Supporting Information

Total Synthesis of Remdesivir

Kishore Kumar Palli,[a,b] Palash Ghosh,[a,b] Shiva Krishna Avula, [a,b] Sridhara Shanmukha Rao B., [a,b] Amol D. Patil, [a,b] Subhash Ghosh, [a,b] Gangarajula Sudhakar, [a,b] Chada Raji Reddy, [a,b] Prathama S. Mainkar, [a,b] and Srivari Chandrasekhar* [a,b]

[a]*Department of Organic Synthesis & Process Chemistry, CSIR-Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad 500007, India.*

[b]*Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India.*

E-mail: *srivaric@iict.res.in*

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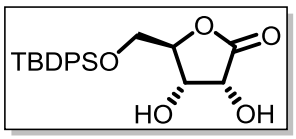
I. General details

***General information*:** Unless otherwise noted, all reactions were carried out in flame-dried or oven-dried glassware under a nitrogen atmosphere with magnetic stirring. Commercially available solvents and reagents were used as received without further purification. All solvents were reagent grade or HPLC grade. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone, dichloromethane (CH_2Cl_2) was distilled from calcium hydride under nitrogen atmosphere. Pyrrolo[2,1-*f*][1,2,4]triazin-4-amine **16** was prepared using the literature protocol[1] and D-(+)-Ribono-1,4-lactone (**12**) was purchased from commercial sources. Reactions were monitored by thin-layer chromatography (TLC) silica gel glass plates (60 F_{254}). TLC plates were visualized under UV light at 254 nm and *p*-Anisaldehyde stain. Column chromatography was carried out using silica gel (60-120 mesh & 100-200 mesh) packed in glass columns. NMR spectra were recorded at 300, 400, 500 MHz (H) and 75, 101, 126 MHz (C), respectively. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (H: δ = 7.26 and C: δ = 77.16 ppm), DMSO-d_6 (H: δ = 2.50 and C: δ = 39.00 ppm) and methanol-d_4 (H: δ = 3.31 and C: δ = 49.00 ppm) as internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, brs = broad singlet, app = apparent), coupling constants (J) in (Hz), integration. Phosphorus-31 nuclear magnetic resonance spectra are reported in parts per million on the δ scale. Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet), coupling constants (J) in Hertz. Purities of the final compounds were determined by high-performance liquid chromatography (HPLC) and were greater than 95% unless otherwise noted. HPLC conditions to assess purity were as follows: waters alliance (system), Lunar C18, 250 × 4.6 mm column; 2-98% gradient of 0.1% trifluoroacetic acid in water and 0.1% trifluoroacetic acid in acetonitrile; flow rate, 1 mL/min; acquisition time, 25 min; wavelength, 254 nm. Specific Optical rotations were recorded on an Anton Paar Polarimeter at 589 nm and reported as follows: $[\alpha]^{20}_{D}$, concentration (*c* in g/100 mL), and solvent. Infrared spectra were recorded on a Bruker Alpha spectrophotometer. HRMS spectra were recorded by using ESI-TOF techniques.

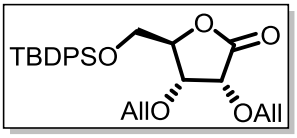
II. Experimental procedures and analytical data

(3*R*,4*S*,5*R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-3,4-dihydroxydihydrofuran-2(3*H*)-one (13)[2]:



Compound **13** was prepared (10 g, 84% yield) as a white solid. According to a previously established protocol, analytical data were consistent with data previously reported literature. m.p.= 94–96 °C; $[\alpha]^{20}_{D}$ = +48.80° (*c* = 0.5 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 – 7.58 (m, 4H), 7.47 – 7.37 (m, 6H), 4.87 – 4.78 (m, 1H), 4.52 – 4.50 (m, 2H), 3.91 (dd, *J* = 11.9, 2.8 Hz, 1H), 3.80 (dd, *J* = 11.9, 2.0 Hz, 1H), 3.51 (d, *J* = 4.2 Hz, 1H), 3.18 (s, 1H), 1.03 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 176.7, 135.7, 135.6, 132.4, 131.9, 130.3, 128.2, 85.6, 70.3, 69.4, 63.5, 26.9, 19.3; **IR** (neat): υ_{max} 3400, 2956, 2935, 2862, 1781, 1466, 1428, 1182, 1112, 974, 938, 706 cm^{-1}; **HRMS** (ESI-TOF): m/z $[M+H]^+$calcd for $C_{21}H_{27}O_5Si$: 387.1621; found: 387.1624.

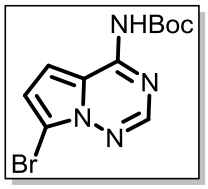
(3*R*,4*R*,5*R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-3,4-*bis*(((*E*)-prop-1-en-1-yl)oxy)dihydrofuran-2(3*H*)-one (15):



To a stirred solution of (3*R*,4*S*,5*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3,4-dihydroxydihydrofuran-2(3*H*)-one **13** (10.0 g, 25.89 mmol, 1 equiv) in dry THF (100 mL) was added allyl *tert*-butyl carbonate **14** (12.3 g, 77.74 mmol, 3 equiv). The reaction mixture was degassed with argon for 15 min, $Pd(PPh_3)_4$ (598 mg, 0.51 mmol, 0.02 equiv) was added and again degassed with argon for 10 min, The reaction mixture was refluxed for 3h. Then again allyl *tert*-butyl carbonate **14** (8.2 g, 51.83 mmol, 2 equiv) was added at room temperature. Further, the reaction mixture was refluxed for 3 h. After completion of reaction, monitored by TLC, the solvent was removed by vacuum distillation. The crude residue was purified by silica gel column chromatography eluting with 0–20% ethyl acetate in hexanes to afford compound **15** (10.8 g, 89% yield) as a colorless oil. R_f = 0.5 (ethyl acetate/hexane 1:4); $[\alpha]^{20}_{D}$ = +37.30° (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 – 7.60 (m, 4H), 7.48 – 7.38 (m, 6H), 6.00 –

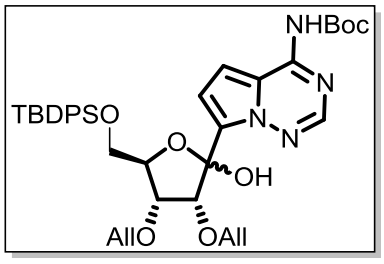
5.85 (m, 2H), 5.39 – 5.18 (m, 4H), 4.52 (d, *J* = 5.7 Hz, 1H), 4.47 (dd, *J* = 4.0, 2.5 Hz, 1H), 4.41 (ddt, *J* = 12.9, 5.3, 1.3 Hz, 1H), 4.30 – 4.18 (m, 3H), 4.09 (ddt, *J* = 12.8, 5.8, 1.3 Hz, 1H), 3.90 (dd, *J* = 11.8, 3.0 Hz, 1H), 3.76 (dd, *J* = 11.8, 2.3 Hz, 1H), 1.05 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.9, 135.7, 135.6, 134.1, 133.8, 132.6, 132.0, 130.3, 128.1, 118.7, 118.0, 83.0, 75.5, 74.3, 72.1, 71.6, 63.3, 27.0, 19.3; **IR** (neat): υ_{max} 3072,2934, 2860, 1787, 1466, 1427, 1108,996, 932, 821, 704 cm^{-1}; **HRMS** (ESI-TOF): m/z $[M+NH_4]^+$ calcd for $C_{27}H_{38}NO_5Si$: 484.2513; found: 484.2490.

***tert*-Butyl (7-bromopyrrolo[2,1-*f*][1,2,4]triazin-4-yl)carbamate (16)[3]:**



Compound **16** was prepared (6.5 g, 80% yield) as a white solid. According to a previously established protocol, analytical data were consistent with data previously reported literature. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.28 (s, 1H), 7.41 (d, *J* = 4.9 Hz, 1H), 6.90 (d, *J* = 4.9 Hz, 1H), 1.57 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 151.4, 150.5, 147.1, 116.7, 115.3, 108.3, 103.3, 83.3, 28.3; **IR** (neat): υ_{max} 3173, 2985, 1746, 1601, 1537, 1463, 1409, 1243, 1155, 856 cm^{-1}; **HRMS** (ESI-TOF): m/z $[M+H]^+$calcd for $C_{11}H_{14}O_2N_4Br$: 313.0294; found: 313.0284.

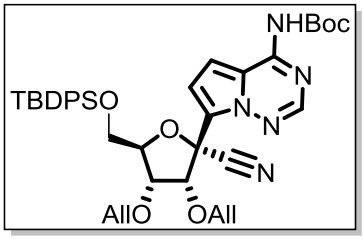
***tert*-Butyl(7-((3*R*,4*R*,5*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-hydroxy-3,4-*bis*(((*E*)-prop-1-en-1-yl)oxy)tetrahydrofuran-2-yl)pyrr olo[2,1-*f*][1,2,4]triazin-4-yl)carbamate (17):**



To a stirred solution of *tert*-butyl(7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl)carbamate **16** (2.5 g, 8.01 mmol, 1 equiv) in anhydrous THF (50 mL), pre-cooled to –78 °C was added *n*-BuLi (2.5 M solution in hexane) (9.6 mL, 24.03 mmol, 3.0 equiv) dropwise at –78 °C and stirred for 30 min. A solution of compound **15** (4.85 g, 10.41 mmol, 1.3 equiv) in anhydrous THF (15 mL) was added at –78 °C. The reaction mixture was stirred at same temperature for 3 h. After completion of reaction was

monitored by TLC, quenched with sat. NH_4Cl solution (20 mL), and extracted with ethyl acetate (2 X 50 mL). The organic layer was separated, washed the organics with brine solution (30 mL), dried over sat. Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 0–50% ethyl acetate in hexanes to afford the mixture of isomers (2:1 anomers) **17** (3.2 g, 58% yield) as a yellow solid. R_f = 0.2 (ethyl acetate/hexane 3:7); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.36 – 7.95 (s, 1H), 7.72 – 7.60 (m, 4H), 7.43 – 7.33 (m, 6H), 7.15 – 7.00 (m, 2H), 5.97 – 5.64 (m, 2H), 5.33 – 5.14 (m, 3H), 5.05 – 4.78 (m, 3H), 4.40 – 4.29 (m, 1H), 4.26 – 4.16 (m, 2H), 4.01 – 3.95 (m, 3H), 3.84 – 3.79 (m, 1H), 1.57 – 1.55 (s, 9H), 1.07 – 0.99 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 151.1, 149.8, 145.6, 135.8, 135.6, 134.4, 134.2, 134.0, 133.3, 130.5, 129.8, 129.7, 127.8, 119.6, 117.8, 117.5, 113.7, 103.5, 99.9, 82.9, 81.4, 71.9, 71.8, 62.9, 28.1, 26.9, 26.9, 19.3; **IR** (neat): υ_{max} 3484, 3257, 3070, 2932, 2861, 1752, 1606, 1511, 1463, 1232, 1145, 1111, 754, 704 cm^{-1}; **HRMS** (ESI-TOF): m/z $[M+H]^+$ calcd for $C_{38}H_{49}N_4O_7Si$: 701.3365; found: 701.3343**.**

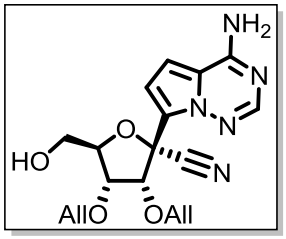
***tert*-Butyl(7-((2*R*,3*R*,4*R*,5*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-cyano-3,4-*bis*(((*E*)-prop-1-en-1-yl)oxy)tetrahydrofuran-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)carbamate (18):**



To a solution of *tert*-butyl(7-((3*R*,4*R*,5*R*)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-hydroxy-3,4-bis(((*E*)-prop-1-en-1-yl)oxy)tetrahydrofuran-2-yl) pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)carbamate **17** (3.0 g, 4.28 mmol, 1 equiv) in dry dichloromethane (50 mL) pre-cooled to –78 °C was added TfOH (0.76 mL, 8.57 mmol, 2 equiv) at –78 °C and stirred for 15 min. After TMSOTf (1.7 mL, 9.41 mmol, 2.2 equiv) was slowly added to the reaction mixture and stirred at same temperature for 30 min. TMSCN (2.1 mL, 17.12 mmol, 4 equiv) was then added slowly and the mixture was stirred at –78 °C for 2 h. After completion of reaction, monitored by TLC, reaction mixture was quenched with triethylamine (4 mL), the reaction mixture was allowed to warm to room temperature. The mixture was diluted with dichloromethane (50 mL), solid sodium bicarbonate (5 g) was then added followed by the slow addition of water (25 mL) and the resulting mixture was stirred for 10 min. The layers were then separated and the aqueous layer was further extracted with CH_2Cl_2 (2 X 75 mL). The combined organic extracts were

washed with brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 0–30% ethyl acetate in hexanes to afford the product **18** (2.58 g, 85% yield) as a white solid. R_f = 0.5 (ethyl acetate/hexane 1:4); m.p. = 75 °C; $[\alpha]^{20}_D$ = +13.70° (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 8.00 (s, 1H), 7.68 – 7.64 (m, 4H), 7.46 – 7.33 (m, 6H), 7.13 (s, 2H), 5.95 – 5.85 (m, 2H), 5.31 – 5.26 (m, 2H), 5.20 – 5.16 (m, 2H), 4.70 (d, *J* = 4.9 Hz, 1H), 4.47 – 4.42 (m, 2H), 4.33 (dd, *J* = 12.8, 6.5 Hz, 1H), 4.15 – 3.98 (m, 4H), 3.83 (dd, *J* = 11.8, 3.2 Hz, 1H), 1.57 (s, 9H), 1.06 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 151.6, 150.1, 146.2, 135.7, 135.7, 134.2, 134.0, 133.1, 132.9, 130.0, 130.0, 127.9, 125.6, 118.6, 117.7, 117.2, 116.2, 113.7, 105.4, 83.3, 83.1, 79.4, 78.7, 76.0, 72.7, 71.6, 62.2, 28.2, 27.0, 19.4; **IR** (neat): υ_{max} 3272, 3073, 2933, 2863, 1754, 1608, 1539, 1511, 1235, 1147, 1041, 1001, 932, 759, 706 cm^{-1}; **HRMS** (ESI-TOF): m/z $[M+H]^+$ calcd for $C_{39}H_{48}N_5O_6Si$: 710.3368; found: 710.3346; **HPLC**: t_R = 9.413 min.

