Supporting information

Synthesis of Tricyclic 3-Hydroxyisoindolin-1-ones via Triethylamine-Catalyzed Domino Reactions of Electron-Deficient Alkynes with Phthalimidomalonate Derivatives

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Contents

I. Instrumentation and chemicals S2
II. Optimization study of Triethylamine - Catalyzed Domino Reactions of 3a S3
III. Synthetic procedures and characterization data S4-S17
IV. X-Ray crystallographic analysis of 3m S18-S19
V. NMR spectra S20-S42
I. Instrumentation and chemicals

All reactions were performed under N\textsubscript{2} unless otherwise indicated. Reagents and solvents were purchased as reagent grade and were used without further purification. Flash column chromatography was performed over silica gel (200 - 300 m) using a mixture of ethyl acetate (EA) and petroleum ether (PE).

\textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra were obtained at room temperature using a Bruker Avance 300 spectrometer. DMSO-d\textsubscript{6} containing 0.03% tetramethylsilane (TMS) (99.8\%D, Adamas, Inc.) was used as a solvent for NMR measurements. Chemical shifts (\(\delta\)) for \textsuperscript{1}H NMR are given in parts per million (ppm) relative to residual DMSO (\(\delta\) 2.50 ppm) or H\textsubscript{2}O (\(\delta\) 3.33 ppm). Chemical shifts (\(\delta\)) for \textsuperscript{13}C NMR are given in ppm relative to DMSO (\(\delta\) 39.50 ppm). The abbreviations s, d, t, q and m signify singlet, doublet, triplet, quartet and multiplet, respectively.

High resolution mass spectrometry (HRMS) was obtained on a Q-TOF micro spectrometer. Melting points were determined with a Micro melting point apparatus. TLC plates were visualized by exposure to ultraviolet light.
II. Optimization study of Triethylamine - Catalyzed Domino Reactions of 3a

General procedure for Optimization study of Triethylamine - Catalyzed Domino Reactions of 3a

To a mixture of 1a (122 mg, 0.4 mmol) and 2a (128 mg, 0.8 mmol) in solvent (5 mL) catalyst was added. The resulting solution was stirred at different temperature until the TLC indicated that the total consumption of 1a. After removal of solvent, the residue was column chromatographed on silica and eluted with PE/EA (5:1) to give 3a.
III. Synthetic procedures and characterization data

General procedure for synthesis of Tricyclic 3-Hydroxyisoindolin-1-ones (3)

To a mixture of phthalimidomalonate derivative 1 (0.4 mmol) and electron-deficient alkyne 2 (0.8 mmol) in CH$_3$CN (5 mL) Et$_3$N (8.0 mg, 0.08 mol) was added. The resulting solution was stirred at 0 °C for 100 h. After removal of solvent, the residue was column chromatographed on silica and eluted with PE/EA (5:1) to give tricyclic 3-hydroxyisoindolin-1-ones (3).

1-benzyl3,3-diethyl9b-hydroxy-5-oxo-5,9b-hydroxy-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3a)

![Chemical structure of 3a](image)

Yield: 55% (102.2 mg, 0.220 mmol);
White solid (mp 119-121 °C);
$^1$H NMR (DMSO) δ 7.95 (d, $J = 7.5$ Hz, 1H), 7.73 - 7.55 (m, 3H), 7.55 - 7.30 (m, 6H), 7.16 (s, 1H), 5.41 - 5.25 (m, 2H), 4.47 - 4.01 (m, 4H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.10 (t, $J = 7.1$ Hz, 3H);
$^{13}$C NMR (DMSO) δ 14.52 (1C), 14.71 (1C), 63.01 (1C), 63.61 (1C), 67.49 (1C), 75.21 (1C), 99.93 (1C), 124.18 (1C), 126.69 (1C), 129.26 (1C), 129.37 (2C), 129.42 (2C), 131.12 (1C), 132.22 (1C), 134.34 (1C), 136.30 (1C), 137.00 (1C), 143.05 (1C), 146.33 (1C), 161.92 (1C), 165.38 (1C), 166.52 (1C), 169.52 (1C);
HRMS (ESI$^+$) $m/z$ 488.1326 (488.1321 calcd for C$_{25}$H$_{22}$NO$_8$Na$^+$, [M+Na$^+$]).

