Supporting information

Diverse Synthetic Approaches Towards C1′-Branched Acyclic Nucleoside Phosphonates

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EXPERIMENTAL PART

General information

All solvents and reagents were purchased from commercial suppliers and were not further purified. Reactions were monitored using thin-layer chromatography (TLC) on silica gel 60 F254 plates (Merck KGaA, Germany) and/or ultra-high performance liquid chromatography with mass spectrometer (UPLC-MS Acquity Waters, USA, H-Class Core System with Waters Acquity UPLC BEH C18 1.7 μm, 2.1 × 100 mm column, Waters Acquity UPLC PDA detector, and mass spectrometer Waters SQD2, linear gradient elution with 0–100 % MeCN in water with 0.1% HCOOH). The column and flash chromatography (ISCO Teledyne, USA) were performed on 60A silica gel (Acros Organics, Belgium). Solvents were evaporated using rotary evaporator at 40 – 70 °C/2 mbar. Microwave (MW) heating was performed using microwave reactor Discover (CEM, USA) with the Explorer module. The reactor frequency was 2.45 GHz and radiation power up to 300 W. Reactions were stirred in the reactor. Temperature and pressure were monitored by an infrared temperature sensor (outside the reaction mixture) and CEM Explorer pressure sensor, respectively. NMR spectra were measured using Bruker Avance III HD 400 MHz equipped with Prodigy cryoprobe operating at 9.39 T. ^{1}H, ^{13}C, ^{19}F, and ^{31}P spectra were acquired at 400, 100, 377, and 162 MHz, respectively. Two-dimensional spectra ^{1}H^{1}H COSY, ^{1}H^{13}C HSQC, ^{1}H^{13}C HMBC were acquired for assignment purposes. Chemical shifts (δ) are listed in ppm, coupling constants (J) in Hz. NMR multiplicities are abbreviated as follows – singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of doublets of doublets of doublets (dddd), doublet of triplets (dt), doublet of quartets (dq), doublet of pentets (dp), triplet of doublets (td), and multiplet (m). All spectra were referenced to residual signal of DMSO (2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C), $CDCl_3$ (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C), or 1,4-dioxane (3.75 ppm for ^{1}H and 67.19 ppm for ^{13}C, for samples measured in D_2O). High-resolution mass spectra were obtained using LTQ Orbitrap XL (Thermo Fisher Scientific, USA) for ESI ionization. Purity of target compounds was ≥ 95%. Purity was determined by the combination of UPLC−PDAMS, NMR, and HR-MS. Optical purity was determined using Waters UPC2 UHPSFC/MS system with PDA detector (YMC Alcyon Cellulose-SC column, 150 x 3 mm, 3 um, linear gradient elution 2–40% *i*PrOH in CO_2). The optical rotation was determined using Autopol IV polarimeter (Rudolph Research Analytical, USA). The value of optical rotation for compounds (*R*)-**15b**, (*R*)-**16b**, and (*R*)-**18**–(*R*)-**23** had to be extrapolated to 66 – 70% *ee*, as it was

retrospectively revealed that the starting compound from the commercial supplier, (*R*)-2-aminobutan-1-ol, contained 15 – 17% of (*S*)-enantiomer and the free phosphonates did not separate on the chiral column in reversed phase. On the contrary, the precursors of these compounds (i.e. compounds (*R*)-**2a**, (*R*)-**3**, (*R*)-**4a**, and (*R*)-**5**) did separate well on the chiral column in normal phase and were therefore separated to determine *ee* and to obtain accurate optical rotation data. Yields were determined based on the amount of isolated compound.

STANDARD PROCEDURES A-J

STANDARD PROCEDURE A

Freshly prepared compound **1a** or commercially available **1b** (1.2 mmol) were mixed with suitable amino alcohol (1.0 mmol) and DIPEA (2.0 mmol or 3.0 mmol when starting from a hydrochloride) in the appropriate solvent. The mixture was heated in a MW reactor for 1 h and then separated using silica gel flash chromatography (linear gradient elution 0 – 10% MeOH in $CHCl_3$) to afford the desired product.

STANDARD PROCEDURE B

The starting purine (1.0 mmol) was dissolved in anhydrous THF and the solution was cooled to −78 °C. *n*-BuLi (1.1 mmol) was added dropwise, the mixture was stirred at −78 °C for 10 min, and finally diisopropyl triflyloxymethanephosphonate (1.5 mmol) was added. The mixture was stirred at −78 °C and after the consumption of the starting purine, the reaction was quenched with sat. NH_4Cl solution, concentrated, and extracted with EtOAc (3 × 50 mL). Organic fractions were combined, washed with brine (1 × 50 mL), dried over $MgSO_4$, and concentrated. The residue was purified using silica gel flash chromatography (linear gradient elution 0 – 10% MeOH in $CHCl_3$) to afford the desired product.

STANDARD PROCEDURE C

6-Chloropurine or 2-amino-6-chloropurine (1.0 mmol) was mixed with Ac_2O (1.0 mmol) and compound **6a** or **6b** (1.0 mmol) in anhydrous MeCN (5 mL). TMSOTf (1.5 mmol) was added and the mixture was stirred at 25 °C for 15 min. The reaction was quenched with H_2O and extracted with DCM (3 × 50 mL). Organic fractions were combined, washed with brine (1 × 50 mL), dried

over $MgSO_4$, and concentrated. The residue was purified using silica gel flash chromatography (linear gradient elution 0 – 10% MeOH in $CHCl_3$) to afford the desired product.

STANDARD PROCEDURE D

To a solution of compound **8** (1.0 mmol) in anhydrous THF (2 mL) was dropwise added at −78 °C Grignard reagent (2.0 mmol). The mixture was stirred at −78 °C for 30 min, allowed to warm up to 25 °C over the period of 20 min and then quenched with sat. NH_4Cl solution. The mixture was concentrated, extracted with DCM (3 × 50 mL). Organic fractions were combined, washed with brine (1 × 50 mL), dried over $MgSO_4$, and concentrated to yield the desired compound.

STANDARD PROCEDURE E

A mixture of 6-chloropurine or 2-amino-6-chloropurine (1.0 mmol), PPh_3 (1.05 mmol), and corresponding alcohol **9** (1.05 mmol) in THF (7 mL) was cooled to 0 °C. DIAD (1.05 mmol) was added and the mixture was allowed to warm up to 25 °C and stirred for 15 min. The mixture was concentrated and purified using silica gel flash chromatography (linear gradient elution 0 – 10% MeOH in $CHCl_3$) to afford the desired product.

STANDARD PROCEDURE F

Starting compound was stirred in a TFA:H_2O (3:1 ratio) mixture at 25 °C for 24 h, concentrated, and co-distilled twice with H_2O. The residue was purified using silica gel flash chromatography (linear gradient elution 0 – 20% MeOH in $CHCl_3$) to afford the desired product.

STANDARD PROCEDURE G

To a solution of starting compound (0.5 mmol) in 5 mL of anhydrous MeCN (or pyridine in case of acid labile compounds) was added TMSBr (500 μL). The mixture was stirred at 25 °C until full conversion (16–60 h), concentrated, and co-distilled 2 × with toluene to ensure complete removal of residual TMSBr. The residue was added to a MeOH:H_2O (1:1 ratio) mixture and stirred at 25 °C for 15 min. Solvents were evaporated and the residue was dissolved in 2M TEAB (5 mL). After evaporation, the residue was separated using C_{18}-reversed phase flash chromatography (linear gradient elution 0 – 50% MeOH in water). Purified product was taken through DOWEX 50 (Na^+ cycle) to secure unified sodium salt.

STANDARD PROCEDURE H

Starting compound (1.0 eq.), DABCO (0.8 eq.), and K_2CO_3 (1.0 eq.) were stirred in a 1,4-dioxane:H_2O (5:1 ratio) mixture at 90 °C for 2 h, concentrated, and co-distilled with EtOH (2 ×). The residue was purified using silica gel flash chromatography (linear gradient elution 0 – 20% MeOH in $CHCl_3$) to afford the desired product.

STANDARD PROCEDURE I

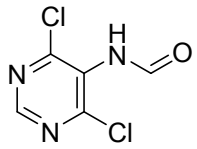
A 1,4-dioxane:water (4:1) mixture was bubbled with argon for 2 min. Starting compound (1.0 eq.), corresponding boronic acid (1.5 eq.), Cs_2CO_3 (2.5 eq.) and $Pd(Ph_3P)_4$ (5 mol%) were added and the reaction mixture was stirred at 110 °C for 30 min. Solvents were evaporated, the residue was co-distilled with EtOH (2 ×) and purified using silica gel flash chromatography (linear gradient elution 0 – 50% (EtOAc:MeOH 9:1) in hexane) to afford the desired product.

STANDARD PROCEDURE J

Starting compound and cyclopropyl amine (10 eq.) were stirred in anhydrous MeCN at 70 °C for 24 h. The mixture was concentrated and the residue purified using silica gel flash chromatography (linear gradient elution 0 – 15% MeOH in $CHCl_3$) to afford the desired product.

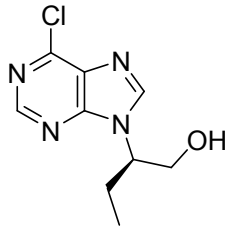
SPECTRAL DATA AND CHARACTERIZATION OF PREPARED COMPOUNDS

4,6-Dichloro-5-formamidopyrimidine (**1a**)



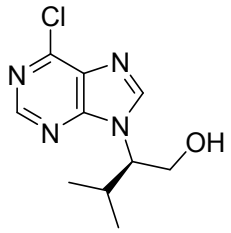
Compound **1a** was prepared from 4,6-dichloro-5-aminopyrimidine according to previously published procedure.[1] **^{1}H NMR** (401 MHz, DMSO-d_6) δ 10.52 (s, 1H), 8.86 (s, 1H), 8.36 (s, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 159.94, 159.24, 155.98, 128.07. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_5H_2ON_3Cl_2$ 189.95804, found 189.95797.

(*R*)-2-(6-Chloro-9*H*-purin-9-yl)butan-1-ol ((*R*)-**2a**)



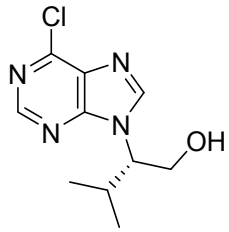
Following standard procedure A, compound **1a** (1.70 g, 8.85 mmol), (*R*)-2-aminobutan-1-ol (0.70 mL, 7.38 mmol), and DIPEA (2.57 mL, 14.76 mmol) were stirred in 1,4-dioxane (15 mL) at 160 °C for 1 h to obtain (*R*)-**2a** (0.93 g, 56%) as a orangish solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.75 (s, 1H), 5.02 (t, J = 5.6 Hz, 1H), 4.55 (dddd, J = 9.7, 7.6, 5.6, 4.3 Hz, 1H), 3.90 (ddd, J = 11.5, 7.7, 5.6 Hz, 1H), 3.75 (ddd, J = 11.5, 5.6, 4.3 Hz, 1H), 2.09–1.87 (m, 2H), 0.75 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 152.30, 151.22, 148.89, 146.92, 131.05, 62.04, 60.27, 22.99, 10.37. **HRMS** (ESI) m/z $[M+H]^+$ calcd for $C_9H_{12}ON_4Cl$ 227.06942, found 227.06942. **$[\alpha]^{25}_D$** = +24.1 (c 0.299 g/100 mL, $CHCl_3$/MeOH 1/1).

(*R*)-2-(6-Chloro-9*H*-purin-9-yl)-3-methylbutan-1-ol ((*R*)-**2b**)



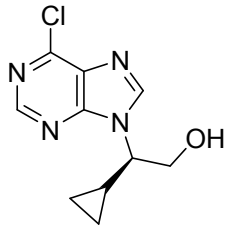
Following standard procedure A, compound **1a** (1.16 g, 6.04 mmol), (*R*)-valinol (0.52 g, 5.03 mmol), and DIPEA (1.75 mL, 10.06 mmol) were stirred in 1,4-dioxane (12 mL) at 160 °C for 1 h to obtain (*R*)-**2b** (0.76 g, 63%) as a yellowish solid. **^{1}H NMR** (401 MHz, DMSO-d_6) and **^{13}C NMR** (101 MHz, DMSO-d_6) spectra were identical to those of (*S*)-**2b**. **HRMS** (ESI) m/z $[M+H]^+$ calcd for $C_{10}H_{14}ON_4Cl$ 241.08507, found 241.08503. **$[\alpha]^{25}_D$** = +31.2 (c 0.173 g/100 mL, $CHCl_3$/MeOH 1/1).

(*S*)-2-(6-Chloro-9*H*-purin-9-yl)-3-methylbutan-1-ol ((*S*)-**2b**)



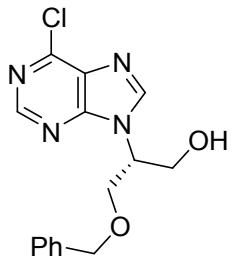
Following standard procedure A, compound **1a** (1.16 g, 6.04 mmol), (*S*)-valinol (0.52 g, 5.03 mmol), and DIPEA (1.75 mL, 10.06 mmol) were stirred in 1,4-dioxane (12 mL) at 160 °C for 1 h to obtain (*S*)-**2b** (1.10 g, 91%) as a yellowish solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.75 (s, 1H), 4.36 (ddd, J = 9.2, 8.1, 3.8 Hz, 1H), 4.02 (dd, J = 11.6, 8.2 Hz, 1H), 3.83 (dd, J = 11.6, 3.8 Hz, 1H), 2.39 (d of septets, J = 9.1, 6.7 Hz, 1H), 1.02 (d, J = 6.7 Hz, 3H), 0.66 (d, J = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 152.49, 151.26, 148.91, 147.10, 130.83, 64.26, 60.29, 28.74, 19.64, 19.22. **HRMS** (ESI) m/z $[M+H]^+$ calcd for $C_{10}H_{14}ON_4Cl$ 241.08507, found 241.08462. **$[\alpha]^{25}_D$** = −26.5 (c 0.268 g/100 mL, $CHCl_3$/MeOH 1/1).

(*R*)-2-(6-Chloro-9*H*-purin-9-yl)-2-cyclopropylethan-1-ol ((*R*)-**2c**)



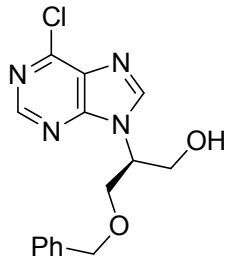
Following standard procedure A, compound **1a** (1.59 g, 8.28 mmol), (*R*)-2-amino-2-cyclopropylethan-1-ol hydrochloride (0.95 mg, 6.90 mmol), and DIPEA (3.61 mL, 20.70 mmol) were stirred in 1,4-dioxane (15 mL) at 160 °C for 1 h to obtain (*R*)-**2c** (1.08 g, 66%) as a yellowish solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.76 (s, 1H), 4.09–4.04 (m, 1H), 3.93–3.83 (m, 2H), 1.64–1.55 (m, 1H), 0.69 (tdd, J = 8.6, 6.0, 4.4 Hz, 1H), 0.55–0.48 (m, 1H), 0.47–0.41 (m, 1H), 0.25 (ddt, J = 9.3, 6.0, 4.5 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 152.06, 151.20, 148.89, 146.94, 131.06, 63.81, 61.96, 11.91, 4.70, 3.11. **HRMS** (ESI) m/z $[M+H]^+$ calcd for $C_{10}H_{12}ON_4Cl$ 239.06942, found 239.06944. **$[\alpha]^{25}_D$** = +36.2 (c 0.398 g/100 mL, $CHCl_3$/MeOH 1/1).

(*R*)-3-(Benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propan-1-ol ((*R*)-**2d**)



Compound (*S*)-**12a** (0.50 g, 0.89 mmol) was stirred at 0 °C in DCM/TFA (5 mL, 4:1 ratio) for 30 min. The mixture was diluted with 50 mL of DCM and TFA was washed away with H_2O (3 × 50 mL). DCM was washed with brine and dried over $MgSO_4$. The residue was purified using silica gel flash chromatography (linear gradient elution 0 – 10% MeOH in $CHCl_3$) to afford (*R*)-**2d** (269 mg, 95%) as a white solid. **^{1}H NMR** (401 MHz, DMSO-d_6) and **^{13}C NMR** (101 MHz, DMSO-d_6) spectra were identical to those of (*S*)-**2d**. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{15}H_{15}O_2N_4ClNa$ 341.07757, found 341.07735. **$[\alpha]^{25}_D$** = +3.5 (c 0.255 g/100 mL, $CHCl_3$/MeOH 1/1).

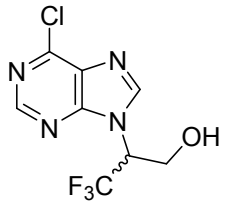
(*S*)-3-(Benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propan-1-ol ((*S*)-**2d**)



(*R*)-2-Amino-3-benzyloxypropionic acid (1.50 g, 7.68 mmol) was mixed with $NaBH_4$ (0.72 g, 19.20 mmol) in anhydrous THF (10 mL). The mixture was cooled to 0 °C and I_2 (1.95 g, 7.68 mmol) was added. The mixture was stirred at 0 °C for 10 min and then at 55 °C for 19 h. The reaction was quenched with H_2O, concentrated and extracted with EtOAc (3 × 50 mL). Organic fractions were combined, washed with brine (1 × 50 mL), dried over $MgSO_4$, and concentrated to afford (*R*)-2-amino-3-(benzyloxy)propan-1-ol (1.22 g, 88%) as a colorless oil which was directly used in the following reaction. Following standard procedure A, compound **1a** (1.46 g, 7.62 mmol), (*R*)-2-amino-3-(benzyloxy)propan-1-ol (1.15 mg, 6.35 mmol), and DIPEA (2.21 mL,

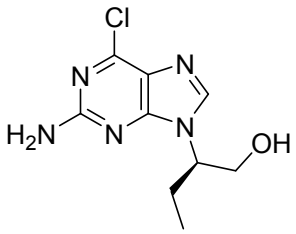
12.70 mmol) were stirred in 1,4-dioxane (15 mL) at 160 °C for 1 h to obtain (*S*)-**2d** (1.08 g, 53%) as a yellowish solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.74 (s, 1H), 7.28–7.21 (m, 3H), 7.15–7.09 (m, 2H), 5.13 (t, J = 5.5 Hz, 1H), 4.91 (ddt, J = 8.1, 7.1, 4.7 Hz, 1H), 4.52–4.39 (m, 2H), 4.04 (dd, J = 10.4, 8.2 Hz, 1H), 3.96 (ddd, J = 11.5, 7.1, 5.4 Hz, 1H), 3.91–3.82 (m, 2H). **^{13}C NMR** 101 MHz, DMSO-d_6) δ 152.23, 151.25, 148.90, 146.97, 137.79, 130.92, 128.16, 127.49, 127.35, 71.98, 67.57, 59.62, 57.89. **HRMS** (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{16}O_2N_4Cl$ 319.09563, found 319.09567. **$[\alpha]^{25}_D$** = +26.9 (c 0.104 g/100 mL, $CHCl_3$/MeOH 1/1).

2-(6-Chloro-9*H*-purin-9-yl)-3,3,3-trifluoropropan-1-ol ((*RS*)-**2e**)



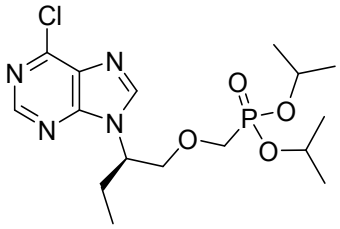
To a solution of 6-chloropurine (0.58 g, 3.75 mmol) in anhydrous DMF (10 mL) was added K_2CO_3 (0.78 g, 5.63 mmol). The mixture was stirred at 25 °C for 10 min and 2-bromo-3,3,3-trifluoropropan-1-ol (0.39 mL, 3.75 mmol) was added. The mixture was stirred at 60 °C for 24 h, filtered through Celite, and concentrated. The residue was dissolved in EtOAc (50 mL), washed with H_2O (3 × 50 mL), with brine (1 × 50 mL), dried over $MgSO_4$, and concentrated. The residue was purified using silica gel flash chromatography (linear gradient elution 0 – 10% MeOH in $CHCl_3$) to afford (*RS*)-**2e** (165 mg, 16%) as colorless oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.71 (s, 1H), 6.84–6.76 (m, 1H), 4.64–4.54 (m, 2H), 4.52–4.42 (m, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 152.11, 151.69, 149.04, 148.07, 131.11, 124.67 (q, J = 283.2 Hz), 66.71 (q, J = 30.0 Hz), 43.64. **^{19}F NMR** (377 MHz, DMSO-d_6) δ −76.97 (d, J = 7.1 Hz). **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_8H_5ON_4ClF_3$ 265.01095, found 265.01097.

(*R*)-2-(2-Amino-6-chloro-9*H*-purin-9-yl)butan-1-ol ((*R*)-**3**)



Following standard procedure A, compound **1b** (commercially available, 5.00 g, 24.15 mmol), (*R*)-2-aminobutan-1-ol (1.90 mg, 20.13 mmol), and DIPEA (7.01 mL, 40.26 mmol) were stirred in H_2O:EtOH (1:1 ratio) (50 mL) at 120 °C for 1 h to obtain (*R*)-**3** (2.91 g, 60%) as a yellowish solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.16 (s, 1H), 6.84 (s, 2H), 5.01 (t, J = 5.4 Hz, 1H), 4.34–4.22 (m, 1H), 3.81 (ddd, J = 11.2, 7.2, 5.2 Hz, 1H), 3.67 (dt, J = 11.2, 4.8 Hz, 1H), 1.97–1.82 (m, 2H), 0.75 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 159.54, 154.46, 149.21, 142.55, 123.57, 61.99, 58.95, 23.01, 10.43. **HRMS** (ESI) m/z $[M+H]^+$ calcd for $C_9H_{13}ON_5Cl$ 242.08031, found 242.08034. **$[\alpha]^{25}_D$** = −5.6 (c 0.266 g/100 mL, $CHCl_3$/MeOH 1/1).

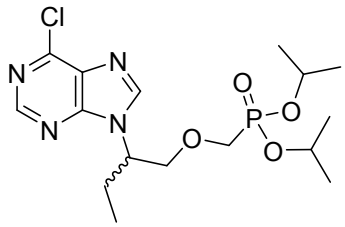
Diisopropyl (*R*)-((2-(6-chloro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**4a**)



Following standard procedure B, compound (*R*)-**2a** (0.90 g, 3.97 mmol) reacted with *n*-BuLi (2.5 M in hexanes, 1.75 mL, 4.37 mmol) and diisopropyl triflyloxymethanephosphonate (1.95 g, 5.96 mmol) in anhydrous THF (10 mL) to afford (*R*)-**4a** (1.17 g, 73%) as a light orange viscose oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.77 (s, 2H), 4.82–4.75 (m, 1H), 4.45–4.30 (m, 2H), 4.11 (dd, J = 10.4, 8.6 Hz, 1H), 3.89 (dd, J = 10.4, 4.0 Hz, 1H), 3.77 (dd, J = 13.9, 8.3 Hz, 1H), 3.68 (dd, J = 13.9, 8.3 Hz, 1H), 2.11–1.87 (m, 2H), 1.13–1.07 (m, 6H), 1.05–0.98 (m, 6H), 0.77 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 152.14, 151.36, 149.05, 146.63, 130.97, 72.66 (d, J = 11.4 Hz), 70.15–69.95 (m), 64.65 (d, J = 164.0 Hz), 57.13, 23.62 (d, J = 3.7 Hz), 23.50–23.38 (m), 23.11, 10.20. **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.22. **HRMS** (ESI) m/z $[M+H]^+$ calcd for

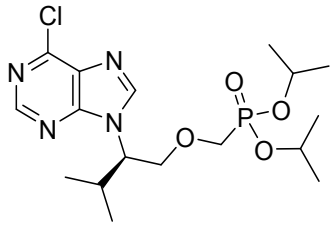
$C_{16}H_{27}O_4N_4ClP$ 405.14530, found 405.14554. **[α]$^{25}_{D}$** = +18.3 (c 0.142 g/100 mL, $CHCl_3$/MeOH 1/1).

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*RS*)-**4a**)



Following standard procedure E, compound (*RS*)-**9b** (390 mg, 1.45 mmol) reacted with 6-chloropurine (213 mg, 1.38 mmol), PPh_3 (380 mg, 1.45 mmol), and DIAD (284 μL, 1.45 mmol) in anhydrous THF (10 mL) to afford (*RS*)-**4a** (342 mg, 61%), as a yellow oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.77 (s, 2H), 4.82–4.75 (m, 1H), 4.44–4.31 (m, 2H), 4.12 (dd, J = 10.4, 8.6 Hz, 1H), 3.89 (dd, J = 10.3, 4.0 Hz, 1H), 3.77 (dd, J = 14.0, 8.3 Hz, 1H), 3.68 (dd, J = 13.9, 8.2 Hz, 1H), 2.11–1.87 (m, 2H), 1.13–1.08 (m, 6H), 1.07–0.98 (m, 6H), 0.76 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 152.14, 151.35, 149.05, 146.62, 130.97, 72.66 (d, J = 11.3 Hz), 70.17–69.93 (m), 64.65 (d, J = 163.7 Hz), 57.13, 23.62 (d, J = 3.9 Hz), 23.51–23.34 (m), 23.11, 10.19. **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.22. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{16}H_{25}O_4N_4ClNaP$ 427.12724, found 427.12702.

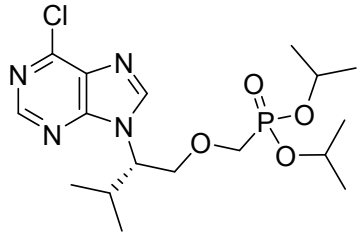
Diisopropyl (*R*)-((2-(6-chloro-9*H*-purin-9-yl)-3-methylbutoxy)methyl)phosphonate ((*R*)-**4b**)



Following standard procedure B, compound (*R*)-**2b** (0.73 g, 3.03 mmol) reacted with *n*-BuLi (2.5 M in hexanes, 1.33 mL, 3.33 mmol) and diisopropyl triflyloxymethanephosphonate (1.49 g, 4.55 mmol) in anhydrous THF (10 mL) to afford (*R*)-**4b** (1.02 g, 80%) as a light orange viscose

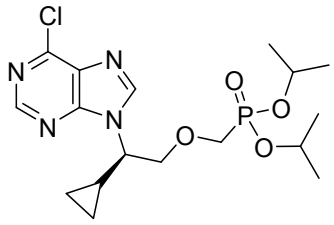
oil. **^{1}H NMR** (401 MHz, DMSO-d_6) and **^{13}C NMR** (101 MHz, DMSO-d_6) were identical to those of (*R*)-**4b**. **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.23. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{17}H_{28}O_4N_4ClNaP$ 441.14289, found 441.14345. **$[\alpha]^{25}_D$** = +13.1 (c 0.245 g/100 mL, $CHCl_3$/MeOH 1/1).

Diisopropyl (*S*)-((2-(6-chloro-9*H*-purin-9-yl)-3-methylbutoxy)methyl)phosphonate ((*S*)-**4b**)



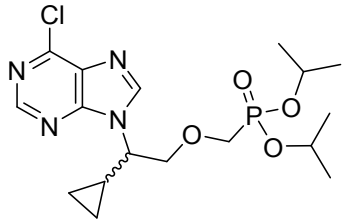
Following standard procedure B, compound (*S*)-**2b** (1.00 g, 4.15 mmol) reacted with *n*-BuLi (1.6 M in hexanes, 2.86 mL, 4.57 mmol) and diisopropyl triflyloxymethanephosphonate (2.04 g, 6.23 mmol) in anhydrous THF (12 mL) to afford (*S*)-**4b** (1.59 g, 91%) as a light-yellow viscose oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.76 (s, 1H), 4.64–4.55 (m, 1H), 4.42–4.32 (m, 2H), 4.23 (dd, J = 10.4, 8.8 Hz, 1H), 3.95 (dd, J = 10.5, 3.7 Hz, 1H), 3.80–3.63 (m, 2H), 2.44–2.32 (m, 1H), 1.13–1.06 (m, 6H), 1.06–0.99 (m, 9H), 0.68 (d, J = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 152.32, 151.40, 149.08, 146.73, 130.75, 71.19 (d, J = 11.8 Hz), 70.18–69.85 (m), 64.65 (d, J = 164.1 Hz), 61.12, 29.17, 23.67–23.53 (m), 23.51–23.35 (m), 19.42, 19.15. **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.23. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{17}H_{28}O_4N_4ClNaP$ 441.14289, found 441.14325. **$[\alpha]^{25}_D$** = −11.0 (c 0.371 g/100 mL, $CHCl_3$/MeOH 1/1).

Diisopropyl (*R*)-((2-(6-chloro-9*H*-purin-9-yl)-2-cyclopropylethoxy)methyl)phosphonate ((*R*)-**4c**)



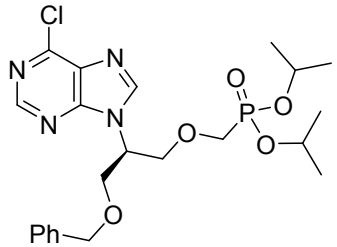
Following standard procedure B, compound (*R*)-**2c** (0.95 g, 3.98 mmol) reacted with *n*-BuLi (2.5 M in hexanes, 1.75 mL, 4.38 mmol) and diisopropyl triflyloxymethanephosphonate (1.96 g, 5.97 mmol) in anhydrous THF (10 mL) to afford (*R*)-**4c** (1.15 g, 69%) as a light orange viscose oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.77 (s, 1H), 4.43–4.32 (m, 2H), 4.32–4.24 (m, 1H), 4.13 (ddd, J = 10.1, 8.6, 3.7 Hz, 1H), 3.99 (dd, J = 10.2, 3.7 Hz, 1H), 3.77 (dd, J = 13.9, 8.3 Hz, 1H), 3.69 (dd, J = 13.9, 8.2 Hz, 1H), 1.63–1.54 (m, 1H), 1.13–1.06 (m, 6H), 1.06–0.97 (m, 6H), 0.75–0.63 (m, 1H), 0.63–0.55 (m, 1H), 0.48–0.41 (m, 1H), 0.32–0.26 (m, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 151.88, 151.36, 149.07, 146.60, 130.94, 72.48 (d, J = 11.6 Hz), 70.13–69.96 (m), 64.66 (d, J = 164.1 Hz), 60.51, 23.61 (d, J = 3.7 Hz), 23.48–23.33 (m), 11.97, 4.48, 3.26. **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.22. **HRMS** (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{27}O_4N_4ClP$ 417.14530, found 417.14535. **$[\alpha]^{25}_D$** = +12.7 (c 0.456 g/100 mL, $CHCl_3$/MeOH 1/1).

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)-2-cyclopropylethoxy)methyl)phosphonate ((*RS*)-**4c**)



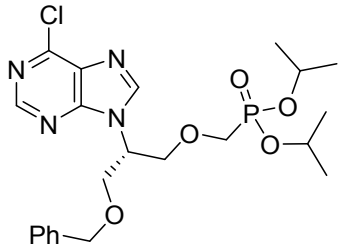
Following standard procedure E, compound (*RS*)-**9e** (1.20 g, 4.28 mmol) reacted with 6-chloropurine (0.63 g, 4.08 mmol), PPh_3 (1.12 g, 4.28 mmol), and DIAD (0.84 mL, 4.28 mmol) in anhydrous THF (20 mL) to afford (*RS*)-**4c** (0.51 g, 30%), as a yellow oil. **^{1}H NMR** (401 MHz, DMSO-d_6), **^{13}C NMR** (101 MHz, DMSO-d_6) and **^{31}P NMR** (162 MHz, DMSO-d_6) were identical with those of (*R*)-**4c**. **HRMS** (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{27}O_4N_4ClP$ 417.14530, found 417.14500.

Diisopropyl (*R*)-((3-(benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*R*)-**4d**)



Following standard procedure B, compound (*S*)-**2d** (0.95 g, 2.98 mmol) reacted with *n*-BuLi (2.5 M in hexanes, 1.31 mL, 3.28 mmol) and diisopropyl triflyloxymethanephosphonate (1.47 g, 4.47 mmol) in anhydrous THF (10 mL) to afford (*R*)-**4d** (0.53 g, 36%) as a light yellow-orange viscose oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.75 (s, 1H), 7.29–7.22 (m, 3H), 7.15–7.10 (m, 2H), 5.13 (tt, J = 8.5, 4.4 Hz, 1H), 4.52–4.33 (m, 4H), 4.20 (dd, J = 10.4, 8.3 Hz, 1H), 4.05–3.95 (m, 2H), 3.86 (dd, J = 10.4, 4.6 Hz, 1H), 3.79 (dd, J = 14.0, 8.3 Hz, 1H), 3.72 (dd, J = 14.0, 8.2, 1H), 1.13–1.09 (m, 6H), 1.05–1.01 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 152.11, 151.40, 149.05, 146.73, 137.67, 130.84, 128.19, 127.57, 127.40, 72.05, 70.24–70.05 (m), 69.86 (d, J = 7.2 Hz), 67.52, 64.75 (d, J = 163.3 Hz), 55.08, 23.66 (d, J = 3.6 Hz), 23.56–23.39 (m). **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.26. **HRMS** (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{31}O_5N_4ClP$ 497.17151, found 497.17142. **$[\alpha]^{25}_D$** = −5.1 (c 0.295 g/100 mL, $CHCl_3$/MeOH 1/1).

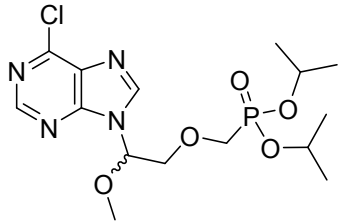
Diisopropyl (*S*)-((3-(benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*S*)-**4d**)



Following standard procedure B, compound (*R*)-**2d** (95 mg, 0.30 mmol) reacted with *n*-BuLi (2.5 M in hexanes, 131 µL, 0.33 mmol) and diisopropyl triflyloxymethanephosphonate (148 mg, 0.45 mmol) in anhydrous THF (2 mL) to afford (*S*)-**4d** (119 mg, 80%) as a as a colorless viscose

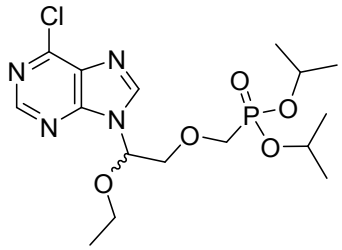
oil. **^{1}H NMR** (400 MHz, DMSO-d_6), **^{13}C NMR** (101 MHz, DMSO-d_6) and **^{31}P NMR** (162 MHz, DMSO-d_6) spectra were identical to those of (*R*)-**4d**. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{22}H_{30}O_5N_4ClNaP$ 519.15346, found 519.15254. **$[\alpha]^{25}_D$** = +3.0 (c 0.919 g/100 mL, $CHCl_3$/MeOH 1/1).

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)-2-methoxyethoxy)methyl)phosphonate ((*RS*)-**4e**)



Following standard procedure C, compound **6a** (299 mg, 1.05 mmol) reacted with 6-chloropurine (162 mg, 1.05 mmol), Ac_2O (99 µL, 1.05 mmol), and TMSOTf (286 µL, 1.58 mmol) to afford (*RS*)-**4e** (351 mg, 82%) as a colorless oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.82 (s, 1H), 5.95 (dd, J = 7.0, 4.8 Hz, 1H), 4.47–4.36 (m, 2H), 4.21 (dd, J = 10.6, 7.1 Hz, 1H), 4.08 (dd, J = 10.6, 4.8 Hz, 1H), 3.88–3.72 (m, 2H), 3.27 (s, 3H), 1.15–1.09 (m, 6H), 1.09–1.01 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 152.22, 151.89, 149.30, 146.01, 131.06, 84.14, 71.20 (d, J = 12.1 Hz), 70.17 (d, J = 6.5 Hz), 70.15 (d, J = 6.5 Hz), 65.08 (d, J = 164.3 Hz), 56.48, 23.64 (d, J = 3.7 Hz), 23.44 (d, J = 4.4 Hz). **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.04. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{15}H_{24}O_5N_4ClNaP$ 429.10651, found 429.10693.

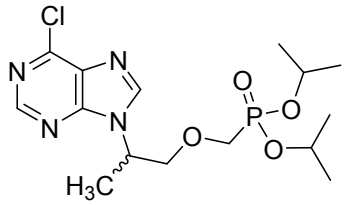
Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)-2-ethoxyethoxy)methyl)phosphonate ((*RS*)-**4f**)



Following standard procedure C, compound **6b** (1.01 g, 3.23 mmol) reacted with 6-chloropurine (0.50 g, 3.23 mmol), Ac_2O (305 µL, 3.23 mmol), and TMSOTf (0.88 mL, 4.85 mmol) to afford

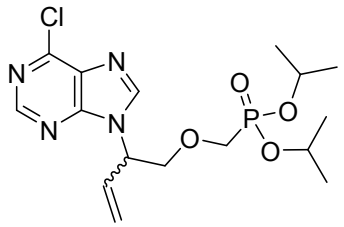
(*RS*)-**4f** (1.18 g, 87%) as a colorless oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.82 (s, 1H), 6.05 (dd, J = 7.0, 4.9 Hz, 1H), 4.50–4.34 (m, 2H), 4.19 (dd, J = 10.6, 7.1 Hz, 1H), 4.07 (dd, J = 10.6, 4.9 Hz, 1H), 3.88–3.73 (m, 2H), 3.58 (dq, J = 9.6, 7.0 Hz, 1H), 3.41 (dq, J = 9.6, 7.0 Hz, 1H), 1.12 (d, J = 6.2 Hz, 6H), 1.10–1.02 (m, 9H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 152.12, 151.87, 149.26, 145.93, 131.00, 82.48, 71.42 (d, J = 11.9 Hz), 70.15 (d, J = 6.7 Hz), 65.06 (d, J = 164.3 Hz), 64.56, 23.63 (d, J = 3.8 Hz), 23.44 (d, J = 4.6 Hz), 14.62. **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.05. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{16}H_{26}O_5N_4ClNaP$ 443.12216, found 443.12164.

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**4g**)



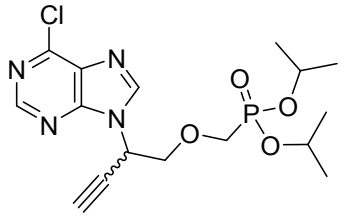
Following standard procedure E, compound (*RS*)-**9a** (600 mg, 2.36 mmol) reacted with 6-chloropurine (348 mg, 2.25 mmol), PPh_3 (619 mg, 2.36 mmol), and DIAD (463 µL, 2.36 mmol) in anhydrous THF (12 mL) to afford (*RS*)-**4g** (463 mg, 53%), as a yellow oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.78 (s, 1H), 5.03–4.95 (m, 1H), 4.46–4.30 (m, 2H), 4.06 (dd, J = 10.3, 8.4 Hz, 1H), 3.87 (dd, J = 10.3, 4.1 Hz, 1H), 3.78 (dd, J = 13.9, 8.3 Hz, 1H), 3.69 (dd, J = 13.9, 8.3 Hz, 1H), 1.56 (d, J = 7.1 Hz, 3H), 1.13–1.08 (m, 6H), 1.06–1.00 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 151.82, 151.27, 148.98, 146.37, 131.03, 73.75 (d, J = 11.3 Hz), 70.30–69.81 (m), 64.66 (d, J = 164.1 Hz), 51.08, 23.63 (d, J = 3.6 Hz), 23.51–23.36 (m), 16.25. **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.23. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{15}H_{24}O_4N_4ClNaP$ 413.11159, found 413.11210.

Diisopropyl (((2-(6-chloro-9*H*-purin-9-yl)but-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**4h**)



Following standard procedure E, compound (*RS*)-**9c** (600 mg, 2.25 mmol) reacted with 6-chloropurine (331 mg, 2.14 mmol), PPh_3 (590 mg, 2.25 mmol), and DIAD (442 μL, 2.25 mmol) in anhydrous THF (12 mL) to afford (*RS*)-**4h** (688 mg, 80%), as a yellow oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.79 (s, 1H) 6.22 (ddd, J = 17.0, 10.6, 6.2 Hz, 1H), 5.57–5.51 (m, 1H), 5.33 (dt, J = 10.6, 1.1 Hz, 1H), 5.21 (ddd, J = 17.2, 1.5, 0.9 Hz, 1H), 4.46–4.34 (m, 2H), 4.25 (dd, J = 10.5, 8.9 Hz, 1H), 3.99 (dd, J = 10.5, 4.4 Hz, 1H), 3.82 (dd, J = 13.9, 8.4 Hz), 3.74 (d, J = 13.9, 8.3 Hz), 1.12 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.2 Hz), 1.04 (d, J = 6.2 Hz, 3H), 1.03 (d, J = 6.2 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 151.80, 151.51, 149.17, 146.50, 132.59, 130.87, 119.34, 71.97 (d, J = 12.1 Hz), 70.22–70.01 (m), 64.64 (d, J = 164.2 Hz), 56.96, 23.63 (d, J = 3.8 Hz), 23.51–23.36 (m). **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.17. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{16}H_{24}O_4N_4ClNaP$ 425.11159, found 425.11218.

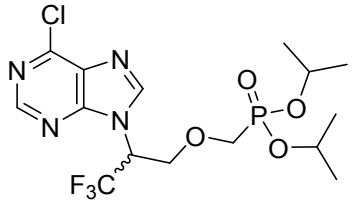
Diisopropyl (((2-(6-chloro-9*H*-purin-9-yl)but-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**4i**)



Following standard procedure E, compound (*RS*)-**9d** (600 mg, 2.27 mmol) reacted with 6-chloropurine (334 mg, 2.16 mmol), PPh_3 (595 mg, 2.27 mmol), and DIAD (446 μL, 2.27 mmol) in anhydrous THF (12 mL) to afford (*RS*)-**4i** (791 mg, 91%), as a yellow oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.80 (s, 1H), 5.92 (ddd, J = 8.2, 4.3, 2.5 Hz, 1H), 4.46–4.35 (m, 2H), 4.27 (dd, J = 10.5, 8.1 Hz, 1H), 4.05 (dd, J = 10.5, 4.4 Hz, 1H), 3.89–3.72 (m, 3H), 1.14–1.08 (m, 6H), 1.07–1.01 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 151.79, 151.25, 149.37, 146.17,

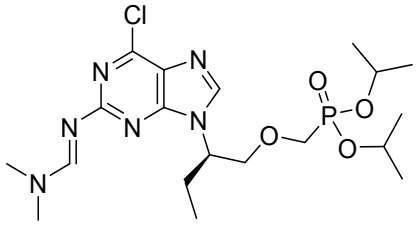
130.90, 78.22, 77.16, 72.03 (d, J = 11.7 Hz), 70.17 (d, J = 6.5 Hz), 64.65 (d, J = 163.9 Hz), 46.16, 23.64 (d, J = 3.7 Hz), 23.53–23.38 (m). **^{31}P NMR** (162 MHz, DMSO-d_6) δ 20.96. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{16}H_{22}O_4N_4ClNaP$ 423.09594, found 423.09655.

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)-3,3,3-trifluoropropoxy)methyl)phosphonate ((*RS*)-**4j**)



Following standard procedure B, compound (*RS*)-**2e** (145 mg, 0.54 mmol) reacted with *n*-BuLi (2.5 M in hexanes, 237 µL, 0.59 mmol) and diisopropyl triflyloxymethanephosphonate (266 mg, 0.81 mmol) in anhydrous THF (10 mL) to afford (*RS*)-**4j** (182 mg, 78%) as a orangish solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.66 (s, 1H), 4.81–4.70 (m, 2H), 4.70–4.61 (m, 1H), 4.58–4.43 (m, 2H), 4.07–3.93 (m, 2H), 1.20 (d, J = 6.1 Hz, 3H), 1.19–1.15 (m, 6H), 1.10 (d, J = 6.2 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 152.62, 152.23, 149.55, 148.29, 131.04, 124.48 (q, J = 285.0 Hz), 76.71–76.10 (m), 71.13–70.85 (m), 66.32 (d, J = 165.7 Hz), 41.70, 24.24–23.81 (m). **^{19}F NMR** (377 MHz, DMSO-d_6) δ −74.65 (d, J = 6.9 Hz). **^{31}P NMR** (162 MHz, DMSO-d_6) δ 19.64. **HRMS** (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{22}O_4N_4ClF_3P$ 445.10138, found 445.10126.

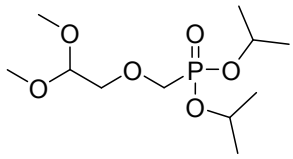
Diisopropyl (*R*)-((2-(6-chloro-2-(((dimethylamino)methylene)amino)-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**5**)



Compound (*R*)-**3** (2.80 g, 11.59 mmol) was stirred with DMF DMA (4.63 mL, 34.77 mmol) in DMF (15 mL) at 80 °C for 1 h. The mixture was concentrated and co-distilled 3 × with toluene to

yield (*R*)-*N*′-(6-chloro-9-(1-hydroxybutan-2-yl)-9*H*-purin-2-yl)-*N*,*N*-dimethylformimidamide (3.32 g, 97%), which was used directly in the following reaction. Following standard procedure B, (*R*)-*N*′-(6-chloro-9-(1-hydroxybutan-2-yl)-9*H*-purin-2-yl)-*N*,*N*-dimethylformimidamide (0.95 g, 2.98 mmol) reacted with *n*-BuLi (2.5 M in hexanes, 1.31 mL, 3.28 mmol) and diisopropyl triflyloxymethanephosphonate (1.47 g, 4.47 mmol) in anhydrous THF (10 mL) to afford (*R*)-**5** (3.91 g, 81%) as a light orange viscose oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.38 (s, 1H), 4.70–4.60 (m, 1H), 4.41 (d of septets, J = 7.7, 6.1 Hz, 2H), 4.08 (dd, J = 10.3, 8.3 Hz, 1H), 3.89–3.83 (m, 1H), 3.83–3.65 (m, 2H), 3.16 (s, 3H), 3.04 (s, 3H), 2.04–1.82 (m, 2H), 1.15–1.09 (m, 6H), 1.08–1.02 (m, 6H), 0.77 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 161.71, 158.46, 153.91, 148.75, 144.05, 126.28, 72.82 (d, J = 11.7 Hz), 70.23–69.99 (m), 64.69 (d, J = 163.7 Hz), 56.15, 40.48, 34.66, 23.66 (d, J = 4.1 Hz), 23.52–23.39 (m), 23.14, 10.25. **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.27. **HRMS** (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{33}O_4N_6ClP$ 475.19839, found 475.19871. **$[\alpha]^{25}_D$** = −10.3 (c 0.068 g/100 mL, $CHCl_3$/MeOH 1/1).

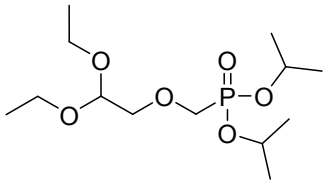
Diisopropyl ((2,2-dimethoxyethoxy)methyl)phosphonate (**6a**)



A suspension of NaH (0.41 g, 10.19 mmol, 60% in mineral oil) in anhydrous DMF (20 mL) was cooled to 0 °C. Diisopropyl (hydroxymethyl)phosphonate (2.00 g, 10.19 mmol) was added dropwise over the period of 5 min. The mixture was stirred at 0 °C for 10 min followed by addition of acetaldehyde dimethyl acetal (1.44 mL, 12.23 mmol). The reaction mixture was allowed to warm up to 25 °C and further stirred for 19 h. After quenching with H_2O, the mixture was concentrated and extracted with DCM (3 × 70 mL). Organic fractions were combined, washed with brine (1 × 70 mL), dried over $MgSO_4$, and concentrated to afford **6a** (2.51 g, 87%) as a colorless oil. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 4.81–4.69 (m, 2H), 4.51 (t, J = 5.2 Hz, 1H), 3.86–3.77 (m, 2H), 3.62 (dd, J = 5.2, 0.6 Hz, 2H), 3.38 (s, 6H), 1.38–1.30 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 102.85, 72.62 (d, J = 10.0 Hz), 71.22 (d, J = 6.6 Hz), 66.39 (d, J = 167.2 Hz), 54.16,

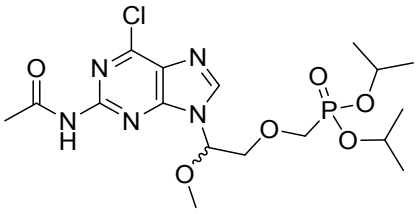
24.34–23.96 (m). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.86. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{11}H_{25}O_6NaP$ 307.12810, found 307.12832.

Diisopropyl ((2,2-diethoxyethoxy)methyl)phosphonate (**6b**)



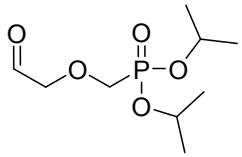
A suspension of NaH (11.72 g, 293.10 mmol, 60% in mineral oil) in anhydrous DMF (20 mL) was cooled to 0 °C. Diisopropyl (hydroxymethyl)phosphonate (57.50 g, 293.10 mmol) was added dropwise over the period of 20 min. The mixture was stirred at 0 °C for 20 min followed by addition of acetaldehyde dimethyl acetal (52.91 mL, 351.72 mmol). The reaction mixture was allowed to warm up to 25 °C and further stirred for 19 h. After quenching with H_2O, the mixture was concentrated and extracted with DCM (3 × 600 mL). Organic fractions were combined, washed with brine (1 × 500 mL), dried over $MgSO_4$, and concentrated to afford **6b** (82.36 g, 90%) as a yellowish oil. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 4.75 (d of septets, J = 7.7, 6.2 Hz, 2H), 4.62 (t, J = 5.2 Hz, 1H), 3.82 (d, J = 8.1 Hz, 2H), 3.69 (dq, J = 9.4, 7.1 Hz, 2H), 3.61 (dd, J = 5.2, 0.5 Hz, 2H), 3.55 (dq, J = 9.3, 7.0 Hz, 2H), 1.35–1.30 (m, 12H), 1.20 (t, J = 7.0 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 101.25, 73.63 (d, J = 11.0 Hz), 71.16 (d, J = 6.5 Hz), 66.43 (d, J = 166.9 Hz), 62.62, 24.07–24.30 (m), 15.46. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.95. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{13}H_{29}O_6NaP$ 335.15940, found 335.15935.

Diisopropyl ((2-(2-amino-6-chloro-9*H*-purin-9-yl)-2-methoxyethoxy)methyl)phosphonate ((*RS*)-**7**)



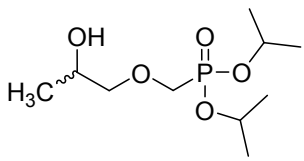
Following standard procedure C, compound **6a** (284 mg, 1.00 mmol) reacted with 2-amino-6-chloropurine (170 mg, 1.00 mmol), Ac_2O (94 µL, 1.00 mmol), and TMSOTf (271 µL, 1.50 mmol) to afford (*RS*)-**7** (101 mg, 24%) as a colorless oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.65 (s, 1H), 5.79 (dd, J = 7.2, 4.9 Hz, 1H), 4.50–4.37 (m, 2H), 4.23 (dd, J = 10.6, 7.2 Hz, 1H), 4.08 (td, J = 10.6, 4.9 Hz, 1H), 3.87–3.74 (m, 2H), 3.27 (s, 3H), 2.21 (s, 3H), 1.17–1.10 (m, 6H), 1.09–1.03 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 169.29, 153.49, 152.67, 149.69, 145.41, 127.79, 84.43, 71.47 (d, J = 12.4 Hz), 70.65 (d, J = 6.7 Hz), 70.61 (d, J = 6.7 Hz), 65.57 (d, J = 164.3 Hz), 56.92, 25.09, 24.12 (d, J = 3.7 Hz), 23.92 (d, J = 4.6 Hz). **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{17}H_{27}O_6N_5ClNaP$ 486.12797, found 486.12822.

Diisopropyl ((2-oxoethoxy)methyl)phosphonate (**8**)



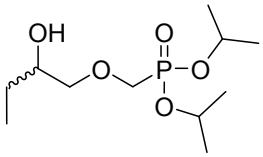
To a solution of compound **6b** (83.00 g, 265.74 mmol) in H_2O:1,4-dioxane (1:1 ratio) was slowly added H_2SO_4 (14.88 mL, 279.03 mmol). The mixture was stirred at 80 °C for 30 min, poured into a sat. $NaHCO_3$ solution, and extracted with DCM (3 × 500 mL). Organic fractions were combined, washed with brine (1 × 500 mL), dried over $MgSO_4$, and distilled in vacuo to afford **8** (60.78 g, 96%) as a colorless oil. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 9.72 (s, 1H), 4.86–4.70 (m, 2H), 4.27 (d, J = 0.9 Hz, 2H), 3.86 (d, J = 8.1 Hz, 2H), 1.35 (d, J = 6.3 Hz, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.66, 77.80 (d, J = 8.9 Hz), 71.58 (d, J = 6.6 Hz), 66.52 (d, J = 167.4 Hz), 24.23 (d, J = 3.7 Hz), 24.19 (d, J = 4.5 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.79. **HRMS** (ESI) m/z $[M+H]^+$ calcd for $C_9H_{20}O_5P$ 239.10429, found 239.10431.

Diisopropyl ((2-hydroxypropoxy)methyl)phosphonate ((*RS*)-**9a**)



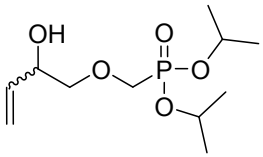
Following standard procedure D, compound **8** (1.15 g, 4.83 mmol) reacted with 3.0 M methylmagnesium bromide (3.0 M in Et_2O, 3.22 mL, 9.66 mmol) in anhydrous THF (10 mL) to yield (*RS*)-**9a** (0.98 g, 80%) as a colorless oil. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 4.82–4.70 (m, 2H), 3.99 (dqd, J = 8.1, 6.4, 2.9 Hz, 1H), 3.79 (d, J = 8.1 Hz, 2H), 3.61 (ddd, J = 9.9, 2.8, 0.6 Hz, 1H), 3.42–3.33 (m, 1H), 1.38–1.29 (m, 12H), 1.14 (d, J = 6.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 79.39 (d, J = 9.5 Hz), 71.38 (d, J = 6.6 Hz), 71.34 (d, J = 6.7 Hz), 66.39, 66.37 (d, J = 167.9 Hz), 24.23 (d, J = 3.7 Hz), 24.16 (d, J = 4.9 Hz), 18.50. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.32. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{10}H_{23}O_5PNa$ 277.11753, found 277.11763.

Diisopropyl ((2-hydroxybutoxy)methyl)phosphonate ((*RS*)-**9b**)



Following standard procedure D, compound **8** (476 mg, 2.00 mmol) reacted with ethylmagnesium bromide (3.0 M in Et_2O, 1.33 mL, 4.00 mmol) in anhydrous THF (4 mL) to yield (*RS*)-**9b** (428 mg, 80%) as a colorless oil. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 4.83–4.67 (m, 2H), 3.78 (d, J = 8.1 Hz, 2H), 3.76–3.68 (m, 1H), 3.64 (dd, J = 9.9, 2.8 Hz, 1H), 3.46–3.39 (m, 1H), 1.51–1.42 (m, 2H), 1.36–1.31 (m, 12H), 0.95 (t, J = 7.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 77.94 (d, J = 9.8 Hz), 71.68, 71.50–71.32 (m), 66.36 (d, J = 168.0 Hz), 25.96, 24.22 (d, J = 4.4 Hz), 24.14 (d, J = 4.3 Hz), 10.04. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.38. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{11}H_{25}O_5PNa$ 291.13318, found 291.13307.

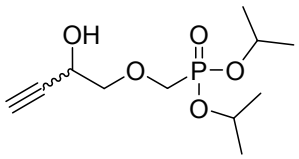
Diisopropyl (((2-hydroxybut-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**9c**)



Following standard procedure D, compound **8** (1.15 g, 4.83 mmol) reacted with vinylmagnesium bromide (0.7 M in THF, 13.80 mL, 9.66 mmol) in anhydrous THF (10 mL) to yield (*RS*)-**9c**

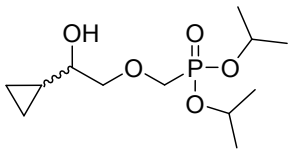
(1.19 g, 92%) as a colorless oil. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 5.81 (ddd, J = 17.3, 10.6, 5.4 Hz, 1H), 5.37 (dt, J = 17.2, 1.6 Hz, 1H), 5.20 (dt, J = 10.6, 1.5 Hz, 1H), 4.82–4.69 (m, 2H), 4.37–4.32 (m, 1H), 3.81 (d, J = 8.0 Hz, 2H), 3.70 (ddd, J = 10.2, 3.1, 0.7 Hz, 1H), 3.48 (dd, J = 10.2, 7.9 Hz, 1H), 1.38–1.30 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.26, 116.70, 77.71 (d, J = 8.9 Hz), 71.58–71.26 (m), 67.31, 65.64, 24.24 (dd, J = 4.0 Hz), 24.17 (d, J = 4.5 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.28. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{11}H_{23}O_5PNa$ 289.11753, found 289.11754.

Diisopropyl (((2-hydroxybut-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**9d**)



Following standard procedure D, compound **8** (1.15 g, 4.83 mmol) reacted with ethynylmagnesium bromide (0.5 M in THF, 19.34 mL, 9.66 mmol) in anhydrous THF (10 mL) to yield (*RS*)-**9d** (1.05 g, 83%) as a colorless oil. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 4.8–4.71 (m, 2H), 4.58–4.55 (m, 1H), 3.93–3.78 (m, 3H), 3.70 (ddd, J = 10.2, 7.3, 1.9 Hz, 1H), 2.43 (d, J = 2.3 Hz, 1H), 1.39–1.24 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 77.38, 73.86 (d, J = 13.5 Hz), 71.82–71.53 (m), 66.85 (d, J = 168.0 Hz), 61.76 (d, J = 2.9 Hz), 24.18 (d, J = 4.9 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.34. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{11}H_{21}O_5PNa$ 287.10188, found 287.10208.

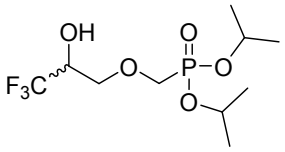
Diisopropyl ((2-cyclopropyl-2-hydroxyethoxy)methyl)phosphonate ((*RS*)-**9e**)



Following standard procedure D, compound **8** (2.00 g, 8.40 mmol) reacted with cyclopropylmagnesium bromide (1.0 M in 2-MeTHF, 16.80 mL, 16.80 mmol) in anhydrous THF (15 mL) to yield (*RS*)-**9e** (2.15 g, 91%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.82–4.67 (m, 2H), 3.88–3.73 (m, 3H), 3.56 (dd, J = 10.0, 7.9 Hz, 1H), 3.12 (td, J = 8.1, 2.8 Hz, 1H), 1.38–

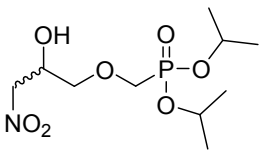
1.29 (m, 12H), 0.84 (qt, J = 8.2, 4.9 Hz, 1H), 0.59–0.49 (m, 1H), 0.49–0.42 (m, 1H), 0.38 (dtd, J = 9.1, 5.2, 3.9 Hz, 1H), 0.22 (dtd, J = 9.1, 5.3, 4.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 77.94 (d, J = 9.5 Hz), 74.83, 71.37 (d, J = 6.6 Hz), 71.34 (d, J = 6.6 Hz), 66.41 (d, J = 167.9 Hz), 24.22 (d, J = 3.8 Hz), 24.15 (d, J = 4.4 Hz), 13.33, 2.63, 1.85. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.08. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{12}H_{25}O_5PNa$ 303.13318, found 303.13345.

Diisopropyl ((3,3,3-trifluoro-2-hydroxypropoxy)methyl)phosphonate ((*RS*)-**9f**)



$TMSCF_3$ (522 µL, 3.53 mmol) and TBAF (1M in THF, 291 µL, 0.29 mmol) were added to a solution of compound **8** (700 mg, 2.94 mmol) in anhydrous THF (10 mL). The mixture was stirred at 25 °C for 1 h, quenched with H_2O, and extracted with EtOAc (3 × 70 mL). Combined organic fractions were washed with brine (1 × 70 mL), dried over $MgSO_4$, and concentrated to afford (*RS*)-**9f** (867 mg, 96%) as a brownish oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.82–4.65 (m, 2H), 4.20–4.09 (m, 1H), 3.92–3.72 (m, 4H), 1.36–1.28 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 124.40 (q, J = 282.3 Hz), 72.25–72.04 (m), 72.00–71.83 (m), 69.80 (q, J = 30.6 Hz), 66.95 (d, J = 168.1 Hz), 24.34–23.89 (m). **^{19}F NMR** (376 MHz, $CDCl_3$) δ −77.47. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.92. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{10}H_{20}O_5F_3PNa$ 331.08927, found 331.08930.

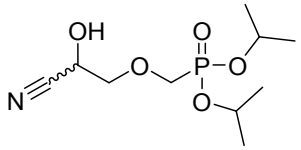
Diisopropyl ((2-hydroxy-3-nitropropoxy)methyl)phosphonate ((*RS*)-**9g**)



Nitromethane (68 µL, 1.26 mmol) was added to a suspension of NaH (50 mg, 1.26 mmol, 60% in mineral oil) in anhydrous THF (1 mL). The mixture was stirred for 10 min and the solution of compound **8** (100 mg, 0.42 mmol) in anhydrous THF (1 mL) was added. The mixture was stirred at 25 °C for 1 h, quenched with H_2O, and extracted with EtOAc (3 × 30 mL). Combined organic

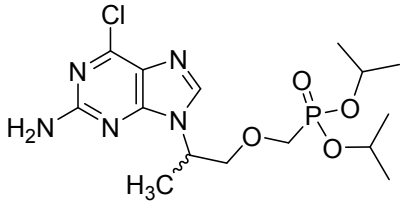
fractions were washed with brine (1 × 30 mL), dried over $MgSO_4$, and concentrated to afford (*RS*)-**9g** (68 mg, 54%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.80–4.68 (m, 2H), 4.54–4.45 (m, 3H), 3.86–3.67 (m, 4H), 1.33 (d, J = 6.3, 12H). **^{13}C NMR** (101 MHz, CDCl3) δ 77.98, 74.52 (d, J = 8.9 Hz), 71.78 (d, J = 6.6 Hz), 71.74 (d, J = 6.7 Hz), 67.94, 66.75 (d, J = 168.0 Hz), 24.32–24.01 (m). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.82. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{10}H_{22}O_7NPNa$ 322.10261, found 322.10283.

Diisopropyl ((2-cyano-2-hydroxyethoxy)methyl)phosphonate ((*RS*)-**9h**)



KCN (684 mg, 10.50 mmol) was added to a solution of compound **8** (50 mg, 0.21 mmol) in H_2O/1,4-dioxane (1:1 ratio) (5 mL). The mixture was stirred at 25 °C for 1 h and extracted with EtOAc (3 × 30 mL). Combined organic fractions were washed with brine (1 × 30 mL), dried over $MgSO_4$, and concentrated to afford (*RS*)-**9h** (50 mg, 89%) as a colorless oil. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 4.89–4.71 (m, 2H), 4.59 (dd, J = 4.8, 3.1 Hz, 1H), 4.04–3.92 (m, 2H), 3.87–3.78 (m, 2H), 1.37–1.32 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 118.05, 75.82 (d, J = 6.7 Hz), 72.65 (d, J = 7.1 Hz), 72.15 (d, J = 7.1 Hz), 67.73 (d, J = 168.1 Hz), 61.69, 24.29–24.05 (m). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.54. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{10}H_{20}O_5NPNa$ 288.09713, found 288.09721.

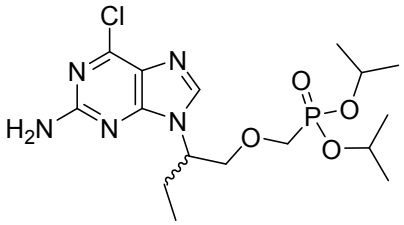
Diisopropyl ((2-(2-amino-6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**10a**)



Following standard procedure E, compound (*RS*)-**9a** (300 mg, 1.18 mmol) reacted with 2-amino-6-chloropurine (190 mg, 1.12 mmol), PPh_3 (310 mg, 1.18 mmol), and DIAD (232 µL, 1.18 mmol)

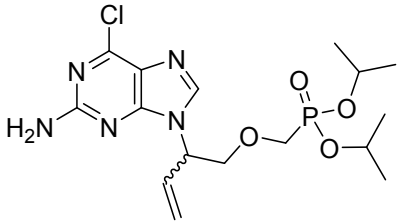
in anhydrous THF (6 mL) to afford (*RS*)-**10a** (336 mg, 74%), as a yellow oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.19 (s, 1H), 6.86 (s, 2H), 4.75–4.64 (m, 1H), 4.50–4.38 (m, 2H), 3.97 (dd, J = 10.2, 8.0 Hz, 1H), 3.84–3.66 (m, 3H), 1.46 (d, J = 7.0 Hz, 3H), 1.18–1.12 (m, 6H), 1.12–1.04 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 159.56, 153.94, 149.27, 141.79, 123.49, 73.82 (d, J = 11.5 Hz), 70.98–69.41 (m), 64.76 (d, J = 163.7 Hz), 49.83, 23.70 (d, J = 3.7 Hz), 23.52 (d, J = 4.4 Hz), 16.41. **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.24. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{15}H_{25}O_4N_5ClNaP$ 428.12249, found 428.12297.

Diisopropyl ((2-(2-amino-6-chloro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*RS*)-**10b**)



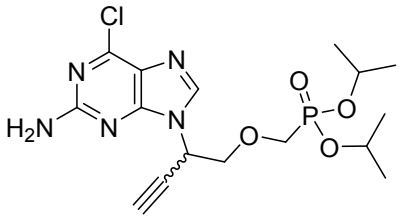
Following standard procedure E, compound (*RS*)-**9b** (400 mg, 1.49 mmol) reacted with 2-amino-6-chloropurine (241 mg, 1.42 mmol), PPh_3 (391 mg, 1.49 mmol), and DIAD (292 µL, 1.49 mmol) in anhydrous THF (10 mL) to afford (*RS*)-**10b** (385 mg, 65%), as a yellow oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.18 (s, 1H), 6.86 (s, 2H), 4.52–4.35 (m, 3H), 4.02 (dd, J = 10.3, 8.2 Hz, 1H), 3.84–3.64 (m, 3H), 1.99–1.79 (m, 2H), 1.18–1.11 (m, 6H), 1.11–1.04 (m, 6H), 0.76 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 159.59, 154.33, 149.28, 142.12, 123.42, 72.78 (d, J = 11.6 Hz), 70.34–70.05 (m), 64.73 (d, J = 163.7 Hz), 55.89, 23.69 (d, J = 3.7 Hz), 23.49 (d, J = 4.6 Hz), 23.11, 10.24. **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.21. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{16}H_{27}O_4N_5ClNaP$ 442.13814, found 442.13807.

Diisopropyl (((2-(2-amino-6-chloro-9*H*-purin-9-yl)but-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**10c**)



Following standard procedure E, compound (*RS*)-**9c** (300 mg, 1.13 mmol) reacted with 2-amino-6-chloropurine (183 mg, 1.08 mmol), PPh_3 (296 mg, 1.13 mmol), and DIAD (221 µL, 1.13 mmol) in anhydrous THF (6 mL) to afford (*RS*)-**10c** (182 mg, 40%), as a yellow oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.20 (s, 1H), 6.90 (s, 2H), 6.14 (ddd, J = 17.3, 10.5, 5.9 Hz, 1H), 5.28 (dt, J = 10.5, 1.2 Hz, 1H), 5.22 (dddt, J = 8.7, 5.8, 4.2, 1.5 Hz, 1H), 5.09 (dt, J = 17.2, 1.2 Hz, 1H), 4.51–4.39 (m, 2H), 4.16 (dd, J = 10.4, 8.7 Hz, 1H), 3.92 (dd, J = 10.4, 4.3 Hz, 1H), 3.81 (dd, J = 13.9, 8.4 Hz, 1H), 3.74 (dd, J = 13.9, 8.4 Hz, 1H), 1.17–1.13 (m, 6H), 1.11–1.06 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 159.68, 153.99, 149.41, 141.97, 133.18, 123.25, 118.54, 72.12 (d, J = 11.3 Hz), 70.24 (d, J = 6.1 Hz), 64.70 (d, J = 164.3 Hz), 55.90, 23.69 (d, J = 3.8 Hz), 23.50 (d, J = 4.7 Hz). **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.15. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{16}H_{25}O_4N_5ClNaP$ 440.12249, found 440.12295.

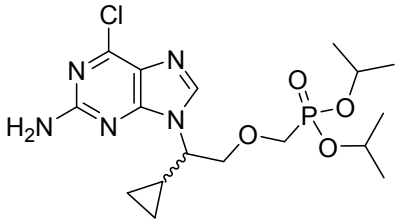
Diisopropyl (((2-(2-amino-6-chloro-9*H*-purin-9-yl)but-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**10d**)



Following standard procedure E, compound (*RS*)-**9d** (300 mg, 1.14 mmol) reacted with 2-amino-6-chloropurine (185 mg, 1.09 mmol), PPh_3 (299 mg, 1.14 mmol), and DIAD (224 µL, 1.14 mmol) in anhydrous THF (6 mL) to afford (*RS*)-**10d** (139 mg, 43%), as a yellow oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.00 (s, 2H), 5.54 (ddd, J = 7.9, 4.4, 2.5 Hz, 1H), 4.52–4.38 (m, 2H),

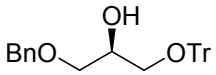
4.21 (dd, J = 10.4, 8.0 Hz, 1H), 3.98 (dd, J = 10.4, 4.4 Hz, 1H), 3.88–3.74 (m, 2H), 3.70 (d, J = 2.5 Hz, 1H), 1.17–1.13 (m, 6H), 1.11–1.06 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 159.79, 153.43, 149.61, 141.51, 123.15, 77.78, 77.54, 71.98 (d, J = 11.9 Hz), 70.27 (d, J = 6.6 Hz), 70.24 (d, J = 6.4 Hz, 1H), 64.72 (d, J = 164.0 Hz), 45.11, 23.69 (d, J = 3.8 Hz), 23.58–23.43 (m). **^{31}P NMR** (162 MHz, DMSO-d_6) δ 20.91. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{16}H_{23}O_4N_5ClNaP$ 438.10684, found 438.10743.

Diisopropyl ((2-(2-amino-6-chloro-9*H*-purin-9-yl)-2-cyclopropylethoxy)methyl)phosphonate ((*RS*)-**10e**)



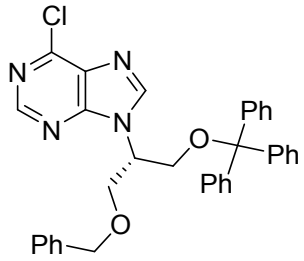
Following standard procedure E, compound (*RS*)-**9e** (600 mg, 2.14 mmol) reacted with 2-amino-6-chloropurine (346 mg, 2.04 mmol), PPh_3 (561 mg, 2.14 mmol), and DIAD (420 µL, 2.14 mmol) in anhydrous THF (10 mL) to afford (*RS*)-**10e** (221 mg, 25%), as a yellow oil. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.24 (s, 1H), 6.85 (s, 2H), 4.48–4.36 (m, 2H), 4.20 (dd, J = 10.3, 8.6 Hz, 1H), 3.91 (dd, J = 10.2, 3.8 Hz, 1H), 3.84–3.78 (m, 1H), 3.78–3.65 (m, 2H), 1.48 (dddd, J = 12.8, 9.8, 7.9, 4.9 Hz, 1H), 1.16–1.11 (m, 6H), 1.09–1.03 (m, 6H), 0.71–0.59 (m, 1H), 0.52–0.39 (m, 2H), 0.32–0.21 (m, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 159.59, 154.09, 149.29, 142.18, 123.41, 72.59 (d, J = 11.7 Hz), 70.36–69.81 (m), 64.73 (d, J = 163.7 Hz), 59.35, 23.68 (d, J = 3.8 Hz), 23.48 (d, J = 4.4 Hz), 12.01, 4.31, 3.17. **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.18. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{17}H_{27}O_4N_5ClNaP$ 454.13814, found 454.13776.

(*R*)-1-(Benzyloxy)-3-(trityloxy)propan-2-ol (**11**)



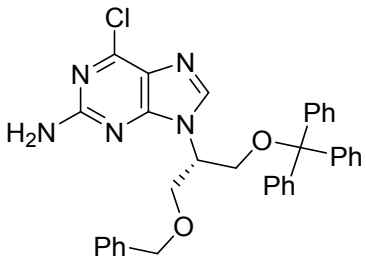
To a suspension of NaH (3.79 g, 94.82 mmol) in anhydrous DMF (85 mL) was at 25 °C added BnOH (9.81 mL, 94.82 mmol) over the period of 15 min. The mixture was stirred for further 10 min at 25 °C. A solution of (*R*)-glycidyl trityl ether (25.00 g, 79.02 mmol) in anhydrous DMF (40 mL) was added over the period of 15 min and the mixture was stirred at 100 °C for 3 h. The reaction was quenched with H_2O and extracted with EtOAc (3 × 300 mL). Organic fractions were combined, washed with brine (1 × 200 mL), dried over $MgSO_4$, and concentrated. The residual BnOH was removed using in vacuo distillation to afford **11** (32.93 g, 98%) as a white solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 7.43–7.17 (m, 20H), 4.96 (d, J = 5.5 Hz, 1H), 4.45 (s, 2H), 3.87–3.77 (m, 1H), 3.53–3.40 (m, 2H), 3.01–2.93 (m, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 143.93, 138.50, 128.45–126.68 (m), 85.71, 72.15, 71.71, 68.67, 65.12. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{29}H_{28}O_3Na$ 447.19307, found 447.19295. **$[\alpha]^{25}_D$** = +1.7 (c 0.356 g/100 mL, $CHCl_3$/MeOH 1/1).

(*S*)-9-(1-(Benzyloxy)-3-(trityloxy)propan-2-yl)-6-chloro-9*H*-purine ((*S*)-**12a**)



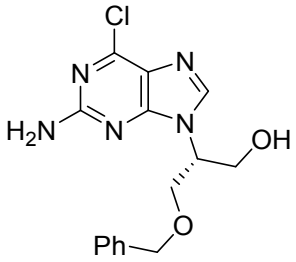
Following standard procedure E, compound **11** (550 mg, 1.30 mmol) reacted with 6-chloropurine (192 mg, 1.24 mmol), PPh_3 (340 g, 1.30 mmol), and DIAD (255 µL, 1.30 mmol) in anhydrous THF (8 mL) to obtain (*S*)-**12a** (600 mg, 86%) as a white solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.64 (s, 1H), 7.26–7.05 (m, 20H), 5.16–5.10 (m, 1H), 4.47 (d, J = 3.4 Hz, 2H), 4.19 (dd, J = 10.4, 8.2 Hz, 1H), 3.97 (dd, J = 10.3, 5.2 Hz, 1H), 3.56 (dd, J = 9.9, 7.3 Hz, 1H), 3.46 (dd, J = 9.9, 3.9 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 151.92, 151.20, 149.02, 147.03, 143.02, 137.69, 130.95, 128.56–126.57 (m), 86.12, 71.96, 66.83, 61.59, 56.10. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{34}H_{29}O_2N_4ClNa$ 583.18713, found 583.18640. **$[\alpha]^{25}_D$** = +8.9 (c 0.293 g/100 mL, $CHCl_3$/MeOH 1/1).

(*S*)-9-(1-(Benzyloxy)-3-(trityloxy)propan-2-yl)-6-chloro-9*H*-purin-2-amine ((*S*)-**12b**)



Following standard procedure E, compound **11** (550 mg, 1.30 mmol) reacted with 2-amino-6-chloropurine (210 mg, 1.24 mmol), PPh_3 (340 g, 1.30 mmol), and DIAD (255 µL, 1.30 mmol) in anhydrous THF (8 mL) to obtain (*S*)-**12b** (495 mg, 69%) as a white solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.34–7.09 (m, 20H), 6.87 (s, 2H), 4.87–4.81 (m, 1H), 4.48 (s, 2H), 4.10 (dd, J = 10.2, 7.7 Hz, 1H), 3.90 (dd, J = 10.2, 5.4 Hz, 1H), 3.45 (dd, J = 9.7, 7.0 Hz, 1H), 3.32–3.25 (m, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 159.65, 154.36, 149.34, 143.15, 142.39, 137.81, 128.69–126.67 (m), 123.33, 86.08, 72.02, 67.22, 62.07, 54.71. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{34}H_{30}O_2N_5ClNa$ 598.19802, found 598.19763. **$[\alpha]^{25}_D$** = −10.1 (c 0.345 g/100 mL, $CHCl_3$/MeOH 1/1).

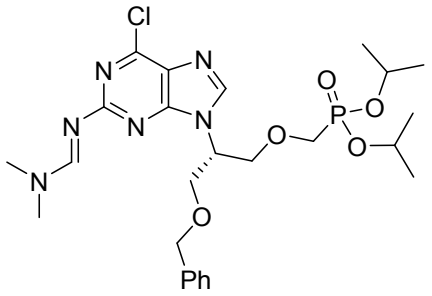
(*R*)-2-(2-Amino-6-chloro-9*H*-purin-9-yl)-3-(benzyloxy)propan-1-ol ((*R*)-**13**)



Compound (*S*)-**12b** (180 mg, 0.31 mmol) was stirred at 0 °C in DCM/TFA (2.5 mL, 4:1 ratio) for 30 min. The mixture was diluted with 25 mL of DCM and TFA was washed away with H_2O (3 × 25 mL). DCM was washed with brine and dried over $MgSO_4$. The residue was purified using silica gel flash chromatography (linear gradient elution 0 – 10% MeOH in $CHCl_3$) to afford (*R*)-**13** (102 mg, 99%) as a white solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.33–7.20 (m, 3H), 7.20–7.15 (m, 2H), 6.86 (s, 2H), 5.12 (t, J = 5.4 Hz, 1H), 4.63 (ddt, J = 7.8, 6.7, 4.9 Hz, 1H), 4.49 (d, J = 12.2 Hz, 1H), 4.44 (d, J = 12.1 Hz, 1H), 3.96–3.74 (m, 4H), 3.13–2.91 (m, 4H). **^{13}C**

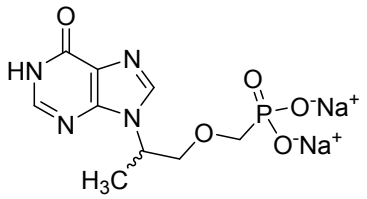
NMR (101 MHz, DMSO-d_6) δ 159.56, 154.38, 149.22, 142.49, 137.93, 128.23, 127.51, 127.38, 123.37, 72.04, 67.87, 59.68, 56.59. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{15}H_{16}O_2N_5ClNa$ 356.08847, found 356.08820. $\mathbf{[\alpha]^{25}_D}$ = +15.8 (c 0.277 g/100 mL, $CHCl_3$/MeOH 1/1).

Diisopropyl (*S*)-((3-(benzyloxy)-2-(6-chloro-2-((((dimethylamino)methylene)amino)-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*S*)-**14**)



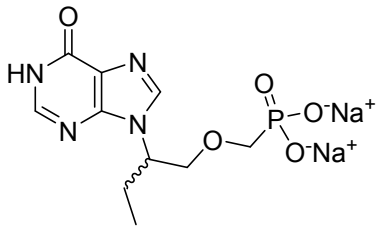
Compound (*R*)-**13** (50 mg, 0.15 mmol) was stirred with DMF DMA (60 µL, 0.45 mmol) in DMF (1 mL) at 80 °C for 15 min. The mixture was concentrated and co-distilled 3 × with toluene to yield (*R*)-*N*′-(9-(1-(benzyloxy)-3-hydroxypropan-2-yl)-6-chloro-9*H*-purin-2-yl)-*N*,*N*-dimethylformimidamide (58 mg, 99%) as a white solid which was used directly in the following reaction. Following standard procedure B, (*R*)-*N*′-(9-(1-(benzyloxy)-3-hydroxypropan-2-yl)-6-chloro-9*H*-purin-2-yl)-*N*,*N*-dimethylformimidamide (58 mg, 0.15 mmol) reacted with *n*-BuLi (2.5 M in hexanes, 69 µL, 0.17 mmol) and diisopropyl triflyloxymethanephosphonate (75 mg, 0.23 mmol) in anhydrous THF (1 mL) to afford (*S*)-**14** (53 mg, 62%) as a colorless viscose oil. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.38 (s, 1H), 7.31–7.22 (m, 3H), 7.21–7.13 (m, 2H), 5.00 (tt, J = 7.8, 4.6 Hz, 1H), 4.53–4.39 (m, 4H), 4.16 (dd, J = 10.4, 8.1 Hz, 1H), 4.01–3.91 (m, 2H), 3.90–3.70 (m, 3H), 3.15 (s, 3H), 3.04 (s, 3H), 1.15–1.12 (m, 6H), 1.06 (d, J = 6.1 Hz, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 161.73, 158.45, 153.81, 148.75, 144.09, 137.76, 128.18, 127.52, 127.38, 126.11, 72.05, 70.48 (d, J = 11.6 Hz), 70.24–69.91 (m), 67.28, 64.77 (d, J = 163.5 Hz), 54.13, 40.45, 34.62, 23.65 (d, J = 3.7 Hz), 23.47 (d, J = 4.4 Hz). **^{31}P NMR** (162 MHz, DMSO-d_6) δ 21.04. **HRMS** (ESI) m/z $[M+Na]^+$ calcd for $C_{25}H_{36}O_5N_6ClNaP$ 589.20655, found 589.20581. $\mathbf{[\alpha]^{25}_D}$ = +4.9 (c 0.061 g/100 mL, $CHCl_3$/MeOH 1/1).

Sodium ((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**15a**)



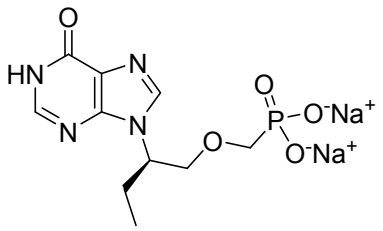
Following standard procedure F, compound (*RS*)-**4g** (180 mg, 0.46 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (145 mg, 0.39 mmol) was stirred in anhydrous MeCN (3.9 mL) and TMSBr (390 μL) at 25 °C for 16 h to yield (*RS*)-**15a** (108 mg, 71% over 2 steps) as an off-white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.31 (s, 1H), 8.17 (s, 1H), 4.97–4.87 (m, 1H), 4.02–3.93 (m, 2H), 3.50–3.44 (m, 2H), 1.58 (d, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 159.23, 149.34, 145.97, 141.44, 123.90, 75.07 (d, J = 10.3 Hz), 67.96 (d, J = 155.5 Hz), 51.93, 16.84. **^{31}P NMR** (162 MHz, D_2O) δ 18.04. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_9H_{12}O_5N_4P$ 287.05508, found 287.05535.

Sodium ((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*RS*)-**15b**)



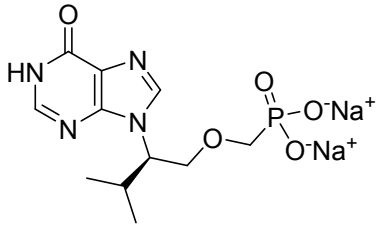
Following standard procedure F, compound (*RS*)-**4a** (121 mg, 0.30 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (65 mg, 0.17 mmol) was stirred in anhydrous MeCN (1.7 mL) and TMSBr (170 μL) at 25 °C for 16 h to yield (*RS*)-**15b** (40 mg, 38% over 2 steps) as an off-white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.31 (s, 1H), 8.17 (s, 1H), 4.75–4.66 (m, 1H), 4.05 (dd, J = 11.0, 7.8 Hz, 1H), 3.99 (dd, J = 11.0, 4.0 Hz, 1H), 3.49 (d, J = 8.3 Hz, 2H), 2.05–1.92 (m, 2H), 0.79 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 159.35, 149.84, 146.06, 141.78, 123.88, 74.14, 67.72 (d, J = 156.6 Hz), 57.99, 24.49, 10.11. **^{31}P NMR** (162 MHz, D_2O) δ 18.15. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{10}H_{14}O_5N_4P$ 301.07073, found 301.06995.

Sodium (*R*)-((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**15b**)



Following standard procedure F, compound (*R*)-**4a** (174 mg, 0.43 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivatives (125 mg, 0.32 mmol) was stirred in anhydrous MeCN (3.2 mL) and TMSBr (320 µL) at 25 °C for 16 h to yield (*R*)-**15b** (103 mg, 69% over 2 steps) as an off-white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.31 (s, 1H), 8.17 (s, 1H), 4.70 (dddd, J = 9.0, 7.7, 6.0, 4.3 Hz, 1H), 4.09–3.95 (m, 2H), 3.48 (d, J = 8.3 Hz, 2H), 2.07–1.90 (m, 2H), 0.79 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 159.47, 149.85, 146.18, 141.85, 123.88, 73.89 (d, J = 9.5 Hz), 69.36 (d, J = 151.2 Hz), 58.15, 24.71, 10.10. **^{31}P NMR** (162 MHz, D_2O) δ 16.23. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{10}H_{14}O_5N_4P$ 301.07073, found 301.07027. **$[\alpha]^{25}_{D}$** = +3.8 (c 0.280 g/100 mL, H_2O/MeOH 1/1).

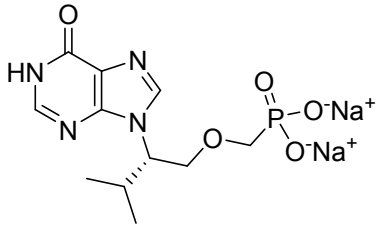
Sodium (*R*)-((3-methyl-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**15c**)



Following standard procedure F, compound (*R*)-**4b** (235 mg, 0.56 mmol) was converted to 6-oxo derivative. Following standard procedure G, 6-oxo derivatives (140 mg, 0.35 mmol) was stirred in anhydrous MeCN (3.5 mL) and TMSBr (350 µL) at 25 °C for 16 h to yield (*R*)-**15c** (84 mg, 42% over 2 steps) as an off-white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.33 (s, 1H), 8.17 (s, 1H), 4.49 (td, J = 8.6, 3.5 Hz, 1H), 4.16 (dd, J = 11.1, 8.2 Hz, 1H), 4.04 (dd, J = 11.1, 3.5 Hz, 1H), 3.56–3.47 (m, 2H), 2.34 (d of septets, J = 8.9, 6.7 Hz, 1H), 1.05 (d, J = 6.7 Hz, 3H), 0.72 (d, J = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 159.39, 149.97, 146.11, 142.10, 123.64, 72.33 (d, J = 10.2 Hz), 68.68

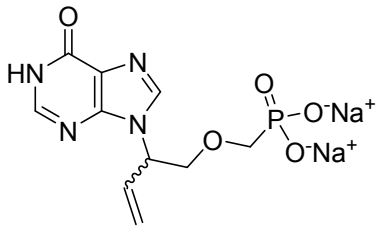
(d, J = 153.2 Hz), 62.12, 30.48, 19.51, 18.97. **^{31}P NMR** (162 MHz, D_2O) δ 16.95. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{11}H_{16}O_5N_4P$ 315.08638, found 315.08615. **$[\alpha]^{25}_D$** = +4.7 (c 0.232 g/100 mL, H_2O/MeOH 1/1).

Sodium (*S*)-((3-methyl-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*S*)-**15c**)



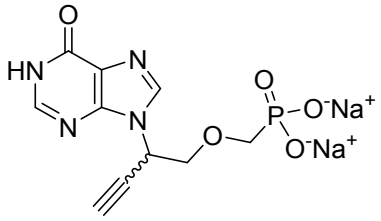
Following standard procedure F, compound (*S*)-**4b** (209 mg, 0.50 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (135 mg, 0.30 mmol) was stirred in anhydrous MeCN (3.0 mL) and TMSBr (300 μL) at 25 °C for 16 h to yield (*S*)-**15c** (65 mg, 36% over 2 steps) as an off-white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.26 (s, 1H), 8.09 (s, 1H), 4.41 (td, J = 8.6, 3.5 Hz, 1H), 4.07 (dd, J = 11.1, 8.2 Hz, 1H), 3.97 (dd, J = 11.1, 3.6 Hz, 1H), 3.40 (d, J = 8.3 Hz, 2H), 2.26 (d of septets, J = 9.1, 6.8 Hz, 1H), 0.97 (d, J = 6.7 Hz, 3H), 0.65 (d, J = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 159.45, 150.01, 146.13, 142.12, 123.66, 72.32 (d, J = 10.1 Hz), 69.02 (d, J = 152.4 Hz), 62.15, 30.51, 19.55, 18.95. **^{31}P NMR** (162 MHz, D_2O) δ 16.56. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{11}H_{16}O_5N_4P$ 315.08638, found 315.08628. **$[\alpha]^{25}_D$** = −3.7 (c 0.240 g/100 mL, H_2O/MeOH 1/1).

Sodium (((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)but-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**15d**)



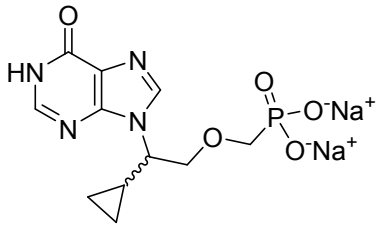
Following standard procedure F, compound (*RS*)-**4h** (209 mg, 0.52 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (70 mg, 0.18 mmol) was stirred in anhydrous MeCN (1.8 mL) and TMSBr (180 µL) at 25 °C for 16 h to yield (*RS*)-**15d** (53 mg, 30% over 2 steps) as an off-white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.32 (s, 1H), 8.16 (s, 1H), 6.18 (ddd, J = 17.3, 10.6, 5.5 Hz, 1H), 5.45–5.40 (m, 1H), 5.39–5.33 (m, 1H), 5.13–5.05 (m, 1H), 4.18 (dd, J = 10.9, 7.8 Hz, 1H), 4.12 (dd, J = 10.9, 4.5 Hz, 1H), 3.59 (d, J = 8.3 Hz, 2H). **^{13}C NMR** (101 MHz, D_2O) δ 159.32, 149.42, 146.22, 142.02, 133.11, 123.94, 119.41, 73.09 (d, J = 10.3 Hz), 68.73 (d, J = 153.3 Hz), 57.81. **^{31}P NMR** (162 MHz, D_2O) δ 17.41. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{10}H_{12}O_5N_4P$ 299.05508, found 299.05441.

Sodium (((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)but-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**15e**)



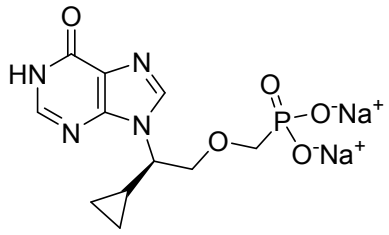
Following standard procedure F, compound (*RS*)-**4i** (184 mg, 0.46 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (120 mg, 0.31 mmol) was stirred in anhydrous MeCN (3.1 mL) and TMSBr (310 µL) at 25 °C for 16 h to yield (*RS*)-**15e** (88 mg, 56% over 2 steps) as an off-white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.38 (s, 1H), 8.18 (s, 1H), 5.70 (ddd, J = 6.9, 4.7, 1.9 Hz, 1H), 4.20–4.06 (m, 2H), 3.64–3.53 (m, 2H), 3.07 (d, J = 2.5 Hz, 1H). **^{13}C NMR** (101 MHz, D_2O) δ 159.25, 148.94, 146.43, 141.88, 124.12, 77.43, 77.20, 77.16, 73.85 (d, J = 10.4 Hz), 68.96 (d, J = 154.1 Hz), 47.52. **^{31}P NMR** (162 MHz, D_2O) δ 17.35. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{10}H_{10}O_5N_4P$ 297.03943, found 297.03932.

Sodium ((2-cyclopropyl-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethoxy)methyl)phosphonate ((*RS*)-**15f**)



Following standard procedure F, compound (*RS*)-**4c** (100 mg, 0.24 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (90 mg, 0.23 mmol) was stirred in anhydrous MeCN (2.3 mL) and TMSBr (230 µL) at 25 °C for 16 h to yield (*RS*)-**15f** (75 mg, 87% over 2 steps) as an off-white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.39 (s, 1H), 8.15 (s, 1H), 4.20–4.08 (m, 2H), 4.05 – 3.98 (m, 1H), 3.46 (d, J = 8.3 Hz, 2H), 1.58–1.48 (m, 1H), 0.82–0.73 (m, 1H), 0.60–0.47 (m, 2H), 0.32–0.24 (m, 1H). **^{13}C NMR** (101 MHz, D_2O) δ 159.67, 149.59, 146.27, 141.97, 123.84, 73.93 (d, J = 9.5 Hz), 69.75 (d, J = 150.4 Hz), 61.62, 12.76, 5.15, 3.26. **^{31}P NMR** (162 MHz, D_2O) δ 17.82. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{11}H_{14}O_5N_4P$ 313.07073, found 313.07028.

