Electronic Supplementary Material (ESI) for Chemical Communications.

Supporting Information

Direct N^9-arylation of purines with aryl halides

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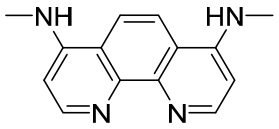
General Methods

All commercial solvents and reagents were used as obtained without further purification, except for CH_2Cl_2 which was distilled before use. Water was purified by a Milli-Q system and degassed by letting through nitrogen gas. All reactions were carried out under a nitrogen atmosphere. Semi-automatic flash chromatography was performed using Merck silica gel 60 (0.040-0.063 mm), on a Biotage HPFC SP4 Flash Purification System. ^{1}H and ^{13}C NMR spectra were recorded at 300 K on a Bruker Avance III 400 operating at 400 MHz and 101 MHz, respectively, with chemical shifts calibrated relative to solvent residual peaks (^{1}H NMR (DMSO-d_6): δ 2.50 ppm; ^{1}H NMR ($CDCl_3$): δ 7.26 ppm; ^{13}C NMR (DMSO-d_6): δ 39.52 ppm; ^{13}C NMR ($CDCl_3$): δ 77.16 ppm). Assignments are based on chemical shifts and/or COSY, HSQC and NOESY spectra. Mass spectra were recorded on a Bruker MicroTOF-Q II (ESI) spectrometer. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV-light and HPLC using a Dionex 120A C18 column (5µ, 4.6x150 mm) with gradient elution of MeCN and water, both solvents containing 0.05% trifluoroacetic acid (TFA), at a flow rate of 1 mL min^{-1} and UV detection at 230, 254 and 320 nm. HPLC purification was performed by using a Phenomenex Luna C18 5µ column (250x21.20 mm) with gradient elution of MeCN and water, both solvents containing 0.05% TFA, at a flow rate of 20 mL min^{-1}.

Synthesis of phenanthroline ligands

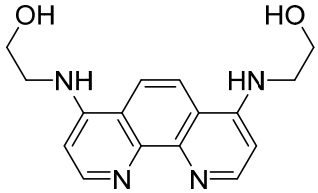
Ligands **L1**(DPPhen)[1] and **G**[2] were prepared as described previously.

N^4,*N*^{7}-Dimethyl-1,10-phenanthroline-4,7-diamine (Ligand L2)



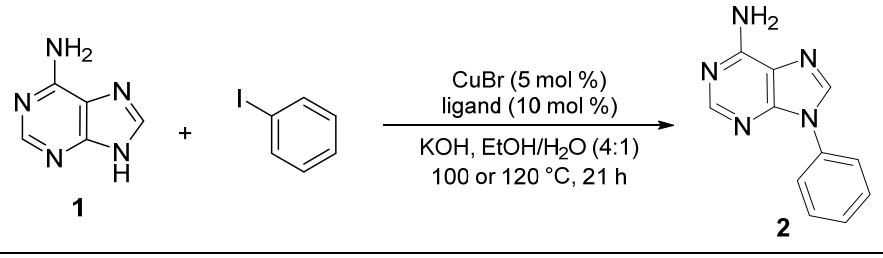
A sealed vial containing 4,7-dichloro-1,10-phenanthroline (300 mg, 1.2 mmol) and methylamine (5.0 mL, 33% in EtOH, 40 mmol) was heated in a microwave reactor (Emrys Creator) at 150 °C for 40 min to give an orange mixture with a precipitate. The precipitate was isolated by filtration, washed with water, ethanol and diethyl ether, and dried under vacuum to give the title compound as a pale yellow solid (255 mg, 89% yield). m.p. > 250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 2H), 8.53 (d, J = 6.2 Hz, 2H), 8.36 (s, 2H), 6.84 (d, J = 6.3 Hz, 2H), 3.04 ppm (d, J = 4.4 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.6, 145.8, 137.3, 118.2, 117.0, 101.1, 29.7 ppm. HRMS-ESI: m/z calcd for $C_{14}H_{15}N_4^+$: 239.1291 [M+H$^+$], found: 239.1298.

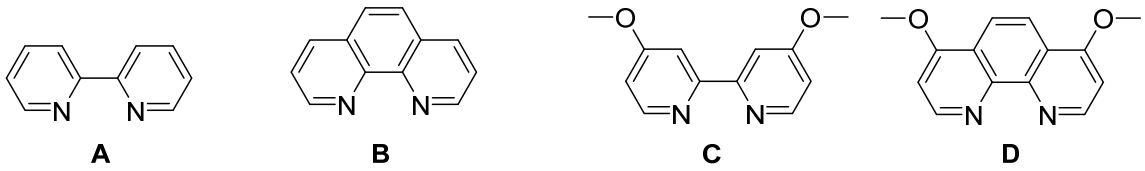
N^4,*N*^{7}-Bis(2-hydroxyethyl)-1,10-phenanthroline-4,7-diamine (Ligand L3, BHPhen)

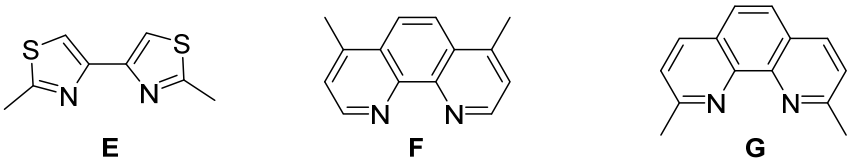


A sealed vial containing 4,7-dichloro-1,10-phenanthroline (747 mg, 3.0 mmol), 2-aminoethanol (1.81 mL, 30.0 mmol) and anhydrous EtOH (15.0 mL) was heated in a microwave reactor (Biotage Initiator$^+$ EU) at 140 °C for 3 hours to give a red mixture with a precipitate. The precipitate was isolated by filtration, washed sequentially with water, ethanol and diethyl ether, and dried under vacuum to give the title compound as a pale yellow solid (795 mg, 89% yield). m.p. > 250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 5.3 Hz, 2H), 8.06 (s, 2H), 7.19–7.03 (m, 2H), 6.67 (d, J = 5.4 Hz, 2H), 4.91 (s, 2H), 3.70 (t, J = 5.7 Hz, 4H), 3.42–3.35 ppm (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 150.2, 149.4, 146.3, 117.4, 117.2, 100.7, 58.9, 45.3 ppm. HRMS-ESI: m/z calcd for $C_{16}H_{19}N_4O_2^+$: 299.1503 [M+H$^+$], found: 299.1514.

Table S1: Ligand screening for the coupling of adenine and iodobenzene







entry	ligand	temp (°C)	conversion (%)[b]	yield (%)[c]
1	**A**	100	<1	ND
2	**B**	100	6	ND
3	**C**	100	2	ND
4	**D**	100	13	ND
5	**E**	100	<1	ND
6	**L1**	100	22	19
7	**L2**	100	31	20
8	**F**	120	32	30
9	**G**	120	<1	ND
10	**L1**	120	65	46
11	**L2**	120	ND	56

Reaction conditions: **1** (0.60 mmol), iodobenzene (0.50 mmol), ligand (10 mol %), CuBr (5 mol %), KOH (1.0 mmol), EtOH/H_2O (1.0 mL, 4:1), heated in a sealed vial to 100 °C or 120 °C for 18 h. [b] Determined from integration of the area under the signal of **2** (HPLC; UV absorbtion at 254 nm) as the percentage of the total area of the signals corresponding to **1** and **2**. [c] Yield of isolated product. ND: not determined.

Reaction optimisation

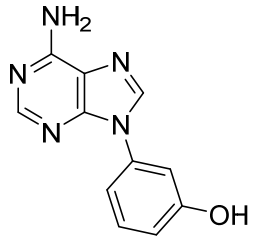
Entry 1: A reaction tube equipped with a magnetic stirring bar was charged with CuBr (3.6 mg, 0.025 mmol), ligand (**L1**, 15.9 mg, 0.05 mmol), adenine (**1**, 81 mg, 0.60 mmol) and KOH (56.1 mg, 1.0 mmol). The tube was sealed with a rubber septum, evacuated and back-filled with nitrogen three times. EtOH/H_2O (4:1 v/v, 1 mL) and iodobenzene (56 μL, 0.50 mmol) was added by syringe. The rubber septum was exchanged with a cap designed to withstand moderate pressure under a stream of nitrogen and the reaction tube was placed in a preheated oil bath at 120 °C. After 21 hours, the reaction mixture was cooled to RT, silica (1.5 g) was added and the mixture was concentrated to dryness on a rotary evaporator. The dry residue was purified by semi-automated flash column chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (3% → 5%)), to provide 49 mg (46%) of 9-phenyladenine (**2**).[3]

Entries 2-19 were performed by the same procedure, but with the modifications indicated in Table 1.