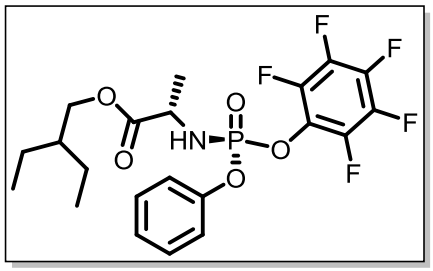
(2*R*,3*R*,4*R*,5*R*)-2-(4-Aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-(hydroxymethyl)-3,4-*bis*(((*E*)-prop-1-en-1-yl)oxy)tetrahydrofuran-2-carbonitrile (19):



In a Teflon coated vial *tert*-butyl (7-((2*R*,3*R*,4*R*,5*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-cyano-3,4-*bis*(((*E*)-prop-1-en-1-yl)oxy)tetrahydrofuran-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl) carbamate **18** (1.5 g, 2.11 mmol, 1 equiv) was dissolved in acetonitrile (20 mL) and 70% HF.py (3 mL) was added with a Teflon syringe at 0 °C. The reaction mixture was allowed to room temperature and stirred for 6 h. After completion of the reaction, monitored by TLC, the reaction mixture was poured into a saturated $NaHCO_3$ solution (15 mL). After gas evolution subsided, the mixture was extracted with ethyl acetate (2 x 20 mL). The organic layers were combined, and washed with brine solution (10 mL), dried over Na_2SO_4, and filtered, concentrated under reduced pressure. The crude residue was purified by silica column chromatography eluting with 0–80% ethyl acetate in hexanes to afford the amino-alcohol **19** (698 mg, 89% yield) as a white solid. R_f = 0.3 (ethyl acetate/hexane 4:1); m.p. = 125 °C; $[\alpha]^{20}_D$ = –74.79° (*c* = 0.5 in $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.16 (d, *J* = 4.5 Hz, 1H), 6.70

(d, *J* = 4.7 Hz, 1H), 6.00 – 5.93 (m, 3H), 5.54 – 5.46 (m, 1H), 5.40 – 5.36 (m, 1H), 5.24 – 5.22 (m, 1H), 5.00 (d, *J* = 9.4 Hz, 1H), 4.94 (d, *J* = 5.5 Hz, 1H), 4.89 (dq, *J* = 7.9, 1.4 Hz, 1H), 4.87 – 4.86 (m, 1H), 4.53 – 4.52 (m, 1H), 4.36 – 4.33 (m, 1H), 4.30 (dd, *J* = 5.5, 1.6 Hz, 1H), 4.19 – 4.14 (m, 1H), 3.93 (dd, *J* = 12.7, 1.8 Hz, 1H), 3.89 – 3.87 (m, 2H), 3.73 (t, *J* = 10.8 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 155.9, 147.7, 134.5, 133.4, 123.7, 118.2, 117.6, 117.2, 117.2, 115.0, 100.9, 87.5, 79.9, 79.3, 72.4, 72.1, 63.1; **^{1}H NMR** (400 MHz, DMSO-d_6): *δ* 8.05 – 7.81 (m, 3H), 6.92 (d, *J* = 4.4 Hz, 1H), 6.88 (d, *J* = 4.2 Hz, 1H), 5.93 – 5.79 (m, 2H), 5.30 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.24 – 5.20 (m, 1H), 5.15 – 5.09 (m, 2H), 5.03 – 5.02 (m, 1H), 4.76 (d, *J* = 4.9 Hz, 1H), 4.27 – 4.17 (m, 3H), 4.11 – 3.98 (m, 3H), 3.66 (d, *J* = 12.2 Hz, 1H), 3.56 – 3.49 (m, 1H); **^{13}C NMR** (101 MHz, DMSO-d_6): *δ* 155.7, 148.0, 134.9, 134.3, 123.0, 117.4, 117.0, 116.8, 116.6, 111.0, 101.0, 84.3, 79.6, 77.6, 76.0, 71.5, 70.5, 60.6; **IR** (neat): υ_{max} 3389, 3328, 3115, 2927, 2876, 1658, 1608, 1529, 1475, 1423, 1266, 1154, 1093, 1050, 931, 748 cm^{-1}; **HRMS** (ESI-TOF): m/z $[M+H]^+$ calcd for $C_{18}H_{22}N_5O_4$: 372.1664; found: 372.1663.

2-Ethylbutyl ((*S*)-(perfluorophenoxy)(phenoxy)phosphoryl)-*L*-alaninate (20)[4]:

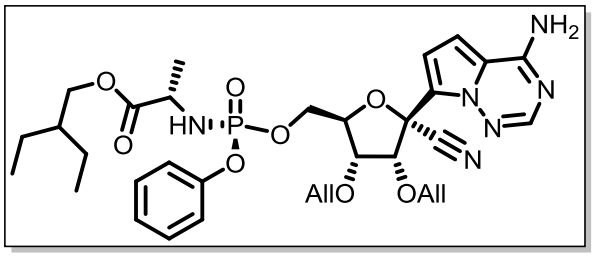


Compound **20** was prepared according to a previously established protocol; analytical data were consistent with data previously reported literature.

$[\alpha]^{20}_D$ = –0.40° (*c* = 0.5 in $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 7.37 – 7.34 (m, 2H), 7.25 – 7.20 (m, 3H), 4.22 – 4.15 (m, 1H), 4.07 (dd, *J* = 5.8, 1.7 Hz, 2H), 4.01 – 3.97 (m, 1H), 1.52 (dt, *J* = 12.6, 6.3 Hz, 1H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.37 – 1.31 (m, 4H), 0.88 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 173.2, 150.3, 130.0, 125.8, 120.2, 120.2, 68.0, 50.7, 40.4, 23.3, 21.2, 11.1; **^{1}H NMR** (500 MHz, DMSO-d_6); *δ* 7.42 – 7.39 (m, 2H), 7.26 – 7.21 (m, 3H), 6..89 (dd, J= 14.1, 9.9 Hz) 4.04 – 3.91 (m, 3H), 1.46 – 1.38 (m, 1H), 1.30 – 1.24 (m, 7H), 0.81 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6): *δ* 172.7, 150.0, 150.0, 129.9, 125.4, 120.1, 120.0, 66.3, 50.2, 22.6, 19.7, 19.6, 10.8; **^{31}P NMR** (202 MHz, $CDCl_3$) *δ* –1.65 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): *δ* –153.33 (d, *J* = 19.8 Hz, 2F), –159.56 (t, *J* = 21.7 Hz, 1F), –162.21 (t, *J* = 20.4 Hz, 2F). **IR** (neat): υ_{max} 3185, 2968, 1745, 1525, 1266,

1202, 1146, 1024, 952, 775 cm^{-1}; **HRMS** (ESI-TOF): m/z $[M+H]^+$calcd for $C_{21}H_{24}F_5O_5NP$: 496.1306; found: 496.1312.

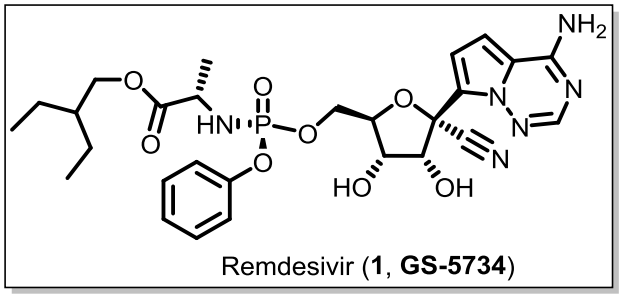
2-Ethylbutyl((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-*f*][1,2,4] triazin-7-yl)-5-cyano-3,4-*bis*(((*E*)-prop-1-en-1-yl)oxy)tetrahydro furan-2-yl)methoxy)(phenoxy)phosphoryl)-*L*-alaninate (21):



To a stirred solution of amino-alcohol compound **19** (250 mg, 0.673 mmol, 1 equiv) in anhydrous tetrahydrofuran solution (4 mL) was added 1.7 M solution of *tert*-butyl magnesium chloride in THF (1.4 mL, 1.41 mmol, 2.1 equiv) over a period of 3 min at room temperature. The yellow suspension was stirred at this temperature for 30 min, and then was added a solution of 2-ethylbutyl ((*S*)-(perfluoro phenoxy) (phenoxy)phosphoryl)-*L*-alaninate **20** (400 mg, 0.808 mmol, 1.2 equiv) in anhydrous THF (2 mL) over a period of 3 min. The reaction mixture was then allowed to stir at 50 °C for 2 h. After completion of the reaction, monitored by TLC, the reaction was quenched with saturated NH_4Cl solution (4 mL) and extracted with ethyl acetate (2 X 25 mL). The separated organic layer was washed with brine solution (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 0–10% methanol/ dichloromethane to afford the product **21** (393 mg, 86% yield) as a yellow sticky solid. There was no other isomer detectable by ^{31}P or ^1H NMR. Stereochemistry was assigned as Sp on the basis of the known stereochemistry of the compound **20**. R_f = 0.6 (methanol/dichloromethane 1:9); $[\alpha]^{20}_D$ = +6.20° (*c* = 0.5 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.33 – 7.29 (m, 2H), 7.23 – 7.21 (m, 2H), 7.16 – 7.14 (m, 1H), 6.96 (d, *J* = 4.5 Hz, 1H), 6.60 (d, *J* = 4.6 Hz, 1H), 5.92 – 5.81 (m, 4H), 5.28 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.23 (dd, *J* = 7.7, 1.5 Hz, 1H), 5.15 (td, *J* = 10.9, 1.1 Hz, 2H), 4.82 (d, *J* = 4.9 Hz, 1H), 4.51 (dd, *J* = 11.1, 4.4 Hz, 1H), 4.45 – 4.38 (m, 2H), 4.32 – 4.25 (m, 2H), 4.09 – 4.03 (m, 3H), 3.99 – 3.89 (m, 4H), 1.52 – 1.45 (m, 1H), 1.38 (d, *J* = 6.9 Hz, 3H), 1.33 – 1.25 (m, 4H), 0.85 (t, *J* = 7.4 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.8, 173.7, 155.4, 150.9, 150.8, 147.5, 133.9, 133.8, 129.9, 125.2, 123.9, 120.3, 120.3, 118.7, 118.0, 116.6, 116.3, 112.8, 100.4, 80.9, 80.9, 79.5, 78.9, 76.6, 72.8,

71.7, 67.8, 65.8, 65.7, 50.4, 40.3, 23.3, 23.3, 21.4, 21.4, 11.1, 11.1; **^{1}H NMR** (500 MHz, methanol-d_4): δ 7.89 (s, 1H), 7.36 – 7.33 (m, 2H), 7.24 – 7.22 (m, 2H), 7.20 – 7.19 (m, 1H), 6.93 (d, J = 4.6 Hz, 1H), 6.88 (d, J = 4.6 Hz, 1H), 5.94 – 5.83 (m, 2H), 5.31 (dq, J = 17.3, 1.7 Hz, 1H), 5.24 (dq, J = 17.2, 1.6 Hz, 1H), 5.17 – 5.14 (m, 1H), 5.12 – 5.09 (m, 1H), 4.94 (d, J = 5.0 Hz, 1H), 4.44 – 4.40 (m, 2H), 4.35 – 4.22 (m, 3H), 4.12 – 4.07 (m, 1H), 4.05 – 3.99 (m, 3H), 3.96 – 3.92 (m, 2H), 1.47 –1.44 (m, 1H), 1.35 – 1.29 (m, 7H), 0.85 (t, J = 7.5 Hz, 6H); **^{13}C NMR** (101 MHz, methanol-d_4): δ 174.9, 174.9, 157.2, 152.2, 152.1, 148.3, 135.5, 135.2, 130.8, 126.2, 124.7, 121.4, 121.4, 118.4, 118.2, 117.7, 117.6, 112.8, 102.6, 82.7, 82.6, 80.5, 80.4, 77.8, 73.6, 72.6, 68.1, 66.7, 66.6, 51.5, 41.7, 24.2, 20.6, 20.5, 11.3, 11.3; **^{31}P NMR** (202 MHz, methanol-d_4): δ 3.49 (s); **IR** (neat): υ_{max} 3331, 3221, 3189, 2966, 2930, 2881, 1737, 1647, 1602, 1526, 1477, 1250, 1210, 1155, 1033, 938, 769 cm^{-1}; **HRMS** (ESI-TOF): m/z $[M+H]^+$ calcd for $C_{33}H_{44}N_6O_8P$: 683.2954; found: 683.2953; **HPLC**: t_R = 7.973 min.

Remdesivir (1, GS-5734):



Remdesivir (**1**, **GS-5734**)

To a stirred solution of compound **21** (200 mg, 0.29 mmol, 1 equiv) in anhydrous THF (3 mL) was added PMHS (200 mg) and degassed with nitrogen for 15 min. Then $Pd(PPh_3)_4$ (17 mg, 0.01 mmol, 0.05 equiv) and $ZnCl_2$ (40mg, 0.29 mmol, 1 equiv) was added at room temperature and stirred for 6 h. After completion of the reaction, monitored by TLC, it was quenched with water (5 mL) and stirred for 10 min, extracted with ethyl acetate (2 X 20 mL). The separated organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 0–10% methanol/dichloromethane to afford Remdesivir (**1**, **GS-5734)** (160 mg, 91% yield) as a white solid. R_f = 0.4 (methanol/dichloromethane 1:9); m.p. = 137 °C; $[\alpha]^{25}_{D}$ = –22.00° (c = 0.2 in CH_2Cl_2), reported $[\alpha]^{25}_{D}$ = –24.00° (c = 0.2 in CH_2Cl_2)[5]; **^{1}H NMR** (400 MHz, methanol-d_4): δ 7.87 (s, 1H), 7.33 – 7.26 (m, 2H), 7.21 – 7.12 (m, 3H), 6.91 (d, J = 4.6 Hz, 1H), 6.88 (d, J = 4.6 Hz, 1H), 4.79 (d, J = 5.4 Hz, 1H),

4.43 – 4.34 (m, 2H), 4.28 (ddd, J = 10.3 5.9, 4.2 Hz , 1H), 4.17 (t, J = 5.6 Hz, 1H), 4.02 (dd, J = 10.9, 5.8 Hz, 1H), 3.96 – 3.85 (m, 2H), 1.49 – 1.41 (m, 1H), 1.35 – 1.27 (m, 8H), 0.85 (t, J = 7.5 Hz, 6H); **^{13}C NMR** (126 MHz, methanol-d_4): δ 174.99, 174.94, 157.15, 152.17, 152.12, 148.15, 130.71, 126.06, 125.62, 121.35, 121.31, 117.90, 117.57, 112.33, 102.69, 84.32, 84.25, 81.27, 75.65, 71.63, 68.10, 67.17, 67.13, 51.48, 41.69, 24.22, 24.19, 20.54, 20.49, 11.33, 11.28; **^{31}P NMR** (202 MHz, methanol-d_4): δ 3.50 (s); **IR** (neat): υ_{max} 3337, 3222, 2961, 2927, 1732, 1644, 1602, 1525, 1478, 1245, 1207, 1148, 1013, 936, 758, 693 cm^{-1}; **HRMS** (ESI-TOF): m/z $[M+H]^+$calcd for $C_{27}H_{36}N_6O_8P$: 603.2326; found: 603.2310; **HPLC**: t_R = 3.542 min.

