Supporting information

Facile access to 4'-(*N*-acylsulfonamide) modified nucleosides and evaluation of their inhibitory activity against SARS-CoV-2 RNA cap *N*7-guanine-methyltransferase nsp14

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General

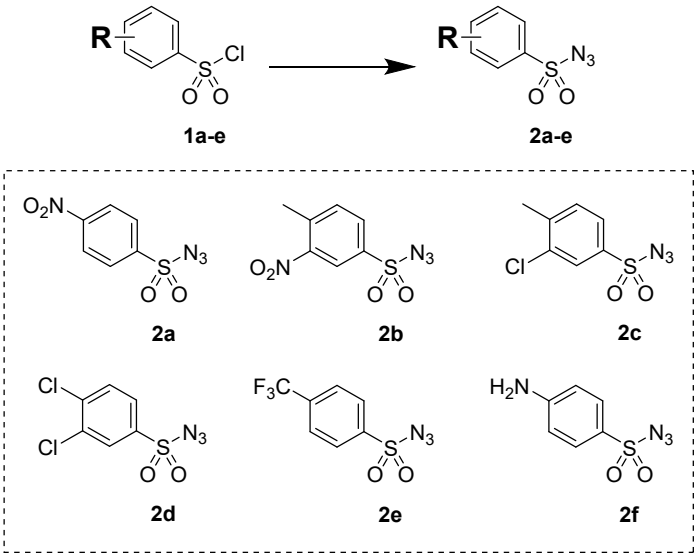
All dry solvents and reagents were purchased from commercial suppliers and were used without further purification. Thin-layer chromatography (TLC) analyses were carried out on 60 F-254 aluminium sheets. Purifications by column chromatography were performed using a Biotage Isolera 1 system with Column Flash Pure from Büchi. NMR experiments were recorded on Bruker 400, 500 or 600 spectrometers at 20°C. Chemical shifts are expressed in parts per million (ppm) relative to the residual solvent signal: $CDCl_3$ (δ_H = 7.26, δ_C = 77.36), CD_3OD (δ_H = 3.31, δ_C = 49.00 (CH_3), DMSO (δ_H = 2.5, δ_C = 39.52).[1] *J* values are in Hz. HRMS analyses were obtained with electrospray ionization (ESI) in positive or negative mode on a Q-TOF Micromass spectrometer. Analytical RP-HPLC was performed on a UHPLC Thermoscientific Ultimate3000 system equipped with a LPG-3400RS pump, a DAD 3000 detector and an WPS-3000TBRS Autosampler, Column Oven TCC-3000SD. Buffers and aqueous mobile-phases for RP-HPLC were prepared using water purified with a Milli-Q system (purified to 18.2 MΩ.cm). 4-aminobenzenesulfonyl azide **2f** and 9-Fluorenylmethyl thiol were synthesized as previously described.[2, 3]

RP-HPLC analysis: System A: RP-HPLC (Accucore™ C18 aQ column, 2.6 μm, 4.6×50 mm) with CH_3CN and 0.1% aqueous trifluoroacetic acid (aq. TFA, 0.1%, v/v, pH 2.0) as the eluents [0% CH_3CN (2 min), followed by linear gradient from 0 to 100% (25 min) of CH_3CN] at a flow rate of 1 mL.min^{-1}. Triple UV detection was achieved at 210, 260 and 650 nm.

The purity of the final compounds was determined by RP-HPLC analysis with detection at 260 nm. Under this condition we did not notice any depurination as demonstrated by the NMR spectra and the purity provided.

Chemical synthesis

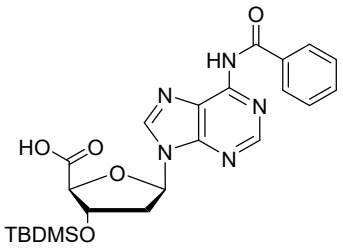
General method for the synthesis of sulfonyl azide derivatives (2a-e)



To a solution of commercially available sulfonyl chloride **1a-e** at 0.1 M in dry MeCN was added NaN_3 (2 eq.). The solution was stirred at 60°C for 16 h. Thereafter, the solution was diluted by 10 with AcOEt, washed by water and brine. The organic layer was dried over Na_2SO_4, filtrated and evaporated to dryness. The resulting sulfonyl azide derivative **2a-e** was used for the sulfo-click reaction without further purification or analysis.

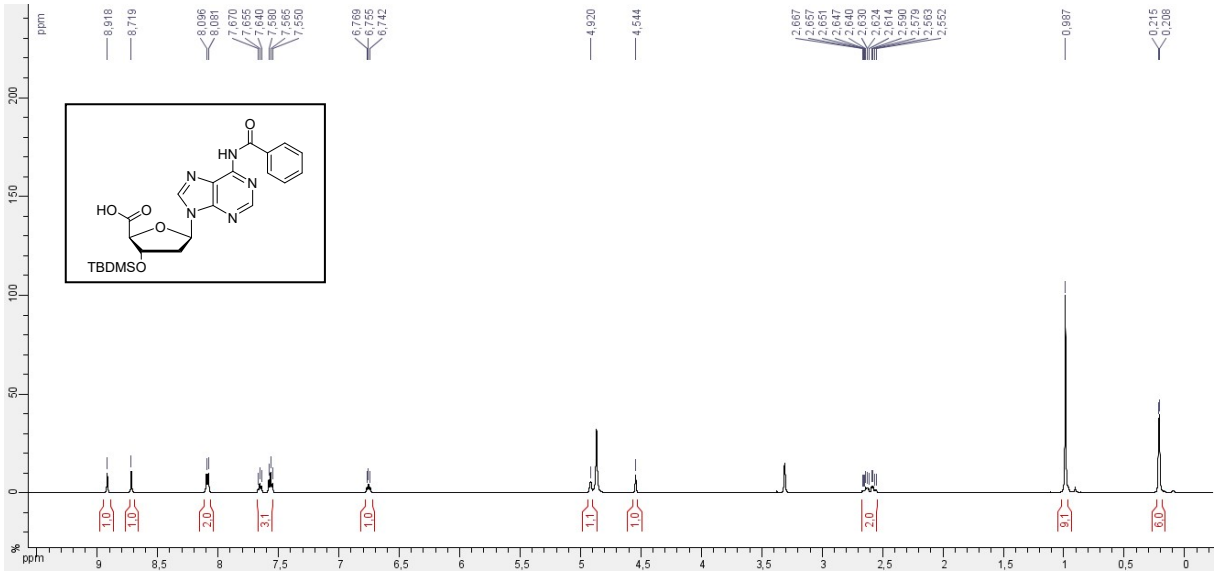
Synthesis of tetrabutylammonium thioacetate derivatives

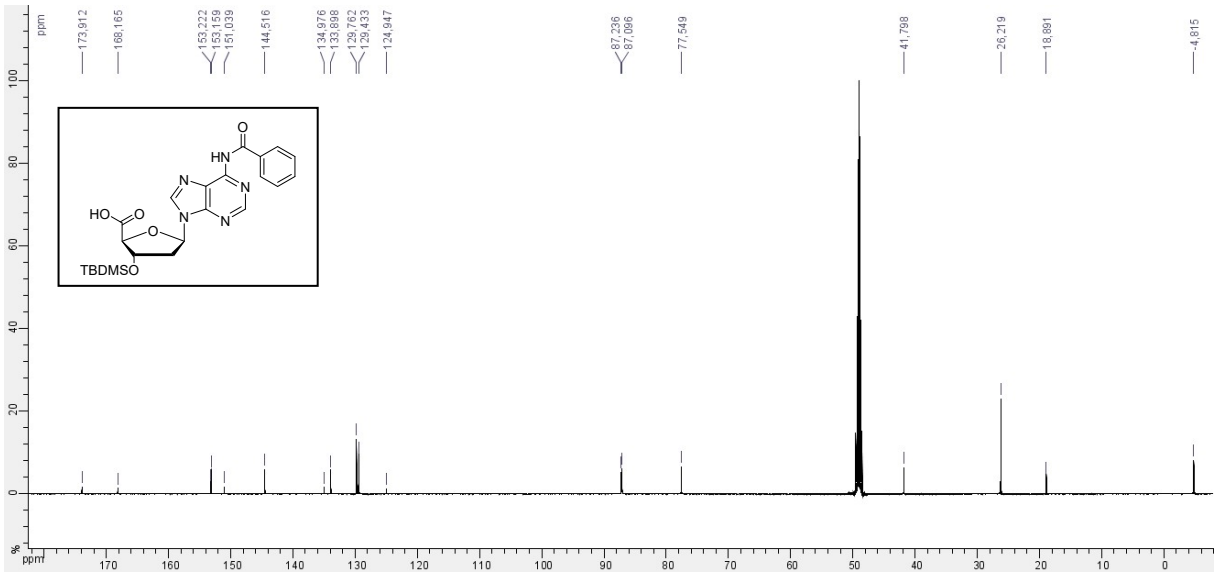
4'-carboxylic acid-3'-*O*-TBDMS-2'-deoxy-*N*-Bz-adenosine (4a)



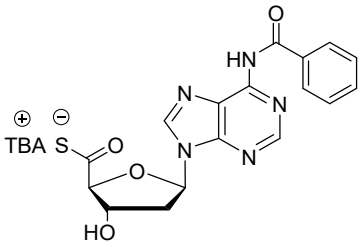
3'-*O*-TBDMS-adenosine **3a** (1.0 g, 2.1 mmol) was dissolved in a mixture of CH_3CN-H_2O (10 mL, 1:1, v/v). Thereafter, BAIB (1.51 g, 4.7 mmol) and TEMPO (70 mg, 0.4 mmol) were sequentially added. The resulting mixture was stirred at room temperature for 3h. The reaction was checked for completion by TLC (DCM-MeOH, 9:1, v/v) and the solvent was evaporated under reduced pressure. The resulting yellow powder was triturated with *n*-pentane at 0°C. The resulting white solid in suspension was filtrated and dried under vacuum giving the product **4a** as a white powder (804 mg, 1.6 mmol, 78%). ^{1}H NMR (500 MHz, MeOD) δ = 0.21 (s, 3H), 0.22 (s, 3H), 0.99 (s, 9H), 2.55-2.67 (m, 2H), 4.54 (bs, 1H), 4.92 (bs, 1H), 6.76 (t, *J* = 6.8 Hz, 1H), 7.55-7.67 (m, 3H), 8.09 (d, *J* = 7.6 Hz, 2H), 8.72 (s,1H), 8.92 (s, 1H) ppm. ^{13}C NMR (125 MHz, MeOD): δ = -4.8, 18.9, 26.2, 41.8, 77.5, 87.1, 87.2, 124.9, 129.4, 129.8, 133.9, 135.0, 144.5, 151.0, 153.16, 153.22, 168.2, 173.9 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{29}N_5O_5Si$: 484.2016; found 484.2022. R_f (DCM-MeOH, 9:1, v/v) 0.17.

^{1}H and ^{13}C NMR Spectra (MeOD)





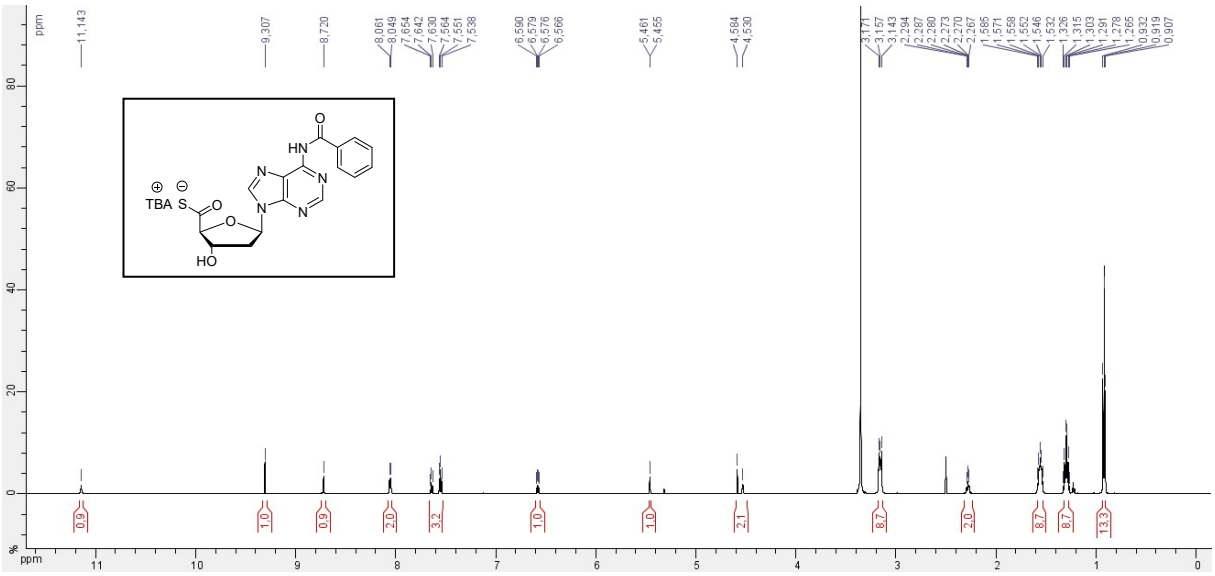
4'-tetrabutylammonium thioacetate-2'-deoxy-*N*-Bz-adenosine (6a)

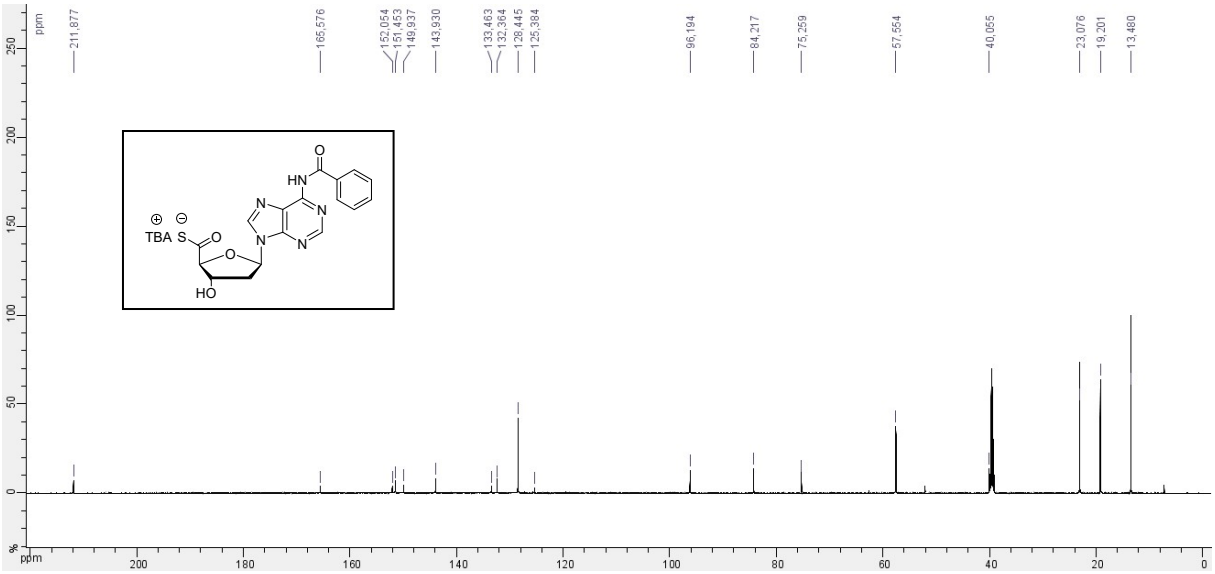


(a) Coupling reaction: 4'-carboxylic acid-3'-*O*-TBDMS-2'-deoxy-*N*-Bz-adenosine **4a** (400 mg, 800 μmol) was dissolved in dry DMF (5 mL). Thereafter, 9-fluorenylmethanethiol (200 mg, 1.0 mmol), BOP reagent (530 mg, 1.2 mmol) and dry DIEA (230 μL, 2.4 mmol) were sequentially added. The resulting mixture was stirred at room temperature for 3h. The reaction was checked for completion by TLC (DCM-MeOH, 9 : 1, v/v), then diluted with AcOEt (100 mL), washed by aq. 10% citric acid (100 mL), aq. sat. $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, filtrated and evaporated to dryness. The resulting residue was purified by chromatography on a silica gel column with a linear gradient of AcOEt (0-80%) in cyclohexane as the mobile phase, giving the 4'-(9-fluorenylmethyl thioester)-3'-*O*-TBDMS-2'-deoxy-*N*-Bz-adenosine **5a** as a white powder (460 mg, 670 μmol, 84%).

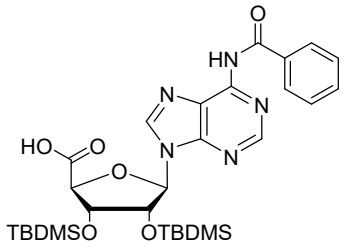
(b) Deprotection: 4'-(9-fluorenylmethyl thioester)-3'-*O*-TBDMS-2'-deoxy-*N*-Bz-adenosine **5a** (250 mg, 400 μmol) was dissolved in dry THF (3 mL). Thereafter, a solution of TBAF 1M in THF (950 μL, 950 μmol) was added. The resulting mixture was stirred at room temperature for 3 h. The reaction was checked for completion by RP-HPLC (system A). The crude was diluted with DCM (10 mL) and the resulting mixture purified by chromatography on a silica gel column in with a linear gradient of MeOH (0-20%) in DCM as the mobile phase, giving the product **6a** as a white amorphous powder after lyophilization in H_2O (202 mg, 330 μmol, 83%). R_f (DCM-MeOH, 9:1, v/v) = 0.1. ^{1}H NMR (600 MHz, DMSO) δ = 0.92 (t, J = 7.3 Hz, 12H), 1.30 (hex., J = 7.4 Hz, 8H), 1.53-1.59 (m, 8H), 2.27-2.29 (m, 2H), 3.14-3.17 (m, 8H), 4.53 (bs, 1H), 4.58 (s, 1H), 5.46 (d, J = 3.6 Hz, 1H), 6.57-6.59 (m, 1H), 7.54-7.65 (m, 3H), 8.05 (d, J = 7.6 Hz, 1H), 8.72 (s, 1H), 9.31 (s, 1H), 11.14 (s, 1H) ppm. ^{13}C NMR (150 MHz, DMSO) δ = 13.5, 19.2, 23.1, 40.1, 57.6, 75.3, 84.2, 96.2, 125.4, 128.4, 132.4, 133.5, 143.9, 151.5, 152.1, 165.6, 211.9 ppm. HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{17}H_{14}N_5O_4S$: 384.0766; found 384.0772.

