Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supplementary Information

Trifluoroethanol solvent facilitates selective N-7 methylation of purines

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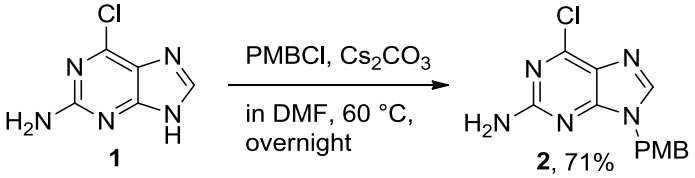
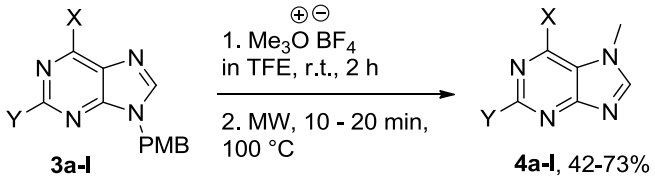
General information: ^{1}H, ^{19}F and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained as DMSO-d_6 solutions and recorded at 500 MHz, 470 MHz and 125 MHz respectively on a Bruker Avance III 500 spectrometer. Chemical shifts are reported in parts per million (δ) referenced to the appropriate deuterated solvent employed. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad) or combinations thereof. LCMS was carried out on a Waters Acquity SQD operating in positive and negative ion electrospray mode, employing a 50 × 2.1 mm, Waters Acquity UPLC BEH C18, 1.7µm column and a 1.5 min gradient elution of 0.1% formic acid and acetonitrile (5 - 95%) running at a flow rate of 0.6 mL/min.. High resolution mass spectrometry were measured using a Finnigan MAT 95 XP or a Finnigan MAT 900 XLT by the EPSRC National Mass Spectrometry Service Centre, University of Wales (Swansea), Singleton Park, Swansea, SA2 8PP. Infrared (IR) spectra were recorded on a Bio-Rad FTS 3000MX diamond ATR as a neat sample. UV spectra were obtained using a U-2001 Hitachi Spectrophotometer with the sample dissolved in ethanol. Thin layer chromatography for monitoring reaction progress was conducted on plates pre-coated with silica gel (Merck 60F254). The eluent was as stated (where this consisted of more than one solvent, the ratio is stated as volume:volume) and visualisation was by ultraviolet light. The products were purified by medium pressure liquid chromatography (MPLC), using the Varian automated purification system. All commercial reagents and solvents were purchased from reputable suppliers. The chemicals were of the highest available purity and were used as supplied unless otherwise stated. Anhydrous solvents were stored under nitrogen. Petrol refers to the fraction with a boiling point between 40 and 60 °C. Reactions needing microwave irradiation were carried out in a Biotage Initiator™ Sixty reactor.

Synthesis of substrate 2



2-Amino-6-chloropurine **1** (6 g, 35.5 mmol) and cesium carbonate (13.8 g, 42.6 mmol) were dissolved in anhydrous DMF (80 mL). 4-Methoxybenzylchloride was then added and the reaction was stirred at 60 °C overnight. The solvent was removed *in vacuo*. The residue obtained was resuspended in EtOAc (50 mL) and washed with brine (50 mL) and water (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The product was purified by MPC on silica (DCM: MeOH 95: 5) to afford **6-chloro-9-(4-methoxybenzyl)-9*H*-purin-2-amine (2)** as an off-white solid (7.2 g, 25.0 mmol, 60%); mp 176-177 °C; R_f 0.64 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 3.73 (3H, s, OCH_3), 5.21 (2H, s, CH_2), 6.91 (2H, d, J = 8.7 Hz, Ar-H), 6.94 (2H, s, NH_2), 7.26 (2H, d, J = 8.7 Hz, Ar-H), 8.21 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 45.5, 54.9, 114.1, 123.3, 128.5, 128.8, 143.0, 149.4, 153.9, 158.9, 159.9; IR (cm^{-1}) 3440, 3208, 2830, 1614, 1560, 1514, 1244, 906, 761; λ_{max} 310 nm (in EtOH); HRMS (ES^+) *m/z* 290.0808 $[M+H]^+$ (calcd for $C_{13}H_{13}ON_5Cl$ 290.0803).

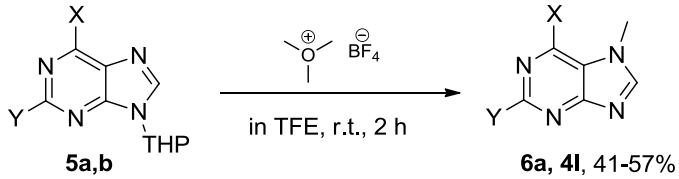
General procedure A for selective N-7 methylation of 9-(4-methoxybenzyl)-purines



3a-l **4a-l**, 42-73%

The 9*H*-purine-6-carbonitrile (67 mg, 0.16 mmol) and trimethyloxonium tetrafluoroborate (24 mg, 0.16 mmol) were solubilised in TFE (2 mL). The resulting solution was stirred at room temperature for 2 h. The reaction was purged with nitrogen, sealed and subjected to microwave heating at 100 °C. The solvent was removed *in vacuo* and the crude product was purified as indicated.

General procedure B for selective N-7 methylation of 9-tetrahydropyranyl-purines



5a,b **6a, 4l**, 41-57%

The 9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (100 mg, 0.45 mmol) and trimethyloxonium tetrafluoroborate (80 mg, 0.54 mmol) were solubilised in TFE (2 mL). The resulting solution was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the crude product was purified as indicated.

2-amino-7-methyl-7*H*-purine-6-carbonitrile (4a)
The title compound was synthesised following **general procedure A** using 2-amino-9-(4-methoxybenzyl)-9*H*-purine-6-carbonitrile **3a** (100 mg, 0.36 mmol) and trimethyloxonium tetrafluoroborate (54 mg, 0.36 mmol). The reaction was heated for 20 min at 100 °C. The crude product was purified by MPC on silica (DCM: MeOH 95: 5) to give the product **4a** as a beige solid (40 mg, 0.23 mmol, 65%); mp 273-275 °C; R_f 0.30 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 3.94 (3H, s, NCH_3), 6.79 (2H, s, NH_2), 8.51 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 32.2, 114.5, 120.1, 122.9, 151.9, 160.5, 164.6; IR (cm^{-1}) 3412, 3185, 2360, 1610, 1501; λ_{max} 254 nm (in EtOH); HRMS (ES^+) *m/z* 175.0726 $[M+H]^+$ (calcd for $C_7H_7N_6$ 175.0721).

2-iodo-7-methyl-7*H*-purine-6-carbonitrile (4b)
The title compound was synthesised following **general procedure A** using 2-iodo-9-(4-methoxybenzyl)-9*H*-purine-6-carbonitrile **3b** (110 mg, 0.28 mmol) and trimethyloxonium tetrafluoroborate (42 mg, 0.28 mmol). The reaction was heated for 10 min at 100 °C. The crude product was purified by MPC on silica (Petrol: EtOAc 40: 60) to give the product **4b** as a colourless oil (53 mg, 0.19 mmol, 66%); R_f 0.63 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 4.07 (3H, s, NCH_3), 8.91 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 32.7, 113.4, 118.4, 123.7, 126.4, 153.9, 163.4; IR (cm^{-1}) 2360, 1604, 1345; λ_{max} 302 nm (in EtOH); HRMS (ES^+) *m/z* 285.9589 $[M+H]^+$ (calcd for $C_7H_5IN_5$ 285.9584)**.**

2-(3-((6-cyano-7-methyl-7*H*-purin-2-yl)amino)phenyl)acetamide (4c)
The title compound was synthesised following **general procedure A** using 2-(3-((6-cyano-9-(4-methoxybenzyl)-9*H*-purin-2-yl)amino)phenyl)acetamide **3c** (67 mg, 0.16 mmol) and trimethyloxonium tetrafluoroborate (24 mg, 0.16 mmol). The reaction was heated for 20 min at 100 °C. The crude product was purified by MPC on silica (DCM: MeOH 95: 5) to give the product **4c** as a yellow solid (28 mg, 0.09 mmol, 56%); mp 259-261 °C; R_f 0.55 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 3.36 (2H, s, CH_2), 4.01 (3H, s, NCH_3), 6.89 (1H, bs, $CONH_2$), 6.90 (1H, d, *J* = 7.8 Hz, Ar-H), 7.24 (1H, dd, *J1* = 7.8 Hz, *J2* = 7.8 Hz, Ar-H), 7.46 (1H, bs, $CONH_2$), 7.57 (1H, s, Ar-H), 7.71 (1H, d, *J* = 7.8 Hz, Ar-H), 8.66 (1H, s, H-8), 9.86 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 32.3, 42.4, 116.5, 119.2, 120.8, 121.7, 122.2, 123.1, 128.1, 136.6, 140.0, 152.4, 156.4, 163.9, 171.9; IR (cm^{-1}) 3390, 3190, 2364, 1669, 1611, 1560, 1493, 1390, 788; λ_{max} = 254 nm (in EtOH); HRMS (ES^+) *m/z* 308.1259 $[M+H]^+$ (calcd for $C_{15}H_{14}N_7O$ 308.1254).

TFA salt of 6-chloro-7-methyl-7*H*-purin-2-amine (4d)
The title compound was synthesised following **general procedure A** using 2-amino-9-(4-methoxybenzyl)-9*H*-purine-6-carbonitrile **3d** (100 mg, 0.34 mmol) and trimethyloxonium tetrafluoroborate (50 mg, 0.34 mmol). 3mL of TFA were added after completion of the methylation to have a 50% TFA solution. The reaction was heated for 10 min at 100 °C. The crude product was recrystallised using Petrol and DCM to afford the product **4d** as a beige solid (70 mg, 0.24 mmol, 68%); mp 168-171 °C; R_f 0.42 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) 4.00 (3H, s, NCH_3), 8.90 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 34.6, 107.6, 114.2, 130.0, 138.8, 149.6, 153.3, 154.8; ^{19}F NMR (470 MHz, DMSO-d_6) ppm -75.2; IR (cm^{-1}) 2380, 1630, 1583, 1391, 1030; λ_{max} = 302 nm (in EtOH); HRMS (ES$^+$) *m/z* 184.0384 $[M+H]^+$ (calcd for $C_6H_7ClN_5$ 184.0384).

6-(cyclohexylmethoxy)-7-methyl-7*H*-purin-2-amine (4e)
The title compound was synthesised following **general procedure A** using 6-(cyclohexylmethoxy)-9-(4-methoxybenzyl)-9*H*-purin-2-amine **3e** (100 mg, 0.27 mmol) and trimethyloxonium tetrafluoroborate (40 mg, 0.27 mmol). The reaction was heated for 10 min at 100 °C. The crude product was purified by MPC on silica (DCM: MeOH 90: 10) to give the product **4e** as a white solid (43 mg, 0.11 mmol, 60%); mp 167-169 °C; R_f 0.46 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 1.05-1.12 (2H, m, H-cyclohexyl), 1.17-1.30 (3H, m, H-cyclohexyl), 1.65-1.68 (1H, m, H-cyclohexyl), 1.72-1.75 (2H, m, H-cyclohexyl), 1.79-1.82 (3H, m, H-cyclohexyl), 3.84 (3H, s, NCH_3), 4.21 (2H, d, *J* = 6.2 Hz, OCH_2), 6.07 (2H, s, NH_2), 7.99 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 25.3, 26.0, 29.2, 33.4, 36.7, 70.1, 106.5, 145.5, 157.2, 159.6, 163.6; IR (cm^{-1}) 3162, 2926, 2852, 1575, 1390, 1324, 1159; λ_{max} 274 nm (in EtOH); HRMS (ES$^+$) *m/z* 262.1667 $[M+H]^+$ (calcd for $C_{13}H_{20}N_5O$ 262.1662).

6-(cyclohexylmethoxy)-2-iodo-7-methyl-7*H*-purine (4f)
The title compound was synthesised following **general procedure A** using 6-(cyclohexylmethoxy)-2-iodo-9-(4-methoxybenzyl)-9*H*-purine **3f** (100 mg, 0.21 mmol) and trimethyloxonium tetrafluoroborate (31 mg, 0.21 mmol). The reaction was heated for 20 min at 100 °C. The crude product was purified by MPC on silica (DCM: MeOH 90: 10) to give the product **4f** as a yellow solid (33 mg, 0.09 mmol, 45%); mp 187-189 °C; R_f 0.30 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 1.10-1.15 (2H, m, H-cyclohexyl), 1.17-1.31 (3H, m, H-cyclohexyl), 1.65-1.68 (1H, m, H-cyclohexyl), 1.72-1.74 (2H, m, H-cyclohexyl), 1.81-1.83 (3H, m, H-cyclohexyl), 3.96 (3H, s, NCH_3), 4.28 (2H, d, *J* = 6.2 Hz, OCH_2), 8.38 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 25.2, 25.9, 29.0, 33.9, 36.6, 72.2, 113.2, 117.4, 147.7, 156.0, 162.3; IR (cm^{-1}) 2927, 2851, 1536, 1415, 1332, 1123; λ_{max} 248 nm (in EtOH), HRMS (ES$^+$) *m/z* 373.0524 $[M+H]^+$ (calcd for $C_{13}H_{18}IN_4O$ 373.0520).

6-(cyclohexylmethoxy)-7-methyl-7*H*-purine-2-carbonitrile (4g)
The title compound was synthesised following **general procedure A** using 6-(cyclohexylmethoxy)-9-(4-methoxybenzyl)-9*H*-purine-2-carbonitrile **3g** (33 mg, 0.09 mmol) and trimethyloxonium tetrafluoroborate (13 mg, 0.09 mmol). The reaction was heated for 20 min at 100 °C. The crude product was purified by MPC on silica (DCM: MeOH 95: 5) to give the product **4g** as a beige solid (17 mg, 0.06 mmol, 70%); mp 168-170 °C; R_f 0.65 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 1.05-1.12 (2H, m, H-cyclohexyl), 1.14-1.30 (3H, m, H-cyclohexyl), 1.64-1.66 (1H, m, H-cyclohexyl), 1.70-1.74 (2H, m, H-cyclohexyl), 1.80-1.85 (3H, m, H-cyclohexyl), 4.03 (3H, s, NCH_3), 4.38 (2H, d, *J* = 6.2 Hz, OCH_2), 8.67 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 25.2, 25.9, 29.0, 34.1, 36.6, 72.6, 115.3, 116.6, 134.9, 149.7, 157.2, 160.4; IR (cm^{-1}) 2927, 2853, 2190, 1546, 1442, 1341, 1140; λ_{max} 250 nm (in EtOH); HRMS (ES$^+$) *m/z* 272.1511 $[M+H]^+$ (calcd for $C_{14}H_{18}N_5O$ 272.1506).

6-ethoxy-7-methyl-7*H*-purin-2-amine (4h)
The title compound was synthesised following **general procedure A** using 6-ethoxy-9-(4-methoxybenzyl)-9*H*-purin-2-amine **3h** (100 mg, 0.28 mmol) and trimethyloxonium tetrafluoroborate (41 mg, 0.28 mmol). The reaction was heated for 10 min at 100 °C. The crude product was purified by MPC on silica (DCM: MeOH 95: 5) to give the product **4h** as a colourless oil (35 mg, 0.18 mmol, 66%); R_f 0.60 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 1.38 (3H, t, *J* = 7.1 Hz, CH_3), 3.84 (3H, s, NCH_3), 4.45 (2H, q, *J* = 7.1 Hz, OCH_2), 6.09 (2H, s, NH_2), 8.00 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 14.3, 33.3, 61.5, 114.3, 130.0, 145.6, 157.0, 159.5; IR (cm^{-1}) 3347, 3081, 2895, 1568, 1385, 1290; λ_{max} 275 nm (in EtOH); HRMS (ES$^+$) *m/z* 194.1037 $[M+H]^+$ (calcd for $C_8H_{12}N_5O$ 194.1036).