3,3-diethyl1-(4-methylbenzyl)9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3b)

![Chemical structure of 3b](image)

Yield: 39% (74.8 mg, 0.156 mmol);
White solid (mp 137-139 °C);
$^1$H NMR (DMSO) $\delta$ 7.97 (dt, $J = 7.7$, 0.9 Hz, 1H), 7.70 (td, $J = 7.4$, 6.0 Hz, 2H), 7.61 (td, $J = 7.5$, 1.1 Hz, 1H), 7.43 - 7.35 (m, 3H), 7.25 (d, $J = 7.8$ Hz, 2H), 7.15 (s, 1H), 5.35 - 5.25 (m, 2H), 4.40 - 4.07 (m, 4H), 2.34 (s, 3H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.12 (t, $J = 7.1$ Hz, 3H);

$^{13}$C NMR (DMSO) $\delta$ 14.13 (1C), 14.32 (1C), 21.24 (1C), 62.60 (1C), 63.21 (1C), 67.04 (1C), 74.81 (1C), 99.53 (1C), 123.76 (1C), 126.31 (1C), 129.19 (2C), 129.56 (2C), 130.71 (1C), 131.84 (1C), 132.88 (1C), 133.92 (1C), 136.70 (1C), 138.30 (1C), 142.53 (1C), 145.95 (1C), 161.54 (1C), 164.98 (1C), 166.13 (1C), 169.11 (1C);

HRMS (ESI$^+$) $m/z$ 502.1473 (502.1478 calcd for $C_{26}H_{25}NO_8Na^+$, [M+Na$^+$]).

3,3-diethyl1-(4-methoxybenzyl)9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3c)

![Structure of 3c](image)

Yield: 24% (47.6 mg, 0.096 mmol);

White solid (mp 46-48 °C);

$^1$H NMR (DMSO) $\delta$ 7.94 (dd, $J = 7.4$, 1.7 Hz, 1H), 7.73 - 7.62 (m, 2H), 7.62 - 7.53 (m, 1H), 7.49 - 7.32 (m, 3H), 7.11 (s, 1H), 7.02 - 6.89 (m, 2H), 5.33 - 5.16 (m, 2H), 4.38 - 4.03 (m, 4H), 3.76 (s, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.08 (t, $J = 7.1$ Hz, 3H);

$^{13}$C NMR (DMSO) $\delta$ 13.64 (1C), 13.82 (1C), 55.11 (1C), 62.11 (1C), 62.71 (1C), 66.48 (1C), 74.24 (1C), 98.99 (1C), 113.89 (2C), 123.26 (1C), 125.82 (1C), 127.24 (1C), 130.22 (1C), 130.57 (2C), 131.28 (1C), 133.43 (1C), 136.20 (1C), 141.97 (1C), 145.40 (1C), 159.41 (1C), 161.03 (1C), 164.47 (1C), 165.60 (1C), 168.59 (1C);

HRMS (ESI$^+$) $m/z$ 518.1436 (518.1427 calcd for $C_{26}H_{25}NO_9Na^+$, [M+Na$^+$]).

1-(4-bromobenzyl)3,3-diethyl9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3d)
Yield: 60% (130.6 mg, 0.240 mmol); White solid (mp 154-156 °C);

$^1$H NMR (DMSO) $\delta$ 7.95 (d, $J = 6.9$ Hz, 1H), 7.75 - 7.54 (m, 5H), 7.52 - 7.38 (m, 3H), 7.19 (s, 1H), 5.30 (s, 2H), 4.40 - 4.01 (m, 4H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.09 (t, $J = 7.1$ Hz, 3H);

$^{13}$C NMR (DMSO) $\delta$ 13.64 (1C), 13.83 (1C), 62.13 (1C), 62.74 (1C), 65.81 (1C), 74.30 (1C), 99.00 (1C), 121.60 (1C), 123.30 (1C), 125.75 (1C), 130.26 (1C), 130.66 (1C), 131.27 (1C), 131.45 (1C), 133.48 (1C), 134.84 (1C), 135.92 (1C), 142.31 (1C), 145.38 (1C), 160.93 (1C), 164.45 (1C), 165.59 (1C), 168.62 (1C);

HRMS (ESI$^+$) $m/z$ 566.0438 (566.0426 calcd for C$_{25}$H$_{22}$NO$_8$Na$^+$, [M+Na]$^+$).

1-(4-chlorobenzyl)3,3-diethyl9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3e)

Yield: 47% (94.0 mg, 0.188 mmol); White solid (mp 149-151 °C);

$^1$H NMR (DMSO) $\delta$ 7.98 (d, $J = 5.0$ Hz, 1H), 7.74 - 7.67 (m, 2H), 7.62 (t, $J = 7.5$ Hz, 1H), 7.57 - 7.48 (m, 4H), 7.40 (d, $J = 1.9$ Hz, 1H), 7.20 (d, $J = 1.7$ Hz, 1H), 5.40 - 5.30 (m, 2H), 4.41 - 4.07 (m, 4H), 1.30 (td, $J = 7.1$, 1.2 Hz, 3H), 1.13 (td, $J = 7.1$, 1.2 Hz, 3H);

$^{13}$C NMR (DMSO) $\delta$ 14.13 (1C), 14.32 (1C), 62.62 (1C), 63.23 (1C), 66.27 (1C), 74.85 (1C), 99.54 (1C), 123.79 (1C), 126.26 (1C), 129.03 (2C), 130.74 (1C), 130.85 (1C), 131.84 (1C), 133.56 (1C), 133.95 (1C), 134.96 (1C), 136.52 (1C), 142.78 (1C), 145.94 (1C), 161.47 (1C), 164.97 (1C), 166.12 (1C), 169.12 (1C);

HRMS (ESI$^+$) $m/z$ 522.0941 (522.0932 calcd for C$_{25}$H$_{22}$NO$_8$NaCl$^+$, [M+Na]$^+$).

