Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Diastereoselective synthesis of *P*-chirogenic phosphoroamidate prodrugs of nucleoside analogues (ProTides) *via* copper catalysed reaction.

F. Pertusati,[a] and C. McGuigan[a]

[a] School of Pharmacy and Pharmaceutical Sciences
Redwood building, King Edwrds VII avenue, CF10 3AB, Cardiff, Wales, United Kingdom.

General Experimental

All solvents used were anhydrous and used as supplied by Aldrich. All nucleosides and solid reagents were dried for several hours under high vacuum over potassium hydroxide. All glassware was oven-dried at 130 °C for several hours or overnight and allowed to cool in a desiccator or under a stream of dry nitrogen. For analytical thin-layer chromatography (TLC), precoated aluminium-backed plates (60 F-54, 0.2 mm thickness; supplied by E. Merck AG, Darmstadt, Germany) were used and developed by an ascending elution method. After solvent evaporation, compounds were detected by quenching of the fluorescence, at 254 nm upon irradiation with a UV lamp. For column chromatography: Glass columns were slurry-packed in the appropriate eluent or pre-adsorbed onto silica gel. Fractions containing the product were identified by TLC and pooled, and the solvent was removed *in vacuo*.

^{1}H, ^{31}P and ^{13}C NMR spectra were recorded in a Bruker Avance 500 spectrometer at 500 MHz, 202 MHz and 125 MHz, respectively and auto-calibrated to the deuterated solvent reRrence peak in case of ^{1}H and ^{13}C-NMR and 85% H_3PO_4 for ^{31}P-NMR experiments. All ^{31}P and ^{13}C NMR spectra were proton-decoupled. Coupling constants (*J*) are measured in Hertz. The following abbreviations are used in the assignment of NMR signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet).

All analytical high-performance liquid chromatography (HPLC) experiments were done on a Thermo Fisher Scientific Spectra System SCM1000 provided with a System Controller SN4000, a pump Spectra System P4000 and a Spectra UV2000 detector set or a Varian Prostar (LC Workstation-Varian Prostar 335 LC detector) using a C18-Varian Pursuit (150 × 4.6 mm, 5 μM) reverse phase column. Low resolution Mass spectrometry was perfomed on a Bruker Daltonics microTof-LC system (atmospheric pressure ionization, electron spray mass spectroscopy) in positive mode. All final compounds were isolated with purity ≥ 95%..

General Procedure

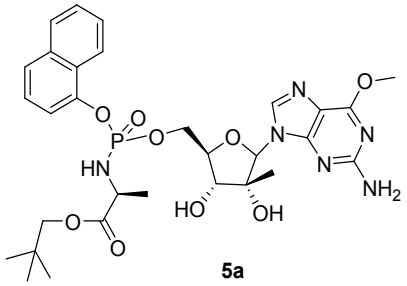
A dry round bottomed flask is charged with a magnetic stirring bar, the appropriate nucleoside (typically 100 mg) and a catalytic amount of the metal salt (0.1 equiv.). The flask is sealed with a rubber septum and purged with dry argon. Anhydrous solvent (10 mL) is added via syringe and the resulting light blue solution is stirred at room temperature for 5-10 minutes. To this solution is then added the base (1.5 equiv.) followed by the dropwise addition of the appropriate phosphorochloridate (1 equiv.) solution (2-3 mL anhydrous solvent) previously prepared in a separate flask under nitrogen, according to literature procedure.[1] The mixture is then stirred at room temperature for 12 hours. When the reaction is completed,

the solvent is evaporated under reduced pressure, and the residue is purified by column chromatography on silica gel with gradient elution CH_2Cl_2/CH_3OH as reported. If trace of base are still present after column chromatography the compound is taken up in dichloromethane and washed with 0.5 M HCl (3 x 10 mL). The organic layer is separated, dried over sodium sulfate, filtered and evaporated to give the title compound as white solid.

The reaction is monitored by HPLC, according to the following protocol:

A 0.1-0.2 mL aliquot of solution is withdraw from the flask, under argon, via syringe and diluted with HPLC grade methanol, filtered and further diluted with a mixture of acetonitrile/ water 10:90. The resulting solution is then injected into HPLC and analyzed (Reverse-phase C-18 column, eluting with a gradient of H_2O/MeCN: From ACN/H_2O 10:90 to ACN/H_2O 40/60 in 15 min. keep this ratio for 15 min. then from ACN/H_2O 40:60 to 100% ACN in 10 min. keep this ratio for 1 min then a re-equilibration period of 3 minutes. Flow = 1 mL/min, λ = 254 nm and λ = 280 nm.

1. M. Serpi, K. Madela, F. Pertusati, and M. Slusarczyk." Synthesis of nucleotide prodrugs using the proTide approach", *Curr. Protoc. Nucleic Acid Chem*. **2013,** 53: 15.5.1-15.5.15.

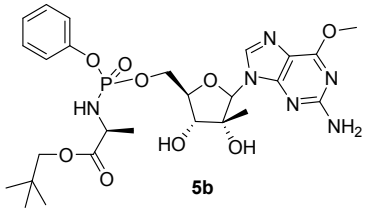


5a

Synthesis of 2-amino-6-methoxy-9-(2'-C-methyl- β -D -ribofuranosyl) purine 5'-O-[α -Naphthyl-(2,2-dimethylpropoxy- L -alaninyl)] phosphate (5a).

Prepared according to the general procedure from 0.200 g of 2-amino-6-methoxy-9-(2'-*C*-methyl- β -*D*-ribofuranosyl) purine **3** and 0.246 g of (2*S*)-2,2-dimethylpropyl-2-(chloro(-[α -Naphthyloxy)phosphorylamino)propanoate **4a**. Purification by column chromatography (eluent system CH_3OH/CH_2Cl_2 2/98 to 5/95) afforded the desired compound **5a** (*R*p/*S*p dr = 12/88) as a white solid (0.161 g, 38% yield). ^{1}H-NMR (500 MHz, CD_3OD) δ_H 8.19–8.15 (m, 1H, Napht), 7.97 (s, 0.12H, H-8, *R isomer*), 7.94 (s, 0.88H, H-8, *Sp isomer*), 7.89–7.84 (m, 1H, Napht), 7.70, (d, *J* = 7.0 Hz, 0.88H, Napht, *S isomer*), 7.67, (d, *J* = 7.0 Hz, 0.12H, Napht, *Rp isomer*), 7.54–7.46 (m, 3H, Napht), 7.39 (t *J* = 8.0 Hz, 0.88H, Napht, *Sp isomer*), 7.38 (t *J* = 8.0 Hz, 0.12, Napht, *Rp isomer*), 5.99, (s, 0.88H, H-1', *Sp isomer*), 5.98 (s, 012H, H-1', *Rp isomer*), 4.65–4.55 (m, 2H, CH_2-5'), 4.36- 4.32 (m, 1H, H-3'), 4.28-4.24 (m, 1H, H-4'), 4.09–4.05 (m, 1H, C*H*CH_3), 4.05 (s, 3H, OCH_3), 3.75, 3.64 (AB, J_{AB} = 10.5 Hz, 0.24H, C*H*$_2$ $C(CH_3)_3$, *Rp isomer*), 3.72, 3.58 (AB, J_{AB} = 10.3Hz, 1.76H, C*H*$_2$ $C(CH_3)_3$, *Sp isomer*), 1.32 (d *J* = 7.0 Hz, 3H, CHC*H*$_3$), 0.97(s, 2.64H, 2'CCH_3 *Sp isomer*), 0.96 (s, 0.36H, 2'CCH_3, *Rp isomer*), 0.85 (s, 7.92H, $C(CH_3)_3$, *Sp isomer*), 0.84 (s, 1.08H, $C(CH_3)_3$, *Rp isomer*). ^{13}C-Pendant-NMR (125 MHz, CD_3OD) δ_C 175.07 (d $^3J_{CP}$ = 5.0 Hz, CO_2, *Rp isomer*), 174.80 (d $^3J_{CP}$ = 5.0 Hz, CO_2 *Sp isomer*), 162.75 (C-6), 161.90 (C-2),154.57 (C4, *Rp* isomer), 154.52 (C-4, *Sp isomer*), 148.02 (d $^2J_{CP}$ = 3.8 Hz, C-*ipso* Napht), 139.39 (CH-8, *Sp isomer*), 139.11 (CH-8, *Sp isomer*), 136.31 (C-Napht, *S p isomer*), 136.28 (C-Napht, *Rp isomer*), 128.85 (CH-Napht, *Sp isomer*), 128.79 (CH-Napht, *Rp isomer*), 127.90 (d $^3J_{CP}$ = 6.3 Hz, C-Napht), 127.75 (CH-Napht, *Sp isomer*), 127. 72 (CH-Napht, *Rp isomer*), 127.47 (CH-Napht), 126.52 (CH-Napht, *Sp isomer*), 126.48 (CH-Napht, *Rp isomer*), 125.96 (CH-Napht), 122.81 (CH-Napht, *Rp isomer*), 122.77 (CH-Napht, *Sp isomer*), 116.23 (d $^3J_{CP}$ = 2.62 Hz, CH-Napht, *Sp isomer*), 116.20 (d $^3J_{CP}$ = 2.62 Hz, CH-Napht, *Rp isomer*), 115.63 (C-5), 93.38 (CH-1'), 93.22 (CH-1'), 82.32 (d $^3J_{CP}$ = 8.8 Hz, CH-4', *S p isomer*), 82.16 (d $^3J_{CP}$ = 8.8 Hz, CH-4', *Rp isomer*), 79.97 (C2', *Sp isomer*), 79.92 (C2', *Rp isomer*), 75.36 ($CH_2C(CH_3)_3$), 74.96 (CH-3', *Sp isomer*), 74.71 (CH-3' *Rp isomer*), 68.12 (d $^2J_{CP}$ = 5.0 Hz, CH_2-5'), 67.63 (d $^2J_{CP}$ = 5.0 Hz, CH_2-5'), 54.22 (OCH_3), 51.72 ($CHCH_3$, *Rp isomer*), 51.70 ($CHCH_3$, *Sp isomer*), 32.24 ($C(CH_3)_3$ *Rp isomer*), 32.21 ($C(CH_3)_3$ *Sp isomer*), 26.69($C(CH_3)_3$, *Rp isomer*), 26.66

(C(CH_3)$_3$, *Sp isomer*), 20.82 (d $^3J_{CP}$ = 6.3 Hz, CHCH_3), 20.62 (d $^3J_{CP}$ = 6.3 Hz, CHCH_3), 20.31 (2'CCH_3, *Rp isomer*), 20.28 (2'CCH_3, *Sp isomer*). ^{31}P-NMR (202 MHz, CD_3OD) δ_P 4.00 (s, 0.85P, *Sp isomer*), 3.85 (s, 0.15P, *Rp isomer*). MS (ES+) *m/z*: Found: 659.25 (M + H^+), 681.25 (M + Na^+). HRMS (ESI) *m/z:* Found: 659.2601 (M + H^+); $C_{30}H_{40}N_6O_9P^+$ required: 659.2594 (M+H^+); HPLC λ= 280; nm F = 1ml/min; t_R = 31.05, 31.75 min.

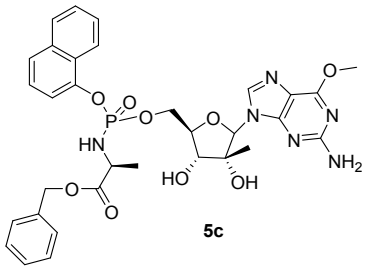


5b

Synthesis of 2-amino-6-methoxy-9-(2'-C-methyl-β-D-ribofuranosyl) purine 5'-O-[phenyl-(2,2-dimethylpropoxy- L-alaninyl)] phosphate (5b).

Prepared according to the general procedure from 0.200g of 2-amino-6-methoxy-9-(2'-*C*-methyl-β-*D*-ribofuranosyl) purine **3** and 0.214g of (2*S*)-2,2-dimethylpropyl-2-(chloro(phenoxy)phosphorylamino)propanoate **5b**. Purification by column chromatography (eluent system CH_3OH/CH_2Cl_2 2/98 to 5/95) afforded the desired compound **5b** (*Rp/Sp* dr = 23/77) as a white solid (0.106g, 27%)**.** ^{1}H-NMR (500 MHz, CD_3OD) δ_H 8.1 (s, 1H, H-8), 7.24-7.21 (m, 2H, Ph), 7.15-7.13 (m, 2H, Ph) 7.04 (1H, m), 5.92 (s, 0.23H, H-1', *Rp isomer*), (s, 0.77H, H-1', *Sp isomer*), 4.49-4.46 (m, 0.23H, CH_{2a}-5'*, Rp isomer*), 4.40-4.38 (m, 1.77H, CH_{2b}-5', *Rp isomer* and CH_2-5' *Sp isomer*), 4.15-4.08 (m, 2H, H-3' and H-4'), 3.96 (s, 3H, OCH_3), 3.90-3.87 (m, 1H, C*H*CH_3), 3.71, 3.63 (AB, J_{AB} = 10.5Hz, 0.46H, CH_2, *Rp isomer*), 3.71, 3.63 (AB, J_{AB} = 10.5Hz, 1.54H, CH_2, *Sp isomer*), 1.23 (d *J* = 7.0 Hz, 3H, CH_3), 0.87(s, 2.31H, 2'CCH_3, *Sp isomer*), 0.85 (s, 0.69H, 2'CCH_3, *Rp isomer*), 0.80 (s, 2.07H, 3 C(CH_3)$_3$), 0.76 (s, 6.93H, 3 C(CH_3)$_3$). ^{13} C-Pendant-NMR (125 MHz, CD_3OD) δ_C 175.13 (d $^3J_{CP}$ = 5.0 Hz, CO_2, *Rp isomer*), 174.83 (d $^3J_{CP}$ = 5.0 Hz, CO_2, *S p isomer*), 162.52 (C-6), 162.13 (C-2, *Rp isomer*), 162.09 (C-2, *S p isomer*), 154.57 (C-4, *Rp isomer*), 154.52 (C-4, *Sp isomer*), 152.18 (d $^2J_{CP}$ = 5.9 Hz, *C-ipso* Ph), 139.39 (CH-8, *Sp isomer*), 139.11 (CH-8, *Sp isomer*), 130.70 (CH-Ph, *Rp isomer*), 130.82 (CH-Ph, *Sp isomer*), 126.17 (CH-Ph), 121.48 (d $^3J_{CP}$= 5.4 Hz, CH-Ph), 115.63 (C-5), 93.33 (CH-1', *Sp isomer*), 93.24 (CH-1', *Rp isomer*), 82.30 (d $^3J_{CP}$ = 9.0 Hz, CH-4', *Sp isomer*), 82.17 (d $^3J_{CP}$ = 9.0 Hz, CH-4', *Rp isomer*), 80.02 (C-2', *Rp isomer*), 79.94 (C-2', *Sp isomer*), 74.44 (*C*H_2C(CH_3)$_3$, *Rp isomer*), 74.40(*C*H_2C(CH_3)$_3$, *Sp isomer*), 74.68 (CH-3' *Sp isomer*), 74.23 (CH-3' *Rp isomer*), 67.64 (d $^2J_{CP}$ = 5.4 Hz, CH_2-5', *Sp isomer*), 66.83 (d $^2J_{CP}$ = 5.4 Hz, CH_2-5', *Rp isomer*), 54.45 (OCH_3), 51.76 (*C*HCH_3, *Rp isomer*), 51.71 (*C*HCH_3, *S p isomer*), 32.31 (*C*(CH_3)$_3$ *R p isomer*), 32.24 (*C*(CH_3)$_3$ *Sp isomer*), 26.73 (C(*C*H_3)$_3$, *Rp isomer*), 26.69

(C(CH_3)$_3$, *Sp isomer*), 20.78 (d $^3J_{CP}$ = 6.3 Hz, CHCH_3 *Sp isomer*), 20.55(d $^3J_{CP}$ = 6.3 Hz, CHCH_3 *Rp isomer*), 20.25 (2'CCH_3). ^{31}P NMR (202 MHz, CD_3OD) δ_P 4.00 (s, 0.23P, *Rp isomer*), 3.86 (s, 0.77P, *Sp isomer*). MS (ES+) *m/z*: Found: 609.58 (M + H^+), 631.58 (M + Na^+). HRMS (ESI) *m/z*: Found: 609.2455 (M + H^+); Melting point (120-123 ^oC), $C_{26}H_{38}N_6O_9P^+$ required: 609.2438 (M+H^+); HPLC: λ= 280; nm F = 1ml/min; t_R = 21.80, 22.15min.

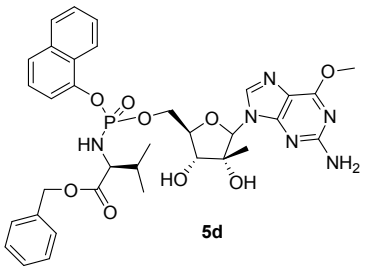


5c

Synthesis of 2-amino-6-methoxy-9-(2'-C-methyl-β-D-ribofuranosyl) purine 5'-O-[α-Naphthyl-(benzyloxy- L-alaninyl)] phosphate (5c).

Prepared according to general procedure from 0.200 g of 2-amino-6-methoxy-9-(2'-*C*-methyl- β -*D*-ribofuranosyl) purine **3** and 0.259g of (2*S*)-benzyl-2-(chloro(phenoxy)phosphorylamino)propanoate **5c**. Purification by column chromatography (eluent system CH_3OH/CH_2Cl_2 2/98 to 5/95) afforded the desired compound **5c** (R/S dr = 16/84) as a white solid (0.287 g, 66%). ^{1}H-NMR (500 MHz, CD_3OD) δ_H 8.04 (d *J* = 8.5Hz, 0.77H, Napht, *Sp isomer*), 8.02 (d *J* = 8.5Hz, 0.23H, Napht, *Rp isomer*), 7.82 (s, 0.84H, H-8, *S p isomer*), 7.78 (s, 0.16H, H-8, *Rp isomer*), 7.75 (d *J* = 8.5 Hz, 0.84 Napht, *Sp isomer*), 7.73 (d *J* = 8.5 Hz, 0.16H, Napht, *Rp isomer*), 7.56 (d, *J* = 8.5 Hz, 0.84H, Napht, *Sp isomer*), 7.54 (d, *J* = 8.5 Hz, 0.16H, Napht, *Rp isomer*), 7.41–7.32 (m, 3H, Napht), 7.24 (t *J* = 8.0 Hz, 0.84H, Napht), 7.23 (t *J* = 8.0 Hz, 0.16H, Napht), 7.17-7.10 (m, 5H, CH_2*Ph*), 5.86 (s, 0.16H, H-1'), 5.85 (s, 0.84H, H-1'), 4.91-4.83 (m, 2H, C*H*$_2$Ph), 4.46-4.44 (m, 2H, CH_2-5'), 4.22-4.20 (m, 1H, H-3'), 4.13-4.09 (m, 1H, H4'), 3.97-3.93 (m, 1H, C*H*CH_3), 3.91(s, 0.48H, OCH_3), 3.90(s, 2.52H, OCH_3), 1.17 (d *J* = 7.0 Hz, 3H, CHC*H*$_3$), 0.85 (s, 2.52H, 2'CCH_3), 0.82 (s, 0.48H, 2'CCH_3). ^{13} C-Pendant-NMR (125 MHz, CD_3OD) δ_C 174.81 (d $^3J_{CP}$ = 5.0 Hz, CO_2, *R p isomer*), 174.57 (d $^3J_{CP}$ = 5.0 Hz, CO_2, *Sp isomer*), 162.74 (C-6), 162.92 (C-2, *Sp isomer*), 162.62 (C-2, *Rp isomer*), 148.97 (d $^2J_{CP}$ = 6.4 Hz, C-*ipso* Napht), 139.36 (CH-8), 137.14 (*C-ipso* CH_2Ph), 136.29, (C-Napht, *Sp isomer*), 136.27 (C-Napht, *Rp isomer*), 129.50, 129.21, 129.17, 129.11, 128.83, 128.78 (CH-Ar), 127.88 (d $^3J_{CP}$ = 6.3 Hz, C-Napht), 127.74, 127.48, 126.51, 126.48, 125.95, 122.82, 122.75 (CH-Ar), 116.23 (d $^3J_{CP}$ = 2.62 Hz, CH-2-Napht,), 116.20 (d $^3J_{CP}$ = 2.62 Hz, CH-Napht, *Rp isomer*), 115.63 (C-5), 93.40 (CH-1', *Sp isomer*), 93.20 (CH-1', *Rp isomer*), 82.20 (d $^3J_{CP}$ = 8.1 Hz, CH-4', *Sp isomer*), 82.12 (d $^3J_{CP}$ = 8.1 Hz, CH-4', *Rp isomer*), 79.95 (C2', *Rp isomer*), 79.90 (C2', *Sp*

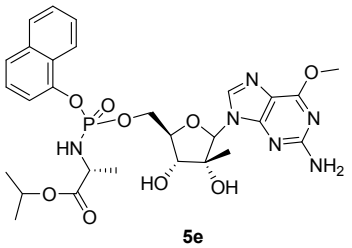
isomer), 75.19 (CH-3' *Sp isomer*), 74.56 (CH-3' *Rp isomer*), 68.00 (d $^{2}J_{CP}$ = 5.4 Hz, CH_2-5', *Sp isomer*), 67.90 (*C*H_2Ph), 67.87 (*C*H_2Ph), 67.43 (d $^{2}J_{CP}$ = 5.4 Hz, CH_2-5', *Rp isomer*), 54.20 (OCH_3), 51.81 (*C*HCH_3, *Rp isomer*), 51.72 (*C*HCH_3, *Sp isomer*), 20.49 (d $^{3}J_{CP}$ = 6.25 Hz, CH*C*H$_3$), 20.32 (2'C*C*H$_3$, *Rp isomer*), 20.26 (2'C*C*H$_3$, *Sp isomer*). ^{31}P NMR (202 MHz, CD_3OD) δ_P 4.32 (s, 0.18P, *Rp isomer*), 4.25 (s, 0.84P, *Sp isomer*). MS (ES+) *m/z*: Found: 679.22 (M + H^+), 701.22 (M + Na^+). HRMS (ESI) *m/z*: Found: 679.2310 (M + H^+); $C_{32}H_{36}N_6O_9P^+$ required: 679.2281 (M+H^+); HPLC: λ= 280; nm F = 1ml/min; t_R = 26.41, 26.85min.



5d

Synthesis of 2-amino-6-methoxy-9-(2'-C-methyl-β-D-ribofuranosyl) purine -5'-O-[α -Naphthyl-(benzyloxy- *L*-valininyl)] phosphate (5d).

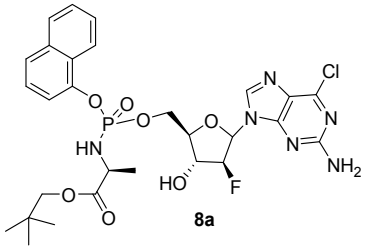
Prepared according to general procedure from 0.200 g of 2-amino-6-methoxy-9-(2'-C-methyl-β-D-ribofuranosyl) purine and 0.277g of (2*S*)-benzyl 2-(chloro(napthyloxy)phosphorylamino)-3-methylbutanoate **4d**. Purification by column chromatography (eluent system CH_3OH/CH_2Cl_2 2/98 to 5/95) afforded the desired compound **5d** (*Rp/Sp* dr = 15/85) as a white solid (0.158 g, 35%). ^{1}H-NMR (500 MHz, CD_3OD) δ_H 8.39 (s, 1H, H-8), 8.17 (d *J* = 8.5Hz, 0.85H, Napht, *Sp isomer*), 8.14 (d *J* = 8.5Hz, 0.15H, Napht, *Rp isomer*), 7.88 (d *J* = 8.5 Hz, 0.85 Napht, *Sp isomer*), 7.82 (d *J* = 8.5 Hz, 0.15H, Napht, *Rp isomer*), 7.68 (d *J* = 8.5 Hz, 0.85H, Napht, *Sp isomer*), 7.65 (d, *J* = 8.5 Hz, 0.15H, Napht, *Sp isomer*), 7.54–7.43 (m, 3H, Napht), 7.37 (t *J* = 8.0 Hz, 0.85H, Napht, *Sp isomer*), 7.35 (t *J* = 8.0 Hz, 0.15H, Napht, *Rp isomer*), 7.28-7.24 (m, 5H, CH_2*Ph*), 6.01 (s, 0.15H, H-1', *Rp isomer*), 5.98 (s, 0.85H, H-1', *Sp isomer*), 5.07-4.96 (m, 2H, C*H*$_2$Ph), 4.64-4.55 (m, 2H, CH_2-5'), 4.32-4.30 (m, 1H, H-3'), 4.28-4.24 (m, 1H, H-4'), 4.08 (s, 0.45H, OCH_3, *Rp isomer*), 4.07 (s, 2.65H, OCH_3, *Sp isomer*), 3.81 (dd *J* = 6.0, 9.5 Hz, 0.15H, C*H*NH, *Rp isomer*), 3.77 (dd *J* = 6.0, 9.5 Hz, 0.85H, C*H*NH, *Sp isomer*), 2.06-1.93 (m, 1H, C*H*$(CH_3)_2$), 0.99 (s, 2.55H, 2'CCH_3, *Sp isomer*), 0.98 (s, 0.45H, 2'CCH_3, *Rp isomer*), 0.83-0.79 (m, 6H, CH(C*H*$_3)_2$). ^{31}P-NMR (202 MHz, CD_3OD) δ_P 5.22 (s, 0.15P, *Rp isomer*), 5.09 (s, 0.85P, *Rp isomer*). MS (ES+) *m/z*: Found: 707.25 (M + H^+), 729.25 (M + Na^+). HRMS (ESI) *m/z*: Found: 707.2423 (M + H^+); $C_{34}H_{40}N_6O_9P^+$ required: 707.2516 (M+H^+); HPLC: λ= 280; nm F = 1ml/min; t_R =36.46, 36.95 min.



5e

Synthesis of 2-amino-6-methoxy-9-(2'-*C*-methyl-β-D-ribofuranosyl) purine 5'-O-[α-naphthyl-(isopropoxy-*L*-alanyl)] phosphate (5e).