General procedure for *N*^{9}-arylation of adenine (Table 2)

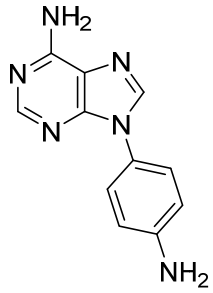
A reaction tube equipped with a magnetic stirring bar was charged with CuBr (3.6 mg, 0.025 mmol), ligand (**L3**, 14.9 mg, 0.05 mmol), sodium ascorbate (10 mg, 0.05 mmol), adenine (67.6 mg, 0.50 mmol), KOH (56.1 mg, 1.0 mmol) and aryl halide (if solid, 0.75 mmol). The reaction tube was sealed with a rubber septum, evacuated and back-filled with nitrogen three times. DMF/H_2O (4:1 v/v, 1 mL) and aryl halide (if liquid, 0.75 mmol) was added by syringe. The rubber septum was exchanged with a cap designed to withstand moderate pressure under a stream of nitrogen and the reaction tube was placed in a preheated oil bath at 120 °C. After 21 hours (for aryl bromides 48 hours), the reaction mixture was cooled to RT, silica (1.5 g) was added and the mixture was concentrated to dryness on a rotary evaporator. The dry residue was purified by semi-automated flash column chromatography. In some cases an inorganic iodide salt eluted with the product on the column, which was removed by recrystallisation from H_2O or MeOH. Known compounds exhibited ^{1}H and ^{13}C NMR in agreement with previously reported data cited below and ESI-MS was in agreement with the predicted molecular mass.

3-(6-Aminopurin-9-yl)phenol (3a)



Following the general procedure using 3-iodophenol (165 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (4% → 7%)), followed by a recrystallisation from water. Yield: 101 mg (89%). m.p. >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.54 (s, 1H), 8.22 (s, 1H), 7.45–7.29 (m, 4H), 7.29–7.24 (m, 1H), 6.88–6.78 ppm (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.1, 156.3, 153.1, 149.1, 139.6, 136.1, 130.3, 119.4, 114.4, 113.2, 110.0 ppm; HRMS-ESI: *m*/*z* calcd for $C_{11}H_{10}N_5O^+$: 228.0880 [M+H^+], found: 228.0884.

9-(4-Aminophenyl)purin-6-amine (3b)

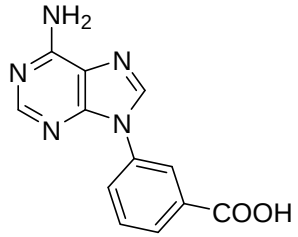


Using 4-iodoaniline: Following the general procedure using 4-iodoaniline (164 mg, 0.75 mmol) and heating for 21 hours provided the title compound as a pale tan solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (6% → 10%)), followed by a recrystallisation from water. Yield: 100 mg (88%).

Using 4-bromoaniline: Following the general procedure using 4-bromoaniline (129 mg, 0.75 mmol) and heating for 48 hours provided the title compound as a pale tan solid after semi-automated flash chromatography (Biotage SNAP 25 g, 10% MeOH in CH_2Cl_2). Yield: 86 mg (76%).

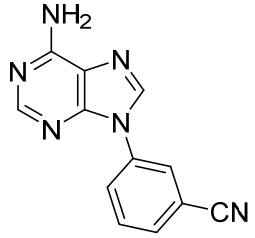
9-(4-Aminophenyl)purin-6-amine (3b): m.p. > 250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.14 (s, 1H), 7.38 (d, J = 8.6 Hz, 2H), 7.26 (s, 2H), 6.69 (d, J = 8.6 Hz, 2H), 5.36 ppm (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.1, 152.7, 149.3, 148.4, 140.0, 124.6, 123.5, 119.0, 113.8 ppm; HRMS-ESI: m/z calcd for $C_{11}H_{11}N_6^+$: 227.1040 [M+H$^+$], found: 227.1042.

3-(6-Aminopurin-9-yl)benzoic acid (3c)



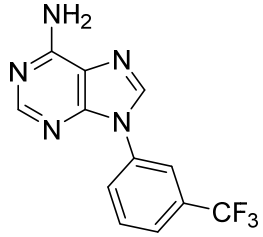
Following the general procedure using 3-iodobenzoic acid (186 mg, 0.75 mmol) provided the title compound as a tan solid after semi-automated flash chromatography (Biotage SNAP 25 g, MeOH/AcOH 2:1 in CH_2Cl_2 (6% → 12%)), followed by a recrystallisation from MeOH. Yield: 84 mg (66%). m.p. >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.32 (s, 1H), 8.68 (s, 1H), 8.51 (s, 1H), 8.32–8.20 (m, 1H), 8.19–8.11 (m, 1H), 8.07–7.94 (m, 1H), 7.81–7.68 (m, 1H), 7.42 ppm (s, 2H); HRMS-ESI: m/z calcd for $C_{12}H_{10}N_5O_2^+$: 256.0829 [M+H$^+$], found: 256.0831.

3-(6-Aminopurin-9-yl)benzonitrile (3d)



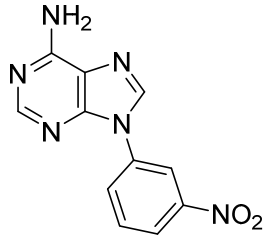
Following the general procedure using 3-iodobenzonitrile (172 mg, 0.75 mmol) provided the title compound as an off-white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (4% → 8%)), followed by a recrystallisation from H_2O. Yield: 91 mg (77%). m.p. >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.48 (t, J = 1.7 Hz, 1H), 8.40–8.32 (m, 1H), 8.25 (s, 1H), 7.95–7.87 (m, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.47 ppm (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.4, 153.4, 149.0, 139.3, 135.9, 130.8, 130.8, 127.2, 125.8, 119.3, 118.1, 112.3 ppm; HRMS-ESI: m/z calcd for $C_{12}H_9N_6^+$: 237.0883 [M+H$^+$], found: 237.0881.

9-(3-(Trifluoromethyl)phenyl)purin-6-amine (3e)



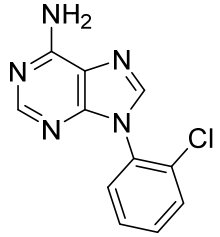
Following the general procedure using 1-iodo-3-(trifluoromethyl)benzene (204 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (4% → 6%)). Yield: 116.5 mg (83%). m.p. 226-228°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.40 (s, 1H), 8.33–8.26 (m, 1H), 8.25 (s, 1H), 7.88–7.76 (m, 2H), 7.46 ppm (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.4, 153.4, 149.1, 139.5, 135.9, 130.8, 130.2 (q, J = 32.2 Hz), 126.4, 123.8 (q, J = 272.5 Hz), 123.8 (q, J = 3.6 Hz), 119.3, 119.2 ppm (q, J = 3.9 Hz); HRMS-ESI: m/z calcd for $C_{12}H_9F_3N_5^+$: 280.0805 [M+H$^+$], found: 280.0818.

9-(3-Nitrophenyl)purin-6-amine (3f)



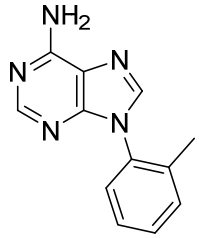
Following the general procedure using 1-iodo-3-nitrobenzene (187 mg, 0.75 mmol) provided the title compound as a yellow solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (3% → 5%)), followed by a recrystallisation from water. Yield: 104 mg (81%). m.p. >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (t, J = 2.2 Hz, 1H), 8.80 (s, 1H), 8.48–8.40 (m, 1H), 8.31–8.24 (m, 2H), 7.89 (t, J = 8.2 Hz, 1H), 7.49 ppm (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.4, 153.4, 149.1, 148.3, 139.4, 136.2, 131.0, 128.4, 121.7, 119.3, 117.1 ppm; HRMS-ESI: m/z calcd for $C_{11}H_9N_6O_2^+$: 257.0781 [M+H$^+$], found: 257.0794.