6-ethoxy-2-iodo-7-methyl-7*H*-purine (4i)
The title compound was synthesised following **general procedure A** using 6-ethoxy-2-iodo-9-(4-methoxybenzyl)-9*H*-purine **3i** (100 mg, 0.24 mmol) and trimethyloxonium tetrafluoroborate (36 mg, 0.24 mmol). The reaction was heated for 10 min at 100 °C. The crude product was purified by MPC on silica (DCM: MeOH 98: 2) to give the product **4i** as a pale beige solid (55 mg, 0.19 mmol, 73%); mp 122-124 °C; R_f 0.84 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 1.41 (3H, t, J = 7.1 Hz, CH_3), 3.95 (3H, s, NCH_3), 4.53 (2H, q, J = 7.1 Hz, OCH_2), 8.38 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 14.1, 33.8, 63.5, 117.4, 147.8, 155.8, 162.3; IR (cm^{-1}) 2980, 1610, 1484, 1331, 1128; λ_{max} 266 nm (in EtOH); HRMS (ES$^+$) *m/z* 304.9899 [M+H]$^+$ (calcd for $C_8H_{10}IN_4O$ 304.9894).

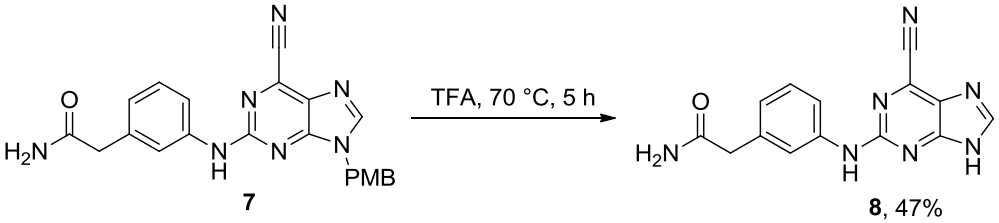
7-methyl-6-((triisopropylsilyl)ethynyl)-7*H*-purin-2-amine (4j)
The title compound was synthesised following **general procedure A** using 9-(4-methoxybenzyl)-6-((triisopropylsilyl)ethynyl)-9*H*-purin-2-amine **3j** (100 mg, 0.23 mmol) and trimethyloxonium tetrafluoroborate (34 mg, 0.23 mmol). The reaction was heated for 20 min at 100 °C. The crude product was purified by MPC on silica (DCM: MeOH 90: 10) to give the product **4j** as a yellow oil (30 mg, 0.09 mmol, 40%); R_f 0.40 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) 1.12-1.15 (21H, m, 3 x $CH(CH_3)_2$), 3.96 (3H, s, NCH_3), 6.41 (2H, s, NH_2), 8.30 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 10.6, 18.4, 32.7, 97.5, 133.1, 160.6; IR (cm^{-1}) 3311, 2943, 2865, 1562, 1295, 880; λ_{max} = 337 nm (in EtOH); HRMS (ES$^+$) *m/z* 330.2114 [M+H]$^+$ (calcd for $C_{17}H_{28}N_5Si$ 330.2108).

2-iodo-7-methyl-6-((triisopropylsilyl)ethynyl)-7*H*-purine (4k)
The title compound was synthesised following **general procedure A** using 2-iodo-9-(4-methoxybenzyl)-6-((triisopropylsilyl)ethynyl)-9*H*-purine **3k** (65 mg, 0.12 mmol) and trimethyloxonium tetrafluoroborate (18 mg, 0.12 mmol). The reaction was heated for 10 min at 100 °C. The crude product was purified by MPC on silica (DCM: MeOH 98: 2) to give the product **4k** as a colourless oil (30 mg, 0.07 mmol, 58%); R_f 0.63 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) 1.15-1.17 (21H, m, 3 x $CH(CH_3)_2$), 4.08 (3H, s, NCH_3), 8.68 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 10.5, 18.4, 33.1, 99.8, 102.0, 119.2, 125.7, 133.6, 151.9, 162.3; IR (cm^{-1}) 2943, 2864, 1590, 1470, 1388, 1350, 883; λ_{max} = 294 nm (in EtOH); HRMS (ES$^+$) *m/z* 441.0966 [M+H]$^+$ (calcd for $C_{17}H_{26}IN_4Si$ 441.0966).

2-fluoro-7-methyl-6-((triisopropylsilyl)ethynyl)-7*H*-purine (4l)
The title compound was synthesised following **general procedure A** using 2-fluoro-9-(4-methoxybenzyl)-6-((triisopropylsilyl)ethynyl)-9*H*-purine **3l** (110 mg, 0.25 mmol) and trimethyloxonium tetrafluoroborate (37 mg, 0.25 mmol). The reaction was heated for 10 min at 100 °C. The crude product was purified by MPC on silica (Petrol: EtOAc 90: 10) to give the product **4l** as a yellow solid (35 mg, 0.10 mmol, 42 %); mp 97-99 °C; R_f 0.18 (Petrol: EtOAc 60: 40); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 1.13-1.18 (21H, m, 3 x $CH(CH_3)_2$), 4.11 (3H, s, NCH_3), 8.79 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 10.6, 18.3, 33.2, 99.9, 102.4, 124.7 (J = 4 Hz), 133.8 (J = 18 Hz), 153.4, 157.0 (J = 207 Hz), 164.0; ^{19}F NMR (470 MHz, DMSO-d_6) ppm -52.58; IR (cm^{-1}) 2940, 2870, 1560, 1460, 1430, 1295; λ_{max} 310 nm (in EtOH); HRMS (ES+) *m/z* 333.1911 [M+H]$^+$ (calcd for $C_{17}H_{26}FN_4Si$ 333.1905).
It was also synthesised following **general procedure B** using 2-fluoro-9-(tetrahydro-2*H*-pyran-2-yl)-6-((triisopropylsilyl)ethynyl)-9*H*-purine **5b** (150 mg, 0.37 mmol) and trimethyloxonium tetrafluoroborate (55 mg, 0.37 mmol). The crude product was purified by MPC on silica (DCM: MeOH 95: 5) to give the product **14** as a yellow solid (51 mg, 0.15 mmol, 41%).

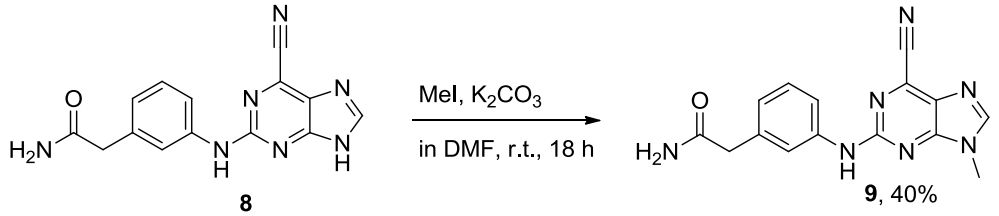
2-fluoro-7-methyl-7*H*-purine (6a)
The title compound was synthesised following **general procedure B** using 2-fluoro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **5a** (100 mg, 0.67 mmol) and trimethyloxonium tetrafluoroborate (80 mg, 0.45 mmol). The crude product was purified by MPC on silica (DCM: MeOH 98: 2) to give the product **6a** as a colourless oil (39 mg, 0.26 mmol, 57%); R_f 0.41 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) 3.81 (3H, s, NCH_3), 8.59 (1H, s, H-8), 9.05 (1H, s, H-6); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 33.2, 143.5 (J = 16 Hz), 148.7 (J = 3 Hz), 150.0 (J = 16 Hz), 152.1, 158.0 (J = 206 Hz); ^{19}F NMR (470 MHz, DMSO-d_6) ppm -53.1; IR (cm^{-1}) 3091, 2945, 1606, 1399, 793; λ_{max} 267 nm (in EtOH); HRMS (ES$^+$) *m/z* 153.0568 [M+H]$^+$ (calcd for $C_6H_6FN_4$ 153.0571).

Synthesis of compound 8



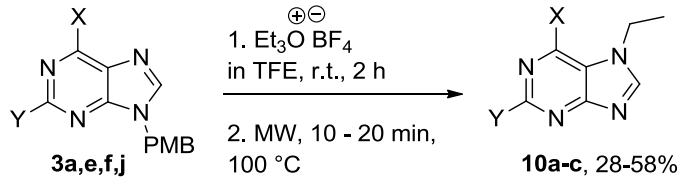
2-(3-((6-Cyano-9-(4-methoxybenzyl)-9*H*-purin-2-yl)amino)phenyl)acetamide **7** (110mg, 0.27 mmol) was solubilised in TFA (5 mL). The resulting solution was heated at 70 °C for 5 h. The solvent was then removed *in vacuo*. The product was purified by MPC on silica (DCM: MeOH 95: 5) to give **2-(3-((6-cyano-9*H*-purin-2-yl)amino)phenyl)acetamide (8)** as a yellow oil (30 mg, 0.10 mmol, 47%); R_f 0.28 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 3.36 (2H, s, CH_2), 6.89 (1H, bs, $CONH_2$), 6.91 (1H, d, *J* = 7.8 Hz, Ar-H), 7.24 (1H, dd, *J1* = 7.8 Hz, *J2* = 7.8 Hz, Ar-H), 7.45 (1H, bs, $CONH_2$), 7.52 (1H, s, Ar-H), 7.71 (1H, d, *J* = 7.8 Hz, Ar-H), 8.48 (1H, s, H-8), 9.90 (1H, s, NH), 13.51 (1H, bs, NH); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 42.4, 114.6, 117.0, 119.8, 122.7, 126.7,128.3, 136.8, 140.0, 146.6, 150.1, 156.3, 172.1; IR (cm^{-1}) 3430, 3122, 2340, 1664, 1600, 1590, 1510, 1447, 710; λ_{max} 254 nm (in EtOH); HRMS (ES$^+$) *m/z* 294.1103 $[M+H]^+$ (calcd for $C_{14}H_{12}N_7O$ 294.1098).

Synthesis of compound 9



2-(3-((6-Cyano-9*H*-purin-2-yl)amino)phenyl)acetamide **8** (106 mg, 0.36 mmol) and potassium carbonate (60 mg, 0.43 mmol) were suspended in anhydrous DMF (10 mL). Then methyl iodide (0.027 mL, 0.43 mmol) was added and the resulting solution was stirred at room temperature overnight. The solvent was removed *in vacuo*. The crude product was purified by MPC on silica (DCM: MeOH 95: 5) to give **2-(3-((6-cyano-9-methyl-9*H*-purin-2-yl)amino)phenyl)acetamide (9)** as a yellow solid (44 mg, 0.14 mmol, 40%); mp 207-209 °C; R_f 0.55 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 3.37 (2H, s, CH_2), 3.79 (3H, s, NCH_3), 6.90 (1H, bs, $CONH_2$), 6.91 (1H, d, *J* = 7.8 Hz, Ar-H), 7.25 (1H, dd, *J1* = 7.8 Hz, *J2* = 7.8 Hz, Ar-H), 7.47 (1H, bs, $CONH_2$), 7.62 (1H, d, *J* = 7.8 Hz, Ar-H), 7.78 (1H, s, Ar-H), 8.48 (1H, s, H-8), 10.07 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 29.6, 42.5, 114.3, 117.0, 119.4, 122.8, 128.3, 129.1, 136.9, 139.9, 148.2, 154.8, 156.2, 164.5, 172.1; IR (cm^{-1}) 3430, 3122, 2340, 1664, 1600, 1590, 1510, 1447, 710; λ_{max} 266 nm (in EtOH); HRMS (ES$^+$) *m/z* 308.1260 $[M+H]^+$ (calcd for $C_{15}H_{14}N_7O$ 308.1254).

General procedure C for selective N-7 ethylation of 9-(4-methoxybenzyl)-purines



The 9*H*-purine-6-carbonitrile (90 mg, 0.30 mmol) and triethyloxonium tetrafluoroborate (69 mg, 0.36 mmol) were solubilised in TFE (3 mL). The resulting solution was stirred at room temperature for 2 h. The reaction was purged with nitrogen, sealed and subjected to microwave heating at 100 °C. The solvent was removed in vacuo and the crude product was purified as indicated.

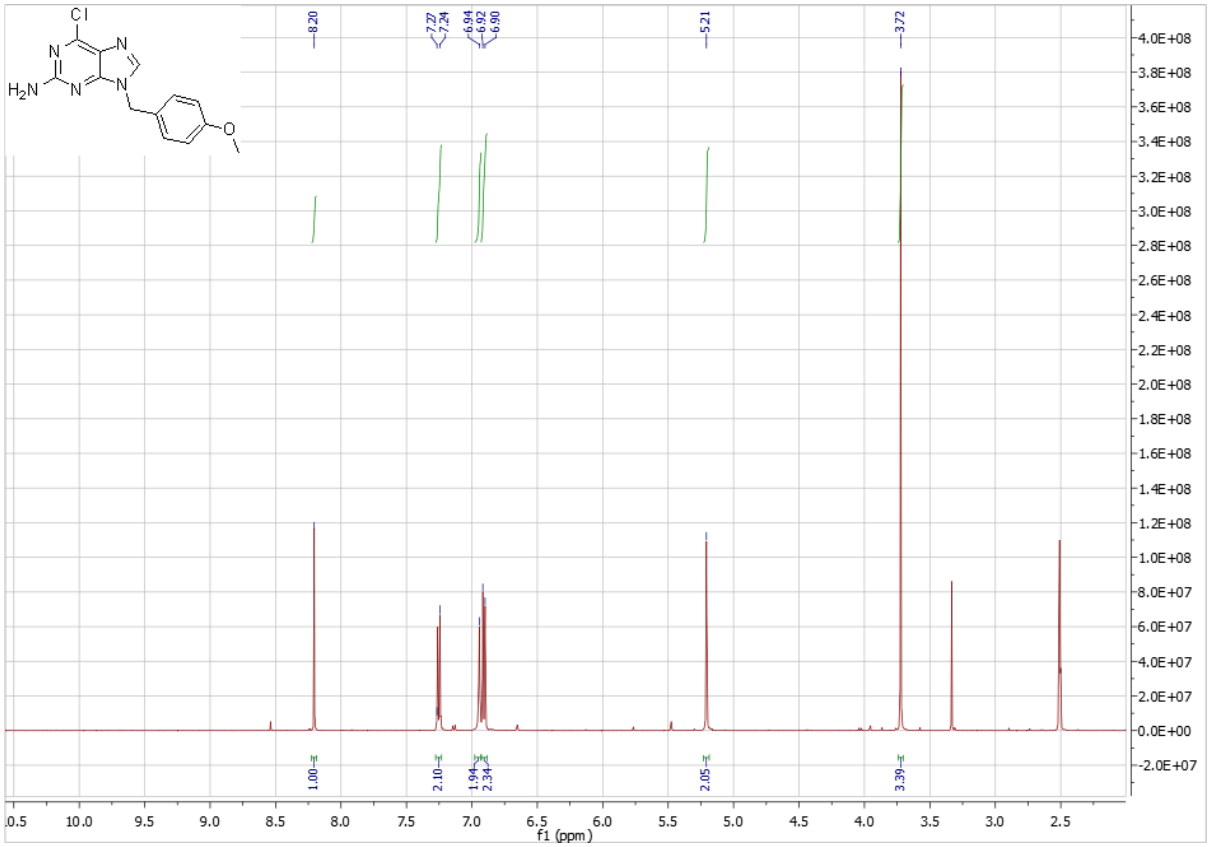
2-amino-7-ethyl-7*H*-purine-6-carbonitrile (10a)