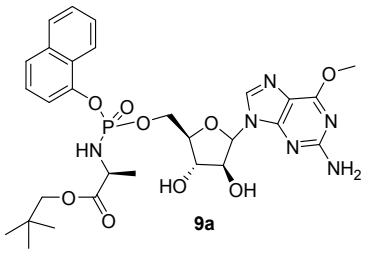
Prepared according to general procedure from 0.200 mg of 2-amino-6-methoxy-9-(2'-C-methyl-β-D-ribofuranosyl) purine **3** and 0.228g of (2*S*)-*iso*propyl-2-(chloro(napthyloxy)phosphorylamino)propanoate **4e**. Purification by column chromatography (eluent system CH_3OH/CH_2Cl_2 2/98 to 5/95) afforded the desired compound **5e** (*Rp/Sp* 18/82) as a white solid (0.048 mg, 12%). ^{1}H-NMR (500 MHz, CD_3OD) δ_H 8.19–8.15 (m, 2H, Napht and H-8), 7.77–7.72 (m, 1H, Napht), 7.58, (d *J* = 7.0 Hz, 0.82H, Napht, *Sp isomer*), 7.67 (d *J* = 7.0 Hz, 0.18H, Napht, *Rp isomer*), 7.42–7.34 (m, 3H, Napht) 7.27 (t *J* = 8.0 Hz, 0.88H, Napht, *Sp isomer*), 7.26 (t *J* = 8.0 Hz, 0.12H, Napht, *Rp isomer*), 5.90, (s, 1H, H-1'), 4.70 (m, C*H*$(CH_3)_2$ overlap with the solvent), 4.53–4.43 (m, 2H, CH_2-5'), 4.24- 4.22 (m, 1H, H-3'), 4.15-4.11 (m, 1H, H-4'), 3.95 (s, 3H, OCH_3), 3.88–3.82 (m, 1H, C*H*CH_3), 1.17 (d *J* = 7.0 Hz, 3H, CHC*H*$_3$), 1.02 (d *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 1.01 (d *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 0.86 (s, 2.46H, 2'CCH_3,), 0.83 (s, 0.54H, 2'CCH_3). ^{13}C-Pendant-NMR (125 MHz, CD_3OD) δ_C 174.35 (d $^3J_{CP}$ = 5.0 Hz, CO_2), 162.05 (C-6), 161.90 (C-2),154.00 (C-4), 148.02 (d $^2J_{CP}$ = 3.8 Hz, C-*ipso* Napht), 139.39 (CH-8, *Sp isomer*), 139.11 (CH-8, *Sp isomer*), 136.31 (C-Napht, *Sp isomer*), 136.26 (C-Napht, *Rp isomer*), 128.83 (CH-Napht, *Sp isomer*), 128.78 (CH-Napht, *Rp isomer*), 127.92 (d $^3J_{CP}$ = 6.3 Hz, C-Napht), 127.74, 127.45 (CH-Napht), 126.51 (CH-Napht, *Sp isomer*), 126.47 (CH-Napht, *Rp isomer*), 125.94 (CH-Napht), 122.81 (CH-Napht, *Rp isomer*), 122.77 (CH-Napht, *Sp isomer*), 116.22 (d $^3J_{CP}$ = 2.75 Hz, CH-Napht), 115.63 (C-5), 93.71 (CH-1'), 82.31 (d $^3J_{CP}$ = 8.8 Hz, CH-4', *S p isomer*), 82.17 (d $^3J_{CP}$ = 8.8 Hz, CH-4', *R p isomer*), 79.87 (C-2'), 74.91 (CH-3', *Sp isomer*), 74.65 (CH-3', *Rp isomer*), 70.17 (*C*H$(CH_3)_2$, *R p isomer*), 70.14 (*C*H$(CH_3)_2$, *Sp isomer*), 67.97 (d $^2J_{CP}$ = 5.0 Hz, CH_2-5', *Sp isomer*), 67.53 (d $^2J_{CP}$ = 5.0 Hz, CH_2-5', *Rp isomer*), 54.23 (OCH_3), 51.86 (*C*HCH_3, *Rp isomer*), 51.78 (*C*HCH_3, *Sp isomer*), 21.88 (CH(*C*H$_3$)$_2$), 21.80 (CH(*C*H$_3$)$_2$) 20.60 (d $^3J_{CP}$ = 6.3 Hz, CH*C*H$_3$, *Sp isomer*), 20.37 (d $^3J_{CP}$ = 6.3 Hz, CH*C*H$_3$, *Rp isomer*), 20.24 (2'C*C*H$_3$). ^{31}P-NMR (202 MHz, CD_3OD) δ_P 4.37 (s, 1P). MS (ES+) *m/z*: Found: 631.22 (M + H^+), 653.22 (M + Na^+). HRMS (ESI) *m/z*: Found: 631.2312 (M + H^+); $C_{28}H_{36}N_6O_9P^+$ required: 631.2281 (M+H^+); HPLC: λ= 280 nm F = 1ml/min; t_R = 20.72, 21.43 min.



8a

Synthesis of 2-amino-6-chloro-9-(2'-fluoro-2'deoxy-β-D-arabinofuranosyl) purine 5'-O-[α-naphthyl-(isopropoxy-*L*-alanyl)] phosphate (8a).

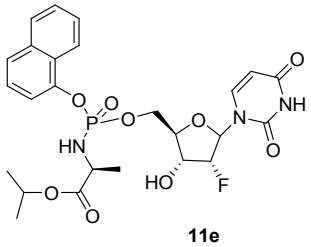
Prepared according to general procedure from 0.150 g of 2-amino-6-chloro-9-(2'-fluoro-2'-deoxy- β -*D*-arabinofuranosyl) purine **6** and 0.189 g of (2*S*)-neopentyl 2-(chloro(naphthalen-1-yloxy)phosphorylamino)propanoate **4a**. Purification by column chromatography (eluent system CH_3OH/CH_2Cl_2 2/98 to 5/95) afforded the desired compound **8a** as a white solid (0.085 g, 26%). ^{1}H-NMR (500 MHz, CD_3OD): δ_H 8.19-8.12 (m, 2H, Napht and H8), 7.89-7.84 (m, 1 H, Napht), 7.71 (d J = 8.5 Hz, 0.6 H, Napht), 7.68 (d J = 8.5 Hz, 0.4 H, Napht), 7.55-7.49 (m, 3H, Napht), 7.41 (t J =8.0 Hz, 0.6H, Napht), 7.38 (t J = 8.0 Hz, 0.4H, Napht), 6.43 (dd J = 4.5 Hz, J_{HF} = 17.5 Hz, 0.6H, H-1'), 6.40 (dd J = 4.5 Hz, J_{HF} = 17.5 Hz, 0.4H, H-1'), 5.20-5.19 (m, 0.6H, H-2'), 5.10-5.08 (m, 0.4H, H-2',), 4.59-4.58 (m, 0.4H, H-3'), 4.55-4.53 (m, 0.6H, H-3'), 4.50 (dd J = 5.0, 6.5 Hz, 0.8H , H-5'), 4.46 (dd J = 5.0, 6.5 Hz, 1.2H, H-5'), 4.24-4.18 (m, 1H, H-4'), 4.10-4.05 (m, 1H, C*H*CH_3), 3.79, 3.71, 3.78, 3.70 (2AB, 2H, J_{AB} = 10.5 Hz, 2x OC*H*$_2$C$(CH_3)_3$), 1.37-1.34 (m, 3H, CHC*H*$_3$),), 0.90 (s, 3.6H, C(C*H*$_3)_3$), 0.89 (s, 5.4H, C(C*H*$_3)_3$); ^{13}C-Pendant-NMR (125 MHz, CD_3OD): δ_C 174.63 (d J_{C-P} = 4.37 Hz, CO_2), 158.12 (C-6), 155.64 (C-2), 151.65 (C-4), 148.02 (d J_{CP}= 8.62 Hz, C-*ipso* Napht), 141.88 (d J_{CF} = 5.0 Hz, CH-8), 141.78 (d J_{CF} = 5.0 Hz, CH-8), 136.28, 136.32 (*C* Napht), 128.88, 128.82, 127.78, 127.72, 127.49, 127.40, 126.50, 126.47, 126.02, 125.97 (*CH*-Napht), 122.77, 122.67, 118.60 (C-5), 116.29 (d J_{CP} = 3.5 Hz, *CH*-Napht), 116.22 (d J_{CP} = 3.5 Hz, *CH*-Napht), 96.46 (d J_{CF} = 191.75 Hz, CH-2'), 84.38 (d J_{CF} = 16.87 Hz, CH-1'), 84.37 (d J_{CF} = 16.37 Hz, CH-1'), 83.72 (dd J_{C-P} = 3.5 Hz, J_{CF} = 7.5 Hz, CH-4'), 83.69 (dd, J_{CF} = 3. 5 Hz, J_{CP} = 7.5 Hz, CH-4'), 75.40 (OC*H*$_2$C$(CH_3)_3$), 75.43 (OC*H*$_2$C$(CH_3)_3$), 75.23 (d $^2J_{CF}$ = 25.12 Hz, CH-3'), 75.17 (d J_{CF} = 24.87 Hz, CH-3'), 67.32 (dd J_{CP} = 5.4 Hz J_{CF} = 1.25 Hz, CH_2-5'), 67.18 (dd J_{CP} = 5.4 Hz J_{CF} = 1.25 Hz, CH_2-5'), 51.84(*C*HCH$_3$), 51.76 (*C*HCH$_3$), 32.29 (*C*$(CH_3)_3$), 26.72 (C(*C*H$_3)_3$), 20.70 (d J_{CP} = 7.75 CH*C*H$_3$), 20.57 (d, J_{CP} = 7.75 Hz, CH*C*H$_3$); ^{31}P NMR (202 MHz, CD_3OD): δ_P 4.13 (s); ^{19}F-NMR (470 MHz, CD_3OD): δ_F -198.81 (s, 0.6F), -198.88 (s, 0.4F); MS (ES-) *m/z*: Found: 685, 687 (M + Cl^-); HRMS (ESI) *m/z* Found: 651.1908 (M + H^+); $C_{28}H_{34}ClFN_6O_7P$+ required: 651.1899 (M+H^+). HPLC: λ = 280 nm, F = 1ml/min, t_R 35.34, 35.73 min.



9a

Synthesis of 2-amino-6- methoxy-9-(β-D-arabinofuranosyl) purine 5'-O-[α-naphthyl-(isopropoxy-*L*-alanyl)] phosphate (9a).

Prepared according to general procedure from 0.200 g of 2-amino-6-methoxy-9-(arabinofuranosyl) purine **7** and 0.258 mg of (2*S*)-benzyl 2-(chloro(phenoxy)phosphorylamino)propanoate **4a**. Purification by column chromatography (eluent system CH_3OH/CH_2Cl_2 2/98 to 5/95) afforded the desired compound **9a** as a white solid (0.235 g, 70%). ^{1}H-NMR (500 MHz, CD_3OD): δ_H 8.02 (s, 1 H, H-8), 8.17-8.15 (m, 1H, Napht), 7.85-7.83 (m, 1H, Napht), 7.66 (d *J* = 7.5Hz, 1H, Napht),7.50-7.48 (m, 3H, Napht), 7.42-7.43 (m, 1H, Napht), 6.48 (s, 1H, H-1'), 4.57-4.48 (m, 2H, H-5'), 4.32-4.28(m, 2H, H-2' and H-3'), 4.20-4.17 (m, 1H, H-4'), 4.11-4.02 (m, 4H, OCH_3 and C*H*CH_3), 3.78, 3.69 (AB, 2H, *J* = 10.5 Hz, C*H*$_2$C$(CH_3)_3$), 1.31 (d *J* = 7.0 Hz, 3H, CHC*H*$_3$); ^{13}C-Pendant-NMR (125 MHz, CD_3OD): δ_C 175.10 (d J_{CP} = 4.7.5 Hz, CO_2), 174.71 (d J_{CP} = 4.7.5 Hz, CO_2), 162.1 (C-6), 156.38 (C-2), 146.70 (C-4), 130.85 (d J_{CF} = 5.0 Hz, CH-8), 148.99 (d J_{CP}= 8.62 Hz, C-*ipso* Napht), 136.26 (*C* Napht), 128.80 (*CH*-Napht), 127. 90 (d J_{CP} = 6.3 Hz, C-Napht), 127.71, 127.43, 126.49, 125.93 122.81 (*CH*-Napht), 118.60 (C-5), 116.29 (d J_{CP} = 3.5 Hz, *CH*-Napht), 86.21 (C1'), 83.99 (d *J* =7.2Hz, C4'), 77.55, (CH-2'), 76.97 (CH-3'), 75.37 (*C*H$_2$C$(CH_3)_3$), 67.80 (d J_{CP}= 5.5 Hz, C-5'), 54.36 (OCH_3), 51.80 (*C*HCH_3), 32.27 (*C*$(CH_3)_3$), 26.69 (C(*C*$H_3)_3$), 20.58 (d J_{CP} = 7.75 Hz, CH*C*H_3); ^{31}P-NMR (202 MHz, CD_3OD): δ_P 4.16 (s, 1P); MS (ES+) *m/z:* Found: 645.35 (M + H^+), 668.35 (M + Na^+). HRMS (ESI) *m/z*: Found: 645.2452 (M + H^+); $C_{29}H_{38}N_6O_9P^+$ required: 645.2438 (M+H^+); HPLC: λ = 280 nm, F = 1ml/min, t_R 26.78, 27.77 min.



11e

2'-deoxy 2'-fluoro-β–D-ribofuranosyl uridine 5'-O-[phenyl-(isopropoxy-L-alaninyl)] phosphate (11e)

Prepared according to general procedure from 0.200 g of 2'-deoxy-2'-fluoro-β–D-ribofuranosyl uridine **10** and 0.289 g of (2*S*)-isopropyl 2-(chloro(Naphtyloxy) phosphorylamino) propanoate **4a**. Purification by column chromatography (eluent system CH_3OH/CH_2Cl_2 2/98 to 5/95) afforded the desired compound **11e** as a white solid (0.120 g, 28%). ^{1}H-NMR (500 MHz, CD_3OD): δ_H 8.21-8.19 (m, 1H, Napht), 7.92-7.91 (m, 1H, Napht), 7.74 (d *J* =8.0 Hz, 0.77H, H-6), 7.73 (d *J* =8.0 Hz,0.33H H-6), 7.60-7.52 (m, 3H, Napht), 7.47-7.44 (m, 2H, Napht), 5.94 (dd *J* = 2.5 Hz, J_{HF} = 19.0 Hz, 0.33H, H-1'), 5.92 (dd *J* = 2.5 Hz, J_{HF} = 19.0 Hz, 0.77H, H-1'), 5.53 (d *J*=8.0Hz, 0.33H, H-5), 5.53 (d *J*= 8.0Hz, 0.77H, H-5) 5.03-4.90 (m, 2H, H-2'and C*H*$(CH_3)_2$), 4.59-4.58 (m, 0.33H, H-3'), 4.56-4.52 (m, 0.77H, H-3'), 4.36-4.42 (m, 2H H-5'), 4.20-4.18 (m, 1H, H-4'), 4.03-3.97 (m, 1H, C*H*CH_3), 1.35 (d *J* = 7.5Hz, 1.5H, CHC*H*$_3$), 1.32 (d *J* = 7.5Hz, 1.5H, CHC*H*$_3$), 1.22-1.19 (m 12H, CH(C*H*$_3)_2$); ^{13}C-Pendant-NMR (125 MHz, CD_3OD): δ_C 173.28 (d J_{CP} = 4.5 Hz, CO_2), 172.97 (d J_{CP} = 5.4 Hz, CO_2), 164.59, 164.57 (C-4). 150.44 (C-2), 150.40 (C-2), 146.58 (d J_{CP}= 7.25 Hz, C-*ipso* Napht), 146.58 (d J_{CP}= 6.25 Hz, C-*ipso* Napht), 141.07, 141.00 (C-6), 134.95 (*C* Napht), 127.61, 127.58, 126.52 (*CH*-Napht), 126. 39 (d J_{CP} = 6.3 Hz, C-Napht), 126.22, 125.22, 125.20, 125.19, 124.73, 124.78, 121.33, 121.24 (*CH*-Napht), 114.87 (d J_{CP} = 3.6 Hz, *CH*-Napht), 114.73 (d J_{CP} = 3.6 Hz, *CH*-Napht), 101.65 101.56 (C-5), 92.22 (d J_{CF}= 186.0 Hz, C2'), 89.31 (d J_{CF}= 35.25 Hz, C1'), 89.10 (d J_{CF}= 35.25 Hz, C1'), 81.05 (d J_{CF}= 8.13 Hz, C4'), 81.02 (d J_{CF}= 8.13 Hz, C4'), 68.30 (d J_{CF}= 19.92 Hz, C3'), 68.14 (d J_{CF}= 17.13 Hz, C3'), 68.85 (C*H*$(CH_3)_2$), 68.82 (C*H*$(CH_3)_2$), 65.30 (d J_{CP}= 5.4 Hz, C-5'), 64.90 (d J_{CP}= 5.4 Hz, C-5'), 50.50 (d J_{CP} = 1.9 Hz *C*HCH_3), 50.42 (d J_{CP} = 1.9 Hz *C*HCH_3), 20.67, 20.49 (CH(*C*H$_3)_2$),19.29 (d J_{CP} = 6.4 Hz, CH*C*H$_3$), 19.00 (d J_{CP} = 8.1 Hz, CH*C*H$_3$); ^{31}P-NMR (202 MHz, CD_3OD): δ_P 4.28 (s, 0.77P), 4.29 (s, 0.33P); ^{19}F-NMR (470 MHz, CD_3OD): δ_F -203.39 (s, 0.77F), -203.83 (s, 0.33F); MS (ES+) *m/z*: Found: 566.16 (M + H^+), 589.16 (M + Na^+). HRMS (ESI) *m/z* 566.1615 (M + H^+); $C_{25}H_{30}FN_3O_9P$+ required: 566.1625 (M+H^+); HPLC: λ = 280 nm, F = 1ml/min, t_R 23.17, 23.93 min.

Separation of the two diastereoisomer of **11e** was achieved by semi-preparative HPLC (Reverse-phase C-18 column, Varian Pursuit 150 × 21.2 mm, 5 μM) eluting with a gradient of H_2O/MeOH: From /H_2O/MeOH 90:10 to H_2O/MeOH 0/100 in 40 min. Flow = 20 mL/min, λ = 254 nm and λ = 280 nm; Melting point (102-104 °C).

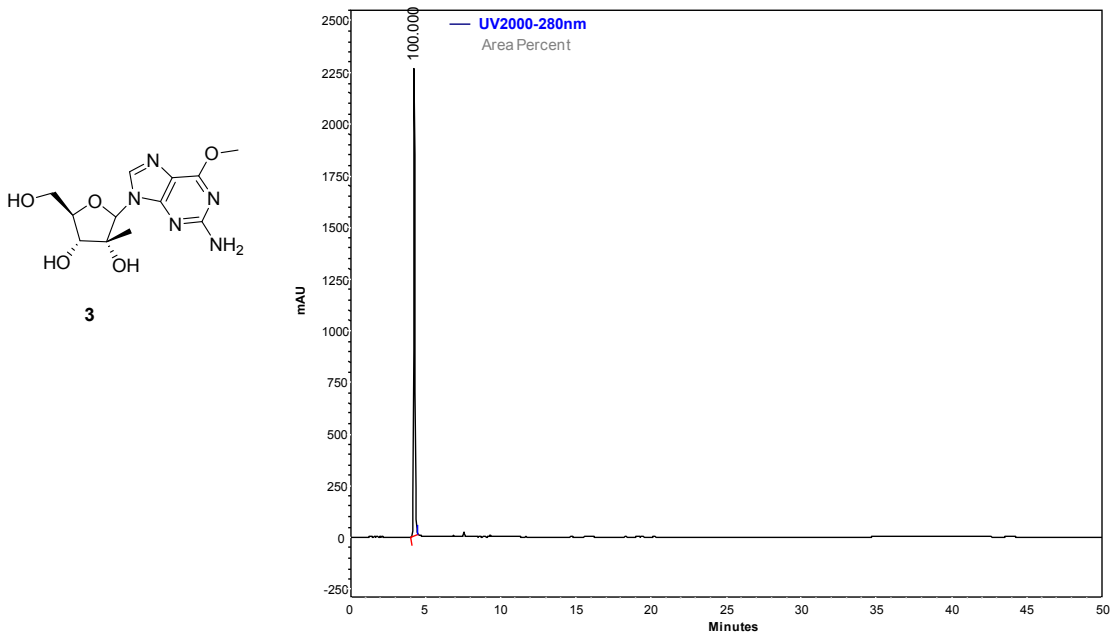


Fig.1. HPLC trace of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine **3**

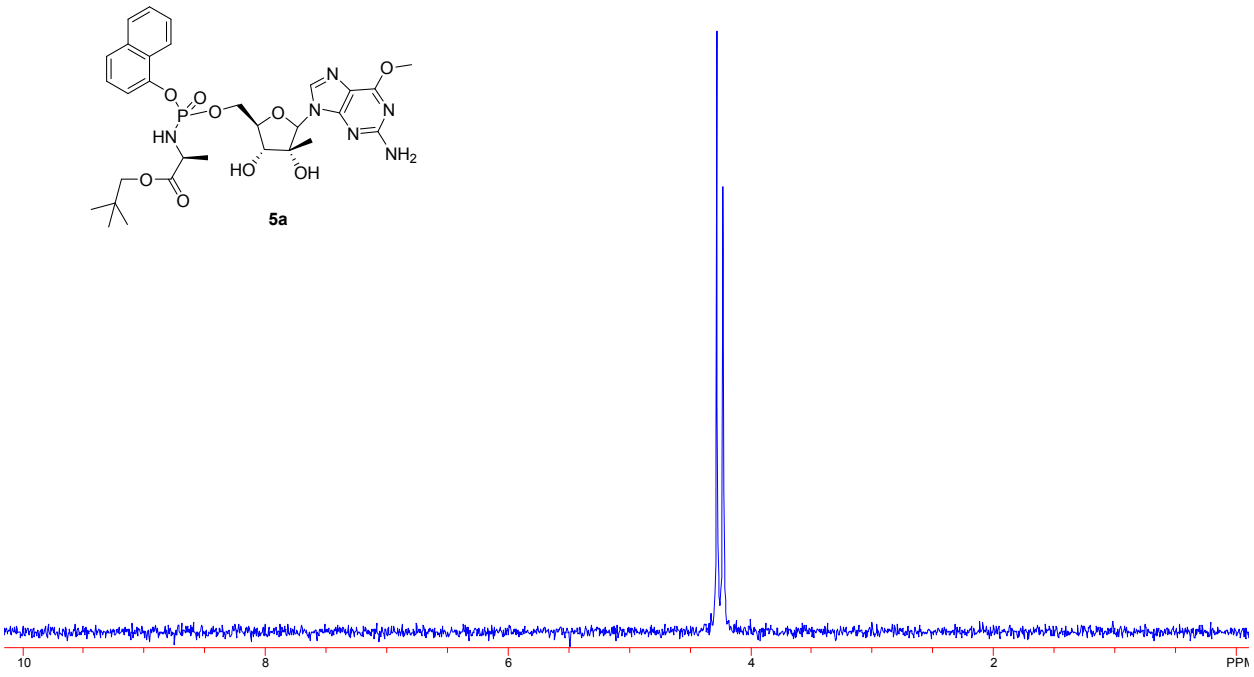


Fig.2. ^{31}PNMR (CD_3OD, 202 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α - naphthyl-(2,2-dimethylpropoxy- *L* -alaninyl)] phosphate **5a** (*R*p:*S*p dr 1:1).

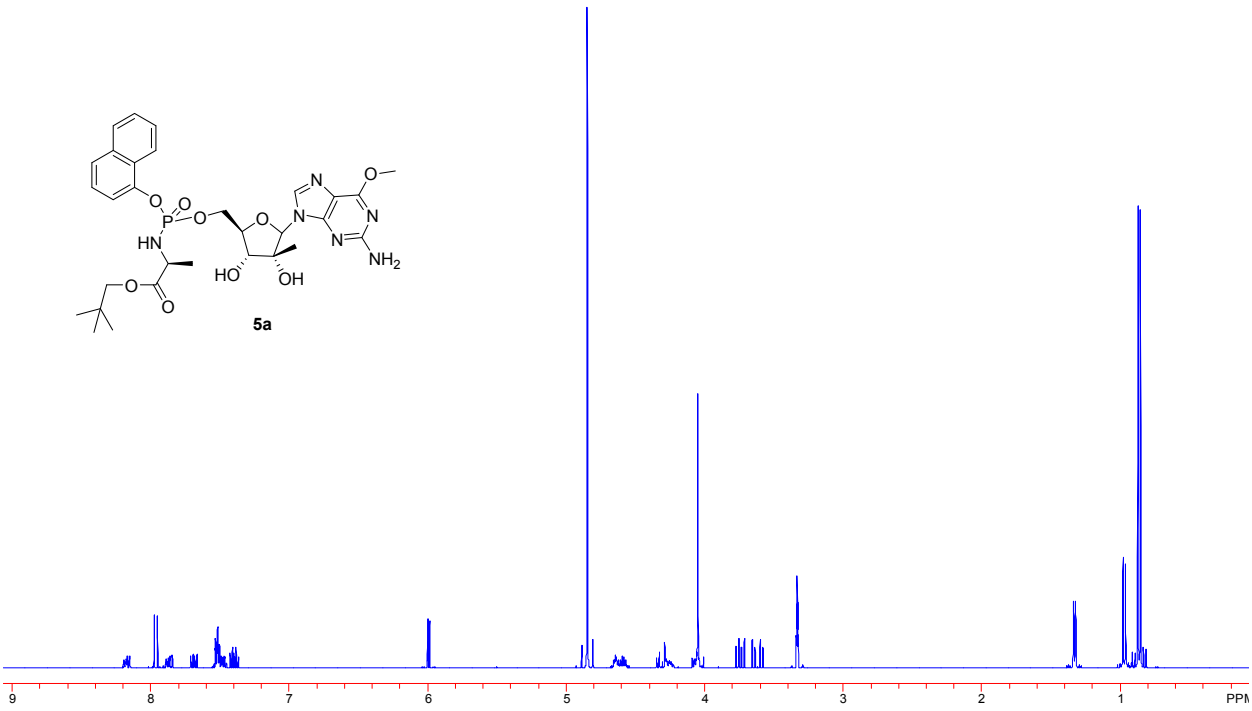


Fig.3. ^{1}HNMR (CD_3OD, 500 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α -naphthyl-(2,2-dimethylpropoxy- *L* -alaninyl)] phosphate **5a** (*R*p:*S*p dr 1:1).

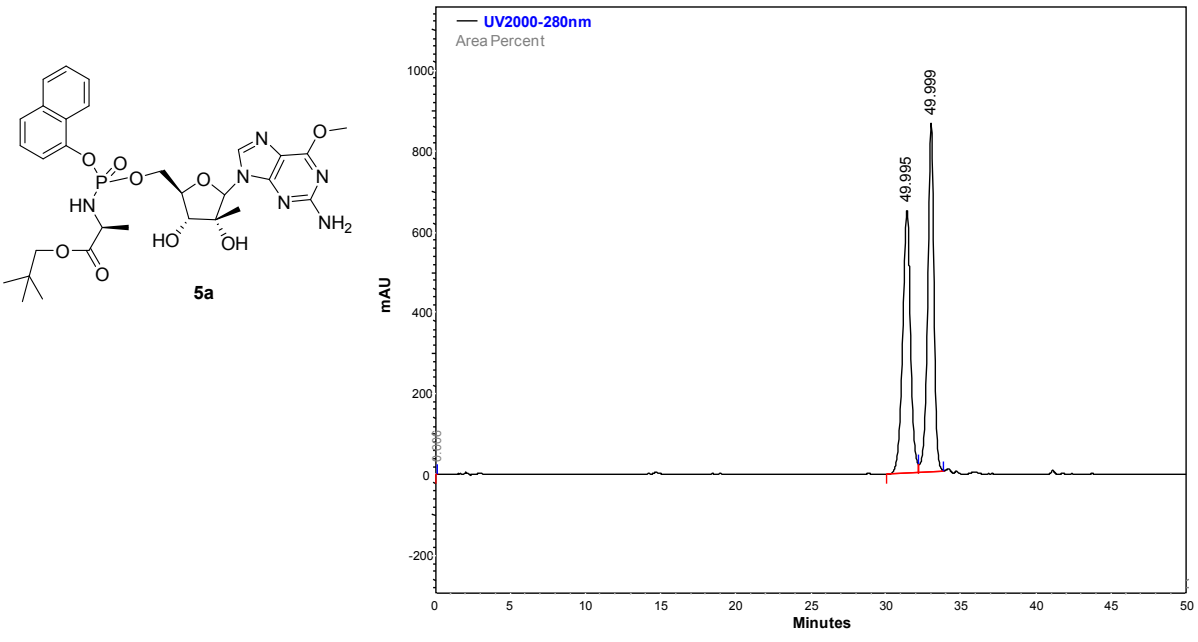


Fig.4. HPLC trace of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α -naphthyl-(2,2-dimethylpropoxy- *L* -alaninyl)] phosphate **5a** (*R*p : *S*p dr 1:1)

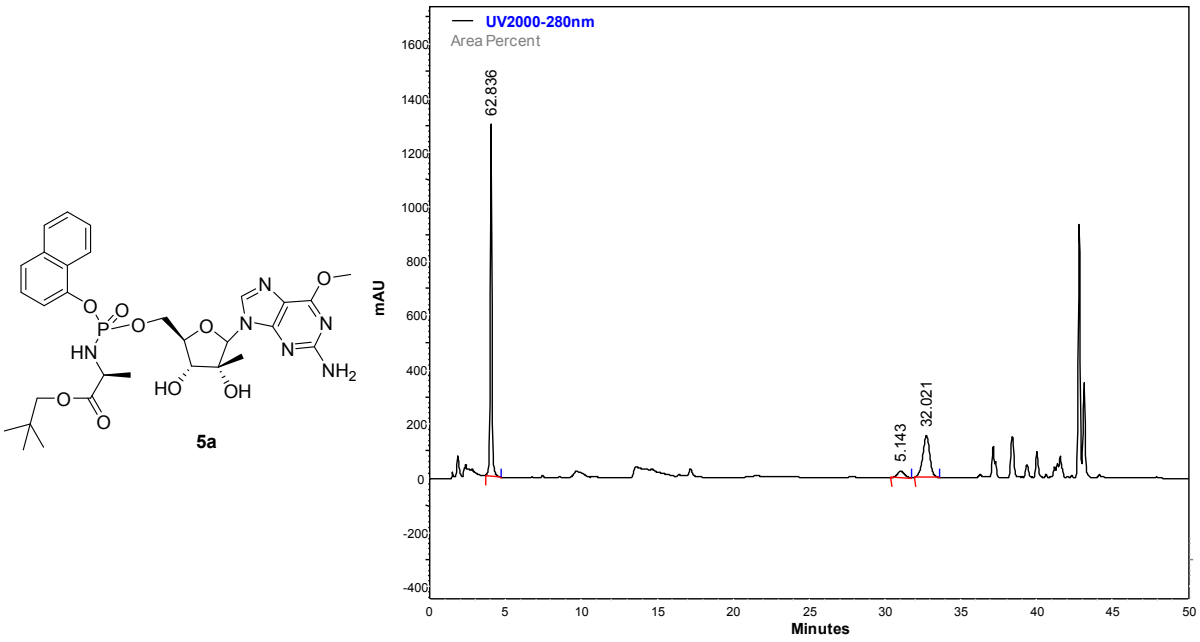


Fig.5. HPLC trace of **5a**, crude reaction mixture (Entry 3 Table 1).