^{1}H and ^{13}C NMR Spectra (DMSO)



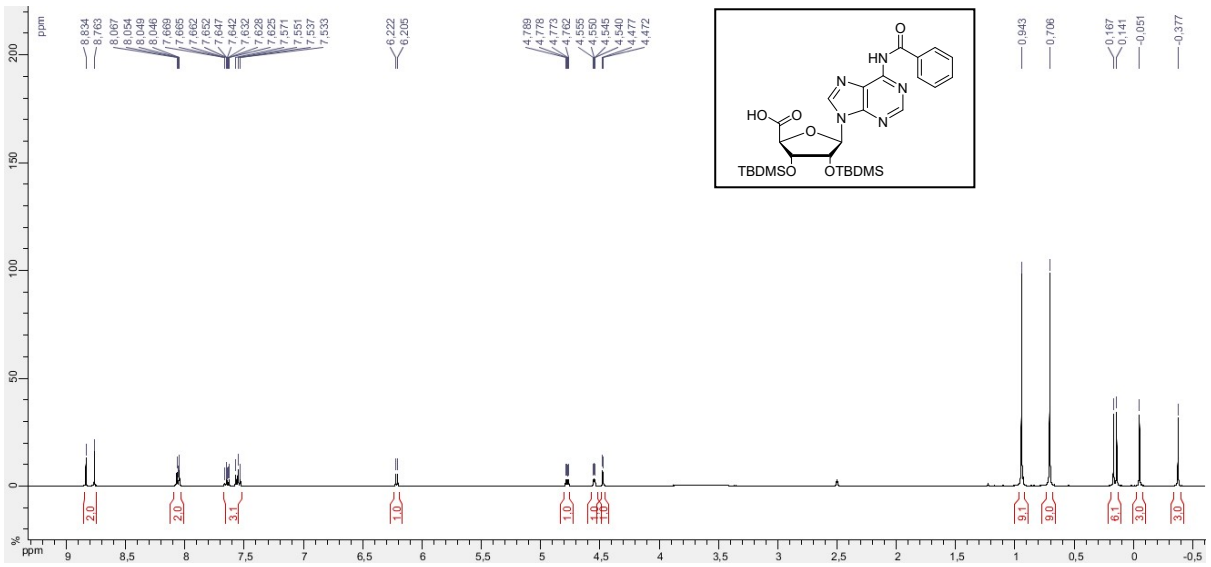


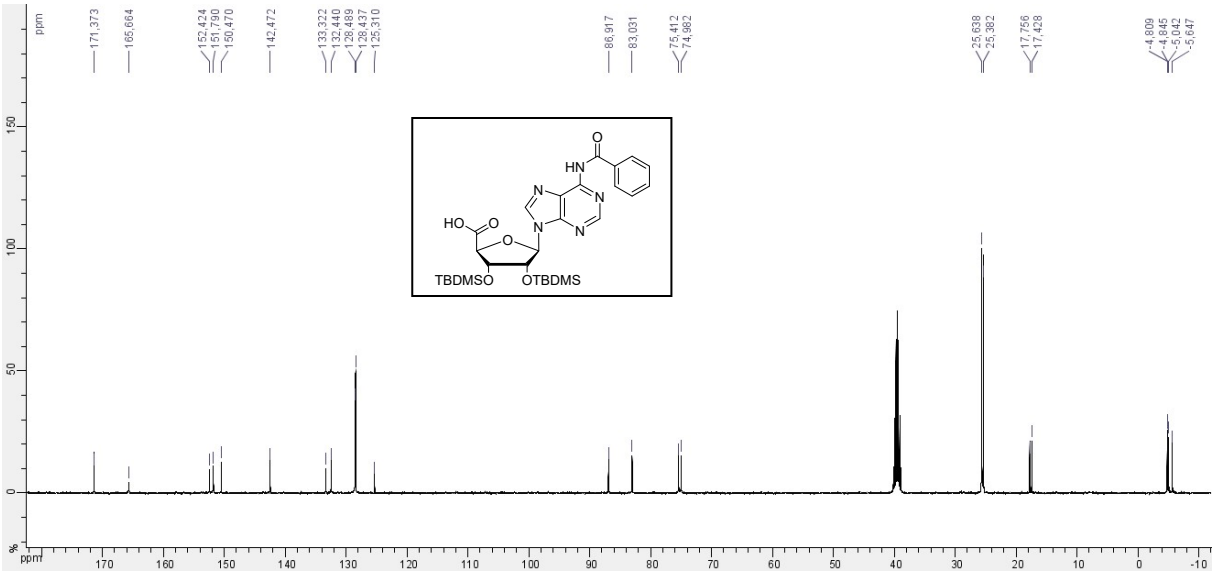
4'-carboxylic acid-2',3'-*O*-TBDMS-*N*-Bz-adenosine (4b)



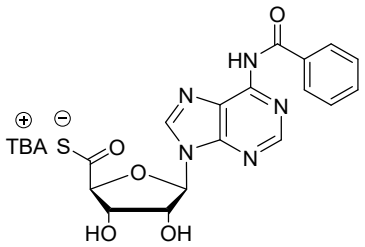
2',3'-*O*-TBDMS-adenosine **3b** (500 mg, 834 mmol) was dissolved in a mixture of CH_3CN-THF-H_2O (15 mL, 1:1:1, v/v/v). Thereafter, BAIB (538 mg, 1.7 mmol) and TEMPO (52 mg, 334 μmol) were sequentially added. The resulting mixture was stirred at room temperature for 16 hours. The reaction was checked for completion by TLC (DCM-MeOH, 9:1, v/v) and the solvent was evaporated under reduced pressure. The resulting residue was purified by chromatography on a silica gel column in with a linear gradient of MeOH (0-8%) in DCM as the mobile phase, giving the product **4b** as a white powder (373 mg, 608 μmol, 87%). ^{1}H NMR (400 MHz, DMSO) δ = -0.38 (s, 3H), -0.05 (s, 3H), 0.14 (s, 3H), 0.17 (s, 3H), 0.71 (s, 9H), 0.94 (s, 9H), 4.47 (d, J = 1.9 Hz, 1H), 4.54-4.56 (m, 1H), 4.76-4.79 (m, 1H), 6.21 (s, J = 6.5 Hz, 1H), 7.53-7.67 (m, 3H), 8.05-8.07 (m, 2H), 8.76 (s, 1H), 8.83 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = -5.6, -5.0, -4.85, -4.81, 17.4, 17.8, 25.4, 25.6, 75.0, 75.4, 83.0, 86.9, 125.3, 128.44, 128.49, 132.4, 133.3, 142.5, 150.5, 151.8, 152.4, 165.7, 171.4 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{42}N_5O_6Si_2$: 612.2679; found 612.2690. R_f (DCM-MeOH, 9:1, v/v) 0.5.

^{1}H and ^{13}C NMR Spectra (DMSO)





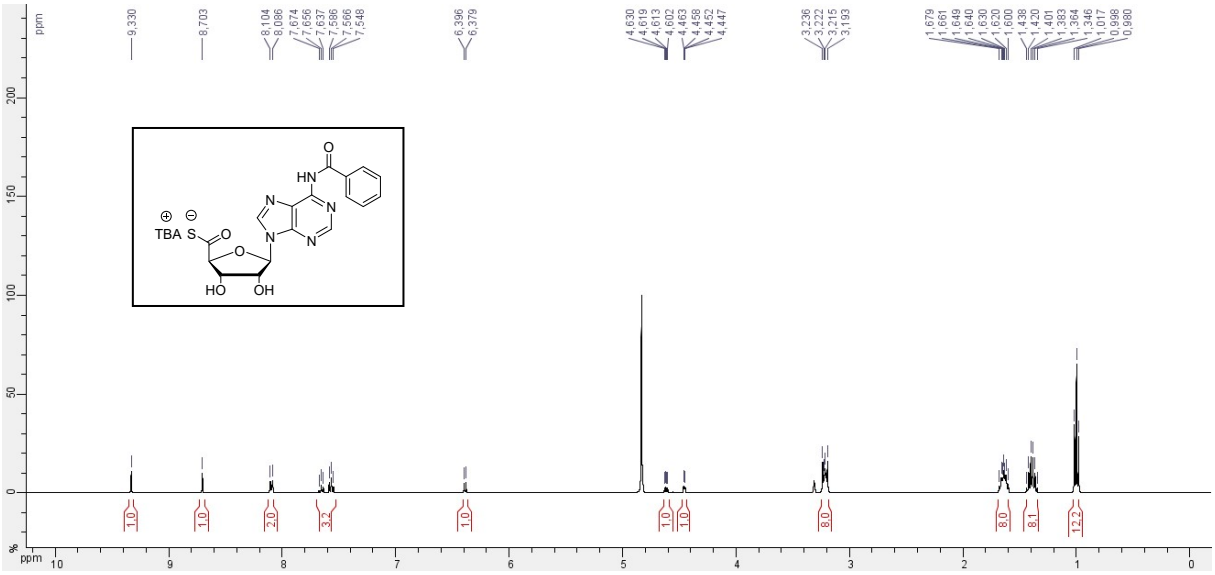
4'-tetrabutylammonium thioacetate-*N*-Bz-adenosine (6b)

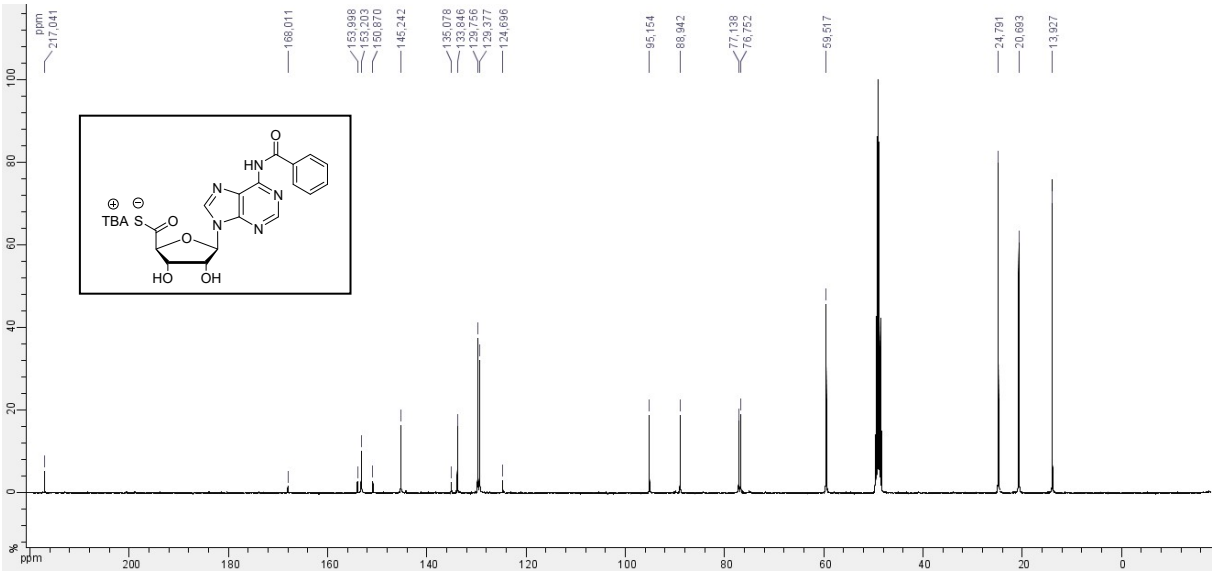


(a) Coupling reaction: 4'-carboxylic acid-2',3'-*O*-TBDMS-*N*-Bz-adenosine **4b** (500 mg, 815 μmol) was dissolved in dry DMF (10 mL). Thereafter, 9-fluorenylmethanethiol (242 mg, 1.14 mmol), BOP reagent (503 mg, 1.14 mmol) and dry DIEA (426 μL, 2.4 mmol) were sequentially added. The resulting mixture was stirred at room temperature for 4 h. The reaction was checked for completion by TLC (DCM-MeOH, 9 : 1, v/v), diluted with AcOEt (100 mL), washed by aq. 10% citric acid (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, filtrated and evaporated to dryness. The resulting residue was purified by chromatography on a silica gel column with a linear gradient of MeOH (0-10%) in DCM as the mobile phase, giving the 4'-(9-fluorenylmethyl thioester)-2',3'-*O*-TBDMS-*N*-Bz-adenosine **5b** as a white powder (453 mg, 562 μmol, 69%).

(b) Deprotection: 4'-(9-fluorenylmethyl thioester)-2',3'-*O*-TBDMS-*N*-Bz-adenosine **5b** (453 mg, 562 μmol) was dissolved in dry THF (16 mL). Thereafter, a solution of TBAF 1M in THF (2 mL, 2 mmol) was added. The resulting mixture was stirred at room temperature for 3 h. The reaction was checked for completion by RP-HPLC (system A). The crude was diluted with DCM (20 mL) and the resulting mixture purified by chromatography on a silica gel column in with a linear gradient of MeOH (0-16%) in DCM as the mobile phase, giving the product **6b** as a white amorphous powder after lyophilization in H_2O (318 mg, 495 μmol, 88%). R_f (DCM-MeOH, 9:1, v/v) = 0.1. ^{1}H NMR (400 MHz, MeOD) δ = 1.0 (t, J = 7.3 Hz, 12H), 1.39 (hex., $_J$ = 7.4 Hz, 8H), 1.60-1.68 (m, 8H), 3.19-3.24 (m, 2H), 4.45 (dd, J_1 = 4.4, J_2 = 1.8 Hz, 1H), 4.60-4.63 (m, 1H), 6.39 (d, J = 6.8 Hz, 1H), 7.55-7.67 (m, 3H), 8.10 (d, J = 7.7 Hz, 1H), 8.70 (s, 1H), 9.33 (s, 1H). ^{13}C NMR (100 MHz, MeOD) δ = 13.9, 20.7, 24.8, 59.5, 76.8, 77.1, 88.9, 95.2, 124.7, 129.4, 129.8, 133.8, 135.1, 145.2, 150.9, 153.2, 154.0, 168.0, 217.0 ppm. HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{17}H_{14}N_5O_5S$: 400.0721; found 400.0741.

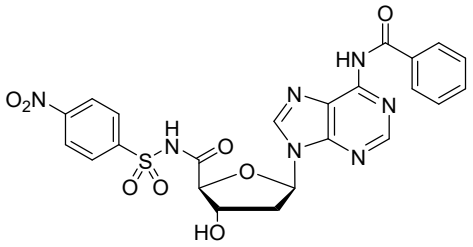
^{1}H and ^{13}C NMR Spectra (MeOD)





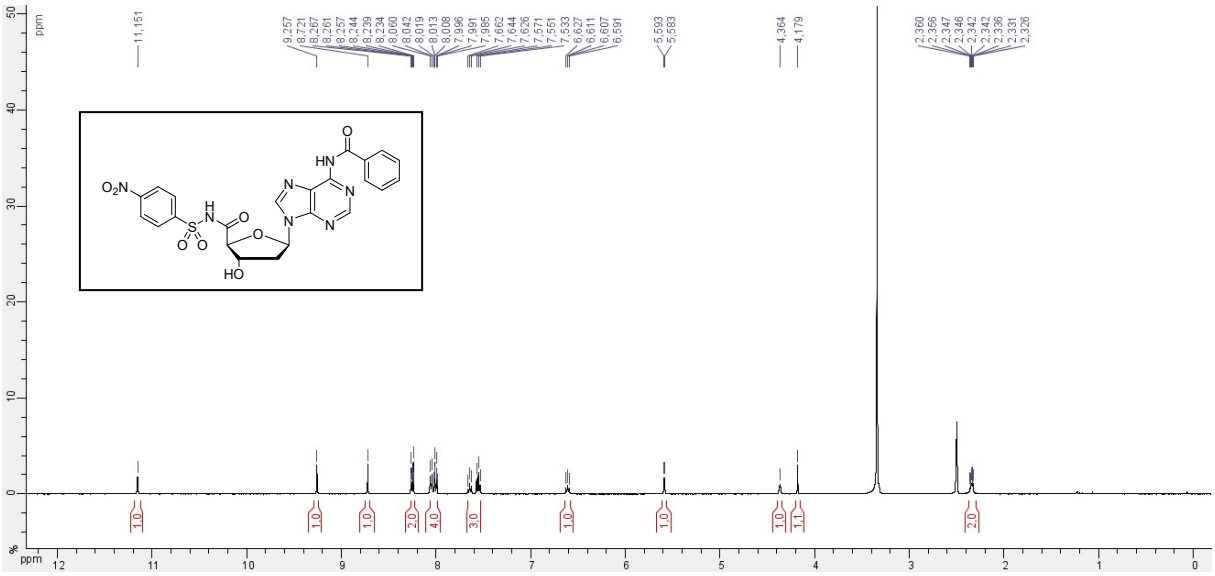
Synthesis of 4'-(*N*-acylsulfonamide)-2'-deoxy-adenosine derivatives

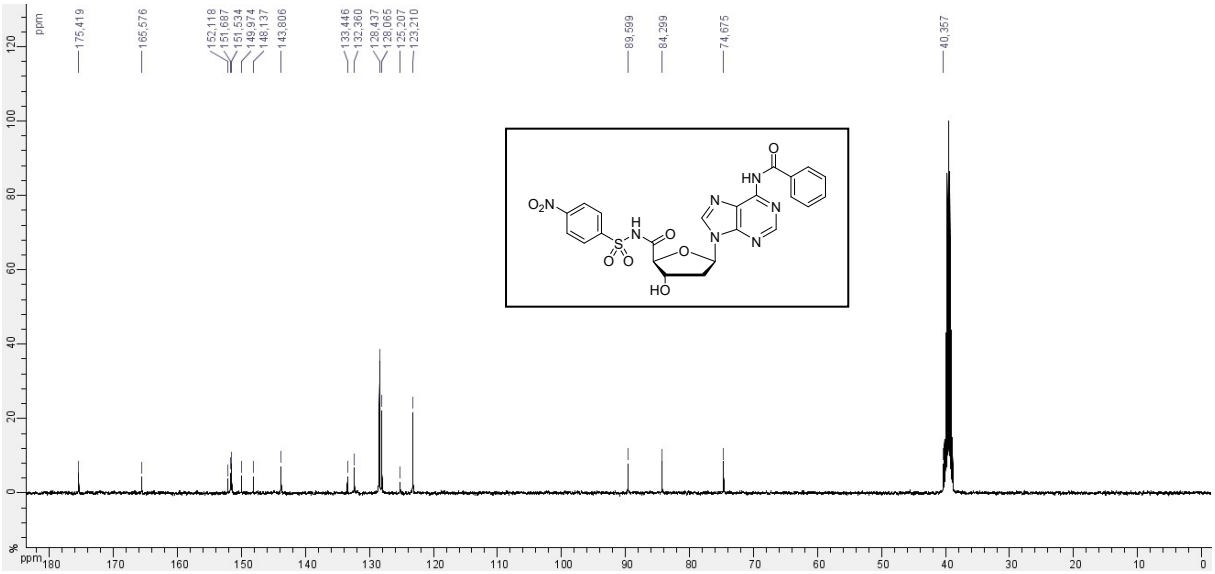
4'-(*N*-((4-nitrophenyl)sulfonyl)acetamide)-2'-deoxy-*N*-Bz-adenosine (7a)



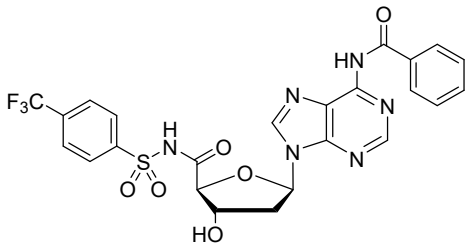
4-nitrobenzenesulfonyl azide **2a** (8 mg, 35 μmol) was dissolved in dry NMP (1 mL). Thereafter, 4'-tetrabutylammonium thioacetate-2'-deoxy-*N*-Bz-adenosine **6a** (20 mg, 32 μmol), water (300 μL) and $NaHCO_3$ (8 mg, 96 μmol) were sequentially added. The resulting mixture was stirred at room temperature for 10 min. The reaction was checked for completion by RP-HPLC (system A). 0.1% aq. TFA (pH 2.0, 10 mL) was added and the resulting mixture was purified by RP-chromatography with a linear gradient of MeCN (0-50%) in 0.1% aq. TFA as the mobile phase, giving the desired product **7a** as a white amorphous powder after lyophilization (16 mg, 29 μmol, 90%, 94% purity). ^{1}H NMR (400 MHz, DMSO): δ = 2.33-2.36 (m, 2H), 4.18 (s, 1H), 4.36 (bs, 1H), 5.59 (d, *J* = 3.6 Hz, 1H), 6.59-6.63 (m, 1H), 7.53-7.66 (m, 3H), 7.99-8.06 (m, 4H), 8.23-8.27 (m, 2H), 8.72 (s, 1H), 9.26 (s, 1H), 11.15 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 40.4, 74.7, 84.3, 89.6, 123.2, 125.2, 128.1, 128.4, 132.4, 133.4, 143.8, 148.1, 150.0, 151.5, 151.7, 152.1, 165.6, 175.4 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{20}N_7O_8S$: 554.1089; found 554.1088.

