Data S1. The chemical synthesis and physicochemical data.

General remarks

The proton nuclear magnetic resonance (^{1}H NMR) spectra were determined on a Bruker AVANCE II (300 MHz or 400 MHz) spectrometer. Chemical shifts for ^{1}H NMR were reported in parts per million (ppm) downfield from tetramethylsilane (δ) as the internal standard in deuterated solvent and coupling constants (*J*) are in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublet, dt = doublet of triplet, qd = quartet of doublet, dquin = doublet of quintet, m = multiplet, and br s = broad singlet. Reaction progress was determined by thin layer chromatography (TLC) analysis on silica gel 60 F_{254} plates (Merck) or NH TLC plate (Fuji Silysia Chemical Ltd.). Column chromatography was carried out on a silica gel column (Chromatorex® NH-DM1020, 100–200 mesh, Fuji Silysia chemical) or on Purif-Pack (SI ϕ 60 μM or NH ϕ 60 μM, Fuji Silysia Chemical, Ltd.). Low-resolution mass spectra (MS) were acquired using an Agilent LC/MS system (Agilent1200SL/Agilent6130MS or Agilent1200SL/Agilent1956MS or Agilent1200SL/Agilent6110MS), Shimadzu UFLC/MS (Shimazu LC-20AD/LCMS-2020) operating in electron spray ionization mode (ESI+). The column used was an L-column 2 ODS (3.0 × 50 mm I.D., 3 μm, CERI, Japan) with a temperature of 40 °C and a flow rate of 1.2 or 1.5 mL/min or an Waters X-Bridge C18 (4.6 × 50 mm I.D., 3.5 μm) with a temperature of 40 °C and a flow rate of 2.0 mL/min. Mobile Phase: Condition 1: Mobile phases A and B under an acidic condition were 0.05% TFA in water and 0.05% TFA in MeCN, respectively. The ratio of mobile phase B was increased linearly from 5% to 90% over 0.9 min, 90% over the next 1.1 min, or the ratio of mobile phase B was increased linearly from 5% to 100% over 1.6 min, 100% over the next 1.4 min, or the ratio of mobile phase B was increased linearly from 5% to 100% over 3.0 min, 100% over the next 1.0 min. Condition 2: Mobile phases A and B under a neutral condition were a mixture of 5 mmol/L $AcONH_4$ and MeCN (9:1, v/v) and a mixture of 5 mmol/L $AcONH_4$ and MeCN (1:9, v/v), respectively. The ratio of mobile phase B was increased linearly from 5% to 90% over 0.9 min, 90% over the next 1.1 min. The purities of all compounds tested in biological systems were assessed as being > 95% using elemental analysis or

analytical HPLC. Purity data were collected by HPLC with NQAD (Nano Quality Analyte Detector) or Corona CAD (Charged Aerosol Detector). The column was an L-column 2 ODS (30 × 2.1 mm I.D., CERI, Japan) or a Capcell Pak C18AQ (50 mm × 3.0 mm I.D., Shiseido, Japan) with a temperature of 50 °C and a flow rate of 0.5 mL/min. Mobile phases A and B under a neutral condition were a mixture of 50 mmol/L ammonium acetate, water and acetonitrile (1:8:1, v/v/v) and a mixture of 50 mmol/L ammonium acetate and MeCN (1:9, v/v), respectively. The ratio of mobile phase B was increased linearly from 5% to 95% over 3 min, 95% over the next 1 min. All commercially available solvents and reagents were used without further purification. Yields were not optimized.

Abbreviations are used as follows: AcOH, acetic acid; Boc_2O, Di-*t*-butyl dicarbonate; CD_3OD, deuterated methanol; $CDCl_3$, deuterated chloroform; CPME, cyclopentyl methyl ether; DIPEA, *N*,*N*′-diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DMF, *N,N*-dimethylformamide; DMSO, dimethyl sulfoxide; DMSO-d_6, dimethyl sulfoxide-d_6; EDC, 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide; Et_3N, triethylamine; EtOAc, ethyl acetate; EtOH, ethanol; HATU, 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate; HOBt, 1-hydroxybenzotriazole; IPA, isopropyl alcohol; MeCN, acetonitrile; MeI, iodomethane; MeOH, methanol; MNBA, 2-methyl-6-nitrobenzoic anhydride; NMP, *N*-methylpyrrolidone; NBS, *N*-Bromosuccinimide; *n*-BuLi, *n*-butyl lithium; Oxone, potassium peroxymonosulfate; $Pd(dppf)Cl_2$, [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II); $Pd(PPh_3)_4$, tetrakis(triphenylphosphine)palladium(0); Pd/C, palladium on carbon; PPh_3, triphenylphosphine; PPTS, pyridinium *p*-toluenesulfonate; TBAI, tetra-*n*-butylammonium iodide; TFA, trifluoroacetic acid; TfOH, trifluoromethanesulfonic acid; THF, tetrahydrofuran; *p*-TsCl, *p*-toluenesulfonyl chloride.

2-Chloro-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (3).

To a solution of 2-chlorothiazole (**1**) (2.92 g, 24.4 mmol) in dry THF (60 mL) was dropwise added 1.6M *n*-BuLi in hexane (16.0 mL, 25.6 mmol) at −78 °C. After the

mixture was stirred at − 78 °C for 15 min, a solution of 1-chloro-2-isocyanato-3-methylbenzene (**2**) (4.5 g, 26.9 mmol) in dry THF (30 mL) was dropwise added. The mixture was stirred at −78 °C for 2 h, quenched by addition of sat. NH_4Cl aq. (60 mL), and partitioned between EtOAc and water. The EtOAc extract was separated, washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was crystallized from EtOAc–hexane to give the title compound **3** (5.43 g, 77%) as pale yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (3H, s), 7.14–7.24 (2H, m), 7.27–7.38 (1H, m), 7.49 (1H, br s), 8.09 (1H, br s). MS *m*/*z* 287.1 $(M+H)^+$.

2-Chloro-*N*-(2-chloro-6-methylphenyl)-*N*-(4-methoxybenzyl)thiazole-5-carboxamide (4).

To a solution of **3** (5.43 g, 18.9 mmol) in dry DMF (36 mL) was portionwise added 60% NaH in oil (0.91 g, 22.8 mmol) at 0 °C. After the mixture was stirred at 0 °C for 30 min, to the mixture were added 4-methoxybenzyl chloride (3.1 mL, 23 mmol) and TBAI (1.4 g, 3.8 mmol). The mixture was stirred at room temperature overnight. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 5–30% EtOAc in hexane) to give the title compound **4** (6.03 g, 78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (3H, s), 3.78 (3H, s), 4.38 (1H, d, *J* = 14.0 Hz), 5.44 (1H, d, *J* = 14.0 Hz), 6.72–6.81 (2H, m), 7.11 (1H, d, *J* = 7.6 Hz), 7.13–7.20 (2H, m), 7.31 (1H, t, *J* = 7.8 Hz), 7.37–7.45 (2H, m). MS *m*/*z* 407.1 $(M+H)^+$.

2-((6-Chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)-*N*-(4-methoxybenzyl)thiazole-5-carboxamide (6).

To a mixture of 60% NaH in oil (2.66 g, 66.6 mmol) in dry THF (50 mL) was portionwise added 6-chloro-2-methylpyrimidin-4-amine (**4**) (3.19 g, 22.2 mmol) at 0 °C. After the mixture was stirred at 0 °C for 30 min, **5** (6.03 g, 14.8 mmol) in dry THF (20 mL) was added. The mixture was stirred at 70 °C for 4 h. After cooling to 0 °C, water (2 mL) was added. The mixture was neutralized with 1M HCl aq. (ca. 50 mL) at 0 °C and extracted with EtOAc. The organic layer was separated, washed with 1M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was triturated with ether to give the title compound **6** (6.99 g, 92%) as a yellow solid. ^{1}H

NMR (300 MHz, DMSO-d_6) δ 1.73 (3H, s), 2.46 (3H, s), 3.71 (3H, s), 4.43 (1H, d, J = 13.9 Hz), 5.22 (1H, d, J = 13.9 Hz), 6.77–6.89 (3H, m), 7.16 (2H, d, J = 8.7 Hz), 7.30 (1H, d, J = 7.0 Hz), 7.38–7.49 (2H, m), 7.50–7.58 (1H, m), 12.07 (1H, br s). MS m/z 514.2 $(M+H)^+$.

2-((6-Chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (7).

A mixture of **6** (2.1 g, 4.08 mmol) in TFA (16 mL) and TfOH (1.3 mL, 14.7 mmol) was stirred at room temperature for 3 h. The mixture was poured into crushed ice (50 g), and THF (5 mL) was added. After the mixture was neutralized with 8M NaOH aq., the precipitate was collected by filtration, washed with water and Et_2O, and dried to give the title compound **7** (1.68 g, quant.) as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (3H, s), 2.59 (3H, s), 6.95 (1H, s), 7.18–7.50 (3H, m), 8.32 (1H, s), 10.03 (1H, s), 12.25 (1H, br s). MS m/z 394.1 $(M+H)^+$.

***N*-(2-Chloro-6-methylphenyl)-2-((2-methyl-6-(piperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (8).**

A mixture of **7** (750 mg, 1.90 mmol), piperazine (1.64 g, 19.0 mmol), and DIPEA (0.66 mL, 3.8 mmol) in DMSO (6 mL) was stirred at 60 °C for 3 h. Water (12 mL) was added to the reaction and cooled. The precipitate was collected by filtration, washed with water and dried to give the title compound **8** (776 mg, 92%) as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.24 (3H, s), 2.40 (3H, s), 2.67–2.83 (4H, m), 3.20–3.51 (4H, m), 6.02 (1H, s), 7.20–7.35 (2H, m), 7.40 (1H, dd, J = 7.2, 2.0 Hz), 8.22 (1H, s), 9.88 (1H, s). MS m/z 444.2 $(M+H)^+$.

2-((6-(4-(2-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)acetyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (10).

A mixture of **8** (355 mg, 0.80 mmol), 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)acetic acid (**9**) (261 mg, 1.12 mmol), HOBt (151 mg, 1.12 mmol), and EDC (0.20 mL, 1.1 mmol) in DMF (6 mL) was stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with 5% $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0–20%MeOH in EtOAc) to give the title compound **10** (456 mg, 87%) as a

pale yellow solid. ^{1}H NMR (300 MHz, CD_3OD) δ 2.32 (3H, s), 2.48 (3H, s), 3.32–3.39 (2H, m), 3.60–3.81 (18H, m), 4.30 (2H, s), 6.03 (1H, s), 7.18–7.30 (2H, m), 7.35 (1H, dd, *J* = 7.0, 2.3 Hz), 8.15 (1H, s). MS *m*/*z* 659.4 $(M+H)^+$.

2-((6-(4-(2-(2-(2-(2-Aminoethoxy)ethoxy)ethoxy)acetyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (11).

A mixture of **10** (456 mg, 0.69 mmol) and triphenylphosphine (363 mg, 1.38 mmol) in THF (6 mL)–water (0.2 mL) was stirred at room temperature overnight. After the mixture was concentrated in vacuo, the residue was purified by column chromatography (NH silica gel, eluted with 0–40% MeOH in EtOAc) to give the title compound **11** (466 mg, quant.) as a pale yellow solid. ^{1}H NMR (300 MHz, CD_3OD) δ 2.32 (3H, s), 2.48 (3H, s), 2.77 (2H, t, *J* = 5.3 Hz), 3.51 (2H, t, *J* = 5.3 Hz), 3.58–3.82 (16H, m), 4.30 (2H, s), 6.03 (1H, s), 7.17–7.29 (2H, m), 7.35 (1H, dd, *J* = 7.0, 2.2 Hz), 8.15 (1H, s). MS *m*/*z* 633.4 $(M+H)^+$.

(9*H*-Fluoren-9-yl)methyl ((14*S*,17*S*,18*R*)-1-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)-17-hydroxy-14-isobutyl-1,13,16-trioxo-19-phenyl-3,6,9-trioxa-12,15-diazanonadecan-18-yl)carbamate (13).

