Electronic Supplementary Information

Total synthesis and structural revision of a Mangrove alkaloid

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S1. General Comments

Organic solvents were dried over Na₂SO₄ or MgSO₄. Starting materials and solvents were purchased from commercial suppliers and were used without further purification. Flash silica chromatography was performed using either Sigma-Aldrich high-purity grade, pore size 60 Å, 200-400 mesh particle size silica gel or Biotage Isolera automated column chromatographic equipment with pre-packed silica SNAP cartridges. ¹H and ¹³C NMR spectra were recorded on a JEOL ECS 400 NMR Spectrometer at 400 MHz or Bruker AVIII 300 or 400 MHz spectrometers. Chemical shifts (δ) are reported relative to TMS (δ=0) and/or referenced to the solvent in which they were measured. Low and High-resolution mass spectrometry analysis was obtained using an Agilent 6450 LC-MS/MS. Infrared (IR) spectra were recorded on a ThermoScientific Nicolet Impact-380 ATR-FTIR spectrometer. Melting points were recorded on a Bibby Sterlin Ltd. Stuart SMP10 melting point apparatus and are uncorrected.
S2. X-ray crystallographic data for 1

Crystal Data for C$_{12}$H$_{8}$N$_{2}$O$_{3}$ ($M =228.20$ g/mol): triclinic, space group P-1, $a = 7.2887(8)$ Å, $b = 7.9722(7)$ Å, $c = 9.8335(10)$ Å, $\alpha = 95.529(8)^\circ$, $\beta = 103.372(9)^\circ$, $\gamma = 115.215(10)^\circ$, $V = 490.45(9)$ Å$^3$, $Z = 2$, $T = 150$ K, $\mu$(CuKα) = 0.114 mm$^{-1}$, $D_{calc} = 1.545$ g/cm$^3$. The final $R_1$ was 0.0592 ($I > 2\sigma(I)$) and $wR_2$ was 0.1690 (all data).

The CIF for the crystal structure of 1 has been deposited with the CCDC and has been given the deposition number CCDC 1569814.

Data collection for 1 was performed using an Oxford Xcalibur Gemini diffractometer equipped with a Sapphire3 CCD detector. The datasets for 7 and 9 was measured on an Agilent SuperNova diffractometer using an Atlas detector. The data collection was driven and processed and an absorption correction was applied using CrysAlisPro.$^{[S1]}$ The structure was solved using ShelXS$^{[S2]}$ and refined by a full-matrix least-squares procedure on $F^2$ in ShelXL$^{[S2]}$. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter ($U_{eq}$) of the parent atom. Figures and reports were produced using OLEX2.$^{[S3]}$
S3. X-ray crystallographic data for 7

Crystal Data for C_{12}H_{10}N_{2}O_{4} (M = 246.22 g/mol): monoclinic, space group P21/c, \( a = 25.8352(11) \, \text{Å} \), \( b = 7.7514(3) \, \text{Å} \), \( c = 11.3697(4) \, \text{Å} \), \( \alpha = 90^\circ \), \( \beta = 102.229(4)^\circ \), \( \gamma = 90^\circ \), \( V = 2225.20(15) \, \text{Å}^3 \), \( Z = 8 \), \( T = 100 \, \text{K} \), \( \mu(\text{CuKα}) = 0.113 \, \text{mm}^{-1} \), \( D_{\text{calc}} = 1.470 \, \text{g/cm}^3 \). The final \( R_1 \) was 0.0426 (I > 2σ(I)) and \( wR_2 \) was 0.1110 (all data).

The CIF for the crystal structure of 7 has been deposited with the CCDC and has been given the deposition number CCDC 1569815.
S4. X-ray crystallographic data for 9

Crystal Data for C_{12}H_{8}N_{2}O_{3} (M = 228.20 g/mol): triclinic, space group P-1 (no. 2), a = 5.6166(3) Å, b = 10.8878(9) Å, c = 16.1616(7) Å, α = 98.989(5)°, β = 90.256(4)°, γ = 98.291(6)°, V = 965.60(11) Å³, Z = 4, T = 100.01(10) K, μ(CuKα) = 0.970 mm⁻¹, Dcalc = 1.570 g/cm³, 6140 reflections measured (8.312° ≤ 2Θ ≤ 140.144°), 3634 unique (Rint = 0.0239, Rsigma = 0.0326) which were used in all calculations. The final R₁ was 0.0451 (I > 2σ(I)) and wR₂ was 0.1247 (all data).