3,3-diethyl1-(4-fluorobenzyl)9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3f)
Yield: 40% (77.4 mg, 0.160 mmol);
White solid (mp 131-133 °C);

${^1}H$ NMR (DMSO) $\delta$ 7.95 (d, $J = 7.5$ Hz, 1H), 7.68 (t, $J = 7.4$ Hz, 2H), 7.64 - 7.49 (m, 3H), 7.42 (s, 1H), 7.25 (dd, $J = 8.7, 8.6$ Hz, 2H), 7.18 (s, 1H), 5.31 (s, 2H), 4.41 - 4.00 (m, 4H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.09 (t, $J = 7.1$ Hz, 3H);

${^{13}}C$ NMR (DMSO) $\delta$ 13.63 (1C), 13.82 (1C), 62.12 (1C), 62.73 (1C), 65.88 (1C), 74.29 (1C), 99.00 (1C), 115.51(d, $J_{C-F} = 21.7$ Hz, 2C), 123.29 (1C), 125.77 (1C), 130.25 (1C), 130.89 (d, $J_{C-F} = 8.3$ Hz, 2C), 131.00 (1C), 131.28 (1C), 131.68(d, $J_{C-F} = 3.0$ Hz, 1C), 133.46 (1C), 136.01 (1C), 142.23 (1C), 145.39 (1C), 160.97(1C), 163.66(d, $J_{C-F} = 243.0$ Hz, 1C), 164.46 (1C), 165.60 (1C), 168.61 (1C);

HRMS (ESI$^+$) $m/z$ 506.1222 (506.1227 calcd for C$_{25}$H$_{22}$NO$_8$FNa$^+$, [M+Na]$^+$).

$3,3$-diethyl$1$-(4-(trifluoromethyl)benzyl)$9b$-hydroxy-$5$-oxo-$5,9b$-dihydro-$3H$-pyrrolo[2,1$a$]isoindole-$1,3,3$-tricarboxylate (3g)

Yield: 70% (149.4 mg, 0.280 mmol);
White solid (mp 179-181 °C);

${^1}H$ NMR (DMSO) $\delta$ 7.97 (d, $J = 7.2$ Hz, 1H), 7.79 (d, $J = 8.2$ Hz, 2H), 7.76 - 7.65 (m, 4H), 7.60 (ddd, $J = 8.4, 6.4, 1.1$ Hz, 1H), 7.45 (s, 1H), 7.25 (s, 1H), 5.43 (s, 2H), 4.41 - 4.02 (m, 4H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.10 (t, $J = 7.1$ Hz, 3H);

${^{13}}C$ NMR (DMSO) $\delta$ 13.63 (1C), 13.82 (1C), 62.14 (1C), 62.74 (1C), 65.66 (1C), 74.35 (1C), 99.02 (1C), 123.31 (1C), 125.36 (2C), 125.42 (1C), 125.72 (1C), 128.80 (2C), 130.27 (1C), 131.29 (1C), 133.49 (1C), 135.82 (1C), 140.21 (1C), 142.48 (1C), 145.39 (1C), 160.90 (1C), 164.44 (1C), 165.60 (1C), 168.63 (1C);

HRMS (ESI$^+$) $m/z$ 556.1201 (556.1195 calcd for C$_{26}$H$_{25}$NO$_8$F$_3$Na$^+$, [M+Na]$^+$).
3,3-diethyl1-(4-nitrobenzyl)9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3h)

Yield: 45% (91.9 mg, 0.180 mmol);
White solid (mp 169-171 °C);

1H NMR (DMSO) δ 8.27 (d, J = 8.7 Hz, 2H), 7.97 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 6.9 Hz, 2H), 7.60 (t, J = 6.6 Hz, 1H), 7.46 (s, 1H), 7.28 (s, 1H), 5.48 (s, 2H), 4.37 - 4.07 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H);

13C NMR (DMSO) δ 13.65 (1C), 13.83 (1C), 62.16 (1C), 62.76 (1C), 65.33 (1C), 74.37 (1C), 99.02 (1C), 123.33 (1C), 123.62 (2C), 125.72 (1C), 129.01 (1C), 130.29 (1C), 131.26 (1C), 133.56 (1C), 135.72 (1C), 142.62 (1C), 143.11 (1C), 145.37 (1C), 147.25 (1C), 160.84 (1C), 164.44 (1C), 165.59 (1C), 168.63 (1C);

HRMS (ESI+) m/z 533.1180 (533.1172 calcd for C_{25}H_{22}N_{2}O_{10}Na+, [M+Na]^+).

