Synthesis of a novel suppressor of beta-cell apoptosis *via* diversity-oriented synthesis

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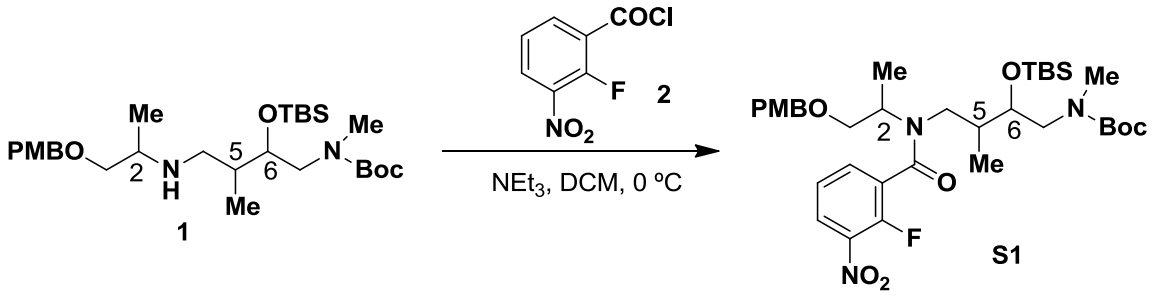
Supporting Information

General Information

All oxygen and/or moisture sensitive reactions were carried out under N_2 atmosphere in glassware that had been flame-dried under vacuum (~0.5 mmHg) and purged with N_2 prior to use. All reagents and solvents were purchased from commercial vendors and used

as received, or synthesized according to the footnoted references. NMR spectra were recorded on a Bruker 300 (300 MHz ^{1}H, 75 MHz ^{13}C) or Varian UNITY INOVA 500 (500 MHz ^{1}H, 125 MHz ^{13}C) spectrometer. Proton and carbon chemical shifts are reported in ppm (δ) referenced to the NMR solvent.[1] Data are reported as follows: chemical shifts, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet; coupling constant(s) in Hz; integration). Unless otherwise indicated NMR data were collected at 25 °C. Infrared spectra were obtained on a Perkin-Elmer Model 2000 FT-IR spectrometer and are reported in cm^{-1}. Flash chromatography was performed using 40-60 μm Silica Gel (60 Å mesh) on a Teledyne Isco Combiflash R_f. Tandem Liquid Chromotography/Mass Spectrometry (LCMS) was performed on a Waters 2795 separations module and 3100 mass detector. Analytical thin layer chromatography (TLC) was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and aqueous potassium permanganate ($KMnO_4$) stain followed by heating. High-resolution mass spectra were obtained at the MIT Mass Spectrometry Facility.

General Protocol for Preparation of S_NAr Precursors:



Triethylamine (5.0 equiv) was added to a solution of amine **1** (1.0 equiv) and 2-fluoro-3-benzoic acid chloride **2** (2.5 equiv) in CH_2Cl_2 (0.2 M) at 0 ºC under dry nitrogen atmosphere. The reaction was warmed to room temperature and stirred until complete consumption of starting amine was observed (1-2 h). The reaction was quenched with a saturated NH_4Cl solution and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Flash

[1] Gottlieb, H. E., Kotlyar, V., Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512-7515.

chromatography on silica gel (gradient: 10% to 30% EtOAc in hexanes) provided desired product **S1**.

S_NAr Precursor, S1a

Following the general reaction protocol (2*S*,5*R*,6*S*)-**1a** (22.5 g, 42.9 mmol) was reacted with **2** (21.8 g, 107 mmol) and triethylamine (29.7 mL, 214 mmol), which provided pure product (2*S*,5*R*,6*S*)-**S1a** (28.0 g, 94%).

(2*S*,5*R*,6*S*)-**S1a**: $[\alpha]_D^{20}$ -19.7 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 2930, 1694, 1644, 1538, 1458, 1350, 1248, 1154. ^{1}H NMR (500 MHz, DMSO-d_6, 150 ºC) δ 8.12 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.64 (dd, *J* = 6.6, 6.6 Hz, 1H), 7.46 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.42 (d, *J* = 12.3 Hz, 1H), 4.39 (d, *J* = 12.3 Hz, 1H), 3.96-3.83 (m, 2H), 3.78 (s, 3H), 3.69-3.59 (m, 1H), 3.54-3.30 (m, 2H), 3.31-3.23 (m, 2H), 3.10-3.02 (m, 1H), 2.82 (s, 3H), 2.04-1.96 (m, 1H), 1.42 (s, 9H), 1.24 (br s, 3H), 0.89 (br s, 3H), 0.84 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 150 ºC) δ 164.0, 158.5, 154.3, 149.4 (d, *J* = 254 Hz), 137.0 (d, *J* = 10 Hz), 133.4 (d, *J* = 5 Hz), 129.7, 128.2 (2C), 128.0 (d, *J* = 19 Hz), 125.3 (d, *J* = 3 Hz), 124.6 (d, *J* = 4 Hz), 113.3 (2C), 78.2, 71.5 (2C), 70.3, 54.6, 53.7, 51.3, 35.3, 34.7, 27.5 (3C), 25.0 (3C), 16.9, 14.9, 10.1, -5.1, -5.5 (1 carbon absent). HRMS (ESI) calcd for $C_{35}H_{55}FN_3O_8Si$ $[M + H]^+$: 692.3737. Found: 692.3746.

S_NAr Precursor, S1b

Following the general reaction protocol (2*R*,5*R*,6*S*)-**1b** (22.0 g, 41.9 mmol) was reacted with **2** (21.3 g, 105 mmol) and triethylamine (29.1 mL, 210 mmol), which provided pure product (2*R*,5*R*,6*S*)-**S1b** (28.2 g, 97%).

(2*R*,5*R*,6*S*)-**S1b**: $[\alpha]_D^{20}$ +38.2 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 2930, 1694, 1646, 1538, 1457, 1348, 1248, 1154. ^{1}H NMR (500 MHz, DMSO-d_6, 150 ºC) δ 8.12 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.63 (dd, *J* = 6.6, 6.6 Hz, 1H), 7.45 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.44-4.36 (m, 2H), 3.96-3.84 (m, 2H), 3.78 (s, 3H), 3.69-3.59 (m, 1H), 3.46-3.35 (m, 2H), 3.33-3.25 (m, 2H), 3.15 (dd, *J* = 10.5, 13.4 Hz, 1H), 3.10-3.05 (m, 1H), 2.81 (s, 3H), 2.18-2.02 (m, 1H), 1.43 (s, 9H), 1.24 (br s, 3H), 0.89 (br s, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 150 ºC) δ 164.1, 158.5,

154.4, 149.5 (d, *J* = 254 Hz), 137.1 (d, *J* = 10 Hz), 133.5 (d, *J* = 5 Hz), 129.7, 128.1 (2C), 128.0 (d, *J* = 19 Hz), 125.4 (d, *J* = 3 Hz), 124.6 (d, *J* = 4 Hz), 113.3 (2C), 78.1, 71.5, 71.3, 70.5, 54.6, 53.7, 51.4, 34.6, 34.2, 27.5 (3C), 25.0 (3C), 16.9, 14.6, 10.0, -5.1, -5.5 (1 carbon absent). HRMS (ESI) calcd for $C_{35}H_{55}FN_3O_8Si$ $[M + H]^+$: 692.3737. Found: 692.3752.

S_NAr Precursor, S1c

Following the general reaction protocol (2*S*,5*R*,6*R*)-**1c** (21.0 g, 40.0 mmol) was reacted with **2** (20.4 g, 100 mmol) and triethylamine (27.7 mL, 200 mmol), which provided pure product (2*S*,5*R*,6*R*)-**S1c** (27.6 g, 100%).

(2*S*,5*R*,6*R*)-**S1c**: $[\alpha]_D^{20}$ -49.5 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 2930, 1691, 1644, 1537, 1458, 1349, 1248, 1157. ^1H NMR (500 MHz, DMSO-d_6, 150 ºC) δ 8.12 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.64 (dd, *J* = 6.6, 6.6 Hz, 1H), 7.45 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.41 (s, 2H), 3.95-3.83 (m, 2H), 3.78 (s, 3H), 3.54-3.45 (m, 1H), 3.40-3.24 (m, 4H), 3.16-3.08 (m, 1H), 2.84 (s, 3H), 2.15-2.06 (m, 1H), 1.43 (s, 9H), 1.25 (br s, 3H), 0.94 (br s, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 150 ºC) δ 164.2, 158.5, 154.5, 149.7 (d, *J* = 254 Hz), 137.1 (d, *J* = 10 Hz), 133.5 (d, *J* = 5 Hz), 129.7, 128.2 (2C), 128.0 (d, *J* = 19 Hz), 125.3 (d, *J* = 3 Hz), 124.6 (d, *J* = 4 Hz), 113.3 (2C), 78.1, 72.4 71.5, 70.4, 54.6, 54.0, 51.0, 36.3 (br), 34.8, 27.5 (3C), 25.0 (3C), 16.9, 14.7, 12.5, -5.4, -5.6 (1 carbon absent). HRMS (ESI) calcd for $C_{35}H_{55}FN_3O_8Si$ $[M + H]^+$: 692.3737. Found: 692.3764.

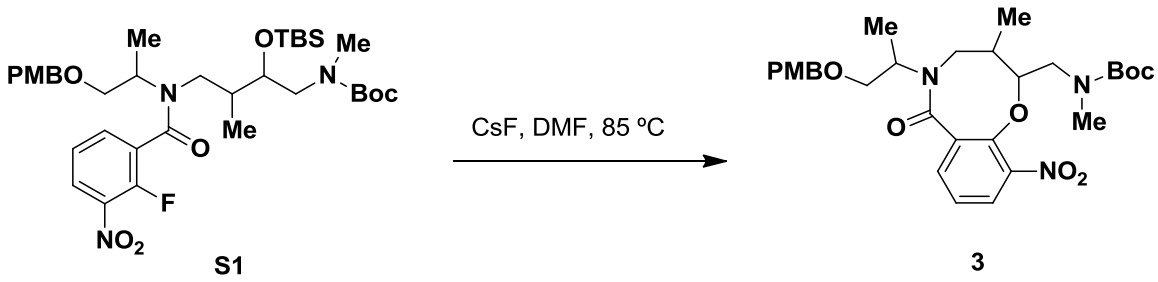
S_NAr Precursor, S1d

Following the general reaction protocol (2*S*,5*S*,6*S*)-**1d** (20.9 g, 39.8 mmol) was reacted with **2** (20.3 g, 100 mmol) and triethylamine (27.7 mL, 200 mmol), which provided pure product (2*S*,5*S*,6*S*)-**S1d** (23.3 g, 84%).

(2*S*,5*S*,6*S*)-**S1d**: $[\alpha]_D^{20}$ -49.8 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 2930, 1692, 1644, 1537, 1456, 1346, 1248, 1157. ^1H NMR (500 MHz, DMSO-d_6, 150 ºC) δ 8.11 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.63 (dd, *J* = 6.6, 6.6 Hz, 1H), 7.44 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 4.42 (s, 2H), 3.98-3.85 (m, 2H), 3.79 (s, 3H), 3.68-3.59 (m, 1H), 3.52-3.41 (m, 2H), 3.31-3.25 (m, 1H), 3.20-3.12 (m, 2H), 2.85 (s, 3H), 2.21-2.12 (m, 1H),

1.44 (s, 9H), 1.25 (br s, 3H), 0.97 (d,*J* = 6.5 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 150 ºC) δ 164.1, 158.5, 154.4, 149.5 (d, *J* = 254 Hz), 137.1 (d, *J* = 10 Hz), 133.4 (d, *J* = 5 Hz), 129.7, 128.0 (2C), 127.9 (d, *J* = 19 Hz), 125.2 (d, *J* = 3 Hz), 124.4 (d, *J* = 4 Hz), 113.3 (2C), 78.0, 72.4 71.4, 70.5, 54.5, 53.8, 51.1, 35.3, 34.7, 27.4 (3C), 24.9 (3C), 16.8, 14.6, 12.5, -5.5, -5.7 (1 carbon absent). HRMS (ESI) calcd for $C_{35}H_{55}FN_3O_8Si$ $[M + H]^+$: 692.3737. Found: 692.3739.

