Realisation of Small Molecule Libraries based on Frameworks
Distantly Related to Natural Products

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Supplementary Information

Contents:

1.0 Computational analysis of the compound libraries ........................................ 3
1.0 Experimental ...................................................................................................... 4
1.1 General experimental ......................................................................................... 4
1.2 General procedures ............................................................................................ 5
1.3 Compound data ................................................................................................ 7
1.3.1 Preparation of cycloaddition precursors and cycloadducts ......................... 7
  1.3.1.1 Preparation of O-bridged cycloadduct 1 ............................................... 7
  1.3.1.1.1 Preparation of each intermediate in the synthesis of cycloaddition precursor 11
  1.3.1.1.2 Telescop ed synthesis of cycloaddition precursor 11 ............................... 10
  1.3.1.1.3 Preparation of O-bridged cycloadduct 1 ............................................. 12
  1.3.1.1.4 Scaled-up synthesis of O-bridged cycloadduct 1 ................................. 13
  1.3.1.2 Preparation of N-bridged cycloadduct 2 ................................................ 14
  1.3.1.2.1 Preparation of precursors to N-bridged cycloadduct 2 ....................... 14
  1.3.1.2.2 Preparation of N-bridged cycloadduct 2 .......................................... 16
  1.3.1.2.3 Scaled-up synthesis of N-bridged cycloadduct 2 ............................... 17
  1.3.2 Preparation of scaffolds 3 .......................................................................... 18
  1.3.2.1 Initial procedure to prepare diol 18 ......................................................... 18
  1.3.2.2 Optimised synthetic route to prepare diol 18 ......................................... 20
  1.3.2.3 Initial route to prepare scaffold 3a ....................................................... 21
  1.3.2.4 Telescoped synthesis of scaffolds 3b-e .................................................. 22
  1.3.2.5 Exemplar decorations of scaffold 3b ..................................................... 26
  1.3.3 Preparation of scaffolds 4 .......................................................................... 29
  1.3.3.1 Initial procedure to prepare scaffolds 4a-b ............................................. 29
  1.3.3.2 Optimised synthetic route to scaffolds 4 .............................................. 32
1.0 Computational analysis of the compound libraries

Molecular properties analysis of the compound libraries produced (pale blue squares) and exemplar compounds described in this paper (large, green squares).

- Scaffold 3: 751 compounds, 87% of attempted decorations were successful.
- Scaffold 4: 594 compounds, 94% of attempted decorations were successful.
- Scaffold 5: 1082 compounds, 88% of attempted decorations were successful.
- Scaffold 6: 476 compounds, 76% of attempted decorations were successful.

The molecular properties for the library compounds were calculated using Datawarrior (open access: http://www.openmolecules.org/datawarrior). The molecular properties of the exemplar compounds prepared in this paper were calculated using the LLAMA webtool.¹
1.0 Experimental

1.1 General experimental

All non-aqueous reactions were performed under an atmosphere of nitrogen unless otherwise stated. Water-sensitive reactions were performed in oven-dried glassware, cooled under nitrogen before use. THF, CH₂Cl₂, PhMe and MeCN were dried and purified by means of a Pure Solv MD solvent purification system (Innovative Technology Inc.). Anhydrous DMA and DMF were obtained in SureSeal bottles from Sigma-Aldrich. All other solvents used were of chromatography or analytical grade. Petrol refers to petroleum spirit (b.p. 40-60 °C). Commercially available starting materials were obtained from Sigma-Aldrich, Fluka, Acros, Alfa Aesar or Fluorochem and were used without purification.

Thin layer chromatography (TLC) was carried out on aluminium backed silica plates (Merck silica gel 60 F254). Visualisation of the plates was achieved using an ultraviolet lamp (λmax = 254 nm) and KMnO₄. Flash chromatography was carried out using silica gel 60 (60-63 µm particles) supplied by Merck. Strong cation exchange solid phase extraction (SCX SPE) was carried out using pre-packed Discovery DSC-SCX cartridges supplied by Supelco, see the general procedure, below.

Melting points were measured on a Reichert hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Bruker Alpha Platinum-ATR, with absorption reported in wavenumbers (cm⁻¹). High resolution mass spectra (HRMS) were recorded on a Bruker MaXis Impact spectrometer with electrospray ionisation (ESI) source. Low resolution mass spectra (LRMS) were recorded by HP-LCMS, which was generally carried out on an Agilent 1200 series LC system comprising a Bruker HCT Ultra ion trap mass spectrometer. The solvent system used was CH₃CN/H₂O + 0.1% formic acid with a Phenomenex Luna C18 50 × 2 mm 5 micron column. Mass-directed HPLC purification was carried out using an Agilent 1260 Infinity HPLC system comprising an Agilent 6120 Quadrupole LC/MS and Agilent G1968D active splitter. A Genevac EZ-2 Elite centrifugal evaporator was used for the removal of MeOH–H₂O or MeCN–H₂O after mass-directed purification.

Proton (¹H) and carbon (¹³C) NMR spectral data were collected on Bruker Advance 500, Bruker DPX500, Bruker Advance 400 and Bruker DPX300 spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the residual solvent peak. Coupling constants (J) are quoted in Hertz (Hz) and splitting patterns reported in an abbreviated manner: app. (apparent), br. (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). All fully characterised products were assigned with the aid of COSY, DEPT-135 and HMQC experiments. Where stated NOESY experiments were also used to aid assignments. Compounds are numbered with respect to their IUPAC names. Where necessary, coloured text was used to distinguish similar protons and carbons (e.g. for major and minor diastereomers). Diastereomeric ratios were calculated by integration of the
\(^1\)H NMR spectra. Diastereomers were assigned through the interpretation of coupling constants, NOESY spectra, and by small molecule crystallographic studies. Small molecule X-ray crystallography studies were performed by Dr Christopher Pask.

**A note regarding NMR assignments**

Where compounds have been assigned through analysis of the corresponding NOESY spectrum, protons labelled ‘A’ are on the ‘bottom’ face of the molecules (as drawn), while protons labelled ‘B’ are on the ‘top’ face of the molecules (as drawn), see compound 18 below as an example.

Where the polycyclic assemblies were not assigned using NOESY the ‘A’ and ‘B’ descriptors are reported through analysis of the coupling constants or otherwise arbitrarily.

### 1.2 General procedures

**General procedure A: Strong cation exchange solid phase extraction (SCX SPE)**

TfOH (0.5 M in MeOH, 10 mL / 5 g SCX SPE) was dripped through the SCX SPE cartridge prior to use. MeOH (20 mL) was then flushed through using pressurised air. The crude residue was loaded (3.5 mmol / 5 g SCX SPE silica) in the minimum amount of MeOH. The cartridge was flushed with MeOH and the fractions were collected and monitored by TLC. The cartridge was then flushed with sat. NH\(_3\)/MeOH and the fractions were collected and monitored by TLC. Fractions containing product were combined and concentrated.

**General Procedure B: Hydrogenation using Pd/C**

The substrate (1.0 eq.) was dissolved in MeOH or EtOH (~20 mL g\(^{-1}\)) and added via syringe to a round-bottomed flask containing 10 wt% Pd/C (% w/w as specified) which was pre-submerged in minimal EtOH under N\(_2\). If required, conc. HCl (~12 M) was added as specified. The head-space of the flask was subjected to a sequence of vacuum/H\(_2\) flushes (×3), then exposed to an atmosphere of H\(_2\) (balloon). The reaction was monitored by TLC until complete (generally reactions were complete in ≤18 h). At this point the balloon was removed and the reaction mixture was purged with
\( \text{N}_2 \) (with a gas outlet) for 5 minutes. The reaction mixture was filtered through Celite® eluting with MeOH, then concentrated in vacuo. The product was typically used in the next step without further purification.

**General Procedure C: Amide formation**

TBTU (1.6 eq.) was added to a stirred solution of the appropriate carboxylic acid (1.5 eq.), amine (1.0 eq.) and DIPEA (2.5 eq.) in DMA (0.13 M). The reaction mixture was stirred at rt for 24 h, then H\(_2\)O (0.1 volumes) was added. Reaction mixtures were purified by mass-directed preparative HPLC.

**General procedure D: Reductive amination**

The appropriate aldehyde or ketone (2.5 eq.) was added to a stirred solution of amine (1.0 eq.) and AcOH (2.0 eq.) in DMA (0.13 M). NaBH(OAc)\(_3\) (3.0 eq.) was added and the reaction mixture was heated to 60 °C and stirred for 24 h. The reaction mixture was cooled to rt then H\(_2\)O (0.1 volumes) was added. Reaction mixtures were purified by mass-directed preparative HPLC.

**General procedure E: Sulfonamide formation**

RSO\(_2\)Cl (3.0 eq.) was added to a mixture of amine (1.0 eq.) and NaHCO\(_3\) (6.0 eq.) in DMA (0.13 M). The reaction mixture was stirred at rt for 2.5 h, then H\(_2\)O (0.1 volumes) was added. Reaction mixtures were purified by mass-directed preparative HPLC.

**General procedure F: Urea formation**

The appropriate isocyanate (2.0 eq.) was added to a mixture of amine (1.0 eq.) and NaHCO\(_3\) (6.0 eq.) in DMA (0.13 M). The reaction mixture was stirred at rt for 16 h, then H\(_2\)O (0.1 volumes) was added. Reaction mixtures were purified by mass-directed preparative HPLC.
1.3 Compound data

1.3.1 Preparation of cycloaddition precursors and cycloadducts

1.3.1.1 Preparation of O-bridged cycloadduct 1

1.3.1.1.1 Preparation of each intermediate in the synthesis of cycloaddition precursor 11
5-[(tert-Butyldimethylsilyloxy)-2-(hydroxymethyl)-4H-pyran-4-one 8

Following a procedure by Miyazaki,2 TBSCI (5.3 g, 35 mmol, 1.0 eq.) was added to a stirred suspension of kojic acid 7 (5.0 g, 35 mmol, 1.0 eq.), Et3N (7.4 mL, 100 mmol, 2.90 eq.) and DMAP (5 mg, 0.04 mmol, 0.001 eq.) in CHCl3 (50 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1 h then aqueous KHSO4 (5 wt%, 50 mL) was added. The phases were separated and the organic phase was washed with brine (50 mL), dried, filtered, and concentrated in vacuo. Flash chromatography eluting with 1:1 pentane–EtOAc gave the title compound 8 (8.1 g, 32 mmol, 90%) as a colourless amorphous solid. *Rf 0.57 (1:1 petrol–EtOAc). 1H NMR (500 MHz, CDCl3): δ 7.65 (1H, s, 6-H), 6.47 (1H, s, 3-H), 4.46 (2H, d, J 6.3, CH2OH), 3.13 (1H, t, J 6.3, OH), 0.95 (9H, s, SiC(CH3)3), 0.21 (6H, s, 2 × SiCH3). 13C NMR (125 MHz, CDCl3): δ 176.1 (4-C), 166.6 (2-C), 144.6 (5-C), 144.2 (6-C), 112.4 (3-C), 61.1 (CH2OH), 25.8 (SiC(CH3)3), 18.7 (SiCq), −4.4 (2 × SiCH3). IR νmax(film)/cm−1 3358 (br., OH), 2954, 2857, 1651 (CO), 1629, 1268, 1211, 874. LRMS (HPLC-MS): C12H21O4Si; found 257.1 [M+H]+. Spectral data are consistent with the literature values.8

{5-[(tert-Butyldimethylsilyloxy)-4-oxo-4H-pyran-2-yl]methyl methanesulfonate 9

Et3N (3.30 mL, 23.4 mmol, 2.00 eq.) was added to a stirred solution of compound 8 (3.00 g, 11.7 mmol, 1.00 eq.) in CH2Cl2 (24 mL). The reaction mixture was cooled to 0 °C, then methanesulfonyl chloride (1.1 mL, 14 mmol, 1.2 eq.) was added dropwise. The reaction mixture was stirred at 0 °C for 0.5 h, then warmed to rt and partitioned with H2O (25 mL). The phases were separated and the aqueous phase was extracted with CH2Cl2 (25 mL). The combined organic phases were dried over MgSO4, filtered, and concentrated in vacuo to give the title compound 9 (3.31 g, 9.89 mmol, 85% mass recovery) which was used subsequently without further purification. *Rf 0.62 (1:1 petrol–EtOAc). 1H NMR (300 MHz, CDCl3, characteristic peaks): δ 7.69 (1H, s, 6-H), 6.48 (1H, s, 3-H), 4.97 (2H, s, CH2), 3.11 (3H, s, SO2CH3), 0.95 (9H, s, SiC(CH3)3), 0.23 (6H, s, 2 × SiCH3).

*Compound 8 and related silylated pyranone derivatives 9-11 slowly decomposed on standing in air or in mildly acidic solvents (e.g. CDCl3). Compounds of this type should be stored in a freezer at −18 °C. N.b. derived cycloadduct 1 was bench stable at rt for several weeks.
5-{[(tert-Butyldimethylsilyl)oxy]-2-[[[prop-2-en-1-yl]amino]methyl]-4H-pyrano-4-one 10

Et$_3$N (3.5 mL, 35 mmol, 1.0 eq.) was added to a stirred solution of compound 9 (11.8 g, 35 mmol, 1.0 eq.) in THF (120 mL). Allylamine (8.0 mL, 106 mmol, 3.0 eq.) was added and the reaction mixture was stirred for 15 h, then concentrated in vacuo. The resulting residue was diluted in EtOAc (50 mL) and washed with sat. aq. NaHCO$_3$ solution (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (50 mL). The combined organics were washed with brine (50 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was washed through a pad of silica with 9:1 EtOAc–MeOH to give the title compound 10 (5.9 g, 20 mmol, 56%) as a dark brown oil. Rp 0.57 (1:1 petrol–EtOAc). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.64 (1H, s, 6-H), 6.36 (1H, s, 3-H), 5.86 (1H, ddt, $J$ 16.8, 10.3, 6.0, CH=CH$_2$), 5.20 (1H, app. dq, $J$ 16.8, 1.4, CH=CH$_2$H$_3$), 5.14 (1H, ddd, $J$ 10.3, 2.7, 1.4, CH=CH$_2$H$_5$), 3.62 (2H, s, C$_9$H$_2$NH), 3.27 (2H, dt, $J$ 6.0, 1.4, NHCH$_2$CH=CH$_2$), 0.96 (9H, s, SiC(CH$_3$)$_3$), 0.23 (6H, s, 2 × SiCH$_3$). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 175.7 (4-C), 165.7 (2-C), 145.5 (5-C), 144.2 (6-C), 135.9 (CH=CH$_2$), 117.1 (CH=CH$_2$), 113.7 (3-C), 51.5 (CH$_2$CH=CH$_2$), 49.8 (C$_9$H$_2$NH), 25.8 (SiC(CH$_3$)$_3$), 18.7 (SiC$_q$), −4.3 (2 × SiCH$_3$). IR $v_{\text{max}}$(film)/cm$^{-1}$ 2954, 2930, 2857, 1651 (CO), 1232, 919, 879, 786. LRMS (HPLC-MS): C$_{15}$H$_{25}$NO$_3$Si; found 296.1 [M+H]$^+$.  

Benzyl N-{[(tert-butyldimethylsilyl)oxy]-4-oxo-4H-pyrano-2-yl}methyl-N- (prop-2-en-1-yl)carbamate 11