3,3-diethyl1-(naphthalen-2-ylmethyl)9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3i)

Yield: 54% (111.4 mg, 0.216 mmol);
White solid (mp 64-66 °C);

1H NMR (DMSO) δ 8.33 - 7.88 (m, 6H), 7.75 - 7.54 (m, 5H), 7.41 (s, 1H), 7.22 (s, 1H), 5.59 - 5.47 (m, 2H), 4.73 - 3.78 (m, 4H), 1.30 (t, J = 4.5 Hz, 3H), 1.11 (t, J = 4.6 Hz, 3H);

13C NMR (DMSO) δ 14.12 (1C), 14.32 (1C), 62.61 (1C), 63.21 (1C), 67.27 (1C), 74.85 (1C), 99.56 (1C), 123.78 (1C), 126.30 (1C), 126.76 (1C), 126.93 (2C), 128.04 (1C), 128.10 (1C), 128.34 (1C), 128.70 (1C), 130.72 (1C), 131.85 (1C), 133.18 (1C), 133.21 (1C), 133.45 (1C), 133.91 (1C), 136.64 (1C), 142.72 (1C), 145.95 (1C), 161.59 (1C), 164.98 (1C),

S8
166.13 (1C), 169.12 (1C);
HRMS (ESI') m/z 538.1488 (538.1478 calcd for C_{29}H_{25}NO_{8}Na^+, [M+Na]^+).

3,3-diethyl1-(furan-2-ylmethyl)9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3j)

Yield: 55% (100.2 mg, 0.220 mmol);
White solid (mp 136-138 °C);
{H NMR (DMSO) δ 7.96 - 7.88 (m, 1H), 7.76 (dd, J = 1.9, 0.9 Hz, 1H), 7.73 - 7.64 (m, 2H), 7.59 (ddd, J = 8.3, 6.5, 1.2 Hz, 1H), 7.41 (s, 1H), 7.13 (s, 1H), 6.65 (dd, J = 3.2, 1.9 Hz, 1H), 6.51 (dd, J = 3.2, 1.9 Hz, 1H), 5.41-5.20 (m, 2H), 4.37 - 4.03 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz);
{C NMR (DMSO) δ 13.63 (1C), 13.82 (1C), 58.41 (1C), 62.13 (1C), 62.74 (1C), 74.27 (1C), 98.97 (1C), 110.85 (1C), 111.70 (1C), 123.29 (1C), 125.70 (1C), 130.24 (1C), 131.27 (1C), 133.46 (1C), 135.85 (1C), 142.32 (1C), 144.09 (1C), 145.34 (1C), 148.60 (1C), 160.72 (1C), 164.40 (1C), 165.55 (1C), 168.59 (1C);
HRMS (ESI') m/z 478.1121 (396.1059 calcd for C_{23}H_{21}NO_{9}Na^+, [M+Na]^+).

3,3-diethyl1-(thiophen-2-ylmethyl)9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3k)

Yield: 39% (73.6 mg, 0.156 mmol);
White solid (mp 146-148 °C);
{H NMR (DMSO) δ 7.97 (d, J = 7.6 Hz, 1H), 7.74 - 7.65 (m, 2H), 7.65 - 7.53 (m, 2H), 7.40 (s, 1H), 7.29 (d, J = 3.5, 1H), 7.12 (s, 1H), 7.06 (t, J = 4.4 Hz, 1H), 5.60-5.40 (m, 2H), 4.37 - 4.03 (m, 4H), 1.26 (t, J = 7.0 Hz, 3H), 1.08 (t, J =
7.1 Hz);

$^{13}$C NMR (DMSO) δ 13.64 (1C), 13.82 (1C), 60.86 (1C), 62.13 (1C), 62.74 (1C), 74.27 (1C), 98.96 (1C), 123.29 (1C), 125.76 (1C), 126.98 (1C), 128.05 (1C), 129.44 (1C), 130.25 (1C), 131.26 (1C), 133.48 (1C), 135.91 (1C), 136.96 (1C), 142.26 (1C), 145.35 (1C), 160.85 (1C), 164.42 (1C), 165.55 (1C), 168.59 (1C);

HRMS (ESI$^+$) m/z 494.0878 (494.0886 calcd for C$_{23}$H$_{21}$NO$_8$Na$^+$, [M+Na$^+$]).

3,3-diethyl1-methyl9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3l)

![Structure](image)

Yield: 53% (82.5 mg, 0.212 mmol);

White solid (mp 153-155 °C);

$^1$H NMR (DMSO) δ 8.02 (d, $J = 7.6$ Hz, 1H), 7.79 - 7.66 (m, 2H), 7.60 (t, $J = 7.4$, 1H), 7.39 (s, 1H), 7.13 (s, 1H), 4.40 - 4.02 (m, 4H), 3.82 (s, 1H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.08 (t, $J = 7.1$ Hz, 3H);

$^{13}$C NMR (DMSO) δ 13.63 (1C), 13.83 (1C), 52.23 (1C), 62.12 (1C), 62.70 (1C), 74.29 (1C), 99.00 (1C), 123.28 (1C), 125.72 (1C), 130.23 (1C), 131.27 (1C), 133.59 (1C), 135.95 (1C), 141.82 (1C), 145.48 (1C), 161.61 (1C), 164.48 (1C), 165.60 (1C), 168.65 (1C);

HRMS (ESI$^+$) m/z 412.1001 (412.1008 calcd for C$_{19}$H$_{19}$NO$_8$Na$^+$, [M+Na$^+$]).