General Protocol for the S_NAr Cycloetherification:



S1 3

Cesium fluoride (3 equiv) was added to a solution of amide **S1** (1.0 equiv) in DMF (0.1 M) at room temperature under N_2. The reaction was heated to 85 ºC and stirred until complete consumption of starting material was observed (~5h). The reaction was cooled and the solvent was removed under reduced pressure. The resulting oil was dissolved in EtOAc, washed with a saturated NH_4Cl solution, dried over $MgSO_4$, filtered and concentrated to provide desired **3** in >95% purity. The material was used without further purification.

8-Membered Lactam, 3a

Following the general reaction protocol (2*S*,5*R*,6*S*)-**S1a** (28.0 g, 40.5 mmol) was reacted with cesium fluoride (12.2 g, 80.1 mmol) to yield product (2*S*,5*R*,6*S*)-**3a** (22.3 g, 99%).

(2*S*,5*R*,6*S*)-**3a**: $[\alpha]_D^{20}$ -12.0 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 2974, 1693, 1633, 1531, 1445, 1365, 1248, 1154. ^{1}H NMR (500 MHz, DMSO-d_6, 150 ºC) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.09 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 4.87 (dd, *J* = 6.0, 6.0 Hz, 1H), 4.54-4.48 (m, 1H), 4.49 (s, 2H), 3.80-3.76 (m, 1H), 3.78 (s, 3H), 3.58 (dd, *J* = 5.5, 10.2 Hz, 1H), 3.48 (dd, *J* = 4.5, 14.8 Hz, 1H), 3.43 (dd, *J* = 5.5, 15.5 Hz, 1H), 3.36 (dd, *J* = 7.4, 14.2 Hz, 1H), 3.08 (dd, *J* = 12.3, 15.0

Hz, 1H), 2.78 (s, 3H), 2.16-2.11 (m, 1H), 1.40 (s, 9H), 1.29 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 150 ºC) δ 166.7, 158.5, 154.1, 146.3, 140.7, 134.8, 129.9, 128.1, 124.6, 124.2, 119.4, 113.4, 78.4, 75.7, 71.4, 70.5, 54.6, 51.7, 50.0, 48.6, 34.3, 33.6, 27.3, 13.8, 9.1. HRMS (ESI) calcd for $C_{29}H_{39}N_3NaO_6$ $[M + Na]^+$: 580.2629. Found: 580.2626.

8-Membered Lactam, 3b

Following the general reaction protocol (2*R*,5*R*,6*S*)-**S1b** (18.5 g, 26.7 mmol) was reacted with cesium fluoride (12.2 g, 80 mmol) to yield product (2*R*,5*R*,6*S*)-**3b** (14.6 g, 98%).

(2*R*,5*R*,6*S*)-**3b**: $[\alpha]_D^{20}$ -23.9 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 2974, 1692, 1632, 1530, 1444, 1365, 1248, 1153. ^{1}H NMR (500 MHz, DMSO-d_6, 150 ºC) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.08 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.88 (dd, *J* = 6.0, 6.0 Hz, 1H), 4.72-4.67 (m, 1H), 4.46 (s, 2H), 3.78 (s, 3H), 3.69 (dd, *J* = 7.4, 10.0 Hz, 1H), 3.59 (dd, *J* = 5.5, 10.2 Hz, 1H), 3.53 (dd, *J* = 4.5, 14.8 Hz, 1H), 3.47 (dd, *J* = 5.5, 15.5 Hz, 1H), 3.33 (dd, *J* = 7.4, 14.2 Hz, 1H), 3.03 (dd, *J* = 12.3, 15.0 Hz, 1H), 2.82 (s, 3H), 2.14-2.07 (m, 1H), 1.41 (s, 9H), 1.27 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 150 ºC) δ 167.1, 158.5, 154.1, 146.1, 140.7, 134.7, 129.9, 128.1, 124.5, 124.3, 119.4, 113.3, 78.5, 75.6, 71.3, 70.3, 54.6, 50.2 (2C), 47.5, 34.6, 34.4, 27.3, 13.8, 9.2. HRMS (ESI) calcd for $C_{29}H_{39}N_3NaO_6$ $[M + Na]^+$: 580.2629. Found: 580.2633.

8-Membered Lactam, 3c

Following the general reaction protocol (2*S*,5*R*,6*R*)-**S1c** (27.8 g, 40.2 mmol) was reacted with cesium fluoride (18.3 g, 120.6 mmol) to yield product (2*S*,5*R*,6*R*)-**3c** (22.0 g, 98%).

(2*S*,5*R*,6*R*)-**3c**: $[\alpha]_D^{20}$ -52.1 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 2973, 1691, 1638, 1533, 1452, 1365, 1246, 1152. ^{1}H NMR (500 MHz, DMSO-d_6, 150 ºC) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.39 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.35-4.28 (m, 1H), 3.96-3.91 (m, 1H), 3.86 (dd, *J* = 7.3, 9.8 Hz, 1H), 3.79 (s, 3H), 3.66 (dd, *J* = 5.8, 10.2 Hz, 1H), 3.63 (dd, *J* = 5.0, 15.0 Hz, 1H), 3.50 (dd, *J* = 2.0, 15.0 Hz, 1H), 3.38 (dd, *J* = 10.0,

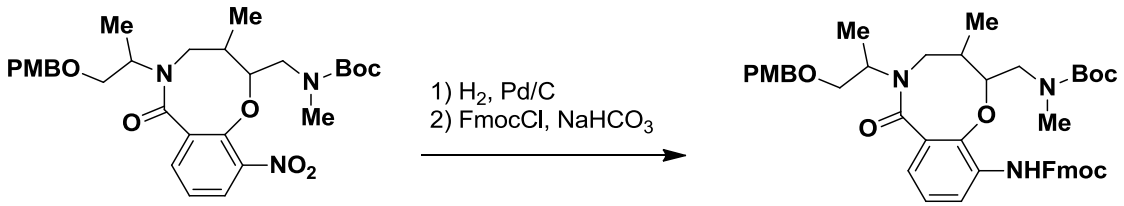
16.0 Hz, 1H), 3.15 (br d, *J* = 16.0 Hz, 1H), 2.89 (s, 3H), 2.18-2.12 (m, 1H), 1.47 (s, 9H), 1.34 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 150 ºC) δ 165.0, 158.5, 154.5, 146.6, 143.0, 133.7, 132.2, 130.0, 128.0, 125.4, 124.3, 113.3, 88.5, 78.2, 71.4, 71.0, 54.6, 52.4, 51.5, 50.4, 35.2, 34.4, 27.4, 15.2, 13.9. HRMS (ESI) calcd for $C_{29}H_{39}N_3NaO_6$ $[M + Na]^+$: 580.2629. Found: 580.2614.

8-Membered Lactam, 3d

Following the general reaction protocol (2*S*,5*S*,6*S*)-**S1d** (23.6 g, 34.1 mmol) was reacted with cesium fluoride (15.5 g, 102 mmol) to yield product (2*S*,5*S*,6*S*)-**3d** (18.4 g, 97%).

(2*S*,5*S*,6*S*)-**3d**: $[\alpha]_D^{20}$ +64.1 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 2973, 1692, 1637, 1533, 1453, 1365, 1246, 1153. ^{1}H NMR (500 MHz, DMSO-d_6, 150 ºC) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.38 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.45-4.30 (m, 1H), 3.96-3.91 (m, 1H), 3.80-3.75 (m, 1H), 3.78 (s, 3H), 3.67 (dd, *J* = 5.8, 10.2 Hz, 1H), 3.64 (dd, *J* = 5.0, 15.0 Hz, 1H), 3.50 (dd, *J* = 2.0, 15.0 Hz, 1H), 3.36 (dd, *J* = 10.0, 16.0 Hz, 1H), 3.19 (br d, *J* = 16.0 Hz, 1H), 2.89 (s, 3H), 2.19-2.13 (m, 1H), 1.46 (s, 9H), 1.37 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 150 ºC) δ 165.2, 158.5, 154.5, 146.5, 142.9, 133.6, 132.2, 130.0, 128.0, 125.4, 124.2, 113.3, 88.4, 78.2, 71.4, 70.3, 54.5, 51.6, 51.4, 49.7, 35.2, 35.0, 27.4, 15.1, 14.6. HRMS (ESI) calcd for $C_{29}H_{39}N_3NaO_6$ $[M + Na]^+$: 580.2629. Found: 580.2651.

Elaboration to Final Library Scaffold:



3 **S2**

Lactam **3** (1.0 equiv) and palladium (10% on activated carbon, 0.10 equiv) were stirred in EtOH (0.05 M) at 35 ºC under a hydrogen atmosphere. The reaction was monitored by LC-MS for complete consumption of starting material (1-2 h). After the reaction was

complete, the mixture was cooled, filtered through Celite and concentrated to give the desired aniline. This crude material was dissolved in dioxane (0.5 M) before 10% $NaHCO_3$ solution (15% by volume) was added. The mixture was cooled to 0 ºC and FmocCl (5 equiv) in minimal dioxane was added over 2-3 minutes. The mixture was stirred for 30 min at 0 ºC and then for an additional 1.5 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Flash chromatography on silica gel (0% to 5% MeOH in CH_2Cl_2) gave product **S2**.

Fmoc protected lactam, S2a

Following the general reaction protocol (2*S*,5*R*,6*S*)-**3a** (22.3 g, 40.0 mmol) was reacted with palladium (4.1 g, 4.0 mmol). Fmoc protection was carried out using FmocCl (47.8 g, 184.8 mmol) and a 10% $NaHCO_3$ solution which provided pure product (2*S*,5*R*,6*S*)-**S2a** (25.1 g, 84% over 2 steps).

(2*S*,5*R*,6*S*)-**S2a**: $[\alpha]_D^{20}$ -9.1 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 2973, 1732, 1708, 1631, 1528, 1514, 1365, 1231, 1151. ^1H NMR (500 MHz, DMSO-d_6, 130 ºC) δ 8.18 (s, 1H), 7.95 (d, J = 7.5 Hz, 2H), 7.88-7.78 (m, 3H), 7.50 (t, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.34 (d, J = 8 Hz, 2H), 7.16 (d, J = 8.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 2H), 6.96 (t, J = 7.5 Hz, 1H), 4.78 (d, J = 7.3 Hz, 1H), 4.69 (dd, J = 6.5, 12.7 Hz, 1H), 4.59-4.53 (m, 4H), 4.39 (t, *J* = 6.8 Hz, 1H), 3.86-3.81 (m, 5H), 3.63 (dd, *J* = 5.2, 10.3 Hz, 1H), 3.42 (dd, *J* = 5.8, 15.3 Hz, 1H), 3.29 (m, 1H), 3.20-3.07 (m, 1H), 2.81 (s, 3H), 2.21-2.05 (m, 1H), 1.47 (m, 9H), 1.33 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 130 ºC, reported as a mixture of rotomers) δ 169.3, 168.3, 158.5, 153.0, 143.3, 143.2, 142.3, 141.7, 140.3, 139.0, 137.0, 129.9, 128.5, 127.0, 124.5, 120.6, 119.4, 119.2, 114.2, 113.4, 108.2, 78.6, 78.4, 71.5, 71.3, 65.8, 54.7, 54.6, 50.3, 48.4, 46.4, 33.9, 27.5, 27.4, 9.7. HRMS (ESI) calcd for $C_{44}H_{52}N_3O_8$ $[M + H]^+$: 750.3749. Found: 750.3757.