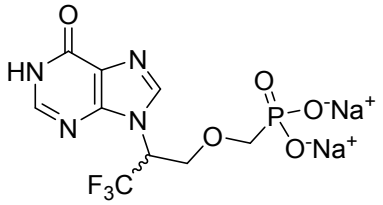
Sodium (*R*)-((2-cyclopropyl-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethoxy)methyl)phosphonate ((*R*)-**15f**)



Following standard procedure F, compound (*R*)-**4c** (100 mg, 0.24 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (88 mg, 0.22 mmol) was stirred in anhydrous MeCN (2.3 mL) and TMSBr (230 µL) at 25 °C for 16 h to yield (*R*)-**15f** (76 mg, 88% over 2 steps) as an off-white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.38 (s, 1H), 8.15 (s, 1H), 4.18 (dd, J = 11.1, 7.7 Hz, 1H), 4.14–4.02 (m, 1H), 4.02–3.96 (m, 1H), 3.62–3.48 (m, 2H), 1.58–1.49 (m, 1H), 0.78 (tdd, J = 9.4, 4.5, 3.1 Hz, 1H), 0.57–0.47 (m, 2H), 0.29 (tdd, J = 9.3, 6.8, 4.1 Hz,

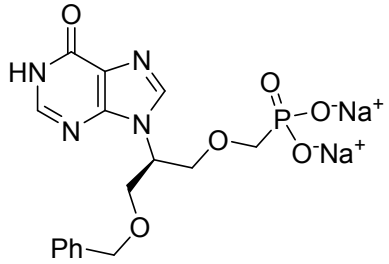
1H). **^{13}C NMR** (101 MHz, D_2O) δ 159.33, 149.51, 146.03, 141.94, 123.83, 74.06 (d, J = 10.2 Hz), 68.59 (d, J = 154.1 Hz), 61.55, 12.58, 5.13, 3.32. **^{31}P NMR** (162 MHz, D_2O) δ 17.28. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{11}H_{14}O_5N_4P$ 313.07073, found 313.07041. **$[\alpha]^{25}_D$** = +7.3 (c 0.246 g/100 mL, H_2O/MeOH 1/1).

Sodium ((3,3,3-trifluoro-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**15g**)



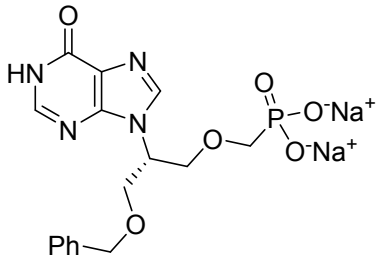
Following standard procedure F, compound (*RS*)-**4j** (67 mg, 0.15 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (48 mg, 0.11 mmol) was stirred in anhydrous MeCN (1.1 mL) and TMSBr (110 µL) at 25 °C for 16 h to yield (*RS*)-**15g** (24 mg, 41% over 2 steps) as an off-white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.35 (s, 1H), 8.19 (s, 1H), 4.71 (dd, J = 15.2, 4.3 Hz, 1H), 4.61 (dd, J = 15.1, 6.0 Hz, 1H), 4.52–4.40 (m, 1H), 3.81 (dd, J = 12.3, 9.3 Hz, 1H), 3.58 (dd, J = 12.4, 9.1 Hz, 1H). **^{13}C NMR** (101 MHz, D_2O) δ 159.42, 149.64, 146.52, 143.92, 124.87 (q, J = 250.1 Hz), 123.29, 78.01–76.54 (m), 71.15 (d, J = 150.7 Hz), 42.76. **^{31}P NMR** (162 MHz, D_2O) δ 14.46. **^{19}F NMR** (377 MHz, D_2O) δ −75.39 (d, J = 6.3 Hz). **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_9H_9O_5N_4F_3P$ 341.02681, found 341.02600.

Sodium (*R*)-((3-(benzyloxy)-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*R*)-**15h**)



Following standard procedure F, compound (*R*)-**4d** (89 mg, 0.18 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (80 mg, 0.17 mmol) was stirred in anhydrous MeCN (1.7 mL) and TMSBr (170 μL) at 25 °C for 60 h to yield (*R*)-**15h** (22 mg, 28% over 2 steps) as a white solid (and (*R*)-**15i** (21 mg, 33% over 2 steps) as a white solid). [Note: Shorter reaction time preferentially leads to the cleavage of phosphonate esters while longer reaction time leads also to the product with cleaved benzyl group.] **^{1}H NMR** (401 MHz, D_2O) δ 8.19 (s, 1H), 7.96 (s, 1H), 7.25–7.12 (m, 3H), 7.03–6.96 (m, 2H), 4.89 (tt, J = 7.5, 4.6 Hz, 1H), 4.49 (d, J = 12.2 Hz, 1H), 4.38 (d, J = 12.2 Hz, 1H), 4.13–3.96 (m, 4H), 3.52 (d, J = 8.5 Hz, 2H). **^{13}C NMR** (101 MHz, D_2O) δ 159.16, 149.28, 145.69, 142.30, 137.17, 128.94, 128.84, 128.68, 123.98, 73.24, 70.75 (d, J = 10.6 Hz), 69.05 (d, J = 153.0 Hz), 67.85, 56.63. **^{31}P NMR** (162 MHz, D_2O) δ 16.57. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{16}H_{18}O_6N_4P$ 393.09694, found 393.09641. **$[\alpha]^{25}_D$** = +15.3 (c 0.183 g/100 mL, H_2O/MeOH 1/1).

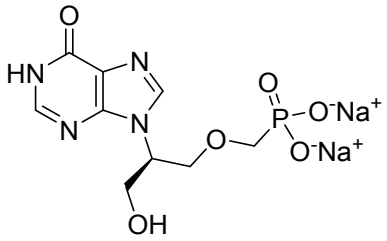
Sodium (*S*)-((3-(benzyloxy)-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*S*)-**15h**)



Following standard procedure F, compound (*S*)-**4d** (119 mg, 0.24 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (100 mg, 0.21 mmol) was stirred in anhydrous MeCN (2.1 mL) and TMSBr (210 μL) at 25 °C for 16 h to yield (*S*)-**15h** (32 mg, 30% over 2 steps) as an off-white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.19 (s, 1H), 7.96 (s, 1H), 7.28–7.15 (m, 3H), 7.00–6.97 (m, 2H), 4.89 (tt, J = 7.6, 4.6 Hz, 1H), 4.50 (d, J = 12.3 Hz, 1H), 4.38 (d, J = 12.2 Hz, 1H), 4.11–3.96 (m, 4H), 3.53 (d, J = 8.4 Hz, 2H). **^{13}C NMR** (101 MHz, D_2O) δ 149.29, 145.69, 142.30, 137.18, 128.94, 128.84, 128.69, 123.98, 73.25, 70.76 (d, J = 10.5 Hz), 68.96 (d, J = 152.8 Hz), 67.85, 56.63. **^{31}P NMR** (162 MHz, D_2O) δ 16.68. **HRMS** (ESI) m/z

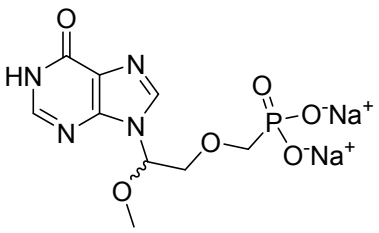
[M−H]$^-$ calcd for $C_{16}H_{18}O_6N_4P$ 393.09694, found 393.09663. **[α]$^{25}_D$** = −5.4 (c 0.239 g/100 mL, H_2O/MeOH 1/1).

Sodium (*R*)-((3-hydroxy-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*R*)-**15i**)



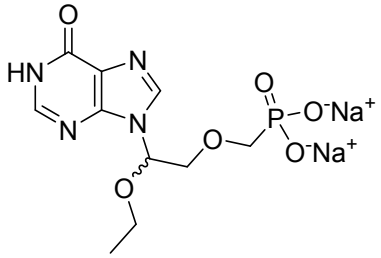
Following standard procedure F, compound (*R*)-**4d** (89 mg, 0.18 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (80 mg, 0.17 mmol) was stirred in anhydrous MeCN (1.7 mL) and TMSBr (170 μL) at 25 °C for 60 h to yield (*R*)-**15i** (21 mg, 33% over 2 steps) as a white solid (and (*R*)-**15h** (22 mg, 28% over 2 steps) as a white solid). [Note: Shorter reaction time preferentially leads to the cleavage of phosphonate esters while longer reaction time leads also to the derivative with cleaved benzyl group.] **^{1}H NMR** (401 MHz, D_2O) δ 8.36 (s, 1H), 8.18 (s, 1H), 4.90 (tt, J = 6.7, 4.8 Hz, 1H), 4.15–3.99 (m, 4H), 3.56 (d, J = 8.4 Hz, 2H). **^{13}C NMR** (101 MHz, D_2O) δ 159.35, 149.77, 146.21, 142.03, 123.78, 71.00 (d, J = 10.4 Hz), 69.06 (d, J = 152.9 Hz), 61.09, 57.44. **^{31}P NMR** (162 MHz, D_2O) δ 16.71. **HRMS** (ESI) m/z [M−H]$^-$ calcd for $C_9H_{12}O_6N_4P$ 303.04999, found 303.04962. **[α]$^{25}_D$** = +3.7 (c 0.214 g/100 mL, H_2O/MeOH 1/1).

Sodium ((2-methoxy-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethoxy)methyl)phosphonate ((*RS*)-**15j**)



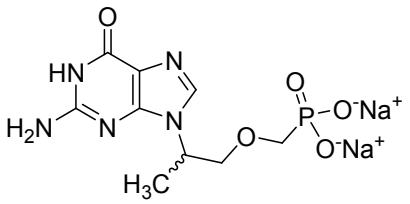
Following standard procedure H, compound (*RS*)-**4e** (281 mg, 0.69 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (150 mg, 0.39 mmol) was stirred in anhydrous pyridine (3.9 mL) and TMSBr (390 µL) at 25 °C for 16 h to yield (*RS*)-**15j** (78 mg, 33% over 2 steps) as a white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.25 (s, 1H), 8.12 (s, 1H), 5.80 (t, J = 5.2 Hz, 1H), 4.04 (dd, J = 11.0, 5.4 Hz, 1H), 3.99 (dd, J = 11.0, 5.1 Hz, 1H), 3.62–3.53 (m, 2H), 3.29 (s, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 159.33, 149.55, 146.63, 141.34, 124.30, 85.38, 72.84 (d, J = 10.9 Hz), 68.52 (d, J = 155.0 Hz), 57.13. **^{31}P NMR** (162 MHz, D_2O) δ 17.42. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_9H_{12}O_6N_4P$ 303.04999, found 303.05003.

Sodium ((2-ethoxy-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethoxy)methyl)phosphonate ((*RS*)-**15k**)



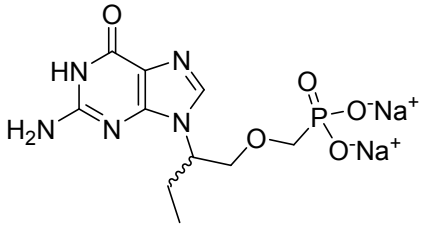
Following standard procedure H, compound (*RS*)-**4f** (555 mg, 1.32 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (250 mg, 0.62 mmol) was stirred in anhydrous pyridine (6.2 mL) and TMSBr (620 µL) at 25 °C for 16 h to yield (*RS*)-**15k** (94 mg, 20% over 2 steps) as an off-white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.35 (s, 1H), 8.19 (s, 1H), 5.98 (t, J = 5.1 Hz, 1H), 4.14–4.02 (m, 2H), 3.72–3.66 (m, 1H), 3.66–3.61 (m, 2H), 3.52 (dq, J = 9.5, 7.1 Hz, 1H), 1.15 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 159.30, 149.46, 146.59, 141.33, 124.15, 83.76, 73.04 (d, J = 11.1 Hz), 68.63 (d, J = 154.8 Hz), 66.25, 14.46. **^{31}P NMR** (162 MHz, D_2O) δ 17.31. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{10}H_{14}O_6N_4P$ 317.06564, found 317.06561.

Sodium ((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**16a**)



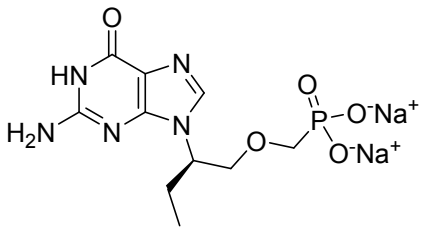
Following standard procedure F, compound (*RS*)-**10a** (219 mg, 0.54 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (160 mg, 0.41 mmol) was stirred in anhydrous MeCN (4.1 mL) and TMSBr (410 μL) at 25 °C for 16 h to yield (*RS*)-**16a** (115 mg, 61% over 2 steps) as a white solid. **^{1}H NMR** (401 MHz, D_2O) δ 7.97 (d, J = 0.5 Hz, 1H), 4.74–4.64 (m, 1H), 3.94 (dd, J = 10.8, 7.5 Hz, 1H), 3.89 (dd, J = 10.8, 4.6 Hz, 1H) 3.63–3.52 (m, 1H), 1.50 (d, J = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 159.60, 154.20, 152.02, 138.99, 116.46, 75.06 (d, J = 10.0 Hz), 68.55 (d, J = 153.9 Hz), 50.87, 17.01. **^{31}P NMR** (162 MHz, D_2O) δ 17.32. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_9H_{13}O_5N_5P$ 302.06598, found 302.06579.

Sodium ((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*RS*)-**16b**)



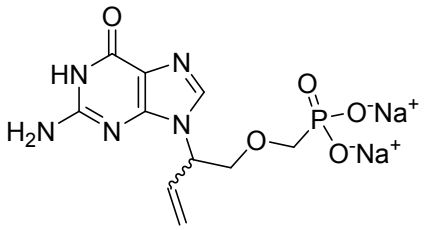
Following standard procedure F, compound (*RS*)-**10b** (327 mg, 0.78 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (269 mg, 0.67 mmol) was stirred in anhydrous MeCN (6.7 mL) and TMSBr (670 μL) at 25 °C for 16 h to yield (*RS*)-**16b** (161 mg, 57% over 2 steps) as a white solid. **^{1}H NMR** (401 MHz, D_2O) δ 7.97 (s, 1H), 4.50 (dddd, J = 8.9, 7.6, 6.0, 4.1 Hz, 1H), 4.04–3.87 (m, 2H), 3.67–3.52 (m, 2H), 2.00–1.81 (m, 2H), 0.80 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 159.65, 154.24, 152.60, 139.38, 116.42, 74.23 (d, J = 10.3 Hz), 67.93 (d, J = 156.1 Hz), 56.88, 24.44, 10.08. **^{31}P NMR** (162 MHz, D_2O) δ 18.04. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{10}H_{15}O_5N_5P$ 316.08163, found 316.08138.

Sodium (*R*)-((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**16b**)



Following standard procedure F, compound (*R*)-**5** (252 mg, 0.53 mmol) was converted to 6-oxo-2-amino derivative. Following standard procedure G, the 6-oxo-2-amino derivative (160 mg, 0.40 mmol) was stirred in anhydrous MeCN (4.0 mL) and TMSBr (400 µL) at 25 °C for 16 h to yield (*R*)-**16b** (55 mg, 29% over 2 steps) as a white solid. **^{1}H NMR** (401 MHz, D_2O) δ 7.98 (s, 1H), 4.56–4.44 (m, 1H), 4.03–3.89 (m, 2H), 3.49 (d, J = 8.3 Hz, 2H), 2.00–1.79 (m, 2H), 0.78 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 159.76, 154.34, 152.57, 139.39, 116.45, 73.99 (d, J = 9.5 Hz), 69.59 (d, J = 150.1 Hz), 57.04, 24.68, 10.03. **^{31}P NMR** (162 MHz, D_2O) δ 16.04. **HRMS** (ESI) m/z $[M-H]^-$calcd for $C_{10}H_{15}O_5N_5P$ 316.08163, found 316.08124. **$[\alpha]^{25}_D$** = +23.4 (c 0.513 g/100 mL, H_2O/MeOH 1/1).

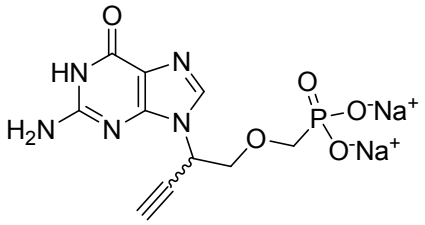
Sodium (((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)but-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**16c**)



Following standard procedure F, compound (*RS*)-**10c** (167 mg, 0.40 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (52 mg, 0.13 mmol) was stirred in anhydrous MeCN (1.3 mL) and TMSBr (130 µL) at 25 °C for 16 h to yield (*RS*)-**16c** (37 mg, 26% over 2 steps) as a white solid. **^{1}H NMR** (401 MHz, D_2O) δ 7.99 (s, 1H), 6.11 (ddd, J = 17.2, 10.6, 5.2 Hz, 1H), 5.33 (dd, J = 10.7, 1.7 Hz, 1H), 5.21 (dtt, J = 8.1, 4.8, 1.8 Hz, 1H), 5.03 (dd, J = 17.3, 1.7 Hz, 1H), 4.12 (dd, J = 10.9, 7.8 Hz, 1H), 4.06 (dd, J = 10.9, 4.6 Hz, 1H),

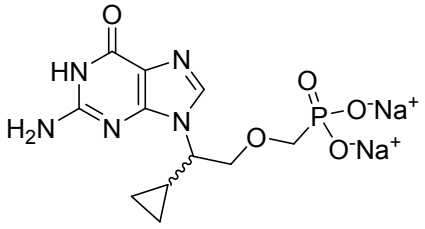
3.68–3.59 (m, 2H). **^{13}C NMR** (101 MHz, D_2O) δ 159.58, 154.31, 152.14, 139.52, 133.42, 118.97, 116.39, 73.13 (d, J = 10.2 Hz), 68.37 (d, J = 154.6 Hz), 56.77. **^{31}P NMR** (162 MHz, D_2O) δ 17.36. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{10}H_{13}O_5N_5P$ 314.06598, found 314.06576.

Sodium (((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)but-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**16d**)



Following standard procedure F, compound (*RS*)-**10d** (166 mg, 0.40 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (55 mg, 0.14 mmol) was stirred in anhydrous MeCN (1.4 mL) and TMSBr (140 µL) at 25 °C for 16 h to yield (*RS*)-**16d** (38 mg, 27% over 2 steps) as a white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.06 (s, 1H), 5.48 (ddd, J = 7.0, 4.8, 2.5 Hz, 1H), 4.16–4.03 (m, 2H), 3.73–3.56 (m, 2H), 3.02 (d, J = 2.5 Hz, 1H). **^{13}C NMR** (101 MHz, D_2O) δ 159.53, 154.41, 151.63, 139.33, 116.44, 78.01, 76.71, 73.73 (d, J = 10.3 Hz), 69.15 (d, J = 152.6 Hz), 46.53. **^{31}P NMR** (162 MHz, D_2O) δ 16.59. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{10}H_{11}O_5N_5P$ 312.05033, found 312.05008.

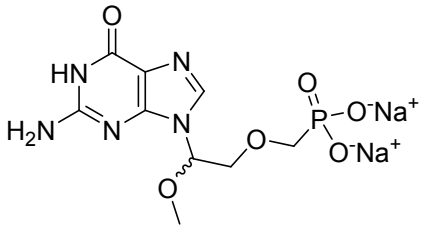
Sodium ((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)-2-cyclopropylethoxy)methyl)-phosphonate ((*RS*)-**16e**)



Following standard procedure F, compound (*RS*)-**10e** (181 mg, 0.42 mmol) was converted to 6-oxo derivative. Following standard procedure G, the 6-oxo derivative (125 mg, 0.30 mmol) was

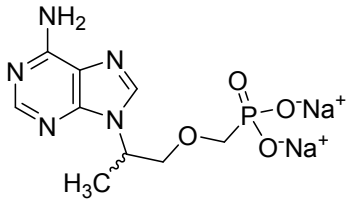
stirred in anhydrous MeCN (3.0 mL) and TMSBr (300 μL) at 25 °C for 16 h to yield (*RS*)-**16e** (78 mg, 50% over 2 steps) as a white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.06 (s, 1H), 4.15–3.99 (m, 2H), 3.82 (ddd, J = 9.9, 7.6, 4.0 Hz, 1H), 3.68–3.50 (m, 2H), 1.46 (dtt, J = 10.0, 7.9, 5.0 Hz, 1H), 0.85–0.70 (m, 1H), 0.54–0.47 (m, 2H), 0.33–0.22 (m, 1H). **^{13}C NMR** (101 MHz, D_2O) δ 152.10, 139.67, 116.27, 74.21 (d, J = 10.1 Hz), 68.28 (d, J = 155.2 Hz), 60.43, 12.47, 5.05, 3.16. **^{31}P NMR** (162 MHz, D_2O) δ 17.73. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{11}H_{15}O_5N_5P$ 328.08163, found 328.08163.

Sodium ((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)-2-methoxyethoxy)methyl)phosphonate ((*RS*)-**16f**)



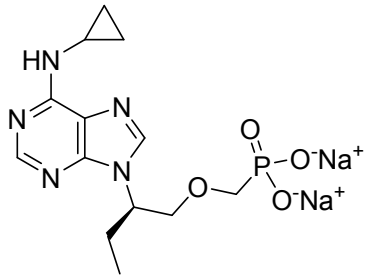
Following standard procedure H, compound (*RS*)-**7** (76 mg, 0.18 mmol) was converted to 6-oxo derivative. Following standard procedure G, 6-oxo derivative (30 mg, 0.07 mmol) was stirred in anhydrous pyridine (0.7 mL) and TMSBr (70 μL) at 25 °C for 16 h to yield (*RS*)-**16f** (7 mg, 11% over 2 steps) as a white solid. **^{1}H NMR** (401 MHz, D_2O) δ 7.99 (s, 1H), 5.68 (t, J = 5.3 Hz, 1H), 4.15–3.95 (m, 2H), 3.70–3.60 (m, 2H), 3.34 (s, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 159.70, 152.41, 138.91, 116.70, 84.54, 72.79 (d, J = 10.7 Hz), 68.56 (d, J = 155.2 Hz), 56.86. **^{31}P NMR** (162 MHz, D_2O) δ 17.43. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_9H_{13}O_6N_5P$ 318.06089, found 318.06067.

Sodium ((2-(6-amino-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**17**)



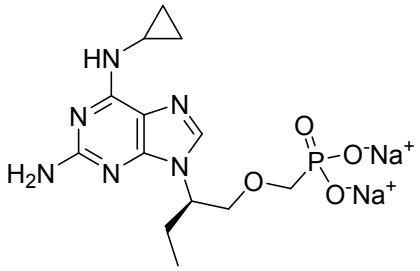
Compound (*RS*)-**4g** (156 mg, 0.40 mmol) was dissolved in ethanolic and aqueous ammonia (1:1 ratio) and stirred in MW reactor at 120 °C for 30 min. The mixture was concentrated and separated using silica gel flash chromatography (linear gradient elution 0 – 20% MeOH in $CHCl_3$) to obtain 6-amino derivative. Following standard procedure G, the 6-amino derivative (115 mg, 0.31 mmol) was stirred in anhydrous MeCN (3.1 mL) and TMSBr (310 µL) at 25 °C for 16 h to yield (*RS*)-**17** (81 mg, 61% over 2 steps) as an off-white solid. **^{1}H NMR** (500 MHz, D_2O) δ 8.28 (s, 1H), 8.15 (s, 1H), 4.87 (pd, J = 7.1, 4.2 Hz, 1H), 4.02 (dd, J = 10.9, 7.5 Hz, 1H), 3.93 (dd, J = 10.9, 4.2 Hz, 1H), 3.61–3.54 (m, 2H), 1.57 (d, J = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, D_2O) δ 155.85, 152.52, 149.27, 141.74, 119.01, 74.83 (d, J = 10.5 Hz), 68.21 (d, J = 155.3 Hz), 51.64, 16.87. **^{31}P NMR** (202 MHz, D_2O) δ 15.74. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_9H_{13}O_4N_5P$ 286.07106, found 286.07097.

Sodium (*R*)-((2-(6-(cyclopropylamino)-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**18**)



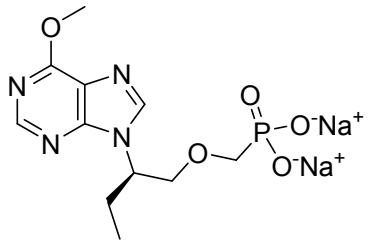
Following standard procedure J, compound (*R*)-**4a** (36 mg, 0.09 mmol) reacted with cyclopropylamine (62 µL, 0.90 mmol) to afford 6-cyclopropylamine derivative. Following standard procedure G, the 6-cyclopropylamine derivative (35 mg, 0.08 mmol) was stirred in anhydrous MeCN (0.8 mL) and TMSBr (80 µL) at 25 °C for 16 h to yield (*R*)-**18** (17 mg, 49% over 2 steps) as a white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.28 (s, 1H), 8.25 (s, 1H), 4.72–4.61 (m, 1H), 4.09–3.92 (m, 2H), 3.49–3.40 (m, 2H), 2.86 (s, 1H), 2.09–1.90 (m, 2H), 0.99–0.85 (m, 2H), 0.76 (t, J = 7.4 Hz, 3H), 0.70–0.61 (m, 2H). **^{13}C NMR** (101 MHz, D_2O) δ 156.29, 152.80, 141.84, 119.48, 73.84 (d, J = 9.5 Hz), 69.67 (d, J = 150.4 Hz), 57.82, 24.66, 23.80, 10.15, 7.21. **^{31}P NMR** (162 MHz, D_2O) δ 15.92. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{13}H_{19}O_4N_5P$ 340.11801, found 340.11768. **$[\alpha]^{25}_D$** = +5.6 (c 0.324 g/100 mL, H_2O/MeOH 1/1).

Sodium (*R*)-((2-(2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**19**)



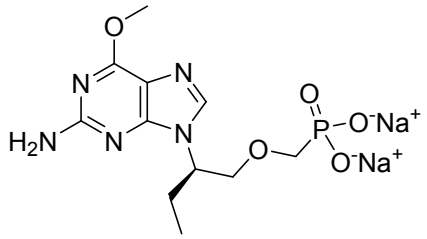
Following standard procedure J, compound (*R*)-**5** (200 mg, 0.42 mmol) reacted with cyclopropylamine (291 µL, 4.20 mmol) to afford 6-cyclopropylamine derivative. To cleave DMAM protecting group, the residue was prior to the separation dissolved in EtOH (2.5 mL) containing 0.25 mL conc. HCl and stirred at 70 °C for 1h. The mixture was neutralized with KOH, concentrated, and separated to afford 2-amino-6-cyclopropylamine derivative. [Note: The yield was considerably lowered due to the formation of 6-dimethylaminopurine derivative (presumably originating from the unstable DMAM protecting group) which was formed approx. in the same amount as the desired 6-cyclopropylamine derivative. Therefore, it might be eligible in this case to remove DMAM group first and then introduce the cyclopropylamine group (or any other amine).] Following standard procedure G, compound 2-amino-6-cyclopropylamine derivative (50 mg, 0.11 mmol) was stirred in anhydrous MeCN (1.1 mL) and TMSBr (110 µL) at 25 °C for 16 h to yield (*R*)-**19** (37 mg, 22% over 2 steps) as a white solid. **^{1}H NMR** (401 MHz, D_2O) δ 7.98 (s, 1H), 4.50 (ddd, J = 12.1, 8.6, 5.1 Hz, 1H), 4.01–3.87 (m, 2H), 3.51–3.42 (m, 2H), 2.84 (bs, 1H), 2.01–1.83 (m, 2H), 0.89–0.82 (m, 2H), 0.77 (t, J = 7.5 Hz, 3H), 0.69–0.61 (m, 2H). **^{13}C NMR** (101 MHz, D_2O) δ 160.71, 156.99, 151.53, 139.01, 113.79, 74.19 (d, J = 9.6 Hz), 69.52 (d, J = 150.9 Hz), 56.78, 24.69, 23.79, 10.11, 7.34. **^{31}P NMR** (162 MHz, D_2O) δ 16.27. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{13}H_{20}O_4N_6P$ 355.12891, found 355.12827. **$[\alpha]^{25}_D$** = +27.9 (c 0.338 g/100 mL, H_2O/MeOH 1/1).

Sodium (*R*)-((2-(6-methoxy-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**20**)



Compound (*R*)-**4a** (9 mg, 0.02 mmol) reacted with MeOK (4 mg, 0.06 mmol) in MeOH (0.5 mL) at 25 °C for 2 h. The mixture was concentrated and the residue purified using silica gel flash chromatography (linear gradient elution 0 – 15% MeOH in $CHCl_3$) to afford the 6-methoxy derivative. Following standard procedure G, the 6-methoxy derivative (9 mg, 0.02 mmol) was stirred in anhydrous pyridine (0.2 mL) and TMSBr (20 μL) at 25 °C for 16 h to yield (*R*)-**20** (7 mg, 88% over 2 steps) as a white solid. [Note: The synthetic sequence can be reversed, i.e. the phosphonate isopropyl esters can be first cleaved with TMSBr leading to 6-bromopurine derivative in only 3 h and then the methoxy group can be introduced to the position C6, thus forming compound (*R*)-**20**. **^{1}H NMR** (401 MHz, D_2O) δ 8.49 (s, 1H), 8.48 (s, 1H), 4.76–4.70 (m, 1H), 4.19 (s, 3H), 4.12–3.97 (m, 2H), 3.48–3.39 (m, 2H), 2.08–1.94 (m, 2H), 0.78 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 161.64, 152.27, 152.17, 144.20, 121.25, 73.70 (d, J = 9.3 Hz), 69.78 (d, J = 150.0 Hz), 58.29, 55.51, 24.62, 10.15. **^{31}P NMR** (162 MHz, D_2O) δ 15.74. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{11}H_{16}O_5N_4P$ 315.08638, found 315.08601. **$[\alpha]^{25}_D$** = +8.9 (c 0.268 g/100 mL, H_2O/MeOH 1/1).

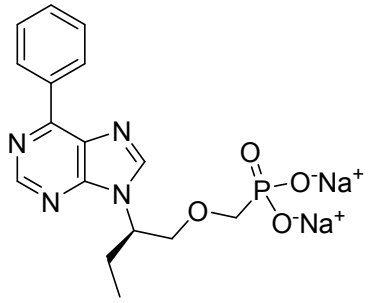
Sodium (*R*)-((2-(2-amino-6-methoxy-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**21**)



Compound (*R*)-**5** (190 mg, 0.40 mmol) and TMSBr (400 μL) were stirred at 25 °C for 3 h. The mixture was concentrated, co-distilled 2 × with toluene, then re-dissolved in MeOH, and MeOK

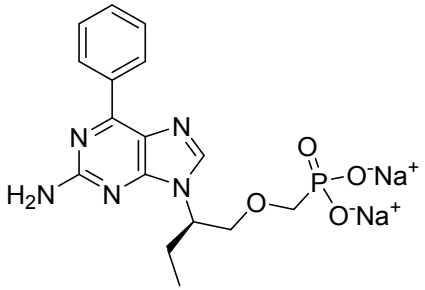
(84 mg, 1.20 mmol) added. The mixture was stirred at 25 °C for 19 h. Solvents were evaporated and the residue was dissolved in 2M TEAB (2 mL). After evaporation, the residue was separated using C_{18}-reversed phase flash chromatography (linear gradient elution 0 – 50% MeOH in water). Purified product was taken through Na^+ DOWEX to yield (*R*)-**21** (51 mg, 34% over 2 steps) as a white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.09 (s, 1H), 4.61–4.50 (m, 1H), 4.08 (s, 3H), 4.04–3.89 (m, 2H), 3.51 (d, J = 8.3 Hz, 2H), 2.02–1.86 (m, 2H), 0.79 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 162.24, 160.52, 154.28, 140.73, 114.71, 74.07 (d, J = 9.7 Hz), 68.99 (d, J = 152.5 Hz), 57.10, 55.00, 24.53, 10.14. **^{31}P NMR** (162 MHz, D_2O) δ 16.83. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{11}H_{17}O_5N_5P$ 330.09728, found 330.09683. **$[\alpha]^{25}_D$** = +35.6 (c 0.296 g/100 mL, H_2O/MeOH 1/1).

Sodium (*R*)-((2-(6-phenyl-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**22**)



Following standard procedure I, compound (*R*)-**4a** (40 mg, 0.10 mmol) reacted with $PhB(OH)_2$ (18 mg, 0.15 mmol), Cs_2CO_3 (81 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (6 mg, 0.005 mmol) to afford 6-phenyl derivative. Following standard procedure G, the 6-phenyl derivative (45 mg, 0.10 mmol) was stirred in anhydrous MeCN (1.0 mL) and TMSBr (100 µL) at 25 °C for 16 h to yield (*R*)-**22** (19 mg, 46% over 2 steps) as a white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.80 (s, 1H), 8.67 (s, 1H), 8.18–8.08 (m, 2H), 7.64–7.52 (m, 3H), 4.88–4.81 (m, 1H), 4.12 (dd, J = 11.0, 7.3 Hz, 1H), 4.01 (dd, J = 10.9, 4.0 Hz, 1H), 3.55 (d, J = 8.4 Hz, 2H), 2.13–1.98 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 156.02, 152.55, 152.00, 146.98, 134.70, 131.93, 130.98, 130.07, 129.42, 73.58 (d, J = 10.2 Hz), 68.87 (d, J = 153.1 Hz), 57.96, 24.48, 10.31. **^{31}P NMR** (162 MHz, D_2O) δ 16.93. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{16}H_{18}O_4N_4P$ 361.10711, found 361.10672. **$[\alpha]^{25}_D$** = +0.6 (c 0.484 g/100 mL, H_2O/MeOH 1/1).

Sodium (*R*)-((2-(2-amino-6-phenyl-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**23**)



Following standard procedure I, compound (*R*)-**5** (400 mg, 0.84 mmol) reacted with $PhB(OH)_2$ (154 mg, 1.26 mmol), Cs_2CO_3 (684 mg, 2.10 mmol), and $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) to afford 6-phenyl derivative. To cleave DMAM protecting group, the residue was prior to the separation dissolved in EtOH (5 mL) containing 0.5 mL conc. HCl and stirred at 70 °C for 1h. The mixture was neutralized with KOH, concentrated, and separated to afford 2-amino-6-phenyl derivative. Following standard procedure G, 2-amino-6-phenyl derivative (250 mg, 0.54 mmol) was stirred in anhydrous MeCN (5.4 mL) and TMSBr (540 µL) at 25 °C for 16 h to yield (*R*)-**23** (100 mg, 28% over 2 steps) as an off-white solid. **^{1}H NMR** (401 MHz, D_2O) δ 8.30 (s, 1H), 8.14–8.03 (m, 2H), 7.62–7.48 (m, 3H), 4.68–4.57 (m, 1H), 4.11–3.88 (m, 2H), 3.55 (d, J = 8.4 Hz, 2H), 2.09–1.87 (m, 2H), 0.83 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, D_2O) δ 160.31, 157.46, 154.69, 143.88, 134.97, 131.70, 129.86, 129.25, 125.02, 73.85 (d, J = 9.7 Hz), 68.87 (d, J = 153.2 Hz), 56.93, 24.42, 10.24. **^{31}P NMR** (162 MHz, D_2O) δ 17.03. **HRMS** (ESI) m/z $[M-H]^-$ calcd for $C_{16}H_{19}O_4N_5P$ 376.11801, found 376.11746. **$[\alpha]^{25}_D$** = +27.4 (c 0.334 g/100 mL, H_2O/MeOH 1/1).

COPIES OF SPECTRA OF PREPARED COMPOUNDS

(*R*)-2-(6-Chloro-9*H*-purin-9-yl)butan-1-ol ((*R*)-**2a**)

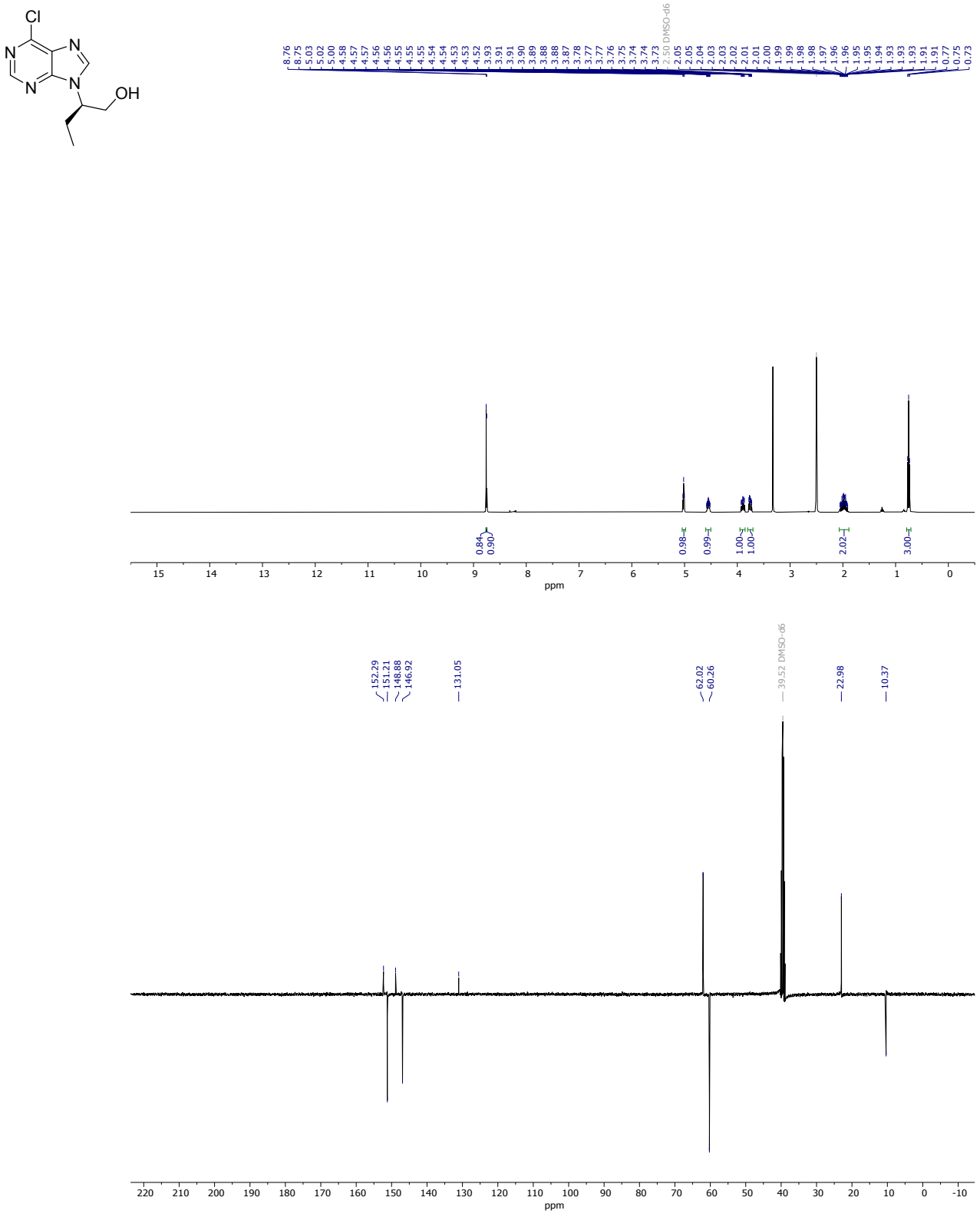


Figure S1. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**2a** measured in DMSO-d_6 at room temperature.

(*R*)-2-(6-Chloro-9*H*-purin-9-yl)butan-1-ol ((*R*)-**2a**)

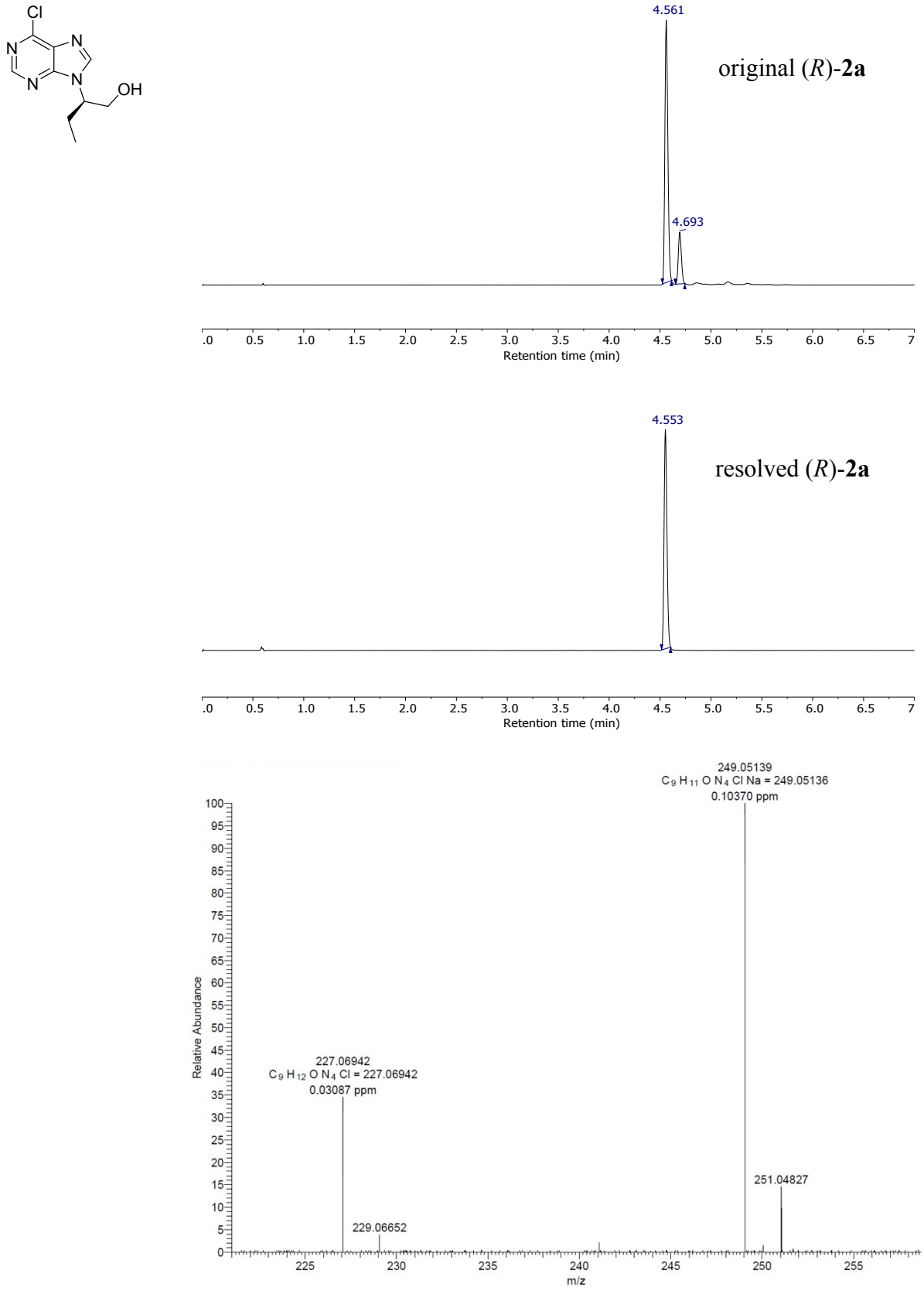


Figure S2. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top for original (*R*)-**2a** contaminated with ~17% of (*S*)-enantiomer due to the impure starting material from the commercial supplier and middle for resolved (*R*)-**2a**) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**2a**.

(*S*)-2-(6-Chloro-9*H*-purin-9-yl)-3-methylbutan-1-ol ((*S*)-**2b**)

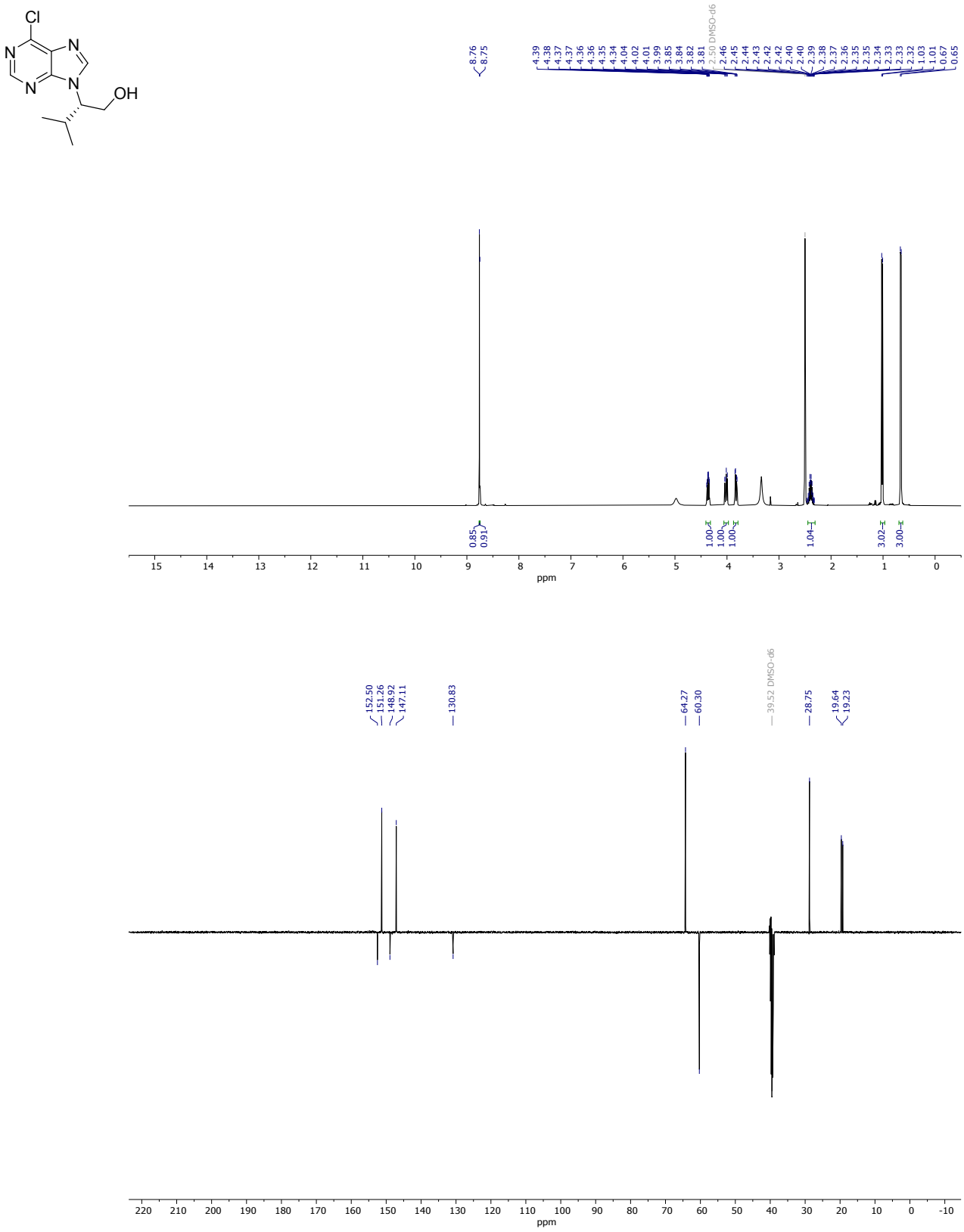


Figure S3. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*S*)-**2b** measured in DMSO-d_6 at room temperature.

(*S*)-2-(6-Chloro-9*H*-purin-9-yl)-3-methylbutan-1-ol ((*S*)-**2b**)

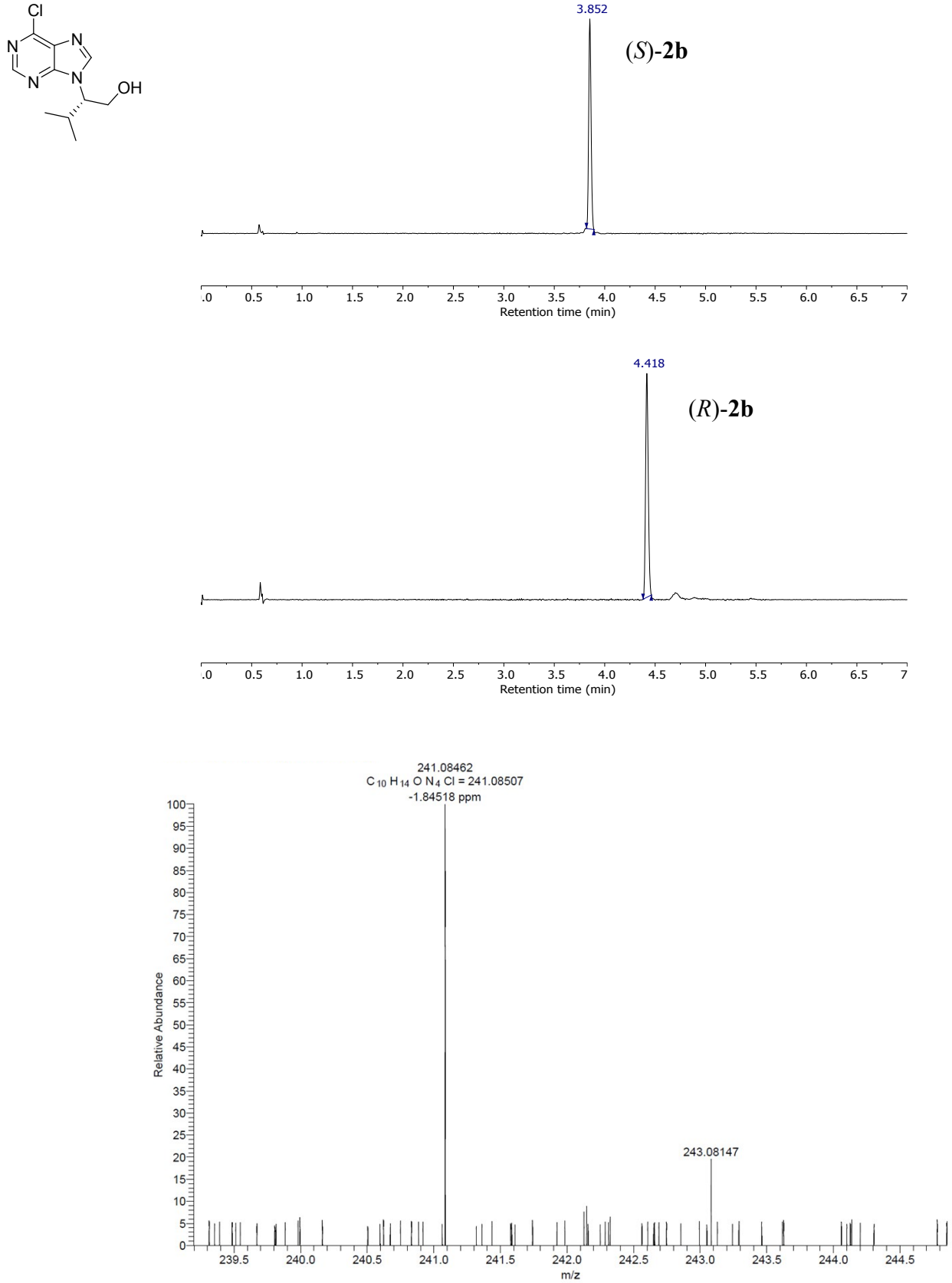


Figure S4. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top for (*S*)-**2b**, middle for (*R*)-**2b**) and high resolution mass spectrum (HRMS, bottom) of compound (*S*)-**2b**.

(*R*)-2-(6-Chloro-9*H*-purin-9-yl)-3-methylbutan-1-ol ((*R*)-**2b**)

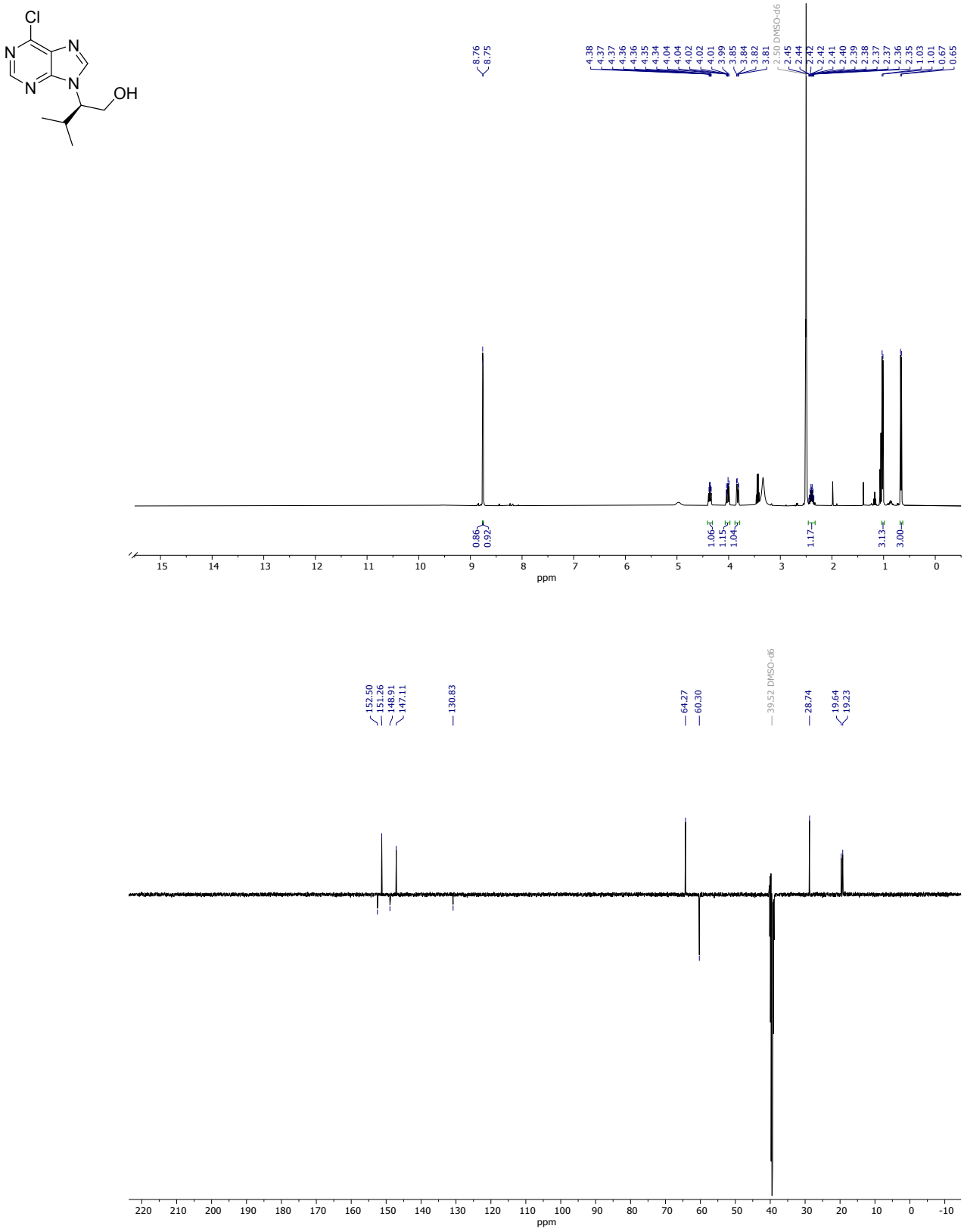


Figure S5. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**2b** measured in DMSO-d_6 at room temperature.

(*R*)-2-(6-Chloro-9*H*-purin-9-yl)-3-methylbutan-1-ol ((*R*)-**2b**)

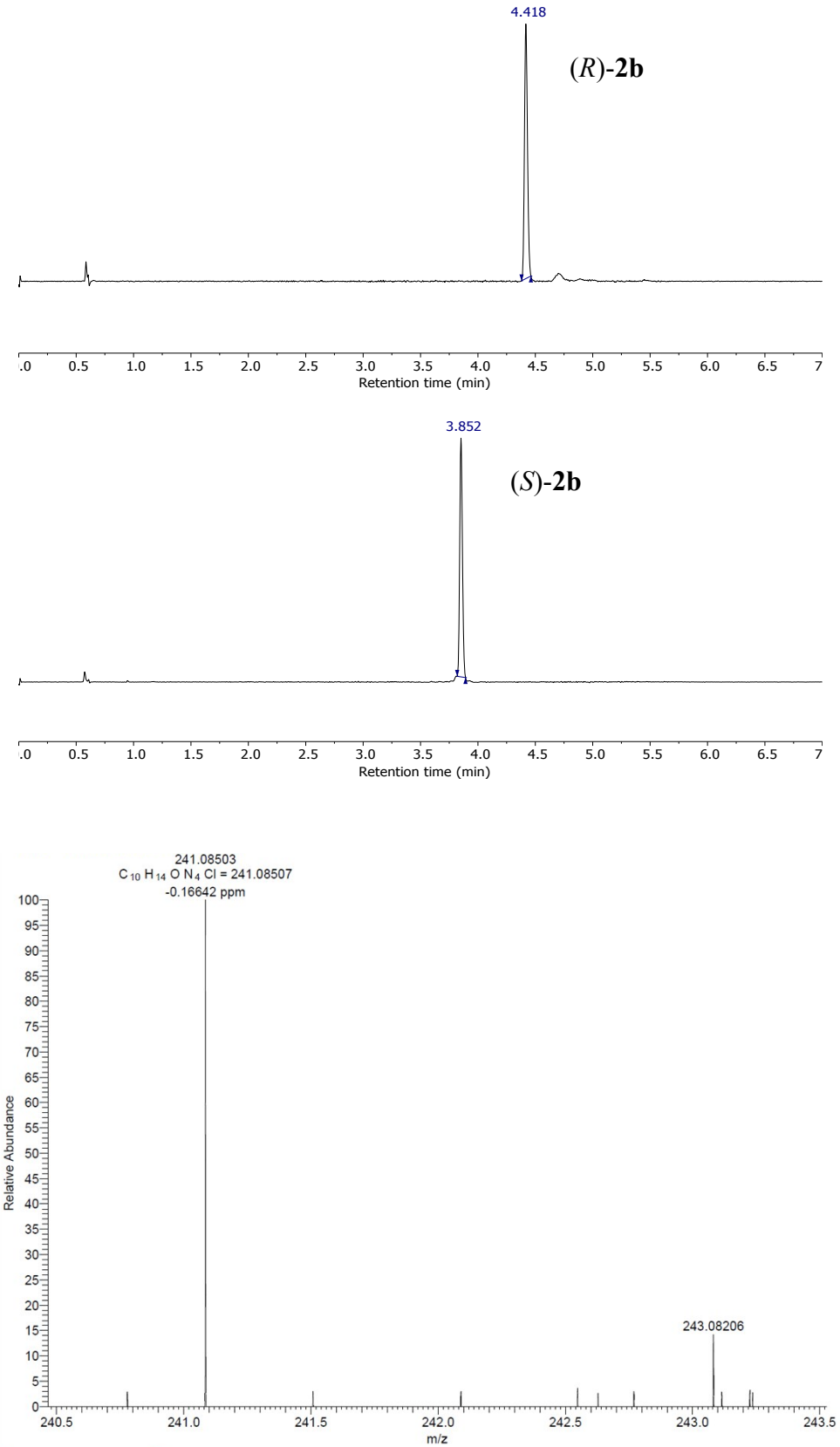


Figure S6. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top for (*R*)-**2b**, middle for (*S*)-**2b**) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**2b**.

(*R*)-2-(6-Chloro-9*H*-purin-9-yl)-2-cyclopropylethan-1-ol ((*R*)-**2c**)

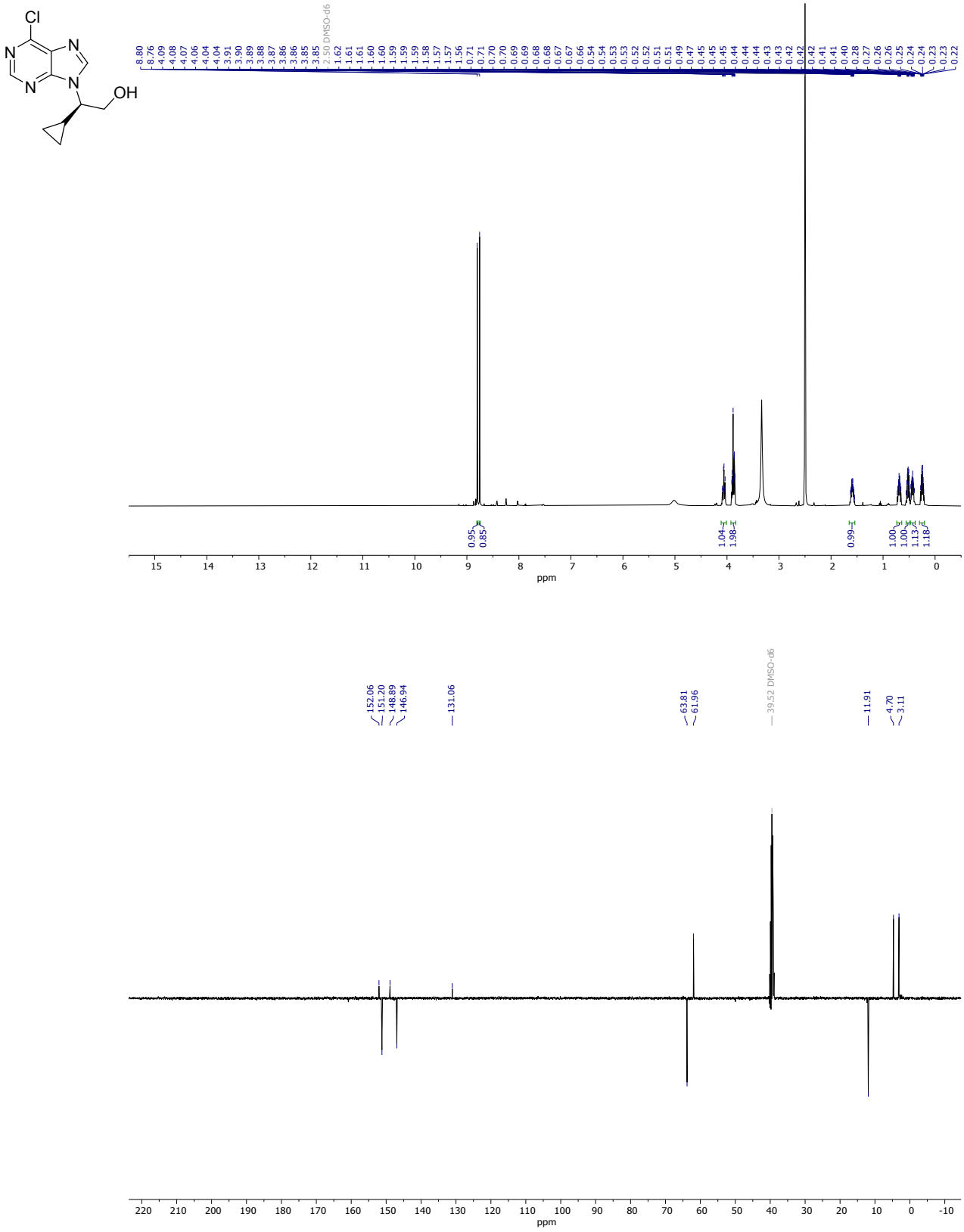


Figure S7. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**2c** measured in DMSO-d_6 at room temperature.

(*R*)-2-(6-Chloro-9*H*-purin-9-yl)-2-cyclopropylethan-1-ol ((*R*)-**2c**)

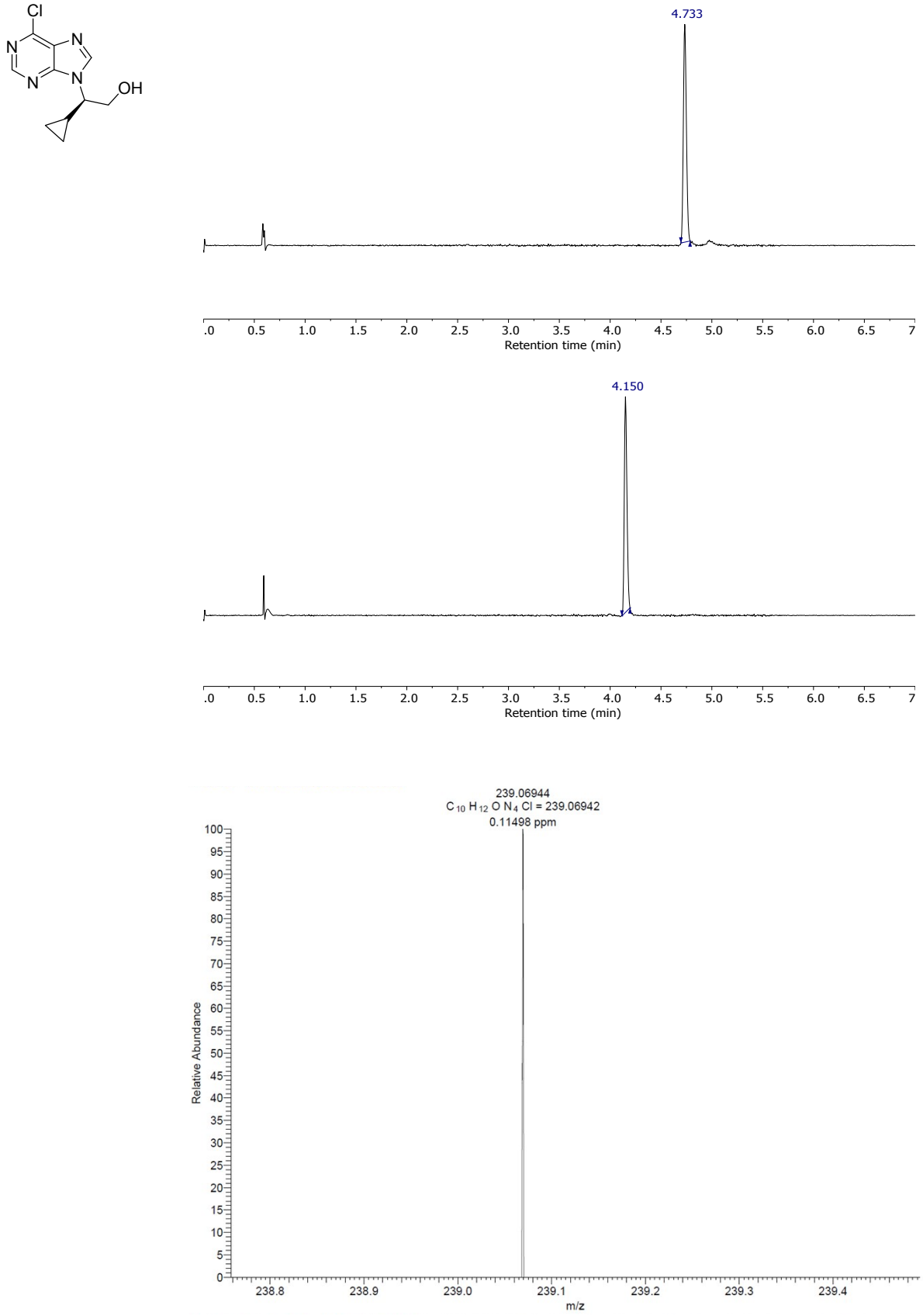


Figure S8. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top) and SB column (middle) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**2c**.

(*R*)-3-(Benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propan-1-ol ((*R*)-**2d**)

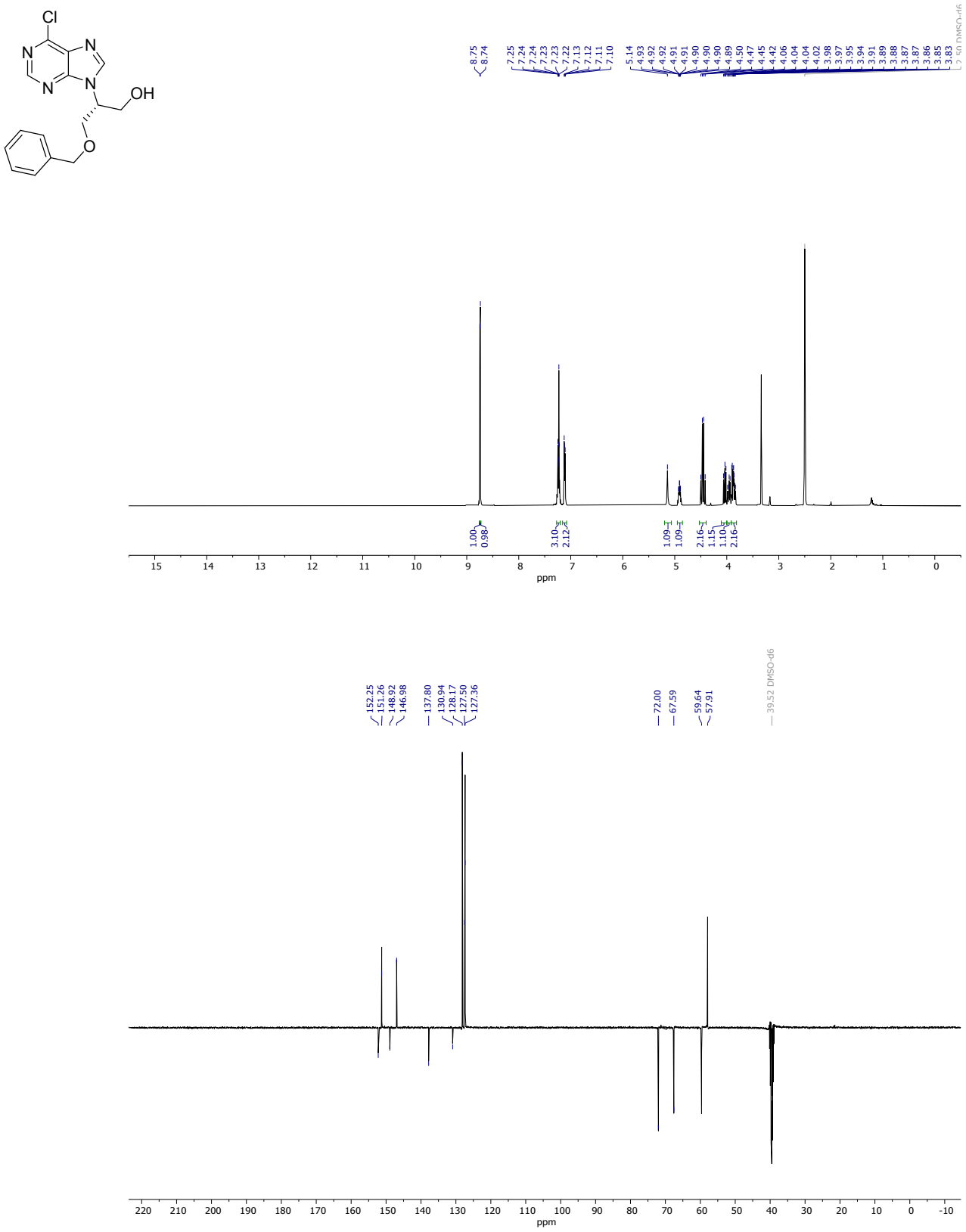


Figure S9. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**2d** measured in DMSO-d_6 at room temperature.

(*R*)-3-(Benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propan-1-ol ((*R*)-**2d**)

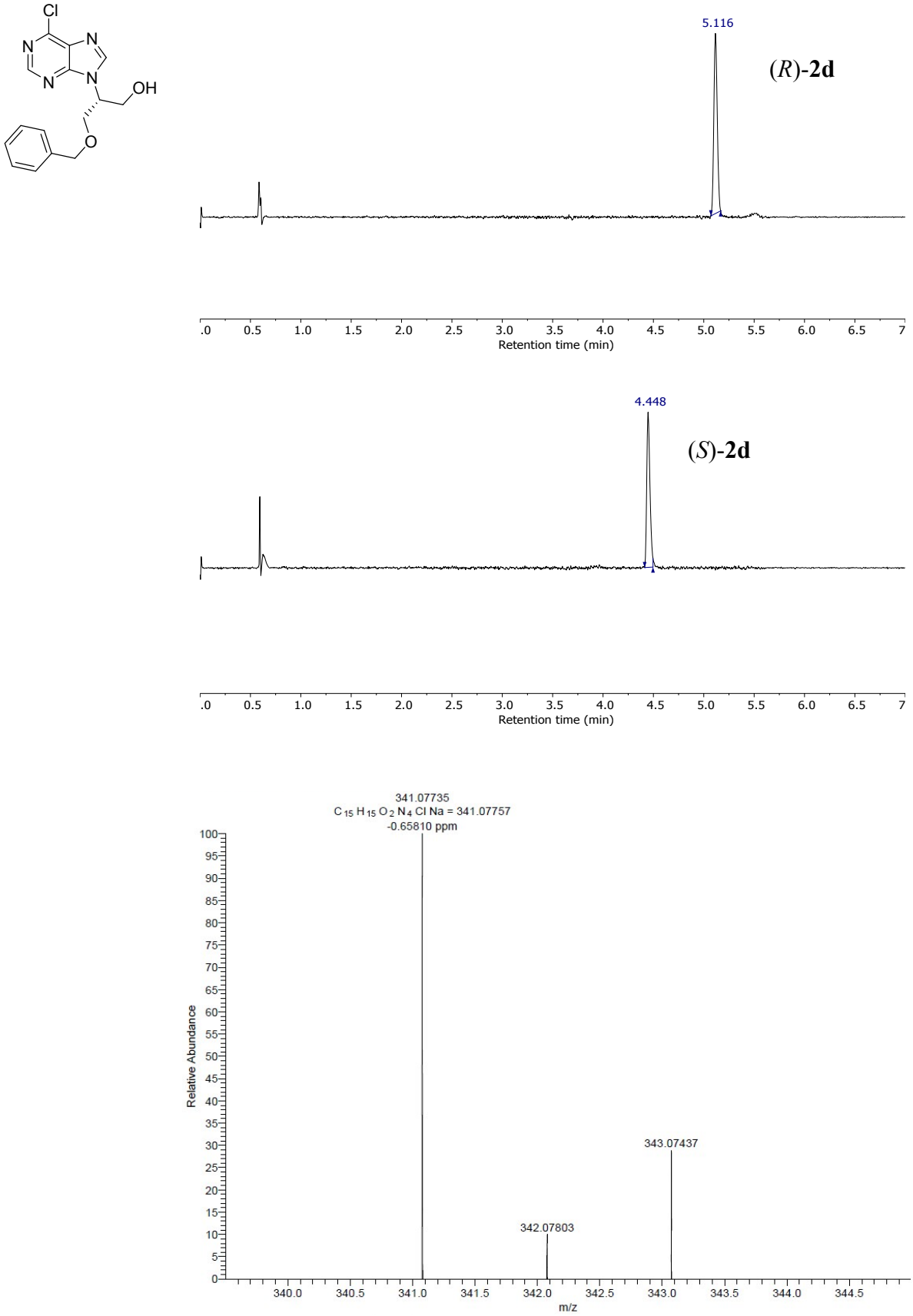


Figure S10. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top for (*R*)-**2d**, middle for (*S*)-**2d**) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**2d**.

(*S*)-3-(Benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propan-1-ol ((*S*)-**2d**)

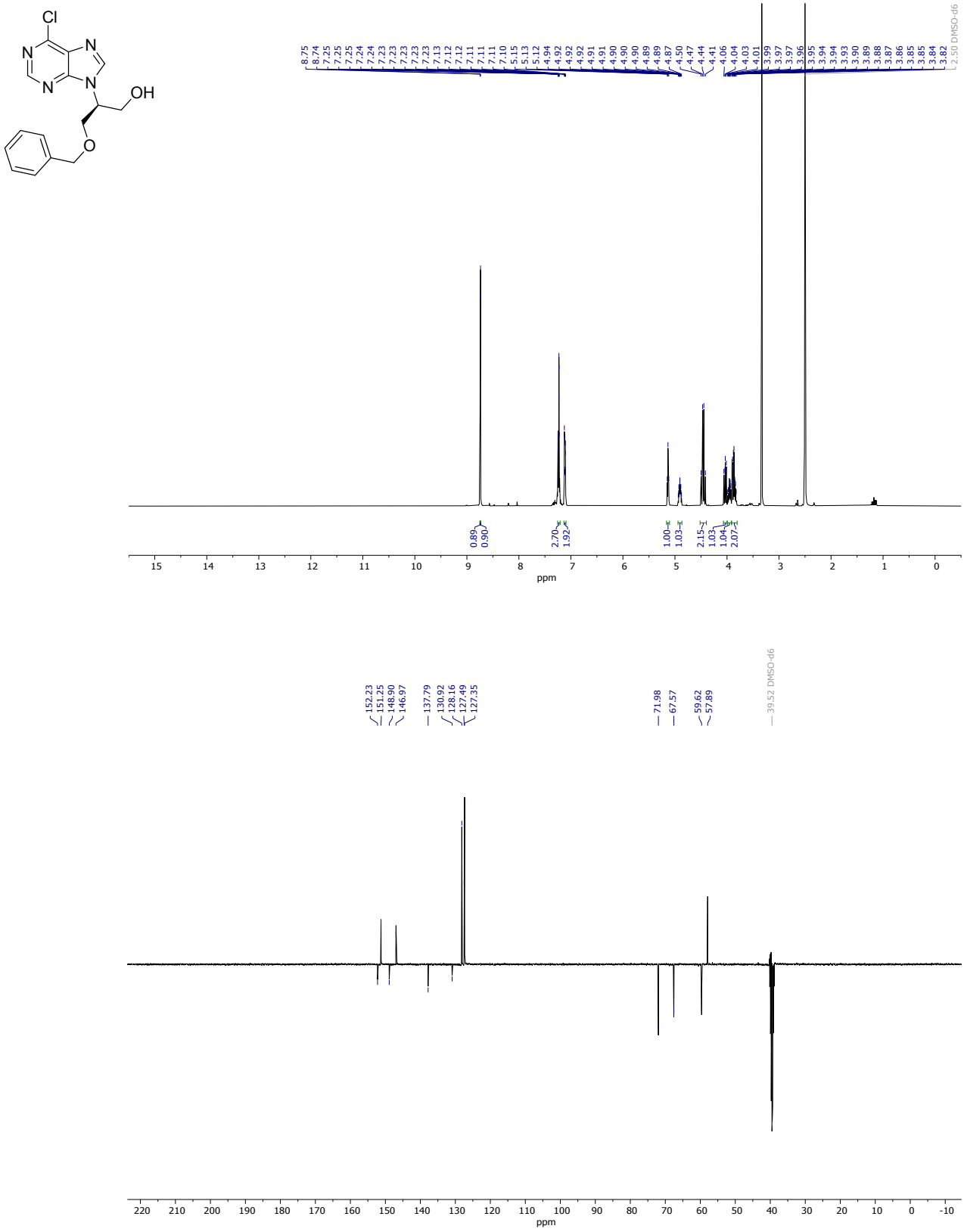


Figure S11. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*S*)-**2d** measured in DMSO-d_6 at room temperature.

(*S*)-3-(Benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propan-1-ol ((*S*)-**2d**)

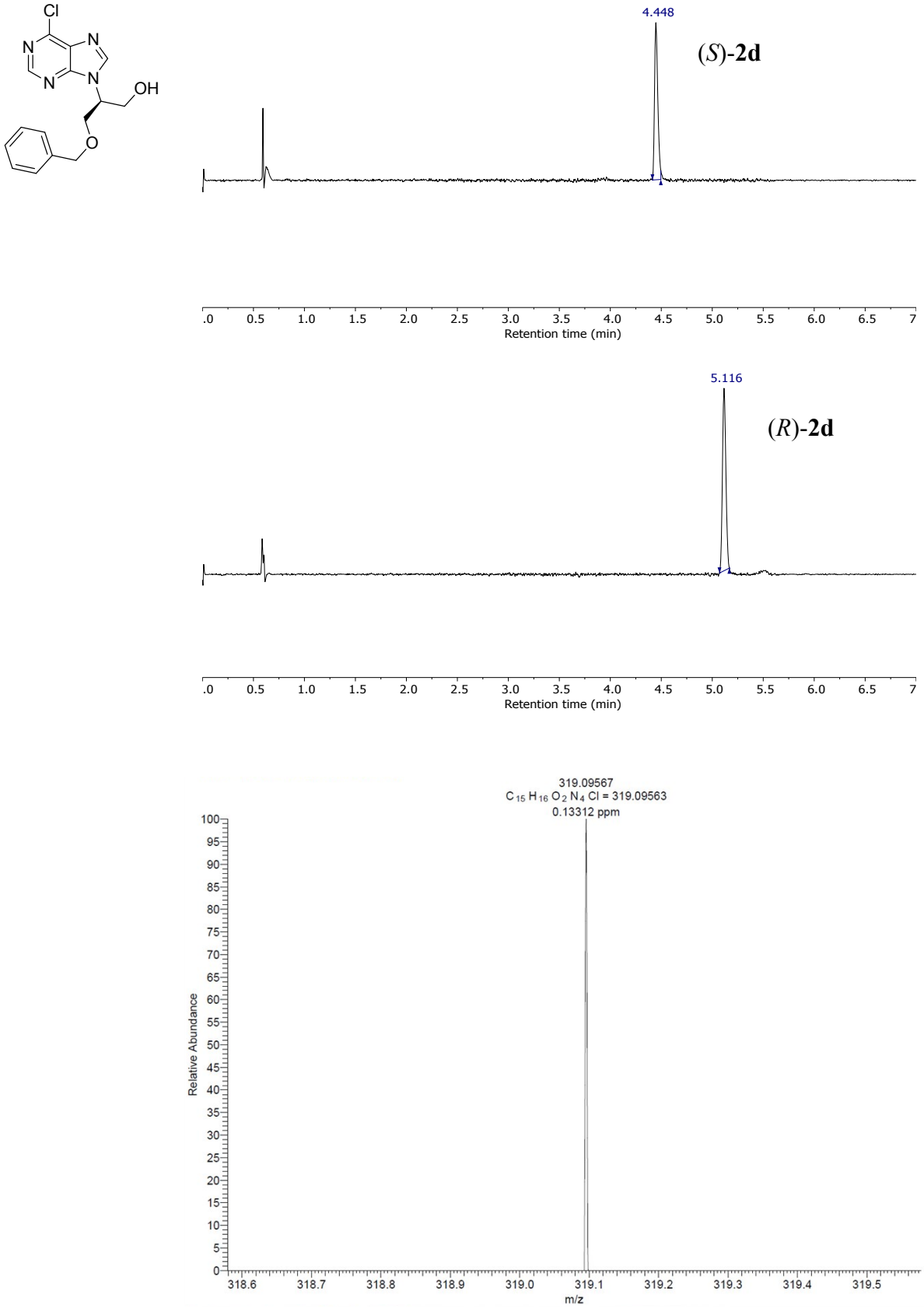


Figure S12. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top for (*S*)-**2d**, middle for (*R*)-**2d**) and high resolution mass spectrum (HRMS, bottom) of compound (*S*)-**2d**.

2-(6-Chloro-9*H*-purin-9-yl)-3,3,3-trifluoropropan-1-ol ((*RS*)-**2e**)

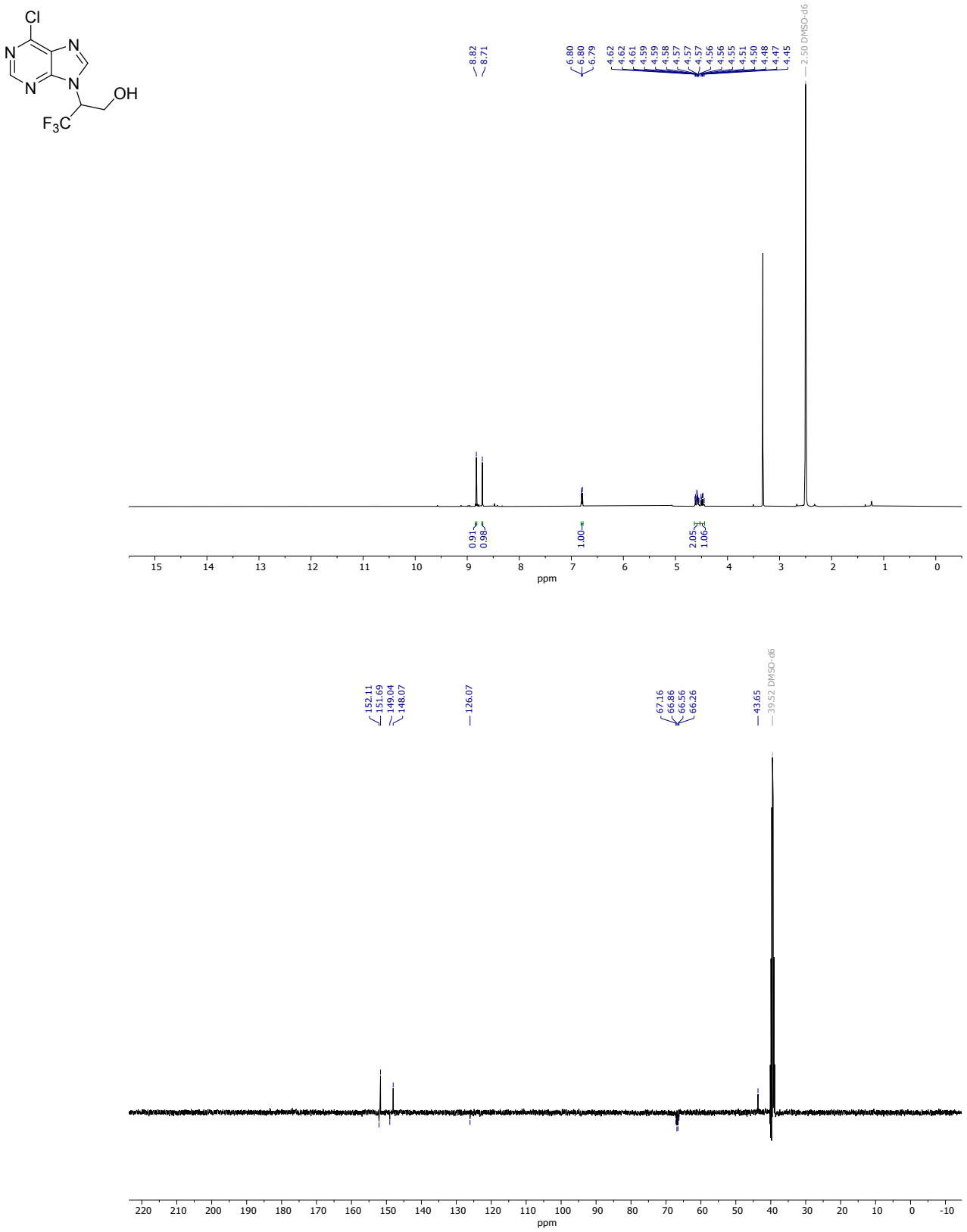


Figure S13. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**2e** measured in DMSO-d_6 at room temperature.

2-(6-Chloro-9*H*-purin-9-yl)-3,3,3-trifluoropropan-1-ol ((*RS*)-**2e**)

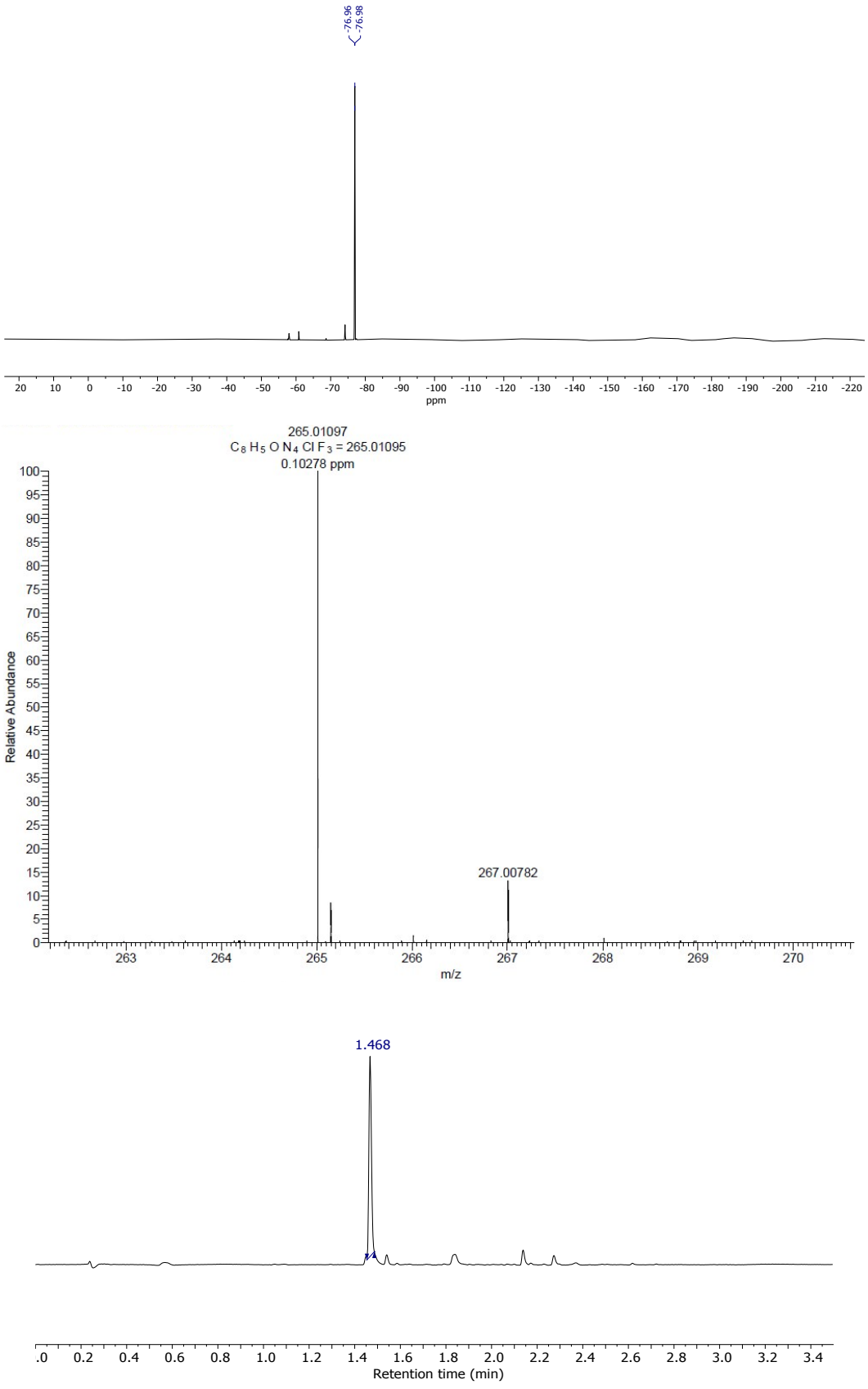


Figure S14. ^{19}F NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**2e**.

(*R*)-2-(2-Amino-6-chloro-9*H*-purin-9-yl)butan-1-ol (**3**)

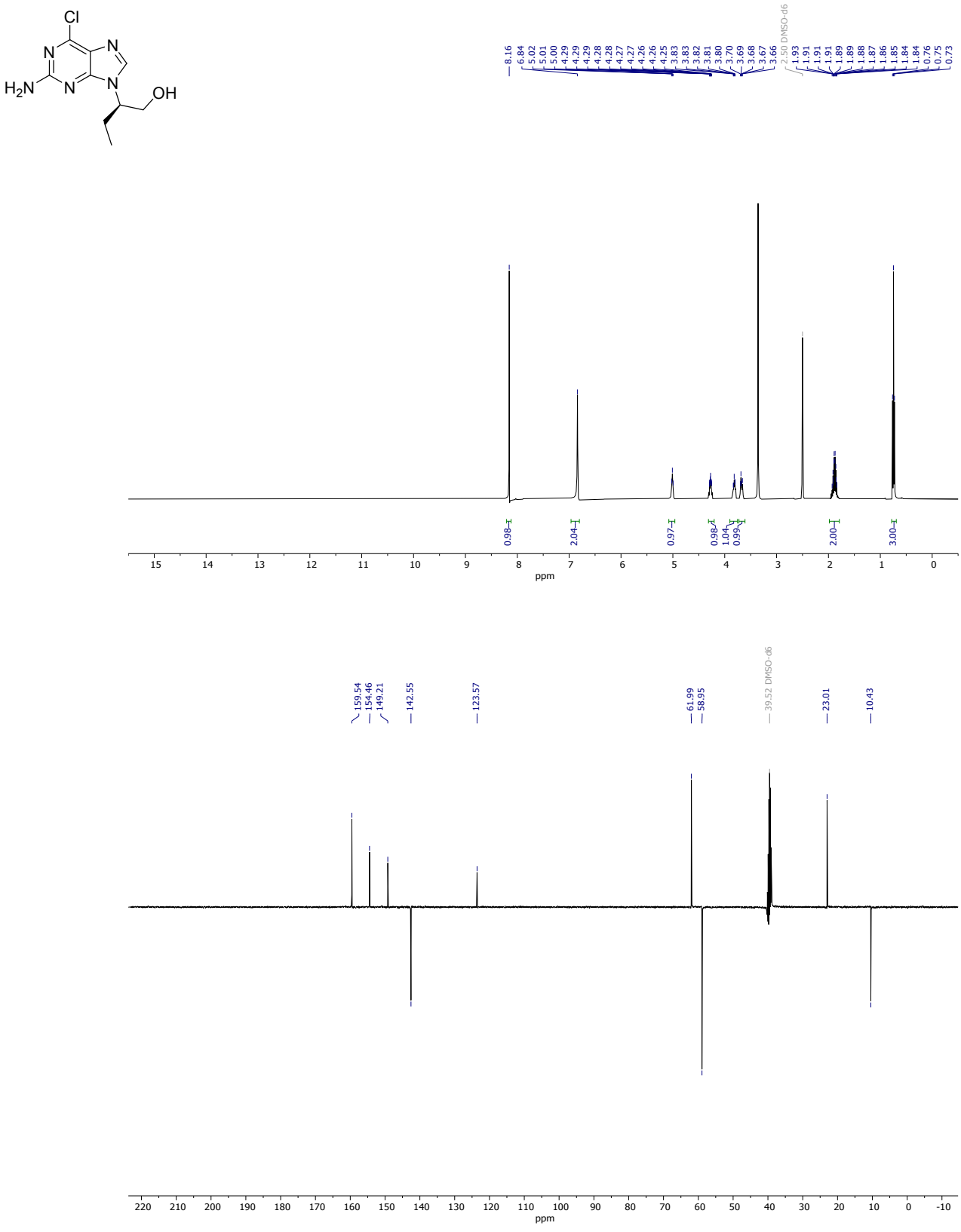


Figure S15. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**3** measured in DMSO-d_6 at room temperature.

