Supporting Information

C7-Sulfonamide Functionalization of 7-Deazaadenosines: Sangivamycin Analogues with Haspin Inhibitory Activity

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1. General information

Starting compounds and reagents were purchased from commercial suppliers (Sigma-Aldrich, Fluorochem, Acros Organics, Carbosynth) and used without further purification. Acetonitrile and 1,4-dioxane were dried using activated 3Å molecular sieves, and CH_2Cl_2 was distilled from P_2O_5 and kept over 4Å molecular sieves. Analytical High-Performance Liquid Chromatography (HPLC), low-resolution mass spectra, UV absorbance and compound purity were measured on a Waters Ultra-high Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS) system consisting of a Waters UPLC H-Class Core System, a UPLC photodiode array (PDA) detector, and a Waters QDa mass spectrometer. The MS method used was electrospray ionization $(ESI)^+$ and/or $(ESI)^-$, cone voltage = 15 V, mass detector range 105–1000 Da. Two sets of HPLC conditions were used as indicated: (a) C18 (column: Waters CORTECS UPLC C18 column, 1.6 µm, 2.1×50 mm; LC method: H_2O/CH_3CN, 0.1% formic acid as a modifier, gradient 0–100 %, run length 3.65 min, flow 0.7 ml/min) and (b) HILIC (column: HILICON iHILIC®-Fusion, 50×2.1mm, 1.8µm, 100Å; LC method: CH_3CN/0.01M aqueous ammonium acetate gradient 10–60 %, run length 7 min, flow 0.3 ml/min). Analytical Thin-Layer Chromatography (TLC) was performed on silica gel-precoated aluminium plates with a fluorescent indicator (Merck 60 F254). For normal flash column chromatography (VWR International Silica gel 60, particle size 0.040–0.063 mm) as well as for reverse-phase flash column chromatography (C18 RediSep Rf columns), a Combiflash® Rf from Teledyne ISCO was used. ^1H and ^{13}C NMR spectra for the reported compounds were recorded on a Bruker Avance III^{TM} HD 400 instrument (400.0 MHz for ^1H and 101 MHz for ^{13}C) with broadband PRODIGY cryoprobe with ATM module (5 mm CPBBO BB-1H/19F/D Z-GRD). Chemical shifts (δ) and coupling constants (*J*) are expressed in ppm and Hz, respectively. The NMR experiments were performed in DMSO-d6 or $CDCl_3$ and referenced to the solvent signal (DMSO: δ 2.50 for ^1H NMR and 39.70 for ^{13}C NMR, δ 7.26 for ^1H NMR and 77.16 for ^{13}C NMR). Shifts of ^1H and ^{13}C, which were only observed in 2D spectra are marked with asterisk (*). Complete assignment of all NMR signals was performed using a combination of 2D NMR (H,H-COSY, H,C-HSQC, and H,C-HMBC) experiments. The numbering of structures was inspired by numbering of nucleosides (normal digits for nucleobase, prime digits for carbohydrate moiety). The sulfonamide substituents were designated with double-prime digits; representative numbering for exo- and endocyclic nitrogen-bound sulfonamides is provided in Figure S1. High-resolution mass spectrometry (HRMS) analyses were carried out on an LTQ XL Orbitrap XL (Thermo Fisher Scientific) using electrospray ionization (ESI).

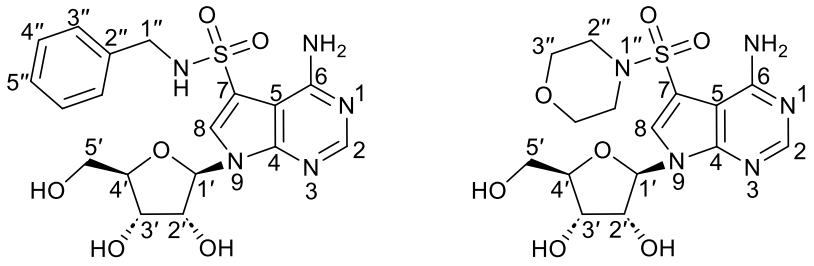
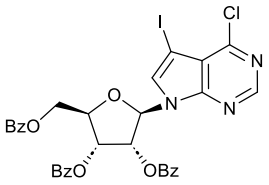


Figure S1. Examples of numbering used in NMR assignments.

2. Synthetic procedures

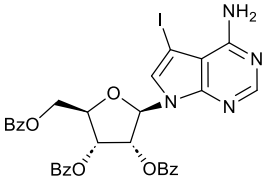
2.1. Preparation of intermediate **7** and its reactions

(2*R*,3*R*,4*R*,5*R*)-2-((Benzoyloxy)methyl)-5-(4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)tetrahydrofuran-3,4-diyl dibenzoate (4)



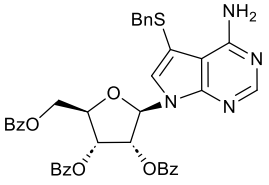
Compound **4** was prepared according to the reported procedure [1]. NMR characteristics were consistent with the published data.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (5)



Compound **5** was prepared by a modified published procedure [2]. Substrate **4** (13.73 g, 18.97 mmol) was dissolved in DMF (75 mL) and NaN_3 (1.48 g, 22.8 mmol, 1.2 eq) was added. After stirring at 80 °C for 90 minutes, the reaction reached completion. Triphenylphosphine (6.47 g, 24.7 mmol, 1.3 eq) was added, and the stirring was continued at the same temperature for 4 hours. Water (20 mL) and acetic acid (10.9 mL, 190 mmol, 10 eq) were added, and the mixture was further stirred at the same temperature overnight. The volatiles were evaporated, and the residue was subjected to reversed-phase flash column chromatography (RP-FCC) (50–100% of ACN in water, 0.1% of formic acid (FA) as modifier) affording **5** (11.90 g, 16.9 mmol, 89 %) as a colourless solid. NMR characteristics were consistent with the published data [2].

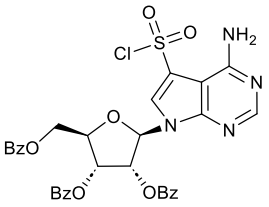
(2*R*,3*R*,4*R*,5*R*)-*2*-(4-Amino-5-(benzylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (6)



To a solution of **5** (11.89 g, 16.9 mmol), $Pd_2(dba)_3$ (396 mg, 0.43 mmol, 2.5 mol%) and Xantphos (553 mg, 0.96 mmol, 5.7 mol%) in an anhydrous 1,4-dioxane (280 mL) were added benzyl mercaptan (3.7 mL, 31 mmol, 1.86 eq) and DIPEA (7.4 mL, 42 mmol, 2.5 eq), and the mixture was stirred under an argon atmosphere at 80°C for 2 hours. The reaction mixture was concentrated, diluted with methanol, adsorbed onto silica and flash column chromatography (FCC) (10–40% of a 4:1 EtOAc/EtOH mixture in cyclohexane) gave **6** (11.3 g, 16.1 mmol, 95 %) as a yellowish oil. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 8.19 (s, 1H, H-2), 8.15 - 8.07 (m, 2H, Bz), 8.03 - 7.88 (m, 4H, Bz), 7.64 - 7.52 (m, 3H, Bz), 7.52 - 7.45 (m, 2H, Bz), 7.43 - 7.33 (m, 4H, Bz), 7.18 - 7.11 (m, 3H, SBn-Ar), 6.98 - 6.92 (m, 2H, SBn-Ar), 6.91 (s, 1H, H-8), 6.60 (d, $J_{1',2'}$ = 5.0 Hz, 1H, H-1'), 6.36 (s, 2H, NH_2), 6.06 - 5.95 (m, 2H, H-2',H-3'), 4.80 (dd, J_{gem} = 12.0 Hz, $J_{5'a,4'}$ = 3.2 Hz, 1H, H-5'a), 4.77 - 4.70 (m, 1H, H-4'), 4.64 (dd, J_{gem} = 12.0 Hz, $J_{5'b,4'}$ = 3.9 Hz, 1H, H-5'b), 3.75 (s, 2H, SBn-CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (5'-CO), 165.5 (3'-CO or 2'-CO), 165.2 (2'-CO or 3'-CO), 156.6 (C-6), 150.5 (C-2), 150.4 (C-4), 137.2 (Bn), 133.9 (Bz), 133.8 (Bz), 133.6 (Bz),

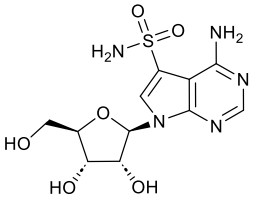
130.0 (Bz), 130.0 (Bz), 129.9 (Bz), 129.5 (Bz), 129.1 (Bz), 128.8 (Bz), 128.7 (Bz, Bn), 128.4 (C-8), 127.7 (Bn), 105.4 (C-7), 104.4 (C-5), 86.1 (C-1'), 80.5 (C-4'), 74.3 (C-2'), 71.6 (C-3'), 63.9 (C-5'), 43.0 (SBn-CH_2). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{39}H_{33}N_4O_7S$) calculated 701.2065, found 701.2058.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(chlorosulfonyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (7)



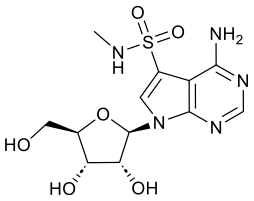
Compound **6** (11.27 g, 16.08 mmol) was dissolved in a 3:1 AcOH/water mixture (300 mL). *N*-Chlorosuccinimide (NCS) (8.59 g, 64.3 mmol, 4.0 eq) was added, and the reaction was stirred at room temperature (RT) overnight. Volatiles were evaporated, the residue was diluted with DCM, adsorbed onto silica, and subjected to RP-FCC (30–100% of ACN in water). Sulfonyl chloride **7** (9.60 g, 14.2 mmol, 88 %) was obtained as a white solid. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 8.32 (s, 1H, H-2), 8.13 - 8.06 (m, 2H, Bz), 8.02 (s, 1H, H-8), 8.01 - 7.97 (m, 2H, Bz), 7.96 - 7.91 (m, 2H, Bz), 7.64 - 7.52 (m, 3H, Bz), 7.51 - 7.44 (m, 2H, Bz), 7.44 - 7.34 (m, 4H, Bz), 6.58 (d, $J_{1',2'}$ = 4.3 Hz, 1H, H-1′), 6.27 (s, 2H, NH_2), 6.19 - 6.10 (m, 2H, H-2′, H-3′), 4.89 (dd, J_{gem} = 11.9 Hz, $J_{H\text{-}5'a,4'}$ = 3.0 Hz, 1H, H-5′a), 4.86 - 4.82 (m, 1H, H-4′), 4.77 (dd, J_{gem} = 11.9 Hz, $J_{H\text{-}5'b,4'}$ = 3.7 Hz, 1H, H-5′b). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (5′-CO), 165.4 (3′-CO or 2′-CO), 165.2 (2′-CO or 3′-CO), 156.3 (C-6), 154.1 (C-2), 151.4 (C-4), 134.0 (Bz), 134.0 (Bz), 133.8 (Bz), 130.0 (Bz), 130.0 (Bz), 129.9 (Bz), 129.5 (C--8), 129.3 (Bz), 128.9 (Bz), 128.7 (Bz), 128.7 (Bz), 128.5 (Bz), 120.4 (C-7), 98.6 (C-5), 88.3 (C-1′), 81.3 (C-4′), 74.7 (C-2′), 71.5 (C-3′), 63.5 (C-5′). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{32}H_{26}ClN_4O_9S$) calculated 677.1104, found 677.1101.

4-Amino-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (9a)



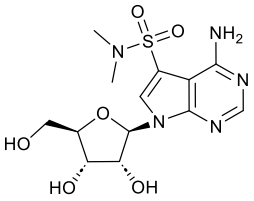
The benzoyl-protected sulfonyl chloride **7** (300 mg, 0.44 mmol) was dissolved in 7M ammonia in methanol (4.5 mL) and was stirred at 60 °C in a pressure-resistant tube overnight. The solvent was evaporated, and the residue was subjected to RP-FCC (10–50% of ACN in water, 0.1% of FA as modifier), affording nucleoside analogue **9a** (107 mg, 0.31 mmol, 70%) as a white solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.17 (s, 1H, H-2), 8.01 (s, 1H, H-8), 7.57 (s, 2H, SO_2-NH_2), 7.19 (s, 2H, NH_2), 6.09 (d, $J_{1',2'}$ = 6.2 Hz, 1H, H-1'), 5.39 (d, $J_{2'\text{-}OH,2'}$ = 6.5 Hz, 1H, 2'-OH), 5.24 - 5.15 (m, 2H, 3'-OH, 5'-OH), 4.42 - 4.33 (m, 1H, H-2'), 4.12 - 4.05 (m, 1H, H-3'), 3.97 - 3.90 (m, 1H, H-4'), 3.64 (ddd, J_{gem} = 11.9 Hz, $J_{5'a,5'\text{-}OH}$ = 4.8 Hz, $J_{5'a,4'}$ = 3.6 Hz, 1H, H-5'a), 3.56 (ddd, J_{gem} = 11.9 Hz, $J_{5'b,5'\text{-}OH}$ = 5.8 Hz, $J_{5'b,4'}$ = 3.6 Hz, 1H, H-5'b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.1 (C-6), 153.3 (C-2), 150.9 (C-4), 125.9 (C-8), 119.0 (C-7), 98.3 (C-5), 87.5 (C-1'), 85.7 (C-4'), 74.4 (C-2'), 70.7 (C-3'), 61.7 (C-5'). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{11}H_{16}N_5O_6S$) calculated 346.0816, found 346.0815.

4-Amino-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-*N*-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (9b)



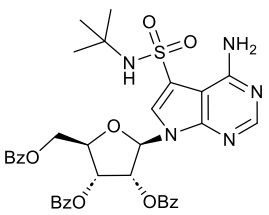
Sulfonyl chloride **7** (200 mg, 0.30 mmol) was dissolved in 33% $MeNH_2$ (3.0 mL) in ethanol. After stirring at RT for 6 hours, the reaction was complete. The volatiles were removed under reduced pressure, and the residue was subjected to RP-FCC (10–50% of ACN in water, 0.1 % of FA as modifier), affording product **9b** (84 mg, 0.23 mmol, 79%) as a white solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.18 (s, 1H, H-2), 8.11 (s, 1H, H-8), 7.52 (s, 1H, SO_2-NH), 7.23 (s, 2H, NH_2), 6.09 (d, $J_{1',2'}$ = 5.7 Hz, 1H, H-1'), 5.45 (d, $J_{2'\text{-OH},2'}$ = 6.1 Hz, 1H, 2'-OH), 5.23 (m, 1H, 5'-OH), 5.18 (d, $J_{3'\text{-OH},3'}$ = 4.8 Hz, 1H, 3'-OH), 4.44 - 4.36 (m, 1H, H-2'), 4.14 - 4.06 (m, 1H, H-3'), 3.97 - 3.90 (m, 1H, H-4'), 3.71 - 3.61 (m, 1H, H-5'a), 3.57 (ddd, J_{gem} = 12.0 Hz, $J_{5'b,5'\text{-OH}}$ = 5.4 Hz, $J_{5'b,4'}$ = 3.3 Hz, 1H, H-5'b), 2.47 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.1 (C-6), 153.3 (C-2), 151.0 (C-4), 127.8 (C-8), 113.3 (C-7), 98.4 (C-5), 87.8 (C-1'), 85.6 (C-4'), 74.4 (C-2'), 70.5 (C-3'), 61.4 (C-5'), 28.6 (CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{12}H_{18}N_5O_6S$) calculated 360.0972, found 360.0971.

4-Amino-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-*N*,*N*-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (9c)



The starting sulfonyl chloride **7** (200 mg, 0.30 mmol) was dissolved in DCM (3.0 mL) and 40% Me_2NH in water (0.246 mL, 1.48 mmol, 5.0 eq) was added. After stirring at RT for 10 minutes, the starting material was converted to a sulfonamide. The volatiles were evaporated, and the residue was codistilled with ethanol to remove water. The solid residue was dissolved in 33% $MeNH_2$ solution in ethanol (3.0 mL), and the mixture was stirred in a closed flask at RT for 6 hours. The volatiles were removed under reduced pressure, and the residue was subjected to RP-FCC (10–40% of ACN in water, 0.1 % of FA), affording pure **9c** (98 mg, 0.26 mmol, 89%). **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.27 (s, 1H, H-8), 8.21 (s, 1H, H-2), 7.63 (s, 1H, NH_2a), 6.96 (s, 1H, NH_2b), 6.12 (d, $J_{1',2'}$ = 5.2 Hz, 1H, H-1'), 5.47 (d, $J_{2'\text{-OH},2'}$ = 5.9 Hz, 1H, 2'-OH), 5.26 (dd, $J_{5'\text{-OH},5'b}$ = 5.7 Hz, $J_{5'\text{-OH},5'a}$ = 4.7 Hz, 1H, 5'-OH), 5.15 (d, $J_{3'\text{-OH},3'}$ = 5.1 Hz, 1H, 3'-OH), 4.46 - 4.37 (m, 1H, H-2'), 4.17 - 4.08 (m, 1H, H-3'), 3.99 - 3.92 (m, 1H, H-4'), 3.70 (ddd, J_{gem} = 11.9 Hz, $J_{5'a,5'\text{-OH}}$ = 4.7 Hz, $J_{5'a,4'}$ = 3.4 Hz, 1H, H-5'a), 3.58 (ddd, J_{gem} = 12.0 Hz, $J_{5'b,5'\text{-OH}}$ = 5.7 Hz, $J_{5'b,4'}$ = 3.2 Hz, 1H, H-5'b), 2.61 (s, 6H, 2xMe). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.1 (C-6), 153.3 (C-2), 150.7 (C-4), 128.9 (C-8), 107.9 (C-7), 99.2 (C-5), 88.1 (C-1'), 85.4 (C-4'), 74.5 (C-2'), 70.2 (C-3'), 61.1 (C-5'), 37.7 (C-Me). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{13}H_{20}N_5O_6S$) calculated 374.1129, found 374.1128.

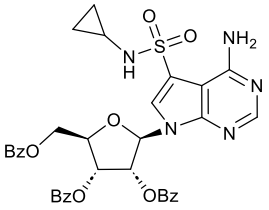
(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(*N*-(*tert*-butyl)sulfamoyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8d)



To a solution of **7** (250 mg, 0.37 mmol) in anhydrous DCM (3.8 mL), *tert*-butylamine (98 µL, 0.92 mmol, 2.5 eq) was added, and the mixture was stirred under argon at RT overnight. The solvent was evaporated, and the residue was subjected to FCC (2–20% of a 4:1 EtOAc/EtOH mixture in DCM), affording **8d** (233 mg, 0.33 mmol, 88%) as a colourless solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.22 (s, 1H, H-8), 8.17 (s, 1H, H-2), 8.04 - 7.93 (m, 4H, Bz), 7.86 - 7.79 (m, 2H, Bz), 7.74 (s, 1H, SO_2-NH), 7.71 - 7.60 (m, 3H, Bz), 7.55 -

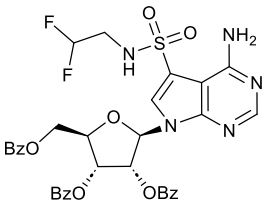
7.47 (m, 4H, Bz), 7.45 - 7.38 (m, 2H, Bz), 6.63 (d, $J_{1',2'}$ = 5.4 Hz, 1H, H-1'), 6.40 - 6.35 (m, 1H, H-2'), 6.18 - 6.10 (m, 1H, H-3'), 4.87 - 4.81 (m, 1H, H-4'), 4.79 (dd, J_{gem} = 12.0 Hz, $J_{5'a,4'}$ = 3.8 Hz, 1H, H-5'a), 4.69 (dd, J_{gem} = 12.0 Hz, $J_{5'b,4'}$ = 5.1 Hz, 1H, H-5'b), 1.11 (s, 9H, t-Bu). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.9 (5'-CO), 165.2 (3'-CO), 164.9 (2'-CO), 156.0 (C-6), 152.2 (C-2), 150.8 (C-4), 134.5 (Bz), 134.4 (Bz), 134.0 (Bz), 129.9 (Bz), 129.8 (Bz), 129.7 (Bz), 129.3 (Bz), 129.2 (C-8, Bz), 129.1 (Bz), 128.7 (Bz), 120.3 (C-7), 98.8 (C-5), 87.3 (C-1'), 79.7 (C-4'), 73.5 (C-2'), 71.3 (C-3'), 63.9 (C-5'), 54.2 (t-Bu-C), 29.9 (t-Bu-CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{36}H_{36}N_5O_9S$) calculated 714.2228, found 714.2226.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(*N*-cyclopropylsulfamoyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8e)



To a stirred solution of **7** (250 mg, 0.37 mmol) in anhydrous DCM (3.7 mL), cyclopropylamine (77 µL, 1.1 mmol, 3.0 eq) was added in one portion. After stirring at RT for 40 minutes, the reaction reached completion. The solvent was evaporated, and the crude product was adsorbed onto silica. FCC (5–25% of a 4:1 EtOAc/EtOH mixture in DCM) afforded pure product **8e** (235 mg, 0.34 mmol, 91%) as a white solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.28 (s, 1H, H-8), 8.20 (s, 1H, H-2), 8.16 (d, $J_{SO2\text{-}NH,H\text{-}1''}$ = 2.4 Hz, 1H, SO_2-NH), 8.02 - 7.94 (m, 4H, Bz), 7.90 - 7.78 (m, 2H, Bz), 7.72 - 7.57 (m, 3H, Bz), 7.55 - 7.45 (m, 4H, Bz), 7.45 - 7.39 (m, 2H, Bz), 6.67 (d, $J_{1',2'}$ = 5.2 Hz, 1H, H-1'), 6.37 (dd, $J_{2',3'}$ = 6.3 Hz, $J_{2',1'}$ = 5.2 Hz, 1H, H-2'), 6.17 - 6.11 (m, 1H, H-3'), 4.88 - 4.83 (m, 1H, H-4'), 4.80 (dd, J_{gem} = 12.1 Hz, $J_{5'a,4'}$ = 3.7 Hz, 1H, H-5'a), 4.70 (dd, J_{gem} = 12.0 Hz, $J_{5'b,4'}$ = 5.2 Hz, 1H, H-5'b), 2.23 - 2.13 (m, 1H, H-1''), 0.47 - 0.41 (m, 2H, H-2''a), 0.35 - 0.30 (m, 2H, H-2''b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6 (5′-CO), 164.9 (3′-CO), 164.6 (2′-CO), 155.8 (C-6), 151.7 (C-2), 150.4 (C-4), 134.2 (Bz), 134.1 (Bz), 133.7 (Bz), 129.7 (C-8), 129.6 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Bz), 128.9 (Bz), 128.8 (Bz), 128.4 (Bz), 115.7 (C-7), 98.6 (C-5), 87.2 (C-1′), 79.5 (C-4′), 73.4 (C-2′), 70.9 (C-3′), 63.7 (C-5′), 23.9 (C-1''), 5.2 (C-2''a), 5.2 (C-2''b). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{35}H_{32}N_5O_9S$) calculated 698.1915, found 698.1914.

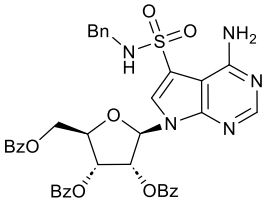
(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(*N*-(2,2-difluoroethyl)sulfamoyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8f)



A mixture of **7** (250.0 mg, 0.37 mmol), 2,2-difluoroethylamine hydrochloride (52 mg, 0.44 mmol, 1.2 eq), and DMAP (108 mg, 0.89 mmol, 2.4 eq) in anhydrous DCM (3.7 mL) was stirred at RT for 30 minutes, until the starting material was fully consumed. The solvent was evaporated, and the residue was purified by FCC (5–20% of a 4:1 EtOAc/EtOH mixture in DCM), yielding product **8f** (233 mg, 0.32 mmol, 87%) as a colourless solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.54 (t, $J_{SO2\text{-}NH,\ H\text{-}1''}$ = 6.3 Hz, 1H, SO_2-NH), 8.32 (s, 1H, H-8), 8.20 (s, 1H, H-2), 8.03 - 7.97 (m, 2H, Bz), 7.97 - 7.92 (m, 2H, Bz), 7.89 - 7.81 (m, 2H, Bz), 7.71 - 7.59 (m, 3H, Bz), 7.57 - 7.37 (m, 6H, Bz), 6.63 (d, $J_{1',2'}$ = 5.0 Hz, 1H, H-1'), 6.35 (dd, $J_{2',3'}$ = 6.3 Hz, $J_{2',1'}$ = 5.0 Hz, 1H, H-2′), 6.19 - 6.14 (m, 1H, H-3′), 6.14 - 5.83 (m, 1H, H-2′′), 4.88 - 4.82 (m, 1H, H-4′), 4.78 (dd, J_{gem} = 12.1 Hz, $J_{5'a,4'}$ = 3.8 Hz, 1H, H-5'a), 4.70 (dd, J_{gem} = 12.1 Hz, $J_{5'b,4'}$ = 5.2 Hz, 1H, H-5'b), 3.27 (tdd, $J_{H\text{-}1'',F}$ = 15.4 Hz, $J_{H\text{-}1'',SO2\text{-}NH}$ = 6.4 Hz, $J_{H\text{-}1'',H\text{-}2''}$ = 3.9 Hz, 2H, H-1''). **^{13}C**

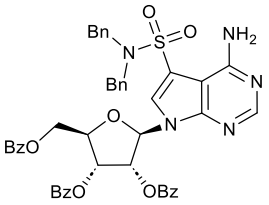
NMR (101 MHz, DMSO-d_6) δ 165.6 (5′-CO), 164.9 (3′-CO), 164.7 (2′-CO), 155.9 (C-6), 152.1 (C-2), 150.6 (C-4), 134.2 (Bz), 134.1 (Bz), 133.7 (Bz), 129.6 (Bz), 129.5 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Bz), 128.9 (Bz), 128.8 (Bz), 128.4 (Bz), 115.6 (C-7), 114.6 (t, $J_{C\text{-}2'',F}$ = 240.5 Hz, C-2''), 98.4 (C-5), 87.3 (C-1'), 79.4 (C-4'), 73.5 (C-2'), 70.8 (C-3'), 63.6 (C-5'), 44.2 (t, $J_{C\text{-}1'',F}$ = 26.4 Hz, C-1''). **^{19}F NMR** (376 MHz, DMSO-d_6) δ -121.89 (dt, $J_{F,H\text{-}2''}$ = 55.3 Hz, $J_{F,H\text{-}1''}$ = 15.4 Hz). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{34}H_{30}F_2N_5O_9S$) calculated 722.1727, found 722.1729.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(*N*-benzylsulfamoyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8g)



Compound **7** (248 mg, 0.37 mmol) was dissolved in anhydrous DCM (5.2 mL) and cooled to 0 °C. Benzylamine (88 µL, 0.81 mmol, 2.2 eq) was added, and the reaction was stirred for 30 minutes before the bath was removed, and the stirring was continued overnight. The resulting suspension was diluted with MeOH, and the obtained solution was adsorbed onto silica. FCC (10–40% of a 4:1 EtOAc/EtOH mixture in cyclohexane) afforded **8g** (272 mg, 0.36 mmol, 99%) as a colourless solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.42 (t, $J_{SO2\text{-}NH,H\text{-}1''}$ = 6.2 Hz, 1H, SO_2-NH), 8.22 (s, 1H, H-8), 8.14 (s, 1H, H-2), 8.02 - 7.97 (m, 2H, Bz), 7.97 - 7.92 (m, 2H, Bz), 7.90 - 7.83 (m, 2H, Bz), 7.71 - 7.59 (m, 3H, Bz), 7.55 - 7.39 (m, 6H, Bz), 7.17 - 7.05 (m, 5H, Bn-Ar), 6.61 (d, $J_{1',2'}$ = 5.0 Hz, 1H, H-1'), 6.33 (dd, $J_{2',3',2',1'}$ = 6.3 Hz, J = 5.0 Hz, 1H, H-2'), 6.20 - 6.12 (m, 1H, H-3'), 4.86 - 4.81 (m, 1H, H-4'), 4.78 (dd, J_{gem} = 12.1 Hz, $J_{5'a,4'}$ = 3.7 Hz, 1H, H-5'a), 4.70 (dd, J_{gem} = 12.1 Hz, $J_{5'b,4'}$ = 5.2 Hz, 1H, H-5'b), 4.03 (d, $J_{H\text{-}1'',SO2\text{-}NH}$ = 6.2 Hz, 2H, H-1''). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.7 (5'-CO), 164.9 (3'-CO), 164.7 (2'-CO), 156.3 (C-6), 152.6 (C-2), 150.7 (C-4), 137.5 (C-2''), 134.2 (Bz), 134.1 (Bz), 133.7 (Bz), 129.6 (Bz), 129.5 (Bz), 129.5 (Bz), 129.4 (Bz), 129.1 (C-8), 129.0 (Bz), 129.0 (Bz), 128.9 (Bz), 128.8 (Bz), 128.5 (Bz), 128.2 (C-4''), 127.6 (C-3''), 127.2 (C-5''), 116.0 (C-7), 98.5 (C-5), 87.1 (C-1'), 79.3 (C-4'), 73.5 (C-2'), 70.8 (C-3'), 63.6 (C-5'), 45.9 (C-1''). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{39}H_{34}N_5O_9S$) calculated 748.2072, found 748.2071.

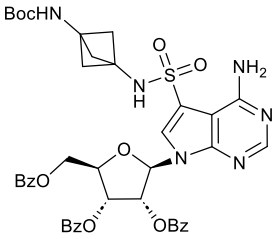
(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(*N*,*N*-dibenzylsulfamoyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8h)



Sulfonyl chloride **7** (241 mg, 0.36 mmol) was dissolved in anhydrous DCM (5.1 mL). Dibenzylamine (151 µL, 0.78 mmol, 2.2 eq) was added at 0 °C, and the reaction was stirred for 30 minutes before the bath was removed, and the stirring was continued overnight. The resulting suspension was diluted with MeOH, affording a clear solution, which was adsorbed onto silica. FCC (10–40% of a 4:1 EtOAc/EtOH mixture in cyclohexane) yielded **8h** (296 mg, 0.35 mmol, 99%) as a colourless solid. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 8.28 (s, 1H, H-2), 8.12 - 8.05 (m, 2H, Bz), 8.04 - 7.98 (m, 2H, Bz), 7.94 - 7.87 (m, 2H, Bz), 7.62 (s, 1H, H-8), 7.61 - 7.47 (m, 3H, Bz), 7.44 - 7.33 (m, 6H, Bz), 7.23 - 7.12 (m, 6H, Bn-Ar), 7.09 - 7.00 (m, 4H, Bn-Ar), 6.58 (d, $J_{1',2'}$ = 5.3 Hz, 1H, H-1'), 6.17 - 6.07 (m, 2H, H-2', H-3'), 4.83 (dd, J_{gem} = 11.8 Hz, $J_{5'a,4'}$ = 3.1 Hz, 1H, H-5'a), 4.81 - 4.77 (m, 1H, H-4'), 4.71 (dd, J_{gem} = 11.8 Hz, $J_{5'b,4'}$ = 3.9 Hz, 1H, H-5'b), 4.26 (s, 4H, H-1''). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (5'-CO), 165.5 (3'-CO), 165.2 (2'-

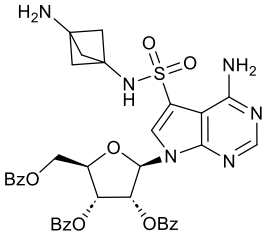
CO), 156.8 (C-6), *153.2 (C-2), 151.3 (C-4), 135.4 (C-2"), 133.9 (Bz), 133.9 (Bz), 133.7 (Bz), 130.0 (Bz), 130.0 (Bz), 129.8 (Bz), 129.3 (Bz), 128.9 (Bz), 128.7 (Bz), 128.7 (Bz), 128.6 (C-3" or C-4"), 128.6 (C-4" or C-3"), 127.9 (C-5"), 127.1 (C-8), 116.4 (C-7), 99.8 (C-5), 87.1 (C-1'), 81.0 (C-4'), 74.2 (C-2'), 71.7 (C-3'), 63.9 (C-5'), 51.1 (C-1"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{46}H_{40}N_5O_9S$) calculated 838.2541, found 838.2538.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(*N*-(3-((*tert*-butoxycarbonyl)amino)bicyclo[1.1.1]pentan-1-yl)sulfamoyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8i)



Sulfonyl chloride **7** (271 mg, 0.40 mmol), DMAP (59 mg, 0.48 mmol, 1.2 eq), and *tert*-butyl (3-aminobicyclo[1.1.1]pentan-1-yl)carbamate (95 mg, 0.48 mmol, 1.2 eq) were dissolved in anhydrous DCM (4.0 mL) and the solution was stirred at RT under argon for 20 minutes. After this time, the mixture was adsorbed onto silica and purified by FCC (10–30% of a 4:1 EtOAc/EtOH mixture in DCM). The product **8i** (287 mg, 0.34 mmol, 86%) was obtained as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.78 (s, 1H, SO_2-NH), 8.19 (s, 1H, H-8), 8.10 (s, 1H, H-2), 8.04 - 7.93 (m, 4H, Bz), 7.87 - 7.80 (m, 2H, Bz), 7.72 - 7.59 (m, 3H, Bz), 7.55 - 7.45 (m, 4H, Bz), 7.44 - 7.38 (m, 2H, Bz), 6.62 (d, $J_{1',2'}$ = 5.2 Hz, 1H, H-1'), 6.40 (dd, $J_{2',3'}$ = 6.2 Hz, $J_{2',1'}$ = 5.2 Hz, 1H, H-2'), 6.20 - 6.12 (m, 1H, H-3'), 4.87 - 4.74 (m, 2H, H-4',H-5'a), 4.69 (dd, J_{gem} = 11.9 Hz, $J_{5'b,4'}$ = 4.8 Hz, 1H, H-5'b), 1.91 (s, 6H, H-2"), 1.30 (s, 9H, t-Bu). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.7 (5'-CO), 164.9 (3'-CO), 164.6 (2'-CO), 157.0 (C-6), 154.6 (Boc-CO), 153.6 (C-2), 151.0 (C-4), 134.2 (Bz), 134.1 (Bz), 133.7 (Bz), 129.6 (Bz), 129.5 (C-8, Bz), 129.4 (Bz), 129.0 (Bz), 128.9 (Bz), 128.4 (Bz), 116.5 (C-7), 98.6 (C-5), 87.4 (C-1'), 79.3 (C-4'), *78.0 (t-Bu-C), 73.2 (C-2'), 71.0 (C-3'), 63.6 (C-5'), 54.4 (C-2"), 44.4 (C-1" or C-3"), 44.2 (C-3" or C-1"), 28.3 (t-Bu-CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{42}H_{43}N_6O_{11}S$) calculated 839.2705, found 839.2703.

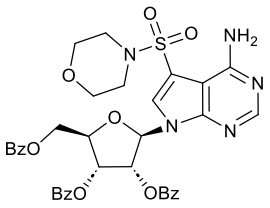
(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(*N*-(3-aminobicyclo[1.1.1]pentan-1-yl)sulfamoyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8i-Dep)



Boc-protected starting material **8i** (278 mg, 0.33 mmol) was dissolved in DCM (6.8 mL), and TFA (0.75 mL, 9.8 mmol, 30 eq) was added to the solution. After stirring at RT for 90 minutes, the Boc group was fully cleaved. The reaction mixture was concentrated, and the residue was co-evaporated with methanol, removing the residual TFA. The residue was subjected to FCC (2–15% of a 9:1 MeOH/NH_4OH (aq., conc.) mixture in DCM), affording product **8i-Dep** (235 mg, 0.32 mmol, 96%) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.17 (s, 1H, H-8), 8.10 (s, 1H, H-2), 8.05 - 7.94 (m, 4H, Bz), 7.90 - 7.80 (m, 2H, Bz), 7.72 - 7.58 (m, 3H, Bz), 7.55 - 7.46 (m, 4H, Bz), 7.46 - 7.38 (m, 2H, Bz), 6.64 (d, $J_{1',2'}$ = 5.4 Hz, 1H, H-1'), 6.45 - 6.38 (m, 1H, H-2'), 6.18 - 6.11 (m, 1H, H-3'), 4.87 - 4.76 (m, 2H, H-4',H-5'a), 4.70 (dd, J_{gem} = 12.0 Hz, $J_{5'b,4'}$ = 5.0 Hz, 1H, H-5'b), 1.66 (s, 6H, H-2"). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.7 (5'-CO), 164.9 (3'-CO), 164.6 (2'-CO), 157.1 (C-6), 153.6 (C-2), 151.0 (C-4), 134.2 (Bz), 134.1 (Bz), 133.7 (Bz), 129.6 (Bz), 129.5 (Bz), 129.4 (Bz), 129.3

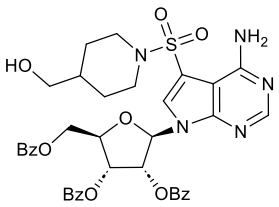
(C-8), 129.0 (Bz), 128.8 (Bz), 128.4 (Bz), 116.7 (C-7), 98.6 (C-5), 87.1 (C-1'), 79.4 (C-4'), 73.1 (C-2'), 71.1 (C-3'), 63.7 (C-5'), 55.3 (C-2"), 48.1 (C-1" or C-3"), 42.9 (C-3" or C-1"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{37}H_{35}N_6O_9S$) calculated 739.2181, found 739.2182.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(morpholinosulfonyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8j)



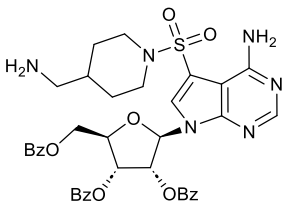
To a stirred solution of sulfonyl chloride **7** (250 mg, 0.37 mmol) in anhydrous DCM (3.7 mL), morpholine (96 µL, 1.1 mmol, 3.0 eq) was added. After stirring for 15 minutes at RT, the reaction reached completion. The volatiles were evaporated, and the residue was subjected to FCC (5–20% of a 4:1 EtOAc/EtOH mixture in DCM), affording product **8j** (244 mg, 0.34 mmol, 91%) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.29 (s, 1H, H-8), 8.15 (s, 1H, H-2), 8.05 - 7.93 (m, 4H, Bz), 7.88 - 7.81 (m, 2H, Bz), 7.73 - 7.55 (m, 3H, Bz), 7.53 - 7.38 (m, 6H, Bz), 6.89 (s, 1H, NH_2), 6.64 (d, $J_{1',2'}$ = 5.1 Hz, 1H, H-1′), 6.41 (dd, $J_{2',3'}$ = 6.3 Hz, $J_{2',1'}$ = 5.1 Hz, 1H, H-2′), 6.20 (dd, $J_{3',2'}$ = 6.2 Hz, $J_{3',4'}$ = 5.3 Hz, 1H, H-3′), 4.89 - 4.77 (m, 2H, H-4′,H-5′a), 4.70 (dd, J_{gem} = 12.0 Hz, $J_{H\text{-}5'b,4'}$ = 5.0 Hz, 1H, H-5′b), 3.61 (m, 4H, H-3″), 2.86 (m, 4H, H-2″). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6 (5′-CO), 164.9 (3′-CO), 164.6 (2′-CO), 157.2 (C-6), 153.6 (C-2), 151.0 (C-4), 134.2 (Bz), 134.1 (Bz), 133.7 (Bz), 130.4 (C-8), 129.6 (Bz), 129.5 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Bz), 128.9 (Bz), 128.8 (Bz), 128.5 (Bz), 108.8 (C-7), 99.2 (C-5), 87.4 (C-1′), 79.5 (C-4′), 73.5 (C-2′), 71.0 (C-3′), 65.2 (C-3″), 63.5 (C-5′), 45.6 (C-2″). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{36}H_{34}N_5O_{10}S$) calculated 728.2021, found 728.2019.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-((4-(hydroxymethyl)piperidin-1-yl)sulfonyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8k)



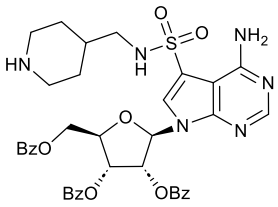
7 (250 mg, 0.37 mmol), 4-(hydroxymethyl)piperidine (51 mg, 0.44 mmol, 1.2 eq), and DMAP (54 mg, 0.44 mmol, 1.2 eq) were mixed in anhydrous DCM (3.7 mL). After 40 minutes at RT, the reaction was complete. The reaction mixture was adsorbed onto silica, and the product was purified by FCC (10–30% of a 4:1 EtOAc/EtOH mixture in DCM). The compound **8k** (257 mg, 0.34 mmol, 92%) was obtained as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.24 (s, 1H, H-8), 8.13 (s, 1H, H-2), 8.05 - 7.93 (m, 4H, Bz), 7.87 - 7.79 (m, 2H, Bz), 7.72 - 7.58 (m, 3H, Bz), 7.56 - 7.46 (m, 4H, Bz), 7.46 - 7.38 (m, 2H, Bz), 6.94 (s, 1H, NH_2), 6.63 (d, $J_{1',2'}$ = 5.3 Hz, 1H, H-1'), 6.40 (dd, $J_{2',3'}$ = 6.2 Hz, $J_{2',1'}$ = 5.3 Hz, 1H, H-2'), 6.18 (dd, $J_{3',2'}$ = 6.2 Hz, $J_{3',4'}$ = 5.1 Hz, 1H, H-3'), 4.89 - 4.76 (m, 2H, H-4', H-5'a), 4.70 (dd, J_{gem} = 12.0 Hz, $J_{5',4'}$ = 5.0 Hz, 1H, H-5'b), 4.50 - 4.43 (m, 1H, 5"-OH), 3.63 - 3.53 (m, 2H, H-2"a), 3.21 - 3.12 (m, 2H, H-5"), 2.30 - 2.13 (m, 2H, H-2"b), 1.72 - 1.55 (m, 2H, H-3"a), 1.30 - 1.20 (m, 1H, H-4"), 1.20 - 1.06 (m, 2H, H-3"b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6 (5'-CO), 164.9 (3'-CO), 164.6 (2'-CO), 157.2 (C-6), 153.5 (C-2), 150.9 (C-4), 134.2 (Bz), 134.1 (Bz), 133.8 (Bz), 129.7 (C-8), 129.6 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Bz), 129.0 (Bz), 128.9 (Bz), 128.8 (Bz), 128.4 (Bz), 110.2 (C-7), 99.2 (C-5), 87.2 (C-1'), 79.5 (C-4'), 73.4 (C-2'), 71.0 (C-3'), 65.3 (C-5"), 63.6 (C-5'), 45.7 (C-2"), 37.2 (C-4"), 27.7 (C-3"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{38}H_{38}N_5O_{10}S$) calculated 756.2334, found 756.2333.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-((4-(aminomethyl)piperidin-1-yl)sulfonyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8l)



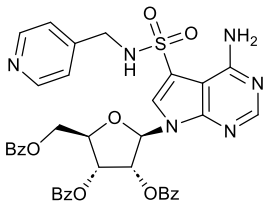
To an ice-cold solution of **7** (250 mg, 0.37 mmol) in anhydrous DCM (3.8 mL), 4-(aminomethyl)piperidine (55 mg, 0.48 mmol, 1.3 eq) was added. The mixture immediately turned turbid. After 10 minutes at 0°C, the starting material was consumed, as monitored by UPLC, and only a single peak with the appropriate mass was observed. The suspension was diluted with MeOH, adsorbed onto silica, and the product was purified by FCC (2–20% of a 9:1 MeOH/NH_4OH (aq., conc.) mixture in DCM). The compound **8l** (165.0 mg, 0.219 mmol, 59.2%) was obtained as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.25 (s, 1H, H-8), 8.14 (s, 1H, H-2), 8.06 - 7.94 (m, 4H, Bz), 7.88 - 7.79 (m, 2H, Bz), 7.73 - 7.59 (m, 3H, Bz), 7.57 - 7.47 (m, 4H, Bz), 7.47 - 7.38 (m, 2H, Bz), 6.95 (s, 1H, NH_2), 6.64 (d, $J_{1',2'}$ = 5.3 Hz, 1H, H-1'), 6.41 (dd, $J_{2',3'}$ = 6.2 Hz, $J_{2',1'}$ = 5.3 Hz, 1H, H-2'), 6.18 (dd, $J_{3',2'}$ = 6.2 Hz, $J_{3',4'}$ = 5.1 Hz, 1H, H-3'), 4.90 - 4.77 (m, 2H, H-4',H-5'a), 4.71 (dd, J_{gem} = 12.0 Hz, $J_{5',4'}$ = 5.0 Hz, 1H, H-5'b), 3.62 - 3.54 (m, 2H, H-2"a), 2.34 - 2.29 (m, 2H, H-5"), 2.28 - 2.12 (m, 2H, H-2"b), 1.75 - 1.56 (m, 2H, H-3"a), 1.22 - 1.00 (m, 3H, H-3"b,H-4"). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6 (5'-CO), 164.9 (3'-CO), 164.6 (2'-CO), 157.2 (C-6), 153.5 (C-2), 150.9 (C-4), 134.2 (Bz), 134.1 (Bz), 133.7 (Bz), 129.7 (C-8), 129.6 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Bz), 129.0 (Bz), 128.9 (Bz), 128.8 (Bz), 128.4 (Bz), 110.2 (C-7), 99.1 (C-5), 87.1 (C-1'), 79.5 (C-4'), 73.3 (C-2'), 71.0 (C-3'), 63.6 (C-5'), 47.1 (C-5"), 45.8 (C-2"), 37.8 (C-4"), 28.6 (C-3"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{38}H_{39}N_6O_9S$) calculated 755.2494, found 755.2490.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(*N*-(piperidin-4-ylmethyl)sulfamoyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8m)



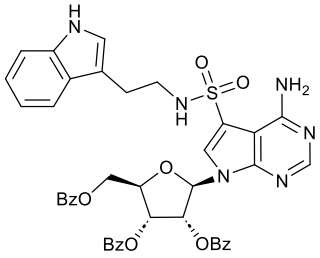
To a stirred solution of starting material **7** (250 mg, 0.37 mmol) in anhydrous DCM (3.7 mL), DMAP (54 mg, 0.44 mmol, 1.2 eq) and 1-Boc-4-(aminomethyl)piperidine (95 mg, 0.44 mmol, 1.2 eq) were added. After stirring for 15 minutes at RT, the reaction reached completion. The volatiles were evaporated, and the residue was redissolved in DCM (3.7 mL), TFA (368 µL, 4.8 mmol, 13 eq) was added to the mixture. After stirring at RT for 1 hour, the solvents were evaporated, and the residue was subjected to FCC (10–30% of 9:1 MeOH/NH_4OH (aq., conc.) mixture in DCM). The product **8m** (141 mg, 0.19 mmol, 51%) was obtained as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.18 (s, 1H, H-8), 8.12 (s, 1H, H-2), 8.04 - 7.90 (m, 4H, Bz), 7.87 - 7.81 (m, 2H, Bz), 7.71 - 7.56 (m, 3H, Bz), 7.55 - 7.38 (m, 6H, Bz), 6.62 (d, $J_{1',2'}$ = 5.2 Hz, 1H, H-1'), 6.42 - 6.35 (m, 1H, H-2'), 6.19 - 6.11 (m, 1H, H-3'), 4.87 - 4.74 (m, 2H, H-4',H-5'a), 4.69 (dd, J_{gem} = 11.9 Hz, $J_{5',4'}$ = 5.0 Hz, 1H, H-5'b), 2.82 - 2.73 (m, 2H, H-4"a), 2.67 - 2.61 (m, 2H, H-1"), 2.30 - 2.19 (m, 2H, H-4"a), 1.47 - 1.40 (m, 2H, H-3"a), 1.38 - 1.26 (m, 1H, H-2"), 0.88 - 0.75 (m, 2H, H-3"b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6 (5'-CO), 164.9 (3'-CO), 164.6 (2'-CO), 157.1 (C-6), 153.6 (C-2), 151.1 (C-4), 134.2 (Bz), 134.1 (Bz), 133.7 (Bz), 129.6 (Bz), 129.5 (Bz), 129.4 (Bz), 128.9 (Bz), 128.8 (Bz), 128.6 (C-8), 128.4 (Bz), 115.8 (C-7), 98.5 (C-5), 86.9 (C-1'), 79.3 (C-4'), 73.3 (C-2'), 70.9 (C-3'), 63.7 (C-5'), 48.3 (C-1"), 45.6 (C-4"), 35.9 (C-2"), 30.4 (C-3"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{38}H_{39}N_6O_9S$) calculated 755.2494, found 755.2490.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(*N*-(pyridin-4-ylmethyl)sulfamoyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8n)



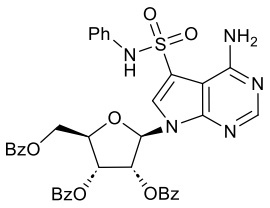
Sulfonyl chloride **7** (250 mg, 0.37 mmol), 4-(aminomethyl)pyridine (45 µL, 0.44 mmol, 1.2 eq), and DMAP (54 mg, 0.44 mmol, 1.2 eq) were dissolved in anhydrous DCM (3.7 mL) and stirred at RT for 30 minutes. The reaction mixture was diluted with MeOH, adsorbed onto silica, and subjected to FCC (10–65% of a 4:1 EtOAc/EtOH mixture in DCM), affording product **8n** (241 mg, 0.32 mmol, 87%) as a colourless solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.54 (s, 1H, SO_2-NH), 8.37 - 8.31 (m, 2H, H-4''), 8.22 (s, 1H, C-8), 8.11 (s, 1H, C-2), 8.02 - 7.98 (m, 2H, Bz), 7.97 - 7.92 (m, 2H, Bz), 7.91 - 7.82 (m, 2H, Bz), 7.71 - 7.59 (m, 3H, Bz), 7.54 - 7.39 (m, 6H, Bz), 7.19 - 7.13 (m, 2H, H-3''), 6.59 (d, $J_{1',2'}$ = 5.0 Hz, 1H, H-1'), 6.34 (dd, $J_{2',3'}$ = 6.2 Hz, $J_{2',1'}$ = 5.0 Hz, 1H, H-2'), 6.20 - 6.13 (m, 1H, H-3'), 4.85 - 4.80 (m, 1H, H-4'), 4.78 (dd, J_{gem} = 12.0 Hz, $J_{5'a,4'}$ = 3.7 Hz, 1H, H-5'a), 4.69 (dd, J_{gem} = 12.0 Hz, $J_{5'b,4'}$ = 5.2 Hz, 1H, H-5'b), 4.10 - 4.03 (m, 2H, H-1''). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6 (5'-CO), 164.9 (3'-CO), 164.7 (2'-CO), 157.1 (C-6), 153.7 (C-2), 151.1 (C-4), 149.4 (C-4''), 146.8 (C-2''), 134.2 (Bz), 134.1 (Bz), 133.7 (Bz), 129.6 (Bz), 129.5 (Bz), 129.5 (Bz), 129.4 (Bz), 129.1 (C-8), 129.0 (Bz), 128.9 (Bz), 128.8 (Bz), 128.5 (Bz), 122.4 (C-3''), 115.3 (C-7), 98.4 (C-5), 87.0 (C-1'), 79.3 (C-4'), 73.5 (C-2'), 70.8 (C-3'), 63.7 (C-5'), 44.7 (C-1''). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{38}H_{33}N_6O_9S$) calculated 749.2024, found 749.2023.

(2*R*,3*R*,4*R*,5*R*)-2-(5-(*N*-(2-(1*H*-Indol-3-yl)ethyl)sulfamoyl)-4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8o)



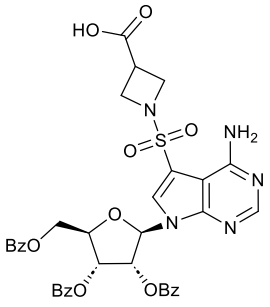
Compound **7** (250 mg, 0.37 mmol), tryptamine (71 mg, 0.44 mmol, 1.2 eq), and DMAP (54 mg, 0.44 mmol, 1.2 eq) were dissolved in anhydrous DCM (3.7 mL), and the solution was stirred at RT for 25 minutes. The reaction mixture was diluted with MeOH, adsorbed onto silica, and subjected to FCC (5–25% of a 4:1 EtOAc/EtOH mixture in DCM). Product **8o** (254 mg, 0.32 mmol, 86%) was obtained as a colourless solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.80 (s, 1H, indole-NH), 8.20 (s, 1H, H-8), 8.11 (s, 1H, H-2), 8.01 - 7.90 (m, 5H, Bz,SO_2-NH), 7.83 - 7.76 (m, 2H, Bz), 7.71 - 7.56 (m, 3H, Bz), 7.51 - 7.44 (m, 4H, Bz), 7.42 - 7.35 (m, 3H, Bz,indole-H4), 7.30 (dt, J = m Hz, 1H, indole-H7), 7.08 (d, $J_{In-H2,In-NH}$ = 2.4 Hz, 1H, indole-H2), 7.00 (ddd, $J_{In-H6,In-H7}$ = 8.1 Hz, $J_{In-H6,In-H5}$ = 7.0 Hz, $J_{In-H6,In-H4}$ = 1.2 Hz, 1H, indole-H6), 6.91 (ddd, $J_{In-H5,In-H4}$ = 8.0 Hz, $J_{In-H5,In-H6}$ = 7.0 Hz, $J_{In-H5,In-H7}$ = 1.1 Hz, 1H, indole-H5), 6.60 (d, $J_{1',2'}$ = 5.1 Hz, 1H, H-1'), 6.38 (dd, $J_{2',3'}$ = 6.3 Hz, $J_{2',1'}$ = 5.1 Hz, 1H, H-2'), 6.20 - 6.13 (m, 1H, H-3'), 4.85 - 4.79 (m, 1H, H-4'), 4.76 (dd, J_{gem} = 12.1 Hz, $J_{5'a,4'}$ = 3.7 Hz, 1H, H-5'a), 4.67 (dd, J_{gem} = 12.1 Hz, $J_{5'b,4'}$ = 5.0 Hz, 1H, H-5'b), 3.15 - 3.05 (m, 2H, H-1''), 2.84 - 2.76 (m, 2H, H-2''). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6 (5'-CO), 164.9 (3'-CO), 164.6 (2'-CO), 157.2 (C-6), 153.6 (C-2), 151.0 (C-4), 136.3 (indole-C7a), 134.1 (Bz), 134.1 (Bz), 133.7 (Bz), 129.6 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Bz), 128.9 (Bz), 128.9 (Bz), 128.8 (Bz), 128.7 (C-8), 128.4 (Bz), 127.1 (indole-C3a), 123.1 (indole-C2), 121.1 (indole-C6), 118.5 (indole-C5), 118.2 (indole-C4), 115.7 (C-7), 111.5 (indole-C7), 111.1 (indole-C3), 98.6 (C-5), 87.3 (C-1'), 79.2 (C-4'), 73.4 (C-2'), 70.9 (C-3'), 63.6 (C-5'), 43.3 (C-1''), 25.5 (C-2''). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{42}H_{37}N_6O_9S$) calculated 801.2337, found 801.2335.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(*N*-phenylsulfamoyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (8p)



7 (542 mg, 0.80 mmol) was dissolved in anhydrous DCM (8.0 mL), and aniline (217 µL, 2.40 mmol, 3.0 eq) was added. After stirring at RT for 1 hour, a white suspension was formed. DMAP (117 mg, 0.96 mmol, 1.2 eq) was added to the mixture, which immediately turned clear. After 15 minutes, the reaction reached completion. The volatiles were evaporated, and the residue was subjected to FCC (15–35 % of a 4:1 EtOAc/EtOH mixture in cyclohexane), which afforded **8p** (514 mg, 0.70 mmol, 88%) as a white solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 10.48 (s, 1H, SO_2-NH), 8.29 (s, 1H, H-8), 8.08 (s, 1H, H-2), 8.05 - 7.98 (m, 2H, Bz), 7.98 - 7.91 (m, 2H, Bz), 7.86 - 7.78 (m, 2H, Bz), 7.72 - 7.58 (m, 3H, Bz), 7.55 - 7.45 (m, 4H, Bz), 7.45 - 7.40 (m, 2H, Bz), 7.17 - 7.07 (m, 2H, H-3''), 7.07 - 6.99 (m, 2H, H-2''), 6.88 (td, $J_{4'',3''}$ = 7.2 Hz, $J_{4'',2''}$ = 1.2 Hz, 1H, H-4''), 6.58 (d, $J_{1',2'}$ = 5.5 Hz, 1H, H-1'), 6.37 - 6.29 (m, 1H, H-2'), 6.14 - 6.06 (m, 1H, H-3'), 4.84 - 4.71 (m, 2H, H-4', H-5'a), 4.66 (dd, J_{gem} = 11.9 Hz, $J_{5'b,4'}$ = 5.2 Hz, 1H, H-5'b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6 (5'-CO), 164.9 (3'-CO), 164.5 (2'-CO), 156.9 (C-6), 153.7 (C-2), 151.2 (C-4), 137.3 (C-1''), 134.2 (Bz), 134.1 (Bz), 133.7 (Bz), 130.3 (C-8), 129.6 (Bz), 129.5 (Bz), 129.4 (Bz), 129.2 (C-3''), 128.9 (Bz), 128.8 (Bz), 128.4 (Bz), 124.0 (C-4''), 119.6 (C-2''), 114.1 (C-7), 98.2 (C-5), 86.7 (C-1'), 79.4 (C-4'), 73.1 (C-2'), 71.0 (C-3'), 63.8 (C-5'). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{38}H_{32}N_5O_9S$) calculated 734.1915, found 734.1914.

