SAR and Structural Analysis of Siderophore-Conjugated Monocarbam Inhibitors of *Pseudomonas aeruginosa* PBP3

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Crystallography

P. aeruginosa PBP3 was co-crystallized by hanging drop vapor diffusion under previously described crystallization conditions[1]. X-ray diffraction data was collected at the IMCA-CAT beam line 17-ID using the Pilatus 6M detector from vitrified crystals under cryogenic conditions. The diffraction data for each liganded complex was collected from a single crystal. Use of the IMCA-CAT beamline 17-ID at the Advanced Photon Source was supported by the companies of the Industrial Macromolecular Crystallography Association through a contract with Hauptman-Woodward Medical Research Institute. Use of the Advanced Photon Source was supported by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences, under Contract No. DE-AC02-06CH11357. Diffraction data was reduced with XDS[2] and scaled using Aimless[3] as defined in the autoPROC routines within the Global Phasing software suite[4]. These crystals belong to the

space group $P2_12_12_1$ and contain one protein molecule in the asymmetric unit (Table S1). The structures were solved by molecular replacement using the program MOLREP[5]. Examination of the electron density maps for all liganded complexes showed clear unambiguous difference density with the expected molecular features of the compound (Figure S1). The refinement dictionaries for these compounds were generated with GRADE[6] and the stereochemistry checked with MOGUL[7]. Sequential rounds of manual rebuilding using Coot[8] and refinement using autoBUSTER[9] with TLS and target restraints produced the final models for the liganded complexes[10]. The final refinement statistics are shown in Table S1. All figures were prepared using PyMOL (Schrödinger, LLC). The coordinates and structure factors have been deposited with the Protein Data Bank with accession codes: 4WEJ, 4WEK and 4WEL.

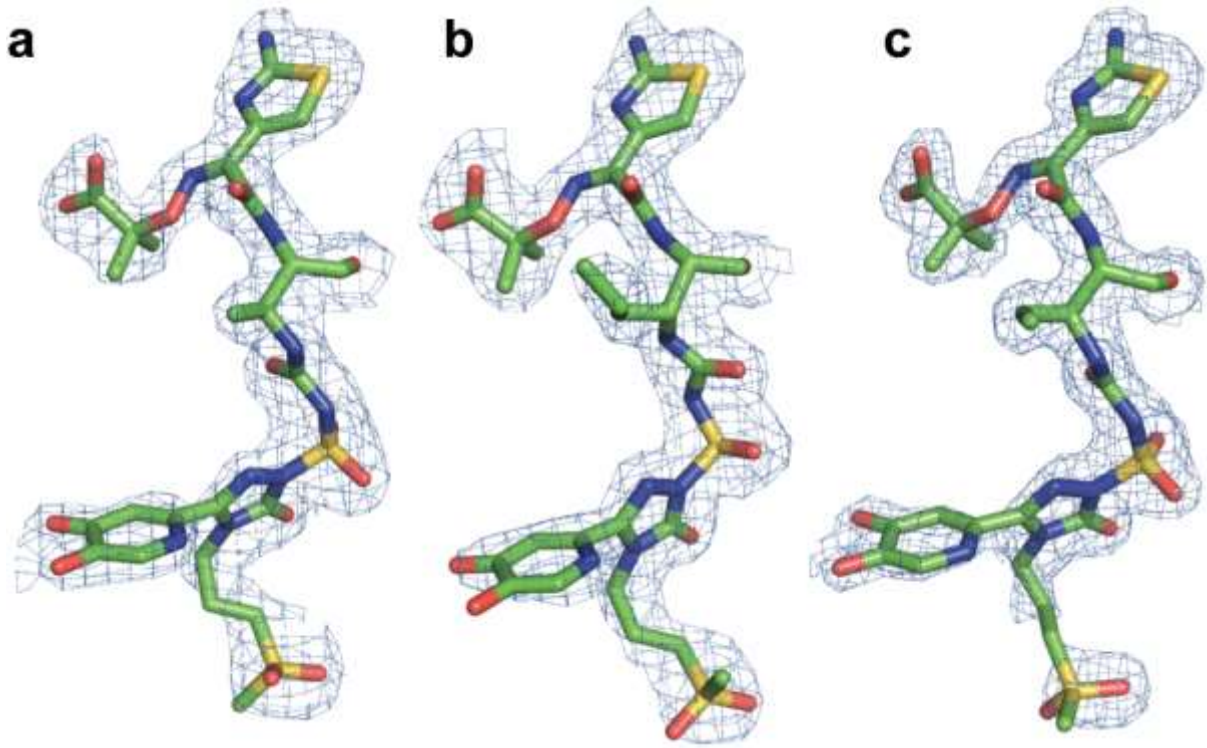


Figure S1. Electron density maps for liganded *P. aeruginosa* PBP3 complexes. (**a**) Compound **7b** (**b**) Compound **24e**; and (**c**) Compound **24c**. The compounds are shown as stick models with green carbon atoms, blue nitrogen atoms, red oxygen atoms and yellow sulfur atoms. The final 2Fo-Fc electron density map surrounding the inhibitor is shown as blue mesh (contoured at 1σ).

Table S1. Crystallographic statistics

Compound	**7b**	**24e**	**24c**
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions (Å)			
$a=b=c=90°$	68.44, 83.33, 89.41	67.78, 83.05, 88.80	68.92, 83.23, 89.89
Beam line	17-ID	17-ID	17-ID
Wavelength (Å)	1.0000	1.0000	1.0000
Resolution (Å)	89 - 1.99	89 -2.04	89 - 1.73
Total number of reflections	286857 (3017)	255603 (2586)	434049 (4204)
Unique reflections	35818 (360)	32015 (333)	54364 (523)
Multiplicity	8.0 (8.4)	8.0 (7.8)	8.0 (8.0)
Completeness (%)	100.0 (100.0)	98.8 (98.2)	100.0 (99.2)
$\langle I/\sigma I \rangle$	24.6 (4.0)	18.0 (3.8)	22.3 (8.0)
R_{merge} (%)[a]	0.052 (0.591)	0.077 (0.584)	0.053 (0.606)
Refinement			
R_{work}[b] / R_{free}[c] (%)	18.9 / 21.9	18.4 / 22.5	18.6 / 20.7
Water	216	171	308
Inhibitor	1	1	1
Root mean square deviation from ideal			
Bond lengths (Å)	0.010	0.10	0.010
Bond angles (°)	1.04	1.04	1.03

[a] $R_{merge} = \Sigma|I-\langle I\rangle|/\Sigma I$, where I is the integrated intensity of a given reflection and $\langle I\rangle$ is the average intensity of multiple observations of symmetry-related reflections. [b] $R_{work} = \Sigma|F_o-F_c|/\Sigma F_o$), where F_o and F_c are observed and calculated structure factors. [c] R_{free} was calculated from a 5% subset of reflections that were excluded from the refinement. Brackets indicate highest resolution shell.

Hydrolytic Stability. Compounds were incubated in commercially supplied PBS buffer containing EDTA (Teknova) for a 24 hour period at 37°C to predict a $t_{1/2}$. Initial DMSO stocks of compounds were prepared at 800 µM. 50 µL of the DMSO stock was diluted with 950 µL of a pH 7.4 PBS buffer (Teknova, cat# P0203) to yield a final concentration of 40 µM of target compound. Samples were prepared as singletons and monitored continuously for a 24 hour period at 37 °C. Hydrolysis of the target compounds were monitored via LC-DAD with mass spectrometer confirmation. During the 24 hour time period, samples were injected directly multiple times to determine loss of the compound over time. Sample response data was then ln transformed and plotted against time. First-order kinetics was used in deriving $t_{1/2}$ values. Samples are typically analyzed as singletons, due to this, sample regressions were calculated using the excel data analysis package with a 95% confidence interval. Based on the regression, the coefficients, lower and upper values were used for the calculation of the half-life. The coefficients value is the slope, which is used to calculate the half-life. The lower and upper values represent the error in the slope and are used to determine the % D in the half-life value. The method has a reporting criteria of ≤ 25% D with an upper limit of 150 hours. Samples with a $t_{1/2}$ ≥ 150 hours have % D reported as ND. Additionally, the method has 3 controls: acetaminophen, aspirin, and ceftazidime built into each analysis. Acetaminophen has a half-life that exceeds 150 hours (method upper limit for reporting), aspirin (approximately 15 hours), and ceftazidime (approximately 80 hours).

Samples were analyzed on a Waters Acquity UPLC system configured with a Waters SQD mass spectrometer. The system was equipped with a Waters Acquity HSS T3 2.1 x 50 mm, 1.8 µM column, sample flow was 1 mL/min, and sample injections were 2 µL. The gradient used for analysis was 0-2 minutes at 5-95% mobile phase B, a hold a 95% mobile phase B until 2.5 minutes, then a return to initial conditions from 2.5 to 3.0 minutes of

5% mobile phase B. Mobile phase A consisted of 0.1% formic acid in water, mobile phase B consisted of 0.1% formic acid in acetonitrile. The diode array detector scanned a range of wavelengths from 210-400 nm. Sample flow to the mass spectrometer was diverted to waste from 0 to 0.3 minutes. The mass spectrometer scanned in ESI+ and ESI- modes from 100-1500 m/z. The strong wash on the system was methanol and the weak wash was 95% water/5% acetonitrile.

Biological Experimental Procedures:

Plasma protein binding determination. Human plasma protein binding was determined from a 10 µM compound solution in a Dianorm plasma well incubating at 37 ºC for 16 hours. Free fractions were calculated from ratios of drug concentration in buffer and plasma wells determined by LC-MS/MS.

Bacterial isolates. Clinical isolates of *P. aeruginosa* were obtained from the culture collections at AstraZeneca. All isolates were grown and tested in cation-adjusted Mueller-Hinton broth (MHB) unless otherwise indicated.

Susceptibility assays. Minimum Inhibitory Concentration (MIC) values were determined by the broth microdilution method in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines.[11]

***P. aeruginosa* PBP3 acylation**. Data was generated according to published methods.[12] Reported values for test compounds are from single measurements. From replicate testing of BOCILLIN FL in this assay, the averaged acylation rate constant was 21,000 $M^{-1}s^{-1}$, with a standard deviation of 2,000 $M^{-1}s^{-1}$. From this observation, values reported for test compounds are estimated to contain standard deviations of at least 10%.

Pharmacokinetic studies.

Compounds for iv dosing in mice were formulated in 0.1M meglumine or pH = 5 saline. Wistar Hannover rats used for pharmacokinetic studies were obtained from Charles River Laboratories (Raleigh, NC). All animals were housed and acclimated in the animal facility on site before each study. All experimental procedures were conducted in accordance with protocols approved by the Institutional Animal Care and Use Committee.

Pharmacokinetic properties of selected compounds were studied in male rats. Plasma pharmacokinetics were determined from 0 to 24 hr following 15 min iv infusions at 1 mg/kg. Serial 200 μl samples of whole blood were taken from the jugular vein of each animal at time intervals. Concentration of compound in plasma was determined by LC-MS/MS and pharmacokinetic parameters were estimated using a non-compartmental model in WinNonLin (Pharsight). Mean results were determined for each experiment with 2 rats.

Wistar Han rats were used for pharmacokinetic studies. Blood samples were collected and centrifuged to obtain the plasma samples and stored in -20 °C for analysis. The plasma samples were extracted in acetonitrile containing 10% trichloroacetic acid (TCA) and 250 ng/mL Carbutamide as an internal standard (IS) and centrifuged. The extracts were loaded on the liquid chromatography tandem mass spectrometer (LC-MS/MS) for analysis.

Extracts were loaded onto a Polaris C18 analytical column (20 mm ´ 2.1 mm, 3μm pore size). The HPLC system consists of mobile phase A (0.1% formic acid in water) and mobile phase B (0.1% formic acid in acetonitrile). The mobile phase B was increased in a linear fashion from 5% to 95% over 2 min; flow rate was 0.8 mL/min. For each compound, the mass spectrometer was tuned to the most intense mass transition using multiple Reaction Monitoring (MRM) mode.

Quantitation was performed for each sample against a set of standard curve with concentrations ranging from 1.0 to 10,000 ng analyte per mL plasma. The

pharmacokinetics (PK) analysis was conducted in AstraZeneca in-house SEA template using the linear/log trapezoidal method.

Synthesis of compounds 7a – j, 9a, 9b, 10a, 10b, 24a – 24g, 25b

General Considerations: All solvents and reagents used were obtained commercially and used as such unless noted otherwise. ^{1}H NMR spectra were recorded in $CDCl_3$, D_2O, Dichloromethane or DMSO-d_6 solutions at 300 K using a Brucker Ultrashield 300 MHz instrument or a Brucker Ultrashield 400 MHz instrument. ^{13}C NMR spectra were recorded in DMSO-d_6 solutions at 300 K and 126 MHz using a Brucker DRX-500 500 MHz instrument with a QNP cryoprobe, at 75.5 MHz using a Brucker Ultrashield 300 MHz instrument, or at 100 MHz using a Brucker Ultrashield 400 MHz instrument. Chemical shifts are reported as parts per million (ppm) relative to TMS (0.00) for ^{1}H and ^{13}C NMR. High-resolution mass spectra (HRMS) were obtained using a hybrid quadrupole time-of-flight mass spectrometer (microTOFq II, Bruker Daltonics) in ESI^+ mode. Silica gel chromatographies were performed on ISCO Combiflash Companion Instruments using ISCO RediSep Flash Cartridges (particle size: 35-70 microns) or Silicycle SiliaSep Flash Cartridges (particle size: 40-63 microns). Reverse phase chromatographies were performed on ISCO Combiflash Companion Instruments using RediSep High Performance Gold C18 columns. Preparative reverse phase HPLC was carried out using YMC Pack ODS-AQ (100 × 20 mm ID, S-5 μ particle size, 12 nm pore size) on Agilent instruments. When not indicated, compound intermediates and reagents were purchased from chemical supply houses. All final compounds were determined to be greater than 95% pure *via* analysis by reverse phase UPLC-MS (retention times, RT, in minutes) using one of two methods: (1) Waters Acquity UPLC instrument with DAD and ELSD and a UPLC HSS T3, 2.1 x 30 mm, 1.8 μm column and a gradient of 2 to 98% acetonitrile in water with 0.1% formic acid over 2.0 minutes at 1

mL/min. Injection volume was 1 µL and the column temperature was 30 °C. Detection was based on electrospray ionization (ESI) in positive and negative polarity using Waters SQD mass spectrometer (Milford, MA, USA), diode-array UV detector from 210 to 400 nm, and evaporative light scattering detector ; (2) Waters Acquity UPLC instrument with DAD and ELSD and a Ace Excel 2 C18-AR, 4.6 x 50 mm, 2 µm column and a gradient of 5 to 50% acetonitrile in water with 0.1% formic acid over 5.0 minutes at 1 mL/min. Injection volume was 6 µL and the column temperature was 30 °C. Detection was based on electrospray ionization (ESI) in positive and negative polarity using Waters SQD mass spectrometer (Milford, MA, USA), diode-array UV detector from 210 to 400 nm, and evaporative light scattering detector.

Abbreviations:

MSTFA, *N*-Methyl-*N*-(trimethylsilyl) trifluoroacetamide;

THF, Tetrahydrofuran;

CSI, Chlorosulfonyl isocyanate;

DCM, Dichloromethane;

TFA, Trifluoroacetic acid;

m-CPBA, 3-Chloroperbenzoic acid;

MsCl, Methanesulfonyl chloride;

TBSCl, *tert*-Butyldimethylsilyl chloride;

DMF, *N*,*N*-Dimethylformamide;

imid., Imidazole;

DIBAL-H, Diisobutylaluminum hydride;

TEMPO, 2,2,6,6-Tetramethylpiperidine 1-oxyl;

DIAD, Diisopropyl azodicarboxylate;

EDC·HCl, *N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride;

TBAF, Tetrabutylammonium fluoride.

DMSO, Dimethyl sulfoxide;

DIPEA, *N*,*N*-Diisopropylethylamine;

EtOAc, Ethyl acetate;

MeCN, Acetonitrile;

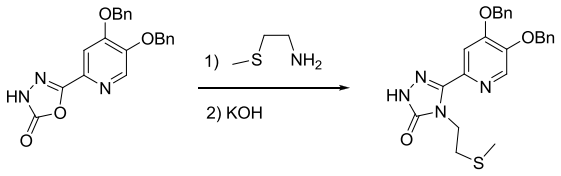
UPLC, Ultra Performance Liquid Chromatography;

LCMS, Liquid chromatography–mass spectrometry;

MPLC, Medium pressure liquid chromatography;

Compound 7a.

General Procedure A: Triazolone synthesis 1

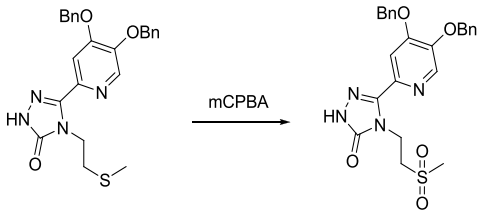


3-(4,5-Bis(benzyloxy)pyridin-2-yl)-4-(2-(methylthio)ethyl)-1*H*-1,2,4-triazol-5(4*H*)-one: A mixture of 5-(4,5-bis(benzyloxy)pyridin-2-yl)-1,3,4-oxadiazol-2(3*H*)-one[13] (8.60 g, 22.9 mmol) and 2-(methylthio)ethanamine (2.11 g, 23.1 mmol) in triethylamine (6.39 mL, 45.8 mmol) in THF (100 mL) was heated at 80 °C for 3h. The reaction mixture was concentrated. The residue was treated with water (137 mL) and KOH (15.4 g, 275 mmol). The reaction mixture was heated at 100 °C until the intermediate was consumed (about one or two days). The reaction mixture was diluted with water, cooled to 0 °C and then neutralized to pH 7 with conc. HCl. The resulting solid was filtered and washed with water, dried under high vacuum to give the desired product as a white solid (10.3 g, 100%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.31 (s, 1H), 7.60 (s, 1H), 7.31 - 7.50 (m, 10H), 5.32 (s, 2H), 5.29 (s, 2H), 4.19 - 4.28 (m, 2H), 2.65 - 2.75 (m, 2H), 2.02 (s, 3H).

ESI-MS m/z: 449 $[M + H]^+$.

General Procedure B: Oxidation

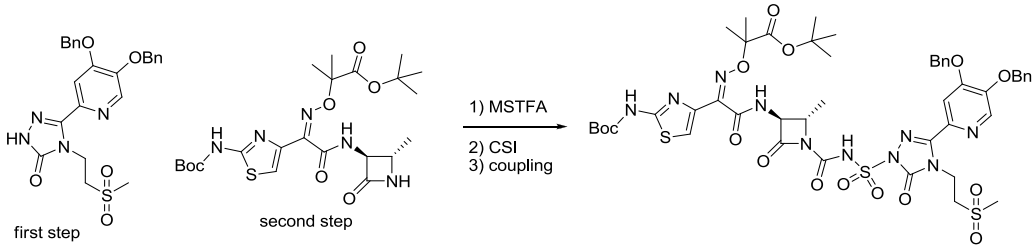


3-(4,5-Bis(benzyloxy)pyridin-2-yl)-4-(2-(methylsulfonyl)ethyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**6a**)**:** 3-Chlorobenzoperoxoic acid (1.45 g, 6.45 mmol) was added to a mixture of 3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(methylthio)ethyl)-1*H*-1,2,4-triazol-5(4*H*)-one (0.965 g, 2.15 mmol) in DCM (50 mL). The reaction mixture was stirred at rt overnight. After the reaction mixture was concentrated, the residue was washed with acetone and filtered. The white solid was collected *via* filtration, washed with acetone and dried to give the desired product (780 mg, 75%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.10 (s, 1H), 8.35 (s, 1H), 7.63 (s, 1H), 7.31 - 7.50 (m, 10H), 5.33 (s, 2H), 5.30 (s, 2H), 4.46 (t, J = 7.03 Hz, 2H), 3.52 (t, J = 7.15 Hz, 2H), 3.07 (s, 3H).

ESI-MS m/z: 481 $[M + H]^+$.

General Procedure C: MSTFA and CSI Coupling

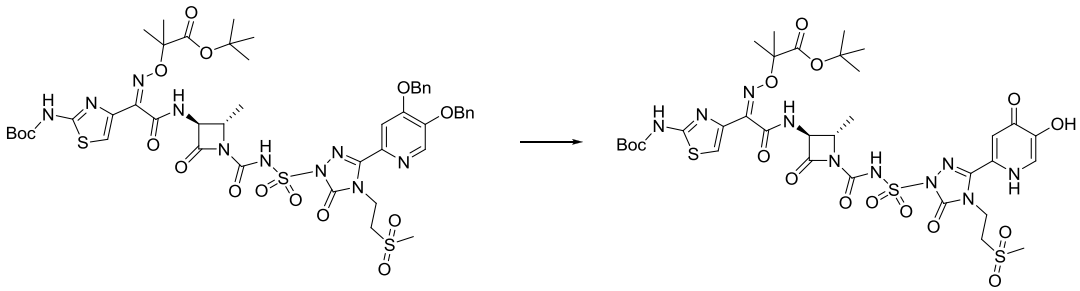


***tert*-Butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-**

methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate: Step 1**:** 2,2,2-Trifluoro-*N*-methyl-*N*-(trimethylsilyl)acetamide (0.31 mL, 1.7 mmol) (MSTFA) was added to a mixture of 3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(methylsulfonyl)ethyl)-1*H*-1,2,4-triazol-5(4*H*)-one (0.40 g, 0.83 mmol) in THF (3.0 mL). The reaction was stirred at 40 °C for 2h. The reaction solution was concentrated *via* rotary evaporation and then dried under high vacuum for 2h. The resulting residue was dissolved in THF (1.8 mL) and cooled to 0 °C. Step 2: A solution of *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**5**)[14, 15] (0.43 g, 0.83 mmol) in dichloromethane (2.4 mL) was cooled to 0 °C. Chlorosulfonyl isocyanate (0.086 mL, 1.0 mmol) was added and the reaction was stirred at 0 °C for 30min. Step 3: The reaction solution from step 2 was added to the cooled THF solution from Step 1 at 0 °C. The resulting mixture was stirred at 0 °C for 1h, and then stirred at rt for 1h. The reaction mixture was quenched with MeOH, and concentrated. The residue was purified by silica gel column (20-100% EtOAc/DCM) to give the desired product as a white solid (709 mg, 78%).

ESI-MS m/z: 1097 $[M + H]^+$.

General Procedure D: Hydrogenation

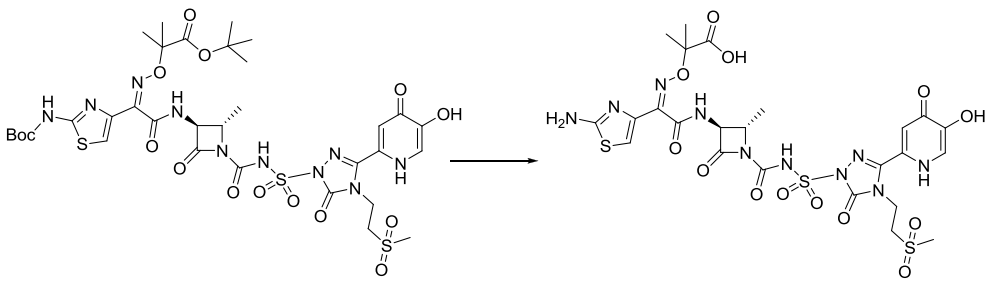


***tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** A mixture of *tert*-butyl 2-(((*Z*)-(2-

(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.33 g, 0.30 mmol) and palladium black (0.096 g, 0.90 mmol) in MeOH (15 mL) was degassed and purged with hydrogen three times. The mixture was stirred at rt under hydrogen balloon (1 atm) for 1h. The mixture was filtered through celite and washed with MeOH. The filtrate was concentrated. The residue was purified by RediSep reverse phase C18 column (50 g, 0-50% MeCN/water with 0.1% formic acid) to give the desired product as a white solid (145 mg, 53%).

ESI-MS m/z: 917 $[M + H]^+$

General Procedure E: TFA deprotection



2-((*Z*)-1-(2-aminothiazol-4-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid

2-(((*Z*)-(1-(2-Aminothiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (7a): TFA (0.25 mL, 3.2 mmol) was added to a solution of *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.15 g, 0.16 mmol) in DCM

(0.25 mL) at 0 °C. The reaction solution was stirred at rt for 3h. After the reaction solution was concentrated, the residue was dissolved in water/DMSO and purified by RediSep reverse phase C18 column (30 g, 0-20% MeCN/water with 0.1% formic acid) to give the desired product as a white solid (77 mg, 64%).

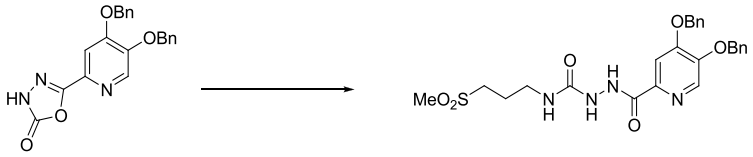
UPLC RT = 0.49 min, MS (ES) MH^+: 761.0 for $C_{24}H_{28}N_{10}O_{13}S_3$

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.12 (d, *J* = 8.28 Hz, 1H), 8.03 (s, 1H), 7.38 (s, 1H), 6.88 (s, 1H), 4.47 (dd, *J* = 2.89, 8.16 Hz, 1H), 4.37 - 4.44 (m, 2H), 3.79 (dq, *J* = 3.01, 6.11 Hz, 1H), 3.43 - 3.50 (m, 2H), 3.04 (s, 3H), 1.39 - 1.48 (m, 9H).

^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 174.3, 169.7, 163.9, 160.7, 153.1, 151.9, 151.4, 144.4, 142.1, 138.3, 136.2, 110.9, 109.7, 82.1, 60.5, 55.0, 52.2, 40.4, 36.4, 23.8, 23.7, 17.6.

HRMS: (ES^+) Calcd. for $C_{24}H_{29}N_{10}O_{13}S_3$ $[M + H]^+$: 761.1072; Found 761.1065.

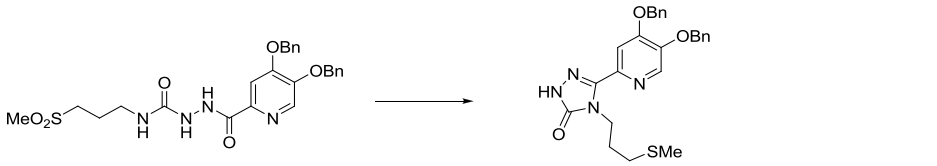
Compound 7b.



2-(4,5-*bis*(Benzyloxy)piconiloyl)-*N*-(3-(methylthio)propyl)hydrazinecarboxamide: In a 2-L glass round bottom flask, 5-(4,5-*bis*(benzyloxy)pyridin-2-yl)-1,3,4-oxadiazol-2(3*H*)-one (50 g, 134 mmol) was suspended in anhydrous THF (1L). To the suspension was added 3-(methylthio)propan-1-amine (14.8 g, 140 mmol) in a single portion. The reaction suspension was heated to reflux for 4 hours. The reaction mixture was cooled to room temperature and then filtered through a sintered glass funnel. The filter cake was washed with THF and then dried to a constant weight. Isolation gave 51g of the title compound in a 79% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.55 - 1.71 (m, 2 H) 1.97 - 2.07 (m, 3 H) 2.38 - 2.47 (m, 2 H) 2.98 - 3.14 (m, 2 H) 3.24 - 3.37 (m, 1 H) 5.27 - 5.40 (m, 4 H) 6.35 - 6.48 (m, 1 H) 7.26 - 7.53 (m, 10 H) 7.62 - 7.73 (m, 1 H) 7.73 - 7.89 (m, 1 H) 8.08 - 8.44 (m, 1 H) 9.52 - 10.06 (m, 1 H).

ESI-MS m/z: 481 $[M + H]^+$.