Benzyl chloroformate (180 µL, 1.28 mmol, 2.6 eq.) was added to a stirred solution of compound 10 (145 mg, 0.49 mmol, 1.0 eq.) and Et$_3$N (180 µL, 1.28 mmol, 2.6 eq.) in CH$_2$Cl$_2$ (5.0 mL) at 0 °C. The reaction mixture warmed to rt and stirred for 15 h, then concentrated in vacuo. Flash chromatography eluting with 9:1 EtOAc–MeOH gave the title compound 11 (145 mg, 0.34 mmol, 69%) as a pale yellow oil. Rp 0.82 (1:1 petrol–EtOAc). $^1$H NMR (500 MHz, CDCl$_3$, 330 K): $\delta$ 7.56 (1H, s, 6-H), 7.39-7.27 (5H, m, Cbz Ar-H), 6.23 (1H, s, 3-H), 5.81-5.70 (1H, m, CH=CH$_2$), 5.21-5.10 (4H, m, CH=CH$_2$ and OCH$_2$Ph), 4.26 (2H, s, C$_9$H$_2$N), 3.96 (2H, s, NCH$_2$CH=CH$_2$), 0.97 (9H, s, SiC(CH$_3$)$_3$), 0.24 (6H, s, 2 × SiCH$_3$). $^{13}$C NMR (125 MHz, CDCl$_3$, 330 K): $\delta$ 175.3 (4-C), 163.3 (2-C), 156.1 (N(CO)O), 145.8 (5-C), 144.0 (6-C), 136.5 (CH=CH$_2$), 132.9 (Ar-C$_q$), 128.7 (Ar-C), 128.4 (Ar-C), 128.2 (Ar-C), 118.2 (CH=CH$_2$), 113.7 (3-C), 65.6 (OCH$_2$Ph), 50.3 (CH$_2$CH=CH$_2$), 47.6 (C$_9$H$_2$NH), 25.8 (SiC(CH$_3$)$_3$), 18.7 (SiC$_q$), −4.3 (2 × SiCH$_3$). IR $v_{\text{max}}$(film)/cm$^{-1}$ 2953, 2929, 2857, 1702 (CO), 1649, 1460, 1410, 1210. HRMS (ESI): C$_{23}$H$_{32}$NO$_5$Si [M+H]$^+$; calculated 430.2058, found 430.2044.
1.3.1.1.2 Telescopéd synthesis of cycloaddition precursor 11

```
kojic acid 7
10.0 g, 70.4 mmol

<table>
<thead>
<tr>
<th>Reaction 1</th>
<th>Reaction 2</th>
<th>Reaction 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBSCI (1.0 eq.), Et₃N (1.1 eq.), DMAP (3.0 mol%), CH₂Cl₂, 0 °C, 1 h</td>
<td>MsCl (1.1 eq.), Et₃N (1.2 eq.), CH₂Cl₂, 0 °C, 0.5 h</td>
<td>allylamine (3.8 eq.), Et₃N (1.0 eq.), CH₂Cl₂, rt, 15 h</td>
</tr>
</tbody>
</table>

11 53% [4 steps]
15.9 g, 37.0 mmol
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Benzyl N-{{5-[(tert-butyldimethylsilyl)oxy]-4-oxo-4H-pyran-2-yl}methyl}-N- (prop-2-en-1-yl)carbamate 11

TBSCl (10.7 g, 71.0 mmol, 1.01 eq.) was added to a stirred solution of kojic acid 7 (10.0 g, 70.4 mmol, 1.00 eq.), Et₃N (10.8 mL, 77.9 mmol, 1.10 eq.) and DMAP (258 mg, 2.11 mmol, 0.03 eq.) in CH₂Cl₂ (150 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 45 min. The reaction mixture was quenched with sat. aq. NH₄Cl solution (100 mL) and H₂O (100 mL). After separation, the aqueous phase was extracted with CH₂Cl₂ (2 × 150 mL). The organic extracts were combined, dried over Na₂SO₄ and concentrated in vacuo.

To the residue 8 (70.4 mmol) in CH₂Cl₂ (150 mL) at 0 °C was added Et₃N (12.0 mL, 86.5 mmol, 1.23 eq.) and methanesulfonyl chloride (6.0 mL, 78 mmol, 1.1 eq.) dropwise. The reaction mixture was warmed to rt and stirred for 0.5 h, then quenched with water (150 mL). After phase separation, the aqueous phase was extracted using CH₂Cl₂ (2 × 150 mL). The organic extracts were combined, dried over Na₂SO₄, filtered, and concentrated in vacuo.

To the residue 9 (70.4 mmol) in CH₂Cl₂ (150 mL) at 0 °C was added Et₃N (17.0 mL, 121 mmol, [1.72 eq.,] followed by the very slow addition (gas outlet necessary) of benzyl chloroformate (15.0 mL, 106 mmol, 1.50 eq.). The reaction mixture warmed to rt and stirred 2 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (150 mL) and H₂O (150 mL). After phase separation, the aqueous phase was extracted with CH₂Cl₂ (2 × 150 mL). The organic extracts were combined, dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography eluting with 9:1 to 8:2 pentane–EtOAc gave the title compound 11 (15.9 g, 37.0 mmol, 53%, 4 steps) as a pale yellow oil (see above for spectral data).
1.3.1.1.3 Preparation of O-bridged cycloadduct 1

\[
\text{[15.9 g, 37.0 mmol]}
\]

Benzyl (1R*,5S*,7S*)-9-[(tert-butyldimethylsilyl)oxy]-8-oxo-11-oxa-3-zatricyclo[5.3.1.0^1,5]undec-9-ene-3-carboxylate 1

A stirred solution of compound 11 (15.9 g, 37.0 mmol) in xylenes (36 mL) was heated at reflux (155 °C) for 15 h. The reaction mixture was cooled to rt then concentrated in vacuo. Flash chromatography eluting with 9:1 to 8:2 pentane–EtOAc gave the title compound 1 (13.8 g, 32.1 mmol, 87%) as a colourless amorphous solid.† M.p. 96-98 °C, colourless plates, hexane–EtOAc. \( R_f 0.18 \) (4:1 petrol–EtOAc).

\(^1\)H NMR (500 MHz, CDCl\(_3\), 50:50 mixture of rotamers): δ 7.41-7.29 (5H, m, Cbz Ar-H), 6.29 (0.5H, s, 10-H), 6.26 (0.5H, s, 10-H), 5.15 (1H, app. d, \( J = 12.0 \), OCH\(_A\)H\(_B\)Ph), 5.12 (1H, app. d, \( J = 12.0 \), OCH\(_A\)H\(_A\)Ph), 4.78 (1H, d, \( J = 8.2 \), 7-H), 4.04-3.90 (2H, m, 2-H\(_B\) and 4-H\(_A\)), 3.68 (0.5H, d, \( J = 12.8 \), 2-H\(_A\), 2-H\(_B\)), 3.22-3.13 (1H, m, 4-H\(_B\)), 2.84-2.74 (1H, m, 5-H), 2.34-2.21 (1H, m, 6-H\(_A\)), 1.89 (1H, app. d, \( J = 13.2 \), 8.2, 6-H\(_A\)), 0.94 (4H, s, SiC(CH\(_3\)_3)), 0.93 (5H, s, SiC(CH\(_3\)_3)), 0.16 (6H, m, 2 × SiCH\(_3\)).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\), mixture of two rotamers): δ 193.7 (8-C), 154.5 (N(CO)O), 154.3 (N(CO)O), 148.1 (9-C), 136.8 (Ar-C\(_A\)), 138.7 (Ar 1-C), 128.7 (Ar-C), 128.3 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 127.3 (10-C), 127.2 (10-C), 90.6 (1-C), 89.8 (1-C), 83.4 (7-C), 67.2 (OCH\(_2\)Ph), 53.9 (2-C or 4-C), 53.5 (2-C or 4-C), 53.1 (2-C or 4-C), 52.7 (2-C or 4-C), 47.1 (5-C), 46.2 (5-C), 31.6 (6-C), 31.5 (6-C), 25.7 (SiC(CH\(_3\)_3)), 18.6 (SiC\(_A\)), −4.5 (2 × SiCH\(_3\)) [28 of 36 expected peaks observed]. IR \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 2954, 2953, 1703 (CO), 1652, 1419, 1347, 1163, 919. HRMS (ESI): \( C_{23}H_{32}NO_5Si \ [M+H]^+ \); calculated 430.2044, found 430.2048.

X-ray crystallography: CCDC 1526777 contains the supplementary crystallographic data for this compound. Crystals were grown by slow evaporation from diethyl ether.

† Compound 1 was stable for several months when stored in a freezer at −18 °C.
1.3.1.1.4 Scaled-up synthesis of O-bridged cycloadduct 1

The route to compound 1 outlined above in Sections 1.3.1.1.2 and 1.3.1.1.3 was followed starting with 50 g (0.35 mol) kojic acid 7 to prepare 57.2 g (0.13 mmol, 38% overall yield) cycloadduct 1.

![Diagram of synthesis process]

- **Kojic acid 7**
  - 50 g, 0.35 mol

- **Compound 1**
  - 75% 57.2 g, 0.13 mol

- **Cycloadduct 1**
  - 99% (crude) 90.2 g, 0.35 mol
  - 93% (crude) 109.1 g, 0.33 mol

- **Allylamine (3.8 eq.), Et3N (1.0 eq.), CH2Cl2, rt**
1.3.1.2 Preparation of N-bridged cycloadduct 2

1.3.1.2.1 Preparation of precursors to N-bridged cycloadduct 2

![Chemical structure diagram]

Methyl iodide (8.40 mL, 132 mmol, 1.00 eq.) was added to stirred solution of 2-(dimethylaminomethyl)-3-hydroxypyridine 12 (20.1 g, 132 mmol, 1.00 eq.) in acetone (66 mL) at 0 °C. The resulting mixture was warmed to rt and stirred for 2 h, during which time a pale yellow precipitate formed. The solid was collected by filtration to give the title compound 13 (34.1 g, 115.9, 88%) as a pale yellow solid. **M.p.** Decomposition observed above 164 °C. \(^1\)H NMR (D\(_2\)O, 400 MHz): 8.21 (1H, dd, J 3.9, 2.1, 5-H), 7.56-7.47 (2H, m, 4-H and 6-H), 4.61 (2H, s, CH\(_2\)Ar), 3.21 (9H, s, N\(^+\)(CH\(_3\))\(_3\)). \(^{13}\)C NMR (D\(_2\)O, 100 MHz): 154.3, 141.1, 134.7, 127.6, 125.7, 64.5, 53.2. IR \(\nu_{\text{max}}\)(film)/cm\(^{-1}\): 3381, 1629, 1583, 1484, 1462, 1300. **HRMS** (ESI): C\(_9\)H\(_{15}\)N\(_2\)O [M]+; calculated 167.1184, found 167.1186.
tert-Butyl N-[(3-hydroxy-2-pyridinyl)methyl]-N-(prop-2-en-1-yl)carbamate 14

N-Boc-allylamine (10.2 g, 65.1 mmol, 1.00 eq.) was added to a stirred suspension of NaH (60% dispersion in mineral oil, 5.47 g, 137 mmol, 2.10 eq.) in THF (280 mL) at 0 °C. The resulting suspension was stirred at rt for 2 h. After this time, the suspension was cooled to 0 °C and compound 13 (21.1 g, 71.6 mmol, 1.10 eq.) was added in one portion. The suspension was stirred at reflux for 2 h, then cooled to rt and quenched with sat. aq. NH₄Cl solution (100 mL). EtOAc (100 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo to deliver a crude brown oil. Flash chromatography eluting with (4:5:1 petrol–CH₂Cl₂–EtOAc) gave the title compound 14 (9.47 g, 35.8 mmol, 55%) as a colourless solid. ¹H NMR (MeOD-d₄, 500 MHz, 333 K): 7.87 (1H, dd, J 4.4, 1.7, 6-H), 7.08 (1H, dd, J 8.1, 1.6, 4-H), 7.05 (1H, dd, J 8.1, 4.4, 5-H), 5.67 (1H, ddt, J 17.0, 10.4, 5.6, CH=CH₂), 4.98 (1H, app. dq, J 17.0, 1.7, CH=CH₃Br), 4.96 (1H, app dq, J 10.4, 1.5, CH=CH₃Br), 4.37 (2H, s, CH₂Ar), 3.80 (2H, d, J 5.6, NCH₂CH=CH₂), 1.33 (9H, s, C₃q(CH₃)₃). ¹³C NMR (MeOD-d₄, 125 MHz, 333 K): 158.3, 153.7, 146.0, 140.6, 134.9, 124.9, 124.3, 116.7, 81.7, 50.9, 48.7, 28.7. IR vₘₐₓ(film)/cm⁻¹ 3271, 1651, 1447, 1414, 1161. HRMS (ESI): C₁₄H₂₁N₂O₃ [MH]⁺; calculated 265.1547, found 265.1551.
1.3.1.2.2 Preparation of N-bridged cycloadduct 2

![Chemical Structure](image)

**Benzyl (1R*, 5R*, 7R*)-11-benzyl-10-oxo-3,11-diazatricyclo[5.3.1.0^1,5]undec-8-ene-3-carboxylate 2**

Benzyl bromide (4.2 mL, 35.6 mmol, 1.10 eq.) was added to a stirred solution of compound 14 (8.57 g, 32.4 mmol, 1.00 eq.) in MeCN (65 mL). The resulting solution was stirred at reflux for 18 h. After cooling to rt, DABCO (10.9 g, 97.2 mmol, 3.00 eq.) was added in one portion and the resulting suspension was stirred at reflux for 2 h, then cooled to rt. H₂O (200 mL) and CH₂Cl₂ (200 mL) were added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (200 mL) and the combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography eluting with 4:5:1 petrol–CH₂Cl₂–EtOAc gave the title compound 2 (7.42 g, 20.9 mmol, 65%) as a yellow oil. ¹H NMR (MeOD-d₄, 500 MHz, 333 K): 7.21-7.09 (5H, m, Bn Ar-H), 6.95 (1H, dd, J 9.8, 4.8, 8-H), 5.99 (1H, d, J 9.8, 9-H), 3.98 (1H, d, J 12.5, 2-Hₐ), 3.82 (1H, dd, J 10.9, 9.2, 4-Hₐ), 3.76-3.69 (1H, m, 7-H), 3.63 (1H, d, J 13.7, NCHₐHₐPh), 3.56 (1H, d, J 13.7, NCHₐHₐPh), 3.31 (1H, dd, J 10.9, 7.9, 4-Hₐ), 3.30-3.23 (1H, m, 2-Hₐ), 2.55 (1H, app. qd, J 8.5, 4.7, 5-H), 1.93 (1H, dd, J 12.1, 8.5, 6-Hₐ), 1.80-1.89 (1H, m, 6-Hₐ), 1.36 (9H, s, C₉(CH₃)₃). ¹³C NMR (MeOD-d₄, 125 MHz, 333 K): 197.3, 156.1, 152.1, 140.3, 129.4, 129.3, 128.2, 127.9, 82.7, 81.1, 61.4, 54.3, 50.4, 47.6, 45.8, 35.3, 28.7. IR νmax(film)/cm⁻¹: 1681, 1403, 1365, 1167, 1125, 882. HRMS (ESI): C₂₁H₂₇N₂O₃ [MH]+; calculated 355.2016, found 355.2023.
1.3.1.2.3 Scaled-up synthesis of $N$-bridged cycloadduct 2

The route to compound 2 outlined above in Sections 1.3.1.2.1 and 1.3.1.2.2 was followed starting with 60 g (0.35 mol) compound 12 to prepare 25.8 g (72.8 mmol, 32% overall yield) cycloadduct 2.
1.3.2 Preparation of scaffolds 3

1.3.2.1 Initial procedure to prepare diol 18

\[
\text{CbzN} \begin{array}{c}
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{OTBS}
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{OTBS}
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{H} \\
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\begin{array}{c}
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{OTBS}
\end{array}
\end{array}
\end{array}
\text{NaBH}_4 (2.0 \text{ eq.})
\text{MeOH, 0 }{\circ}\text{C, then rt, 0.5 h}
\text{0.58 mmol scale}
\]

\[
\text{CbzN} \begin{array}{c}
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{OTBS}
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{H} \\
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\text{OTBS}
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\end{array}
\begin{array}{c}
\begin{array}{c}
\text{H} \\
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\text{OTBS}
\end{array}
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{TBAF (2.0 eq.), THF, 2 h}
\end{array}
\end{array}
\]

\[
\text{CbzN} \begin{array}{c}
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{OTBS}
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{OTBS}
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{OTBS}
\end{array}
\end{array}
\end{array}
\text{18 41% (2 steps)}
\]
Benzyl (1\textsuperscript{R\textdagger},5\textsuperscript{R\textdagger},7\textsuperscript{R\textdagger},8\textsuperscript{R\textdagger},9\textsuperscript{R\textdagger})-8,9-dihydroxy-11-oxa-3-azatricyclo[5.3.1.0\textsubscript{1,5}]undecane-3-carboxylate 18

\[