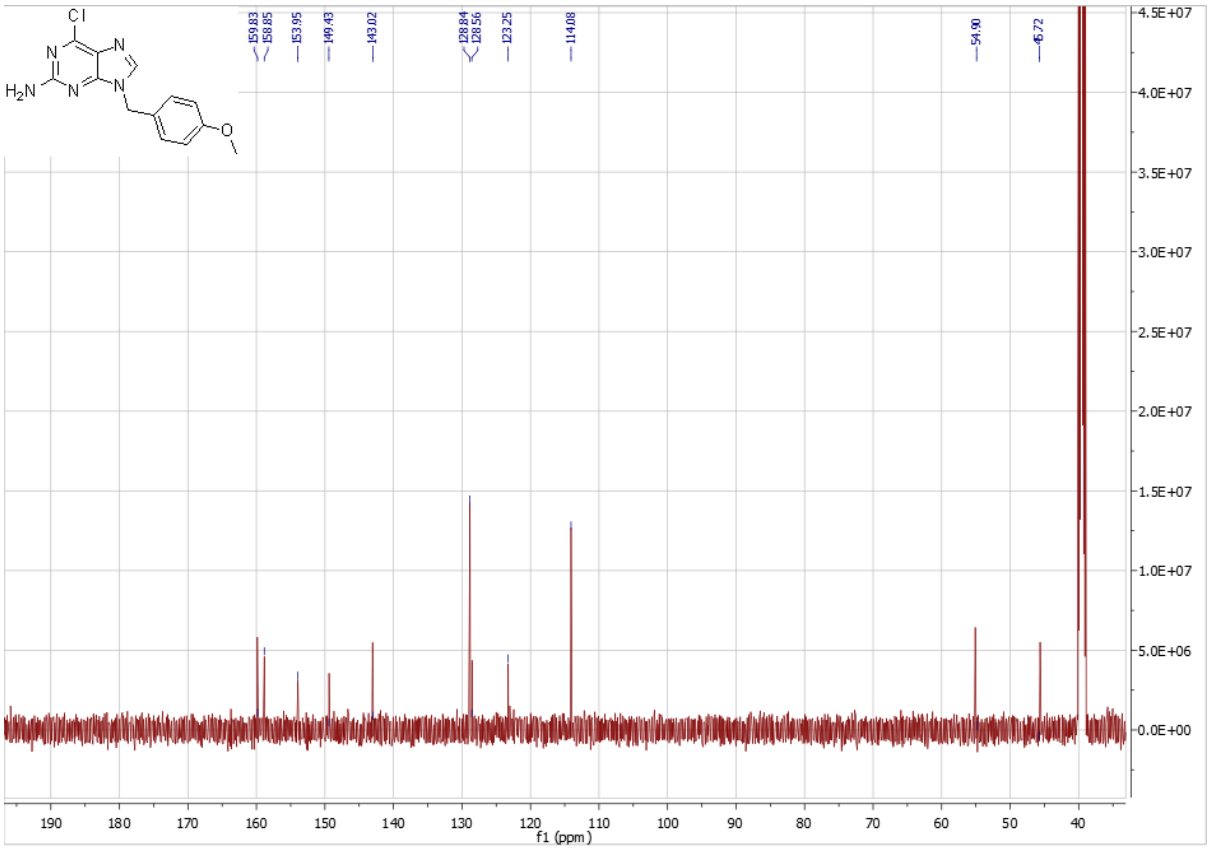
The title compound was synthesised following **general procedure C** using 2-amino-9-(4-methoxybenzyl)-9*H*-purine-6-carbonitrile **3a** (220 mg, 0.79 mmol) and trimethyloxonium

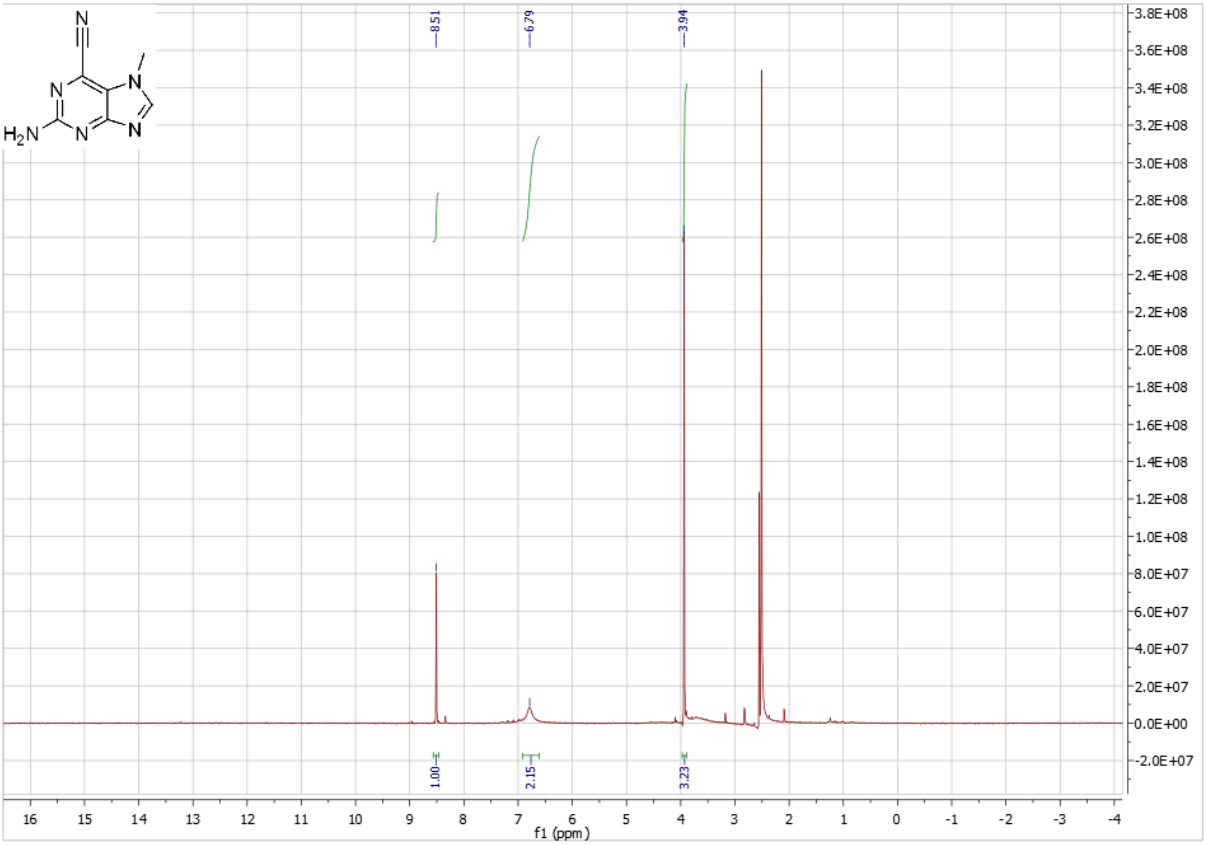
tetrafluoroborate (150 mg, 0.79 mmol). The reaction was heated for 10 min at 100 °C. The crude product was purified by MPC on silica (DCM: MeOH 95: 5) to give the product **10a** as a pale yellow solid (41 mg, 0.22 mmol, 28%); mp 271-273 °C; R_f 0.43 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 1.47 (3H, t, J = 7.3 Hz, CH_3), 4.34 (2H, q, J = 7.3 Hz, OCH_2), 6.80 (2H, s, NH_2), 8.59 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 15.7, 40.7, 114.5, 119.0, 122.7, 151.0, 160.5, 164.9; IR (cm^{-1}) 3416, 3190, 2360, 1640, 1567, 1502, 1302; λ_{max} 370 nm (in EtOH); HRMS (ES$^+$) *m/z* 189.0880 $[M+H]^+$ (calcd for $C_8H_9N_6$ 188.0883).

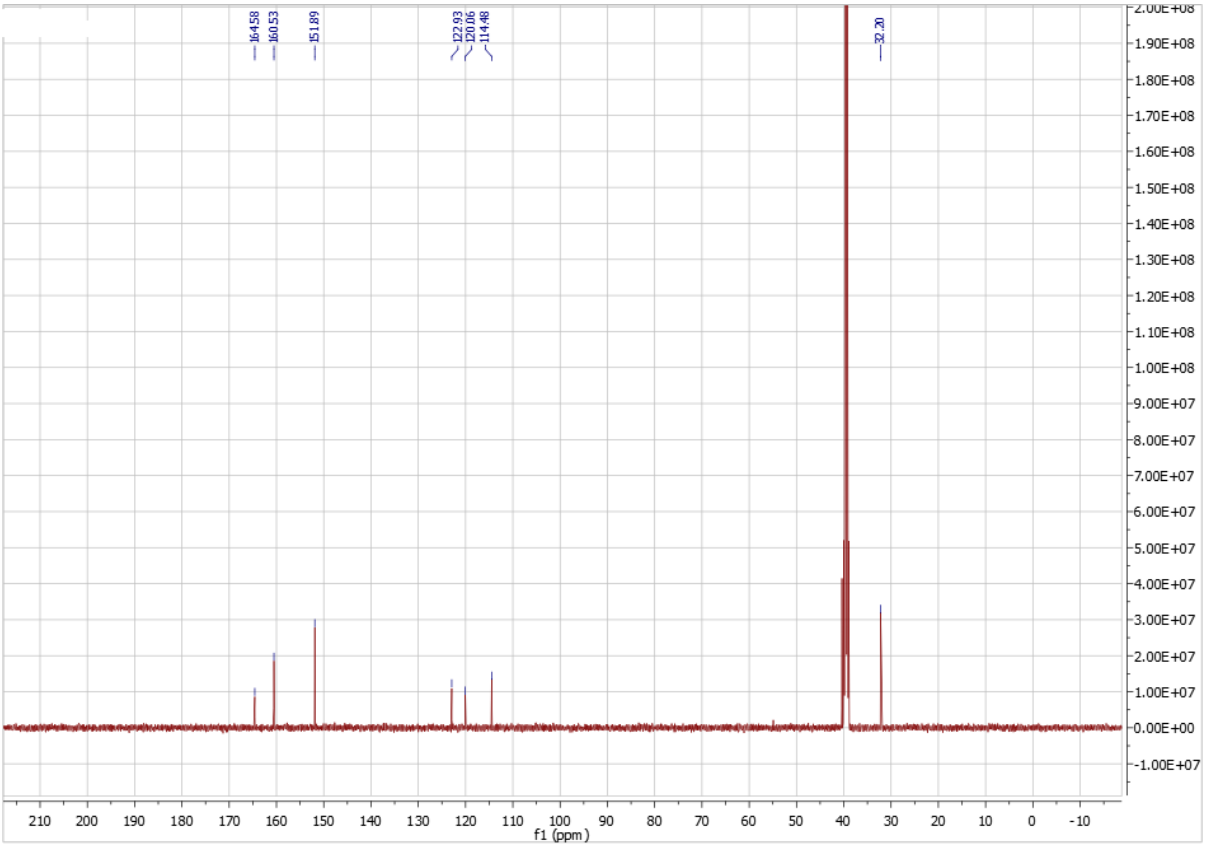
6-(cyclohexylmethoxy)-7-ethyl-7*H*-purin-2-amine (10b)
The title compound was synthesised following **general procedure C** using 6-(cyclohexylmethoxy)-9-(4-methoxybenzyl)-9*H*-purin-2-amine **3e** (150 mg, 0.41 mmol) and trimethyloxonium tetrafluoroborate (78 mg, 0.41 mmol). The reaction was heated for 10 min at 100 °C. The crude product was purified by MPC on silica (DCM: MeOH 90: 10) to give the product **10b** as a pale yellow solid (45 mg, 0.16 mmol, 40%); mp 73-75 °C; R_f 0.45 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) ppm 1.03-1.11 (2H, m, H-cyclohexyl), 1.16-1.31 (3H, m, H-cyclohexyl), 1.38 (3H, t, J = 7.2 Hz, CH_3), 1.66-1.68 (1H, m, H-cyclohexyl), 1.72-1.75 (2H, m, H-cyclohexyl), 1.80-1.82 (3H, m, H-cyclohexyl), 4.20-4.24 (4H, m, OCH_2, OCH_2), 6.13 (2H, s, NH_2), 8.09 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 16.6, 25.3, 26.0, 29.2, 36.8, 41.8, 70.7, 105.2, 144.7, 156.8, 159.5, 163.5; IR (cm^{-1}) 3101, 2925, 2863, 1577, 1358, 1017; λ_{max} 258 nm (in EtOH); HRMS (ES$^+$) *m/z* 276.1820 $[M+H]^+$ (calcd for $C_{14}H_{22}N_5O$ 276.1819).

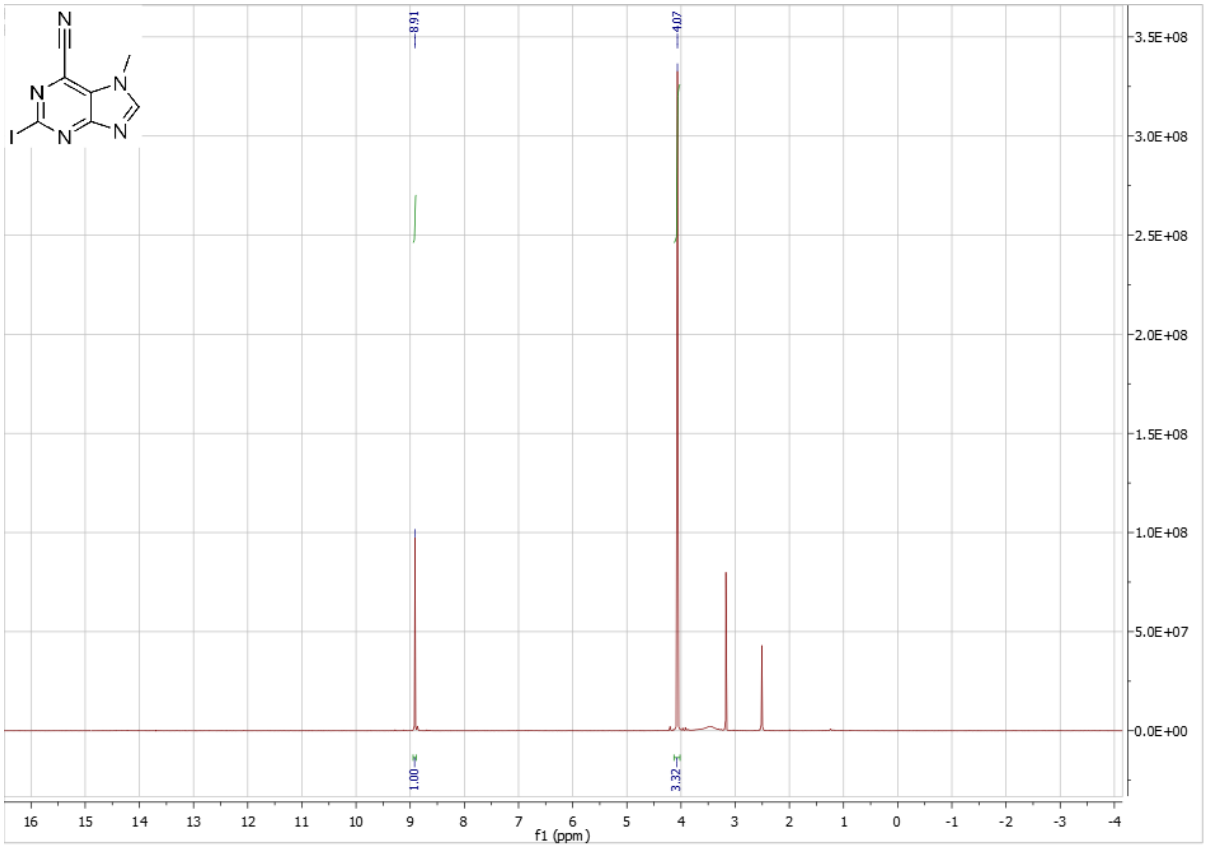
6-ethoxy-7-ethyl-7*H*-purin-2-amine (10c)
The title compound was synthesised following **general procedure C** using 6-ethoxy-9-(4-methoxybenzyl)-9*H*-purin-2-amine **3h** (90 mg, 0.30 mmol) and trimethyloxonium tetrafluoroborate (57 mg, 0.30 mmol). The reaction was heated for 10 min at 100 °C. The crude product was purified by MPC on silica (DCM: MeOH 90: 10) to give the product **10c** as a pale yellow solid (36 mg, 0.17 mmol, 58%); mp 158-160 °C; R_f 0.43 (DCM: MeOH 90: 10); ^{1}H NMR (500 MHz, DMSO-d_6) 1.36-1.39 (6H, m, 2 x CH_3), 4.20 (2H, q, J = 7.2 Hz, OCH_2), 4.46 (2H, q, J = 7.1 Hz, OCH_2), 6.18 (2H, s, NH_2), 8.11 (1H, s, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 14.4, 16.4, 41.7, 61.7, 105.6, 144.7, 156.7, 159.4, 163.2; IR (cm^{-1}) 3451, 3178, 2828, 1569, 1382, 1255; λ_{max} 258 nm (in EtOH); HRMS (ES$^+$) *m/z* 208.1191 $[M+H]^+$ (calcd for $C_9H_{14}N_5O$ 208.1193).

