Supporting Information
Bioorganic and Medicinal Chemistry Letters

Imidazo[1,2-*a*]pyridine-based peptidomimetics as inhibitors of Akt

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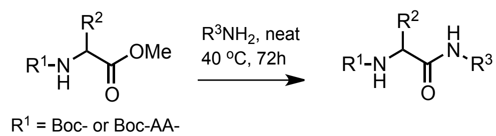
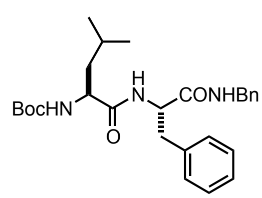
EXPERIMENTAL PROCEDURES

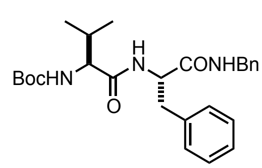
General synthesis notes. Unless stated otherwise, reactions were performed in flame-dried glassware under a positive pressure of argon or nitrogen gas using dry solvents. Commercial grade reagents and solvents were used without further purification except where noted. Diethyl ether, toluene, dimethylformamide dichloromethane, and tetrahydrofuran were purified by a Glass Contour column-based solvent purification system. Other anhydrous solvents were purchased directly from chemical suppliers. Thin-layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was performed using silica gel (60 μm particle size). The purity of all compounds was judged by TLC analysis (single spot/two solvent systems) using a UV lamp, CAM (ceric ammonium molybdate), ninhydrin, or basic $KMnO_4$ stain(s) for detection purposes. 1D and 2D NMR spectra were recorded on a 400 or 500 MHz spectrometer. Proton chemical shifts are reported as δ values relative to residual signals from deuterated solvents ($CDCl_3$ or DMSO-d_6).



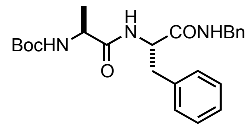
General procedure for C-terminal amidation of dipeptide methyl esters. A solution of the N-Boc α-amino methyl ester or N-Boc dipeptide methyl ester (500 μmol) was dissolved in the desired amine and heated to 40 °C in a sealed tube and stirred until TLC indicated consumption of the starting material (3 to 4 days). The crude residue was diluted with EtOAc and washed with 1M aq. HCl. The organic layer was dried over Na_2SO_4, concentrated, and purified by flash chromatography over silica gel (EtOAc/Hexanes) to afford the desired amides.



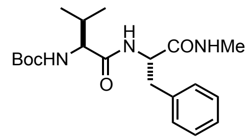
Boc-Leu-Phe-NHBn. Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.27 – 7.13 (m, 9H), 7.07 (d, *J* = 6.8 Hz, 2H), 6.87 – 6.84 (m, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 4.91 (d, *J* = 5.6 Hz, 1H), 4.75 (dd, *J* = 14.7, 7.0 Hz, 1H), 4.32 – 4.29 (m, 2H), 4.06 – 4.02 (m, 1H), 3.17 (dd, *J* = 13.6, 5.8 Hz, 1H), 3.05 (dd, *J* = 13.6, 7.3 Hz, 1H), 1.53 – 1.49 (m, 2H), 1.31 (s, 9H), 0.87 (dd, *J* = 7.2, 6.7 Hz, 5.4H), 0.82 (dd, *J* = 6.1, 3.2 Hz, 0.6H; ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 170.6, 155.9, 137.9, 136.6, 129.5, 128.7, 128.6, 127.8, 127.3, 127.0, 80.5, 54.1, 53.8, 43.5, 41.1, 38.1, 28.3, 24.8, 23.1, 21.8; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{27}H_{38}N_3O_4$ 468.2857, found 468.2849



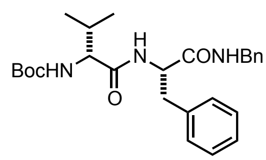
Boc-Val-Phe-NHBn. Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.2 Hz, 1H), 7.37 – 7.35 (m, 1H), 7.24 – 7.11 (m, 8H), 6.97 (d, *J* = 5.5 Hz, 2H), 5.42 (d, *J* = 8.1 Hz, 1H), 4.89 (q, *J* = 7.5 Hz, 1H), 4.31 (dd, *J* = 14.9, 6.2 Hz, 1H), 4.12 (dd, *J* = 14.8, 5.2 Hz, 1H), 4.04 (t, *J* = 7.6 Hz, 1H), 3.10 – 3.04 (m, 2H), 1.96 (dq, *J* = 13.5, 6.8 Hz, 1H), 1.36 (s, 9H), 0.87 – 0.76 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 170.9, 156.0, 138.0, 136.6, 129.5, 128.6, 128.4, 127.6, 127.1, 126.8, 79.7, 60.1, 54.3, 43.2, 38.6, 30.9, 28.4, 19.3, 18.0; HRMS (ESI-TOF) (*m/z*) $[MNa]^+$ calcd for $C_{26}H_{35}N_3O_4Na$ 476.2520, found 476.2540.



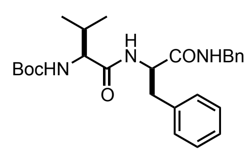
Boc-Ala-Phe-NHBn. Yield: 80%; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.43 (t, J = 5.5 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.30 – 7.17 (m, 9H), 7.12 (d, J = 7.2 Hz, 2H), 7.00 (d, J = 7.1 Hz, 1H), 4.52 (dd, J = 14.3, 8.0 Hz, 1H), 4.25 (t, J = 5.7 Hz, 2H), 3.93 – 3.86 (m, 1H), 3.00 (dd, J = 13.7, 5.6 Hz, 1H), 2.88 (dd, J = 13.4, 8.6 Hz, 1H), 1.35 (s, 7.7H), 1.33 (s, 1.3H), 1.08 (d, J = 7.2 Hz, 2.7H), 0.94 (d, J = 7.2 Hz, 0.3H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.5, 170.7, 155.2, 139.0, 137.6, 129.3, 128.2, 128.1, 127.1, 126.7, 126.3, 78.3, 53.8, 50.1, 42.0, 37.7, 28.2, 18.1; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{24}H_{32}N_3O_4$ 426.2387, found 426.2386.



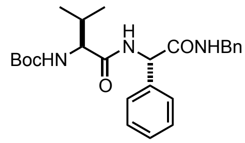
Boc-Val-Phe-NHMe. Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.12 (m, 5H), 6.47 – 6.43 (m, 1H), 6.35 – 6.31 (m, 1H), 4.86 – 4.88 (m, 1H), 4.68 – 4.65 (m, 1H), 3.85 – 3.83 (m, 1H), 3.15 – 3.06 (m, 1H), 3.07 (dd, J = 13.4, 6.7 Hz, 1H), 2.71 (d, J = 4.2 Hz, 3H), 2.11 – 2.08 (m, 1H), 1.38 (s, 9H), 0.89 (d, J = 6.7 Hz, 3H), 0.78 (d, J = 5.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 171.2, 156.4, 136.7, 129.3, 128.8, 127.1, 80.6, 60.7, 54.0, 38.0, 30.3, 28.3, 26.3, 19.4, 17.6; HRMS (ESI-TOF) (*m/z*) $[MNa]^+$ calcd for $C_{20}H_{31}N_3O_4Na$ 400.2207, found 400.2229.



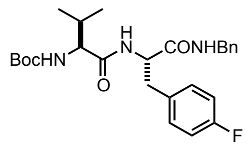
Boc-(D)Val-Phe-NHBn. Yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.14 (m, 10H), 7.09 (d, J = 7.0 Hz, 2H), 6.73 (d, J = 8.4 Hz, 1H), 5.26 (d, J = 7.7 Hz, 1H), 4.83 (dd, J = 15.1, 7.2 Hz, 1H), 4.38 (dd, J = 15.0, 5.8 Hz, 1H), 4.28 (dd, J = 14.9, 5.7 Hz, 1H), 3.72 (t, J = 7.3 Hz, 1H), 3.12 (d, J = 6.9 Hz, 2H), 1.88 (dt, J = 13.3, 6.7 Hz, 1H), 1.35 (s, 9H), 0.76 (dd, J = 13.4, 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 170.7, 156.2, 138.1, 136.7, 129.4, 128.8, 128.6, 127.6, 127.3, 127.0, 80.1, 60.9, 54.4, 43.4, 38.0, 30.6, 28.4, 19.2, 18.2; HRMS (ESI-TOF) (*m/z*) $[MNa]^+$ calcd for $C_{26}H_{35}N_3O_4$ 476.2520, found 476.2540.



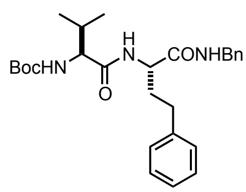
Boc-Val-(D)Phe-NHBn. Yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J = 12.9, 7.2 Hz, 1H), 7.26 – 7.14 (m, 9H), 7.06 (t, J = 9.7 Hz, 1H), 6.97 (d, J = 8.6 Hz, 1H), 5.41 (d, J = 7.9 Hz, 1H), 4.86 (dd, J = 15.3, 7.4 Hz, 1H), 4.31 (t, J = 5.7 Hz, 2H), 3.78 (t, J = 7.5 Hz, 1H), 3.09 (dt, J = 13.7, 6.9 Hz, 2H), 1.87 (dq, J = 13.4, 6.6 Hz, 1H), 1.35 (s, 9H), 0.78 – 0.68 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 170.8, 156.2, 138.0, 136.7, 129.4, 128.7, 128.5, 127.5, 127.2, 127.0, 80.0, 60.7, 54.4, 43.3, 38.0, 30.7, 28.4, 19.2, 18.1; HRMS (ESI-TOF) (*m/z*) $[MNa]^+$ calcd for $C_{26}H_{35}N_3O_4$ 476.2520, found 476.2541.



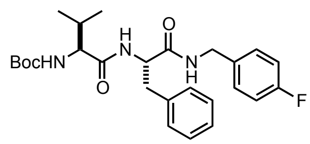
Boc-Val-Phg-NHBn. Yield: 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.4 Hz, 0.4H), 7.30 (d, *J* = 7.4 Hz, 0.6H), 7.08 – 6.81 (m, 9H), 6.72 (d, *J* = 4.8 Hz, 2H), 5.42 (d, *J* = 7.1 Hz, 1H), 5.02 (d, *J* = 8.4 Hz, 0.5H), 4.89 (d, *J* = 8.3 Hz, 0.5H), 4.07 – 3.87 (m, 2H), 3.80 – 3.65 (m, 1H), 1.73 – 1.52 (m, 1H), 1.05 (d, *J* = 10.0 Hz, 9H), 0.49 (ddd, *J* = 32.2, 19.4, 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 170.0, 156.0, 137.8, 128.9, 128.9, 128.6, 128.2, 127.6, 127.5, 127.4, 127.2, 79.9, 59.9, 57.0, 43.6, 31.2, 28.4, 19.4, 17.8; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{26}H_{36}N_3O_4$ 440.2544, found 440.2517



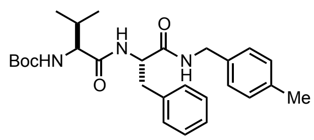
Boc-Val-(4-F)Phe-NHBn. Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.13 (m, 5H), 7.11 – 6.98 (m, 4H), 6.87 (dd, *J* = 10.9, 6.4 Hz, 2H), 5.23 (d, *J* = 7.6 Hz, 1H), 4.80 (dd, *J* = 15.1, 7.3 Hz, 1H), 4.33 (dd, *J* = 14.7, 6.0 Hz, 1H), 4.19 (dd, *J* = 14.8, 5.1 Hz, 1H), 3.96 (t, *J* = 6.9 Hz, 1H), 3.13 – 2.92 (m, 2H), 2.00 (dd, *J* = 13.5, 6.8 Hz, 1H), 1.35 (s, 9H), 0.83 (dd, *J* = 15.1, 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 170.6, 163.2, 160.7, 156.1, 137.9, 132.2, 131.0, 128.6, 127.7, 127.4, 115.6, 115.4, 80.2, 60.4, 54.2, 43.4, 37.6, 30.7, 28.4, 19.3, 17.9; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{26}H_{35}N_3O_4F$ 472.2606, found 472.2583.



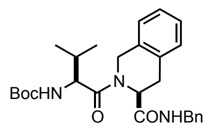
Boc-Val-homoPhe-NHBn. Yield: 62% (15% RSM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 6.94 (m, 12H), 5.15 (d, *J* = 7.6 Hz, 1H), 4.55 (d, *J* = 6.3 Hz, 1H), 4.36 (dd, *J* = 36.7, 14.9 Hz, 2H), 3.95 – 3.92 (m, 1H), 2.61 (d, *J* = 7.1 Hz, 2H), 2.16 – 2.14 (m, 1H), 2.02 (dd, *J* = 7.8, 5.6 Hz, 2H), 1.39 (s, 9H), 0.85 (t, *J* = 8.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 171.2, 156.1, 141.0, 138.1, 128.7, 128.6, 128.5, 127.8, 127.5, 126.2, 80.2, 60.3, 53.0, 43.6, 34.0, 31.9, 30.8, 28.4, 19.4, 18.0; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{27}H_{38}N_3O_4$ 468.2857, found 468.2852.



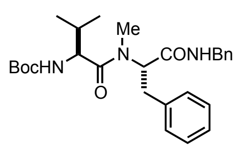
Boc-Val-Phe-NH(4-F)Bn. Yield: 66% (20% RSM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.09 (m, 7H), 7.03 – 6.91 (m, 2H), 6.90 – 6.81 (m, 2H), 5.21 (d, *J* = 7.3 Hz, 1H), 4.83 (dd, *J* = 15.2, 7.3 Hz, 1H), 4.28 (dd, *J* = 14.9, 6.0 Hz, 1H), 4.14 (dd, *J* = 14.9, 5.0 Hz, 1H), 3.96 (t, *J* = 6.6 Hz, 1H), 3.12 (dd, *J* = 13.6, 6.4 Hz, 1H), 3.05 (dd, *J* = 13.4, 7.7 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.33 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 170.8, 163.2, 160.8, 156.2, 136.5, 133.8, 129.4, 128.7, 127.0, 115.4, 80.2, 60.4, 54.2, 42.6, 38.3, 30.7, 28.3, 19.3, 17.8; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{26}H_{35}N_3O_4$ 472.2606, found 472.2605.



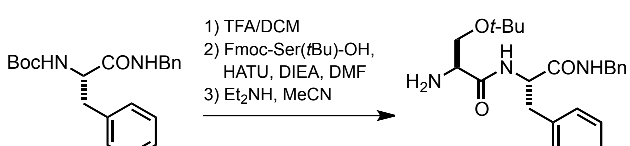
Boc-Val-Phe-NHMe. Yield: 61% (18% RSM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 6.86 (m, 11H), 5.08 (d, *J* = 7.3 Hz, 1H), 4.82 – 4.73 (m, 1H), 4.28 (dd, *J* = 14.6, 5.7 Hz, 1H), 4.23 – 4.13 (m, 1H), 3.94 – 3.92 (m, 1H), 3.12 (dd, *J* = 13.4, 6.1 Hz, 1H), 3.04 (dd, *J* = 13.4, 7.6 Hz, 1H), 2.28 (s, 3H), 2.06 – 1.96 (m, 1H), 1.35 (s, 9H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 170.5, 156.1, 136.9, 136.6, 134.8, 129.4, 129.2, 128.7, 127.8, 127.0, 80.2, 60.4, 54.2, 43.3, 38.4, 30.6, 28.3, 21.2, 19.4, 17.7; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{27}H_{38}N_3O_4$ 468.2857, found 468.2861.



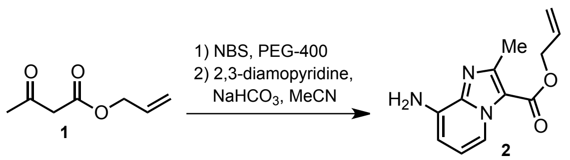
Bo-Val-Tic-NHBn. Yield: 53% (34% RSM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.26 – 7.24 (m, 6H), 7.09 – 7.06 (m, 1H), 6.99 – 6.92 (m, 1H), 6.32 (s, 1H), 5.22 (d, *J* = 9.1 Hz, 0.5H), 5.07 (dd, *J* = 18.4, 12.1 Hz, 1.5H), 4.95 (d, *J* = 5.1 Hz, 0.5H), 4.84 (d, *J* = 14.9 Hz, 0.5H), 4.56 – 4.52 (m, 1.5H), 4.40 – 4.32 (m, 1.5H), 4.26 (t, *J* = 7.6 Hz, 0.5H), 4.18 – 4.10 (m, 0.5H), 3.66 – 3.58 (m, 0.5H), 3.38 (dd, *J* = 15.7, 6.0 Hz, 0.5H), 3.03 (td, *J* = 15.3, 6.1 Hz, 1H), 1.98 – 1.96 (m, 1H), 1.41 (s, 4.5H), 1.36 (s, 4.5H), 1.04 – 0.94 (m, 4.5H), 0.83 (d, *J* = 6.8 Hz, 1.5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 168.9, 156.7, 138.0, 132.7, 132.6, 128.8, 128.5, 128.1, 127.6, 127.2, 127.0, 126.5, 80.6, 56.4, 54.0, 43.8, 43.7, 31.7, 30.5, 28.5, 19.9, 17.1; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{27}H_{36}N_3O_4$ 466.2700, found 466.2698.



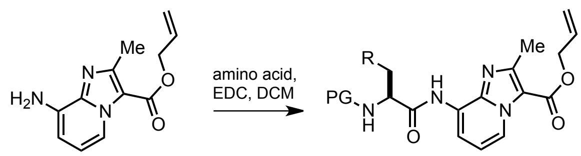
Boc-Val-(N-Me)Phe-NHBn. Yield: 39% (37% RSM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (t, *J* = 5.8 Hz, 0.5H), 7.39 – 7.22 (m, 9H), 7.15 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.52 (t, *J* = 5.6 Hz, 0.5H), 5.35 (t, *J* = 7.9 Hz, 0.6H), 5.16 (dd, *J* = 22.8, 9.1 Hz, 1H), 4.86 (t, *J* = 7.2 Hz, 0.4H), 4.48 – 4.32 (m, 2.6H), 4.19 (dd, *J* = 8.8, 6.7 Hz, 0.4H), 3.60 – 3.52 (m, 0.5H), 3.44 (dd, *J* = 14.0, 8.3 Hz, 0.5H), 3.13 (s, 1.5H), 3.07 – 2.92 (m, 2.5H), 1.87 (dq, *J* = 13.3, 6.7 Hz, 0.5H), 1.48 (s, 4.4H), 1.39 (d, *J* = 7.7 Hz, 0.6H), 1.33 (d, *J* = 5.3 Hz, 4H), 1.25 – 1.15 (m, 0.4H), 1.03 – 1.01 (m, 0.2H), 0.96 (d, *J* = 6.7 Hz, 0.2H), 0.92 – 0.83 (m, 4.2H), 0.71 (d, *J* = 6.7 Hz, 1.2H), 0.47 (d, *J* = 6.7 Hz, 0.2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 169.4, 157.1, 138.0, 137.7, 129.4, 128.7, 128.6, 127.6, 127.5, 126.9, 80.7, 62.6, 54.9, 43.4, 34.1, 31.2, 29.8, 28.4, 19.6, 17.7; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{27}H_{38}N_3O_4$ 468.2857, found 490.2835.