(*R*)-2-(2-Amino-6-chloro-9*H*-purin-9-yl)butan-1-ol ((*R*)-**3**)

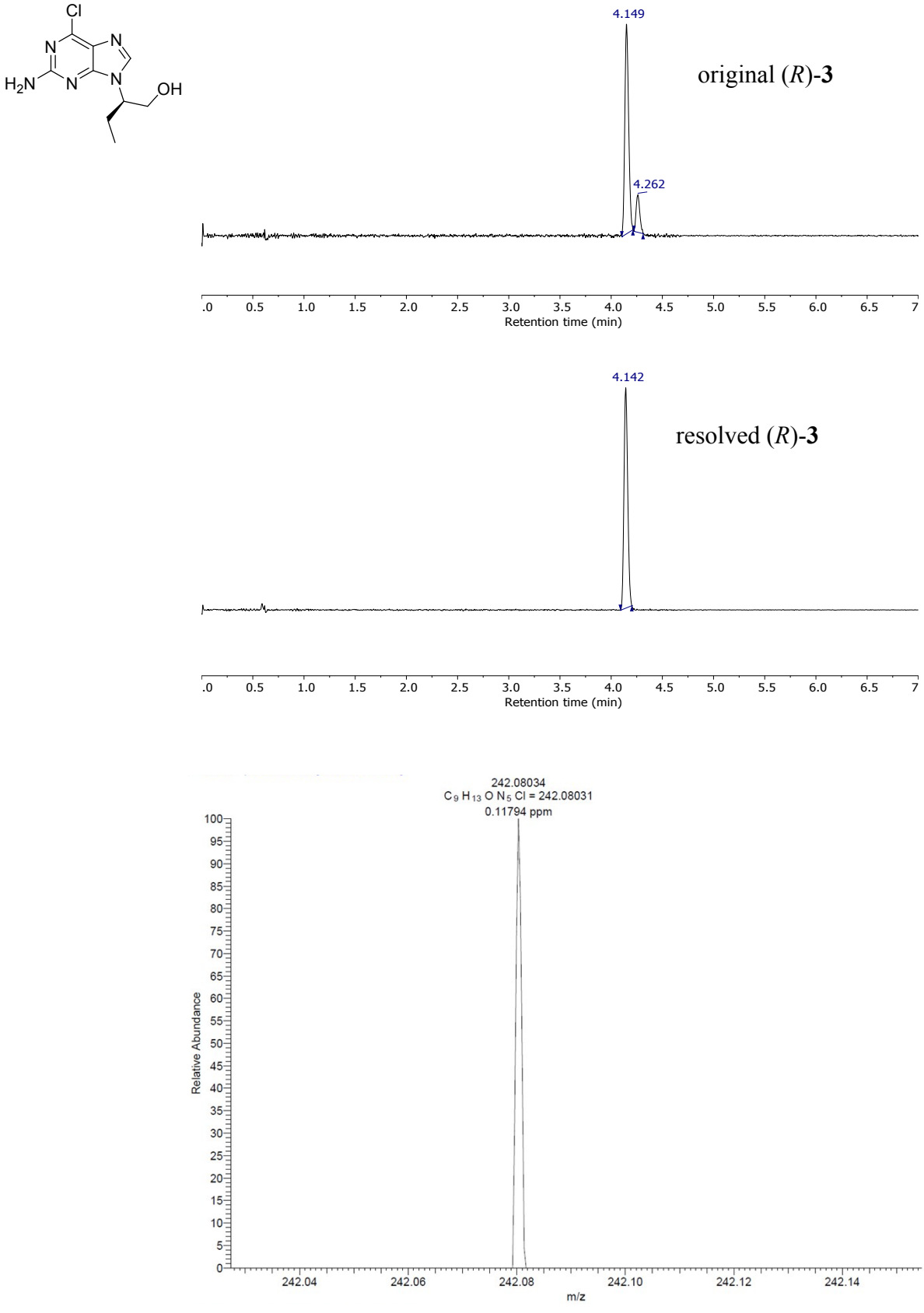


Figure S16. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top for original (*R*)-**3** contaminated with ~15% of (*S*)-enantiomer due to the impure starting material from the commercial supplier and middle for resolved (*R*)-**3**) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**3**.

Diisopropyl (*R*)-((2-(6-chloro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**4a**)

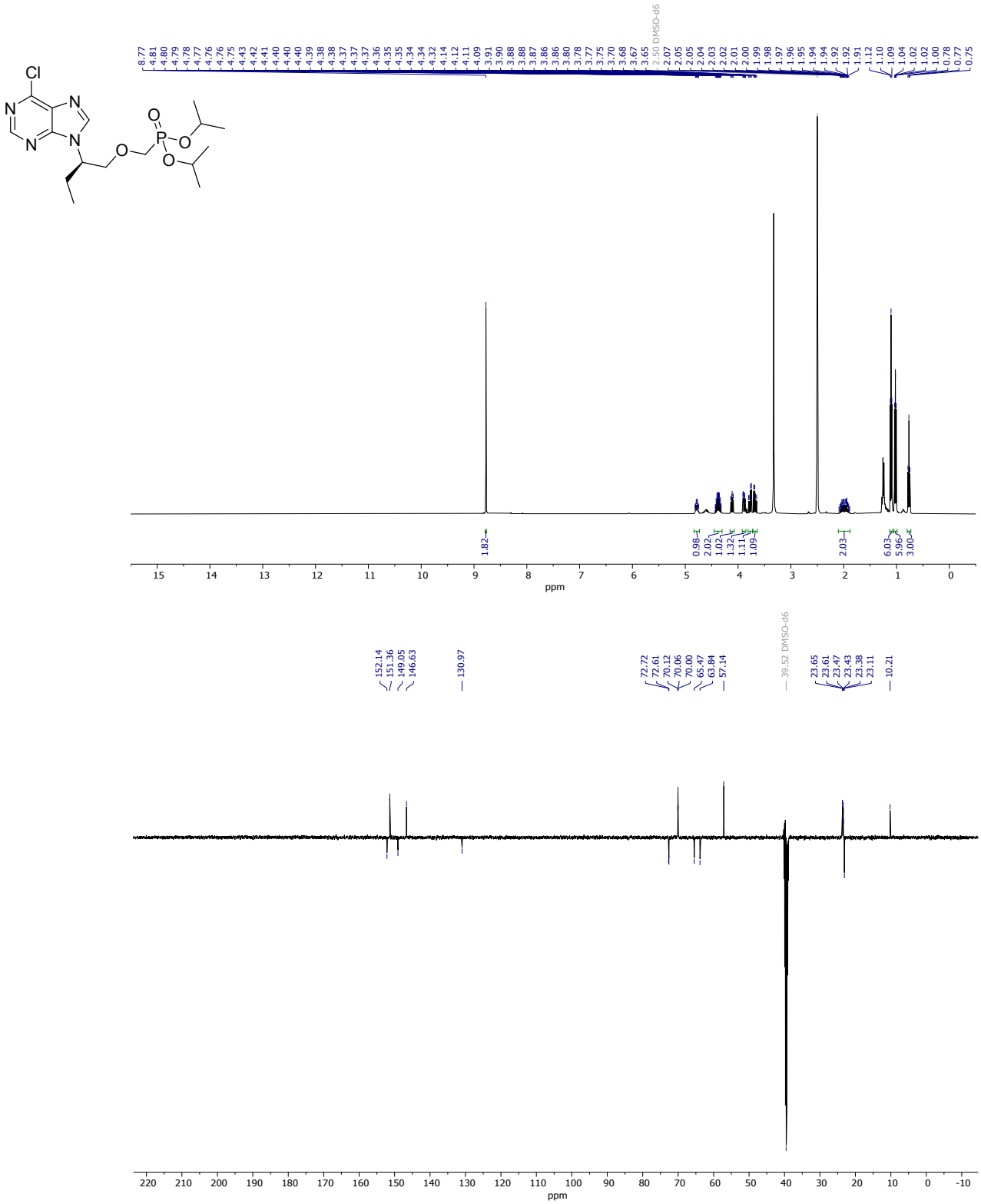


Figure S17. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**4a** measured in DMSO-d_6 at room temperature.

Diisopropyl (*R*)-((2-(6-chloro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**4a**)

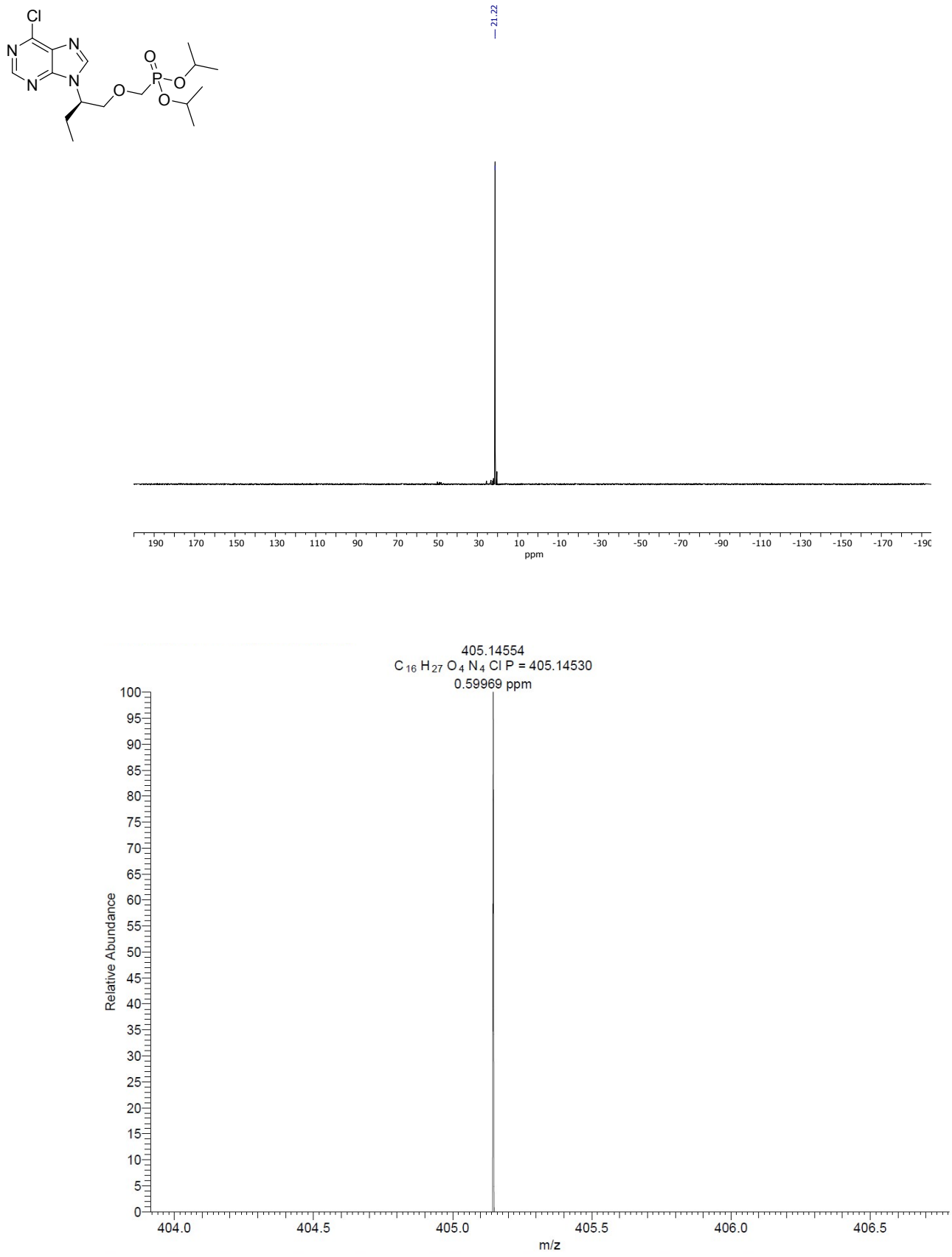


Figure S18. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**4a**.

Diisopropyl (*R*)-((2-(6-chloro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**4a**)

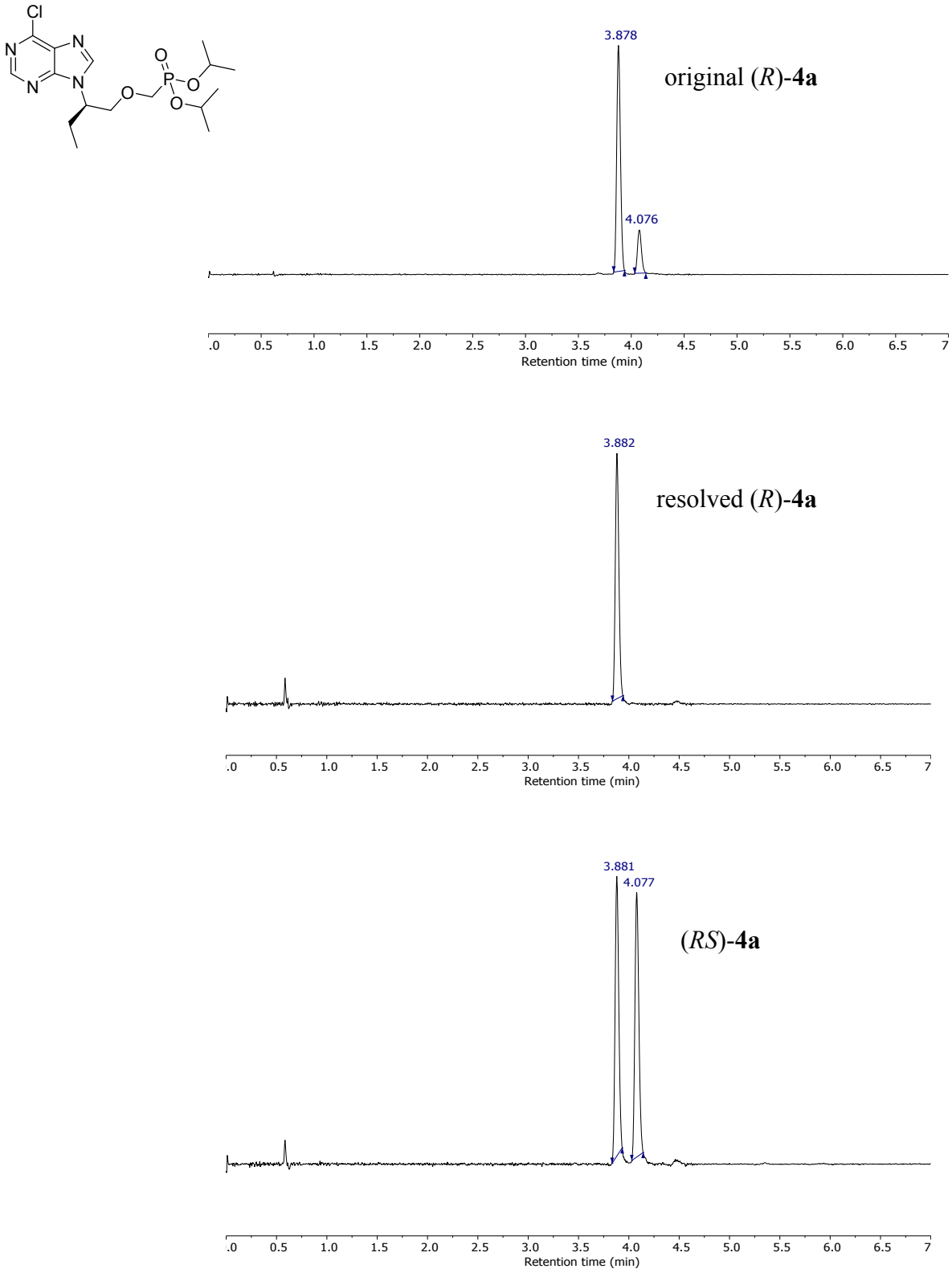


Figure S19. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top for original (*R*)-**4a** contaminated with ~17% of (*S*)-enantiomer due to the impure starting material from the commercial supplier, middle for (*R*)-**4a** and bottom for (*RS*)-**4a**).

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*RS*)-**4a**)

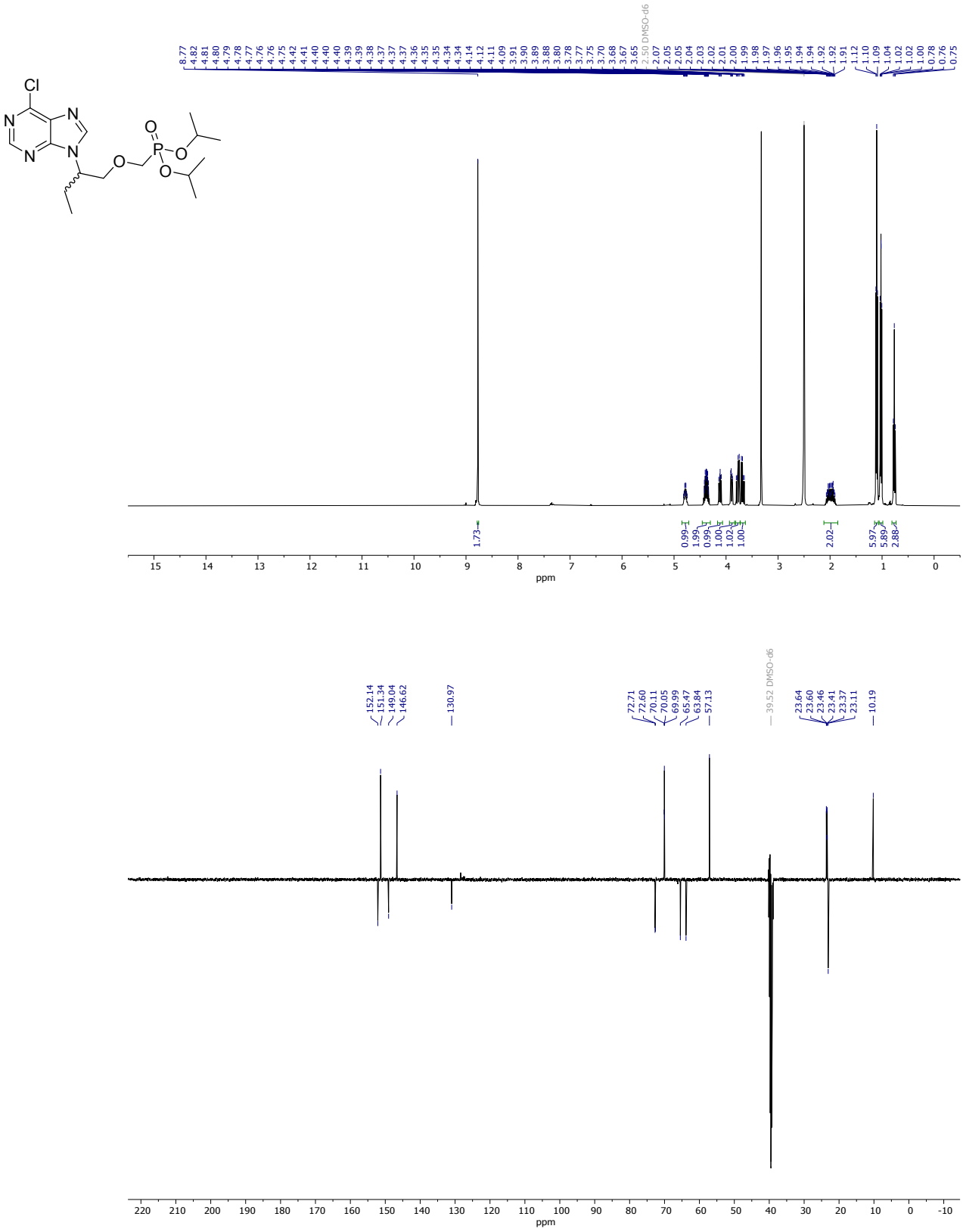


Figure S20. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**4a** measured in DMSO-d_6 at room temperature.

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*RS*)-**4a**)

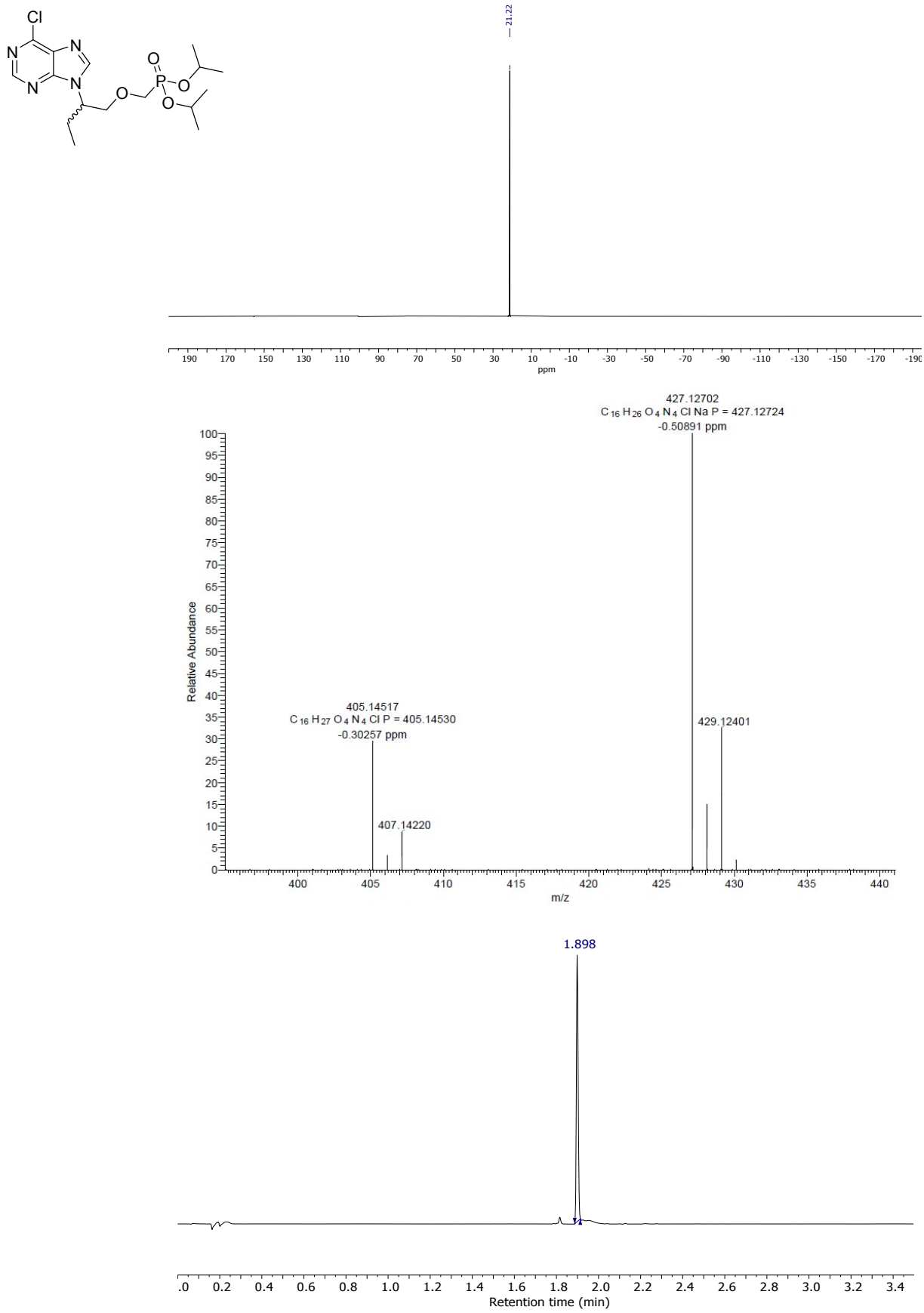


Figure S21. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**4a**.

Diisopropyl (*S*)-((2-(6-chloro-9*H*-purin-9-yl)-3-methylbutoxy)methyl)phosphonate ((*S*)-**4b**)

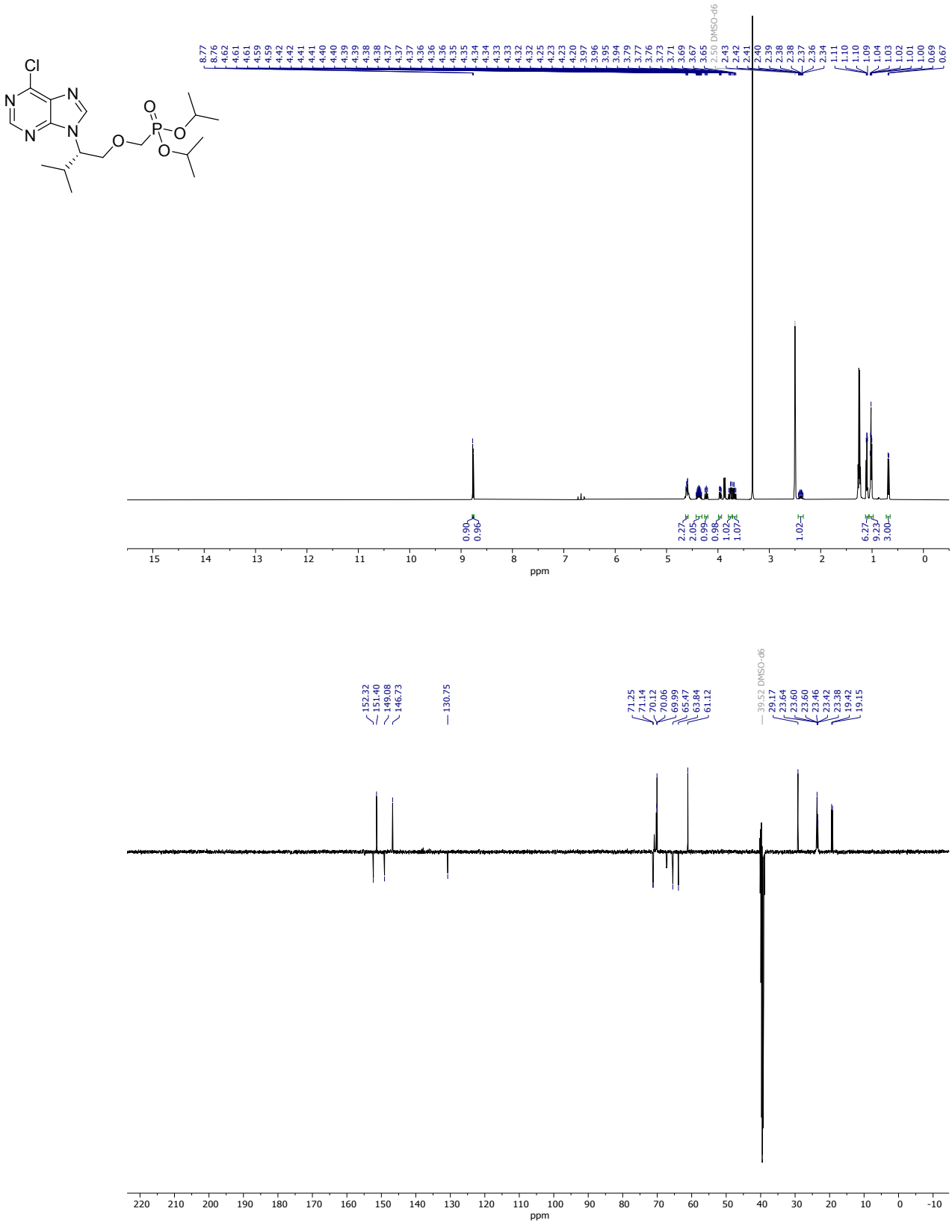


Figure S22. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*S*)-**4b** measured in DMSO-d_6 at room temperature.

Diisopropyl (*S*)-((2-(6-chloro-9*H*-purin-9-yl)-3-methylbutoxy)methyl)phosphonate ((*S*)-**4b**)

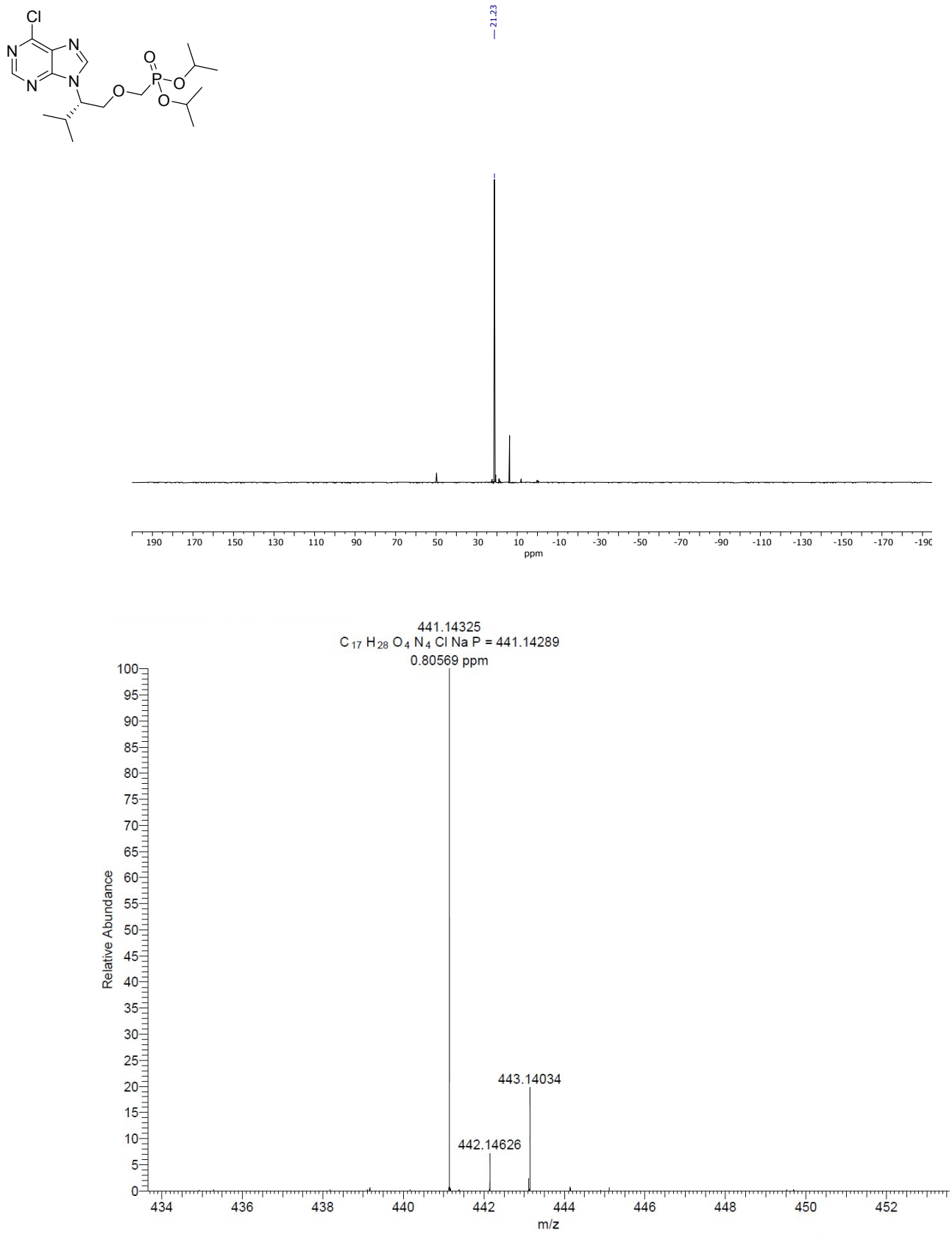


Figure S23. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*S*)-**4b**.

Diisopropyl (*S*)-((2-(6-chloro-9*H*-purin-9-yl)-3-methylbutoxy)methyl)phosphonate ((*S*)-**4b**)

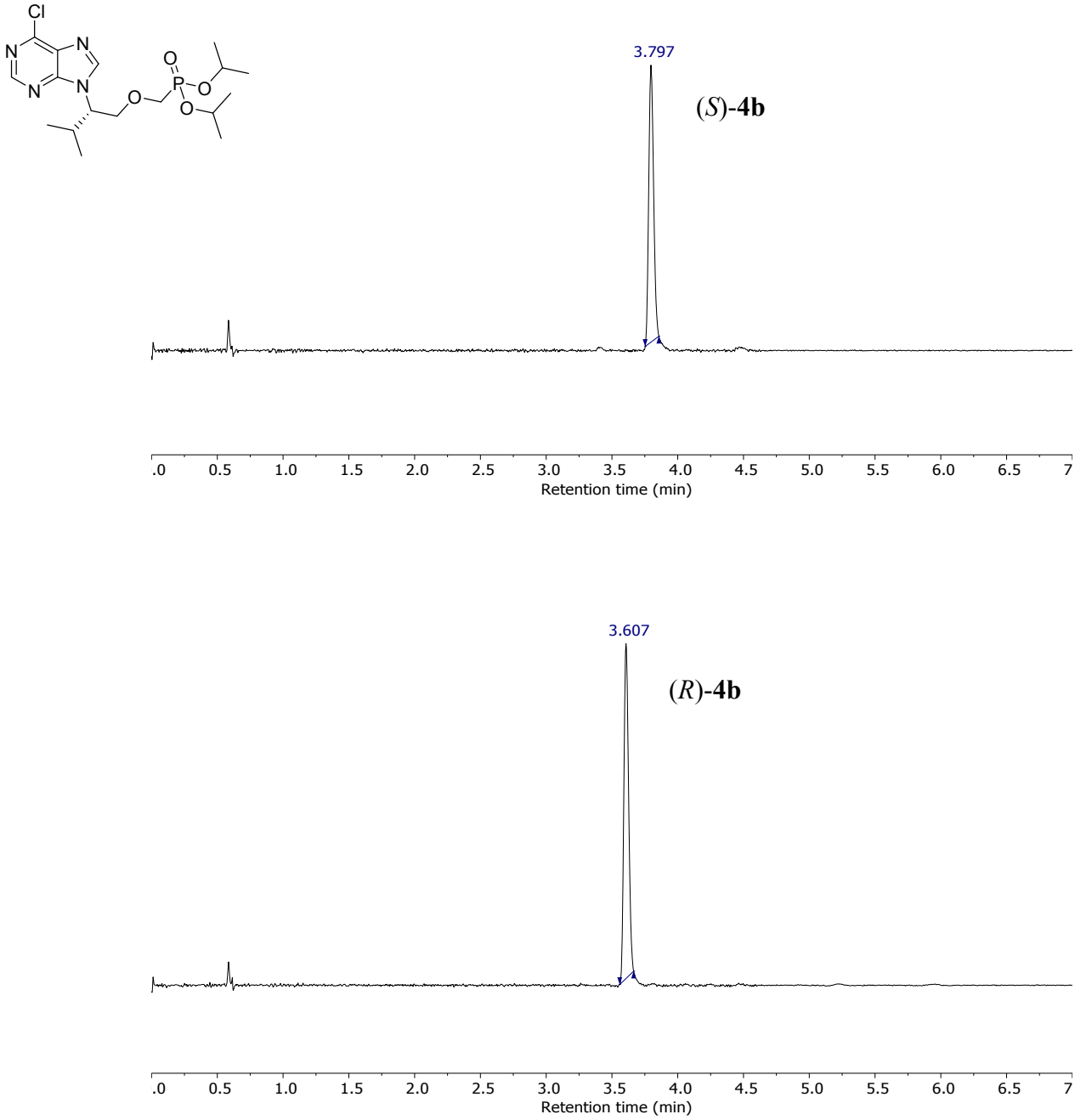


Figure S24. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top for (*S*)-**4b**, bottom for (*R*)-**4b**).

Diisopropyl (*R*)-((2-(6-chloro-9*H*-purin-9-yl)-3-methylbutoxy)methyl)phosphonate ((*R*)-**4b**)

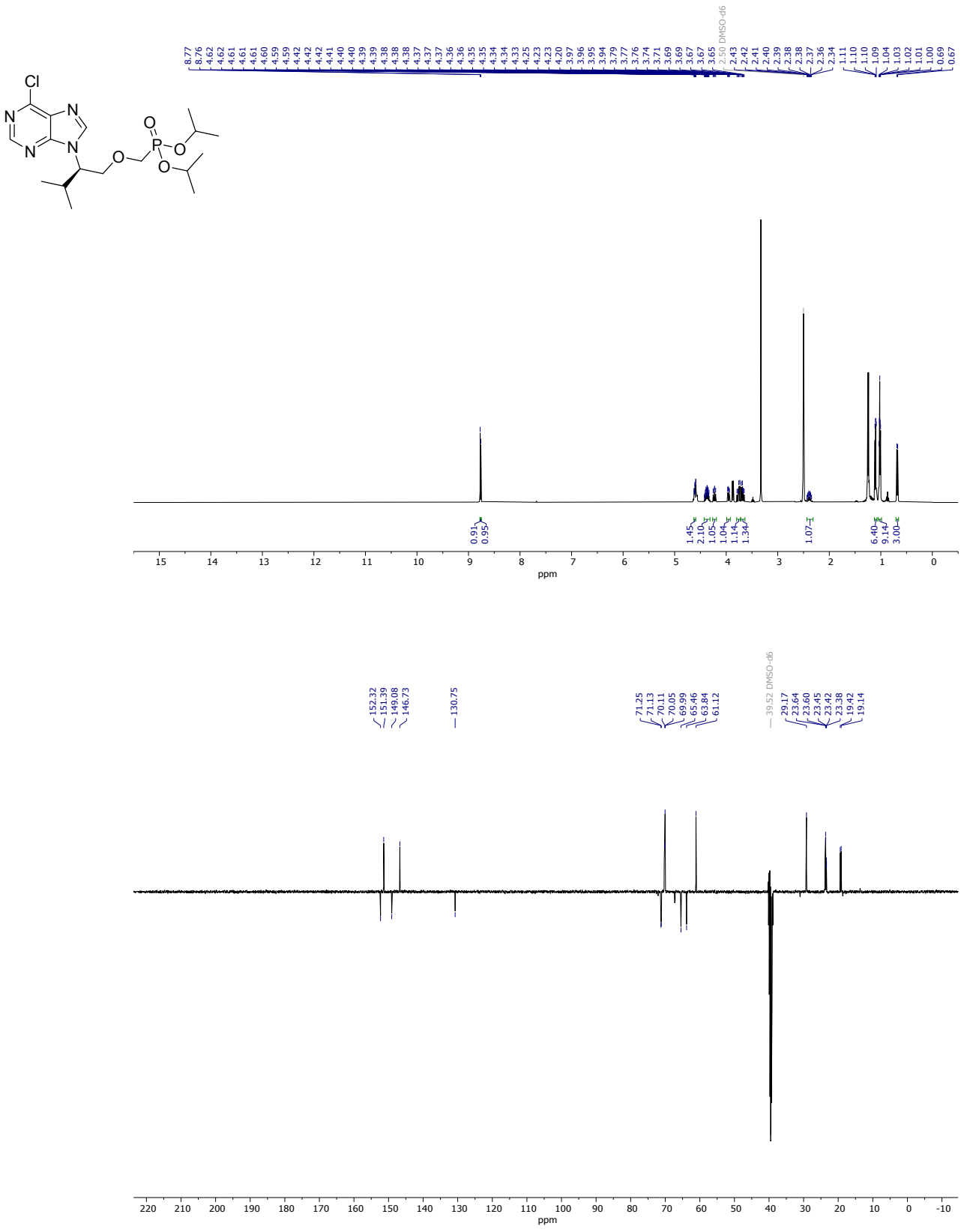


Figure S25. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**4b** measured in DMSO-d_6 at room temperature.

Diisopropyl (*R*)-((2-(6-chloro-9*H*-purin-9-yl)-3-methylbutoxy)methyl)phosphonate ((*R*)-**4b**)

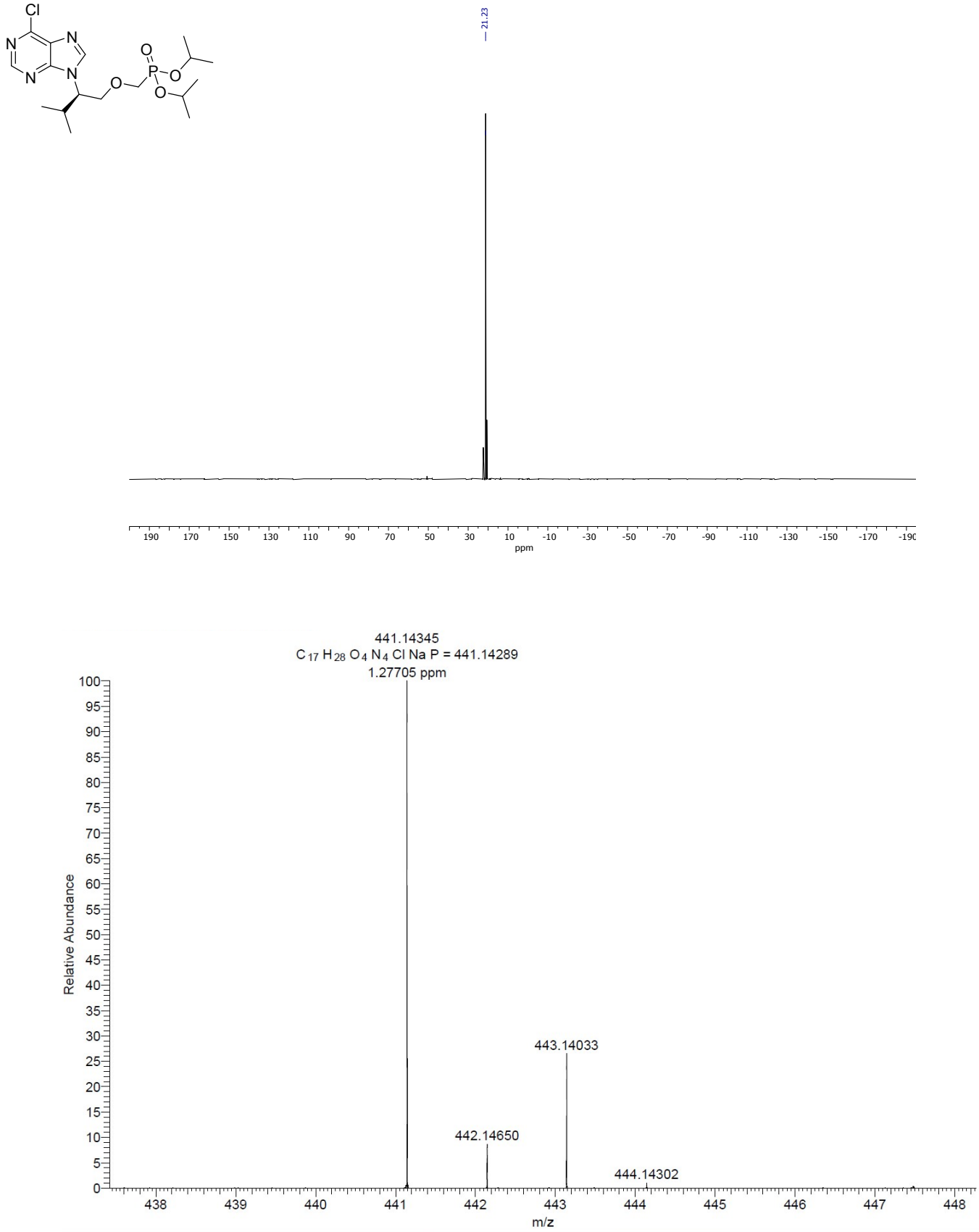
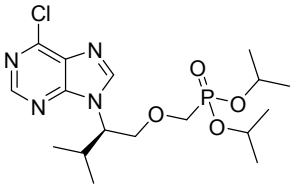
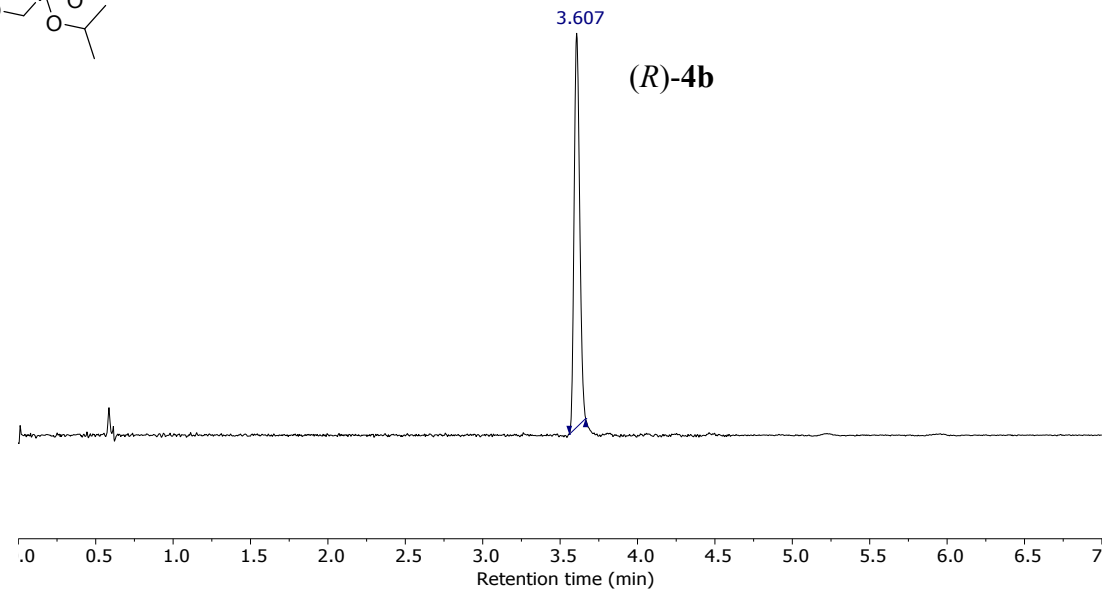


Figure S26. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top) high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**4b**.

Diisopropyl (*R*)-((2-(6-chloro-9*H*-purin-9-yl)-3-methylbutoxy)methyl)phosphonate ((*R*)-**4b**)





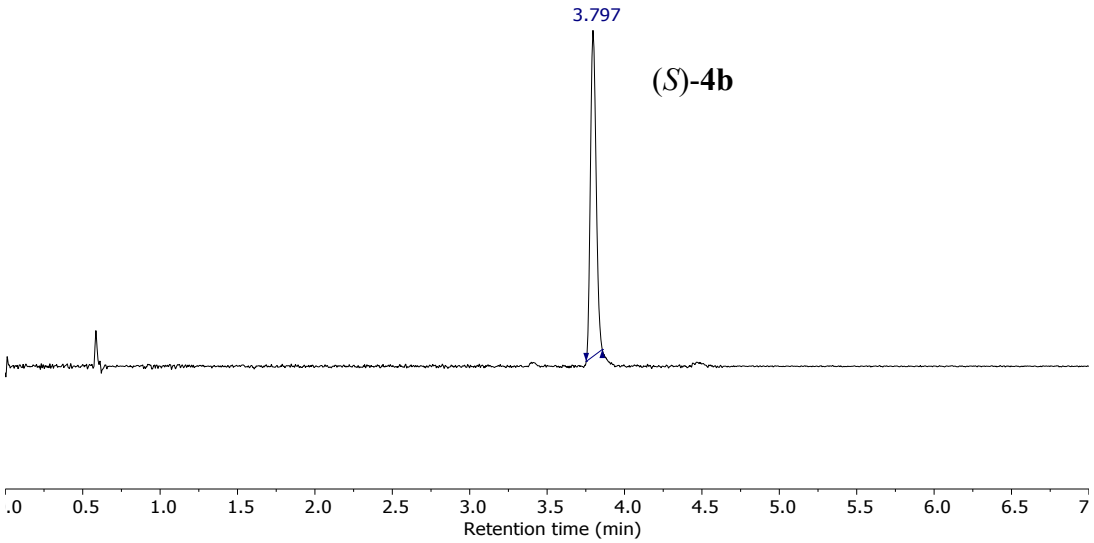


Figure S27. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top for (*R*)-**4b**, bottom for (*S*)-**4b**).

Diisopropyl (*R*)-((2-(6-chloro-9*H*-purin-9-yl)-2-cyclopropylethoxy)methyl)phosphonate ((*R*)-**4c**)

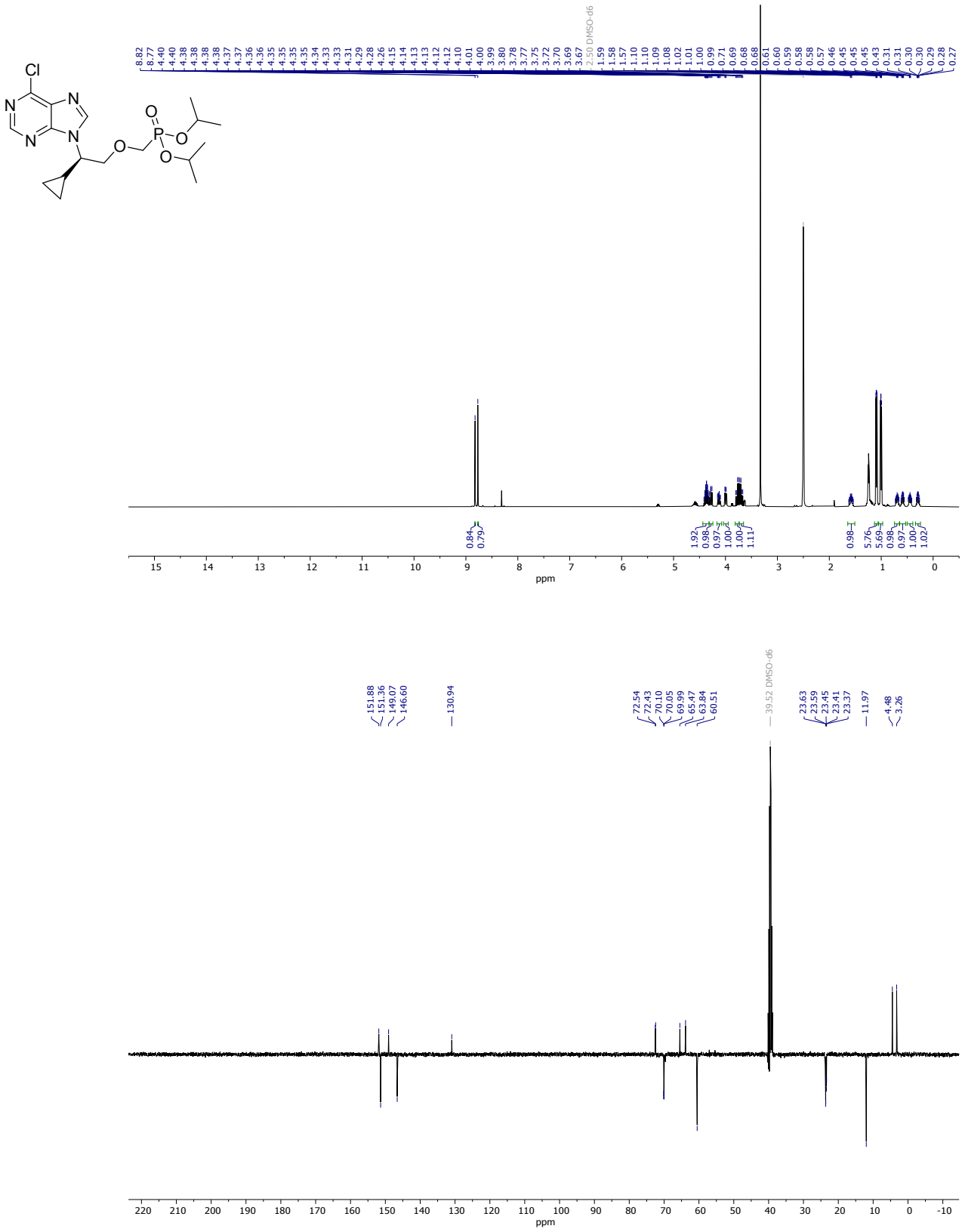


Figure S28. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**4c** measured in DMSO-d_6 at room temperature.

Diisopropyl (*R*)-((2-(6-chloro-9*H*-purin-9-yl)-2-cyclopropylethoxy)methyl)phosphonate ((*R*)-**4c**)

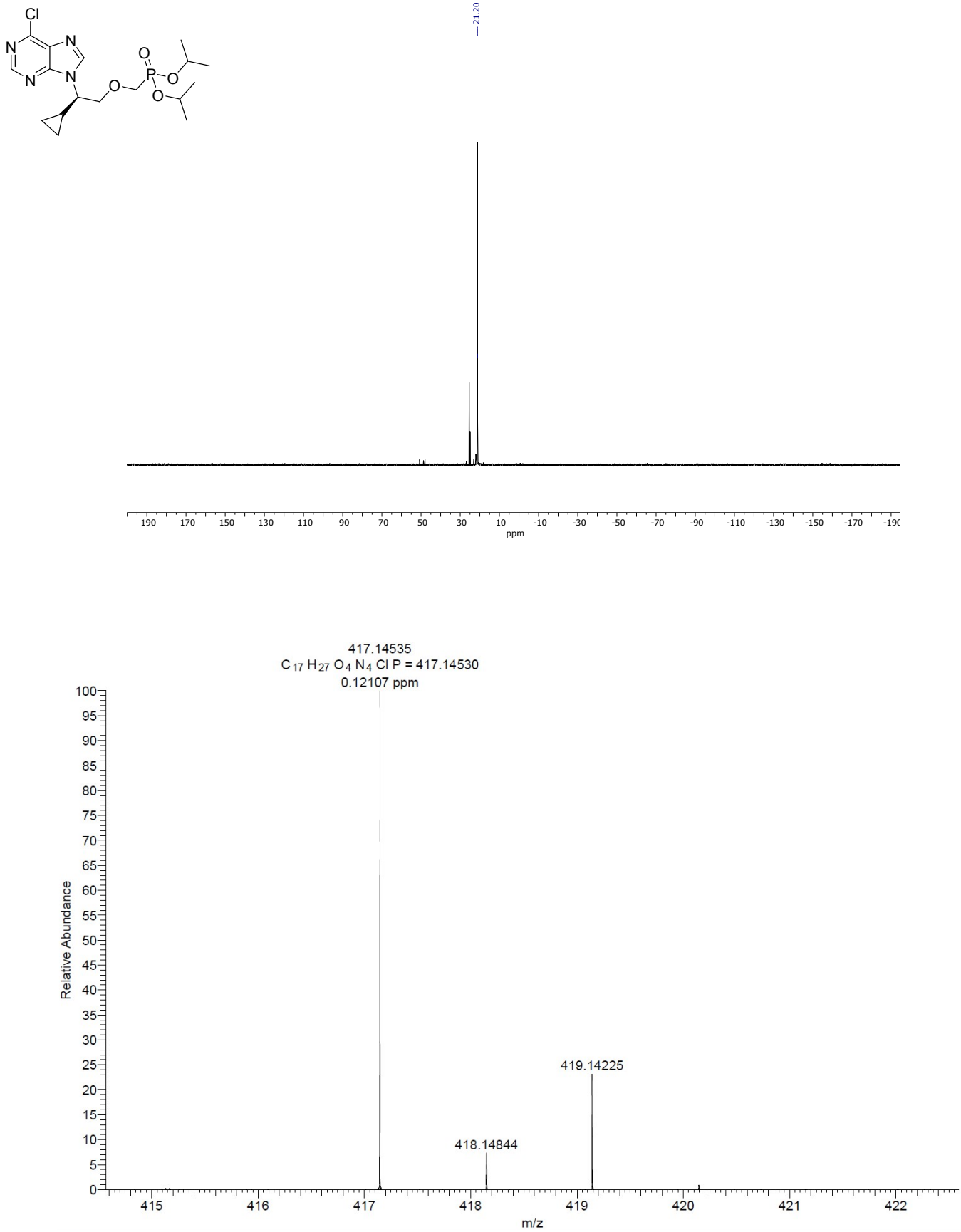
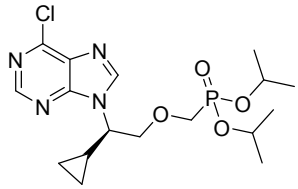
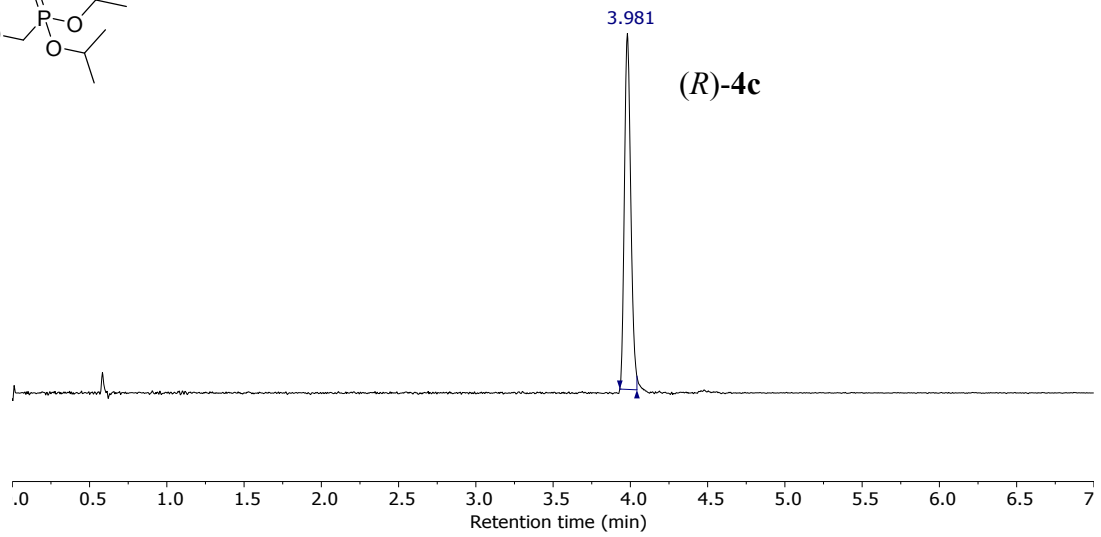


Figure S29. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**4c**.

Diisopropyl (*R*)-((2-(6-chloro-9*H*-purin-9-yl)-2-cyclopropylethoxy)methyl)phosphonate ((*R*)-**4c**)





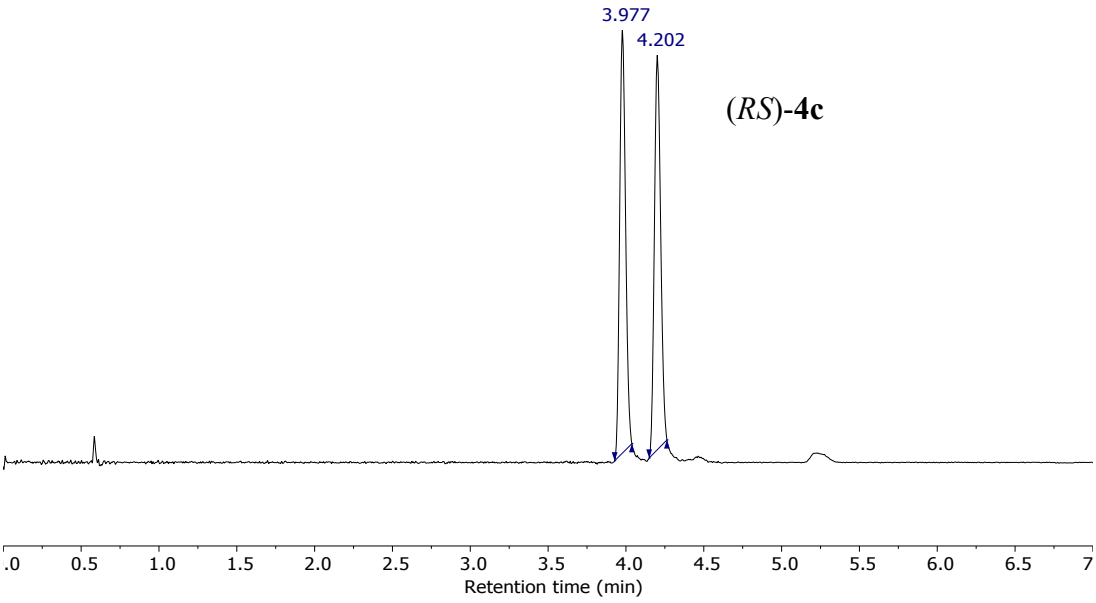


Figure S30. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top for (*R*)-**4c**, bottom for (*RS*)-**4c**).

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)-2-cyclopropylethoxy)methyl)phosphonate ((*RS*)-**4c**)

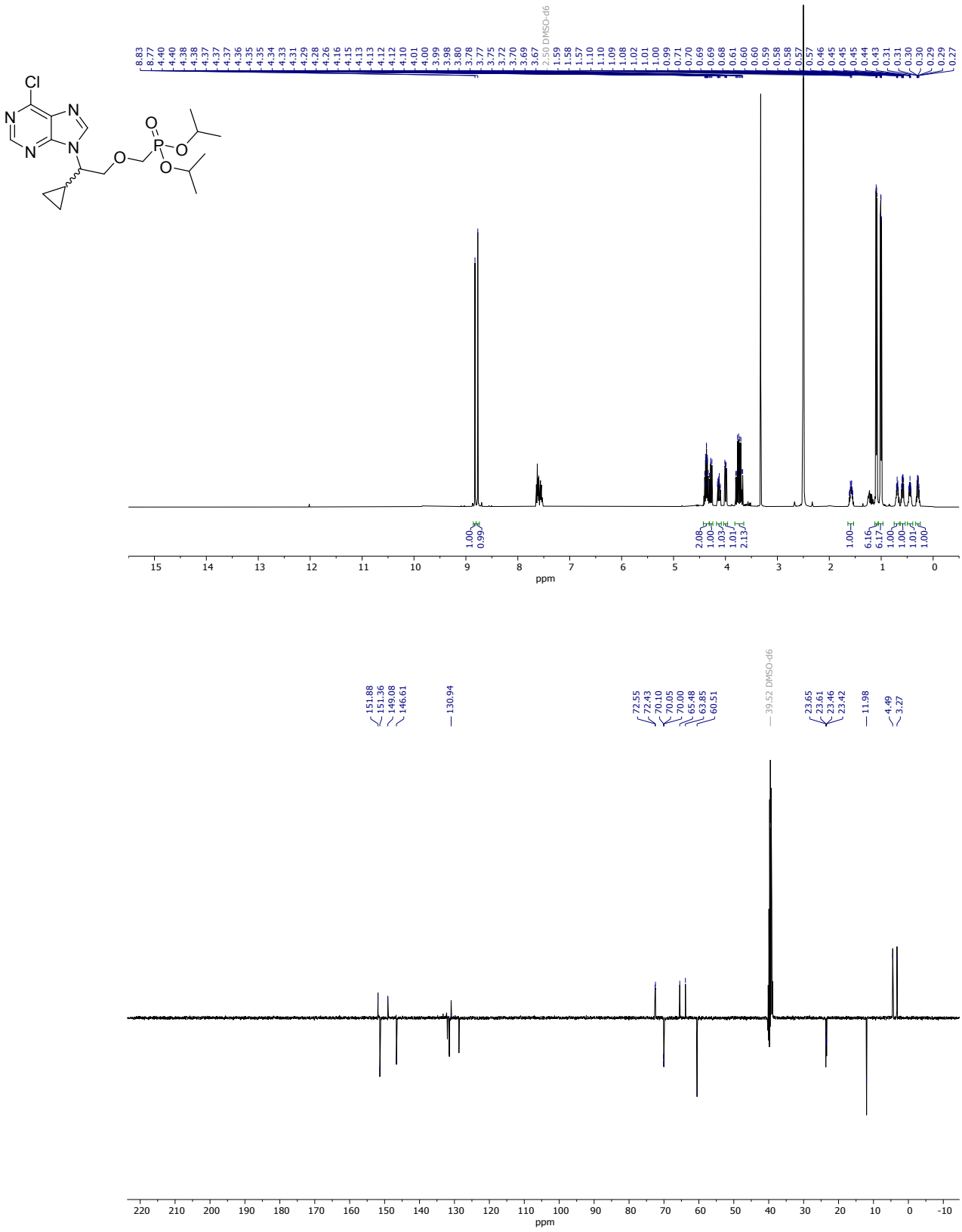


Figure S31. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**4c** measured in DMSO-d_6 at room temperature.

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)-2-cyclopropylethoxy)methyl)phosphonate ((*RS*)-**4c**)

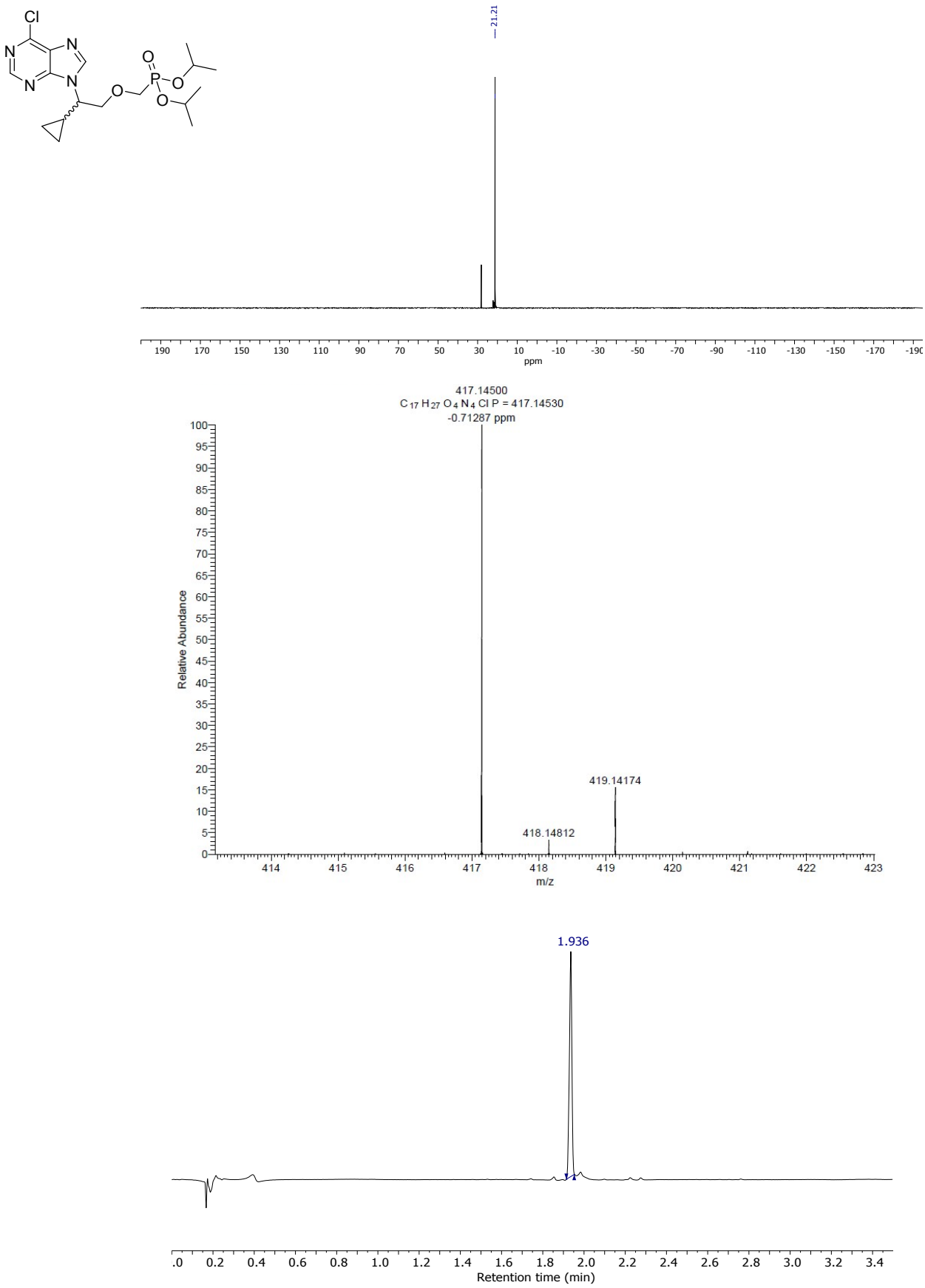


Figure S32. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**4c**.

Diisopropyl (*R*)-((3-(benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*R*)-**4d**)

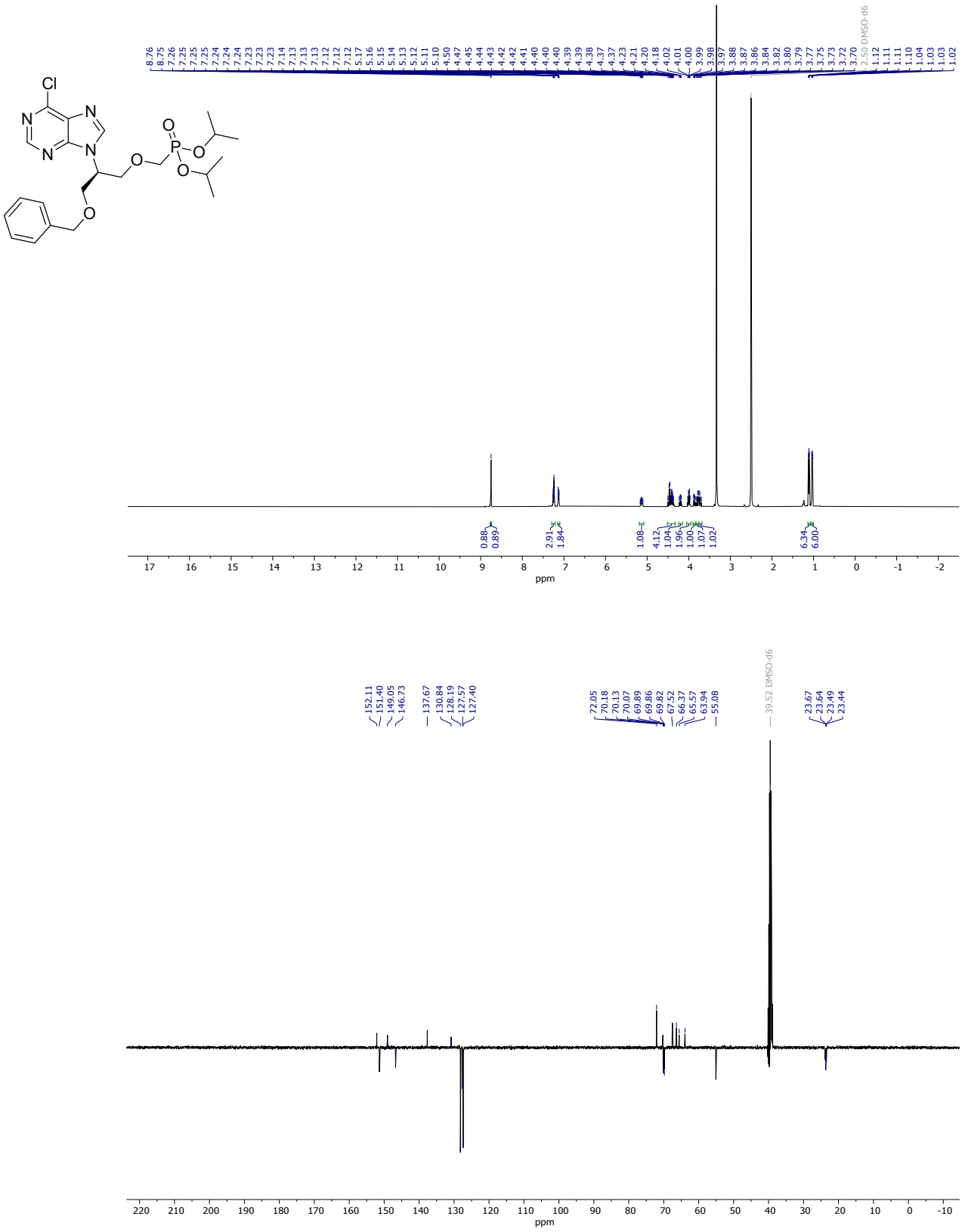


Figure S33. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**4d** measured in DMSO-d_6 at room temperature.

Diisopropyl (*R*)-((3-(benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*R*)-**4d**)

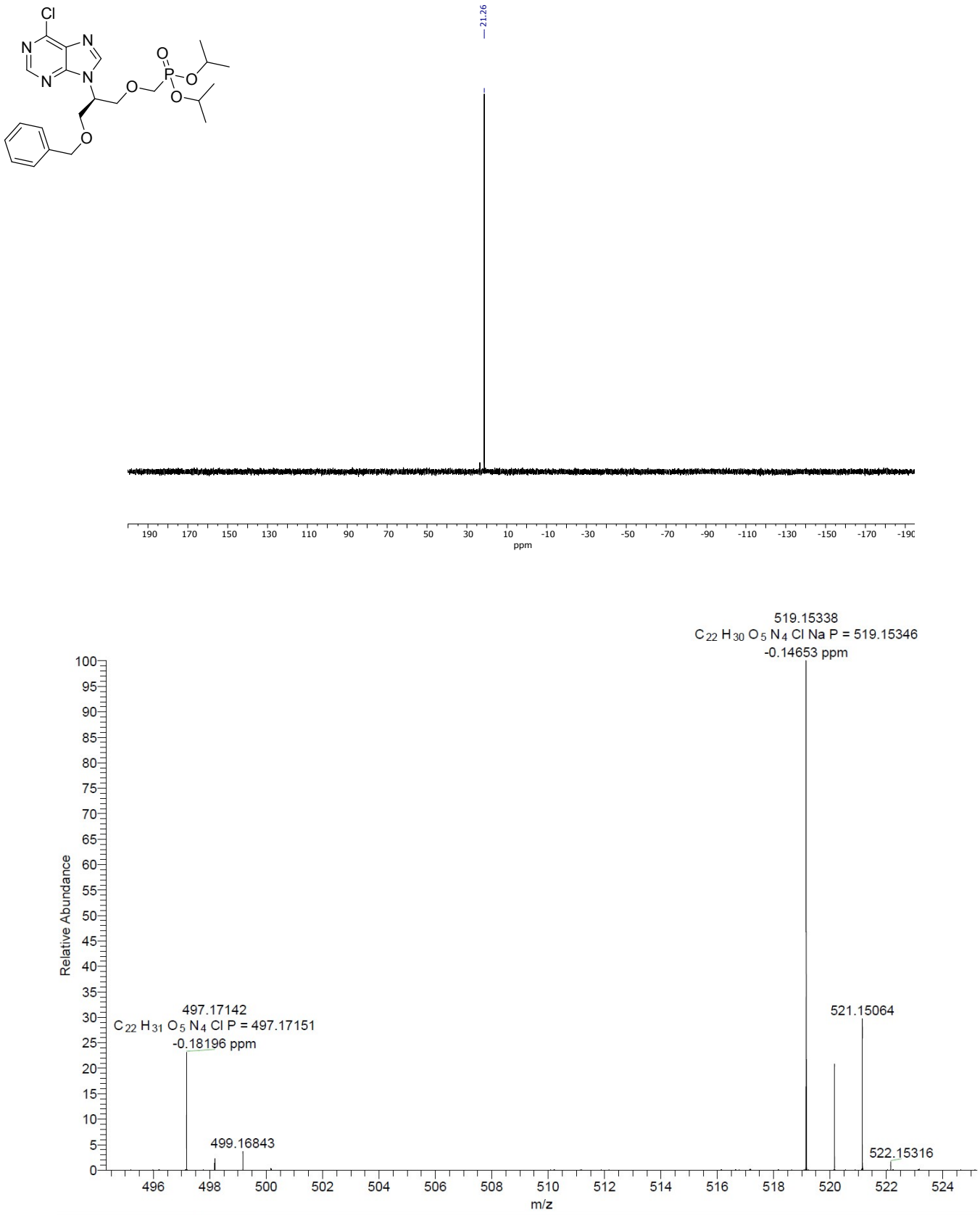


Figure S34. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**4d**.

Diisopropyl (*R*)-((3-(benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*R*)-**4d**)

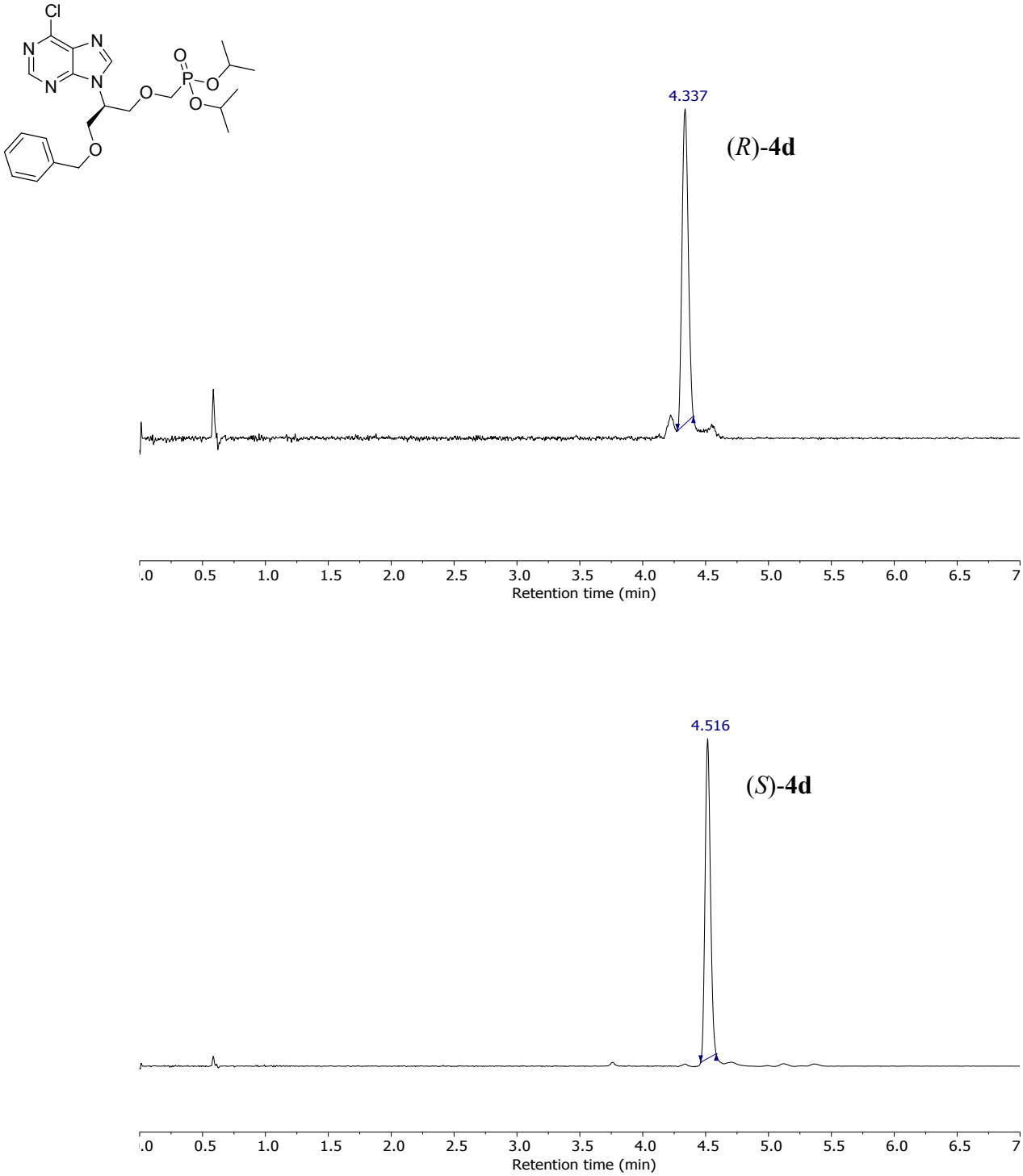


Figure S35. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top for (*R*)-**4d**, bottom for (*S*)-**4d**).

Diisopropyl (*S*)-((3-(benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*S*)-**4d**)

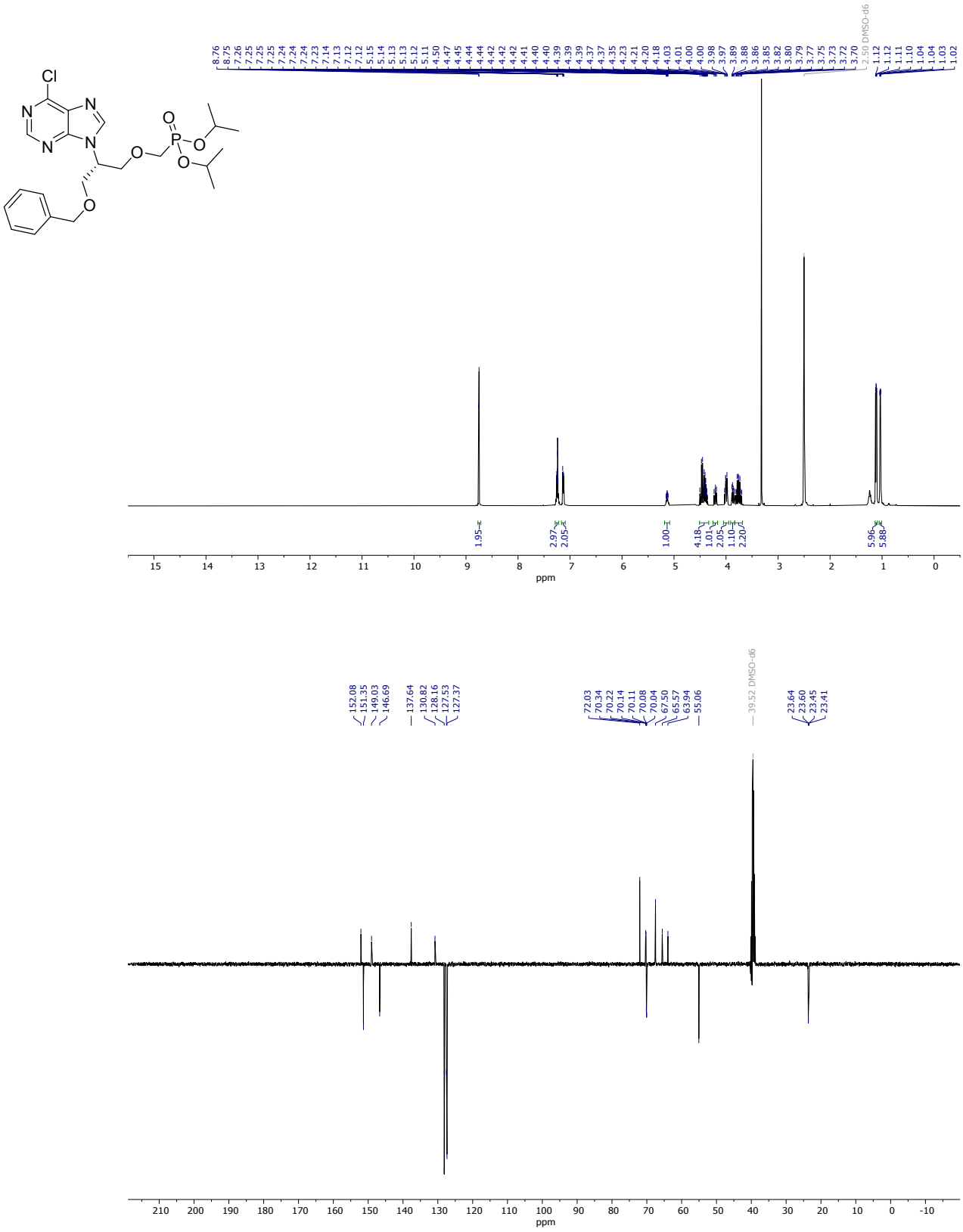


Figure S36. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*S*)-**4d** measured in DMSO-d_6 at room temperature.

Diisopropyl (*S*)-((3-(benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*S*)-**4d**)

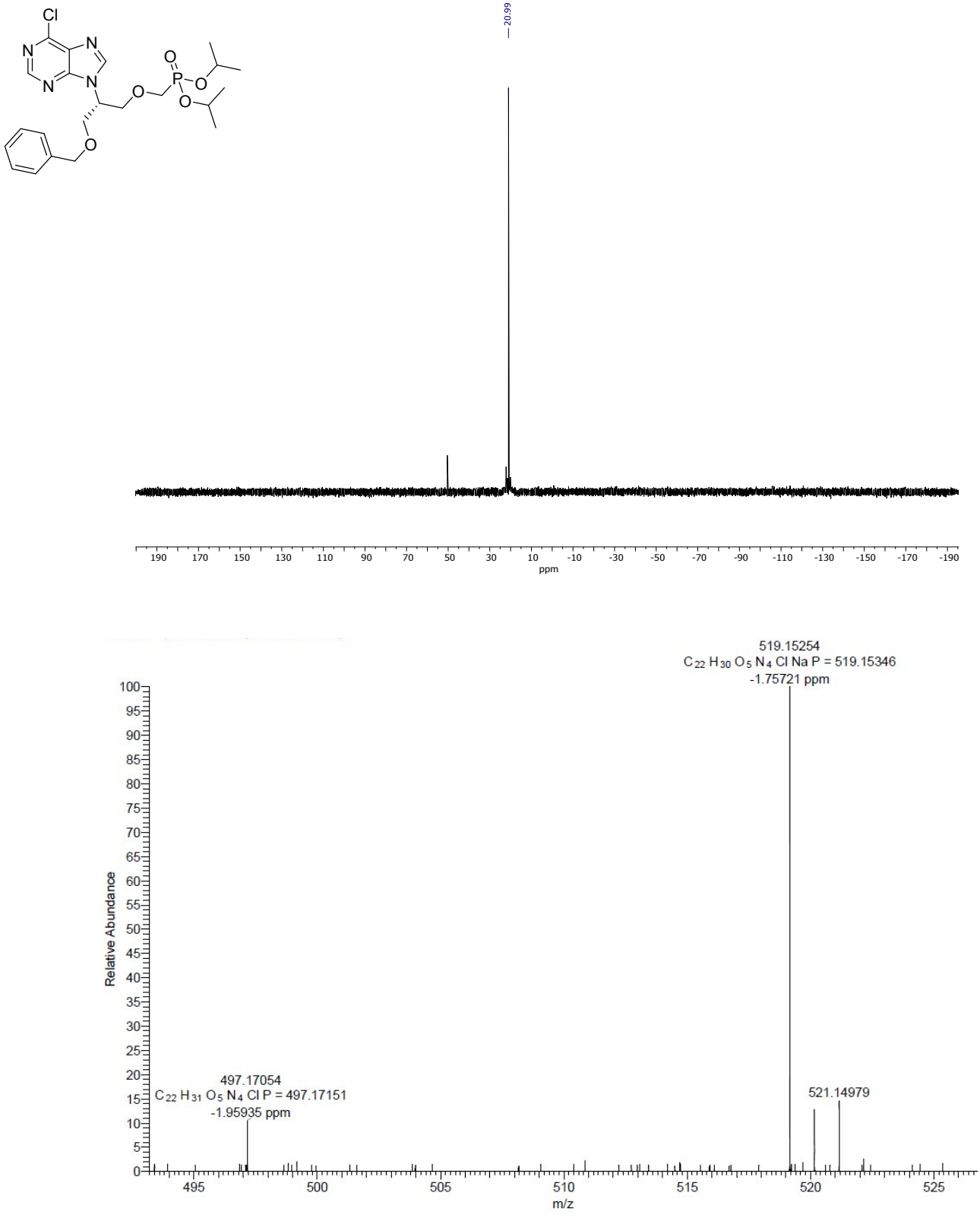


Figure S37. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*S*)-**4d**.

Diisopropyl (*S*)-((3-(benzyloxy)-2-(6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*S*)-**4d**)

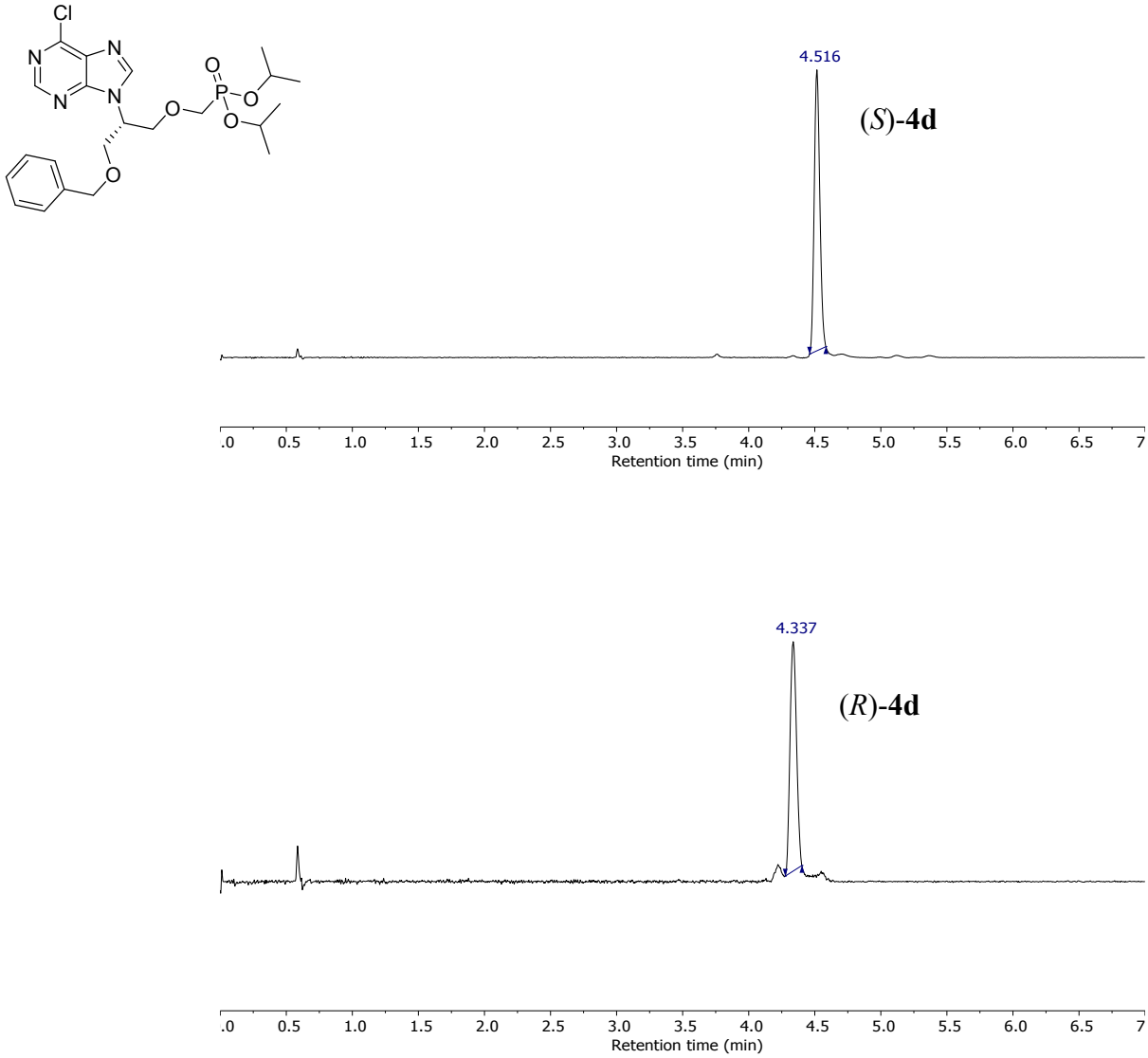


Figure S38. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top for (*S*)-**4d**, bottom for (*R*)-**4d**).

