Supporting Information

Discovery of Narlaprevir (SCH 900518): A Potent, Second Generation HCV NS3 Serine Protease Inhibitor

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Experimental Section

General Methods. Reagents and solvents, including anhydrous THF, dichloromethane and DMF, were purchased from Aldrich, Acros or other commercial sources and were used without further purification. Reactions that were moisture sensitive or using anhydrous solvents were performed under either nitrogen or argon atmosphere. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel plates obtained from Analtech. Visualization was accomplished with UV light or by staining with basic $KMnO_4$ solution or ethanolic H_2SO_4 solution. Compounds were purified by flash chromatography either on a glass column using Merck silica gel 60 (230-400 mesh) or on an automated purification system (ISCO, Biotage, Analogix) using disposable silica gel prepacked cartridges. NMR spectra were recorded at 300, 400 or 500 MHz for ^{1}H and at 75, 100 or 125 MHz for ^{13}C on a Bruker or Varian spectrometer with $CDCl_3$ or DMSO-d_6 as solvent. The chemical shifts are given in ppm, referenced to the deuterated solvent signal. Purity of target compounds were determined using LC-MS and HPLC. LC/MS analyses were performed using an Applied Biosystems API-150 mass spectrometer and Shimadzu SCL-10A LC system. Column: Phenomenex Gemini C18, 5 micron, 50 mm x 4.6 mm ID, gradient: from 90% water, 10% CH_3CN, 0.05%TFA, 5 min to 5% water, 95% CH_3CN, 0.05% TFA in 5 minutes, UV detection: 254nm. Analytical HPLC were done using YMC-Pack Diol NP column, 150x3 mm; 6%-8% [CH_3CN (0.3), *i*-PrOH (1.7), DCM (2)] in Hexanes; 0.8-1.0 mL/min, UV detection: 254 nm. Purity of targets compounds were ≥95%.

Methyl 1-(benzyloxymethyl)cyclohexanecarboxylate (5). KHMDS (3.1L of a 0.5M solution in THF) was added dropwise, over a period of 50min., to a stirred solution of methyl cyclohexane carboxylate (**4**, 200g, 1.41mol) in anhydrous THF (4.5L) at -78C, under an atmosphere of nitrogen. The mixture was stirred for 50min. and chloromethylbenzyl ether (220.5g, 1.41mol) in anhydrous THF (1L) was added over 40 min. The reaction mixture was allowed to reach room temperature overnight. The reaction was quenched with 1N aq. HCL (1L) and extracted into EtOAc (2x2L). The combined organic phases were washed with water, dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc:Hexanes (1:20) as eluent to give **5** (133g, 36%) as a colorless

oil. ^{1}HNMR ($CDCl_3$) 7.21-7.35 (5H, m), 4.50 (2H, s), 3.72 (3H, s), 3.25 (2H, s), 2.00-2.12 (2H, m), 1.49-1.60 (3H, m), 1.18-1.42 (5H, m).

Methyl 1-((methylsulfonyloxy)methyl)cyclohexanecarboxylate (6). 10% Pd/C (10g) was added to a stirred solution of the benzyl ether, **5** (133g, 0.51 mol) in THF (1.2L) and the resulting black suspension was placed under an atmosphere of hydrogen for 1h. The reaction mixture was filtered through a pad of celite and the solid was washed thoroughly with THF. The filtrate was concentrated under reduced pressure to give the desired alcohol (91.0g) as a colorless oil. ^{1}HNMR ($CDCl_3$) δ 3.73 (3H, s), 3.63 (2H, s), 2.14 (1H, br. s), 1.93-2.14 (2H, m), 1.28-1.60 (8H, m). Triethylamine (4.62ml, 33 mmol) was added dropwise to a stirred solution of the primary alcohol from above (3.80g, 22 mmol) and methane sulfonylchloride (2.05ml, 27mmol) in anhydrous dichloromethane (20ml). The resulting mixture was stirred for 1h, partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat aq. sodium bicarbonate, water, dried ($MgSO_4$) and the volatiles removed under reduced pressure to give the mesylate, **6** (5.42g) that was carried forward without purification.

Methyl 1-(tert-butylthiomethyl)cyclohexanecarboxylate (7). To the mesylate, **6** (1.36g, 5.4mmol) in EtOH/H_2O (10ml/2ml) was added sodium tert-butylthiolate (1.22g, 10.9mmol) and the resulting solution was refluxed for 2h. After cooling, the reaction mixture was partitioned between EtOAc and water. The organic phase was separated, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography using hexanes/EtOAc to give the desired sulfide, **7** (0.470g, 36% for 3 steps). ^{1}H NMR ($CDCl_3$, 400MHz) δ 3.67 (3H, s), 2.67 (2H, s), 2.04 (2H, m), 1.53 (2H, m), 1.35 (6H, m), 1.26 (9H, s); ^{13}C NMR ($CDCl_3$, 100MHz) δ 175.9, 51.9, 47.7, 42.0, 37.8, 34.1, 31.0, 26.0, 23.3.

(1*R*,2*S*,5*S*)-N-(4-(allylamino)-1-cyclopropyl-3,4-dioxobutan-2-yl)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (**11**, P1 = -CH_2cyclopropyl). A solution of the isocyanate **9** (three step conversion of **7** to isocyanate **9** is described below, 1.35 mmol) in dichloromethane (2.5ml) and added to a mixture of intermediate **10** (P1 = -CH_2cyclopropyl, 0.329g, 0.67mmol) and triethylamine

(0.47ml, 3.39mmol) in dichloromethane (2.5ml) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was partitioned between EtOAc and 1M aq. HCl. The organic phase was separated, washed with satd. aq. sodium bicarbonate, water, dried ($MgSO_4$), filtered and the volatiles removed under reduced pressure to provide the hydroxyl amide intermediate that was carried forward without purification. The intermediate from above was dissolved in dichloromethane (5ml) and Dess-Martin periodinane (0.574g, 1.35 mmol) was added, in one portion. The resulting mixture was stirred at room temperature for 2h and partitioned between EtOAc and 10% aq. sodium thiosulfate solution. The organic phase was separated, washed with satd. aq. sodium bicarbonate, water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 3:7 acetone/hexanes as eluent to give the desired keto-amide **11** (0.401g, 84%, P1 = -CH_2cyclopropyl, diastereomeric mixture), as a white solid. ^{1}H NMR ($CDCl_3$; 500 MHz): δ 7.67 (1H, d, J = 6.5 Hz), 7.50 (1H, d, J=6.9Hz), 7.12 (1H, t, J=6.0Hz), 6.97 (1H, t, J=5.9Hz), 5.78-5.87 (2H, m), 5.42-5.47 (1H, m), 5.34-5.40 (1H, m), 5.29 (1H, d, J=9.6Hz), 5.15-5.25 (5H, m), 4.74 (1H, s), 4.65 (1H, s), 4.52 (1H, s), 4.51 (1H, s), 4.40-4.46 (2H, m), 4.01-4.09 (4H, m), 3.86-3.98 (4H, m), 3.75-3.84 (2H, m), 2.92 (2H, d, J=13.6Hz), 2.38-2.48 (2H, m), 2.19-2.28 (2H, m), 1.20-1.91 (24H, m), 1.34 (9H, s), 1.33 (9H, s), 1.02 (3H, s), 1.01 (3H, s), 0.99 (9H, s), 0.96 (9H, s), 0.84 (3H, s), 0.83 (3H, s), 0.69-0.80 (2H, m), 0.40-0.51 (4H, m), 0.00-0.16 (4H, m). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 196.81, 195.75 172.96, 172.58 170.40, 170.17, 159.11, 158.99, 157.08, 156.99, 132.78, 132.75, 117.40, 117.32, 60.28, 60.27, 59.90, 59.79, 57.78, 57.60, 54.99, 54.90, 54.62, 54.59, 50.22 (2C), 48.46, 48.40, 41.63, 41.59, 36.59, 36.29, 35.82 (2C), 35.55, 35.46, 35.03, 35.02, 29.49, 28.81, 27.44, 27.32, 26.38 (6C), 26.34 (2C), 25.37, 25.34, 23.02 (6C), 21.18, 21.13, 21.08, 21.03, 18.79, 18.70, 12.70, 12.63, 7.53, 7.36, 5.31, 5.19, 4.57, 4.42ppm. HRMS (FAB) calcd. for $C_{36}H_{60}N_5O_7S$ $[M+H]^+$: 706.4213, found 706.4227.

