Supporting Information

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SI Text

Chemistry. Unless otherwise indicated, all reactions were run under nitrogen gas. Anhydrous solvents were obtained from commercial suppliers. ^{1}H NMR and ^{13}C NMR spectra were recorded on an AM-500 spectrometer or DRX-500 spectrometer. Chemical shifts are reported relative to internal DMSO-d_6 (δ 2.50 for ^{1}H, 39.52 for ^{13}C). High-resolution mass spectra were obtained by using an Autospec high-resolution double-focusing electrospray ionization/chemical ionization spectrometer with either the DEC 11/73 or OPUS software data system. Preparative HPLC was performed on a Varian HPLC system, using a Vydac C-18 column (Grace), 250 × 22 mm, 100 Å, running at a flow rate of 10 mL/min; λ = 254 nm; mobile phase A, 0.1% trifluoroacetic acid in H_2O, and mobile phase B, 0.1% trifluoroacetic acid in 90% CH_3CN and 10% H_2O. The purity was assessed by using an analytical HPLC Vydac C-18 column, 250 × 5 mm, at a flow rate of 1.0 mL/min; λ = 254 nm; mobile phase A, 0.1% trifluoroacetic acid in H_2O, and mobile phase B, 0.1% trifluoroacetic acid in CH_3CN. The purified fractions were lyophilized.

Fmoc-Dap(Boc)-OBn (1). To a solution of Fmoc-Dap(Boc)-OH (1 g, 2.34 mmol) in dimethylformamide (DMF) (12 mL) at 0 °C was added $NaHCO_3$ (0.4 g, 4.68 mmol) followed by benzyl bromide (112 mL, 9.38 mmol). After stirring the solution at 0 °C for 2 h then at 25 °C for 22 h, EtOAc (50 mL) was added and washed with saturated $NaHCO_3$ (2 × 50 mL) followed by saturated NaCl (3 × 50 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo to give a clear oil, which was purified by column chromatography (SiO_2; 75% hexanes/EtOAc to 50% hexanes/EtOAc) to afford a white solid **1** (1.14 g, 95%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 (s, 9H), 3.55 (br, 2H), 4.20–4.24 (m, 1H), 4.31–4.57 (m, 2H), 4.51 (s, 1H), 4.82 (br, 1H), 5.21 (s, 2H), 5.95 (br, 1H), 7.23–7.47 (m, 9H), 7.64 (d, J = 10.2 Hz, 2H), 7.77 (d, J = 10.4 Hz, 2H).

Benzyl 3-(3-Benzylureido)-2-(Fmoc-amino)propanoate (2). To a solution of **1** (1.0 g, 1.94 mmol) in CH_2Cl_2 (15 mL) was added trifluoroacetic acid (15 mL) at 25 °C and stirred for 18 h. After removal of solvent in vacuo, the residue was dissolved in DMF (15 mL) and cooled to 0 °C. Diisopropylethylamine (DIEA) (1.0 mL, 5.83 mmol) was then added over 5 min, followed by benzylisocyanate (0.26 mL, 2.32 mmol). After 40 min, the reaction was quenched with 1 M HCl (2 mL), diluted with EtOAc (20 mL), and washed with saturated $NaHCO_3$ (2 × 10 mL) followed by saturated NaCl (2 × 50 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo to give a pale yellow solid, **2** (1.0 g, 95%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.57 (s, 2H), 4.05–4.34 (m, 6H), 4.85 (br, 2H), 5.03 (s, 2H), 6.30 (s, 1H), 7.20–7.38 (m, 14H), 7.55 (br, 2H), 7.73 (d, J = 7.4 Hz, 2H).

Benzyl 2-Amino-3-(3-benzylureido)propanoate (3). To a solution of **2** in CH_2Cl_2 (15 mL) cooled to 0 °C was added Et_2NH (5 mL). After 4 h, the solvent was removed in vacuo and triturated with hexanes to give an cream solid **3** (0.65, 97%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.13 (br, 2H), 3.38–3.54 (m, 1H), 3.60–3.73 (m, 1H), 3.73–3.78 (m, 1H), 4.32–4.29 (m, 2H), 5.20 (s, 2H), 5.57 (br, 1H), 5.70 (br, 1H), 7.30–7.45 (10 H, m).