9-(2-Chlorophenyl)purin-6-amine (3g)



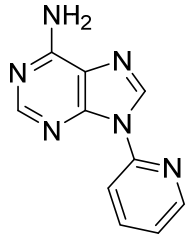
Following the general procedure using 1-chloro-2-iodobenzene (179 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (3% → 5%)). Yield: 2.2 mg (2%). m.p. 233-234 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 1H), 8.11 (s, 1H), 7.79–7.73 (m, 1H), 7.69–7.64 (m, 1H), 7.64–7.53 (m, 2H), 7.39 ppm (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.2, 153.2, 150.2, 140.6, 132.1, 131.0, 130.7, 130.2, 130.1, 128.3, 118.2 ppm; HRMS-ESI: *m*/*z* calcd for $C_{11}H_9ClN_5^+$: 246.0541 [*M*+H$^+$], found: 246.0553.[4]

9-(*o*-Tolyl)purin-6-amine (3h)



Following the general procedure using 2-iodotoluene (164 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (3% → 5%). Yield: 7.5 mg (7%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 8.11 (s, 1H), 7.49–7.45 (m, 2H), 7.40–7.37 (m, 2H), 7.35 (s, 2H), 2.08 ppm (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.3, 153.0, 150.1, 140.8, 134.9, 133.7, 131.0, 129.2, 127.8, 126.8, 118.4, 17.5 ppm; HRMS-ESI: *m*/*z* calcd for $C_{12}H_{12}N_5^+$: 226.1087 [*M*+H$^+$], found: 226.1088.[5*]

9-(Pyridin-2-yl)purin-6-amine (3i)



Following the general procedure using 2-bromopyridine (118 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (4% → 6%)). Yield: 87 mg (82%). m.p. 230-231 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.62–8.53 (m, 2H), 8.29 (s, 1H), 8.15–8.07 (m, 1H), 7.54–7.40 ppm (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.4, 153.3, 148.7, 148.7, 148.2, 139.5, 138.0, 122.7, 119.9, 115.1 ppm; HRMS-ESI: *m*/*z* calcd for $C_{10}H_9N_6^+$: 213.0883 [*M*+H$^+$], found: 213.0876.

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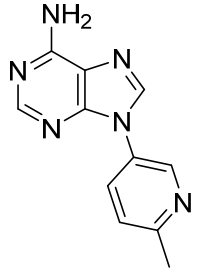
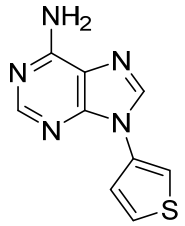
[*] ^{1}H NMR is not in agreement with that reported by Tao *et al*.[5] No ^{13}C NMR has been reported previously.

9-(6-Methylpyridin-3-yl)purin-6-amine (3j)



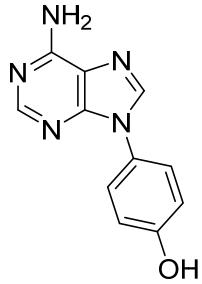
Following the general procedure using 5-bromo-2-methylpyridine (129 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (3% → 6%)). Yield: 92 mg (81%). m.p. 259-260 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (d, J = 2.4 Hz, 1H), 8.61 (s, 1H), 8.27 – 8.16 (m, 2H), 7.48 (d, J = 8.4 Hz, 1H), 7.43 (s, 2H), 2.55 ppm (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.0, 156.4, 153.3, 149.2, 143.1, 139.4, 130.9, 129.6, 123.4, 119.1, 23.7 ppm; HRMS-ESI: m/z calcd for $C_{11}H_{11}N_6^+$: 227.1040 [M+H$^+$], found: 227.1029.

9-(Thiophen-3-yl)purin-6-amine (3k)



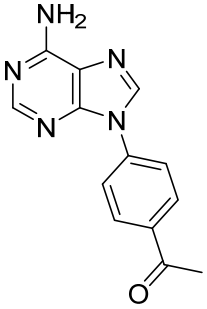
Following the general procedure using 3-bromothiophene (122 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (4% → 8%)). Yield: 83 mg (76%). m.p. 218-219 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.24 (s, 1H), 8.16 – 8.08 (m, 1H), 7.84 – 7.73 (m, 2H), 7.40 ppm (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.3, 153.3, 148.7, 139.3, 133.3, 127.1, 121.8, 119.0, 114.5 ppm; HRMS-ESI: m/z calcd for $C_9H_8N_5S^+$: 218.0495 [M+H$^+$], found: 218.0487.

4-(6-Aminopurin-9-yl)phenol (3l)



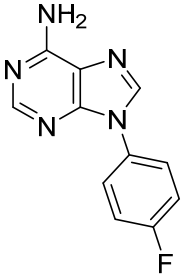
Following the general procedure using 4-bromophenol (130 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 25 g, 10% MeOH in CH_2Cl_2). Yield: 72 mg (63%). m.p. 303-305 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.41 (s, 1H), 8.17 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.31 (s, 2H), 6.93 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.8, 156.3, 153.0, 149.2, 139.9, 126.6, 124.9, 119.0, 115.8 ppm; HRMS-ESI: m/z calcd for $C_{11}H_{10}N_5O^+$: 228.0880 [M+H$^+$], found: 228.0873.

1-(4-(6-Aminopurin-9-yl)phenyl)ethan-1-one (3m)



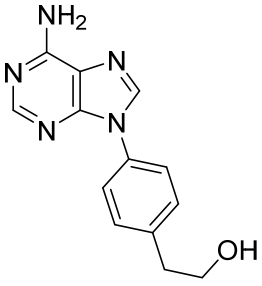
Following the general procedure using 4'-bromoacetophenone (149 mg, 0.75 mmol) provided the title compound as a yellow solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (3% → 5%). Yield: 98 mg (77%). m.p. >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.25 (s, 1H), 8.19–8.14 (m, 4H), 7.45 (s, 2H), 2.64 ppm (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.0, 156.4, 153.4, 149.1, 139.3, 139.0, 135.1, 129.6, 122.0, 119.5, 26.8 ppm; HRMS-ESI: *m*/*z* calcd for $C_{13}H_{12}N_5O^+$: 254.1036 [M+H^+], found: 254.1047.

9-(4-Fluorophenyl)purin-6-amine (3n)



Following the general procedure using 1-bromo-4-fluorobenzene (131 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (3% → 5%)). Yield: 96 mg (84%). m.p. 255-256 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.20 (s, 1H), 7.96–7.90 (m, 2H), 7.47–7.42 (m, 2H), 7.39 ppm (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.9 (d, J = 244.4 Hz), 156.3, 153.2, 149.1, 139.7, 131.5 (d, J = 2.8 Hz), 125.2 (d, J = 8.6 Hz), 119.1, 116.3 ppm (d, J = 22.9 Hz); HRMS-ESI: *m*/*z* calcd for $C_{11}H_9FN_5^+$: 230.0836 [M+H^+], found: 230.0836.[6]

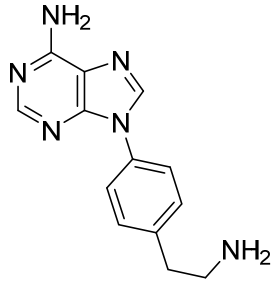
2-(4-(6-Aminopurin-9-yl)phenyl)ethan-1-ol (3o)



Following the general procedure using 4-bromophenethyl alcohol (151 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 25 g, MeOH in CH_2Cl_2 (5% → 8%)), followed by recrystallisation from H_2O. Yield: 105 mg (82%). m.p. >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.20 (s, 1H), 7.80–7.73 (m, 2H), 7.44–7.40 (m, 2H), 7.37 (s, 2H), 4.70 (t, J = 5.2 Hz, 1H), 3.65 (td, J = 6.9, 5.3 Hz, 2H), 2.80 ppm (t, J = 6.9 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-

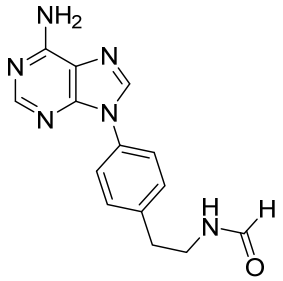
d_6) δ 156.3, 153.1, 149.2, 139.6, 139.1, 133.1, 129.9, 122.8, 119.2, 62.0, 38.5 ppm; HRMS-ESI: *m*/*z* calcd for $C_{13}H_{14}N_5O^+$: 256.1193 [*M*+H^+], found: 256.1204.

