Supporting information

N-arylsulfonamide-based adenosine analogues to target RNA cap *N*7-methyltransferase nsp14 of SARS-CoV-2

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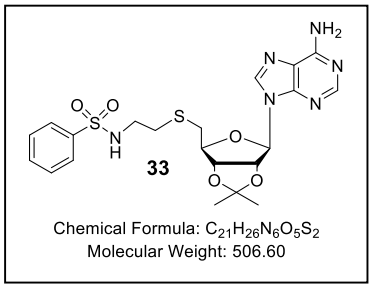
Detailed synthetic procedures and spectral characterization data for compounds 1-53

General information

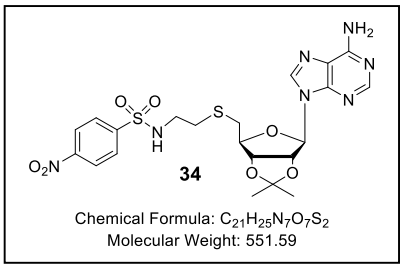
All dry solvents and reagents were purchased from commercial suppliers and were used without further purification. Thin-layer chromatography (TLC) analyses were carried out on silica plate 60 F_{254}. Purifications by column chromatography were performed using Biotage Isolera 1 system or Buchi C-815 system with Flash-Pure cartridges (Buchi). NMR experiments were recorded on Bruker 500 or 600 MHz spectrometers at 20°C. HRMS analyses were obtained with electrospray ionization (ESI) in positive mode on a Q-TOF Micromass spectrometer. Analytical HPLC was performed on a UHPLC Thermoscientific Ultimate 3000 system equipped with a LPG-3400RS pump, a DAD 3000 detector and an WPS-3000TBRS Autosampler, Column Oven TCC-3000SD. Final compounds **1-31** were stored at -20 °C for several months without any degradation.

Synthesis of *N*-arylsulfonamide adenosine analogues with an *N*-ethylthioether linker (33-40 ; 1-8)



Chemical Formula: $C_{21}H_{26}N_6O_5S_2$
Molecular Weight: 506.60

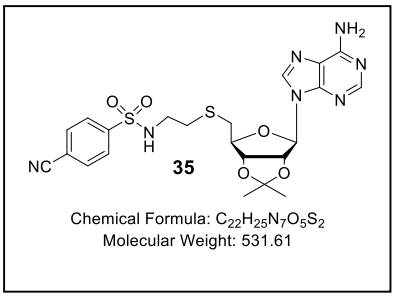
N-(2-((((3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)thio)ethyl)benzene-sulfonamide (33). Following method **A** with **32** (100 mg, 0.27 mmol, 1.00 eq) and benzenesufonyl chloride (60 mg, 0.34 mmol, 1.25 eq), **33** was obtained as a white solid (77 mg, 56%). R_f 0.56 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.31 (s, 1H, H_8) ; 8.16 (s, 1H, H_2) ; 7.79 – 7.76 (m, 2H, H_{Ar}) ; 7.65 – 7.60 (m, 1H, H_{Ar}) ; 7.58 (m, 2H, H_{Ar}) ; 7.34 (br s, 2H, NH_2) ; 6.15 (d, *J* = 2.5 Hz, 1H, $H_{1'}$) ; 5.47 (dd, *J* = 6.2, 2.4 Hz, 1H, $H_{2'}$) ; 4.96 (dd, *J* = 6.3, 2.9 Hz, 1H, $H_{3'}$) ; 4.17 (m, 1H, $H_{4'}$) ; 2.87 (t, *J* = 7.2 Hz, 2H, $CH_{2\ Et}$) ; 2.76 (dd, *J* = 13.5, 8.0 Hz, 1H, $H_{5'}$) ; 2.69 (dd, *J* = 13.5, 6.4 Hz, 1H, $H_{5''}$) ; 2.54 – 2.47 (m, 2H, $CH_{2\ Et}$) ; 1.52 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 148.7 (C_4) ; 140.5 ($C_{q\ Ar}$) ; 140.0 (C_8) ; 132.4 (C_{Ar}) ; 129.2 (C_{Ar}) ; 126.9 (C_{Ar}) ; 119.1 (C_5) ; 113.3 ($C_{q\ isopr}$) ; 89.2 ($C_{1'}$) ; 85.5 ($C_{4'}$) ; 83.3 ($C_{3'}$) ; 83.1 ($C_{2'}$) ; 42.6 ($CH_{2\ Et}$) ; 33.3 ($C_{5'}$) ; 31.0 ($CH_{2\ Et}$) ; 26.9 ($CH_{3\ isopr}$) ; 25.1 ($CH_{3\ isopr}$). **HRMS** (ESI+): m/z calc. for $C_{21}H_{27}N_6O_5S_2$ $[M+H]^+$: 507.1479, Found 507.1483.



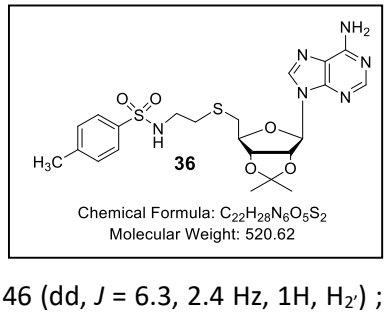
Chemical Formula: $C_{21}H_{25}N_7O_7S_2$
Molecular Weight: 551.59

N-(2-((((3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)thio)ethyl)-4-nitro-benzenesulfonamide (34). Following method **A** with **32** (150 mg, 0.41 mmol, 1.00 eq) and 4-nitrobenzenesufonyl chloride (113 mg, 0.51 mmol, 1.25 eq), **34** was obtained as a white solid (180 mg, 80%). R_f 0.48 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.44 – 8.37 (m, 2H, 2H $_{Ar}$) ; 8.30 (s, 1H, H_8) ; 8.19 – 8.11 (m, 2H, H_2, NH) ; 8.06 – 7.99 (m, 2H, 2H $_{Ar}$) ; 7.33 (br. s, 2H, NH_2) ; 6.14 (d, *J* = 2.4 Hz, 1H, $H_{1'}$) ; 5.47 (dd, *J* = 6.3, 2.4 Hz, 1H, $H_{2'}$) ; 4.95 (dd, *J* = 6.3, 2.9 Hz, 1H, $H_{3'}$) ; 4.16 (td, *J* = 6.5, 3.0 Hz, 1H, $H_{4'}$) ; 2.93 (t, *J* = 7.1 Hz, 2H, $CH_{2\ Et}$) ; 2.76 (dd, *J* = 13.6, 7.8 Hz, 1H, $H_{5'}$) ; 2.71 (dd, *J* = 13.5, 6.5 Hz, 1H, $H_{5''}$) ; 2.52 (m, 2H, $CH_{2\ Et}$) ; 1.52 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 149.5 ($C_{q\ Ar}$) ; 148.7 (C_4) ; 146.1 ($C_{q\ Ar}$) ; 140.0 (C_8) ; 128.0 ($CH_{\ Ar}$) ; 124.6 ($CH_{\ Ar}$) ; 119.1 (C_5), 113.3 ($C_{q\ isopr}$) ; 89.2 ($C_{1'}$) ; 85.6 ($C_{4'}$) ; 83.3 ($C_{3'}$) ; 83.1 ($C_{2'}$) ; 42.5 ($CH_{2\ Et}$) ; 33.2 ($C_{5'}$) ; 31.1 ($CH_{2\ Et}$) ; 26.9 ($CH_{3\ isopr}$) ; 25.1 ($CH_{3\ isopr}$). **HRMS** (ESI+): m/z calc. for $C_{21}H_{26}N_7O_7S_2$ $[M+H]^+$: 552.1330, Found 552.1340.

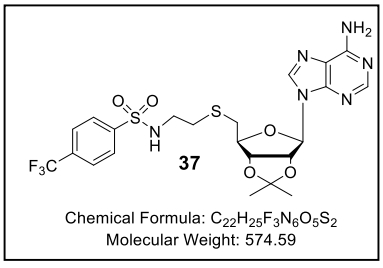
N-(2-((((3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)thio)ethyl)-4-cyanobenzenesulfonamide (35). Following method **A** with **32** (150 mg, 0.41 mmol, 1.00 eq) and 4-cyanobenzenesufonyl chloride (103 mg, 0.51 mmol, 1.25 eq), **35** was obtained as a white solid (129 mg, 59%). R_f 0.38 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.31 (s, 1H, H_8) ; 8.16 (s, 1H, H_2) ; 8.09 – 8.05 (m, 2H, H_{Ar}) ; 7.94 – 7.91 (m, 2H, H_{Ar}) ; 7.34 (br s, 2H, NH_2) ; 6.15 (d, *J* = 2.4, 1H, $H_{1'}$) ; 5.47 (dd, *J* = 6.3, 2.4 Hz, 1H, $H_{2'}$) ; 4.96 (dd, *J* = 6.3, 2.9 Hz, 1H, $H_{3'}$) ; 4.17 (td, *J* = 6.8, 2.7 Hz, 1H, $H_{4'}$) ; 2.90 (t, *J* = 7.2 Hz, 2H, $CH_{2\ Et}$) ; 2.76 (dd, *J* = 13.6, 7.8 Hz, 1H, $H_{5'}$) ; 2.71 (dd, *J* = 13.6, 6.5 Hz, 1H, $H_{5''}$) ; 2.53 – 2.47 (m, 2H, $CH_{2\ Et}$) ; 1.52 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 148.7 (C_4) ; 144.7 (CN) ; 140.0 (C_4) ; 133.4 (C_{Ar}) ; 127.2 (C_{Ar}) ; 119.1 (C_5) ; 117.7 ($C_{q\ Ar}$) ; 114.9 ($C_{q\ Az}$) ; 113.3 ($C_{q\ isopr}$) ; 89.2 ($C_{1'}$) ; 85.6 ($C_{4'}$) ; 83.3 ($C_{3'}$) ; 83.1 ($C_{2'}$) ; 42.5 ($CH_{2\ Et}$) ; 33.2 ($C_{5'}$) ; 31.1 ($CH_{2\ Et}$) ; 26.9 ($CH_{3\ isopr}$) ; 25.13 ($CH_{3\ isopr}$). **HRMS** (ESI+): m/z calc. for $C_{22}H_{26}N_7O_5S_2$ $[M+H]^+$: 532.1437, Found 532.1443.



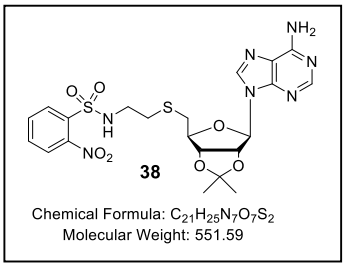
N-(2-((((3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)thio)ethyl)-4-methylbenzenesulfonamide (36). Following method **A** with **32** (150 mg, 0.41 mmol, 1.00 eq) and 4-methylbenzenesufonyl chloride (98 mg, 0.51 mmol, 1.25 eq), **36** was obtained as a white solid (164 mg, 77%). R_f 0.46 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.31 (s, 1H, H_8) ; 8.16 (s, 1H, H_2) ; 7.65 (d, *J* = 8.2 Hz, 2H, H_{Ar}) ; 7.37 (d, *J* = 8.3 Hz, 2H, H_{Ar}) ; 7.34 (br s, 2H, NH_2) ; 6.15 (d, *J* = 2.3 Hz, 1H, $H_{1'}$) ; 5.46 (dd, *J* = 6.3, 2.4 Hz, 1H, $H_{2'}$) ; 4.96 (dd, *J* = 6.3, 2.8 Hz, 1H, $H_{3'}$) ; 4.19 – 4.14 (m, 1H, $H_{4'}$) ; 2.84 (t, *J* = 7.2 Hz, 2H, $CH_{2\ Et}$) ; 2.77 (dd, , *J* = 13.6, 8.1 Hz, 1H, $H_{5'}$) ; 2.71 (dd, *J* = 13.5, 6.4 Hz, 1H, $H_{5''}$) ; 2.51 – 2.47 (m, 2H, $CH_{2\ Et}$) ; 2.37 (s, 3H, CH_3 Ar) ; 1.52 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.2 (C_6) ; 152.7 (C_2) ; 148.7 (C_4) ; 142.6 ($C_{q\ Ar}$) ; 140.0 (C_8) ; 137.6 ($C_{q\ Ar}$) ; 129.6 (C_{Ar}) ; 126.5 (C_{Ar}) ; 119.1 (C_5) ; 113.3 ($C_{q\ isopr}$) ; 89.2 ($C_{1'}$) ; 85.5 ($C_{4'}$) ; 83.3 ($C_{3'}$) ; 83.1 ($C_{2'}$) ; 42.7 ($CH_{2\ Et}$) ; 33.3 ($C_{5'}$) ; 31.0 ($CH_{2\ Et}$) ; 26.9 ($CH_{3\ isopr}$) ; 25.1 ($CH_{3\ isopr}$) ; 20.9 ($CH_{3\ Ar}$). **HRMS** (ESI+): m/z calc. for $C_{22}H_{29}N_6O_5S_2$ $[M+H]^+$: 521.1635, Found 521.1638.



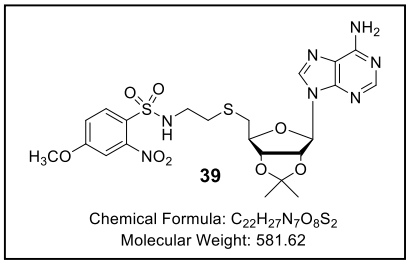
N-(2-((((3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)thio)ethyl)-4-(trifluoromethyl)benzenesulfonamide (37). Following method **A** with **32** (150 mg, 0.41 mmol, 1.00 eq) and 4-trifluoromethylbenzenesufonyl chloride (125 mg, 0.51 mmol, 1.25 eq), **37** was obtained as a white solid (157 mg, 67%). R_f 0.51 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.31 (s, 1H, H_8) ; 8.16 (s, 1H, H_2) ; 8.04 (br s, 1H, NH) ; 8.00 – 7.95 (m, 4H, H_{Ar}) ; 7.34 (s, 2H, NH_2) ; 6.15 (d, *J* = 2.4 Hz, 1H, $H_{1'}$) ; 5.47 (dd, *J* = 6.3, 2.4 Hz, 1H, $H_{2'}$) ; 4.96 (dd, *J* = 6.3, 2.9 Hz, 1H, $H_{3'}$) ; 4.17 (m, 1H, $H_{4'}$) ; 2.91 (t, *J* = 7.1 Hz, 2H, $CH_{2\ Et}$) ; 2.78-2.75 (dd, *J* = 13.6, 7.9 Hz, 1H, $H_{5'}$) ; 2.73-2.69 (dd, *J* = 13.6, 6.5 Hz, 1H, $H_{5''}$) ; 2.54 – 2.51 (m, 2H, $CH_{2\ Et}$) ; 1.51 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 148.7 (C_4) ; 144.5 ($C_{q\ Ar}$) ; 140.0 (C_8) ; 132.4, 132.2, 132.0, 131.8 ($C_{q\ Ar}$) ; 127.4 (C_{Ar}) ; 126.5 (C_{Ar}) ; 126.2, 124.4, 122.6, 120.8 (CF_3) ; 119.1 (C_5) ; 113.3 ($C_{q\ isopr}$) ; 89.2 ($C_{1'}$) ; 85.6 ($C_{4'}$) ; 83.3 ($C_{3'}$) ; 83.1 ($C_{2'}$) ; 42.6 ($CH_{2\ Et}$) ; 33.3 ; 31.1 (CH_2 Et) ; 26.9 ($CH_{3\ isopr}$) ; 25.1 ($CH_{3\ isopr}$). **HRMS** (ESI+): m/z calc. for $C_{22}H_{26}F_3N_6O_5S_2$ $[M+H]^+$: 575.1358, Found 575.1364.



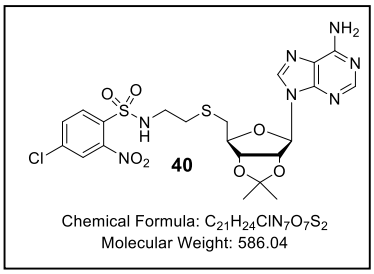
N-(2-((((3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)thio)ethyl)-2-nitro-benzenesulfonamide (38). Following method **A** with **32** (110 mg, 0.30 mmol, 1.00 eq) and 2-nitrobenzenesufonyl chloride (83 mg, 0.38 mmol, 1.25 eq), **38** was obtained as a white solid (117 mg, 71%). R_f 0.41 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.31 (s, 1H, H_8) ; 8.16 (br s, 1H, NH) ; 8.15 (s, 1H, H_2) ; 7.99 – 7.94 (m, 2H, H_{Ar}) ; 7.86 – 7.83 (m, 2H, H_{Ar}) ; 7.35 (s, 2H, NH_2) ; 6.15 (d, *J* = 2.4 Hz, 1H, $H_{1'}$) ; 5.47 (dd, *J* = 6.3, 2.4 Hz, 1H, $H_{2'}$) ; 4.96 (dd, *J* = 6.3, 2.9 Hz, 1H, $H_{3'}$) ; 4.18 (m, 1H, $H_{4'}$) ; 3.04 (t, *J* = 7.1 Hz, 2H, $CH_{2\ Et}$) ; 2.78-2.74 (dd, *J* = 13.6, 7.9 Hz, 1H, $H_{5'}$) ; 2.73-2.69 (dd, *J* = 13.5, 6.4 Hz, 1H, $H_{5''}$) ; 2.59 – 2.53 (m, 2H, $CH_{2\ Et}$) ; 1.52 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 148.7 (C_4) ; 147.5 ($C_{q\ Ar}$) ; 140.0 (C_8) ; 134.1 (C_{Ar}) ; 132.8 ($C_{q\ Ar}$) ; 132.7 (C_{Ar}) ; 129.4 (C_{Ar}) ; 124.5 (C_{Ar}) ; 119.2 (C_5) ; 113.3 ($C_{q\ isopr}$) ; 89.2 ($C_{1'}$) ; 85.5 ($C_{4'}$) ; 83.3 ($C_{3'}$) ; 83.2 ($C_{2'}$) ; 42.7 ($CH_{2\ Et}$) ; 33.2 ($C_{5'}$) ; 31.1 ($CH_{2\ Et}$) ; 27.0 ($CH_{3\ isopr}$) ; 25.2 ($CH_{3\ isopr}$). **HRMS** (ESI+): m/z calc. for $C_{21}H_{26}N_7O_7S_2$ $[M+H]^+$: 552.1330, Found 552.1330.



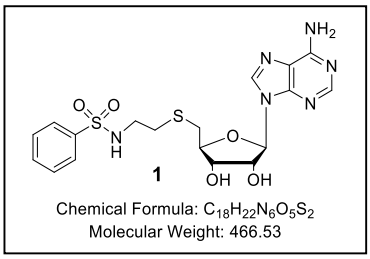
N-(2-((((3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)thio)ethyl)-4-methoxy-2-nitrobenzenesulfonamide (39). Following method **A** with **32** (110 mg, 0.30 mmol, 1.00 eq) and 2-nitro-4-methoxybenzenesufonyl chloride (94 mg, 0.38 mmol, 1.25 eq), **39** was obtained as a white solid (98 mg, 56%). R_f 0.5 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.31 (s, 1H, H_8) ; 8.15 (s, 1H, H_2) ; 7.96 (br s, 1H, NH) ; 7.87 (m, 1H, H_{Ar}) ; 7.56 (m, 1H, H_{Ar}) ; 7.34 (m, 3H, NH_2, H_{Ar}) ; 6.15 (d, *J* = 2.4 Hz, 1H, $H_{1'}$) ; 5.47 (dd, *J* = 6.3, 2.4 Hz, 1H, $H_{2'}$) ; 4.97 (dd, *J* = 6.3, 2.9 Hz, 1H, $H_{3'}$) ; 4.19 (m, 1H, $H_{4'}$) ; 3.90 (s, 3H, OCH_3) ; 3.00 (t, *J* = 7.1 Hz, 2H, $CH_{2\ Et}$) ; 2.79-2.75 (dd, *J* = 13.4, 8.0 Hz, 1H, $H_{5'}$) ; 2.74-2.70 (dd, *J* = 13.5, 6.4 Hz, 1H, $H_{5''}$) ; 2.57 – 2.53 (m, 2H, $CH_{2\ Et}$) ; 1.52 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 162.5 ($C_{q\ Ar}$) ; 156.2 (C_6) ; 152.8 (C_2) ; 149.1 ($C_{q\ Ar}$) ; 148.8 (C_4) ; 140.0 (C_8) ; 131.4 (C_{Ar}) ; 124.2 ($C_{q\ Ar}$) ; 119.2 (C_5) ; 117.4 (C_{Ar}) ; 113.3 ($C_{q\ isopr}$) ; 109.9 (C_{Ar}) ; 89.2 ($C_{1'}$) ; 85.5 ($C_{4'}$) ; 83.3 ($C_{3'}$) ; 83.1 ($C_{2'}$) ; 56.7 (OCH_3) ; 42.6 ($CH_{2\ Et}$) ; 33.3 ($C_{5'}$) ; 31.0 ($CH_{2\ Et}$) ; 26.9 ($CH_{3\ isopr}$) ; 25.1 ($CH_{3\ isopr}$). **HRMS** (ESI+): m/z calc. for $C_{22}H_{28}N_7O_8S_2$ $[M+H]^+$: 582,1435, Found 582,1433.



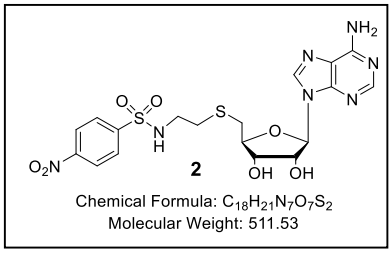
N-(2-((((3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)thio)ethyl)-4-chloro-2-nitrobenzenesulfonamide (40). Following method **A** with **32** (120 mg, 0.33 mmol, 1.00 eq) and 2-nitro-4-chlorobenzenesufonyl chloride (105 mg, 0.41 mmol, 1.25 eq), **40** was obtained as a white solid (85 mg, 44%). R_f 0.56 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.31 (s, 1H, H_8) ; 8.24 (m, 1H, H_{Ar}) ; 8.15 (s, 1H, H_2) ; 7.97 (m, 1H, H_{Ar}) ; 7.94 (m, 1H, H_{Ar}) ; 7.34 (br s, 2H, NH_2) ; 6.15 (d, *J* = 2.4 Hz, 1H, $H_{1'}$) ; 5.47 (dd, *J* = 6.3, 2.4 Hz, 1H, $H_{2'}$) ; 4.96 (dd, *J* = 6.3, 2.9 Hz, 1H, $H_{3'}$) ; 4.18 (m, 1H, $H_{4'}$) ; 3.04 (t, *J* = 7.1 Hz, 2H, $CH_{2\ Et}$) ; 2.79-2.75 (dd, *J* = 13.4, 7.9 Hz, 1H, $H_{5'}$) ; 2.74-2.70 (dd, *J* = 13.6, 6.4 Hz, 1H, $H_{5''}$) ; 2.57 – 2.54 (m, 2H, $CH_{2\ Et}$) ; 1.52 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.2 (C_6) ; 152.8 (C_2) ; 148.7 (C_4) ; 148.0 ($C_{q\ Ar}$) ; 140.0 (C_8) ; 138.1 ($C_{q\ Ar}$) ; 132.6 (C_{Ar}) ; 131.7 ($C_{q\ Ar}$) ; 131.1 (C_{Ar}) ; 124.4 (C_{Ar}) ; 119.2 (C_5) ; 113.4 ($C_{q\ isopr}$) ; 89.2 ($C_{1'}$) ; 85.5 ($C_{4'}$) ; 83.3 ($C_{3'}$) ; 83.2 ($C_{2'}$) ; 42.7 ($CH_{2\ Et}$) ; 33.2 ($C_{5'}$) ; 31.1 ($CH_{2\ Et}$) ; 26.9 ($CH_{3\ isopr}$) ; 25.2 ($CH_{3\ isopr}$). **HRMS** (ESI+): m/z calc. for $C_{21}H_{25}ClN_7O_7S_2$ $[M+H]^+$: 586.0940, Found 586.0950.



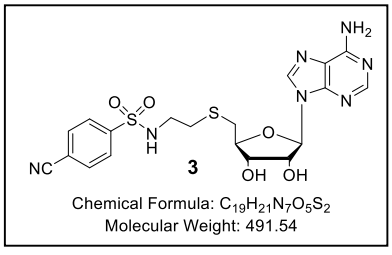
N-(2-((((2S,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)thio)ethyl)benzenesulfonamide (1). Following method **C** with intermediate **33** (70 mg, 0.14 mmol, 1.00 eq), **1** was obtained as a white solid (53 mg, 82%). R_f 0.14 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.32 (s, 1H, H_8) ; 8.14 (s, 1H, H_2) ; 7.79 – 7.74 (m, 2H, H_{Ar}) ; 7.64 – 7.60 (m, 1H, H_{Ar}) ; 7.59 – 7.55 (m, 2H, H_{Ar}) ; 7.27 (s, 2H, NH_2) ; 5.87 (d, *J* = 5.7 Hz, 1H, $H_{1'}$) ; 5.51 (br s, 1H, $OH_{2'}$) ; 5.32 (br s, 1H, $OH_{3'}$) ; 4.71 (t, *J* = 5.4 Hz, 1H, $H_{2'}$) ; 4.11 (m, 1H, $H_{3'}$) ; 3.97 – 3.92 (m, 1H, $H_{4'}$) ; 2.93 – 2.83 (m, 3H, $H_{5''}$, $CH_{2\ Et}$) ; 2.79 (dd, *J* = 13.8, 7.1 Hz, 1H, $H_{5''}$) ; 2.53 (m, 2H, $CH_{2\ Et}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.4 (C_4) ; 140.5 ($C_{q\ Ar}$) ; 139.8 (C_8) ; 132.4 (C_{Ar}) ; 129.2 (C_{Ar}) ; 126.4 (C_{Ar}) ; 119.2 (C_5) ; 87.4 ($C_{1'}$) ; 83.7 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 72.5 ($C_{3'}$) ; 42.7 ($CH_{2\ Et}$) ; 33.9 ($C_{5'}$) ; 31.5 ($CH_{2\ Et}$). **HRMS** (ESI+): m/z calc. for $C_{18}H_{23}N_6O_5S_2$ $[M+H]^+$: 467.1171, Found 467.1176.



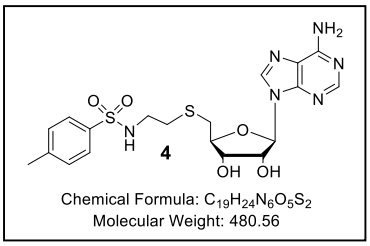
N-(2-((((2S,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)thio)ethyl)-4-nitrobenzene-sulfonamide (2). Following method **C** with intermediate **34** (170 mg, 0.31 mmol, 1.00 eq), **2** was obtained as a white solid (103 mg, 65%). R_f 0.14 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.43 – 8.37 (m, 2H, H_{Ar}) ; 8.31 (s, 1H, H_8) ; 8.15 (br s, 1H, NH) ; 8.14 (s, 1H, H_2) ; 8.05 – 8.01 (m, 2H, H_{Ar}) ; 7.26 (br s, 2H, NH_2) ; 5.86 (d, *J* = 5.6 Hz, 1H, $H_{1'}$) ; 5.48 (d, *J* = 6.0 Hz, 1H, $OH_{2'}$) ; 5.28 (br s, 1H, $OH_{3'}$) ; 4.71 (dd, *J* = 11.0, 5.6 Hz, 1H, $H_{2'}$) ; 4.11 (t, *J* = 4.2 Hz, 1H, $H_{3'}$) ; 3.94 (m, 1H, $H_{4'}$) ; 2.98 (m, 2H, $CH_{2\ Et}$) ; 2.87 (dd, *J* = 13.8, 5.7 Hz, 1H, $H_{5'}$) ; 2.80 (dd, *J* = 13.8, 7.1 Hz, 1H, $H_{5''}$) ; 2.80 (dd, *J* = 13.8, 7.1 Hz, 1H) ; 2.61 – 2.52 (m, 2H, $CH_{2\ Et}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.6 ($C_{q\ Ar}$) ; 149.4 (C_4) ; 146.1 ($C_{q\ Ar}$) ; 139.8 (C_8) ; 128.0 (C_{Ar}) ; 124.6 (C_{Ar}) ; 119.2 (C_5) ; 87.4 ($C_{1'}$) ; 83.8 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 72.5 ($C_{3'}$) ; 42.7 ($CH_{2\ Et}$) ; 33.8 ($C_{5'}$) ; 31.6 ($CH_{2\ Et}$). **HRMS** (ESI+): m/z calc. for $C_{18}H_{22}N_7O_7S_2$ $[M+H]^+$: 512.1017, Found 512.1011.



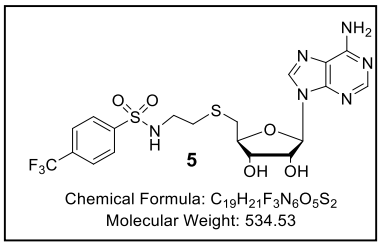
N-(2-((((2S,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)thio)ethyl)-4-cyanobenzen-esulfonamide (3). Following method **C** with intermediate **35** (124 mg, 0.23 mmol, 1.00 eq), **3** was obtained as a white solid (100 mg, 87%). R_f 0.11 (1:9 MeOH/DCM). **^{1}H--NMR** (600 MHz, DMSO-d_6) δ 8.32 (s, 1H, H_8) ; 8.14 (s, 1H, H_2) ; 8.09 (s, 1H, NH) ; 8.07 – 8.05 (m, 2H, H_{Ar}) ; 7.94 – 7.91 (m, 2H, H_{Ar}) ; 7.27 (s, 2H, NH_2) ; 5.87 (d, *J* = 5.6 Hz, 1H, $H_{1'}$) ; 5.49 (d, *J* = 5.8 Hz, 1H, $OH_{2'}$) ; 5.29 (d, *J* = 3.9 Hz, 1H, $OH_{3'}$) ; 4.71 (q, *J* = 5.3 Hz, 1H, $H_{2'}$) ; 4.11 (m, 1H, $H_{3'}$) ; 3.95 (ddd, *J* = 6.9, 5.7, 3.9 Hz, 1H, $H_{4'}$) ; 2.95 (m, 2H, $CH_{2\ Et}$) ; 2.87 (dd, *J* = 13.8, 5.7 Hz, 1H, $H_{5'}$) ; 2.80 (dd, *J* = 13.8, 7.1 Hz, 1H, $H_{5''}$) ; 2.55 (m, 2H, $CH_{2\ Et}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.4 (C_4) ; 144.7 (CN) ; 139.8 (C_8) ; 133.4 (C_{Ar}) ; 127.2 (C_{Ar}) ; 119.2 (C_5) ; 117.7 ($C_{q\ Ar}$) ; 114.9 ($C_{q\ Ar}$) ; 87.4 ($C_{1'}$) ; 83.8 ($C_{4'}$) ; 72.6 ($C_{3'}$) ; 72.5 ($C_{2'}$) ; 42.6 ($CH_{2\ Et}$) ; 33.8 ($C_{5'}$) ; 31.6 ($CH_{2\ Et}$). **HRMS** (ESI+): m/z calc. for $C_{19}H_{22}N_7O_5S_2$ $[M+H]^+$: 492.1124, Found 492.1137.



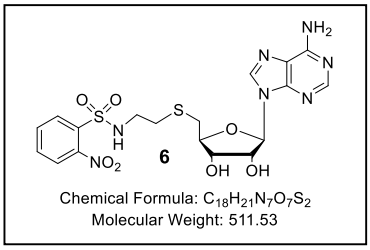
N-(2-((((2S,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)thio)ethyl)-4-methylbenzene-sulfonamide (4). Following method **C** with intermediate **36** (150 mg, 0.29 mmol, 1.00 eq), **4** was obtained as a white solid (96 mg, 69%). R_f 0.16 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.32 (s, 1H, H_8) ; 8.14 (s, 1H, H_2) ; 7.66 – 7.63 (m, 2H, H_{Ar}) ; 7.37 (m, 2H, H_{Ar}) ; 7.27 (s, 2H, NH_2) ; 5.87 (d, *J* = 5.7 Hz, 1H, $H_{1'}$) ; 5.48 (s, 1H, $OH_{2'}$) ; 5.29 (s, 1H, $OH_{3'}$) ; 4.71 (m, 1H, $H_{2'}$) ; 4.12 – 4.09 (m, 1H, $H_{3'}$) ; 3.94 (m, 1H, $H_{4'}$) ; 2.87 (m, 3H, $CH_{2\ Et}$, $H_{5'}$) ; 2.78 (dd, *J* = 13.8, 7.1 Hz, 1H, $H_{5''}$) ; 2.53 (m, 2H, $CH_{2\ Et}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.4 (C_4) ; 142.6 ($C_{q\ Ar}$) ; 139.8 (C_8) ; 137.6 ($C_{q\ Ar}$) ; 129.6 (C_{Ar}) ; 126.5 (C_{Ar}) ; 119.2 (C_5) ; 87.4 ($C_{1'}$) ; 83.7 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 72.5 ($C_{3'}$) ; 42.7 ($CH_{2\ Et}$) ; 33.9 ($C_{5'}$) ; 31.5 ($CH_{2\ Et}$) ; 20.9 ($CH_{3\ Ar}$). **HRMS** (ESI+): m/z calc. for $C_{19}H_{25}N_6O_5S_2$ $[M+H]^+$: 481.1328, Found 481.1335.



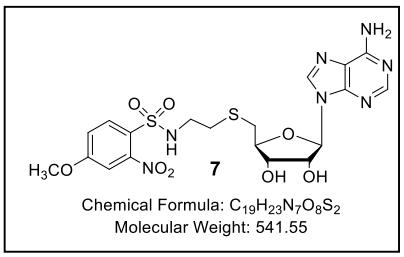
N-(2-((((2S,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)thio)ethyl)-4-(trifluoromethyl)-benzenesulfonamide (5). Following method **C** with intermediate **37** (115 mg, 0.20 mmol, 1.00 eq), **5** was obtained as a white solid (68 mg, 64%). R_f 0.19 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.32 (s, 1H, H_8) ; 8.14 (s, 1H, H_2) ; 8.05 (br s, 1H, NH) ; 8.00 – 7.95 (m, 4H, H_{Ar}) ; 7.27 (s, 2H, NH_2) ; 5.87 (d, *J* = 5.7 Hz, 1H, $H_{1'}$) ; 5.49 (d, *J* = 6.0 Hz, 1H, $OH_{2'}$) ; 5.29 (d, *J* = 4.6 Hz, 1H, $OH_{3'}$) ; 4.71 (q, *J* = 5.5 Hz, 1H, $H_{2'}$) ; 4.14 – 4.09 (m, 1H, $H_{3'}$) ; 3.95 (m, 1H, $H_{4'}$) ; 2.95 (t, *J* = 6.6 Hz, 2H, $CH_{2\ Et}$) ; 2.88 (dd, *J* = 13.8, 5.7 Hz, 1H, $H_{5'}$) ; 2.80 (dd, *J* = 13.8, 7.1 Hz, 1H, $H_{5''}$) ; 2.60 – 2.51 (m, 2H, $CH_{2\ Et}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.4 (C_4) ; 144.5 ($C_{q\ Ar}$) ; 139.8 (C_8) ; 132.5, 132.3, 132.0, 131.8 ($C_{q\ Ar}$) ; 127.4 (C_{Ar}) ; 126.5 (C_{Ar}) ; 126.2, 124.4, 122.6, 120.8 (CF_3) ; 119.2 (C_5) ; 87.4 ($C_{1'}$) ; 83.8 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 72.5 ($C_{3'}$) ; 42.7 ($CH_{2\ Et}$) ; 33.9 ($C_{5'}$) ; 31.6 ($CH_{2\ Et}$). **HRMS** (ESI+): m/z calc. for $C_{19}H_{22}F_3N_6O_5S_2$ $[M+H]^+$: 535.1040, Found 535.1041.



N-(2-((((2S,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)thio)ethyl)-2-nitrobenzene-sulfonamide (**6**). Following method **C** with intermediate **38** (117 mg, 0.21 mmol, 1.00 eq), **6** (83 mg, 77%) was obtained as a white solid (83 mg, 77%). R_f 0.14 (1:9 MeOH/DCM). **^{1}H-NMR** (500 MHz, DMSO-d_6) δ 8.33 (s, 1H, H_8) ; 8.20 (br s, 1H, NH); 8.14 (s, 1H, H_2) ; 8.00 – 7.94 (m, 2H, H_{Ar}) ; 7.84 (m, 2H, H_{Ar}) ; 7.31 (s, 2H, NH_2) ; 5.87 (d, *J* = 5.8 Hz, 1H, $H_{1'}$) ; 5.52 (d, *J* = 6.1 Hz, 1H, $OH_{2'}$) ; 5.33 (d, *J* = 5.0 Hz, 1H, $OH_{3'}$) ; 4.71 (q, *J* = 5.7 Hz, 1H, $H_{2'}$) ; 4.10 (dd, *J* = 8.7, 4.7 Hz, 1H, $H_{3'}$) ; 3.95 (m, 1H, $H_{4'}$) ; 3.07 (m, 2H, $CH_{2\ Et}$) ; 2.88 (dd, *J* = 13.8, 5.8 Hz, 1H, $H_{5'}$) ; 2.80 (dd, *J* = 13.8, 7.1 Hz, 1H, $H_{5''}$) ; 2.58 (m, 2H, $CH_{2\ Et}$). **^{13}C-NMR** (126 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7(C_2) ; 149.5 (C_4) ; 147.6 ($C_{q\ Ar}$) ; 139.9 (C_8) ; 134.1 (C_{Ar}) ; 132.9 ($C_{q\ Ar}$) ; 132.8 (C_{Ar}) ; 129.5 (C_{Ar}) ; 124.5 (C_{Ar}) ; 119.2 (C_5) ; 87.4 ($C_{1'}$) ; 83.8 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 72.6 ($C_{3'}$) ; 42.8 ($CH_{2\ Et}$) ; 33.8 ($C_{5'}$) ; 31.6 ($CH_{2\ Et}$). **HRMS** (ESI+): m/z calc. for $C_{18}H_{22}N_7O_7S_2$ $[M+H]^+$: 512.1017, Found 512.1018.

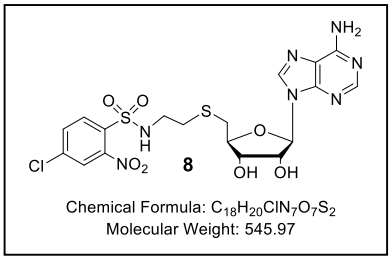


N-(2-((((2S,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)thio)ethyl)-4-methoxy-2-nitro-benzenesulfonamide (7). Following method **C** with intermediate **39** (92 mg, 0.16 mmol, 1.00 eq), **7** was obtained as a white solid (79 mg, 92%). R_f 0.15 (1:9 MeOH/DCM). **^{1}H-NMR** (500 MHz, DMSO-d_6) δ 8.33 (s, 1H, H_8) ; 8.14 (s, 1H, H_2), 8.00 (br s, 1H, NH) ; 7.87 (m, 1H, H_{Ar}) ; 7.56 (m, 1H, H_{Ar}) ; 7.34 (dd, *J* = 8.9, 2.6 Hz, 1H, H_{Ar}) ; 7.31 (br s, 2H, NH_2) ; 5.87 (d, *J* = 5.8 Hz, 1H, $H_{1'}$) ; 5.53 (d, *J* = 6.1 Hz, 1H, $OH_{2'}$) ; 5.34 (d, *J* = 4.9 Hz, 1H, $OH_{3'}$) ; 4.72 (dd, *J* = 11.1, 5.7 Hz, 1H, $H_{2'}$) ; 4.11 (dd, *J* = 8.6, 4.7 Hz, 1H, $H_{3'}$) ; 3.97 – 3.92 (m, 1H, $H_{4'}$) ; 3.89 (s, 3H, OCH_3) ; 3.03 (t, *J* = 7.2 Hz, 2H, $CH_{2\ Et}$) ; 2.88 (dd, *J* = 13.7, 5.9 Hz, 1H, $H_{5'}$) ; 2.80 (dd, *J* = 13.8, 7.1 Hz, 1H, $H_{5''}$) ; 2.57 (m, 2H, $CH_{2\ Et}$). **^{13}C-NMR** (126 MHz, DMSO-d_6) δ 162.6 ($C_{q\ Ar}$) ; 156.1 (C_6) ; 152.7 (C_2) ; 149.5 (C_4) ; 149.1 ($C_{q\ Ar}$) ; 139.9 (C_8) ; 131.3 (C_{Ar}) ; 124.1 ($C_{q\ Ar}$) ; 119.2 (C_5) ; 117.5 (C_{Ar}) ; 109.9 (C_{Ar}) ; 87.4 ($C_{1'}$) ; 83.8 ($C_{4'}$) ; 72.6 ($C_{3'}$) ; 72.6 ($C_{2'}$) ; 56.7 (OCH_3) ; 42.7 ($CH_{2\ Et}$) ; 33.8 ($C_{5'}$) ; 31.5 ($CH_{2\ Et}$). **HRMS** (ESI+): m/z calc. for $C_{19}H_{24}N_7O_8S_2$ $[M+H]^+$: 542.1122, Found 542.1126.



Chemical Formula: $C_{19}H_{23}N_7O_8S_2$
Molecular Weight: 541.55

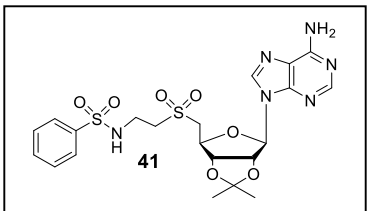
N-(2-((((2S,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)thio)ethyl)-4-chloro-2-nitro-benzenesulfonamide (8). Following method **C** with intermediate **40** (75 mg, 0.13 mmol, 1.00 eq), **8** was obtained as a white solid (57 mg, 82%). R_f 0.1 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.32 (s, 1H, H_8) ; 8.29 (br s, 1H, NH) ; 8.23 (d, *J* = 2.1 Hz, 1H, H_{Ar}) ; 8.14 (s, 1H, H_2); 7.97 (d, *J* = 8.6 Hz 1H, H_{Ar}) ; 7.93 (dd, *J* = 8.6, 2.1 Hz, 1H, H_{Ar}) ; 7.26 (br s, 2H, NH_2) ; 5.87 (d, *J* = 5.6 Hz, 1H, $H_{1'}$) ; 5.49 (d, *J* = 6.0 Hz, 1H, $OH_{2'}$) ; 5.30 (m, 1H, $OH_{3'}$) ; 4.71 (dd, *J* = 10.9, 5.5 Hz, 1H, $H_{2'}$) ; 4.11 (m, 1H, $H_{3'}$) ; 3.97 – 3.94 (m, 1H, $H_{4'}$) ; 3.08 (t, *J* = 7.2 Hz, 2H, $CH_{2\ Et}$) ; 2.88 (dd, *J* = 13.8, 5.7 Hz, 1H, $H_{5'}$) ; 2.81 (dd, *J* = 13.8, 7.1 Hz, 1H, $H_{5''}$) ; 2.59 (m, 2H, $CH_{2\ Et}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 149.4 (C_4) ; 148.0 ($C_{q\ Ar}$) ; 139.8 (C_8) ; 138.1 ($C_{q\ Ar}$) ; 132.6 (C_{Ar}) ; 131.7 (C_{Ar}) ; 131.1 (C_{Ar}) ; 124.4 ($C_{q\ Ar}$) ; 119.2 (C_5) ; 87.4 ($C_{1'}$) ; 83.8 ($C_{4'}$) ; 72.6 ($C_{3'}$) ; 72.5 ($C_{2'}$) ; 42.7 ($CH_{2\ Et}$) ; 33.8 ($C_{5'}$) ; 31.6 ($CH_{2\ Et}$). **HRMS** (ESI+): m/z calc. for $C_{18}H_{21}ClN_7O_7S_2$ $[M+H]^+$: 546.0627, Found 546.0626.



Chemical Formula: $C_{18}H_{20}ClN_7O_7S_2$
Molecular Weight: 545.97

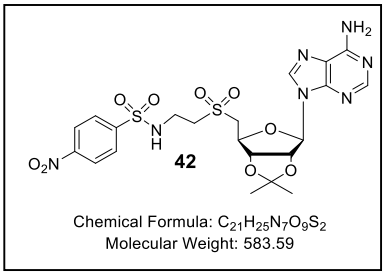
Synthesis of *N*-arylsulfonamide adenosine analogues with an *N*-ethylsulfone linker (41-45 ; 9-13)

N-(2-((((3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)sulfonyl)ethyl)-benzenesulfonamide (41). Following method **B** with intermediate **33** (135 mg, 0.27 mmol, 1.00 eq) and mCPBA (161 mg, 0.93 mmol, 3.50 eq), **41** was obtained as a white solid (119 mg, 83%). R_f 0.26 (5:95 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.32 (s, 1H, H_8) ; 8.18 (s, 1H, H_2) ; 7.82 (br s, 1H, NH) ; 7.74 – 7.71 (m, 2H, H_{Ar}) ; 7.64 (m, 1H, H_{Ar}) ; 7.61 – 7.57 (m, 2H, H_{Ar}) ; 7.37 (br s, 2H, NH_2) ; 6.24 (d, *J* = 2.2 Hz, 1H, $H_{1'}$) ; 5.39 (dd, *J* = 6.2, 2.2 Hz, 1H, $H_{2'}$) ; 5.12 (dd, *J* = 6.2, 3.2 Hz, 1H, $H_{3'}$) ; 4.53 (m, 1H, $H_{4'}$) ; 3.74 (dd, *J* = 14.7, 5.0 Hz, 1H, $H_{5'}$) ; 3.69 (dd, *J* = 14.7, 7.9 Hz, 1H, $H_{5''}$) ; 3.11 (t, *J* = 7.2 Hz, 2H, $CH_{2\ Et}$) ; 3.01 (m, 2H, $CH_{2\ Et}$) ; 1.55 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.2 (C_6) ; 152.8 (C_2) ; 148.5 (C_4) ; 140.1 (C_8) ; 139.6 ($C_{q\ Ar}$) ; 132.7 (C_{Ar}) ; 129.3 (C_{Ar}) ; 126.4 (C_{Ar}) ; 119.3 (C_5) ; 113.6 ($C_{q\ isopr}$) ; 89.3 ($C_{1'}$) ; 83.5 ($C_{3'}$)

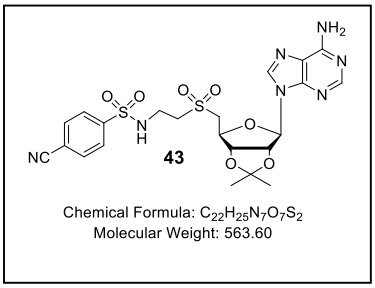


Chemical Formula: $C_{21}H_{26}N_6O_7S_2$
Molecular Weight: 538.59

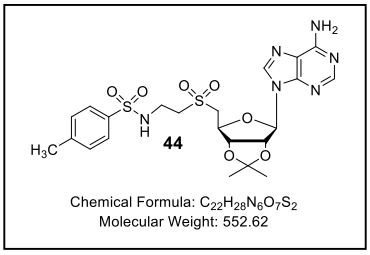
; 83.3 ($C_{2'}$) ; 80.6 ($C_{4'}$) ; 55.6 ($C_{5'}$) ; 52.9 ($CH_{2\ Et}$) ; 35.8 ($CH_{2\ Et}$) ; 26.9 ($CH_{3\ isopr}$) ; 25.2 ($CH_{3\ isopr}$). **HRMS** (ESI+): m/z calc. for $C_{21}H_{27}N_6O_7S_2$ $[M+H]^+$: 539.1377, Found 539.1377.



N-(2-((((3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)sulfonyl)ethyl)-4-nitrobenzenesulfonamide (42). Following method **B** with intermediate **34** (138 mg, 0.25 mmol, 1.00 eq) and mCPBA (151 mg, 0.88 mmol, 3.50 eq), **42** was obtained as a white solid (105 mg, 72%). R_f 0.43 (5:95 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.43 – 8.39 (m, 2H, H_{Ar}) ; 8.32 (s, 1H, H_8) ; 8.24 (br s, 1H, NH) ; 8.18 (s, 1H, H_2) ; 8.00 – 7.96 (m, 2H, H_{Ar}) ; 7.37 (s, 2H, NH_2) ; 6.24 (d, J = 2.1 Hz, 1H, $H_{1'}$) ; 5.40 (dd, J = 6.2, 2.2 Hz, 1H, $H_{2'}$) ; 5.11 (dd, J = 6.2, 3.1 Hz, 1H, $H_{3'}$) ; 4.52 (m, 1H, $H_{4'}$) ; 3.77 – 3.67 (m, 2H, $H_{5'}$) ; 3.14 (t, J = 7.1 Hz, 2H, $CH_{2\ Et}$) ; 3.09 – 3.04 (m, 2H, $CH_{2\ Et}$) ; 1.54 (s, 3H, $CH_{3\ isopr}$) ; 1.33 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.2 (C_6) ; 152.8 (C_2) ; 149.7 ($C_{q\ Ar}$) ; 148.5 (C_4) ; 145.3 ($C_{q\ Ar}$) ; 140.1 (C_8) ; 128.1 (C_{Ar}) ; 124.7 (C_{Ar}) ; 119.3 (C_5) ; 113.6 ($C_{q\ isopr}$) ; 89.3 ($C_{1'}$) ; 83.5 ($C_{3'}$) ; 83.2 ($C_{2'}$) ; 80.6 ($C_{4'}$) ; 55.6 ($C_{5'}$) ; 53.0 ($CH_{2\ Et}$) ; 35.8 ($CH_{2\ Et}$) ; 26.9 ($CH_{3\ isopr}$) ; 25.1 ($CH_{3\ isopr}$). **HRMS** (ESI+): m/z calc. for $C_{21}H_{26}N_7O_9S_2$ $[M+H]^+$: 584.1228, Found 584.1233.

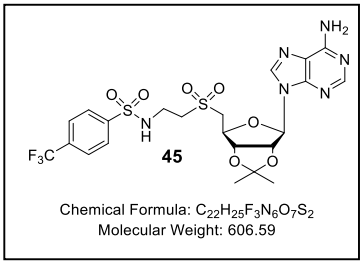


N-(2-((((3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)sulfonyl)ethyl)-4-cyanobenzenesulfonamide (43). Following method **B** with intermediate **35** (123 mg, 0.23 mmol, 1.00 eq) and mCPBA (140 mg, 0.81 mmol, 3.50 eq), **43** was obtained as a white solid (67 mg, 51%). R_f 0.46 (5:95 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.32 (s, 1H, H_8) ; 8.18 (s, 1H, H_2) ; 8.10 – 8.07 (m, 2H, H_{Ar}) ; 7.90 – 7.86 (m, 2H, H_{Ar}) ; 7.38 (br s, 2H, NH_2) ; 6.25 (d, J = 2.2 Hz, 1H, $H_{1'}$) ; 5.40 (dd, J = 6.1, 2.3 Hz, 1H, $H_{2'}$) ; 5.12 (dd, J = 6.2, 3.1 Hz, 1H, $H_{3'}$) ; 4.51 – 4.54 (m, 1H, $H_{4'}$) ; 3.76 – 3.68 (m, 2H, $H_{5'}$) ; 3.16 – 3.11 (m, 2H, $CH_{2\ Et}$) ; 3.06 – 3.00 (m, 2H, $CH_{2\ Et}$) ; 1.55 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.2 (C_6) ; 152.8 (C_2) ; 148.5 (C_4) ; 143.9 (CN) ; 140.1 (C_8) ; 133.5 (C_{Ar}) ; 127.2 (C_{Ar}) ; 119.3 (C_5) ; 117.7 ($C_{q\ Ar}$) ; 115.1 ($C_{q\ Ar}$) ; 113.6 ($C_{q\ isopr}$) ; 89.4 ($C_{1'}$) ; 83.5 ($C_{3'}$) ; 83.2 ($C_{2'}$) ; 80.7 ($C_{4'}$) ; 54.9 ($C_{5'}$) ; 53.0 ($CH_{2\ Et}$) ; 35.8 ($CH_{2\ Et}$) ; 26.9 ($CH_{3\ isopr}$) ; 25.2 ($CH_{3\ isopr}$). **HRMS** (ESI+): m/z calc. for $C_{22}H_{26}N_7O_7S_2$ $[M+H]^+$: 564.1330, Found 564.1325.

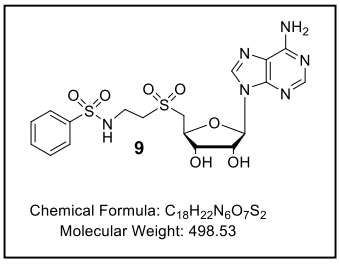


N-(2-((((3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)sulfonyl)ethyl)-4-methylbenzenesulfonamide (44). Following method **B** with intermediate **36** (120 mg, 0.23 mmol, 1.00 eq) and mCPBA (139 mg, 0.81 mmol, 3.50 eq), **44** was obtained as a white solid (78 mg, 61%). R_f 0.42 (5:95 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.33 (s, 1H, H_8) ; 8.17 (s, 1H, H_2) ; 7.73 (br s, 1H, NH) ; 7.60 (m, 2H, H_{Ar}) ; 7.40 – 7.37 (m, 4H, H_{Ar}, NH_2) ; 6.24 (d, J = 2.2 Hz, 1H, $H_{1'}$) ; 5.39 (dd, J = 6.1, 2.2 Hz, 1H, $H_{2'}$) ; 5.12 (dd, J = 6.2, 3.1 Hz, 1H, $H_{3'}$) ; 4.52 (m, 1H, $H_{4'}$) ; 3.74 (dd, J = 14.7, 5.0 Hz, 1H, $H_{5'}$) ; 3.69 (dd, J = 14.6, 7.9 Hz, 1H, $H_{5''}$) ; 3.11 (t, J = 7.2 Hz, 2H, $CH_{2\ Et}$) ; 3.00 – 2.95 (m, 2H, $CH_{2\ Et}$) ; 2.38 (s, 3H, $CH_{3\ Ar}$) ; 1.55 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.2 (C_6) ; 152.8 (C_2) ; 148.5 (C_4) ; 143.0 ($C_{q\ Ar}$) ; 140.1 (C_8) ; 136.7 ($C_{q\ Ar}$) ; 129.8 (C_{Ar}) ; 126.6 (C_{Ar}) ; 119.3 (C_5) ; 113.6 ($C_{q\ isopr}$) ; 89.3 ($C_{1'}$) ; 83.5 ($C_{3'}$) ; 83.3 ($C_{2'}$) ;

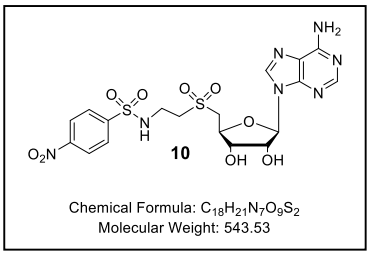
80.6 ($C_{4'}$) ; 55.6 ($C_{5'}$) ; 52.9 ($CH_{2\ Et}$) ; 35.8 ($CH_{2\ Et}$) ; 26.9 ($CH_{3\ isopr}$) ; 25.2 ($CH_{3\ isopr}$) ; 21.0 ($CH_{3\ Ar}$). **HRMS** (ESI+): m/z calc. for $C_{22}H_{29}N_6O_7S_2$ $[M+H]^+$: 553.1534, Found 553.1545.



