155.55, 135.82, 135.73, 118.04, 115.20, 113.55, 110.71, 110.31, 57.27, 55.87, 50.35, 31.75, 19.80.
3'-acetyl-6'-amino-7-chloro-2'-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile<sup>4</sup>

Mp 276-277 °C, <sup>1</sup>H NMR (300 MHz, DMSO-d6) δ 10.80 (s, 1H), 7.20 (d, J = 9.4 Hz, 3H), 7.00 (d, J = 7.0 Hz, 1H), 6.91 (t, J = 7.7 Hz, 1H), 2.33 (s, 3H), 2.16 (s, 3H). <sup>13</sup>C NMR (75 MHz, DMSO-d6) δ 197.66, 178.95, 159.47, 157.98, 140.16, 136.63, 128.80, 123.48, 122.21, 117.78, 115.09, 113.93, 56.59, 50.66, 31.93, 20.08.

2'-amino-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyran][3,2-c]chromene]-3'-carbonitrile<sup>5,6</sup>

Mp >300 °C (lit. 6 >300 °C), <sup>1</sup>H NMR (300 MHz, DMSO-d6) δ 10.69 (s, 1H), 7.92 (dd, J = 7.8, 1.1 Hz, 1H), 7.80 – 7.71 (m, 1H), 7.68 (s, 2H), 7.57 – 7.43 (m, 2H), 7.20 (dt, J = 7.4, 3.6 Hz, 2H), 6.92 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H). <sup>13</sup>C NMR (75 MHz, DMSO-d6) δ 177.58, 158.84, 158.69, 155.48, 152.43, 142.57, 134.08, 133.45, 129.34, 125.42, 124.54, 123.07, 122.47, 117.41, 117.07, 112.85, 109.92, 101.80, 57.37, 48.00.

2'-amino-1-methyl-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyran][3,2-c]chromene]-3'-carbonitrile<sup>6</sup>

Mp 227-229 °C (lit. 6 225 °C), <sup>1</sup>H NMR (600 MHz, DMSO-d6) δ 7.96 (d, J = 7.8 Hz, 1H), 7.74 (s, 2H), 7.53 (t, J = 7.7 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.3 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 3.23 (s, 3H). <sup>13</sup>C NMR (151 MHz, DMSO-
2'-amino-5-nitro-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile

Mp 200-202 °C (lit. 198 °C), $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta$ 11.46 (s, 1H), 8.37 (d, $J = 2.0$ Hz, 1H), 8.23 (dd, $J = 8.7, 2.1$ Hz, 1H), 7.97 (d, $J = 7.9$ Hz, 1H), 7.87 (s, 2H), 7.77 (t, $J = 7.8$ Hz, 1H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.49 (d, $J = 8.3$ Hz, 1H), 7.12 (d, $J = 8.7$ Hz, 1H). $^{13}$C NMR (151 MHz, DMSO-d$_6$) $\delta$ 178.41, 159.30, 159.19, 156.31, 152.61, 149.10, 143.25, 134.48, 134.22, 126.79, 125.47, 123.29, 121.01, 117.32, 117.14, 113.13, 110.20, 100.71, 56.54, 56.14, 48.28.

2'-amino-5-fluoro-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile

Mp >300 °C (lit. >300 °C), $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta$ 10.73 (s, 1H), 7.96 (d, $J = 7.8$ Hz, 1H), 7.73 (s, 2H), 7.54 (t, $J = 7.6$ Hz, 1H), 7.50 (d, $J = 8.3$ Hz, 1H), 7.27 (d, $J = 7.5$ Hz, 1H), 7.07 (t, $J = 8.7$ Hz, 1H), 6.88 (dd, $J = 8.1, 3.9$ Hz, 1H). $^{13}$C NMR (151 MHz, DMSO-d$_6$) $\delta$ 177.74, 159.64, 159.04, 158.88, 158.06, 155.82, 152.58, 138.90, 135.20, 135.15, 134.16, 125.45, 123.21, 117.35, 117.12, 115.75, 113.01, 112.71, 112.54, 110.74, 110.69, 101.41, 57.13, 48.61.
2'-amino-5-chloro-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile\textsuperscript{5,6}