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)-2-methoxyethoxy)methyl)phosphonate ((*RS*)-**4e**)

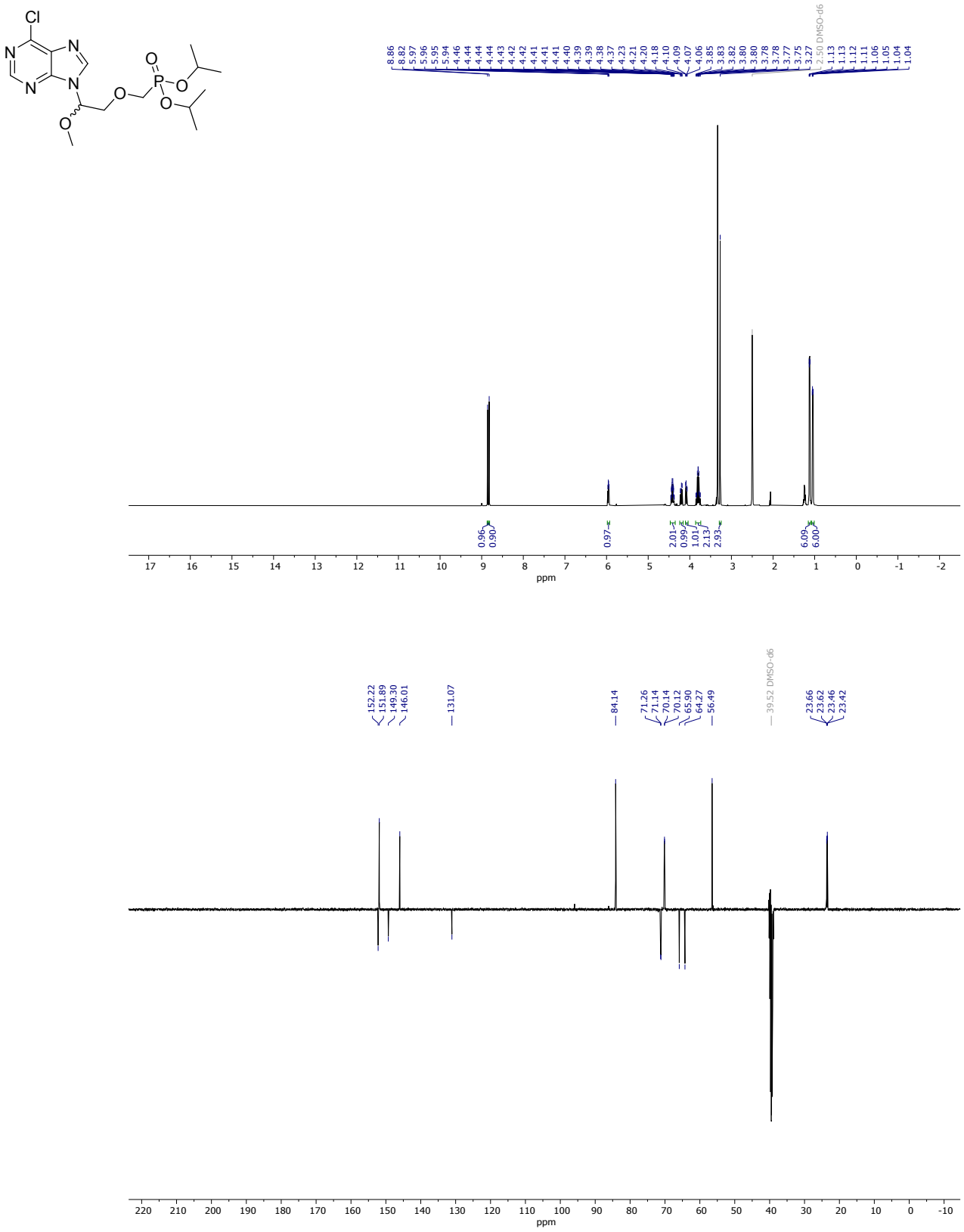


Figure S39. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**4e** measured in DMSO-d_6 at room temperature.

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)-2-methoxyethoxy)methyl)phosphonate ((*RS*)-**4e**)

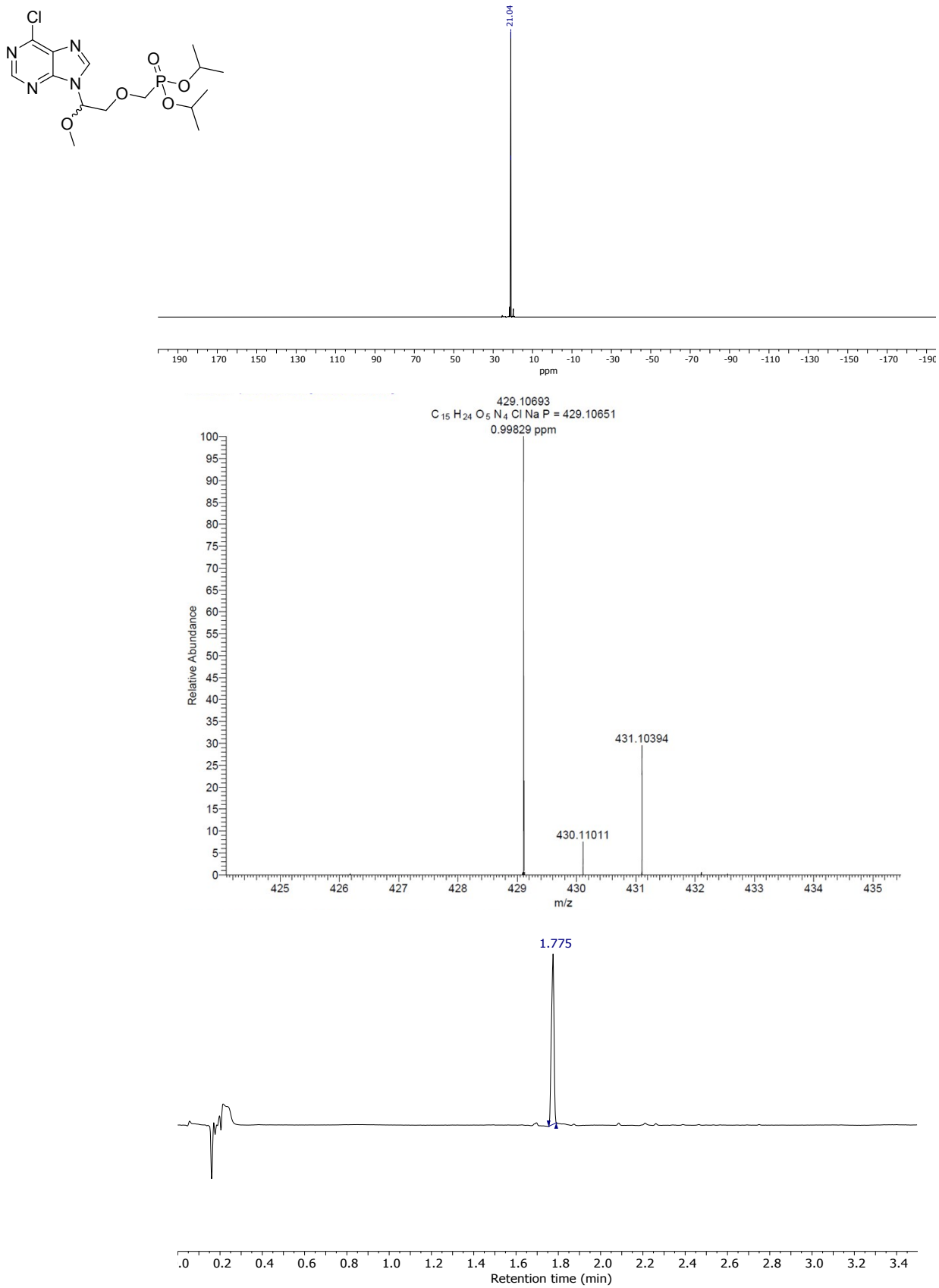


Figure S40. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**4e**.

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)-2-ethoxyethoxy)methyl)phosphonate ((*RS*)-**4f**)

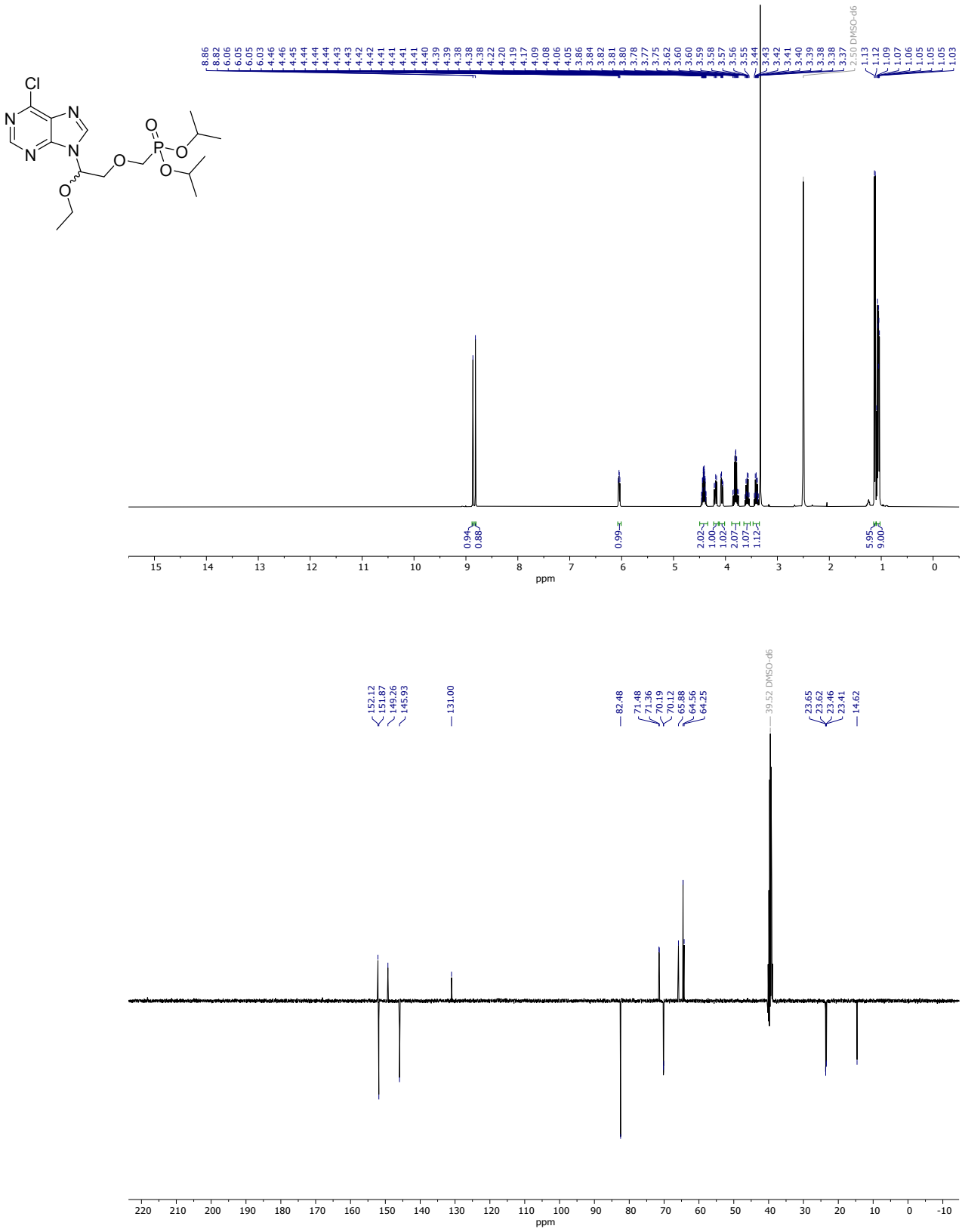


Figure S41. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**4f** measured in DMSO-d_6 at room temperature.

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)-2-ethoxyethoxy)methyl)phosphonate ((*RS*)-**4f**)

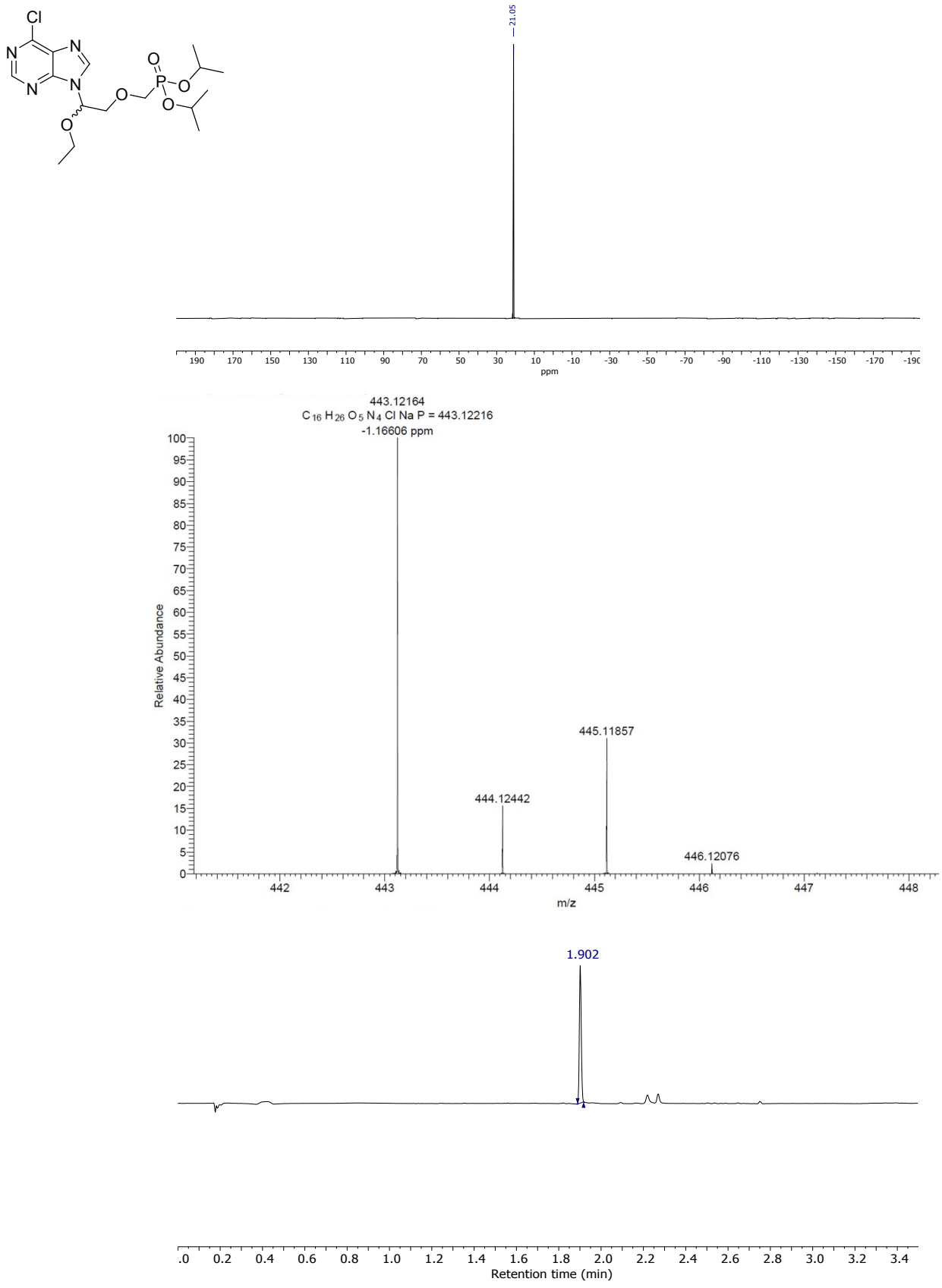


Figure S42. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**4f**.

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**4g**)

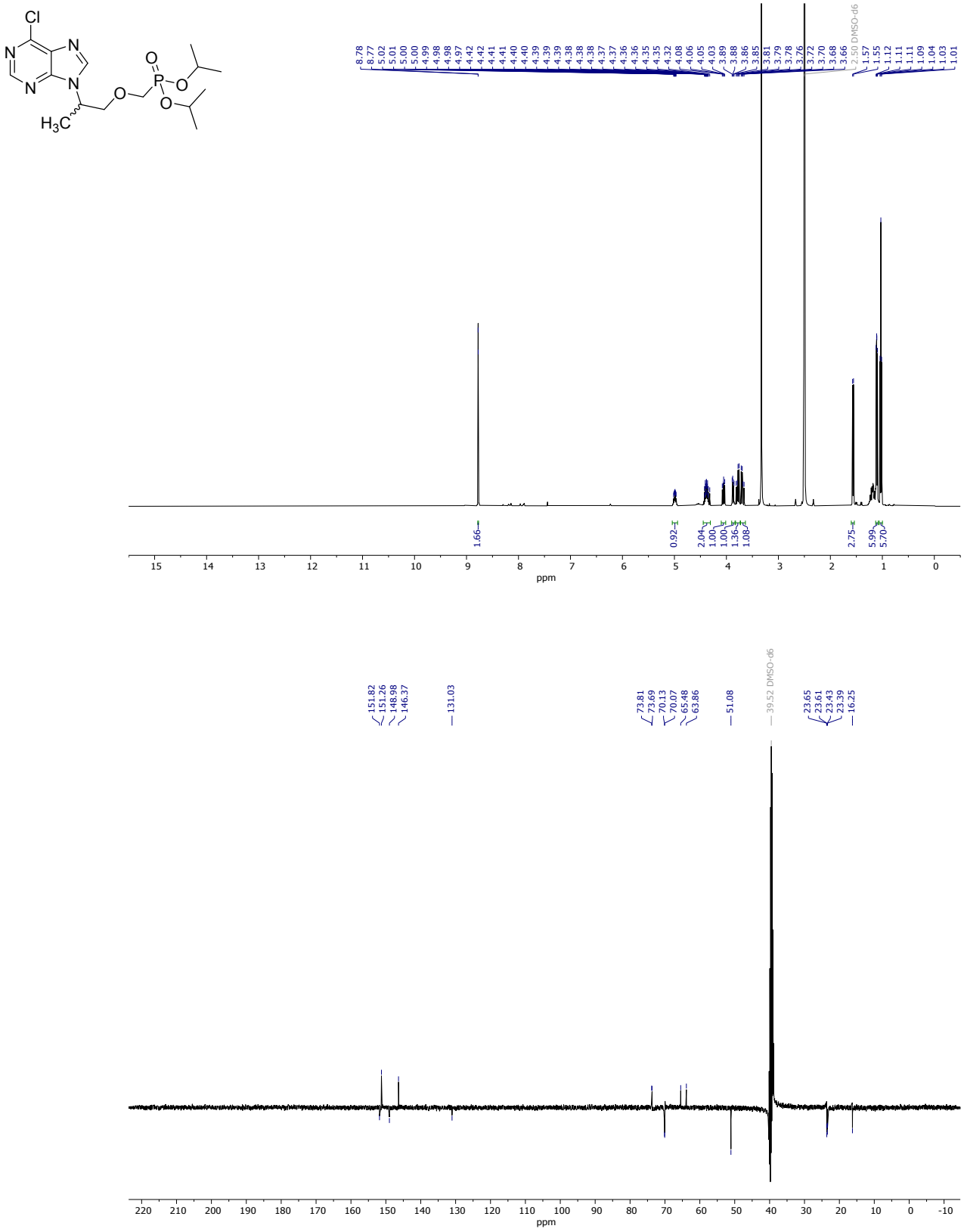


Figure S43. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**4g** measured in DMSO-d_6 at room temperature.

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**4g**)

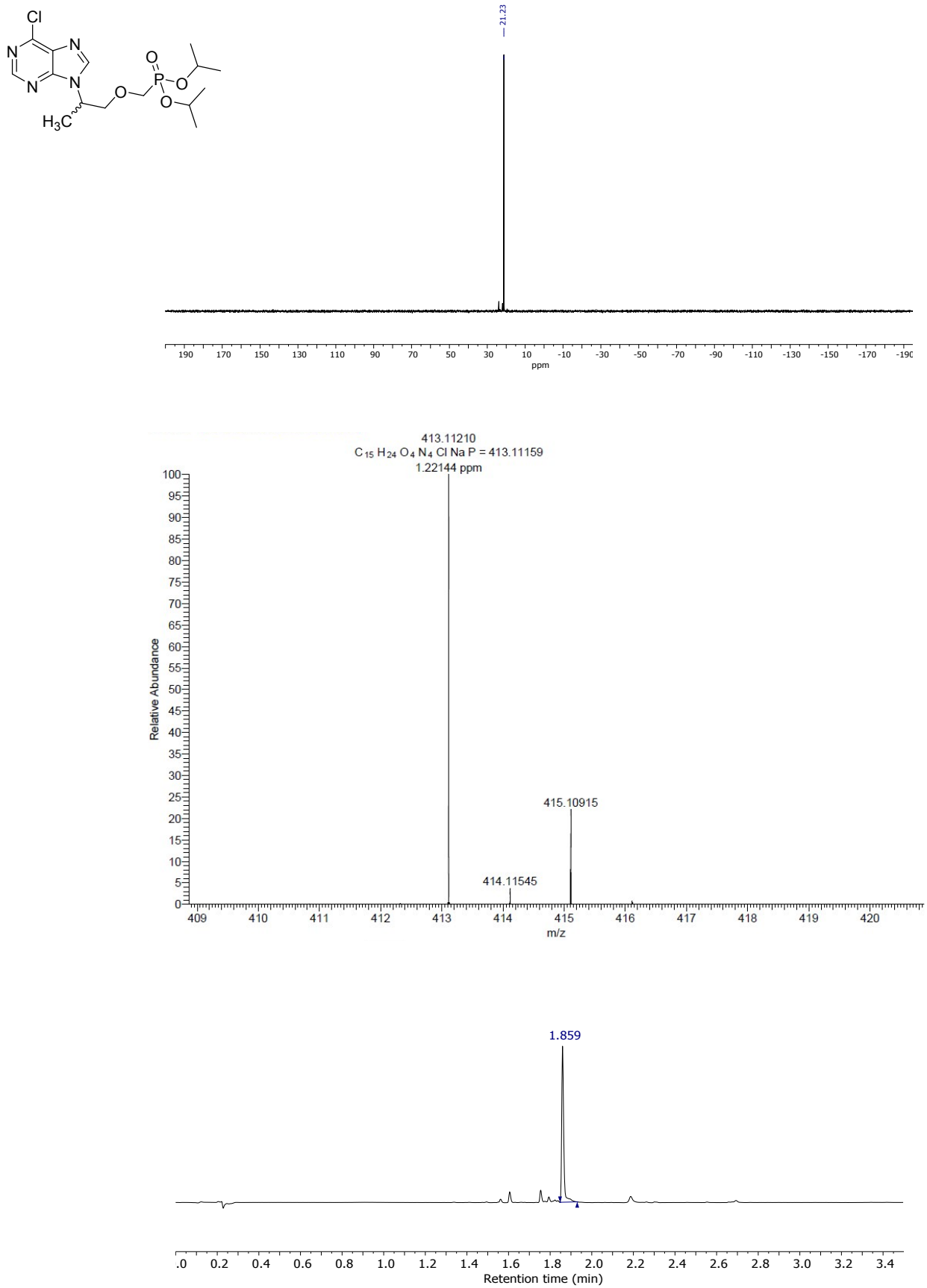


Figure S44. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**4g**.

Diisopropyl (((2-(6-chloro-9*H*-purin-9-yl)but-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**4h**)

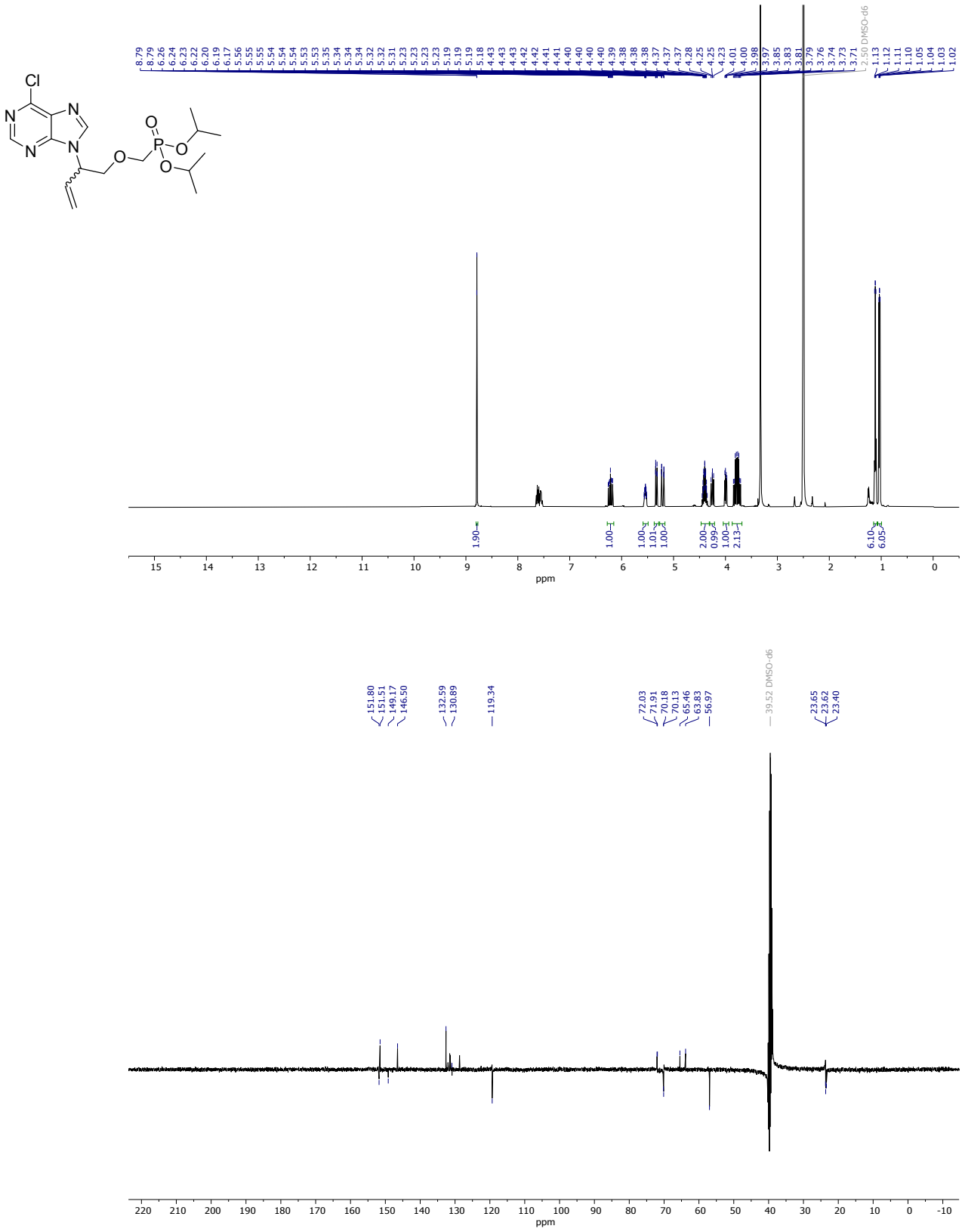


Figure S45. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**4h** measured in DMSO-d_6 at room temperature.

Diisopropyl (((2-(6-chloro-9*H*-purin-9-yl)but-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**4h**)

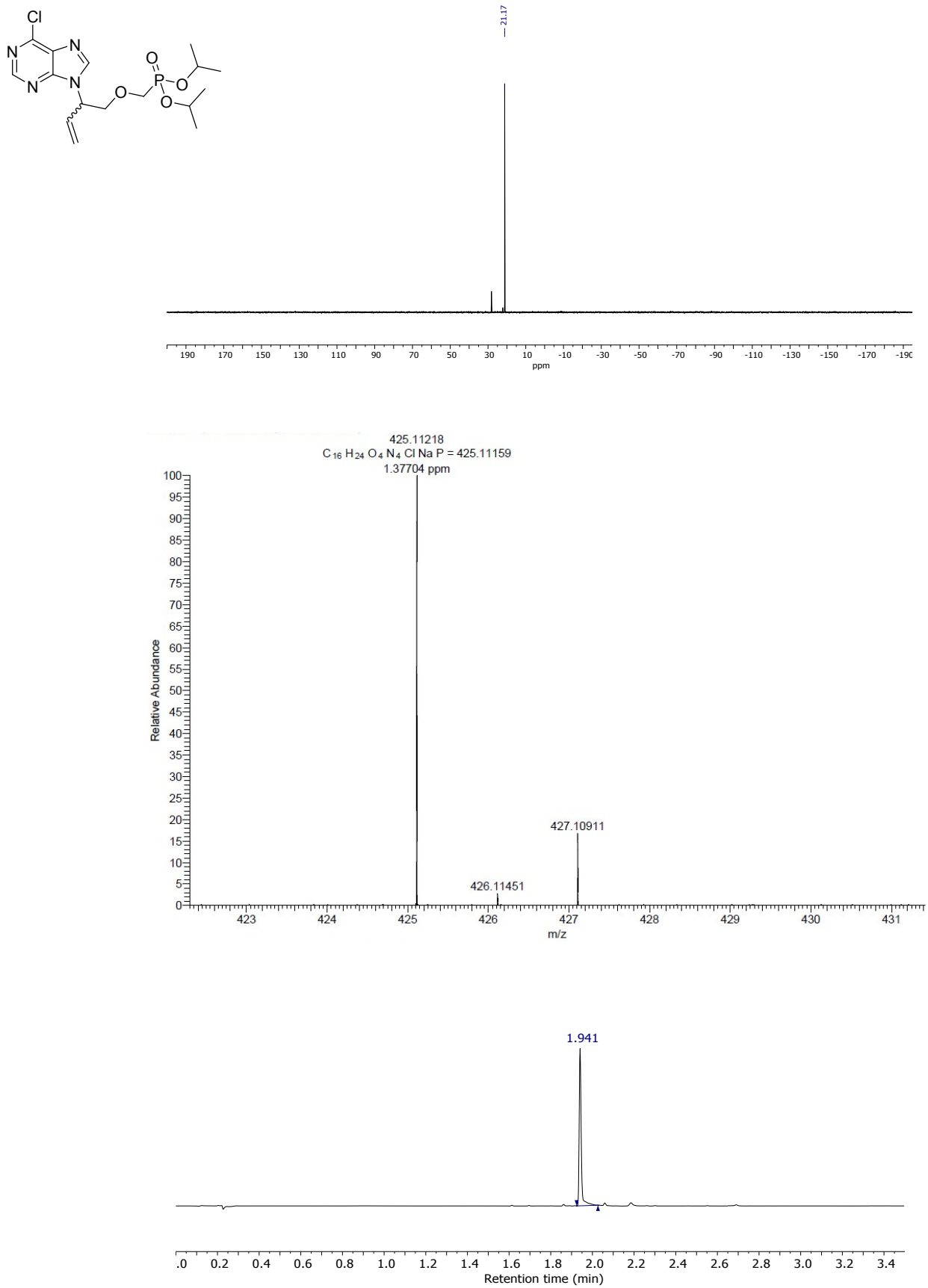


Figure S46. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**4h**.

Diisopropyl (((2-(6-chloro-9*H*-purin-9-yl)but-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**4i**)

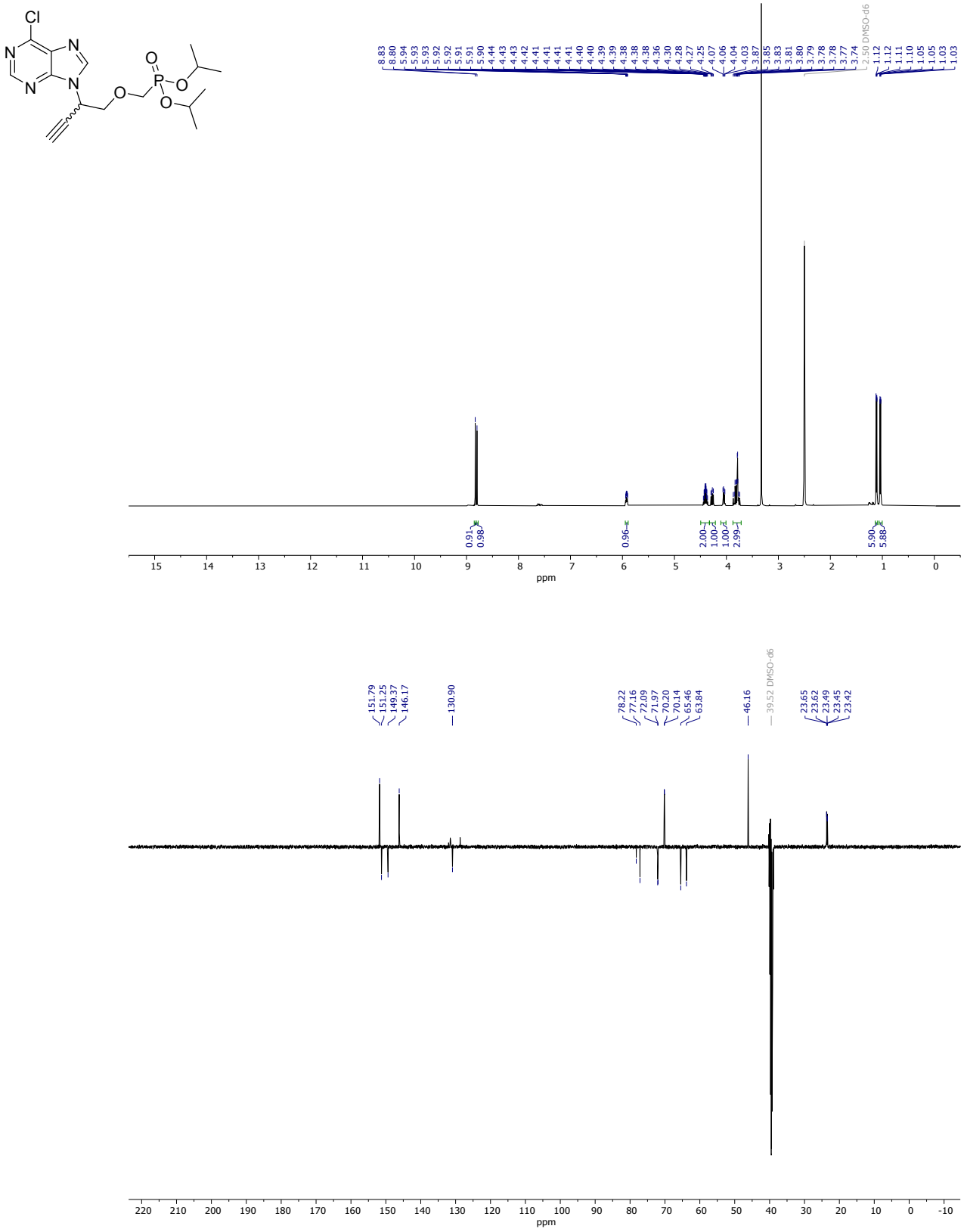


Figure S47. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**4i** measured in DMSO-d_6 at room temperature.

Diisopropyl (((2-(6-chloro-9*H*-purin-9-yl)but-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**4i**)

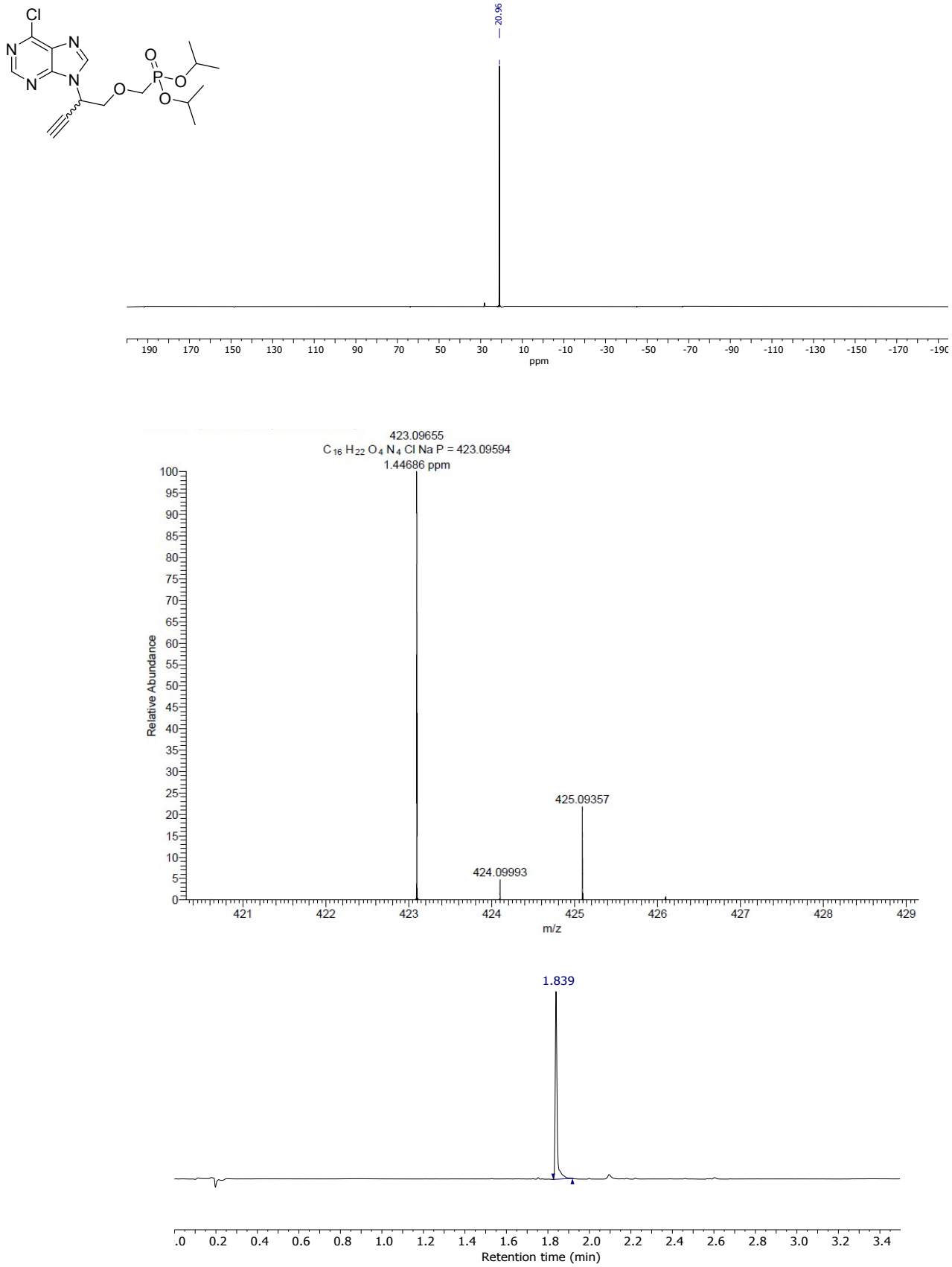


Figure S48. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**4i**.

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)-3,3,3-trifluoropropoxy)methyl)phosphonate ((*RS*)-**4j**)

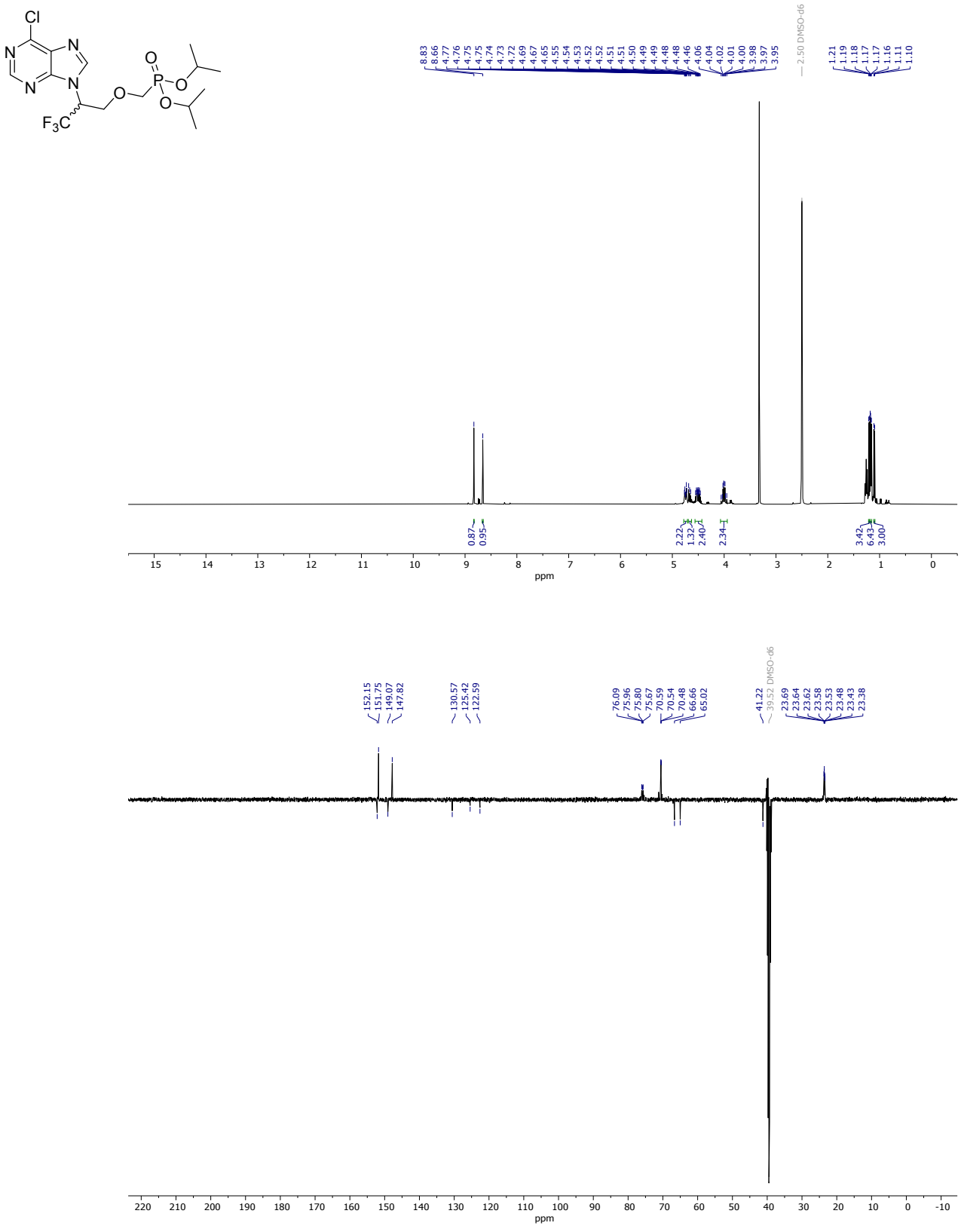


Figure S49. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**4j** measured in DMSO-d_6 at room temperature.

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)-3,3,3-trifluoropropoxy)methyl)phosphonate ((*RS*)-**4j**)

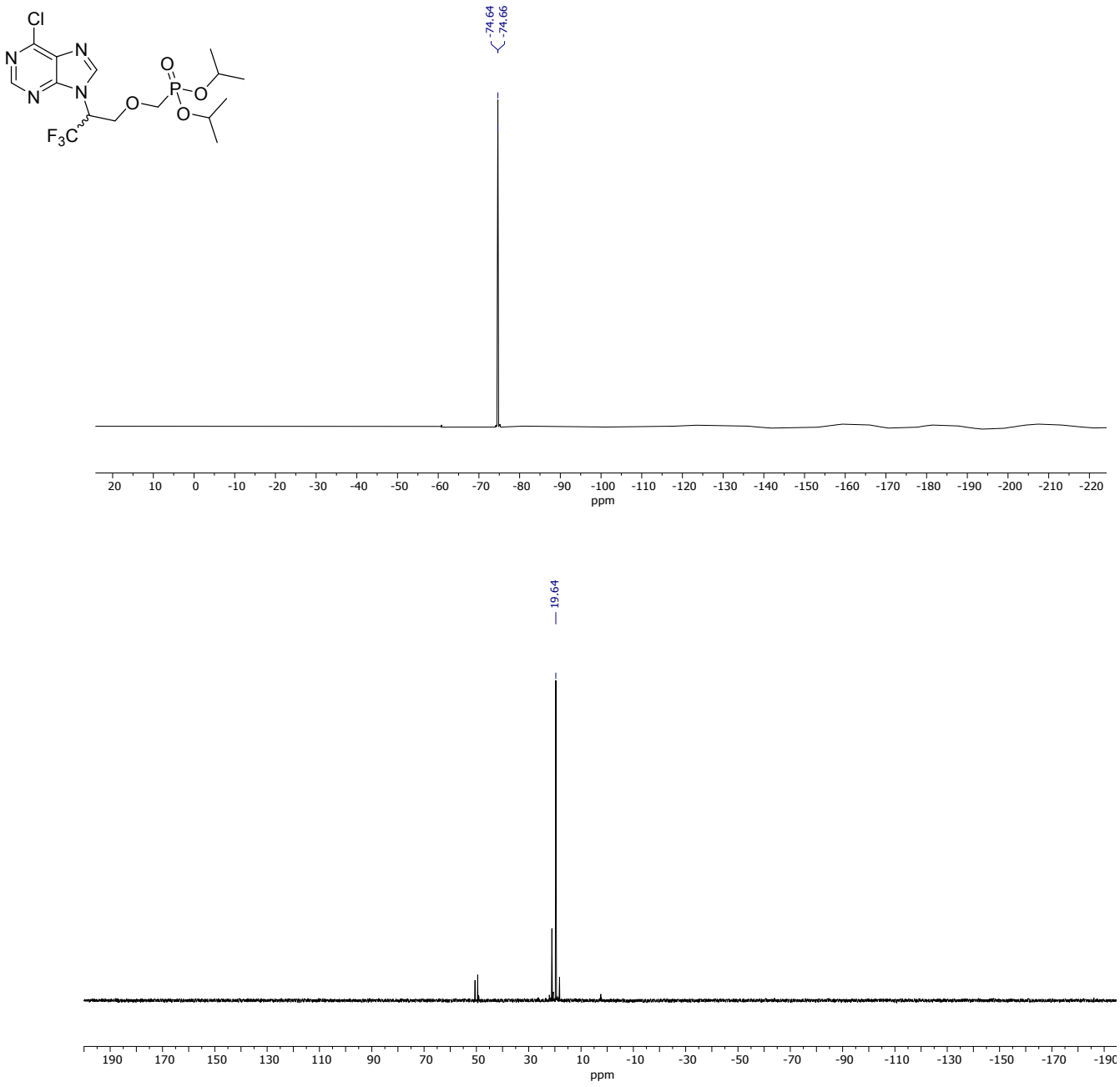


Figure S50. ^{19}F (top) and ^{31}P (bottom) NMR spectra of compound (*RS*)-**4j** measured in DMSO-d_6 at room temperature.

Diisopropyl ((2-(6-chloro-9*H*-purin-9-yl)-3,3,3-trifluoropropoxy)methyl)phosphonate ((*RS*)-**4j**)

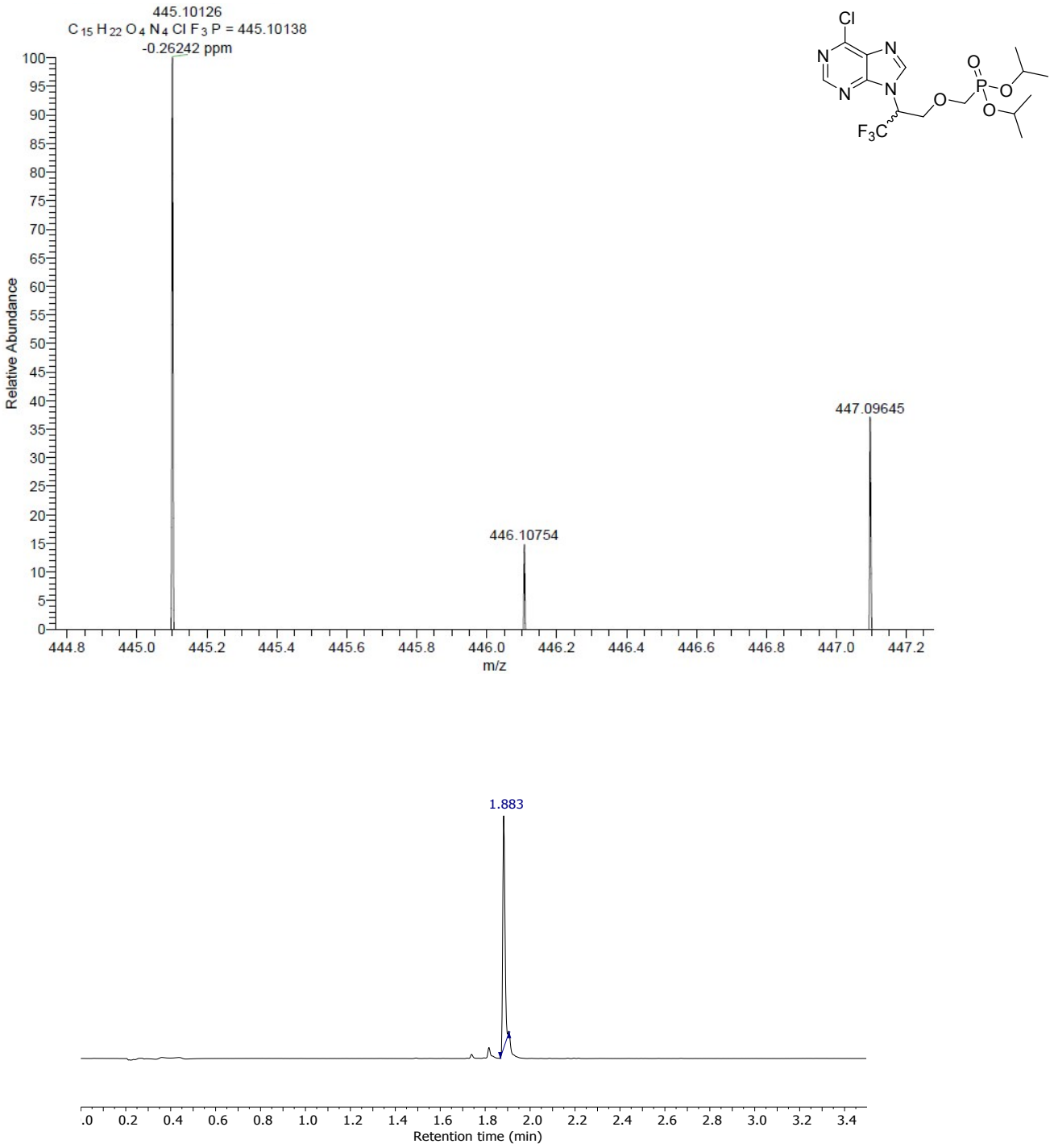


Figure S51. High resolution mass spectrum (HRMS, top) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**4j**.

Diisopropyl (*R*)-((2-(6-chloro-2-(((dimethylamino)methylene)amino)-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**5**)

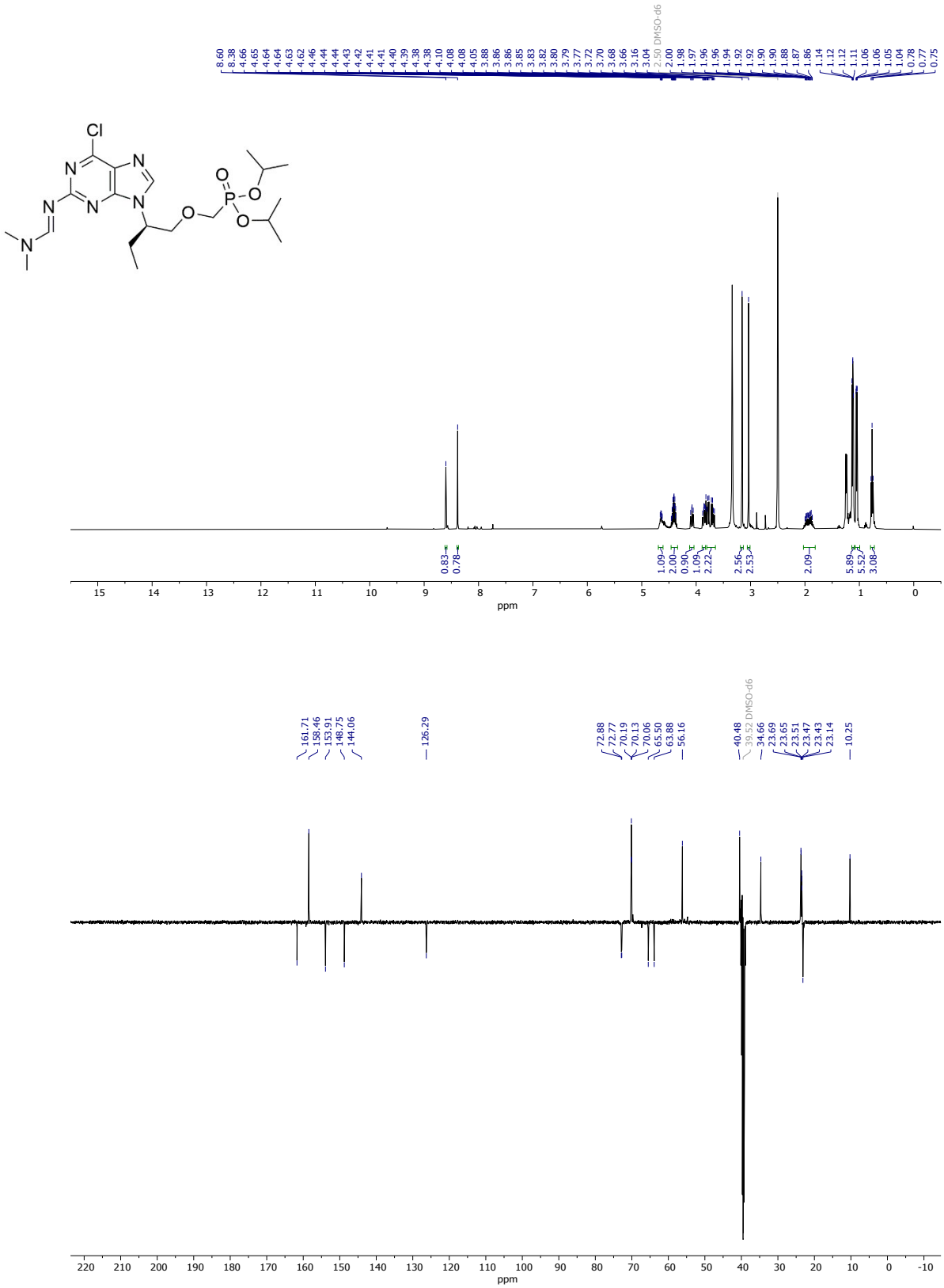


Figure S52. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**5** measured in DMSO-d_6 at room temperature.

Diisopropyl (*R*)-((2-(6-chloro-2-(((dimethylamino)methylene)amino)-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**5**)

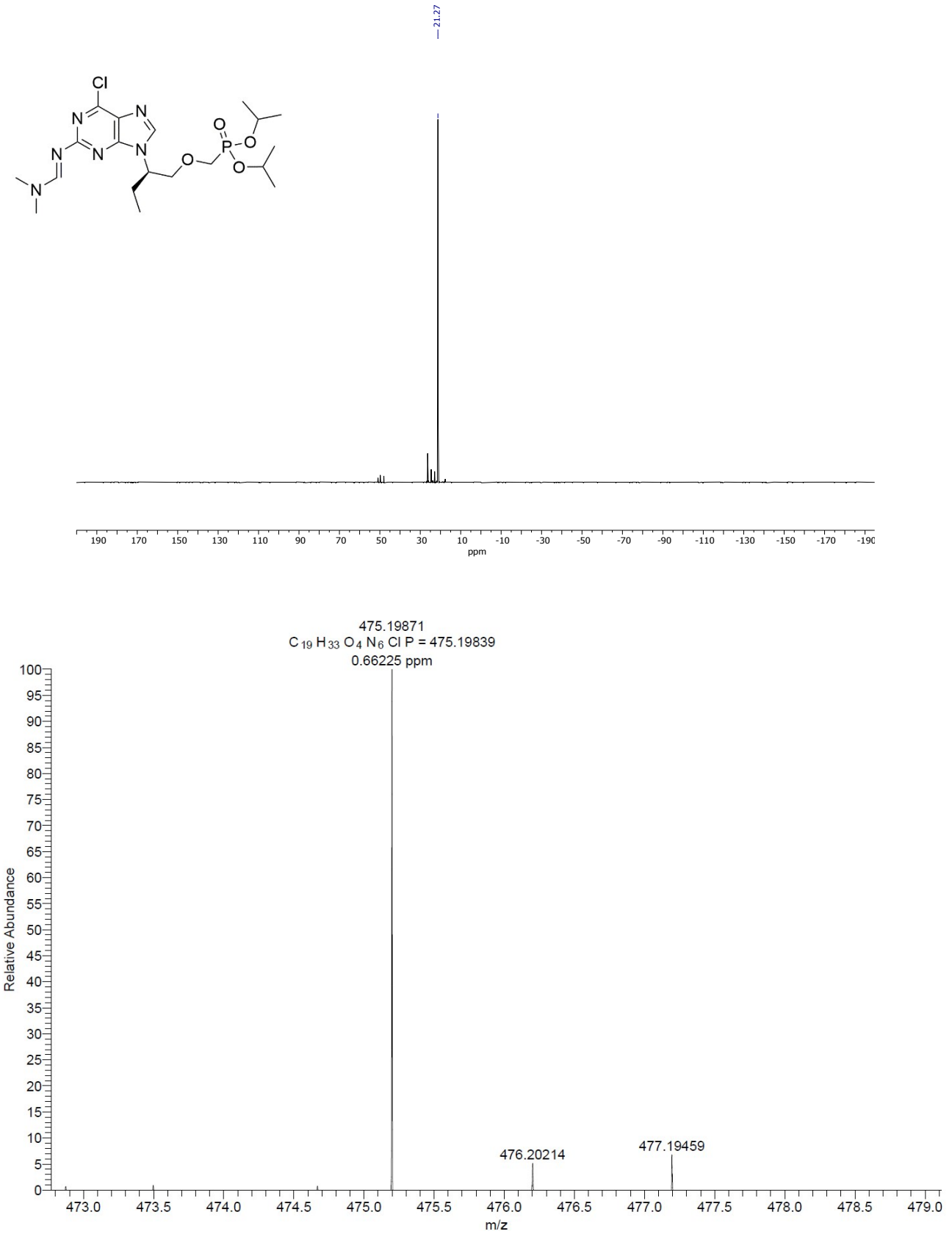
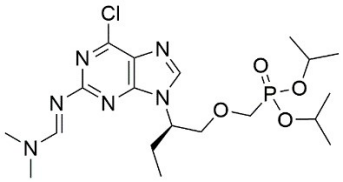


Figure S53. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**5**.

Diisopropyl (*R*)-((2-(6-chloro-2-(((dimethylamino)methylene)amino)-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**5**)



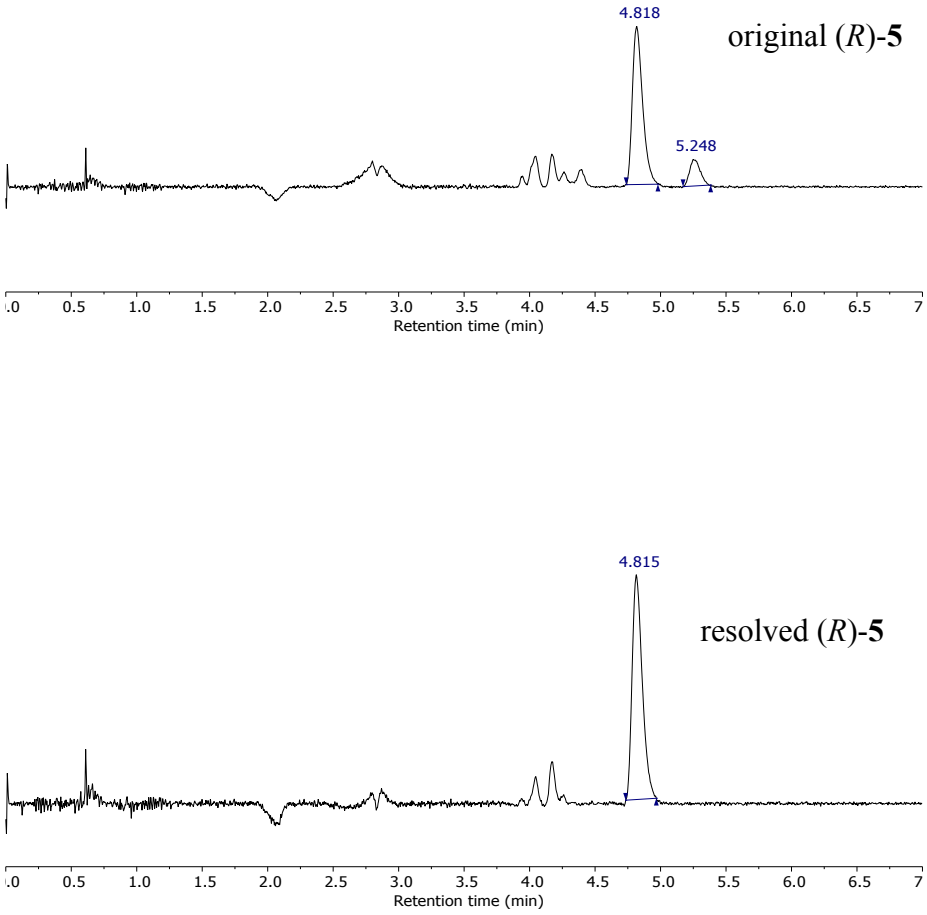


Figure S54. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top for original (*R*)-**5** contaminated with ~15% of (*S*)-enantiomer due to the impure starting material from the commercial supplier and bottom for resolved (*R*)-**5**). Due to the low stability of compound (*R*)-**5**, the chromatograms are not perfect.

Diisopropyl ((2,2-dimethoxyethoxy)methyl)phosphonate (**6a**)

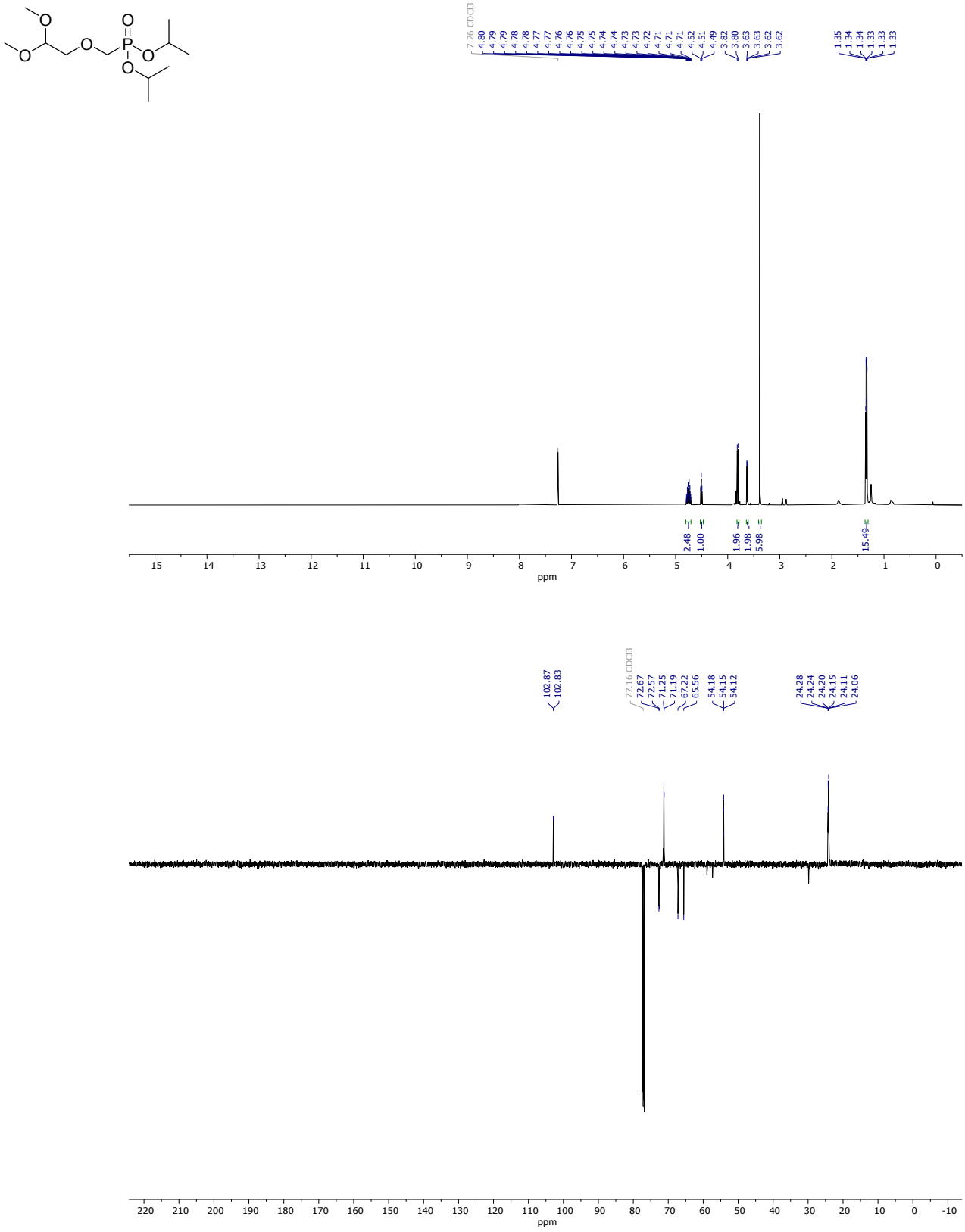
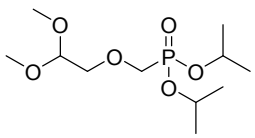
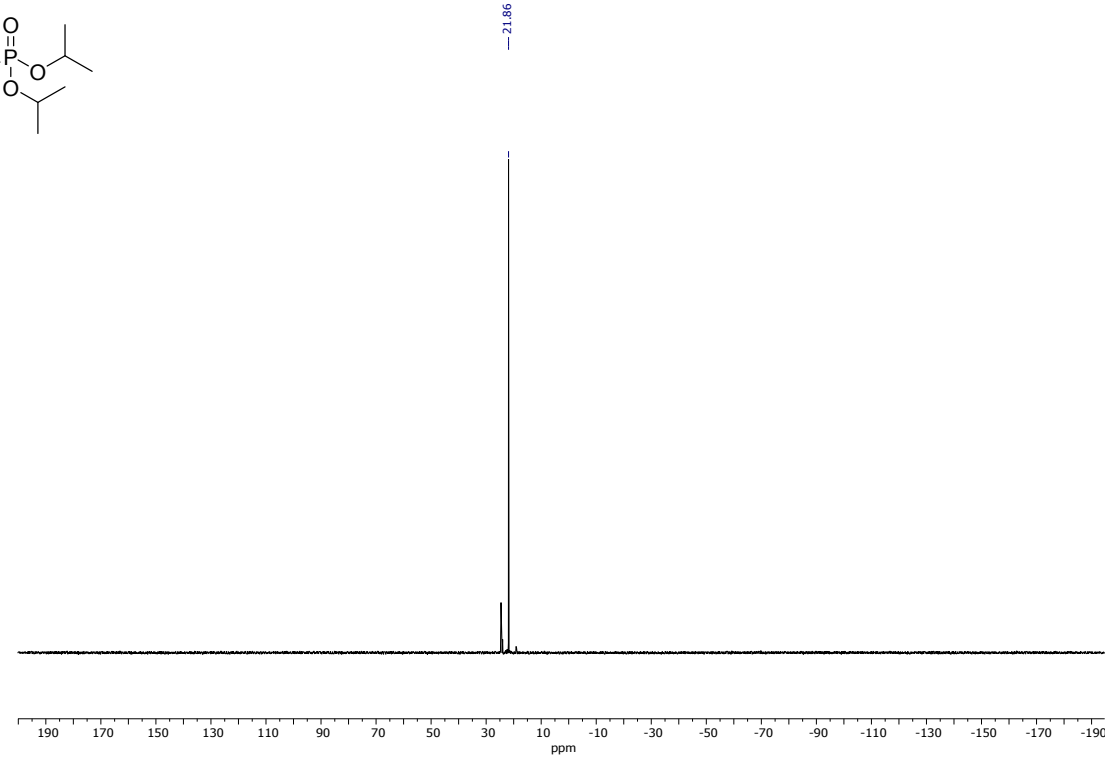


Figure S55. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound **6a** measured in $CDCl_3$ at room temperature.

Diisopropyl ((2,2-dimethoxyethoxy)methyl)phosphonate (**6a**)





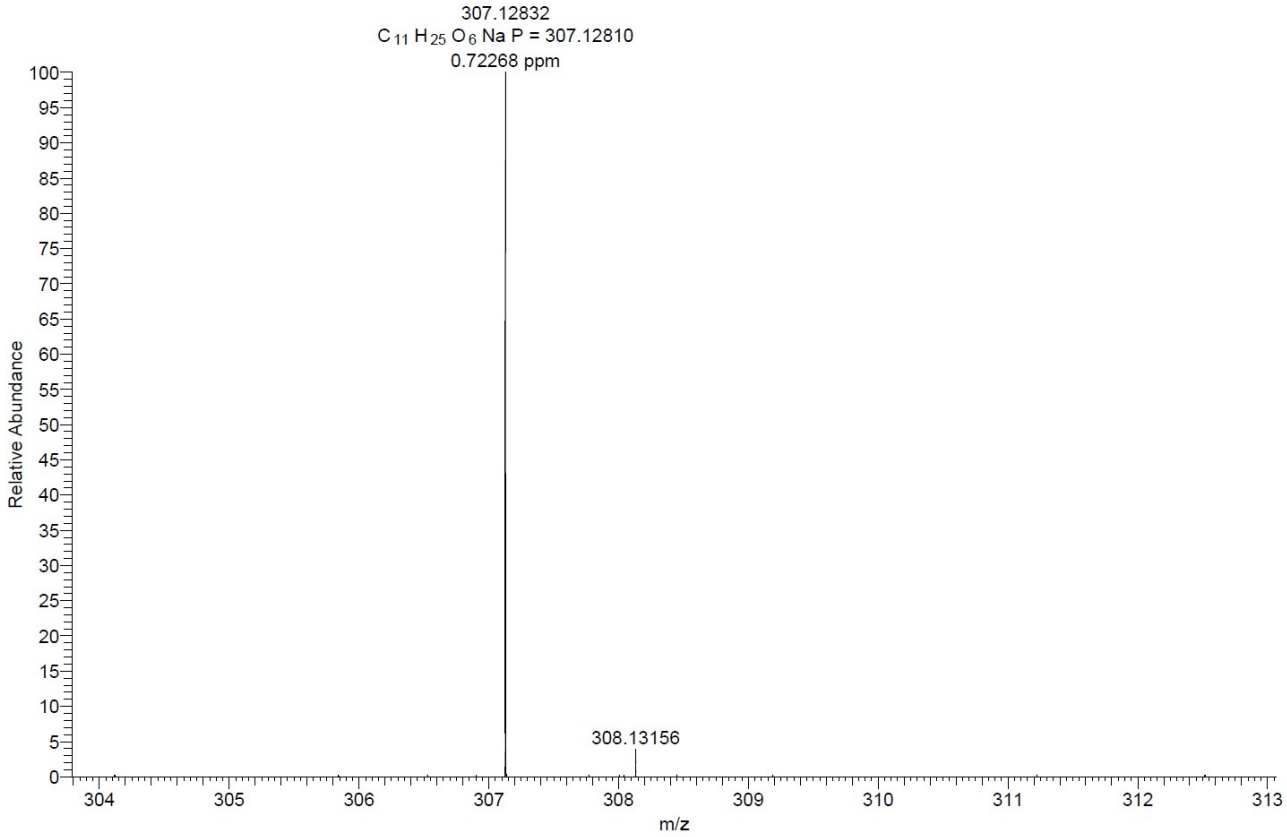
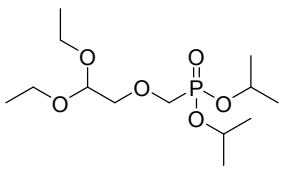


Figure S56. ^{31}P NMR (measured in $CDCl_3$ at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound **6a**.

Diisopropyl ((2,2-diethoxyethoxy)methyl)phosphonate (**6b**)



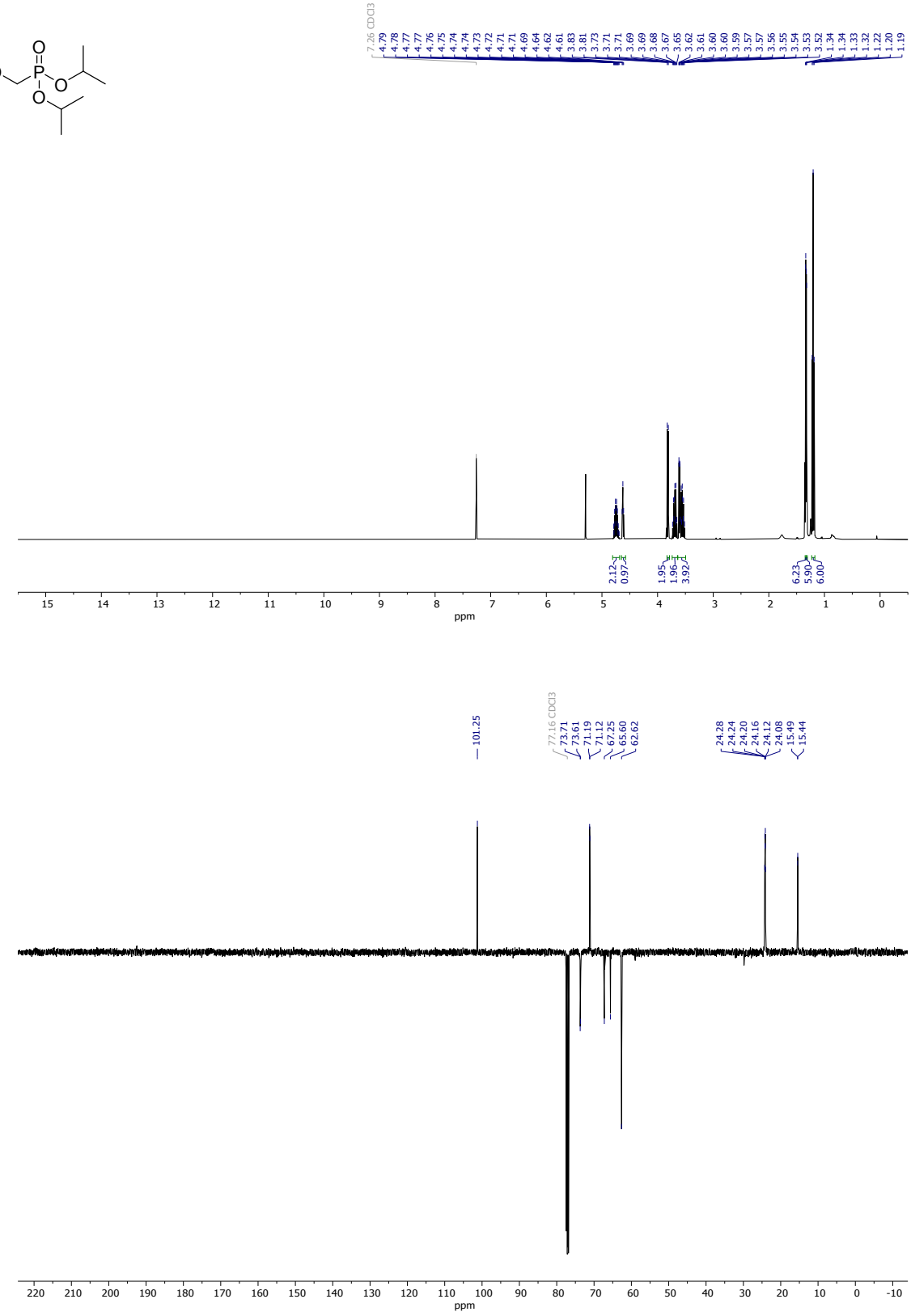
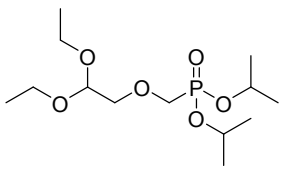
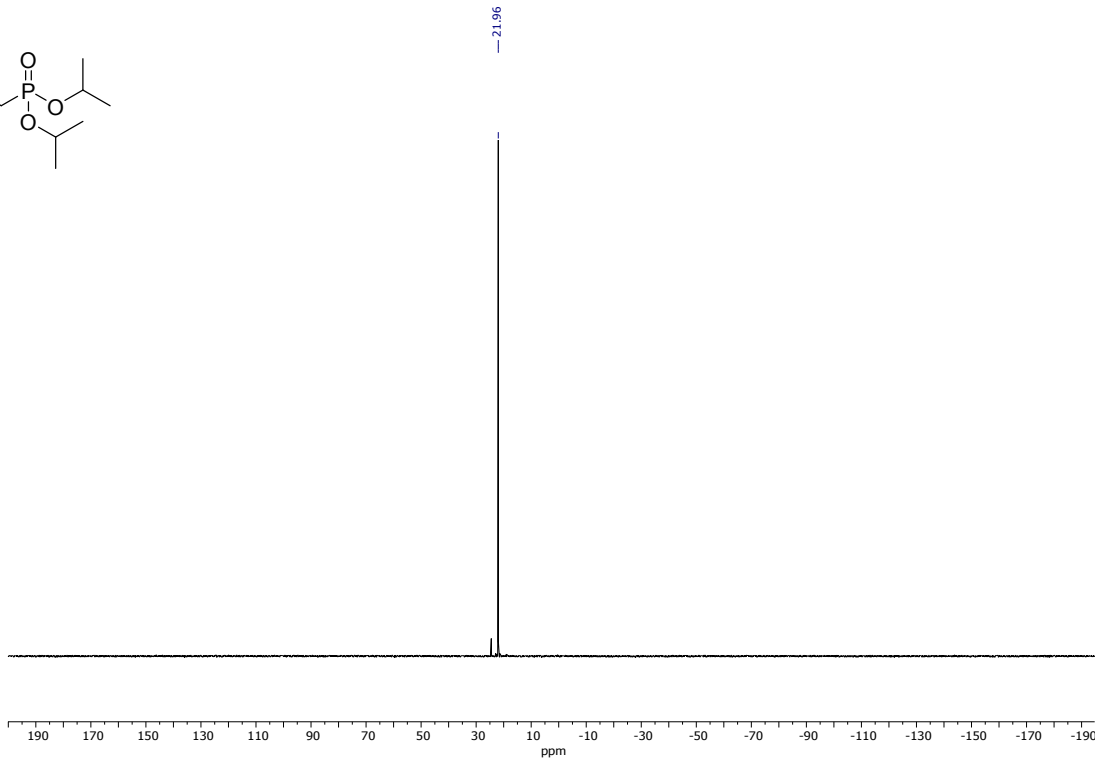


Figure S57. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound **6b** measured in $CDCl_3$ at room temperature.

Diisopropyl ((2,2-diethoxyethoxy)methyl)phosphonate (**6b**)





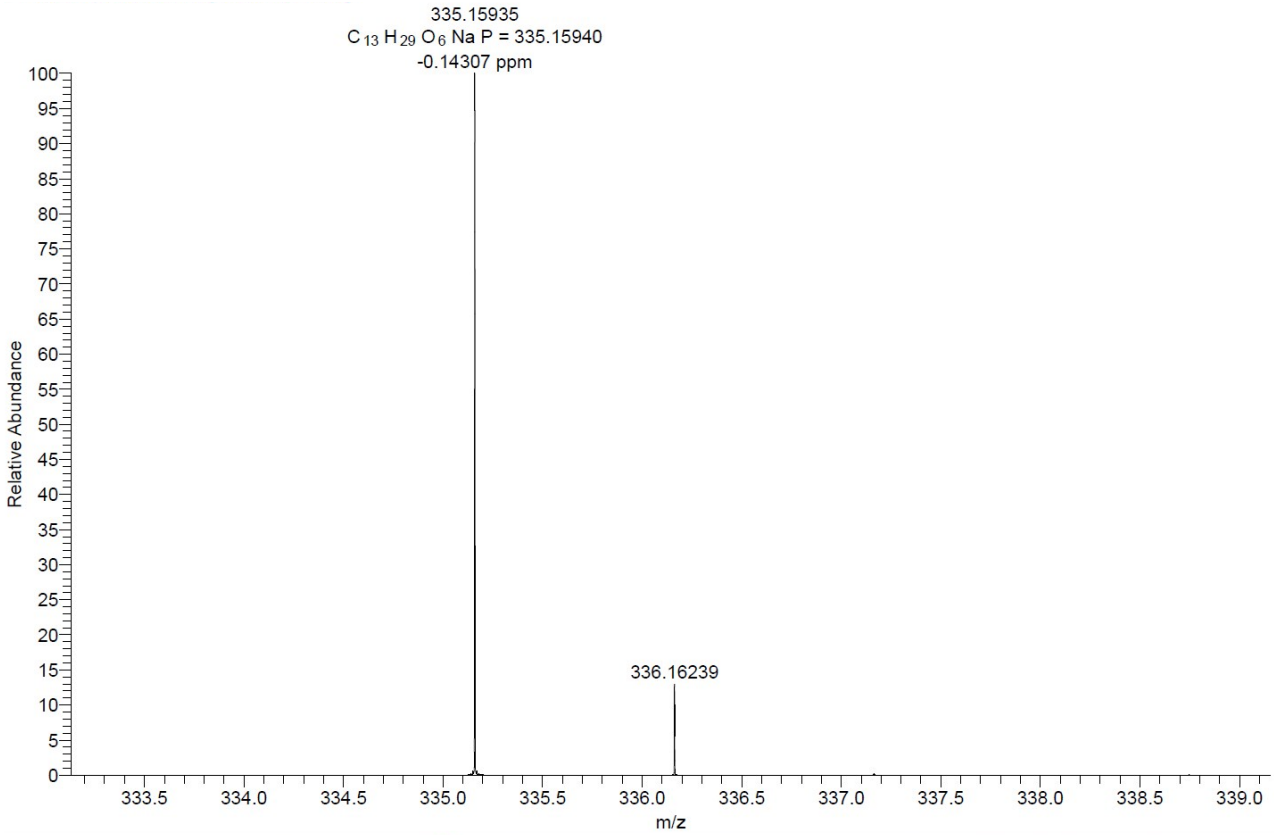


Figure S58. ^{31}P NMR (measured in $CDCl_3$ at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound **6b**.

Diisopropyl ((2-(2-amino-6-chloro-9*H*-purin-9-yl)-2-methoxyethoxy)methyl)phosphonate ((*RS*)-**7**)

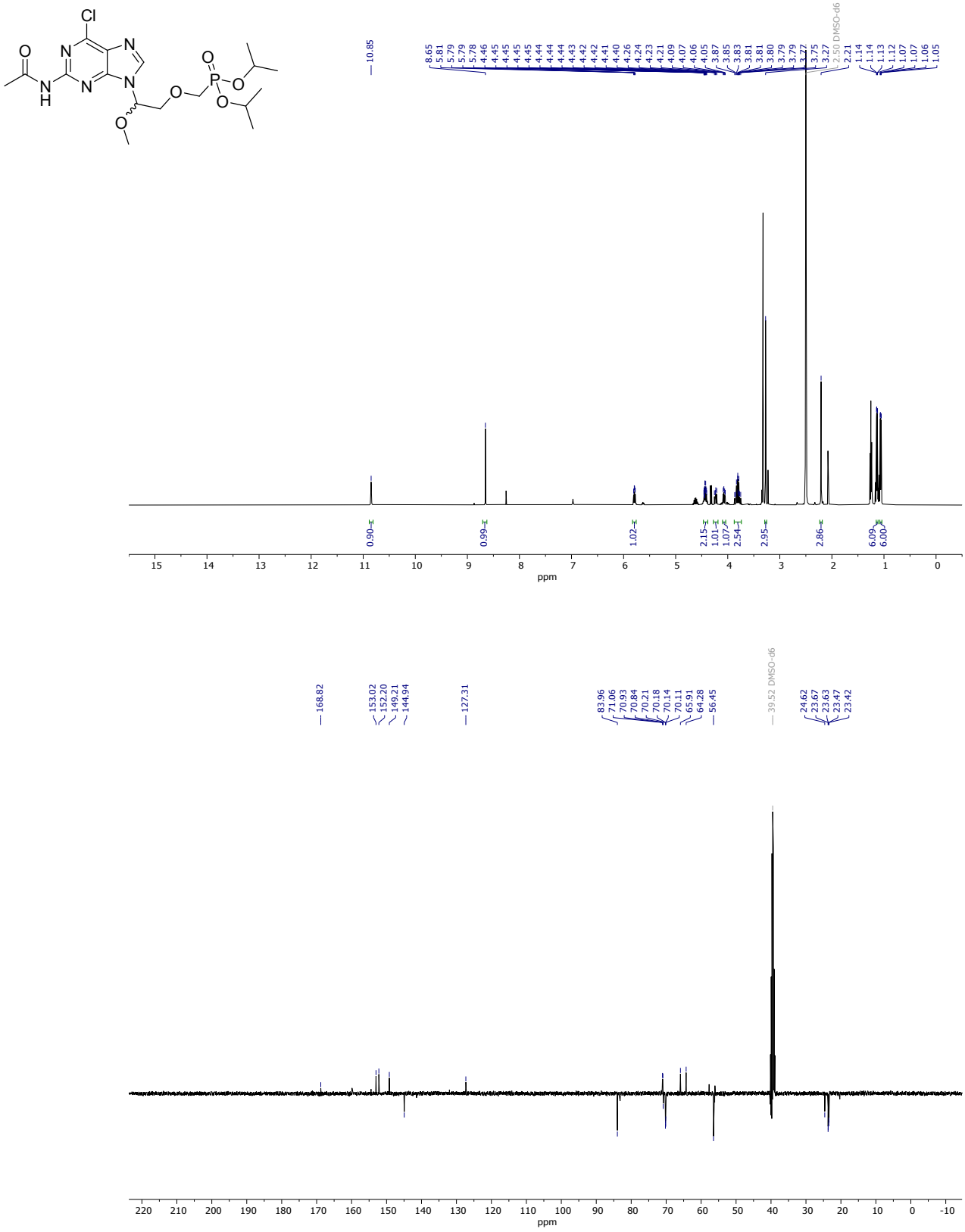


Figure S59. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**7** measured in DMSO-d_6 at room temperature.

Diisopropyl ((2-(2-amino-6-chloro-9*H*-purin-9-yl)-2-methoxyethoxy)methyl)phosphonate ((*RS*)-**7**)

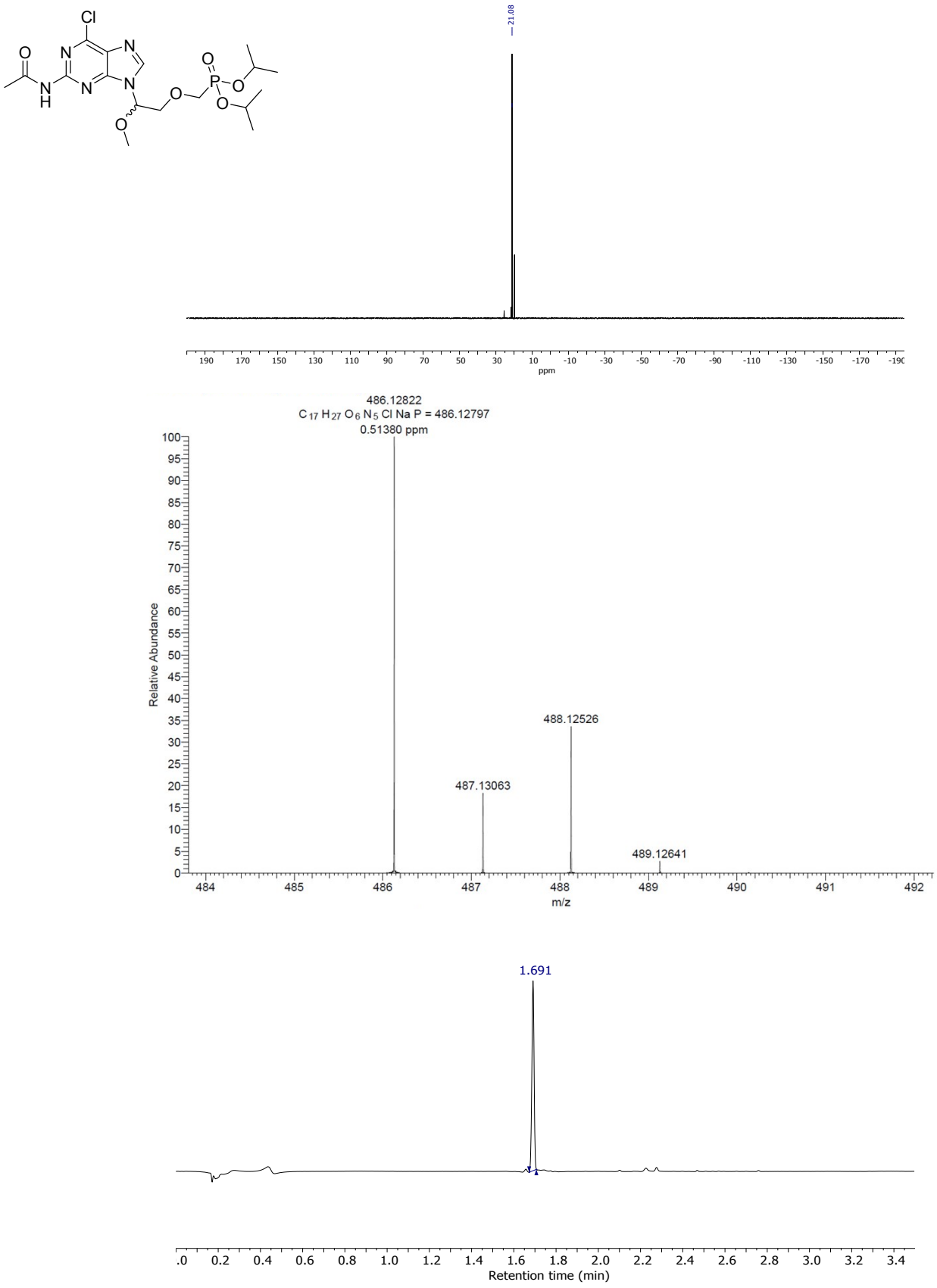
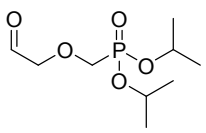


Figure S60. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**7**.

Diisopropyl ((2-oxoethoxy)methyl)phosphonate (**8**)



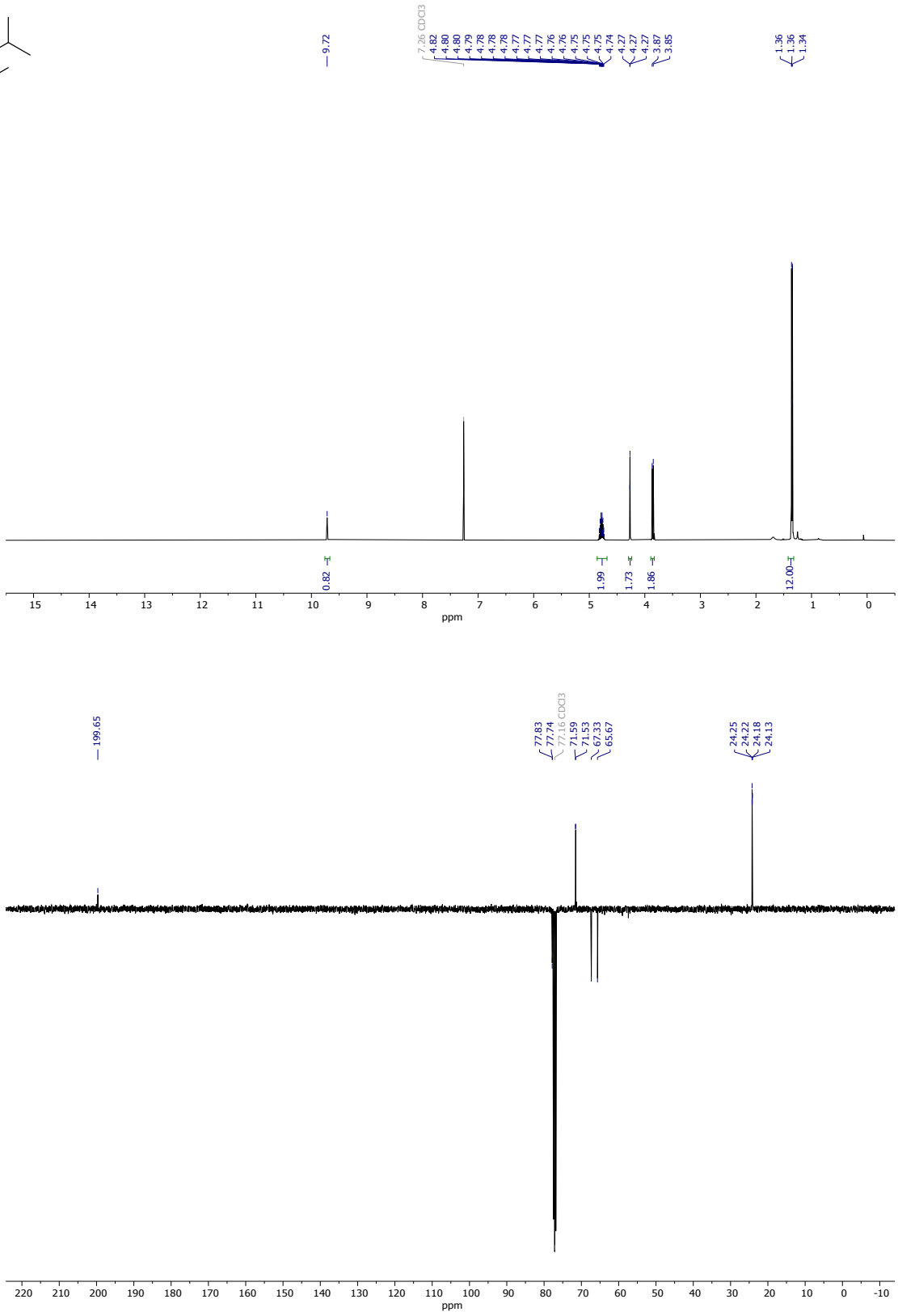
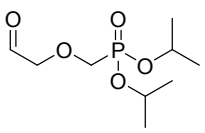
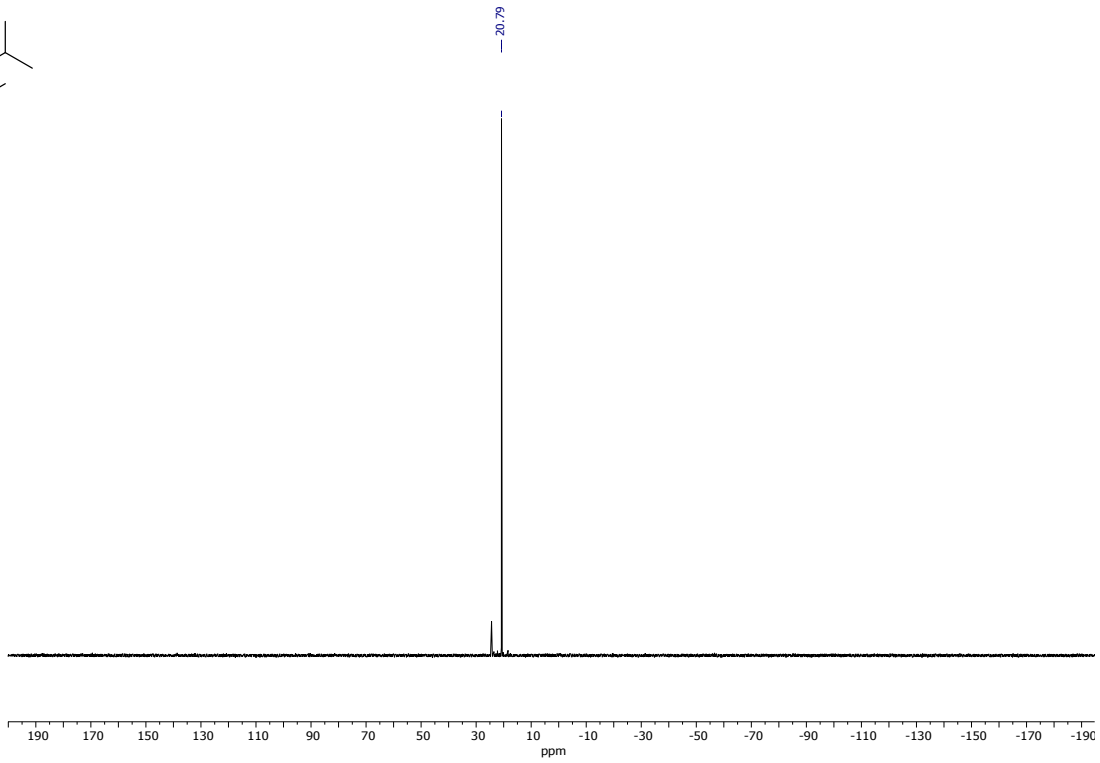


Figure S61. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound **8** measured in $CDCl_3$ at room temperature.