\text{NaBH}_4 \text{ (44 mg, 1.2 mmol, 2.0 eq.) was added to a stirred solution of compound 1 (250 mg, 0.58 mmol, 1.00 eq.) in MeOH (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h, then H}_2\text{O} \text{ (1.0 mL) was added. The reaction mixture was warmed to rt, then concentrated in vacuo to give a 2:3 mixture of TBS-protected diols 16 and 17 as a colourless oil (characteristic } \textsuperscript{1}H NMR peaks given below). To a stirred solution of the residue in THF (10 mL) was added TBAF (1.0 M in THF, 1.2 mL, 1.2 mmol, 2.0 eq.). The reaction mixture was stirred for 2 h then concentrated in vacuo. Flash chromatography eluting with 0-10% MeOH in EtOAc gave a mixture of the title compound with TBAF. Further purification by SCX following general procedure A, eluting with MeOH, gave the title compound 18 (76 mg, 0.24 mmol, 41%) as a colourless oil. \textit{R}f 0.58 (9:1 EtOAc–MeOH).  \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}, 50:50 mixture of rotamers): \(\delta \text{ } 7.41-7.27 \text{ (5H, m, Cbz Ar-H)}, 5.11 \text{ (2H, s, OCH}_2\text{Ph)}, 4.35 \text{ (1H, dd, J 7.2, 4.8, 7-H)}, 4.15-4.10 \text{ (1H, m, 9-H)}, 3.93-3.85 \text{ (1H, m, 4-\text{Ha}, includes at } \delta \text{ } 3.91: 0.5H, d, J, 10.5; \text{ and at } \delta \text{ } 3.87: 0.5H, d, J, 10.5), 3.86-3.80 \text{ (1H, m, 8-H)}, 3.79-3.71 \text{ (1H, m, 2-\text{Ha}, includes at } \delta \text{ } 3.76: 0.5H, d, J, 12.6; \text{ and at } \delta \text{ } 3.74: 0.5H, d, J, 12.6), 3.41 \text{ (0.5H, d, J 12.6, 2-\text{Ha})}, 3.36 \text{ (0.5H, d, J 12.6, 2-\text{Ha})}, 3.24-3.15 \text{ (1H, m, 4-\text{Ha})}, 3.08-3.00 \text{ (1H, m, 5-H)}, 2.63 \text{ (1H, app. td, J 12.7, 8.5, 6-\text{Ha})}, 2.49 \text{ (2H, br, s, 2 × OH)}, 2.19 \text{ (0.5H, dd, J 14.7, 4.3, 10-\text{Ha})}, 2.13 \text{ (0.5H, dd, J 14.7, 4.3, 10-\text{Ha})}, 1.97-1.90 \text{ (1H, m, 10-\text{Ha}, includes at } \delta \text{ } 1.95: 0.5H, d, J 14.7; \text{ and at } \delta \text{ } 1.93: 0.5H, d, J 14.7), 1.78-1.66 \text{ (1H, m, 6-\text{Ha})).} \textsuperscript{13}C NMR (125 MHz, DMSO-d\textsubscript{6}, mixture of two rotamers): \(\delta \text{ } 153.5 \text{ (N(CO)O), 153.4 (N(CO)O), 137.1 (Ar-C\textsubscript{q}), 128.4 (Ar-C), 127.7 (Ar-C), 127.5 (Ar-C), 88.7 (1-C), 87.7 (1-C), 79.0 (7-C), 68.0 (8-C), 65.9 (9-C), 65.7 (OCH}_2\text{Ph), 54.8 (2-C or 4-C), 54.5 (2-C or 4-C), 54.2 (2-C or 4-C), 54.0 (2-C or 4-C), 44.2 (5-C), 43.2 (5-C), 38.0 (10-C), 37.9 (10-C), 32.7 (6-C), 32.6 (6-C) [22 of 30 expected peaks observed].} \textit{IR} v_{\text{max}}(\text{film})/\text{cm}^{-1} \text{ 3423 (OH), 2948, 2884, 1683 (CO), 1425, 1350, 1149, 1107.} \textsuperscript{HRMS} (ESI): \text{C}_{17}\text{H}_{22}\text{NO}_5 [\text{M+H}]^+; \text{calculated 320.1495, found 320.1496.}

Characteristic \textsuperscript{1}H NMR peaks for compounds 16 and 17 (500 MHz, CDCl\textsubscript{3}, 40:60 mixture of regioisomers): \(\delta \text{ } 7.38-7.28 \text{ (major and minor, 5H, m, Cbz Ar-H)}, 5.15-5.07 \text{ (major and minor, 2H, m, OCH}_2\text{Ph), 4.36 \text{ (minor, 0.4H, dd, J 7.3, 4.6), 4.25-4.20 (major, 0.6H, dd, J 6.9, 5.2), 4.13-4.09 (minor, 0.4H, m), 3.98-3.93 (major, 0.6H, m), 3.93-3.86 (major and minor, 1H, m), 3.84-3.79 (major, 0.6H, m), 3.77-3.68 (major and minor, 1.4H, m), 3.44-3.32 (major and minor, 1H, m), 3.24-3.13 (major and minor, 1H, m), 3.09-3.01 \text{ (major, 0.6H, m), 2.95-2.86 (minor, 0.4H, m), 2.77 (major, 0.6H, d, J 4.5), 2.62 (major, 0.6H, td, J 13.2, 8.5), 2.57-2.50 (minor, 0.4H, m), 2.49 (minor, 0.4H, d, J 10.6),

\footnote{1 As judged by analysis of the crude reaction product by \textsuperscript{1}H NMR spectroscopy (500 MHz, CDCl\textsubscript{3}). Identity of the major regioisomer not determined.}
2.24-2.10 (major, 0.6H, m), 2.07 (minor, 0.4H, dd, J 14.6, 3.7), 1.98 (major, 0.6H, dd, J 14.5, 7.9),
1.80 (minor, 0.4H, dd, J 14.6, 9.3), 1.76-1.56 (major and minor, 1H, m), 0.94 (minor, 3.6H, s,
SiC(CH₃)₃), 0.91 (major, 5.4H, s, SiC(CH₃)₃), 0.13-0.10 (major and minor, 6H, m, SiCH₃)].

1.3.2.2 Optimised synthetic route to prepare diol 18

Benzyl (1R⁺,5R⁺,7R⁺,8R⁺,9R⁺)-8,9-dihydroxy-11-oxa-3-azatricyclo[5.3.1.0₁⁵]undecane-3-
 carboxylate 18

NaBH₄ (832 mg, 22.0 mmol, 2.20 eq.) was added to a stirred solution of compound 1 (4.30 g, 10.0 mmol, 1.0 eq.) in MeOH (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, warmed to rt, stirred for 0.5 h, then concentrated in vacuo to give a 2:3 mixture of TBS-protected diols 16 and 17 as a colourless oil (see above for characteristic ¹H NMR peaks). The residue containing 16 and 17 was diluted in CH₂Cl₂ (50 mL) and washed with 1.0 M HCl (50 mL). The aqueous phase was extracted with CH₂Cl₂ (50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue (10.0 mmol) was dissolved in MeOH (60 mL) and (±)-camphorsulfonic acid (3.02 g, 13.0 mmol, 1.30 eq.) was added. The reaction mixture was heated at 45 °C for 15 h, then concentrated in vacuo. The residue was diluted in CH₂Cl₂ (50 mL). Sat. aq. NaHCO₃ (50 mL) and H₂O (50 mL) were added and the phases were separated. The aqueous phase was extracted using CH₂Cl₂ (2 × 50 mL). The organic extracts were combined, dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography eluting with 0-10% MeOH in EtOAc gave the title compound 18 (2.45 g, 7.67 mmol, 77%, 2 steps) as a colourless oil (see above for spectral data).
1.3.2.3 Initial route to prepare scaffold 3a

Benzyl (1R*,5R*,7R*)-9-benzyl-12-oxa-3,9-diazatricyclo[5.4.1.01,5]dodecane-3-carboxylate 3a

NaIO₄ (105 mg, 0.490 mmol, 2.00 eq.) was added to a stirred solution of compound 18 (78 mg, 0.24 mmol, 1.0 eq.) in 8:2 MeOH–H₂O (10 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for 2 h, then concentrated in vacuo. The residue was diluted in CH₂Cl₂ (10 mL) and washed with H₂O (10 mL). The phases were separated and the aqueous phase extracted with CH₂Cl₂ (2 × 10 mL). The resulting crude dialdehyde was dissolved in CH₂Cl₂ (10 mL). BnNH₂ (26 µL, 0.25 mmol, 1.0 eq.), NaBH(OAc)₃ (153 mg, 0.72 mmol, 3.0 eq.) and 4 Å MS (10 mg) were added. The reaction mixture was stirred for 15 h, then filtered through Celite® and concentrated in vacuo. The resulting residue was diluted in EtOAc (25 mL) and washed with brine (25 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phase was dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography eluting with 0-100% EtOAc in pentane gave the title compound 3a (30 mg, 76 µmol, 32%, 2 steps) as a colourless oil. Rₚ 0.74 (1:1 petrol–EtOAc). ¹H NMR (500 MHz, CDCl₃, 50:50 mixture of rotamers): δ 7.39-7.21 (10H, m, Ar-H), 5.11 (2H, s, OC=), 4.43-4.38 (1H, m, 7-H, includes at δ 4.41: 0.5H, d, J 8.1; and at δ 4.40: 0.5H, d, J 8.1), 3.89 (1H, d, J 12.3, 2-Ph), 3.64-3.53 (3H, includes: 1H, m, 4-Ph; at δ 3.61: 1H, d, J 13.3, NCH₆H₅Ph; and at δ 3.55: 1H, d, J 13.3, NCH₆H₅Ph), 3.52-3.33 (1H, m, 4-Ph), 3.22-3.06 (1H, m, 2-Ph), 2.90-2.80 (1H, m, 5-H), 2.77-2.68 (1H, m, 10-Ph), 2.58-2.44 (2H, includes: 1H, m, 10-Ph; and at δ 2.52: 1H, d, J 12.4, 8-Ph), 2.43-2.36 (1H, m, 8-Ph, includes at δ 2.40: 0.5H, d, J 12.4; and at δ 2.39: 0.5H, d, J 12.4), 2.28-2.21 (1H, m, 6-Ph), 1.92-1.74 (3H, m, 6-Ph and 11-H).

¹³C NMR (125 MHz, CDCl₃, mixture of two rotamers): δ 155.1 (N(CO)O), 139.9 (Ar-C₉), 137.1 (Ar-C₉), 128.8 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.0 (2 peaks, 2 × Ar-C), 127.2 (Ar-C), 93.2 (1-C), 92.2 (1-C), 80.2 (7-C), 66.9 (OCH₂Ph), 64.3 (NCH₂Ph), 63.6 (8-C), 57.9 (2-C), 57.5 (2-C), 54.0 (4-C), 53.8 (4-C), 53.6 (10-C), 50.1 (5-C), 38.3 (11-C), 36.6 (6-C) [23 of 40 expected peaks observed].

IR νmax (film)/cm⁻¹ 2930, 2865, 1702 (CO), 1451, 1419, 1360, 1217, 1143. HRMS (ESI): C₂₄H₂₉N₂O₃ [M+H]⁺; calculated 393.2173, found 393.2185.
1.3.2.4 Telescopede synthesis of scaffolds 3b-e

\[
\text{NaBH}_4 (832 \text{ mg}, 22.0 \text{ mmol}, 2.20 \text{ eq.}) \text{ was added to a stirred solution of compound 1 (4.30 g, 10.0 mmol, 1.0 eq.) in MeOH (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, warmed to rt, stirred for 0.5 h, then concentrated in vacuo. The residue was diluted in CH}_2\text{Cl}_2 (50 mL) and washed with 1.0 M HCl (50 mL). The aqueous phase was extracted with CH}_2\text{Cl}_2 (50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na}_2\text{SO}_4 and concentrated in vacuo. The residue 10.0 mmol was dissolved in MeOH (60 mL) and (±)-camphorsulfonic acid (3.02 g, 13.0 mmol, 1.30 eq.) was added. The reaction mixture was heated at 45 °C for 15 h, then concentrated in vacuo. The residue was diluted in CH}_2\text{Cl}_2 (50 mL). Sat. aq. NaHCO}_3 (50 mL) and H}_2O (50 mL) were added and the phases were separated, The aqueous phase was extracted using CH}_2\text{Cl}_2 (2 \times 50 \text{ mL}). The organic extracts were combined, dried over Na}_2\text{SO}_4, filtered, and concentrated in vacuo. The crude residue of compound 18 (3.12 g) was used directly in the next step. NaIO}_4 (4.28 g, 20.0 mmol, 2.00 eq.) was added to a stirred solution of compound 18 (3.12 g) in MeOH–H}_2O (150 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 1.5 h, then concentrated in vacuo. The residue was diluted in CH}_2\text{Cl}_2 (100 mL) and washed with H}_2O (100 mL). The phases were separated, and the aqueous phase was extracted with CH}_2\text{Cl}_2 (2 \times 50 \text{ mL}). The organic extracts were combined, washed with brine (50 mL), dried over Na}_2\text{SO}_4, and concentrated in vacuo. The crude residue 19 was not purified further and was divided into separate flasks to prepare compounds 3b-e using General Procedure G (see below).}
General procedure G: Double reductive amination to give amines 3b-e

The appropriate amine (1.2 eq.) was added to a stirred solution of crude dialdehyde 19 (1.0 eq.) in CH₂Cl₂ (0.1 M). The reaction mixture was stirred for 10 min, then NaBH(OAc)₃ (2.6 eq.) was added. The reaction mixture was stirred overnight, then H₂O (1 volume) was added. The phases separated and the aqueous phase was extracted using CH₂Cl₂ (2 × 1 volume). The organic extracts were combined, washed with brine (1 volume), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude reaction products were purified by flash column chromatography.

Benzyl (1R*,5R*,7S*)-9-cyclopropyl-12-oxa-3,9-diazatricyclo[5.4.1.0₁,₅]dodecane-3-carboxylate 3b

General procedure G was followed using the crude dialdehyde 19 (9.19 mmol) and cyclopropylamine. Flash chromatography eluting with 7:3 hexane–EtOAc gave the title compound 3b (1.90 g, 5.55 mmol, 60% over 4 steps) as a colourless oil. Rf 0.55 (1:1 petrol–EtOAc).

¹H NMR (400 MHz, CDCl₃, 50:50 mixture of rotamers): δ 7.39-7.27 (5H, m, Cbz Ar-H), 5.11 (1H, s, OC₄H₂Ph), 5.10 (1H, s, OC₄H₂Ph), 4.41 (1H, app. d, J 6.5, 7-H), 3.86 (1H, d, J 12.3, 2-Hₐ), 3.60-3.49 (1H, m, 4-Hₐ), 3.45-3.23 (1H, m, 4-Hₐ), 3.23-3.05 (1H, m, 2-Hₐ), 2.94 (1H, dd, J 13.0, 6.4, 10-Hₐ), 2.74-2.54 (4H, m, 10-Hₐ, 5-H, and 8-H), 2.09 (1H, app. t, J 10.2, 6-Hₐ), 1.93-1.68 (4H, m, includes 6-Hₐ, 11-H, and cyclopropyl CH₃), 0.48-0.35 (3H, m, cyclopropyl (CH₃)₃ and cyclopropyl (CH₂)₃), 0.31-0.19 (1H, m, cyclopropyl (CH₃)₃ and cyclopropyl (CH₂)₃). ¹³C NMR (100 MHz, CDCl₃, mixture of two rotamers, 1 C₉ not observed): δ 137.1 (Ar-C₉), 128.6 (Ar-C), 128.0 (Ar-C), 80.0 (7-C), 66.9 (OCH₂Ph), 63.9 (8-C), 63.8 (8-C), 57.5 (2-C), 57.4 (2-C), 53.9 (4-C and 10-C), 50.3 (5-C), 40.3 (cyclopropyl CH₃), 38.6 (11-C), 36.4 (6-C), 8.1 (cyclopropyl (CH₂)₃), 7.5 (cyclopropyl (CH₂)₃) [16 of 34 expected peaks observed]. IR v_max (film)/cm⁻¹ 2821, 1705 (CO), 1449, 1419, 1364, 1351, 1236, 1127. HRMS (ESI): C₂₀H₂₇N₂O₃ [M+H]⁺; calculated 343.2022, found 343.2015.

§ Inferred by HMQC analysis.
Benzyl (1R*,5R*,7S*)-9-[2-(2-chlorophenyl)ethyl]-12-oxa-3,9-
diazatricyclo[5.4.1.01,5]dodecane-3-carboxylate 3c

General procedure G was followed using the crude dialdehyde 19 (0.27 mmol) and 2-(2-chlorophenyl)ethylamine. Flash chromatography eluting with 7:3 hexane–EtOAc gave the title compound 3c (65 mg, 0.15 mmol, 56% over 4 steps) as a colourless oil. ¹H NMR (400 MHz, CDCl₃, 50:50 mixture of rotamers): δ 7.46-7.03 (9H, m, Ar-H), 5.11 (2H, s, OCH₂Ph), 4.47-4.40 (1H, m, 7-H, includes δ 4.44: 0.5H, d, J 8.1; and at δ 4.43: 0.5H, d, J 8.1), 3.87 (1H, d, J 12.3, 2-HA), 3.65-3.52 (1H, m, 4-Hₐ, includes at δ 3.58: 0.5H, d, J 11.0; and at δ 3.57: 0.5H, d, J 11.0), 3.44-3.26 (1H, m, 4-Hₐ), 3.24-3.07 (1H, m, 2-Hₐ), 2.92-2.69 (4H, m, 8-Hₐ, 10-Hₐ and NCH₂CH₂Ph), 2.69-2.47 (4H, m, 8-Hₐ, 10-Hₐ and NCH₂CH₂Ph), 2.22-2.10 (1H, m, 6-Hₐ), 1.97-1.66 (4H, m, 11-H, 5-H and 6-Hₐ). IR ν max(film)/cm⁻¹ 2926, 1703 (CO), 1420, 1350, 1218, 1146, 1112, 1086. HRMS (ESI): C₂₅H₃₅ClN₂O₃ [M+H]+; calculated 441.1945, found 441.1936.

Benzyl (1R*,5R*,7S*)-9-(4-phenoxyphenyl)-12-oxa-3,9-diazatricyclo[5.4.1.01,5]dodecane-3-
carboxylate 3d

General procedure G was followed using the crude dialdehyde 19 (0.27 mmol) and 4-phenoxyaniline. Flash chromatography eluting with 7:3 hexane–EtOAc gave the title compound 3d (71 mg, 0.15 mmol, 56% over 4 steps) as a colourless oil. ¹H NMR (400 MHz, CDCl₃, 50:50 mixture of rotamers): δ 7.39-7.23 (7H, m), 7.02 (1H, t, J 7.3, Ar-H), 6.93 (4H, dd, J 8.4, 4.1, Ar-H), 6.85-6.68 (2H, m, Ar-H), 5.19-5.04 (2H, m, OCH₂Ph), 4.56 (1H, d, J 7.7, 7-H), 3.97 (1H, d, J 12.7, 2-Hₐ), 3.75-3.59 (2H, m, includes 8-Hₐ and 10-Hₐ), 3.54-3.31 (3H, m, 4-H and 10-Hₐ), 3.19 (2H, app. d, J 12.7, 2-Hₐ and 8-Hₐ), 2.61-2.45 (1H, m, 5-H), 2.33-1.94 (3H, m, includes 6-Hₐ and 11-H), 1.91-1.72 (1H, m, 6-Hₐ). ¹³C NMR (100 MHz, CDCl₃, 2 × Ar-Cₐ not observed): δ 158.9 (Ar-Cₐ), 155.1 (N(CO)O), 137.0 (Ar-Cₐ), 129.7 (Ar-C), 128.6 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 122.4 (Ar-C), 121.3 (Ar-C), 117.5 (Ar-C), 113.4 (Ar-C), 92.6 (1-C), 81.2 (7-C), 67.0 (OCH₂Ph), 57.8 (2-C), 57.6 (2-C), 56.2 (8-C), 53.6 (4-C), 49.3 (5-C or 10-C), 48.9 (5-C or 10-C), 36.7 (6-C and 11-C) [21 of 46 expected peaks observed]. IR ν max(film)/cm⁻¹ 2924, 1701 (CO), 1510, 1488, 1420, 1231, 1091. HRMS (ESI): C₂₉H₃₁N₂O₄ [M+H]+; calculated 471.2284, found 471.2278.