General Procedure for Sulfonation of Cyclic Amino Acids (4). A suspension of cyclic amino acid (1.5 mmol) in H_2O:DMF (10 mL:5 mL) was cooled to 0 °C, and $NaHCO_3$ (3 mmol) was added followed by $PhSO_2Cl$ (1.5 mmol). After stirring for 2 h at 0 °C, $PhSO_2Cl$ (1.5 mmol) was added and stirred for a further 2 h. The reaction was quenched with 1 M HCl at 0 °C, and EtOAc was added. The organic phase was washed with saturated NaCl and water and dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo to yield **4**.

General Procedure for Coupling of 3 and 4 to Synthesize 5. To the corresponding derivative **4** (0.5 mmol) in CH_2Cl_2 (6 mL) was added HATU (0.6 mmol), HOAt (0.6 mmol), and DIEA (1.5 mmol) at 25 °C. To this mixture was added a solution of **3** (0.5 mmol) in CH_2Cl_2 (6 mL), and the resulting solution was stirred for 18 h. The solvent was removed in vacuo, and EtOAc (15 mL) was added and then washed with 10% citric acid (15 mL), saturated $NaHCO_3$ (15 mL), and saturated NaCl (15 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo.

General Procedure for the Generation of Thiazolidine Analogs (14–23). A series of thiazolidines was accessed by reacting cysteine (**14–21**) or penicillamine (**22** and **23**) (4.12 mmol) with the corresponding aldehyde (4.12 mmol) in EtOH (15 mL) at room temperature for 5 h (1). The solid product was filtered, washed with Et_2O, and dried. The oxazoline derivatives were synthesized similarly, replacing cysteine with serine (compound **25**) or threonine (compounds **26** and **27**) (2). Briefly, L-serine or L-threonine (30 mmol) was treated with 37% formaldehyde (3 mL) in 2 N NaOH (15 mL) overnight at 0 °C. Then $NaHCO_3$ (30 mmol) and acetone (15 mL) were added. CbzCl (30.5 mmol) was subsequently added at −4 °C. After 1 h, the solution was diluted with water, washed with Et_2O, acidified with HCl, extracted with Et_2O, washed with Na_2SO_4, and evaporated. Compound **24** was prepared by treatment of compound **15** in aqueous solution (0.5 M, pH 7) with $KMnO_4$ (1.2 eq) dropwise at 0 °C, stirring for 40 min, basifying to pH 8 with NaOH, and filtering the product over Celite (3). The filtrate was acidified to pH 3 with H_3PO_4, extracted with EtOAc, dried over Na_2SO_4, and concentrated.

General Procedure for Cleavage of 5 to Synthesize 6–27. ***Sulfur-containing compounds.*** The corresponding derivative **5** (0.25 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C, and BCl_3 (1 M in hexane, 2.5 mmol) was added to give a brown solution. After 2 h, the reaction was quenched with saturated $NaHCO_3$ and warmed to 25 °C. The product was then extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by reverse-phased HPLC.
Oxygen-containing compounds. To the corresponding derivative **5** (0.25 mmol) in MeOH (5 mL) was added Pd/C (10% wt/wt, 0.025 mmol). The mixture was placed under an atmosphere of H_2 (g) and stirred for 18 h. The suspension was then filtered through a plug of Celite, and the solvent was removed in vacuo. The crude product was purified by reverse-phased HPLC.

2-[(1-Benzenesulfonylpyrrolidine-2-carbonyl)-amino]-3-(3-benzylureido)-propionic acid (6). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.42–1.48 (m, 1H), 1.55–1.62 (m, 1H), 1.67–1.75 (m, 1H), 1.77–1.82 (s, 1H), 3.13 (dt, J = 7.4 Hz, J = 8.7 Hz, 1H), 3.32–3.38 (m, 1H), 3.40–3.50 (m, 2H), 4.12 (dd, J = 3.3 Hz, J = 8.7 Hz, 1H), 4.20 (d, J = 5.3 Hz, 2H), 4.23 (dt, J = J = 7.2 Hz, 1H), 6.08 (t, J = 5.9 Hz, 1H), 6.60 (t, J = 5.7 Hz, 1H), 7.19–7.24 (m, 2H), 7.29 (dd, J = J = 7.5 Hz, 2H), 7.63 (dd, J = J = 7.7 Hz, 2H), 7.72 (dd, J = J = 7.4 Hz,

1H), 7.87 (d, J = 7.4 Hz, 2H), 8.15 (d, J = 7.4 Hz, 1H). 12.73 (br, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 23.83, 30.46, 40.50, 42.91, 48.94, 53.55, 61.59, 126.54, 127.01, 127.42, 128.18, 129.41, 133.24, 136.78, 140.61, 158.34, 171.03, 171.71; EI-MS: m/z ($M+Na^+$) 497.147 (calculated), 497.147 (found).