N-(2-((((3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)sulfonyl)ethyl)-4-(trifluoromethyl)benzenesulfonamide (45). Following method **B** with intermediate **37** (157 mg, 0.27 mmol, 1.00 eq) and mCPBA (165 mg, 0.96 mmol, 3.50 eq), **45** was obtained as a white solid (118 mg, 71%). R_f 0.41 (5:95 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.32 (s, 1H, H_8) ; 8.18 (s, 1H, H_2) ; 8.12 (br s, 1H, NH) ; 8.00 – 7.98 (m, 2H, H_{Ar}) ; 7.95 – 7.93 (m, 2H, H_{Ar}) ; 7.37 (br s, 2H, NH_2) ; 6.25 (d, *J* = 2.2 Hz, 1H, $H_{1'}$) ; 5.40 (dd, *J* = 6.2, 2.2 Hz, 1H, $H_{2'}$) ; 5.12 (dd, *J* = 6.2, 3.1 Hz, 1H, $H_{3'}$) ; 4.53 (m, 1H, $H_{4'}$) ; 3.75 (dd, *J* = 14.7, 5.0 Hz, 1H, $H_{5'}$) ; 3.70 (dd, *J* = 14.7, 7.9 Hz, 1H, $H_{5''}$) ; 3.14 (t, *J* = 7.2 Hz, 2H, $CH_{2\ Et}$) ; 3.07 – 3.03 (m, 2H, $CH_{2\ Et}$) ; 1.54 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.2 (C_6) ; 152.8 (C_2) ; 148.5 (C_4) ; 143.7 ($C_{q\ Ar}$) ; 140.1 (C_8) ; 132.7, 132.5, 132.3, 132.1 ($C_{q\ Ar}$) ; 127.5 (C_{Ar}) ; 126.6 (C_{Ar}) ; 126.2, 124.4, 122.6, 120.8 (CF_3) ; 119.3 (C_5) ; 113.6 ($C_{q\ isopr}$) ; 89.3 ($C_{1'}$) ; 83.5 ($C_{3'}$) ; 83.3 ($C_{2'}$) ; 80.6 ($C_{4'}$) ; 55.6 ($C_{5'}$) ; 53.0 ($CH_{2\ Et}$) ; 35.8 ($CH_{2\ Et}$) ; 26.9 ($CH_{3\ isopr}$) ; 25.1 ($CH_{3\ isopr}$). **HRMS** (ESI+): m/z calc. for $C_{22}H_{26}F_3N_6O_7S_2$ $[M+H]^+$: 607.1251, Found 607.1234.

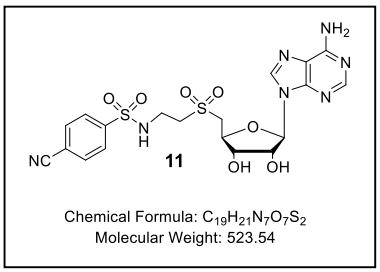


N-(2-((((2S,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)sulfonyl)ethyl)benzenesulfonamide (9). Following method **C** with intermediate **41** (135 mg, 0.27 mmol, 1.00 eq), **9** was obtained as a white solid (119 mg, 83%). R_f 0.09 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.35 (s, 1H, H_8) ; 8.16 (s, 1H, H_2) ; 7.82 (t, *J* = 5.1 Hz, 1H, NH) ; 7.71 – 7.68 (m, 2H, H_{Ar}) ; 7.64 – 7.60 (m, 1H, H_{Ar}) ; 7.58 – 7.54 (m, 2H, H_{Ar}) ; 7.31 (br s, 2H, NH_2) ; 5.92 (d, *J* = 5.4 Hz, 1H, $H_{1'}$) ; 5.60 (d, *J* = 5.8 Hz, 1H, $OH_{2'}$) ; 5.53 (d, *J* = 5.0 Hz, 1H, $OH_{3'}$) ; 4.65 (dd, *J* = 10.5, 5.3 Hz, 1H, $H_{2'}$) ; 4.31 – 4.26 (m, 1H, $H_{4'}$) ; 4.21 (dd, *J* = 9.0, 4.6 Hz, 1H, $H_{3'}$) ; 3.95 (dd, *J* = 14.9, 9.4 Hz, 1H, $H_{5'}$) ; 3.52 (dd, *J* = 14.9, 2.8 Hz, 1H, $H_{5''}$) ; 3.20 – 3.13 (m, 1H, $CH_{2\ Et}$) ; 3.12 – 3.05 (m, 3H, $CH_{2\ Et}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.1 (C_4) ; 140.0 (C_8) ; 139.7 ($C_{q\ Ar}$) ; 132.6 (C_{Ar}) ; 129.3 (C_{Ar}) ; 126.4 (C_{Ar}) ; 119.4 (C_5) ; 88.2 ($C_{1'}$) ; 78.3 ($C_{4'}$) ; 73.0 ($C_{3'}$) ; 72.4 ($C_{2'}$) ; 56.1 ($C_{5'}$) ; 53.0 ($CH_{2\ Et}$) ; 35.7 ($CH_{2\ Et}$). **HRMS** (ESI+): m/z calc. for $C_{18}H_{23}N_6O_7S_2$ $[M+H]^+$: 499.1064, Found 499.1063.

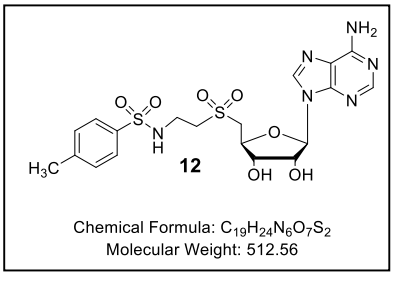


N-(2-((((2S,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)sulfonyl)ethyl)-4-nitrobenzenesulfonamide (10). Following method **C** with intermediate **42** (100 mg, 0.17 mmol, 1.00 eq), **10** was obtained as a white solid (64 mg, 69%). R_f 0.09 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.42 – 8.38 (m, 2H, H_{Ar}) ; 8.34 (s, 1H, H_8) ; 8.23 (t, *J* = 5.3 Hz, 1H, NH) ; 8.15 (s, 1H, H_2) ; 7.97 – 7.94 (m, 2H, H_{Ar}) ; 7.30 (br s, 2H, NH_2) ; 5.92 (d, *J* = 5.4 Hz, 1H, $H_{1'}$) ; 5.60 (d, *J* = 5.9 Hz, 1H, $OH_{2'}$) ; 5.52 (d, *J* = 5.0 Hz, 1H, $OH_{3'}$) ; 4.66 (dd, *J* = 10.6, 5.5 Hz, 1H, $H_{2'}$) ; 4.29 (ddd, *J* = 9.4, 3.8, 2.9 Hz, 1H, $H_{4'}$) ; 4.21 (dd, *J* = 9.1, 4.7 Hz, 1H, $H_{3'}$) ; 3.96 (dd, *J* = 14.9, 9.4 Hz, 1H, $H_{5'}$) ; 3.53 (dd, *J* = 14.9, 2.7 Hz, 1H, $H_{5''}$) ; 3.24 – 3.18 (m, 1H, $CH_{2\ Et}$) ; 3.17 – 3.11 (m, 3H, $CH_{2\ Et}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.7 ($C_{q\ Ar}$) ; 149.1 (C_4) ; 145.4 ($C_{q\ Ar}$) ; 140.0 (C_8) ; 128.1 (C_{Ar}) ; 124.7 (C_{Ar}) ; 119.4 (C_5) ; 88.2 ($C_{1'}$) ; 78.3 ($C_{4'}$) ; 73.0 ($C_{3'}$) ; 72.4 ($C_{2'}$) ; 56.2 ($C_{5'}$) ; 53.1 ($CH_{2\ Et}$) ; 35.7 ($CH_{2\ Et}$). **HRMS** (ESI+): m/z calc. for $C_{18}H_{22}N_7O_9S_2$ $[M+H]^+$: 544.0915, Found 544.0912.

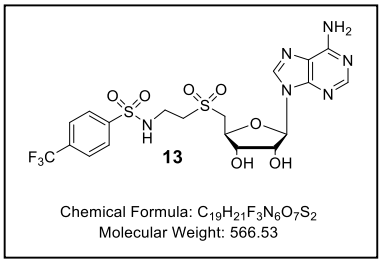
N-(2-((((2S,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)sulfonyl)ethyl)-4-cyanobenzene-sulfonamide (11). Following method **C** with intermediate **43** (67 mg, 0.12 mmol, 1.00 eq), **11** was obtained as a white solid (53 mg, 85%). R_f 0.10 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.35 (s, 1H, H_8) ; 8.18 – 8.14 (m, 2H, NH, H_2) ; 8.09 – 8.05 (m, 2H, H_{Ar}) ; 7.88 – 7.84 (m, 2H, H_{Ar}) ; 7.32 (br s, 2H, NH_2) ; 5.93 (d, *J* = 5.4 Hz, 1H, $H_{1'}$) ; 5.60 (d, *J* = 5.9 Hz, 1H, $OH_{2'}$) ; 5.53 (d, *J* = 5.0 Hz, 1H, $OH_{3'}$) ; 4.66 (dd, *J* = 10.6, 5.5 Hz, 1H, $H_{2'}$) ; 4.29 (ddd, *J* = 9.4, 3.8, 2.9 Hz, 1H, $H_{4'}$) ; 4.22 (dd, *J* = 9.1, 4.7 Hz, 1H, $H_{3'}$) ; 3.97 (dd, *J* = 14.9, 9.4 Hz, 1H, $H_{5'}$) ; 3.53 (dd, *J* = 14.9, 2.7 Hz, 1H, $H_{5''}$) ; 3.20 (m, 1H, $CH_{2\ Et}$) ; 3.15 – 3.08 (m, 3H, $CH_{2\ Et}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.1 (C_4) ; 143.9 (CN) ; 140.1 (C_8) ; 133.5 (C_{Ar}) ; 127.2 (C_{Ar}) ; 119.4 (C_5) ; 117.7 ($C_{q\ Ar}$) ; 115.1 ($C_{q\ Ar}$) ; 88.2 ($C_{1'}$) ; 78.3 ($C_{4'}$) ; 73.0 ($C_{3'}$) ; 72.4 ($C_{2'}$) ; 56.1 ($C_{5'}$) ; 53.1 ($CH_{2\ Et}$) ; 35.7 ($CH_{2\ Et}$). **HRMS** (ESI+): m/z calc. for $C_{19}H_{22}N_7O_7S_2$ $[M+H]^+$: 524.1017, Found 524.1011.



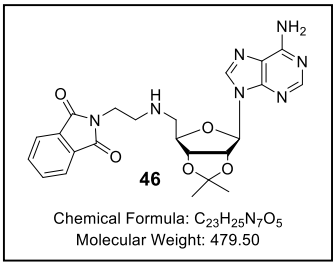
N-(2-((((2S,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)sulfonyl)ethyl)-4-methylbenzene-sulfonamide (12). Following method **C** with intermediate **44** (72 mg, 0.13 mmol, 1.00 eq), **12** was obtained as a white solid (44 mg, 66%). R_f 0.11 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.35 (s, 1H, H_8) ; 8.16 (s, 1H, H_2) ; 7.72 (br s, 1H, NH) ; 7.59 – 7.56 (m, 2H, H_{Ar}) ; 7.36 (m, 2H, H_{Ar}) ; 7.31 (br s, 2H, NH_2) ; 5.92 (d, *J* = 5.3 Hz, 1H, $H_{1'}$) ; 5.60 (d, *J* = 5.8 Hz, 1H, $OH_{2'}$) ; 5.53 (d, *J* = 4.8 Hz, 1H, $OH_{3'}$) ; 4.65 (q, *J* = 5.2 Hz, 1H, $H_{2'}$) ; 4.31 – 4.27 (m, 1H, $H_{4'}$) ; 4.21 (q, *J* = 4.3 Hz, 1H, $H_{3'}$) ; 3.95 (dd, *J* = 14.8, 9.3 Hz, 1H, $H_{5'}$) ; 3.52 (dd, *J* = 14.8, 2.7 Hz, 1H, $H_{5''}$) ; 3.21 – 3.07 (m, 2H, $CH_{2\ Et}$) ; 3.06 – 3.01 (m, 2H, $CH_{2\ Et}$) ; 2.37 (s, 3H, $CH_{3\ Ar}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.1 (C_4) ; 143.0 ($C_{q\ Ar}$) ; 140.0 (C_8) ; 136.8 ($C_{q\ Ar}$) ; 129.7 (C_{Ar}) ; 126.5 (C_{Ar}) ; 119.4 (C_5) ; 88.2 ($C_{1'}$) ; 78.2 ($C_{4'}$) ; 73.0 ($C_{3'}$) ; 72.4 ($C_{2'}$) ; 56.1 ($C_{5'}$) ; 53.0 ($CH_{2\ Et}$) ; 35.7 ($CH_{2\ Et}$) ; 21.0 ($CH_{3\ Ar}$). **HRMS** (ESI+): m/z calc. for $C_{19}H_{25}N_6O_7S_2$ $[M+H]^+$: 513.1221, Found 513.1216.



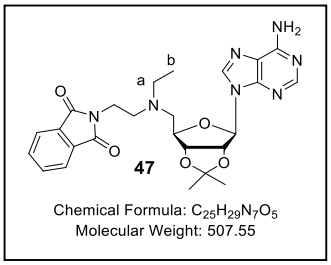
N-(2-((((2S,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)sulfonyl)ethyl)-4-(trifluoromethyl)-benzenesulfonamide (13). Following method **C** with intermediate **45** (107 mg, 0.18 mmol, 1.00 eq), **13** was obtained as a white solid (77 mg, 77%). R_f 0.08 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.36 (s, 1H, H_8) ; 8.16 (s, 1H, H_2) ; 8.13 (br s, 1H, NH) ; 7.97 (d, *J* = 8.4 Hz, 2H, H_{Ar}) ; 7.92 (d, *J* = 8.3 Hz, 2H, H_{Ar}) ; 7.31 (br s, 2H, NH_2) ; 5.93 (d, *J* = 5.4 Hz, 1H, $H_{1'}$) ; 5.61 (d, *J* = 5.8 Hz, 1H, $OH_{2'}$) ; 5.53 (d, *J* = 3.4 Hz, 1H, $OH_{3'}$) ; 4.66 (q, *J* = 5.2 Hz, 1H, $H_{2'}$) ; 4.32 – 4.28 (m, 1H, $H_{4'}$) ; 4.22 (d, *J* = 3.1 Hz, 1H, $H_{3'}$) ; 3.96 (dd, *J* = 14.9, 9.4 Hz, 1H, $H_{5'}$) ; 3.54 (dd, *J* = 14.9, 2.8 Hz, 1H, $H_{5''}$) ; 3.22 (m, 1H, $CH_{2\ Et}$) ; 3.18 – 3.09 (m, 3H, $CH_{2\ Et}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.1 (C_4) ; 143.7 ($C_{q\ Ar}$) ; 140.0 (C_8) ; 132.7, 132.5, 132.3, 132.1 (CF_3) ; 127.5 (C_{Ar}) ; 126.6 (C_{Ar}) ; 126.2, 124.4, 122.6, 120.8 ($C_{q\ Ar}$) ; 119.4 (C_5) ; 88.2 ($C_{1'}$) ; 78.3 ($C_{4'}$) ; 73.0 ($C_{3'}$) ; 72.4 ($C_{2'}$) ; 56.1 ($C_{5'}$) ; 53.1 ($CH_{2\ Et}$) ; 35.7 ($CH_{2\ Et}$). **HRMS** (ESI+): m/z calc. for $C_{19}H_{22}F_3N_6O_7S_2$ $[M+H]^+$: 567.0938, Found 567.0945.



Synthesis of *N*-arylsulfonamide adenosine analogues with an *N*-ethylamino linker (46-53 ; 14-18)

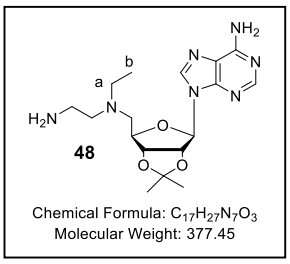


2-(2-((((3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)amino)ethyl)-isoindoline-1,3-dione (46). $NaBH(OAc)_3$ (6.00 g, 28.4 mmol, 8.70 eq) was slowly added to a solution under argon of 5'-amino-2',3'-*O*-*iso*propylideneadenosine (1.00 g, 3.26 mmol, 1.00 eq) and *N*-(2-oxoethyl)phthalimide (710 mg, 3.75 mmol, 1.15 eq) in anhydrous THF (0.12M). After stirring at r.t for 18 h, the reaction mixture was filtered twice through celite and concentrated under vacuum. The residue was purified by flash column chromatography (dry sample, silica gel, linear gradient 0-8% MeOH in DCM) to give **46** as a white solid (816 mg, 52%). R_f 0.55 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.32 (s, 1H, H_8) ; 8.14 (s, 1H, H_2) ; 7.85 – 7.79 (m, 4H, H_{Ar}) ; 7.30 (br s, 2H, NH_2) ; 6.04 (d, *J* = 3.3 Hz, 1H, $H_{1'}$) ; 5.35 (dd, *J* = 6.3, 3.3 Hz, 1H, $H_{2'}$) ; 4.88 (dd, *J* = 6.3, 2.7 Hz, 1H, $H_{3'}$) ; 4.14 (td, *J* = 5.9, 2.7 Hz, 1H, $H_{4'}$) ; 3.66 – 3.58 (m, 2H, $CH_{2\ Et}$) ; 2.75 (m, 3H, $H_{5'}$, $CH_{2\ Et}$) ; 2.68 (dd, *J* = 12.3, 5.8 Hz, 1H, $H_{5''}$) ; 1.90 (s, 1H) ; 1.50 (s, 3H, $CH_{3\ isopr}$) ; 1.25 (s, 3H, $CH_{3\ isopr}$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 168.0 (CO) ; 156.1 (C_6) ; 152.7 (C_2) ; 148.9 (C_4) ; 139.8 (C_8) ; 134.2 (C_{Ar}) ; 131.7 ($C_{q\ Ar}$) ; 122.9 (C_{Ar}) ; 119.2 (C_5) ; 113.1 ($C_{q\ isopr}$) ; 89.1 ($C_{1'}$) ; 84.8 ($C_{4'}$) ; 82.6 ($C_{2'}$) ; 82.1 ($C_{3'}$) ; 50.2 ($C_{5'}$) ; 46.7 ($CH_{2\ Et}$) ; 37.3 ($CH_{2\ Et}$) ; 27.0 ($CH_{3\ isopr}$) ; 25.1 ($CH_{3\ isopr}$). **HRMS** (ESI+): m/z calc. for $C_{23}H_{26}N_7O_5$ $[M+H]^+$: 480.1990, Found 480.1990.



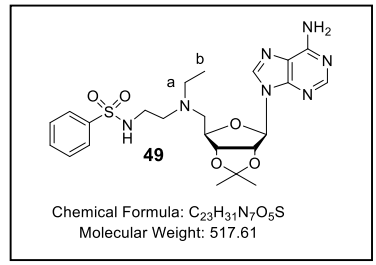
2-(2-((((3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)(ethyl)amino)ethyl)-isoindoline-1,3-dione (47). Acetic acid (179 mg, 2.99 mmol, 1.80 eq) was added to a solution under argon of **46** (796 mg, 1.66 mmol, 1.00 eq) and ethanal (132 mg, 2.99 mmol, 1.80 eq) in anhydrous DCE (0.017 M). After stirring at r.t for 20 min, $NaBH(OAc)_3$ (792 mg, 3.74 mmol, 2.25 eq) was added. After stirring at r.t for 18 h, the reaction mixture was diluted with DCM and saturated $NaHCO_3$. The aqueous layer was extracted with DCM and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, linear gradient 0-4% MeOH in DCM) to give **47** as a white solid (611 mg, 1.20 mmol, 72.5%). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.24 (s, 1H, H_8) ; 8.15 (s, 1H, H_2) ; 7.86 – 7.80 (m, 4H, H_{Ar}) ; 7.30 (br s, 2H, NH_2) ; 6.00 (d, *J* = 2.3 Hz, 1H, $H_{1'}$) ; 5.37 (dd, *J* = 6.3, 2.3 Hz, 1H, $H_{2'}$) ; 4.79 (dd, *J* = 6.3, 2.7 Hz, 1H, $H_{3'}$) ; 4.00 (ddd, *J* = 8.6, 6.1, 2.7 Hz, 1H, $H_{4'}$) ; 3.69 (ddd, *J* = 14.0, 8.2, 5.8 Hz, 1H, $CH_{2\ Et}$) ; 3.54 (dt, *J* = 14.0, 5.5 Hz, 1H, $CH_{2\ Et}$) ; 2.74 – 2.63 (m, 2H, $CH_{2\ Et}$) ; 2.61 – 2.55 (m, 2H, $CH_{2\ Et}$, $H_{5'}$) ; 2.45 – 2.37 (m, 2H, H_a, $H_{5''}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$) ; 1.05 (s, 3H, $CH_{3\ isopr}$) ; 0.88 (t, *J* = 7.1 Hz, 3H, H_b). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 168.0 (CO) ; 156.1 (C_6) ; 152.6 (C_2) ; 148.6 (C_4) ; 140.1 (C_8) ; 134.1 (C_{Ar}) ; 131.8 ($C_{q\ Ar}$) ; 122.9 (C_{Ar}) ; 119.2 (C_5) ; 112.7 ($C_{q\ isopr}$) ; 89.4 ($C_{1'}$) ; 84.6 ($C_{4'}$) ; 82.9 ($C_{3'}$) ; 82.7 ($C_{2'}$) ; 54.9 ($C_{5'}$) ; 50.7 ($CH_{2\ Et}$) ; 47.2 (C_a) ; 35.7 ($CH_{2\ Et}$) ; 26.7 ($CH_{3\ isopr}$) ; 24.8 ($CH_{3\ isopr}$) ; 11.5 (C_b). **HRMS** (ESI+): m/z calc. for $C_{25}H_{30}N_7O_5$ $[M+H]^+$: 508.2303, Found 508.2301.

N1-(((3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)-N1-ethylethane-1,2-diamine (48). Compound **47** (600 mg, 1.18 mmol, 1eq) was dissolved in a solution of methylamine in EtOH (33%, 20 mL) and stirred at r.t overnight. After concentration under vacuum, the residue was dissolved in $CHCl_3$ and extracted with 10% aqueous CH_3COOH. The aqueous layer was washed with $CHCl_3$ (3x) and pH was adjusted to > 12 using NaOH (2N) and then extracted with $CHCl_3$ (4x). The final organic layers were dried over Na_2SO_4 and concentrated under vacuum to give **48** as a white solid (407 mg, 91%). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.33 (s, 1H, H_8) ; 8.16 (s, 1H, H_2) ; 7.31 (br s, 2H, NH_2) ; 6.14 (d, J = 2.3 Hz, 1H, $H_{1'}$) ; 5.49 (dd, J = 6.3, 2.3 Hz, 1H, $H_{2'}$) ; 4.97 (dd, J = 6.3, 3.0 Hz, 1H, $H_{3'}$) ; 4.19 (td, J = 7.4, 2.9 Hz, 1H, $H_{4'}$) ; 2.64 (dd, J = 13.3, 7.6 Hz, 1H, $H_{5'}$) ; 2.49 – 2.40 (m, 5H, $H_{5''}$, H_a, $CH_{2\ Et}$) ; 2.36 (m, 2H, $CH_{2\ Et}$) ; 1.52 (s, 3H, $CH_{3\ isopr}$) ; 1.33 (s, 3H, $CH_{3\ isopr}$) ; 0.87 (t, J = 7.1 Hz, 3H, H_b). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 148.8 (C_4) ; 140.1 (C_8) ; 119.2 (C_5) ; 113.0 ($C_{q\ isopr}$) ; 89.1 ($C_{1'}$) ; 84.8 ($C_{4'}$) ; 83.0 ($C_{3'}$) ; 83.0 ($C_{2'}$) ; 57.1 ($CH_{2\ Et}$) ; 55.4 ($C_{5'}$) ; 47.9 (C_a) ; 39.7 ($CH_{2\ Et}$) ; 27.0 ($CH_{3\ isopr}$) ; 25.2 ($CH_{3\ isopr}$) ; 11.5 (C_b). **HRMS** (ESI+): m/z calc. for $C_{17}H_{28}N_7O_3$ $[M+H]^+$: 378.2248, Found 378.2245.



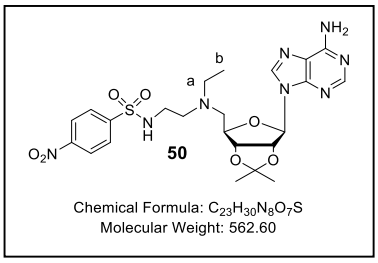
Chemical Formula: $C_{17}H_{27}N_7O_3$
Molecular Weight: 377.45

N-(2-((((3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)(ethyl)amino)ethyl)benzenesulfonamide (49). Following method **A** with **48** (130 mg, 0.34 mmol, 1.00 eq) and benzenesufonyl chloride (76 mg, 0.43 mmol, 1.25 eq), **49** was obtained as a white solid (117 mg, 66%). R_f 0.42 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.30 (s, 1H, H_8) ; 8.14 (s, 1H, H_2) ; 7.79 – 7.76 (m, 2H, H_{Ar}) ; 7.65 – 7.61 (m, 1H, H_{Ar}) ; 7.60 – 7.56 (m, 2H, H_{Ar}) ; 7.37 (m, 1H, NH) ; 7.32 (br s, 2H, NH_2) ; 6.13 (s, 1H, $H_{1'}$) ; 5.44 (dd, J = 6.3, 2.2 Hz, 1H, $H_{2'}$) ; 4.92 (d, J = 3.0 Hz, 1H, $H_{3'}$) ; 4.11 (s, 1H, $H_{4'}$) ; 2.77 (d, J = 6.1 Hz, 2H, $CH_{2\ Et}$) ; 2.65 – 2.59 (m, 1H, $H_{5'}$) ; 2.48 – 2.30 (m, 5H, $H_{5''}$, H_a, $CH_{2\ Et}$) ; 1.53 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$) ; 0.78 (t, J = 6.9 Hz, 3H, H_b). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 148.7 (C_4) ; 140.4 ($C_{q\ Ar}$) ; 140.1 (C_8) ; 132.3 (C_{Ar}) ; 129.2 (C_{Ar}) ; 126.4 (C_{Ar}) ; 119.2 (C_5) ; 113.2 ($C_{q\ isopr}$) ; 89.1 ($C_{1'}$) ; 84.4 ($C_{4'}$) ; 83.0 ($C_{2'}$) ; 82.8 ($C_{3'}$) ; 55.0 ($C_{5'}$) ; 52.5 ($CH_{2\ Et}$) ; 47.7 (C_a) ; 40.7 ($CH_{2\ Et}$) ; 27.0 ($CH_{3\ isopr}$) ; 25.2 ($CH_{3\ isopr}$) ; 11.4 (C_b). **HRMS** (ESI+): m/z calc. for $C_{23}H_{32}N_7O_5S$ $[M+H]^+$: 518.2180, Found 518.2181.



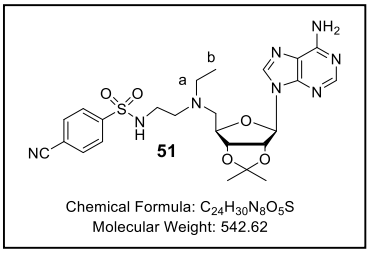
Chemical Formula: $C_{23}H_{31}N_7O_5S$
Molecular Weight: 517.61

N-(2-((((3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)(ethyl)amino)ethyl)-4-nitrobenzenesulfonamide (50). Following method **A** with **48** (110 mg, 0.29 mmol, 1.00 eq) and 4-nitrobenzenesufonyl chloride (81 mg, 0.36 mmol, 1.25 eq), **50** was obtained as a white solid (79 mg, 48%). R_f 0.63 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.43 – 8.39 (m, 2H, H_{Ar}) ; 8.30 (s, 1H, H_8) ; 8.14 (s, 1H, H_2) ; 8.05 – 8.01 (m, 2H, H_{Ar}) ; 7.80 (br s, 1H, NH) ; 7.31 (br s, 2H, NH_2) ; 6.12 (d, J = 2.3 Hz, 1H, $H_{1'}$) ; 5.44 (dd, J = 6.3, 2.4 Hz, 1H, $H_{2'}$) ; 4.91 (dd, J = 6.3, 3.1 Hz, 1H, $H_{3'}$) ; 4.11 (td, J = 6.9, 3.1 Hz, 1H, $H_{4'}$) ; 2.83 (t, J = 7.0 Hz, 2H, $CH_{2\ Et}$) ; 2.62 (dd, J = 13.4, 7.3 Hz, 1H, $H_{5'}$) ; 2.48 – 2.33 (m, 5H, $H_{5''}$, H_a, $CH_{2\ Et}$) ; 1.51 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$) ; 0.78 (t, J = 7.1 Hz, 3H, H_b). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 149.5 ($C_{q\ Ar}$) ; 148.7 (C_4) ; 146.2 ($C_{q\ Ar}$) ; 140.1 (C_8) ; 128.0 (C_{Ar}) ; 124.6 (C_{Ar}) ; 119.2 (C_5) ; 113.1 ($C_{q\ isopr}$) ; 89.1 ($C_{1'}$) ; 84.5 ($C_{4'}$) ; 82.9 ($C_{2'}$) ; 82.8 ($C_{3'}$) ; 55.0 ($C_{5'}$) ; 52.6 ($CH_{2\ Et}$) ; 47.6 (C_a) ; 40.8 ($CH_{2\ Et}$) ; 26.9 ($CH_{3\ isopr}$) ; 25.2 ($CH_{3\ isopr}$) ; 11.3 (C_b). **HRMS** (ESI+): m/z calc. for $C_{23}H_{31}N_8O_7S$ $[M+H]^+$: 563.2031, Found 563.2031.



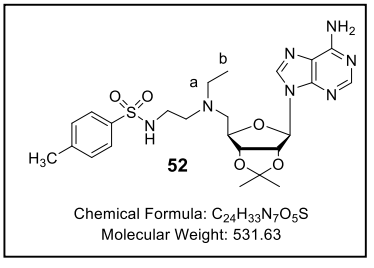
Chemical Formula: $C_{23}H_{30}N_8O_7S$
Molecular Weight: 562.60

N-(2-((((3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)(ethyl)amino)ethyl)-4-cyanobenzenesulfonamide (51). Following method **A** with **48** (110 mg, 0.29 mmol, 1.00 eq) and 4-cyanobenzenesufonyl chloride (73 mg, 0.36 mmol, 1.25 eq), **51** was obtained as a white solid (60 mg, 38%). R_f 0.49 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.30 (s, 1H, H_8) ; 8.14 (s, 1H, H_2) ; 8.09 – 8.06 (m, 2H, H_{Ar}) ; 7.95 – 7.92 (m, 2H, H_{Ar}) ; 7.71 (br s, 1H, NH) ; 7.32 (br s, 2H, NH_2) ; 6.12 (d, J = 2.3 Hz, 1H, $H_{1'}$) ; 5.45 (dd, J = 6.3, 2.4 Hz, 1H, $H_{2'}$) ; 4.92 (dd, J = 6.3, 3.1 Hz, 1H, $H_{3'}$) ; 4.11 (td, J = 7.0, 3.1 Hz, 1H, $H_{4'}$) ; 2.80 (t, J = 7.0 Hz, 2H, $CH_{2\ Et}$) ; 2.62 (dd, J = 13.4, 7.4 Hz, 1H, $H_{5'}$) ; 2.47 – 2.33 (m, 5H, $H_{5''}$, H_a, $CH_{2\ Et}$) ; 1.52 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$) ; 0.78 (t, J = 7.1 Hz, 3H, H_b).**^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 148.7 (C_4) ; 144.7 (CN) ; 140.1 (C_8) ; 133.4 (C_{Ar}) ; 127.2 (C_{Ar}) ; 119.2 (C_5) ; 117.8 ($C_{q\ Ar}$) ; 114.8 ($C_{q\ Ar}$) ; 113.1 ($C_{q\ isopr}$) ; 89.1 ($C_{1'}$) ; 84.5 ($C_{4'}$) ; 82.9 ($C_{2'}$) ; 82.8 ($C_{3'}$) ; 54.9 ($C_{5'}$) ; 52.6 ($CH_{2\ Et}$) ; 47.6 (C_a) ; 40.7 ($CH_{2\ Et}$) ; 27.0 ($CH_{3\ isopr}$) ; 25.2 ($CH_{3\ isopr}$) ; 11.3 (C_b). **HRMS** (ESI+): m/z calc. for $C_{24}H_{31}N_8O_5S$ $[M+H]^+$: 543.2133, Found 543.2136.



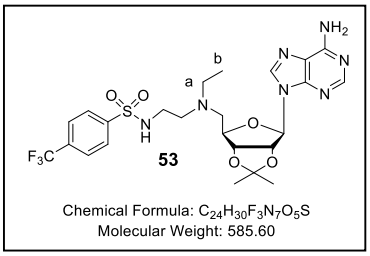
Chemical Formula: $C_{24}H_{30}N_8O_5S$
Molecular Weight: 542.62

N-(2-((((3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)(ethyl)amino)ethyl)-4-methylbenzenesulfonamide (52). Following method **A** with **48** (130 mg, 0.34 mmol, 1.00 eq) and 4-methylbenzenesufonyl chloride (82 mg, 0.43 mmol, 1.25 eq), **52** was obtained as a white solid (120 mg, 66%). R_f 0.56 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.30 (s, 1H, H_8) ; 8.14 (s, 1H, H_2) ; 7.67 – 7.63 (m, 2H, H_{Ar}) ; 7.37 (m, 2H, H_{Ar}) ; 7.32 (br. s, 2H, NH_2) ; 7.26 (t, J = 5.8 Hz, 1H, NH) ; 6.12 (d, J = 2.3 Hz, 1H, $H_{1'}$) ; 5.43 (dd, J = 6.3, 2.4 Hz, 1H, $H_{2'}$) ; 4.91 (dd, J = 6.3, 3.1 Hz, 1H, $H_{3'}$) ; 4.11 (td, J = 7.2, 3.1 Hz, 1H, $H_{4'}$) ; 2.74 (dd, J = 13.4, 7.0 Hz, 2H, $CH_{2\ Et}$) ; 2.62 (dd, J = 13.4, 7.6 Hz, 1H, $H_{5'}$) ; 2.47 – 2.32 (m, 8H, $H_{5''}$, H_a, $CH_{3\ Ar}$, $CH_{2\ Et}$) ; 1.52 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$) ; 0.79 (t, J = 7.1 Hz, 3H, H_b). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_v) ; 148.7 (C_4) ; 142.6 ($C_{q\ Ar}$) ; 140.1 (C_8) ; 137.5 ($C_{q\ Ar}$) ; 129.6 (C_{Ar}) ; 126.5 (C_{Ar}) ; 119.2 (C_5) ; 113.1 ($C_{q\ isopr}$) ; 89.1 ($C_{1'}$) ; 84.4 ($C_{4'}$) ; 83.0 ($C_{2'}$) ; 82.8 ($C_{3'}$) ; 55.1 ($C_{5'}$) ; 52.5 ($CH_{2\ Et}$) ; 47.7 (C_a) ; 40.7 ($CH_{2\ Et}$) ; 27.0 ($CH_{3\ isopr}$) ; 25.2 ($CH_{3\ isopr}$) ; 20.9 ($CH_{3\ Ar}$) ; 11.4 (C_b). **HRMS** (ESI+): m/z calc. for $C_{24}H_{34}N_7O_5S$ $[M+H]^+$: 532.2337, Found 532.2340.



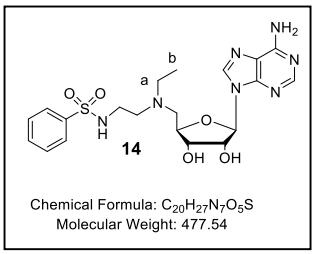
Chemical Formula: $C_{24}H_{33}N_7O_5S$
Molecular Weight: 531.63

N-(2-((((3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)(ethyl)amino)ethyl)-4-(trifluoromethyl)benzenesulfonamide (53). Following method **A** with **48** (117 mg, 0.31 mmol, 1.00 eq) and 4-trifluoromethylbenzenesufonyl chloride (95 mg, 0.39 mmol, 1.25 eq), **53** was obtained as a white solid (78 mg, 43%). R_f 0.45 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.30 (s, 1H, H_8) ; 8.14 (s, 1H, H_2) ; 8.01 – 7.96 (m, 4H, H_{Ar}) ; 7.67 (br s, 1H, NH) ; 7.32 (br s, 2H, NH_2) ; 6.12 (d, J = 2.3 Hz, 1H, $H_{1'}$) ; 5.44 (dd, J = 6.3, 2.4 Hz, 1H, $H_{2'}$) ; 4.92 (dd, J = 6.3, 3.1 Hz, 1H, $H_{3'}$) ; 4.12 (td, J = 7.0, 3.1 Hz, 1H, $H_{4'}$) ; 2.81 (m, 2H, $CH_{2\ Et}$) ; 2.63 (dd, J = 13.4, 7.5 Hz, 1H, $H_{5'}$) ; 2.49 – 2.31 (m, 5H, $H_{5''}$, H_a, $CH_{2\ Et}$) ; 1.51 (s, 3H, $CH_{3\ isopr}$) ; 1.32 (s, 3H, $CH_{3\ isopr}$) ; 0.77 (t, J = 7.1 Hz, 3H, H_b). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 148.7 (C_4) ; 144.4 ($C_{q\ Ar}$) ; 140.1 (C_8) ; 132.4, 132.2, 132.0, 131.8 (CF_3) ; 127.4 (C_{Ar}) ; 126.4 (C_{Ar}) ; 126.2, 124.4, 122.6, 120.8 ($C_{q\ Ar}$) ; 119.2 (C_5) ; 113.1 ($C_{q\ isopr}$) ; 89.1 ($C_{1'}$) ; 84.5 ($C_{4'}$) ; 82.9 ($C_{2'}$)

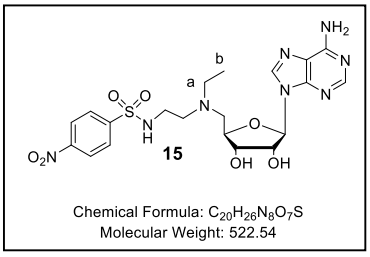


Chemical Formula: $C_{24}H_{30}F_3N_7O_5S$
Molecular Weight: 585.60

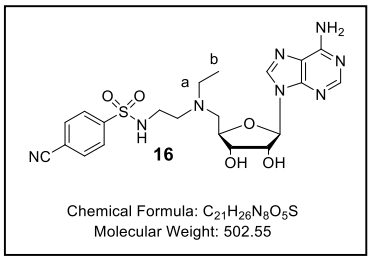
; 82.8 ($C_{3'}$) ; 55.0 ($C_{5'}$) ; 52.6 ($CH_{2\ Et}$) ; 47.6 (C_a) ; 40.8 ($CH_{2\ Et}$) ; 26.9 ($CH_{3\ isopr}$) ; 25.2 ($CH_{3\ isopr}$) ; 11.3 (C_b). **HRMS** (ESI+): m/z calc. for $C_{24}H_{31}F_3N_7O_5S$ $[M+H]^+$: 586.2054, Found 586.2060.



N-(2-((((2R,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)(ethyl)amino)ethyl)benzenesulfonamide (14). Following method **C** with intermediate **49** (117 mg, 0.23 mmol, 1.00 eq), **14** was obtained as a white solid (95 mg, 88%). R_f 0.23 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.30 (s, 1H, H_8) ; 8.13 (s, 1H, H_2) ; 7.77 – 7.74 (m, 2H, H_{Ar}) ; 7.63 – 7.59 (m, 1H, H_{Ar}) ; 7.58 – 7.54 (m, 2H, H_{Ar}) ; 7.42 (t, *J* = 5.6 Hz, 1H, NH) ; 7.28 (br s, 2H, NH_2) ; 5.83 (d, *J* = 5.2 Hz, 1H, $H_{1'}$) ; 5.44 (br s, 1H, $OH_{2'}$) ; 5.16 (br s, 1H, $OH_{3'}$) ; 4.60 (t, *J* = 5.2 Hz, 1H, $H_{2'}$) ; 4.05 (t, *J* = 4.9 Hz, 1H, $H_{3'}$) ; 3.88 (dt, *J* = 6.6, 4.8 Hz, 1H, $H_{4'}$) ; 2.78 (m, 2H, $CH_{2\ Et}$) ; 2.73 (dd, *J* = 13.9, 5.0 Hz, 1H, $H_{5'}$) ; 2.61 – 2.56 (dd, *J* = 13.9, 6.9 Hz, 1H, $H_{5''}$) ; 2.47 – 2.38 (m, 4H, $CH_{2\ Et}$, H_a) ; 0.84 (t, *J* = 7.1 Hz, 3H, H_b). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.4 (C_4) ; 140.5 ($C_{q\ Ar}$) ; 139.9 (C_8) ; 132.3 (C_{Ar}) ; 129.2 (C_{Ar}) ; 126.4 (C_{Ar}) ; 119.2 (C_5) ; 87.6 ($C_{1'}$) ; 82.5 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 71.7 ($C_{3'}$) ; 55.8 ($C_{5'}$) ; 52.8 ($CH_{2\ Et}$) ; 47.8 (C_a) ; 40.8 ($CH_{2\ Et}$) ; 11.6 (C_b). **HRMS** (ESI+): m/z calc. for $C_{20}H_{28}N_7O_5S$ $[M+H]^+$: 478.1867, Found 478.1863.

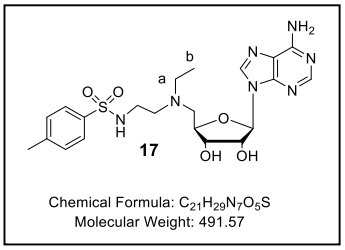


N-(2-((((2R,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)(ethyl)amino)ethyl)-4-nitrobenzene-sulfonamide (15). Following method **C** with intermediate **50** (73 mg, 0.13 mmol, 1.00 eq), **15** was obtained as a white solid (65 mg, 96%). R_f 0.32 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.40 – 8.37 (m, 2H, H_{Ar}) ; 8.30 (s, 1H, H_8) ; 8.13 (s, 1H, H_2) ; 8.03 – 8.00 (m, 2H, H_{Ar}) ; 7.85 (s, 1H, NH) ; 7.27 (s, 2H, NH_2) ; 5.83 (d, *J* = 5.1 Hz, 1H, $H_{1'}$) ; 5.45 (br s, 1H, $OH_{2'}$) ; 5.16 (br s, 1H, $OH_{3'}$) ; 4.59 (t, *J* = 5.2 Hz, 1H, $H_{2'}$) ; 4.05 (t, *J* = 4.9 Hz, 1H, $H_{3'}$) ; 3.88 (m, 1H, $H_{4'}$) ; 2.85 (m, 2H, $CH_{2\ Et}$) ; 2.74 (dd, *J* = 13.9, 4.9 Hz, 1H, $H_{5'}$) ; 2.60 (dd, *J* = 13.9, 6.9 Hz, 1H, $H_{5''}$) ; 2.49 – 2.41 (m, 4H, H_a, $CH_{2\ Et}$) ; 0.85 (t, *J* = 7.1 Hz, 3H, H_b). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.5 ($C_{q\ Ar}$) ; 149.3 (C_4) ; 146.2 ($C_{q\ Ar}$) ; 139.8 (C_8) ; 128.0 (C_{Ar}) ; 124.6 (C_{Ar}) ; 119.2 (C_5) ; 87.6 ($C_{1'}$) ; 82.5 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 71.7 ($C_{3'}$) ; 55.7 ($C_{5'}$) ; 52.9 ($CH_{2\ Et}$) ; 47.8 (C_a) ; 40.9 ($CH_{2\ Et}$) ; 11.6 (C_b). **HRMS** (ESI+): m/z calc. for $C_{20}H_{27}N_8O_7S$ $[M+H]^+$: 523.1718, Found 523.1718.



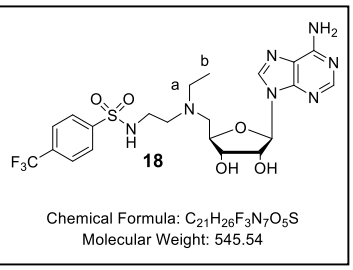
N-(2-((((2R,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)(ethyl)amino)ethyl)-4-cyanobenzene-sulfonamide (16). Following method **C** with intermediate **51** (57 mg, 0.11 mmol, 1.00 eq), **16** was obtained as a white solid (42 mg, 80%). R_f 0.24 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.30 (s, 1H, H_8) ; 8.14 (s, 1H, H_2) ; 8.07 – 8.04 (m, 2H, H_{Ar}) ; 7.94 – 7.90 (m, 2H, H_{Ar}) ; 7.77 (br s, 1H, NH) ; 7.28 (s, 2H, NH_2) ; 5.84 (d, *J* = 5.1 Hz, 1H, $H_{1'}$) ; 5.45 (br s, 1H, $OH_{2'}$) ; 5.17 (br s, 1H, $OH_{3'}$) ; 4.60 (t, *J* = 5.2 Hz, 1H, $H_{2'}$) ; 4.05 (t, *J* = 4.9 Hz, 1H, $H_{3'}$) ; 3.88 (dt, *J* = 6.7, 4.8 Hz, 1H, $H_{4'}$) ; 2.83 (br s, 2H, $CH_{2\ Et}$) ; 2.74 (dd, *J* = 13.9, 4.9 Hz, 1H, $H_{5'}$) ; 2.60 (dd, *J* = 13.9, 6.9 Hz, 1H, $H_{5''}$) ; 2.49 – 2.41 (m, 4H, $CH_{2\ Et}$, H_a) ; 0.84 (t, *J* = 7.1 Hz, 3H, H_b). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.3 (C_4) ; 144.8 (C_{CN}) ; 139.9 (C_8) ; 133.4 (C_{Ar}) ; 127.2 (C_{Ar}) ; 119.2 (C_5) ; 117.8 ($C_{q\ Ar}$) ; 114.8 ($C_{q\ Ar}$) ; 87.6 ($C_{1'}$) ; 82.5 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 71.8 ($C_{3'}$) ; 55.7 ($C_{5'}$) ; 52.9 ($CH_{2\ Et}$) ; 47.8 (C_a) ; 40.8 ($CH_{2\ Et}$) ; 11.6 (C_b). **HRMS** (ESI+): m/z calc. for $C_{21}H_{27}N_8O_5S$ $[M+H]^+$: 503.1820, Found 503.1819.

N-(2-((((2R,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)(ethyl)amino)ethyl)-4-methylbenzene-sulfonamide (17). Following method **C** with intermediate **52** (116 mg, 0.22 mmol, 1.00 eq), **17** was obtained as a white solid (91 mg, 85%). R_f 0.31 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.30 (s, 1H, H_8) ; 8.13 (s, 1H, H_2) ; 7.65 – 7.61 (m, 2H, H_{Ar}) ; 7.34 (m, 2H, H_{Ar}) ; 7.32 (t, *J* = 5.8 Hz, 1H, NH) ; 7.28 (br. s, 2H, NH_2) ; 5.84 (d, *J* = 5.2 Hz, 1H, $H_{1'}$) ; 5.44 (br s, 1H, $OH_{2'}$) ; 5.16 (br s, 1H, $OH_{3'}$) ; 4.60 (t, *J* = 5.2 Hz, 1H, $H_{2'}$) ; 4.05 (t, *J* = 4.9 Hz, 1H, $H_{3'}$) ; 3.88 (dt, *J* = 6.6, 4.9 Hz, 1H, $H_{4'}$) ; 2.79 – 2.70 (m, 3H, $CH_{2\ Et}$, $H_{5'}$) ; 2.59 (dd, *J* = 13.9, 6.8 Hz, 1H, $H_{5''}$) ; 2.49 – 2.40 (m, 4H, $CH_{2\ Et}$, H_a) ; 2.36 (s, 3H, $CH_{3\ Ar}$) ; 0.85 (t, *J* = 7.1 Hz, 3H, H_b). **^{13}C-NMR** (151 MHz, DMSO-d_6) 156.1 (C_6) ; 152.6 (C_2) ; 149.4 (C_4) ; 142.5 ($C_{q\ Ar}$) ; 139.8 (C_8) ; 137.6 ($C_{q\ Ar}$) ; 129.6 (C_{Ar}) ; 126.5 (C_{Ar}) ; 119.2 (C_5) ; 87.6 ($C_{1'}$) ; 82.5 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 71.7 ($C_{3'}$) ; 55.8 ($C_{5'}$) ; 52.8 ($CH_{2\ Et}$) ; 47.8 (C_a) ; 40.7 ($CH_{2\ Et}$) ; 20.9 ($CH_{3\ Ar}$) ; 11.6 (C_b). **HRMS** (ESI+): m/z calc. for $C_{21}H_{30}N_7O_5S$ $[M+H]^+$: 492.2024, Found 492.2022.



Chemical Formula: $C_{21}H_{29}N_7O_5S$
Molecular Weight: 491.57

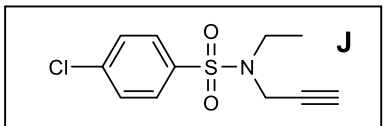
N-(2-((((2R,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl)(ethyl)amino)ethyl)-4-(trifluoromethyl)benzenesulfonamide (18). Following method **C** with intermediate **53** (78 mg, 0.13 mmol, 1.00 eq), **18** was obtained as a white solid (53 mg, 73%). R_f 0.30 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.31 (s, 1H, H_8) ; 8.13 (s, 1H, H_2) ; 7.96 (q, *J* = 8.5 Hz, 4H, H_{Ar}) ; 7.73 (br s, 1H, NH) ; 7.28 (br s, 2H, NH_2) ; 5.84 (d, *J* = 5.1 Hz, 1H, $H_{1'}$) ; 5.45 (br s, 1H, $OH_{2'}$) ; 5.16 (br s, 1H, $OH_{3'}$) ; 4.60 (t, *J* = 5.2 Hz, 1H, $H_{2'}$) ; 4.06 (t, *J* = 4.9 Hz, 1H, $H_{3'}$) ; 3.89 (dt, *J* = 6.7, 4.8 Hz, 1H, $H_{4'}$) ; 2.83 (br s, 2H, $CH_{2\ Et}$) ; 2.74 (dd, *J* = 13.9, 4.9 Hz, 1H, $H_{5'}$) ; 2.61 (dd, *J* = 13.9, 6.9 Hz, 1H, $H_{5''}$) ; 2.49 – 2.40 (m, 4H, $CH_{2\ Et}$, H_a) ; 0.83 (t, *J* = 7.1, 3H, H_b). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.4 (C_4) ; 144.5 ($C_{q\ Ar}$) ; 139.8 (C_8) ; 132.4, 132.2, 132.0, 131.8 (CF_3) ; 127.4 (C_{Ar}) ; 126.4 (C_{Ar}) ; 126.2, 124.4, 122.6, 120.8 ($C_{q\ Ar}$) ; 119.2 (C_5) ; 87.6 ($C_{1'}$) ; 82.5 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 71.8 ($C_{3'}$) ; 55.7 ($C_{5'}$) ; 52.9 ($CH_{2\ Et}$) ; 47.8 (C_a) ; 40.8 ($CH_{2\ Et}$) ; 11.6 (C_b). **HRMS** (ESI+): m/z calc. for $C_{21}H_{27}F_3N_7O_5S$ $[M+H]^+$: 546.1741, Found 546.1740.



Chemical Formula: $C_{21}H_{26}F_3N_7O_5S$
Molecular Weight: 545.54

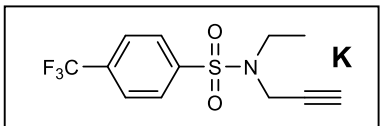
N-propargyl-*N*-ethylsulfonamide reagents (J-M)

4-chloro-*N*-ethyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (J). Following method **D** with reagent **D** (200 mg, 0.87 mmol, 1.00 eq), **J** was obtained as an orange oil (170 mg, 76%). R_f 0.60 (99:1 DCM/MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.74 (m, 2H) ; 7.51 – 7.43 (m, 2H) ; 4.16 (d, J = 2.5 Hz, 2H) ; 3.28 (q, J = 7.2 Hz, 2H) ; 2.03 (t, J = 2.5 Hz, 1H) ; 1.20 (t, J = 7.1 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 139.3 ($C_{q\ Ar}$), 137.6 ($C_{q\ Ar}$), 129.3 (CH_{Ar}), 129.3 (CH_{Ar}), 76.4 ($C_{q\ alkyne}$), 74.0 (CH_{alkyne}), 41.4 (CH_2), 35.8 (CH_2), 13.3 (CH_3). **HRMS (ESI+):** m/z calcd for $C_{11}H_{13}ClNO_2S$ $[M+H]$+: 258.0350, Found 258.0350.