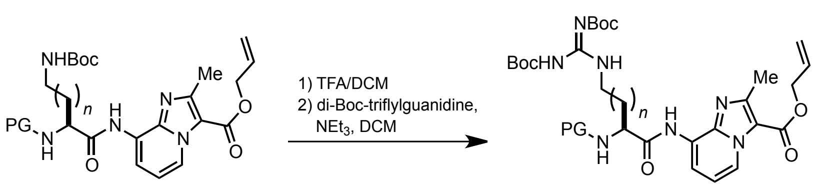
2-Amino-N-(1-benzylcarbamoly-(*S*)-2-phenyl-ethyl)-(*S*)-3-*t*butoxyl-propionamide. A solution of Boc-Phe-NHBn (86 mg, 0.243 mmol) in 4 mL of 25% TFA/ DCM was stirred for 2 h at RT. The solvent was concentrated under reduced pressure. The crude material was dried under reduced pressure. The amine·TFA salt intermediate was dissolved in 5 mL DMF and treated with Fmoc-Ser(*t*-Bu)-OH (186 mg, 0.49 mmol), HATU (184 mg, 0.49 mmol), and DIEA (188 mg, 1.46 mmol). After stirring at RT for 12 h, the reaction was concentrated under reduced pressure. The residue was diluted with EtOAc and washed with 1M aq. HCl, sat. aq. $NaHCO_3$, and brine. The organic layer was evaporated, and the crude material was stirred for 2 h in 10 mL DEA/MeCN (1:1) for Fmoc deprotection. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (1% to 5% MeOH/$CHCl_3$, gradient) to give the product as colorless oil. (77 mg, 0.194 mmol, 90% for 3 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 1H), 7.32 – 7.17 (m, 8H), 7.09 (d, *J* = 7.2 Hz, 1H), 6.43 (t, *J* = 7.7 Hz, 1H), 4.66 (q, *J* = 7.5 Hz, 1H), 4.36 (ddd, *J* = 39.5, 14.8, 5.7 Hz, 2H), 3.44 – 3.35 (m, 2H), 3.31 – 3.24 (m, 1H), 3.11 (d, *J* = 7.1 Hz, 2H), 1.65 (s, 2H), 1.10 (s, 9H); 13C NMR (101 MHz, $CDCl_3$) δ 173.6, 170.7, 137.7, 136.8, 129.4, 128.6, 128.5, 127.6, 127.4, 126.9, 73.5, 63.7, 55.2, 54.4, 43.4, 38.0, 27.4; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{23}H_{32}N_3O_3$ 398.2438, found 398.2438.



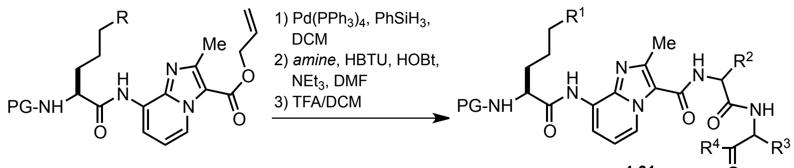
H-IP(Me)-OAllyl. A mixture of allyl acetoacetate (71.0 mg, 0.50 mmol) and solid *N*-bromosuccinimide (97.9 mg, 0.55 mmol) in PEG-400 (2 mL) was stirred at RT until TLC indicated consumption of the starting material (30 – 60 min). The reaction mixture was diluted with water and extracted with Et_2O. The combined organic layers were washed with water and brine, dried over Na_2SO_4, then filtered and concentrated. The crude residue was then dissolved in 2.5 mL MeCN and treated with 2,3-diaminopyridine (54.6 mg, 0.50 mmol) and $NaHCO_3$ (46.2 mg, 0.55 mmol). The reaction mixture was heated to 90 ºC in a sealed tube and stirred for 15 h. The solution was then cooled to RT, diluted with EtOAc, filtered through a pad of celite, and concentrated. Purification by flash chromatography over silica gel (50 % EtOAc/Hexanes) afforded 2 as a tan solid (67% yield for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 – 8.69 (m, 1H), 6.77 (t, *J* = 7.2 Hz, 1H), 6.54 (ddd, *J* = 3.8, 2.2, 0.7 Hz, 1H), 6.14 – 5.96 (m, 1H), 5.44 – 5.38 (m, 1H), 5.31 – 5.27 (m, 1H), 4.86 (dt, *J* = 5.6, 1.4 Hz, 2H), 4.56 (bs, 2H), 2.70 (s, 3H); ^{13}C NMR (101 MHz, CDCl) δ 161.2, 151.1, 140.2, 135.1, 132.5, 118.3, 118.3, 114.8, 113.5, 106.6, 64.9, 16.8; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{12}H_{14}N_3O_2$ 232.1081, found 232.1111.



General procedure for N-terminal amidation of the IP scaffold. A solution of H-IP(Me)-OAllyl (0.433 mmol) in 5 mL DCM was treated with the desired N-protected amino acid (0.866 mmol) and EDC·HCl (0.866mmol). After stirring at RT for 15 h, the reaction was concentrated under reduced pressure and purified by flash chromatography over silica gel (75 % EtOAc/Hexanes) afforded the desired products.



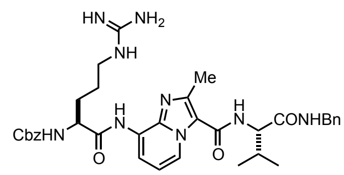
General procedure for guanidinylation of amine side chains. Guanidine-containing analogs were prepared by treatment of the intermediate Boc-protected tripeptide mimics with 20% TFA/DCM for 4 h followed by concentration under reduced pressure. The residue was diluted with EtOAc, concentrated under reduced pressure, and dried under vacuum. The crude residue was then dissolved in 20 mL DCM and treated with NEt_3 (1.25 mmol) and N,N'-di-Boc triflylguanidine (0.374 mmol). After stirring at RT for 18 h, the reaction was concentrated under reduced pressure and purified by flash chromatography over silica gel (50 % EtOAc/Hexanes) to afford the di-Boc guanidine derivatives.



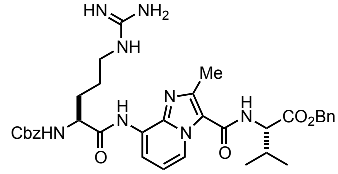
General procedure for synthesis of inhibitors 4-31. A mixture of the allyl ester subunit (1.00 mmol), $Pd(PPh_3)_4$ (0.050 mmol), and PhSiH (3.00 mmol) in DCM (50 mL) was stirred at RT until TLC indicated consumption of the starting material (30 – 60 min). The reaction mixture was concentrated under reduced pressure and purified by flash chromatography over silica gel (5 % MeOH/$CHCl_3$) afforded the desired carboxylic acids.

A solution of above carboxylic acid (0.098 mmol) in DMF (4 mL) was treated with HBTU (0.117 mmol), HOBt (0.019 mmol), NEt_3 (0.392 mmol), and the appropriate C-terminal dipeptide amide (or amino amide) building block (0.117 mmol). After stirring at RT for 20 h, the reaction was concentrated under reduced pressure. The residue was diluted with EtOAc and washed with sat. aq. NH_4Cl. The organic layer was dried over Na_2SO_4 and evaporated. Purification by flash column chromatography over silica gel (1% MeOH/$CHCl_3$) afforded the desired coupled products.

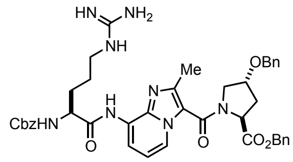
A solution of above product (0.029 mmol) was treated with 20% TFA/DCM (2.4 mL). After stirring RT 12 h, the reaction was concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (85/16/2 $CHCl_3$/MeOH/NH_4OH) afforded the desired products.



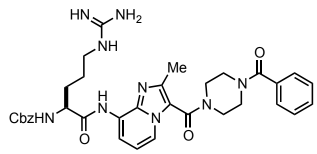
Cbz-Arg-IP(Me)-Val-NHBn (4). Yield: 64%; mp 161 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.00 (s, 1H), 8.70 (t, *J* = 5.8 Hz, 1H), 8.65 (d, *J* = 6.9 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 7.93 – 7.82 (m, 2H), 7.64 (t, *J* = 4.0 Hz, 1H), 7.42 – 7.20 (m, 11H), 7.17 (s, 1H), 7.04 (s, 1H), 7.01 (t, *J* = 7.3 Hz, 1H), 5.07 (q, *J* = 12.5 Hz, 2H), 4.52 – 4.42 (m, 1H), 4.41 (t, *J* = 7.7 Hz, 1H), 4.35 (d, *J* = 5.8 Hz, 2H), 3.17 – 3.07 (m, 2H), 2.64 (s, 3H), 2.21 – 2.09 (m, 1H), 1.89 – 1.73 (m, 1H), 1.70 – 1.50 (m, 3H), 1.02 – 0.92 (m, 6H); 13C NMR (101 MHz, $(CD_3)_2SO$) δ 172.5, 171.4, 161.1, 158.9, 157.1, 156.6, 144.5, 139.8, 139.0, 137.3, 128.8, 128.7, 128.3, 128.1, 127.7, 127.2, 126.6, 122.2, 117.7, 113.6, 66.1, 58.9, 55.4, 42.5, 40.8, 30.8, 29.1, 25.7, 19.9, 19.0, 15.9; HRMS (ESI-TOF) *m*/*z* $[MH]^+$ calcd for $C_{35}H_{44}N_9O_5$ 670.3460, found 670.3454.



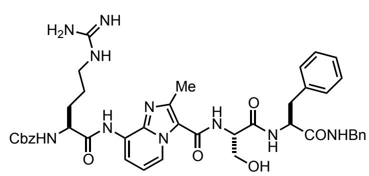
Cbz-Arg-IP(Me)-Val-OBn (5). Yield: 13%; ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (d, *J* = 6.9 Hz, 1H), 8.14 (d, *J* = 7.5 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.58 – 7.44 (m, 2H), 7.42 – 7.25 (m, 8H), 6.96 (t, *J* = 7.3 Hz, 1H), 5.23 (dd, *J* = 47.9, 12.1 Hz, 2H), 5.13 (s, 2H), 4.58 (t, *J* = 5.5 Hz, 1H), 4.44 – 4.38 (m, 1H), 3.23 (t, *J* = 7.1 Hz, 2H), 2.63 (s, 3H), 2.31 (dq, *J* = 13.6, 6.8 Hz, 1H), 1.87 – 1.62 (m, 4H), 1.05 (d, *J* = 1.9 Hz, 3H), 1.03 (d, *J* = 1.9 Hz, 3H); 13C NMR (101 MHz, CD_3OD) δ 171.9, 171.5, 161.8, 157.2, 144.4, 135.7, 128.3, 128.2, 128.1, 127.7, 127.5, 126.9, 125.8, 125.5, 122.5, 117.2, 115.1, 113.3, 110.0, 105.0, 66.6, 66.5, 58.5, 55.4, 40.5, 30.3, 28.8, 25.0, 18.2, 17.5, 13.9; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{35}H_{43}N_8O_6$ 671.3306, found 671.3284.



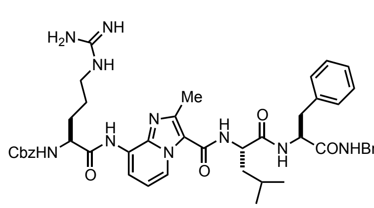
Cbz-Arg-IP(Me)-Hyp(Bn)-OBn (6). Yield: 8%; ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (d, *J* = 6.9 Hz, 1H), 7.42 – 7.09 (m, 16H), 6.99 (t, *J* = 7.3 Hz, 1H), 5.28 – 5.15 (m, 2H), 5.14 (s, 2H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.42 (s, 1H), 4.27 (s, 1H), 3.73 (d, *J* = 11.8 Hz, 1H), 3.52 (s, 1H), 3.23 (t, *J* = 6.6 Hz, 2H,), 2.72 – 2.60 (m, 1H), 2.48 (d, *J* = 9.3 Hz, 1H), 2.40 (s, 3H), 2.22 – 2.11 (m, 1H), 2.08 – 1.95 (m, 1H), 1.87 – 1.56 (m, 4H) ; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{42}H_{46}N_9O_7$ 775.3662, found 775.3558.



Cbz-Arg-IP(Me)-Hyp(Bn)-OBn (7). Yield: 22%; ^{1}H NMR (400 MHz, CD_3OD) δ 8.26 (d, *J* = 6.9 Hz, 1H), 8.12 (d, *J* = 7.5 Hz, 1H), 7.53 – 7.43 (m, 5H), 7.40 – 7.17 (m, 5H), 6.93 (t, *J* = 7.3 Hz, 1H), , 5.12 (s, 2H), 4.41 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.96 – 3.47 (m, 8H), 3.22 (t, *J* = 6.9 Hz, 2H), 2.49 (s, 3H), 1.87 – 1.64 (m, 4H); 13C NMR (101 MHz, CD_3OD) δ 171.9, 171.3, 162.0, 157.3, 157.2, 145.8, 142.6, 136.6, 134.9, 130.0, 128.4, 128.0, 127.6, 127.5, 126.8, 125.6, 122.1, 116.3, 115.0, 113.3, 66.5, 55.4, 40.5, 28.8, 25.0, 13.2; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{34}H_{40}N_9O_5$ 654.3147, found 654.3140.

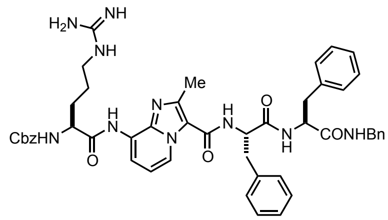


Cbz-Arg-IP(Me)-Ser-Phe-NHBn (8). Yield: 65%; mp 129 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.00 (s, 1H), 8.68 (d, *J* = 6.9 Hz, 1H), 8.53 (t, *J* = 5.9 Hz, 1H), 8.35 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 7.7 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 4.0 Hz, 1H), 7.47 – 7.12 (m, 17H), 7.03 (s, 1H), 6.96 (t, *J* = 7.3 Hz, 1H), 5.20 (s, 1H), 5.07 (q, *J* = 12.5 Hz, 2H), 4.67 – 4.52 (m, 2H), 4.51 – 4.41 (m, 1H), 4.28 (d, *J* = 6.0 Hz, 2H), 3.78 – 3.65 (m, 2H), 3.18 – 3.01 (m, 3H), 2.89 (dd, *J* = 13.4, 9.1 Hz, 1H), 2.61 (s, 3H), 1.87 – 1.75 (m, 1H), 1.71 – 1.49 (m, 3H); 13C NMR (101 MHz, $(CD_3)_2SO$) δ 172.5, 171.1, 170.2, 160.9, 158.8, 158.5, 157.1, 156.6, 144.9, 139.4, 139.0, 138.1, 137.3, 129.6, 128.8, 128.7, 128.5, 128.3, 128.1, 127.5, 127.2, 126.7, 126.6, 117.4, 113.6, 66.1, 62.1, 55.7, 55.4, 54.7, 42.5, 40.8, 37.9, 29.1, 25.7, 15.9; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{42}H_{49}N_{10}O_7$ 805.3780, found 805.3802.

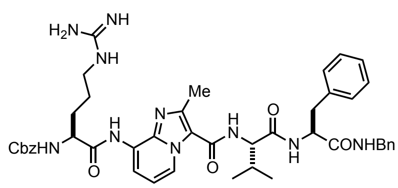


Cbz-Arg-IP(Me)-Leu-Phe-NHBn (9). Yield: 63%; mp 129 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.97 (s, 1H), 8.54 – 8.48 (m, 2H), 8.28 (d, *J* = 8.1 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.92 – 7.85 (m, 1H), 7.32 – 7.25 (m, 13H), 7.17 – 7.12 (m, 4H), 7.04 (s, 1H), 6.95 – 6.90 (m, 1H), 5.07 (q, *J* = 12.5 Hz, 2H), 4.60 (dd, *J* = 14.3, 8.4 Hz, 1H), 4.54 – 4.39 (m, 2H), 4.27 (d, *J* = 5.8 Hz, 2H), 3.12 (d, *J* = 6.5 Hz, 2H), 3.07 –

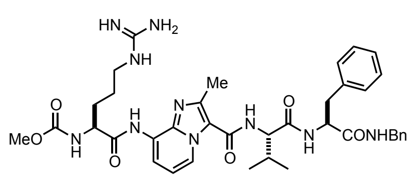
3.01 (m, 1H), 2.95 (s, 2H), 2.89 (dd, J = 9.2, 4.4 Hz, 1H), 2.57 (s, 3H), 1.85 – 1.78 (m, 1H), 1.58 – 1.63 (m, 3H), 1.51 – 1.46 (m, 1H), 1.25 – 1.20 (m, 1H), 0.90 (dd, J = 6.3, 2.3 Hz, 4.8H), 0.81 (t, J = 5.5 Hz, 1.2H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 171.9, 170.8, 160.6, 158.3, 158.0, 156.7, 156.2, 144.2, 139.1, 138.6, 137.7, 136.9, 131.5, 129.2, 128.4, 128.2, 128.0, 127.7, 127.0, 126.7, 126.3, 118.7, 117.3, 115.7, 113.1, 65.6, 55.0, 54.1, 51.7, 42.0, 37.6, 28.7, 25.3, 24.5, 23.2, 22.8, 22.0, 21.5, 15.4; HRMS (ESI-TOF) (m/z) $[MH]^+$ calcd for $C_{45}H_{55}N_{10}O_6$ 831.4301, found 831.4277.



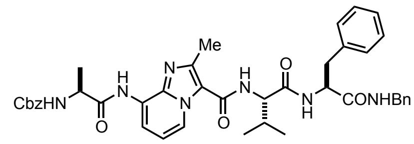
Cbz-Arg-IP(Me)-Phe-Phe-NHBn (10). Yield: 76%; mp 110 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.96 (s, 1H), 8.73 (d, J = 8.6 Hz, 0.5H), 8.62 (t, J = 5.9 Hz, 0.5H), 8.54 (t, J = 6.0 Hz, 0.5H), 8.48 (d, J = 8.1 Hz, 0.5H), 8.39 (t, J = 7.2 Hz, 1H), 8.05 (dd, J = 7.4, 3.9 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 7.2 Hz, 1H), 7.65 (s, 1H), 7.39 – 7.13 (m, 22H), 7.05 (s, 1H), 6.90 (t, J = 7.3 Hz, 0.5H), 6.86 (t, J = 7.3 Hz, 0.5H), 5.06 (q, J = 12.5 Hz, 2H), 4.78 – 4.75 (m, 1H), 4.63 (dd, J = 14.2, 8.1 Hz, 1H), 4.47 – 4.40 (m, 1H), 4.38 – 4.33 (m, 1H), 4.29 (d, J = 6.1 Hz, 1H), 3.17 – 2.69 (m, 7H), 2.31 (s, 3H), 1.78 – 1.74 (m, 1H), 1.66 – 1.53 (m, 2H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.1, 171.1, 171.0, 170.8, 160.5, 158.4, 158.1, 156.7, 156.2, 144.2, 139.1, 138.5, 137.9, 137.6, 136.9, 129.3, 128.4, 128.3, 128.3, 128.1, 127.9, 127.7, 127.1, 126.8, 126.4, 126.1, 121.8, 117.1, 113.0, 65.7, 55.0, 54.5, 54.3, 42.1, 40.4, 37.8, 37.0, 28.7, 25.3, 15.1; HRMS (ESI-TOF) (m/z) $[MH]^+$ calcd for $C_{48}H_{53}N_{10}O_6$ 865.4144, found 865.4108.