Triethyl 9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3m)

![Structure](image)

Yield: 50% (80.7 mg, 0.200 mmol);

White solid (mp 169-171 °C);

$^1$H NMR (DMSO) δ 8.02 (d, $J = 7.0$ Hz, 1H), 7.74 (ddd, $J = 7.6$, 7.4, 1.4 Hz, 1H), 7.69 (d, 7.4Hz, 1H), 7.60 (dd, 7.5, 1.1 Hz, 1H), 7.38 (s, 1H), 7.10 (s, 1H), 4.40 - 4.01 (m, 6H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.10 (t, $J
$= 7.1\text{Hz, }3\text{H});$

$^{13}$C NMR (DMSO) $\delta$ 14013 (1C), 14.32 (1C), 14.46 (1C), 61.69 (1C), 62.62 (1C), 63.22 (1C), 74.73 (1C), 99.50 (1C), 123.76 (1C), 126.28 (1C), 130.73 (1C), 131.79 (1C), 134.05 (1C), 136.79 (1C), 142.14 (1C), 146.00 (1C), 161.67 (1C), 165.05 (1C), 166.15 (1C), 169.15 (1C);

HRMS (ESI$^+$) $m/z$ 426.1169 (426.1165 calcd for C$_{20}$H$_{21}$NO$_8$Na$^+$, [M+Na$^+$]).

1- (tert-butyl)-3,3-diethyl9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-α]isoindole-1,3,3-tricarboxylate (3n)

![Chemical Structure of 3n](image)

Yield: 16% (27.6 mg, 0.064 mmol);
White solid (mp 164-166 °C);

$^1$H NMR (DMSO) $\delta$ 8.03 (d, $J = 7.6$ Hz, 1H), 7.75 (dd, $J = 7.4$, 7.5 Hz, 1H), 7.69 (d, $J = 7.4$ Hz, 1H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.34 (s, 1H), 6.97 (s, 1H), 4.41-4.03 (m, 4H), 1.52 (s, 9H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.11 (t, $J = 7.1$ Hz, 3H);

$^{13}$C NMR (DMSO) $\delta$ 13.65 (1C), 13.82 (1C), 27.70 (3C), 62.09 (1C), 62.73 (1C), 74.04 (1C), 82.18 (1C), 98.93 (1C), 123.25 (1C), 125.77 (1C), 130.15 (1C), 131.30 (1C), 133.49 (1C), 137.65 (1C), 140.92 (1C), 145.61 (1C), 160.47 (1C), 164.69 (1C), 165.76 (1C), 168.59 (1C);

HRMS (ESI$^+$) $m/z$ 454.1465 (454.1478 calcd for C$_{22}$H$_{25}$NO$_8$Na$^+$, [M+Na$^+$]).

Diethyl1-acetyl9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-α]isoindole-3,3-dicarboxylate (3p)

![Chemical Structure of 3p](image)

Yield: 87% (129.9 mg, 0.348 mmol);
White solid (mp 153-155 °C);

$^1$H NMR (DMSO) δ 8.05 (d, $J = 7.6$ Hz, 1H), 7.77 - 7.62 (m, 2H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.44 (s, 1H), 7.14 (s, 1H), 4.44 - 4.03 (m, 4H), 2.42 (s, 3H), 1.29 (t, $J = 7.0$ Hz, 3H), 1.12 (t, $J = 7.1$ Hz, 3H);

$^{13}$C NMR (DMSO) δ 14.55 (1C), 14.75 (1C), 28.67 (1C), 62.95 (1C), 63.53 (1C), 75.30 (1C), 100.52 (1C), 123.99 (1C), 127.21 (1C), 130.87 (1C), 132.32 (1C), 134.29 (1C), 143.59 (1C), 143.78 (1C), 146.80 (1C), 165.66 (1C), 166.73 (1C), 169.51 (1C), 194.75 (1C);

HRMS (ESI$^+$) m/z 396.1049 (396.1059 calcd for C$_{19}$H$_{19}$NO$_7$Na$^+$, [M+Na$^+$]).