A mixture of **11** (229 mg, 0.36 mmol), (*S*)-2-((2*S*,3*R*)-3-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-amino)-2-hydroxy-4-phenylbutanamido)-4-methylpentanoic acid[(1)] (**12**) (230 mg, 0.43 mmol), HATU (193 mg, 0.51 mmol), and DIPEA (0.13 mL, 0.75 mmol) was stirred at 0 °C for 10 min. The mixture was diluted with EtOAc, washed with 5% $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0–20%MeOH in EtOAc) to give the title compound **13** (335 mg, 81%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.80 (6H, dd, *J* = 5.9, 2.8 Hz), 1.40–1.73 (3H, m), 2.31 (3H, s), 2.46 (3H, s), 2.76–3.04 (2H, m), 3.31–3.38 (2H, m), 3.45–3.72 (17H, m), 3.92–4.08 (3H, m), 4.20–4.64 (5H, m), 5.92–6.06 (1H, m), 6.95–7.42 (13H, m), 7.44–7.60 (2H, m), 7.67–7.79 (2H, m), 8.16 (1H, s). MS *m*/*z* 1145.9 $(M+H)^+$.

2-((6-(4-((14*S*,17*S*,18*R*)-18-Amino-17-hydroxy-14-isobutyl-13,16-dioxo-19-phenyl-3

,6,9-trioxa-12,15-diazanonadecan-1-oyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (14, SNIPER(ABL)-020).
A mixture of **13** (335 mg, 0.29 mmol) and 2M dimethylamine in MeOH (6 mL, 12 mmol) was stirred at room temperature overnight. After the mixture was concentrated in vacuo, the residue was purified by column chromatography (NH silica gel, eluted with 0–20% MeOH in EtOAc) to give the title compound **14** (233 mg, 86%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.86–0.97 (6H, m), 1.53–1.76 (3H, m), 2.32 (3H, s), 2.48 (3H, s), 2.64 (1H, dd, *J* = 13.4, 7.8 Hz), 2.88 (1H, dd, *J* = 13.4, 6.8 Hz), 3.26–3.40 (3H, m), 3.46–3.77 (18H, m), 3.93 (1H, d, *J* = 3.1 Hz), 4.29 (2H, s), 4.38–4.49 (1H, m), 6.04 (1H, s), 7.13–7.40 (8H, m), 8.15 (1H, s). MS *m*/*z* 923.7 $(M+H)^+$. Purity 98.9% (HPLC).

***tert*-Butyl ((*S*)-1-(((*S*)-2-((*S*)-2-(((*S*)-1-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)-thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)-1,13-dioxo-15,15-diphenyl-3,6,9-trioxa-12-azapentadecan-14-yl)carbamoyl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate (16).**
A mixture of **11** (229 mg, 0.36 mmol), (*S*)-2-((*S*)-1-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)propanamido)-2-cyclohexylacetyl)pyrrolidine-2-carboxamido)-3,3-diphenylpropanoic acid[2] (**15**) (288 mg, 0.43 mmol), DIPEA (0.13 mL, 0.75 mmol), and HATU (193 mg, 0.51 mmol) in DMF (6 mL) was stirred at 0 °C for 10 min. The mixture was diluted with EtOAc, washed with 5% $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0–30% MeOH in EtOAc) to give the title compound **16** (373 mg, 81%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.95–1.34 (9H, m), 1.39–1.54 (9H, m), 1.59–2.00 (9H, m), 2.32 (3H, s), 2.50 (3H, s), 2.73–3.27 (7H, m), 3.37–3.85 (18H, m), 4.17–4.65 (6H, m), 5.10–5.27 (1H, m), 6.03–6.16 (1H, m), 7.04–7.50 (13H, m), 8.13 (1H, s). MS *m*/*z* 1278.0 $(M+H)^+$.

2-((6-(4-((*S*)-3-Benzhydryl-1-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)-1,4-dioxo-8,11,14-trioxa-2,5-diazahexadecan-16-oyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (17, SNIPER(ABL)-019).

A mixture of **16** (373 mg, 0.29 mmol) in TFA (6 mL) was stirred at room temperature for 10 min. The mixture was diluted with toluene (5 mL) and concentrated in vacuo. The residue was dissolved in EtOAc–THF(ca 3:1), washed with sat. $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–20% MeOH in EtOAc) to give the title compound **17** (317 mg, 92%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.97–1.39 (8H, m), 1.60–2.00 (10H, m), 2.26 (3H, s), 2.32 (3H, s), 2.50 (3H, s), 2.83–3.28 (5H, m), 3.42 (2H, dd, *J* = 5.3, 3.4 Hz), 3.52–3.85 (16H, m), 4.20–4.53 (5H, m), 5.09–5.26 (1H, m), 6.03–6.14 (1H, m), 7.10–7.48 (13H, m), 8.13 (1H, s). MS *m*/*z* 1177.9 $(M+H)^+$. Purity 97.4% (HPLC).

***tert*-Butyl ((2*S*)-1-(((1*S*)-1-cyclohexyl-2-oxo-2-((2*S*)-2-(4-(3-(2-((tetrahydro-2*H*-pyran-2-yl)-oxy)ethoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)ethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate (20).**

A mixture of *tert*-butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(3-hydroxybenzoyl)thiazol-2-yl)-pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate[(2)] (**18**) (600 mg, 1.00 mmol), 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (**19**) (0.46 mL, 3.04 mmol), and K_2CO_3 (415 mg, 3.00 mmol) in dry DMF (3 mL) was stirred at 50 °C for 3 h. After cooling, the mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 50–100% EtOAc in hexane) to give the title compound **20** (612 mg, 84%) as a colorless amorphous powder. ^{1}H NMR (300 MHz, CD_3OD) δ 0.95–1.92 (29H, m), 2.06–2.47 (4H, m), 2.66–2.90 (3H, m), 3.46–3.58 (1H, m), 3.75–4.15 (5H, m), 4.19–4.27 (2H, m), 4.44–4.66 (2H, m), 4.68–4.75 (1H, m), 5.43–5.68 (1H, m), 7.24 (1H, ddd, *J* = 8.2, 2.6, 0.9 Hz), 7.43 (1H, t, *J* = 7.9 Hz), 7.68–7.79 (2H, m), 8.32 (1H, s). MS *m*/*z* 749.5 $(M+H)^+$.

***tert*-Butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(3-(2-hydroxyethoxy)benzoyl)thiazol-2-yl)-pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate (21).**

A mixture of **20** (602 mg, 0.83 mmol) and PPTS (24 mg, 0.10 mmol) in MeOH (4 mL)

was stirred at room temperature overnight. The mixture was neutralized with sat. $NaHCO_3$ aq., diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 50–100% EtOAc in hexane) to give the title compound **21** (433 mg, 81%) as a colorless amorphous powder. ^{1}H NMR (300 MHz, CD_3OD) δ 0.94–1.38 (8H, m), 1.39–1.50 (9H, m), 1.51–1.87 (6H, m), 2.07–2.50 (4H, m), 2.66–2.91 (3H, m), 3.79–4.04 (4H, m), 4.09–4.16 (2H, m), 4.44–4.68 (2H, m), 5.43–5.68 (1H, m), 7.24 (1H, ddd, *J* = 8.3, 2.5, 1.1 Hz), 7.39–7.49 (1H, m), 7.67–7.75 (2H, m), 8.29–8.35 (1H, m). MS *m*/*z* 643.5 $(M+H)^+$.

***tert*-Butyl 2-(2-(3-(2-((*S*)-1-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)propanamido)-2-cyclohexylacetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)acetate (23).**

To a mixture of **21** (206 mg, 0.32 mmol) in dry DMF (3 mL) was added 60% NaH in oil (20 mg, 0.50 mmol) at 0 °C. After being stirred at 0 °C for 10 min, *tert*-butyl 2-bromoacetate (**22**) (93 μL, 0.64 mmol) was added to the reaction mixture. The mixture was stirred at 0 °C for 2 h. The mixture was poured into 5% $NaHCO_3$ aq. and extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 50–100% EtOAc in hexane) to give the title compound **23** (128 mg, 53%) as a colorless amorphous powder. ^{1}H NMR (300 MHz, CD_3OD) δ 0.95–1.40 (8H, m), 1.44–1.50 (18H, m), 1.52–1.83 (6H, m), 1.95–2.48 (4H, m), 2.68–2.91 (3H, m), 3.79–4.04 (4H, m), 4.11 (2H, s), 4.23 (2H, dd, *J* = 5.5, 3.7 Hz), 4.45–4.71 (2H, m), 5.44–5.69 (1H, m), 7.23 (1H, ddd, *J* = 8.3, 2.6, 0.8 Hz), 7.44 (1H, t, *J* = 7.9 Hz), 7.67–7.81 (2H, m), 8.28–8.38 (1H, m). MS *m*/*z* 747.5 $(M+H)^+$.

2-(2-(3-(2-((*S*)-1-((*S*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)propanamido)-2-cyclohexylacetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)acetic acid (24a).

A mixture of **23** (128 mg, 0.17 mmol) in TFA (3 mL) was stirred at room temperature for 30 min. After the mixture was concentrated in vacuo, the residue was dissolved in THF (3 mL) and neutralized with sat. $NaHCO_3$ aq. To the mixture was added BOC_2O

(74 μL, 0.32 mmol) at 0 °C and the whole was stirred at room temperature overnight. The mixture was acidified with 1M HCl aq. and diluted with EtOAc. The mixture was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give the title compound **24a** (132 mg, quant.) as a colorless amorphous powder. ^{1}H NMR (300 MHz, CD_3OD) δ 0.95–1.87 (23H, m), 2.06–2.57 (4H, m), 2.66–2.94 (3H, m), 3.84–4.02 (4H, m), 4.17–4.28 (4H, m), 4.45–4.68 (2H, m), 5.40–5.68 (1H, m), 7.19–7.30 (1H, m), 7.44 (1H, t, *J* = 8.0 Hz), 7.68–7.81 (2H, m), 8.26–8.38 (1H, m). MS *m*/*z* 701.5 $(M+H)^+$.

***tert*-Butyl ((*S*)-1-(((*S*)-2-((*S*)-2-(4-(3-(2-(2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)-2-oxoethoxy)ethoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate (31a).**

A mixture of **8** (131 mg, 0.30 mmol), **24a** (207 mg, 0.30 mmol), HOBt (47.9 mg, 0.35 mmol), and EDC (0.062 mL, 0.35 mmol) in DMF (1.5 mL) was stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with 5% $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–30% MeOH in EtOAc) to give the title compound **31a** (241 mg, 72%) as a pale yellow amorphous solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87–1.20 (5H, m), 1.34 (3H, d, *J* = 7.1 Hz), 1.47 (9H, s), 1.54–1.78 (6H, m), 2.35 (7H, s), 2.48 (3H, s), 2.81–2.94 (3H, m), 3.56–3.73 (8H, m), 3.85–4.01 (4H, m), 4.24–4.33 (2H, m), 4.38 (2H, s), 4.46–4.69 (2H, m), 5.49 (1H, dd, *J* = 7.6, 3.0 Hz), 6.00 (1H, s), 7.27 (3H, s), 7.33–7.50 (2H, m), 7.69–7.77 (2H, m), 8.18 (1H, s), 8.32 (1H, s). MS *m*/*z* 1126.3 $(M+H)^+$.

***N*-(2-Chloro-6-methylphenyl)-2-((6-(4-(2-(2-(3-(2-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)acetyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (32a, SNIPER(ABL)-056).**

A mixture of **31a** (235 mg, 0.21 mmol) in TFA (3 mL) was stirred at room temperature for 10 min. After the mixture was concentrated in vacuo, the residue was dissolved in EtOAc–IPA (4:1), washed with sat. $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica

gel, eluted with 0–30% MeOH in EtOAc) to give the title compound **32a** (164 mg, 77 %) as a colorless amorphous solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.76–1.13 (8H, m), 1.43–1.73 (6H, m), 1.99–2.38 (13H, m), 3.00–3.12 (1H, m), 3.47–3.61 (8H, m), 3.72–3.93 (4H, m), 4.13–4.21 (2H, m), 4.27 (2H, s), 4.46 (1H, d, J = 7.2 Hz), 5.32–5.44 (1H, m), 5.88 (1H, s), 7.08–7.22 (3H, m), 7.22–7.38 (2H, m), 7.57–7.66 (2H, m), 8.03–8.08 (1H, m), 8.20 (1H, s). MS m/z 1026.3 $(M+Na)^+$. Purity 98.4% (HPLC).