Chemical Formula: $C_{11}H_{12}ClNO_2S$
Molecular Weight: 257.73

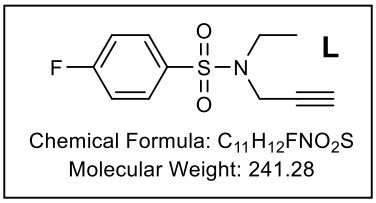
4-trifluoromethyl-*N*-ethyl-*N*-(prop-2-yn-1-yl)benzene-sulfonamide (K). Following method **D** with reagent **E** (200 mg, 0.76 mmol, 1.00 eq), **K** was obtained as a brown oil (168 mg, 76%). R_f 0.68 (99:1 DCM/MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.2 Hz, 2H) ; 7.77 (d, J = 8.2 Hz, 2H) ; 4.19 (d, J = 2.5 Hz, 1H) ; 3.31 (q, J = 7.2 Hz, 1H) ; 2.01 (t, J = 2.4 Hz, 1H) ; 1.21 (t, J = 7.2 Hz, 2H). **^{13}C-NMR** (101 MHz, $CDCl_3$)



Chemical Formula: $C_{12}H_{12}F_3NO_2S$
Molecular Weight: 291.29

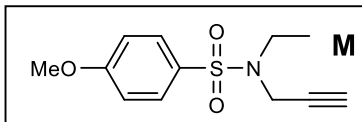
δ 142.7 ($C_{q\ Ar}$), 135.0, 134.7, 134.3, 134.0 ($C_{q\ Ar}$), 128.3 (CH_{Ar}), 126.2 (CH_{Ar}), 127.5, 124.8, 122.1, 119.3 (CF_3), 76.2 ($C_{q\ alkyne}$), 74.1 (CH_{alkyne}), 41.5 (CH_2), 35.8 (CH_2), 13.3 (CH_3). **HRMS (ESI+):** m/z calcd for $C_{12}H_{13}F_3NO_2S$ [M+H]+: 292.0614, Found 292.0615.

4-fluoro-*N*-ethyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (L). Following method **D** with reagent **F** (200 mg, 0.94 mmol, 1.00 eq), **L** was obtained as an orange oil (181 mg, 80%). R_f 0.60 (99:1 DCM/MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.92 – 7.80 (m, 2H) ; 7.22 – 7.11 (m, 2H) ; 4.15 (d, J = 2.5 Hz, 2H) ; 3.28 (q, J = 7.2 Hz, 2H) ; 2.02 (t, J = 2.5 Hz, 1H) ; 1.19 (t, J = 7.2 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 166.6, 164.0 (C-F), 135.1, 135.1 ($C_{q\ Ar}$), 130.5, 130.4 (CH_{Ar}), 116.3, 116.1 (CH_{Ar}), 76.4 ($C_{q\ alkyne}$), 73.9 (CH_{alkyne}), 41.4 (CH_2), 35.7 (CH_2), 13.3 (CH_3). **HRMS (ESI+):** m/z calcd for $C_{11}H_{13}FNO_2S$ [M+H]+: 242.0646, Found 242.0647.



Chemical Formula: $C_{11}H_{12}FNO_2S$
Molecular Weight: 241.28

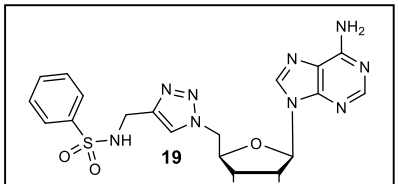
4-methoxy-*N*-ethyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (M). Following method **D** with reagent **G** (200 mg, 0.89 mmol, 1.00 eq), **M** was obtained as a yellow oil (151 mg, 67%). R_f 0.50 (99:1 DCM/MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.73 (m, 2H) ; 7.02 – 6.91 (m, 2H) ; 4.13 (d, J = 2.5 Hz, 2H) ; 3.86 (s, 3H) ; 3.26 (q, J = 7.2 Hz, 2H) ; 2.02 (t, J = 2.5 Hz, 1H) ; 1.18 (t, J = 7.1 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 163.1 ($C_{q\ Ar}$), 130.7 ($C_{q\ Ar}$), 129.9 (CH_{Ar}), 114.1 (CH_{Ar}), 73.6 ($C_{q\ alkyne}$), 73.6 (CH_{alkyne}), 55.7 (OCH_3), 41.3 (CH_2), 35.8 (CH_2), 13.3 (CH_3). **HRMS (ESI+)**: m/z calcd for $C_{12}H_{16}NO_3S$ [M+H]+: 254.0845, Found 254.0844.



Chemical Formula: $C_{12}H_{15}NO_3S$
Molecular Weight: 253.32

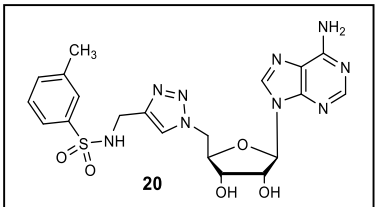
N-arylsulfonamide adenosine analogues with an *N*-methyltriazole linker (19-31)

N-[(1-{[(2R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl}-1H-1,2,3-triazol-4-yl)methyl]benzenesulfonamide (19). Following method **E** with 5'-azido-adenosine (54 mg, 0.185 mmol, 1.20 eq) and reagent **A** (30 mg, 0.154 mmol, 1.0 eq), **19** was obtained as a white powder (34 mg, 38%). R_f 0.50 (8:92 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.28 (s, 1H, H_8) ; 8.16 (s, 1H, H_2) ; 8.08 (t, *J* = 6.0 Hz, 1H, NH) ; 7.76 – 7.71 (m, 2H, $2H_{Ar}$) ; 7.67 (s, 1H, $H_{Triazole}$) ; 7.59 (tt, *J* = 6.6, 1.2 Hz, 1H, H_{Ar}) ; 7.55 – 7.50 (m, 2H, $2H_{Ar}$) ; 7.31 (br. s, 2H, NH_2) ; 5.90 (d, *J* = 5.4 Hz, 1H, $H_{1'}$) ; 5.59 (d, J = 5.7 Hz, 1H, $OH_{2'}$) ; 5.45 (d, J = 4.8 Hz, 1H, $OH_{3'}$) ; 4.75 – 4.60 (m, 3H, $H_{2'}$, $H_{5'5''}$) ; 4.23 (q, *J* = 4.4 Hz, 1H, $H_{3'}$) ; 4.19 (dt, *J* = 7.6, 4.3 Hz, 1H, $H_{4'}$) ; 4.06 – 3.92 (m, 2H, C*H*$_2$-NH). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 149.3 (C_4) ; 143.3 ($C_{q\ Triazole}$) ; 140.4 ($C_{q\ Ar}$) ; 139.9 (C_8) ; 132.3 (*C*H$_{Ar}$) ; 129.1 (*C*H$_{Ar}$) ; 126.5 (*C*H$_{Ar}$) ; 123.8 (*C*H$_{Triazole}$) ; 119.2 (C_5) ; 87.8 ($C_{1'}$) ; 82.4 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 71.0 ($C_{3'}$) ; 51.4 ($C_{5'}$) ; 38.0 (*C*H$_2$-NH). **HRMS** (ESI+): m/z calcd for $C_{19}H_{22}N_9O_5S$ $[M+H]^+$: 488.1459, Found 488.1460.



Chemical Formula: $C_{19}H_{21}N_9O_5S$
Molecular Weight: 487,50

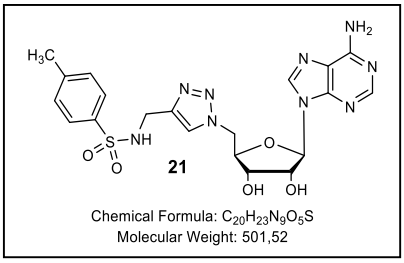
N-[(1-{[(2R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl}-1H-1,2,3-triazol-4-yl)methyl]-3-methylbenzene-1-sulfonamide (20). Following method **E** with 5'-azido-adenosine (63 mg, 0.215 mmol, 1.0 eq) and reagent **B** (50 mg, 0.239 mmol, 1.1 eq), **20** was obtained as a white powder (39 mg, 36%). R_f 0.50 (8:92 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.28 (s, 1H, H_8) ; 8.16 (s, 1H, H_2) ; 8.02 (t, *J* = 6.0 Hz, 1H, NH) ; 7.67 (s, 1H, $H_{Triazole}$) ; 7.57 – 7.51 (m, 2H, $2H_{Ar}$) ; 7.44 – 7.36 (m, 2H, $2H_{Ar}$) ; 7.31 (br. s, 2H, NH_2) ; 5.59 (d, *J* = 5.4 Hz, 1H, $H_{1'}$) ; 5.59 (br. s, 1H, $OH_{2'}$) ; 5.46 (br. s, 1H, $OH_{3'}$) ; 4.75 – 4.62 (m, 3H, $H_{2'}$, $H_{5'5''}$) ; 4.27 – 4.21 (m, 1H, $H_{3'}$) ; 4.19 (dt,



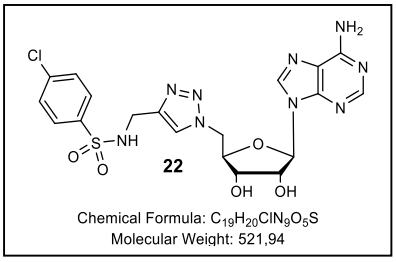
Chemical Formula: $C_{20}H_{23}N_9O_5S$
Molecular Weight: 501,52

J = 7.7, 4.3 Hz, 1H, $H_{4'}$) ; 4.04 – 3.93 (m, 2H, CH_2-NH) ; 2.35 (s, 3H, CH_3). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 149.3 (C_4) ; 143.3 ($C_{q\ Triazole}$) ; 140.3 (C_8) ; 139.9 ($C_{q\ Ar}$) ; 138.7 ($C_{q\ Ar}$) ; 132.9 (*C*H_{Ar}) ; 128.9 (*C*H_{Ar}) ; 126.7 (*C*H_{Ar}) ; 123.8 (*C*$H_{Triazole}$) ; 123.6 (*C*H_{Ar}) ; 119.2 (C_5) ; 87.8 ($C_{1'}$) ; 82.4 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 71.0 ($C_{3'}$) ; 51.4 ($C_{5'}$) ; 38.0 (*C*H_2-NH) ; 20.8 (CH_3). **HRMS** (ESI+): m/z calcd for $C_{20}H_{24}N_9O_5S$ $[M+H]^+$: 502.1616, Found 502.1617.

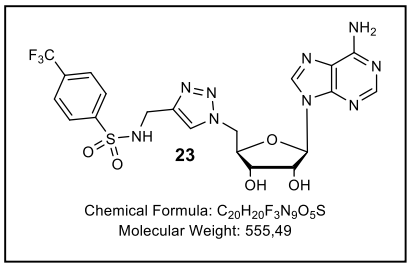
N-[(1-{[(2R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl}-1H-1,2,3-triazol-4-yl)methyl]-4-methylbenzene-1-sulfonamide (21). Following method **E** with 5'-azido-adenosine (77 mg, 0.263 mmol, 1.10 eq) and reagent **C** (50 mg, 0.239 mmol, 1.0 eq), **21** was obtained as a white powder (73 mg, 61%). R_f 0.50 (1:9 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.28 (s, 1H, H_8) ; 8.15 (s, 1H, H_2) ; 7.98 (t, *J* = 6.0 Hz, 1H, NH) ; 7.69 (s, 1H, $H_{Triazole}$) ; 7.64 – 7.60 (m, 2H, 2H_{Ar}) ; 7.36 – 7.27 (m, 4H, 2H_{Ar}, NH_2) ; 5.90 (d, *J* = 5.4 Hz, 1H, $H_{1'}$) ; 5.59 (d, *J* = 5.6 Hz, 1H, $OH_{2'}$) ; 5.46 (d, *J* = 4.7 Hz, 1H, $OH_{3'}$) ; 4.75 – 4.62 (m, 3H, $H_{2'}$, $H_{5'5''}$) ; 4.25 – 4.16 (m, 2H, $H_{3'}$, $H_{4'}$) ; 4.01 – 3.87 (m, 2H, CH_2-NH) ; 2.36 (s, 3H, CH_3). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 149.3 (C_4) ; 143.3 ($C_{q\ Triazole}$) ; 142.6 ($C_{q\ Ar}$) ; 139.9 (C_8) ; 137.4 ($C_{q\ Ar}$) ; 129.5 (*C*H_{Ar}) ; 126.6 (*C*H_{Ar}) ; 123.8 (*C*$H_{Triazole}$) ; 119.2 (C_5) ; 87.8 ($C_{1'}$) ; 82.4 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 71.0 ($C_{3'}$) ; 51.4 ($C_{5'}$) ; 38.0 (*C*H_2-NH) ; 20.9 (CH_3). **HRMS** (ESI+): m/z calcd for $C_{20}H_{24}N_9O_5S$ $[M+H]^+$: 502.1616, Found 502.1619.



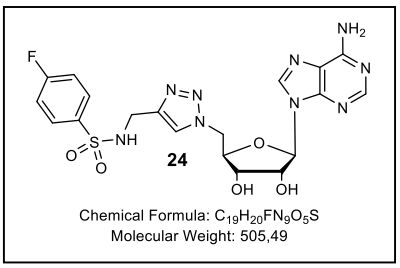
N-[(1-{[(2R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl}-1H-1,2,3-triazol-4-yl)methyl]-4-chlorobenzene-1-sulfonamide (22). Following method **E** with 5'-azido-adenosine (57 mg, 0.195 mmol, 1.0 eq) and reagent **D** (50 mg, 0.218 mmol, 1.1 eq), **22** was obtained as a white powder (43 mg, 38%). R_f 0.50 (8:92 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.28 (s, 1H, H_8) ; 8.19 (t, J = 6.0 Hz, 1H, NH) ; 8.16 (s, 1H, H_2) ; 7.75 – 7.70 (m, 3H, 2H_{Ar}, $H_{Triazole}$) ; 7.63 – 7.56 (m, 2H, 2H_{Ar}) ; 7.31 (br. s, 2H, NH_2) ; 5.91 (d, *J* = 5.4 Hz, 1H, $H_{1'}$) ; 5.59 (d, *J* = 5.8 Hz, 1H, $OH_{2'}$) ; 5.45 (d, *J* = 5.1 Hz, 1H, $OH_{3'}$) ; 4.75 – 4.62 (m, 3H, $H_{2'}$, $H_{5'5''}$) ; 4.27 – 4.16 (m, 2H, $H_{3'}$, $H_{4'}$) ; 4.06 – 3.94 (m, 2H, CH_2-NH). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 149.3 (C_4) ; 143.1 ($C_{q\ Triazole}$) ; 139.9 (C_8) ; 139.3 ($C_{q\ Ar}$) ; 137.2 ($C_{q\ Ar}$) ; 129.2 (*C*H_{Ar}) ; 128.5 (*C*H_{Ar}) ; 123.9 (*C*$H_{Triazole}$) ; 119.3 (C_5) ; 87.8 ($C_{1'}$) ; 82.4 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 71.0 ($C_{3'}$) ; 51.4 ($C_{5'}$) ; 37.9 (*C*H_2-NH). **HRMS (ESI+)**: m/z calcd for $C_{19}H_{21}ClN_9O_5S$ $[M+H]^+$: 522.1069, Found 522.1063.



N-[(1-{[(2R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl}-1H-1,2,3-triazol-4-yl)methyl]-4-trifluoromethyl benzene-1-sulfonamide (23). Following method **E** with 5'-azido-adenosine (50 mg, 0.171 mmol, 1.0 eq) and reagent **E** (50 mg, 0.189 mmol, 1.10 eq), **23** was obtained as a white powder (24 mg, 23%). R_f 0.57 (8:92 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.37 (t, *J* = 6.0 Hz, 1H, NH) ; 8.27 (s, 1H, H_8) ; 8.15 (s, 1H, H_2) ; 7.96 – 7.90 (m, 4H, 4H_{Ar}) ; 7.75 (s, 1H, $H_{Triazole}$) ; 7.31 (br. s, 2H, NH_2) ; 5.90 (d, *J* = 5.4 Hz, 1H, $H_{1'}$) ; 5.59 (d, *J* = 5.9 Hz, 1H, $OH_{2'}$) ; 5.45 (d, *J* = 5.1 Hz, 1H, $OH_{3'}$) ; 4.73 – 4.62 (m, 3H, $H_{2'}$, $H_{5'5''}$) ; 4.27 – 4.14 (m, 2H, $H_{3'}$, $H_{4'}$) ; 4.10 – 3.97 (m, 2H, CH_2-NH). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 149.3 (C_4) ; 144.4 ($C_{q\ Ar}$) ; 142.9 ($C_{q\ Triazole}$) ; 139.9 (C_8) ; 132.4, 132.2, 132.0, 131.7 (*C*-CF_3) ; 128.0, 126.2, 124.4, 122.6 (*C*F_3) ; 127.5 (*C*H_{Ar}) ; 126.3, 126.3 (*C*H_{Ar}) ; 124.0 (*C*$H_{Triazole}$) ; 119.3 (C_5) ; 87.8 ($C_{1'}$) ; 82.4 ($C_{4'}$) ; 72.5 ($C_{2'}$) ;

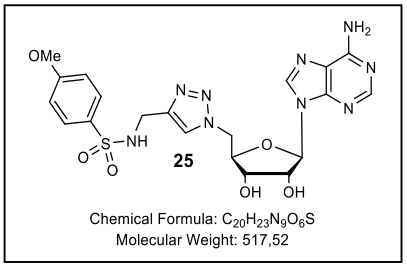


71.0 ($C_{3'}$) ; 51.3 ($C_{5'}$) ; 37.9 (CH_2-NH). **HRMS** (ESI+): m/z calcd for $C_{20}H_{21}F_3N_9O_5S$ $[M+H]^+$: 556.1333, Found 556.1332.



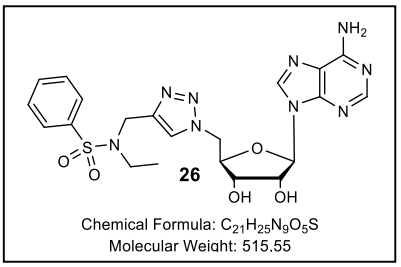
Chemical Formula: $C_{19}H_{20}FN_9O_5S$
Molecular Weight: 505,49

N-[(1-{[(2R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl}-1H-1,2,3-triazol-4-yl)methyl]-4-fluorobenzene-1-sulfonamide (24). Following method **E** with 5'-azido-adenosine (50 mg, 0.171 mmol, 1.0 eq) and reagent **F** (50 mg, 0.234 mmol, 1.37 eq), **24** was obtained as a white powder (15 mg, 13%). R_f 0.50 (8:92 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.28 (s, 1H, H_8) ; 8.19 (t, J = 6.0 Hz, 1H, NH) ; 8.16 (s, 1H, H_2) ; 7.75 – 7.70 (m, 3H, $2H_{Ar}$, $H_{Triazole}$) ; 7.63 – 7.56 (m, 2H, $2H_{Ar}$) ; 7.31 (br. s, 2H, NH_2) ; 5.91 (d, *J* = 5.4 Hz, 1H, $H_{1'}$) ; 5.59 (d, *J* = 5.8 Hz, 1H, $OH_{2'}$) ; 5.45 (d, *J* = 5.1 Hz, 1H, $OH_{3'}$) ; 4.75 – 4.62 (m, 3H, $H_{2'}$, $H_{5'5''}$) ; 4.27 – 4.16 (m, 2H, $H_{3'}$, $H_{4'}$) ; 4.06 – 3.94 (m, 2H, C*H*$_2$-NH). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 149.3 (C_4) ; 143.1 ($C_{q\ Triazole}$) ; 139.9 (C_8) ; 139.3 ($C_{q\ Ar}$) ; 137.2 ($C_{q\ Ar}$) ; 129.2 (*C*H$_{Ar}$) ; 128.5 (*C*H$_{Ar}$) ; 123.9 (*C*H$_{Triazole}$) ; 119.3 (C_5) ; 87.8 ($C_{1'}$) ; 82.4 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 71.0 ($C_{3'}$) ; 51.4 ($C_{5'}$) ; 37.9 (*C*H$_2$-NH). **HRMS** (ESI+): m/z calcd for $C_{19}H_{21}ClN_9O_5S$ $[M+H]^+$: 522.1069, Found 522.1063.



Chemical Formula: $C_{20}H_{23}N_9O_6S$
Molecular Weight: 517,52

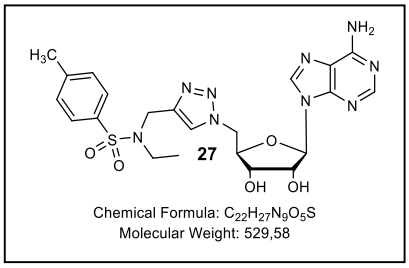
N-[(1-{[(2R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl}-1H-1,2,3-triazol-4-yl)methyl]-4-methoxybenzene-1-sulfonamide (25). Following method **E** with 5'-azido-adenosine (47 mg, 0.161 mmol, 1.0 eq) and reagent **G** (50 mg, 0.222 mmol, 1.38 eq), **25** was obtained as a white powder (32 mg, 28%). R_f 0.52 (8:92 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.28 (s, 1H, H_8) ; 8.19 (t, J = 6.0 Hz, 1H, NH) ; 8.16 (s, 1H, H_2) ; 7.75 – 7.70 (m, 3H, $2H_{Ar}$, $H_{Triazole}$) ; 7.63 – 7.56 (m, 2H, $2H_{Ar}$) ; 7.31 (br. s, 2H, NH_2) ; 5.91 (d, *J* = 5.4 Hz, 1H, $H_{1'}$) ; 5.59 (d, *J* = 5.8 Hz, 1H, $OH_{2'}$) ; 5.45 (d, *J* = 5.1 Hz, 1H, $OH_{3'}$) ; 4.75 – 4.62 (m, 3H, $H_{2'}$, $H_{5'5''}$) ; 4.27 – 4.16 (m, 2H, $H_{3'}$, $H_{4'}$) ; 4.06 – 3.94 (m, 2H, C*H*$_2$-NH). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 149.3 (C_4) ; 143.1 ($C_{q\ Triazole}$) ; 139.9 (C_8) ; 139.3 ($C_{q\ Ar}$) ; 137.2 ($C_{q\ Ar}$) ; 129.2 (*C*H$_{Ar}$) ; 128.5 (*C*H$_{Ar}$) ; 123.9 (*C*H$_{Triazole}$) ; 119.3 (C_5) ; 87.8 ($C_{1'}$) ; 82.4 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 71.0 ($C_{3'}$) ; 56.5 (OCH_3) ; 51.4 ($C_{5'}$) ; 37.9 (*C*H$_2$-NH). **HRMS** (ESI+): m/z calcd for $C_{19}H_{21}ClN_9O_5S$ $[M+H]^+$: 522.1069, Found 522.1063.



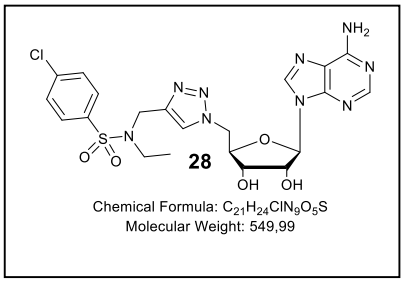
Chemical Formula: $C_{21}H_{25}N_9O_5S$
Molecular Weight: 515,55

N-[(1-{[(2R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl}-1H-1,2,3-triazol-4-yl)methyl]-N-ethylbenzene-sulfonamide (26). Following method **E** with 5'-azido-adenosine (61 mg, 0.209 mmol, 1.1 eq) and reagent **H** (42 mg, 0.190 mmol, 1.0 eq), **26** was obtained as a white powder (53 mg, 54%). R_f 0.50 (15:85 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.27 (s, 1H, H_8) ; 8.15 (s, 1H, H_2) ; 7.77 – 7.70 (m, 3H, $H_{Triazole}$, $2H_{Ar}$) ; 7.60 (tt, *J* = 6.6, 1.2 Hz, 1H, H_{Ar}) ; 7.55 – 7.49 (m, 2H, $2H_{Ar}$) ; 7.55 – 7.50 (m, 2H, $2H_{Ar}$) ; 7.31 (br. s, 2H, NH_2) ; 5.91 (d, *J* = 5.3 Hz, 1H, $H_{1'}$) ; 5.60 (d, J = 5.8 Hz, 1H, $OH_{2'}$) ; 5.45 (d, J = 4.9 Hz, 1H, $OH_{3'}$) ; 4.76 – 4.63 (m, 3H, $H_{2'}$, $H_{5'5''}$) ; 4.41 – 4.30 (m, 2H, $H_{3'}$, $H_{4'}$) ; 4.28 – 4.16 (m, 2H, C*H*$_2$-NH) ; 3.10 (q, J = 7.1 Hz, 2H, C*H*$_2$-CH_3) ; 0.91 (t, J = 7.1 Hz, 3H, CH_2-C*H*$_3$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 149.2 (C_4) ; 142.4 ($C_{q\ Triazole}$) ; 139.9 (C_8) ; 139.4 ($C_{q\ Ar}$) ; 132.6 (*C*H$_{Ar}$) ; 129.2 (*C*H$_{Ar}$) ; 126.8 (*C*H$_{Ar}$) ; 124.6 (*C*H$_{Triazole}$) ; 119.2 (C_5) ; 87.8 ($C_{1'}$) ; 82.4 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 71.0 ($C_{3'}$) ; 51.3 ($C_{5'}$) ; 42.1 (CH_2-CH_3) ; 41.5 (*C*H$_2$-NEt) ; 13.3 (CH_2-*C*H$_3$). **HRMS** (ESI+): m/z calcd for $C_{21}H_{26}N_9O_5S$ $[M+H]^+$: 516.1772, Found 516.1762.

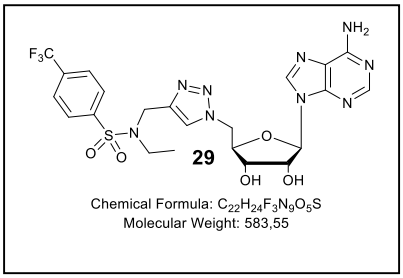
N-[(1-{[(2R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl}-1H-1,2,3-triazol-4-yl)methyl]-N-ethyl-4-methylbenzene-1-sulfonamide (27). Following method **E** with 5'-azido-adenosine (55 mg, 0.188 mmol, 0.90 eq) and reagent **I** (50 mg, 0.211 mmol, 1.0 eq), **27** was obtained as a white powder (34 mg, 30%). R_f 0.50 (8:92 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.27 (s, 1H, H_8) ; 8.15 (s, 1H, H_2) ; 7.76 (s, 1H, $H_{Triazole}$) ; 7.64 – 7.58 (m, 2H, $2H_{Ar}$) ; 7.39 – 7.24 (m, 4H, $2H_{Ar}$, NH_2) ; 5.91 (d, *J* = 5.3 Hz, 1H, $H_{1'}$) ; 5.60 (d, *J* = 5.8 Hz, 1H, $OH_{2'}$) ; 5.45 (d, *J* = 4.8 Hz, 1H, $OH_{3'}$) ; 4.77 – 4.63 (m, 3H, $H_{2'}$, $H_{5'5''}$) ; 4.39 – 4.26 (m, 2H, C*H*$_2$-NH) ; 4.26 – 4.17 (m, 2H, $H_{3'}$, $H_{4'}$) ; 3.07 (q, *J* = 7.1 Hz, 2H, C*H*$_2$-CH_3) ; 2.36 (s, 3H, CH_3) ; 0.90 (t, *J* = 7.1 Hz, 3H, CH_2-C*H*$_3$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 149.2 (C_4) ; 143.0 ($C_{q\ Triazole}$) ; 142.5 ($C_{q\ Ar}$) ; 139.9 (C_8) ; 136.5 ($C_{q\ Ar}$) ; 129.7 (*C*H$_{Ar}$) ; 126.8 (*C*H$_{Ar}$) ; 124.6 (*C*H$_{Triazole}$) ; 119.2 (C_5) ; 87.8 ($C_{1'}$) ; 82.3 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 70.9 ($C_{3'}$) ; 51.3 ($C_{5'}$) ; 42.1 (*C*H$_2$-CH_3) ; 41.5 (*C*H$_2$-NEt) ; 20.9 (CH_3) ; 13.3 (CH_2-*C*H$_3$). **HRMS** (ESI+): m/z calcd for $C_{22}H_{28}N_9O_5S$ $[M+H]^+$: 530.1929, Found 530.1930.



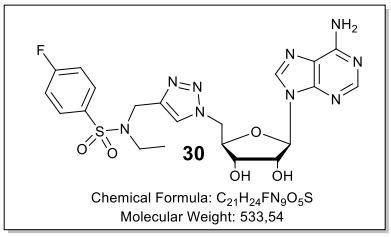
N-[(1-{[(2R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl}-1H-1,2,3-triazol-4-yl)methyl]-N-ethyl-4-chlorobenzene-1-sulfonamide (28). Following method **E** with 5'-azido-adenosine (49 mg, 0.168 mmol, 1.0 eq) and reagent **J** (60 mg, 0.233 mmol, 1.38 eq), **28** was obtained as a white powder (43 mg, 34%). R_f 0.50 (15:85 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.26 (s, 1H, H_8) ; 8.14 (s, 1H, H_2) ; 7.83 (s, 1H, $H_{Triazole}$) ; 7.78 – 7.71 (m, 2H, $2H_{Ar}$) ; 7.63 – 7.54 (m, 2H, $2H_{Ar}$) ; 7.32 (br.s, 2H, NH_2) ; 5.91 (d, *J* = 5.3 Hz, 1H, $H_{1'}$) ; 5.60 (d, *J* = 5.7 Hz, 1H, $OH_{2'}$) ; 5.46 (d, *J* = 4.2 Hz, 1H, $OH_{3'}$) ; 4.76 – 4.66 (m, 3H, $H_{2'}$, $H_{5'5''}$) ; 4.39 – 4.31 (m, 2H, C*H*$_2$-NH) ; 4.28 – 4.18 (m, 2H, $H_{3'}$, $H_{4'}$) ; 3.11 (q, *J* = 7.1 Hz, 2H, C*H*$_2$-CH_3) ; 0.92 (t, *J* = 7.1 Hz, 3H, CH_2-C*H*$_3$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.7 (C_2) ; 149.2 (C_4) ; 142.3 ($C_{q\ Triazole}$) ; 139.9 (C_8) ; 138.3 ($C_{q\ Ar}$) ; 137.6 ($C_{q\ Ar}$) ; 129.3 (*C*H$_{Ar}$) ; 128.8 (*C*H$_{Ar}$) ; 124.7 (*C*H$_{Triazole}$) ; 119.2 (C_5) ; 87.9 ($C_{1'}$) ; 82.2 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 70.9 ($C_{3'}$) ; 51.3 ($C_{5'}$) ; 42.2 (*C*H$_2$-CH_3) ; 41.5 (*C*H$_2$-NEt) ; 13.4 (CH_2-*C*H$_3$). **HRMS** (ESI+): m/z calcd for $C_{21}H_{25}ClN_9O_5S$ $[M+H]^+$: 549.9905, Found 549.9915.



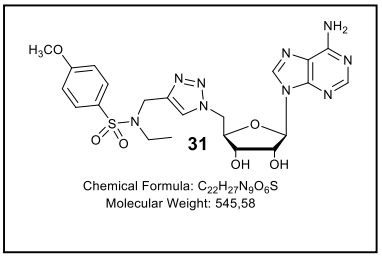
N-[(1-{[(2R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl}-1H-1,2,3-triazol-4-yl)methyl]-N-ethyl-4-trifluoromethylbenzene-1-sulfonamide (29). Following method **E** with 5'-azido-adenosine (43 mg, 0.147 mmol, 1.0 eq) and reagent **K** (60 mg, 0.206 mmol, 1.40 eq), **29** was obtained as a white powder (32 mg, 27%). R_f 0.64 (15:85 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.27 (s, 1H, H_8) ; 8.15 (s, 1H, H_2) ; 8.01 – 7.87 (m, 4H, $4H_{Ar}$) ; 7.85 (s, 1H, $H_{Triazole}$) ; 7.32 (br.s, 2H, NH_2) ; 5.90 (d, *J* = 5.3 Hz, 1H, $H_{1'}$) ; 5.61 (d, *J* = 5.7 Hz, 1H, $OH_{2'}$) ; 5.46 (d, *J* = 4.6 Hz, 1H, $OH_{3'}$) ; 4.75 – 4.63 (m, 3H, $H_{2'}$, $H_{5'5''}$) ; 4.45 – 4.34 (m, 2H, C*H*$_2$-NH) ; 4.26 – 4.18 (m, 2H, $H_{3'}$, $H_{4'}$) ; 3.15 (q, *J* = 7.1 Hz, 2H, C*H*$_2$-CH_3) ; 0.93 (t, *J* = 7.1 Hz, 3H, CH_2-C*H*$_3$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.3 (C_4) ; 143.3 ($C_{q\ Ar}$) ; 142.1 ($C_{q\ Triazole}$) ; 140.0 (C_8) ; 132.6, 132.4, 132.2, 132.0 (*C*-CF_3) ; 127.8 (*C*H$_{Ar}$) ; 126.4, 126.4 (*C*H$_{Ar}$) ; 126.2, 124.3, 122.5, 120.7 (CF_3) ; 124.8 (*C*H$_{Triazole}$) ; 119.3 (C_5) ; 87.9 ($C_{1'}$) ; 82.2 ($C_{4'}$) ; 72.5 ($C_{2'}$) ; 70.9 ($C_{3'}$) ; 51.2 ($C_{5'}$) ; 42.4 (*C*H$_2$-CH_3) ; 41.6 (*C*H$_2$-NEt) ; 13.4 (CH_2-*C*H$_3$). **HRMS** (ESI+): m/z calcd for $C_{22}H_{25}F_3N_9O_5S$ $[M+H]^+$: 583.5541, Found 583.5539.



N-[(1-{[(2R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-oxolan-2-yl]methyl}-1H-1,2,3-triazol-4-yl)methyl]-N-ethyl-4-fluorobenzene-1-sulfonamide (30). Following method **E** with 5'-azido-adenosine (52 mg, 0.177 mmol, 1.0 eq) and reagent **L** (60 mg, 0.249 mmol, 1.40 eq), **30** was obtained as a white powder (36 mg, 38%). R_f 0.48 (15:85 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.27 (s, 1H, H_8) ; 8.15 (s, 1H, H_2) ; 7.83 – 7.77 (m, 3H, $H_{Triazole}$, $2H_{Ar}$) ; 7.40 – 7.26 (m, 4H, $2H_{Ar}$, NH_2) ; 5.90 (d, *J* = 5.3 Hz, 1H, $H_{1'}$) ; 5.61 (d, *J* = 5.8 Hz, 1H, $OH_{2'}$) ; 5.46 (d, *J* = 4.4 Hz, 1H, $OH_{3'}$) ; 4.74 – 4.64 (m, 3H, $H_{2'}$, $H_{5'5''}$) ; 4.39 – 4.30 (m, 2H, C*H*$_2$-NH) ; 4.28 – 4.17 (m, 2H, $H_{3'}$, $H_{4'}$) ; 3.11 (q, *J* = 7.1 Hz, 2H, C*H*$_2$-CH_3) ; 0.92 (t, *J* = 7.1 Hz, 3H, CH_2-C*H*$_3$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 156.1 (C_6) ; 152.6 (C_2) ; 149.3 (C_4) ; 142.3 ($C_{q\ Triazole}$) ; 139.9 (C_8) ; 135.8 ($C_{q\ Ar}$) ; 129.9, 129.8 (*C*H$_{Ar}$) ; 124.7 (*C*H$_{Triazole}$) ; 119.3 (C_5) ; 116.4, 116.3 (*C*H$_{Ar}$) ; 87.8 ($C_{1'}$) ; 82.2 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 70.9 ($C_{3'}$) ; 51.3 ($C_{5'}$) ; 42.1 (*C*H$_2$-CH_3) ; 41.6 (*C*H$_2$-NEt) ; 13.3 (CH_2-*C*H$_3$). **HRMS** (ESI+): m/z calcd for $C_{21}H_{25}FN_9O_5S$ $[M+H]^+$: 533.5400, Found 533.5397.



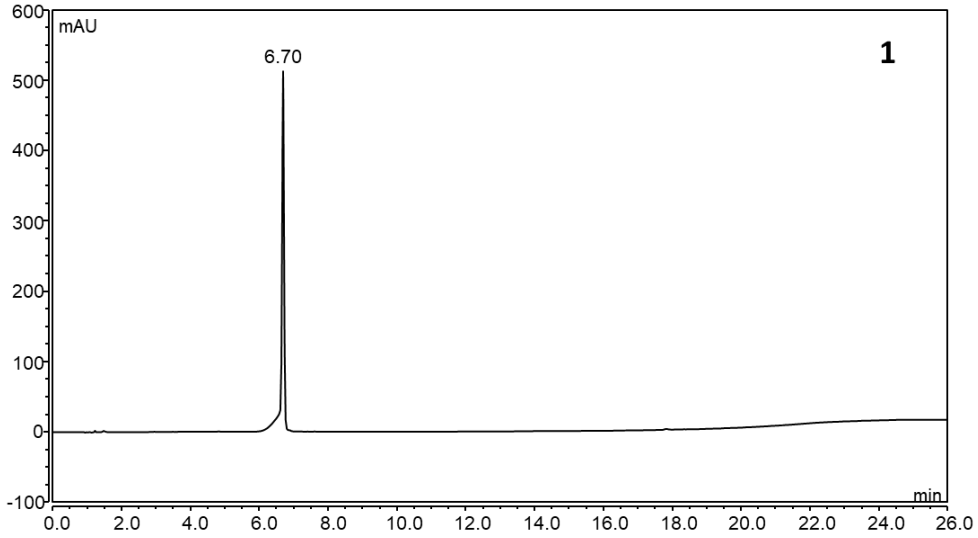
N-[(1-{[(2R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl}-1H-1,2,3-triazol-4-yl)methyl]-N-ethyl-4-methoxybenzene-1-sulfonamide (31). Following method **E** with 5'-azido-adenosine (50 mg, 0.171 mmol, 1.0 eq) and reagent **M** (60 mg, 0.240 mmol, 1.40 eq), **31** was obtained as a white powder (21 mg, 23%). R_f 0.42 (15:95 MeOH/DCM). **^{1}H-NMR** (600 MHz, DMSO-d_6) δ 8.26 (s, 1H, H_8) ; 8.14 (s, 1H, H_2) ; 7.79 (s, 1H, $H_{Triazole}$) ; 7.70 – 7.64 (m, 2H, , $2H_{Ar}$) ; 7.32 (br.s, 2H, NH_2) ; 7.07 – 7.01 (m, 2H, $2H_{Ar}$) ; 5.90 (d, *J* = 5.3 Hz, 1H, $H_{1'}$) ; 5.61 (d, *J* = 5.8 Hz, 1H, $OH_{2'}$) ; 5.46 (d, *J* = 4.4 Hz, 1H, $OH_{3'}$) ; 4.76 – 4.65 (m, 3H, $H_{2'}$, $H_{5'5''}$) ; 4.36 – 4.25 (m, 2H, C*H*$_2$-NH) ; 4.25 – 4.18 (m, 2H, $H_{3'}$, $H_{4'}$) ; 3.82 (s, 3H, OMe) ; 3.06 (q, *J* = 7.1 Hz, 2H, C*H*$_2$-CH_3) ; 0.89 (t, *J* = 7.1 Hz, 3H, CH_2-C*H*$_3$). **^{13}C-NMR** (151 MHz, DMSO-d_6) δ 162.3 ($C_{q\ Ar}$) ; 156.1 (C_6) ; 152.7 (C_2) ; 149.2 (C_4) ; 142.6 ($C_{q\ Triazole}$) ; 139.9 (C_8) ; 129.0 (*C*H$_{Ar}$) ; 124.6 (*C*H$_{Triazole}$) ; 119.3 (C_5) ; 114.3 (*C*H$_{Ar}$) ; 87.8 ($C_{1'}$) ; 82.3 ($C_{4'}$) ; 72.6 ($C_{2'}$) ; 70.9 ($C_{3'}$) ; 55.6 (OCH_3) ; 51.2 ($C_{5'}$) ; 42.0 (*C*H$_2$-CH_3) ; 41.6 (*C*H$_2$-NEt) ; 13.3 (CH_2-*C*H$_3$). **HRMS** (ESI+): m/z calcd for $C_{22}H_{28}N_9O_6S$ $[M+H]^+$: 545.5836, Found 545.5841.

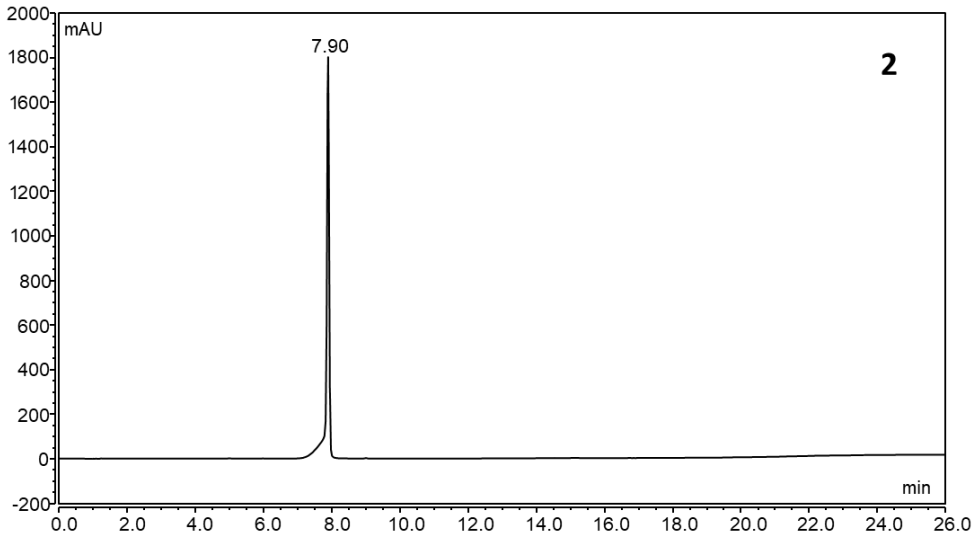


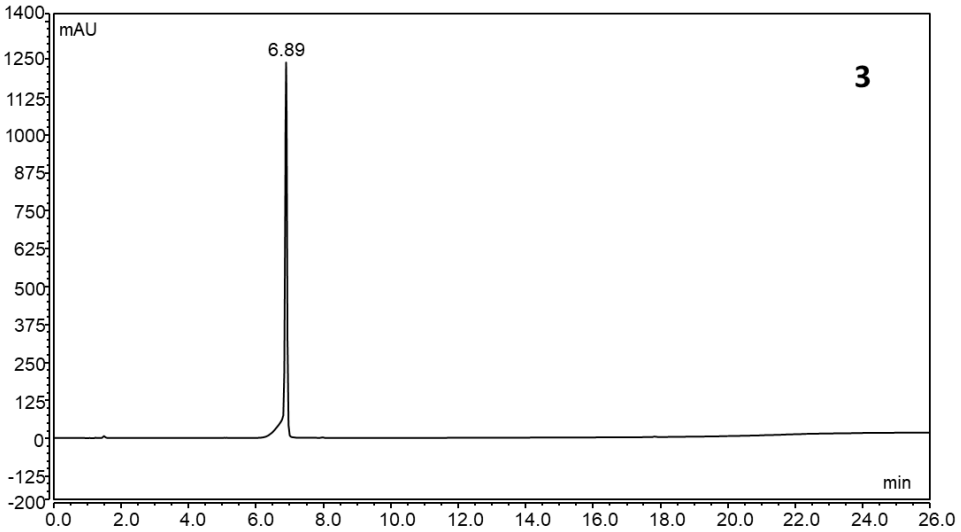
HPLC analysis of final compounds 1-31

HPLC analysis conditions:
Column: HPLC Column Nucleodur 75/4.6 100-3 C_{18} EC (Macherey Nagel)
Temperature: 30 °C
Mobile phase: eluent A: 1% ACN in 12.5 mM TEAAc buffer, pH 7; eluent B: 80% ACN in 12.5 mM TEAAc buffer, pH 7
Gradient: 10% to 100% of eluent B during 20 min. Flow rate: 1.0 mL/min
UV detection at wavelength 260 nm

N-arylsulfonamide adenosine analogues with an *N*-ethylthioether (1-8)



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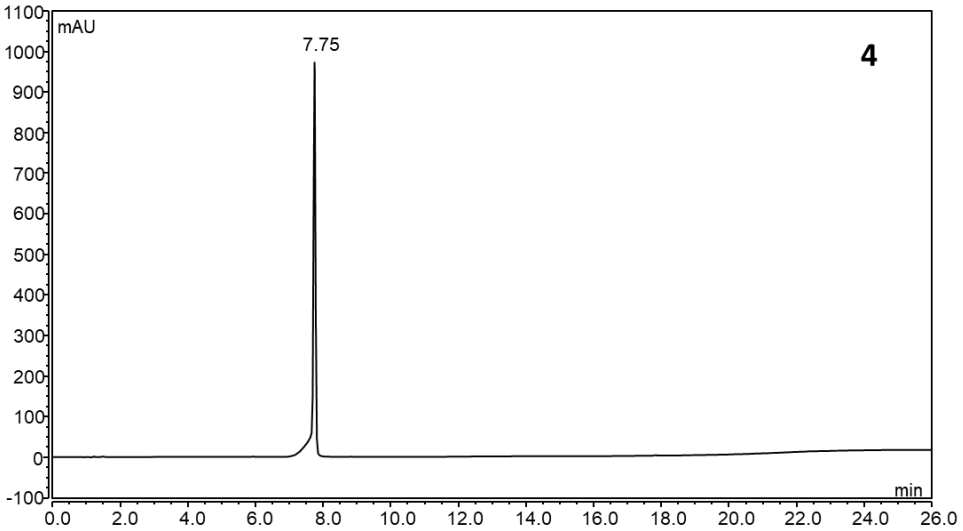
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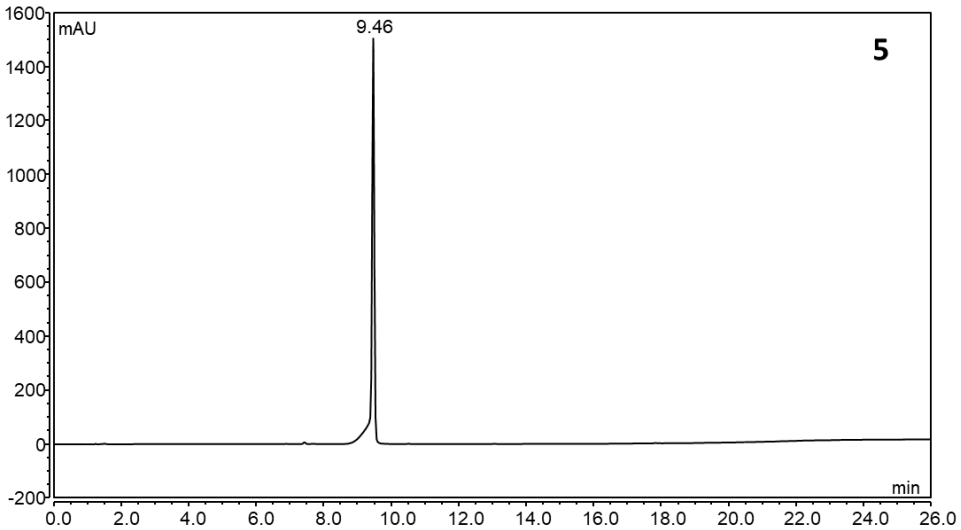
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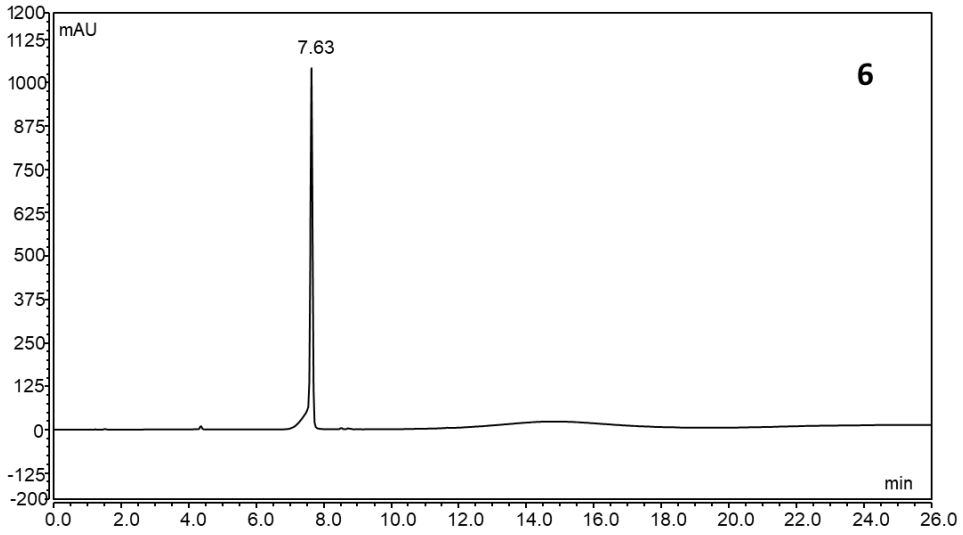
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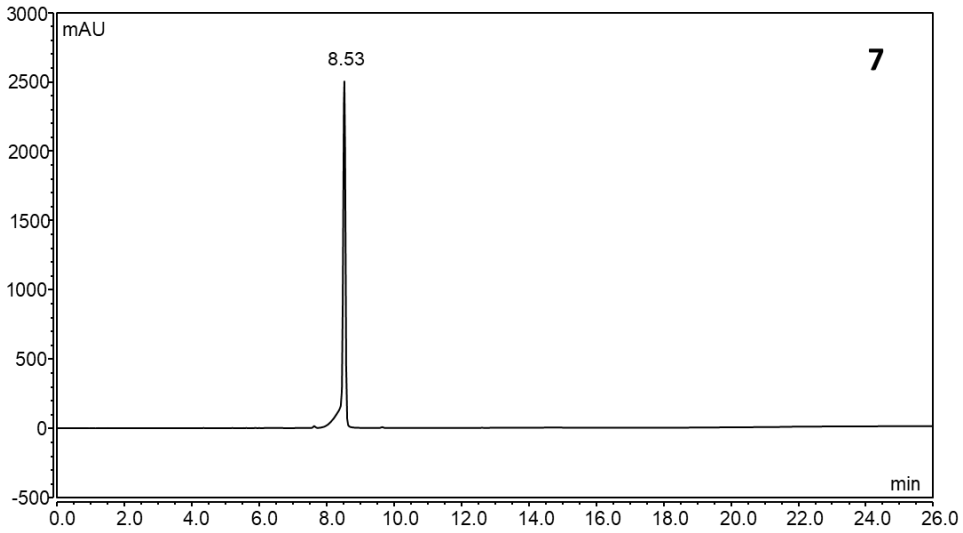
6
min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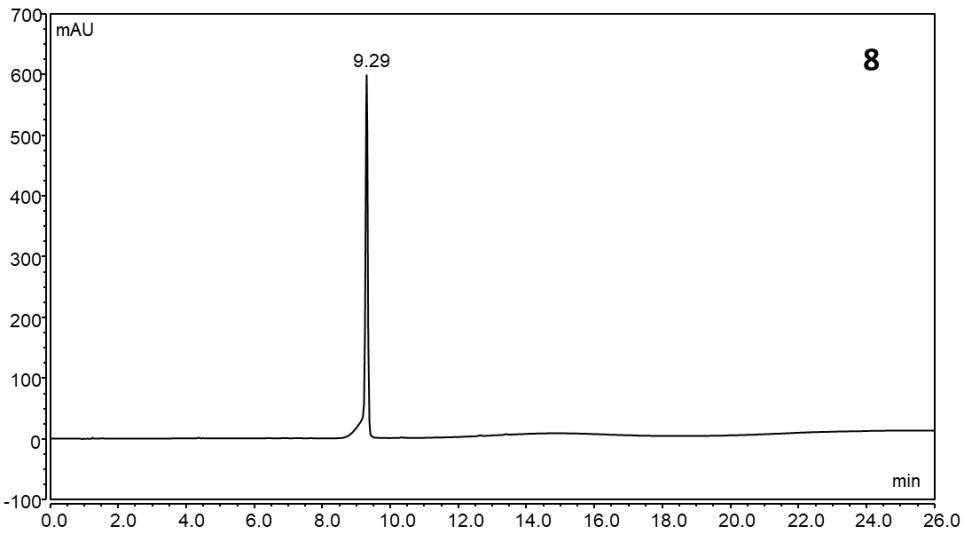
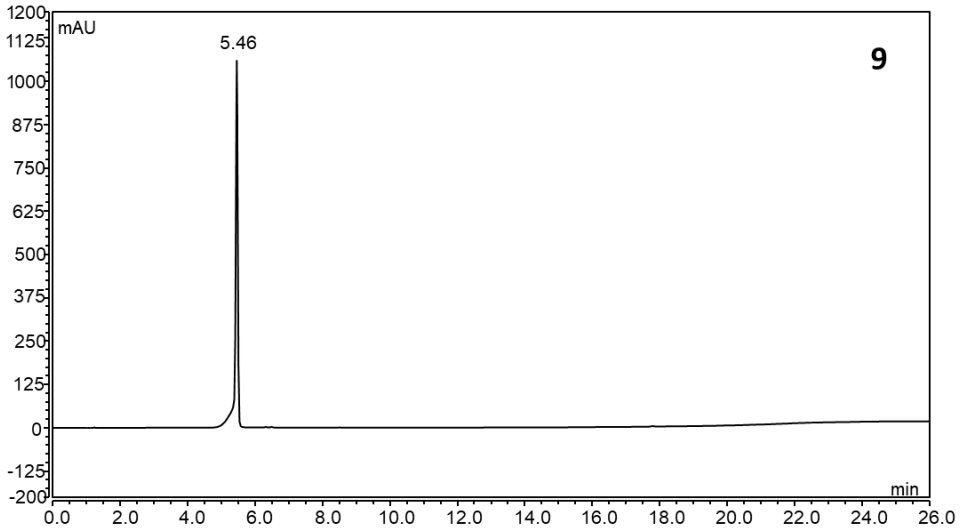
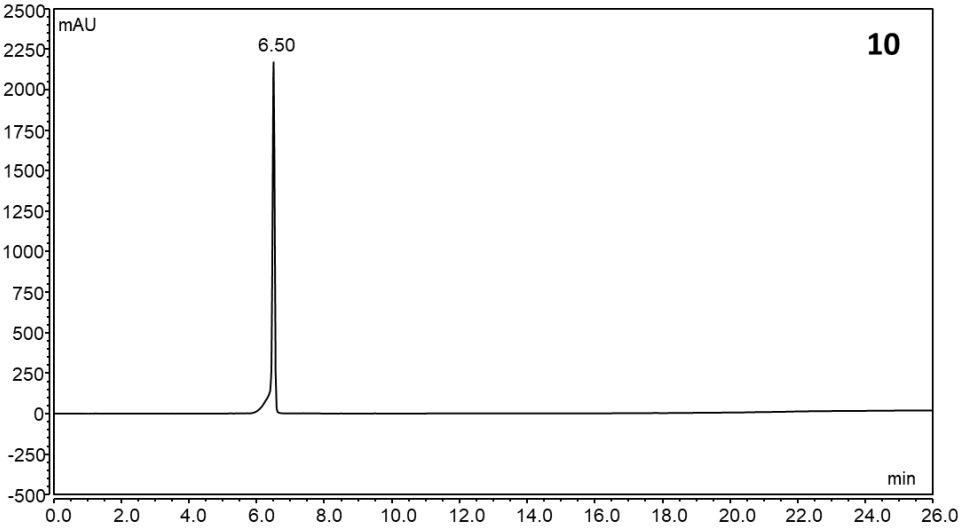
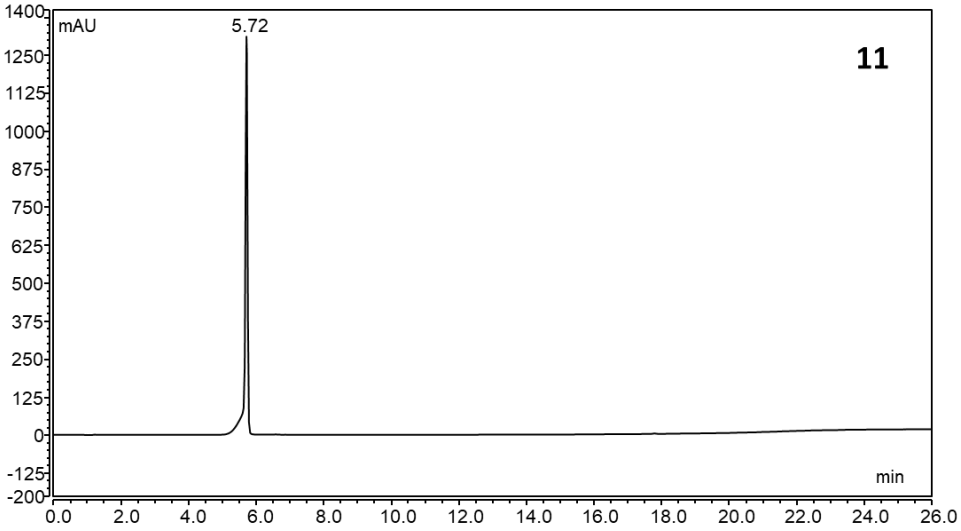
7
min