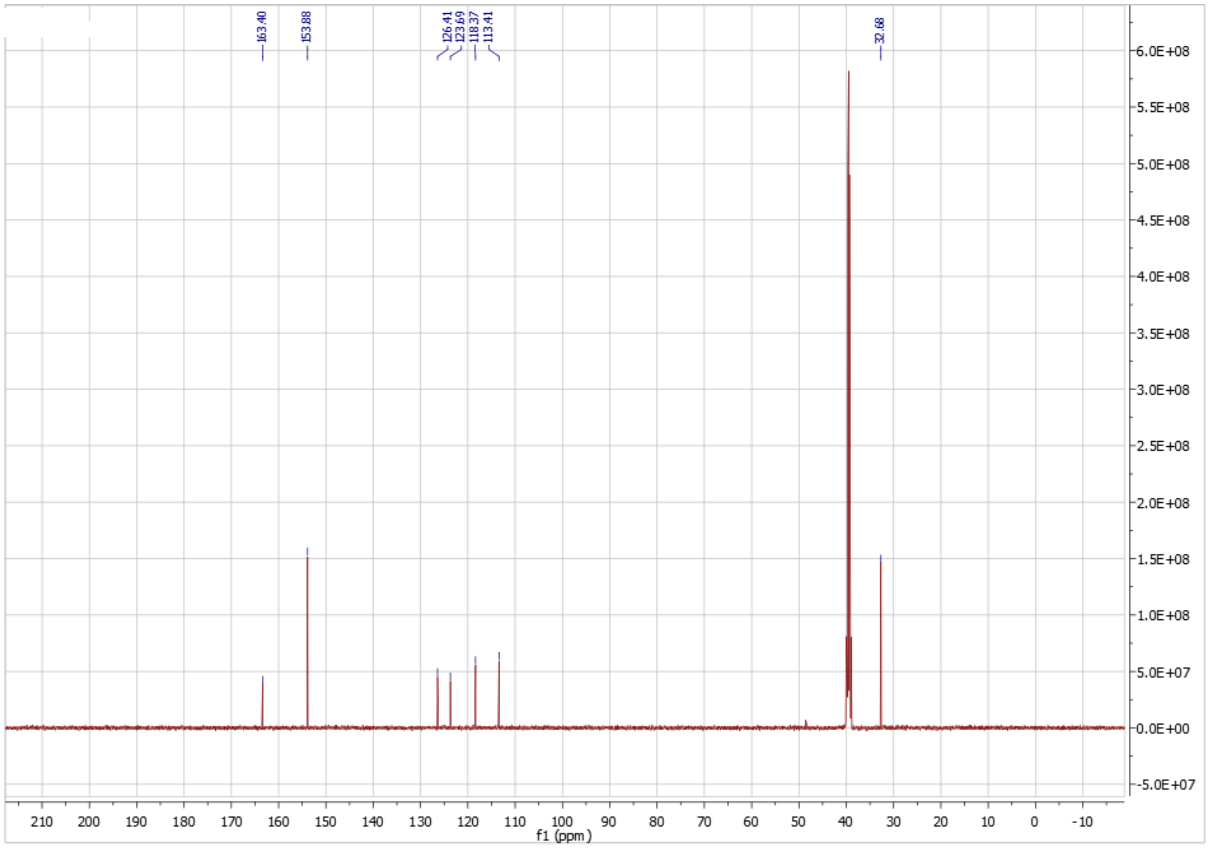


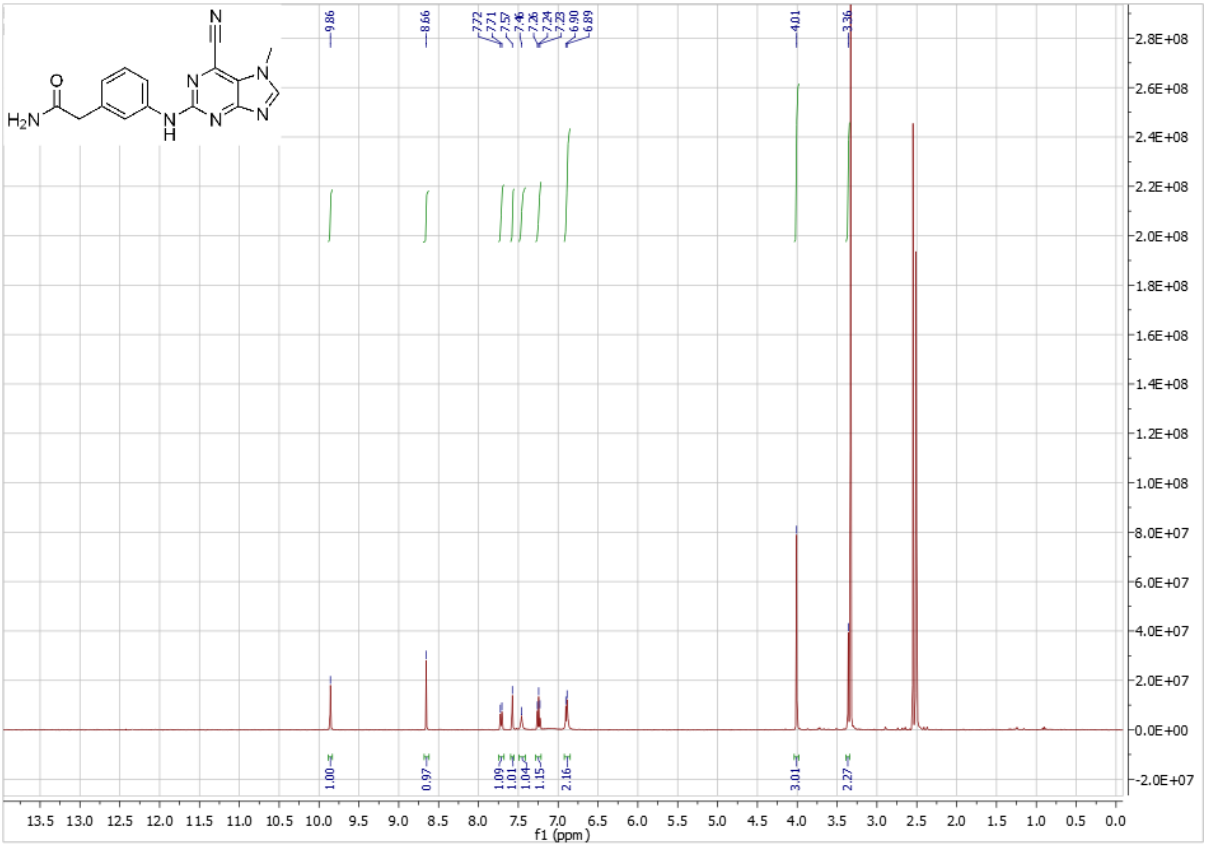


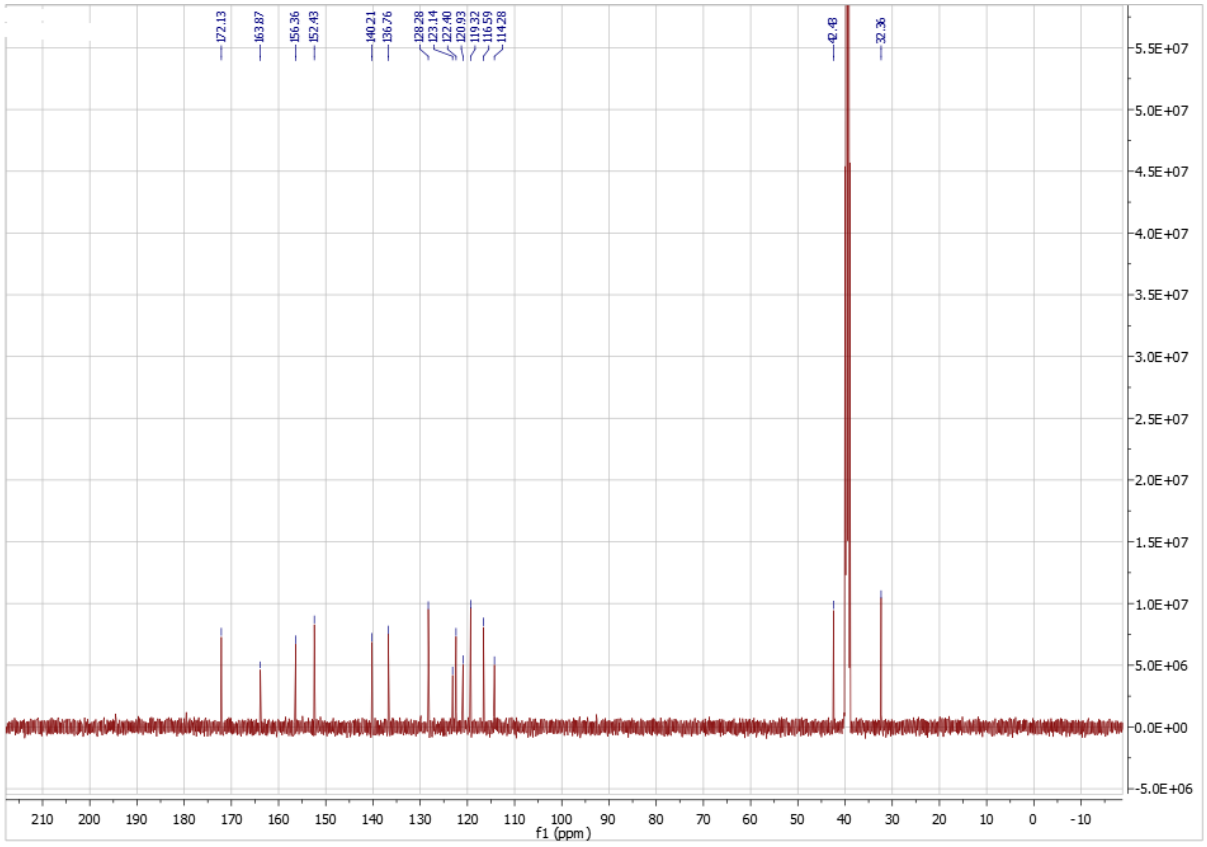


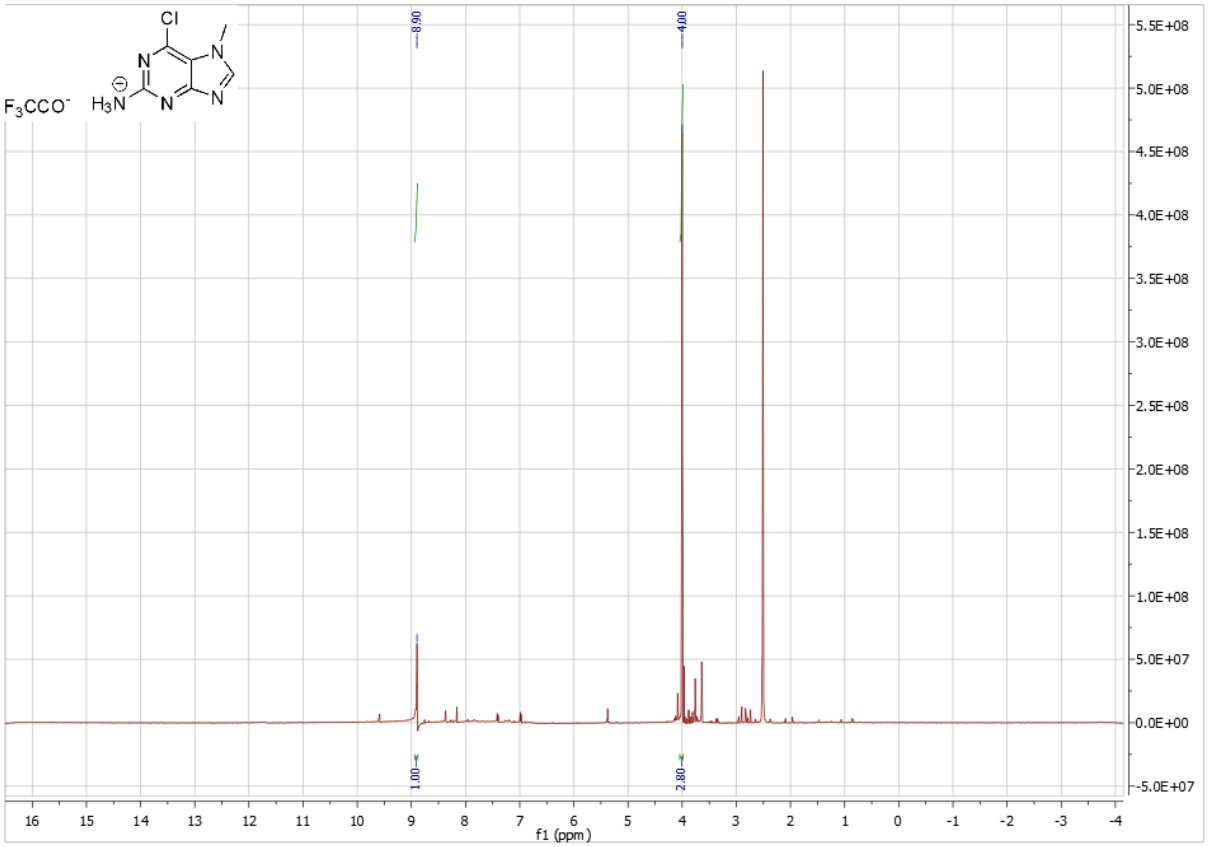


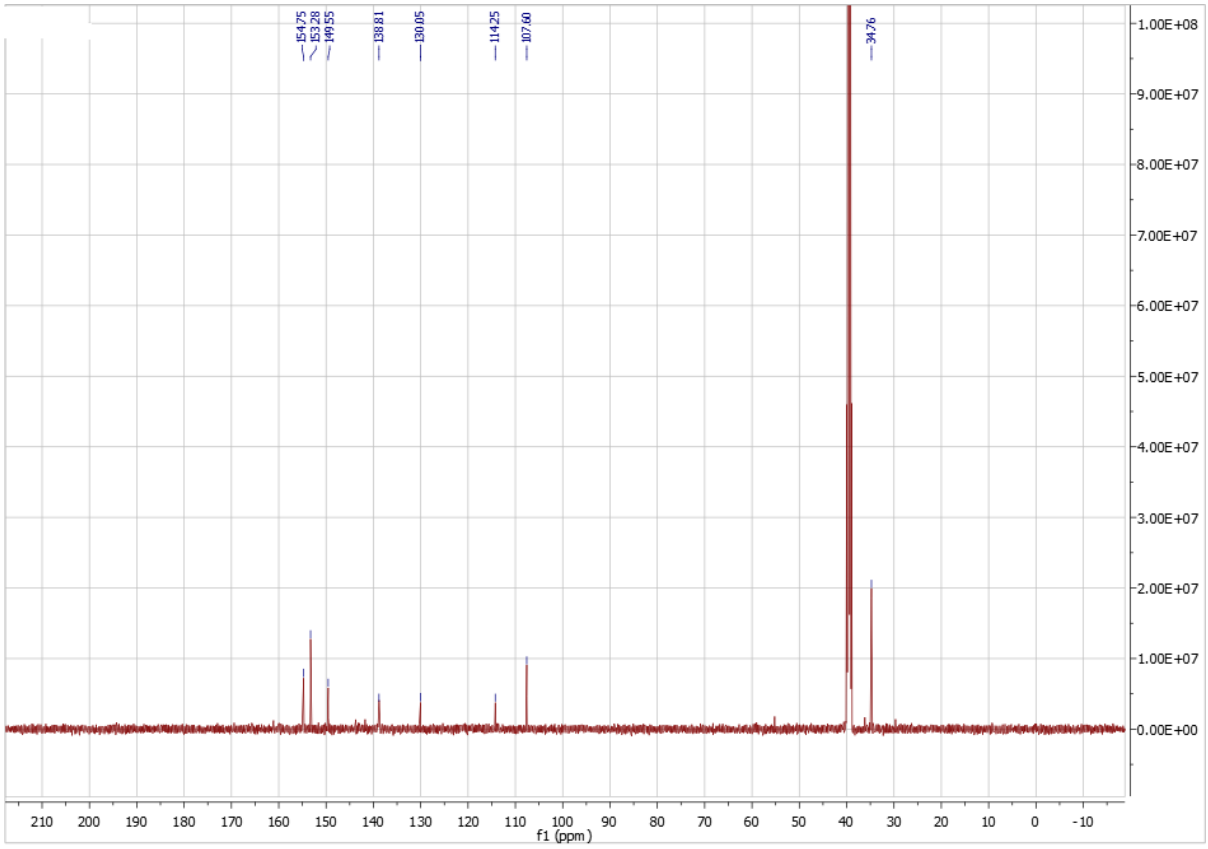