Fmoc protected lactam, S2b

Following the general reaction protocol (2*R*,5*R*,6*S*)-**3b** (14.6 g, 26.2 mmol) was reacted with palladium (2.79 g, 2.62 mmol). Fmoc protection was carried out using FmocCl

(33.9 g, 131 mmol) and a 10% $NaHCO_3$ solution which provided pure product (2*R*,5*R*,6*S*)-**S2b** (19.3 g, 93% over 2 steps).

(2*R*,5*R*,6*S*)-**S2b**: $[\alpha]_D^{20}$ -23.5 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 2973, 1728, 1681, 1625, 1531, 1514, 1333, 1231, 1151. ^1H NMR (500 MHz, DMSO-d_6, 130 ºC) δ 7.95 (s, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.69 (m, 3H), 7.42 (t, *J* = 7.5Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2 Hz), 7.23 (d, *J* = 8.0Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.88 (m, 3H), 4.71 (m, 1H), 4.65-4.64 (m, 1H), 4.49-4.45 (m, 3H), 4.32 (t, *J* = 6.5Hz, 1H), 3.78 (s, 3H), 3.71-3.62 (m, 2H), 3.57 (dd, *J* = 10, 5.5 Hz, 1H), 3.37-3.34 (m, 2H), 3.04 (dd, *J* = 12.5, 12 Hz, 1H), 2.81-2.80(m, 4H), 2.05 (m, 1H), 1.40 (s, 9H), 1.26 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 130 ºC, reported as a mixture of rotomers) δ 169.8, 160.0, 159.2, 158.6, 156.0, 154.8, 154.4, 145.5, 144.6, 144.5, 141.6, 131.0, 129.6, 127.6, 127.8, 127.5, 125.7, 125.6, 123.4, 123.2, 122.7, 120.7, 120.6, 114.8, 79.9, 75.8, 72.7, 71.8, 67.1, 56.1, 51.8, 51.6, 49.2, 47.8, 35.9, 35.8, 28.9, 28.7, 15.5, 10.9. HRMS (ESI) calcd for $C_{44}H_{52}N_3O_8$ $[M + H]^+$: 750.3749. Found: 750.3737.

Fmoc protected lactam, S2c

Following the general reaction protocol (2*S*,5*R*,6*R*)-**3c** (23.3 g, 41.8 mmol) was reacted with palladium (4.3 g, 4.2 mmol). Fmoc protection was carried out using FmocCl (54.1 g, 209 mmol) and a 10% $NaHCO_3$ solution which provided pure product (2*S*,5*R*,6*R*)-**S2c** (20.5 g, 65% over 2 steps).

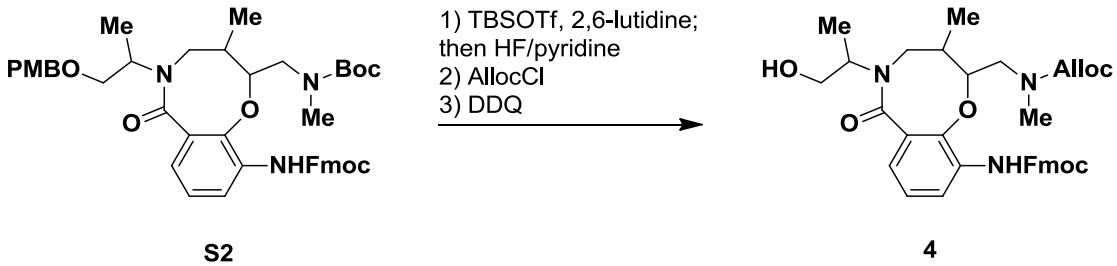
(2*S*,5*R*,6*R*)-**S2c**: $[\alpha]_D^{20}$ -71.7 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 2973, 1732, 1708, 1631, 1528, 1514, 1365, 1231, 1151. ^1H NMR (500 MHz, DMSO-d_6, 130 ºC) 7.84 (d, *J* = 7.5 Hz, 2H), 7.80 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.56 (d, *J* = 7 Hz, 1H), 4.61 (s, 2 H), 4.49 (dd, *J* = 12.0 Hz, 2 H), 4.40 (dd, *J* = 7.0, 6.5 Hz, 1 H), 3.80 (m, 4H), 3.65-3.62 (m, 3 H), 3.38 (dd, *J* = 10.5 Hz, 1H), 3.33 (dd, *J* = 10.0 Hz, 1H), 3.03 (d, *J* = 16 Hz, 1H), 2.97 (s, 3H), 2.82-2.81 (m, 1H), 1.99 (m, 1H), 1.46 (s, 9H), 1.29 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 6.5Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 130 ºC, reported as a mixture of rotomers) δ 169.1, 159.9, 156.1, 143.7, 142.2, 140.9, 140.4, 138.4, 132.6, 131.5, 129.5, 129.4, 127.8, 125.4, 121.8, 120.4, 118.0, 116.6, 114.8,

109.2, 84.4, 80.0, 72.8, 72.7, 72.0, 60.2, 56.0, 54.1 54.0, 52.7, 52.6, 51.4, 51.2, 37.2, 36.9, 28.9, 17.0, 15.4. HRMS (ESI) calcd for $C_{44}H_{52}N_3NaO_8$ $[M + Na]^+$: 772.3568. Found: 772.3593.

Fmoc protected lactam, S2d

Following the general reaction protocol (2*S*,5*S*,6*S*)-**3d** (4.4 g, 7.8 mmol) was reacted with palladium (0.83 g, 0.78 mmol). Fmoc protection was carried out using FmocCl (7.7 g, 31.4 mmol) and a 10% $NaHCO_3$ solution which provided pure product (2*S*,5*S*,6*S*)-**S2d** (5.8 g, 98% over 2 steps).

(2*S*,5*S*,6*S*)-**S2d**: $[\alpha]_D^{20}$ +39.7 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 2973, 1732, 1708, 1631, 1528, 1514, 1365, 1231, 1151. ^{1}H NMR (500 MHz, DMSO-d_6, 130 ºC) 7.83 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.33-7.29 (m, 3H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 8.5 hz, 2H), 6.91-6.86 (m, 3H), 6.83 (d, *J* = 8 Hz, 1H), 6.54 (d, *J* = 7.5 Hz, 1H), 4.45-4.31 (m, 5H), 3.78 (s, 3H), 3.75-3.71 (m, 1H), 3.66-3.62 (m, 3H), 3.41-3.36 (m, 2H), 3.05 (d, *J* = 16 Hz, 1H), 2.97 (s, 3H), 2.91 (s, 1H), 1.99-1.98 (m, 1H), 1.46 (s, 9H), 1.34 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 130 ºC, reported as a mixture of rotomers) δ 169.2, 159.9, 156.2, 143.8, 142, 2, 140.4, 140.3, 138.5, 132.7, 131.7, 129.6, 129.5, 127.8, 125.3, 121.8, 120.4, 118.0, 116.6, 114.9, 109.0, 84.5, 80.1, 72.9, 72.1, 56.1, 54.1, 52.5, 51.3, 37.2, 37.1, 28.9, 28.8, 16.9, 16.3. HRMS (ESI) calcd for $C_{44}H_{52}N_3NaO_8$ $[M + Na]^+$: 772.3568. Found: 772.3537.



S2 **4**

2,6-Lutidine (4.0 equiv) and TBSOTf (3.0 equiv) were added to a solution of **S2** (1.0 equiv) in CH_2Cl_2 (0.1 molar) at room temperature. The mixture was stirred for 2h before being quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined

organic extracts were dried over $MgSO_4$, filtered and concentrated to give the crude silyl carbamate. The resulting oil was dissolved in THF (0.1M) before HF·pyridine (70%, 1.0 equiv) was added. The mixture was stirred for 40 min, quenched with sat'd NH_4Cl solution and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The resulting oil was dissolved in CH_2Cl_2 (0.2M) and cooled to -78 ºC before triethylamine (5.0 equiv) (**NOTE:** In later experiments with different stereo- and regioisomers when the reaction proved to be sluggish, pyridine at 0 ^oC was found to be a suitable alternative.) and allyl chloroformate (1.0 equiv) were added. After 10 min, the mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Flash chromatography on silica gel (30% to 50% EtOAc in hexanes) gave the desired product.

The allyl carbamate (1.0 equiv) was then dissolved in CH_2Cl_2 (200 mL) and pH 7 buffer solution (15 mL). The mixture was cooled to 0 ºC and DDQ (5.66 g, 24.9 mmol, 1.5 equiv) was added. The mixture was stirred for 10 min at 0 ºC and an additional 1h at room temperature before being quenched with water and extracted with CH_2Cl_2. The combined organic extracts were washed with sat'd $NaHCO_3$ solution before activated carbon was added. The mixture was then filtered through Celite, and the filter cake was washed several times with hot CH_2Cl_2. The filtrate was concentrated and flash chromatography on silica gel (0% to 5% MeOH in CH_2Cl_2) gave pure **4**.

S_NAr 8-ortho Library Scaffold, 4a

Following the general reaction protocol (2*S*,5*R*,6*S*)-**S2a** (16.0 g, 21.4 mmol) was reacted with TBSOTf (14.7 mL, 64.1 mmol) and 2,6-lutidine (10.0 mL, 85.0 mmol) before exposure with HF/pyridine (2.8 mL, 21.4 mmol). Alloc protection was achieved with exposure to AllocCl (2.3 mL, 21.4 mmol) and triethylamine (14.8 mL, 107 mmol). The resulting product was reacted with DDQ (6.1 g, 26.8 mmol) to give product (2*S*,5*R*,6*S*)-**4a** (10.2 g, 78 % over 3 steps).

(2*S*,5*R*,6*S*)-**4a**: $[\alpha]_D^{20}$ -51.7 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 3327, 2974, 1727, 1692, 1611, 1531, 1436, 1220. ^1H NMR (500 MHz, DMSO-d_6, 150 ºC, 10:1 mixture of rotomers,

only major rotomer reported) δ 7.85 (d, *J* = 7.5 Hz, 3H), 7.71 (dd, *J* = 7.0, 7.0 Hz, 3H), 7.41 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.32 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.09 (dd, *J* = 1.5, 7.9 Hz, 1H), 6.87 (dd, *J* = 7.9, 7.9 Hz, 1H), 5.90 (ddq, *J* = 5.4, 5.4, 10.7 Hz, 1H), 5.22 (dd, *J* = 1.3, 17.3 Hz, 1H), 5.13 (d, *J* = 10.5 Hz, 1H), 4.88 (dd, *J* = 3.3, 7.7 Hz, 1H), 4.57-4.54 (m, 2H), 4.51-4.44 (m, 3H), 4.32 (dd, *J* = 7.0, 7.0 Hz, 1H), 4.26-4.21 (m, 1H), 3.82 (dd, *J* = 8.6, 14.5 Hz, 1H), 3.69 (dd, *J* = 7.7, 11.0 Hz, 1H), 3.61 (dd, *J* = 5.5, 11.0 Hz, 1H), 3.39 (dd, *J* = 3.7, 14.5 Hz, 1H), 3.35 (dd, *J* = 6.0, 15.5 Hz, 1H), 3.08 (dd, *J* = 12.4, 15.0 Hz, 1H), 2.90 (s, 3H), 2.20-2.14 (m, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-*d*$_6$, 150 ºC, as a mixture of rotomers) δ 168.3, 155.2, 152.8, 144.7, 143.13, 143.09, 140.2, 140.1, 132.6, 127.9, 126.7, 126.6, 126.5, 126.3, 126.1, 125.9, 124.2, 124.1, 121.5, 120.2, 119.1, 119.04, 119.02, 118.9, 118.5, 116.0, 114.2, 107.5, 74.2, 65.7, 64.6, 62.7, 53.1, 50.6, 48.2, 46.3, 33.9, 33.7, 13.4, 9.4. HRMS (ESI) calcd for $C_{35}H_{40}N_3O_7$ $[M + H]^+$: 614.2861. Found: 614.2858.