III. HPLC data of compounds 18, 21 and Remdesivir (1, GS-5734):

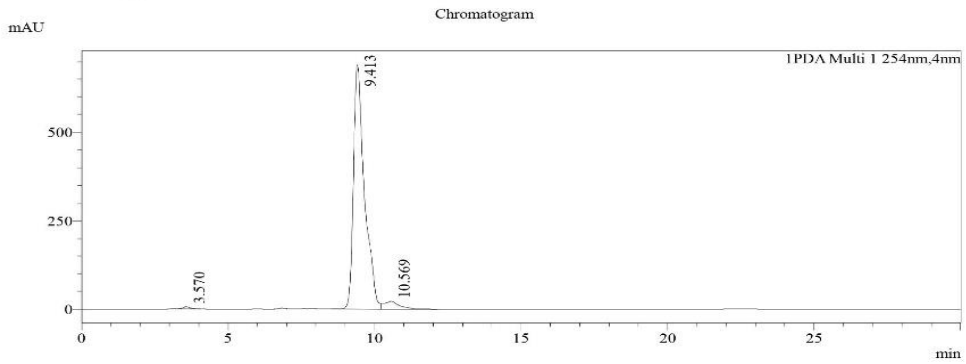
(a) HPLC data of compound **18**

SHIMADZU LabSolutions Analysis Report

<Sample Information>

Sample Name : SCS-KK-709
Sample ID : SCS-KK-709
Method Filename : KK-250621.lcm

<Chromatogram>



Peak Table

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%	Height%
1	3.570	110288	6626	0.582	0.921
2	9.413	18023227	690688	95.128	96.036
3	10.569	812707	21883	4.290	3.043
Total		18946222	719197	100.000	100.000

(b) HPLC data of compound **21**

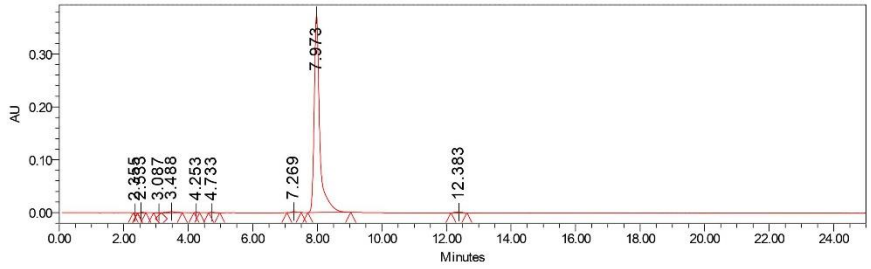
Empower™ 3 SOFTWARE

HPLC REPORT

SAMPLE INFORMATION

Sample Name:	14July21-SCS-KK-682	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	14-07-2021 15:06:32 IST
Vial:	2	Acq. Method Set:	corti2021
Injection #:	1	Date Processed:	14-07-2021 17:19:52 IST
Injection Volume:	10.00 ul	Processing Method	Default
Run Time:	25.0 Minutes	Channel Name:	2998 Ch1 254nm@1.2nm
Sample Set Name	14JULY21	Proc. Chnl. Descr.:	2998 Ch1 254nm@1.2nm

Auto-Scaled Chromatogram



Peak Results

	RT	Area	Height	% Area	% Height
1	2.355	2335	521	0.05	0.14
2	2.533	8379	2402	0.18	0.63
3	3.087	4029	402	0.09	0.10
4	3.488	32014	1985	0.70	0.52
5	4.253	2688	540	0.06	0.14
6	4.733	4328	410	0.09	0.11
7	7.269	17200	1952	0.38	0.51
8	7.973	4482919	374162	98.06	97.55
9	12.383	17599	1197	0.38	0.31

Reported by User: System
Report Method: HPLC REPORT
Report Method ID: 6687
Page: 1 of 2

Project Name: Chandu
Date Printed:
14-07-2021
17:20:27 Asia/Kolkata

(c) HPLC data of Remdesivir **(1, GS-5734)**

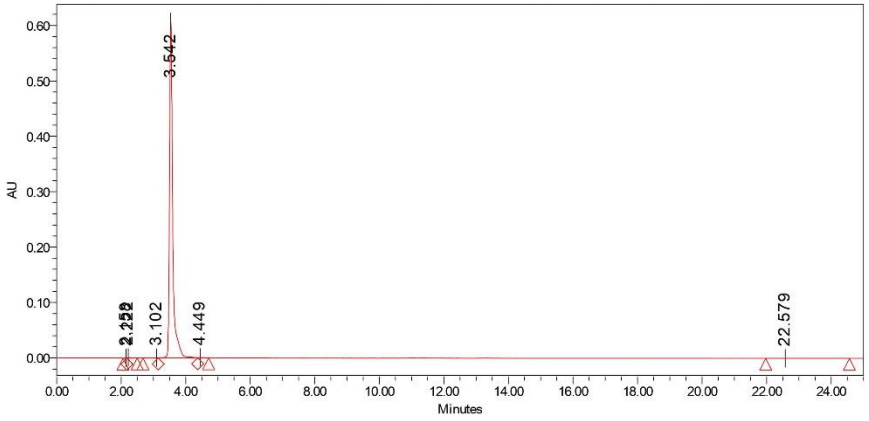
Empower 3 SOFTWARE

HPLC REPORT

SAMPLE INFORMATION

Sample Name:	14July21-SCS-KK-602	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	14-07-2021 15:32:41 IST
Vial:	3	Acq. Method Set:	corti2021
Injection #:	1	Date Processed:	14-07-2021 17:25:08 IST
Injection Volume:	10.00 ul	Processing Method	Default
Run Time:	25.0 Minutes	Channel Name:	2998 Ch1 254nm@1.2nm
Sample Set Name	14JULY21	Proc. Chnl. Descr.:	2998 Ch1 254nm@1.2nm

Auto-Scaled Chromatogram



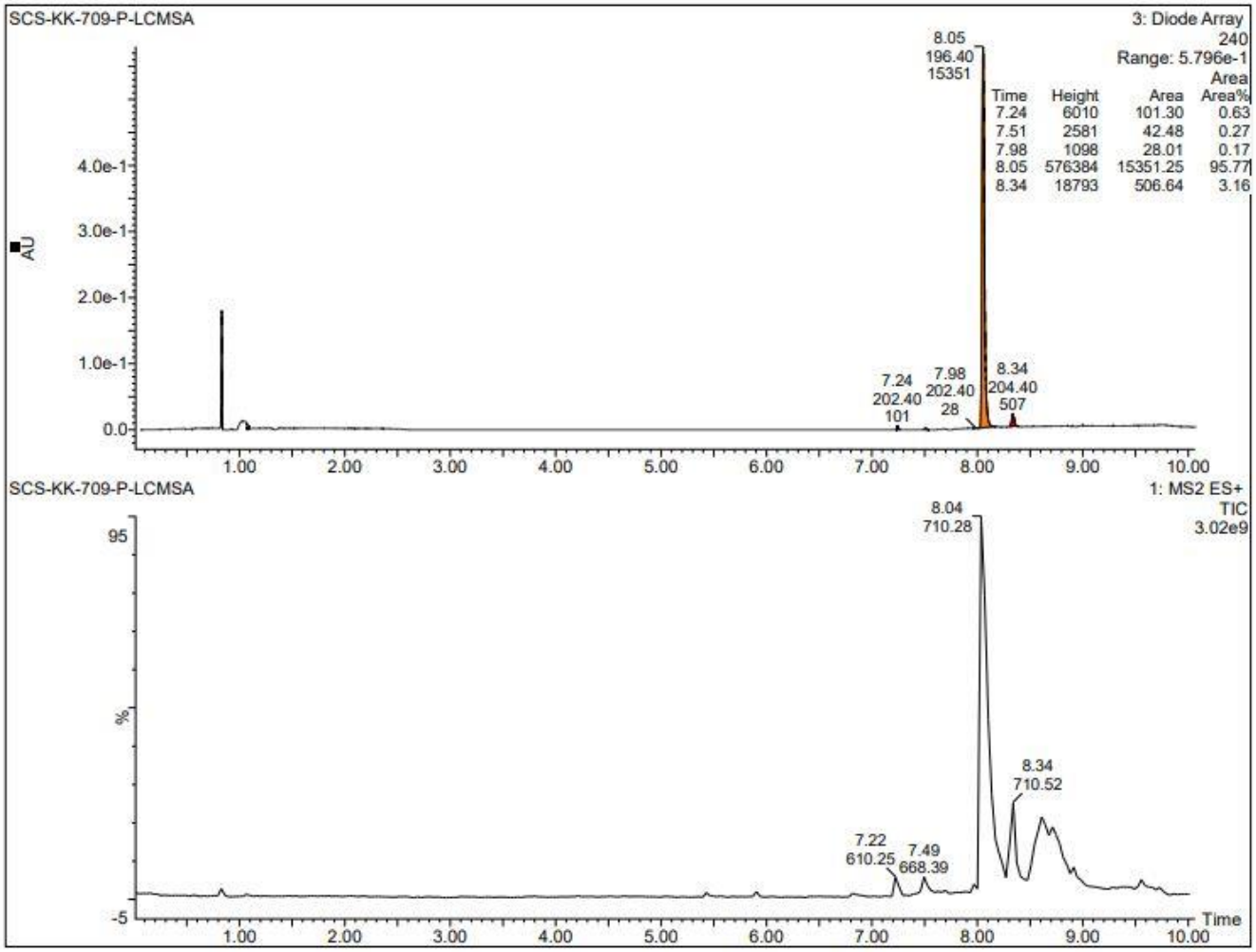
Peak Results

	RT	Area	Height	% Area	% Height
1	2.158	3488	803	0.08	0.13
2	2.222	9999	1389	0.24	0.23
3	3.102	12362	642	0.30	0.10
4	3.542	4135116	607479	98.78	99.36
5	4.449	8633	855	0.21	0.14
6	22.579	16408	218	0.39	0.04

Reported by User: System
Report Method: HPLC REPORT
Report Method ID: 6699
Page: 1 of 2

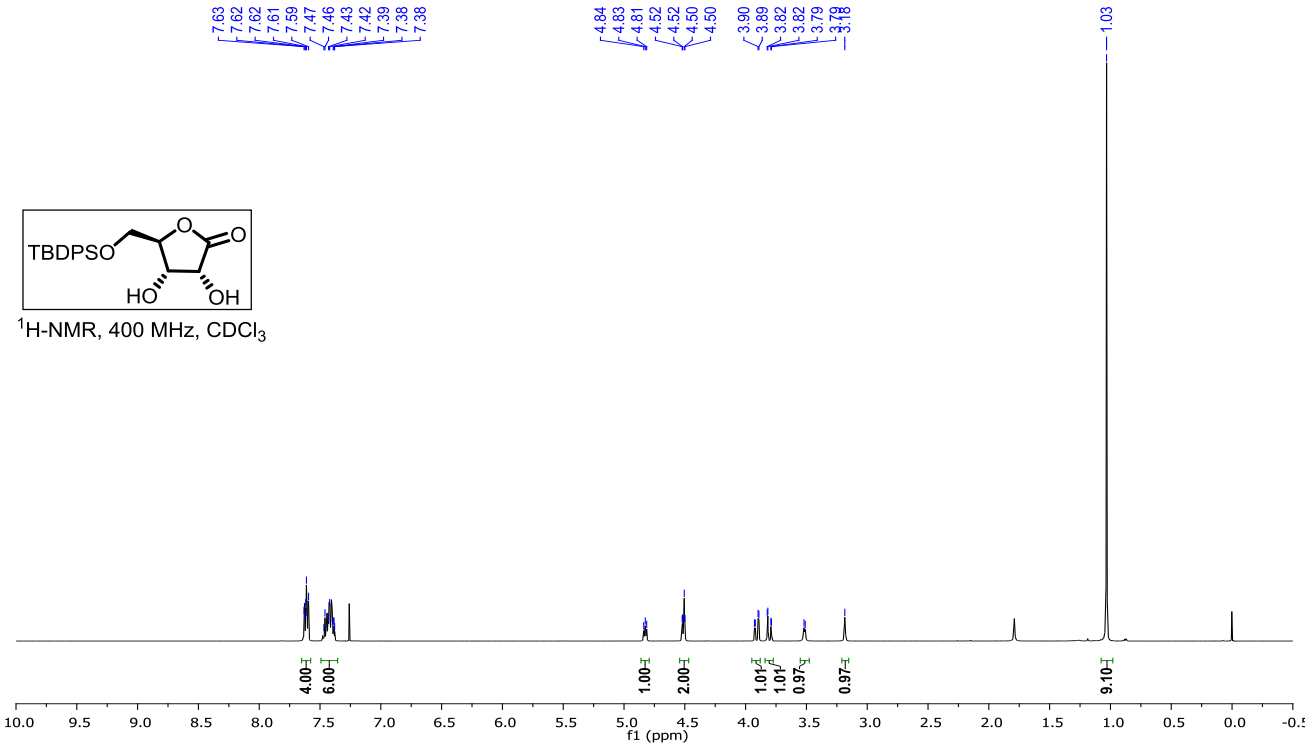
Project Name: Chandu
Date Printed:
14-07-2021
17:29:09 Asia/Kolkata