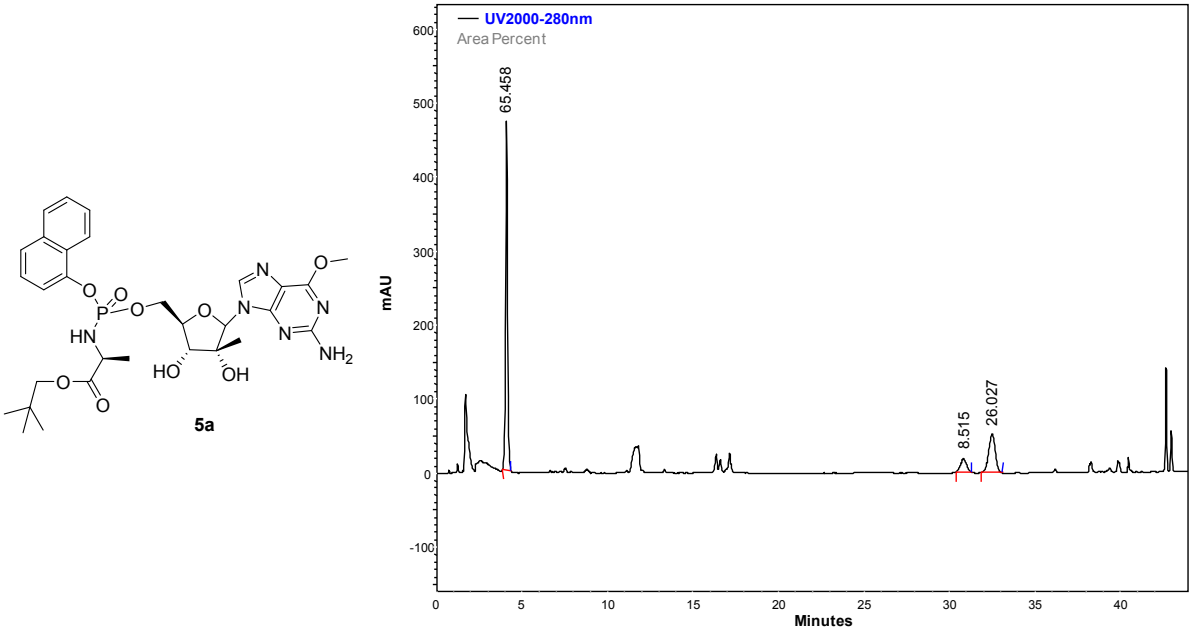


Fig.6. HPLC trace of **5a**, crude reaction mixture (Entry 7 Table 1).

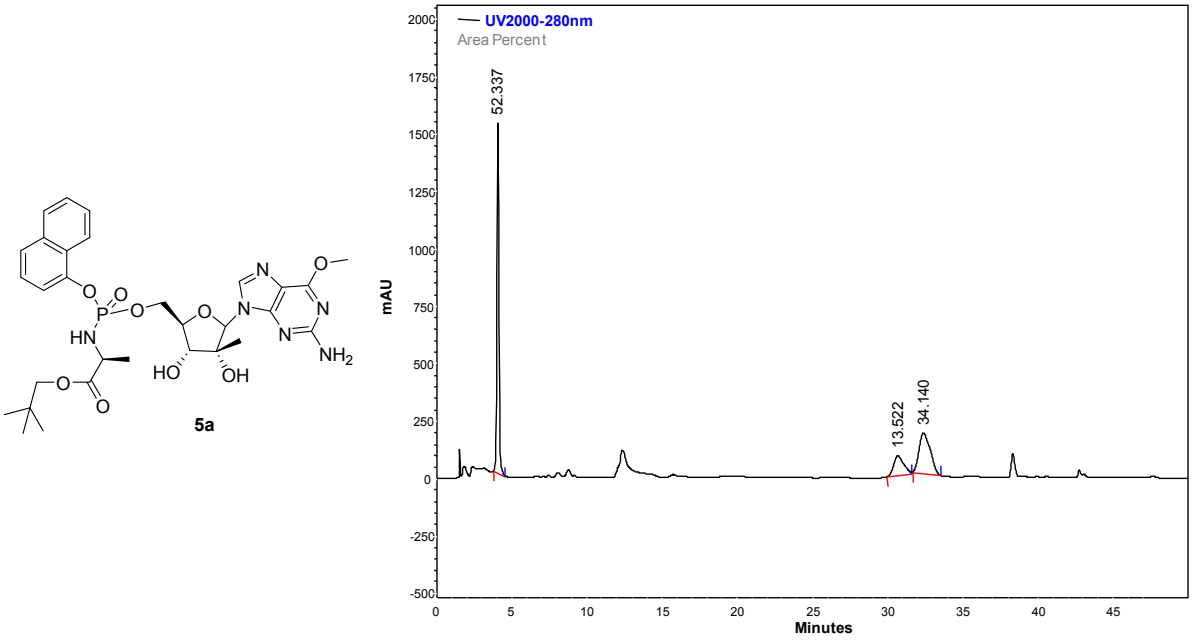


Fig.7 HPLC trace of **5a**, crude reaction mixture (Entry 8 Table 1).

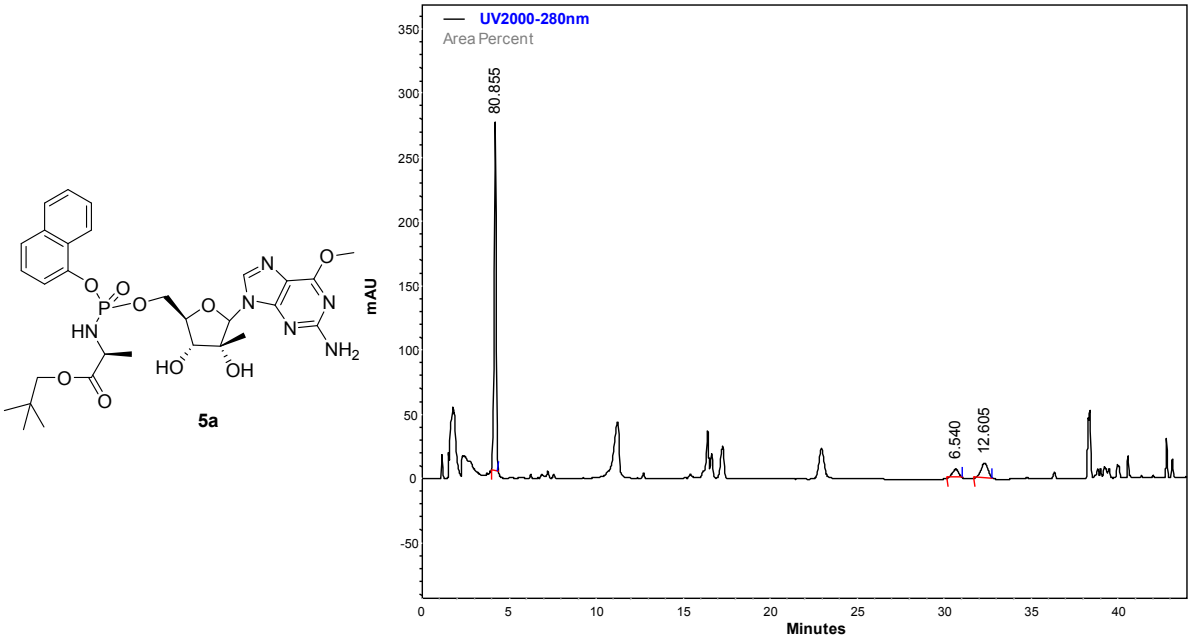


Fig.8 HPLC trace of **5a**, crude reaction mixture (Entry 10 Table 1).

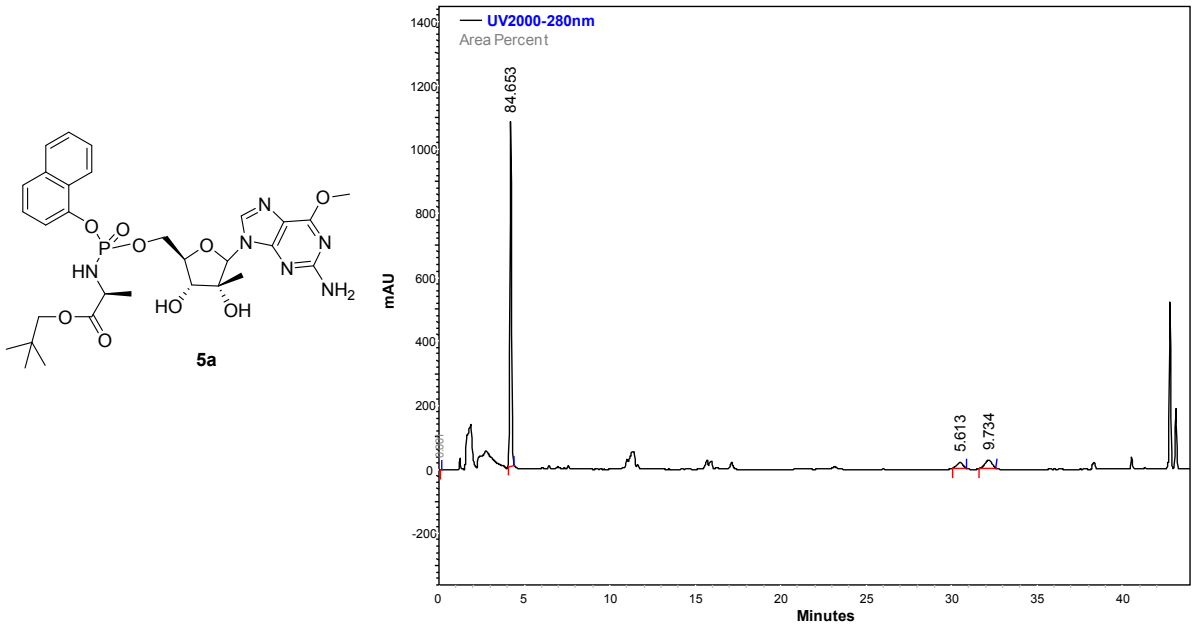


Fig.9. HPLC trace of **5a**, crude reaction mixture (Entry 11 Table 1).

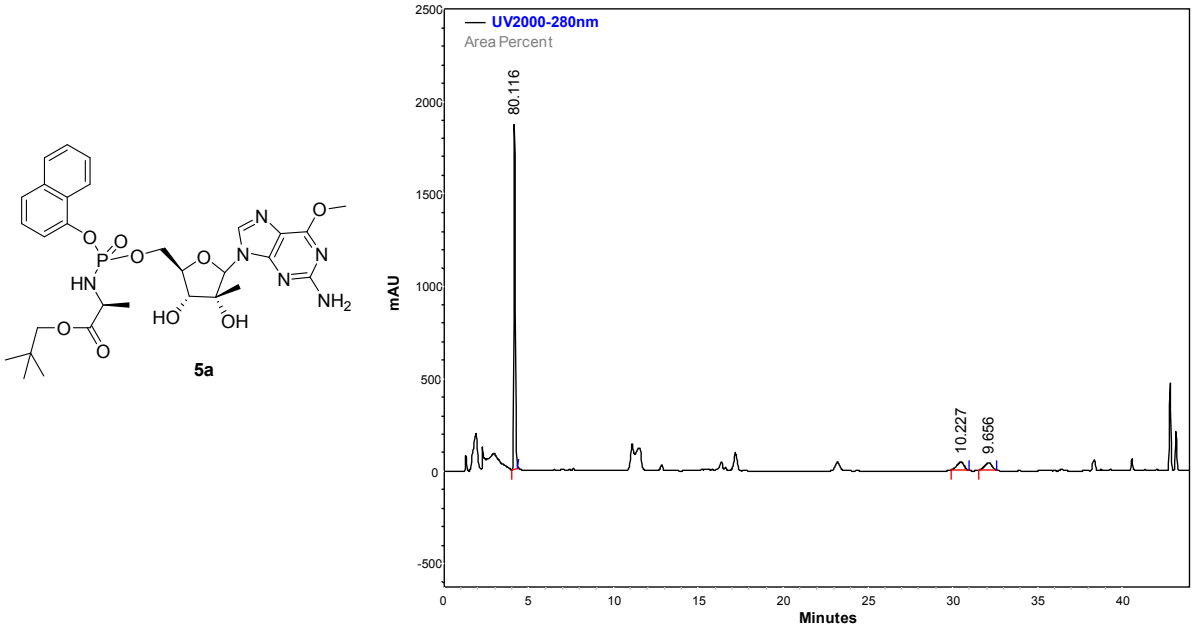


Fig.10. HPLC trace of **5a**, crude reaction mixture (Entry 12 Table 1).

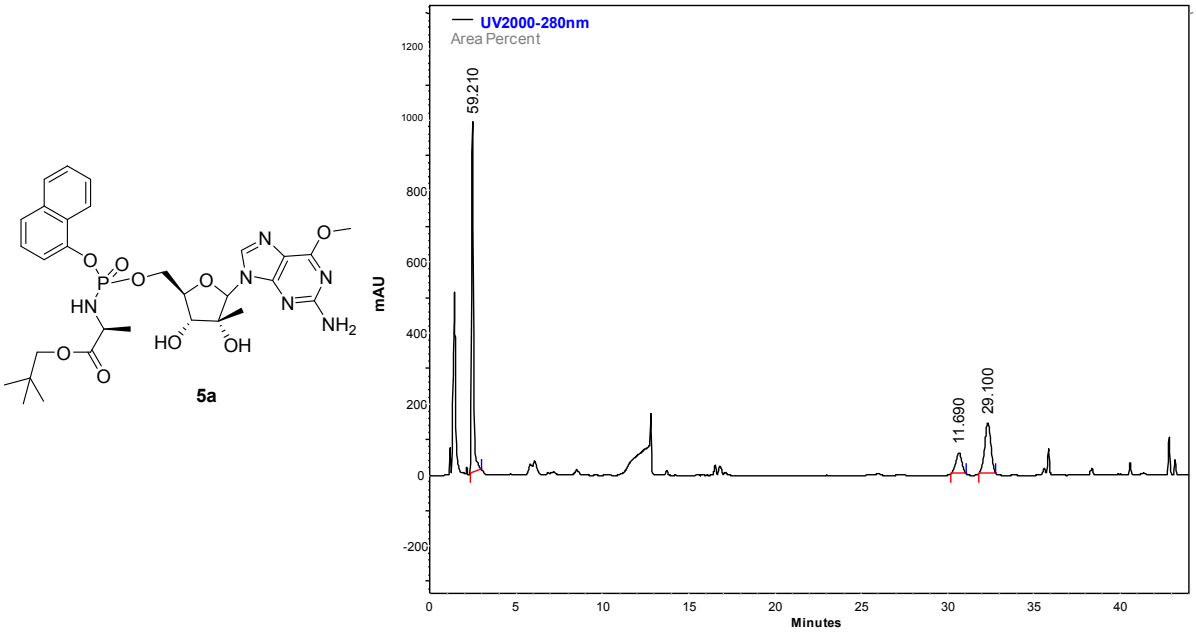


Fig.11. HPLC trace of **5a**, crude reaction mixture (Entry 14 Table 1).

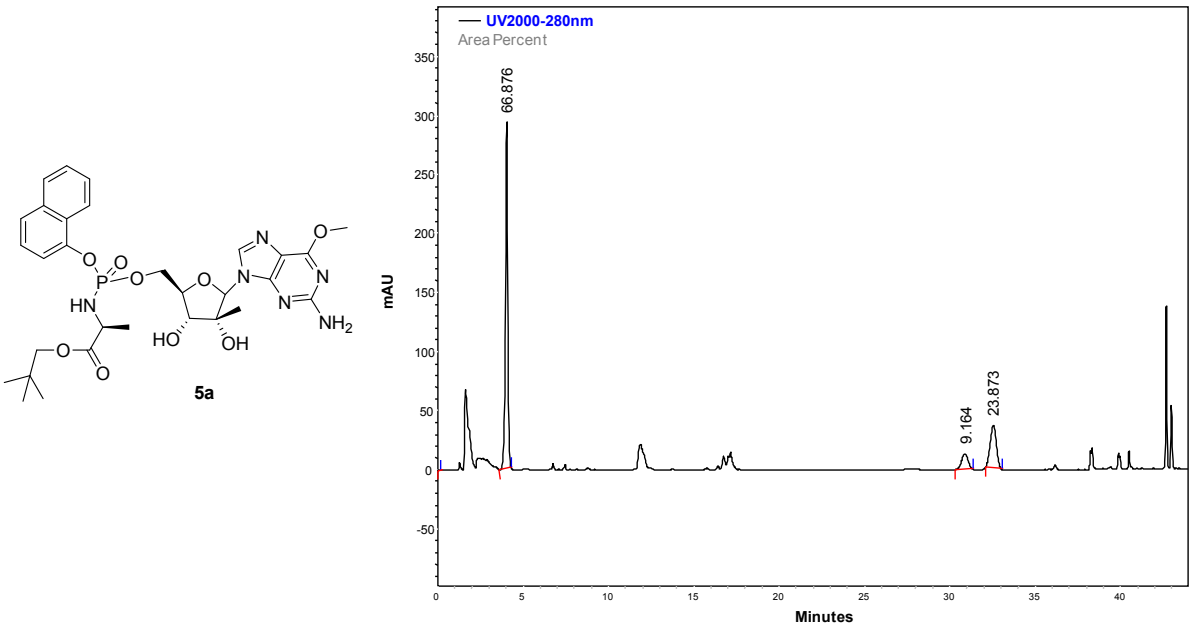


Fig.12. HPLC trace of **5a**, crude reaction mixture (Entry 15 Table 1).

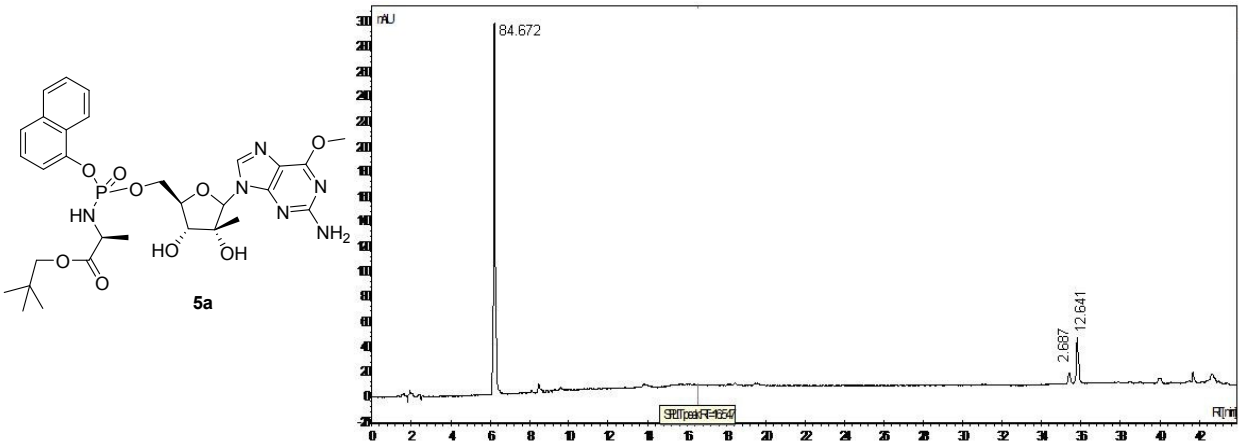


Fig.13. HPLC trace of **5a**, crude reaction mixture (Entry 17 Table 1).

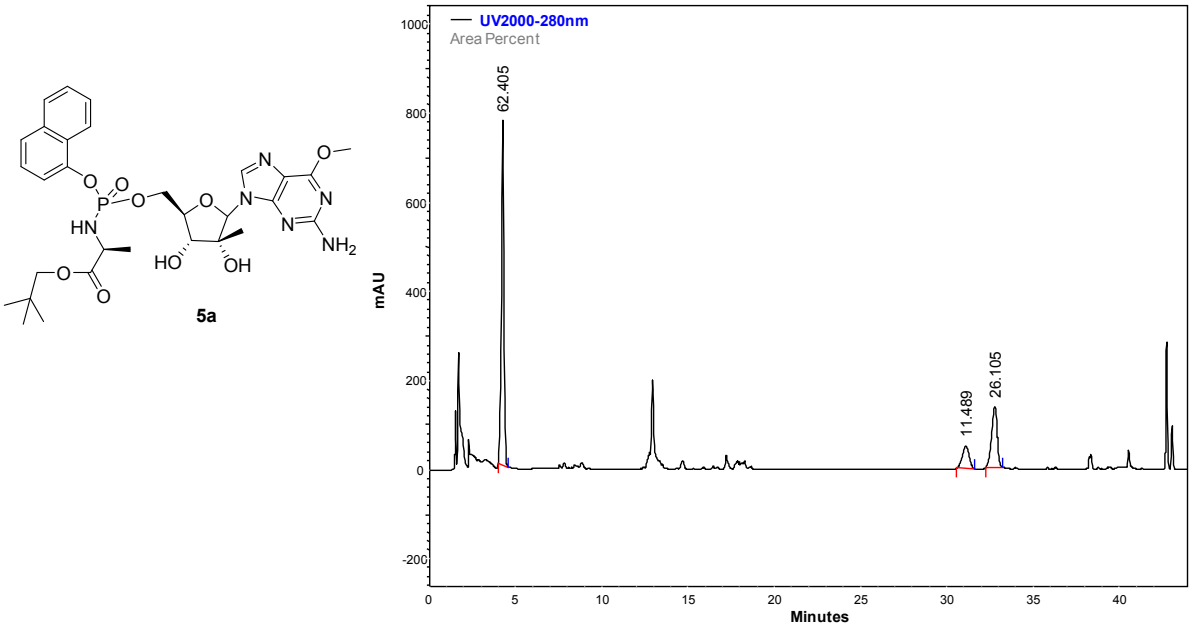


Fig.14. HPLC trace of **5a**, crude reaction mixture (Entry 21 Table 1).

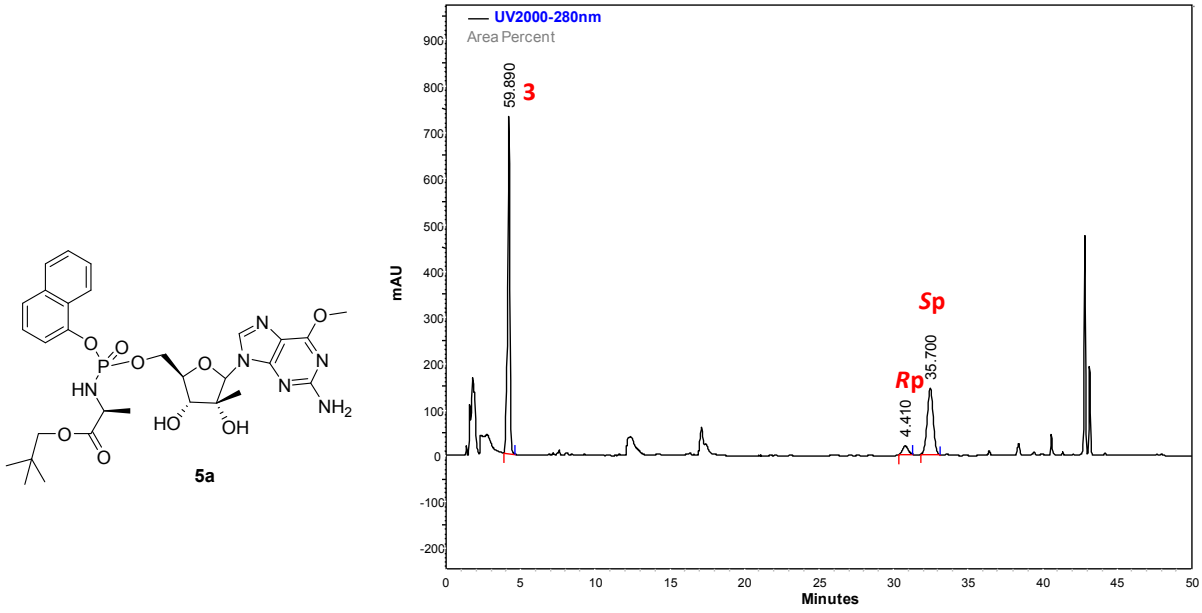


Fig.15. HPLC trace of **5a**, crude reaction mixture (Entry 28 Table 1).

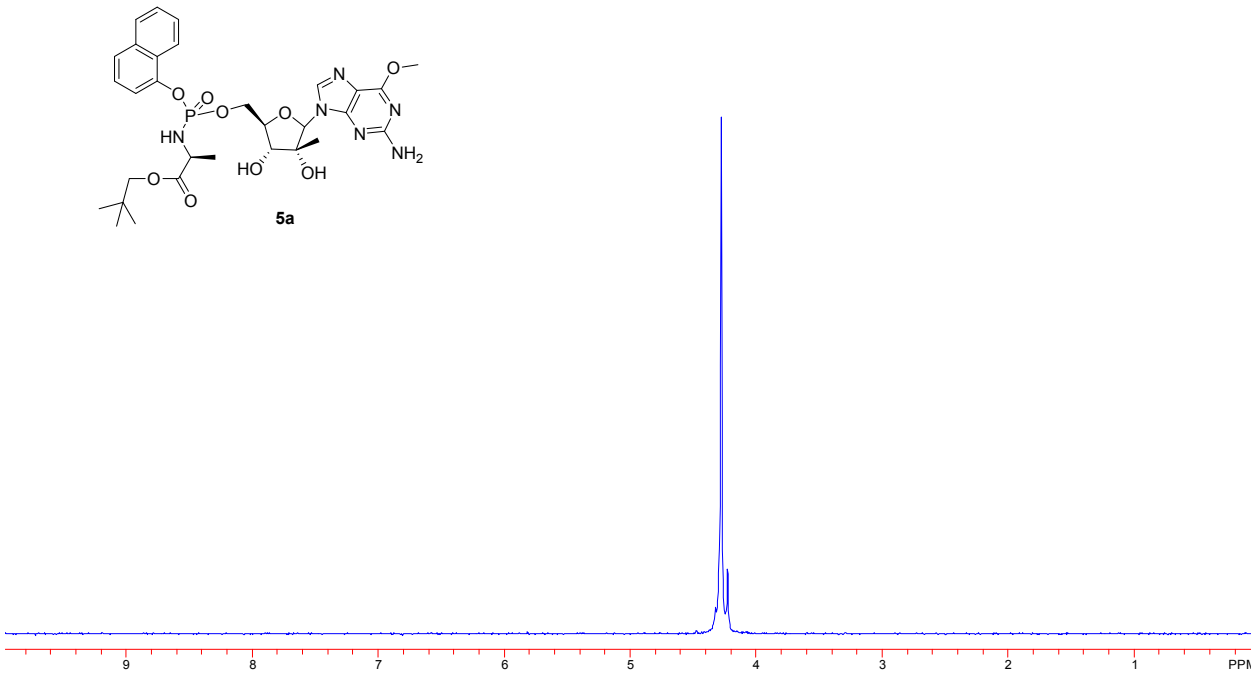


Fig.16. ^{31}PNMR (CD_3OD, 202 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl-β - D -ribofuranosyl) purine 5'-*O*-[α - naphthyl-(2,2-dimethylpropoxy- *L* -alaninyl)] phosphate **5a** (*R*p :*S*p dr 1.2:8.8).