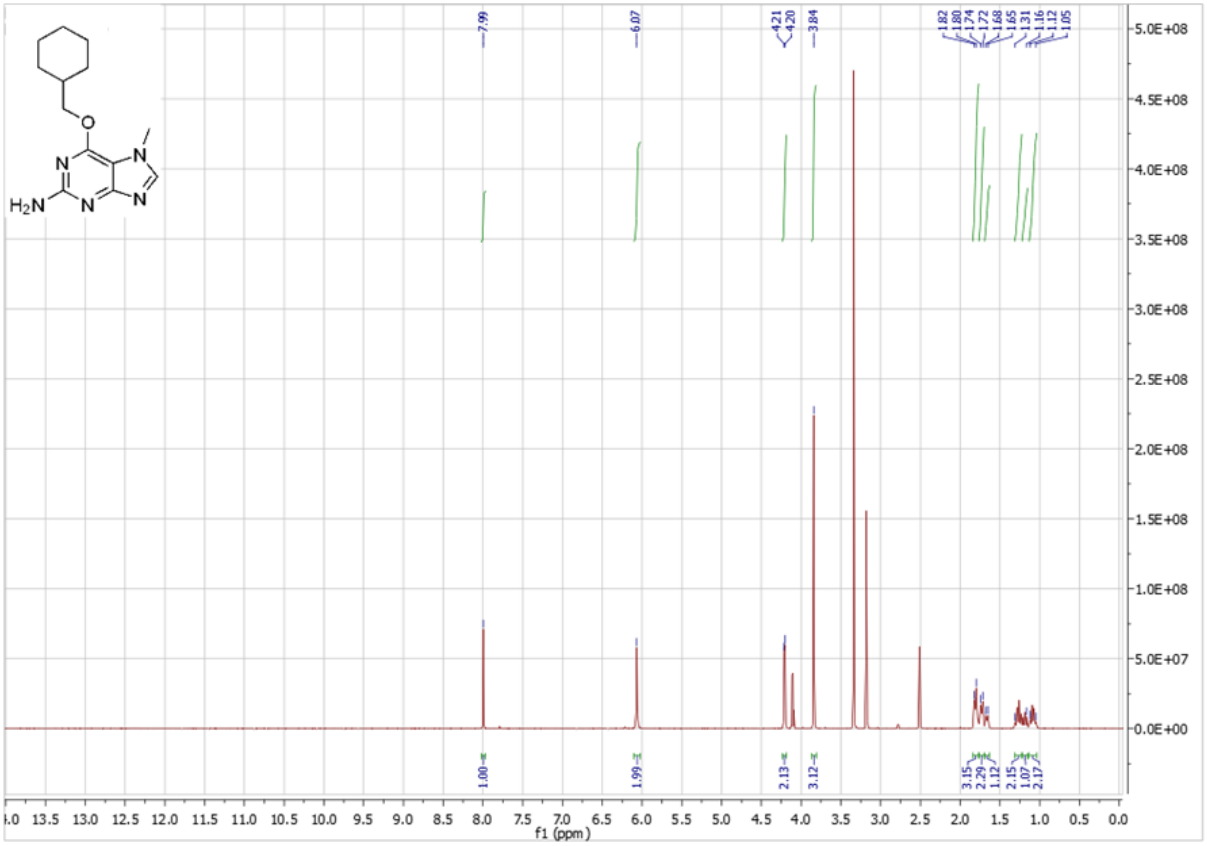


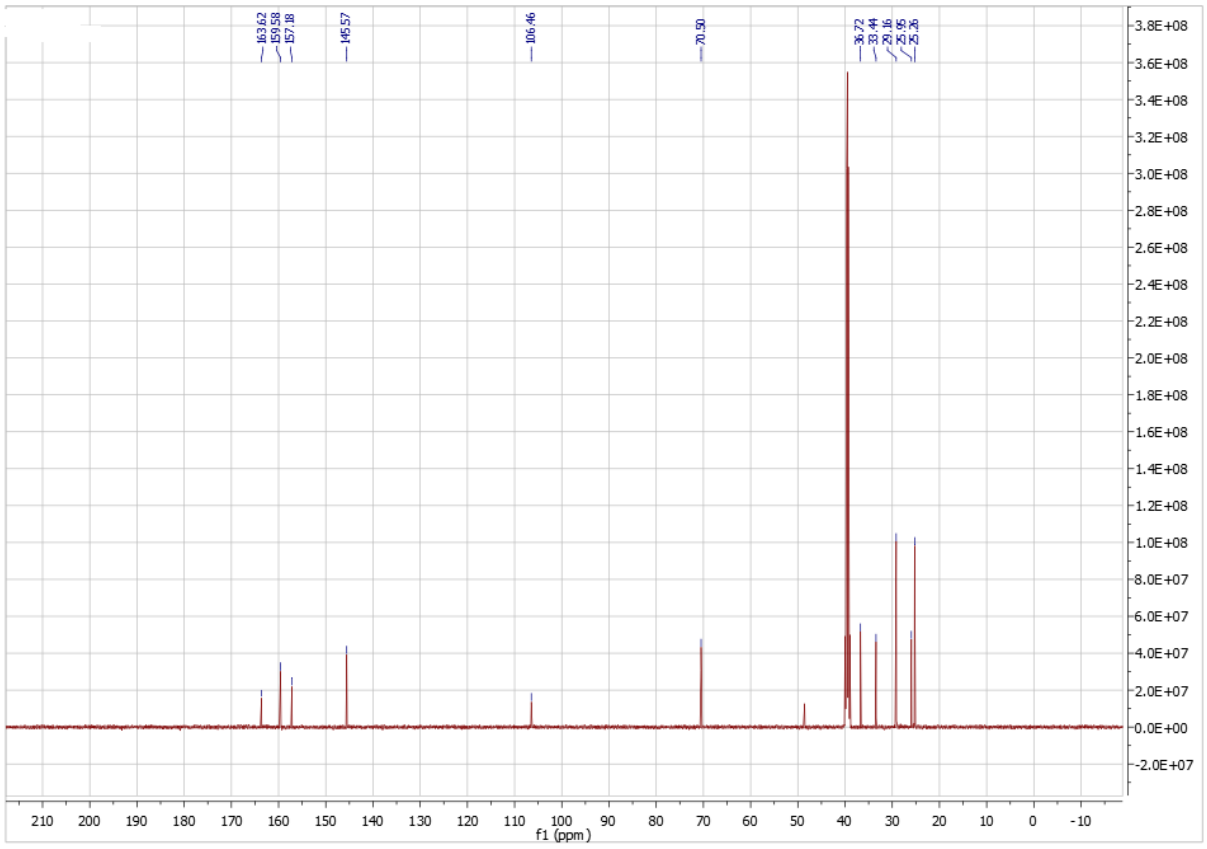


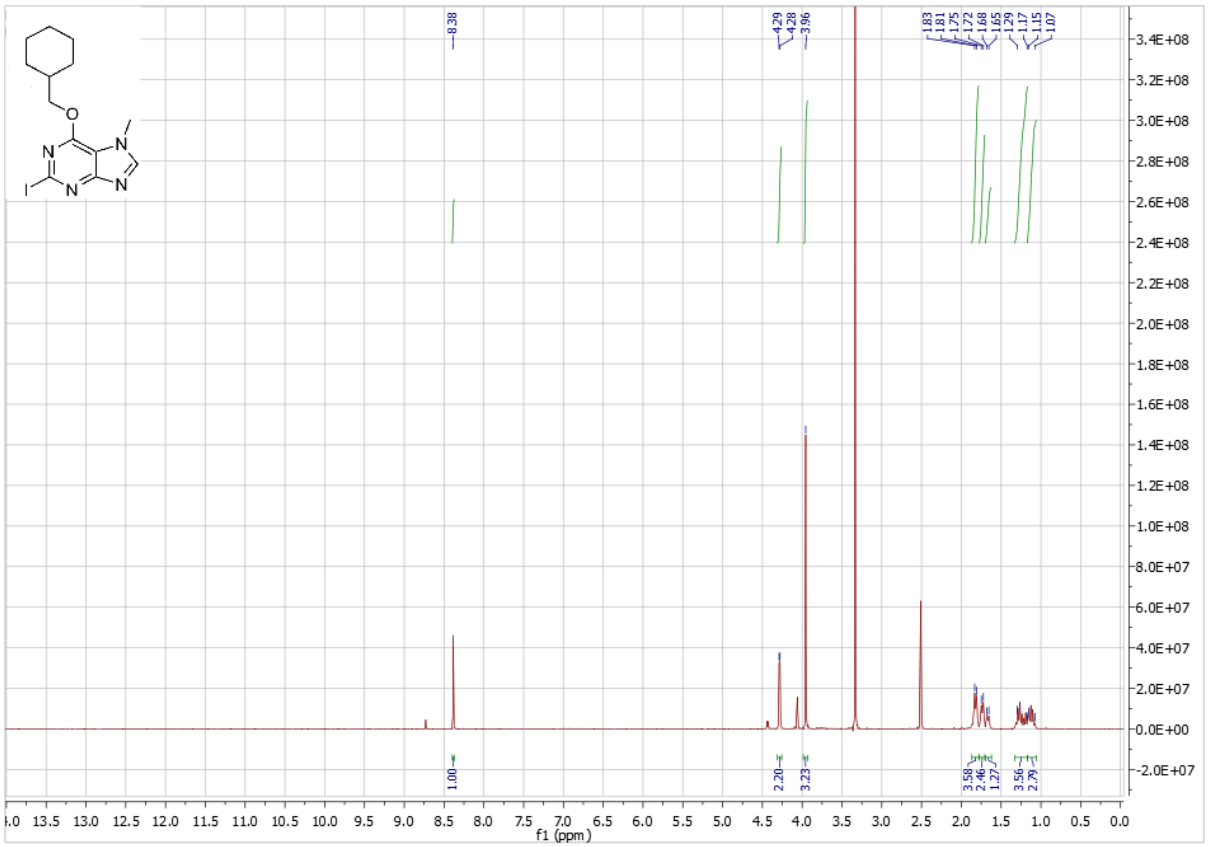


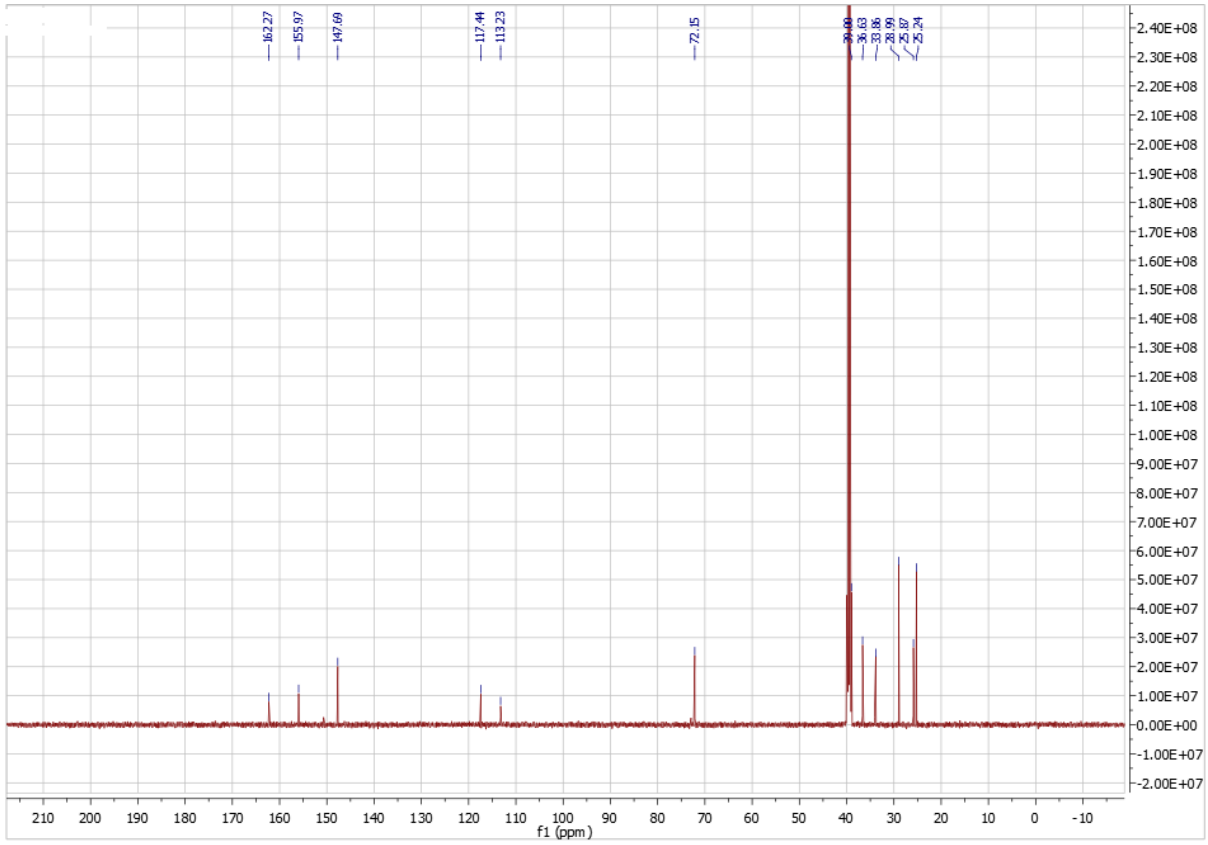


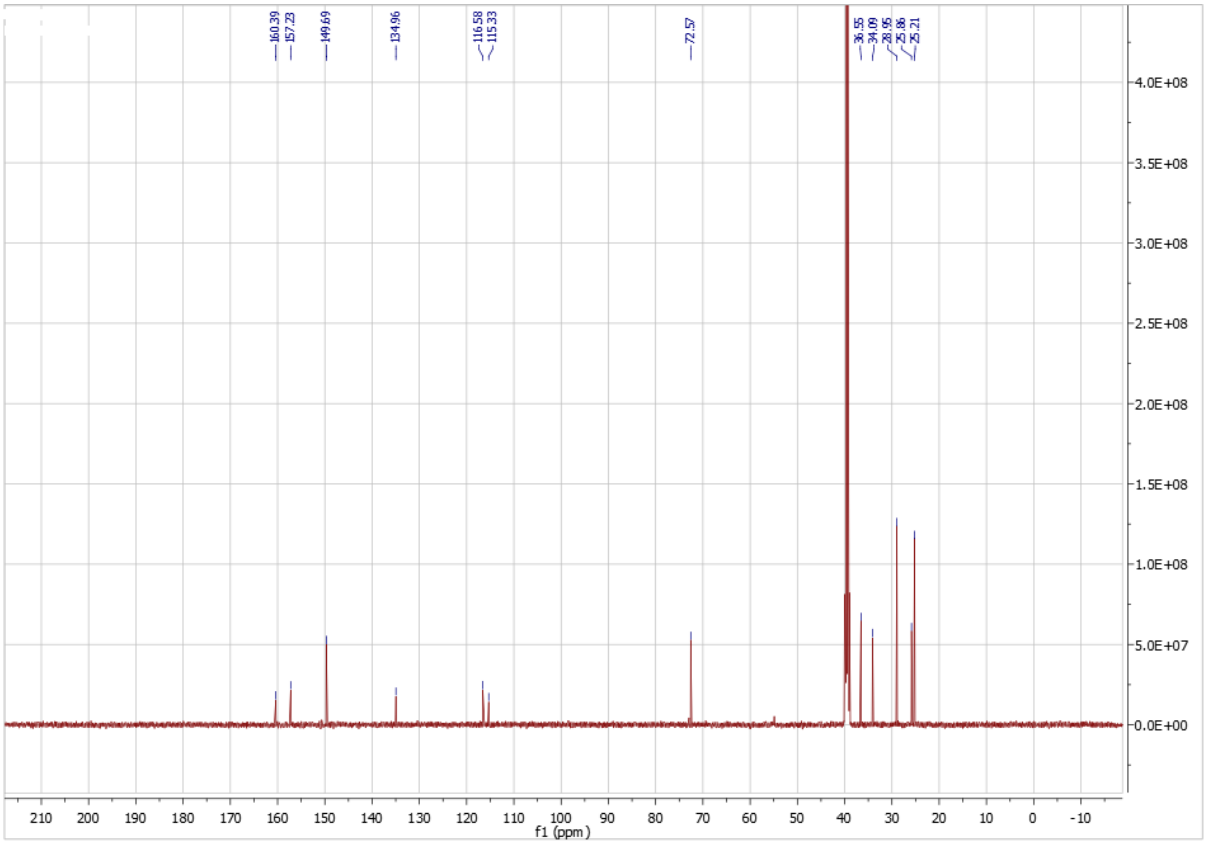