2-(1-Benzenesulfonylaminocyclopentylcarbonyl)-3-(3-benzylureido)-propionic acid (7). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.27–1.33 (m, 2H), 1.41–1.45 (m, 2H), 1.74–1.92 (m, 4H), 3.31–3.35 (m, 1H), 3.37–3.41 (m, 1H), 4.00 (dt, J = 5.7 Hz, J = 6.4 Hz, 1H), 4.17–4.26 (m, 2H), 6.06 (t, J = 5.7 Hz, 1H), 6.55 (br, 1H), 7.19–7.25 (m, 3H), 7.29 (dd, J = J = 7.4 Hz, 2H), 7.54 (dd, J = J = 7.4 Hz, 2H), 7.60 (dd, J = J = 7.3 Hz, 1H), 7.80 (d, J = 7.2 Hz, 2H), 7.85 (d, J = 6.7 Hz, 1H), 8.04 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.61, 22.71, 35.27, 35.84, 40.60, 42.95, 54.13, 68.66, 126.32, 126.53, 127.01, 128.16, 128.83, 132.12, 140.62, 142.76, 158.50, 171.72, 172.52; EI-MS: m/z ($M+Na^+$): 511.163 (calculated), 511.161 (found).

2-(1-Benzenesulfonylaminocyclohexylcarbonyl)-3-(3-benzylureido)-propionic acid (8). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.13–1.26 (m, 6H), 1.69–1.81 (m, 4H), 3.28–3.38 (m, 2H), 3.81 (dt, J = 5.4 Hz, J = 6.1 Hz, 1H), 4.21 (dt, J = 12.6 Hz, J = 15.3 Hz, 2H), 6.10 (br, 1H), 6.57 (br, 1H), 7.19–7.25 (m, 3H), 7.29 (dd, J = J = 7.3 Hz, 2H), 7.52 (dd, J = J = 7.4 Hz, 2H), 7.58 (dd, J = J = 7.3 Hz, 1H), 7.77 (d, J = 7.0 Hz, 2H), 7.83 (d, J = 6.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.02, 24.72, 32.66, 33.35, 40.49, 42.95, 54.25, 61.06, 126.51, 126.97, 128.16, 128.67, 131.97, 140.59, 142.75, 158.66, 171.62, 172.37; EI-MS: m/z ($M+H^+$): 503.196 (calculated), 503.196 (found).

2-[(5-Benzenesulfonyl-2,5-dihydro-1H-pyrrole-1-carbonyl)-amino]-3-(3-benzylureido)-propionic acid (9). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.35–3.45 (m, 2H), 4.07–4.11 (m, 1H), 4.18–4.23 (m, 4H), 4.89 (m, 1H), 5.60 (m, 1H), 5.77 (m, 1H), 6.09 (br, 1H), 6.60 (br, 1H), 7.19–7.23 (m, 3H), 7.29 (dd, J = J = 7.5 Hz, 2H), 7.61 (dd, J = J = 7.8 Hz, 2H), 7.70 (dd, J = J = 7.4 Hz, 1H), 7.87 (d, J = 7.3 Hz, 2H), 8.35 (d, J = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 40.63, 42.95, 53.74, 55.68, 69.29, 126.01, 126.54, 127.03, 127.38, 127.61, 128.18, 129.43, 133.33, 136.61, 140.58, 158.41, 168.81, 171.58; EI-MS: m/z ($M+H^+$): 495.132 (calculated), 495.133 (found).

2-[(1-Benzenesulfonylazetidine-2-carbonyl)-amino]-3-(3-benzylureido)-propionic acid (10). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.09 (m, 2H), 3.34–3.37 (m, 1H), 3.52–3.58 (m, 2H), 3.62–3.65 (m, 1H), 4.21 (s, 2H), 4.26–4.32 (m, 2H), 6.11 (br, 1H), 6,57 (br, 1H), 7.20–7.30 (m, 5H), 7.69 (dd, J = J = 6.2 Hz, 2H), 7.78 (t, J = 7.5 Hz, 1H), 7.89 (d, 8.0 Hz, 2H), 8.16 (d, J = 7.4 Hz, 1H); EI-MS: m/z ($M+H^+$): 461.2495 (calculated), 461.2519 (found).