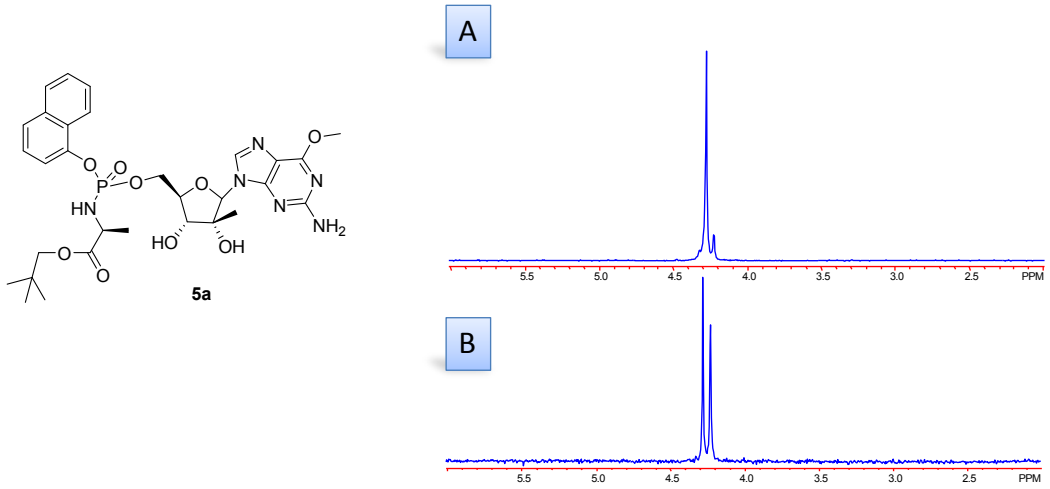


Fig.17. ^{31}PNMR (CD_3OD, 202 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α -naphthyl-(2,2-dimethylpropoxy-*L* -alaninyl)] phosphate **5a** (*R*p : *S*p dr 1.2:8.8) **A**. **5a** (*R*p : *S*p dr 1:1) **B**

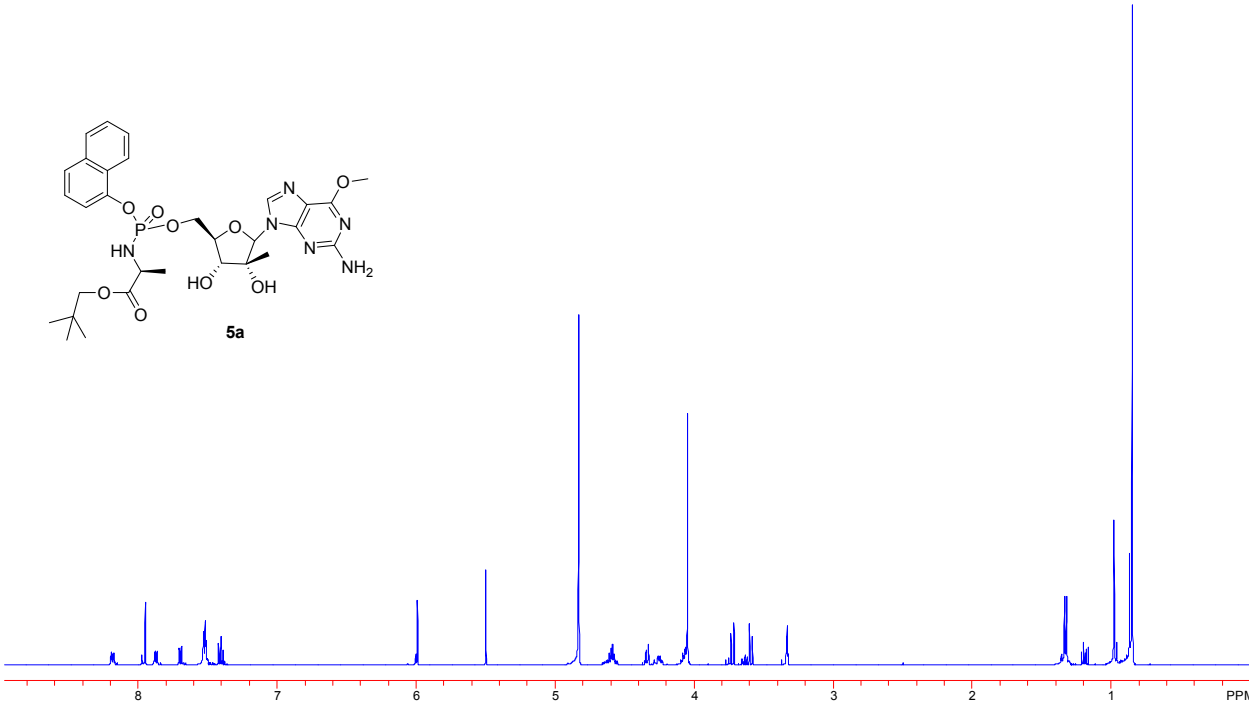


Fig.18. ^{1}HNMR (CD_3OD, 500 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α -naphthyl-(2,2-dimethylpropoxy-*L* -alaninyl)] phosphate **5a** (*R*p : *S*p dr 1.2:8.8).

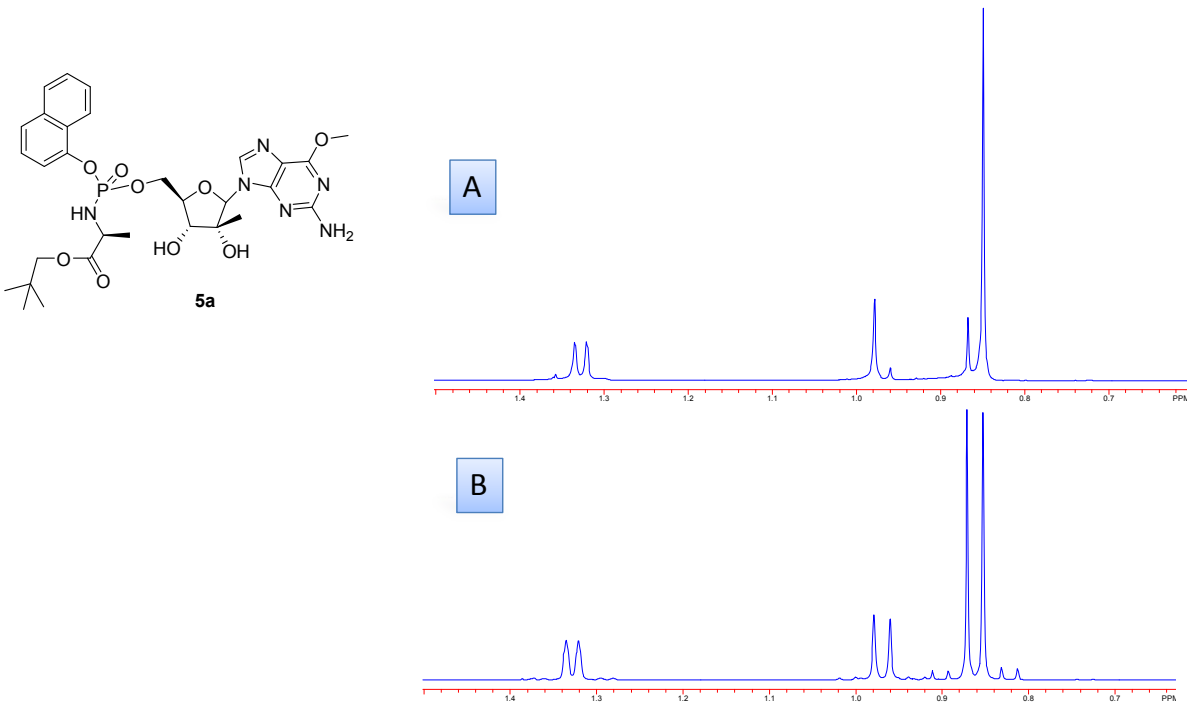


Fig.19. ^{1}HNMR (CD_3OD, 500 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl-β-D-ribofuranosyl) purine 5'-*O*-[α-naphthyl-(2,2-dimethylpropoxy-*L*-alaninyl)] phosphate **5a** (*R*p : *S*p dr 1.2:8.8) **A**. **5a** (*R*p : *S*p dr 1:1) **B**.

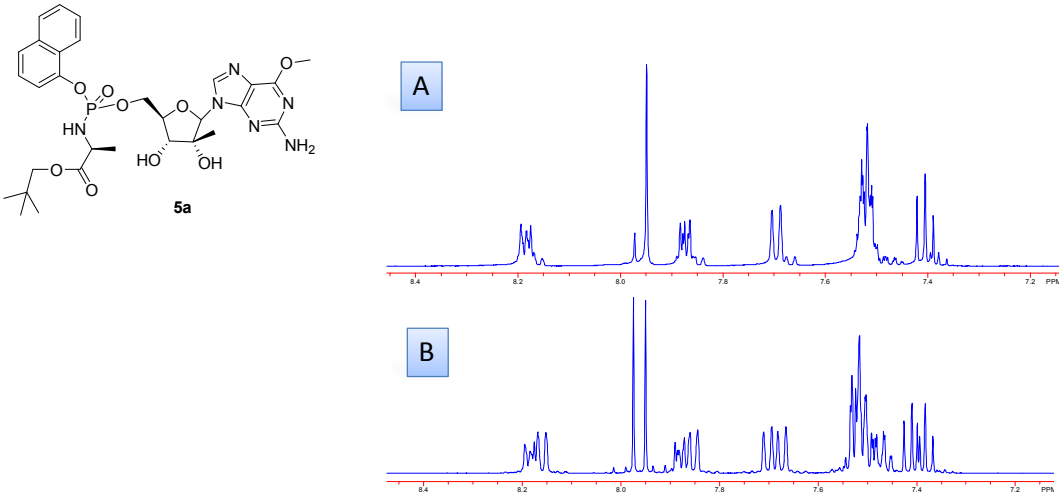


Fig.20 ^{1}HNMR (CD_3OD, 500 MHz) of 2-amino-6-methoxy-9-(2'-C-methyl-β-D-ribofuranosyl) purine 5'-*O*-[α-naphthyl-(2,2-dimethylpropoxy-*L*-alaninyl)] phosphate **5a** (*R*p : *S*p dr 1.2:8.8) **A**. **5a** (*R*p : *S*p dr 1:1) **B**.

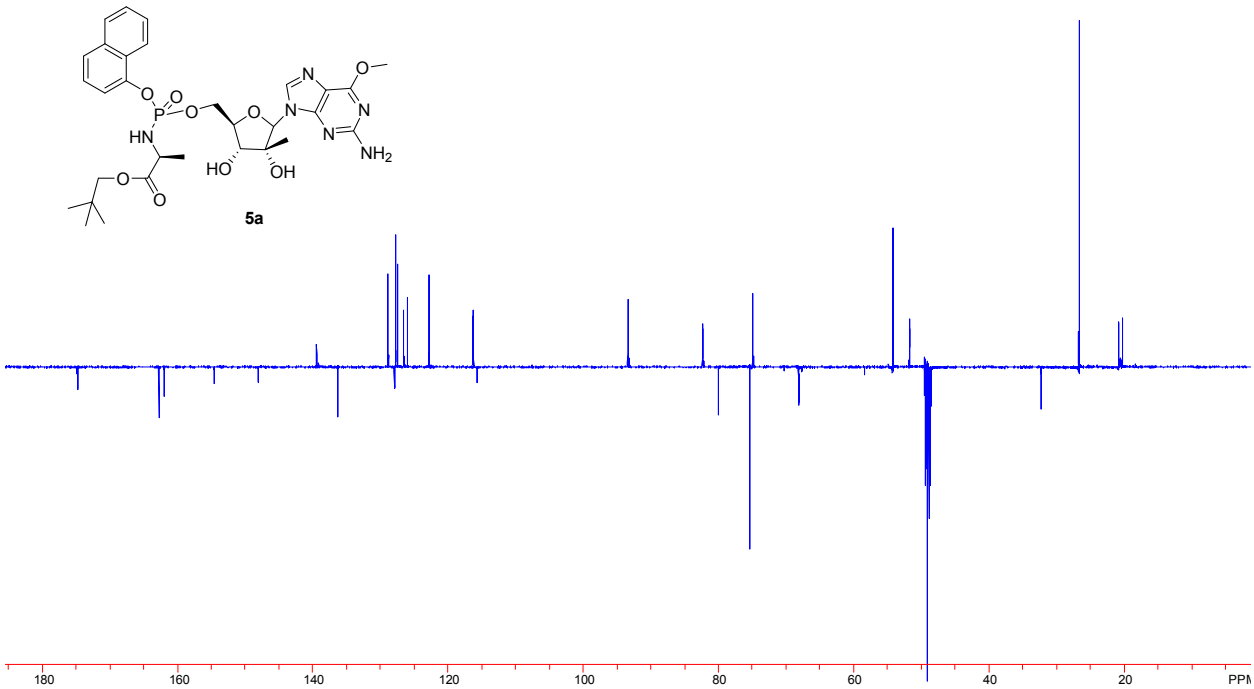


Fig.21. ^{13}C Pendant NMR (CD_3OD, 125 MHz) of 2-amino-6-methoxy-9-(2'-C-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α -naphthyl-(2,2-dimethylpropoxy- *L* -alaninyl)] phosphate **5a** (*R*p : *S*p dr 1.2:8.8).

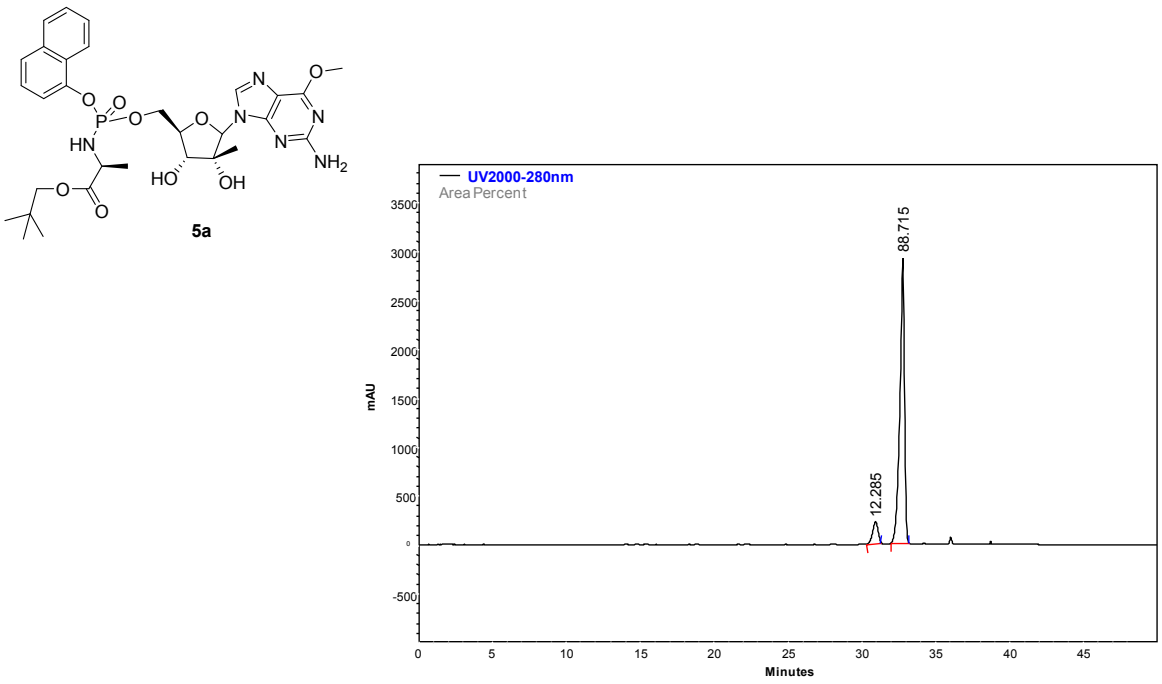


Fig.22. HPLC trace of 2-amino-6-methoxy-9-(2'-*C*-methyl- β- D -ribofuranosyl) purine 5'-*O*-[α -naphthyl-(2,2-dimethylpropoxy- *L* -alaninyl)] phosphate **5a** (*R*p : *S*p dr 1.2:8.8).

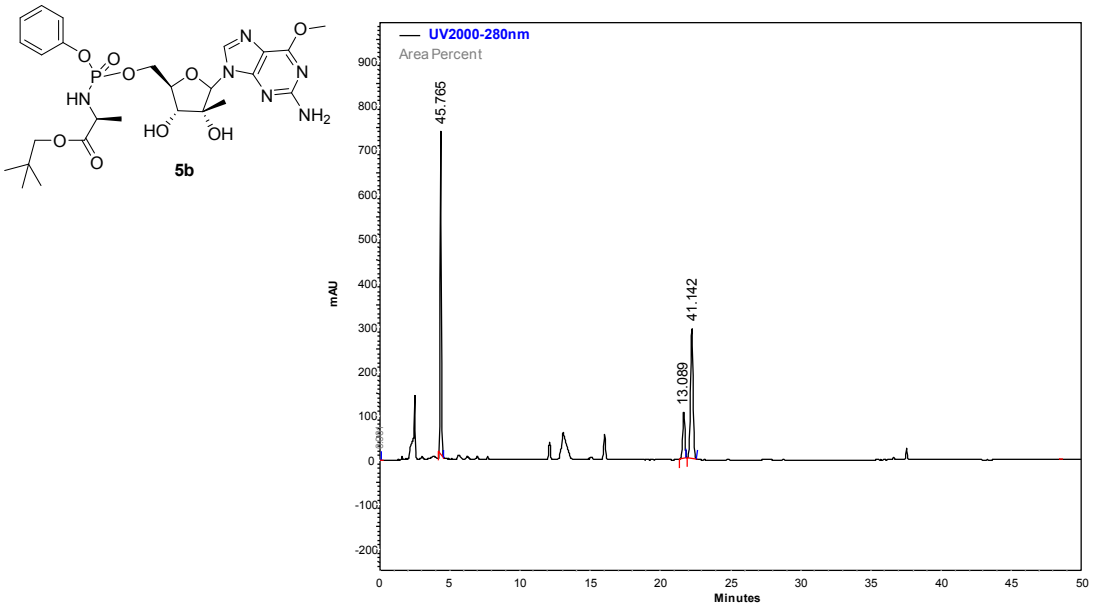
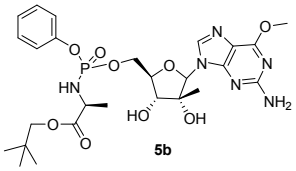


Fig.23. HPLC trace of **5b,** crude reaction mixture (Entry 2 Table 2).



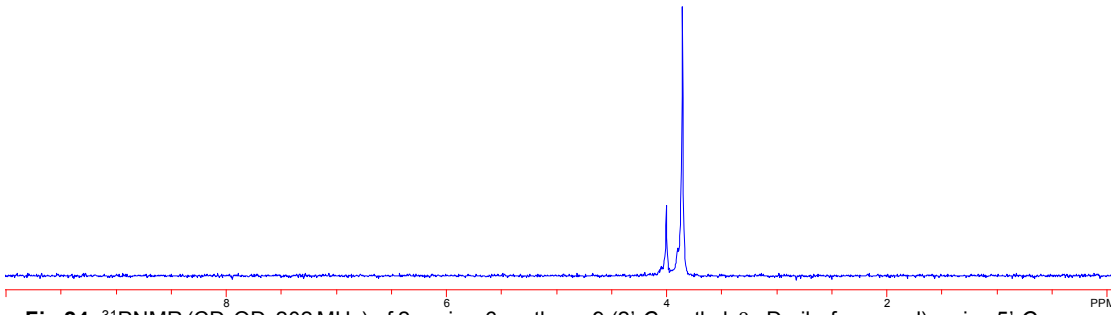


Fig.24. ^{31}PNMR (CD_3OD, 202 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl-β - D -ribofuranosyl) purine 5'-*O*-[phenyl-(2,2-dimethylpropoxy-*L* -alaninyl)] phosphate **5b** (*R*p : *S*p dr 1:4.3).

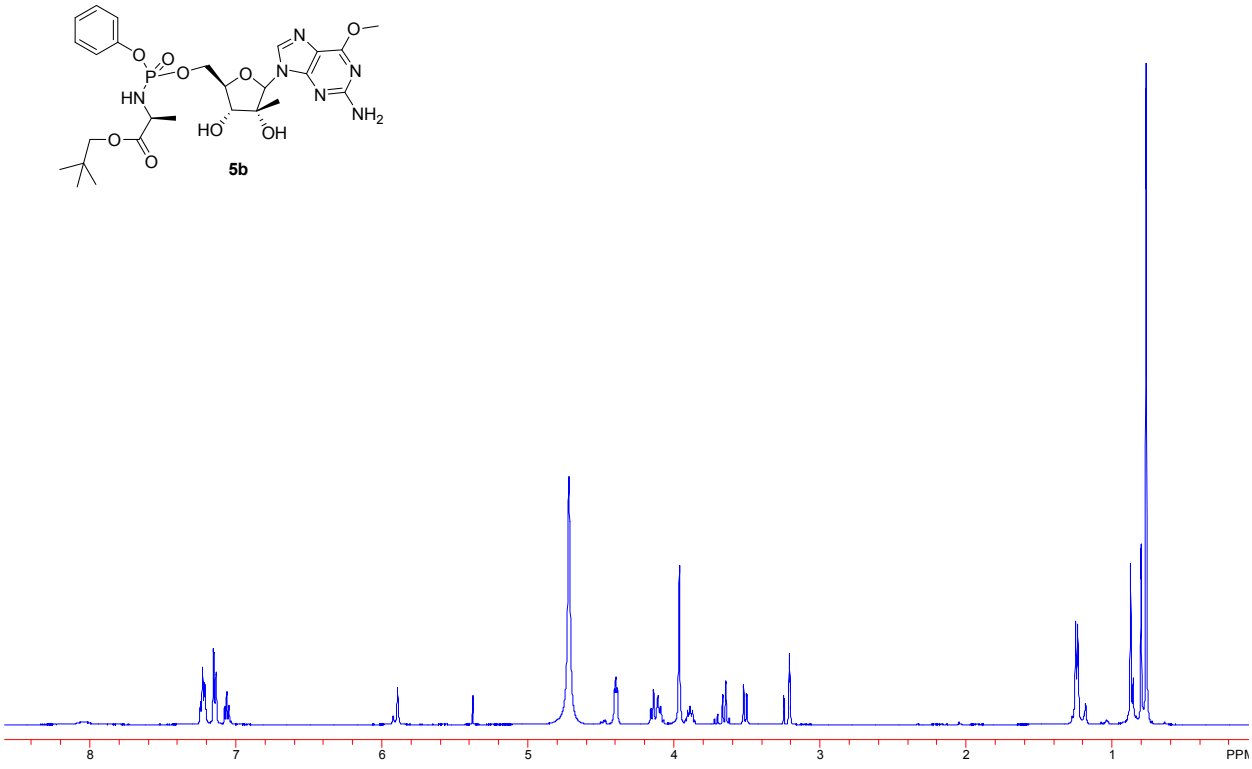


Fig.25. ^{1}HNMR (CD_3OD, 500 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[phenyl-(2,2-dimethylpropoxy- *L* -alaninyl)] phosphate **5b** (*R*p : *S*p dr 1:4.3).

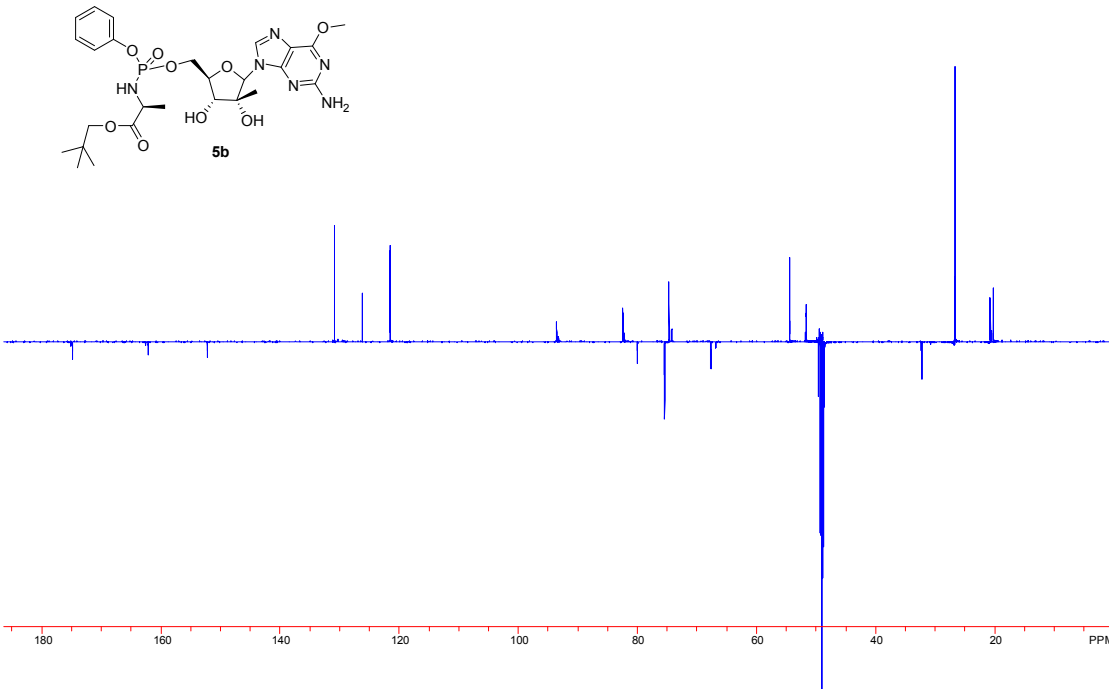


Fig.26. ^{13}C Pendant NMR (CD_3OD, 125 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[phenyl-(2,2-dimethylpropoxy- *L* -alaninyl)] phosphate **5b** (*R*p : *S*p dr 1:4.3).

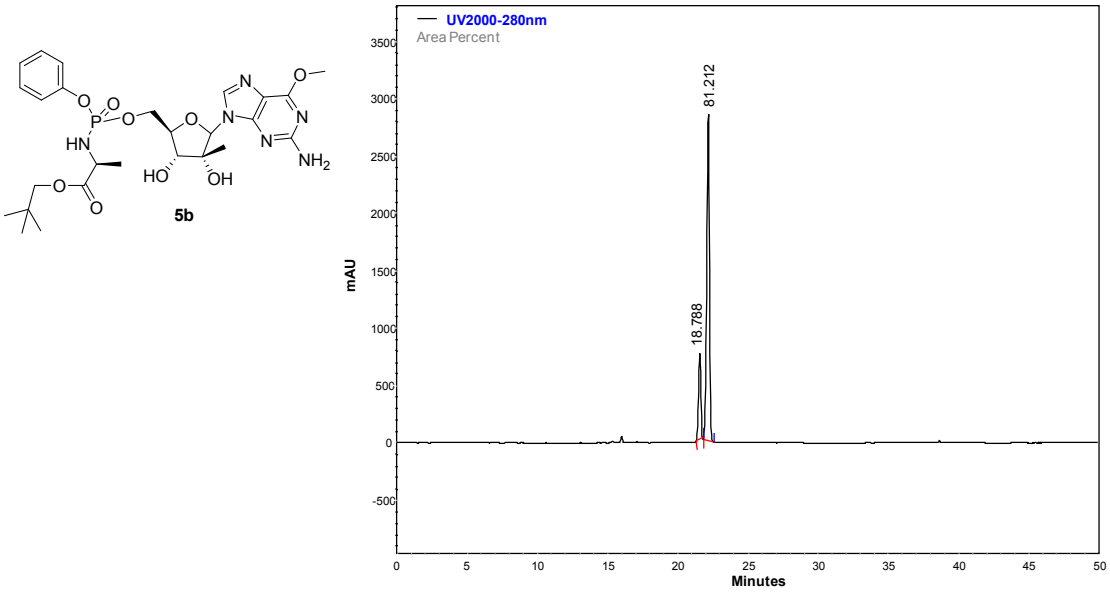


Fig.27. HPLC trace of 2-amino-6-methoxy-9-(2'-C-methyl- β - D -ribofuranosyl) purine 5'-*O*-[phenyl-(2,2-dimethylpropoxy-*L* -alaninyl)] phosphate **5b** (*R*p : *S*p dr 1:4.3).