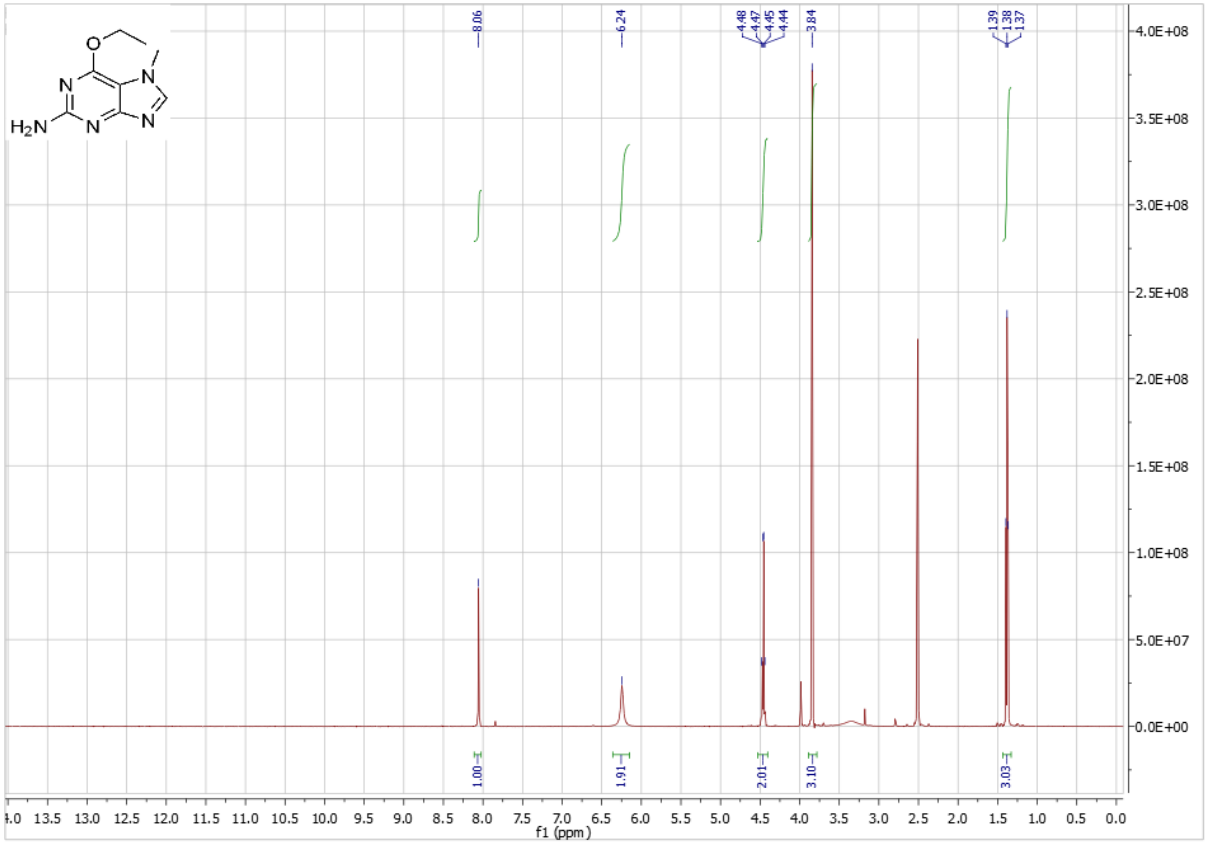


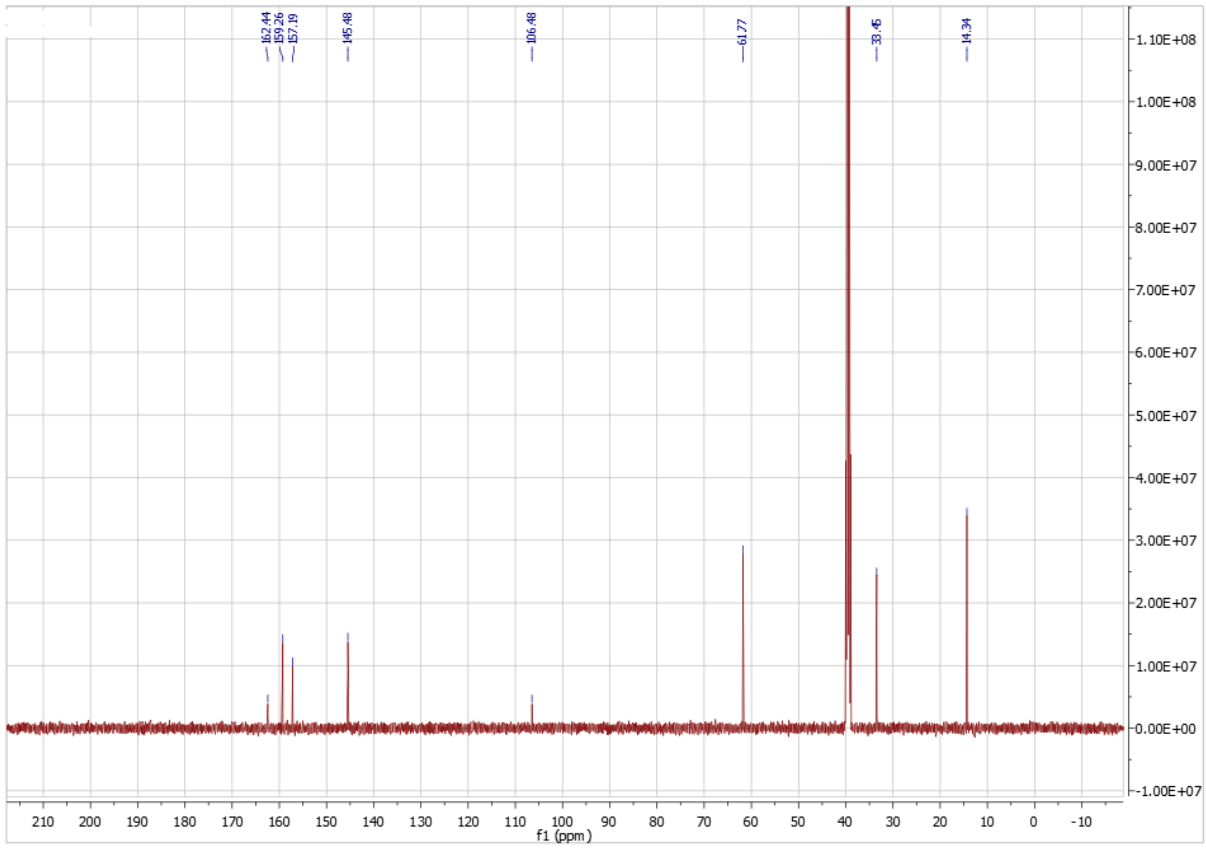


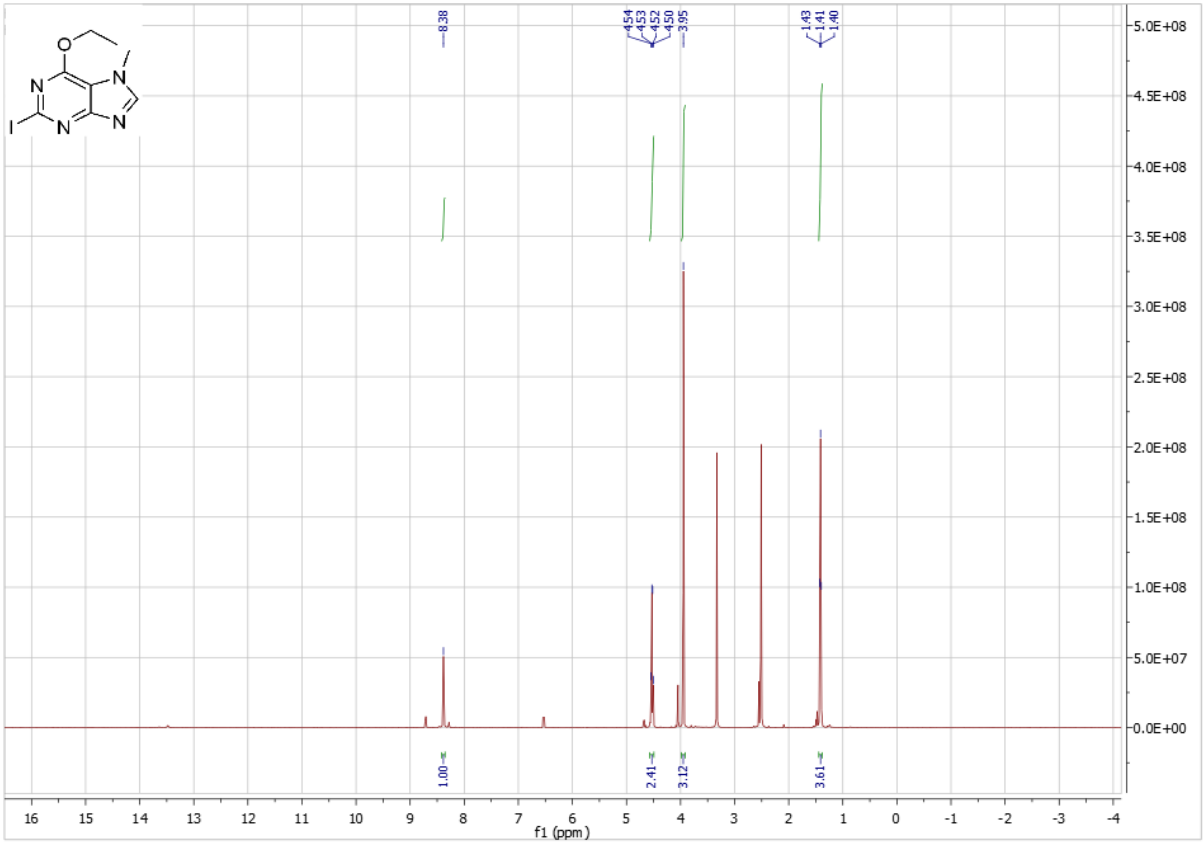


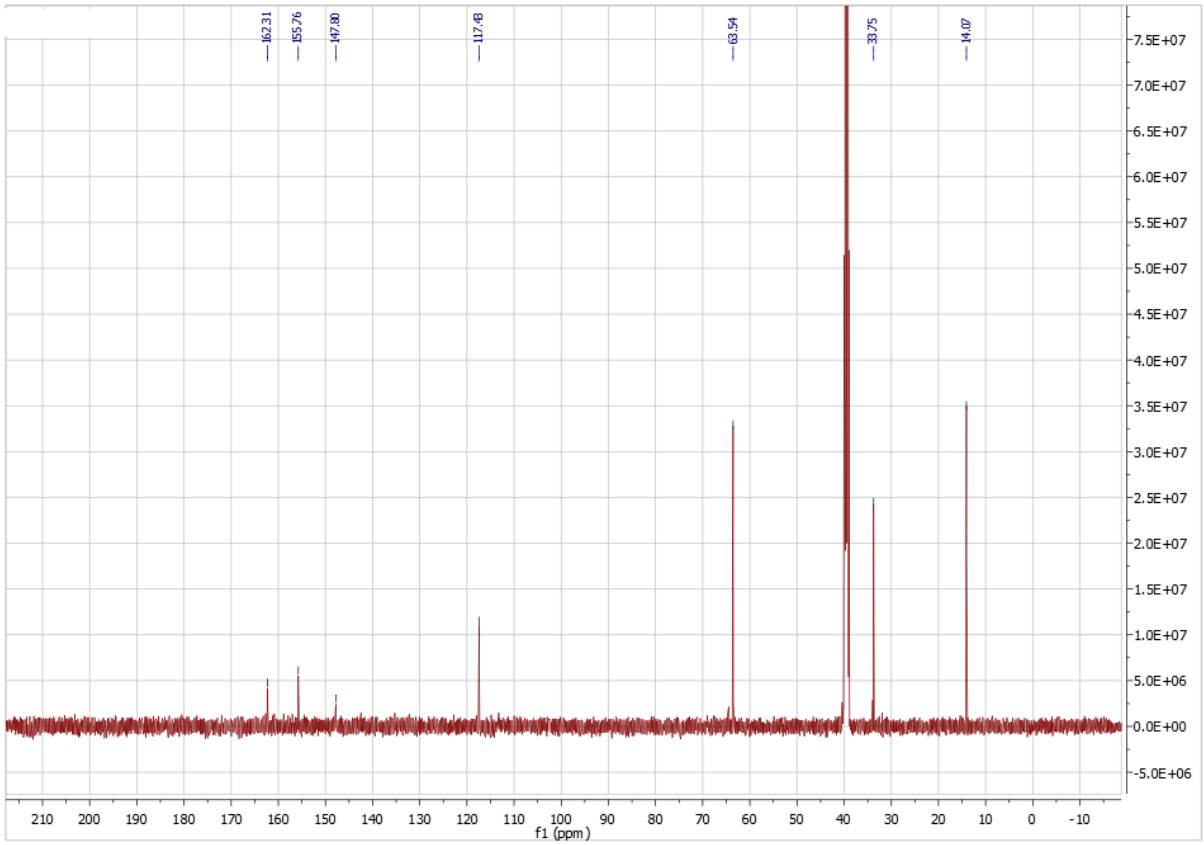




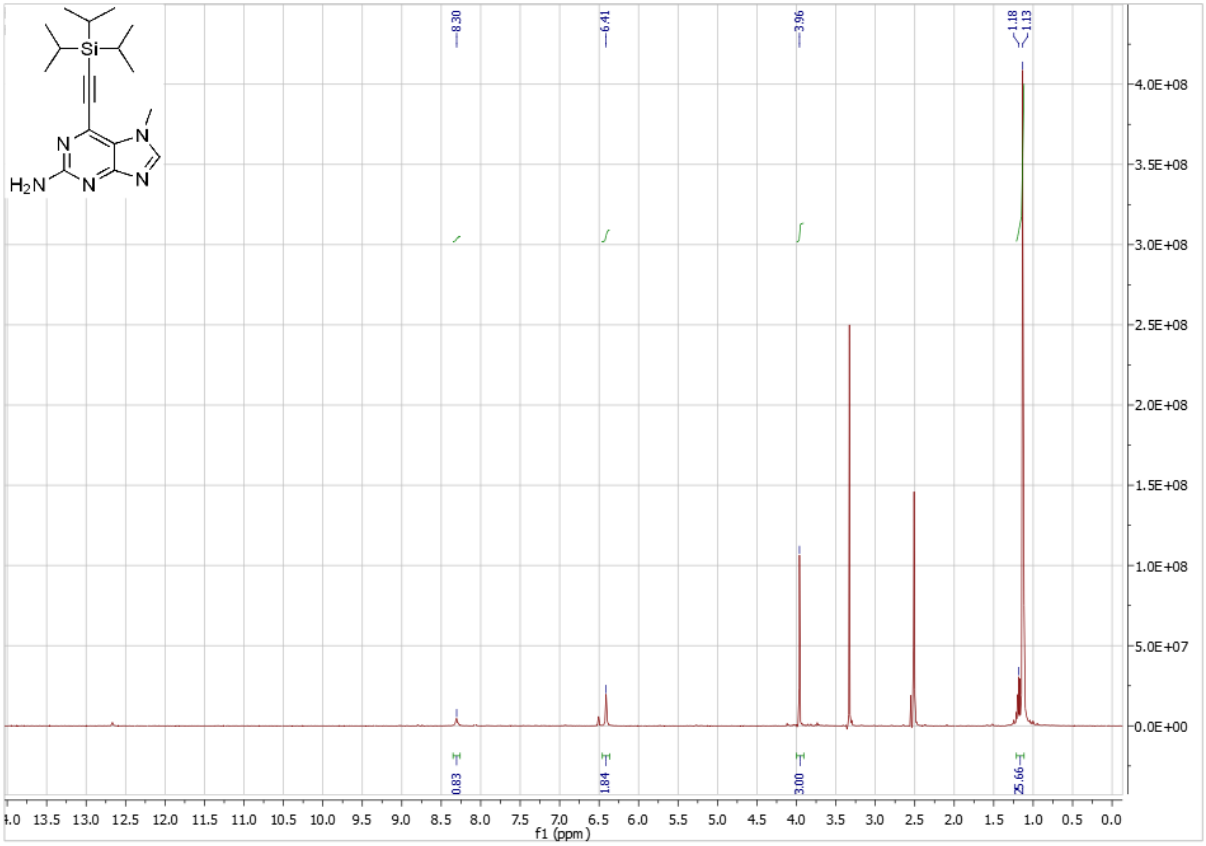