IV. LCMS data of compound 18:

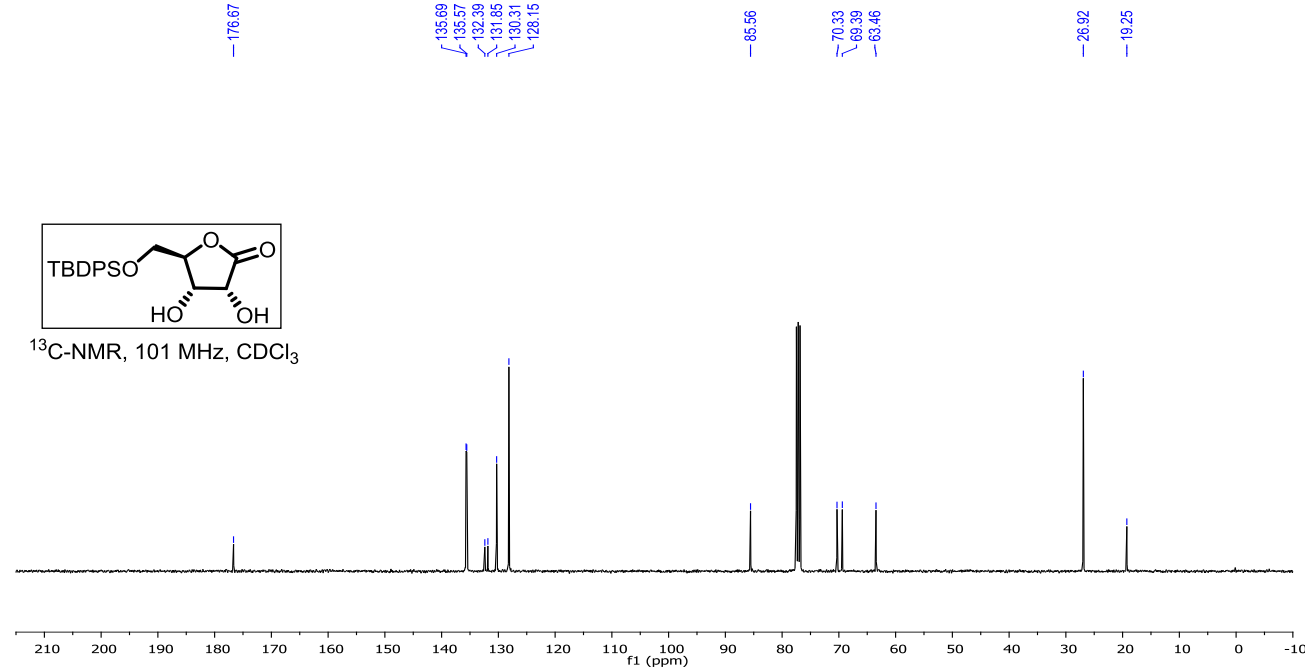


V. ^{1}H NMR & ^{13}C NMR spectra

(3*R*,4*S*,5*R*)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3,4-dihydroxydihydrofuran-2(3*H*)-one (13):

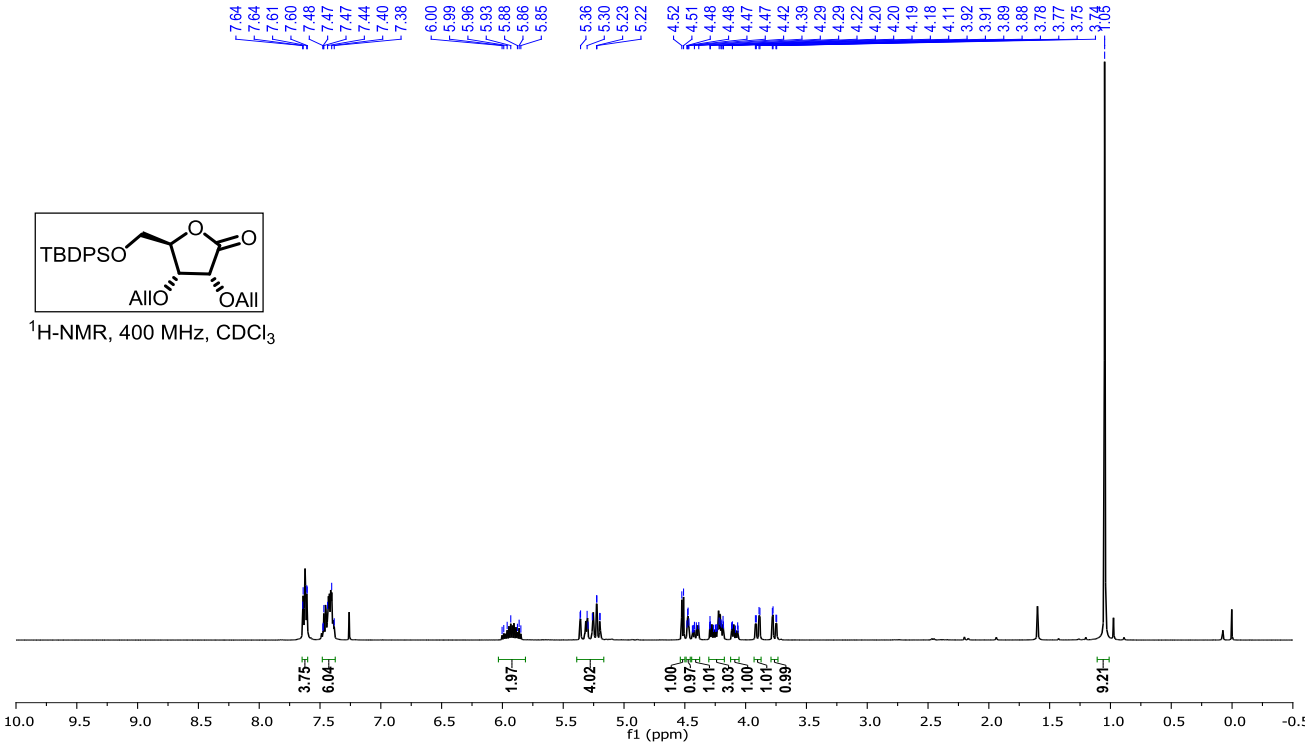


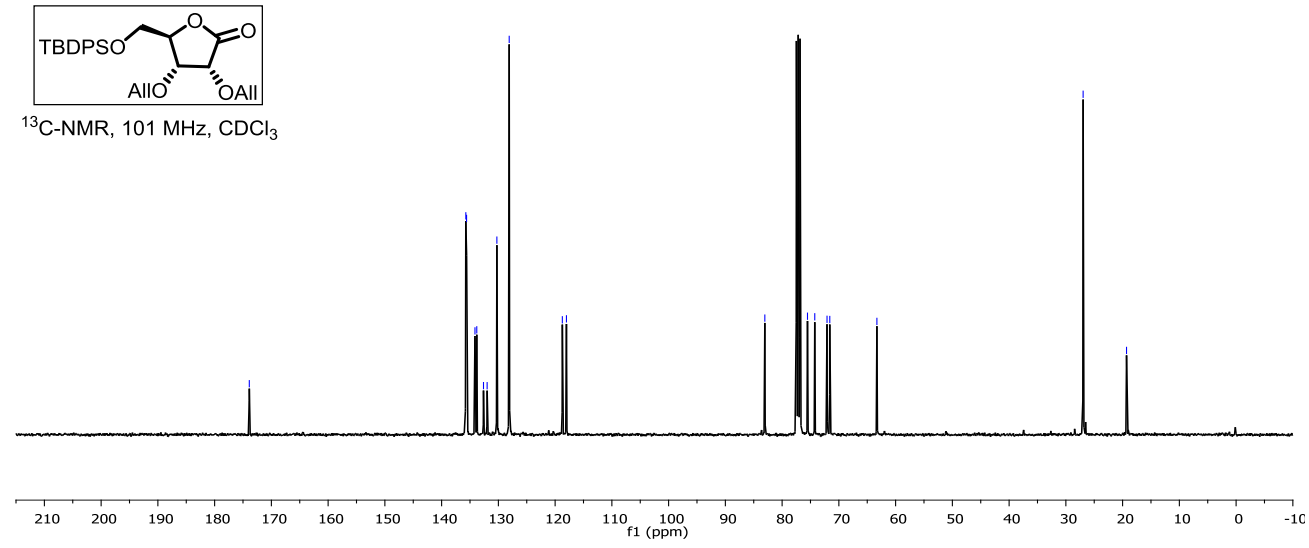
^{1}H-NMR, 400 MHz, $CDCl_3$



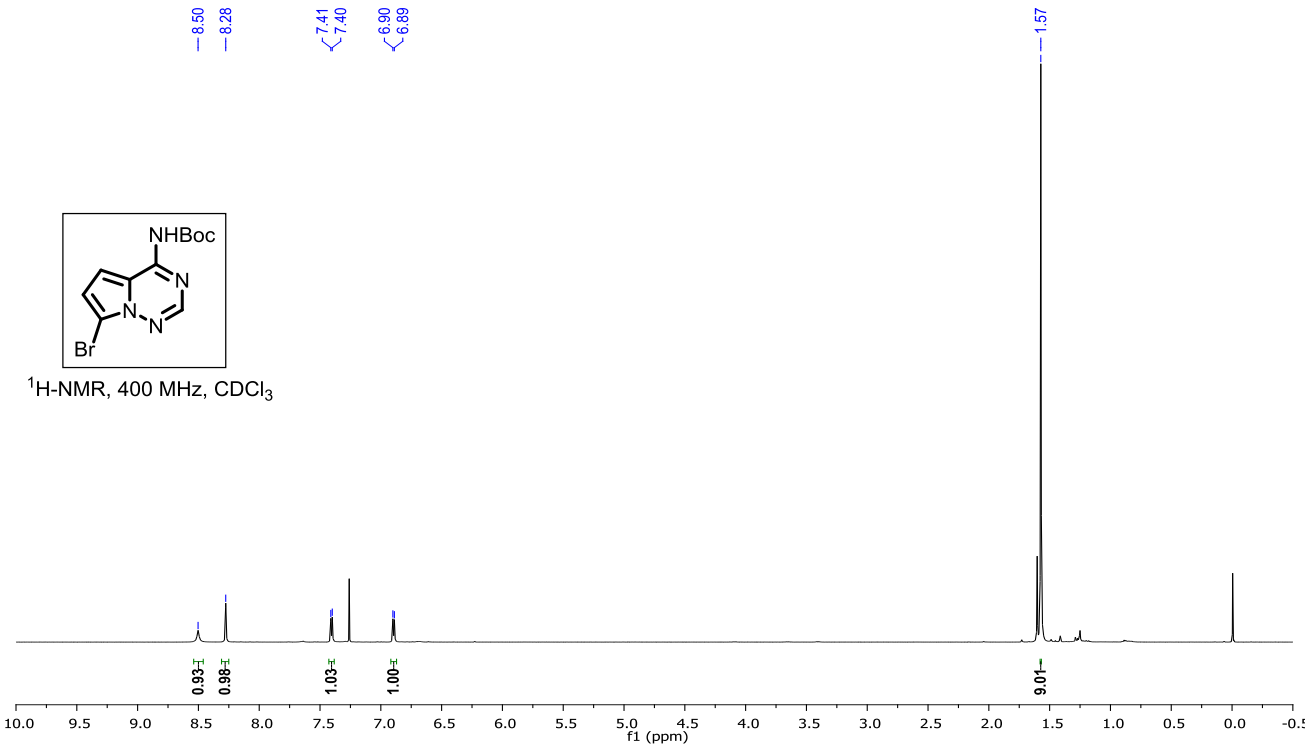
^{13}C-NMR, 101 MHz, $CDCl_3$

(3*R*,4*R*,5*R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-3,4-*bis*(((*E*)-prop-1-en-1-yl)oxy)dihydrofuran-2(3*H*)-one (15):

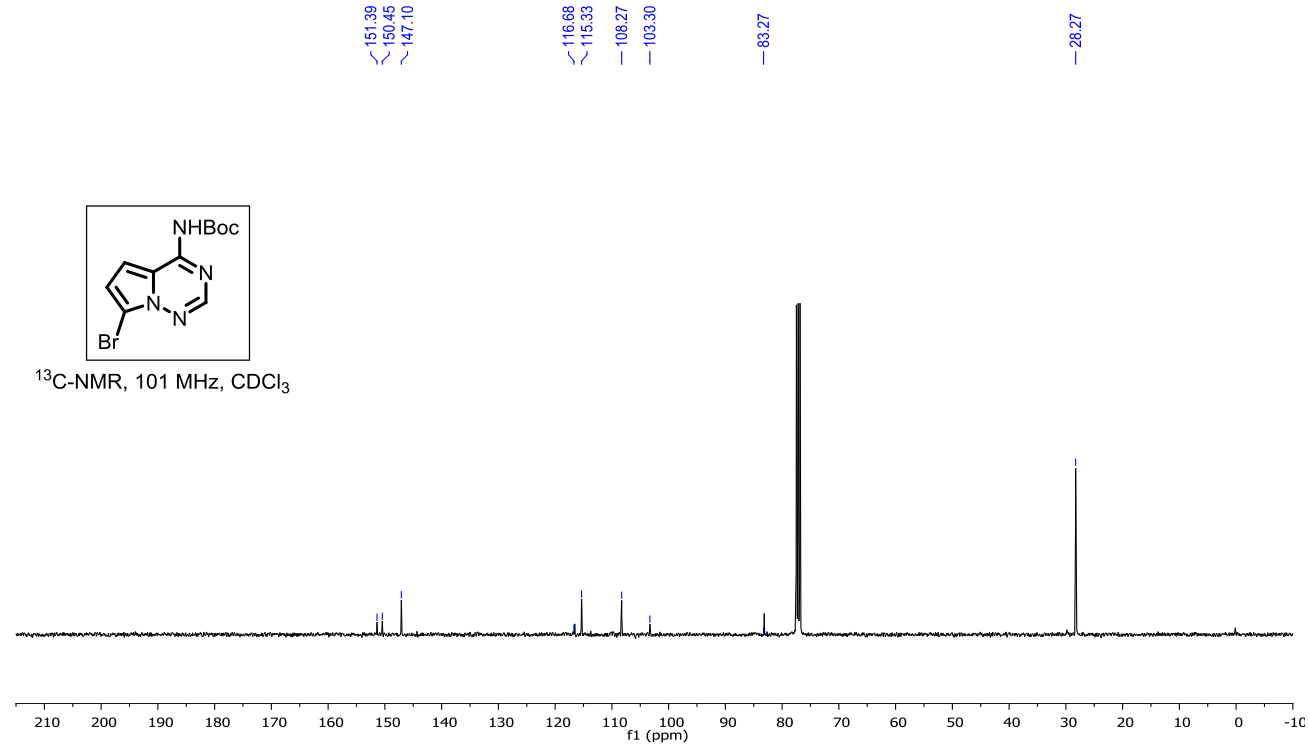




tert-Butyl (7-bromopyrrolo[2,1-_f_][1,2,4]triazin-4-yl)carbamate (16):