9-(4-(2-Aminoethyl)phenyl)purin-6-amine (3p)



Following the general procedure using 4-bromophenethyl amine (151 mg, 0.75 mmol) and EtOH/H_2O (1 mL, 4:1 v/v) as solvent provided the title compound as a pale yellow solid after semi-automated flash chromatography (Biotage SNAP 10 g, 24% $NH_{3(aq)}$/MeOH 1:9 in CH_2Cl_2 (5% → 8%)). Yield: 101 mg (79%). m.p. 219-220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.19 (s, 1H), 7.82–7.74 (m, 2H), 7.42–7.38 (m, 2H), 7.37 (s, 2H), 2.81 (t, *J* = 6.9 Hz, 2H), 2.71 (t, *J* = 7.0 Hz, 2H), 1.47 ppm (s br, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.3, 153.01, 149.1, 139.9, 139.6, 133.0, 129.6, 122.9, 119.2, 43.6, 39.3 ppm (merged with DMSO); HRMS-ESI: *m*/*z* calcd for $C_{13}H_{15}N_6^+$: 255.1353 [*M*+H^+], found: 255.1355.

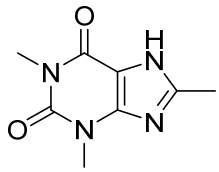
N-(4-(6-Aminopurin-9-yl)phenethyl)formamide



Following the general procedure using 4-bromophenethyl amine (151 mg, 0.75 mmol) and DMF/H_2O (1 mL, 4:1 v/v) as solvent provided *N*-(4-(6-amino-9*H*-purin-9-yl)phenethyl)formamide as a pale yellow solid after semi-automated flash chromatography (Biotage SNAP 10g, MeOH in CH_2Cl_2 (5% → 9%)). Yield: 112 mg (79%). m.p. 169-170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.21 (s, 1H), 8.11 (s, 1H), 8.02 (d, *J* = 1.6 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.46–7.40 (m, 2H), 7.37 (s, 2H), 3.42–3.38 (m, 2H), 2.82 ppm (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.1, 156.3, 153.1, 149.1, 139.6, 138.7, 133.3, 129.7, 122.9, 119.3, 38.6, 34.5 ppm. HRMS-ESI: *m*/*z* calcd for $C_{14}H_{15}N_6O^+$: 283.1302 [*M*+H^+], found: 283.1295.

Synthetic procedure for *N*-arylation of various purines (Table 3)

Preparation of 8-methyltheophylline (4d)

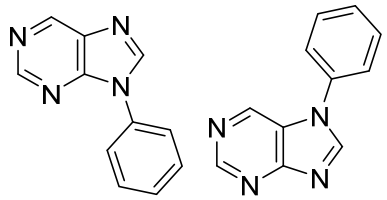


A sealed vial containing 5,6-diamino-1,3-dimethyluracil hydrate (565 mg, 3.0 mmol), acetic anhydride (0.31 mL, 3.3 mmol) and pyridine (6 mL) was heated in a microwave reactor (Emrys Creator) at 110 °C for 20 min to give a red mixture with a precipitate. The solvent was evaporated under vacuum to dryness. The resulting amide was converted to benzimidazole by treatment with *t*-BuOK (1.01 g, 9.0 mmol) in isopropyl alcohol (14 mL) at 60 °C. After 16 hours, the reaction mixture was cooled to RT, silica (5 g) was added and the mixture was concentrated to dryness on a rotary evaporator. The dry residue was purified by semi-automated flash column chromatography (Biotage SNAP 25 g, MeOH in CH_2Cl_2 (3% → 4.5%)), to provide 382 mg (66%) of 8-methyltheophylline (**4d**). m.p. 322-324 °C (lit. 325 °C[7]); ^{1}H NMR (400 MHz, DMSO) δ 3.39 (s, 3H), 3.21 (s, 3H), 2.36 ppm (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.9, 151.2, 150.4, 148.1, 106.1, 29.7, 27.6, 14.3 ppm. HRMS-ESI: *m*/*z* calcd for $C_{14}H_{15}N_6O^+$: 283.1302 [M+H^+], found: 283.1295.

General procedure A - purine, 2,6-diaminopurine, theophylline and 8-methyltheophylline (4a-d): A reaction tube equipped with a magnetic stirring bar was charged with CuBr (3.6 mg, 0.025 mmol), ligand (**L3**, 14.9 mg, 0.05 mmol), sodium ascorbate (10 mg, 0.05 mmol), the purine substrate (**4a**, **4b**, **4c** or **4d**, 0.50 mmol) and KOH (56.1 mg, 1.0 mmol). The tube was sealed with a rubber septum, evacuated and back-filled with nitrogen three times. Then DMF/H_2O (4:1 v/v, 1 mL) and aryl halide (0.75 mmol) was added by syringe. The rubber septum was exchanged with a cap designed to withstand moderate pressure under a stream of nitrogen and the reaction tube was placed in a preheated oil bath at 120 °C. After 21 hours or 48 hours, the reaction mixture was cooled to RT, silica (1.5 g) was added and the mixture was concentrated to dryness on a rotary evaporator. The dry residue was purified by semi-automated flash column chromatography.

General procedure B - guanine and hypoxanthine (4e and 4f): A reaction tube equipped with a magnetic stirring bar was charged with CuBr (3.6 mg, 0.025 mmol), ligand (**L3**, 14.9 mg, 0.05 mmol), the purine substrate (**4e** or **4f**, 0.50 mmol) and KOH (56.1 mg, 1.0 mmol). The tube was sealed with a rubber septum, evacuated and back-filled with nitrogen three times. Then DMSO/H_2O (4:1 v/v, 1 mL) and aryl halide (0.75 mmol) was added by syringe. The rubber septum was exchanged with a cap designed to withstand moderate pressure under a stream of nitrogen and the reaction tube was placed in a preheated oil bath at 120 °C. After 6-48 hours, the reaction mixture was cooled to RT, silica (1.5 g) was added and the mixture concentrated to dryness on a rotary evaporator at 60 °C. The dry residue was purified by semi-automated flash column chromatography.

9-Phenylpurine (5a) and 7-phenylpurine(6a)



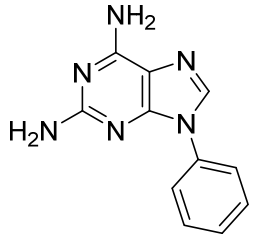
Using iodobenzene: Synthesised by general procedure A using iodobenzene (153 mg, 0.75 mmol) and heating for 21 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (2% → 3%)) gave 61 mg (62%) of 9-phenylpurine (**5a**) and 7 mg (7%) of 7-phenylpurine (**6a**), both products as pale brown solids.

Using bromobenzene: Synthesised by general procedure A using bromobenzene (118 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (2% → 3%)) gave 63 mg (64%) of 9-phenylpurine (**5a**) and 3 mg (3%) of 7-phenylpurine (**6a**), both products as pale brown solids.

9-phenylpurine (5a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 9.05 (s, 1H), 8.38 (s, 1H), 7.78–7.67 (m, 2H), 7.66–7.55 (m, 2H), 7.53–7.44 ppm (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 151.2, 149.4, 144.3, 134.7, 134.3, 130.2, 128.7, 123.6 ppm; HRMS-ESI: *m*/*z* calcd for $C_{11}H_9N_4^+$: 197.0822 [M+H^+], found: 197.0823.[8†]

7-phenylpurine (6a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 9.06 (s, 1H), 8.47 (s, 1H), 7.68–7.62 (m, 2H), 7.59–7.51 ppm (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 154.0, 146.9, 140.8, 135.0, 130.8, 129.4, 125.3, 123.7 ppm; HRMS-ESI: *m*/*z* calcd for $C_{11}H_9N_4^+$: 197.0822 [M+H^+], found: 197.0826.[9‡]

9-Phenylpurine-2,6-diamine (5b)

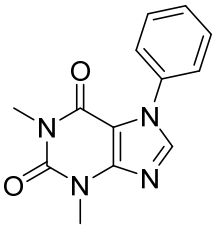


Using iodobenzene: Synthesised by general procedure A using iodobenzene (153 mg, 0.75 mmol) and heating for 21 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (4% → 5%)) gave 106 mg (94%) of the title compound as a white solid.[1]

Using bromobenzene: Synthesised by general procedure A using bromobenzene (118 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (4% → 5%)) gave 68 mg (60%) of the title compound as a white solid.