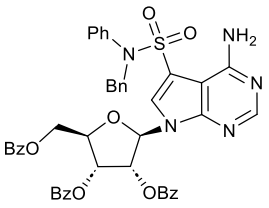
1-((4-Amino-7-((2*R*,3*R*,4*R*,5*R*)-3,4-bis(benzoyloxy)-5-((benzoyloxy)methyl)tetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)sulfonyl)azetidine-3-carboxylic acid (8q)



The compound **8q** was prepared by a modified published procedure [3]. To a mixture of azetidine-3-carboxylic acid (445 mg, 0.44 mmol, 1.2 eq) and Na_2CO_3 (235 mg, 2.2 mmol, 6.0 eq) in THF (2.2 mL) and water (2.2 mL), compound **7** (250 mg, 0.37 mmol) was added. After 1 hour at RT, the reaction went to completion. The reaction mixture was diluted with EtOAc and water. The aqueous layer was acidified with 1M HCl to pH 2. The layers were separated, the organic layer was washed with water and brine and dried over Na_2SO_4. FCC (2–10 % of a 10:1 MeOH/AcOH mixture in DCM), afforded **8q** (215 mg, 0.29 mmol, 79%) as a white solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 12.68 (s, 1H, COOH), 8.42 (s, 1H, H-8), 8.18 (s, 1H, H-2), 8.03 - 7.92 (m, 4H, Bz), 7.90 - 7.81 (m, 2H, Bz), 7.71 - 7.58 (m, 3H, Bz), 7.57 - 7.38 (m, 6H, Bz), 6.79 (s, 1H, NH_2), 6.68 (d, $J_{1',2'}$ = 5.0 Hz, 1H, H-1'), 6.38 (dd, $J_{2',3'}$ = 6.3 Hz, $J_{2',1'}$ = 5.0 Hz, 1H, H-2'), 6.27 - 6.16 (m, 1H, H-3'), 4.85 (m, 1H, H-4'), 4.80 (dd, J_{gem} = 12.0 Hz, $J_{5'a,4'}$ = 3.9 Hz, 1H, H-5'a), 4.71 (dd, J_{gem} = 12.0 Hz, $J_{5'b,4'}$ = 5.2 Hz, 1H, H-5'b), 3.94 - 3.84 (m, 2H, H-2''a), 3.83 - 3.73 (m, 2H, H-2''b), 3.28 - 3.15 (m, 1H, H-3''). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 172.8 (C-4''), 165.6 (5'-CO), 164.9 (3'-CO), 164.6 (2'-CO), 157.2 (C-6), 153.7 (C-2), 151.3 (C-4), 134.1 (Bz), 134.1 (Bz), 133.7 (Bz), 131.0 (C-8), 129.6 (Bz), 129.5 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Bz), 128.9 (Bz), 128.8 (Bz), 128.5 (Bz), 107.8 (C-7), 99.5 (C-5), 87.2 (C-1'), 79.4 (C-4'), 73.7 (C-2'), 70.9 (C-3'), 63.6 (C-5'), 52.8 (C-2''a), 52.7 (C-2''b), 31.2 (C-3''). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{36}H_{32}N_5O_{11}S$) calculated 742.1814, found 742.1814.

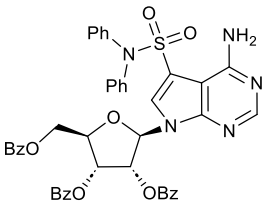
2.2. Further modification of sulfonamides **8p** and **8q**

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(*N*-benzyl-N-phenylsulfamoyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (10)

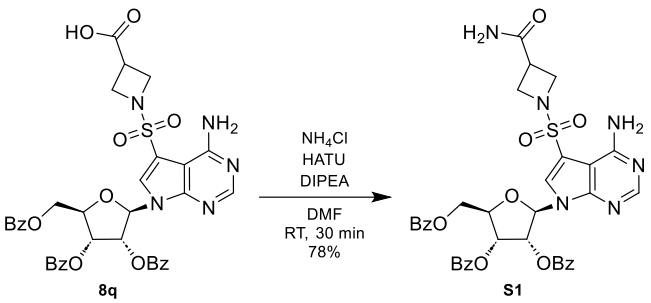


To a solution of **8p** (50 mg, 0.068 mmol) and PPh_3 (23 mg, 0.089 mmol, 1.3 eq) in THF (0.7 mL), DIAD (16 µL, 0.082 mmol, 1.2 eq) was added. Benzyl alcohol (14 µL, 0.14 mmol, 2.0 eq) was added at ambient temperature and the reaction was stirred for 1 hour. The reaction mixture was concentrated, and the residue was subjected to RP-FCC (30–100% of ACN in water), affording product **10** (51 mg, 0.062 mmol, 91%) as a colourless solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.32 (s, 1H, H-8), 8.10 (s, 1H, H-2), 8.04 - 7.94 (m, 4H, Bz), 7.92 - 7.82 (m, 2H, Bz), 7.73 - 7.59 (m, 3H, Bz), 7.55 - 7.40 (m, 6H, Bz), 7.26 - 7.11 (m, 8H, Bn, Ph), 7.08 - 7.01 (m, 2H, Ph), 6.67 (d, $J_{1',2'}$ = 5.3 Hz, 1H, H-1'), 6.41 (dd, $J_{2',3'}$ = 6.3 Hz, $J_{2',1'}$ = 5.3 Hz, 1H, H-2'), 6.16 (dd, $J_{3',2'}$ = 6.3 Hz, $J_{3',4'}$ = 5.2 Hz, 1H, H-3'), 4.90 - 4.84 (m, 1H, H-4'), 4.81 (dd, J_{gem} = 12.1 Hz, $J_{5'a,4'}$ = 3.8 Hz, 1H, H-5'a), 4.76 - 4.64 (m, 3H, H-5'b, Bn-H1"). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.7 (5'-CO), 164.9 (3'-CO), 164.7 (2'-CO), 156.9 (C-6), 153.6 (C-2), 150.9 (C-4), 138.4 (Ph-C1"), 135.9 (Bn-C2"), 134.2 (Bz), 134.1 (Bz), 133.7 (Bz), 130.0 (C-8), 129.6 (Bz), 129.5 (Bz), 129.5 (Bz), 129.4 (Bz), 129.1 (Bz), 129.0 (Bn, Ph), 128.9 (Bz), 128.8 (Bz), 128.8 (Ph), 128.5 (Bn or Ph), 128.5 (Bz), 128.3 (Bn or Ph), 127.7 (Ph), 112.0 (C-7), 98.9 (C-5), 87.0 (C-1'), 79.5 (C-4'), 73.5 (C-2'), 71.0 (C-3'), 63.7 (C-5'), 53.5 (Bn-C1"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{45}H_{38}N_5O_9S$) calculated 824.2385, found 824.2386.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(*N*,*N*-diphenylsulfamoyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (12)

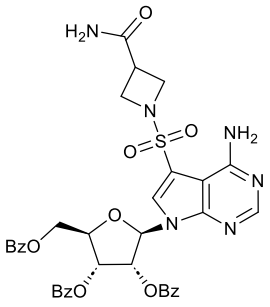


Sulfonamide **8p** (75 mg, 0.10 mmol), diphenyloidonium triflate (53 mg, 0.12 mmol, 1.2 eq), potassium phosphate (44 mg, 0.20 mmol, 2.0 eq), and CuCl (2.0 mg, 0.020 mmol, 0.20 eq) were mixed in anhydrous DCM (1.5 mL) and stirred under argon at RT for 3 hours. After this time, diphenyliodonium triflate (9 mg, 0.02 mmol, 0.2 eq) was added, and stirring was continued for 2 hours, until all starting material was consumed. The reaction was diluted with EtOAc and washed with water. The aqueous layer was extracted once with EtOAc, and the combined organic fractions were washed with brine, dried over sodium sulfate, and evaporated. RP-FCC (50–100% of ACN in water) yielded **12** (41 mg, 0.051 mmol, 50%) as a yellowish solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.17 (s, 1H, H-8), 8.13 (s, 1H, H-2), 8.02 - 7.93 (m, 4H, Bz), 7.92 - 7.83 (m, 2H, Bz), 7.73 - 7.60 (m, 3H, Bz), 7.54 - 7.40 (m, 6H, Bz), 7.34 - 7.21 (m, 10H, Ph), 6.62 (d, $J_{1',2'}$ = 5.3 Hz, 1H, H-1'), 6.42 - 6.35 (m, 1H, H-2'), 6.16 - 6.08 (m, 1H, H-3'), 4.87 - 4.74 (m, 2H, H-4', H-5'a), 4.68 (dd, J_{gem} = 11.9 Hz, $J_{5'b,4'}$ = 5.3 Hz, 1H, H-5'b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6 (5'-CO), 164.9 (3'-CO), 164.7 (2'-CO), 156.9 (C-6), 153.8 (C-2), 151.0 (C-4), 140.8 (C-1"), 134.2 (Bz), 134.1 (Bz), 133.7 (Bz), 130.9 (C-8), 129.7 (C-3"), 129.6 (Bz), 129.5 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Bz), 129.0 (Bz), 128.9 (Bz, C-2"), 128.8 (Bz), 128.5 (Bz), 128.4 (C-4"), 113.8 (C-7), 98.6 (C-5), 87.2 (C-1'), 79.5 (C-4'), 73.2 (C-2'), 71.0 (C-3'), 63.7 (C-5'). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{44}H_{36}N_5O_9S$) calculated 810.2228, found 810.2225.



Scheme S1. Preparation of carboxamide **S1** from compound **10q**

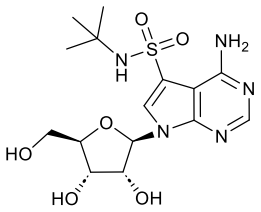
(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-((3-carbamoylazetidin-1-yl)sulfonyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (S1)



Carboxylic acid **8q** (58 mg, 0.078 mmol), NH_4Cl (42 mg, 0.78 mmol, 10 eq), and HATU (45 mg, 0.12 mmol, 1.5 eq) were suspended in anhydrous DMF (1.3 mL). DIPEA (68 µL, 0.39 mmol, 5.0 eq) was added, and the resulting mixture was stirred at RT for 30 minutes. The solvent was evaporated, and the residue was subjected to RP-FCC (20–80 % of ACN in water), affording product **S1** (45 mg, 0.061 mmol, 78%) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.41 (s, 1H, H-8), 8.17 (s, 1H, H-2), 8.03 - 7.98 (m, 2H, Bz), 7.98 - 7.92 (m, 2H, Bz), 7.89 - 7.81 (m, 2H, Bz), 7.75 (s, 1H, NH_2a), 7.71 - 7.59 (m, 3H, Bz), 7.55 - 7.39 (m, 6H, Bz), 7.32 (s, 1H, $CONH_2$a), 6.90 (s, 1H, $CONH_2$b), 6.81 (s, 1H, NH_2b), 6.68 (d, $J_{1',2'}$ = 4.9 Hz, 1H, H-1'), 6.37 (dd, $J_{2',3'}$ = 6.3 Hz, $J_{2',1'}$ = 5.0 Hz, 1H, H-2'), 6.23 - 6.16 (m, 1H, H-3'), 4.88 - 4.83 (m, 1H, H-4'), 4.80 (dd, J_{gem} = 12.0 Hz, $J_{5'a,4'}$ = 3.8 Hz, 1H, H-5'a), 4.71 (dd, J_{gem} = 12.0 Hz, $J_{5'b,4'}$ = 5.2 Hz, 1H, H-5'b), 3.85 - 3.72 (m, 4H, H-2"), 3.14 - 3.02 (m, 1H, H-3"). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 172.0 (C-4"), 165.7 (5'-CO), 164.9 (3'-CO), 164.7 (2'-CO), 157.2 (C-6), 153.7 (C-2), 151.2 (C-4), 134.2 (Bz), 134.1 (Bz), 133.7 (Bz), 130.8 (H-8), 129.6 (Bz), 129.5 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Bz), 128.9 (Bz), 128.8 (Bz), 128.5 (Bz), 108.0 (C-7), 99.6 (C-5), 87.3 (C-1'), 79.4 (C-4'), 73.7 (C-2'), 70.9 (C-3'), 63.6 (C-5'), 52.8 (C-2"a), 52.7 (C-2"b), 31.6 (C-3"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{36}H_{33}N_6O_{10}S$) calculated 741.1973, found 741.1976.

2.3. Final deprotection

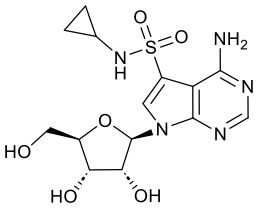
4-Amino-*N*-(*tert*-butyl)-7-((2*R*,3R,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (9d)



Benzoyl-protected sulfonamide **8d** (221 mg, 0.31 mmol) was dissolved in 33% $MeNH_2$ in ethanol (3.0 mL) and was stirred at RT for 6 hours. The mixture was concentrated, and the residue was co-evaporated with ethanol to remove the residual amine. The crude product was adsorbed onto silica and subjected to FCC (50–100% of a 72:12:10:6 EtOAc/acetone/EtOH/water mixture in EtOAc). The appropriate fractions were collected and repurified by RP-FCC (10–40% of ACN in water, 0.1% of FA). The product **9d**

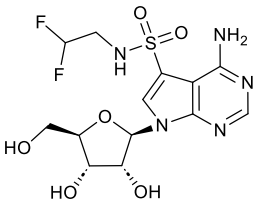
(112 mg, 0.28 mmol, 90%) was obtained as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.16 (s, 1H, H-2), 8.08 (s, 1H, H-8), 7.60 (s, 1H, SO_2-NH), 7.14 (bs, 2H, NH_2), 6.07 (d, $J_{1',2'}$ = 5.7 Hz, 1H, 1',2'), 5.41 (d, $J_{2'\text{-OH},2'}$ = 6.2 Hz, 1H, 2'-OH), 5.24 (dd, $J_{5'\text{-OH},5'}$ = 5.8 Hz, $J_{5'\text{-OH},5'}$ = 4.6 Hz, 1H, 5'-OH), 5.17 (d, $J_{3'\text{-OH},3'}$ = 4.8 Hz, 1H, 3'-OH), 4.40 - 4.31 (m, 1H, H-2'), 4.13 - 4.05 (m, 1H, H-3'), 3.97 - 3.90 (m, 1H, H-4'), 3.71 - 3.61 (m, 1H, H-5'a), 3.61 - 3.51 (m, 1H, H-5'b), 1.15 (s, 9H, t-Bu). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.0 (C-6), 153.2 (C-2), 150.9 (C-4), 127.4 (C-8), 118.6 (C-7), 98.4 (C-5), 87.8 (C-1'), 85.5 (C-4'), 74.6 (C-2'), 70.5 (C-3'), 61.4 (C-5'), 53.8 (t-Bu-C), 29.8 (t-Bu-CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{15}H_{24}N_5O_6S$) calculated 402.1442, found 402.1444.

4-Amino-*N*-cyclopropyl-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (9e)



Compound **8e** (210 mg, 0.30 mmol) was dissolved in 33% $MeNH_2$ in ethanol (3.0 mL) and stirred at RT for 6 hours. The volatiles were removed under reduced pressure, and the residue was co-evaporated with ethanol to remove the residual amine. The crude product was diluted with MeOH, adsorbed onto silica, and purified by RP-FCC (10–40 % of ACN in water, 0.1% of FA as modifier). Product **9e** (109 mg, 0.28 mmol, 94%) was obtained as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.18 (s, 1H, H-2), 8.12 (s, 1H, H-8), 8.01 (s, 1H, SO_2-NH), 6.11 (d, $J_{1',2'}$ = 5.7 Hz, 1H, H-1'), 5.43 (d, $J_{2'\text{-OH},2'}$ = 6.1 Hz, 1H, 2'-OH), 5.23 (dd, $J_{5'\text{-OH},5'\text{b}}$ = 5.7 Hz, $J_{5'\text{-OH},5'\text{a}}$ = 4.7 Hz, 1H, 5'-OH), 5.17 (d, $J_{3'\text{-OH},3'}$ = 4.8 Hz, 1H, 3'-OH), 4.43 - 4.34 (m, 1H, H-2'), 4.14 - 4.06 (m, 1H, H-3'), 3.98 - 3.91 (m, 1H, H-4'), 3.66 (ddd, J_{gem} = 11.9 Hz, $J_{5'\text{a},5'\text{-OH}}$ = 4.7 Hz, $J_{5'\text{a},4'}$ = 3.4 Hz, 1H, H-5'a), 3.57 (ddd, J_{gem} = 11.9 Hz, $J_{5'\text{b},5'\text{-OH}}$ = 5.7 Hz, $J_{5'\text{b},4'}$ = 3.3 Hz, 1H, H-5'b), 2.21 (tt, $J_{\text{H-1''},\text{H-2''a}}$ = 6.9 Hz, $J_{\text{H-1''},\text{H-2''b}}$ = 3.5 Hz, 1H, H-1''), 0.57 - 0.46 (m, 2H, H-2''a), 0.44 - 0.31 (m, 2H, H-2''b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.1 (C-6), 153.3 (C-2), 150.9 (C-4), 128.1 (C-8), 114.5 (C-7), 98.5 (C-5), 87.8 (C-1'), 85.6 (C-4'), 74.6 (C-2'), 70.5 (C-3'), 61.4 (C-5'), 24.0 (C-1''), 5.4 (C-2''a), 5.3 (C-2''b). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{14}H_{20}N_5O_6S$) calculated 386.1129, found 386.1128.

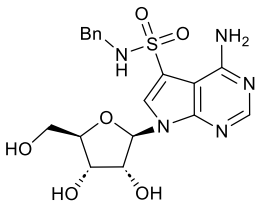
4-Amino-*N*-(2,2-difluoroethyl)-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (9f)



8f (283 mg, 0.39 mmol) was dissolved in 33 % $MeNH_2$ in ethanol (2.5 mL) and stirred at RT for 4 hours. The solvent was removed under vacuum, and the residue was co-evaporated three times with ethanol. RP-FCC (10–50% of ACN in water, 0.1% of FA) afforded pure product **9f** (146.0 mg, 0.357 mmol, 91%). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.40 (s, 1H, SO_2-NH), 8.20 (s, 1H, H-2), 8.17 (s, 1H, H-8), 6.09 (d, $J_{1',2'}$ = 5.6 Hz, 1H, H-1'), 6.01 (tt, $J_{\text{H-2''},F}$ = 55.6 Hz, $J_{\text{H-2''},\text{H-1''}}$ = 3.8 Hz, 1H, H-2''), 5.44 (d, $J_{2'\text{-OH},2'}$ = 6.1 Hz, 1H, 2'-OH), 5.23 (dd, $J_{5'\text{-OH},5'\text{b}}$ = 5.8 Hz, $J_{5'\text{-OH},5'\text{a}}$ = 4.8 Hz, 1H, 5'-OH), 5.16 (d, $J_{3'\text{-OH},3'}$ = 5.0 Hz, 1H, 3'-OH), 4.44 - 4.37 (m, 1H, H-2'), 4.15 - 4.08 (m, 1H, H-3'), 3.98 - 3.91 (m, 1H, H-4'), 3.68 (ddd, J_{gem} = 11.9 Hz, $J_{5'\text{a},5'\text{-OH}}$ = 4.8 Hz, $J_{5'\text{a},4'}$ = 3.5 Hz, 1H, H-5'a), 3.58 (ddd, J_{gem} = 11.9 Hz, $J_{5'\text{b},5'\text{-OH}}$ = 5.9 Hz, $J_{5'\text{b},4'}$ = 3.5 Hz, 1H, H-5'b), 3.27 (tt, $J_{\text{H-1''},F}$ = 15.3 Hz, $J_{\text{H-1''},\text{H-2''}}$ = 3.8 Hz, 2H, H-1''). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.0 (C-6), 153.4 (C-2), 151.1 (C-4), 128.0 (C-8), 114.8 (t, $J_{\text{C-2''},F}$ = 240.4 Hz, C-2''), 114.3 (C-7), 98.2 (C-5), 87.9 (C-1'), 85.5 (C-4'), 74.3 (C-2'), 70.4 (C-3'), 61.3 (C-5'), 44.2 (t, $J_{\text{C-1''},F}$ = 26.6

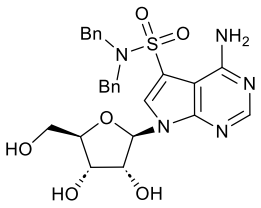
Hz, C-1"). **^{19}F NMR** (376 MHz, DMSO-d_6) δ -121.83 (dt, $J_{F,H-2''}$ = 55.5 Hz, $J_{F,H-1''}$ = 15.3 Hz). **HRMS** (ESI) m/z: $[M+Na]^+$ ($C_{13}H_{17}F_2N_5O_6SNa$) calculated 432.0760, found 432.0757.

4-Amino-*N*-benzyl-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (9g)



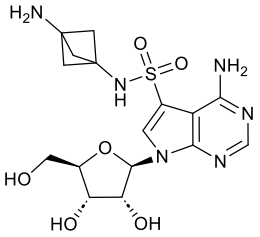
Benzoyl-protected sulfonamide **8g** (263 mg, 0.35 mmol) was dissolved in 7M ammonia in MeOH (5 mL) in a pressure tube. The reaction was stirred in a closed tube at 60 °C overnight. The reaction mixture was transferred into a round-bottom flask, the volatiles were evaporated, and the product was purified by RP-FCC (15–60% of ACN in water). Compound **9g** (131 mg, 0.30 mmol, 86%) was obtained as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.31 (s, 1H, SO_2-NH), 8.16 (s, 1H, H-2), 8.13 (s, 1H, H-8), 7.28 - 7.14 (m, 5H, Bn-Ar), 6.07 (d, $J_{1',2'}$ = 5.4 Hz, 1H, H-1'), 5.45 (d, $J_{2'\text{-OH},2'}$ = 6.1 Hz, 1H, 2'-OH), 5.24 (dd, $J_{5'\text{-OH},5'a}$ = 5.3 Hz, $J_{5'\text{-OH},5'b}$ = 5.3 Hz, 1H, 5'-OH), 5.18 (d, $J_{3'\text{-OH},3'}$ = 5.0 Hz, 1H, 3'-OH), 4.40 - 4.32 (m, 1H, H-2'), 4.14 - 4.08 (m, 1H, H-3'), 4.05 (s, 2H, H-1"), 3.97 - 3.90 (m, 1H, H-4'), 3.73 - 3.63 (m, 1H, H-5'a), 3.62 - 3.52 (m, 1H, H-5'b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.0 (C-6), 153.3 (C-2), 151.0 (C-4), 137.8 (C-2"), 128.3 (C-4"), 127.8 (C-8), 127.7 (C-3"), 127.3 (C-5"), 114.9 (C-7), 98.4 (C-5), 87.9 (C-1'), 85.4 (C-4'), 74.5 (C-2'), 70.4 (C-3'), 61.3 (C-5'), 46.0 (C-1"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{18}H_{22}N_5O_6S$) calculated 436.1285, found 436.1283.

4-Amino-*N*,*N*-dibenzyl-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (9h)



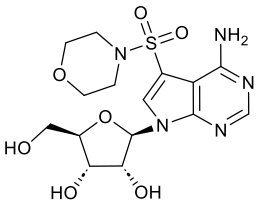
Starting protected nucleoside analogue **8h** (160 mg, 0.19 mmol) was dissolved in 7M methanolic ammonia (5.3 mL) and stirred at RT for 20 hours. After this time, the volatiles were removed under reduced pressure, and the residue was adsorbed onto silica. Purification by FCC (2–20% of MeOH in DCM) afforded **9h** (84 mg, 0.16 mmol, 84%). **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.42 (s, 1H, H-8), 8.24 (s, 1H, H-2), 7.25 - 7.15 (m, 6H, Bn-Ar), 7.13 - 7.05 (m, 4H, Bn-Ar), 6.12 (d, $J_{1',2'}$ = 5.0 Hz, 1H, H-1'), 5.49 (d, $J_{2'\text{-OH},2'}$ = 5.9 Hz, 1H, 2'-OH), 5.28 (dd, $J_{5'\text{-OH},5'a}$ = 5.3 Hz, $J_{5'\text{-OH},5'b}$ = 5.3 Hz, 1H, 5'-OH), 5.17 (d, $J_{3'\text{-OH},3'}$ = 5.1 Hz, 1H, 3'-OH), 4.43 - 4.35 (m, 1H, H-2'), 4.34 - 4.22 (m, 4H, H-1"), 4.18 - 4.08 (m, 1H, H-3'), 3.99 - 3.92 (m, 1H, H-4'), 3.76 - 3.67 (m, 1H, H-5'a), 3.62 - 3.53 (m, 1H, H-5'b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.1 (C-6), 153.4 (C-2), 150.8 (C-4), 136.4 (C-2"), 128.7 (C-8), 128.4 (C-3" or C-4"), 128.3 (C-4" or C-3"), 127.6 (C-5"), 112.5 (C-7), 98.7 (C-5), 88.2 (C-1'), 85.3 (C-4'), 74.5 (C-2'), 70.0 (C-3'), 61.0 (C-5'), 51.6 (C-1"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{25}H_{28}N_5O_6S$) calculated 526.1755, found 526.1751.

4-Amino-*N*-(3-aminobicyclo[1.1.1]pentan-1-yl)-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (9i)



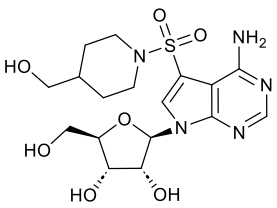
8i-Dep (235 mg, 0.32 mmol) was dissolved in 33% $MeNH_2$ solution in ethanol (2.5 mL) and the mixture was stirred at RT overnight. The solvent was removed under vacuum, and the crude product was co-evaporated with ethanol. The residue was diluted with methanol and adsorbed onto silica. RP-FCC (10–40% of ACN in water) afforded product **9i** (111 mg, 0.26 mmol, 82%) as an off-white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.17 (s, 1H, H-2), 8.09 (s, 1H, H-8), 6.10 (d, $J_{1',2'}$ = 5.7 Hz, 1H, H-1'), 5.41 (d, $J_{2'\text{-}OH,2'}$ = 6.3 Hz, 1H, 2'-OH), 5.24 (s, 1H, 5'-OH), 5.18 (d, $J_{3'\text{-}OH,3'}$ = 4.9 Hz, 1H, 3'-OH), 4.40 - 4.31 (m, 1H, H-2'), 4.14 - 4.06 (m, 1H, H-3'), 3.98 - 3.91 (m, 1H, H-4'), 3.72 - 3.63 (m, 1H, H-5'a), 3.62 - 3.55 (m, 1H, H-5'b), 1.69 (s, 6H, H-2''). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.0 (C-6), 153.3 (C-2), 150.9 (C-4), 128.1 (C-8), 115.9 (C-7), 98.4 (C-5), 87.8 (C-1'), 85.6 (C-4'), 74.8 (C-2'), 70.6 (C-3'), 61.5 (C-5'), 55.3 (C-2''), 48.1 (C-1'' or C-3''), 43.0 (C-3'' or C-1''). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{16}H_{23}N_6O_6S$) calculated 427.1394, found 427.1393.

(2*R*,3*R*,4*S*,5*R*)-2-(4-Amino-5-(morpholinosulfonyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (9j)



Protected sulfonamide **8j** (235 mg, 0.32 mmol) was dissolved in 33% $MeNH_2$ in ethanol (3.0 mL) and stirred at RT for 6 hours. The solvent was evaporated, and the residual amine was removed by repeated co-evaporation with ethanol. The crude product was adsorbed onto silica and purified by FCC (50–70% of 72:12:10:6 EA/acetone/EtOH/water mixture in EtOAc), followed by RP-FCC (10–40% of ACN in water, 0.1 % of FA), affording product **9j** (111 mg, 0.27 mmol, 83%) as a white solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.28 (s, 1H, H-8), 8.22 (s, 1H, H-2), 7.63 (s, 1H, NH_2a), 6.90 (s, 1H, NH_2b), 6.12 (d, $J_{1',2'}$ = 5.1 Hz, 1H, H-1'), 5.54 (d, $J_{2'\text{-}OH,2'}$ = 5.6 Hz, 1H, 2'-OH), 5.31 - 5.23 (m, 1H, 5'-OH), 5.19 (d, $J_{3'\text{-}OH,3'}$ = 5.0 Hz, 1H, 3'-OH), 4.46 - 4.38 (m, 1H, H-2'), 4.17 - 4.09 (m, 1H, H-3'), 3.99 - 3.92 (m, 1H, H-4'), 3.77 - 3.62 (m, 5H, H-5′a, H-3′′), 3.62 - 3.54 (m, 1H, H-5′b), 2.94 - 2.81 (m, 4H, H-2′′). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.1 (C-6), 153.3 (C-2), 150.8 (C-4), 129.3 (C-8), 107.7 (C-7), 99.1 (C-5), 88.3 (C-1′), 85.4 (C-4′), 74.5 (C-2′), 70.1 (C-3′), 65.3 (C-3′′), 61.0 (C-5′), 45.7 (C-2′′). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{15}H_{22}N_5O_7S$) calculated 416.1235, found 416.1233.

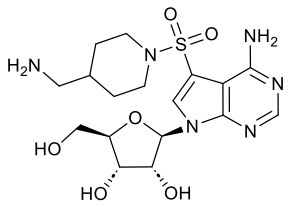
(2*R*,3*R*,4*S*,5*R*)-2-(4-Amino-5-((4-(hydroxymethyl)piperidin-1-yl)sulfonyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (9k)



8k (295 mg, 0.39 mmol) was dissolved in 33% $MeNH_2$ solution in ethanol (2.5 mL). After stirring at RT overnight, the solvent was evaporated, and the residue was co-evaporated with ethanol. The crude product was adsorbed onto silica and subjected to FCC (5–25 % of MeOH in DCM), affording pure **9k** (149 mg, 0.34 mmol, 86%) as a white fluffy solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.24 (s, 1H, H-8), 8.21 (s, 1H, H-2), 7.60 (s, 1H, NH_2a), 6.95 (s, 1H, NH_2b), 6.10 (d, $J_{1',2'}$ = 5.1 Hz, 1H, H-1'), 5.47 (d, $J_{2'\text{-}OH,2'}$ = 5.9 Hz, 1H, 2'-OH), 5.26 (dd, $J_{5'\text{-}OH,5'b}$ = 5.6 Hz, $J_{5'\text{-}OH,5'a}$ = 4.7 Hz, 1H, 5'-OH), 5.15 (d, $J_{3'\text{-}OH,3'}$ = 5.1 Hz, 1H, 3'-OH), 4.51 - 4.45 (m, 1H, 5''-OH), 4.43 - 4.35 (m, 1H, H-2'), 4.16 - 4.08 (m, 1H, H-3'), 3.98 - 3.89 (m, 1H, H-4'), 3.70 (ddd, J_{gem} = 11.9 Hz, $J_{5'a,5'\text{-}OH}$ = 4.7 Hz, $J_{5'a,4'}$ = 3.4 Hz, 1H, H-5'a), 3.66 -

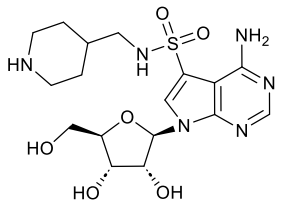
3.54 (m, 3H, H-5'b, H-2"a), 3.23 - 3.16 (m, 2H, H-5"), 2.29 - 2.19 (m, 2H, H-2"b), 1.75 - 1.68 (m, 3H, H-3"a), 1.41 - 1.27 (m, 1H, H-4"), 1.22 - 1.09 (m, 2H, H-3"b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.4 (C-6), 153.5 (C-2), 151.0 (C-4), 129.1 (C-8), 109.5 (C-7), 99.3 (C-5), 88.5 (C-1'), 85.7 (C-4'), 74.8 (C-2'), 70.4 (C-3'), 65.6 (C-5"), 61.3 (C-5'), 46.1 (C-2"a), 46.0 (C-2"b), 37.5 (C-4"), 28.1 (C-3"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{17}H_{26}N_5O_7S$) calculated 444.1548, found 444.1544.

(2*R*,3*R*,4*S*,5*R*)-2-(4-Amino-5-((4-(aminomethyl)piperidin-1-yl)sulfonyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (9l)



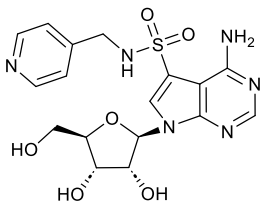
8l (204 mg, 0.27 mmol) was dissolved in 33 % $MeNH_2$ in ethanol (2.5 mL) and stirred at RT overnight. The volatiles were evaporated, and the residue was co-evaporated three times with ethanol to remove methylamine. The crude product was subjected to HILIC FCC (SiO_2, 5–40% of a 9:1 H_2O/NH_4OH (aq., conc.) mixture in ACN). The appropriate fractions were evaporated. The residue was dissolved in DCM with a minimal amount of MeOH and filtered using a syringe filter to remove washed-out silica. Product **9l** (100 mg, 0.23 mmol, 84%) was obtained as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.26 (s, 1H, H-8), 8.20 (s, 1H, H-2), 7.60 (s, 1H, NH_2a), 6.95 (s, 1H, NH_2b), 6.09 (d, $J_{1',2'}$ = 4.9 Hz, 1H, H-1'), 5.32 (bs, 3H, 3xOH), 4.41 - 4.34 (m, 1H, H-2'), 4.17 - 4.10 (m, 1H, H-3'), 3.98 - 3.91 (m, 1H, H-4'), 3.74 - 3.66 (m, 1H, H-5'a), 3.65 - 3.55 (m, 3H, H-2"a, H-5'b), 2.40 (d, $J_{H\text{-}5'',\ H\text{-}4''}$ = 6.3 Hz, 2H, H-5"), 2.31 - 2.18 (m, 2H, H-2"b), 1.81 - 1.70 (m, 2H, H-3"a), 1.32 - 1.05 (m, 3H, H-3"b,H-4"). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.1 (C-6), 153.2 (C-2), 150.6 (C-4), 128.8 (C-8), 109.0 (C-7), 99.1 (C-5), 88.2 (C-1'), 85.3 (C-4'), 74.6 (C-2'), 69.9 (C-3'), 60.9 (C-5'), 46.4 (C-5"), 45.9 (C-2"a), 45.8 (C-2"b), 36.9 (C-4"), 28.6 (C-3"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{17}H_{27}N_6O_6S$) calculated 443.1707, found 443.1704.

4-Amino-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-*N*-(piperidin-4-ylmethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (9m)



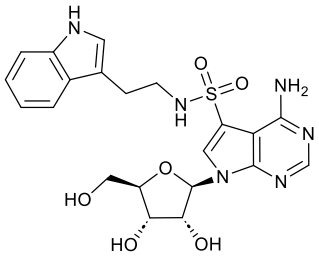
8m (181 mg, 0.24 mmol) was dissolved in 33% $MeNH_2$ in ethanol (2.5 mL) and stirred at RT for 6 hours. The mixture was concentrated under vacuum, and the residue was co-evaporated twice with ethanol. The product was purified by HILIC FCC (SiO_2, 10–60% of a 9:1 H_2O/NH_4OH (aq., conc.) mixture in ACN). After the appropriate fractions were evaporated, the residue was dissolved in a DCM/MeOH mixture and filtered using a syringe filter to remove washed-out silica. Nucleoside analogue **9m** (84 mg, 0.19 mmol, 79%) was obtained as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.17 (s, 1H, H-2), 8.08 (s, 1H, H-8), 7.22 (bs, 2H, NH_2), 6.08 (d, J = 5.7 Hz, 1H, H-1'), 5.42 (bs, 1H, OH), 5.19 (bs, 2H, 2xOH), 4.42 - 4.35 (m, 1H, H-2'), 4.13 - 4.06 (m, 1H, H-3'), 3.97 - 3.90 (m, 1H, H-4'), 3.70 - 3.62 (m, 1H, H-5'a), 3.60 - 3.52 (m, 1H, H-5'b), 2.86 - 2.77 (m, 2H, H-4"a), 2.72 - 2.64 (m, 2H, H-1"), 2.34 - 2.23 (m, 2H, H-4"a), 1.54 - 1.45 (m, 2H, H-3"a), 1.44 - 1.31 (m, 1H, H-2"), 0.93 - 0.78 (m, 2H, H-3"b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.3 (C-6), 153.6 (C-2), 151.3 (C-4), 127.8 (C-8), 115.3 (C-7), 98.7 (C-5), 88.1 (C-1'), 85.8 (C-4'), 74.7 (C-2'), 70.8 (C-3'), 61.7 (C-5'), 48.8 (C-1"), 46.1 (C-4"), 36.5 (C-2"), 31.0 (C-3"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{17}H_{27}N_6O_6S$) calculated 443.1707, found 443.1704.

4-Amino-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-*N*-(pyridin-4-ylmethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (9n)



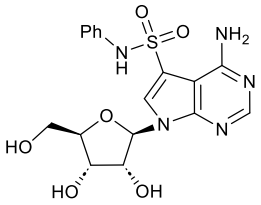
Benzoyl-protected sulfonamide **8n** (283 mg, 0.38 mmol) in 33% $MeNH_2$ solution in ethanol (2.5 mL) was stirred at RT overnight. The solvent was removed under vacuum, and the residue was co-evaporated twice with ethanol. The crude product was adsorbed onto silica and subjected to RP-FCC (10–40 % of ACN in water, 0.1 % of FA). The product **9n** (157 mg, 0.36 mmol, 95%) was obtained as a colourless solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.48 (s, 1H, SO_2-NH), 8.43 - 8.37 (m, 2H, H-4''), 8.16 (s, 1H, H-2), 8.13 (s, 1H, H-8), 7.25 - 7.19 (m, 2H, H-3''), 7.18 (bs, 2H, NH_2), 6.05 (d, $J_{1',2'}$ = 5.4 Hz, 1H, H-1'), 5.45 (s, 1H, OH), 5.23 (s, 2H, 2xOH), 4.38 - 4.30 (m, 1H, H-2'), 4.16 - 4.03 (m, 3H, H-3',H-1''), 3.97 - 3.90 (m, 1H, H-4'), 3.68 (dd, J_{gem} = 12.0 Hz, $J_{5'a,4'}$ = 3.4 Hz, 1H, H-5'a), 3.57 (dd, J_{gem} = 12.0 Hz, $J_{5'b,4'}$ = 3.4 Hz, 1H, H-5'b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.0 (C-6), 153.3 (C-2), 151.0 (C-4), 149.5 (C-4''), 147.0 (C-2''), 128.0 (C-8), 122.4 (C-3''), 114.4 (C-7), 98.3 (C-5), 87.9 (C-1'), 85.4 (C-4'), 74.4 (C-2'), 70.3 (C-3'), 61.2 (C-5'), 44.7 (C-1''). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{17}H_{21}N_6O_6S$) calculated 437.1238, found 437.1235.

***N*-(2-(1*H*-Indol-3-yl)ethyl)-4-amino-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (9o)**



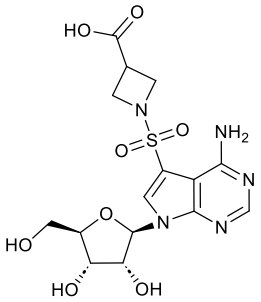
8o (308 mg, 0.39 mmol) was dissolved in 33% $MeNH_2$ solution in ethanol (2.5 mL) and stirred at RT overnight. The reaction mixture was concentrated, and the residue was co-evaporated three times with ethanol. The crude material was dissolved in methanol, adsorbed onto silica, and RP-FCC (20–60% of ACN in water) gave pure product **9o** (178 mg, 0.36 mmol, 95%). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.83 - 10.78 (m, 1H, indole-NH), 8.18 (s, 1H, H-2), 8.15 (s, 1H, H-8), 7.87 (s, 1H, SO_2-NH), 7.43 - 7.37 (m, 1H, indole-H7), 7.31 (m, 1H, indole-H7), 7.23 (s, 2H, NH_2), 7.10 (d, $J_{In-H2,In-NH}$ = 2.3 Hz, 1H, indole-H2), 7.04 (ddd, $J_{In-H6,In-H7}$ = 8.2 Hz, $J_{In-H6,In-H5}$ = 7.0 Hz, $J_{In-H6,In-H4}$ = 1.2 Hz, 1H, indole-H6), 6.95 (ddd, $J_{In-H5,In-H4}$ = 7.9 Hz, $J_{In-H5,In-H6}$ = 7.0 Hz, $J_{In-H5,In-H7}$ = 1.1 Hz, 1H, indole-H5), 6.09 (d, $J_{1',2'}$ = 5.8 Hz, 1H, H-1'), 5.41 (d, $J_{2'-OH,2'}$ = 6.0 Hz, 1H, 2'-OH), 5.28 - 5.20 (m, 1H, 5'-OH), 5.16 (d, $J_{3'-OH,3'}$ = 4.8 Hz, 1H, 3'-OH), 4.45 - 4.36 (m, 1H, H-2'), 4.14 - 4.06 (m, 1H, H-3'), 3.98 - 3.91 (m, 1H, H-4'), 3.72 - 3.62 (m, 1H, H-5'a), 3.57 (ddd, J_{gem} = 11.9 Hz, $J_{5'b,5'-OH}$ = 5.9 Hz, $J_{5'b,4'}$ = 3.4 Hz, 1H, H-5'b), 3.14 - 3.08 (m, 2H, H-1''), 2.81 (m, 2H, H-2''). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.1 (C-6), 153.3 (C-2), 151.0 (C-4), 136.3 (indole-C7a), 127.6 (C-8), 127.2 (indole-C3a), 123.1 (indole-C2), 121.1 (indole-C6), 118.5 (indole-C5), 118.2 (indole-C4), 114.9 (C-7), 111.6 (indole-C7), 111.1 (indole-C3), 98.4 (C-5), 87.8 (C-1'), 85.6 (C-4'), 74.4 (C-2'), 70.5 (C-3'), 61.5 (C-5'), 43.3 (C-1''), 25.6 (C-2''). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{21}H_{25}N_6O_6S$) calculated 489.1551, found 489.1548.

4-Amino-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-*N*-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (9p)



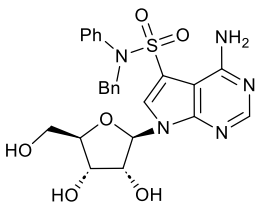
Benzoyl-protected sulfonamide **8p** (204 mg, 0.28 mmol) was dissolved in 33% $MeNH_2$ solution in ethanol (2.5 mL). After stirring at RT for 6 hours, the solvent was removed under vacuum, and the residue was co-evaporated twice with ethanol. The crude product was adsorbed onto silica, and FCC (5–25% of MeOH in DCM) yielded pure product **9p** (106 mg, 0.25 mmol, 91%) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.43 (s, 1H, SO_2-NH), 8.23 (s, 1H, H-8), 8.15 (s, 1H, H-2), 7.28 - 7.19 (m, 2H, H-3''), 7.13 - 7.06 (m, 2H, H-2''), 7.02 (tt, $J_{4'',3''}$ = 7.5 Hz, $J_{4'',2''}$ = 1.2 Hz, 1H, H-4''), 6.02 (d, $J_{1',2'}$ = 5.3 Hz, 1H, H-1'), 5.39 (d, $J_{2'\text{-OH},2'}$ = 6.1 Hz, 1H, 2'-OH), 5.25 (dd, $J_{5'\text{-OH},5'b}$ = 5.6 Hz, $J_{5'\text{-OH},5'a}$ = 4.6 Hz, 1H, 5'-OH), 5.13 (d, $J_{3'\text{-OH},3'}$ = 5.0 Hz, 1H, 3'-OH), 4.32 - 4.23 (m, 1H, H-2'), 4.09 – 4.00 (m, 1H, H-3'), 3.95 - 3.88 (m, 1H, H-4'), 3.66 (ddd, J_{gem} = 11.9 Hz, $J_{5'a,5'\text{-OH}}$ = 4.6 Hz, $J_{5'a,4'}$ = 3.4 Hz, 1H, H-5'a), 3.55 (ddd, J_{gem} = 11.9 Hz, $J_{5'b,5'\text{-OH}}$ = 5.7 Hz, $J_{5'b,4'}$ = 3.4 Hz, 1H, H-5'b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 156.9 (C-6), 153.4 (C-2), 151.0 (C-4), 137.6 (C-1''), 129.4 (C-8, C-3''), 124.0 (C-4''), 119.5 (C-2''), 113.2 (C-7), 98.1 (C-5), 88.1 (C-1'), 85.5 (C-4'), 74.6 (C-2'), 70.4 (C-3'), 61.3 (C-5'). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{17}H_{20}N_5O_6S$) calculated 422.1129, found 422.1128.

1-((4-Amino-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)sulfonyl)azetidine-3-carboxylic acid (9q)



8q (202 mg, 0.27 mmol) was dissolved in 33% $MeNH_2$ solution in ethanol (3.0 mL) and stirred for 5 hours at RT. The volatiles were removed under vacuum, and the residue was co-evaporated with ethanol. Purification by RP-FCC (10–50% of ACN in water, 0.1 % of FA as a modifier) afforded product **9q** (107 mg, 0.25 mmol, 92%) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.38 (s, 1H, H-8), 8.24 (s, 1H, H-2), 7.66 (s, 1H, NH_2a), 6.80 (s, 1H, NH_2b), 6.13 (d, $J_{1',2'}$ = 4.7 Hz, 1H, H-1'), 5.28 (bs, 1H, OH), 5.15 (bs, 2H, 2xOH), 4.43 - 4.36 (m, 1H, H-2'), 4.19 - 4.12 (m, 1H, H-3'), 4.01 - 3.93 (m, 1H, H-4'), 3.93 – 3.84 (m, 2H, H-2''a), 3.81 - 3.68 (m, 3H, H-2''b, H-5'a), 3.59 (dd, J_{gem} = 12.0 Hz, $J_{5'b,4'}$ = 3.2 Hz, 1H, H-5'b), 3.30 - 3.14 (m, 1H, H-3''). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 172.9 (C-4''), 157.1 (C-6), 153.4 (C-2), 151.0 (C-4), 130.0 (C-8), 106.5 (C-7), 99.5 (C-5), 88.5 (C-1'), 85.2 (C-4'), 74.6 (C-2'), 69.9 (C-3'), 60.8 (C-5'), 52.7 (C-2''), 31.2 (C-3''). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{15}H_{20}N_5O_8S$) calculated 430.1027, found 430.1026.

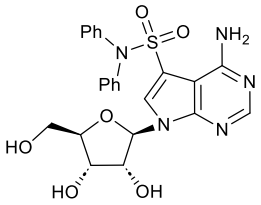
4-Amino-*N*-benzyl-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-*N*-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (11)



The solution of **10** (45 mg, 0.055 mmol) in 33% $MeNH_2$ in ethanol (1.5 mL) was stirred at RT overnight. The mixture was concentrated, and the residue was co-evaporated twice with ethanol before being diluted with methanol and adsorbed onto silica. The RP-FCC (20–100% of ACN in water) afforded pure **11** (27 mg, 0.053 mmol, 97%). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.28 (s, 1H, H-8), 8.17 (s, 1H, H-2), 7.28 - 7.15 (m, 8H, Bn, Ph), 7.12 - 7.03 (m, 2H, Ph), 6.13 (d, $J_{1',2'}$ = 5.1 Hz, 1H, H-1'), 5.52 (s, 1H, 2'-OH), 5.24 (t, $J_{5'\text{-OH},5'}$ = 5.2 Hz, 1H, 5'-OH), 5.20 (s, 1H, 3'-OH), 4.78 - 4.65 (m, 2H, Bn-H1''), 4.42 – 4.38 (m, 1H, H-2'), 4.15 – 4.11 (m, 1H, H-3'), 4.00 - 3.92 (m, 1H, H-4'), 3.75 - 3.65 (m, 1H, H-5'a), 3.62 - 3.52 (m, 1H, H-5'b). **^{13}C**

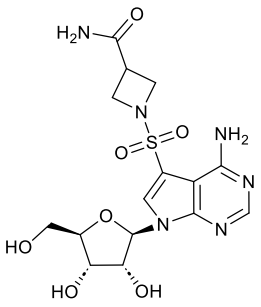
NMR (101 MHz, DMSO-d_6) δ 156.8 (C-6), 153.3 (C-2), 150.7 (C-4), 138.5 (Ph-C1"), 136.1 (Bn-C2"), 129.1 (C-8), 129.1 (Ph-Ar), 128.8 (Ph-Ar), 128.5 (Bn-Ar), 128.4 (Bn-Ar), 128.3 (Ph-Ar), 127.6 (Bn-Ar), 111.1 (C-7), 98.7 (C-5), 88.3 (C-1'), 85.4 (C-4'), 74.6 (C-2'), 70.1 (C-3'), 61.1 (C-5'), 53.4 (Bn-C1"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{24}H_{26}N_5O_6S$) calculated 512.1598, found 512.1596.

4-Amino-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-*N*,*N*-diphenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (13)



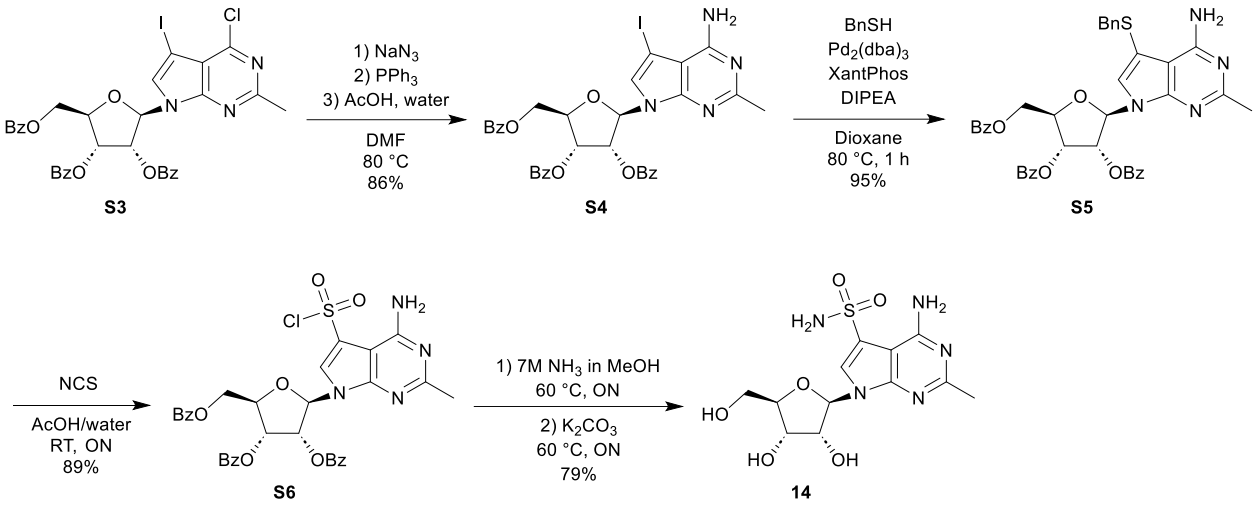
The solution of sulfonamide **12** (27 mg, 0.033 mmol) in 33% $MeNH_2$ in ethanol was stirred at RT overnight. The reaction mixture was concentrated, and the residue was co-evaporated three times with ethanol. RP-FCC (20–60 % of ACN in water, 0.1 % of FA) afforded product **13** (15 mg, 0.030 mmol, 91%). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.19 (s, 1H, H-2), 8.09 (s, 1H, H-8), 7.42 - 7.27 (m, 10H, Ph), 6.21 (bs, 2H, NH_2), 6.10 (d, $J_{1',2'}$ = 5.2 Hz, 1H, H-1'), 5.47 (d, $J_{2'\text{-OH},2'}$ = 5.7 Hz, 1H, 2'-OH), 5.22 - 5.15 (m, 2H, 3'-OH, 5'-OH), 4.33 - 4.27 (m, 1H, H-2'), 4.07 - 4.01 (m, 1H, H-3'), 3.97 - 3.90 (m, 1H, H-4'), 3.69 - 3.59 (m, 1H, H-5'a), 3.58 - 3.48 (m, 1H, H-5'b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 156.8 (C-6), 153.5 (C-2), 150.8 (C-4), 141.0 (C-1"), 129.7 (C-8, C-3"), 128.7 (C-2"), 128.2 (C-4"), 112.9 (C-7), 98.4 (C-5), 88.2 (C-1'), 85.5 (C-4'), 74.8 (C-2'), 70.3 (C-3'), 61.2 (C-5'). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{23}H_{24}N_5O_6S$) calculated 498.1442, found 498.1441.

1-((4-Amino-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)sulfonyl)azetidine-3-carboxamide (S2)



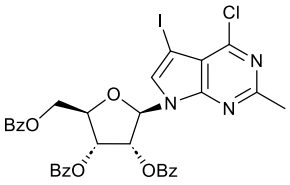
S1 (39 mg, 0.053 mmol) was dissolved in 33% $MeNH_2$ in ethanol (2.0 mL) and stirred at RT overnight. The volatiles were removed under vacuum, and the residue was co-evaporated three times with ethanol before being subjected to RP-FCC (5–50% of ACN in water, 0.1 % of FA). Compound **S2** (22 mg, 0.051 mmol, 98%) was obtained as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.36 (s, 1H, H-8), 8.24 (s, 1H, H-2), 7.65 (s, 1H, NH_2a), 7.34 (s, 1H, $CONH_2$a), 6.95 (m, 1H, $CONH_2$b), 6.84 (s, 1H, NH_2b), 6.14 (d, $J_{1',2'}$ = 4.7 Hz, 1H, H-1'), 5.48 (d, $J_{2'\text{-OH},2'}$ = 5.4 Hz, 1H, 2'-OH), 5.35 - 5.24 (m, 1H, 5'-OH), 5.13 (d, $J_{3'\text{-OH},3'}$ = 5.0 Hz, 1H, 3'-OH), 4.44 - 4.36 (m, 1H, H-2'), 4.19 - 4.13 (m, 1H, H-3'), 3.99 - 3.92 (m, 1H, H-4'), 3.85 - 3.65 (m, 4H, H-2", H-5'a), 3.64 - 3.55 (m, 1H, H-5'b), 3.16 - 3.06 (m, 1H, H-3"). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 172.1 (C-4"), 157.1 (C-6), 153.3 (C-2), 151.0 (C-4), 129.8 (C-8), 106.7 (C-7), 99.5 (C-5), 88.4 (C-1'), 85.3 (C-4'), 74.7 (C-2'), 69.9 (C-3'), 60.9 (C-5'), 52.8 (C-2"a), 52.7 (C-2"b), 31.6 (C-3"). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{15}H_{21}N_6O_7S$) calculated 429.1187, found 429.1186.