^{1}H and ^{13}C NMR Spectra (DMSO)



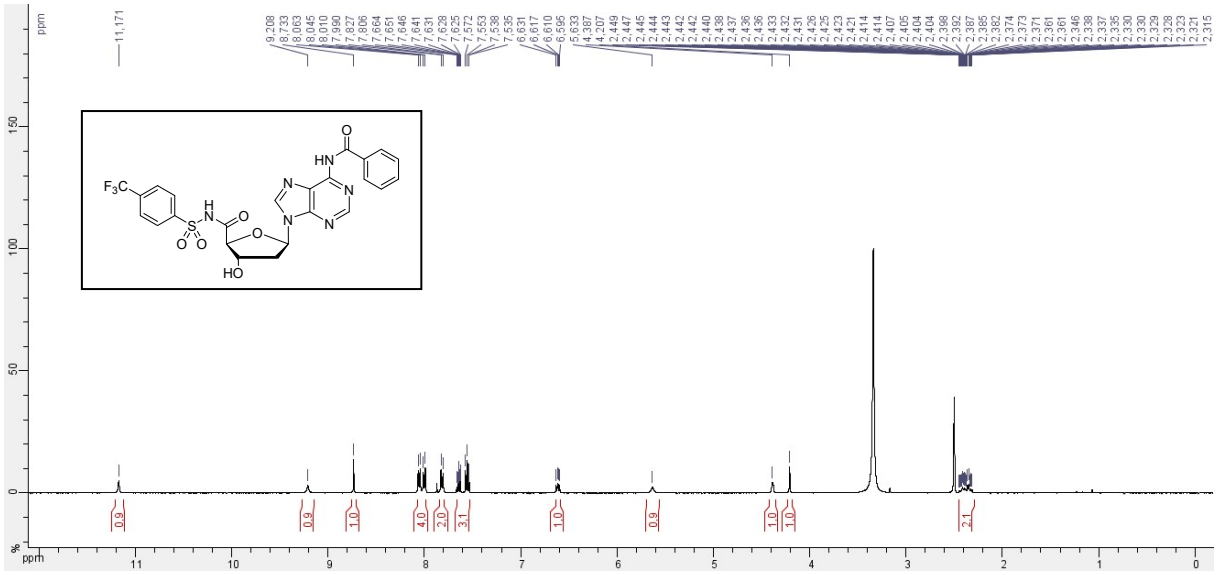


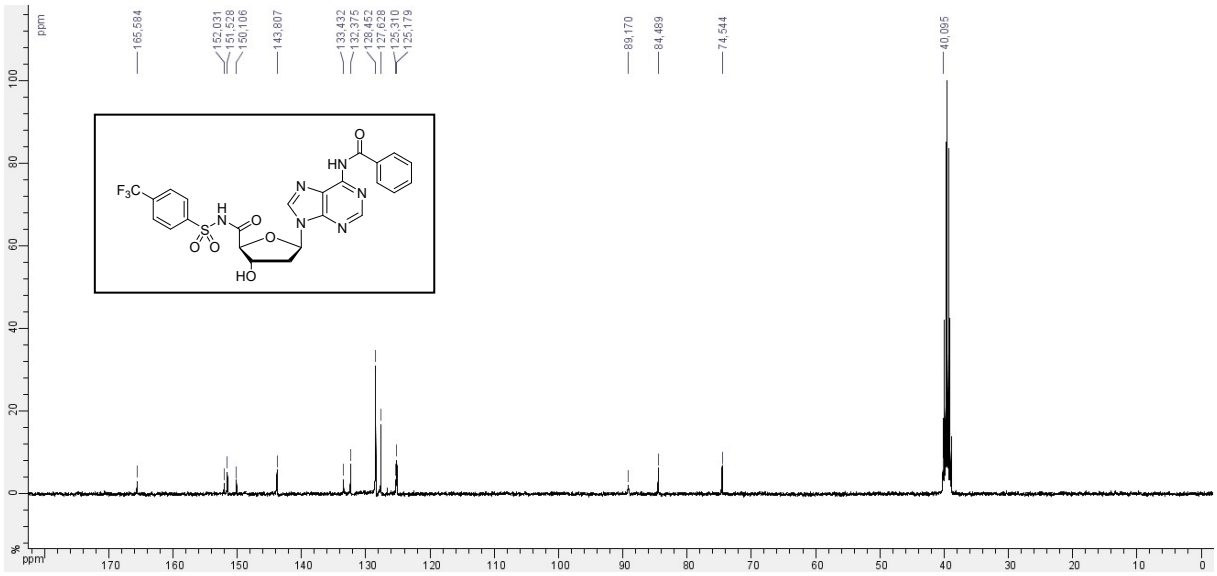
4'-(*N*-((4-trifluoromethyl)sulfonyl)acetamide)-2'-deoxy-*N*-Bz-adenosine (7b)



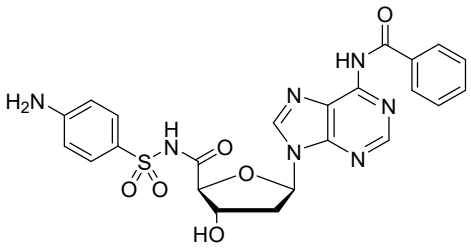
4-(trifluoromethyl)benzenesulfonyl azide (23 mg, 93 μmol) **2e** was dissolved in dry NMP (1 mL). Thereafter, 4'-tetrabutylammonium thioacetate-2'-deoxy-*N*-Bz-adenosine **6a** (40 mg, 62 μmol), water (300 μL) and $NaHCO_3$ (16 mg, 186 μmol) were sequentially added. The resulting mixture was stirred at room temperature for 10 min. The reaction was checked for completion by RP-HPLC (system A). 0.1% aq. TFA (pH 2.0, 10 mL) was added and the resulting mixture was purified by RP-chromatography with a linear gradient of MeCN (0-50%) in 0.1% aq. TFA as the mobile phase, giving the desired product **7b** as a white amorphous powder after lyophilization (34 mg, 58 μmol, 94%, 97% purity). ^{1}H NMR (400 MHz, DMSO): δ = 2.32-2.45 (m, 2H), 4.21 (s, 1H), 4.39 (bs, 1H), 5.63 (bs, 1H), 6.60-6.63 (m, 1H), 7.54-7.66 (m, 3H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.99-8.06 (m, 4H), 8.73 (s, 1H), 9.21 (bs, 1H), 11.17 (bs, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 40.1, 74.5, 84.5, 89.2, 125.2, 125.3, 127.6, 128.5, 132.4, 133.4, 143.8, 150.1, 151.5, 152.0, 165.6 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{20}F_3N_6O_6S$: 577.1112; found 577.1115.

^{1}H and ^{13}C NMR Spectra (DMSO)



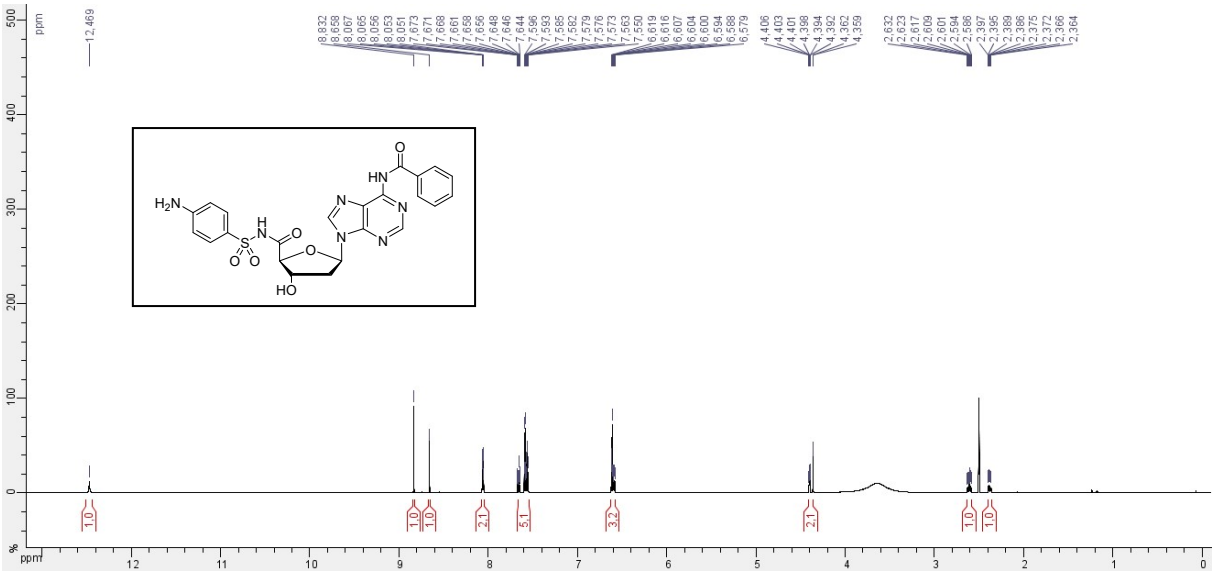


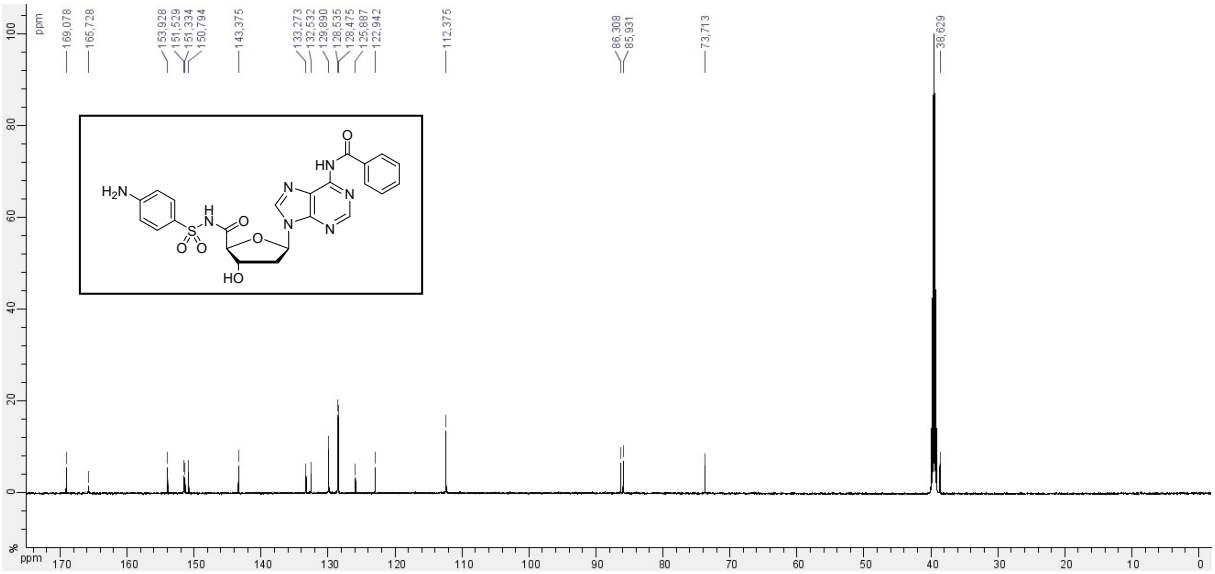
4'-(*N*-((4-aminophenyl)sulfonyl)acetamide)-2'-deoxy-*N*-Bz-adenosine (7c)



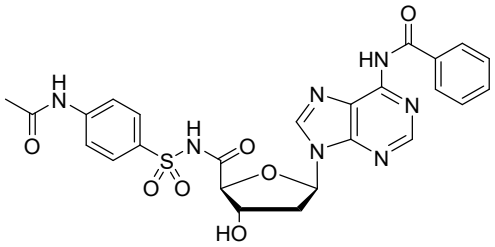
4-aminobenzenesulfonyl azide **2f** (21 mg, 88 μmol) was dissolved in dry NMP (1 mL). Thereafter, 4'-tetrabutylammonium thioacetate-2'-deoxy-*N*-Bz-adenosine **6a** (50 mg, 80 μmol), water (250 μL) and $NaHCO_3$ (15 mg, 176 μmol) were sequentially added. The resulting mixture was stirred at room temperature for 10 min. The reaction was checked for completion by RP-HPLC (system A). 0.1% aq. TFA (pH 2.0, 10 mL) was added and the resulting mixture was purified by RP-chromatography with a linear gradient of MeCN (0-50%) in 0.1% aq. TFA as the mobile phase, giving the desired product **7c** as a white amorphous powder after lyophilization (35 mg, 67 μmol, 85%, 99% purity). ^{1}H NMR (600 MHz, DMSO): δ = 2.36-2.40 (m, 1H), 2.59-2.63 (m, 1H), 4.36 (d, *J* = 1.6 Hz, 1H), 4.39-4.41 (m, 1H), 6.58-6.62 (m, 3H), 7.55-7.67 (m, 5H), 8.05-8.07 (m, 2H), 8.66 (s, 1H), 8.83 (s, 1H), 12.47 (bs, 1H).^{13}C NMR (150 MHz, DMSO): δ = 38.6, 73.7, 85.9, 86.3, 112.4, 122.9, 125.9, 128.4, 128.5, 129.9, 132.5, 133.3, 143.4, 150.8, 151.3, 151.5, 153.9, 165.7, 169.1 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{22}N_7O_6S$: 524.1352; found 524.1357.

^{1}H and ^{13}C NMR Spectra (DMSO)



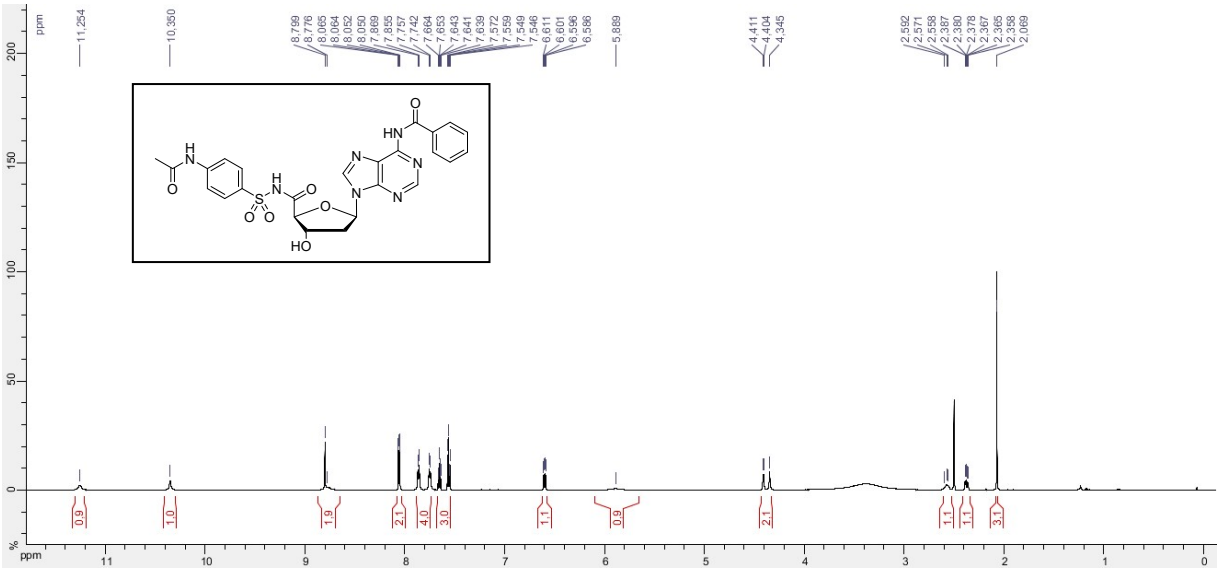


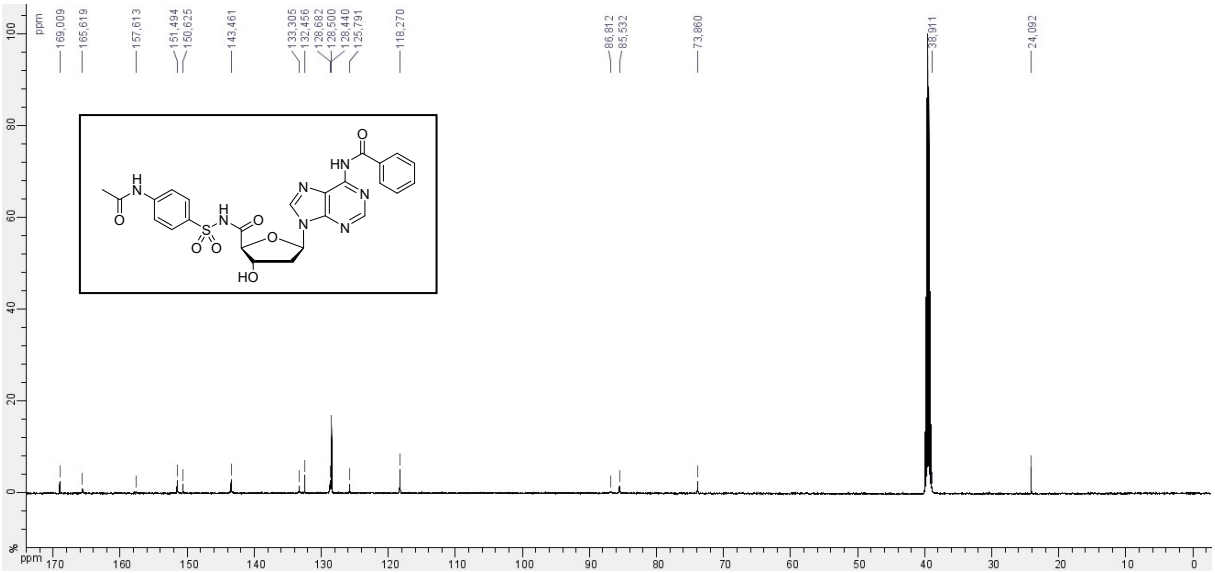
4'-(*N*-((4-acetamidophenyl)sulfonyl)acetamide)-2'-deoxy-*N*-Bz-adenosine (7d)



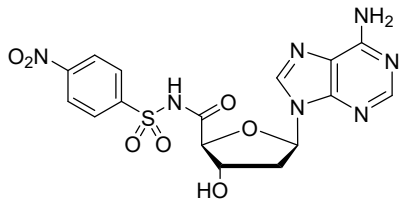
4-acetamidobenzenesulfonyl azide (25 mg, 105 μmol) was dissolved in dry NMP (1 mL). Thereafter, 4'-tetrabutylammonium thioacetate-2'-deoxy-*N*-Bz-adenosine **6a** (60 mg, 96 μmol), water (250 μL) and $NaHCO_3$ (18 mg, 210 μmol) were sequentially added. The resulting mixture was stirred at room temperature for 10 min. The reaction was checked for completion by RP-HPLC (system A). 0.1% aq. TFA (pH 2.0, 10 mL) was added and the resulting mixture was purified by RP-chromatography with a linear gradient of MeCN (0-60%) in 0.1% aq. TFA as the mobile phase, giving the desired product **7d** as a white amorphous powder after lyophilization (42 mg, 80 μmol, 84%, 96% purity). ^{1}H NMR (600 MHz, DMSO) δ = 2.07 (s, 3H), 2.36-2.39 (m, 1H), 2.56-2.59 (m, 1H), 4.35 (bs, 1H), 4.41 (d, *J* = 2.1 Hz, 1H), 5.89 (bs, 1H), 6.59-6.61 (m, 1H), 7.55-7.66 (m, 3H), 7.74-7.87 (m, 4H), 8.05-8.07 (m, 2H), 8.77 (bs, 1H), 8.80 (s, 1H), 10.35 (s, 1H), 11.25 (bs, 1H). ^{13}C NMR (150 MHz, DMSO): δ = 24.1, 38.9, 73.9, 85.5, 86.8, 118.3, 125.8, 128.4, 128.5, 128.7, 132.5, 133.3, 143.5, 150.6, 151.5, 157.6, 165.6, 169.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{24}N_7O_7S$: 566.1452; found 566.1447.