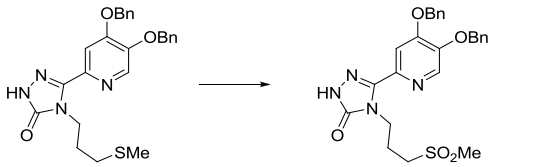
3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylthio)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one

3-(4,5-*bis*(Benzyloxy)pyridin-2-yl)-4-(3-(methylthio)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one:

In a 1-L glass round bottom flask, KOH (60 g, 1069 mmol) was dissolved in water (600 mL). To the warm basic solution was added 2-(4,5-bis(benzyloxy)picolinoyl)-*N*-(3-(methylthio)propyl)hydrazinecarboxamide (51.4 g, 107 mmol). The suspension was heated to 100 °C for 20h. The reaction mixture was transferred to a 4-L Erlenmeyer flask. The reaction mixture was diluted with water (1.5 L) and acidified (pH = 2-3) with conc. HCl (~80 mL). The suspension was filtered through Watman paper and the cake washed with water (2L). The solids were dried under vacuum for 2 hours. Excess water was removed by slurrying the solids in minimal acetone and filtering. The first crop was then dried in a vacuum oven at 60 °C until a constant weight was achieved. The mother liquor from the acetone slurry was concentrated to 1/3 the volume and a second crop was isolated as described above. The two crops were combined to yield 43.6 g of the title compound in a 88% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.74 - 1.89 (m, 2 H) 1.92 - 2.02 (m, 3 H) 2.36 - 2.47 (m, 2 H) 4.02 - 4.18 (m, 2 H) 5.23 - 5.37 (m, 4 H) 7.27 - 7.51 (m, 10 H) 7.54 - 7.67 (m, 1 H) 8.24 - 8.41 (m, 1 H) 11.89 - 12.10 (m, 1 H).

ESI-MS m/z: 463 $[M + H]^+$.

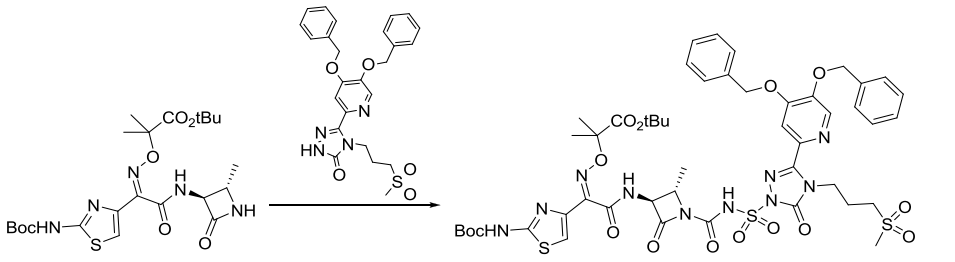


3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one

3-(4,5-*bis*(Benzyloxy)pyridin-2-yl)-4-(3-(methanesulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**6b**): In a 1-L glass round bottom flask, 3-(4,5-*bis*(benzyloxy)pyridin-2-yl)-4-(3-(methylthio)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (43.6 g, 94.2 mmol) was suspended in dichloromethane (1 L). The reaction slurry was cooled to 0 °C. In a 250 mL beaker, a dichloromethane suspension (250 mL) containing 3-chlorobenzoperoxoic acid (48.8 g, 283 mmol) was prepared. The suspension was added to the reaction mixture in portions so as to not let the internal temperature rise above 10 °C. Reaction mixture was concentrated to dryness by rotary evaporation. The solids were triturated in acetone and then filtered, washed and dried *in vacuo*. Isolation gave 40 g of the title compound in 86% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.98 - 2.16 (m, 2 H) 2.87 - 3.00 (m, 3 H) 3.05 - 3.19 (m, 2 H) 4.10 - 4.23 (m, 2 H) 5.21 - 5.38 (m, 4 H) 7.28 - 7.49 (m, 10 H) 7.57 - 7.71 (m, 1 H) 8.23 - 8.44 (m, 1 H) 11.98 - 12.15 (m, 1 H).

ESI-MS m/z: 495 $[M + H]^+$.

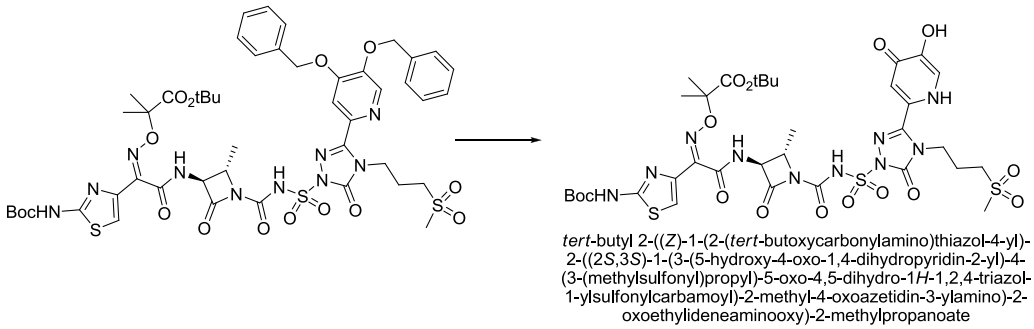


tert-butyl 2-((*Z*)-2-((2*S*,3*S*)-1-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-oxoethylideneaminooxy)-2-methylpropanoate

***tert*-Butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-*bis*(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-**

oxoethylidene)amino)oxy)-2-methylpropanoate: In an oven dried flask, 3-(4,5-*bis*(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (22.2 g, 45.1 mmol) was suspended in THF (200 mL). *N*-Methyl-*N*-trimethylsilyltrifluoroacetamide (11.2 mL, 60.0 mmol) was added and the reaction was allowed to stir at rt for 1 h. After this time the reaction was concentrated *in vacuo* and then allowed to dry under high vacuum for 1 h to afford the silyl intermediate, which was confirmed by NMR. In a separate oven dried flask, *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**5**) (15.3 g, 30.0 mmol) was dissolved in dichloromethane (100 mL) and cooled to 0 °C in an ice bath. A dichloromethane solution (10 mL) containing chlorosulfonyl isocyanate (2.61 mL, 30.0 mmol) was then added slowly to the reaction mixture *via* syringe and the resultant solution was allowed to stir at that temperature for 10 min. The dry silyl intermediate was slurried in dichloromethane (100 mL) and cooled to 0 °C. The solution containing the isocyanate intermediate was then added dropwise to the slurry of silyl intermediate *via* an addition funnel. The reaction was complete after 90 min. The reaction was quenched with MeOH (25 mL) and then concentrated by rotary evaporation. The crude reaction mixture was triturated in acetone and the solids removed by filtration. The mother liquor was concentrated and then purified by silica gel flash column chromatography (0-100% EtOAc in hexanes). Isolation gave 18.6 g of the title compound in 56% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 - 1.59 (m, 30 H) 2.02 - 2.17 (m, 2 H) 2.87 - 3.01 (m, 3 H) 3.03 - 3.23 (m, 2 H) 3.84 (qd, *J*=6.15, 2.64 Hz, 1 H) 4.09 - 4.24 (m, 2 H) 4.47 (dd, *J*=8.16, 2.89 Hz, 1 H) 5.23 - 5.37 (m, 4 H) 7.19 - 7.28 (m, 1 H) 7.29 - 7.53 (m, 10 H) 7.56 - 7.70 (m, 1 H) 8.26 - 8.52 (m, 1 H) 8.94-9.16 (m, 1 H) 11.81 (br. s., 1 H) 13.74 (br. s., 1 H). ESI-MS m/z: 1112 $[M + H]^+$.



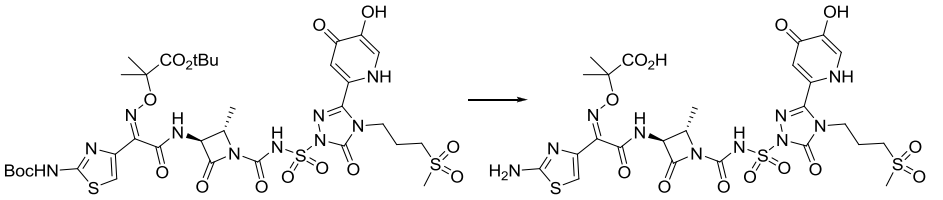
tert-butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate

tert-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate: In an oven dried flask, *tert*-butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-*bis*(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (18.6 g, 16.7 mmol) was suspended in EtOH (400 mL). The solution was evacuated and back-filled with argon. Palladium black (100 mg, 0.94 mmol) was added using caution, keeping a stream of argon flowing into the flask to keep the surrounding inert. The suspension was stirred vigorously under a balloon pressure of hydrogen for 5 h. Celite was added and the reaction mixture was filtered. The mother liquor was concentrated to dryness by rotary evaporation. The crude reaction mixture was purified by reverse phase column chromatography (C18, 5-95% MeCN/H_2O w/ 0.1% TFA). The fractions were collected and concentrated. Once the acetonitrile was removed, the product began to precipitate from solution. The suspension was extracted with EtOAc (200 mL x 2). Brine was added to aid in the separation. The organic phases were dried over Na_2SO_4, filtered and concentrated to dryness. Isolation gave 10.3 g of the title compound in 66% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 - 1.50 (m, 34 H) 2.00 - 2.10 (m, 2 H) 2.90 - 2.99 (m, 4 H) 3.06 - 3.19 (m, 2 H) 3.74 - 3.87 (m, 1 H) 4.07 - 4.16 (m, 2 H) 4.40 - 4.54 (m, 1 H)

7.05 - 7.34 (m, 1 H) 7.34 - 7.56 (m, 1 H) 7.89 - 8.26 (m, 1 H) 8.79 - 9.16 (m, 2 H) 11.68 - 11.90 (m, 1 H).

ESI-MS m/z: 931 $[M + H]^+$.



2-((*Z*)-1-(2-aminothiazol-4-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid

2-(((*Z*)-(1-(2-Aminothiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (**7b**): *tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (10.3 g, 11.1 mmol) was dissolved in 100 mL of a 50% v/v dichloromethane solution containing TFA and the reaction was allowed to stir at room temperature for 30 min. The reaction was concentrated to dryness and azeotropically removed excess TFA by rotary evaporation. The crude reaction mixture was purified by reverse phase column chromatography (C18, 5-95% MeCN/H_2O w/ 0.1% TFA). Fractions were collected, acetronitrile removed by rotary evaporation, froze and then lyopholized. Isolation gave 5.38 grams of the title compound in 63% yield.

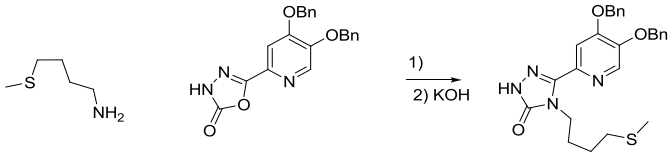
UPLC RT = 0.51 min, MS (ES) MH^+ 775.2 for $C_{25}H_{30}N_{10}O_{13}S_3$

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.39 - 1.44 (m, 2 H) 1.46 (d, *J*=2.51 Hz, 6 H) 1.96 - 2.08 (m, 2 H) 2.91 - 2.98 (m, 3 H) 3.06 - 3.16 (m, 2 H) 3.73 - 3.83 (m, 1 H) 4.11 (t, *J*=6.65

Hz, 2 H) 4.48 (dd, *J*=8.16, 2.89 Hz, 1 H) 6.83 - 6.93 (m, 1 H) 7.37 - 7.41 (m, 1 H) 8.03 (s, 1 H) 9.13 (d, *J*=8.28 Hz, 1 H).

HRMS (ES+) Calcd for $C_{25}H_{31}N_{10}O_{13}S_3$ $[M + H]^+$ 775.1189; Found 775.1229.

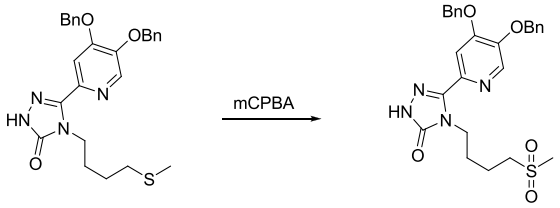
Compound 7c.



3-(4,5-Bis(benzyloxy)pyridin-2-yl)-4-(4-(methylthio)butyl)-1*H*-1,2,4-triazol-5(4*H*)-one: General procedure A was followed using 5-(4,5-bis(benzyloxy)pyridin-2-yl)-1,3,4-oxadiazol-2(3*H*)-one (0.31 g, 0.84 mmol) and 4-(methylthio)butan-1-amine, HCl (0.13 g, 0.84 mmol). The desired product was obtained as a white solid (2.7 g, 87%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.98 (br. s., 1H), 8.33 (s, 1H), 7.60 (s, 1H), 7.29 - 7.49 (m, 10H), 5.31 (s, 2H), 5.29 (s, 2H), 4.07 (t, *J* = 7.03 Hz, 2H), 2.42 (t, *J* = 7.28 Hz, 2H), 1.97 (s, 3H), 1.64 (quin, *J* = 7.28 Hz, 2H), 1.45 (quin, *J* = 7.40 Hz, 2H).

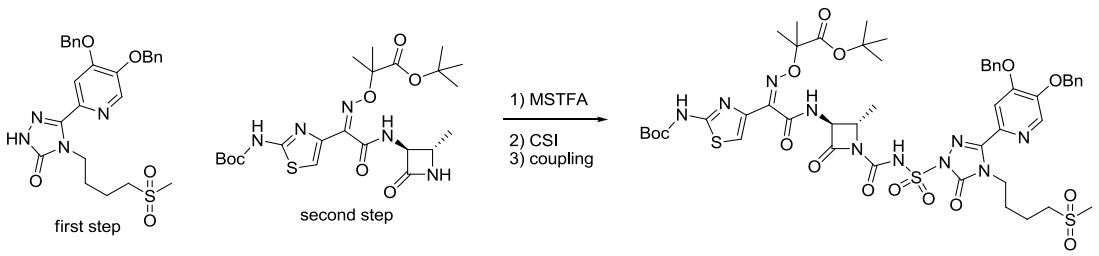
ESI-MS m/z: 477 $[M + H]^+$.



3-(4,5-Bis(benzyloxy)pyridin-2-yl)-4-(4-(methylsulfonyl)butyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**6a**)**:** General procedure B was followed using 3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(4-(methylthio)butyl)-1*H*-1,2,4-triazol-5(4*H*)-one. The reaction mixture was stirred at rt for 2.5h. The reaction mixture was diluted with DCM, washed with sat. $NaHCO_3$, brine and then water. The organic layer was concentrated. The mixture was diluted with water and filtered. The collected solid was washed with water and dried to give the desired product as a pink solid (447 mg, 84%).

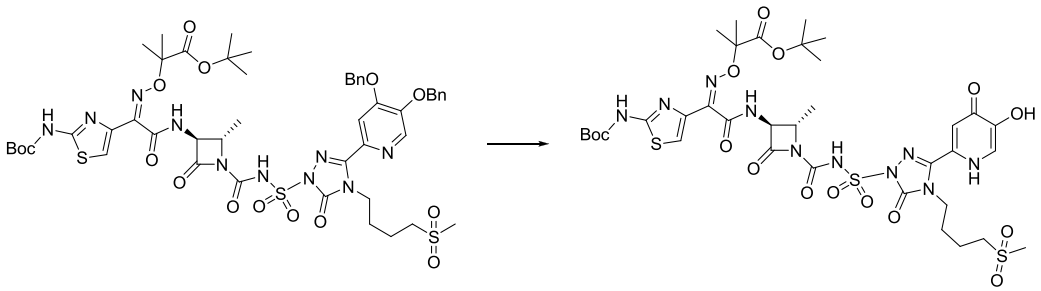
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.03 (s, 1H), 8.34 (s, 1H), 7.62 (s, 1H), 7.30 - 7.51 (m, 10H), 5.32 (s, 2H), 5.29 (s, 2H), 4.09 (t, *J* = 6.65 Hz, 2H), 3.07 - 3.15 (m, 2H), 2.91 (s, 3H), 1.67 - 1.77 (m, *J* = 6.27 Hz, 2H), 1.58 - 1.67 (m, *J* = 9.54 Hz, 2H).

ESI-MS m/z: 509 $[M + H]^+$.



***tert*-Butyl 2-(((Z)-(2-(((2S,3S)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(4-(methylsulfonyl)butyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure C was followed using 3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(4-(methylsulfonyl)butyl)-1*H*-1,2,4-triazol-5(4*H*)-one (0.45 g, 0.88 mmol) and *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**5**) (0.45 g, 0.88 mmol). The crude was purified by silica gel chromatoraphy (0-100% EtOAc/DCM) to give the desired product as a white solid (575 mg, 58% yield).

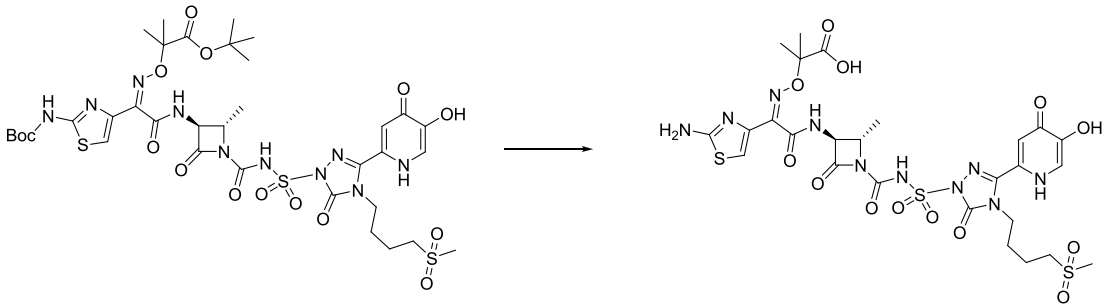
ESI-MS m/z: 1125 $[M + H]^+$.



***tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(4-(methylsulfonyl)butyl)-5-oxo-4,5-dihydro-**

1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate: General Procedure D was followed using *tert*-butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(4-(methylsulfonyl)butyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.36 g, 0.32 mmol). The crude was purified by RediSep reverse phase C18 column (50 g, 0-60% MeCN/water with 0.1% formic acid) to give the desired product as a white solid (146 mg, 49%).

ESI-MS m/z: 945 $[M + H]^+$.



2-(((*Z*)-(1-(2-Aminothiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(4-(methylsulfonyl)butyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (7c): General procedure E was followed using *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(4-(methylsulfonyl)butyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.15 g, 0.15 mmol). The crude was purified by RediSep reverse phase C18 column (30 g, 0-20% MeCN/water with 0.1% formic acid) to give the desired product as a white solid (87 mg, 71%).

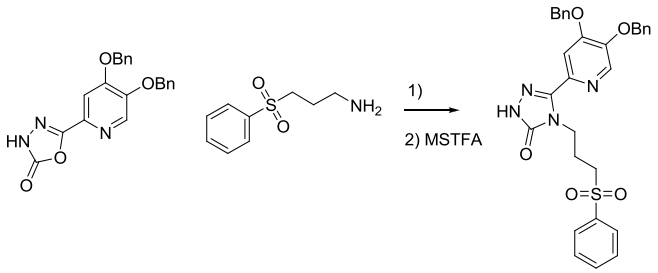
UPLC RT = 0.50 min, MS (ES) MH^+: 789.2 for $C_{26}H_{32}N_{10}O_{13}S_3$

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.12 (d, J = 8.03 Hz, 1H), 8.03 (s, 1H), 7.37 (s, 1H), 6.88 (s, 1H), 4.47 (dd, J = 2.89, 8.16 Hz, 1H), 4.02 (t, J = 6.27 Hz, 2H), 3.79 (ddd, J = 3.01, 6.09, 12.23 Hz, 1H), 3.04 - 3.15 (m, 2H), 2.90 (s, 3H), 1.58 - 1.74 (m, 4H), 1.36 - 1.53 (m, 9H).

^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 174.3, 169.6, 163.9, 163.0, 160.8, 153.3, 151.8, 151.7, 146.3, 144.4, 142.2, 138.3, 135.9, 110.9, 110.0, 82.0, 60.5, 55.1, 53.0, 41.2, 27.4, 23.8, 23.70, 19.1, 17.6.

HRMS: (ES$^+$) Calcd. for $C_{26}H_{33}N_{10}O_{13}S_3$ $[M + H]^+$: 789.1385; Found 789.1363.

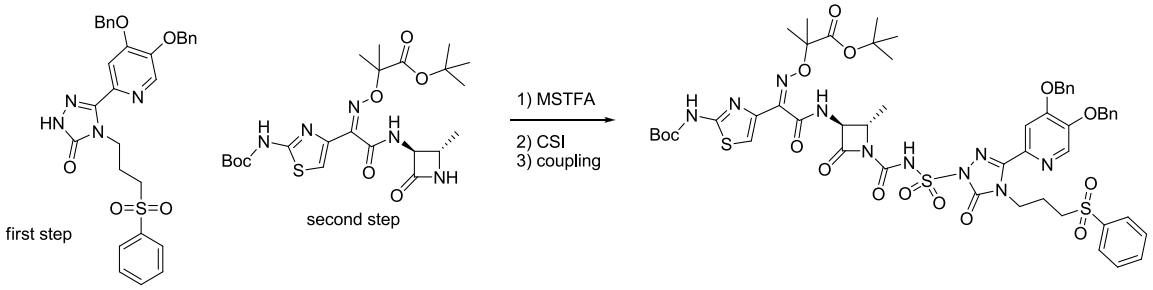
Compound 7d.



3-(4,5-Bis(benzyloxy)pyridin-2-yl)-4-(3-(phenylsulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**6d**)**:** A mixture of (2-(4,5-bis(benzyloxy)picolinoyl)-*N*-(3-(phenylsulfonyl)propyl)hydrazinecarboxamide (1.0 g, 1.74 mmol) in 2,2,2-trifluoro-*N*-methyl-*N*-(trimethylsilyl)acetamide (6 mL, 1.74 mmol) was microwave heated at 150 °C for 2.5h. After this time the reaction mixture was concentrated. The crude was purified by silica gel chromatography (0-100% EtOAc/hexane, then 0-10% MeOH/DCM). The resulting solid was then washed with EtOAc and ether and dried to give the clean desired product (477 mg, 48%).

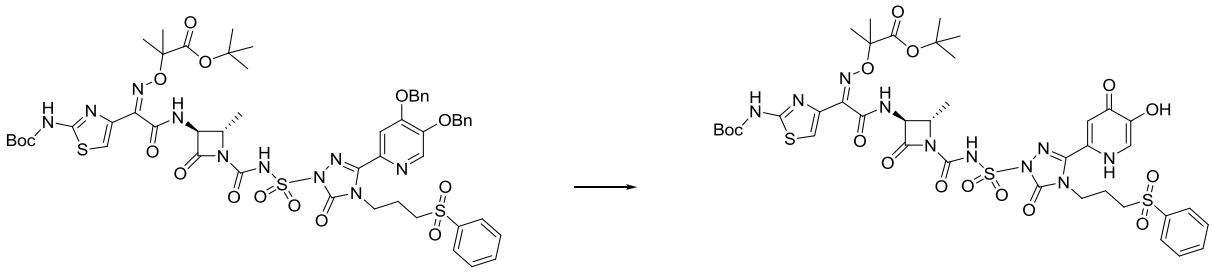
^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 9.14 (s, 1H), 8.14 (s, 1H), 7.85 (dd, J = 1.25, 8.28 Hz, 2H), 7.60 - 7.67 (m, J = 7.53 Hz, 1H), 7.58 (s, 1H), 7.50 - 7.56 (m, 2H), 7.44 - 7.49 (m, 4H), 7.32 - 7.44 (m, 6H), 5.24 (s, 4H), 4.26 (t, J = 6.65 Hz, 2H), 3.16 - 3.25 (m, 2H), 2.12 - 2.22 (m, 2H).

ESI-MS m/z: 557 $[M + H]^+$.



***tert*-Butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-5-oxo-4-(3-(phenylsulfonyl)propyl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure C was followed using 3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(phenylsulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**6d**) (0.48 g, 0.86 mmol) and *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**5**) (0.44 g, 0.86 mmol). The crude was purified by silica gel column (0-100% EtOAc/hexane) to give the desired product (380 mg, 38%).

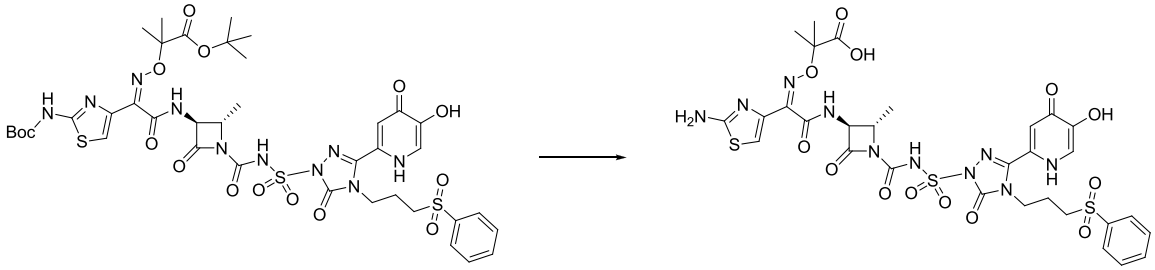
ESI-MS m/z: 1173 $[M + H]^+$.



***tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-5-oxo-4-(3-(phenylsulfonyl)propyl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure D was followed using *tert*-butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-5-oxo-4-(3-

(phenylsulfonyl)propyl)-4,5-dihydro-*1H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.38 g, 0.32 mmol). The crude was purified by RediSep reverse phase C18 column (30 g, 0-60% MeCN/water with 0.1% formic acid) to give the desired product (90 mg, 28%).

ESI-MS m/z: 993 $[M + H]^+$.



2-(((*Z*)-(1-(2-Aminothiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-5-oxo-4-(3-(phenylsulfonyl)propyl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (7d): General procedure E was followed using *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-5-oxo-4-(3-(phenylsulfonyl)propyl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.090 g, 0.09 mmol). The crude was purified by RediSep reverse phase C18 column (30 g, 0-20% MeCN/water with 0.1% formic acid) to give the desired product (49 mg, 65%).

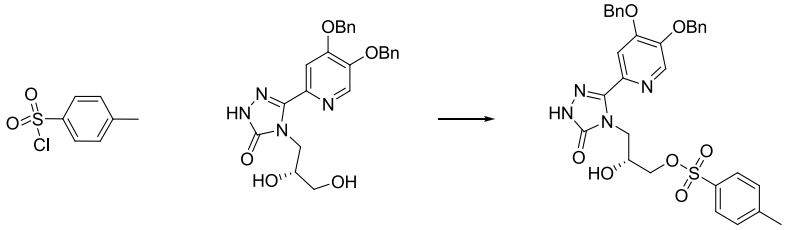
UPLC RT = 0.57 min, MS (ES) MH^+: 837.1 for $C_{30}H_{32}N_{10}O_{13}S_3$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.05 (d, *J* = 8.10 Hz, 1H), 7.93 (s, 1H), 7.82 - 7.89 (m, 2H), 7.66 - 7.74 (m, 1H), 7.55 - 7.64 (m, 2H), 7.30 (s, 1H), 6.83 (s, 1H), 4.46 (dd, *J* = 2.92, 8.19 Hz, 1H), 4.02 (t, *J* = 6.69 Hz, 2H), 3.78 (dd, *J* = 2.92, 6.12 Hz, 1H), 3.27 - 3.38 (m, 2H), 1.80 - 1.95 (m, 2H), 1.39 - 1.46 (m, 9H).

^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 174.3, 169.5, 163.9, 163.0, 160.9, 153.0, 151.8, 151.8, 144.3, 142.4, 138.6, 138.2, 136.1, 133.7, 129.4, 127.7, 110.8, 109.8, 82.0, 60.5, 55.0, 52.0, 23.8, 23.7, 22.6, 17.6.

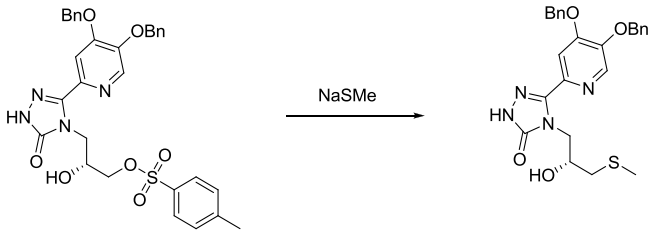
HRMS: (ES$^+$) Calcd. for $C_{30}H_{33}N_{10}O_{13}S_3$ $[M + H]^+$: 837.1385; Found 837.1385.

Compound 7e.



(*R*)-3-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-2-hydroxypropyl 4-methylbenzenesulfonate: *p*-Toluenesulfonyl chloride (0.514 g, 2.70 mmol) was added to a solution of (*R*)-3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2,3-dihydroxypropyl)-1*H*-1,2,4-triazol-5(4*H*)-one (1.10 g, 2.45 mmol) in pyridine (20 ml) at 0 °C. The reaction was stirred at 0 °C for 1h and then at rt overnight. The reaction solution was concentrated. The crude material was purified by silica gel column (0-100% EtOAc/hexane) to give the desired product (345 mg, 23%).

ESI-MS m/z: 603 $[M + H]^+$.