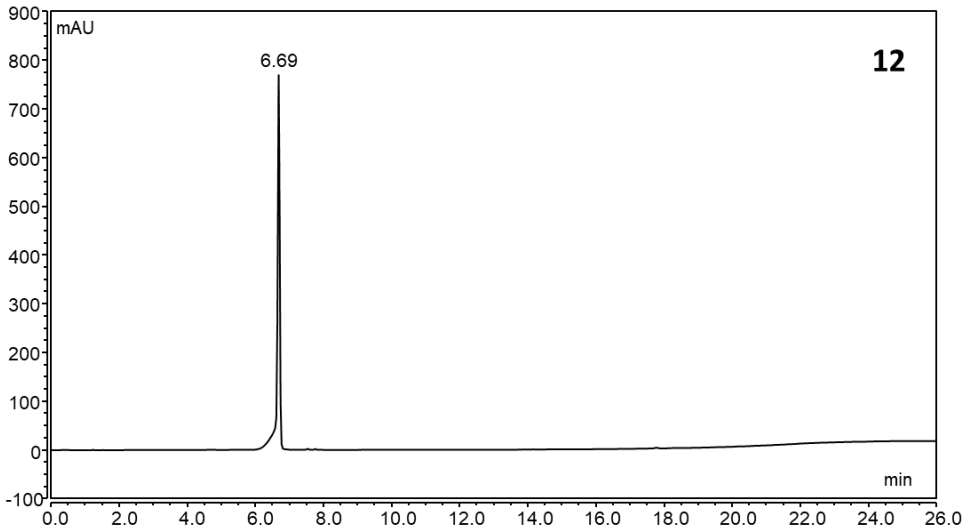

mAU
9.29
8
min

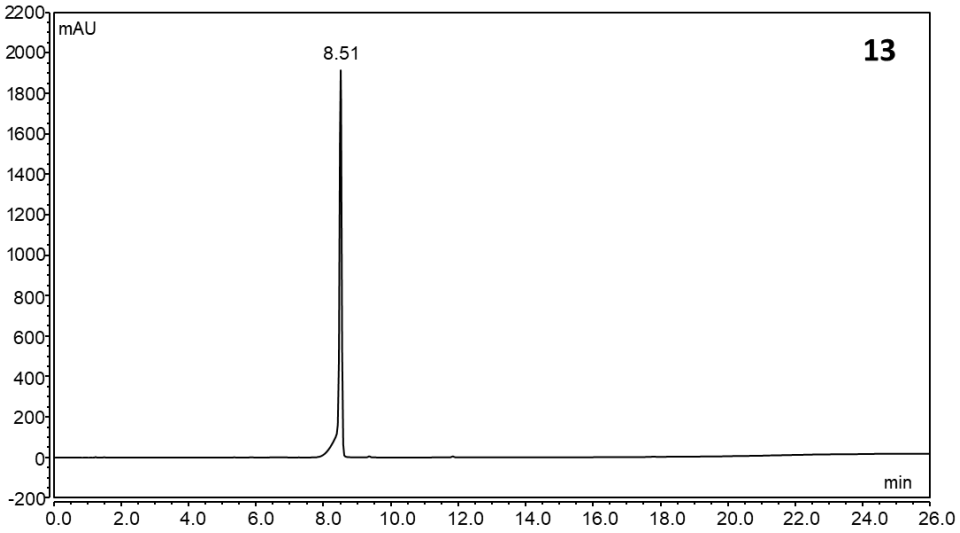
N-arylsulfonamide adenosine analogues with an *N*-ethylsulfone linker (9-13)



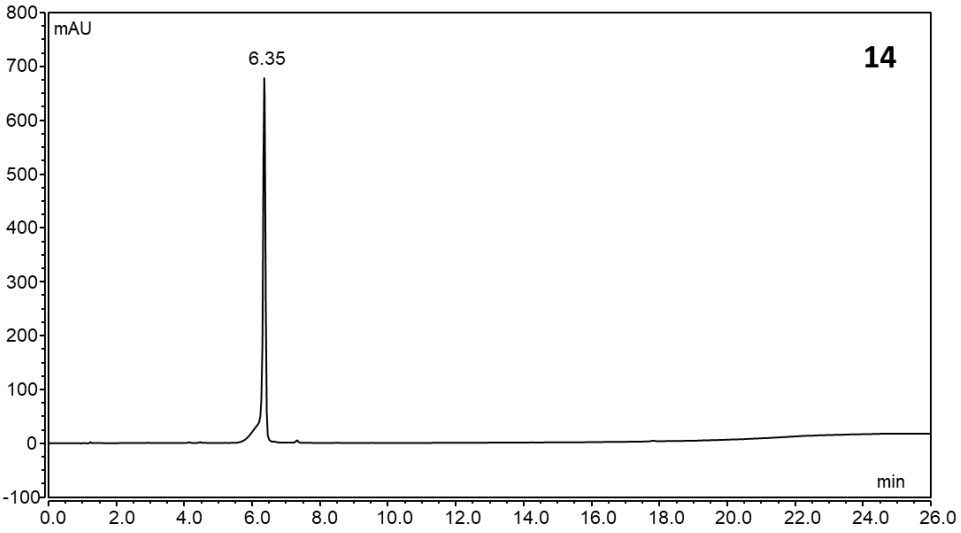


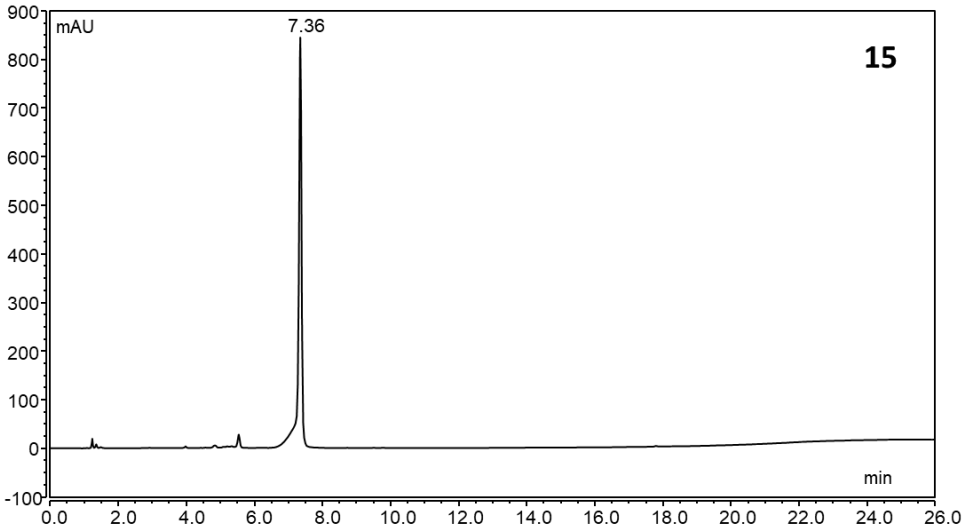






***N*-arylsulfonamide adenosine analogues with an *N*-ethylamino linker (14-18)**

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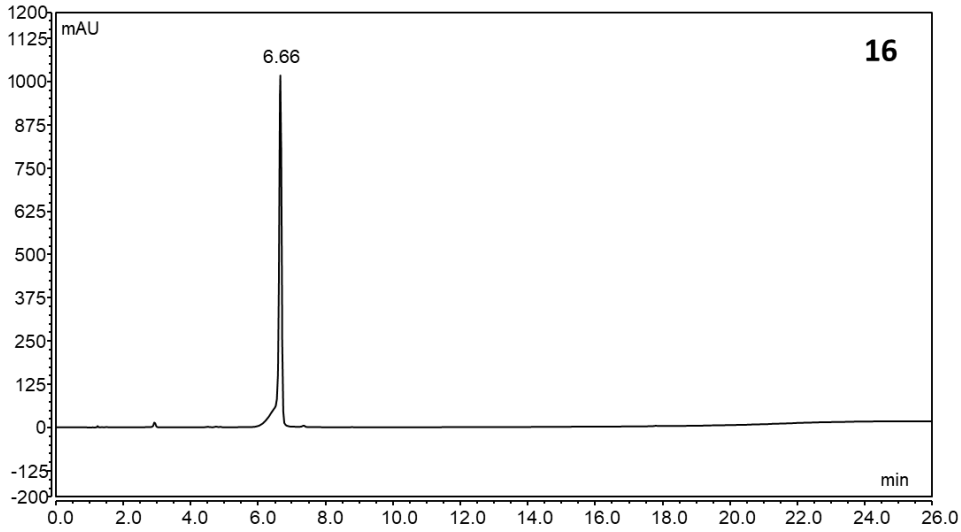
min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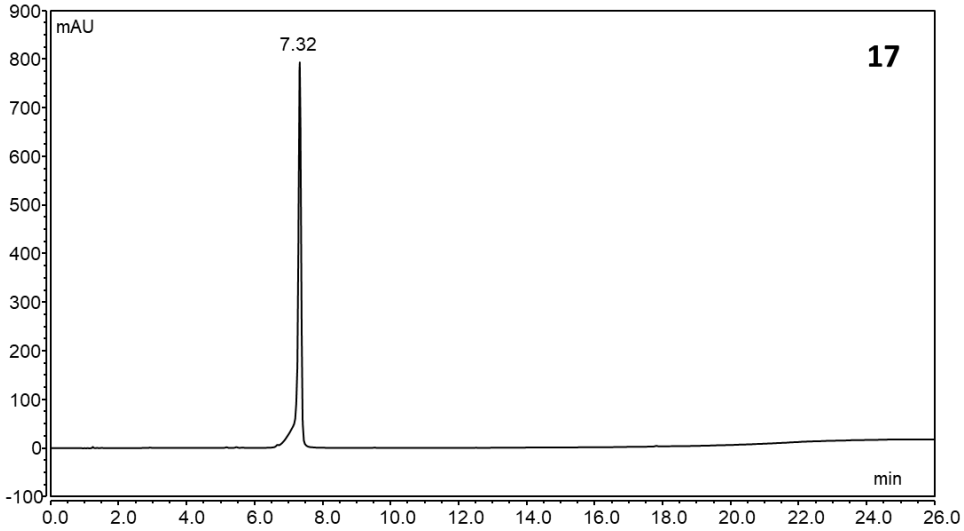
mAU
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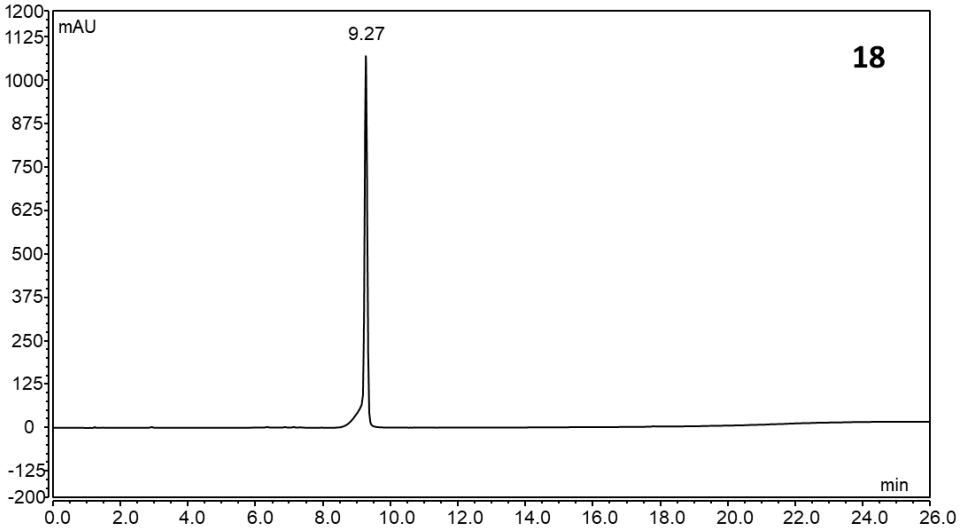
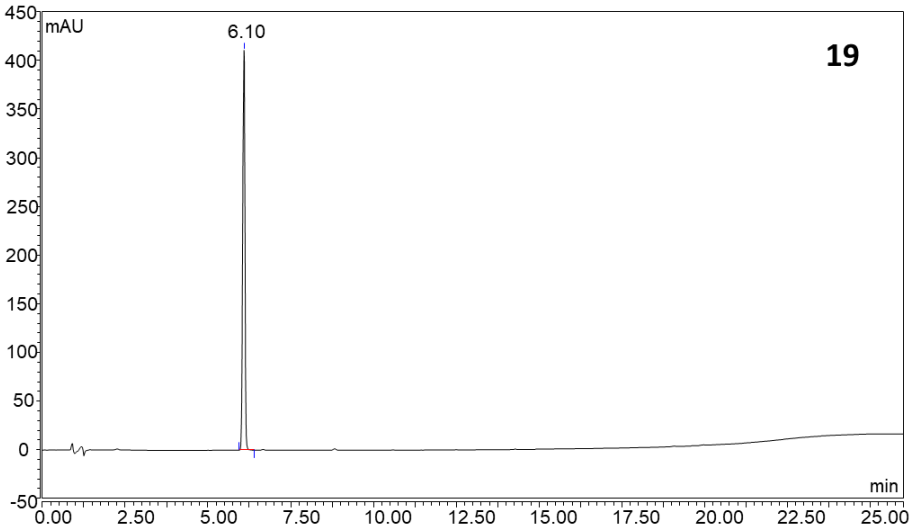
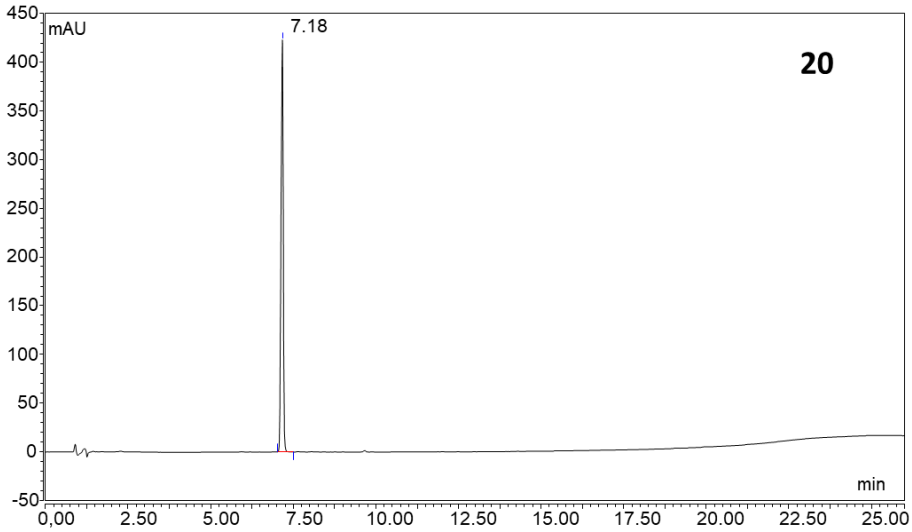
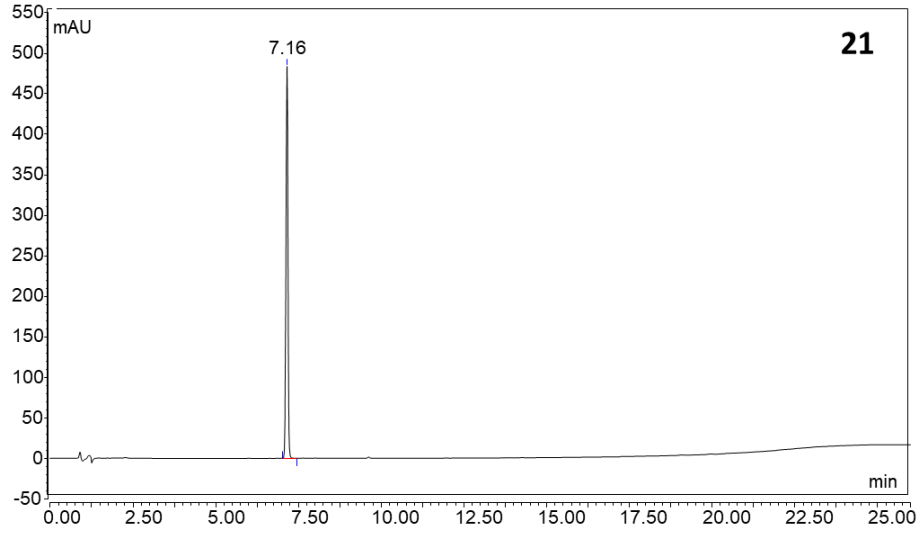
17
min

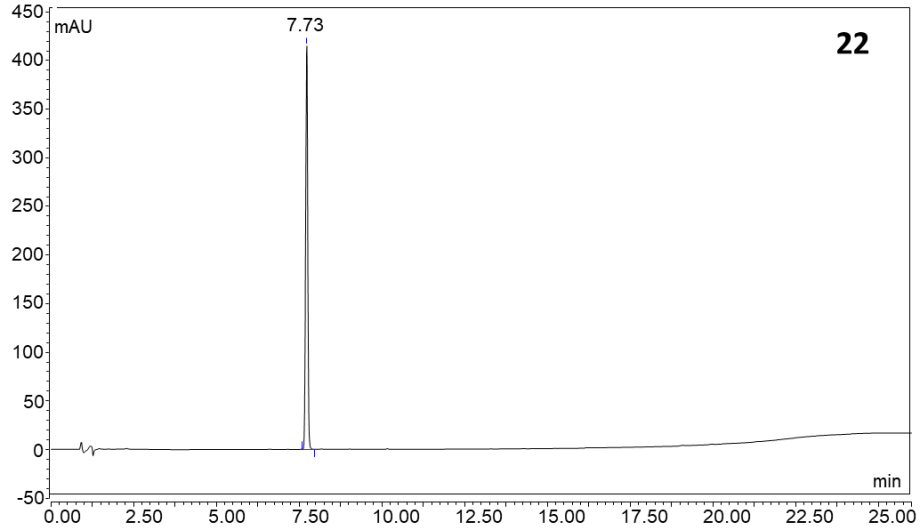


N-arylsulfonamide adenosine analogues with an N-methyltriazole linker 19-31






mAU
7.16
21
min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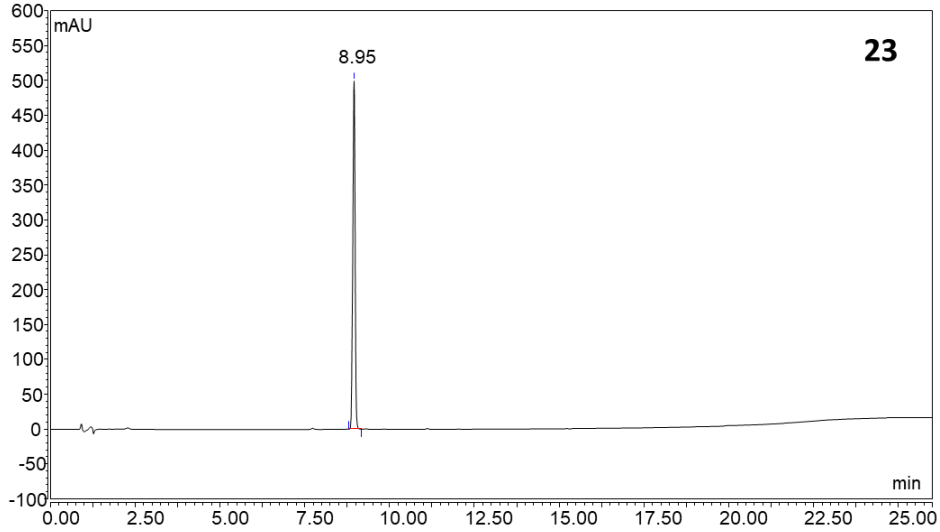
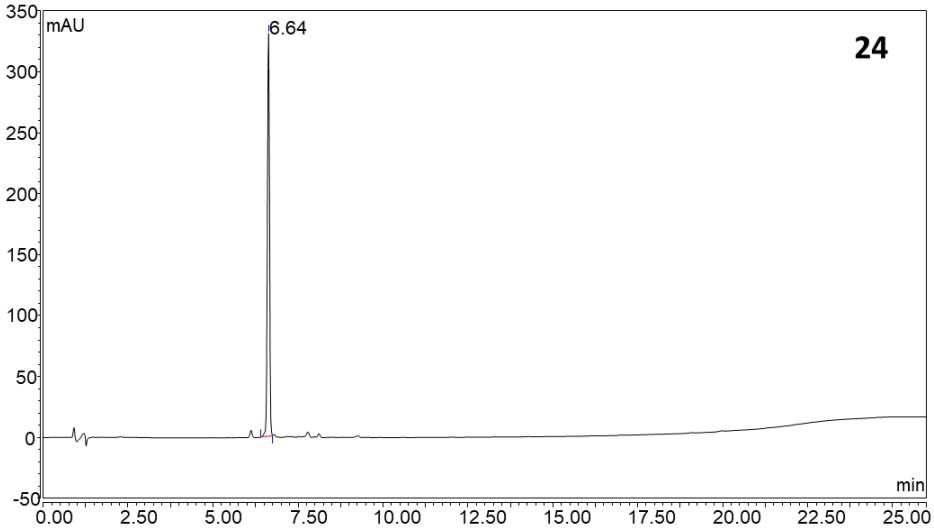
7.73
22
min


mAU
8.95
23
min


mAU
6.64
24
350
300
250
200
150
100
50
0
-50
min
0.00
2.50
5.00
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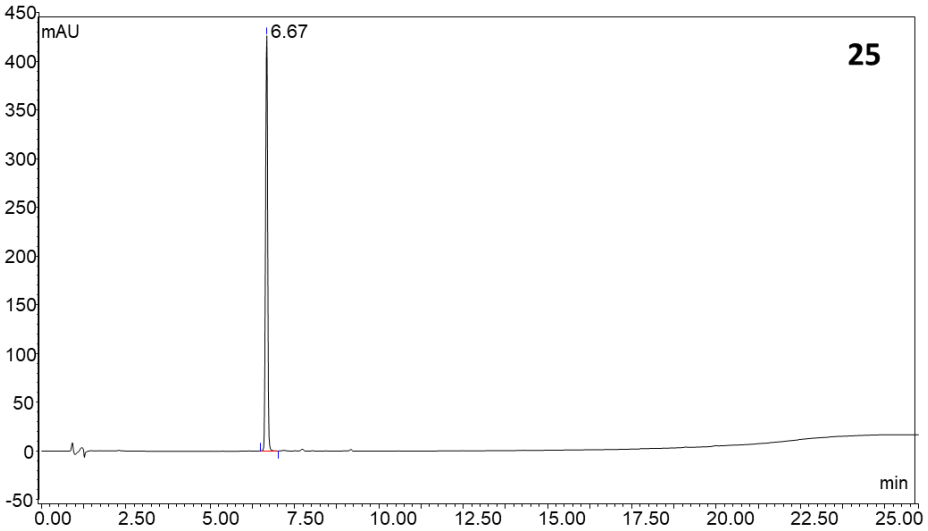
12.50
15.00
17.50
20.00
22.50
25.00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6.67
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300
250
200
150
100
50
0
-50
min
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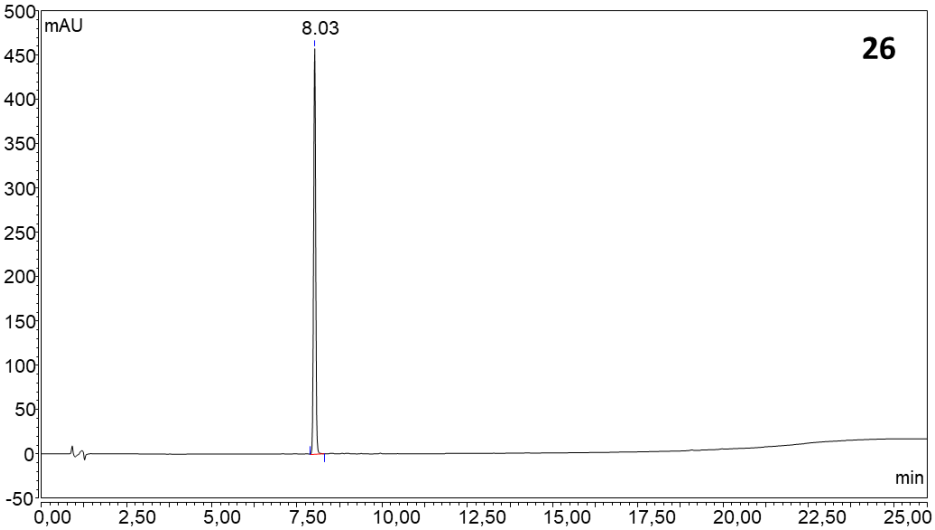
5.00
7.50
10.00
12.50
15.00
17.50
20.00
22.50
25.00


mAU
8.03
26
500
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300
250
200
150
100
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min
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5,00
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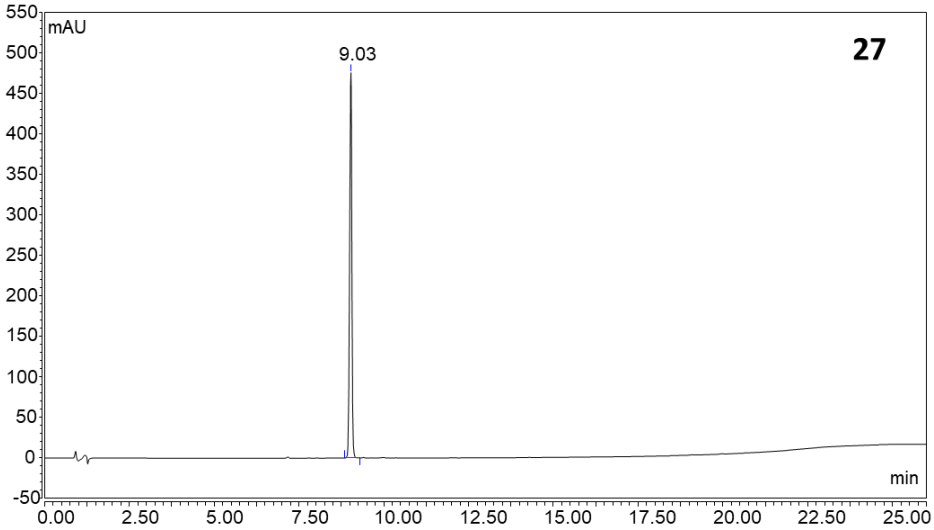
10,00
12,50
15,00
17,50
20,00
22,50
25,00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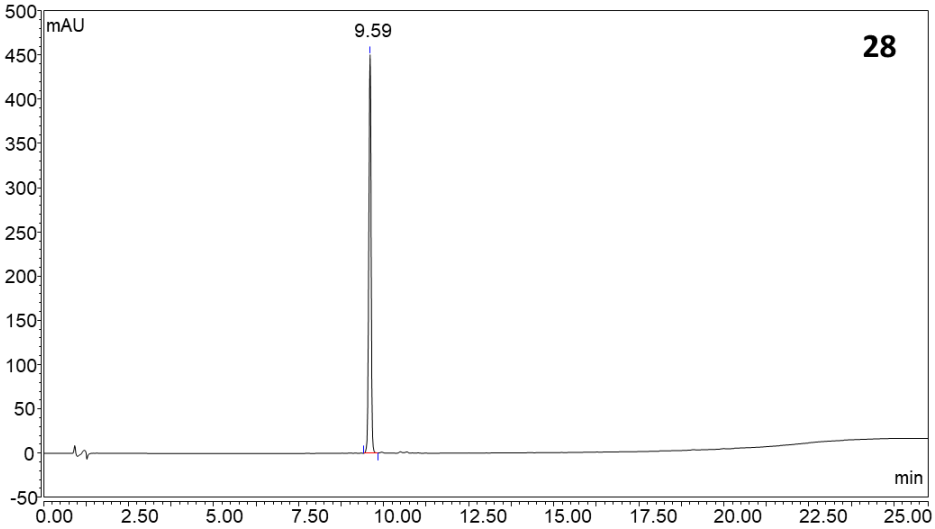
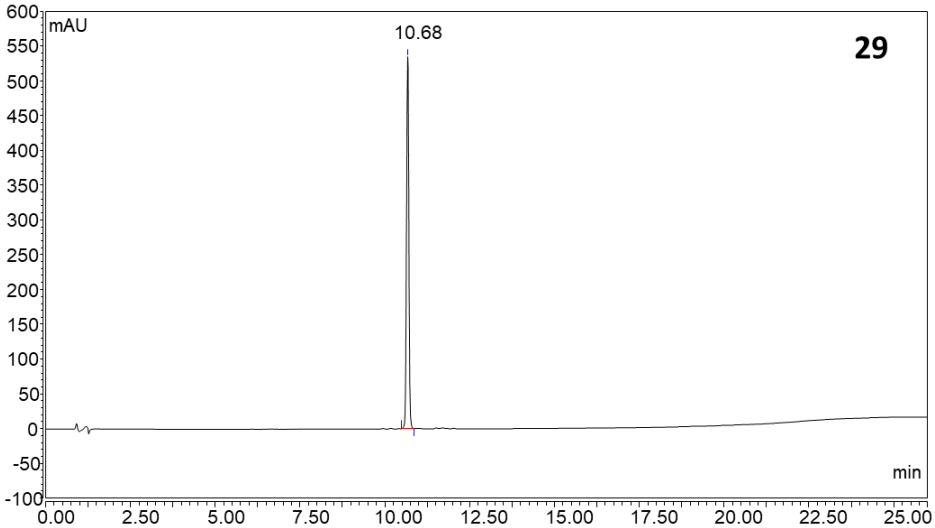
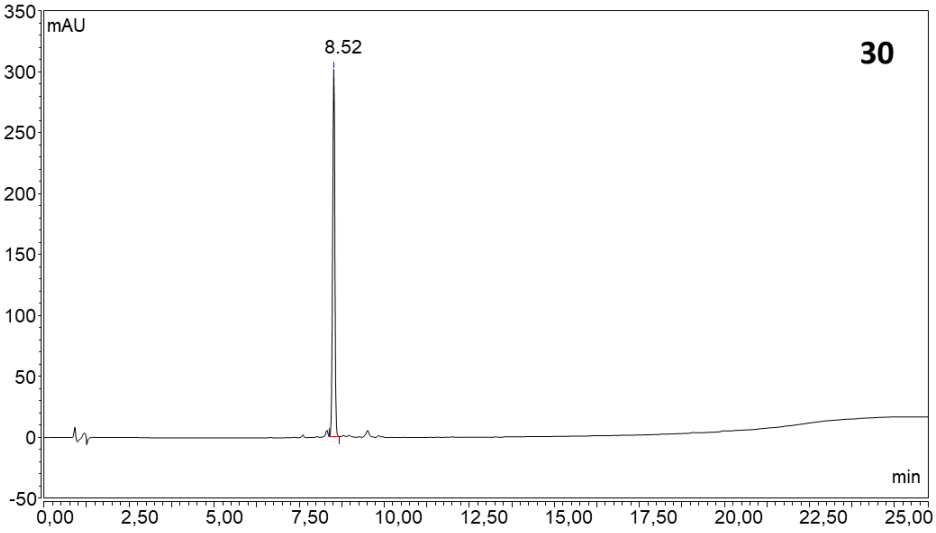

mAU
9.59
28
min


mAU
10.68
29
min


mAU
8.52
30
350
300
250
200
150
100
50
0
-50
min
0,00
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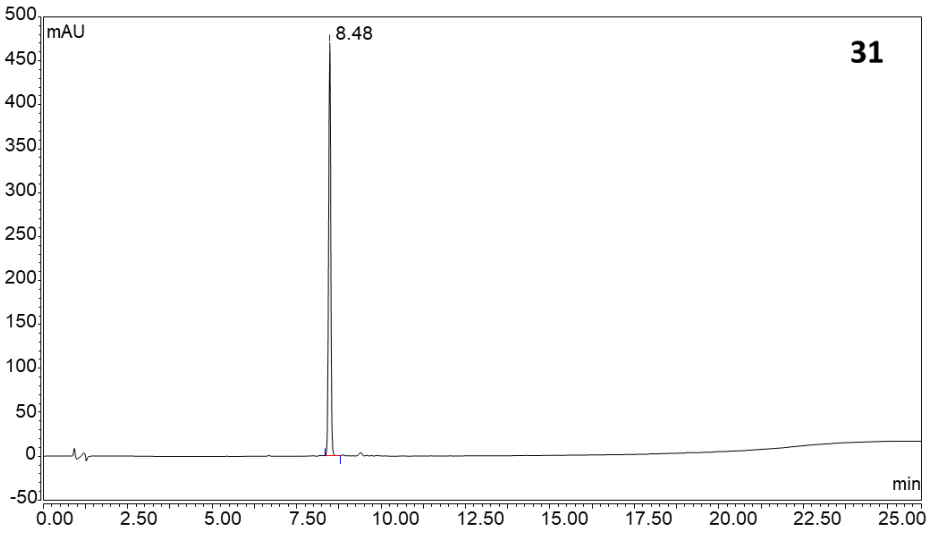
22,50
25,00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400
350
300
250
200
150
100
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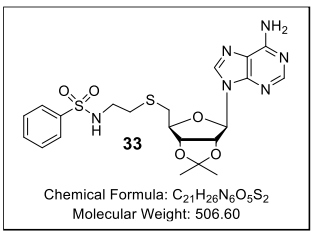
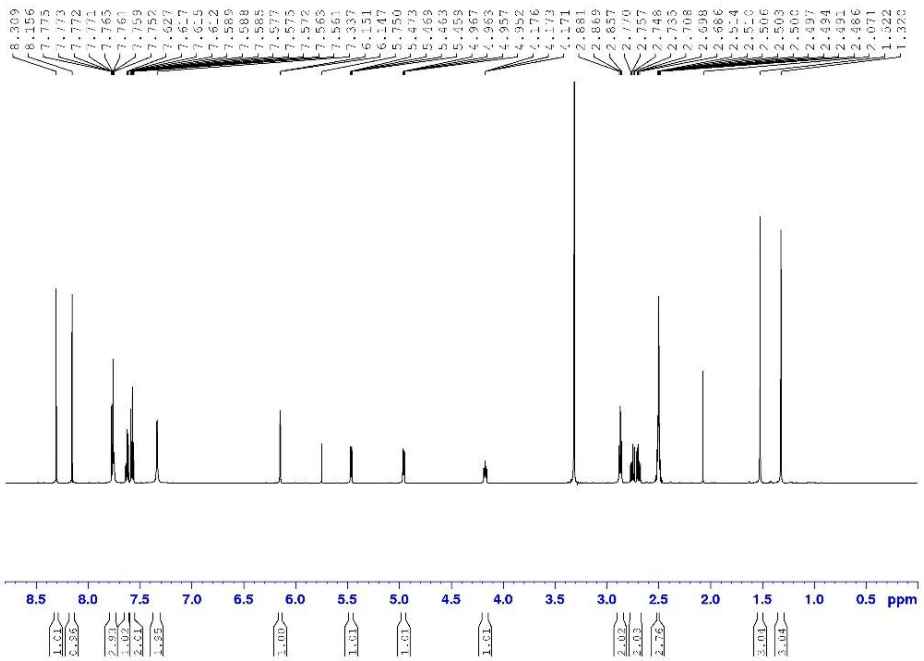
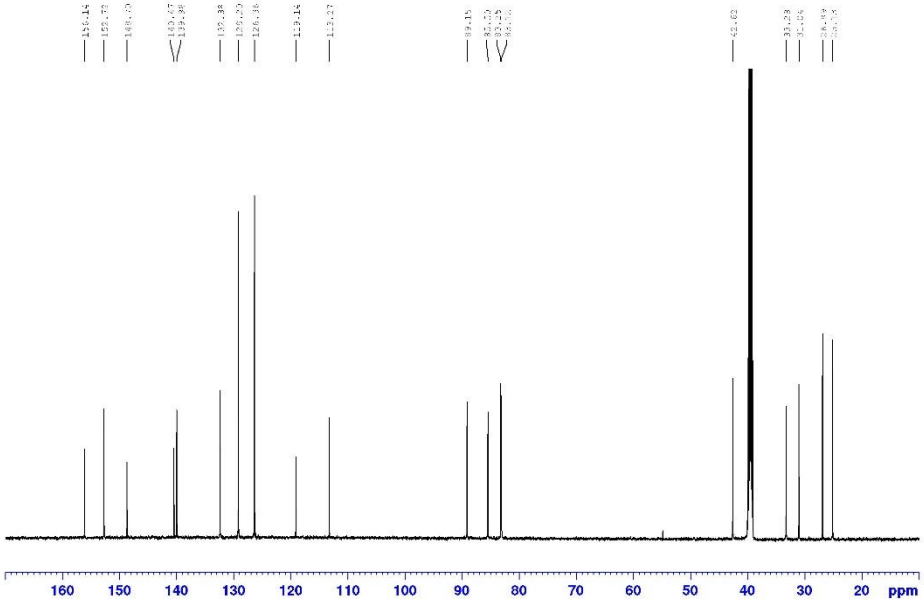
-50
min
0.00
2.50
5.00
7.50
10.00
12.50
15.00
17.50
20.00
22.50
25.00

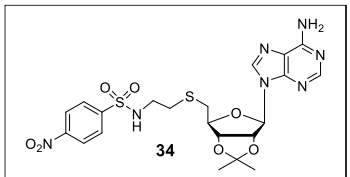
^{1}H-NMR and ^{13}C-NMR spectra of compounds 1-53

N-arylsulfonamide adenosine analogues with an *N*-ethylthioether linker (33-40 and 1-8)

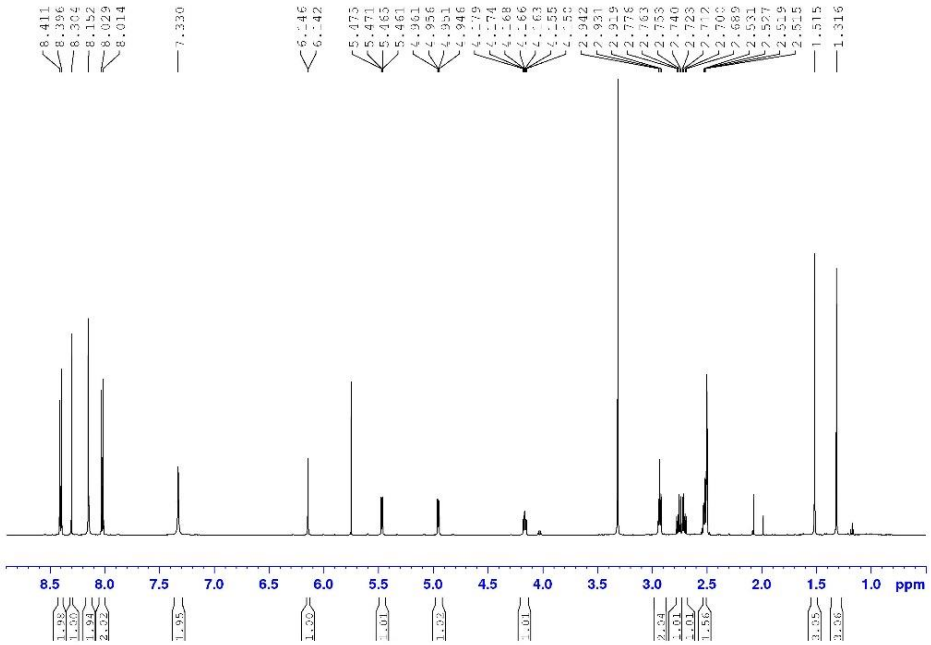


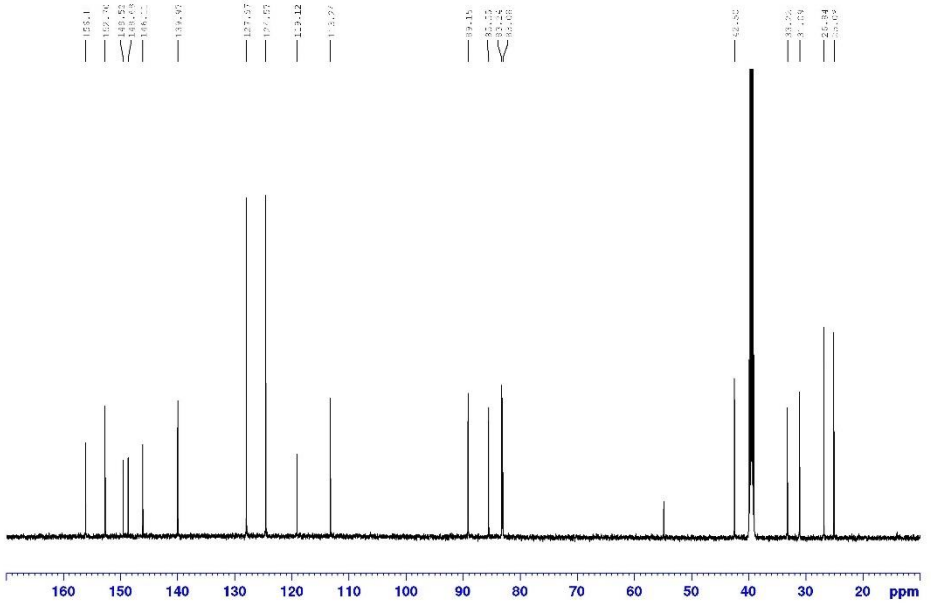


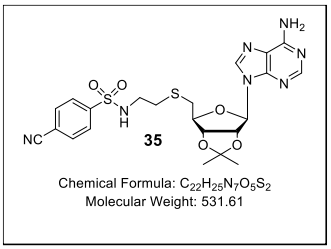




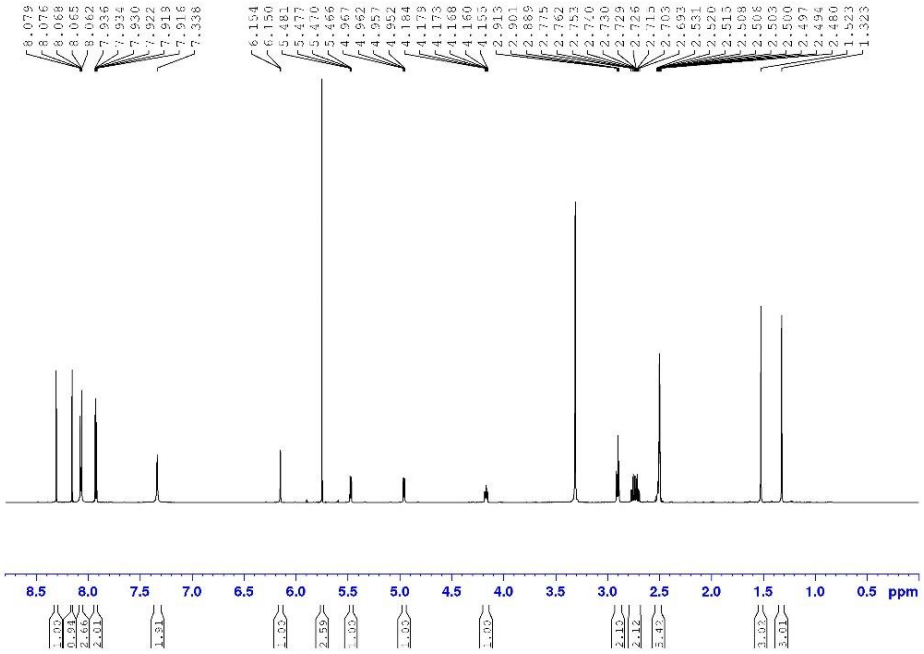
Chemical Formula: $C_{21}H_{25}N_7O_7S_2$
Molecular Weight: 551.59

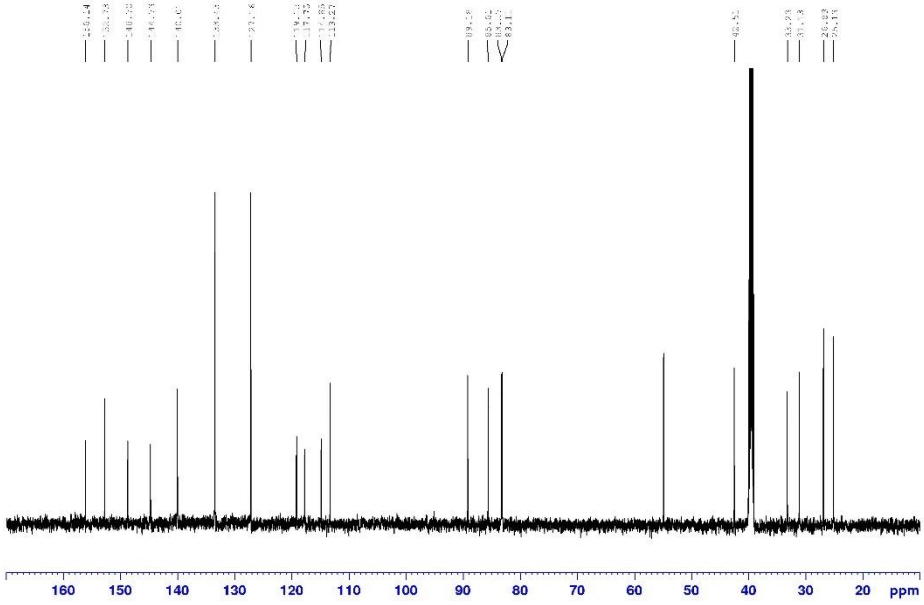


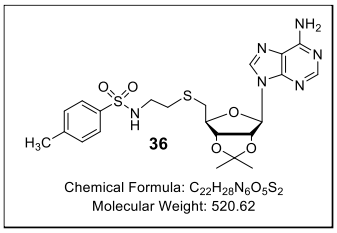




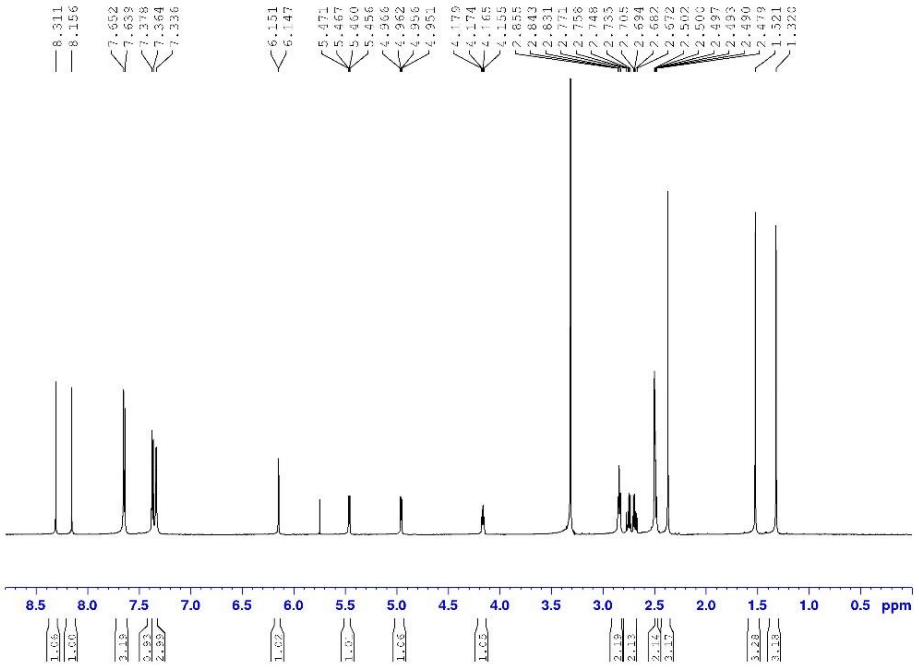
Chemical Formula: $C_{22}H_{25}N_7O_5S_2$
Molecular Weight: 531.61

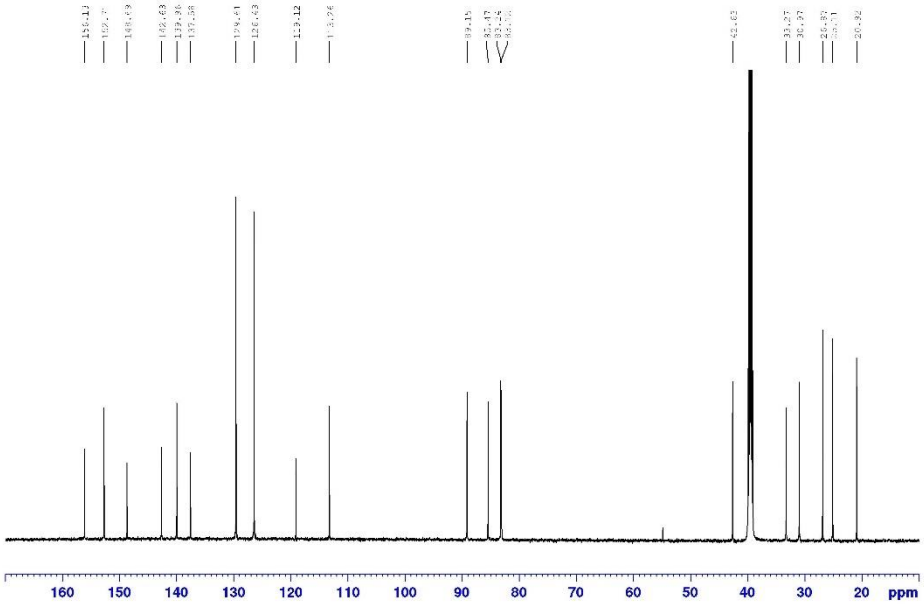


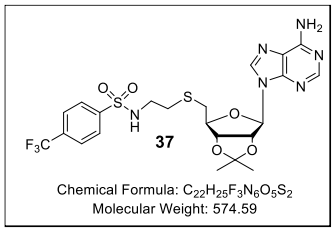




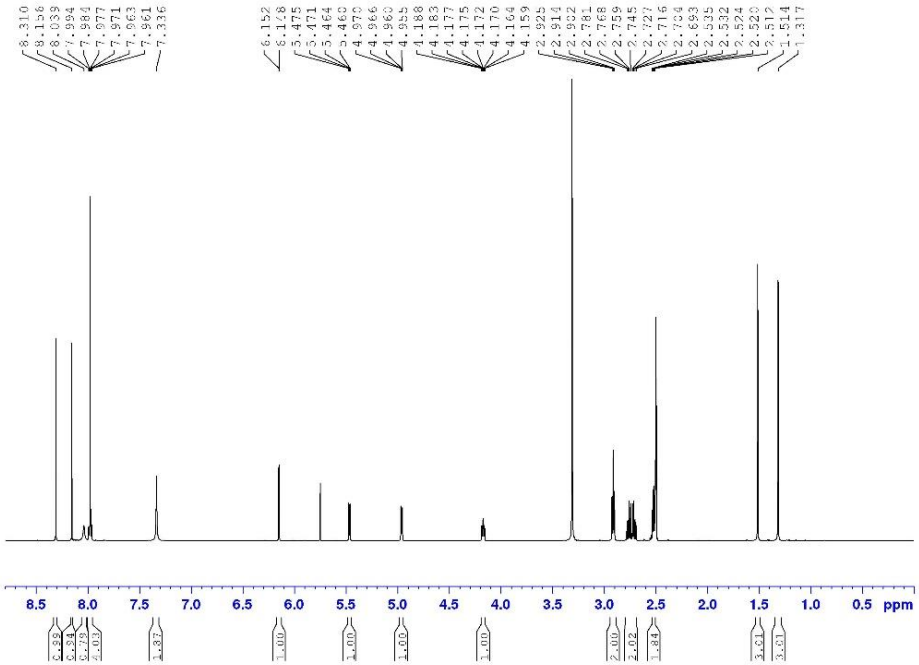
Chemical Formula: $C_{22}H_{28}N_6O_5S_2$
Molecular Weight: 520.62