Methyl 2-(2-(2-(benzyloxy)ethoxy)ethoxy)acetate (27b).

To a solution of 2-(2-(benzyloxy)ethoxy)ethanol (**25b**) (10.0 g, 51.0 mmol) in THF (200 mL) was added NaH (3.06 g, 76.4 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 min. To the mixture was added methyl bromoacetate (**26**) (10.9g, 71.3 mmol) in THF (20 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h. The mixture was quenched with AcOH (4 mL) and MeOH (1 mL) at 0 °C. The mixture was concentrated, dissolved in EtOAc–hexane and removed insoluble material by filtration. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluted with 5–50% EtOAc in hexane) to give the title compound **27b** (11.7 g, 86%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59–3.82 (11H, m), 4.18 (2H, s), 4.57 (2H, s), 7.27–7.38 (5H, m). MS m/z 269.3 $(M+H)^+$.

Methyl 2-(2-(2-hydroxyethoxy)ethoxy)acetate (28b).

A mixture of **27b** (1.0 g, 3.73 mmol) and 10% Pd/C (170 mg, 0.16 mmol) in MeOH (30 mL) was hydrogenated under balloon pressure at room temperature overnight. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give the title compound **28b** (0.672 g, quant.) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (1H, br s), 3.58–3.66 (2H, m), 3.68–3.81 (9H, m), 4.17 (2H, s).

Methyl 2-(2-(2-(tosyloxy)ethoxy)ethoxy)acetate (29b).

To a mixture of **28b** (667 mg, 3.74 mmol) in pyridine (16 mL) was added *p*-TsCl (2.85 g, 15.0 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h. After the mixture was concentrated in vacuo, the residue was dissolved in EtOAc, washed with 1M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 50–100% EtOAc in hexane) to give the title compound **29b** (606 mg, 49%) as a colorless oil. ^{1}H

NMR (300 MHz, $CDCl_3$) δ 2.45 (3H, s), 3.60–3.72 (6H, m), 3.75 (3H, s), 4.12 (2H, s), 4.14–4.20 (2H, m), 7.34 (2H, d, *J* = 8.0 Hz), 7.75–7.85 (2H, m). MS *m*/*z* 333.2 $(M+H)^+$.

Methyl 2-(2-(2-(3-(2-((*S*)-1-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)propanamido)-2-cyclohexylacetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)ethoxy)acetate (30b).

A mixture of **29b** (200 mg, 0.60 mmol), **18** (360 mg, 0.60 mmol), and K_2CO_3 (125 mg, 0.90 mmol) in dry DMF (3 mL) was stirred at 50 °C for 2 days. After cooling, the mixture was diluted with EtOAc, washed with 5% $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 50–100% EtOAc in hexane) to give the title compound **30b** (306 mg, 67%) as a colorless oil. ^{1}H NMR (300 MHz, CD_3OD) δ 0.95–1.39 (8H, m), 1.42–1.50 (9H, m), 1.52–1.83 (6H, m), 1.98–2.47 (4H, m), 2.68–2.90 (3H, m), 3.68–3.78 (7H, m), 3.84–4.04 (4H, m), 4.17 (2H, s), 4.21 (2H, dd, *J* = 5.4, 3.8 Hz), 4.45–4.69 (2H, m), 5.41–5.69 (1H, m), 7.23 (1H, ddd, *J* = 8.2, 2.6, 0.9 Hz), 7.43 (1H, t, *J* = 7.9 Hz), 7.68–7.80 (2H, m), 8.32 (1H, s). MS *m*/*z* 759.5 $(M+H)^+$.

2-(2-(2-(3-(2-((*S*)-1-((*S*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)propanamido)-2-cyclohexylacetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)ethoxy)acetic acid (24b).

To a mixture of **30b** (306 mg, 0.40 mmol) and THF (3 mL)–MeOH (3 mL)–water (3 mL) was added 4M LiOH aq. (0.3 mL, 1.2 mmol) at room temperature. The mixture was stirred at room temperature for 30 min. The mixture was acidified with 1M HCl aq. (1.4 mL), diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give the title compound **24b** (308 mg, quant.) as a colorless gum. ^{1}H NMR (300 MHz, CD_3OD) δ 0.94–1.38 (8H, m), 1.41–1.51 (9H, m), 1.53–1.85 (6H, m), 2.07–2.48 (4H, m), 2.68–2.90 (3H, m), 3.69–3.79 (4H, m), 3.83–4.03 (4H, m), 4.13 (2H, s), 4.21 (2H, dd, *J* = 5.5, 3.9 Hz), 4.45–4.68 (2H, m), 5.42–5.69 (1H, m), 7.24 (1H, ddd, *J* = 8.3, 2.5, 0.9 Hz), 7.43 (1H, t, *J* = 7.9 Hz), 7.68–7.78 (2H, m), 8.29–8.36 (1H, m). MS *m*/*z* 745.5 $(M+H)^+$.

***tert*-Butyl**

((*S*)-1-(((*S*)-2-((*S*)-2-(4-(3-(2-(2-(2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)-2-oxoethoxy)ethoxy)ethoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)-carbamate (31b).

A mixture of **8** (89 mg, 0.20 mmol), **24b** (149 mg, 0.20 mmol), HOBt (38 mg, 0.28 mmol), and EDC (49 μL, 0.28 mmol) in DMF (1.5 mL) was stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with 5% $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0–40% MeOH in EtOAc) to give the title compound **31b** (197 mg, 84%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.94–1.37 (8H, m), 1.39–1.49 (9H, m), 1.51–1.85 (6H, m), 2.06–2.51 (10H, m), 2.65–2.89 (3H, m), 3.45–4.02 (16H, m), 4.20 (2H, dd, *J* = 5.3, 3.4 Hz), 4.28 (2H, s), 4.45–4.65 (2H, m), 5.39–5.66 (1H, m), 5.87 (1H, s), 7.15–7.29 (3H, m), 7.31–7.41 (2H, m), 7.64–7.77 (2H, m), 8.15 (1H, s), 8.22–8.29 (1H, m). MS *m*/*z* 1170.8 $(M+H)^+$.

***N*-(2-Chloro-6-methylphenyl)-2-((6-(4-(2-(2-(2-(3-(2-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)ethoxy)acetyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (32b, SNIPER(ABL)-038).**

A mixture of **31b** (189 mg, 0.16 mmol) in TFA (4.5 mL) was stirred at room temperature for 10 min. The mixture was diluted with toluene (5 mL) and concentrated in vacuo. The residue was diluted with EtOAc, washed with 5% Na_2CO_3 and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–30% MeOH in EtOAc) to give the title compound **32b** (160 mg, 93%) as a colorless amorphous solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.96–1.35 (8H, m), 1.50–1.85 (6H, m), 2.05–2.48 (13H, m), 3.13 (1H, q, *J* = 6.8 Hz), 3.49–4.03 (16H, m), 4.20 (2H, dd, *J* = 5.2, 3.6 Hz), 4.28 (2H, s), 4.50–4.59 (1H, m), 5.40–5.66 (1H, m), 5.87 (1H, s), 7.14–7.41 (5H, m), 7.61–7.74 (2H, m), 8.15 (1H, s), 8.21–8.29 (1H, m). MS *m*/*z* 1070.7 $(M+H)^+$. Purity 98.2% (HPLC).

Methyl 1-phenyl-2,5,8,11-tetraoxatridecan-13-oate (27c).

To a solution of 2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethanol (**25c**) (15.0 g, 62.4 mmol) in THF (220 mL) was added NaH (3.75 g, 93.6 mmol) at 0 °C. The mixture was stirred at

0 °C for 5 min. To the mixture was added **26** (13.4 g, 87.4 mmol) in THF (20 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h. The mixture was quenched with AcOH (4 mL) and MeOH (1 mL) at 0 °C. The mixture was concentrated, dissolved in EtOAc–hexane and removed insoluble material by filtration. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluted with 5–70% EtOAc in hexane) to give the title compound **27c** (16.2 g, 83%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55–3.84 (15H, m), 4.17 (2H, s), 4.57 (2H, s), 7.27–7.40 (5H, m). MS *m*/*z* 313.3 $(M+H)^+$.

Methyl 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)acetate (28c).

A mixture of methyl **27c** (1.0 g, 3.20 mmol) and 10% Pd/C (170 mg, 0.16 mmol) in MeOH (30 mL) was hydrogenated under balloon pressure at room temperature overnight. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give the title compound **28c** (0.680 g, 96%) as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (1H, br s), 3.58–3.80 (15H, m), 4.18 (2H, s).

Methyl 2-(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)acetate (29c).

To a mixture of **28c** (680 mg, 3.06 mmol) in pyridine (12 mL) was added *p*-TsCl (583 mg, 3.06 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h. After the mixture was concentrated in vacuo, the residue was dissolved in EtOAc, washed with 1M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 30–100% EtOAc in hexane) to give the title compound **29c** (670 mg, 58%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (3H, s), 3.59 (4H, s), 3.63–3.74 (6H, m), 3.75 (3H, s), 4.11–4.21 (4H, m), 7.34 (2H, d, *J* = 7.9 Hz), 7.76–7.85 (2H, m). MS *m*/*z* 377.2 $(M+H)^+$.

Methyl
2-(2-(2-(2-(3-(2-((*S*)-1-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)propanamido)-2-cyclohexylacetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)ethoxy)ethoxy)acetate (30c).

A mixture of **29c** (320 mg, 0.85 mmol), **18** (509 mg, 0.85 mmol), and K_2CO_3 (235 mg, 1.70 mmol) in DMSO (3 mL) was stirred at 50 °C overnight. After cooling, the mixture was diluted with EtOAc, washed with 5% $NaHCO_3$ aq. and brine, dried over Na_2SO_4,

and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 50–100% EtOAc in hexane) to give the title compound **30c** (506 mg, 74%) as a colorless oil. ^{1}H NMR (300 MHz, CD_3OD) δ 0.94–1.38 (8H, m), 1.41–1.49 (9H, m), 1.52–1.84 (6H, m), 2.04–2.48 (4H, m), 2.67–2.91 (3H, m), 3.62–3.76 (11H, m), 3.84–4.03 (4H, m), 4.15 (2H, s), 4.21 (2H, dd, *J* = 5.3, 3.8 Hz), 4.46–4.68 (2H, m), 5.44–5.68 (1H, m), 7.20–7.27 (1H, m), 7.43 (1H, t, *J* = 8.0 Hz), 7.69–7.77 (2H, m), 8.32 (1H, s). MS *m*/*z* 803.7 $(M+H)^+$.

2-(2-(2-(2-(3-(2-((*S*)-1-((*S*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)propanamido)-2-cyclohexylacetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)ethoxy)ethoxy)acetic acid (24c).

To a mixture of **30c** (506 mg, 0.63 mmol) in THF (5 mL)–MeOH (5 mL)–water (5 mL) was added 4M LiOH aq. (0.5 mL, 2 mmol) at room temperature. The mixture was stirred at room temperature for 30 min. The mixture was acidified with 1M HCl aq. (2.5 mL), diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give the title compound **24c** (486 mg, 98%) as a colorless sticky amorphous solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.95–1.38 (8H, m), 1.41–1.52 (9H, m), 1.52–1.85 (6H, m), 2.07–2.46 (4H, m), 2.68–2.92 (3H, m), 3.61–3.77 (8H, m), 3.83–4.02 (4H, m), 4.11 (2H, s), 4.21 (2H, dd, *J* = 5.4, 3.8 Hz), 4.46–4.69 (2H, m), 5.42–5.72 (1H, m), 7.23 (1H, ddd, *J* = 8.2, 2.5, 0.9 Hz), 7.43 (1H, t, *J* = 7.9 Hz), 7.68–7.75 (2H, m), 8.32 (1H, s). MS *m*/*z* 789.6 $(M+H)^+$.