(*S*)-tert-butyl 1-hydroxyhexan-2-ylcarbamate (17). A 22L three-neck round bottom flask was fitted with mechanical stirrer, condenser, and a 1L solid addition flask with flexible teflon neck. The three-neck round bottom flask was charged with anhydrous THF (6.2L) and 13 mm. LAH pellets (148.2 g) at room temperature and stirred over night under N_2 to disperse pellets. The reaction was cooled to 0-5 ºC

and treated portion wise with L norleucine, **16** (250 g) over 2.5 hours then refluxed for 3 hours. The reaction was allowed to cool over night and the reflux continued the next day for an additional 3 hours. The slurry was cooled to 0 ºC in an ice bath followed by drop-wise addition of H_2O (70 ml), 10% NaOH (187 ml), H_2O (70 ml) then added 150 ml additional water and 10% NaOH in 20 ml portions while warming to 30-35 ºC with hot water bath over 2 more hours. The reaction was then stirred over night at room temperature. The white heavy precipitate formed was filtered through celite. The filtrate was treated with di-*tert*-butyldicarbonate (391 g) at ~10 ºC warming to room temperature and stirred over the weekend. The reaction mixture was evaporated to an oil which crystallized on standing to yield **17** (417 g, 82%) off white waxy solid. ^{1}H NMR (500 MHz, d_6-DMSO) δ, 6.41 (d, 1 H, J = 8.5 Hz), 4.52 (t, 1 H, J = 5.4 Hz), 3.34-3.27 (m, 2 H), 3.21-3.17 (m, 1 H), 1.39 (s, 9 H), 1.28-1.19 (m, 6 H), 0.85 (t, 3 H, J = 6.9 Hz). ^{13}C NMR (125 MHz, d_6-DMSO) δ 156.2, 78.1, 64.5, 52.9, 31.5, 29.1, 28.6, 23.0, 14.8; MS (ESI, m/z, relative intensity) 240 [$(M+Na)^+$, 40], 162(45), 118 (100) .

(*S*)-tert-butyl 1-oxohexan-2-ylcarbamate (18). To a solution of (*S*)-tert-butyl 1-hydroxyhexan-2-ylcarbamate **17** (10 g, 46.08 mmol) in ethyl acetate (100 mL) was added a solution of LiBr (305 mg. 3.51 mmol) TEMPO (101 mg. 0.64 mmol) and $NaHCO_3$ (4.8 g, 63.6 mmol) in water (50 mL) and cooled to 0 °C (internal temperature 3 °C). To this solution was added drop-wise commercial bleach (29 ml, 13 wt% soln). On the completion of bleach addition, TLC analysis indicated incomplete consumption of starting material. Additional bleach in portions of 1.5 mL each was added. On the completion of reaction, the mixture was cooled to 0 °C and treated with $Na_2S_2O_3$ (1M. 50mL) and 50 mL of EtOAc. The organic layer was separated and the aq. layer was extracted with EtOAc (2x250 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and to provide aldehyde, **18** (8.6 g, ~ 87%) as a pale yellow oil that was carried forward.

(3*S*)-3-(tert-butoxycarbonylamino)-1-(cyclopropylamino)-1-oxoheptan-2-yl acetate (20). A solution of aldehyde **18** (8.6 g, 39.95 mmol) in EtOAc (100 mL) was treated with cyclopropylisocyanide **19** (3.35 g. 50.00 mmol) and acetic acid (3.35 g. 50.0 mmol) at 0 °C and the ice bath was allowed to warm

up slowly and stirred at RT for 12 h. The reaction mixture was concentrated *in vacuo* to yield **20** as a pale yellow solid, as a mixture of diastereomers (13.3g). ^{1}H NMR (500 MHz, d_6-DMSO, mixture of diastereomers, proton count represents diastereomers of **20**), δ 8.31 (d, 1 H, J = 3.8 Hz), 7.94 (d, 1 H, J = 3.8 Hz), 6.68 (d, 1 H, J = 8.8 Hz), 6.47 (d, 1 H, J = 9.5 Hz), 4.91 (d, 1 H, J = 4.1 Hz), 4.70 (d, 1 H, J = 5.04 Hz), 3.86-3.80 (m, 2 H), 2.61-2.55 (m, 1 H), 2.54-2.48 (m, 1 H), 2.08 (s, 3 H), 2.05 (s, 3 H), 1.31 (s, 18 H), 1.40-1.11 (m, 12 H), 0.83 (t, 6 H, J = 6.9 Hz), 0.62-0.55 (m, 4 H), 0.45-0.37 (m, 4 H). ^{13}C NMR (125 MHz, d_6-DMSO, mixture of diastereomers). δ 169.8, 169.7, 168.6, 168.5, 155.15, 155.17, 77.6, 77.4, 75.0, 74.4, 50.9, 50.8, 30.3, 28.2, 28.1, 28.0, 27.5, 27.4, 22.0, 21.9, 21.6, 20.8, 20.5, 13.79, 13.74, 5.5, 5.4, 5.4. MS (ESI. m/z. % relative intensity) 707 [(2M+Na), 5], 365 [(M+Na), 5], 343 [(M+1), 10], 243 (60), 225 (100).

(3*S*)-3-amino-N-cyclopropyl-2-hydroxyheptanamide hydrochloride (21). The mixture of diastereomers, **20** was taken up in methanol (20 mL). THF (30 mL) and water (40 mL) and treated with $LiOH{\cdot}H_2O$ (2.51 g, 60 mmoles) and stirred at room temperature for 1 h. Analysis by TLC (EtOAc/Hexanes 2:1) showed complete consumption of starting material. The reaction mixture was concentrated *in vacuo* to remove the organics and the aqueous layer was extracted in ethyl acetate (2x300 mL). The combined organic layers were dried ($MgSO_4$) filtered concentrated in vacuo and used as it is in the next step with out further purification. Yield 11.05g (91.7% for 2 steps, Passerini reaction and hydrolysis) ^{1}H NMR (500 MHz, d6-DMSO), d, 7.75 (d, 1 H, J = 4.1 Hz), 7.67 (d, 1 H, J = 4.4 Hz), 6.34 (d, 1 H, J = 9.1 Hz), 6.00 (d, 1 H, J = 9.5 Hz), 5.48 (d, 1 H, J = 5.4 Hz), 5.32 (d, 1 H, J = 6.3 Hz), 3.83 (dd, 1 H, J = 3.8 & 5.7 Hz) 3.78 (dd, 1 H, J = 3.2 & 6.6 Hz), 3.73-3.63 (m, 2 H), 2.66-2.61 (m, 1 H), 2.61-2.55 (m, 1 H), 1.37 (s, 9 H), 1.35 (s, 9 H), 1.47-1.15 (m, 12 H), 0.84 (t, 3 H, J = 6.9 Hz), 0.81 (t, 3 H, J = 6.9 Hz), 0.58-0.51 (m, 4 H), 0.5-0.41 (m, 4 H). ^{13}C NMR (125 MHz, d_6-DMSO, mixture of diastereomers). δ 173.3, 172.9, 155.07, 77.3, 73.6, 72.3, 52.7, 52.5, 30.8, 28.1, 28.0, 27.7, 27.6, 22.0, 21.9, 21.8, 13.8, 13.7, 5.5, 5.4 MS (ESI. m/z. % relative intensity) 623 [(2M+Na), 5], 323 [(M+Na), 10], 301 [(M+1), 30], 245 (60), 201 (100). The product from above (283 g, 0.942 moles) was treated

