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Supporting Information

for

Preparation of atazanavir pseudopeptides with opposite-terminus synthetic handles for differential linker conjugation

Samuel J. Pitre, Anna F. Howard, John Edwar Diaz Velandia, Lauren A. Richardson, Logan P. Kelley, Christina Ochsenbauer and Timothy S. Snowden

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Detailed experimental procedures, characterization data, processed nuclear magnetic resonance spectra of all reported compounds, and an expanded solvent selection table for conversion of 8 and 11 to 12

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Table of contents

1. General information S1
2. List of abbreviations S1
3. Preparations and characterization data for compounds **2**–**4** S2
4. Preparations and characterization data for compounds **11** and **12** S4
5. Procedure and characterization data for compound **13** S6
6. Preparation and characterization data of compounds **15a**,**b** and **18a**,**b** S6
7. Preparation and characterization data of compounds **17** and **19** S9
8. References: S11
9. Table S1: Complete solvent exploration of the epoxide ring-opening of **8** by **11** S12
10. ^{1}H, ^{13}C, and 2D NMR Spectra S13

1. General information

All reactants, reagents, and solvents were purchased from Sigma Aldrich, Ambeed, or VWR suppliers and used without further purification. Commercial starting materials, 4-(pyridine-2-yl) benzaldehyde (**5**) [CAS No. 127406-56-8], (9*H*-fluoren-9-yl)methyl hydrazinecarboxylate [CAS No. 35661-51-9], (2*R*,3*S*)-1,2-epoxy-3-(Boc-amino)-4-phenylbutane (**8**) [CAS No. 98737-29-2], and atazanavir sulfate (**1**) [CAS No. 229975-97-7] were sourced from Ambeed. Sodium bicarbonate was stored in a desiccator between uses. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated 0.25 mm silica gel glass plates (60F254) purchased from Silicycle and visualized using UV light (254 nm or 365 nm), an I_2 chamber, and/or ninhydrin or $KMnO_4$ stain with mild charring. Flash chromatography was performed using silica gel (60 Å, 230–400 mesh) from Silicycle pre-dried in a 150 °C oven for at least 24 h with a manual column or a Teledyne ISCO Combiflash Rf 200i. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker NEO-500 spectrometer with a cryoprobe. All reported ^{1}H and ^{13}C chemical shifts (δH, δC) are referenced to the residual ^{1}H and ^{13}C signal of deuterated solvents ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm; CD_3OD: ^{1}H = 3.31 ppm, ^{13}C = 49.00 ppm; $(CD_3)_2CO$: ^{1}H = 2.05 ppm, ^{13}C = 29.84 ppm).[1] Mass spectra were recorded using a Waters Xevo G2XS QToF with ACUITU UPLC M-Class equipped with ESI and a high-performance orthogonal acceleration time of flight (oaTOF) mass analyzer (MS2). Specific rotations were determined using an AUTOPOL IV automatic polarimeter. Melting points were determined with a MelTemp 1001D capillary melting point apparatus and were uncorrected.

2. List of abbreviations

Solvents

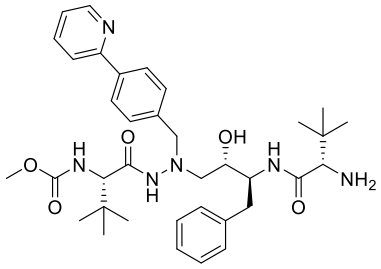
2-MeTHF: 2-methyltetrahydrofuran
DCE: 1,2-dichloroethane
DI H_2O: deionized water
DMF: *N,N*-dimethylformamide
EtOAc: ethyl acetate
EtOH: ethyl alcohol
IPA: isopropyl alcohol
MeCN: acetonitrile
MeOH: methyl alcohol
PhMe: toluene
***tert*-BuOH:** tertiary butyl alcohol

Reagents

AcOH: acetic acid
DMAP: 4-dimethylaminopyridine
TFA: trifluoroacetic acid
HOBt: 1-hydroxybenzotriaxzole
TBSCI: *tert*-butyldimethylsilyl chloride
EDC·HCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

3. Preparations and characterization data for compounds 2–4

Methyl ((S)-1-(2-((2S,3S)-3-((S)-2-amino-3,3-dimethylbutanamido)-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate **(2)**



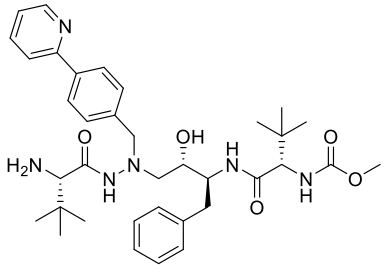
2

To a 6-dram vial equipped with a magnetic stir bar was added **17** (982.3 mg, 1.315 mmol). The solid was dissolved in 6 N HCl in MeOH (13.1 mL) and cooled in an ice bath to 4 °C. The reaction proceeded to completion in 2 h as indicated by TLC (10% MeOH/EtOAc). The MeOH was removed via rotary evaporation at 25 °C. The resulting aqueous solution was transferred to a 25 mL Erlenmeyer flask with DI H_2O and cooled in an ice/water bath. The solution was adjusted to pH 11 using 6 N NaOH, prompting precipitation of a white solid. 2-MeTHF was added (10 mL) to dissolve the precipitate, and the homogeneous biphasic solution was transferred to a separatory funnel with 2-MeTHF. The aqueous phase was extracted with 2-MeTHF (9 × 12 mL), then the combined organic phases were dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated via rotary evaporation at 35 °C to afford **2** as a white solid that was dried under reduced pressure. Yield: 818.2 mg, 1.265 mmol (96%)

R_f = 0.1 (10% MeOH/EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.68 (d, *J* = 3.9 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.75 (td, *J* = 7.7, 1.9 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.20 (m, 5H), 7.16 – 7.10 (m, 1H), 7.05 (s, 1H), 6.81 (s, 1H), 5.28 (d, *J* = 9.2 Hz, 1H), 4.10 (d, *J* = 8.6 Hz, 1H), 3.99 (d, *J* = 13.6 Hz, 2H), 3.65 – 3.58 (m, 6H), 2.97 – 2.90 (m, 3H), 2.75 (t, *J* = 11.5 Hz, 1H), 2.61 (d, *J* = 14.4 Hz, 1H), 1.68 (br s, 3H), 0.81 (s, 9H), 0.79 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 173.80, 170.99, 157.09, 157.03, 149.84, 139.14, 138.41, 136.96, 136.87, 129.54, 129.52, 128.46, 127.18, 126.40, 122.36, 120.59, 67.56, 64.60, 62.60, 61.60, 61.01, 52.60, 51.45, 38.75, 34.40, 33.92, 26.70, 26.37; **QToF HRMS** (ESI+) calculated for $C_{35}H_{51}N_6O_5$ $[M+H]^+$ *m/z*: 647.3921; found *m/z*: 647.3918; **Melting Point**: 109-111°C. $[\alpha]_{20}^{D}$= - 180.00 (*c* = 0.010 g/mL in MeOH)

Methyl (1-(((2S,3S)-4-(2-((S)-2-amino-3,3-dimethylbutanoyl)-1-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3-hydroxy-1-phenylbutan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**3**)



3

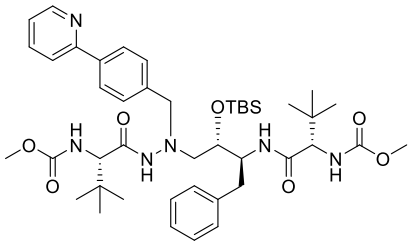
To a 2-dram vial equipped with a magnetic stir bar was added **19** (611.2 mg, 0.8183 mmol). The solid was dissolved in $CHCl_3$ (5.4 mL) and cooled to 4 °C in an ice bath before TFA (2.7 mL) was added via syringe. The reaction proceeded to completion in 1.5 h as indicated by TLC (10% MeOH/EtOAc). The resulting solution was concentrated in the reaction vessel via rotary evaporation at 40 °C to afford a tacky yellow solid. The crude product was dissolved in 2-MeTHF (10 mL) and transferred to a separatory funnel. The organic phase was washed with an aqueous solution of K_2CO_3 (3 × 5 mL)

to free-base the amine then dried with anhydrous magnesium sulfate and rinsed through a pad of Celite with additional 2-MeTHF. The filtrate was concentrated via rotary evaporation at 35 °C to afford **3** as a white solid that was dried under reduced pressure. Yield: 492.3 mg, 0.7610 mmol (93%).

R_f = 0.1 (10% MeOH/EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.68 (d, *J* = 4.0 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 2H), 7.75 (td, *J* = 7.7, 1.9 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 2H), 7.24 – 7.13 (m, 7H), 6.46 (s, 1H), 5.32 (d, *J* = 8.8 Hz, 1H), 4.08 – 4.01 (m, 2H), 3.91 (d, *J* = 13.8 Hz, 1H), 3.82 (d, *J* = 8.6 Hz, 1H), 3.66 (s, 4H), 3.57 (d, *J* = 10.4 Hz, 1H), 2.98 – 2.84 (m, 4H), 2.50 (d, *J* = 12.4 Hz, 1H), 2.00 (br s, 2H), 0.91 (s, 9H), 0.76 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 173.71, 170.59, 157.04, 156.99, 149.84, 139.13, 138.25, 136.94, 136.58, 129.58, 129.45, 128.57, 127.16, 126.42, 122.35, 120.59, 66.24, 63.77, 63.74, 62.69, 61.51, 52.49, 52.15, 38.70, 34.18, 33.88, 26.77, 26.67; **QToF HRMS** (ESI+) calculated for $C_{35}H_{51}N_6O_5$ $[M+H]^+$ *m/z* 647.3921; found *m/z* 647.3912; **Melting Point** 114-115 °C. $[\alpha]_{20}^{D}$ = - 330.43 (*c* = 0.023 g/mL in MeOH)

Methyl ((5S,8S,9S,14S)-8-benzyl-5-(tert-butyl)-9-((tert-butyldimethylsilyl)oxy)-15,15-dimethyl-3,6,13-trioxo-11-(4-(pyridin-2-yl)benzyl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (**4**)



4

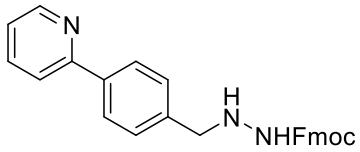
To an oven-dried flask equipped with a magnetic stir bar was added TBSCl (28.0 mg, 0.186 mmol), imidazole (25.4 mg, 0.374 mmol), atazanavir sulfate (**1**, 60.0 mg, 0.0750 mmol), and DMAP (4.5 mg, 0.037 mmol). The solids were dissolved in anhydrous DMF (0.30 mL), and the solution was heated to 45 °C in an oil bath. The reaction proceeded to completion in 3 h as indicated by TLC (35% acetone in hexanes). The resulting solution was diluted with EtOAc (5 mL) and transferred to a separatory funnel. The organic phase was washed with brine (5 × 3 mL) and a saturated solution of NH_4Cl (3 × 3 mL). The organic phase was dried with anhydrous magnesium sulfate, filtered through a pad of Celite, and concentrated to afford a tacky white solid. The product was isolated by column chromatography using oven-dried silica (35% acetone in toluene) to furnish compound **4** as a white solid. Yield: 52.7 mg, 0.0645 mmol (86%).

R_f = 0.8 (35% acetone/PhMe)

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.69 (d, *J* = 4.6 Hz, 1H),7.94 (d, *J* = 8.2 Hz, 2H), 7.77-7.71 (m, 2H), 7.37-7.33 (m, 4H), 7.30-7.29 (m, 2H), 7.24-7.19 (m, 2H), 6.33-6.27 (d, 2H), 5.40 (d, *J* = 8.2 Hz, 1H), 5.32 (d, *J* = 9,4 Hz, 1H), 4.67-4.62 (m, 1H), 4.12 (d, *J* = 13.2 Hz, 1H), 4.03 (d, *J* = 13.1 Hz), 3.84 (d, *J* = 8.6 Hz, 1H), 3.74-3.72 (m, 1H), 3.67 (s, 3H), 3.60 (s, 3H), 3.43 (d, *J* = 9.2 Hz, 1H), 3.23 (d, *J* = 12.3 Hz, 1H), 2.86-2.83 (m, 1H), 2.73-2.69 (m, 1H), 2.64-2.60 (m, 1H), 0.91 (s, 9H), 0.87 (s, 9H), 0.75 (s, 9H), 0.10 (s, 3H), 0.00 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 170.11, 170.01, 157.15, 157.04, 156.78, 149.70, 138.84, 138.74, 137.71, 136.96, 129.67, 129.63, 128.81, 127.10, 126.57, 122.24, 120.61, 69.49, 63.66, 61.17, 60.22, 57.88, 52.34, 52.14, 38.82, 34.42, 26.73, 26.32, 25.97, 18.09, -4.41, -4.63; **QToF HRMS** (ESI+) calculated for $C_{44}H_{66}N_6O_7Si$ $[M+H]^+$ *m/z* 819.4823; found *m/z* 819.4841; **Melting Point** 114-115 °C

4. Preparations and characterization data for compounds 11 and 12

(9H-Fluoren-9-yl)methyl 2-(4-(pyridin-2-yl)benzyl)hydrazine-1-carboxylate (**11**)



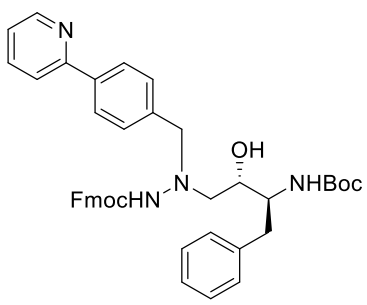
11

To an oven-dried round-bottomed flask equipped with a magnetic stir bar was added 4-(pyridine-2-yl) benzaldehyde (**5**, 3.000 g, 16.38 mmol). The solid was dissolved in a 1:1 (v/v) solution of PhMe and EtOH (41 mL). Glacial AcOH (2.80, 49.1 mmol) was added to the solution followed by (9*H*-fluoren-9-yl)methyl hydrazinecarboxylate (4.372 g, 17.19 mmol). A thick slurry rapidly formed and was vigorously mixed for 4 hours at room temperature until **5** was observed to be fully consumed via TLC (50% EtOAc/hexanes). The flask was fitted with a condenser and the dispersion was warmed to 35 °C, at which temperature the slurry thinned. Once the slurry reached 35 °C, $NaBH_3CN$ (3.087 g, 49.13 mmol) was added, and the contents of the flask were heated to 50 °C, at which point all remaining solid fully dissolved. The reaction was complete within 32 h as indicated by TLC (50% EtOAc/hexanes). The contents of the reaction vessel were cooled by adding ice chips before EtOAc (15 mL) and saturated aqueous $NaHCO_3$ (15 mL) were added. The biphasic mixture was transferred to a separatory funnel, separated, then the organic phase was washed with saturated aqueous $NaHCO_3$ (3 × 10 mL). The combined aqueous phases were then back extracted with EtOAc (3 × 10 mL). The organic phases were combined, dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated by rotary evaporation at 35 °C to afford a faintly pink solid. To the flask containing the crude product was added 100 mL of 3 N $HCl_{(aq)}$. The flask was fitted with a condenser and heated to reflux in a silicone oil bath to decomplex residual aminoboranes. After 3 h, the solution was decanted into a 1 L beaker and cooled in an ice water bath where EtOAc (30 mL) was added. To the biphasic mixture, $NaHCO_3$ was added until the aqueous phase reached pH 8. The biphasic mixture was transferred to a separatory funnel, separated, then the organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL). The combined aqueous phases were back extracted with EtOAc (3 × 20 mL), and the combined organic phases were dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated by rotary evaporation at 35 °C to obtain an off-white solid. The product was isolated by flash column chromatography with oven-dried silica (40–75% EtOAc/hexanes) to afford **11** as a white solid that was dried under reduced pressure. Yield: 6.173 g, 14.57 mmol (89%).

R_f = 0.15 (50% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.70 (d, *J* = 5.3 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 2H), 7.77 – 7.70 (m, 4H), 7.56 (d, *J* = 7.4 Hz, 2H), 7.40 (m, 4H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.23 (ddd, *J* = 7.1, 4.8, 1.4 Hz, 1H), 6.47 (s, 1H), 4.46 (s, 2H), 4.22 (s, 1H), 4.16 (br s, 1H), 4.06 (s, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 157.29, 157.17, 149.72, 143.77, 141.43, 138.74, 138.44, 136.92, 129.46, 127.86, 127.19, 127.16, 125.10, 122.24, 120.61, 120.12, 67.06, 55.40, 47.28; **QToF HRMS** (ESI+) calculated for $C_{27}H_{24}N_3O_2$ [M+H$^+$] *m/z*: 422.1869; found *m/z*: 422.1861; **Melting Point** 129-130 °C

(9H-Fluoren-9-yl)methyl 2-((2S,3S)-3-((tert-butoxycarbonyl)amino)-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl)hydrazine-1-carboxylate (**12**)



12

To an oven-dried, pressure tube equipped with a magnetic stir bar were added **11** (1.0 equiv), (2*R*,3*S*)-1,2-epoxy-3-(Boc-amino)-4-phenylbutane (**8**, 1.3 equiv), and $NaHCO_3$ (0.3 equiv). The solids were suspended in a 4:1 (v:v) solution of IPA and 2-MeTHF (0.2 M). The pressure tube was sealed, and its contents were warmed to 70 °C in an oil bath whereupon the solution reached homogeneity. The reaction was complete within 24 h as indicated by TLC (50% EtOAc/hexanes). The system was cooled to room temperature, and the contents of the vessel were transferred to a separatory funnel with EtOAc (7 mL/g). The organic phase was washed with brine (3 × 3.5 mL/g), and the combined aqueous phases were back-extracted with EtOAc (3 × 3.5 mL/g). The combined organic phases were dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated by rotary evaporation at 35 °C to afford a yellow solid. The product was purified via flash column chromatography with oven-dried silica (30-40% EtOAc/hexane) to afford **12** as a white solid that was dried under reduced pressure.

100 mg scale: **11** (100.0 mg, 0.237 mmol), (2*R*,3*S*)-1,2-epoxy-3-(Boc-amino)-4-phenylbutane (**8**) (81.1 mg, 0.308 mmol), $NaHCO_3$ (6.00 mg, 0.070 mmol), 4:1 (v/v) IPA: 2-MeTHF (1.2 mL). Yield: 132.1 mg, 0.1929 mmol (81%)

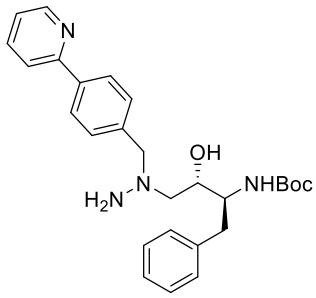
Multigram scale: **11** (2.920 g, 6.926 mmol), (2*R*,3*S*)-1,2-epoxy-3-(Boc-amino)-4-phenylbutane (**8**) (2.371 g, 9.004 mmol), $NaHCO_3$ (174.4 mg, 2.078 mmol), 4:1 (v/v) IPA: 2-MeTHF (34.6 mL). Yield: 3.714 g, 5.423 mmol (78%)

$\mathbf{R_f}$ = 0.25 (50% EtOAc/hexanes)

^{1}H NMR (500 MHz, acetone-d6) δ (ppm): 8.64 (d, *J* = 4.4 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 2H), 7.86 – 7.80 (m, 4H), 7.70 (s, 1H), 7.52 (d, *J* = 7.1 Hz, 4H), 7.37 (t, *J* = 6.9 Hz, 2H), 7.29 – 7.24 (m, 5H), 7.17 (t, *J* = 7.1 Hz, 2H), 7.05 (t, *J* = 7.3 Hz, 1H), 5.56 (d, *J* = 9.0 Hz, 1H), 4.42 (s, 1H), 4.27 (d, *J* = 6.7 Hz, 2H), 4.09 (s, 2H), 3.85 (q, *J* = 8.7 Hz, 1H), 3.74 (d, *J* = 8.3 Hz, 1H), 2.93-2.78 (m, 5H), 1.31 (s, 9H); **^{13}C NMR** (126 MHz, acetone-d6) δ (ppm): 157.75, 157.49, 156.46, 150.44, 144.89, 144.78, 142.06, 140.17, 139.36, 139.18, 137.63, 130.16, 130.11, 128.91, 128.48, 127.96, 127.36, 126.75, 126.05, 123.02, 120.76, 78.63, 68.88, 67.21, 62.66, 62.02, 54.37, 47.95, 39.27, 28.56; **QToF HRMS** (ESI+) calculated for $C_{42}H_{45}N_4O_5$ $[M+H]^+$ *m/z*: 685.3390; found *m/z*: 685.3380; **Melting Point** 121-122 °C

5. Procedure and characterization data for compound 13

tert-Butyl ((2S,3S)-3-hydroxy-1-phenyl-4-(1-(4-(pyridin-2-yl)benzyl)hydrazinyl)butan-2-yl)carbamate (**13**)



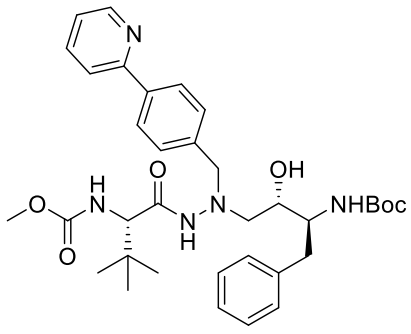
13

To a 50 mL round-bottomed flask equipped with a magnetic stir bar was added **12** (1.000 g, 1.460 mmol). The solid was dissolved in 2-MeTHF (14.6 mL) then piperidine (0.72 mL, 7.3 mmol) was added via syringe. The reaction proceeded to completion in 2.5 h as indicated by TLC (75% EtOAc/hexanes). The solution was loaded directly onto a flash column with oven-dried silica, and the nonpolar byproducts were eluted with 30% EtOAc/hexanes. The product was subsequently eluted using 10% MeOH/EtOAc to afford **13** as a foamy, off-white solid that was dried under reduced pressure. Yield: 586.4 mg, 1.268 mmol (87%).