2.4. Preparation of sulfonamides **14-19**



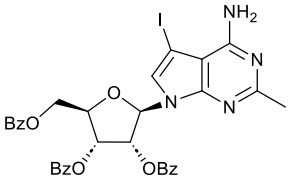
Scheme S2. Synthesis of C7-sulfonamide nucleoside analogue **14**

(2*R*,3*R*,4*R*,5*R*)-2-((Benzoyloxy)methyl)-5-(4-chloro-5-iodo-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)tetrahydrofuran-3,4-diyl dibenzoate (S3)



Compound **S3** was prepared according to the reported procedure [4]. NMR characteristics were consistent with the published data.

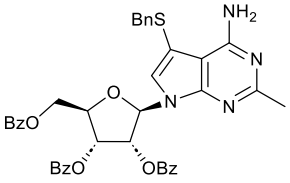
(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-iodo-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (S4)



The mixture of **S3** (2.04 g, 2.76 mmol) and NaN_3 (220 mg, 3.38 mmol, 1.2 eq) in anhydrous DMF (11 mL) was stirred at 80 °C for 90 minutes. Triphenylphosphine (961 mg, 3.66 mmol, 1.3 eq) was added, and the stirring was continued at the same temperature overnight. Since the intermediate azide was not consumed, further PPh_3 (517 mg, 1.97 mmol, 0.7 eq) was added to the mixture. After 6 hours, water (3.0 mL) and acetic acid (0.97 mL, 16.91 mmol, 6.1 eq) were added, and stirring was continued at 80 °C overnight. The volatiles were evaporated, the residue was diluted with MeOH and adsorbed onto silica. RP-FCC (50–100% of ACN in water, 0.1 % of FA as a modifier) afforded pure product **S4** (1.70 g, 2.37 mmol, 86%) as a colourless solid. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 7.97 - 7.90 (m, 4H, Bz), 7.90 - 7.85 (m, 2H, Bz), 7.69 - 7.63 (m, 3H, Bz), 7.62 (s, 1H, H-8), 7.54 - 7.41 (m, 6H, Bz), 6.66 (s, 2H, NH_2), 6.49 (d,

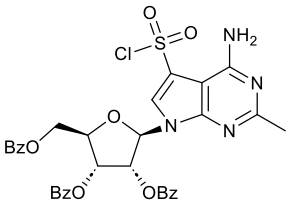
$J_{1',2'}$ = 4.4 Hz, 1H, H-1'), 6.31 - 6.19 (m, 2H, H-2', H-3'), 4.84 - 4.78 (m, 1H, H-4'), 4.75 (dd, J_{gem} = 12.0 Hz, $J_{5'a,4'}$ = 3.9 Hz, 1H, H-5'a), 4.64 (dd, J_{gem} = 12.0 Hz, $J_{5'b,4'}$ = 4.9 Hz, 1H, H-5'b), 2.35 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6 (5'-CO), 164.9 (3'-CO), 164.7 (2'-CO), 161.3 (C-2), 157.4 (C-6), 151.1 (C-4), 134.2 (Bz), 134.0 (Bz), 133.7 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Bz), 129.0 (Bz), 128.9 (Bz), 128.8 (Bz), 128.5 (Bz), 127.1 (C-8), 101.5 (C-5), 86.3 (C-1'), 78.9 (C-4'), 73.7 (C-2'), 71.0 (C-3'), 63.7 (C-5'), 53.3 (C-7), 25.5 (Me). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{33}H_{28}IN_4O_7$) calculated 719.0997, found 719.0992.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(benzylthio)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (S5)



To a solution of **S4** (1.69 g, 2.36 mmol) in anhydrous 1,4-dioxane (40 mL) were added benzyl mercaptan (498 µL, 4.24 mmol, 1.8 eq), DIPEA (1.0 mL, 5.89 mmol, 2.5 eq), $Pd_2(dba)_3$ (54 mg, 0.059 mmol, 0.025 eq), and XantPhos (78 mg, 0.134 mmol, 0.057 eq). The resulting mixture was stirred at 80 °C under argon for 1 hour. The volatiles were evaporated, and the residue was subjected to FCC (10–40% of a 4:1 EtOAc/EtOH mixture in cyclohexane), affording the compound **S5** (1.60 g, 2.24 mmol, 95%) as an off-white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.98 - 7.86 (m, 6H, Bz), 7.71 - 7.61 (m, 3H, Bz), 7.54 - 7.42 (m, 6H, Bz), 7.25 (s, 1H, H-8), 7.16 - 7.05 (m, 3H, SBn-Ar), 7.04 - 6.98 (m, 2H, SBn-Ar), 6.75 (bs, 2H, NH_2), 6.48 (d, $J_{1',2'}$ = 4.6 Hz, 1H, H-1'), 6.25 - 6.14 (m, 2H, H-2', H-3'), 4.83 - 4.77 (m, 1H, H-4'), 4.74 (dd, J_{gem} = 11.9 Hz, $J_{5'a,4'}$ = 3.9 Hz, 1H, H-5'a), 4.63 (dd, J_{gem} = 11.9 Hz, $J_{5'b,4'}$ = 4.9 Hz, 1H, H-5'b), 3.85 (s, 2H, SBn-CH_2), 2.36 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6 (5'-CO), 164.9 (3'-CO or 2'-CO), 164.7 (2'-CO or 3'-CO), 161.5 (C-2), 157.8 (C-6), 151.5 (C-4), 137.6 (Bn), 134.2 (Bz), 134.0 (Bz), 133.7 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Bz), 128.9 (Bz, Bn), 128.8 (Bz), 128.5 (Bz), 128.3 (Bn), 128.0 (C-8), 127.1 (Bn), 103.6 (C-7), 101.3 (C-5'), 86.1 (C-1'), 79.0 (C-4'), 73.6 (C-2'), 71.1 (C-3'), 63.8 (C-5'), 41.9 (SBn-CH_2), 25.5 (CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{40}H_{35}N_4O_7S$) calculated 715.2221, found 715.2216.

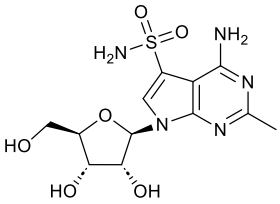
(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(chlorosulfonyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (S6)



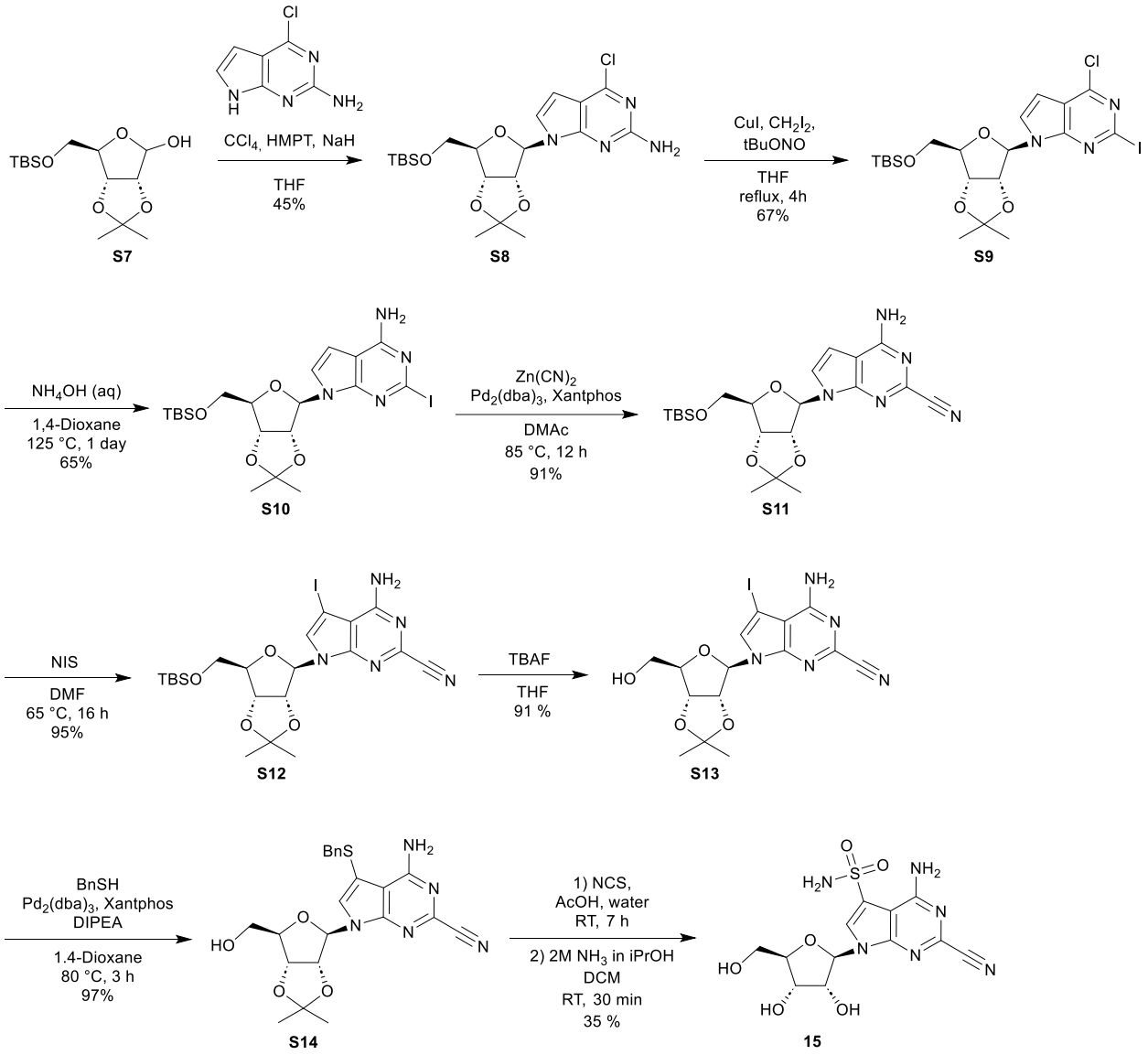
NCS (1.19 g, 8.90 mmol, 4.0 eq) was added in one portion to a solution of **S5** (1.59 g, 2.22 mmol) in a mixture of acetic acid (33.0 mL) and water (11.0 mL). After stirring at ambient temperature overnight, the solvents were evaporated, and the residue was subjected to RP-FCC (30–100% of ACN in water), affording sulfonyl chloride **S6** (1.37 g, 1.98 mmol, 89%) as a white solid. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 8.08 - 7.97 (m, 5H, Bz, H-8), 7.97 - 7.91 (m, 2H, Bz), 7.63 - 7.53 (m, 3H, Bz), 7.49 - 7.32 (m, 6H, Bz), 6.83 (s, 2H, NH_2), 6.52 (d, $J_{1',2'}$ = 4.6 Hz, 1H, H-1'), 6.21 - 6.10 (m, 2H, H-2', H-3'), 4.92 - 4.83 (m, 2H, H-4', H-5'a), 4.81 - 4.71 (m, 1H, H-5'b), 2.53 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (5'-CO), 165.4 (3'-CO), 165.2 (2'-CO), 162.0 (C-2), 154.9 (C-6), 151.3 (C-4), 134.1 (Bz), 134.0 (Bz), 133.8 (Bz), 130.0 (Bz), 130.0 (Bz), 129.8 (Bz), 129.5 (C-8), 129.1 (Bz), 128.9 (Bz), 128.7 (Bz), 128.7 (Bz),

128.5 (Bz), 120.8 (C-7), 96.3 (C-5), 88.7 (C-1'), 81.5 (C-4'), 74.9 (C-2'), 71.7 (C-3'), 63.5 (C-5'), 24.3 (CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{33}H_{28}ClN_4O_9S$) calculated 691.1260, found 691.1257.

4-Amino-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (14)

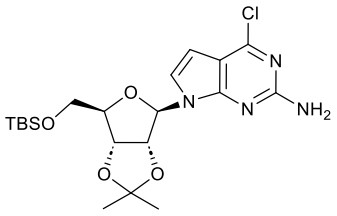


S6 (276.4 mg, 0.400 mmol, 1.0 eq) was dissolved in 7M ammonia in methanol (4 ml) in a pressure-resistant tube. The solution was then stirred in the closed tube at 60 °C for 11 hours. After this time, the sulfonyl chloride was fully converted to sulfonamide. Potassium carbonate (55 mg, 0.40 mmol, 1.0 eq) was added to the mixture, and heating was continued overnight. The solvent was evaporated, and the residue was adsorbed onto silica. RP-FCC (5–50% of ACN in water, 0.1 % of FA) yielded pure product **14** (113 mg, 0.31 mmol, 79%) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.89 (s, 1H, H-8), 7.54 (s, 2H, SO_2-NH_2), 7.11 (s, 2H, NH_2), 6.04 (d, $J_{1',2'}$ = 6.6 Hz, 1H, H-1'), 5.35 - 5.31 (m, 3H, 3xOH), 4.46 - 4.39 (m, 1H, H-2'), 4.11 - 4.05 (m, 1H, H-3'), 3.97 - 3.90 (m, 1H, H-4'), 3.67 - 3.60 (m, 1H, H-5'a), 3.59 - 3.52 (m, 1H, H-5'b), 2.39 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 162.0 (C-2), 156.9 (C-6), 151.8 (C-4), 125.6 (C-8), 118.9 (C-7), 96.3 (C-5), 87.5 (C-1'), 85.9 (C-4'), 74.1 (C-2'), 71.0 (C-3'), 61.9 (C-5'), 25.4 (CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{12}H_{18}N_5O_6S$) calculated 360.0972, found 360.0974.



Scheme S3. Synthesis of C7-sulfonamide nucleoside analogue **15**

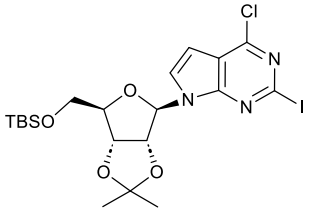
7-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (S8)



Protected sugar **S7**[5] (4 g, 13.1 mmol) was dissolved in THF (50 mL) under argon, followed by the addition of CCl_4 (1.7 mL, 17.5 mmol, 1.33 eq). The mixture was cooled to –78 °C, HMPA (2.9 mL, 16.4 mmol, 1.25 eq) was added dropwise over 30 minutes, and the solution was stirred for 1 hour at -20 °C. In a separate flask, NaH (1.2 g, 26.3 mmol, 2.0 eq) was added in several portions to a suspension of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (4.4 g, 26.3 mmol, 2.0 eq) in dry ACN (44 mL), stirred at RT for 1 hour, and then added to the solution of the chlorosugar over 30 minutes at RT.

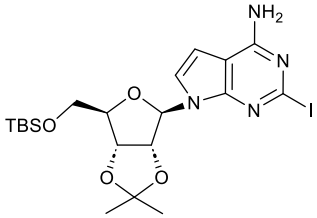
The reaction was stirred overnight under an argon atmosphere. Saturated aqueous NH_4Cl was added, and the mixture was extracted with DCM (3 x). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated, and the product was purified by FCC (10–30% of EtOAc in cyclohexane). The product **S8** (2.75 g, 6.0 mmol, 46%) was obtained as a light-yellow foam. NMR spectra were consistent with the literature [6].

7-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-4-chloro-2-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (S9)



Protected nucleoside **S8** (4 g, 8.8 mmol), CuI (1.67 g, 8.8 mmol, 1.0 eq), and diiodomethane (2.8 mL, 35.2 mmol, 4.0 eq) were mixed in THF (88 mL) and treated with *t*-BuONO (3.1 mL, 26.4 mmol, 3.0 eq) dropwise. The reaction mixture was stirred at reflux for 4 hours, diluted with ethyl acetate, and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over sodium sulfate and evaporated. The residue was subjected to FCC (10–50 % of EtOAc in cyclohexane) to afford **S9** (3.34 g, 5.9 mmol, 67%) as a light-yellow foam. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 7.44 (d, $J_{8,7}$ = 3.8 Hz, H-8), 6.59 (d, $J_{7,8}$ = 3.7 Hz, H-7), 6.33 (d, $J_{1',2'}$ = 2.8 Hz, H-1'), 4.98 (dd, $J_{2',3'}$ = 6.2, $J_{2',1'}$ = 2.8 Hz, H-2'), 4.95 (dd, $J_{3',2'}$ = 6.2, $J_{3',4'}$ = 3.0 Hz, H-3'), 4.31 (q, $J_{4',3'}$ = 3.5, $J_{4',5'a}$ = 3.5, $J_{4',5'b}$ = 3.5 Hz, H-4'), 3.89 (d, J_{gem} = 11.3, $J_{5'a,4'}$ = 3.4 Hz, 1H, H-5'a), 3.81 (dd, J_{gem} = 11.3, $J_{5'b,4'}$ = 3.9 Hz, 1H, H-5'b), 1.64 (s, 3H, CH_3–iPr), 1.38 (s, 3H, CH_3–iPr), 0.91 (s, 3H, CH_3–tBu), 0.07 (s, 3H, CH_3–Si), 0.07 (s, 3H, CH_3–Si). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 151.4 (C-4/C-6), 151.4 (C-4/C-6), 127.5 (C-8), 117.9 (C-2), 115.8 (C-5), 114.5 (C-iPr), 101.0 (C-7), 90.3 (C-1'), 86.4 (C-4'), 85.1 (C-2'), 80.9 (C-3'), 63.6 (C-5'), 27.5 (CH_3-iPr), 26.1 (CH_3–tBu), 25.7 (CH_3–iPr), 18.6 (C-tBu), -5.2 (Si–CH_3), -5.3 (Si–CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{20}H_{30}ClIN_3O_4Si$) calculated: 566.0739; found: 566.0741.

7-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (S10)

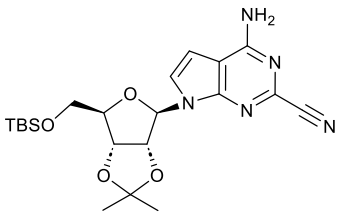


S9 (2 g, 3.5 mmol) was dissolved in a mixture of NH_4OH (12 mL, aq., conc.) and dioxane (12 mL), and the reaction was stirred in a pressure tube at 125 °C for 24 hours. The volatiles were evaporated, and the crude product was adsorbed onto silica. The product was purified by column chromatography on silica gel (10–50% of EtOAc in cyclohexane), affording **S10** (1.25 g, 65%) as a white foam. The main side product, 5′-OH-deprotected nucleoside **S10-Dep,** was also isolated (360 mg, 24%). **S10: ^{1}H NMR** (401 MHz, DMSO-d_6) δ 7.06 (d, $J_{8,7}$ = 3.7 Hz, H-8), 6.32 (d, $J_{7,8}$ = 3.7 Hz, H-7), 6.21 (d, $J_{1',2'}$ = 2.8 Hz, H-1'), 5.49 (bs, 2H, NH_2), 5.06 (dd, $J_{2',3'}$ = 6.2, $J_{2',1'}$ = 2.8 Hz, H-2'), 4.96 (dd, $J_{3',2'}$ = 6.3, $J_{3',4'}$ = 3.5 Hz, H-3'), 4.26 (q, $J_{4',5'a}$ = 4.1, $J_{4',5'b}$ = 4.1, $J_{4',3'}$ = 4.1 Hz, H-4'), 3.87 (dd, J_{gem} = 11.1, $J_{5'a,4'}$ = 4.0 Hz, H-5'a), 3.81 (dd, J_{gem} = 11.1, $J_{5'b,4'}$ = 4.7 Hz, H-5'b), 1.62 (s, 3H, CH_3–iPr), 1.38 (s, 3H, CH_3–iPr), 0.89 (s, 9H, CH_3–tBu), 0.04 (s, 3H, CH_3–Si), 0.04 (s, 3H, CH_3–Si). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 156.5 (C-6), 150.4 (C-4), 123.3 (C-8), 119.0 (C-2), 114.3 (C–iPr), 103.2 (C-5), 99.1 (C-7), 90.3 (C-1'), 86.6 (C-4'), 85.0 (C-2'), 81.2 (C-3'), 63.6 (C-5'), 27.5 (CH_3–iPr), 26.1 (CH_3–

tBu), 25.7 (CH_3–iPr), 18.6 (C–tBu), -5.2 (CH_3–Si), -5.3 (CH_3–Si). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{20}H_{32}IN_4O_4Si$) calculated: 547.1238; found: 547.1237.

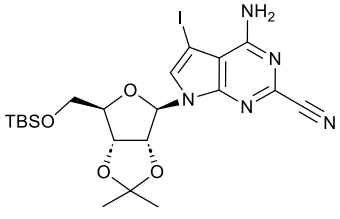
S10-Dep: ^{1}H NMR (401 MHz, DMSO-d_6) δ 6.90 (d, $J_{8,7}$ = 3.7 Hz, H-8), 6,31 (d, $J_{7,8}$ = 3.7 Hz, H-7), 5.70 (d, $J_{1',2'}$ = 5.1 Hz, H-1'), 5.65 (bs, 2H, NH_2), 5.25 (dd, $J_{2',3'}$ = 6.1, $J_{2',1'}$ = 5.0 Hz, H-2'), 5.10 (dd, $J_{3',2'}$ = 6.1, $J_{3',4'}$ = 1.7 Hz, H-3'), 4.46 (q, $J_{4',3'}$ = 1.9, $J_{4',5'a}$ = 1.9, $J_{4',5'b}$ = 1.9 Hz, H-4'), 3.99 (dd, J_{gem} = 12.6, $J_{5'a,4'}$ = 1.8 Hz, H-5'a), 3.82 (dd, J_{gem} = 12.6, $J_{5'b,4'}$ = 2.1 Hz, H-5'b), 1.62 (s, 3H, CH_3–iPr), 1.37 (s, 3H, CH_3–iPr). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 156.7 (C-6), 149.2 (C-4), 125.6 (C-8), 118.3 (C-2), 114.1 (C–iPr), 104.7 (C-5), 98.5 (C-7), 95.7 (C-1'), 85.4 (C-4'), 82.8 (C-2'), 81.6 (C-3'), 63.5 (C-5'), 27.8 (CH_3–iPr), 25.5 (CH_3–iPr). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{14}H_{18}IN_4O_4$) calculated: 433.0373; found 433.0379.

4-Amino-7-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2-carbonitrile (S11)



A solution of $Pd_2(dba)_3$ (261 mg, 0.25 mmol, 0.03 eq) and Xantphos (292 mg, 0.51 mmol, 0.06 eq) in *N*,*N*-dimethylacetamide (DMA) (28 mL) was stirred at ambient temperature under argon for 5 minutes. **S10** (4.6 g, 8.4 mmol, 1.0 eq) was added, followed by $Zn(CN)_2$ (1.2 g, 10.1 mmol, 1.2 eq) and DMA (28 mL), and the resulting mixture was stirred at 85 °C for 12 hours until the reaction went to completion. The volatiles were evaporated, and the crude product was adsorbed onto silica. The product was purified by column chromatography on silica gel (10–80% of EtOAc in cyclohexane), affording **S11** (3.4 g, 91%) as a white foam. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 7.43 (d, $J_{8,7}$ = 3.7 Hz, H-8), 6.46 (d, $J_{7,8}$ = 3.7 Hz, H-7), 6.32 (d, $J_{1',2'}$ = 3.1 Hz, H-1'), 5.69 (bs, 2H, NH_2), 5.03 (dd, $J_{2',3'}$ = 6.3, $J_{2',1'}$ = 3.2 Hz, H-2'), 4.95 (dd, $J_{3',2'}$ = 6.3, $J_{3',4'}$ = 3.2 Hz, H-3'), 4.31 (q, $J_{4',3'}$ = 3.6, $J_{4',5'a}$ = 3.6, $J_{4',5'b}$ = 3.6 Hz, H-4'), 3.89 (dd, J_{gem} = 11.2, $J_{5'a,4'}$ = 3.6 Hz, H-5'a), 3.81 (dd, J_{gem} = 11.2, $J_{5'b,4'}$ = 3.9 Hz, H-5'b), 1.65 (s, 3H, CH_3–iPr), 1.39 (s, 3H, CH_3–iPr), 0.90 (s, 9H, CH_3–tBu), 0.07 (s, 3H, Si–CH_3), 0.07 (s, 3H, Si–CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 156.8 (C-6), 149.2 (C-4), 136.5 (C-2), 126.0 (C-8), 117.1 (CN), 114.5 (C–iPr), 105.4 (C-5), 99.6 (C-7), 90.4 (C-1'), 86.2 (C-4'), 85.0 (C-2'), 81.0 (C-3'), 63.6 (C-5'), 27.6 (CH_3–iPr), 26.1 (CH_3–tBu), 25.7 (CH_3–iPr), 18.6 (C–tBu), -5.2 (CH_3–Si). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{21}H_{32}N_5O_4Si$) calculated: 446.2224; found: 446.2226.

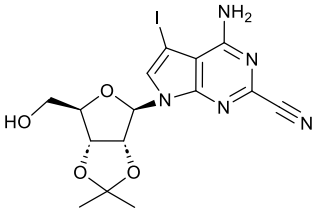
4-Amino-7-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine-2-carbonitrile (S12)



To a solution of **S11** (3.6 g, 8.1 mmol, 1.0 eq) in DMF (54 mL) was added *N*-iodosuccinimide (2 g, 8.9 mmol, 1.1 eq), and the mixture was stirred at 65 °C for 16 hours. The resulting solution was diluted with ethyl acetate and washed consecutively with saturated aqueous $Na_2S_2O_3$, $NaHCO_3$, and brine. The organic layer was dried over sodium sulfate and evaporated. The product was purified by FCC (10–40% of EtOAc in cyclohexane), affording **S12** (4.38 g, 7.7 mmol, 95%) as a light-yellow foam. **^{1}H**

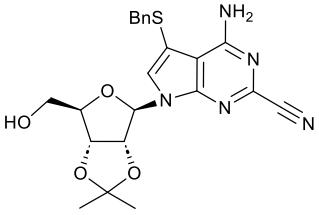
NMR (401 MHz, DMSO-d_6) δ 7.59 (s, H-8), 6.33 (d, $J_{1',2'}$ = 1,4 Hz, H-1'), 6.09 (bs, 2H, NH_2), 4.90 - 4.88 (m, 2H, H-2',H-3'), 4.35 (m, H-4'), 3.91 (dd, J_{gem} = 11.1, $J_{5'a,4'}$ = 3.8 Hz, H-5'a), 3.81 (dd, J_{gem} = 11.1, $J_{5'b,4'}$ = 3.2 Hz, H-5'b), 1.64 (s, 3H, CH_3–iPr), 1.37 (s, 3H, CH_3–iPr), 0.93 (s, 9H, CH_3–tBu), 0.12 (s, 3H, Si–CH_3), 0.12 (s, 3H, Si–CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.1 (C-6), 149.1 (C-4), 137.1 (C-2), 129.5 (C-8), 116.7 (CN), 114.5 (C–iPr), 105.9 (C-5), 90.4 (C-1'), 86.2 (C-4'), 85.4 (C-2'), 80.9 (C-3'), 63.7 (C-5'), 51.6 (C-7), 27.5 (CH_3–iPr), 26.2 (CH_3–tBu), 25.6 (CH_3–iPr), 18.6 (C–tBu), -5.1 (Si–CH_3), -5.2 (Si–CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{21}H_{31}IN_5O_4Si$) calculated: 572.1190; found: 572.1188.

4-Amino-7-((3a*R*,4*R*,6*R*,6a*R*)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine-2-carbonitrile (S13)



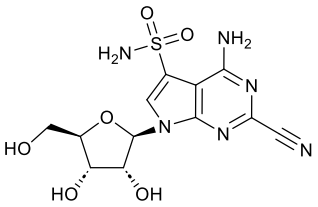
To a solution of **S12** (4.4 g, 7.7 mmol) in THF (50 mL) was added TBAF (1M solution in THF, 10 mL), and the mixture was stirred at ambient temperature for 2 hours. The volatiles were evaporated, and the product was isolated on FCC (10–80% of EtOAc in cyclohexane), to afford **S13** (3.2 g, 7.0 mmol, 91%) as a white foam. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.94 (s, 1H, C-8), 6.17 (d, 1H, $J_{1',2'}$ = 3.1, C-1′), 5.14 - 5.08 (m, 2H, C-2′, OH), 4.90 (dd, 1H, $J_{3',2'}$ = 6.3, $J_{3',4'}$ = 3.9 Hz, C-3′), 4.15 (td, 1H, $J_{4',5'}$ = 4.7, $J_{4',3'}$ = 3.0 Hz, C-5′), 3.54 (t, 1H, $J_{5',4'}$ = $J_{5',OH}$ = 5.1 Hz, C-5′), 1.54 and 1.31 (s, 3H, CH_3-iPr). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.5 (C-6), 148.4 (C-4), 136.3 (C-2), 130.1 (C-8), 116.9 (CN), 113.3 (C-iPr), 105.0 (C-5), 88.8 (C-1′), 86.0 (C-4′), 83.8 (C-2′), 80.9 (C-3′), 61.4 (C-5′), 53.6 (C-7), 27.0, 25.2 (CH_3-iPr). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{15}H_{17}IN_5O_4$) calculated: 458.0325; found: 458.0325.

4-Amino-5-(benzylthio)-7-((3a*R*,4*R*,6*R*,6a*R*)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2-carbonitrile (S14)

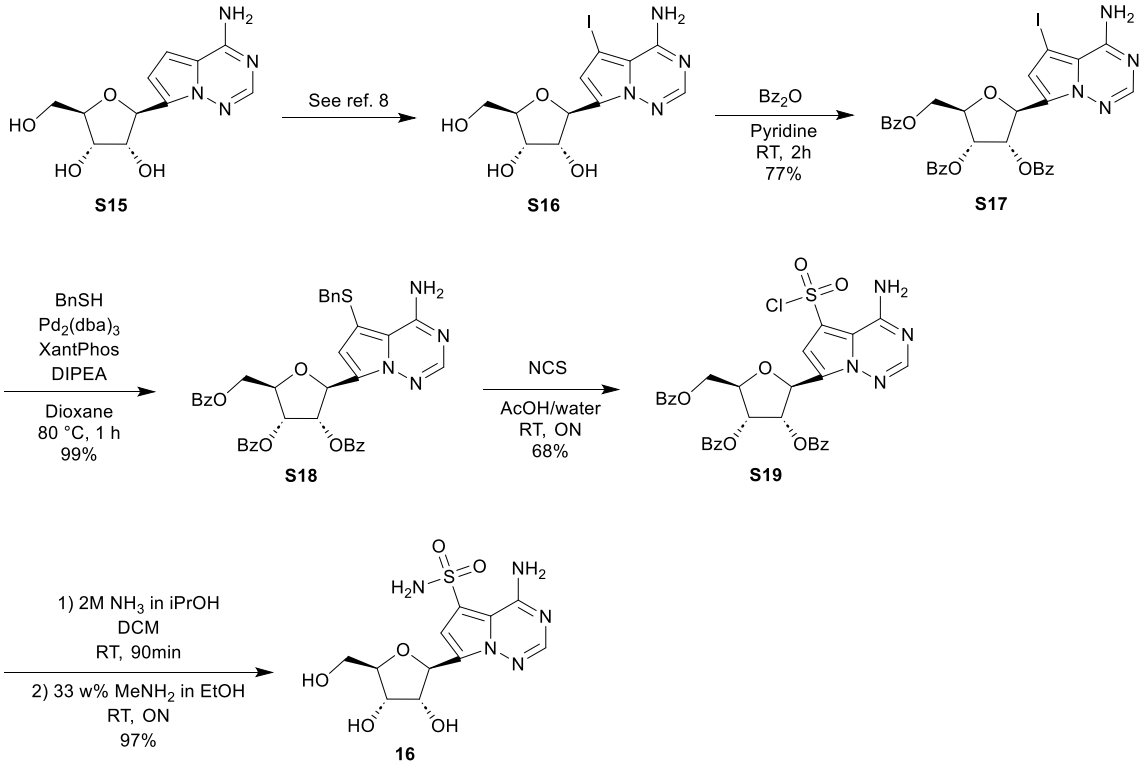


To a solution of **S13** (300 mg, 0.66 mmol) in anhydrous 1,4-dioxane (11.0 mL) were added benzyl mercaptan (139 µL, 1.18 mmol, 1.80 eq), DIPEA (286 µL, 1.64 mmol, 2.50 eq), $Pd_2(dba)_3$ (15 mg, 0.016 mmol, 0.025 eq), and XantPhos (22 mg, 0.037 mmol, 0.057 eq). The resulting mixture was stirred at 80 °C under argon for 3 hours. The volatiles were evaporated, and the residue was subjected to FCC (10–40% of a 4:1 EtOAc/EtOH mixture in cyclohexane), affording product **S14** (288 mg, 0.64 mmol, 97%) as a colourless solid. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 7.28 - 7.23 (m, 3H, SBn), 7.07 - 6.97 (m, 2H, SBn), 6.94 (s, 1H, H-8), 5.79 (d, $J_{1',2'}$ = 4.0 Hz, 1H, H-1'), 5.11 - 5.00 (m, 2H, H-2',H-3'), 4.46 - 4.38 (m, 1H, H-4'), 3.93 (dd, J_{gem} = 12.5 Hz, $J_{H\text{-}5'a,4'}$ = 2.1 Hz, 1H, H-5'a), 3.84 (s, 2H, SBn-CH_2), 3.79 (dd, J_{gem} = 12.5 Hz, $J_{H\text{-}5'b,4'}$ = 2.6 Hz, 1H, H-5'b), 1.62 (s, 3H, iPr-CH_3), 1.37 (s, 3H, iPr-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.9 (C-6), 148.2 (C-4), 137.3 (Bn), 136.9 (C-2), 133.3 (C-8), 129.2 (Bn), 128.8 (Bn), 127.8 (Bn), 116.2 (CN), 114.5 (iPr-C), 107.1 (C-5), 104.0 (C-7), 94.2 (C-1'), 85.8 (C-4'), 83.5 (C-2'), 81.3 (C-3'), 63.3 (C-5'), 43.2 (SBn-CH_2), 27.7 (iPr-CH_3), 25.4 (iPr-CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{22}H_{24}N_5O_4S$) calculated 454.1544, found 454.1541.

4-Amino-2-cyano-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (15)

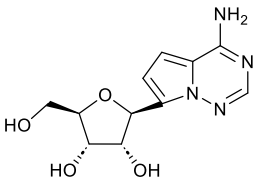


S14 (113 mg, 0.25 mmol) was dissolved in a 3:1 AcOH/water mixture (5 mL). NCS (134 mg, 1.00 mmol, 4.0 eq) was added, and the mixture was stirred at RT for 7 hours. After this time, the sulfonyl chloride was formed and the isopropylidene protecting group was fully cleaved (LC/MS analysis). The solvents were removed under reduced pressure, and the residue was co-evaporated twice with toluene. The crude intermediate was dissolved in a mixture of anhydrous DCM (1.5 mL) and 2M ammonia in *i*-PrOH (1.0 mL, 2.00 mmol, 8.0 eq). The resulting solution was stirred at RT for 30 minutes. The volatiles were evaporated, and the crude product was subjected to RP-FCC (10–100% of ACN in water, 0.1% of FA). The appropriate fractions were evaporated, and the residue was further purified by FCC (5–25% of a 15:3:4:3 EtOAc/acetone/EtOH/water mixture in a 20:3:1.2:0.8 EtOAc/acetone/EtOH/water system) and finally by RP-FCC (10–50% of ACN in water). Compound **15** (32 mg, 0.086 mmol, 35%) was obtained as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.24 (m, 2H, H-8, NH_2a), 7.64 (s, 2H, SO_2-NH_2), 7.30 (s, 1H, NH_2b), 6.09 (d, $J_{1',2'}$ = 6.1 Hz, 1H, H-1'), 5.47 (s, 1H, 2'-OH), 5.25 (s, 1H, 3'-OH), 5.11 (s, 1H, 5'-OH), 4.34 (s, 1H, H-2'), 4.12 - 4.05 (m, 1H, H-3'), 3.99 - 3.92 (m, 1H, H-4'), 3.64 (dd, J_{gem} = 11.9 Hz, $J_{5'a,4'}$ = 3.7 Hz, 2H, H-5'a), 3.58 (dd, J_{gem} = 11.9 Hz, $J_{5'b,4'}$ = 3.6 Hz, 1H, H-5'b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.2 (C-6), 149.5 (C-4), 137.6 (C-2), 127.7 (C-8), 120.5 (C-7), 116.9 (CN), 99.8 (C-5), 87.3 (C-1'), 85.9 (C-4'), 74.8 (C-2'), 70.6 (C-3'), 61.4 (C-5'). **HRMS** (ESI) m/z: $[M+Na]^+$ ($C_{12}H_{14}N_6O_6SNa$) calculated 393.0588, found 393.0589.



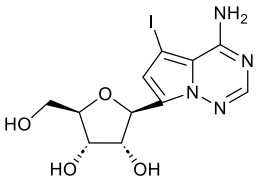
Scheme S4. Synthesis of C7-sulfonamide nucleoside analogue **16**

(2*S*,3*R*,4*S*,5*R*)-2-(4-Aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (S15)



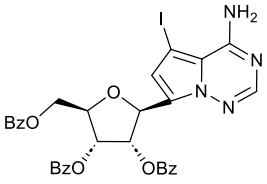
Compound **S15** was prepared according to the reported procedure [7]. NMR characteristics were consistent with the published data.

(2*S*,3*R*,4*S*,5*R*)-2-(4-Amino-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (S16)



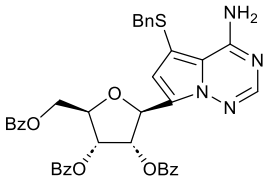
Compound **S16** was prepared according to the reported procedure [8]. NMR characteristics were consistent with the published data.

(2*S*,3*S*,4*R*,5*R*)-2-(4-Amino-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (S17)



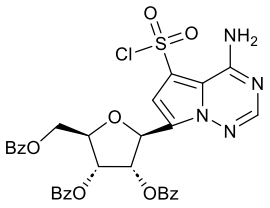
The reaction was performed similarly to the procedure described previously for the benzoylation of adenosine [9]. The iodinated nucleoside **S16** (1.17 g, 2.98 mmol) was dried by co-evaporation with anhydrous pyridine before being suspended in anhydrous pyridine (30 mL). DMAP (91 mg, 0.75 mmol, 0.25 eq) and Bz_2O (3.38 g, 14.9 mmol, 5.0 eq) were added, and the reaction was stirred at RT in a flask equipped with a drying tube for 2 hours. The mixture was treated with MeOH (2 mL), concentrated, and the residue was partitioned between DCM and saturated $NaHCO_3$ solution. The aqueous layer was extracted with DCM. The combined organic solutions were washed with brine and dried over Na_2SO_4. The solution was concentrated, adsorbed onto silica, and purified by FCC (3–15% of a 4:1 EtOAc/EtOH mixture in DCM). The product was not fully separated from by-products. Appropriate fractions were concentrated and subjected to RP-FCC (30–100 % of ACN in water), yielding **S17** (1.61 g, 2.29 mmol, 77%). **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.08 - 7.96 (m, 2H, Bz), 7.93 - 7.83 (m, 4H, Bz), 7.81 (s, 1H, C-2), 7.72 - 7.59 (m, 3H, Bz), 7.58 - 7.50 (m, 2H, Bz), 7.49 - 7.40 (m, 4H, Bz), 6.98 (s, 1H, C-8), 6.05 - 5.98 (m, 1H, H-2'), 5.93 - 5.85 (m, 1H, H-3'), 5.70 (d, $J_{1',2'}$ = 6.0 Hz, 1H, H-1'), 4.78 - 4.69 (m, 2H, H-4', H-5'a), 4.63 - 4.53 (m, 1H, H-5'b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6 (5'-CO), 164.9 (3'-CO), 164.8 (2'-CO), 155.7 (C-6), 148.2 (C-2), 134.0 (Bz), 134.0 (Bz), 133.7 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Bz), 128.9 (Bz), 128.9 (Bz), 128.9 (Bz), 128.7 (Bz), 128.6 (C-9), 118.6 (C-8), 115.0 (C-5), 79.2 (C-4'), 74.2 (C-1'), 73.7 (C-2'), 72.1 (C-3'), 63.8 (C-5'), 52.9 (C-7). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{32}H_{26}IN_4O_7$) calculated 705.0841, found 705.0837.

(2*S*,3*S*,4*R*,5*R*)-2-(4-Amino-5-(benzylthio)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (S18)



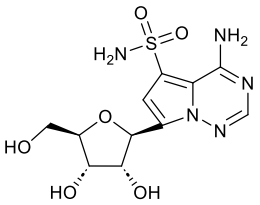
To a solution of **S17** (1.60 g, 2.27 mmol) in an anhydrous 1,4-dioxane (38.0 mL) were added benzyl mercaptan (479 µL, 4.08 mmol, 1.80 eq), DIPEA (987 µL, 5.67 mmol, 2.50 eq), $Pd_2(dba)_3$ (52 mg, 0.057 mmol, 0.025 eq), and XantPhos (75 mg, 0.13 mmol, 0.057 eq). The resulting mixture was stirred at 80 °C under argon for 1 hour. The volatiles were evaporated, and the residue was subjected to FCC (10–40% of a 4:1 EtOAc/EtOH mixture in cyclohexane), affording **S18** (1.58 g, 2.25 mmol, 99%) as an off-white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.08 - 8.00 (m, 2H, Bz), 7.94 - 7.84 (m, 4H, Bz), 7.77 (s, 1H, H-2), 7.72 - 7.59 (m, 3H, Bz), 7.58 - 7.50 (m, 2H, Bz), 7.50 - 7.41 (m, 4H, Bz), 7.14 - 7.04 (m, 3H, Bn), 7.04 - 6.96 (m, 2H, Bn), 6.69 (s, 1H, H-8), 6.04 - 5.96 (m, 1H, H-2'), 5.92 - 5.85 (m, 1H, H-3'), 5.69 (d, $J_{1',2'}$ = 6.4 Hz, 1H, H-1'), 4.78 - 4.69 (m, 2H, H-4', H-5'a), 4.62 - 4.53 (m, 1H, H-5'b), 3.86 (s, 2H, SBn-CH_2). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.6 (5'-CO), 165.0 (3'-CO), 164.8 (2'-CO), 155.9 (C-6), 148.5 (C-2), 137.5 (Bn), 134.0 (Bz), 134.0 (Bz), 133.8 (Bz), 129.5 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Bz), 128.9 (Bn, Bz), 128.9 (Bz), 128.7 (Bz), 128.2 (Bn), 127.2 (Bn), 126.5 (C-9), 116.8 (C-8), 116.3 (C-5), 103.5 (C-7), 79.3 (C-4'), 73.9 (C-1'), 73.7 (C-2'), 72.3 (C-3'), 64.0 (C-5'), 42.3 (SBn-CH_2). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{39}H_{33}N_4O_7S$) calculated 701.2065, found 701.2063.

(2*S*,3*S*,4*R*,5*R*)-2-(4-Amino-5-(chlorosulfonyl)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (S19)

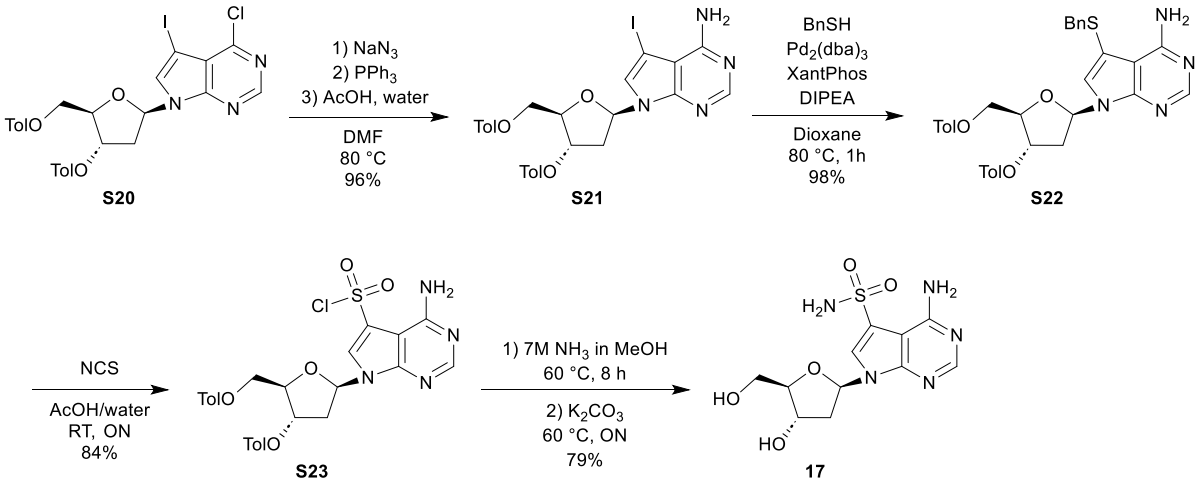


S18 (1.56 g, 2.23 mmol) was dissolved in a 3:1 AcOH/water mixture (44 mL). NCS (1.19 g, 8.90 mmol, 4.0 eq) was added, and the mixture was stirred at RT overnight. Solvents were evaporated, and the product was purified by RP-FCC (30–100% of ACN in water). Compound **S19** (1.02 g, 1.51 mmol, 68%) was obtained as a white solid. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 8.12 - 8.07 (m, 2H, Bz), 8.01 (s, 1H, H-2), 7.95 (m, 4H, Bz), 7.61 - 7.52 (m, 3H, Bz), 7.49 - 7.43 (m, 2H, Bz), 7.41 - 7.34 (m, 5H, Bz, H-8), 6.64 (s, 1H, NH_2), 6.16 - 6.06 (m, 1H, H-2'), 5.99 - 5.90 (m, 1H, H-3'), 5.76 (d, $J_{1',2'}$ = 5.8 Hz, 1H, H-1'), 4.87 (dd, J_{gem} = 12.1 Hz, $J_{5'a,4'}$ = 3.2 Hz, 1H, H-5'a), 4.80 - 4.73 (m, 1H, H-4'), 4.64 (dd, J_{gem} = 12.1 Hz, $J_{5'b,4'}$ = 3.9 Hz, 1H, H-5'b). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (5'-CO), 165.5 (3'-CO), 165.3 (2'-CO), 153.2 (C-6), 147.3 (C-2), 133.8 (Bz), 133.8 (Bz), 133.6 (Bz), 130.0 (C-9), 129.9 (Bz), 129.9 (Bz), 129.5 (Bz), 129.0 (Bz), 128.9 (Bz), 128.8 (Bz), 128.6 (Bz), 120.2 (C-7), 114.1 (C-8), 113.7 (C-5), 80.5 (C-4'), 75.5 (C-1'), 73.9 (C-2'), 72.4 (C-3'), 63.6 (C-5'). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{32}H_{26}ClN_4O_9S$) calculated 677.1104, found 677.1100.

4-Amino-7-((2*S*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-5-sulfonamide (16)

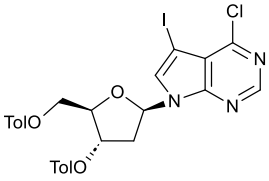


To a solution of **S19** (305 mg, 0.45 mmol) in anhydrous DCM (2.7 mL) was added 2M ammonia in *i*-PrOH (1.8 mL, 3.60 mmol, 8.0 eq). After stirring at RT for 90 minutes, the conversion to sulfonamide reached completion. The solvents were evaporated, and the residue was redissolved in a 33% ethanolic $MeNH_2$ solution (3.0 mL) and stirred at RT overnight. The reaction mixture was directly adsorbed onto silica and dried. RP-FCC (5–50% of ACN in water, 0.1 % of FA) failed to produce pure product. Appropriate fractions were combined and concentrated. This impure product was dissolved, adsorbed onto silica, and subjected to FCC (0-50 % of a 15:3:4:3 EtOAc/acetone/EtOH/water mixture in a 20:3:1.2:0.8 EtOAc/acetone/EtOH/water system), affording pure deprotected sulfonamide **16** (151 mg, 0.44 mmol, 97%). **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.36 (s, 1H, NH_2a), 8.02 (s, 1H, H-2), 7.93 (s, 1H, NH_2b), 7.66 (s, 2H, SO_2-NH_2), 7.14 (s, 1H, C-8), 5.15 (d, $J_{1',2'}$ = 6.2 Hz, 1H, H-1'), 5.08 (d, $J_{2'\text{-OH},2'}$ = 6.3 Hz, 1H, 2'-OH), 4.97 (d, $J_{3'\text{-OH},3'}$ = 5.3 Hz, 1H, 3'-OH), 4.83 - 4.74 (m, 1H, 5'-OH), 4.21 - 4.12 (m, 1H, H-2'), 3.97 - 3.89 (m, 1H, H-3'), 3.86 - 3.78 (m, 1H, H-4'), 3.59 - 3.52 (m, 1H, H-5'a), 3.51 - 3.43 (m, 1H, H-5'b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 154.8 (C-6), 148.9 (C-2), 129.7 (C-9), 119.0 (C-7), 111.6 (C-5), 111.3 (C-8), 84.8 (C-4'), 74.9 (C-1'), 74.3 (C-2'), 71.3 (C-3'), 62.1 (C-5'). **HRMS** (ESI) m/z: $[M+Na]^+$ ($C_{11}H_{15}N_5O_6SNa$) calculated 368.0635, found 368.0636.



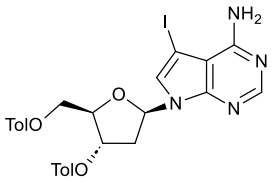
Scheme S5. Synthesis of C7-sulfonamide nucleoside analogue **17**

(2*R*,3*S*,5*R*)-5-(4-Chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2-(((4-methylbenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-methylbenzoate (S20)



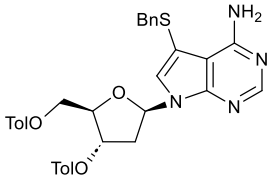
Compound **S20** was prepared according to the reported procedure [10]. NMR characteristics were consistent with the published data.

(2*R*,3*S*,5*R*)-5-(4-Amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2-(((4-methylbenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-methylbenzoate (S21)



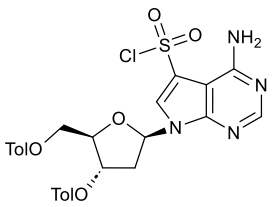
The reaction mixture containing **S20** (1.41g, 2.23 mmol) and NaN_3 (174 mg, 2.68 mmol, 1.2 eq) in anhydrous DMF (8.9 mL) was stirred under argon at 80 °C for 30 minutes. Triphenylphosphine (760 mg, 2.90 mmol, 1.3 eq) was added, and stirring was continued at the same temperature for 3 hours until the azido-intermediate was consumed. Water (2.4 mL) and acetic acid (0.77 mL, 13.4 mmol, 6.0 eq) were added, and stirring was continued at 80 °C overnight. The solvents were evaporated, and the residue was adsorbed onto silica. RP FCC (30–100% of ACN in water) afforded compound **S21** (1.31 g, 2.13 mmol, 96%) as a white solid. The product contained 4 mol% of PPh_3 as an impurity. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.11 (s, 1H, H-2), 7.97 - 7.92 (m, 2H, Tol), 7.91 - 7.86 (m, 2H, Tol), 7.61 (s, 1H, H-8), 7.39 - 7.32 (m, 4H, Tol), 6.70 (s, 2H, NH_2), 6.63 (dd, $J_{1',2'a}$ = 8.5 Hz, $J_{1',2'b}$ = 6.0 Hz, 1H, H-1'), 5.70 (ddd, $J_{H\text{-}3',H\text{-}2'a}$ = 6.6 Hz, $J_{H\text{-}3',H\text{-}2'b}$ = 2.4 Hz, $J_{H\text{-}3',H\text{-}4'}$ = 2.4 Hz, 1H, H-3'), 4.67 - 4.57 (m, 1H, H-5'a), 4.56 - 4.46 (m, 2H, H-5'b, H-4'), 2.99 (ddd, J_{gem} = 14.7 Hz, $J_{2'a,1'}$ = 8.5 Hz, $J_{2'a,3'}$ = 6.5 Hz, 1H, H-2'a), 2.65 (ddd, J_{gem} = 14.1 Hz, $J_{2'b,1'}$ = 6.0 Hz, $J_{2'b,3'}$ = 2.4 Hz, 1H, H-2'b), 2.40 (s, 3H, Tol-CH_3), 2.39 (s, 3H, Tol-CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.7 (5'-CO), 165.4 (3'-CO), 157.4 (C-6), 152.4 (C-2), 150.2 (C-4), 144.2 (Tol), 144.1 (Tol), 129.7 (Tol), 129.6 (Tol), 129.5 (Tol), 129.5 (Tol), 126.8 (Tol), 126.7 (Tol), 126.6 (C-8), 103.4 (C-5), 83.0 (C-1'), 81.4 (C-4'), 75.1 (C-3'), 64.3 (C-5'), 53.0 (C-7), 36.3 (C-2'), 21.4 (Tol-CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{27}H_{26}IN_4O_5$) calculated 613.0942, found 613.0940.

(2*R*,3*S*,5*R*)-5-(4-Amino-5-(benzylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2-(((4-methylbenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-methylbenzoate (S22)



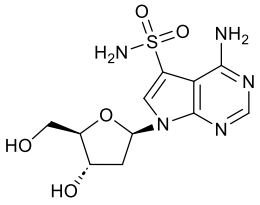
To a solution of **S21** (1.30 g, 2.12 mmol) in anhydrous 1,4-dioxane (35.0 mL) were added benzyl mercaptan (447 µL, 3.81 mmol, 1.8 eq), DIPEA (921 µL, 5.29 mmol, 2.5 eq), $Pd_2(dba)_3$ (48 mg, 0.053 mmol, 0.025 eq), and XantPhos (70 mg, 0.12 mmol, 0.057 eq). The resulting mixture was stirred at 80 °C under argon for 1 hour. The volatiles were evaporated, and the residue was subjected to FCC (10–40% of a 4:1 EtOAc/EtOH mixture in cyclohexane), affording the product **S22** (1.26 g, 2.06 mmol, 97%) as an off-white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.10 (s, 1H, H-2), 7.98 - 7.92 (m, 2H, Tol), 7.90 - 7.85 (m, 2H, Tol), 7.40 - 7.35 (m, 2H, Tol), 7.35 - 7.30 (m, 2H, Tol), 7.28 (s, 1H, H-8), 7.25 - 7.12 (m, 3H, SBn-Ar), 7.08 - 7.01 (m, 2H, SBn-Ar), 6.81 (s, 2H, NH_2), 6.62 (dd, $J_{1',2'a}$ = 8.5 Hz, $J_{1',2'b}$ = 6.0 Hz, 1H, H-1'), 5.67 (ddd, $J_{H\text{-}3',H\text{-}2'a}$ = 6.4 Hz, $J_{H\text{-}3',H\text{-}2'b}$ = 2.4 Hz, $J_{H\text{-}3',H\text{-}4'}$ = 2.4 Hz, 1H, H-3'), 4.60 - 4.53 (m, 1H, H-5'a), 4.52 - 4.45 (m, 2H, H-5'b, H-4'), 3.91 - 3.82 (m, 2H, SBn-CH_2), 2.89 (ddd, J_{gem} = 14.6 Hz, $J_{2'a,1'}$ = 8.5 Hz, $J_{2'a,3'}$ = 6.5 Hz, 1H, H-2'a), 2.63 (ddd, J_{gem} = 14.1 Hz, $J_{2'b,1'}$ = 6.1 Hz, $J_{2'b,3'}$ = 2.3 Hz, 1H, H-2'b), 2.40 (s, 3H, Tol-CH_3), 2.37 (s, 3H, Tol-CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.7 (5'-CO), 165.4 (3'-CO), 157.9 (C-6), 152.6 (C-2), 150.5 (C-4), 144.2 (Tol), 144.0 (Tol), 137.5 (Bn), 129.7 (Tol), 129.5 (Tol), 129.5 (Tol), 129.5 (Tol), 129.0 (SBn), 128.4 (SBn), 127.3 (C-8), 127.2 (SBn), 126.8 (Tol), 126.7 (Tol), 103.5 (C-5), 103.2 (C-7), 83.0 (C-1'), 81.4 (C-4'), 75.2 (C-3'), 64.4 (C-5'), 42.1 (SBn-CH_2), 36.4 (C-2'), 21.4 (Tol-CH_3), 21.4 (Tol-CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{34}H_{33}N_4O_5S$) calculated 609.2166, found 609.2161.