Benzyl (1R*,5R*,7S*)-9-[4-chloro-3-(trifluoromethyl)phenyl]-12-oxa-3,9-diazatricyclo[5.4.1.01,5]dodecane-3-carboxylate 3e

General procedure G was followed using the crude dialdehyde 19 (0.27 mmol) and 4-chloro-3-(trifluoromethyl)aniline. Flash chromatography eluting with 7:3 hexane–EtOAc gave the title compound 3e (16 mg, 33.3 µmol, 12% over 4 steps) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$, 50:50 mixture of rotamers): $\delta$ 7.40-7.29 (5H, m, Cbz Ar-H), 7.29-7.21 (1H, m, Ar 5-H), 6.96 (1H, d, $J$ 2.9, Ar 2-H), 6.76 (1H, dd, $J$ 8.9, 2.9, Ar 6-H), 5.18-5.05 (2H, m, OCH$_2$Ph), 4.56 (1H, app. d, $J$ 7.8, 7-H), 3.97 (1H, d, $J$ 12.3, 2-H), 3.78 (1H, d, $J$ 14.5, 8-H$\alpha$), 3.67 (1H, dd, $J$ 15.4, 5.4, 10-H$\alpha$), 3.56-3.45 (1H, m, 10-H$_B$), 3.45-3.34 (2H, m, 4-H), 3.23 (1H, dd, $J$ 14.5, 2.3, 8-H$\beta$), 3.15 (1H, d, $J$ 12.3, 2-H$_B$), 2.39-2.29 (1H, m, 5-H), 2.26-2.10 (1H, m, 11-H$\alpha$), 2.10-1.87 (2H, m, 6-H$_A$ and 11-H$_B$), 1.87-1.72 (1H, m, 6-H$_B$).

$^{13}$C NMR (100 MHz, CDCl$_3$, mixture of two rotamers): $\delta$ 155.1 (N(CO)O), 147.4 (Ar 1-C), 136.9 (Cbz Ar 1-C), 132.5 (Ar 5-C), 129.1 (q, $^2J$ 31.0, Ar 3-C), 128.6 (Cbz Ar-C), 128.1 (Cbz Ar-C), 128.0 (Cbz Ar-C), 123.2 (q, $^1J$ 273, CF$_3$), 118.0 (Ar 4-C), 115.0 (Ar 6-C), 109.8 (q, $^3J$ 5.4, Ar 2-C), 81.2 (7-C), 67.1 (OCH$_2$Ph), 57.6 (2-C), 57.5 (2-C), 55.1 (8-C), 53.6 (4-C), 48.0 (5-C and 10-C)**, 36.8 (6-C), 35.9 (11-C) [22 of 44 expected peaks observed]. IR $\nu_{\text{max}}$(film)/cm$^{-1}$ 2934, 1703 (CO), 1606, 1500, 1432, 1315, 1236, 1218, 1126 HRMS (ESI): C$_{24}$H$_{25}$ClF$_3$N$_2$O$_3$ [M+H]$^+$; calculated 481.1506, found 481.1502.

** Inferred by HMQC analysis.
1.3.2.5 Exemplar decorations of scaffold 3b

(1R*,5R*,7S*)-9-Cyclopropyl-12-oxa-3,9-diazatricyclo[5.4.1.01,5]dodecane 21

Hydrogenation was carried out following general procedure B, using compound 3b (1.75 g, 5.10 mmol, 1.00 eq.) to give the title compound 21 (1.05 g, 5.04 mmol, 99%) as a colourless oil. ^1H NMR (500 MHz, CDCl₃): δ 4.31 (1H, d, J 8.1, 7-H), 3.08-3.02 (2H, m, includes 10-H_A and at δ 3.06: 1H, d, J 12.3, 2-H_A), 2.83 (1H, dd, J 11.9, 6.9, 4-H_A), 2.77 (1H, d, H 11.9, 4-H_B), 2.72 (1H, app. dt, J 12.3 and 1.5, 8-H_A), 2.66-2.57 (2H, m, 5-H and 10-H_B), 2.55 (1H, dd, J 12.3, 2.8, 8-H_B), 2.41 (1H, d, J 12.3, 2-H_B), 2.02 (1H, dd, J 12.0, 9.8, 6-H_B), 1.90-1.86 (1H, m, cyclopropyl CH), 1.82 (1H, dd, J 13.4, 5.2, 11-H_A), 1.76-1.68 (2H, m, includes at δ 1.73: 1H, dd, J 13.4, 7.7, 11-H_B; and at δ 1.71: 1H, dd, J 13.5, 7.7, 6-H_A), 1.62 (1H, app. dt, J 12.2, 7.4, 6-H_B), 0.45-0.39 (3H, m, cyclopropyl (CH_AH_B) and cyclopropyl (CH_B)₈), 0.28-0.24 (1H, cyclopropyl (CH_AH_B)₈) ^13C NMR (125 MHz, CDCl₃): δ 94.3 (1-C), 80.2 (7-C), 64.9 (8-C), 59.6 (2-C), 55.8 (4-C), 54.5 (10-C), 51.9 (5-C), 40.4 (cyclopropyl CH), 39.2 (6-C), 37.8 (11-C), 8.1 (cyclopropyl CH₂), 7.5 (cyclopropyl CH₂). IR νmax(film)/cm⁻¹ 2912, 2818, 1460, 1451, 1366, 1186, 1043, 1014. HRMS (ESI): C₁₂H₂₁N₂O [M+H]⁺; calculated: 209.1654, found: 209.1643.
1-[(1R*,5R*,7S*)-9-Cyclopropyl-12-oxa-3,9-diazatricyclo[5.4.1.01,5]dodecan-3-yl]-3-(4-fluorophenoxy)propan-1-one 22

TBTU (63 mg, 0.20 mmol, 1.30 eq.) was added to a solution of 3-(4-fluorophenoxy)propanoic acid (36 mg, 0.20 mmol, 1.30 eq.) and DIPEA (34 µL, 0.20 mmol, 1.30 eq.) in DMF (0.5 mL). The reaction mixture was stirred for 10 min at rt then a solution of compound 21 (32 mg, 0.15 mmol, 1.00 eq.) in DMF (0.5 mL) was added. The reaction mixture was stirred overnight at rt. The insolubles were removed by filtration, and the filtrate was purified by mass-directed preparative HPLC to give the title compound 22 (26 mg, 69 µmol, 46%).

**1H NMR** (500 MHz, CDCl₃, two stable conformations observed at the pyrrolidine ring): δ 6.99-6.91 (2H, m, Ar-H), 6.87-6.81 (2H, m, Ar-H), 4.46-4.36 (1H, m, includes at δ 4.43: 0.5H, dd, J 8.2, 2.4, 7-H; and at δ 4.40: 0.5H, J 8.2, 2.4, 7-H), 4.32-4.18 (2H, m, OCH₃HₘCH₂(CO) and OCH₂CHₙHₙ(CO)), 4.03 (0.5H, d, J 13.4, 2-Hₐ-cont1), 3.83 (0.5H, d, J 11.8, 2-Hₐ-cont2), 3.71 (0.5H, dd, J 10.7, 8.5, 4-Hₐ-cont1), 3.62-3.51 (1H, m, 4-Hₐ-cont2 and 4-Hₜ-cont2), 3.33 (0.5H, dd, J 10.7, 5.9, 4-Hₜ-cont1), 3.26 (0.5H, d, J 11.8, 2-Hₜ-cont2), 3.19 (0.5H, d, J 13.4, 2-Hₜ-cont1), 3.01-2.89 (1H, m, 10-Hₐ), 2.79-2.56 (6H, m, OCH₂CH₂(CO), 5-H, 8-H, 10-Hₐ), 2.18-2.08 (1H, m, 11-Hₐ), 1.96-1.71 (4H, m, cyclopropyl CH, 6-H, 11-Hₐ), 0.52-0.37 (3H, m, cyclopropyl (CHₙHₘ)ₐ and cyclopropyl (CH₂)ₐ), 0.32-0.21 (1H, m, cyclopropyl (CHₙHₘ)ₐ).

**13C NMR** (125 MHz, CDCl₃, mixture of two rotamers, unable to discern the ¹³C – ¹⁹F coupling constants): δ 168.9 (major, N(CO)), 168.7 (minor, N(CO)), 158.4 (Ar-C), 156.6 (Ar-C), 155.0 (Ar-C), 116.0 (Ar 2-C), 116.0 (Ar 2-C), 115.8 (4 peaks, Ar 3-C), 115.7 (Ar 3-C), 92.0 (major, 1-C), 90.4 (minor, 1-C), 80.1 (major, 7-C), 79.7 (minor, 7-C), 65.0 (minor, OCH₂CH₂(CO)), 64.9 (major, OCH₂CH₂(CO)), 63.8 (major, 8-C), 63.5 (minor, 8-C), 58.4 (major, 2-C), 57.1 (minor, 2-C), 54.5 (minor, 4-C), 53.9 (major, 4-C), 53.8 (minor, 10-C), 53.0 (major, 10-C), 50.9 (minor, 5-C), 49.5 (major, 5-C), 40.3 (major, cyclopropyl CH), 40.2 (minor, cyclopropyl CH), 38.8 (minor, 11-C), 38.5 (major, 11-C), 36.4 (major, 6-C), 35.3 (minor, 6-C), 34.5 (major, OCH₂CH₂(CO)), 34.3 (minor, OCH₂CH₂(CO)), 8.2 (major, cyclopropyl (CHₙHₘ)ₐ), 8.1 (minor, cyclopropyl (CHₙHₘ)ₐ), 7.5 (2 peaks, major and minor, cyclopropyl (CH₂)ₐ).
(1R*,5R*,7S*)-9-Cyclopropyl-3-(pyridin-4-ylmethyl)-12-oxa-3,9-diazatricyclo[5.4.1.01,5]dodecane 23

Isonicotinaldehyde (40 mg, 0.38 mmol, 2.50 eq.) was added to a solution of compound 21 (32 mg, 0.15 mmol, 1.00 eq.) and AcOH (1.8 µL, 31.5 µmol, 0.2 eq.) in CH₂Cl₂ (1.0 mL). The reaction mixture was stirred for 10 min then NaBH(OAc)₃ (64 mg, 0.30 mmol, 2.0 eq.) was added. The reaction mixture was stirred overnight at rt. DMF (1.0 mL) was added, followed by 1.0 M NaOH (0.2 mL, 0.2 mmol, 1.3 eq.). The reaction mixture was partially concentrated in vacuo, the insolubles were removed by filtration, and the filtrate was purified by mass-directed preparative HPLC to give the title compound 23 (23 mg, 77 µmol, 51%).

¹H NMR (500 MHz, CDCl₃): δ 8.51 (2H, dd, J 4.1 and 1.3, Py 3-H), 7.27 (2H, dd, J 4.1 and 1.3, Py 2-H), 4.37 (1H, d, J 7.3, 7-H), 3.67 (1H, d, J 14.2, 8-H), 3.40 (1H, d, J 14.2, 2-H), 3.04 (1H, d, J 9.7, NCH₃H₃Py), 3.03-2.97 (1H, m, 10-H), 2.72 (1H, d, J 12.2, 8-H), 2.68-2.58 (3H, m, 4-H, 5-H and 10-H), 2.55 (1H, d, J 12.2, 8-H), 2.12 (1H, dd, J 9.2 and 6.9, 4-H), 1.94 (1H, d, J 9.7, NCH₃H₃Py), 1.91-1.75 (4H, m, cyclopropyl CH, 6-H and 11-H), 1.70 (1H, m, 6-H), 0.46-0.37 (3H, m, cyclopropyl (CH₃H₃) and cyclopropyl (CH₂)₃), 0.28-0.22 (1H, m, cyclopropyl (CH₃H₃)₃).

¹³C NMR (125 MHz, CDCl₃): δ 149.8 (Py 3-C), 148.2 (Py 1-C), 123.8 (Py 2-C), 92.1 (1-C), 80.2 (7-C), 66.3 (NCH₂Py), 65.1 (8-C), 60.9 (4-C), 58.6 (2-C), 54.6 (10-C), 50.7 (5-C), 40.6 (cyclopropyl CH), 39.1 (6-C or 11-C), 38.7 (6-C or 11-C), 8.3 (cyclopropyl CH₂), 7.6 (cyclopropyl CH₂).
(1R*,5R*,7S*)-3-(Benzenesulfonyl)-9-cyclopropyl-12-oxa-3,9-diazatricyclo[5.4.1.0^1,5]dodecane 24

Benzenesulfonyl chloride (21 µL, 0.16 mmol, 1.10 eq.) was added to a solution of compound 21 (32 mg, 0.15 mmol, 1.00 eq.) and DIPEA (31 µL, 0.18 mmol, 1.20 eq.) in DMF (1.0 mL). The reaction mixture was stirred overnight at rt. The insolubles were removed by filtration and the filtrate was purified by mass-directed preparative HPLC to give the title compound 24 (21 mg, 60 µmol, 40%). \(^{1}H\) NMR (500 MHz, CDCl\(_3\)): δ 7.82-7.77 (2H, m, Ar-2,7-H), 7.63-7.56 (1H, m, Ar-3-H), 7.55-7.51 (2H, Ar-H), 4.29 (1H, d, J 7.5, 7-H), 3.58 (1H, d, J 10.7, 2-H\(_A\)), 3.19 (1H, dd J 9.8 and 2.2, 4-H\(_A\)), 2.95 (1H, ddt, J 13.3, 7.5, 1.5, 10-H\(_A\)), 2.87 (1H, dd, J 9.8 and 7.4, 4-H\(_B\)), 2.67 (1H, d, J 12.6, 8-H\(_A\)), 2.66-2.56 (2H, m, 5-H and 10-H\(_B\)), 2.55-2.50 (2H, m, includes 8-H\(_B\), and at δ 2.52: 1H, d, J 10.7, 2-H\(_B\)), 1.94 (1H, dd, J 11.7 and 9.4, 6-H\(_A\)), 1.87-1.82 (1H, m, cyclopropyl CH\(_A\)), 1.80-1.70 (2H, m, 6-H\(_B\) and 11-H\(_A\)), 1.66-1.58 (1H, m, 11-H\(_B\)), 0.44-0.37 (2H, m, cyclopropyl (CH\(_2\))\(_A\)), 0.34-0.30 (1H, cyclopropyl (CH\(_A\))\(_B\)), 0.23-0.18 (1H, cyclopropyl (CH\(_A\))\(_B\)). \(^{13}C\) NMR (125 MHz, CDCl\(_3\)): δ 135.7 (Ar 1-C), 132.9 (Ar 3-C), 129.0 (Ar-C), 128.2 (Ar-C), 91.8 (1-C), 80.3 (7-C), 64.6 (8-C), 59.4 (2-C), 55.2 (4-C or 10-C), 54.2 (4-C or 10-C), 50.5 (5-C), 40.5 (cyclopropyl 1-C), 38.4 (6-C or 11-C), 38.1 (6-C or 11-C), 8.2 (cyclopropyl CH\(_2\)), 7.6 (cyclopropyl CH\(_2\)).

1.3.3 Preparation of scaffolds 4

1.3.3.1 Initial procedure to prepare scaffolds 4a-b
Benzyl (1R*,8R*,10R*)-14-oxa-4,6,12-triazatetracyclo[6.5.1.01,10.03,7]tetradeca-3(7),4-diene-12-carboxylate 4a

In two equally sized batches, p-formaldehyde (245 mg, 8.20 mmol, 2.00 eq.) and NH₄OAc (3.10 g, 41.0 mmol, 10.0 eq.) were added to a suspension of compound 1 (1.75 g, 4.10 mmol, 1.00 eq. [8.20 mmol over two batches]) in AcOH (5 mL). The reaction mixture was stirred at rt for 10 mins, then heated at 180 °C under microwave irradiation for 5 min. The batches were combined and concentrated in vacuo. The residue was diluted in EtOAc (50 mL) and washed with sat. aq. NaHCO₃ (50 mL). The aqueous layer was extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with H₂O (2 x 25 mL) and brine (25 mL), then dried over MgSO₄, filtered and concentrated in vacuo. Purification by SCX SPE following general procedure A, eluting with MeOH, then sat. NH₃/MeOH, followed by flash chromatography eluting with 90:9:1 CH₂Cl₂–EtOH–NH₃/MeOH gave the title compound 4a (2.24 g, 6.9 mmol, 84%) as a pale brown foam. Rₜ 0.64 (50:8:1 CH₂Cl₂–EtOH–NH₃/MeOH).

¹H NMR (400 MHz, CDCl₃, imidazole NH not observed): δ 7.43 (1H, s, 5-H), 7.40-7.28 (5H, m, Cbz Ar-H), 5.25 (1H, d, J 5.9, 8-H), 5.16 (1H, app. d, J 13.0, OCH₃H₉Ph), 5.11 (1H, app. d, J 13.0, OCH₃H₂Ph), 4.06 (1H, d, J 12.7, 13-Hₐ), 3.82-3.71 (1H, m, 11-Hₐ), 3.54-3.34 (2H, m, 11-Hₐ and 13-Hₐ), 3.26-3.10 (1H, m, 2-Hₐ), 2.70-2.61 (1H, m, 10-H), 2.58 (1H, d, J 15.4, 2-Hₐ), 2.53-2.42 (1H, m, 9-Hₐ), 2.15-2.03 (1H, m, 9-Hₐ). ¹³C NMR (100 MHz, CDCl₃, mixture of two rotamers, 2 x imidazole C₉ not observed): δ 154.9 (N(CO)O), 136.8 (Cbz Ar-C₉), 136.7 (Cbz Ar-C₉), 133.6 (2 peaks, Ar-C), 128.6 (Ar-C), 128.2 (Ar-C), 128.0 (Ar-C), 91.1 (1-C), 90.2 (1-C), 76.4 (8-C), 67.2 (OCH₃Ph), 55.4 (13-C), 55.0 (13-C), 53.6 (11-C), 47.1 (10-C), 46.1 (10-C), 45.8 (9-C), 45.7 (9-C), 32.7 (2-C) [20 of 32 expected peaks observed]. IR νmax(film)/cm⁻¹ 2958, 1694 (CO), 1423, 1352, 1239, 1218, 1115, 732. HRMS (ESI): C₁₈H₂₀N₃O₃ [M+H]+; calculated 326.1499, found 326.1500.
Benzyl (1R*,8R*)-5-phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.0^1,10.0^3,7]tetradeca-3(7),4-diene-12-carboxylate 4b

PhCHO (18 µL, 0.17 mmol, 1.0 eq.) and NH$_4$OAc (135 mg, 1.70 mmol, 10.0 eq.) were added to a suspension of compound 1 (75 mg, 0.17 mmol, 1.0 eq.) in AcOH (1.0 mL). The resulting mixture was heated under microwave irradiation at 180 °C for 5 min. The reaction mixture was concentrated in vacuo, then partitioned between CH$_2$Cl$_2$ (25 mL) and NaHCO$_3$ (25 mL). The phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. Flash chromatography eluting with 0-100% EtOAc in pentane gave the title compound 4b (64 mg, 0.16 mmol, 91%) as a pale brown oil. R$_f$ 0.12 (1:1 petrol–EtOAc). $^1$H NMR (500 MHz, CDCl$_3$, imidazole NH not observed): δ 7.76 (2H, d, J 7.3, Ar-H), 7.43-7.28 (8H, m, Ar-H), 5.28 (1H, d, J 5.7, 8-H), 5.25-5.17 (2H, m, OCH$_2$Ph), 4.07 (1H, d, J 12.6, 13-H$_A$), 3.85-3.73 (1H, m, 11-H$_A$), 3.55-3.36 (2H, m, 11-H$_B$ and 13-H$_B$), 3.28-3.16 (1H, m, 2-H$_A$), 2.73-2.64 (1H, m, 10-H), 2.61 (1H, d, J 15.4, 2-H$_B$), 2.58-2.47 (1H, m, 9-H$_A$), 2.16-2.05 (1H, m, 9-H$_B$). $^{13}$C NMR (125 MHz, CDCl$_3$, mixture of two rotamers, 2 × imidazole C$_q$ not observed): δ 154.9 (N(CO)O), 145.6 (7-C), 136.7 (Ar-C$_q$), 130.4 (Ar-C$_q$), 129.1 (Ar-C), 128.6 (Ar-C), 128.2 (Ar-C), 128.0 (2 peaks, Ar-C), 125.1 (Ar-C), 91.1 (1-C), 90.1 (1-C), 77.4 (8-C), 67.2 (OCH$_2$Ph), 55.4 (13-C), 55.0 (13-C), 53.6 (11-C), 53.5 (11-C), 47.1 (10-C), 46.1 (10-C), 45.8 (9-C), 45.6 (9-C), 32.8 (2-C) [23 of 40 expected peaks observed]. IR $v_{max}$(film)/cm$^{-1}$ 3274, 2241, 1682 (CO), 1448, 1418, 1348, 1116, 909. HRMS (ESI): C$_{24}$H$_{24}$N$_3$O$_3$ [M+H]$^+$; calculated 402.1812, found 402.1825.
1.3.3.2 Optimised synthetic route to scaffolds 4

The initial route (above) was adapted to enable preparation of imidazoles 4 using conventional thermal heating.