2-[(1-Benzenesulfonylpiperidine-2-carbonyl)-amino]-3-(3-benzylureido)-propionic acid (11). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.10–1.16 (m, 1H), 1.23–1.45 (m, 4H), 1.95 (d, J = 13.1 Hz, 1H), 3.27–3.34 (m, 2H), 3.50 (d, J = 13.7 Hz, 1H), 3.64 (d, J = 10.1 Hz, 1H), 4.07 (dt, J = 6.0 Hz, J = 7.2 Hz, 1H), 4.23 (br, 2H), 4.50 (d, J = 4.7 Hz, 1H), 7.20–7.26 (m, 3H), 7.30 (dd, J = J = 7.6 Hz, 2H), 7.56 (dd, J = J = 7.8 Hz, 2H), 7.63 (dd, J = J = 7.4 Hz, 1H), 7.80 (d, J = 7.3 Hz, 2H), 8.19 (d, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 18.91, 23.55, 26.59, 40.27, 42.60, 42.95, 53.63, 54.54, 126.58, 126.87, 127.05, 128.19, 129.16, 132.69, 139.70, 140.62, 158.34, 169.67, 171.74; EI-MS: m/z ($M+Na^+$): 511.163 (calculated), 511.161 (found).

2-[(1-Benzenesulfonyl-tetrahydroisoquinoline-2-carbonyl)-amino]-3-(3-benzylureido)-propionic acid (12). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.82–2.97 (m, 2H), 3.24–3.29 (m, 3H), 4.01–4.05 (m, 1H), 4.23 (d, J = 5.7 Hz, 1H), 4.50–4.63 (m, 3H), 6.07 (br, 1H), 6.63 (br, 1H), 6.98–7.00 (m, 1H), 7.05–7.07 (m, 3H), 7.19–7.31 (m, 5H), 7.45–7.48 (m, 2H), 7.55–7.58 (m, 1H), 7.74–7.76 (m, 2H), 8.36 (d, J = 6.9Hz, 1H); EI-MS: m/z ($M+Na^+$): 559.1638 (calculated), 559.1655 (found).

2-[(1-Benzenesulfonyl-tetrahydroquinoline-2-carbonyl)-amino]-3-(3-benzylureido)-propionic acid (13). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.65–1.77 (m, 2H), 1.92–2.04 (m, 1H), 2.32–2.41 (m, 1H), 3.30–3.33 (m, 1H), 4.11–4.20 (m, 3H), 4.82 (t, J = 6.9 Hz, 1H), 6.06 (br, 1H), 6.56 (br, 1H), 6.98–7.09 (m, 2H), 7.19–7.32 (m, 6H), 7.48–7.57 (m, 5H), 7.64–7.68 (m, 2H), 8.39 (d, J = 6.9Hz, 1H); EI-MS: m/z ($M+Na^+$): 559.1638 (calculated), 559.1627 (found).

2-(3-Benzenesulfonylaminothiazolidine-4-carbonyl)-3-(3-benzylureido)-propionic acid (14). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.62–2.64 (m, 1H), 3.06 (dd, J = 3.8 Hz, J = 11.2 Hz, 1H), 3.38–3.46 (m, 2H), 4.26 (m, 3H), 4.42 (d, J = 10.8 Hz, 1H), 4.74 (d, J = 10.8 Hz, 1H), 4.76 −4.79 (m, 1H), 6.13 (br, 1H), 6.61 (br, 1H), 7.21–7.31 (m, 5H), 7.62 (dd, J = J = 7.9 Hz, 2H), 7.72 (dd, J = J = 7.4 Hz, 1H), 7.94 (d, J = 7.5 Hz, 2H), 8.34 (d, J = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 39.12, 45.83, 48.42, 59.40, 70.02, 132.03, 132.52, 133.23, 133.66, 134.95, 139.27, 142.40, 146.02, 163.98, 174.10, 176.93; EI-MS: m/z ($M+Na^+$): 515.1036 (calculated), 515.1022 (found).