with 4 M solution of HCl in dioxane (1.4 L) and stirred with the help of a mechanical stirrer at RT for 1 h. Copious amounts of precipitate was formed after completion of reaction. Analysis by TLC (acetone/hexanes 1:2) indicted complete consumption of starting material. The reaction mixture was diluted with of diethyl ether (2L) and the solid was filtered. The solid cake was washed with excess diethyl ether (4 L) and dried in a vacuum oven for 48 h to yield **21 (**220 g) as a colorless solid. ^{1}H NMR (500 MHz. d_6-DMSO. mixture of diasteromers. proton count represents diastereomers of **21**), δ 8.16 (d, 1 H, J = 4.4 Hz), 8.07 (d, 1 H, J = 4.7 Hz), 8.05 (b, 3 H), 7.85 (b, 3 H), 6.37 (s, 1 H), 6.27 (s, 1 H), 4.18 (b, 1 H), 3.98 (b 1 H). 3.35 (b, 1H), 3.23-3.20 (m, 1 H), 2.71-2.65 (m, 2 H), 1.59-1.16 (m, 12 H), 0.86 (t, 3 H, J = 6.9 Hz), 0.84 (t, 3 H, J = 7.3 Hz), 0.64-0.59 (m, 4 H), 0.56-0.46 (m, 4 H). ^{13}C NMR (125 MHz, d_6 DMSO) δ 183.4, 183.1, 82.0, 80.9, 64.3, 64.1, 39.7, 38.2, 38.15, 38.1, 33.7, 33.6, 33.28, 33.22, 25.0, 24.9, 16.90, 16.81, 16.78, 16.71. MS (ESI) $[M+1]^+$ 201.

Methyl 1-(tert-butylthiomethyl)cyclohexanecarboxylate (7, Improved procedure). To freshly prepared LDA (1L, 1 mol) was added a solution of the ester **4** (142g, 1 mol) in THF (1L) at -78°C over 45 min. Maintained at that temp for 30 min. Then TMSCl (128 ml, 1 mol) was added over 5 min. Temp rose to -55°C. Reaction mixture was warmed to -10°C over 70 min. At this time, THF was removed in vacuo (water bath temp <35°C). The residue (~300 g) was diluted with dichloromethane (1.3 L). A solution of chloromethyl thioether **30** (138.5 g, 1 mol) in dichloromethane (200ml) was added over 25 min followed by zinc bromide (30g). Reaction mixture was stirred at RT for 1 hr. (Similar procedure was carried out with 213g, 1.5 mol of ester **4**). Both reaction mixtures were then combined, diluted with dichloromethane (4L) and washed with satd sodium bicarbonate (1.5L). The aq layer was extracted with dichloromethane (2L). The combined organic layer was washed with water (2 x 1.5 L), dried ($MgSO_4$) and concentrated to provide 625g of **7** as orange-yellow oil.

1-(tert-butylthiomethyl)cyclohexanecarboxylic acid (31). Ester **7** from above was taken in THF (3L), MeOH (1.8L) and water (1.8L). Lithium hydroxide (250g, 5.95 mol) was added and the mixture was refluxed at 80°C for 42 hr. The reaction mixture was concentrated (to remove THF and MeOH). The

residue was acidified with 2N HCl (pH = 2). The aq layer was extracted with ethyl acetate (3 x 2.5L). The combined EtOAc layer was washed with water (2L), dried ($MgSO_4$) and concentrated to afford 557g of **31** as an oil. ^{1}H NMR ($CDCl_3$, 400MHz) δ 2.72 (2H, s), 2.03 (2H, m), 1.55 (3H, m), 1.43 (4H, m), 1.26 (10H, s). ^{13}C NMR ($CDCl_3$, 100MHz) δ 182.2, 47.3, 41.9, 37.1, 33.4, 30.7, 25.6, 22.8 ppm.

1-(tert-butylsulfonylmethyl)cyclohexanecarboxylic acid (8). To a solution of **31** from above, in MeOH (7L) was added a suspension of Oxone (3500 g, 5.688 mol) in water (5L). Temp rose to 45°C. The reaction mixture was stirred at room temp overnight. At this time, the white solid was filtered off and washed with MeOH (1L). The filtrate was concentrated *in vacuo* resulting in a white solid. The solid was washed with water (3 x 1L). The crude solid was dried under vacuum at 50°C. This material was dissolved in EtOAc (6L) and washed with water (2 x 500 ml), dried and concentrated to afford 405g of **8** as white solid (62% for 3 steps). ^{1}H NMR ($CDCl_3$, 400MHz) δ 3.34 (2H, s), 2.05 (2H, m), 1.76 (2H, m), 1.63 (2H, m), 1.53 (2H, m), 1.45 (2H, m), 1.37 (9H, s). ^{13}C NMR ($CDCl_3$, 100MHz) δ 180.2, 60.0, 51.0, 44.5, 33.2, 25.3, 23.1, 21.9 ppm.

(*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoic acid (33). To a solution of acid **8** (343g, 1.31 mol) in toluene (2 L) at room temp was added diphenylphosphoryl azide (298 ml) followed by triethylamine (182 ml). The reaction mixture was heated slowly (exothermic reaction) and refluxed (110°C) for 3 hr. The reaction mixture was cooled to room temp and washed with satd sodium bicarbonate (2 x 1.2L). The toluene layer (containing isocyanate **9**) was then added to a vigorously stirred mixture of L-tert-leucine (**32**, 170.5g, 1.3 mol), water (1.7L) and Et_3N (500 ml). This mixture was rapidly stirred at room temp for 48h. At this time 10% aq sodium carbonate (2.05L) was added, stirred for 15 min and filtered to remove the solids. The toluene layer was separated and extracted with water (2x 400 ml). The combined aq layer was acidified with 3N HCl (~1.6L) till pH 3 which resulted in formation of white solid. The solid was filtered, washed with water (1.2 L), diethyl ether (700 ml), dried under vacuum resulting in 435g of **33** as a white solid (85% for two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.30 (d, J= 9.5 Hz, 1H), 6.08 (s, 1H), 3.92 (d, J= 9.5 Hz, 1H), 3.65 (d, J=

13.8 Hz, 1H), 3.39 (d, J=13.8 Hz, 1H), 2.20 (br. d, 2H), 1.60-1.38 (m, 7H), 1.22 (s, 9H), 1.21-1.14 (m, 1H), 0.90 (s, 9H). MS $(M+H)^+$: 391.

(1*R*,2*S*,5*S*)-methyl 3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate (35). To a 0°C solution of the acid **33** (168g, 0.43 mol) in MeCN (10X, 1.7L) was added EDCI (103g, 0.538 mol), HOBt (11.62g, 0.086 mol), previously described amine salt **34** (100g, 0.486 mol) followed by NMM (71 mL, 0.645 mol). The reaction was gradually warmed to room temperature overnight with stirring. After 18h, the reaction was diluted with EtOAc (3L) and washed with aq 1N HCl (2 x 2L), saturated $NaHCO_3$ (2L), aq 10% K_2CO_3 (wt/vol, 2L) and brine (2L). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an off-white foam. After drying under vacuum overnight 244.6g of **35** (theory: 232.9g) was obtained that was carried forward.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (13). To 0-10°C solution of the crude methyl ester **35** from above (0.43 mol) in THF/MeOH (1:1, 1.3L each, 2.6L total) was added aq 1M LiOH (1.3L, 1.29 mol) over 5 min (temp rose to ~30°C). After 2h, the ice bath was removed and the reaction was warmed to room temperature over additional 2.5h. TLC and mass spectral analysis indicated reaction completion. The reaction mixture was concentrated to ~1L and diluted with water (2L). The aqueous layer was washed with EtOAc (3 x 1.5L) and then acidified with aq 3N HCl to pH 1-3. The aqueous layer was extracted with EtOAc (4L). The organic layer was washed with brine (2L), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dried under vacuum overnight to give 220g of crude **13** as an off-white foam. The above crude acid **13** (220g) was dissolved in acetone (1L). The solution was filtered to remove undissolved material and the flask/funnel was rinsed with acetone (~500 mL). The filtrate was taken in a three neck 12L flask and diluted with acetone (total volume of acetone = 2.2-2.5L). Water was slowly added with stirring (mechanical) till the solution turned turbid (volume of water = 2.9L). Seed crystals were added (~500 mg) and stirred vigorously, overnight. At