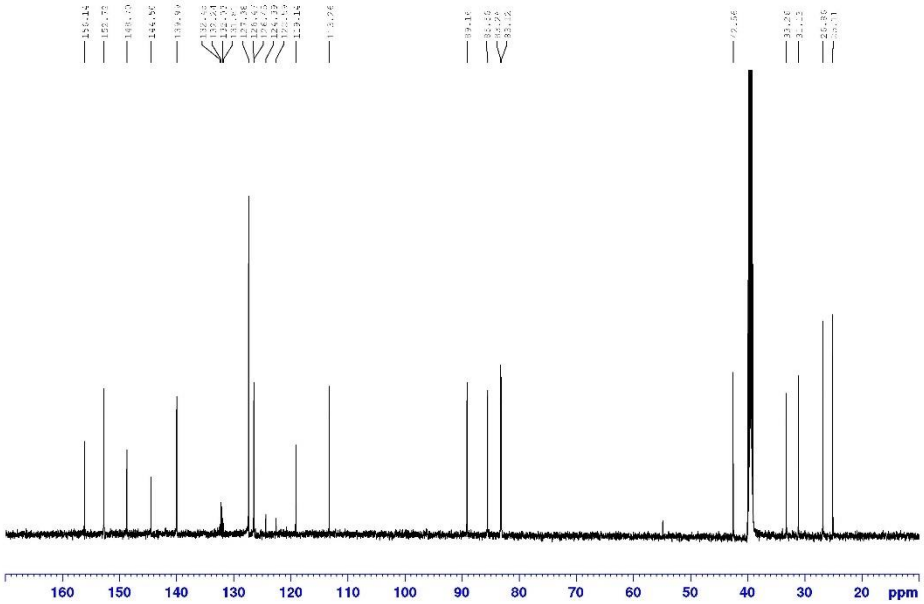


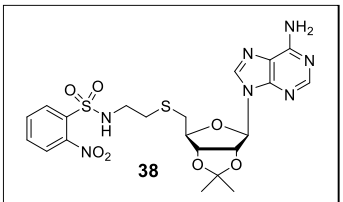




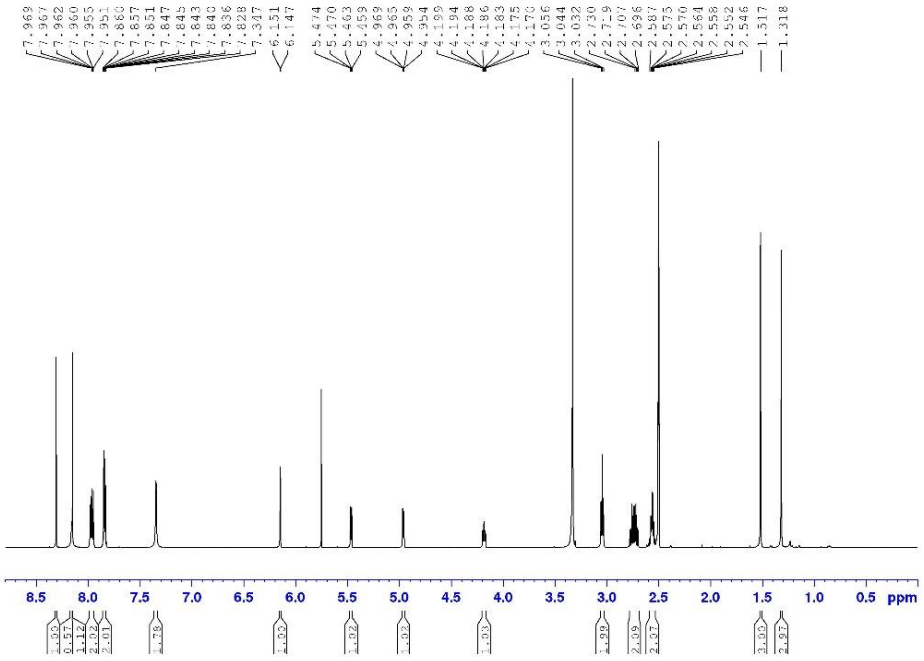
Chemical Formula: $C_{22}H_{25}F_3N_6O_5S_2$
Molecular Weight: 574.59

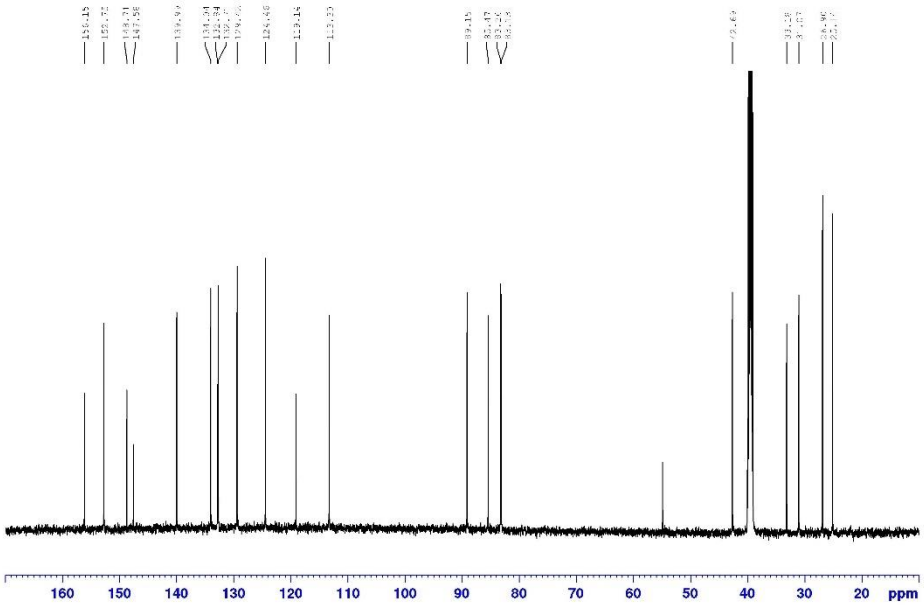


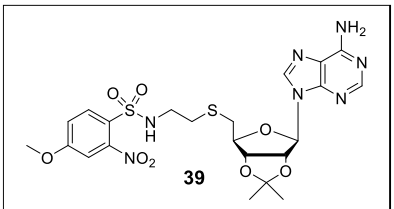




Chemical Formula: $C_{21}H_{25}N_7O_7S_2$
Molecular Weight: 551.59

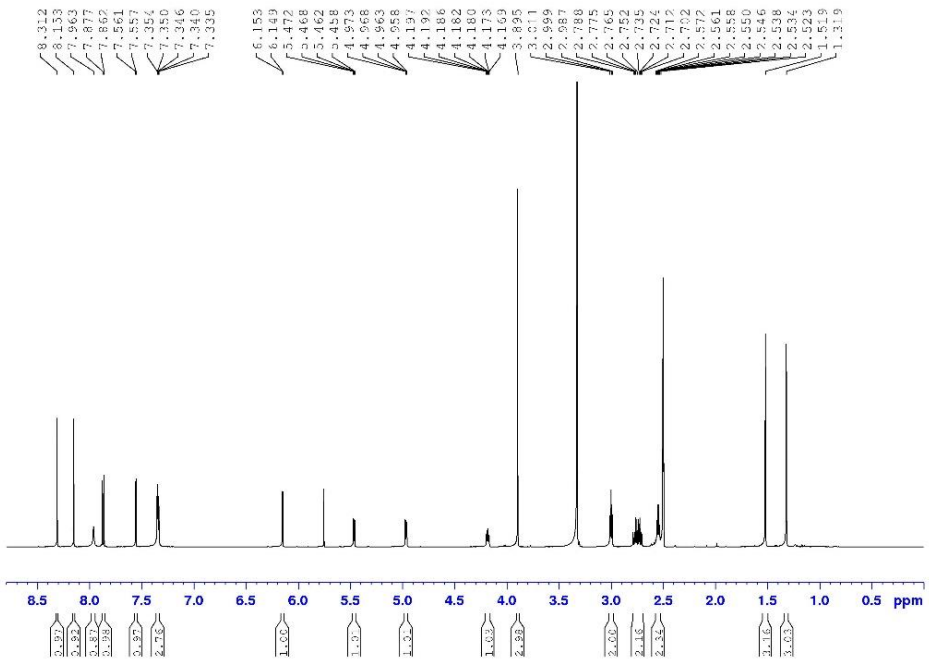


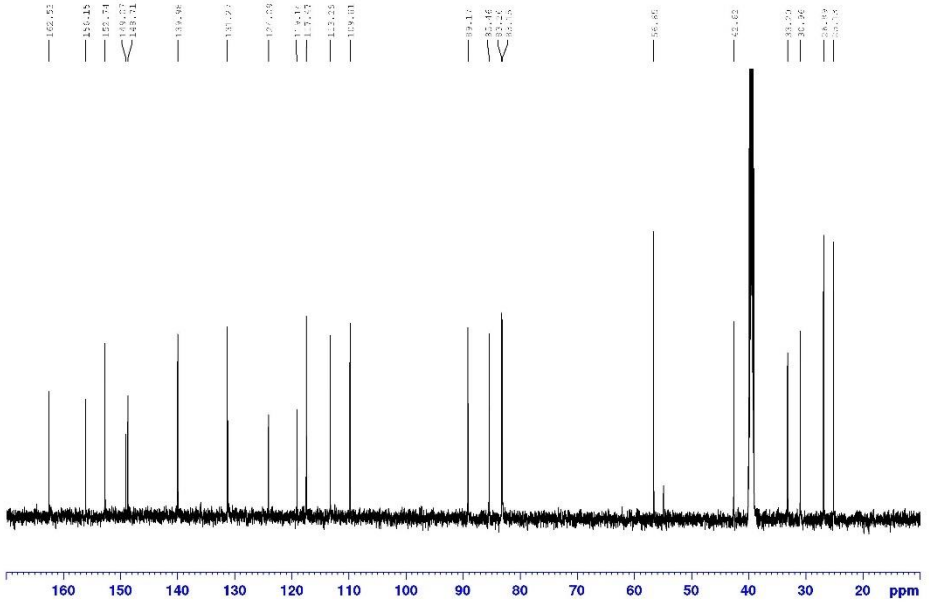


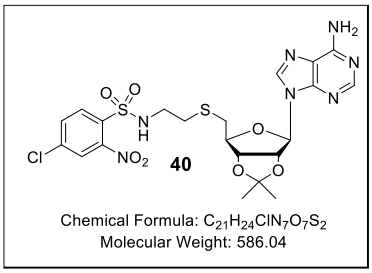


39

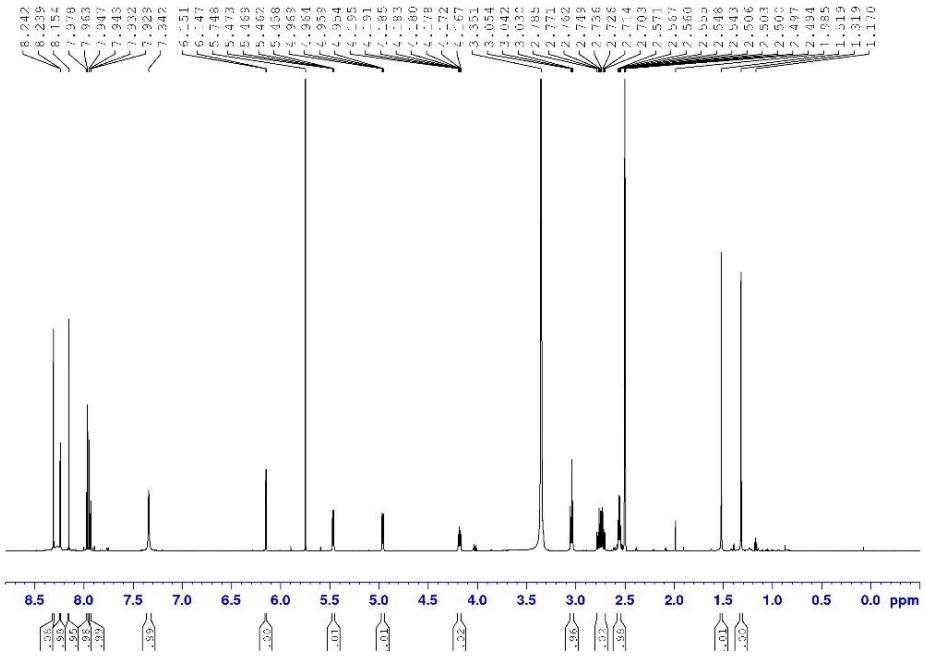
Chemical Formula: $C_{22}H_{27}N_7O_8S_2$
Molecular Weight: 581.62

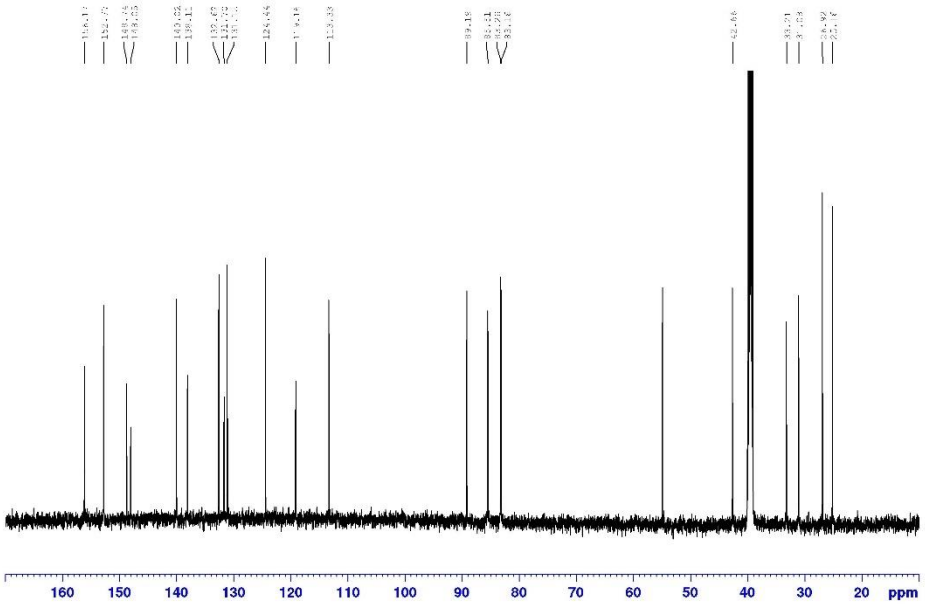


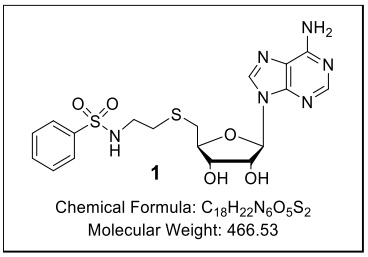




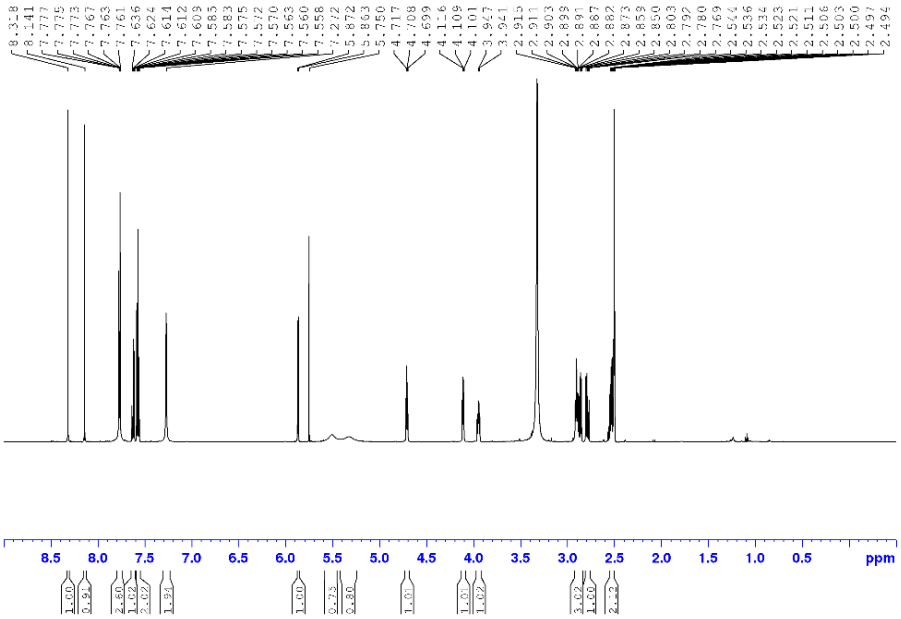
Chemical Formula: $C_{21}H_{24}ClN_7O_7S_2$
Molecular Weight: 586.04

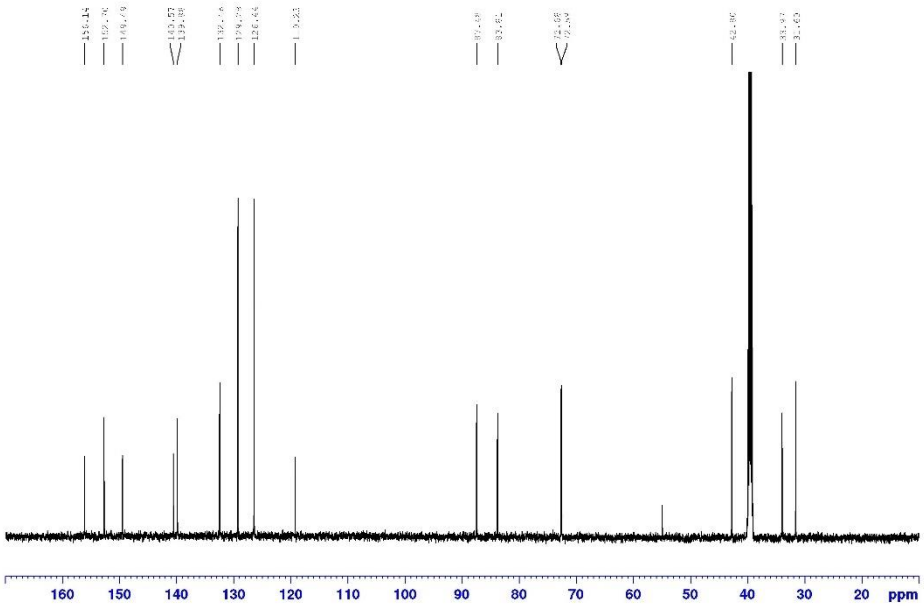


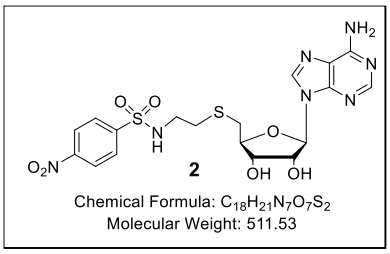




Chemical Formula: $C_{18}H_{22}N_6O_5S_2$
Molecular Weight: 466.53

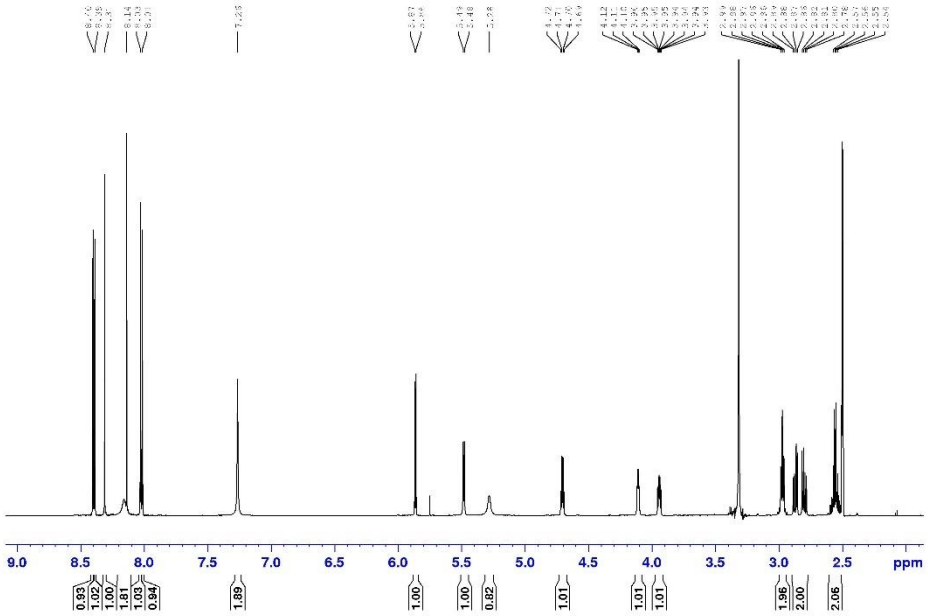


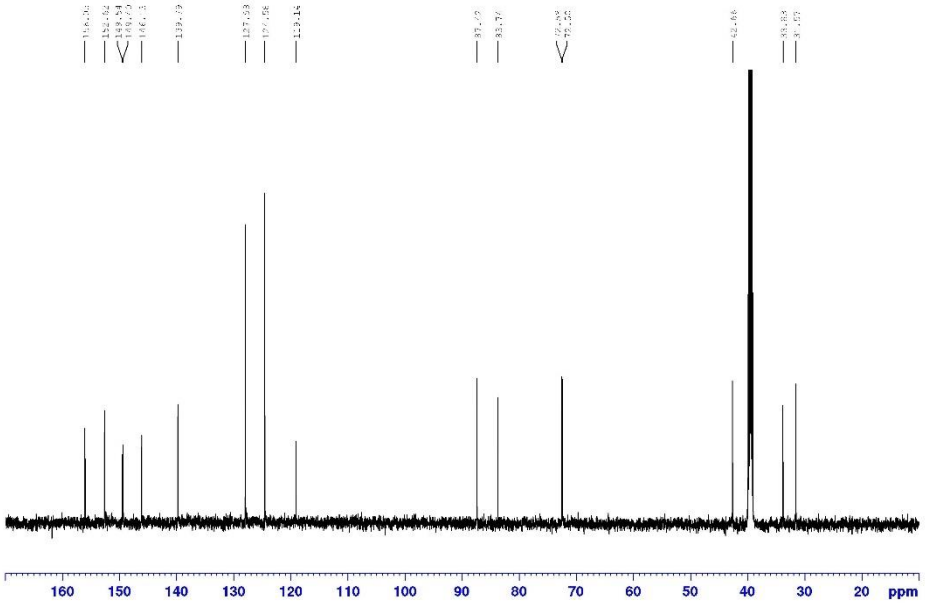


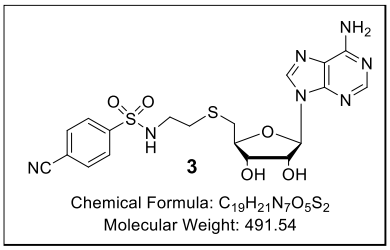


2

Chemical Formula: $C_{18}H_{21}N_7O_7S_2$
Molecular Weight: 511.53

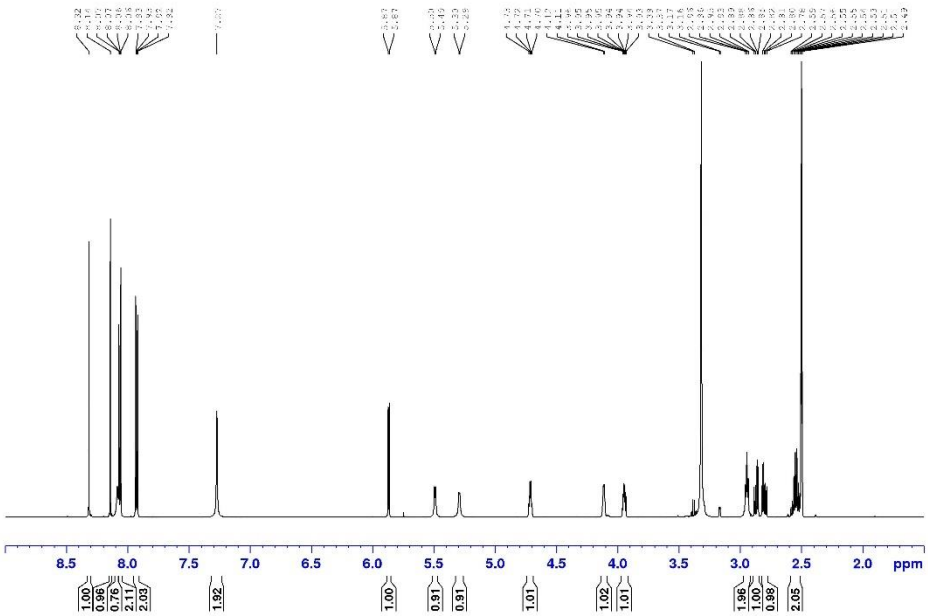


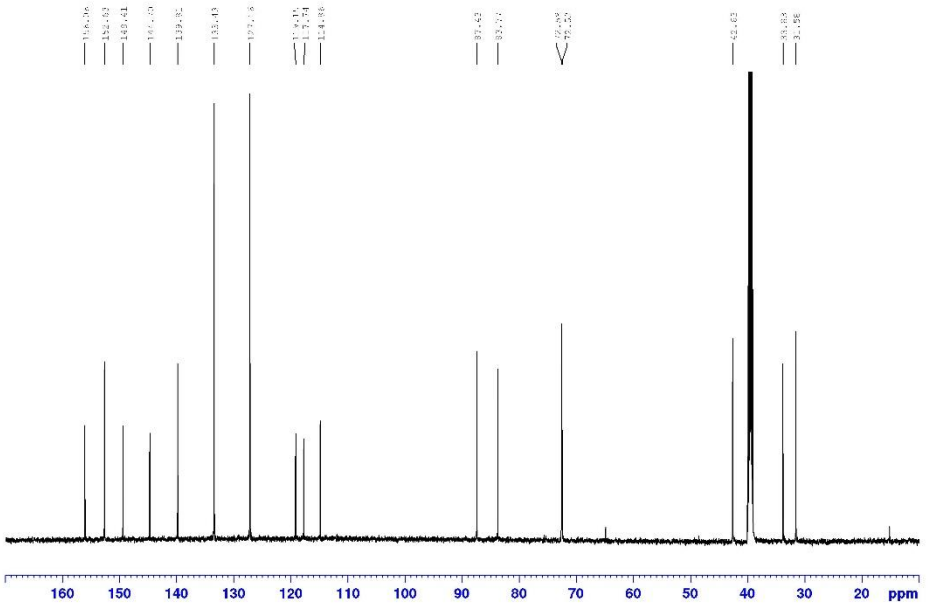


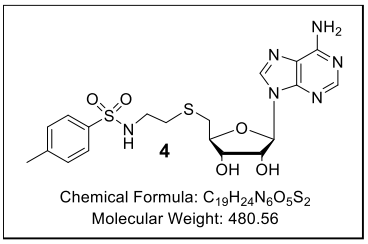


3

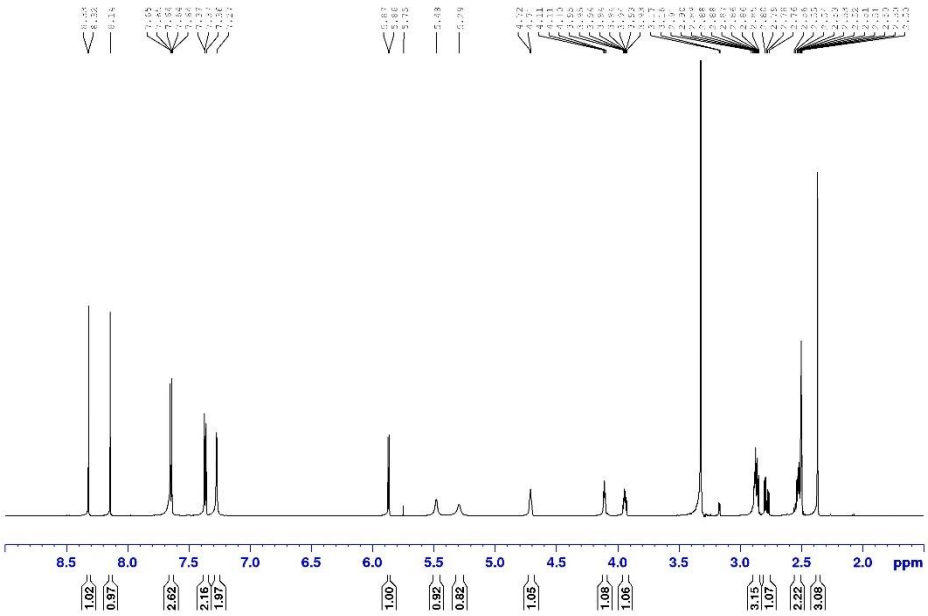
Chemical Formula: $C_{19}H_{21}N_7O_5S_2$
Molecular Weight: 491.54

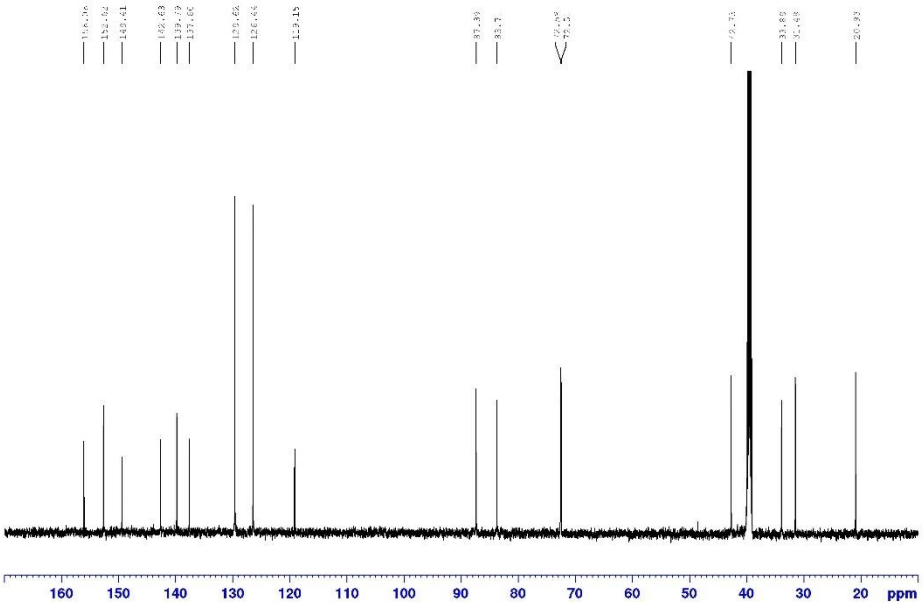


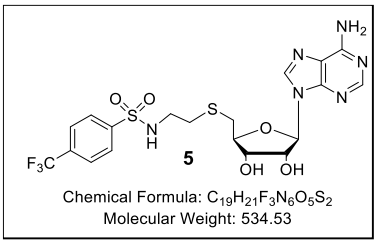




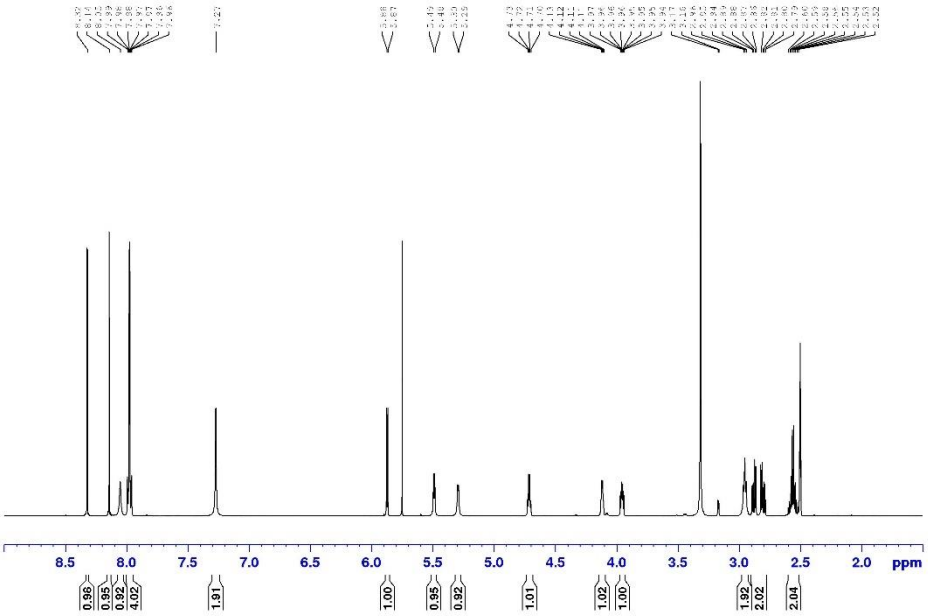
Chemical Formula: $C_{19}H_{24}N_6O_5S_2$
Molecular Weight: 480.56

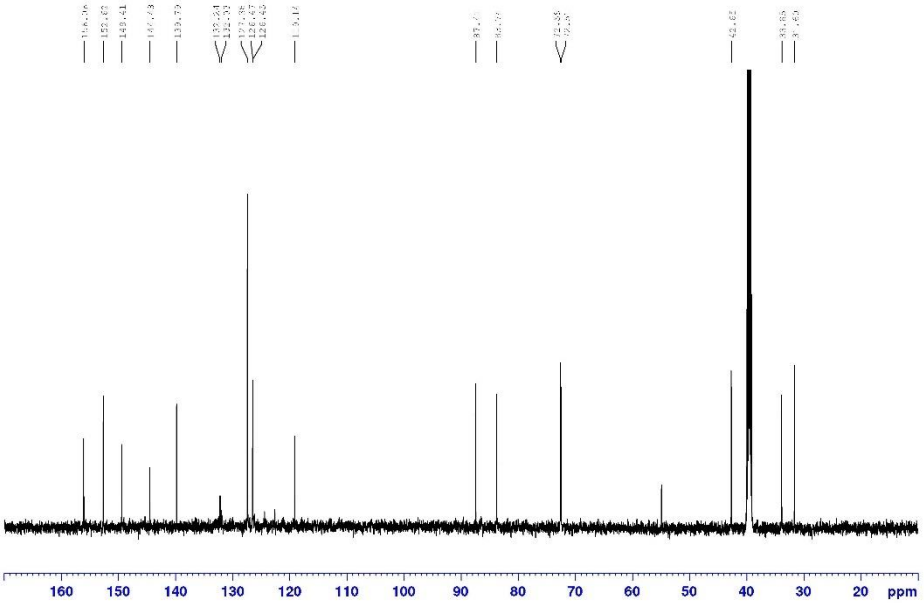


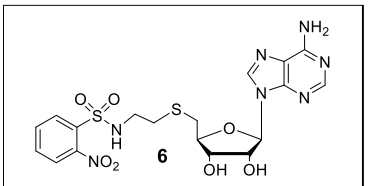




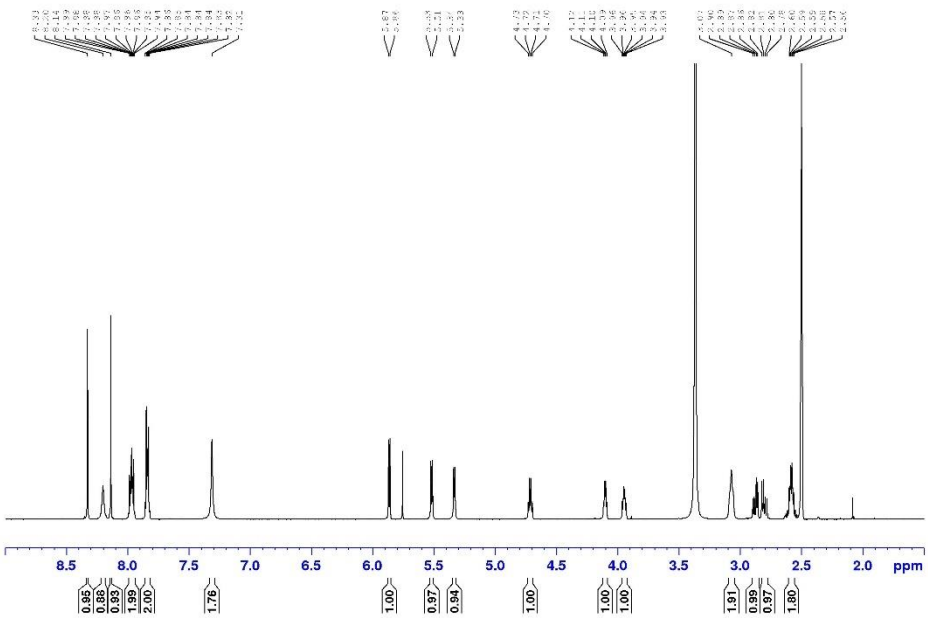
Chemical Formula: $C_{19}H_{21}F_3N_6O_5S_2$
Molecular Weight: 534.53

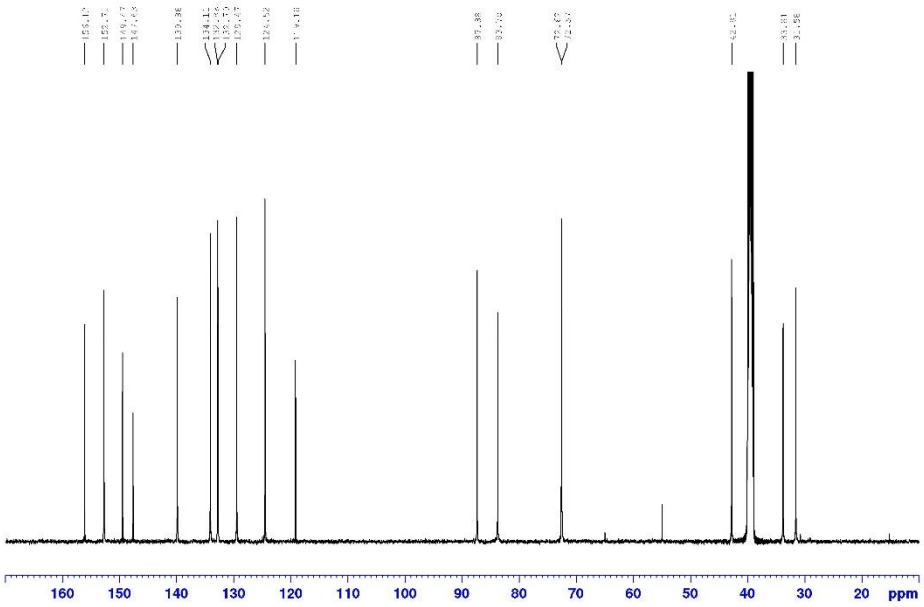


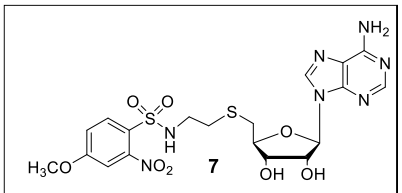




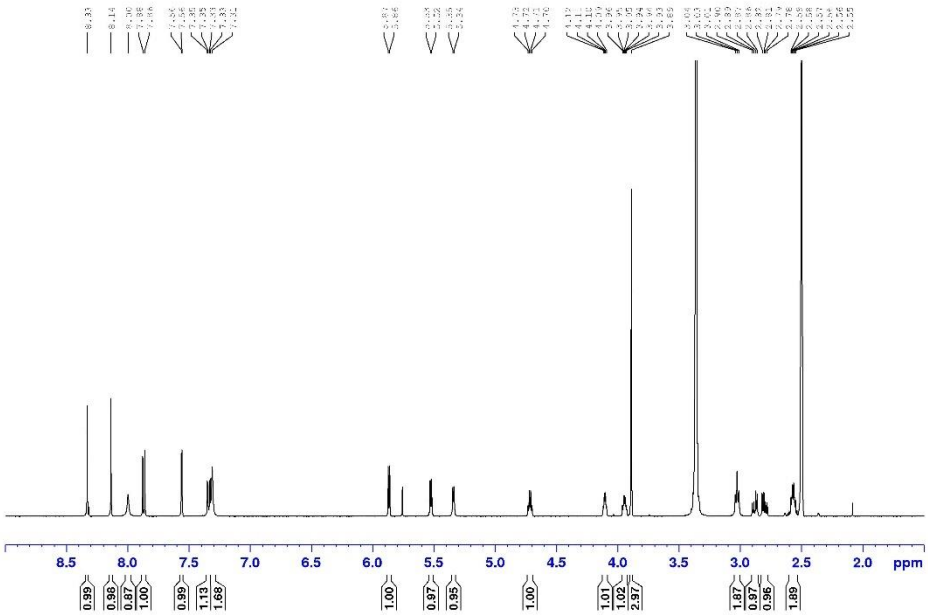
Chemical Formula: $C_{18}H_{21}N_7O_7S_2$
Molecular Weight: 511.53

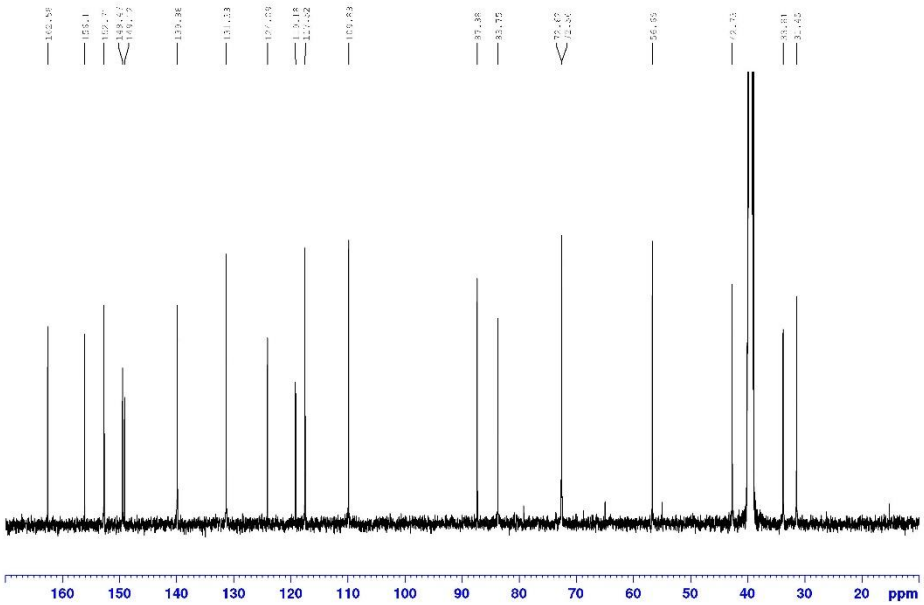


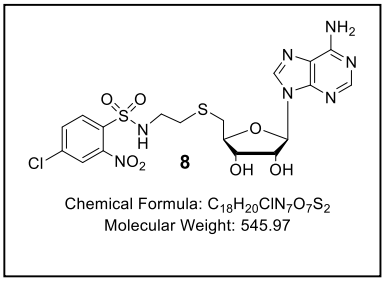




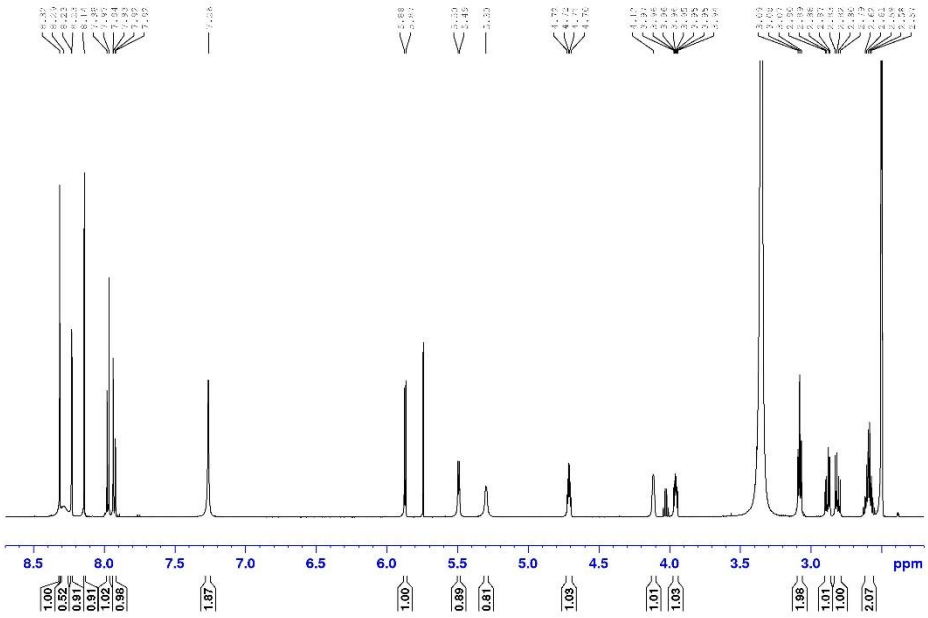
Chemical Formula: $C_{19}H_{23}N_7O_8S_2$
Molecular Weight: 541.55

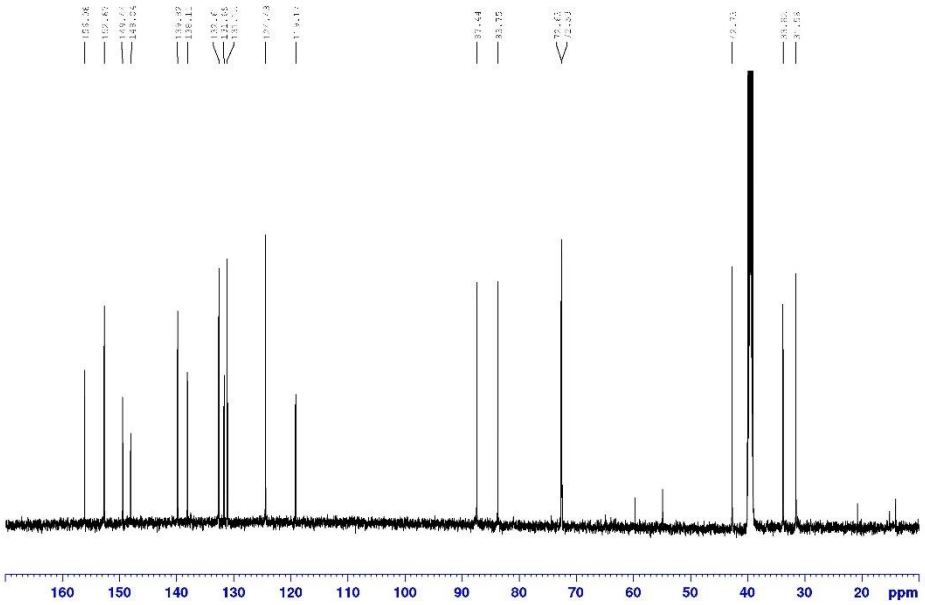




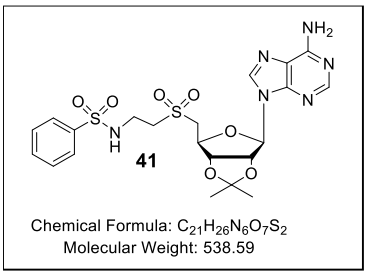


Chemical Formula: $C_{18}H_{20}ClN_7O_7S_2$
Molecular Weight: 545.97

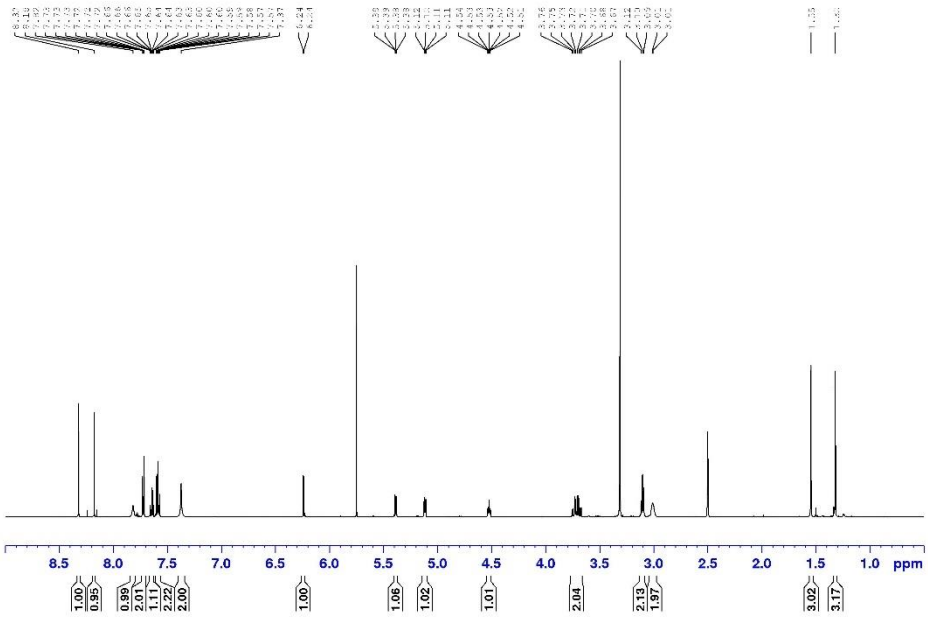


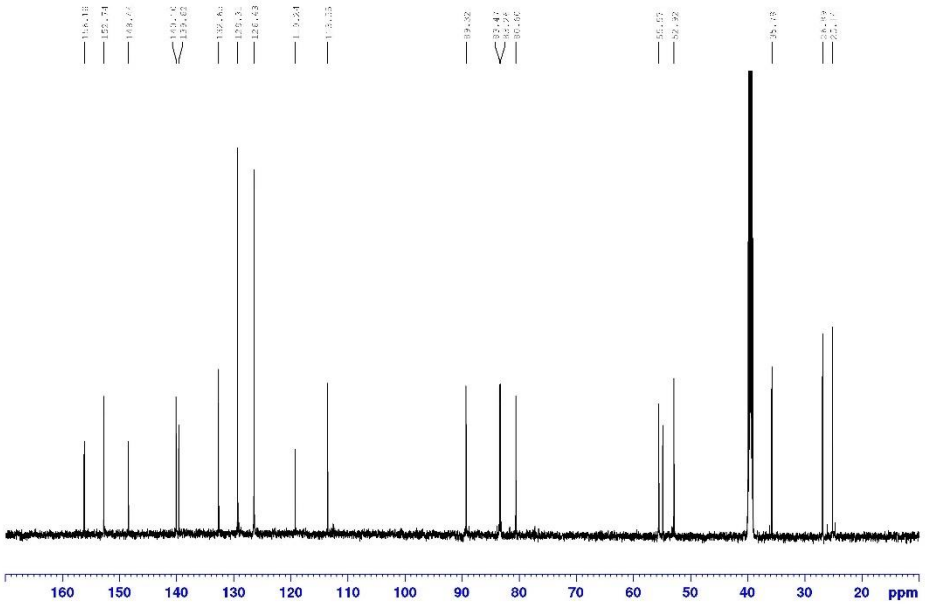


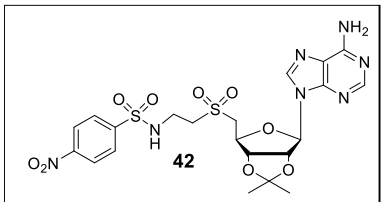
N-arylsulfonamide adenosine analogues with an *N*-ethylsulfone linker (41-45 and 9-13)



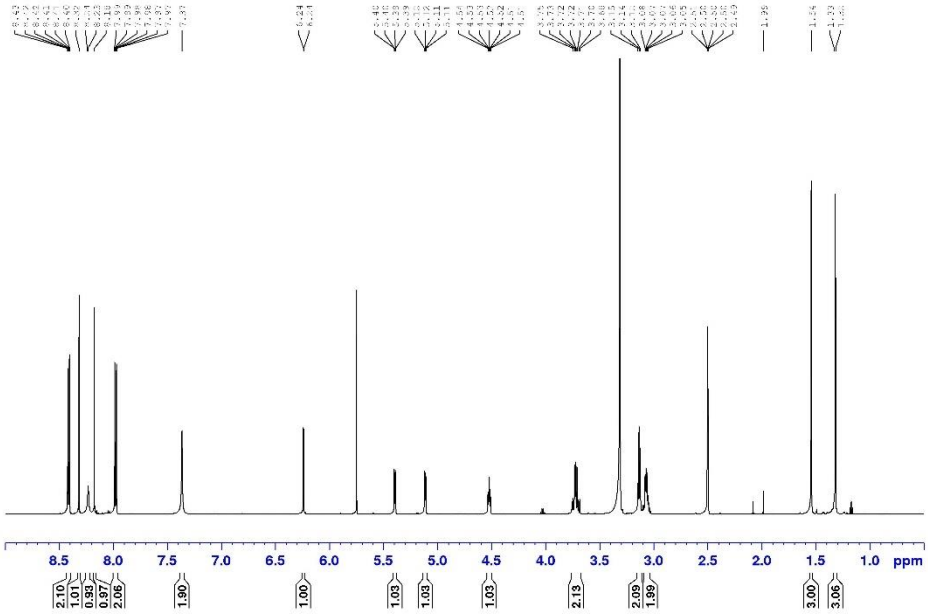
Chemical Formula: $C_{21}H_{26}N_6O_7S_2$
Molecular Weight: 538.59