Diisopropyl ((2-oxoethoxy)methyl)phosphonate (**8**)





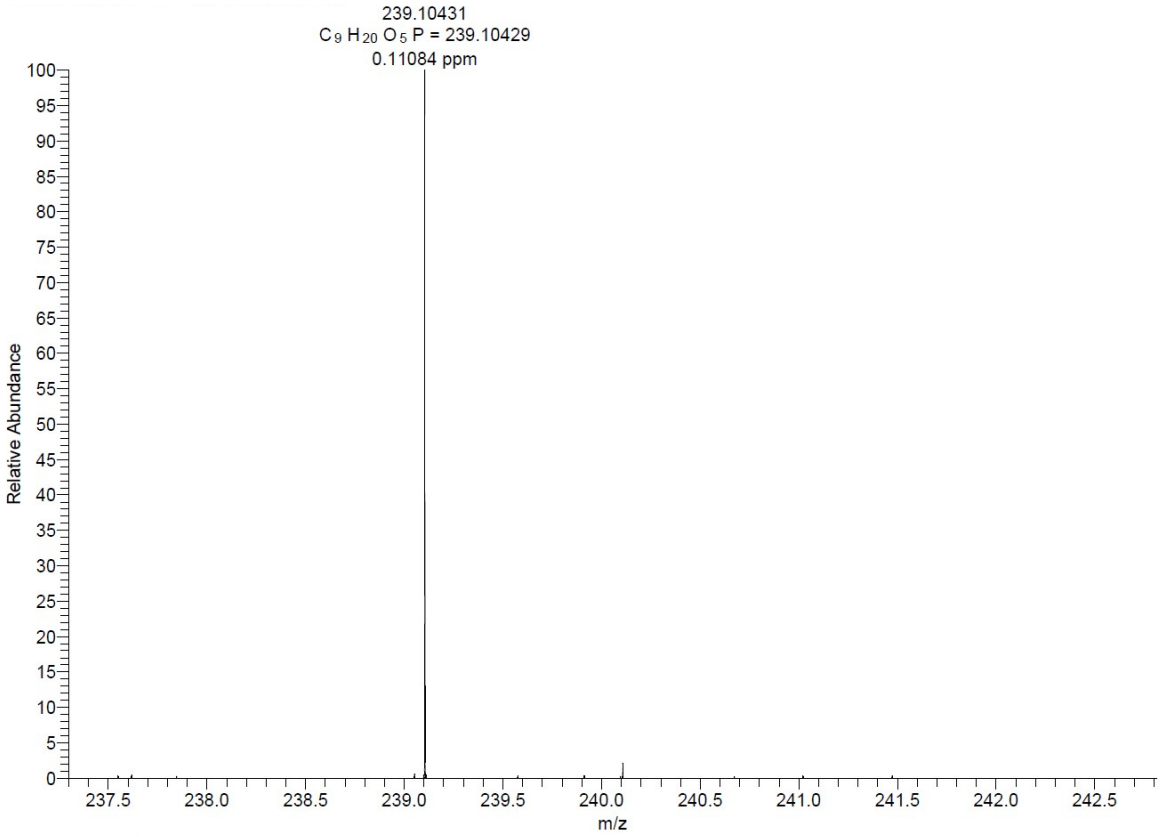


Figure S62. ^{31}P NMR (measured in $CDCl_3$ at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound **8**.

Diisopropyl ((2-hydroxypropoxy)methyl)phosphonate ((*RS*)-**9a**)

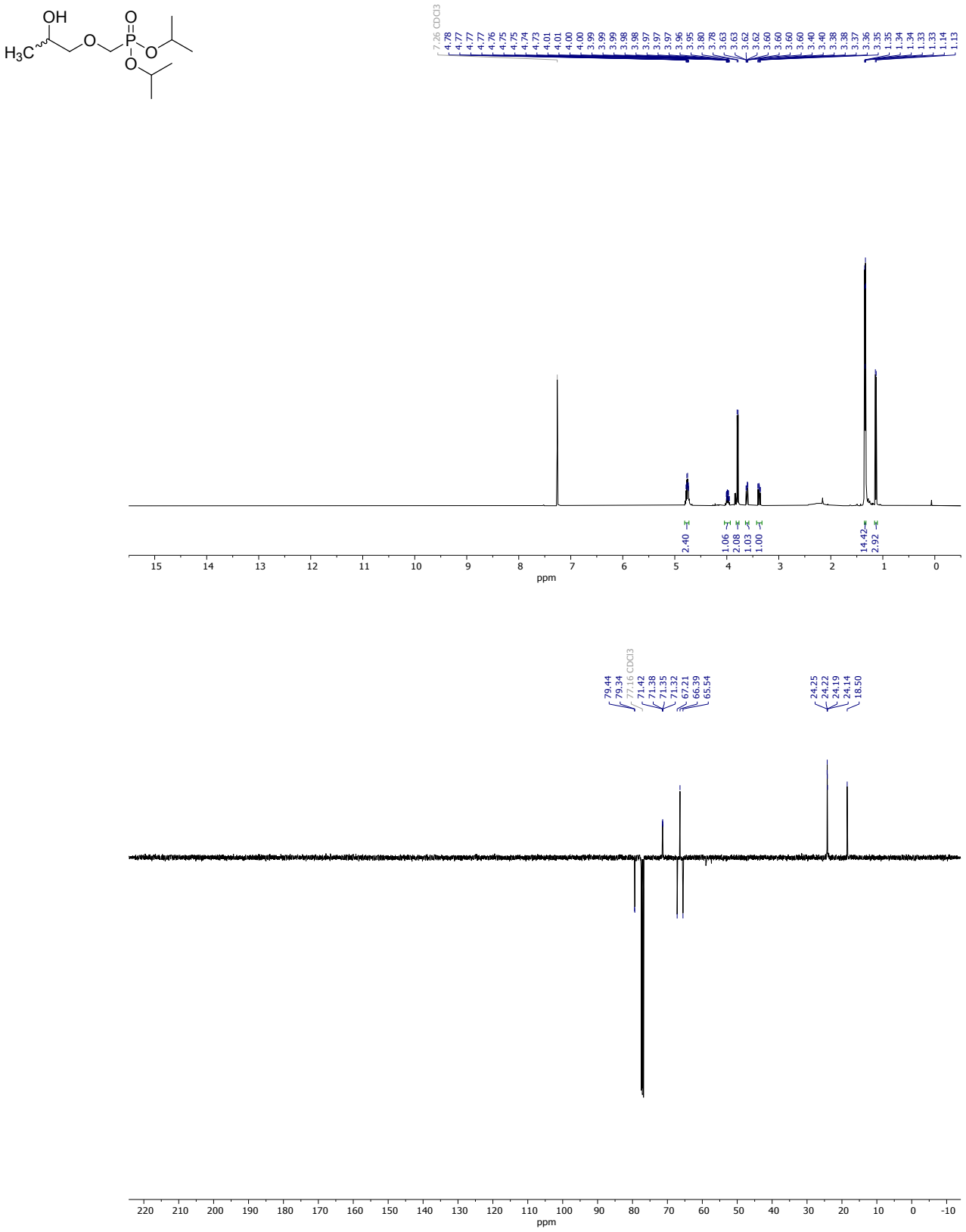


Figure S63. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**9a** measured in $CDCl_3$ at room temperature.

Diisopropyl ((2-hydroxypropoxy)methyl)phosphonate ((*RS*)-**9a**)

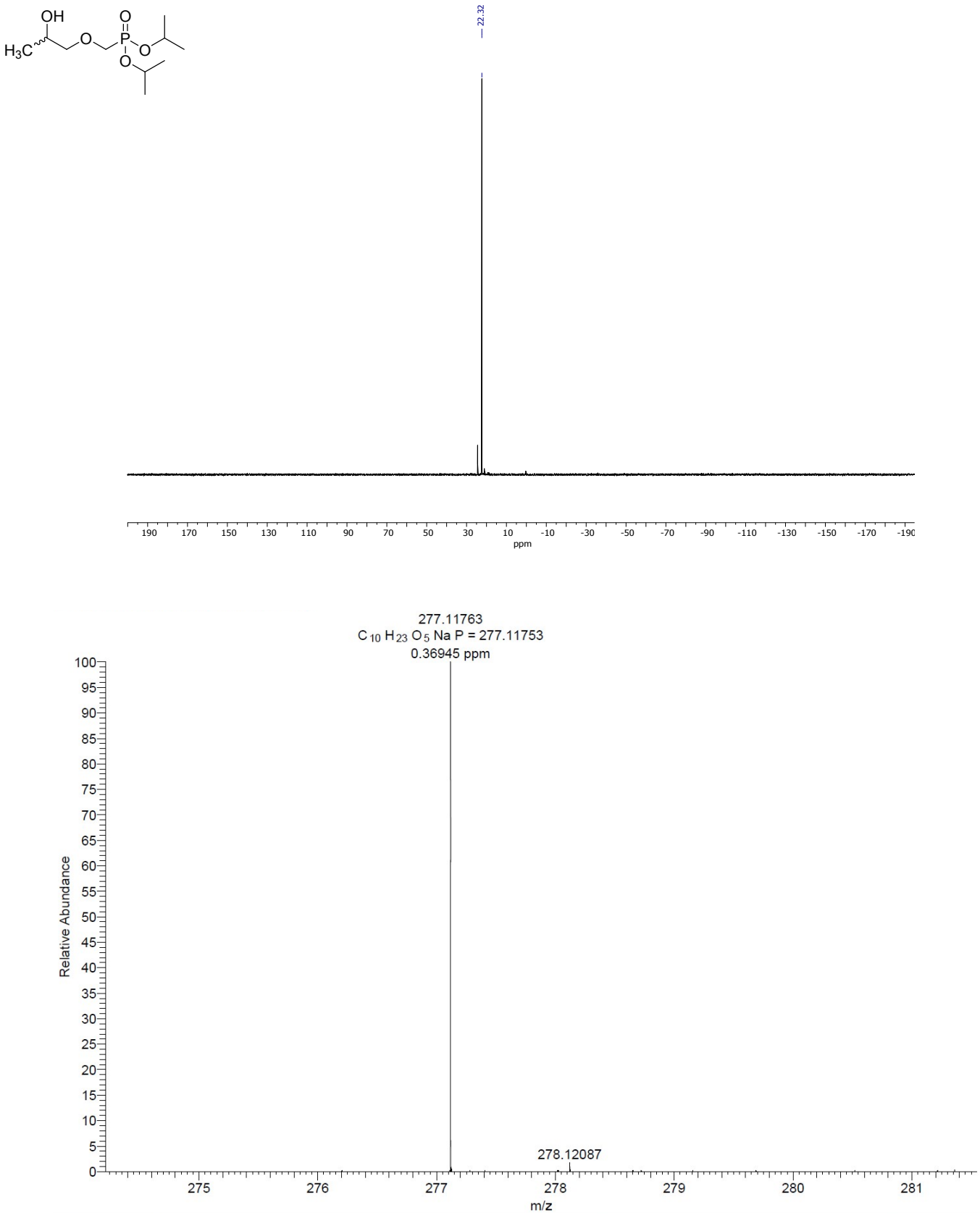


Figure S64. ^{31}P NMR (measured in $CDCl_3$ at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**9a**.

Diisopropyl ((2-hydroxybutoxy)methyl)phosphonate ((*RS*)-**9b**)

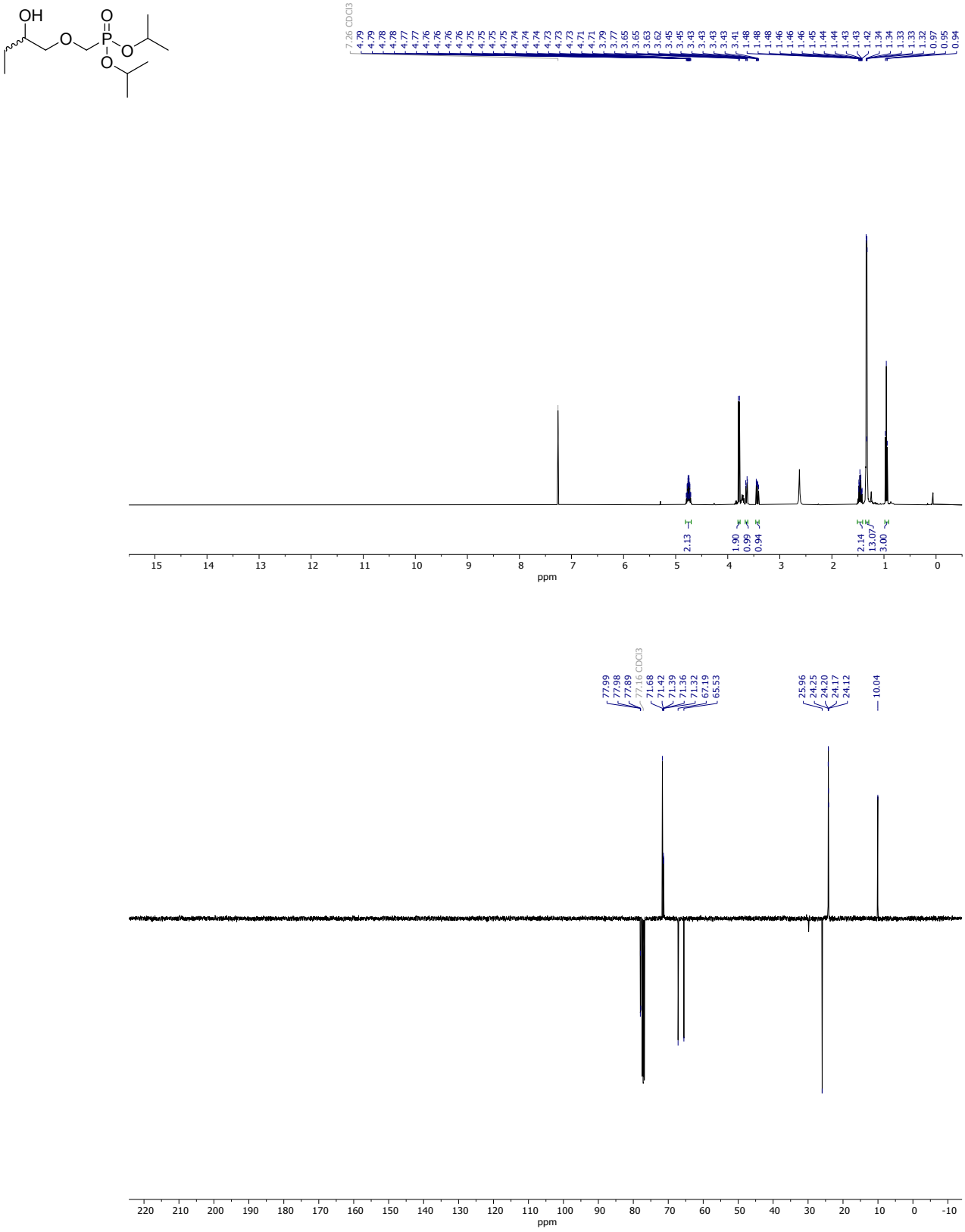
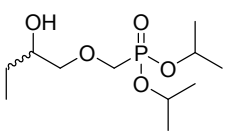
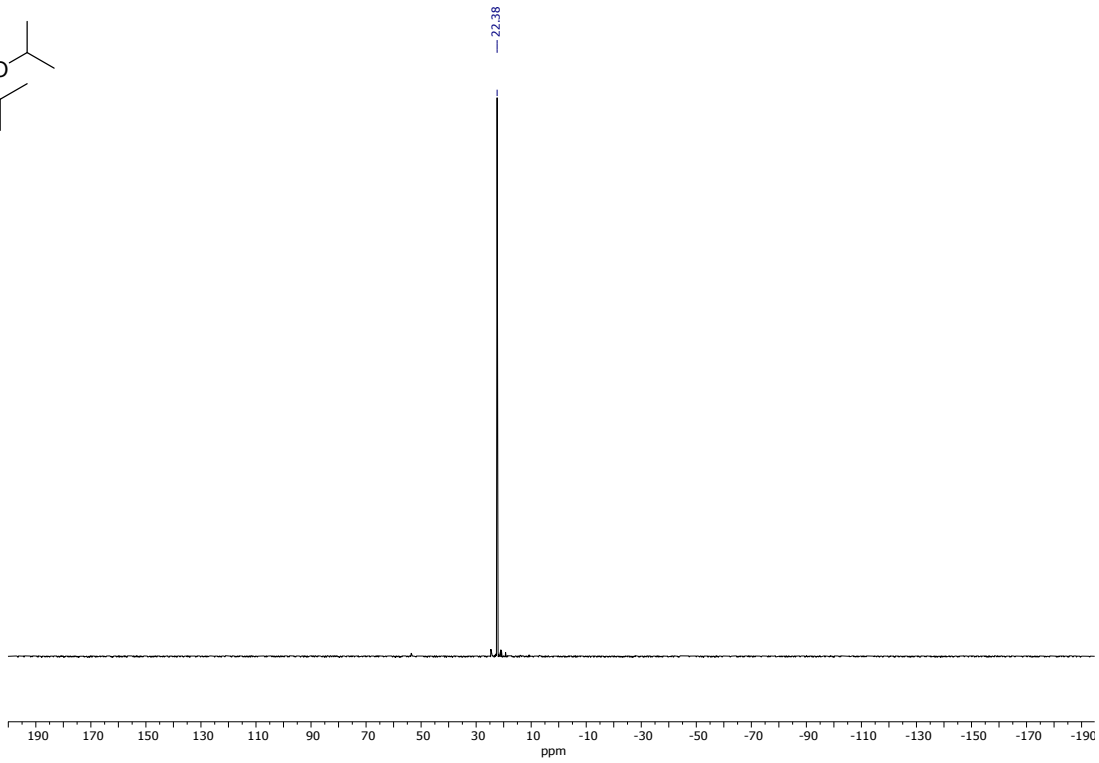


Figure S65. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**9b** measured in $CDCl_3$ at room temperature.

Diisopropyl ((2-hydroxybutoxy)methyl)phosphonate ((*RS*)-**9b**)





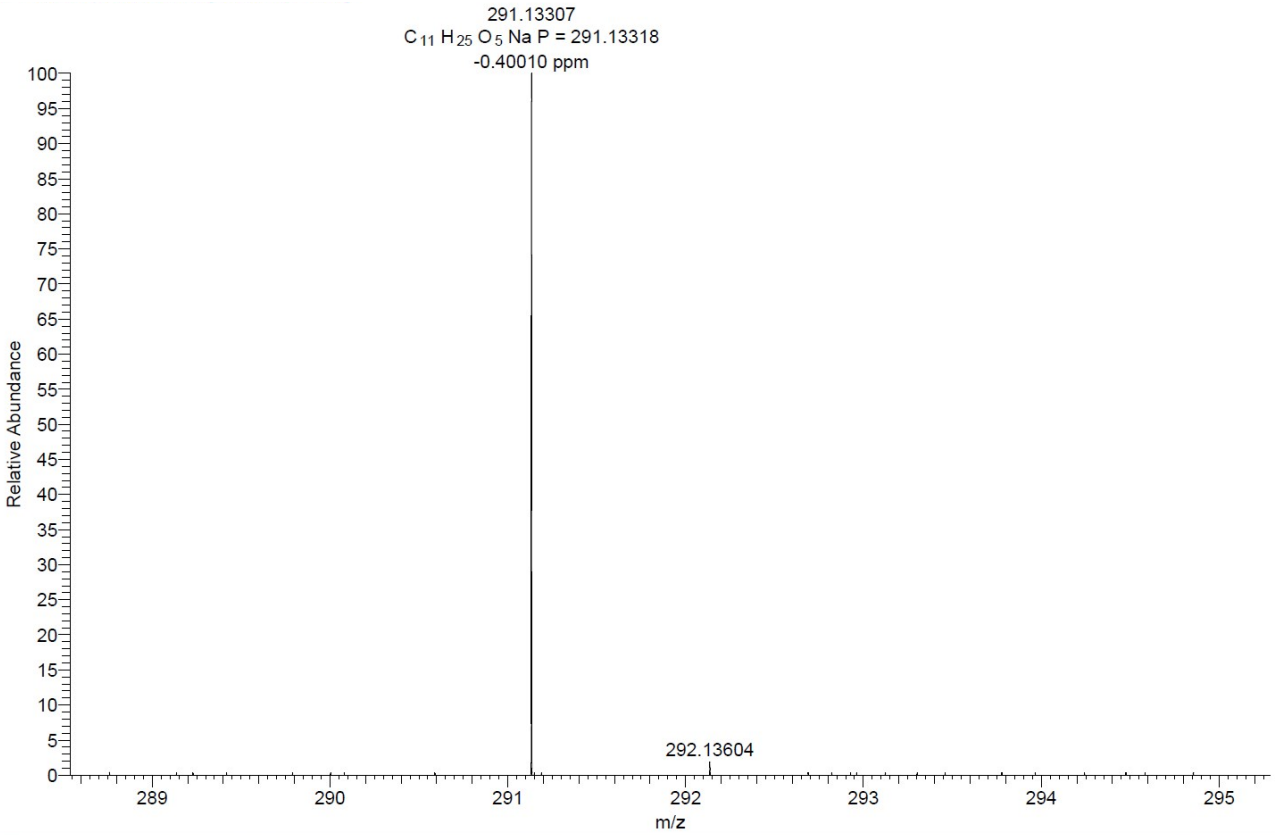


Figure S66. ^{31}P NMR (measured in $CDCl_3$ at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**9b**.

Diisopropyl (((2-hydroxybut-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**9c**)

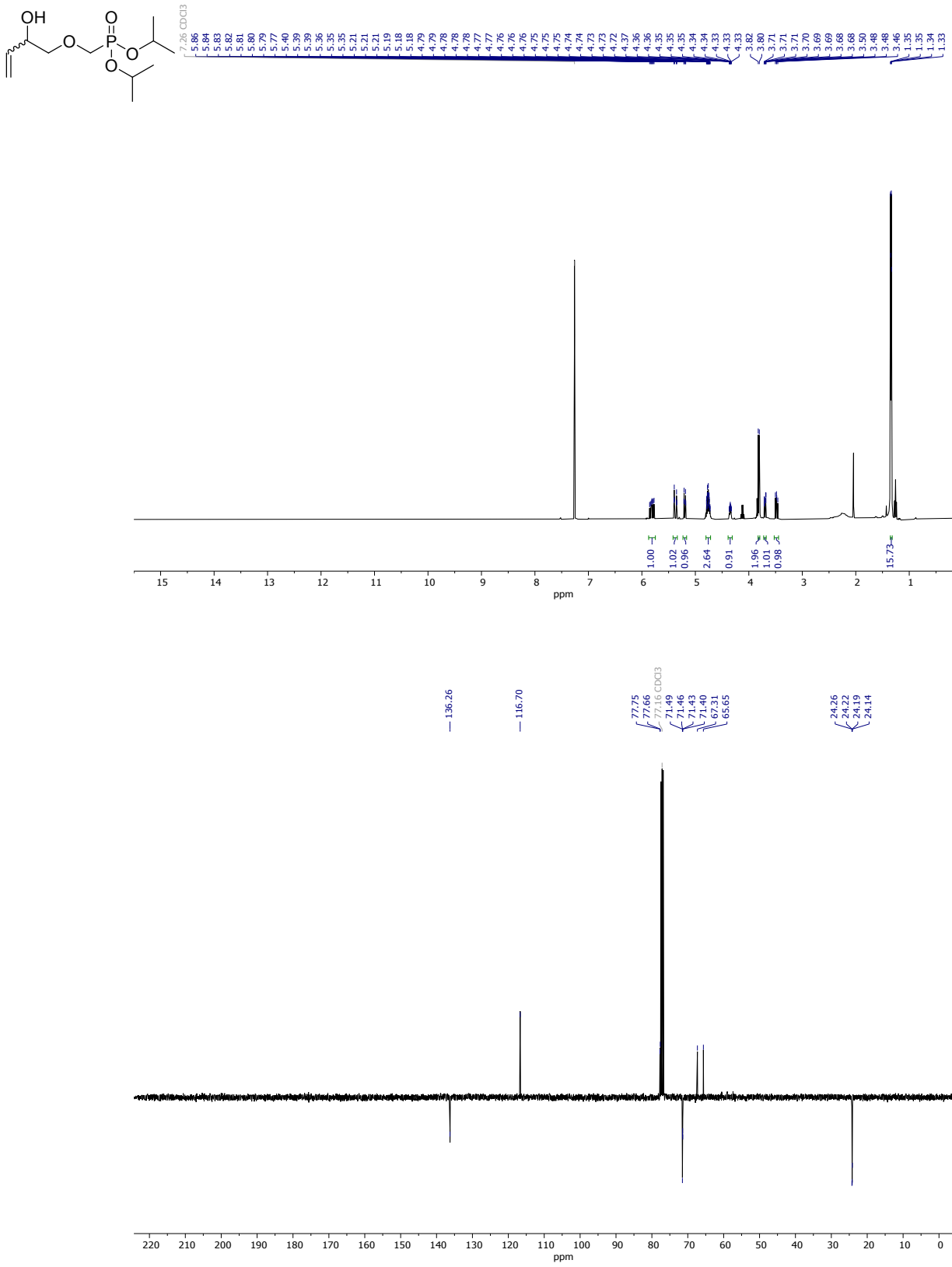


Figure S67. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**9c** measured in $CDCl_3$ at room temperature.

Diisopropyl (((2-hydroxybut-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**9c**)

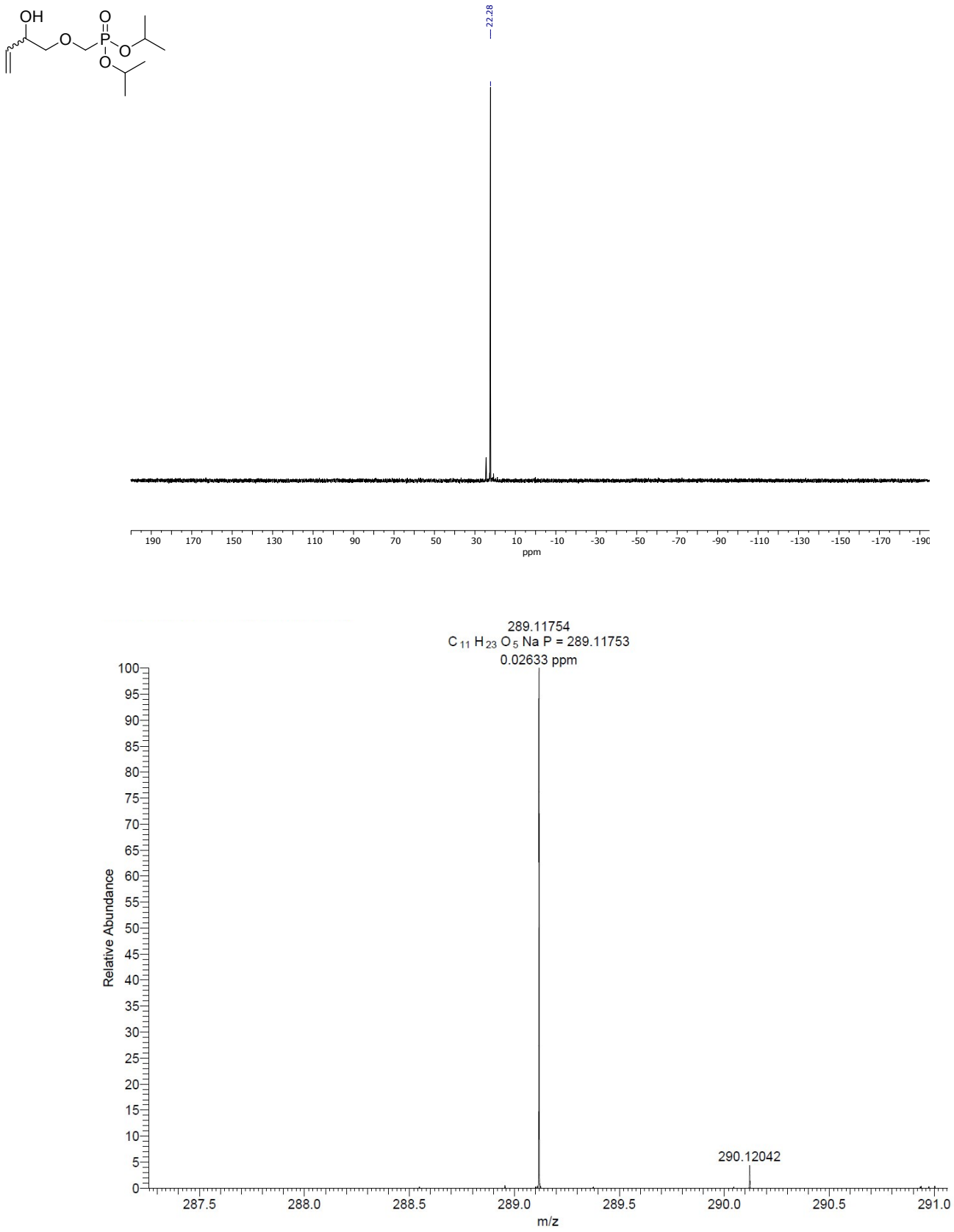


Figure S68. ^{31}P NMR (measured in $CDCl_3$ at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**9c**.

Diisopropyl (((2-hydroxybut-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**9d**)

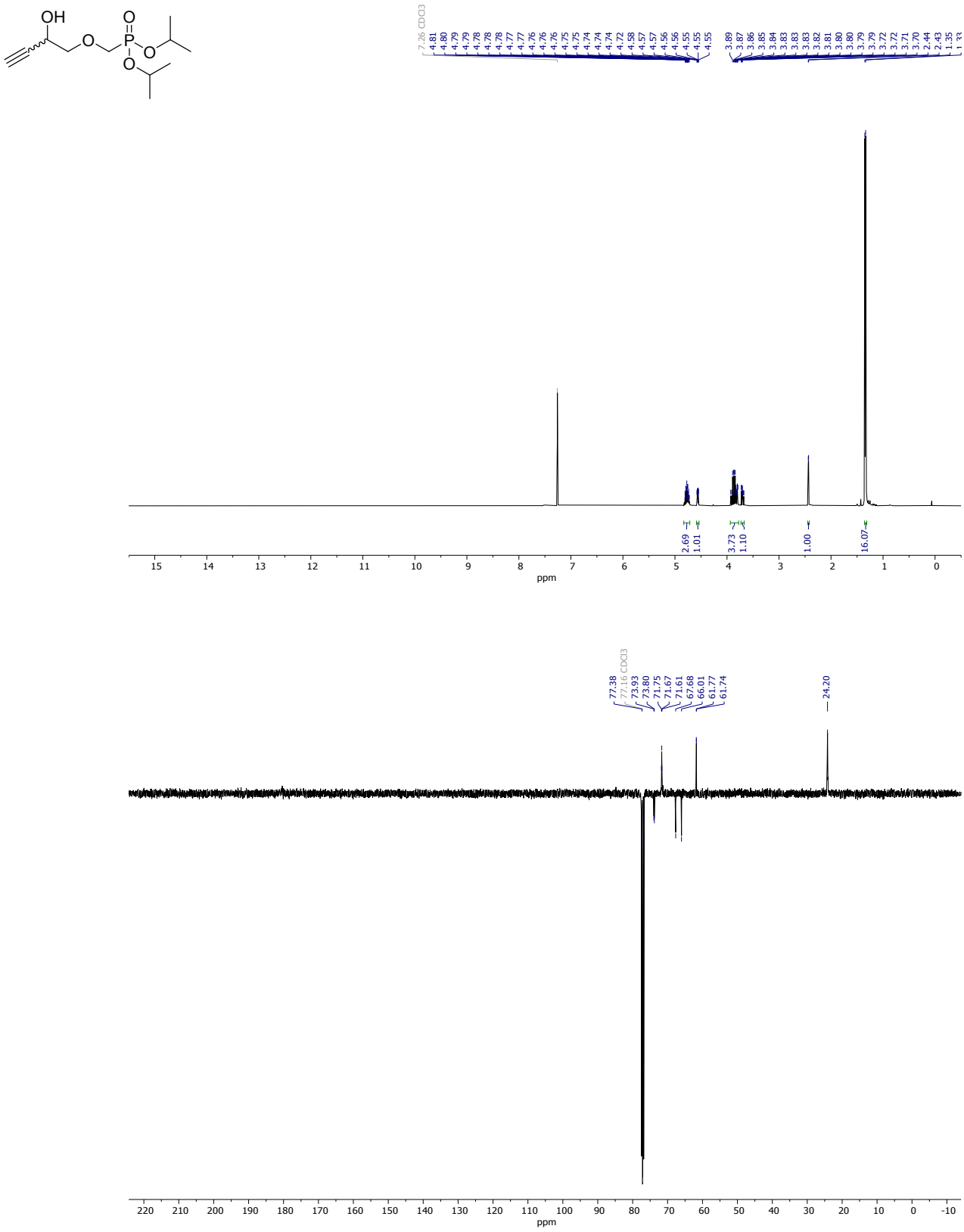


Figure S69. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**9d** measured in $CDCl_3$ at room temperature.

Diisopropyl (((2-hydroxybut-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**9d**)

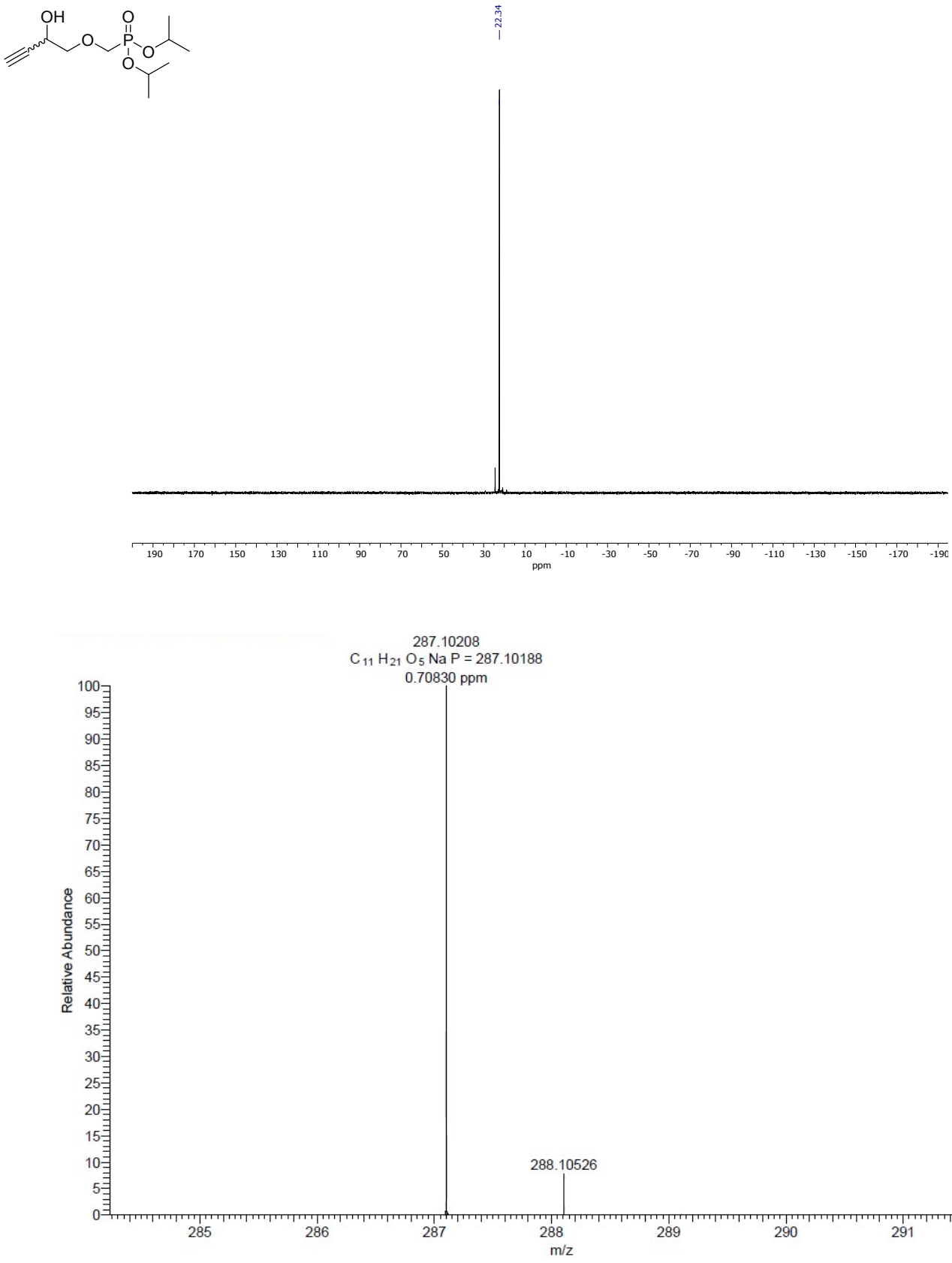


Figure S70. ^{31}P NMR (measured in $CDCl_3$ at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**9d**.

Diisopropyl ((2-cyclopropyl-2-hydroxyethoxy)methyl)phosphonate ((*RS*)-**9e**)

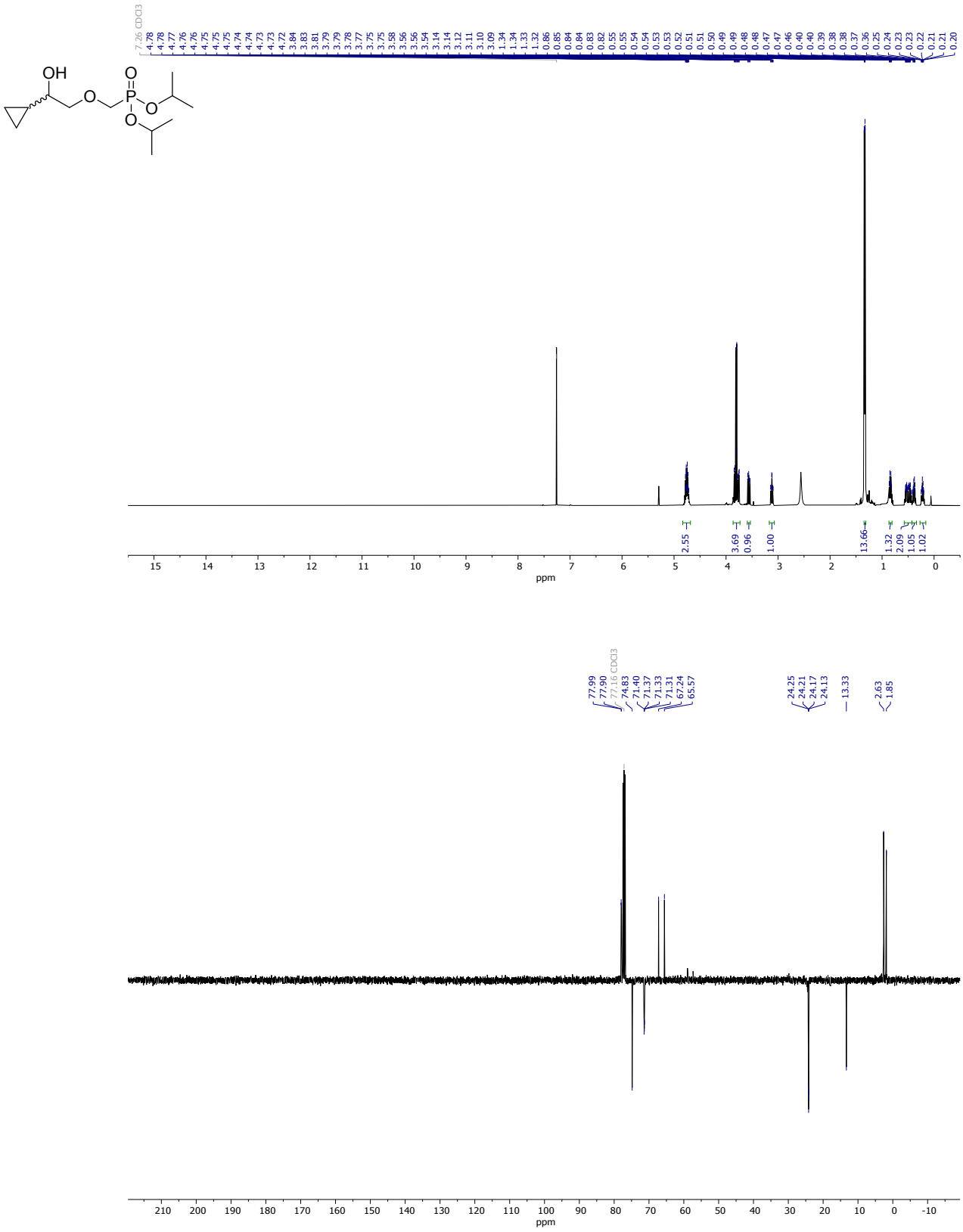
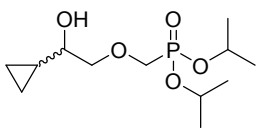
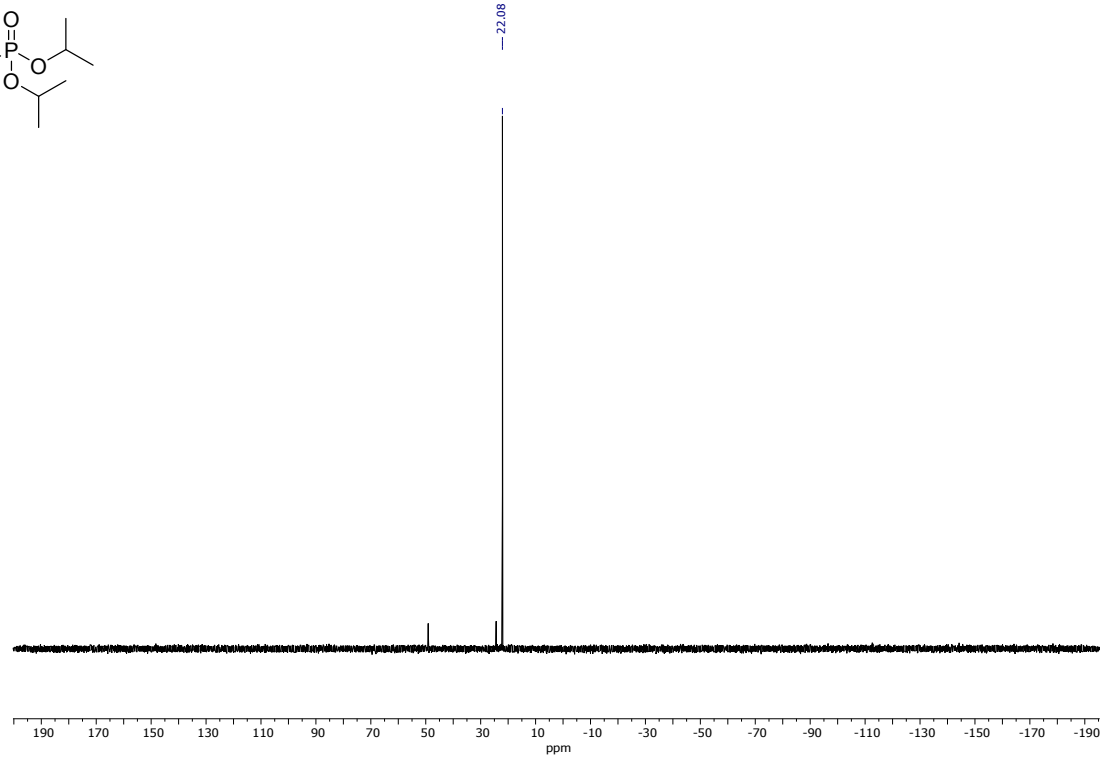


Figure S71. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**9e** measured in $CDCl_3$ at room temperature.

Diisopropyl ((2-cyclopropyl-2-hydroxyethoxy)methyl)phosphonate ((*RS*)-**9e**)





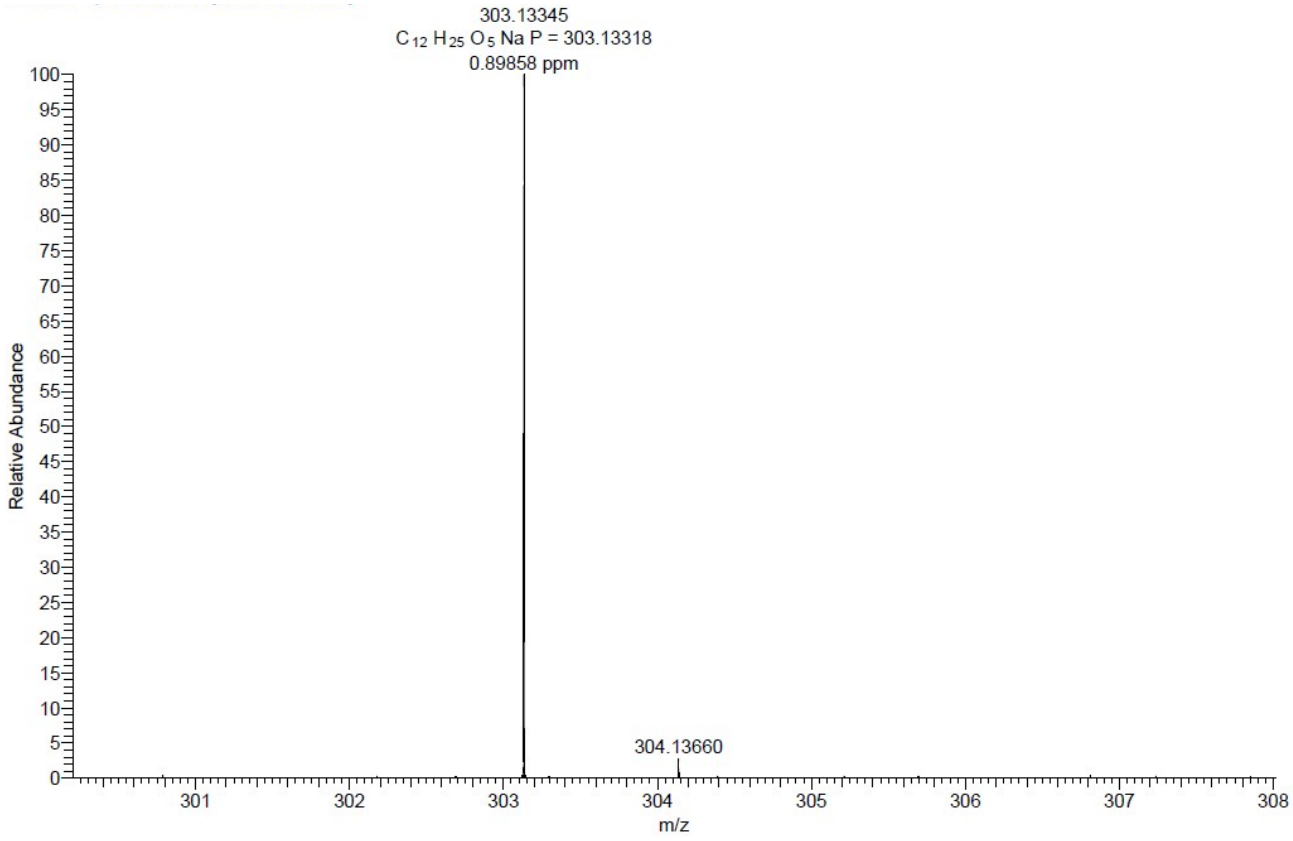


Figure S72. ^{31}P NMR (measured in $CDCl_3$ at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**9e**.

Diisopropyl ((3,3,3-trifluoro-2-hydroxypropoxy)methyl)phosphonate ((*RS*)-**9f**)

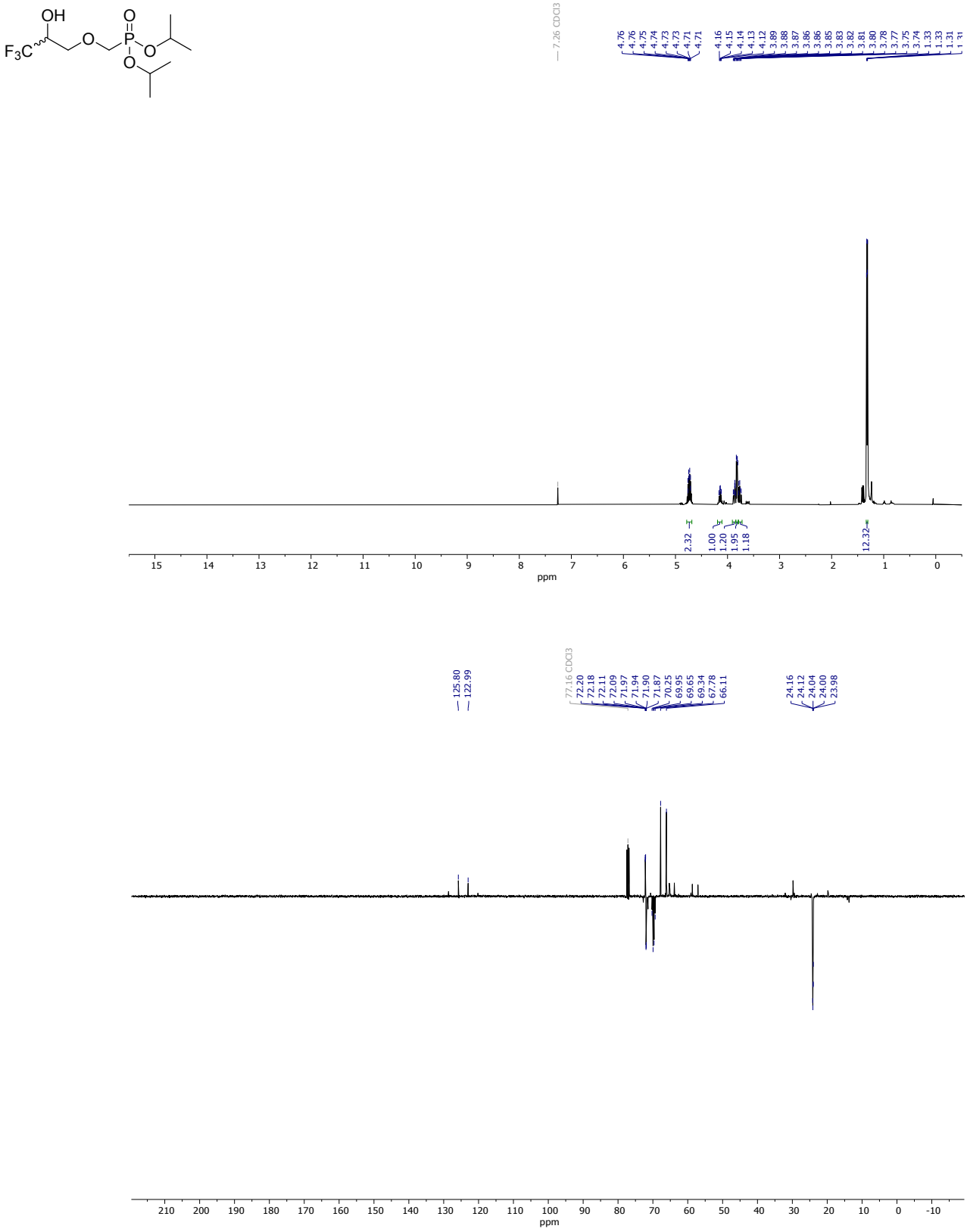


Figure S73. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**9f** measured in $CDCl_3$ at room temperature.

Diisopropyl ((3,3,3-trifluoro-2-hydroxypropoxy)methyl)phosphonate ((*RS*)-**9f**)

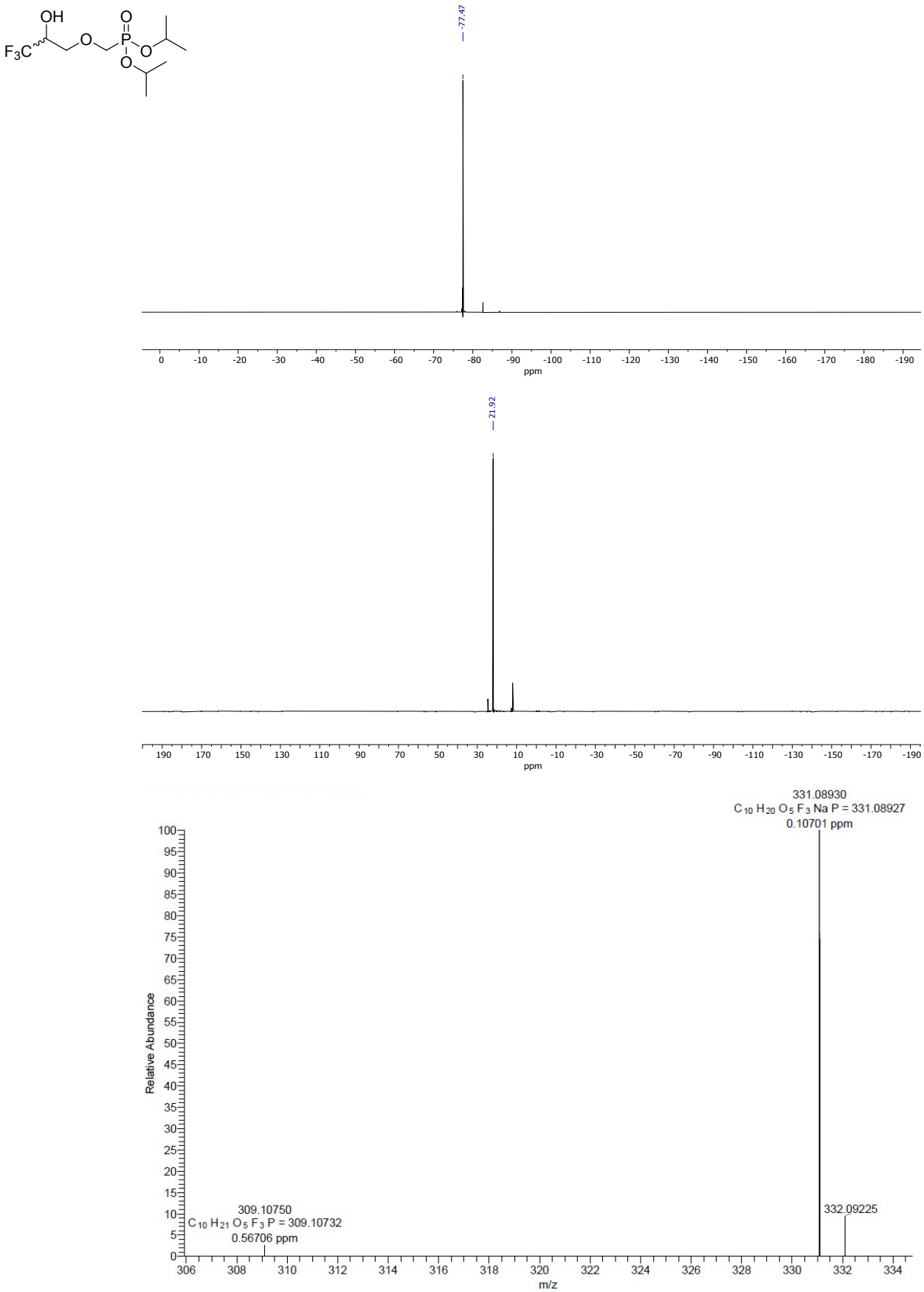


Figure S74. ^{19}F (top) and ^{31}P (middle) NMR measured in $CDCl_3$ at room temperature and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**9f**.

Diisopropyl ((2-hydroxy-3-nitropropoxy)methyl)phosphonate ((*RS*)-**9g**)

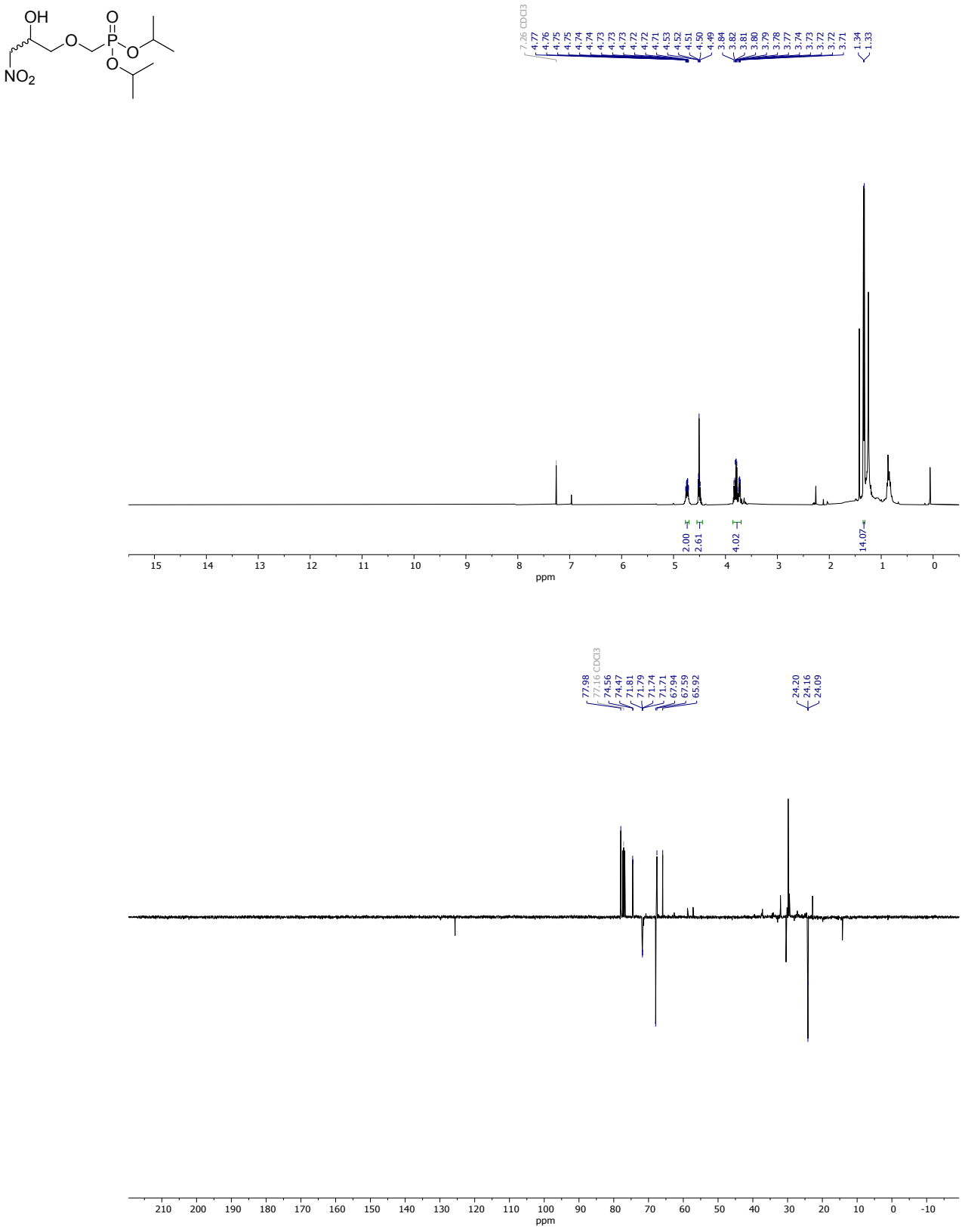


Figure S75. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**9g** measured in $CDCl_3$ at room temperature.

Diisopropyl ((2-hydroxy-3-nitropropoxy)methyl)phosphonate ((*RS*)-**9g**)

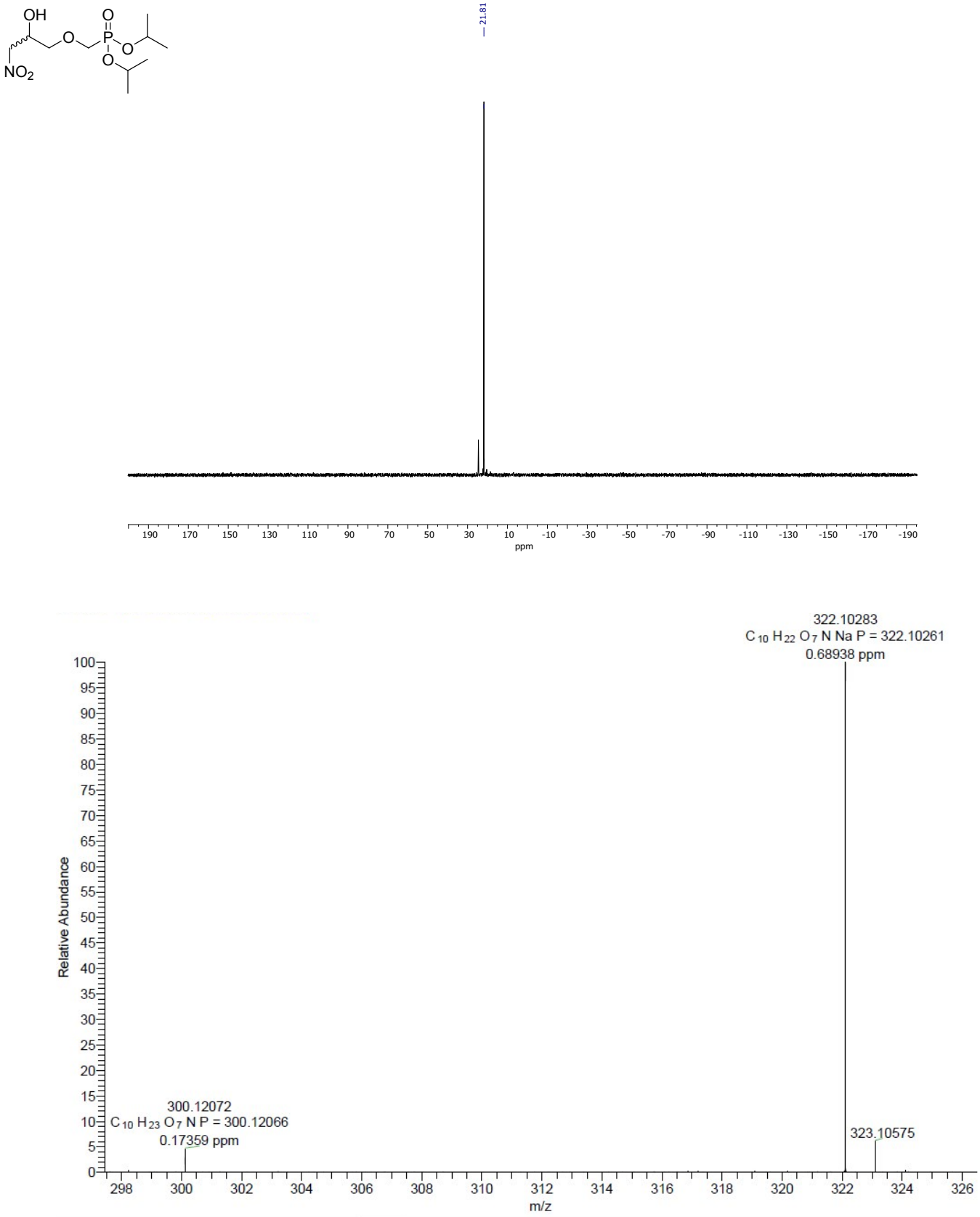


Figure S76. ^{31}P NMR (measured in $CDCl_3$ at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**9g**.

Diisopropyl ((2-cyano-2-hydroxyethoxy)methyl)phosphonate ((*RS*)-**9h**)

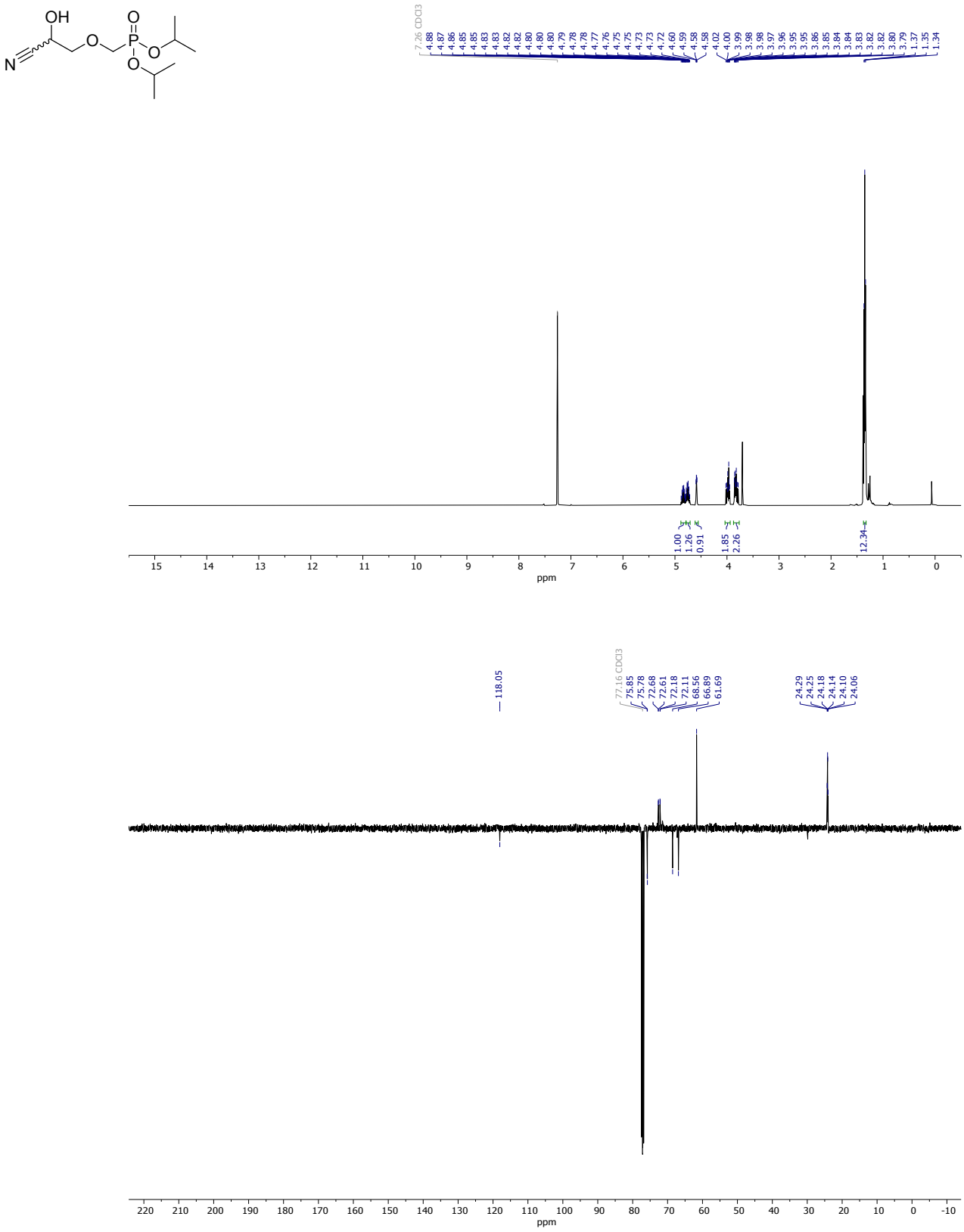


Figure S77. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**9h** measured in $CDCl_3$ at room temperature.

Diisopropyl ((2-cyano-2-hydroxyethoxy)methyl)phosphonate ((*RS*)-**9h**)

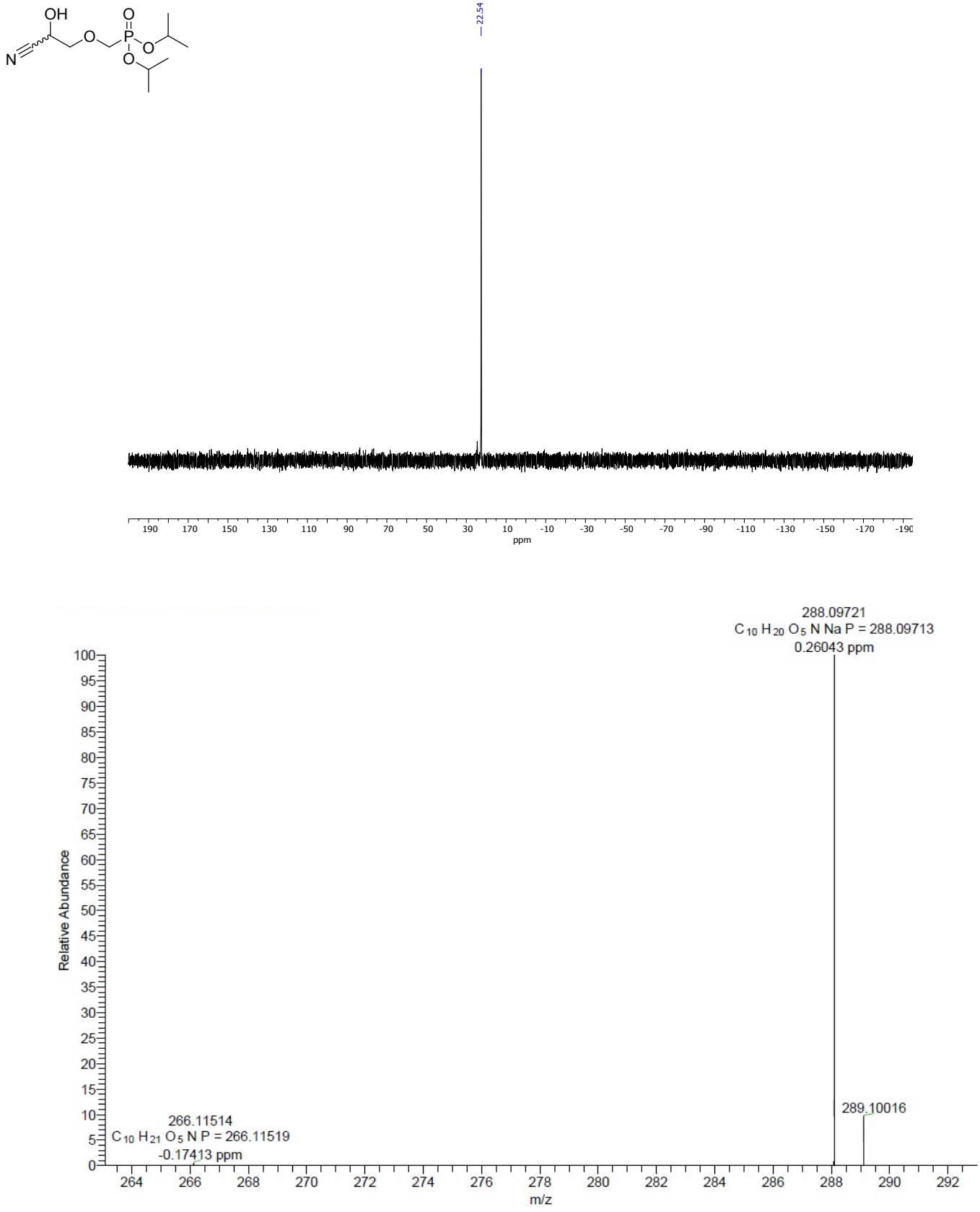


Figure S78. ^{31}P NMR (measured in $CDCl_3$ at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**9h**.

Diisopropyl ((2-(2-amino-6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**10a**)

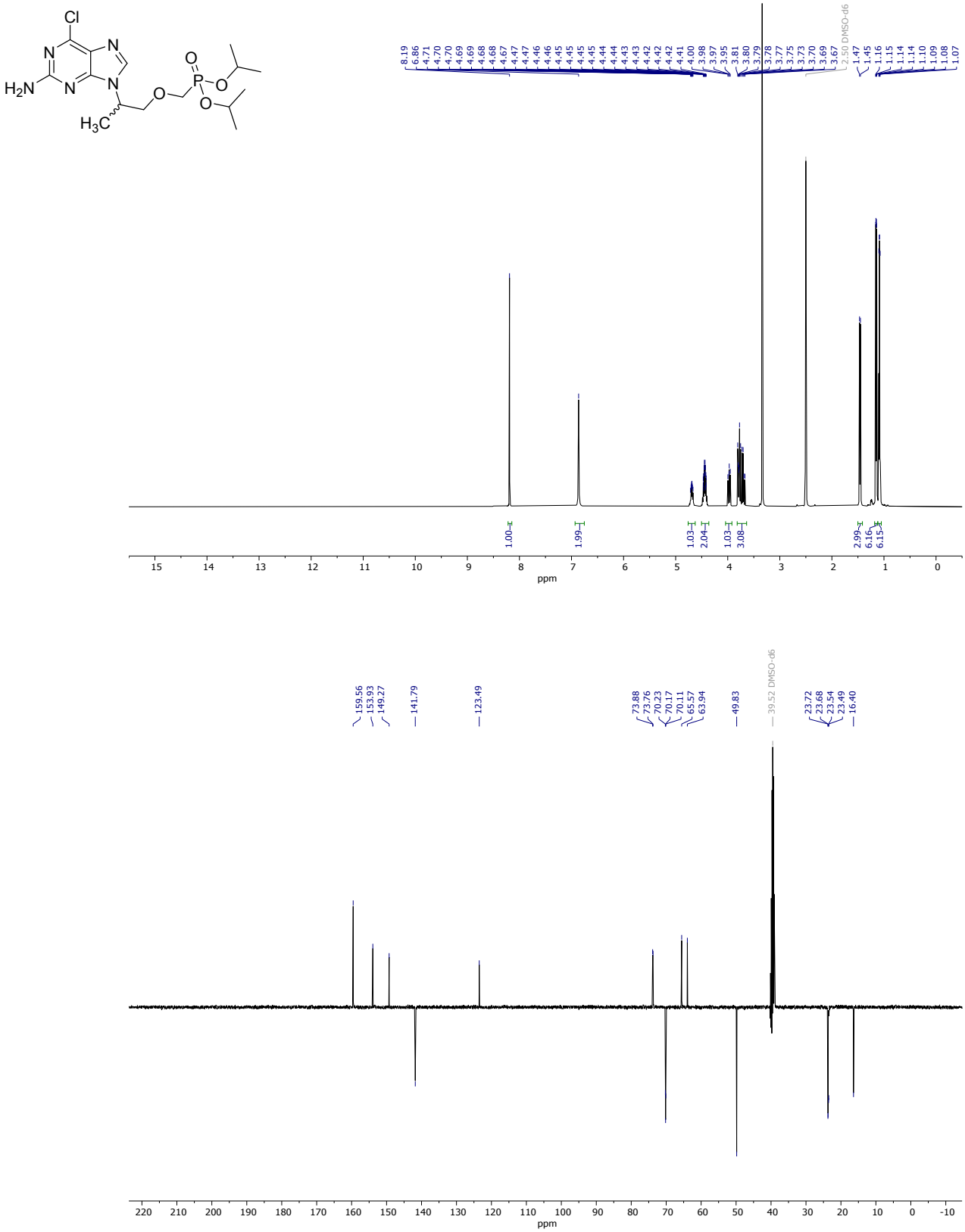


Figure S79. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**10a** measured in DMSO-d_6 at room temperature.

Diisopropyl ((2-(2-amino-6-chloro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**10a**)

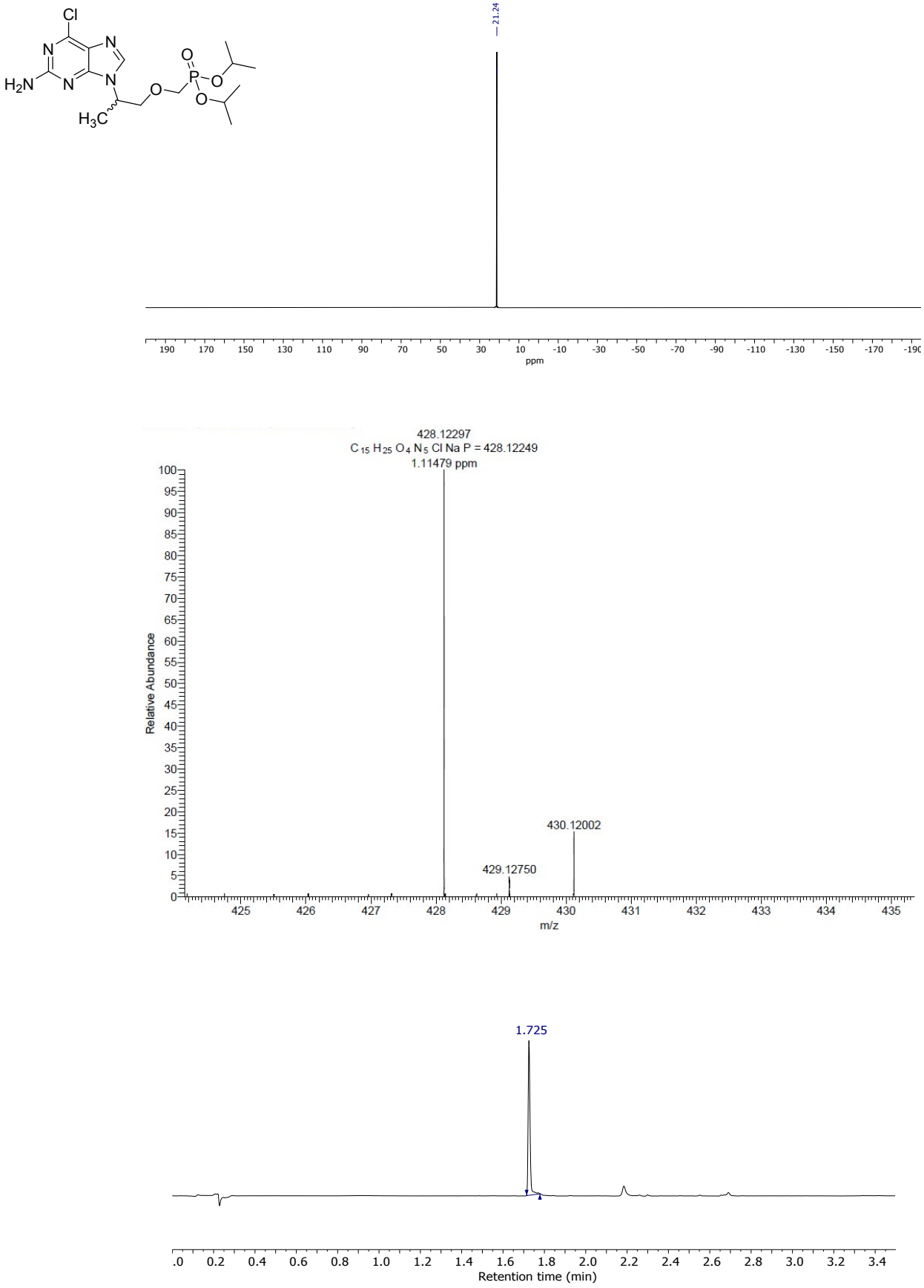


Figure S80. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**10a**.

Diisopropyl ((2-(2-amino-6-chloro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*RS*)-**10b**)

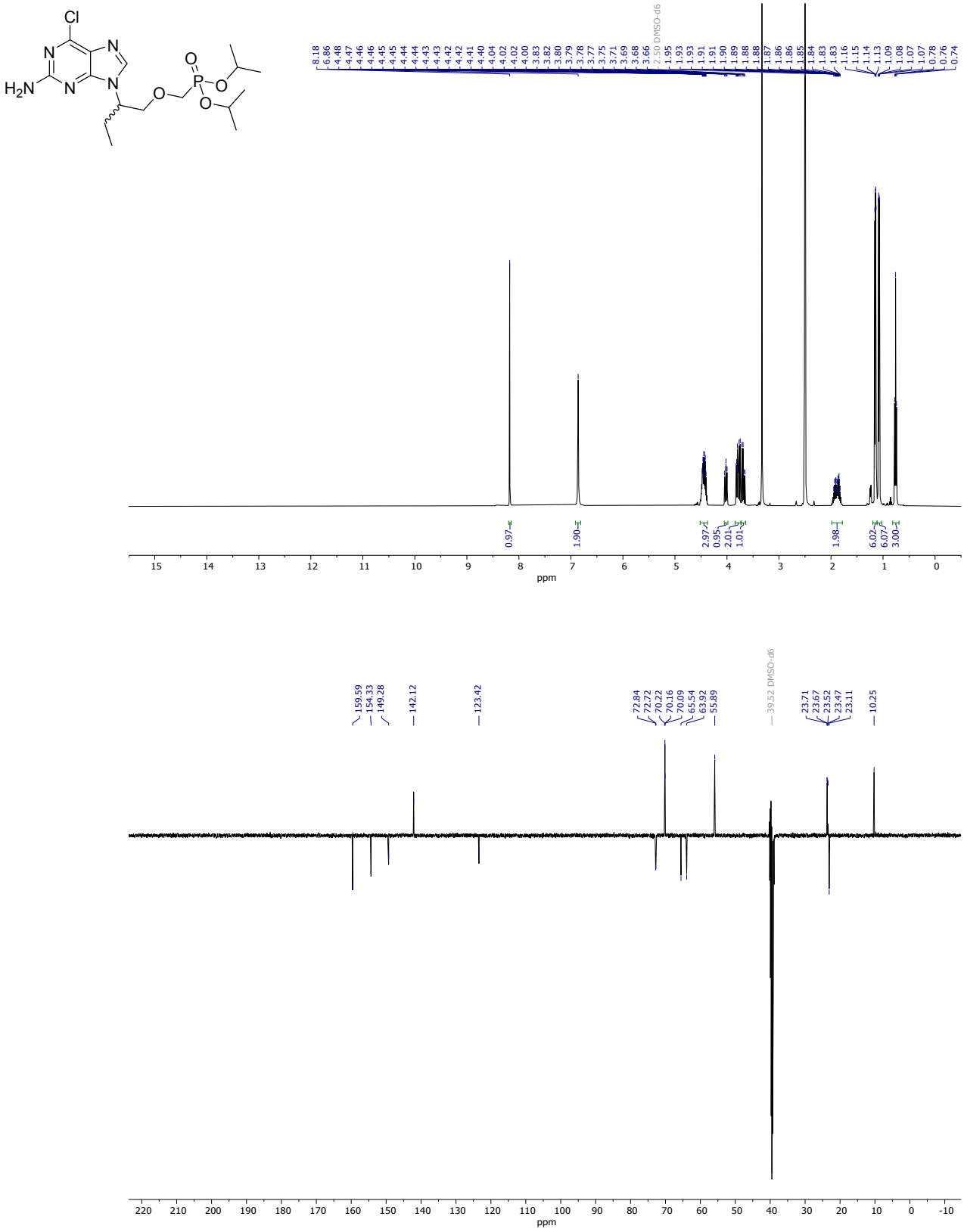


Figure S81. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**10b** measured in DMSO-d_6 at room temperature.

Diisopropyl ((2-(2-amino-6-chloro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*RS*)-**10b**)

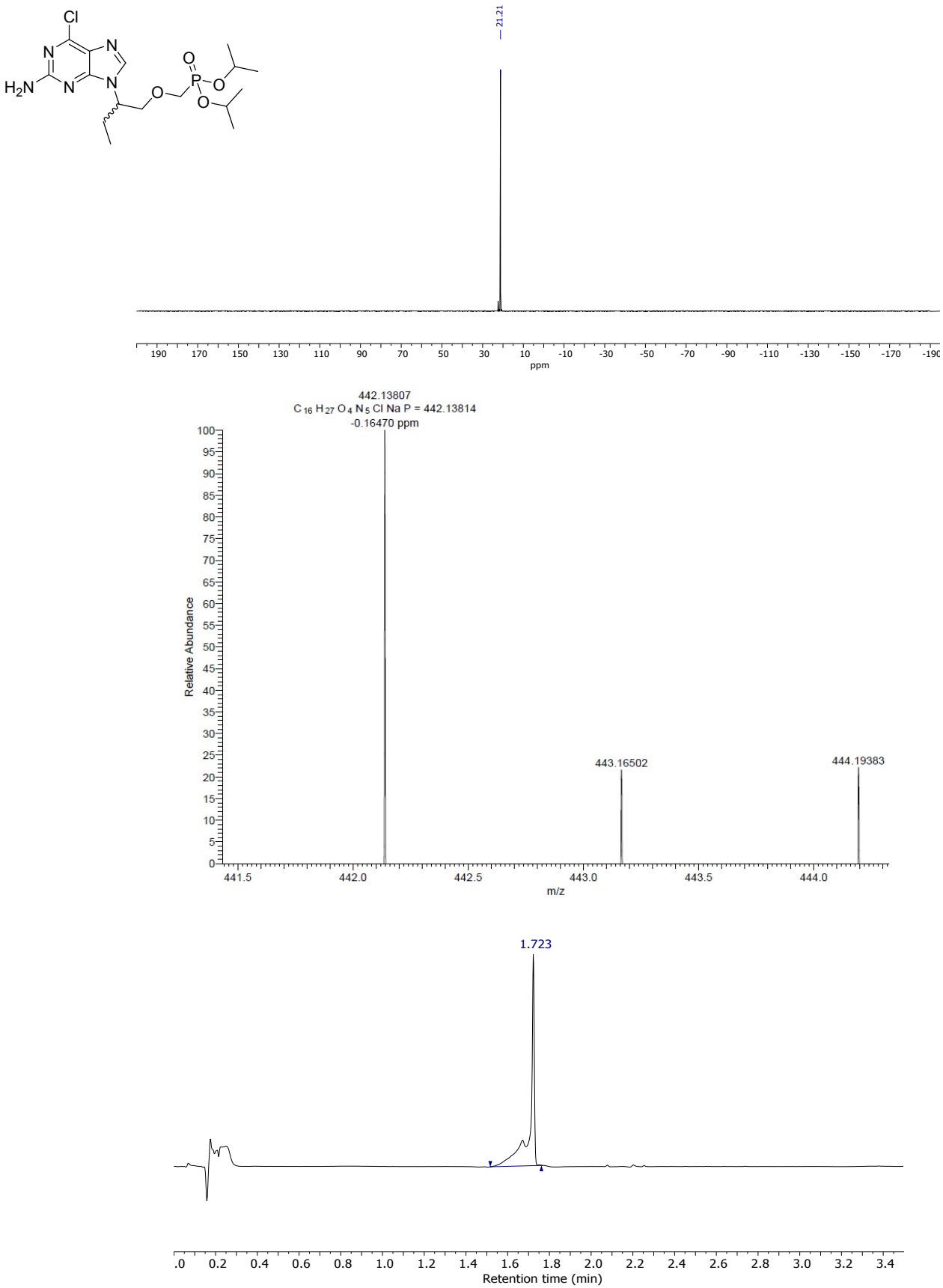


Figure S82. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**10b**.

Diisopropyl (((2-(2-amino-6-chloro-9*H*-purin-9-yl)but-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**10c**)

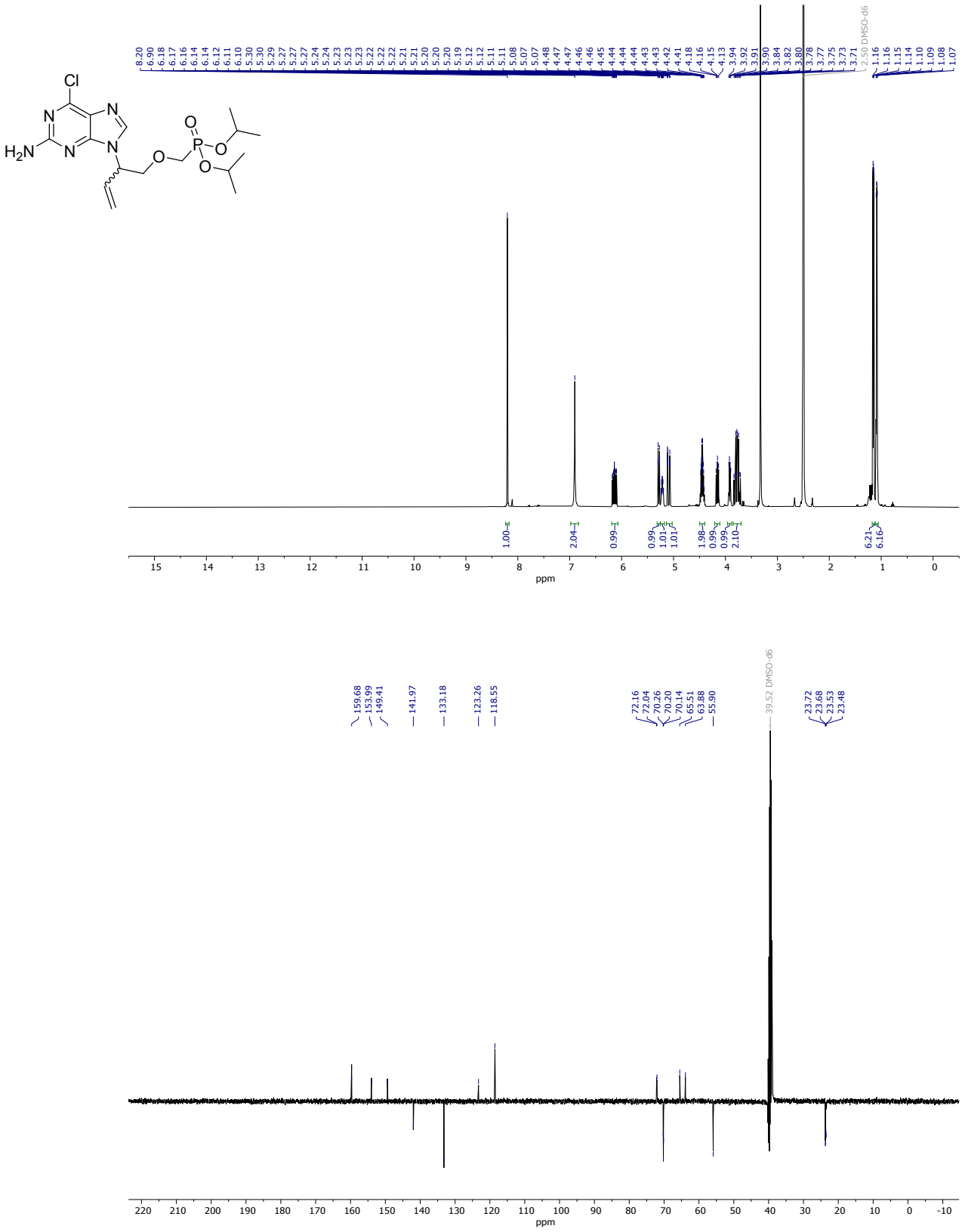


Figure S83. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**10c** measured in DMSO-d_6 at room temperature.