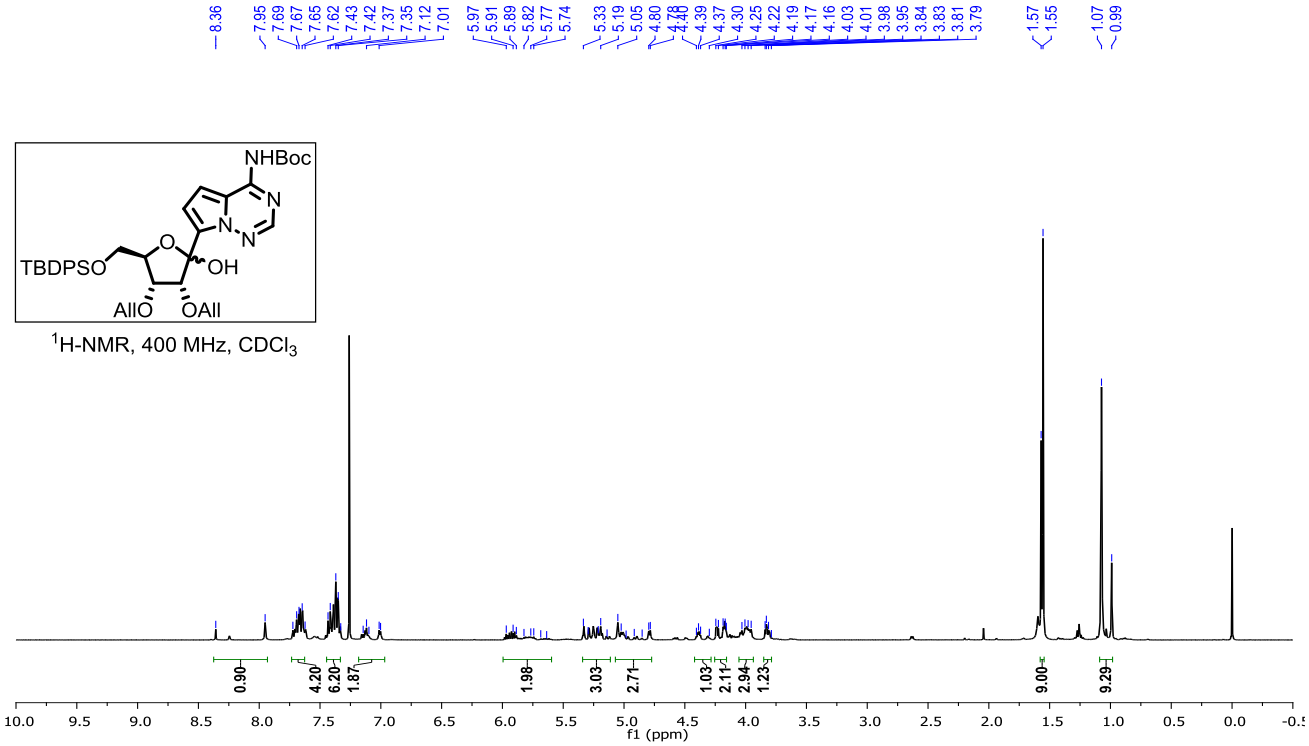


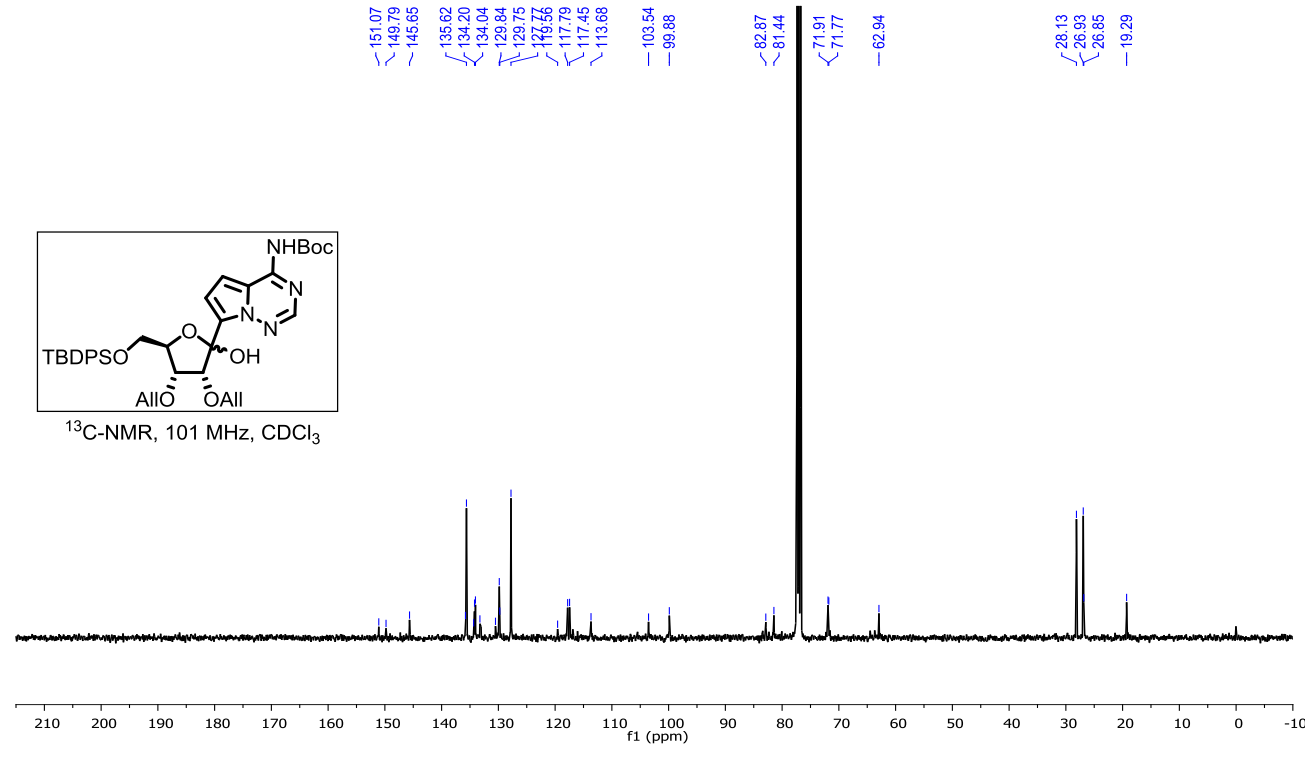
^{1}H-NMR, 400 MHz, $CDCl_3$



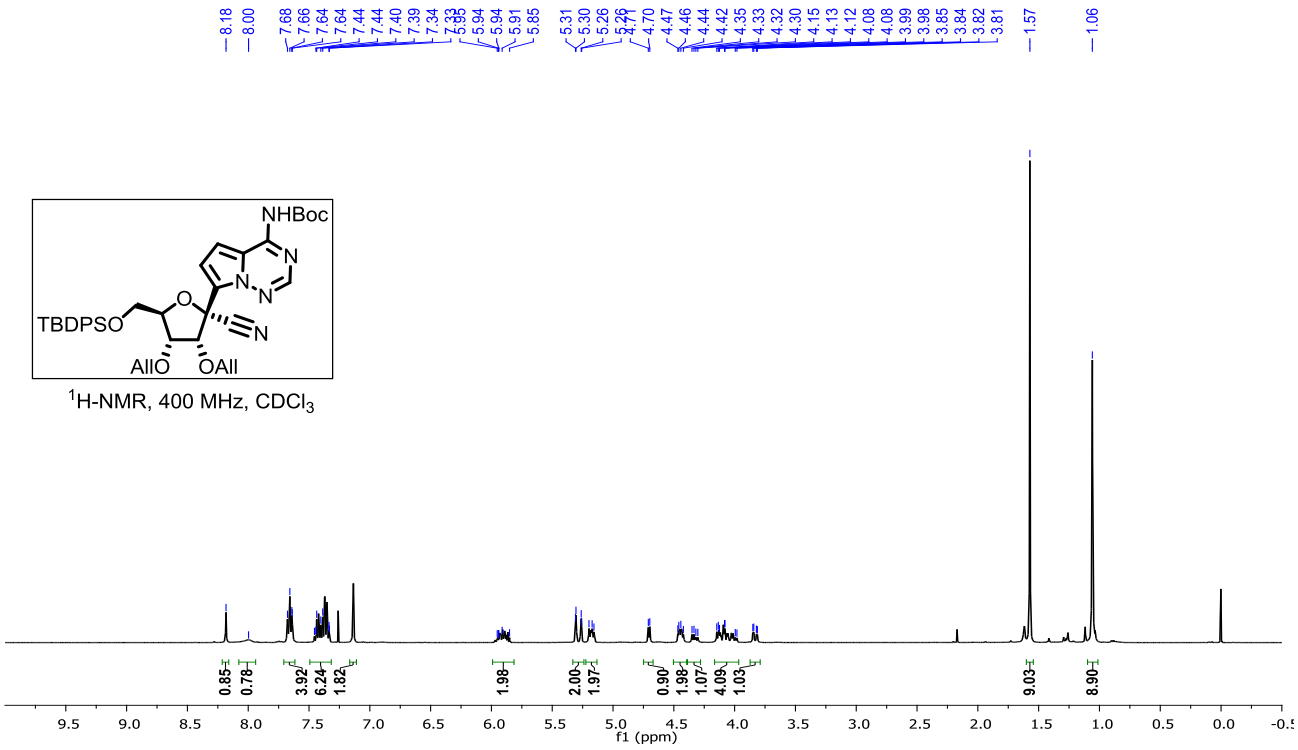
^{13}C-NMR, 101 MHz, $CDCl_3$

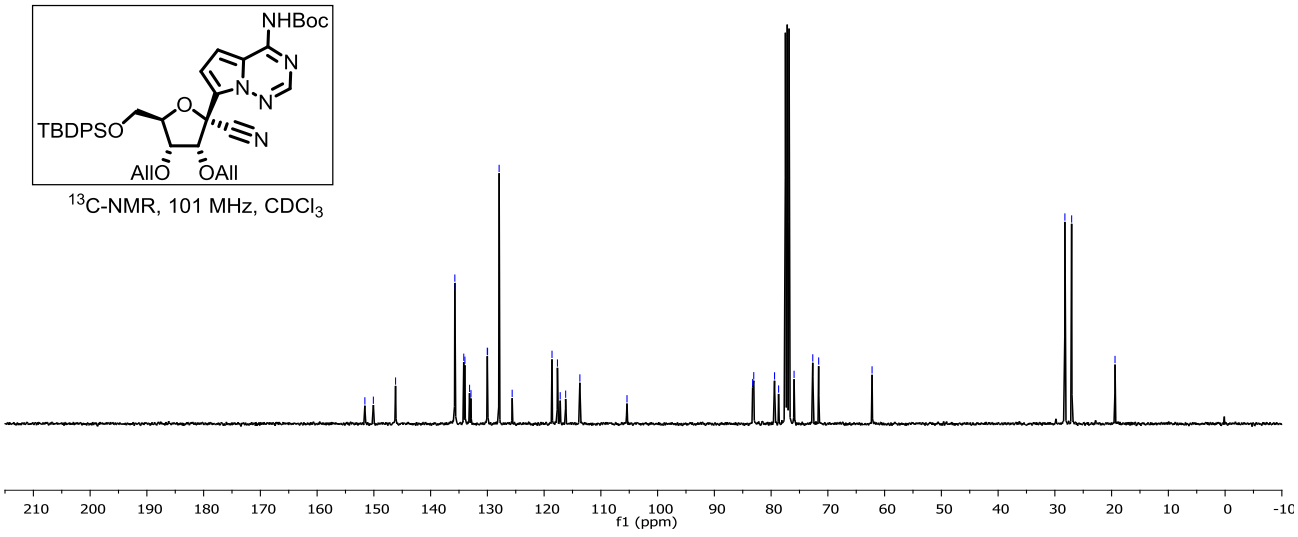
***tert*-Butyl (7-((3*R*,4*R*,5*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-hydroxy-3,4-*bis*(((*E*)-prop-1-en-1-yl)oxy)tetrahydrofuran-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)carbamate (17):**



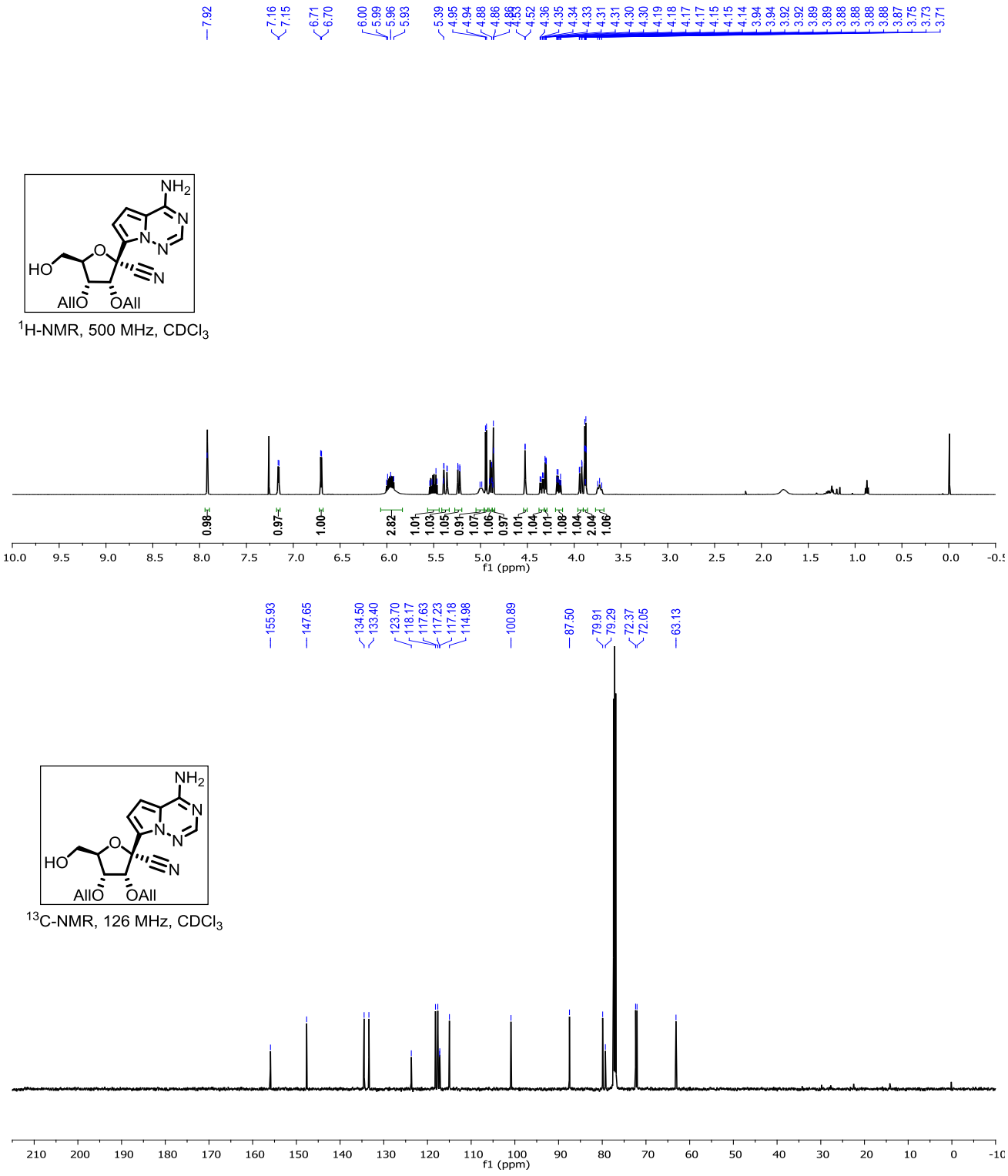


***tert*-Butyl (7-((2*R*,3*R*,4*R*,5*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-cyano-3,4-bis(((*E*)-prop-1-en-1-yl)oxy)tetrahydrofuran-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)carbamate (18):**