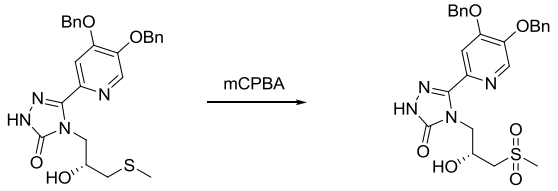


(*R*)-3-(4,5-Bis(benzyloxy)pyridin-2-yl)-4-(2-hydroxy-3-(methylthio)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one: Sodium thiomethoxide (0.080 g, 1.1 mmol) was added to a solution of (*R*)-3-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-2-hydroxypropyl 4-methylbenzenesulfonate (0.35 g, 0.57 mmol) in DMF (2 mL) at 0 °C. The reaction mixture

was stirred at rt for 2h. After concentration, the residue was purified by silica gel column (0-100% EtOAc/hexane) to give the desired product as a white solid (198 mg, 72%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.97 (s, 1H), 8.29 (s, 1H), 7.59 (s, 1H), 7.29 - 7.51 (m, 10H), 5.31 (s, 2H), 5.29 (s, 2H), 5.18 (d, *J* = 5.77 Hz, 1H), 4.05 - 4.21 (m, 2H), 3.80 - 3.91 (m, 1H), 2.46 - 2.48 (m, *J* = 6.27 Hz, 2H), 1.99 (s, 3H).

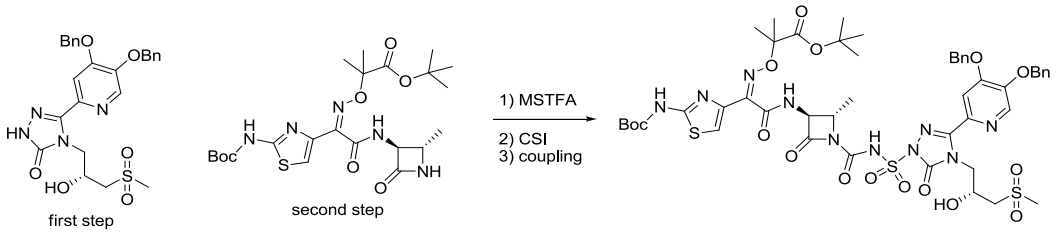
ESI-MS m/z: 479 $[M + H]^+$.



(*R*)-3-(4,5-Bis(benzyloxy)pyridin-2-yl)-4-(2-hydroxy-3-(methylsulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**6e**)**:** General Procedure B was followed using (*R*)-3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-hydroxy-3-(methylthio)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (0.24 g, 0.49 mmol). After the reaction was concentrated, the residue was purified by silica gel column (50-100% EtOAc/hexane, then 10% MeOH/EtOAc) to give the desired product as a white solid (0.21 g, 85%).

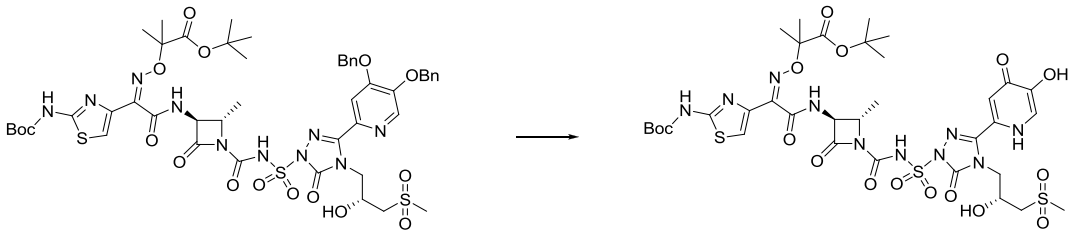
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.06 (s, 1H), 8.32 (s, 1H), 7.61 (s, 1H), 7.30 - 7.49 (m, 10H), 5.78 (d, *J* = 6.02 Hz, 1H), 5.32 (s, 2H), 5.29 (s, 2H), 4.26 - 4.37 (m, *J* = 6.27 Hz, 1H), 4.19 (dd, *J* = 7.15, 13.68 Hz, 1H), 4.09 (dd, *J* = 5.65, 13.43 Hz, 1H), 3.26 - 3.36 (m, *J* = 8.03 Hz, 1H), 3.04 (d, *J* = 14.31 Hz, 1H), 2.97 (s, 3H).

ESI-MS m/z: 511 $[M + H]^+$.



***tert*-Butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-((*R*)-2-hydroxy-3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure C was followed using (*R*)-3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-hydroxy-3-(methylsulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**6e**) (0.21 g, 0.41 mmol) and *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**5**) (0.21 g, 0.41 mmol). The crude was purified by silica gel column (0-10% MeOH/EtOAc) and then purified by RediSep reverse phase C18 column (30 g, 0-100% MeCN/water with 0.1% formic acid) to give the desired product (292 mg, 63%).

ESI-MS m/z: 1127 $[M + H]^+$.

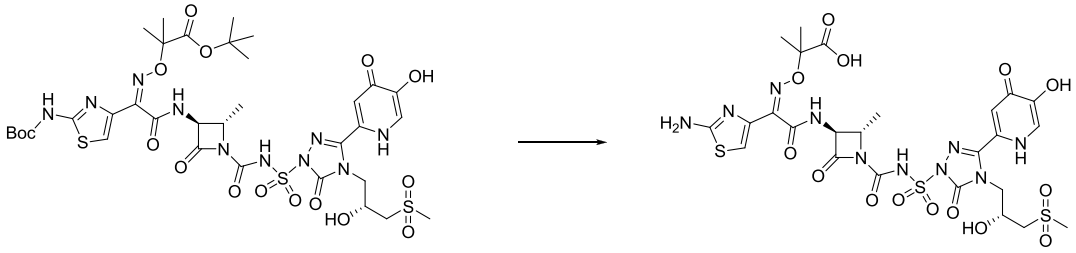


***tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((4-((*R*)-2-hydroxy-3-(methylsulfonyl)propyl)-3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure D was followed using *tert*-butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-((*R*)-2-hydroxy-3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.29 g, 0.26 mmol). The crude was purified by RediSep reverse phase C18 column (30 g, 0-51%

MeCN/water with 0.1% formic acid) to give the desired product as a white solid (127 mg, 52%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.81 (s, 1H), 9.00 (d, *J* = 8.28 Hz, 1H), 8.01 (s, 1H), 7.35 (s, 1H), 7.25 (s, 1H), 4.47 (dd, *J* = 3.01, 8.28 Hz, 1H), 4.22 - 4.32 (m, *J* = 8.78 Hz, 1H), 4.07 - 4.17 (m, 1H), 4.02 (dd, *J* = 5.52, 13.80 Hz, 1H), 3.76 (dd, *J* = 2.89, 6.15 Hz, 1H), 3.28 (dd, *J* = 9.91, 14.68 Hz, 1H), 3.06 (d, *J* = 14.31 Hz, 1H), 2.95 (s, 3H), 1.46 (s, 9H), 1.43 (d, *J* = 6.02 Hz, 3H), 1.40 (d, *J* = 4.52 Hz, 6H), 1.38 (s, 9H).

ESI-MS m/z: 947 $[M + H]^+$.



2-(((*Z*)-(1-(2-Aminothiazol-4-yl)-2-(((2*S*,3*S*)-1-(((4-((*R*)-2-hydroxy-3-(methylsulfonyl)propyl)-3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (**7e**)**:** General procedure E was followed using *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((4-((*R*)-2-hydroxy-3-(methylsulfonyl)propyl)-3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.13 g, 0.13 mmol). The crude was purified by RediSep reverse phase C18 column (30 g, 0-24% MeCN/water with 0.1% formic acid) to give the desired product as a white solid (95 mg, 90%).

UPLC RT = 0.50 min, MS (ES) MH^+: 790.9 for $C_{25}H_{30}N_{10}O_{14}S_3$

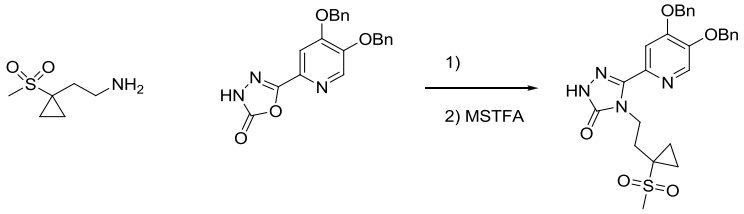
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.99 (d, *J* = 8.53 Hz, 1H), 8.01 (s, 1H), 7.35 (s, 1H), 6.75 (s, 1H), 4.45 (dd, *J* = 2.89, 8.41 Hz, 1H), 4.23 - 4.33 (m, *J* = 10.29 Hz, 1H), 4.06 - 4.16

(m, *J* = 6.53 Hz, 1H), 3.98 - 4.06 (m, 1H), 3.76 (dd, *J* = 2.89, 6.15 Hz, 1H), 3.28 (dd, *J* = 9.54, 15.06 Hz, 1H), 3.06 (d, *J* = 14.81 Hz, 1H), 2.95 (s, 3H), 1.36 - 1.47 (m, 9H).

^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 174.3, 169.5, 163.9, 160.9, 154.0, 151.9, 151.9, 146.7, 144.5, 142.5, 137.7, 135.1, 110.8, 110.5, 82.0, 64.5, 60.5, 58.2, 55.1, 46.8, 42.5, 40.4, 23.8, 23.7, 17.6.

HRMS: (ES$^+$) Calcd. for $C_{25}H_{31}N_{10}O_{14}S_3$ $[M + H]^+$: 791.1178; Found 791.1185.

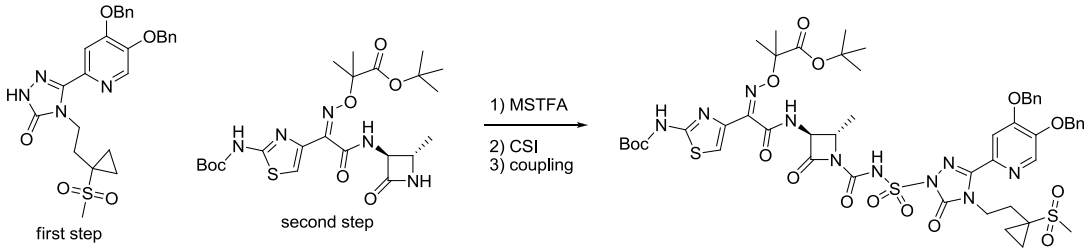
Compound 7f.



3-(4,5-Bis(benzyloxy)pyridin-2-yl)-4-(2-(1-(methylsulfonyl)cyclopropyl)ethyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**6f**)**:** A mixture of (5-(4,5-bis(benzyloxy)pyridin-2-yl)-1,3,4-oxadiazol-2(3*H*)-one (1.0 g, 2.7 mmol) and 2-(1-(methylsulfonyl)cyclopropyl)ethanamine, HCl (0.53 g, 2.7 mmol) in triethylamine (1.1 mL, 8.0 mmol) and THF (10 mL) was microwave heated at 100 °C for 3h. The reaction mixture was concentrated and treated with 2,2,2-trifluoro-*N*-methyl-*N*-(trimethylsilyl)acetamide (10 mL, 54 mmol). The reaction mixture was microwave heated at 150 °C for 3h. After it was concentrated, the residue was washed with DCM, filtered and dried to give 3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(1-(methylsulfonyl)cyclopropyl)ethyl)-1*H*-1,2,4-triazol-5(4*H*)-one (0.49 g, 35%) as a white solid.

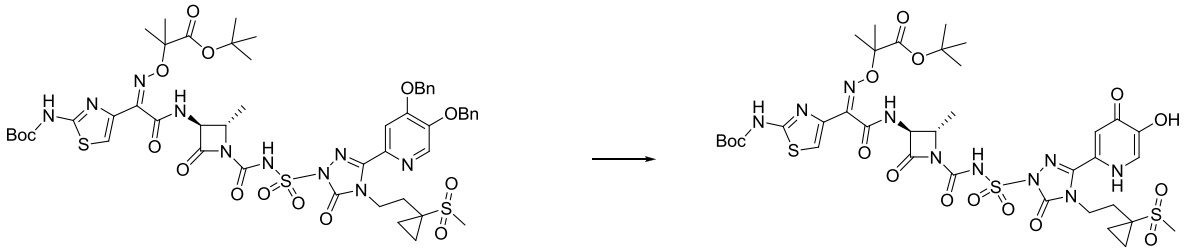
^{1}H NMR (300 MHz, DICHLOROMETHANE-d_2) δ ppm 9.05 (s, 1H), 8.14 (s, 1H), 7.60 (s, 1H), 7.32 - 7.52 (m, 10H), 5.24 (s, 4H), 4.33 - 4.48 (m, 2H), 2.96 (s, 3H), 2.15 - 2.29 (m, 2H), 1.38 - 1.48 (m, 2H), 0.96 - 1.07 (m, 2H).

ESI-MS m/z: 521 $[M + H]^+$.



***tert*-Butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(1-(methylsulfonyl)cyclopropyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure C was followed using 3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(1-(methylsulfonyl)cyclopropyl)ethyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**6f**) (0.38 g, 0.73 mmol) and *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**5**) (0.37 g, 0.73 mmol). The crude material was purified by silica gel column (0-100% EtOAc/hexane) to give the desired product as a solid (500 mg, 60%).

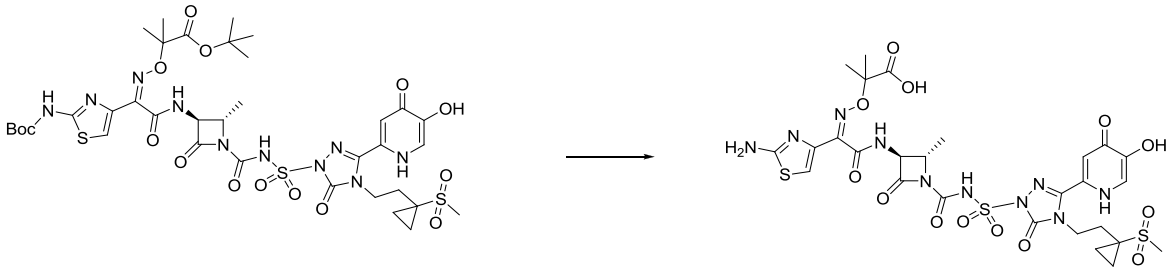
ESI-MS m/z: 1137 $[M + H]^+$.



***tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(1-(methylsulfonyl)cyclopropyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure D was followed using *tert*-butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(1-(methylsulfonyl)cyclopropyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-

butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.50 g, 0.44 mmol). The crude was purified by RediSep reverse phase C18 column (30 g, 0-60% MeCN/water with 0.1% formic acid) to give the desired product (230 mg, 55%).

ESI-MS m/z: 957 $[M + H]^+$.



2-(((*Z*)-(1-(2-Aminothiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(1-(methylsulfonyl)cyclopropyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (**7f**)**:** General procedure E was followed using *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(1-(methylsulfonyl)cyclopropyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.23 g, 0.24 mmol). The crude was purified by RediSep reverse phase C18 column (30 g, 0-20% MeCN/water with 0.1% formic acid) to give the desired product as a white solid (102 mg, 53%).

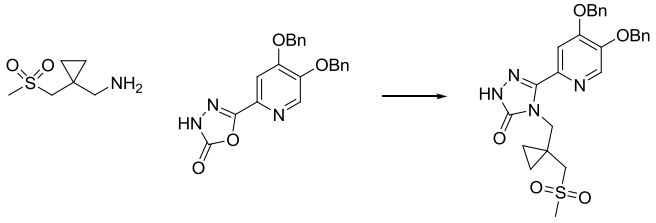
UPLC RT = 0.54 min, MS (ES) MH^+: 801.0 for $C_{27}H_{32}N_{10}O_{13}S_3$

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 (d, *J* = 8.28 Hz, 1H), 8.02 (s, 1H), 7.37 (s, 1H), 6.89 (s, 1H), 4.47 (dd, *J* = 2.89, 8.16 Hz, 1H), 4.16 (dd, *J* = 6.15, 10.16 Hz, 2H), 3.74 - 3.85 (m, *J* = 2.89, 6.15 Hz, 1H), 3.05 (s, 3H), 2.04 - 2.17 (m, 2H), 1.40 - 1.54 (m, 9H), 1.21 - 1.29 (m, 2H), 0.90 - 1.04 (m, 2H).

^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 174.3, 169.6, 163.9, 160.7, 155.0, 153.3, 151.9, 151.3, 146.3, 144.5, 142.1, 138.2, 135.9, 110.9, 109.9, 82.1, 60.5, 55.0, 38.2, 30.8, 23.8, 23.7, 17.6, 10.8.

HRMS: (ES$^+$) Calcd. for $C_{27}H_{33}N_{10}O_{13}S_3$ $[M + H]^+$: 801.1385; Found 801.1376.

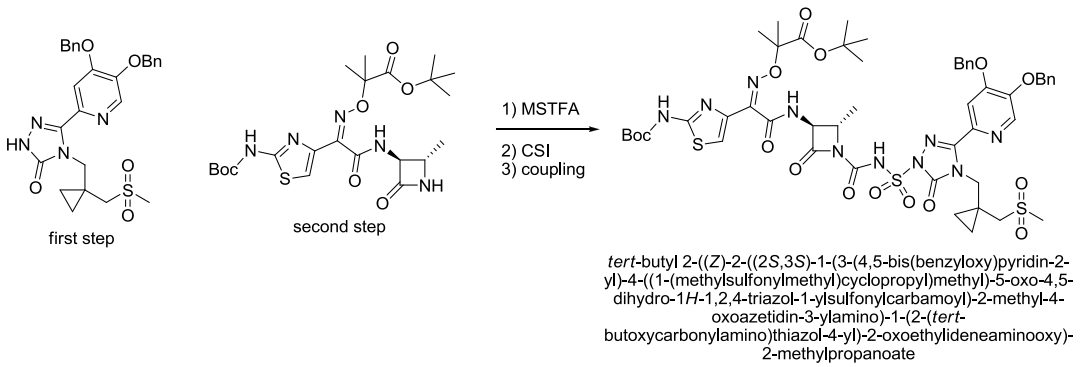
Compound 7g.



3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-((1-(methylsulfonylmethyl)cyclopropyl)methyl)-1*H*-1,2,4-triazol-5(4*H*)-one

3-(4,5-Bis(benzyloxy)pyridin-2-yl)-4-((1-(methylsulfonylmethyl)cyclopropyl)methyl)-1H-1,2,4-triazol-5(4H)-one (**6g**): To a suspension of 5-(4,5-bis(benzyloxy)pyridin-2-yl)-1,3,4-oxadiazol-2(3H)-one (1 g, 2.66 mmol) in THF (50 mL) was added (1-((methylsulfonyl)methyl)cyclopropyl)methanamine, HCl (0.585 g, 2.93 mmol) followed by triethylamine (0.743 mL, 5.33 mmol). This was stirred in the microwave at 100 °C for 4 hr. After this time, the reaction was cooled to rt. The reaction was diluted with ethyl acetate and the reaction was concentrated. The residue was suspended in *N*-Methyl-*N*-(trimethylsilyl)trifluoroacetamide (15 mL, 7.99 mmol) and the reaction was stirred in the microwave at 150 °C for 1 hr. The reaction was concentrated. The residue was purified (ISCO 50-100% ethyl acetate/hexanes) and concentrated (1.2 g, 87%).

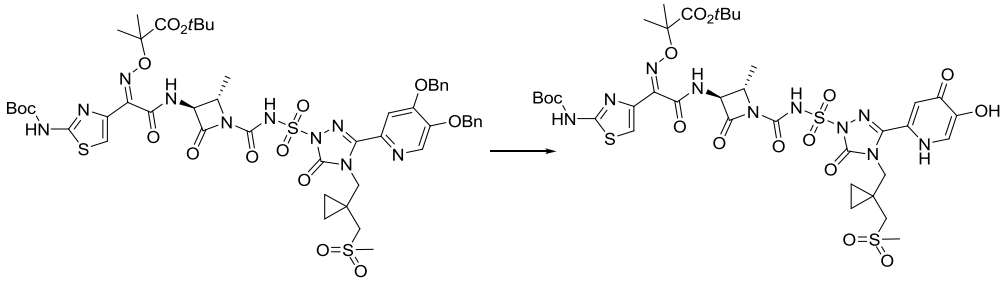
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 12.06 (s, 1H), 8.32 (s, 1H), 7.61 (s, 1H), 7.37-7.48 (m, 10H), 5.28-5.32 (m, 6H), 4.48 (s, 2H), 2.97 (s, 3H), 0.5-0.62 (m, 4H).



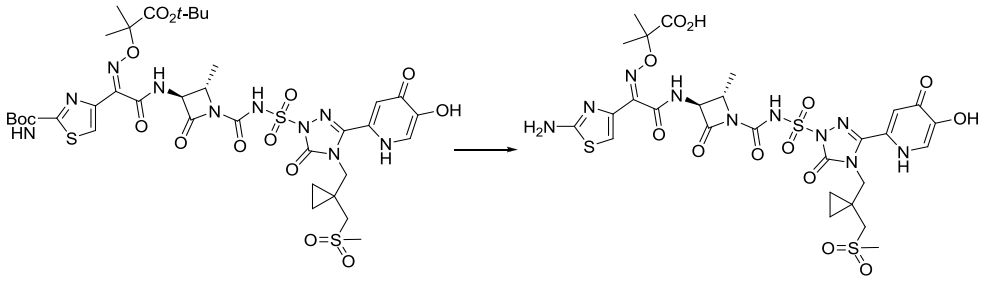
tert-butyl 2-((*Z*)-2-((2*S*,3*S*)-1-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-((1-(methylsulfonylmethyl)cyclopropyl)methyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-oxoethylideneaminooxy)-2-methylpropanoate

***tert*-Butyl 4-((*Z*)-2-((2*S*,3*S*)-1-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-((1-(methylsulfonylmethyl)cyclopropyl)methyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxo-1-(2,4,4-trimethyl-3-oxopentan-2-yloxyimino)ethyl)thiazol-2-ylcarbamate**: General Procedure C was followed using *tert*-butyl 2-(((*E*)-(1-(2-((tert-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate **5** (148 mg, 0.29 mmol) and 4,5-bis(benzyloxy)-2-(4-((1-((methylsulfonyl)methyl)cyclopropyl)methyl)-5-((trimethylsilyl)oxy)-4*H*-1,2,4-triazol-3-yl)pyridine (**6g**) (171 mg, 0.29 mmol). The crude material was purified by silica gel chromatography (ISCO 30-70% ethyl acetate/hexanes -> 70-100% ethyl acetate/hexanes) to afford the desired compound (186 mg, 57%).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.78 (s, 1H), 9.0 (s, 1H), 8.34 (s, 1H), 7.6 (s, 1H), 7.38-7.49 (m, 10H), 7.36 (s, 1H), 5.29-5.31 (m, 4H), 4.42-4.46 (m, 2H), 3.77-3.79 (m, 1H), 2.97 (s, 3H), 1.46 (s, 6H), 1.38 (s, 18H), 0.48-0.58 (m, 4H).



***tert*-Butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-((1-(methylsulfonylmethyl)cyclopropyl)methyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate**: General Procedure D was followed using *tert*-butyl 2-(((*E*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-((1-((methylsulfonyl)methyl)cyclopropyl)methyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (275.3 mg, 0.24 mmol). The crude material was carried on with no purification.



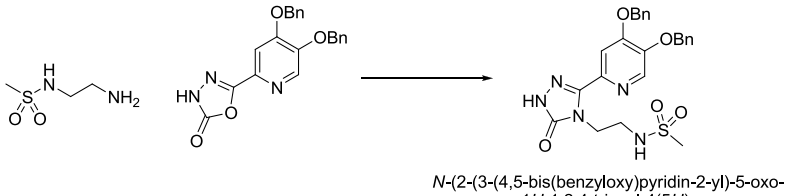
2-((*Z*)-1-(2-Aminothiazol-4-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-((1-(methylsulfonylmethyl)cyclopropyl)methyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid (**7g**): General Procedure E was followed using *tert*-butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-((1-(methylsulfonylmethyl)cyclopropyl)methyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate. The crude material was purified twice by reverse phase chromatography (ISCO C18 5-20% MeCN/water with 0.1% formic acid) to afford the desired product (19 mg, 10% over two steps).

UPLC RT = 2.55 min, MS (ES) MH^+: 801.0 for $C_{27}H_{32}N_{10}O_{13}S_3$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.03 (s, 1H), 8.0 (s, 1H), 7.35 (s, 1H), 7.34 (s, 1H), 6.76 (s, 1H), 4.41-4.48 (m, 4H), 3.76-3.79 (m, 2H), 2.99 (s, 3H), 1.43 (s, 6H), 0.5-0.59 (m, 4H).

HRMS: (ES^+) Calcd. for $C_{27}H_{33}N_{10}O_{13}S_3$ $[M + 1]^+$: 801.1346; Found 801.1407.

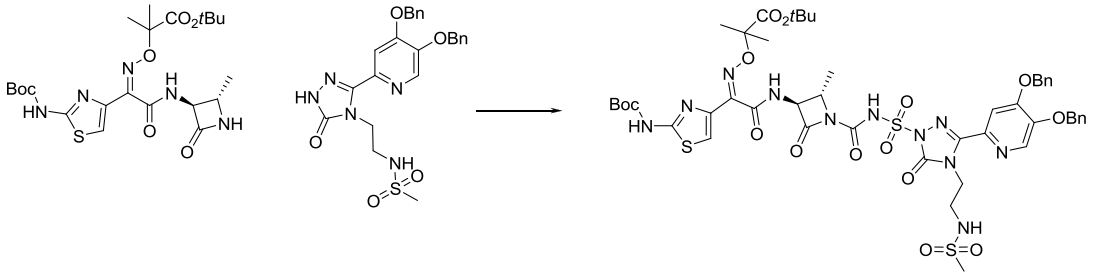
Compound 7h.



N-(2-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)ethyl)methanesulfonamide

***N*-(2-(3-(4,5-Bis(benzyloxy)pyridin-2-yl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)ethyl)methanesulfonamide** (**6h**): General Procedure A was followed using *N*-(2-aminoethyl)methanesulfonamide (1.40 g, 7.99 mmol) and 5-(4,5-bis(benzyloxy)pyridin-2-yl)-1,3,4-oxadiazol-2(3*H*)-one (3 g, 7.99 mmol). The crude material was triturated with diethyl ether and DCM to provide *N*-(2-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)ethyl)methanesulfonamide (1.6 mg, 40%) as a solid.

ESI-MS m/z: 496.1 $[M + H]^+$.

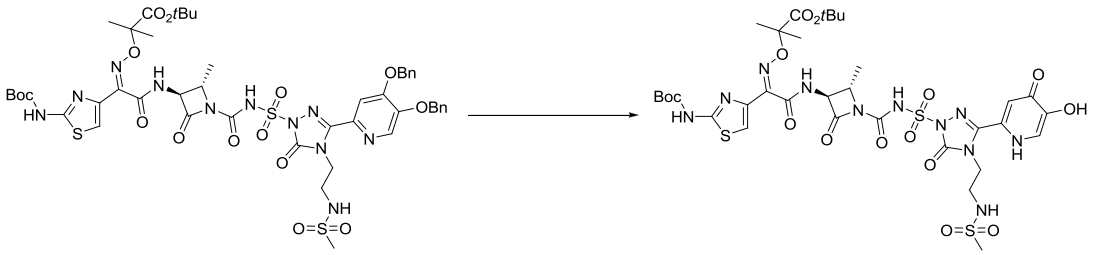


tert-butyl 2-((*Z*)-2-((2*S*,3*S*)-1-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(methylsulfonamido)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-oxoethylideneaminooxy)-2-methylpropanoate

***tert*-Butyl 2-((*Z*)-2-((2*S*,3*S*)-1-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(methylsulfonamido)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-oxoethylideneaminooxy)-2-methylpropanoate**: General Procedure C was followed using *N*-

(2-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)ethyl)methanesulfonamide (**6h**) (300 mg, 0.61 mmol) and *tert*-butyl 2-(((*E*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**5**) (310 mg, 0.61 mmol). The crude material was purified (silica gel chromatography) to provide *tert*-butyl 2-((*Z*)-2-((2*S*,3*S*)-1-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(methylsulfonamido)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-oxoethylideneaminooxy)-2-methylpropanoate as a solid (291 mg, 43 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.78 (s, 1H), 9.01 (s, 1H), 8.33 (s, 1H), 7.96 (s, 1H), 7.6 (s, 1H), 7.33-7.47 (m, 10H), 7.16-7.24 (m, 1H), 5.29-5.34 (m, 1H), 4.9-5.0 (m, 2H), 4.44-4.47 (m, 1H), 4.07-4.13 (m, 2H), 3.8-4.0 (m, 1H), 3.16-3.21 (m, 2H), 2.84 (s, 3H), 1.46 (s, 6H), 1.38 (s, 18H).