Diisopropyl (((2-(2-amino-6-chloro-9*H*-purin-9-yl)but-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**10c**)

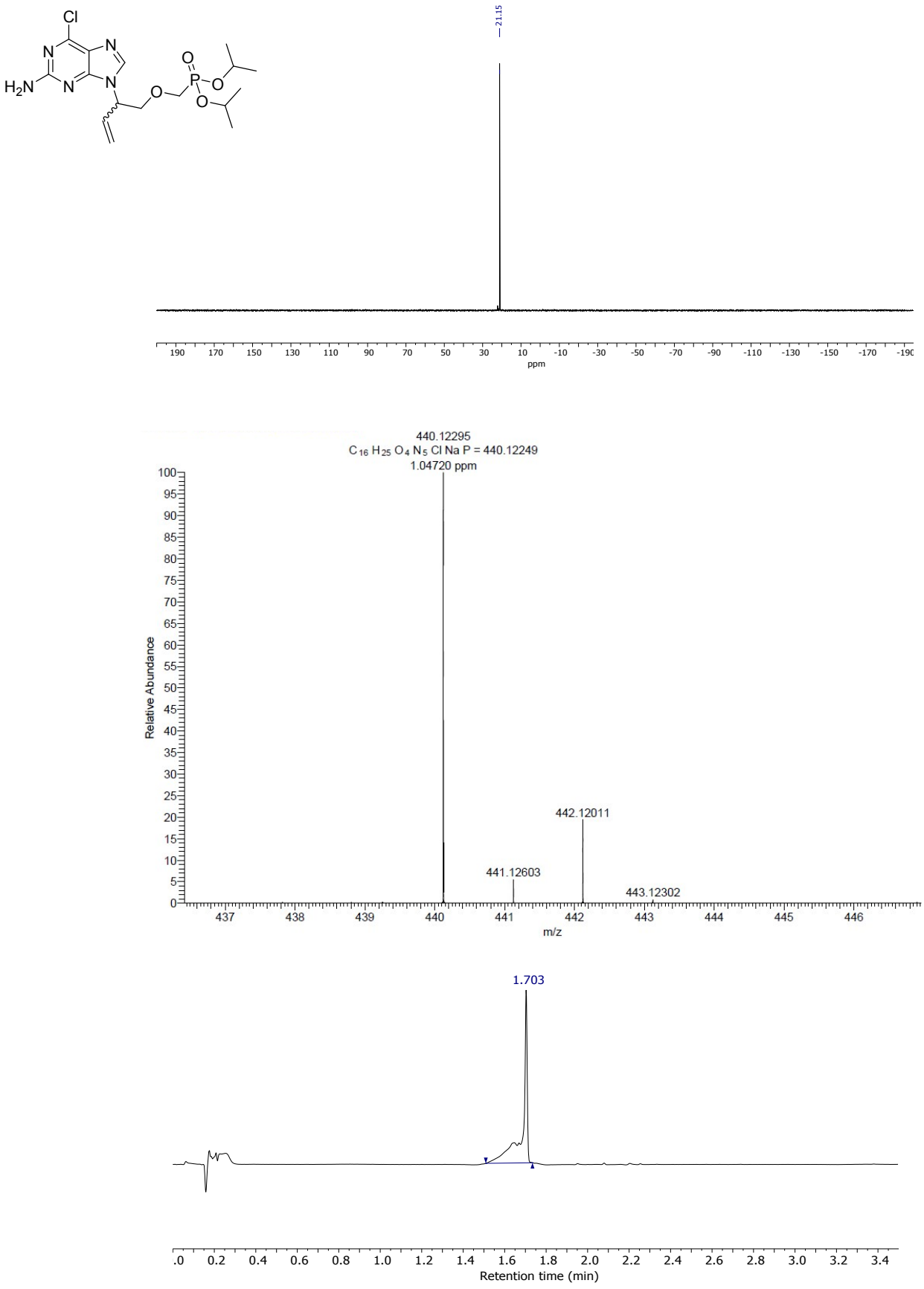


Figure S84. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**10c**.

Diisopropyl (((2-(2-amino-6-chloro-9*H*-purin-9-yl)but-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**10d**)

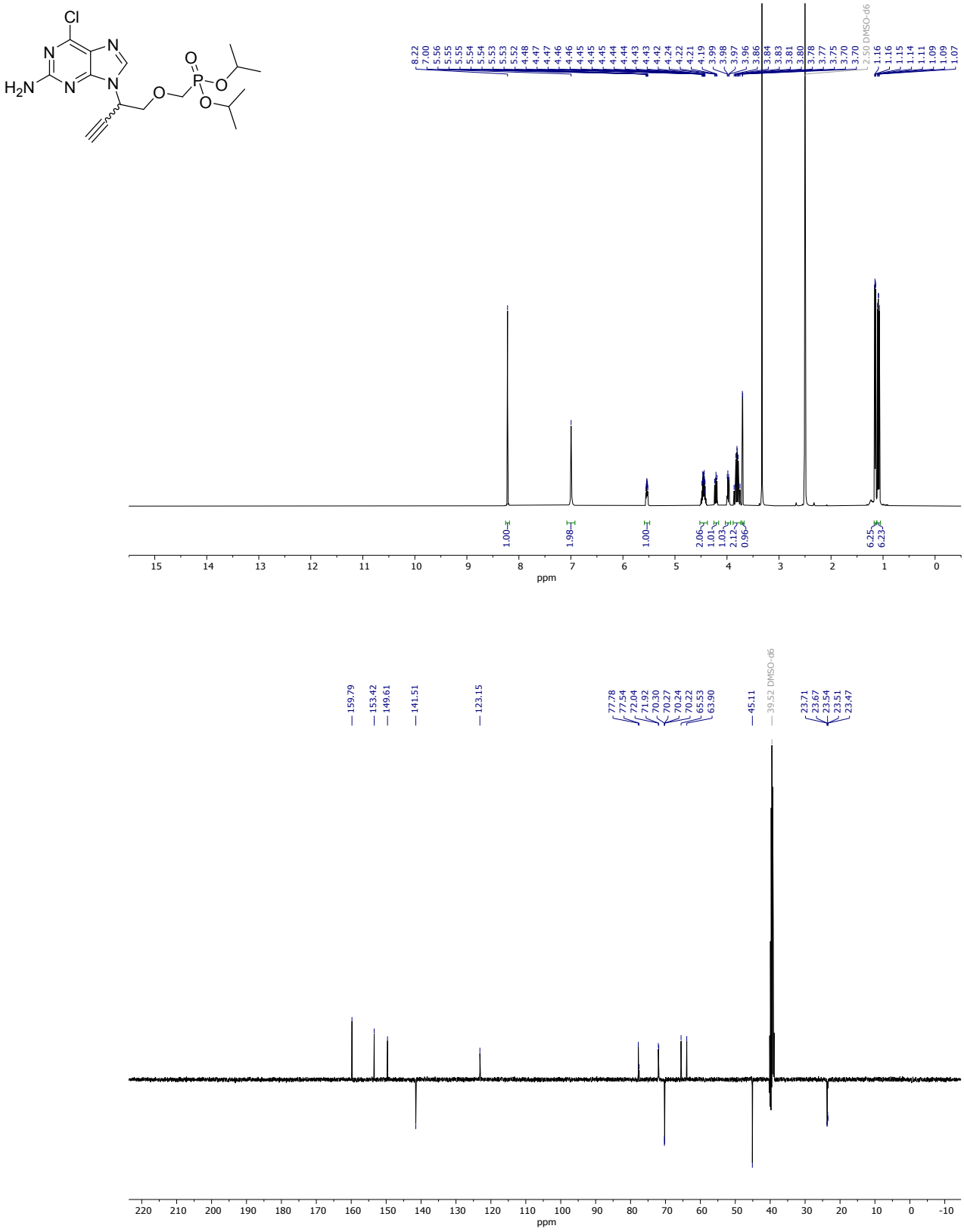


Figure S85. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**10d** measured in DMSO-d_6 at room temperature.

Diisopropyl (((2-(2-amino-6-chloro-9*H*-purin-9-yl)but-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**10d**)

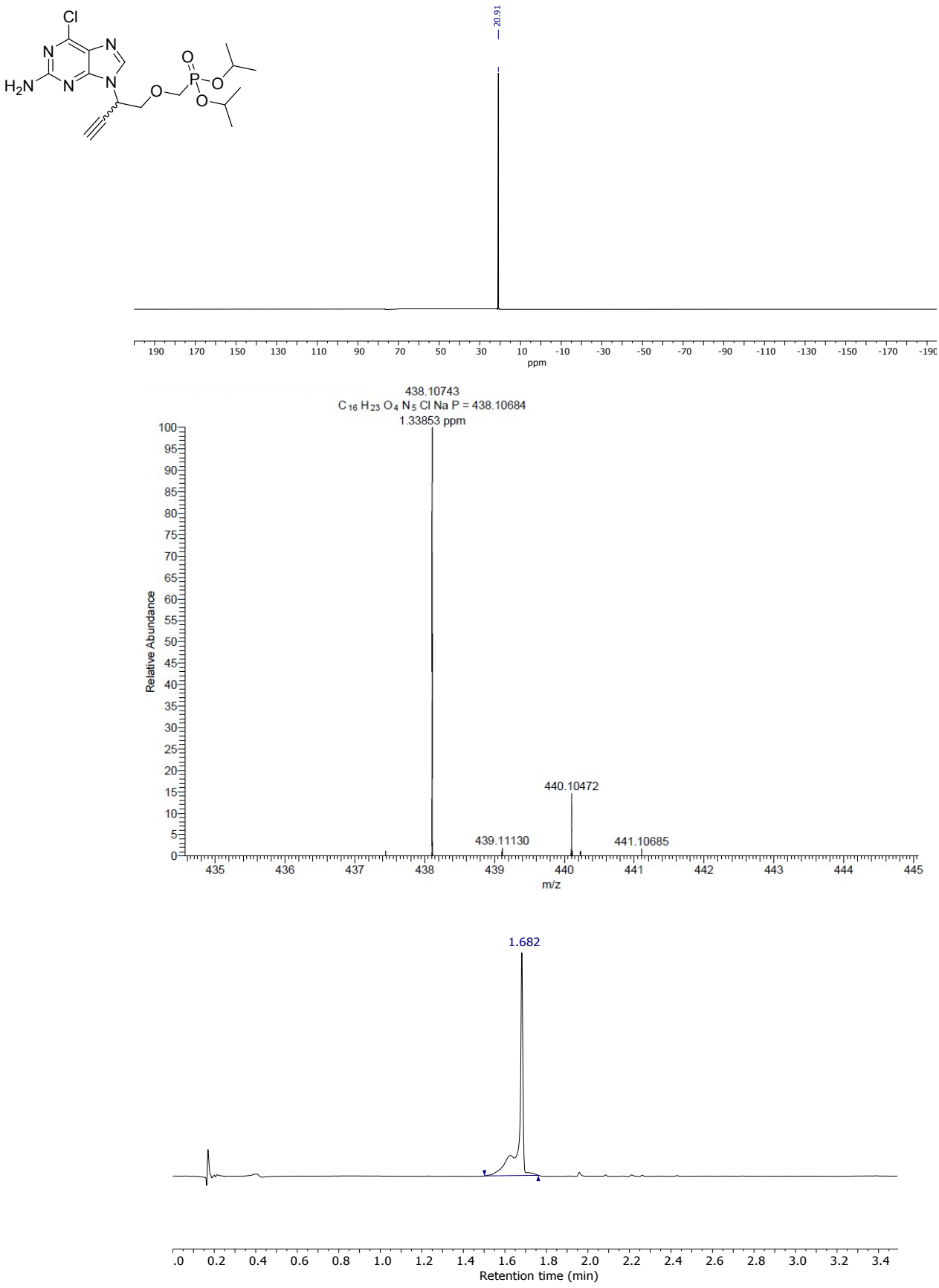


Figure S86. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**10d**.

Diisopropyl ((2-(2-amino-6-chloro-9*H*-purin-9-yl)-2-cyclopropylethoxy)methyl)phosphonate ((*RS*)-**10e**)

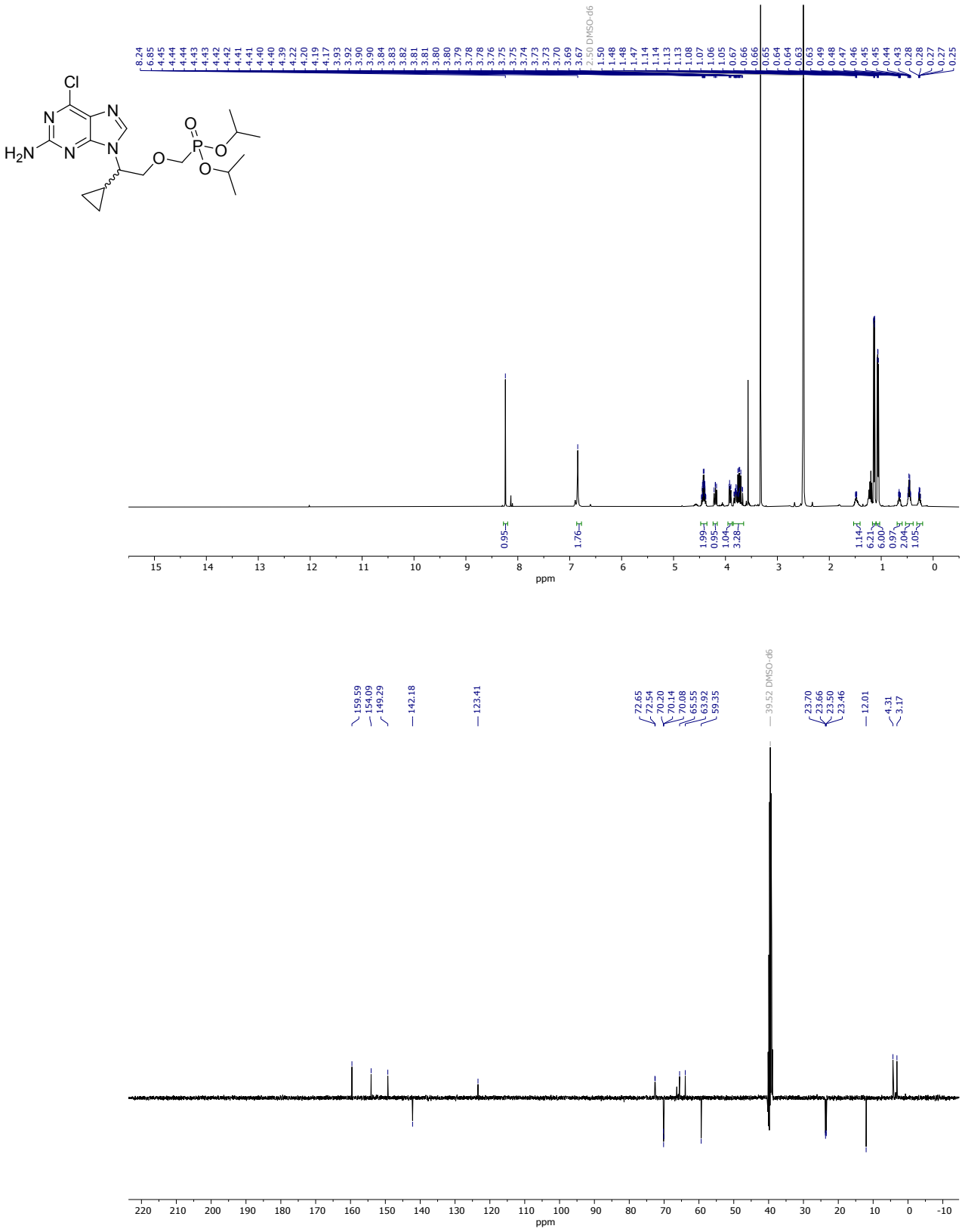


Figure S87. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**10e** measured in DMSO-d_6 at room temperature.

Diisopropyl ((2-(2-amino-6-chloro-9*H*-purin-9-yl)-2-cyclopropylethoxy)methyl)phosphonate ((*RS*)-**10e**)

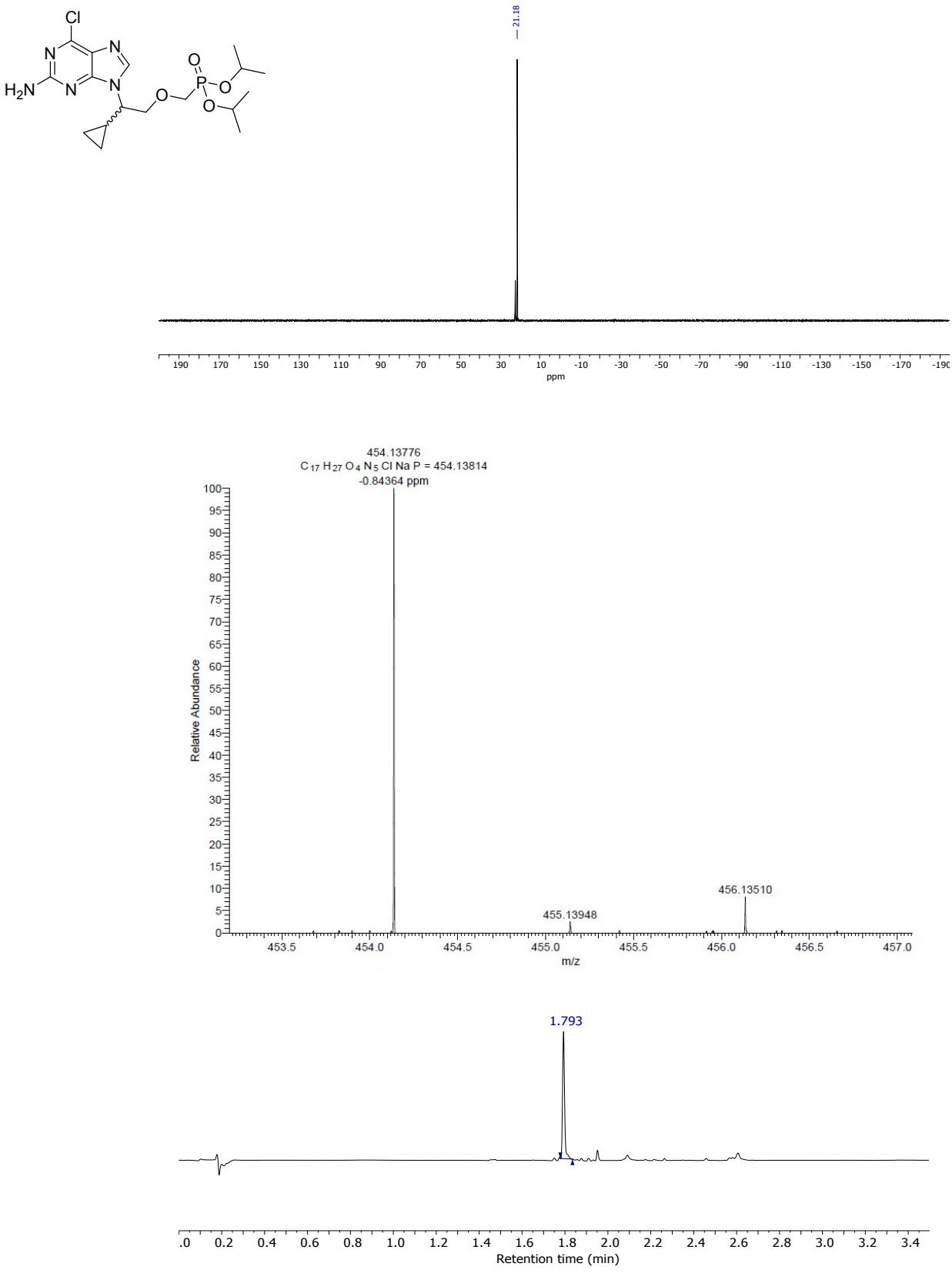


Figure S88. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top), high resolution mass spectrum (HRMS, middle) and UPLC chromatogram (at 254 nm, bottom) of compound (*RS*)-**10e**.

(*S*)-9-(1-(Benzyloxy)-3-(trityloxy)propan-2-yl)-6-chloro-9*H*-purine ((*S*)-**12a**)

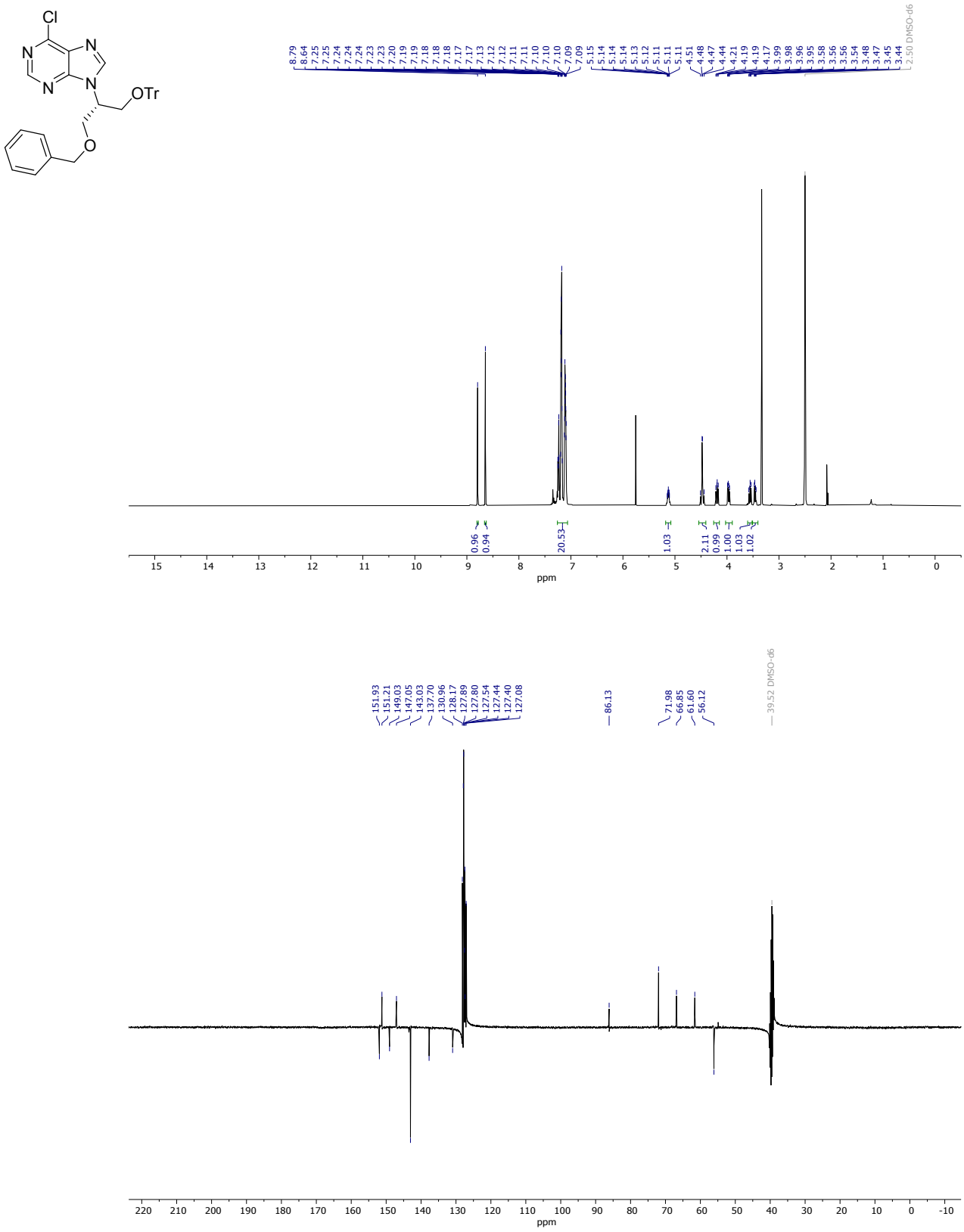


Figure S89. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*S*)-**12a** measured in DMSO-d_6 at room temperature.

(*S*)-9-(1-(Benzyloxy)-3-(trityloxy)propan-2-yl)-6-chloro-9*H*-purine ((*S*)-**12a**)

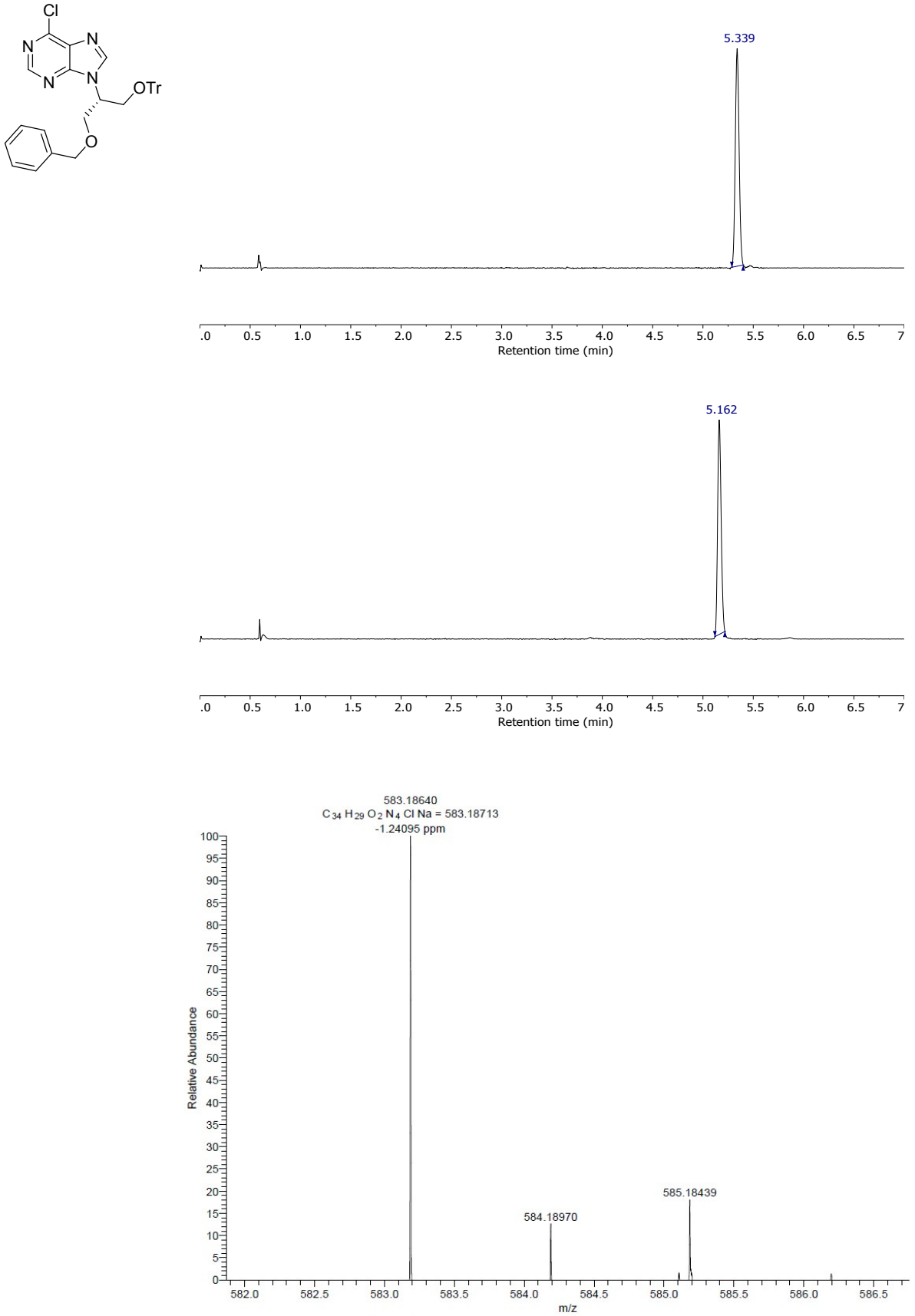


Figure S90. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top) and SB column (middle), and high resolution mass spectrum (HRMS, bottom) of compound (*S*)-**12a**.

(*S*)-9-(1-(Benzyloxy)-3-(trityloxy)propan-2-yl)-6-chloro-9*H*-purin-2-amine ((*S*)-**12b**)

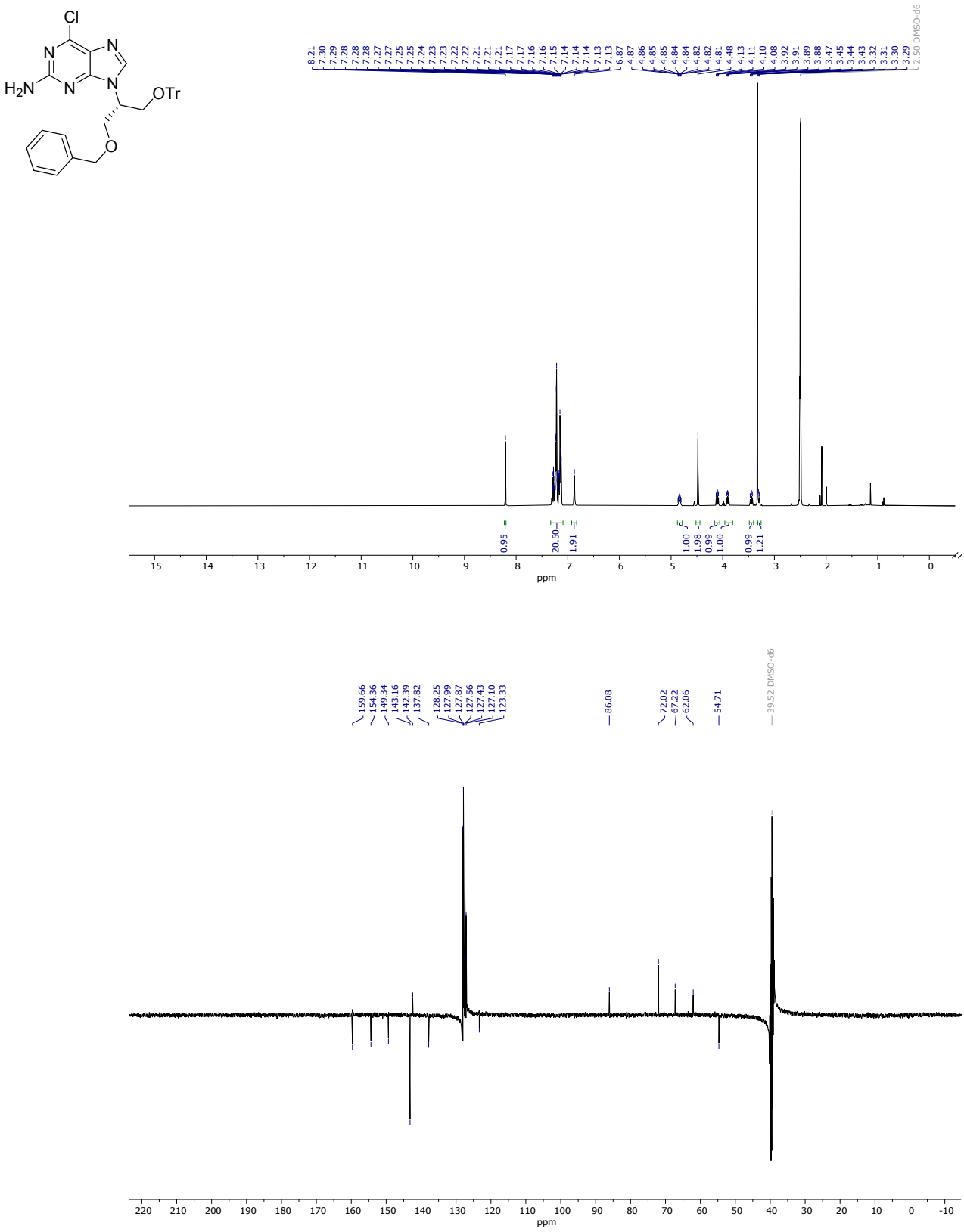


Figure S91. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*S*)-**12b** measured in DMSO-d_6 at room temperature.

(*S*)-9-(1-(Benzyloxy)-3-(trityloxy)propan-2-yl)-6-chloro-9*H*-purin-2-amine ((*S*)-**12b**)

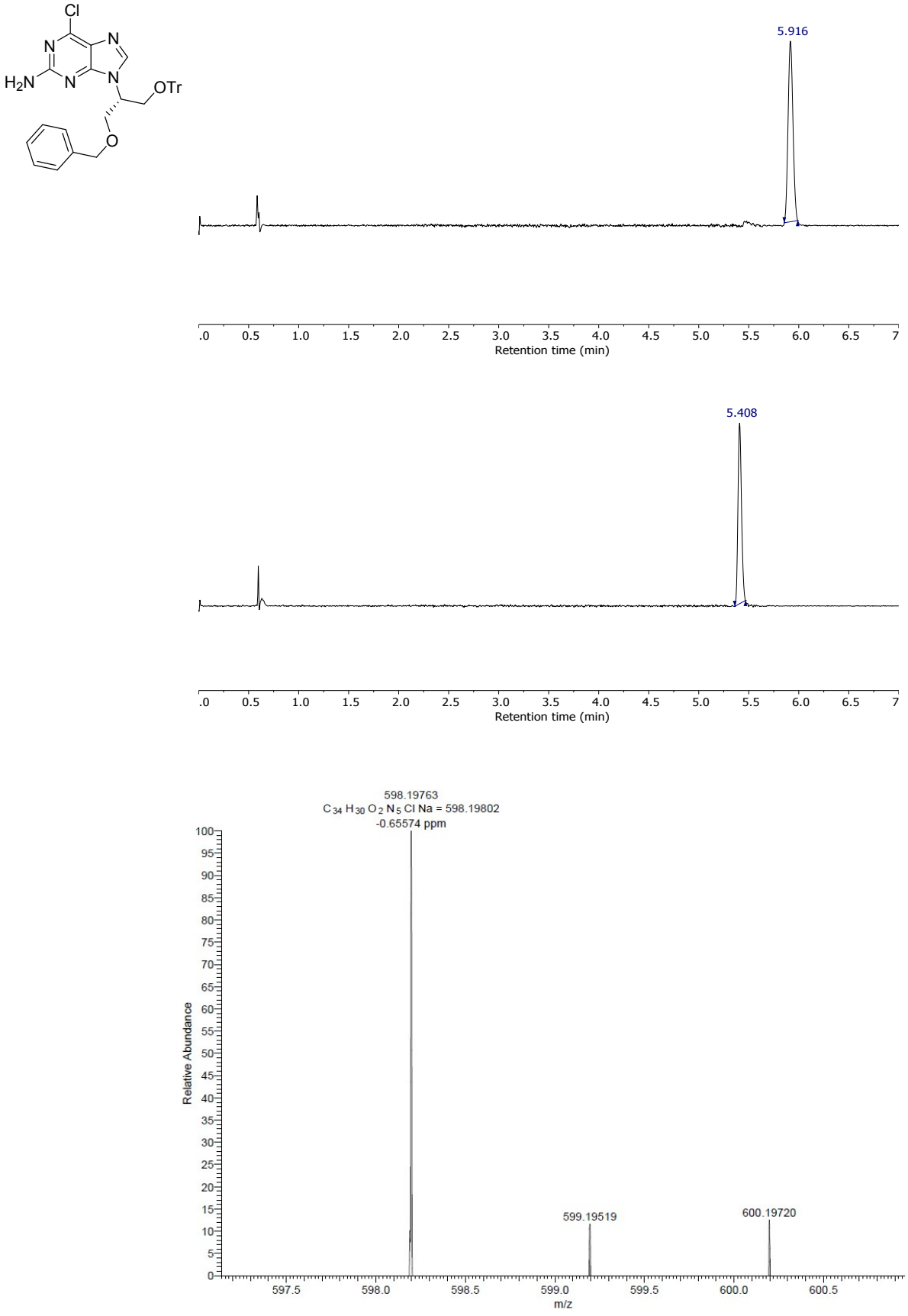


Figure S92. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top) and SB column (middle), and high resolution mass spectrum (HRMS, bottom) of compound (*S*)-**12b**.

(*R*)-2-(2-Amino-6-chloro-9*H*-purin-9-yl)-3-(benzyloxy)propan-1-ol ((*R*)-**13**)

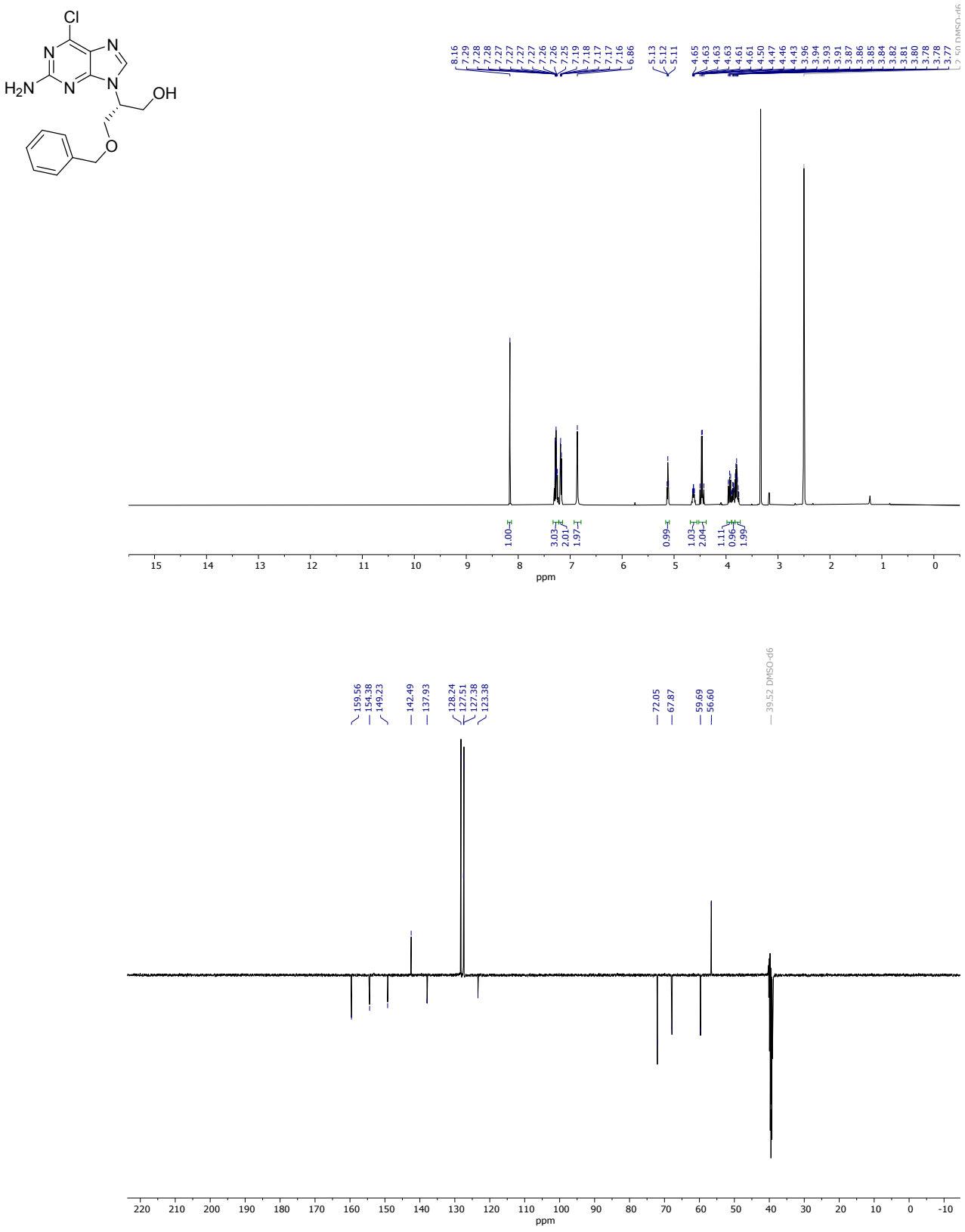


Figure S93. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**13** measured in DMSO-d_6 at room temperature.

(*R*)-2-(2-Amino-6-chloro-9*H*-purin-9-yl)-3-(benzyloxy)propan-1-ol ((*R*)-**13**)

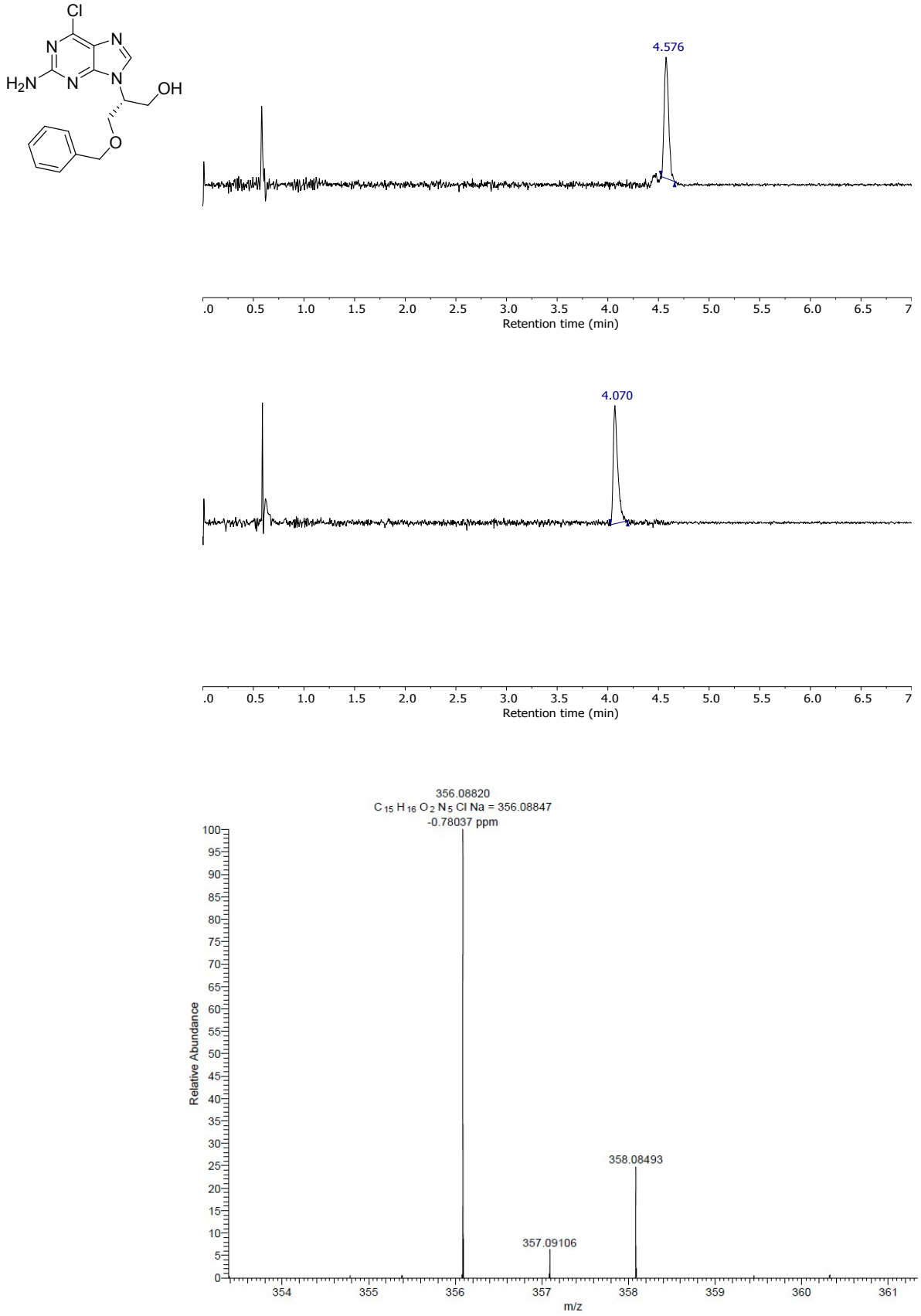


Figure S94. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top) and SB column (middle), and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**13**.

Diisopropyl (*S*)-((3-(benzyloxy)-2-(6-chloro-2-(((dimethylamino)methylene)amino)-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*S*)-**14**)

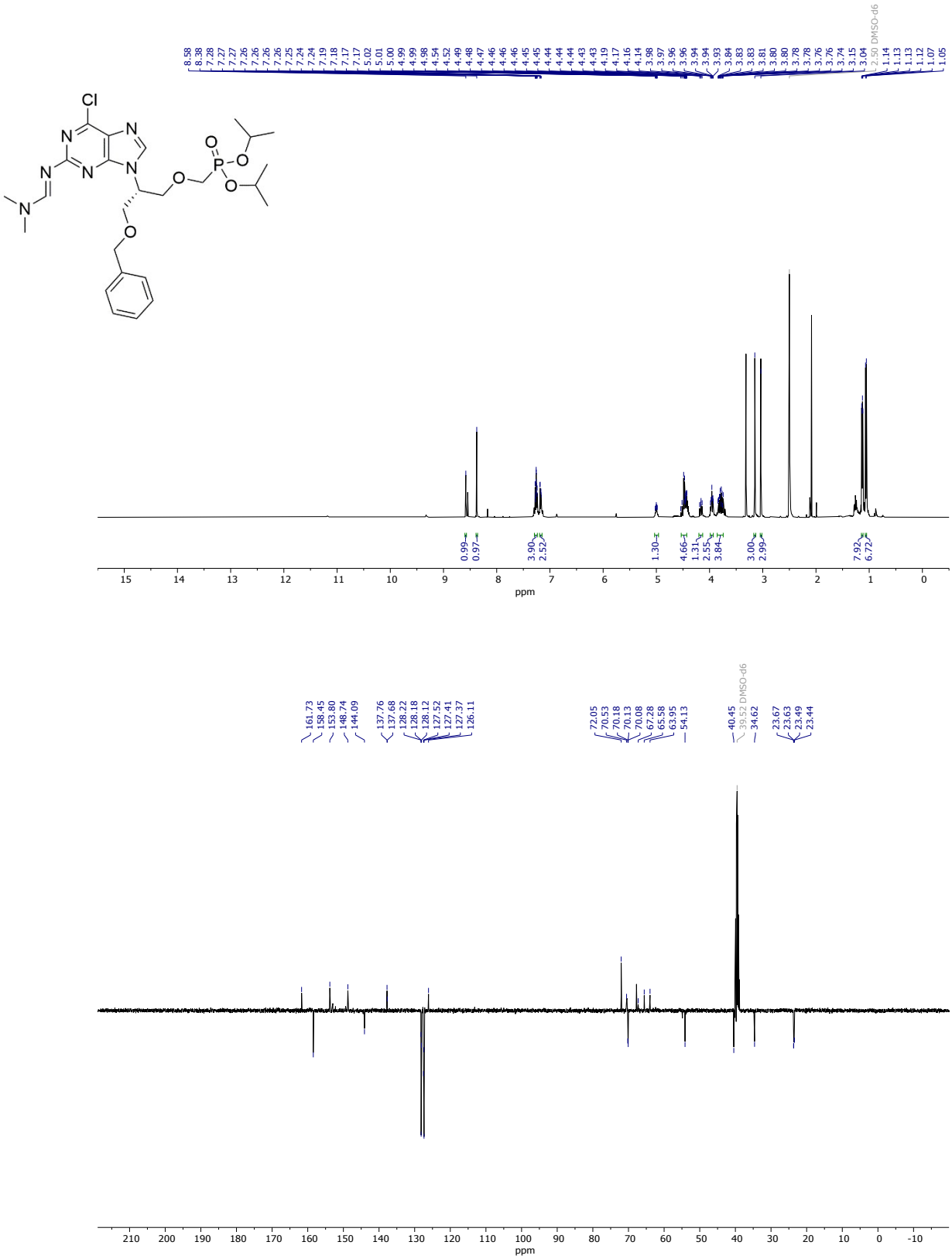


Figure S95. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*S*)-**14** measured in DMSO-d_6 at room temperature.

Diisopropyl (*S*)-((3-(benzyloxy)-2-(6-chloro-2-(((dimethylamino)methylene)amino)-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*S*)-**14**)

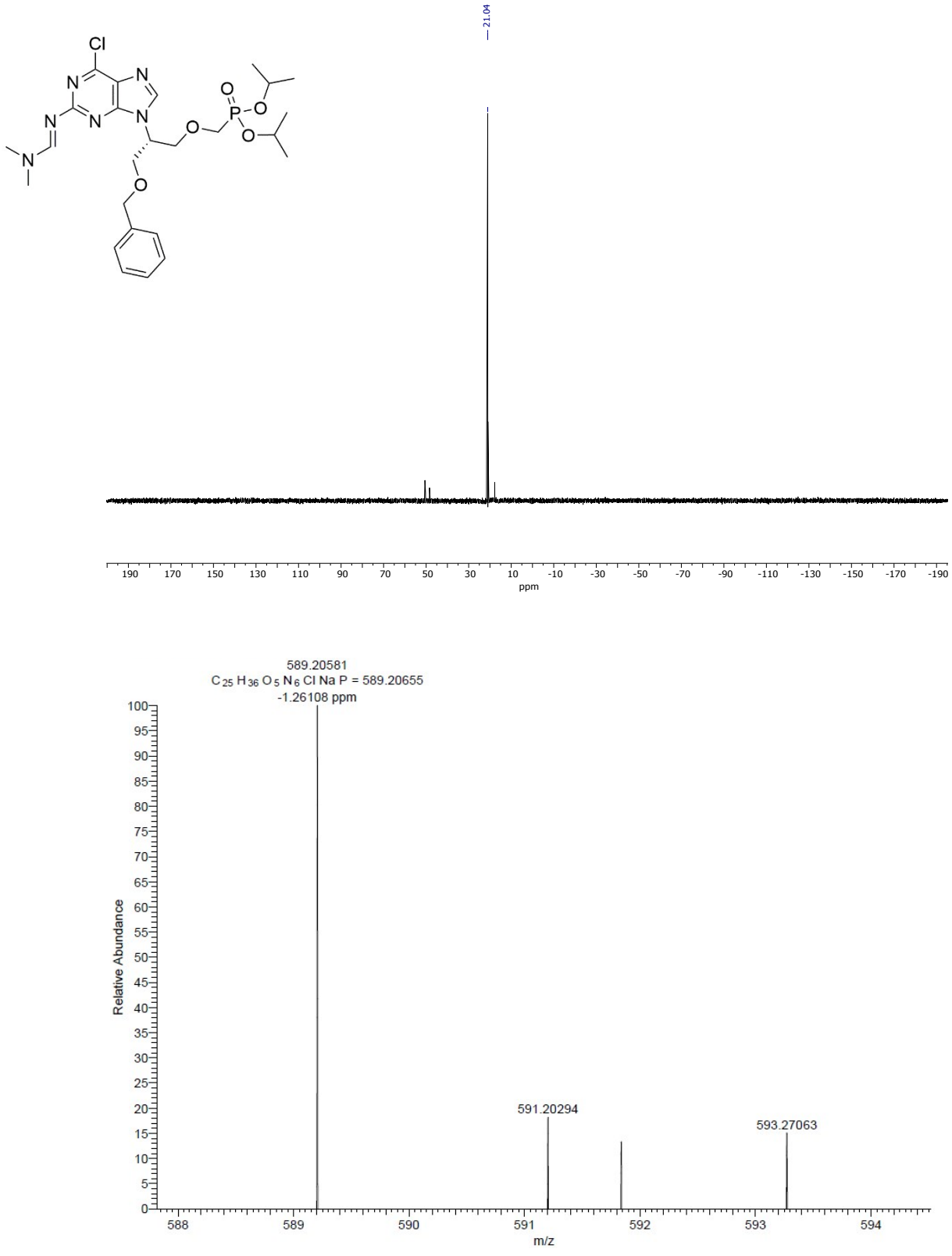


Figure S96. ^{31}P NMR (measured in DMSO-d_6 at room temperature, top) and high resolution mass spectrum (HRMS, bottom) of compound (*S*)-**14**.

Diisopropyl (*S*)-((3-(benzyloxy)-2-(6-chloro-2-(((dimethylamino)methylene)amino)-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*S*)-**14**)

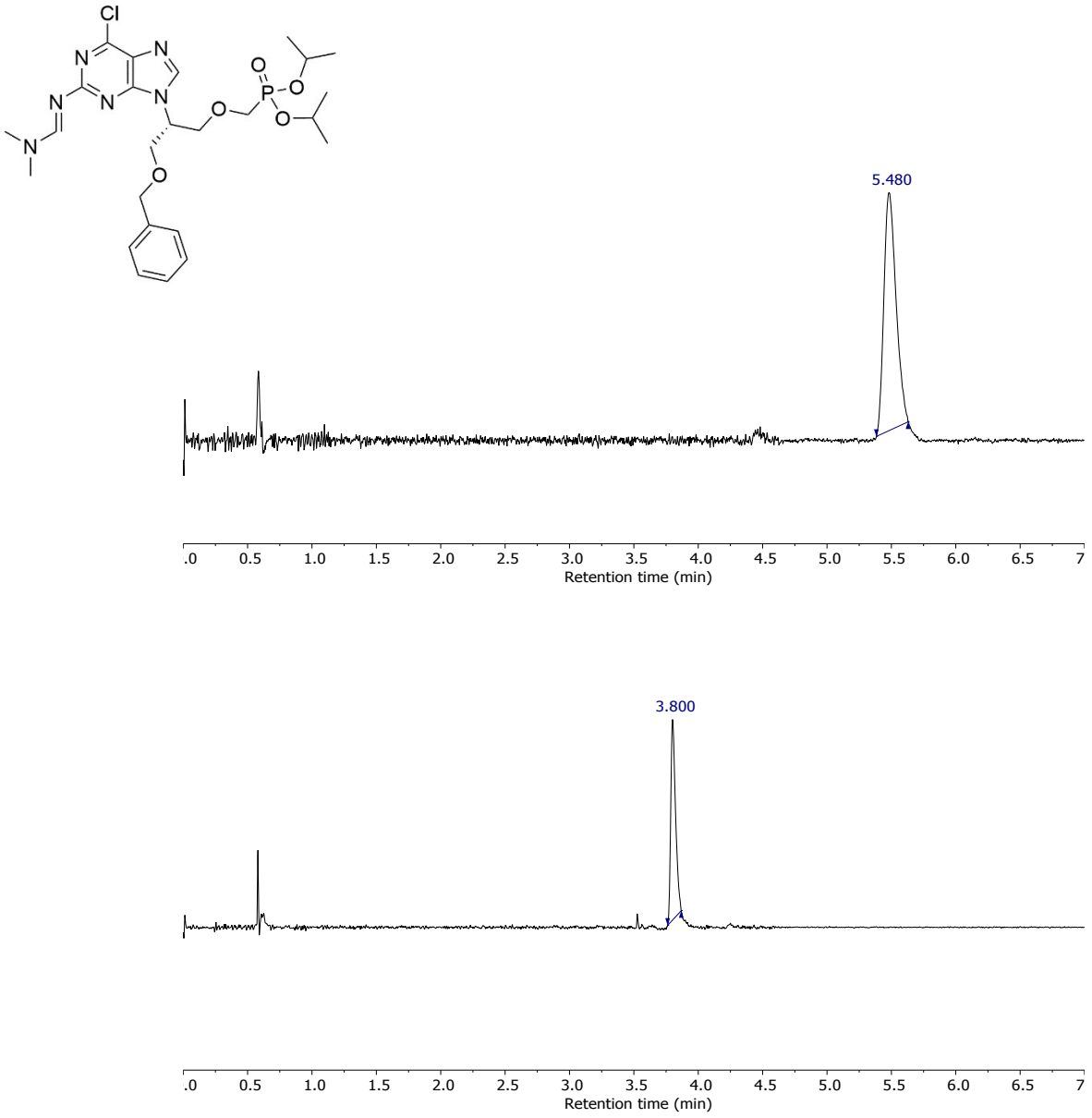


Figure S97. SFC chromatogram at 254 nm using chiral YMC Alcyon SC column (top) and SB column (middle) of compound (*S*)-**14**.

Sodium ((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**15a**)

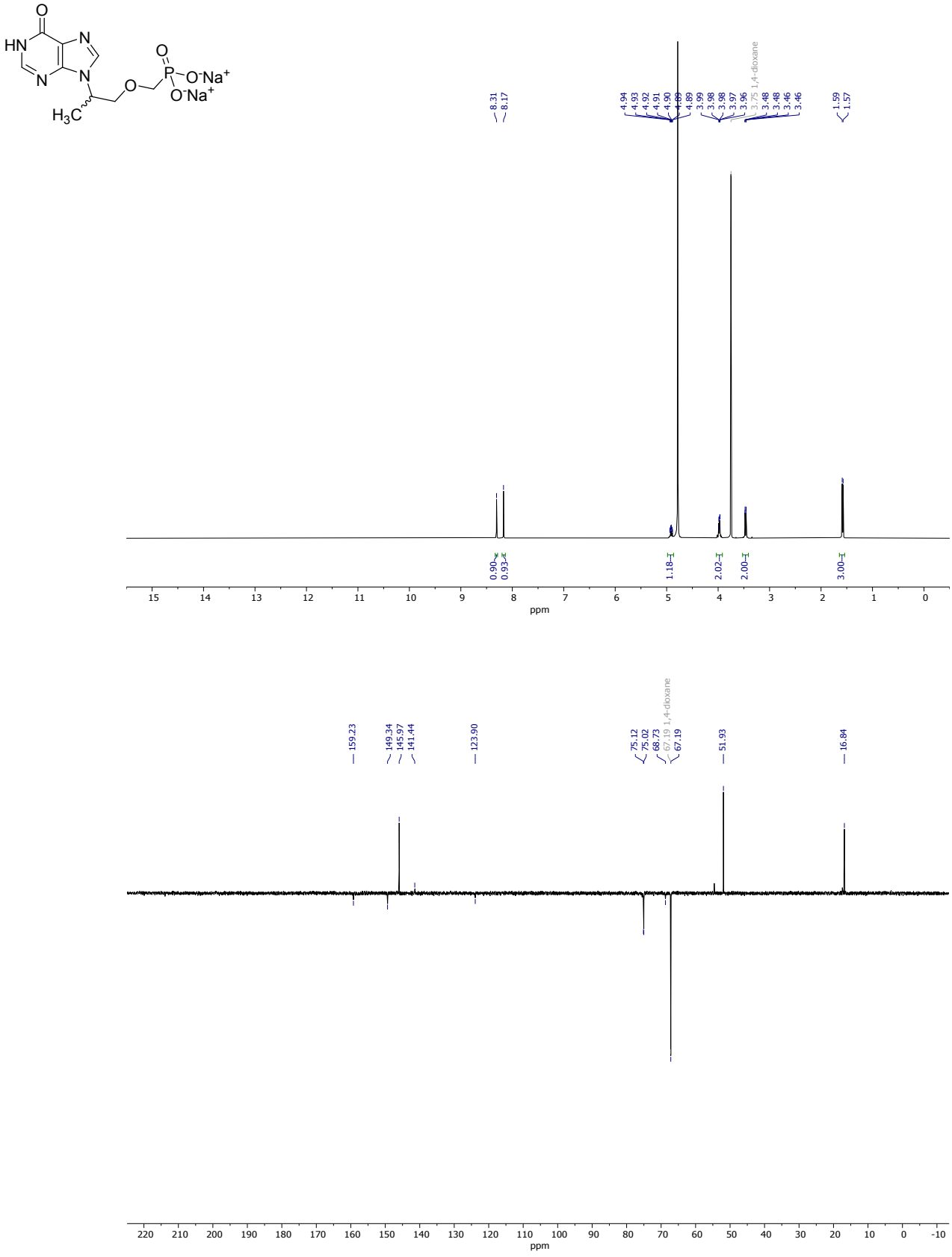


Figure S98. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**15a** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium ((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**15a**)

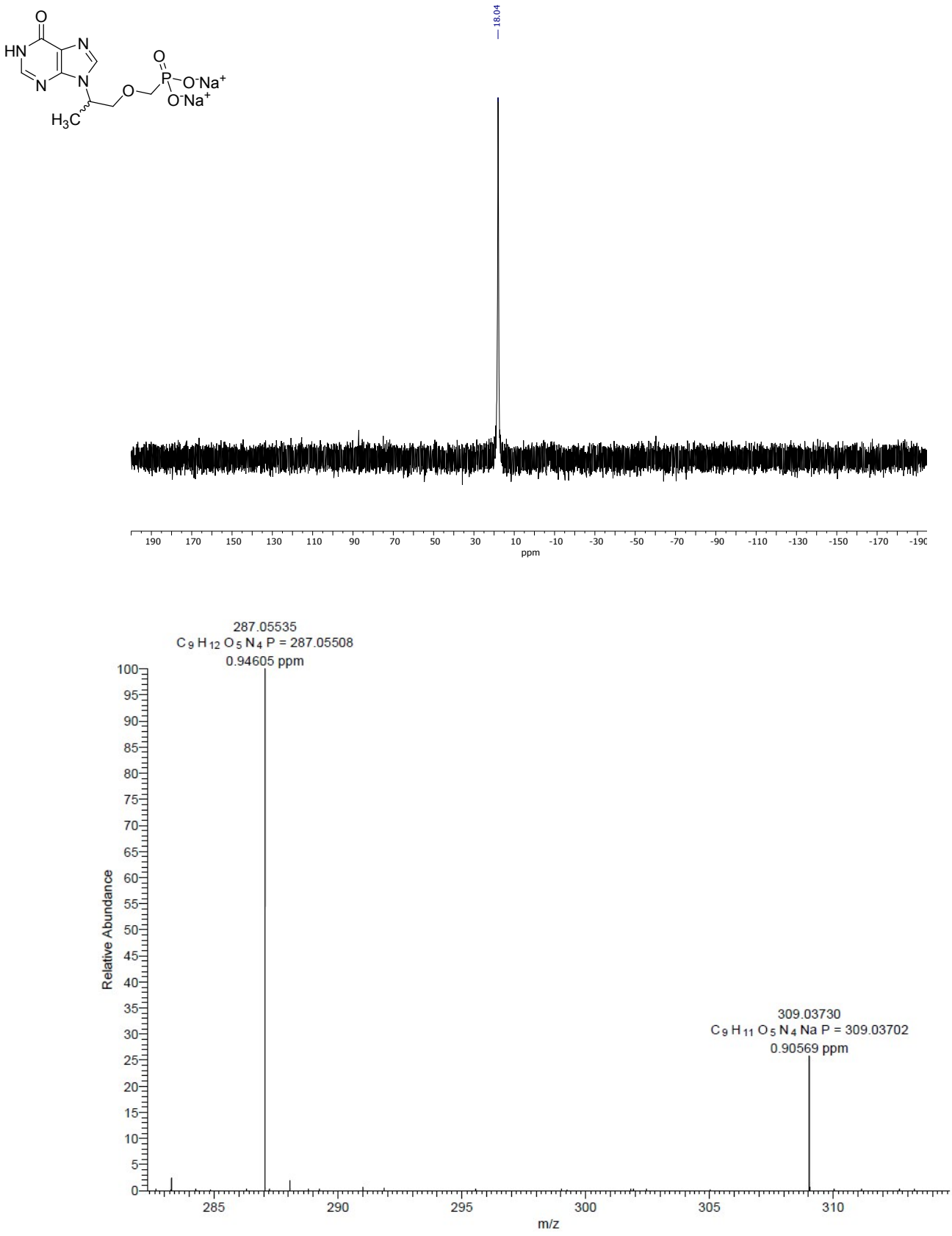


Figure S99. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**15a**.

Sodium ((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*RS*)-**15b**)

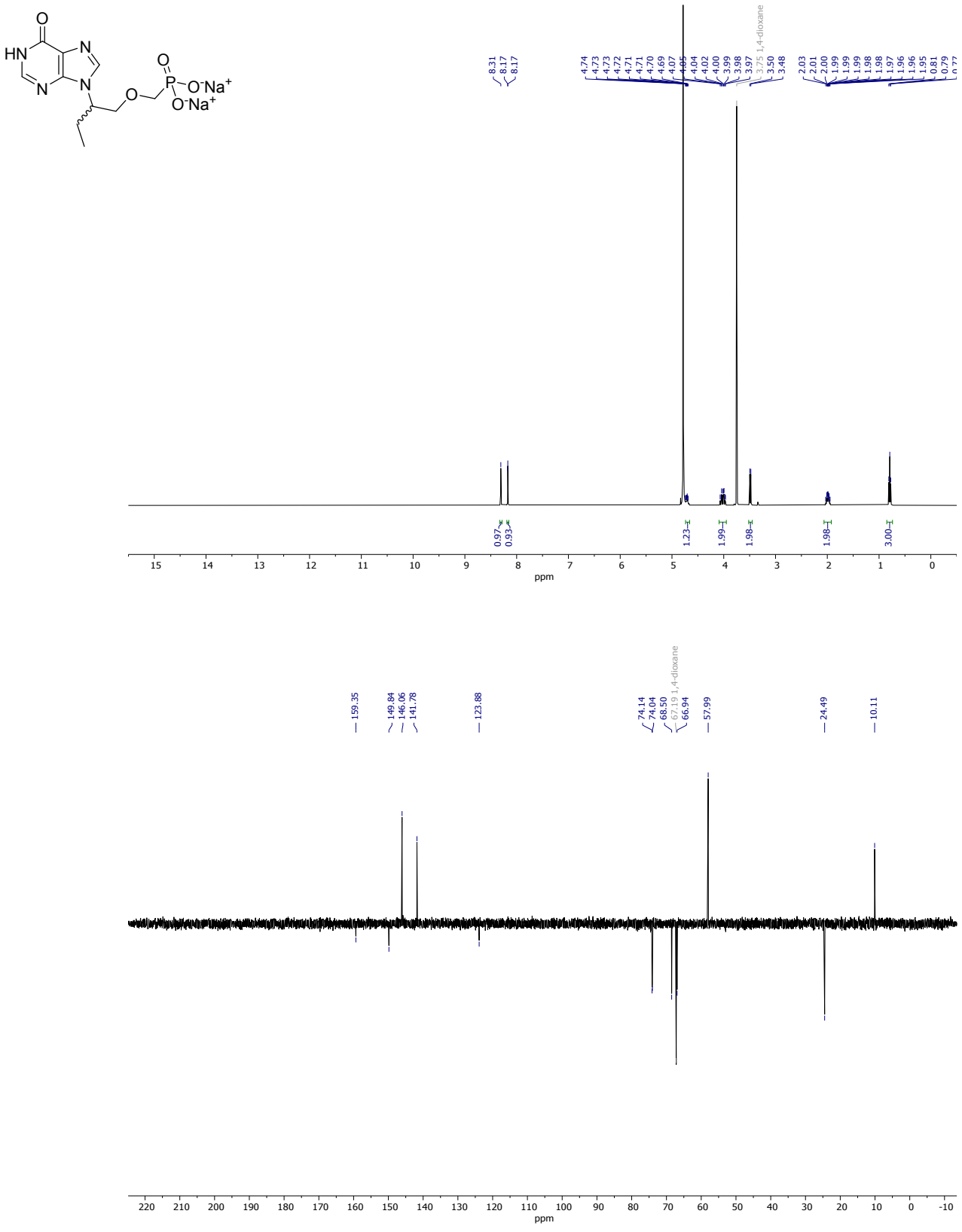


Figure S100. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**15b** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium ((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*RS*)-**15b**)

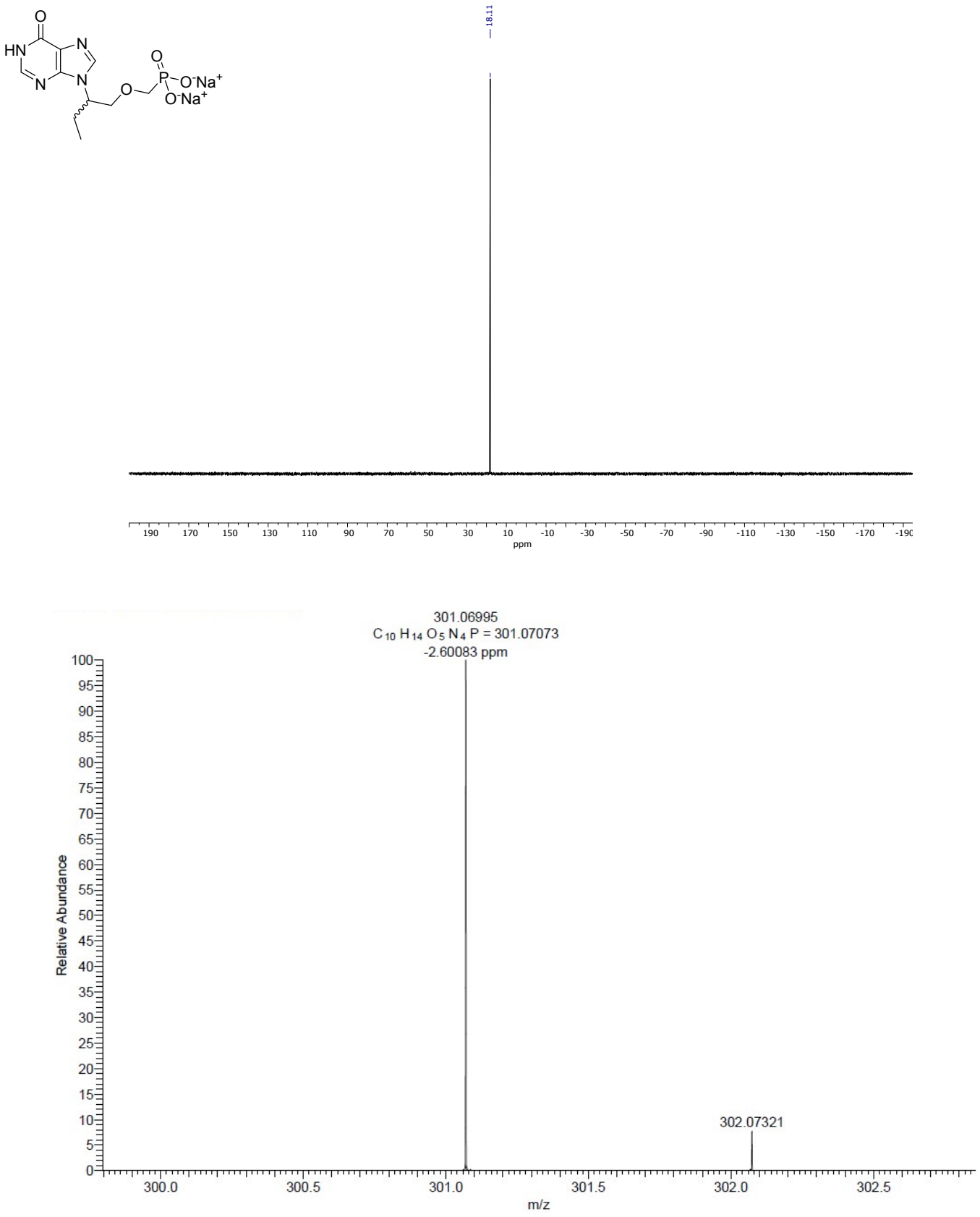


Figure S101. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**15b**.

Sodium (*R*)-((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**15b**)

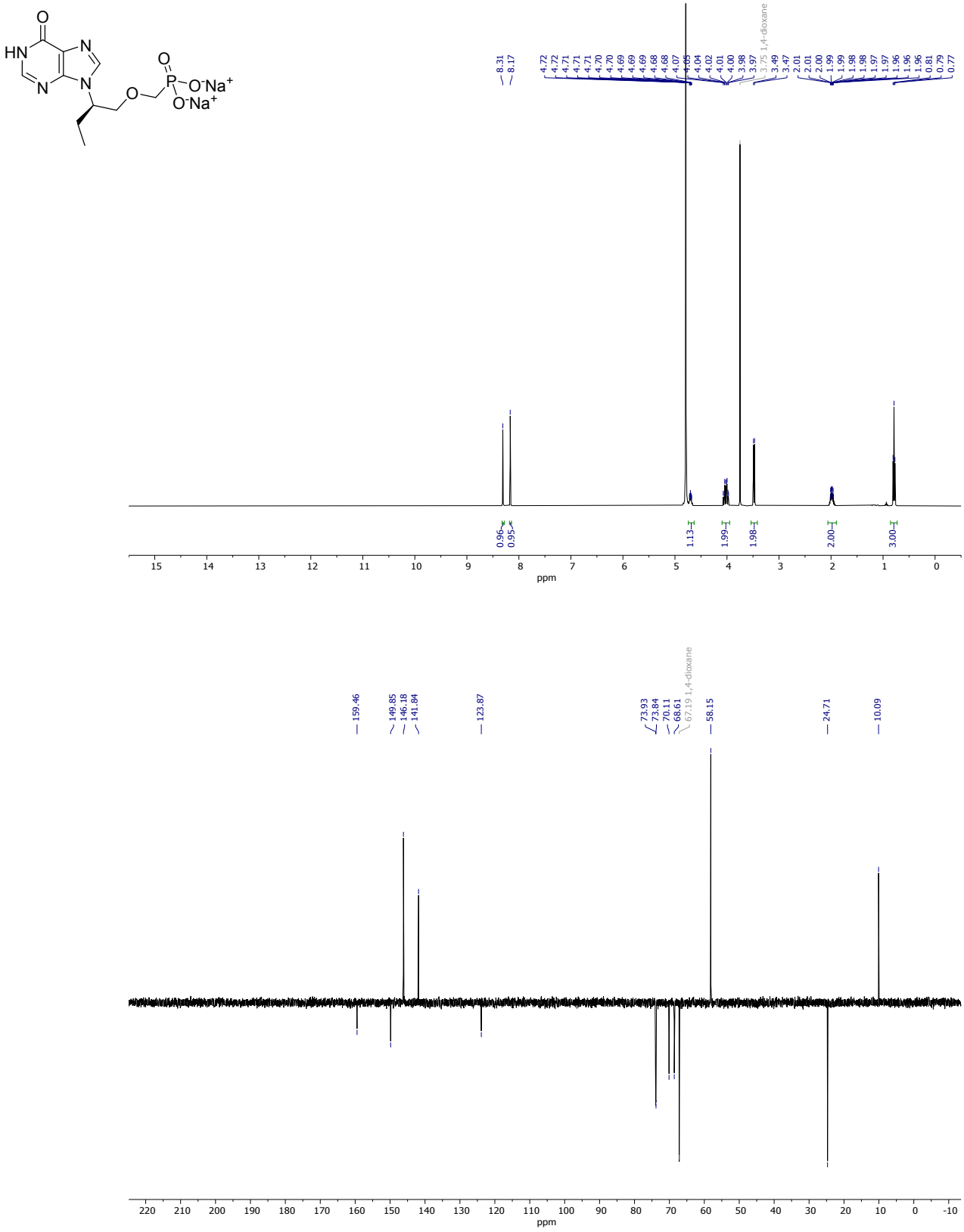


Figure S102. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**15b** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*R*)-((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**15b**)

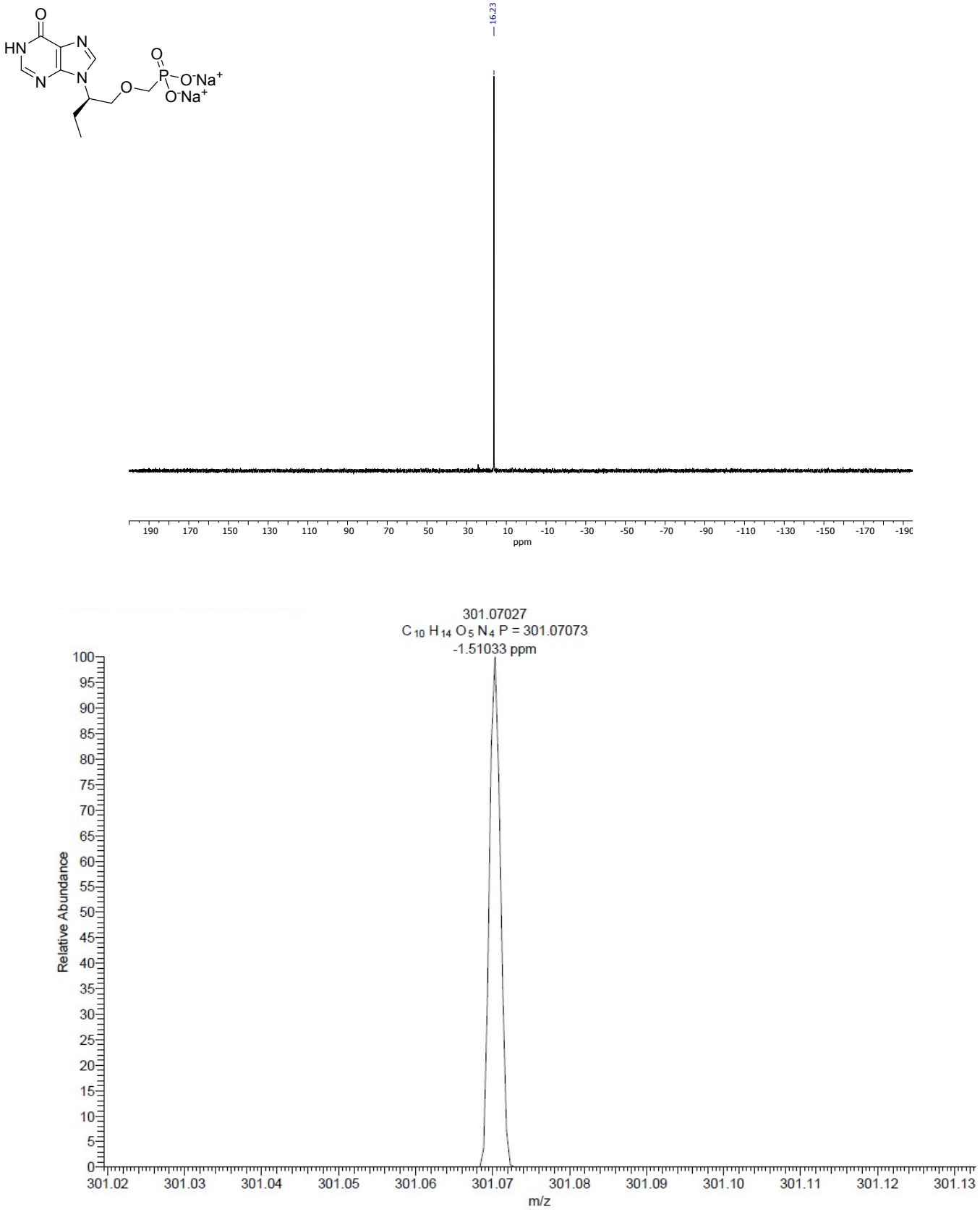


Figure S103. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**15b**.

Sodium (*S*)-((3-methyl-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*S*)-**15c**)

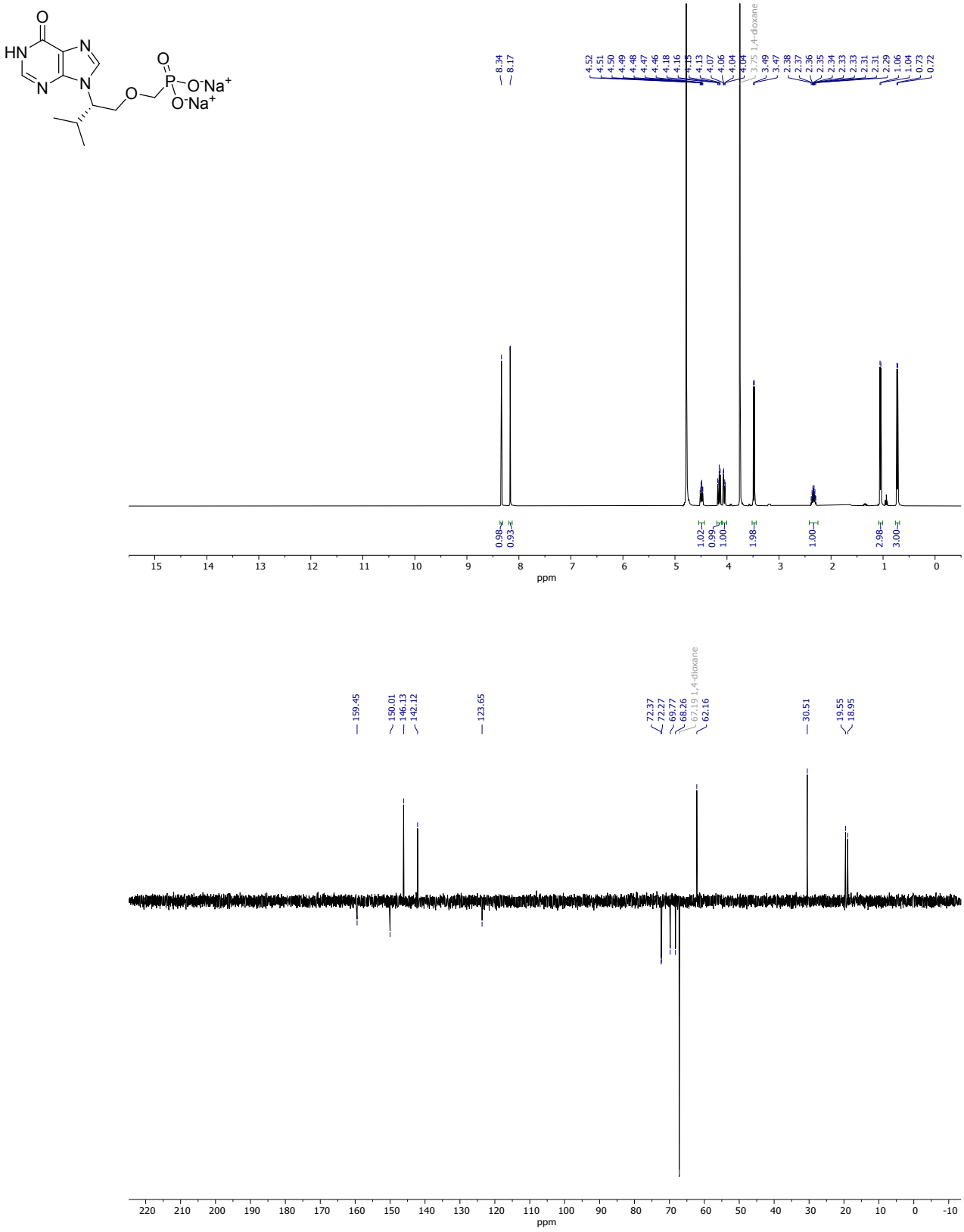


Figure S104. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*S*)-**15c** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*S*)-((3-methyl-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*S*)-**15c**)

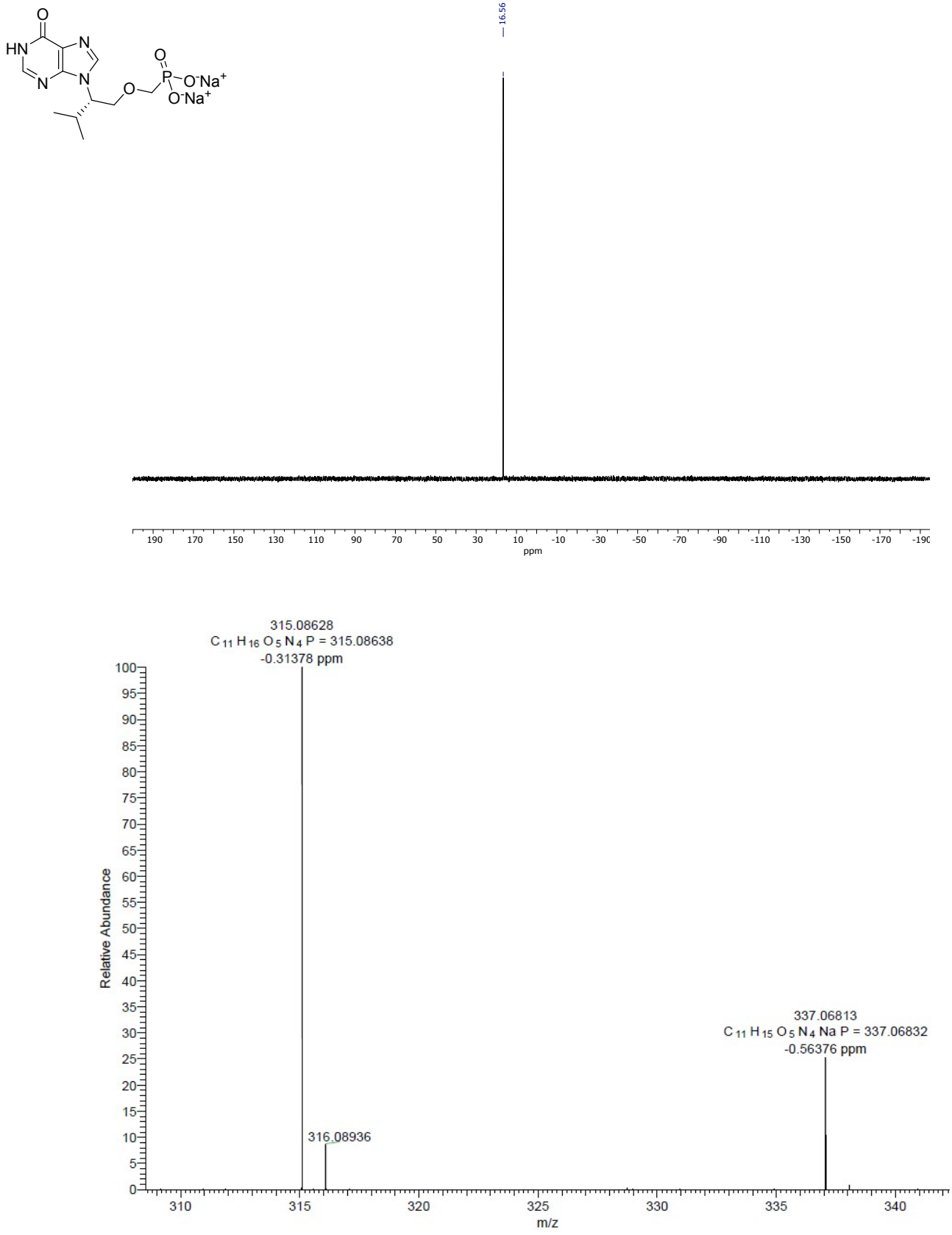


Figure S105. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*S*)-**15c**.

Sodium (*R*)-((3-methyl-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**15c**)

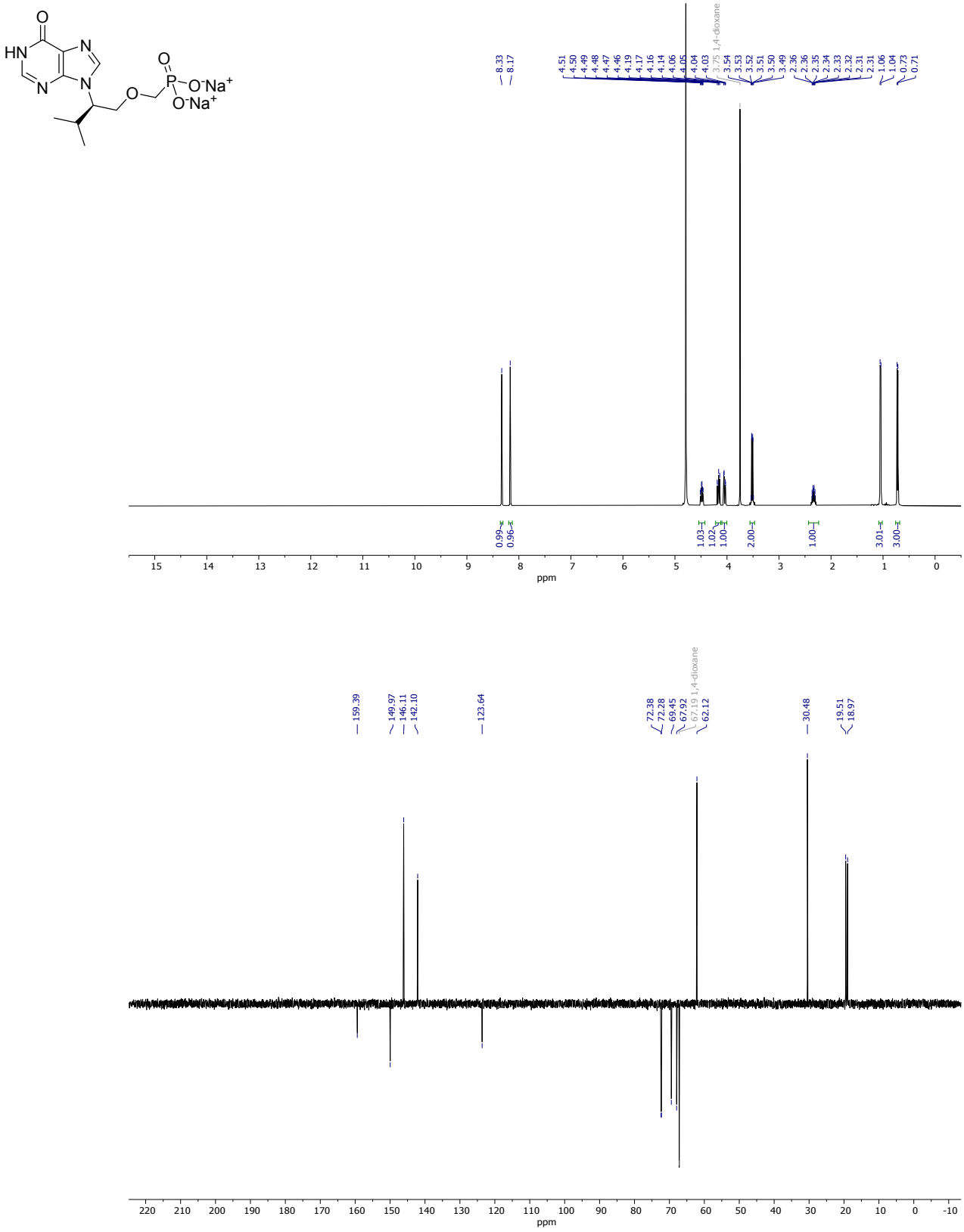


Figure S106. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**15c** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*R*)-((3-methyl-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**15c**)

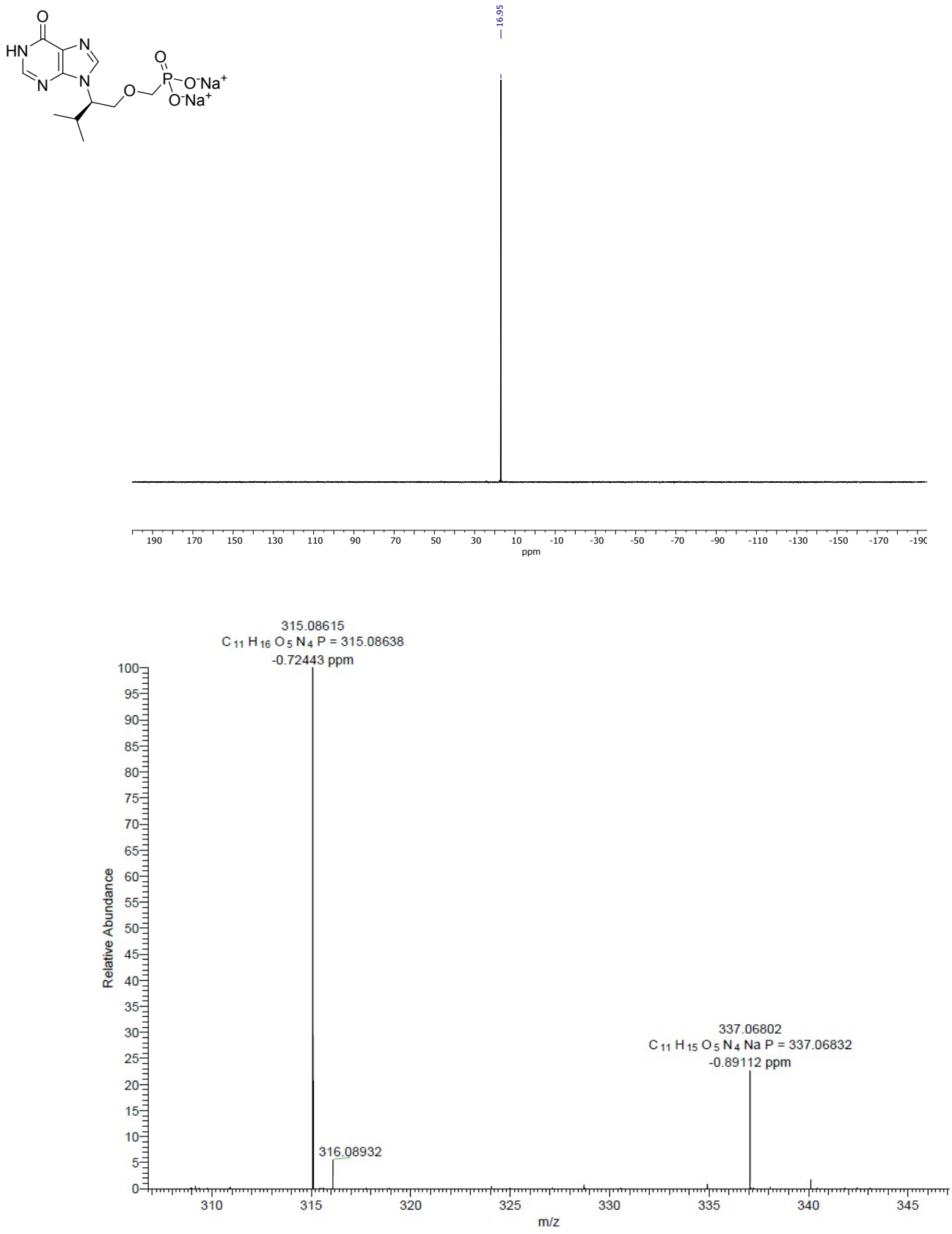


Figure S107. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**15c**.