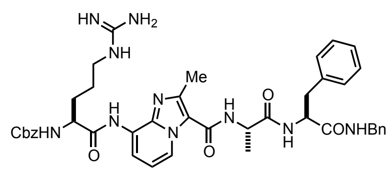
Cbz-Arg-IP(Me)-Val-Phe-NHBn (11). Yield: 54%; mp 159 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.98 (s, 1H), 8.57 (d, J = 6.8 Hz, 1H), 8.53 (t, J = 6.0 Hz, 1H), 8.34 (d, J = 8.2 Hz, 1H), 8.06 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.39 – 7.11 (m, 18H), 6.92 (t, J = 7.2 Hz, 1H), 5.01 (dd, J = 12.0 19.2 Hz, 2H,) 4.62 (m, 1H), 4.44 (m, 1H), 4.35 (t, J = 7.4 Hz, 1H), 4.24 (d, J = 2.8 Hz, 2H), 3.10 (m, 2H), 2.99 (dd, J = 5.0, 13.8 Hz, 1H), 2.84 (dd, J = 10.0, 12.0 Hz, 1H), 2.58 (s, 3H), 2.07 (m, 1H), 1.80 (s, 1H), 1.59 (m, 3H), 0.84 (t, J = 7.0 Hz, 5.6H), 0.72 (d, J = 6.7 Hz, 0.2H), 0.62 (d, J = 6.8 Hz, 0.2H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.2, 170.9, 170.8, 160.6, 158.9, 158.6, 156.9, 156.3, 144.1, 139.1, 138.6, 137.7, 137.0, 129.3, 128.4, 128.2, 128.1, 127.7, 127.1, 126.7, 126.3, 121.9, 118.6, 117.3, 115.6, 113.2, 65.7, 58.4, 55.1, 54.2, 42.1, 37.8, 30.5, 28.8, 25.4, 19.4, 18.4, 15.3; HRMS (ESI-TOF) (m/z) $[MH]^+$ calcd for $C_{44}H_{53}N_{10}O_6$ 817.4144, found 817.4127.



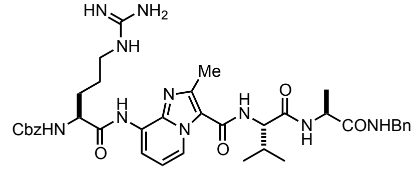
Moc-Arg-IP(Me)-Val-Phe-NHBn (12). Yield: 38%; mp 146 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.98 (s, 1H), 8.59 (dd, J = 6.9, 1.0 Hz, 1H), 8.53 (t, J = 6.0 Hz, 1H), 8.34 (t, J = 6.3 Hz, 1H), 8.07 (dd, J = 7.6, 0.8 Hz, 1H), 7.75 – 7.63 (m, 3H), 7.30 – 7.10 (m, 12H), 7.04 (s, 1H), 7.00 – 6.91 (m, 1H), 4.64 (td, J = 8.6, 6.0 Hz, 1H), 4.45 (d, J = 4.1 Hz, 1H), 4.37 (dd, J = 8.3, 7.1 Hz, 1H), 4.26 (d, J = 5.9 Hz, 2H), 3.57 (s, 3H), 3.12 (dd, J = 12.5, 6.5 Hz, 2H), 3.02 (dd, J = 13.7, 5.8 Hz, 1H), 2.92 – 2.83 (m, 1H), 2.59 (s, 3H), 2.08 (dt, J = 14.9, 6.8 Hz, 1H), 1.79 – 1.74 (m, 1H), 1.66 – 1.51 (m, 3H), 0.87 (t, J = 6.3 Hz, 5.6H), 0.72 (d, J = 6.7 Hz, 0.2H), 0.62 (d, J = 6.9 Hz, 0.2H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.2, 170.9, 170.7, 160.5, 158.4, 158.1, 156.8, 156.7, 144.1, 139.1, 138.6, 137.7, 129.2, 128.2, 128.1, 127.0, 126.7, 126.3, 126.2, 121.9, 117.2, 113.1, 58.3, 54.9, 54.1, 51.7, 42.0, 37.8, 30.5, 28.8, 25.3, 19.4, 18.4, 15.5; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{38}H_{49}N_{10}O_6$ 741.3831, found 741.3876.



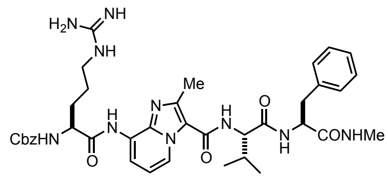
Cbz-Ala-IP(Me)-Val-Phe-NHBn (13). Yield: 29%; mp 160 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.94 (s, 1H), 8.59 (dd, *J* = 6.9, 1.0 Hz, 1H), 8.54 (t, *J* = 5.9 Hz, 1H), 8.35 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.39 – 7.11 (m, 15H), 6.97 (t, *J* = 7.3 Hz, 1H), 5.10 – 5.02 (m, 2H), 4.69 – 4.61 (m, 1H), 4.48 (dd, *J* = 14.3, 7.1 Hz, 1H), 4.37 (dd, *J* = 8.4, 7.1 Hz, 1H), 4.27 (d, *J* = 6.0 Hz, 2H), 3.03 (dd, *J* = 13.6, 5.9 Hz, 1H), 2.93 – 2.84 (m, 1H), 2.59 (s, 3H), 2.08 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.34 (d, *J* = 7.1 Hz, 3H), 0.87 (dd, *J* = 13.0, 6.6 Hz, 5.6H), 0.73 (d, *J* = 6.5 Hz, 0.2H), 0.62 (d, *J* = 6.8 Hz, 0.2H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.8, 170.8, 170.7, 162.3, 160.5, 156.0, 139.1, 137.7, 137.0, 129.2, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.0, 126.8, 126.7, 126.3, 126.2, 121.9, 117.3, 113.4, 65.6, 58.4, 54.1, 51.0, 42.0, 37.8, 30.5, 19.4, 18.4, 17.8, 15.4; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{41}H_{46}N_7O_6$ 732.3504, found 732.3483.



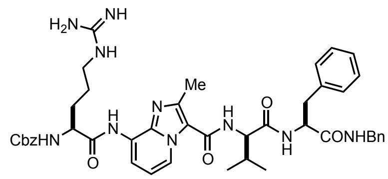
Cbz-Arg-IP(Me)-Ala-Phe-NHBn (14). Yield: 49%; mp 157 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.98 (s, 1H), 8.62 (dd, *J* = 6.9, 1.0 Hz, 1H), 8.52 (t, *J* = 6.0 Hz, 1H), 8.27 (d, *J* = 8.2 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.72 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.67 (t, *J* = 5.4 Hz, 1H), 7.54 (ddd, *J* = 8.3, 5.9, 0.9 Hz, 1H), 7.44 – 7.31 (m, 5H), 7.27 – 7.12 (m, 10H), 7.05 (s, 1H), 6.96 – 6.91 (m, 1H), 5.07 (q, *J* = 12.5 Hz, 2H), 4.60 – 4.42 (m, 3H), 4.36 – 4.25 (m, 2H), 3.15 – 3.08 (m, 2H), 3.05 (dd, *J* = 13.6, 5.6 Hz, 1H), 2.91 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.59 (s, 3H), 1.82 – 1.79 (m, 1H), 1.69 – 1.54 (m, 3H), 1.33 (d, *J* = 7.1 Hz, 2.5H), 1.15 (d, *J* = 7.0 Hz, 0.5H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.1, 170.8, 160.4, 158.5, 158.2, 156.8, 156.2, 144.4, 139.1, 138.6, 137.7, 137.0, 129.3, 128.2, 128.1, 127.7, 127.0, 126.7, 126.3, 124.5, 122.0, 119.2, 117.1, 113.1, 109.7, 65.7, 55.0, 54.3, 48.7, 42.1, 37.6, 28.7, 25.3, 21.1, 18.1, 15.5; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{42}H_{49}N_{10}O_6$ 789.3831, found 789.3847.



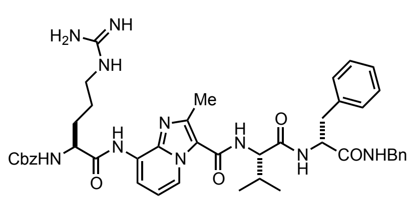
Cbz-Arg-IP(Me)-Val-Ala-NHBn (15). Yield: 42%; mp 127 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.13 (s, 1H), 8.96 – 8.94 (m, 1H), 8.61 (d, *J* = 6.9 Hz, 1H), 8.49 – 8.41 (m, 3H), 8.35 (d, *J* = 7.2 Hz, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.38 – 7.19 (m, 10H), 6.95 (t, *J* = 7.3 Hz, 1H), 5.06 (q, *J* = 12.6 Hz, 2H), 4.46 – 4.40 (m, 2H), 4.39 – 4.34 (m, 1H), 4.27 (dd, *J* = 12.4, 7.3 Hz, 2H), 3.08 – 3.05 (m, 2H), 2.64 (s, 3H), 2.15 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.82 – 1.80 (m, 1H), 1.63 – 1.58 (m, 3H), 1.27 (d, *J* = 7.0 Hz, 3H), 0.96 (dd, *J* = 12.3, 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.3, 172.1, 170.6, 167.1, 162.2, 160.7, 157.4, 156.3, 144.1, 139.3, 138.6, 137.0, 128.4, 128.3, 127.9, 127.7, 127.0, 126.7, 126.3, 117.2, 113.1, 112.9, 79.2, 65.6, 58.1, 54.9, 48.4, 42.0, 30.6, 25.1, 19.5, 18.4, 18.3, 15.5; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{38}H_{49}N_{10}O_6$ 741.3831, found 741.3805.



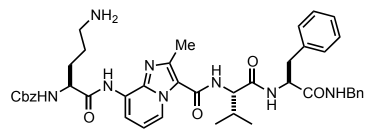
Cbz-Arg-IP(Me)-Val-Phe-NHMe (16). Yield: 36%; mp 136 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.98 (s, 1H), 8.60 – 8.56 (m, 1H), 8.25 (d, *J* = 8.3 Hz, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 7.93 (d, *J* = 4.7 Hz, 1H), 7.87 (d, *J* = 7.4 Hz, 1H), 7.71 (t, *J* = 5.5 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.37 – 7.29 (m, 5H), 7.24 – 7.15 (m, 5H), 7.12 – 7.05 (m, 3H), 6.98 (t, *J* = 7.3 Hz, 1H), 5.05 (q, *J* = 12.6 Hz, 2H), 4.52 – 4.40 (m, 2H), 4.31 (t, *J* = 7.4 Hz, 1H), 3.10 (d, *J* = 6.1 Hz, 2H), 2.95 (dd, *J* = 13.7, 5.2 Hz, 1H), 2.79 (dd, *J* = 13.6, 9.3 Hz, 1H), 2.56 (dd, *J* = 13.4, 7.3 Hz, 6H), 2.06 (dt, *J* = 13.7, 6.7 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.68 – 1.47 (m, 3H), 0.84 (dd, *J* = 9.7, 6.8 Hz, 5.6H), 0.66 (d, *J* = 6.8 Hz, 0.2H), 0.60 (d, *J* = 6.8 Hz, 0.2H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.5, 171.7, 171.0, 161.0, 158.8, 158.5, 157.2, 156.6, 144.5, 139.0, 138.2, 137.3, 129.6, 128.8, 128.4, 128.1, 126.6, 122.3, 119.1, 117.6, 116.1, 113.6, 66.1, 58.8, 55.4, 54.4, 38.2, 30.8, 29.1, 25.9, 25.7, 19.8, 18.8, 15.9; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{38}H_{49}N_{10}O_6$ 741.3831, found 741.3820.



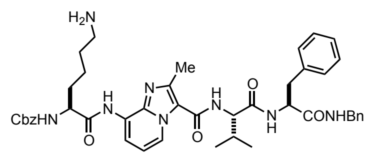
Cbz-Arg-IP(Me)-(D)Val-Phe-NHBn (17). Yield: 54%; mp 160 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.99 (s, 1H), 8.66 (d, *J* = 8.5 Hz, 1H), 8.59 (t, *J* = 6.0 Hz, 1H), 8.44 (dd, *J* = 6.9, 0.9 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.89 (t, *J* = 7.9 Hz, 2H), 7.76 (t, *J* = 5.5 Hz, 1H), 7.38 – 7.11 (m, 18H), 6.83 (t, *J* = 7.3 Hz, 1H), 5.06 (dd, *J* = 12.5 Hz, 2H), 4.67 – 4.38 (m, 1H), 4.48 – 4.42 (m, 1H), 4.37 (d, *J* = 6.0 Hz, 2H), 4.23 (t, *J* = 7.6 Hz, 1H), 3.20 (dd, *J* = 13.6, 3.9 Hz, 1H), 3.12 (dd, *J* = 12.4,. 6.4 Hz, 2H), 2.80 (dd, *J* = 13.5 Hz, 1H), 2.60 (s, 3H), 1.98 – 1.88 (m, 1H), 1.84 – 1.76 (m, 1H), 1.68 – 1.53 (m, 3H), 0.74 (d, *J* = 6.2 Hz, 3H), 0.62 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.2, 171.4, 171.1, 161.1, 158.8, 158.5, 156.8, 156.3, 144.6, 139.1, 138.6, 138.1, 137.0, 129.2, 128.4, 128.3, 128.1, 127.7, 126.8, 126.7, 126.3, 121.6, 118.6, 117.1, 115.7, 113.1, 65.7, 59.3, 55.0, 54.7, 42.1, 37.4, 29.9, 28.8, 25.4, 19.2, 18.6, 15.6; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{44}H_{53}N_{10}O_6$ 817.4144, found 817.4177.



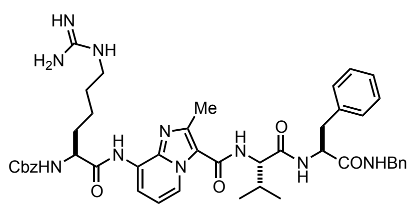
Cbz-Arg-IP(Me)-Val-(D)Phe-NHBn (18). Yield: 54%; mp 105 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.98 (s, 1H), 8.66 (d, *J* = 8.5 Hz, 1H), 8.58 (t, *J* = 6.0 Hz, 1H), 8.45 (d, *J* = 6.9 Hz, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.87 (t, *J* = 7.9 Hz, 2H), 7.70 (t, *J* = 5.3 Hz, 1H), 7.39 – 7.06 (m, 17H), 7.30 – 7.25 (m, 1H), 6.84 (t, *J* = 7.3 Hz, 1H), 5.06 (dd, *J* = 12.5 Hz, 2H), 4.67 – 4.57 (m, 1H), 4.50 – 4.41 (m, 1H), 4.37 (d, *J* = 6.0 Hz, 2H), 4.24 (t, *J* = 7.5 Hz, 1H), 3.25 – 3.06 (m, 3H), 2.85 – 2.74 (m, 1H), 2.58 (s, 3H). 1.99 – 1.86 (m, 1H), 1.84 – 1.72 (m, 1H), 1.70 – 1.52 (m, 3H), 0.73 (d, *J* = 6.7 Hz, 3H), 0.62 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.1, 171.4, 171.1, 161.0, 158.6, 158.3, 1569.8, 156.2, 144.5, 139.1, 138.6, 138.1, 137.0, 129.2, 128.4, 128.3, 128.1, 127.9, 127.7, 126.8, 126.7, 126.3, 121.7, 117.0, 113.1, 65.8, 59.2, 55.0, 54.6, 42.1, 40.4, 37.4, 30.0, 28.7, 25.3, 19.2, 18.6, 15.6; HRMS (ESI-TOF) (*m/z*) $[MNa]^+$ calcd for $C_{44}H_{52}N_{10}O_6Na$ 839.3964, found 839.3969.



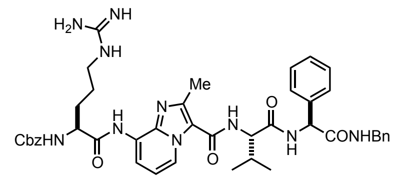
Cbz-Orn-IP(Me)-Val-Phe-NHBn (19). Yield: 42%; mp 147 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.56 (dd, *J* = 14.7, 6.4 Hz, 2H), 8.36 (d, *J* = 8.2 Hz, 1H), 8.08 (d, *J* = 7.7 Hz, 1H), 7.95 – 7.82 (m, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.41 – 7.09 (m, 16H), 6.95 (t, *J* = 7.3 Hz, 1H), 5.06 (q, *J* = 12.7 Hz, 2H), 4.64 (dd, *J* = 14.4, 8.4 Hz, 1H), 4.42 – 4.32 (m, 3H), 4.26 (d, *J* = 6.0 Hz, 2H), 3.02 (dd, *J* = 13.7, 5.8 Hz, 1H), 2.88 (m, 2H), 2.59 (s, 3H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.09 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.69 – 1.56 (m, 1H), 1.51 – 1.43 (m, 2H), 0.87 (t, *J* = 6.9 Hz, 5.4H), 0.73 (d, *J* = 6.6 Hz, 0.3H), 0.61 (d, *J* = 6.9 Hz, 0.3H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.5, 170.9, 170.7, 160.6, 156.2, 144.1, 139.1, 138.6, 137.7, 137.0, 129.2, 128.4, 128.2, 128.1, 127.9, 127.7, 127.3, 127.0, 126.7, 126.3, 121.8, 117.2, 113.2, 112.9, 65.6, 58.4, 55.3, 54.1, 42.0, 41.1, 37.8, 30.9, 29.4, 29.2, 19.4, 18.4, 15.6; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{43}H_{51}N_8O_6$ 775.3926, found 775.3939.



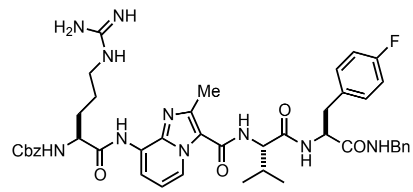
Cbz-Lys-IP(Me)-Val-Phe-NHBn (20). Yield: 36%; mp 165 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.66 (d, *J* = 8.9 Hz, 0.4H), 8.62 – 8.48 (m, 1.6H), 8.42 (d, *J* = 6.9 Hz, 0.3H), 8.35 (d, *J* = 8.1 Hz, 0.7H), 8.08 – 8.02 (m, 1H), 7.89 – 7.78 (m, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.40 – 7.11 (m, 15H), 6.94 (t, *J* = 7.3 Hz, 0.8H), 6.82 (t, *J* = 7.3 Hz, 0.2H), 5.06 (q, *J* = 12.5 Hz, 2H), 4.64 (dd, *J* = 14.4, 8.7 Hz, 1H), 4.30 (m, 5H), 3.02 (dd, *J* = 13.6, 5.6 Hz, 1H), 2.88 (dd, *J* = 13.6, 8.9 Hz, 1H), 2.59 (s, 3H), 2.55 – 2.51 (m, 2H), 2.08 (dd, *J* = 13.2, 6.4 Hz, 1H), 1.79 – 1.65 (m, 1H), 1.62 – 1.58 (m, 1H), 1.39 – 1.32 (m, 5H), 1.25 – 1.16 (m, 1H), 0.87 (t, *J* = 6.9 Hz, 4.2H), 0.73 (d, *J* = 6.7 Hz, 0.6H), 0.61 (d, *J* = 6.7 Hz, 0.6H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.5, 170.9, 170.7, 160.6, 156.3, 144.1, 139.1, 138.6, 137.7, 137.0, 129.2, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.0, 126.8, 126.7, 126.3, 117.2, 113.2, 104.6, 65.6, 58.4, 55.6, 54.1, 42.0, 41.1, 37.8, 32.3, 31.4, 30.5, 23.0, 19.4, 18.4, 15.5; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{44}H_{54}N_8O_6$ 789.4083, found 789.4087.