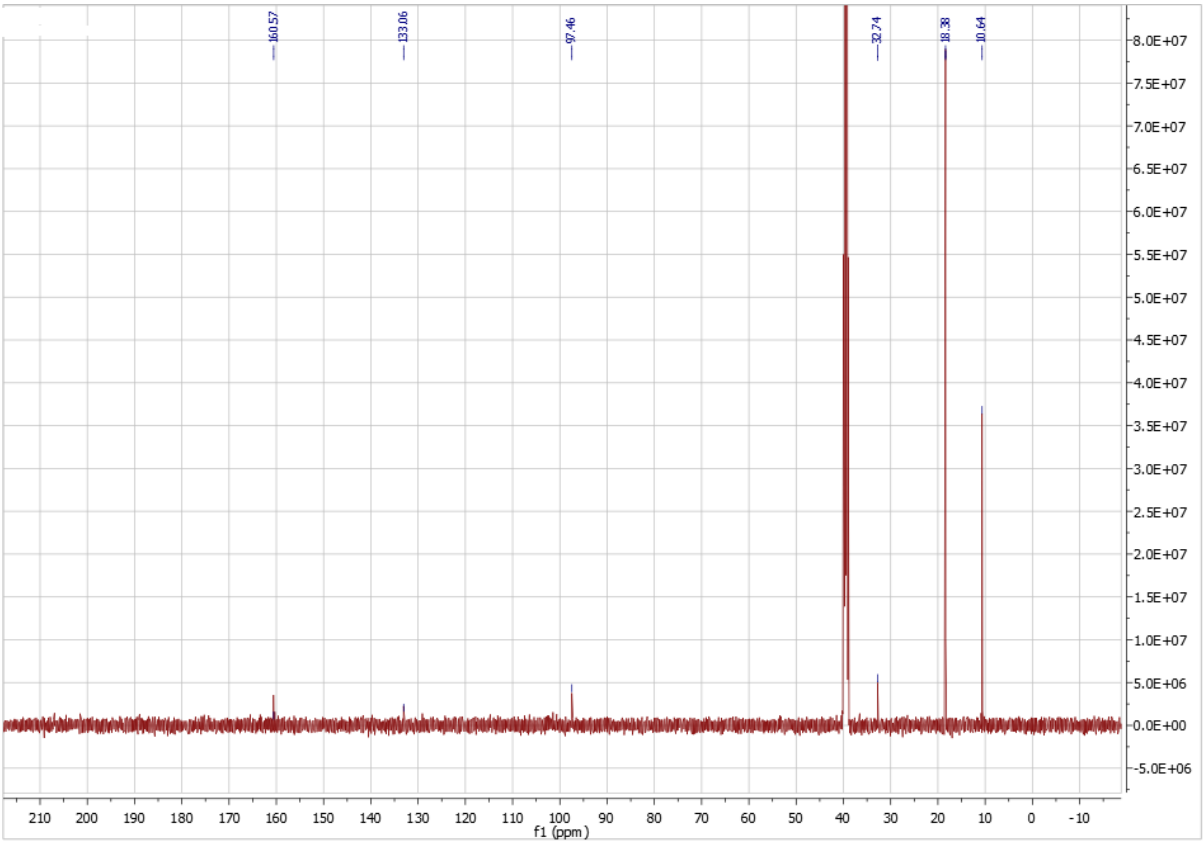






Not every tertiary carbons of the purine scaffold are visible.





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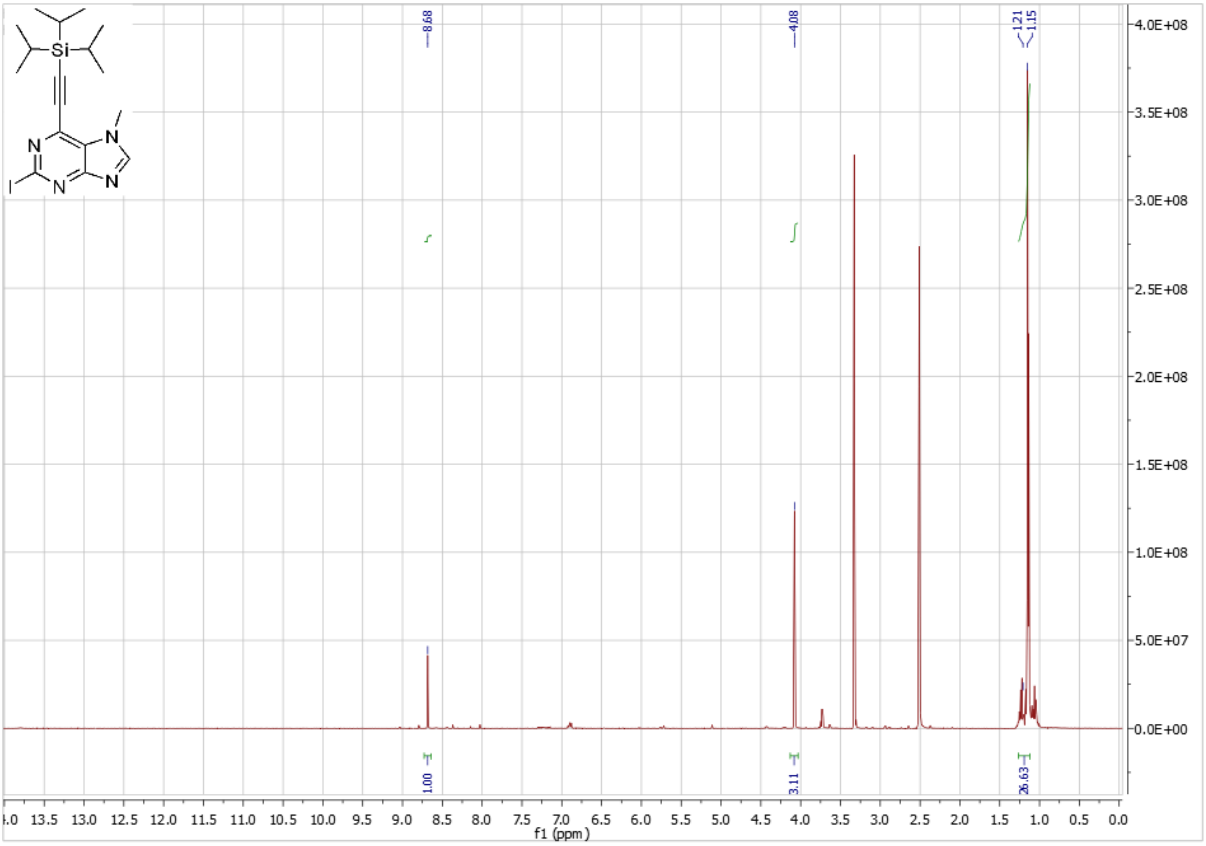