(2*R*,5*S*,6*R*)-***ent*-4a**: $[\alpha]_D^{20}$ +51.7 (*c* 1.0, $CHCl_3$).

S_NAr 8-ortho Library Scaffold, 4b

Following the general reaction protocol (2*R*,5*R*,6*S*)-**S2b** (14.0 g, 18.7 mmol) was reacted with TBSOTf (12.9 mL, 56.0 mmol) and 2,6-lutidine (8.7 mL, 74.7 mmol) before exposure with HF/pyridine (2.4 mL, 18.7 mmol). Alloc protection was achieved with exposure to AllocCl (2.0 mL, 18.7 mmol) and triethylamine (13.0 mL, 93.0 mmol). The resulting product was reacted with DDQ (5.8 g, 25.6 mmol) to give product (2*R*,5*R*,6*S*)-**4b** (9.9 g, 86% over 3 steps).

(2*R*,5*R*,6*S*)-**4b**: $[\alpha]_D^{20}$ -49.9 (*c* 1.0, $CHCl_3$). IR (cm^{-1}). ^{1}H NMR (500 MHz, DMSO-*d*$_6$, 150 ºC, 10:1 mixture of rotomers, only major rotomer reported) δ 7.85 (d, *J* = 7.5 Hz, 3H), 7.71 (dd, *J* = 7.0, 7.0 Hz, 3H), 7.41 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.32 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.09 (dd, *J* = 1.5, 7.9 Hz, 1H), 6.88 (dd, *J* = 7.9, 7.9 Hz, 1H), 5.90 (ddq, *J* = 5.4, 5.4, 10.7 Hz, 1H), 5.23 (dd, *J* = 1.3, 17.3 Hz, 1H), 5.14 (d, *J* = 10.5 Hz, 1H), 4.83 (dd, *J* = 3.3, 7.7 Hz, 1H), 4.58-4.54 (m, 2H), 4.52-4.48 (m, 2H), 4.36-4.31 (m, 2H), 4.20-4.17 (m, 1H), 3.77 (dd, *J* = 8.6, 14.5 Hz, 1H), 3.77-3.72 (m, 1H), 3.62-3.58 (m, 1H), 3.44 (dd, *J* = 3.7, 14.5 Hz, 1H), 3.39 (dd, *J* = 6.0, 15.5 Hz, 1H), 3.11 (dd, *J* = 12.4, 15.0 Hz, 1H), 2.90

(s, 3H), 2.16-2.10 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 150 ºC, as a mixture of rotomers) δ 168.3, 155.1, 152.8, 144.7, 143.13, 143.10, 140.2, 140.1, 137.0, 136.7, 132.6, 130.9, 127.9, 126.7, 126.6, 126.5, 126.1, 126.0, 124.13, 124.11, 121.6, 120.2, 119.5, 119.2, 119.04, 119.03, 118.9, 118.5, 116.11, 116.05, 114.2, 107.5, 74.1, 73.0, 65.7, 64.7, 64.6, 62.4, 62.2, 53.5, 53.1, 50.7, 50.6, 48.6, 46.4, 34.3, 34.2, 34.1, 13.69, 13.65, 9.40, 9.38. HRMS (ESI) calcd for $C_{35}H_{40}N_3O_7$ $[M + H]^+$: 614.2861. Found: 614.2840.

(2*S*,5*S*,6*R*)-***ent*-4b**: $[\alpha]_D^{20}$ +46.2 (*c* 1.0, $CHCl_3$).

S_NAr 8-ortho Library Scaffold, 4c

Following the general reaction protocol (2*S*,5*R*,6*R*)-**S2c** (19.5 g, 26.0 mmol) was reacted with TBSOTf (17.9 mL, 78.0 mmol) and 2,6-lutidine (12.1 mL, 104 mmol) before exposure with HF/pyridine (3.3 mL, 26.0 mmol). Alloc protection was achieved with exposure to AllocCl (8.3 mL, 78.0 mmol) and pyridine (10.4 mL, 104 mmol). The resulting product was reacted with DDQ (8.5 g, 37.6 mmol) to give product (2*S*,5*R*,6*R*)-**4c** (14.2 g, 89 % over 3 steps).

(2*S*,5*R*,6*R*)-**4c**: $[\alpha]_D^{20}$ -23.8 (*c* 1.0, $CHCl_3$). IR (cm^{-1}) 3350, 2968, 1701, 1618, 1529, 1450, 1229. ^{1}H NMR (500 MHz, DMSO-d_6, 150 ºC, as a 10:1 mixture of rotomers, only major rotomer reported) δ 8.04 (br s, 1H), 7.83 (d, *J* = 7.3 Hz, 2H), 7.66 (dd, *J* = 2.3, 7.3 Hz, 2H), 7.64 (dd, *J* = 2.3, 7.0 Hz, 1H), 7.40 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.30 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.15-7.11 (m, 2H), 5.93 (ddq, *J* = 5.4, 5.4, 10.7 Hz, 1H), 5.28 (d, *J* = 17.2 Hz, 1H), 5.17 (d, *J* = 10.5 Hz, 1H), 4.61-4.51 (m, 4H), 4.33 (dd, *J* = 6.4, 6.4 Hz, 1H), 4.23-4.13 (m, 2H), 3.79 (dd, *J* = 6.7, 10.5 Hz, 1H), 3.72-3.60 (m, 4H), 3.31 (dd, *J* = 10.0, 15.5 Hz, 1H), 3.11 (d, *J* = 15.5 Hz, 1H), 3.01 (s, 3H), 2.21-2.14 (m, 1H), 1.30 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, 150 ºC, as a mixture of rotomers) δ 167.7, 166.7, 155.7, 155.3, 153.0, 146.7, 143.1, 141.0, 140.2, 139.3, 139.0, 137.0, 132.7, 131.3, 131.2, 129.9, 128.0, 126.7, 126.3, 126.1, 125.8, 124.5, 124.1, 123.8, 123.6, 120.3, 119.1, 118.9, 116.7, 116.2, 116.1, 115.5, 107.5, 85.7, 82.9, 65.7, 64.8, 63.1, 63.0, 54.6, 54.2, 52.7, 51.6, 50.8, 50.5, 46.4, 35.7, 35.4, 34.8, 34.2, 15.4, 15.1, 13.5. HRMS (ESI) calcd for $C_{35}H_{40}N_3O_7$ $[M + H]^+$: 614.2861. Found: 614.2840.

(2*R*,5*S*,6*S*)-***ent*-4c**: $[\alpha]_D^{20}$ +22.5 (*c* 1.0, $CHCl_3$).

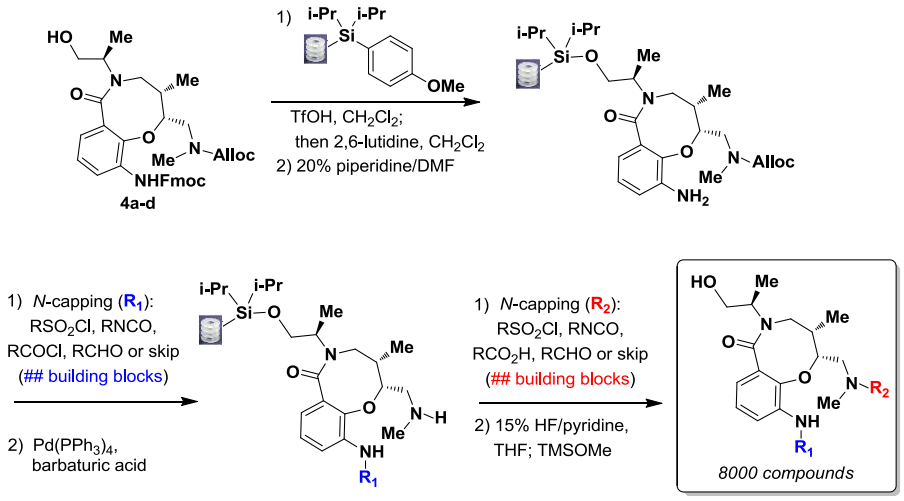
S_NAr 8-ortho Library Scaffold, 4d

Following the general reaction protocol (2*S*,5*S*,6*S*)-**S2d** (5.9 g, 7.8 mmol) was reacted with TBSOTf (5.4 mL, 23.5 mmol) and 2,6-lutidine (4.6 mL, 39.2 mmol) before exposure with HF/pyridine (1.0 mL, 7.8 mmol). Alloc protection was achieved with exposure to AllocCl (2.5 mL, 23.6 mmol) and pyridine (3.1 mL, 31.4 mmol). The resulting product was reacted with DDQ (2.0 g, 8.8 mmol) to give product (2*S*,5*S*,6*S*)-**4d** (3.6 g, 75 % over 3 steps).

(2*S*,5*S*,6*S*)-**4d**: $[\alpha]_D^{20}$ +36.1 (*c* 0.84, $CHCl_3$). IR (cm^{-1}) 3359, 2963, 1698, 1620, 1529, 1450, 1228. ^{1}H NMR (500 MHz, DMSO-d_6, 150 ºC, 2:1 mixture of rotomers) δ 8.03 (br s, 1H x 0.66), 7.83 (d, *J* = 7.5 Hz, 3H x 0.66), 7.78 (d, *J* = 7.5 Hz, 3H x 0.33), 7.66 (dd, *J* = 2.6, 7.5 Hz, 2H x 0.66), 7.63 (dd, *J* = 4.0, 5.6 Hz, 1H x 0.66), 7.40 (dd, *J* = 7.5, 7.5 Hz, 3H x 0.66), 7.33 (dd, *J* = 7.5, 7.5 Hz, 2H x 0.33), 7.31 (dd, *J* = 7.5, 7.5 Hz, 2H x 0.66), 7.13-7.11 (m, 1H), 6.90 (dd, *J* = 7.5, 7.5 Hz, 1H x 0.33), 6.83 (dd, *J* = 1.5, 8.0 Hz, 1H x 0.33), 6.57 (dd, *J* = 1.5, 7.5 Hz, 1H x 0.33), 6.00-5.89 (m, 1H), 5.30 (dd, *J* = 17.0, 23.0 Hz, 1H), 5.19 (dd, *J* = 10.7, 19.8 Hz, 1H), 4.62-4.50 (m, 4H), 4.33 (dd, *J* = 6.3, 6.3 Hz, 1H x 0.66), 4.26-4.20 (m, 1H), 4.15-4.05 (m, 1H), 3.74-3.60 (m, 5H), 3.56 (dd, *J* = 6.7, 14.0 Hz, 1H x 0.33), 3.40 (dd, *J* = 10.2, 15.8 Hz, 1H x 0.33), 3.31 (dd, *J* = 10.2, 15.8 Hz, 1H x 0.66), 3.17 (dd, *J* = 1.5, 15.5 Hz, 1H x 0.66), 3.11 (dd, *J* = 1.5, 15.5 Hz, 1H x 0.33), 3.07 (s, 3H x 0.33), 3.00 (s, 3H x 0.66), 2.16-2.10 (m, 1H x 0.66), 2.08-2.01 (m, 1H x 0.33), 1.33 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H x 0.33), 0.84 (d, *J* = 6.7 Hz, 3H x 0.66). ^{13}C NMR (125 MHz, DMSO-d_6, 150 ºC, as a mixture of rotomers) δ 167.7, 155.3, 153.0, 143.1, 140.8, 140.2, 139.2, 138.9, 137.0, 132.6, 131.2, 127.9, 126.7, 126.3, 126.13, 126.08, 125.8, 124.4, 124.07, 124.05, 123.8, 123.5, 123.4, 120.2, 119.0, 118.9, 118.7, 116.5, 116.2, 116.1, 115.3, 107.5, 85.6, 82.9, 65.7, 64.7, 62.5, 62.4, 53.7, 53.5, 52.6, 51.5, 50.1, 50.0, 46.3, 35.6, 35.5, 35.4, 35.0, 34.7, 15.3, 15.0, 14.2. HRMS (ESI) calcd for $C_{35}H_{40}N_3O_7$ $[M + H]^+$: 614.2861. Found: 614.2873.