this more water was added (dropwise, 1L) to push crystallization to completion. The slurry was filtered off and rinsed with water (~1L). The white cake was dried *in vacuo* to yield 194g of pure crystalline acid **13** (86% for two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.27 (d, *J*= 10.4 Hz, 1H), 6.04 (s, 1H), 4.19 (d, J= 9.5 Hz, 1H), 4.09 (s, 1H), 3.92 (d, J=10.8 Hz, 1H), 3.77-3.73 (m, 1H), 3.70 (d, J=13.2 Hz, 1H), 3.31 (d, J= 13.7 Hz, 1H), 2.20 (br. t, 2H), 1.59-1.06 (m, 10H), 1.22 (s, 9H), 0.99 (s, 3H), 0.91 (s, 9H), 0.79 (s, 3H); MS $(M+H)^+$: 528.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((3*S*)-1-(cyclopropylamino)-2-hydroxy-1-oxoheptan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (36). The suspension of the acid **13** (24.3g, 46 mmol) and amine salt **21** (12.1g, 51.1 mmol) in anhydrous MeCN (500 mL) was cooled to -5 to 0°C (ice/NaCl). To this mixture was added HOBt (1.25g, 9.25 mmol), EDCI (11g, 57.3 mmol) and DIPEA (12 mL, 69 mmol) sequentially. The mixture was stirred and allowed to warm to room temperature overnight (~20h). The reaction mixture was concentrated to a third of its volume, and then poured into a separatory funnel containing 1N HCl (1 L) and EtOAc (1 L). The flask was rinsed with EtOAc (2 x 20 mL) and the rinsings were poured into the separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (1 L). The combined EtOAc layers was washed with 1N HCl (1 L), aq. 10% K_2CO_3 solution (1 L, wt/vol), saturated $NaHCO_3$ (1 L) and brine (1 L). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 33.9g of hydroxylamide **36** (theory: 32.6g) that was carried forward.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-1-(cyclopropylamino)-1,2-dioxoheptan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (37). To a room temperature solution of the hydroxylamide **36** from above (2g, 2.82 mmol) in EtOAc (20 mL) was added KBr (132 mg, 1.12 mmol), $NaHCO_3$ (332 mg, 3.94 mmol), water (10 mL), TEMPO (132 mg, 0.85 mmol) followed by drop-wise addition of bleach (4 mL, 2.96 mmol). The mixture was stirred at room temperature for 30 min when TLC indicated reaction completion. The reaction mixture was diluted with EtOAc (100 mL) and washed with aq. saturated sodium thiosulfate

(50 mL), saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 2.05g of crude material. This material was dissolved in minimum amount of MTBE and the solution was poured into n-heptane (3-10x vol). The precipitated white solid was filtered and washed with hexanes, resulting in essentially quantitative recovery. The precipitated solid thus obtained from few runs (11.2g, 99% recovery) was dissolved in acetone (10x) and water was added under mechanical stirring till white turbidity appeared. Stirring was continued for 18h, at which time addition of water did not produce any more precipitate. The solid was filtered off, washed with water and dried under vacuum to provide 10.4g (93% isolated yield) of **37** as a white crystalline solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (d, *J*= 5.2 Hz, 1H), 8.38 (d, *J*= 6.7 Hz, 1H), 6.21 (d, *J*= 9.8 Hz, 1H), 6.06 (s, 1H), 4.96-4.91 (m, 1H), 4.28 (s, 1H), 4.17 (d, *J*= 10.0 Hz, 1H), 3.89 (d, *J*= 10.3 Hz, 1H), 3.74-3.69 (m, 2H), 3.30 (d, *J*= 13.9 Hz, 1H), 2.78-2.71 (m, 1H), 2.24 (br. d, *J*= 11.8 Hz, 1H), 2.17 (br. d, *J*= 13.1 Hz, 1H), 1.77-1.70 (m, 1H), 1.60-0.82 (m, 18H), 1.22 (s, 9H), 0.99 (s, 3H), 0.89 (s, 9H), 0.82 (s, 3H), 0.68-0.63 (m, 2H), 0.58-0.55(m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.14, 171.12, 170.39, 162.00, 156.79, 59.16, 59.01, 56.35, 53.61, 53.38, 50.57, 47.40, 34.38, 34.16, 30.71, 29.32, 27.52, 26.88, 26.25, 26.12, 24.93, 22.47, 21.68, 20.60, 20.55, 18.44, 13.67, 12.55, 5.38, 5.35; LCMS for $C_{36}H_{62}N_5O_7S$ $[M + H]^+$: 708.4. Analytical HPLC (YMC-Pack Diol NP column, 150x3 mm; 6% [CH_3CN (0.3), *i*-PrOH (1.7), DCM (2)] in Hexanes; 0.8 mL.min; 254 nm) Rt= 15.78 min, purity >99%.

(1*R*,2*S*,5*S*)-N-(1-(allylamino)-1,2-dioxohexan-3-yl)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl) cyclohexyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (40). Isolated as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.86 & 8.81 (1H, t, J = 6.1 & 6.2 Hz), 8.37 & 8.30 (1H, d, J = 6.7 & 7.4 Hz), 6.22 (1H, d, J = 9.7 Hz), 6.05-6.03 (1H, m), 5.83-5.75 (1H, m), 5.12-5.04 (2H, m), 4.99-4.85 (1H, m), 4.28 (1H, d, J = 7.8 Hz), 4.19-4.16 (1H, m), 3.91-3.87 (1H, m), 3.77-3.69 (3H, m), 2.23 (1H, d, J = 13.6 Hz), 2.17 (1H, d, J = 14.5 Hz), 1.76-1.26 (13H, m), 1.23 (9H, s), 1.19-1.10 (1H, m), 0.99 (3H, d, J = 9.5 Hz), 0.89 (9H, s), 0.91-0.79 (8H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.2, 196.6, 171.0, 170.5, 170.3, 161.0, 160.7, 156.7, 156.7, 134.1, 134.0, 115.5,

115.4, 59.1, 56.4, 56.3, 53.4, 53.3, 50.5, 47.3, 47.2, 40.7, 40.0, 34.3, 34.1, 31.5, 30.5, 26.8, 26.7. 26.2, 26.1, 26.0, 24.8, 22.4, 20.5, 20.4, 18.6, 18.3, 13.4, 13.3, 12.5 ppm. HRMS (ESI) calcd. for $C_{35}H_{59}N_5O_7S$ $[M+H]^+$: 694.4213, found 694.4213.