![Chemical structure](image)

**General procedure H: formation of imidazoles**

NH$_4$OAc (10.0 eq.) was added to a stirred suspension of compound 1 (1.0 eq.) and aldehyde (1.0 eq.) in AcOH (0.5 M). The resulting mixture was heated at 60 °C for 17 h. The reaction was cooled to rt then slowly added to sat. aq. NaHCO$_3$ (until no further evolution of gas was observed). The mixture was extracted with EtOAc (4 × 1 volume) and the combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo. The crude reaction products were purified by flash column chromatography.

**Benzyl (1R*,8R*)-5-phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.0$^{1,10}$.0$^{3,7}$]tetradeca-3(7),4-diene-12-carboxylate 4b**

General procedure H was followed using compound 1 (1.00 mmol) and PhCHO. Flash chromatography eluting with 50-100% EtOAc in pentane gave the title compound 4b (225 mg, 0.56 mmol, 56%) as a brown amorphous solid. See above for spectral data.
Benzyl (1R*,8R*,10R*)-5-(furan-2-yl)-14-oxa-4,6,12-triazatetracyclo[6.5.1.03.7]tetradeca-3(7),4-diene-12-carboxylate 4c

General procedure H was followed using compound 1 (1.00 mmol) and furfural. Flash chromatography eluting with 50-100% EtOAc in hexane gave the title compound 4c (254 mg, 0.65 mmol, 65%) as a brown amorphous solid. $^1$H NMR (500 MHz, CDCl$_3$, imidazole NH not observed): 7.40-7.28 (6H, m, Ar-H and furan 5-H), 6.82 (1H, d, J 3.4, furan 3-H), 6.48 (1H, dd, J 3.5, 1.8, furan 4-H), 5.26 (1H, d, J 5.9, 8-H), 5.21-5.07 (2H, m, OCH$_2$Ph), 4.07 (1H, d, J 12.6, 13-H$_A$), 3.83-3.72 (1H, m, 11-H$_A$), 3.55-3.36 (2H, m, 11-H$_B$ and 13-H$_B$), 3.27-3.14 (1H, m, 2-H$_A$), 2.71-2.64 (1H, m, 10-H), 2.61 (1H, d, J 15.5, 2-H$_B$), 2.56-2.45 (1H, m, 9-H$_A$), 2.16-2.05 (1H, m, 9-H$_B$). $^{13}$C NMR (100 MHz, CDCl$_3$, 2 × Ar-C$_q$ not observed, mixture of two rotamers): 154.9 (N(CO)O), 146.1 (Ar-C$_q$), 142.1 (furan 5-C), 138.2 (Ar-C$_q$), 136.7 (Ar-C$_q$), 128.6 (Ph-C), 128.1 (Ph-C), 128.0 (Ph-C), 112.0 (furan 4-C), 106.7 (furan 3-C), 91.1 (1-C), 90.2 (1-C), 67.1 (OCH$_2$Ph), 55.0 (13-C), 53.3 (11-C), 53.5 (11-C), 47.1 (10-C), 46.1 (10-C), 45.7 (9-C), 45.6 (9-C), 32.8 (2-C) [21 of 40 expected peaks observed]. IR $\nu_{max}$(neat)/cm$^{-1}$ 3118, 3031, 2953, 2874, 1694, 1590. HRMS (ESI): C$_{22}$H$_{22}$N$_5$O$_4$ [M+H]$^+$ 392.1605, found 392.1608.

Benzyl (1R*,8R*,10R*)-5-(thiophen-3-yl)-14-oxa-4,6,12-triazatetracyclo[6.5.1.03.7]tetradeca-3(7),4-diene-12-carboxylate 4d

General procedure H was followed using compound 1 (1.00 mmol) and 3-thiophenecarboxaldehyde. Flash chromatography eluting with 50-100% EtOAc in hexane gave the title compound 4d (244 mg, 0.60 mmol, 60%, imidazole NH not observed) as a brown amorphous solid. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.61 (1H, s), 7.48 (1H, d, J 4.9), 7.43-7.25 (5H, m), 5.24-5.07 (3H, m), 4.06-3.97 (1H, m), 3.81-3.68 (1H, m), 3.50-3.38 (1H, m), 3.33 (1H, d, J 12.5), 3.07 (1H, d, J 15.4), 2.68-2.57 (1H, m), 2.54-2.39 (2H, m), 2.32-2.31 (1H, m), 2.04-1.97 (1H, m).
Benzyl (1R*,8R*,10R*)-5-cyclohexyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.01,10.03,7]tetradeca-3(7),4-diene-12-carboxylate 4e

General procedure H was followed using compound 1 (1.00 mmol) and cyclohexane carboxaldehyde. Flash chromatography eluting with 50-100% EtOAc in hexane gave the title compound 4e (94 mg, 0.23 mmol, 23%) as a brown amorphous solid. 1H NMR (400 MHz, CDCl3, imidazole NH not observed): 7.36-7.28 (5H, m, Ar-H), 5.18-5.09 (3H, m, OCH2Ph and 8-H), 4.01 (1H, dd, J 12.6, 2.4, 13-HA), 3.80-3.70 (1H, m, 11-HA), 3.48-3.31 (2H, m, 11-Ha and 13-Ha), 3.14-3.03 (1H, m, 2-HA), 2.68-2.59 (2H, m, Cy 1-H and 10-H), 2.48-2.35 (2H, m, includes 9-Ha and at δ 2.44: 1H, d, J 15.3, 2-Ha), 2.04-1.88 (3H, m, 9-Hb, and Cy 2-Ha), 1.78-1.59 (3H, m, Cy-H), 1.47-1.08 (5H, m, Cy 2-Hb and Cy-H). 13C NMR (125 MHz, CDCl3, 2 × Ar-Cq not observed, mixture of two rotamers): 154.7 (N(CO)O), 151.6 (Ar-Cq), 136.7 (Ar-Cq), 128.5 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 91.1 (1-C), 90.0 (1-C), 67.0 (OCH2Ph), 55.0 (13-C), 53.5 (11-C), 47.0 (10-C), 46.0 (10-C), 45.7 (9-C), 45.5 (9-C), 37.9 (Cy 1-C), 32.7 (2-C), 32.2 (Cy 2-C), 32.1 (Cy 2-C), 26.0 (Cy 3-C or Cy 4-C), 25.8 (Cy 3-C or Cy 4-C) [21 of 40 expected peaks observed]. IR νmax(neat)/cm⁻¹ 3065, 2925, 2851, 1684, 1612, 1522. HRMS (ESI): C24H30N3O3 [M+H]+ 408.2282, found 408.2283.

1.3.3.3 Preparation of disubstituted imidazoles 25

General procedure I: formation of disubstituted imidazoles

NH4OAc (5.0 eq.) was added to a stirred suspension of the compound 1 (1.0 eq.), aldehyde (1.0 eq.), and aniline (5.0 eq.) in AcOH (0.5 M). The resulting mixture was heated at 60 °C for 17 h. The reaction was cooled to rt then slowly added to sat. aq. NaHCO3 (until no further evolution of gas was observed). The mixture was extracted with EtOAc (4 × 1 volume) and the combined organic layers were dried over MgSO4, filtered and concentrated in vacuo. The crude reaction products were purified by flash column chromatography.
Benzyl (\(1R^*, 8R^*, 10R^*\))-5,6-diphenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.0^1,10.0^3,7]tetradeca-3(7),4-diene-12-carboxylate 25a

General procedure I was followed using compound 1 (1.00 mmol), benzaldehyde and 3,5-dimethyl aniline. Flash chromatography eluting with 50-100% EtOAc in hexane gave the title compound 25a (296 mg, 0.62 mmol, 62\%) as a pale yellow amorphous solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.46-7.40 (3H, m, Ar-H), 7.38-7.29 (7H, m, Ar-H), 7.24-7.19 (3H, m, Ar-H), 7.19-7.14 (2H, m, Ar-H), 5.36 (1H, d, J 5.9, 8-H), 5.19-5.07 (2H, m, OCH\(_2\)Ph), 4.06 (1H, d, J 12.0, 13-H\(A\)), 3.77 (1H, dd, J 11.5, 8.9, 11-H\(A\)), 3.56-3.43 (1H, m, 13-H\(B\)), 3.41-3.30 (1H, m, 11-H\(B\)), 3.16-2.99 (1H, m, 9-H\(A\)), 2.78-2.60 (2H, m, 2-H\(A\) and 10-H), 2.39 (1H, d, J 15.7, 2-H\(B\)), 2.20-2.10 (1H, m, 9-H\(B\)). \(^{13}\)C NMR (125 MHz, CDCl\(_3\), mixture of two rotamers): δ 154.8 (N(CO)O), 145.8 (Ar-C), 141.4 (Ar-C), 136.9 (Ar-C), 136.8 (Ar-C), 130.2 (Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 128.8 (Ar-C), 128.6 (Ar-C), 128.4 (2 peaks, Ar-C), 128.3 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 126.9 (Ar-C), 124.9 (Ar-C), 90.9 (1-C), 89.9 (1-C), 73.8 (8-C), 67.1 (OCH\(_2\)Ph), 55.3 (13-C), 55.0 (13-C), 53.5 (2 × peaks, 11-C), 47.3 (10-C), 46.4 (10-C), 45.4 (9-C), 32.5 (2-C) [29 of 48 expected peaks observed]. \(\text{IR } \nu_{\text{max}}(\text{neat})/\text{cm}^{-1}\) 3062, 2953, 2874, 1696, 1597. \(\text{HRMS (ESI): } \text{C}_{30}\text{H}_{28}\text{N}_{3}\text{O}_{3} [\text{M+H}]^+ 478.2125\), found 478.2123.
Benzyl (1R,8R,10R)-6-(4-methoxyphenyl)-5-phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.0^1,10^3,7^0]tetradeca-3(7),4-diene-12-carboxylate 25b

General procedure I was followed using compound 1 (1.00 mmol), benzaldehyde and p-anisidine. Flash chromatography eluting with 50-100% EtOAc in hexane gave the title compound 25b (294 mg, 0.58 mmol, 58%) as a dark brown amorphous solid. $^1$H NMR (500 MHz, CDCl$_3$): 7.39-7.28 (7H, m, Ar-H), 7.25-7.17 (3H, m, Ar-H), 7.08 (2H, d, $J$ 8.8, PMP 2-H), 6.92 (2H, d, $J$ 8.8, PMP 3-H), 5.35 (1H, d, $J$ 5.9, 8-H), 5.18-5.08 (2H, m, OCH$_2$Ph), 4.10-3.99 (1H, m, 13-H$_A$), 3.84 (3H, s, OCH$_3$), 3.77 (1H, dd, $J$ 11.6, 8.9, 11-H$_A$), 3.55-3.42 (1H, m, 13-H$_B$), 3.41-3.30 (1H, m, 11-H$_B$), 3.10-2.97 (1H, m, 2-H$_A$), 2.79-2.56 (2H, m, 9-H$_A$ and 10-H), 2.38 (1H, d, $J$ 15.6, 2-H$_B$), 2.21-2.09 (1H, m, 9-H$_B$). $^{13}$C NMR (125 MHz, CDCl$_3$, mixture of two rotamers): 159.7 (PMP 4-C), 154.8 (N(CO)O), 145.9 (Ar-C$_q$), 141.4 (Ar-C$_q$), 136.9 (Ar-C$_q$), 130.6 (Ar-C$_q$), 129.8 (Ar-C$_q$), 128.6 (Ar-C), 128.3 (2 peaks, Ar-C), 128.2 (Ar-C), 128.1 (2 peaks, Ar-C), 128.0 (Ar-C), 125.1 (Ar-C), 115.0 (PMP 3-C), 90.9 (1-C), 90.0 (1-C), 77.5 (8-C), 67.1 (OCH$_2$Ph), 55.7 (OCH$_3$), 55.4 (13-C), 55.1 (11-C), 53.5 (11-C), 47.4 (10-C), 46.4 (10-C), 45.5 (9-C), 32.5 (2-C) [28 of 50 expected peaks observed]. IR $\nu_{\text{max}}$(neat)/cm$^{-1}$ 3060, 2953, 2837, 1698, 1608, 1584, 1511. HRMS (ESI): C$_{31}$H$_{36}$N$_2$O$_4$ [M+H]$^+$ 508.2231, found 508.2226.
Benzyl (1R*,8R*,10R*)-6-(3,5-dimethylphenyl)-5-phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.0\(^1\),10\(^6\)].0\(^3\),7\(^7\)]tetradeca-3(7),4-diene-12-carboxylate 25c

General procedure I was followed using compound 1 (1.00 mmol), benzaldehyde and 3,5-dimethylaniline. Flash chromatography eluting with 50-100% EtOAc in hexane gave the title compound 25c (278 mg, 0.55 mmol, 55%) as a pale yellow amorphous solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.45-7.27 (7H, m, Ar-H), 7.10-7.00 (1H, m, Ar-H), 6.77 (2H, s, Ar-H), 5.34 (1H, d, \(J 5.9, 8\)-H), 5.20-5.05 (2H, m, OCH\(_2\)Ph), 4.15-3.99 (1H, m, 13-H\(_A\)), 3.77 (1H, dd, \(J 11.5, 8.8, 11\)-H\(_A\)), 3.55-3.31 (2H, m, 11-H\(_B\) and 13-H\(_B\)), 3.13-2.95 (1H, m, 2-H\(_A\)), 2.76-2.60 (2H, m, 10-H and 9-H\(_A\)), 2.38 (1H, d, \(J 15.8, 2\)-H\(_B\)), 2.30 (6H, s, CH\(_3\)), 2.20-2.09 (9-H\(_B\)). \(^13\)C NMR (125 MHz, CDCl\(_3\), mixture of two rotamers): \(\delta\) 154.7 (N(CO)O), 145.6 (Ar-C), 141.3 (Ar-C), 139.7 (Ar-C), 139.6 (Ar-C), 136.9 (Ar-C), 136.8 (Ar-C), 130.2 (Ar-C), 130.3 (Ar-C), 128.5 (Ar-C), 128.2 (Ar-C), 128.1 (2 peaks, Ar-C), 128.0 (2 peaks, Ar-C), 124.8 (Ar-C), 124.4 (Ar-C), 90.8 (1-C), 89.9 (1-C), 73.8 (8-C), 67.0 (OCH\(_2\)Ph), 55.3 (13-C), 55.0 (13-C), 53.5 (11-C), 47.3 (10-C), 46.3 (10-C), 45.4 (9-C), 32.4 (2-C), 21.2 (CH\(_3\)) [29 of 50 expected peaks observed]. IR \(\nu_{\text{max}}\) (heat) cm\(^{-1}\): 3058, 3018, 2973, 2944, 2877, 1701, 1612, 1597, 1510. HRMS (ESI): C\(_{32}\)H\(_{32}\)N\(_3\)O\(_3\) [M+H]\(^+\) 506.2438, found 506.2432.
1.3.3.4 Exemplar decorations of scaffold 4b

\[
\text{(1}^{R*},8^{R*},10^{R*})-5\text{-Phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.0^{1,10}.0^{3,7}]tetradeca-3(7),4-diene 26}
\]

Pd/C (0.46 g, 10 wt%, 10% w/w) was added to a stirred solution of compound 4b (4.63 g, 11.5 mmol, 1.00 eq.) and NH\textsubscript{4}CO\textsubscript{2}H (3.64 g, 57.7 mmol, 5.00 eq.) in EtOH (115 mL, 0.10 M). The mixture was stirred at reflux for 2 h. The reaction mixture was allowed to cool to rt, filtered through a pad of Celite\textsuperscript{®}, flushed through with EtOH, and concentrated. The crude product was filtered through a pad of silica, eluting with a 1:9 NH\textsubscript{3}(sat)/MeOH:CH\textsubscript{2}Cl\textsubscript{2} to afford the title compound 26 (3.05 g, 11.2 mmol, 98%) as a yellow solid. \textsuperscript{1}H NMR (500 MHz; MeOD, 2 × NH not observed): \(\delta\) 7.73 (2H, dd, \(J\) 8.4, 1.2, Ar-H), 7.34 (2H, t, \(J\) 7.5, Ar-H), 7.26 (1H, app. tt, \(J\) 7.5, 1.2, Ar-H), 5.08 (1H, d, \(J\) 5.7, 8-H), 3.27 (1H, d, \(J\) 12.6, 13-H\textsubscript{A}), 3.12-3.03 (2H, m, includes 11-H\textsubscript{s}; and at \(\delta\) 3.08: 1H, d, \(J\) 15.5, 2-H\textsubscript{A}), 2.87 (1H, d, \(J\) 12.0, 11-H\textsubscript{A}), 2.77 (1H, d, \(J\) 12.6, 13-H\textsubscript{A}), 2.63-2.53 (2H, m, includes 10-H; and at \(\delta\) 2.60: 1H, d, \(J\) 15.5, 2-H\textsubscript{B}), 2.45 (1H, dd, \(J\) 11.9, 8.8, 9-H\textsubscript{A}), 1.95 (1H, dt, \(J\) 11.9, 6.2, 9-H\textsubscript{B}).
1-[(1R*,8R*,10R*)-5-Phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.0^1,10.0^3,7]tetradeca-3(7),4-dien-12-yl]-3-(pyridin-3-yl)propan-1-one 27

TBTU (59 mg, 0.19 mmol, 1.5 eq.) was added to a solution of 3-(pyridin-3-yl)propanoic acid (28 mg, 0.19 mmol, 1.5 eq.) and DIPEA (32 µL, 0.19 mmol, 1.5 eq.) in DMF (0.5 mL). The reaction mixture was stirred for 10 min at rt, then a solution of amine 26 (33 mg, 0.12 mmol, 1.0 eq.) in DMF (0.5 mL) was added. The reaction mixture was stirred overnight at rt. The insolubles were removed by filtration, and the filtrate was purified by mass-directed preparative HPLC to give the title compound 27 (25 mg, 62 µmol, 52%).

$^1$H NMR (500 MHz, CDCl$_3$, 1:1 mixture of rotamers, two stable conformations observed at the pyrrolidine ring): δ 8.49 (1H, s, Py 2-H), 8.46 (1H, dd, J 4.8, 1.5, Py 4-H), 7.79 (2H, d, J 7.5, Ar-H), 7.58 (1H, app. t, J 7.5, Py 5-H), 7.40 (2H, t, J 7.5, Ar-H), 7.33 (1H, app. td, J 7.5, 1.5, Ar-H), 7.26-7.19 (1H, m, Py 6-H), 5.26-5.24 (1H, m, 8-H), 4.17 (0.5H, d, J 13.6, 13-HA-conf1), 3.94 (0.5H, d, J 12.0, 13-HA-conf2), 3.82-3.63 (1.5H, m, 11-HA-conf1+2 and 11-HB-conf1), 3.45 (0.5H, d, J 13.6, 13-HB-conf1), 3.37 (0.5H, d, J 12.0, 13-HB-conf2), 3.31 (0.5H, dd, J 11.0, 5.4, 11-HB-conf2), 3.23 (0.5H, dd, J 15.5, 2-HA), 3.18 (0.5H, dd, J 15.5, 2-HA), 3.11-2.92 (2H, m, CH$_2$CH$_2$Py), 2.79-2.46 (5H, m, CH$_2$CH$_2$Py, 2-HB, 9-HA, 10-H), 2.10-1.97 (1H, m, 9-HB).