Mp 277-279 °C (lit. \textsuperscript{6} 275 °C), \textsuperscript{1}H NMR (300 MHz, DMSO-d\textsubscript{6}) δ 10.85 (s, 1H), 7.97 – 7.87 (m, 1H), 7.81 – 7.69 (m, 3H), 7.56 – 7.39 (m, 3H), 7.26 (dd, J = 8.3, 2.1 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H). \textsuperscript{13}C NMR (75 MHz, DMSO-d\textsubscript{6}) δ 177.48, 158.98, 158.91, 155.84, 152.48, 141.50, 135.44, 134.07, 129.23, 126.53, 125.36, 125.00, 123.13, 117.37, 117.04, 112.96, 111.31, 101.15, 56.74, 48.28.

![Diagram of 13f](image)

2'-amino-5-iodo-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile\textsuperscript{6}

Mp >300 °C, \textsuperscript{1}H NMR (600 MHz, DMSO-d\textsubscript{6}) δ 10.85 (s, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.75 (s, 2H), 7.67 (s, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H). \textsuperscript{13}C NMR (151 MHz, DMSO-d\textsubscript{6}) δ 177.24, 159.06, 159.00, 155.92, 152.55, 142.48, 137.97, 136.11, 134.10, 133.08, 125.42, 123.23, 117.48, 117.10, 113.08, 112.48, 101.31, 85.49, 56.99, 56.59, 48.12.

![Diagram of 13g](image)

2'-amino-5-methyl-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile\textsuperscript{7}

Mp >300 °C, \textsuperscript{1}H NMR (300 MHz, DMSO-d\textsubscript{6}) δ 10.59 (s, 1H), 7.96 – 7.88 (m, 1H), 7.78 – 7.70 (m, 1H), 7.66 (s, 2H), 7.49 (dd, J = 18.9, 8.0 Hz, 2H), 7.01 (d, J = 10.0 Hz, 2H), 6.74 (d, J = 7.7 Hz, 1H), 2.18 (s, 3H). \textsuperscript{13}C NMR (75 MHz, DMSO-d\textsubscript{6}) δ 177.55, 158.81, 158.70, 155.42, 152.41, 140.10, 134.03, 133.57, 131.41, 129.59, 125.40, 125.07, 123.05, 117.48, 117.04, 112.86, 109.66, 101.92, 57.57, 48.03, 20.98.
2'-amino-5-methoxy-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile

Mp 271-273 °C (lit. 6 269 °C), $^1$H NMR (600 MHz, DMSO-d6) $\delta$ 10.53 (s, 1H), 7.95 (dd, $J = 7.9$, 1.4 Hz, 1H), 7.78 – 7.72 (m, 1H), 7.67 (s, 2H), 7.52 (dd, $J = 11.4$, 4.1 Hz, 1H), 7.48 (d, $J = 8.3$ Hz, 1H), 6.94 (s, 1H), 6.80 (d, $J = 1.4$ Hz, 2H), 3.67 (s, 3H).

$^{13}$C NMR (151 MHz, DMSO-d6) $\delta$ 177.62, 158.92, 158.82, 155.78, 155.61, 152.53, 135.93, 134.79, 134.03, 125.38, 123.16, 117.55, 117.08, 114.26, 113.04, 111.40, 110.40, 101.89, 57.71, 55.89, 48.61

2'-amino-6-bromo-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile

Mp >300 °C, $^1$H NMR (600 MHz, DMSO-d6) $\delta$ 10.88 (s, 1H), 7.95 (d, $J = 7.9$ Hz, 1H), 7.75 (s, 2H), 7.54 (t, $J = 7.6$ Hz, 1H), 7.49 (d, $J = 8.3$ Hz, 1H), 7.24 (d, $J = 7.9$ Hz, 1H), 7.15 (d, $J = 7.9$ Hz, 1H), 7.04 (s, 1H). $^{13}$C NMR (151 MHz, DMSO-d6) $\delta$ 177.59, 159.02, 158.89, 155.80, 152.54, 144.34, 134.23, 132.81, 126.60, 125.51, 125.22, 123.19, 122.02, 117.37, 117.16, 112.91, 112.81, 101.30, 56.78, 56.53, 47.92.