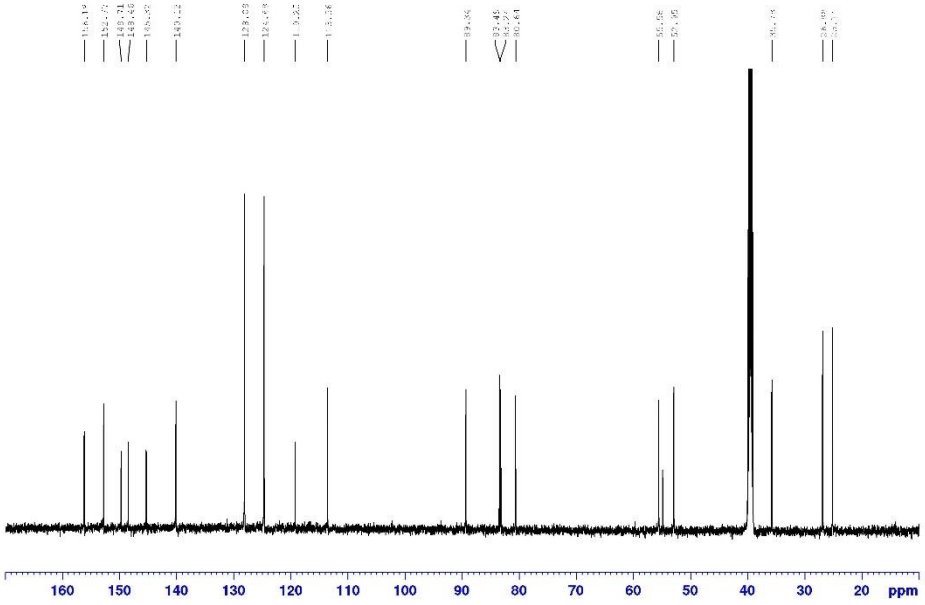


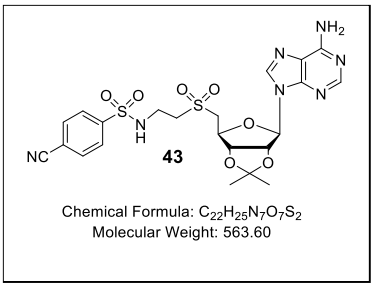




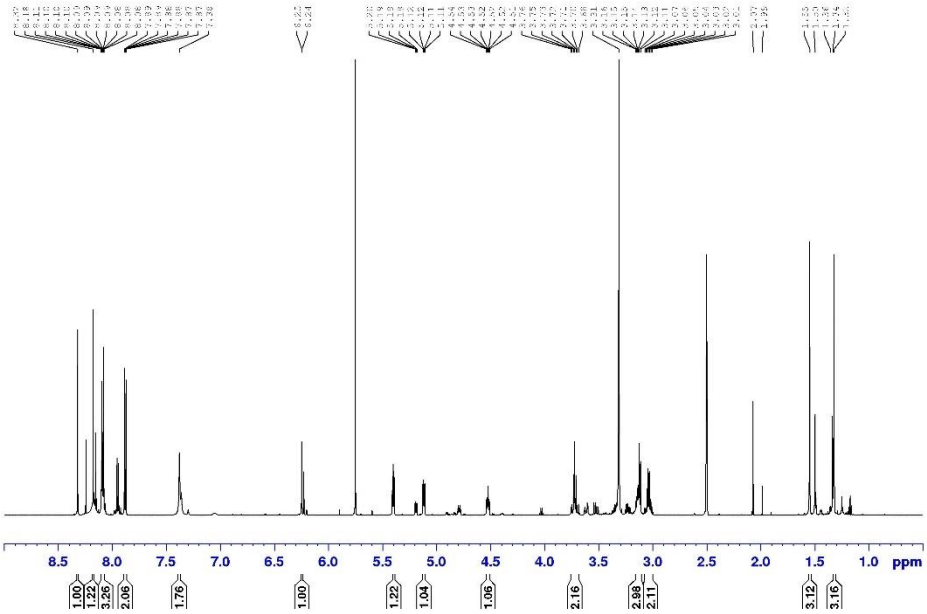
Chemical Formula: $C_{21}H_{25}N_7O_9S_2$
Molecular Weight: 583.59

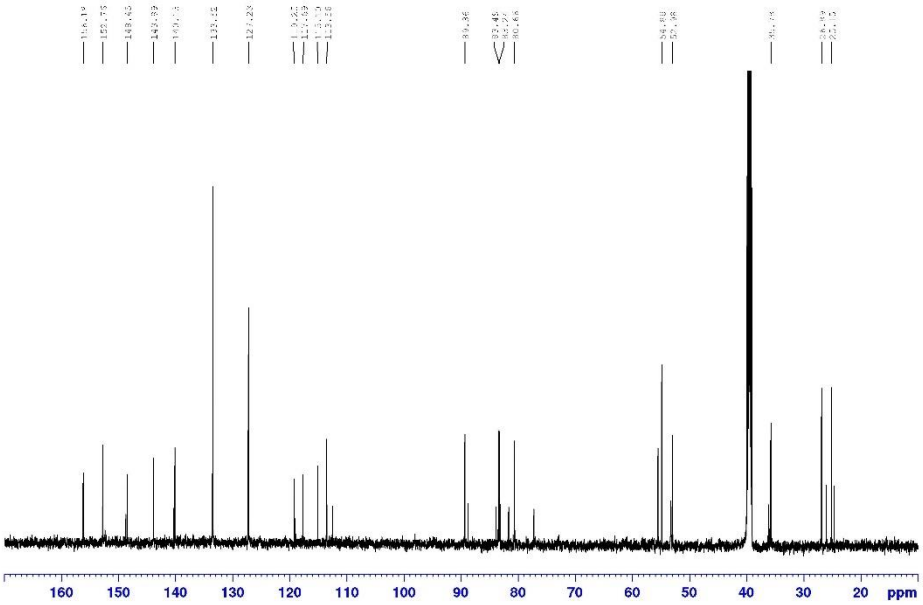


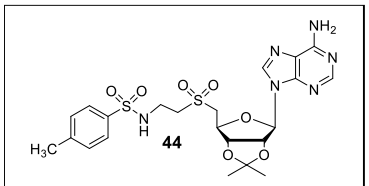




Chemical Formula: $C_{22}H_{25}N_7O_7S_2$
Molecular Weight: 563.60

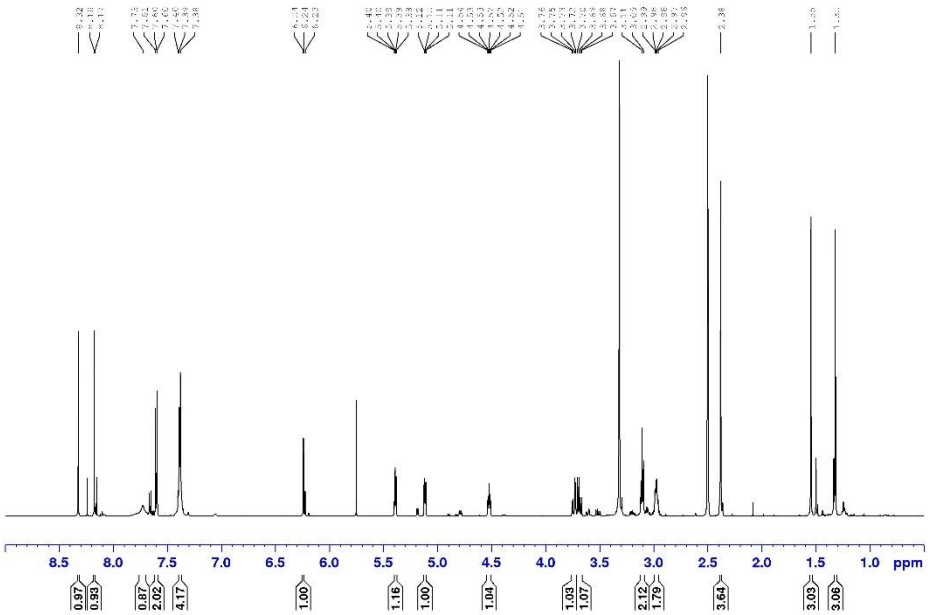


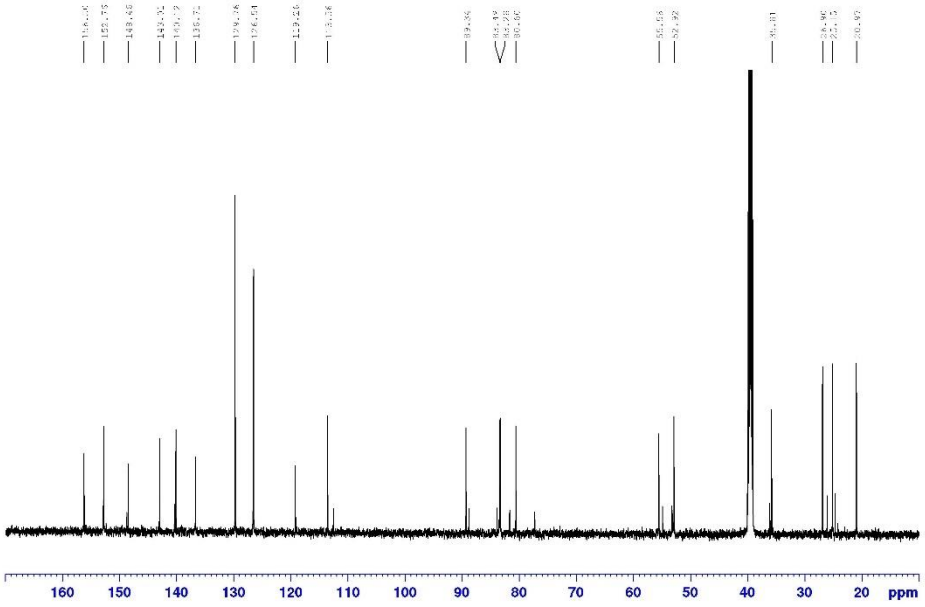


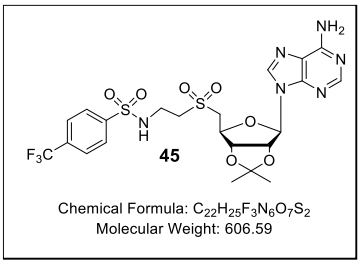


44

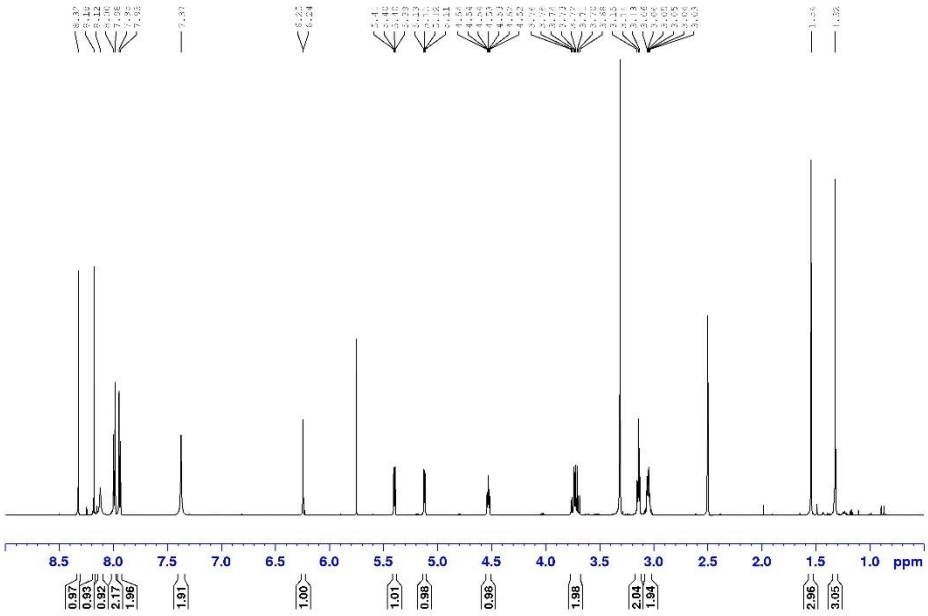
Chemical Formula: $C_{22}H_{28}N_6O_7S_2$
Molecular Weight: 552.62

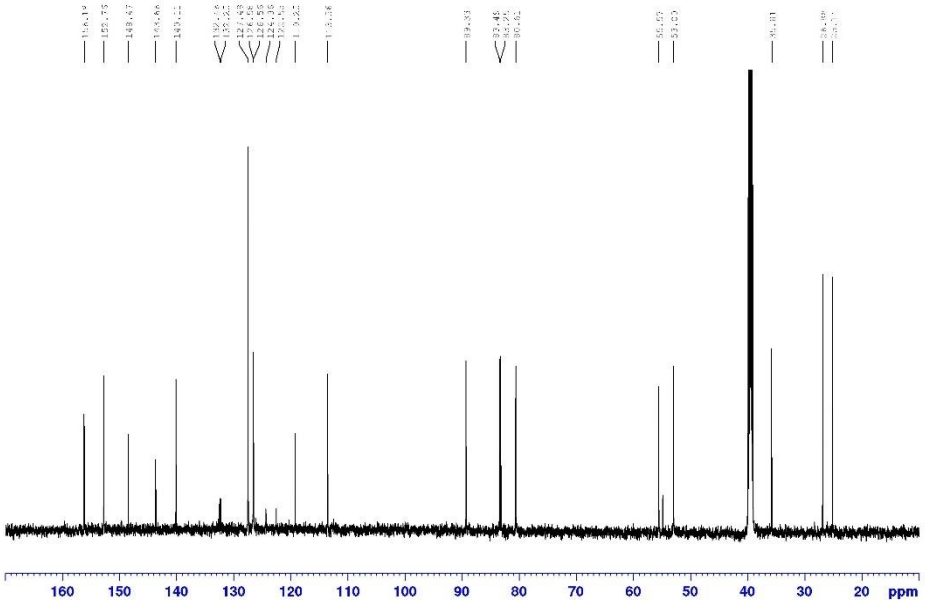


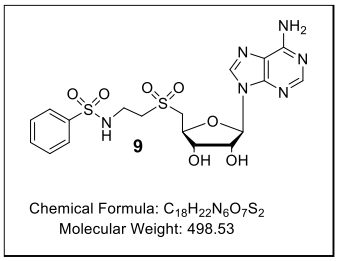




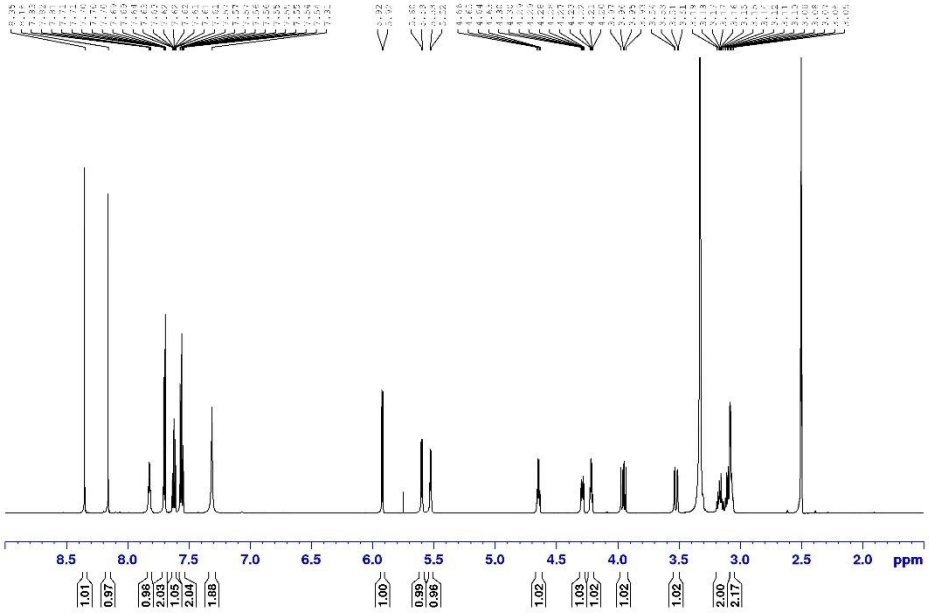
Chemical Formula: $C_{22}H_{25}F_3N_6O_7S_2$
Molecular Weight: 606.59

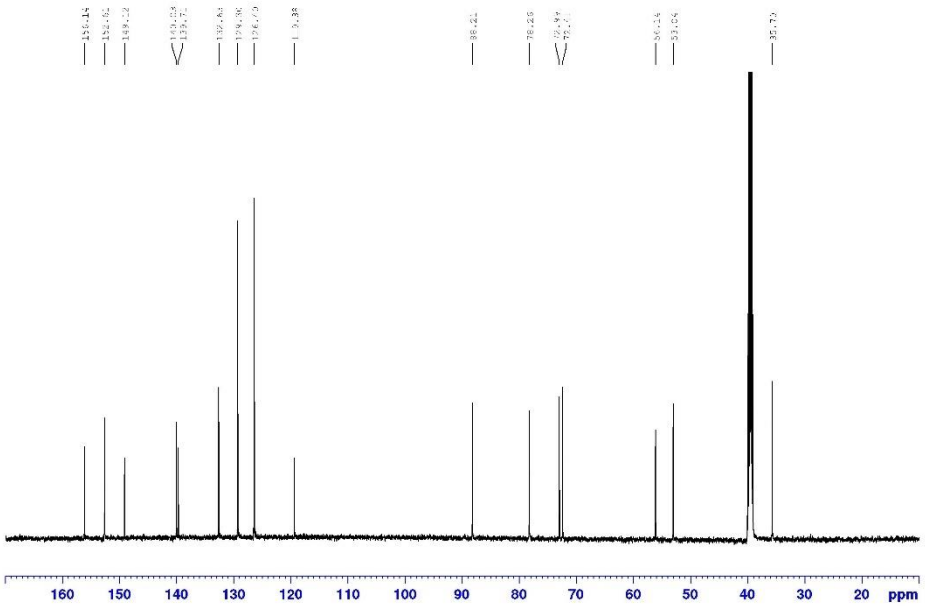


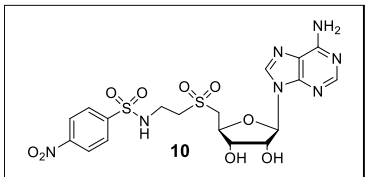




Chemical Formula: $C_{18}H_{22}N_6O_7S_2$
Molecular Weight: 498.53

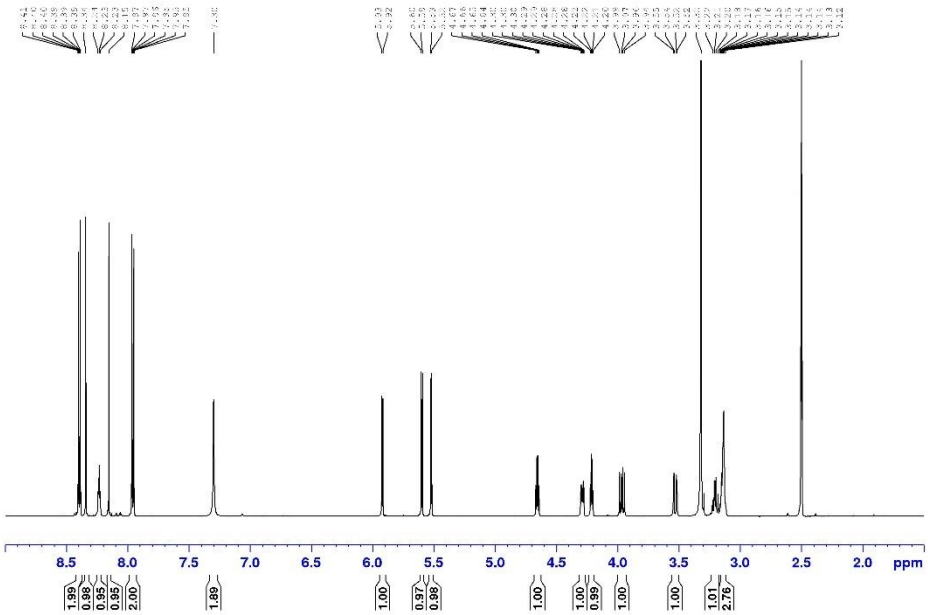


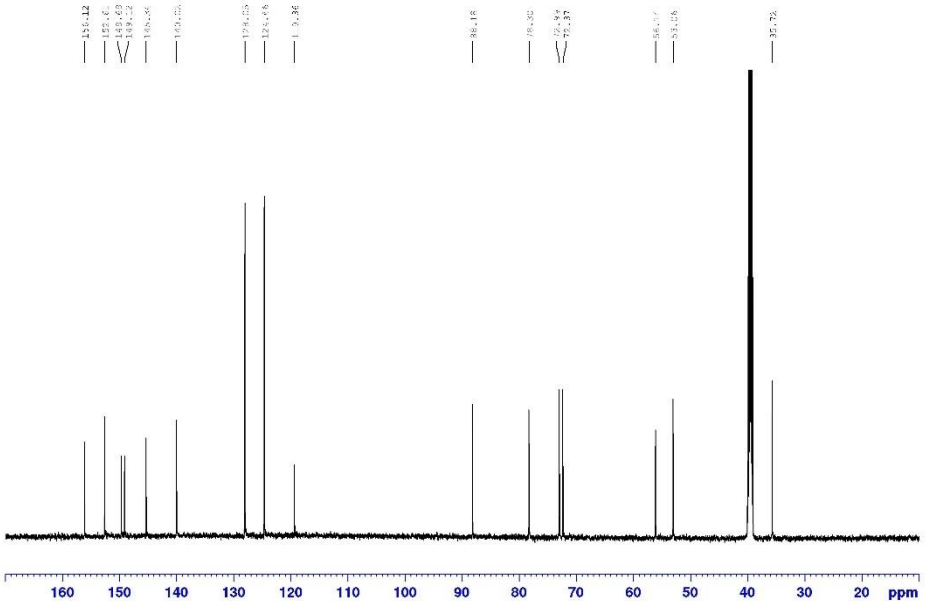


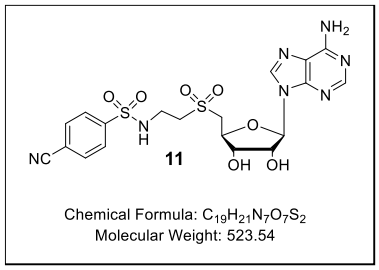


10

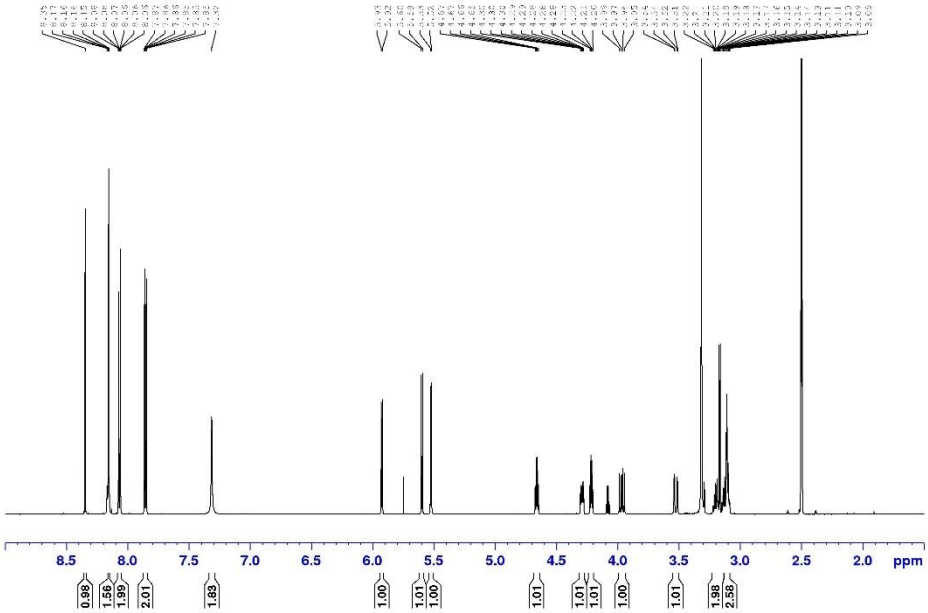
Chemical Formula: $C_{18}H_{21}N_7O_9S_2$
Molecular Weight: 543.53

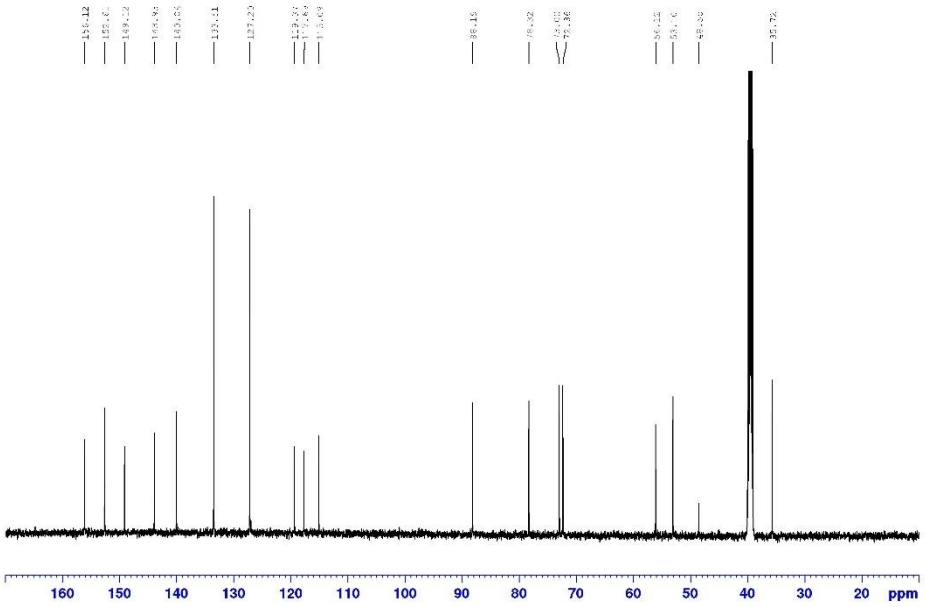


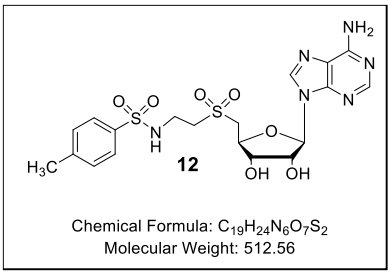




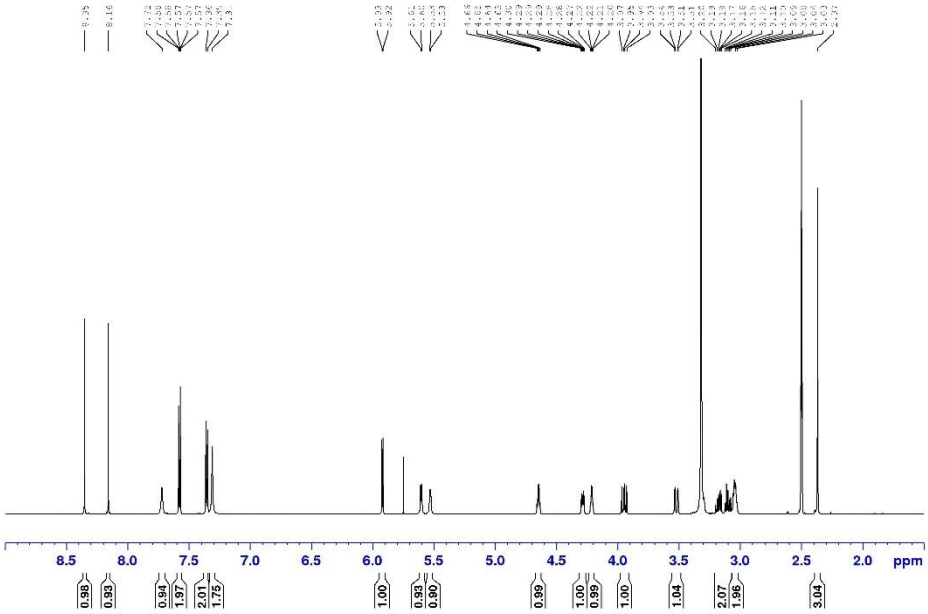
Chemical Formula: $C_{19}H_{21}N_7O_7S_2$
Molecular Weight: 523.54

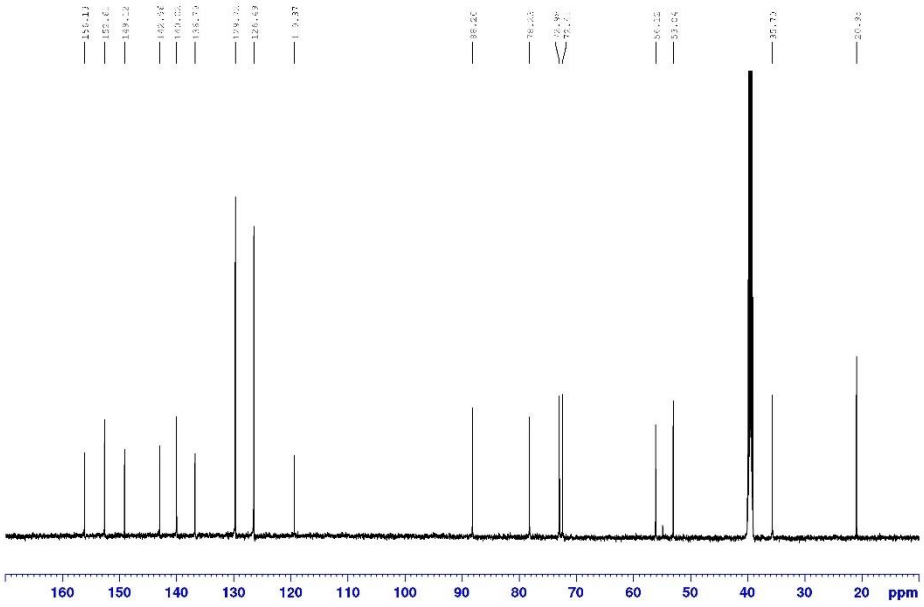


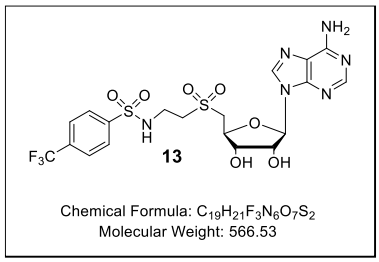




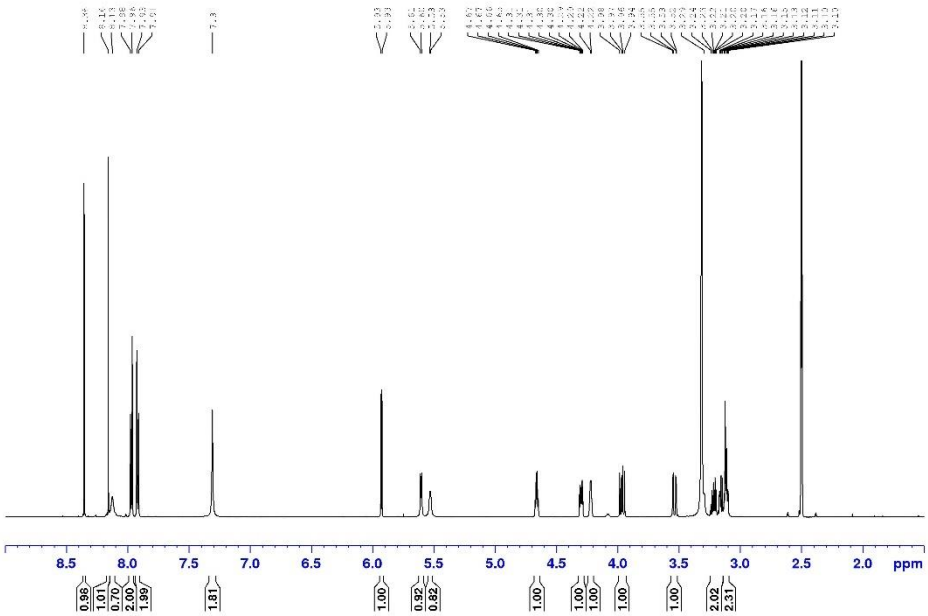
Chemical Formula: $C_{19}H_{24}N_6O_7S_2$
Molecular Weight: 512.56

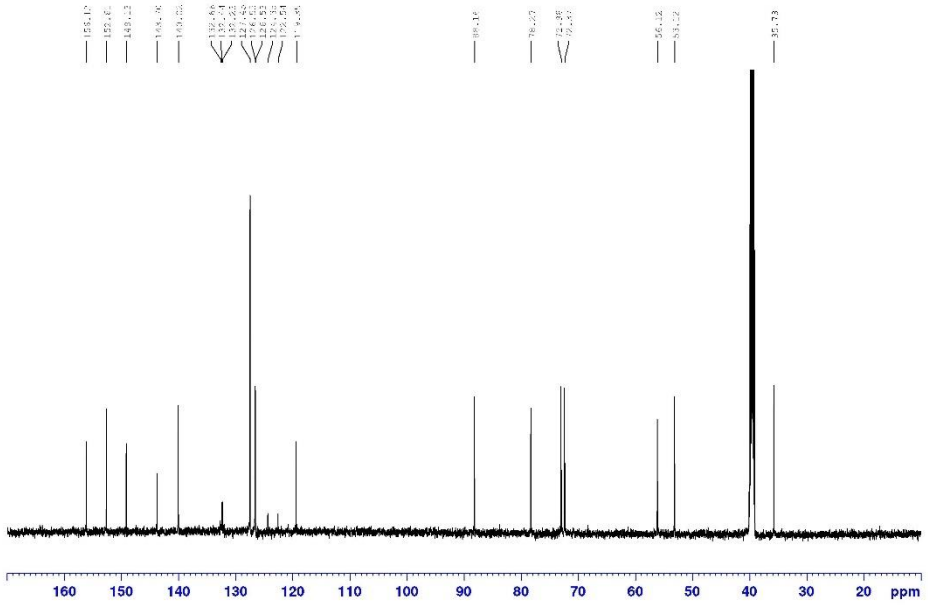




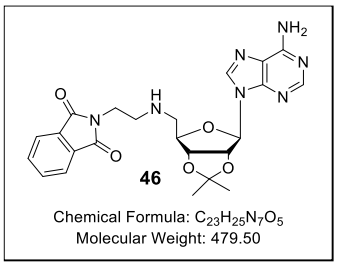


Chemical Formula: $C_{19}H_{21}F_3N_6O_7S_2$
Molecular Weight: 566.53



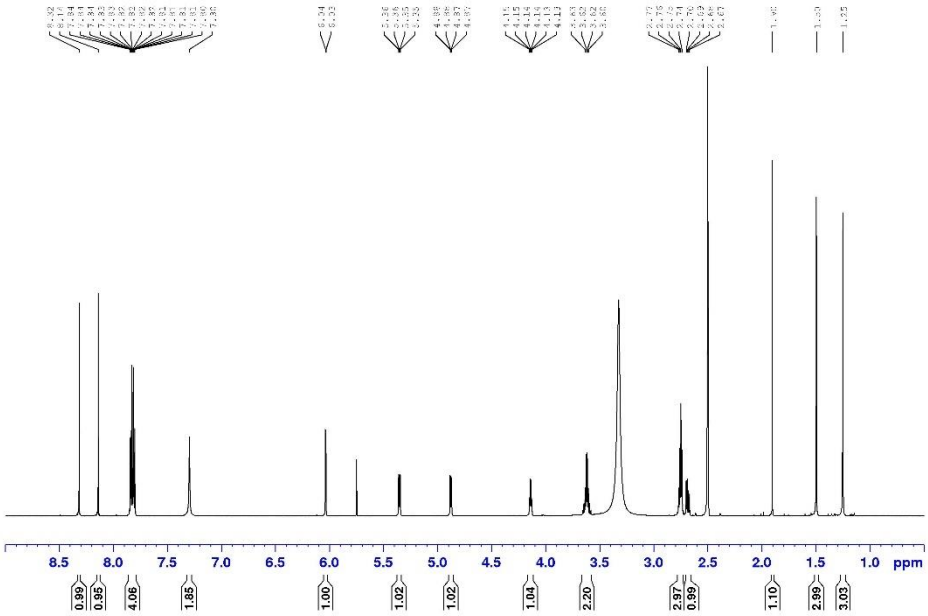


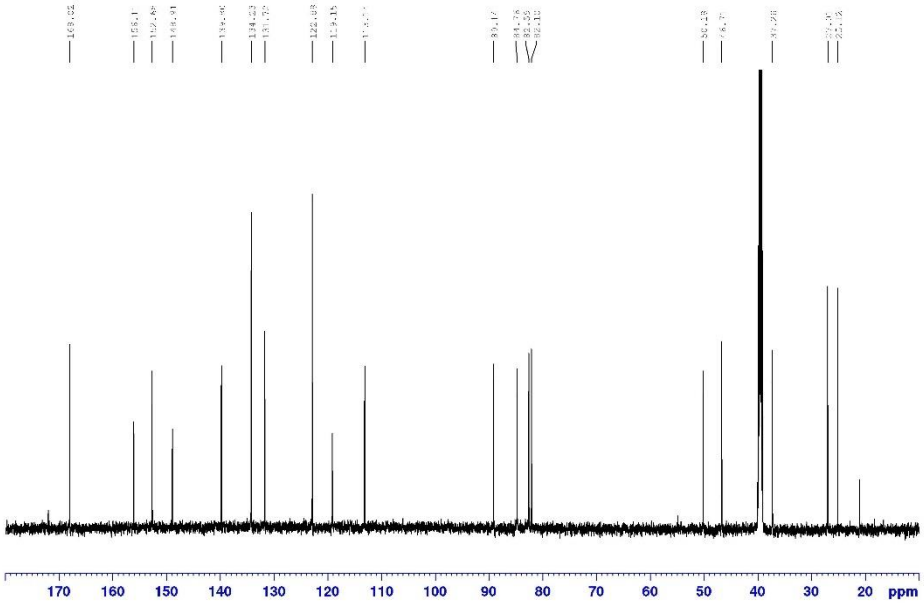
N-arylsulfonamide adenosine analogues with an *N*-ethylamino linker (46-53 and 14-18)

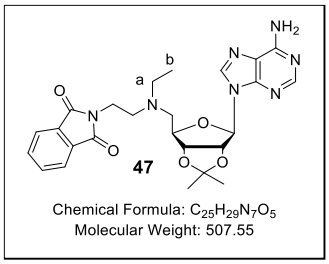


46

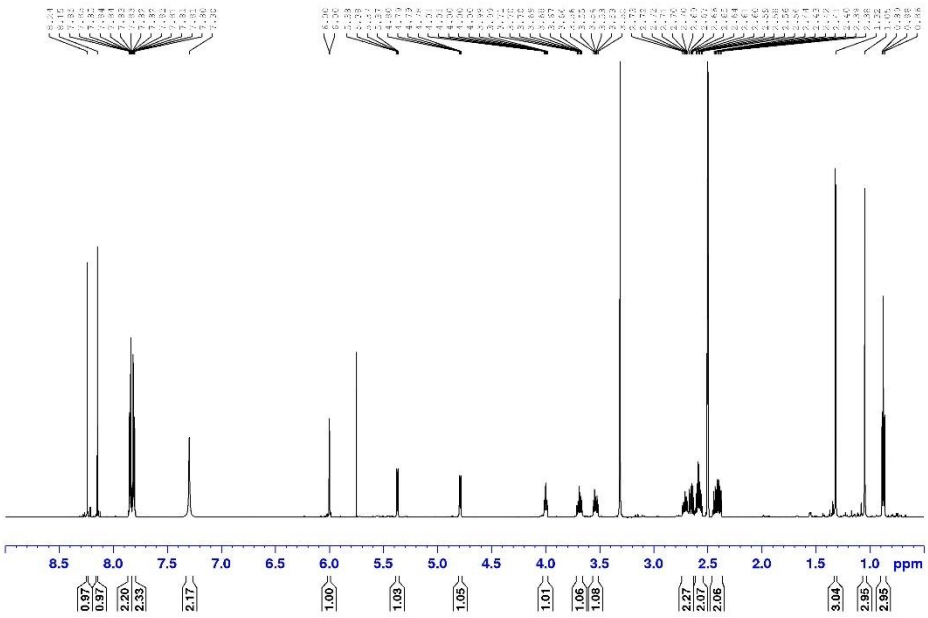
Chemical Formula: $C_{23}H_{25}N_7O_5$
Molecular Weight: 479.50

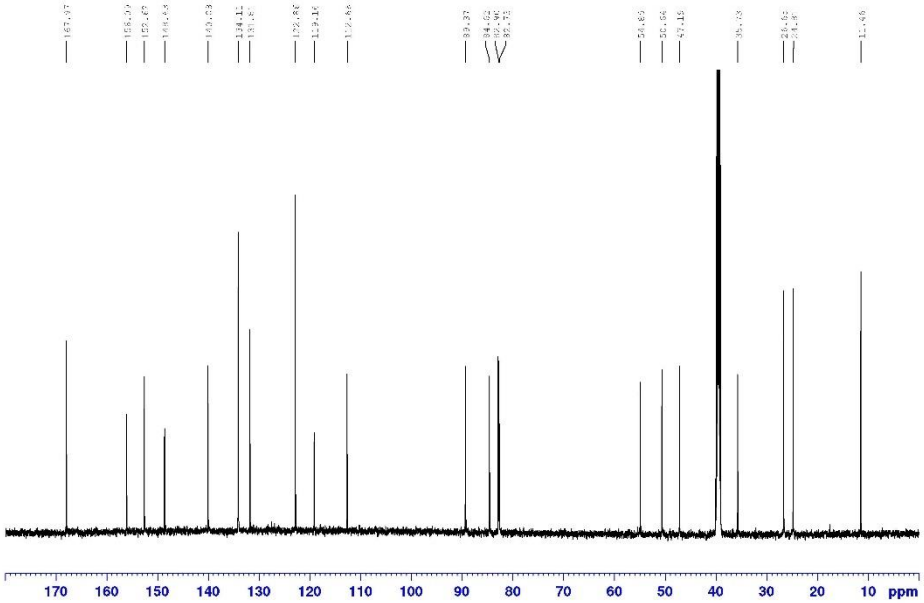


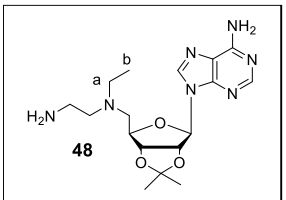




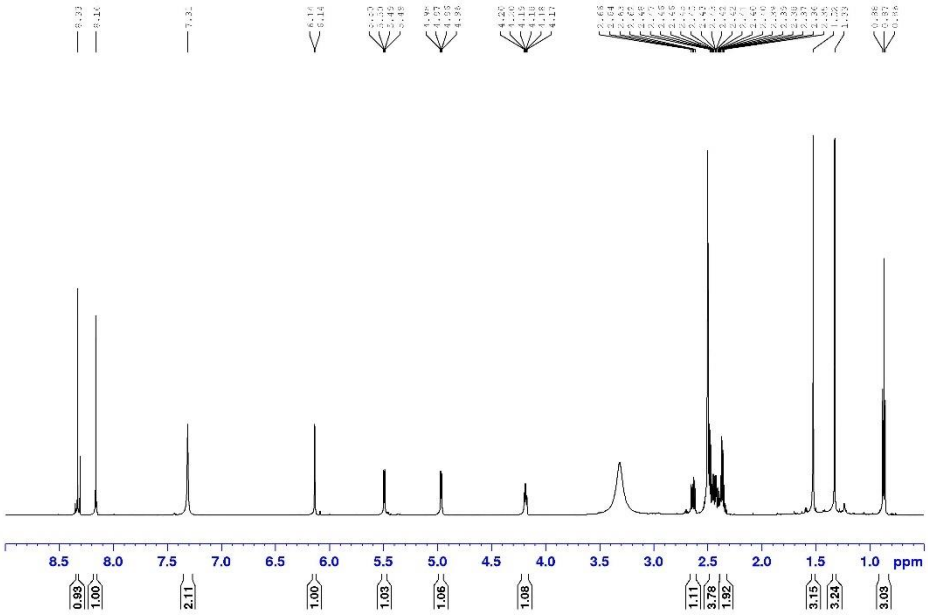
Chemical Formula: $C_{25}H_{29}N_7O_5$
Molecular Weight: 507.55

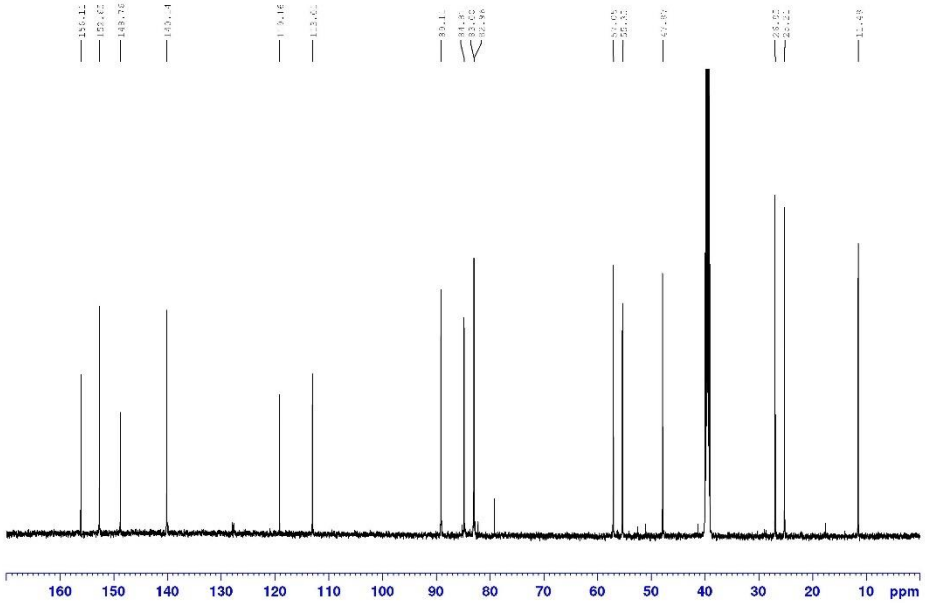


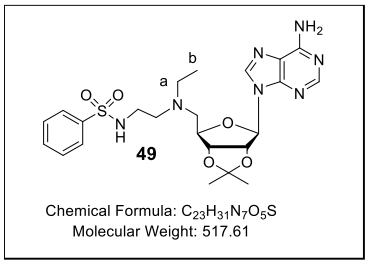




Chemical Formula: $C_{17}H_{27}N_7O_3$
Molecular Weight: 377.45







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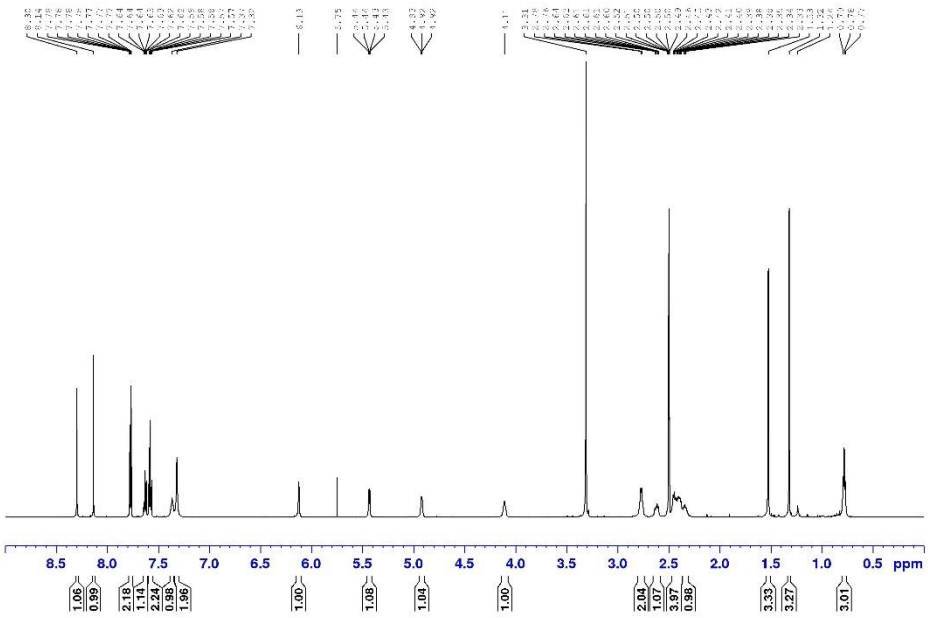
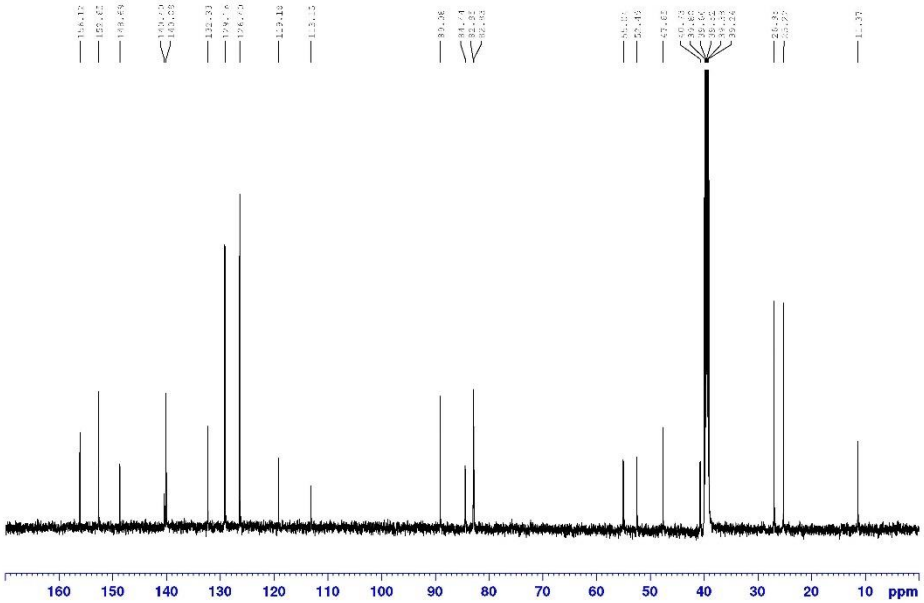
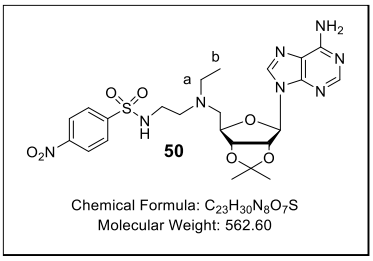
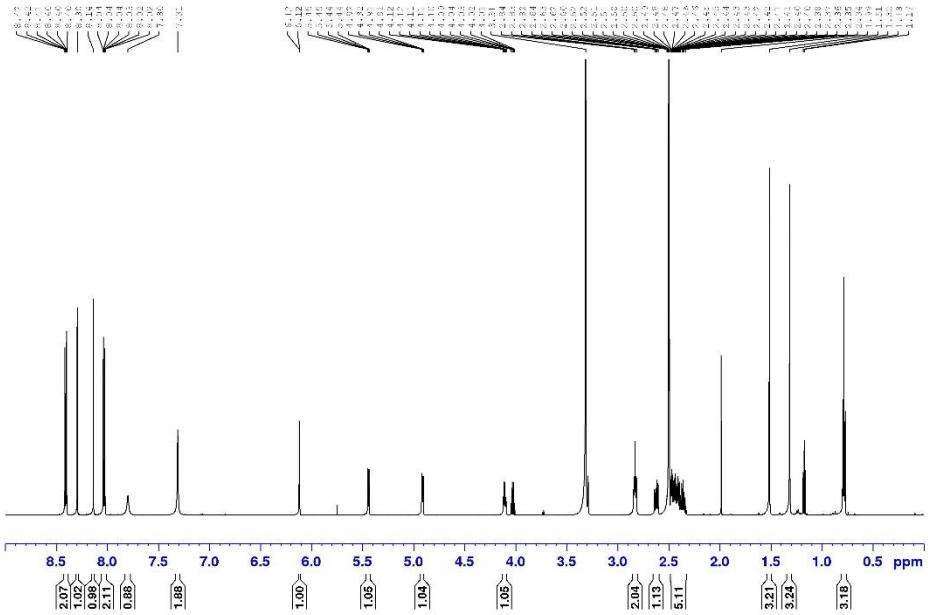
Chemical Formula: $C_{23}H_{31}N_7O_5S$
Molecular Weight: 517.61

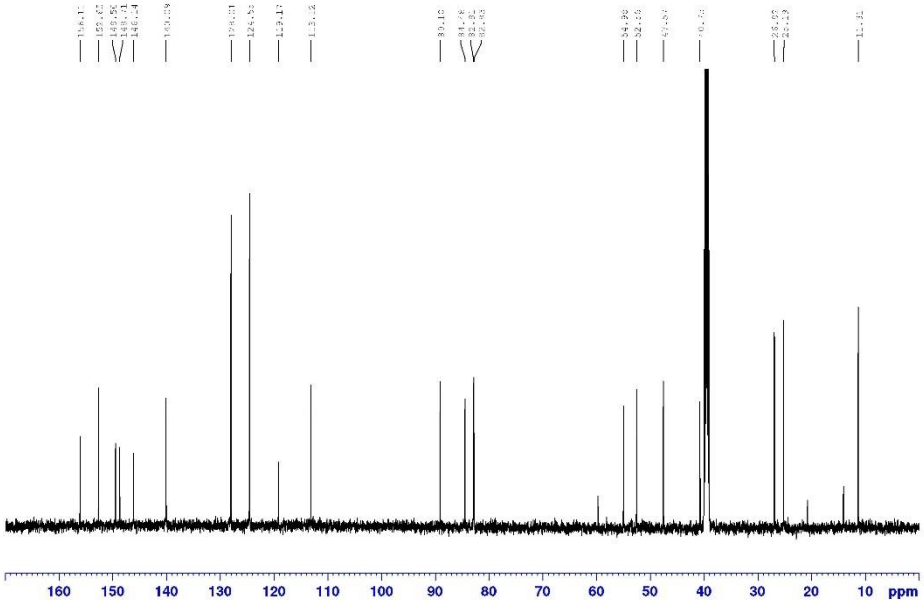


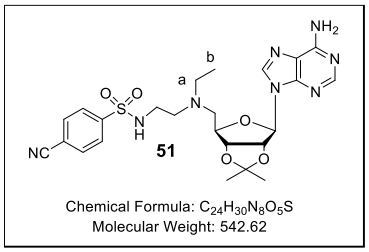




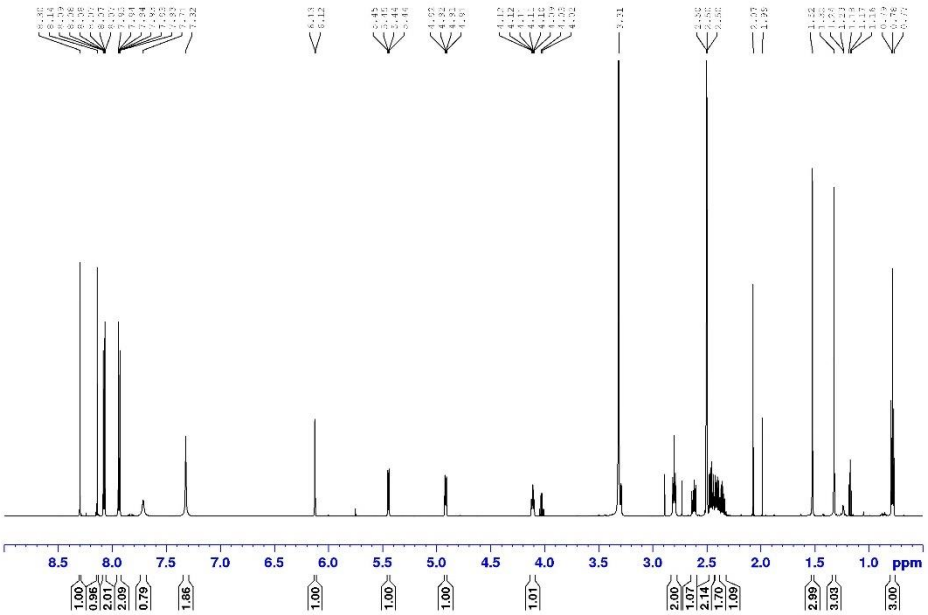
Chemical Formula: $C_{23}H_{30}N_8O_7S$
Molecular Weight: 562.60