$^{13}$C NMR (100 MHz, CDCl$_3$, 2 x Ar-C$_q$ not observed, mixture of rotamers): δ 170.3 (N(CO)), 170.2 (N(CO)), 149.9 (Py 2-C), 149.8 (Py 2-C), 147.6 (2 peaks, Py 4-C), 145.6 (Ar-C$_q$), 139.7 (Ar-C$_q$), 136.9 (Ar-C$_q$), 136.6 (Py 5-C), 130.3 (2 peaks, Ar-C), 129.1 (Ar-C), 128.7 (2 peaks, Ar-C), 125.1 (Ar-C), 123.7 (Py 6-C), 91.1 (1-C), 89.5 (1-C), 77.4 (8-C), 55.7 (13-C), 54.7 (13-C), 54.5 (11-C), 52.8 (11-C), 47.3 (10-C), 46.0 (10-C), 45.6 (9-C), 45.5 (9-C), 35.9 (CH$_2$CH$_2$Py), 35.7 (CH$_2$CH$_2$Py), 32.9 (2-C), 28.2 (CH$_2$CH$_2$Py).
(1R*, 8R*, 10R*)-12-[(5-Methoxypyridin-3-yl)methyl]-5-phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.01,10.03,7]tetradeca-3(7),4-diene 28

5-Methoxynicotinaldehyde (25 mg, 0.19 mmol, 1.50 eq.) was added to a stirred solution of compound 26 (33 mg, 0.12 mmol, 1.00 eq.) and AcOH (1.4 µL, 0.025 mmol, 0.20 eq.) in DMF (0.5 mL). The reaction mixture was stirred for 0.5 h then a solution of tetramethylammonium triacetoxyborohydride (49 mg, 0.19 mmol, 1.5 eq.) in DMF (0.5 mL) was added. The reaction mixture was stirred overnight at rt, then 30% NH₃OH solution (0.2 mL) was added. The insolubles were removed by filtration. The filtrate was purified by mass-directed preparative HPLC gave the title compound 28 (23 mg, 59 µmol, 49%).

**1H NMR** (400 MHz, CDCl₃): δ 8.20 (1H, d, J 2.9, Py 4-H), 8.15 (1H, s, Py 2-H), 7.80 (2H, d, J 8.6, Ar-H), 7.37 (2H, td, J 7.7, 1.9, Ar-H), 7.32-7.24 (2H, m, Ar-H, including Py 6-H), 5.28-5.16 (1H, m, 8-H), 3.86 (3H, s, OCH₃), 3.75 (1H, d, J 13.6, 13-Hₐ), 3.55 (1H, d, J 13.6, 13-Hₐ), 3.24-3.08 (2H, m, NCHₐHₐPy and 2-Hₐ), 2.70-2.62 (1H, m, 11-Hₐ), 2.56-2.41 (3H, m, 2-Hₐ, 9-Hₐ, 10-H and 11-Hₐ), 2.37 (1H, app. dd, J 10.3, 3.3, NCHₐHₐPy), 2.12-1.93 (1H, m, 9-Hₐ).

**13C NMR** (100 MHz, CDCl₃, 2 × Ar-C₉ not observed): δ 156.0 (Py 5-C), 145.2 (Ar-C), 142.3 (Py 2-C), 136.5 (Py 4-C), 134.8 (Ar-C), 130.6 (Ar-C), 129.0 (Ar-C), 128.4 (Ar-C), 125.0 (Ar-C), 121.3 (Py 6-C), 90.5 (1-C), 77.4 (8-C), 63.0 (NCH₂Py), 59.5 (11-C), 57.0 (13-C), 55.8 (OCH₃), 46.8 (10-C), 44.2 (9-C), 32.9†† (2-C).

†† Inferred by HMOC analysis.
(1R*,8R*,10R*)-5-Phenyl-12-(thiophene-2-sulfonyl)-14-oxa-4,6,12-
triazatetracyclo[6.5.1.0 \textsuperscript{1,10}.0 \textsuperscript{3,7}]tetradeca-3(7),4-diene 29

Thiophene-2-sulfonyl chloride (24 mg, 0.14 mmol, 1.1 eq.) was
added to a solution of amine 26 (33 mg, 0.12 mmol, 1.0 eq.) and
DIPEA (26 µL, 0.15 mmol, 1.2 eq.) in DMF (1.0 mL). The
reaction mixture was stirred overnight at rt. The insolubles were
removed by filtration. The filtrate was purified by mass-directed
preparative HPLC to give the **title compound 29** (24 mg,
58 µmol, 48%). \textsuperscript{1}H NMR (500 MHz, DMSO-d\textsubscript{6}): \textdelta 8.08 (1H, dd, J 5.0, 1.3, Ar-H), 7.82 (2H, d, J 7.0, Ar-H), 7.69 (1H, dd, J 3.7, 1.4, Ar-H), 7.38 (2H, t, J 7.7, Ar-H), 7.32 (1H, dd, J 5.0, 3.7, Ar-H), 7.37 (1H, t, J 7.4, Ar-H), 5.07 (1H, app. s, 8-H), 3.60 (1H, d, J 10.9, 13-H\textsubscript{A}), 3.22-3.11 (1H, m, 13-H\textsubscript{B}), 3.08-2.99 (1H, m, 2-H\textsubscript{A}), 2.96 (1H, d, J 10.9, 13-H\textsubscript{B}), 2.68-2.54 (2H, m, 2-H\textsubscript{B} and 10-H), 2.34 (1H, dd, J 11.9, 8.5, 9-H\textsubscript{A}), 1.93 (1H, dt, J 11.9, 6.2, 9-H\textsubscript{B}). \textsuperscript{13}C NMR (100 MHz, DMSO-d\textsubscript{6}): \textdelta 143.8 (Ar-C), 141.0 (Ar-C), 134.4 (Ar-C), 134.0 (Ar-C), 133.4 (Ar-C), 130.9 (Ar-C), 128.7 (Ar-C), 128.4 (Ar-C), 127.6 (Ar-C), 124.3 (Ar-C), 122.2 (Ar-C), 89.5 (1-C), 79.2 (8-C), 56.3 (13-C), 54.2 (11-C), 45.9 (10-C), 44.4 (9-C), 30.9 (2-C).
1.3.4 Preparation of scaffolds 5

1.3.4.1 Initial procedure to prepare compound 31
Benzyl (1R*,5R*,7R*,8S*)-8-[(tert-butyldimethylsilyl)oxy]-8-methyl-9-oxo-11-oxa-3-azatricyclo[5.3.1.0^1,5]undecane-3-carboxylate 30a

MeLi (1.6 M in Et₂O, 0.37 mL, 0.60 mmol, 1.30 eq.) was added to a stirred solution of compound 1 (200 mg, 0.46 mmol, 1.00 eq.) in THF (15 mL) at −78 °C. The reaction mixture was stirred at this temperature for 0.5 h, then sat. aq. brine (1.0 mL) was added. The reaction mixture was warmed to rt, then partitioned between EtOAc (25 mL) and brine (25 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. Flash chromatography eluting with 95:5 pentane–EtOAc gave the title compound 30a (187 mg, 0.42 mmol, 91%) as a yellow oil. R_f 0.30 (3:1 petrol–EtOAc).

^1H NMR (500 MHz, CDCl₃, 50:50 mixture of rotamers): δ 7.39-7.28 (5H, m, Cbz Ar-H), 5.12 (2H, s, OCH₂Ph), 4.21-4.15 (1H, m, 7-H), 3.95-3.83 (2H, m, 2-H_B and 4-H_A), 3.43 (0.5H, d, J 12.6, 2-H_A), 3.38 (0.5H, d, J 12.6, 2-H_A), 3.20-3.09 (1H, m, 5-H), 2.92 (0.5H, d, J 15.3, 10-H_B), 2.86 (0.5H, d, J 15.3, 10-H_B), 2.55-2.46 (1H, m, 5-H), 2.37 (0.5H, d, J 3.3, 10-H_A), 2.34 (0.5H, d, J 3.3, 10-H_A), 2.27-2.14 (1H, m, 6-H_A), 1.91-1.76 (1H, m, 6-H_B), 1.46 (1.5H, s, Cq(CH₃)), 1.45 (1.5H, s, Cq(CH₃)), 0.85 (9H, s, SiC(CH₃)₃), 0.17 (3H, s, SiCH₃), 0.13 (3H, s, SiCH₃).

^13C NMR (125 MHz, CDCl₃, mixture of two rotamers): δ 208.0 (9-C), 207.9 (9-C), 154.4 (N(CO)O), 136.8 (Ar-C), 128.6 (Ar-C), 128.2 (Ar-C), 128.12 (Ar-C), 91.5 (1-C), 90.7 (1-C), 85.4 (7-C), 81.4 (8-C), 67.1 (OCH₂Ph), 54.2 (2-C or 4-C), 53.8 (2-C or 4-C), 53.7 (2-C or 4-C), 47.3 (10-C), 45.7 (5-C), 44.8 (5-C), 31.7 (6-C), 31.4 (6-C), 26.0 (SiC(CH₃)₃), 24.4 (CqCH₃), 18.5 (SiC₃), −2.3 (SiCH₃), −2.6 (SiCH₃) [25 of 38 expected peaks observed]. IR ν_max(film)/cm⁻¹ 2954, 2953, 2930, 2887, 1702 (CO), 1629,1593, 1419 HRMS (ESI): C₂₄H₃₆NO₅Si [M+H]^+; calculated 446.2357, found 446.2360.
Benzyl \((1R^*, 5R^*, 7R^*, 8R^*, 9R^*)\)-9-amino-8-[(tert-butyldimethylsilyl)oxy]-8-methyl-11-oxa-3-azatricyclo[5.3.1.0\(^1,5\)]undecane-3-carboxylate 31

\[
\text{Ti(O/Pr)}_4 (4.30 \text{ mL}, 14.4 \text{ mmol}, 2.00 \text{ eq.}) \text{ was added to a stirred solution of compound } 30a (3.21 \text{ g}, 7.20 \text{ mmol}, 1.00 \text{ eq.) in sat. NH}_3/\text{MeOH (100 mL). The reaction mixture was stirred for 15 h then NaBH}_4 (409 mg, 10.8 \text{ mmol}, 1.5 \text{ eq.) was added at 0 °C. The reaction mixture was warmed to rt, stirred for 2 h then concentrated in vacuo. The residue was diluted in EtOAc (50 mL) and sat. aq. brine (50 mL) and stirred vigorously. The phases were separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phase was dried over MgSO}_4, filtered, and concentrated in vacuo. Flash chromatography eluting with EtOAc, then 9:1 EtOAc–MeOH, gave the title compound 31 (2.46 g, 5.51 mmol, 77%) as a colourless oil.}

\[\text{1H NMR} (500 MHz, CDCl}_3, 50:50 \text{ mixture of rotamers, NH}_2 \text{ not observed): } \delta 7.38-7.27 (5\text{H, m, Cbz Ar-H}), 5.10 (2\text{H, s, OCH}_2\text{Ph}), 4.00 (1\text{H, d, J 7.5, 7-H}), 3.92-3.82 (1\text{H, m, 4-H}_A), 3.75-3.68 (1\text{H, m, 2-H}_B, \text{ includes at } \delta 3.72: 0.5\text{H, d, J 12.5}; \text{ and at } \delta 3.71: 0.5\text{H, d, J 12.5}), 3.38 (0.5\text{H, d, J 12.5, 2-H}_A), 3.33 (0.5\text{H, d, J 12.5, 2-H}_A), 3.23-3.12 (2\text{H, m, 4-H}_B \text{ and 9-H}), 3.11-3.03 (1\text{H, m, 5-H}), 2.96-2.87 (1\text{H, m, 6-H}_A), 2.16 (0.5\text{H, dd, J 14.2, 5.4, 10-H}_B), 2.11 (0.5\text{H, dd, J 14.2, 5.4, 10-H}_B), 1.72-1.60 (1\text{H, m, 6-H}_B), 1.57-1.50 (1\text{H, m, 10-H}_A, \text{ includes at } \delta 1.54: 0.5\text{H, d, J 14.2}; \text{ and at } \delta 1.53: 0.5\text{H, d, J 14.2}), 1.37 (1.5\text{H, s, C}_q\text{C}_3\text{H}_3), 1.36 (1.5\text{H, s, C}_q\text{C}_3\text{H}_3), 0.91 (9\text{H, s, SiC(CH}_3)_3), 0.13 (3\text{H, s, SiCH}_3), 0.12-0.10 (3\text{H, m, SiCH}_3).
\]

\[\text{13C NMR} (125 MHz, DMSO-d}_6, \text{ mixture of two rotamers): } \delta 153.6 (\text{N(CO)O}), 153.4 (\text{N(CO)O}), 137.1 (\text{Ar-C}_q), 128.4 (\text{Ar-C}), 127.7 (\text{Ar-C}), 127.5 (\text{Ar-C}), 89.3 (1\text{-C}), 88.4 (1\text{-C}), 83.2 (7\text{-C}), 73.1 (8\text{-C}), 65.7 (\text{OCH}_2\text{Ph}), 54.7 (2\text{-C or 4-C}), 54.6 (2\text{-C or 4-C}), 54.1 (2\text{-C or 4-C}), 54.0 (2\text{-C or 4-C}), 53.8 (9\text{-C}), 44.4 (5\text{-C}), 43.4 (5\text{-C}), 36.7 (10\text{-C}), 36.6 (10\text{-C}), 32.9 (6\text{-C}), 32.8 (6\text{-C}), 27.5 (\text{C}_9\text{CH}_3), 25.8 (\text{SiC(CH}_3)_3), 18.0 (\text{SiC}_3), -2.0 (\text{SiCH}_3), -2.2 (\text{SiCH}_3) [27 of 38 expected peaks observed].
\]

\[\text{IR } \nu_{\text{max}} (\text{film})/\text{cm}^{-1} \text{ 2952, 2931, 2882, 2856, 1704 (CO), 1419, 1362, 1346.}
\]

\[\text{HRMS (ESI): C}_{24}\text{H}_{39}\text{N}_2\text{O}_4\text{Si \([M+H]^+\); calculated 447.2674, found 447.2679.}
\]
1.3.4.2  Optimised synthetic route to prepare scaffolds 5a-b

![Chemical structure](image)

Benzyl (1R*,5R*,7R*,8S*)-8-hydroxy-8-methyl-9-oxo-11-oxa-3-azatricyclo [5.3.1.0]1,5 -undecane-3-carboxylate 33a

MeMgBr (3.0 M in Et₂O, 2.3 mL, 6.9 mmol, 1.5 eq.) was added to a stirred solution of compound 1 (2.0 g, 4.6 mmol, 1.0 eq.) in THF (4.6 mL) at 0 °C. The reaction was stirred at 0 °C for 10 min, then warmed to rt and stirred for 1 h. The reaction was cooled to 0 °C, H₂O (1.0 mL) was added dropwise, followed by HCl (2.0 M, 10 mL). The reaction mixture was warmed to 40 °C and stirred for 2 h. The reaction mixture was cooled, transferred to a separatory funnel and extracted with EtOAc (3 × 50 mL). The combined organics were concentrated in vacuo. Flash chromatography eluting with EtOAc–hexanes (20:80) gave the title compound 33a (1.05 g, 3.17 mmol, 69%) as a colourless foam. ¹H NMR (500 MHz, CDCl₃, 50:50 mixture of rotamers): δ 7.39-7.28 (5H, m, Cbz Ar-H), 5.12 (2H, s, OC₂H₅Ph), 4.39 (1H, d, J 7.4, 7-H), 3.99-3.92 (1H, m, includes at δ 3.96: 0.5H, d, J 12.8; and at δ 3.94: 0.5H, d, J 12.8, 2-Ha), 3.92-3.84 (1H, m, 4-Ha), 3.72 (1H, s, OH), 3.45 (0.5H, d, J 12.8, 2-Ha), 3.40 (0.5H, d, J 12.8, 2-Ha), 3.21-3.10 (1H, m, 4-HB), 3.05 (0.5H, d, J 15.0, 10-Ha), 2.99 (0.5H, d, J 15.0, 10-Ha), 2.54-2.42 (2H, m, 5-H and 10-Ha), 2.15 (1H, td, J 14.5, 8.7, 6-Ha), 1.91-1.78 (1H, m, 6-Ha), 1.48 (1.5H, s, CH₃), 1.47 (1.5H, s, CH₃). ¹³C NMR (125 MHz, CDCl₃, 329 K, mixture of two rotamers): δ 210.0 (9-C), 154.4 (N(CO)O), 137.0 (Ar-C₆), 128.7 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 91.5 (1-C), 91.4 (1-C), 84.7 (7-C), 78.5 (8-C), 67.2 (OCH₂Ph), 54.1 (2-C and 4-C), 46.5 (10-C), 45.9 (5-C), 45.0 (5-C), 31.5 (6-C), 24.5 (CH₃) [17 of 34 expected peaks observed]. IR \( \nu_{\text{max}} \) (film)/cm⁻¹ 2954, 2887, 1703 (CO), 1454, 1422, 1350, 1108, 771. HRMS (ESI): C_{18}H_{22}NO₅ [M+H]^+; calculated 332.1492, found 332.1491.
Benzyl (1R*,5R*,7R*,8S*)-8-hydroxy-9-oxo-8-phenyl-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecane-3-carboxylate 33b

PhMgBr (1.0 M in THF, 6.9 mL, 6.9 mmol, 1.5 eq.) was added to a stirred solution of compound 1 (2.0 g, 4.6 mmol, 1.0 eq.) in THF (4.6 mL) at 0 °C. The reaction was stirred at 0 °C for 10 min, then warmed to rt and stirred for 1 h. The reaction was cooled to 0 °C, H$_2$O (1.0 mL) was added dropwise, followed by HCl (2.0 M, 10 mL). The reaction mixture was warmed to 40 °C and stirred for 2 h. The reaction mixture was cooled, transferred to a separatory funnel and extracted with EtOAc (3 × 50 mL). The combined organics were concentrated in vacuo. Flash chromatography eluting with EtOAc–hexanes (20:80) gave the title compound 33a (1.41 g, 3.59 mmol, 78%) as a colourless foam. 

$^1$H NMR (500 MHz, CDCl$_3$, 1:1 mixture of rotamers): $\delta$ 7.52-7.46 (2H, m, Ar-H), 7.40-7.27 (8H, m, Ar-H), 5.15-5.06 (3H, m, OCH$_2$Ph and 7-H), 4.39 (1H, s, OH), 3.97-3.87 (2H, m, includes 4-H$_A$; and at $\delta$ 3.94: 1H, d, J 12.7, 2-H$_A$), 3.41 (0.5H, d, J 12.7, 2-H$_B$), 3.37 (0.5H, d, J 12.7, 2-H$_B$), 3.25-3.15 (1H, m, 4-H$_B$), 3.01 (0.5H, d, J 14.8, 10-H$_A$), 2.96 (0.5H, d, J 14.8, 10-H$_A$), 2.64-2.55 (1H, m, 5-H), 2.52 (1H, d, J 14.8, 10-H$_B$), 2.41-2.30 (1H, m, 6-H$_B$), 2.08-1.95 (1H, m, 6-H$_A$). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 207.8 (9-C), 154.3 (N(CO)O), 154.2 (N(CO)O), 139.6 (Ar-C$_A$), 136.7 (Ar-C$_A$), 136.7 (Ar-C$_A$), 128.9 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 126.9 (Ar-C), 92.3 (1-C), 91.5 (1-C), 82.3 (7-C), 81.1 (8-C), 67.1 (OCH$_2$Ph), 54.2 (2-C), 54.1 (2-C), 53.8 (4-C), 53.7 (4-C), 47.2 (5-C), 46.0 (10-C), 45.1 (10-C), 31.9 (6-C), 31.7 (6-C) [26 of 38 expected peaks observed].

IR $\nu_{\text{max}}$(film)/cm$^{-1}$: 3420 (OH), 2956, 2884, 1695 (CO), 1418, 1178, 1097, 935. HRMS (ESI): C$_{23}$H$_{24}$NO$_5$ [M+H]$^+$; calculated: 394.1654, found: 394.1663.
Benzyl (1\(^R\),5\(^R\),7\(^R\),8\(^R\),9\(^R\))-9-amino-8-hydroxy-8-methyl-11-oxa-3-azatricyclo[5.3.1.0\(^1,5\)]undecane-3-carboxylate 5a

Compound 33a (1.0 g, 3.1 mmol, 1.0 eq.) was dissolved in sat. NH\(_3\)/MeOH (6.1 mL) and the reaction mixture was stirred at rt for 10 min. Ti(O\(_i\)Pr)\(_4\) (1.36 mL, 4.6 mmol, 1.5 eq.) was added and the reaction mixture was stirred at rt for 4 h. The reaction mixture was then cooled to 0 °C and NaBH\(_4\) (243 mg, 6.2 mmol, 2.0 eq.) was added. After 1 h at 0 °C, the reaction mixture was warmed to rt and stirred for 1 h. NH\(_4\)OH (aq. 35%, 5 mL) was added and the reaction mixture was concentrated in vacuo. The residue was diluted with NH\(_4\)OH (aq. 35%, 5 mL) and EtOAc (20 mL), and the resulting suspension was stirred for 5 min. The suspension was dried with MgSO\(_4\) (caution – exotherm!)‡‡ then filtered through a pad of Celite®. The filtrate was concentrated in vacuo to give the title compound 5a (715 mg, 2.2 mmol, 71%), which was not purified further.