***tert*-Butyl ((*S*)-1-(((*S*)-2-((*S*)-2-(4-(3-(2-(2-(2-(2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)-2-oxoethoxy)ethoxy)ethoxy)ethoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)amino)-1-oxo-propan-2-yl)(methyl)carbamate (31c).**

A mixture of **8** (89 mg, 0.20 mmol), **24c** (158 mg, 0.20 mmol), HOBt (38 mg, 0.28 mmol), and EDC (49 μL, 0.28 mmol) in DMF (1.5 mL) was stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with 5% $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0–40% MeOH in EtOAc) to give the title compound **31c** (250 mg, quant.) as a yellow solid. ^{1}H NMR (300 MHz, CD_3OD) δ

1.02–1.37 (8H, m), 1.41–1.49 (9H, m), 1.51–1.87 (6H, m), 2.07–2.50 (10H, m), 2.65–2.90 (3H, m), 3.50–3.77 (16H, m), 3.79–4.02 (4H, m), 4.14–4.21 (2H, m), 4.27 (2H, s), 4.45–4.67 (2H, m), 5.40–5.68 (1H, m), 5.94 (1H, s), 7.13–7.29 (3H, m), 7.32–7.43 (2H, m), 7.65–7.77 (2H, m), 8.15 (1H, s), 8.23–8.32 (1H, m). MS *m*/*z* 1214.8 $(M+H)^+$.

***N*-(2-Chloro-6-methylphenyl)-2-((6-(4-(2-(2-(2-(2-(3-(2-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)ethoxy)ethoxy)acetyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (32c, SNIPER(ABL)-039).**

A mixture of **31c** (242 mg, 0.20 mmol) in TFA (4.5 mL) was stirred at room temperature for 10 min. The mixture was diluted with toluene (5 mL) and concentrated in vacuo. The residue was diluted with EtOAc, washed with 5% Na_2CO_3 and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–30% MeOH in EtOAc) to give the title compound **32c** (167 mg, 75%) as a colorless amorphous solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.95–1.36 (8H, m), 1.51–1.85 (6H, m), 2.04–2.54 (13H, m), 3.14 (1H, q, J = 6.9 Hz), 3.51–3.77 (16H, m), 3.80–4.03 (4H, m), 4.14–4.21 (2H, m), 4.27 (2H, s), 4.50–4.60 (1H, m), 5.42–5.68 (1H, m), 5.93 (1H, s), 7.12–7.42 (5H, m), 7.63–7.73 (2H, m), 8.14 (1H, s), 8.23–8.30 (1H, m). MS *m*/*z* 1114.7 $(M+H)^+$. Purity 98.1% (HPLC).

Methyl 1-phenyl-2,5,8,11,14-pentaoxahexadecan-16-oate (27d).

To a solution of 1-phenyl-2,5,8,11-tetraoxatridecan-13-ol (**25d**) (10 g, 35.2 mmol) in THF (160 mL) was added NaH (2.11 g, 52.8 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 min. To the mixture was added **26** (7.53 g, 49.2 mmol) in THF (20 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h. The mixture was quenched with AcOH (4 mL) and MeOH (1 mL) at 0 °C. The mixture was concentrated, dissolved in EtOAc–hexane and removed insoluble material by filtration. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluted with 5–70% EtOAc in hexane) to give the title compound **27d** (9.10 g, 73%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56–3.77 (19H, m), 4.16 (2H, s), 4.57 (2H, s), 7.27–7.40 (5H, m). MS *m*/*z* 357.3 $(M+H)^+$.

Methyl 14-hydroxy-3,6,9,12-tetraoxatetradecan-1-oate (28d).

A mixture of **27d** (1.0 g, 2.81 mmol) and 10% Pd/C (170 mg, 0.16 mmol) in MeOH (30 mL) was hydrogenated under balloon pressure at room temperature overnight. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give the title compound **28d** (0.752 g, quant.) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (1H, br s), 3.57-3.82 (19H, m), 4.17 (2H, s).

Methyl 14-(tosyloxy)-3,6,9,12-tetraoxatetradecan-1-oate (29d).

To a mixture of **28d** (747 mg, 2.81 mmol) in pyridine (12 mL) was added TsCl (2.14 g, 11.2 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h. After the mixture was concentrated in vacuo, the residue was dissolved in EtOAc, washed with 1M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 50–100% EtOAc in hexane) to give the title compound **29d** (613 mg, 52%) as a colorless oil. ^{1}H NMR (300 MHz, CDCl3) δ 2.45 (3H, s), 3.56–3.80 (16H, m), 4.09–4.25 (5H, m), 7.34 (2H, d, *J* = 7.9 Hz), 7.73–7.88 (2H, m). MS *m*/*z* 421.2 $(M+H)^+$.

Methyl
14-(3-(2-((*S*)-1-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)propanamido)-2-cyclohexylacetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)-3,6,9,12-tetraoxatetradecan-1-oate (30d).

A mixture of **29d** (300 mg, 0.71 mmol), **18** (427 mg, 0.71 mmol), and K_2CO_3 (148 mg, 1.07 mmol) in dry DMF (3 mL) was stirred at 50 °C for 2 days. After cooling, the mixture was diluted with EtOAc, washed with 5% $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 50–100% EtOAc in hexane) to give the title compound **30d** (376 mg, 62%) as a colorless oil. ^{1}H NMR (300 MHz, CD_3OD) δ 0.97–1.37 (8H, m), 1.41–1.50 (9H, m), 1.53–1.83 (6H, m), 2.06–2.48 (4H, m), 2.68–2.91 (3H, m), 3.55–3.76 (15H, m), 3.82–4.02 (4H, m), 4.14 (2H, s), 4.21 (2H, dd, *J* = 5.4, 3.9 Hz), 4.45–4.68 (2H, m), 5.43–5.68 (1H, m), 7.23 (1H, ddd, *J* = 8.3, 2.5, 1.2 Hz), 7.38–7.48 (1H, m), 7.66–7.78 (2H, m), 8.32 (1H, s). MS *m*/*z* 847.7 $(M+H)^+$.

14-(3-(2-((*S*)-1-((*S*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)propanamido)-2-cyclohexylacetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)-3,6,9,12-tetraoxatet

radecan-1-oic acid (24d).

To a mixture of **30d** (376 mg, 0.44 mmol) and in THF (3.5 mL)–MeOH (3.5 mL)–water (3.5 mL) was added 4M LiOH aq. (0.35 mL, 1.40 mmol) at room temperature. The mixture was stirred at room temperature for 30 min. The mixture was acidified with 1M HCl aq. (1.7 mL), diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give the title compound **24d** (335 mg, 91%) as a colorless gum. ^{1}H NMR (300 MHz, CD_3OD) δ 0.95–1.38 (8H, m), 1.41–1.50 (9H, m), 1.53–1.83 (6H, m), 2.07–2.56 (4H, m), 2.68–2.91 (3H, m), 3.56–3.78 (12H, m), 3.81–4.15 (6H, m), 4.21 (2H, dd, *J* = 5.4, 3.8 Hz), 4.44–4.67 (2H, m), 5.39–5.70 (1H, m), 7.19–7.35 (1H, m), 7.38–7.49 (1H, m), 7.68–7.79 (2H, m), 8.32 (1H, s). MS *m*/*z* 833.7 $(M+H)^+$.

***tert*-Butyl ((*S*)-1-(((*S*)-2-((*S*)-2-(4-(3-((14-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)-14-oxo-3,6,9,12-tetraoxatetradecyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate (31d).**

A mixture of **8** (150 mg, 0.34 mmol), **24d** (281 mg, 0.34 mmol), HOBt (54.8 mg, 0.41 mmol), and EDC (0.071 mL, 0.41 mmol) in DMF (1.5 mL) was stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with water, sat. $NaHCO_3$ aq., and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–40% MeOH in EtOAc and then silica gel, eluted with 0–40% MeOH in EtOAc) to give the title compound **31d** (307 mg, 72%) as a pale yellow amorphous solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87–1.21 (6H, m), 1.27–1.39 (3H, m), 1.39–1.49 (9H, m), 1.54–1.79 (6H, m), 2.32 (6H, s), 2.41–2.46 (3H, m), 2.81–2.91 (3H, m), 3.62 (20H, d, *J* = 8.1 Hz), 3.78–3.98 (4H, m), 4.13–4.18 (2H, m), 4.21–4.29 (2H, m), 4.44–4.56 (1H, m), 5.40–5.52 (1H, m), 5.92–6.02 (1H, m), 7.13–7.25 (3H, m), 7.31–7.41 (2H, m), 7.63–7.83 (3H, m), 8.12–8.19 (1H, m), 8.28 (1H, s). MS *m*/*z* 1280.3 $(M+Na)^+$.

***N*-(2-Chloro-6-methylphenyl)-2-((6-(4-(14-(3-(2-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)-3,6,9,12-tetraoxatetradecan-1-oyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (32d, SNIPER(ABL)-057).**

A mixture of **31d** (190 mg, 0.15 mmol) in TFA (3 mL) was stirred at room temperature for 10 min. After the mixture was concentrated in vacuo, the residue was dissolved in EtOAc–IPA (4:1), washed with sat. $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (Silica gel, eluted with 50–100% MeOH in EtOAc) to give the title compound **32d** (100 mg, 57%) as a colorless amorphous solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.86–1.19 (8H, m), 1.44–1.74 (6H, m), 1.98–2.38 (13H, m), 3.02–3.16 (1H, m), 3.48–3.62 (20H, m), 3.73–3.94 (4H, m), 4.04–4.12 (2H, m), 4.13–4.21 (2H, m), 4.42–4.51 (1H, m), 5.28–5.43 (1H, m), 5.89 (1H, s), 7.01–7.19 (3H, m), 7.22–7.36 (2H, m), 7.53–7.67 (2H, m), 8.05 (1H, s), 8.19 (1H, s). MS *m*/*z* 1180.3 $(M+Na)^+$. Purity 98.1% (HPLC).

***tert*-Butyl 4-(4-(ethoxycarbonyl)benzyl)piperazine-1-carboxylate (34).**

A mixture of ethyl 4-(chloromethyl)benzoate (**33**) (2.0 g, 10.07 mmol), *tert*-butyl piperazine-1-carboxylate (1.88 g, 10.1 mmol), and K_2CO_3 (1.67 g, 12.08 mmol) in EtOH (25 mL) was stirred at 60 °C overnight. After cooling, the mixture was concentrated in vacuo. The residue was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–30% EtOAc in hexane) to give the title compound **34** (3.40 g, 97%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (3H, t, *J* = 7.1 Hz), 1.45 (9H, s), 2.38 (4H, t, *J* = 4.8 Hz), 3.43 (4H, t, *J* = 4.8 Hz), 3.55 (2H, s), 4.37 (2H, q, *J* = 7.1 Hz), 7.40 (2H, d, *J* = 8.1 Hz), 8.00 (2H, d, *J* = 8.1 Hz). MS *m*/*z* 349.2 $(M+H)^+$.

4-((4-(*tert*-Butoxycarbonyl)piperazin-1-yl)methyl)benzoic acid (35).

A mixture of **34** (1.65 g, 4.74 mmol) and 1M NaOH aq. (7.0 mL, 7.00 mmol) in EtOH (7 mL)–THF (14 mL) was stirred at room temperature overnight. The mixture was neutralized with 1M HCl aq. (7 mL) and concentrated in vacuo. The precipitate was collected by filtration, washed with water and dried to give the title compound **35** (1.40 g, 92%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.45 (9H, s), 2.49 (4H, t, *J* = 4.8 Hz), 3.40-3.51 (4H, m), 3.66 (2H, s), 7.46 (2H, d, *J* = 8.0 Hz), 7.99 (2H, d, *J* = 8.0 Hz). MS *m*/*z* 321.2 $(M+H)^+$.

***tert*-Butyl**

4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazine-1-carboxylate (37).