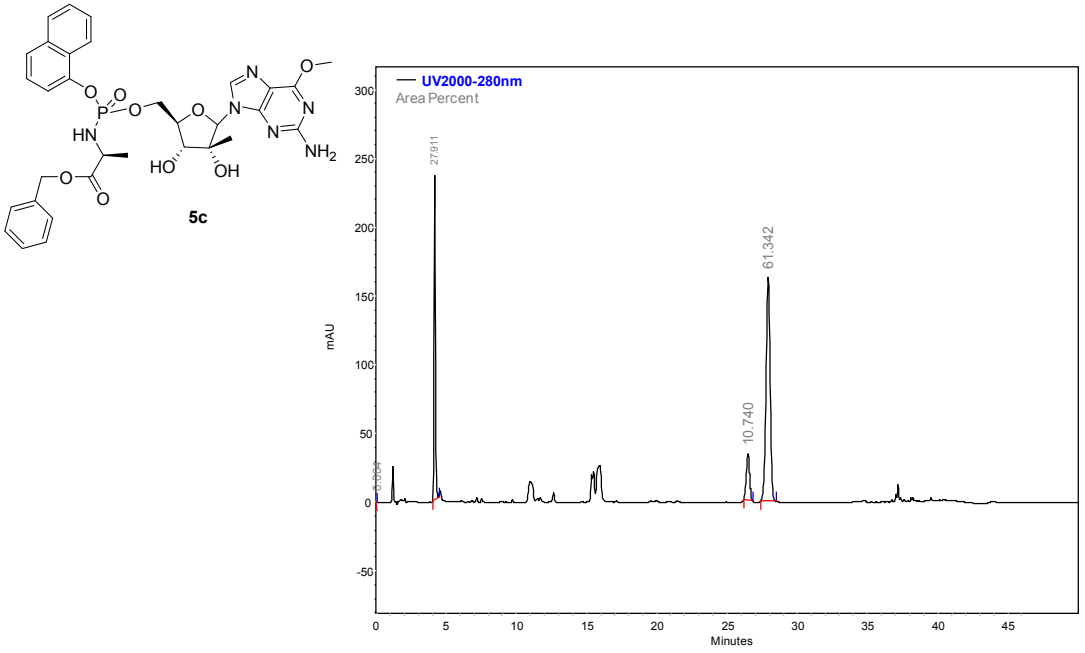


Fig.28. HPLC trace of **5c,** Crude reaction mixture (Entry 3, Table 2).

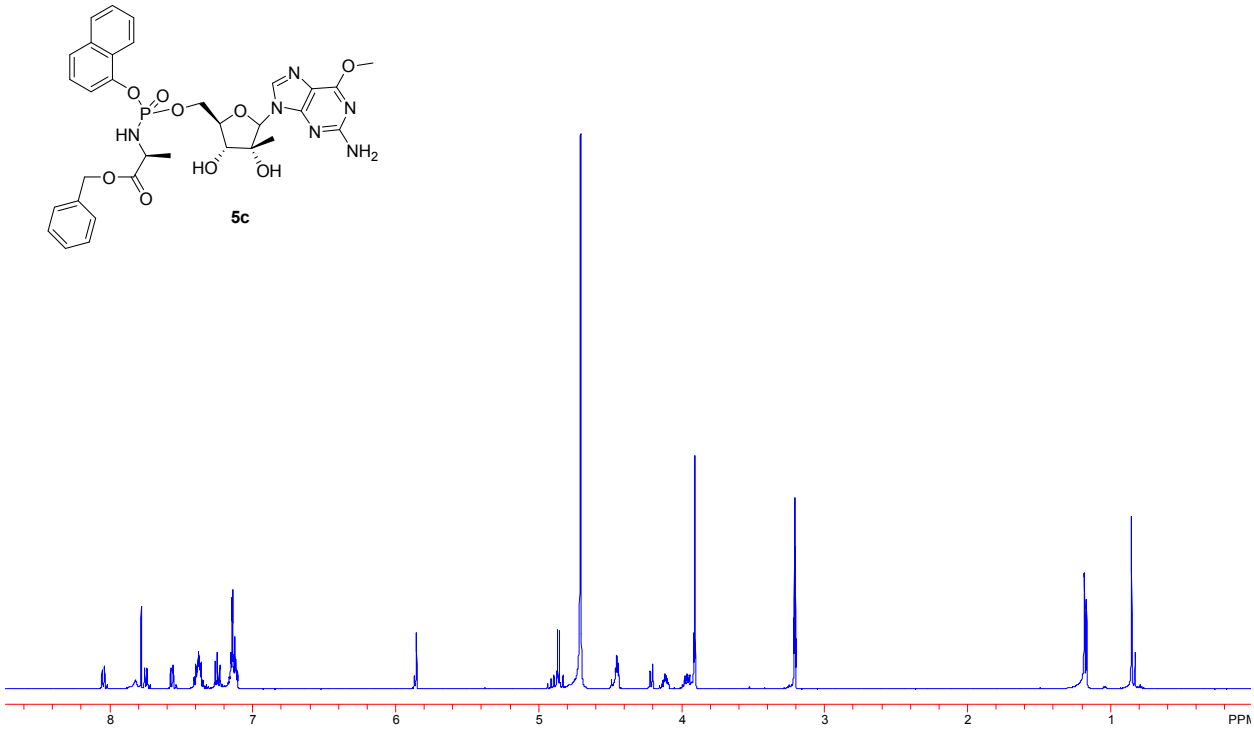


Fig.29. ^{1}HNMR (CD_3OD, 500 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α-napthyl-(benzyloxy-*L*-alaninyl)] phosphate **5c** (*R*p : *S*p dr 1:4.9).

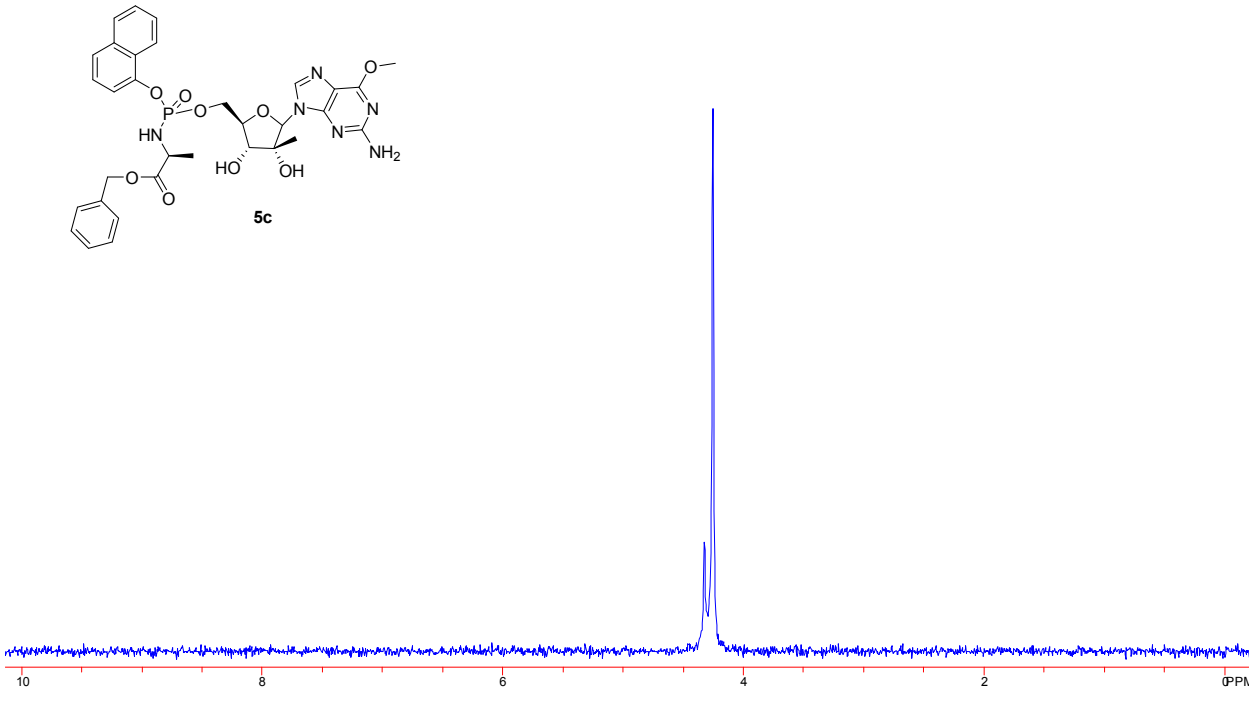


Fig.30. ^{31}PNMR (CD_3OD, 202 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α-napthyl-(benzyloxy-*L*-alaninyl)] phosphate **5c** (*R*p : *S*p dr 1:4.9).

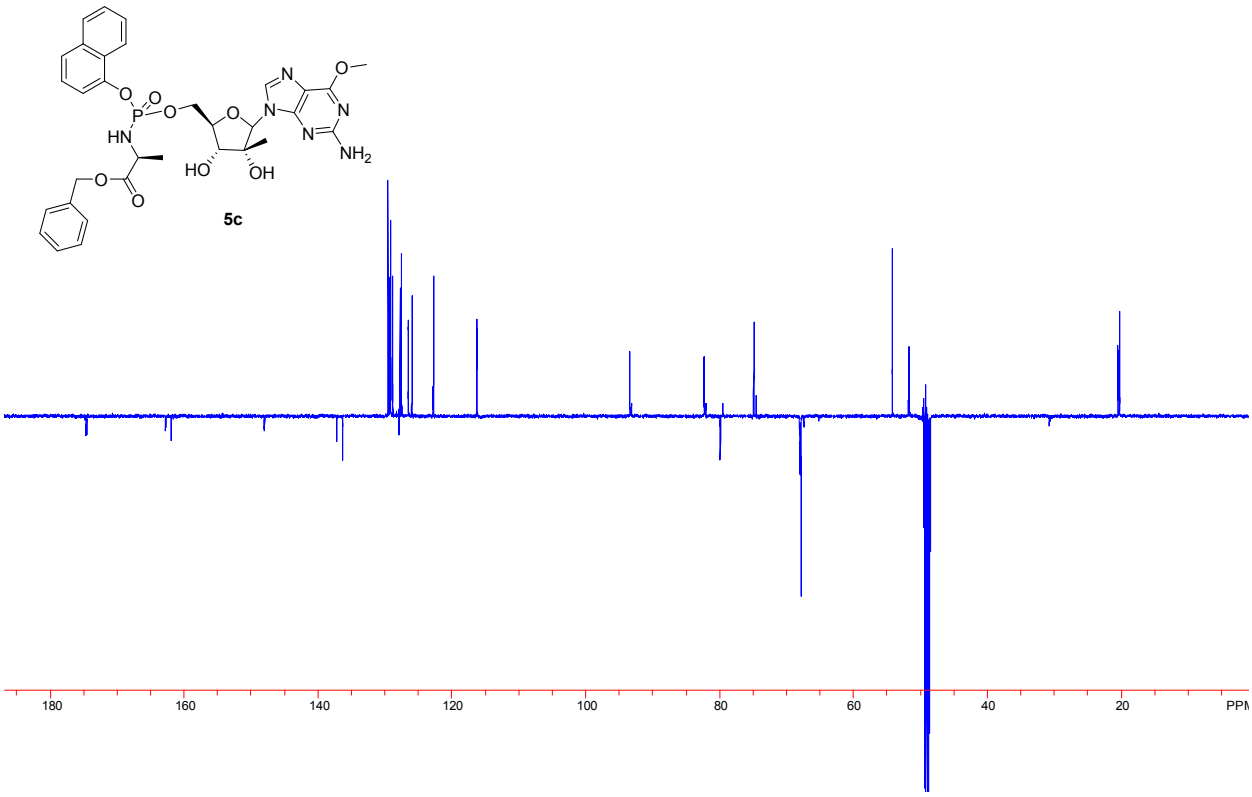


Fig.31. ^{13}C Pendant NMR (CD_3OD, 125 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α-napthyl-(benzyloxy-*L* -alaninyl)] phosphate **5c** (*R*p : *S*p dr 1:4.9).

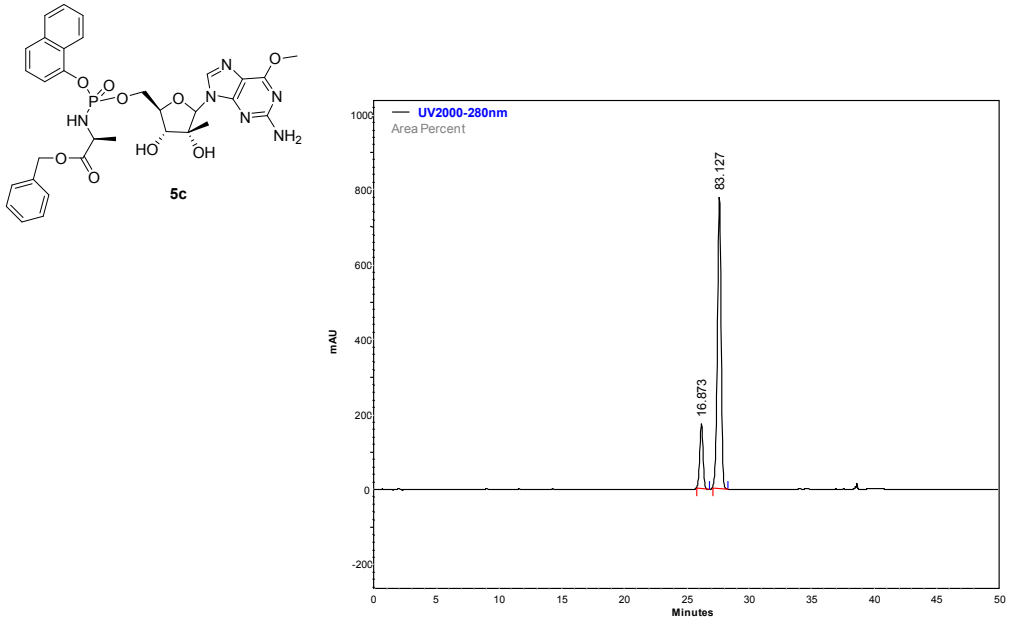


Fig.32. HPLC trace of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α-napthyl-(benzyloxy-*L* -alaninyl)] phosphate **5c** (*R*p : *S*p dr 1:4.9).

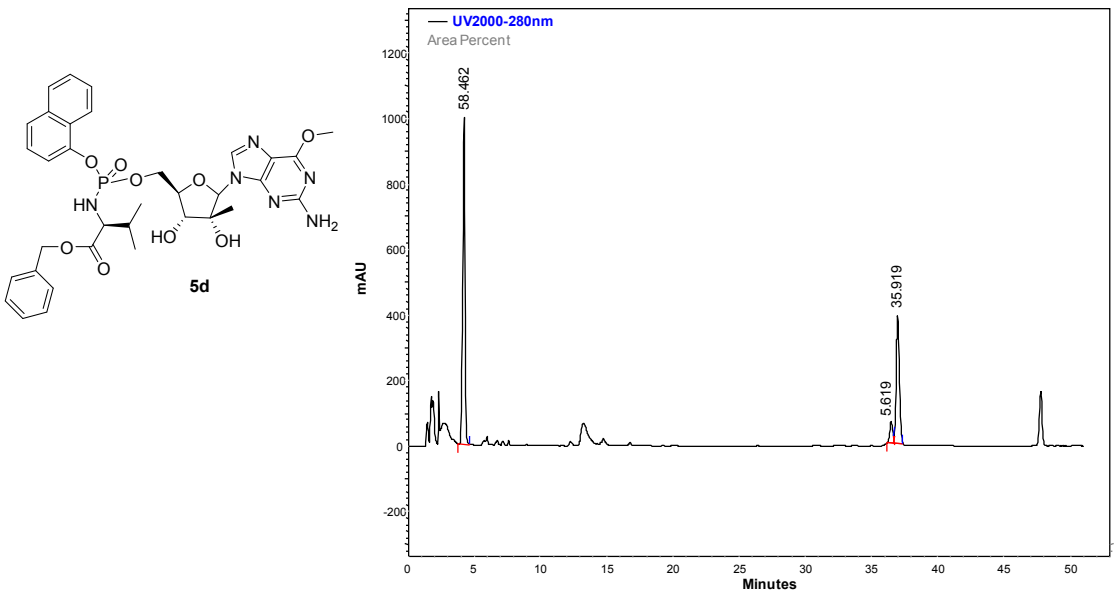


Fig.33. HPLC trace of **5d,** crude reaction mixture (Entry 4, Table 2).

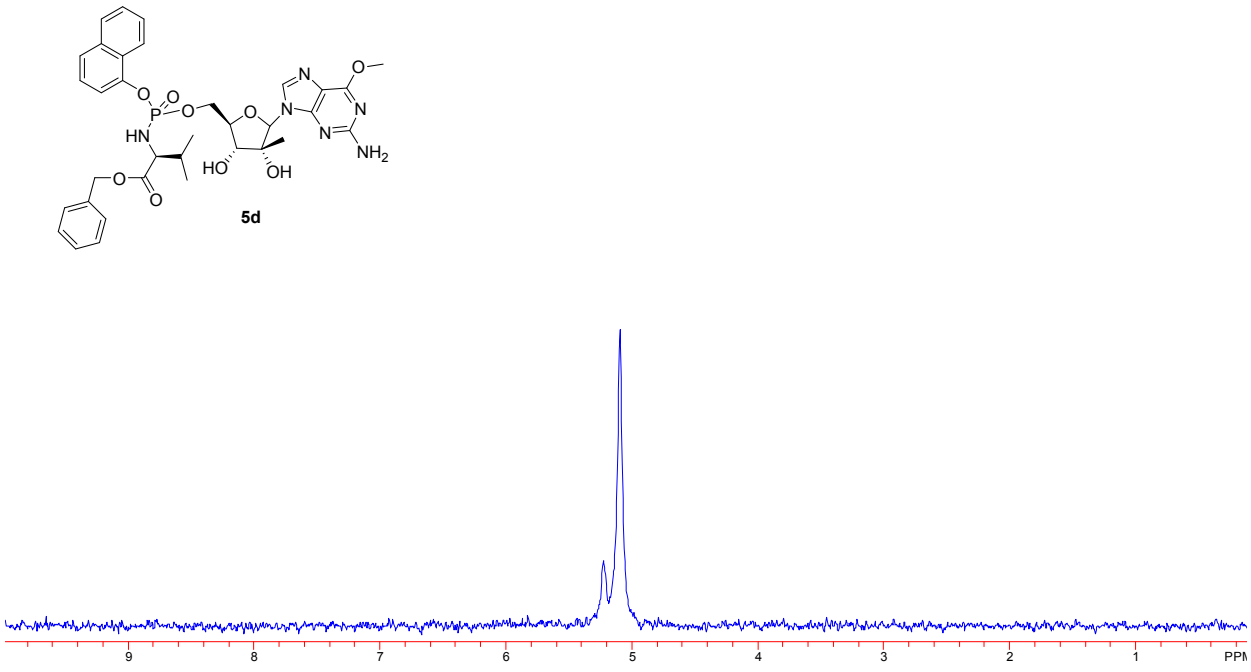


Fig.34. ^{31}PNMR (CD_3OD, 202 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α-napthyl-(benzyloxy-*L*-alaninyl)] phosphate **5d** (*R*p : *S*p dr 1:5).

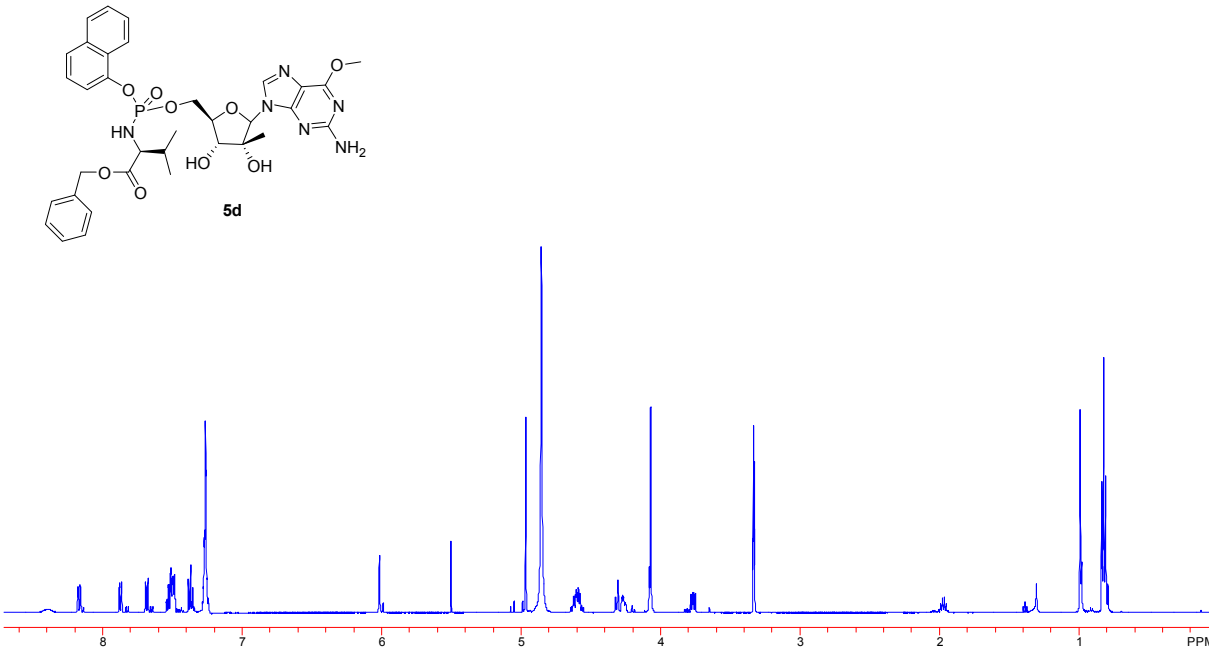


Fig.35. ^{1}HNMR (CD_3OD, 500 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α-napthyl-(benzyloxy-*L* -alaninyl)] phosphate **5d** (*R*p : *S*p dr 1:5).

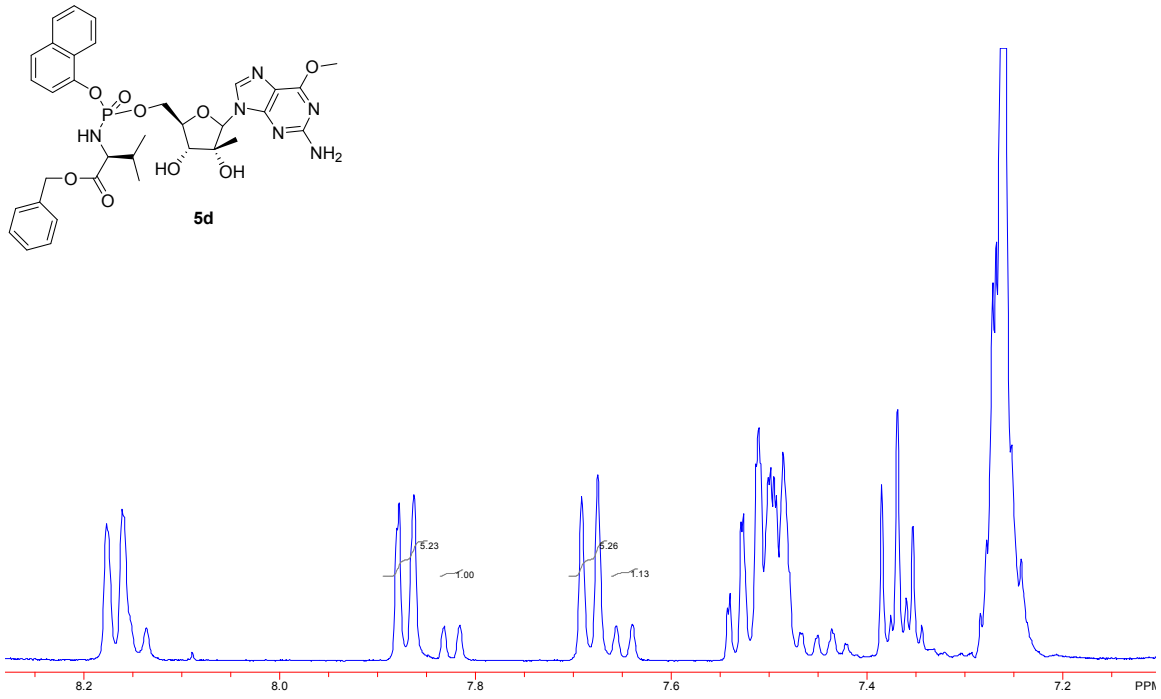


Fig.36. ^{1}HNMR (CD_3OD, 500 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α–napthyl-(benzyloxy-*L* -alaninyl)] phosphate **5d** (*R*p : *S*p dr 1:5).

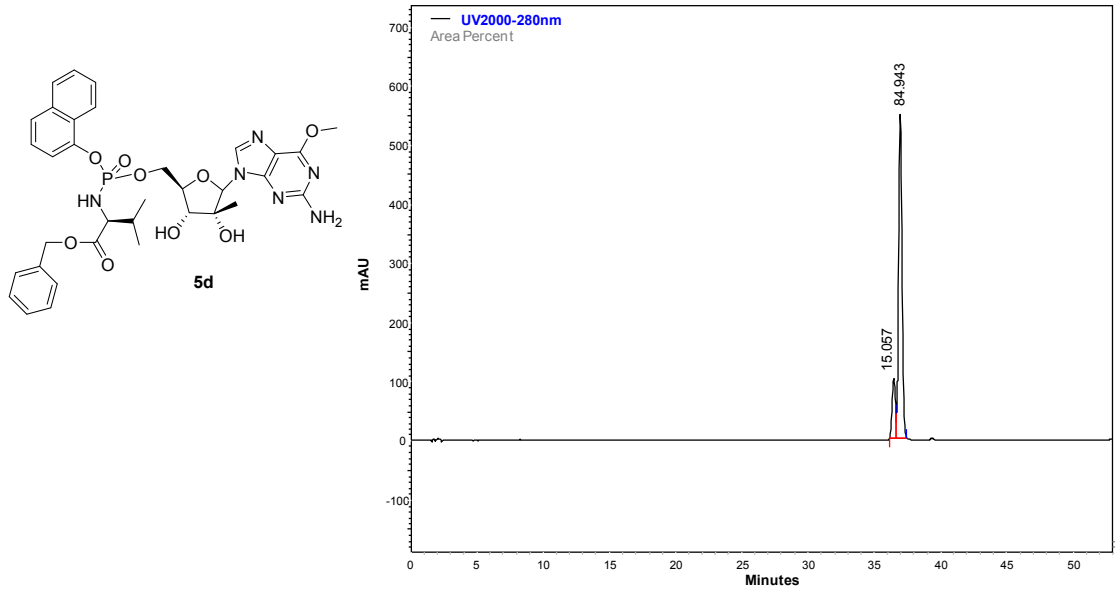


Fig.37. HPLC trace of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α-napthyl-(benzyloxy-*L* -alaninyl)] phosphate **5d** (*R*p : *S*p dr 1:5).

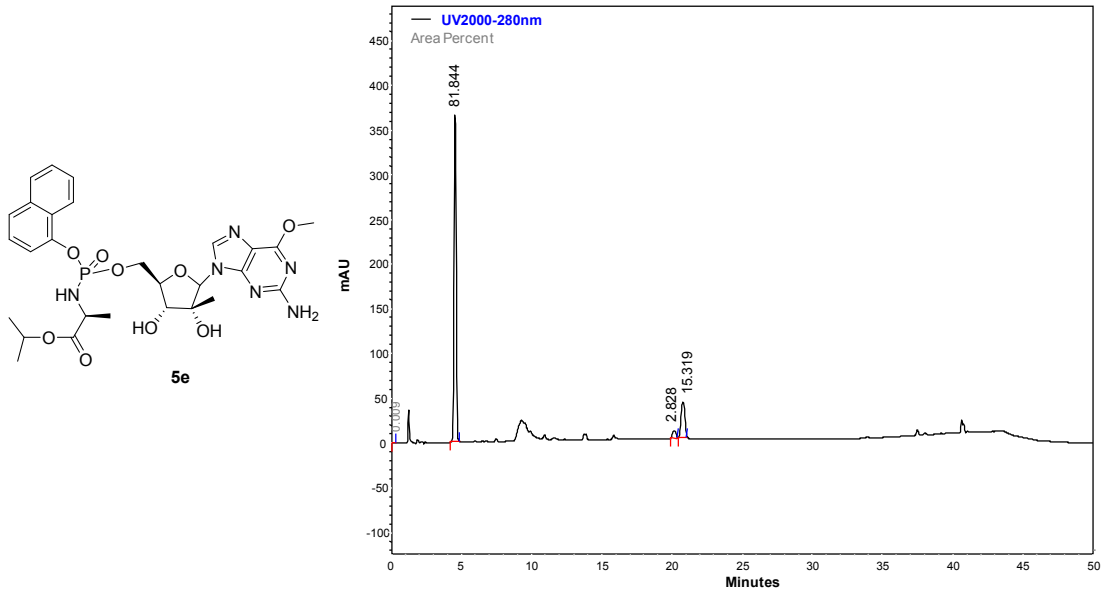


Fig.38. HPLC trace of **5e**, crude reaction mixture (Entry 5, Table 2).