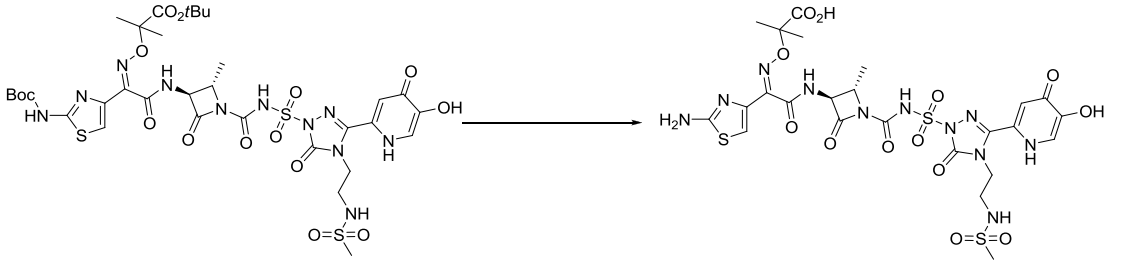


tert-butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(methylsulfonamido)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate

***tert*-Butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(methylsulfonamido)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate**: General Procedure D was followed using *tert*-butyl 2-((*Z*)-2-((2*S*,3*S*)-1-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(methylsulfonamido)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-

oxoethylideneaminooxy)-2-methylpropanoate (291 mg, 0.26 mmol). The crude material was carried on with no purification (190 mg, 77 %).

ESI-MS m/z: 932.2 $[M + H]^+$.



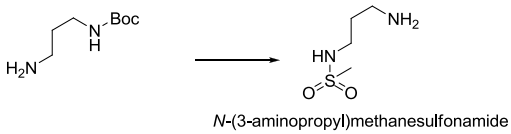
2-((*Z*)-1-(2-Aminothiazol-4-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(methylsulfonamido)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid (**7h**): General procedure E was followed using *tert*-butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(methylsulfonamido)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate (190 mg, 0.2 mmol). The crude material was purified by reverse phase chromatography (ISCO, C18 ISCO 5-15% MeCN/Water with 0.1% formic acid) and lyophilized to the desired product as a solid (46 mg, 29%).

UPLC RT = 0.49 min, MS (ES) MH^+: 776.2 for $C_{24}H_{29}N_{11}O_{13}S_3$

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.01 (s, 1H), 7.35 (s, 1H), 7.22 (s, 1H), 6.81 (s, 1H), 4.45-4.47 (m, 1H), 4.08-4.1 (m, 2H), 3.76-3.78 (m, 2H), 3.16-3.2 (m, 3H), 2.85 (s, 3H), 1.44 (s, 6H).

HRMS: (ES^+) Calcd. for $C_{24}H_{30}N_{11}O_{13}S_3$ $[M + 1]^+$: 776.1142; Found 776.1182.

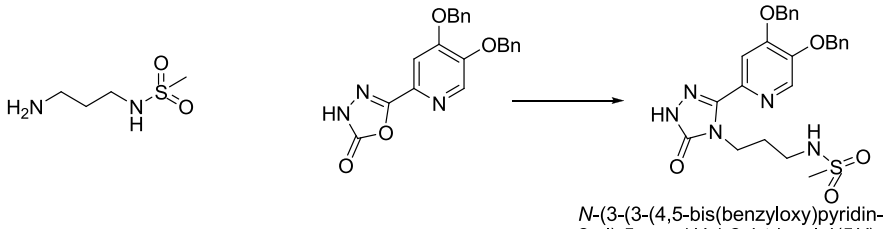
Compound 7i.



N-(3-aminopropyl)methanesulfonamide

***N*-(3-Aminopropyl)methanesulfonamide**: To a solution of *tert*-butyl (3-aminopropyl)carbamate, HCl (5 g, 23.7 mmol) in THF (98 mL) cooled to 0 °C was added triethylamine (6.62 mL, 47.5 mmol). This was stirred for 20 min and MsCl (2.40 mL, 30.9 mmol) was subsequently added. The reaction was stirred at 0 °C for 1 hr, warmed to rt and stirred overnight. The reaction was partitioned between water (100 mL) and ethyl acetate (100 mL). The aq. layer was extracted with ethyl acetate (2 x 50 mL). The organics were dried and concentrated. The residue was dissolved in ethyl acetate (80 mL) and HCl (11.9 mL, 47.5 mmol) was added. The solution was stirred at 23 °C overnight. The reaction was concentrated to provide *N*-(3-aminopropyl)methanesulfonamide (2.8 g, 63%).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.97 (s, 2H), 7.13 (s, 1H), 3.01-3.05 (m, 2H), 2.9 (s, 3H), 2.78-2.84 (m, 2H), 1.71-1.78 (m, 2H).

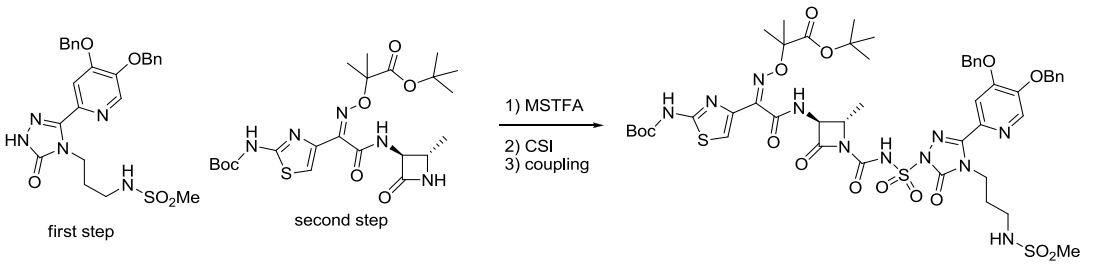


N-(3-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)propyl)methanesulfonamide

***N*-(3-(3-(4,5-Bis(benzyloxy)pyridin-2-yl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)propyl)methanesulfonamide** (**6i**): General procedure A was followed using of 5-(4,5-bis(benzyloxy)pyridin-2-yl)-1,3,4-oxadiazol-2(3*H*)-one (1 g, 2.66 mmol) and *N*-(3-aminopropyl)methanesulfonamide, HCl (0.553 g, 2.93 mmol).

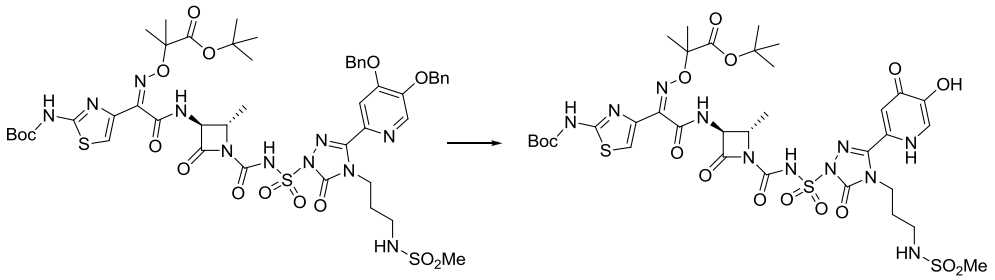
The crude material was purified (ISCO 50-100% ethyl acetate/hexanes) and to afford the desired product (686 mg, 51%).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.69 (s, 1H), 8.28 (s, 1H), 7.59 (s, 1H), 7.36-7.4 (m, 10H), 5.28 (s, 4H), 4.27-4.31 (m, 2H), 3.12-3.16 (m, 2H), 2.88 (s, 3H), 2.15-2.18 (m, 2H).



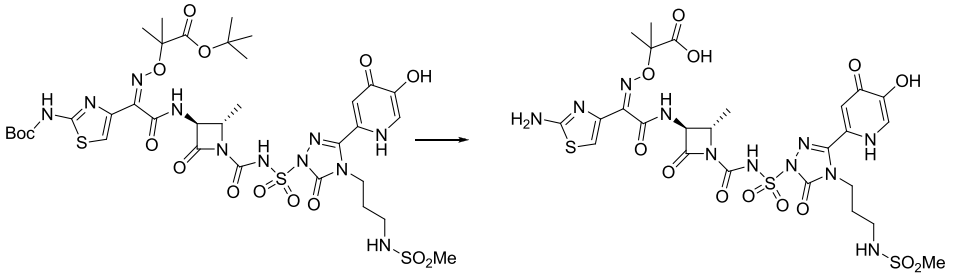
***tert*-Butyl 4-((*Z*)-2-((2*S*,3*S*)-1-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonamido)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxo-1-(2,4,4-trimethyl-3-oxopentan-2-yloxyimino)ethyl)thiazol-2-ylcarbamate**: General Procedure C was followed using of *N*-(3-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)propyl)methanesulfonamide (**6i**) (154 mg, 0.30 mmol) and *tert*-butyl 2-(((*E*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**5**) (202 mg, 0.40 mmol). The crude material was purified by silica gel chromatography (ISCO 30-70% ethyl acetate/hexanes) (97.1 mg, 19%).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.81 (s, 1H), 9.02 (s, 1H), 8.37 (s, 1H), 7.6 (s, 1H), 7.35-7.45 (m, 10H), 7.36 (s, 1H), 5.29-5.3 (m, 2H), 4.47-5.06 (m, 1H), 4.44-4.47 (m, 1H), 4.02-4.07 (m, 2H), 2.86 (s, 3H), 1.46 (s, 6H), 1.4 (s, 3H), 1.38 (s, 18H).



tert-butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonamido)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate

***tert*-Butyl 4-((*Z*)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonamido)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxo-1-(2,4,4-trimethyl-3-oxopentan-2-yloxyimino)ethyl)thiazol-2-ylcarbamate**: General Procedure D was followed using of *tert*-butyl 2-(((*E*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonamido)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (97.1 mg, 0.09 mmol). The crude material was carried on with no further purification.



2-((*Z*)-1-(2-aminothiazol-4-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonamido)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid

2-((*Z*)-1-(2-Aminothiazol-4-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonamido)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid (**7i**): General Procedure E was followed using the crude material from

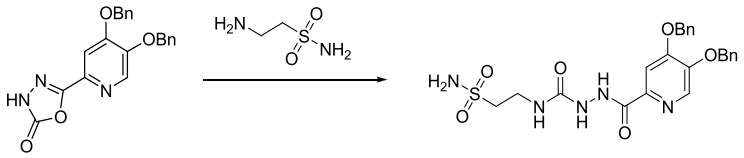
the subsequent reaction. The crude reaction mixture was purified by reverse phase chromatography (C18 ISCO 5-15% MeCN/Water with 0.1% formic acid) (11 mg, 16%).

UPLC RT = 2.47 min, MS (ES) MH^+: 790.2 for $C_{25}H_{31}N_{11}O_{13}S_3$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.95 (s, 1H), 8.02 (s, 1H), 7.36 (s, 1H), 6.94 (s, 1H), 6.74 (s, 1H), 4.45-4.47 (m, 1H), 4.0-4.04 (m, 2H), 3.76-3.79 (m, 2H), 2.94-2.96 (m, 3H), 2.86 (s, 3H), 1.78-1.8 (m, 2H), 1.44 (s, 6H).

HRMS: (ES^+) Calcd. For $C_{25}H_{32}N_{11}O_{13}S_3$ $[M + 1]^+$: 790.1298; Found 790.1341.

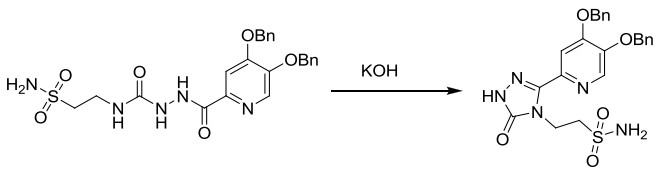
Compound 7j.



2-(4,5-Bis(benzyloxy)picolinoyl)-*N*-(2-sulfamoylethyl)hydrazinecarboxamide: A mixture of 5-(4,5-bis(benzyloxy)pyridin-2-yl)-1,3,4-oxadiazol-2(3*H*)-one (6 g, 16.0 mmol), 2-aminoethanesulfonamide hydrochloride (2.82 g, 17.6 mmol) and TEA (4.46 mL, 32.0 mmol) in acetonitrile (60 mL) was refluxed for 2 hrs and evaporated. The residue was stirred in water (100 ml) for 10 minutes and filtered. The solid was washed with water and dried under vacuum to give the desired product (7.70 g, 96 %) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.08 (t, *J*=7.06 Hz, 2 H) 3.35 - 3.48 (m, 2 H) 5.34 (s, 4 H) 6.56 (t, *J*=5.56 Hz, 1 H) 6.85 (s, 2 H) 7.24 - 7.56 (m, 10 H) 7.64 - 7.76 (m, 1 H) 8.09 (s, 1 H) 8.28 (s, 1 H) 10.00 (br. s., 1 H).

ESI-MS m/z: 500 $[M + H]^+$.



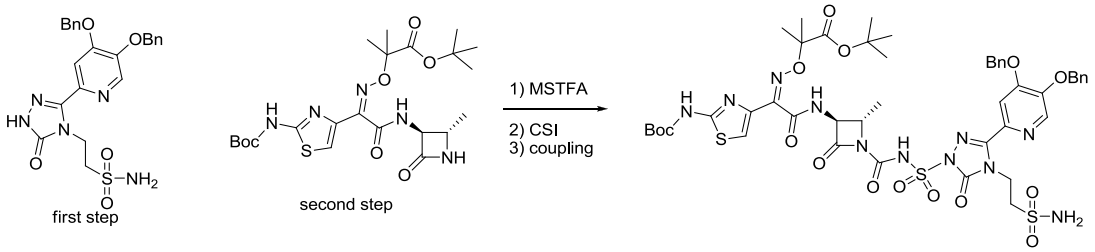
2-(3-(4,5-Bis(benzyloxy)pyridin-2-yl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)ethanesulfonamide: A mixture of 2-(4,5-bis(benzyloxy)picolinoyl)-*N*-(2-

sulfamoylethyl)hydrazinecarboxamide (7.7 g, 15.4 mmol) and 1N KOH (77 ml, 77.1 mmol) was stirred at 95 °C for 2 days. The reaction was complete by LCMS. The mixture was allowed to cool to rt and acidified with 20% acetic acid (44.1 ml, 154 mmol) (pH 5). The white solid was filtered, washed with water and dried under vacuum. The crude product was purified by reverse phase HPLC to provide the desired product (4.04 g, 54.4 %) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.34 - 3.50 (m, 2 H) 4.34 - 4.52 (m, 2 H) 5.29 (s, 2 H) 5.33 (s, 2 H) 6.99 (s, 2 H) 7.27 - 7.53 (m, 10 H) 7.62 (s, 1 H)

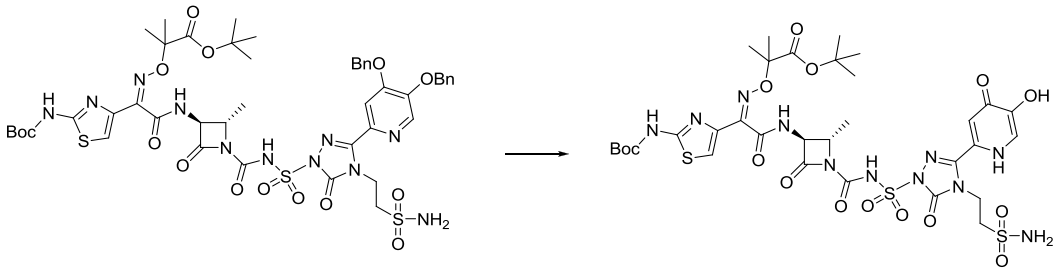
8.36 (s, 1 H) 12.10 (s, 1 H).

ESI-MS m/z: 482 $[M + H]^+$.



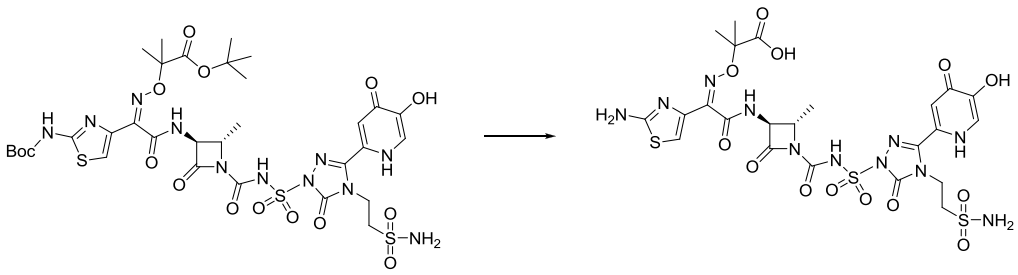
***tert*-Butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-5-oxo-4-(2-sulfamoylethyl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure C was followed using 2-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)ethanesulfonamide (**6j**) (0.50, 1.04 mmol) and tert-butyl 2-(((*Z*)-(1-(2-((tert-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**5**) (0.530 g, 1.04 mmol). The crude was purified by RediSep reversed phase C18 column (50 g, 0-100% MeCN/water with 0.1% formic acid) to give the desired product as a white solid (670 mg, 59%).

ESI-MS m/z: 1098 $[M + H]^+$.



***tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-5-oxo-4-(2-sulfamoylethyl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure D was followed using *tert*-butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-5-oxo-4-(2-sulfamoylethyl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.67 g, 0.61 mmol). The crude was purified by ISCO RediSep reversed phase C18 column (50 g, 0-60 % MeCN/water with 0.1% formic acid) to give the desired products as a white solid (147 mg, 26%).

ESI-MS m/z: 918 $[M + H]^+$.



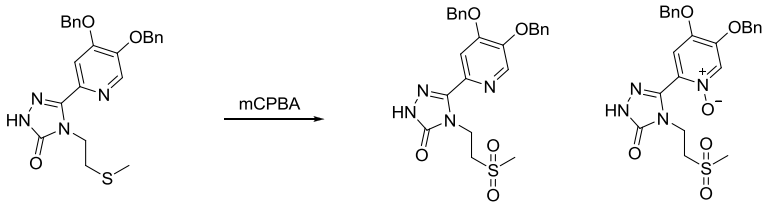
2-(((*Z*)-(1-(2-Aminothiazol-4-yl)-2-(((2S,3S)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-5-oxo-4-(2-sulfamoylethyl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (7j): General procedure E was followed using *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-5-oxo-4-(2-sulfamoylethyl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-

methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.043 g, 0.05 mmol). The residue was treated with water and DMSO, purified by ISCO RediSep reversed phase C18 column (30 g, 0-20 %MeCN/water with 0.1% formic acid) to give the desired product as a white solid (12 mg, 34%).

UPLC RT = 0.47 min, MS (ES) MH^+: 762.1 for $C_{23}H_{28}N_{11}O_{13}S_3$.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.07 (d, *J*=8.28 Hz, 1 H) 8.04 (s, 1 H) 7.35 (s, 1 H) 7.02 (br. s., 2 H) 6.83 (s, 1 H) 4.47 (dd, *J*=8.16, 2.89 Hz, 1 H) 4.30 - 4.38 (m, 2 H) 3.78 (td, *J*=6.21, 2.89 Hz, 1 H) 3.29 - 3.37 (m, 2 H) 1.39 - 1.47 (m, 9 H).

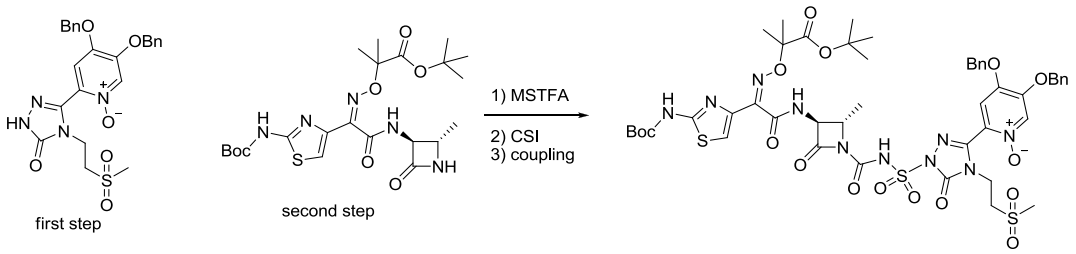
Compound 9a.



4,5-Bis(benzyloxy)-2-(4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (**8a**)**:** 3-Chlorobenzoperoxoic acid (0.878 g, 3.92 mmol) was added to a solution of 3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(methylthio)ethyl)-1*H*-1,2,4-triazol-5(4*H*)-one (0.586 g, 1.31 mmol) and TFA (0.302 mL, 3.92 mmol) in DCM (12 mL). The reaction mixture was stirred at rt for 6h. Then 825mg of *m*-CPBA was added. The reaction mixture was stirred at rt overnight. Then 813 mg *m*-CPBA was added. The reaction mixture was stirred at rt for 5h. After the reaction mixture was concentrated, the residue was washed with MeOH and filtered. The solid was collected *via* filtration, washed with MeOH, and dried to give 3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(2-(methylsulfonyl)ethyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**6a**) (185 mg, 30%, ESI-MS m/z: 481 $[M + H]^+$). The filtrate was concentrated and purified by silica gel column (0-30% MeOH/EtOAc) to give 4,5-bis(benzyloxy)-2-(4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (**8a**) (446 mg, 69%) as a white solid.

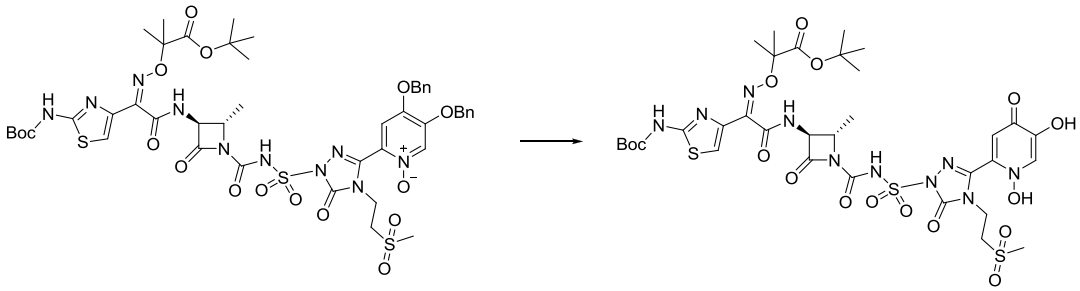
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.24 (s, 1H), 8.36 (s, 1H), 7.31 - 7.49 (m, 11H), 5.26 (s, 2H), 5.24 (s, 2H), 4.00 (t, *J* = 7.15 Hz, 2H), 3.41 - 3.47 (m, 2H), 2.95 (s, 3H).

ESI-MS m/z: 497 $[M + H]^+$.



4,5-Bis(benzyloxy)-2-(1-(*N*-((2*S*,3*S*)-3-((*Z*)-2-(((1-(*tert*-butoxy)-2-methyl-1-oxopropan-2-yl)oxy)imino)-2-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)acetamido)-2-methyl-4-oxoazetidine-1-carbonyl)sulfamoyl)-4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide: General procedure C was followed using 4,5-bis(benzyloxy)-2-(4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (**8a**) (0.43 g, 0.87 mmol) and *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**5**) (0.44 g, 0.87 mmol). The crude was purified by silica gel column twice (0-100 % EtOAc/DCM, then 0-30% MeOH/EtOAc) to give the desired product (230 mg, 24% yield) as a white solid.

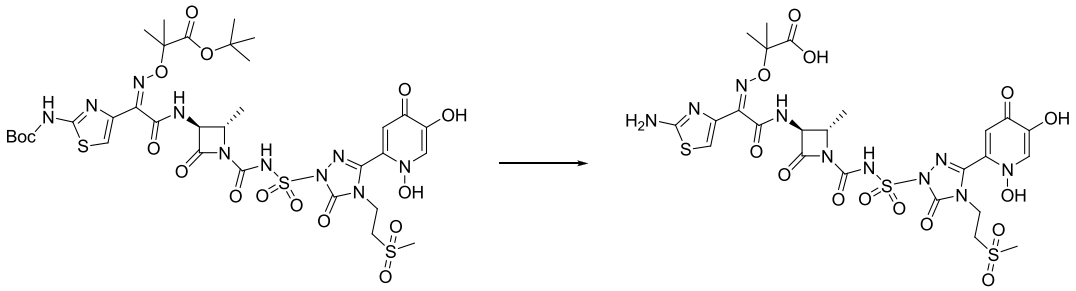
ESI-MS m/z: 1113 $[M + H]^+$.



***tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(1,5-dihydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-**

2-oxoethylidene)amino)oxy)-2-methylpropanoate: General procedure D was followed using 4,5-bis(benzyloxy)-2-(1-(*N*-((2*S*,3*S*)-3-((*Z*)-2-(((1-(*tert*-butoxy)-2-methyl-1-oxopropan-2-yl)oxy)imino)-2-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)acetamido)-2-methyl-4-oxoazetidine-1-carbonyl)sulfamoyl)-4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (0.23 g, 0.21 mmol). The crude was purified by RediSep reverse phase C18 column (50 g, 0-50% MeCN/water with 0.1% formic acid) to give the desired product as a white solid (111 mg, 58%).

ESI-MS m/z: 933 $[M + H]^{+\cdot}$



2-(((*Z*)-(1-(2-Aminothiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(1,5-dihydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (**9a**)**:** General procedure E was followed using *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(1,5-dihydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(2-(methylsulfonyl)ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.11 g, 0.12 mmol). The crude was dissolved in water and purified by RediSep reverse phase C18 column (30 g, 0-20% MeCN/water with 0.1% formic acid) to give the desired product as a white solid (50 mg, 54%).

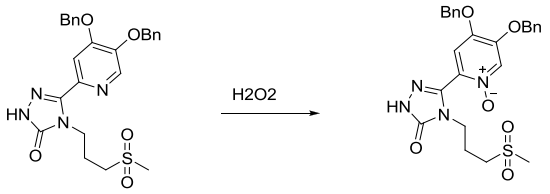
UPLC RT = 0.46 min, MS (ES) MH^+: 777.1 for $C_{24}H_{28}N_{10}O_{14}S_3$

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.12 (d, *J* = 8.28 Hz, 1H), 7.99 (s, 1H), 7.00 (s, 1H), 6.87 (s, 1H), 4.48 (dd, *J* = 3.01, 8.03 Hz, 1H), 3.98 (t, *J* = 7.03 Hz, 2H), 3.81 (dq, *J* = 2.89, 6.15 Hz, 1H), 3.43 (t, *J* = 7.03 Hz, 2H), 2.95 (s, 3H), 1.39 - 1.53 (m, 9H).

^{13}C NMR (500 MHz, DMSO-d_6): δ ppm 174.3, 169.5, 164.0, 161.0, 152.0, 150.5, 148.6, 146.6, 139.0, 128.7, 128.5, 114.5, 110.8, 82.0, 60.6, 55.1, 50.8, 40.6, 36.5, 23.8, 23.7, 17.6.

HRMS: (ES$^+$) Calcd. for $C_{24}H_{29}N_{10}O_{14}S_3$ $[M + H]^+$: 777.1021; Found 777.1022.

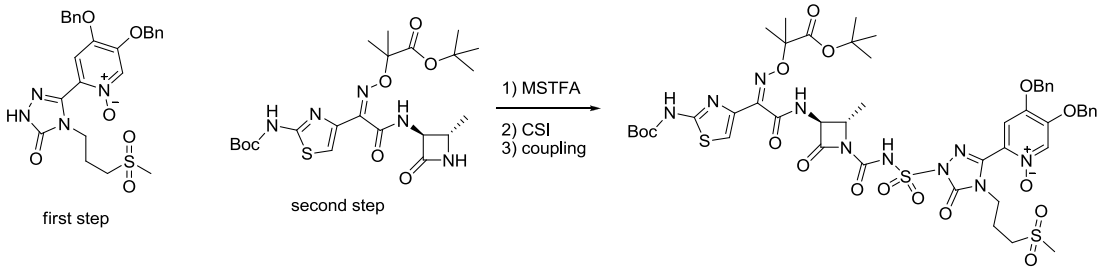
Compound 9b.



4,5-Bis(benzyloxy)-2-(4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (**8b**)**:** Hydrogen peroxide (50 wt % solution in water, 10 mL, 176 mmol) was added to a mixture of 3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**6b**) (1.18 g, 2.39 mmol) in acetic acid (20 mL) and TFA (2 mL). The reaction mixture was heated at 60 °C for 2h. After this time hydrogen peroxide (50 wt% solution in water, 20 mL) was added. The reaction mixture was heated at 60 °C overnight. The reaction was cooled to rt and most of solvent was removed. The residue was diluted with water and neutralized to pH 7 with sat. $NaHCO_3$. The mixture was filtered and the solid was collected and washed with water and dried. The filtrate was extracted with EtOAc twice. The combined organic layers were concentrated. The residue was combined with the solid to be purified by silica gel column (0-50 % MeOH/EtOAc) to give the desired product as a white solid (409 mg, 34%).