(2*R*,3*S*,5*R*)-5-(4-Amino-5-(chlorosulfonyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2-(((4-methylbenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-methylbenzoate (S23)

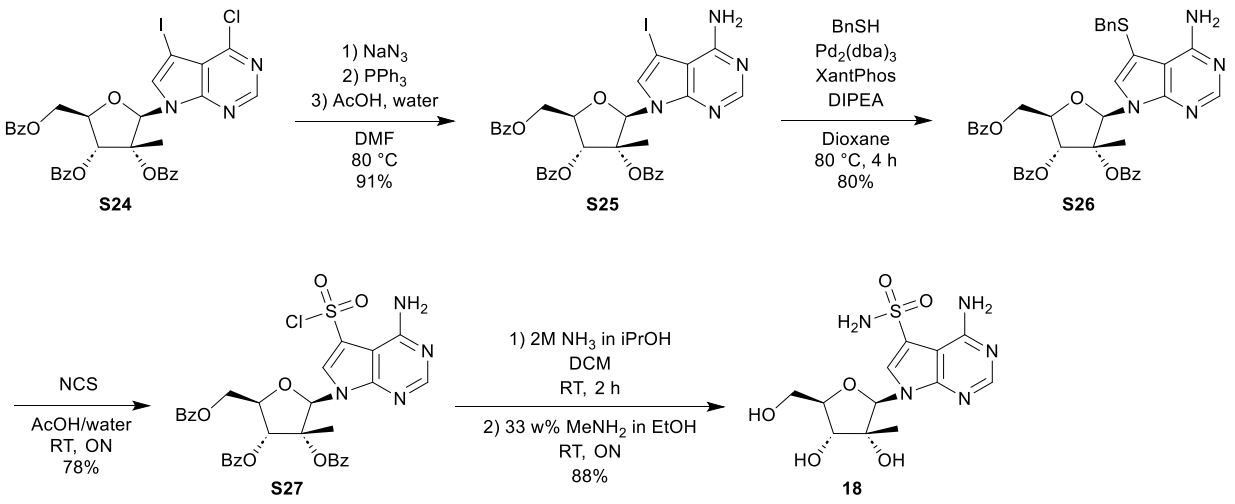


To a solution of **S22** (1.25 g, 2.05 mmol) in a 3:1 AcOH/water mixture (40 mL) was added NCS (1.09 g, 8.18 mmol, 4.0 eq), and the mixture was stirred at RT overnight. The volatiles were evaporated, and the product was purified by RP-FCC (30–100% of ACN in water). Compound **S23** (1.01 g, 1.72 mmol, 84%) was obtained as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (s, 1H, H-2), 8.13 (s, 1H, H-8), 8.00 - 7.93 (m, 2H, Tol), 7.92 - 7.84 (m, 2H, Tol), 7.31 - 7.27 (m, 2H, Tol), 7.25 - 7.21 (m, 2H, Tol), 6.90 - 6.85 (bs, 2H, NH_2), 6.70 (dd, $J_{1',2'b}$ = 8.2 Hz, $J_{1',2'a}$ = 5.6 Hz, 1H, H-1'), 5.72 (ddd, $J_{H\text{-}3',H\text{-}2'b}$ = 6.4 Hz, $J_{H\text{-}3',H\text{-}2'a}$ = 2.0 Hz, $J_{H\text{-}3',H\text{-}4'}$ = 2.0 Hz, 1H, H-3'), 4.83 - 4.72 (m, 2H, H-5'), 4.71 - 4.66 (m, 1H, H-4'), 2.95 (ddd, J_{gem} = 14.3 Hz, $J_{2'a,1'}$ = 5.7 Hz, $J_{2'a,3'}$ = 1.9 Hz, 1H, H-2'a), 2.66 (ddd, J_{gem} = 14.4 Hz, $J_{2'b,1'}$ = 8.2 Hz, $J_{2'b,3'}$ = 6.3 Hz, 1H, H-2'b), 2.44 (s, 3H, Tol-CH_3), 2.40 (s, 3H, Tol-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (5'-CO), 166.1 (3'-CO), 155.3 (C-6), 152.0 (C-2), 150.2 (C-4), 144.8 (Tol), 144.7 (Tol), 130.0 (Tol), 129.8 (Tol), 129.6 (Tol), 129.5 (Tol), 129.2 (C-8), 126.5 (Tol), 126.3 (Tol), 120.2 (C-7), 98.4 (C-5), 86.0 (C-1'), 84.0 (C-4'), 75.2 (C-3'), 63.9 (C-5'), 39.6 (C-2'), 21.9 (Tol-CH_3), 21.9 (Tol-CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{27}H_{26}ClN_4O_7S$) calculated 585.1205, found 585.1201.

4-Amino-7-((2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (17)

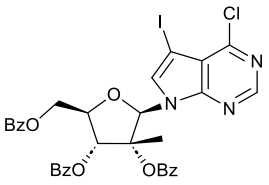


S23 (263 mg, 0.45 mmol) was placed into a pressure-resistant tube and dissolved in 7M methanolic ammonia (4 mL). The reaction was then stirred in the closed tube at 60 °C for 8 hours. After this time, sulfonamide was formed, and the mixture contained partially unprotected intermediates. Potassium carbonate (62 mg, 0.45 mmol, 1.000 eq) was added, and heating was continued overnight at 60 °C. The solvent was evaporated, and the residue was subjected to RP-FCC (5–50% of ACN in water, 0.1 % of FA), yielding pure **19** (117 mg, 0.36 mmol, 79%). **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.17 (s, 1H, H-2), 7.97 (s, 1H, H-8), 7.55 (s, 2H, SO_2-NH_2), 7.17 (s, 2H, NH_2), 6.54 (dd, $J_{1',2'a}$ = 8.0 Hz, $J_{1',2'b}$ = 5.9 Hz, 1H, H-1'), 5.33 - 5.28 (m, 1H, 3'-OH), 5.11 - 5.04 (m, 1H, 5'-OH), 4.38 - 4.32 (m, 1H, H-3'), 3.90 - 3.83 (m, 1H, H-4'), 3.64 - 3.50 (m, 2H, H-5'), 2.44 (ddd, J_{gem} = 13.5 Hz, $J_{2'a,1'}$ = 8.0 Hz, $J_{2'a,3'}$ = 5.8 Hz, 1H, H-2'a), 2.24 (ddd, J_{gem} = 13.1 Hz, $J_{2'b,1'}$ = 6.0 Hz, $J_{2'b,3'}$ = 2.8 Hz, 1H, H-2'b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.0 (C-6), 153.3 (C-2), 150.4 (C-4), 125.5 (C-8), 119.0 (C-7), 98.2 (C-5), 87.9 (C-4'), 83.7 (C-1'), 71.1 (C-3'), 62.0 (C-5'), 40.4 (C-2'). **HRMS** (ESI) m/z: $[M+Na]^+$ ($C_{11}H_{15}N_5O_5SNa$) calculated 352.0686, found 352.0687.



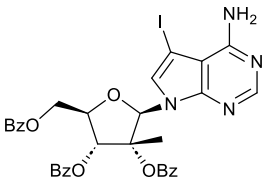
Scheme S6. Synthesis of C7-sulfonamide nucleoside analogue **18**

(2*R*,3*R*,4*R*,5*R*)-5-((Benzoyloxy)methyl)-2-(4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-methyltetrahydrofuran-3,4-diyl dibenzoate (S24)



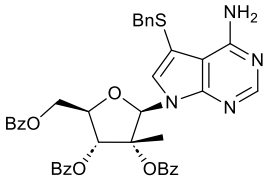
Compound **S24** was prepared according to the reported procedure [11]. NMR characteristics were consistent with the published data.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)-3-methyltetrahydrofuran-3,4-diyl dibenzoate (S25)



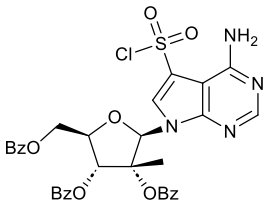
To a solution of **S24** (1.90 g, 2.58 mmol) in DMF (10.3 mL) was added NaN_3 (201 mg, 3.09 mmol, 1.2 eq), and the mixture was stirred at 80 °C for 20 minutes. Triphenylphosphine (878 mg, 3.35 mmol, 1.3 eq), water (2.8 mL), and acetic acid (888 µL, 15.5 mmol, 6.0 eq) were added, and stirring was continued at 80 °C overnight. The solvents were evaporated, and the residue was subjected to RP-FCC (30–100% of ACN in water, 0.1 % of FA), affording product **S25** (1.68 g, 2.34 mmol, 91%) as a light brown foam. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.26 (s, 1H, H-2), 8.11 - 7.97 (m, 4H, Bz), 7.91 - 7.83 (m, 2H, Bz), 7.70 (s, 1H, H-8), 7.69 - 7.64 (m, 2H, Bz), 7.64 - 7.59 (m, 1H, Bz), 7.56 - 7.49 (m, 4H, Bz), 7.45 - 7.35 (m, 2H, Bz), 6.84 (s, 1H, H-1'), 6.79 (s, 2H, NH_2), 5.95 (d, $J_{H\text{-}3',H\text{-}4'}$ = 4.9 Hz, 1H, H-3'), 4.86 - 4.79 (m, 1H, H-5'a), 4.79 - 4.71 (m, 2H, H-4', H-5'b), 1.55 (s, 3H, 2'-CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.8 (5'-CO), 164.8 (3'-CO), 164.5 (2'-CO), 157.6 (C-6), 152.6 (C-2), 150.2 (C-4), 134.1 (Bz), 134.0 (Bz), 133.7 (Bz), 129.7 (Bz), 129.6 (Bz), 129.5 (Bz), 129.0 (Bz), 129.0 (Bz), 128.9 (Bz), 128.8 (Bz), 127.5 (C-8), 103.5 (C-5), 87.9 (C-1'), 84.8 (C-2'), 79.0 (C-4'), 75.6 (C-3'), 64.0 (C-5'), 52.9 (C-7), 18.0 (2'-CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{33}H_{28}IN_4O_7$) calculated 719.0997, found 719.0992.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(benzylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)-3-methyltetrahydrofuran-3,4-diyl dibenzoate (S26)



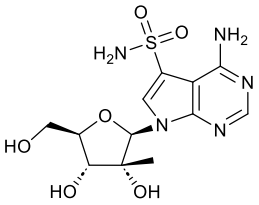
To a solution of **S25** (1.67 g, 2.32 mmol) in anhydrous 1,4-dioxane (39 mL) were added benzyl mercaptan (491 µL, 4.18 mmol, 1.8 eq), DIPEA (1.0 mL, 5.80 mmol, 2.5 eq), $Pd_2(dba)_3$ (53 mg, 0.058 mmol, 0.025 eq), and XantPhos (77 mg, 0.13 mmol, 0.057 eq). The resulting mixture was stirred at 80 °C under argon for 4 hours. The volatiles were evaporated, and the residue was subjected to RP-FCC (30–100% of ACN in water), affording product **S26** (1.33 g, 1.86 mmol, 80%) as a white foam. **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.25 (s, 1H, H-2), 8.10 - 7.97 (m, 4H, Bz), 7.89 - 7.82 (m, 2H, Bz), 7.73 - 7.65 (m, 2H, Bz), 7.64 - 7.57 (m, 1H, Bz), 7.57 - 7.50 (m, 4H, Bz), 7.45 - 7.34 (m, 2H, Bz), 7.26 (s, 1H, H-8), 7.19 - 7.06 (m, 5H, Bn), 6.90 (s, 2H, NH_2), 6.79 (s, 1H, H-1'), 5.88 (d, J = 4.8 Hz, 1H, H-3'), 4.85 - 4.77 (m, 1H, H-5'a), 4.77 - 4.69 (m, 2H, H-4', H-5'b), 3.99 - 3.88 (m, 2H, SBn-CH_2), 1.39 (s, 3H, 2'-CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.7 (5'-CO), 164.7 (3'-CO or 2'-CO), 164.5 (2'-CO or 3'-CO), 158.0 (C-6), 152.9 (C-2), 150.5 (C-4), 137.7 (Bn), 134.0 (Bz), 134.0 (Bz), 133.8 (Bz), 129.7 (Bz), 129.6 (Bz), 129.5 (Bz), 129.4 (Bz), 129.0 (Ar), 129.0 (Ar), 128.8 (Ar), 128.8 (Ar), 128.4 (Bn), 128.3 (C-8), 127.1 (Bn), 103.3 (C-5), 103.0 (C-7), 87.7 (C-1'), 84.6 (C-2'), 79.1 (C-4'), 75.4 (C-3'), 64.0 (C-5'), 41.9 (SBn-CH_2), 17.8 (2'-CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{40}H_{35}N_4O_7S$) calculated 715.2221, found 715.2217.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Amino-5-(chlorosulfonyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-((benzoyloxy)methyl)-3-methyltetrahydrofuran-3,4-diyl dibenzoate (S27)

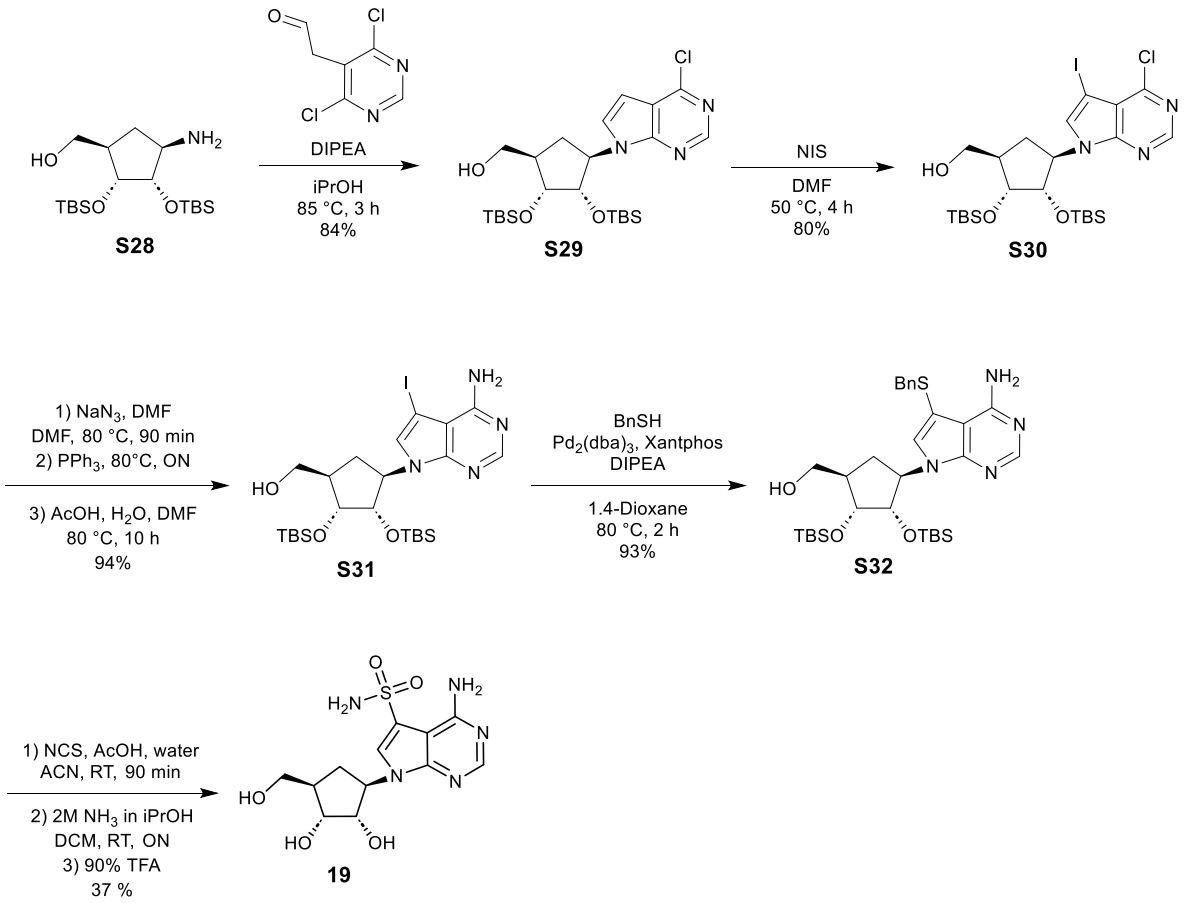


NCS (980 mg, 7.34 mmol, 4.0 eq) was added to a solution of **S26** (1.31 g, 1.83 mmol) in a 3:1 AcOH/water mixture (36 mL). After stirring at RT overnight, the solvents were evaporated, and the product was purified by RP-FCC (30–100% of ACN in water). Compound **S27** (987 mg, 1.43 mmol, 78%) was obtained as a white solid. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 8.51 (s, 1H, H-2), 8.18 - 8.07 (m, 5H, H-8, Bz), 7.97 - 7.86 (m, 2H, Bz), 7.64 - 7.54 (m, 2H, Bz), 7.54 - 7.49 (m, 1H, Bz), 7.49 - 7.41 (m, 4H, Bz), 7.35 - 7.27 (m, 2H, Bz), 6.89 (s, 1H, H-1'), 6.04 (d, $J_{H\text{-}3',H\text{-}4'}$ = 5.2 Hz, 1H, H-3'), 5.00 - 4.88 (m, 2H, H-5'a, H-5'b), 4.72 (ddd, $J_{H\text{-}4',H\text{-}5'a}$ = 5.9 Hz, $J_{H\text{-}4',H\text{-}3'}$ = 5.1 Hz, $J_{H\text{-}4',H\text{-}5'b}$ = 3.9 Hz, 1H, H-4'), 1.61 (s, 2'-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.6 (5'-CO), 165.5 (3'-CO), 165.3 (2'-CO), 156.6 (C-6), 154.8 (C-2), 151.5 (C-4), 133.9 (Bz), 133.6 (Bz), 130.5 (C-8), 130.2 (Bz), 130.0 (Bz), 129.6 (Bz), 129.6 (Bz), 128.8 (Bz), 128.7 (Bz), 128.7 (Bz), 128.6 (Bz), 119.8 (C-7), 98.6 (C-5), 89.6 (C-1'), 84.6 (C-2'), 81.0 (C-4'), 75.9 (C-3'), 63.5 (C-5'), 18.1 (2'-CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{33}H_{28}ClN_4O_9S$) calculated 691.1260, found 691.1258.

4-Amino-7-((2*R*,3*R*,4*R*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (18)

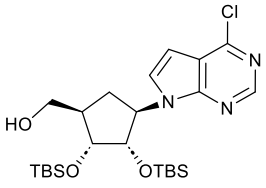


To a solution of **S27** (311 mg, 0.45 mmol) in anhydrous DCM (2.7 mL) was added 2M ammonia in *i*-PrOH (1.8 mL, 3.6 mmol, 8.0 eq). After stirring at RT for 90 minutes, the conversion to sulfonamide went to completion. The solvents were evaporated, and the residue was redissolved in 33% $MeNH_2$ in ethanol (3.0 mL) and stirred at RT overnight. The mixture was concentrated under vacuum, and the residue was co-evaporated twice with ethanol. RP-FCC (10–50 % of ACN in water, 0.1 % of FA as modifier) afforded pure product **18** (142 mg, 0.40 mmol, 88%). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.19 (s, 1H, H-8), 8.18 (s, 1H, H-2), 7.50 (s, 2H, SO_2-NH_2), 7.17 (s, 2H, NH_2), 6.17 (s, 1H, H-1'), 5.21 (s, 1H, OH), 5.17 (s, 2H, 2xOH), 3.96 - 3.86 (m, 2H, H-3', H-4'), 3.86 - 3.80 (m, 1H, H-5'a), 3.70 - 3.62 (m, 1H, H-5'5), 0.72 (s, 3H, 2'-CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.0 (C-6), 153.3 (C-2), 150.5 (C-4), 125.5 (C-8), 118.7 (C-7), 97.9 (C-5), 90.7 (C-1'), 82.5 (C-4'), 78.8 (C-2'), 71.8 (C-3'), 59.4 (C-5'), 19.9 (2'-CH_3). **HRMS** (ESI) m/z: $[M+Na]^+$ ($C_{12}H_{17}N_5O_6SNa$) calculated 382.0792, found 382.0792.



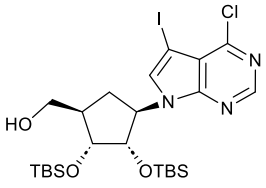
Scheme S7. Synthesis of C7-sulfonamide nucleoside analogue **19**

((1*R*,2*R*,3*S*,4*R*)-2,3-Bis((*tert*-butyldimethylsilyl)oxy)-4-(4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)cyclopentyl)methanol (S29)



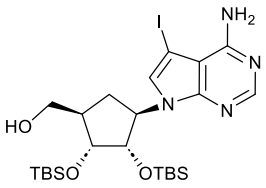
A mixture of **S28**[12] (5 g, 13 mmol), DIPEA (7 mL, 40 mmol, 3.0 eq), and 2-(4,6-dichloropyrimidin-5-yl)acetaldehyde (3 g, 16 mmol, 1.20 eq) in *i*-PrOH (133 mL) was heated to 85 °C for 3 hours. The volatiles were evaporated, and the residue was adsorbed onto silica. Product was purified by FCC (5–30% of EtOAc in cyclohexane), affording **S29** (5.7 g, 11 mmol, 84%). **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.61 (s, H-2), 7.29 (d, $J_{8,7}$ = 3.5 Hz, H-8), 6.57 (d, $J_{7,8}$ = 3.5 Hz, H-7), 4.80 (d, $J_{2',3'}$ = 3.8 Hz, H-2'), 4.75 (m, H-1'), 4.06 (bd, $J_{3',2'}$ = 3.7 Hz, H-3'), 3.82 (d, $J_{5',4'}$ = 3.6 Hz, 2H, H-5'), 2.58 (dt, J_{gem} = 14.1, $J_{6'a,1'}$ = 10.4, $J_{6'a,4'}$ = 10.4 Hz, H-6'a), 2.35 - 2.30 (m, 2H, H-6'b, H-4'), 0.93 (s, 9H, CH_3–tBu), 0.70 (s, 9H, CH_3–tBu), 0.10 (s, 6H, Si–CH_3), -0.20 (s, 3H, Si–CH_3), -0.76 (s, 3H, Si–CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 152.8 (C-6), 149.8 (C-4), 149.5 (C-2), 131.9 (C-8), 119.6 (C-5), 98.9 (C-7), 77.0 (C-2'/C-3'), 76.8 (C-3'/C-2'), 65.1 (C-5'), 64.7 (C-1'), 46.3 (C-4'), 27.5 (C-6'), 26.0 (CH_3–tBu), 25.9 (CH_3–tBu), 18.2 (C–tBu), 17.9 (C–tBu), -4.3 (Si–CH_3), -4.5 (Si–CH_3), -4.5 (Si–CH_3), -5.9 (Si–CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{24}H_{43}ClN_3O_3Si_2$) calculated: 512.2531; found: 512.2537.

((1*R*,2*R*,3*S*,4*R*)-2,3-Bis((*tert*-butyldimethylsilyl)oxy)-4-(4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)cyclopentyl)methanol (S30)



To a solution of **S29** (3.7 g, 7.2 mmol) in DMF (24 mL) was added *N*-iodosuccinimide (1.8 g, 8 mmol, 1.10 eq), and the reaction was stirred at 50 °C for 4 hours. The mixture was diluted with ethyl acetate and washed consecutively with saturated aqueous $Na_2S_2O_3$, $NaHCO_3$ and brine. The organic layer was dried over sodium sulfate and evaporated. The product was purified by FCC (0–30% of EtOAc in cyclohexane) to afford **S30** (3.7 g, 5.8 mmol, 80%). **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.59 (s, H-2), 7.49 (s, H-8), 4.80 (ddd, $J_{1',6'a}$ = 10.6, $J_{1',2'}$ = 9.0, $J_{1',6'b}$ = 8.0 Hz, H-1'), 4.69 (dd, $J_{2',1'}$ = 9.1, $J_{2',3'}$ = 3.9 Hz, H-2'), 4.03 (dd, $J_{3',2'}$ = 3.7, $J_{3',4'}$ = 1.0 Hz, H-3'), 3.81 (m, 2H, H-5'), 2.54 (m, H-6'a), 2.30 - 2.20 (m, 2H, H-6'b, H-4'), 0.93 (s, 9H, CH_3–tBu), 0.71 (s, 9H, CH_3–tBu), 0.10 (s, 3H, Si–CH_3), 0.09 (s, 3H, Si–CH_3), -0.18 (s, 3H, Si–CH_3), -0.70 (s, 3H, Si–CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 153.3 (C-6), 149.9 (C-4), 149.8 (C-2), 136.9 (C-8), 118.6 (C-5), 77.0 (C-2'), 76.4 (C-3'), 64.9 (C-5'), 64.6 (C-1'), 49.7 (C-7), 46.2 (C-4'), 27.2 (C-6'), 26.0 (CH_3–tBu), 25.8 (CH_3–tBu), 18.2 (C–tBu), 17.9 (C–tBu), -4.3 (Si–CH_3), -4.4 (Si–CH_3), -4.4 (Si–CH_3), -5.8 (Si–CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{24}H_{42}ClIN_3O_3Si_2$) calculated: 638.1498; found: 638.1453.

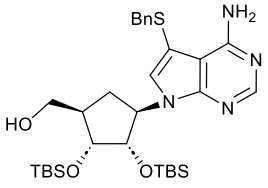
((1*R*,2*R*,3*S*,4*R*)-4-(4-Amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,3-bis((*tert*-butyldimethylsilyl)oxy)cyclopentyl)methanol (S31)



A mixture of **S30** (4.38 g, 6.86 mmol) and NaN_3 (535 mg, 8.23 mmol, 1.20 eq) in DMF (34 mL) was stirred at 80 °C for 90 minutes. Triphenylphosphine (2.34 g, 8.92 mmol, 1.30 eq) was added, and stirring was continued at the same temperature overnight. Water (7.3 mL) and acetic acid (2.4 mL, 41.1 mmol, 6.0 eq) were added, and stirring was continued at 80 °C for 10 hours. The volatiles were removed under reduced pressure, and the residue was subjected to FCC (10–30% of a 4:1 EtOAc/EtOH mixture in cyclohexane), affording product **S31** (3.98 g, 6.43 mmol, 94%) as a colourless solid. **^{1}H NMR** (401 MHz, $CDCl_3$) δ 8.21 (s, 1H, H-2),

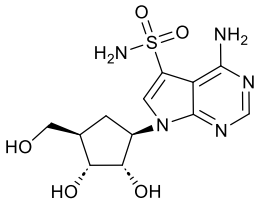
7.07 (s, 1H, H-8), 5.84 (s, 2H, NH_2), 5.22 (s, 1H, 5'-OH), 4.82 (dd, $J_{H\text{-}2',H\text{-}1'}$ = 9.3 Hz, $J_{H\text{-}2',H\text{-}3'}$ = 3.9 Hz, 1H, H-2'), 4.58 (ddd, $J_{H\text{-}1',H\text{-}6'a}$ = 11.2 Hz, $J_{H\text{-}1',H\text{-}2'}$ = 9.3 Hz, $J_{H\text{-}1',H\text{-}6'b}$ = 7.9 Hz, 1H, H-1'), 4.02 (d, $J_{H\text{-}3',H\text{-}2'}$ = 3.8 Hz, 1H, H-3'), 3.81 - 3.75 (m, 2H, H-5'), 2.55 (ddd, J_{gem} = 14.5 Hz, $J_{H\text{-}6'a,H\text{-}1'}$ = 11.0,11.0 Hz, 1H, H-6'a), 2.32 (ddd, J_{gem} = 14.5 Hz, $J_{H\text{-}6'b,H\text{-}1'}$ = 8.0 Hz, $J_{H\text{-}6'b,H\text{-}4'}$ = 3.7 Hz, 1H, H-6'b), 2.23 - 2.13 (m, 1H, H-4'), 0.92 (s, 9H, tBu-CH_3), 0.73 (s, 9H, tBu-CH_3), 0.13 - 0.05 (m, 6H, Si-CH_3), -0.18 (s, 3H, Si-CH_3), -0.68 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.1 (C-6), 150.4 (C-2), 148.7 (C-4), 132.2 (C-8), 105.7 (C-5), 77.2 (C-3'), 77.0 (C-2'), 65.4 (C-1'), 65.1 (C-5'), 47.2 (C-7), 46.6 (C-4'), 27.6 (C-6'), 26.0 (tBu-CH_3), 25.9 (tBu-CH_3), 18.2 (tBu-C), 18.0 (tBu-C), -4.3 (Si-CH_3), -4.4 (Si-CH_3), -4.5 (Si-CH_3), -6.0 (Si-CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{24}H_{44}IN_4O_3Si_2$) calculated: 619.1991; found: 619.1985.

((1*R*,2*R*,3*S*,4*R*)-4-(4-Amino-5-(benzylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,3-bis((*tert*-butyldimethylsilyl)oxy)cyclopentyl)methanol (S32)



To a solution of **S31** (495 mg, 0.80 mmol), $Pd_2(dba)_3$ (19 mg, 0.021 mmol, 0.026 eq) and XantPhos (26 mg, 0.045 mmol, 0.057 eq) in 1,4-dioxane (13.3 mL) were added benzyl mercaptan (175 µL, 1.49 mmol, 1.9 eq) and DIPEA (350 µL, 2.01 mmol, 2.5 eq), and the mixture was stirred under argon atmosphere at 80 °C for 2 hours. The reaction mixture was adsorbed onto silica, and RP-FCC (30–100% of ACN in water) afforded product **S32** (458 mg, 0.75 mmol, 93%). **^{1}H NMR** (401 MHz, $CDCl_3$) δ 8.22 (s, 1H, H-2), 7.31 - 7.24 (m, 3H, Bn), 7.15 - 7.10 (m, 2H, Bn), 6.96 (s, 1H, H-8), 5.95 (s, 2H, NH_2), 5.32 (s, 1H, 5'-OH), 4.88 (dd, $J_{H\text{-}2',H\text{-}1'}$ = 9.1 Hz, $J_{H\text{-}2',H\text{-}3'}$ = 3.9 Hz, 1H, H-2'), 4.56 (ddd, $J_{H\text{-}1',H\text{-}6'}$ = 11.2 Hz, $J_{H\text{-}1',H\text{-}2'}$ = 9.2 Hz, $J_{H\text{-}1',H\text{-}6'}$ = 7.7 Hz, 1H, H-1'), 4.08 - 4.03 (m, 1H, H-3'), 3.94 - 3.82 (m, 2H, SBn-CH_2), 3.80 (s, 2H, H-5'), 2.63 - 2.50 (m, 1H, H-6'a), 2.31 - 2.15 (m, 2H, H-6'b, H-4'), 0.95 (s, 9H, tBu-CH_3), 0.75 (s, 9H, tBu-CH_3), 0.11 (m, 6H, Si-CH_3), -0.16 (s, 3H, Si-CH_3), -0.63 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.6 (C-6), 150.5 (C-2), 148.8 (C-4), 137.7 (SBn), 133.8 (C-8), 129.0 (SBn), 128.8 (SBn), 127.6 (SBn), 105.7 (C-5), 101.5 (C-7), 77.3 (C-3'), 77.0 (C-2'), 65.1 (C-5'), 65.1 (C-1'), 46.5 (C-4'), 44.2 (SBn-CH_2), 28.1 (C-6'), 26.0 (tBu-CH_3), 18.2 (tBu-C), 17.9 (tBu-C), -4.3 (Si-CH_3), -4.4 (Si-CH_3), -4.5 (Si-CH_3), -5.7 (Si-CH_3). **HRMS** (ESI) m/z: $[M+H]^+$ ($C_{31}H_{51}N_4O_3SSi_2$) calculated 615.3215, found 615.3211.

4-Amino-7-((1*R*,2*S*,3*R*,4*R*)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-sulfonamide (19)



To a solution of **S32** (150 mg, 0.24 mmol) in acetonitrile (1.0 mL) were added acetic acid (80 µL, 1.40 mmol, 5.7 eq), water (40 µL, 2.2 mmol, 9.1 eq), and finally NCS (98 mg, 0.73 mmol, 3.0 eq). The resulting solution was stirred at RT for 90 minutes. The starting material was fully converted to sulfonyl chloride, which was partially deprotected. The solvents were evaporated, and the crude material was co-evaporated with a toluene/ACN mixture. The oily residue was suspended in anhydrous DCM (1.5 mL) with 2M NH_3 in *i*-PrOH (976 µL, 1.95 mmol, 8.0 eq) and stirred at RT overnight. The volatiles were removed under reduced pressure, and the residue was co-evaporated several times with ethanol. The residue was dissolved in a 9:1 TFA/water mixture (2 mL), and the solution was stirred for 4 hours at an ambient

temperature. The solvents were removed under vacuum, and the residue was co-evaporated with a water/methanol mixture to hydrolyse the formed trifluoroacetates. HILIC FCC (silica, 5–40% of water in ACN) afforded the product. TFA was identified in the NMR spectra. The compound was dissolved in methanol, treated with aqueous NH_4OH, and concentrated. Repeated HILIC FCC (5–40% of water in ACN) afforded pure product **19** (31 mg, 0.090 mmol, 37%). **^{1}H NMR** (401 MHz, DMSO-d_6) δ 8.15 (s, 1H, H-2), 7.86 (s, 1H, H-8), 7.49 (s, 2H, SO_2-NH_2), 7.12 (s, 2H, NH_2), 4.99 - 4.87 (m, 2H, H-1', 2'-OH), 4.78 - 4.69 (m, 2H, 3'-OH, 5'-OH), 4.25 - 4.15 (m, 1H, H-2'), 3.84 - 3.78 (m, 1H, H-3'), 3.53 - 3.43 (m, 2H, H-5'), 2.21 (m, 1H, H-6'a), 2.09 - 1.96 (m, 1H, H-4'), 1.54 (ddd, J_{gem} = 12.7 Hz, $J_{H\text{-}6'b,H\text{-}1'}$ = 10.5 Hz, $J_{H\text{-}6'b,H\text{-}4'}$ = 7.9 Hz, 1H, H-6'b). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 157.0 (C-6), 153.0 (C-2), 151.0 (C-4), 126.2 (C-8), 117.7 (C-7), 98.3 (C-5), 75.3 (C-2'), 72.0 (C-3'), 63.0 (C-5'), 59.3 (C-1'), 45.3 (C-4'), 29.9 (C-6'). **HRMS** (ESI) m/z: $[M+Na]^+$ ($C_{12}H_{17}N_5O_5SNa$) calculated 366.0843, found 366.0843.

3. Biochemical assays

3.1. Haspin IC_{50} evaluation assay

The Haspin IC_{50} for selected compounds was evaluated by KinaseProfiler (Eurofins Cerep, Celle l'Evescault, France). The enzyme inhibition was measured at K_m ATP (70µM) in duplicate at 9 concentrations ranging from 10µM to 0.001µM. Experimental procedure is described in detail at https://emea.eurofinsdiscovery.com/catalog/haspin-human-other-protein-kinase-enzymatic-radiometric-km-atp-kinaseprofiler-leadhunter-assay-fr/14-744KP.

3.2. Kinase selectivity profiling

3.2.1. Activity-based assay

The activity-based kinase selectivity profiling was performed at Eurofins Cerep (Celle l'Evescault, France). Compound **9a** and Sangivamycin were evaluated against a panel of 62 kinases. This comprised Diversity Kinase [Km ATP] KinaseProfiler LeadHunter Panel (58 kinases), Haspin and 3 selected known Sangivamycin off-targets (DYRK1A, DYRK2 and PKCdelta) [13]. The enzyme inhibition was measured K_m ATP in duplicate at 1µM. Experimental conditions used in these radiometric protein kinase assays are described in detail at https://emea.eurofinsdiscovery.com/solution/kinase-profiler.

3.2.2. Binding assay

Compound **9a** and Sangivamycin were evaluated against YSK4 human kinase at Eurofins DiscoverX (San Diego, CA, USA). The active site-directed competition binding assay scanELECT was performed using KINOMEscan™ technology in duplicate at 1µM. Detailed information about the assay can be found at https://emea.eurofinsdiscovery.com/solution/kinomescan-technology.

4. Dose-response curves for Haspin IC50 evaluation

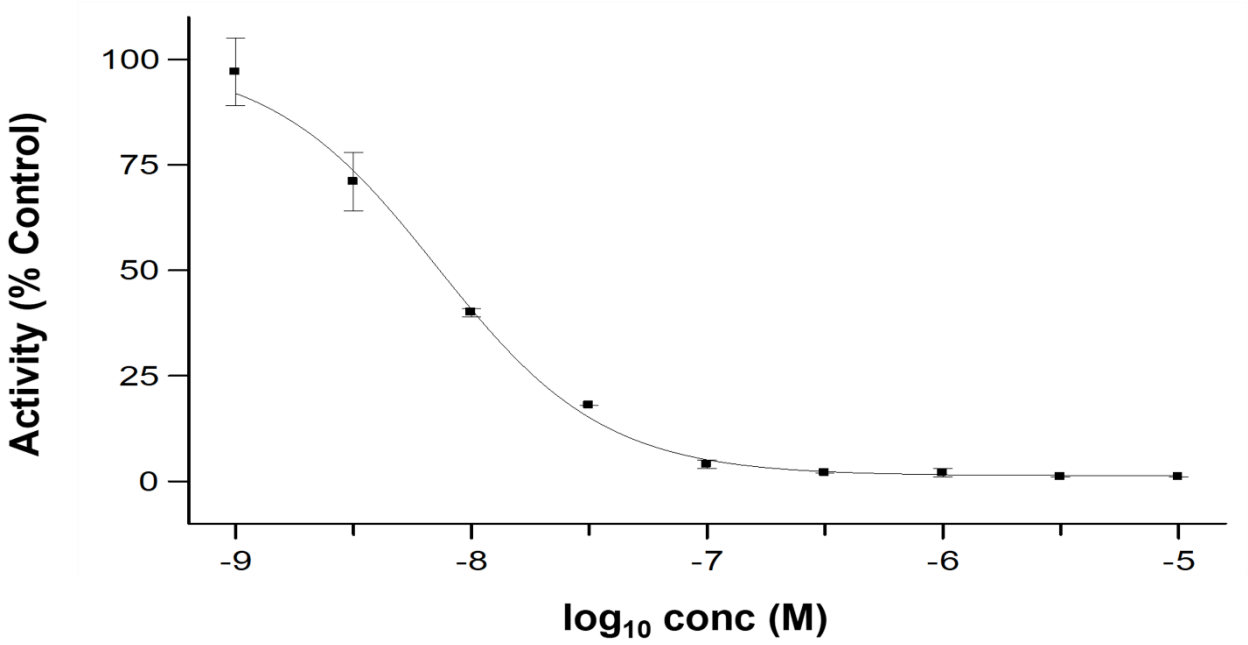


Figure S2. Concentration–response curve for **Sangivamycin** against Haspin. Points show mean ± SD.

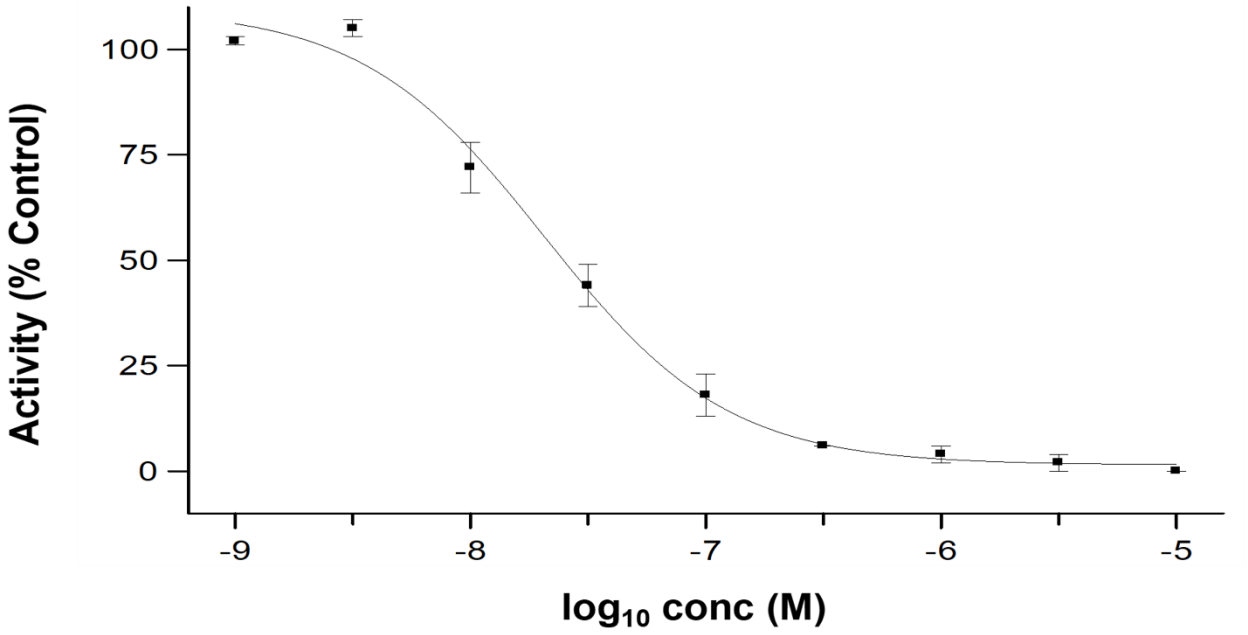


Figure S3. Concentration–response curve for compound **9a** against Haspin. Points show mean ± SD.

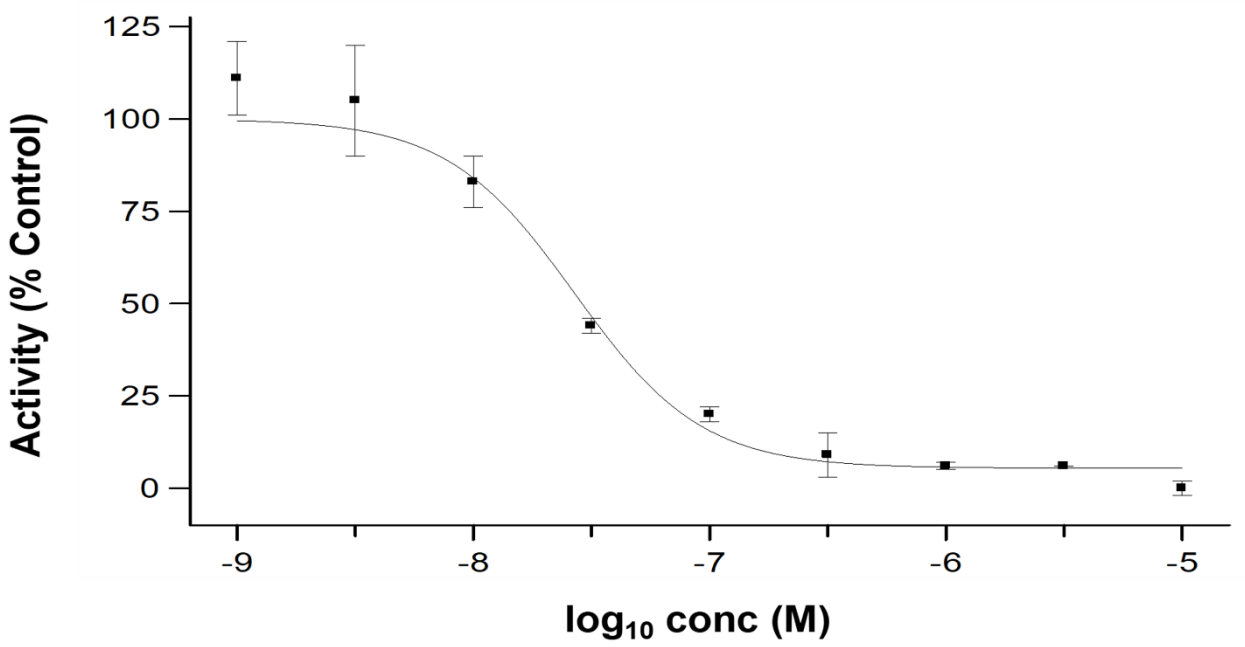


Figure S4. Concentration–response curve for compound **9b** against Haspin. Points show mean ± SD.

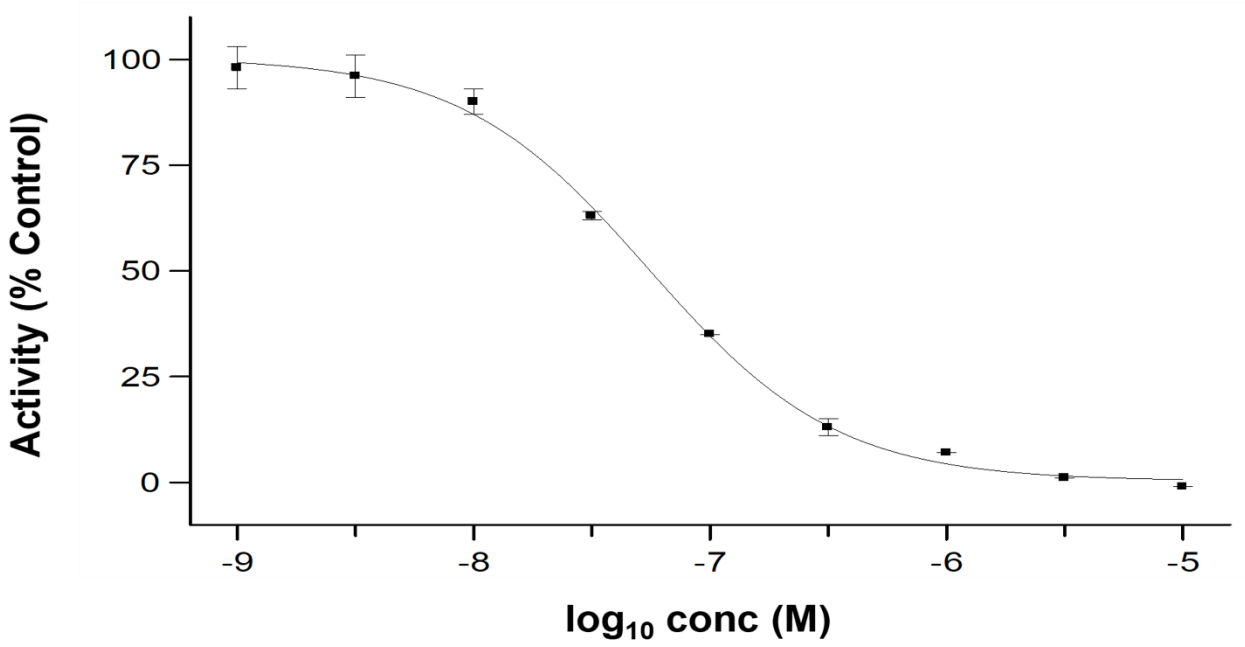


Figure S5. Concentration–response curve for compound **9c** against Haspin. Points show mean ± SD.

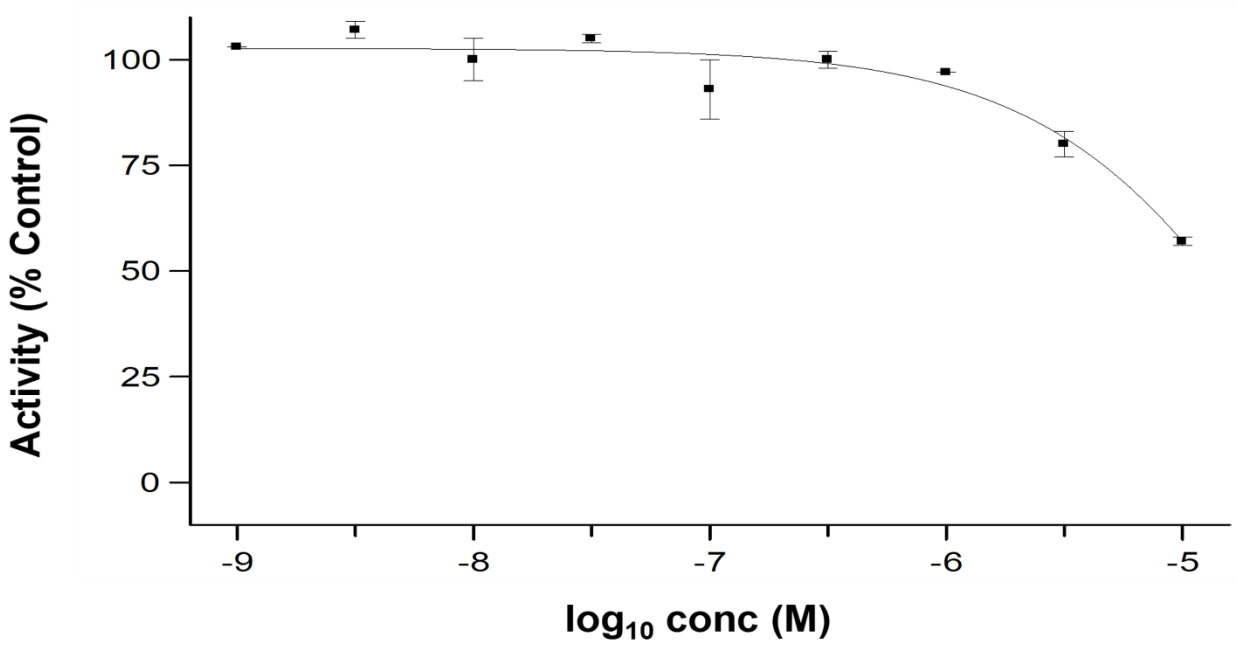


Figure S6. Concentration–response curve for compound **14** against Haspin. Points show mean ± SD.

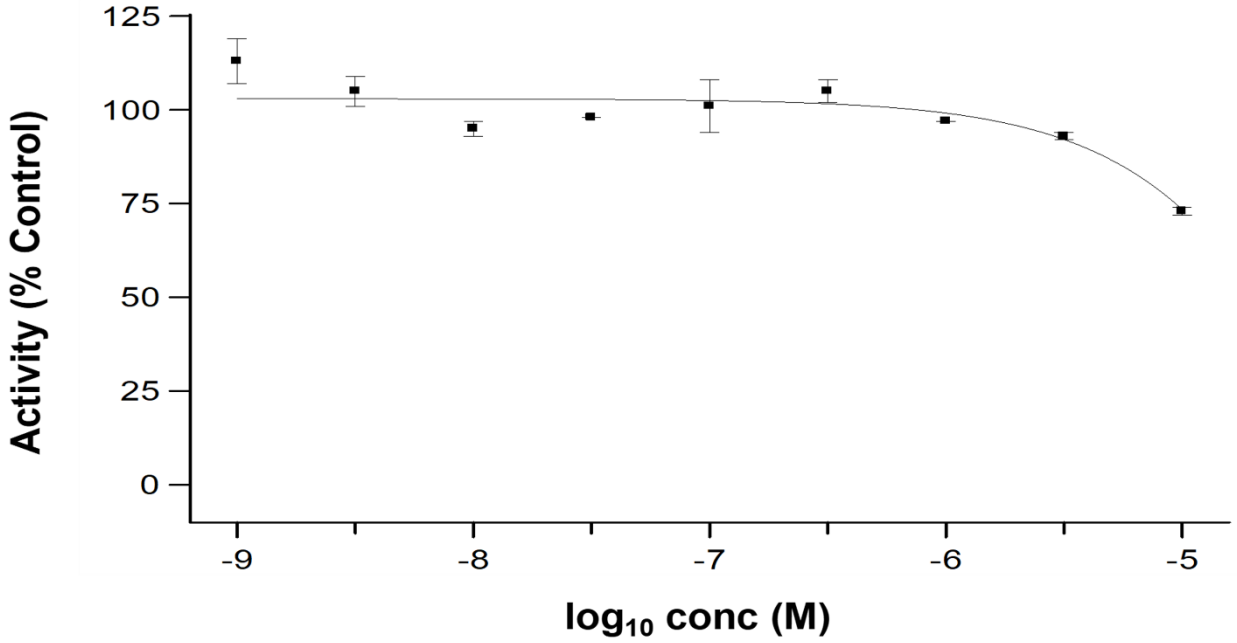


Figure S7. Concentration–response curve for compound **15** against Haspin. Points show mean ± SD.

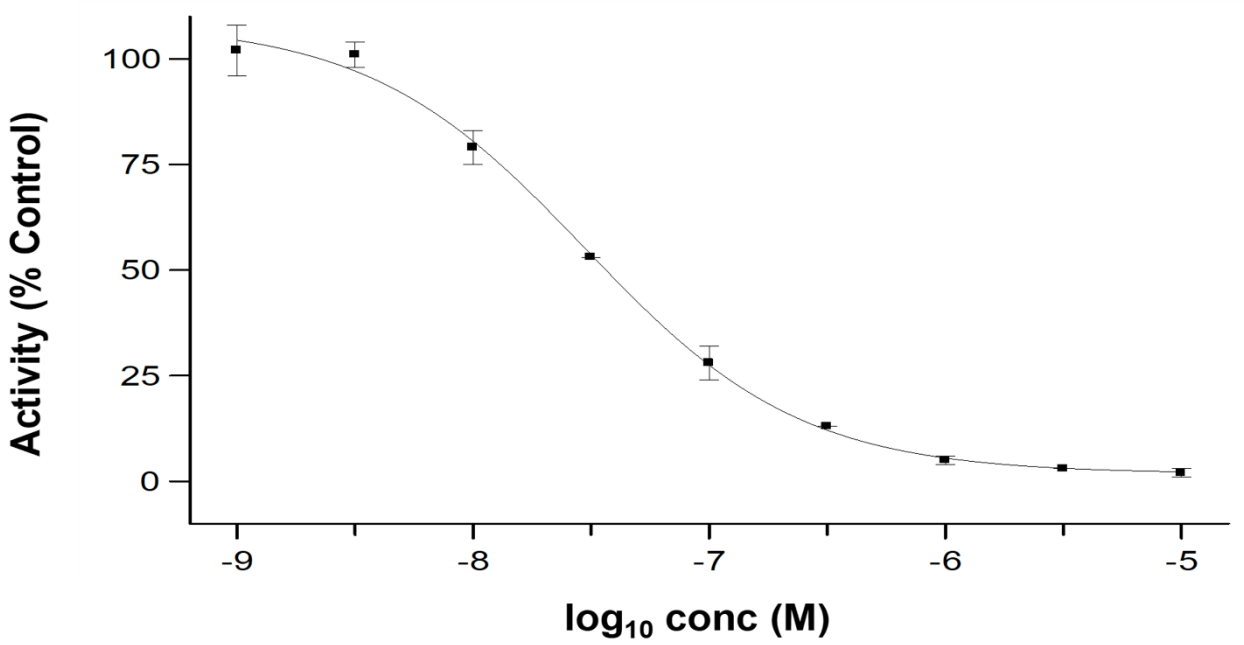


Figure S8. Concentration–response curve for compound **16** against Haspin. Points show mean ± SD.