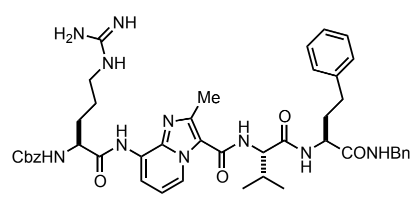
Cbz-Har-IP(Me)-Val-Phe-NHBn (21). Yield: 59%; mp 153 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.00 (s, 1H), 8.58 (d, *J* = 6.9 Hz, 1H), 8.54 (t, *J* = 5.9 Hz, 1H), 8.35 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 7.5 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.65 (t, *J* = 5.4 Hz, 1H), 7.40 – 7.11 (m, 17H), 7.06 (s, 1H), 6.95 (t, *J* = 7.3 Hz, 1H), 5.06 (q, *J* = 12.5 Hz, 2H), 4.64 (dd, *J* = 14.3, 8.5 Hz, 1H), 4.41 – 4.35 (m, 2H), 4.26 (d, *J* = 5.9 Hz, 2H), 3.11 – 3.06 (m, 2H), 3.02 (dd, *J* = 13.7, 5.7 Hz, 1H), 2.88 (dd, *J* = 13.8, 8.8 Hz, 1H), 2.59 (s, 3H), 2.11 – 2.07 (m, 1H), 1.81 – 1.77 (m, 1H), 1.68 – 1.62 (m, 1H), 1.48 – 1.42 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 5.4H), 0.73 (d, *J* = 6.7 Hz, 0.3H), 0.62 (d, *J* = 6.8 Hz, 0.3H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.3, 170.8, 170.7, 160.6, 158.5, 158.2, 156.8, 156.3, 144.1, 139.1, 138.6, 137.7, 137.0, 129.2, 128.4, 128.2, 128.1, 127.7, 127.0, 126.7, 126.3, 118.7, 117.2, 115.7, 113.2, 65.8, 58.3, 55.4,54.1, 42.0, 40.6, 37.8, 31.2, 30.5, 28.2, 22.9, 19.4, 18.4, 15.5; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{45}H_{55}N_{10}O_6$ 831.4301, found 831.4278.



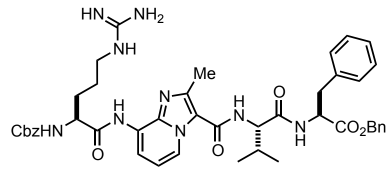
Cbz-Arg-IP(Me)-Val-Phg-NHBn (22). Yield: 49%; mp 154 °C; [1]H NMR (400 MHz, $(CD_3)_2SO$) δ 10.00 (s, 1H), 8.91 (d, *J* = 8.0 Hz, 1H), 8.86 (t, *J* = 6.0 Hz, 1H), 8.63 – 8.56 (m, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.95 – 7.84 (m, 2H), 7.75 – 7.70 (m, 1H), 7.50 – 7.42 (m, 2H), 7.39 – 7.27 (m, 8H), 7.25 – 7.18 (m, 7H), 7.08 (s, 1H), 6.96 – 6.91 (m, 1H), 5.58 (dd, *J* = 15.2, 7.9 Hz, 1H), 5.07 (q, *J* = 12.6 Hz, 2H), 4.54 (t, *J* = 7.8 Hz, 1H), 4.50 – 4.41 (m, 1H), 4.31 – 4.27 (m, 2H), 3.12 (d, *J* = 6.1 Hz, 2H), 2.64 (s, 3H), 2.18 – 2.13 (m, 1H), 1.84 – 1.79 (m, 1H), 1.72 – 1.50 (m, 3H), 0.94 (ddd, *J* = 11.4, 6.6, 4.3 Hz, 6H); [13]C NMR (101 MHz, $(CD_3)_2SO$) δ 172.2, 171.0, 170.7, 169.8, 160.9, 158.5, 156.3, 156.2, 144.3, 139.0, 138.8, 138.6, 137.0, 128.4, 128.3, 128.3, 127.9, 127.7, 127.2, 127.0, 126.8, 126.2, 121.8, 117.2, 113.2, 65.7, 58.4, 56.3, 55.0, 42.1, 40.4, 30.5, 28.8, 25.3, 19.4, 18.6, 15.5; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{43}H_{51}N_{10}O_6$ 803.3988, found 803.3962.



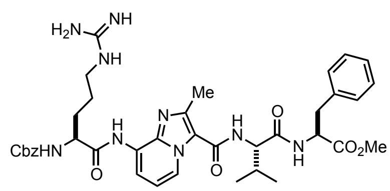
Cbz-Arg-IP(Me)-Val-(4-F)Phe-NHBn (23). Yield 44%; mp 139 °C; [1]H NMR (400 MHz, $(CD_3)_2SO$) δ 10.00 (s, 1H), 8.60 – 8.52 (m, 2H), 8.36 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 6.9 Hz, 1H), 7.39 – 7.18 (m, 12H), 7.14 (d, *J* = 6.9 Hz, 2H), 7.08 – 6.98 (m, 4H), 6.95 (t, *J* = 7.3 Hz, 1H), 5.07 (q, *J* = 12.5 Hz, 2H), 4.66 – 4.58 (m, 1H), 4.49 – 4.41 (m, 1H), 4.36 (t, *J* = 7.7 Hz, 1H), 4.27 (d, *J* = 5.8 Hz, 2H), 3.12 (d, *J* = 6.0 Hz, 2H), 3.01 (dd, *J* = 13.7, 5.7 Hz, 1H), 2.85 (dd, *J* = 13.6, 9.3 Hz, 1H), 2.58 (s, 3H), 2.07 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.85 – 1.79 (m, 1H), 1.68 – 1.52 (m, 3H), 0.88 (t, *J* = 6.9 Hz, 5.4H), 0.73 (d, *J* = 6.7 Hz, 0.3H), 0.63 (d, *J* = 6.7 Hz, 0.3H); [13]C NMR (101 MHz, $(CD_3)_2SO$) δ 172.2, 170.7, 162.2, 160.6, 159.8, 158.6, 156.8, 156.2, 144.1, 139.1, 138.6, 136.9, 133.8, 131.1, 128.4, 128.2, 127.7, 127.1, 126.8, 126.2, 118.6, 117.2, 115.7, 114.6, 113.2, 65.7, 58.3, 55.0, 54.2, 42.0, 40.4, 37.0, 30.5, 28.8, 25.3, 19.4, 18.5, 15.4; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{44}H_{52}FN_{10}O_6$ 835.4050, found 835.4032.



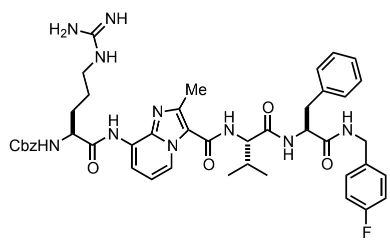
Cbz-Arg-IP(Me)-Val-homoPhe-NHBn (24). Yield: 52%; mp 162 °C; [1]H NMR (400 MHz, $(CD_3)_2SO$) δ 10.00 (s, 1H), 8.60 (d, *J* = 6.9 Hz, 1H), 8.49 (t, *J* = 6.0 Hz, 1H), 8.38 (d, *J* = 7.9 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 5.6 Hz, 1H), 7.38 – 7.22 (m, 13H), 7.20 – 7.14 (m, 4H), 7.06 (s, 1H), 6.92 (t, *J* = 7.3 Hz, 1H), 5.07 (q, *J* = 12.5 Hz, 2H), 4.49 – 4.40 (m, 2H), 4.35 (dd, *J* = 8.4, 5.0 Hz, 1H), 4.29 (d, *J* = 5.9 Hz, 2H), 3.12 (dd, *J* = 12.3, 6.3 Hz, 2H), 2.69 – 2.53 (m, 5H), 2.18 (dq, *J* = 13.7, 6.7 Hz, 1H), 1.96 – 1.87 (m, 3H), 1.69 – 1.53 (m, 3H), 0.98 (dd, *J* = 6.7, 2.9 Hz, 6H); [13]C NMR (101 MHz, $(CD_3)_2SO$) δ 172.2, 171.3, 171.0, 160.8, 158.5, 158.2, 156.8, 156.2, 144.2, 141.3, 139.4, 138.6, 136.9, 128.4, 128.4, 128.3, 128.3, 127.7, 127.1, 126.8, 126.2, 125.9, 121.7, 117.4, 113.1, 112.9, 65.7, 58.6, 55.0, 52.5, 42.1, 34.0, 31.4, 30.3, 28.8, 25.3, 19.5, 18.6, 15.5; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{45}H_{54}N_{10}O_6$ 831.4306, found 831.4325.



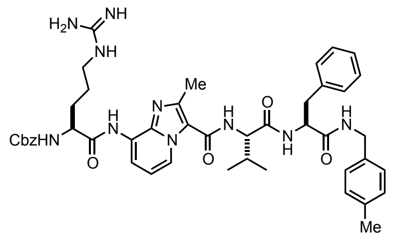
Cbz-Arg-IP(Me)-Val-Phe-OBn (25). Yield: 43%; mp 64 °C; ^{1}H NMR (400 MHz, CD_3OD) δ ^{1}H NMR (400 MHz, CD_3OD) δ 8.73 – 8.66 (m, 2H), 8.14 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.40 – 7.10 (m, 13H), 7.08 (d, *J* = 7.2 Hz, 1H), 7.02 (t, *J* = 7.2 Hz, 1H), 5.13 (s, 4H), 4.78 (dd, *J* = 14.2, 8.6 Hz, 1H), 4.45 – 4.38 (m, 2H), 3.27 – 3.15 (m, 3H), 2.99 (dd, *J* = 13.8, 9.0 Hz, 1H), 2.16 – 1.96 (m, 2H), 1.87 – 1.64 (m, 3H), 1.01 – 0.92 (m, 6H); 13C NMR (101 MHz, CD_3OD) δ 172.1, 172.0, 171.1, 161.5, 160.9, 157.3, 157.2, 143.6, 136.6, 135.5, 134.8, 128.9, 128.1, 128.1, 128.1, 128.0, 127.9, 127.7, 127.5, 126.4, 125.3, 123.0, 117.1, 116.1, 113.6, 66.7, 66.5, 58.7, 55.4, 53.9, 40.5, 37.0, 30.8, 28.8, 25.0, 18.4, 17.6, 13.9; HRMS (ESI-TOF) *m/z* $[M\quad H]^+$ calcd for $C_{44}H_{52}N_9O_7$ 818.3984, found 818.3948.



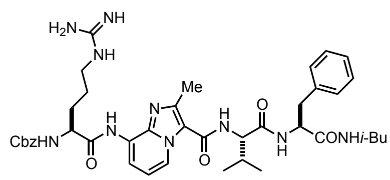
Cbz-Arg-IP(Me)-Val-Phe-OMe (26). Yield: 65%; mp 127 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.98 (s, 1H), 8.61 (dd, *J* = 11.8, 4.8 Hz, 2H), 8.09 (d, *J* = 7.4 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.69 – 7.64 (m, 2H), 7.39 – 7.30 (m, 6H), 7.26 – 7.13 (m, 6H), 7.05 (s, 1H), 7.02 – 6.97 (m, 1H), 5.07 (q, *J* = 12.5 Hz, 2H), 4.54 (ddd, *J* = 9.1, 7.5, 5.8 Hz, 1H), 4.50 – 4.37 (m, 2H), 3.59 (s, 3H), 3.16 – 3.02 (m, 3H), 3.01 – 2.88 (m, 1H), 2.57 (s, 3H), 2.10 (dq, *J* = 13.6, 6.8 Hz, 1H), 1.78 (bs, 1H), 1.65 – 1.58 (m, 3H), 0.93 (dd, *J* = 6.7, 3.5 Hz, 5.6H), 0.77 (d, *J* = 6.7 Hz, 0.2H), 0.70 (d, *J* = 6.8 Hz, 0.2H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.1, 171.8, 171.1, 160.4, 158.1, 156.8, 156.2, 144.1, 138.6, 137.2, 136.9, 129.1, 128.4, 128.2, 127.9, 127.7, 126.5, 126.2, 121.9, 117.2, 113.2, 65.7, 57.8, 55.0, 53.6, 51.8, 40.4, 36.6, 30.6, 28.7, 25.3, 19.3, 18.4, 15.4; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{38}H_{48}N_9O_7$ 742.3677, found 742.3709.



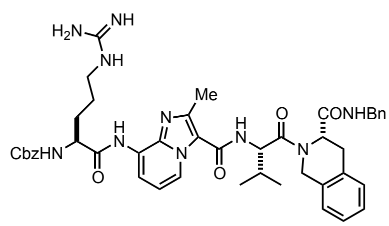
Cbz-Arg-IP(Me)-Val-Phe-NH(4-F)Bn (27). Yield: 64%; mp 142 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.98 (s, 1H), 8.61 – 8.58 (m, 1H), 8.54 (t, *J* = 5.9 Hz, 1H), 8.35 (d, *J* = 8.2 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.67 (dd, *J* = 11.9, 7.1 Hz, 2H), 7.39 – 7.28 (m, 5H), 7.27 – 7.13 (m, 9H), 7.10 – 7.03 (m, 3H), 6.96 (t, *J* = 7.3 Hz, 1H), 5.07 (q, *J* = 12.5 Hz, 2H), 4.62 (dd, *J* = 14.4, 8.4 Hz, 1H), 4.50 – 4.42 (m, 1H), 4.41 – 4.34 (m, 1H), 4.24 (d, *J* = 6.0 Hz, 2H), 3.12 (dd, *J* = 12.4, 6.4 Hz, 2H), 3.01 (dd, *J* = 13.7, 5.9, 1H), 2.93 – 2.81 (m, 1H), 2.59 (s, 3H), 2.09 (dq, *J* = 13.6, 6.7 Hz, 1H), 1.83 – 1.80 (m, 1H), 1.64 – 1.58 (m, 3H), 0.90 – 0.85 (m, 5.6H), 0.73 (d, *J* = 6.7 Hz, 0.2H), 0.63 (d, *J* = 6.7 Hz, 0.2H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.1, 170.8, 162.3, 160.5, 159.9, 158.4, 158.1, 156.7, 156.2, 144.1, 138.6, 137.6, 136.9, 135.3, 129.2, 129.0, 128.9, 128.4, 128.1, 127.7, 126.3, 121.9, 117.2, 115.0, 113.1, 65.7, 58.3, 55.0, 54.1, 41.3, 40.4, 37.7, 30.5, 28.7, 25.3, 19.4, 18.4, 15.5; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{44}H_{52}FN_{10}O_6$ 835.4050, found 835.4027.



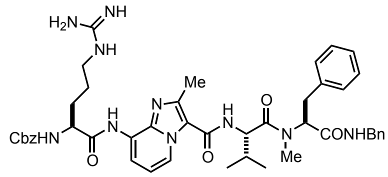
Cbz-Arg-IP(Me)-Val-Phe-NH(4-Me)Bn (28). Yield: 52%; mp 161 °C; [1]H NMR (400 MHz, $(CD_3)_2SO$) δ 9.98 (s, 1H), 8.59 (d, *J* = 6.9 Hz, 1H), 8.47 (t, *J* = 5.9 Hz, 1H), 8.32 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.63 (t, *J* = 5.5 Hz, 1H), 7.41 – 7.28 (m, 5H), 7.29 – 7.12 (m, 7H), 7.05 – 6.98 (m, 5H), 6.96 (t, *J* = 7.3 Hz, 1H), 5.07 (q, *J* = 12.5 Hz, 2H), 4.63 (dd, *J* = 14.3, 8.6 Hz, 1H), 4.45 (d, *J* = 4.4 Hz, 1H), 4.42 – 4.33 (m, 1H), 4.21 (d, *J* = 6.0 Hz, 2H), 3.12 (d, *J* = 6.0 Hz, 2H), 3.01 (dd, *J* = 13.7, 5.6 Hz, 1H), 2.86 (dd, *J* = 13.6, 9.0 Hz, 1H), 2.59 (s, 3H), 2.24 (s, 3H), 2.09 (dd, *J* = 13.5, 6.8 Hz, 1H), 1.82 – 1.79 (m, 1H), 1.68 – 1.49 (m, 3H), 0.88 (t, *J* = 6.8 Hz, 5.6H), 0.72 (d, *J* = 6.6 Hz, 0.2H), 0.62 (d, *J* = 6.7 Hz, 0.2H); [13]C NMR (101 MHz, $(CD_3)_2SO$) δ 171.1, 169.7, 169.7, 159.6, 157.5, 157.2, 155.7, 155.2, 143.1, 137.6, 136.7, 135.9, 135.0, 134.7, 128.2, 127.7, 127.4, 127.1, 126.7, 126.0, 125.3, 120.9, 116.2, 112.2, 111.9, 64.7, 57.4, 54.0, 53.1, 40.8, 39.4, 36.8, 29.5, 27.7, 24.3, 19.7, 18.4, 17.4, 14.5; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{45}H_{55}N_{10}O_6$ 831.4301, found 831.4266.



Cbz-Arg-IP(Me)-Val-Phe-NH*i*Bu (29). Yield: 63%; mp 159 °C; [1]H NMR (400 MHz, $(CD_3)_2SO$) δ 9.99 (s, 1H), 8.61 (d, *J* = 6.9 Hz, 1H), 8.27 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 7.97 (t, *J* = 5.9 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.75 – 7.70 (m, 2H), 7.39 – 7.30 (m, 5H), 7.26 – 7.17 (m, 6H), 7.15 – 7.06 (m, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 5.07 (q, *J* = 12.5 Hz, 2H), 4.58 (dd, *J* = 14.5, 8.7 Hz, 1H), 4.50 – 4.42 (m, 1H), 4.40 – 4.30 (m, 1H), 3.15 – 3.09 (m, 2H), 2.90 – 2.78 (m, 4H), 2.59 (s, 3H), 2.07 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.83 – 1.78 (m, 1H), 1.62 (td, *J* = 13.3, 6.7 Hz, 4H), 0.87 (t, *J* = 7.1 Hz, 6H), 0.76 (dd, *J* = 6.6, 5.1 Hz, 5.4H), 0.71 (d, *J* = 6.7 Hz, 0.3H), 0.63 (d, *J* = 6.7 Hz, 0.3H); [13]C NMR (101 MHz, $(CD_3)_2SO$) δ 172.2, 170.7, 170.6, 160.5, 158.3, 156.8, 156.2, 144.0, 138.6, 137.8, 137.0, 129.2, 128.4, 128.0, 127.7, 126.2, 121.9, 117.3, 113.2, 104.6, 65.7, 58.4, 55.0, 54.1, 46.1, 38.0, 30.5, 28.8, 28.0, 25.3, 20.1, 20.0, 19.4, 18.4, 15.5; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{41}H_{55}N_{10}O_6$ 783.4301, found 783.4292.