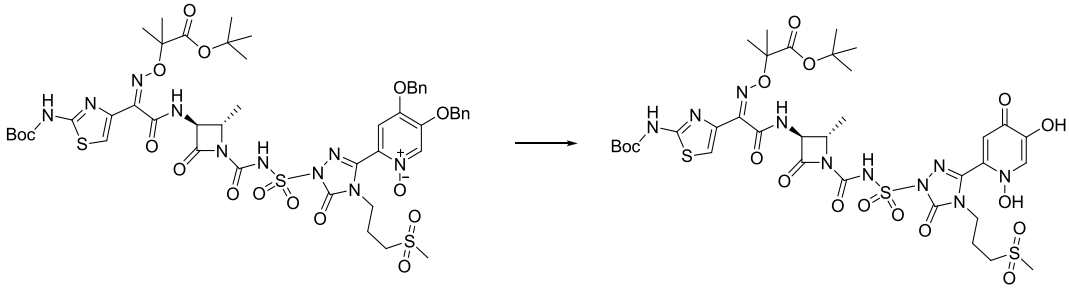
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.16 (s, 1H), 8.33 (s, 1H), 7.50 (s, 1H), 7.33 - 7.46 (m, 10H), 5.25 (s, 2H), 5.22 (s, 2H), 3.67 (t, *J* = 7.03 Hz, 2H), 3.00 - 3.09 (m, 2H), 2.91 (s, 3H), 1.93 (quin, *J* = 7.40 Hz, 2H).

ESI-MS m/z: 511 $[M + H]^+$.



4,5-Bis(benzyloxy)-2-(1-(*N*-((2*S*,3*S*)-3-((*Z*)-2-(((1-(*tert*-butoxy)-2-methyl-1-oxopropan-2-yl)oxy)imino)-2-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)acetamido)-2-methyl-4-oxoazetidine-1-carbonyl)sulfamoyl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide: General procedure C was followed using 4,5-bis(benzyloxy)-2-(4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine-1-oxide (**8b**) (0.40 g, 0.79 mmol) and *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**5**) (0.40 g, 0.79 mmol). The crude was purified by silica gel column (30-100% EtOAc/hexane, then 10-50% MeOH/EtOAc) to give the desired product (428 mg, 48%) as a solid.

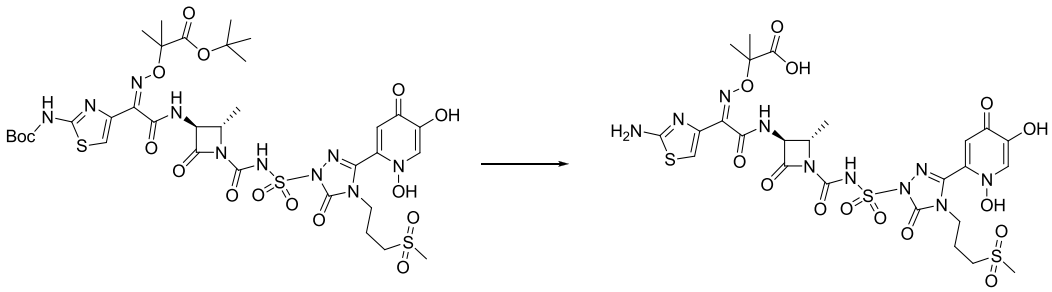
ESI-MS m/z: 1127 $[M + H]^+$.



***tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(1,5-dihydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure D was followed using 4,5-bis(benzyloxy)-2-(1-(*N*-((2*S*,3*S*)-3-((*Z*)-2-(((1-(*tert*-butoxy)-2-methyl-1-oxopropan-

2-yl)oxy)imino)-2-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)acetamido)-2-methyl-4-oxoazetidine-1-carbonyl)sulfamoyl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (0.51 g, 0.45 mmol). The crude was purified by RediSep reverse phase C18 column (50 g, 0-50% MeCN/water with 0.1% formic acid) to give the desired product as a white solid (0.19 g, 46%).

ESI-MS m/z: 947 $[M + H]^+$.



2-(((*Z*)-(1-(2-Aminothiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(1,5-dihydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (9b): General procedure E was followed using *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(1,5-dihydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.19 g, 0.20 mmol). The crude was dissolved in water and purified by RediSep reverse phase C18 column (30 g, 0-20% MeCN/water with 0.1% formic acid) to give the desired product as a solid (62 mg, 38%).

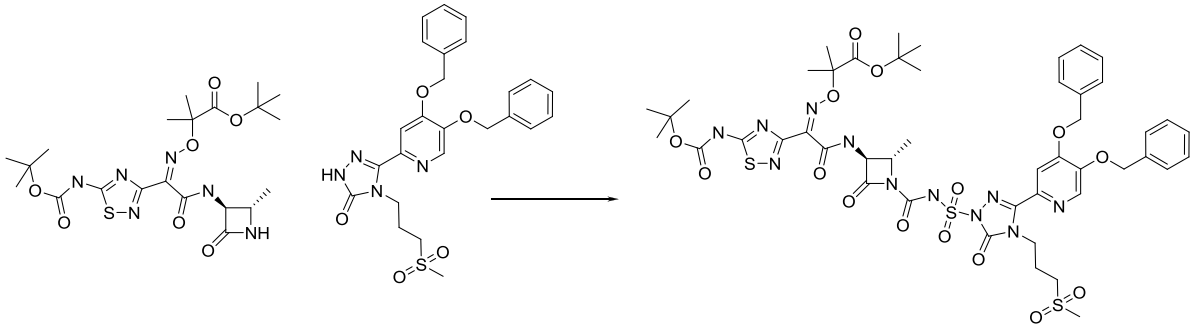
UPLC RT = 0.46 min, MS (ES) MH^+: 791.0 for $C_{25}H_{30}N_{10}O_{14}S_3$

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.06 (d, *J* = 8.03 Hz, 1H), 7.94 (s, 1H), 6.97 (s, 1H), 6.80 (s, 1H), 4.47 (dd, *J* = 2.89, 8.16 Hz, 1H), 3.80 (dd, *J* = 3.01, 6.27 Hz, 1H), 3.69 (t, *J* = 7.03 Hz, 2H), 3.00 - 3.09 (m, 2H), 2.91 (s, 3H), 1.84 - 1.95 (m, 2H), 1.39 - 1.51 (m, 9H).

^{13}C NMR (500 MHz, DMSO-d_6) δ ppm 174.4, 169.3, 164.0, 151.9, 151.2, 147.3, 146.6, 140.5, 139.2, 128.8, 128.6, 114.1, 110.7, 81.8, 60.6, 55.1, 50.6, 40.7, 23.8, 23.7, 21.3, 17.6.

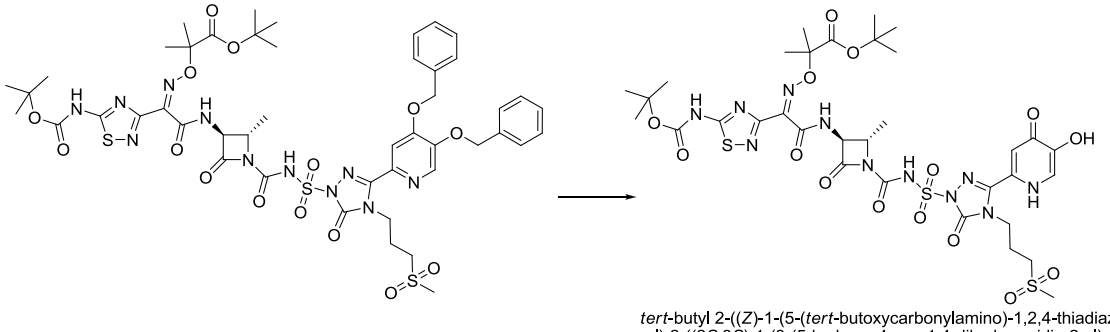
HRMS: (ES$^+$) Calcd. for $C_{25}H_{31}N_{10}O_{14}S_3$ $[M + H]^+$: 791.1178; Found 791.1178.

Compound 10a.



***tert*-Butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(5-((*tert*-butoxycarbonyl)amino)-1,2,4-thiadiazol-3-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure C was followed using *tert*-butyl 2-(((*Z*)-(1-(5-((*tert*-butoxycarbonyl)amino)-1,2,4-thiadiazol-3-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (518 mg, 1.01 mmol) which had been prepared according to literature methods[16] to give the title compound (368 mg, 33% yield) as a white solid.

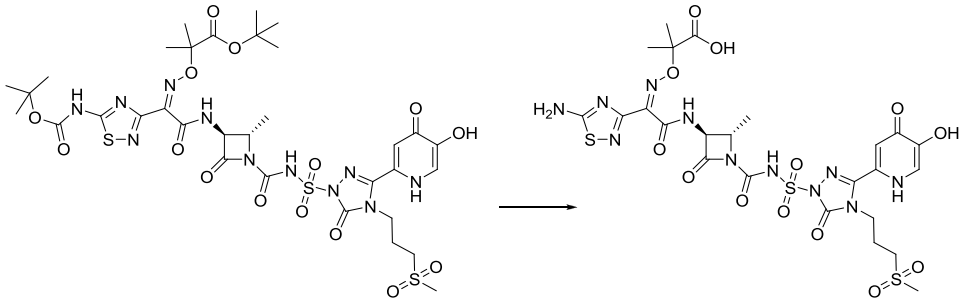
ESI-MS m/z: 1112.0 $[M + H]^+$.



tert-butyl 2-((*Z*)-1-(5-(*tert*-butoxycarbonylamino)-1,2,4-thiadiazol-3-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate

***tert*-Butyl 2-(((*Z*)-(1-(5-((*tert*-butoxycarbonyl)amino)-1,2,4-thiadiazol-3-yl)-2-(((2*S*,3*S*)-1-(((3-(4,5-dihydroxypyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure D was followed using *tert*-butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(5-((*tert*-butoxycarbonyl)amino)-1,2,4-thiadiazol-3-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (370 mg, 0.33 mmol) to give the title compound 96 mg, 31% yield as a white solid.

ESI-MS m/z: 932.0 $[M + H]^+$.



2-((*Z*)-1-(5-amino-1,2,4-thiadiazol-3-yl)-2-((2*S*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid

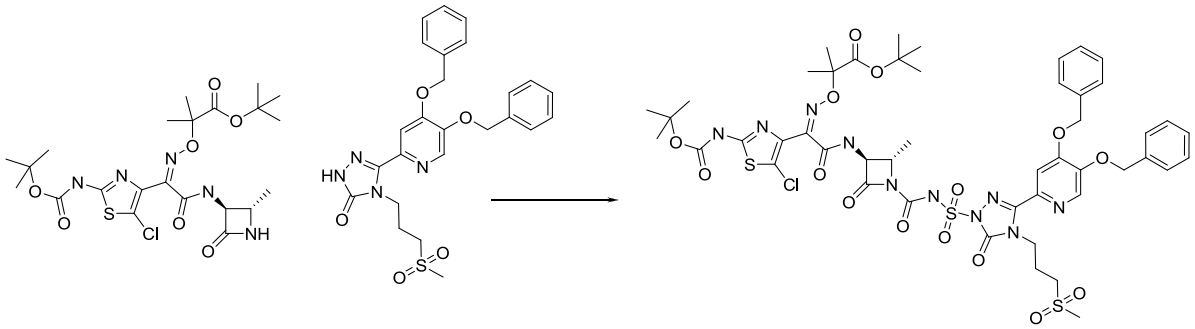
2-(((*Z*)-(1-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (**10a**): General procedure E was followed using *tert*-butyl 2-(((*Z*)-(1-(5-((*tert*-butoxycarbonyl)amino)-1,2,4-thiadiazol-3-yl)-2-(((2*S*,3*S*)-1-(((3-(4,5-dihydroxypyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (96 mg, 0.10 mmol) was deprotected according to previous procedures to give the title compound as a white solid (37 mg, 46%).

UPLC RT = 0.48 min, MS (ES) MH^+: 776.0 for $C_{24}H_{29}N_{11}O_{13}S_3$.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 - 1.50 (m, 9H) 1.92 - 2.15 (m, 2H) 2.95 (s, 3H) 3.04 - 3.21 (m, 2H) 3.35 - 3.55 (m, 1H) 3.72 (dd,*J*=6.12, 2.92 Hz, 1H) 4.13 (t, *J*=6.50 Hz, 2H) 4.47 (dd, *J*=8.29, 2.83 Hz, 1H) 7.35 - 7.45 (m, 1H) 7.97 - 8.38 (m, 3H) 9.02 (d, *J*=8.29 Hz, 1H).

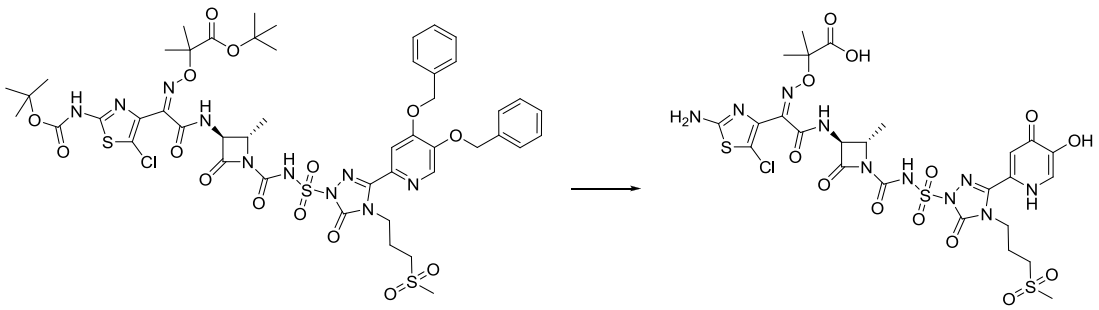
HRMS (ES+) Calcd for $C_{24}H_{30}N_{11}O_{13}S_3$ [M + H]+ 776.1181; Found 776.1181.

Compound 10b.



***tert*-Butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)-5-chlorothiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** The title intermediate was prepared according to General procedure C using *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)-5-chlorothiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (144 mg, 0.26 mmol) which had been prepared according to literature methods[16] to give the title compound (150 mg, 50% yield) as a white solid.

ESI-MS m/z: 1144.9 $[M + H]^+$.



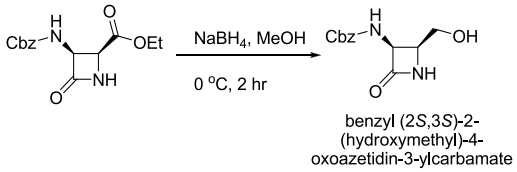
2-(((*Z*)-(1-(2-Amino-5-chlorothiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (**10b**): *tert*-Butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)-5-chlorothiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (150 mg, 0.13 mmol) was deprotected by previous methods using BCl_3 to give the product as a pinkish solid (28 mg, 23%).

UPLC RT = 0.60 min, MS (ES) MH^+: 808.8 for $C_{25}H_{29}ClN_{10}O_{13}S_3$.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.33 - 1.54 (m, 8H) 1.94 - 2.11 (m, 2H) 2.88 - 2.98 (m, 3H) 3.02 - 3.20 (m, 2H) 3.45 (dd, *J*=17.14, 5.09Hz, 1H) 3.73 (br. s., 1H) 4.14 (t, *J*=6.59 Hz, 3H) 4.47 (dd, *J*=8.48, 2.83 Hz, 3H) 7.37 (s, 3H) 8.02 (s, 1H) 8.97 (d, *J*=8.29 Hz, 1H) 9.67 - 10.16(m, 1H).

HRMS (ES+) Calcd for $C_{25}H_{30}ClN_{10}O_{13}S_3$ $[M + H]^+$ 809.0839; Found 809.0833.

Compound 24a.

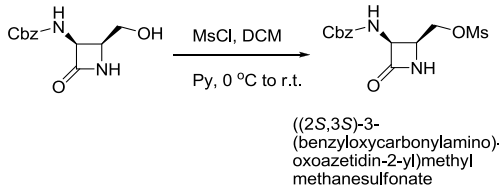


benzyl (2*S*,3*S*)-2-(hydroxymethyl)-4-oxoazetidin-3-ylcarbamate

Benzyl (2*S*,3*S*)-2-(hydroxymethyl)-4-oxoazetidin-3-ylcarbamate: To a solution of (2*R*,3*R*)-ethyl 3-(((benzyloxy)carbonyl)amino)-4-oxoazetidine-2-carboxylate (2.0 g, 4.68 mmol) in MeOH (12 mL) at 0 °C was added sodium borohydride (0.354 g, 9.37 mmol). After two hours of stirring at 0 °C, the reaction was quenched by addition of water (10 mL) and brine (10 mL). The mixture was concentrated *in vacuo* to remove the MeOH; the residual aqueous solution was extracted with EtOAc (2x50 mL). The combined organic

solution was dried with Na_2SO_4, filtered and concentrated *in vacuo* to give a white solid. The crude product was purified by silica gel chromatography (eluted with 0-100% MeOH in CH_2Cl_2) to give the title product (1.70 g, 99%).

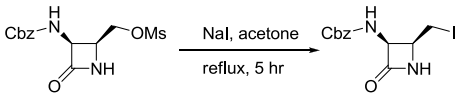
ESI-MS m/z: 251.1 $[M + H]^+$, 273.0 $[M + Na]^+$.



((2*S*,3*S*)-3-(benzyloxycarbonylamino)-4-oxoazetidin-2-yl)methyl methanesulfonate

((2*S*,3*S*)-3-(Benzyloxycarbonylamino)-4-oxoazetidin-2-yl)methyl methanesulfonate: To a solution of benzyl ((2*S*,3*S*)-2-(hydroxymethyl)-4-oxoazetidin-3-yl)carbamate (1.80 g, 7.19 mmol) in CH_2Cl_2 (24 mL) at 0 °C was added pyridine (2.30 mL, 28.8 mmol) and methanesulfonyl chloride (2.9 mL). The mixture was stirred at room temperature until the reaction was complete as judged by HPLC analysis. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ and concentrated by evaporation. The residue was purified by silica gel chromatography (eluted with 0-100% EtOAc in hexane). The product was purified again by slurry in EtOAc at 70 °C for 10 min, cooled and filtered to afford a white solid (1.7 g, 70%).

ESI-MS m/z: 329.0 $[M + H]^+$.



benzyl (2*S*,3*S*)-2-(iodomethyl)-4-oxoazetidin-3-ylcarbamate

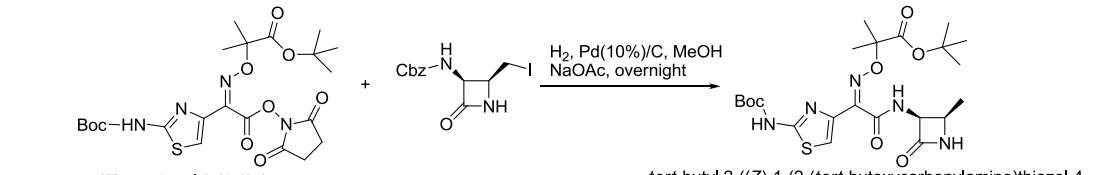
Benzyl (2*S*,3*S*)-2-(iodomethyl)-4-oxoazetidin-3-ylcarbamate (**12**): A solution of ((2*S*,3*S*)-3-(((benzyloxy)carbonyl)amino)-4-oxoazetidin-2-yl)methyl methanesulfonate (1.10 g, 3.35 mmol) and NaI (4.91 g, 32.8 mmol) in acetone (35 mL) was heated at 65 °C overnight. Solvent was removed by evaporation. The solid residue was dissolved in EtOAc (500 mL),

washed with a dilute solution of sodium thiosulfate ($Na_2S_2O_3$) and brine, dried over Na_2SO_4 and evaporated to give a white solid, which was recrystallizated from EtOAc (1.05 g, 87%).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.54 (s, 1H), 8.04 (d, *J*=10.01 Hz, 1H), 7.31-7.40 (m, 5 H), 5.07 (s, 2 H), 4.93 (ddd, *J*=10.01, 4.91, 1.32 Hz), 4.00 (td, *J*=7.27, 4.91 Hz, 1H), 3.16-3.32 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 167.1, 155.7, 136.7, 128.3, 127.8, 65.8, 60.2, 54.5, 5.1.

ESI-MS m/z: 361.0 $[M + H]^+$, 383.0 $[M + Na]^+$



(*Z*)-*tert*-butyl 2-(1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-(2,5-dioxopyrrolidin-1-yloxy)-2-oxoethylideneaminooxy)-2-methylpropanoate

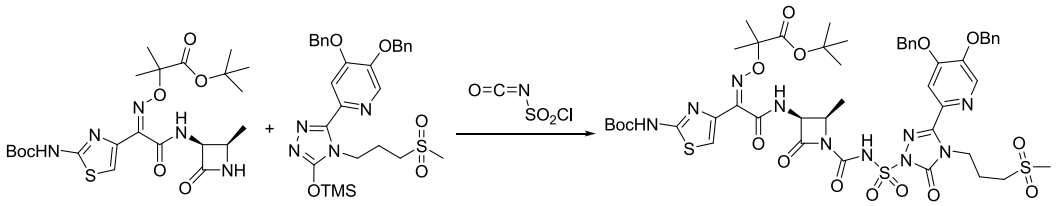
tert-butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((2*R*,3*S*)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate

***tert*-Butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((2*R*,3*S*)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate** (**14a**): A mixture of benzyl ((2*S*,3*S*)-2-(iodomethyl)-4-oxoazetidin-3-yl)carbamate (528 mg), Pd/C (10%, 250 mg) and NaOAc (470 mg) in MeOH (12 mL) was degassed/back-refilled with H_2 and stirred under H_2 (balloon) overnight. Pd/C was removed by filtration through a celite pad and rinsed with MeOH. The clear filtrate was concentrated to about 15-20 mL, cooled by ice-water bath and (*Z*)-*tert*-butyl 2-(((1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-((2,5-dioxopyrrolidin-1-yl)oxy)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**23**) (822 mg) was added. The suspension was stirred at room temperature for 8 h to give a clear solution. The reaction was concentrated to about 3 mL and was loaded onto a 40 gram silica gel column (eluting with 20% -100% EtOAc in hexane) to give an off-white solid (377 mg, 50%).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.00 (d, *J*=8.12 Hz, 1H), 7.37 (s, 1H), 6.04 (s, 1H), 5.42 (ddd, *J*=8.21, 5.10, 1.42 Hz, 1H), 4.06 - 4.18 (m, 2 H), 1.64 (s, 3H), 1.61 (s, 3H), 1.55 (s, 9H), 1.46 (s, 9H), 1.34 (d, *J*=6.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$), δ ppm 173.8, 166.5, 162.1, 152.0, 115.3, 83.4, 82.2, 60.4, 59.3, 50.4, 28.1, 27.9, 23.9, 23.7, 21.0, 20.8, 16.6, 14.2.

ESI-MS m/z: 512.2 $[M + H]^+$.



tert-butyl 2-((*Z*)-2-((2*R*,3*S*)-1-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-oxoethylideneaminooxy)-2-methylpropanoate

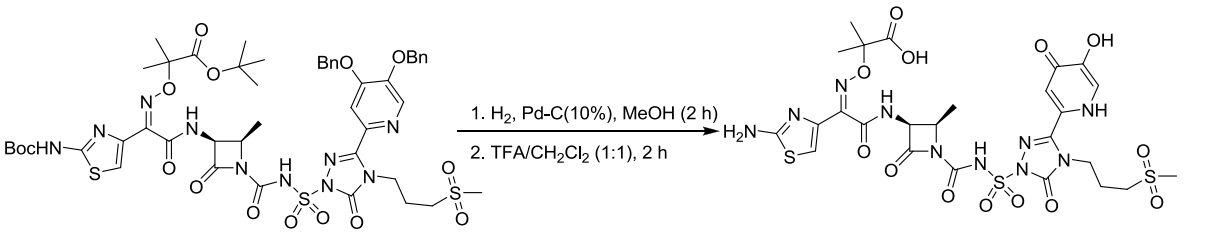
***tert*-Butyl 2-((*Z*)-2-((2*R*,3*S*)-1-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-**

methyl-4-oxoazetidin-3-ylamino)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-oxoethylideneaminooxy)-2-methylpropanoate: Solution **A**: To a solution of 3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (261 mg, 0.53 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was added 2,2,2-trifluoro-*N*-methyl-*N*-(trimethylsilyl)acetamide (802 mg). The clear solution was stirred at room temperature for 1h. Solvent was removed by evaporation and the residue was dried under high vacuum for 1h to remove excess reagent and 2,2,2-trifluoro-*N*-methylacetamide. The residue was dissolve in anhydrous CH_2Cl_2 (2 mL) ready for use in next step.

Solution B: To a clear solution of *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*R*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**14a**) (270 mg, 0.53 mmol) in anhydrous CH_2Cl_2 (2 mL) at -78 °C was added chlorosulfonyl isocyanate (75.0 mg, 0.53 mmol). After stirring at -78 °C for 35 min, the mixture was warmed to 0 °C for 15 min and ready for use in the next step.

To the cold solution **A** at -78 °C was added solution **B**. The mixture was stirred from -78 °C to room temperature overnight. The reaction was concentrated and was loaded onto a 20 gram silica gel column and eluted with 0-5% MeOH/CH_2Cl_2 to give 400 mg of product, which was further purified by reverse phase HPLC (MeCN/H_2O with 0.05% TFA) to give a white solid (65 mg, 11%).

ESI-MS m/z: 1111.3 $[M+H]^+$.



2-((*Z*)-1-(2-aminothiazol-4-yl)-2-((2*R*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid

2-((*Z*)-1-(2-Aminothiazol-4-yl)-2-((2*R*,3*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-

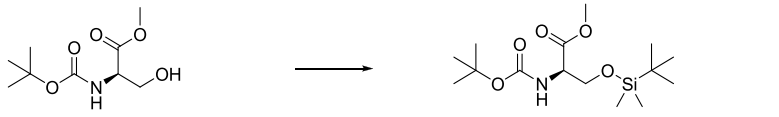
yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-methyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid (**24a**): To a 25 mL round-bottom flask at -78 ^{o}C under nitrogen was charged Pd-C (10%, 60 mg), MeOH (2 mL) and a solution of *tert*-butyl 2-(((*Z*)-(2-(((2*R*,3*S*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (64 mg, 0.06 mmol) in MeOH (4 mL). The mixture was evacuated/back refilled with H_2 and stirred at room temperature until the reaction was complete. Pd-C was removed by filtration through a short celite pad and the filtrate was concentrated. The crude product was dissolved in CH_2Cl_2 (1 mL), and cooled by dry ice acetone bath. TFA (1 mL) was added. The mixture was warmed to room temperature and stirred for 3 hours. Solvent and excess TFA were removed by evaporation. The sample was purified by reverse phase HPLC purification (30-60% MeOH/H_2O with 0.1% TFA) (17.1 mg, 38%).

UPLC RT = 0.45 min, MS (ES) MH^+ 775.0 for $C_{25}H_{30}N_{10}O_{13}S_3$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.18 (d, *J*=8.69, 1H), 8.04 (s, 1H), 7.38 (s, 1H), 6.82 (s, 1 H), 5.75 (s, 2H), 5.14 (dd, *J*=8.59,5.95 Hz, 2H), 4.12 (m, 2H), 3.12 (m, 1H), 2.95 (s, 2H), 2.05 (m, 1H), 1.44 (d, *J*=9.44 Hz, 5H), 1.26 (d, *J*=6.23 Hz, 3H).

HRMS (ES+) Calcd for $C_{25}H_{31}N_{10}O_{13}S_3$ $[M + H]^+$ 775.1229; Found 775.1222.

Compounds 14b and **14c.**



(*R*)-methyl 2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate

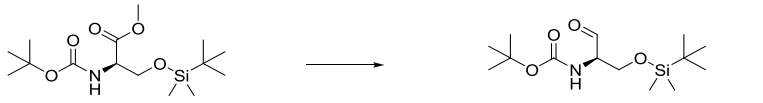
(*R*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)propanoate

(*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)propanoate: To a solution of (*R*)-methyl 2-(*tert*-butoxycarbonylamino)-3 hydroxypropanoate (**15**) (445 g,

2.02 mol) in dimethylformamide (4.5 L) was added imidazole (414 g, 6.08 mol), followed by chloro-*tert*-butyldimethylsilane (336 g, 2.23 mol) and the reaction mixture was allowed to stir for 4 h at room temperature. The solvents were removed *in vacuo* and the crude material was dissolved in ethyl acetate (5 L). The solution was washed with saturated ammonium chloride (2 × 2 L), then with saturated sodium bicarbonate (2.0 L), and saturated sodium chloride solution (1.0 L). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to yield the product as an oil that was used in the next step without further purification (738 g, quantitative).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.36 ppm (d, *J* = 7.5 Hz, 1H), 4.37 (d, *J* = 8.7 Hz, 1H), 4.08 (dd, *J* = 10.1, 2.7 Hz, 1H), 3.83 (dd, *J* = 10.1, 3.0 Hz, 1H), 3.76 (s, 3H), 1.48 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H)

ESI-MS m/z: 234 $[M\text{-BOC} + H]^+$.