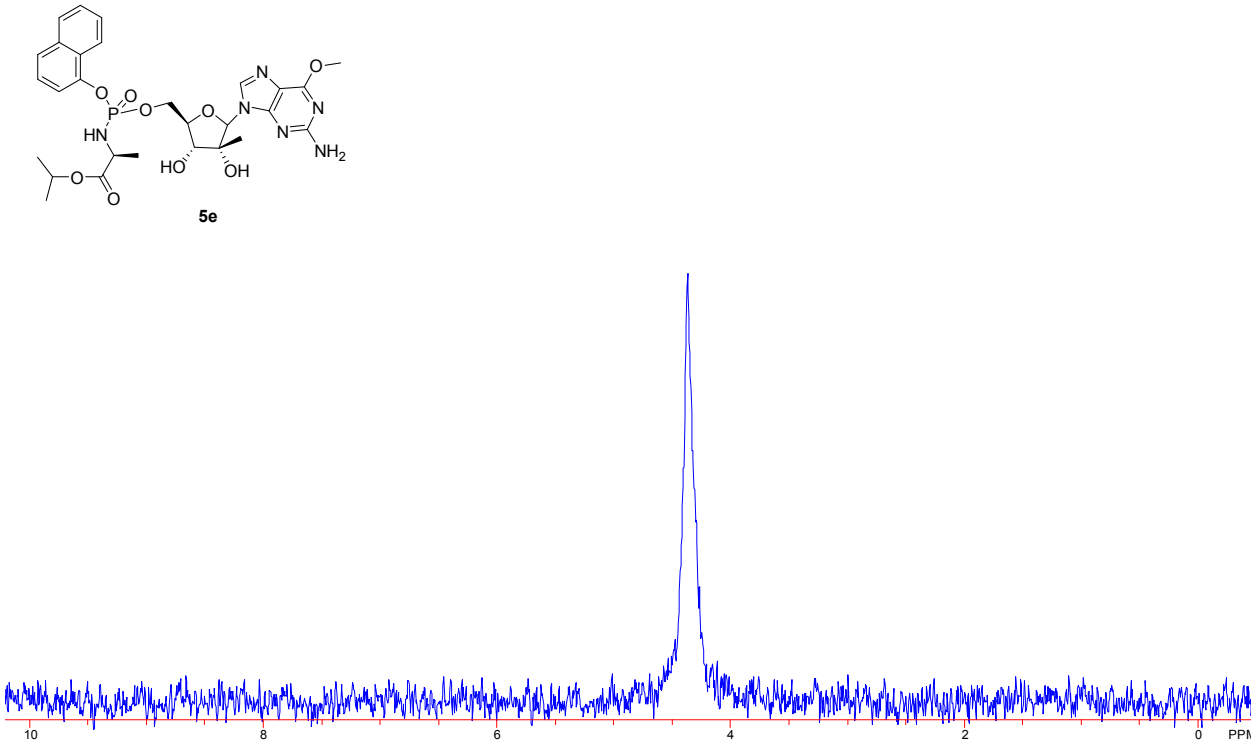


Fig.39. ^{31}PNMR (CD_3OD, 202 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α-napthyl-(i*so*propoxy-*L* -alaninyl)] phosphate **5e** (*R*p : *S*p dr 1:4.5).

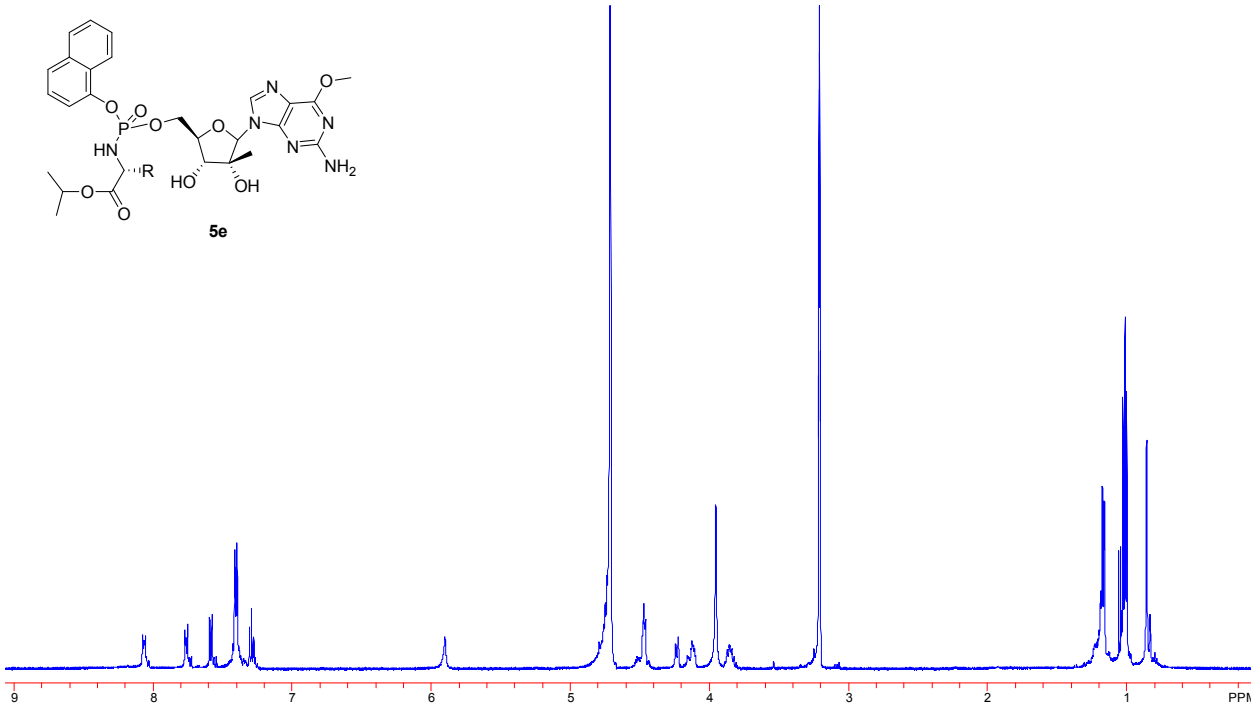


Fig.40. ^{1}HNMR (CD_3OD, 500 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α-napthyl-(i*so*propoxy-*L* -alaninyl)] phosphate **5e** (*R*p : *S*p dr 1:4.5).

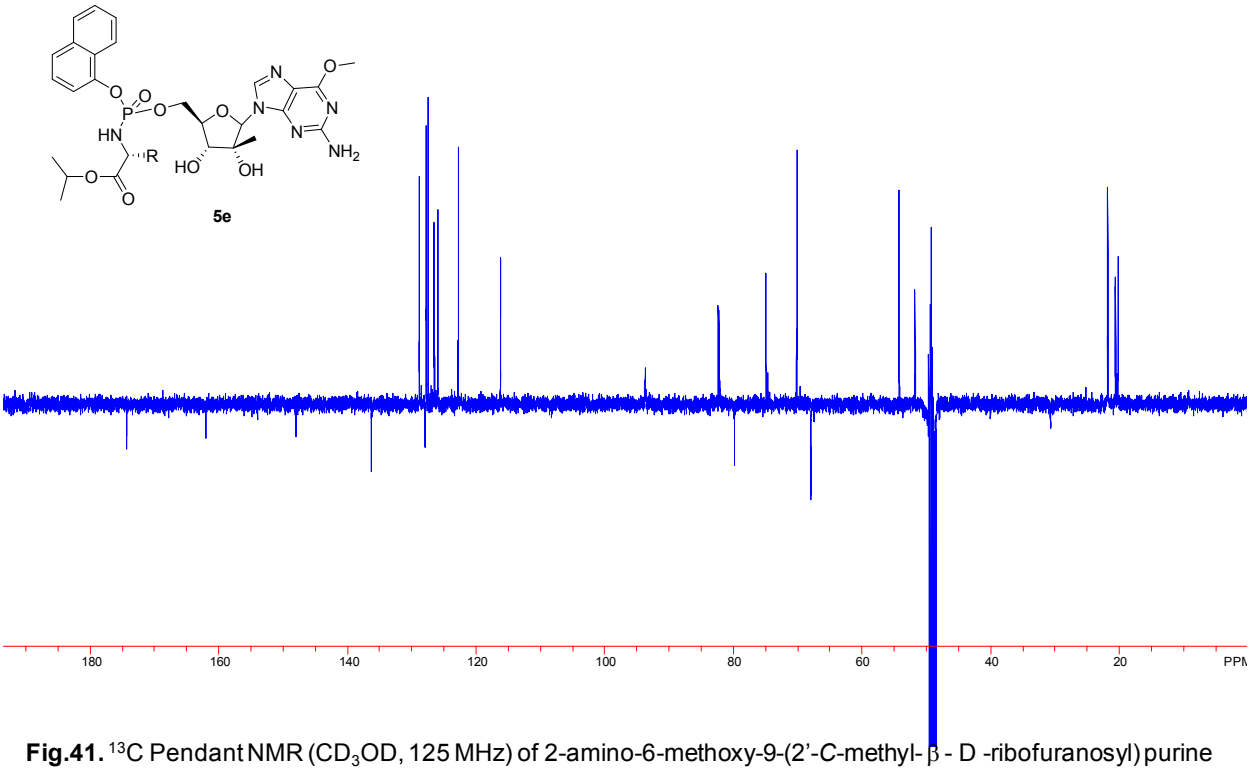


Fig.41. ^{13}C Pendant NMR (CD_3OD, 125 MHz) of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α-napthyl-(i*so*propoxy-*L* -alaninyl)] phosphate **5e** (*R*p : *S*p dr 1:4.5).

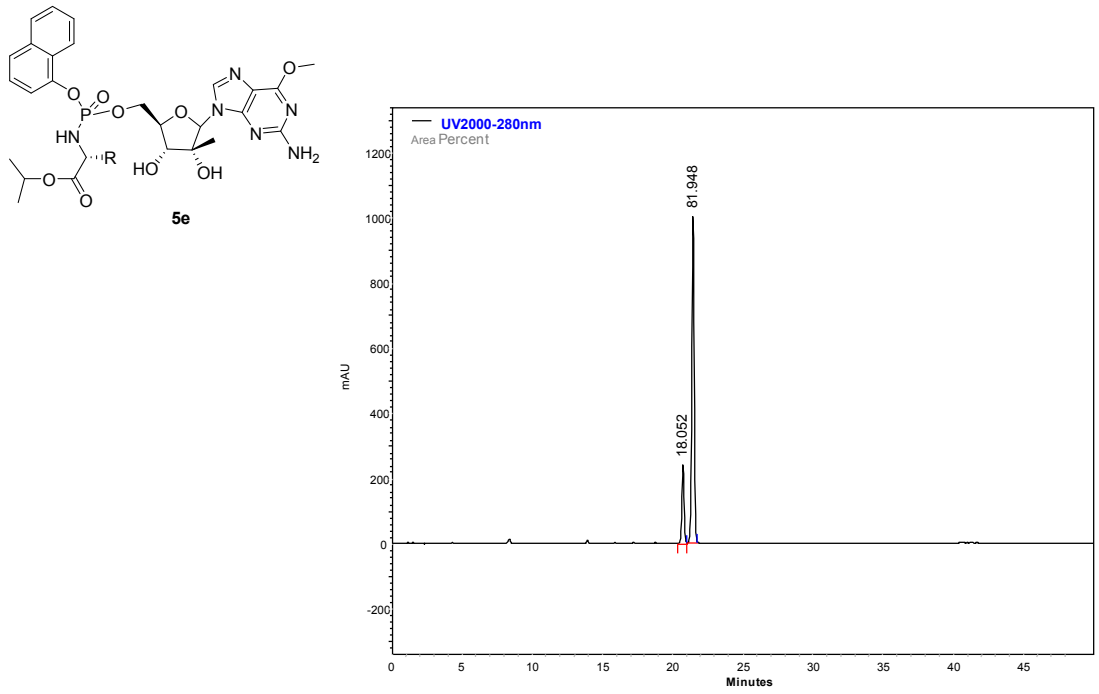


Fig.42. HPLC trace of 2-amino-6-methoxy-9-(2'-*C*-methyl- β - D -ribofuranosyl) purine 5'-*O*-[α-napthyl-(i*so*propoxy-*L* -alaninyl)] phosphate **5e** (*R*p : *S*p dr 1:4.5).

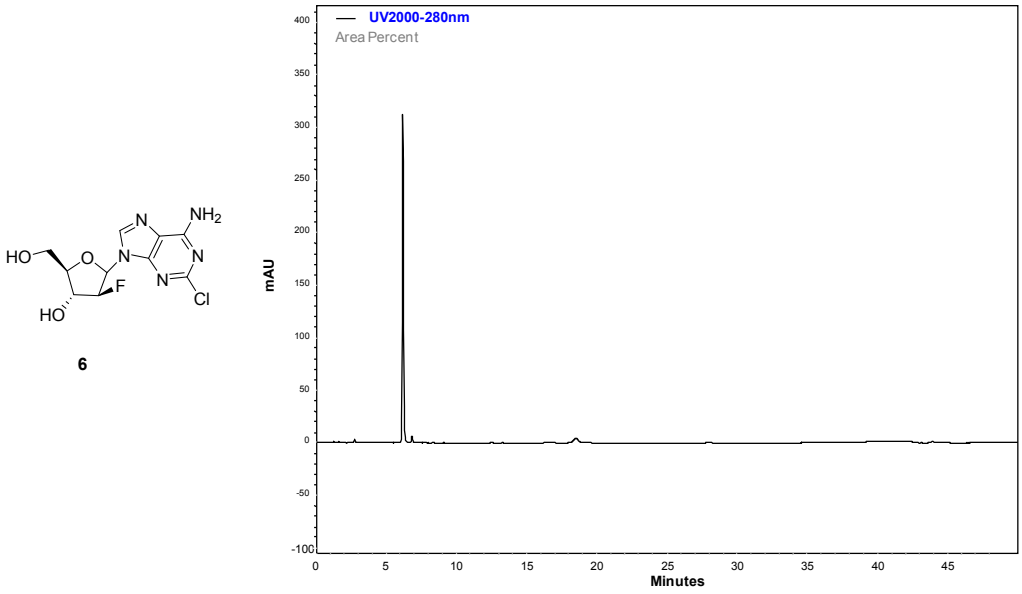


Fig.43. HPLC trace of 2-chloro-6-amino-9-(2'-fluoro-β - D -arabinofuranosyl) purine **3**

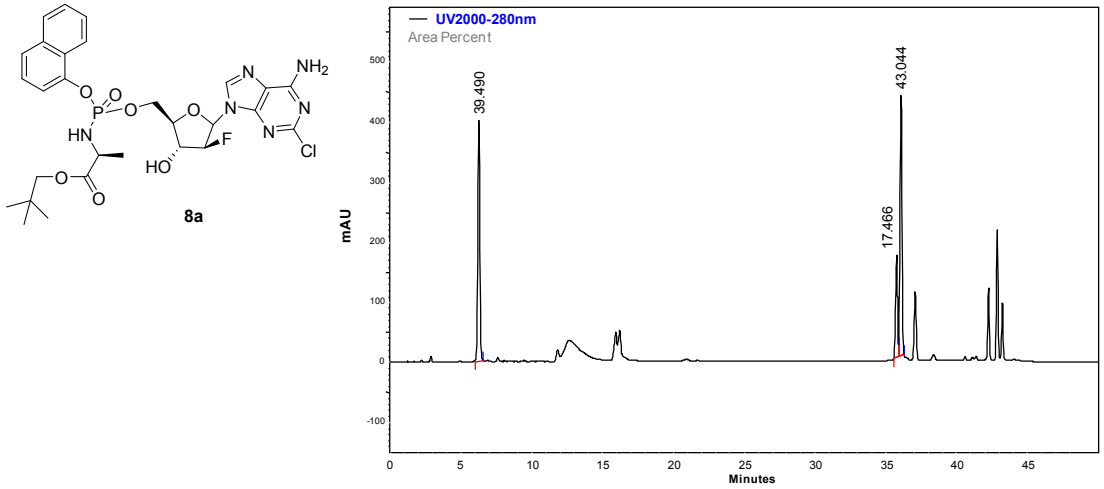


Fig.44. HPLC trace of **8a**, crude reaction mixture (Scheme 3).

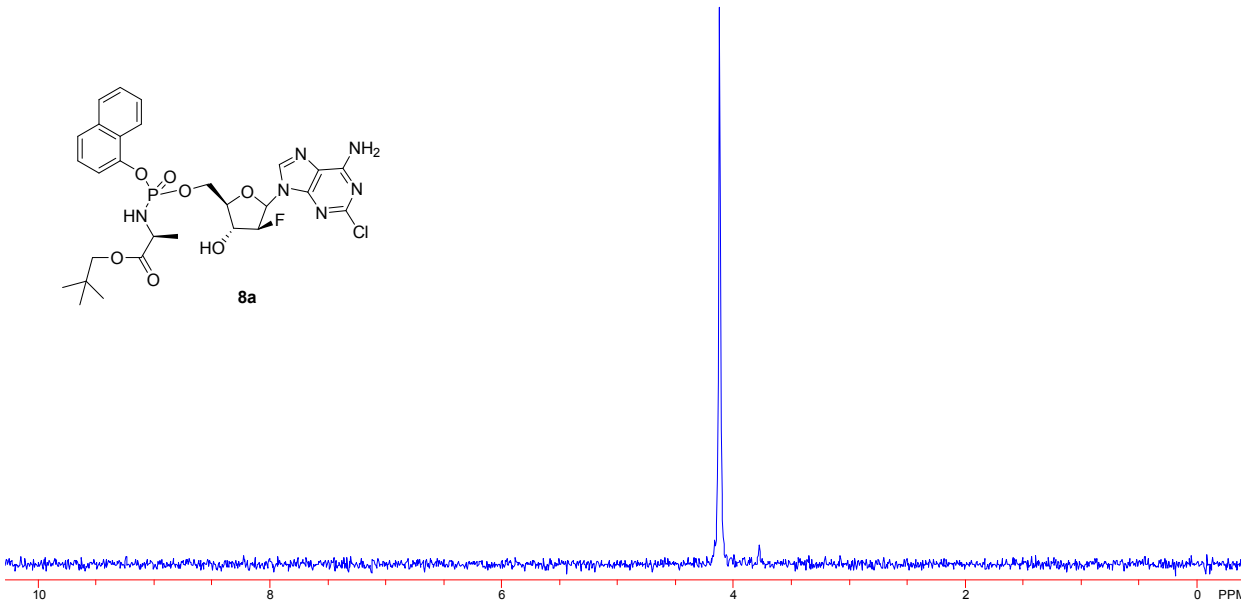


Fig.45. ^{13}PNMR (CD_3OD, 202 MHz) trace of 2-chloro-6-amino-9-(2'-fluoro-β-D-arabinofuranosyl) purine 5'-*O*-[α-napthyl-(2,2-dimethylpropoxy-*L*-alaninyl)] phosphate **8a**.

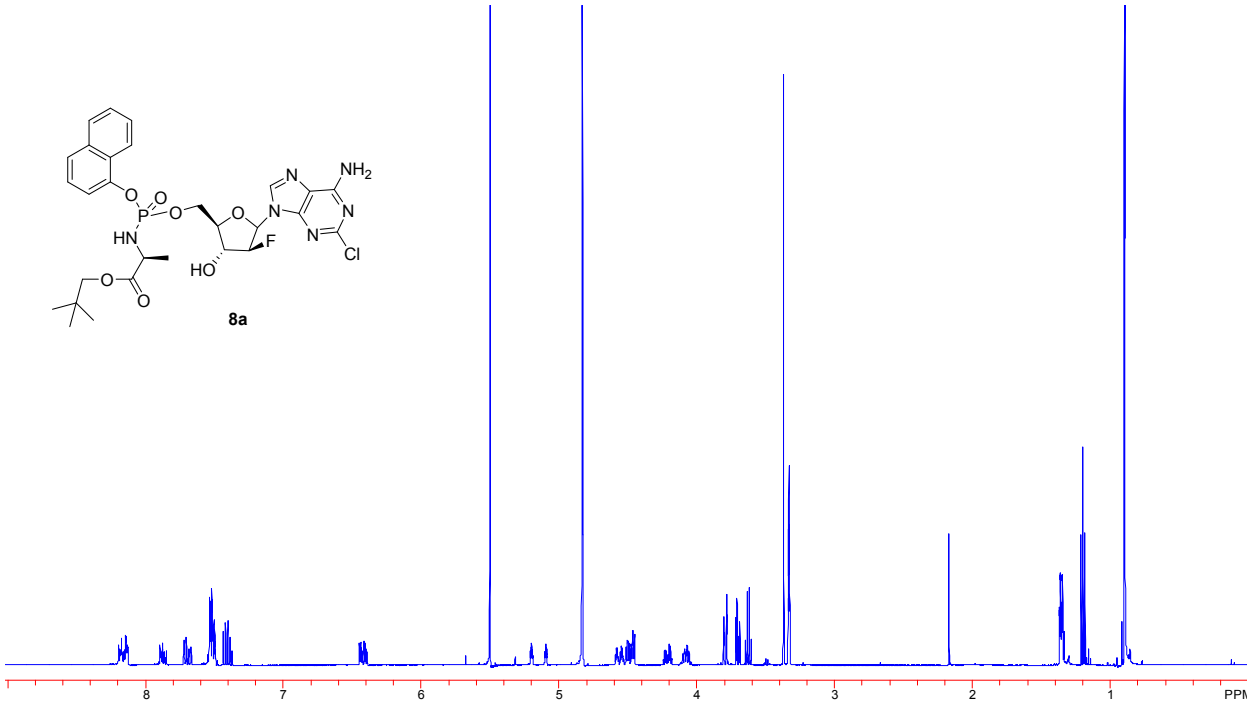


Fig.46. ^{1}HNMR (CD_3OD, 500 MHz) of 2-chloro-6-amino-9-(2'-fluoro-β-D-arabinofuranosyl) purine 5'-*O*-[α-napthyl-(2,2-dimethylpropoxy-*L*-alaninyl)] phosphate **8a**.

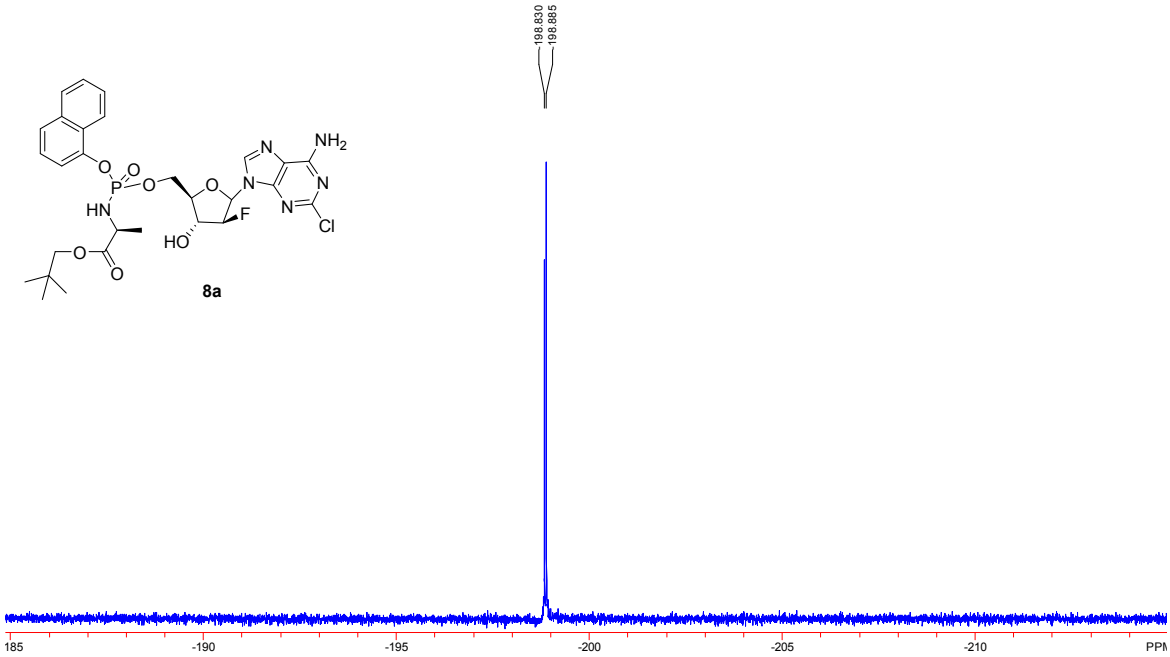


Fig.47. ^{19}F-NMR (CD_3OD, 470 MHz) of 2-chloro-6-amino-9-(2'-fluoro-β-D -arabinofuranosyl) purine 5'-*O*-[α-napthyl-(2,2-dimethylpropoxy-*L* -alaninyl)] phosphate **8a**.