The CIF for the crystal structure of 9 has been deposited with the CCDC and has been given the deposition number CCDC 1569797.
Compound characterisation

2-Methylimidazo[1,5-b]isoquinoline-1,3,5(2H)-trione (1)

Desulphurisation Route 1

To a solution of 2-methyl-3-(methylthio)-1,5-dioxo-1,5-dihydroimidazo[1,5-b]isoquinolin-2-ium (8) (10 mg, 0.04 mmol) in EtOH (0.04 mL) was added saturated aqueous HCl (37% w/v, 0.04 mL) and refluxed for 3 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The resultant solid was purified using chromatography (SiO₂; MeOH/DCM; 0-10%) to afford the title compound as a pale yellow solid (7 mg, 81%).

Photosynthesis Route 2

In a round bottom flask, 2-methyl-3-thioxo-2,3-dihydroimidazo[1,5-b]isoquinoline-1,5-dione (5b) (23 mg, 0.09 mmol) and eosinY (2 mg, 3.2 mol%) were dissolved in DMF (0.8 mL). The reaction was heated gently to 40 °C and irradiated under either conditions (a) 530 nM green emitting LED or (b) a 60 W desk lamp for 18 h. The reaction was cooled to room temperature followed by the addition of water (2 mL). The mixture was filtered to recover unreacted starting material. The filtrate was concentrated *in vacuo*. The resultant solid was purified using chromatography (SiO₂; MeOH/DCM; 0-10%) to afford the title compound as a pale yellow solid (conditions a 4 mg, 18% or conditions b 2 mg, 7%). Analytical data was in accordance with Route 1.

Mp 247-248 °C

IR \(\nu_{\text{max}}/\text{cm}^{-1}\) 1691, 1726, 1789

\(^1\text{H NMR}\) (400 MHz, CDCl₃): \(\delta\) 8.56 (d, \(J = 7.5\) Hz, 1H), 7.81 (ddd, \(J = 7.5\) (x2), 1.5 Hz, 1H), 7.74-7.69 (m, 2H), 7.36 (s, 1H), 3.27 (s, 3H)

\(^{13}\text{C NMR}\) (101 MHz, CDCl₃): \(\delta\) 159.3, 156.9, 149.4, 134.1, 133.7, 130.4, 129.3, 129.1, 128.7, 126.8, 109.1, 24.7
LCMS (ESI?): m/z 229.06 [M+H]^+

HRMS (ESI?): m/z calcd for C_{12}H_{9}N_{2}O_{3} [M+H]^+: 229.0613; found 229.0608.

3-Thioxo-2,3-dihydroimidazo[1,5-b]isoquinoline-1,5-dione (5a)^{54}

2-Carboxybenzaldehyde (3) (0.75 g, 5 mmol), anhydrous sodium acetate (1.47 g, 18 mmol) and thiohydantoin (4a) (0.59 g, 5 mmol) were dissolved in glacial acetic acid (7 mL) and heated at reflux for 4 h. After cooling to room temperature, ice-cold water (7 mL) was added to the reaction mixture. The resultant crystals were collected by filtration. The collected material was then recrystallised from EtOH, to yield an orange powder (0.92 g, 80%).

Mp 278°C (lit. 278-278°C)^{54}

IR ν_{max}/cm^{-1}, 3172, 1727 and 1686

^1H NMR (400 MHz, DMSO-d_6) δ 8.37 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.89 (dd, J = 7.8 Hz, 1H), 7.76 (dd, J = 7.8 Hz, 1H), 7.51 (s, 1H);

LCMS (ESI?): m/z 231.02 [M+H]^+

2-Methyl-3-thioxo-2,3-dihydroimidazo[1,5-b]isoquinoline-1,5-dione (5b)^{54}

A mixture of 2-carboxybenzaldehyde (3) (0.15 g, 1.0 mmol) and anhydrous sodium acetate (0.28 g, 3.0 mmol) was added to a solution of 3-methyl-2-thioxo-4-imidazolidinone (4b) (0.13 g, 1.0 mmol) in glacial acetic acid (1.4 mL) and refluxed for 4 h. After cooling to room temperature, ice-cold water (2 mL) was poured into the reaction mixture. Then the
resultant crystals were collected by filtration. The collected material was then recrystallised from EtOH, to yield orange crystals (0.15 g, 63%).