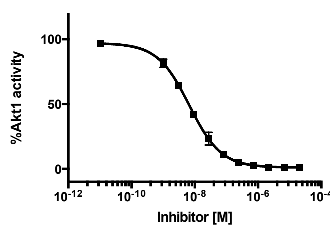


Cbz-Arg-IP(Me)-Val-Tic-NHBn (30). Yield: 68%; mp 43 °C; [1]H NMR (400 MHz, $(CD_3)_2SO$) δ 9.98 (d, *J* = 8.1 Hz, 1H), 8.58 (d, *J* = 7.0 Hz, 1H), 8.46 – 8.43 (m, 1H), 8.11 – 8.00 (m, 2H), 7.88 (d, *J* = 7.1 Hz, 1H), 7.69 (s, 1H), 7.33 (dd, *J* = 19.4, 9.3 Hz, 6H), 7.21 (dd, *J* = 9.7, 5.3 Hz, 7H), 7.13 – 7.05 (m, 4H), 6.95 (dd, *J* = 12.9, 5.8 Hz, 1H), 6.87 (bs, 0.8H), 5.33 (bs, 0.2H), 5.13 – 4.99 (m, 3H), 4.93 (t, *J* = 6.0 Hz, 1H), 4.75 (d, *J* = 15.2 Hz, 0.7H), 4.45 (bs, 1H), 4.35 (d, *J* = 17.5 Hz, 0.3H), 4.27 – 4.15 (m, 1.5H), 3.95 (dd, *J* = 15.3, 5.1 Hz, 0.4H), 3.13 (d, *J* = 5.9 Hz, 3H), 2.66 (s, 1H), 2.56 (s, 2H), 2.30 (dd, *J* = 13.6, 6.8 Hz, 0.6H), 2.24 – 2.16 (m, 0.4H), 2.05 (d, *J* = 52.2 Hz, 0.3H), 1.79 – 1.75 (m, 1H), 1.68 – 1.59 (m, 3H), 1.29 (d, *J* = 46.4 Hz, 0.7H), 1.12 – 0.96 (m, 6H); [13]C NMR (101 MHz, $(CD_3)_2SO$) δ 172.1, 171.0, 170.7, 169.2, 160.6, 158.3, 156.2, 156.8, 144.2, 139.4, 139.0, 138.6, 136.9, 134.3, 133.7, 132.5, 128.4, 128.1, 127.9, 127.7, 127.1, 126.7, 126.6, 126.0, 121.8, 117.1, 113.2, 79.2, 65.7, 55.0, 54.6, 53.8, 45.7, 41.9, 31.5, 30.1, 28.7, 25.3, 19.6, 18.3, 15.3; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{45}H_{53}N_{10}O_6$ 829.4144, found 829.4174.



Cbz-Arg-IP(Me)-Val-(N-Me)Phe-NHBn (31). Yield: 33%; mp 46 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.98 (s, 1H), 8.53 – 8.47 (m, 1H), 8.42 – 8.36 (m, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 0.4H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 0.6H), 7.77 (t, *J* = 5.1 Hz, 1H), 7.38 – 7.29 (m, 6H), 7.25 – 7.20 (m, 5H), 7.18 – 7.14 (m, 3H), 7.12 – 7.09 (m, 2H), 7.07 – 6.91 (m, 3H), 5.33 (dd, *J* = 9.6, 6.2 Hz, 0.5H), 5.10 – 4.98 (m, 2.5H), 4.71 (t, *J* = 8.1 Hz, 0.6H), 4.51 – 4.42 (m, 1.4H), 4.33 (dd, *J* = 15.3, 6.2 Hz, 1H), 4.22 (dd, *J* = 15.1, 5.8 Hz, 1H), 3.91 (dd, *J* = 15.1, 5.3 Hz, 0.6H), 3.40 (dd, *J* = 14.0, 4.1 Hz, 0.4H), 3.23 (dd, *J* = 14.4, 6.0 Hz, 1H), 3.15 – 3.10 (m, 3H), 3.03 – 2.95 (m, 1H), 2.88 – 2.84 (m, 1H), 2.58 – 2.53 (m, 3H), 2.09 – 2.06 (m, 1H), 1.88 – 1.75 (m, 1H), 1.69 – 1.52 (m, 3H), 0.93 (dd, *J* = 13.6, 6.7 Hz, 3.5H), 0.69 (d, *J* = 6.8 Hz, 1H), 0.64 (d, *J* = 6.6 Hz, 0.2H), 0.52 (d, *J* = 6.6 Hz, 1H), 0.46 (d, *J* = 6.8 Hz, 0.2H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 172.1, 172.1, 171.1, 169.7, 160.4, 158.6, 156.8, 144.2, 139.3, 138.8, 137.8, 137.0, 129.3, 128.8, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.0, 127.0, 126.7, 126.2, 121.8, 118.6, 117.0, 115.7, 113.1, 112.9, 104.6, 65.4, 55.1, 54.3, 42.1, 34.2, 32.2, 30.1, 28.7, 25.3, 19.5, 19.2, 18.5, 17.7, 15.4; HRMS (ESI-TOF) (*m/z*) $[MH]^+$ calcd for $C_{45}H_{55}N_{10}O_6$ 831.4301, found 831.4290.

In vitro hotspot kinase assay. Inhibition of Akt1-3 kinase activity was performed at Reaction Biology Corporation using the “HotSpot” assay platform. The substrate Crosstide (GRPRTSSFAEG) was prepared in base reaction buffer containing 20 mM Hepes (pH 7.5), 10 mM $MgCl_2$, 1 mM EGTA, 0.02% Brij35, 0.02 mg/ml BSA, 0.1 mM Na_3VO_4, 2 mM DTT, 1% DMSO to achieve a final substrate concentration of 20 μM. N-terminal His_6-tagged, recombinant human kinase purified from insect cells was added to achieve a final enzyme concentration of 2.5 nM. Compounds were delivered as DMSO stock solutions in varying concentrations and ^{33}P-ATP (specific activity 0.01 μCi/μl final) was added into the reaction mixture to initiate the reaction. The kinase reaction was incubated for 120 min at rt and the reactions spotted onto P81 ion exchange paper. Dose-response data points are an average of N = 3 experiments and curves were fit using GraphPad Prism software and a variable slope 4-parameter model. A control inhibitor, staurosporine, was determined to have an IC_{50} of 6.71 nM:



Staurosporine IC50 = 6.71 nM
95% CI = 6.01 nM to 7.48 nM

Inhibition of seven different AGC family kinases by compound **11** was performed at Reaction Biology Corporation using the same HotSpot assay platform. Inhibtion of these kinases by 10 μM **11** is provided below:

Kinase	%inhibition at 10 μM
PDK1	0
PKA	54
PKCa	7
LATS1	0
MSK1	65
ROCK1	11
RSK1	49

Western blot kinase assay. The effect of **11** on Akt1 kinase activity was determined by using immunoprecipitated Akt protein from HEK293 cells transfected with Myc-tagged wild-type Akt1. The non-radioactive in vitro Akt kinase assay was performed in the presence of 200 μM ATP with GSK3βfusion protein as a substrate, according to the manufacturer's instructions (Cell Signaling Assay Kit #9840), except that Myc antibody was used in place of immobilized Akt antibody to immunoprecipitate Akt. The phosphorylation of GSK3β (S9) is detected by western blot analysis with anti-phospho-GSK3β (S9) antibody (#5558, Cell Signaling) and GSK3β antibody (#5558, and #9315, Cell Signaling).

Peptide digestion studies. The stability of **11** and control peptides (Cbz-RTSVF-NHBn and Crosstide) to degradation by chymotrypsin and pronase was determined by integration of HPLC peaks relative to an internal standard sample of Fmoc-Phe-OH. A 1 mM sample of analyte in pH 7.4 ammonium bicarbonate buffer (with 2% DMSO) was incubated at 37ºC in the presence of chymotrypsin or pronase (0.1 mg/mL). Aliquots as various timepoints were analyzed by RP-HPLC (C_{18} 4 x 150 mm column with acetonitrile/water + 0.1% formic acid eluent, 1 mL/min flow rate). Integrated analyte peaks normalized to internal standard were plotted as a percentage of analyte amount in the absence of enzymes.

Computational docking studies. The three-dimensional structural coordinates for the activated Akt/protein kinase B ternary complex with glycogen synthase kinase-3 beta (GSK3)-peptide (Ac-GRPRTTSFAE-NH3) and AMP-PNP (Phosphoaminophosphonic acid - adenylate ester) were obtained from the Protein Databank (PDB ID: 1O6K) [1]. After assigning bond orders and atom types, the original hydrogen atoms were removed and then added with an assumed physiological pH of 7.4 for predicting protonation states. Partial atomic charges were assigned using the OPLS-2005 force field [2]. These procedures were performed with the Protein Preparation Wizard [3] from Schrödinger, Inc. Energy minimization was carried out with the Impact Refinement module [4] using the OPLS-2005 force field and truncated newtonian method [5]. Minimization was concluded when the root-mean-square deviation (RMSD) reached a maximum cutoff of 0.30 Å. This step allows hydrogen atoms to be freely minimized, while allowing for heavy-atom movement to relax strained bonds, angles, and clashes. This procedure minimizes potential crystal artifacts that may be present in the PDB input structure. X-ray structures served as reference structures for the calculation of the RMSD. The GSK3 ligand in the crystal structure was used to determine the location of a docking grid box and was then removed along with the AMP-PNP co-crystallized ligand prior to grid generation. The grid size was expanded to fit the length of the GSK3 ligand and all thiol and hydroxyl groups in the grid where allowed to rotate. The rigid receptor docking of the GSK3 control and BE10 was carried out using the Glide [6], version 6.2, program in the extra-precision (XP) mode [7]. No constraints were applied for all docking studies. For both ligands, a maximum of five poses were saved after the docking process.

[1] Yang, Jing, et al. "Crystal structure of an activated Akt/protein kinase B ternary complex with GSK3-peptide and AMP-PNP." *Nature Structural & Molecular Biology* 9.12 (2002): 940-944.

[2] Banks, Jay L., et al. "Integrated modeling program, applied chemical theory (IMPACT)." *Journal of computational chemistry* 26.16 (2005): 1752-1780.

[3] Maestro v9.7, Schrödinger, Inc.: Portland, OR

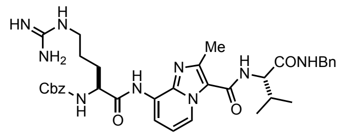
[4] Impact version 6.2, Schrödinger, LLC, New York, NY, 2009

[5] Dembo, Ron S., and Trond Steihaug. "Truncated-newtono algorithms for large-scale unconstrained optimization." *Mathematical Programming* 26.2 (1983): 190-212.

[6] Glide, version 6.2, Schrödinger, LLC, New York, NY, 2014.

[7] Friesner, R.A.; Murphy, R.B.; Repasky, M.P.; Frye, L.L.; Greenwood, J.R.; Halgren, T.A.; Sanschagrin, P.C.; Mainz, D.T., "Extra Precision Glide: Docking and Scoring Incorporating a Model of Hydrophobic Enclosure for Protein-Ligand Complexes," *J. Med. Chem.*, 2006, *49*, 6177–619

[1]H NMR SPECTRA FOR COMPOUNDS 4-31.



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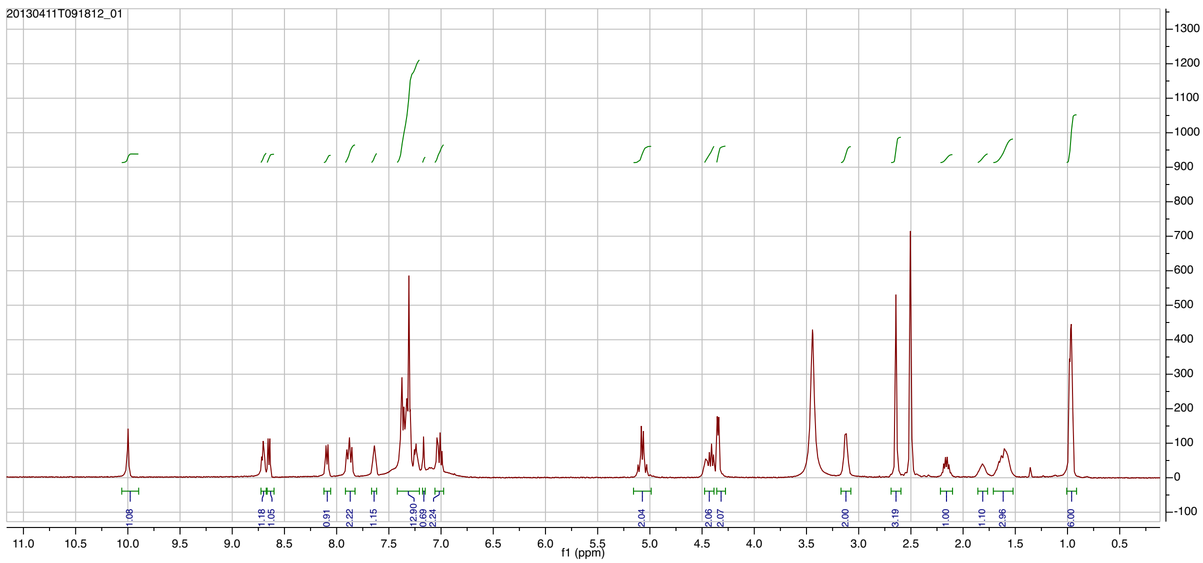

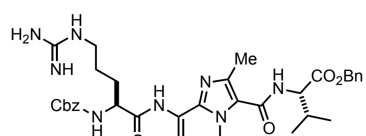

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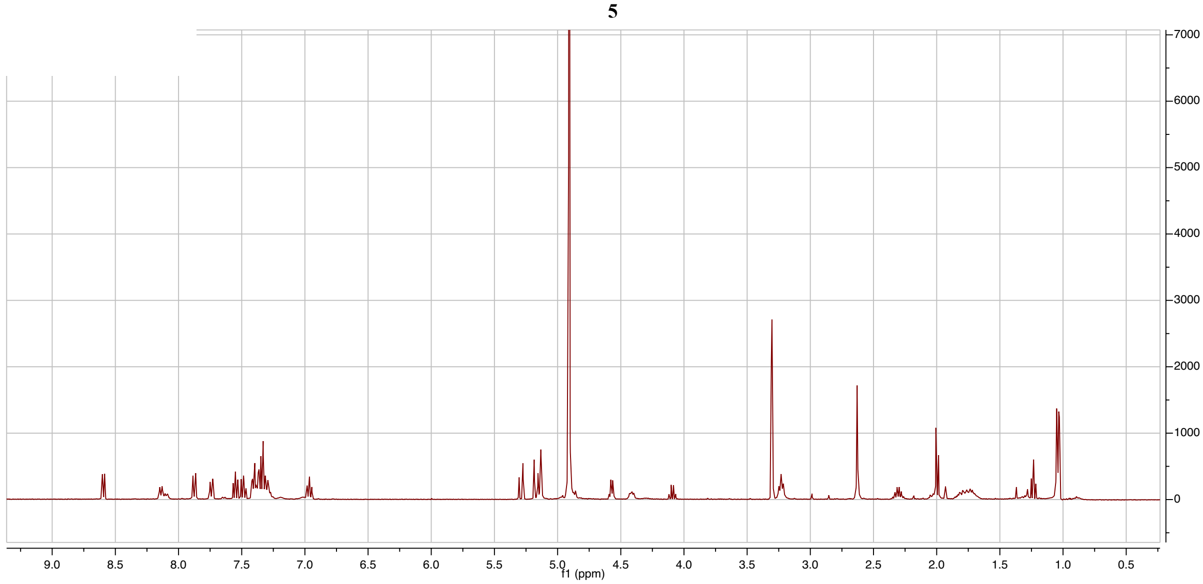

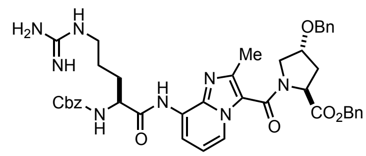
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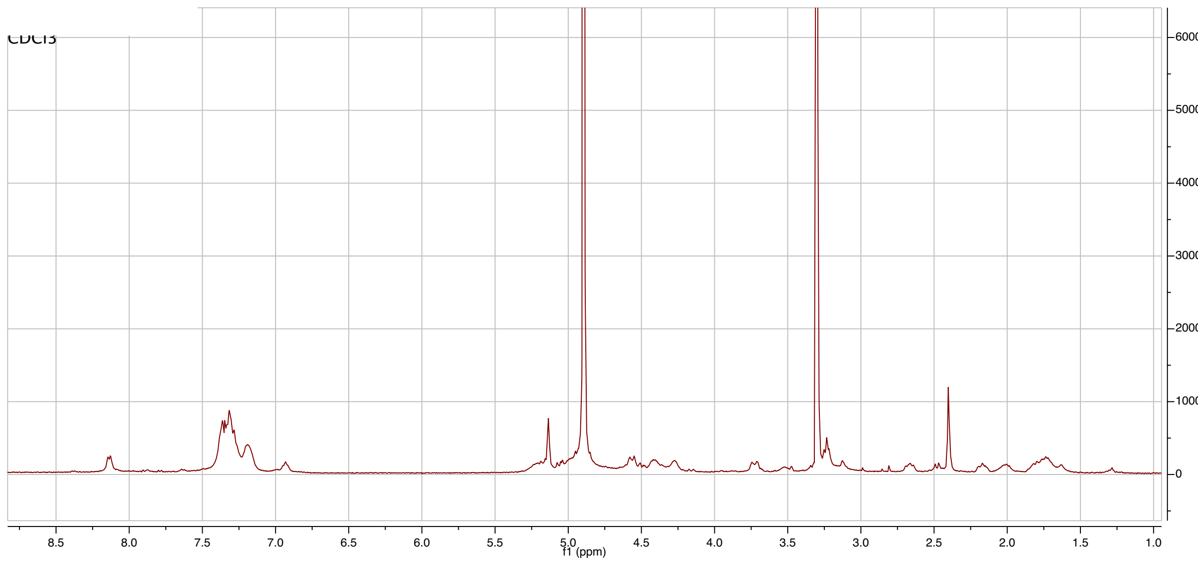
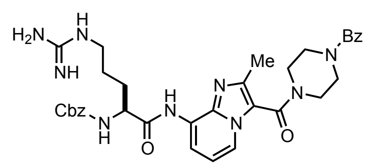
N
NH
OBn
Me
N
H
N
N
N
Cbz
N
H
O
O
CO2Bn

6


CDCl3
f1 (ppm)


H2N
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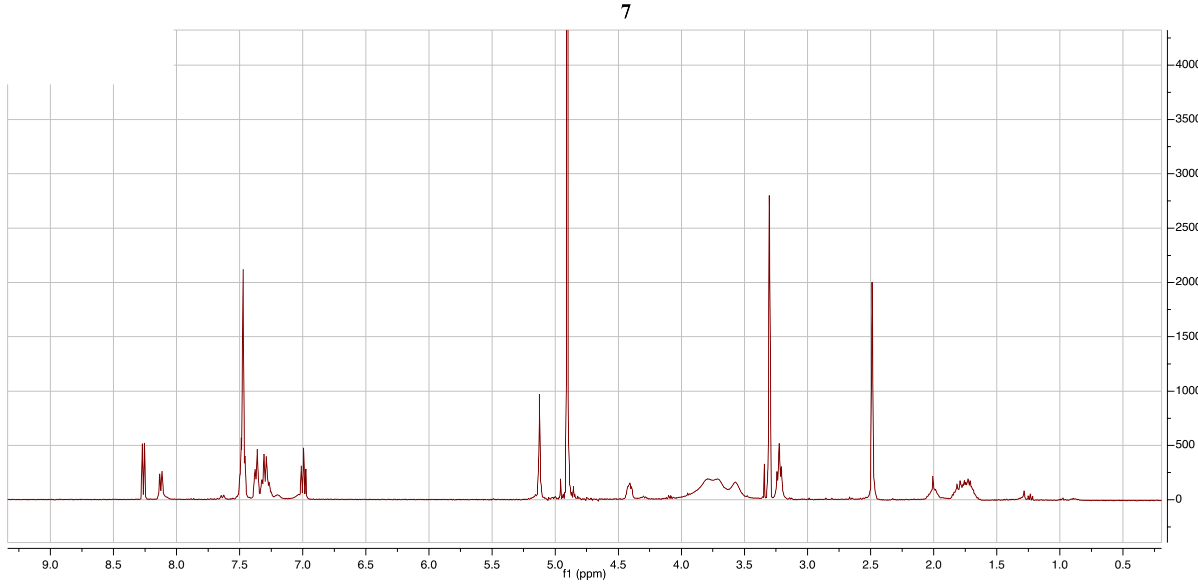
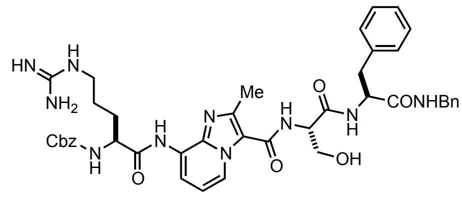
N
NH
Bz
N
Me
N
H
N
N
N
Cbz
N
H
O
O