2'-amino-7-chloro-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile

24
carbonitrile

Mp >300 °C (lit. 6 >300 °C), H NMR (300 MHz, DMSO-d6) δ 11.17 (s, 1H), 8.00 – 7.88 (m, 1H), 7.78 (s, 2H), 7.76 – 7.70 (m, 1H), 7.50 (dd, J = 16.7, 8.1 Hz, 2H), 7.25 (dd, J = 16.2, 7.7 Hz, 2H), 6.96 (t, J = 7.8 Hz, 1H). C NMR (75 MHz, DMSO-d6) δ 177.67, 158.92, 158.84, 155.68, 152.45, 140.34, 135.15, 134.21, 129.43, 125.46, 123.82, 123.35, 123.14, 117.29, 117.10, 114.14, 112.78, 101.29, 56.80, 56.45, 48.87, 18.93.

2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile

Mp >300 °C (lit. 10 >300 °C), H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 7.23 (s, 2H), 7.12 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 7.0 Hz, 1H), 6.88 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 2.59 – 2.47 (m, 2H), 2.12 (q, J = 16.0 Hz, 2H), 0.99 (d, J = 9.8 Hz, 6H). C NMR (75 MHz, DMSO-d6) δ 195.34, 178.48, 164.58, 159.17, 142.42, 134.81, 128.59, 123.41, 122.12, 117.78, 111.16, 109.67, 57.84, 50.38, 47.20, 32.34, 28.01, 27.40, 18.96.

2-amino-1',7,7-trimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile

Mp 237-239 °C, H NMR (300 MHz, DMSO-d6) δ 7.34 – 7.19 (m, 3H), 7.03 (d, J = 7.0 Hz, 1H), 6.96 (t, J = 7.5 Hz, 2H), 3.12 (s, 3H), 2.52 (d, J = 19.8 Hz, 2H), 2.10 (q, J = 16.0 Hz, 2H), 0.99 (d, J = 10.1 Hz, 6H). C NMR (75 MHz, DMSO-d6) δ 195.35, 176.97, 164.69, 159.28, 143.93, 133.93, 128.82, 123.17, 122.87, 117.64, 111.10, 108.60, 57.37, 50.31, 46.84, 32.38, 27.93, 27.44, 26.77.
2-amino-4’-chloro-7,7-dimethyl-2’,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3’-indoline]-3-carbonitrile

Mp >300 °C, $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 10.70 (s, 1H), 7.36 (s, 2H), 7.18 (t, J = 8.0 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 2.64 – 2.38 (m, 2H), 2.15 (dd, J = 51.2, 16.1 Hz, 1H), 1.01 (d, J = 11.7 Hz, 6H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 195.52, 177.67, 165.53, 160.23, 144.40, 130.47, 129.49, 129.38, 122.51, 117.56, 109.73, 108.82, 54.79, 50.25, 47.68, 32.16, 28.55, 26.96, 18.97.

2-amino-7,7-dimethyl-5’-nitro-2’,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3’-indoline]-3-carbonitrile

Mp >300 °C, $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.20 (s, 1H), 8.14 (dd, J = 8.6, 2.2 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.47 (s, 2H), 7.01 (d, J = 8.6 Hz, 1H), 2.57 (dd, J = 43.3, 17.5 Hz, 2H), 2.23 – 2.06 (m, 2H), 1.02 (d, J = 10.7 Hz, 6H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 195.81, 179.05, 165.63, 159.49, 149.04, 142.80, 135.76, 126.21, 119.27, 117.50, 110.14, 109.85, 56.44, 56.22, 50.17, 47.35, 32.45, 28.05, 27.38, 18.93.