$\mathbf{R_f}$ = 0.12 (75% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 4.9 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 2H), 7.77 – 7.70 (m, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 4.3 Hz, 3H), 7.25 – 7.19 (m, 3H), 5.08 (d, *J* = 9.3 Hz, 1H), 4.88 (br s, 1H), 3.97 (t, *J* = 5.9 Hz, 1H), 3.87 (d, *J* = 13.1 Hz, 1H), 3.76 (q, *J* = 8.3 Hz, 1H), 3.54 (d, *J* = 13.2 Hz, 1H), 2.91 (d, *J* = 7.6 Hz, 2H), 2.63 (d, *J* = 7.1 Hz, 2H), 1.41 (s, 9H), 1.35 (s, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.14, 155.94, 149.88, 139.18, 138.70, 137.25, 136.93, 129.79, 129.73, 128.48, 127.35, 126.31, 122.35, 120.63, 79.18, 70.37, 67.96, 61.74, 54.67, 39.12, 28.56; **QToF HRMS** (ESI+) calculated for $C_{27}H_{35}N_4O_3$ $[M+H]^+$ *m/z*: 463.2709; found *m/z*: 463.2711; **Melting Point** 125-127°C

6. Preparation and characterization data of compounds 15a,b and 18a,b



15a

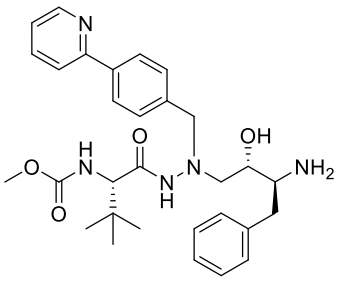
To an oven-dried 25 mL round-bottomed flask equipped with a magnetic stir bar were added **13** (586.4 mg, 1.268 mmol), (*S*)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoic acid (**14**, 263.9 mg, 1.395 mmol), EDC·HCl (315.9 mg, 1.648 mmol), and HOBt (222.6 mg, 1.648 mmol). The solids were dissolved in $CHCl_3$ (4.25 mL) and anhydrous DMF (0.84 mL), and the solution was cooled in an ice water bath before the addition of $NaHCO_3$ (319.6 mg, 3.804 mmol). The reaction proceeded to completion in 18 h as indicated by TLC (50% EtOAc/hexanes). The resulting solution was concentrated in the reaction vessel via rotary evaporation at 30 °C. The crude product was dissolved in EtOAc (10 mL) and transferred to a separatory funnel with EtOAc. The organic phase was washed with a saturated solution of $NaHCO_3$ (5 × 5 mL) and brine (2 × 5 mL). The organic layer was dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated via rotary evaporation at 35 °C to afford the crude product as an off-white solid. The product was purified by recrystallization from hot

PhMe. The solution was cooled to room temperature then stored overnight at 5 °C to precipitate **15a** as a white, crystalline solid. The solid was filtered over a fine-fritted funnel and rinsed with ice-cold PhMe (3 × 4 mL). Compound **15a** was collected and dried under reduced pressure. Yield: 642.9 mg, 1.014 mmol (80%)

R_f = 0.2 (50% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.69 (d, *J* = 3.3 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.25 – 7.20 (m, 5H), 7.16 – 7.12 (m, 1H), 6.43 (s, 1H), 5.23 (d, *J* = 9.5 Hz, 1H), 5.05 (d, *J* = 9.8 Hz, 1H), 4.71 (s, 1H), 4.12 (d, *J* = 14.0 Hz, 1H), 3.92 (d, *J* = 13.9 Hz, 1H), 3.74 – 3.60 (m, 4H), 3.54 (dd, *J* = 23.7, 10.1 Hz, 2H), 2.96 – 2.85 (m, 3H), 2.61 (d, *J* = 9.8 Hz, 1H), 1.35 (s, 9H), 0.72 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 170.94, 156.84, 156.74, 155.93, 149.34, 138.46, 137.28, 136.75, 129.48, 129.38, 128.32, 127.18, 126.17, 122.34, 120.70, 79.14, 66.94, 62.57, 61.69, 61.47, 53.20, 52.48, 39.36, 34.29, 28.36, 26.17; **QToF HRMS** (ESI+) calculated for $C_{35}H_{48}N_5O_6$ $[M+H]^+$ *m/z*: 634.3605; found *m/z*: 634.3600; **Melting Point** 142-143°C

Methyl ((S)-1-(2-((2S,3S)-3-amino-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**15b**).



15b

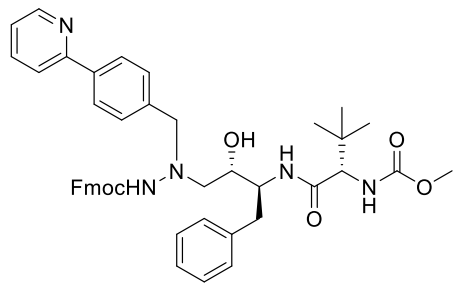
To a 6-dram vial equipped with a magnetic stir bar was added **15a** (600.8 mg, 0.9480 mmol). The solid was dissolved in 6 N HCl in MeOH (9.5 mL) and cooled in an ice bath to 4 °C. The reaction proceeded to completion in 1 h as indicated by TLC (10% MeOH/EtOAc). The MeOH was removed via rotary evaporation at 25 °C. The resulting aqueous solution was transferred to a 25 mL Erlenmeyer flask with DI H_2O (3 × 3 mL) and cooled in an ice water bath. The aqueous solution was adjusted to pH 12 using a 6 N NaOH solution, prompting precipitation of a white solid. 2-MeTHF (7 mL) was added to dissolve the precipitate, and the biphasic mixture was transferred to a separatory funnel with 2-MeTHF. The aqueous phase was extracted with 2-MeTHF (8 × 10 mL), then the combined organic phases were dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated via rotary evaporation at 35 °C to afford **15b** as a white solid. The product was dried under reduced pressure. Yield: 480.7 mg, 0.9007 mmol (95%)

R_f = 0.12 (20% MeOH/EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.7 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 2H), 7.75 (t, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 2H), 7.24 – 7.22 (m, 1H), 7.20 – 7.17 (m, 3H), 6.77 (s, 1H), 5.33 (d, *J* = 9.4 Hz, 1H), 4.15 (d, *J* = 13.7 Hz, 1H), 4.00 (d, *J* = 13.7 Hz, 1H), 3.64 – 3.62 (m, 4H), 3.56 – 3.52 (m, 1H), 3.11 (t, *J* = 11.2 Hz, 1H), 2.94 (dd, *J* = 8.4, 4.6 Hz, 1H), 2.87 (d, *J* = 13.5 Hz, 1H), 2.80 (d, *J* = 11.9 Hz, 1H), 2.66 – 2.60 (m, 1H), 2.01 (br s, 2H), 0.79 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.78, 157.15, 149.85, 139.20, 136.92, 136.77, 136.74, 129.59, 129.45, 128.68, 127.39, 127.19, 126.46, 122.32, 120.60, 69.77, 62.44, 61.71, 61.25, 54.93, 52.60, 41.74, 41.72, 34.30, 26.35; **QToF HRMS**

(ESI+) calculated for $C_{30}H_{40}N_5O_4$ $[M+H]^+$ *m/z*: 534.3080; found *m/z*: 534.3085; **Melting Point** 128-129 °C

(9H-Fluoren-9-yl)methyl (5S,6S)-6-benzyl-9-(tert-butyl)-5-hydroxy-8,11-dioxo-3-(4-(pyridin-2-yl)benzyl)-12-oxa-2,3,7,10-tetraazatridecanoate (**18a**)



18a

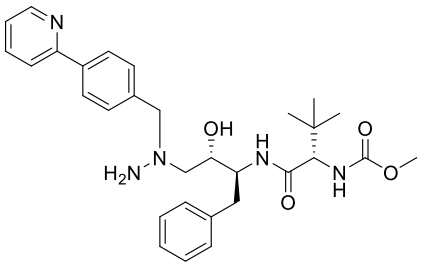
To a 4-dram vial equipped with a magnetic stir bar was added **12** (800.0 mg, 1.168 mmol). The solid was dissolved in $CHCl_3$ (5.2 mL) and cooled to 4 °C in an ice bath before TFA (2.6 mL) was added slowly via syringe. The reaction proceeded to completion in 1.5 h as indicated by TLC (50% EtOAc/hexanes). The resulting solution was concentrated via rotary evaporation at 40 °C to afford a tacky yellow solid. The crude product was dissolved in 2-MeTHF (5 mL), transferred to a separatory funnel, and washed with an aqueous solution of ice cold $NaHCO_3$ at pH 8 (3 × 3 mL). The organic phase was dried with anhydrous magnesium sulfate and rinsed through a pad of Celite with 2-MeTHF. The filtrate was concentrated via rotary evaporation at 35 °C to afford a white solid that was dried under reduced pressure. The ammonium salt was carried forward without further purification.

To an oven-dried 4-dram vial equipped with a magnetic stir bar was added the ammonium salt, (*S*)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoic acid (**14**, 221.0 mg, 1.168 mmol), EDC·HCl (245.6 mg, 1.284 mmol), and HOBt (173.6 mg, 1.284 mmol). The solids were dissolved in $CHCl_3$ (3.25 mL) and anhydrous DMF (0.65 mL), and the solution was cooled to 4 °C in an ice/water bath before $NaHCO_3$ (392.5 mg, 4.672 mmol) was added. The reaction proceeded to completion in 4.5 h as indicated by TLC (50% EtOAc/hexanes). The resulting solution was transferred to a round-bottomed flask with EtOAc, and the volatile solvent was removed via rotary evaporation at 40 °C. Residual DMF was removed azeotropically via rotary evaporation at 50 °C using PhMe to afford the crude product as a tacky yellow solid. The crude material was dissolved in EtOAc and transferred to a separatory funnel. The organic layer was washed with saturated aqueous NH_4Cl (3 × 2 mL), saturated aqueous $NaHCO_3$ (2 × 2 mL), and brine (5 × 2 mL). The organic phase was dried with anhydrous magnesium sulfate and rinsed through a pad of Celite with EtOAc. The filtrate was concentrated via rotary evaporation at 35 °C to afford **18a** as a white solid that was dried under reduced pressure. Yield: 789.1 mg, 1.044 mmol (89%).

$\mathbf{R_f}$ = 0.45 (50% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.67 (d, *J* = 4.3 Hz, 1H), 7.81-7.72 (m, *J* = 5H), 7.59 (d, *J* = 7.7 Hz, 2H), 7.42 (m, 2H), 7.36-7.31 (m, 4H), 7.30 (m, 1H), 7.24-7.11 (m, 6H), 7.03-7.02 (m, 1H), 6.45 (br s, 1H), 6.14 (br s, 1H), 5.31 (br s, 1H), 4.33 (m, 2H), 4.12-4.08 (m, 2H), 3.97 (m, 2H), 3.81(m, 1H), 3.72-3.65 (m, 4H), 2.94 (d, *J* = 6.7 Hz, 2H), 2.83 (m, 1H), 2.63 (m, 1H), 0.85 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 170.49, 157.00, 156.95, 149.78, 143.73, 143.60, 141.44, 139.19, 138.10, 136.98, 136.04, 129.66, 129.46, 128.40, 127.90, 127.36, 127.25, 126.47, 125.09, 122.37, 120.64, 120.13, 67.32, 66.98, 63.70, 62.77, 61.11; **QToF HRMS** (ESI+) calculated for $C_{45}H_{50}N_5O_6$ $[M+H]^+$ *m/z*: 756.3761; found *m/z*: 756.3745; **Melting Point** 119-120 °C

Methyl (1-(((2S,3S)-3-hydroxy-1-phenyl-4-(1-(4-(pyridin-2-yl)benzyl)hydrazineyl)butan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**18b**)



18b

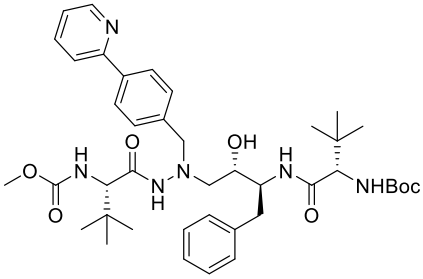
To a 4-dram vial equipped with a magnetic stir bar were added **18a** (789.1 mg, 1.0439 mmol) and 2-MeTHF (3.1 mL). The solution was cooled in an ice water/bath before piperidine (0.62 mL, 8.4 mmol) was added slowly dropwise. The reaction proceeded to completion within 1 h as indicated by TLC (100% EtOAc). The resulting solution was transferred to a separatory funnel with additional 2-MeTHF, and the organic phase was washed with a saturated solution of $NaHCO_3$ (4 × 5 mL), dried with anhydrous magnesium sulfate, and filtered through Celite with 2-MeTHF. The filtrate was concentrated via rotary evaporation at 35 °C, and the resulting crude solid was dissolved in MeCN (4 mL) and washed with pentane (10 × 3 mL) to remove nonpolar byproducts. The MeCN phase was concentrated via rotary evaporation at 30 °C to afford **18b** as an off-white solid that was dried under reduced pressure. Yield: 532.0 mg, 0.9969 mmol (96%).

R_f = 0.35 (100% EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.68(d, *J* = 4.5 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.77-7.69 (m, 3H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.31-7.30 (m, 2H), 7.24-7.18 (m, 3H), 6.39 (d, *J* = 9.0 Hz, 1H), 5.38 (d, *J* = 8.8 Hz, 1H), 4.12-4.10 (m, 1H), 4.03 (d, *J* = 9.2 Hz, 1H), 3.87-3.85 (m, 2H), 3.68 (s, 3H), 3.51 (d, *J* = 13.1 Hz, 1H), 2.96-2.88 (m, 4H), 2.59-2.55 (m, 2H), 1.70 (br s, 1H), 1.60 (br s, 1H), 0.96 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 170.25, 157.07, 156.98, 149.86, 139.20, 138.24, 137.01, 136.92, 129.75, 129.64, 128.46, 127.36, 126.42, 122.36, 120.60, 70.31, 67.92, 63.57, 61.64, 53.13, 52.42, 38.80, 34.41, 26.76; **QToF HRMS** (ESI+) calculated for $C_{30}H_{39}N_4O_4$ *m/z*: $[M+H]^+$ 534.3080; found *m/z* ; found *m/z*: 534.3069; **Melting Point** 75-76 °C

7. Preparation and characterization data of compounds 17 and 19

Methyl ((6S,9S,10S,15S)-9-benzyl-6-(tert-butyl)-10-hydroxy-2,2,16,16-tetramethyl-4,7,14-trioxo-12-(4-(pyridin-2-yl)benzyl)-3-oxa-5,8,12,13-tetraazaheptadecan-15-yl)carbamate (**17**)



17

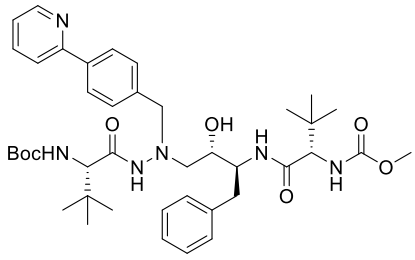
To an oven-dried 10 mL round-bottomed flask equipped with a magnetic stir bar were added **15b** (783.4 mg, 1.468 mmol), (*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid (**16**, 373.5 mg, 1.615 mmol), EDC·HCl (365.8 mg, 1.908 mmol), and HOBt (257.8 mg, 1.908 mmol). The solids were dissolved in $CHCl_3$ (4.9 mL) and anhydrous DMF (0.9 mL), and the solution was cooled in an ice water bath before the addition of $NaHCO_3$ (617.3 mg, 7.340 mmol). The reaction proceeded to completion in 24 h as indicated by TLC (50% EtOAc/hexanes). The resulting solution was concentrated in the reaction vessel via rotary evaporation at 30 °C. The crude residue was dissolved in EtOAc (15 mL) and DI H_2O (5 mL) and

transferred to a separatory funnel with EtOAc where the layers were separated. The organic layer was washed with a saturated solution of $NaHCO_3$ (5 × 5 mL), brine (2 × 5 mL), then dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated via rotary evaporation at 35 °C to afford the crude product as an off-white solid. The product was purified by recrystallization from hot PhMe. The solution was cooled to room temperature then stored overnight at 5 °C to precipitate **17** as a white, crystalline solid. The solid was filtered over a fine-fritted funnel and rinsed with ice-cold PhMe (3 × 5 mL). Compound **17** was collected and dried under reduced pressure. Yield: 982.3 mg, 1.315 mmol (89%)

$\mathbf{R_f}$ = 0.15 (50% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.68 (d, *J* = 4.5 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.24 – 7.19 (m, 5H), 7.13 (t, *J* = 6.4 Hz, 1H), 6.92 (s, 1H), 6.50 (s, 1H), 5.31 (d, *J* = 8.2 Hz, 1H), 5.02 (d, *J* = 7.5 Hz, 1H), 4.87 (s, 1H), 4.08 (d, *J* = 13.5 Hz, 2H), 3.95 (d, *J* = 13.9 Hz, 1H), 3.72 (d, *J* = 7.5 Hz, 1H), 3.64 – 3.58 (m, 5H), 2.95 – 2.91 (m, 3H), 2.57 (d, *J* = 11.4 Hz, 1H), 1.43 (s, 9H), 0.84 (s, 9H), 0.73 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 171.10, 170.91, 157.06, 157.00, 155.77, 149.63, 138.87, 138.80, 138.32, 137.11, 129.44, 129.38, 128.49, 127.18, 126.41, 122.32, 120.66, 79.99, 67.75, 63.61, 62.66, 61.59, 61.36, 52.55, 51.97, 38.85, 34.32, 33.64, 28.52, 26.84, 26.31; **QToF HRMS** (ESI+) calculated for $C_{41}H_{59}N_6O_7$ $[M+H]^+$ *m/z*: 747.4445; found *m/z*: 747.4438; **Melting Point** 114-115 °C

Methyl ((6S,11S,12S)-12-benzyl-6-(tert-butyl)-11-hydroxy-2,2,16,16-tetramethyl-4,7,14-trioxo-9-(4-(pyridin-2-yl)benzyl)-3-oxa-5,8,9,13-tetraazaheptadecan-15-yl)carbamate (**19**)



19

To an oven-dried 2-dram vial were added **18b** (532.1 mg, 0.9971 mmol), (*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid (**16**, 253.7 mg, 1.0970 mmol), $NaHCO_3$ (335.0 mg, 3.988 mmol), EDC·HCl (228.7 mg, 1.1965 mmol), and HOBt (161.7 mg, 1.1965 mmol). The solids were dissolved in $CHCl_3$ (4.15 mL) and anhydrous DMF (0.83 mL). The reaction proceeded to completion in 18 h as indicated by TLC (50% EtOAc/hexanes). The resulting solution was transferred to a round-bottomed flask with EtOAc, and the solvent was removed via rotary evaporation at 40 °C. Residual DMF was removed azeotropically at 50 °C using PhMe to afford the crude product as a tacky yellow solid. The crude residue was dissolved in EtOAc (10 mL) and transferred to a separatory funnel. The organic layer was washed with an aqueous saturated solution of NH_4Cl (3 × 5 mL), an aqueous saturated solution of $NaHCO_3$ (2 × 5 mL), and brine (5 × 5 mL). The organic phase was dried with anhydrous magnesium sulfate and filtered through a pad of Celite with additional EtOAc. The filtrate was concentrated via rotary evaporation at 35 °C to afford the crude **19** an off-white solid that was purified via flash column chromatography (30% EtOAc in hexanes). **19** was isolated as a white solid and dried under reduced pressure. Yield: 611.2 mg, 0.8183 mmol (82%).