(1*R*,2*S*,5*S*)-N-(1-(allylamino)-1,2-dioxoheptan-3-yl)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl) cyclohexyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (41). Isolated as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.87 & 8.81 (1H, t, J = 6.0 & 6.0 Hz), 8.36 & 8.29 (1H, d, J = 6.7 & 7.3 Hz), 6.24-6.20 (1H, m), 6.05 (1H, d, J = 4.1 Hz), 5.84-5.75 (1H, m), 5.12-5.03 (2H, m), 4.98-4.94 & 4.87-4.83 (1H, m), 4.28 (1H, d, J = 11.1 Hz), 4.18 (1H, dd, J = 10.0, 4.6 Hz), 3.92-3.88 (1H, m), 3.79-3.68 (3H, m), 2.23 (1H, d, J = 12.3 Hz), 2.17 (1H, d, J = 12.9 Hz), 1.76-1.68 (1H, m), 1.60-1.24 (14H, m), 1.23 (9H, s), 1.17-1.10 (1H, m), 0.99 (3H, d, J = 9.5 Hz), 0.89 (9H, s), 0.87-0.80 (8H, m). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.2, 196.6, 171.0, 170.8, 170.5, 170.3, 161.0, 160.7, 156.7, 156.6, 134.1, 134.0, 115.5, 115.4, 59.1, 58.9, 56.34, 56.26, 53.55, 53.53, 50.5, 47.3, 47.2, 40.7, 40.0, 34.3, 34.1, 30.6, 29.2, 29.0, 27.4, 27.2, 26.8, 26.7. 26.1, 26.0, 24.8, 22.4, 21.61, 20.49, 20.45, 18.3, 13.6, 12.5, 12.4 ppm. HRMS (ESI) calcd. for $C_{36}H_{61}N_5O_7S$ $[M+H]^+$: 708.4370, found 708.4366.

(1*R*,2*S*,5*S*)-N-(1-(allylamino)-1,2-dioxohept-6-yn-3-yl)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl) cyclohexyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (42). Isolated as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.87-8.85 & 8.46-8.44 (1H, m), 6.21 (1H, d, J = 9.7 Hz), 6.05-6.03 (1H, m), 5.84-5.74 (1H, m), 5.13-4.96 (3H, m), 4.25-4.14 (2H, m), 3.88 (1H, d, J = 10.4 Hz), 3.77-3.68 (4H, m), 3.61-3.55 (1H, m), 2.79-2.78 (1H, m), 2.32-2.16 (3H, m), 2.00-1.95 (1H, m), 1.77-1.24 (13H, m), 1.23 (9H, s), 1.17-1.10 (1H, m), 1.02-0.96 (3H, m), 0.89 (9H, s), 0.82-0.79 (3H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 196.5, 171.1, 170.3, 160.7, 156.7, 156.69, 134.0, 115.5, 83.2, 71.7, 59.1, 56.3, 53.3, 53.2, 47.2, 40.7, 40.0, 34.3, 34.1, 29.0, 26.9, 26.2. 26.0, 24.8, 22.4, 20.5, 20.46, 18.4, 14.6, 12.5 ppm. HRMS (ESI) calcd. for $C_{36}H_{57}N_5O_7S$ $[M+H]^+$: 704.4057, found 704.4063.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-1-(ethylamino)-1,2-dioxoheptan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (44). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (app. t, *J*= 5.94 Hz, 1H), 8.35 (d, *J*= 6.92 Hz, 1H), 6.21 (d, *J*= 9.68 Hz, 1H), 6.05 (s, 1H), 4.99-4.94 (m, 1H), 4.29 (s, 1H), 4.17 (d, *J*= 9.85 Hz, 1H), 3.90 (d, 1H), 3.74-3.69 (m, 2H), 3.30 (d, *J*= 13.45 Hz, 1H), 3.17-3.10 (m, 2H), 2.23 (br. d, *J*= 12.2 Hz, 1H), 2.17 (br. d, *J*= 13.2 Hz, 1H), 1.77-1.71 (m, 1H), 1.60-0.79 (m, 15H), 1.24 (s, 9H), 1.04 (t, 3H), 1.00 (s, 3H), 0.90 (s, 9H), 0.86 (t, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.42, 171.02, 170.30, 160.38, 156.71, 59.08, 58.92, 56.27, 53.51, 53.30, 50.49, 47.31, 34.30, 34.07, 33.32, 30.60, 29.23, 27.43, 26.79, 26.16, 26.04, 24.83, 22.38, 21.57, 20.51, 20.46, 18.34, 14.12, 13.57, 12.46. HRMS calcd for $C_{36}H_{65}N_5NaO_8S$ $[M + Na+CH_3OH]^+$: 750.4452. Found: 750.4465.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-1,2-dioxo-1-(propylamino)heptan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (45). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (app. t, *J*= 6.12 Hz, 1H), 8.35 (d, *J*= 6.92 Hz, 1H), 6.21 (d, *J*= 9.85 Hz, 1H), 6.06 (s, 1H), 4.99-4.95 (m, 1H), 4.29 (s, 1H), 4.17 (d, *J*= 10.11 Hz, 1H), 3.89 (d, *J*= 10.39 Hz, 1H), 3.74-3.69 (m, 2H), 3.30 (d, *J*= 13.60 Hz, 1H), 3.09-3.04 (m, 2H), 2.23 (br. d, *J*= 12.65 Hz, 1H), 2.17 (br. d, *J*= 13.44 Hz, 1H), 1.77-1.70 (m, 1H), 1.59-0.79 (m, 17H), 1.23 (s, 9H), 1.00 (s, 3H), 0.89 (s, 9H), 0.85 (t, 3H), 0.82 (s, 3H), 0.82 (t, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.45, 171.02, 170.31, 160.71, 156.71, 59.09, 58.94, 56.27, 53.53, 53.30, 50.50, 47.32, 34.31, 34.08, 30.61, 29.24, 27.41, 26.80, 26.17, 26.04, 24.85, 22.39, 21.85, 21.59, 20.52, 20.47, 18.36, 13.59, 12.48, 11.17. HRMS calcd for $C_{36}H_{64}N_5O_7S$ $[M + H]^+$: 710.4526. Found: 710.4530.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-1-(cyclopropylmethylamino)-1,2-dioxoheptan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (46). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (t, *J*= 6.0 Hz, 1H), 8.35 (d, *J*= 6.9 Hz, 1H), 6.22 (app. t, *J*= 11.2 Hz, 1H), 6.06 (br. s, 1H), 5.01-4.97 (m, 1H), 4.30 (s, 1H), 4.63 (d, 1H), 3.89 (d, *J*= 10.6 Hz, 1H), 3.76-3.69 (m, 2H), 3.28 (partially solvent hidden, m, 1H), 3.04-2.92 (m, 2H), 2.25-2.16

(m, 2H), 1.78-1.71 (m, 1H), 1.58-0.79 (m, 19H), 1.23 (s, 9H), 1.00 (s, 3H), 0.89 (s, 9H), 0.82 (s, 3H), 0.40-0.38 (m, 2H), 0.19-0.17 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.42, 170.97, 170.23, 160.42, 156.63, 59.01, 58.86, 56.18, 53.42, 53.22, 47.25, 42.69, 34.23, 33.99, 30.53, 29.13, 27.36, 26.71, 26.09, 25.97, 24.77, 22.31, 21.92, 21.51, 20.43, 18.28, 13.69, 13.51, 12.41, 10.44. LCMS for $C_{37}H_{64}N_5O_7S$ $[M + H]^+$: 722.2.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-1-(2-(cyclobutylamino)-2-oxoethylamino)-1,2-dioxoheptan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (47). ^{1}H NMR (500 MHz, d_6-DMSO): δ, 8.93 (d, 1 H, J = 7.9 Hz), 8.36 (d, 1 H, J = 6.9 Hz), 6.21 (d, 1 H, J = 10.1 Hz), 6.06 (s, 1 H), 4.96-4.92 (m, 1 H), 4.30 (s, 1 H), 4.23 (q, 1 H, J = 8.2 Hz), 4.18 (d, 1 H, J = 9.8 Hz), 3.91 (d, 1 H, J = 10.4 Hz), 3.73 (dd, 1 H, J = 5.4 & 5.0 Hz), 3.712 (d, 1 H, J = 13.8 Hz), 3.316 (d, 1 H, J = 13.9 Hz), 2.26-2.05 (m, 4 H), 1.77-1.26 (m, 20 H) 1.24 (s, 9 H), 1.08 (s, 3 H), 0.90 (s, 3 H), 0.87 (t, 3 H, J = 6.6 Hz), 0.83 (s, 3 H). ^{13}C (125 MHz, d_6-DMSO) δ, 198.3, 172.0, 171.2, 160.6, 157.6, 60.0, 59.9, 57.2, 54.5, 54.2, 51.4, 48.2, 44.6, 35.2, 35.0, 31.5, 30.3, 30.29, 30.21, 28.4, 27.1, 27.0, 25.8, 23.3, 22.5, 21.4, 19.3, 15.5, 14.5, 13.4, MS (ESI) $[M+H]^+$: 722.