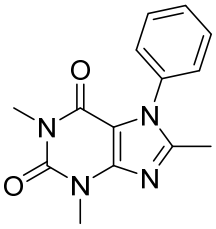
† In accordance with the ^{1}H-NMR reported by *Hayashi et al.* No ^{13}C-NMR has been reported previously.
‡ ^{1}H-NMR reported by *Laufer et al*. used DMSO-d_6 as solvent. No ^{13}C-NMR has been reported previously.

7-Phenyltheophylline (6c)



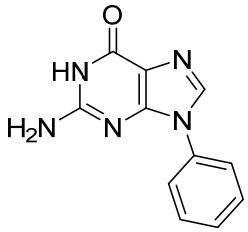
Using iodobenzene: Synthesised by general procedure A using iodobenzene (153 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, EtOAc in PE (50% → 100%)) gave 101 mg (79%) of the title compound as a white solid.[10]
Using bromobenzene: Synthesised by general procedure A using bromobenzene (118 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, EtOAc in PE (50% → 100%)) gave 100 mg (78%) of the title compound as a white solid.

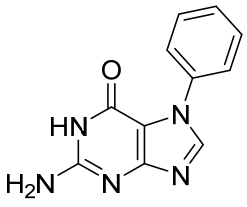
8-methyl-7-phenyltheophylline (6d)



Using iodobenzene: Synthesised by general procedure A using iodobenzene (153 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, EtOAc in PE (60% → 100%)) gave 16 mg (12%) of the title compound as a white solid.
Using bromobenzene: Synthesised by general procedure A using bromobenzene (118 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, EtOAc in PE (60% → 100%)) gave 13 mg (10%) of the title compound as a white solid.
m.p. 230-231 °C (lit. 235 °C[11]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 3H), 7.38 – 7.28 (m, 2H), 3.63 (s, 3H), 3.34 (s, 3H), 2.36 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 151.8, 151.2, 148.6, 135.0, 129.6, 129.5, 127.1, 108.3, 29.9, 28.1, 13.9 ppm; HRMS-ESI: *m*/*z* calcd for $C_{14}H_{15}N_4O_2^+$: 271.1190 [M+H^+], found: 271.1184.

9-Phenylguanine (5e) and 7-phenylguanine (6e)

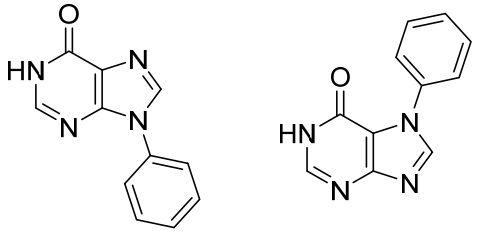




Using iodobenzene: Synthesised by general procedure B using iodobenzene (153 mg, 0.75 mmol) and heating for 21 hours. Purification by semi-automated flash chromatography (Biotage SNAP 25 g, MeOH in CH_2Cl_2 (4% → 8%)) gave a mixture of two isomers: 9-phenylguanine (**5e**) and 7-phenylguanine (**6e**) that were separated on HPLC (5-22% MeCN in H_2O (0-5 min), R_t(**6e**) = 3.9 min, R_t(**5e**) = 4.7 min) to give 68 mg (60%) of **5e** as a white solid and 24 mg (21%) of **6e** as a pale yellow solid.[3,12]

Using bromobenzene: Synthesised by general procedure B using bromobenzene (118 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (5% → 10%)) gave a mixture of two isomers: 9-phenylguanine (**5e**) and 7-phenylguanine (**6e**) that were separated on HPLC (5-22% MeCN in H_2O (0-5 min), R_t(**6e**) = 3.9 min, R_t(**5e**) = 4.7 min) to give 67 mg (59%) of **5e** as a white solid and 15 mg (13%) of **6e** as a pale yellow solid.

9-Phenylhypoxanthine (5f) and 7-phenylhypoxanthine (6f)



Using iodobenzene: Synthesised by general procedure B using iodobenzene (153 mg, 0.75 mmol) and heating for 3 hours, after which the starting material was almost consumed, and diarylated products had started to form. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (3% → 5%)) gave a mixture of two isomers: 9-phenylhypoxanthine (**5f**) and 7-phenylhypoxanthine (**6f**) that were separated on HPLC (10-21% MeCN in H_2O (0-6 min), R_t(**6f**) = 4.4 min, R_t(**5f**) = 5.3 min) to give 46 mg (43%) of **5f** and 15 mg (14%) of **6f**, both as white solids.

Using bromobenzene: Synthesised by general procedure B using bromobenzene (118 mg, 0.75 mmol) and heating for 32 hours, after which the starting material was almost consumed, and diarylated products had started to form. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (3% → 5%)) gave a mixture of two isomers: 9-phenylhypoxanthine (**5f**) and 7-phenylhypoxanthine (**6f**) that were separated on HPLC (10-21% MeCN in H_2O (0-6 min), R_t(**6f**) = 4.4 min, R_t(**5f**) = 5.3 min) to give 51 mg (48%) of **5f** and 12 mg (11%) of **6f**, both as white solids.

9-phenylhypoxanthine (5f): m.p. 317-318 °C (lit. 316-318 °C[13]); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 8.47 (s, 1H), 8.09 (s, 1H), 7.83–7.69 (m, 2H), 7.67–7.55 (m, 2H), 7.55–7.44 ppm (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.7, 147.9, 146.1, 139.4, 134.5, 129.5, 128.1, 124.8, 123.8 ppm; HRMS-ESI: *m*/*z* calcd for $C_{11}H_9N_4O^+$: 213.0771 [M+H^+], found: 213.0761.[13]

7-phenylhypoxanthine (6f): m.p. 295-296 °C (lit. 295-297 °C[14]); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.43 (s, 1H), 8.51 (s, 1H), 8.06 (s, 1H), 7.68–7.59 (m, 2H), 7.57–7.51 (m, 2H), 7.51–7.44 ppm (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.2, 153.6, 145.2, 144.0, 135.4, 128.9, 128.2, 125.2, 114.6 ppm; HRMS-ESI: *m*/*z* calcd for $C_{11}H_9N_4^+$: 213.0771 [M+H^+], found: 213.0761.[14]