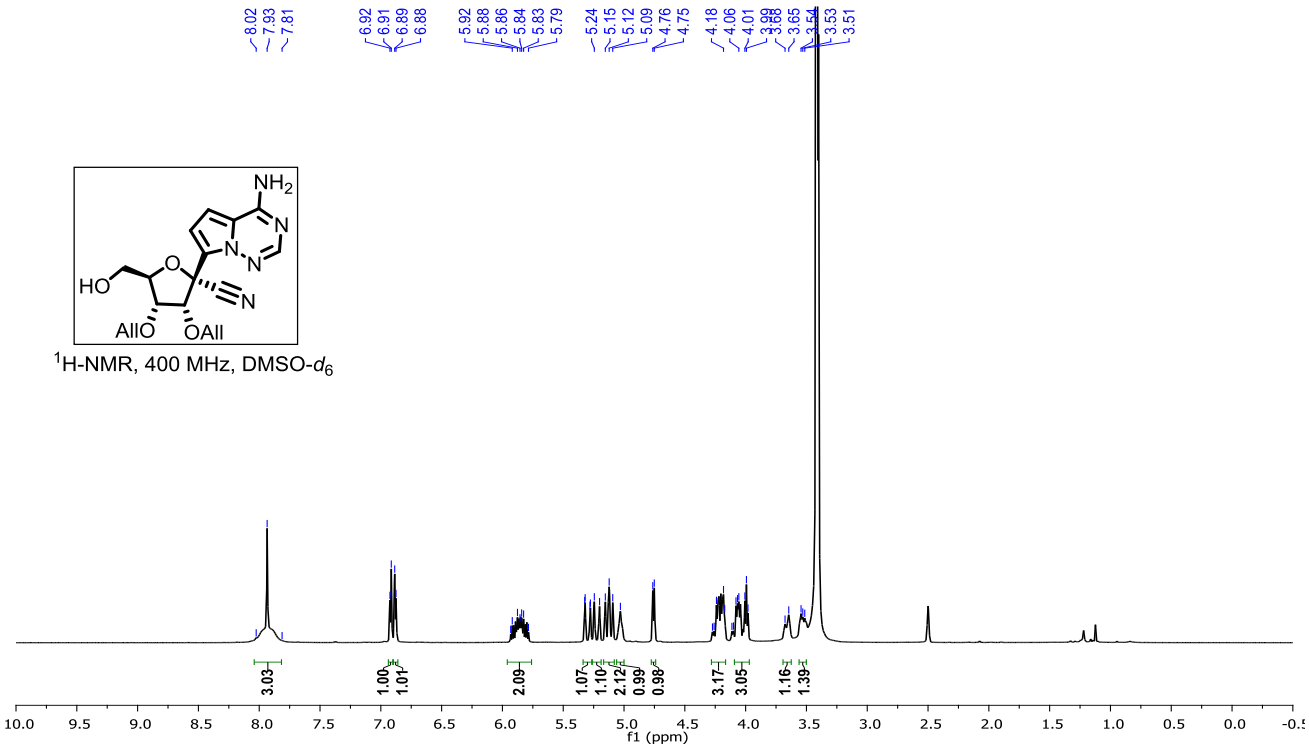




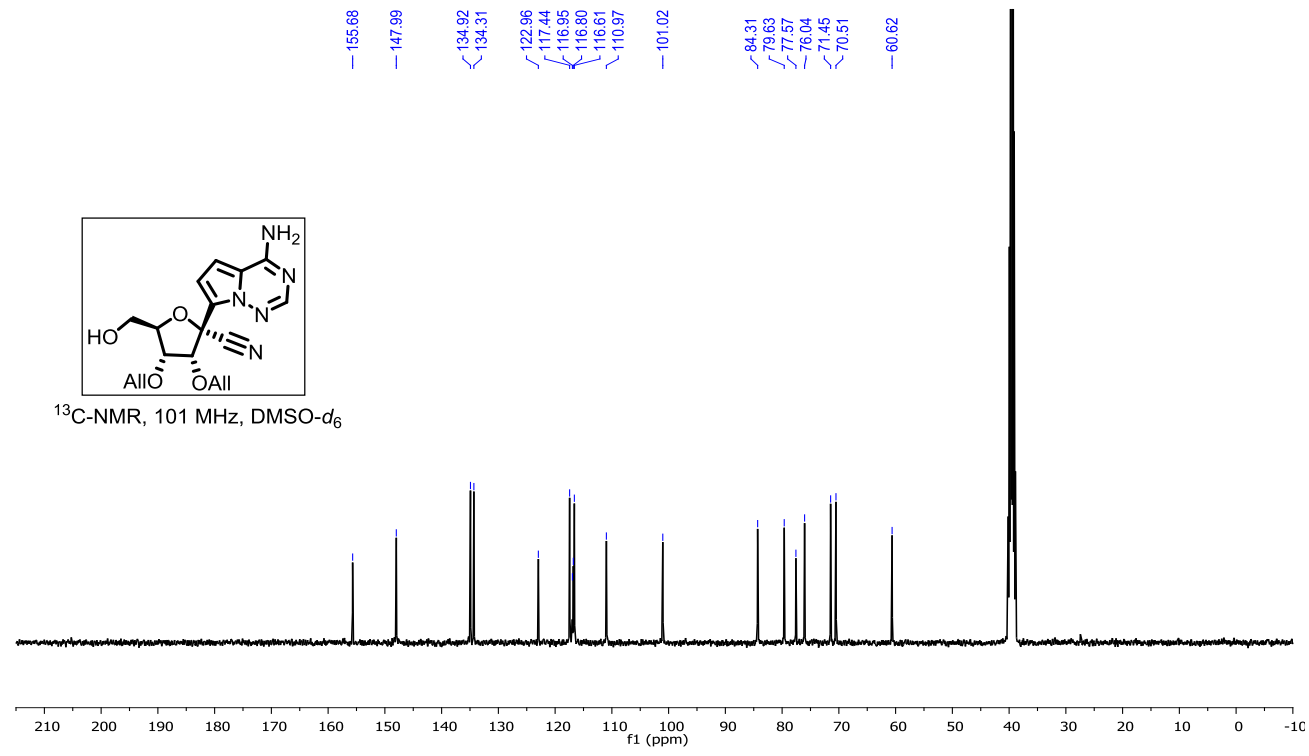
(2*R*,3*R*,4*R*,5*R*)-2-(4-Aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-(hydroxymethyl)-3,4-*bis*(((*E*)-prop-1-en-1-yl)oxy)tetrahydrofuran-2-carbonitrile (19):



(2*R*,3*R*,4*R*,5*R*)-2-(4-Aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-(hydroxymethyl)-3,4-*bis*(((*E*)-prop-1-en-1-yl)oxy)tetrahydrofuran-2-carbonitrile (19):

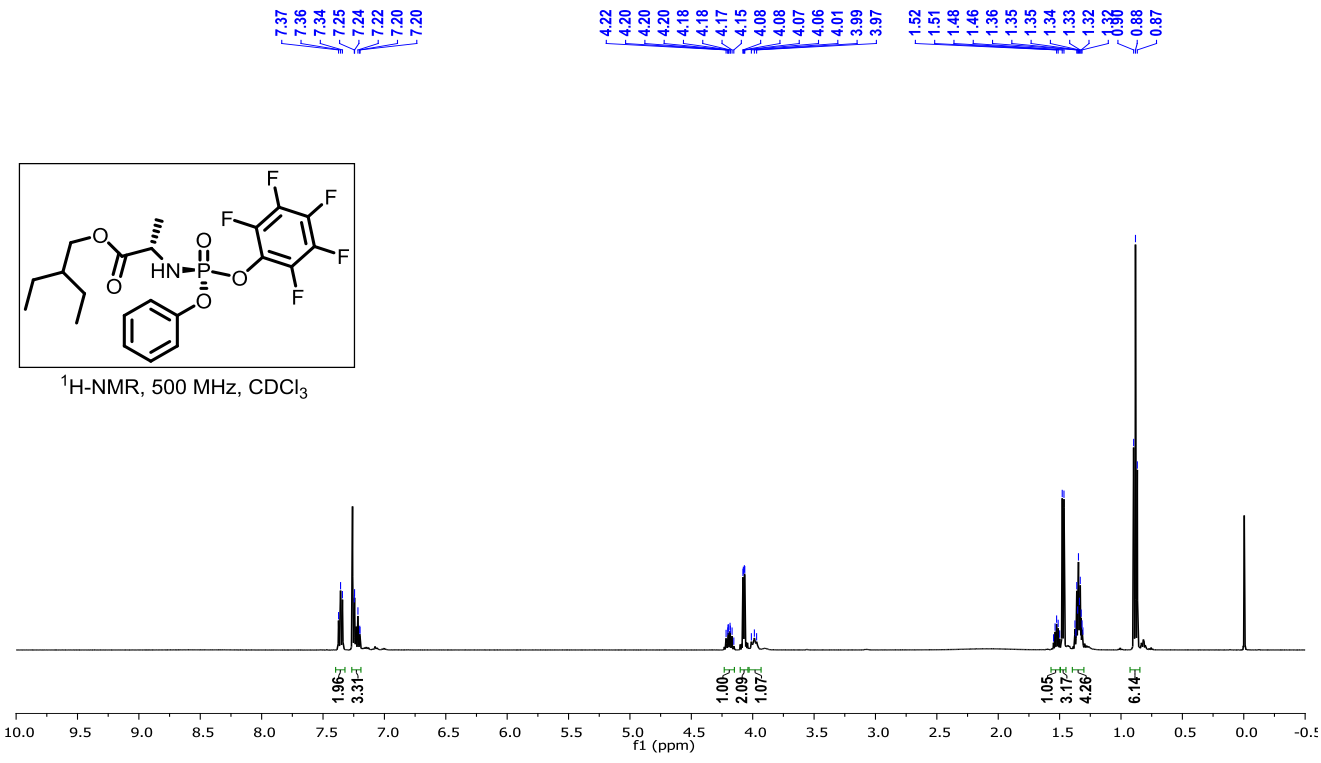


^{1}H-NMR, 400 MHz, DMSO-d_6

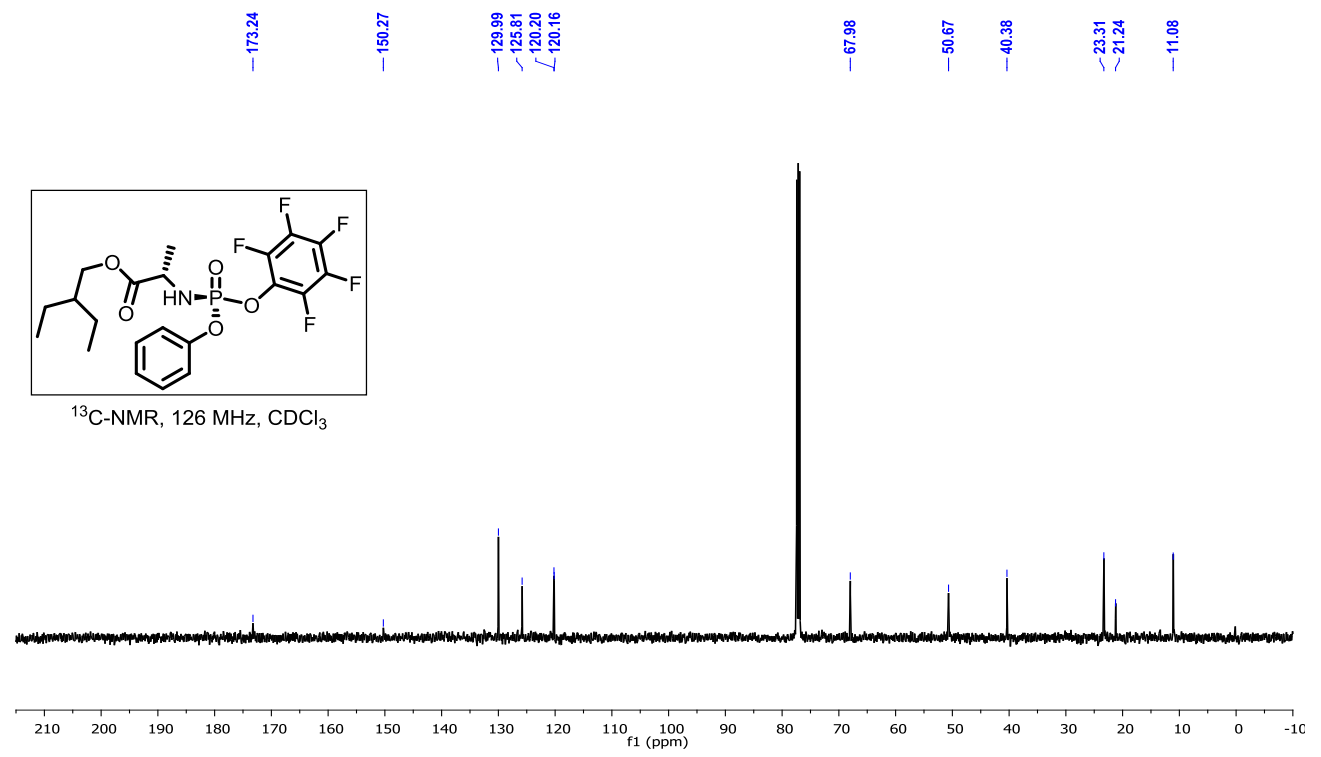


^{13}C-NMR, 101 MHz, DMSO-d_6

2-Ethylbutyl ((*S*)-(perfluorophenoxy)(phenoxy)phosphoryl)-*L*-alaninate (20):