**Mp 242-244 °C (Lit. 240-242 °C)**

**H NMR** (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.40 (d, \(J = 8.4\) Hz, 1H), 8.00 (d, \(J = 8.4\) Hz, 1H), 7.90 (dd, \(J = 8.4\) Hz, 1H), 7.80 (dd, \(J = 8.4\) Hz, 1H), 7.67 (s, 1H), 3.28 (s, 3H)

**C NMR** (101 MHz, DMSO-\(d_6\)) \(\delta\) 173.8, 160.7, 157.1, 134.2, 133.2, 130.5, 129.7, 128.64, 128.61, 127.3, 108.5, 27.2

**LCMS (ESI\(^{+}\))**: \(m/z\) 245.04 [M+H]\(^{+}\)

3-Methylimidazolidine-2,4-dione (6)

To a round bottom flask was added hydantoin (100 mg, 1.0 mmol), toluene (10 mL) and \(N,N\)-dimethylacetamide dimethylacetal (0.44 mL, 3.0 mmol). The reaction mixture was refluxed for 3 h, cooled to room temperature and the precipitate that formed was recrystallized from toluene to afford the title compound as a pale yellow powder (60 mg, 53%).

**Mp 181-183 °C (lit. 181-183 °C)**

**H NMR** (CDCl\(_3\), 400 MHz) \(\delta\): 5.66 (br s, 1 H), 3.99 (s, 2H), 3.04 (s, 3H)

**C NMR** (CDCl\(_3\), 101 MHz) \(\delta\): 171.2, 158.2, 46.4, 24.6

**LCMS (ESI\(^{+}\))**: \(m/z\) 115.04 [M+H]\(^{+}\)
3-Methyl-1-(3-oxo-1,3-dihydroisobenzofuran-1-yl)imidazolidine-2,4-dione (7)

![structure](image)

2-Carboxybenzaldehyde (3) (66 mg, 0.44 mmol), 3-Methylimidazolidine-2,4-dione (6) (51 mg, 0.44 mmol) and anhydrous sodium acetate (123 mg, 1.50 mmol) were dissolved in glacial acetic acid (1 mL) and heated at reflux for 4h. Upon cooling to room temperature, the reaction mixture was poured into ice-cold water, neutralised with NaHCO₃ (aq.) and extracted with DCM (3 x 10 mL). The organic layer was combined, dried (MgSO₄) and evaporated to afford the crude product. Flash column chromatography (SiO₂, 1:1; EtOAc/petroleum ether) afforded the title compound as a white powder (42 mg, 42%).

**Mp** 162-163 °C

**¹H NMR** (CDCl₃, 400 MHz) δ: 7.98 (d, J = 7.5 Hz, 1H), 7.82-7.77 (m, 1H), 7.71-7.66 (m, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.32 (s, 1H), 3.64 (d, J = 16.5 Hz, 1H), 3.40 (d, J = 16.5 Hz, 1H), 3.10 (s, 3H)

**¹³C NMR** (CDCl₃, 101 MHz) δ: 168.6, 167.7, 157.0, 142.8, 135.1, 131.4, 127.1, 126.3, 122.9, 81.3, 44.7, 25.1

**LRMS** (ESI⁺): m/z 247.07 [M+H]⁺

2-Methyl-3-(methylthio)-1,5-dioxo-1,5-dihydroimidazo[1,5-b]isoquinolin-2-ium iodide (8)

A suspension of 2-methyl-3-thioxo-2,3-dihydroimidazo[1,5-b]isoquinoline-1,5-dione (5b) (0.1 g, 0.41 mmol) in aq. NaOH (0.87 mL, 2% w/v) and MeOH (1.64 mL) was added MeI (0.1 mL, 1.6 mmol) dropwise and stirred for 20 h. The precipitate (unreacted starting material) was filtered and washed with MeOH. The filtrate was partially concentrated in vacuo and the crystals that formed were filtered to afford the title compound as yellow crystals (68 mg, 43%) and used directly in the next step.