Sodium (((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)but-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**15d**)

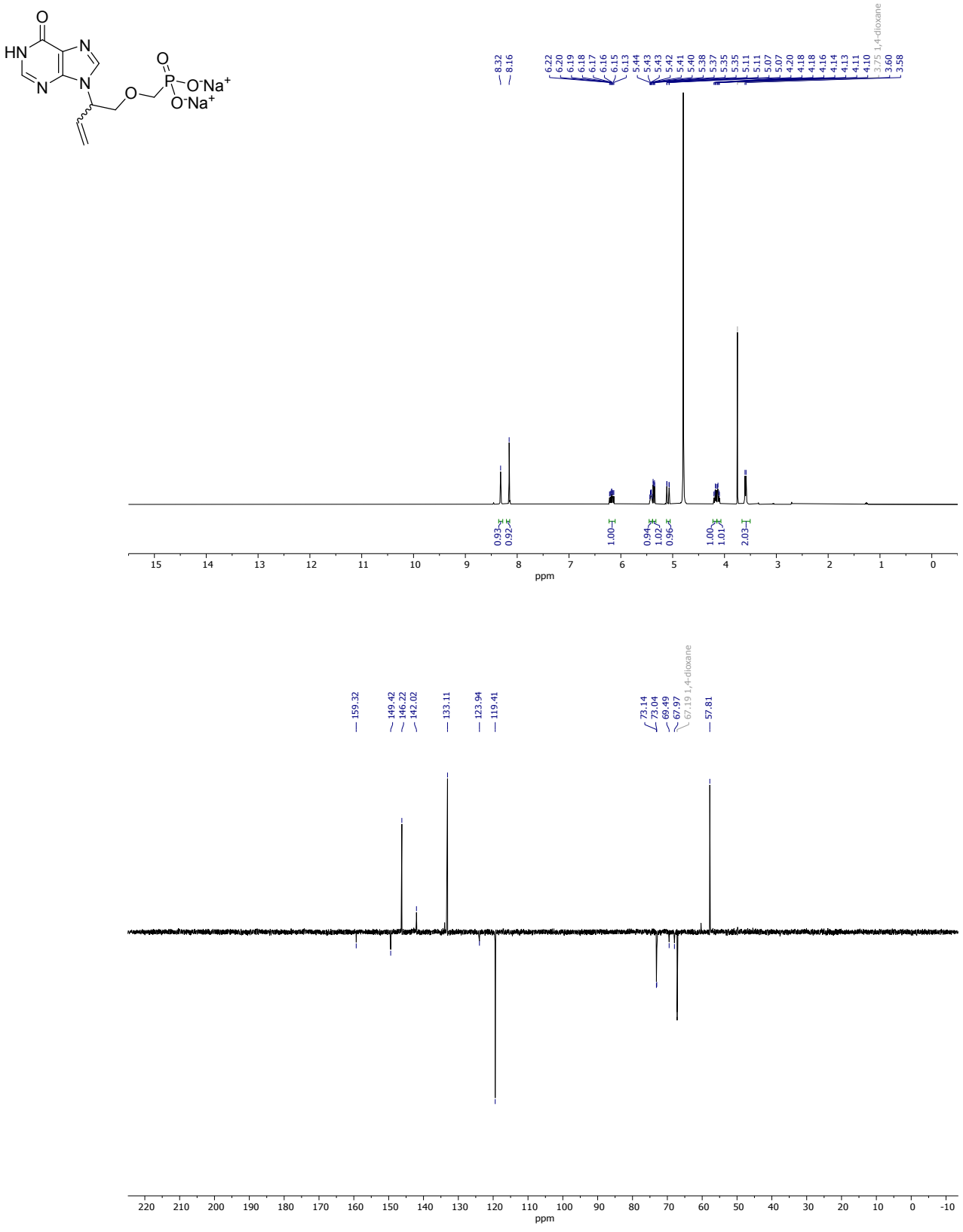


Figure S108. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**15d** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)but-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**15d**)

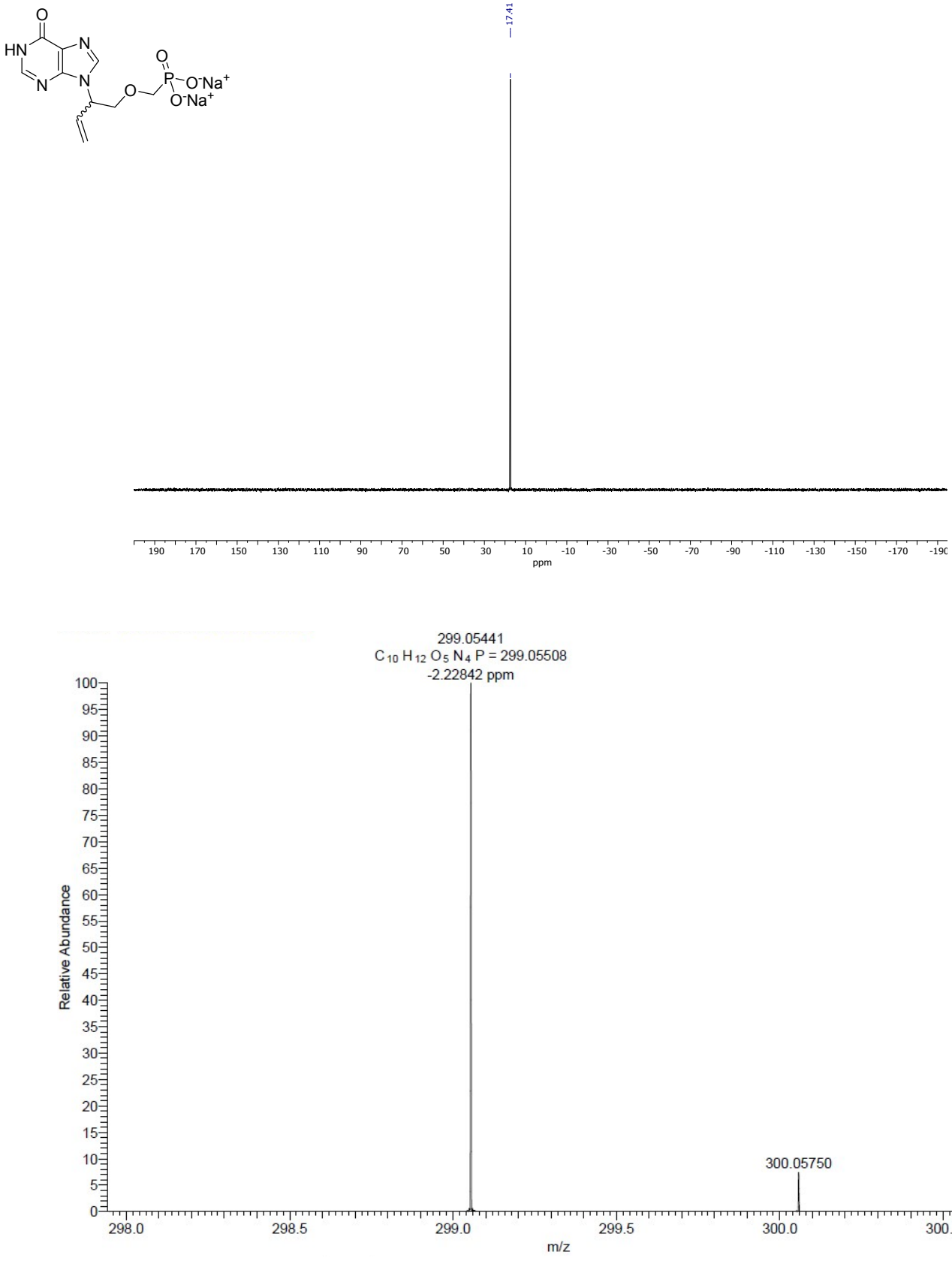


Figure S109. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**15d**.

Sodium (((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)but-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**15e**)

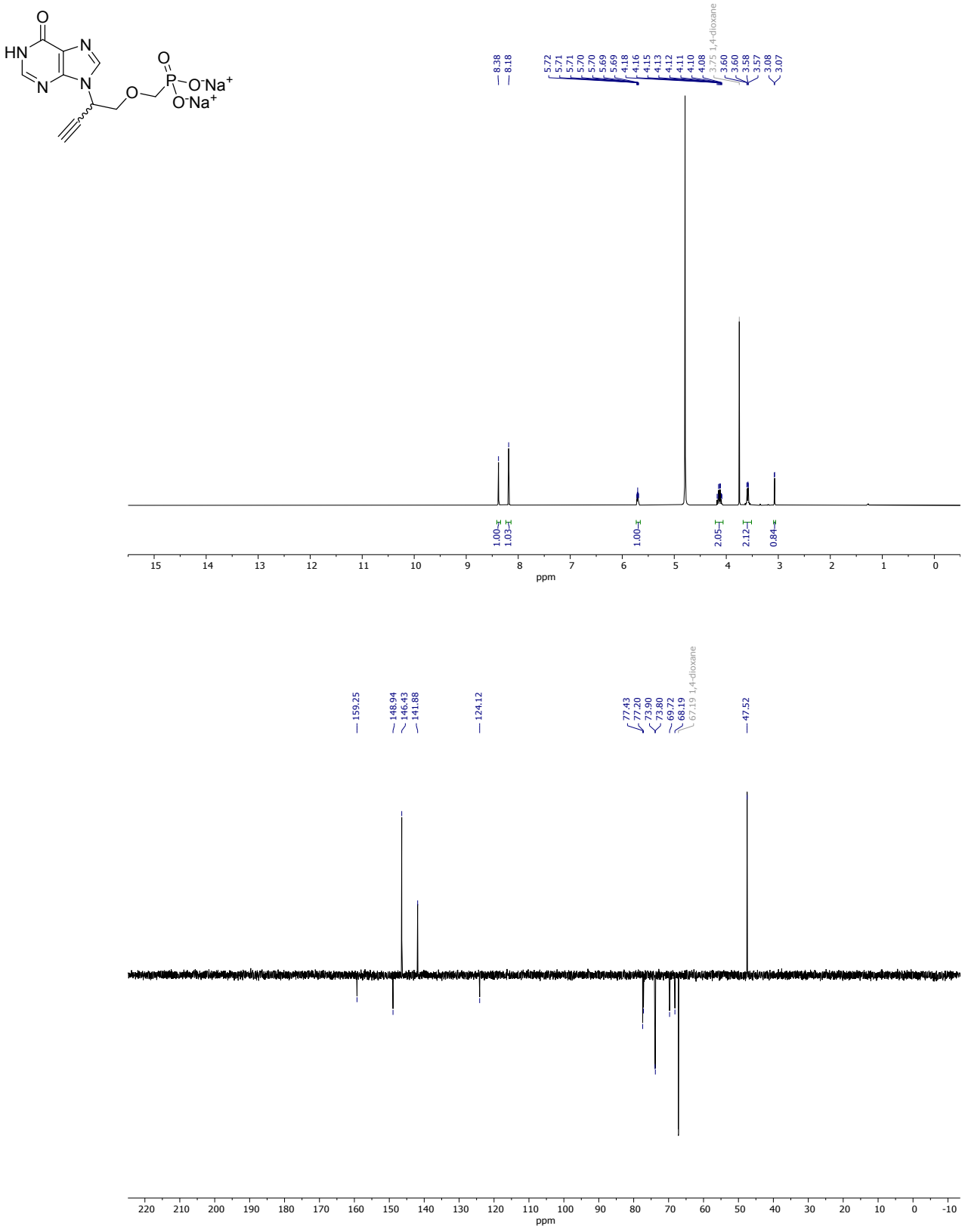


Figure S110. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**15e** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (((2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)but-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**15e**)

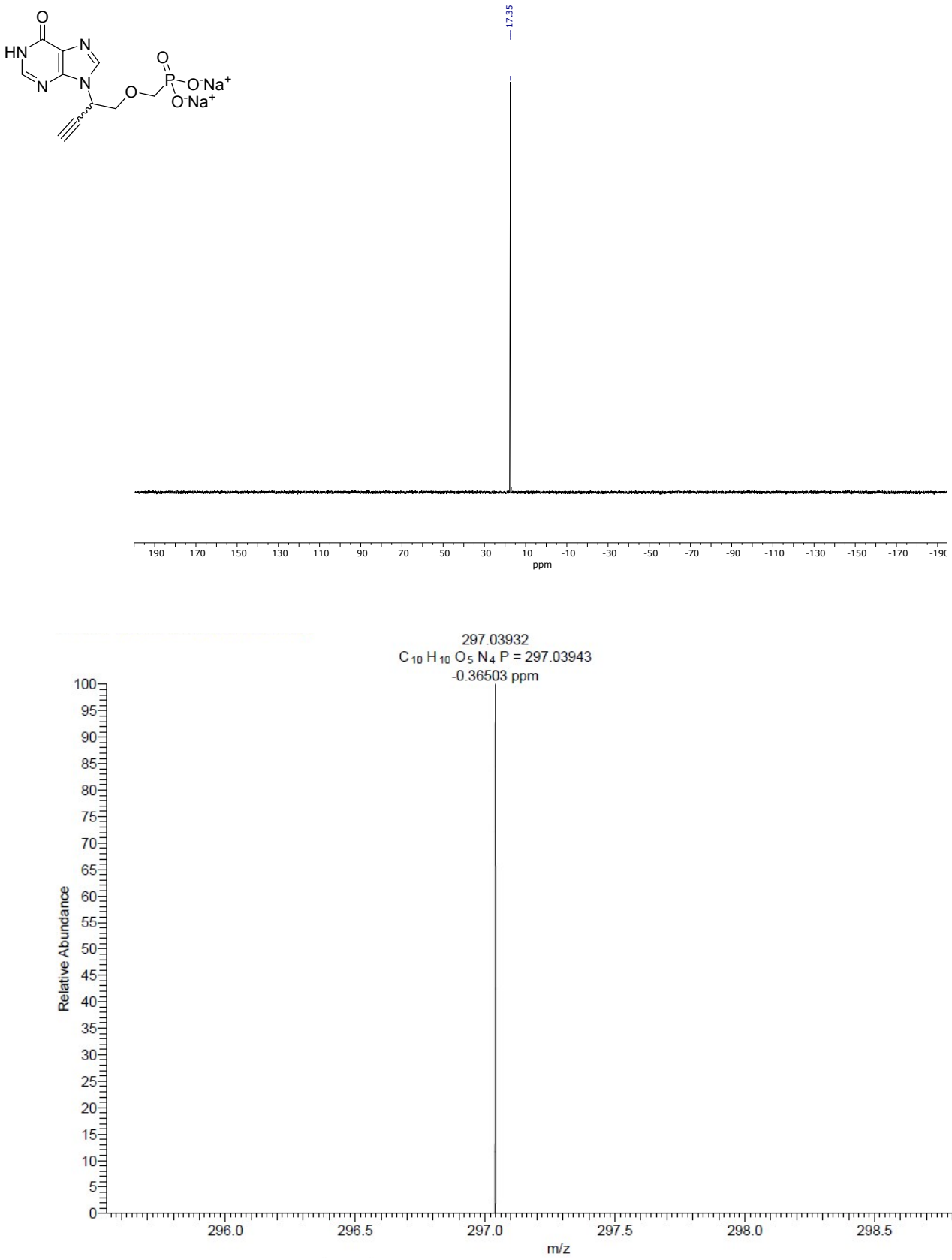


Figure S111. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**15e**.

Sodium ((2-cyclopropyl-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethoxy)methyl)phosphonate ((*RS*)-**15f**)

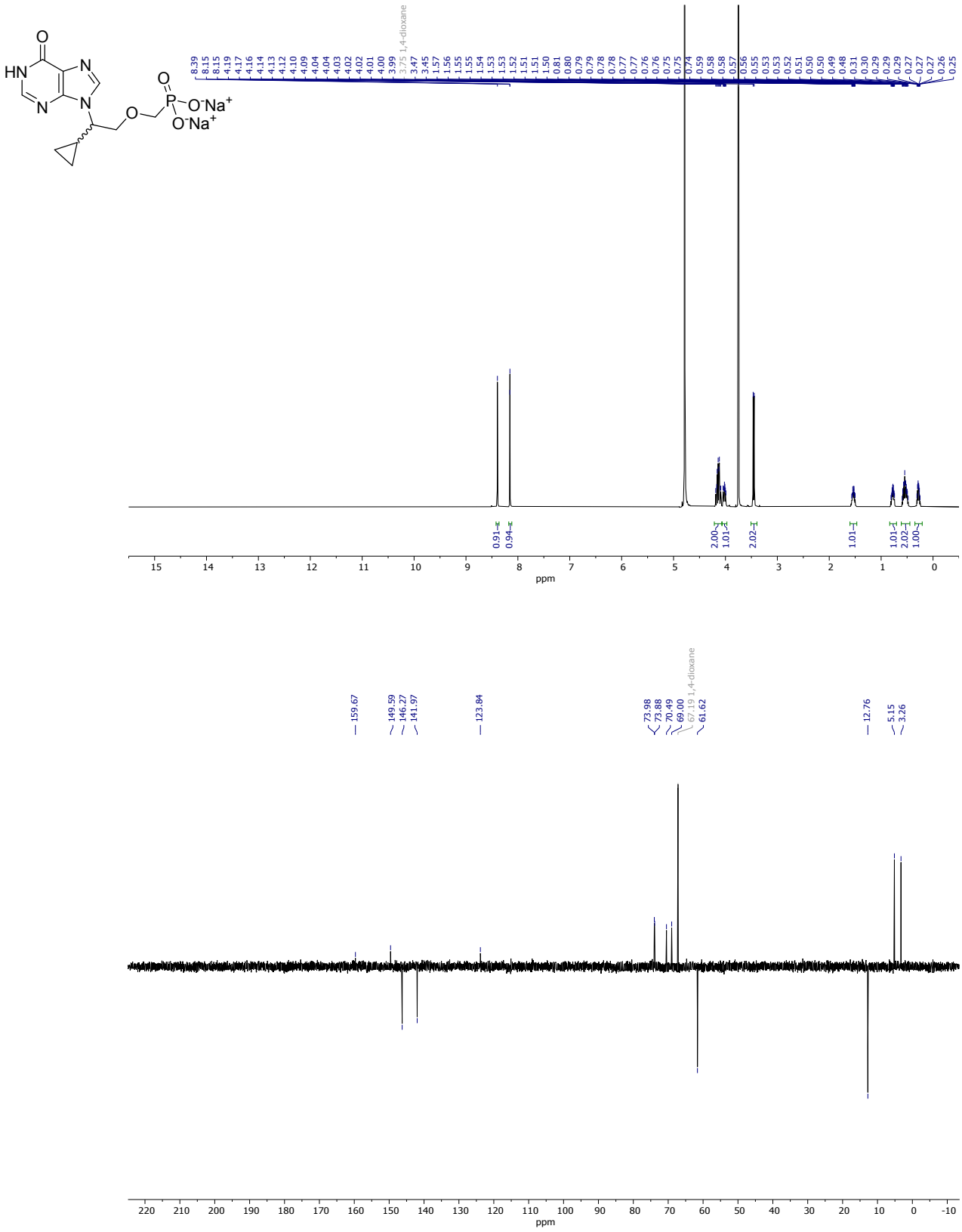


Figure S112. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**15f** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium ((2-cyclopropyl-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethoxy)methyl)phosphonate ((*RS*)-**15f**)

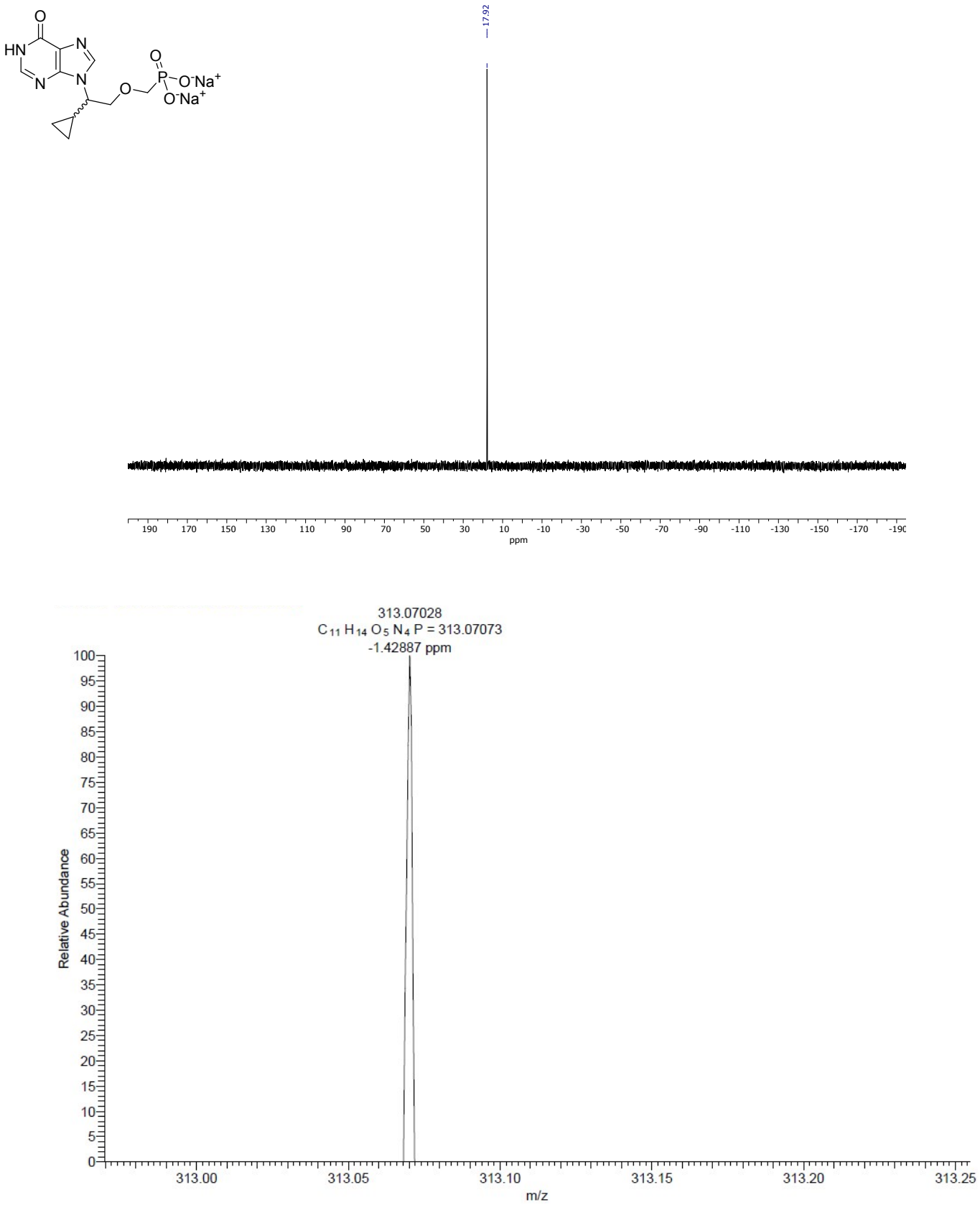


Figure S113. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**15f**.

Sodium (*R*)-((2-cyclopropyl-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethoxy)methyl)phosphonate ((*R*)-**15f**)

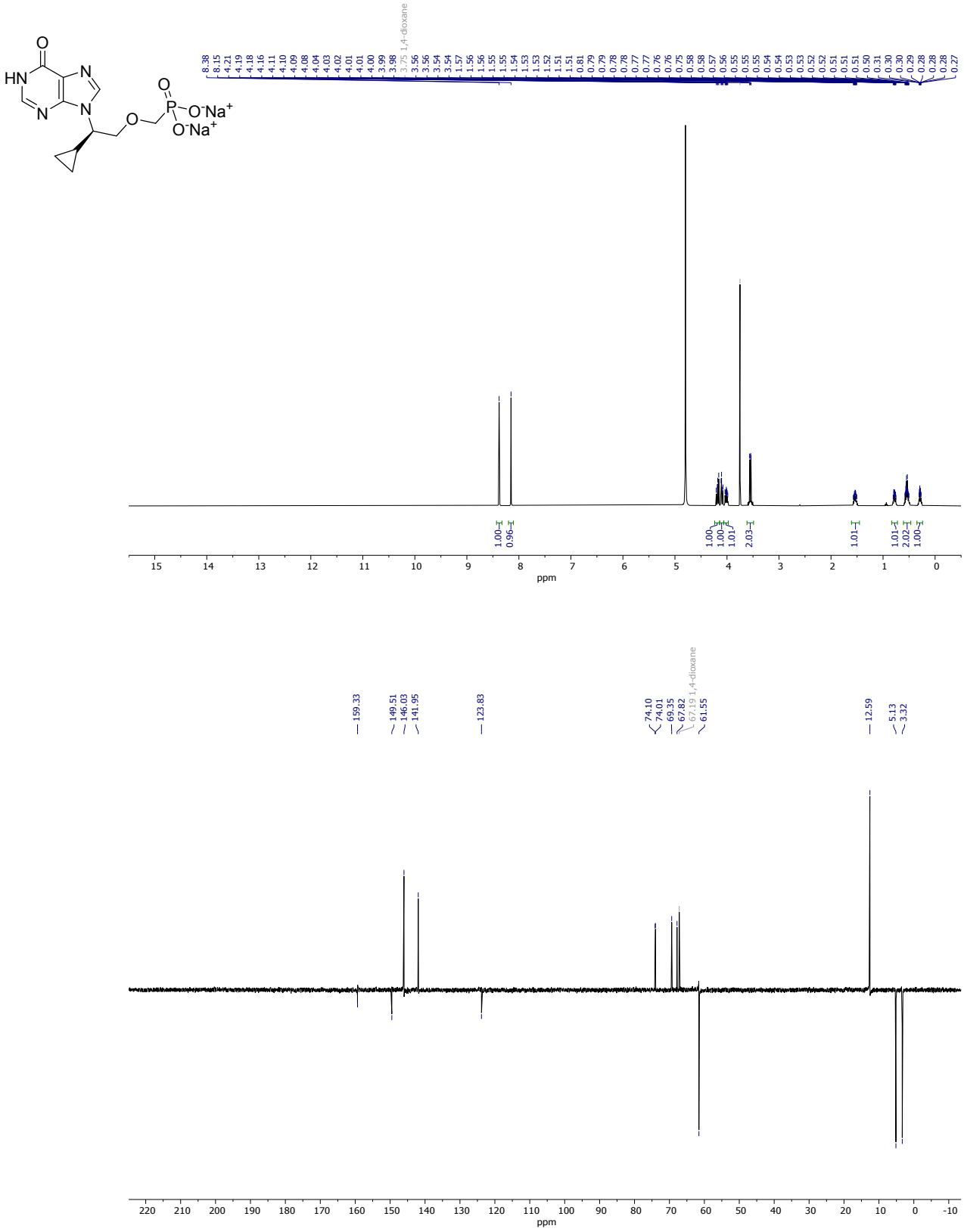


Figure S114. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**15f** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*R*)-((2-cyclopropyl-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethoxy)methyl)phosphonate ((*R*)-**15f**)

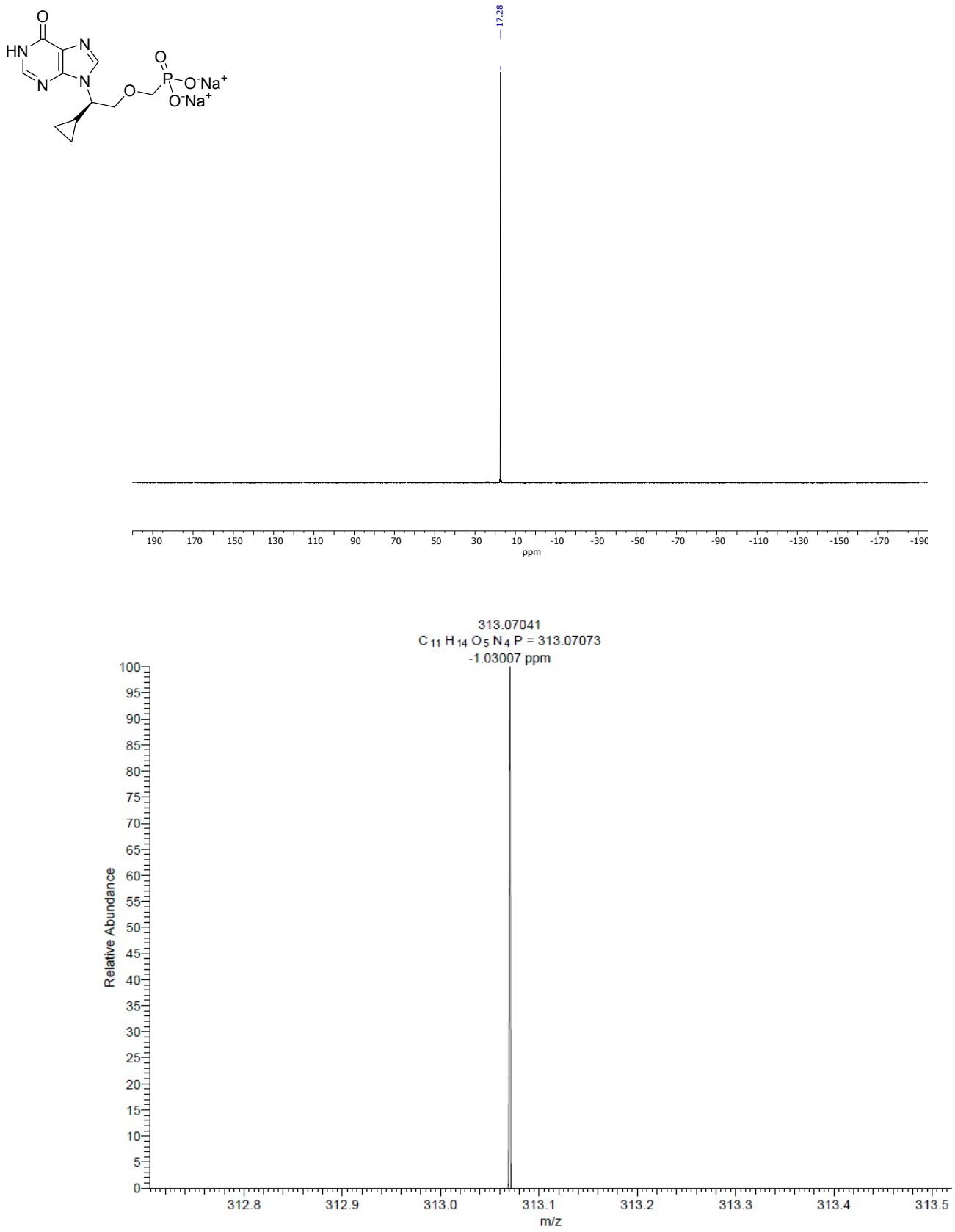


Figure S115. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**15f**.

Sodium ((3,3,3-trifluoro-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**15g**)

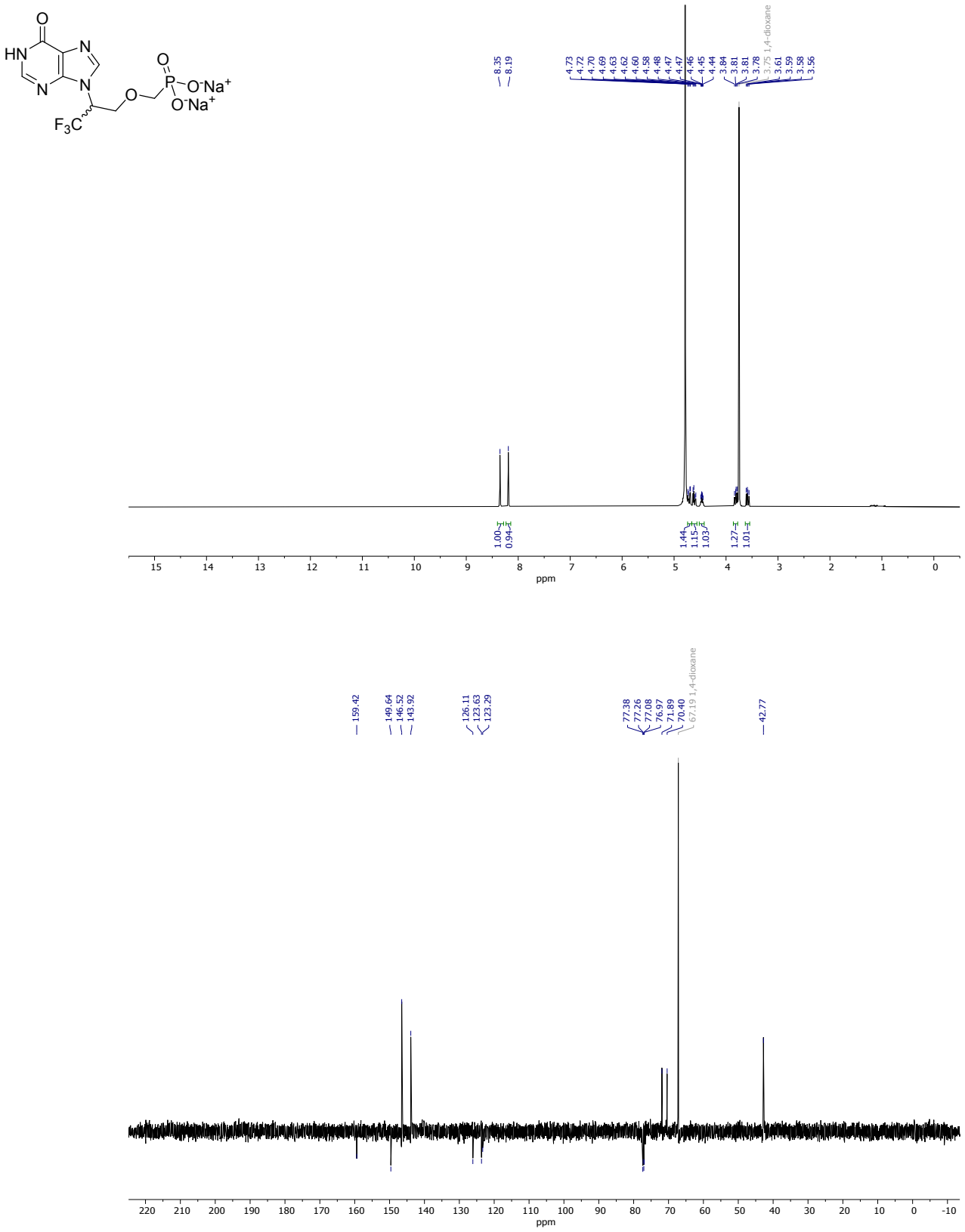


Figure S116. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**15g** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium ((3,3,3-trifluoro-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**15g**)

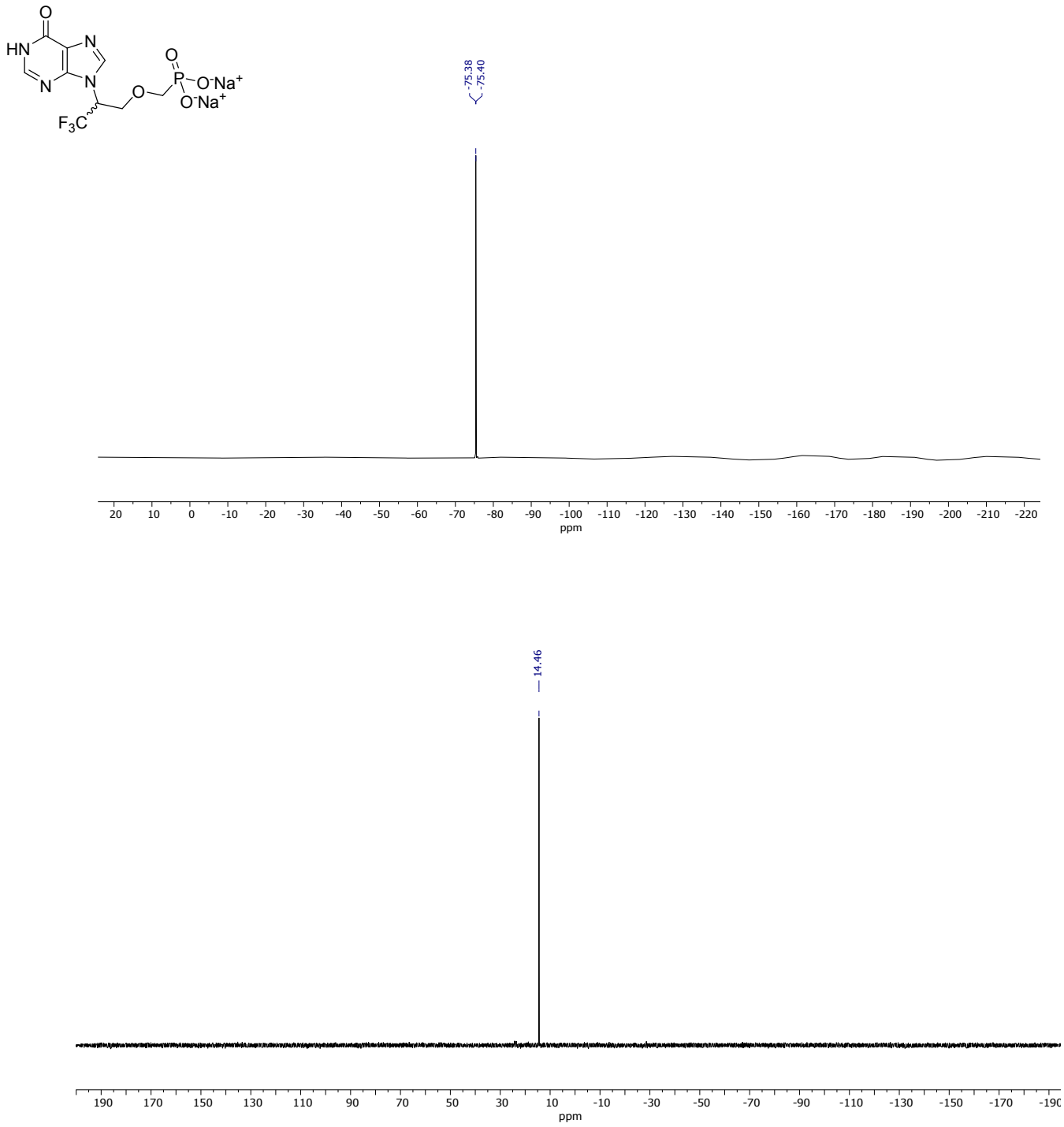


Figure S117. ^{19}F (top) and ^{31}P (bottom) NMR spectra of compound (*RS*)-**15g** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium ((3,3,3-trifluoro-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**15g**)

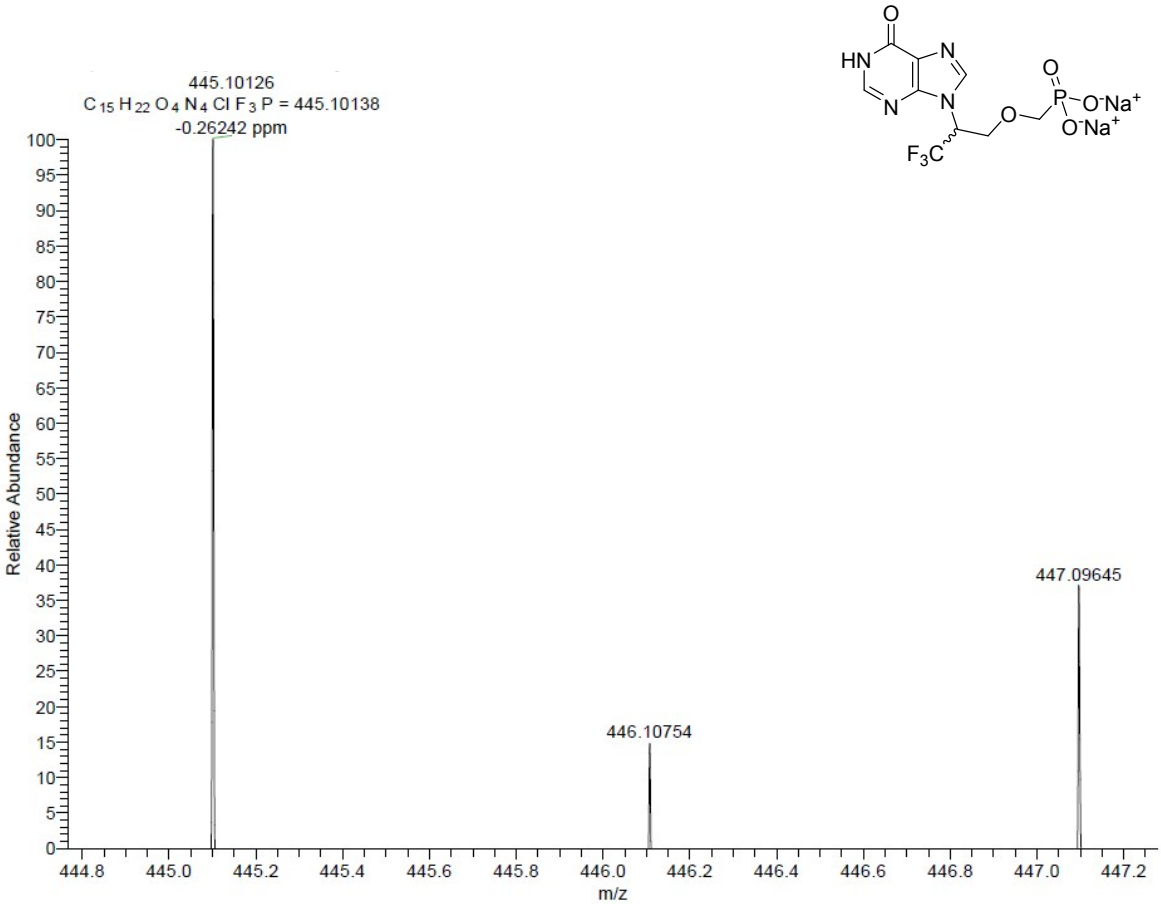


Figure S118. High resolution mass spectrum (HRMS) of compound (*RS*)-**15g**.

Sodium (*S*)-((3-(benzyloxy)-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*S*)-**15h**)

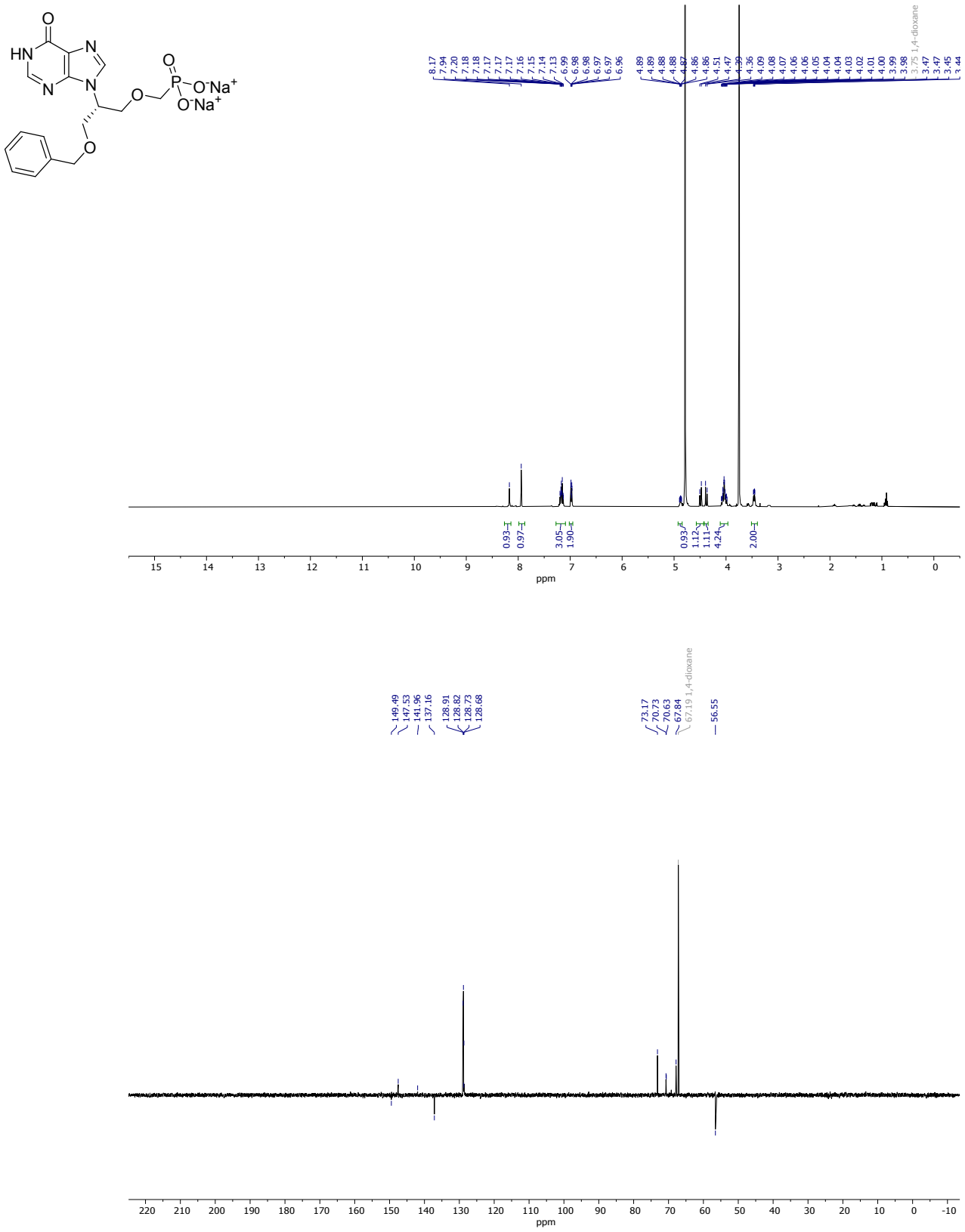


Figure S119. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*S*)-**15h** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*S*)-((3-(benzyloxy)-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*S*)-**15h**)

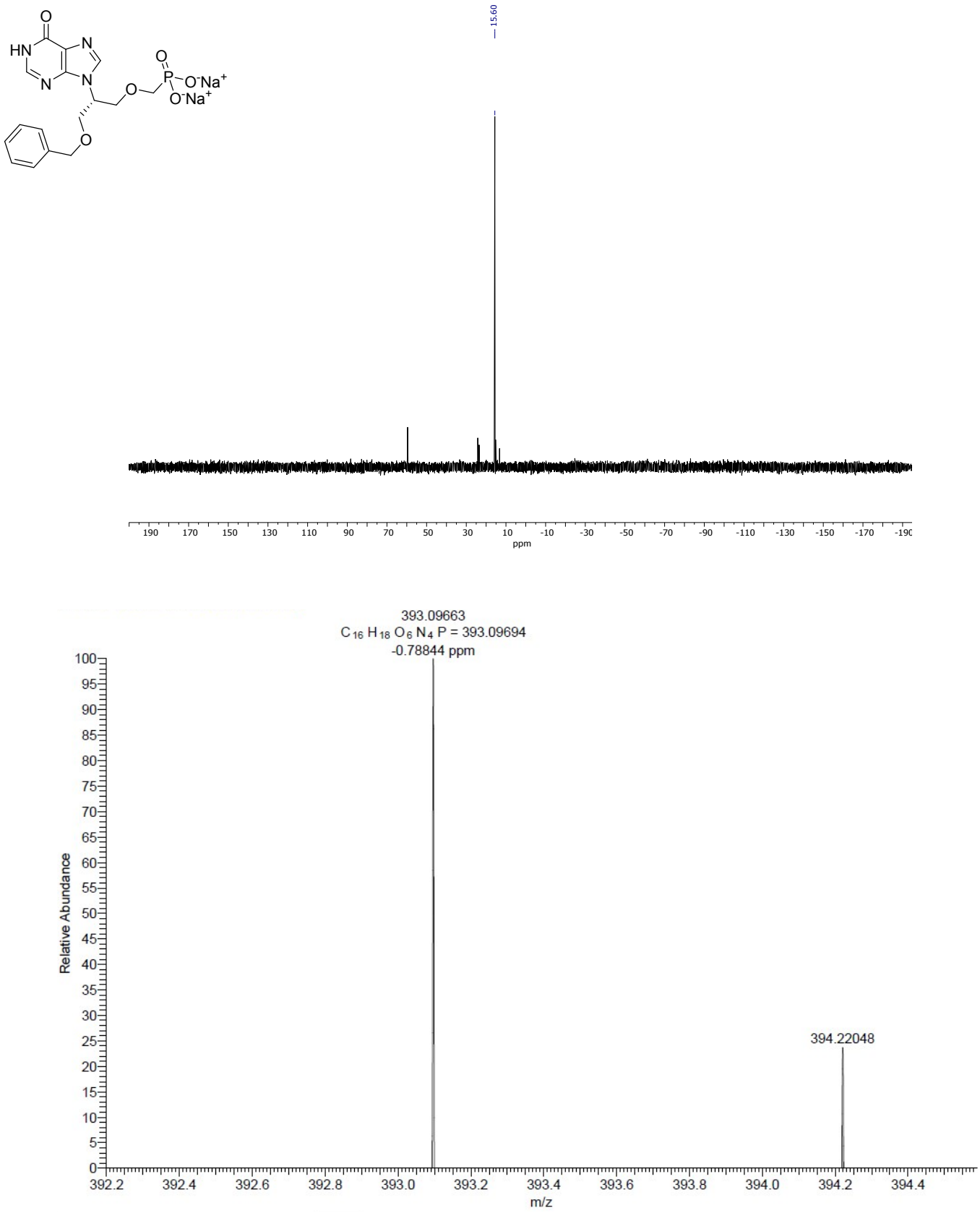


Figure S120. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*S*)-**15h**.

Sodium (*R*)-((3-(benzyloxy)-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*R*)-**15h**)

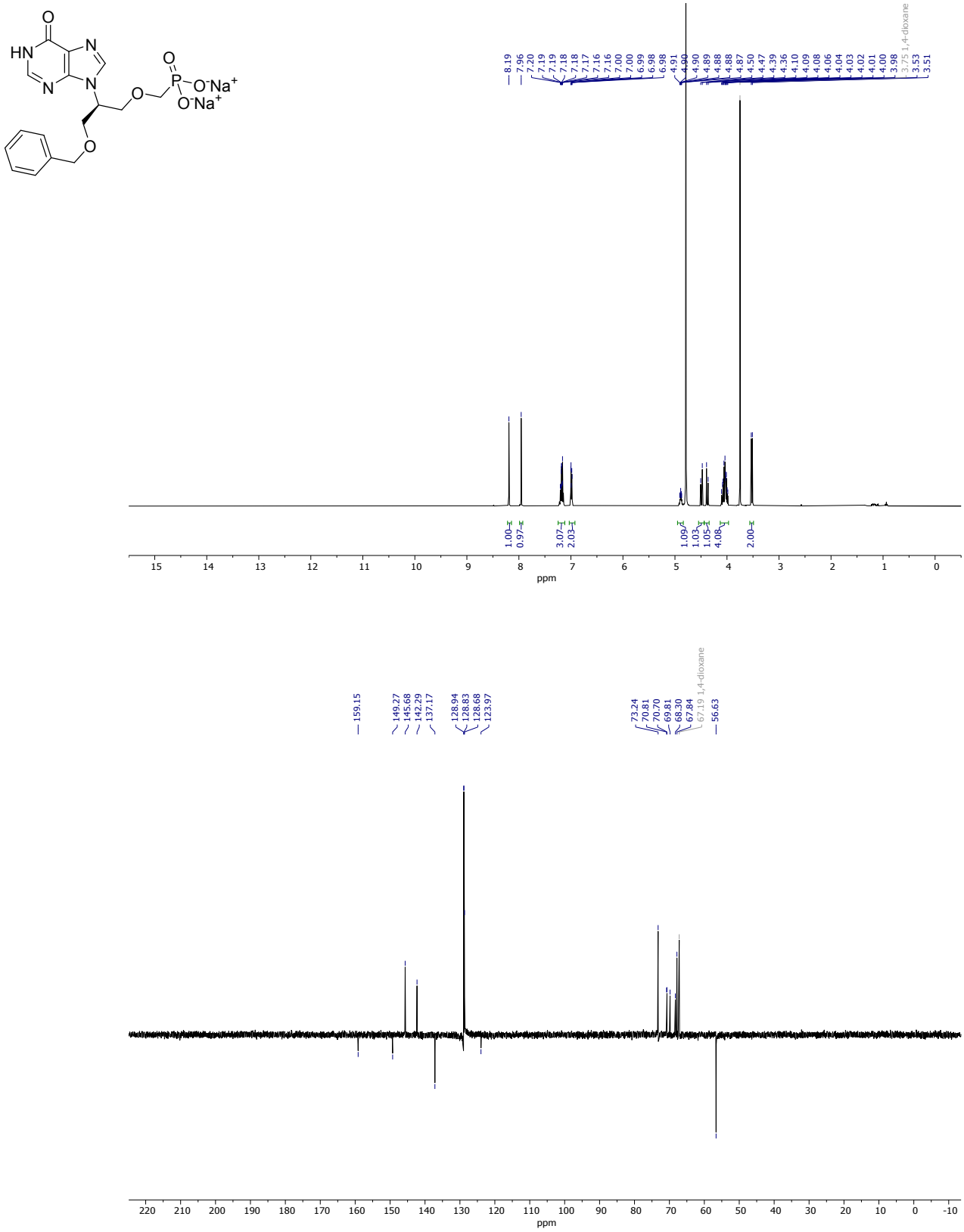


Figure S121. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**15h** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*R*)-((3-(benzyloxy)-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*R*)-**15h**)

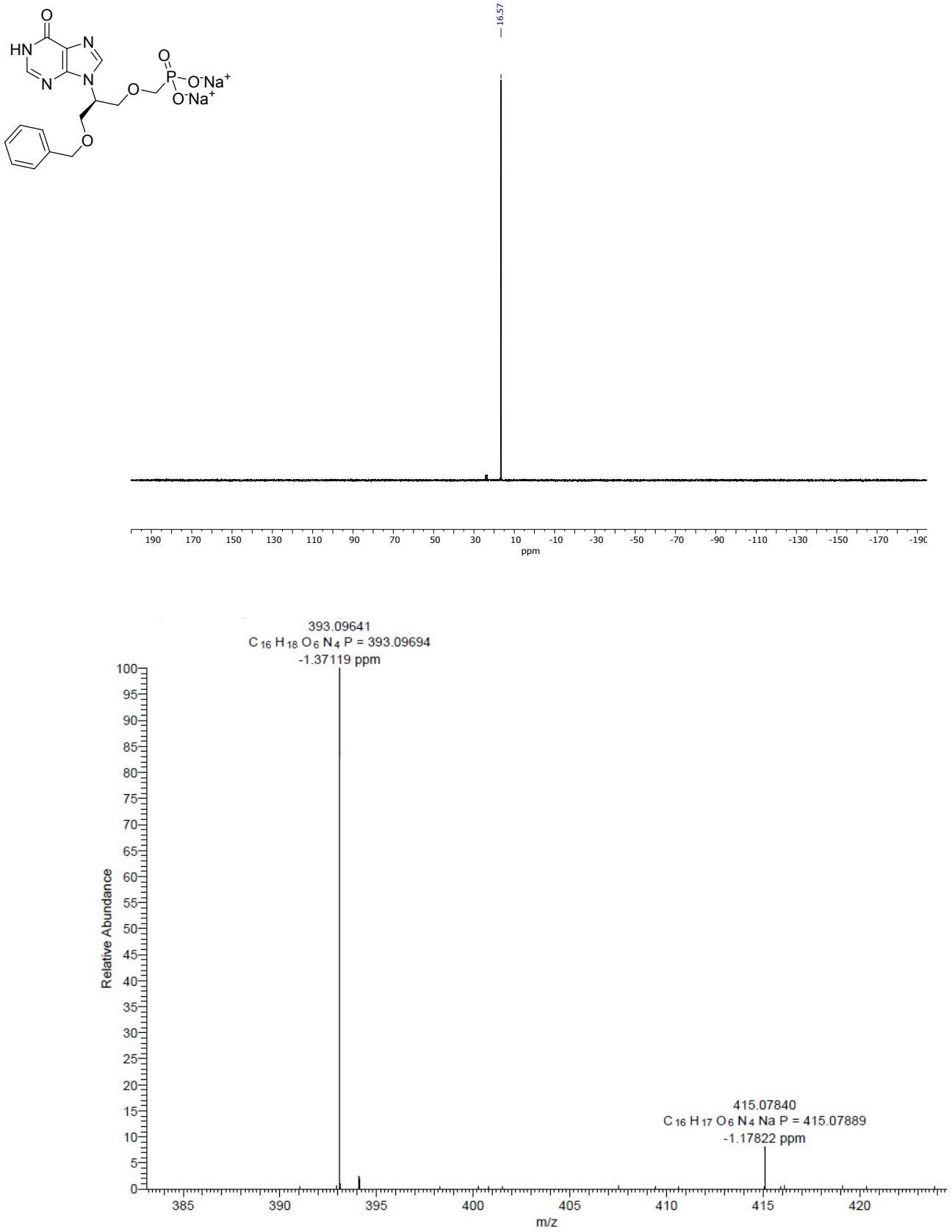


Figure S122. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**15h**.

Sodium (*R*)-((3-hydroxy-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*R*)-**15i**)

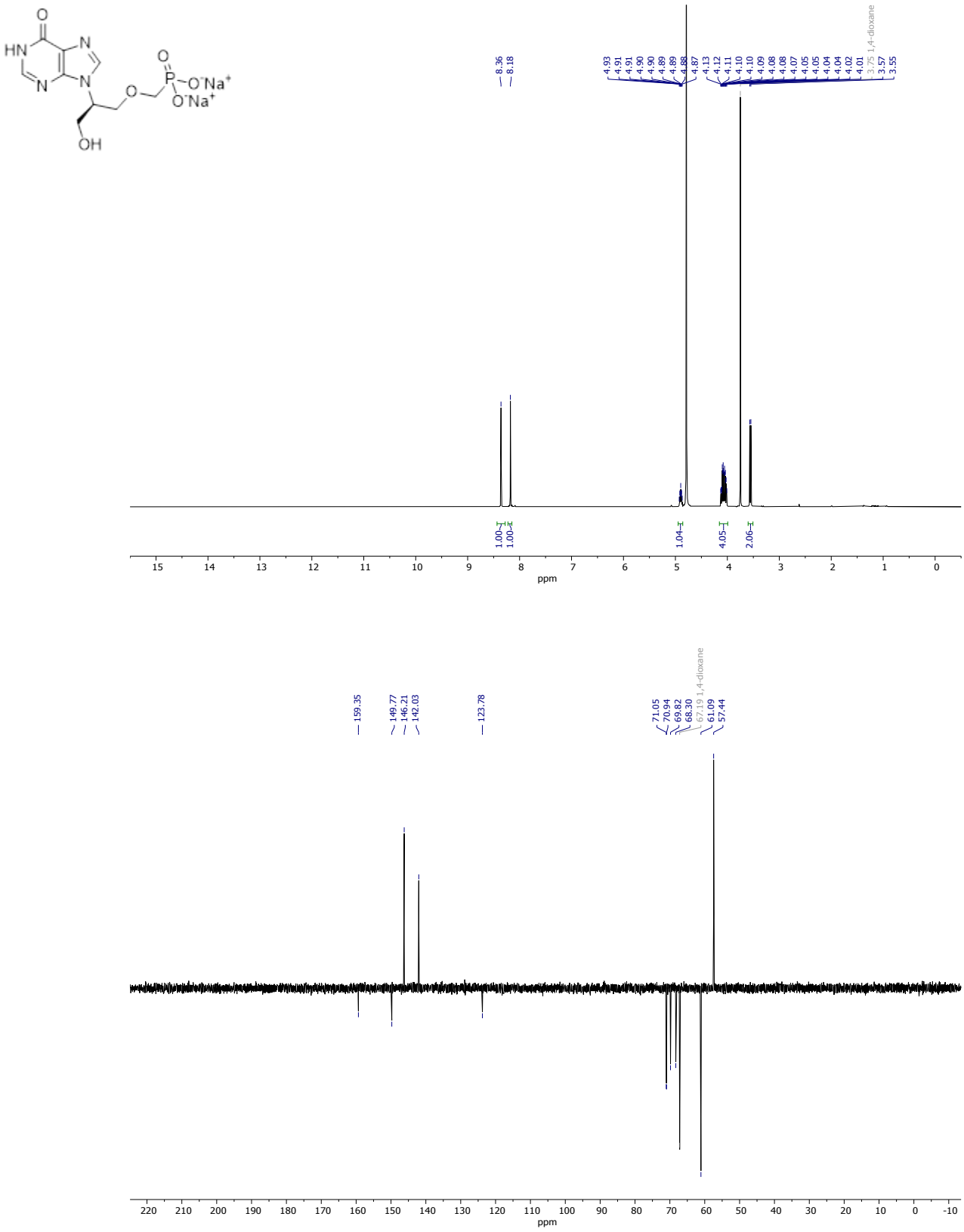


Figure S123. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**15i** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*R*)-((3-hydroxy-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*R*)-**15i**)

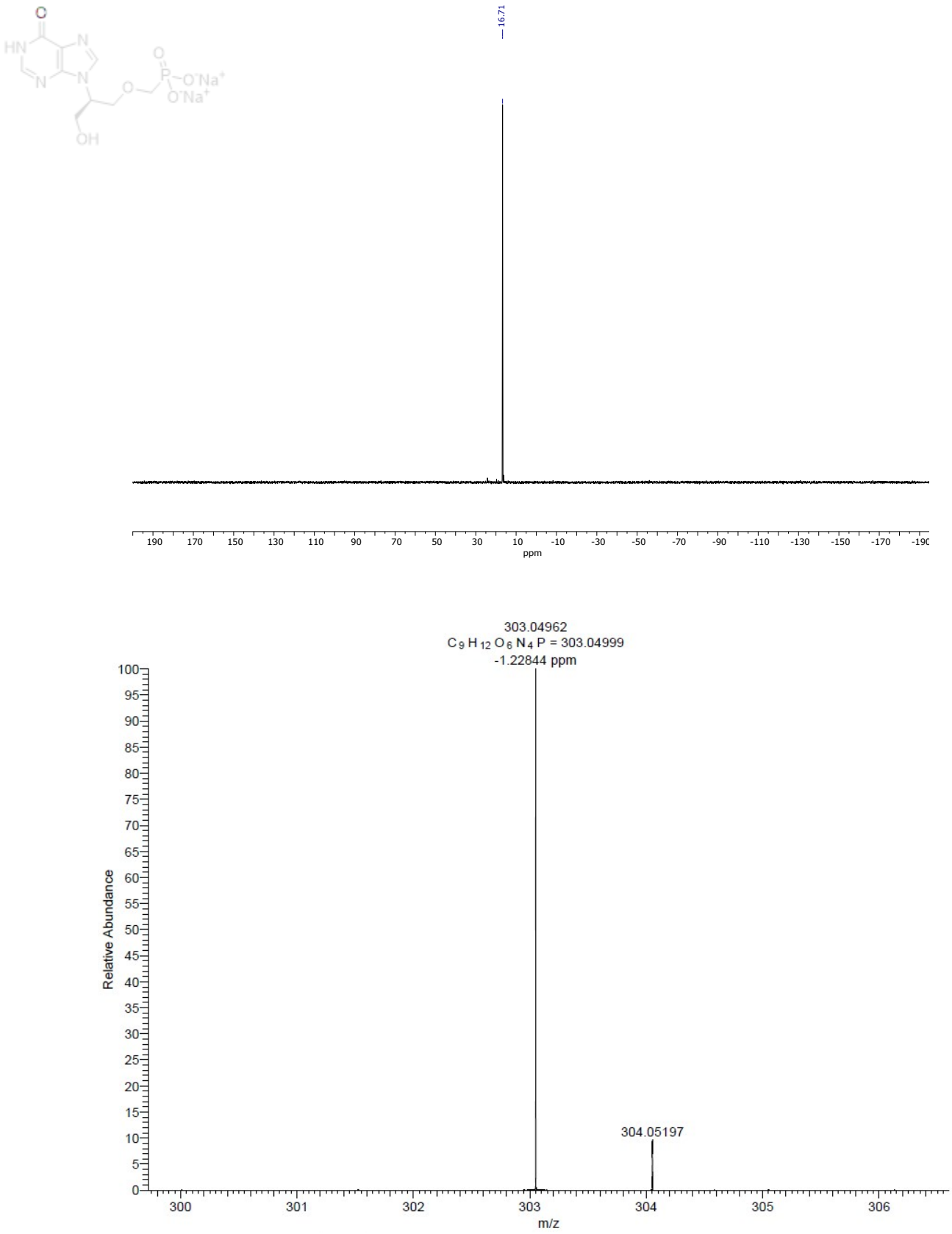


Figure S124. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**15i**.

Sodium ((2-methoxy-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethoxy)methyl)phosphonate ((*RS*)-**15j**)

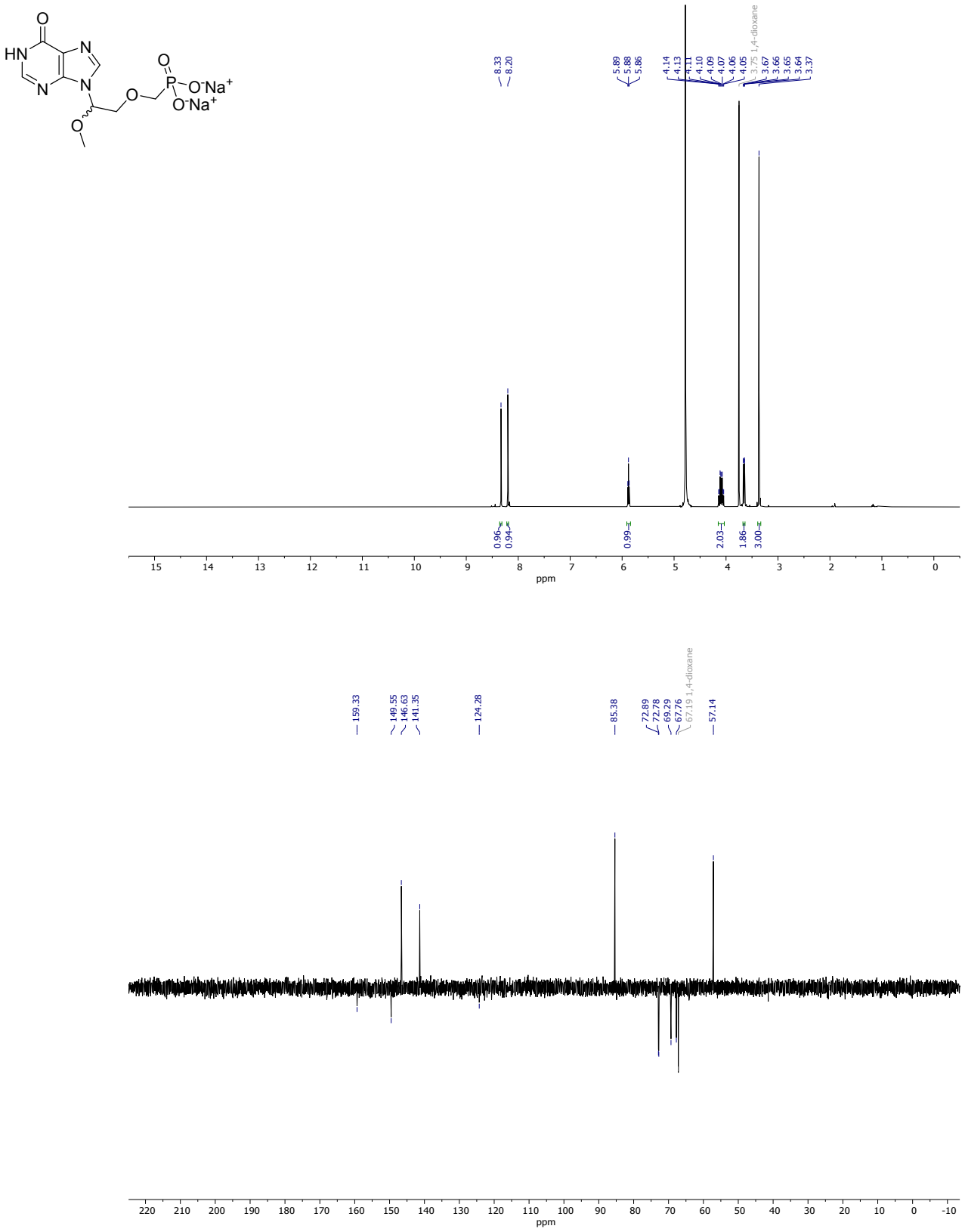


Figure S125. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**15j** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium ((2-methoxy-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethoxy)methyl)phosphonate ((*RS*)-**15j**)

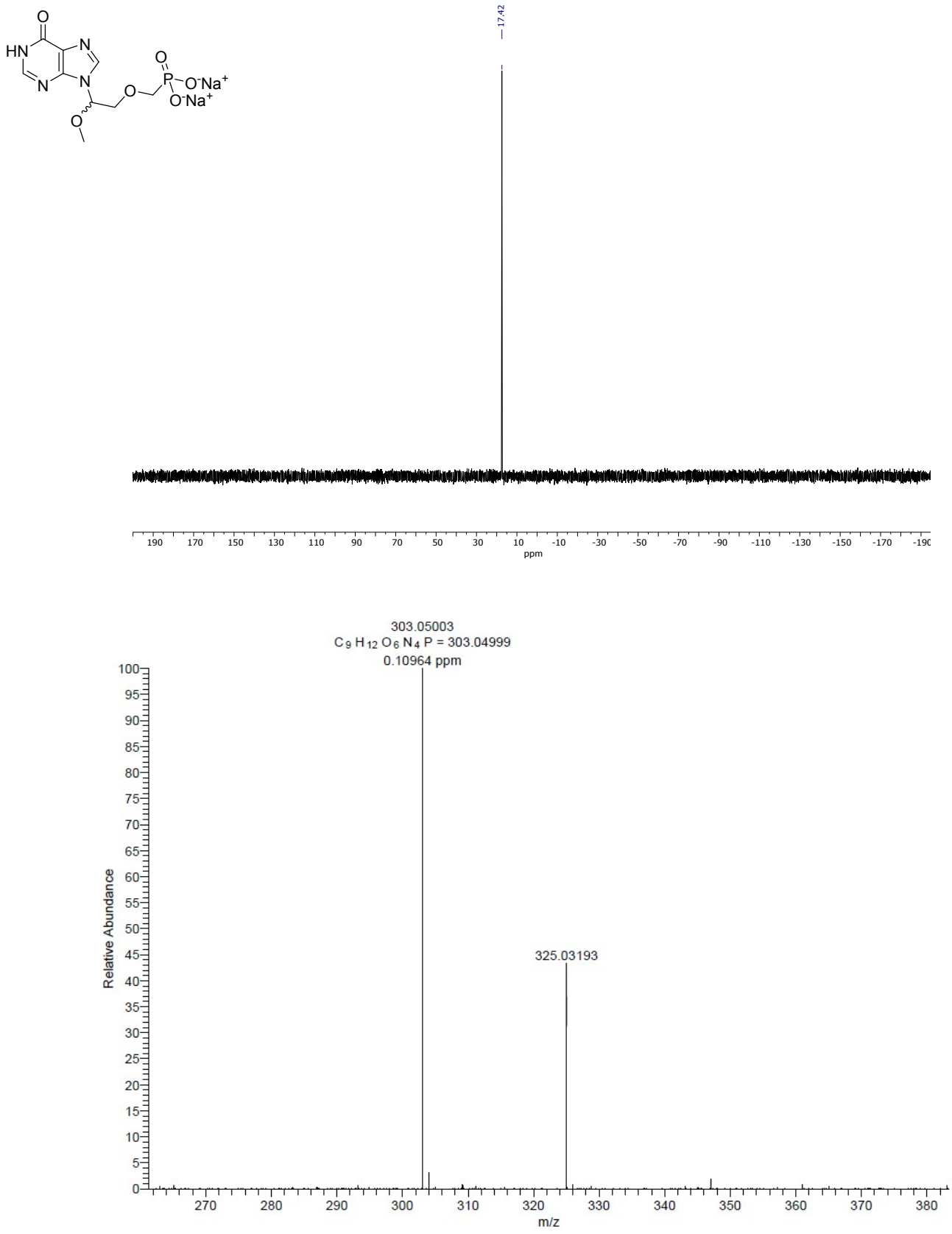


Figure S126. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**15j**.

Sodium ((2-ethoxy-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethoxy)methyl)phosphonate ((*RS*)-**15k**)

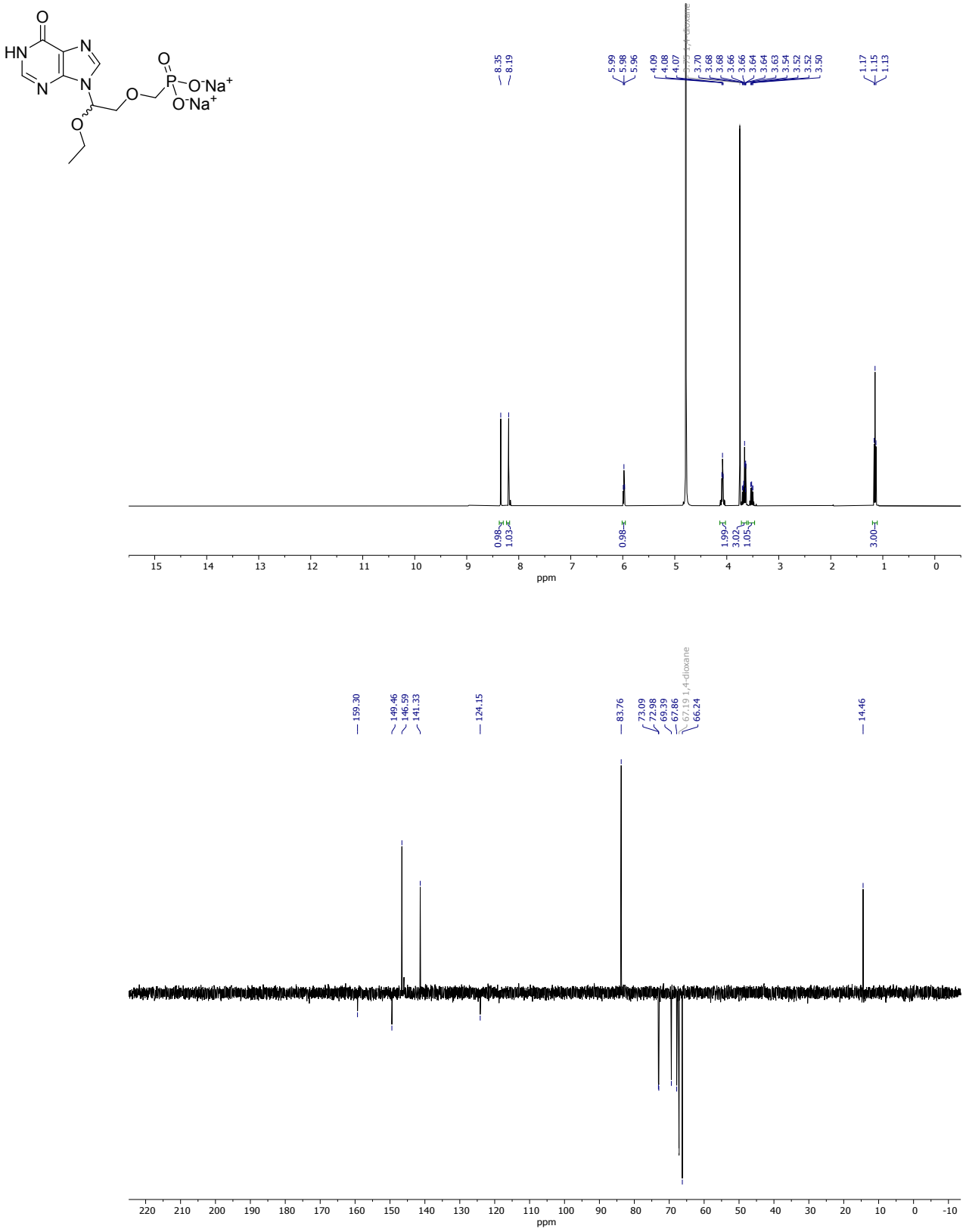


Figure S127. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**15k** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium ((2-ethoxy-2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethoxy)methyl)phosphonate ((*RS*)-**15k**)

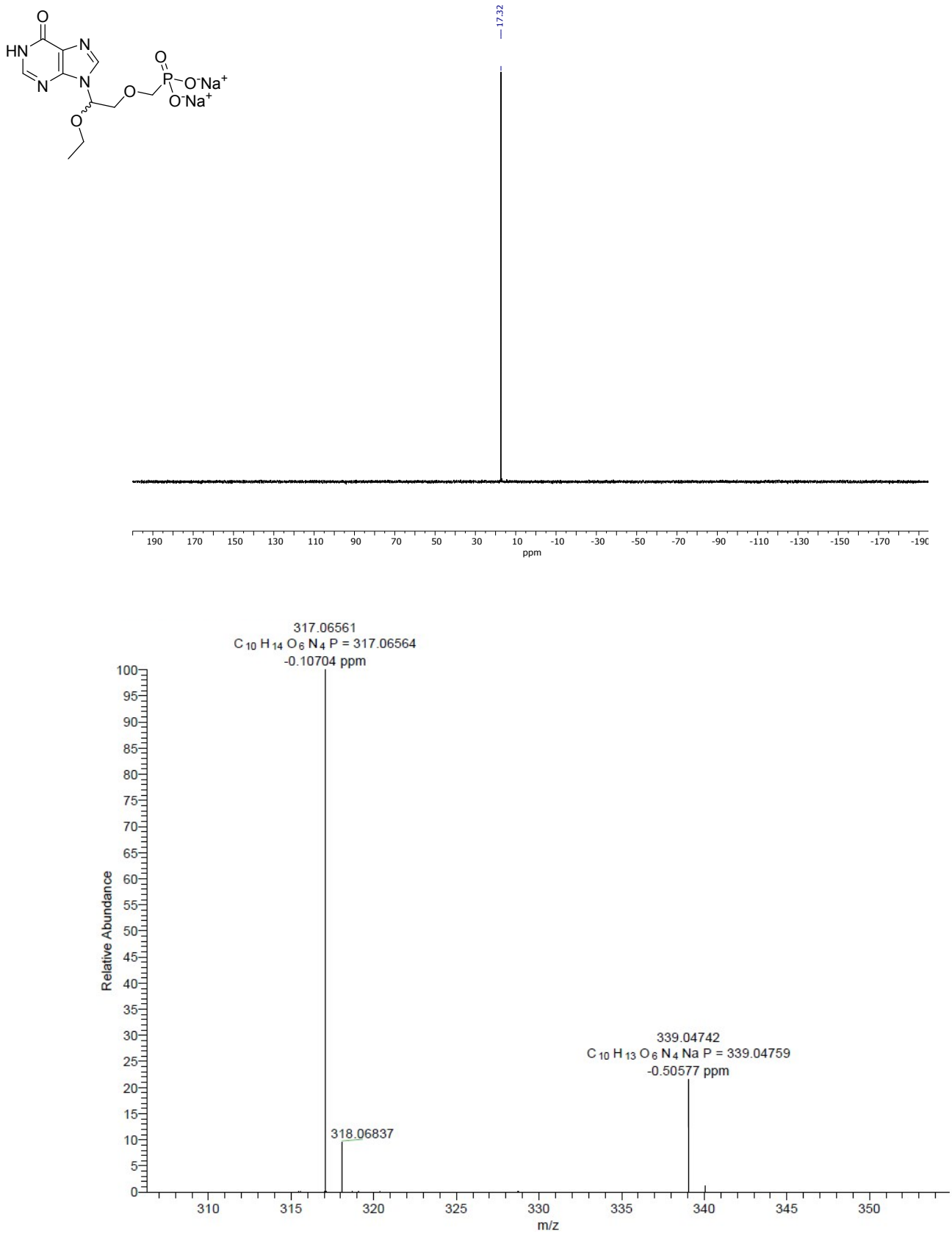


Figure S128. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**15k**.

Sodium ((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**16a**)

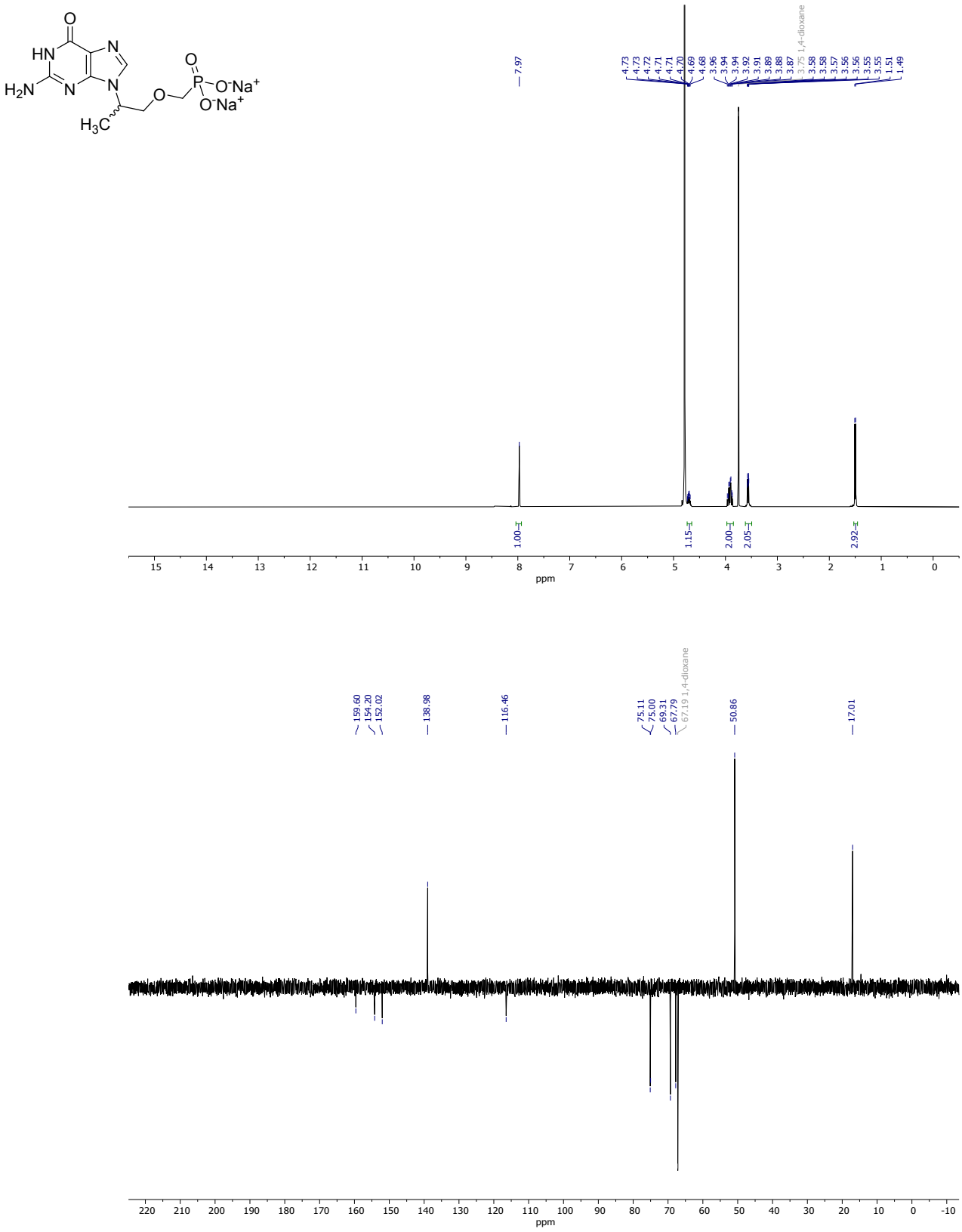


Figure S129. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**16a** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium ((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**16a**)

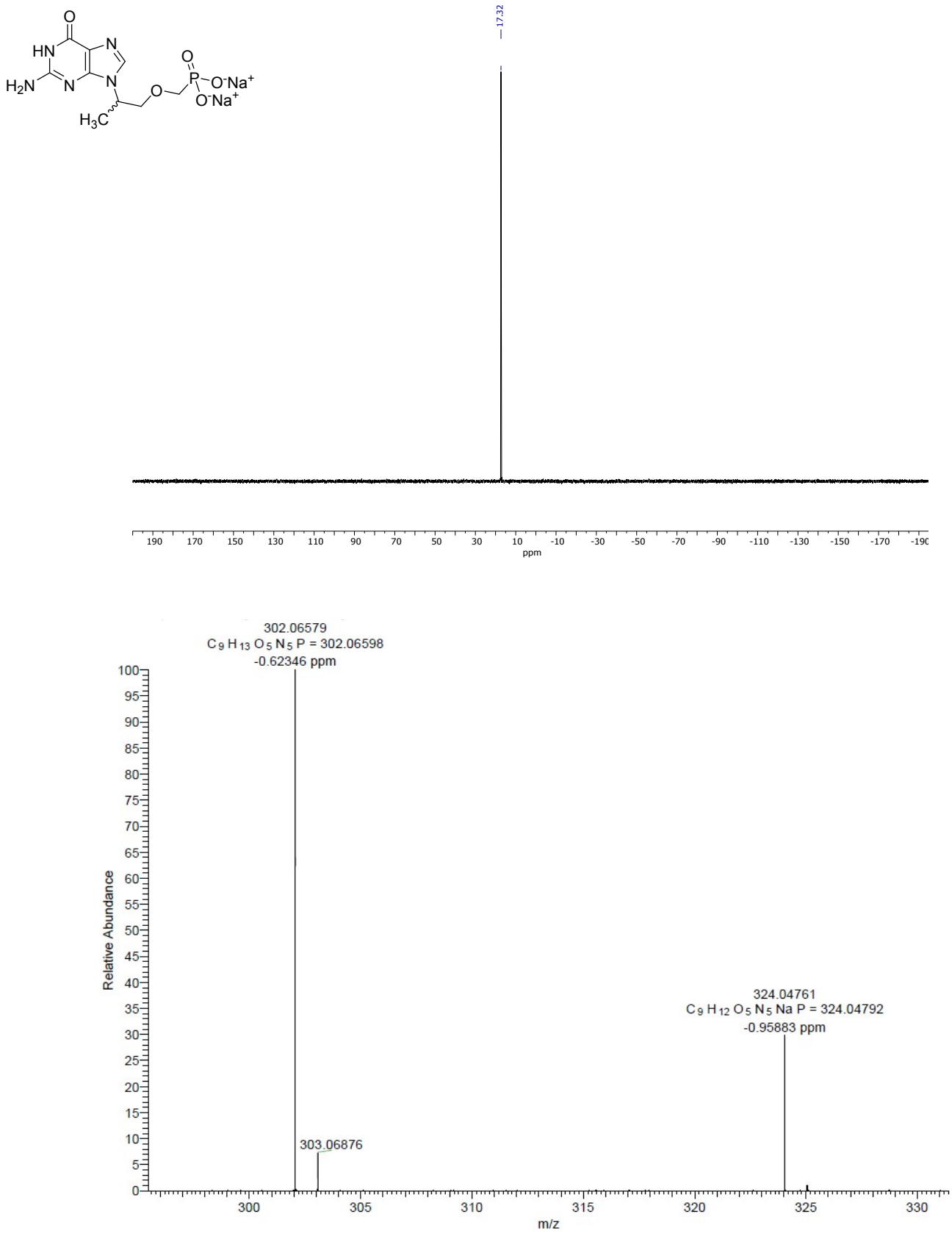


Figure S130. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**16a**.

Sodium ((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*RS*)-**16b**)

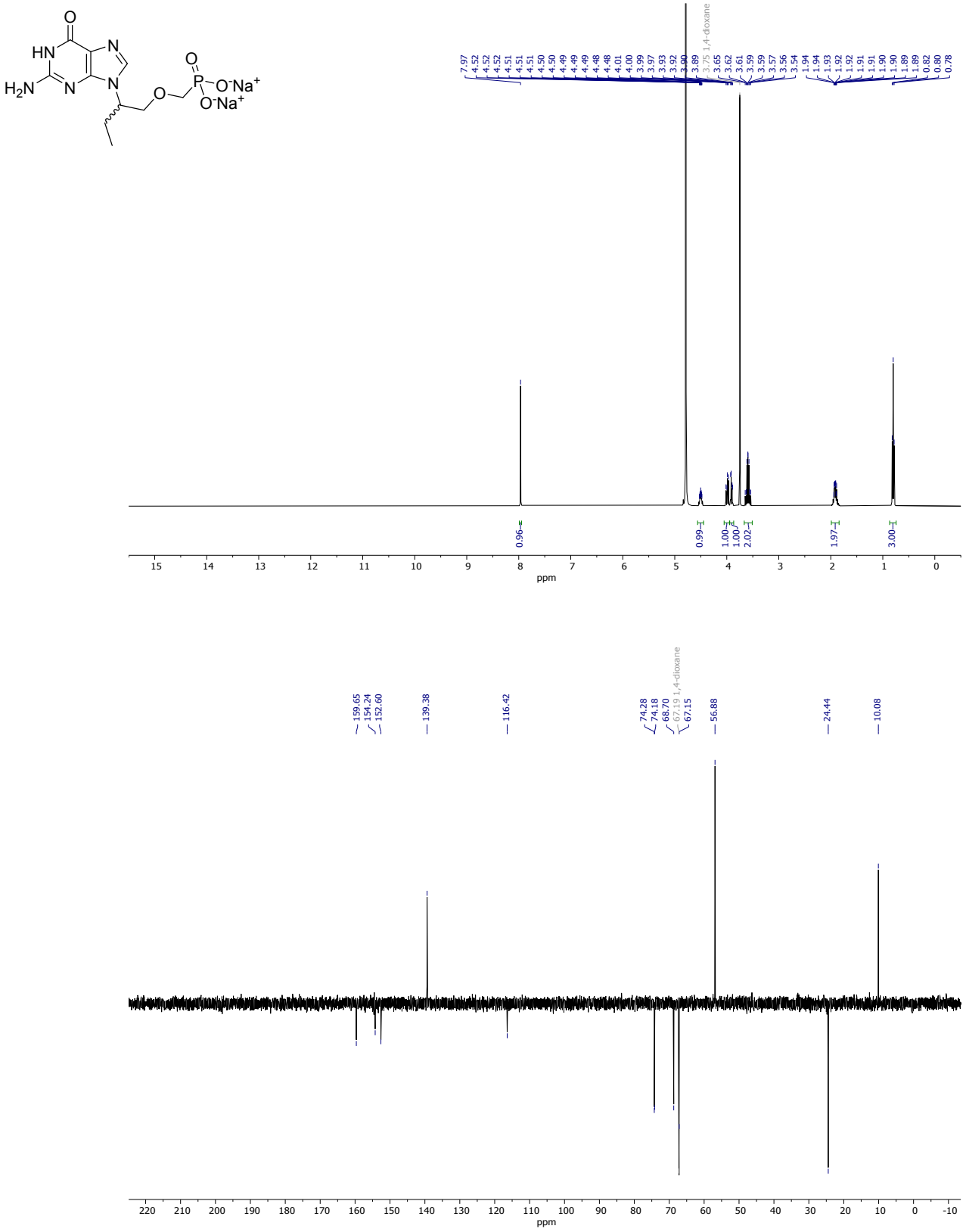


Figure S131. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**16b** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium ((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*RS*)-**16b**)

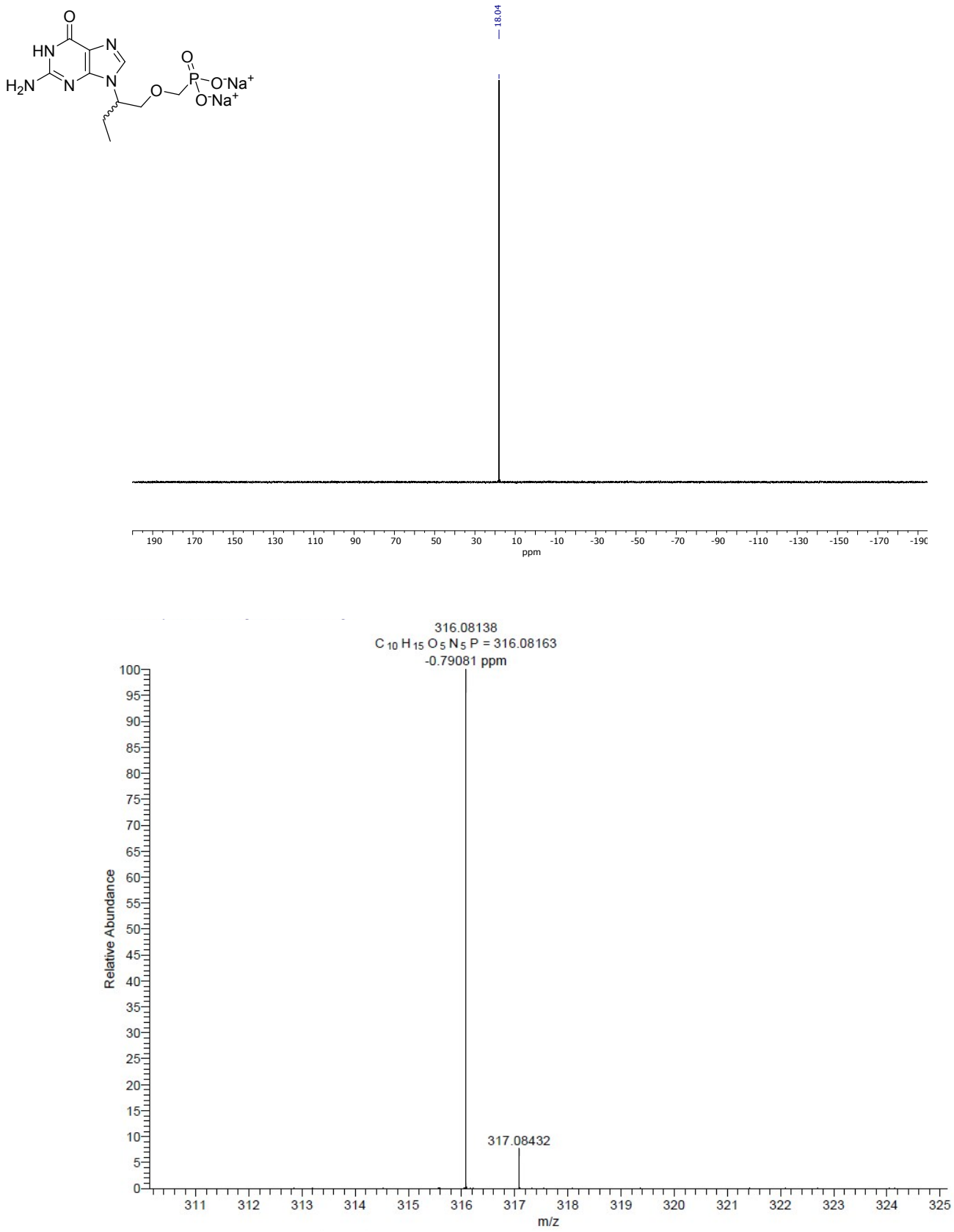


Figure S132. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**16b**.