(**1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(*tert*-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-1-(2-(cyclopentylamino)-2-oxoethylamino)-1,2-dioxoheptan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (48)**. ^{1}H NMR (500 MHz, d_6-DMSO): δ, 8.62 (d, 1 H, J = 7.9 Hz), 8.35 (d, 1 H, J = 6.9 Hz), 6.22 (d, 1 H, J = 10.1 Hz), 6.07 (s, 1 H), 4.98-4.94 (m, 1 H), 4.31 (s, 1 H), 4.19 (d, 1 H, J = 9.8 Hz), 4.03 (dd, 1 H, J = 6.9 & 7.3 Hz), 3.90 (d, 1 H, J = 10.4 Hz), 3.74 (dd, 1 H, J = 5.4 & 6.6 Hz), 3.72 (d, 1 H, J = 13.9 Hz), 3.26 (d, 1 H, J = 13.9 Hz), 2.23-2.14 (m, 2 H), 1.83-1.26 (m, 24 H) 1.24 (s, 9 H), 1.01 (s, 3 H), 0.90 (s, 3 H), 0.87 (t, 3 H, J = 6.6 Hz), 0.83 (s, 3 H). ^{13}C (125 MHz, d_6-DMSO) δ, 198.6, 172.1, 171.4, 161.7, 157.8, 60.2, 60.1, 57.4, 54.8, 54.4, 51.3, 48.4, 35.4, 32.7, 32.7, 31.7, 30.3, 28.5, 27.9, 27.3, 27.2, 26.0, 24.6, 23.5, 22.7, 21.6, 19.5, 14.7, 13.6. MS (ESI) $[M+H]^+$: 736.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-N-((*S*)-1-(1-methylcyclopropylamino)-1,2-dioxoheptan-3-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide (49). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (1H, d. J=7.7Hz), 7.39 (1H, br.s), 5.60 (1H, d. J=9.50Hz), 5.32-5.42 (1H, m), 5.03 (1H, s), 4.51 (1H, s), 4.44 (1H, d, J=9.8Hz), 4.09 (1H, d, J=13.5Hz), 4.03 (1H, d, J=10.5Hz), 3.81 (1H, dd, J=10.5 and 4.8Hz), 2.86 (1H, d, J=13.5Hz), 2.34-2.52 (1H, m), 2.10-2.26 (1H, m), 1.84-1.98 (1H, m), 1.16-1.78 (15H, m), 1.38 (3H, m), 1.34 (9H, s), 1.00 (3H, s), 0.95 (9H, s), 0.83 (3H, s), 0.77-0.89 (5H, m), 0.65-0.71 (2H, m). HRMS (FAB) calcd. for $C_{36}H_{64}N_6O_9S_2$ $[M+H]^+$: 772.4526, found 772.4525.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-1-(2-methoxyethylamino)-1,2-dioxoheptan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (50). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (t, J= 5.8 Hz, 1H), 8.35 (d, *J*= 6.9 Hz, 1H), 6.21 (d, *J*= 9.8 Hz, 1H), 6.06 (s, 1H), 5.00-4.96 (m, 1H), 4.29 (s, 1H), 4.17 (d, *J*= 9.8 Hz, 1H), 3.89 (d, *J*= 10.7 Hz, 1H), 3.74-3.69 (m, 2H), 3.40-3.38 (m, 2H), 3.26-3.22 (m, 3H), 3.23 (s, 3H), 2.22-2.15 (m, 2H), 1.76-1.70 (m, 1H), 1.60-0.79 (m, 18H), 1.23 (s, 9H), 1.00 (s, 3H), 0.89 (s, 9H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.19, 171.05, 170.32, 160.68, 156.72, 69.61, 59.09, 58.94, 57.71, 56.28, 53.44, 53.31, 50.49, 47.32, 38.13, 34.32, 34.08, 30.61, 29.19, 27.44, 26.80, 26.18, 26.05, 24.85, 22.40, 21.59, 20.47, 18.38, 13.59, 12.49; HRMS calcd for $C_{36}H_{64}N_5O_8S$ $[M + H]^+$: 726.4476. Found: 726.4476.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-N-((*S*)-1-(2-(methylsulfonyl)ethylamino)-1,2-dioxoheptan-3-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide (51). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.30 (1H, br. s), 7.66 (1H, d, J=7.5Hz), 5.54 (1H, d. J=8.8Hz), 5.40-5.50 (1H, m), 5.16 (1H, s), 4.55 (1H, s), 4.45 (1H, d, J=9.2Hz), 4.03 (1H, d, J=10.6Hz), 3.70-3.90 (3H, m), 3.60 (1H, d, J=13.4Hz), 3.23-3.41 (3H, m), 2.96 (3H, s), 2.22-2.40 (1H, m), 1.85-1.97 (1H, m), 1.10-1.61 (16H, m), 1.30 (9H, s), 1.00 (3H, s), 0.94 (9H, s), 0.72-0.86 (6H, m). HRMS (FAB) calcd. for $C_{36}H_{64}N_6O_9S_2$ $[M+H]^+$: 774.4145, found 774.4170.

(1*R*,2*S*,5*S*)-N-((*S*)-1-(benzylamino)-1,2-dioxoheptan-3-yl)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl) cyclohexyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (52). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.23 (t, J= 4.6 Hz, 1H), 8.37 (d, *J*= 6.9 Hz, 1H), 7.31-7.24 (m, 5H), 6.21 (app. t, J= 9.8 Hz, 1H), 6.05 (br.s 1H), 5.01-4.96 (m, 1H), 4.34-4.27 (m, 3H), 4.19 (d, J=15.9 Hz, 1H), 3.89 (d, J= 10.5 Hz, 1H), 3.76-3.69 (m, 2H), 3.28 (partially solvent hidden, m, 1H), 2.22-2.16 (m, 2H), 1.78-1.71 (m, 1H), 1.60-0.79 (m, 18H), 1.23 (s, 9H), 0.99 (s, 3H), 0.89 (s, 9H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.23, 170.97, 170.29, 160.81, 156.67, 138.36, 128.12, 127.14, 126.78, 59.05, 58.90, 56.26, 53.53, 53.28, 50.49, 47.26, 41.86, 34.27, 34.05, 30.52, 29.22, 27.35, 26.13, 24.80, 22.36, 21.54, 18.29, 13.52, 12.43. HRMS calcd for $C_{40}H_{64}N_5O_7S$ $[M + H]^+$: 758.4526. Found 758.4525.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-1-(2,6-difluorobenzylamino)-1,2-dioxoheptan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (53). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (1H, d, J = 6.93 Hz), 7.27 (1H, m), 7.22 (1H, t, J = 5.99 Hz), 6.90 (2H, dd, J = 7.56, 7.88 Hz), 5.33 (1H, m), 5.18 (1H, broad s), 4.63 (1H, s), 4.59 (2H, d, J = 5.99 Hz), 4.47 (1H, s), 4.42 (1H, s), 4.08 (1H, d, J = 13.87 Hz), 4.05 (1H, d, J = 10.71 Hz), 3.78 (1H, dd, J = 5.35, 10.71 Hz), 2.89 (1H, d, J = 13.24 Hz), 2.43 (1H, d, J = 10.71 Hz), 2.23 (1H, d, J = 13.24 Hz), 1.93 (1H, m), 1.73 (1H, m), 1.63 (2H, d, J = 7.56 Hz), 1.33 (9H, s), 1.22 – 1.60 (11H, m), 1.21 (1H, dd, J = 0.63, 6.30 Hz), 1.00 (3H, s), 0.96 (9H, s), 0.86 (3H, t, J = 6.93 Hz), 0.82 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.2, 172.6, 170.4, 162.5, 162.4, 160.5, 160.4, 158.6, 157.0, 130.0, 130.0, 129.9, 112.7, 112.6, 111.6, 111.5, 111.4, 111.4, 60.2, 59.9, 57.6, 54.6, 54.2, 50.2, 48.4, 35.8, 35.4, 34.9, 31.1, 29.0, 27.7, 27.4, 26.3, 26.3, 25.3, 23.0, 22.2, 21.1, 21.0, 18.7, 13.7, 12.6 ppm. HRMS calcd. for $C_{40}H_{62}F_2N_5O_7S$ $[M+H]^+$: 794.4338, found 794.4339.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-1-(furan-2-ylmethylamino)-1,2-dioxoheptan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (54). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.16 (1H, t, J = 6.0 Hz), 8.37 (1H, d, J = 7.0 Hz),