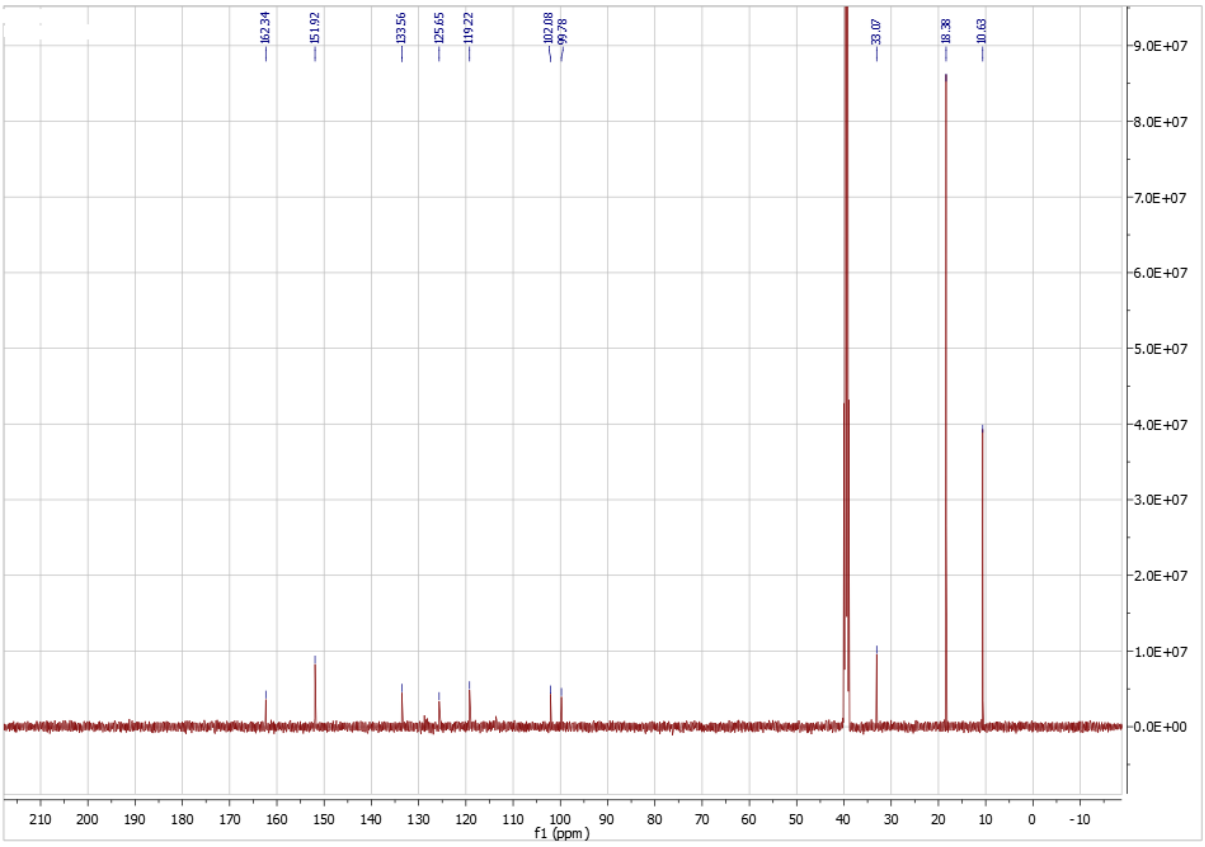

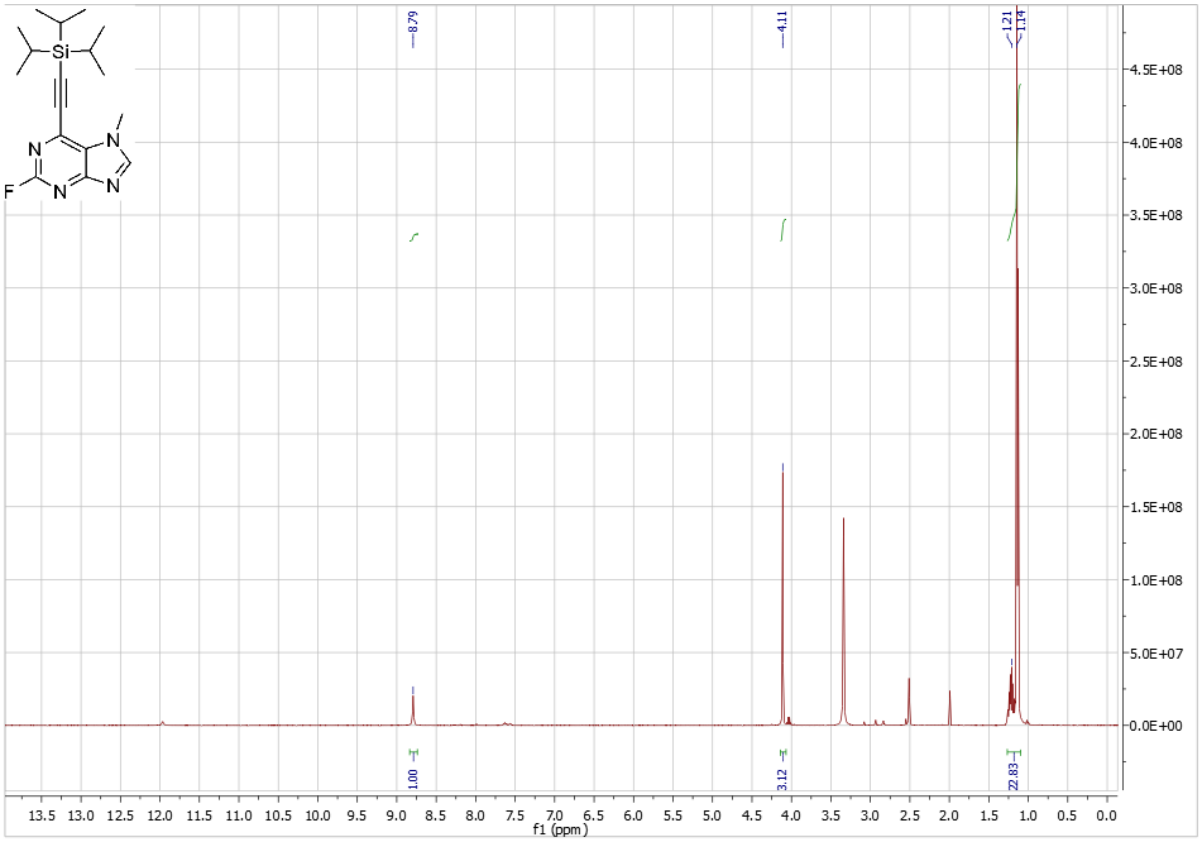

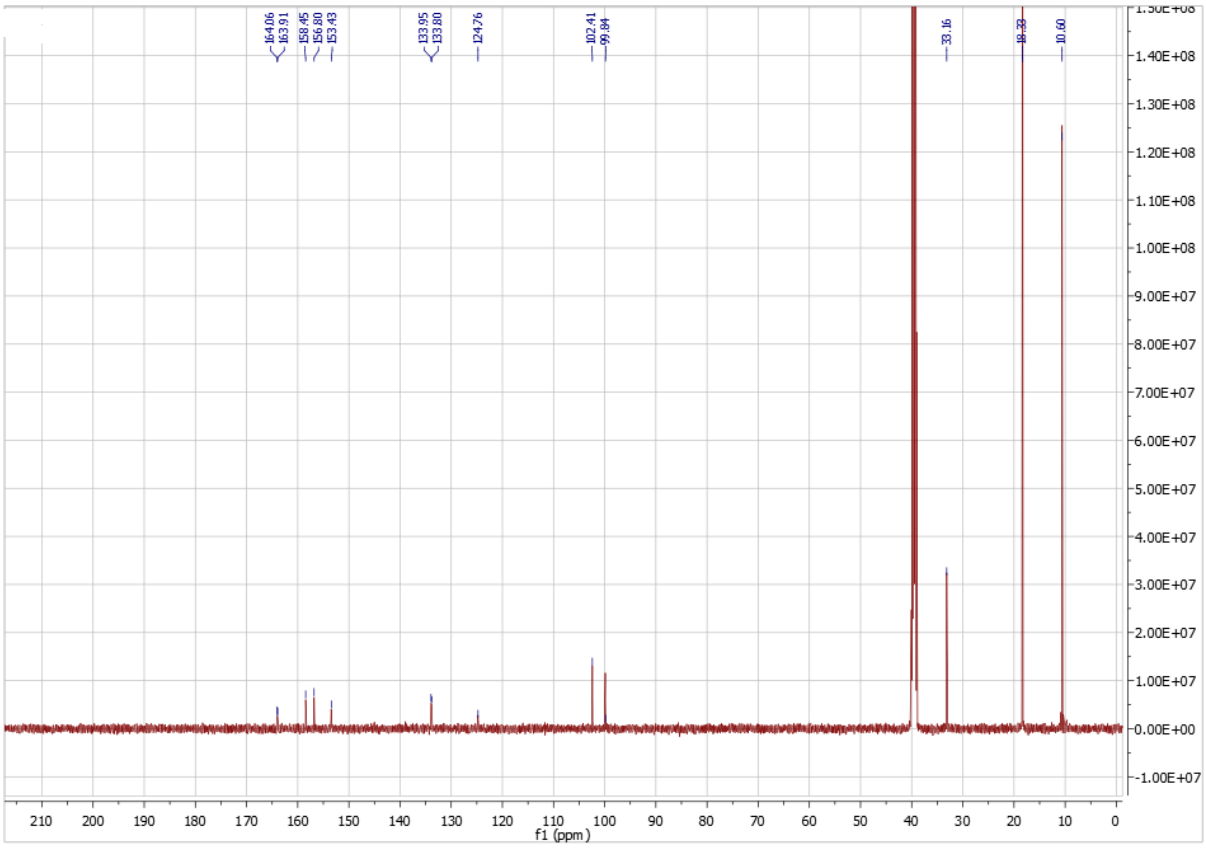

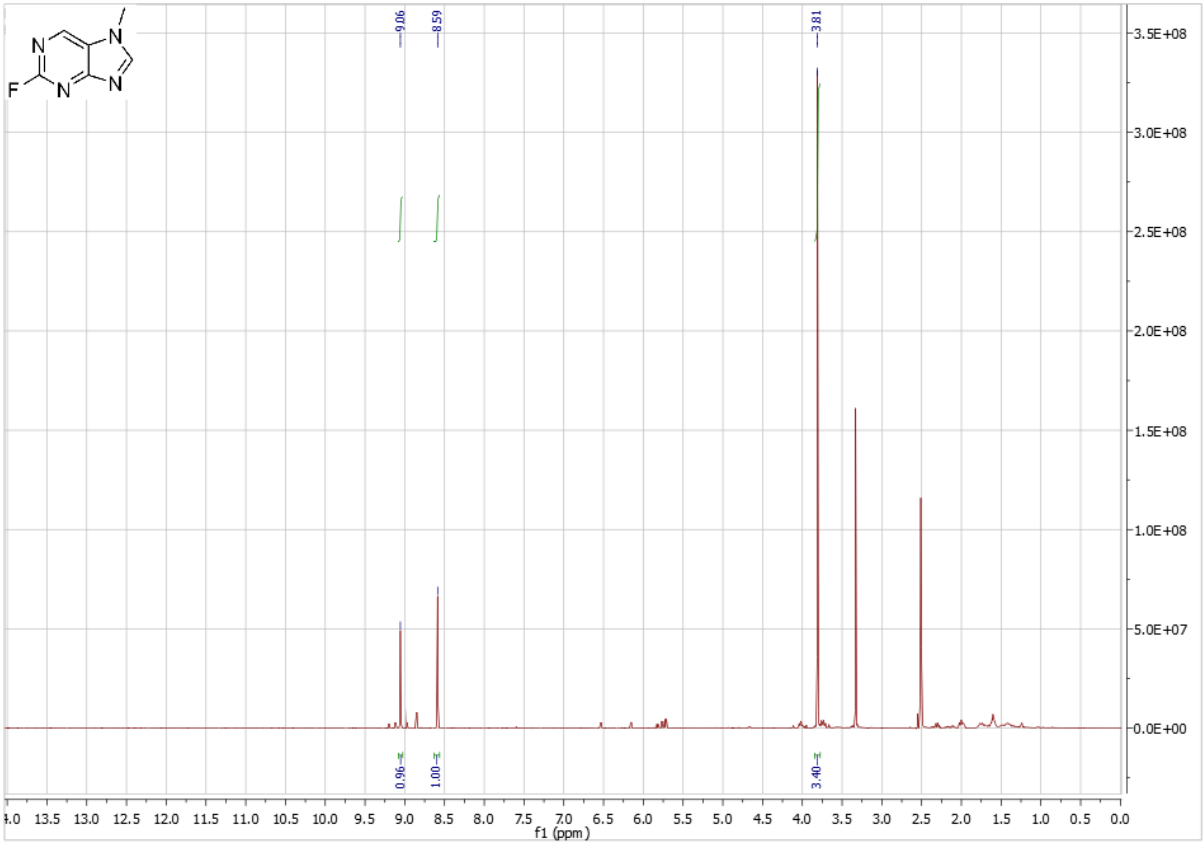

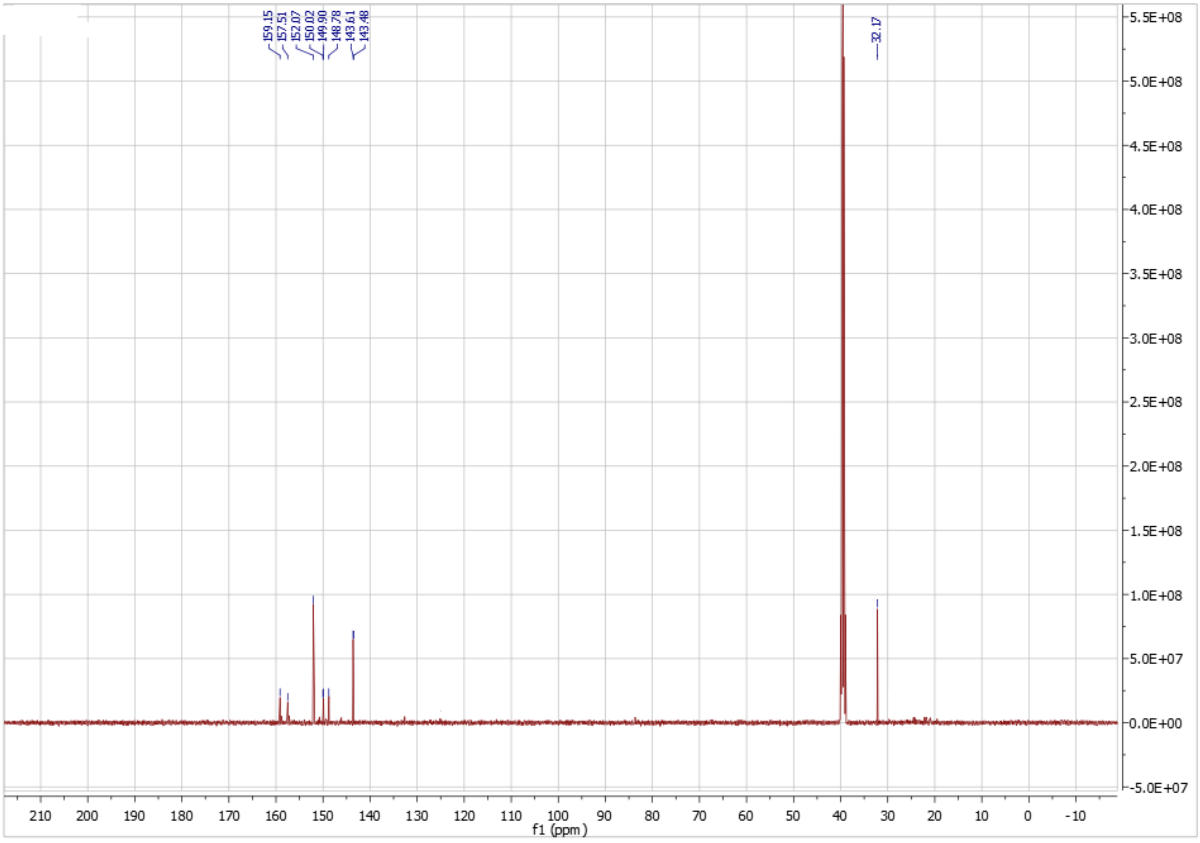

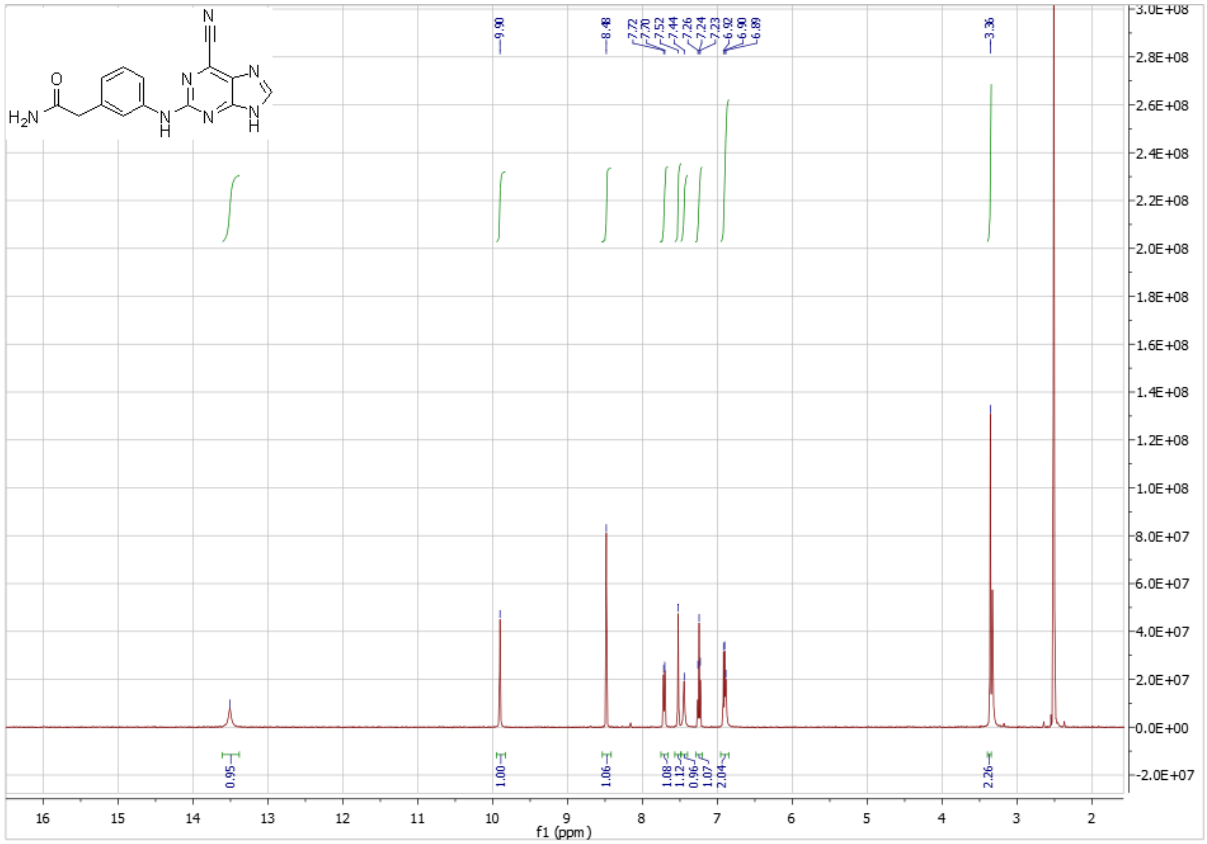

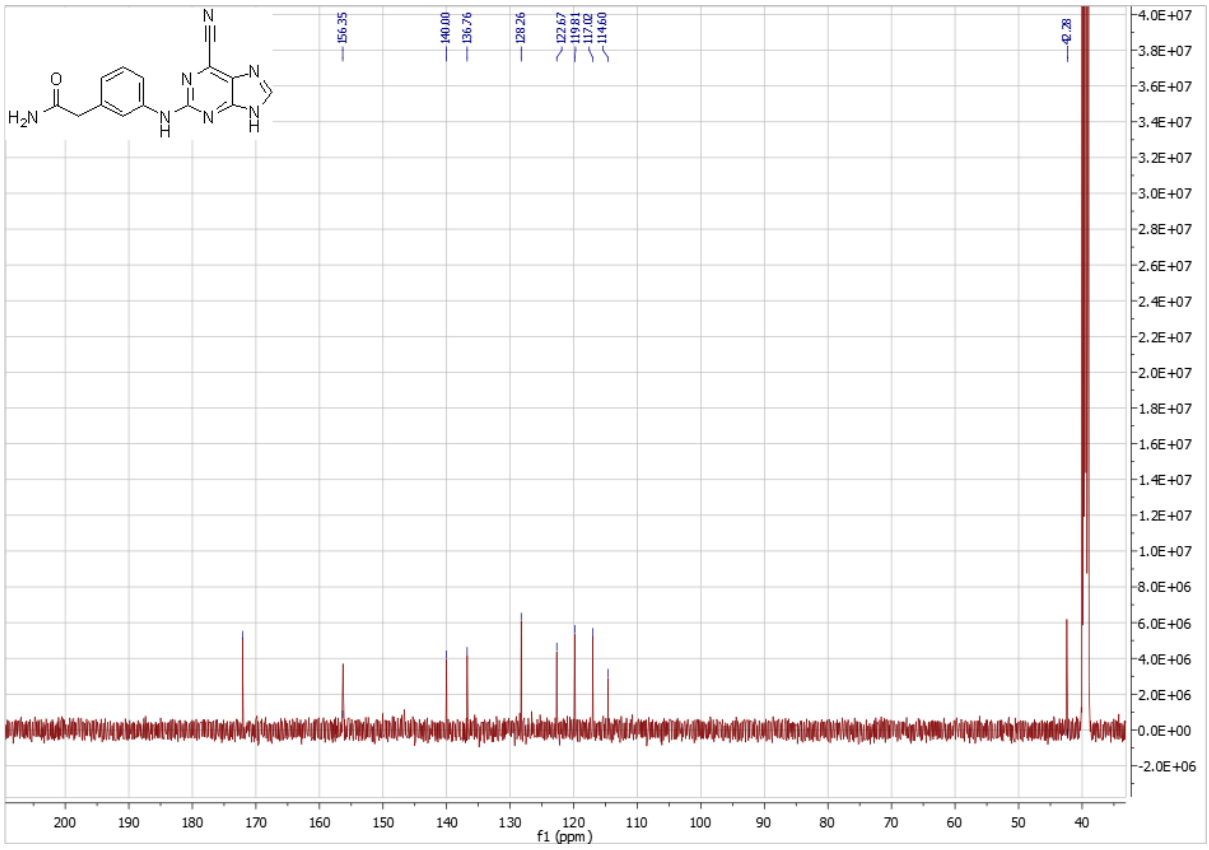

Not every tertiary carbons of this compound are visible.