^{1}H and ^{13}C NMR Spectra (DMSO)



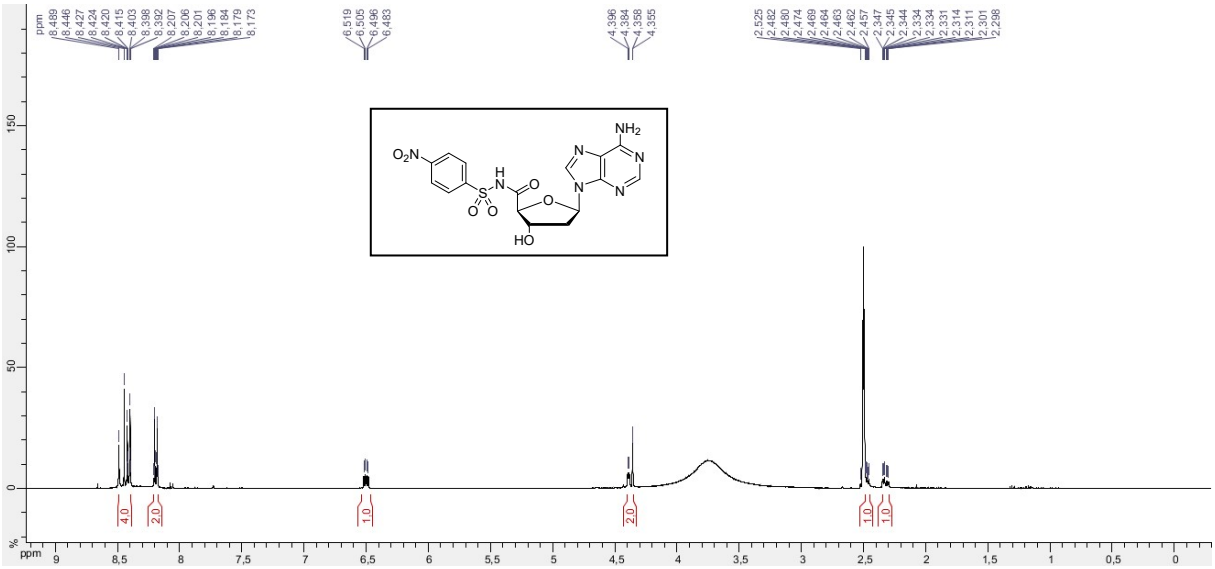


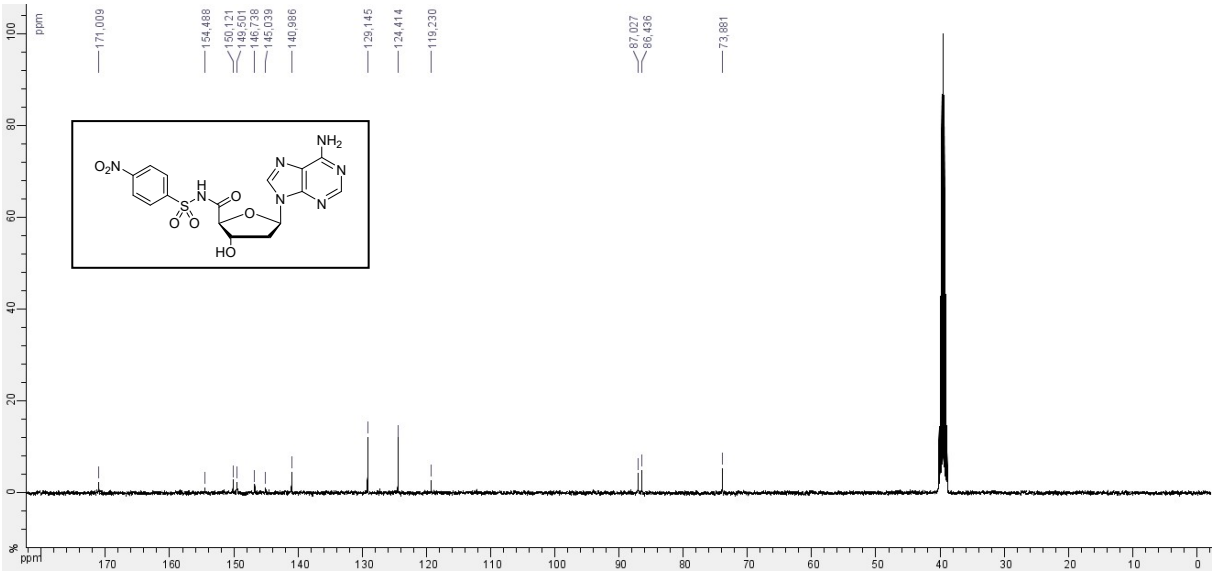
4'-(*N*-((4-nitrophenyl)sulfonyl)acetamide)-2'-deoxy-adenosine (9a)



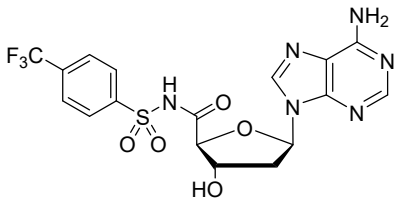
Ammonia aqueous solution 28% (2 mL) was added to a stirred solution of 4'-(*N*-((4-nitrophenyl)sulfonyl))-2'-deoxy-*N*-Bz-adenosine **7a** (8 mg, 14 μmol) in MeOH (1 mL). The reaction was stirred at room temperature for 16h. Volatiles were evaporated *in vacuo* and the residue was purified by RP-chromatography with a linear gradient of MeCN (0-40%) in 0.1% aq. TFA as the mobile phase giving the desired product **9a** as a white amorphous powder after lyophilization (7 mg, 13 μmol 93%, 94% purity). ^{1}H NMR (400 MHz, DMSO) δ = 2.30-2.35 (m, 1H), 2.46-2.53 (m, 1H), 4.35-4.40 (m, 2H), 6.48-6.52 (m, 1H), 8.17-8.21 (m, 2H), 8.39-8.43 (m, 2H), 8.45 (s, 1H), 8.49 (bs, 1H) ppm. ^{13}C NMR (100 MHz, DMSO) δ = 73.9, 86.4, 87.0, 119.2, 124.4, 129.1, 141.0, 145.0, 146.7, 149.5, 150.1, 154.5, 171.0 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{16}N_7O_7S$: 450.0826; found 450.0824.

^{1}H and ^{13}C NMR Spectra (DMSO)



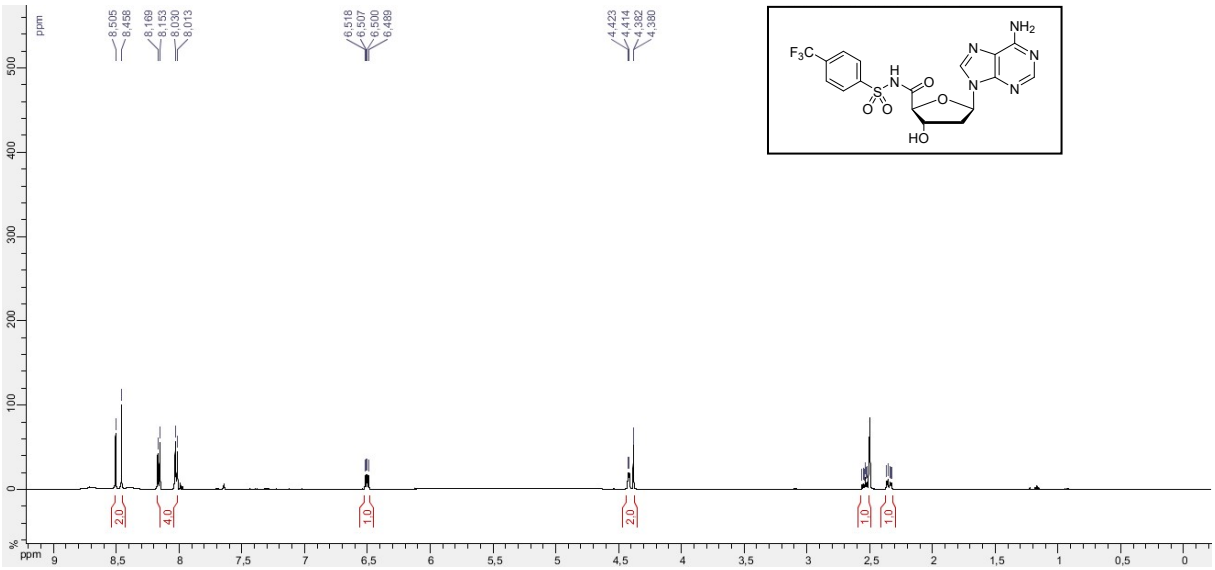


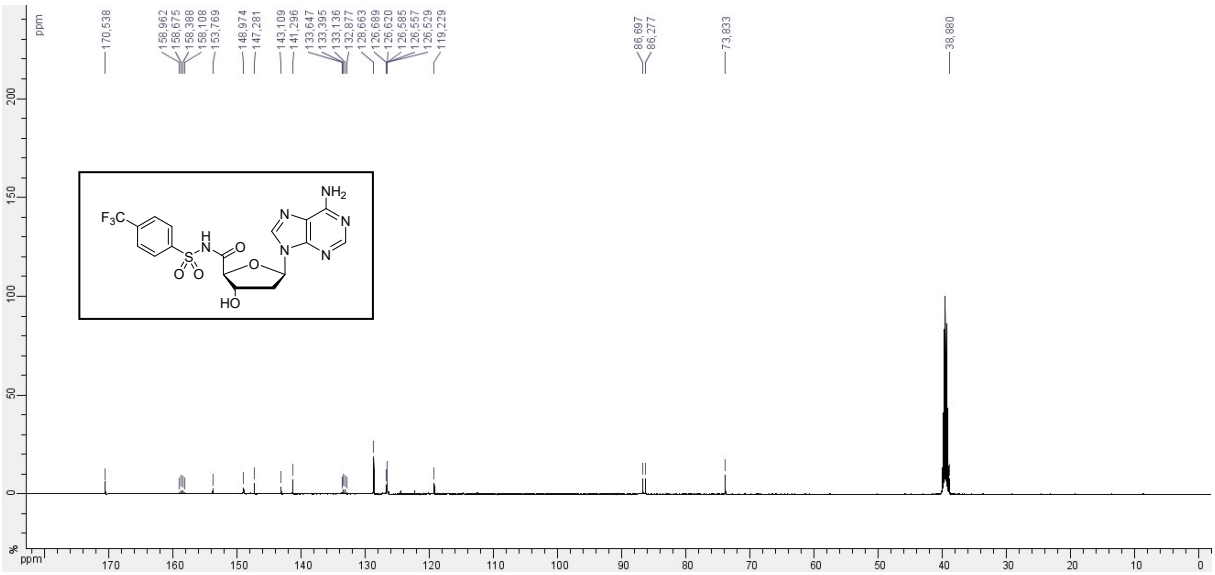
4'-(*N*-((4-trifluoromethyl)sulfonyl)acetamide)-2'-deoxy-adenosine (9b)



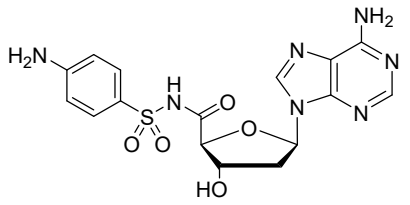
Ammonia aqueous solution 28% **7b** (2 mL) was added to a stirred solution of 4'-(*N*-((4-nitrophenyl)sulfonyl))-2'-deoxy-*N*-Bz-adenosine (20 mg, 35 μmol) in MeOH (1 mL). The reaction was stirred at room temperature for 16h. Volatiles were evaporated *in vacuo* and the residue was purified by RP-chromatography with a linear gradient of MeCN (0-40%) in 0.1% aq. TFA as the mobile phase giving the desired product **9b** as a white amorphous powder after lyophilization (17 mg, 30 μmol 86%, 98% purity). ^{1}H NMR (500 MHz, DMSO) δ = 2.33-2.37 (m, 1H), 2.52-2.56 (m, 1H), 4.38-4.42 (m, 2H), 6.49-6.52 (m, 1H), 8.01-8.17 (m, 4H), 8.46 (s, 1H), 8.51 (s, 1H) ppm. ^{13}C NMR (125 MHz, DMSO) δ = 38.9, 73.8, 86.3, 86.7, 119.2, 126.5-126.7 (m), 128.7, 133.3 (q, $J_{C\text{-}F}$ = 33.1 Hz), 141.3, 143.1, 147.3, 149.0, 153.8, 158.5 (q, $J_{C\text{-}F}$ = 35.8 Hz), 170.5 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}F_3N_6O_5S$: 473.0849; found 473.0849.

^{1}H and ^{13}C NMR Spectra (DMSO)



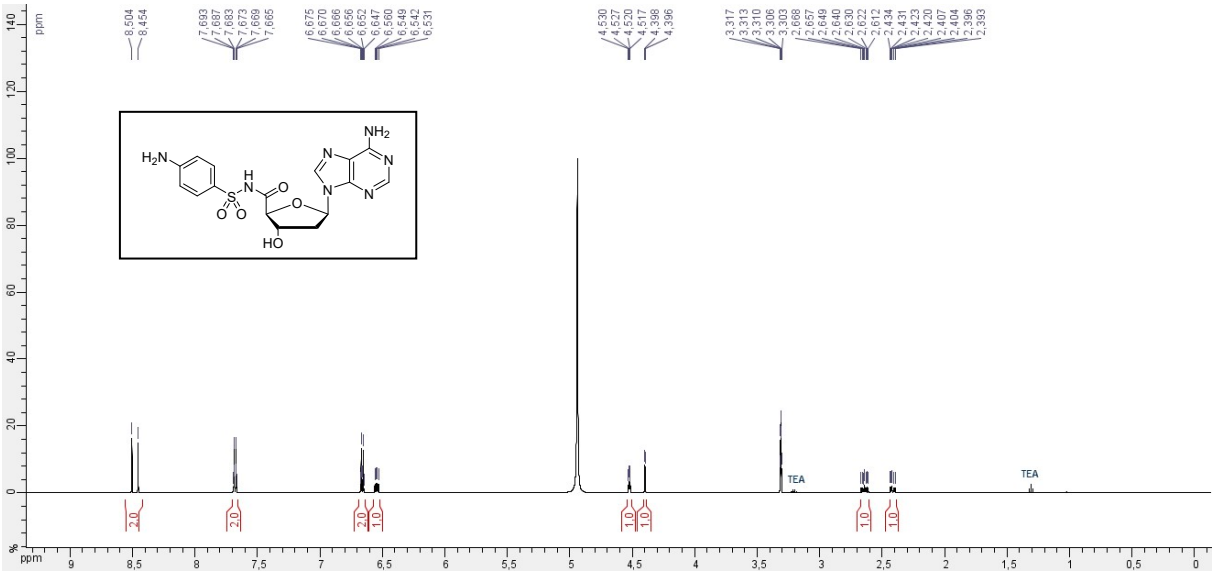


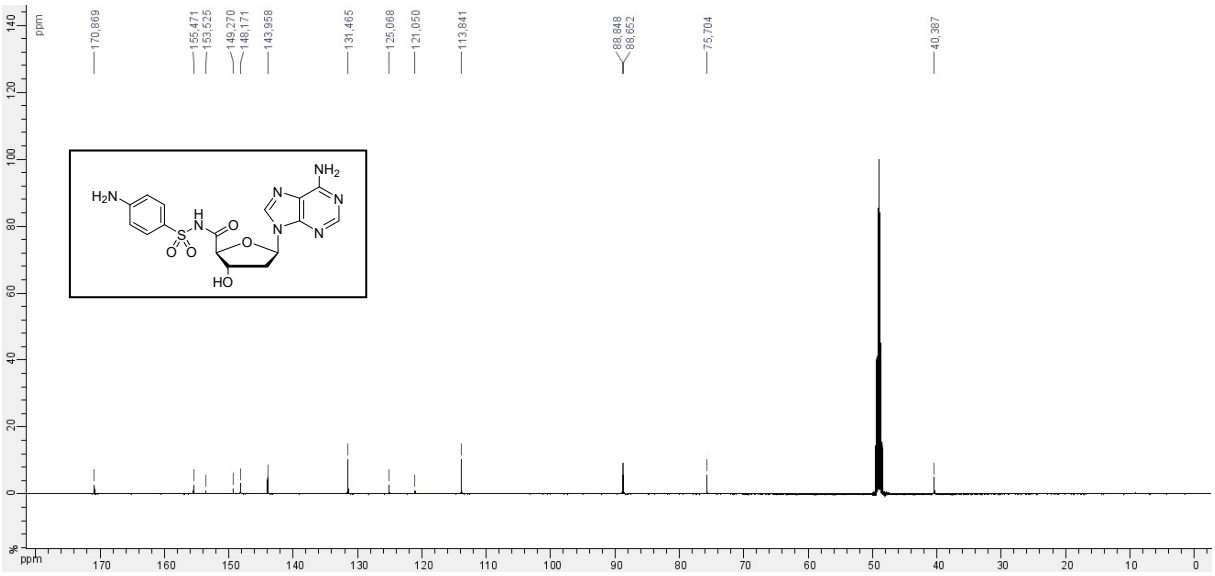
4'-(*N*-((4-aminophenyl)sulfonyl)acetamide)-2'-deoxy-adenosine (9c)



Ammonia aqueous solution 28% (4 mL) was added to a stirred solution of 4'-(*N*-((4-aminophenyl)sulfonyl))-2'-deoxy-*N*-Bz-adenosine **7c** (72 mg, 120 μmol) in MeOH (1 mL). The reaction was stirred at room temperature for 16h. Volatiles were evaporated *in vacuo* and the residue was purified by RP-chromatography with a linear gradient of MeCN (0-50%) in 0.1% aq. TFA as the mobile phase giving the desired product **9c** as a white amorphous powder after lyophilization (58 mg, 111 μmol 98%, 97% purity). ^{1}H NMR (500 MHz, MeOD) δ = 2.39-2.43 (m, 1H), 2.61-2.67 (m, 1H), 4.40 (d, *J* = 9.5, 1.2 Hz, 1H), 4.52-4.53 (m, 1H), 6.53-6.56 (m, 1H), 6.65-6.68 (m, 2H), 7.67-7.69 (m, 2H), 8.45 (s, 1H), 8.50 (s, 1H) ppm. ^{13}C NMR (125 MHz, MeOD) δ = 40.4, 75.7, 88.7, 88.8, 113.8, 121.1, 125.1, 131.5, 144.0, 148.2, 149.3, 153.5, 155.5, 170.9 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{17}N_7O_5S$: 420.1012; found 420.1099.

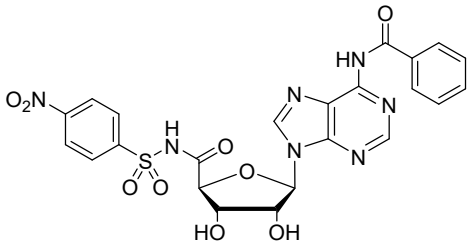
^{1}H and ^{13}C NMR Spectra (MeOD)





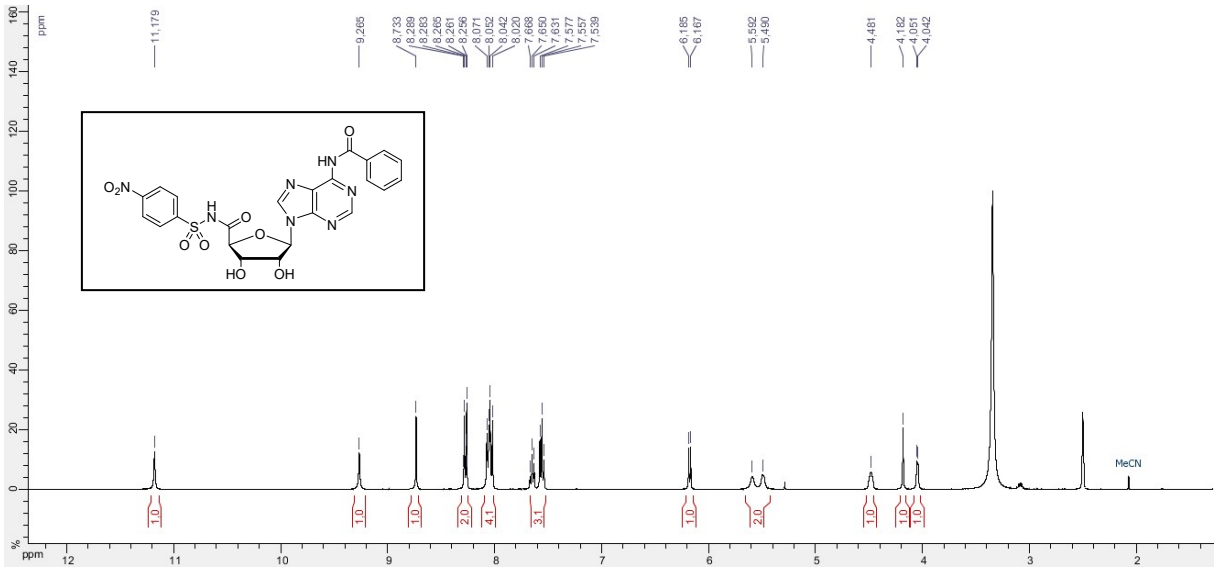
Synthesis of 4'-(*N*-acylsulfonamide)-adenosine derivatives