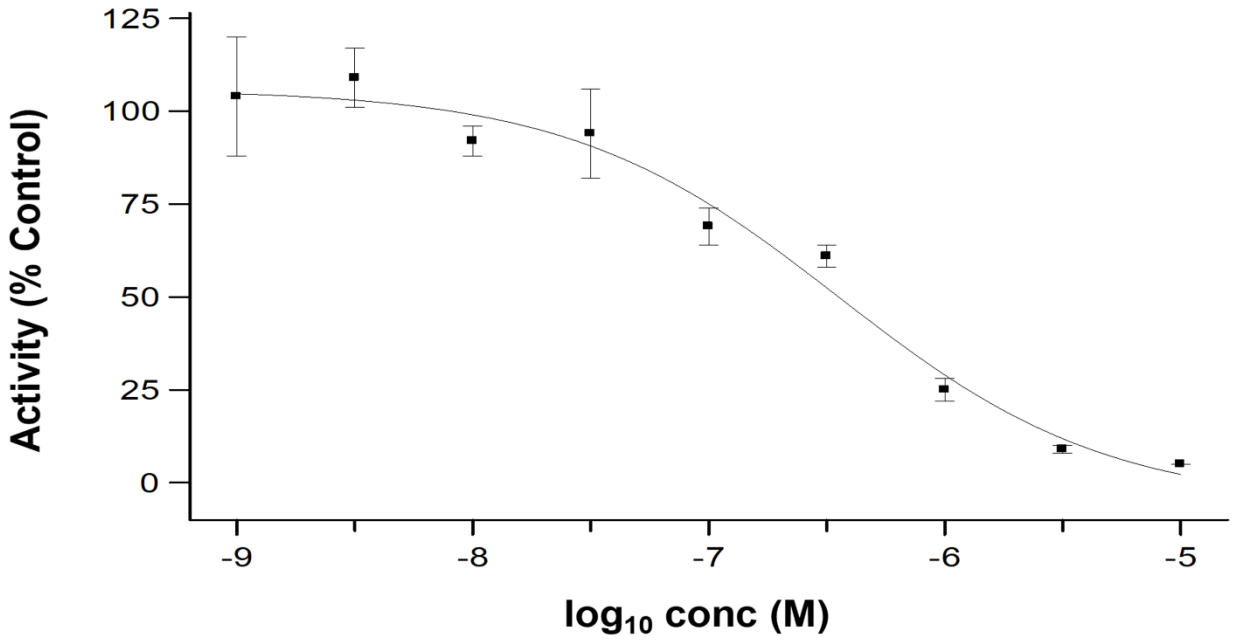


Figure S9. Concentration–response curve for compound **17** against Haspin. Points show mean ± SD.

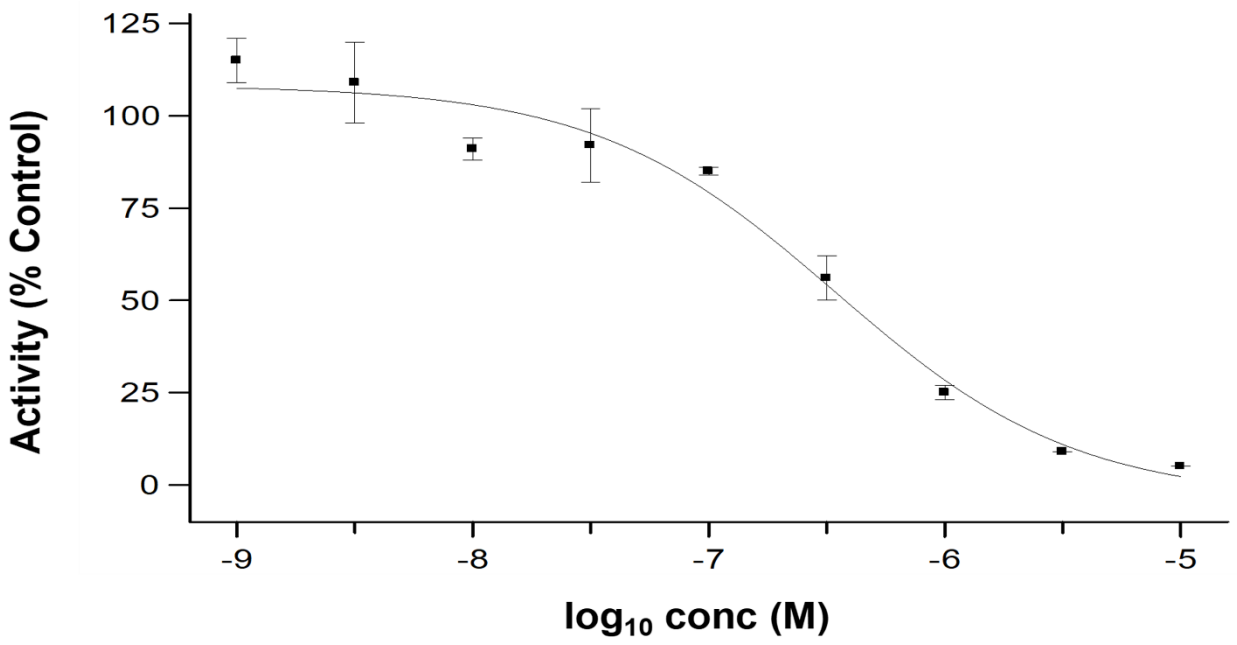


Figure S10. Concentration–response curve for compound **18** against Haspin. Points show mean ± SD.

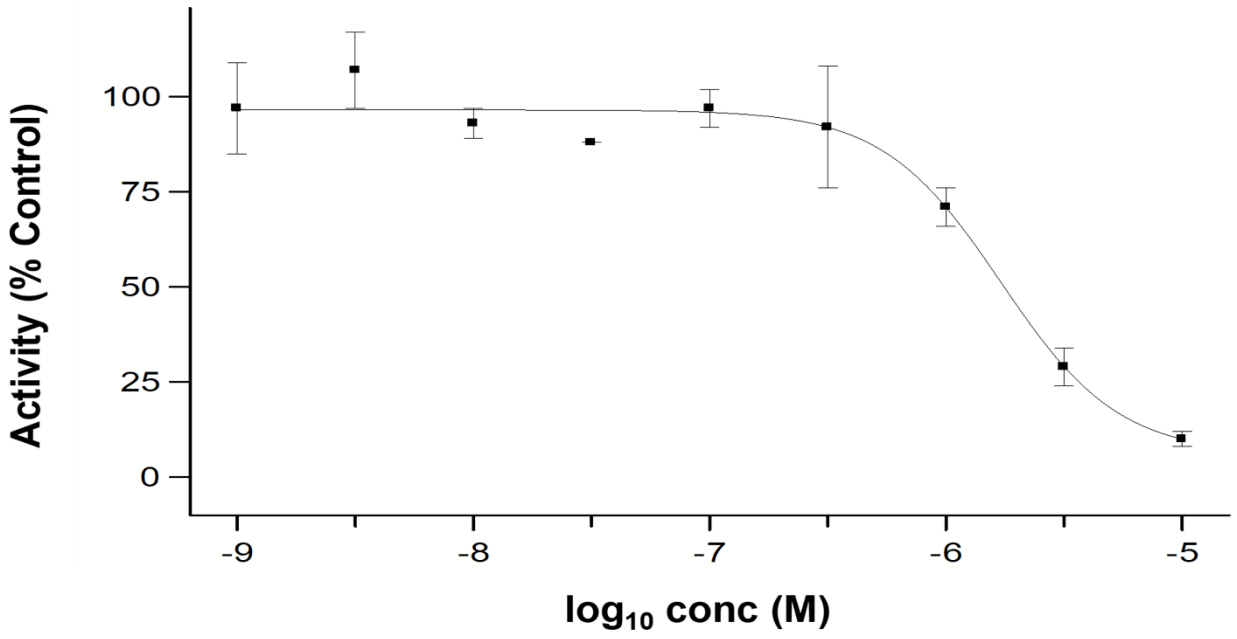


Figure S11. Concentration–response curve for compound **19** against Haspin. Points show mean ± SD.

5. Supporting tables

Table S1. Experimental conditions tested during sulfonamide preparation optimization

Amine	Base	Solvent	Temp.	Time	Yield[a] (%)	Note
Dibenzylamine	TEA	DCM	RT	3 h	41	Sideproduct formation
Dibenzylamine	Pyridine	DCM	RT	6 h	68	Sideproduct formation
Dibenzylamine	none	DCM	RT	12 h	99	
$CHF_2CH_2NH_2$.HCl	K_2CO_3	DCM/water	RT	3 days	74	
$CHF_2CH_2NH_2$.HCl	DBU	DCM	RT	1 h	N.D.[b]	Sideproduct formation
$CHF_2CH_2NH_2$.HCl	K_2CO_3	DMF	RT	1 h	N.D.[b]	Solvolysis
$CHF_2CH_2NH_2$.HCl	Cs_2CO_3	DMF	RT	1 h	54	Solvolysis
$CHF_2CH_2NH_2$.HCl	DMAP	DCM	RT	30 min	87	
Aniline	none	DCM	RT	16 h	75	
Aniline	DMAP	DCM	RT	15 min	88	
Diphenylamine	K_2CO_3	1,4-Dioxane	60 °C	ON	N.O.[c]	Slow hydrolysis
Diphenylamine	Cs_2CO_3	NMP	RT to 70 °C	ON	N.O.[c]	Hydrolysis
Diphenylamine	Cs_2CO_3, DMAP	ACN	RT	ON	N.O.[c]	Slow hydrolysis
Diphenylamine	DMAP	ACN	RT to 60 °C	ON	Traces	Slow hydrolysis
Diphenylamine	NaH	THF	RT	7 h	N.O.[c]	Mixture of sideproducts

[a]Isolated yields. [b]The sulfonamide formed was not isolated and the yield was not determined. [c]The sulfonamide product formation was not observed (UPLC/MS analysis).

Table S2 Results of kinase selectivity profiling (% of residual activity) of **9a** and **sangivamycin** at 1 μM.

Kinase	9a	Sangivamycin
Abl(h)	103	97
ALK(h)	102	94
AMPKα1(h)	16	94
ASK1(h)	102	103
Aurora-A(h)	95	100
CaMKI(h)	106	98
CDK1/cyclinB(h)	89	84
CDK2/cyclinA(h)	88	73
CDK6/cyclinD3(h)	104	101
CDK7/cyclinH/MAT1(h)	104	77
CDK9/cyclin T1(h)	94	84
CHK1(h)	95	96
CK1γ1(h)	86	87
CK2α2(h)	104	102
c-RAF(h)	103	99
DRAK1(h)	101	100
DYRK1A(h)	85	34
DYRK2(h)	78	40
eEF-2K(h)	105	99
EGFR(h)	95	111
EphA5(h)	90	94
EphB4(h)	89	86
Fyn(h)	112	97
GSK3β(h)	91	100
Haspin(h)	2	1
IGF-1R(h)	91	102
IKKα(h)	105	94
IRAK4(h)	53	63
JAK2(h)	112	99
KDR(h)	79	20
LOK(h)	92	81
Lyn(h)	72	103
MAPKAP-K2(h)	100	98
MEK1(h)	107	96
MLK1(h)	86	73
Mnk2(h)	100	94
MSK2(h)	99	94
MST1(h)	97	75
mTOR(h)	104	106
NEK2(h)	89	81
p70S6K(h)	102	90

PAK2(h)	96	95
PDGFRβ(h)	103	97
Pim-1(h)	102	77
PKA(h)	101	96
PKBα(h)	98	93
PKCα(h)	99	97
PKCδ(h)	75	26
PKCθ(h)	102	96
PKG1α(h)	94	94
Plk3(h)	105	103
PRAK(h)	115	120
ROCK-I(h)	99	100
Rse(h)	95	101
Rsk1(h)	19	84
SAPK2a(h)	102	95
SRPK1(h)	106	98
TAK1(h)	91	75
PI3 Kinase (p110b/p85a)(h)	93	101
PI3 Kinase (p120g)(h)	103	92
PI3 Kinase (p110d/p85a)(h)	95	100
PI3 Kinase (p110a/p85a)(h)	99	102
YSK4(h)*	91	3

The values lower than 50% were highlighted (colour scale from red (lowest) to yellow (highest)).

* Competition binding assay (1 μM, duplicate). Reported % = kinase bound to an immobilized ligand with the compound present relative to DMSO.

6. ^{1}H and ^{13}C NMR of final compounds

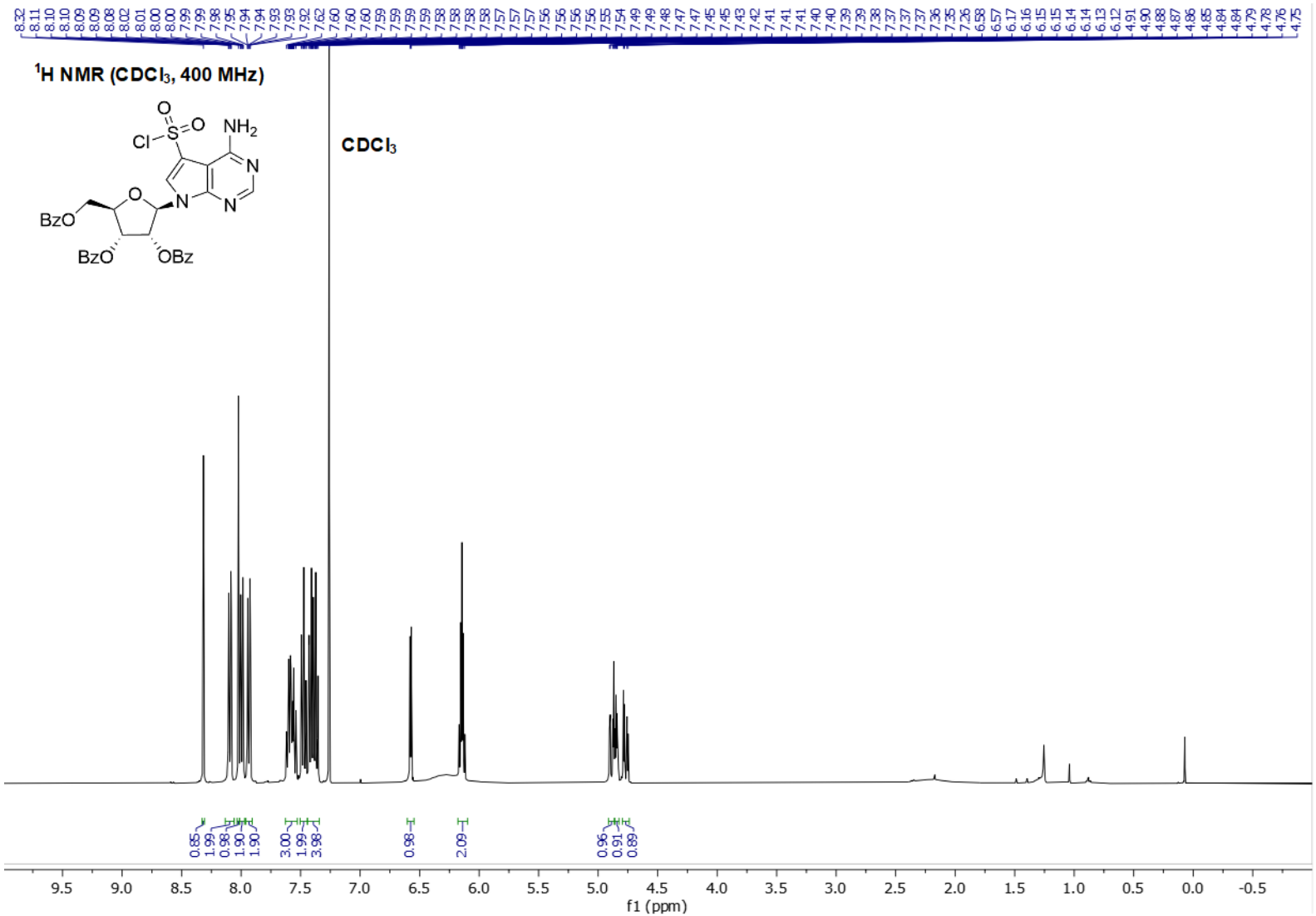


Figure S12. ^{1}H NMR spectra of compound **7** measured in DMSO-d_6.

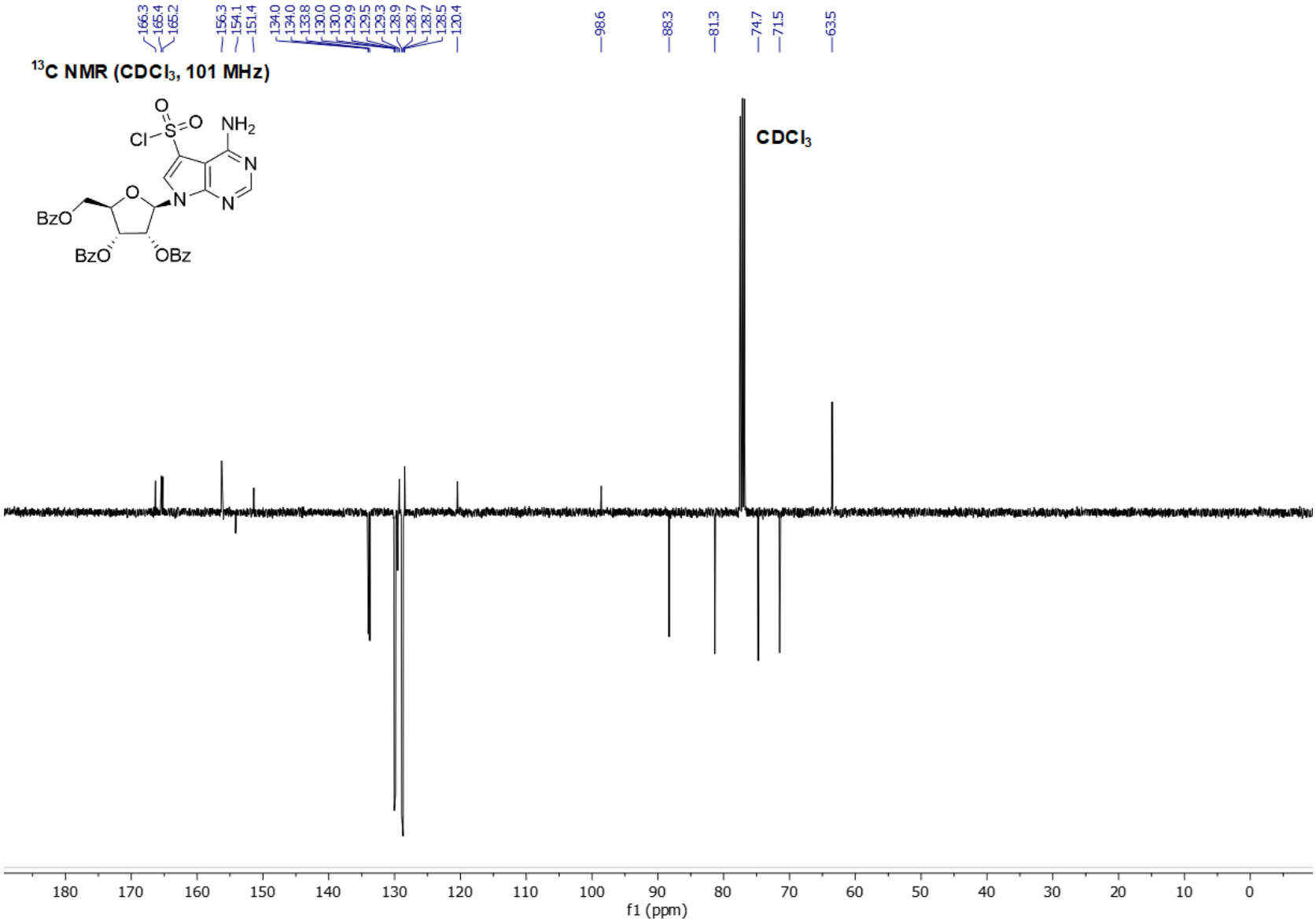


Figure S13. ^{13}C APT NMR spectra of compound **7** measured in DMSO-d_6.

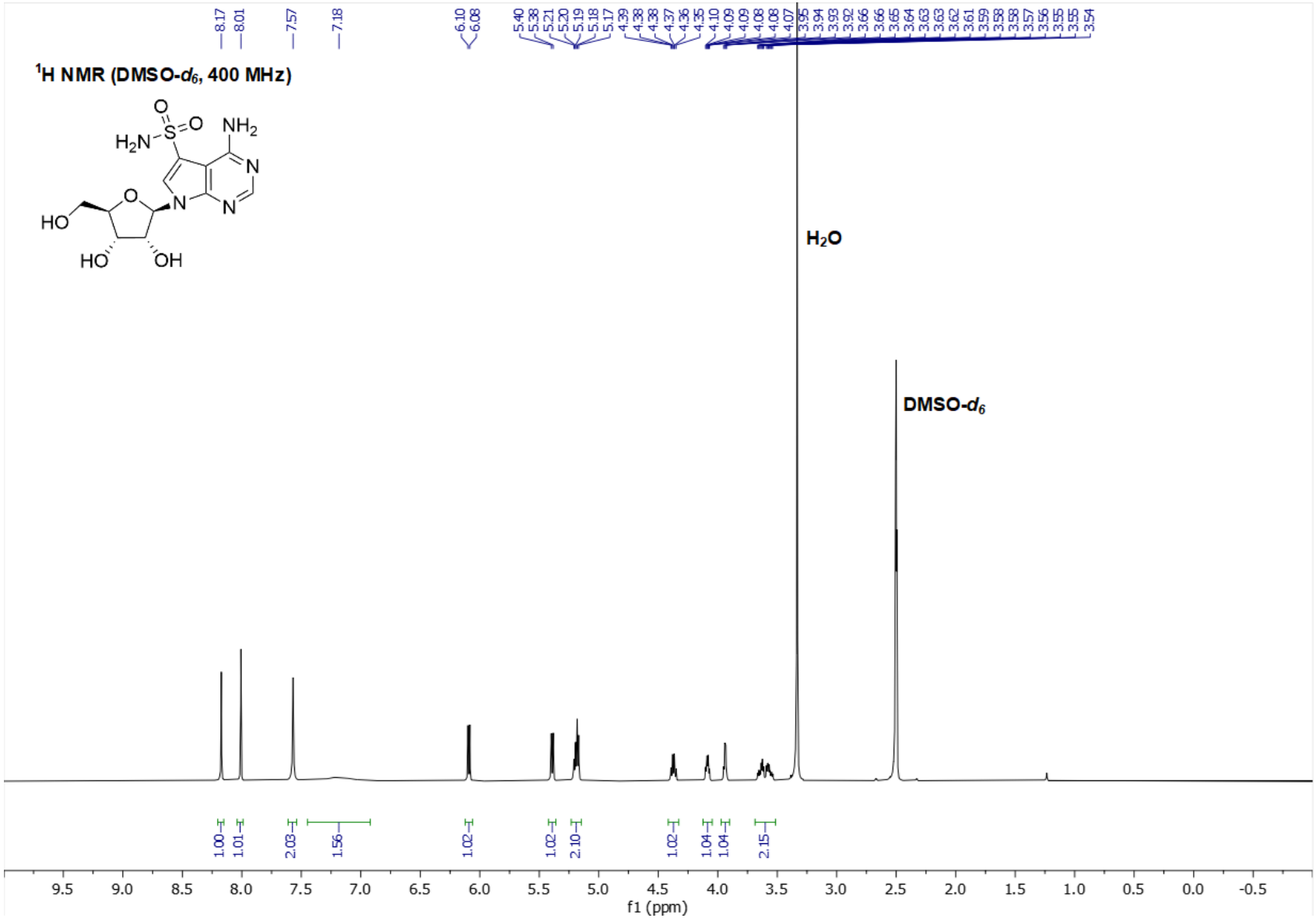


Figure S14. ^{1}H NMR spectra of compound **9a** measured in DMSO-d_6.

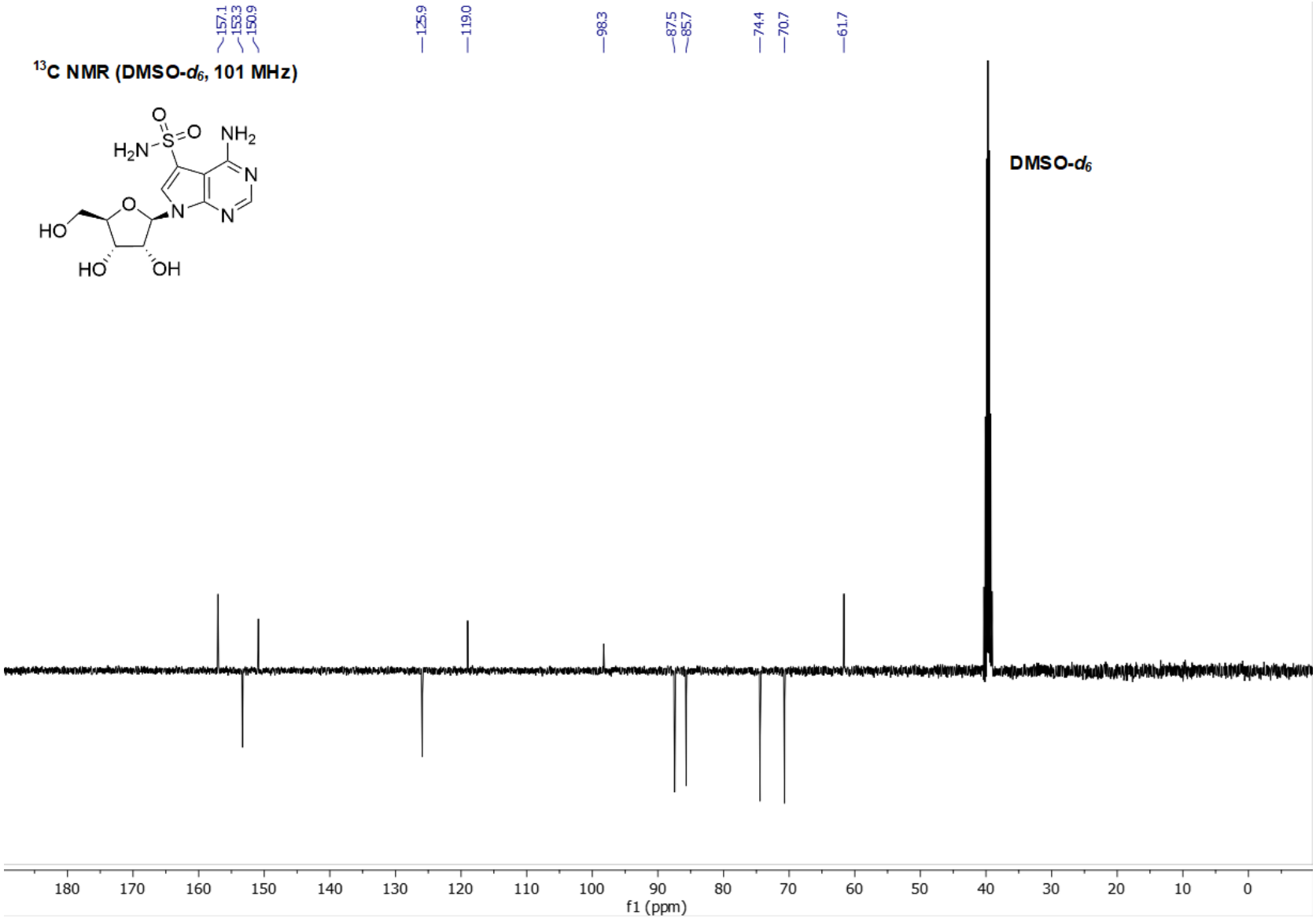


Figure S15. ^{13}C APT NMR spectra of compound **9a** measured in DMSO-d_6.

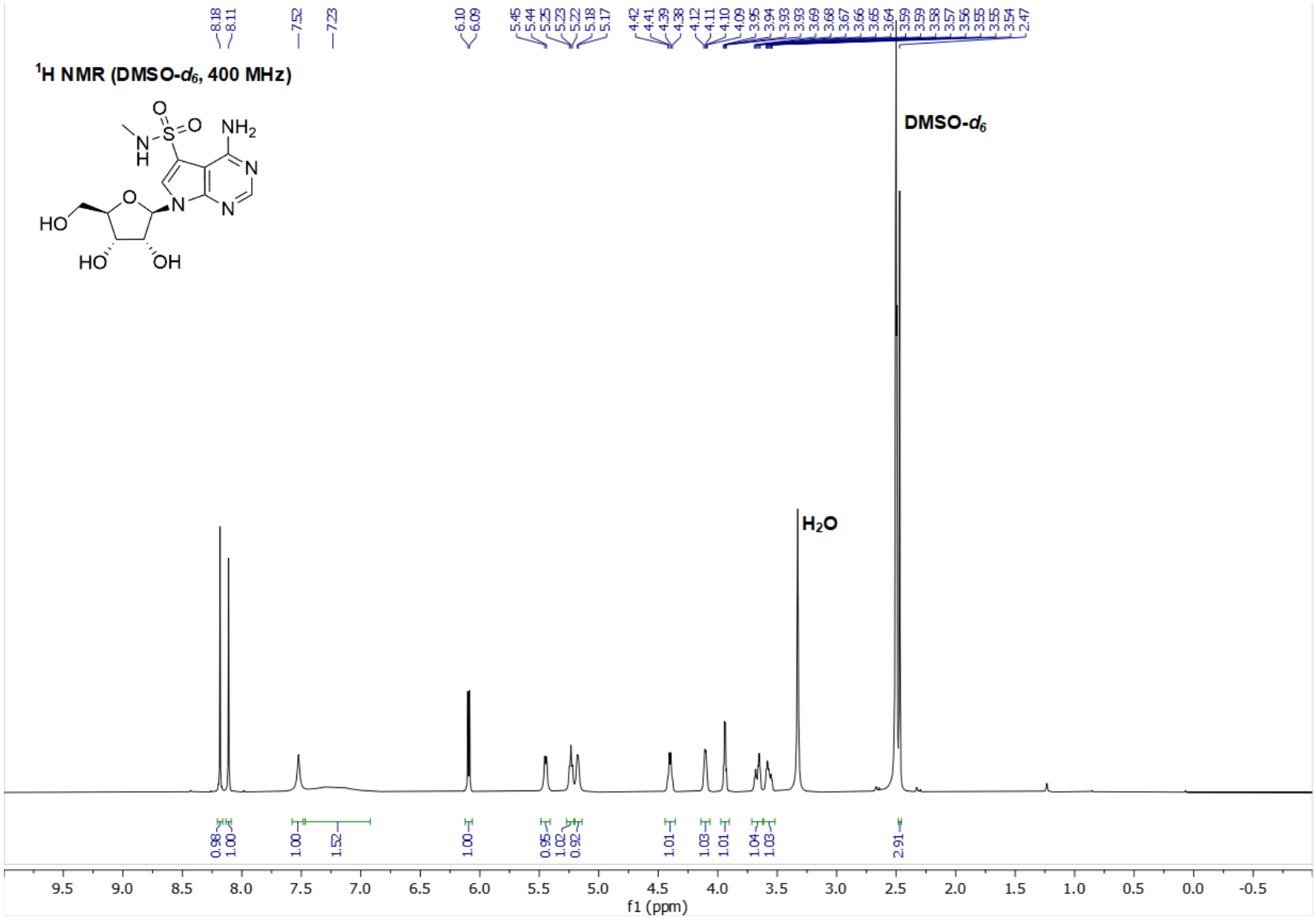


Figure S16. ^{1}H NMR spectra of compound **9b** measured in DMSO-d_6.

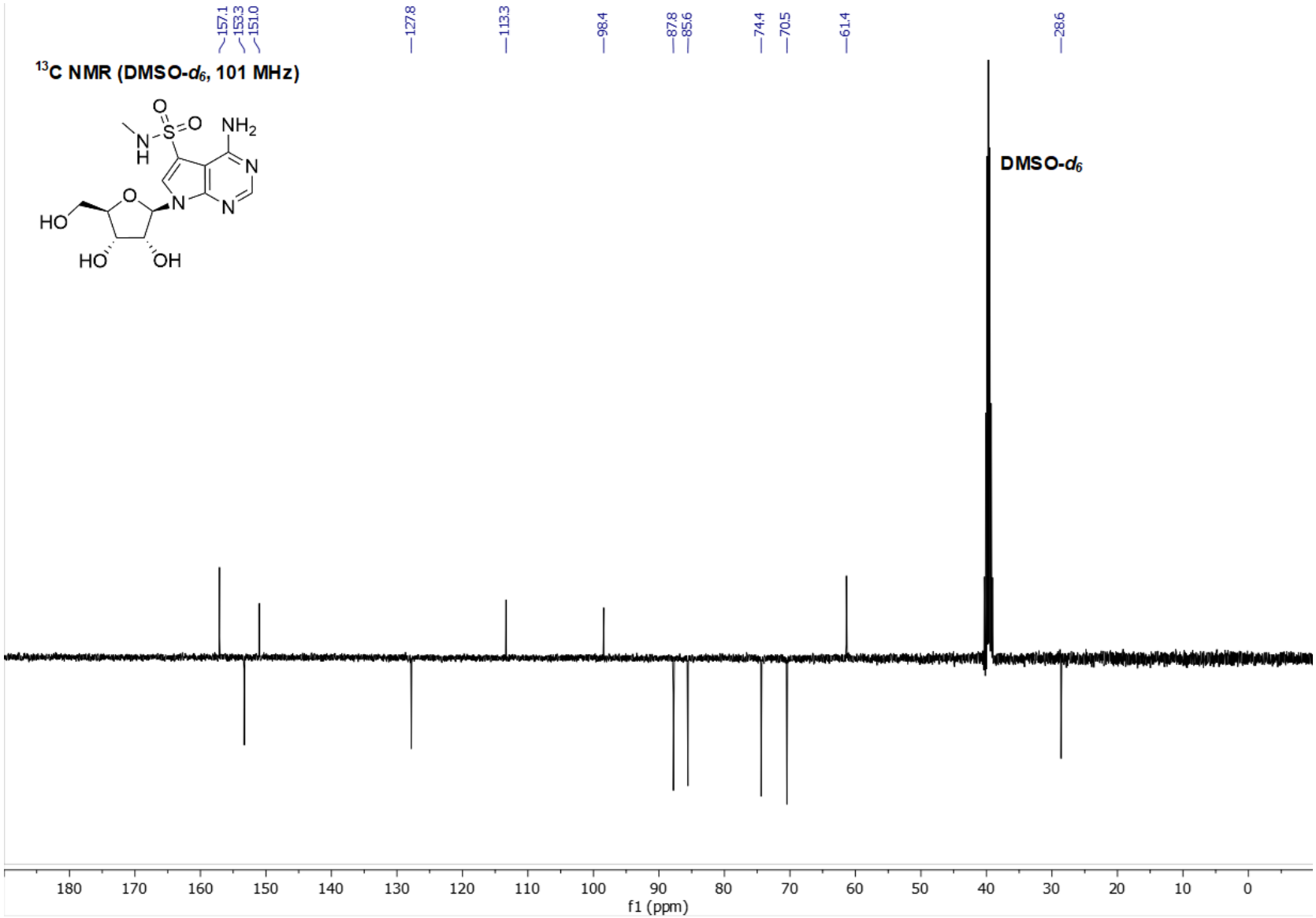


Figure S17. ^{13}C APT NMR spectra of compound **9b** measured in DMSO-d_6.

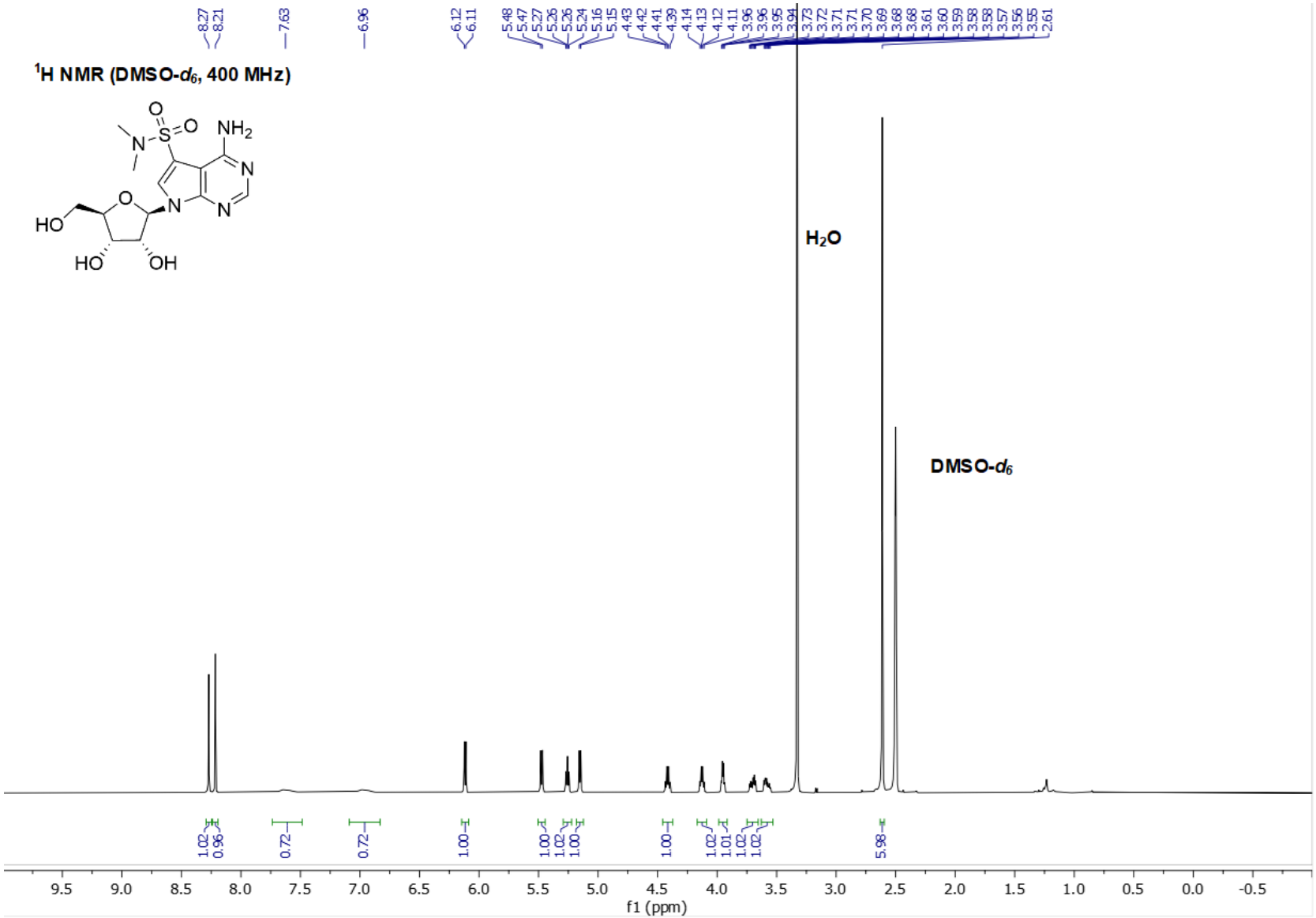


Figure S18. ^{1}H NMR spectra of compound **9c** measured in DMSO-d_6.

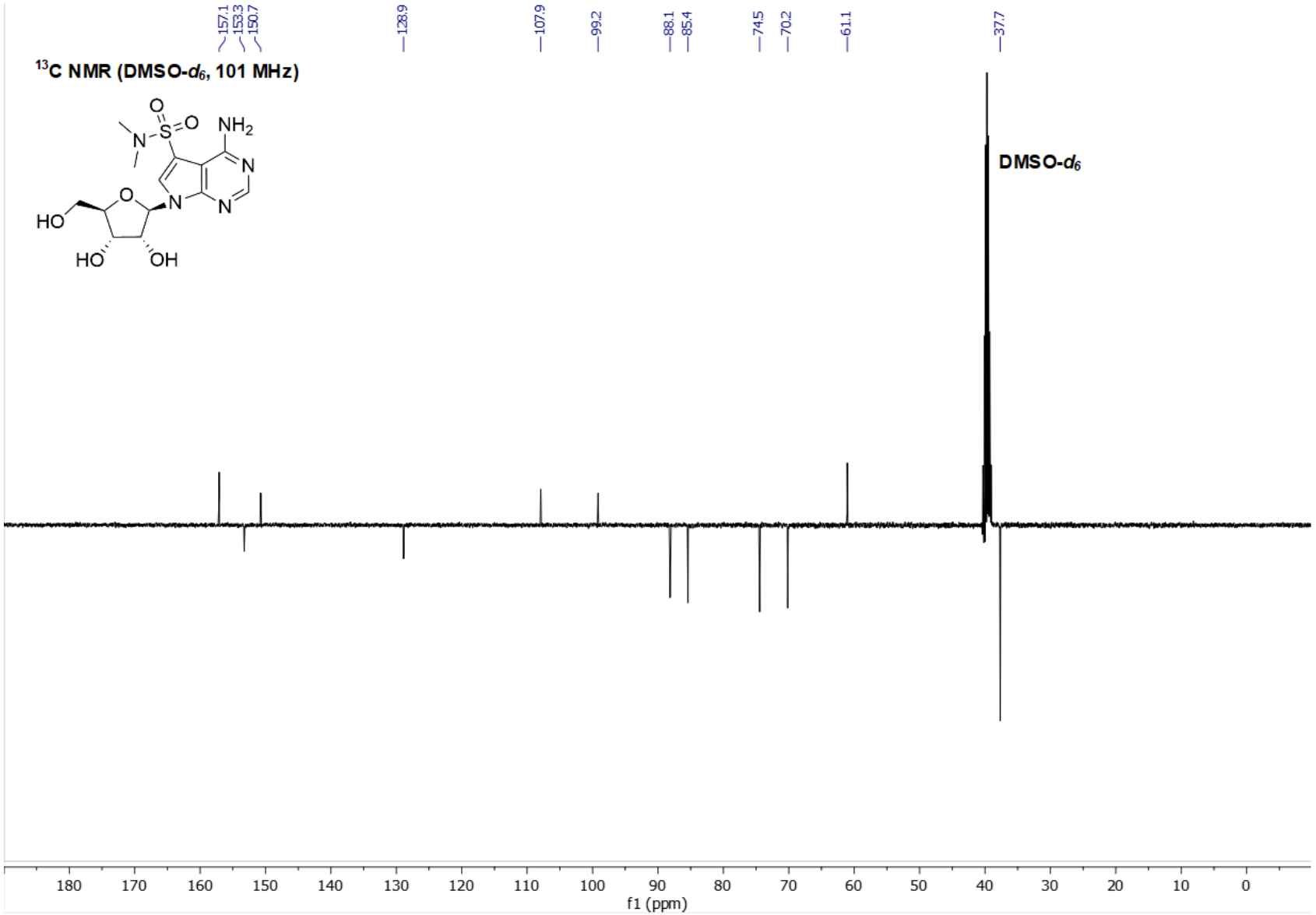


Figure S19. ^{13}C APT NMR spectra of compound **9c** measured in DMSO-d_6.

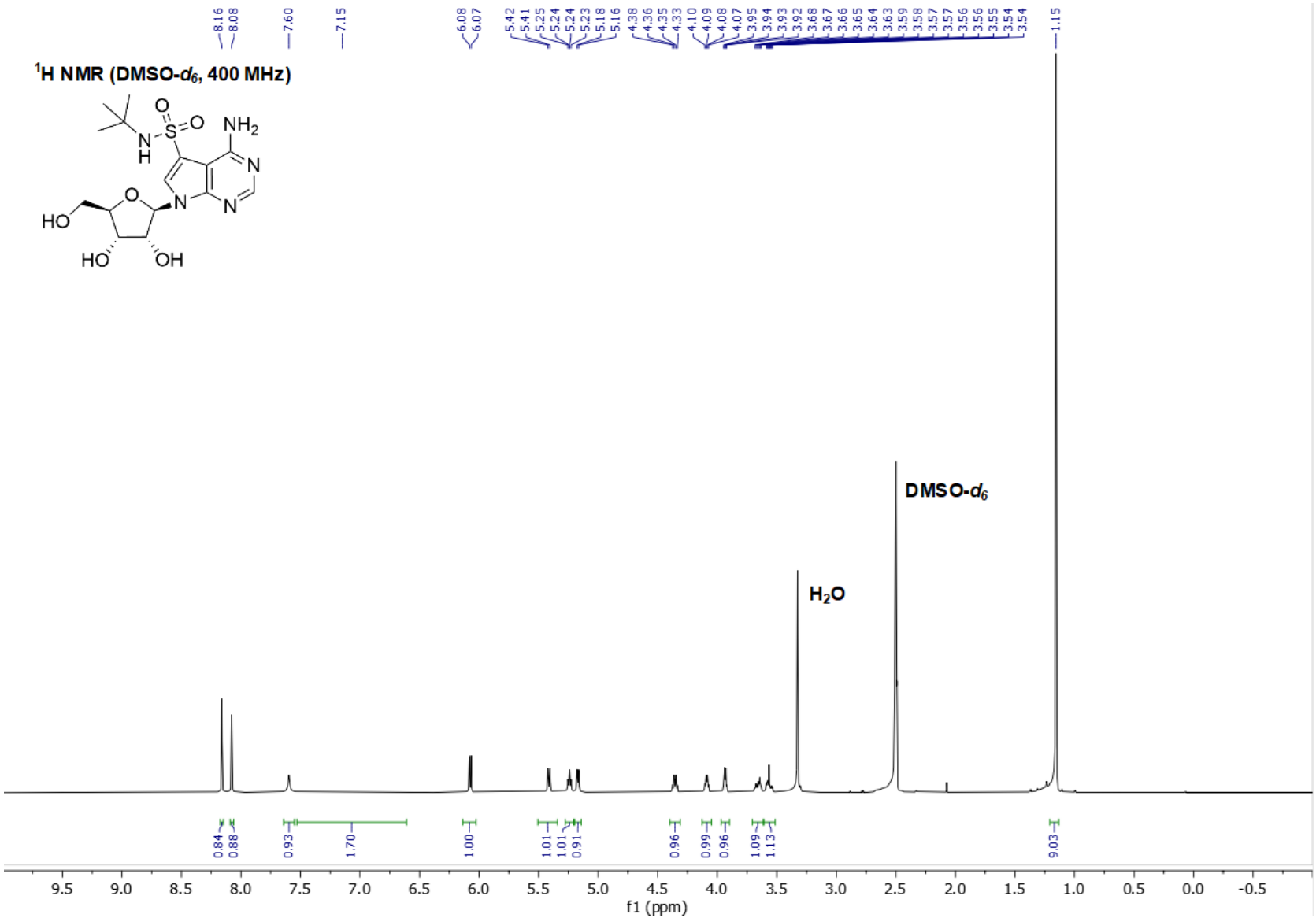


Figure S20. ^{1}H NMR spectra of compound **9d** measured in DMSO-d_6.

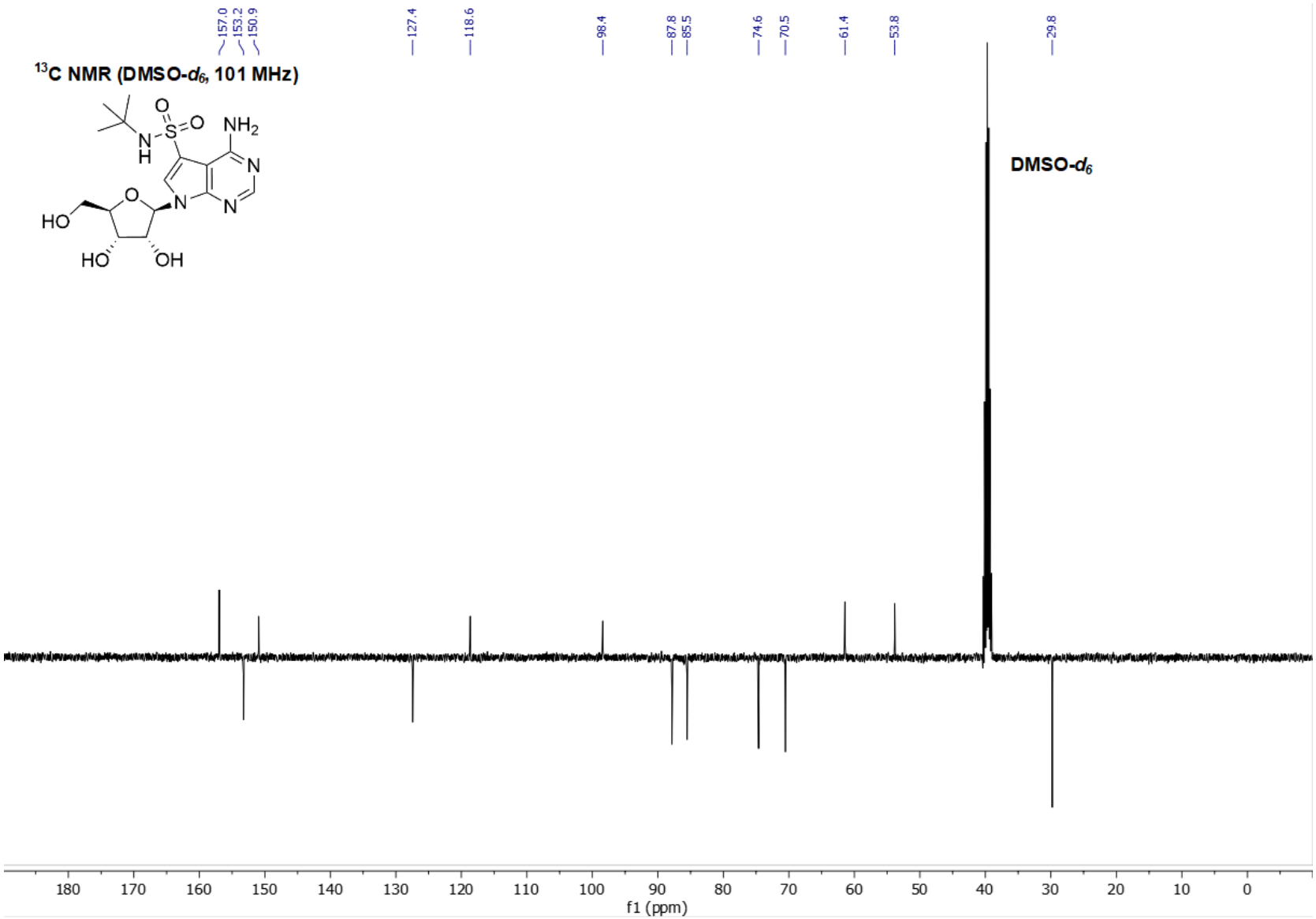


Figure S21. ^{13}C APT NMR spectra of compound **9d** measured in DMSO-d_6.

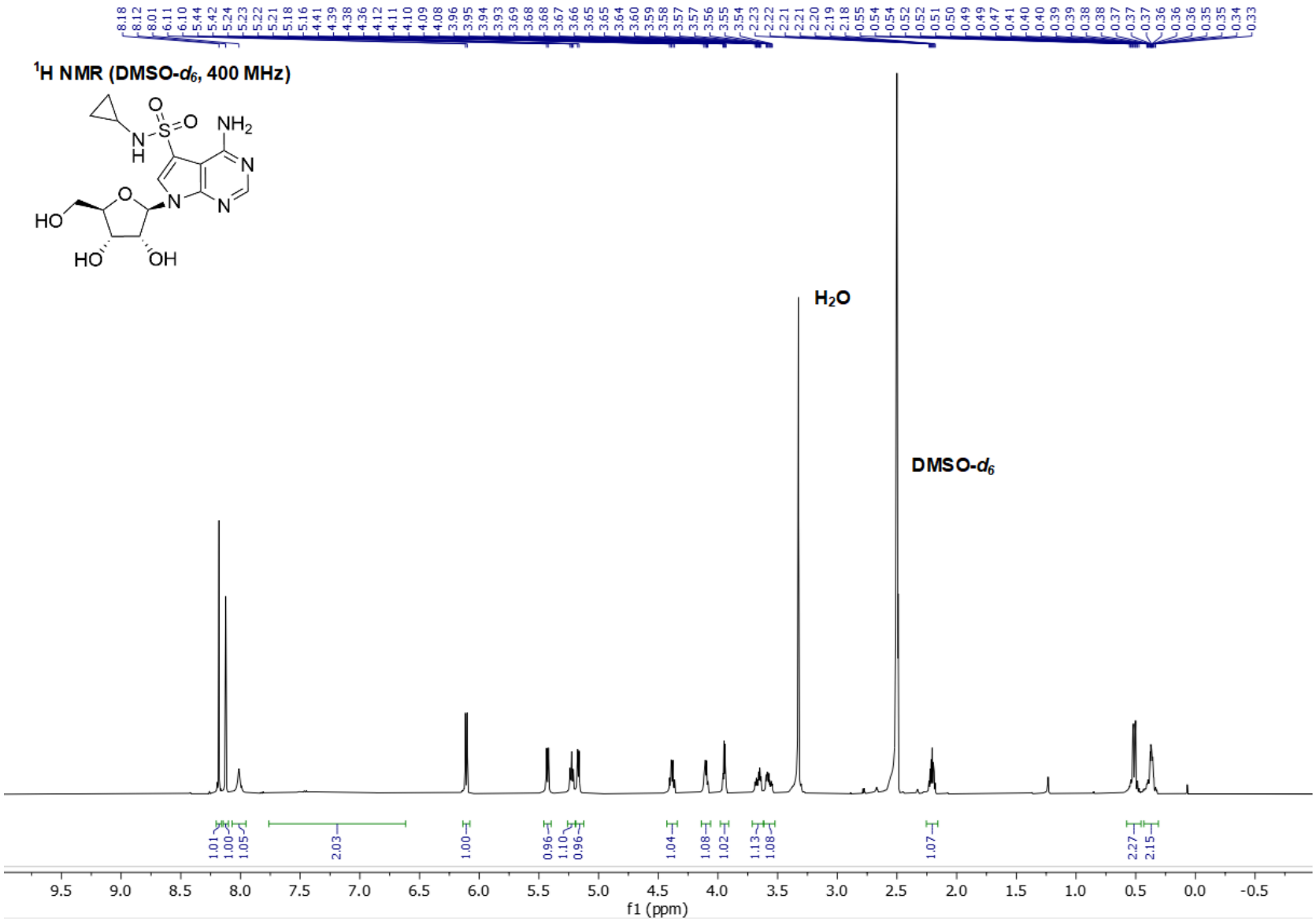


Figure S22. ^{1}H NMR spectra of compound **9e** measured in DMSO-d_6.