2-amino-5’-fluoro-7,7-dimethyl-2’,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3’-indoline]-
3-carbonitrile$^8,9$
Mp 300 °C, $^1$H NMR (300 MHz, DMSO-d$_6$) δ 10.44 (s, 1H), 7.30 (s, 2H), 6.95 (t, $J = 7.5$ Hz, 2H), 6.84 – 6.70 (m, 1H), 2.53 (s, 2H), 2.13 (s, 2H), 1.02 (d, $J = 11.6$ Hz, 6H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 195.44, 195.41, 178.51, 164.88, 160.16, 159.28, 157.03, 138.69, 138.67, 136.53, 136.43, 117.62, 114.94, 114.64, 111.48, 111.15, 110.72, 110.36, 110.26, 57.36, 56.46, 50.37, 47.76, 47.74, 32.32, 27.77, 27.72, 18.93.

![3-carbonitrile](15f)

2-amino-5'-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile$^{5,8-10}$
Mp 289-291 °C (lit. 10 286-288 °C), $^1$H NMR (300 MHz, DMSO-d$_6$) δ 10.56 (s, 1H), 7.32 (s, 2H), 7.18 (dd, $J = 8.2$, 1.6 Hz, 1H), 7.09 (s, 1H), 6.80 (d, $J = 8.2$ Hz, 1H), 2.63 – 2.47 (m, 2H), 2.13 (s, 2H), 1.02 (d, $J = 13.3$ Hz, 6H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 195.55, 177.90, 165.01, 159.24, 142.30, 137.44, 137.17, 131.77, 117.68, 112.19, 110.61, 84.89, 57.16, 56.47, 50.33, 47.22, 32.41, 27.91, 27.59, 18.98.

![2-amino-5'-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile](15g)

2-amino-5'-iodo-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile$^9$
Mp 298-300 °C, $^1$H NMR (300 MHz, DMSO-d$_6$) δ 10.54 (s, 1H), 7.47 (d, $J = 8.1$ Hz, 1H), 7.31 (d, $J = 3.1$ Hz, 3H), 6.65 (d, $J = 8.1$ Hz, 1H), 2.53 (q, $J = 17.5$ Hz, 2H), 2.14 (s, 2H), 1.02 (d, $J = 14.1$ Hz, 2H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 195.55, 177.90, 165.01, 159.24, 142.30, 137.44, 137.17, 131.77, 117.68, 112.19, 110.61, 84.89, 57.16, 56.47, 50.33, 47.22, 32.41, 27.91, 27.59, 18.98.
2-amino-5',7,7-trimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile\textsuperscript{8-11}

Mp 279-281 °C (lit. 11 279-280 °C), \textsuperscript{1}H NMR (300 MHz, DMSO-d\textsubscript{6}) \(\delta\) 10.29 (s, 1H), 7.20 (s, 2H), 6.92 (d, \(J = 7.8\) Hz, 1H), 6.77 (s, 1H), 6.66 (d, \(J = 7.8\) Hz, 1H), 2.54 (s, 2H), 2.15 (d, \(J = 18.9\) Hz, 5H), 1.00 (d, \(J = 6.0\) Hz, 6H). \textsuperscript{13}C NMR (75 MHz, DMSO-d\textsubscript{6}) \(\delta\) 195.32, 178.43, 164.47, 159.11, 139.99, 134.91, 130.87, 128.85, 124.00, 117.82, 111.22, 109.40, 58.03, 50.41, 47.23, 32.36, 27.86, 27.60, 21.07.