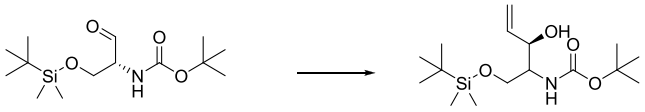


(*R*)-*tert*-butyl 1-(*tert*-butyldimethylsilyloxy)-3-oxopropan-2-ylcarbamate

(*R*)-*tert*-Butyl 1-(*tert*-butyldimethylsilyloxy)-3-oxopropan-2-ylcarbamate: In a 3-neck round bottom flask purged with argon, (*R*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)propanoate (50.0 g, 0.150 mol) was dissolved in dry toluene (650 mL) and cooled to -78 °C. To this solution was added diisobutylaluminum hydride (292 mL, 0.292 mol, 1.0M in toluene) dropwise so as to keep the internal temperature below -70 °C. The reaction mixture was held at that temperature for 60 minutes. After completion of the reaction (as judged by TLC - 20% ethyl acetate/hexanes - ninhydrin), the reaction mixture was quenched *via* slow addition of methanol (200 mL). The reaction mixture was concentrated under reduced pressure and the crude residue was partitioned between ethyl acetate (1.5 L) and cold 10% hydrochloric acid (500 mL). The organic layer was separated, washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and then

concentrated to yield the product as a colorless oil (40 g, 88%). The crude reaction mixture was used as such in the next step without further purification.

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 9.5 (s, 1H), 6.99 (d, J = 8.1 Hz, 1H), 3.78 (d, J = 5.4 Hz, 1H), 3.63 (s, 2H), 1.38 (s, 9H), 0.84 (s, 9H), 0.01 (s, 6H).



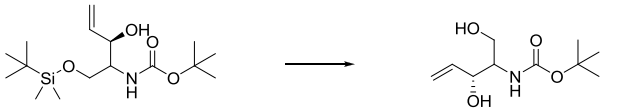
tert-butyl (3*R*)-1-(*tert*-butyldimethylsilyloxy)-3-hydroxypent-4-en-2-ylcarbamate

***tert*-Butyl (3*R*)-1-(*tert*-butyldimethylsilyloxy)-3-hydroxypent-4-en-2-ylcarbamate (16):** In a 3-neck round bottom flask purged with argon, (*R*)-*tert*-butyl 1-(*tert* butyldimethylsilyloxy)-3-oxopropan-2-ylcarbamate (40.0 g, 0.132 mol) was dissolved in dry dichloromethane (600 mL) and cooled to -78 °C. To this solution was added vinylmagnesium bromide (276 mL, 0.276 mol, 1.0 M in tetrahydrofuran) dropwise so as to keep the internal temperature below 0 °C. The reaction mixture was held at that temperature for 1 h. The reaction mixture was then allowed to warm to room temperature and stirred for 12 h. After completion of the reaction (as judged by TLC - 20% ethyl acetate/hexanes - ninhydrin), the reaction mixture was cooled to 0 °C and quenched *via* slow addition of methanol (40 mL). The reaction mixture was concentrated by rotary evaporation to remove the dichloromethane organic phase. The reaction residue was then diluted with water and extracted with ethyl acetate. An emulsion formed. The whole reaction mixture was filtered through a pad of Celite. The organic layer was separated, washed with saturated sodium chloride solution and then dried with sodium sulfate. The solids were removed by filtration. The mother liquor was concentrated to a crude oil. The crude reaction mixture was purified by silica gel flash column chromatography (0 - 20% ethyl acetate/hexanes) to yield the pure product as a mixture of diastereomers (15 g, 34%)

^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 5.92-5.81 (m, 1H), 5.43-5.19 (m, 2H), 5.13 (d, J = 7.8

Hz, 1H), 4.48 (brs, 1H), 3.97-3.82 (m, 2H), 3.68 (brs, 1H), 3.45 (brs, 1H), 1.47 (s, 9H), 0.92 (s, 9H), 0.10 (s, 6H).

ESI-MS m/z: 232 $[M\text{-BOC} + H]^+$.

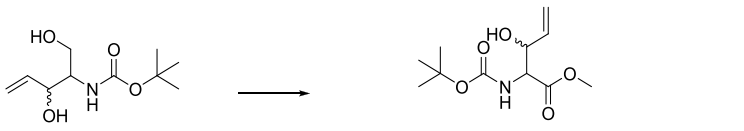


tert-butyl (3*R*)-1,3-dihydroxypent-4-en-2-ylcarbamate

***tert*-Butyl (3*R*)-1,3-dihydroxypent-4-en-2-ylcarbamate:** To a solution of *tert*-Butyl (3*R*)-1-(*tert*-butyldimethylsilyloxy)-3-hydroxypent-4-en-2-ylcarbamate (60.0 g, 0.18 mol) in methanol (180 mL) was added 2N hydrochloric acid (90 mL) at room temperature. After the reaction mixture was stirred at the same temperature for 15 min, saturated sodium chloride was added and the resulting mixture was extracted with ethyl acetate (3 × 250 mL). The organic layers were combined, washed with saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (30% to 50% ethyl acetate in hexane) to the product as a mixture of diastereomers (17 g, 43%).

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 6.06 (d, J = 8.1 Hz, 1H), 5.89-5.77 (m, 1H), 5.22-5.14 (m, 1H), 5.07 (d, J = 10.2 Hz, 1H), 4.80 (d, J = 6.3 Hz, 1H), 4.63-4.59 (m, 1H), 4.16 (brm, 1H), 3.48-3.42 (m, 2H), 3.34-3.26 (m, 1H), 1.35 (s, 9H).

ESI-MS m/z: 118 $[M\text{-BOC} + H]^+$.



methyl 2-(*tert*-butoxycarbonylamino)-3-hydroxypent-4-enoate

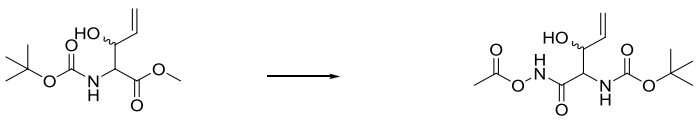
(3*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-hydroxypent-4-enoate (**17**)**:** To a solution of *tert*-butyl (3*R*)-1,3-dihydroxypent-4-en-2-ylcarbamate (17.0 g, 0.078 mol) in acetone (255 mL) containing 2,2,6,6 tetramethylpiperidine 1-oxyl (2.4 g, 0.016 mol) was added a 5% aqueous sodium bicarbonate solution (187 mL) buffered to pH = 9.1. The mixture was

cooled to 0 °C and sodium hypochlorite (435 mL, ca. 4-4.9% w/w) was added dropwise over 15 min while following the reaction by TLC. Ethyl acetate was added to the reaction mixture and the mixture was stirred. The organic layer was separated. The aqueous solution was acidified to pH = 2-3, with 2N hydrochloric acid and then extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated sodium chloride solution (100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The intermediate, (*S*)-2-*tert*-butoxycarbonylamino-3-hydroxy-pent-4-enoic acid, (9.0 g, 50%) was used in the next step without further purification.

To a solution of (*S*)-2-*tert*-butoxycarbonylamino-3-hydroxy-pent-4-enoic acid, (9.0 g, 0.038mol) in dimethylformamide (90 mL) at 0 °C was added potassium carbonate (8.0 g, 0.058 mol) and the reaction was stirred for 10 min prior to the addition of iodomethane (9.5 mL, 0.15 mol). The mixture was stirred for 45 min at 0 °C then allowed to warm to room temperature and kept for 90 min. After this time ethyl acetate (200 mL) and water (600 mL) were added, allowing the separation of the layers. The organic extract was washed with saturated sodium chloride solution (100 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% ethyl acetate in hexane) to yield the product as a colorless solid (5.5 g, 57%).

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 6.54 (d, J = 8.7 Hz, 1H), 5.90-5.79 (m, 1H), 5.36-5.08 (m, 3H), 4.41 (brs, 1H), 4.20-4.17 (m, 1H), 3.65 (s, 3H), 1.38 (s, 9H).

ESI-MS m/z: 146 $[M\text{-BOC} + H]^+$.



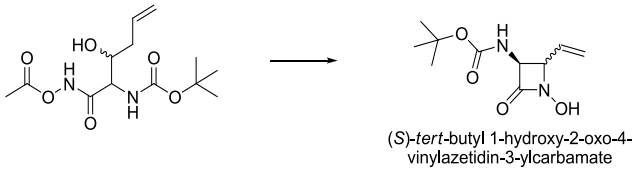
tert-butyl (3*S*)-1-(acetoxyamino)-3-hydroxy-1-oxopent-4-en-2-ylcarbamate

***tert*-Butyl (3*S*)-1-(acetoxyamino)-3-hydroxy-1- oxopent-4-en-2-ylcarbamate:** A solution of (3*S*)-methyl 2-(*tert*-butoxycarbonylamino)-3-hydroxypent-4-enoate (5.5 g, 0.022 mol) in

methanol (50 mL) was cooled to 0 °C and treated with a suspension of hydroxylamine hydrochloride (4.7 g, 0.067 mol) and potassium hydroxide (7.5 g, 0.13 mol) in methanol (165 mL). After completion of addition, the reaction mixture was stirred at the same temperature for 45 min. After this time, acetic anhydride (2.28 g, 2.1 mL, 0.13 mol) was added dropwise at 0 °C. After stirring for 30 minutes more, TLC indicated complete consumption of starting material. The mixture was poured into 5% sodium bicarbonate (200 mL) and extracted with ethyl acetate (3 × 100 mL). The organic phase was separated. The aqueous solution was acidified carefully with 10% citric acid solution to pH=3. The aqueous layer was then extracted with ethyl acetate (3 × 100 mL). The organics were pooled, washed with water (2 × 100 mL), saturated sodium chloride (100 mL), dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography **(**silica gel, 0-100% ethyl acetate in hexane) to yield the product as a colorless solid (3.6 g, 56%).

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 11.58 (brs, 1H), 6.39 (d, J = 9.0 Hz, 1H), 5.90-5.76 (m, 1H), 5.25 (d, J = 17.1 Hz, 2H), 5.11 (d, J = 10.2 Hz, 1H), 4.30 (brs, 1H), 4.02-4.06 (m, 1H), 2.15 (s, 3H), 1.30 (s, 9H).

ESI-MS m/z: 287 $[M - H]^-$.



(*S*)-*tert*-butyl 1-hydroxy-2-oxo-4-vinylazetidin-3-ylcarbamate

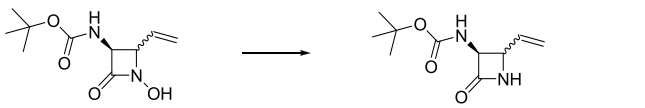
(*S*)-*tert*-Butyl 1-hydroxy-2-oxo-4-vinylazetidin-3-ylcarbamate: To a 0 °C solution of *tert*-butyl (3*S*)-1-(acetoxyamino)-3-hydroxy-1- oxopent-4-en-2-ylcarbamate (10.5 g, 0.036 mol) in tetrahydrofuran (300 mL) was added triphenylphosphine (10.5 g, 0.04 mol) followed by diisopropyl azodicarboxylate (8.1 g, 0.04 mol). The reaction was allowed to attain room temperature and stir for 2 h. After this time, TLC indicated consumption of starting material

and formation of the desired product. The reaction mixture was concentrated. The yellow viscous liquid obtained was taken as such to the next step.

The crude residue was taken-up in a 1:1 methanol, water mixture (100 mL) and cooled to 0 °C. Once dissolved, solid sodium carbonate (9.65 g, 0.091 mol) was added and the reaction mixture was stirred vigorously at the same temperature. After 2 h, TLC indicated consumption of starting material and formation of the desired product. The reaction mixture was filtered through a Celite bed. To the filtrate 5% sodium bicarbonate (300 mL) was added and the solution was extracted with ethyl acetate (2 × 100 mL) to remove unwanted by-products. The aqueous solution was acidified with 3N hydrochloric acid to pH=3. The aqueous layer was then extracted with ethyl acetate (3 × 100 mL). The organics were pooled, washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. The crude material was recrystallized with diethyl ether to yield the product as a mixture of diastereomers (5 g, 60%).

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 10.22 (s, 1H), 7.68 (d, J = 4.8 Hz, 1H), 5.97-5.74 (m, 1H), 5.46 (d, J = 9.9 Hz, 1H), 5.26 (d, J = 9.0 Hz, 1H), 4.10 (d, J = 8.4 Hz, 1H), 4.04 (d, J = 8.1 Hz, 1H), 1.39 (s, 9H).

ESI-MS m/z: 227 $[M - H]^-$.



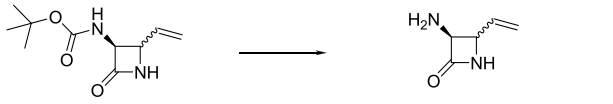
(*S*)-*tert*-butyl 2-oxo-4-vinylazetidin-3-ylcarbamate

(*S*)-*tert*-Butyl 2-oxo-4-vinylazetidin-3-ylcarbamate (18): To a solution of (*S*)-*tert*-butyl 1-hydroxy-2-oxo-4-vinylazetidin-3-ylcarbamate (5.0 g, 21.9 mmol) in methanol (100 mL) was added ammonium acetate (33.8 g, 438 mmol) under nitrogen atmosphere. The reaction mixture was cooled to 0-5 °C and titanium (III) chloride (75 mL, 53.6 mmol, 10% in hydrochloric acid) was added dropwise with constant stirring. The pH of the reaction mixture was then adjusted to pH=7 using 2N sodium hydroxide solution. The mixture was

allowed to attain room temperature and stir for 2h. After completion, *dl*-tartaric acid (4.6 g, 43.8 mmol) was added and the pH of the reaction mixture was adjusted to pH=9 using 2N sodium hydroxide solution. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over sodium sulphate and concentrated *in vacuo*. The crude product was re-crystallized using dichloromethane and hexane to yield the product as colorless solid (2.4 g, 52%).

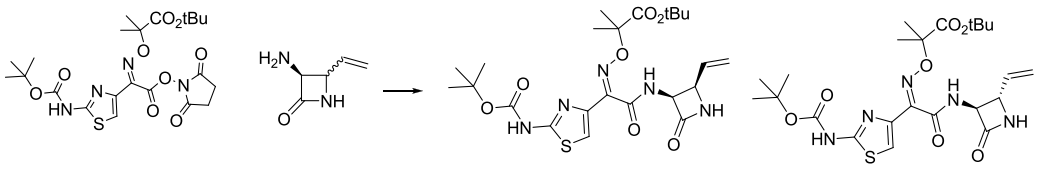
^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 8.30 (s, 1H), 7.63 (d, J = 8.7 Hz, 1H), 6.04-5.93 (m, 1H), 5.31 (d, J = 16.8 Hz, 1H), 5.16 (d, J = 10.2 Hz, 1H), 4.19 (dd, J = 9.0, 3.0 Hz, 1H), 4.16 (dd, J = 6.0, 3.0 Hz, 1H), 1.39 (s, 9H).

ESI-MS m/z: 157 $[M - 56]^+$, 113 $[M – BOC+H]^+$



(3*S*)-3-Amino-4-vinylazetidin-2-one: TFA (4 mL, 53.85 mmol) was added to a solution of *tert*-butyl ((3*S*)-2-oxo-4-vinylazetidin-3-yl)carbamate (0.514 g, 2.42 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The reaction was stirred at rt for 1h. The reaction solution was concentrated under reduced pressure to give the crude product as an oil, which was used in next step without purification.

ESI-MS m/z: 112.0 $[M + H]^+$.



***tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxo-2-(((3*S*,4*S*)-2-oxo-4-vinylazetidin-3-yl)amino)ethylidene)amino)oxy)-2-methylpropanoate** and ***tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxo-2-(((3*S*,4*R*)-2-oxo-4-vinylazetidin-3-yl)amino)ethylidene)amino)oxy)-2-methylpropanoate** (**14b** and **14c**)**:** A

solution of (3*S*)-3-amino-4-vinylazetidin-2-one-TFA salt (0.271 g, 2.42 mmol) in ethanol (2.0 mL) was added to a mixture of (*Z*)-*tert*-butyl 2-(((1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-((2,5-dioxopyrrolidin-1-yl)oxy)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**23**) (1.40 g, 2.66 mmol) in dry toluene (9.0 mL), followed by 4-methyl morpholine (0.798 mL, 7.26 mmol). The reaction solution was stirred at room temperature overnight. The reaction solution was concentrated. The crude material was purified by silica gel flash column chromatography (0-80% EtOAc/hexanes) to give the desired two products as white solids.

***cis*-isomer (14b):**

***tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxo-2-(((3*S*,4*R*)-2-oxo-4-vinylazetidin-3-yl)amino)ethylidene)amino)oxy)-2-methylpropanoate** (**14b**) (160 mg, 13%):

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.82 (s, 1 H) 9.08 (d, *J*=9.03 Hz, 1 H) 8.47 (s, 1 H) 7.19 (s, 1 H) 5.92 (ddd, *J*=17.19, 10.16, 7.03 Hz, 1 H) 5.17 - 5.37 (m, 3 H) 4.23 - 4.33 (m, 1 H) 1.46 (s, 9 H) 1.42 (s, 3 H) 1.39 (s, 12 H).

ESI-MS m/z: 524 $[M + H]^+$.

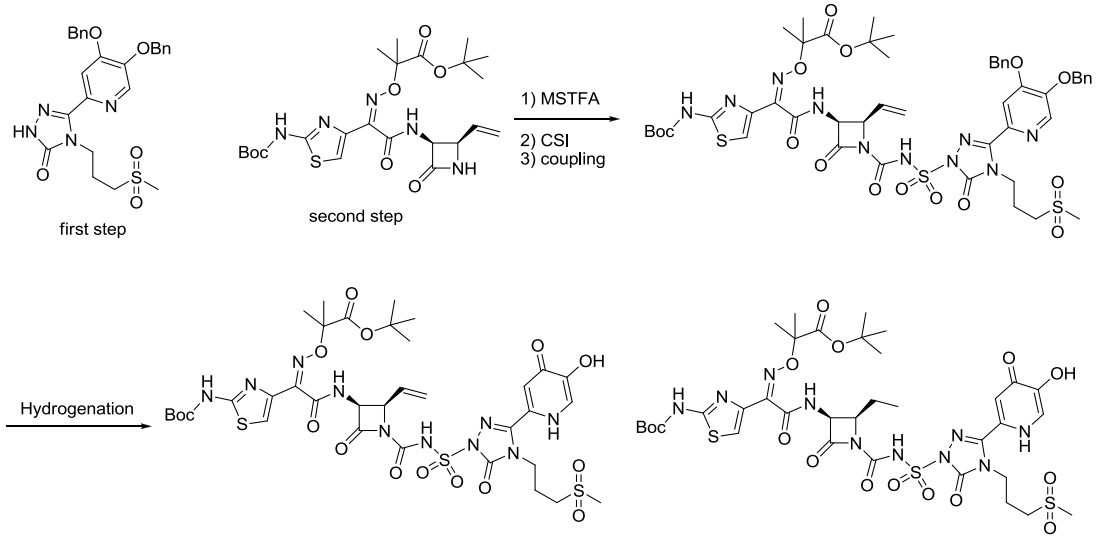
***trans*-isomer (14c):**

***tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxo-2-(((3*S*,4*S*)-2-oxo-4-vinylazetidin-3-yl)amino)ethylidene)amino)oxy)-2-methylpropanoate** (**14c**) (662 mg, 52%):

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.82 (s, 1 H) 9.10 (d, *J*=8.28 Hz, 1 H) 8.46 (s, 1 H) 7.25 (s, 1 H) 6.05 (ddd, *J*=17.07, 10.29, 6.78 Hz, 1 H) 5.33 (d, *J*=17.32 Hz, 1 H) 5.21 (d, *J*=10.54 Hz, 1 H) 4.56 (dd, *J*=8.28, 2.26 Hz, 1 H) 3.98 - 4.04 (m, 1 H) 1.47 (s, 9 H) 1.38 - 1.43 (m, 15 H).

ESI-MS m/z: 524 $[M + H]^+$.

Compound 25b.

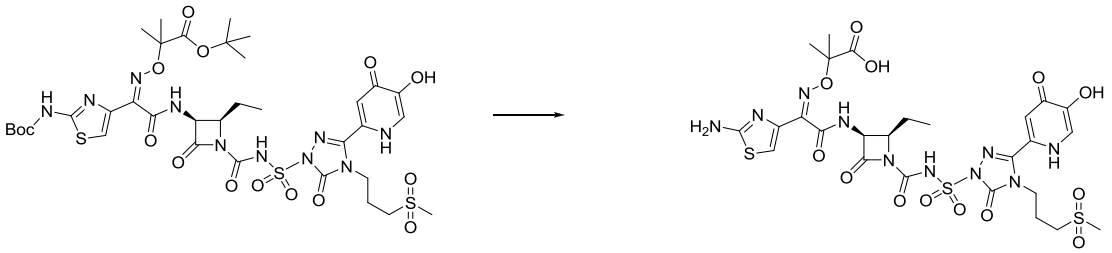


***tert*-Butyl 2-(((*Z*)-(2-(((3*S*,4*R*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-oxo-4-vinylazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure C was followed using 3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**6b**) (0.15 g, 0.30 mmol) and *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxo-2-(((3*S*,4*R*)-2-oxo-4-vinylazetidin-3-yl)amino)ethylidene)amino)oxy)-2-methylpropanoate (**14b**) (0.16 g, 0.30 mmol). The crude was purified by C18 reverse phase (20-70% MeCN/water with 0.1% formic acid) to give the desired product as a white solid, which was used in the next step.

ESI-MS m/z: 1123 $[M + H]^+$.

***tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*R*,3*S*)-2-ethyl-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure D was followed using *tert*-butyl 2-(((*Z*)-(2-(((3S,4*R*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-

(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-oxo-4-vinylazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.34 g, 0.30 mmol). The crude was purified by ISCO RediSep reverse phase C18 column (50 g, 10-60 % MeCN/water with 0.1% formic acid) to give *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((3*S*,4*R*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-oxo-4-vinylazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (20 mg, 7% for two steps, ESI-MS m/z: 943 $[M + H]^+$) and *tert*-butyl 2-(((Z)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*R*,3*S*)-2-ethyl-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (20 mg, 7% for two steps, ESI-MS m/z: 945 $[M + H]^+$).



2-(((*Z*)-(1-(2-Aminothiazol-4-yl)-2-(((2*R*,3*S*)-2-ethyl-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (25b): General procedure E was followed using *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*R*,3*S*)-2-ethyl-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.020 g, 0.02 mmol). The crude material was purified by ISCO RediSep

reverse phase C18 column (30 g, 0-20 % MeCN/water with 0.1% formic acid) to give the desired product as a white solid (11 mg, 66%).

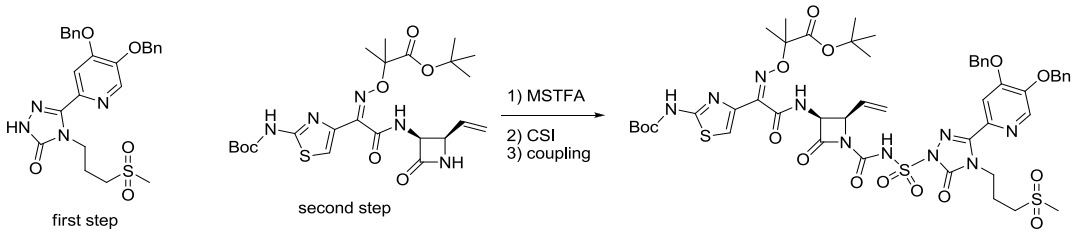
UPLC RT = 0.54 min, MS (ES) MH^+: 789.2 for $C_{26}H_{32}N_{10}O_{13}S_3$

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.67 (s, 1 H) 8.68 (d, *J*=7.78 Hz, 1 H) 8.03 (s, 1 H) 7.38 (s, 1 H) 7.01 (s, 1 H) 5.74 - 5.86 (m, 1 H) 5.49 (ddd, *J*=15.37, 6.09, 1.63 Hz, 1 H) 4.08 - 4.18 (m, 2 H) 3.07 - 3.15 (m, 2 H) 2.95 (s, 3 H) 1.98 - 2.09 (m, 2 H) 1.60 (d, *J*=6.27 Hz, 2 H) 1.39 - 1.46 (m, 9 H).

^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 174.6, 152.0, 144.3, 142.6, 138.7, 136.5, 125.9, 109.7, 81.7, 50.9, 23.8, 22.0, 17.4, 10.4.

HRMS: (ES^+) Calcd. for $C_{26}H_{33}N_{10}O_{13}S_3$ $[M + H]^+$: 789.1385; Found 789.1396.

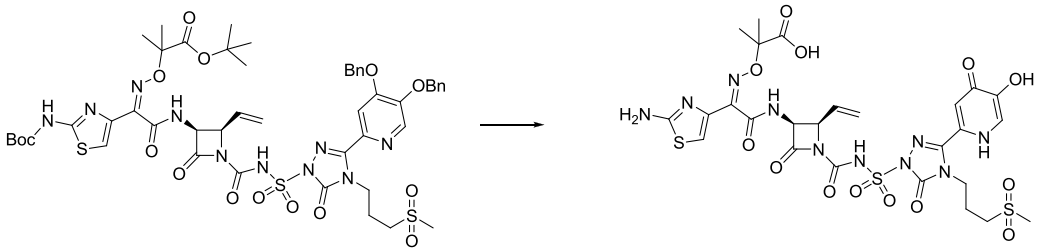
Compound 24b.



***tert*-Butyl 2-(((*Z*)-(2-(((3*S*,4*R*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-oxo-4-vinylazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** General procedure C was followed using 3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**6b**) (0.17 g, 0.34 mmol) and *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxo-2-(((3*S*,4*R*)-2-oxo-4-vinylazetidin-3-yl)amino)ethylidene)amino)oxy)-2-methylpropanoate (**14b**) (0.18 g, 0.34 mmol). The crude was purified by silica gel column (0-60% of 10% EtOAc /MeOH in DCM), then purified by C18 reverse phase (20-70% MeCN/water with 0.1% formic acid) to give the desired product as a white solid (185 mg, 48%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.81 (s, 1 H) 9.05 (d, *J*=8.78 Hz, 1 H) 8.38 (s, 1 H) 7.62 (s, 1 H) 7.27 - 7.53 (m, 10 H) 7.18 (s, 1 H) 5.73 - 5.87 (m, 1 H) 5.14 - 5.35 (m, 7 H) 4.47 - 4.57 (m, 1 H) 4.15 (t, *J*=7.65 Hz, 2 H) 3.08 - 3.17 (m, 2 H) 2.94 (s, 3 H) 2.00 - 2.12 (m, 2 H) 1.46 (s, 9 H) 1.34 - 1.41 (m, 15 H).

ESI-MS m/z: 1123 $[M + H]^+$.



2-(((*Z*)-(1-(2-Aminothiazol-4-yl)-2-(((3*S*,4*R*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-oxo-4-vinylazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (**24b**)**:** A solution of *tert*-butyl 2-(((*Z*)-(2-(((3*S*,4*R*)-1-(((3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-oxo-4-vinylazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (0.183 g, 0.17 mmol) in dichloromethane (3.5 mL) was cooled to -10 °C and trichloroborane, 1M in dichloromethane (1.63 mL, 1.63 mmol) was added dropwise. The reaction mixture was warmed to 10 °C over 1h with stirring, then the cold bath was removed and the reaction slurry was stirred at rt for 15min. The reaction mixture was concentrated. The residue was dissolved in 1M ammonium formate and DMSO, then purified twice by reverse phase column (C-18 column, 0-20% acetonitrile/water, both with 0.1% formic acid) to give the desired product as a white solid (15 mg, 12%).