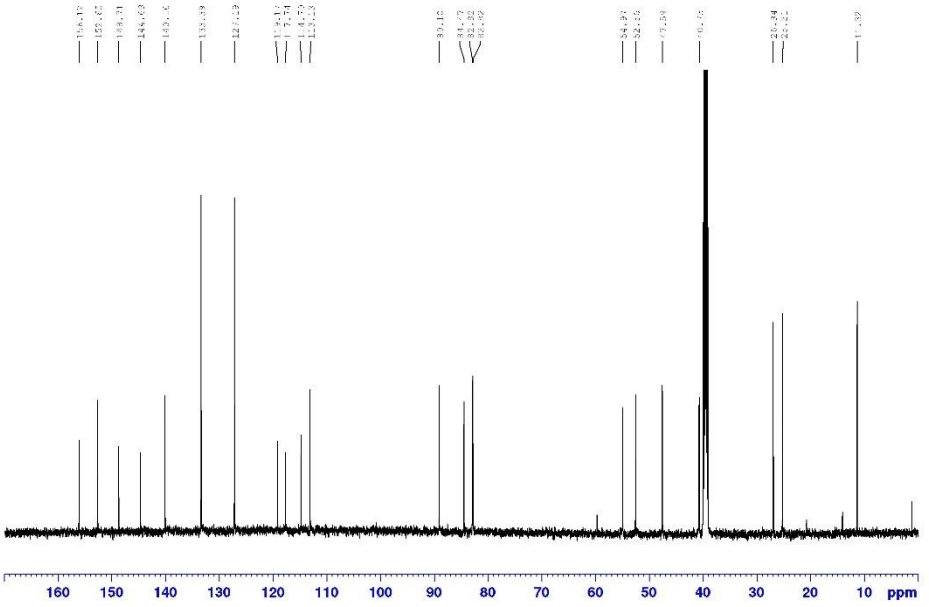


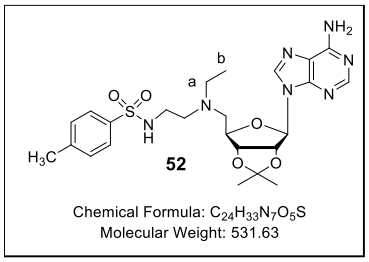




Chemical Formula: $C_{24}H_{30}N_8O_5S$
Molecular Weight: 542.62







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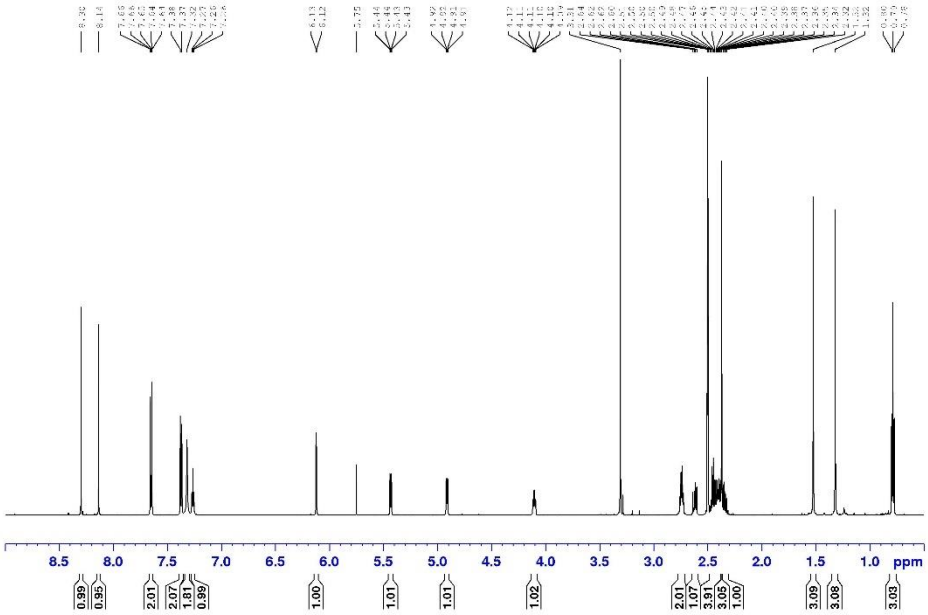
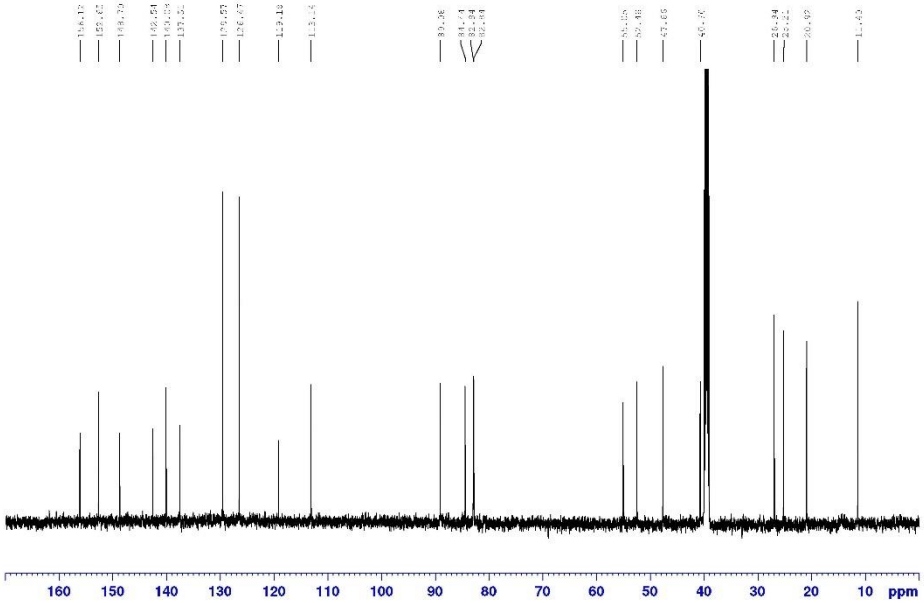
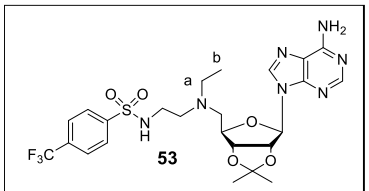
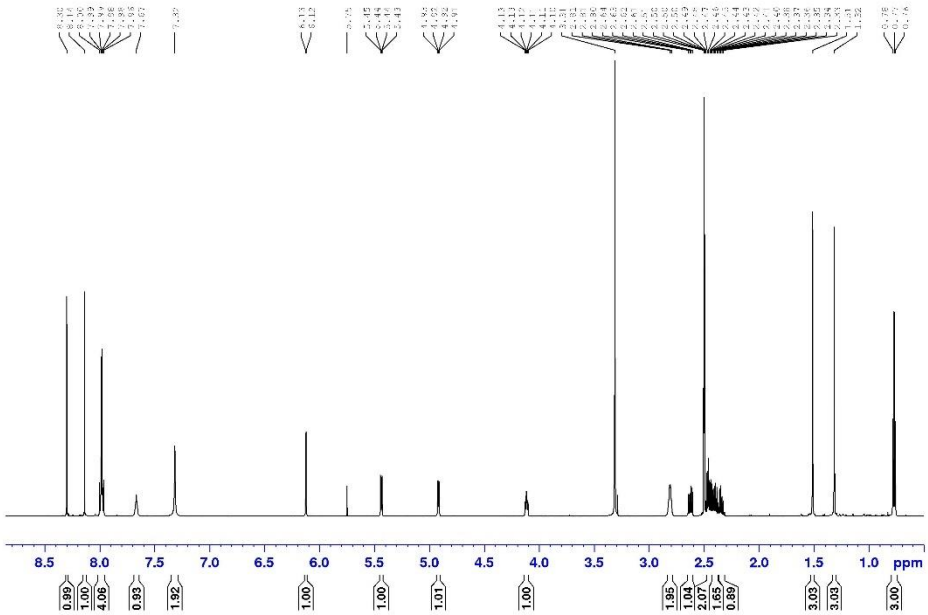
Chemical Formula: $C_{24}H_{33}N_7O_5S$
Molecular Weight: 531.63

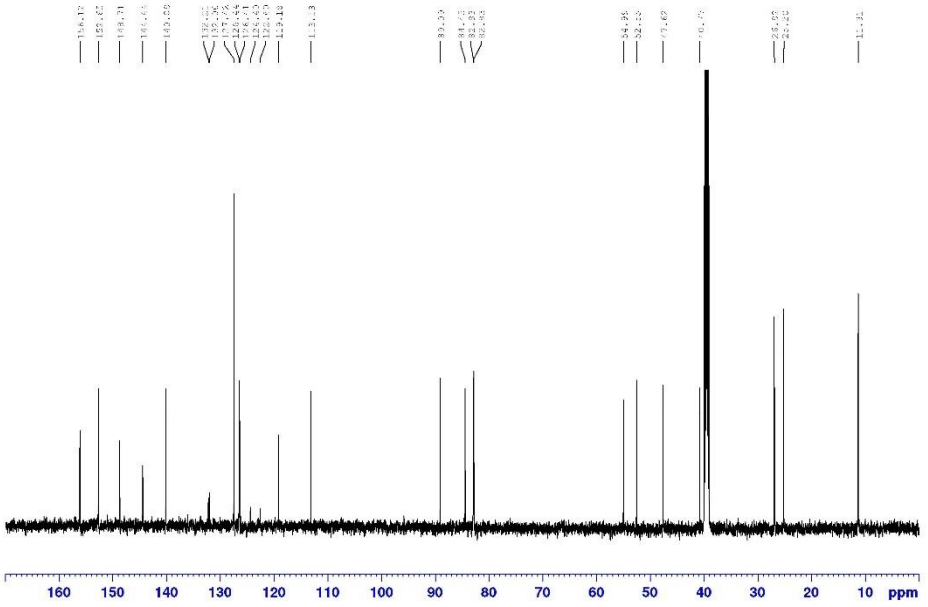


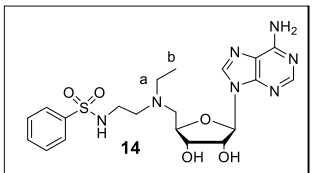




Chemical Formula: $C_{24}H_{30}F_3N_7O_5S$
Molecular Weight: 585.60

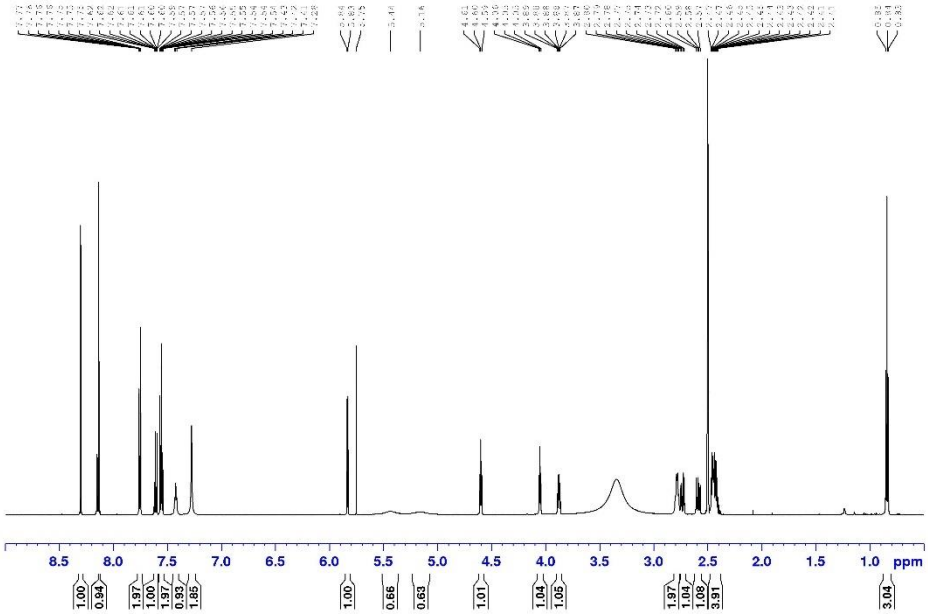


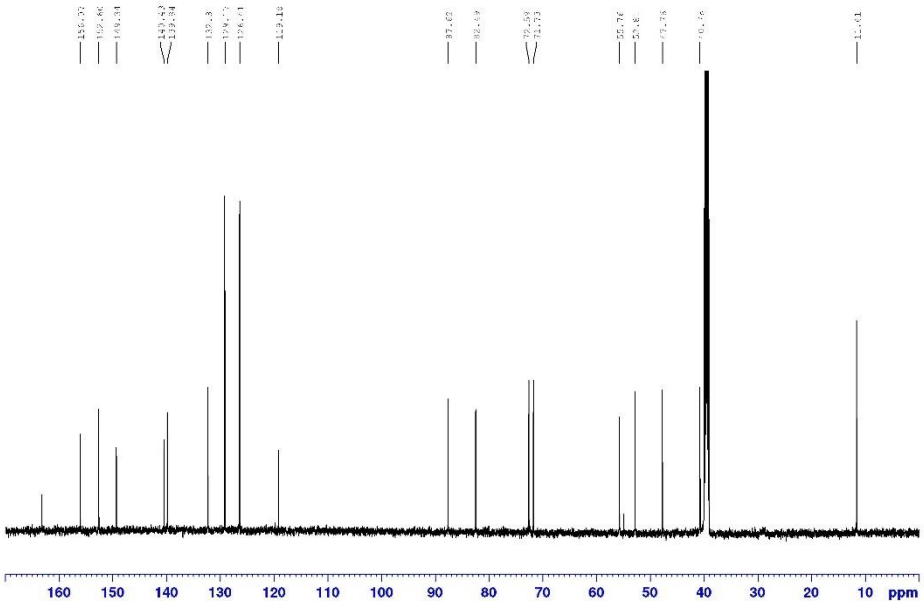


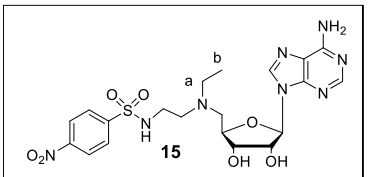


14

Chemical Formula: $C_{20}H_{27}N_7O_5S$
Molecular Weight: 477.54

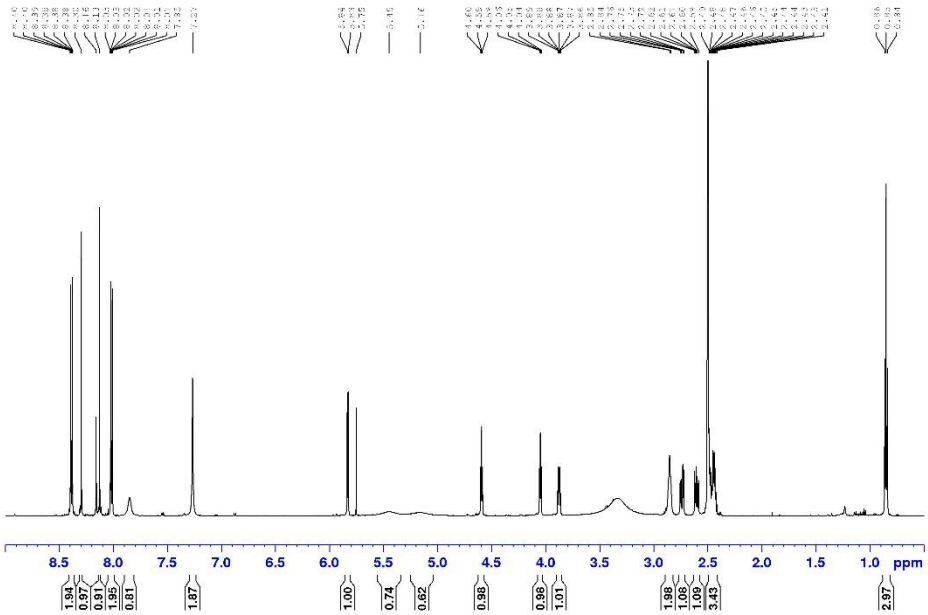


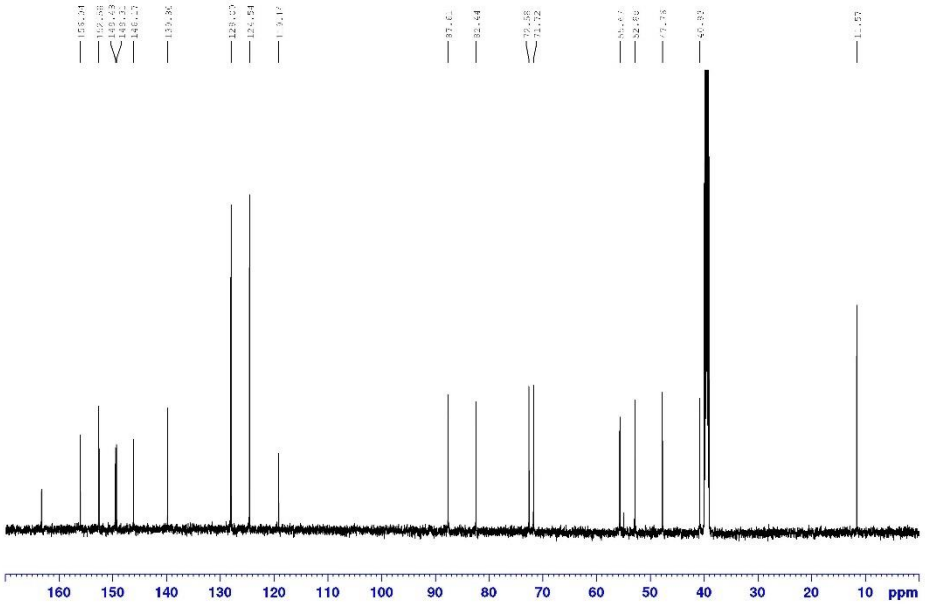


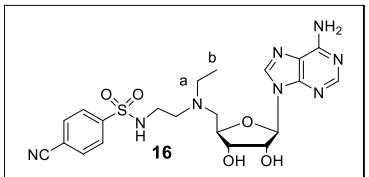


15

Chemical Formula: $C_{20}H_{26}N_8O_7S$
Molecular Weight: 522.54

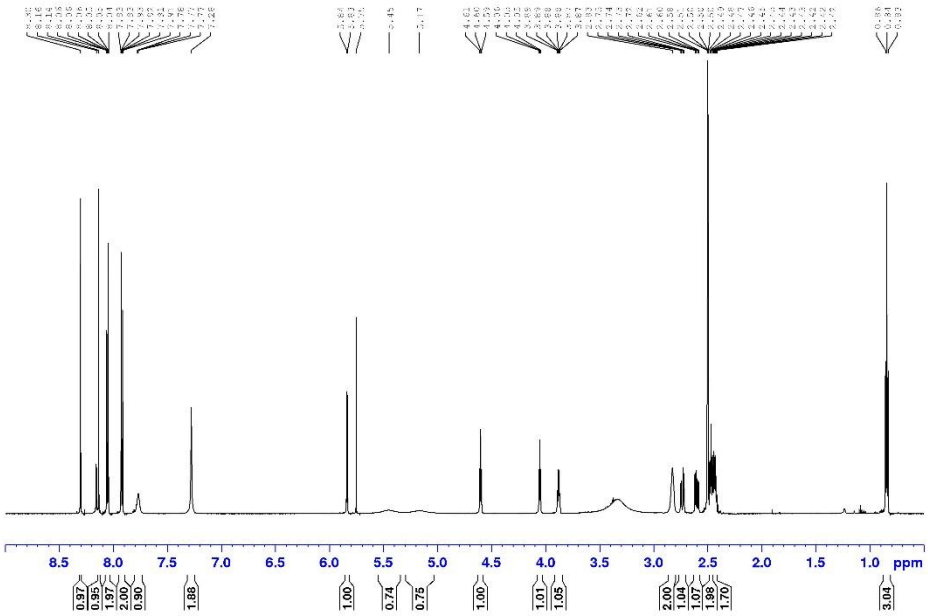


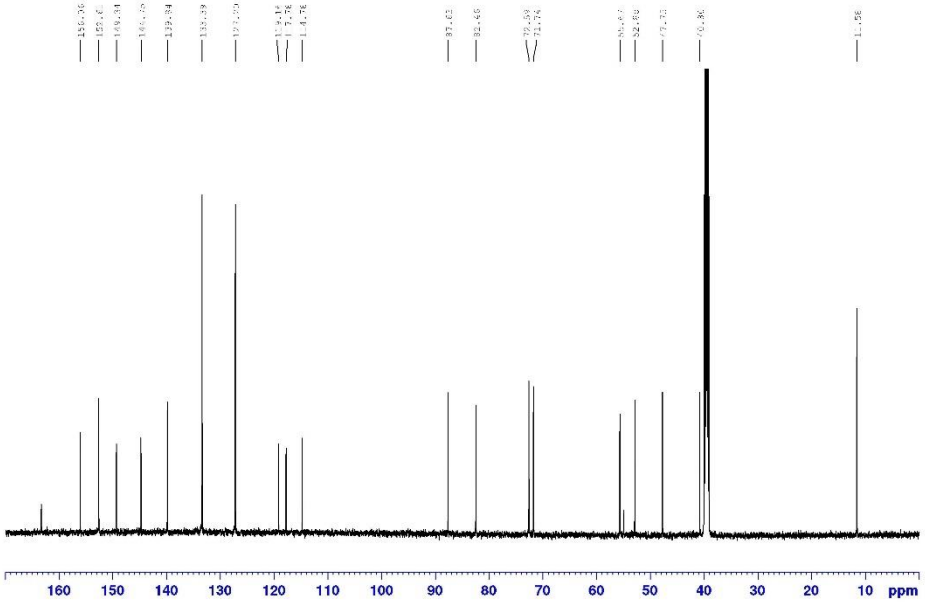


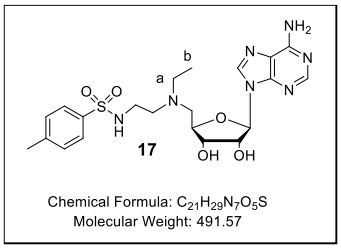


16

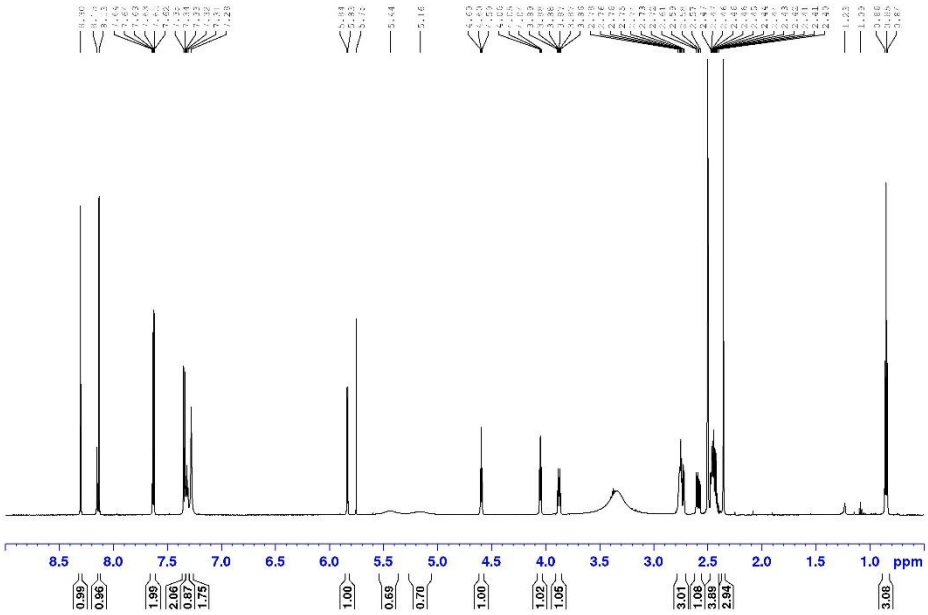
Chemical Formula: $C_{21}H_{26}N_8O_5S$
Molecular Weight: 502.55

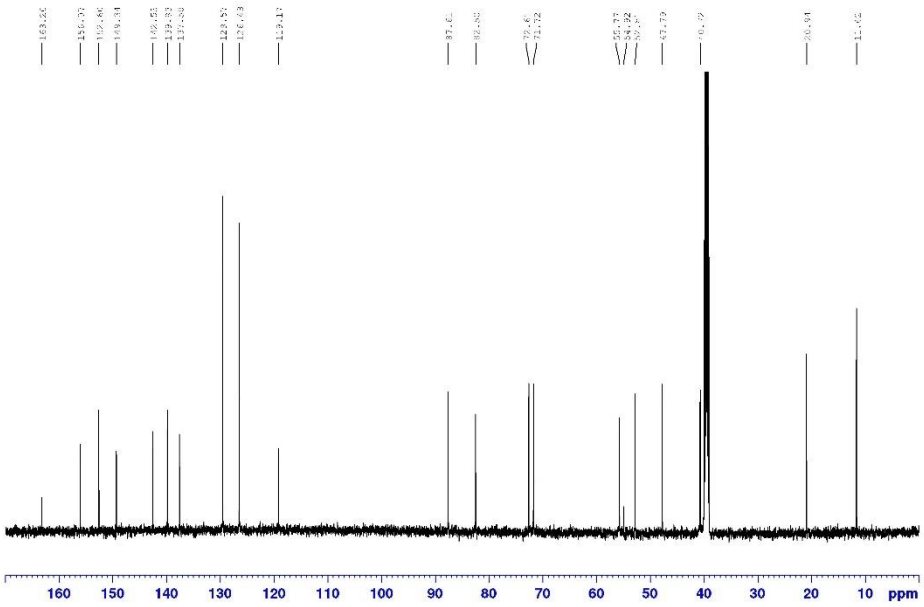


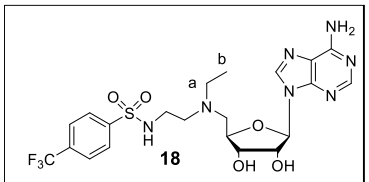




Chemical Formula: $C_{21}H_{29}N_7O_5S$
Molecular Weight: 491.57

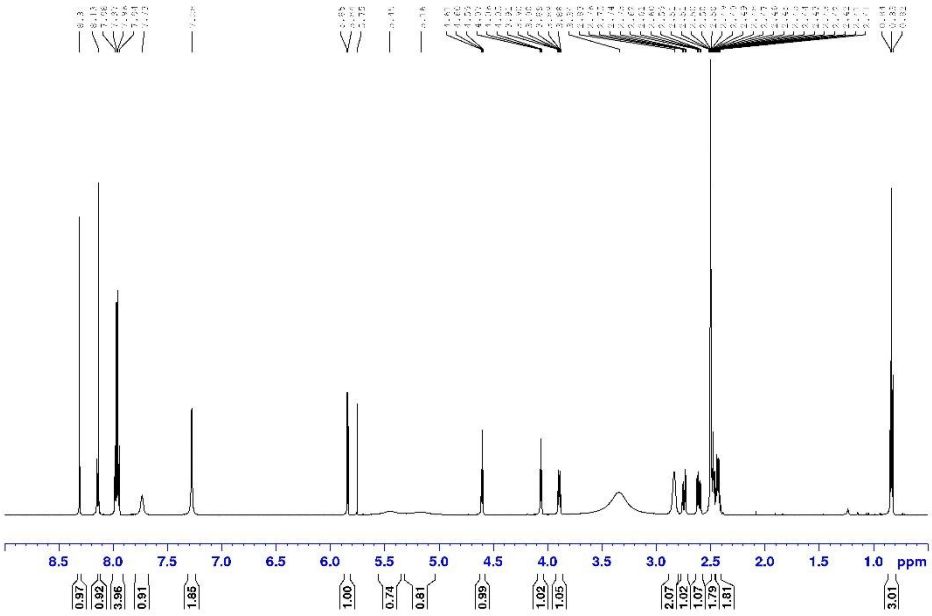


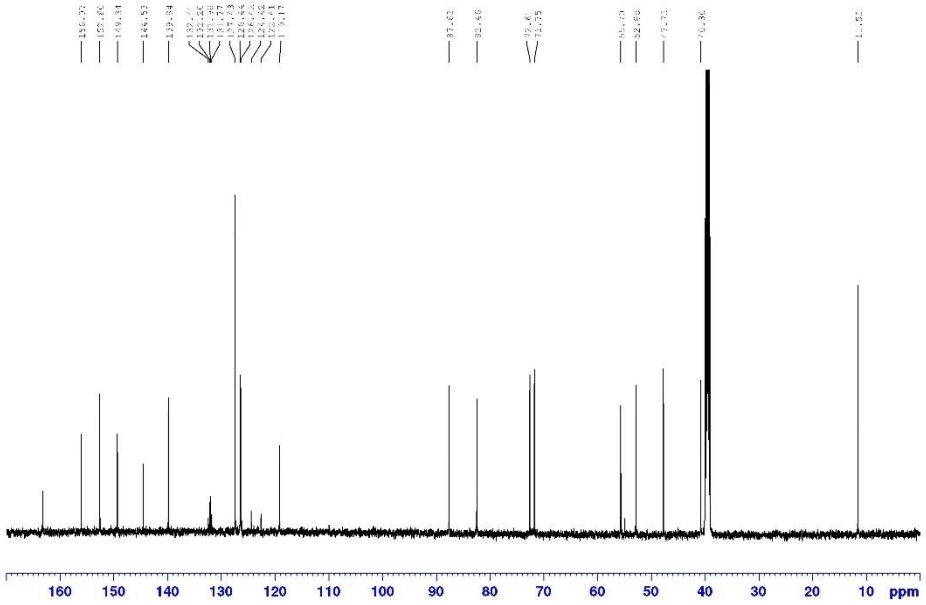




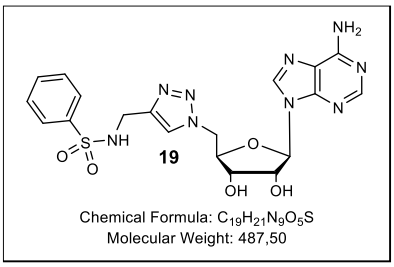
18

Chemical Formula: $C_{21}H_{26}F_3N_7O_5S$
Molecular Weight: 545.54

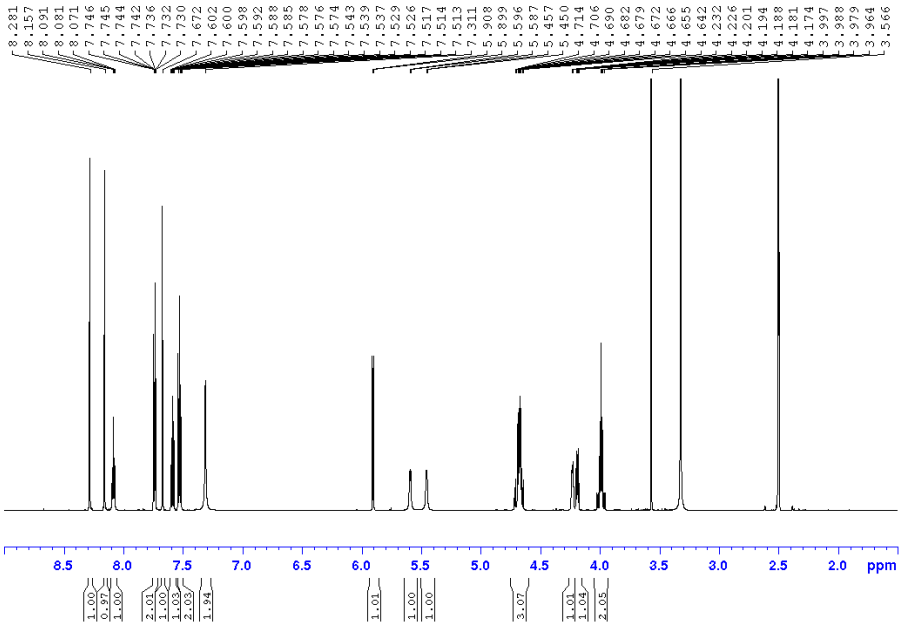


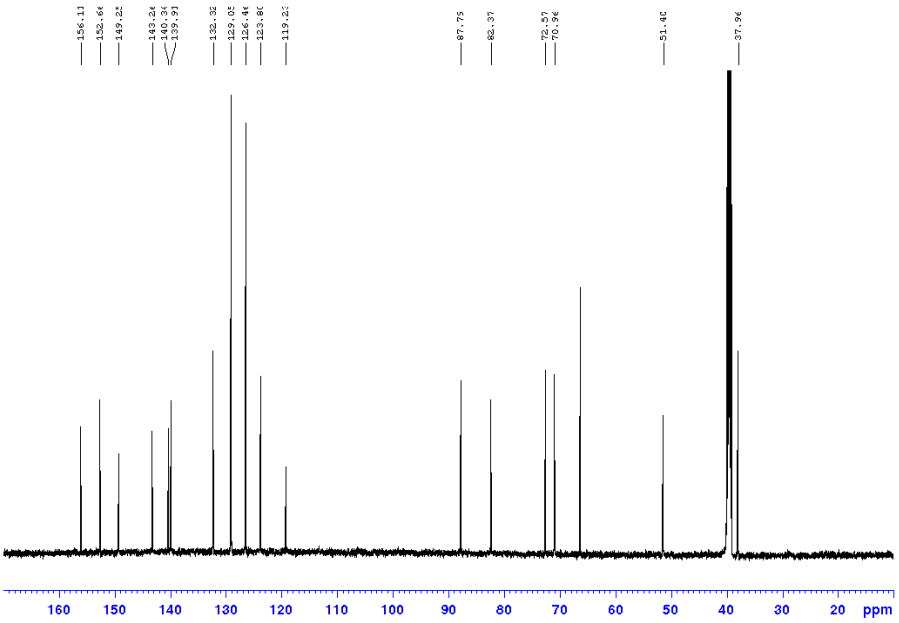


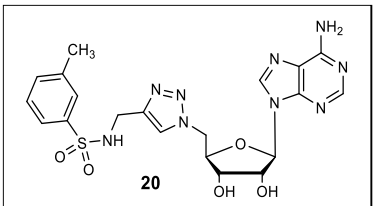
N-arylsulfonamide adenosine analogues with an *N*-methyltriazole linker (19-31)



Chemical Formula: $C_{19}H_{21}N_9O_5S$
Molecular Weight: 487,50

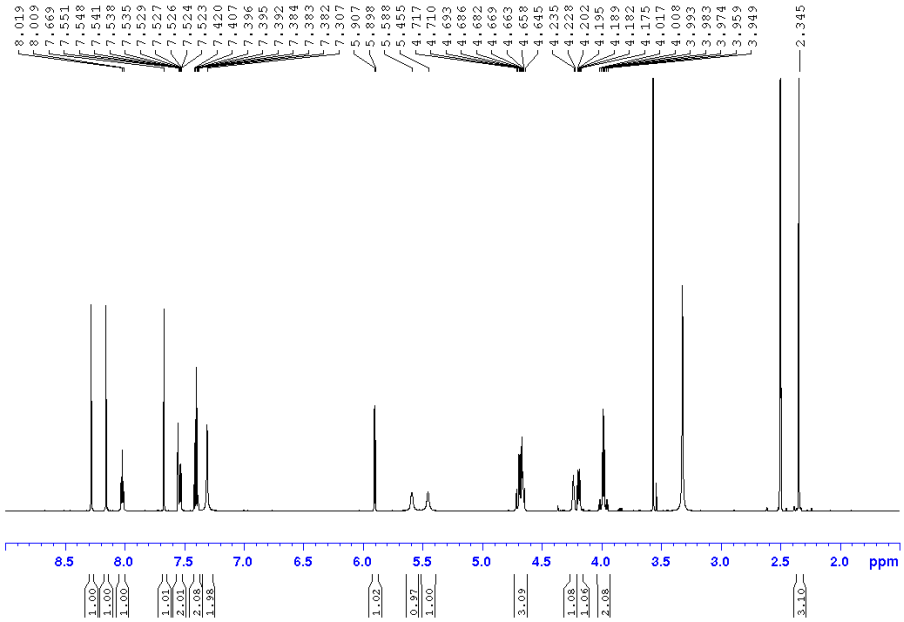


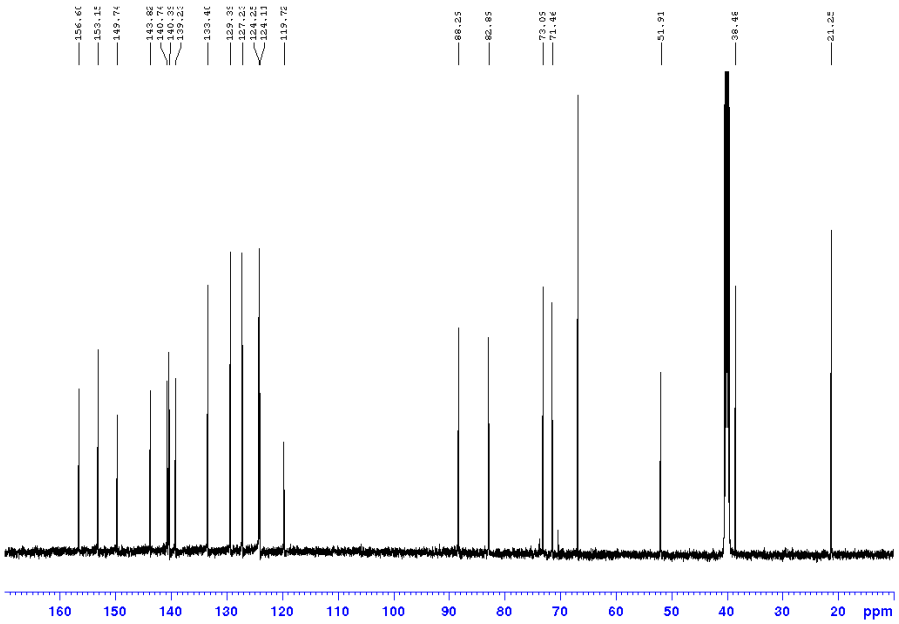


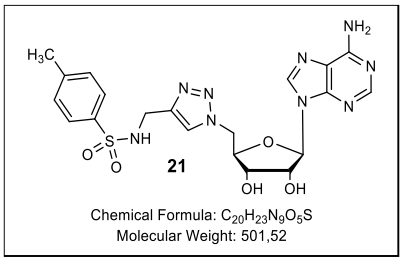


20

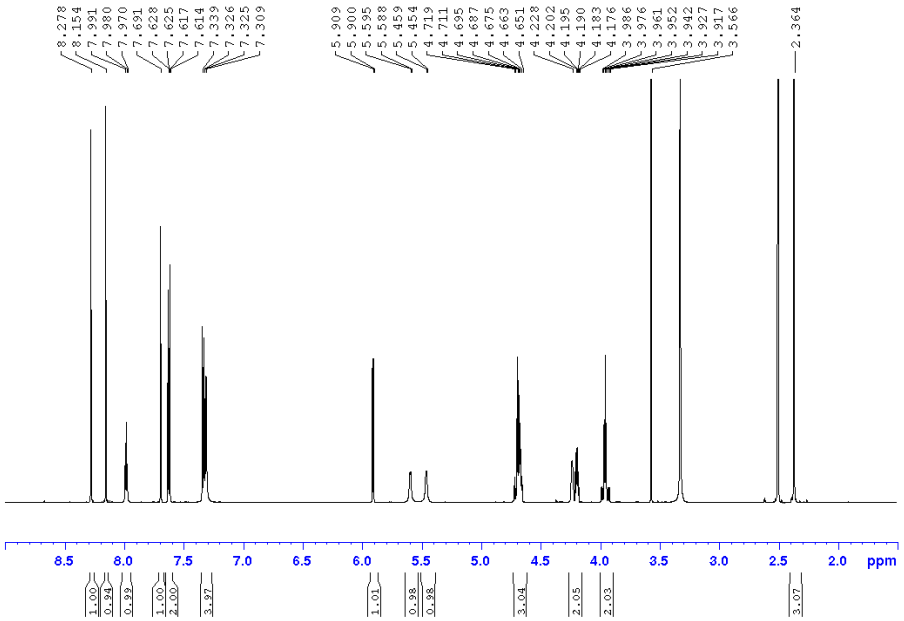
Chemical Formula: $C_{20}H_{23}N_9O_5S$
Molecular Weight: 501,52

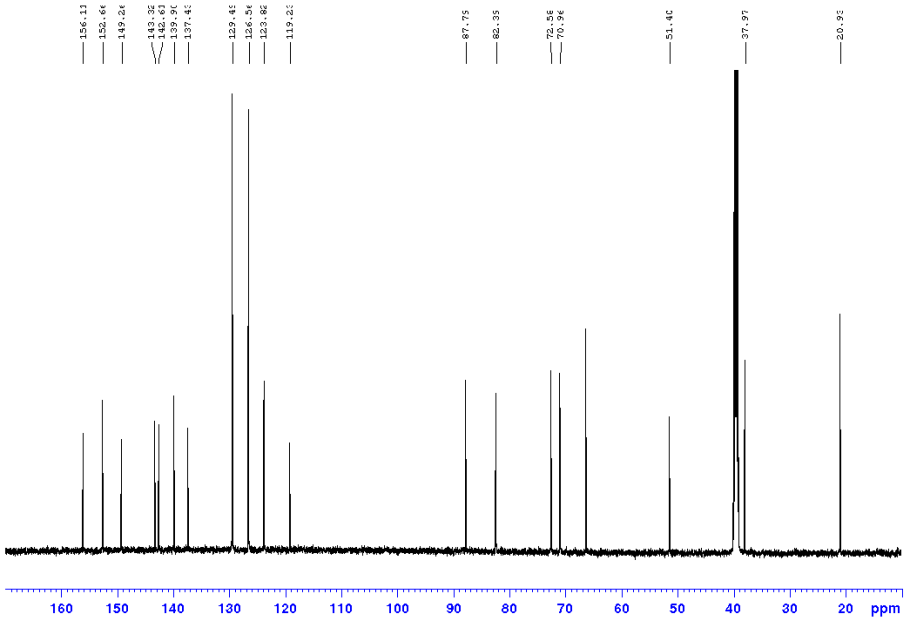


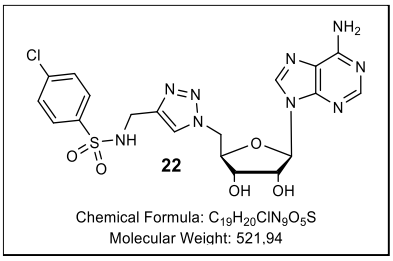




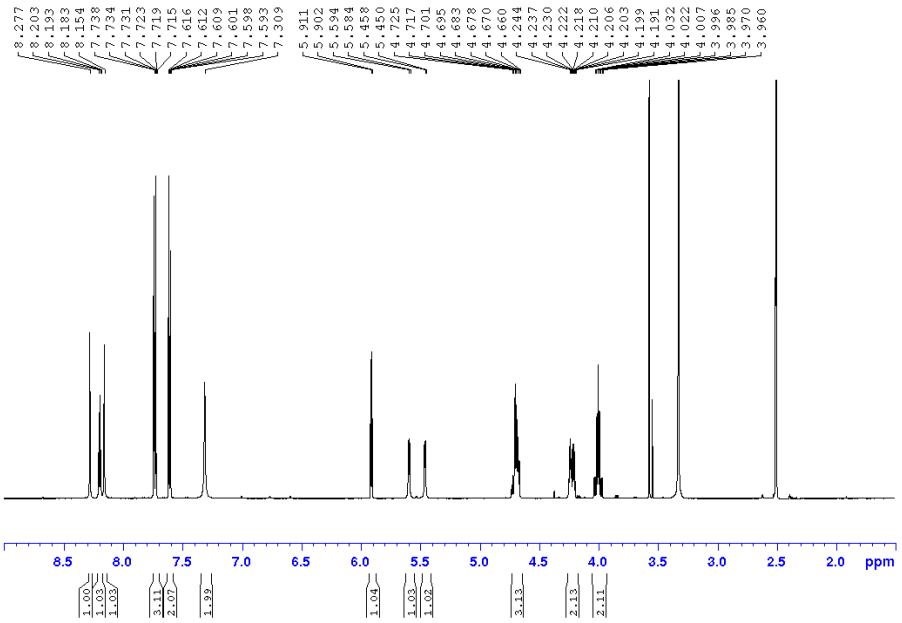
Chemical Formula: $C_{20}H_{23}N_9O_5S$
Molecular Weight: 501,52

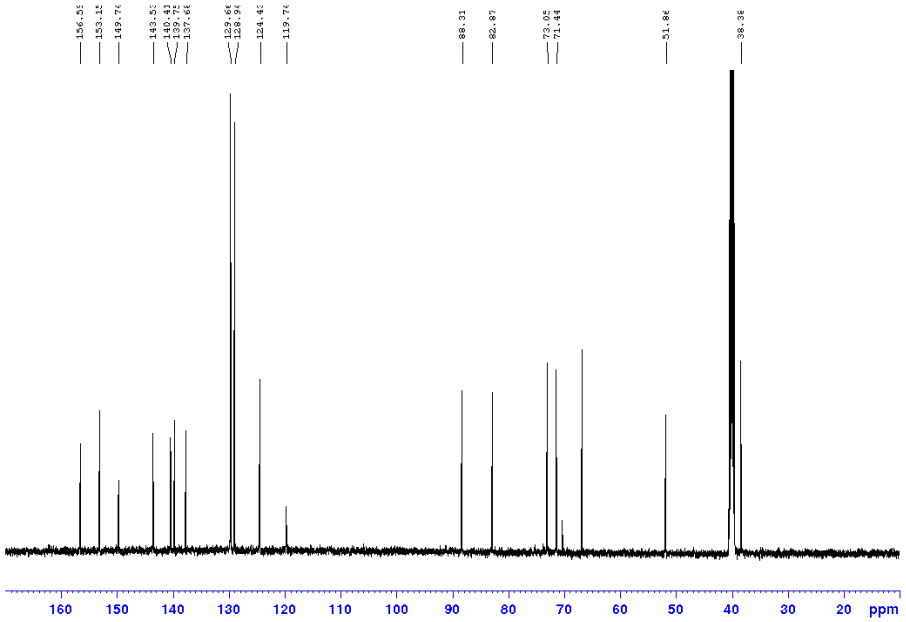


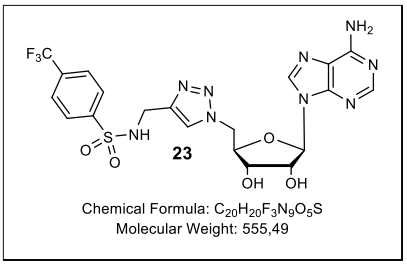




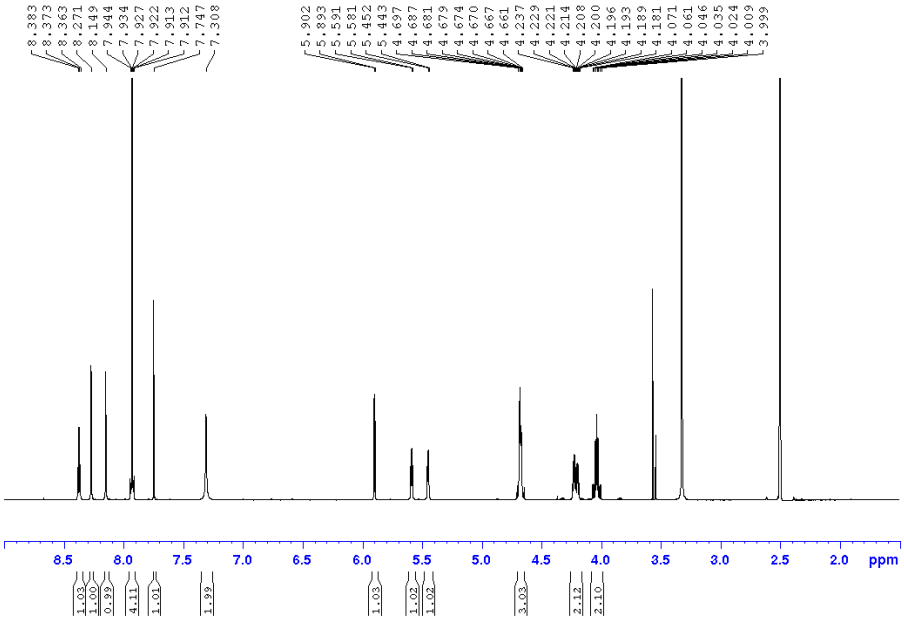
Chemical Formula: $C_{19}H_{20}ClN_9O_5S$
Molecular Weight: 521,94

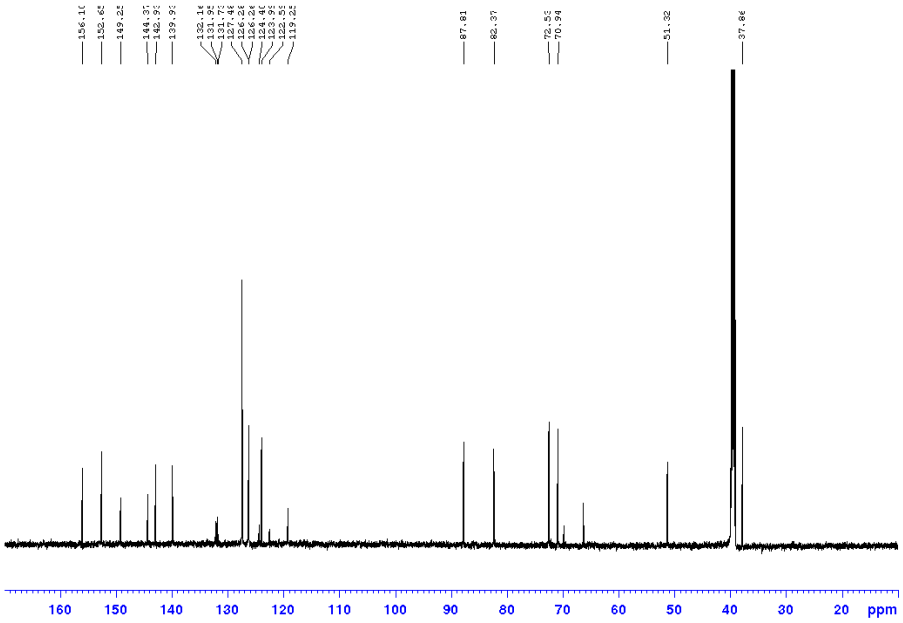


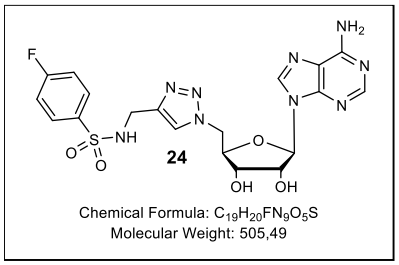




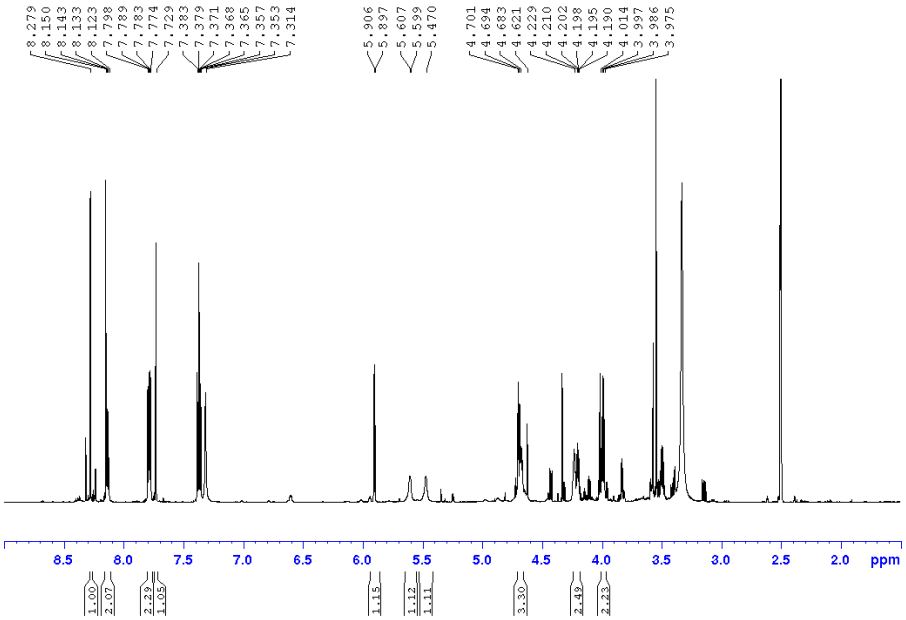
Chemical Formula: $C_{20}H_{20}F_3N_9O_5S$
Molecular Weight: 555,49