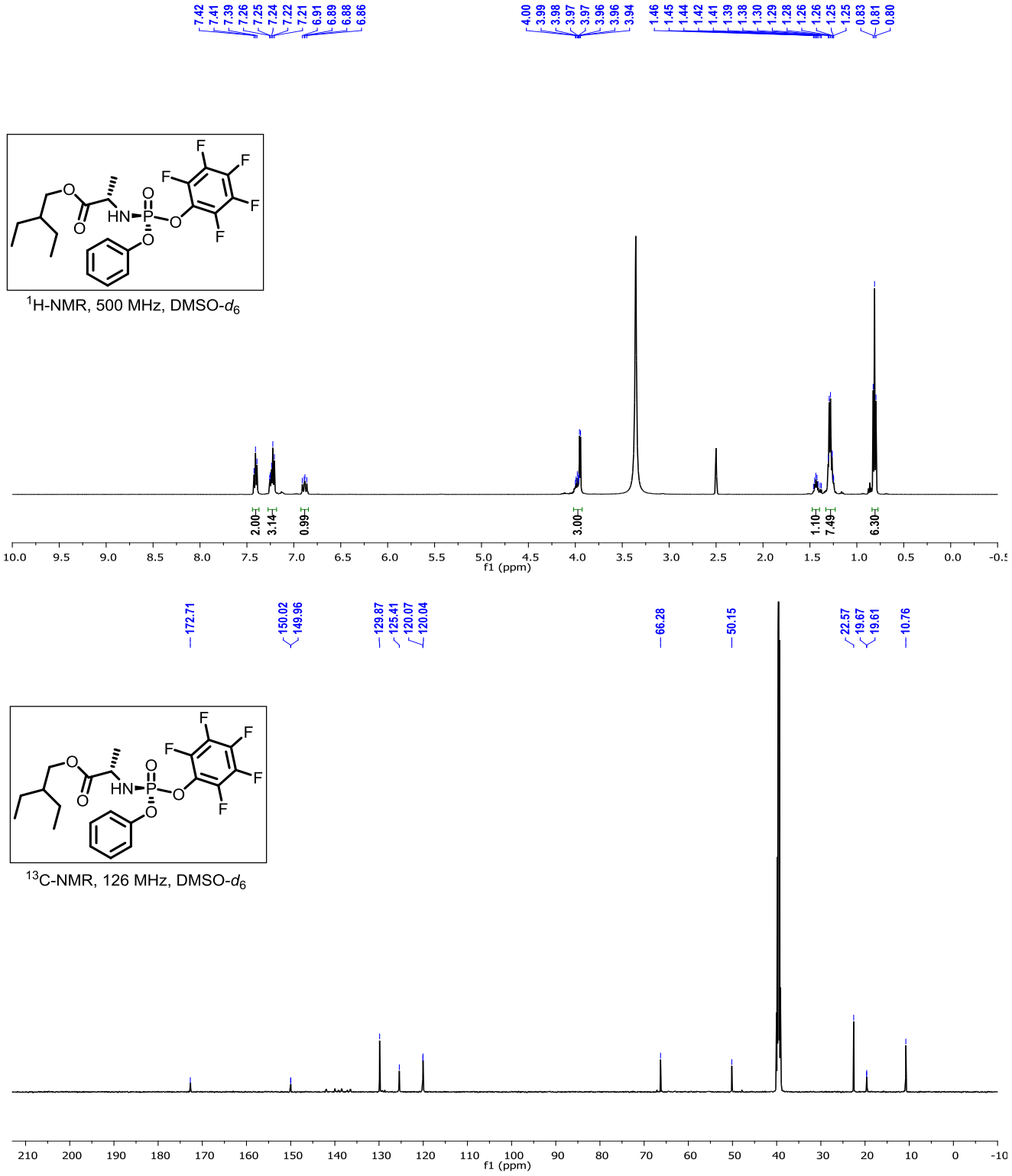


^{1}H-NMR, 500 MHz, $CDCl_3$

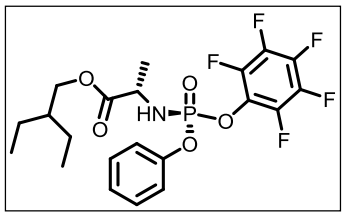


^{13}C-NMR, 126 MHz, $CDCl_3$

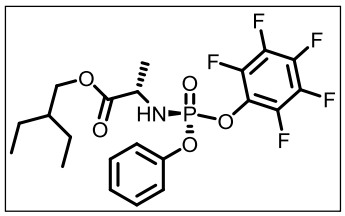
2-Ethylbutyl ((*S*)-(perfluorophenoxy)(phenoxy)phosphoryl)-*L*-alaninate (20):



2-Ethylbutyl ((*S*)-(perfluorophenoxy)(phenoxy)phosphoryl)-*L*-alaninate (20):

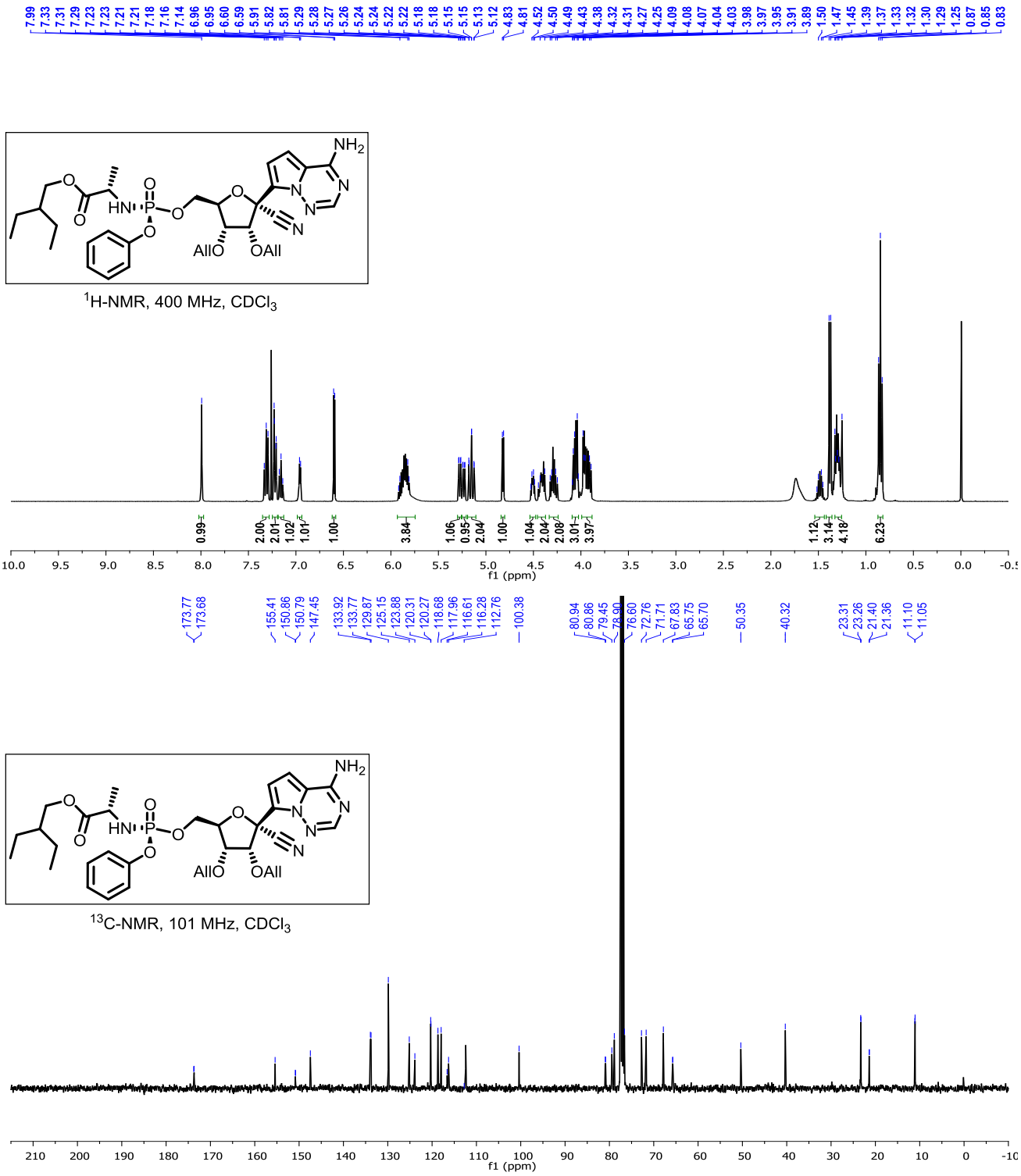


^{31}P-NMR, 202 MHz, $CDCl_3$

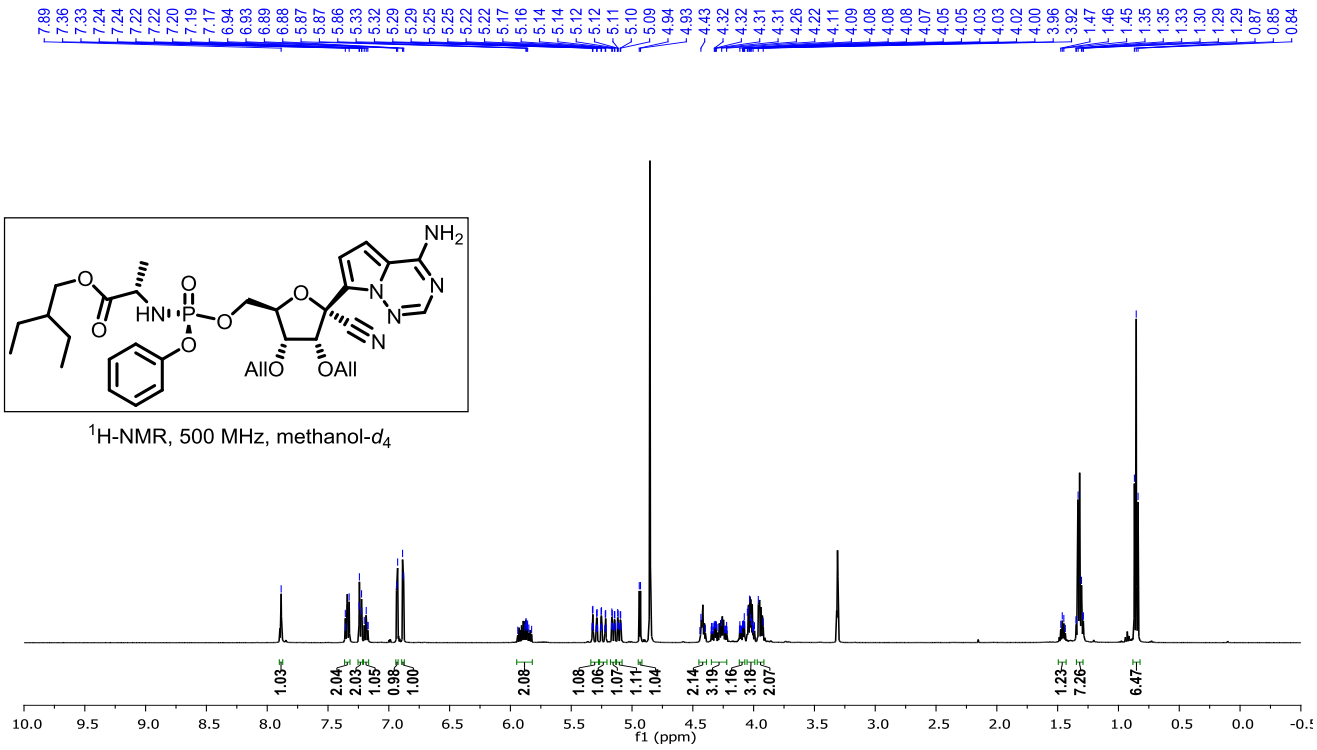


^{19}F-NMR, 376 MHz, $CDCl_3$

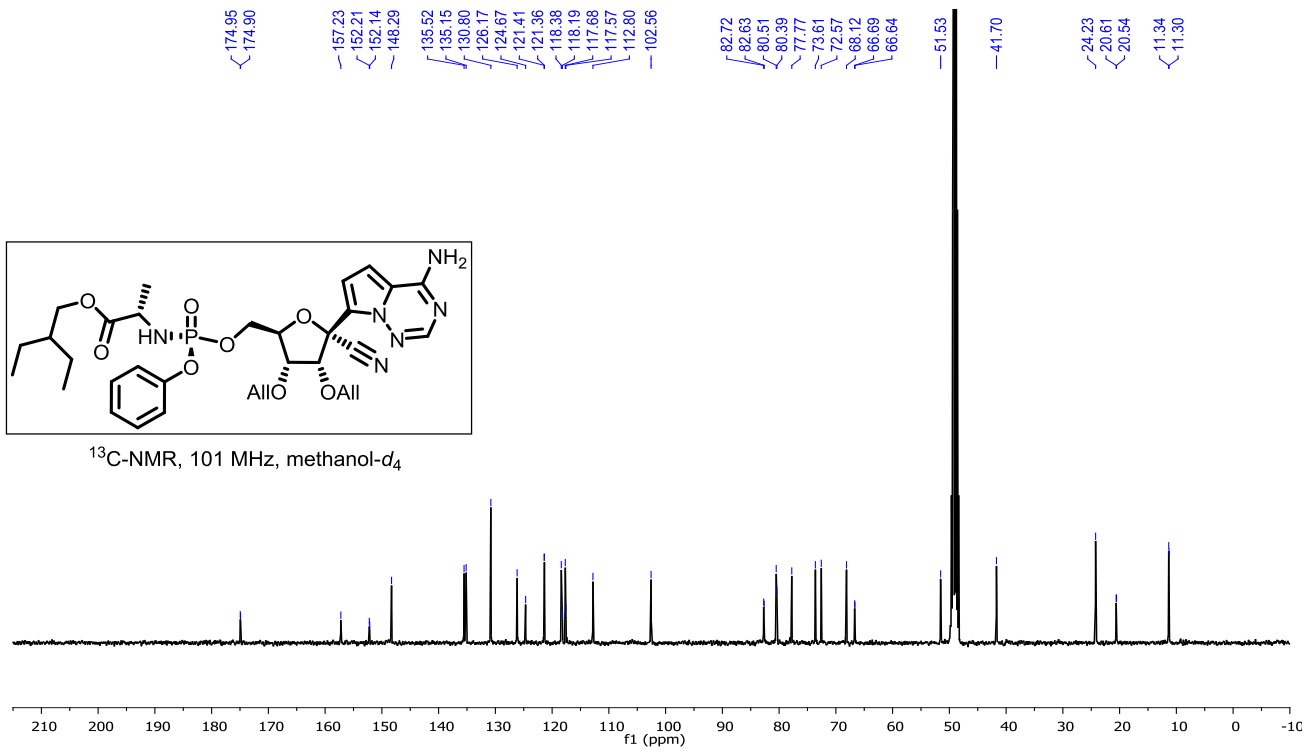
2-Ethylbutyl ((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-cyano-3,4-*bis*(((*E*)-prop-1-en-1-yl)oxy)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-*L*-alaninate (21):



2-Ethylbutyl ((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-cyano-3,4-*bis*(((*E*)-prop-1-en-1-yl)oxy)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-*L*-alaninate (21):