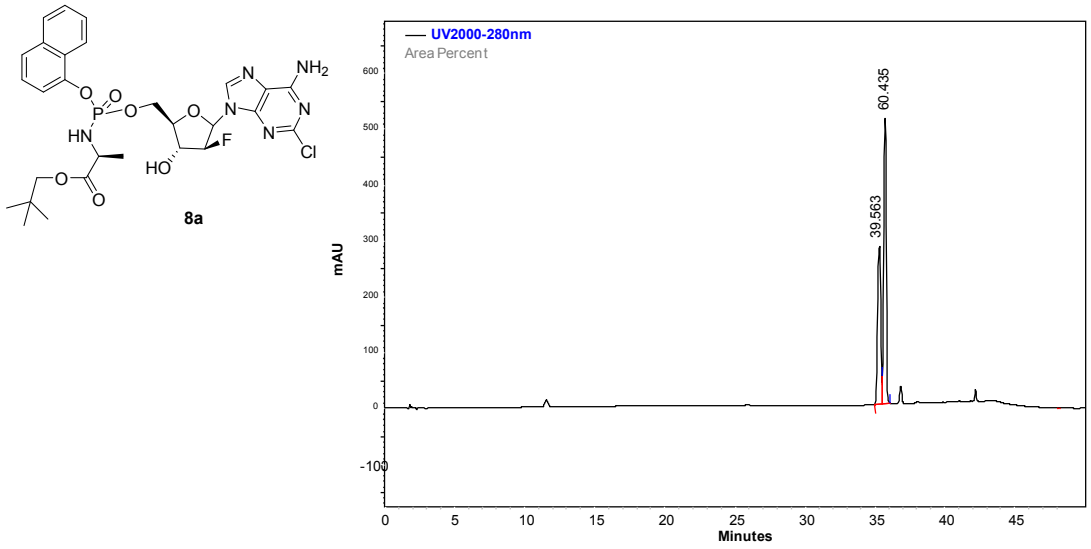


Fig.48. HPLC trace of 2-chloro-6-amino-9-(2'-fluoro-β-D -arabinofuranosyl) purine 5'-*O*-[α-napthyl-(2,2-dimethylpropoxy-*L* -alaninyl)] phosphate **8a.**

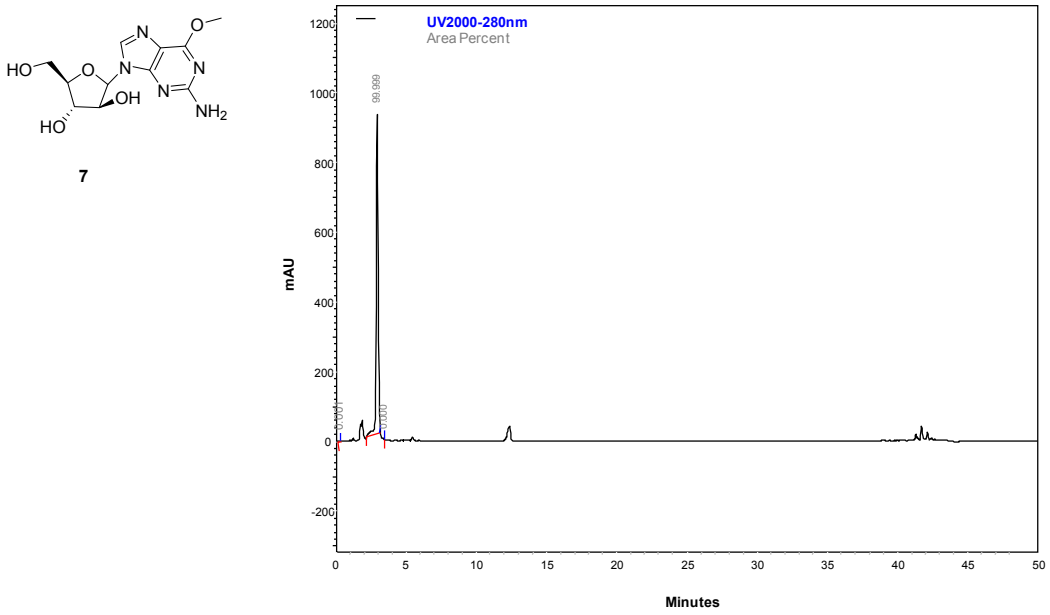


Fig.49. HPLC trace of 2-amino-6-methoxy-9-(β - D -arabinofuranosyl) purine **7**

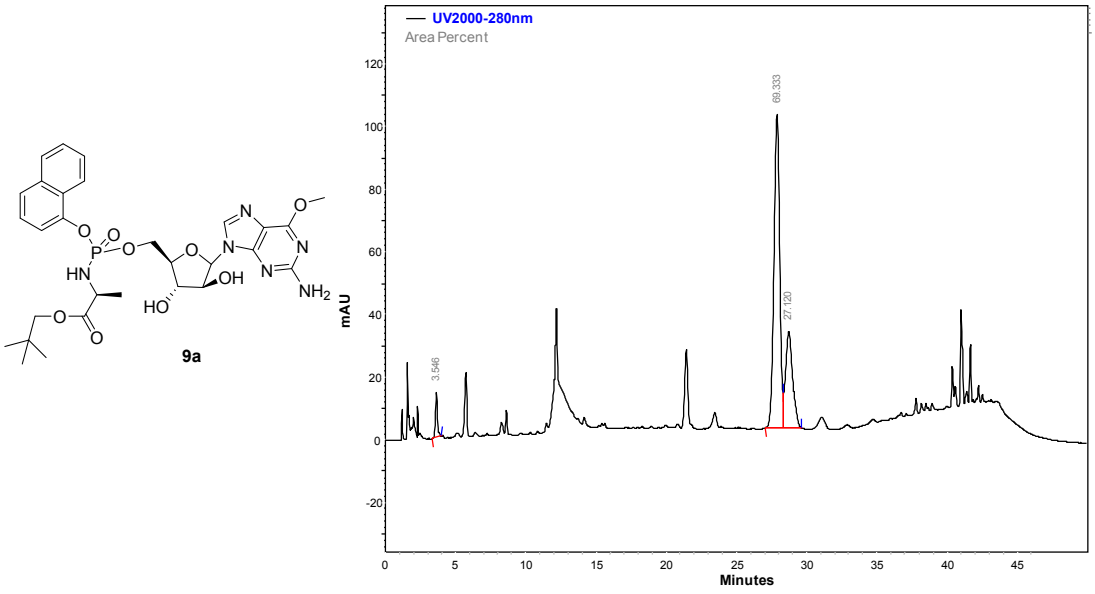


Fig.50. HPLC trace of **9a,** crude reaction mixture (Scheme 3).

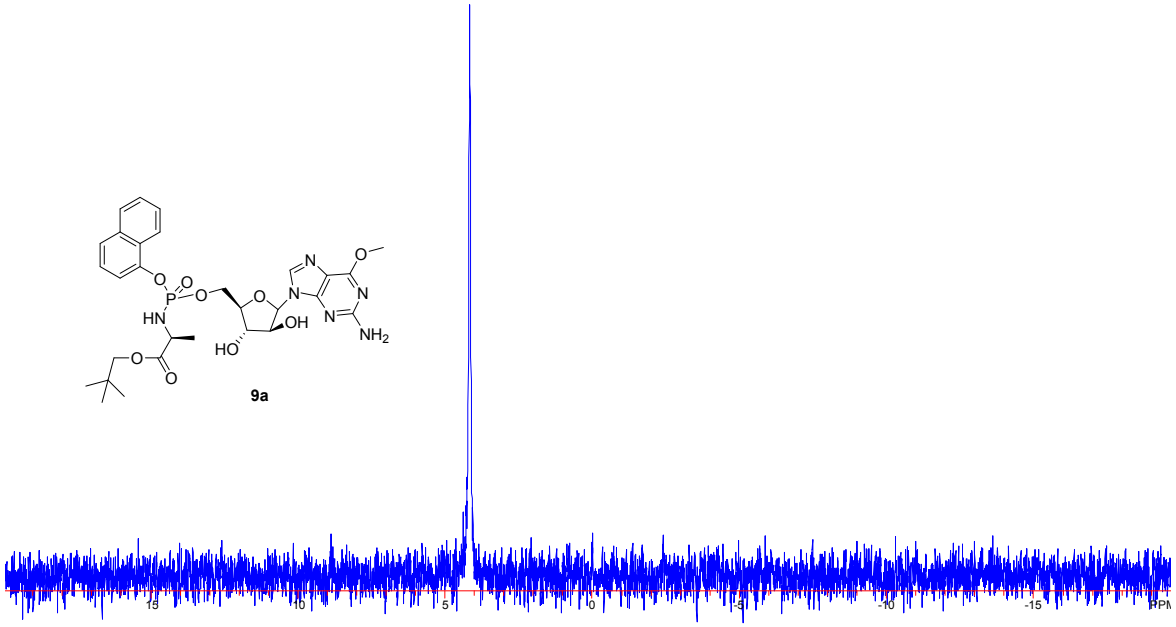


Fig.51. ^{31}PNMR (CD_3OD, 202MHz) of 2-amino-6-methoxy-9-(β - D -arabinofuranosyl) purine 5'-*O*-[α-napthyl-(2,2-dimethylpropoxy-*L* -alaninyl)] phosphate **9a.**

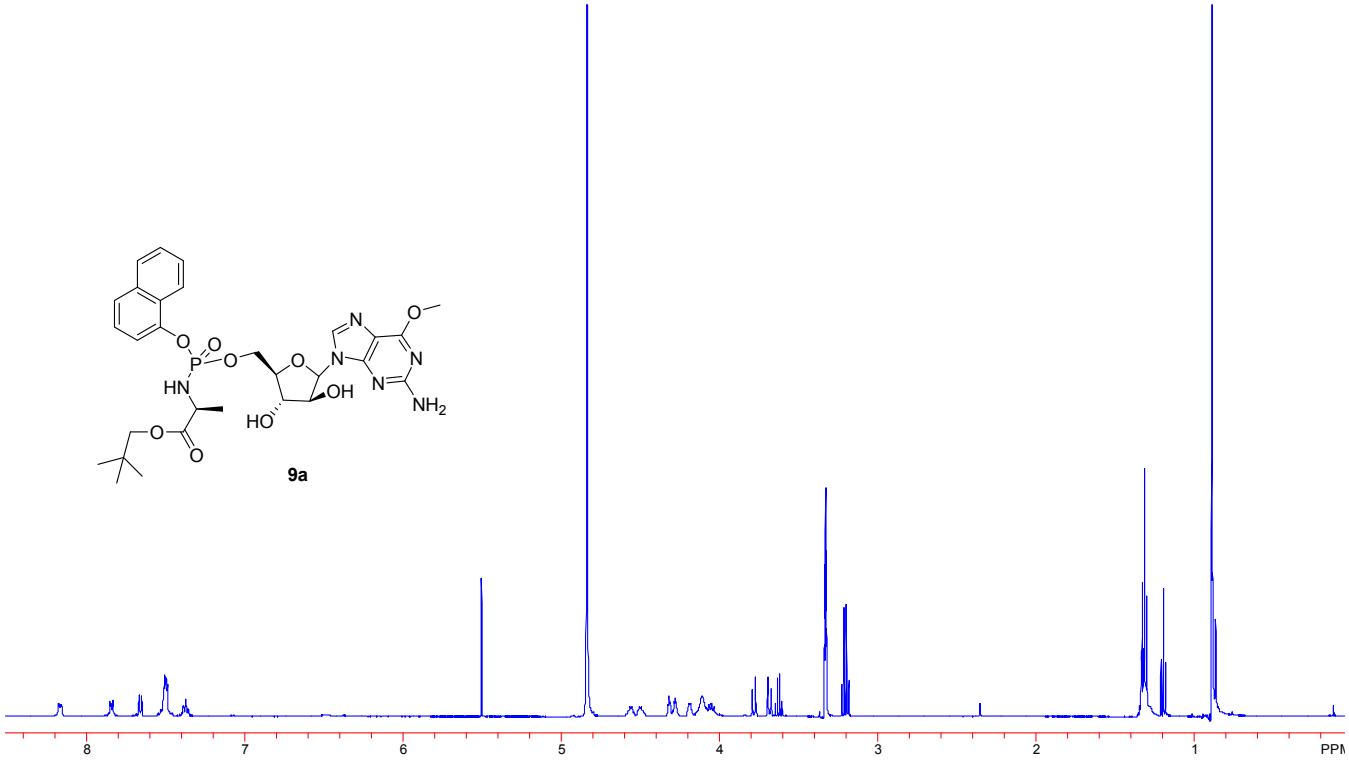


Fig.52. ^{1}HNMR (CD_3OD, 500 MHz) of 2-amino-6-methoxy-9-(β - D -arabinofuranosyl) purine 5'-*O*-[α-napthyl-(2,2-dimethylpropoxy-*L* -alaninyl)] phosphate **9a**.

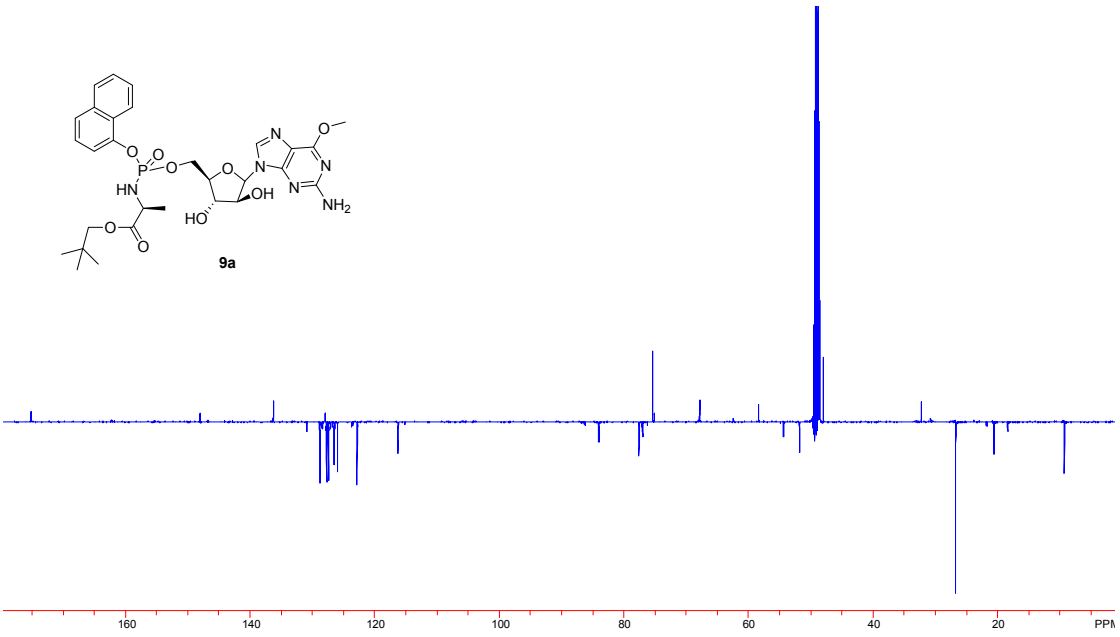


Fig.53. ^{13}C Pendant NMR (CD_3OD, 125 MHz) of 2-amino-6-methoxy-9-(β-D-arabinofuranosyl) purine 5'-*O*-[α-napthyl-(2,2-dimethylpropoxy-*L*-alaninyl)] phosphate **9a.**

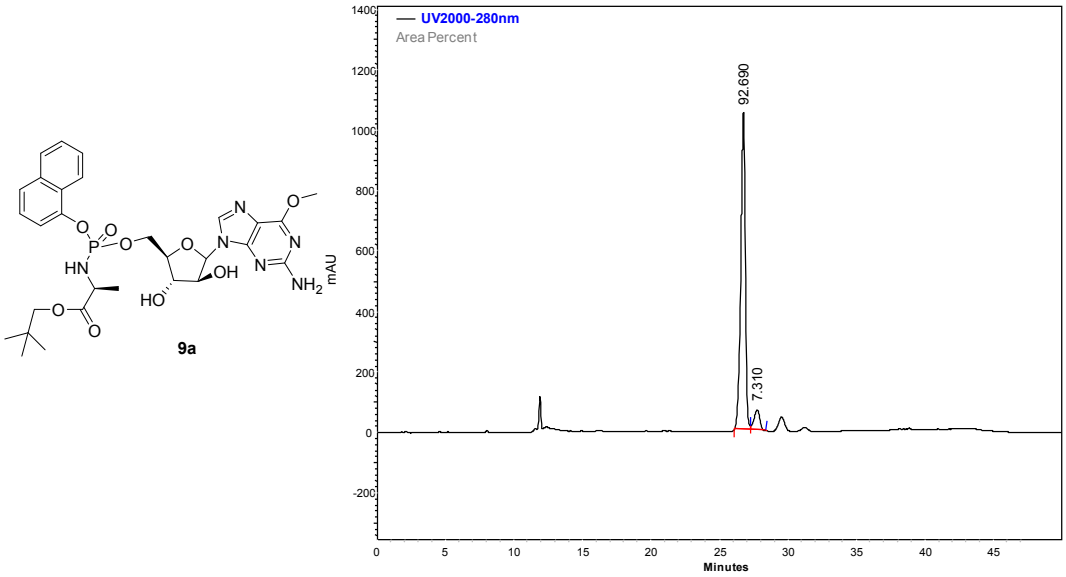


Fig.54. HPLC trace of 2-amino-6-methoxy-9-(β - D -arabinofuranosyl) purine 5'-*O*-[α-napthyl-(2,2-2,2-dimethylpropoxy-*L* -alaninyl)] phosphate **9a.**

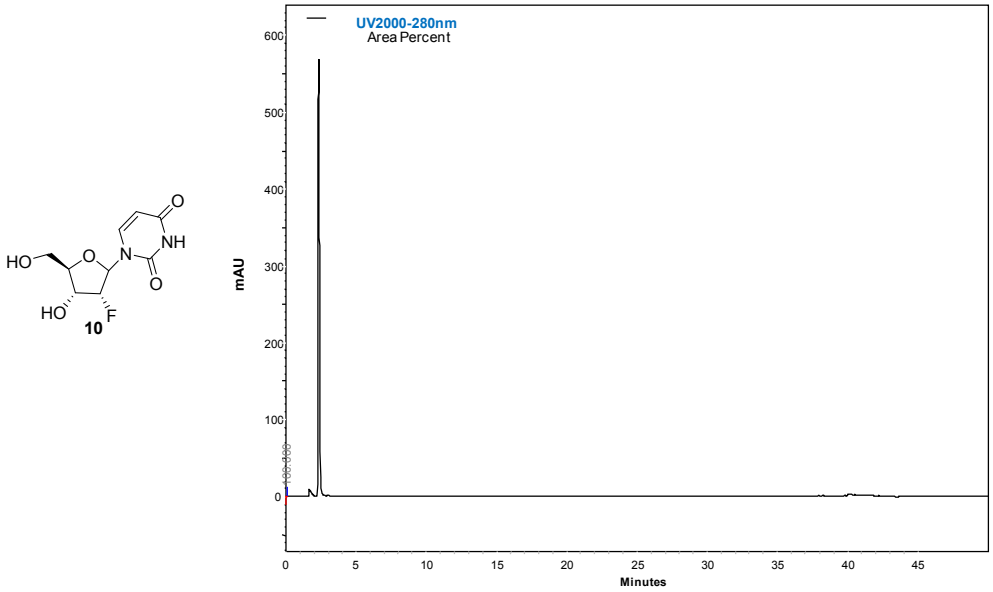


Fig.55 HPLC trace of 2'deoxy-2'fluorouridine **10**

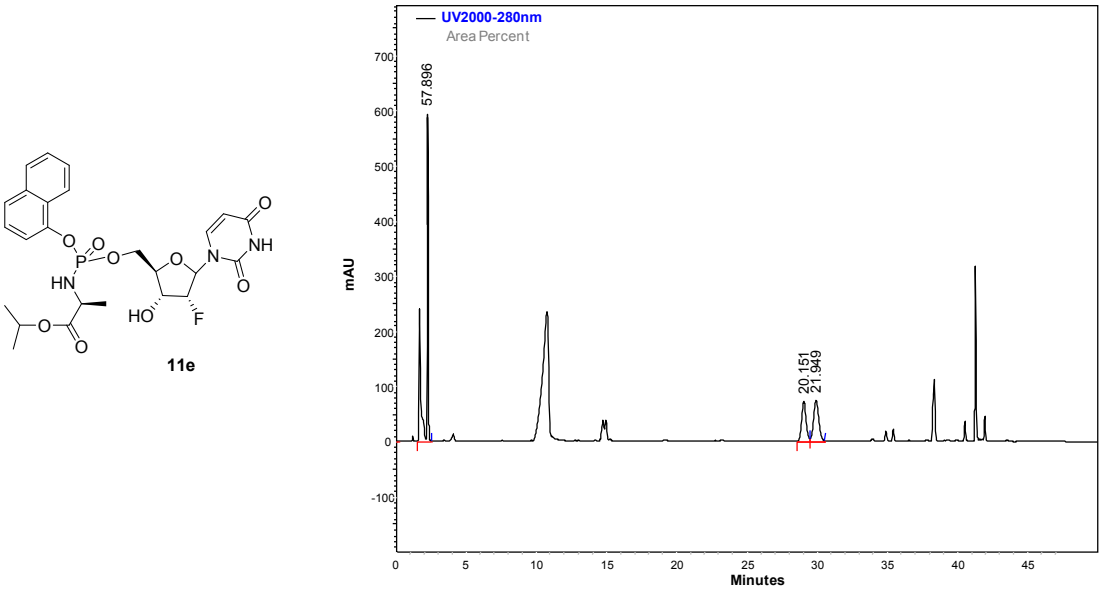


Fig.56 HPLC trace of **11e**, crude reaction mixture (Entry 1, table 3).

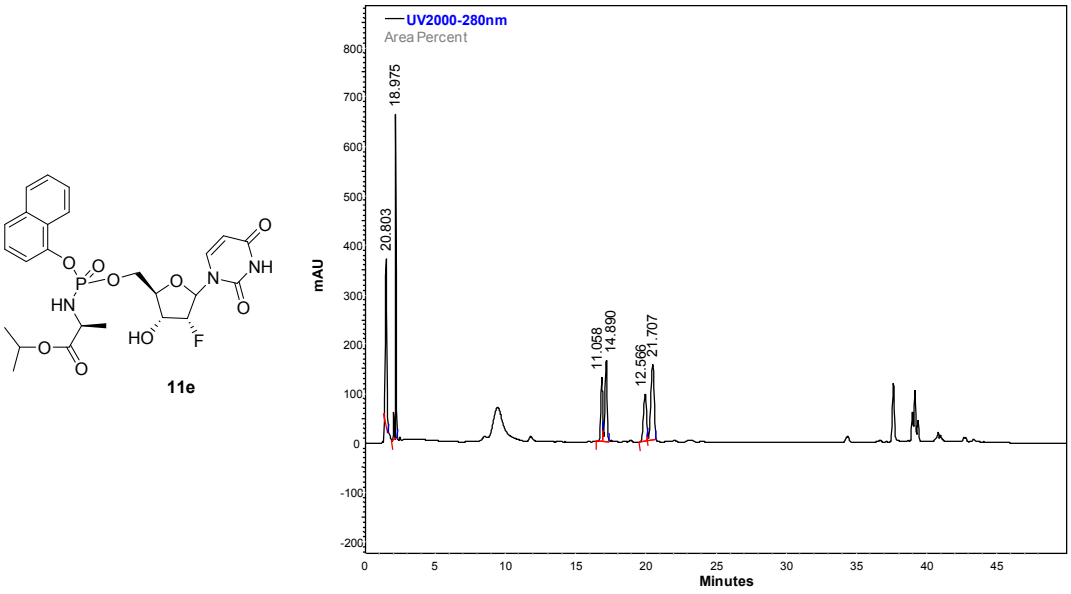


Fig.57. HPLC trace of **11e**, crude reaction mixture (Entry 2, table 3).

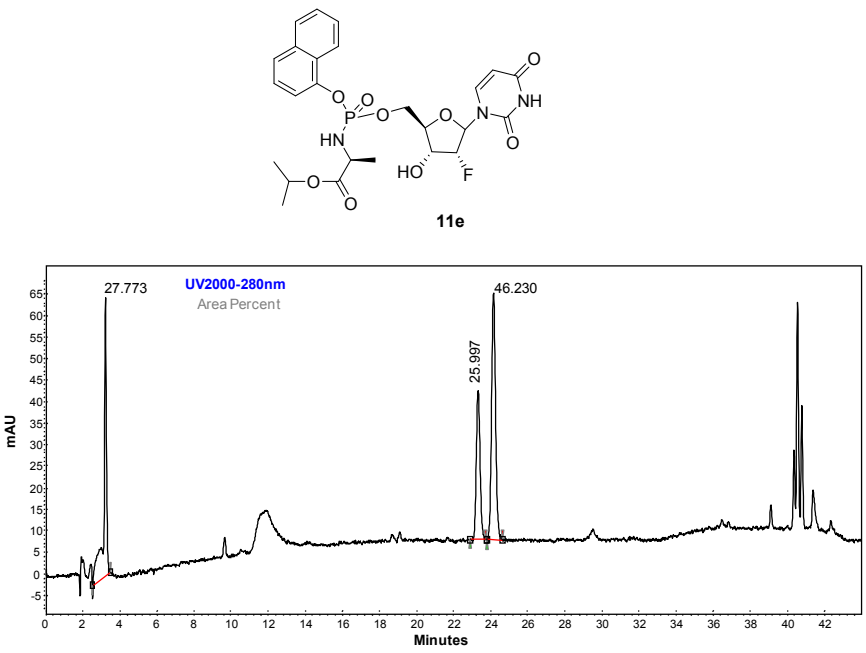


Fig.58. HPLC trace of **11e**, crude reaction mixture (Entry 5, table 3).

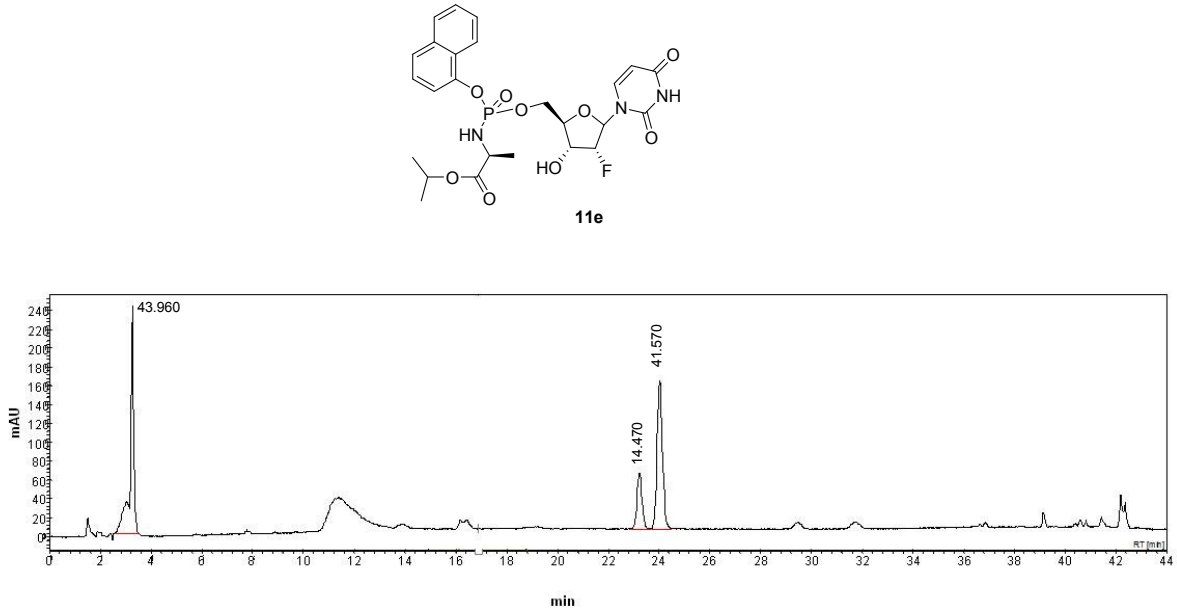


Fig.59. HPLC trace of **11e**, crude reaction mixture (Entry 7, table 3).

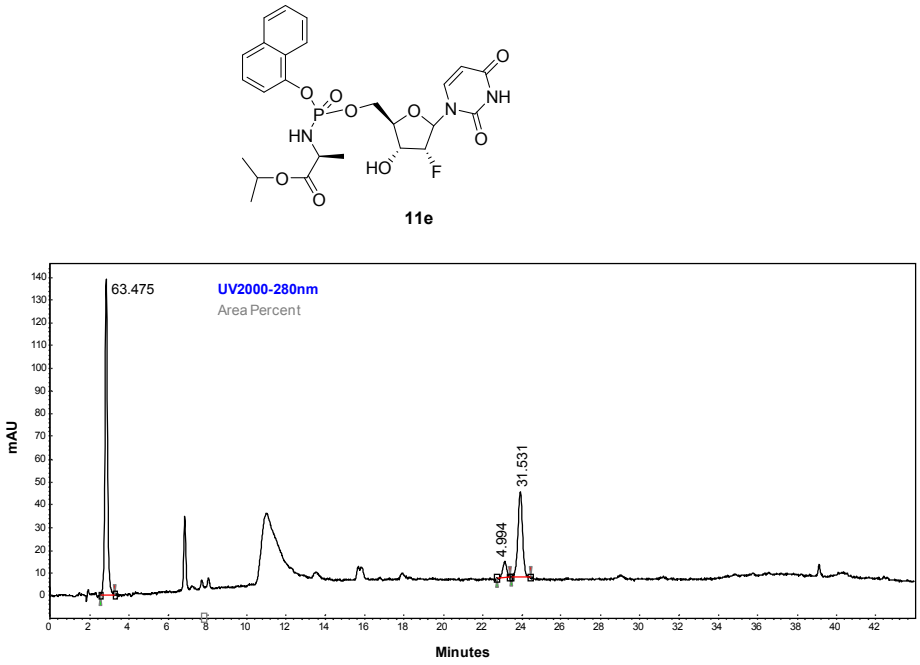


Fig.60. HPLC trace of **11e**, crude reaction mixture (Entry 8, table 3).

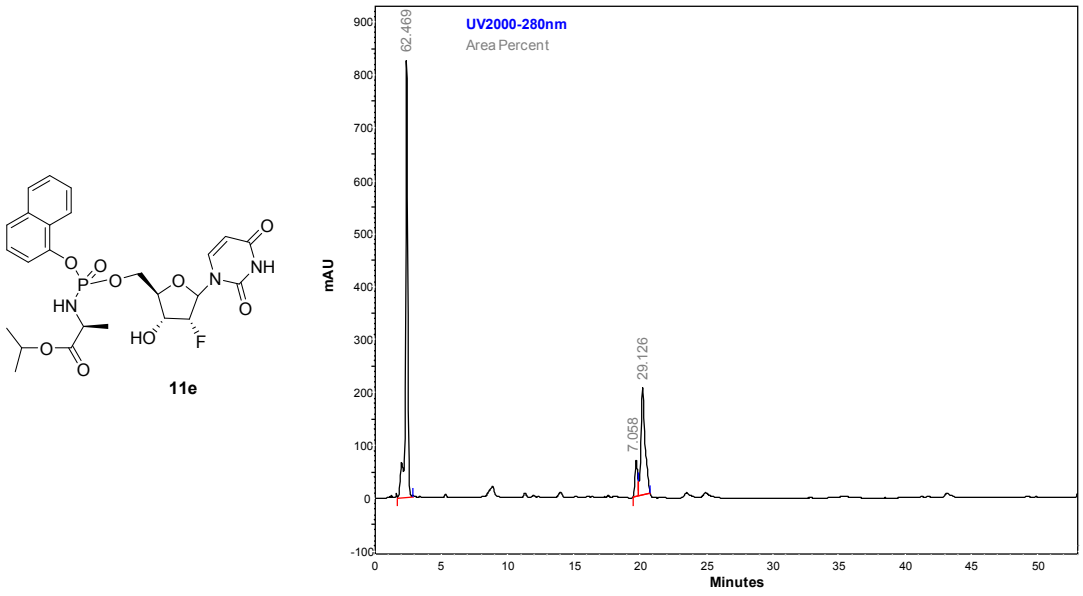


Fig.61. HPLC trace of **11e**, crude reaction mixture (Entry 11, table 3).