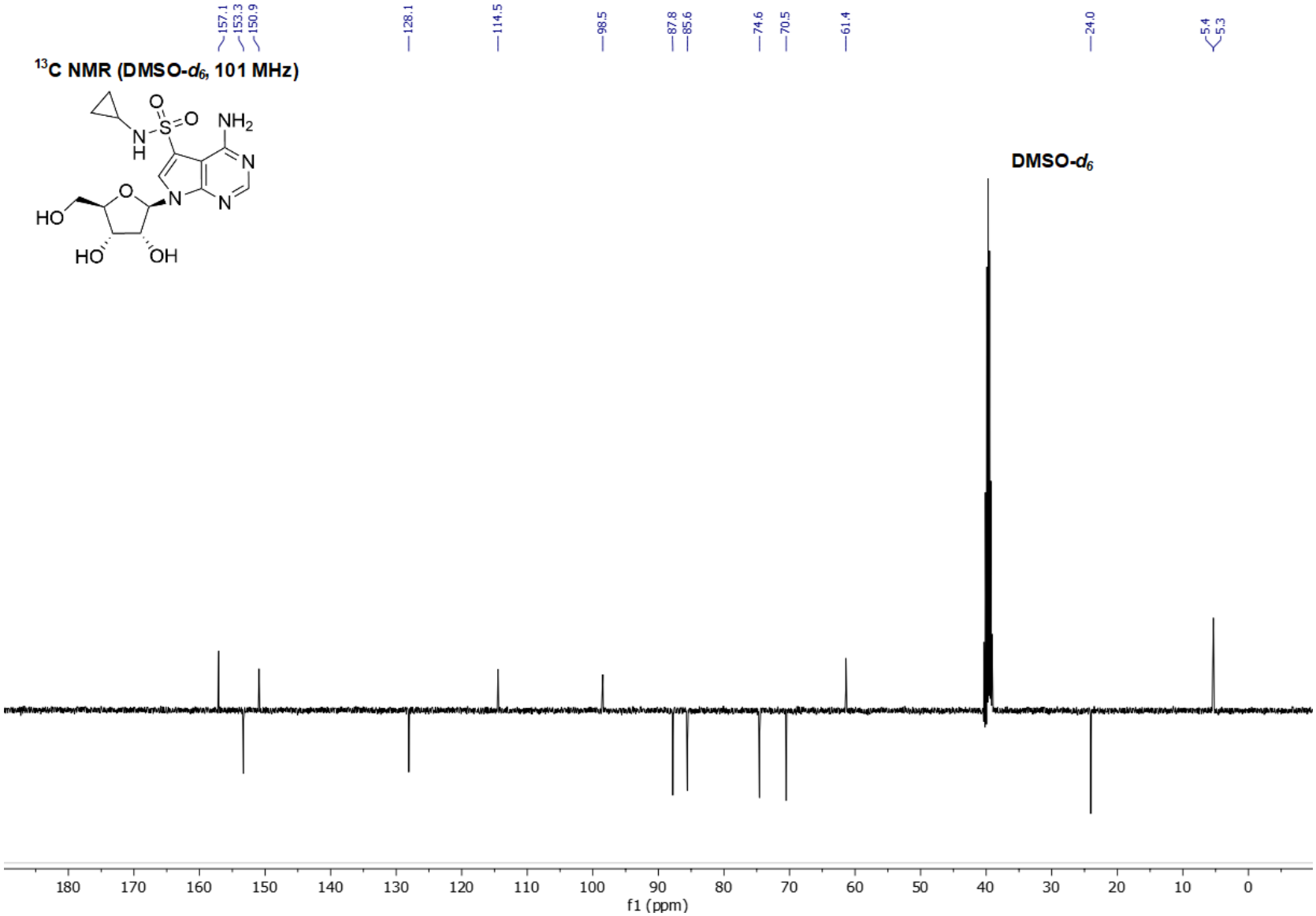


Figure S23. ^{13}C APT NMR spectra of compound **9e** measured in DMSO-d_6.

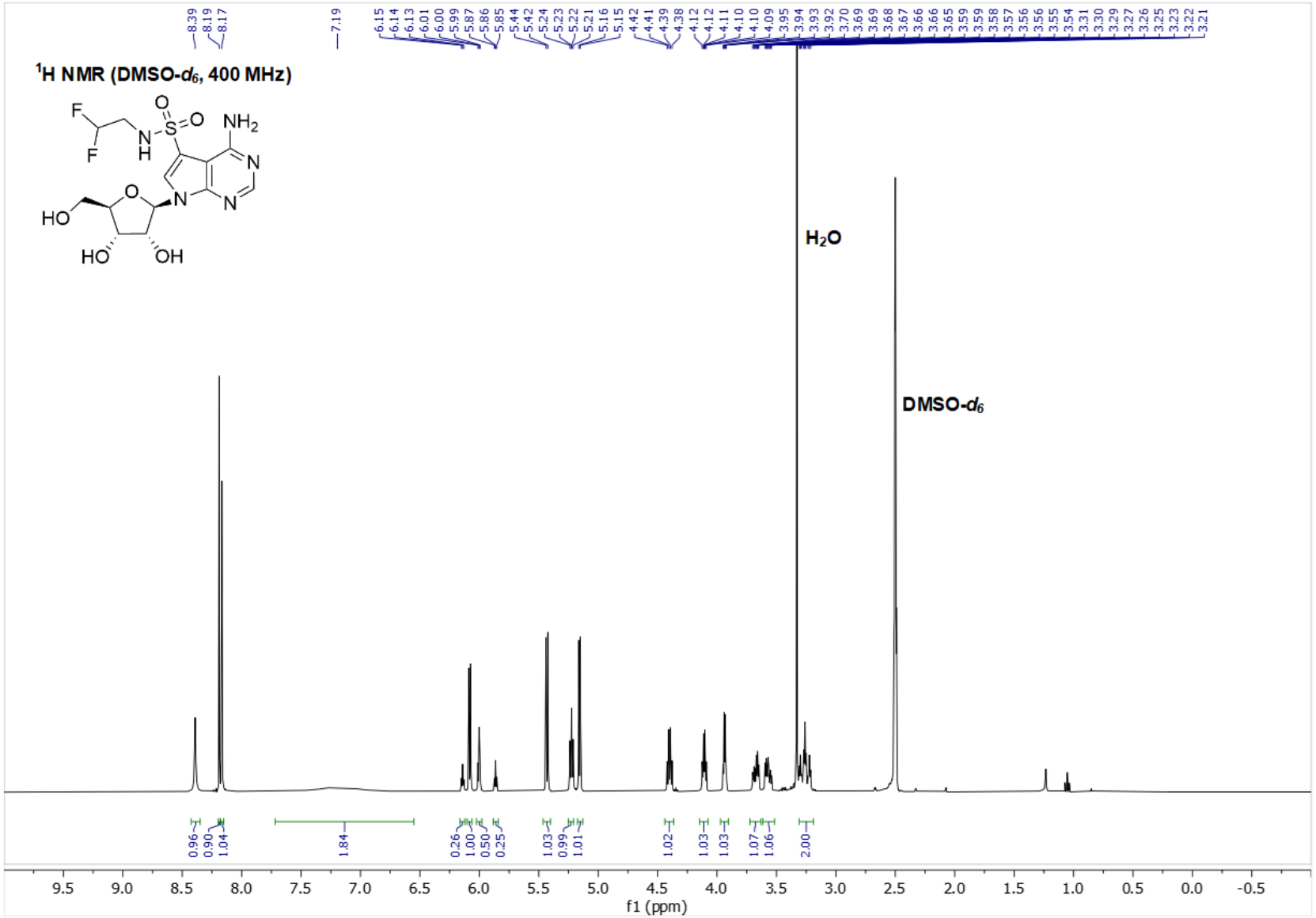


Figure S24. ^{1}H NMR spectra of compound **9f** measured in DMSO-d_6.

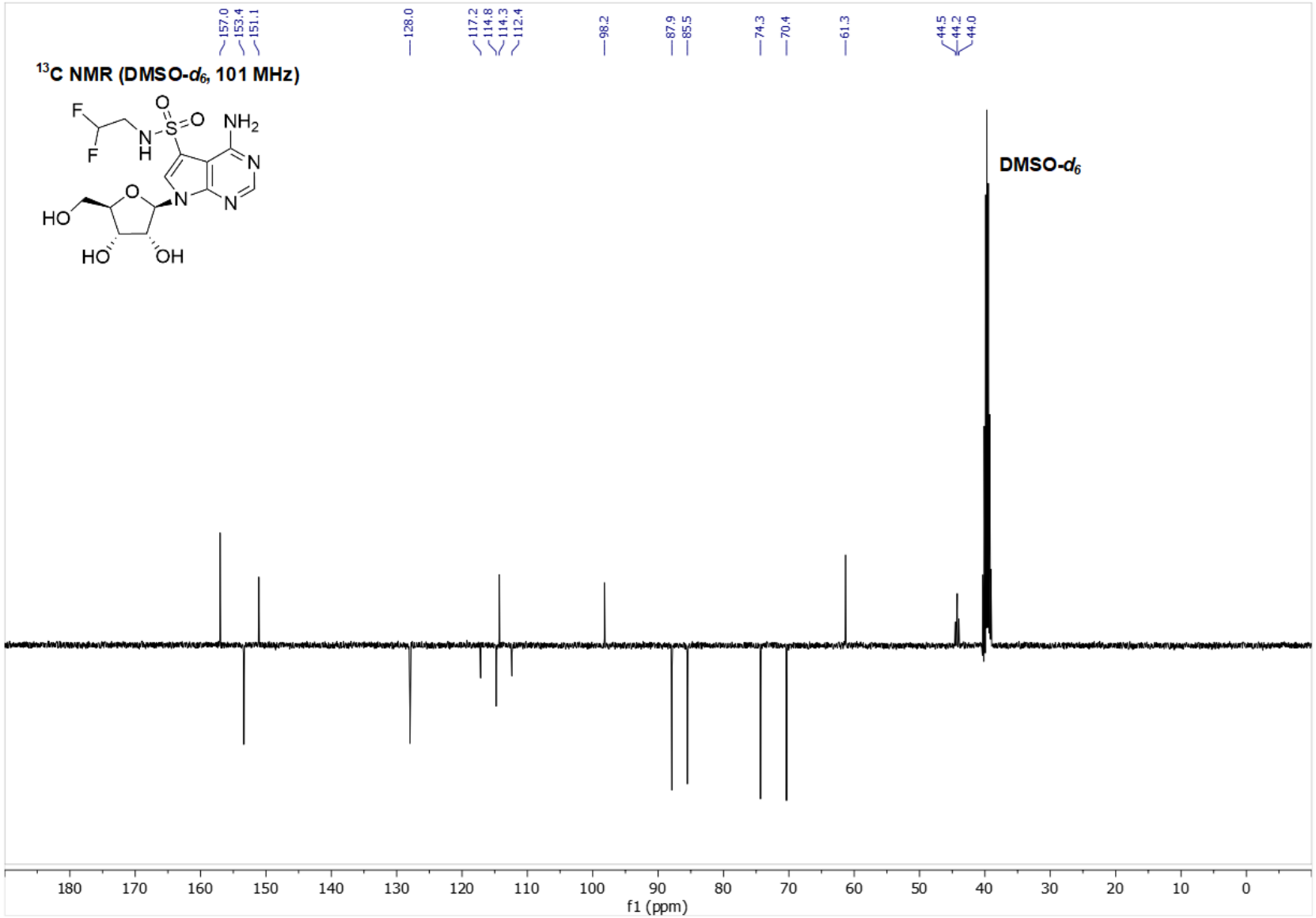


Figure S25. ^{13}C APT NMR spectra of compound **9f** measured in DMSO-d_6.

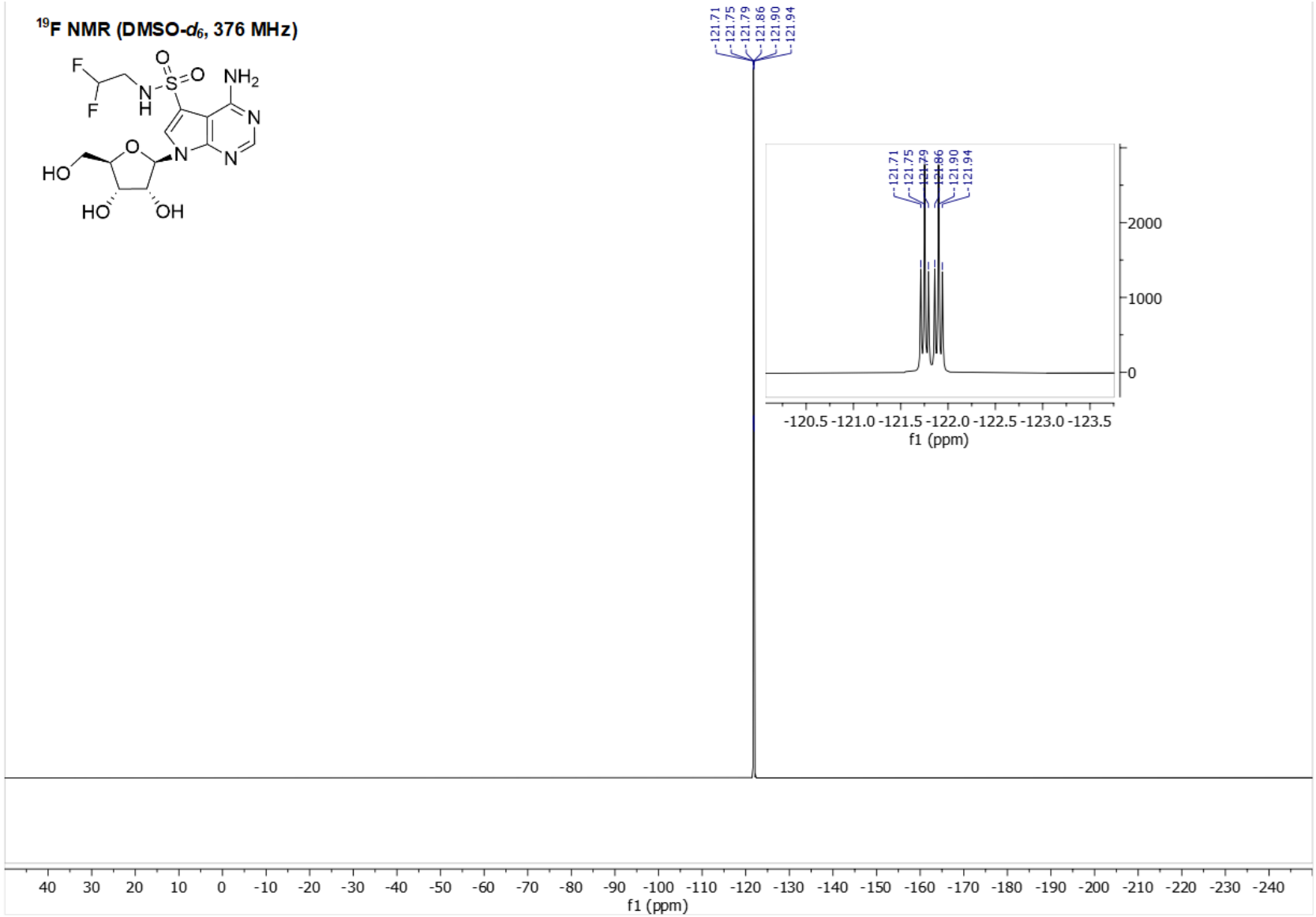


Figure S26. ^{19}F NMR spectra of compound **9f** measured in DMSO-d_6.

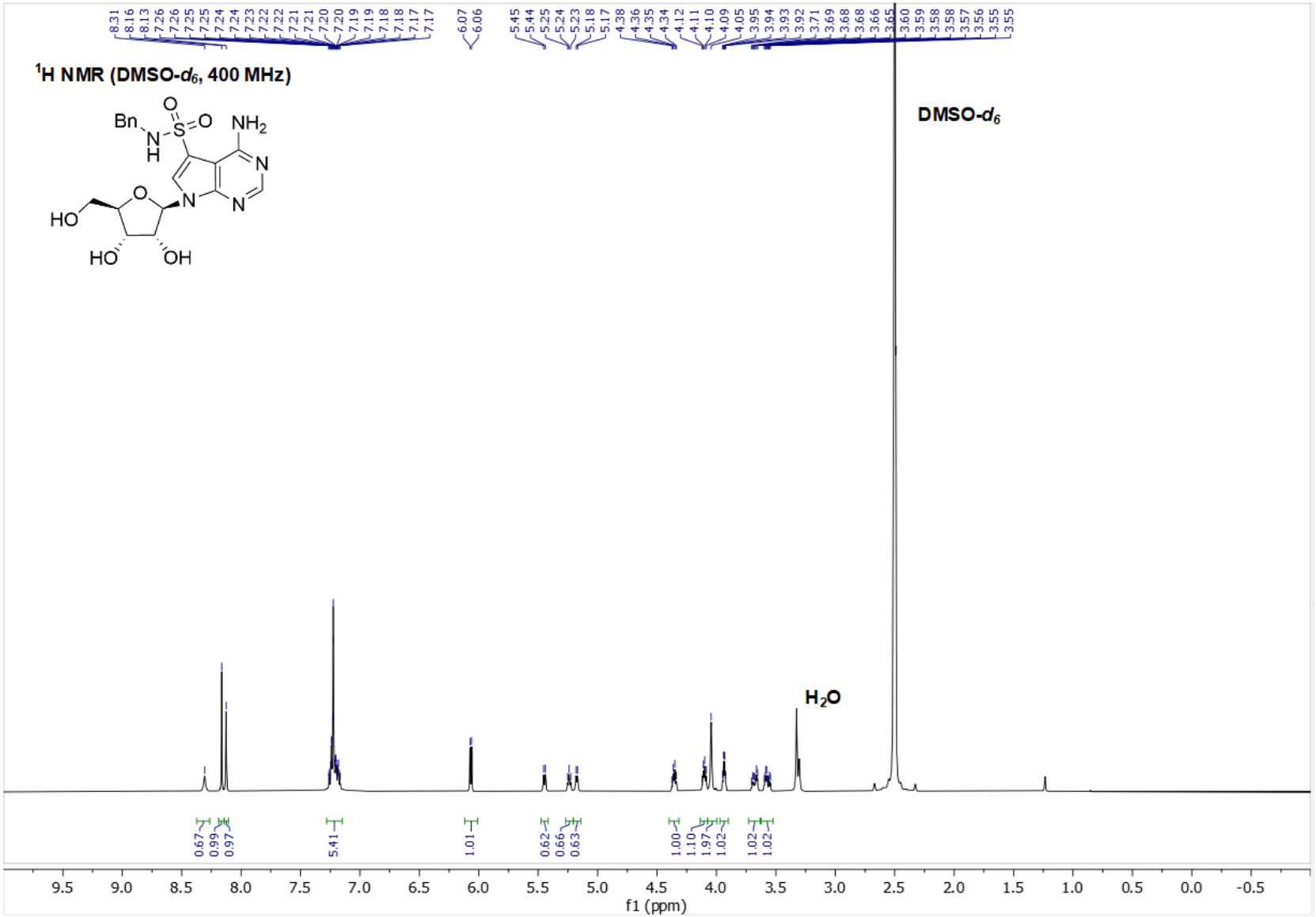


Figure S27. ^{1}H NMR spectra of compound **9g** measured in DMSO-d_6.

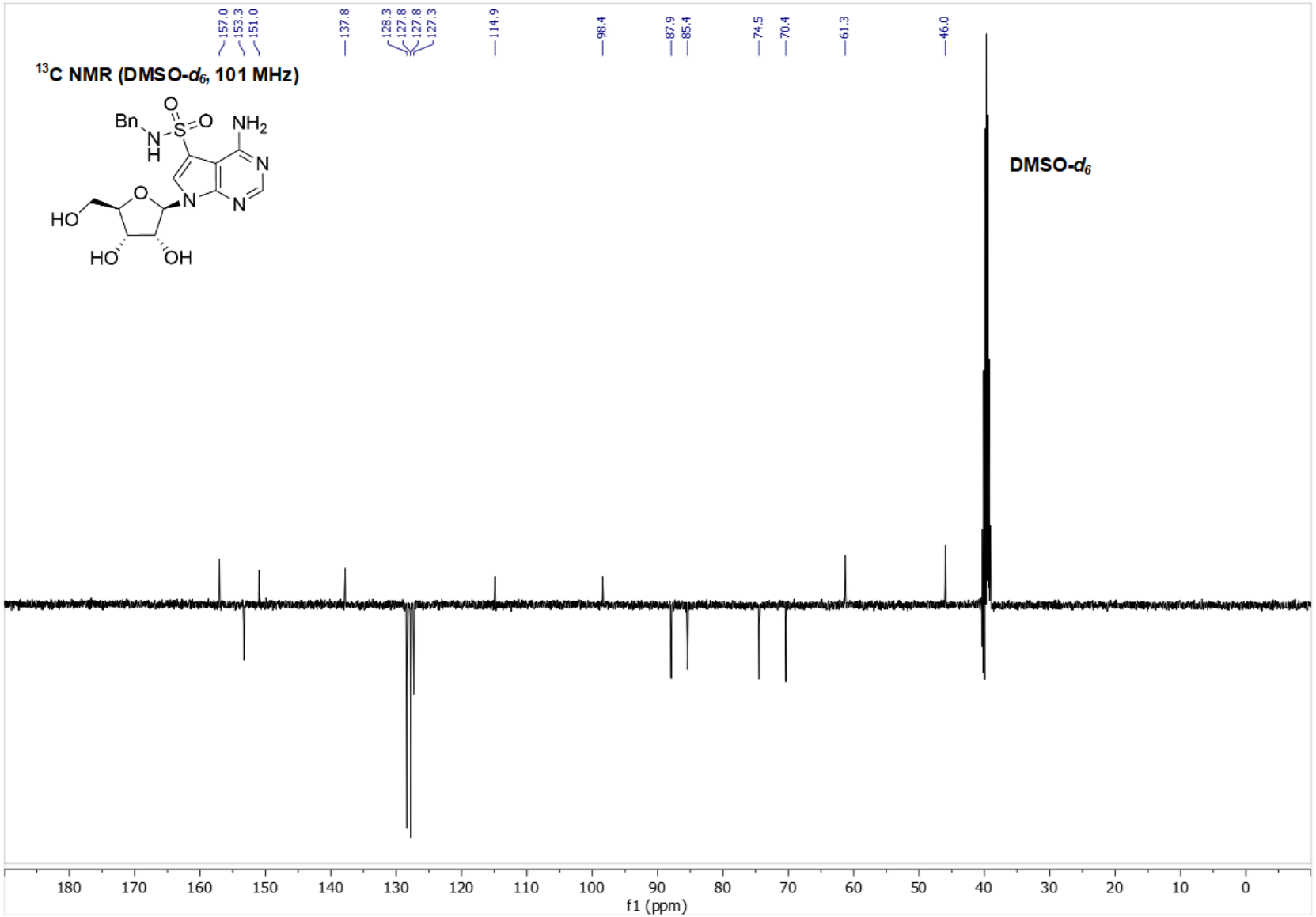


Figure S28. ^{13}C APT NMR spectra of compound **9g** measured in DMSO-d_6.

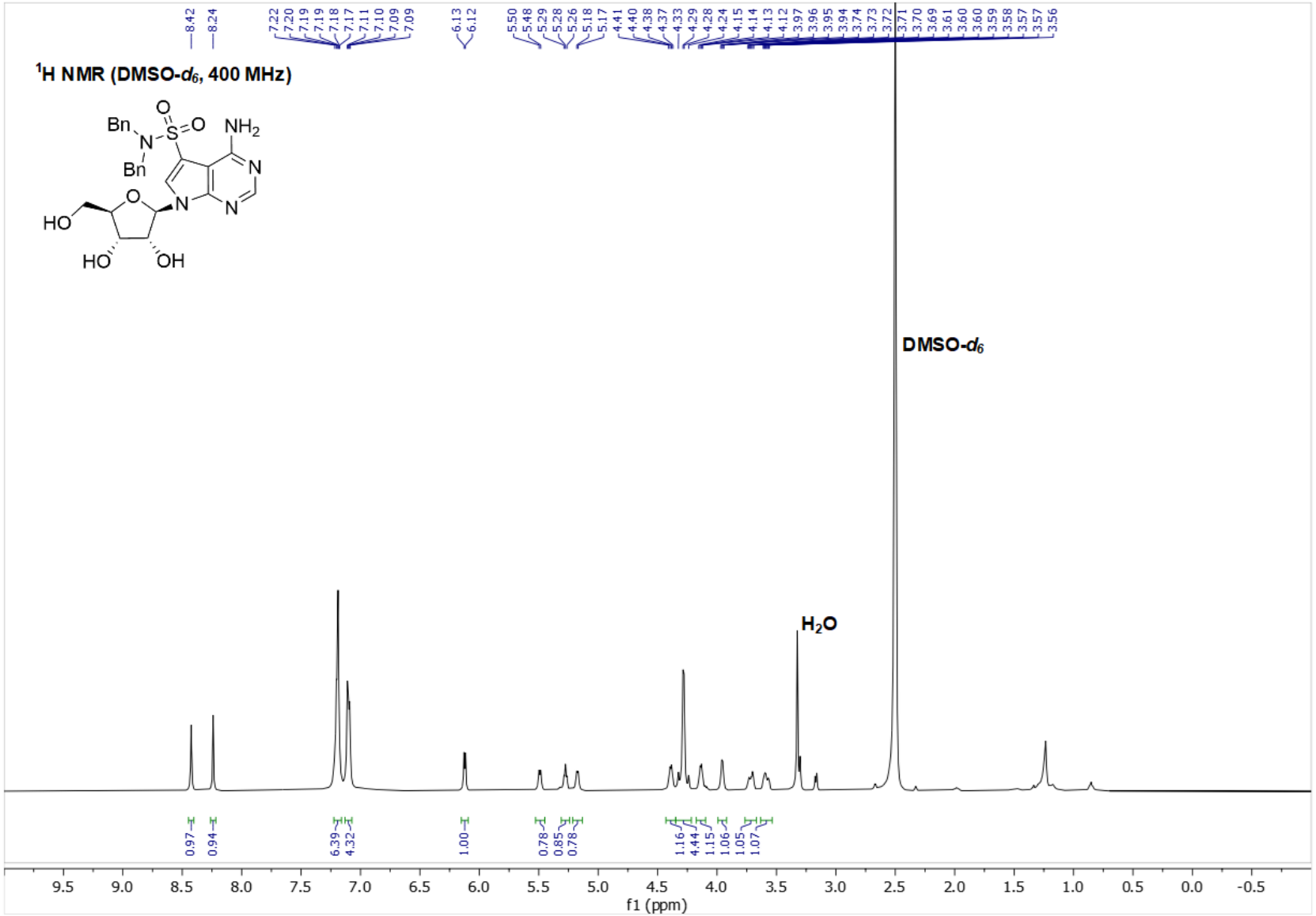


Figure S29. ^{1}H NMR spectra of compound **9h** measured in DMSO-d_6.

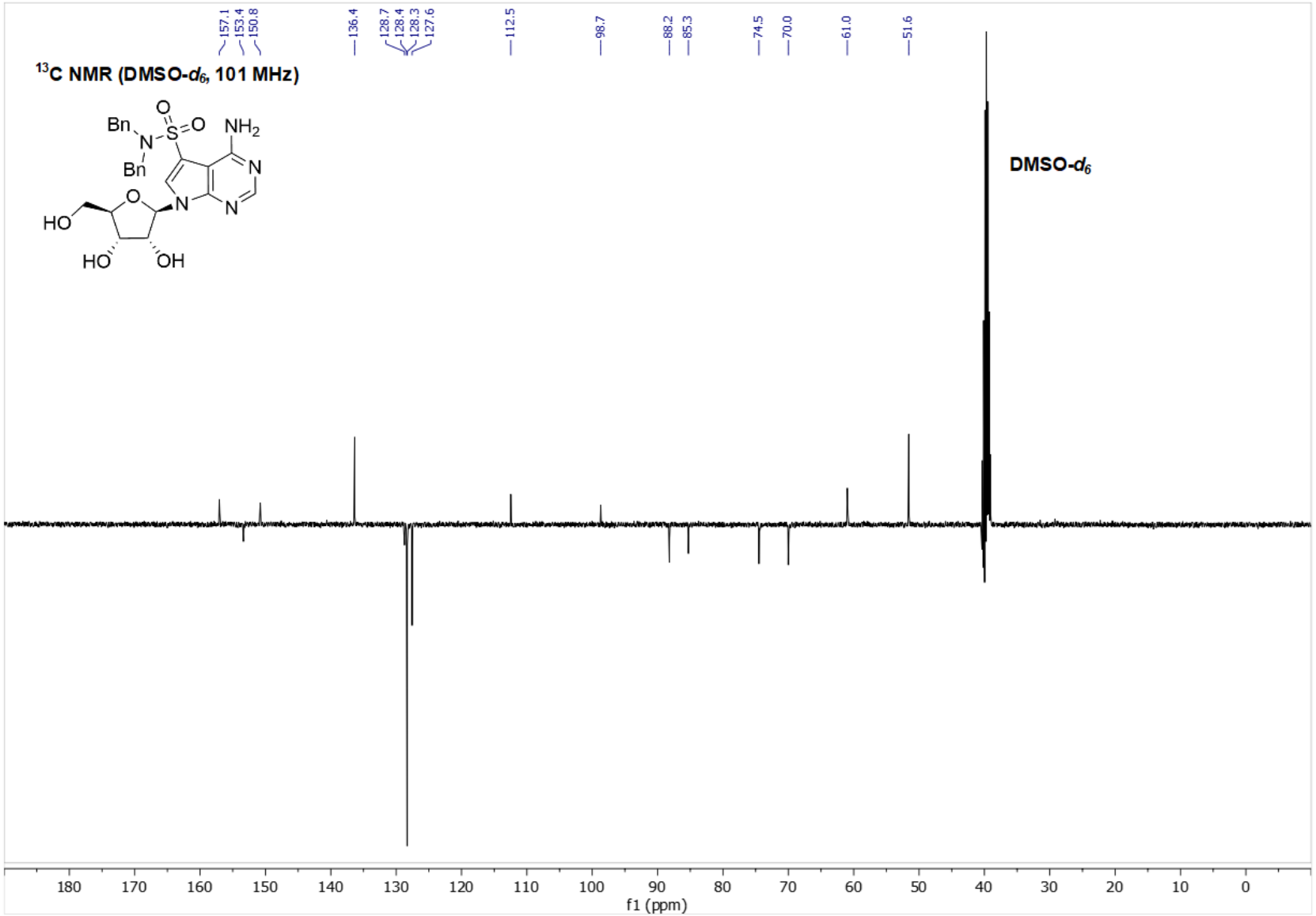


Figure S30. ^{13}C APT NMR spectra of compound **9h** measured in DMSO-d_6.

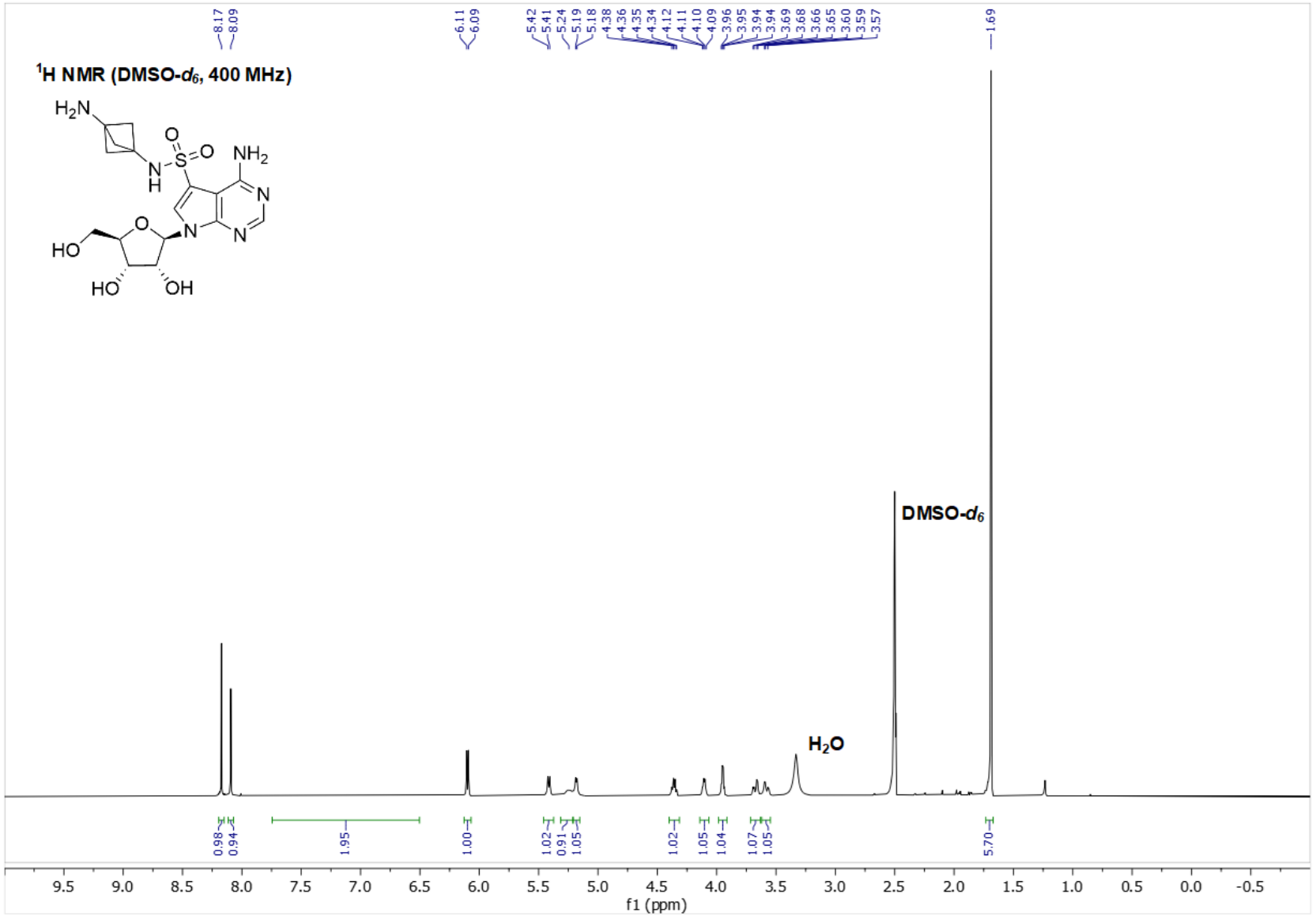


Figure S31. ^{1}H NMR spectra of compound **9i** measured in DMSO-d_6.

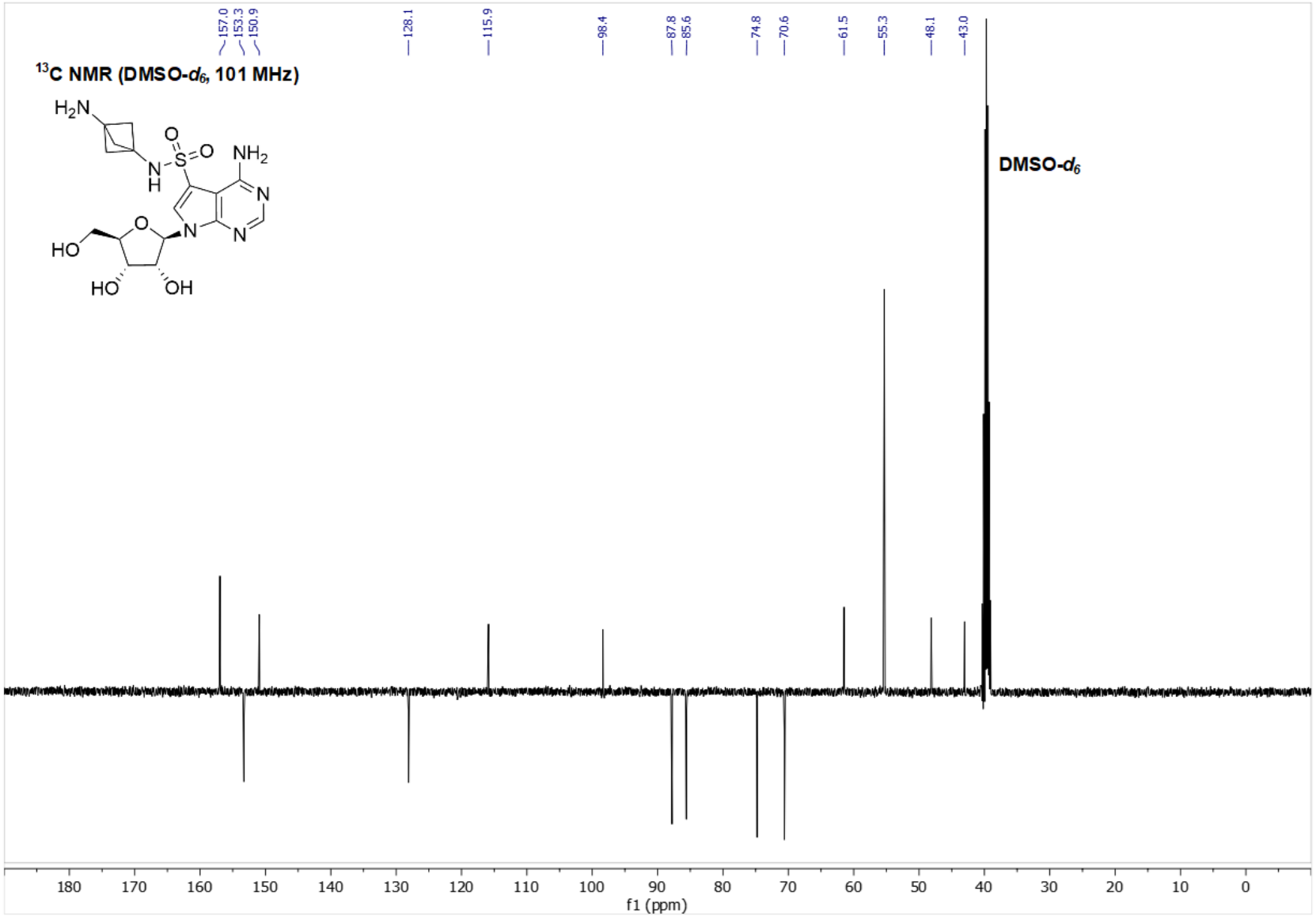


Figure S32. ^{13}C APT NMR spectra of compound **9i** measured in DMSO-d_6.

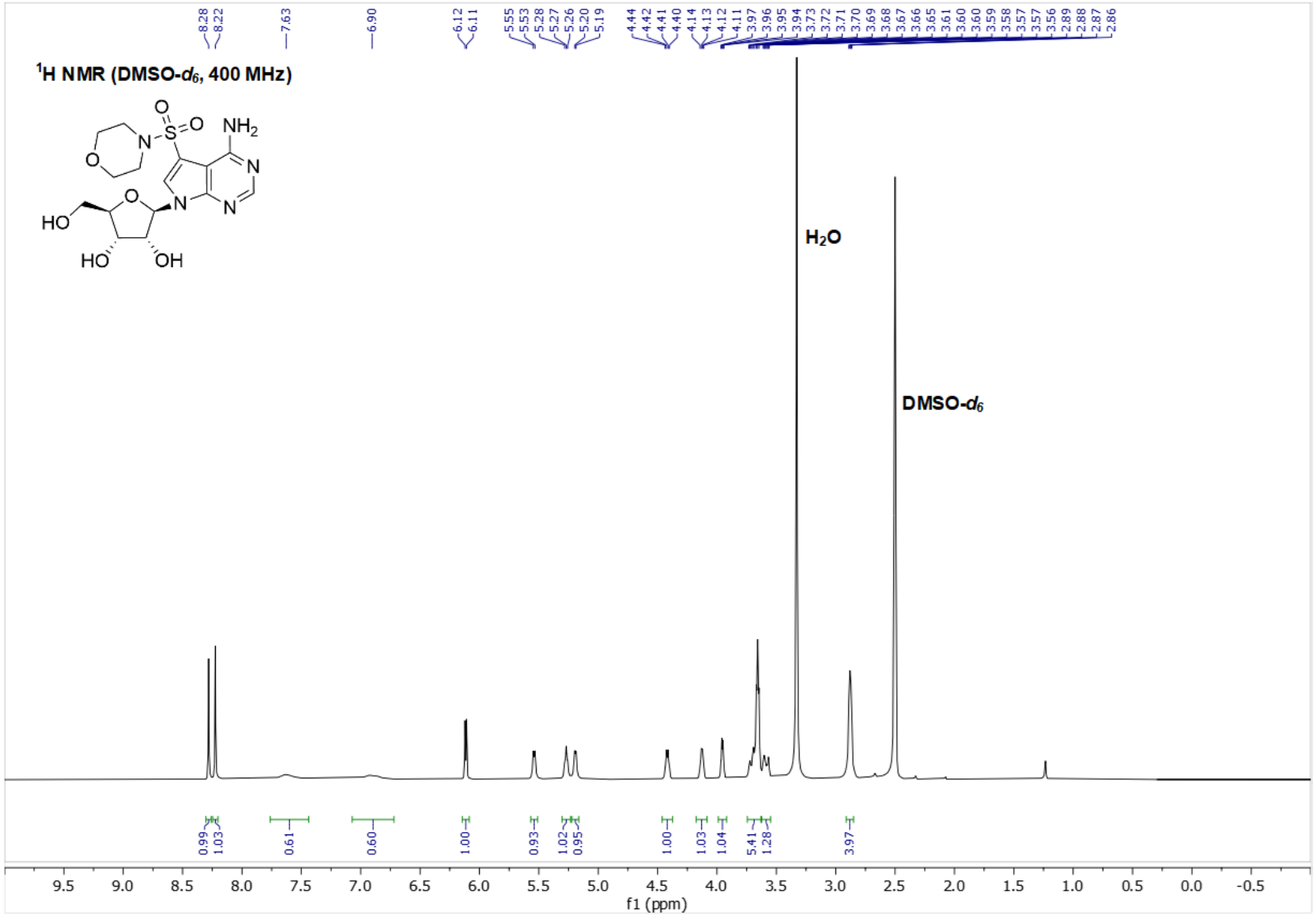


Figure S33. ^{1}H NMR spectra of compound **9j** measured in DMSO-d_6.

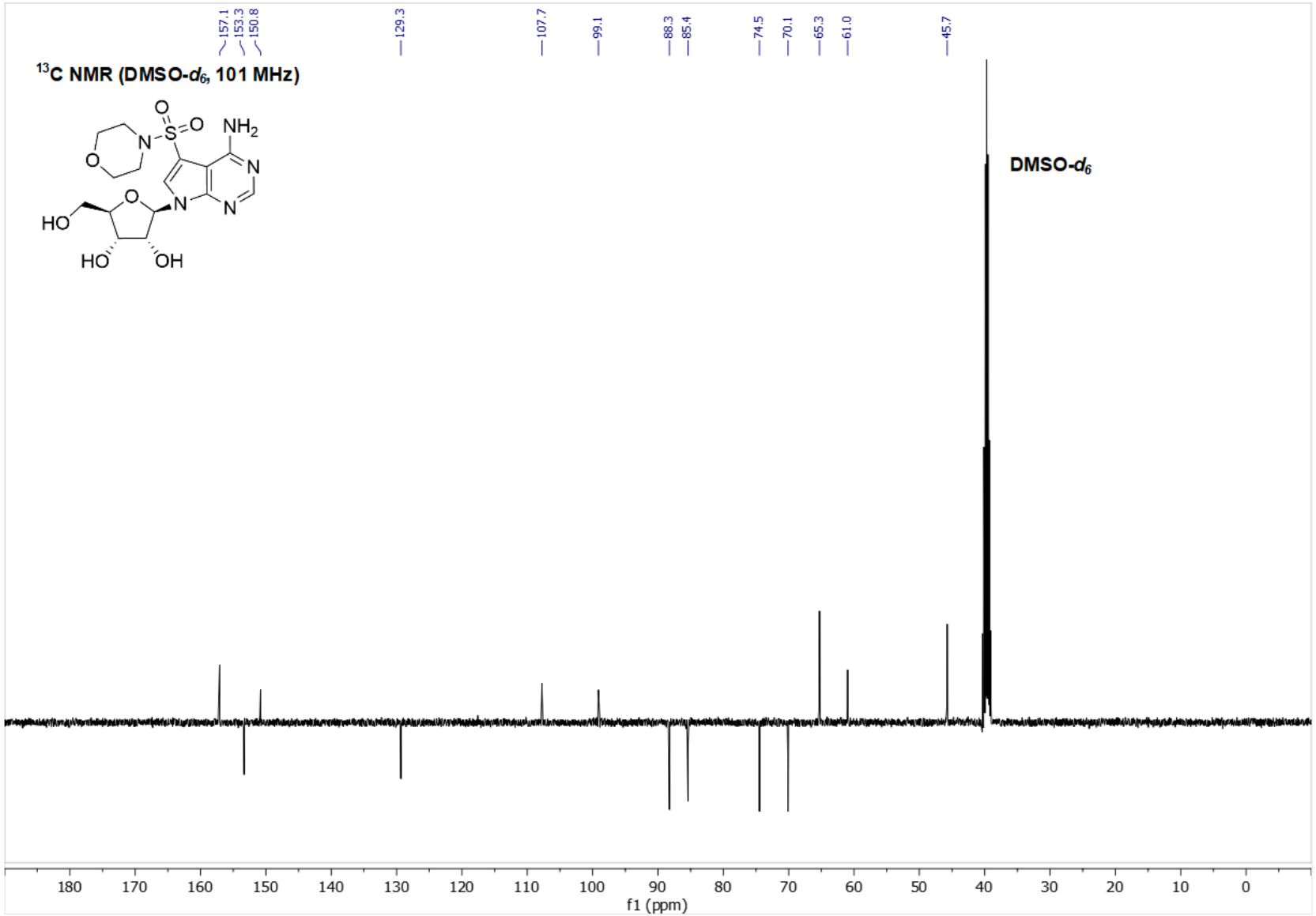


Figure S34. ^{13}C APT NMR spectra of compound **9j** measured in DMSO-d_6.

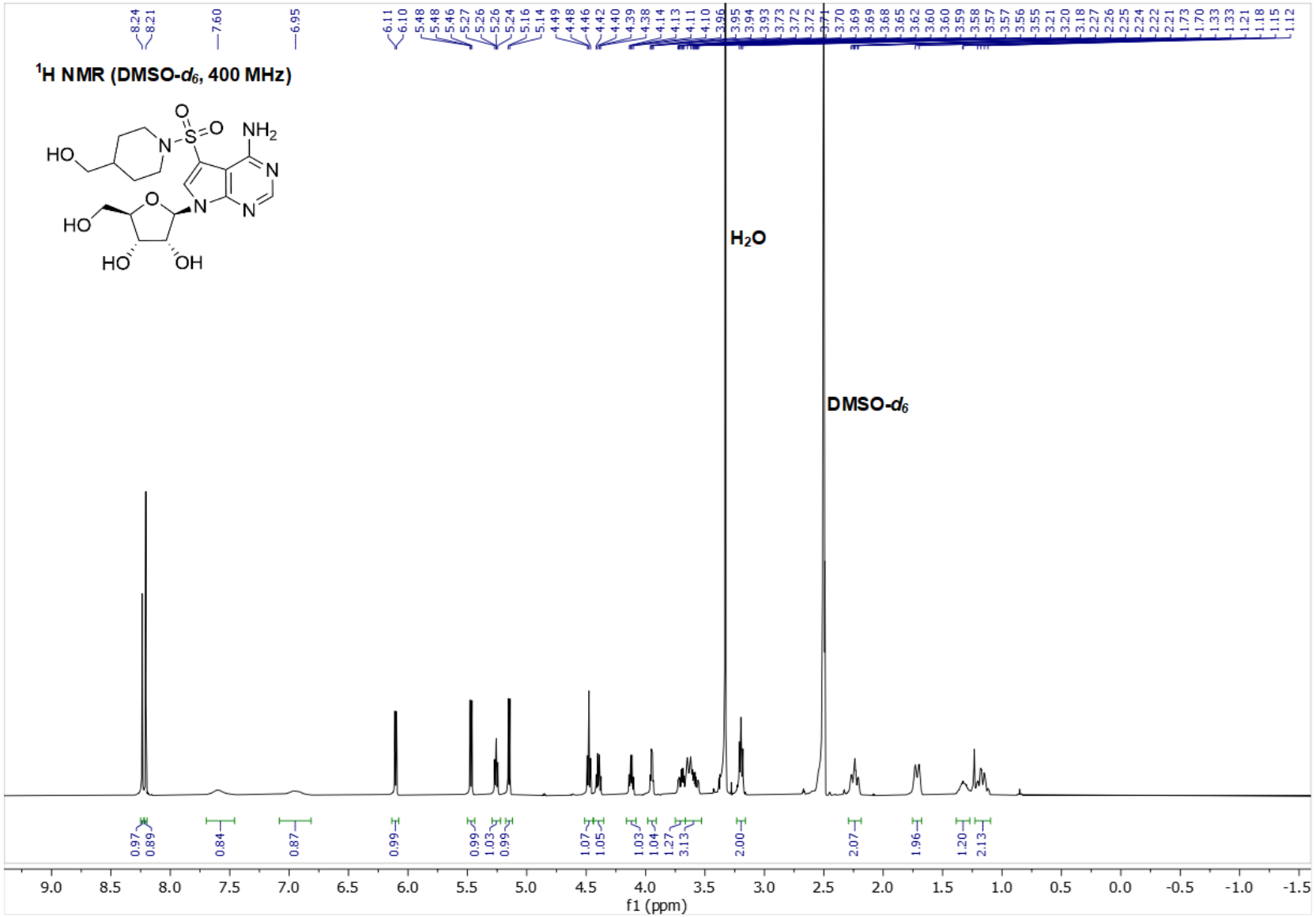


Figure S35. ^{1}H NMR spectra of compound **9k** measured in DMSO-d_6.

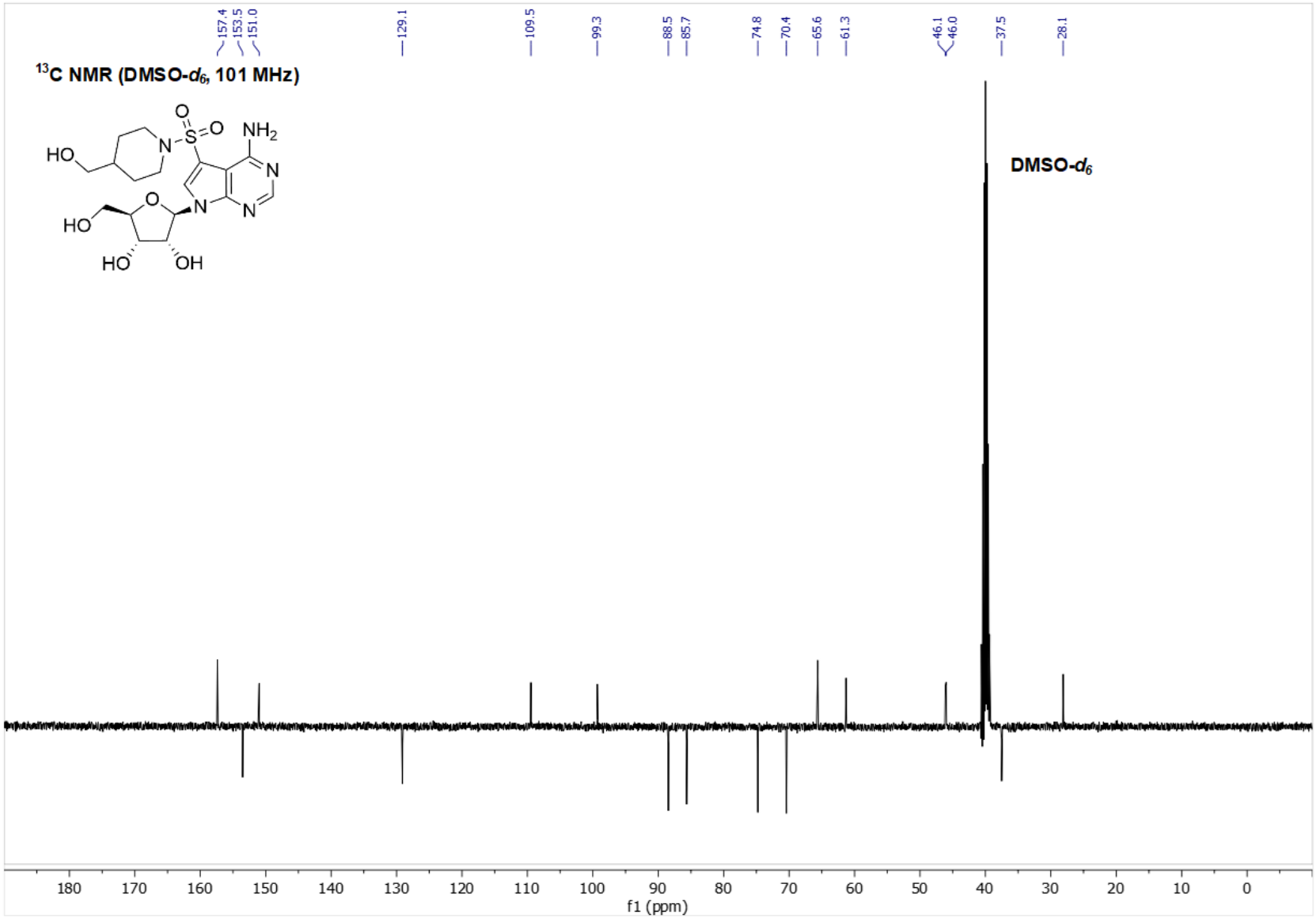


Figure S36. ^{13}C APT NMR spectra of compound **9k** measured in DMSO-d_6.

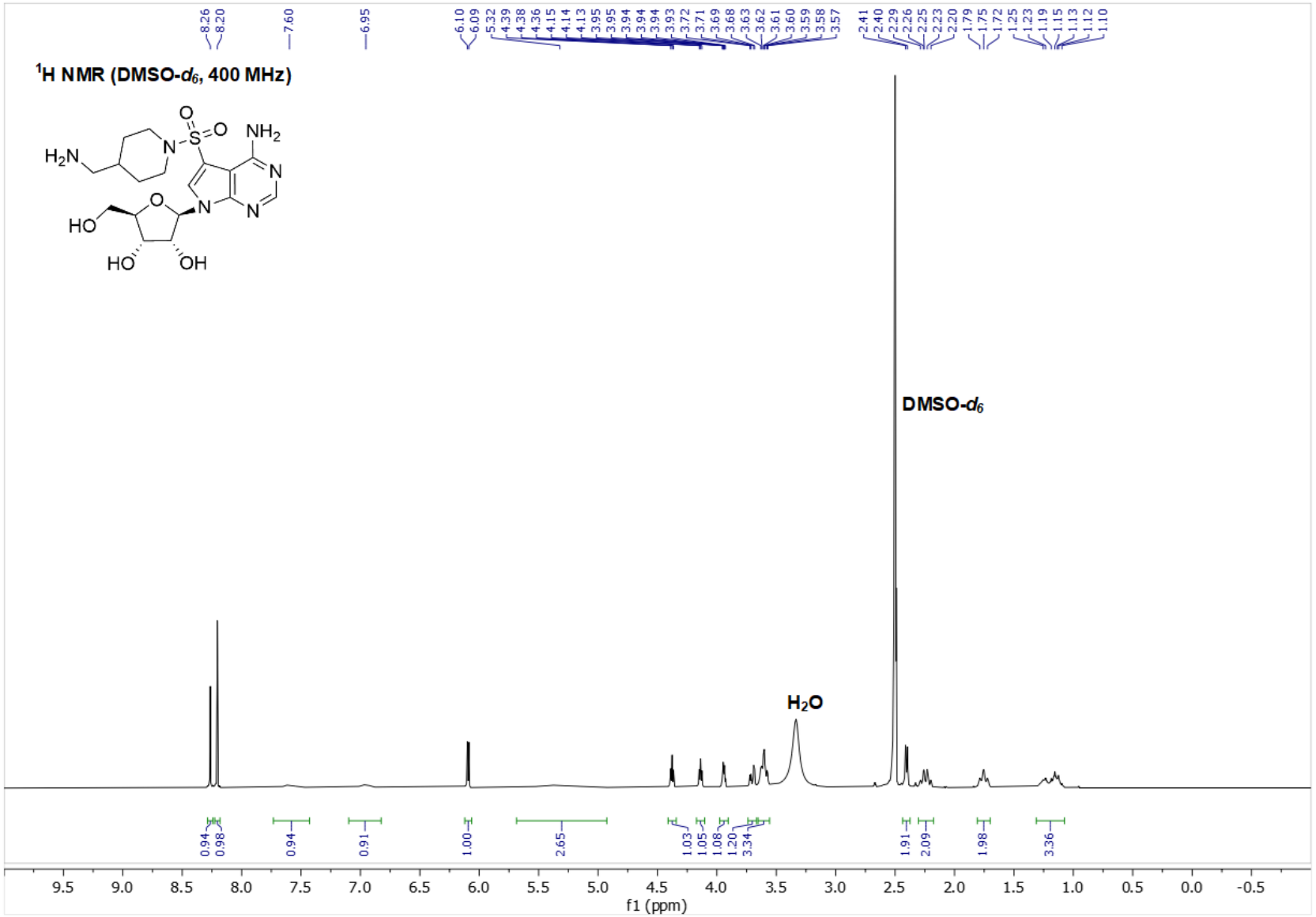


Figure S37. ^{1}H NMR spectra of compound **9l** measured in DMSO-d_6.