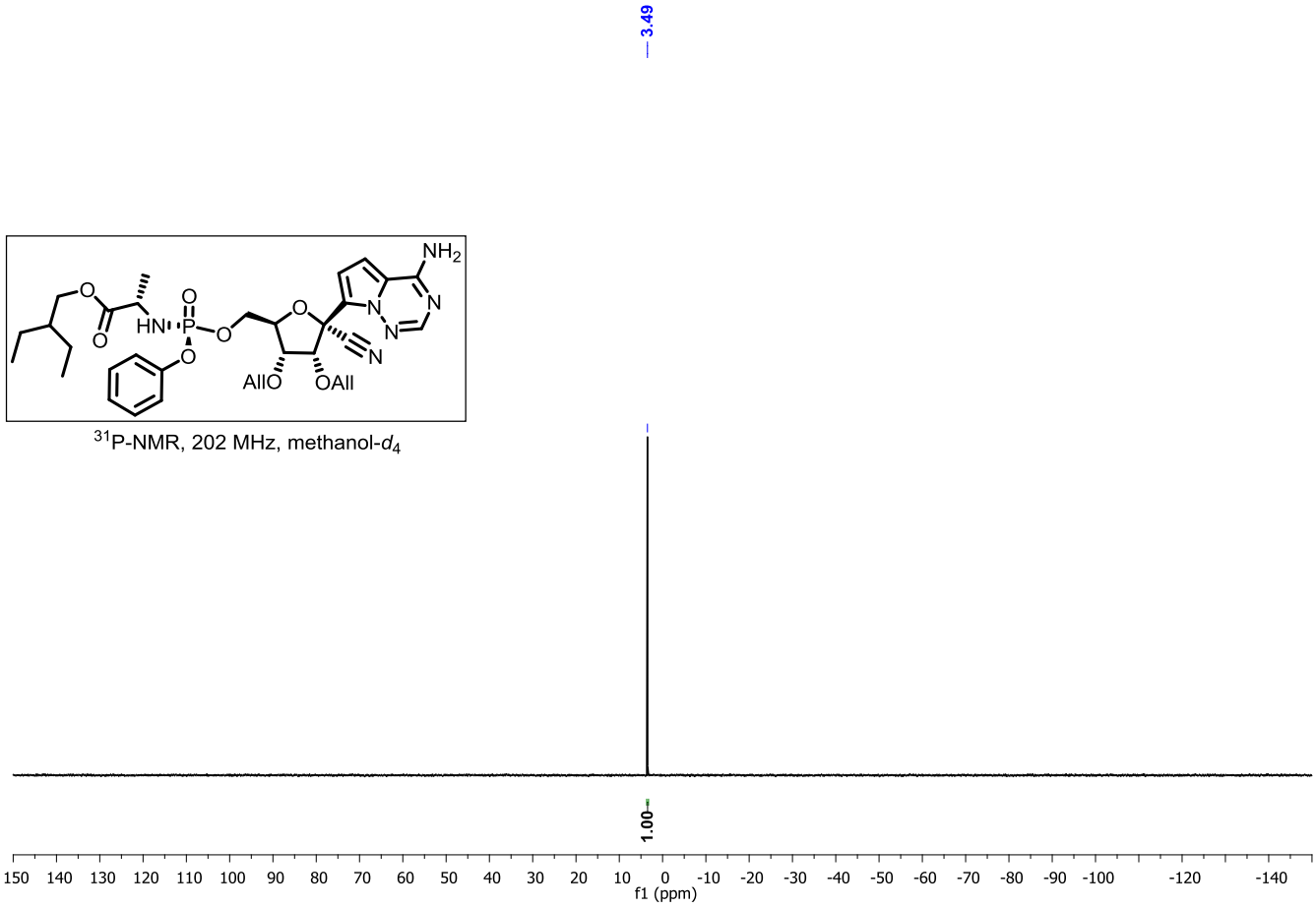


^{1}H-NMR, 500 MHz, methanol-d_4



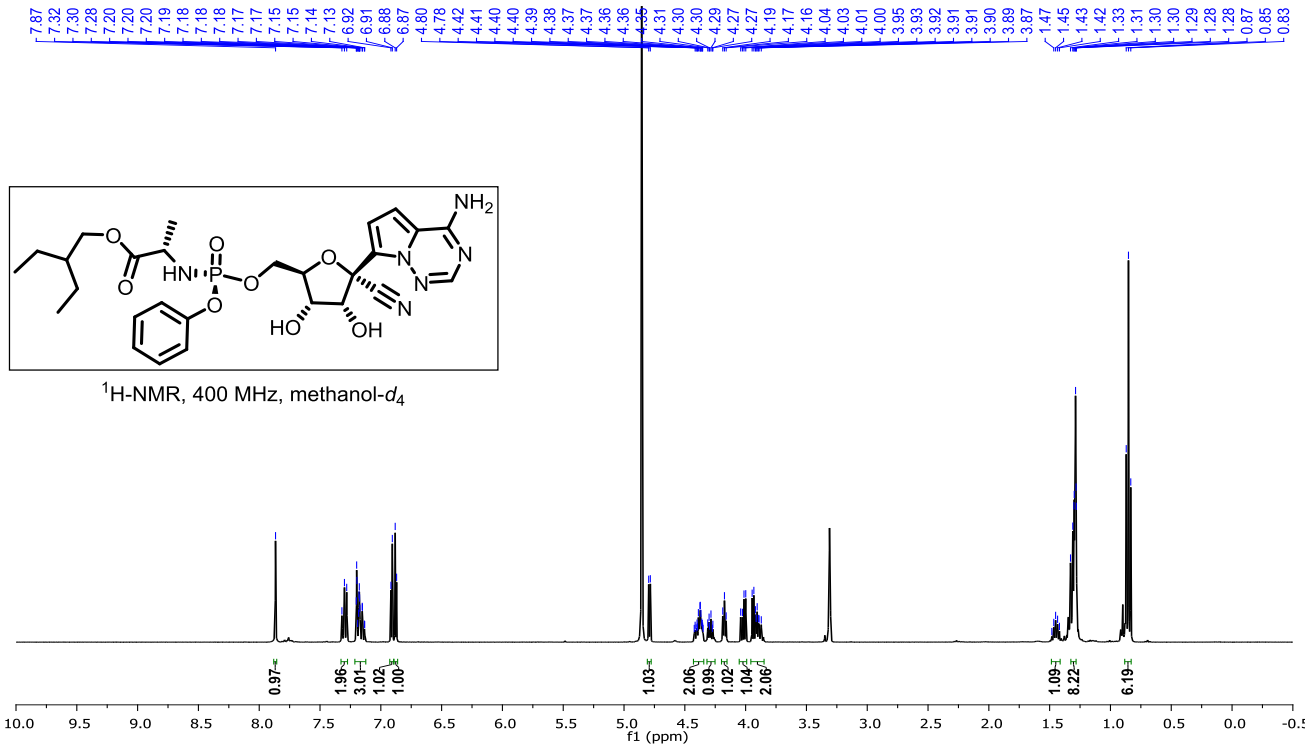
^{13}C-NMR, 101 MHz, methanol-d_4

2-Ethylbutyl ((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-cyano-3,4-*bis*(((*E*)-prop-1-en-1-yl)oxy)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-*L*-alaninate (21):

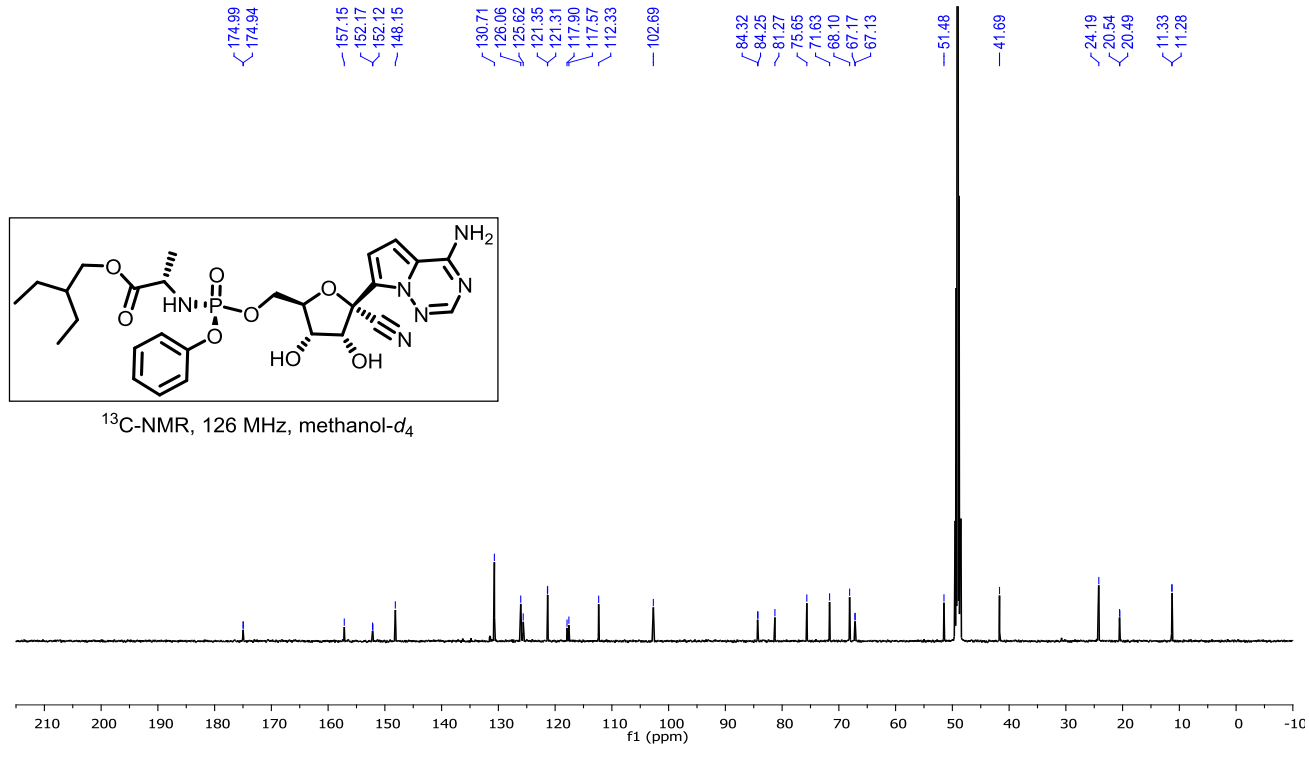


^{31}P-NMR, 202 MHz, methanol-d_4

Remdesivir (1, GS-5734):

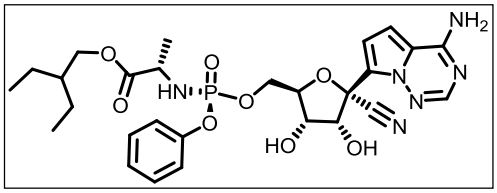


^{1}H-NMR, 400 MHz, methanol-d_4

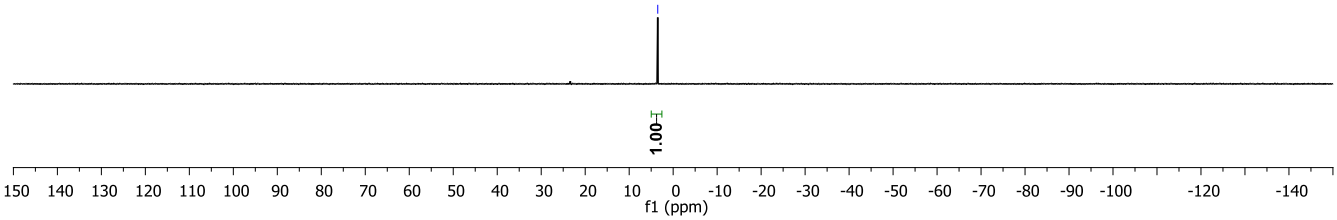


^{13}C-NMR, 126 MHz, methanol-d_4

Remdesivir (1, GS-5734):



^{31}P-NMR, 202 MHz, methanol-d_4



VI. Comparison of ^{1}H and ^{13}C NMR spectral data of Remdesivir (1, GS-5734)

(a) Comparison of ^{1}H and ^{13}C NMR spectral data of Remdesivir (**1**, **GS-5734)** and previously reported lit.data[6]

Table S1:

δ_H (m, J(Hz), xH) (Compound **1**, **GS-5734**) methanol-d_4, 400 MHz	δ_H (m, J(Hz), xH) (Reported lit.) methanol-d_4, 400 MHz	δ_C (xC) (Compound **1**, **GS-5734**) methanol-d_4, 126 MHz	δ_C (xC) (Reported lit.) methanol-d_4, 100 MHz
7.87 (s, 1H)	7.86 (s, 1H)	174.99	174.98
7.33 – 7.26 (m, 2H)	7.33 – 7.26 (m, 2H)	174.94	174.92
7.21 – 7.12 (m, 3H)	7.21 – 7.12 (m, 3H)	157.15	157.18
6.91 (d, *J* = 4.6 Hz, 1H)	6.91 (d, *J* = 4.6 Hz, 1H)	152.17	152.14
6.88 (d, *J* = 4.6 Hz, 1H)	6.87 (d, *J* = 4.6 Hz, 1H)	152.12	152.07
4.79 (d, *J* = 5.4 Hz, 1H)	4.79 (d, *J* = 5.4 Hz, 1H)	148.15	148.27
4.43 – 4.34 (m, 2 H)	4.43 – 4.34 (m, 2 H)	130.71	130.68
4.28 (ddd, *J* = 10.3, 5.9, 4.2 Hz, 1H)	4.28 (ddd, *J* = 10.3, 5.9, 4.2 Hz, 1H)	126.06	126.04
4.17 (t, *J* = 5.6 Hz, 1H)	4.17 (t, *J* = 5.6 Hz, 1H)	125.62	125.51
4.02 (dd, *J* = 10.9, 5.8 Hz 1H)	4.02 (dd, *J* = 10.9, 5.8 Hz 1H)	121.35	121.33
3.96 –3.85 (m, 2H)	3.96 –3.85 (m, 2H)	121.31	121.28
1.49 – 1.41 (m, 1H)	1.49 – 1.41 (m, 1H)	117.90	117.90
1.35 – 1.27 (m, 8H)	1.35 – 1.27 (m, 8H)	117.57	117.58
0.85 (t, *J* = 7.5 Hz, 6H)	0.85 (t, *J* = 7.4 Hz, 6H)	112.33	112.29
		102.69	102.60
		84.32	84.31
		84.25	84.22
		81.27	81.26
		75.65	75.63
		71.63	71.63
		68.10	68.10
		67.17	67.17
		67.13	67.12
		51.48	51.46
		41.69	41.65
		24.19	24.19
		20.54	20.56
		20.49	20.50
		11.33	11.33
		11.28	11.28

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