\(^1\)H NMR (500 MHz, CDCl\(_3\), 1:1 mixture of rotamers, NH\(_2\) and OH not observed): δ 7.39-7.28 (5H, m, Cbz Ar-H), 5.10 (2H, s, OCH\(_2\)Ph), 4.06 (1H, d, J 7.7, 7-H), 3.97-3.87 (1H, m, 4-H\(_A\)), 3.75-3.68 (1H, d, J 12.5, 2-H\(_A\)), 3.41 (0.5H, d, J 12.5, 2-H\(_B\)), 3.35 (0.5H, d, J 12.5, 2-H\(_B\)), 3.23-3.14 (1H, m, 4-H\(_B\)), 2.96 (1H, br. s, 9-H), 2.81-2.72 (1H, m, 5-H), 2.68-2.58 (1H, m, 6-H\(_A\)), 2.41 (0.5H, dd, J 14.8, 6.2, 10-H\(_A\)), 2.35 (0.5H, dd, J 14.8, 6.2, 10-H\(_A\)), 1.80-1.63 (2H, m, 6-H\(_B\) and 10-H\(_B\)), 1.33 (1.5H, s, CH\(_3\)), 1.32 (1.5H, s, CH\(_3\)).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\), mixture of two rotamers): δ 154.4 (N(CO)O), 136.9 (Ar-C\(_q\)), 128.6 (Ar-C), 128.1 (Ar-C), 128.0 (2 × peaks, Ar-C), 89.6 (1-C), 88.7 (1-C), 84.4 (7-C), 68.1 (8-C), 67.0 (OCH\(_2\)Ph), 55.1 (2-C or 4-C), 55.0 (2-C or 4-C), 54.7 (2-C or 4-C), 54.6 (2-C or 4-C), 52.8 (9-C), 45.2 (5-C), 44.2 (5-C), 38.4 (10-C), 31.4 (6-C), 31.0 (6-C), 26.9 (CH\(_3\)) [22 of 32 expected peaks observed]. IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 2946, 1691 (CO), 1424, 1349, 1164, 1122. HRMS (ESI): C\(_{18}\)H\(_{25}\)N\(_2\)O\(_4\) [M+H]\(^+\); calculated: 333.1814, found: 333.1805.

‡‡ Recommend cooling to 0 °C for large scale reactions.
(1R*,5R*,7R*,8R*,9R*)-9-Amino-8-hydroxy-8-phenyl-11-oxa-3-azatricyclo[5.3.1.0¹⁻⁵]undecane-3-carboxylate 5b

Compound 33b (1.0 g, 2.5 mmol, 1.0 eq.) was dissolved in sat. NH₃/MeOH (5.0 mL) and the reaction mixture was stirred at rt for 10 min. Ti(OPr)₄ (1.12 mL, 3.8 mmol, 1.5 eq.) was added and the reaction mixture was stirred at rt for 4 h. The reaction mixture was then cooled to 0 °C and NaBH₄ (190 mg, 5.0 mmol, 2.0 eq.) was added. After 1 hour at 0 °C, the reaction mixture was warmed to rt and stirred for 1 h. NH₄OH (aq. 35%, 5 mL) was added and the reaction mixture was concentrated in vacuo. The residue was diluted with NH₄OH (aq. 35%, 5 mL) and EtOAc (20 mL), and the resulting suspension was stirred for 5 min. The suspension was dried with MgSO₄ (caution – exotherm!)§§ then filtered through a pad of Celite®. Flash chromatography eluting with CH₂Cl₂-EtOH-NH₄OH (50:8:1) gave the title compound 5b (656 mg, 1.66 mmol, 67%).

1H NMR (500 MHz, CDCl₃, 1:1 mixture of rotamers, NH₂ and OH not observed): δ 7.64 (2H, d, J 7.6, Ph-H), 7.37-7.28 (7H, m, Ar-H), 7.26-7.20 (1H, m, Ar-H), 5.19-5.05 (2H, m, OCH₂Ph), 4.61 (1H, d, J 7.5, 7-H), 3.97-3.84 (2H, m, 2-Hₐ and 4-Hₐ), 3.45-3.30 (2H, m, 2-Hₐ and 9-H), 3.29-3.16 (1H, m, 6-Hₐ), 2.87-2.75 (1H, m, 6-Hₐ), 2.75-2.64 (1H, m, 5-H), 2.42-2.29 (1H, m, 10-Hₐ), 1.82-1.69 (1H, m, 6-Hₐ), 1.66 (1H, dd, J 14.2, 5.5, 10-Hₐ).

13C NMR (125 MHz, CDCl₃, mixture of two rotamers): δ 154.6 (N(CO)O), 154.5 (N(CO)O), 147.9 (2 peaks, Ar-Cₐ), 137.0 (Ar-Cₐ), 128.6 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.1 (Ar-C), 126.0 (Ar-C), 89.0 (1-C), 88.1 (1-C), 85.4 (7-C), 71.2 (8-C), 67.0 (OCH₂Ph), 55.6 (2-C or 4-C), 55.2 (2-C or 4-C), 54.9 (2-C or 4-C), 54.6 (2-C or 4-C), 52.6 (9-C), 47.5 (5-C), 46.5 (5-C), 37.7 (10-C), 37.6 (10-C), 32.3 (6-C), 32.0 (6-C) [27 of 38 expected peaks observed].


§§ Recommend cooling to 0 °C for large scale reactions.
1.3.4.3 Preparation of scaffold 5c

\[
\begin{align*}
1 & \overset{\text{THF, \(-78\ \degree C, 1\ h\)}}{\rightarrow} 30c \\
30c & \overset{\text{TBAF, AcOH, 50\ \degree C}}{\rightarrow} \text{33c 54\%} \\
\text{33c} & \overset{\text{NH\textsubscript{3}, Ti(O\textsubscript{2}Pr)}\textsubscript{4}, MeOH, rt, 15\ h\ then\ 0\ \degree C NaBH\textsubscript{4}, 2\ h}}{\rightarrow} \text{5c 75\%}
\end{align*}
\]
Benzyl (1R*,5R*,7R*,8S)-8-hydroxy-8-(1-methyl-1H-imidazol-2-yl)-9-oxo-11-oxa-3-azatricyclo[5.3.1.01,5]undecane-3-carboxylate 33c

Part 1: Addition of the 1-methyl-1H-imidazol-2-yl lithium carbanion to compound 1: To a stirred solution of methylimidazole (5.84 g, 71.2 mmol, 2.20 eq.) in THF (110 mL) at −78 °C was added dropwise BuLi (2.5 M in hexane, 25.9 mL, 64.7 mmol, 2.00 eq.). The reaction mixture was stirred at this temperature for 0.5 h, then a solution of compound 1 (13.9 g, 32.4 mmol) in THF (130 mL) was added dropwise. The solution was stirred at −78 °C for 1 h. The reaction mixture was warmed to 0 °C and used directly in the next step.

Part 2: Deprotection of silyl-protected alcohol 30c: TBAF (1.0 M in THF, 35 mL, 35 mmol, 1.1 eq.) and AcOH (2.0 mL) were added to the stirring reaction mixture at 0 °C. The reaction mixture was warmed to rt and then heated at 35 °C overnight. Additional TBAF (1.0 M in THF, 10 mL, 10 mmol, 0.3 eq.) was added and the reaction mixture was heated at 50 °C for 8 h. The reaction mixture was concentrated in vacuo. The crude reaction mixture was diluted in EtOAc–Et₂O (2:1, 1 volume) and washed with sat. aq. NH₄Cl solution (5 × 1 volumes) and brine (1 volume). The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by dry column vacuum chromatography (DCVC, 200 g silica) eluting with 30-100% EtOAc in c-hexane to give the title compound 33c as a yellow oil (7.0 g, 17.6 mmol, 54%). Rf 0.32 (3:7 c-hexane–EtOAc). ¹H NMR (500 MHz, CDCl₃, 1:1 mixture of rotamers): δ 7.38-7.27 (5H, m, Cbz Ar-H), 6.89 (1H, d, J 8.7, imidazole H), 6.83 (1H, app. s, imidazole H), 5.14-5.06 (2H, m, OCH₂Ph), 4.97 (1H, d, J 7.3, 7-H), 4.30 (1H, s, OH), 3.98-3.84 (3H, m, 2-Hₐ and 4-H), 3.81 (3H, s, NCH₃), 3.45 (0.5H, d, J 12.8, 2-Hₐ), 3.40 (0.5H, d, J 12.8, 2-Hₐ), 3.21-3.09 (1H, m, 10-Hₐ), 2.72-2.66 (1H, m, 10-Hₐ; includes at δ 2.70: 0.5H, d, J 14.7; and at δ 2.68: 0.5H, d, J 14.7), 2.63-2.54 (1H, m, 5-H), 2.28-2.19 (1H, m, 6-Hₐ), 2.06-1.92 (1H, m, 6-Hₐ). LRMS (LCMS): C₂₁H₂₄N₃O₅ [M+H]⁺; found 398.3.
(1R*,5R*,7R*,8R*,9R*)-9-Amino-8-hydroxy-8-(1-methyl-1H-imidazol-2-yl)-11-oxa-3-azatricyclo[5.3.1.0^1,5]undecane-3-carboxylate 5c

Ti(OiPr)_4 (671 µL, 2.26 mmol, 1.50 eq.) was added to a stirred solution of compound 33c (600 mg, 1.51 mmol, 1.00 eq.) in sat. NH_3/MeOH (4.0 mL). The reaction mixture was stirred for 4 h then NaBH_4 (115 mg, 3.02 mmol, 2.0 eq.) was added at 0 °C. The reaction mixture was warmed to rt, stirred overnight. Additional NaBH_4 (58 mg, 1.51 mmol, 1.0 eq.) was added at the reaction mixture was heated at 50 °C for 4 h. The reaction mixture was cooled to rt. NH_4OH (aq. 35%, 4 mL) and EtOAc (10 mL) were added and the reaction mixture was stirred for 5 min then filtered through a short Celite® pad and washing with EtOAc. The filtrate was separated and the aqueous phase was extracted with EtOAc (3 × 1 volume). The combined organics were concentrated in vacuo to give the title compound 5c (450 mg, 1.13 mmol, 75%) as a colourless solid. ^1H NMR (500 MHz, CDCl_3, 1:1 mixture of rotamers, NH_2 not observed): δ 7.38-7.27 (5H, m, Cbz Ar-H), 6.89 (1H, app. s, imidazole H), 6.84-6.79 (1H, m, imidazole H), 5.14-5.05 (2H, m, OCH_2Ph), 4.60 (1H, d, J 7.5, 7-H), 3.94 (1H, d, J 7.5, 7-H), 3.94 (1H, d, J 7.5, 7-H), 3.86-3.79 (5H, m, includes 2-H_A, 4-H_A and at δ 3.81: 3H, s, NCH_3), 3.40 (0.5H, d, J 12.6, 2-H_B), 3.34 (0.5H, d, J 12.6, 2-H_B), 3.24-3.13 (1H, m, 4-H_A), 2.85 (1H, d, J 14.3, 6.9, 10-H_A), 2.78-2.64 (2H, m, 5-H and 6-H_A), 1.88-1.73 (2H, m, includes 6-H_A and at δ 1.76: 1H, dd, J 14.3, 3.9, 10-H_A). LRMS (LCMS): C_{21}H_{27}N_4O_4 [M+H]^+; found 399.4.
1.3.4.4 Exemplar decorations of scaffold 5a

Benzyl (1R*,5R*,7R*,8R*,9R*)-8-hydroxy-9-(2-methoxyacetamido)-8-methyl-11-oxa-3-azatricyclo[5.3.1.01,5]undecane-3-carboxylate 34

Methoxyacetyl chloride (166 μL, 1.81 mmol, 1.20 eq.) was added to a stirred solution of compound 5a (500 mg, 1.51 mmol, 1.0 eq.) and DIPEA (522 μL, 3.00 mmol, 2.0 eq.) in CH₂Cl₂ (3.0 mL). The reaction mixture was stirred for 4 h, then concentrated in vacuo. Flash chromatography eluting with EtOAc gave the title compound 34 (478 mg, 1.18 mmol, 79%).

$^1$H NMR (300 MHz, CDCl₃, 1:1 mixture of rotamers, OH not observed): δ 7.40-7.28 (5H, m, Cbz Ar-H), 7.10 (1H, s, NH), 4.08 (1H, d, J 7.6, 7-H), 4.02-3.85 (4H, m, includes 4-Hₐ and 9-H and at δ 3.91: 2H, s, NH(CO)CH₂), 3.80-3.71 (1H, m, 2-Hₐ, includes at δ 3.76: 0.5H, d, J 12.5; and at δ 3.75: 0.5H, d, J 12.5), 3.49-3.31 (4H, m, includes 2-Hₐ; and at δ 3.45: 3H, s, OCH₃), 3.26-3.13 (1H, m, 4-Hₐ), 2.75-2.62 (1H, m, 5-H), 2.62-2.47 (1H, m, 6-Hₐ), 2.43-2.22 (1H, m, 10-Hₐ), 1.98-1.75 (2H, m, 6-Hₐ and 10-Hₐ), 1.47 (3H, s, C₃CH₃).

$^{13}$C NMR (125 MHz, CDCl₃, mixture of two rotamers): δ 171.2 (NH(CO)), 154.4 (N(CO)O), 136.9 (2 peaks, Ar-Cₐ), 128.6 (Ar-C), 128.1 (2 peaks, Ar-C), 89.8 (1-C), 88.9 (1-C), 83.6 (7-C), 83.5 (7-C), 72.0 (NH(CO)CH₂), 70.0 (8-C), 67.0 (OCH₂Ph), 59.5 (OCH₃), 55.1 (2-C or 4-C), 54.8 (2-C or 4-C), 54.7 (2-C or 4-C), 54.4 (2-C or 4-C), 52.0 (2 peaks, 9-C), 44.8 (5-C), 43.8 (5-C), 34.8 (10-C), 34.7 (10-C), 31.9 (6-C), 31.6 (6-C), 28.5 (C₅CH₃) [28 of 38 expected peaks observed].

IR $\nu_{\text{max}}$(film)/cm⁻¹: 3393, 2939, 1701 (CO), 1677 (CO), 1422, 1350, 1116.

Benzyl (1R*,5R*,7R*,8R*,9R*)-8-hydroxy-9-[(4-methoxyphenyl)carbamoyl]amino)-8-methyl-11-oxa-3-azatricyclo[5.3.1.01,5]undecane-3-carboxylate S-34

4-methoxyphenyl isocyanate (52 mg, 0.35 mmol, 1.1 eq.) was added to a stirred solution of compound 5a (106 mg, 0.32 mmol, 1.0 eq.) in CH2Cl2 (1.0 mL). The reaction mixture was stirred for 1 h, then concentrated in vacuo. Flash chromatography eluting with EtOAc gave the title compound S-34 (141 mg, 0.29 mmol, 92%) as a colourless oil. 

1H NMR (300 MHz, CDCl3, 1:1 mixture of rotamers): δ 7.39-7.29 (5H, m, Cbz Ar-H), 7.18 (2H, d, J 9.1, PMP 2-H), 6.89 (2H, d, J 9.1, PMP 3-H), 6.43 (0.5H, s, NH), 6.34 (0.5H, s, NH), 5.26 (0.5H, d, J 3.2, CHNH), 5.21 (0.5H, d, J 3.2, CHNH), 5.10 (2H, s, OCH2Ph), 4.02 (1H, d, J 7.6, 7-H), 3.93-3.77 (5H, m, includes 4-HA, 9-H, and at δ 3.80: 3H, s, OCH3), 3.76-3.68 (1H, m, 2-HA), includes at δ 3.73: 0.5H, d, J 12.7; and at δ 3.71: 0.5H, d, J 12.7), 3.33 (1H, app. t, J 12.5, 2-HB), 3.22-3.07 (1H, m, 4-HB), 2.89 (0.5H, s, OH), 2.81 (0.5H, s, OH), 2.57-2.17 (3H, m, 5-H, 6-HA and 10-HA), 1.86 (1H, d, J 15.1, 10-HB), 1.78-1.63 (1H, m, 6-HB), 1.43 (3H, s, CqCH3).

13C NMR (125 MHz, CDCl3, mixture of two rotamers, 1 × CO not observed): δ 158.3 (PMP 4-C), 158.2 (PMP 4-C), 154.5 (CO), 136.8 (Ar-Ca), 130.3 (2 peaks, Ar-C), 128.6 (Ar-C), 128.2 (Ar-C), 128.0 (Ar-C), 125.4 (PMP 2-C), 115.0 (PMP 3-C), 89.5 (1-C), 88.9 (1-C), 83.6 (2 peaks, 7-C), 69.9 (2 peaks, 8-C), 67.5 (OCH2Ph), 67.1 (OCH2Ph), 55.7 (OCH3), 55.0 (2-C or 4-C), 54.8 (2-C or 4-C), 54.7 (2-C or 4-C), 54.5 (2-C or 4-C), 53.2 (9-C), 53.1 (9-C), 44.5 (5-C), 43.6 (5-C), 35.3 (10-C), 31.9 (6-C), 31.7 (6-C), 28.5 (CqCH3) [32 of 44 expected peaks observed].

IR νmax (film)/cm⁻¹: 3357 (OH), 1678 (CO), 1551, 1510, 1456, 1429, 1172. HRMS (ESI): C26H31N3NaO6 [M+Na]+; calculated: 504.2111, found: 504.2099.
N-[(1R*,5R*,7R*,8R*,9R*)-8-hydroxy-8-methyl-11-oxa-3-azatricyclo[5.3.1.0^1,5]undecan-9-yl]-2-methoxyacetamide 35

Hydrogenation was carried out following general procedure B, using compound 34 (478 mg, 1.18 mmol) to give the title compound 35 as a colourless oil (296 mg, 1.09 mmol, 93%). \(^1\)H NMR (500 MHz, 333 K, MeOD, NH and OH not observed): \(\delta\) 4.09-4.05 (1H, m, 7-H), 3.93 (1H, d, J 15.3, CH\(_A\)H\(_B\)OCH\(_3\)), 3.85 (1H, d, J 15.3, CH\(_A\)H\(_B\)OCH\(_3\)), 3.81-3.75 (1H, m, 9-H), 3.43-3.32 (5H, m, includes 2-H\(_A\), 4-H\(_A\); and at \(\delta\) 3.35: 3H, s, OCH\(_3\)). 13C NMR (125 MHz, MeOD): \(\delta\) 172.5 (NH(CO)), 91.0 (1-C), 85.2 (7-C), 73.0 (CH\(_2\)OCH\(_3\)), 69.1 (8-C), 59.8 (OCH\(_3\)), 55.1 (2-C or 4-C), 54.8 (2-C or 4-C), 53.3 (9-C), 45.0 (5-C), 34.7 (6-C), 33.2 (10-C), 28.0 (C\(_9\)CH\(_3\)). IR \(\nu_{\text{max}}\)(film)/cm\(^{-1}\): 3391 (OH), 2936, 1658 (CO), 1520, 1453, 1113.


N-[(1R*,5R*,7R*,8R*,9R*)-8-hydroxy-8-methyl-3-(oxan-4-yl)-11-oxa-3-azatricyclo[5.3.1.0^1,5]undecan-9-yl]-2-methoxyacetamide 36