7


f1 (ppm)



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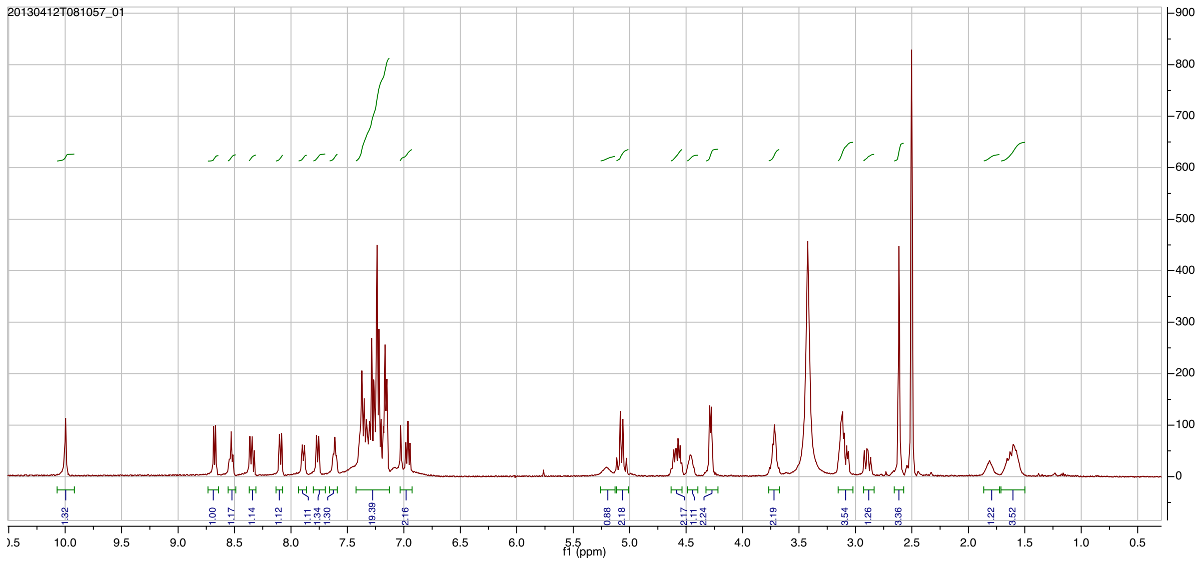

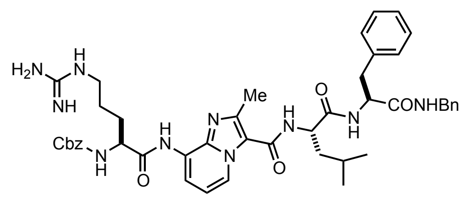

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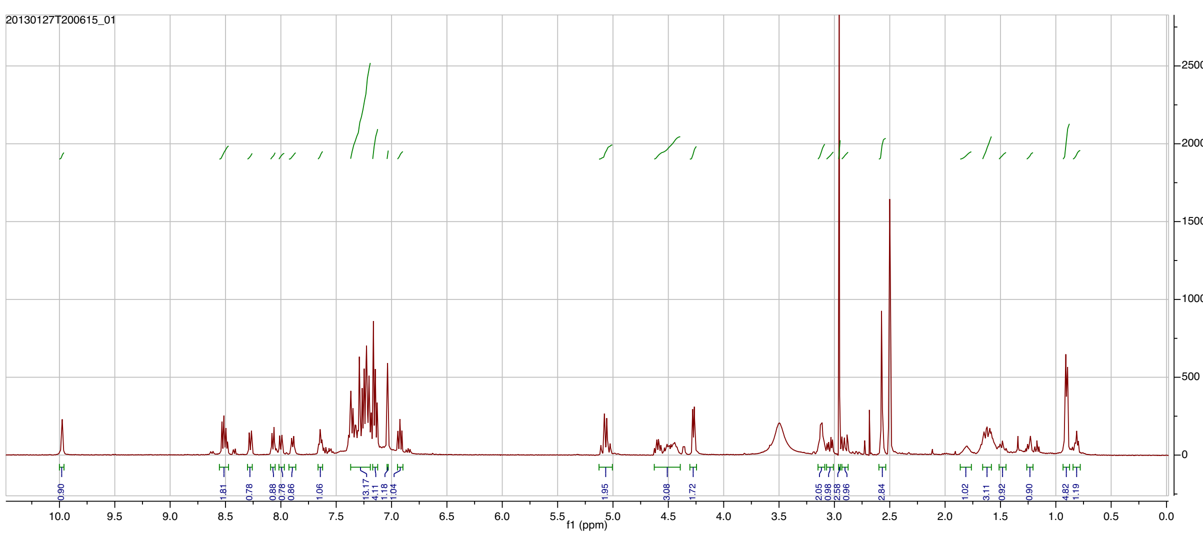
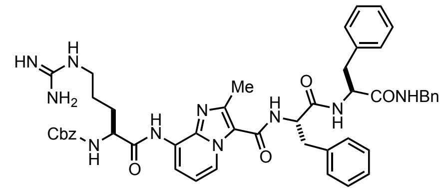
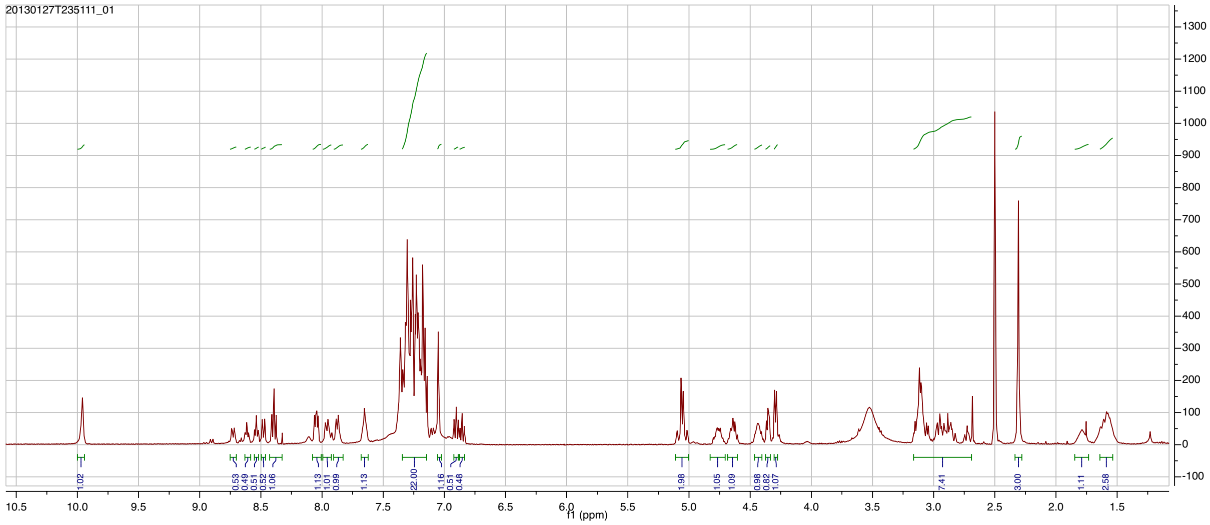



HN
NH2
Cbz
Me
CONHBn

10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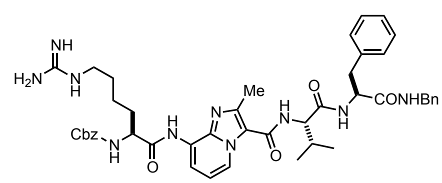
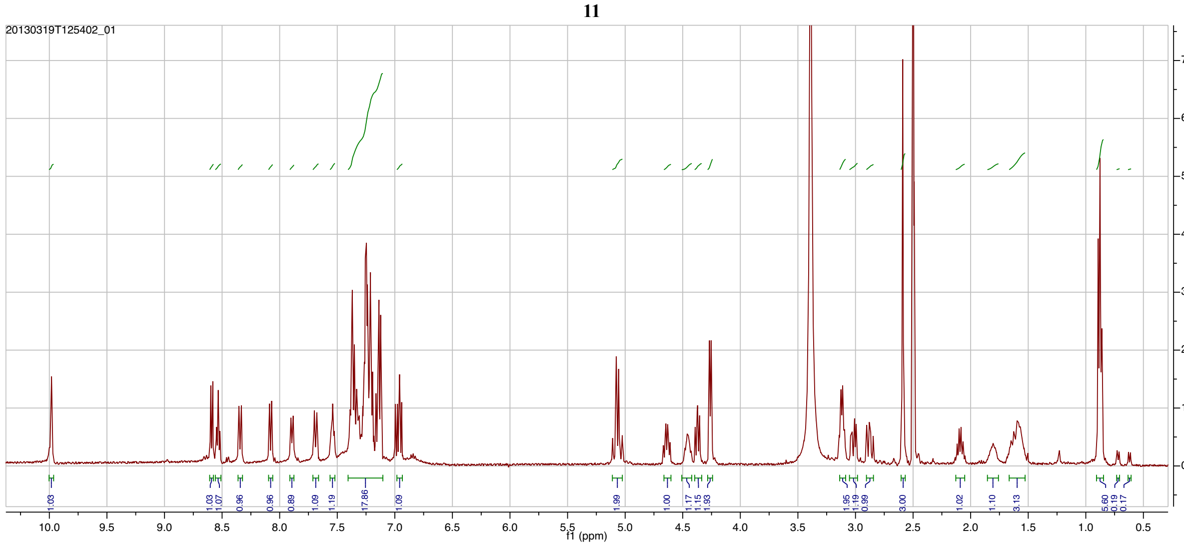
f1 (ppm)


NH
H2N
Cbz
Me
CONHBn

11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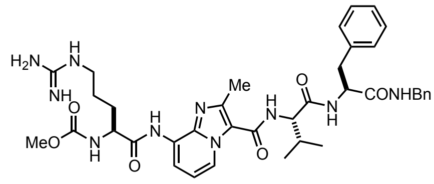
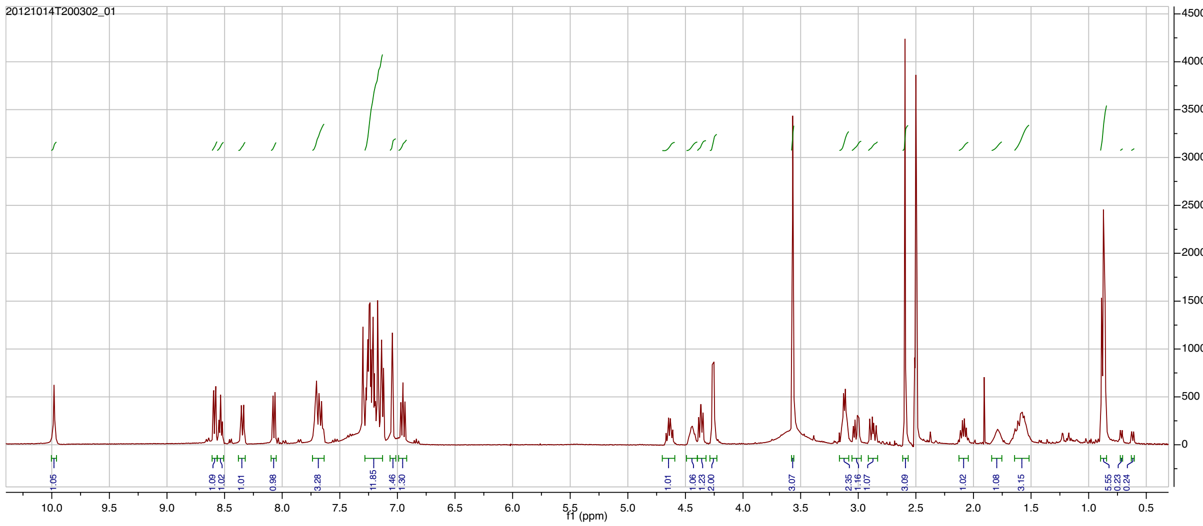

H2N
NH
Me
MeO
CONHBn

12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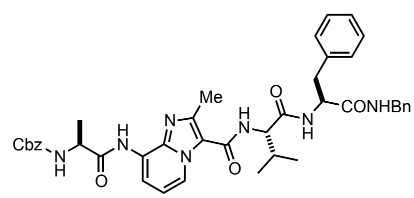
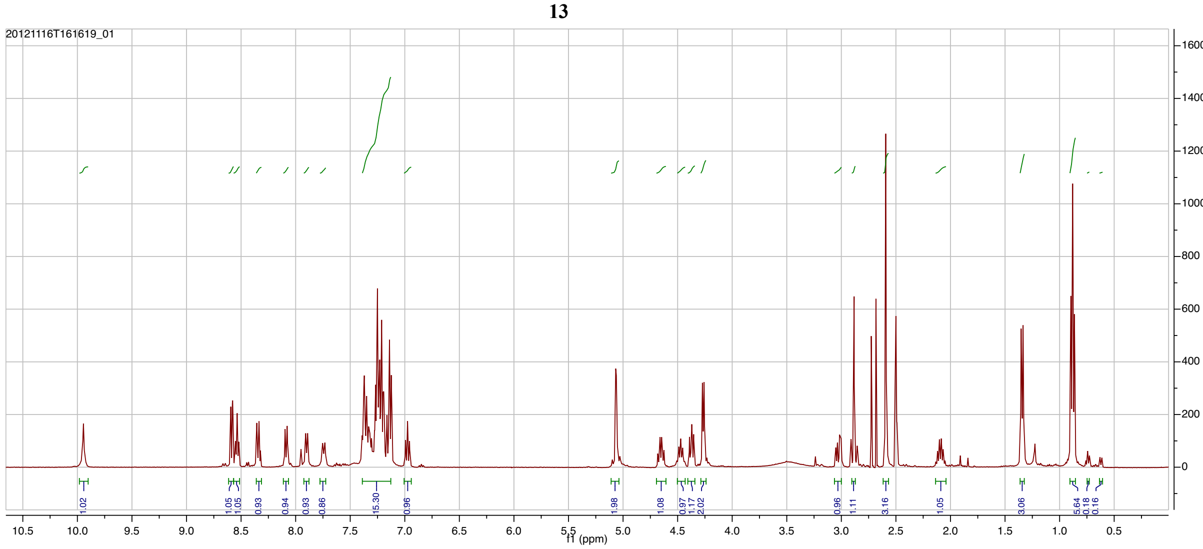
f1 (ppm)


Cbz
Me
CONHBn

13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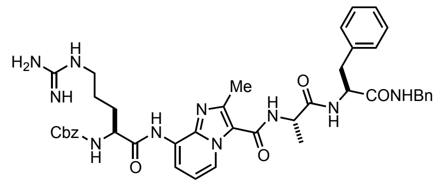
f1 (ppm)



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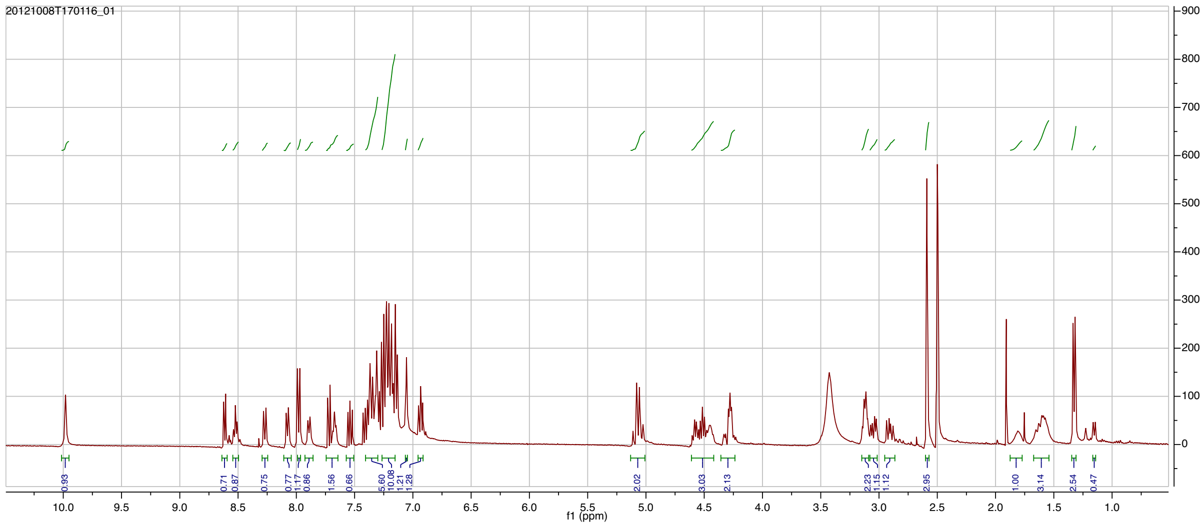

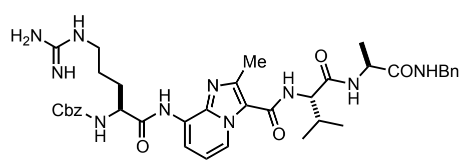

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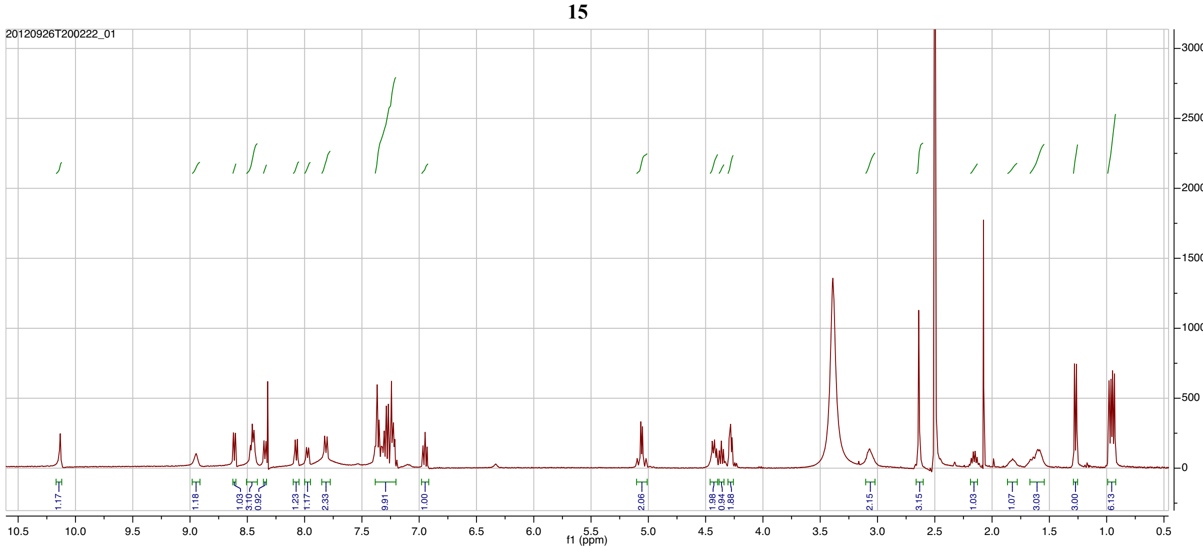
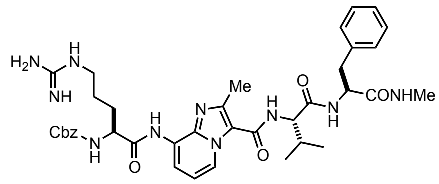
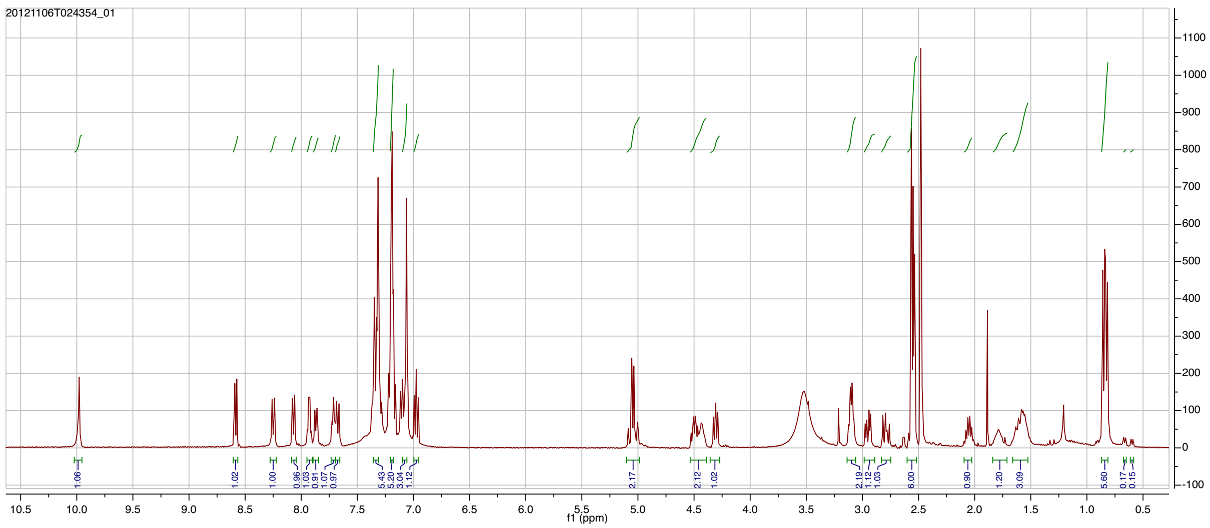