(2*R*,5*R*,6*R*)-***ent*-4d**: $[\alpha]_D^{20}$ -32.5 (*c* 1.0, $CHCl_3$).

Solid-Phase Library Synthesis:



General Methods: Solid-phase synthesis was conducted on silicon-functionalized polystyrene SynPhase™ Lanterns (L-series) equipped with radio frequency transponders (TranStems) for AccuTag directed sorting and compound tracking. Quality-control Lanterns were included at each synthesis step for reaction monitoring by UPLC (UV 210 nM) after HF-cleavage. All reactions were conducted in heavy wall pressure vessels from ChemGlass with agitation in New Brunswick Scientific incubator shakers.

Scaffold loading: To a flame-dried flask containing silicon-functionalized Lanterns was added a freshly prepared solution of TfOH in anhydrous DCM (9.0 equiv, 5 g of TfOH/100 mL of DCM) was added. Each flask was shaken at RT for 10 min at which time the Lanterns had turned bright orange. The deep red TfOH solution was removed via cannula and anhydrous 2,6-lutidine (12.0 equiv relative to Si) was added. Once the Lantern color had changed from orange to white, the scaffold (1.2 equiv. relative to Si) was added as a solution in anhydrous DCM (0.4 mL/Lantern) and the reaction mixture was shaken for 48h overnight. The loading mixture was removed and set aside (to recover any unreacted alcohol) and the Lanterns were washed with the following solvents for 30 min intervals: DCM, THF, 3:1 THF/IPA, 3:1 THF/H_2O, DMF, 3:1 THF/H_2O, 3:1 THF/IPA, THF, DCM. The Lanterns were then dried on a lyophilizer overnight prior to sorting. All 8 stereoisomers of **1** and **2** were loaded via the same protocol.

Fmoc removal: To a flask containing Lanterns was added a solution of 20% piperidine

in DMF (0.8mL/Lantern). After shaking at rt for 30 min, the piperidine solution was removed and the Lanterns were washed with the following solvents for 30 min intervals: DMF, 3:1 THF/H_2O, 3:1 THF/IPA, THF, DCM. The Lanterns were then dried on a lyophilizer overnight prior to sorting.

***N*-Capping/Sulfonyl Chlorides:** To each flask containing Lanterns was added DCM (0.8 mL/Lantern) followed by 2,6-lutidine (20 equiv) and the desired sulfonyl chloride (35 equiv). The Lanterns were shaken at rt overnight and then washed with following solvents for 30 min intervals: DCM, DMF, 3:1 THF/H_2O, 3:1 THF/IPA, THF, DCM. The Lanterns were then dried on a lyophilizer overnight prior to sorting.

***N*-Capping/Isocyanates:** To each flask containing Lanterns was added DCM (0.8 mL/Lantern) followed the desired isocyanate (15 equiv). The Lanterns were shaken at rt overnight and then washed with following solvents for 30 min intervals: DCM, DMF, 3:1 THF/ H_2O, 3:1 THF/IPA, THF, DCM. The Lanterns were then dried on a lyophilizer overnight prior to sorting.

***N*-Capping/Acids:** To each flask containing Lanterns was added DCM (0.8mL/Lantern) followed by triethylamine (30 equiv) and the desired acid (20 equiv). PyBOP (20 equiv) was added and the Lanterns were shaken at rt overnight and then washed with following solvents for 30 min intervals: DCM, DMF, 3:1 THF/H_2O, 3:1 THF/IPA, THF, DCM. The Lanterns were then dried on a lyophilizer overnight prior to sorting

***N*-Capping/Aldehydes:** To each flask containing Lanterns was added DMF with 2% AcOH (0.800 mL/Lantern) followed by the desired aldehyde (20 equiv). The reaction mixture was shaken at rt for 1 hr then sodium triacetoxyborohydride (20 equiv) was added and shaking was continued. After 3 days the reaction mixture was removed and

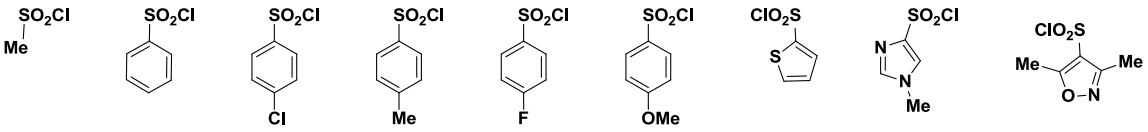
the Lanterns were washed with the following solvents for 30 min intervals: DMF, 3:1 THF/H_2O, 3:1 THF/IPA, THF, DCM. The Lanterns were then dried on a lyophilizer overnight prior to sorting.

Alloc removal: To the reaction vessel containing Lanterns, THF (0.8 mL/Lantern) was added, followed by $Pd(PPh_3)_4$ (1 equiv) and 1,3-dimethylbarbituric acid (30 equiv). The flask was sealed and shaken at rt for 1 day. The reaction mixture was removed and the Lanterns were washed with DMF until the washings were clear (without any yellow color). Subsequently the Lanterns were washed with the following solvents for 30 min intervals: 3:1 THF/H_2O, 3:1 THF/IPA, THF, DCM. The Lanterns were then dried on a lyophilizer overnight prior to sorting.

Cleavage Protocol: To a 96-well plate containing Lanterns was added a 15% solution of HF/pyridine in stabilized THF (350 μL/Lantern). After 2 h the cleavage solution was quenched with TMSOMe (700 μL/Lantern) and the contents of each well were transferred to a pre-weighed 2-mL vial. The Lanterns were washed with an additional 200 μL of stabilized THF (or THF/MeOH) and the solution was transferred to the 2-mL vial. The samples were concentrated on a Genevac® solvent evaporation system overnight without heating. Loading masses for each alcohol was determined on a FlexiWeigh® system.

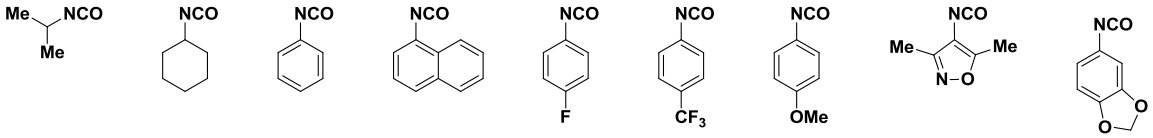
Complete List of Building Blocks:

Sulfonyl Chlorides



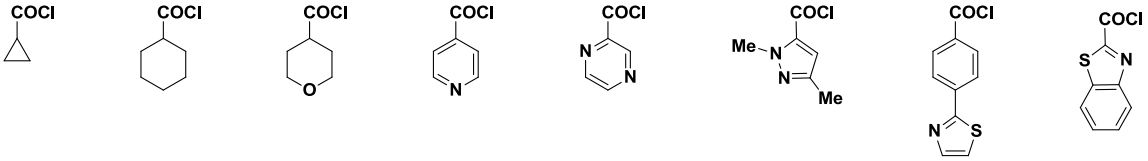
SC1 *SC2* *SC3* *SC4* *SC5* *SC6* *SC7* *SC8* *SC9*

Isocyanates



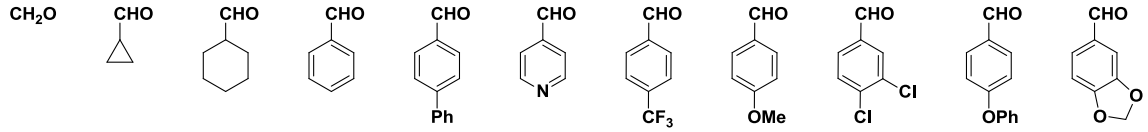
IS1 *IS2* *IS3* *IS4* *IS5* *IS6* *IS7* *IS8* *IS9*

Carboxylic Acid Chlorides



AC1 *AC2* *AC3* *AC4* *AC5* *AC6* *AC7* *AC8*

Aldehydes



AL1 *AL2* *AL3* *AL4* *AL5* *AL6* *AL7* *AL8* *AL9* *AL10* *AL11*

Skip

QC Analysis:

Compound purity and identity were determined by UPLC-MS (Waters, Milford, MA). Purity was measured by UV absorbance at 210 nm. Identity was determined on a SQ mass spectrometer by positive electrospray ionization. Mobile phase A consisted of either 0.01% ammonium hydroxide or 0.01% formic acid in water, while mobile phase B consisted of the same additives in acetonitrile. The gradient ran from 5% to 95% mobile phase B over 0.8 minutes at 0.45 mL/min. An Acquity BEH C18, 1.7 um, 1.0x50 mm column was used with column temperature maintained at 65 ^{o}C. Compounds were dissolved in DMSO at a nominal concentration of 1 mg/mL, and 0.25 uL of this solution was injected.