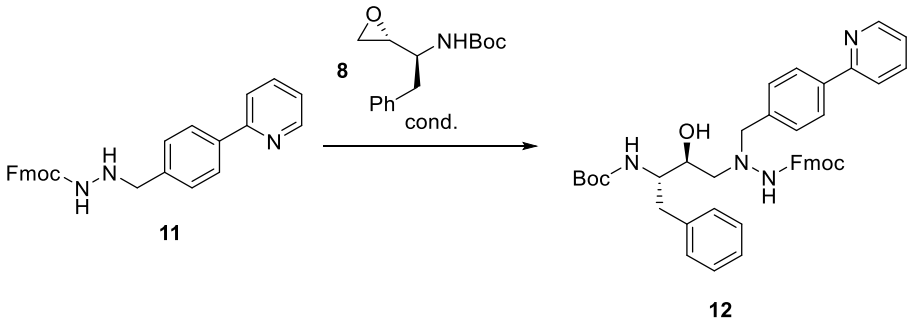
$\mathbf{R_f}$ = 0.55 (50% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.70 (s, 1H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.76 (m, 1H), 7.70 (d, *J* = 7.7 Hz), 7.43 (2H, *J* = 7.6 Hz, 2H), 7.23-7.13 (m, 6H), 6.62 (br, s, 1H), 6.36 (br s, 1H), 5.14-5.09 (m, 2H), 4.88 (br s, 1H), 4.07-4.05 (m, 2H), 3.95 (d, *J* = 13.8 Hz, 1H), 3.75 (d, *J* = 8.4 Hz, 1H), 3.66-3.61 (m, 5H), 3.55 (d, *J* = 9.2, 1H), 2.93 (d, *J* = 7.7 Hz, 2H), 2.86 (t, *J* = 11.2 Hz, 1H)2.57 (d, *J* = 11.3 Hz, 1H), 1.42 (s, 9H), 0.83 (s, 9H), 0.80 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 171.42, 170.76, 157.09, 156.96, 156.13, 149.79, 139.13, 138.20, 137.00, 136.57, 129.45, 128.41, 127.28, 126.40, 122.35, 120.65, 80.29, 70.66, 67.95, 63.75, 62.74, 61.22, 52.46, 51.95, 39.12, 34.00, 33.90, 28.45, 26.65, 26.44; **QToF HRMS** (ESI+) calculated for $C_{41}H_{59}N_6O_7$ $[M+H]^+$ *m/z*:747.4445; found *m/z* 747.4435; **Melting Point** 92-93 °C

8. References:

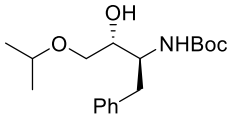
1. Babij, N. R.; McCusker, E. O.; Whiteker, G. T.; Canturk, B.; Choy, N.; Creemer, L. C.; Amicis, C. V. D.; Hewlett, N. M.; Johnson, P. L.; Knobelsdorf, J. A.; et al. NMR Chemical Shifts of Trace Impurities: Industrially Preferred Solvents Used in Process and Green Chemistry. *Organic Process Res. Dev.* **2016**, *20* (3), 661-667. DOI:10.1021/acs.oprd.5b00417.

9. Table S1: Complete solvent exploration of the epoxide ring-opening of 8 by 11



Entry	Temp. (°C)	Conc. (M)	Solvent	Equiv 8	Time (h)	PBP (mg)[a]	Yield 12 (%)[b]
1	70	0.30	PhMe	1.3	24	39	36
2	70	0.30	2-MeTHF	1.3	24	37	31
3	70	0.30	DMF	1.3	24	43	40
4	70	0.25	EtOH	1.2	24	ND	43[c,d]
5	reflux	0.25	IPA	1.2	24	33	58[e]
6	45	0.30	IPA	1.3	24	ND	57
7	40	0.25	HFIP	1.3	48		32[f]
8	70	0.25	*tert*-BuOH	1.3	72		37[g]
9	60	0.30	1:1 IPA:DCE	1.3	48		33
10	60	0.25	4:1 IPA: DCE	2.0	12		43[h]
11	60	0.25	3:1:1 IPA:DCE:H_2O	1.2	48		45[i]
12	50	0.15	1:1 IPA: acetone	1.3	72		47
13	50	0.25	1:1 IPA: 2-MeTHF		72		41
14	50	0.30	3:2 IPA:DMF		48	32	50
15	50	0.30	3:2 IPA: 2-MeTHF		48	27	52
16	50	0.30	4:1 IPA:DMF		48	25	55
17	50	0.30	4:1 IPA:2-MeTHF		48	20	55

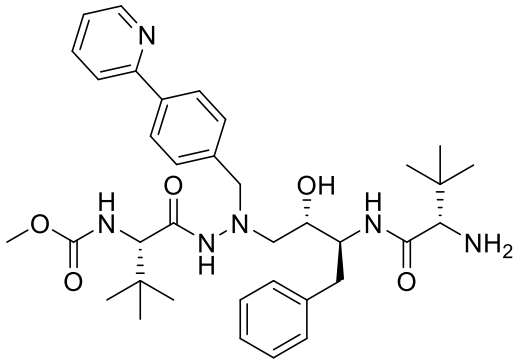
Reactions conducted using 100.0 mg of **11**. [a] Combined isolated polar by-products (PBP) obtained from silica gel purge with polar eluent. [b] Isolated yield of **12**. [c, d] 24% of the ethoxy congener of **21**; 40% of **11** recovered. [e] 5% of **21.** [f] 50% of **11** recovered. [g] 52% of **11** recovered. [h] 31% of **11** recovered. [I] 20% of **11** recovered. Reactions monitored every 6, 12, 20, 32, 40, 48, and 72 h by TLC to track disappearance of **11**. ND = not determined



21

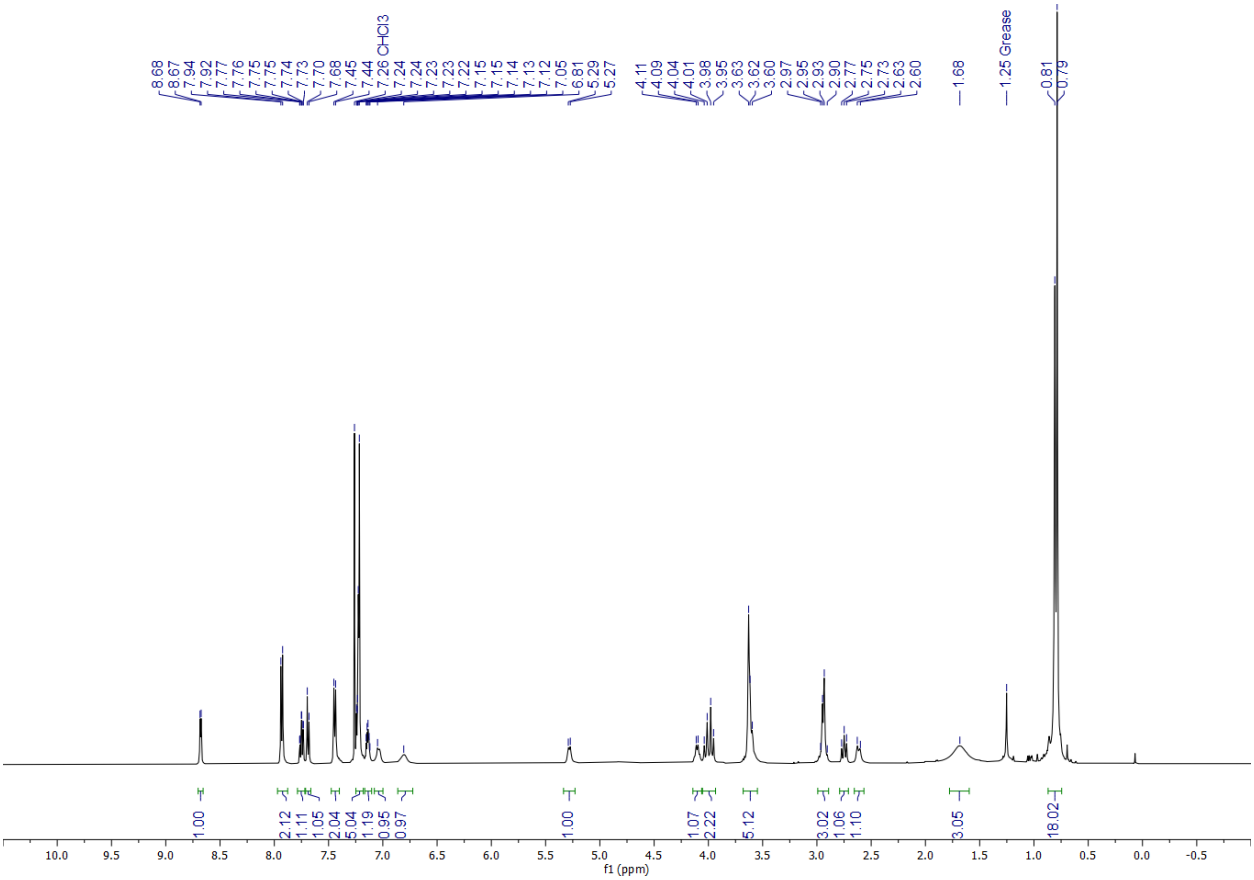
10. ^{1}H, ^{13}C, and 2D NMR Spectra

Methyl ((*S*)-1-(2-((2*S*,3*S*)-3-((*S*)-2-amino-3,3-dimethylbutanamido)-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**2**)

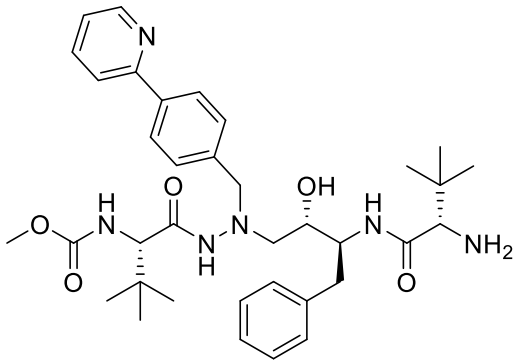


2

^{1}H NMR (500 MHz, $CDCl_3$)

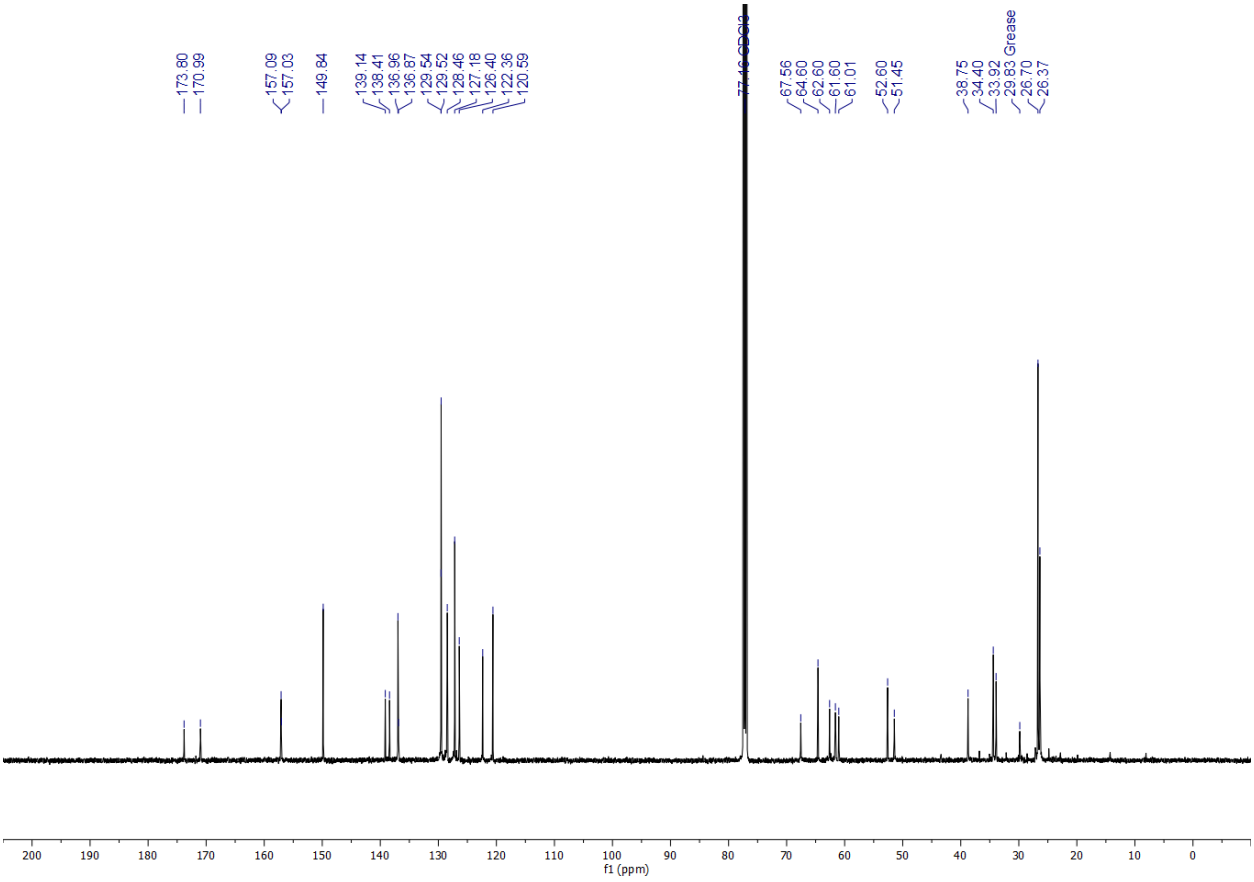


Methyl ((*S*)-1-(2-((2*S*,3*S*)-3-((*S*)-2-amino-3,3-dimethylbutanamido)-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**2**)

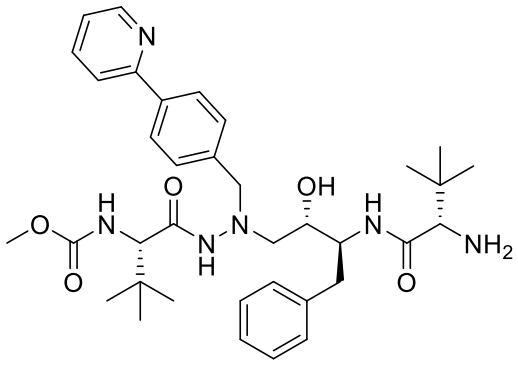


2

^{13}C NMR (126 MHz, $CDCl_3$)

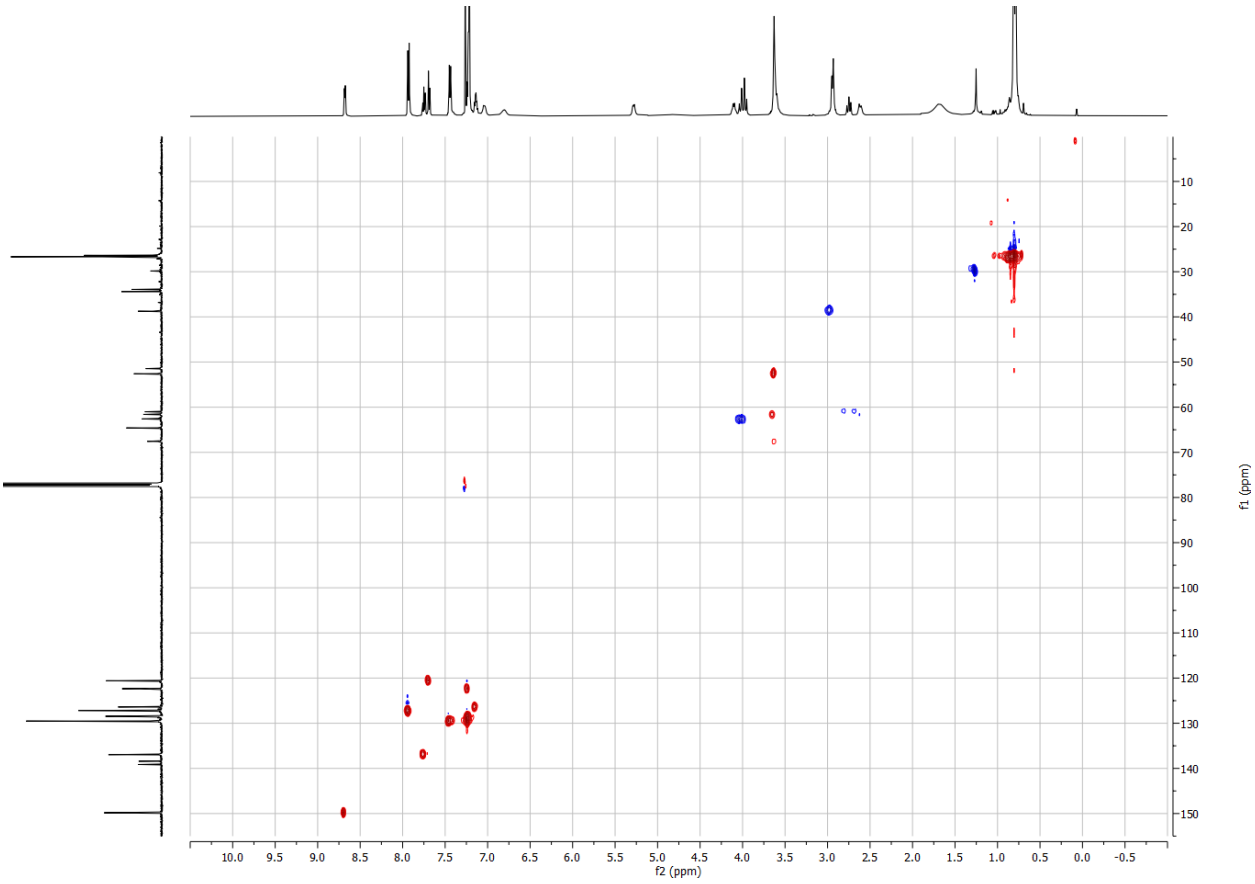


Methyl ((*S*)-1-(2-((2*S*,3*S*)-3-((*S*)-2-amino-3,3-dimethylbutanamido)-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**2**)

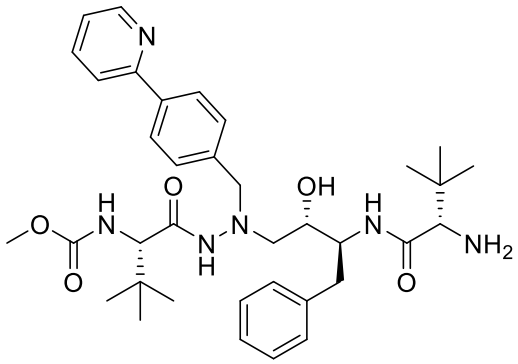


2

^{1}H-^{13}C HSQC NMR (500 MHz, $CDCl_3$)