Mp 196-199 °C

1H NMR (400 MHz, DMSO-d6) δ 8.32 (d, J = 7.5 Hz, 1H), 7.96 (dd, J = 7.5 (x2) Hz, 1H), 7.86 (ddd, J = 7.5 (x2), 2.0 Hz, 1H), 7.71 (ddd, J = 7.5 (x2), 2.0 Hz, 1H), 7.42 (s, 1H), 3.06 (s, 3H), 2.96 (s, 3H)

13C NMR (101 MHz, DMSO-d6) δ 158.4, 156.4, 135.4, 133.3, 130.2, 129.2, 129.1, 128.6, 127.2, 109.0, 103.5, 50.6, 23.4

LCMS (ESI+) m/z: 259.05 [M]+

HRMS (ESI+): m/z calcd for C_{13}H_{13}N_{2}O_{3}S [M+H+2O]⁺: 277.0647; found 277.0641

N-Methylpyrazino[1,2-α]indole-1,3,4(2H)-trione (9)

To a round bottomed flask containing (12) (50 mg, 0.29 mmol) was added toluene (1.5 mL) followed by triethylamine (97 µL, 0.7 mmol) and ethyl chlorooxocacetate (65 µL, 0.58 mmol). The reaction mixture was allowed to stir for 10 minutes and then refluxed overnight. The
reaction was allowed to cool then the solvent was removed under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (15 mL), washed with water (5 mL) and brine (10 mL) and dried over MgSO$_4$. The crude material was recrystallized from methanol to afford (9) as a yellow powder (26.3 mg, 41%).

Mp 224.2-224.5 °C (lit. 255.5-256.5 °C)$^{56}$

IR $\nu_{\text{max}}$/cm$^{-1}$ 2921, 2853, 1734, 1677, 1460, 1347, 738

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.47 (dq, $J = 8.3$, 0.9 Hz, 1H), 7.78 (dt, $J = 7.9$, 1.0 Hz, 1H), 7.70 (d, $J = 0.8$ Hz, 1H), 7.62 (ddd, $J = 8.4$, 7.3, 1.2 Hz, 1H), 7.47 (ddd, $J = 8.2$, 7.3, 1.0 Hz, 1H), 3.47 (s, 3H)

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 156.5, 156.4, 148.8, 136.3, 130.2, 128.7, 126.9, 126.4, 124.0, 119.6, 117.2, 27.6

LRMS (ESI$^+$): m/z 251.04 [M+Na]$^+$

HRMS (TOF ESI$^+$): m/z calcd for C$_{12}$H$_8$N$_2$O$_3$Na [M+Na]$^+$: 251.0433; found 251.0435

Methyl 1H-indole-2-carboxylate (11)$^{57}$

![Methyl 1H-indole-2-carboxylate](image)

To a solution of indole 2-carboxylic acid (10) (1.038 g, 6.44 mmol) in anhydrous methanol (30 mL) was added concentrated sulfuric acid (0.5 mL) dropwise. The reaction mixture was refluxed for 16 h. Upon completion the reaction was cooled to room temperature, concentrated in vacuo and the residue neutralised with satd. NaHCO$_3$ (aq.). The aqueous solution was extracted with ethyl acetate (3 x 20 mL), the combined organic layer was washed with brine (20 mL) and the organic layer dried (MgSO$_4$), filtered and concentrated in vacuo to afford (11) as a pale grey powder (1.074 g, 95%).

Mp 148-149 °C (lit. 152.5-153.0 °C)$^{57}$
**1H NMR** (300 MHz, CDCl₃) δ 8.94 (s, 1H), 7.70 (dd, J = 8.0, 1.0 Hz, 1H), 7.43 (dd, J = 8.3, 1.0 Hz, 1H), 7.33 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 7.23 (dd, J = 2.1, 1.0 Hz, 1H), 7.16 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 3.95 (s, 3H)

**13C NMR** (101 MHz, CDCl₃) δ 162.6, 137.0, 127.6, 127.3, 125.6, 122.8, 121.0, 112.0, 109.0, 52.2

**LRMS** (GCMS⁺): m/z 175.1 [M]⁺

**HRMS** (ESI⁺): m/z calcd for C₁₀H₉NO₂ [M]⁺: 175.0633, found 175.0633

*N*-methyl-1H-indole-2-carboxamide (12)

![Structure of N-methyl-1H-indole-2-carboxamide](image)

To a round bottomed flask containing (11) (500 mg, 2.86 mmol) was added *N*-methylamine (7.5 mL, mmol, 40% in water). The reaction was capped and stirred overnight at room temperature. The resulting suspension was filtered, washed with water (3 × 5 mL) and dried to afford (12) as an off white powder (365.7 mg, 74%).