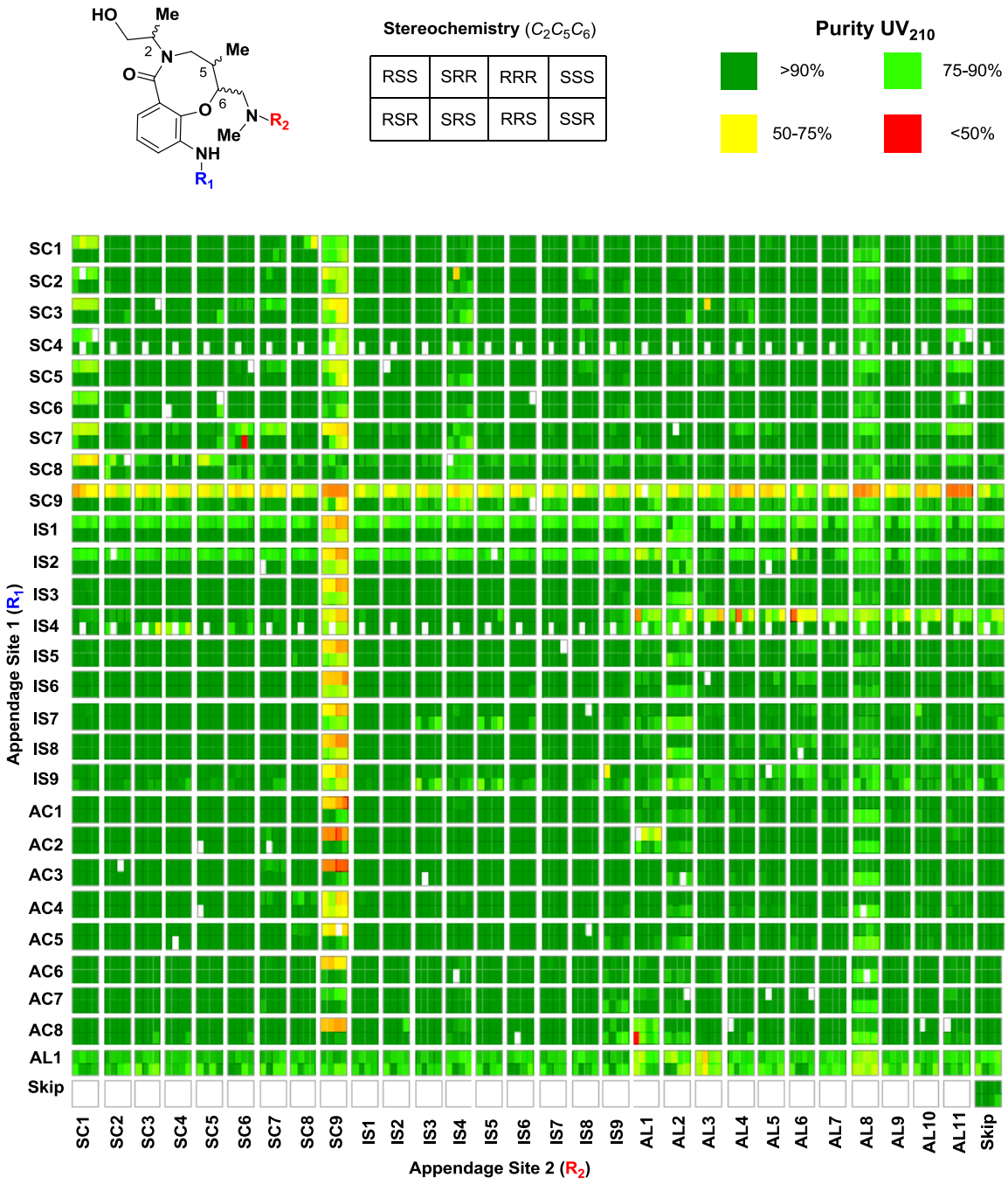


Figure S-1. S_NAr 8-*ortho* library purity analysis.

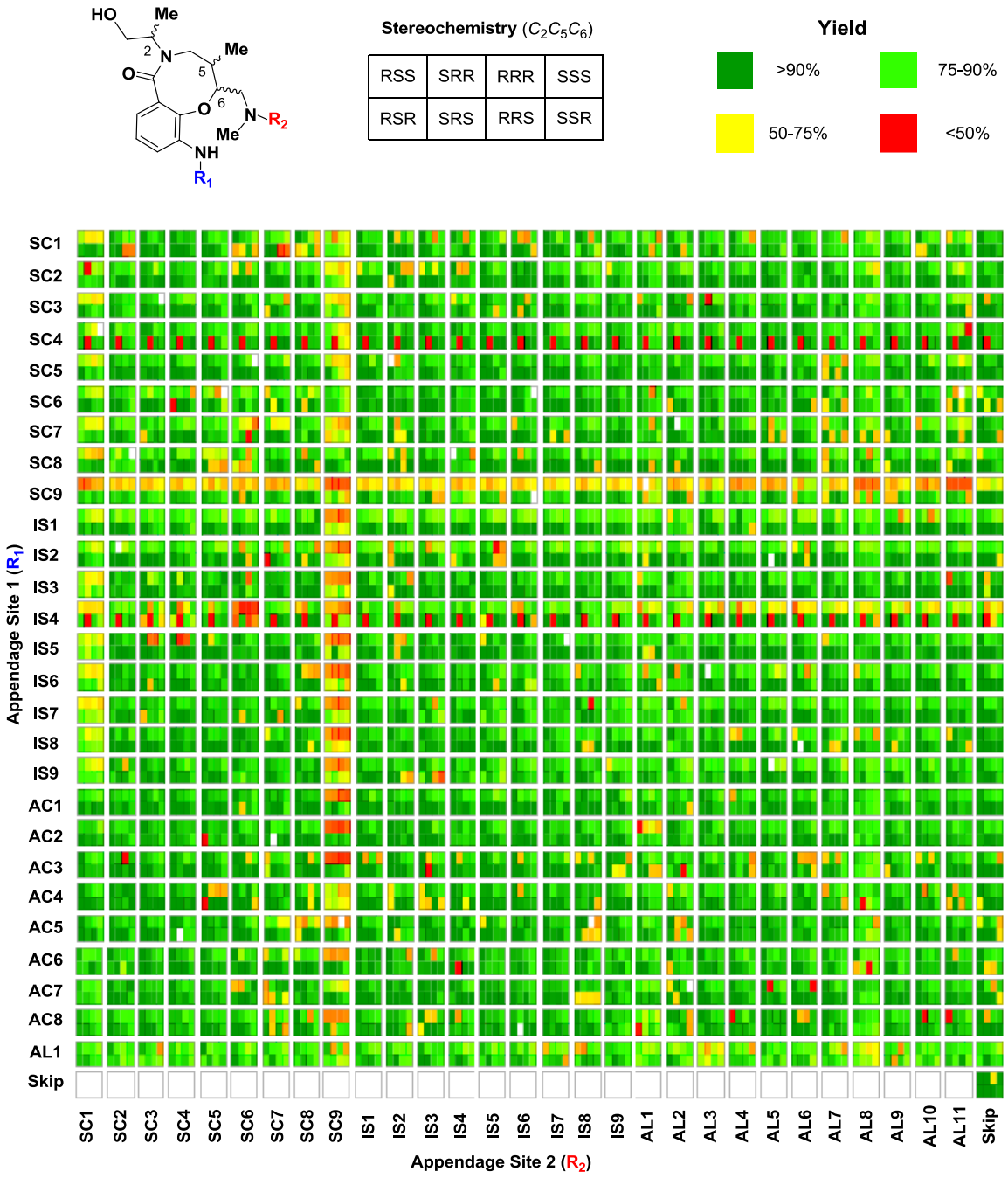
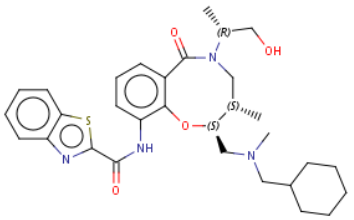
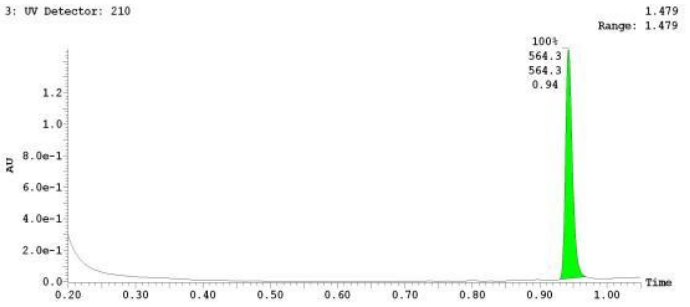
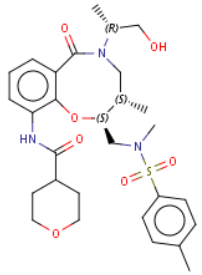


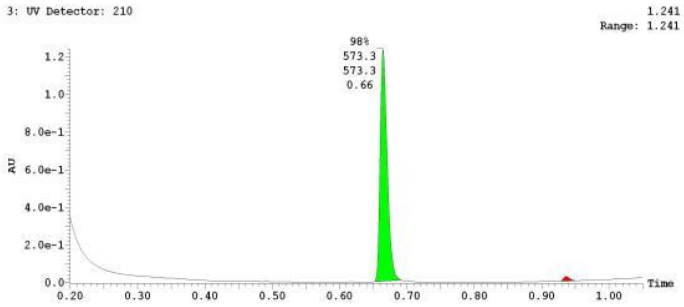
Figure S-2. S_NAr 8-*ortho* library yield analysis. Percent yield was calculated assuming a theoretical loading level of 15 umol. Yields were adjusted by purity as measured by UPLC.

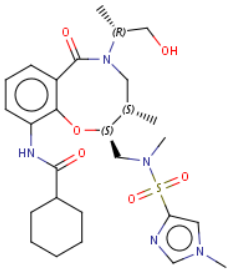
Selected Examples of Library UPLC traces:

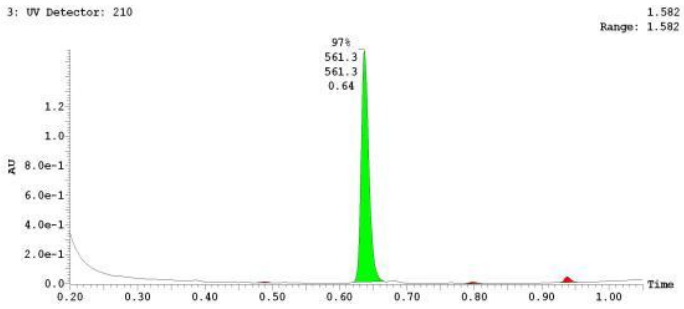


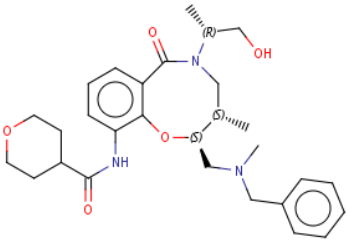


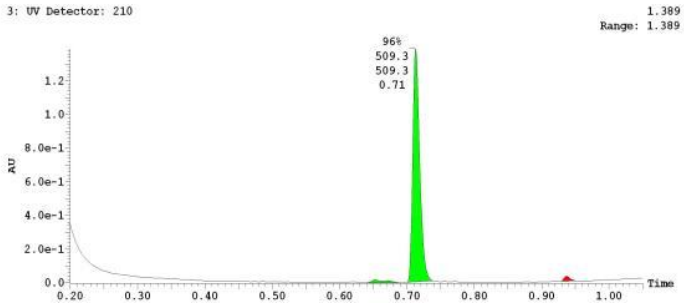


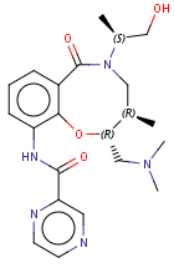


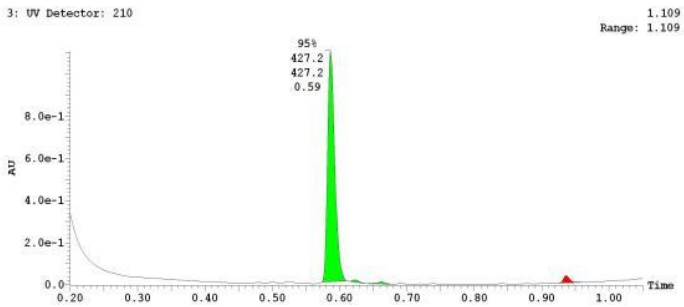


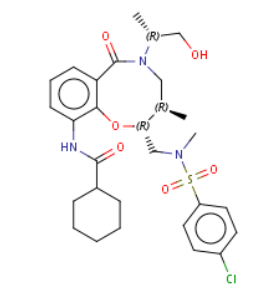


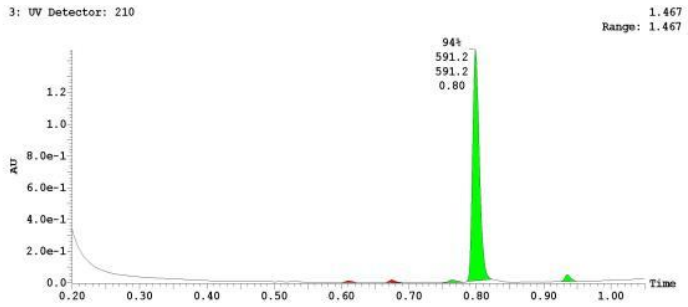








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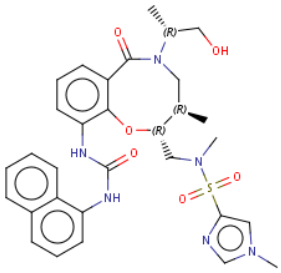
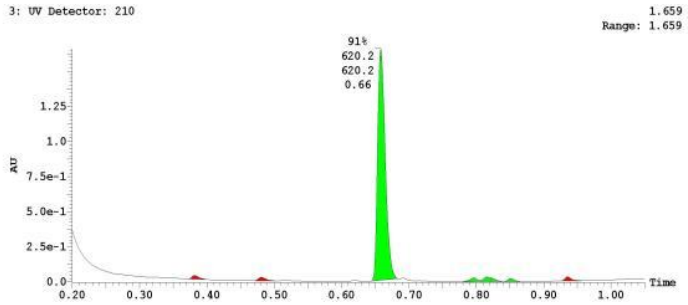
591.2
0.80
AU
Time