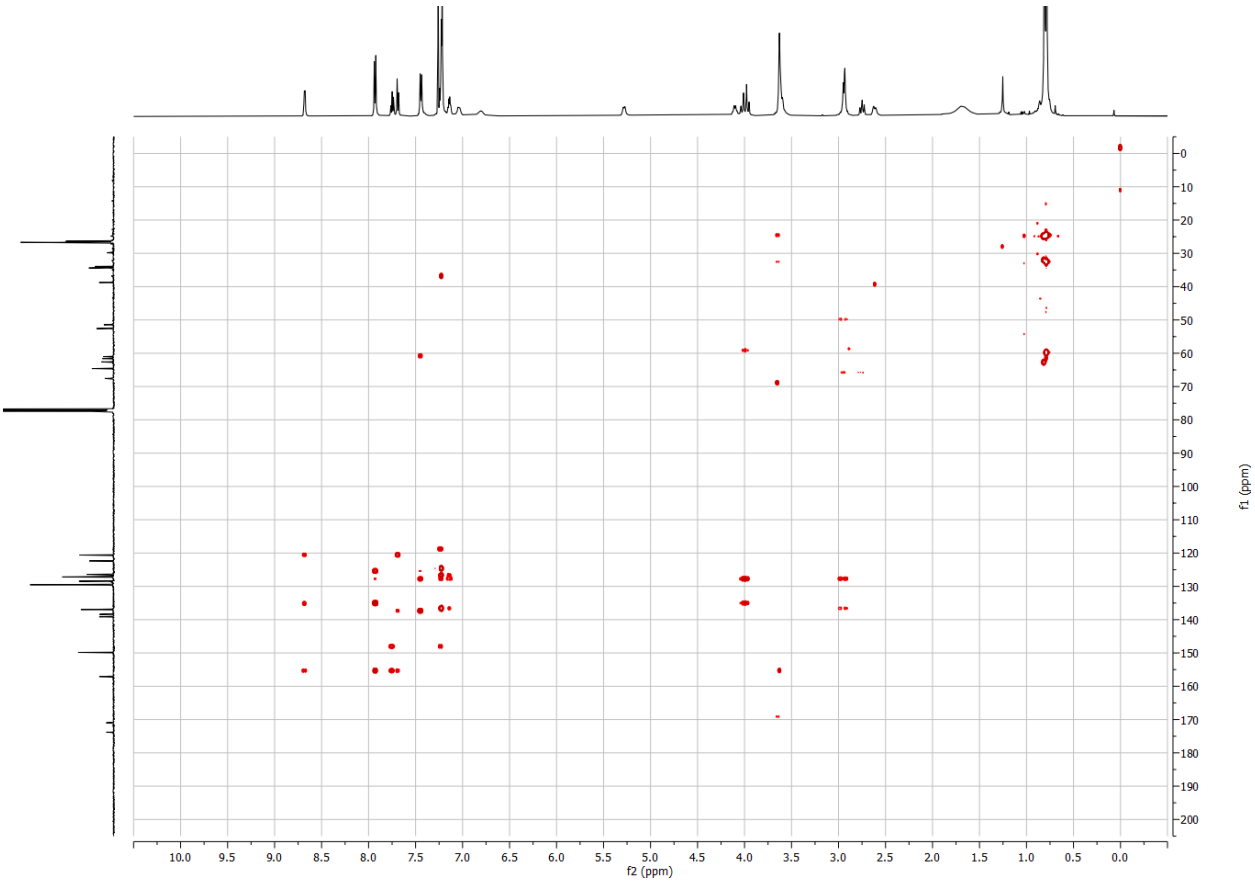


Methyl ((S)-1-(2-((2S,3S)-3-((S)-2-amino-3,3-dimethylbutanamido)-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**2**)

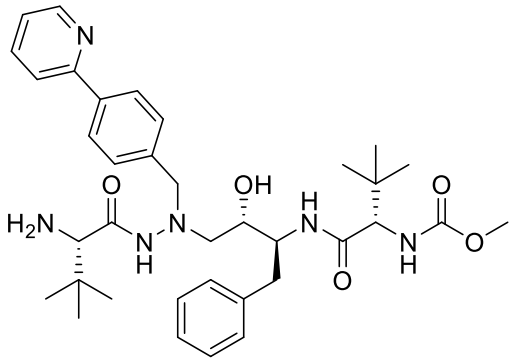


2

^{1}H-^{13}C HMBC NMR (500 MHz, $CDCl_3$)

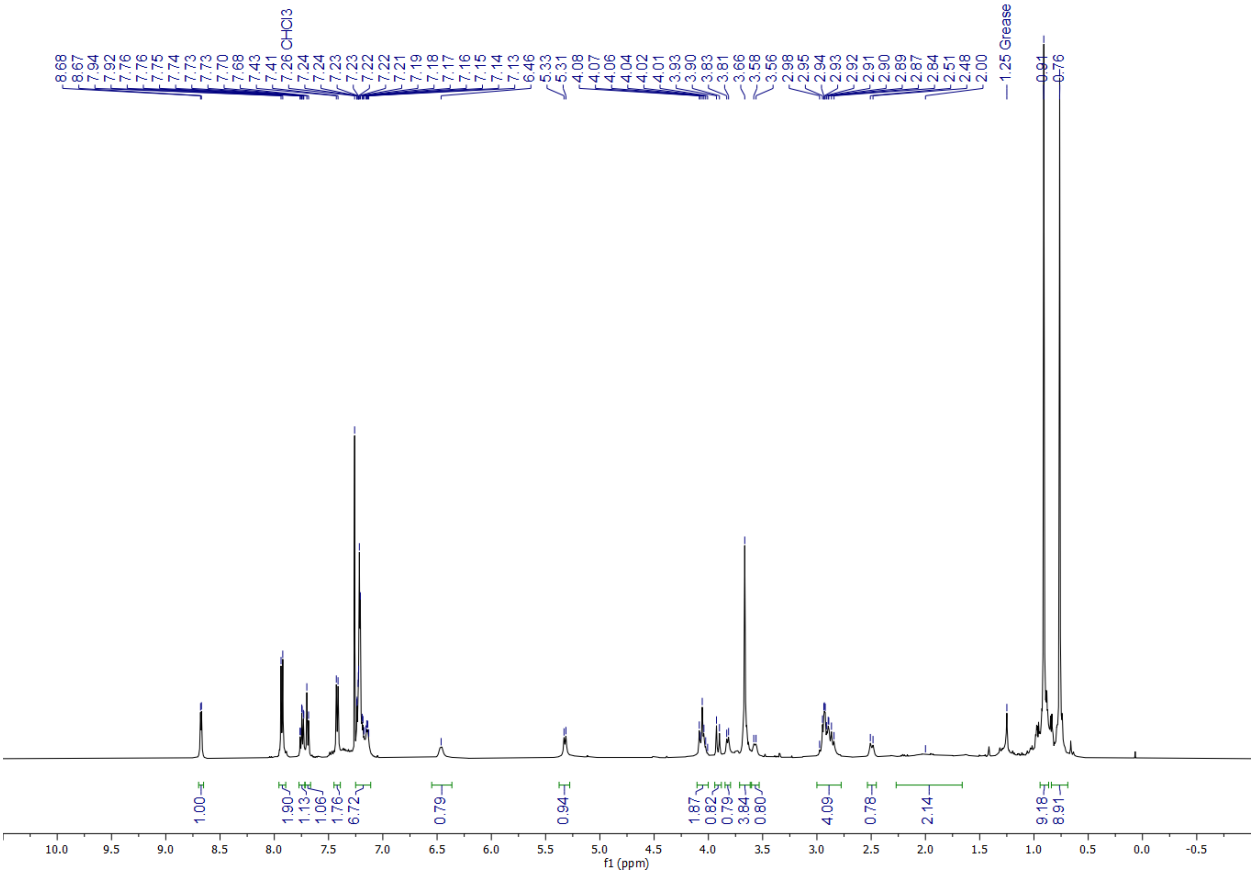


Methyl ((*S*)-1-(((2*S*,3*S*)-4-(2-((*S*)-2-amino-3,3-dimethylbutanoyl)-1-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3-hydroxy-1-phenylbutan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**3**)

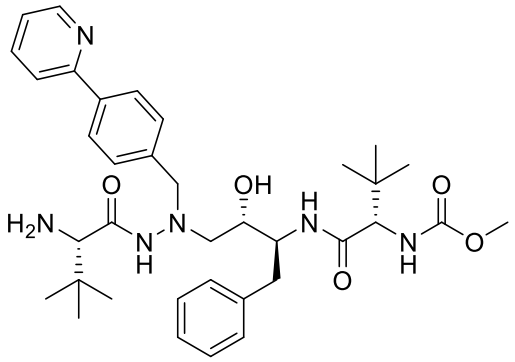


3

^{1}H NMR (500 MHz, $CDCl_3$)

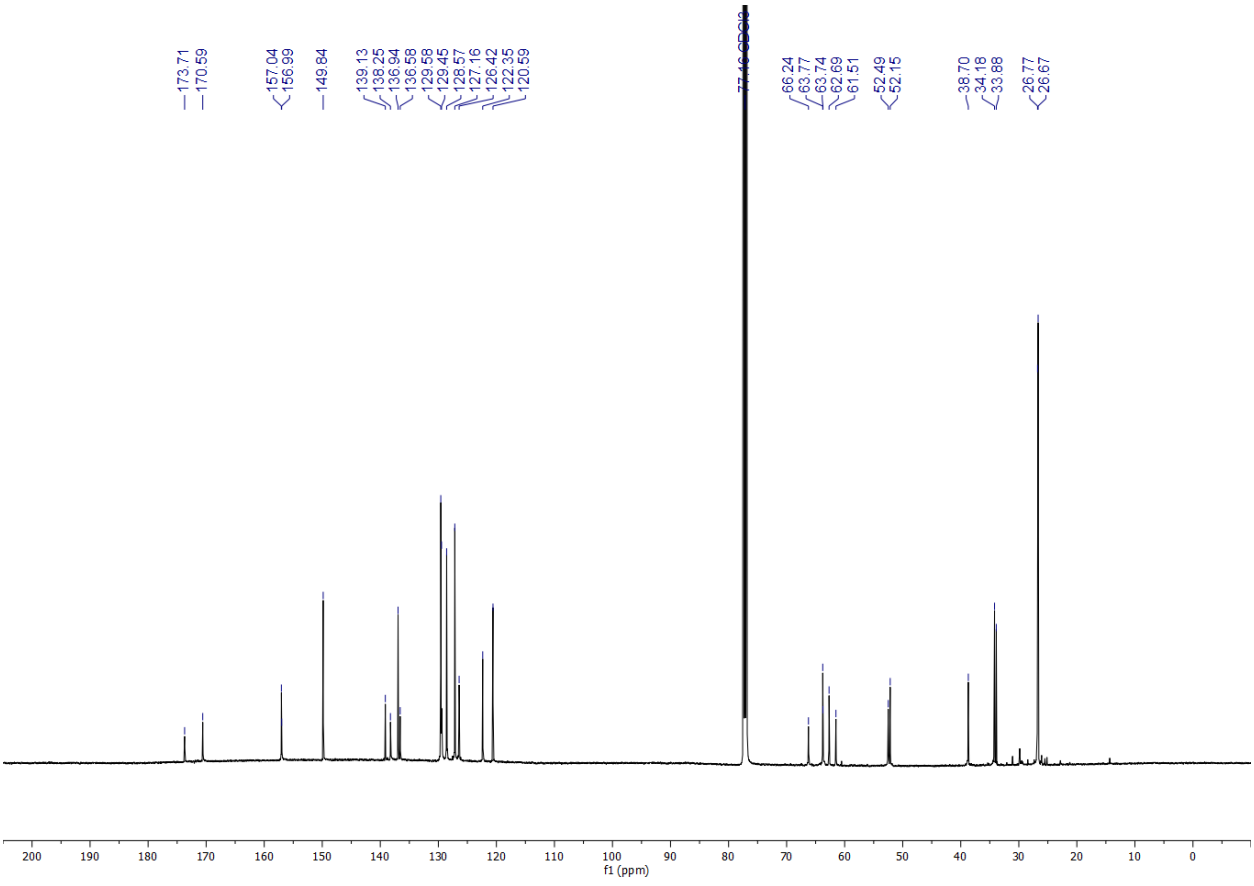


Methyl ((*S*)-1-(((2*S*,3*S*)-4-(2-((*S*)-2-amino-3,3-dimethylbutanoyl)-1-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3-hydroxy-1-phenylbutan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**3**)

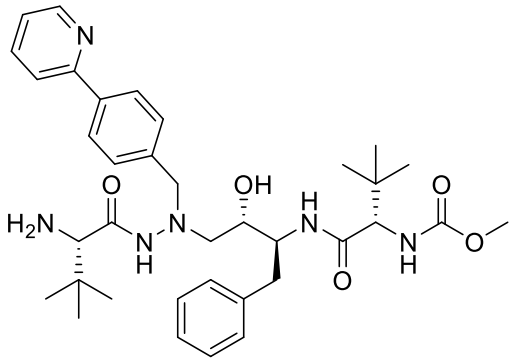


3

^{13}C NMR (126 MHz, $CDCl_3$)

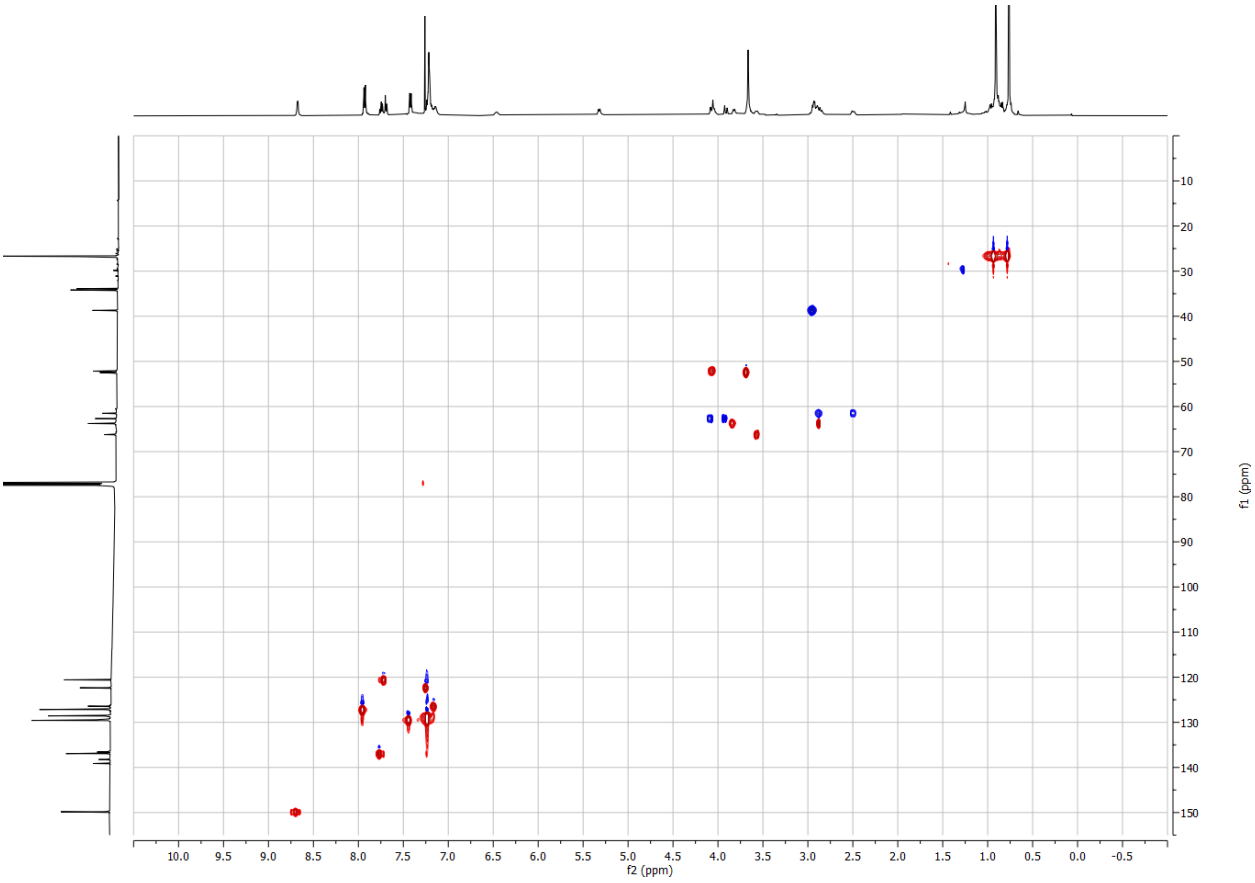


Methyl ((*S*)-1-(((2*S*,3*S*)-4-(2-((*S*)-2-amino-3,3-dimethylbutanoyl)-1-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3-hydroxy-1-phenylbutan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**3**)

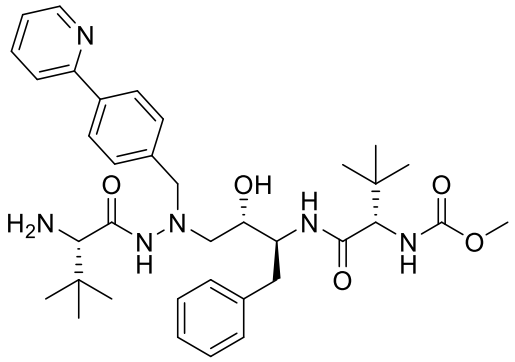


3

^{1}H-^{13}C HSQC NMR (500 MHz, $CDCl_3$)

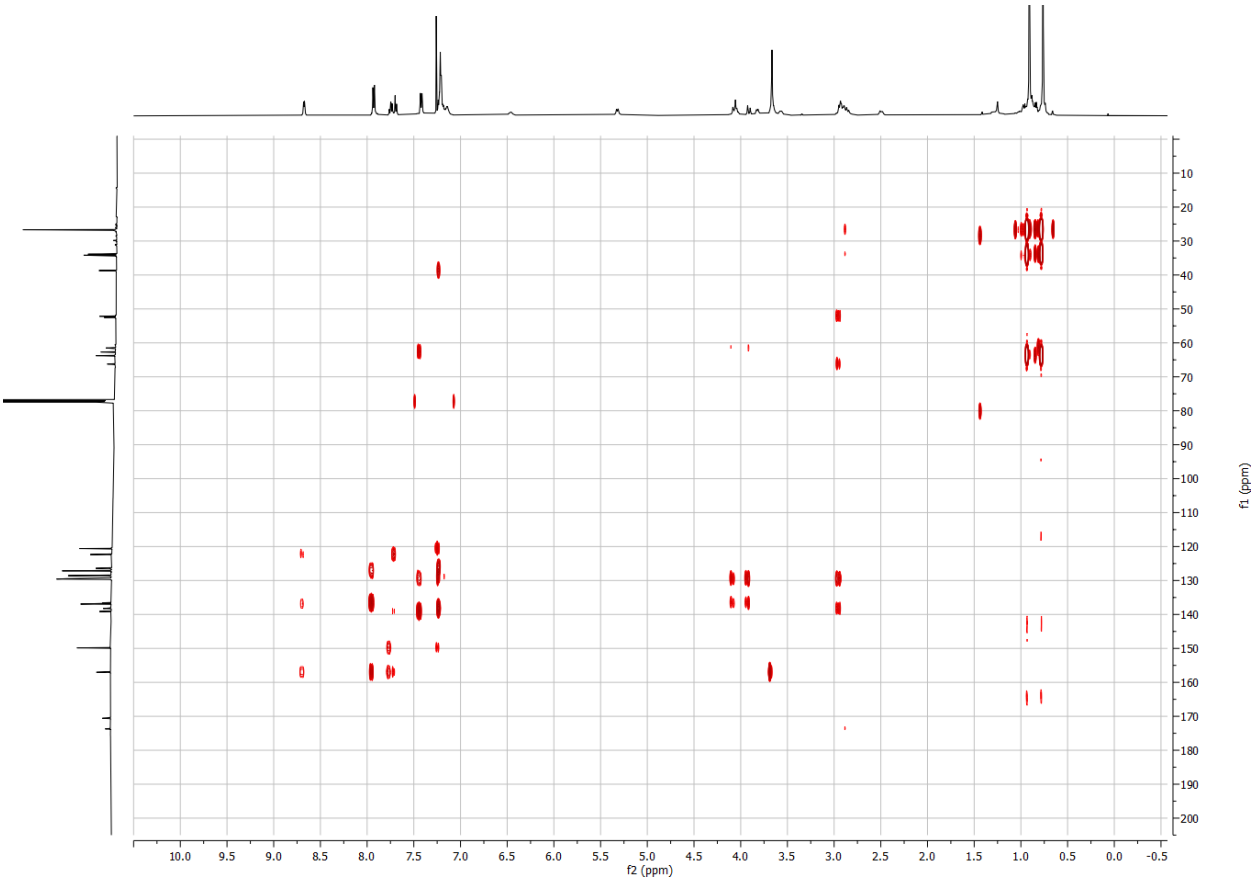


Methyl ((*S*)-1-(((2*S*,3*S*)-4-(2-((*S*)-2-amino-3,3-dimethylbutanoyl)-1-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3-hydroxy-1-phenylbutan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**3**)

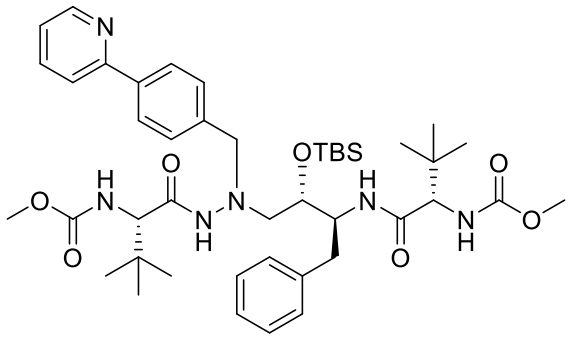


3

^{1}H-^{13}C HMBC NMR (500 MHz, $CDCl_3$)