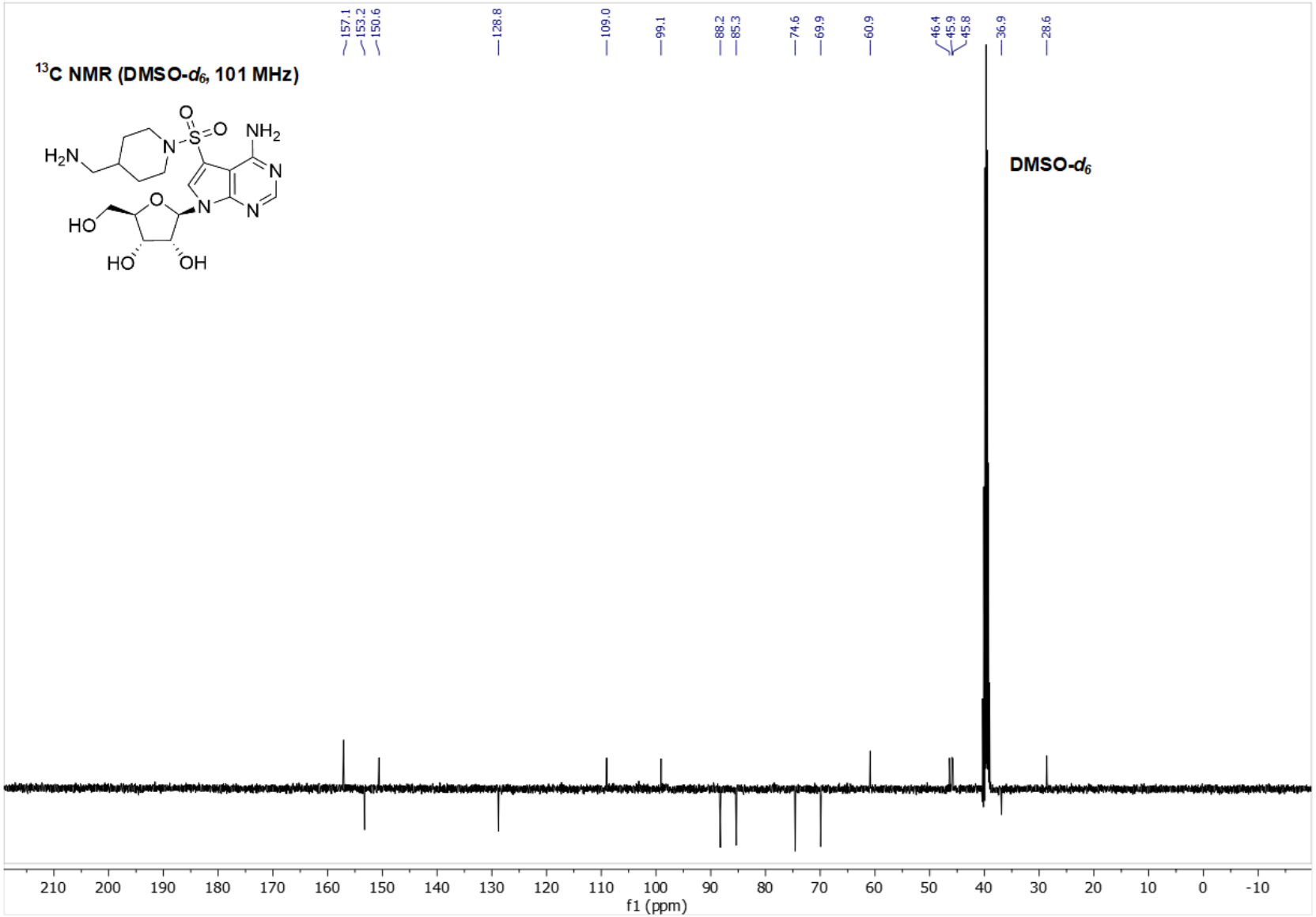


Figure S38. ^{13}C APT NMR spectra of compound **9l** measured in DMSO-d_6.

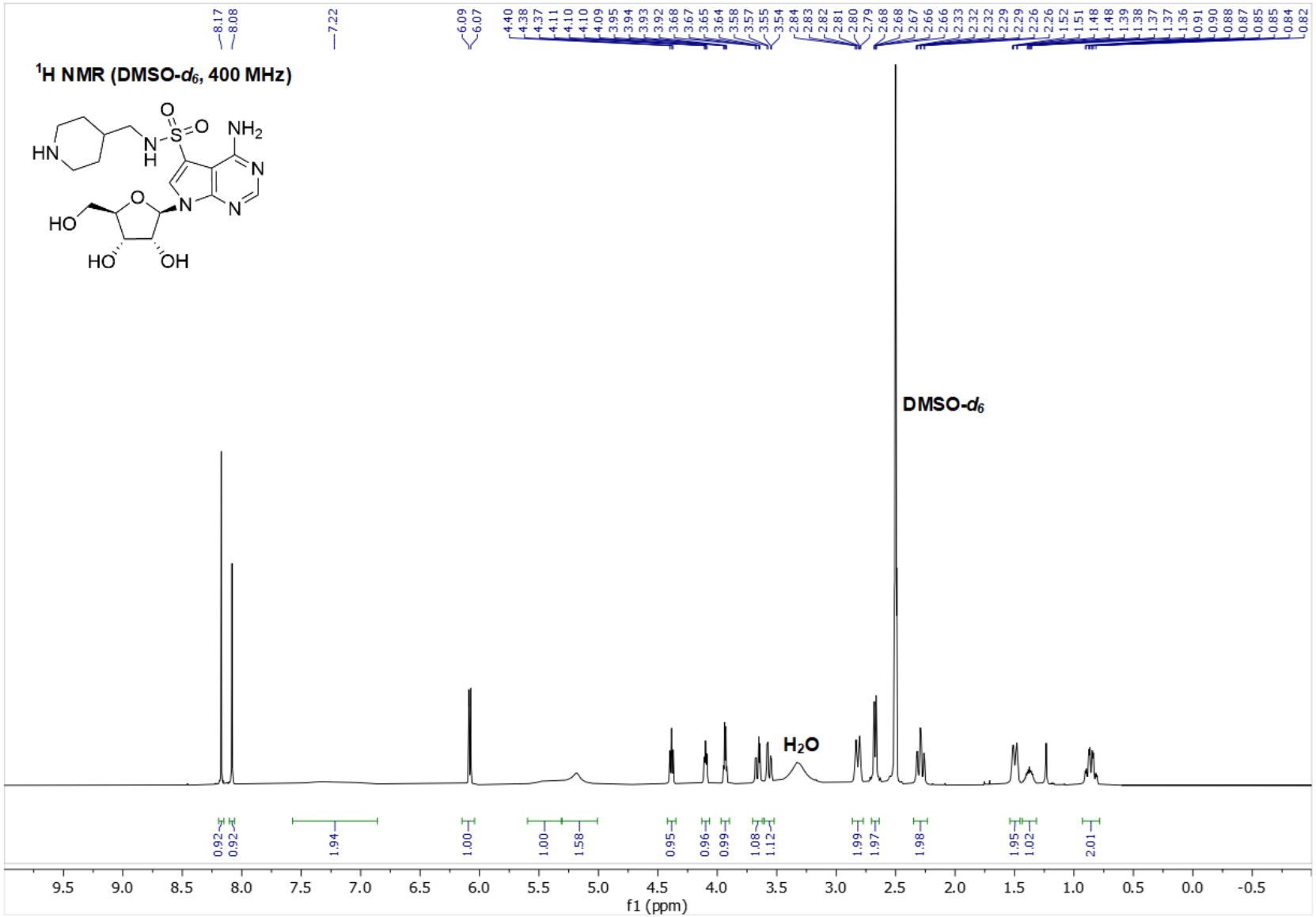


Figure S39. ^{1}H NMR spectra of compound **9m** measured in DMSO-d_6.

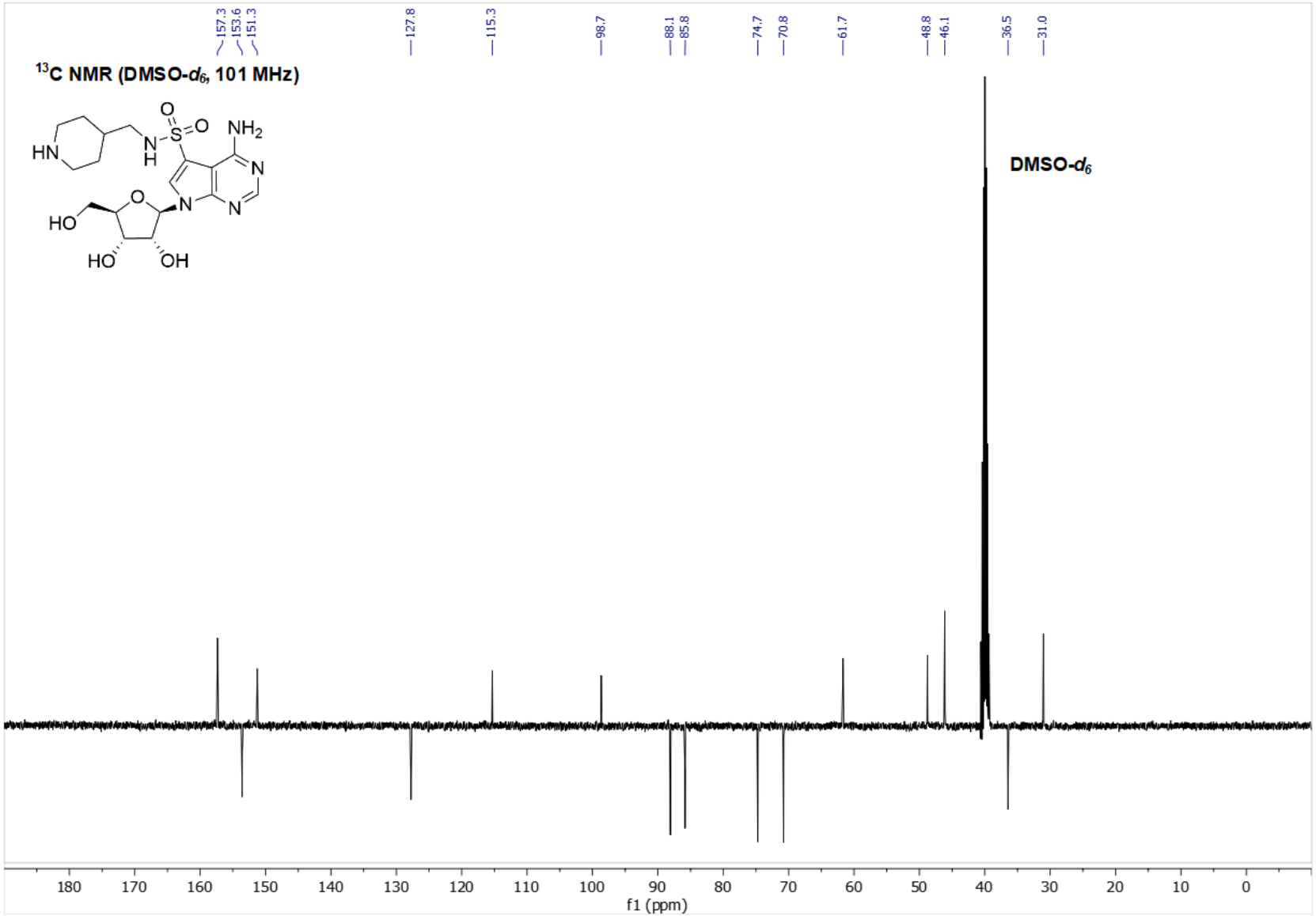


Figure S40. ^{13}C APT NMR spectra of compound **9m** measured in DMSO-d_6.

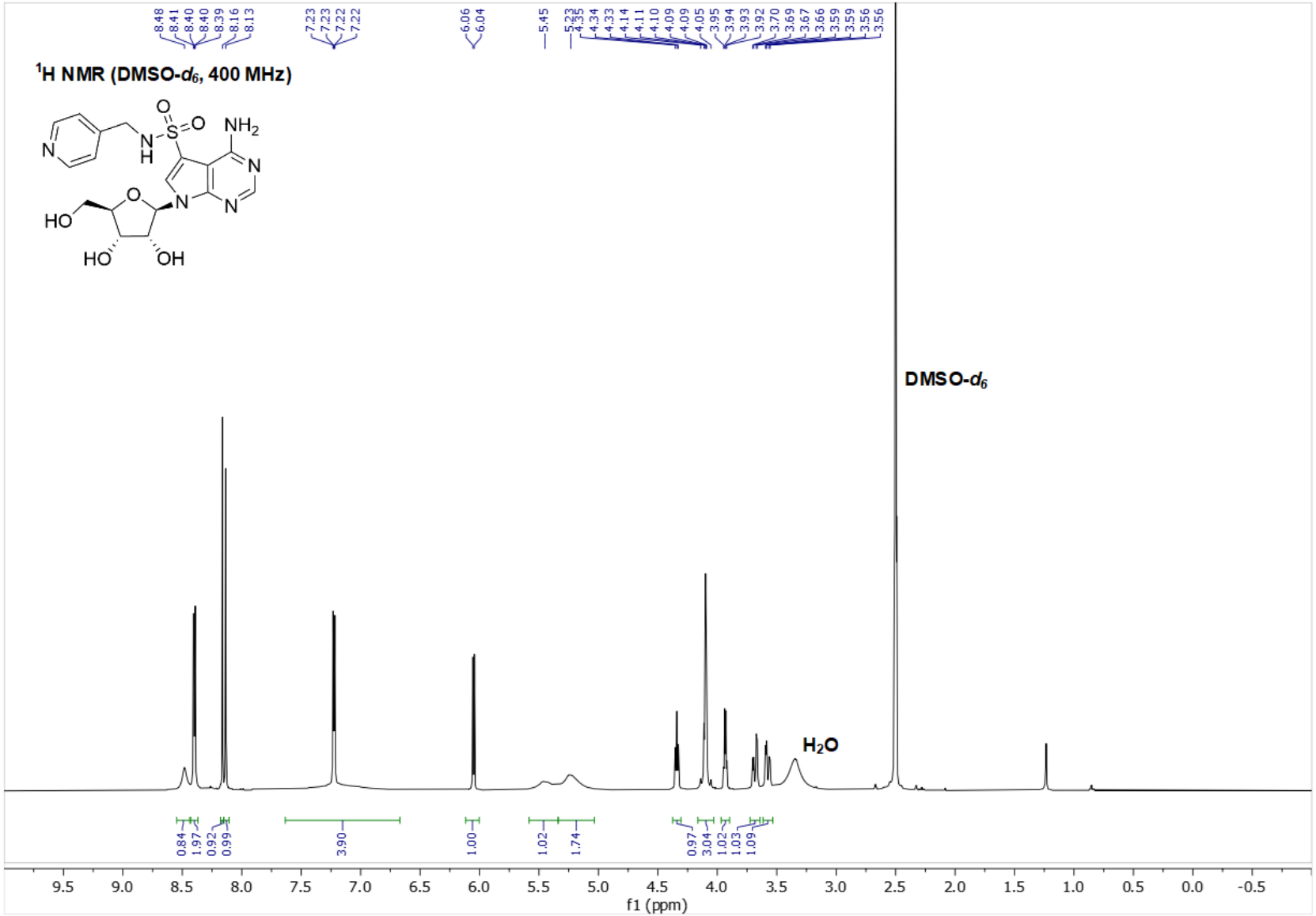


Figure S41. ^{1}H NMR spectra of compound **9n** measured in DMSO-d_6.

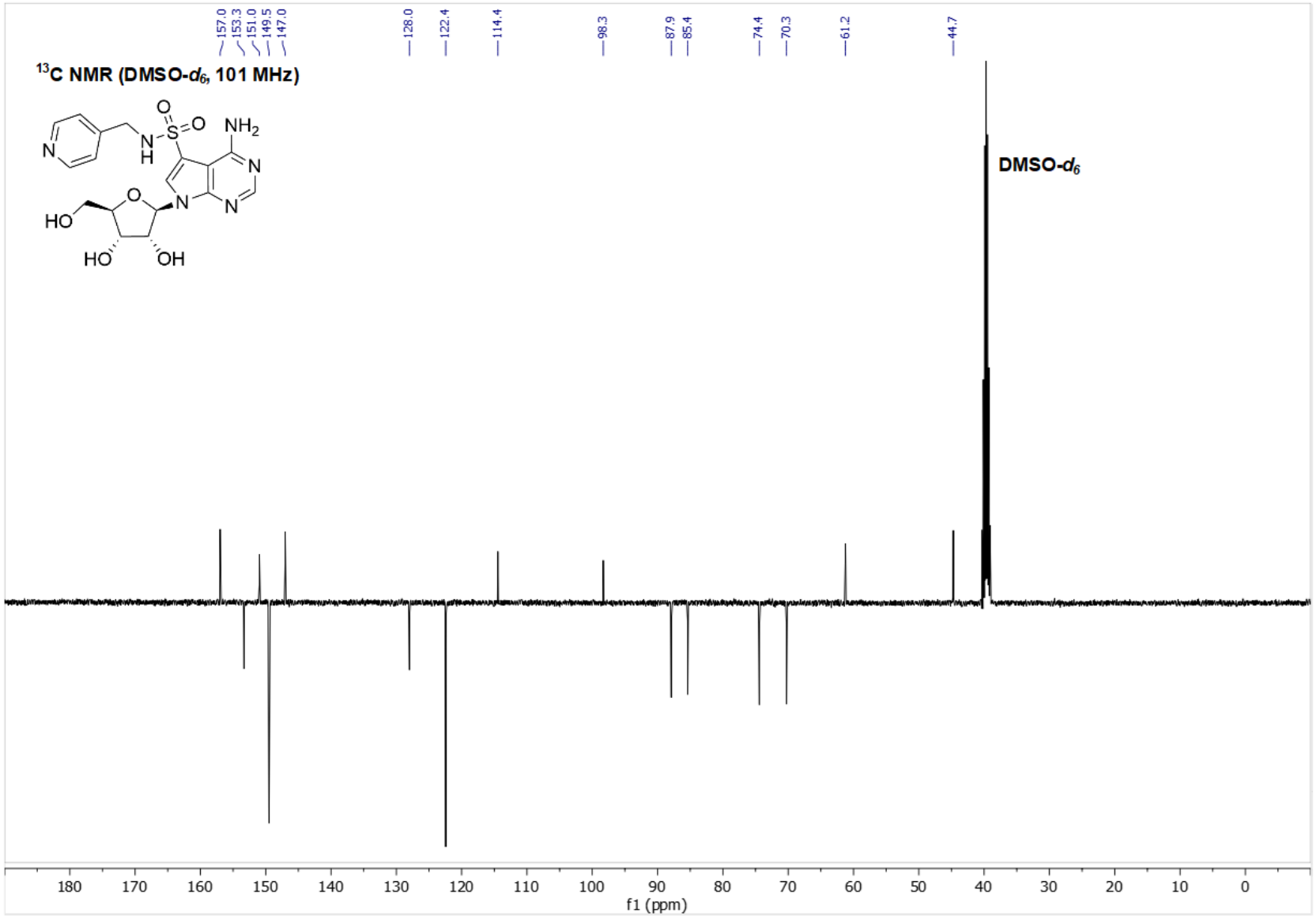


Figure S42. ^{13}C APT NMR spectra of compound **9n** measured in DMSO-d_6.

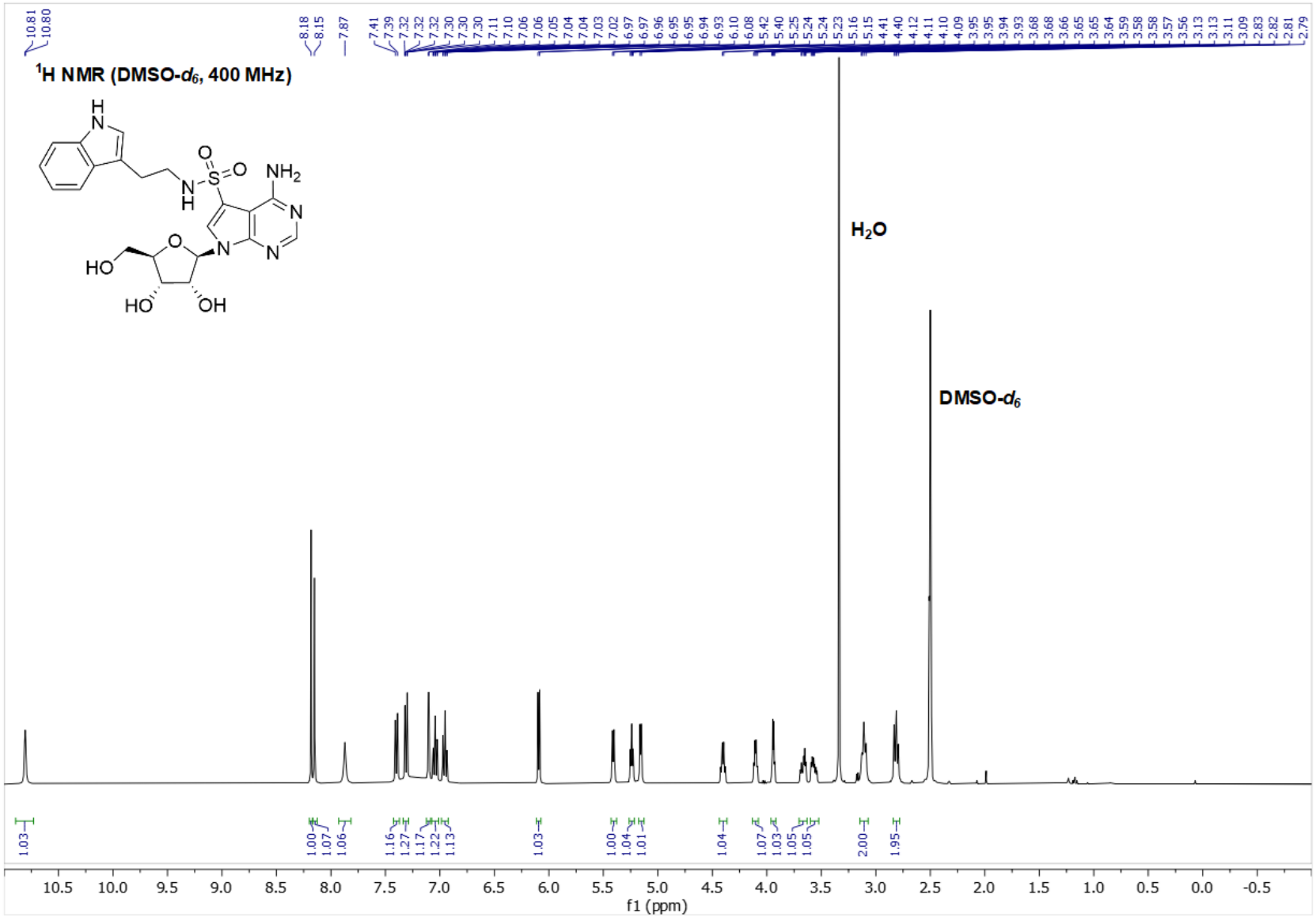


Figure S43. ^{1}H NMR spectra of compound **9o** measured in DMSO-d_6.

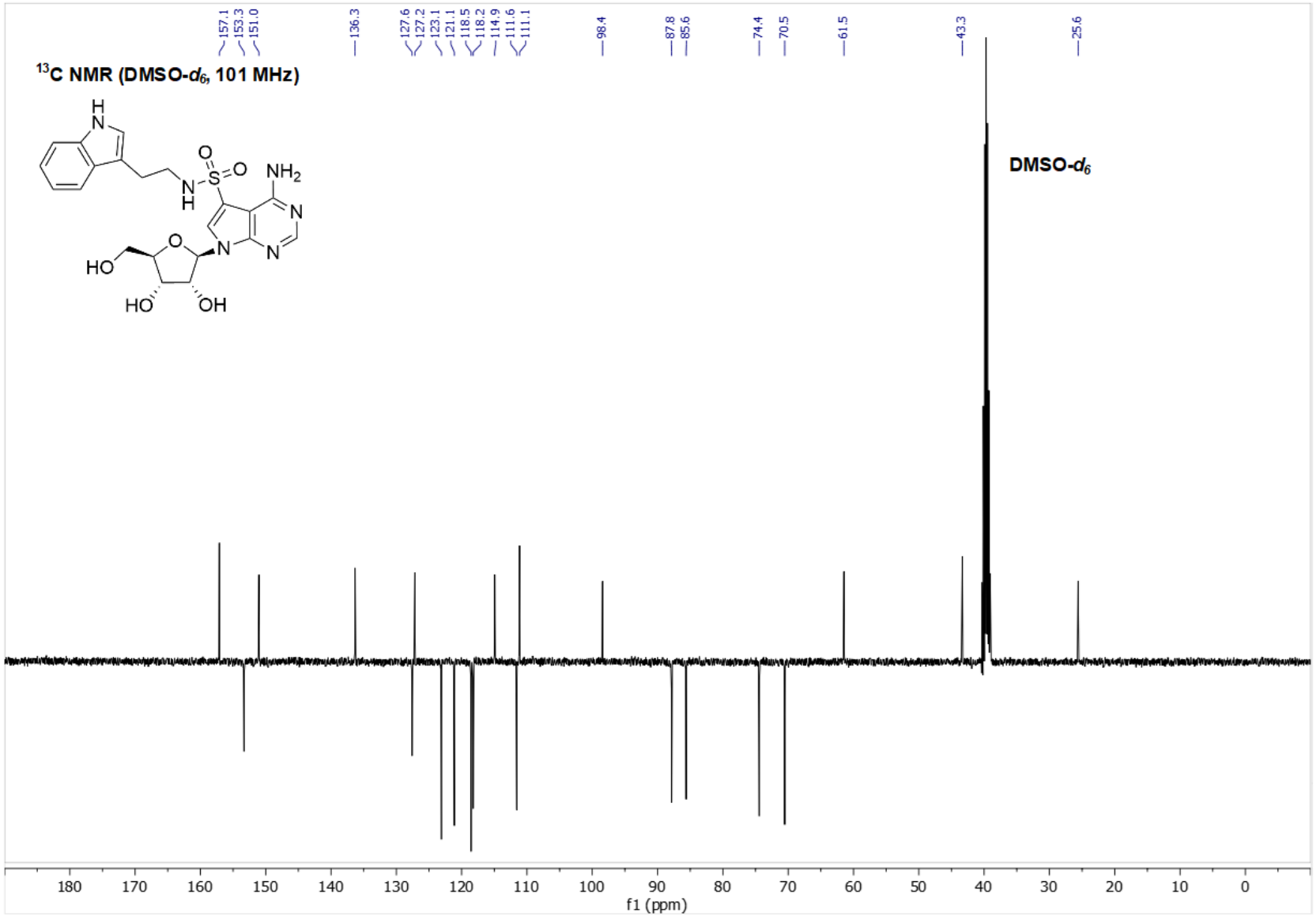


Figure S44. ^{13}C APT NMR spectra of compound **9o** measured in DMSO-d_6.

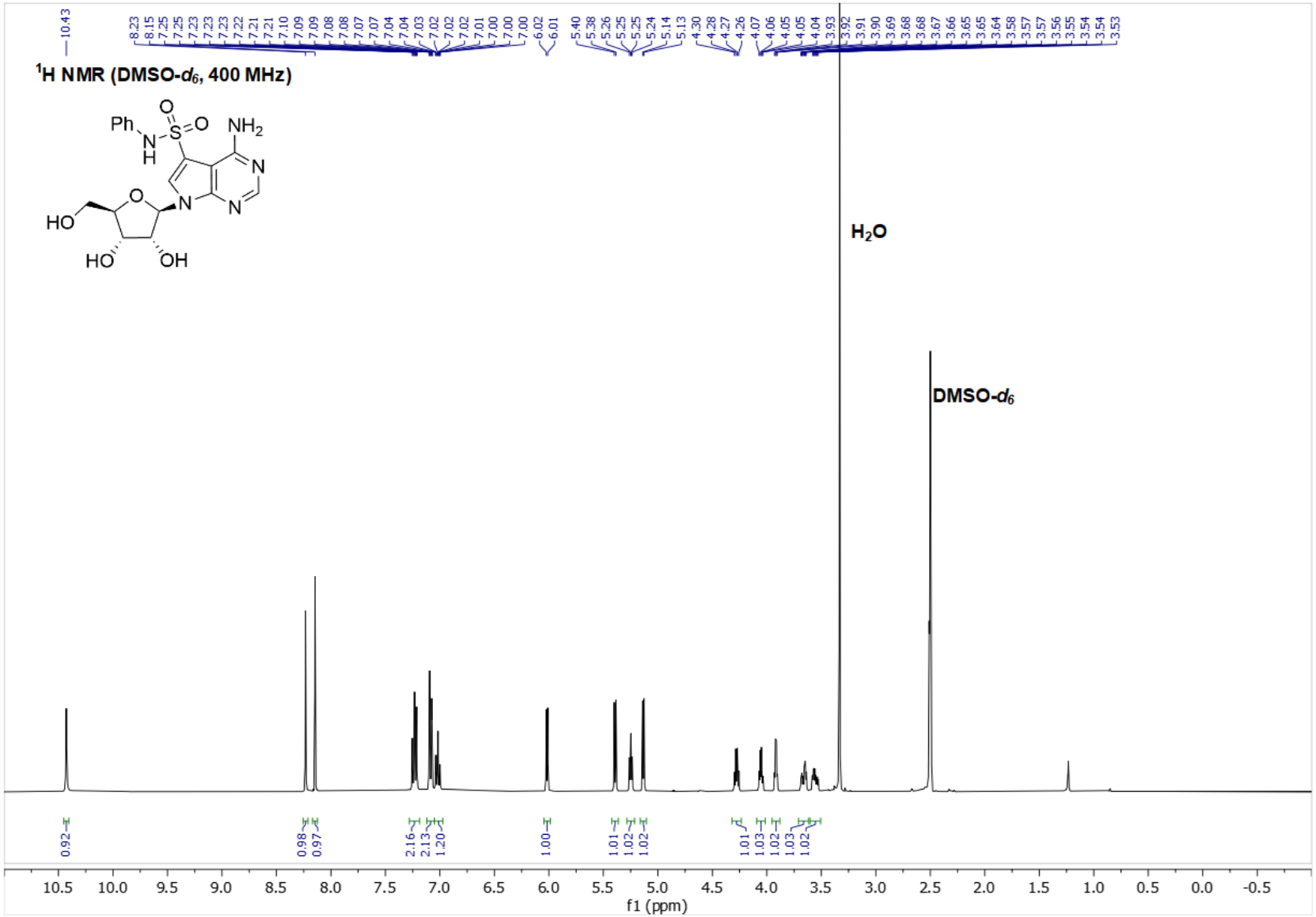


Figure S45. ^{1}H NMR spectra of compound **9p** measured in DMSO-d_6.

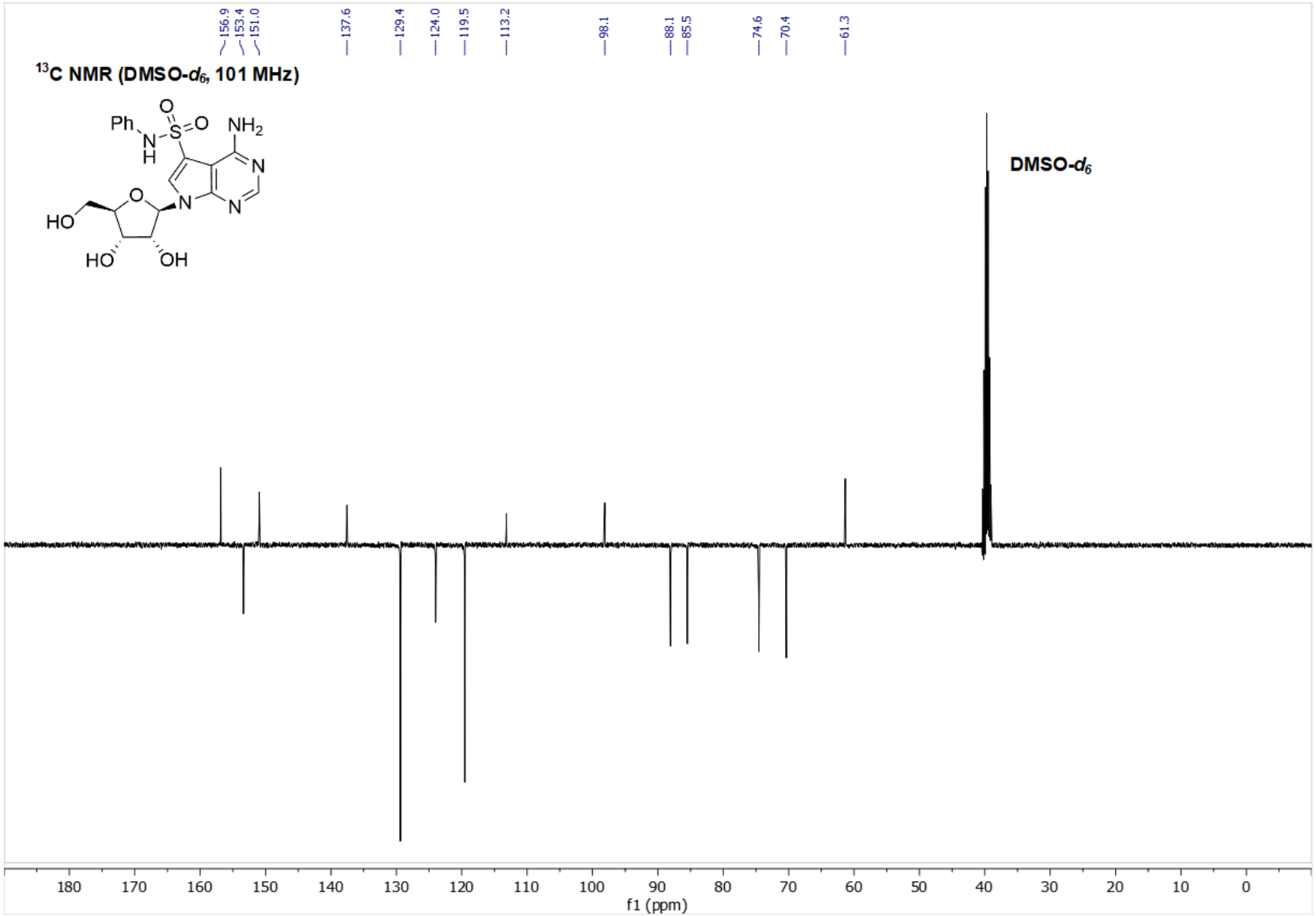


Figure S46. ^{13}C APT NMR spectra of compound **9p** measured in DMSO-d_6.

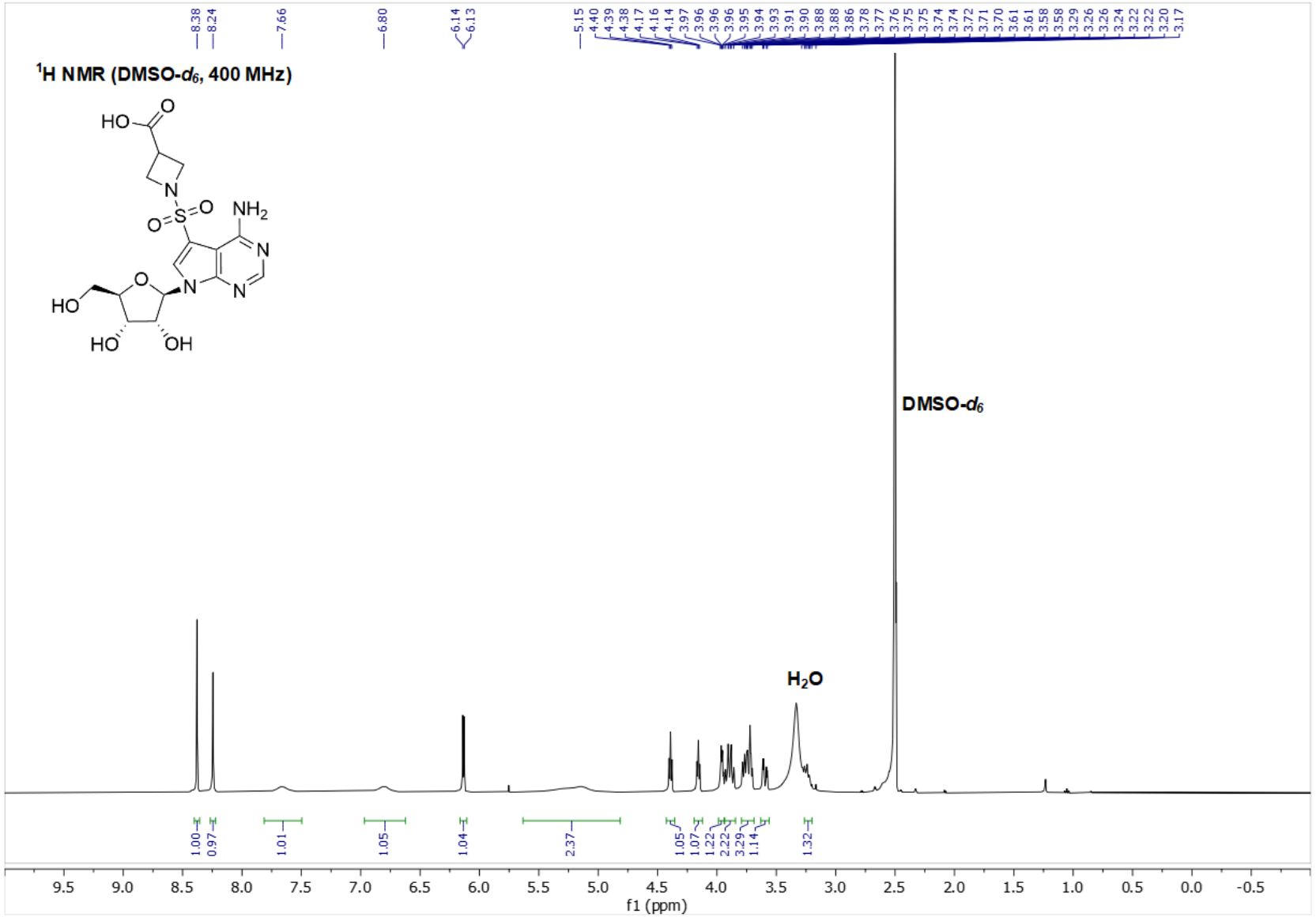


Figure S47. ^{1}H NMR spectra of compound **9q** measured in DMSO-d_6.

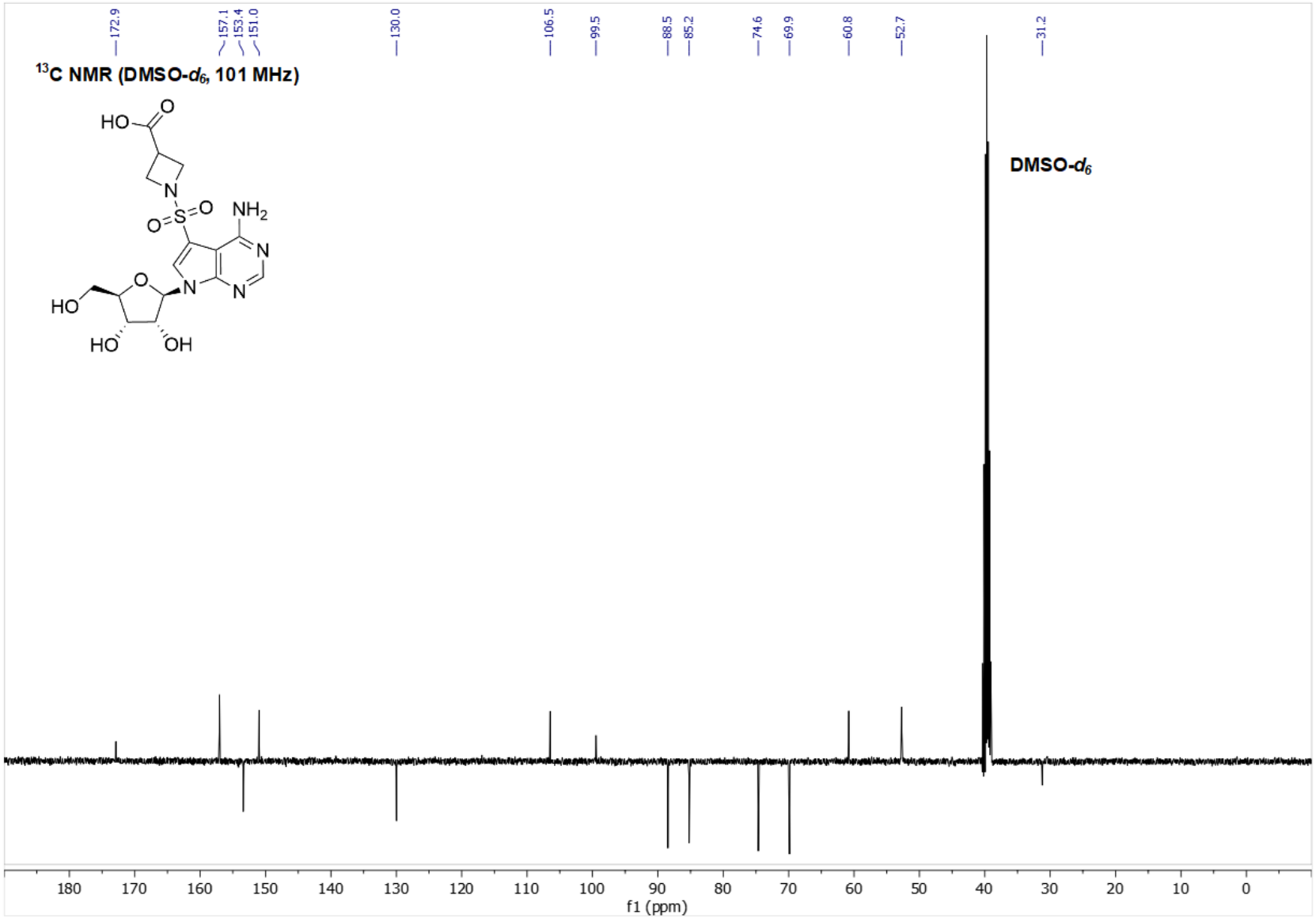


Figure S48. ^{13}C APT NMR spectra of compound **9q** measured in DMSO-d_6.

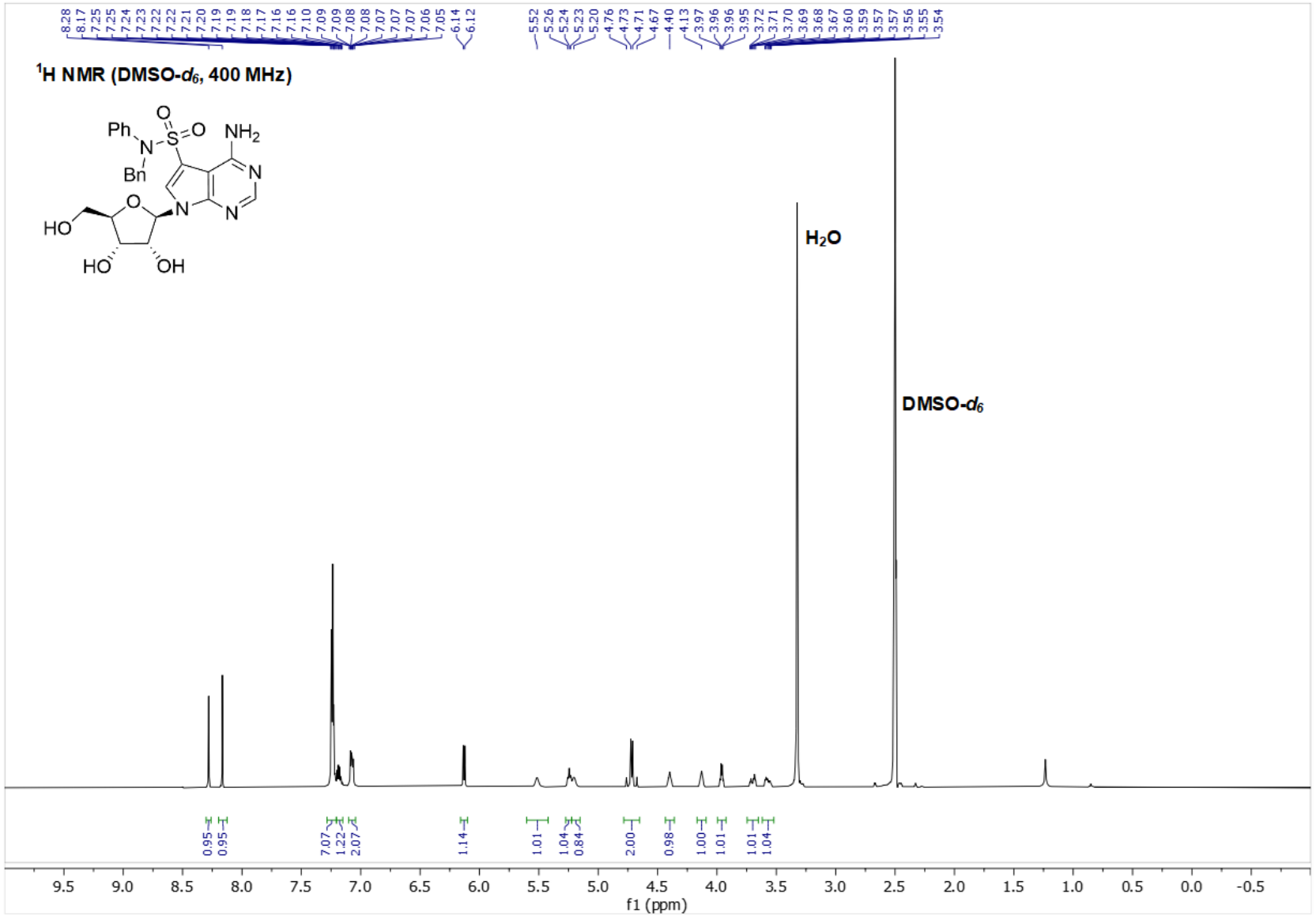


Figure S49. ^{1}H NMR spectra of compound **11** measured in DMSO-d_6.

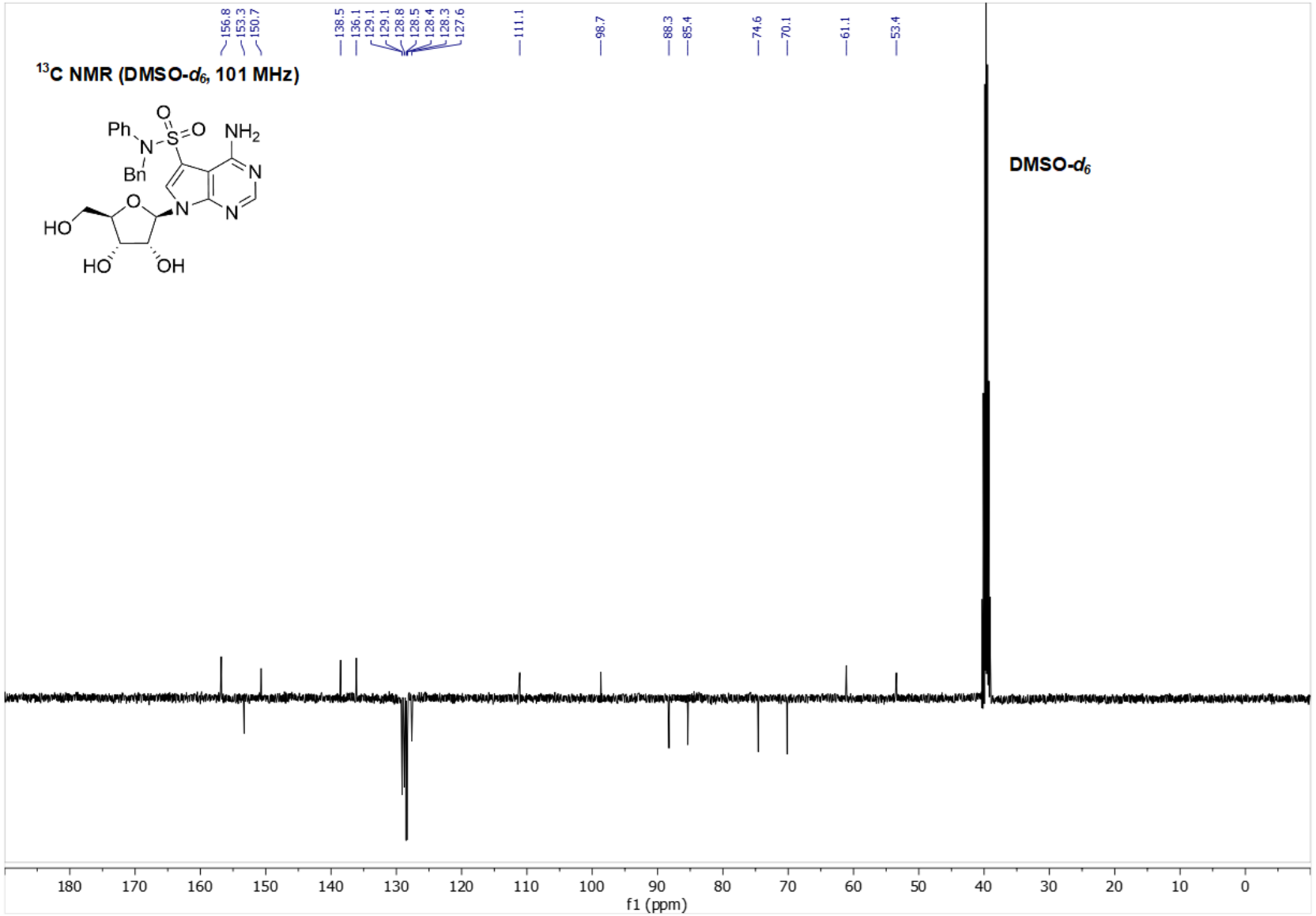


Figure S50. ^{13}C APT NMR spectra of compound **11** measured in DMSO-d_6.

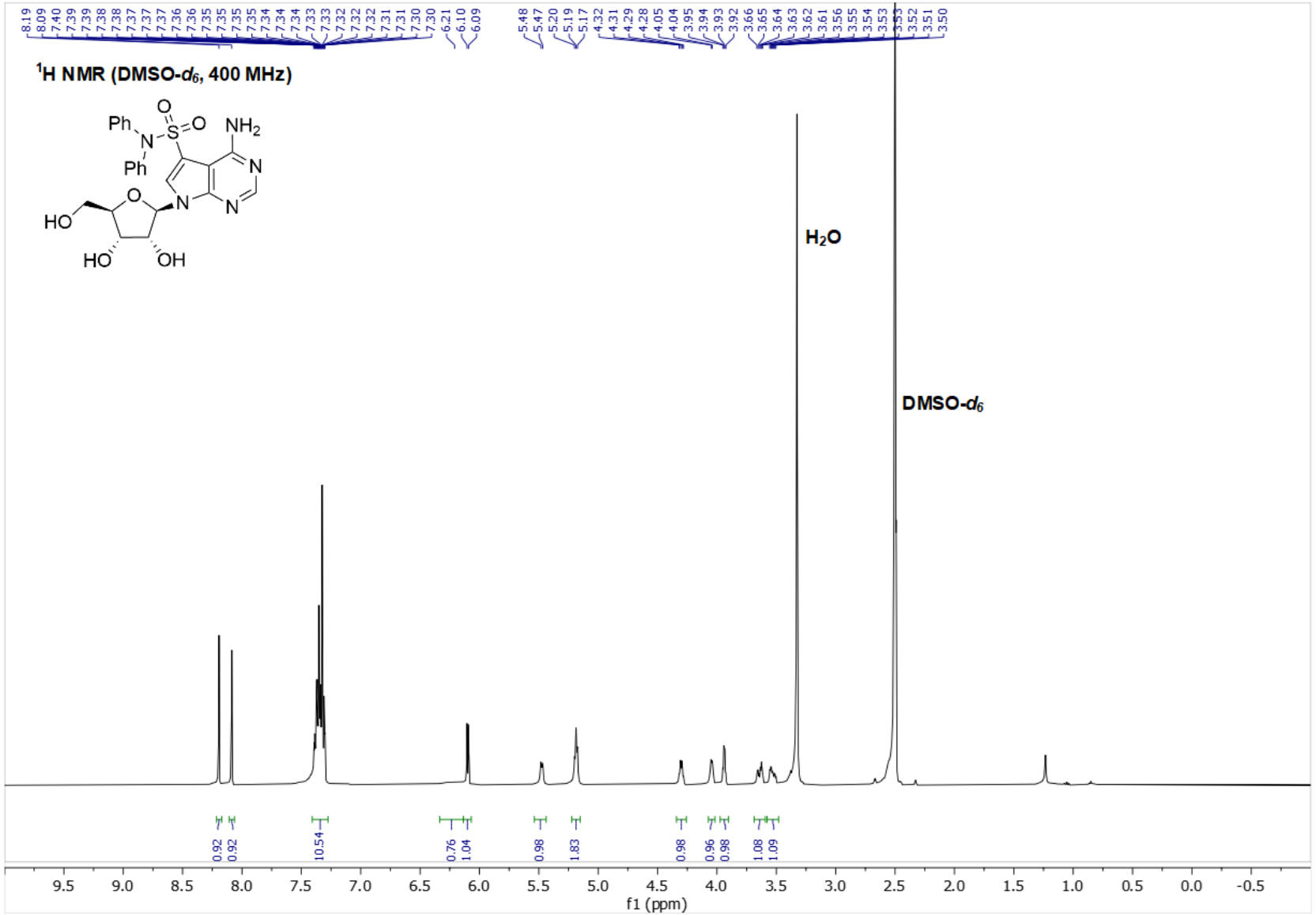


Figure S51. ^{1}H NMR spectra of compound **13** measured in DMSO-d_6.