H2N
H
N
NH
Me
Cbz
CONHMe

16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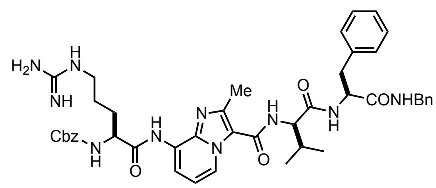
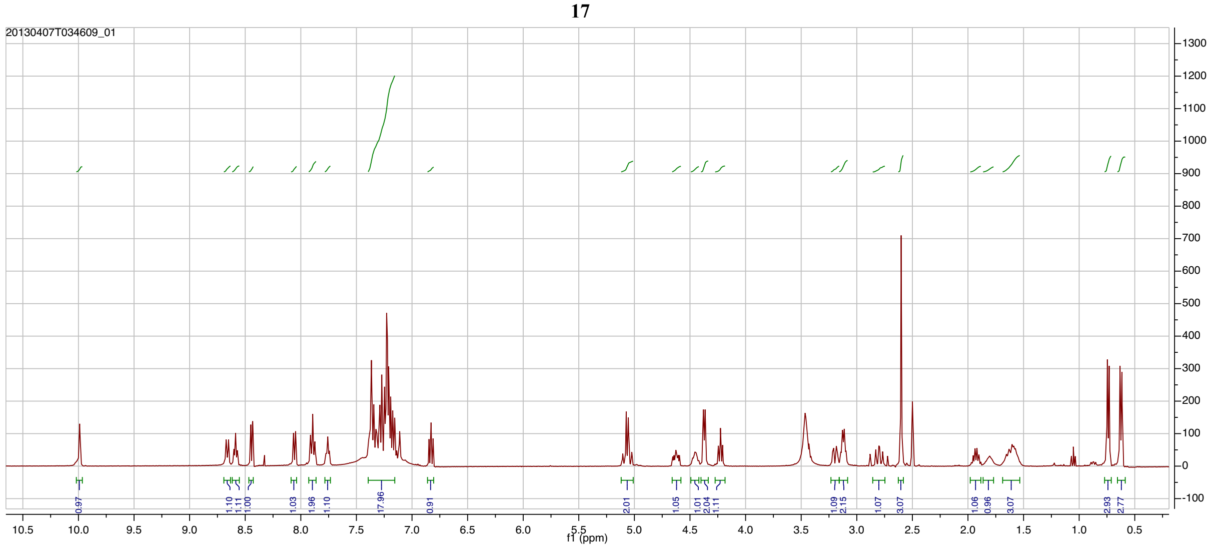

H2N
H
N
NH
Me
Cbz
CONHBn

17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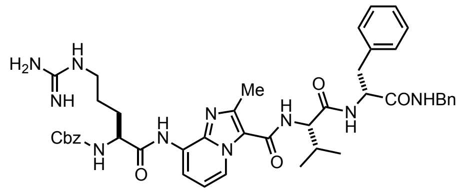
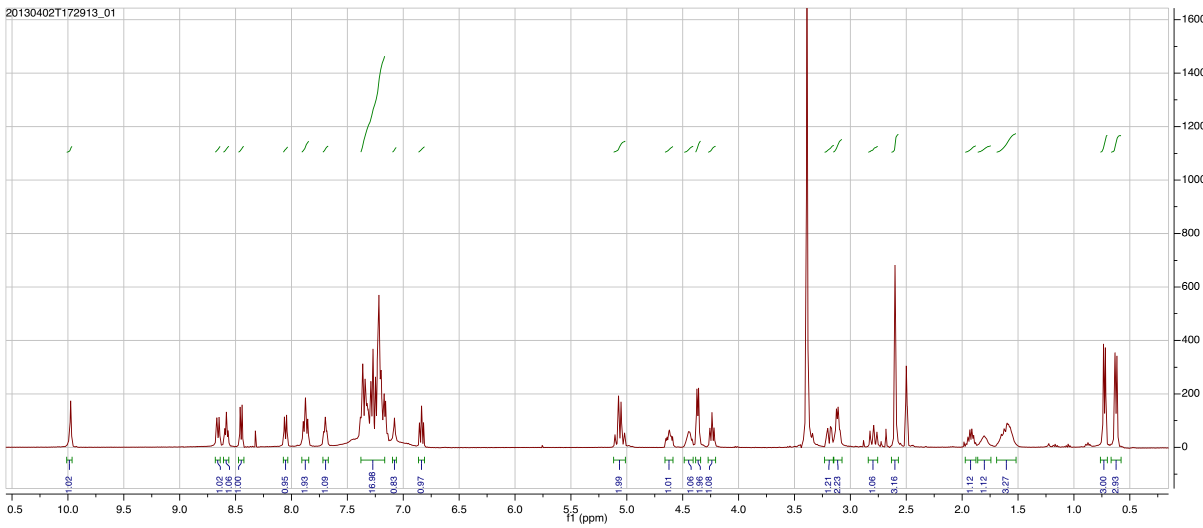

H2N
NH
Me
Cbz
CONHBn

18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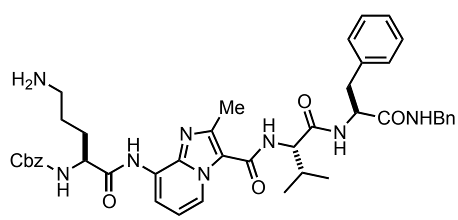
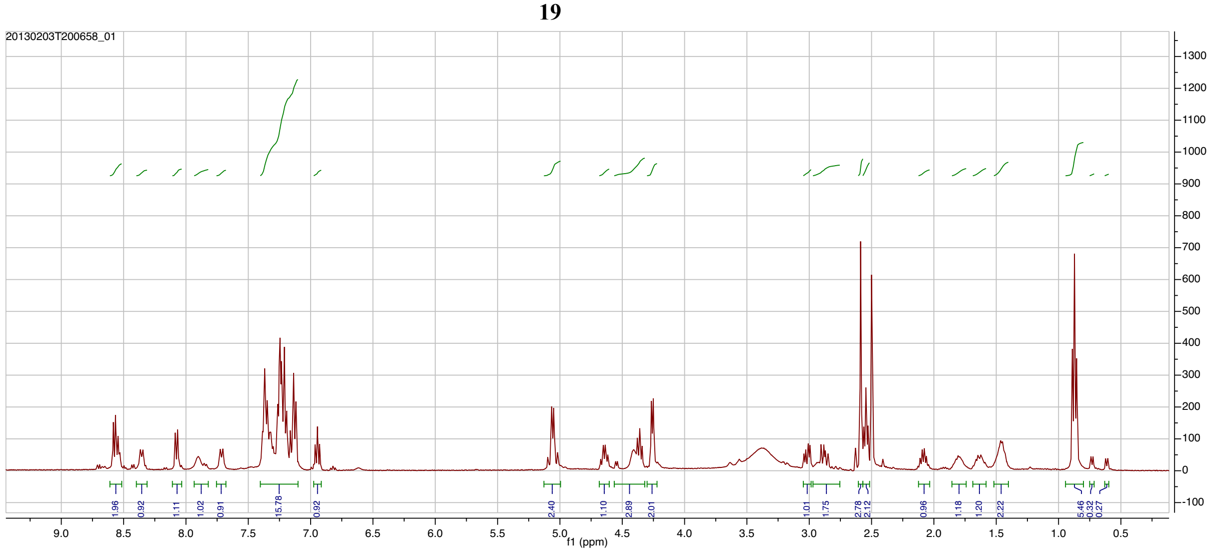

H2N
Me
Cbz
CONHBn

19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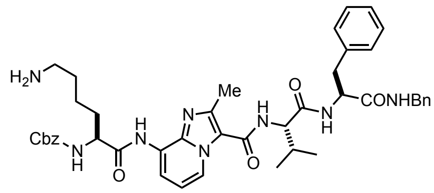
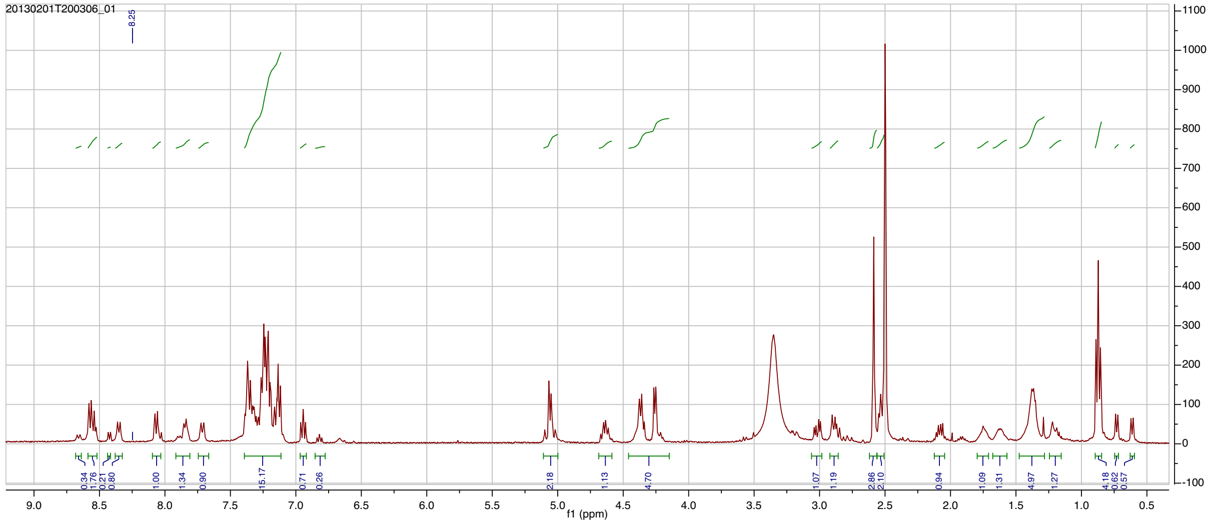

H2N
Me
CONHBn
Cbz
H
N
O

20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f1 (ppm)
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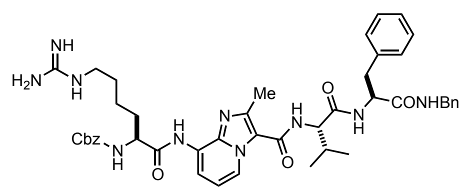
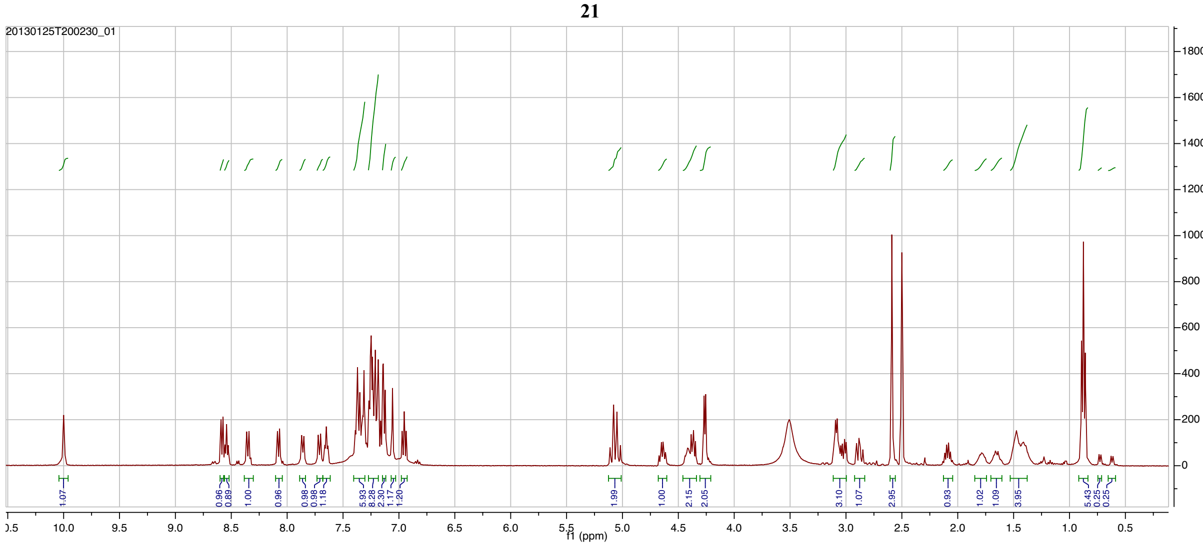
1.76
0.21
0.80
1.00
1.34
0.90
15.17
0.71
0.26
2.18
1.13
4.70
1.07
1.19
2.86
2.10
0.94
1.09
1.31
4.97
1.27
4.18
0.62
0.57


NH
H2N
Me
CONHBn
Cbz
H
N
O

21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0.96
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0.98
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5.93
8.28
2.30
1.17
1.20
1.99
1.00
2.15
2.05
3.10
1.07
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1.09
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5.43
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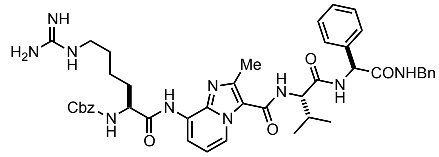
0.25



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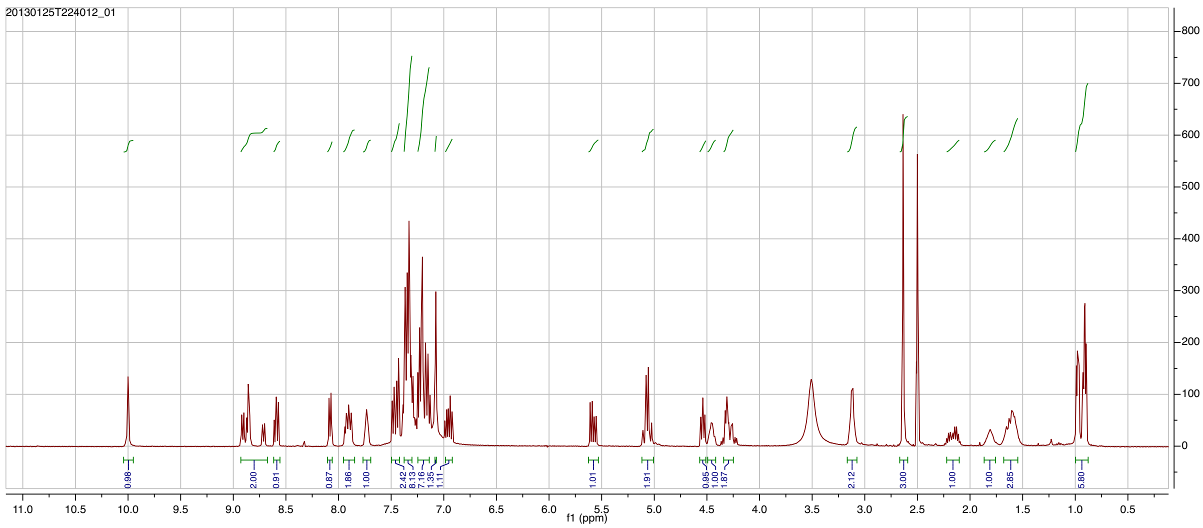