Diethyl-1-hexanoyl9b-hydroxy-5-oxo-5,9b-dihydro-3$^H$-pyrrolo[2,1-a]isoindole-3,3-dicarboxylate (3q)

Yield: 48% (82.5 mg, 0.192 mmol);

White solid (mp 157-159 °C);

$^1$H NMR (DMSO) δ 8.05 (d, $J = 7.7$ Hz, 1H), 7.77 - 7.63 (m, 2H), 7.56 (t, $J = 7.4$ Hz, 1H), 7.44 (s, 1H), 7.15 (s, 1H), 4.41 - 4.22 (m, 2H), 4.20 - 4.06 (m, 2H), 2.80 (td, $J = 7.3$, 2.3 Hz, 2H), 1.59 - 1.46 (m, 2H), 1.35 - 1.19 (m, 7H), 1.10 (t, $J = 7.1$ Hz, 3H), 0.82 (t, $J = 6.8$ Hz, 3H);

$^{13}$C NMR (DMSO) δ 13.65 (1C), 13.74 (1C), 13.87 (1C), 21.84 (1C), 23.39 (1C), 30.53 (1C), 62.02 (1C), 62.58 (1C), 74.38 (1C), 99.76 (1C), 123.08 (1C), 126.30 (1C), 129.96 (1C), 131.37 (1C), 133.39 (1C), 141.85 (1C), 142.14 (1C), 145.90 (1C), 164.78 (1C), 165.84 (1C), 168.61 (1C), 196.48 (1C);

HRMS (ESI$^+$) m/z 452.1689 (452.1685 calcd for C$_{23}$H$_{27}$NO$_7$Na$^+$, [M+Na$^+$]).

Diethyl-1-(cyclohexanecarbonyl)-9b-hydroxy-5-oxo-5,9b-dihydro-3$^H$-pyrrolo[2,1-a]isoindole-3,3-dicarboxylate (3r)
Yield: 53% (93.6 mg, 0.212 mmol);
White solid (mp 171-173 °C);
$^1$H NMR (DMSO) δ 8.02 (d, $J = 7.6$ Hz, 1H), 7.76 - 7.62 (m, 2H), 7.56 (t, $J = 7.4$Hz, 1H), 7.48 (s, 1H), 7.15 (s, 1H), 4.42 - 4.19 (m, 2H), 4.19 - 4.06 (m, 2H), 3.26 - 3.06 (m, 1H), 1.84 - 1.67 (m, 2H), 1.65 - 1.58 (m, 2H), 1.42 - 1.22 (m, 6H), 1.19 - 0.92 (m, 6H);
$^{13}$C NMR (DMSO) δ 13.65 (1C), 13.88 (1C), 24.74 (1C), 24.82 (1C), 25.42 (1C), 28.51 (1C), 29.13 (1C), 46.22 (1C), 61.99 (1C), 62.55 (1C), 74.35 (1C), 99.86 (1C), 123.09 (1C), 126.22 (1C), 129.95 (1C), 131.39 (1C), 133.40 (1C), 140.91 (1C), 141.59 (1C), 145.91 (1C), 164.81 (1C), 165.89 (1C), 168.56 (1C), 199.57 (1C);
HRMS (ESI$^+$) m/z 464.1677 (464.1685 calcd for C$_{24}$H$_{27}$NO$_5$Na$^+$, [M+Na$^+$]).

Diethyl9b-hydroxy-5-oxo-1-(3-phenylpropanoyl)-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-3,3-dicarboxylate (3s)

Yield: 62% (114.9 mg, 0.248 mmol);
White solid (mp 163-165 °C);
$^1$H NMR (DMSO) δ 8.04 (d, $J = 7.6$ Hz, 1H), 7.77 - 7.62 (m, 2H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.51 (s, 1H), 7.29 - 7.20 (m, 4H), 7.20 - 7.03 (m, 2H), 4.37 - 4.05 (m, 4H), 3.24 - 3.05 (m, 2H), 2.85 (t, $J = 7.6$ Hz), 1.27 (t, $J = 7.0$ Hz, 3H), 1.09 (t, $J = 7.1$ Hz);
$^{13}$C NMR (DMSO) δ 13.67 (1C), 13.86 (1C), 29.21 (1C), 40.92 (1C), 62.01 (1C), 62.58 (1C), 74.44 (1C), 99.79 (1C), 123.08 (1C), 125.84 (1C), 126.31 (1C), 128.14 (2C), 128.36 (2C), 129.96 (1C), 131.38 (1C), 133.39 (1C), 140.70 (1C),
141.96 (1C), 142.17 (1C), 145.85 (1C), 164.75 (1C), 165.81 (1C), 168.60 (1C), 195.37 (1C);
HRMS (ESI') m/z 486.1533 (486.1529 calcd for C$_{26}$H$_{25}$NO$_7$Na$^+$, [M+Na$^+$]).

1-benzyl3,3-dimethyl9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3u)

![Structural formula of 3u](image)

Yield: 40% (70.0 mg, 0.160 mmol);
White solid (mp 96-98 °C);
$^1$H NMR (DMSO) $\delta$ 7.95 (d, $J = 7.5$ Hz, 2H), 7.75 - 7.55 (m, 3H), 7.49 - 7.34 (m, 5H), 7.22 (s, 1H), 5.2 - 5.43 (m, 2H), 3.80 (s, 3H), 3.64 (s, 1H);
$^{13}$C NMR (DMSO) $\delta$ 53.29 (1C), 53.51 (1C), 66.62 (1C), 74.08 (1C), 99.02 (1C), 123.42 (1C), 125.82 (1C), 128.38 (1C), 128.53 (2C), 128.55 (2C), 130.28 (1C), 131.14 (1C), 133.54 (1C), 135.36 (1C), 136.11 (1C), 142.12 (1C), 145.37 (1C), 160.96 (2C), 165.00 (1C), 166.18 (1C).
HRMS (ESI') m/z 460.1003 (460.1008 calcd for C$_{23}$H$_{19}$NO$_8$Na$^+$, [M+Na$^+$]).