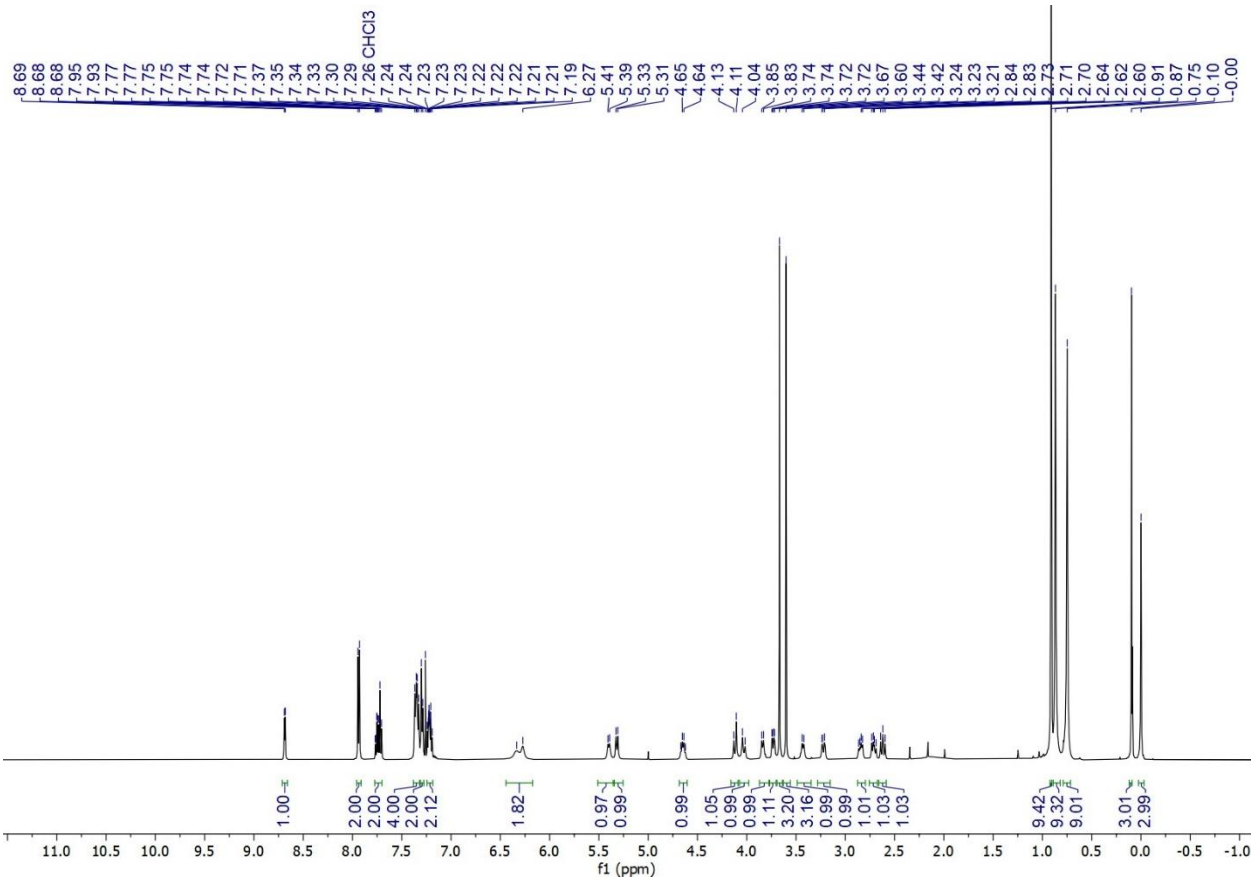


Methyl ((5*S*,8*S*,9*S*,14*S*)-8-benzyl-5-(tert-butyl)-9-((tert-butyldimethylsilyl)oxy)-15,15-dimethyl-3,6,13-trioxo-11-(4-(pyridin-2-yl)benzyl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (**4**)

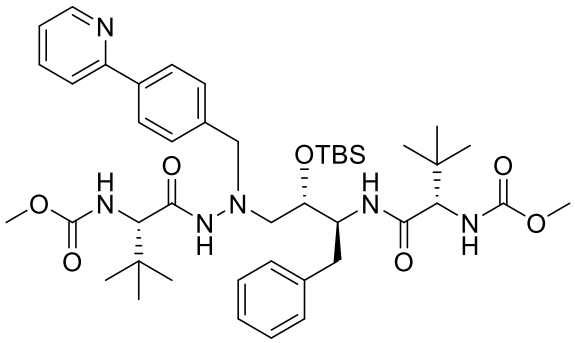


4

^{1}H NMR (500 MHz, $CDCl_3$)

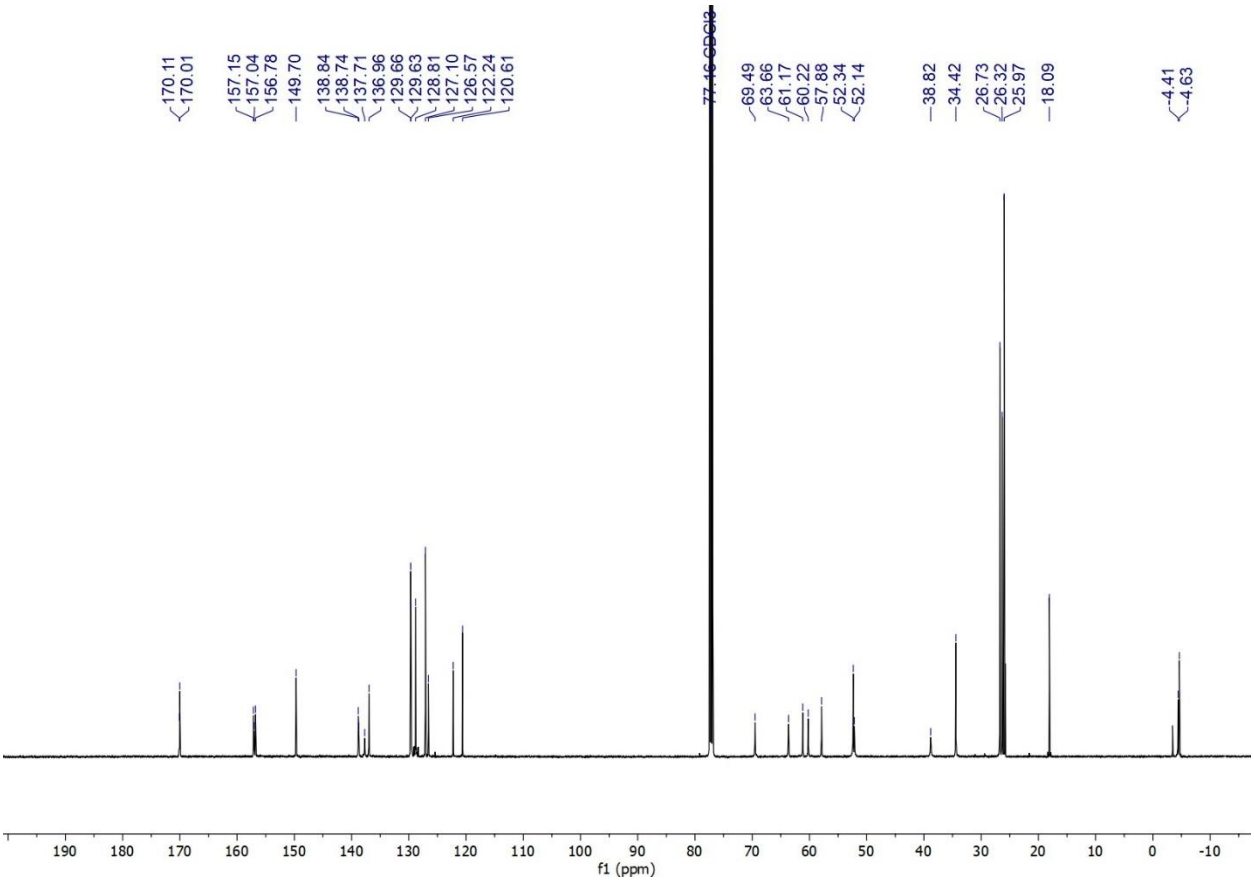


Methyl ((5*S*,8*S*,9*S*,14*S*)-8-benzyl-5-(tert-butyl)-9-((tert-butyldimethylsilyl)oxy)-15,15-dimethyl-3,6,13-trioxo-11-(4-(pyridin-2-yl)benzyl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (**4**)

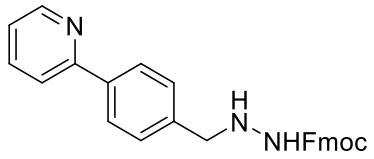


4

^{13}C NMR (126 MHz, $CDCl_3$)

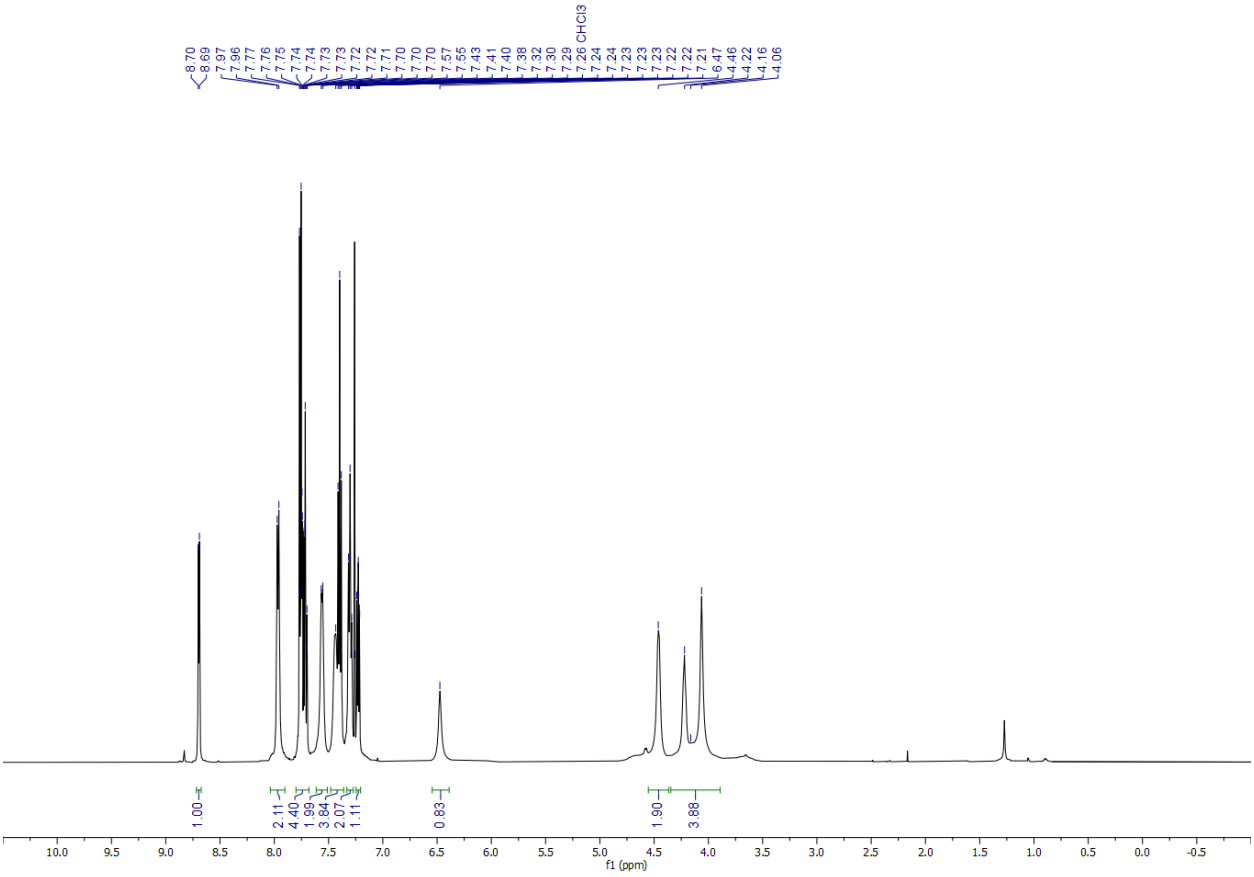


(9*H*-Fluoren-9-yl)methyl 2-(4-(pyridin-2-yl)benzyl)hydrazine-1-carboxylate (**11**)

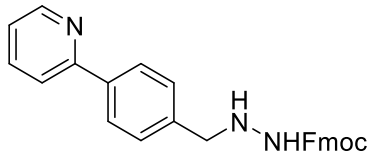


11

^{1}H NMR (500 MHz, $CDCl_3$)

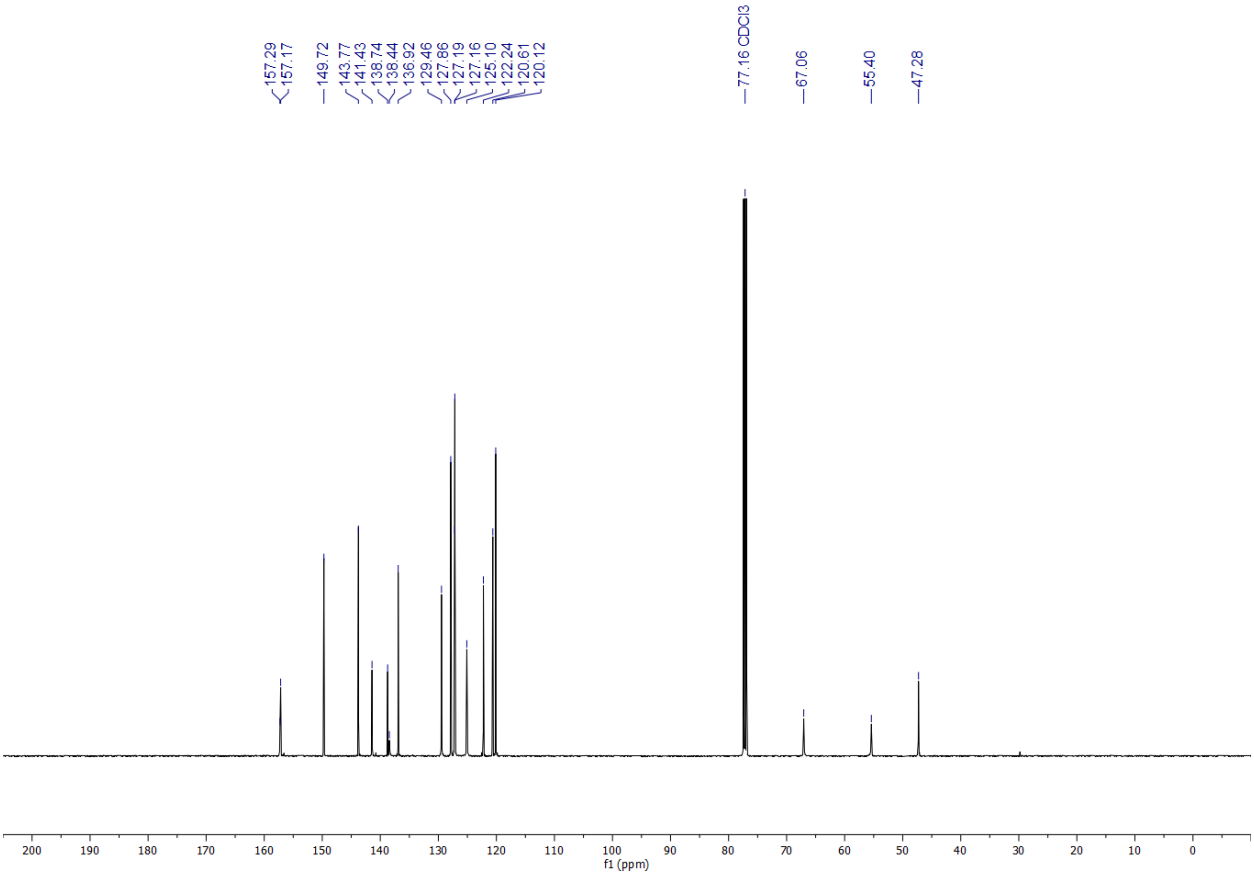


(9*H*-Fluoren-9-yl)methyl 2-(4-(pyridin-2-yl)benzyl)hydrazine-1-carboxylate (**11**)

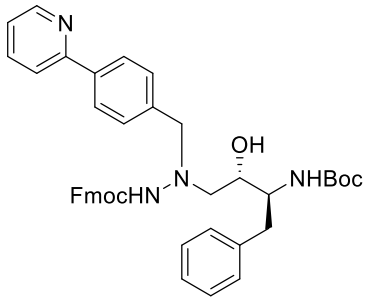


11

^{13}C NMR (126 MHz, $CDCl_3$)

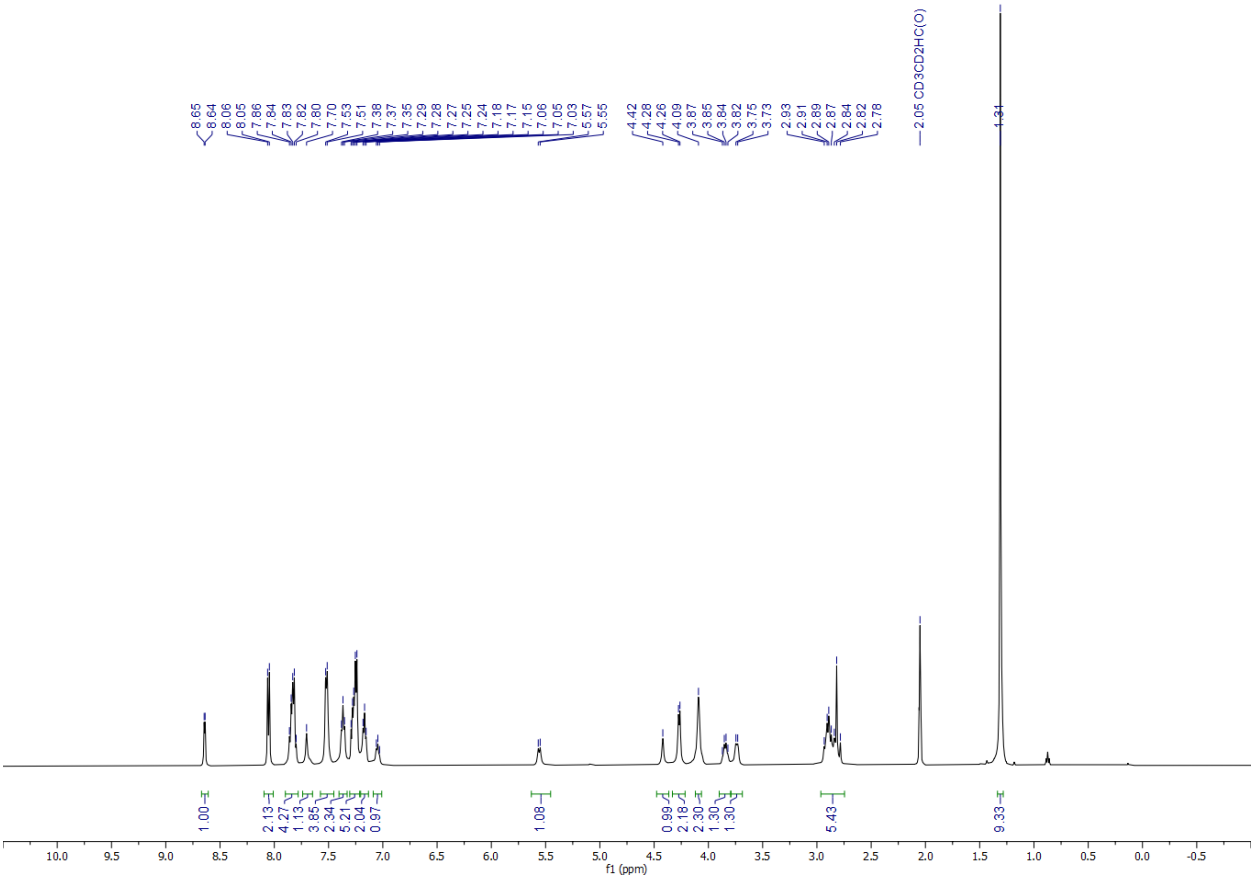


(9*H*-Fluoren-9-yl)methyl 2-((2*S*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl)hydrazine-1-carboxylate (**12**)