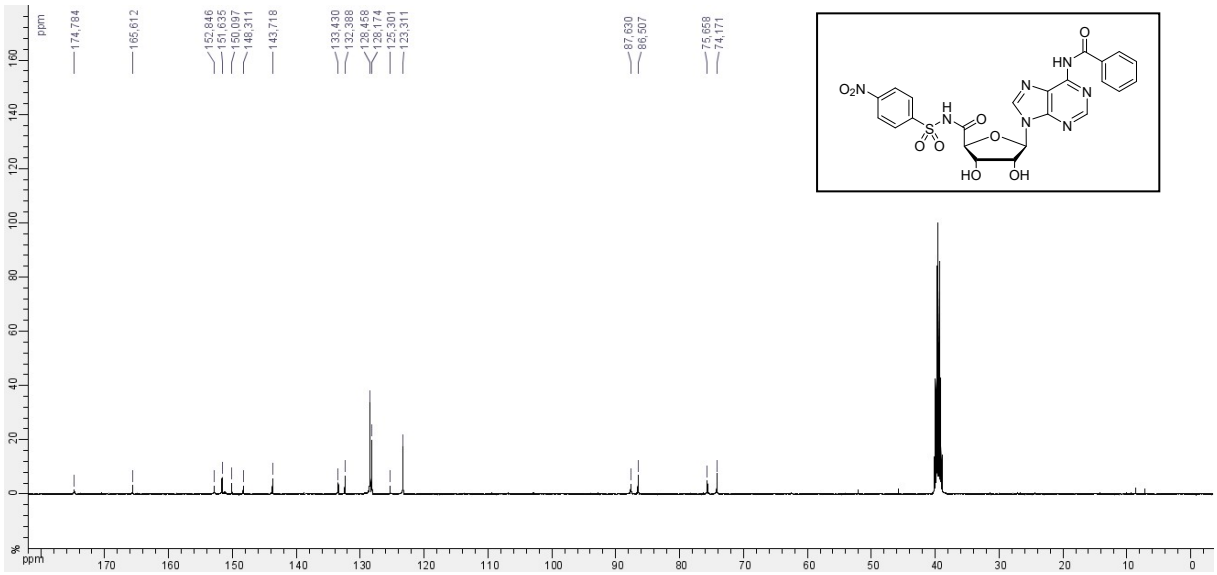
4'-(*N*-((4-nitrophenyl)sulfonyl)acetamide)-*N*-Bz-adenosine (8a)



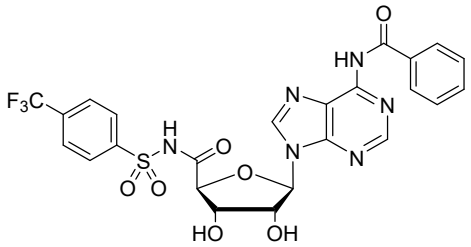
4-nitrobenzenesulfonyl azide **2a** (10 mg, 46 μmol) was dissolved in dry NMP (1 mL). Thereafter, 4'-tetrabutylammonium thioacetate-*N*-Bz-adenosine **6b** (27 mg, 42 μmol), water (300 μL) and $NaHCO_3$ (7 mg, 84 μmol) were sequentially added. The resulting mixture was stirred at room temperature for 10 min. The reaction was checked for completion by RP-HPLC (system A). 0.1% aq. TFA (pH 2.0, 10 mL) was added and the resulting mixture was purified by RP-chromatography with a linear gradient of MeCN (0-50%) in 0.1% aq. TFA as the mobile phase, giving the desired product **8a** as a white amorphous powder after lyophilization (23 mg, 41 μmol, quant., 98% purity). ^{1}H NMR (400 MHz, DMSO): δ = 4.05 (d, *J* = 3.6 Hz, 1H), 4.18 (s, 1H), 4.48 (bs, 1H), 5.49 (bs, 1H), 5.59 (bs, 1H), 6.18 (d, *J* = 7.4 Hz, 1H), 7.54-7.67 (m, 3H), 8.02-8.07 (m, 4H), 8.26-8.29 (m, 2H), 8.73 (s, 1H), 9.27 (s, 1H), 11.18 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 74.2, 75.7, 86.5, 87.6, 123.3, 125.3, 128.2, 128.5, 132.4, 133.4, 143.7, 148.3, 150.1, 151.6, 152.8, 165.6, 174.8 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{20}N_7O_9S$: 570.1038; found 570.1032.

^{1}H and ^{13}C NMR Spectra (DMSO)



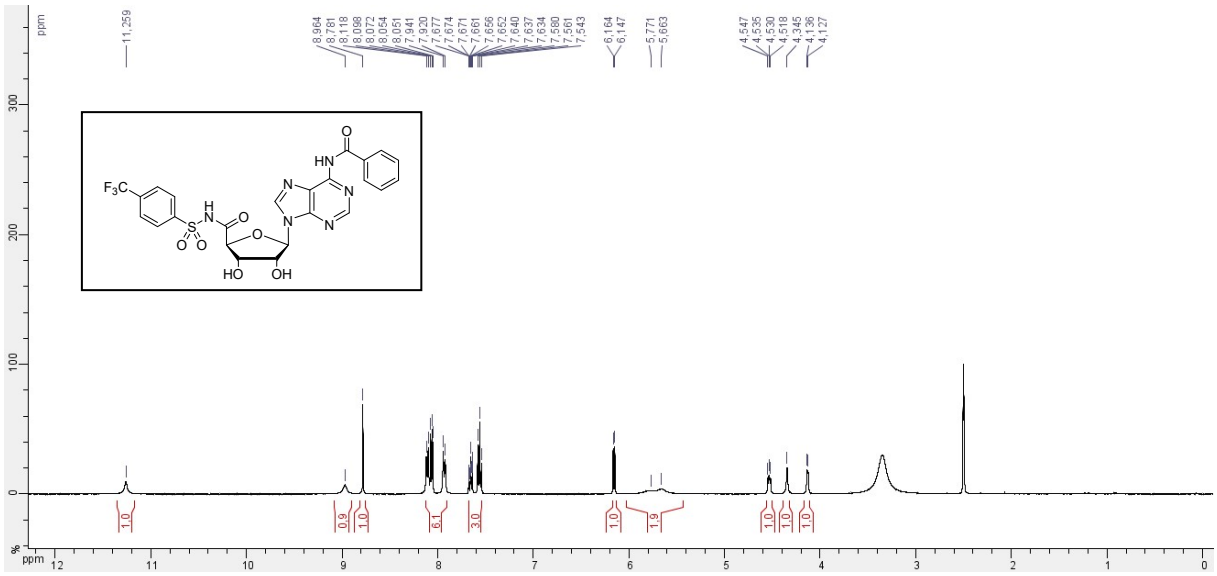


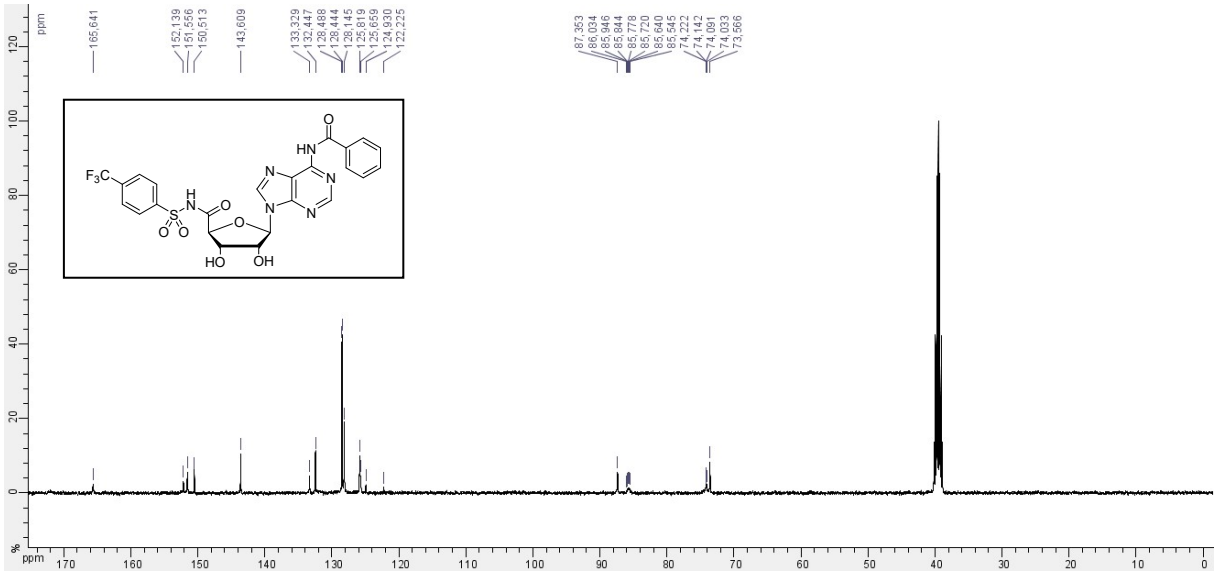
4'-(*N*-((4-trifluoromethyl)sulfonyl)acetamide)-*N*-Bz-adenosine (8b)



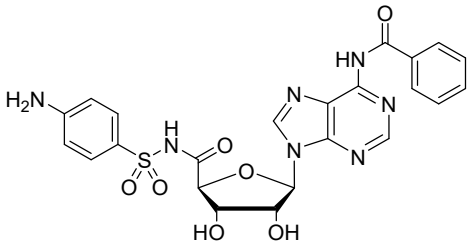
4-(trifluoromethyl)benzenesulfonyl azide **2e** (12 mg, 46 μmol) was dissolved in dry NMP (1 mL). Thereafter, 4'-tetrabutylammonium thioacetate-*N*-Bz-adenosine **6b** (27 mg, 42 μmol), water (300 μL) and $NaHCO_3$ (10 mg, 120 μmol) were sequentially added. The resulting mixture was stirred at room temperature for 10 min. The reaction was checked for completion by RP-HPLC (system A). 0.1% aq. TFA (pH 2.0, 10 mL) was added and the resulting mixture was purified by RP-chromatography with a linear gradient of MeCN (0-50%) in 0.1% aq. TFA as the mobile phase, giving the desired product **8b** as a white amorphous powder after lyophilization (21 mg, 40 μmol, 96%, 100% purity). ^{1}H NMR (400 MHz, DMSO): δ = 4.13 (d, *J* = 3.6 Hz, 1H), 4.35 (s, 1H), 4.52-4.55 (m, 1H), 5.66 (bs, 1H), 5.77 (bs, 1H), 6.16 (d, *J* = 7.0 Hz, 1H), 7.54-7.68 (m, 3H), 7.92-8.12 (m, 6H), 8.78 (s, 1H), 8.96 (bs, 1H), 11.26 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 73.6, 74.0-74.2 (m), 85.5-86.0 (m), 87.4, 122.2, 124.5, 125.7, 125.8, 128.1, 128.4, 128.5, 132.4, 133.3, 143.6, 150.5, 151.6, 152.1, 165.6 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{20}F_3N_6O_7S$: 593.1061; found 593.1060.

^{1}H and ^{13}C NMR Spectra (DMSO)



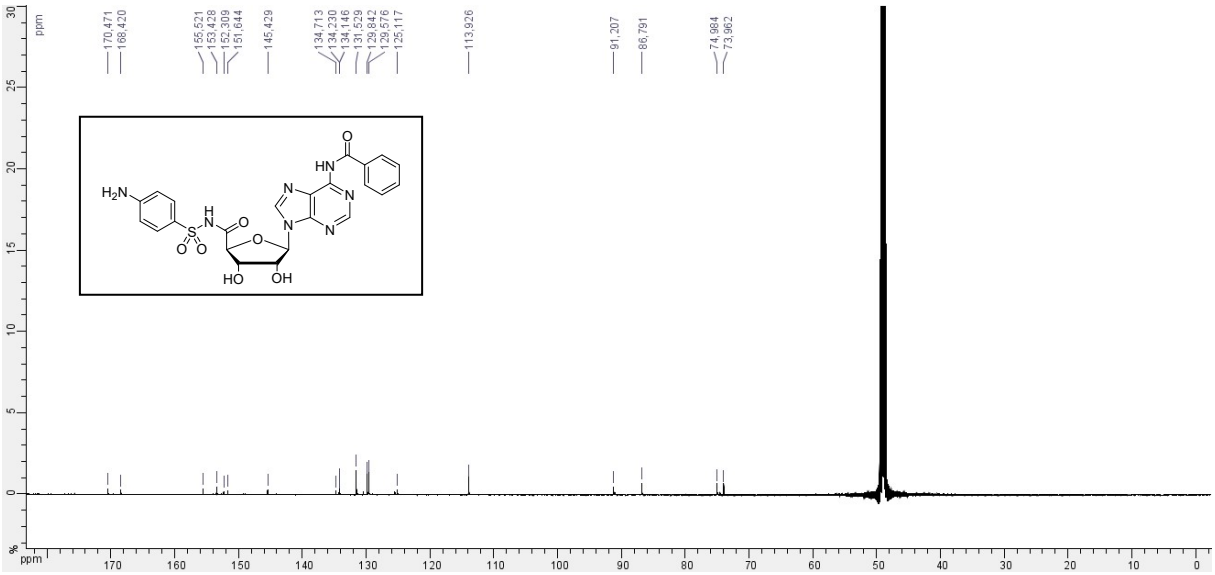


4'-(*N*-((4-aminophenyl)sulfonyl)acetamide)-*N*-Bz-adenosine (8c)

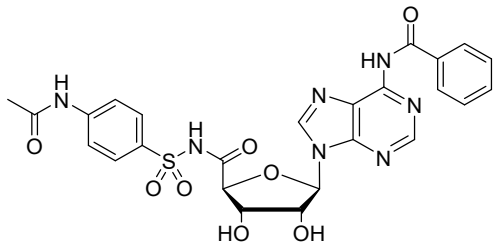


4-aminobenzenesulfonyl azide **2f** (11 mg, 46 μmol) was dissolved in dry NMP (1 mL). Thereafter, 4'-tetrabutylammonium thioacetate-*N*-Bz-adenosine **6b** (27 mg, 42 μmol), water (300 μL) and $NaHCO_3$ (7 mg, 84 μmol) were sequentially added. The resulting mixture was stirred at room temperature for 10 min. The reaction was checked for completion by RP-HPLC (system A). 0.1% aq. TFA (pH 2.0, 10 mL) was added and the resulting mixture was purified by RP-chromatography with a linear gradient of MeCN (0-50%) in 0.1% aq. TFA as the mobile phase, giving the desired product **8c** as a white amorphous powder after lyophilization (22 mg, 40 μmol, 96%, 98% purity). ^{1}H NMR (400 MHz, MeOD): δ = 4.22 (dd, J_1 = 4.8 Hz, J_2 = 1.8 Hz, 1H), 4.51 (d, , J = 1.6 Hz, 1H), 4.59-4.62 (m, 1H), 6.14 (d, , J_1 = 7.6 Hz, 1H), 6.67-6.70 (m, 2H), 7.57-7.74 (m, 5H), 8.10-8.12 (m, 2H), 8.65 (s, 1H), 9.02 (s, 1H).^{13}C NMR (125 MHz, MeOD): δ = 74.0, 75.0, 86.8, 91.2, 113.9, 125.1, 129.6, 129.8, 131.5, 134.1, 134.2, 134.7, 145.4, 151.6, 152.3, 153.4, 155.5, 168.4, 170.5 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{22}N_7O_7S$: 540.1296; found 540.1292.

^{1}H and ^{13}C NMR Spectra (MeOD)

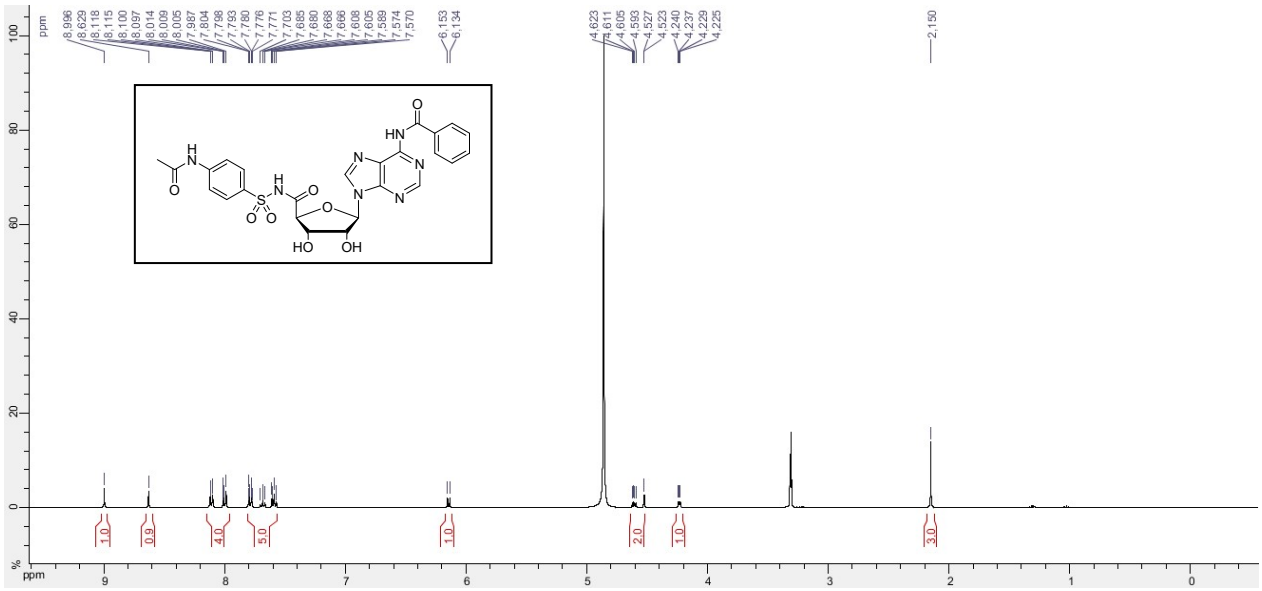


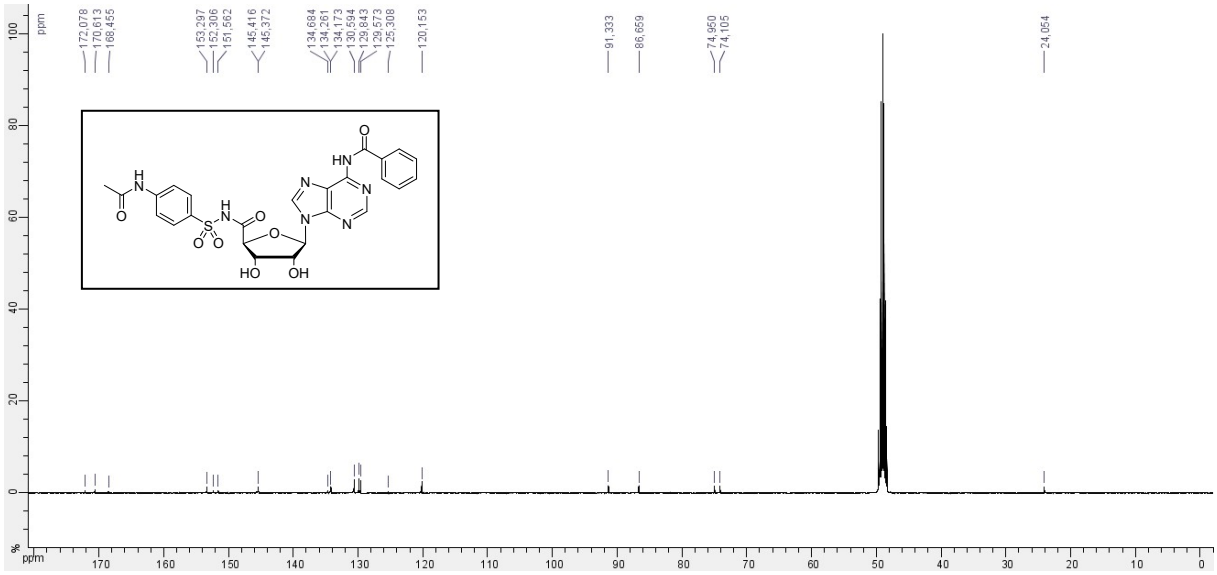
4'-(*N*-((4-acetamidophenyl)sulfonyl)acetamide)-*N*-Bz-adenosine (8d)



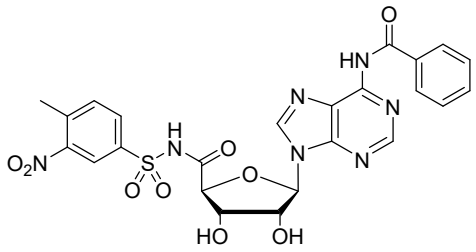
4-acetamidobenzenesulfonyl azide (34 mg, 140 μmol) was dissolved in dry NMP (2 mL). Thereafter, 4'-tetrabutylammonium thioacetate-*N*-Bz-adenosine **6b** (90 mg, 140 μmol), water (600 μL) and $NaHCO_3$ (24 mg, 280 μmol) were sequentially added. The resulting mixture was stirred at room temperature for 10 min. The reaction was checked for completion by RP-HPLC (system A). 0.1% aq. TFA (pH 2.0, 20 mL) was added and the resulting mixture was purified by RP-chromatography with a linear gradient of MeCN (0-50%) in 0.1% aq. TFA as the mobile phase, giving the desired product **8d** as a white amorphous powder after lyophilization (76 mg, 131 μmol, 94%, 94% purity). ^{1}H NMR (400 MHz, MeOD) δ = 2.15 (s, 3H), 4.23 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H), 4.53 (d, J = 1.7 Hz, 1H), 4.61 (dd, J_1 = 7.6 Hz, J_2 = 4.6 Hz, 1H), 6.14 (d, J = 7.6 Hz, 1H), 7.58-7.80 (m, 5H), 7.99-8.12 (m, 4H), 8.63 (s, 1H), 9.0 (s, 1H). ^{13}C NMR (100 MHz, MeOD): δ = 24.1, 74.1, 75.0, 86.7, 91.3, 120.2, 125.3, 129.6, 129.8, 130.6, 134.2, 134.3, 134.7, 145.37, 145.41, 151.6, 152.3, 153.3, 168.5, 170.6, 172.1 . HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{24}N_7O_8S$: 582.1402; found 582.1386.