7.55 (1H, s), 6.38-6.37 (1H, m), 6.24-6.20 (1H, m), 6.05 (1H, s), 4.99-4.95 (1H, m), 4.32-4.29 (2H, m), 4.18-4.14 (2H, m), 3.89 (1H, d, J = 10.4 Hz), 3.74-3.69 (2H, m), 2.23 (1H, d, J = 12.5 Hz), 2.17 (1H, d, J = 13.2 Hz), 1.77-1.70 (1H, m), 1.60-1.25 (14H, m), 1.23 (9H, s), 1.19-1.10 (1H, m), 0.99 (3H, s), 0.89 (9H, s), 0.91-0.79 (8H, m). LCMS for $C_{38}H_{61}N_5O_8S$ $[M+H]^+$: 748.4.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-N-((*S*)-1-(oxazol-2-ylmethylamino)-1,2-dioxoheptan-3-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide (55). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.31 (1H, t, J = 6.1 Hz), 8.38 (1H, d, J = 7.0 Hz), 8.04 (1H, s), 7.14 (1H, s), 6.21 (1H, d, J = 10.1 Hz), 5.01-4.97 (1H, m), 4.43 (1H, d, J = 6.4 Hz), 4.30 (1H, s), 4.18 (1H, d, J = 10.0 Hz), 3.89 (1H, d, J = 10.4 Hz), 3.75-3.69 (2H, m), 2.23 (1H, d, J = 13.1 Hz), 2.17 (1H, d, J = 13.0 Hz), 1.78-1.71 (1H, m), 1.60-1.25 (14H, m), 1.23 (9H, s), 1.19-1.10 (1H, m), 1.00 (3H, s), 0.89 (9H, s), 0.87-0.79 (8H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.6, 171.0, 170.3, 160.8, 160.0, 156.7, 139.7, 126.9, 59.1, 58.9, 56.3, 53.5, 53.3, 50.5, 47.3, 35.7, 34.3, 34.1, 30.6, 29.1, 27.3, 26.8, 26.1, 26.0, 24.8, 22.4, 21.5, 20.5, 20.5, 18.3, 13.5, 12.5. HRMS calcd. for $C_{37}H_{60}N_6O_8S$ $[M+H]^+$: 748.9730, found: 749.4272.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-1,2-dioxo-1-(thiazol-2-ylmethylamino)heptan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (56). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.55 (t, J= 6.3 Hz, 1H), 8.41 (d, *J*= 7.0 Hz, 1H), 7.72 (d, J=3.5 Hz, 1H), 7.64 (d, J= 3.2 Hz, 1H), 6.21 (d, J= 9.7 Hz, 1H), 6.06 (s, 1H), 5.02-4.98 (m, 1H), 4.65-4.57 (m, 2H), 4.30 (s, 1H), 4.18 (d, J=10.0 Hz, 1H), 3.89 (d, J= 10.7 Hz, 1H), 3.75-3.69 (m, 2H), 3.29 (partially solvent hidden, m, 1H), 2.23-2.16 (m, 2H), 1.79-1.72 (m, 1H), 1.60-0.79 (m, 18H), 1.23 (s, 9H), 1.0 (s, 3H), 0.89 (s, 9H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 196.70, 171.06, 170.34, 167.57, 160.96, 156.72, 142.12, 120.22, 59.09, 58.94, 56.28, 53.49, 53.31, 47.32, 34.32, 30.59, 29.17, 27.38, 26.83, 26.18, 24.85, 22.40, 21.61, 20.47, 18.39, 13.60, 12.50; HRMS calcd for $C_{37}H_{61}N_6O_7S_2$ $[M + H]^+$: 765.4043. Found: 765.4051.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-1,2-dioxo-1-(pyridin-2-ylmethylamino)heptan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (59). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (t, J= 6.3 Hz, 1H), 8.50-8.49 (m, 1H), 8.40 (d, J=6.9 Hz, 1H), 7.77-7.73 (m, 1H), 7.28-7.25 (m, 2H), 6.22-6.20 (m, 1H), 6.05 (br.s, 1H), 5.01-4.97 (m, 1H), 4.44-4.42 (m, 2H), 4.30 (s, 1H), 4.21-4.17 (m, 1H), 3.88 (d, 1H), 3.75-3.69 (m, 2H), 3.28 (partially solvent hidden, m, 1H), 2.25-2.16 (m, 2H), 1.80-1.73 (m, 1H), 1.60-0.77 (m, 18H), 1.23 (s, 9H), 0.99 (s, 3H), 0.89 (s, 9H), 0.82 (s, 3H); HRMS calcd for $C_{39}H_{63}N_6O_7S$ $[M + H]^+$: 759.4479. Found: 759.4454.

tert-Butyl 2-((*S*)-3-((1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamido)-2-oxoheptanamido)acetate (62). ^{1}H NMR (500 MHz, d_6-DMSO), δ 8.95 (bs), 8.38 (d, 1 H, J = 6.0 Hz), 6.22 (d, 1 H, J = 9.8 Hz), 6.07 (s, 1 H), 5.05-4.98 (b, 1 H), 4.31 (s, 1 H), 4.19 (d, 1 H, J = 9.5 H z), 3.90 (d, 1 H, J = 9.8 Hz), 3.82-3.68 (m, 4 H), 3.28 (d, 1 H, J = 13.9 Hz), 2.25 (br.d, 1 H, J = 13.6 Hz), 2.20 (br.d, 1 H, J = 13.6 Hz), 1.89-1.61 (m, 1 H), 1.571-1.07 (m, 15 H), 1.41 (s, 9 H), 1.24 (s, 9 H), 1.02 (s, 3 H), 0.90 (s, 9 H), 0.87 (t, 3 H, J = 6.3 Hz), 0.83 (s, 3 H). ^{13}C (125 MHz, d_6-DMSO) δ 197.6, 171.9, 171.3, 168.7, 161.7, 157.6, 81.8, 60.0, 59.9, 57.2, 54.3, 54.2, 51.5, 48.2, 42.1, 35.2, 35.0, 31.5, 30.1, 28.5, 28.3, 27.8, 27.1, 27.0, 25.8, 23.5, 23.3, 22.5, 21.5, 21.4, 19.3, 14.5, 13.4. MS (ESI) $[M+1]^+$: 782.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-Butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-N-((*S*)-1-(2-(methylamino)-2-oxoethylamino)-1,2-dioxoheptan-3-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide (64). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.31 (1H, br. s), 7.63 (1H, d, J=7.2Hz), 6.62 (1H, br. s), 5.94 (1H, d, J=9.4Hz), 5.28-5.37 (2H, m), 4.52 (1H, s), 4.46 (1H, d, J=9.4Hz), 3.78-4.07 (5H, m), 3.16 (1H, d, J=13.4Hz), 2.79 (3H, d, J = 4.4Hz), 2.33-2.43 (1H, m), 2.22-2.29 (1H, m), 1.85-1.96 (1H, m), 1.18-1.71 (15H, m), 1.33 (9H, s), 1.02 (3H, s), 0.96 (9H, s), 0.79-0.90 (6H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.08, 172.82, 170.84, 169.09, 160.22, 157.11 60.21, 60.05, 57.51, 54.37, 54.31, 50.24, 48.55, 43.21 35.68, 35.60, 35.22 31.12, 29.55, 27.60, 27.45, 26.40 (3C),