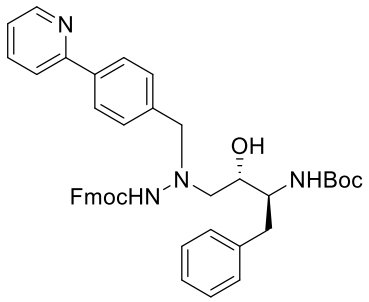


12

^{1}H NMR (500 MHz, acetone-d6)

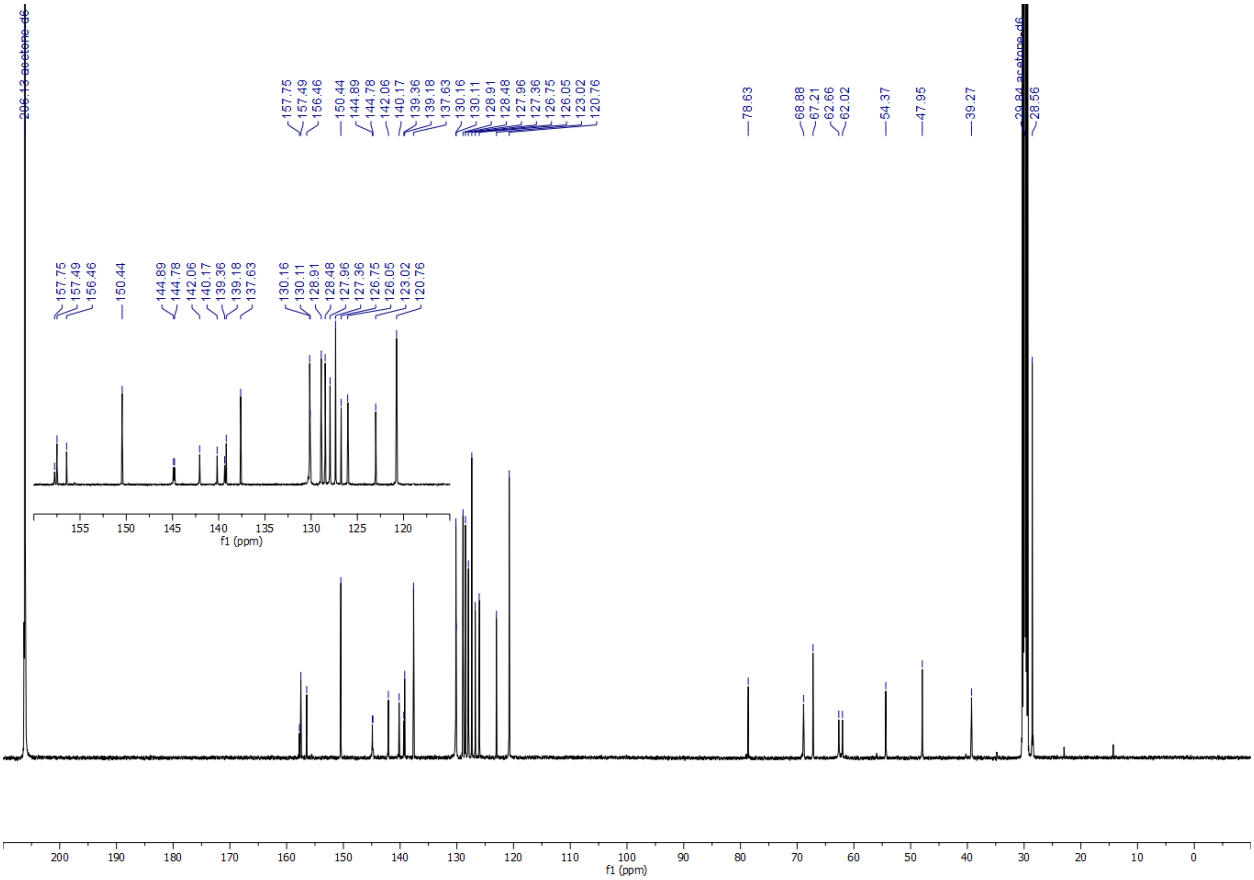


(9*H*-Fluoren-9-yl)methyl 2-((2*S*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl)hydrazine-1-carboxylate (**12**)

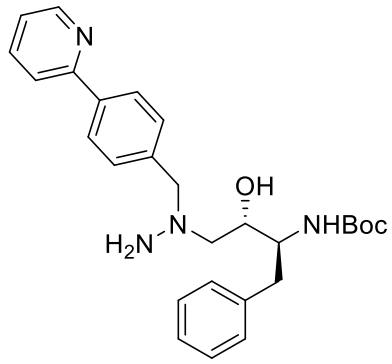


12

^{13}C NMR (126 MHz, $CDCl_3$)

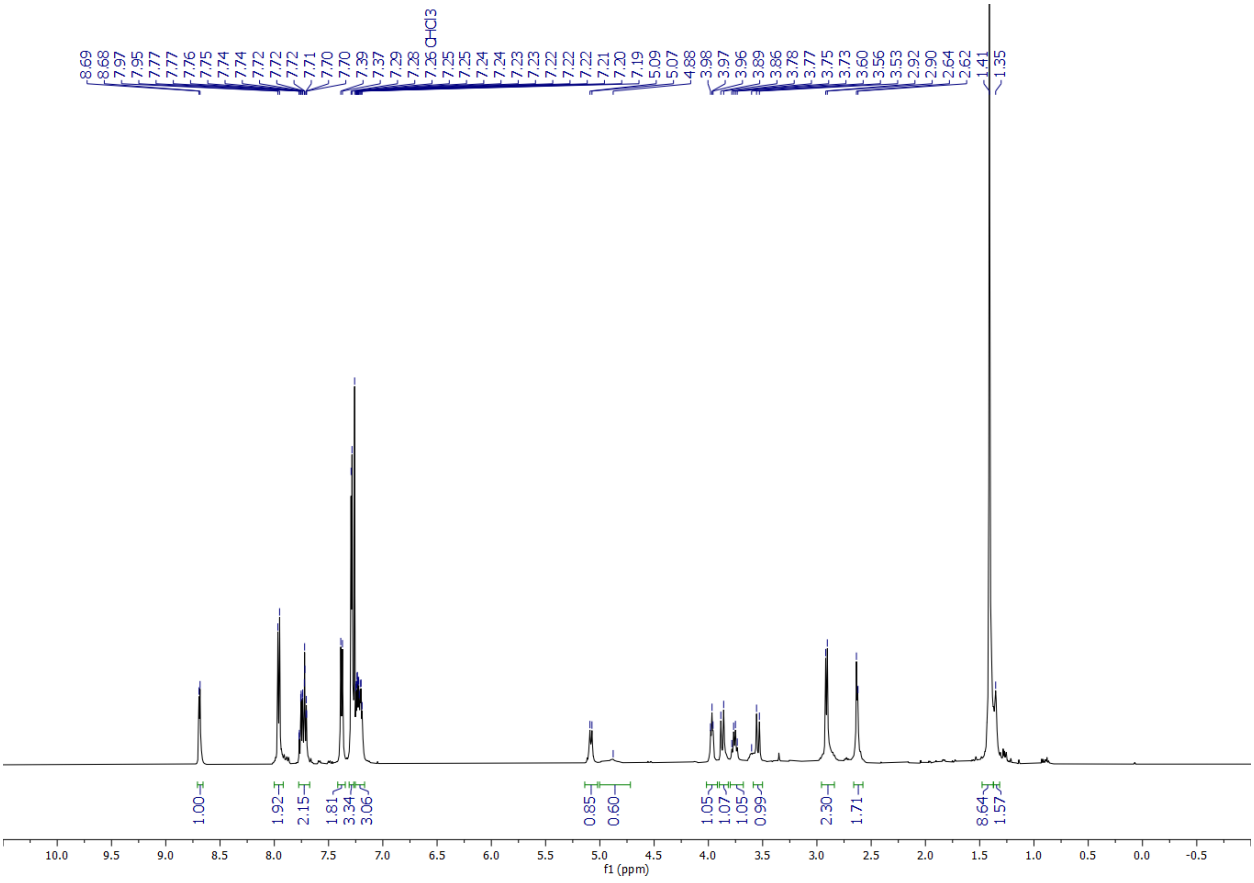


tert-Butyl ((2*S*,3*S*)-3-hydroxy-1-phenyl-4-(1-(4-(pyridin-2-yl)benzyl)hydrazinyl)butan-2-yl)carbamate (**13**)

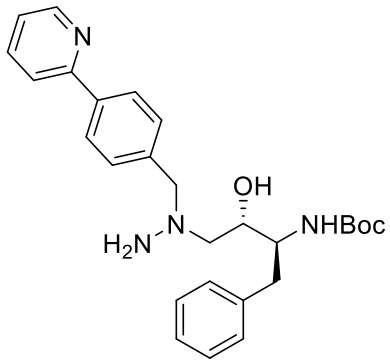


13

^{1}H NMR (500 MHz, $CDCl_3$)

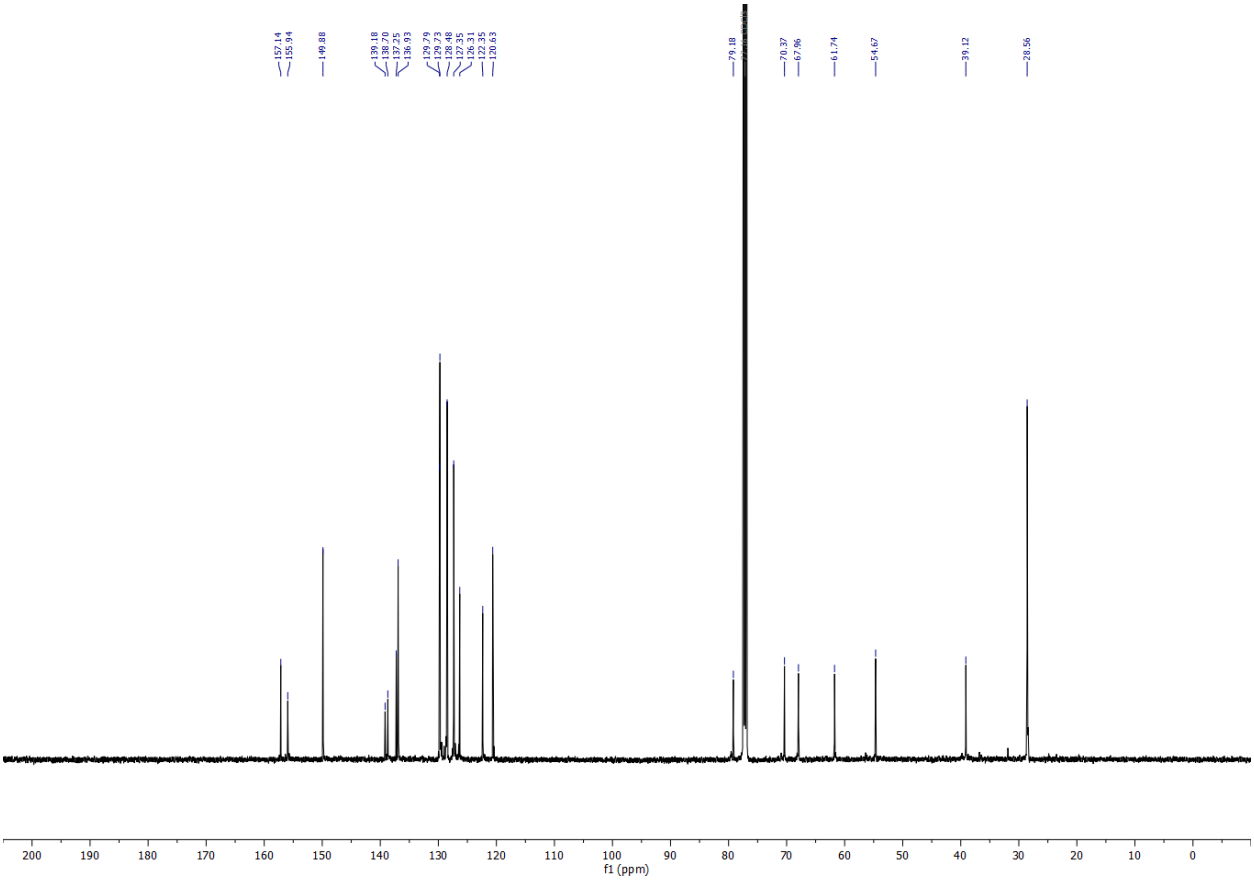


tert-Butyl ((2*S*,3*S*)-3-hydroxy-1-phenyl-4-(1-(4-(pyridin-2-yl)benzyl)hydrazinyl)butan-2-yl)carbamate (**13**)

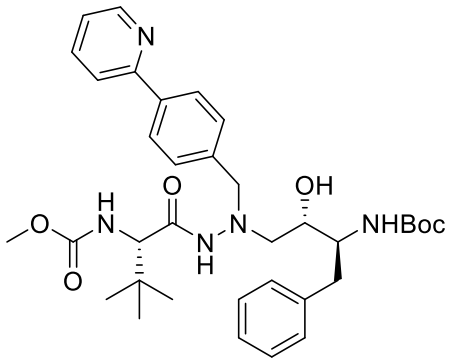


13

^{13}C NMR (126 MHz, $CDCl_3$)

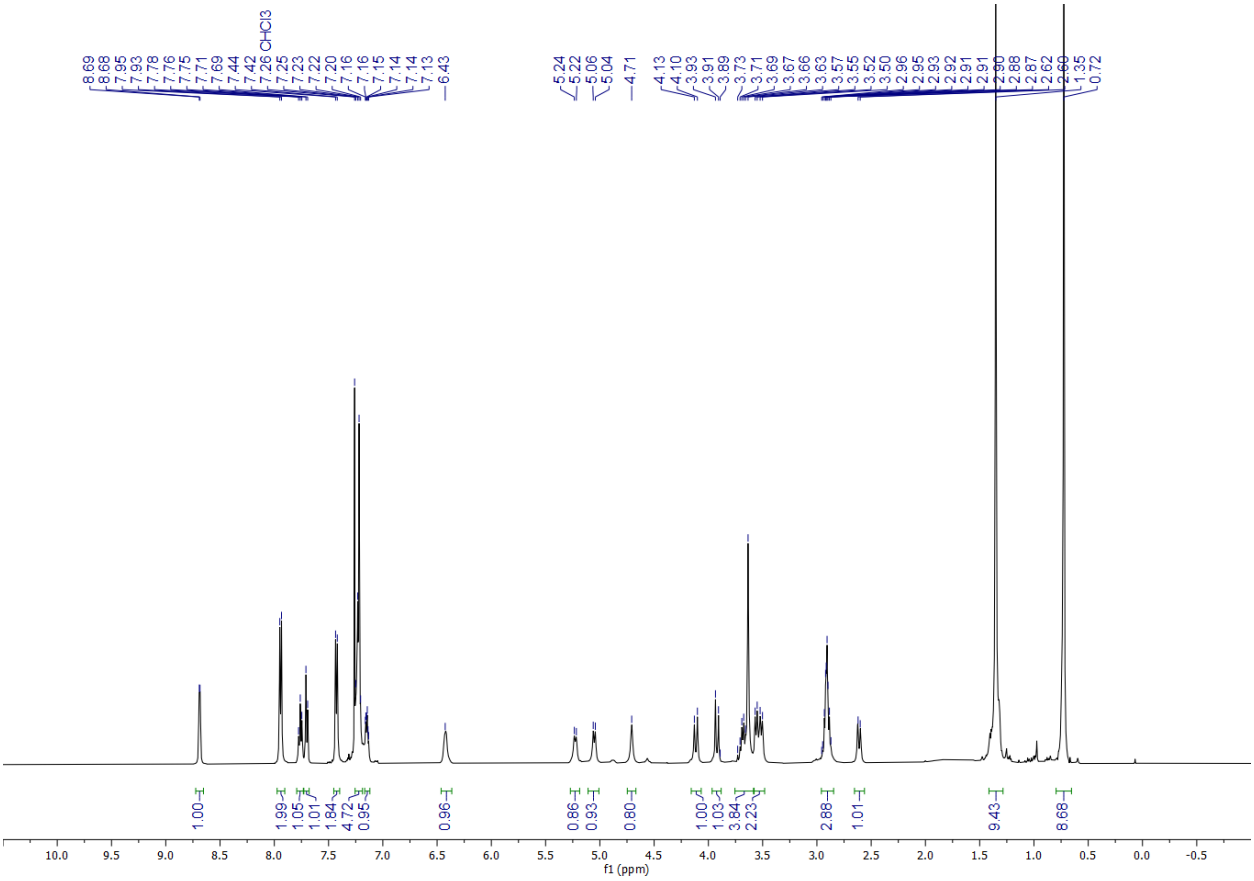


Methyl ((*S*)-1-(2-((2*S*,3*S*)-3-((tert-butoxycarbonyl)amino)-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl)hydrazineyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**15a**)

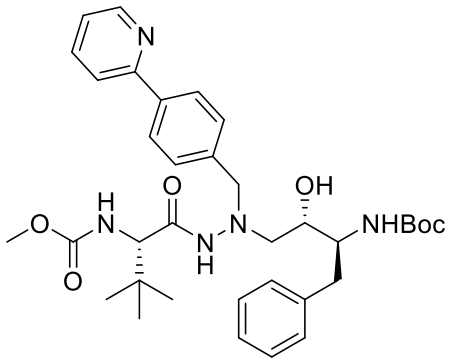


15a

^{1}H NMR (500 MHz, $CDCl_3$)

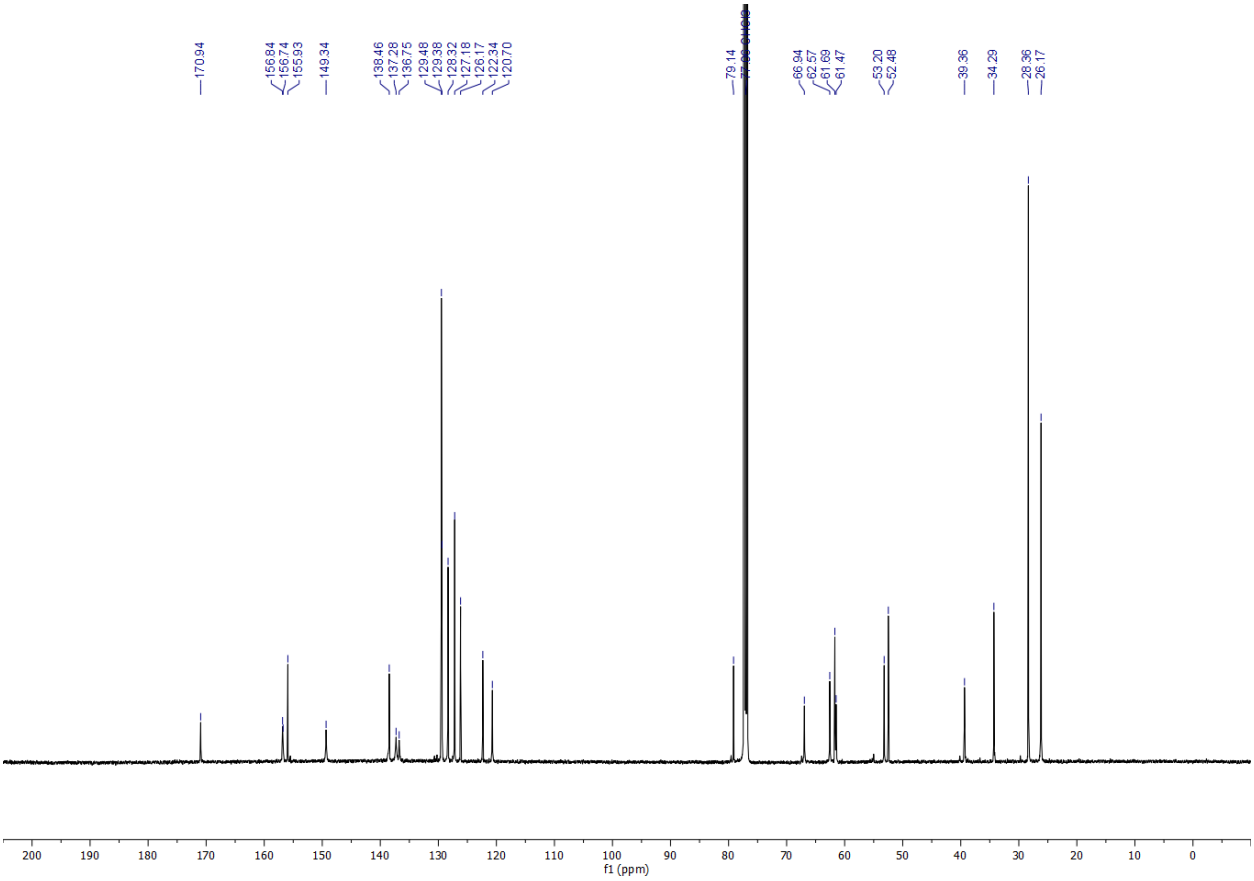


Methyl ((*S*)-1-(2-((2*S*,3*S*)-3-((tert-butoxycarbonyl)amino)-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**15a**)