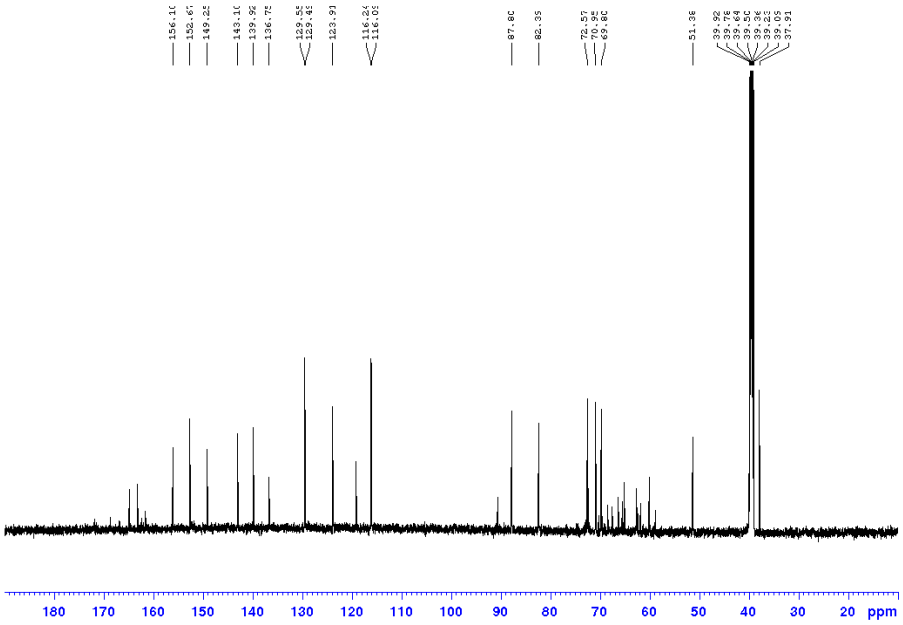


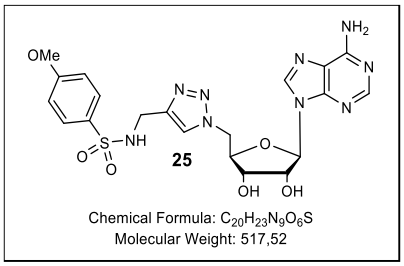




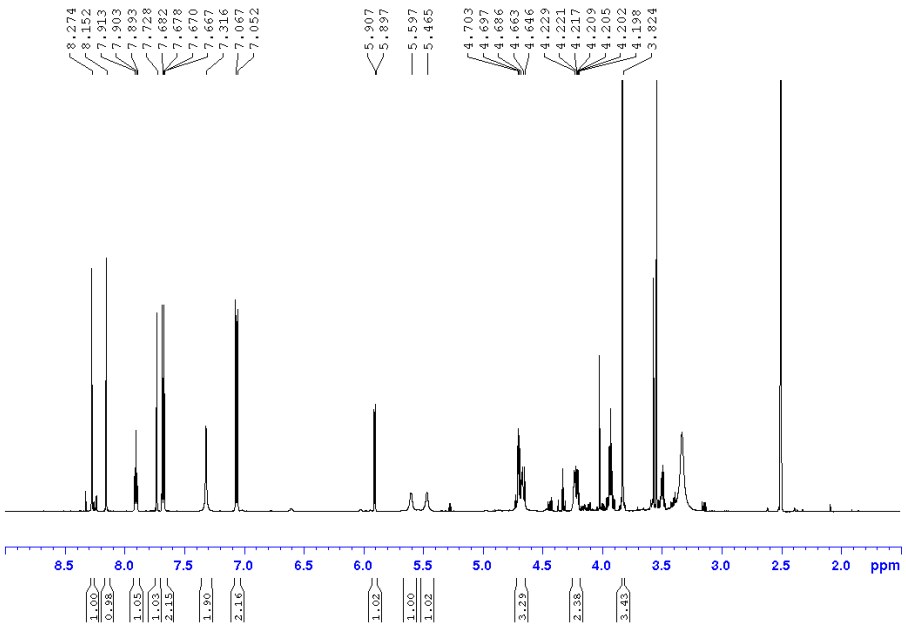
Chemical Formula: $C_{19}H_{20}FN_9O_5S$
Molecular Weight: 505,49

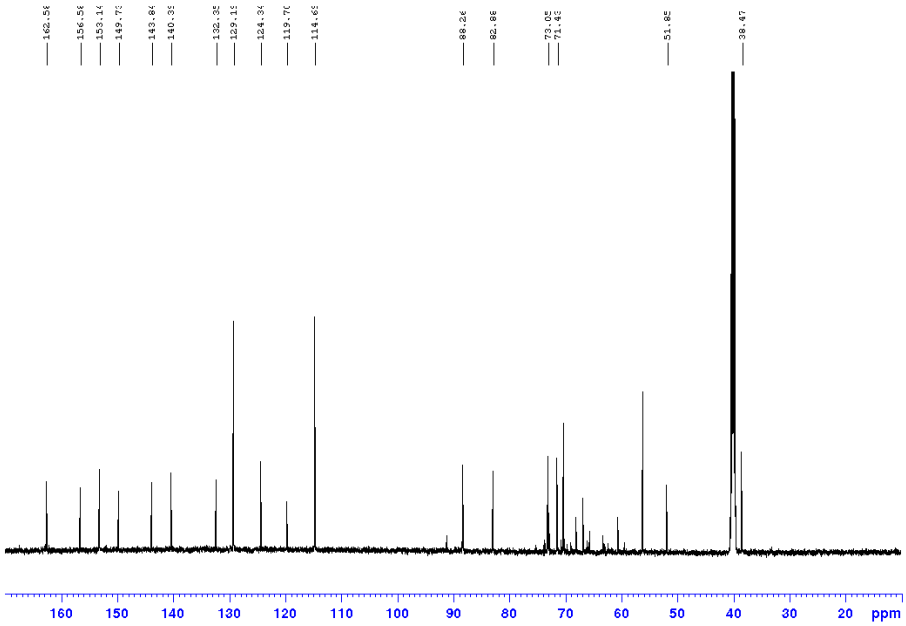


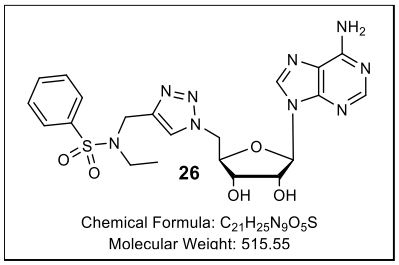




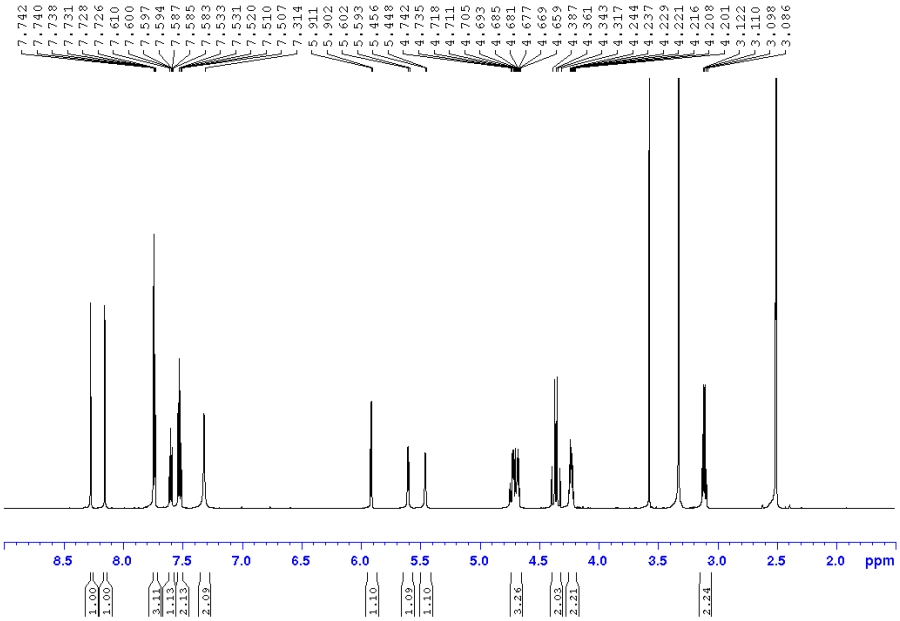
Chemical Formula: $C_{20}H_{23}N_9O_6S$
Molecular Weight: 517,52

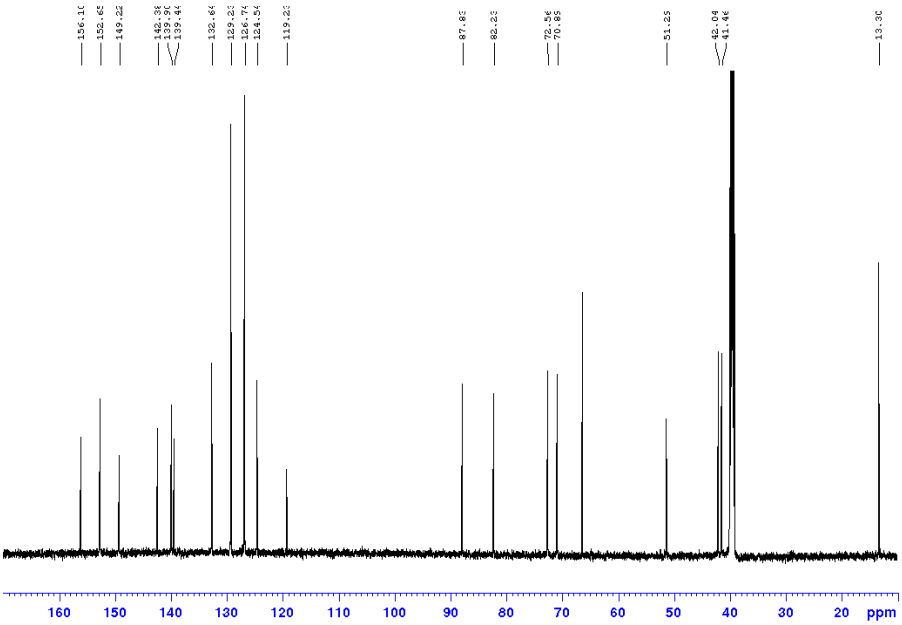


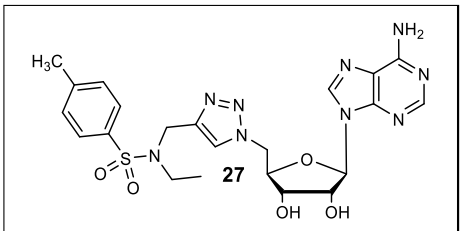




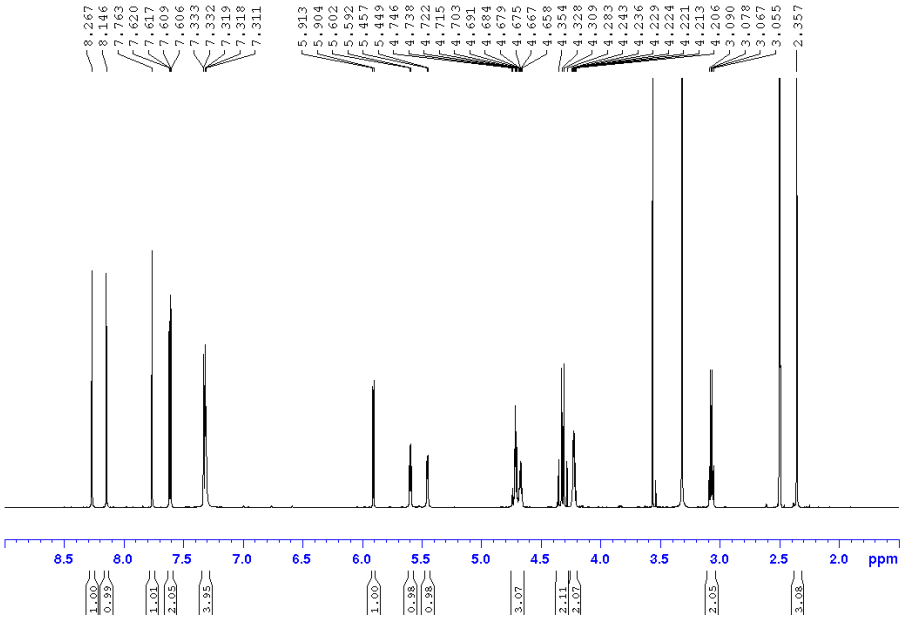
Chemical Formula: $C_{21}H_{25}N_9O_5S$
Molecular Weight: 515.55

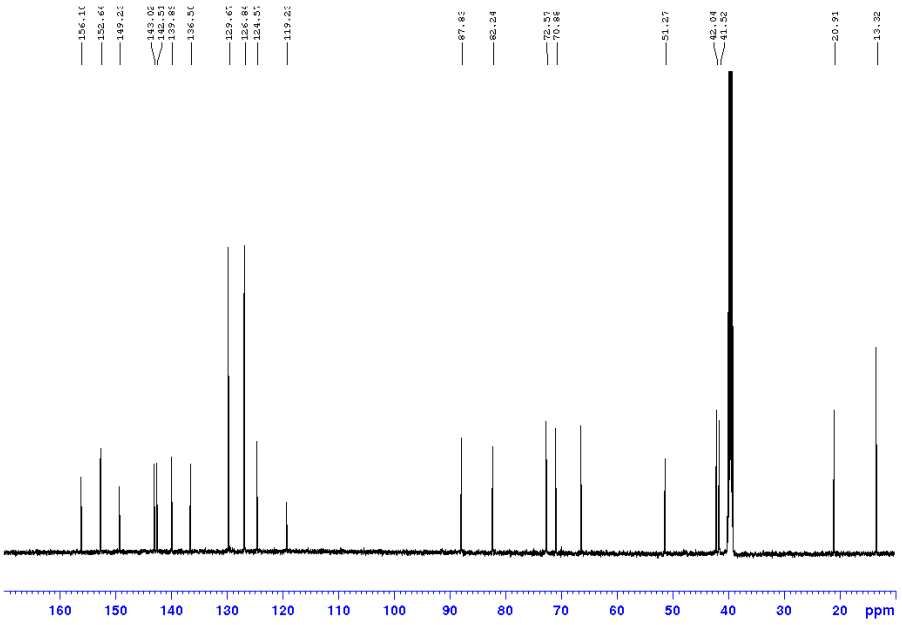


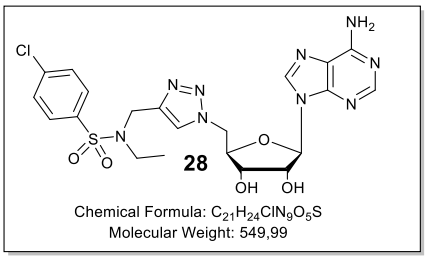




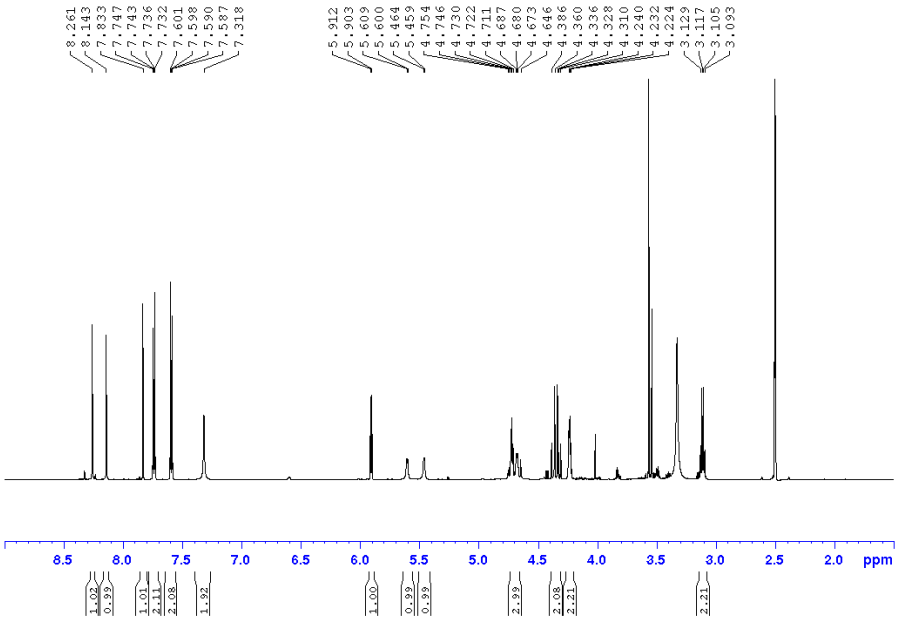
Chemical Formula: $C_{22}H_{27}N_9O_5S$
Molecular Weight: 529,58

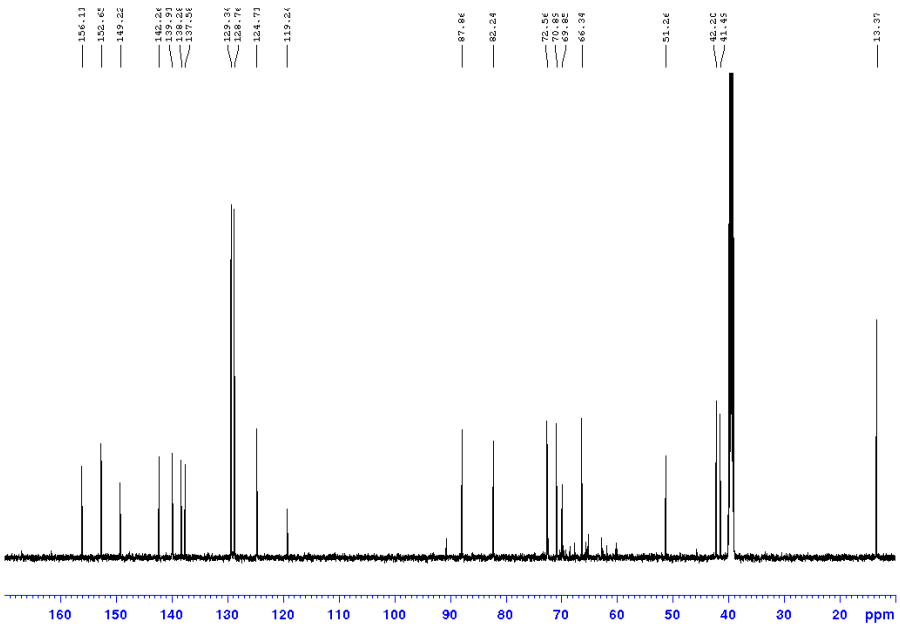


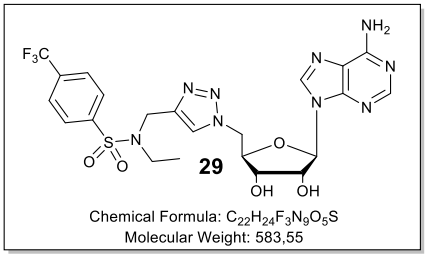




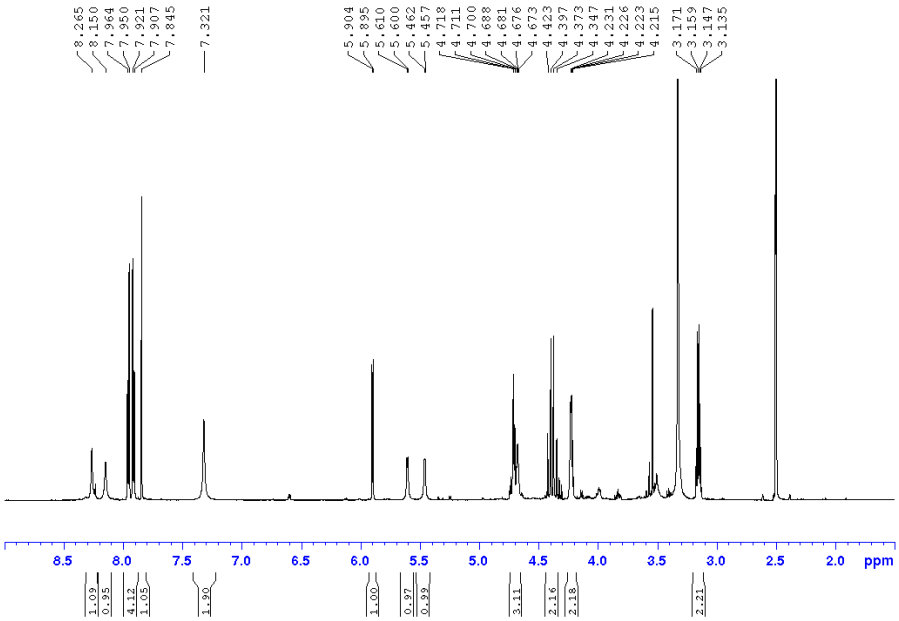
Chemical Formula: $C_{21}H_{24}ClN_9O_5S$
Molecular Weight: 549,99

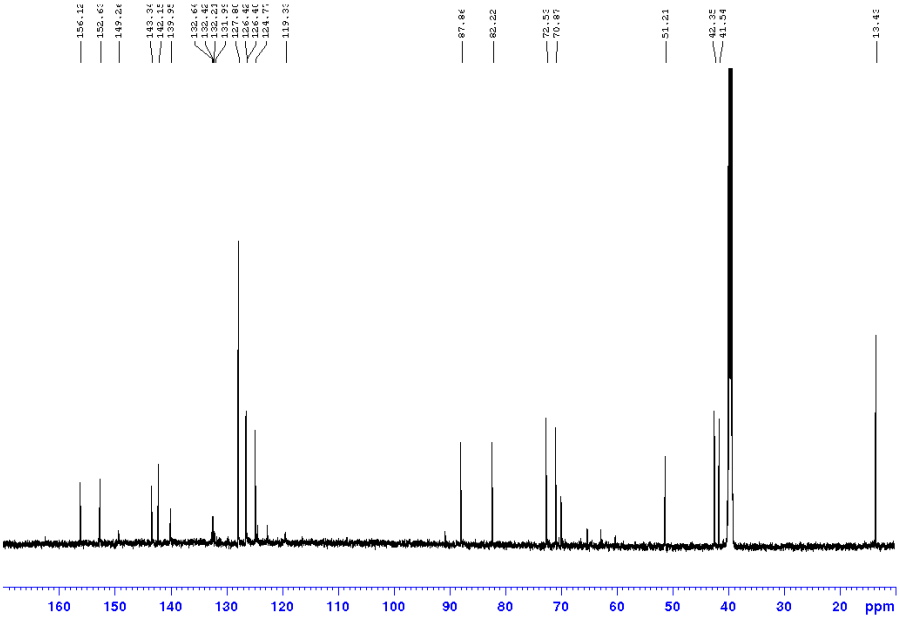


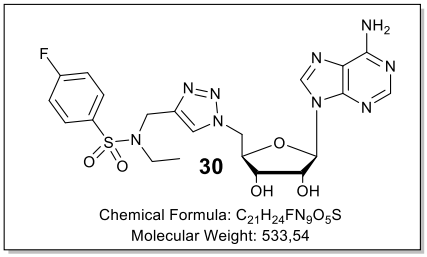




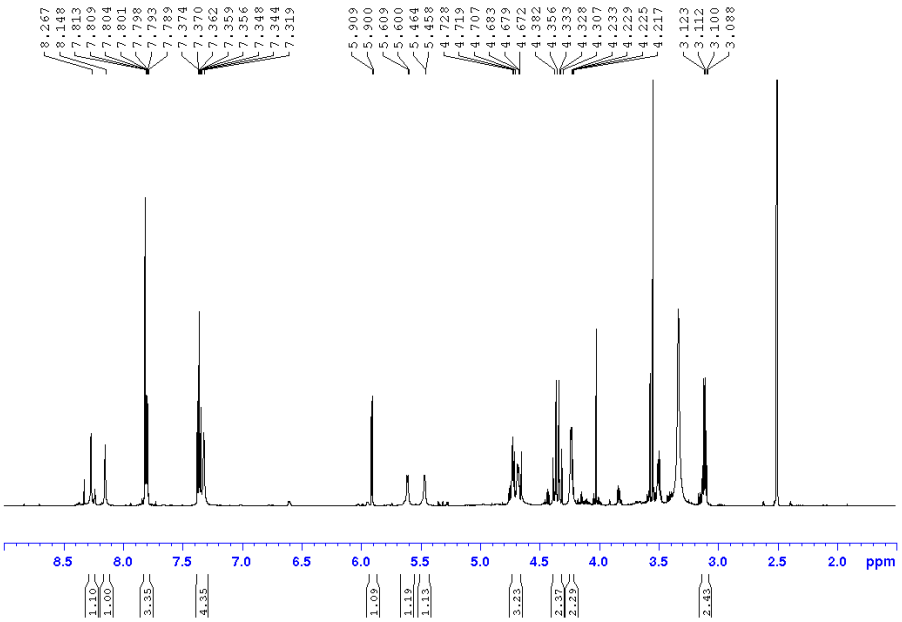
Chemical Formula: $C_{22}H_{24}F_3N_9O_5S$
Molecular Weight: 583,55

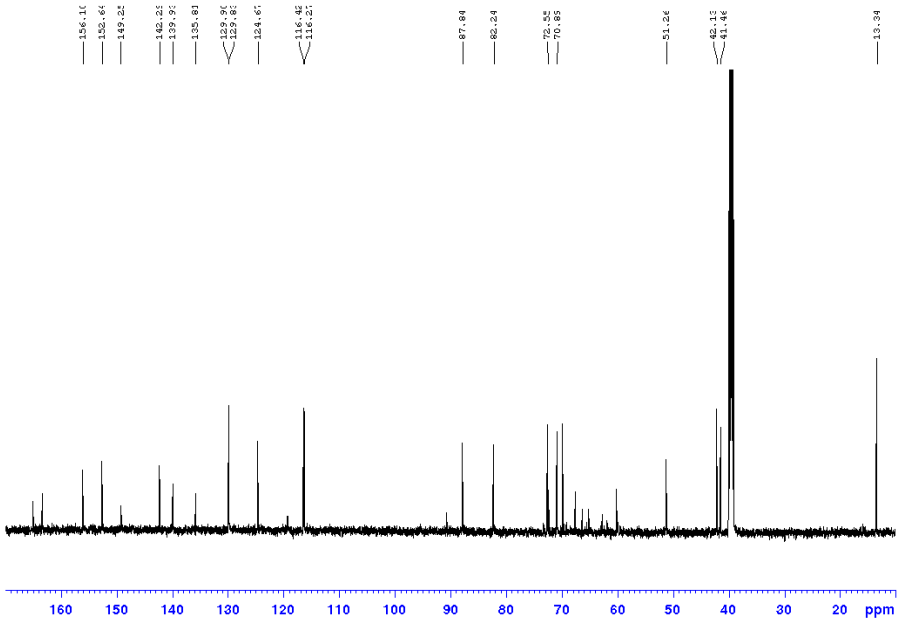


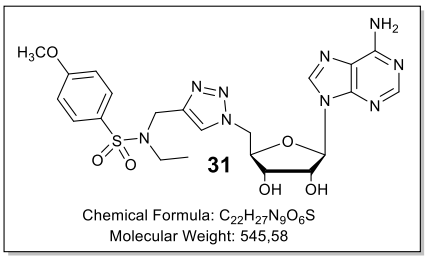




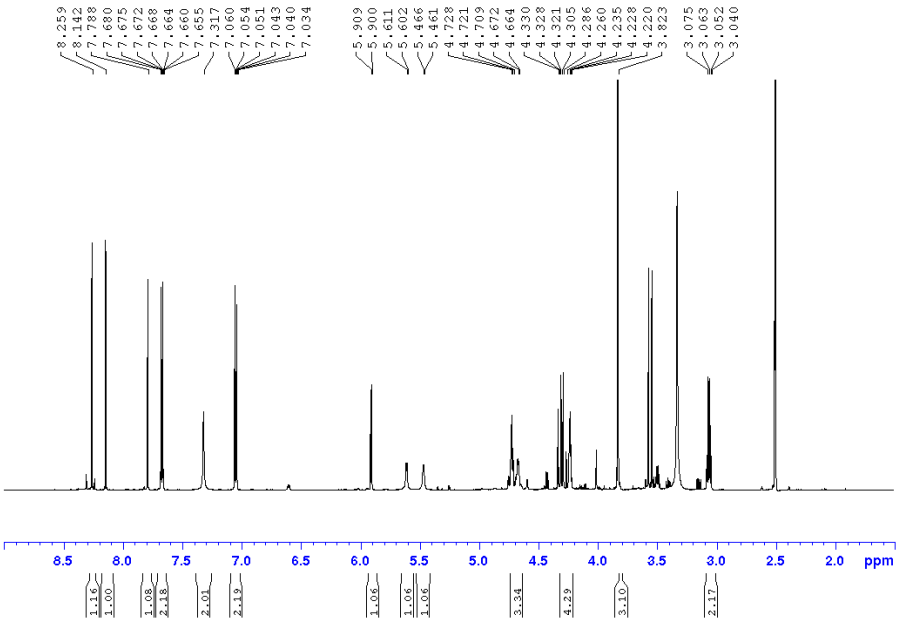
Chemical Formula: $C_{21}H_{24}FN_9O_5S$
Molecular Weight: 533,54

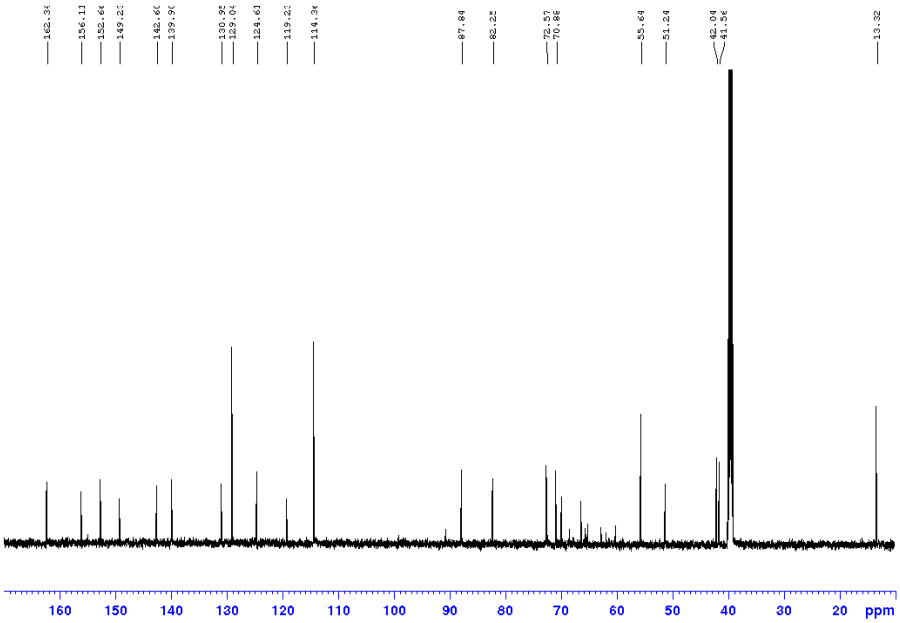




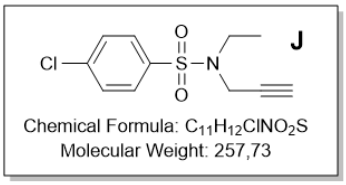


Chemical Formula: $C_{22}H_{27}N_9O_6S$
Molecular Weight: 545,58

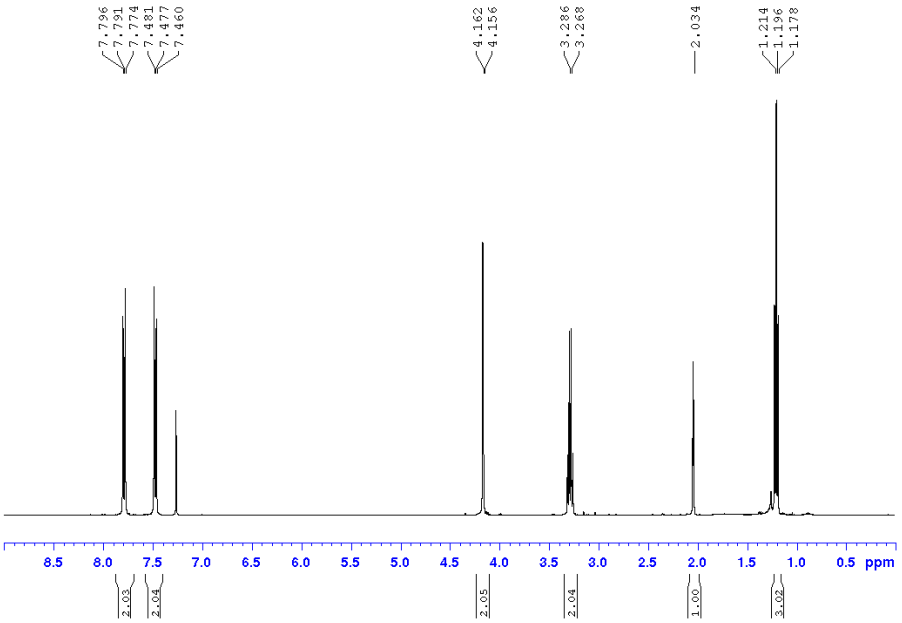


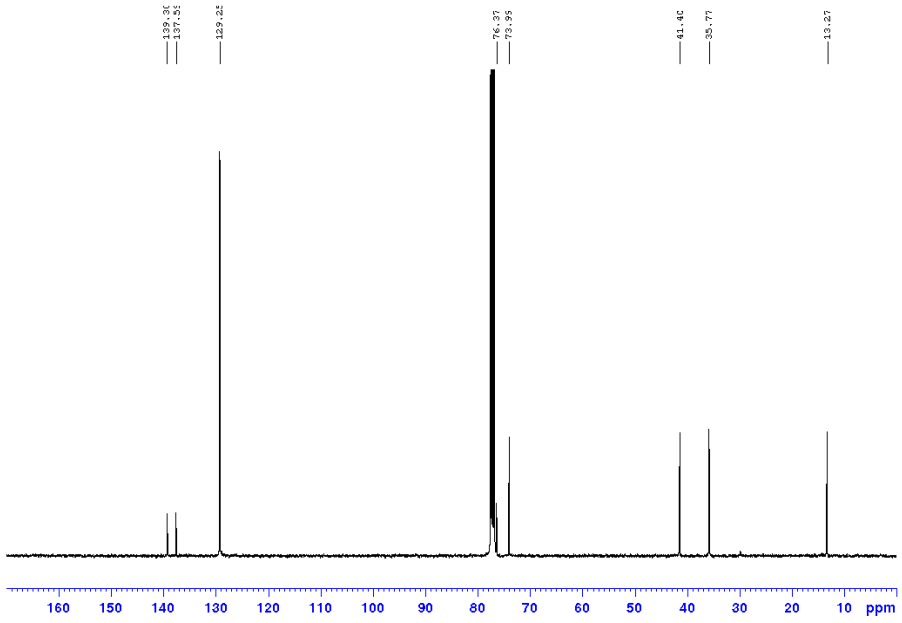


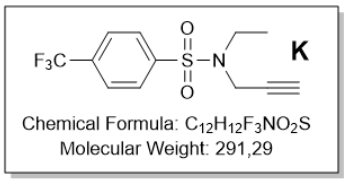
N-ethyl-*N*-propargyl reagents J-M



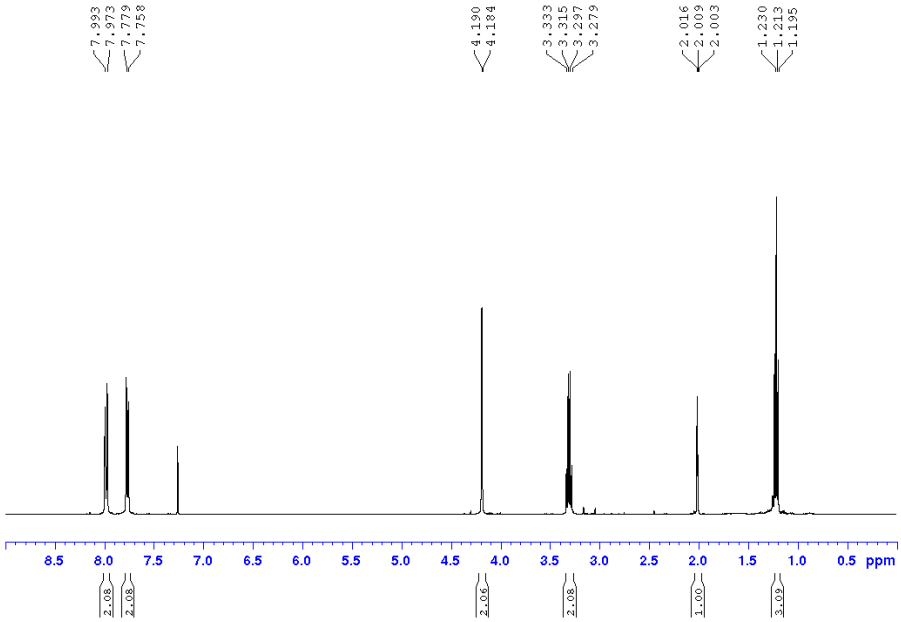
Chemical Formula: $C_{11}H_{12}ClNO_2S$
Molecular Weight: 257,73

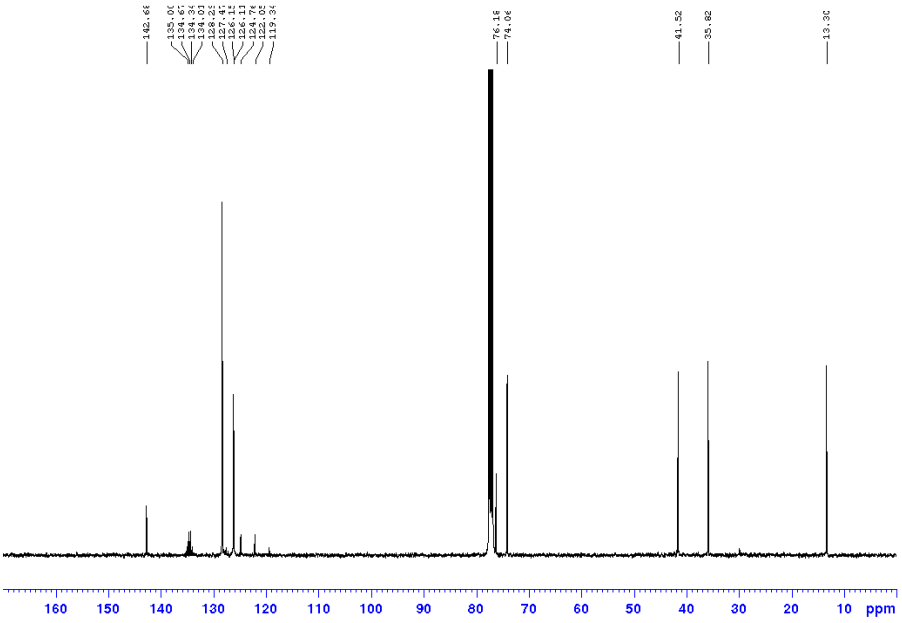


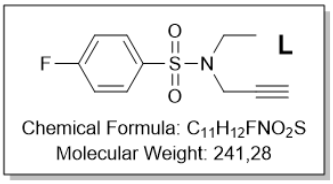




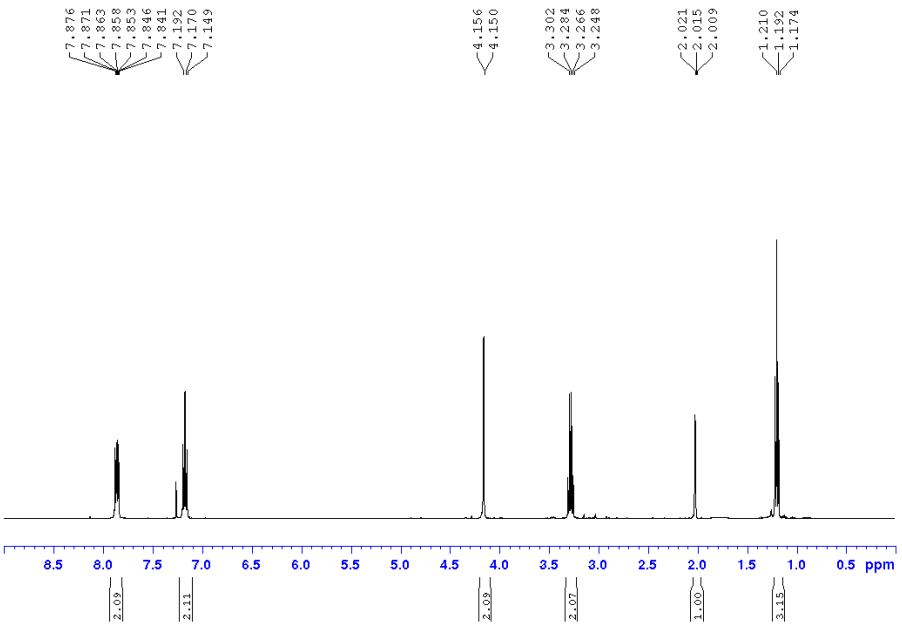
Chemical Formula: $C_{12}H_{12}F_3NO_2S$
Molecular Weight: 291,29

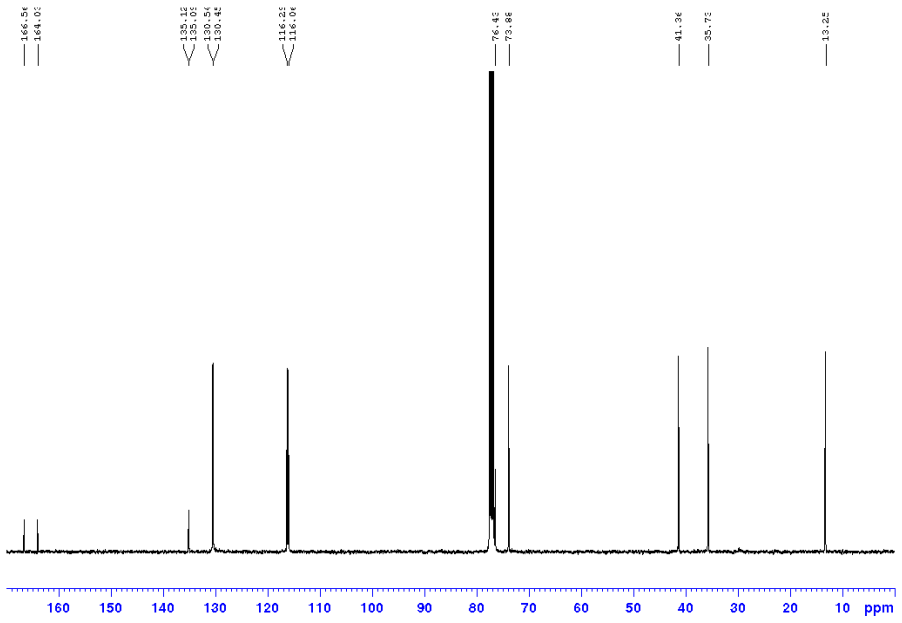


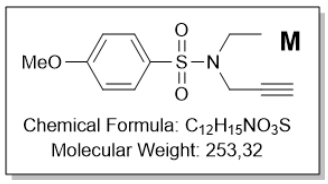


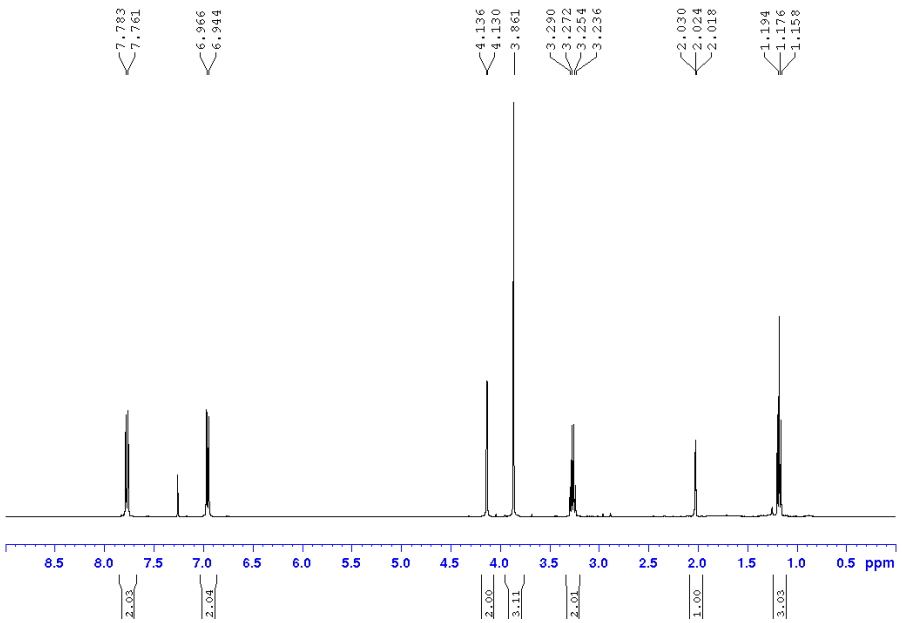


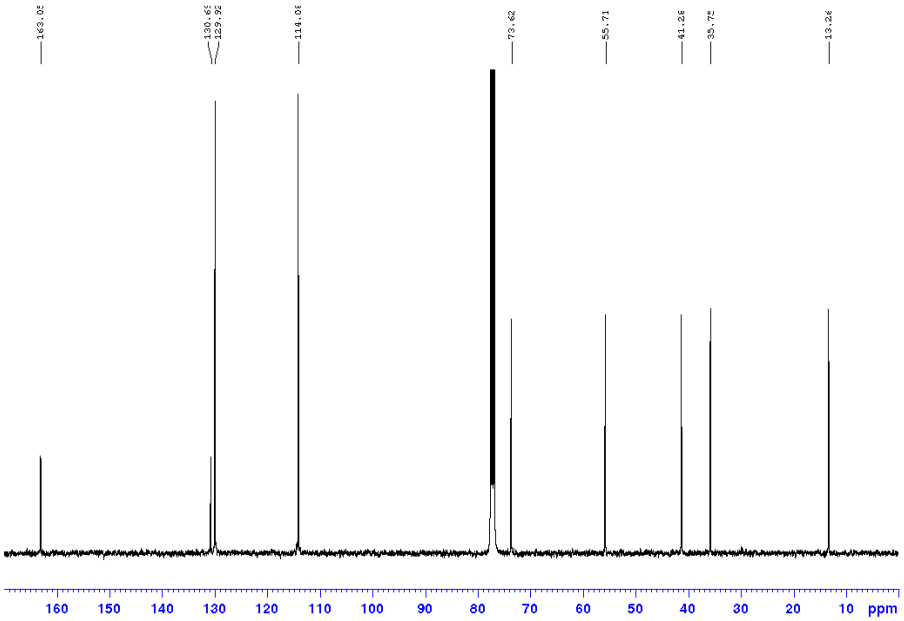
Chemical Formula: $C_{11}H_{12}FNO_2S$
Molecular Weight: 241,28






MeO
O
S
N
O
O
M
Chemical Formula: C12H15NO3S
Molecular Weight: 253,32

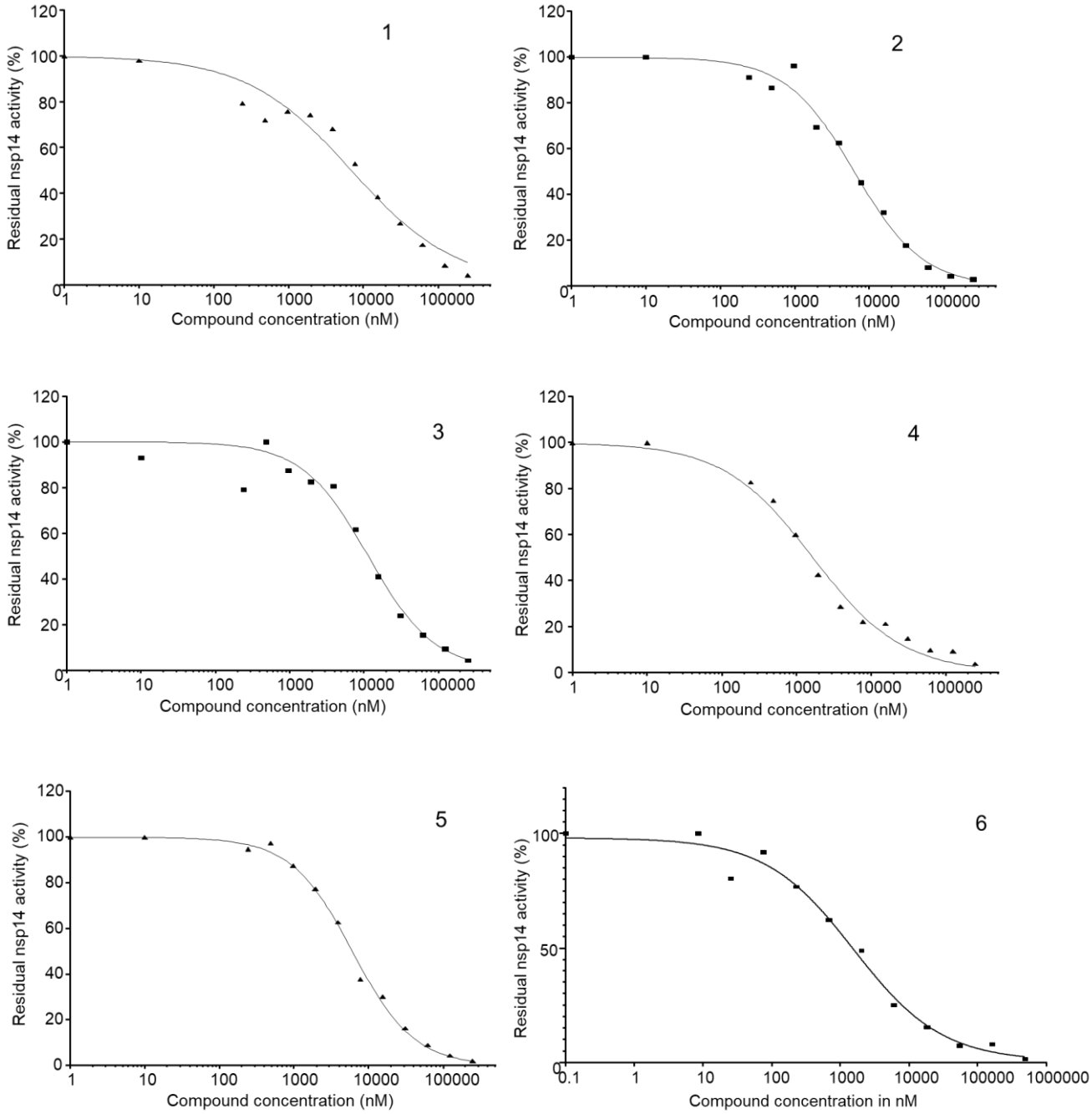

7.783
7.761
6.966
6.944
4.136
4.130
3.861
3.290
3.272
3.254
3.236
2.030
2.024
2.018
1.194
1.176
1.158
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.03
2.04
2.00
3.11
2.01
1.00
3.03

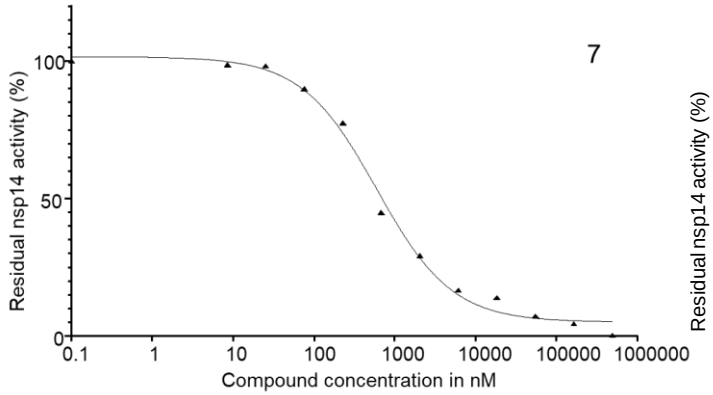

163.05
130.61
129.92
114.04
73.62
55.71
41.26
35.75
13.24
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

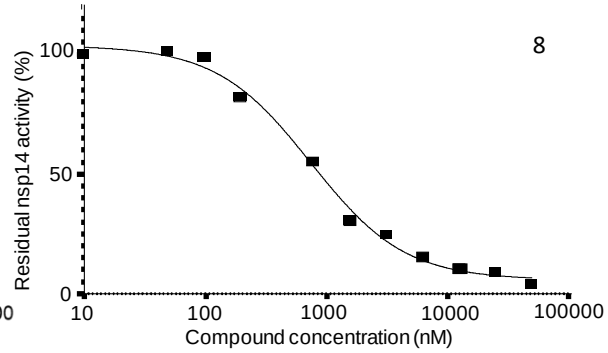
IC_{50} curves of compounds 1-13 against SARS-CoV-2 *N*7-MTase monitored by FBA

Increasing concentrations of compounds **1-13** (dissolved in 50% DMSO) were incubated with 10 nM SARS-CoV-2 nsp14 in reaction mixture [40 mM Tris-HCl (pH 8.0), 1 mM DTT, 1 mM $MgCl_2$, 2 μM SAM and 0.1 μM ^{3}H-SAM (Perkin Elmer)] in the presence of 0.7 μM synthetic RNA $GpppAC_4$. Reactions were incubated at 30°C during 30 min. Values were normalized and fitted with Prism (GraphPad software) using the following equation: Y=100/(1+((X/IC_{50})^Hillslope)) (n=3; mean value ± SD).

N-arylsulfonamide adenosine analogues with an *N*-ethylthioether linker (1-8)







N-arylsulfonamide adenosine analogues with an *N*-ethylsulfone linker (9-13)