1-benzyl3,3-dipropyl9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3v)

![Structural formula of 3v](image)

Yield: 48% (94.8 mg, 0.192 mmol);
White solid (mp 164-166 °C);
$^1$H NMR (DMSO) $\delta$ 7.93 (d, $J = 7.4$ Hz, 1H), 7.72 - 7.54 (m, 3H), 7.52 - 7.32 (m, 6H), 7.10 (s, 1H), 5.33 (s, 2H), 5.10 - 4.99 (m, 1H), 4.99 - 4.88 (m, 1H), 1.27 (d, $J = 6.3$ Hz, 6H), 1.18 (d, $J = 6.2$ Hz, 6H), 1.11 (d, $J = 6.2$ Hz);
$^{13}$C NMR (DMSO) $\delta$ 21.15 (1C), 21.17 (1C), 21.19 (1C), 21.35 (1C), 66.53 (1C), 69.94 (1C), 71.01 (1C), 74.47 (1C), 98.98 (1C), 123.22 (1C), 125.74 (1C), 128.34 (1C), 128.38 (1C), 128.42 (1C), 128.51 (2C), 130.18 (1C), 131.39 (1C),
To a solution of 3m (81.0 mg, 0.2 mmol) in EtOH (5.0 mL), NaOH (48.0 mg, 1.2 mmol) was added at room temperature. After stirring for 12h, the reaction mixture was concentrated and purified by column chromatography on silica gel (50% EA/PE) to afford 4.

Yield: 89% (127.9 mg, 0.356 mmol);

White solid (mp 103-105 °C);

$^1$H NMR (DMSO) $\delta$ 12.61 (s, 1H), 7.93 (dd, $J = 7.7$, 1.7 Hz, 1H), 7.68 - 7.51 (m, 2H), 7.41 (dd, $J = 7.4$, 1.6 Hz, 1H), 7.14 (s, 1H), 4.26 (q, $J = 7.0$ Hz, 2H), 4.03 (q, $J = 7.1$ Hz, 2H), 3.96 (q, $J = 7.1$ Hz, 2H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.02 (t, $J = 7.2$ Hz, 6H);

$^{13}$C NMR (DMSO) $\delta$ 13.58 (1C), 13.75 (1C), 14.24 (1C), 59.06 (1C), 59.92 (1C), 60.27 (1C), 113.75 (1C), 116.30 (1C), 121.77 (1C), 128.72 (1C), 129.31 (1C), 131.19 (1C), 131.35 (1C), 131.91 (1C), 132.03 (1C), 140.33 (1C), 159.99 (1C), 163.01 (1C), 165.97 (1C);

HRMS (ESI$^+$) m/z 382.0915 (382.1267 calcd for C$_{19}$H$_{21}$NO$_6$Na$^+$, [M+Na]$^+$).

To a solution of 3m (81.0 mg, 0.2 mmol) in MeOH (5.0 mL), Pd/C (8.1 mg) was added. The mixture was stirred at room temperature under H$_2$ atmosphere until TLC analysis showed a complete consumption of the starting material. The reaction mixture was filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (20% EA/PE) to afford 5.

Yield: 74% (120.0 mg, 0.296 mmol);
White solid (mp 145-147 °C);

$^1$H NMR (DMSO) δ 7.86 - 7.68 (m, 2H), 7.68 - 7.51 (m, 2H), 7.16 (d, $J = 1.7$ Hz, 1H), 4.37 - 4.17 (m, 4H), 4.17 - 4.02 (m, 2H), 3.37 (dd, $J = 13.4$, 12.2 Hz, 2H), 3.13 (ddd, $J = 12.2$, 7.1, 1.8 Hz, 1H), 2.84 (dd, $J = 13.4$, 7.2 Hz, 1H), 1.32 (t, $J = 7.1$ Hz, 6H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.10 (t, $J = 7.1$ Hz, 3H);

$^{13}$C NMR (DMSO) δ 14.53 (1C), 14.77 (1C), 14.94 (1C), 50.64 (1C), 61.59(1C), 62.44 (1C), 62.80 (1C), 67.71 (1C), 96.38 (1C), 115.00 (1C), 123.80 (1C), 125.47 (1C), 130.96 (1C), 132.17 (1C), 133.96 (1C), 146.57 (1C), 167.33 (1C), 168.74 (1C), 168.89 (1C), 169.20 (1C);

HRMS (ESI$^+$) $m/z$ 428.1309 (428.1321 calcd for C$_{20}$H$_{23}$NO$_8$Na$^+$, [M+Na]$^+$).