2-(3-Benzenesulfonylamino-5,5-dimethylthiazolidine-4-carbonyl)-3-(3-benzylureido)-propionic acid (15). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.20 (s, 3H), 1.28 (s, 3H), 3.32–3.38 (m, 1H), 3.42–3.47 (m, 1H), 4.04 (s, 1H), 4.15–4.22 (m, 3H), 4.63 (dt, J = 8.9 Hz, J = 9.4 Hz, 2H), 6.07 (br, 1H), 6.66 (br, 1H), 7.19–7.25 (m, 3H), 7.30 (dd, J = J = 7.5 Hz, 2H), 7.63 (dd, J = J = 7.8 Hz, 2H), 7.72 (dd, J = J = 7.4 Hz, 1H), 7.88 (d, J = 7.4 Hz, 2H), 8.45 (d, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 24.60, 29.44, 40.68, 42.97, 50.39, 53.48, 54.61, 72.38, 126.56, 127.06, 127.60, 128.18, 129.35, 133.55, 136.60, 140.56, 158.31, 167.57, 171.69; EI-MS: m/z ($M+H^+$): 521.153 (calculated), 521.153 (found).

2-(2-Methyl-3-benzenesulfonylaminothiazolidine-4-carbonyl)-3-(3-benzylureido)-propionic acid (16). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.54 (d, J = 6.4 Hz, 3H), 2.80 (dd, J = 7.2 Hz, J = 11.7 Hz, 1H), 3.23 (dd, J = 6.0 Hz, J = 11.8 Hz, 1H), 3.24–3.35 (m, 1H), 3.35–3.37 (m, 2H), 4.06–4.28 (m, 3H), 4.59 (t, J = 7.0 Hz, 1H), 6.07 (br, 1H), 6.57 (br, 1H), 7.07–7.27 (m, 5H), 7.49–7.62 (m, 2H), 7.66–7.73 (m, 1H), 7.85–7.96 (m, 2H), 8.27 (d, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.06, 38.89, 46.02, 48.45, 59.37, 68.44, 71.47, 131.97, 132.55, 133.31, 137.96, 139.16, 142.00, 146.06, 163.78, 174.47, 177.01; EI-MS: m/z ($M+Na^+$): 529.1192 (calculated), 529.1211 (found).

2-(2-Ethyl-3-benzenesulfonylaminothiazolidine-4-carbonyl)-3-(3-benzylureido)-propionic acid (17). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.90 (t, J = 10.1 Hz, 3H), 1.59–1.71 (m, 1H), 1.91–2.03 (m, 1H), 2.85 (dd, J = 10.4 Hz, J = 16.3 Hz, 1H), 3.19 (dd, J = 9.1 Hz, J = 16.3 Hz, 1H), 3.31–3.41 (m, 1H), 3.45–3.58 (m, 1H), 4.19–4.37 (m, 3H), 4.57 (t, J = 9.6 Hz, 1H), 4.93 (dd, J = 8.8 Hz, J = 11.8 Hz, 1H), 6.05 (br, 1H), 6.56 (br, 1H), 7.21–7.31 (m, 5H), 7.63 (dd, J = J = 10.3 Hz, 2H), 7.73 (d, J = 10.3 Hz, 1H), 7.96 (d, J = 10.3 Hz, 2H), 8.20 (d, J = 9.7 Hz, 1H); EI-MS: m/z ($M+Na^+$): 543.1348 (calculated), 543.1367 (found).

2-(2-Isopropyl-3-benzenesulfonylamino-thiazolidine-4-carbonyl)-3-(3-benzylureido)-propionic acid (18). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.93 (d, 6.6 Hz, 3H), 1.08 (d, 6.6 Hz, 3H), 1.84–1.99 (m, 1H), 2.91 (dd, J = 7.8 Hz, J = 11.8 Hz, 1H), 3.13 (dd, J = 7.5 Hz, J = 11.1 Hz, 1H), 3.48–3.53 (m, 1H), 4.18–4.28 (m, 3H), 4.52 (t, J = 7.5 Hz, 1H), 4.96 (d, 9.4 Hz, 1H), 6.04 (br, 1H), 6.56 (br, 1H), 7.19–7.31 (m, 5H), 7.93 (dd, J = J = 8.1 Hz, 2H), 7.72–7.75 (m,

1H), 7.92–7.96 (m, 2H), 8.20 (d, J = 7.4 Hz, 1H); EI-MS: m/z ($M+Li^+$): 541.1767 (calculated), 541.1789 (found).