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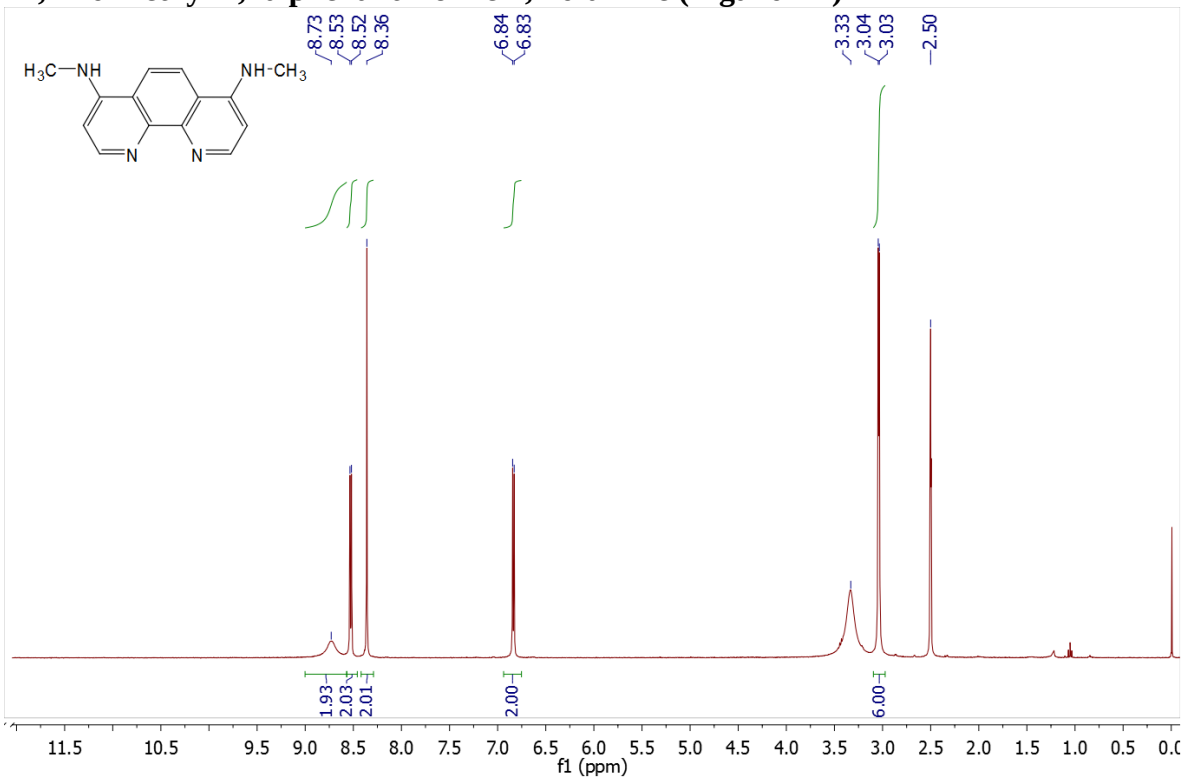
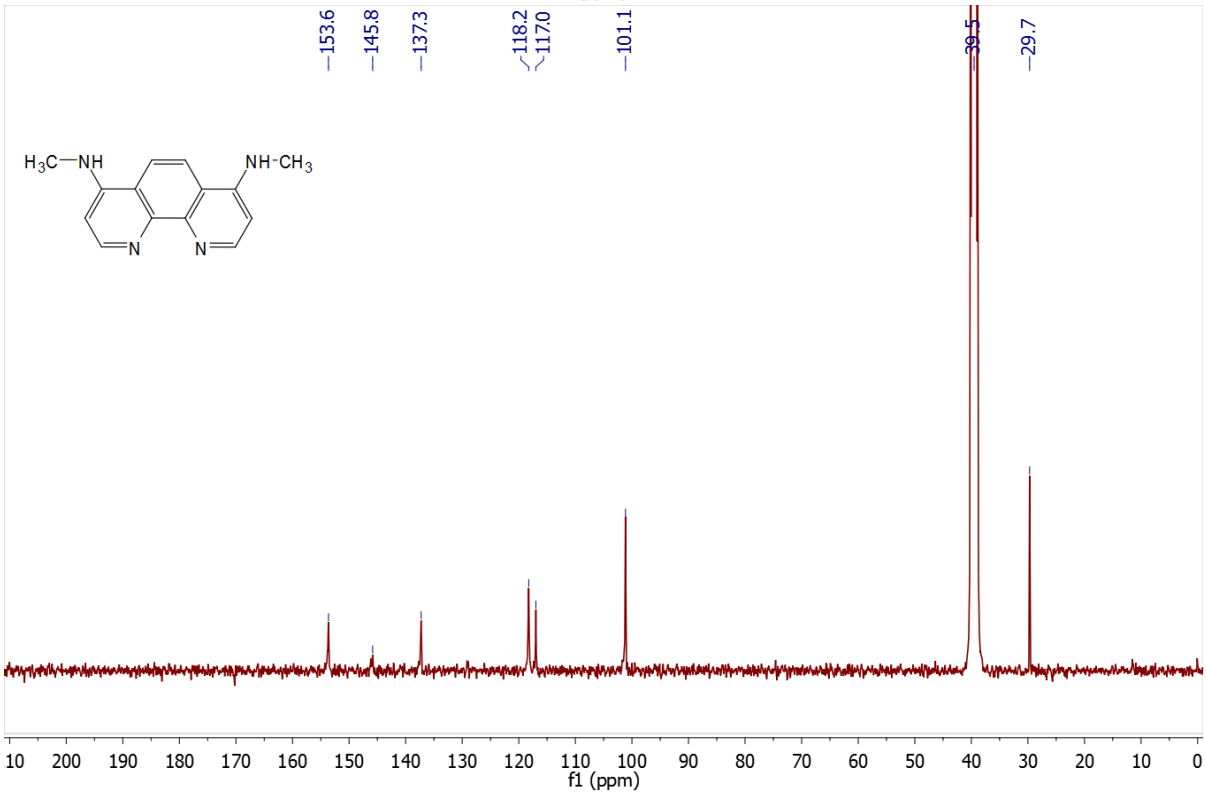
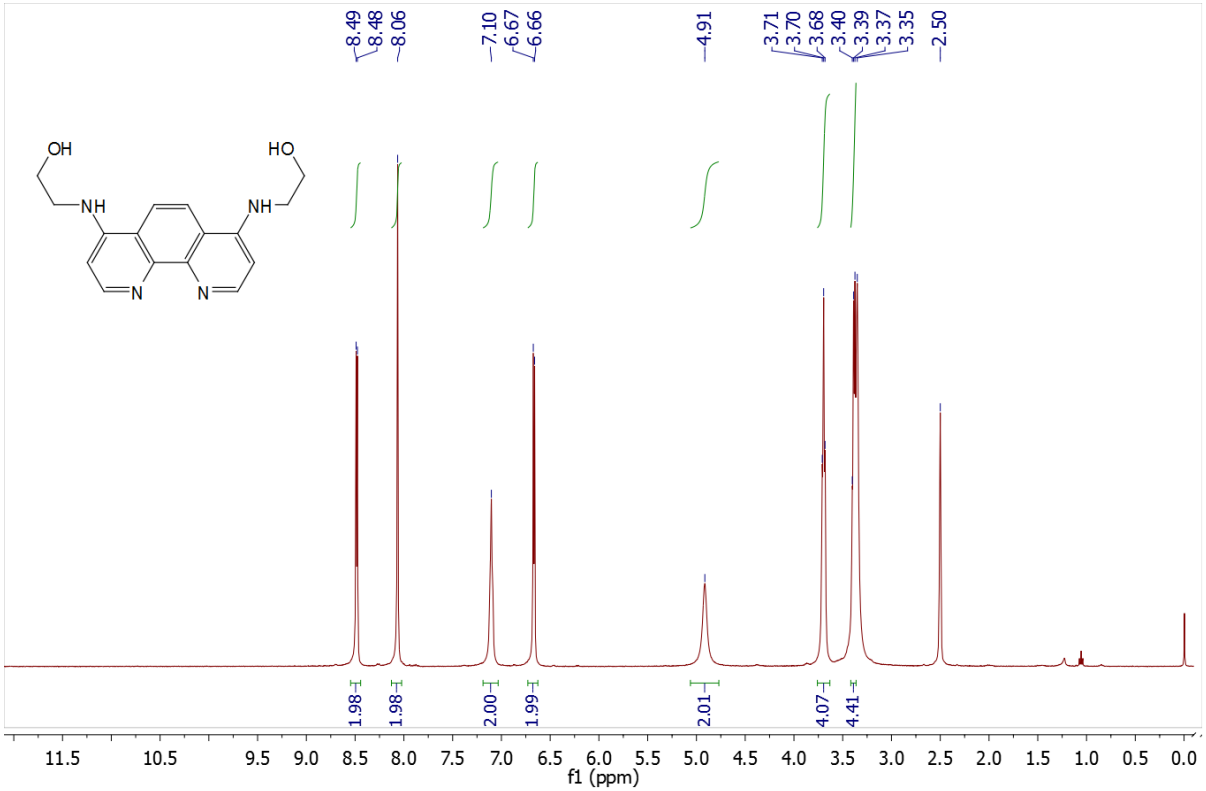
NMR-spectra