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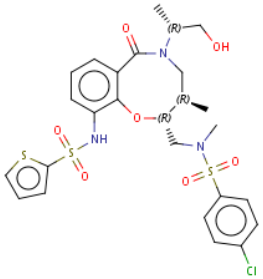
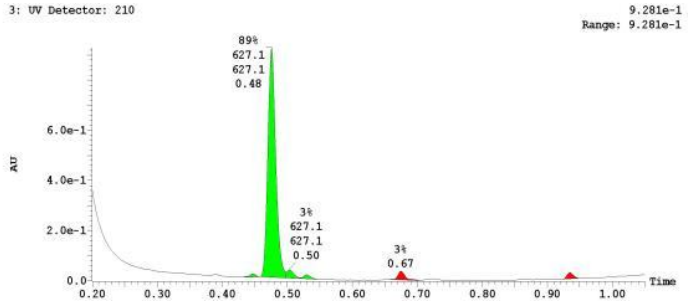
AU
Time

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627.1
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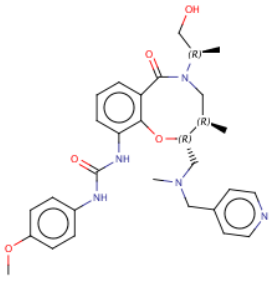
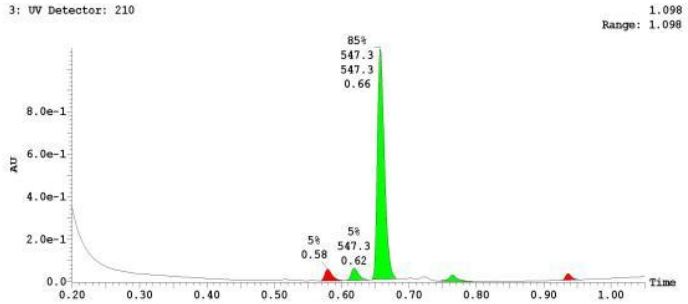
Time

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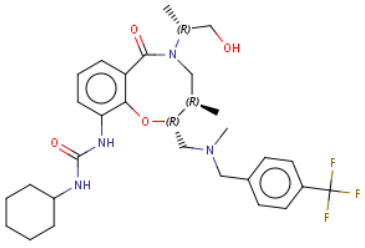
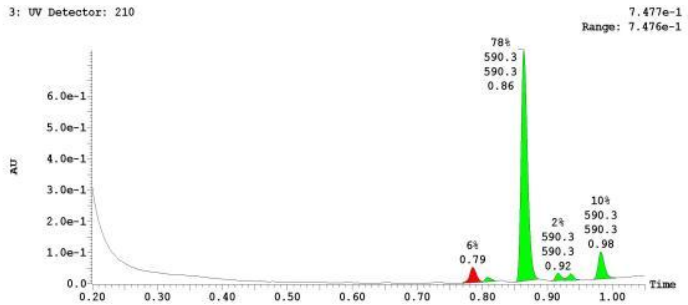
0.66
5%
0.58
5%
547.3
0.62
AU
Time

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Range: 7.476e-1
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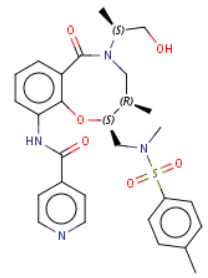
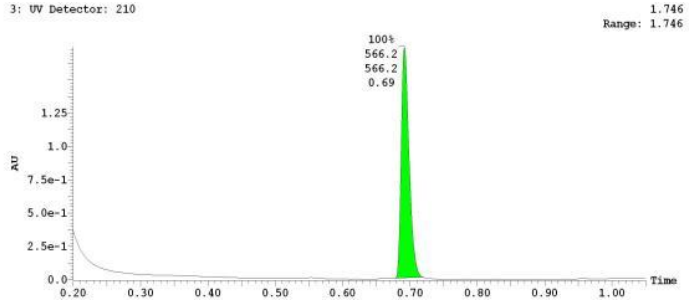
590.3
590.3
0.86
6%
0.79
2%
590.3
590.3
0.92
10%
590.3
590.3
0.98
AU
Time

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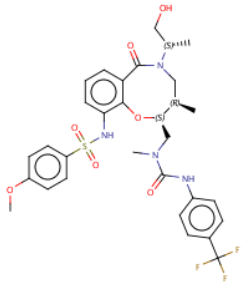
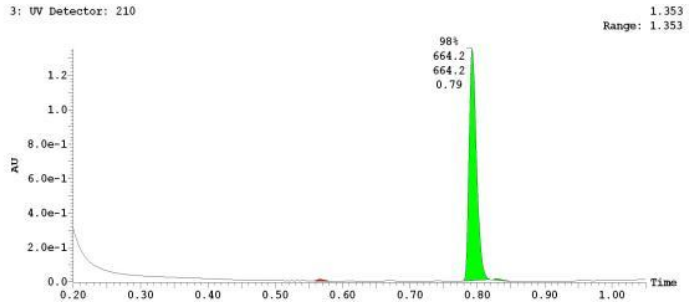
AU
Time

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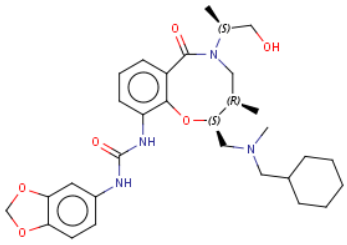
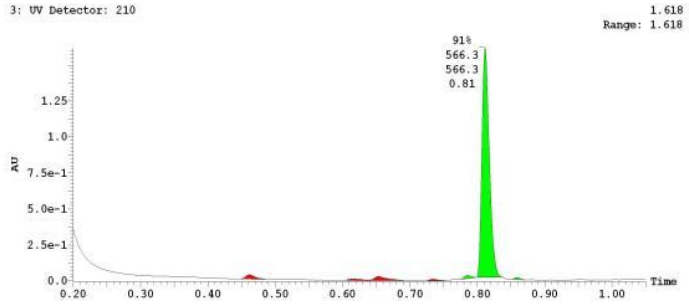
Time

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0.81
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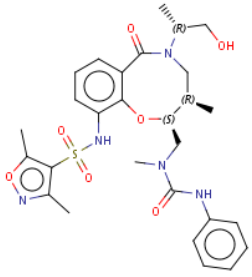
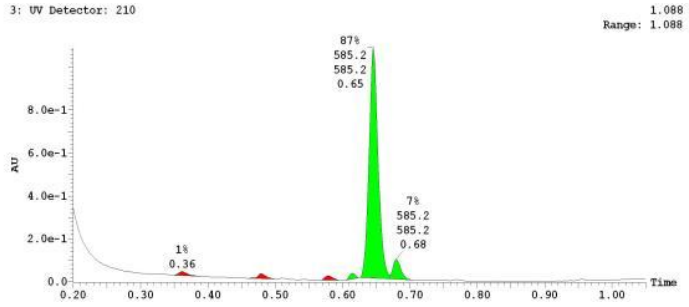
Time

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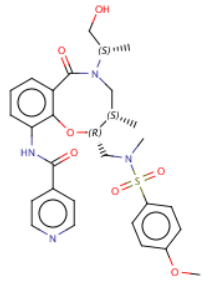
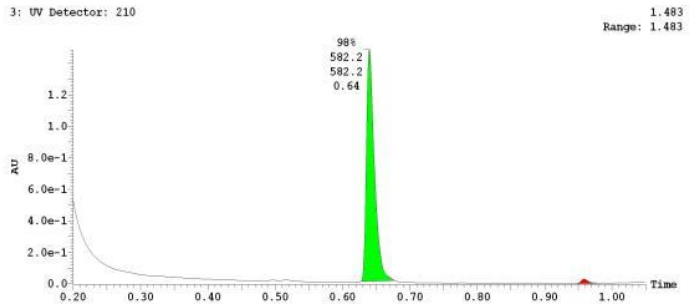
0.36
AU
Time

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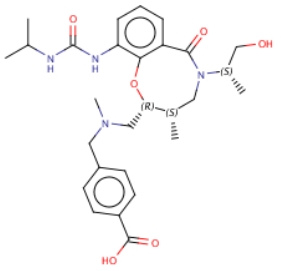
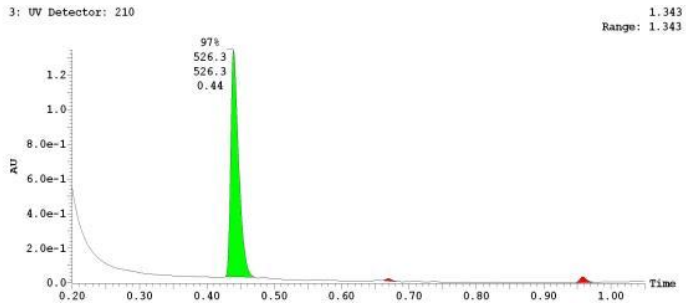
0.64
AU
Time

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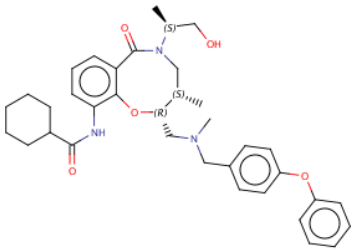
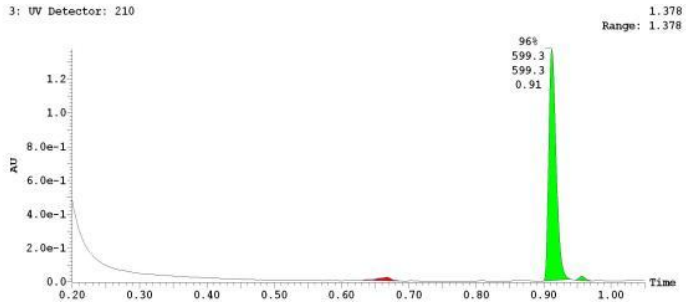
526.3
526.3
0.44
AU
Time

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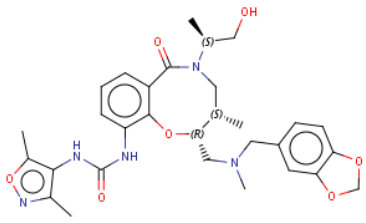
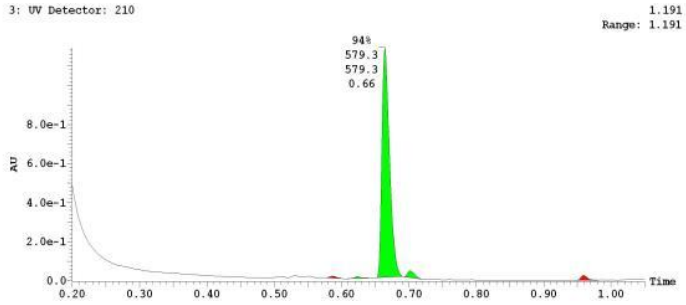
599.3
599.3
0.91
AU
Time