To a mixture of **35** (1.22 g, 3.81 mmol), 4-methyl-3-[4-(3-pyridyl)pyrimidin-2-ylamino]aniline (**36**) (878 mg, 3.17 mmol), Et_3N (1.3 mL, 9.33 mmol), and DMAP (387 mg, 3.17 mmol) in dry DMF (20 mL) was added MNBA (2.18 g, 6.33 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was diluted with EtOAc, washed with 5% Na_2CO_3 aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was washed with EtOAc to give the title compound **37** (1.87 g, quant.) as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.39 (9H, s), 2.22 (3H, s), 2.30–2.40 (4H, m), 3.33 (4H, br s), 3.56 (2H, s), 7.21 (1H, d, J = 8.3 Hz), 7.38–7.59 (5H, m), 7.91 (2H, d, J = 8.0 Hz), 8.08 (1H, s), 8.42–8.57 (2H, m), 8.69 (1H, d, J = 4.6 Hz), 8.98 (1H, s), 9.28 (1H, d, J = 1.8 Hz), 10.18 (1H, s). MS m/z 580.3 $(M+H)^+$.

***N*-(4-Methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-(piperazin-1-ylme thyl)benzamide 4 hydrochloride (38).**

A mixture of **37** (930 mg, 1.60 mmol) and 2M HCl in methanol (30 mL, 60 mmol) was stirred at room temperature overnight. The precipitates were collected by filtration, washed with MeOH, and dried to give the title compound **38** (947 mg, 94%) as an orange solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.24 (3H, s), 3.50 (4H, br s), 4.50 (2H, s), 4.98 (7H, br s), 7.24 (1H, d, J = 8.3 Hz), 7.49 (1H, d, J = 8.5 Hz), 7.62 (1H, d, J = 5.1 Hz), 7.84 (2H, d, J = 8.1 Hz), 8.01–8.13 (3H, m), 8.17 (1H, s), 8.65 (1H, d, J = 5.1 Hz), 8.98 (1H, d, J = 5.4 Hz), 9.12 (1H, d, J = 8.3 Hz), 9.26 (1H, s), 9.52 (1H, s), 9.95 (2H, br s), 10.39 (1H, s).

4-((4-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)acetyl)piperazin-1-yl)methyl)-*N*-(4-me thyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)benzamide (39).

To a mixture of **38** (313 mg, 0.50 mmol), **9** (163 mg, 0.70 mmol), DIPEA (0.52 mL, 2.99 mmol) in DMF (5 mL) was added HATU (266 mg, 0.70 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min. The mixture was diluted with EtOAc, washed with 5% Na_2CO_3 aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–20% MeOH in EtOAc) to give the title compound **39** (162 mg, 47%) as a pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (3H, s), 2.45 (4H, t, *J* = 4.7 Hz), 3.33–3.44 (2H, m), 3.50–3.74 (16H, m), 4.20 (2H, s), 7.04 (1H, s), 7.17–7.24 (2H, m), 7.29–7.36 (1H, m), 7.41–7.53 (3H, m), 7.81–7.96 (3H, m), 8.47–8.56 (2H, m), 8.59 (1H, s), 8.71 (1H, d, *J* = 4.7 Hz), 9.25 (1H, s). MS *m*/*z* 695.4 $(M+H)^+$.

4-((4-(2-(2-(2-(2-Aminoethoxy)ethoxy)ethoxy)acetyl)piperazin-1-yl)methyl)-*N*-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)benzamide (40).

To a mixture of **39** (157 mg, 0.23 mmol) and PPh_3 (119 mg, 0.45 mmol) in THF (2 mL)–water (65 μL) was stirred at room temperature for 3 days. After the mixture was concentrated in vacuo, residue was purified by column chromatography (NH silica gel, eluted with 0–60% MeOH in EtOAc) to give the title compound **40** (143 mg, 95%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (2H, br s), 2.36 (3H, s), 2.45 (4H, br s), 2.83 (2H, t, *J* = 5.2 Hz), 3.48 (2H, t, *J* = 5.2 Hz), 3.51–3.75 (14H, m), 4.20 (2H, s), 7.04 (1H, s), 7.16–7.24 (2H, m), 7.29–7.37 (1H, m), 7.39–7.51 (3H, m), 7.86 (2H, d, *J* = 7.9 Hz), 8.06 (1H, s), 8.47–8.63 (3H, m), 8.71 (1H, d, *J* = 4.9 Hz), 9.25 (1H, s). MS *m*/*z* 669.4 $(M+H)^+$.

(9*H*-Fluoren-9-yl)methyl ((14*S*,17*S*,18*R*)-17-hydroxy-14-isobutyl-1-(4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-yl)-1,13,16-trioxo-19-phenyl-3,6,9-trioxa-12,15-diazanonadecan-18-yl)carbamate (41).

To a mixture of **40** (70 mg, 0.10 mmol) and **12** (67 mg, 0.13 mmol) in DMF (2 mL) were added HATU (56 mg, 0.15 mmol) and DIPEA (26 μL, 0.15 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min. The mixture was diluted with EtOAc, washed with 5% Na_2CO_3 aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0–100% MeOH in EtOAc) to give the title compound **41** (124 mg, quant.) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.72–0.87 (6H, m), 1.44–1.69 (3H, m), 2.30 (3H, s), 2.44 (4H, br s), 2.78–3.05 (2H, m), 3.41–3.71 (16H, m), 3.92–4.61 (10H, m), 7.07–7.64 (17H, m), 7.76 (2H, d, *J* = 7.4 Hz), 7.90 (2H, d, *J* = 8.0 Hz), 8.21 (1H, s), 8.44 (1H, d, *J* = 5.1 Hz), 8.56 (1H, d, *J* = 8.0 Hz), 8.61 (1H, d, *J* = 4.6 Hz), 9.25 (1H, s). MS *m*/*z* 1181.6 $(M+H)^+$.

4-((4-((14*S*,17*S*,18*R*)-18-Amino-17-hydroxy-14-isobutyl-13,16-dioxo-19-phenyl-3,6,9-trioxa-12,15-diazanonadecan-1-oyl)piperazin-1-yl)methyl)-*N*-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)benzamide (42, SNIPER(ABL)-049).

A mixture of **41** (124 mg, 0.10 mmol) and 2M dimethylamine in MeOH (4 mL, 8 mmol) was stirred at room temperature overnight. After the mixture was concentrated in vacuo, the residue was purified by column chromatography (NH silica gel, eluted with 0–30% MeOH in EtOAc) to give the title compound **42** (71 mg, 71%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.86–0.98 (6H, m), 1.54–1.71 (3H, m), 2.31 (3H, s), 2.46 (4H, br s), 2.65 (1H, dd, *J* = 13.3, 7.8 Hz), 2.89 (1H, dd, *J* = 13.4, 6.9 Hz), 3.30–3.73 (19H, m), 3.92 (1H, d, *J* = 2.9 Hz), 4.23 (2H, s), 4.37–4.48 (1H, m), 7.14–7.60 (11H, m), 7.91 (2H, d, *J* = 8.0 Hz), 8.21 (1H, s), 8.45 (1H, d, *J* = 5.2 Hz), 8.58 (1H, d, *J* = 8.3 Hz), 8.62 (1H, d, *J* = 4.9 Hz), 9.27 (1H, s). MS *m*/*z* 959.5 $(M+H)^+$. Purity 99.7% (HPLC).

***tert*-Butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(((*S*)-1-(4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-yl)-1,13-dioxo-15,15-diphenyl-3,6,9-trioxa-12-azapentadecan-14-yl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate (43).**

To a mixture of **40** (70 mg, 0.10 mmol) and **15** (84 mg, 0.13 mmol) in DMF (3 mL) were added HATU (56 mg, 0.15 mmol) and DIPEA (26 μL, 0.15 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min. The mixture was diluted with EtOAc, washed with 5% Na_2CO_3 aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–40% MeOH in EtOAc) to give the title compound **43** (132 mg, 96%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.94–1.36 (8H, m), 1.40–1.54 (9H, m), 1.55–2.14 (10H, m), 2.31 (3H, s), 2.46 (4H, br s), 2.76–3.24 (7H, m), 3.34–3.82 (16H, m), 4.18–4.32 (3H, m), 4.33–4.64 (3H, m), 5.09–5.20 (1H, m), 7.09–7.62 (16H, m), 7.91 (2H, d, *J* = 7.9 Hz), 8.20 (1H, s), 8.45 (1H, d, *J* = 5.1 Hz), 8.58 (1H, d, *J* = 8.1 Hz), 8.62 (1H, d, *J* = 4.9 Hz), 9.26 (1H, s). MS *m*/*z* 1313.7 $(M+H)^+$.

(*S*)-1-((*S*)-2-Cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl)-*N*-((*S*)-1-(4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)pip

erazin-1-yl)-1,13-dioxo-15,15-diphenyl-3,6,9-trioxa-12-azapentadecan-14-yl)pyrrolidine-2-carboxamide (44, SNIPER(ABL)-050).

A mixture of **43** (125 mg, 0.10 mmol) in TFA (4.5 mL) was stirred at room temperature for 10 min. After the mixture was concentrated in vacuo, the residue was dissolved in EtOAc-THF (ca.5:1), washed with 5% Na_2CO_3 aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–30% MeOH in EtOAc) to give the title compound **44** (106 mg, 91%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.96–1.41 (8H, m), 1.59–2.11 (10H, m), 2.22–2.52 (10H, m), 2.85–3.24 (5H, m), 3.35–3.81 (16H, m), 4.19–4.52 (5H, m), 5.07–5.22 (1H, m), 7.09–7.58 (16H, m), 7.91 (2H, d, *J* = 7.9 Hz), 8.20 (1H, s), 8.45 (1H, d, *J* = 5.2 Hz), 8.57 (1H, d, *J* = 8.1 Hz), 8.62 (1H, d, *J* = 4.9 Hz), 9.26 (1H, s). MS *m*/*z* 1213.7 $(M+H)^+$. Purity 95.9% (HPLC).

***tert*-Butyl**
((2*S*)-1-(((1*S*)-1-cyclohexyl-2-((2*S*)-2-(4-(3-(2-(2-(2-(2-(4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-yl)-2-oxoethoxy)ethoxy)ethoxy)ethoxy)benzoyl)-1,3-thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)methylcarbamate (45).

A mixture of **38** (79 mg, 0.13 mmol), **24c** (100 mg, 0.13 mmol), EDC (23.6 mg, 0.15 mmol), HOBt (20.6 mg, 0.15 mmol), and Et_3N (51.3 mg, 0.51 mmol) in DMF (1.5 mL) was stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with water, sat. $NaHCO_3$ aq., and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–15% MeOH in EtOAc) to give the title compound **45** (118 mg, 74 %) as a white amorphous solid. MS *m/z* 1272.4 $(M+Na)^+$.

4-((4-((2-(2-(2-(3-((2-((2*S*)-1-((2*S*)-2-Cyclohexyl-2-((*N*-methyl-L-alanyl)amino)acetyl)pyrrolidin-2-yl)-1,3-thiazol-4-yl)carbonyl)phenoxy)ethoxy)ethoxy)ethoxy)acetyl)piperazin-1-yl)methyl)-*N*-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)benzamide (46, SNIPER(ABL)-058).