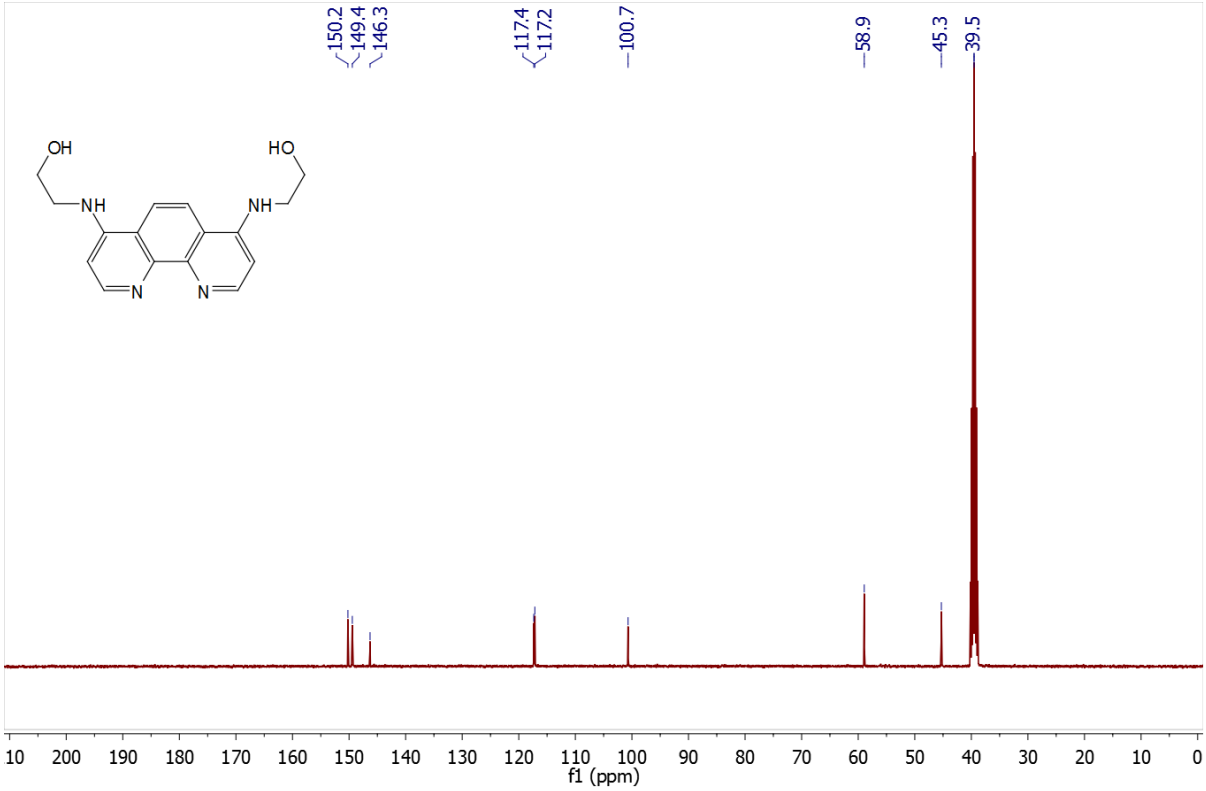
N^4,N^7-dimethyl-1,10-phenanthroline-4,7-diamine (Ligand L2)