**Mp** 212-213 °C (lit. 224 °C)

**1H NMR** (400 MHz, MeOD-d₄) δ 7.59 (dt, J = 8.0, 1.0 Hz, 1H), 7.43 (dq, J = 8.4, 1.0 Hz, 1H), 7.20 (ddd, J = 8.3, 7.0, 1.1 Hz, 1H), 7.05 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.00 (d, J = 0.9 Hz, 1H), 2.93 (s, 3H)

**13C NMR** (101 MHz, MeOD-d₄) δ 164.8, 138.2, 132.2, 129.0, 124.9, 122.7, 121.1, 113.0, 104.0, 26.4

**LRMS** (EI⁺): m/z 174.1 [M]⁺

**HRMS** (ESI⁺): m/z calcd for C₁₀H₁₉N₂O [M]⁺: 174.0793, found 174.0796
S6. Copies of $^1$H and $^{13}$C NMR spectra

$^1$H NMR spectrum of 1 (400 MHz, CDCl$_3$)
$^{13}$C NMR spectrum of 1 (101 MHz, CDCl$_3$)
$^1$H-$^{13}$C HMBC NMR spectrum of 1 (400 MHz, CDCl$_3$)
$^{1}H-^{13}C$ HMBC NMR spectrum of 1 (400 MHz, CDCl$_3$) Expansion
$^1$H-$^{13}$C HSQC NMR spectrum of 1 (400 MHz, CDCl$_3$)
UV Spectra of 1 with Eosin Y in different solvent systems

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<th>Solvent</th>
<th>Initial concentration (mol dm(^{-3}))</th>
<th>Dilution x 5 cm(^3) (mol dm(^{-3}))</th>
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<th>(\varepsilon) dm(^3)mol(^{-1})cm(^{-1})</th>
<th>(\lambda_{\text{max}}) (nm)</th>
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<td>0.709</td>
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</table>
$^1$H NMR spectrum of 5a (400 MHz, DMSO-$d_6$)
$^{13}$C NMR spectrum of 5a (100 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 5b (400 MHz, DMSO-$d_6$)
$^{13}$C NMR spectrum of 5b (101 MHz, DMSO-$d_6$)
$^1$H NMR spectra of 4d (400 MHz, CDCl$_3$)
$^{13}$C NMR spectra of 4d (101 MHz, CDCl$_3$)
$^1$H NMR spectrum of 7 (400 MHz, CDCl$_3$)
$^{13}$C NMR spectrum of 7 (101 MHz, CDCl$_3$)
$^1\text{H}^-^{13}\text{C}$ HMQC NMR spectrum of 7 (400 MHz, CDCl$_3$)
$^{1}H-^{13}C$ HMBC NMR spectrum of 7 (400 MHz, CDCl$_3$)
$^{1}$H-NMR spectrum of 8 (400 MHz, DMSO-$d_6$)
$^{13}$C NMR spectrum of 8 (101 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 9 (400 MHz, CDCl$_3$)
$^{13}$C NMR spectrum of 9 (101 MHz, CDCl$_3$)
$^1$H-$^{13}$C HSQC NMR spectrum of 9 (400 MHz, CDCl$_3$)
$^1$H-$^{13}$C HMBC NMR spectrum of 9 (400 MHz, CDCl$_3$)
$^1$H-$^{13}$C HMBC NMR spectrum of 9 (400 MHz, CDCl$_3$) expansion
$^1$H NMR spectrum of 11 (400 MHz, CDCl$_3$)
$^{13}$C NMR spectrum of 11 (101 MHz, CDCl$_3$)
$^1$H NMR spectrum of 12 (400 MHz, CD$_3$OD)
$^{13}$C NMR spectrum of 12 (101 MHz, CD$_3$OD)
S7. Comparison of isolated NMR for 1 (provided by Prof. Hua)

$^1$H NMR spectrum of isolated 1 (600 MHz, CDCl$_3$)
$^{13}$C NMR spectrum of isolated 1 (150 MHz, CDCl$_3$)

$^{13}$C carbonyl peak at 148.8 ppm from the original isolated material assignment
S8. References