A mixture of **45** (105 mg, 0.08 mmol) in TFA (3 mL) was stirred at room temperature for 10 min. After the mixture was concentrated in vacuo, the residue was dissolved in EtOAc–IPA (4:1), washed with sat. $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and

concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–15% MeOH in EtOAc) to the title compound **46** (65.0 mg, 67 %) as a colorless amorphous solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87–1.06 (5H, m), 1.12 (3H, d, *J* = 6.9 Hz), 1.43–1.71 (6H, m), 1.94–2.25 (10H, m), 2.34 (4H, t, *J* = 4.9 Hz), 3.04 (1H, q, *J* = 6.8 Hz), 3.36–3.61 (14H, m), 3.71–3.92 (4H, m), 4.04–4.09 (2H, m), 4.11 (2H, s), 4.45 (1H, d, *J* = 7.2 Hz), 5.36 (1H, dd, *J* = 7.6, 3.3 Hz), 7.07–7.12 (1H, m), 7.15 (1H, d, *J* = 8.3 Hz), 7.25 (1H, d, *J* = 5.2 Hz), 7.26–7.38 (4H, m), 7.44 (1H, dd, *J* = 8.0, 4.9 Hz), 7.56–7.65 (2H, m), 7.75–7.82 (2H, m), 8.10 (1H, d, *J* = 2.0 Hz), 8.17 (1H, s), 8.36 (1H, d, *J* = 5.2 Hz), 8.46–8.51 (1H, m), 8.53 (1H, dd, *J* = 4.9, 1.6 Hz), 9.13–9.20 (1H, m). MS *m*/*z* 1150.8 $(M+H)^+$. Purity 100% (HPLC).

6-Chloro-*N*-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine (49).

To a solution of 4,6-dichloropyrimidine (**47**) (4.6 g, 31 mmol) and 4-(trifluoromethoxy)aniline (**48**) (5.58 g, 31.5 mmol) in EtOH (25 mL) was dropwise added DIPEA (5.50 mL, 31.5 mmol) at room temperature. The mixture was stirred at 80 °C under a dry atmosphere overnight. After cooling, the mixture was concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 20–100% EtOAc in hexane) to give the title compound **49** (6.90 g, 77%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.83 (1H, s), 7.37 (2H, d, *J* = 8.4 Hz), 7.75 (2H, d, *J* = 8.4 Hz), 8.51 (1H, s), 10.05 (1H, s). MS *m*/*z* 290.1 $(M+H)^+$.

3-(6-((4-(Trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)benzoic acid (51).

To a solution of **49** (2.0 g, 6.9 mmol), 3-boronobenzoic acid (**50**) (1.17 g, 7.04 mmol), and Na_2CO_3 (2.93 g, 27.6 mmol) in CH_3CN (50 mL)–water (50 mL) was added $Pd(PPh_3)_4$ (0.40 g, 0.35 mmol) at room temperature. The mixture was stirred at 90 °C under a dry atmosphere overnight. The insoluble material was removed by filtration, and the filtrate was cooled to rt. The mixture was acidified with 6M HCl aq. (pH is around 4). The precipitate was collected by filtration, washed with water and dried in vacuo to give the title compound **51** (1.71 g, 66%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.34–7.39 (3H, m), 7.68 (1H, t, *J* = 7.7 Hz), 7.86 (2H, d, *J* = 9.0 Hz), 8.08 (1H, d, *J* = 7.5 Hz), 8.29 (1H, d, *J* = 8.1 Hz), 8.63 (1H, s), 8.77 (1H, s), 9.93 (1H, s), 10.05 (1H, s). MS *m*/*z* 376.2 $(M+H)^+$.

***tert*-Butyl (1-oxo-1-(3-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)phenyl)-5,8,11-trioxa-2-azatridecan-13-yl)carbamate (53).**

To a solution of **51** (500 mg, 1.33 mmol), DIPEA (344 mg, 2.66 mmol), and *tert*-butyl (2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)carbamate (**52**) (467 mg, 1.60 mmol) in DMF (6.0 mL) was added HATU (659 mg, 1.73 mmol) at room temperature. The mixture was stirred at room temperature under a dry atmosphere for 2 h. The mixture was poured into sat. $NaHCO_3$ aq. and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–20% MeOH in EtOAc) to give the title compound **53** (735 mg, 85%) as a colorless foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30–1.38 (9H, m), 2.97–3.10 (2H, m), 3.23–3.40 (6H, m), 3.41–3.64 (8H, m), 6.68–6.79 (1H, m), 7.32–7.40 (3H, m), 7.59–7.68 (1H, m), 7.86 (2H, d, J = 9.3 Hz), 7.94–8.02 (1H, m), 8.19 (1H, d, J = 8.1 Hz), 8.53 (1H, s), 8.67–8.73 (1H, m), 8.78 (1H, s), 9.95 (1H, s). MS m/z 650.5. $(M+H)^+$.

(9*H*-Fluoren-9-yl)methyl ((16*S*,19*S*,20*R*)-19-hydroxy-16-isobutyl-1,15,18-trioxo-21-phenyl-1-(3-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)phenyl)-5,8,11-trioxa-2,14,17-triazahenicosan-20-yl)carbamate (54).

To a solution of **53** (367 mg, 0.56 mmol) in THF (7.3 mL) was added 4M HCl in CPME (7.06 mL, 28.2 mmol) at room temperature. The mixture was stirred at room temperature for 3 h. The mixture was concentrated in vacuo. HATU (279 mg, 0.73 mmol) was added to a solution of the residue, DIPEA (365 mg, 2.82 mmol), and **12** (270 mg, 0.51 mmol) in DMF (5.4 mL) at room temperature. The mixture was stirred at room temperature overnight. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–15% MeOH in EtOAc) to give the title compound **54** (278 mg, 46%) as a colorless amorphous powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.67–0.78 (6H, m), 1.28–1.56 (3H, m), 2.66–2.74 (1H, m), 2.79–2.89 (1H, m), 2.97–3.10 (2H, m), 3.12–3.39 (4H, m), 3.42–3.61 (12H, m), 3.85–4.38 (4H, m), 5.99 (1H, d, J = 5.9 Hz), 7.08–7.44 (13H, m), 7.58–7.70 (4H, m), 7.80–7.90 (4H, m), 7.95–8.07 (2H, m), 8.19 (1H, d,

J = 7.8 Hz), 8.53 (1H, s), 8.67–8.73 (1H, m), 8.77 (1H, s), 9.94 (1H, s). MS *m*/*z* 1062.8 $(M+H)^+$.

***N*-((14*S*,17*S*,18*R*)-18-amino-17-hydroxy-14-isobutyl-13,16-dioxo-19-phenyl-3,6,9-trioxa-12,15-diazanonadecyl)-3-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)benzamide (55, SNIPER(ABL)-013).**

A mixture of **54** (275 mg, 0.26 mmol) and 2M dimethylamine in MeOH (4 mL, 8 mmol) was stirred at room temperature for 3 h. The mixture was concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–30%MeOH in EtOAc) and purified by preparative HPLC (L-Column 2 ODS, eluted with H_2O in acetonitrile containing 0.1% TFA). The desired fraction was neutralized with sat. $NaHCO_3$ aq. and extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$ and concentrated in vacuo to give the title compound **55** (87 mg, 40%) as a colorless amorphous powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.78–0.88 (6H, m), 1.40–1.75 (4H, m), 2.50–2.56 (1H, m), 2.72–2.82 (1H, m), 3.09–3.23 (3H, m), 3.29–3.60 (15H, m), 3.73–3.77 (1H, m), 4.23–4.35 (1H, m), 5.55 (1H, br), 7.13–7.39 (8H, m), 7.59–7.68 (1H, m), 7.73 (1H, d, *J* = 8.7 Hz), 7.86 (2H, d, *J* = 9.3 Hz), 7.99 (1H, d, *J* = 8.1 Hz), 8.17–8.28 (2H, m), 8.53 (1H, s), 8.68–8.83 (1H, m), 8.77 (1H, s), 9.95 (1H, s). MS *m*/*z* 840.7 $(M+H)^+$. Purity 99.9% (HPLC).

***tert*-Butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(((*S*)-1,15-dioxo-17,17-diphenyl-1-(3-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)phenyl)-5,8,11-trioxa-2,14-diazaheptadecan-16-yl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate (56).**

To a solution of **53** (367 mg, 0.56 mmol) in THF (7.3 mL) was added 4M HCl in CPME (7.06 mL, 28.2 mmol) at room temperature. The mixture was stirred at room temperature for 3 h. The mixture was concentrated in vacuo. HATU (279 mg, 0.73 mmol) was added to a solution of the residue, DIPEA (365 mg, 2.82 mmol), and **15** (337 mg, 0.51 mmol) in DMF (6.7 mL) at room temperature. The mixture was stirred at room temperature overnight. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (NH silica

gel, eluted with 0–10% MeOH in EtOAc) to give the title compound **56** (407 mg, 60%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80–1.90 (28H, m), 2.73 (3H, s), 2.85–2.99 (5H, m), 3.13–3.62 (12H, m), 4.15–4.35 (3H, m), 4.44 (1H, br), 5.11–5.22 (1H, m), 7.08–7.39 (13H, m), 7.56–7.67 (3H, m), 7.86 (3H, d, J = 9.3 Hz), 7.99 (1H, d, J = 7.8 Hz), 8.19 (1H, d, J = 8.1 Hz), 8.53 (1H, s), 8.67–8.75 (1H, m), 8.78 (1H, s), 9.96 (1H, s). MS m/z 1195.0 $(M+H)^+$.

(*S*)-1-((*S*)-2-Cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl)-*N*-((*S*)-1,15-dioxo-17,17-diphenyl-1-(3-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)phenyl)-5,8,11-tri-oxa-2,14-diazaheptadecan-16-yl)pyrrolidine-2-carboxamide (57, SNIPER(ABL)-015).

To a solution of **56** (403 mg, 0.34 mmol) in THF (7.3 mL) was added 4M HCl in CPME (6.75 mL, 27 mmol) at room temperature. The mixture was stirred at room temperature for 3 h. The mixture was concentrated in vacuo. The residue was partitioned between sat. $NaHCO_3$ aq. and EtOAc and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–15% MeOH in EtOAc) to give the title compound **57** (290 mg, 79%) as a colorless amorphous powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83–1.87 (19H, m), 2.13 (3H, s), 2.81–3.01 (5H, m), 3.28–3.33 (2H, m), 3.40–3.62 (12H, m), 4.18–4.41 (3H, m), 5.11–5.21 (1H, m), 7.08–7.39 (13H, m), 7.59–7.67 (2H, m), 7.77–7.95 (4H, m), 7.99 (1H, d, J = 7.8 Hz), 8.19 (1H, d, J = 7.8 Hz), 8.53 (1H, s), 8.67–8.74 (1H, m), 8.76 (1H, s), 9.95 (1H, s). MS m/z 1094.8 $(M+H)^+$. Purity 96.5% (HPLC).

***N*-(2-(2-(2-(2-Hydroxyethoxy)ethoxy)ethoxy)ethyl)-3-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)benzamide (59).**

To a solution of **51** (1.1 g, 2.93 mmol), 2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethanol (**58**) (1.02 g, 5.28 mmol), and DIPEA (0.77 mL, 4.4 mmol) in dry DMF (10 mL) was added HATU (1.34 g, 3.52 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 5–10% MeOH in EtOAc) to give the title compound **59** (1.15 g, 71%) as a colorless foam. ^{1}H

NMR (300 MHz, DMSO-d_6) δ 3.27–3.64 (16H, m), 4.53–4.59 (1H, m), 7.32–7.40 (3H, m), 7.60–7.68 (1H, m), 7.86 (2H, d, J = 9.0 Hz), 7.99 (1H, d, J = 7.8 Hz), 8.20 (1H, d, J = 7.8 Hz), 8.53 (1H, s), 8.67–8.75 (1H, m), 8.78 (1H, s), 9.95 (1H, s). MS m/z 551.4 $(M+H)^+$.

1-Oxo-1-(3-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)phenyl)-5,8,11-trioxa-2-azatridecan-13-yl 4-methylbenzenesulfonate (60).

To a solution of **59** (1.15 g, 2.09 mmol) in pyridine (15 mL) was added *p*-toluenesulfonyl chloride (0.796 g, 4.18 mmol) at 0 °C. The mixture was stirred at room temperature under Ar for 3 h. The mixture was poured into 1M HCl aq. and extracted with EtOAc. The organic layer was separated, washed with 1M HCl aq. and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 50–100% EtOAc in hexane) to give the title compound **60** (1.05 g, 71%) as a colorless foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.40 (3H, s), 3.40–3.61 (14H, m), 4.05–4.12 (2H, m), 7.32–7.40 (3H, m), 7.44–7.49 (2H, m), 7.60–7.67 (1H, m), 7.73–7.80 (2H, m), 7.86 (2H, d, J = 9.0 Hz), 7.99 (1H, d, J = 7.8 Hz), 8.19 (1H, d, J = 8.1 Hz), 8.53 (1H, s), 8.67–8.74 (1H, m), 8.78 (1H, s), 9.94 (1H, s). MS m/z 705.4 $(M+H)^+$.