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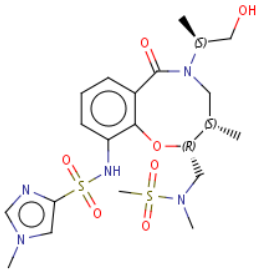
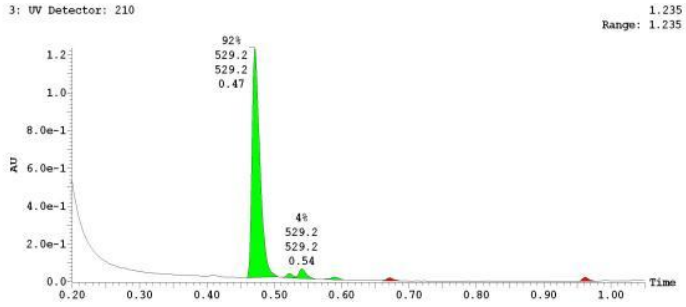
579.3
579.3
0.66
AU
Time

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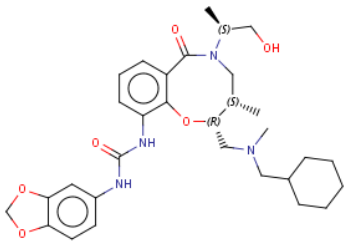
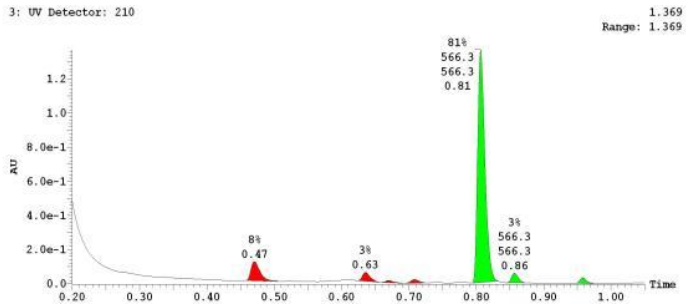
0.47
4%
529.2
529.2
0.54
AU
Time




3: UV Detector: 210
1.369
Range: 1.369
81%
566.3
566.3
0.81
8%
0.47
3%
0.63
3%
566.3
566.3
0.86
AU
Time

Cell Culture and Reagents

INS-1E cells (generously provided by C. Wollheim and P. Maechler, University of Geneva) were maintained in RPMI 1640 containing 11 mM glucose, 10% fetal bovine serum, 10 mM HEPES, 50 μM 2-mercaptoethanol, 1 mM sodium pyruvate, cultivated at 37 °C with 5% CO_2 in a humidified atmosphere, and split every week. Recombinant rat IL-1β and recombinant mouse TNF-α were purchased from R&D Systems. Recombinant mouse IFN-γ and Griess reagent were purchased from Sigma. CellTiter-Glo and Caspase-Glo 3/7 reagents were purchased from Promega. JC-1 was purchased from Invitrogen.

High-Throughput Screening for Compounds Affecting Cellular ATP Levels

INS-1E cells were seeded at 10,000 cells per well using a Multidrop Combi (Thermo Labsystems) in white optical 384-well plates (Corning Life Sciences). After overnight incubation, medium was removed and 50 μL of RPMI containing 1% FBS and a combination of cytokines (10 ng mL^{-1}IL-1β, 50 ng mL^{-1} IFN-γ, 25 ng mL^{-1} TNF-α) was added to every well. Using libraries of compounds dissolved in DMSO and a CyBi-Well pin-transfer robot (CyBio Corp.), 0.1 μL of each compound was added. After 48 h, medium was removed and 20 μL of CellTiter-Glo reagent was added. Luminescence was measured after 10 min of incubation using an EnVision plate reader (PerkinElmer).

Measurement of Cellular Nitrite Production

INS-1E cells were seeded and treated as described for high-throughput screening. After treatment with cytokine and compounds for 48 h, 10 μL of modified Griess reagent (1:1 mixture of 1% sulfanilamide in 30% acetic acid and 0.1% *N*-(1-naphthyl) ethylenediamine dihydrochloride in 60% acetic acid) was added to each well. After 5 min of incubation at RT, the absorbance at 540 nm was measured using an EnVision plate reader.

Caspase-3 Activity Assay

INS-1E cells were seeded at 5,000 cells per well in white optical 384-well plates and treated as described for high-throughput screening. After treatment with cytokines and

compounds for 48 h, medium was removed and 20 μL Caspase-Glo 3/7 reagent was added. Luminescence was measured after 2 h of incubation using an EnVision plate reader.

Glucose-Stimulated Insulin Secretion

INS-1E cells were seeded in 96-well plates at 20,000 cells per well and incubated for 48 h in 100 μL of fresh RPMI containing 1% FBS and the cytokine cocktail, in the presence or absence of compounds. Cells were washed and incubated for 2 h in KRBH (135 mM NaCl, 3.6 mM KCl, 5 mM $NaHCO_3$, 0.5 mM NaH_2PO_4, 0.5 mM $MgCl_2$, 1.5 mM $CaCl_2$, 10 mM HEPES, pH 7.4, 0.1% BSA) without glucose. Cells were subsequently incubated with KRBH containing 2 or 15 mM glucose for 1 h. The supernatant was taken for measurement of released insulin, and 100 μL of acidified ethanol was added to each well for extraction and measurement of cellular insulin content. Insulin was measured with a rat insulin ELISA kit (Alpco).

Measurement of Mitochondrial Membrane Potential.

INS-1E cells were seeded and treated as described for high-throughput screening. After treatment with cytokine and compounds for 48 h, 20 μL per well of 3.25 μM JC-1 in phenol-red media was added. After 2 hours of incubation at 37°C, cells were washed three times with 50 μL per well of PBS. Fluorescence was measured with an Envision plate reader (Perkin-Elmer) at the rhodamine spectra (excitation/emission 530 nm/580 nm) followed by fluorescein (excitation/emission 485nm/530nm). The ratio of rhodamine to fluorescein intensity was determined and represents the degree of mitochondrial membrane potential.

Characterization of Active Compounds

***N*-(((2*R*,3*R*)-5-((*S*)-1-Hydroxypropan-2-yl)-3-methyl-10-(3-(naphthalen-1-yl)ureido)-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)-4-methoxy-Nmethylbenzenesulfonamide, 5**

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.0 Hz, 1H), 8.17 (dd, *J* = 7.5, 18.1 Hz, 2H), 7.85 (d, *J* = 7.0 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 3H), 7.57-7.41 (m, 3H), 7.13 (dd, *J* = 7.2,

16.3 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.15 (s, 1H), 3.81 (d, *J* = 21.9 Hz, 7H), 3.55 (d, *J* = 10.7 Hz, 1H), 3.24 (s, 2H), 3.03 (d, *J* = 15.3 Hz, 1H), 2.92 (s, 3H), 2.06 (s, 1H), 1.40 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 163.8, 153.9, 142.8, 134.4, 133.3, 132.5, 131.1, 130.1, 129.2, 128.3, 126.2, 126.0, 125.9, 125.6, 123.0, 122.7, 122.5, 121.9, 114.7, 85.2, 65.2, 56.1, 55.9, 55.7, 51.9, 38.7, 35.2, 16.8, 14.4. HRMS (ESI) calcd for $C_{34}H_{38}N_4O_7S$ $[M + H]^+$: 647.2534, found: 647.2532.

_N_-(((2_R_,3_R_)-5-((_S_)-1-Hydroxypropan-2-yl)-3-methyl-10-(3-(naphthalen-1-yl)ureido)-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)-_N_-methyl-2,3-dihydrobenzo-[b][1,4]dioxine-6-sulfonamide, 13.

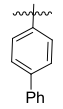
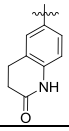
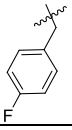
$[\alpha]_D^{20}$ -14.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.45 (d, *J* = 8.3 Hz, 1H), 8.23-8.07 (m, 3H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.69 (dd, *J* = 7.8, 14.5 Hz, 2H), 7.57-7.41 (m, 3H), 7.26 (t, *J* = 10.1 Hz, 2H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 6.6 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 4.28 (dd, *J* = 4.6, 16.9 Hz, 4H), 4.15 (s, 1H), 3.88 (d, *J* = 8.7 Hz, 1H), 3.83-3.68 (m, 2H), 3.58 (dd, *J* = 10.9, 15.6 Hz, 1H), 3.25 (s, 2H), 3.03 (d, *J* = 15.4 Hz, 1H), 2.94 (s, 3H), 2.07 (d, *J* = 7.1 Hz, 1H), 1.41 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 153.8, 148.3, 143.9, 142.7, 134.3, 133.2, 132.4, 130.9, 129.1, 128.2, 126.9, 126.0, 125.9, 125.9, 125.5, 122.9, 122.6, 121.8, 121.7, 118.1, 117.4, 85.1, 77.2, 76.9, 76.7, 65.2, 64.5, 64.1, 56.1, 55.9, 51.8, 38.8, 35.1, 16.8, 14.4. HRMS (ESI) calcd for $C_{35}H_{38}N_4O_8S$ $[M + H]^+$: 675.2483, found: 675.2491.

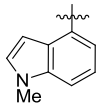
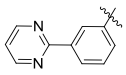
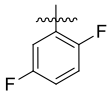
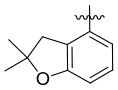
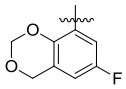
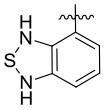
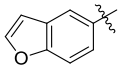
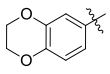
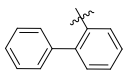
N-(((2R,3R)-5-isopropyl-3-methyl-10-(3-(naphthalen-1-yl)ureido)-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)-4-methoxy-N-methylbenzenesulfonamide, 16.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.0 Hz, 1H), 8.25 (dd, *J* = 7.5, 18.1 Hz, 3H), 7.85 (d, *J* = 7.0 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 4H), 7.57-7.41 (m, 3H), 7.13 (m, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.75 (m, 1H), 3.83 (m, 4H), 3.30 (m, 4H), 3.03 (m, 5H), 1.95 (s, 2H), 1.30 (m, 4H), 0.88 (m, 4H). LRMS calcd for $C_{34}H_{38}N_4O_6S$ $[M + H]^+$: 631.25, found: 631.24.

Table S1. Complete EC_{50} values and maximum activity for all synthesized analogs.

Entry	Structure			Cellular activity	
	R1	R2	R3	**EC_{50} (μM)**	**Maximum Activity (%)**
1	OH			4.89±2.41	62
2	OH			0.78±0.45	99
3	OH			3.48±1.40	76
4	OH			>20	0
5	OH			>20	0
6	OH			>20	0
7	OH			>20	0
8	OH			>20	0
9	OH			>20	0

10	OH			>20	0
11	OH			>20	0
12	OH			>20	0
13	OH			>20	0
14	OH			>20	0
15	OH			>20	0
16	OH			>20	0
17	OH			>20	0
18	OH			>20	0
19	OH			>20	0
20	OH			>20	0
21	OH			>20	0
22	OH			>20	0

23	OH			>20	0
24	OH			>20	0
25	OH			>20	0
26	OH			>20	0
27	OH			>20	0
28	OH			>20	0
29	OH			>20	0
30	OH			>20	0
31	OH			>20	0
32	OH			>20	0
33	OH			>20	0
34	OH			>20	0
35	H			3.06±1.41	76

36	H			2.79±1.73	89