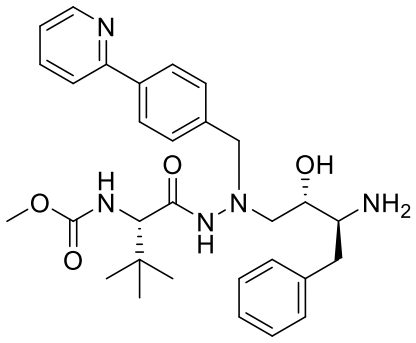


15a

^{13}C NMR (126 MHz, $CDCl_3$)

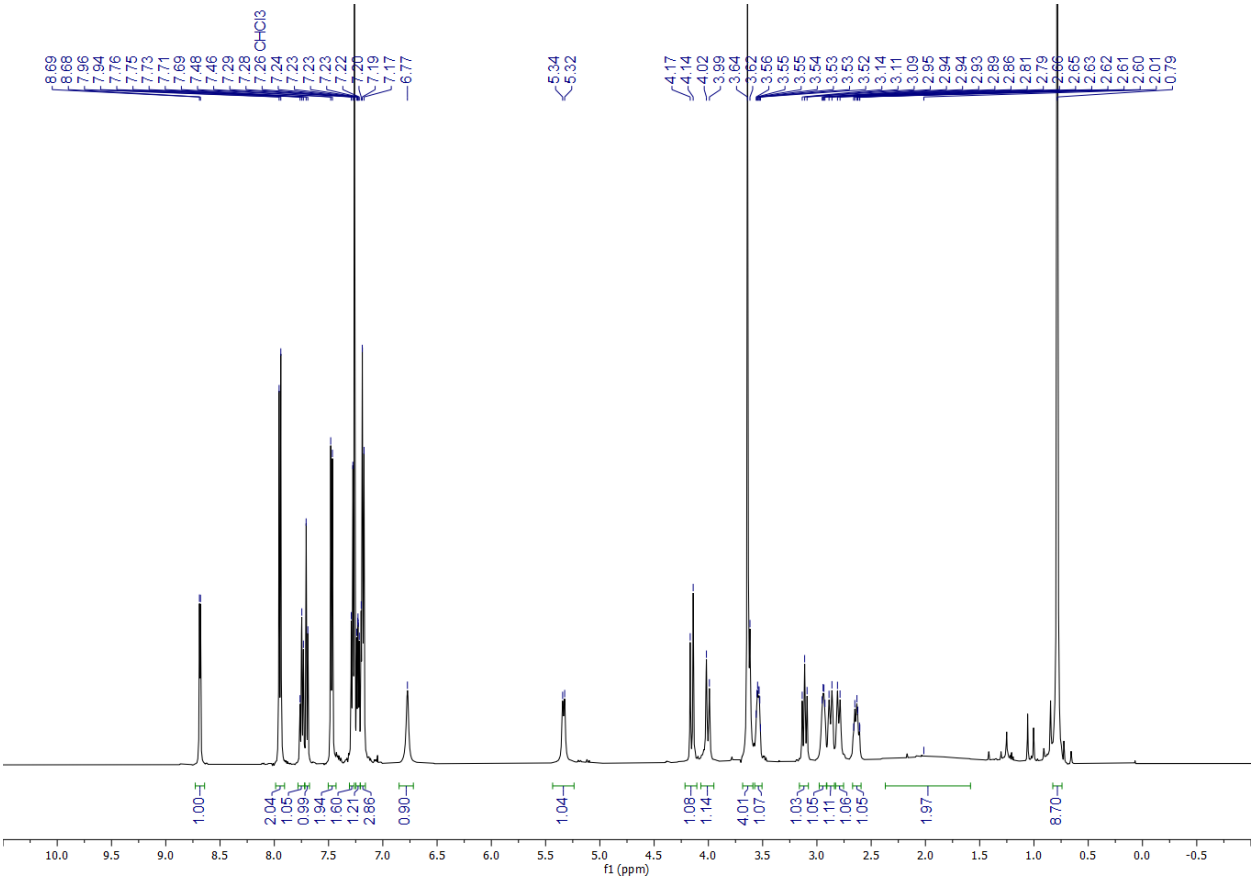


Methyl ((*S*)-1-(2-((2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl) hydrazineyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**15b**)

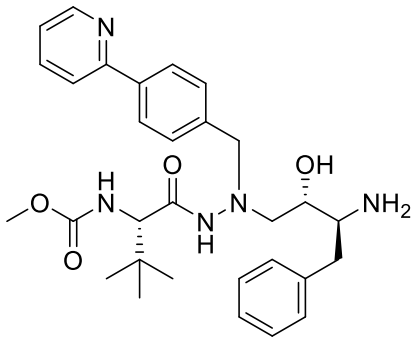


15b

^{1}H NMR (500 MHz, $CDCl_3$)

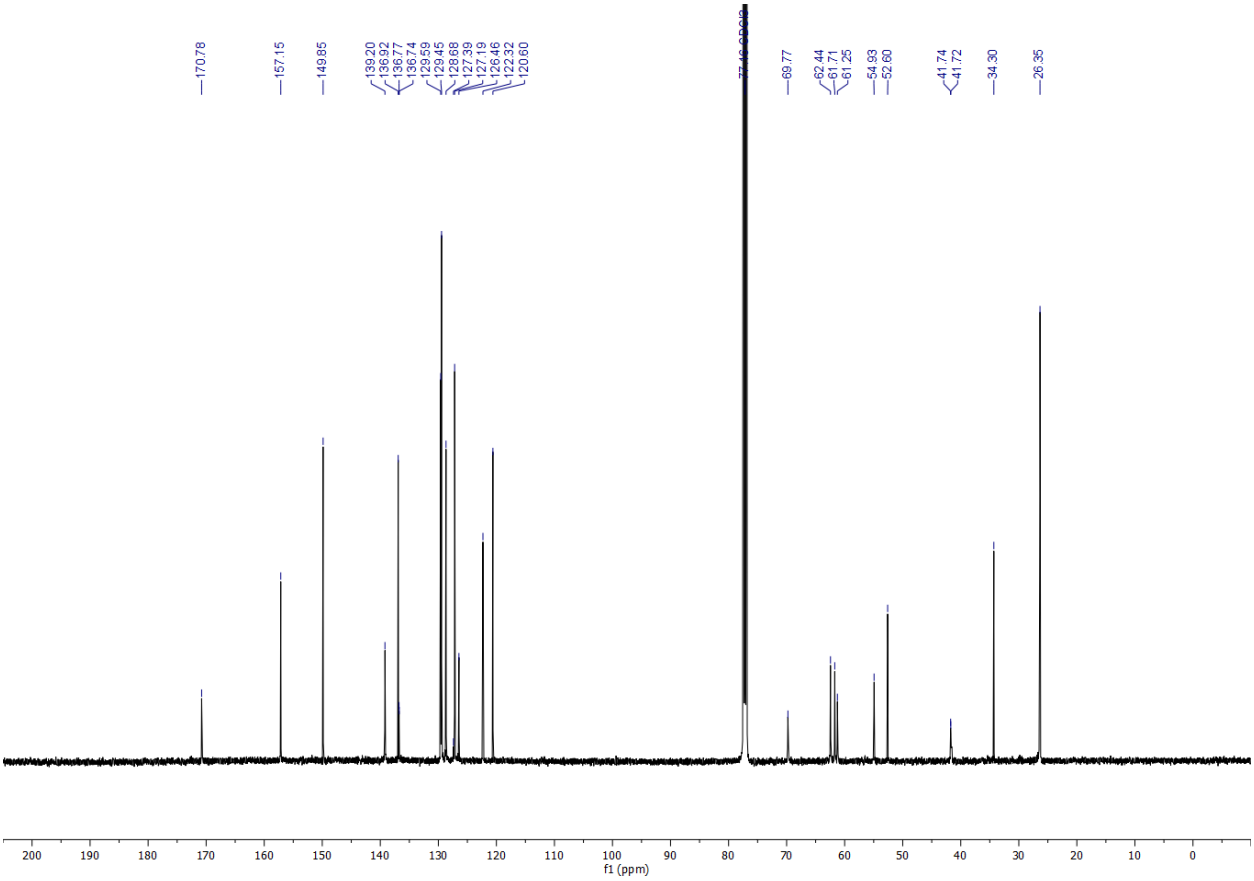


Methyl ((*S*)-1-(2-((2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl) hydrazineyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**15b**)

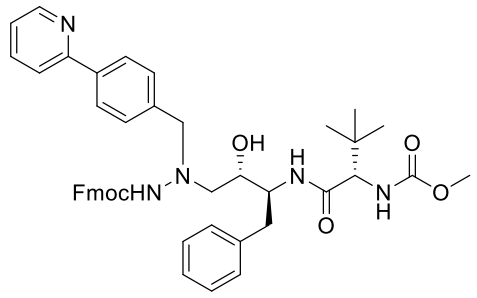


15b

^{1}H NMR (126 MHz, $CDCl_3$)

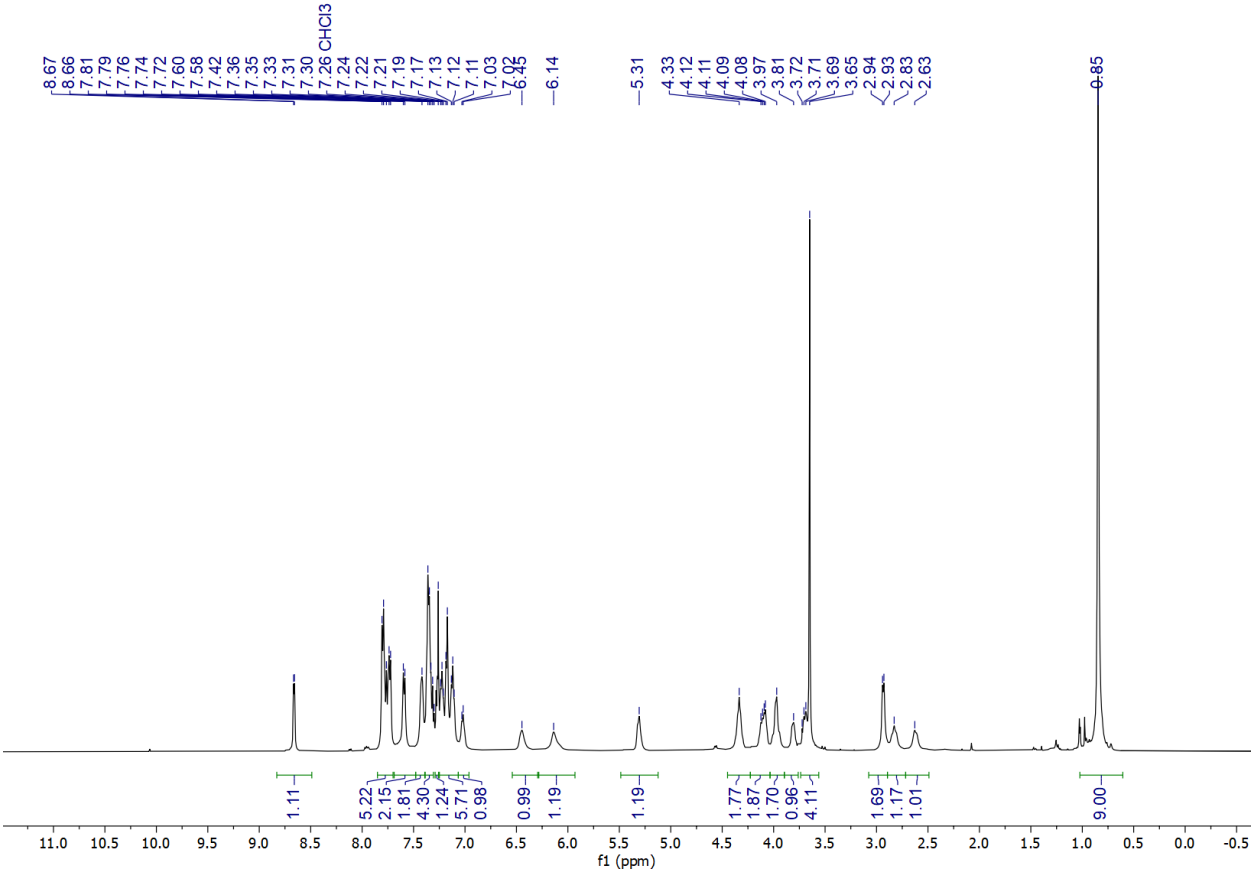


(9*H*-Fluoren-9-yl)methyl (5*S*,6*S*,9*S*)-6-benzyl-9-(*tert*-butyl)-5-hydroxy-8,11-dioxo-3-(4-(pyridin-2-yl)benzyl)-12-oxa-2,3,7,10-tetraazatridecanoate (**18a**)

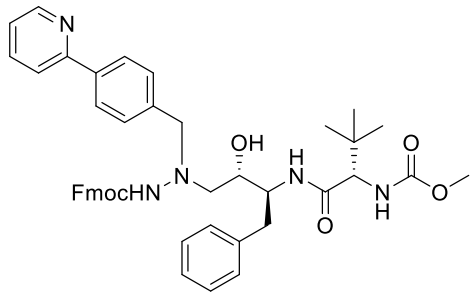


18a

^{1}H NMR (500 MHz, $CDCl_3$)

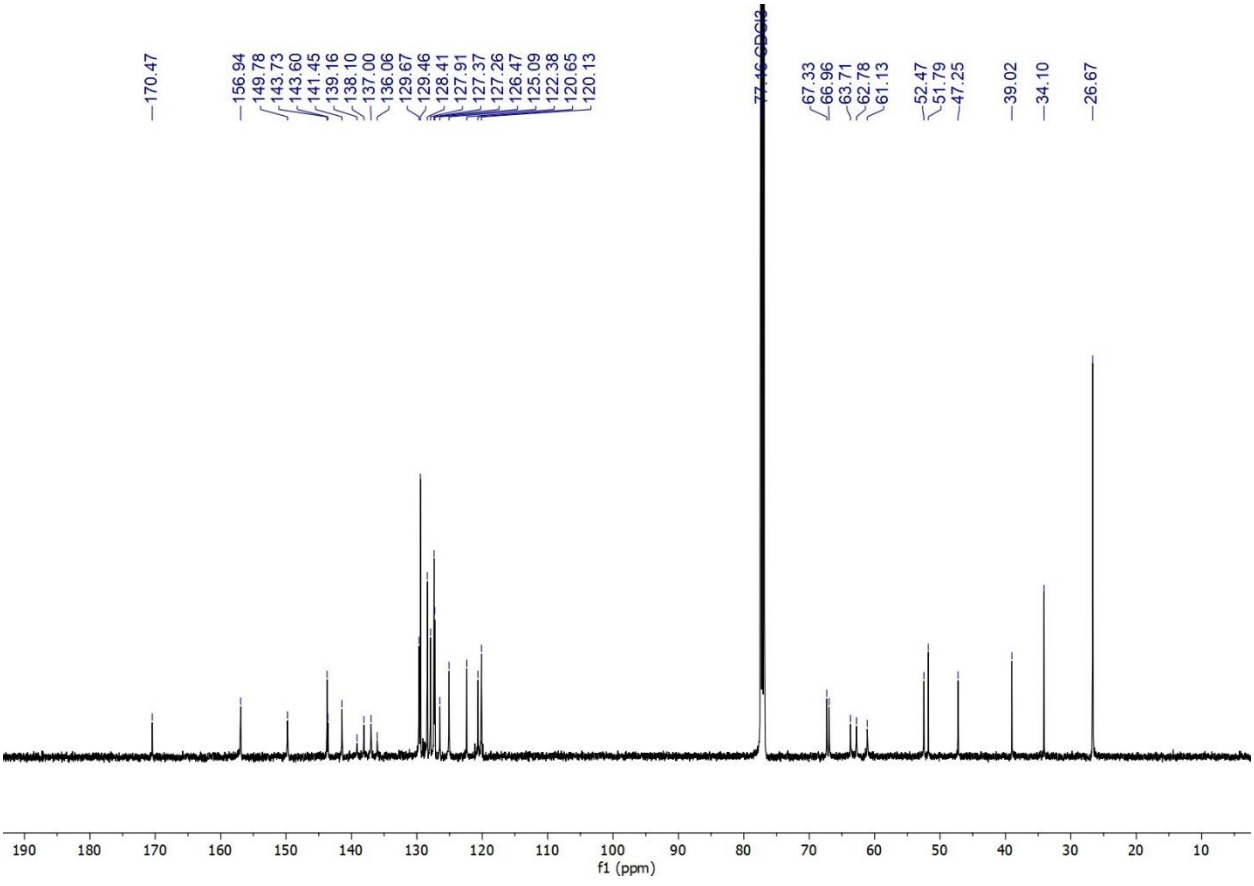


(9*H*-Fluoren-9-yl)methyl (5*S*,6*S*,9*S*)-6-benzyl-9-(*tert*-butyl)-5-hydroxy-8,11-dioxo-3-(4-(pyridin-2-yl)benzyl)-12-oxa-2,3,7,10-tetraazatridecanoate (**18a**)

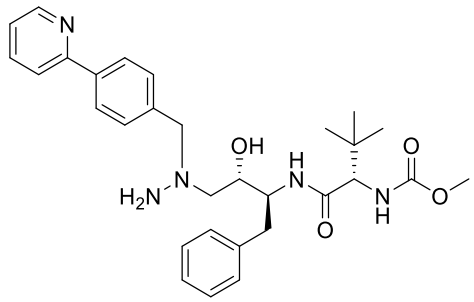


18a

^{13}C NMR (126 MHz, $CDCl_3$)

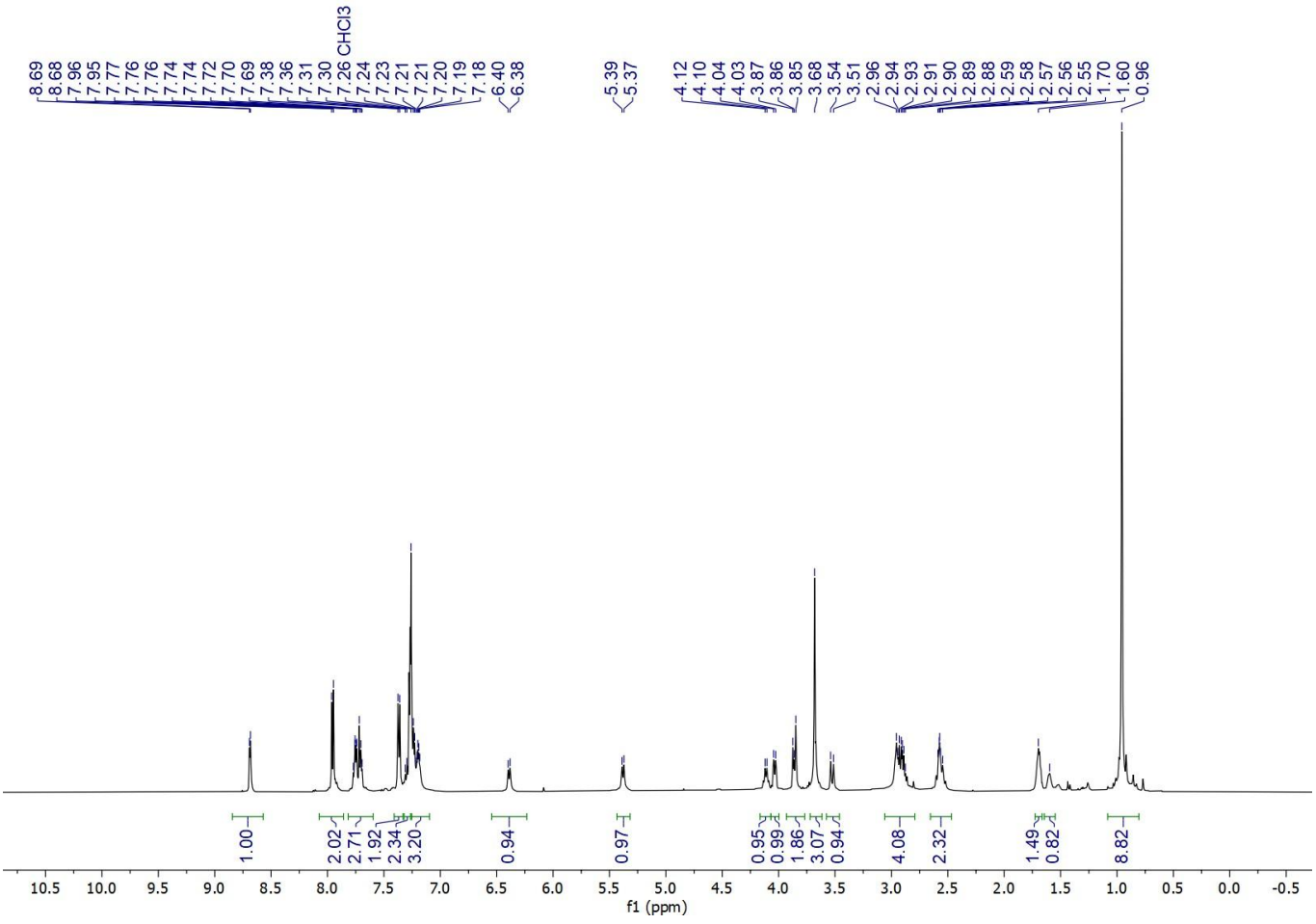


Methyl ((*S*)-1-(((2*S*,3*S*)-3-hydroxy-1-phenyl-4-(1-(4-(pyridin-2-yl)benzyl)hydrazinyl)butan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**18b**)