^{1}H and ^{13}C NMR Spectra (MeOD)



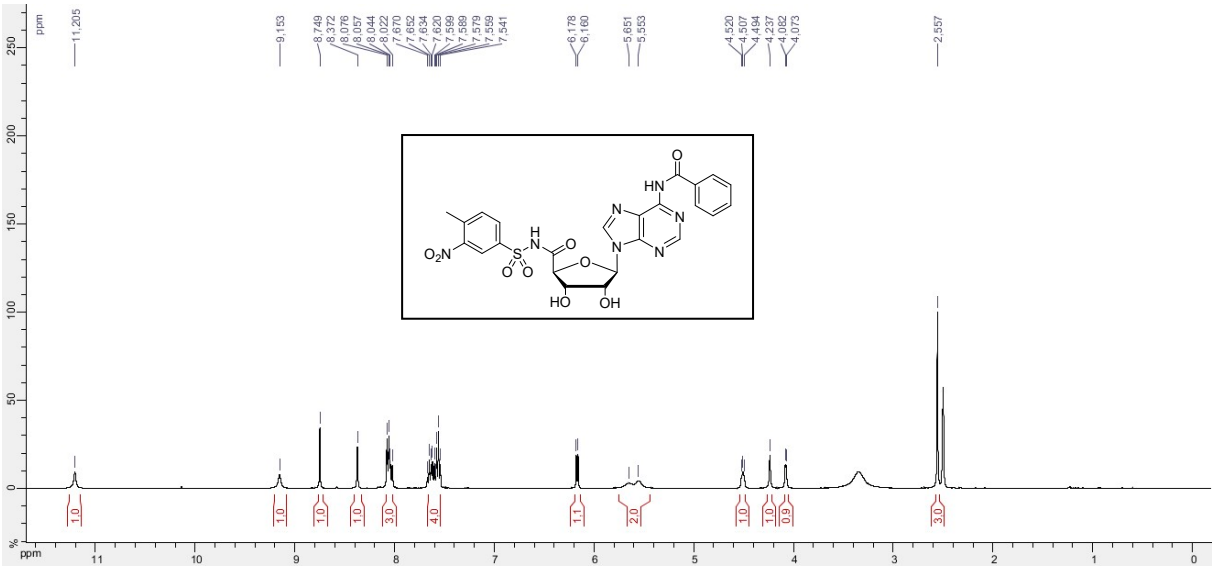


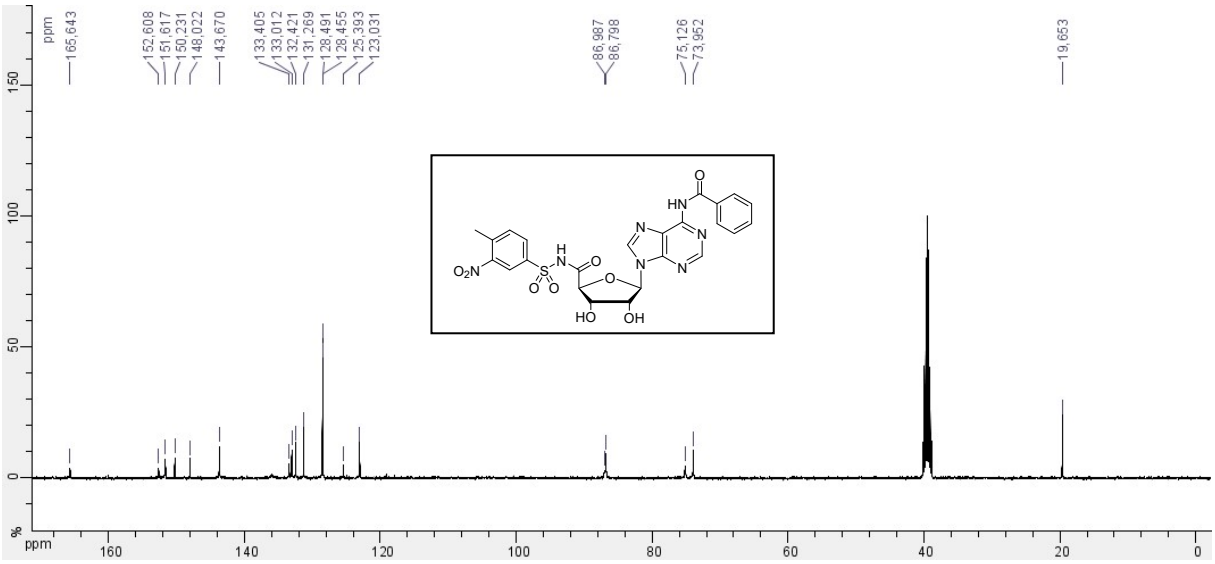
4'-(*N*-((4-methyl-3-nitrophenyl)sulfonyl)acetamide)-*N*-Bz-adenosine (8e)



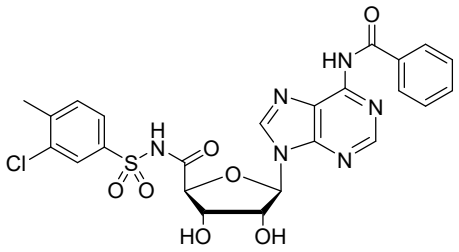
4-methyl-3-nitrobenzenesulfonyl azide **2b** (27 mg, 112 μmol) was dissolved in dry NMP (600 μL). Thereafter, 4'-tetrabutylammonium thioacetate-*N*-Bz-adenosine **6b** (66 mg, 102 μmol), water (300 μL) and $NaHCO_3$ (26 mg, 308 μmol) were sequentially added. The resulting mixture was stirred at room temperature for 10 min. The reaction was checked for completion by RP-HPLC (system A). 0.1% aq. TFA (pH 2.0, 10 mL) was added and the resulting mixture was purified by RP-chromatography with a linear gradient of MeCN (0-60%) in 0.1% aq. TFA as the mobile phase, giving the desired product **8e** as a white amorphous powder after lyophilization (55 mg, 94 μmol, 92%, 95% purity). ^{1}H NMR (400 MHz, DMSO): δ = 2.56 (s, 3H), 4.08 (d, *J* = 3.6 Hz, 1H), 4.23 (s, 1H), 4.51 (t, *J* = 5.0 Hz, 1H), 5.55 (bs, 1H), 5.65 (bs, 1H), 6.17 (d, *J* = 7.2 Hz, 1H), 7.54-7.67 (m, 4H), 8.02-8.08 (m, 3H), 8.37 (s, 1H), 8.75 (s, 1H), 9.15 (bs, 1H), 11.21 (bs, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 19.7, 74.0, 75.1, 86.8, 87.0, 123.0, 125.4, 128.4, 128.5, 131.3, 132.4, 133.0, 133.4, 143.7, 148.0, 150.2, 151.6, 152.6, 165.6 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{22}N_7O_9S$: 584.1194; found 584.1206.

^{1}H and ^{13}C NMR Spectra (DMSO)



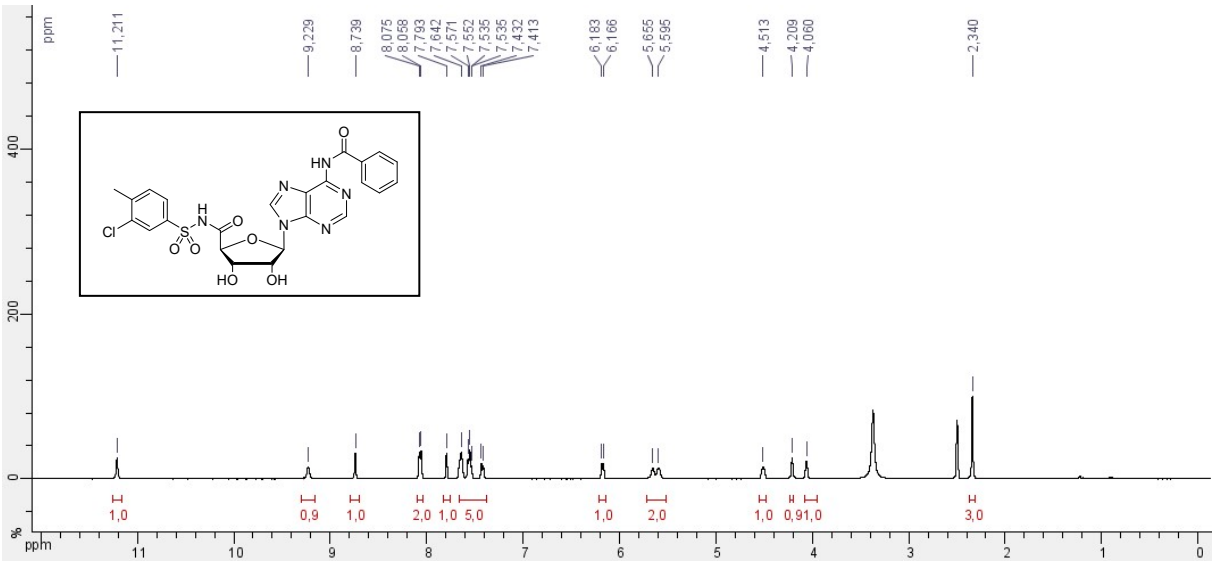


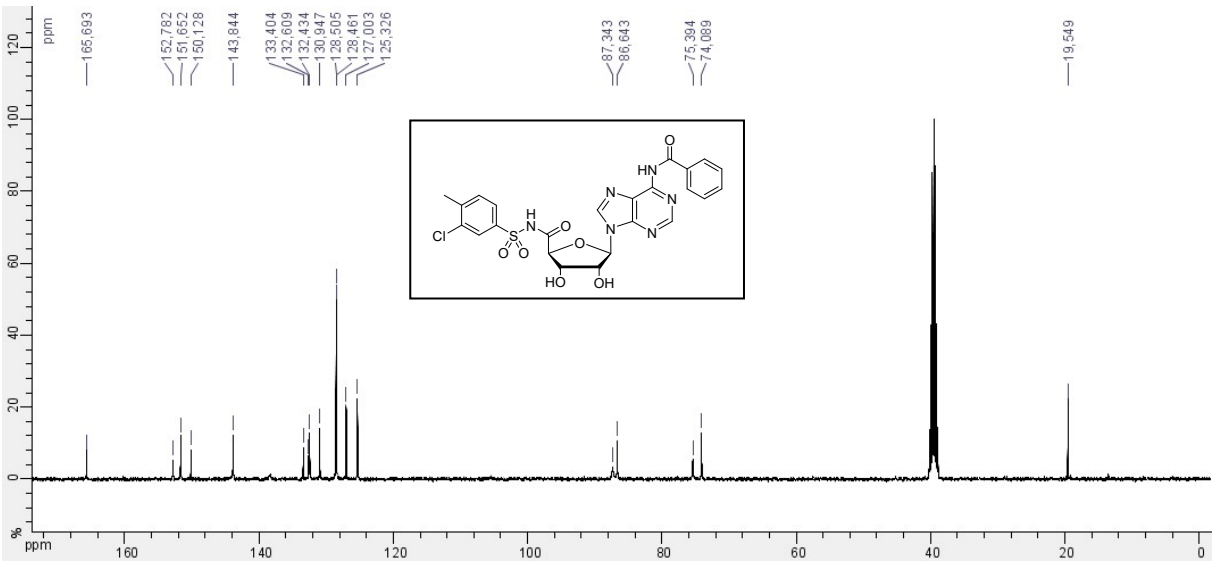
4'-(*N*-((3-chloro-4-methylphenyl)sulfonyl)acetamide)-*N*-Bz-adenosine (8f)



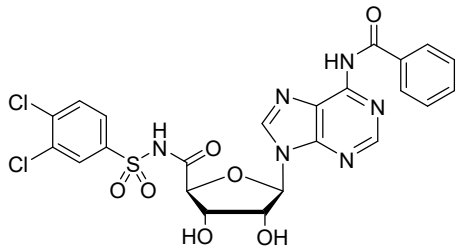
3-chloro-4-methylbenzenesulfonyl azide **2c** (23 mg, 99 μmol) was dissolved in dry NMP (600 μL). Thereafter, 4'-tetrabutylammonium thioacetate-*N*-Bz-adenosine **6b** (58 mg, 90 μmol), water (300 μL) and $NaHCO_3$ (22.8 mg, 272 μmol) were sequentially added. The resulting mixture was stirred at room temperature for 10 min. The reaction was checked for completion by RP-HPLC (system A). 0.1% aq. TFA (pH 2.0, 10 mL) was added and the resulting mixture was purified by RP-chromatography with a linear gradient of MeCN (0-60%) in 0.1% aq. TFA as the mobile phase, giving the desired product **8f** as a white amorphous powder after lyophilization (44 mg, 76 μmol, 85%, 97% purity). ^{1}H NMR (400 MHz, DMSO): δ = 2.34 (s, 3H), 4.06 (s, 1H), 4.21 (s, 1H), 4.51 (bs, 1H), 5.60 (bs, 1H), 5.66 (bs, 1H), 6.17 (d, *J* = 7.2 Hz, 1H), 7.41-7.64 (m, 5H), 7.79 (s, 1H), 8.06 (s, 1H), 8.08 (s, 1H), 8.74 (s, 1H), 9.23 (bs, 1H), 11.21 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 19.5, 74.1, 75.4, 86.6, 87.3, 125.3, 127.0, 128.46, 128.51, 130.9, 132.4, 132.6, 133.4, 143.8, 150.1, 151.7, 152.8, 165.7 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{21}ClN_6O_7S$: 573.0954; found 573.0968.

^{1}H and ^{13}C NMR Spectra (DMSO)



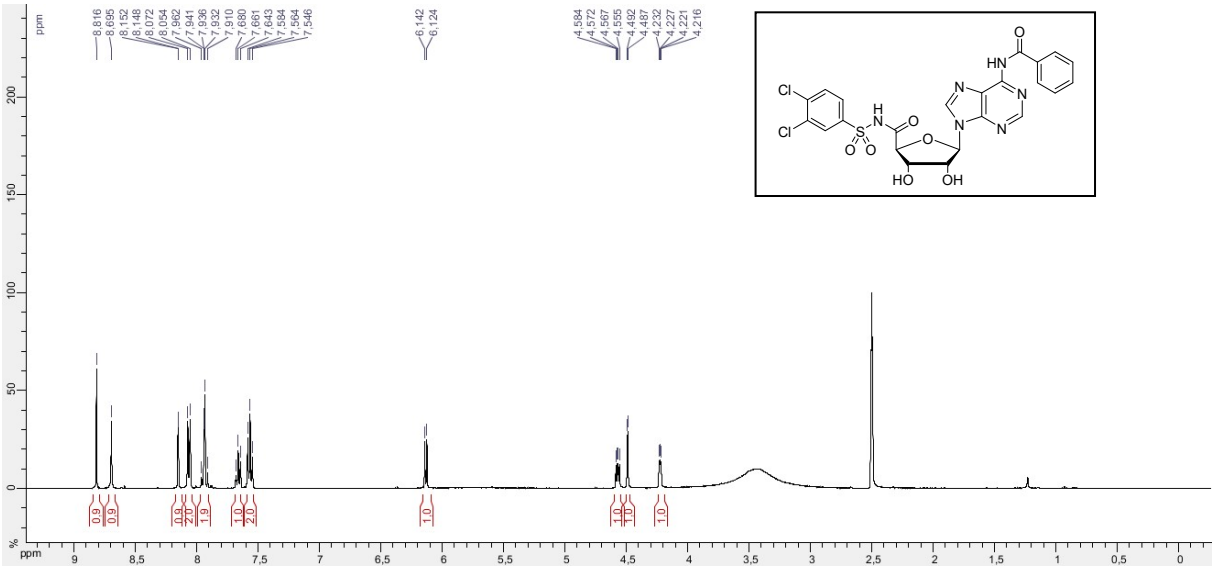


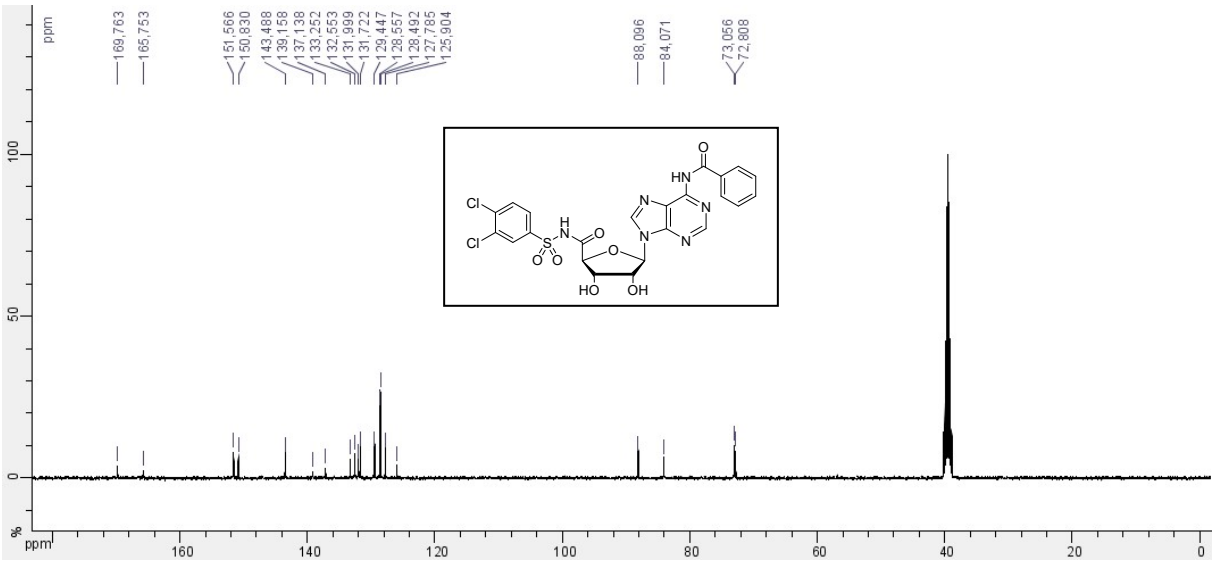
4'-(*N*-((3,4-dichlorophenyl)sulfonyl)acetamide)-*N*-Bz-adenosine (8g)



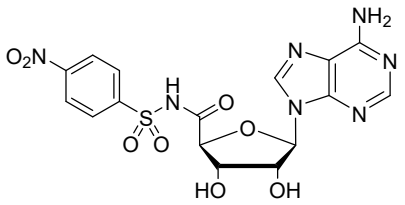
3,4-dichlorobenzenesulfonyl azide **2d** (13 mg, 52 μmol) was dissolved in dry NMP (600 μL). Thereafter, 4'-tetrabutylammonium thioacetate-*N*-Bz-adenosine **6b** (30 mg, 47 μmol), water (300 μL) and $NaHCO_3$ (11.7 mg, 140 μmol) were sequentially added. The resulting mixture was stirred at room temperature for 10 min. The reaction was checked for completion by RP-HPLC (system A). 0.1% aq. TFA (pH 2.0, 10 mL) was added and the resulting mixture was purified by RP-chromatography with a linear gradient of MeCN (0-60%) in 0.1% aq. TFA as the mobile phase, giving the desired product **8g** as a white amorphous powder after lyophilization (24 mg, 40 μmol, 86%, 99% purity). ^{1}H NMR (400 MHz, DMSO): δ = 4.22-4.23 (m, 1H), 4.50 (d, *J* = 2.1 Hz, 1H), 4.56-4.58 (m, 1H), 6.13 (d, *J* = 7.0 Hz, 1H), 7.55-7.68 (m, 3H), 7.91-7.96 (m, 2H), 8.05-8.15 (m, 3H), 8.70 (s, 1H), 8.82 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 72.8, 73.1, 84.1, 88.1, 125.9, 127.8, 128.5, 128.6, 129.4, 131.7, 132.0, 132.6, 133.3, 137.1, 139.2, 143.5, 150.8, 151.6 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{19}Cl_2N_6O_7S$: 593.0407; found 593.0421.

