**Supplementary File 1**

***Synthesis of novel CypI***

CsA-Prtc1 synthesis



**General Method A (metathesis)**

To a solution of Cyclosporin A (72 mg, 0.06 mmol) in DCM (2 mL) was added the olefin (0.072 mmol) and Hoveyda-Grubbs 2nd generation catalyst (6 mg, 0.01 mmol, 17mol%). The reaction was stirred in the microwave at 90oC for 30 minutes and then allowed to cool. Triethylamine was added to the mixture and then stirred overnight with excess P(CH2OH)3 to coordinate the ruthenium catalyst. This was then washed away with brine and water before the mixture was passed through a Stratospheres PL Thiol MP SPE cartridge (polymer Lab, Varian Inc) to remove any remaining catalyst. The crude product was purified by chromatography (as detailed) to give the product*.*

**(2*S*,4*R*)-1-((*S*)-2-(hept-6-enamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (JW4-7)**

To a solution of E3 ligase ligand 1 (0.072 g, 0.169 mmol) in MeCN were added 6-heptenoic acid (25 µL, 0.186 mmol), HATU (0.071 g, 0.186 mmol) and N,N-diisopropylethylamine (59 µL, 0.338 mmol) and this mixture was stirred at room temperature overnight. The mixture was then purified by column chromatography with 30-50% MeOH in DCM, and then re-purified with 25-35% MeOH in DCM.

The productwas isolatedas a pale yellow solid (46 mg, 49% yield).

1H NMR (700MHz, CDCl3) δ 8.81 (s, C=N, 1H), 3.39 (s, NMe, 3H), 8.20 (d, NH, 1H), 7.62 (d, NH, 1H), 7.29 (d, 2H), 7.19 (d, 2H), 5.59 (m, alkene, 3H), 4.95 (s, OH, 1H), 4.82 (q, 1H), 4.79 (q, 1H), 4.33 (d, 1H), 4.24 (t, 1H), 4.04 (sext, 1H), 2.32 (t, 3H), 2.26 (s, 3H), 2.07 (m, 1H), 2.01 (t, 1H), 1.93 (m, 1H), 1.83 (m, 2H), 1.60 (m, 1H), 1.30 (m, 2H), 1.15 (m, 2H), 0.75 (s, 9H).

13C NMR (600 MHz, CDCl3) δ 177.44, 176.01, 174.97, 156.85, 153.10, 150.01, 136.48, 135.03, 74.14, 63.88, 61.73, 61.57, 60.25, 53.94, 53.06, 43.04, 40.51, 40.01, 38.20, 33.16, 33.04, 31.76, 30.24, 29.35, 27.71, 21.29.

LCMS (ESI, *m/z*): [MH]+ calcd. for [C30H42N4O4S+H]+, 555.3005; found 555.3005.

**[Gly-(1*S*,2*R*,*E*)-10-amido (E3 ligase ligand)-1-hydroxy-2-methyloct-4-ene]1 CsA (CsA-Prtc1, JW4-10)**

**Using Method A**

The crude product was purified by flash silica chromatography 0-15% MeOH in DCM, then repurified with 5-9% MeOH in DCM to give **CsA-Prtc1**, **JW4-10**as an off-white solid (41 mg, 22% yield).

1H NMR (600 MHz, CDCl3) δ 3.48 (s, NMe, 3H), 3.39 (s, NMe, 3H), 3.22 (s, NMe, 3H), 3.11 (s, NMe, 3H), 3.09 (s, NMe, 3H), 2.69 (s, NMe, 3H), 2.68 (s, NMe, 3H).

13C NMR (600 MHz, CDCl3) δ 174.04, 173.79, 173.58, 173.51, 171.66, 171.30, 171.26, 170.53, 170.47, 170.22, 170.17.

HRMS (*m/z*): [MH]+ calcd. for C89H147N15O16S, 1715.0944; found 1715.0952.

JW115 synthesis



**1-(pent-4-en-1-yl)-1*H*-imidazole**

To a solution of imidazole (1.702 g, 25 mmol) in THF was added portionwise NaH (60% in mineral oil, 600 mg, 25 mmol). The resulting mixture was refluxed for an hour before cooling to room temperature and the addition of 5-bromo-pent-1-ene (3.25 ml, 27.5 mmol). The mixture was then refluxed for 3 hours, allowed to cool and diluted with diethyl ether. The organic extracts were combined, washed with brine, dried over MgSO4 and concentrated under reduced pressure. Product was purified with column chromatography 0-20% MeOH in DCM, followed by 9-12% MeOH in DCM.

The productwas isolatedas a transparent oil (648.5 mg, 68%).

1H NMR (600 MHz, CDCl3) δ 7.55 (s, 1H), 7.08 (s, 1H), 6.91 (s, 1H), 5.68-5.82 (m, 1H), 4.97-5.10 (m, 2H), 3.95 (t, *J*= 3.95 Hz, 3H), 2.01-2.11 (m, 2H), 1.85-1.92 (m, 2H).

13C NMR (600 MHz, CDCl3) δ 137.16, 136.77, 129.39, 118.85, 116.24, 46.25, 30.46, 30.08.

HRMS (*m/z*): [MH]+ calcd. for [C8H12N+H]+,137.1079; found 137.1079.

**[Gly-(1*S*,2*R*,*E*)-8-(1*H*-imidazole-1-yl)-1-hydroxy-2-methyloct-4-ene]1 CsA (JW115)**

**Using Method A**

The crude product was purified by flash silica chromatography 0-10% MeOH in DCM, and re-purified in 5-9% MeOH in DCM to give **JW115**as an off-white powder (11 mg, 10%).

1H NMR (600 MHz, CDCl3) δ 3.48 (s, NMe, 3H), 3.39 (s, NMe, 3H), 3.21 (s, NMe, 3H), 3.12 (s, NMe, 3H), 3.11 (s, NMe, 3H), 2.68 (s, NMe, 3H), 2.66 (s, NMe, 3H).

13C NMR (600 MHz, CDCl3) δ 173.92, 173.79, 173.55, 173.48, 171.67, 171.32, 171.23, 170.49, 170.44, 170.19, 170.16.

MS (*m/z*): [MH]+ calcd. for C67H117N13O12, 1296.73; found 1296.85.