General procedure D was followed using compound 35 (26 mg, 95 \(\mu\)mol) and tetrahydro-4\(H\)-pyran-4-one. Purification by mass directed preparative HPLC gave the title compound 36 (14 mg, 40 \(\mu\)mol, 42%) as an amorphous solid. \(^1\)H NMR (500 MHz, CDCl\(_3\), OH not observed): \(\delta\) 7.14 (1H, d, J 5.3, NH), 4.06 (1H, d, J 7.4, 7-H), 4.00-3.93 (4H, m, 9-H, THP 2-H\(_A\), and THP 4-H), 3.90 (2H, d, J 5.2, CH\(_2\)OCH\(_3\)), 3.45 (3H, s, OCH\(_3\)), 3.40-3.33 (2H, m, THP 2-H\(_B\)), 3.12 (1H, app. t, J 8.3, 4-H\(_A\)), 2.88 (1H, d, J 10.8, 2-H\(_A\)), 2.75 (1H, d, J 10.8, 2-H\(_B\)), 2.71-2.63 (1H, m, 5-H), 2.47 (1H, dd, J 13.6, 8.7, 6-H\(_A\)), 2.39-2.27 (2H, m, 4-H and 10-H\(_A\)), 1.96 (1H, d, J 14.6, 10-H\(_B\)), 1.80-1.70 (3H, m, 6-H\(_A\) and THP 3-H\(_A\)), 1.62-1.51 (2H, m, THP 3-H\(_B\)), 1.46 (3H, s, C\(_9\)CH\(_3\)). 13C NMR (125 MHz, MeOD): \(\delta\) 171.5 (NH(CO)), 89.3 (1-C), 83.9 (7-C), 72.0 (CH\(_2\)OCH\(_3\)), 70.3 (8-C), 66.8 (THP 2-C), 60.8 (THP 4-C), 60.2 (2-C), 59.5 (OCH\(_3\)), 58.6 (4-C), 52.4 (9-C), 44.8 (5-C), 35.8 (10-C), 31.9 (6-C or THP 3-C), 30.2 (6-C or THP 3-C), 27.3 (C\(_9\)CH\(_3\)). IR \(\nu_{\text{max}}\)(film)/cm\(^{-1}\): 3328 (OH), 2946, 2834, 1648, 1450, 1410, 1114, 1018. HRMS (ESI): C\(_{18}\)H\(_{31}\)N\(_2\)O\(_5\) [M+H]^+; calculated: 355.2233, found: 355.2224.
General procedure F was followed using compound 35 (26 mg, 95 μmol) and 4-methoxyphenylsulfonyl chloride. Purification by mass directed preparative HPLC gave the title compound 37 (29 mg, 66 mmol, 70%) as an amorphous solid. ¹H NMR (500 MHz, MeOD, NH and OH not observed): δ 7.77 (2H, d, J 9.0, Ar 2-H), 7.12 (2H, d, J 9.0, Ar 3-H), 3.96-3.88 (4H, m, includes 7-H; and at δ 3.90: 3H, s, Ar-CH₃), 3.87 (1H, d, J 15.3, CH₃CH₂OCH₃), 3.79 (1H, d, J 15.3, CH₃CH₂OCH₃), 3.68-3.58 (2H, m, 4-HA and 9-H), 3.43 (3H, s, CH₂OCH₃), 3.38 (1H, d, J 12.2, 2-HA), 3.20 (1H, d, J 12.2, 2-Ha), 2.87, (1H, dd, J 10.2 and 8.2, 4-Ha), 2.53-2.44 (1H, m, 5-H), 2.35 (1H, dd, J 13.8, 8.5, 6-Ha), 2.07 (1H, dd, J 14.6 and 5.6, 10-Ha), 1.95 (1H, d, J 14.6, 10-Ha), 1.70-1.62 (1H, m, 6-Ha), 1.35 (3H, s, C₉H₃). ¹³C NMR (125 MHz, MeOD): δ 172.3 (NH(CO)), 164.9 (Ar 4-C), 131.0 (Ar 1-C), 128.9 (Ar 2-C), 115.5 (Ar 3-C), 91.1 (1-C), 85.5 (7-C), 72.7 (CH₂OCH₃), 68.5 (8-C), 59.7 (CH₂OCH₃), 57.6 (2-C or 4-C), 57.1 (2-C or 4-C), 56.2 (Ar-CH₃), 53.3 (9-C), 45.4 (5-C), 35.1 (10-C), 32.1 (6-C), 27.9 (C₉H₃). HRMS (ESI): C₂₀H₂₆N₂O₇S [M+Na]⁺; calculated: 463.1514, found: 463.1507.

General procedure F was followed using compound 35 (26 mg, 95 μmol) and 4-cyanophenylisocyanate. Purification by mass directed preparative HPLC gave the title compound 38 (20 mg, 48 μmol, 50%) as an amorphous solid. ¹H NMR (500 MHz, MeOD, NH and OH not observed): δ 7.69- 7.57 (4H, m, Ar-H), 4.10 (1H, d, J 7.8, 7-H), 4.01-3.93 (2H, m, includes 4-HA; and at δ 3.97: 1H, d, J 15.1, CH₃CH₂OCH₃), 3.88 (1H, d, J 15.1, CH₃CH₂OCH₃), 3.82-3.75 (2H, m, 2-HA and 9-H), 3.50-3.43 (4H, m, includes 2-Hb; and at δ 3.49: 3H, s, OCH₃), 3.28 (1H, dd, J 10.7, 7.8, 4-Hb), 2.94-2.84 (1H, m, 5-H), 2.60 (1H, dd, J 14.2 and 8.6, 6-Hb), 2.26 (1H, dd, J 14.8, 1.7, 10-Hb), 2.20 (1H, dd, J 14.8, 5.5, 10-Ha), 1.94-1.85 (1H, m, 6-Ha), 1.44 (3H, s, C₉H₃). ¹³C NMR (125 MHz, MeOD): δ 172.5 (NH(CO)CH₂), 155.5 (NH(CO)NH), 145.8 (Ar-C₉), 133.9 (Ar-C₉), 120.9 (Ar-C), 120.1 (Ar-C), 105.9 (CN), 90.6 (1-C), 85.2 (7-C), 72.8 (CH₂OCH₃), 68.8 (8-C), 59.7 (OCH₃), 56.1 (2-C or 4-C), 55.6 (2-C or 4-C), 53.3 (9-C), 44.7 (5-C), 34.7 (10-C), 33.6 (6-C), 27.9 (C₉H₃). IR νmax(film)/cm⁻¹: 3400 (OH), 2938, 2222 (CN), 1652 (CO), 1515, 1441, 1414. HRMS (ESI): C₂₁H₂₆N₄O₅ [M+Na]⁺; calculated: 437.1800, found: 437.1795.
1.3.5 Preparation of scaffold 6

1.3.5.1 Initial procedure to prepare scaffold 6

The reaction mixture was stirred at −78 °C 2

C(C-

4H (8

5q (8

36x38]at 500 MHz).

***

Found: 371.2326.

IR

37.131.978.1

diazbicyclo[5.3.1.01,5]undec-8-ene-3-carboxylate 39

The reaction mixture was stirred at −78 °C for 1 h, then

quenched at that temperature with sat. aq. NH₄Cl solution (20 mL).

The reaction mixture was warmed to rt, then EtOAc (70 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 70 mL). The combined organics were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Flash chromatography eluting with 85:15 hexane–EtOAc gave title compound 39 (2.98 g, 8.04 mmol, 61%) as a single diastereomer.”*** ¹H NMR (500 MHz, MeOH-d₄, 40:60 mixture of rotamers, OH not observed): δ 7.33-7.27 (4H, m, Ar-H), 7.23-7.19 (1H, m, Ar-H), 5.92-5.87 (1H, m, 8-H), 5.67 (1H, d, J 9.7, 9-H), 4.03 (1H, d, J 14.7, 2-Ha), 3.91-3.84 (2H, m, includes 4-Ha; and at d 3.90: 1H, d, J 14.7, 2-Hb), 3.72-3.63 (2H, m, NCH₂Ph), 3.47-3.42 (1H, m, 7-H), 3.36-3.34 (1H, m, 4-Hb), 2.71-2.65 (1H, m, 5-H), 1.84-1.75 (1H, m, 6-Ha), 1.71-1.65 (1H, m, 6-Hb), 1.55 (3H, s, N(CO)C(CH₃)₃), 1.51 (5.4H, s, N(CO)C(CH₃)₃), 1.34 (3H, s, C₆H₃). ¹³C NMR (100 MHz, MeOD, mixture of two rotamers): δ 156.3 (N(CO)O), 142.8 (Ar-C₆), 132.5 (8-C or 9-C), 132.4 (8-C or 9-C), 131.9 (8-C or 9-C), 131.8 (8-C or 9-C), 129.1 (Ar-C₆), 129.0 (Ar-C₆), 127.5 (Ar-C₆), 80.8 (2 peaks, OC₆(CH₃)₃), 78.9 (1-C), 78.1 (1-C), 70.0 (10-C), 69.9 (10-C), 58.8 (7-C), 58.4 (7-C), 56.0 (4-C), 55.6 (4-C), 51.4 (NCH₂Ph or 2-C), 50.0 (NCH₂Ph or 2-C), 49.9 (NCH₂Ph or 2-C), 49.7 (NCH₂Ph or 2-C), 44.4 (5-C), 43.6 (5-C), 37.5 (6-C), 37.4 (6-C), 28.9 (OC₆(CH₃)₃), 25.7 (C₆H₃) [29 of 36 expected peaks observed]. IR νₓ(max,film)/cm⁻¹ 3374, 2483, 2072, 1671. HRMS (ESI): C₂₂H₃₁N₂O₃ [M+H]+; calculated 371.2335, Found: 371.2326.

*** N.b. the crude reaction product was a 3:1 mixture of diastereomers (as judged by analysis of the crude reaction product by ¹H NMR spectroscopy at 500 MHz).
**tert-Butyl (1R*,5R*,7S*,10R*)-10-hydroxy-10-methyl-3,11-diazatricyclo[5.3.1.01,5]undecane-3-carboxylate 6**

Hydrogenation was carried out following general procedure B, using compound 39 (2.98 g, 8.05 mmol) and conc. HCl (600 µL, 51.5 mmol, 6.4 eq.). Following completion of the reaction, the reaction mixture was filtered through a pad of Celite® and washed through with EtOAc. The resulting solution was then concentrated in vacuo. The residue was diluted in CH₂Cl₂ (30 mL) and sat. aq. K₂CO₃ was added with stirring until the solution reached basic pH. The solution was stirred for 20 min, then the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (2 × 50 mL). The combined organics were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give the title compound 6 as a colourless oil (1.71 g, 6.05 mmol, 75%).

**¹H NMR** (400 MHz, MeOD): δ 3.86-3.80 (1H, app. t, J 10.4, 4-Hₐ), 3.65 (1H, d, J 12.0, 2-Hₐ), 3.61-3.53 (1H, m, 7-H), 3.30-3.20 (1H, m, 2-Hₐ; includes at δ 3.25: 0.5H, d, J 12.0; and at δ 3.24: 0.5H, d, J 12.0), 3.10 (1H, app. t, J 9.2, 4-Hₐ), 2.67-2.54 (1H, m, 5-H), 1.95-1.78 (3H, m, 6-Hₐ and 9-H), 1.75-1.64 (1H, m, 8-Hₐ), 1.58-1.33 (11H, m, includes 6-Hₐ, 8-Hₐ, and at δ 1.46: 9H, s, C(CH₃)₃), 1.25 (3H, s, C₉CH₃).

**¹³C NMR** (100 MHz, MeOD, mixture of two rotamers): δ 156.1 (N(CO)O), 156.0 (N(CO)O), 80.9 (OC₉(CH₃)₃), 78.5 (1-C), 77.6 (1-C), 71.8 (10-C), 57.8 (2 peaks, 7-C), 55.9 (4-C), 55.4 (4-C), 52.4 (2-C), 52.1 (2-C), 43.9 (5-C), 43.1 (5-C), 36.1 (9-C), 35.9 (9-C), 33.9 (8-C), 30.5 (6-C), 28.8 (OC(CH₃)₃), 25.3 (C₉CH₃) [20 of 26 expected peaks observed].

**IR** ν_max(film)/cm⁻¹ 3374, 2935, 2482, 2071, 1670. **HRMS** (ESI): C₁₅H₂₇N₂O₃ [M+H]^+; calculated 283.2022, found 283.2016.

### 1.3.5.2 Scaled-up synthesis of scaffold 6

The route to compound 6 outlined above was followed starting with 25.7 g (72.6 mmol) of compound 2 to prepare 15.7 g (42.5 mmol, 58%) of compound 39, which was isolated from the crude reaction mixture as a single diasteriomer. Hydrogenation of 18.0 g (48.6 mmol) of compound 39 gave 13.1 g (46.4 mmol, 95%) scaffold 6.
1.3.5.3 Exemplar decorations of scaffold 6

\[
\begin{align*}
\text{BocN} & \quad \text{HO} \\
\text{6} & \quad \text{decorations} \\
\text{BocN} & \quad \text{HO} \\
\end{align*}
\]

tert-Butyl \((1R^*, 5R^*, 7S^*, 10R^*)-11-(4-fluorobenzoyl)-10-hydroxy-10-methyl-3,11-
diazatricyclo[5.3.1.0^1,5]undecane-3-carboxylate 40

4-Fluorobenzoyl chloride (113 µL, 0.96 mmol, 2.0 eq.) was added to a stirred solution of compound 6 (135 mg, 0.48 mmol, 1.0 eq.) and DIPEA (242 µL, 1.44 mmol, 3.0 eq.) in CH\(_2\)Cl\(_2\) (4 mL). After 16 h the reaction was quenched with sat. aq. NH\(_4\)Cl solution (10 mL) and transferred to a separating funnel. The aqueous phase was extracted with CH\(_2\)Cl\(_2\) (3 × 10 mL), then the combined organics were washed with brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated \textit{in vacuo}. Flash chromatography eluting with 90:10 CH\(_2\)Cl\(_2\)–MeOH gave the \textit{title compound} 40 (160 mg, 0.40 mmol, 83%) as a colourless amorphous solid. \(^1\)H NMR (500 MHz, DMSO-\(d_6\), 333 K): δ 7.54 (2H, dd, \(J = 8.3, 5.6\), Ar 2-H), 7.24 (2H, app. t, \(J = 8.7\), Ar 3-H), 4.33–4.14 (2H, m, 2-H\(_A\) and 7-H), 3.83 (1H, dd, \(J = 10.7, 9.0\), 4-H\(_A\)), 3.70 (1H, d, \(J = 13.1\), 2-H\(_B\)), 3.01 (1H, dd, \(J = 10.7, 9.3\), 4-H\(_B\)), 2.76 (1H, qd, \(J = 8.8, 3.8\), 5-H), 1.94–1.85 (1H, m, 8-H\(_A\)), 1.83–1.66 (3H, m, 6-H\(_A\), 8-H\(_B\), 9-H\(_A\)), 1.54–1.46 (1H, m, 9-H\(_B\)), 1.39 (9H, s, C(CH\(_3\))\(_3\)), 1.32–1.24 (1H, m, 6-H\(_B\)), 1.18 (3H, s, C\(_q\)CH\(_3\)). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\), 333 K): δ 169.9 (N(CO)Ar), 162.6 (d, \(J = 247.5\), Ar 4-C), 152.8 (N(CO)O), 133.3 (Ar 1-C), 129.2 (d, \(J = 8.7\), Ar 2-C), 114.9 (d, \(J = 21.7\), Ar 3-C), 78.7 (1-C), 78.1 (C\(_q\)(CH\(_3\))\(_3\)), 73.4 (10-C), 61.0 (7-C), 52.1 (4-C), 46.3 (2-C), 44.4 (5-C), 32.5 (9-C), 30.4 (8-C), 28.6 (6-C), 27.8 (C(CH\(_3\))\(_3\)), 25.1 (C\(_q\)CH\(_3\)). IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3375, 2975, 2933, 2486, 2072, 1692, 1605. HRMS (ESI): C\(_{22}\)H\(_{29}\)F\(_2\)NaO\(_4\) [M+Na]\(^+\); calculated 427.2009, found 427.1997.
**tert-Butyl (1R*,5R*,7S*,10R*)-10-hydroxy-10-methyl-11-(thiophen-2-ylmethyl)-3,11-diazatricyclo[5.3.1.015]undecane-3-carboxylate 41**

2-Thiophene carboxaldehyde (110 µL, 1.18 mmol, 2.18 eq.) was added to a solution of compound 6 (0.54 mmol) in CH₂Cl₂ (5.0 mL). The reaction mixture was stirred for 10 min, then NaBH(OAc)₃ (286 mg, 1.35 mmol, 2.5 eq.) was added. The reaction mixture was stirred at rt for 48 h, then further 2-thiophene carboxaldehyde (1.0 eq.) was added. Following 48 h stirring, the reaction was quenched with sat. aq. NH₄Cl solution (10 mL) and transferred to a separating funnel. The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Flash chromatography eluting with 60:40 to 50:50 hexane–EtOAc gave the *title compound* 41 (86 mg, 0.23 mmol, 43%).

**¹H NMR** (500 MHz, MeOD, 40:60 mixture of rotamers): δ 7.23-7.19 (1H, m, Ar-H), 6.93-6.87 (2H, m, Ar-H), 4.28-4.22 (1H, m, 2-H₆; included at δ 4.26: 0.5H, d, J 15.3; and at δ 4.25: 0.5H, d, J 15.3), 3.99 (1H, d, J 15.3, 2-H₈), 3.85-3.77 (1H, m, 3-H₆), 3.59 (1H, dd, J 13.1, 2.9, NCH₆H₆Ar), 3.55 (1H, dd, J 13.1, 2.9, NCH₆H₆Ar), 3.47-3.42 (1H, m, 7-H), 3.18-3.12 (1H, m, 4-H₈), 2.75-2.64 (1H, m, 5-H), 2.13-2.01 (1H, m, 8-H₆), 1.93-1.78 (2H, m, 6-H), 1.76 (1H, td, J 13.8 and 6.0, 9-H₆), 1.56-1.40 (10H, m, includes 9-H₈; and at δ 1.47: 3.6H, s, OC(CH₃)₃; and at δ 1.43: 5.4H, s, OC(CH₃)₃), 1.22 (3H, s, C₆H₃), 1.20-1.12 (1H, m, 8-H₈).

**¹³C NMR** (125 MHz, MeOD, mixture of two rotamers): δ 156.1 (N(CO)O), 156.0 (N(CO)O), 149.0 (2 peaks, Ar-C₆), 127.5 (Ar-C), 124.9 (Ar-C), 124.2 (Ar-C), 81.0 (OC₆(CH₃)₃), 80.3 (1-C), 79.4 (1-C), 73.2 (10-C), 60.9 (7-C), 60.4 (7-C), 56.3 (4-C), 55.9 (4-C), 47.6 (NCH₂Ar), 47.4 (NCH₂Ar), 45.7 (5-C), 44.9 (5-C), 34.6 (6-C or 9-C), 34.4 (6-C or 9-C), 28.8 (OC₆(CH₃)₃), 26.1 (C₆H₃), 26.0 (C₆H₃), 25.3 (8-C), 25.1 (8-C) [26 of 36 expected peaks observed].

**IR** ν<sub>max</sub>(film)/cm⁻¹ 3374, 2933, 2484, 2071, 1672. **HRMS** (ESI): C₂₀H₃₁N₂O₃S [M+H]⁺; calculated 283.2022, found 283.2016.
tert-Butyl (1R*,5R*,7S*,10R*)-11-[(2-ethoxy-2-oxoethyl)carbamoyl]-10-hydroxy-10-methyl-3,11-diazatricyclo[5.3.1.01,5]undecane-3-carboxylate 42

Ethyl isocyanatoacetate (160 µL, 1.43 mmol, 1.24 eq.) was added to a stirred solution of compound 6 (325 mg, 1.15 mmol, 1.0 eq.) and DIPEA (320 mL, 1.83 mmol, 1.6 eq.) in CH₂Cl₂ (10 mL) and the reaction mixture was stirred overnight at rt. The reaction was quenched with sat. aq. NH₄Cl solution (10 mL) and transferred to a separating funnel. The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Flash chromatography eluting with CH₂Cl₂ then 9:1 CH₂Cl₂–MeOH gave the title compound 42 (425 mg, 1.03 mmol, 89%) as a colourless amorphous solid. ¹H NMR (500 MHz, MeOD, OH not observed): δ 4.56-4.48 (1H, m, 7-H), 4.22 (2H, q, J 7.3, OCH₂CH₃), 3.94-3.89 (3H, m, NHCH₂CO and 4-HA), 2.93 (1H, app. t, J 10.3, 4-Hb), 2.80 (1H, m, 5-H), 2.20-2.12 (1H, m, 8-HA), 1.95-1.82 (3H, m, 6-H and 9-HA), 1.64 (1H, dd, J 14.9 and 5.4, 9-Hb), 1.49 (9H, s, C(CH₃)₃), 1.46-1.40 (1H, m, 8-Hb), 1.31 (3H, t, OCH₂CH₃), 1.27 (3H, s, C₆H₅CH₂). IR ν_{max}(film)/cm⁻¹ 3360, 2976, 2934, 2487, 1741, 1693, 1613. HRMS (ESI): C₂₀H₃₄N₃O₆ [M+H]+; calculated 412.2448, Found: 412.2441.
2.0 Processed NMR Spectra

Compounds are listed in order of appearance within the Supplementary Information. NOESY Spectra (where relevant) are also included in this Section.
30a NOESY correlations:

- C₈CH₃: 7-H; 10-H₉
- 5-H: 4-H₆; 6-H₆; 10-H₆
- 7-H: C₈CH₃; 6-H₆
31 NOESY correlations:
Me: 7-H; 9-H
7-H: Me; 6-H_B
9-H: Me; 10-H_B
3.0 References