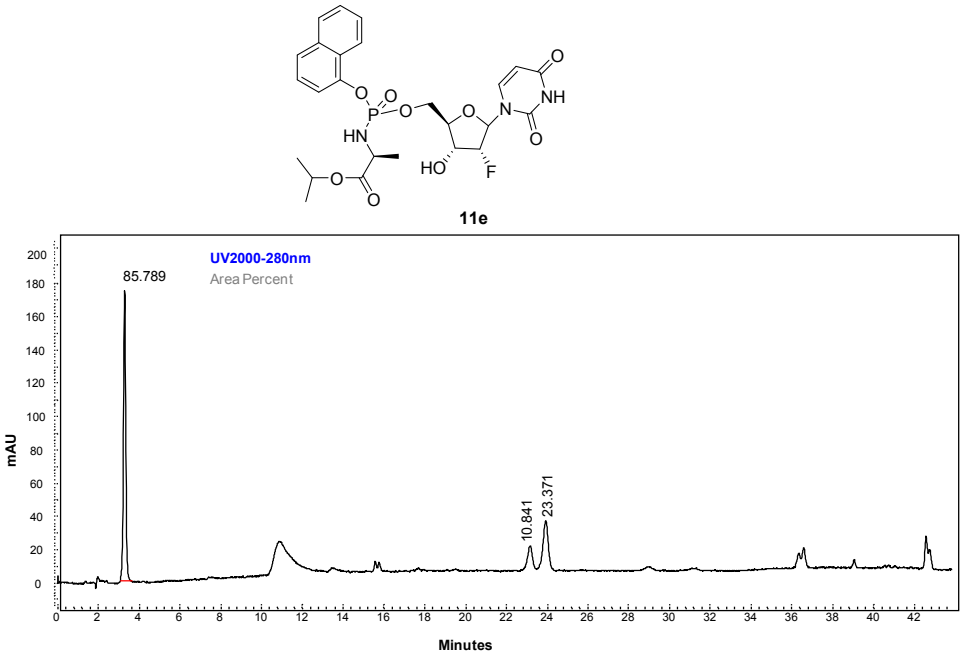


Fig.62. HPLC trace of **11e**, crude reaction mixture (Entry 12, table 3).

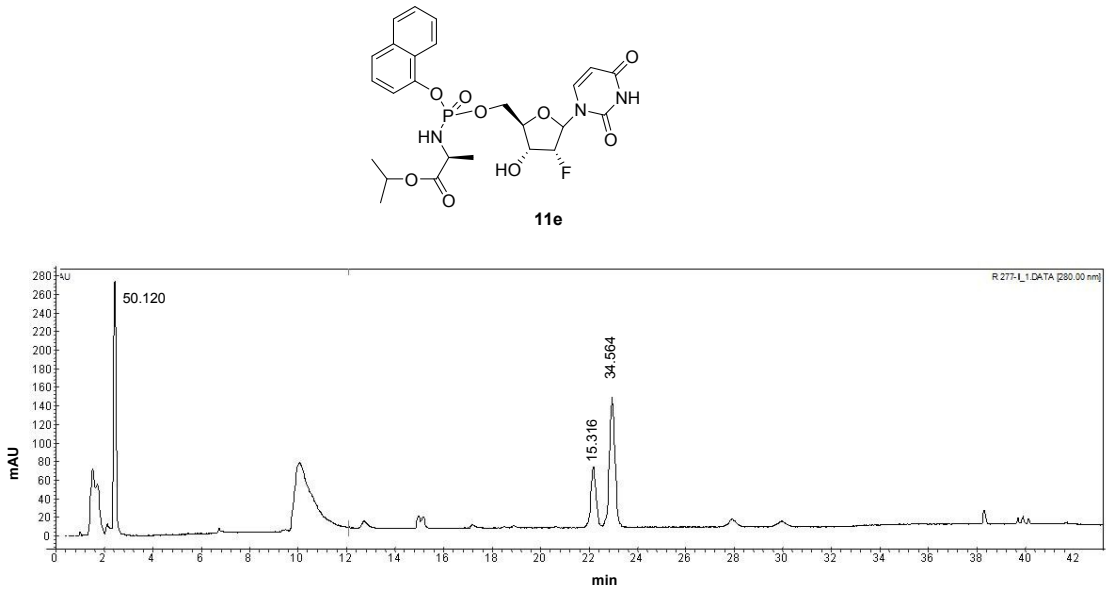


Fig.63. HPLC trace of **11e**, crude reaction mixture (Entry 13, table 3).

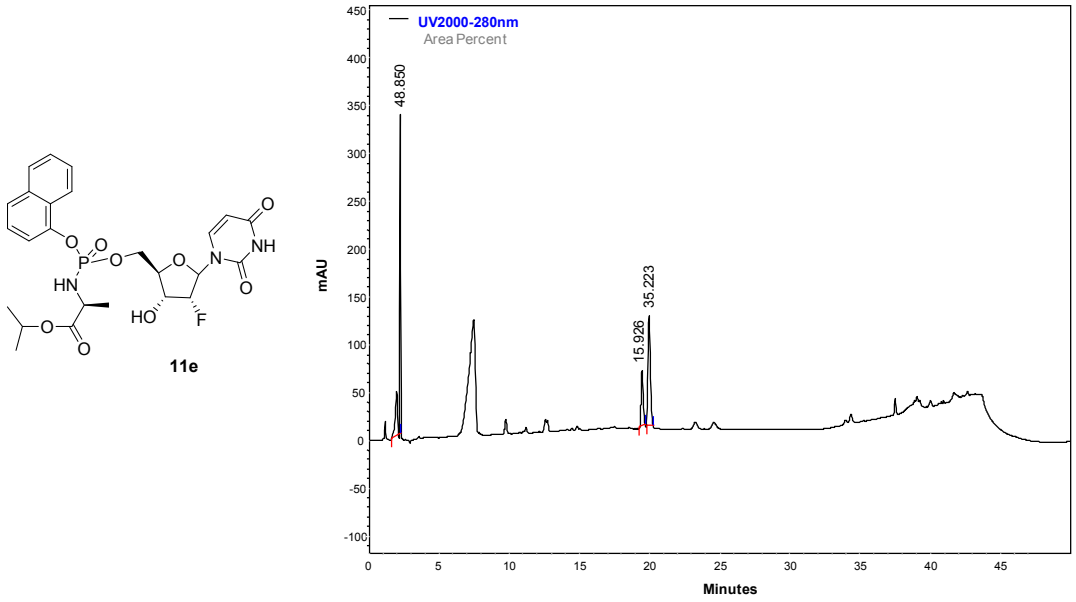


Fig.64. HPLC trace of **11e**, crude reaction mixture (Entry 9, table 3).

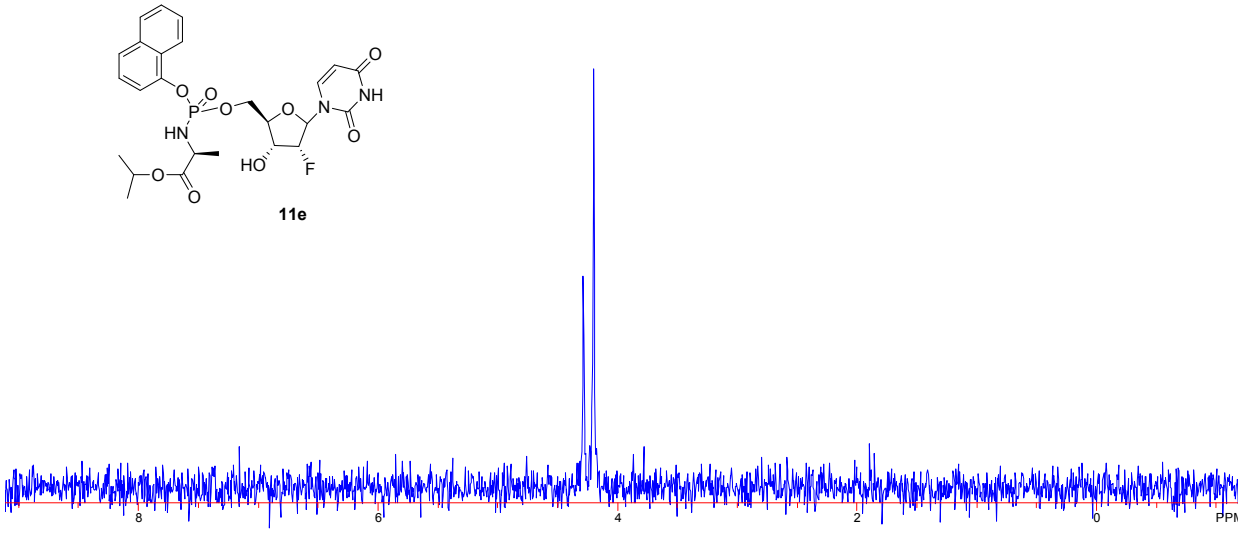


Fig.65. ^{31}PNMR (CD_3OD, 202 MHz) of 2'-fluoro-β-D-ribofuranosyl uridine 5'-*O*-[phenyl-(isopropoxy-*L*-alaninyl)] phosphate **11e.**

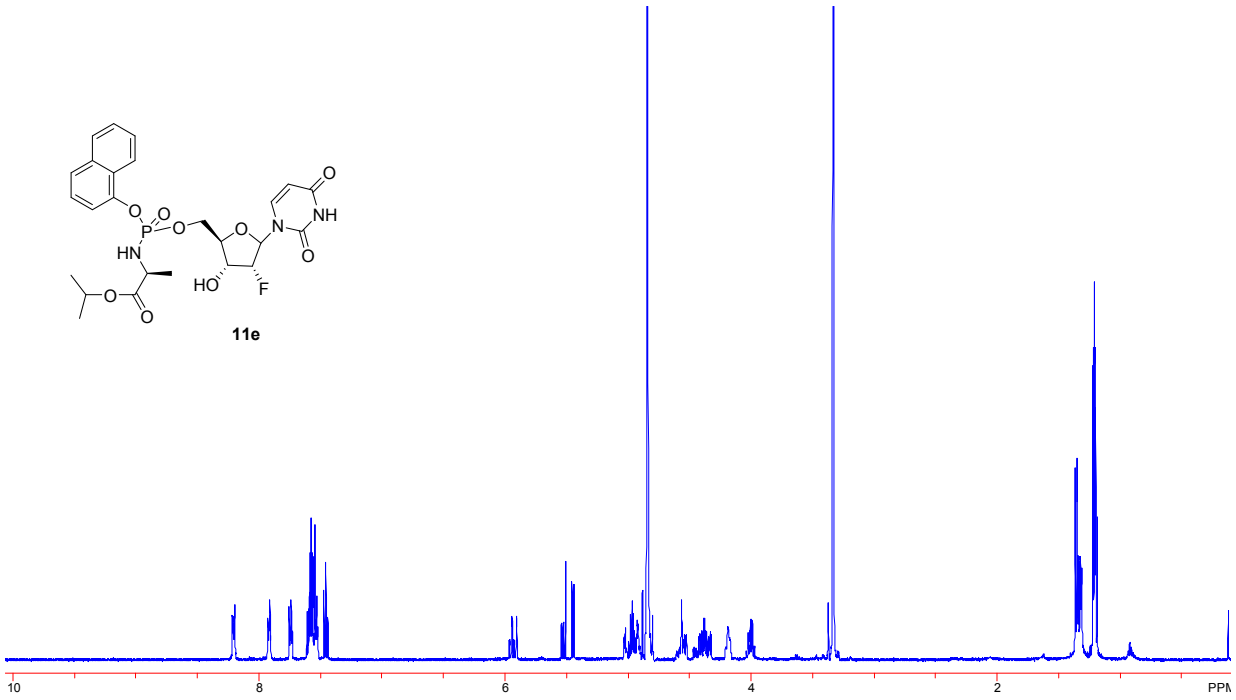


Fig.66. ^{1}HNMR (CD_3OD, 500 MHz) of 2'-deoxy 2'-fluoro- β - D -ribofuranosyl uridine 5'-*O*-[phenyl-(isopropoxy-*L* -alaninyl)] phosphate **11e .**

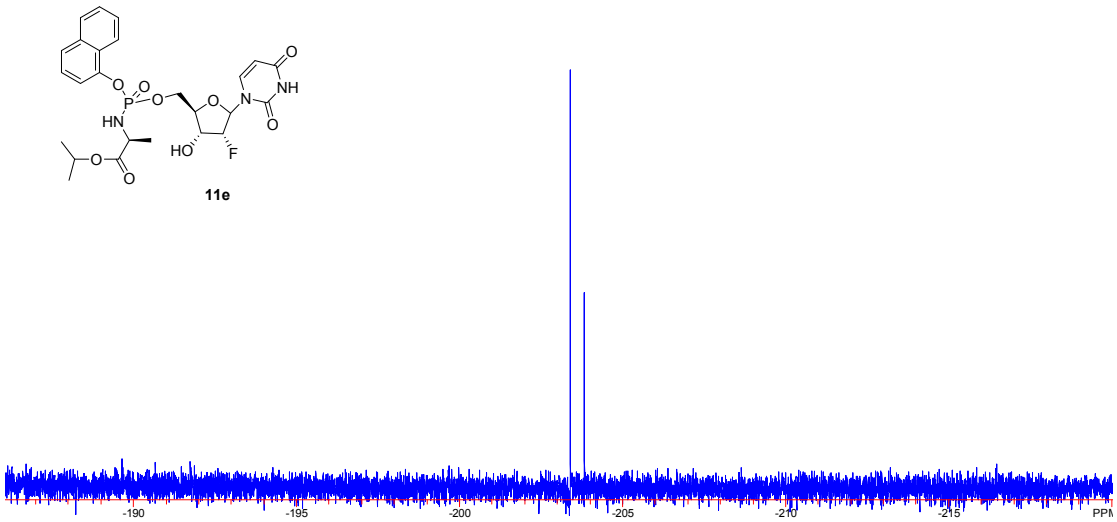


Fig.67. ^{19}FNMR (CD_3OD, 470 MHz) of 2'-deoxy 2'-fluoro- β - D -ribofuranosyl uridine 5'-*O*-[phenyl-(isopropoxy-*L* -alaninyl)] phosphate **11e .**

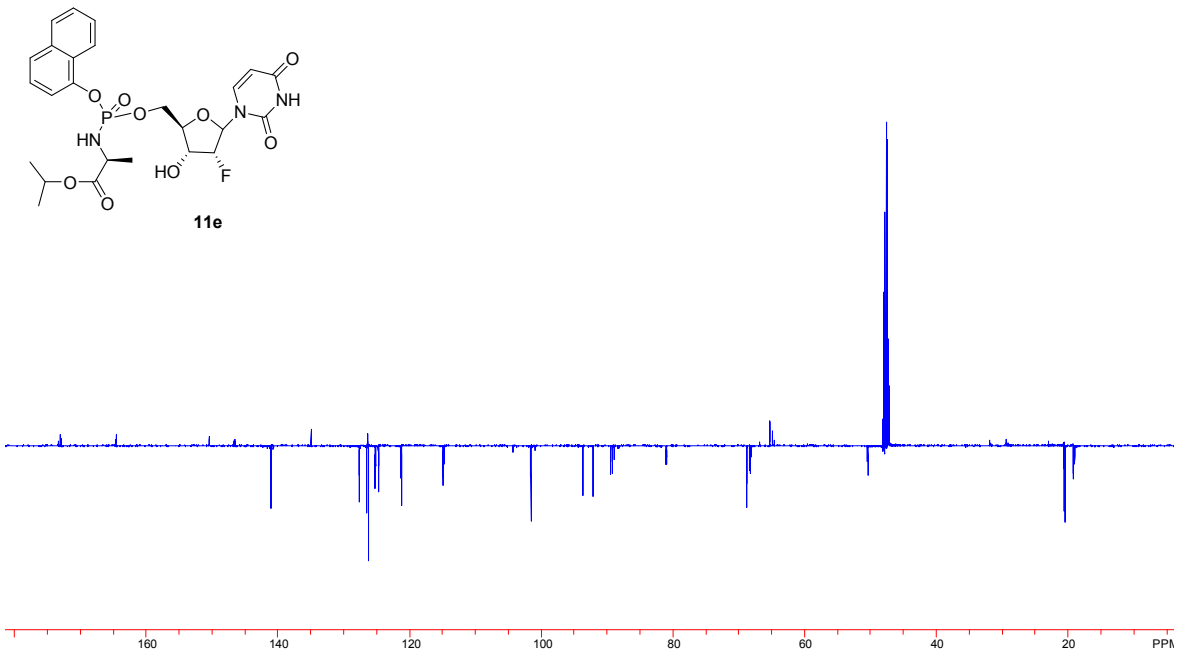


Fig.68. ^{13}C Pendant NMR (CD_3OD, 125 MHz) of 2'-deoxy 2'-fluoro- β - D -ribofuranosyl uridine 5'-*O*-[phenyl-(isopropoxy-*L* -alaninyl)] phosphate **11e**.

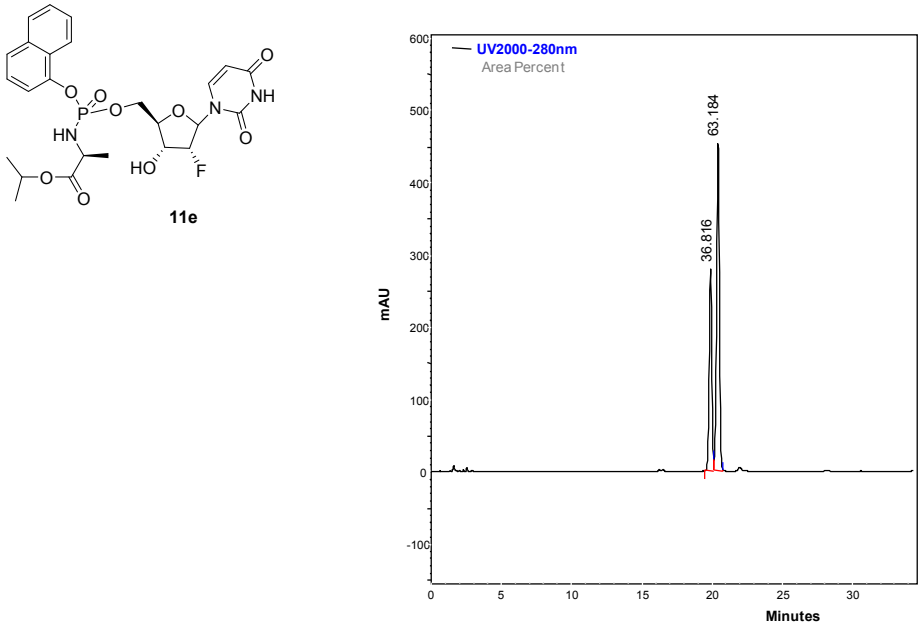


Fig.69. HPLC trace of 2' deoxy-2'-fluoro- β - D -ribofuranosyl uridine 5'-*O*-[phenyl-(isopropoxy-*L* -alaninyl)] phosphate **11e.**

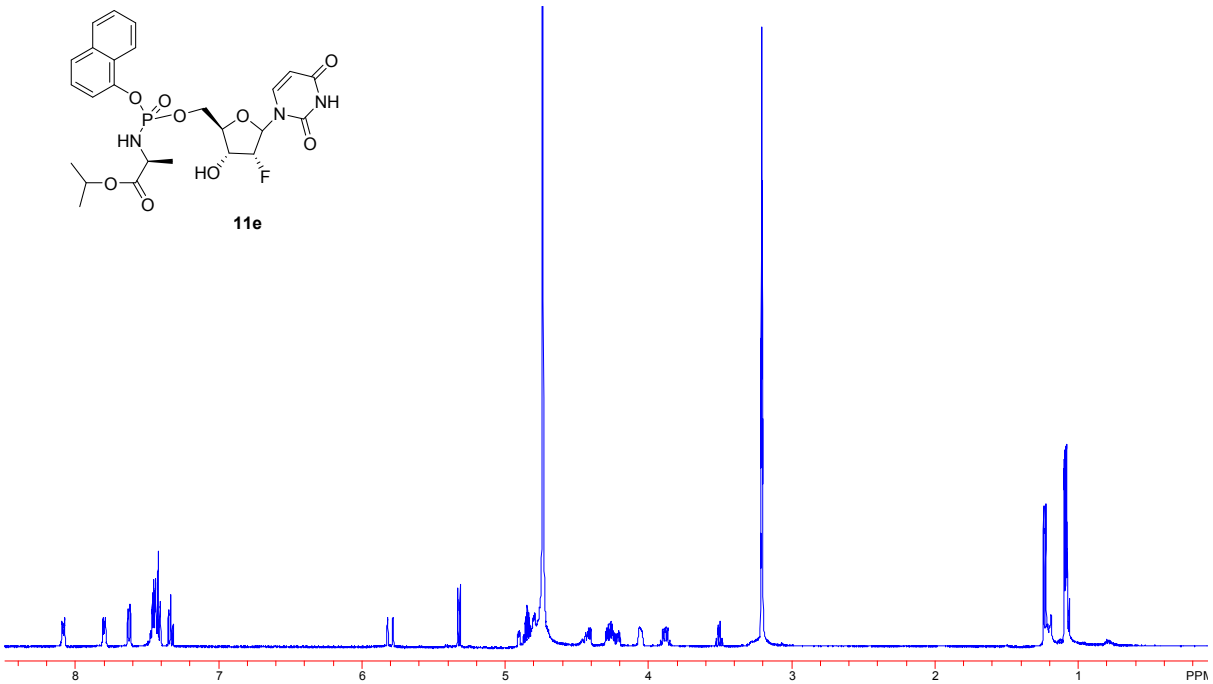


Fig.70. ^{1}HNMR (CD_3OD, 500 MHz) of 2'-fluoro- β - D -ribofuranosyl uridine 5'-*O*-[phenyl-(isopropoxy-*L* -alaninyl)] phosphate **11e** (dr 2:98).

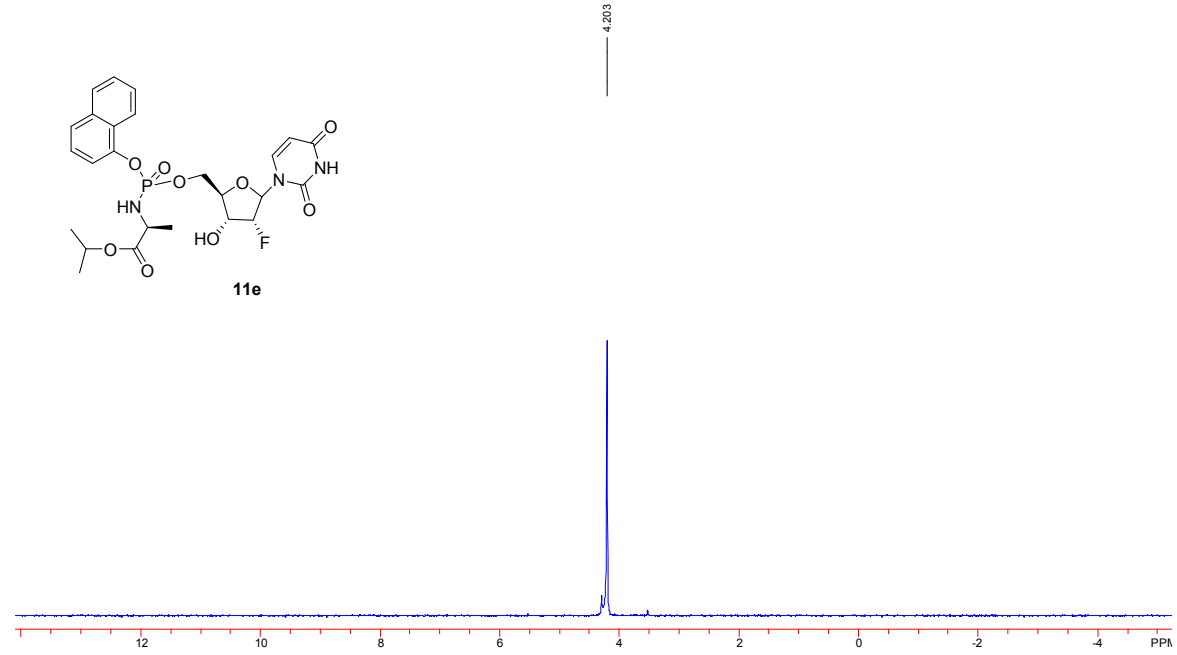


Fig.71. ^{31}PNMR (CD_3OD, 202 MHz) of 2'-fluoro- β - D -ribofuranosyl uridine 5'-*O*-[phenyl-(isopropoxy-*L* -alaninyl)] phosphate **11e** (dr 2:98).

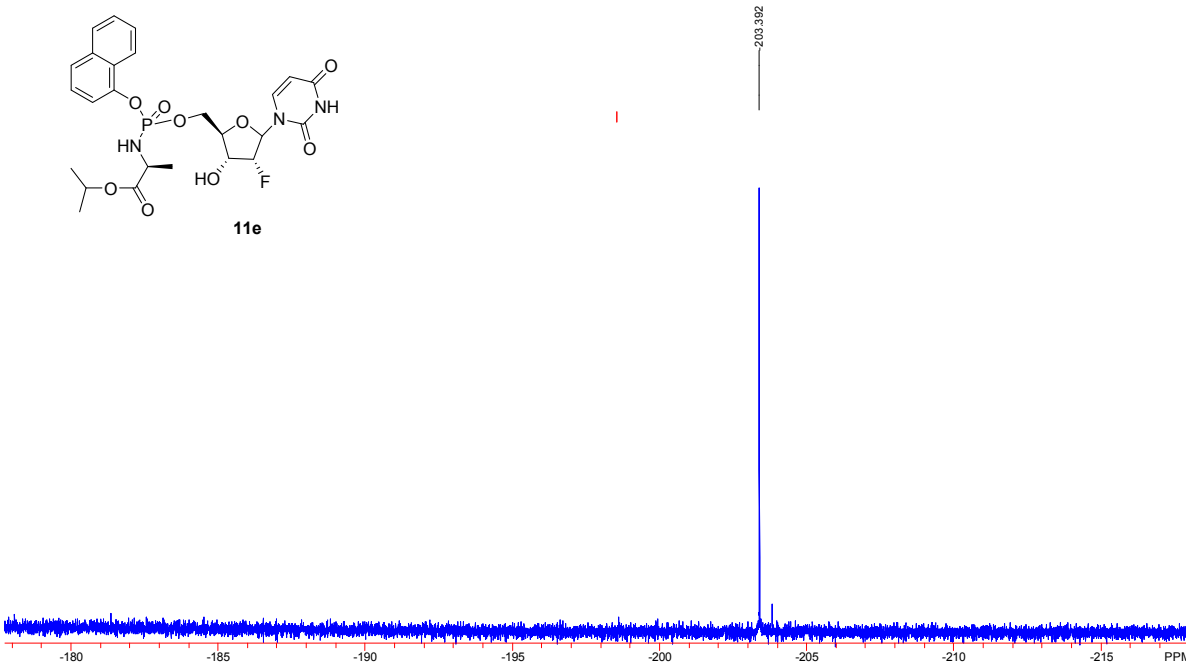


Fig.72. ^{19}FNMR (CD_3OD, 470 MHz) of 2'-fluoro- β - D -ribofuranosyl uridine 5'-*O*-[phenyl-(isopropoxy-*L* -alaninyl)] phosphate **11e** (dr 2:98).