2-(2-Isobutyl-3-benzenesulfonylaminothiazolidine-4-carbonyl)-3-(3-benzylureido)-propionic acid (19). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.87 (d, 6.6 Hz, 3H), 0.91 (d, 6.6 Hz, 3H), 1.54–1.59 (m, 1H), 1.63–1.71 (m, 1H), 1.81–1.86 (m, 1H), 2.90 (dd, J = 7.5 Hz, J = 11.8 Hz, 1H), 3.37 (dd, J = 6.5 Hz, J = 11.7 Hz, 1H), 3.35–3.40 (m, 1H), 4.22–4.27 (m, 3H), 4.59 (t, J = 7.0 Hz, 1H), 4.99 (dd, J = 6.6 Hz, J = 8.3 Hz, 1H), 6.04 (br, 1H), 6.53 (br, 1H), 7.19–7.35 (m, 5H), 7.64 (dd, J = J = 7.9 Hz, 2H), 7.74 (t, J = 7.4 Hz, 1H), 7.95 (d, J = 7.2 Hz, 2H), 8.25 (d, J = 6.9 Hz, 1H); EI-MS: m/z ($M+Na^+$): 571.1661 (calculated), 571.1678 (found).

2-(2-Phenyl-3-benzenesulfonylaminothiazolidine-4-carbonyl)-3-(3-benzylureido)-propionic acid (20). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.93–3.02 (m, 1H), 3.04–3.13 (m, 1H), 3.25–3.40 (m, 2H), 4.21–4.27 (m, 3H), 4.49 (t, J = 11.9 Hz, 1H), 6.06 (br, 1H), 6.14 (s, 1H), 6.62 (br, 1H), 7.23–7.31 (m, 10H), 7.62–7.64 (m, 2H), 7.74–7.79 (m, 1H), 7.97–7.99 (m, 2H), 8.58 (d, J = 7.1Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 34.27, 40.47, 41.18, 43.43, 54.20, 67.44, 68.45, 126.99, 127.46, 127.50, 127.90, 128.24, 128.63, 129.83, 134.16, 136.55, 141.07, 142.30, 158.71, 169.29, 172.13; EI-MS: m/z ($M+Na^+$): 591.1348 (calculated), 591.1343 (found).

2-(2-Phenethyl-3-benzenesulfonylaminothiazolidine-4-carbonyl)-3-(3-benzylureido)-propionic acid (21). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.94–2.01 (m, 1H), 2.20–2.31 (m, 1H), 2.65–2.78 (m, 2H), 2.94 (dd, J = 7.4 Hz, J = 11.8 Hz, 1H), 3.22 (dd, J = 6.7 Hz, J = 11.8 Hz, 1H), 3.31–3.41 (m, 1H), 3.45–3.55 (m, 1H), 4.12–4.32 (m, 3H) 4.60 (t, J = 7.1 Hz, 1H), 4.95 (t, 7.9 Hz, 1H), 6.08 (br, 1H), 6.56 (br, 1H), 7.17–7.28 (m, 10H), 7.51–7.61 (m, 2H), 7.70–7.78 (m, 1H), 7.82–7.90 (m, 2H), 8.35 (d, J = 7.2 Hz, 1H); EI-MS: m/z ($M+Na^+$): 619.1661 (calculated), 619.1688 (found).

2-(2-Methyl-3-benzenesulfonylamino-5,5-dimethylthiazolidine-4-carbonyl)-3-(3-benzylureido)-propionic acid (22). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.91 (s, 3H), 1.26 (s, 3H), 1.67 (d, J = 8.2 Hz, 3H), 3.32–3.44 (m, 2H), 4.20–4.25 (m, 3H), 4.30 (s, 1H), 5.07 (q, J = 8.1 Hz, 1H), 6.00 (br, 1H), 6.62 (br, 1H), 7.21–7.32 (m, 5H), 7.63 (dd, J = 10.8 Hz, J = 10.13 Hz, 2H), 7.71 (d, J = 10.3 Hz, 1H), 7.90 (d, J = 10.7 Hz, 2H), 8.35 (d, J = 9.7 Hz, 1H); EI-MS: m/z ($M+Na^+$): 557.1505 (calculated), 557.1513 (found).