***tert*-Butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-oxo-2-((*S*)-2-(4-(3-((1-oxo-1-(3-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)phenyl)-5,8,11-trioxa-2-azatridecan-13-yl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)ethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate (61)**.

To a solution of **60** (388 mg, 0.55 mmol) and **18** (300 mg, 0.50 mmol) in dry DMF (10 mL) was added K_2CO_3 (97 mg, 0.70 mmol) at room temperature. The mixture was stirred at 60 °C under Ar for 5 h. After cooling to rt, the mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0–10% MeOH in EtOAc) to give the title compound **61** (365 mg, 64%) as a colorless foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85–1.44 (20H, m), 1.50–1.76 (6H, m), 1.95–2.09 (2H, m), 1.96–2.07 (2H, m), 2.14–2.30 (2H, m), 2.75 (3H, s), 3.41–3.49 (2H, m), 3.49–3.61 (6H, m), 3.70–3.82 (4H, m),

4.08–4.17 (2H, m), 4.38–4.59 (2H, m), 5.34–5.41 (1H, m), 7.19–7.26 (1H, m), 7.30–7.48 (4H, m), 7.58–7.69 (3H, m), 7.85 (2H, d, J = 9.0 Hz), 7.98 (1H, d, J = 7.8 Hz), 8.18 (1H, d, J = 8.1 Hz), 8.44–8.54 (2H, m), 8.66–8.73 (1H, m), 8.76 (1H, s), 9.93 (1H, s). MS m/z 1131.8 $(M+H)^+$.

***N*-(2-(2-(2-(2-(3-(2-((*S*)-1-((*S*)-2-Cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-3-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)benzamide (62, SNIPER(ABL)-024).**

A mixture of **61** (360 mg, 0.32 mmol) and TFA (1.2 mL, 16 mmol) was stirred at room temperature for 30 min. The mixture was diluted with toluene (5 mL) and concentrated in vacuo. The residue was partitioned between sat. $NaHCO_3$ aq. and EtOAc. The organic layer was separated, washed with sat. $NaHCO_3$ aq. and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–15% MeOH in EtOAc) to give the title compound **62** (240 mg, 73%) as a colorless amorphous powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 088–1.20 (6H, m), 1.49–1.75 (6H, m), 1.98–2.07 (5H, m), 2.17 (3H, s), 2.22–2.32 (2H, m), 2.90–3.01 (1H, m), 3.40–3.49 (2H, m), 3.50–3.60 (10H, m), 3.68–3.83 (4H, m), 4.09–4.17 (2H, m), 4.45–4.53 (1H, m), 5.35–5.41 (1H, m), 7.18–7.27 (1H, m), 7.30–7.38 (3H, m), 7.40–7.48 (1H, m), 7.59–7.69 (3H, m), 7.57–7.72 (3H, m), 7.98 (1H, d, J = 7.8 Hz), 8.18 (1H, d, J = 8.1 Hz), 8.48 (1H, s), 8.52 (1H, s), 8.67–8.73 (1H, m), 8.76 (1H, s), 9.93 (1H, s). MS m/z 1031.7 $(M+H)^+$. Purity 99.4% (HPLC).

Ethyl 3-(5-nitropyridin-2-yl)benzoate (65).

To a mixture of 2-chloro-5-nitropyridine (**63**) (40.0 g, 0.253 mol), (3-(ethoxycarbonyl)phenyl)-boronic acid (**64**) (58.0 g, 0.300 mol), and Na_2CO_3 (54.0 g, 0.510 mol) in dioxane–water (700 mL, 10:1) was added $Pd(dppf)Cl_2$ (14.0 g, 0.02 mol), the mixture was stirred at 110 °C under N_2 overnight. The mixture was purified by silica gel column chromatography (petroleum–EtOAc = 10:1, 5:1, 3:1) to give the title compound **65** (55 g, 94%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (3H, t, J = 7.28 Hz), 4.45 (2H, q, J = 7.06 Hz), 7.63 (1H, t, J = 7.72 Hz), 8.00 (1H, d, J = 8.82 Hz), 8.21 (1H, dt, J = 7.83, 1.38 Hz), 8.34 (1H, dt, J = 7.94, 1.54 Hz), 8.58 (1H, dd, J = 8.82, 2.65 Hz), 8.73 (1H, t, J = 1.54 Hz).

Ethyl 3-(5-aminopyridin-2-yl)benzoate (66).

To a solution of **65** (55.0 g, 0.202 mol) in EtOAc (1.2 L) was added 5% Pd/C (10.0 g), and the mixture was stirred at room temperature under H_2 (30 psi) for 4 h. The mixture was filtered and concentrated the filtrate to give the title compound **66** (48.0 g, 98%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38–1.45 (3H, m), 3.84 (2H, br s), 4.41 (2H, q, *J* = 7.06 Hz), 7.06 (1H, dd, *J* = 8.38, 2.65 Hz), 7.50 (1H, t, *J* = 7.72 Hz), 7.57–7.62 (1H, m), 8.01 (1H, dt, *J* = 8.05, 1.27 Hz), 8.11–8.16 (1H, m), 8.18–8.21 (1H, m), 8.54 (1H, t, *J* = 1.98 Hz).

Ethyl 3-(5-amino-6-bromopyridin-2-yl)benzoate (67).

To a stirring solution of **66** (48.0 g, 0.200 mol) in DMF (700 mL), NBS (37.4 g, 0.210 mol) was added by portions at 0 °C, the mixture was stirred at 0 °C for 10 min. The mixture was poured into cold $NaHCO_3$ aq. (1000 mL) and extracted with EtOAc. The organic phase was concentrated and purified by silica gel column chromatography (petroleum–EtOAc = 5:1) to give the title compound **67** (30.0 g, 47%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (3H, t, *J* = 7.28 Hz), 4.41 (2H, q, *J* = 7.35 Hz), 7.08 (1H, d, *J* = 7.94 Hz), 7.49 (1H, t, *J* = 7.72 Hz), 7.58 (1H, d, *J* = 8.38 Hz), 7.97–8.04 (1H, m), 8.15 (1H, dt, *J* = 7.39, 1.16 Hz), 8.46–8.51 (1H, m).

Ethyl 3-(2-(methylthio)thiazolo[5,4-*b*]pyridin-5-yl)benzoate (69).

A mixture of **67** (13.0 g, 0.040 mol), potassium ethyl xanthogenate (**68**) (32.0 g, 0.20 mol), and AcOH (12 g, 0.20 mol) in NMP (300 mL) was stirred at 130 °C overnight. Iodomethane (58.0 g, 0.40 mol) was added, and the mixture was stirred at 50 °C for another 30 min. The mixture was diluted with water (2000 mL) and extracted with EtOAc. The organic phase was concentrated and purified by silica gel column chromatography (Petroleum–EtOAc = 5:1, 3:1) to give the title compound **69** (9.50 g, 72%) as a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (3H, td, *J* = 7.17, 1.54 Hz), 2.83 (3H, d, *J* = 1.32 Hz), 4.37–4.48 (2H, m), 7.52–7.62 (1H, m), 7.87 (1H, dd, *J* = 8.38, 1.32 Hz), 8.07–8.16 (2H, m), 8.27 (1H, dd, *J* = 7.72, 1.10 Hz), 8.68 (1H, d, *J* = 1.32 Hz).

Ethyl 3-(2-(methylsulfonyl)thiazolo[5,4-*b*]pyridin-5-yl)benzoate (70).

To a solution of **69** (9.50 g, 28.8 mmol) in THF–MeOH (1:1, 300 mL) was added Oxone (142 g, 0.230 mol) in water (500 mL), and the mixture was stirred at room temperature for 48 h. The precipitate was collected by filtration, washed with water, and dried to give the title compound **70** (9.00 g, 86%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (3H, t, *J* = 7.06 Hz), 3.43 (3H, s), 4.45 (2H, q, *J* = 7.06 Hz), 7.62 (1H, t, *J* = 7.94 Hz), 8.11 (1H, d, *J* = 8.38 Hz), 8.17 (1H, dt, *J* = 7.83, 1.38 Hz), 8.32–8.37 (1H, m), 8.52 (1H, d, *J* = 8.82 Hz), 8.75 (1H, t, *J* = 1.76 Hz).

Ethyl 3-(2-aminothiazolo[5,4-*b*]pyridin-5-yl)benzoate (71).

A solution of **70** (3.00 g, 8.29 mmol) in 2M ammonia in THF (70 mL) was stirred at 90 °C for 30 h in sealed tube. After cooling, the mixture was concentrated in vacuo to give crude the title compound **71** (2.50 g, quant.) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33 (3H, t, *J* = 7.06 Hz), 4.34 (2H, q, *J* = 7.35 Hz), 7.59 (1H, t, *J* = 7.72 Hz), 7.68 (1H, d, *J* = 8.38 Hz), 7.85–7.95 (4H, m), 8.23–8.28 (1H, m), 8.57–8.60 (1H, m).

Ethyl 3-(2-((*tert*-butoxycarbonyl)amino)thiazolo[5,4-*b*]pyridin-5-yl)benzoate (72).

A solution of **71** (4.00 g, 13.4 mmol) in Boc_2O (50 mL) was stirred at 120 °C for 16 h. After cooling, the precipitate was collected by filtration, washed with petroleum, and dried to give the title compound **72** (3.85 g, 72%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (3H, t, *J* = 7.06 Hz), 1.51 (9H, s), 4.36 (2H, q, *J* = 7.20 Hz), 7.64 (1H, t, *J* = 7.72 Hz), 7.99 (1H, dt, *J* = 7.83, 1.38 Hz), 8.05–8.12 (2H, m), 8.33–8.37 (1H, m), 8.65 (1H, t, *J* = 1.76 Hz).

3-(2-((*tert*-Butoxycarbonyl)amino)thiazolo[5,4-*b*]pyridin-5-yl)benzoic acid (73).

To a solution of **72** (3.80 g, 9.50 mmol) in MeOH–THF–water (1:1:1, 90 mL) was added 4M NaOH aq. (4.75 mL) at 0 °C, and the mixture was stirred at room temperature overnight. After the mixture was concentrated in vacuo to remove MeOH and THF, the residue was neutralized with 1M HCl aq.. The precipitate was collected by filtration and dried to give the title compound **73** (2.60 g, 74%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.53 (9H, s), 7.53 (1H, t, *J* = 7.72 Hz), 7.99 (1H, d, *J* = 7.50 Hz), 8.01–8.10 (2H, m), 8.20 (1H, d, *J* = 7.94 Hz), 8.68 (1H, br s).

***tert*-Butyl (5-(3-((4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamoyl)phenyl)thiazolo[5,4-*b*]pyridin-2-yl)carbamate (75).**

To a mixture of **73** (743 mg, 2.00 mmol), 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (**74**) (575 mg, 2.00 mmol), Et_3N (0.84 mL, 6.03 mmol), and DMAP (244 mg, 2.00 mmol) in dry DMF (12 mL) was added MNBA (1.38 g, 4.01 mmol) at 0 °C. The mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with 5% Na_2CO_3 aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by NH silica gel column chromatography (eluted with 0–20% MeOH in EtOAc) to give the title compound **75** (1.02 g, 80%) as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.99 (3H, t, J = 7.1 Hz), 1.54 (9H, s), 2.19–2.48 (10H, m), 3.58 (2H, s), 7.62–7.78 (2H, m), 7.95–8.19 (4H, m), 8.24 (1H, s), 8.34 (1H, d, J = 7.7 Hz), 8.67 (1H, s), 10.67 (1H, s), 12.00 (1H, br s).

3-(2-Aminothiazolo[5,4-*b*]pyridin-5-yl)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide (76).