^{1}H and ^{13}C NMR Spectra (DMSO)



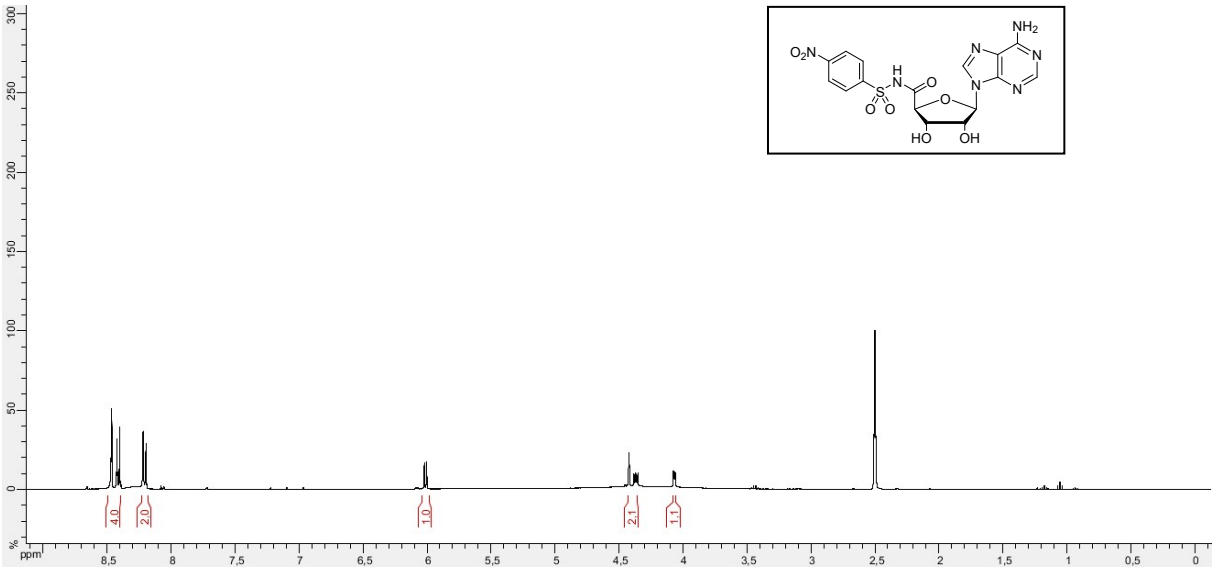


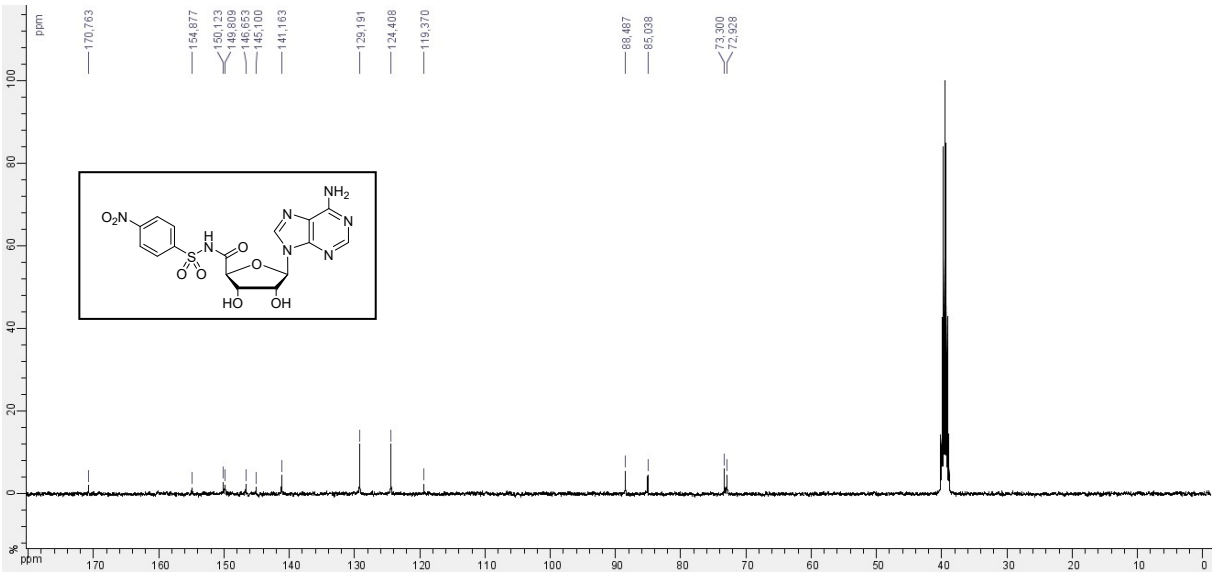
4'-(*N*-((4-nitrophenyl)sulfonyl)acetamide)-adenosine (10a)



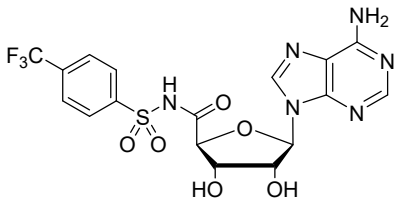
Ammonia aqueous solution 28% (2 mL) was added to a stirred solution of 4'-(*N*-((4-nitrophenyl)sulfonyl))-*N*-Bz-adenosine **8a** (10 mg, 17 μmol) in MeOH (1 mL). The reaction was stirred at room temperature for 16h. Volatiles were evaporated *in vacuo* and the residue was purified by RP-chromatography with a linear gradient of MeCN (0-30%) in 0.1% aq. TFA as the mobile phase giving the desired product **10a** as a white amorphous powder after lyophilization (10 mg, 16 μmol 84%, 96% purity). ^{1}H NMR (500 MHz, DMSO) δ = 4.07 (dd, J_1 = 4.6 Hz, J_2 = 1.6 Hz, 1H), 4.35-4.42 (m, 2H), 6.01 (d, J = 7.4 Hz, 1H), 8.19-8.23 (m, 2H), 8.39-8.43 (m, 2H), 8.46 (s, 1H), 8.47 (bs, 1H) ppm. ^{13}C NMR (125 MHz, DMSO) δ = 72.9, 73.3, 85.0, 88.5, 119.4, 124.4, 129.2, 141.2, 145.1, 146.7, 149.8, 150.1, 154.9, 170.8 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{16}N_7O_8S$: 466.0776; found 466.0760.

^{1}H and ^{13}C NMR Spectra (DMSO)



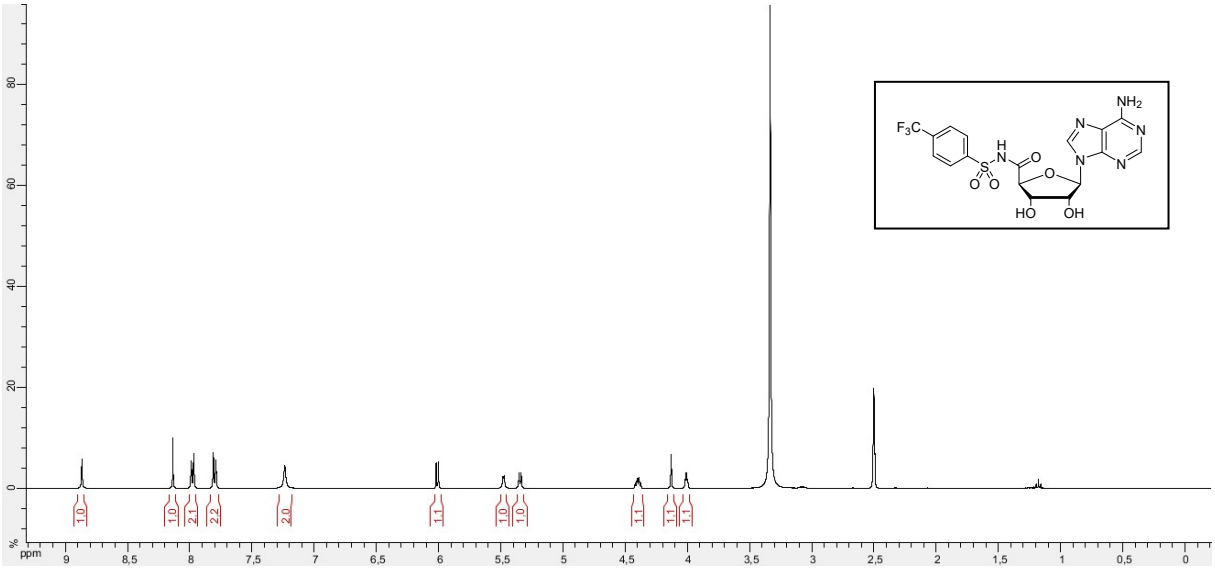


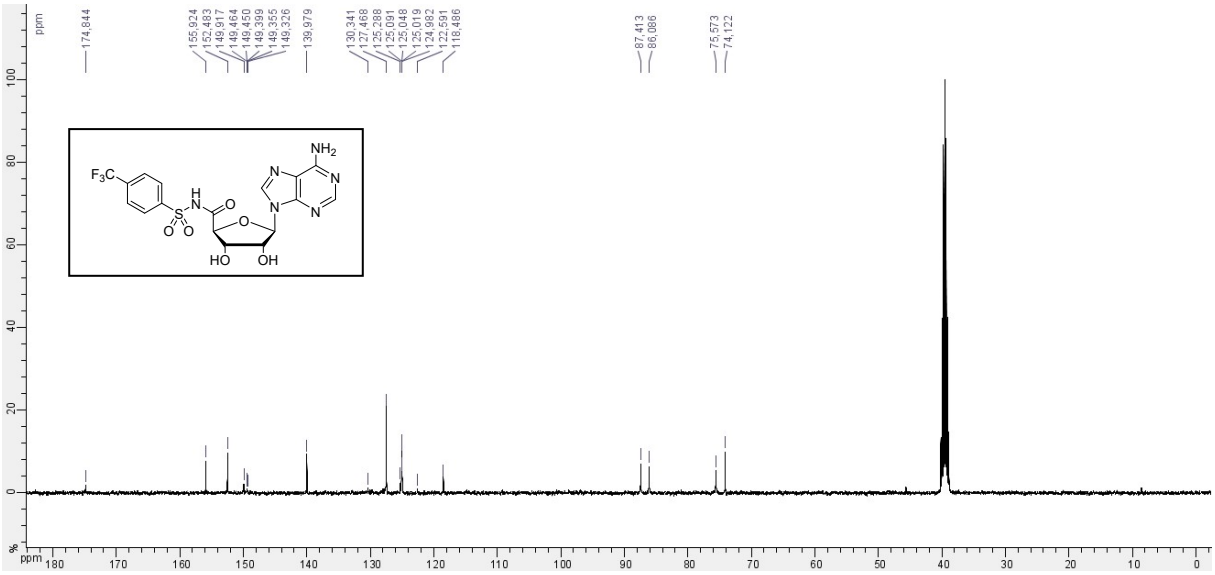
4'-(*N*-((4-trifluoromethyl)sulfonyl)acetamide)-adenosine (10b)



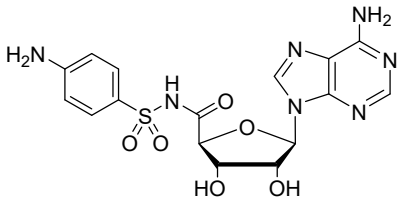
Ammonia aqueous solution 28% (2 mL) was added to a stirred solution of 4'-(*N*-((4-trifluoromethyl)sulfonyl)acetamide)-*N*-Bz-adenosine **8b** (13 mg, 22 μmol) in MeOH (1 mL). The reaction was stirred at room temperature for 16h. Volatiles were evaporated *in vacuo* and the residue was purified by RP-chromatography with a linear gradient of MeCN (0-40%) in 0.1% aq. TFA as the mobile phase giving the desired product **10b** as a white amorphous powder after lyophilization (12 mg, 20 μmol 91%, 93% purity). ^{1}H NMR (500 MHz, DMSO) δ = 4.00 (t, *J* = 3.8 Hz, 1H), 4.13 (s, 1H), 4.37-4.41 (m, 1H), 5.36 (d, *J* = 6.8 Hz, 1H), 5.49 (d, *J* = 3.8 Hz, 1H), 6.01 (d, *J* = 7.4 Hz, 1H), 7.25 (s, 2H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.98 (d, *J* = 8.2 Hz, 2H), 8.14 (s, 1H), 8.87 (s, 1H) ppm. ^{13}C NMR (125 MHz, DMSO) δ = 74.1, 75.6, 86.1, 87.4, 118.5, 122.6, 125.0-125.1 (m), 125.3, 127.5, 130.3, 140.0, 149.3-149.5 (m), 149.9, 152.5, 155.9, 174.8 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}F_3N_6O_6S$: 489.0799; found 489.0796.

^{1}H and ^{13}C NMR Spectra (DMSO)



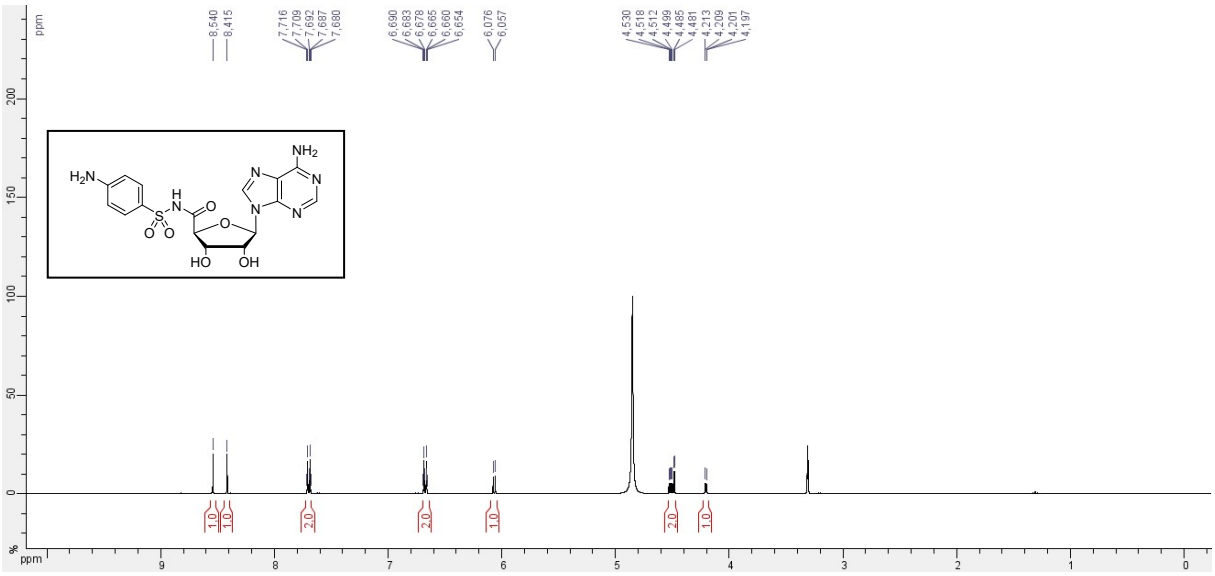


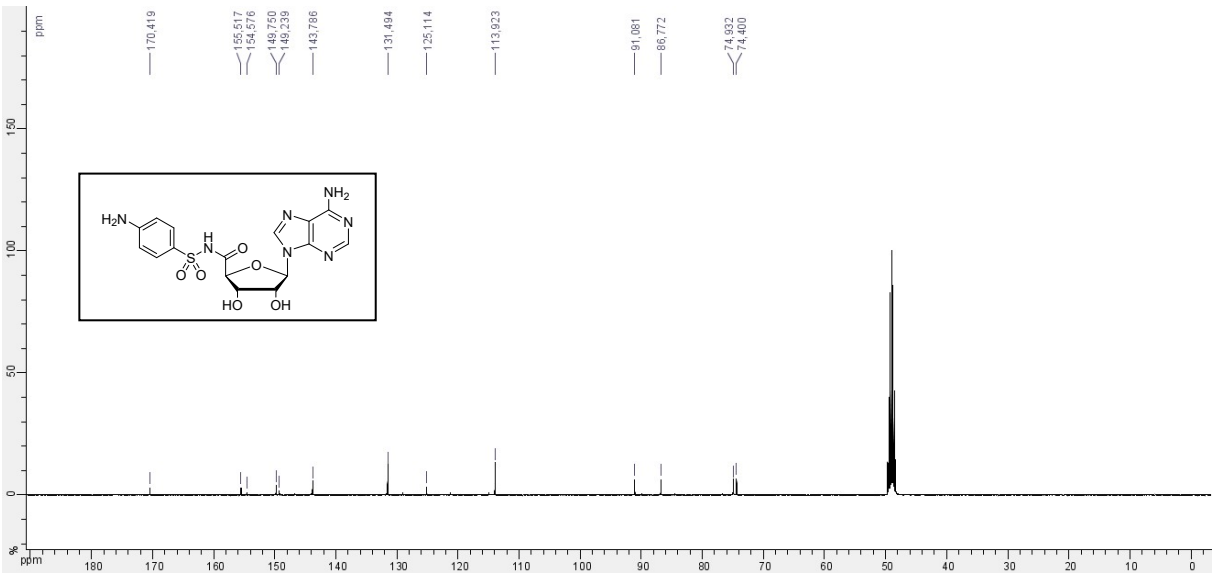
4'-(*N*-((4-aminophenyl)sulfonyl)acetamide)-adenosine (10c)



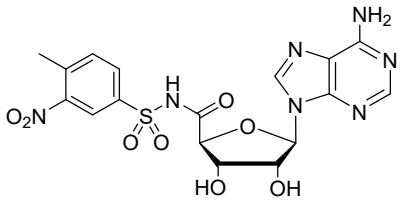
Ammonia aqueous solution 28% (2 mL) was added to a stirred solution of 4'-(*N*-((4-aminophenyl)sulfonyl))-*N*-Bz-adenosine **8c** (12 mg, 18 μmol) in MeOH (1 mL). The reaction was stirred at room temperature for 16h. Volatiles were evaporated *in vacuo* and the residue was purified by RP-chromatography with a linear gradient of MeCN (0-30%) in 0.1% aq. TFA as the mobile phase giving the desired product **10c** as a white amorphous powder after lyophilization (12 mg, 16 μmol 88%, 95% purity). ^{1}H NMR (400 MHz, MeOD) δ = 4.21 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H), 4.48-4.53 (m, 2H), 6.07 (d, J = 7.6 Hz, 1H), 6.65-6.69 (m, 2H), 7.68-7.72 (m, 2H), 8.42 (s, 1H), 8.54 (s, 1H) ppm. ^{13}C NMR (100 MHz, MeOD) δ = 74.4, 74.9, 86.8, 91.1, 113.9, 125.1, 131.5, 143.8, 149.2, 149.8, 154.6, 155.5, 170.4 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{18}N_7O_6S$: 436.1034; found 436.1039.