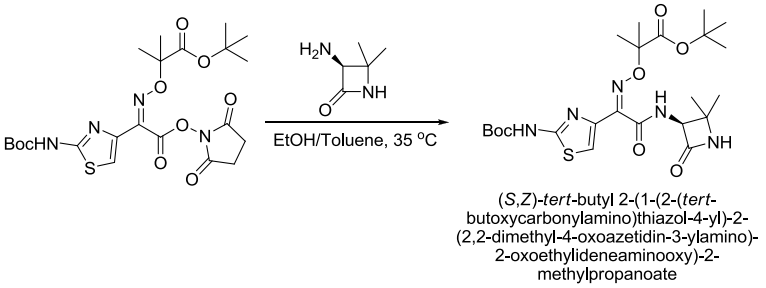
UPLC RT = 0.49 min, MS (ES) MH^+: 787.2 for $C_{26}H_{30}N_{10}O_{13}S_3$

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.08 (d, *J*=8.78 Hz, 1 H) 8.03 (s, 1 H) 7.37 (s, 1 H) 6.74 (s, 1 H) 5.79 (ddd, *J*=17.44, 10.29, 7.40 Hz, 1 H) 5.15 - 5.34 (m, 3 H) 4.47 - 4.57 (m, 1 H) 4.12 (t, *J*=6.90 Hz, 2 H) 3.04 - 3.14 (m, 2 H) 2.94 (s, 3 H) 1.92 - 2.10 (m, 2 H) 1.44 (s, 3 H) 1.42 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 174.5, 169.3, 163.7, 163.1, 161.1, 155.3, 152.9, 152.0, 151.8, 144.3, 142.5, 138.6, 136.3, 133.3, 119.8, 110.6, 109.8, 82.0, 58.9, 56.9, 50.9, 23.9, 23.7, 22.1.

HRMS: (ES$^+$) Calcd. for $C_{26}H_{31}N_{10}O_{13}S_3$ $[M + H]^+$: 787.1229; Found 787.1223.

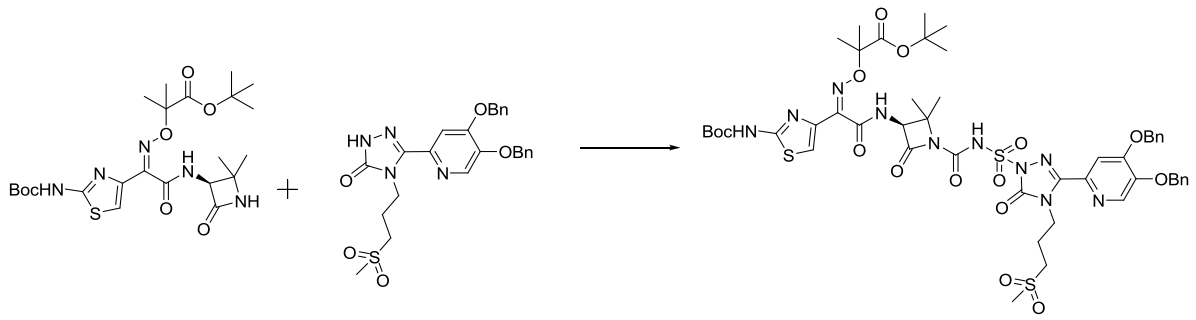
Compound 24g.



(*S*,*Z*)-*tert*-butyl 2-(1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-(2,2-dimethyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate

(*S*,*Z*)-*tert*-Butyl 2-(1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-(2,2-dimethyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate (**14g**)**:** Into a 100-mL round-bottom flask, was placed toluene (10 mL), ethanol (40 mL), *tert*-butyl 2-[[(*Z*)-[1-(2-[[(*tert*-butoxy)carbonyl]amino]-1,3-thiazol-4-yl)-2-[(2,5-dioxopyrrolidin-1-yl)oxy]-2-oxoethylidene]amino]oxy]-2-methylpropanoate (**23**) (2.36 g, 4.48 mmol), and (3*S*)-3-amino-4,4-dimethylazetidin-2-one(**14g**)[17, 18] (511 mg, 4.48 mmol). The resulting solution was stirred for 12 h at 35 °C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel chromatography with dichloromethane/methanol (20:1) to afford the desired product as a yellow solid (0.750 g, 32%).

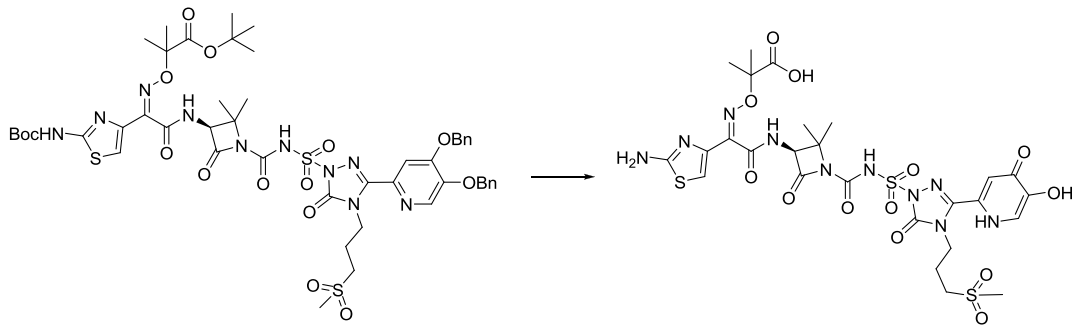
ESI-MS m/z: 498 $[M + 1]^+$



(*S*,*Z*)-*tert*-butyl 2-(2-(1-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2,2-dimethyl-4-oxoazetidin-3-ylamino)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-oxoethylideneaminooxy)-2-methylpropanoate

(*S*,*Z*)-*tert*-Butyl 2-(2-(1-(3-(4,5-bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2,2-dimethyl-4-oxoazetidin-3-ylamino)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-oxoethylideneaminooxy)-2-methylpropanoate: General procedure C was followed using 3-[4,5-bis(benzyloxy)pyridin-2-yl]-4-(3-methanesulfonylpropyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**6b**) (500 mg, 1.01 mmol) and *tert*-butyl 2-[[(Z)-[(2-[[(*tert*-butoxy)carbonyl]amino]-1,3-thiazol-4-yl)([[(3*S*)-2,2-dimethyl-4-oxoazetidin-3-yl]carbamoyl])methylidene]amino]oxy]-2-methylpropanoate (**14g**) (583 mg, 1.11 mmol). The residue was purified by silica gel column (CH_2Cl_2:MeOH = 30:1) to afford the desired product as a yellow solid (0.230 g, 20%).

ESI-MS m/z: 1097 $[M + 1]^+$.



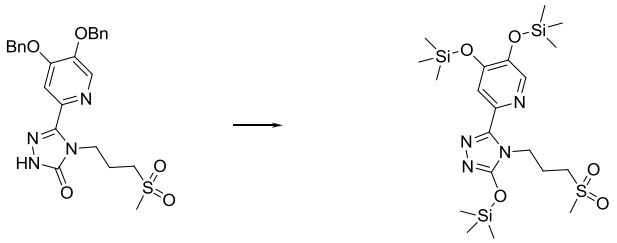
(*S*,*Z*)-2-(1-(2-Aminothiazol-4-yl)-2-(1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2,2-dimethyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid (**24g**): Into a 100-mL round-bottom flask, was placed dichloromethane (60 mL, 944 mmol) and *tert*-butyl 2-[[(Z)-([[(3*S*)-1-([3-[4,5-bis(benzyloxy)pyridin-2-yl]-4-(3-methanesulfonylpropyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazole-1-sulfonyl]carbamoyl)-2,2-dimethyl-4-oxoazetidin-3-yl]carbamoyl](2-[[(*tert*-butoxy)carbonyl]amino]-1,3-thiazol-4-yl)methylidene)amino]oxy]-2-methylpropanoate (230 mg, 0.20 mmol) and the solution was cooled to 0 °C. Trichloroborane (1.24 mL 1N in toluene, 1.24 mmol) was added dropwise. The resulting solution was stirred for 10 min at 0 °C. The resulting mixture was concentrated *in vacuo*. The crude product was purified by Flash-Prep-HPLC (MeCN/H_2O with 0.1% formic acid) to provide the product as a white solid (0.084 g, 49%).

HPLC RT = 0.76 min, MS (ES) MH^+ 761 for $C_{26}H_{32}N_{10}O_{13}S_3$

^{1}H NMR (300MHz, DMSO): δ 1.31 ppm (3H, s), 1.52 (3H, s), 2.03 (2H, m), 2.94 (3H, s), 3.12 (2H, m), 4.12 (2H, m), 4.64 (2H, s), 4.70 (1H, d), 6.86 (1H, s), 7.38 (1H, s), 8.03 (1H, s), 9.36 (1H, d).

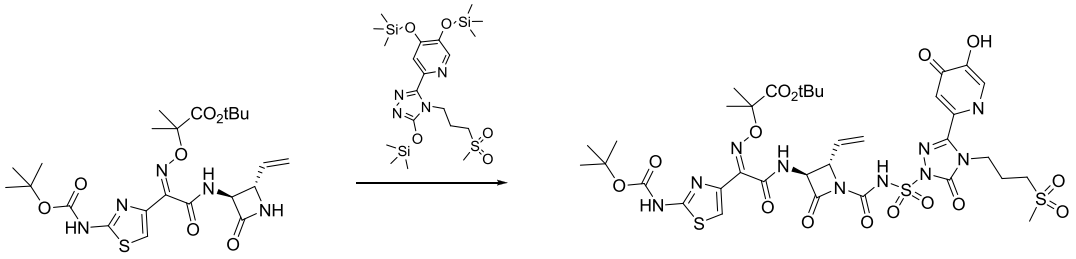
HRMS $(ES)^+$ Calcd for $C_{26}H_{33}N_{10}O_{13}S_3$ $[M + H]^+$ 789.1381; Found 789.1385.

Compound 24c.



2-(4-(3-(methylsulfonyl)propyl)-5-(trimethylsilyloxy)-4*H*-1,2,4-triazol-3-yl)-4,5-bis(trimethylsilyloxy)pyridine

2-(4-(3-(Methylsulfonyl)propyl)-5-(trimethylsilyloxy)-4*H*-1,2,4-triazol-3-yl)-4,5-bis(trimethylsilyloxy)pyridine (**26**): 3-(4,5-Bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (3.5 g, 7.1 mmol) was suspended in dry THF (100 mL). The suspension was evacuated and purged with nitrogen (3x). Pd black (100 mg, 0.94 mmol) was added in a single portion. The reaction slurry was evacuated and back-filled with hydrogen (balloon atmosphere). The suspension was stirred vigorously for 2 hours. The palladium was filtered through a pad of celite and the filter cake was washed with THF. The resultant mother liquor was then reacted with *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (6.59 mL, 35.38 mmol). The clear colorless reaction mixture was stirred at room temperature for 30 minutes before being concentrated to an oil by rotary evaporation. The crude oil was azeotroped with THF (3x) which removed the majority of the *N*-Me-acetamide, used immediately in the next step without further purification.



tert-butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((3*S*,4*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-oxo-4-vinylazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate

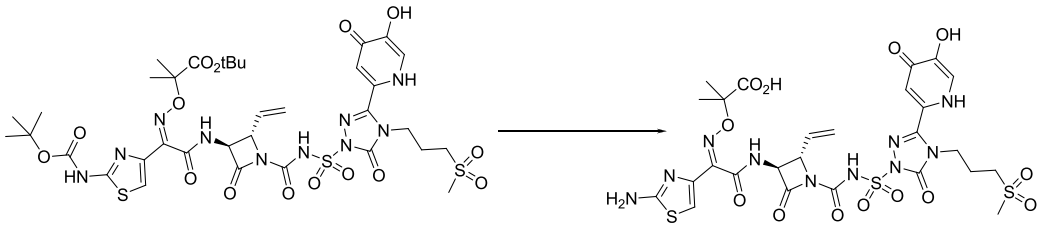
General Procedure F.

***tert*-Butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((3*S*,4*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-**

5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-oxo-4-vinylazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate (**27c**): *tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxo-2-(((3*S*,4*S*)-2-oxo-4-vinylazetidin-3-yl)amino)ethylidene)amino)oxy)-2-methylpropanoate (**14c**) (340 mg, 0.65 mmol) was dissolved in CH_2Cl_2 (6 mL) and cooled to 0 °C with the aide of an ice bath. Chlorosulfonyl isocyanate (0.059 mL, 0.68 mmol) was then added slowly to the reaction mixture via syringe and the resultant solution was allowed to stir at that temperature for 10 min. The progress of the urea formation was monitored by LC/MS (aliquot was quenched with anhydrous MeOH). The CH_2Cl_2 solution containing was added to a reaction vessel containing 2-(4-(3-(methylsulfonyl)propyl)-5-((trimethylsilyl)oxy)-4*H*-1,2,4-triazol-3-yl)-4,5-bis((trimethylsilyl)oxy)pyridine (**26**) (400 mg, 0.75 mmol) which was previously prepared. The reaction mixture was allowed to stir at room temperature overnight. The reaction was quenched with MeOH (1 mL) and then concentrated by rotary evaporation. The crude reaction mixture was purified by reverse phase column chromatography (5-95% MeCN/water w/ 0.1% TFA) to yield the product as a white solid (132 mg , 22%).

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 1.39 (s, 15H), 1.47 (s, 9H), 2.03 (m, 2H), 2.94 (s, 3H), 3.12 (m, 2H), 4.11 (m, 2H), 4.25 (m, 1H), 4.59 (m, 1H), 5.17 (m, 1H), 5.32 (m, 1H), 5.32 (m, 1H), 6.04 (m, 1H), 7.24 (s, 1H), 7.39 (s, 1H), 8.04 (s, 1H), 9.08 (d, 1H), 11.83 (s, 1H).

ESI-MS m/z: 943.1 $[M + H]^+$.



2-((*Z*)-1-(2-aminothiazol-4-yl)-2-((3*S*,4*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-oxo-4-vinylazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid

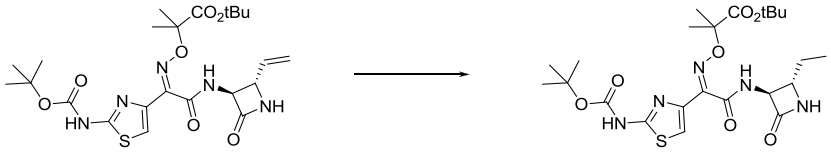
2-((*Z*)-1-(2-Aminothiazol-4-yl)-2-((3*S*,4*S*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-oxo-4-vinylazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid (**24c**)**:** General procedure E was followed using *tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((3*S*,4*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-oxo-4-vinylazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**27c**) (132 mg, 0.14 mmol). The crude reaction mixture was purified by reverse phase column chromatography (5-95% MeCN/H_2O w/ 0.1% TFA) to yield the pure product as a white solid (85 mg, 77%)

UPLC RT = 1.81 min, MS (ES) MH^+: 787.0 for $C_{26}H_{30}N_{10}O_{13}S_3$

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 1.38 (d, 6H), 1.96 (m, 2H), 2.87 (s, 3H), 3.04 (m, 2H), 4.05 (t, 2H), 4.18 (m, 1H), 4.51 (dd, 1H), 5.09 (d, 1H), 5.19 (d, 1H), 5.96 (m, 1H), 6.77 (m, 1H), 7.31 (s, 1H), 7.96 (s, 1H), 9.08 (m, 1H).

HRMS (ES+) Calcd for $C_{26}H_{31}N_{10}O_{13}S_3$ $[M + H]^+$ 787.1224; Found 787.1235

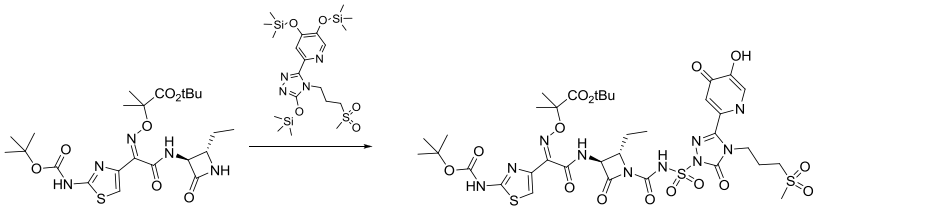
Compound 24d.



tert-butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((2*S*,3*S*)-2-ethyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate

***tert*-Butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((2*S*,3*S*)-2-ethyl-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate** (**14d**)**:** *tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxo-2-(((3*S*,4*S*)-2-oxo-4-vinylazetidin-3-yl)amino)ethylidene)amino)oxy)-2-methylpropanoate (340 mg, 0.65 mmol) was dissolved in EtOH (10 mL). The solution was evacuated and back-filled with argon. Pd-C (10%) (25 mg, 0.02 mmol) was added under argon. The suspension was stirred vigorously under a balloon pressure of hydrogen for 1 hour. Celite was added and the reaction mixture was filtered. The mother liquor was concentrated to dryness by rotary evaporation. The crude product was used in the next step without further purification.

ESI-MS m/z: 526.2 $[M + H]^+$.



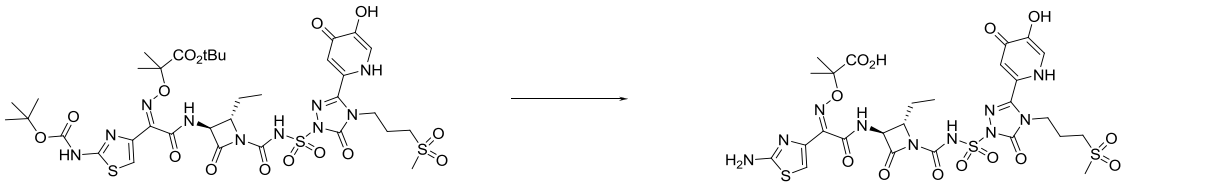
tert-butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((2*S*,3*S*)-2-ethyl-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate

***tert*-Butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((2*S*,3*S*)-2-ethyl-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate** (**27d**)**:** General procedure F was followed using *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-ethyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**14d**) (340 mg,

0.65 mmol), chlorosulfonyl isocyanate (0.059 mL, 0.68 mmol), and 2-(4-(3-(methylsulfonyl)propyl)-5-((trimethylsilyl)oxy)-4*H*-1,2,4-triazol-3-yl)-4,5-bis((trimethylsilyl)oxy)pyridine (**26**) (400 mg, 0.75 mmol). The crude reaction mixture was purified by reverse phase column chromatography (5-95% MeCN/water w/ 0.1% TFA) to yield the product as a white fluffy solid (135 mg, 22%).

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.89 (t, 3H), 1.39 (s, 15H), 1.47 (s, 9H), 2.03 (m, 2H), 2.20 (m, 1H), 3.12 (m, 2H), 3.62 (m, 1H), 4.12 (m, 2H), 4.56 (dd, 1H), 7.20 (s, 1H), 7.39 (s, 1H), 8.04 (s, 1H), 9.03 (d, 1H), 11.83 (s, 1H).

ESI-MS m/z: 945.1 $[M + H]^+$.



2-((*Z*)-1-(2-aminothiazol-4-yl)-2-((2*S*,3*S*)-2-ethyl-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid

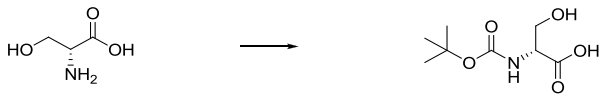
2-((*Z*)-1-(2-Aminothiazol-4-yl)-2-((2*S*,3*S*)-2-ethyl-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-4-oxoazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid (**24d**)**:** General procedure E was followed using *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-ethyl-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**27d**) (135 mg, 0.14 mmol). The crude reaction mixture was purified by reverse phase column chromatography (5-95% MeCN/H_2O w/ 0.1% TFA) to yield the product as a white fluffy solid (67 mg, 60%).

UPLC RT = 1.88 min, MS (ES) MH^+: 789.0 for $C_{26}H_{32}N_{10}O_{13}S_3$

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.81 (t, 3H), 1.38 (s, 6H), 1.41 (m, 1H), 1.97 (m, 2H), 2.14 (m, 1H), 2.88 (s, 3H), 3.06 (m, 2H), 3.56 (dt, 1H), 4.06 (t, 2H), 4.48 (dd, 1H), 6.74 (s, 1H), 7.32 (s, 1H), 7.97 (s, 1H), 9.06 (d, 1H).

HRMS (ES+) Calcd. for $C_{26}H_{33}N_{10}O_{13}S_3$ $[M + H]^+$ 789.1391; Found 789.1399.

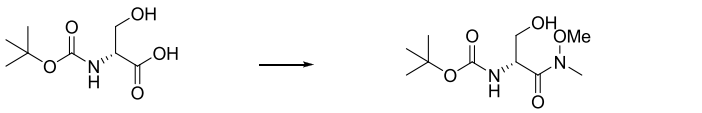
Compound 22.



(*R*)-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoic acid

(*R*)-2-*tert*-Butoxycarbonylamino-3-hydroxy-propionic acid (**19**)**:** To a solution of D-serine (50 g, 0.475 mol) in water (250 mL) at 0 °C was added sodium hydroxide solution (22.8 g, 0.57 mol) in water (600 mL) dropwise. To the clear solution were added di-*tert*-butyl dicarbonate (120.2 mL, 0.523 mol) and *tetra*-butylammonium bromide (2.3 g, 0.007 mol) at the same temperature. The reaction mixture was allowed to attain room temperature and stir for 24 h. The resulting suspension was acidified to pH 3.5-4.0 with aqueous saturated citric acid solution (800 mL) and extracted with ethyl acetate (3 × 250 mL). The organic layers were combined, washed with water (200 mL), brine (200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to the product as a colorless oil which was used as such in the next step without further purification (78 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 6.90 (brs, 1H), 5.80 (brs, 1H), 4.40 (brs, 1H), 4.17-4.01 (m, 2H), 3.89-3.87 (brm, 1H), 1.47 (s, 9H).



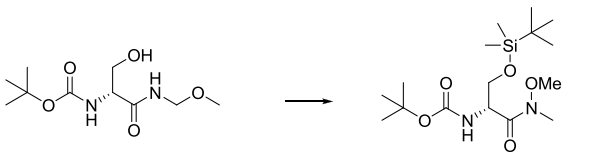
(*R*)-*tert*-butyl 3-hydroxy-1-(methoxymethylamino)-1-oxopropan-2-ylcarbamate

[(*R*)-2-Hydroxy-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid *tert*-butyl ester: To a solution of (*R*)-2-*tert*-butoxycarbonylamino-3-hydroxy-propionic acid (**19**) (340 g, 1.66

mol) in dichloromethane (8.5 L) was added *N*,*O*-dimethyhydroxylamine hydrochloride (178 g, 1.82 mol) portionwise followed by and *N*-methylmorphorine (184 g, 201 mL, 1.81 mol) dropwise at –15 °C. Then, to the resulting mixture was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (348 g, 1.82 mol) over 30 min at the same temperature. After the addition, the reaction mixture was stirred at the same temperature for 1h, ice cold solution of 1N hydrochloric acid (400 mL) was added, and the resulting mixture was extracted with chloroform (6 × 250 mL). The organic layers were combined, and washed with water (200 mL), brine (200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield the product as a colorless solid. Crude product was used as such in the next step without further purification (310 g, 76%).

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 6.80 (d, J = 8.1 Hz, 1H), 4.83 (t, J = 6.0 Hz, 1H), 4.50 (brs, 1H), 3.72 (s, 3H), 3.58-3.44 (m, 2H), 3.10 (s, 3H), 1.37 (s, 9H).

LCMS (m/z): 149 $[M\text{-}BOC+1]^+$

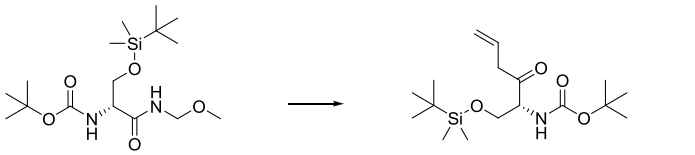


(*R*)-*tert*-butyl 3,8,8,9,9-pentamethyl-4-oxo-2,7-dioxa-3-aza-8-siladecan-5-ylcarbamate

[(*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-(methoxy-methyl- carbamoyl)-ethyl]-carbamic acid tert-butyl ester: To a solution of [(*R*)-2-hydroxy-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid *tert*-butyl ester (330 g, 1.33 mol) in dimethylformamide (2.7 L) was added imidazole (108 g, 1.59 mol) and *tert*-butyldimethylsilyl chloride (210 g, 1.39 mol) at 0 °C. After the reaction mixture was stirred at the same temperature for 10 min, ice was added, and the resulting mixture was extracted with ethyl acetate (3 × 500 mL). The organic layers were combined, washed with saturated sodium chloride (200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield the product as a colorless oil. The crude product was used as such in the next step without further purification (366 g, 76%).

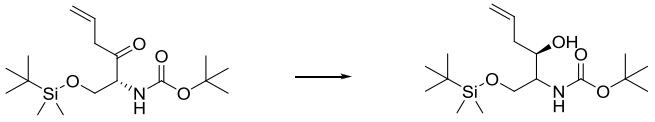
^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 5.38 (d, *J* = 8.7 Hz, 1H), 4.77 (brs, 1H), 3.86-3.77 (m, 2H), 3.76 (s, 3H), 3.23 (s, 3H), 1.45 (s, 9H), 0.87 (s, 9H), 0.04 (s, 6H)

LCMS (m/z): 263[M-BOC+1]$^+$



(*R*)-*tert*-butyl 1-(*tert*-butyldimethylsilyloxy)-3-oxohex-5-en-2-ylcarbamate

[(*R*)-1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-oxo-pent-4-enyl]-carbamic acid *tert*-butyl ester (20): To a solution of [(*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid tert-butyl ester (50.0 g, 0.138 mol) in tetrahydrofuran (1 L) was added a solution of allylmagnesium bromide (789 mL, 0.758 mol, 1M in tetrahydrofuran) at -78 °C. After the reaction mixture was stirred for 24 h at the same temperature, the reaction mixture was poured into saturated ammonium chloride (500 mL) at 0 °C. The resulting mixture was extracted with ethyl acetate (3 × 1 L). The organic layers were combined, washed with brine (500 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield the product as a brown liquid. The crude product was used as such in the next step without further purification (50 g, quantitative).



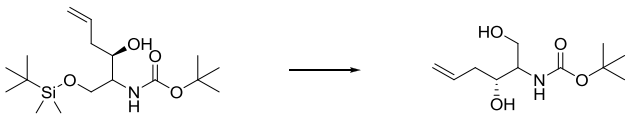
tert-butyl (3*R*)-1-(*tert*-butyldimethylsilyloxy)-3-hydroxyhex-5-en-2-ylcarbamate

[(*R*)-1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-hydroxy-pent-4-enyl]-carbamic acid *tert*-butyl ester: To a solution of [(*R*)-1-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-oxo-pent-4-enyl]-carbamic acid *tert*-butyl ester (25 g, 0.072 mol) in ethanol (250 mL) was added sodiumborohydride (6.88 g, 0.182 mol) at –78 °C and the reaction mixture was stirred at the same temperature for 1-2 h. After completion of the reaction, the reaction mixture was evaporated under reduced pressure. To the crude residue saturated ammonium chloride (1 L)

was added slowly at ice cold condition with vigorous stirring. The resulting mixture was extracted with ethyl acetate (3 × 500 mL). The organic layers were combined, washed with brine (200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the crude product. Purified by flash column chromatography on silica gel (2-4% ethyl acetate in hexane) to the product as a colorless oil and as a mixture of diastereomers (12.3 g, 49%).

^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 5.92-5.83 (m, 1H), 5.18-5.15 (m, 2H), 3.99-3.98 (m, 1H), 3.84-3.72 (m, 2H), 3.56 (brs, 1H), 3.09 (d, *J* = 7.8 Hz, 1H), 2.37 (t, *J* = 6.3 Hz, 2H), 1.47 (s, 9H), 0.91 (s, (H), 0.10 (s, 6H).

LCMS (m/z): 246 $[M\text{-}BOC]^+$

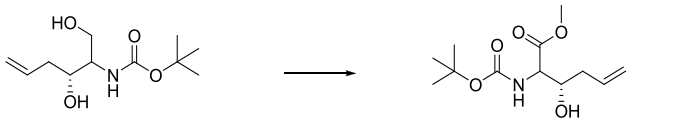


tert-butyl (3*R*)-1,3-dihydroxyhex-5-en-2-ylcarbamate

((*R*)-2-Hydroxy-1-hydroxymethyl-pent-4-enyl)-carbamic acid *tert*-butyl ester: To a solution of [(*R*)-1-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-hydroxy-pent-4-enyl]-carbamic acid tert-butyl ester (100 g, 290 mmol) in tetrahydrofuran (90 mL), tetrabutylammonium fluoride in tetrahydrofuran (361 mL, 1M in tetrahydrofuran, 362 mmol) was added dropwise under nitrogen atmosphere at room temperature and stirred at the same temperature for 1 hour. The reaction mixture was diluted with diethyl ether (600 mL), quenched with saturated ammonium chloride solution (800 mL) and separated the diethyl ether layer. The aqueous layer was further extracted with diethyl ether (2 × 250 mL). The combined organic layers were washed with saturated brine solution (400 mL), dried over anhydrous sodium sulphate, filtered and evaporated. The crude product was purified by flash column chromatography over silica gel (1 - 2% of methanol in chloroform) to yield the product as an off-white solid (52.2 g, 78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 5.90-5.78 (m, 1H), 5.45 (d, *J* = 8.1 Hz, 1H), 5.20-5.13 (m, 2H), 4.02-3.98 (m, 1H), 3.84-3.72 (m, 2H), 3.57 (m, 1H), 3.18 (brs, 1H), 3.05 (brs, 1H), 2.39-2.26 (m, 2H), 1.46 (s, 9H).