Tetraethyl5-oxo-2,5-dihydro-3H-pyrrolo[2,1-a]isoindole-1,2,3,3-tetracarboxylate (6)

\[\text{EtOC} \begin{array}{c} \text{O} \\ \text{Et} \end{array} \]

To a solution of 3m (81.0 mg, 0.2 mmol) in CH$_2$Cl$_2$ (10.0 mL), Et$_3$N (67.1 mg, 0.6 mmol), Acetyl chloride (23.6 mg, 0.3 mmol) were added at room temperature. The mixture was stirred at room temperature until TLC analysis showed a complete consumption of the starting material. The reaction mixture was filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (10% EA/PE) to afford 6.

Yield: 91% (167.2 mg, 0.364 mmol);

White solid (mp 113-117 °C);

$^1$H NMR (DMSO) δ 8.59 (d, $J = 7.38$ Hz, 1H), 7.99 - 7.85 (m, 3H), 7.15 (s, 1H), 4.59 - 3.97 (m, 8H), 2.06 (s, 3H), 1.51 - 0.87 (m, 12H);

$^{13}$C NMR (DMSO) δ 13.64 (1C), 13.79 (1C), 13.94 (1C), 20.22 (1C), 60.74 (1C), 62.88 (1C), 63.02 (1C), 72.31 (1C), 79.98 (1C), 104.80 (1C), 124.17 (1C), 127.21 (1C), 128.28 (1C), 133.55 (1C), 133.81 (1C), 134.33 (1C), 151.26 (1C), 160.91 (1C), 162.05 (1C), 164.10 (1C), 167.86 (1C);

HRMS (ESI$^+$) $m/z$ 468.1262 (468.1271 calcd for C$_{22}$H$_{23}$NO$_9$Na$^+$, [M+Na]$^+$).

Gram-scale preparation of Triethyl 9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3m)

To a mixture of phthalimidomalonate derivative 1 (1.22 g, 4 mmol) and electron - deficient alkyne 2a (0.78 g, 8

S16
mmol) in CH$_3$CN (50 mL) Et$_3$N (0.08 g, 0.8 mol) was added. The resulting solution was stirred at 0 °C for 100 h. After removal of solvent, the residue was column chromatographed on silica and eluted with PE/EA (5:1) to afford 3m. Yield: 47% (0.76 g, 1.88 mmol).
IV. X-Ray crystallographic analysis of 3m

Crystallographic data for 3m have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1493448. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table S1 Crystal data and structure refinement for 3

<table>
<thead>
<tr>
<th>Chemical formula</th>
<th>C&lt;sub&gt;20&lt;/sub&gt;H&lt;sub&gt;21&lt;/sub&gt;NO&lt;sub&gt;8&lt;/sub&gt;</th>
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<tr>
<td>( M_r )</td>
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<td>Crystal system, space group</td>
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<td>Temperature (K)</td>
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<td>( a, b, c ) (Å)</td>
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<td>( \beta ) (°)</td>
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<td>( V ) (Å(^3))</td>
<td>2017.8 (7)</td>
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<tr>
<td>( Z )</td>
<td>4</td>
</tr>
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</table>
Radiation type | Mo Kα  
---|---
\( \mu \) (mm\(^{-1}\)) | 0.10  
Crystal size (mm) | 0.30 × 0.20 × 0.10  

Data collection  
Diffractometer | Nonius CAD4 diffractometer  
Absorption correction | \( \psi \) scan  
\( T_{\min}, T_{\max} \) | 0.970, 0.990  
No. of measured, independent and observed [\( I > 2\sigma(I) \)] reflections | 7831, 3714, 1841  
\( R_{int} \) | 0.135  
\( \sin \theta/\lambda \)\(_{\max} \) (Å\(^{-1}\)) | 0.604  

Refinement  
\( R[F^2 > 2\sigma(F^2)], wR(F^2), S \) | 0.068, 0.181, 1.01  
No. of reflections | 3714  
No. of parameters | 262  
No. of restraints | 1  
H-atom treatment | H-atom parameters constrained  
\( \Delta \rho_{\max}, \Delta \rho_{\min} \) (e Å\(^{-3}\)) | 0.35, −0.35
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3a (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3b (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3c (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3d (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3e (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3f (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3g (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3h (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3i (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3j (DMSO)
\(^{1}\)H NMR (300 MHz) and \(^{13}\)C NMR (300 MHz) spectra of 3k (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3l (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3m (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3n (DMSO)

3n
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3p (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3q (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3r (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3s (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 3u (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of $3v$ (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 4 (DMSO)
$^1$H NMR (300 MHz) and $^{13}$C NMR (300 MHz) spectra of 5 (DMSO)
¹H NMR (300 MHz) and ¹³C NMR (300 MHz) spectra of 6 (DMSO)