^{1}H and ^{13}C NMR Spectra (MeOD)



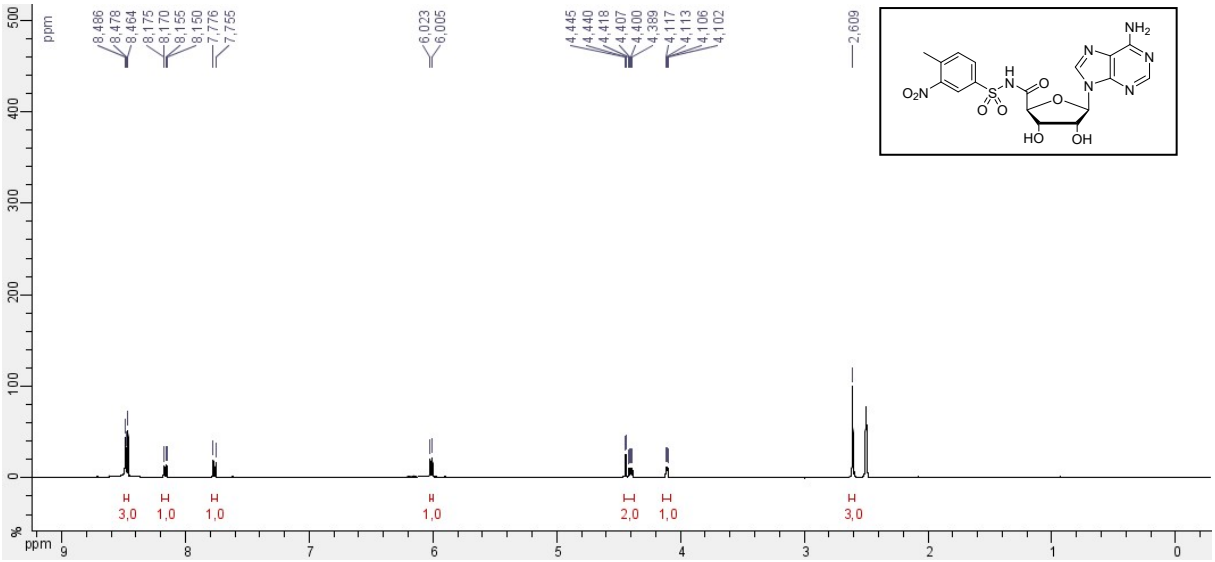


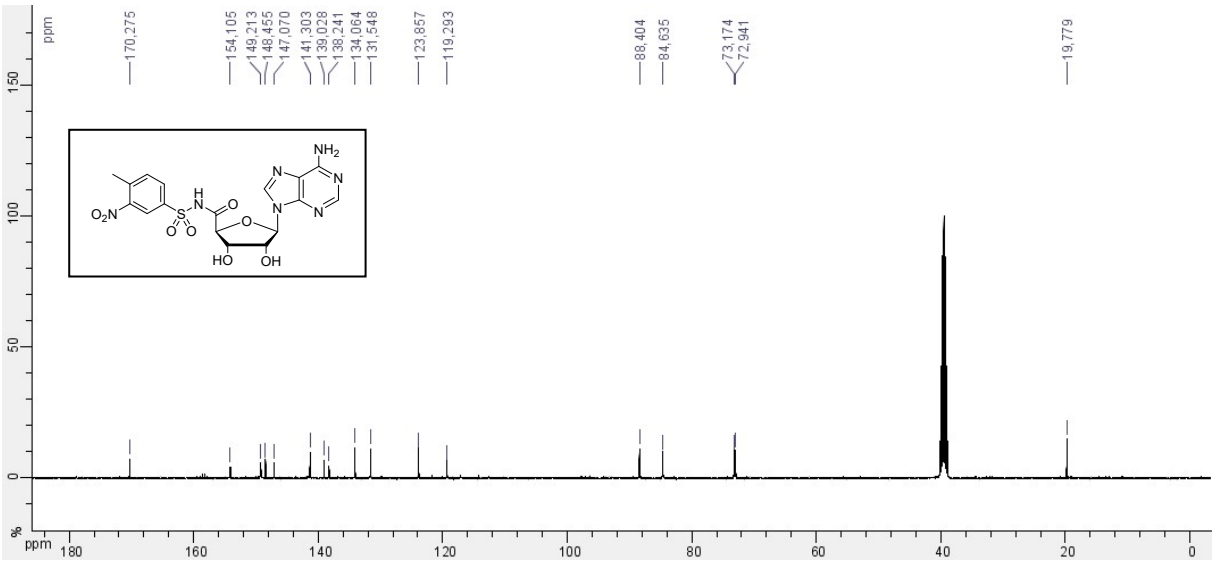
4'-(*N*-((4-methyl-3-nitrophenyl)sulfonyl)acetamide)-adenosine (10d)



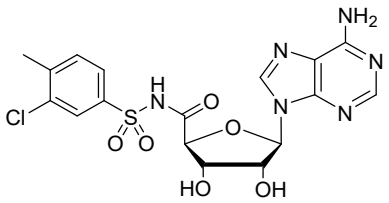
Ammonia aqueous solution 28% (2 mL) was added to a stirred solution of 4'-(*N*-((4-methyl-3-nitrophenyl)sulfonyl)acetamide)-*N*-Bz-adenosine **8e** (34 mg, 58 μmol) in MeOH (1 mL). The reaction was stirred at room temperature for 16h. Volatiles were evaporated *in vacuo* and the residue was purified by RP-chromatography with a linear gradient of MeCN (0-60%) in 0.1% aq. TFA as the mobile phase giving the desired product **10d** as a white amorphous powder after lyophilization (32 mg, 54 μmol, 96%, 96% purity). ^{1}H NMR (400 MHz, DMSO) δ = 2.61 (s, 3H), 4.10-4.12 (m, 1H), 4.39-4.42 (m, 1H), 4.44 (d, J = 1.7 Hz, 1H), 6.01 (d, J = 7.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 8.16 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 8.46-8.49 (m, 3H) ppm. ^{13}C NMR (100 MHz, DMSO) δ = 19.8, 72.9, 73.2, 84.6, 88.4, 119.3, 123.9, 131.5, 134.1, 138.2, 139.0, 141.3, 147.1, 148.5, 149.2, 154.1, 170.3 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}N_7O_8S$: 480.0932; found 480.0949.

^{1}H and ^{13}C NMR Spectra (DMSO)



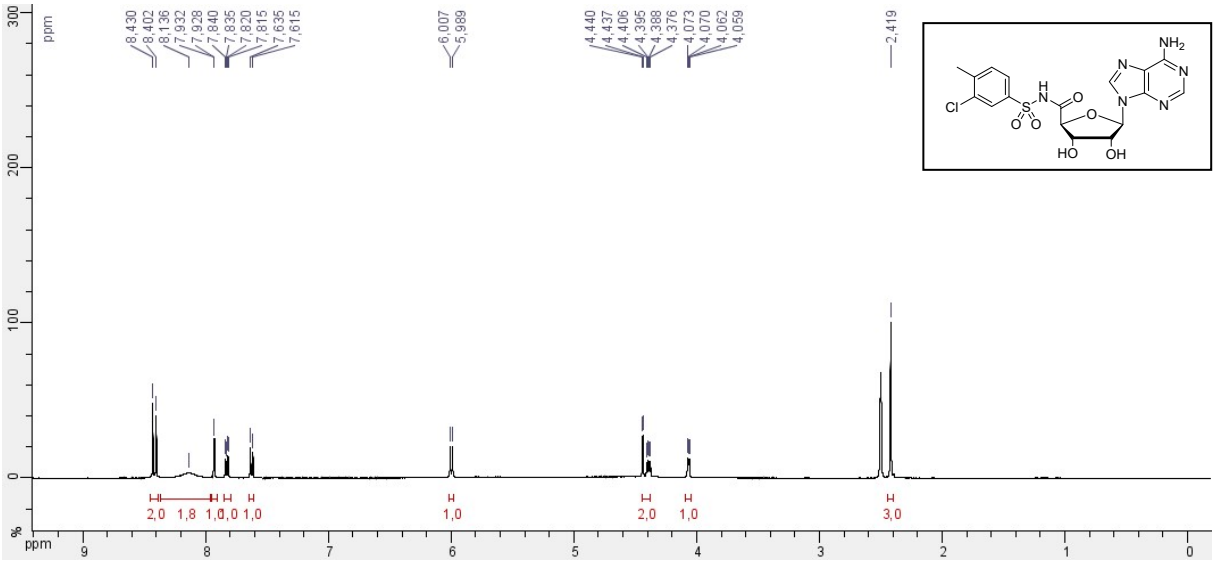


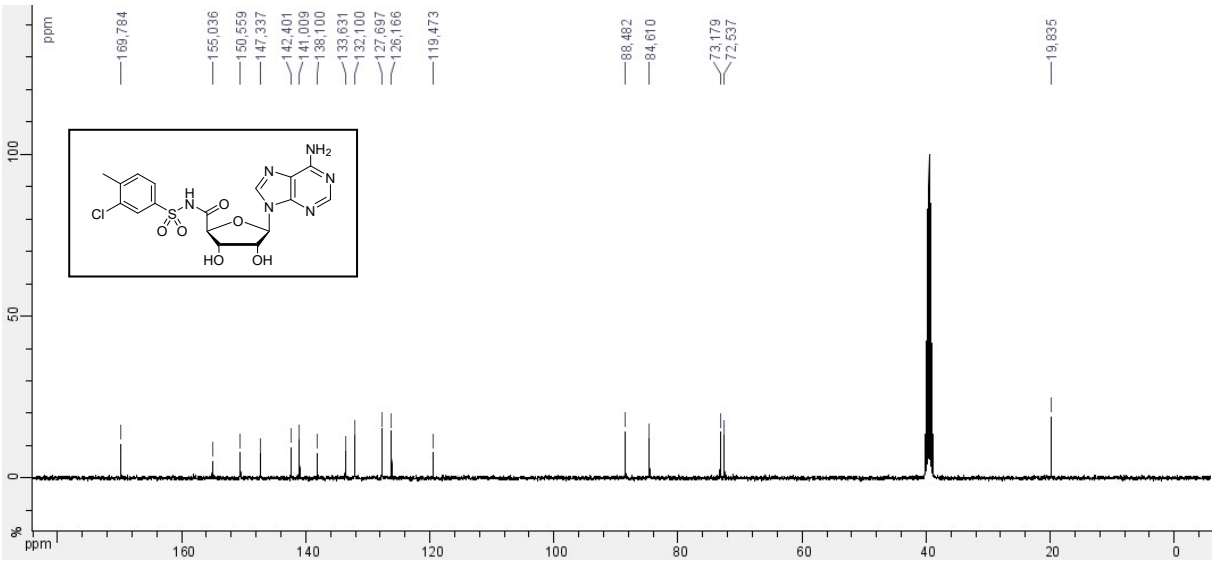
4'-(*N*-((3-chloro-4-methylphenyl)sulfonyl)acetamide)-adenosine (10e)



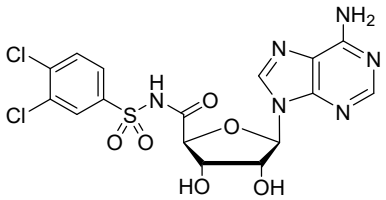
Ammonia aqueous solution 28% (2 mL) was added to a stirred solution of 4'-(*N*-((3-chloro-4-methylphenyl)sulfonyl)acetamide)-*N*-Bz-adenosine **8f** (34 mg, 53 μmol) in MeOH (1 mL). The reaction was stirred at room temperature for 16h. Volatiles were evaporated *in vacuo* and the residue was purified by RP-chromatography with a linear gradient of MeCN (0-60%) in 0.1% aq. TFA as the mobile phase giving the desired product **10e** as a white amorphous powder after lyophilization (30 mg, 52 μmol, quant., 97% purity). ^{1}H NMR (400 MHz, DMSO) δ = 2.42 (s, 3H), 4.06-4.07 (m, 1H), 4.38-4.41 (m, 1H), 4.44 (d, *J* = 1.4 Hz, 1H), 6.00 (d, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.83 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, , 1H), 7.93 (d, *J* = 1.6 Hz, 1H), 8.13 (bs, 2H), 8.40 (s, 1H), 8.43 (s, 1H) ppm. ^{13}C NMR (125 MHz, DMSO) δ = 19.8, 72.5, 73.2, 84.6, 88.5, 119.5, 126.2, 127.7, 132.1, 133.6, 138.1, 141.0, 142.4, 147.3, 150.6, 155.0, 169.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}N_6O_6SCl$: 469.0697; found 469.0695.

^{1}H and ^{13}C NMR Spectra (DMSO)



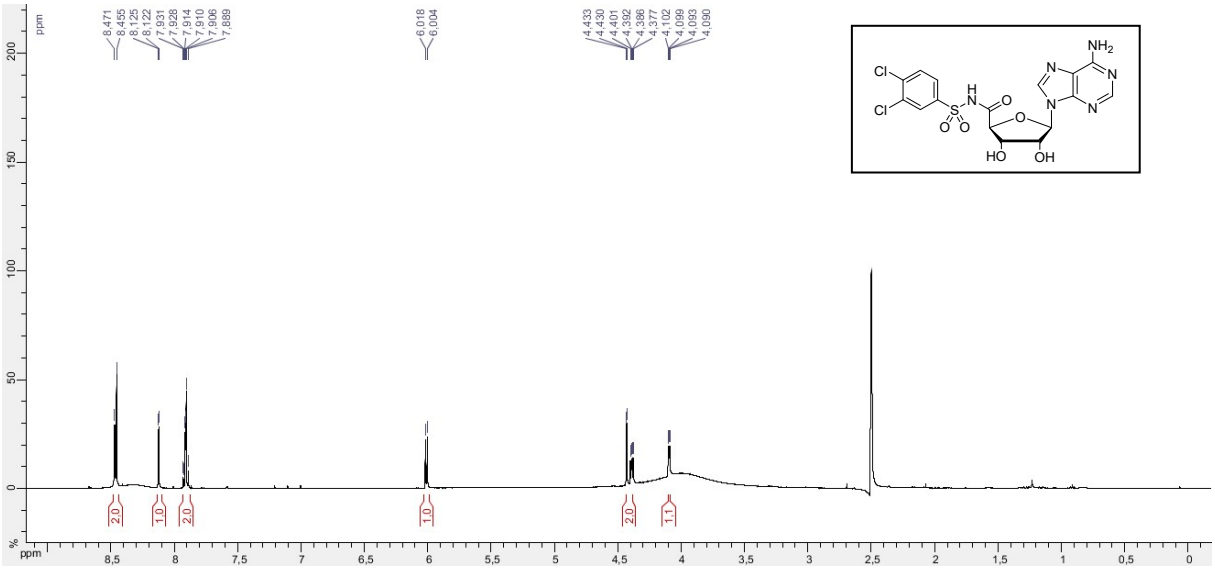


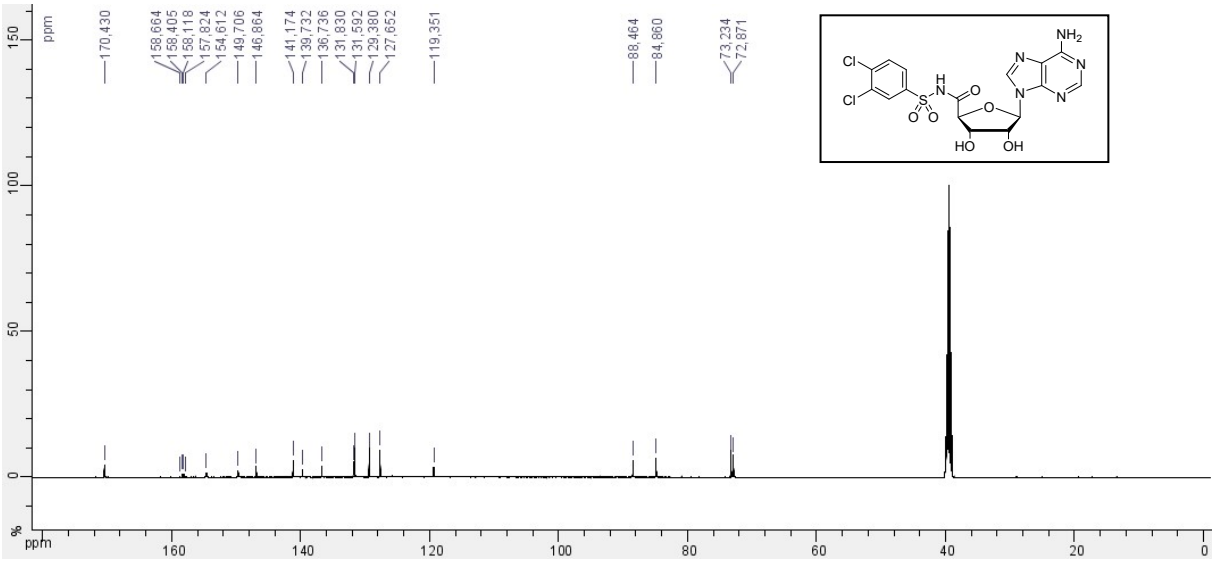
4'-(*N*-((3,4-dichlorophenyl)sulfonyl)acetamide)-adenosine (10f)



Ammonia aqueous solution 28% (2 mL) was added to a stirred solution of 4'-(*N*-((3,4-dichlorophenyl)sulfonyl)acetamide)-*N*-Bz-adenosine **8g** (10 mg, 18 μmol) in MeOH (1 mL). The reaction was stirred at room temperature for 16h. Volatiles were evaporated *in vacuo* and the residue was purified by RP-chromatography with a linear gradient of MeCN (0-60%) in 0.1% aq. TFA as the mobile phase giving the desired product **10f** as a white amorphous powder after lyophilization (11 mg, 18 μmol, quant., 97% purity). ^{1}H NMR (500 MHz, DMSO) δ = 4.09-4.10 (m, 1H), 4.38-4.40 (m, 1H), 4.43 (d, *J* = 1.6 Hz, 1H), 6.01 (d, *J* = 7.4 Hz, 1H), 7.89-7.93 (m, 2H), 8.12 (d, *J* = 1.8 Hz, 1H), 8.46 (s, 1H), 8.47 (s, 1H) ppm. ^{13}C NMR (125 MHz, DMSO) δ = 72.9, 73.2, 84.9, 88.5, 119.4, 127.7, 129.4, 131.6, 131.8, 136.7, 139.7, 141.2, 146.9, 149.7, 154.6, 158.3 (q), 170.4 ppm. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{15}Cl_2N_6O_6S$: 489.0145; found 489.0161.

^{1}H and ^{13}C NMR Spectra (DMSO)

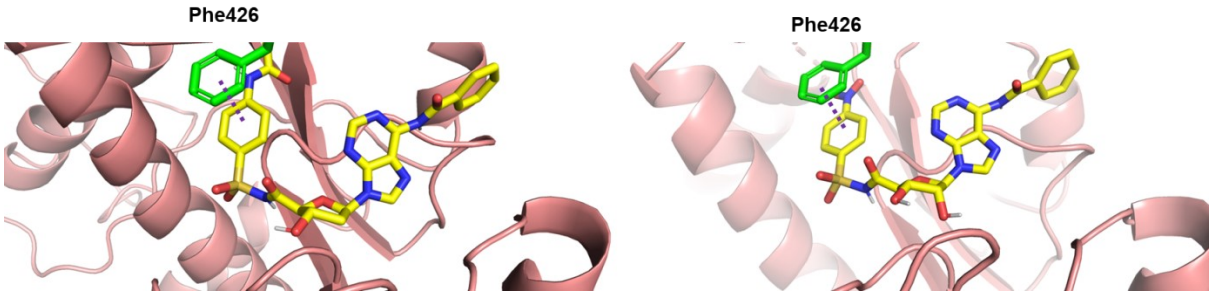




Molecular Docking Studies

All calculations were performed using Autodock Vina (The Scripps Research Institute, La Jolla, CA) on an MSI computer with a 2.30 GHz Intel Core i5-8300H. The solved X-ray crystal structure of SARS-CoV nsp14 (PDB 5C8T) was used as a static receptor for docking. Both the co-crystalized ligand SAM and ions were removed from the SARS-CoV nsp14 protein using VMD 1.9.3 software. The ligand structures were drawn and minimized using MarvinSketch (ChemAxon). Targeted protein and ligand structures with polar hydrogens were converted to the required PDBQT format using MGL Tools (version 1.5.6). The docking was performed with a search box located at x = −11.155, y = −40.77, z = −3.688 coordinates, with a search box size of 25 × 25 × 25 Å3. After calculations, PDB files were analyzed using Pymol (version 2.3).

Figure S1. Modeling results in the cap-binding pocket of SARS-CoV nsp14 with 7d (left) and 8a (right). Phe426 is shown in green. π-π stacking interactions (purple) are shown.



Calculated affinity of **7d** and **8a** about -11 kcal.mol^{-1}.

Bibliography

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3. D. Crich, K. Sana and S. Guo, *Org. Lett.*, 2007, **9**, 4423-4426.