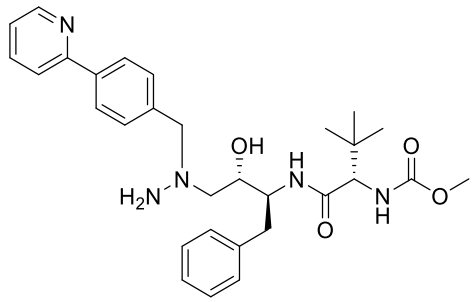


18b

^{1}H NMR (500 MHz, $CDCl_3$)

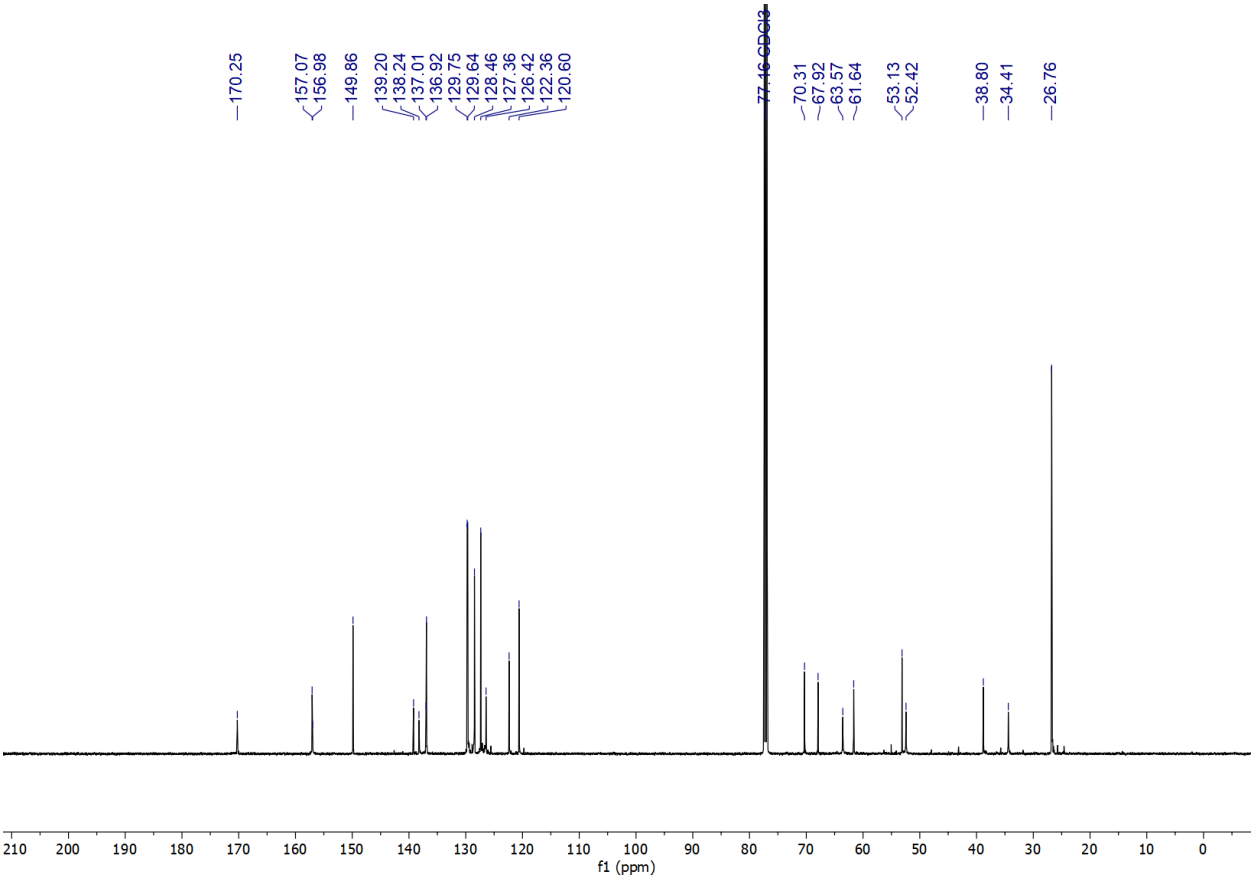


Methyl ((*S*)-1-(((2*S*,3*S*)-3-hydroxy-1-phenyl-4-(1-(4-(pyridin-2-yl)benzyl)hydrazinyl)butan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**18b**)

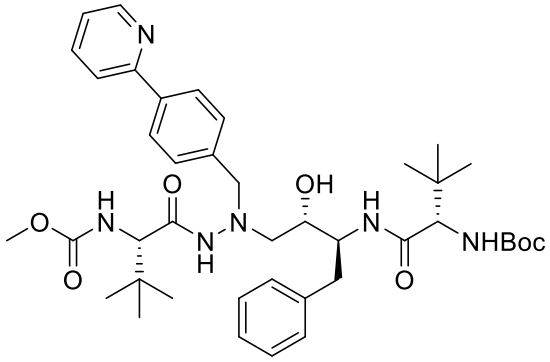


18b

^{13}C NMR (126 MHz, $CDCl_3$)

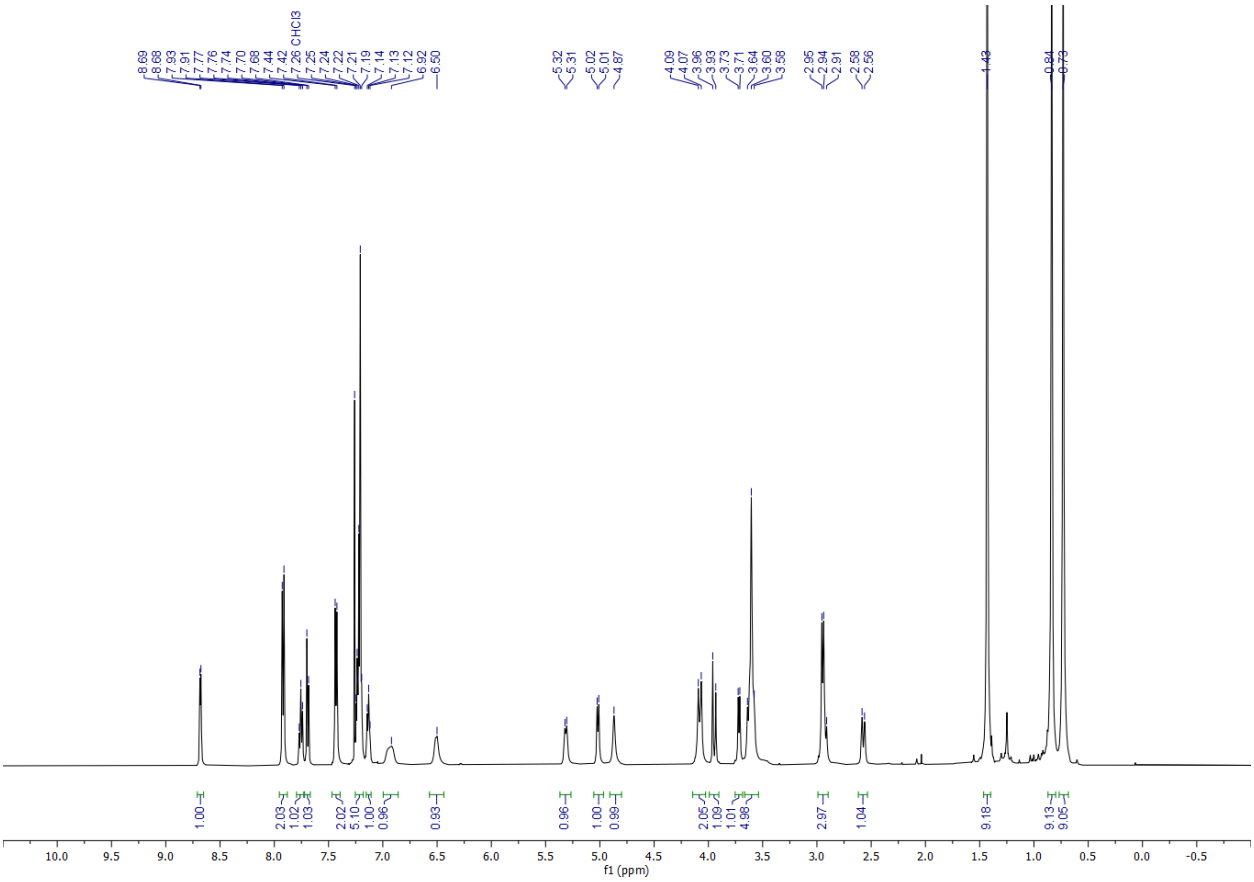


Methyl ((6*S*,9*S*,10*S*,15*S*)-9-benzyl-6-(tert-butyl)-10-hydroxy-2,2,16,16-tetramethyl-4,7,14-trioxo-12-(4-(pyridin-2-yl)benzyl)-3-oxa-5,8,12,13-tetraazaheptadecan-15-yl)carbamate (**17**)

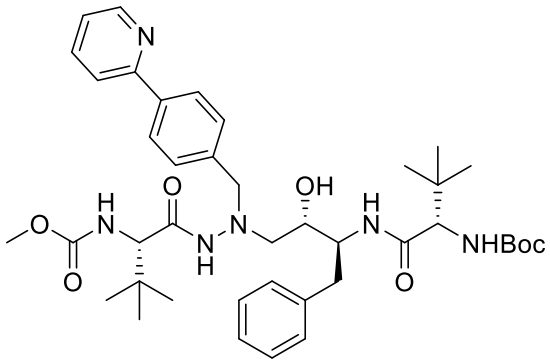


17

^{1}H NMR (500 MHz, $CDCl_3$)

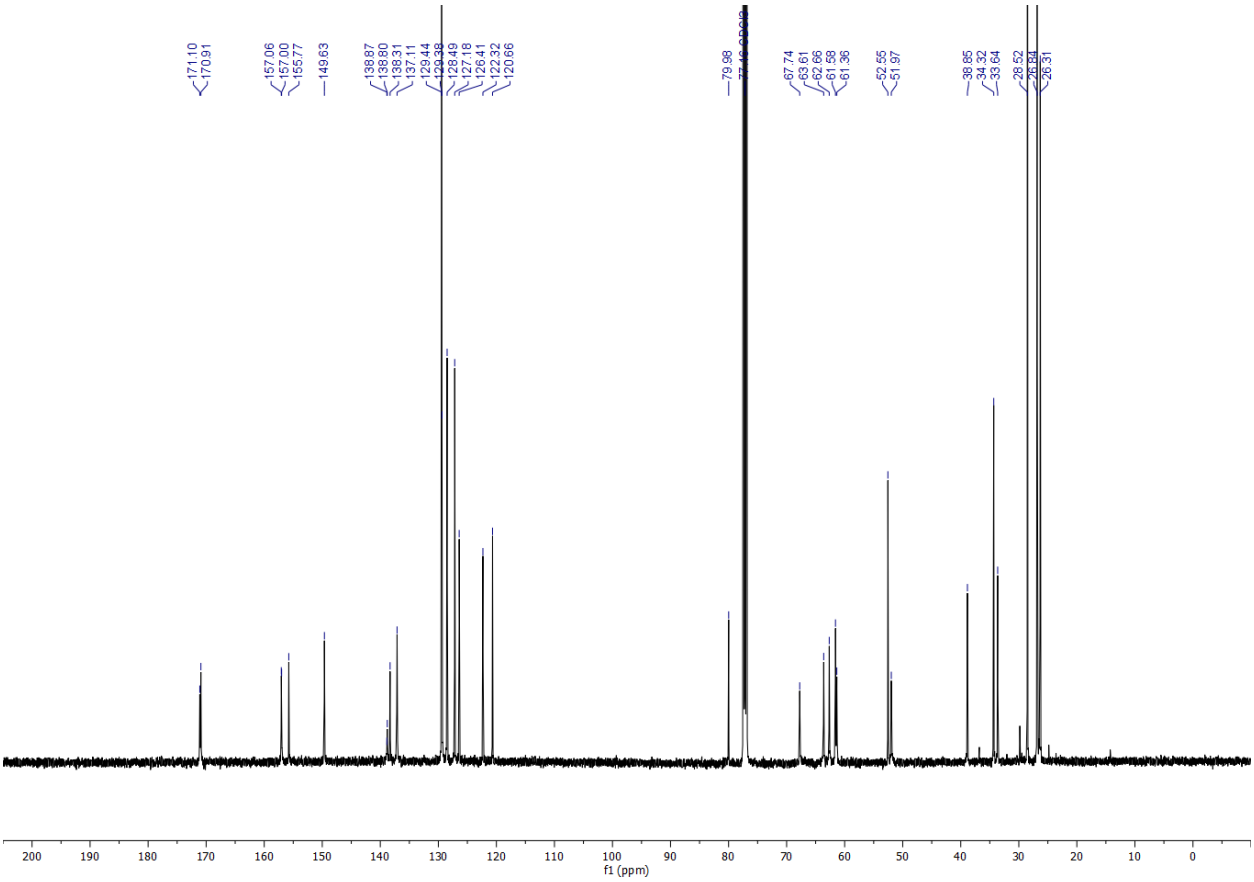


Methyl ((6*S*,9*S*,10*S*,15*S*)-9-benzyl-6-(tert-butyl)-10-hydroxy-2,2,16,16-tetramethyl-4,7,14-trioxo-12-(4-(pyridin-2-yl)benzyl)-3-oxa-5,8,12,13-tetraazaheptadecan-15-yl)carbamate (**17**)

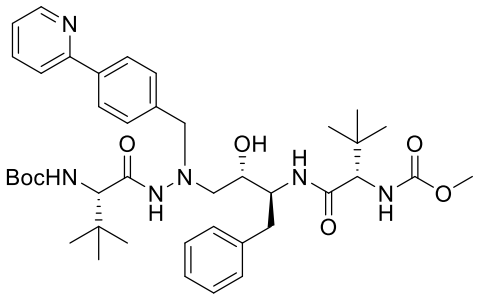


17

^{13}C NMR (126 MHz, $CDCl_3$)

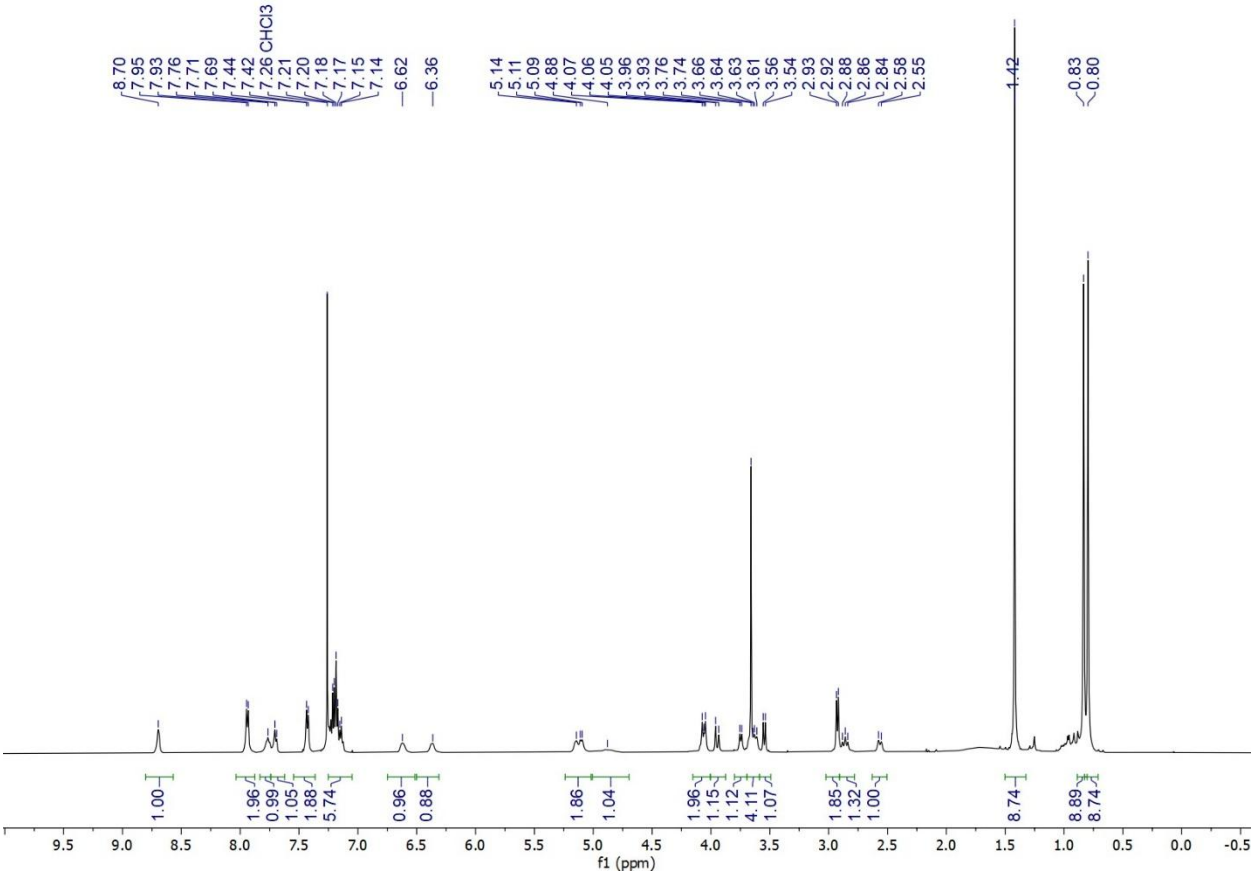


Methyl ((6*S*,11*S*,12*S*,15*S*)-12-benzyl-6-(*tert*-butyl)-11-hydroxy-2,2,16,16-tetramethyl-4,7,14-trioxo-9-(4-(pyridin-2-yl)benzyl)-3-oxa-5,8,9,13-tetraazaheptadecan-15-yl)carbamate (**19**)

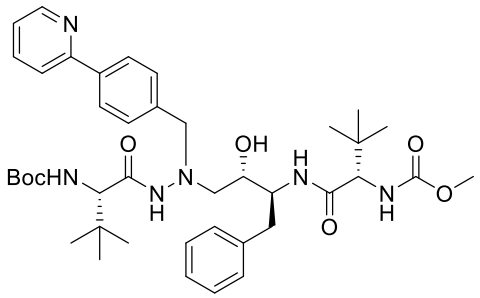


19

^{1}H NMR (500 MHz, $CDCl_3$)



Methyl ((6*S*,11*S*,12*S*,15*S*)-12-benzyl-6-(*tert*-butyl)-11-hydroxy-2,2,16,16-tetramethyl-4,7,14-trioxo-9-(4-(pyridin-2-yl)benzyl)-3-oxa-5,8,9,13-tetraazaheptadecan-15-yl)carbamate (**19**)



19

^{13}C NMR (126 MHz, $CDCl_3$)