Sodium (*R*)-((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**16b**)

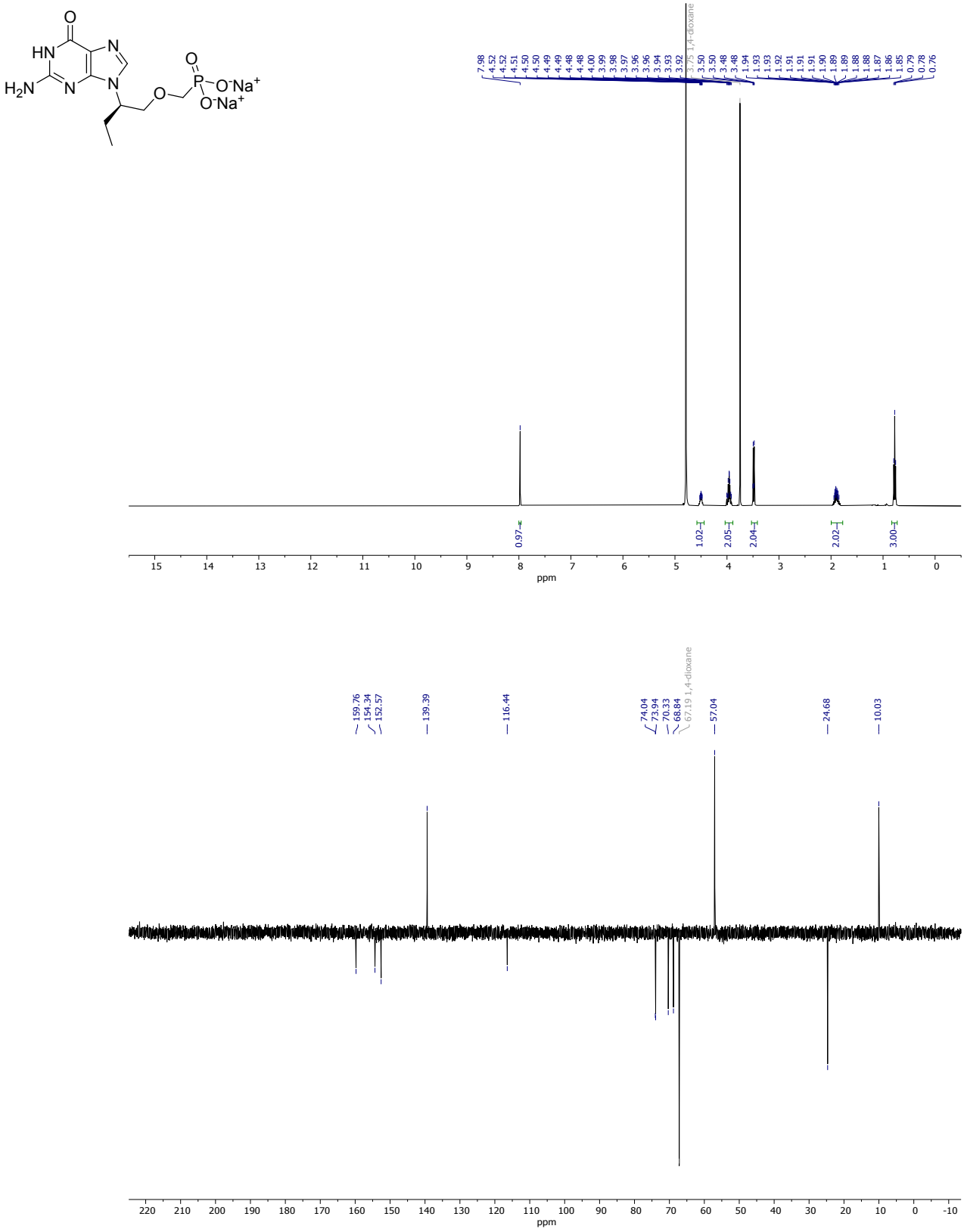


Figure S133. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**16b** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*R*)-((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**16b**)

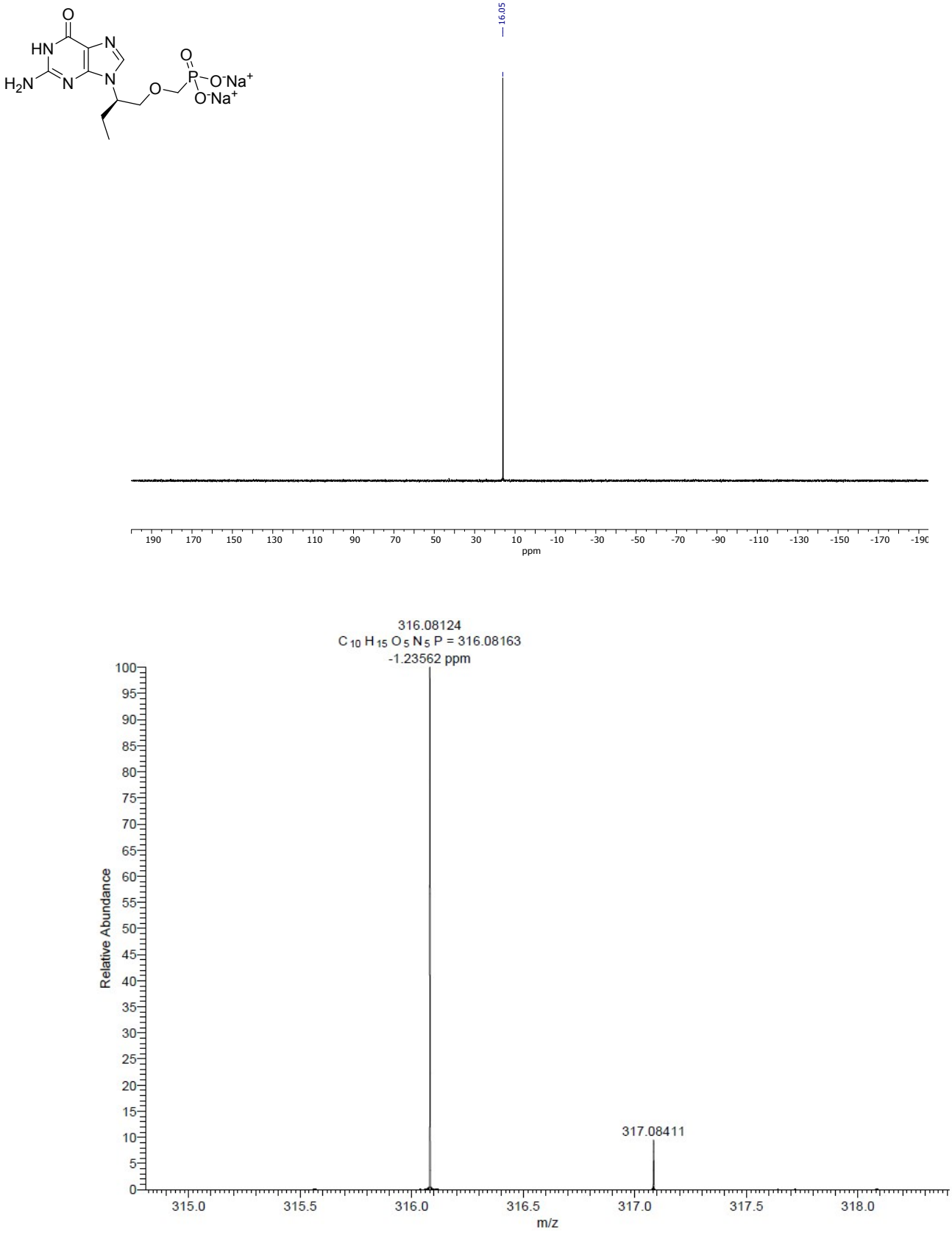


Figure S134. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**16b**.

Sodium (((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)but-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**16c**)

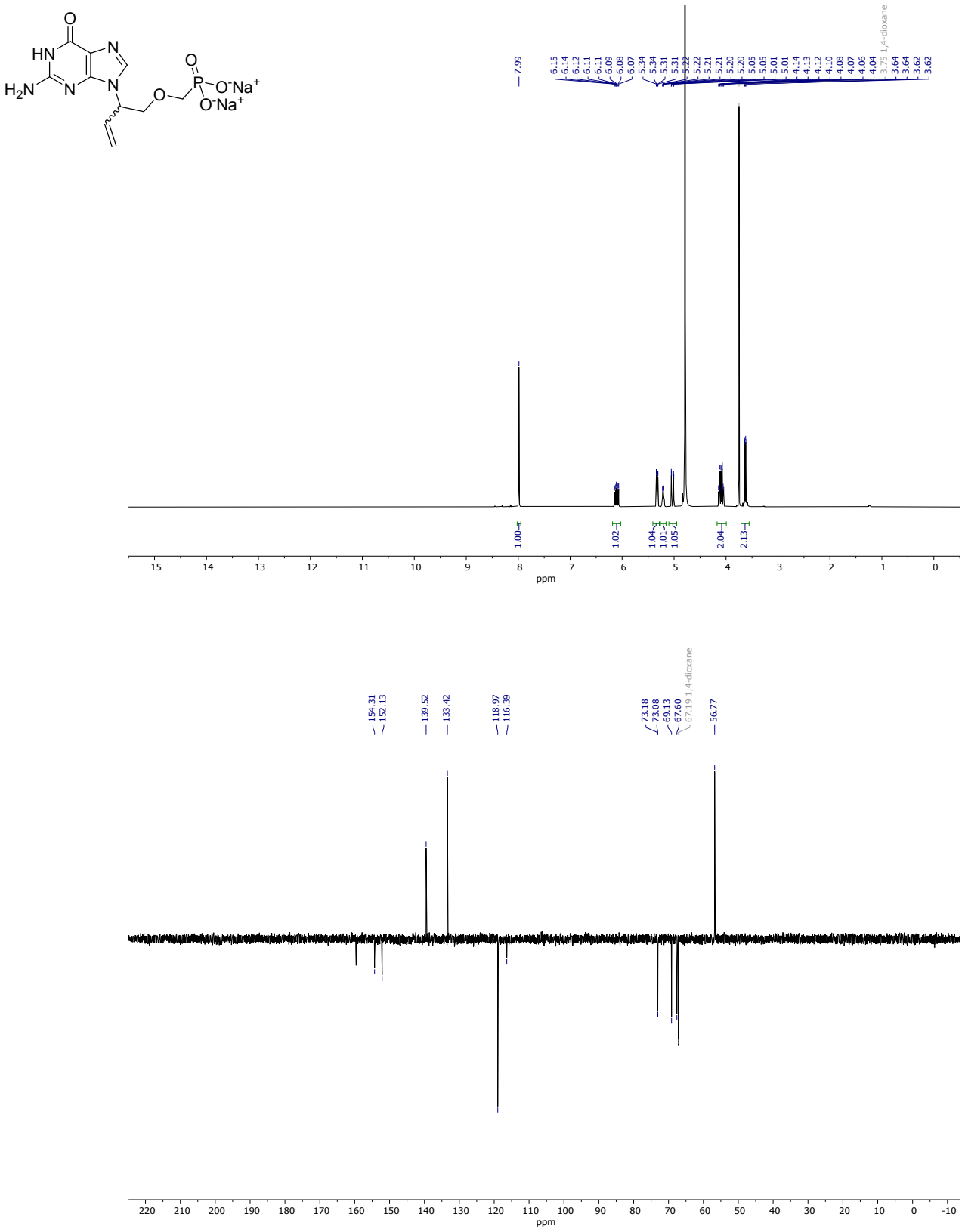


Figure S135. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**16c** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)but-3-en-1-yl)oxy)methyl)phosphonate ((*RS*)-**16c**)

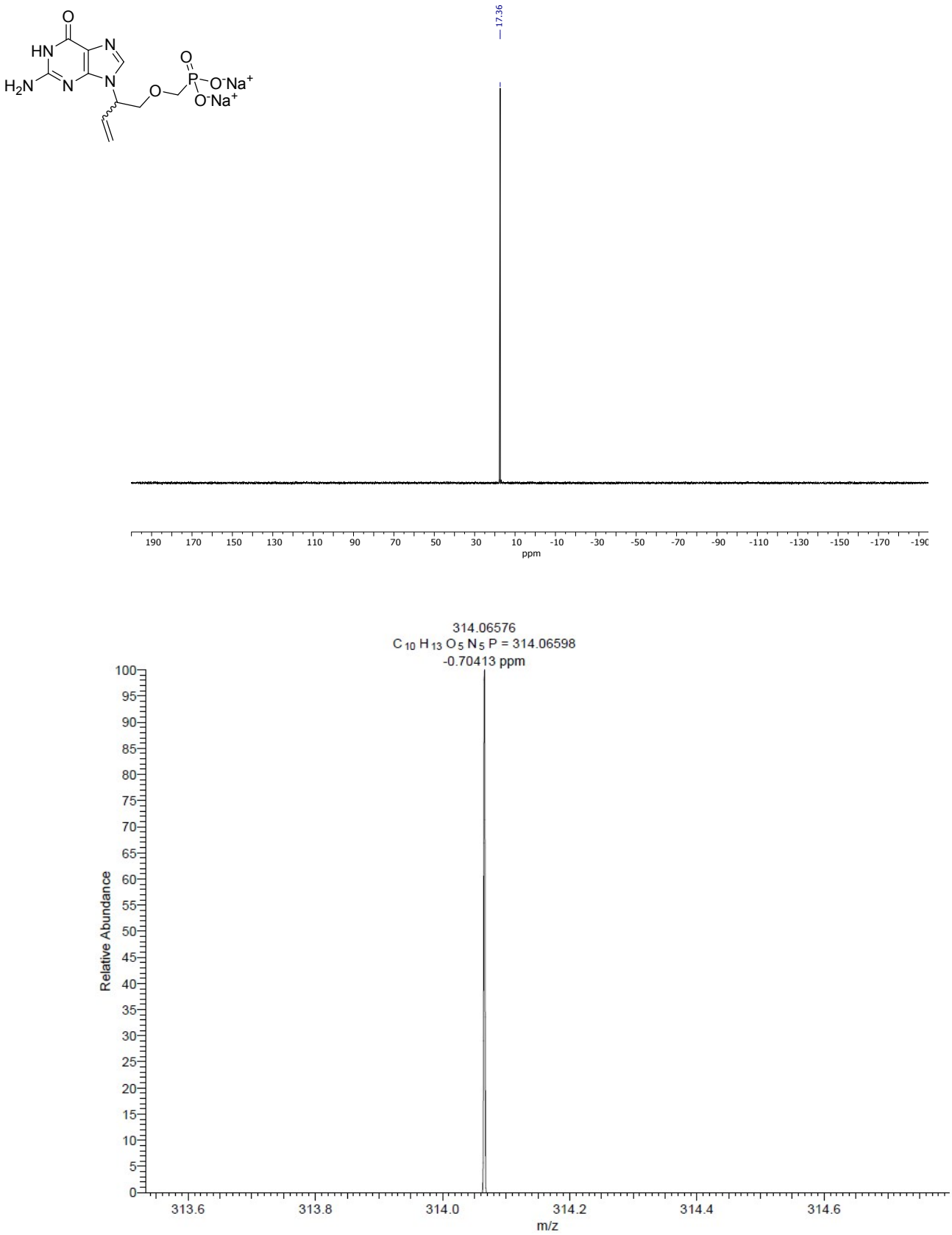


Figure S136. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**16c**.

Sodium (((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)but-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**16d**)

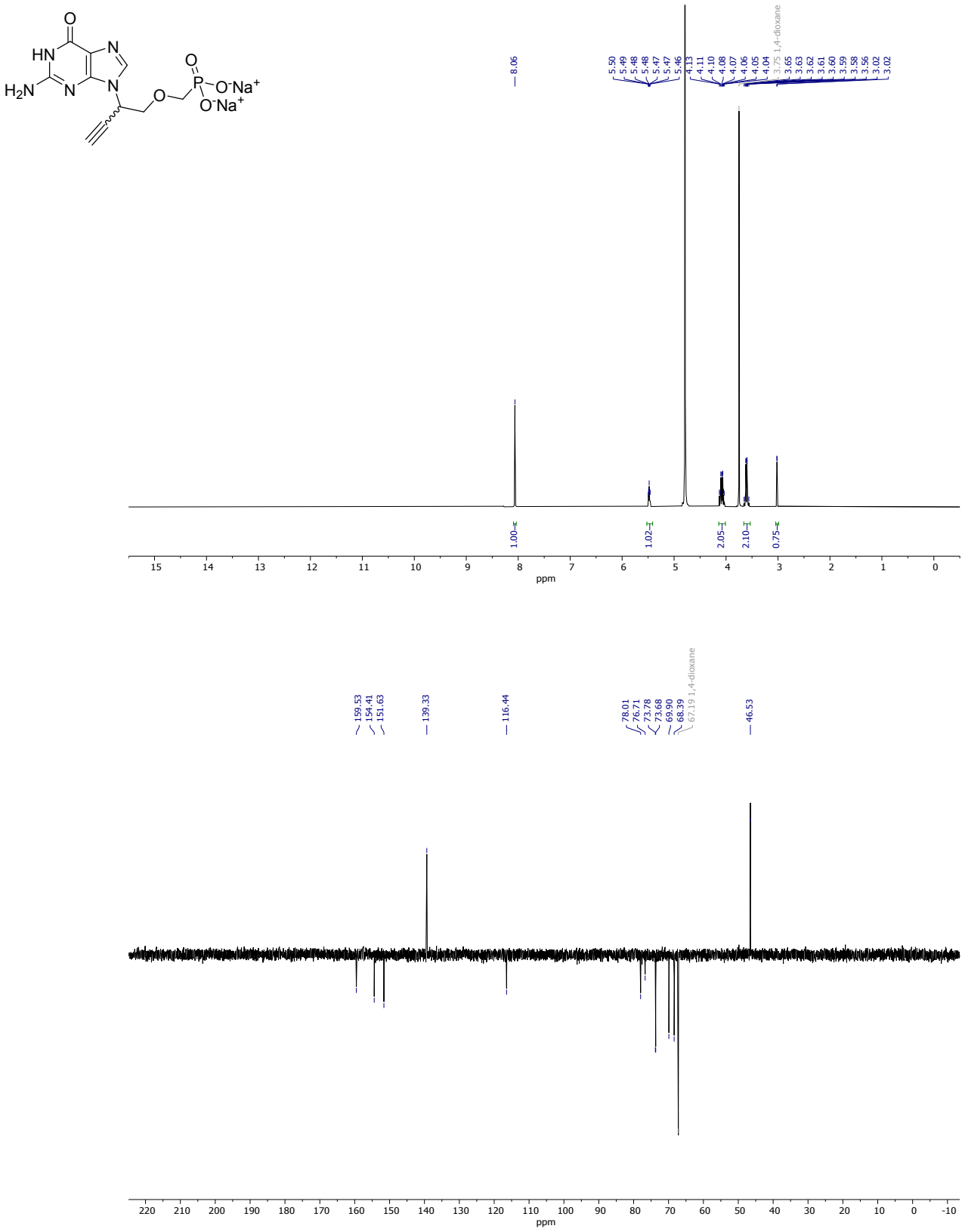


Figure S137. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**16d** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)but-3-yn-1-yl)oxy)methyl)phosphonate ((*RS*)-**16d**)

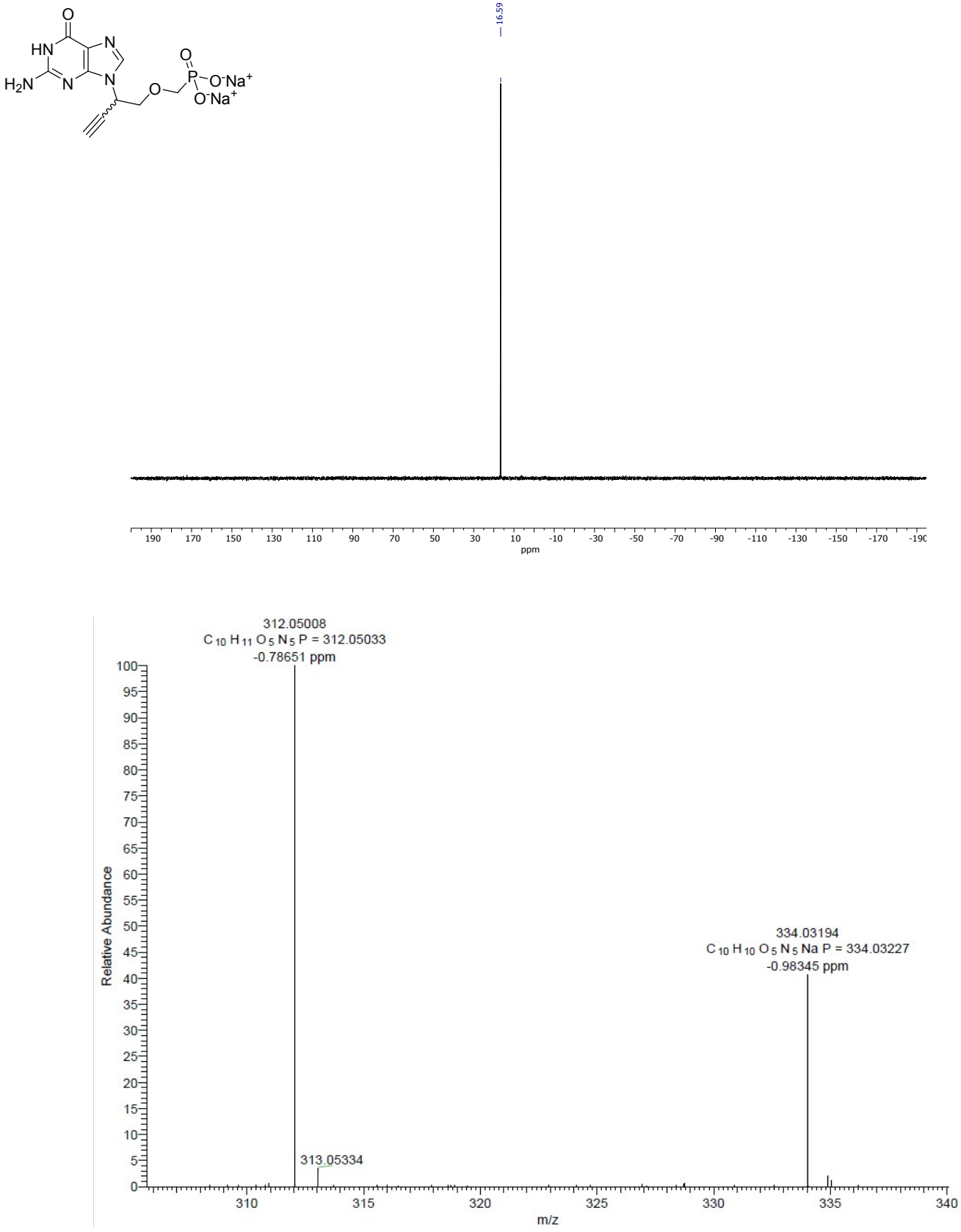


Figure S138. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**16d**.

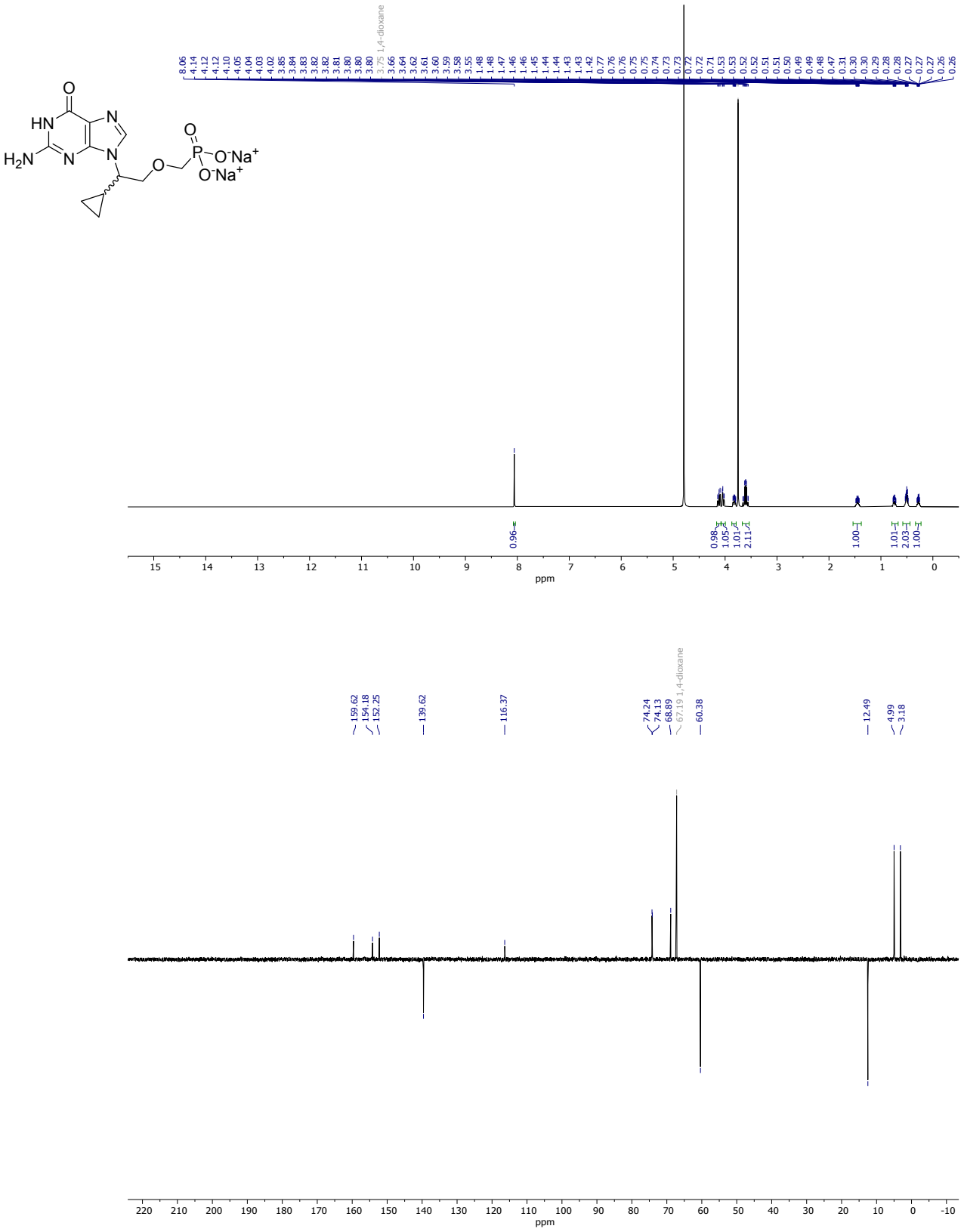


Figure S139. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**16e** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium ((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)-2-cyclopropylethoxy)methyl)phosphonate ((*RS*)-**16e**)

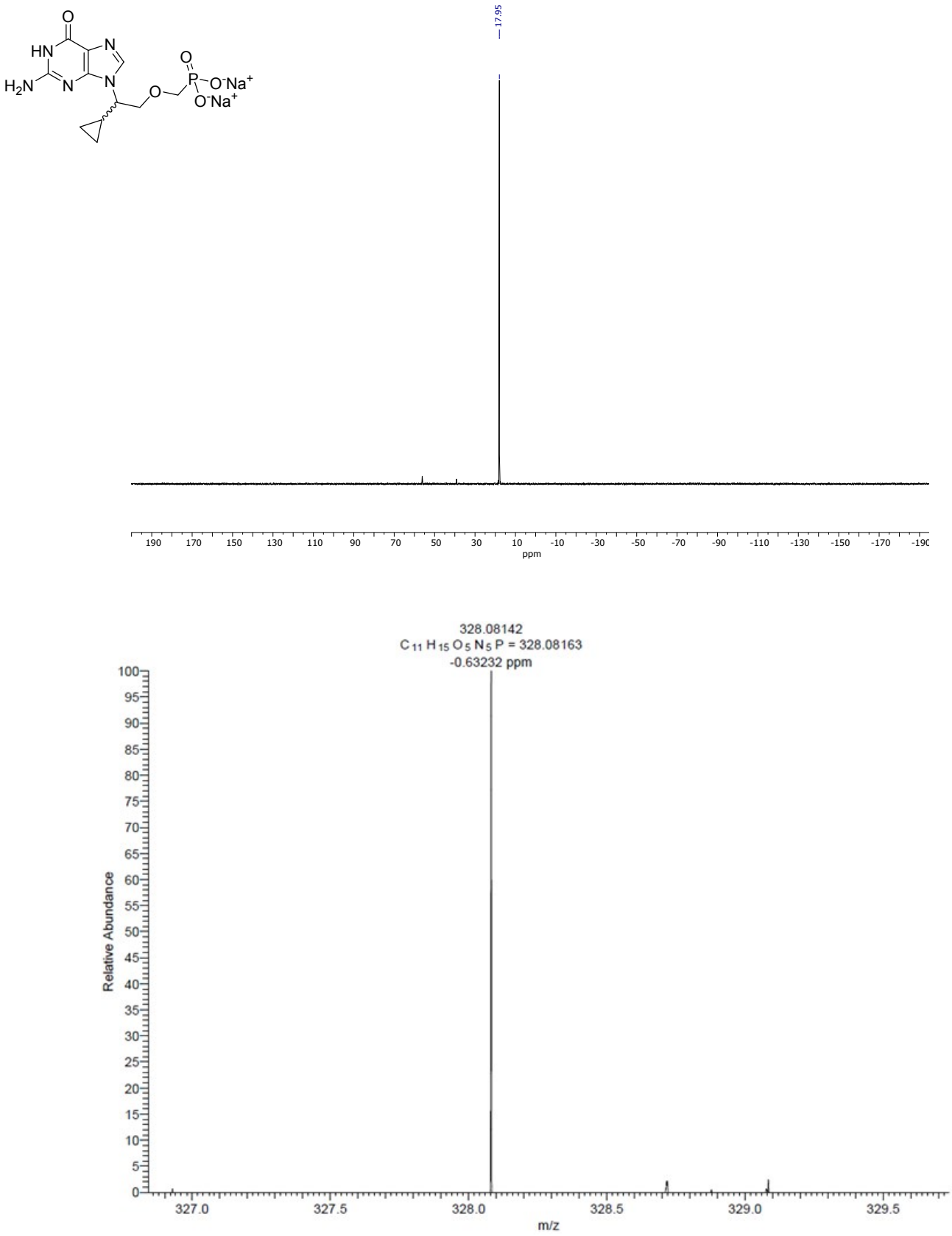


Figure S140. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**16e**.

Sodium ((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)-2-methoxyethoxy)methyl)phosphonate ((*RS*)-**16f**)

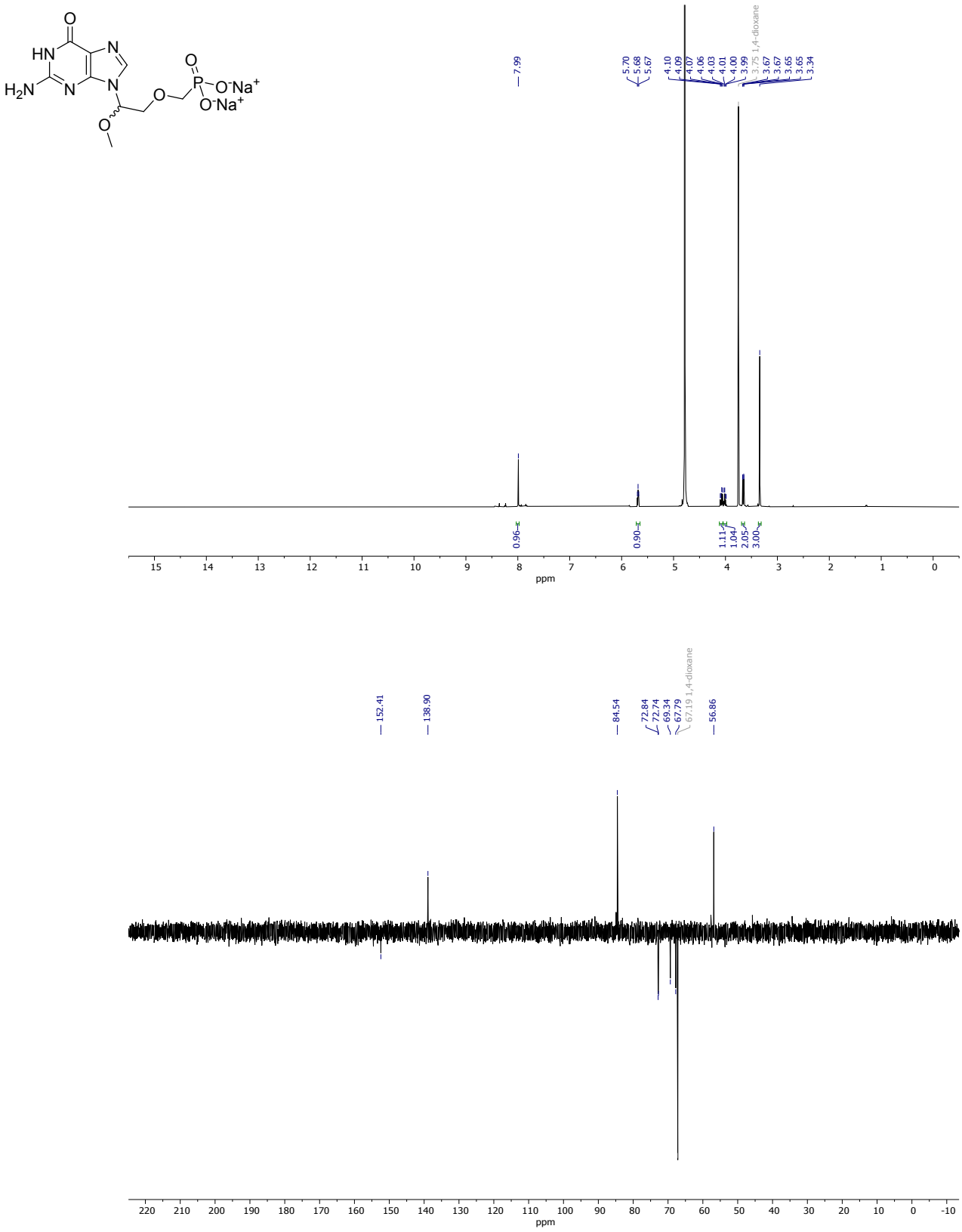


Figure S141. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**16f** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium ((2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)-2-methoxyethoxy)methyl)phosphonate ((*RS*)-**16f**)

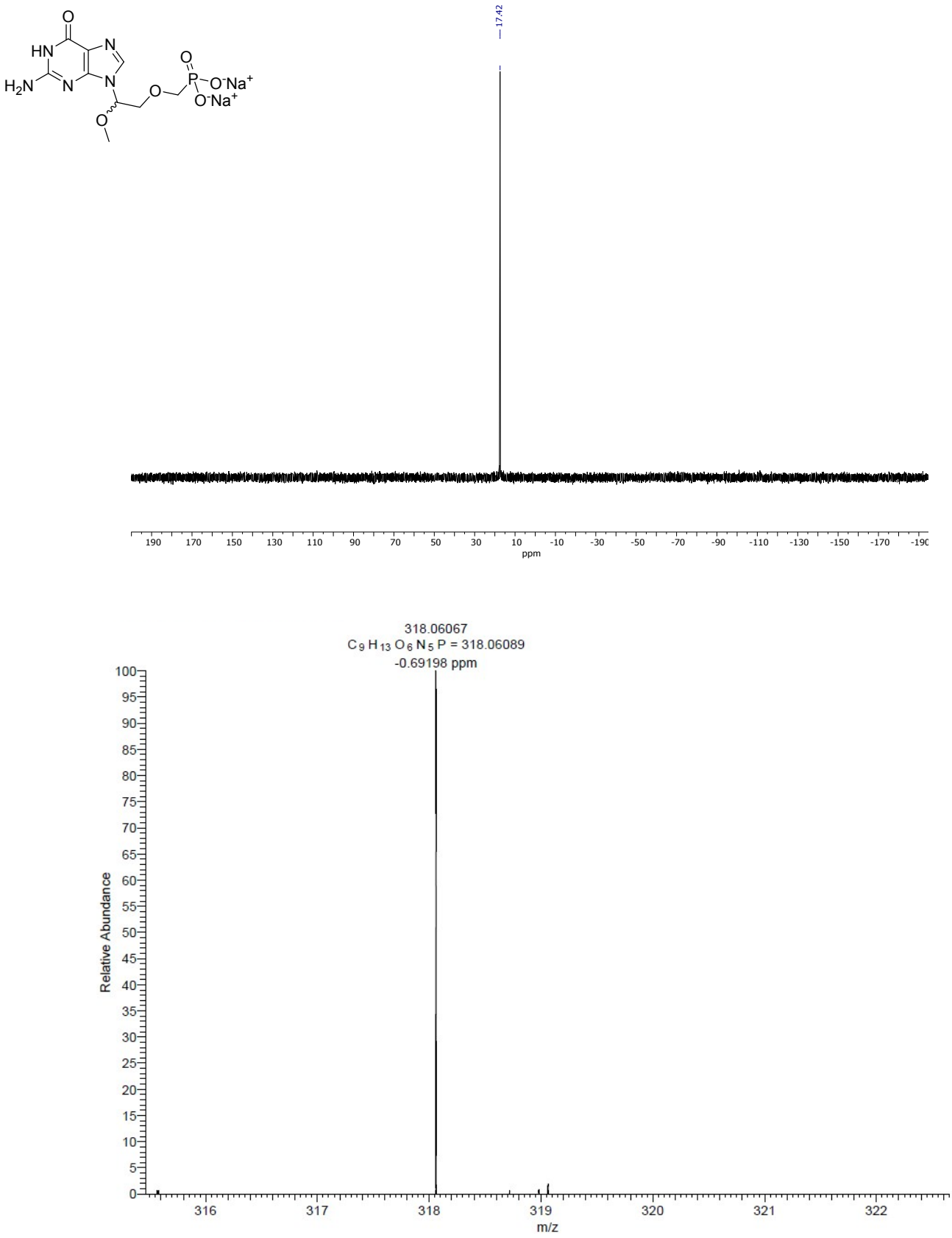


Figure S142. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**16f**.

Sodium ((2-(6-amino-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**17**)

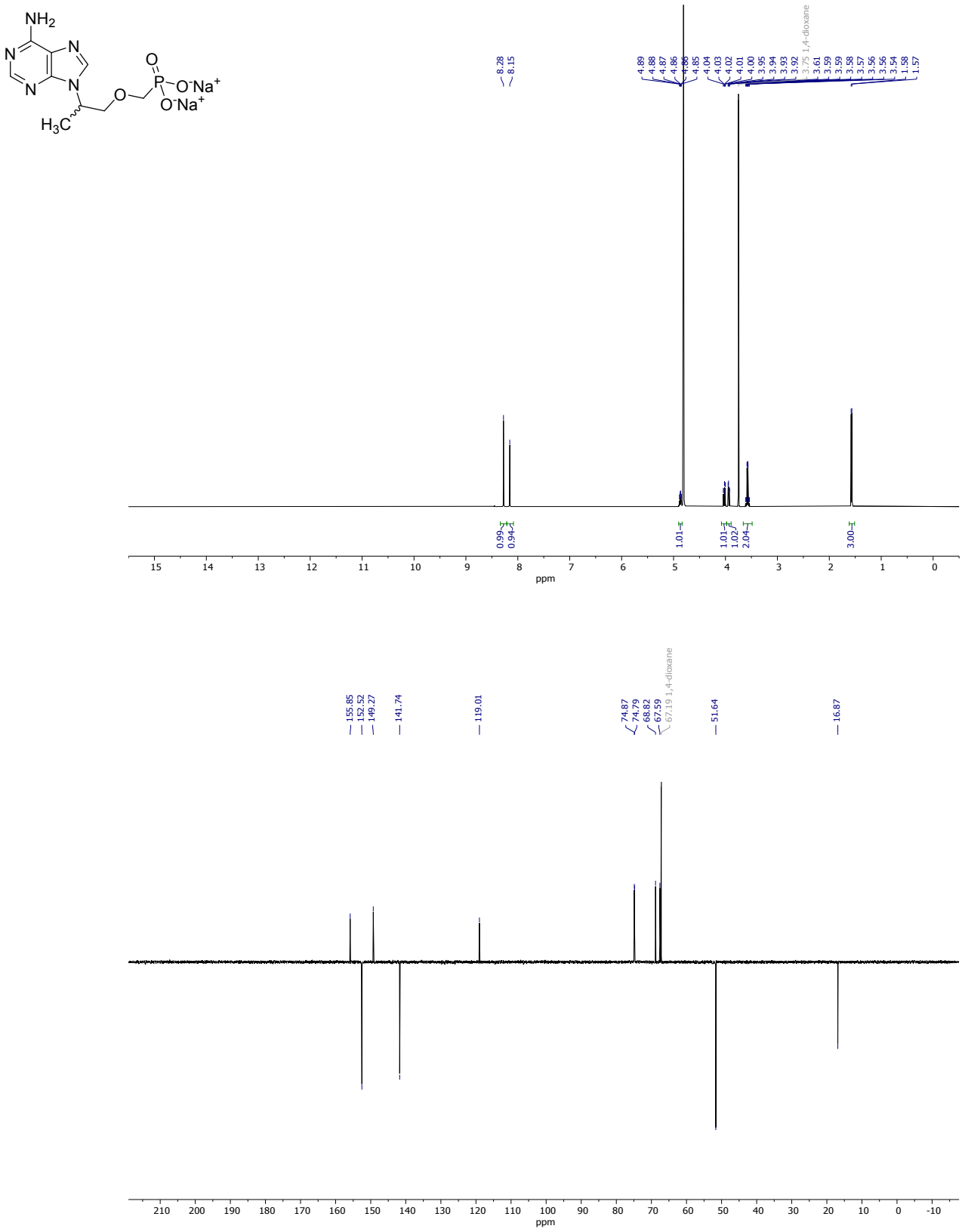


Figure S143. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*RS*)-**17** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium ((2-(6-amino-9*H*-purin-9-yl)propoxy)methyl)phosphonate ((*RS*)-**17**)

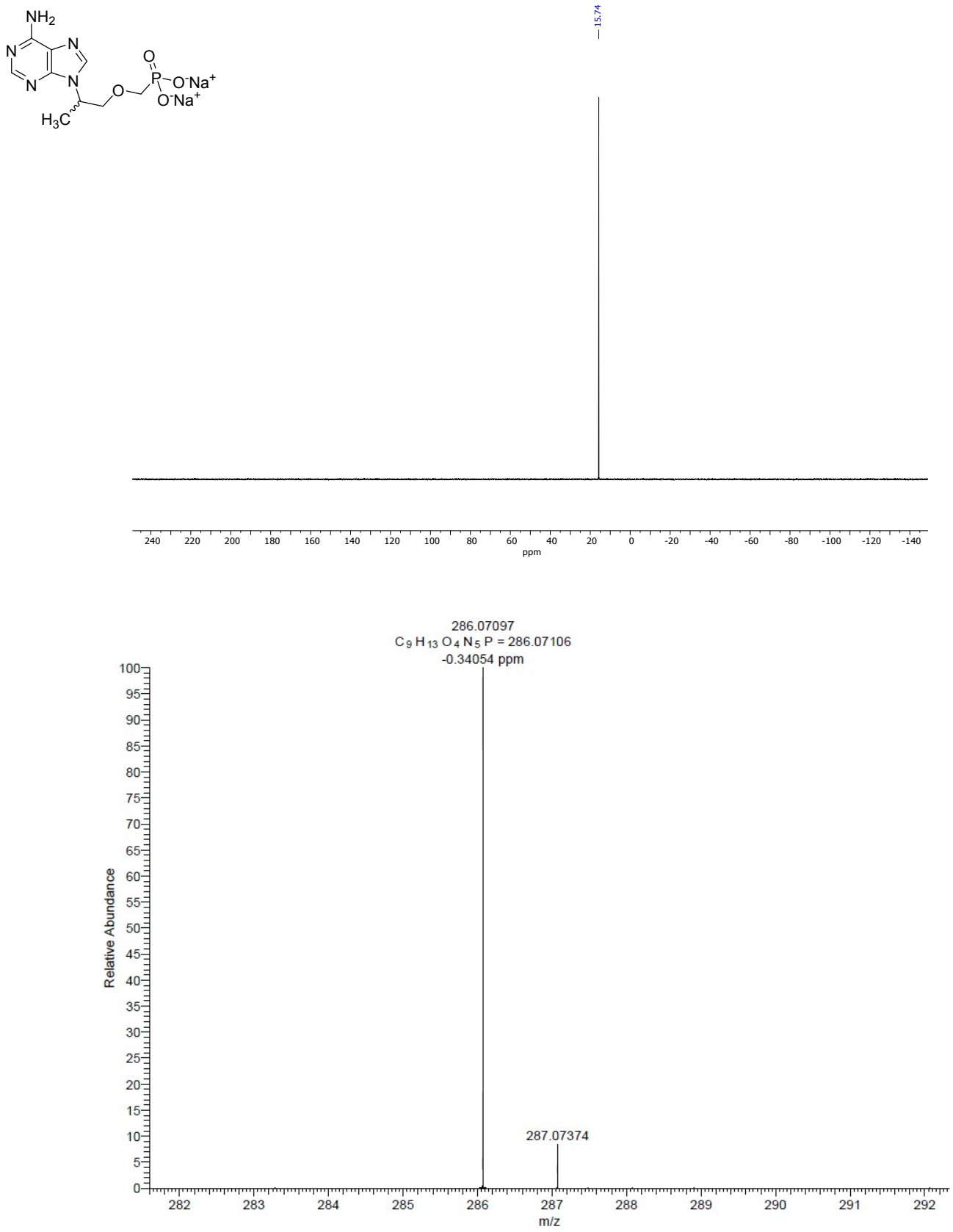


Figure S144. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*RS*)-**17**.

Sodium (*R*)-((2-(6-(cyclopropylamino)-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**18**)

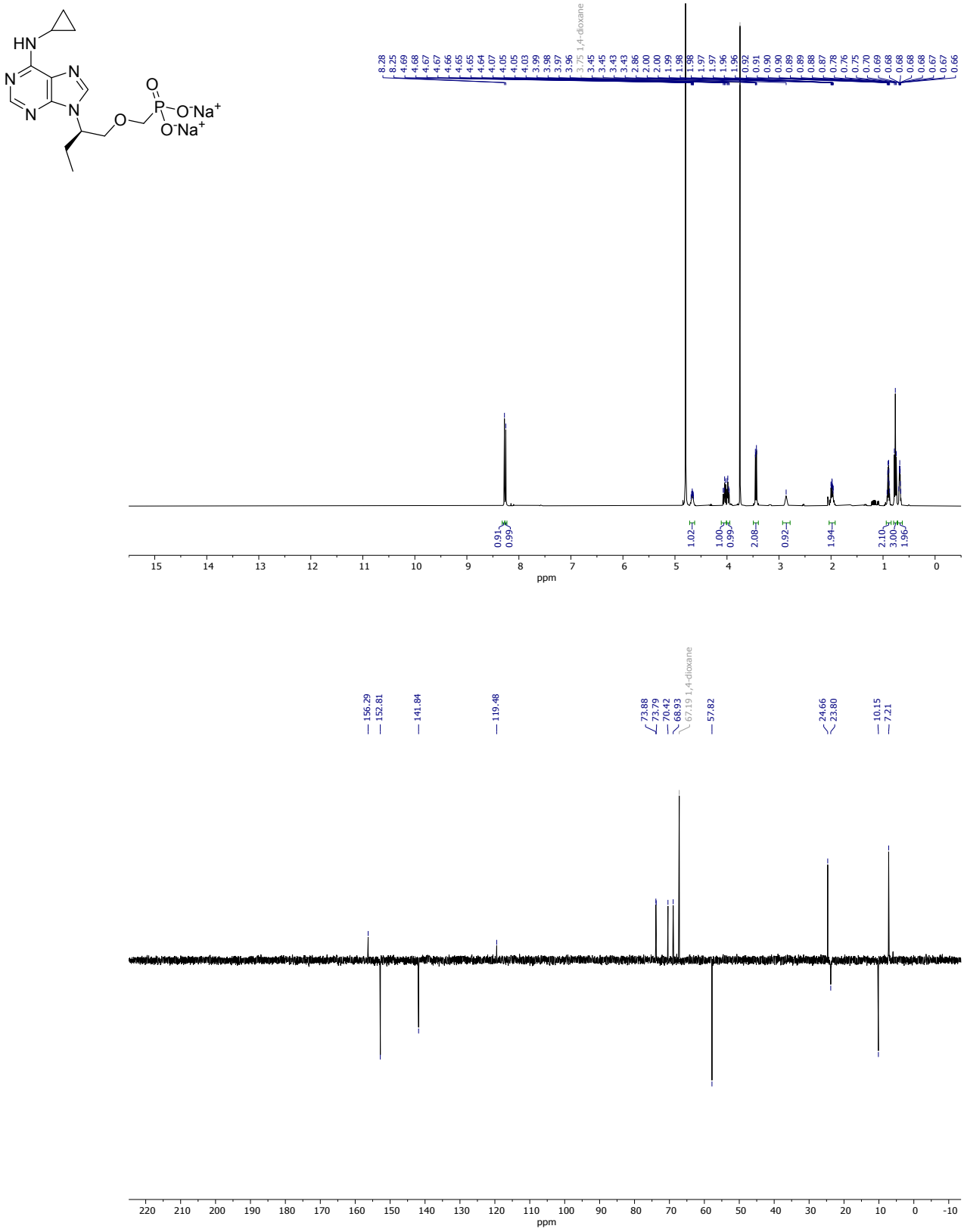


Figure S145. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**18** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*R*)-((2-(6-(cyclopropylamino)-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**18**)

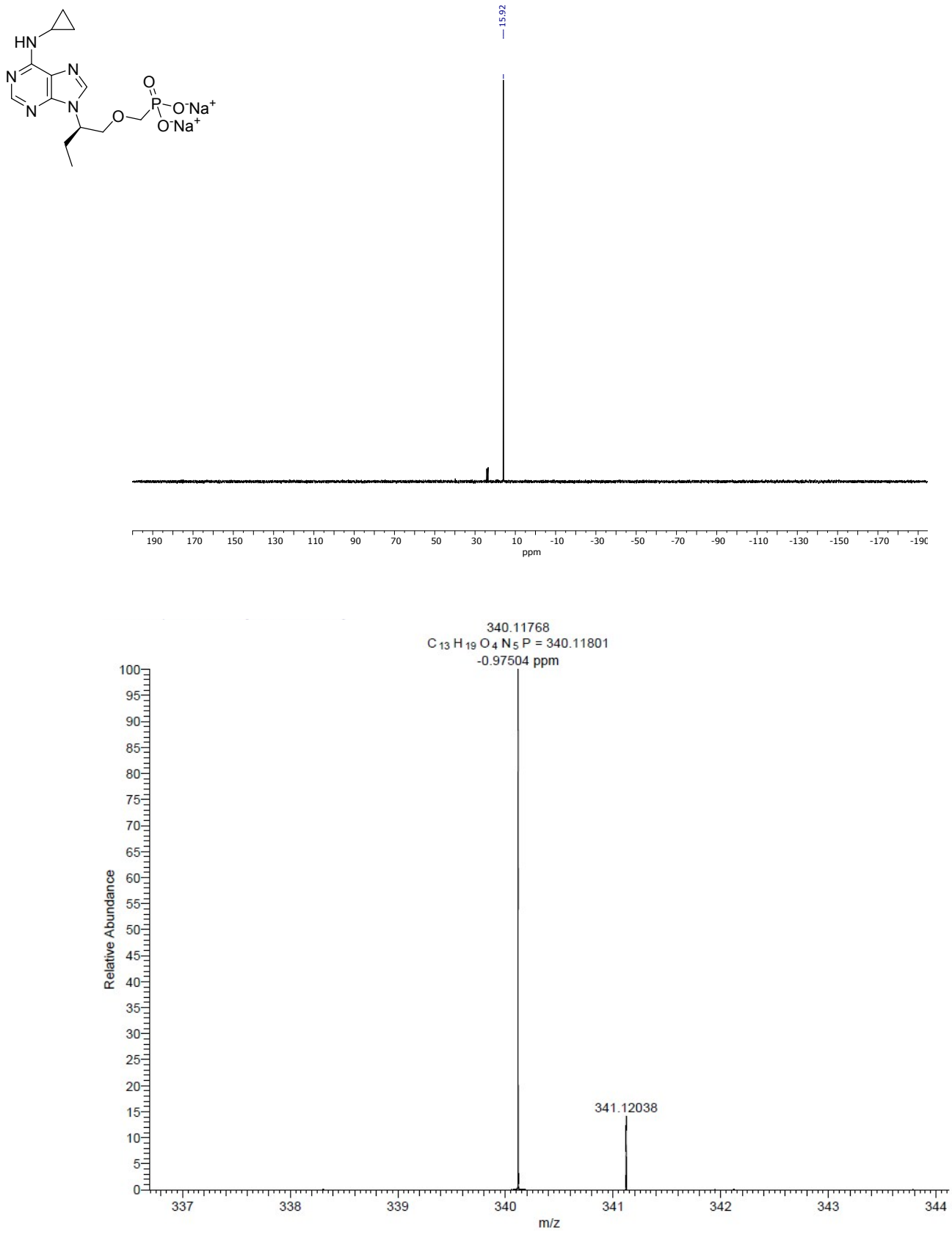


Figure S146. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**18**.

Sodium (*R*)-((2-(2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**19**)

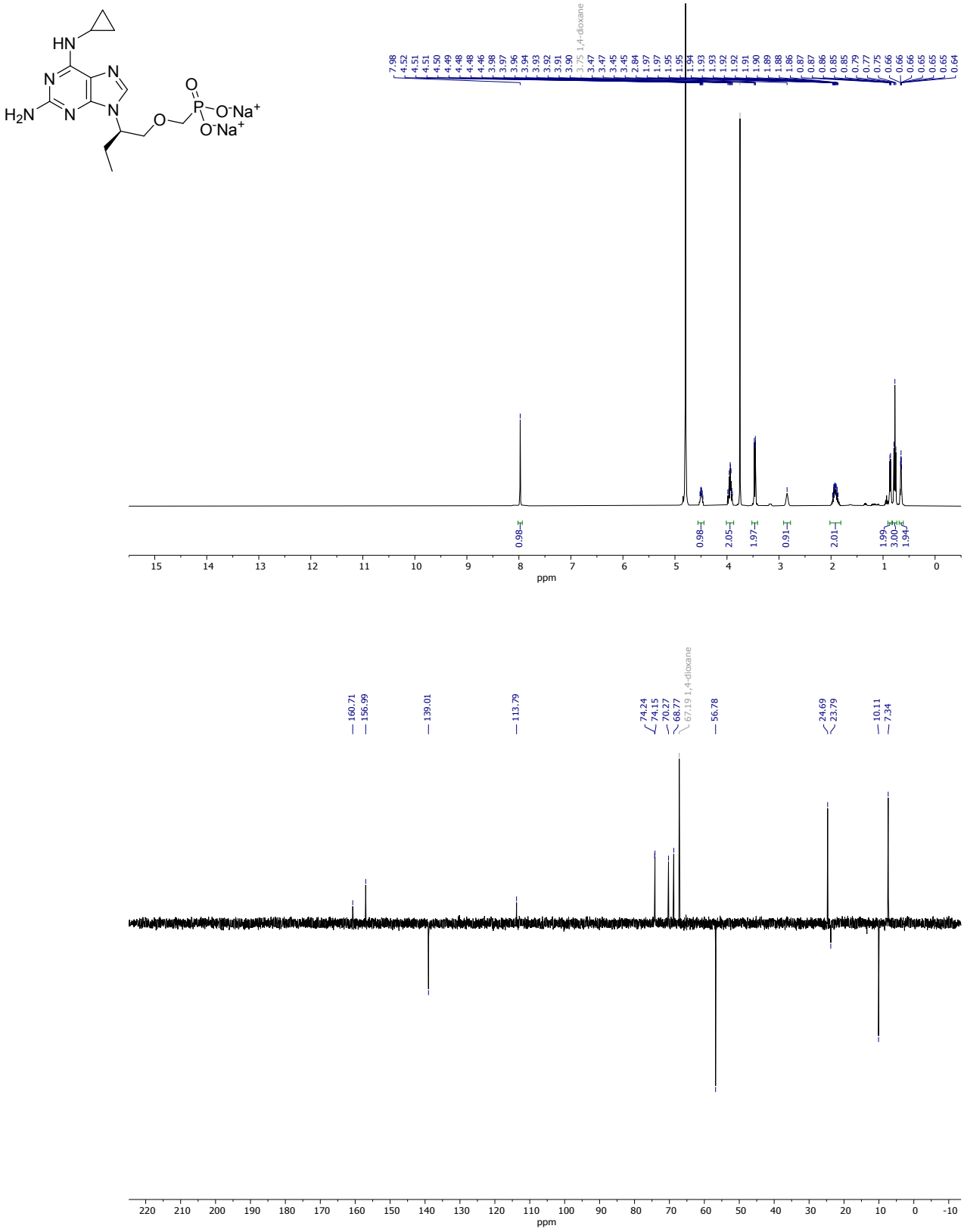


Figure S147. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**19** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*R*)-((2-(2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**19**)

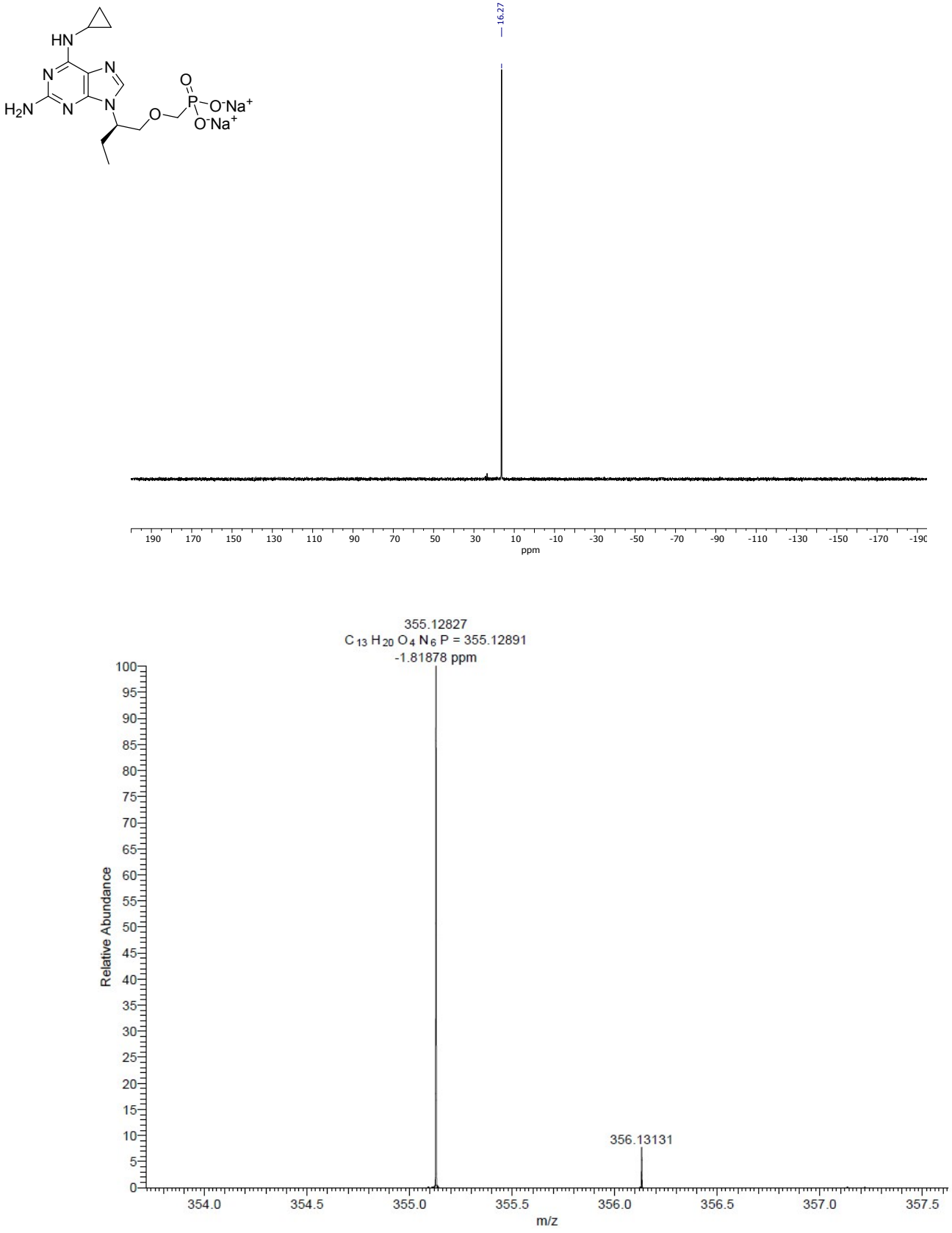


Figure S148. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**19**.

Sodium (*R*)-((2-(6-methoxy-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**20**)

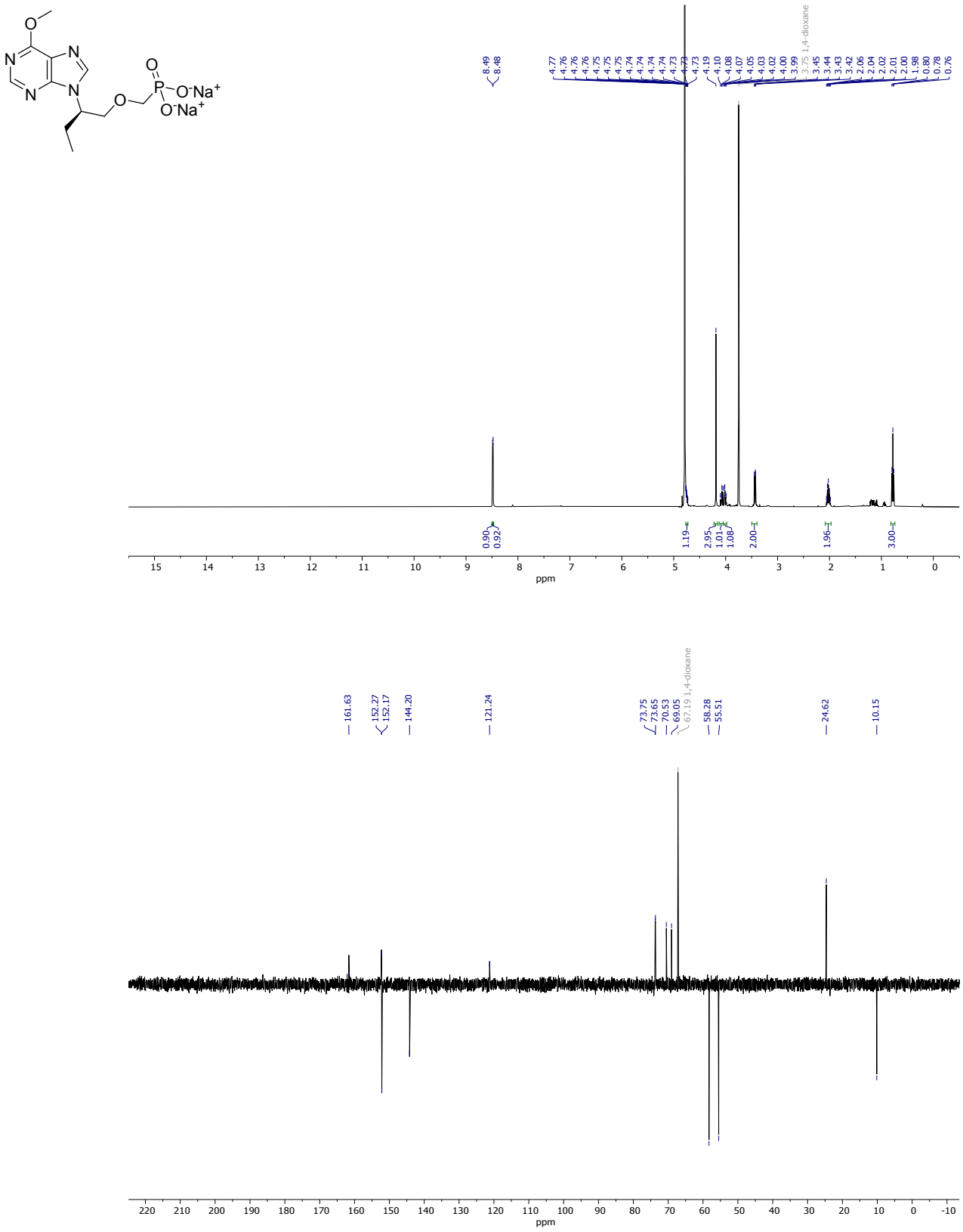


Figure S149. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**20** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*R*)-((2-(6-methoxy-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**20**)

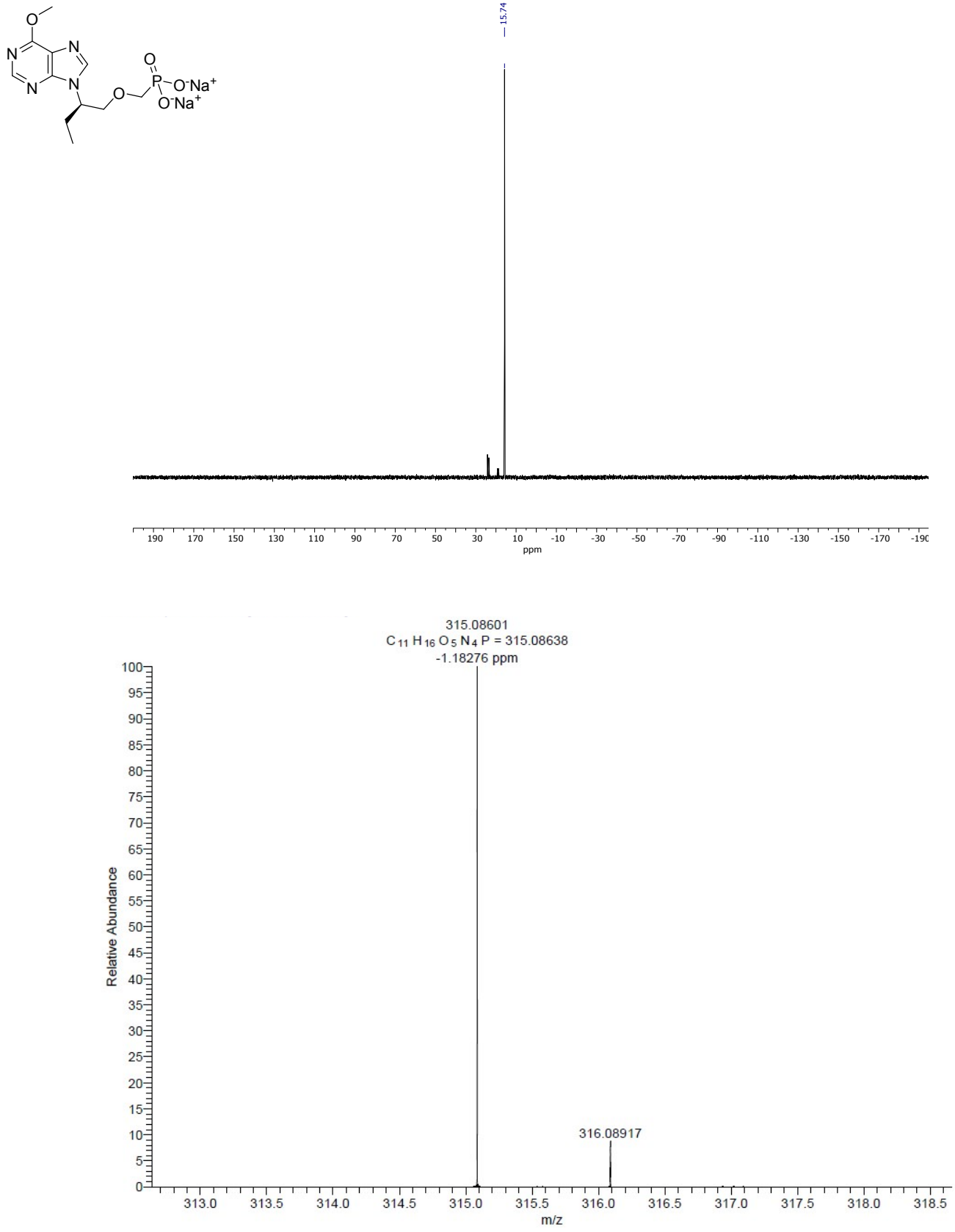


Figure S150. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**20**.

Sodium (*R*)-((2-(2-amino-6-methoxy-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**21**)

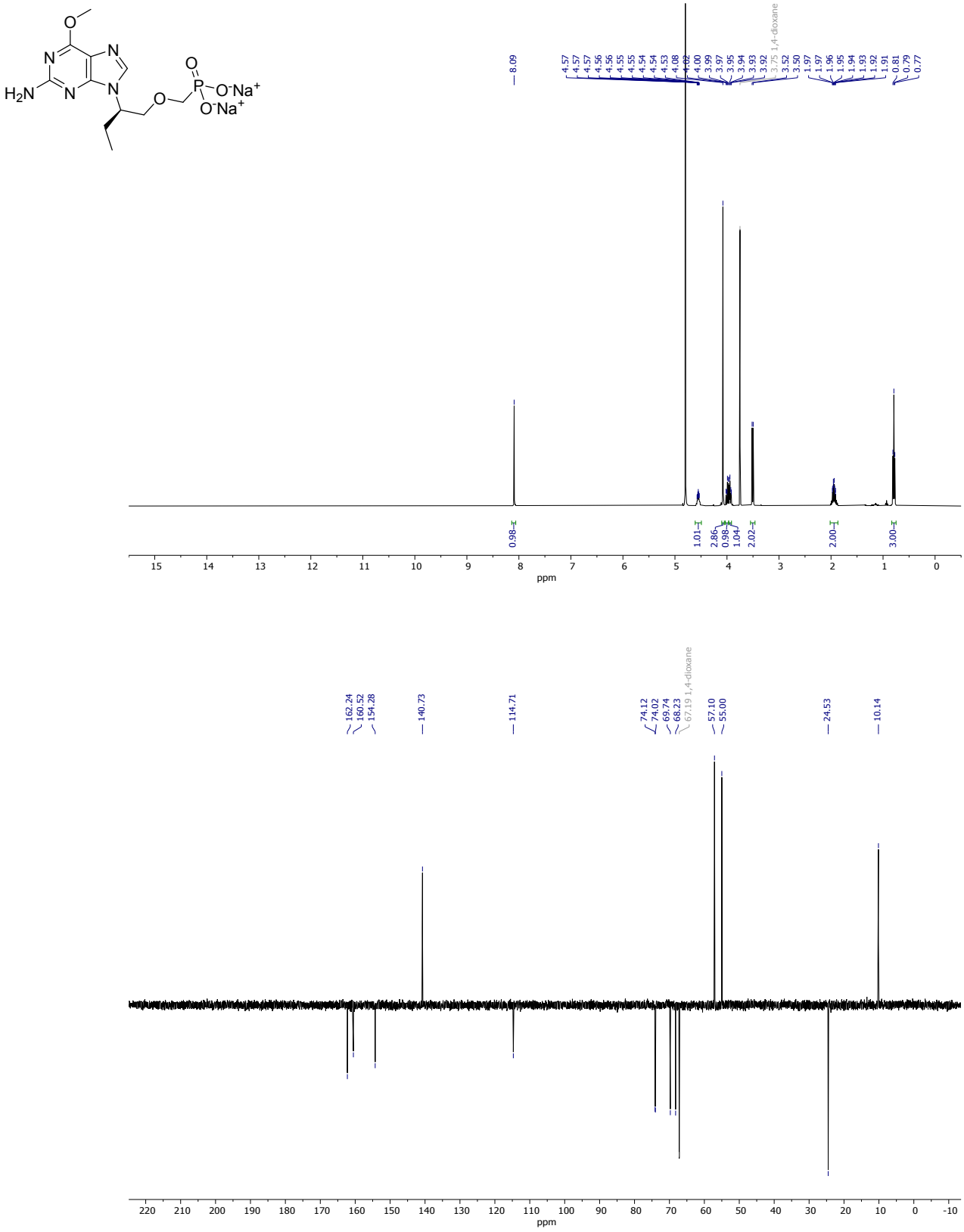


Figure S151. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**21** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*R*)-((2-(2-amino-6-methoxy-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**21**)

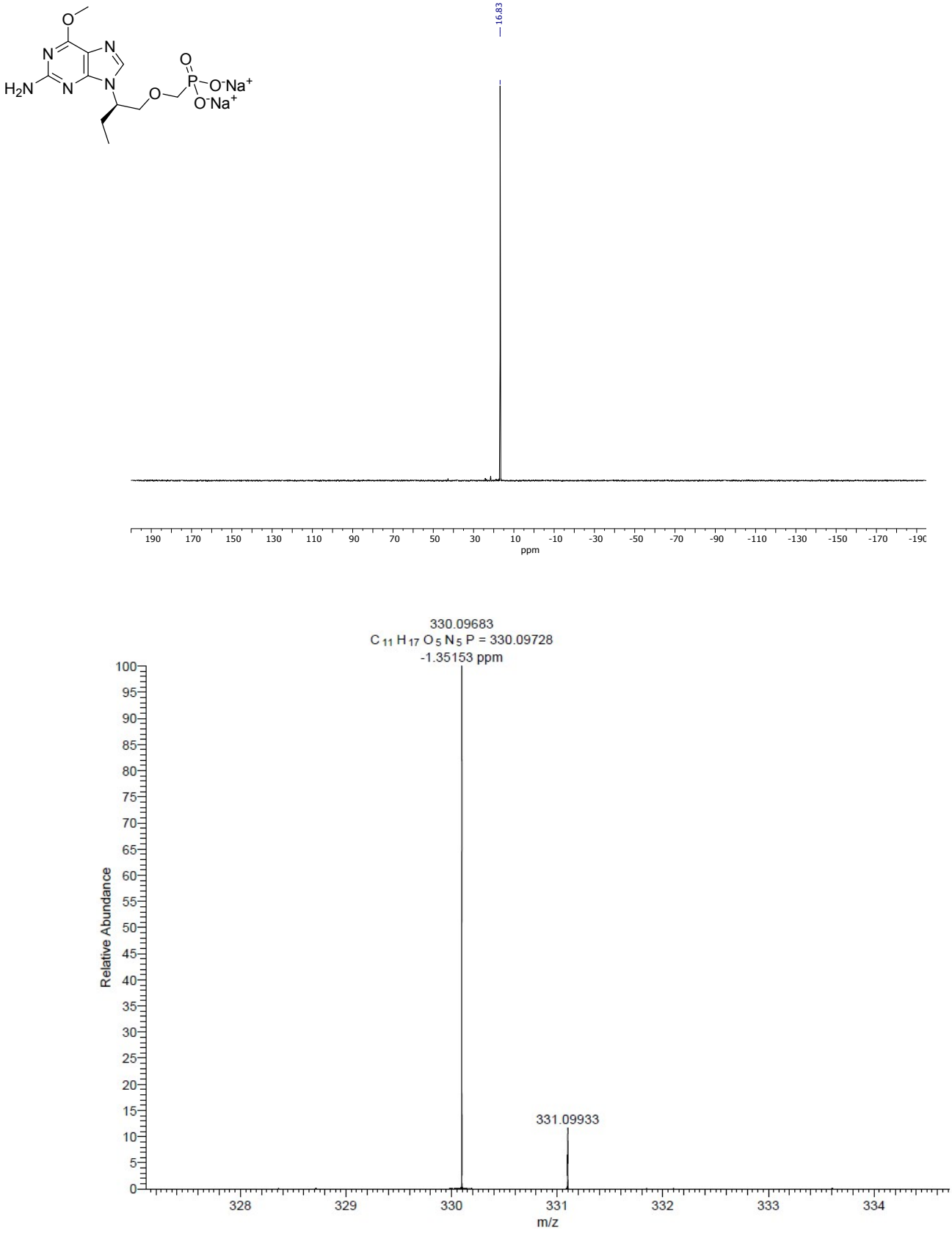


Figure S152. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**21**.

Sodium (*R*)-((2-(6-phenyl-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**22**)

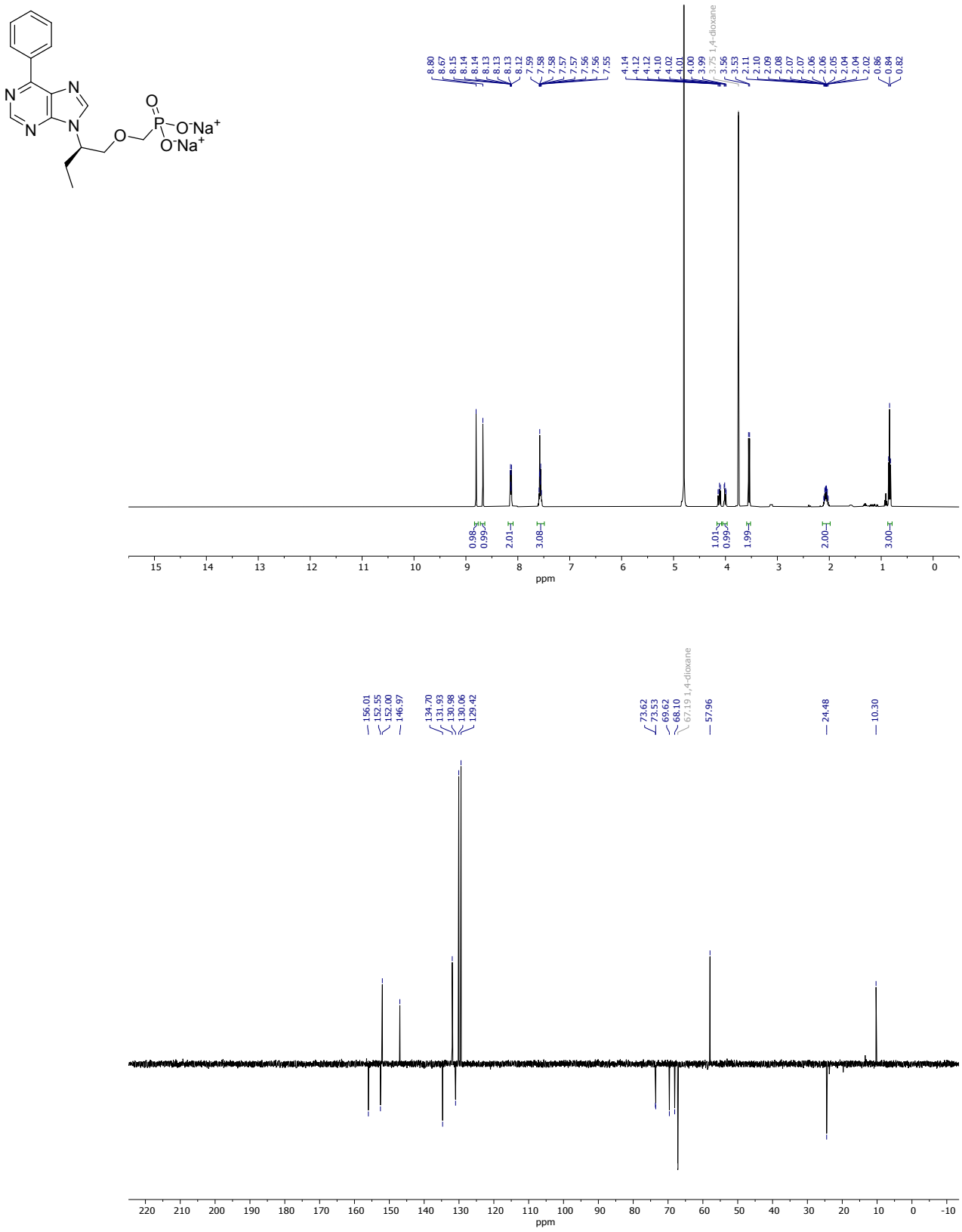


Figure S153. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**22** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*R*)-((2-(6-phenyl-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**22**)

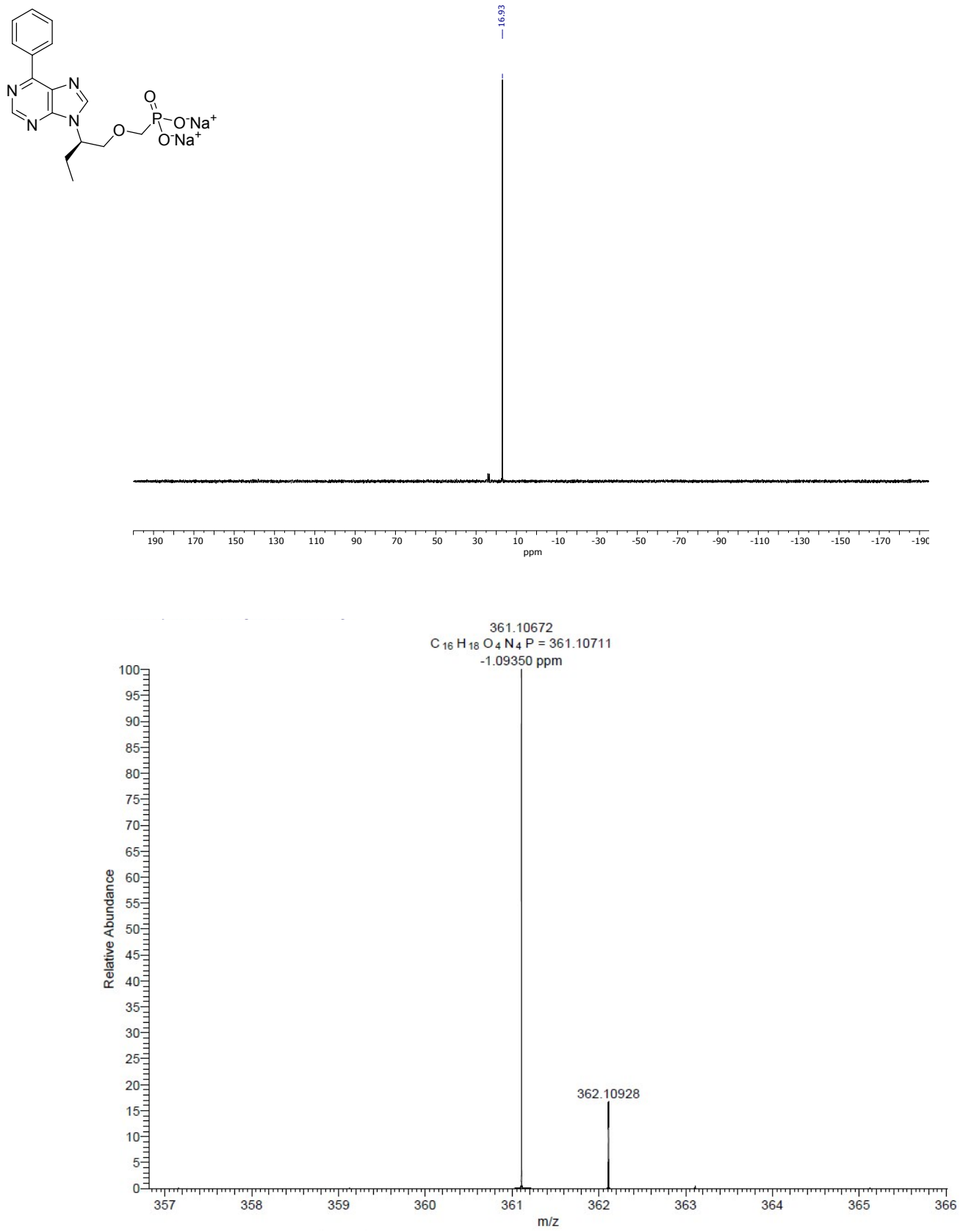


Figure S154. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**22**.

Sodium (*R*)-((2-(2-amino-6-phenyl-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**23**)

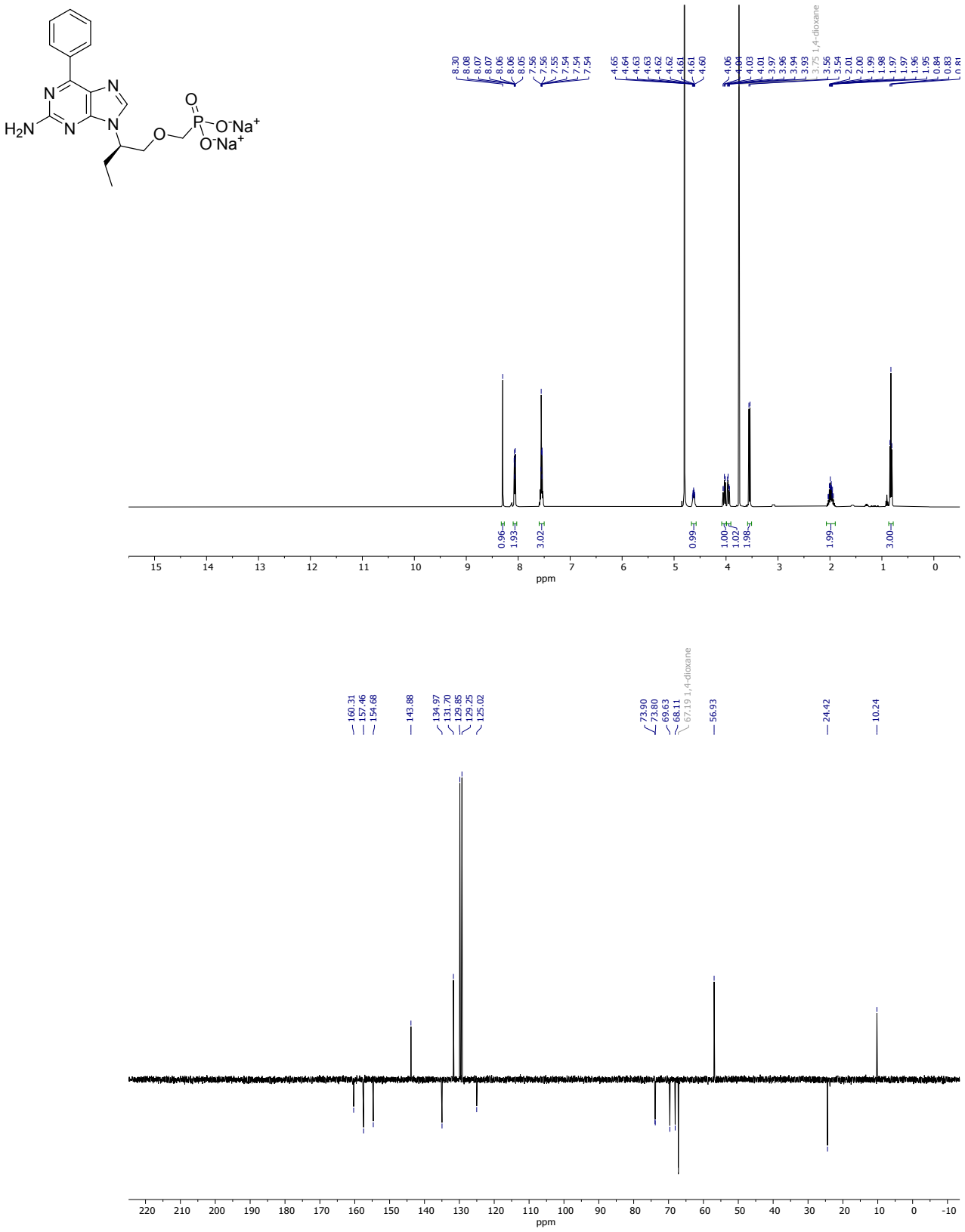


Figure S155. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound (*R*)-**23** measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard.

Sodium (*R*)-((2-(2-amino-6-phenyl-9*H*-purin-9-yl)butoxy)methyl)phosphonate ((*R*)-**23**)

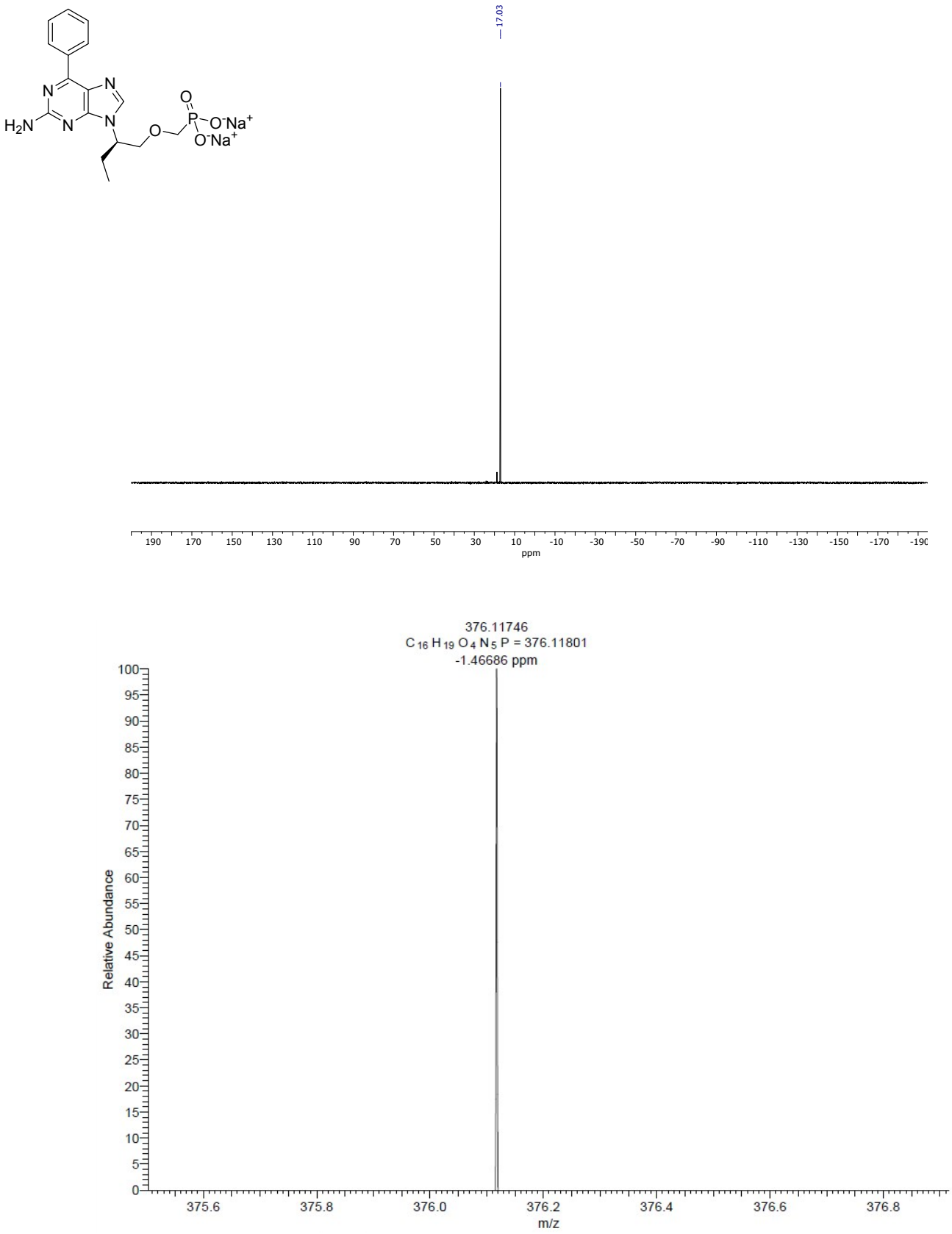


Figure S156. ^{31}P NMR (measured at room temperature in D_2O containing 0.1% of 1,4-dioxane as internal standard, top) and high resolution mass spectrum (HRMS, bottom) of compound (*R*)-**23**.

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(1) Harnden, M. R.; Wyatt, P. G.; Boyd, M. R.; Sutton, D. Synthesis and Antiviral Activity of 9-Alkoxypurines. 1. 9-(3-Hydroxypropoxy)- and 9-[3-Hydroxy-2-(Hydroxymethyl)Propoxy]Purines. *J. Med. Chem.* **1990**, *33* (1), 187–196.