LCMS (m/z): 132[M-BOC]$^+$



(3*S*)-methyl 2-(*tert*-butoxycarbonylamino)-3-hydroxyhex-5-enoate

(*S*)-2-*tert*-Butoxycarbonylamino-3-hydroxy-hex-5-enoic acid methyl ester (21):

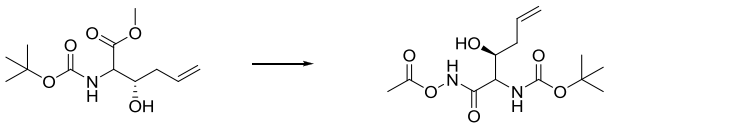
To a solution of ((*R*)-2-hydroxy-1-hydroxymethyl-pent-4-enyl)-carbamic acid *tert*-butyl ester (15 g, 0.065 mol) in acetone (45 mL) containing 2,2,6,6-tetramethylpiperidine 1-oxyl (1.0 g, 0.0064 mol) was added a 5% aqueous sodium bicarbonate solution (165 mL) buffered to pH = 9.1. The mixture was cooled to 0 ^{o}C and sodium hypochlorite (240 mL, ca. 4-4.9% w/w) was added dropwise over 15 min while following the reaction by TLC. After complete consumption of starting material ethyl acetate (200 mL) was added to the reaction mixture. The organic layer was separated. To the aqueous layer 10% aqueous citric acid solution (500 mL) was added and extracted with ethyl acetate (3 ×150 mL). The organic layer was washed with water (100 mL), saturated sodium chloride (100 mL), dried over sodium sulfate and concentrated under reduced pressure to yield the crude product, which was used as such in the next step without further purification (12.0 g, quantitative).

To a solution of (*S*)-2-*tert*-butoxycarbonylamino-3-hydroxy-hex-5-enoic acid (30.0 g, 0.122 mmol) in dimethylformamide (90 mL) at 0 ^{o}C was added potassium carbonate (25.3 g, 0.186 mmol) and left under stirring for 10 min prior to addition of iodomethane (22.9 mL, 0.367 mmol). The mixture was stirred for 45 min. at the same temperature then allowed to warm to room temperature and kept under further stirring for 90 min after which ethyl acetate (250 mL) and water (1 L) were added, allowing the separation of two layers. The organic extract

was washed with saturated sodium chloride (100 mL), dried over sodium sulfate and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (using hexane/ethyl acetate) to yield the pure product as a yellow liquid (17 g, 59%).

^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 5.89-5.77 (m, 1H), 5.47 (brs, 1H), 5.20-5.15 (m, 2H), 4.43 (brs, 1H), 3.99 (brs, 1H), 3.76 (s, 3H), 2.89 (brs, 1H), 2.34-2.29(m, 2H), 1.47 (s, 9H).

LCMS (m/z): 160 $[M\text{-}BOC]^+$

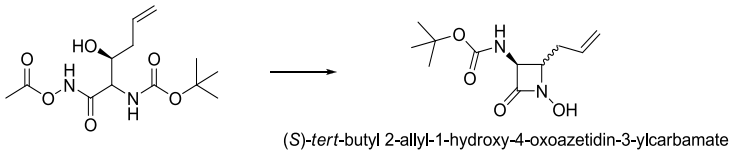


tert-butyl (3*S*)-1-(acetoxyamino)-3-hydroxy-1-oxohex-5-en-2-ylcarbamate

((*S*)-1-Acetoxycarbamoyl-2-hydroxy-pent-4-enyl)-carbamic acid *tert*-butyl ester: A solution of (*S*)-2-*tert*-butoxycarbonylamino-3-hydroxy-hex-5-enoic acid methyl ester (**21**) (17 g, 0.0656 mol) in methanol (50 mL) was cooled to 0 °C and treated with a suspension of hydroxylamine hydrochloride (13.8 g, 0.196 mol) and potassium hydroxide (22.0 g, 0.396 mol) in methanol (50 mL). After completion of addition, the reaction mixture was stirred at the same temperature for 45 min. Acetic anhydride (40.1 g, 40 mL, 0.394 mol) was added dropwise at 0 °C. After stirring for 30 minutes more, TLC indicated complete consumption of starting material. The mixture was poured into 5% sodium bicarbonate (200 mL) and extracted with ethyl acetate (4 × 100 mL). The organic phase was separated. The aqueous solution was acidified carefully with 10% citric acid solution to pH=3. The aqueous layer was then extracted with ethyl acetate (4 × 100 mL). The organics were pooled, washed with water (2 × 100 mL), saturated sodium chloride (100 mL), dried over sodium sulfate, filtered and concentrated. The crude product was purified by recrystallization (ether/*n*-hexane, 1:9) to yield the pure product as a colorless solid (5.5 g, 28%).

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 11.77 (brs, 1H), 6.97 (d, J = 18 Hz, 1H), 5.86-5.77 (m, 1H), 5.05-5.00 (m, 3H), 3.96-3.90 (m, 1H), 3.71 (brs, 1H), 2.23 (brs, 2H), 2.09 (s, 3H), 1.38 (s, 9H).

LCMS (m/z): 203[M-BOC]$^+$

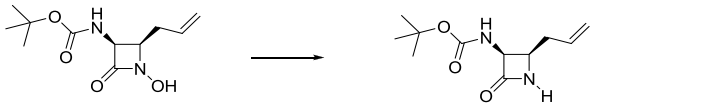


(*S*)-*tert*-butyl 2-allyl-1-hydroxy-4-oxoazetidin-3-ylcarbamate

((*S*)-2-Allyl-1-hydroxy-4-oxo-azetidin-3-yl)-carbamic acid *tert*-butyl ester: To a 0 °C solution of ((*S*)-1-acetoxycarbamoyl-2-hydroxy-pent-4-enyl)-carbamic acid *tert*-butyl ester (25 g, 0.082 mol) in tetrahydrofuran (50 mL), triphenylphosphine (23.6 g, 0.090 mol) was added followed by diisopropyl azodicarboxylate (18.2 g, 0.090 mol) in tetrahydrofuran (18 mL). The reaction was allowed to warm to room temperature and stir. After 2 h, TLC indicated consumption of starting material and formation of the desired product. The reaction mixture was concentrated. The yellow viscous liquid obtained was taken as such to the next step. The crude residue was taken-up in 1:1 methanol, water mixture (100 mL) and cooled to 0 ^{o}C. Once dissolved, solid sodium carbonate (21.9 g, 0.206 mol) was added and the reaction mixture was stirred vigorously at the same temperature. After 2 h, TLC indicated consumption of starting material and formation of the desired product. The reaction mixture was filtered through a Celite bed. To the filtrate 5% sodium bicarbonate (300 mL) was added and the solution was extracted with ethyl acetate (2 × 100 mL) to remove unwanted by-products. The aqueous solution was acidified with 3N hydrochloric acid to pH=3. The aqueous layer was then extracted with ethyl acetate (3 × 100 mL). The organics were pooled, washed with brine, dried over sodium sulfate, filtered and concentrated. Crude product was recrystallized with diethyl ether to yield the pure product as an off-white solid (6 g, 30%).

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 10.19 (s, 1H), 7.73 (d, J = 9.9 Hz, 1H), 5.78-5.65 (m, 1H), 5.09 (d, J = 17.4 Hz, 1H), 5.01 (d, J = 10.2 Hz, 1H), 4.72 (dd, J = 12.0, 4.8 Hz, 1H), 3.86-3.80 (m, 1H), 2.43-2.35 (m, 1H), 2.25-2.20 (m, 1H), 1.36 (s, 9H).

LCMS (m/z): 187 $[M-56]^+$



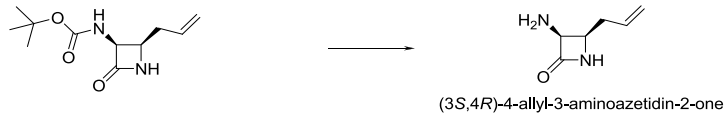
tert-butyl (2*R*,3*S*)-2-allyl-4-oxoazetidin-3-ylcarbamate

((*S*)-2-Oxo-4-allyl-azetidin-3-yl)-carbamic acid *tert*-butyl ester (22): To a solution of ((*S*)-2-allyl-1-hydroxy-4-oxo-azetidin-3-yl)-carbamic acid *tert*-butyl ester (1.0 g, 4.12 mmol) in methanol (20 mL) was added ammonium acetate (6.38 g, 82.5 mmol) under nitrogen atmosphere. The reaction mixture was cooled to 0-5 ^{o}C and titanium(III) chloride (10.7 mL, 8.25 mmol, 10% in hydrochloric acid) was added dropwise with constant stirring. The pH of the reaction mixture was then adjusted to 7 using 2N sodium hydroxide solution. The mixture was allowed to attain room temperature and stirred for 2h. The reaction was monitored with LCMS. After completion, *dl*-tartaric acid (1.23 g, 8.25 mmol) was added and the pH of the reaction mixture was adjusted to 9 using 2N sodium hydroxide solution. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layer was dried over sodium sulphate and concentrated under vacuum. The crude product was re-crystallized using dichloromethane and hexane to yield the pure product as a colorless solid (0.5 g, 54%).

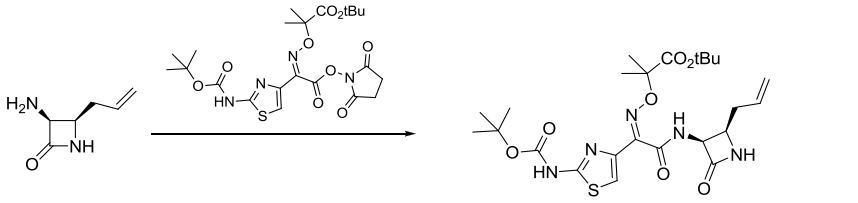
^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 8.25 (s, 1H), 7.68 (d, J = 9.6 Hz, 1H), 5.75-5.67 (m, 1H), 5.10-5.04 (m, 2H), 4.82 (dd, J = 9.75, 5.1 Hz, 1H), 3.62 (q, J = 7.2 Hz, 1H), 2.20 (t, J = 6.6 Hz, 2H), 1.39 (s, 9H).

LCMS (m/z): 171 $[M-56]^+$, 127 $[M-BOC+1]^+$

Compound 24e.



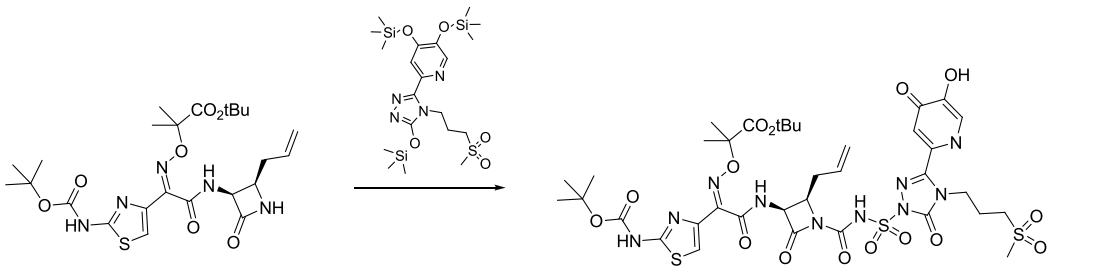
(3*S*,4*R*)-4-Allyl-3-aminoazetidin-2-one: A solution of *tert*-butyl ((2*R*,3*S*)-2-allyl-4-oxoazetidin-3-yl)carbamate (2 g, 8.84 mmol) and 10 mL of a 30% v/v CH_2Cl_2 solution (7 mL CH_2Cl_2/3 mL TFA) containing TFA (trifluoroacetic acid) (3 mL, 40.39 mmol) was allowed to stir for 30 min. The reaction was concentrated to dryness and used in the next step without further purification.



***tert*-Butyl 2-((*Z*)-2-((2*R*,3*S*)-2-allyl-4-oxoazetidin-3-ylamino)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-oxoethylideneaminooxy)-2-methylpropanoate (14e):** The same procedure as **14b** and **14c** was followed using (*Z*)-*tert*-butyl 2-(((1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-((2,5-dioxopyrrolidin-1-yl)oxy)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**23**) (5.46 g, 10.4 mmol), (3*S*,4*R*)-4-allyl-3-aminoazetidin-2-one (1.19 g, 9.42 mmol), and 4-methyl morpholine (3.11 mL, 28.3 mmol). The crude product was purified by silica gel flash column chromatography (1:1 EtOAc/hexanes) to yield the product (1.83 g, 36%).

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 1.39 (s, 18H), 1.46 (s, 9H), 2.19 (m, 1H), 2.30 (m, 1H), 3.73 (m, 1H), 5.05 (m, 2H), 5.18 (m, 1H), 5.81 (m, 1H), 7.25 (s, 1H), 8.46 (s, 1H), 9.26 (d, 1H), 11.86 (s, 1H).

ESI-MS m/z: 538.2 $[M + H]^+$.

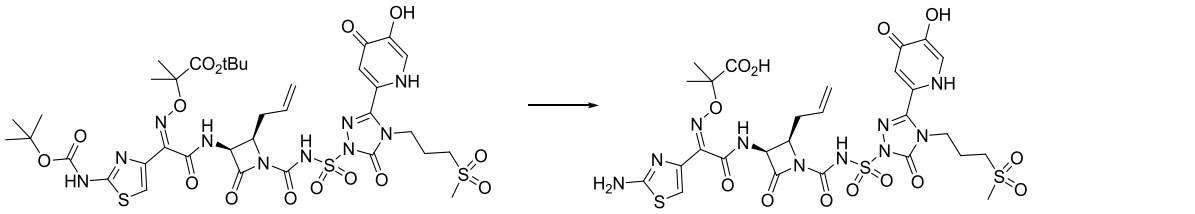


tert-butyl 2-((*Z*)-2-((2*R*,3*S*)-2-allyl-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-4-oxoazetidin-3-ylamino)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-oxoethylideneaminooxy)-2-methylpropanoate

***tert*-Butyl 2-((*Z*)-2-((2*R*,3*S*)-2-allyl-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-4-oxoazetidin-3-ylamino)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-oxoethylideneaminooxy)-2-methylpropanoate** (**27e**): General procedure F was followed using *tert*-butyl 2-(((*Z*)-(2-(((2*R*,3*S*)-2-allyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**14e**) (340 mg, 0.63 mmol), chlorosulfonyl isocyanate (0.058 mL, 0.66 mmol), and 2-(4-(3-(methylsulfonyl)propyl)-5-((trimethylsilyl)oxy)-4*H*-1,2,4-triazol-3-yl)-4,5-bis((trimethylsilyl)oxy)pyridine (**26**) (400 mg, 0.75 mmol). The crude reaction mixture was purified by reverse phase column chromatography (5-95% MeCN/water w/ 0.1% TFA) to yield the product as a white solid (177 mg, 29%).

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 1.39 (s, 15H), 1.47 (s, 9H), 2.04 (m, 2H), 2.47 (m, 1H), 2.68 (m, 1H), 2.95 (s, 3H), 3.12 (m, 2H), 3.97 (m, 1H), 4.12 (m, 2H), 4.92 (d, 1H), 5.01 (d, 1H), 5.22 (m, 1H), 5.88 (m, 1H), 7.21 (s, 1H), 7.39 (s, 1H), 8.04 (s, 1H), 9.22 (d, 1H), 11.83 (s, 1H).

ESI-MS m/z: 957.1 $[M + H]^+$.



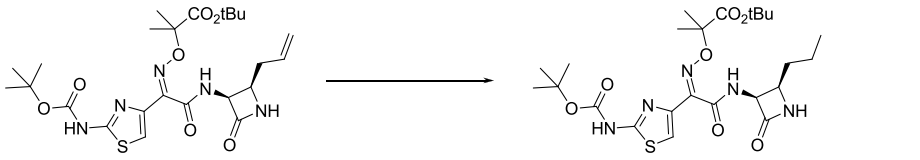
2-((*Z*)-2-((2*R*,3*S*)-2-Allyl-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-4-oxoazetidin-3-ylamino)-1-(2-aminothiazol-4-yl)-2-oxoethylideneaminooxy)-2-methylpropanoic acid (**24e**)**:** General procedure E was followed using *tert*-butyl 2-(((*Z*)-(2-(((2*R*,3*S*)-2-allyl-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**27e**) (177 mg, 0.18 mmol). The crude reaction mixture was purified by reverse phase column chromatography (5-95% MeCN/H_2O w/ 0.1% TFA) to yield the pure product as a white solid (120 mg , 81%).

UPLC RT = 1.92 min, MS (ES) MH^+: 801.0 for $C_{26}H_{32}N_{10}O_{13}S_3$

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 1.44 (d, 6H), 2.04 (m, 2H), 2.33 (m, 1H), 2.74 (m, 1H), 2.95 (s, 3H), 3.13 (m, 2H), 3.99 (m, 1H), 4.13 (m, 2H), 5.01 (m, 2H), 5.22 (m, 1H), 5.83 (m, 1H), 6.80 (s, 1H), 7.38 (s, 1H), 8.04 (s, 1H), 9.23 (d, 1H).

HRMS (ES+) Calcd for $C_{26}H_{33}N_{10}O_{13}S_3$ $[M + H]^+$ 801.1385; Found 801.1398.

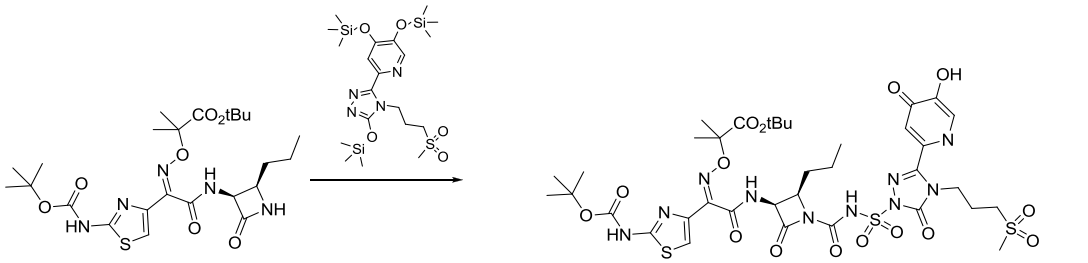
Compound 24f.



tert-butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino) thiazol-4-yl)-2-oxo-2-((3*S*,4*R*)-2-oxo-4-propylazetidin-3-ylamino)ethylideneaminooxy)-2-methylpropanoate

***tert*-Butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-oxo-2-((3*S*,4*R*)-2-oxo-4-propylazetidin-3-ylamino)ethylideneaminooxy)-2-methylpropanoate** (**14f**)**:** In an oven dried flask, *tert*-butyl 2-(((*Z*)-(2-(((2*R*,3*S*)-2-allyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**14e**) (340 mg, 0.63 mmol) was dissolved in EtOH (10 mL). Solution was evacuated and back-filled with argon. Pd-C (10%) (25 mg, 0.02 mmol) was added under argon. The suspension was stirred vigorously under a balloon pressure of hydrogen for 1 hour. Celite was added and the reaction mixture was filtered. The mother liquor was concentrated to dryness by rotary evaporation and the crude material was used in the next step without further purification.

ESI-MS m/z: 540.2 $[M + H]^+$.

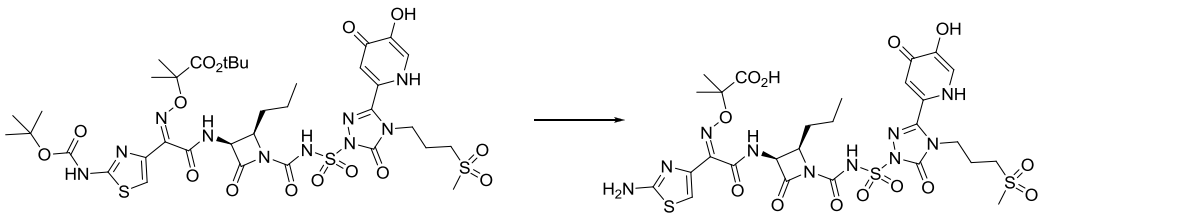


tert-butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((3*S*,4*R*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-oxo-4-propylazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate

***tert*-Butyl 2-((*Z*)-1-(2-(*tert*-butoxycarbonylamino)thiazol-4-yl)-2-((3*S*,4*R*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-oxo-4-propylazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoate** (**27f**)**:** General procedure F was followed using *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxo-2-(((3*S*,4*R*)-2-oxo-4-propylazetidin-3-yl)amino)ethylidene)amino)oxy)-2-methylpropanoate (**14f**) (340 mg, 0.63 mmol), chlorosulfonyl isocyanate (0.058 mL, 0.66 mmol), and 2-(4-(3-(methylsulfonyl)propyl)-5-((trimethylsilyl)oxy)-4*H*-1,2,4-triazol-3-yl)-4,5-bis((trimethylsilyl)oxy)pyridine (**26**) (400 mg, 0.75 mmol). The crude reaction mixture was purified by reverse phase column chromatography (5-95% MeCN/water w/ 0.1% TFA) to yield the product as a white, fluffy solid (145 mg, 24%).

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.83 (t, 3H), 1.39 (s, 15H), 1.47 (s, 9H), 1.26 - 1.54 (m, 3H), 1.84 (m 1H), 2.03 (m, 2H), 2.95 (s, 3H), 3.13 (m, 2H), 3.96 (m, 1H), 4.12 (m, 2H), 5.23 (dd, 1H), 7.20 (s, 1H), 7.38 (s, 1H), 8.04 (s, 1H), 9.14 (d, 1H), 11.82 (s, 1H).

ESI-MS m/z: 959.1 $[M + H]^+$.



2-((*Z*)-1-(2-aminothiazol-4-yl)-2-((3*S*,4*R*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-oxo-4-propylazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid

2-((*Z*)-1-(2-Aminothiazol-4-yl)-2-((3*S*,4*R*)-1-(3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-ylsulfonylcarbamoyl)-2-oxo-4-propylazetidin-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid (24f): General procedure E was followed using *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((3*S*,4*R*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-oxo-4-propylazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (**27f**) (145 mg, 0.15 mmol). The crude reaction mixture was purified by reverse phase column chromatography (5-95% MeCN/H_2O w/ 0.1% TFA) to yield the pure product as a white solid (90 mg, 74%).

UPLC RT = 1.98 min, MS (ES) MH^+: 803.0 for $C_{27}H_{34}N_{10}O_{13}S_3$

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.76 (t, 3H), 1.21 (m, 2H), 1.38 (s, 3H), 1.40 (s, 3H), 1.42 (m 1H), 1.08 (m, 1H), 1.96 (m, 2H), 2.88 (s, 3H), 3.05 (m, 2H), 3.90 (m, 1H), 4.05 (m, 2H), 5.13 (m, 1H), 6.73 (s, 1H), 7.30 (s, 1H), 7.96 (s, 1H), 9.11 (d, 1H).

HRMS (ES+) Calcd. for $C_{27}H_{35}N_{10}O_{13}S_3$ $[M + H]^+$ 803.1547; Found 803.1543.

REFERENCES:

1. Han, S.; Zaniewski, R. P.; Marr, E. S.; Lacey, B. M.; Tomaras, A. P.; Evdokimov, A.; Miller, J. R.; Shanmugasundaram, V. Structural basis for effectiveness of siderophore-conjugated monocarbams against clinically relevant strains of Pseudomonas aeruginosa. *Proc. Natl. Acad. Sci. U. S. A.* 2010, *107*, 22002-22007.

2. Kabsch, W. Xds. *Acta Crystallogr. D Biol. Crystallogr.* 2010, *66,* 125-132.

3. Evans, P. R.; Murshudov, G. N. How good are my data and what is the resolution? *Acta Crystallogr. D Biol. Crystallogr.* 2013, *69,* 1204-1214.

4. Vonrhein, C.; Flensburg, C.; Keller, P.; Sharff, A.; Smart, O.; Paciorek, W.; Womack, T.; Bricogne, G. Data processing and analysis with the autoPROC toolbox. *Acta Crystallogr. D Biol. Crystallogr.* 2011, *67,* 293-302.

5. Vagin, A.; Teplyakov, A. MOLREP: an automated program for molecular replacement. *J. Appl. Crystallogr.* 1997, *30,* 1022-1025.

6. Smart, O. S. GRADE, V1.101 . 2011, (Global Phasing, Ltd., Cambridge, United Kingdom).

7. Bruno, I. J.; Cole, J. C.; Kessler, M.; Luo, J.; Motherwell, W. D. S.; Purkis, L. H.; Smith, B. R.; Taylor, R.; Cooper, R. I.; Harris, S. E.; Orpen, A. G. Retrieval of Crystallographically-Derived Molecular Geometry Information. *J. Chem. Inf. Comput. Sci.* 2004, *44,* 2133-2144.

8. Emsley, P.; Lohkamp, B.; Scott, W. G.; Cowtan, K. Features and development of Coot. *Acta Crystallogr. D Biol. Crystallogr.* 2010, *66,* 486-501.

9. Bricogne, G. Buster V2.11.5. 2011, (Global Phasing Ltd., Cambridge, United Kingdom).

10. Smart, O. S.; Womack, T. O.; Flensburg, C.; Keller, P.; Paciorek, W.; Sharff, A.; Vonrhein, C.; Bricogne, G. Exploiting structure similarity in refinement: automated NCS and target-structure restraints in BUSTER. *Acta Crystallogr. D Biol. Crystallogr.* 2012, *68,* 368-380.

11. Mills, S. D.; Eakin, A. E.; Buurman, E. T.; Newman, J. V.; Gao, N.; Huynh, H.; Johnson, K. D.; Lahiri, S.; Shapiro, A. B.; Walkup, G. K.; Yang, W.; Stokes, S. S. Novel bacterial NAD+-dependent DNA ligase inhibitors with broad-spectrum activity and antibacterial efficacy in vivo. *Antimicrob. Agents Chemother.* 2011, *55*, 1088-1096.

12. Shapiro, A. B.; Gu, R. F.; Gao, N.; Livchak, S.; Thresher, J. Continuous fluorescence anisotropy-based assay of BOCILLIN FL penicillin reaction with penicillin binding protein 3. *Anal. Biochem.* 2013, *439*, 37-43.

13. Brickner, S. J.; Flanagan, M. E.; Lall, M. S. WO2010070523A1, 2010.

14. Flanagan, M. E.; Brickner, S. J.; Lall, M.; Casavant, J.; Deschenes, L.; Finegan, S. M.; George, D. M.; Granskog, K.; Hardink, J. R.; Huband, M. D.; Hoang, T.; Lamb, L.; Marra, A.; Mitton-Fry, M.; Mueller, J. P.; Mullins, L. M.; Noe, M. C.; O'Donnell, J. P.; Pattavina, D.; Penzien, J. B.; Schuff, B. P.; Sun, J.; Whipple, D. A.; Young, J.; Gootz, T. D. Preparation, Gram-Negative Antibacterial Activity, and Hydrolytic Stability of Novel Siderophore-Conjugated Monocarbam Diols. *ACS Med. Chem. Lett.* 2011, *2*, 385-390.

15. Woulfe, S. R.; Miller, M. J. The synthesis of substituted 3(S)-(acylamino)-2-oxo-1-azetidinyl]thio]acetic acids. *J. Org. Chem.* 1986, *51*, 3133-3139.

16. Brown, M. F.; Mitton-Fry, M.; Han, S.; Lall, M.; Plummer, M. S.; Risley, H. L.; Shanmugasundaram, V.; Starr, J. T. WO2012073138A1, 2012.

17. Mattingly, P. G.; Miller, M. J. Titanium trichloride reduction of substituted N-hydroxy-2-azetidinones and other hydroxamic acids. *J. Org. Chem.* 1980, *45*, 410-15.

18. Slusarchyk, W. A.; Dejneka, T.; Gougoutas, J.; Koster, W. H.; Kronenthal, D. R.; Malley, M.; Perri, M. G.; Routh, F. L.; Sundeen, J. E.; et, a. Î²-Lactam synthesis: chemospecific

sulfonation and cyclization of the Î²-hydroxyvaline nucleus. *Tetrahedron Lett.* 1986, *27*, 2789-92.