A mixture of **75** (1.01 g, 1.58 mmol) in TFA (12 mL) was stirred at room temperature for 30 min. After the mixture was concentrated in vacuo, the residue was dissolved in EtOAc washed with 5% Na_2CO_3 aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was crystallized from toluene to give the title compound **76** (0.732 g, 86%) as colorless crystals. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.98 (3H, t, J = 7.1 Hz), 2.23–2.49 (10H, m), 3.58 (2H, s), 7.64 (1H, t, J = 7.7 Hz), 7.70–7.79 (2H, m), 7.88–8.02 (4H, m), 8.08 (1H, d, J = 8.6 Hz), 8.21–8.34 (2H, m), 8.61 (1H, s), 10.64 (1H, s). MS m/z 541.2 $(M+H)^+$.

3-(2-(2-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)acetamido)thiazolo[5,4-*b*]pyridin-5-yl)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide (77).

To a mixture of **76** (270 mg, 0.50 mmol), **9** (140 mg, 0.60 mmol), Et_3N (0.21 mL, 1.51 mmol), and DMAP (61 mg, 0.50 mmol) in dry DMF (5 mL) was added MNBA (344 mg, 1.00 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with 5% Na_2CO_3 aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column

chromatography (NH silica gel, eluted with 0–20% MeOH in EtOAc) to give the title compound **77** (285 mg, 76%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, t, *J* = 7.2 Hz), 2.28–2.87 (10H, m), 3.38 (2H, t, *J* = 4.9 Hz), 3.60–3.92 (12H, m), 4.30 (2H, s), 7.62 (1H, t, *J* = 7.7 Hz), 7.77–7.84 (1H, m), 7.86–8.00 (4H, m), 8.07 (1H, d, *J* = 8.4 Hz), 8.17–8.29 (2H, m), 8.59 (1H, s), 10.57 (1H, br s). MS *m*/*z* 756.2 $(M+H)^+$.

3-(2-(2-(2-(2-(2-Aminoethoxy)ethoxy)ethoxy)acetamido)thiazolo[5,4-*b*]pyridin-5-yl)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide (78).
A mixture of **77** (280 mg, 0.37 mmol) and PPh_3 (194 mg, 0.74 mmol) in THF (3 mL)–water (0.1 mL) was stirred at room temperature overnight. After the mixture was concentrated in vacuo, the residue was purified by column chromatography (NH silica gel, eluted with 0–50% MeOH in EtOAc) to give the title compound **78** (190 mg, 70%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, t, *J* = 7.2 Hz), 2.33–2.70 (10H, m), 2.94 (2H, t, *J* = 4.9 Hz), 3.25–3.86 (11H, m), 4.28 (2H, s), 7.59 (1H, t, *J* = 7.8 Hz), 7.76–7.85 (2H, m), 7.91–8.04 (4H, m), 8.18 (1H, d, *J* = 7.8 Hz), 8.54 (2H, d, *J* = 7.7 Hz). MS *m*/*z* 730.3 $(M+H)^+$.

(9*H*-Fluoren-9-yl)methyl ((14*S*,17*S*,18*R*)-1-((5-(3-((4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamoyl)phenyl)thiazolo[5,4-*b*]pyridin-2-yl)amino)-17-hydroxy-14-isobutyl-1,13,16-trioxo-19-phenyl-3,6,9-trioxa-12,15-diazanonadecan-18-yl)carbamate (79).
To a mixture of **78** (185 mg, 0.25 mmol) and **12** (161 mg, 0.30 mmol) in dry DMF (4.5 mL) were added HATU (135 mg, 0.36 mmol) and DIPEA (88 μL, 0.50 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min. The mixture was diluted with EtOAc, washed with 5% $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0–100% MeOH in EtOAc) to give the title compound **79** (270 mg, 86%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.69–0.86 (6H, m), 1.13 (3H, t, *J* = 7.2 Hz), 1.43–1.72 (3H, m), 2.39–2.99 (12H, m), 3.34 (2H, d, *J* = 5.4 Hz), 3.47–3.82 (13H, m), 3.89–4.08 (3H, m), 4.19–4.53 (5H, m), 7.06–7.40 (9H, m), 7.43–7.80 (6H, m), 7.91–8.10 (4H, m), 8.16 (1H, s), 8.24 (1H, d, *J* = 7.5 Hz), 8.62 (1H, s). MS *m*/*z* 1242.4 $(M+H)^+$.

3-(2-((14*S*,17*S*,18*R*)-18-Amino-17-hydroxy-14-isobutyl-13,16-dioxo-19-phenyl-3,6,9-trioxa-12,15-diazanonadecanamido)thiazolo[5,4-*b*]pyridin-5-yl)-*N*-(4-((4-ethylpiperazin-1-yl)-methyl)-3-(trifluoromethyl)phenyl)benzamide (80, SNIPER(ABL)-044).
A mixture of **79** (260 mg, 0.21 mmol) and 2M dimethylamine in MeOH (4 mL, 8 mmol) was stirred at room temperature for 5 h. After the mixture was concentrated in vacuo, the residue was purified by column chromatography (NH silica gel, eluted with 0–50% MeOH in EtOAc) to give the title compound **80** (76 mg, 36%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.91 (6H, t, *J* = 5.9 Hz), 1.11 (3H, t, *J* = 7.2 Hz), 1.54–1.73 (3H, m), 2.38–2.75 (10H, m), 2.88 (1H, dd, *J* = 13.3, 7.0 Hz), 3.31–3.41 (4H, m), 3.54 (2H, t, *J* = 5.4 Hz), 3.61–3.85 (10H, m), 3.94 (1H, d, *J* = 2.8 Hz), 4.33 (2H, s), 4.38–4.48 (1H, m), 7.12–7.33 (5H, m), 7.64 (1H, t, *J* = 7.7 Hz), 7.77 (1H, d, *J* = 8.5 Hz), 7.93–8.06 (3H, m), 8.08–8.14 (1H, m), 8.17 (1H, s), 8.28 (1H, d, *J* = 7.8 Hz), 8.65 (1H, s). MS *m*/*z* 1020.4 $(M+H)^+$. Purity 99.0% (HPLC).

***tert*-Butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(((*S*)-1-((5-(3-((4-((4-ethylpiperazin-1-yl)-methyl)-3-(trifluoromethyl)phenyl)carbamoyl)phenyl)thiazolo[5,4-*b*]pyridin-2-yl)amino)-1,13-dioxo-15,15-diphenyl-3,6,9-trioxa-12-azapentadecan-14-yl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-amino)-1-oxopropan-2-yl)(methyl)carbamate (81).**
To a mixture of **78** (128 mg, 0.18 mmol), **15** (139 mg, 0.21 mmol), DIPEA (61 μL, 0.35 mmol) in DMF (3 mL) was added HATU (93 mg, 0.24 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min. The mixture was diluted with EtOAc, washed with sat. Na_2CO_3 aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–20% MeOH in EtOAc) to give the title compound **81** (193 mg, 80%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.96–1.37 (11H, m), 1.39–1.52 (9H, m), 1.56–1.99 (10H, m), 2.33–2.72 (10H, m), 2.75–3.29 (8H, m), 3.43–3.90 (12H, m), 4.24–4.65 (6H, m), 5.12 (1H, d, *J* = 11.1 Hz), 7.07–7.47 (10H, m), 7.66 (1H, t, *J* = 7.9 Hz), 7.78 (1H, d, *J* = 8.5 Hz), 7.92–8.20 (5H, m), 8.32 (1H, d, *J* = 7.4 Hz), 8.69 (1H, s). MS *m*/*z* 1374.6 $(M+H)^+$.

(*S*)-1-((*S*)-2-Cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl)-*N*-((*S*)-1-((5-(3-((4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamoyl)phenyl)thiazolo[5,4-*b*]pyridin-2-yl)amino)-1,13-dioxo-15,15-diphenyl-3,6,9-trioxa-12-azape

ntadecan-14-yl)-pyrrolidine-2-carboxamide (82, SNIPER(ABL)-047).

A mixture of **81** (187 mg, 0.14 mmol) in TFA (3 mL) was stirred at room temperature for 10 min. After the mixture was concentrated in vacuo, the residue was dissolved in EtOAc, washed with 5% Na_2CO_3 aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–40% MeOH in EtOAc) to give the title compound **82** (139 mg, 80%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.96–1.39 (11H, m), 1.56–1.99 (10H, m), 2.20–2.76 (13H, m), 2.92–3.28 (5H, m), 3.45–3.89 (12H, m), 4.20–4.55 (5H, m), 5.05–5.23 (1H, m), 7.07–7.50 (10H, m), 7.65 (1H, t, *J* = 7.8 Hz), 7.77 (1H, d, *J* = 8.5 Hz), 7.91–8.22 (5H, m), 8.30 (1H, d, *J* = 8.0 Hz), 8.67 (1H, s). MS *m*/*z* 1274.6 $(M+H)^+$. Purity 98.7% (HPLC).

***tert*-Butyl**
((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(3-(2-(2-(2-(2-((5-(3-((4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamoyl)phenyl)thiazolo[5,4-*b*]pyridin-2-yl)-amino)-2-oxoethoxy)ethoxy)ethoxy)ethoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxo-ethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate (83).

A mixture of **76** (92 mg, 0.17 mmol), **24c** (150 mg, 0.19 mmol), Et_3N (0.072 mL, 0.52 mmol), DMAP (21 mg, 0.17 mmol), and MNBA (118 mg, 0.34 mmol) in dry DMF (1.5 mL) was stirred at room temperature overnight. To the mixture was added Et_3N (0.072 mL, 0.52 mmol) and MNBA (118 mg, 0.34 mmol) and the whole was stirred at room temperature for 1 h. The mixture was diluted with EtOAc, washed with 5% Na_2CO_3 aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–20% MeOH in EtOAc) to give the title compound **83** (170 mg, 76%) as a pale yellow amorphous solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.99–1.37 (11H, m), 1.39–1.48 (9H, m), 1.49–1.80 (6H, m), 2.03–2.37 (4H, m), 2.40–2.88 (13H, m), 3.66 (2H, s), 3.71–3.98 (12H, m), 4.12–4.19 (2H, m), 4.30 (2H, s), 4.40–4.67 (2H, m), 5.37–5.61 (1H, m), 7.11 (1H, dd, *J* = 8.2, 1.6 Hz), 7.31 (1H, t, *J* = 8.2 Hz), 7.57–7.68 (3H, m), 7.77 (1H, d, *J* = 8.5 Hz), 7.90–8.06 (4H, m), 8.15–8.29 (3H, m), 8.61 (1H, s). MS *m*/*z* 1311.9 $(M+H)^+$.

3-(2-(2-(2-(2-(2-(3-(2-((*S*)-1-((*S*)-2-Cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)ethoxy)ethoxy)acetami

do)thiazolo-[5,4-*b*]pyridin-5-yl)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide (84, SNIPER(ABL)-033).

A mixture of **83** (165 mg, 0.13 mmol) in TFA (3 mL) was stirred at room temperature for 10 min. The mixture was diluted with toluene (5 mL) and concentrated in vacuo. The residue was diluted with EtOAc, washed with 5% Na_2CO_3 and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0–20% MeOH in EtOAc) to give the title compound **84** (122 mg, 80%) as a colorless amorphous solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.95–1.27 (12H, m), 1.48–1.81 (6H, m), 2.03–2.35 (7H, m), 2.40–2.74 (9H, m), 3.13 (1H, q, *J* = 6.9 Hz), 3.66 (2H, s), 3.71–3.99 (12H, m), 4.12–4.19 (2H, m), 4.29 (2H, s), 4.44–4.57 (1H, m), 5.37–5.62 (1H, m), 7.11 (1H, ddd, *J* = 8.3, 2.5, 0.9 Hz), 7.25–7.37 (1H, m), 7.55–7.69 (3H, m), 7.76 (1H, d, *J* = 8.6 Hz), 7.89–8.05 (4H, m), 8.14–8.29 (3H, m), 8.60 (1H, t, *J* = 1.7 Hz). MS *m*/*z* 1211.8 $(M+H)^+$. Purity 97.2% (HPLC).

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