2-amino-5'-methoxy-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile\textsuperscript{8}

Mp 289-291 °C (lit. 8 287-289 °C), \textsuperscript{1}H NMR (300 MHz, DMSO-d\textsubscript{6}) \(\delta\) 10.23 (s, 1H), 7.23 (s, 2H), 6.69 (s, 2H), 6.59 (s, 1H), 3.63 (s, 3H), 2.53 (s, 2H), 2.21 – 2.03 (m, 2H), 1.00 (d, \(J = 5.3\) Hz, 6H). \textsuperscript{13}C NMR (75 MHz, DMSO-d\textsubscript{6}) \(\delta\) 195.34, 178.36, 164.56, 159.14, 155.35, 136.13, 135.75, 117.81, 112.91, 111.09, 110.48, 109.96, 57.89, 55.69, 50.40, 47.65, 32.34, 27.95, 27.49.

2-amino-6'-bromo-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile\textsuperscript{7,11}

Mp 289-291 °C (lit. 7 289-291 °C, lit. 11 288-290 °C), \textsuperscript{1}H NMR (300 MHz, DMSO-d\textsubscript{6}) \(\delta\) 10.29 (s, 1H), 7.20 (s, 2H), 6.92 (d, \(J = 7.8\) Hz, 1H), 6.77 (s, 1H), 6.66 (d, \(J = 7.8\) Hz, 1H), 2.54 (s, 2H), 2.15 (d, \(J = 18.9\) Hz, 5H), 1.00 (d, \(J = 6.0\) Hz, 6H). \textsuperscript{13}C NMR (75 MHz, DMSO-d\textsubscript{6}) \(\delta\) 195.32, 178.43, 164.47, 159.11, 139.99, 134.91, 130.87, 128.85, 124.00, 117.82, 111.22, 109.40, 58.03, 50.41, 47.23, 32.36, 27.86, 27.60, 21.07.
Mp >300 °C, (lit. 11 >300 °C) $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 10.58 (s, 1H), 7.32 (s, 2H), 7.07 (d, $J = 7.9$ Hz, 1H), 6.94 (dd, $J = 10.0$, 4.5 Hz, 2H), 2.51 (d, $J = 15.1$ Hz, 2H), 2.12 (q, $J = 16.1$ Hz, 2H), 0.99 (d, $J = 8.1$ Hz, 6H). $^{13}$C NMR (75 MHz, DMSO-d6) $\delta$ 195.50, 178.33, 164.92, 159.23, 144.15, 134.09, 125.36, 124.75, 121.15, 117.63, 112.41, 110.67, 57.00, 56.45, 50.28, 47.00, 32.37, 27.87, 27.52, 18.96.

2-amino-7′-chloro-7,7-dimethyl-2’,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3’-indoline]-3-carbonitrile$^{9-11}$

Mp >300 °C, (lit. 11 >300 °C), $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 10.86 (s, 1H), 7.34 (s, 2H), 7.20 (d, $J = 7.8$ Hz, 1H), 6.97 (d, $J = 6.9$ Hz, 1H), 6.90 (t, $J = 7.6$ Hz, 1H), 2.51 (d, $J = 18.4$ Hz, 2H), 2.13 (q, $J = 16.0$ Hz, 2H), 0.99 (d, $J = 10.1$ Hz, 6H). $^{13}$C NMR (75 MHz, DMSO-d6) $\delta$ 195.51, 178.46, 164.90, 159.23, 140.17, 136.50, 128.69, 123.47, 122.19, 117.62, 113.91, 110.81, 57.17, 56.45, 50.25, 48.07, 32.38, 27.90, 27.44, 18.95.

2-(2-oxoindolin-3-ylidene)malononitrile$^{12}$

Mp 234-235 °C (lit. 232-233 °C), $^1$H NMR (600 MHz, DMSO-d6) $\delta$ 11.20 (s, 1H), 7.88 (d, $J = 7.8$ Hz, 1H), 7.58 (td, $J = 7.9$, 0.9 Hz, 1H), 7.14 (t, $J = 7.7$ Hz, 1H), 6.94 (d, $J = 7.9$ Hz, 1H).
8 $^1$H NMR, $^{13}$C NMR, HRMS Spectra Copies and HPLC traces of the products

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