26.36 (2C), 25.38, 23.04 (3C), 22.19, 21.17, 21.09, 18.78, 13.68, 12.69. HRMS (FAB) calcd. for $C_{36}H_{63}N_6O_8S$ $[M+H]^+$: 739.44281, found 739.44290.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-1-(2-(dimethylamino)-2-oxoethylamino)-1,2-dioxohexan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (65). ^{1}H NMR (500 MHz, d_6-DMSO), δ 8.48 (t, 1 H, J = 5.4 Hz), 8.38 (d, 1 H, J = 6.9 Hz), 6.22 (d, 1 H, J = 10.1 Hz), 6.07 (s, 1 H), 5.07-5.04 (m, 1 H), 4.31 (s, 1 H), 4.19 (d, 1 H, J = 9.8 H z), 3.99 (bt, 2 H, J = 5.7 Hz), 3.90 (d, 1 H, J = 10.4 Hz), 3.72 (d, 2 H, J = 13.6 Hz), 3.31 (d, 1 H, J = 13.7 Hz), 2.96 (s, 3 H), 2.85 (s, 3 H), 2.26-2.18 (m, 2 H), 1.80-1.73 (m, 1 H), 1.61-1.11 (m, 15 H), 1.24 (s, 9 H), 1.02 (s, 3 H), 0.90 (s, 9 H), 0.87 (t, 3 H, J = 6.6 Hz), 0.83 (s, 3 H). ^{13}C (125 MHz, d_6-DMSO) δ 197.8, 171.9, 171.2, 167.8, 161.2, 157.6, 60.0, 59.9, 57.2, 54.2, 54.1, 51.5, 48.2, 41.2, 36.4, 35.9, 35.2, 28.3, 27.1, 26.9, 25.8, 23.3, 22.5, 21.5, 21.4, 19.3, 14.5, 13.4, 27.8, 31.5, 30.1. MS (ESI) $[M+1]^+$: 753.

***tert*-Butyl 2-((*S*)-3-((1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(*tert*-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamido)-2-oxoheptanamido)acetate (66)**. ^{1}H NMR (500 MHz, d_6-DMSO) δ 8.69 (t, 1 H, J = 6.3 Hz), 8.36 (d, 1 H, J = 6.9 Hz), 6.22 (d, 1 H, J = 10.1 Hz), 6.06 (s, 1 H), 4.99-4.95 (m, 1 H), 4.30 (s, 1 H), 4.23-4.15 (m, 2 H), 3.90 (d, 1 H, J = 10.4 Hz), 3.72 (bd, 2 H), 3.29 (b, 2 H), 2.43 (bt, 2 H, J = 6.3 Hz), 2.25 (bd, 1 H, J = 13.6 Hz), 2.20 (bd, 1 H, J = 13.6 Hz), 1.78-1.71 (m, 1 H), 1.61-1.14 (m, 15 H), 1.41 (s, 9 H), 1.24 (s, 9 H), 1.01 (s, 3 H), 0.90 (s, 9 H), 0.87 (t, 3 H, J = 6.9 Hz), 0.83 (s, 3 H). ^{13}C (125 MHz, d_6-DMSO) δ 198.0, 171.9, 171.2, 171.1, 161.5, 157.6, 80.8, 60.0, 59.9, 57.2, 54.4, 54.2, 51.5, 48.2, 35.7, 35.2, 35.0, 31.5, 30.2, 28.5, 28.6, 28.3, 27.7, 27.1, 27.0, 25.8, 23.3, 22.5, 21.4, 21.4, 19.3, 14.5, 13.4. MS (ESI) $[M+H]^+$: 796.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-1-(cyclopropylamino)-6,6,6-trifluoro-1,2-dioxohexan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (68). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, *J* = 5.47Hz,

1H), 8.56 (d, *J*= 7.82 Hz, 1H), 6.24 (d, *J*= 10.16 Hz, 1H), 6.04 (s, 1H), 5.07-5.02 (m, 1H), 4.22 (s, 1H), 4.18 (d, *J*= 9.38Hz, 1H), 3.90 (d, *J*=10.94Hz, 1H), 3.79-3.76 (m, 1H), 3.70 (d, *J*=14.06Hz, 1H), 3.29 (d, *J*= 14.07Hz, 1H), 2.75-2.71 (m, 1H), 2.24-2.15 (m, 2H), 2.06-1.98 (m, 1H), 1.75-1.33 (m, 10H), 1.26 (d, *J*= 7.81Hz, 2H), 1.22 (s, 9H), 0.99 (s, 3H), 0.88 (s, 9H), 0.83-0.81 (m, 1H), 0.82 (s, 3H), 0.68-0.63 (m, 2H), 0.58-0.56 (m, 2H);^{13}C NMR (100 MHz, DMSO-d_6) δ 197.3, 171.8, 171.0, 162.5, 157.3, 129.2, 127.9, 126.5, 59.9, 59.6, 56.7, 53.8, 52.7, 51.0, 47.8, 34.8, 34.6, 30.9, 27.6, 26.7, 26.5, 25.4, 23.2, 23.0, 22.9, 21.1, 21.0, 19.0, 13.0, 5.9. HRMS (ESI) calcd. for $C_{35}H_{56}N_5O_7SF_3$ $[M+H]^+$: 748.3903, found 748.3960.

(1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(1-(tert-butylsulfonylmethyl)cyclohexyl)ureido)-3,3-dimethylbutanoyl)-N-((*S*)-5-cyclopropyl-1-(cyclopropylamino)-1,2-dioxopentan-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (70). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J* = 4.78Hz, 1H), 8.36 (d, *J*= 6.25 Hz, 1H), 6.23 (d, *J*= 10.16 Hz, 1H), 6.05 (s, 1H), 5.03-4.98 (m, 1H), 4.27 (s, 1H), 4.18 (d, *J*= 10.16Hz, 2H), 3.89 (d, *J*=10.16Hz, 1H), 3.75-3.70 (m, 1H), 3.72 (d, *J*=14.07Hz, 1H), 3.31 (d, *J*= 14.07Hz, 1H), 2.77-2.72 (m, 1H), 2.25-2.16 (m, 2H), 1.91-1.82 (m, 1H), 1.59-1.34 (m, 10H), 1.29 (d, *J*= 7.82Hz, 2H), 0.99 (s, 3H), 0.88 (s, 9H), 0.82 (s, 3H), 0.68-0.61 (m, 3H), 0.59-0.55 (m, 2H), 0.37-0.35 (m, 2H), 0.09-0.05 (m, 1H), 0.03-0.0 (m, 1H); ^{13}X NMP (100 MHζ, ΔMΣO–δ6) δ 197.3, 171.1, 170.3, 161.9, 156.8, 59.1, 58.9, 56.3, 53.5, 50.5, 53.3, 47.4, 34.3, 34.1, 30.7, 30.3, 29.8, 29.7, 26.9, 26.2, 26.1, 24.8, 22.6, 22.4, 20.6, 20.5, 18.4, 12.5, 10.1, 5.4, 4.8, 4.5, 4.4, 3.8. HRMS (ESI) calcd. for $C_{37}H_{61}N_5O_7S$ $[M+H]^+$: 720.4383, found 720.4397.