2-(2-Ethyl-3-benzenesulfonylamino-5,5-dimethylthiazolidine-4-carbonyl)-3-(3-benzylureido)-propionic acid (23). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.84 (t, J = 10.2 Hz, 3H), 0.95 (s, 3H), 1.27 (s, 3H), 2.07–2.15 (m, 1H), 2.15–2.29 (m, 1H), 3.30–3.48 (m, 2H), 4.20–4.25 (m, 3H), 4.30 (s, 1H), 4.88 (dd, J = 5.5 Hz, J = 13.7 Hz, 1H), 6.00 (br, 1H), 6.62 (br, 1H), 7.19–7.31 (m, 5H), 7.64 (dd, J = 9.9 Hz, J = 10.9 Hz, 2H), 7.71 (d, J = 10.3 Hz, 1H), 7.9 (d, J = 10.1 Hz, 2H), 8.37 (d, J = 9.6 Hz, 1H); EI-MS: m/z ($M+Na^+$): 571.1661 (calculated), 571.1684 (found).

2-(3-Benzenesulfonylamino-thiazolidylsulfone-4-carbonyl)-3-(3-benzylureido)-propionic acid (24). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.30–3.40 (m, 2H), 3.41–3.62 (m, 2H + H_20), 4.15–4.22 (m, 3H), 4.37 (d, J = 12.5 Hz, 1H), 4.93 (d, J = 12.5 Hz, 1H), 4.97–5.02 (m, 1H), 6.12 (br, 1H), 6.62 (br, 1H), 7.20–7.31 (m, 5H), 7.61 (dd, J = 8.1 Hz, 2H), 7.71 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 7.4 Hz, 2H), 8.59 (d, J = 7.3 Hz, 1H); EI-MS: m/z ($M+Na^+$): 547.0933 (calculated), 547.0933 (found).

2-(3-Benzenesulfonylaminooxazolidine-4-carbonyl)-3-(3-benzylureido)-propionic acid (25). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.34–3.42 (m, 1H), 3.51–3.59 (m, 1H), 3.58–3.61 (m, 1H), 3.68–3.71 (m, 1H), 4.20 (s, 2H), 4.29 (t, J = 4.9 Hz, 1H), 4.38 (t, J = 5.2 Hz, 1H), 4.56 (d, J = 6.6 Hz, 1H), 5.16 (d, J = 6.6 Hz, 1H), 6.07 (br, 1H), 6.54 (br, 1H), 7.19–7.23 (m, 5H), 7.63 (dd, J = J = 7.4 Hz, 2H), 7.74 (dd, J = J = 7.4 Hz, 1H), 7.94 (d, J = 8.0 Hz, 2H), 8.26 (d, J = 7.8 Hz, 1H); EI-MS: m/z ($M+Na^+$): 499.1264 (calculated), 499.1284 (found).

2-(3-Benzenesulfonylamino-5-methyloxazolidine-4-carbonyl)-3-(3-benzylureido)-propionic acid (26). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.86 (d, 6.0 Hz, 3H), 3.29–3.34 (m, 1H), 3.50–3.59 (m, 1H), 3.62 (d, J = 7.0 Hz, 1H), 3.78–3.83 (m, 1H), 4.15–4.23 (m, 1H), 4.30–4.33 (m, 1H), 4.57 (d, J = 7.3 Hz, 1H), 5.26 (d, J = 7.3 Hz, 1H; 20% diastereomer 5.32 (d, J = 7.3 Hz)), 6.07 (br, 1H), 6.57 (br, 1H), 7.19–7.32 (m, 5H), 7.64–7.69 (m, 2H), 7.74–7.79 (m, 1H), 7.95 (d, J = 11.1 Hz, 2H), 8.35 (d, J = 7.7 Hz, 1H; 20% diastereomer 8.47 (d, J = 8.3 Hz)); EI-MS: m/z ($M+Na^+$): 513.1420 (calculated), 513.1403 (found).

2-(2-Methyl-3-Benzenesulfonylamino-5-methyloxazolidine-4-carbonyl)-3-(3-benzylureido)-propionic acid (27). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.77 (d, J = 6.1 Hz, 3H; 1:1 diastereomer 0.83 (d, 6.1 Hz)), 1.39 (d, J = 5.7 Hz, 3H; 1:1 diastereomer 1.43 (d, J = 5.7 Hz)), 3.33–3.37 (m, 2H + H_2O), 3.67 (d, J = 6.2 Hz, 1H; 1:1 diastereomer 3.72 (d, J = 5.9 Hz)), 4.13–4.28 (m, 5H), 5.34–5.40 (m, 1H), 6.05 (br, 1H, 1:1 diastereomer 6.12 (br)), 6.55 (br, 1H; 1:1 diastereomer 6.59 (br)), 7.20–7.32 (m, 5H), 7.64–7.67 (m, 2H), 7.74–7.77 (m, 1H), 7.93–7.96 (m, 2H), 8.38 (d, J = 5.2 Hz, 1H; 1:1 diastereomers 8.63 (d, 5.8 Hz)).