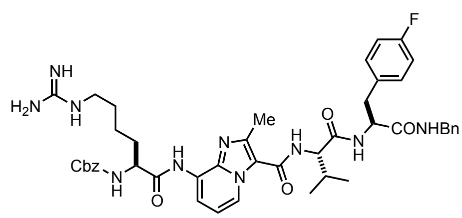

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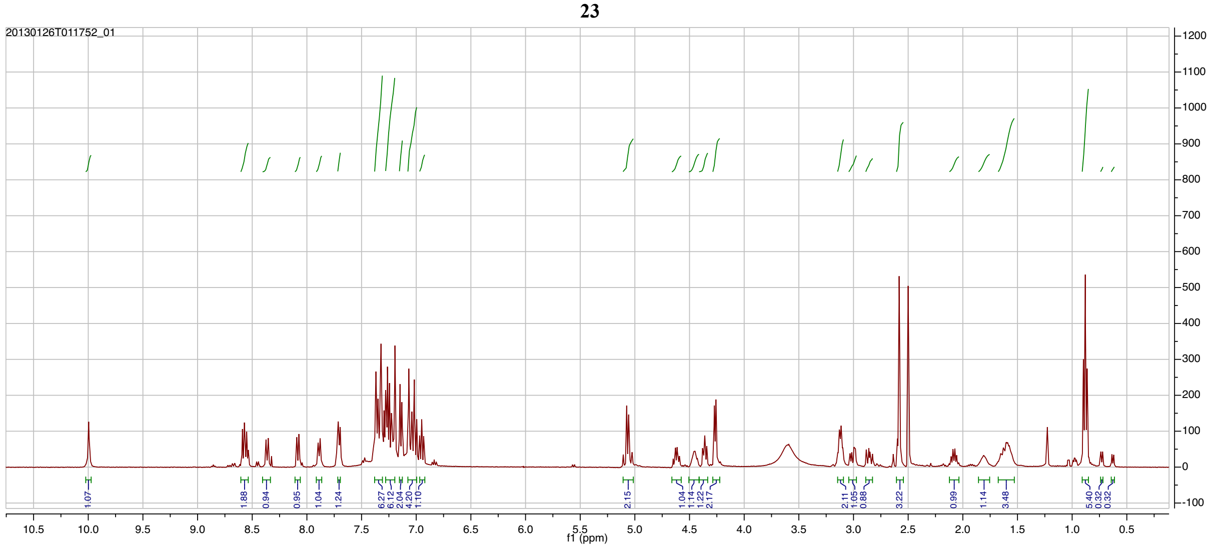
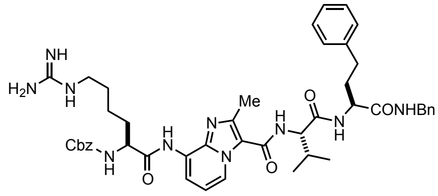
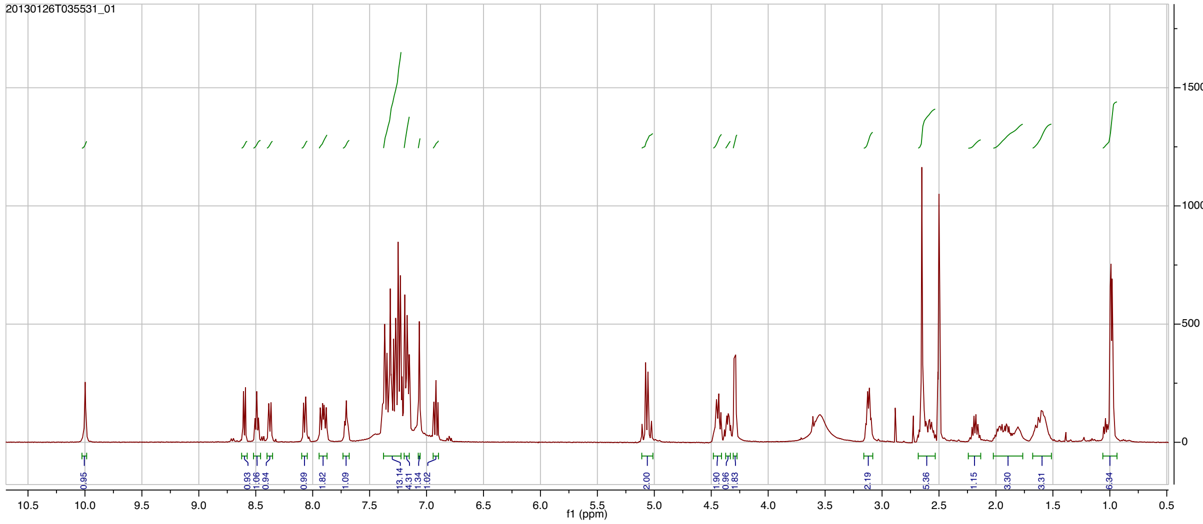



NH
H2N
H
Cbz
H
N
Me
O
CONHBn

24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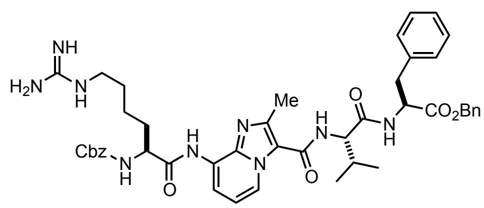
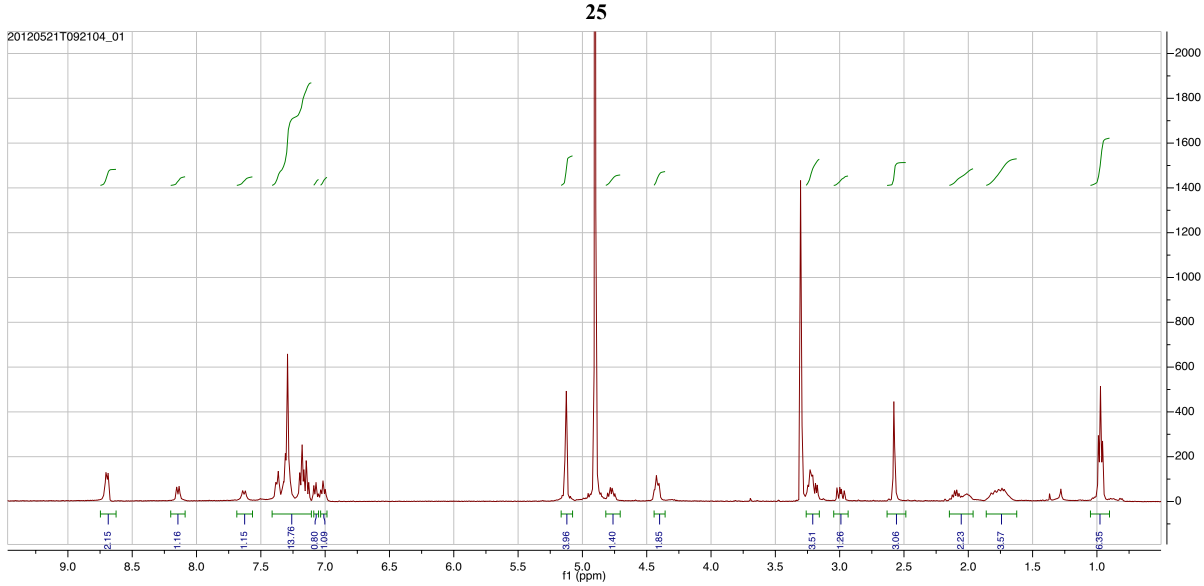

NH
H2N
H
Cbz
N
Me
O
CO2Bn

25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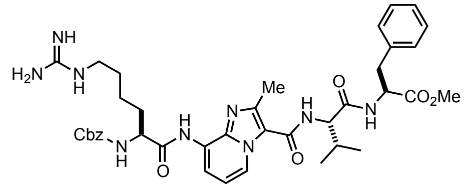
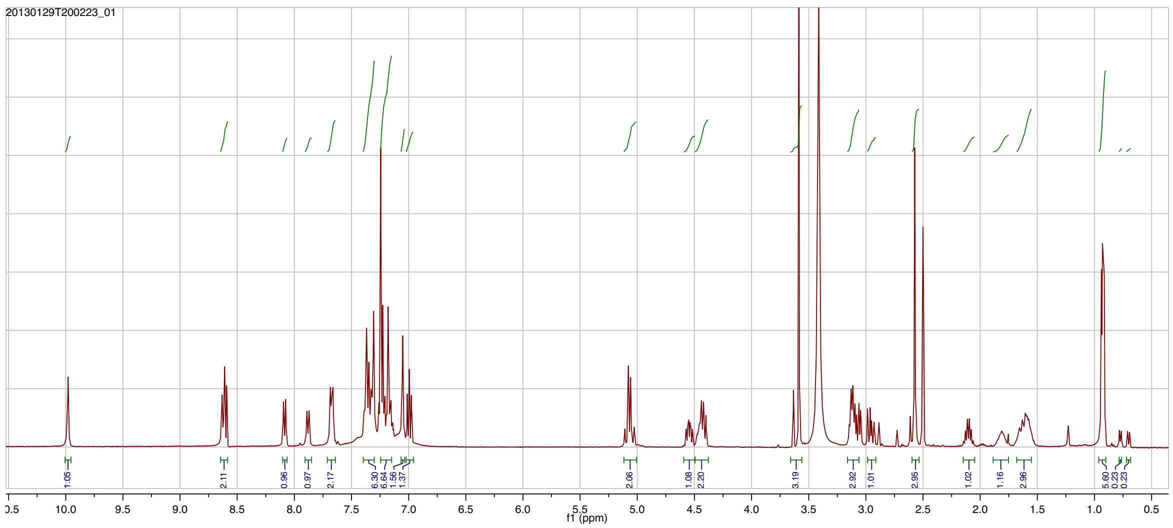

NH
H2N
H
N
Me
CO2Me
Cbz
O

26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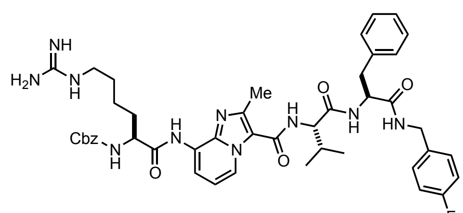
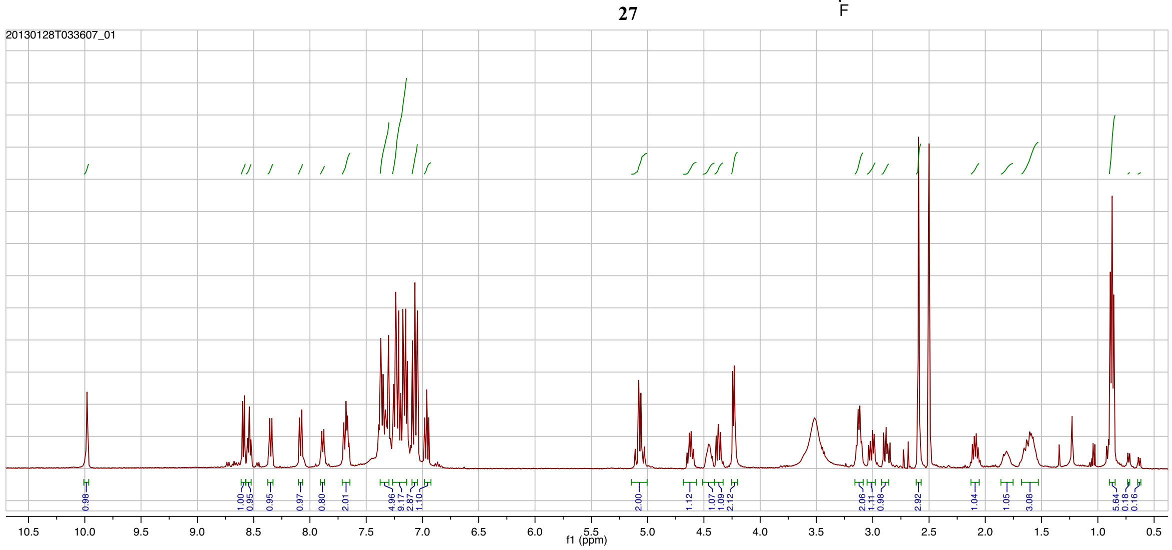

NH
H2N
Me
Cbz
HN
F

27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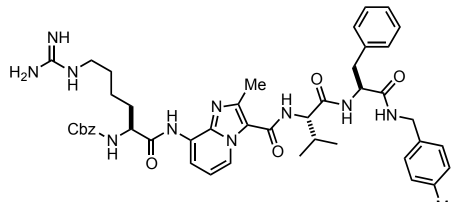

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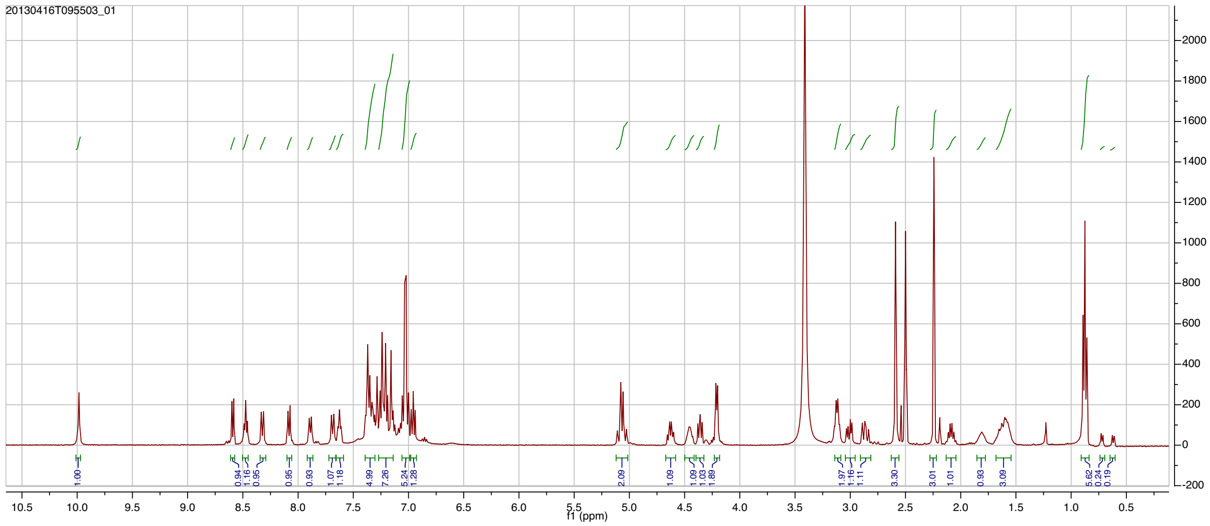

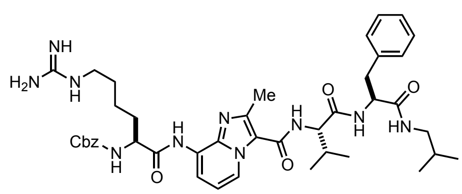

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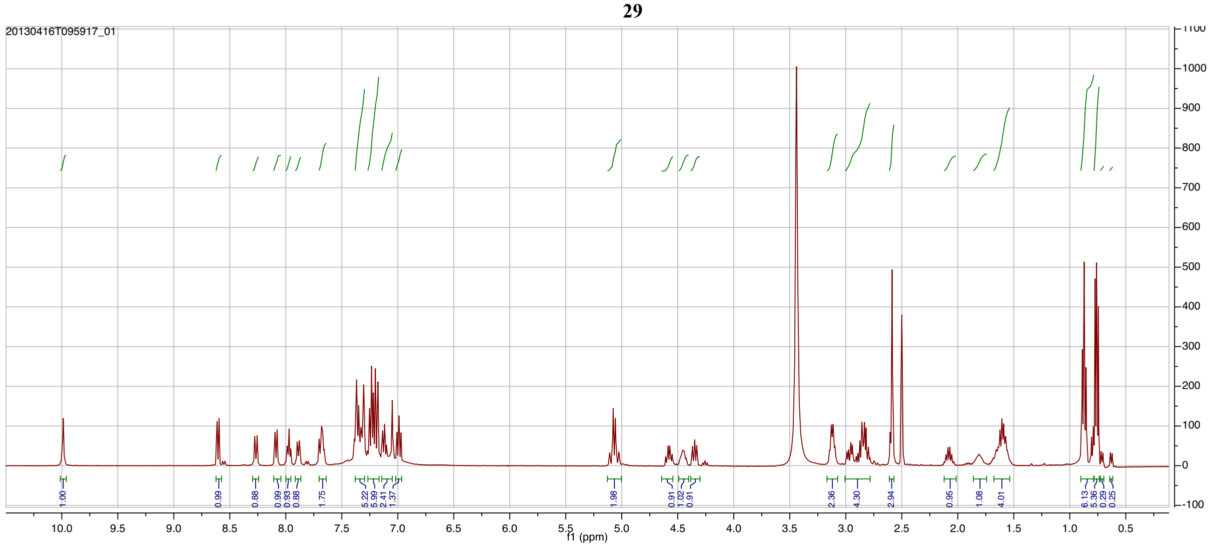
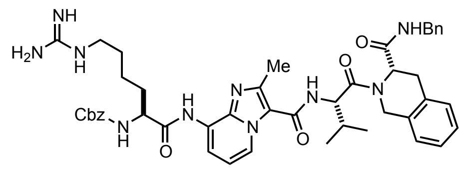
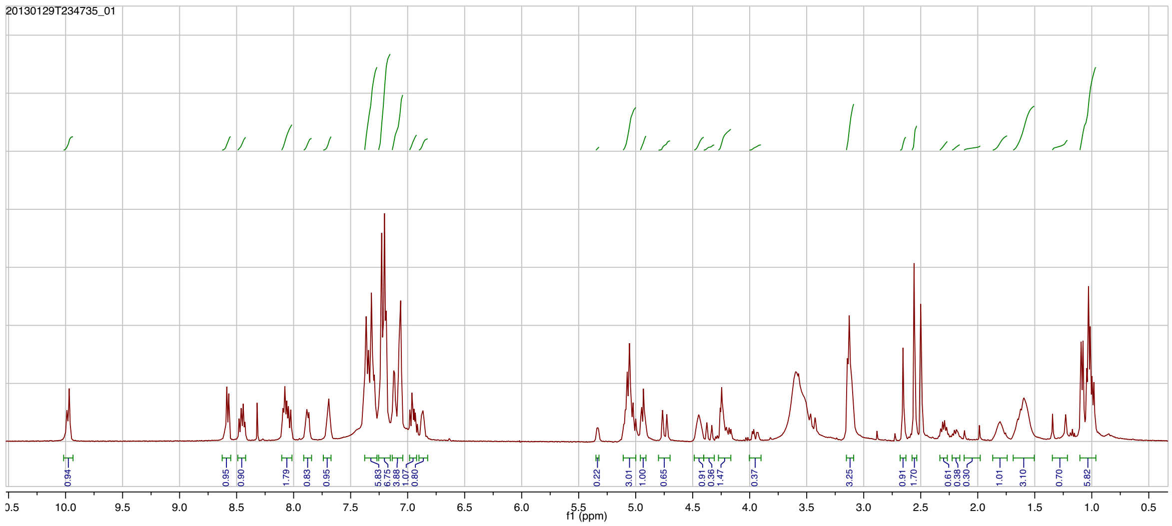




NH
H2N
N
H
Me
NHBn
Cbz

30



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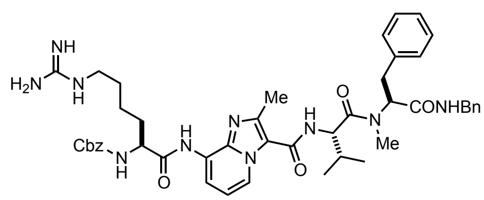
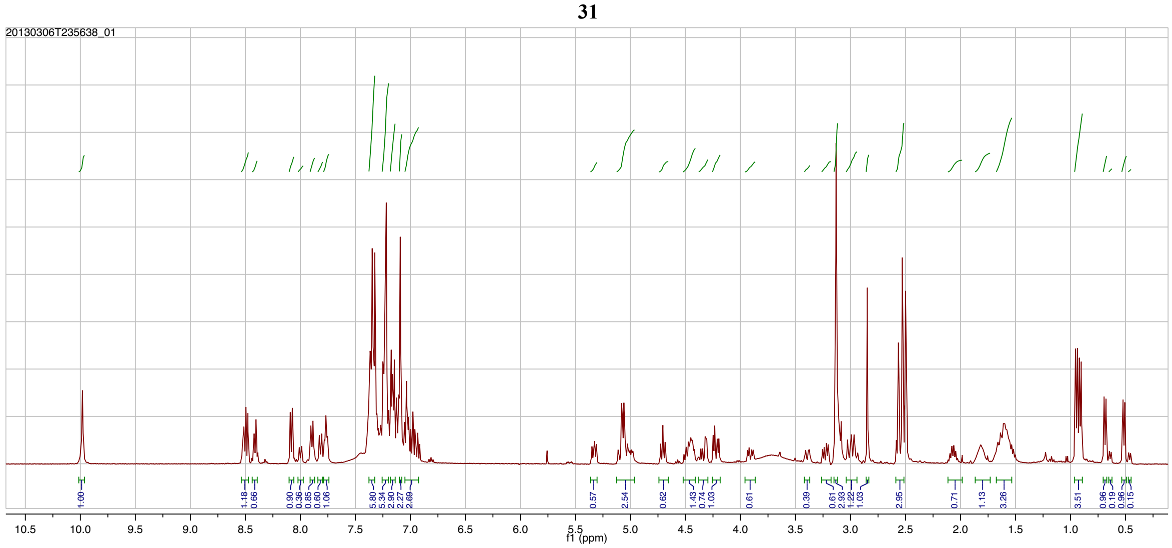


NH
H2N
N
H
Me
CONHBn
Cbz

31



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f1 (ppm)