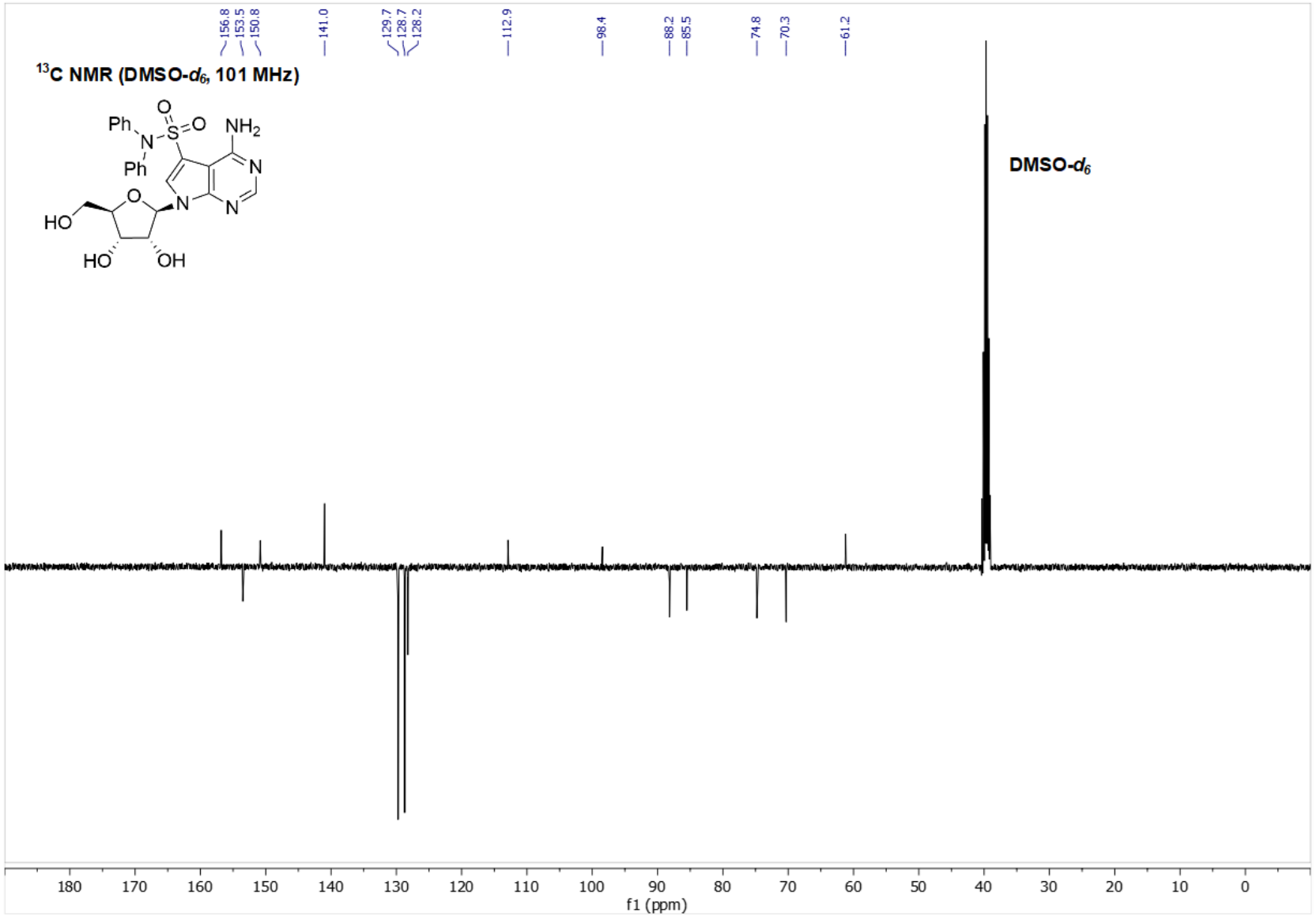


Figure S52. ^{13}C APT NMR spectra of compound **13** measured in DMSO-d_6.

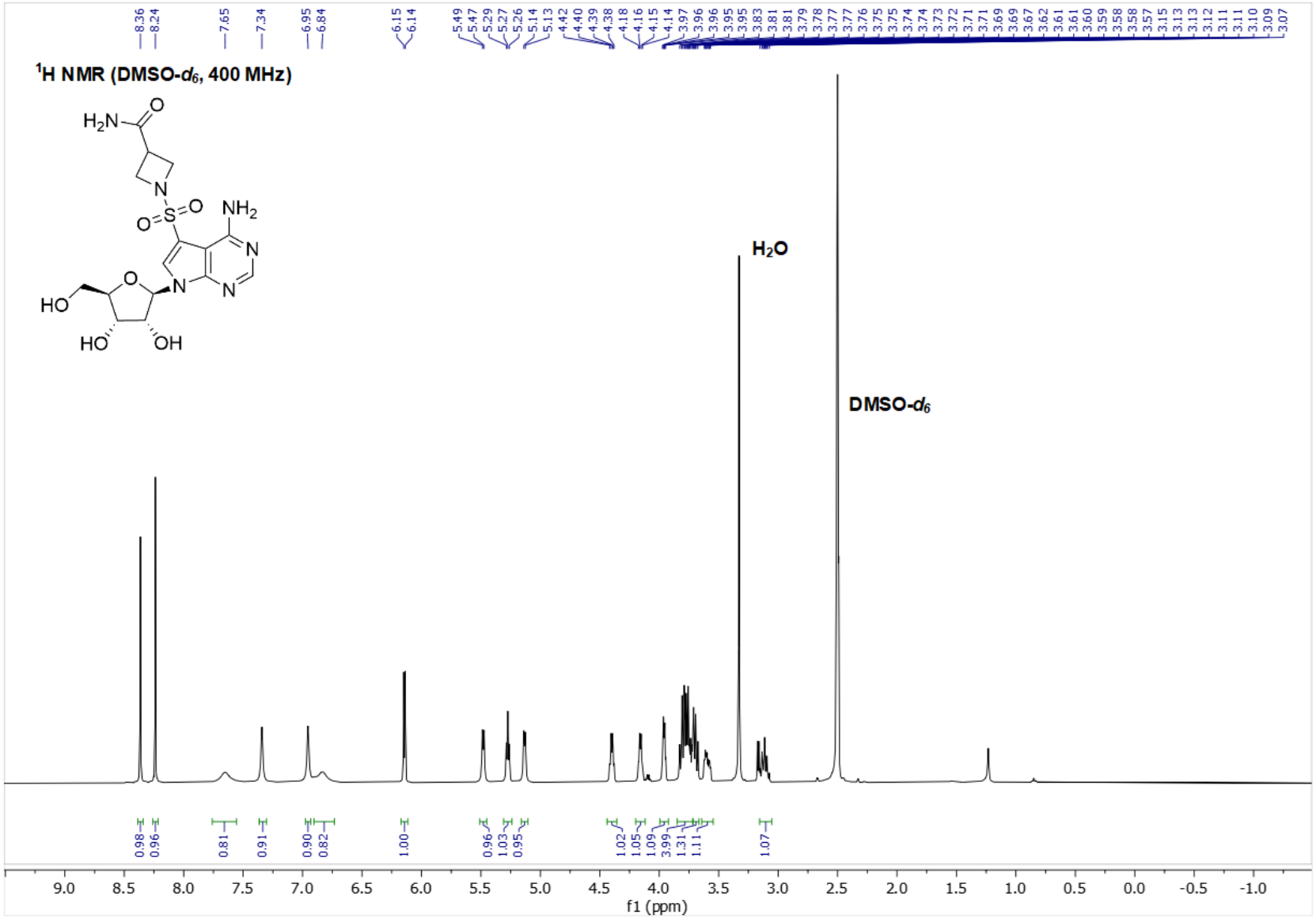


Figure S53. ^{1}H NMR spectra of compound **S2** measured in DMSO-d_6.

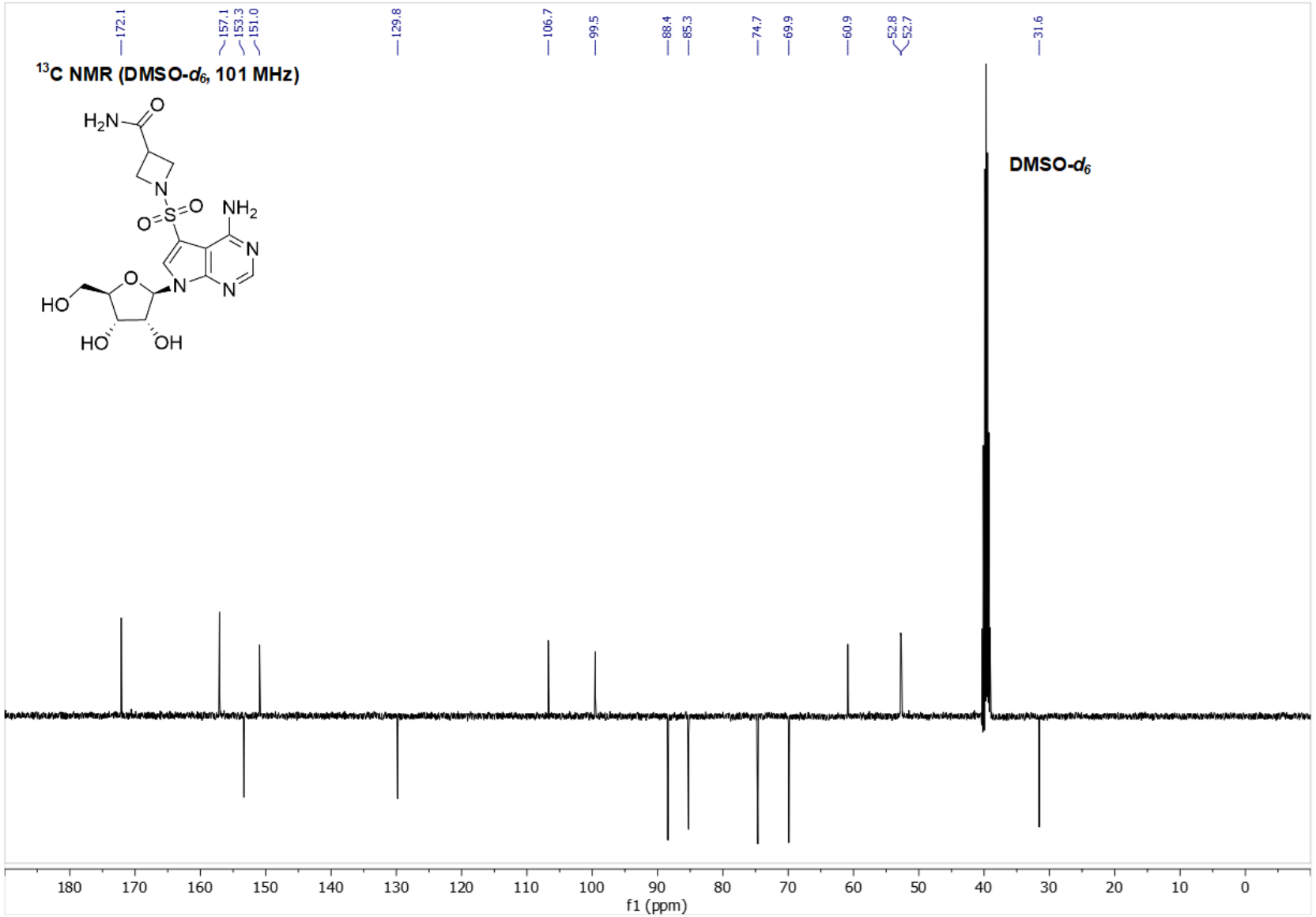


Figure S54. ^{13}C APT NMR spectra of compound **S2** measured in DMSO-d_6.

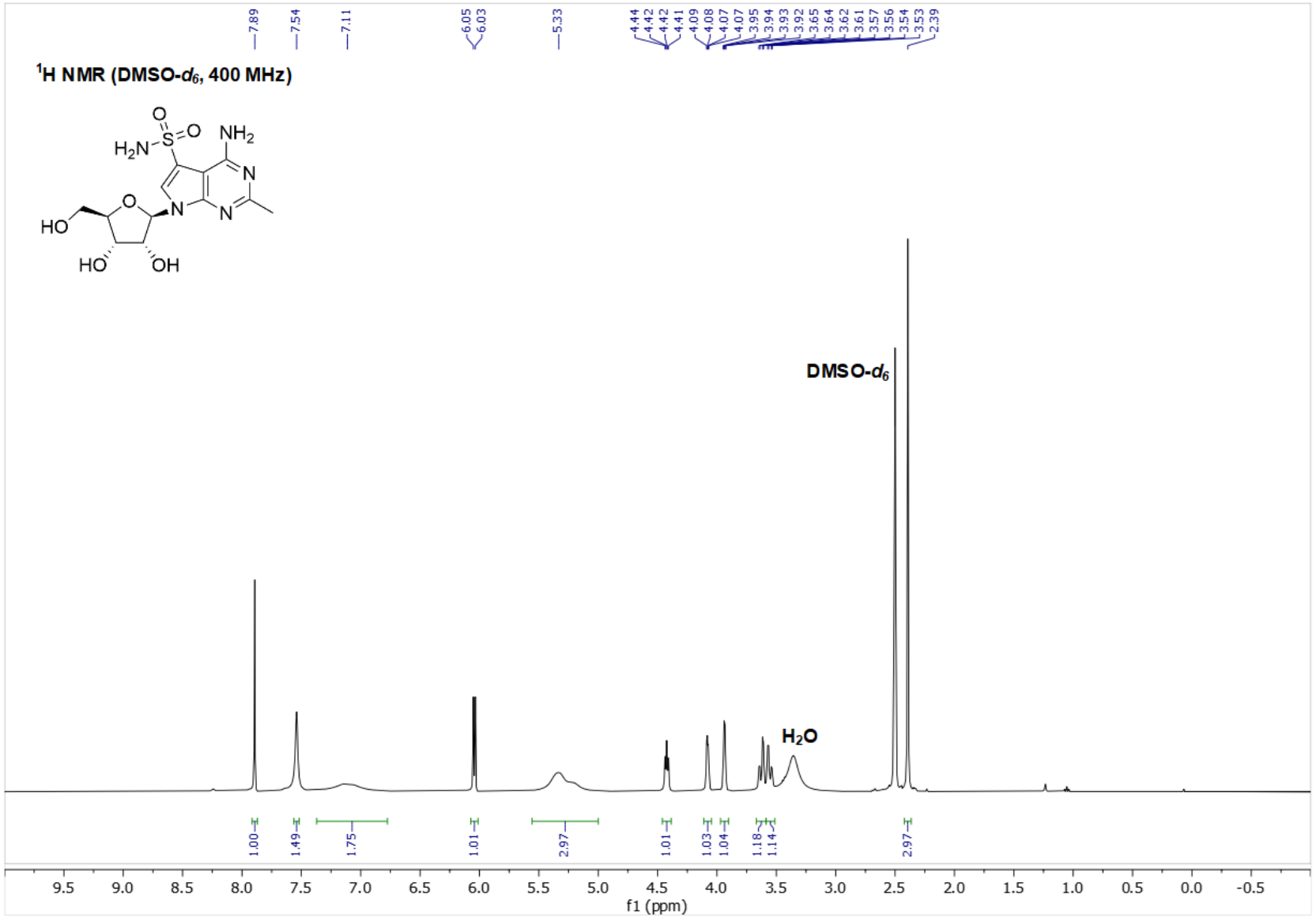


Figure S55. ^{1}H NMR spectra of compound **14** measured in DMSO-d_6.

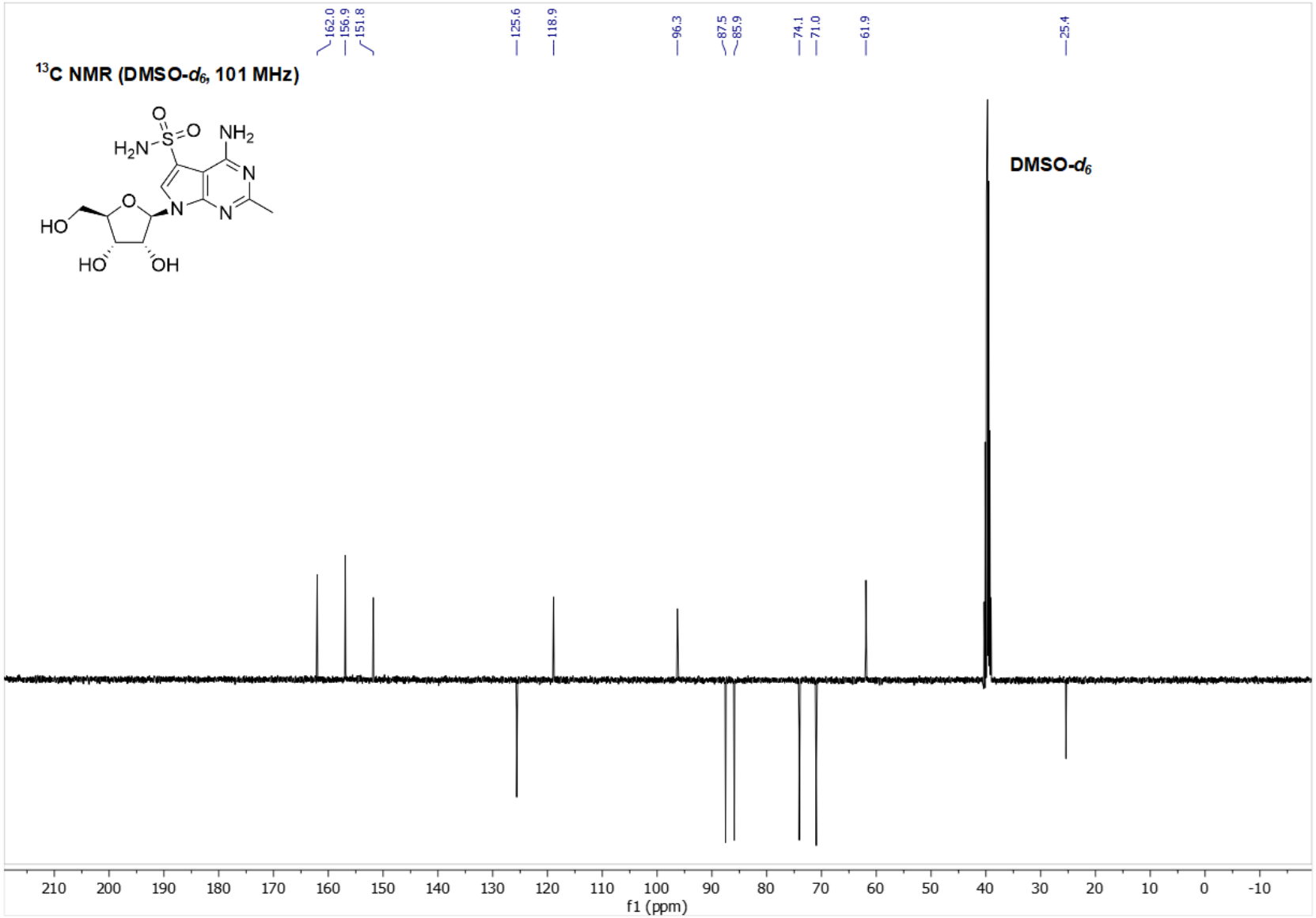


Figure S56. ^{13}C APT NMR spectra of compound **14** measured in DMSO-d_6.

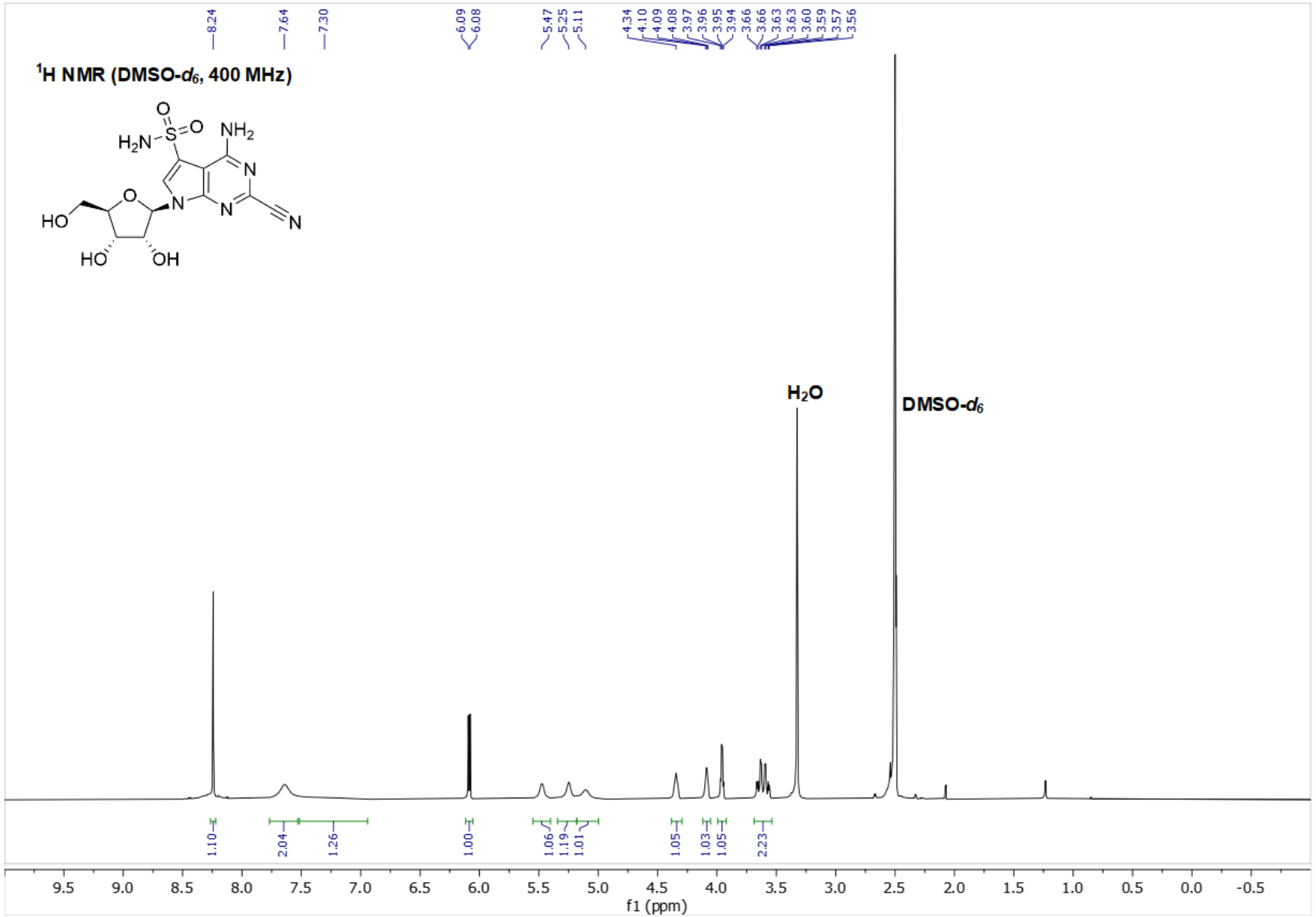


Figure S57. ^{1}H NMR spectra of compound **15** measured in DMSO-d_6.

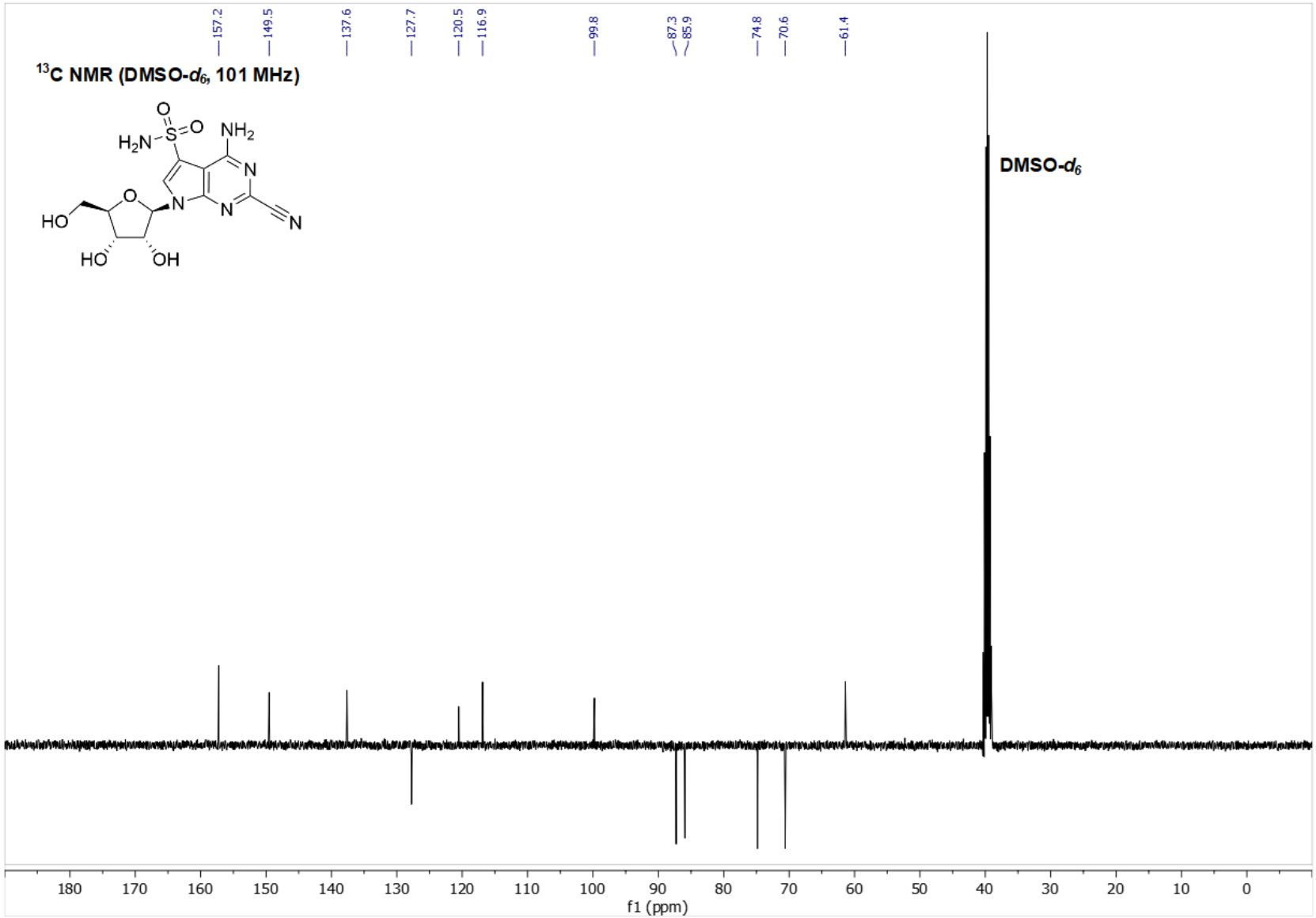


Figure S58. ^{13}C APT NMR spectra of compound **15** measured in DMSO-d_6.

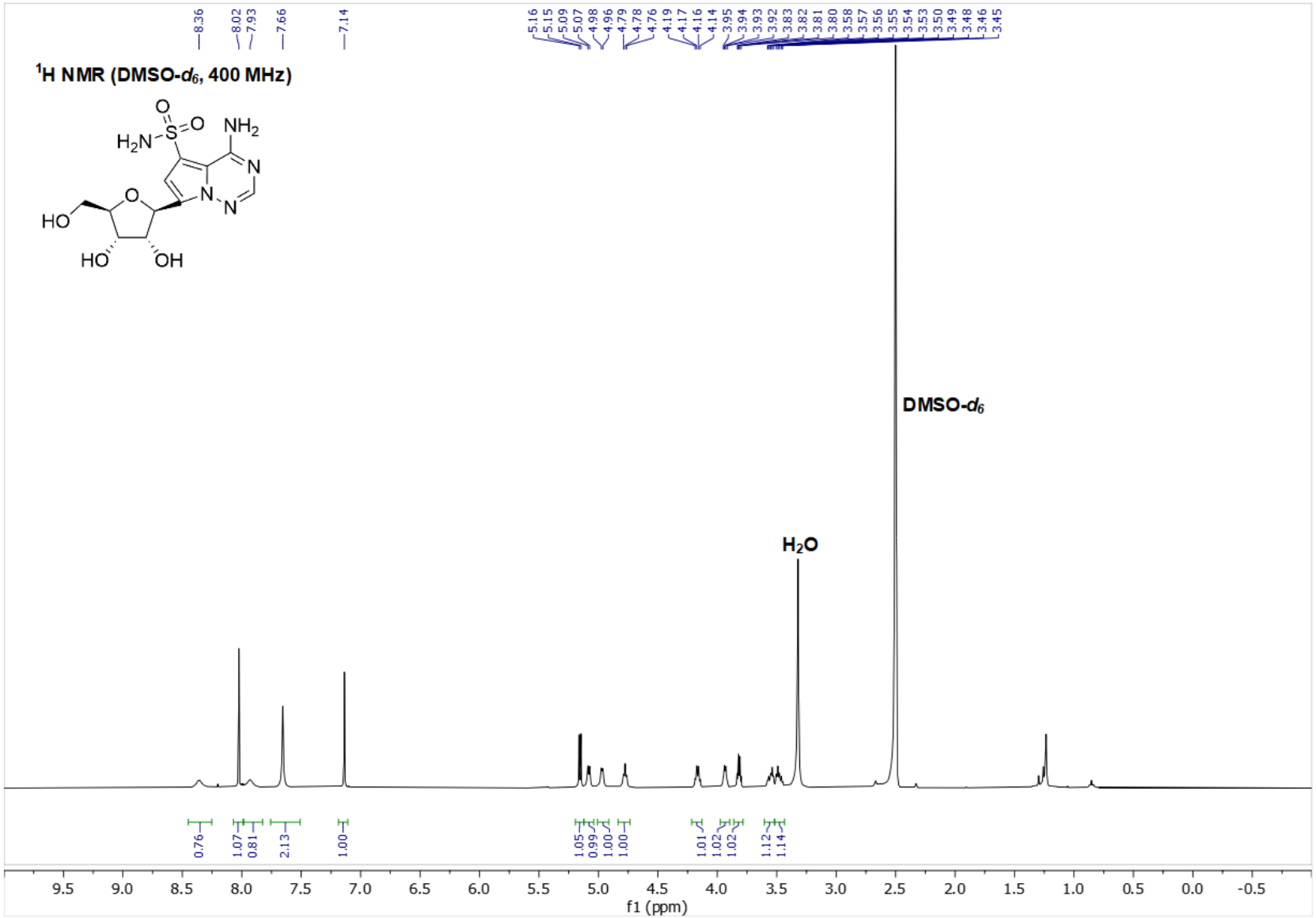


Figure S59. ^{1}H NMR spectra of compound **16** measured in DMSO-d_6.

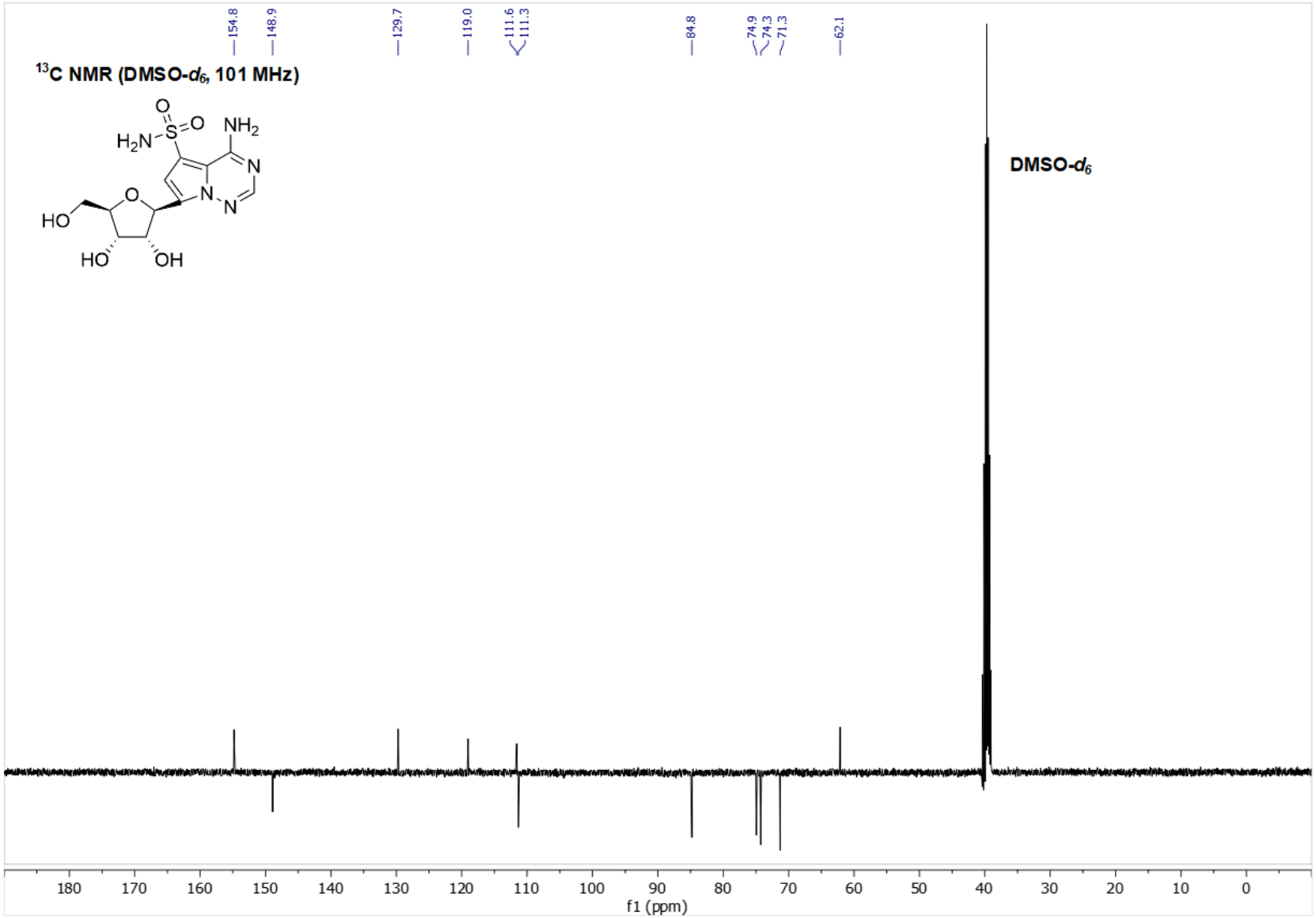


Figure S60. ^{13}C APT NMR spectra of compound **16** measured in DMSO-d_6.

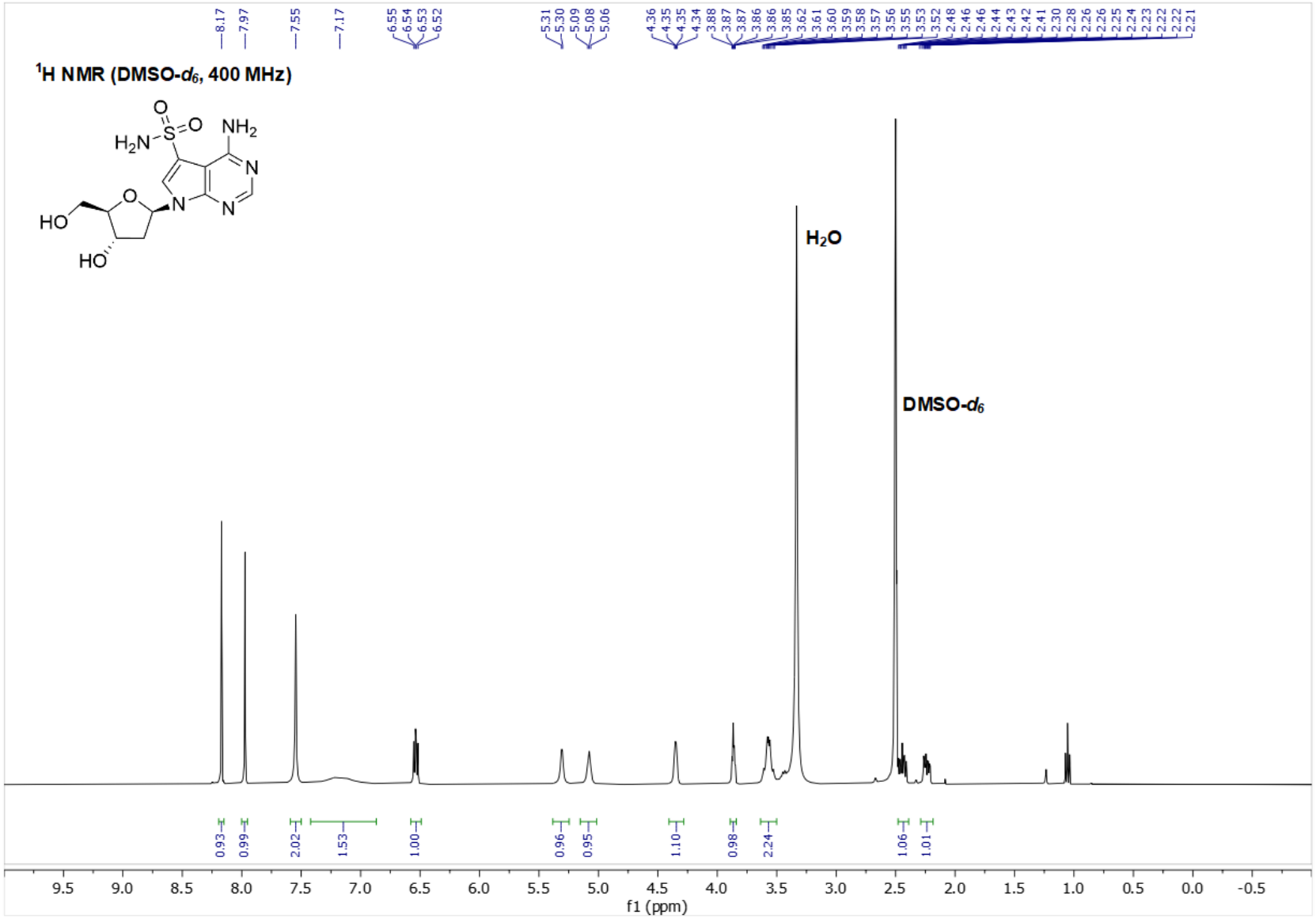


Figure S61. ^{1}H NMR spectra of compound **17** measured in DMSO-d_6.

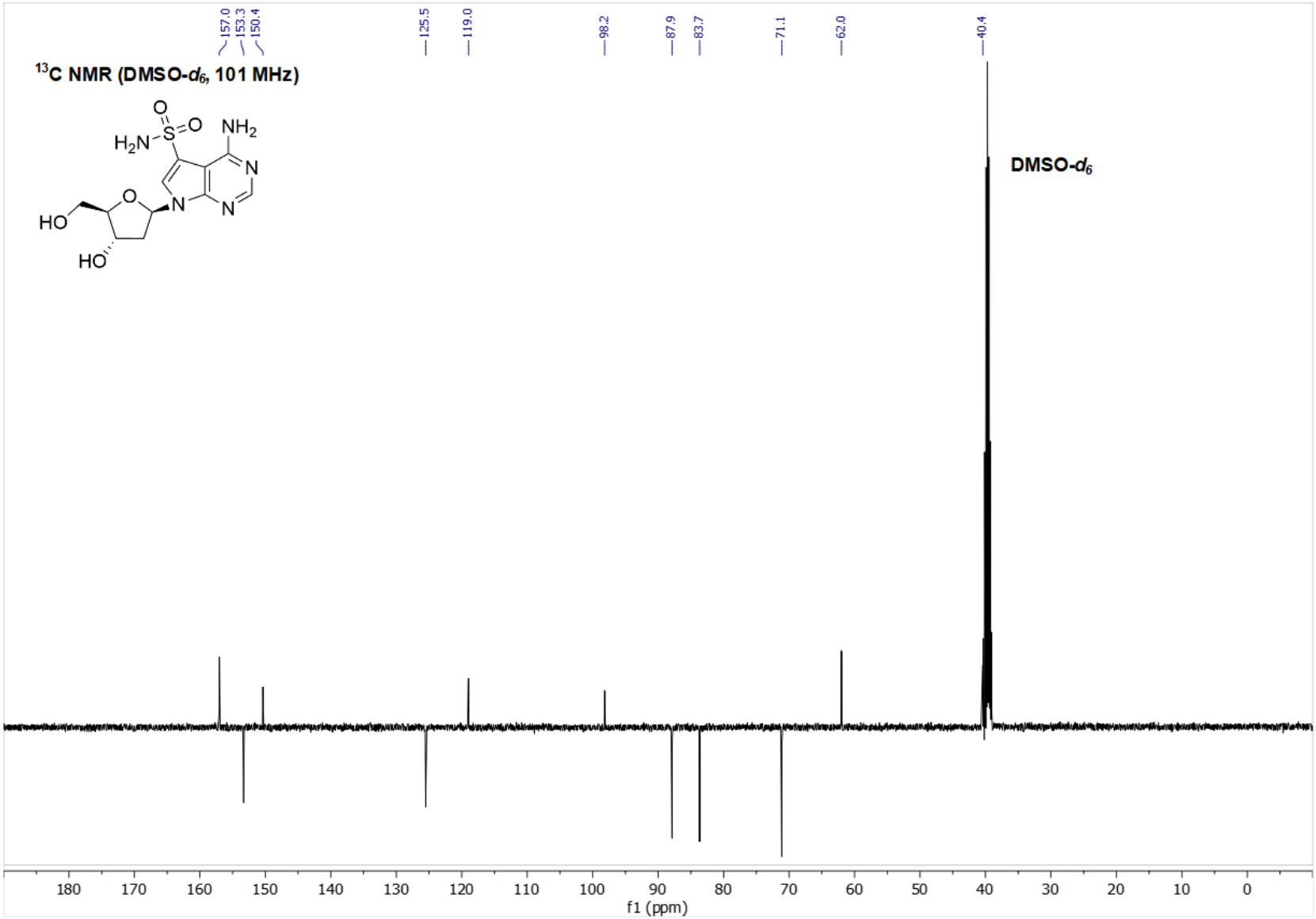


Figure S62. ^{13}C APT NMR spectra of compound **17** measured in DMSO-d_6.

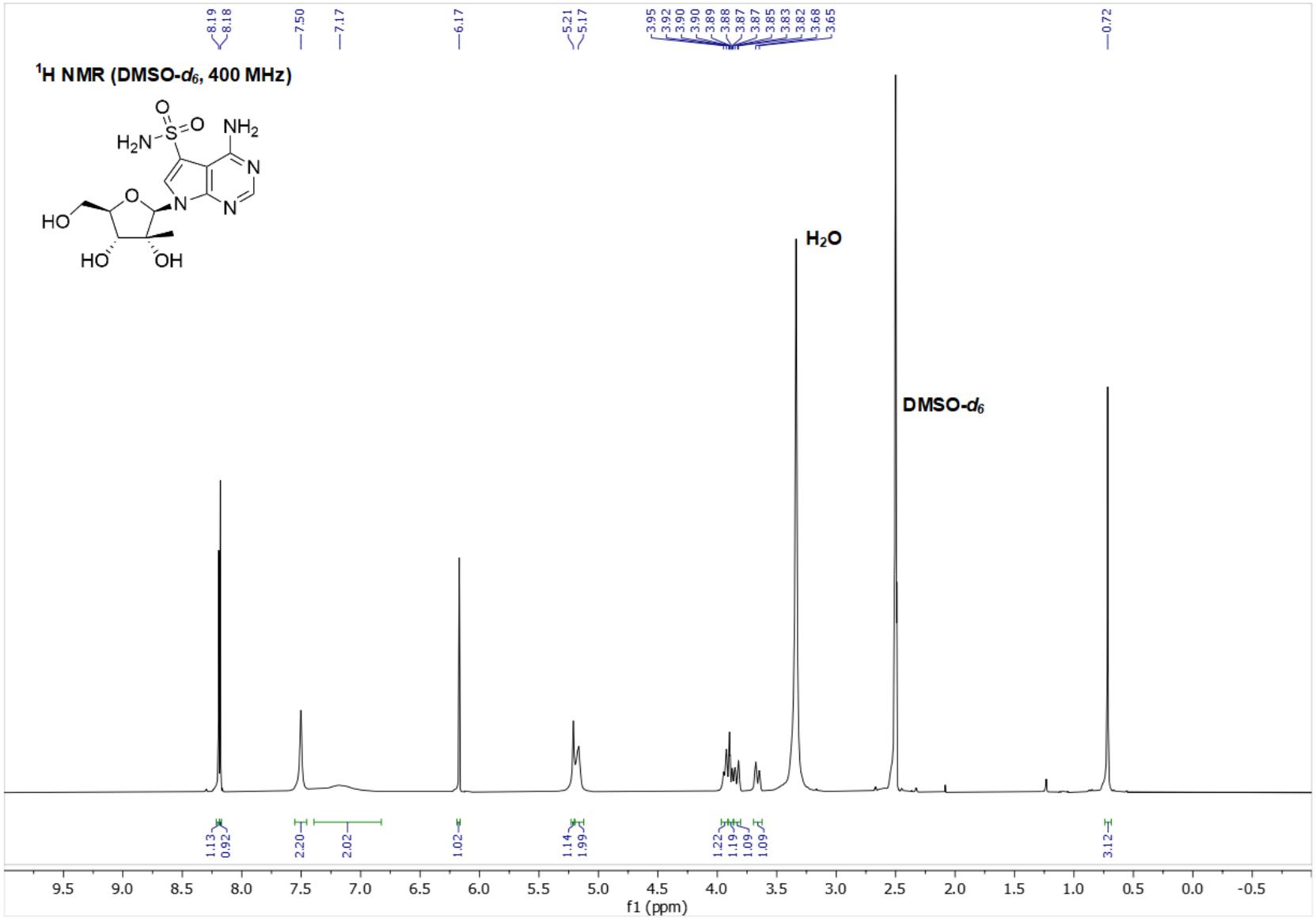


Figure S63. [1]H NMR spectra of compound **18** measured in DMSO-d_6.

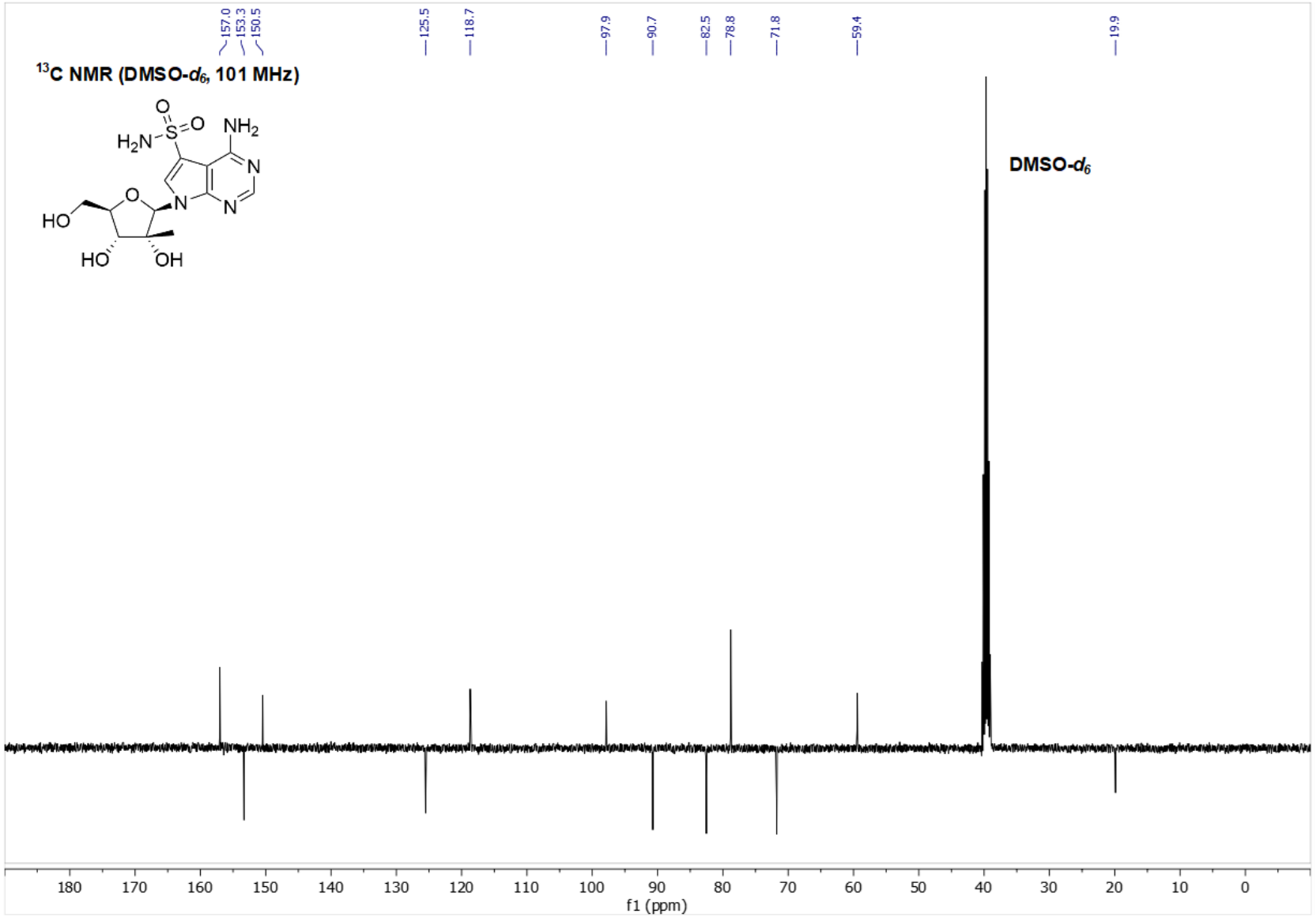


Figure S64. ^{13}C APT NMR spectra of compound **18** measured in DMSO-d_6.

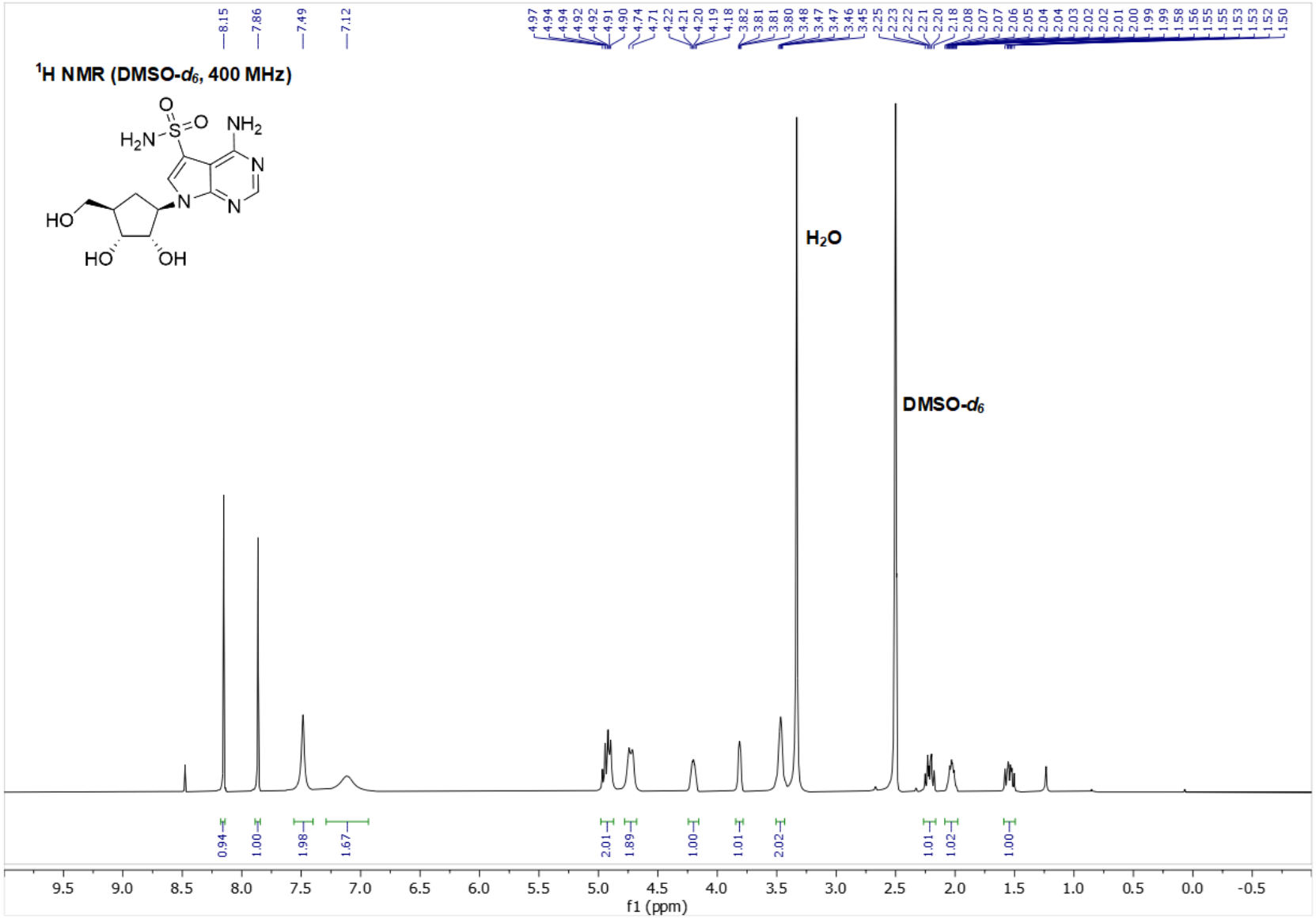


Figure S65. ^{1}H NMR spectra of compound **19** measured in DMSO-d_6.

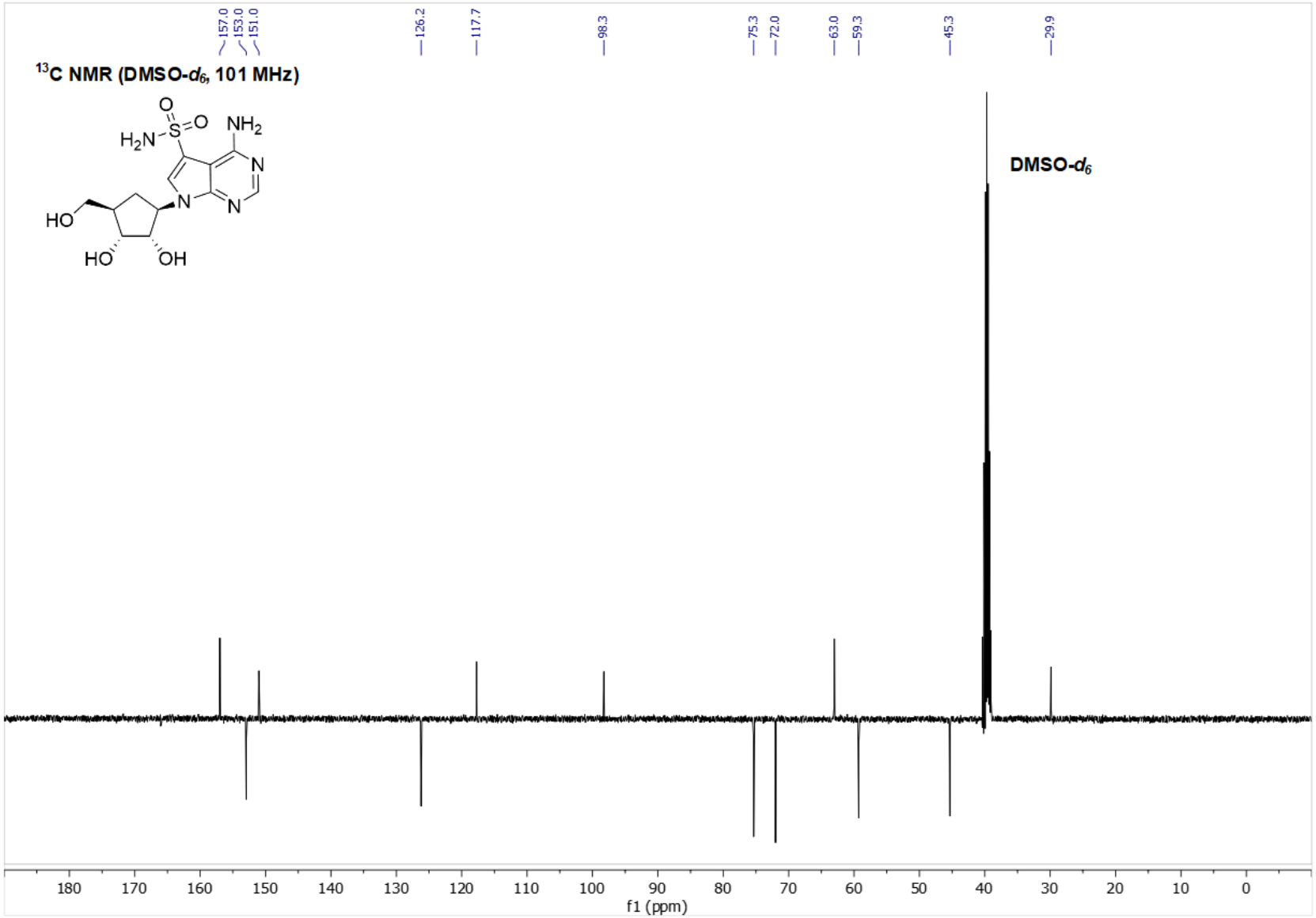


Figure S66. ^{13}C APT NMR spectra of compound **19** measured in DMSO-d_6.

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