EI-MS. m/z ($M+H^+$): 505.1757 (calculated), 505.1758 (found).

Computational Modeling of Inhibitor Docked to Integrin. The modeling process for docking these β1 inhibitors is 3-fold: discover low energy conformations of dimethylthiazolidine-containing molecules, generate a reasonable model of the β1 protein, and dock the compounds into the putative binding site. The conformational space available to these peptidomimetics was explored by restricting some of the degrees of freedom and enumerating others. By using the β3 protein structure as a template, a homology model was built for the β1 protein. After generating initial modes of both the protein and the compounds, a constrained docking procedure helped to identify poses likely to be observed in a β1-dimethylthiazolidine complex.

As a basis for restricting the conformations of proline derivate compounds, the Protein Data Bank (PDB) (4) was searched for high-resolution structures containing proline–tyrosine (a Pro–Tyr compound was tested with an IC_{50} of 166 nM; M.W.M. and unpublished). Of the 1,935 protein structures, there were 347 Pro–Tyr pairs. To narrow this number, the planar Pro ring conformation from the X-ray structures in this work (**xray_14**, **xray_16**) was used. The definition of planar was adapted from the Dill group (5) to include χ^2 angles of up to 20° and down to −20°.

The β3 portion in a set of high-resolution $\alpha_{2b}\beta_3$ integrin protein structures was used for modeling β1 (PDB ID code 1TY5) (6). The sequence of β3 was extracted in FASTA format from the PDB website. The sequence of β1 was retrieved from Swiss-Prot (7) with primary accession number P05556. By using standard pairwise sequence alignment algorithms, a identity match of 43.9% and a significance value (E-value) of 7.6×10^{-118} was achieved. Next, the portion of the β1 sequence corresponding to positions on the β3 structure was threaded on. To alleviate clashes, a standard repacking procedure (dead-end elimination, self-consistent mean-field Monte Carlo) followed by minimization (steepest descent) was run. Although the sequences are quite divergent, the binding site residues are similar except the hydrophobic cavity and the implications of this are discussed above.

The critical Mg^{2+} metal from MIDAS in the β3 structure was used as a guide to steer the docking process. The carboxyl group was coordinating the metal in a number of the β3

structures and locked into place by a hydrogen bond from a backbone amide of loop 2–3. This interaction steered the peptidomimetics into an initial pose in the binding site. The dihedral around the carboxyl and other backbone dihedrals were varied to find nonclashing conformations. A simple clash filter was used, which termed a ''clash'' as 3 pairs (one ligand, one protein) heavy atoms within 2.2 Å. Analysis of the nonclashing conformations showed three clusters of structures. One cluster placed the methyls on the substituted Pro unrealistically close to the Mg^{2+}. Another cluster projected the Tyr into the β1 hydrophobic pocket, but was not well populated. The third cluster placed the dimethylthiazolidine into the hydrophobic pocket and made nice backbone hydrogen bonds with loop 2–3.

1. Gududuru V, Hurh E, Dalton JT, Miller DD (2005) Discovery of 2-arylthiazolidine-4-carboxylic acid amides as a new class of cytotoxic agents for prostate cancer. *J Med Chem* 48:2584–2588.
2. Falorni M, Conti S, Giacomelli G, Cossu S, Soccolini F (1995) Optically active 4-oxaroline derivatives: New useful chiral synthons derived from serine and threonine. *Tetrahedron: Asymmetry* 6:287–294.
3. Amstutz P, *et al.* (2002) In vitro selection for catalytic activity with ribosome display. *J Am Chem Soc* 124:9396–9403.
4. Berman HM, *et al.* (2000) The Protein Data Bank. *Nucleic Acids Res* 28:235–242.
5. Ho B, Coutsias E, Seok C, Dill K (2005) The flexibility in the proline ring couples to the protein backbone. *Protein Sci* 14:1011–1018.
6. Xiao T, Takagi J, Coller BS, Wang J-H, Springer TA (2004) Structural basis for allostery in integrins and binding to fibrinogen-mimetic therapeutics. *Nature* 432:59–67.
7. Bairoch A, *et al.* (2005) The Universal Protein Resource (UniProt). *Nucleic Acids Res* 33:D154–D159.