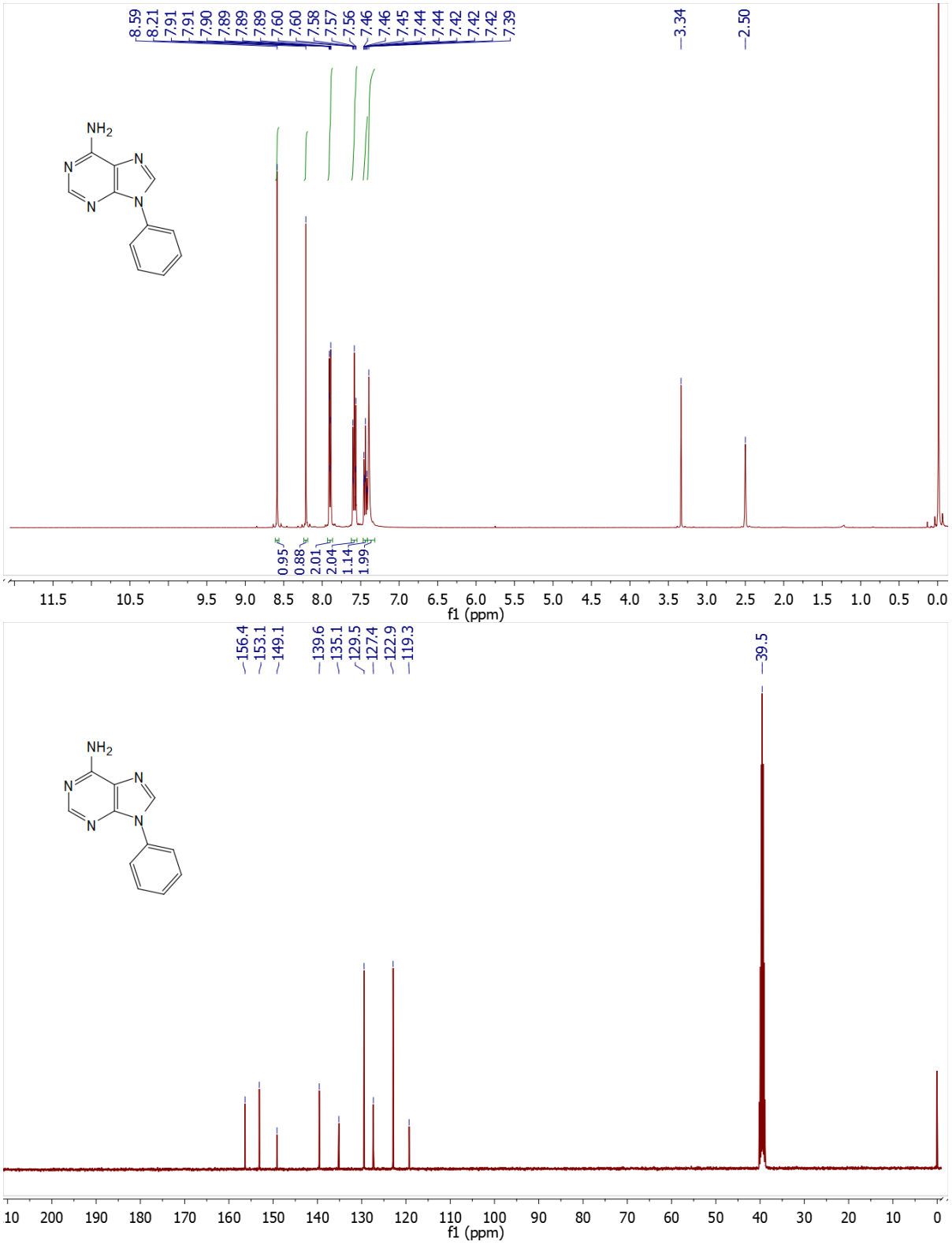


***N*^{4},*N*^{7}-Bis(2-hydroxyethyl)-1,10-phenanthroline-4,7-diamine (Ligand L3)**.

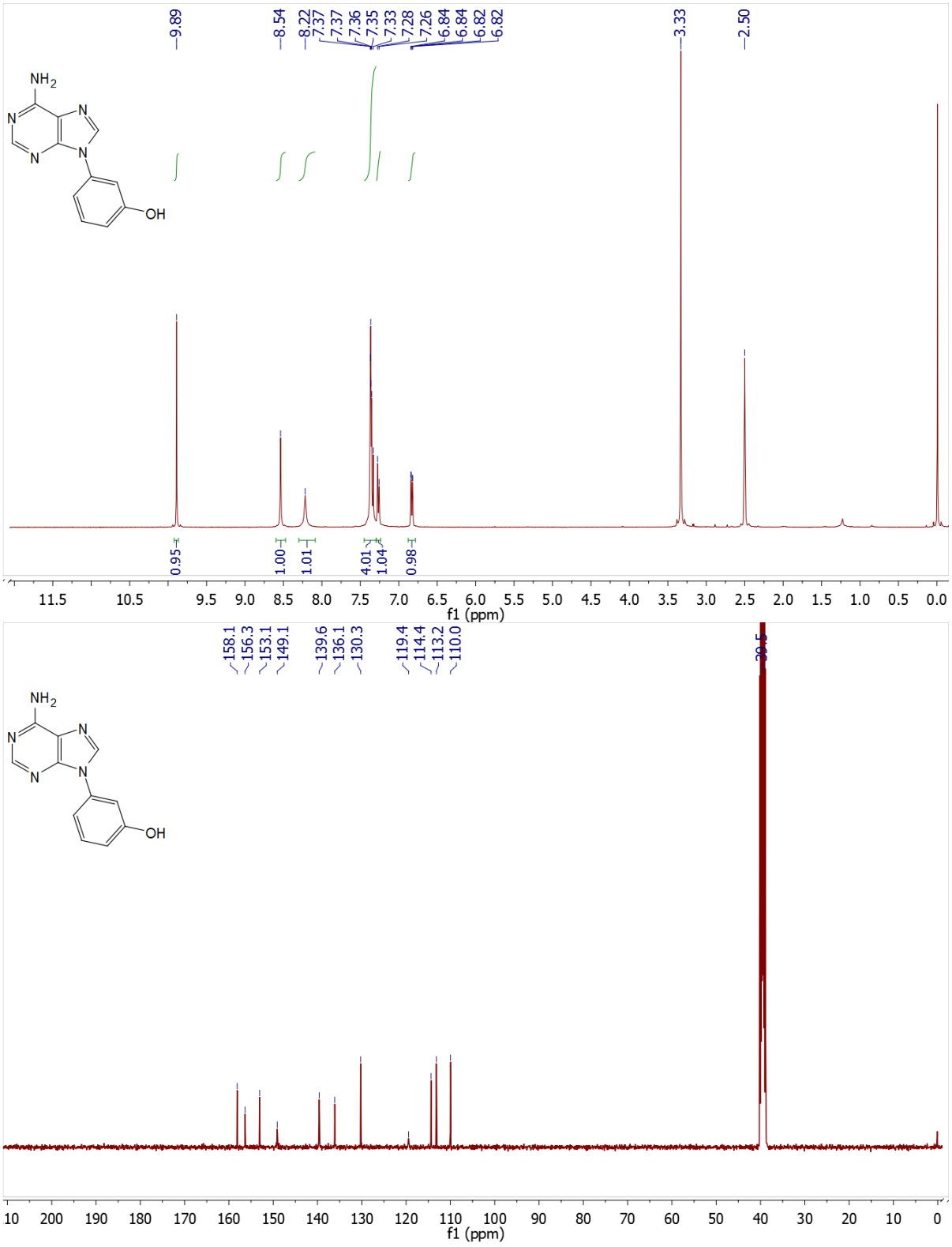




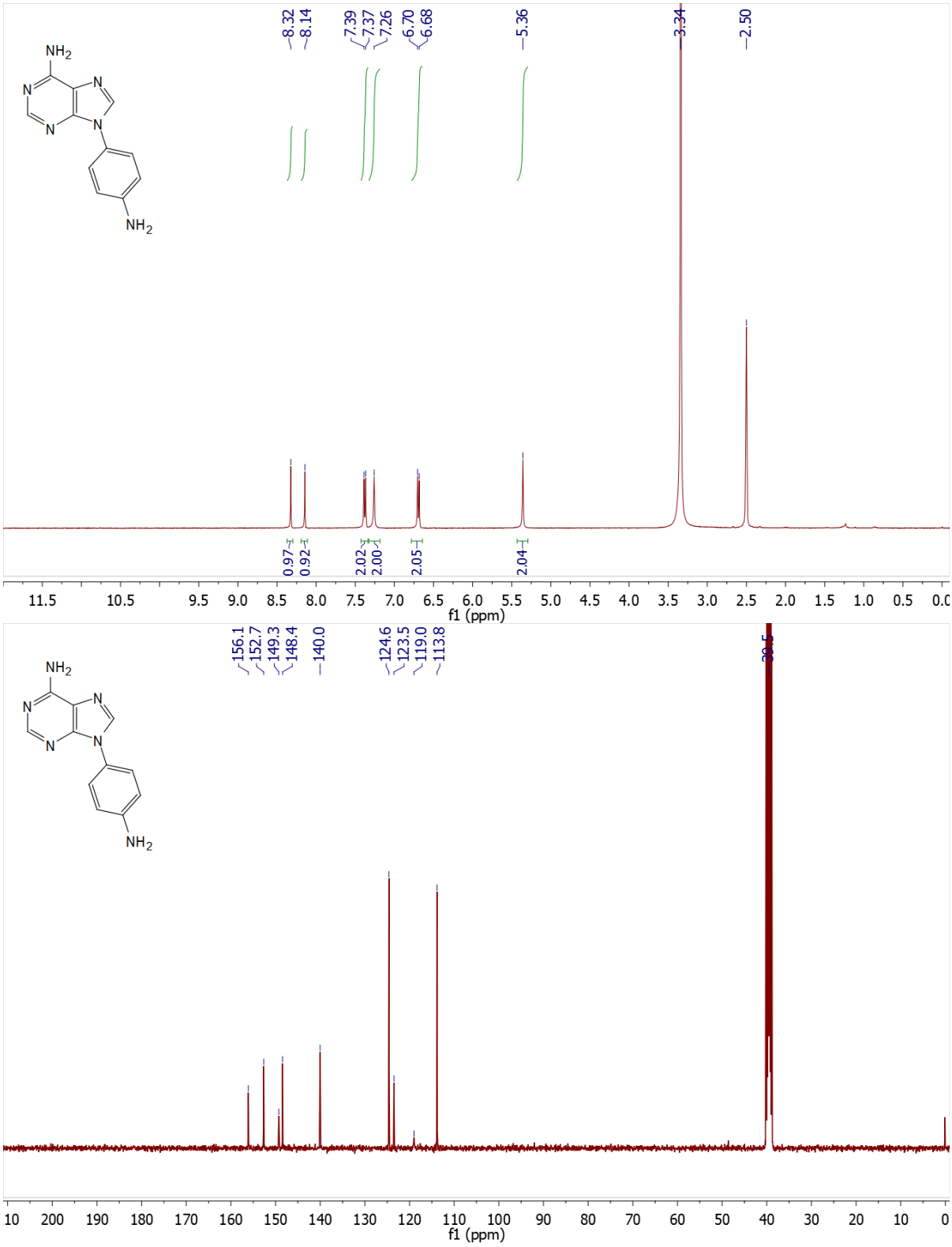
9-phenyladenine (2)



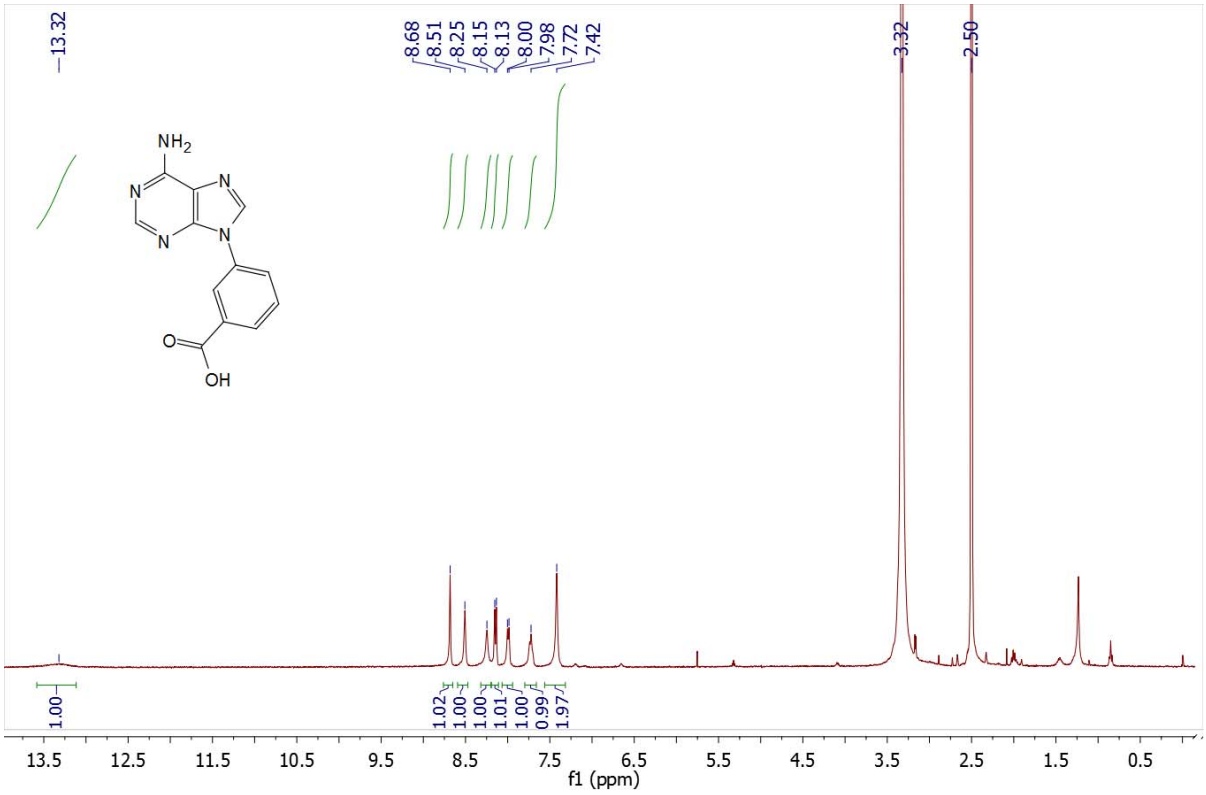
3-(6-Aminopurin-9-yl)phenol (3a)



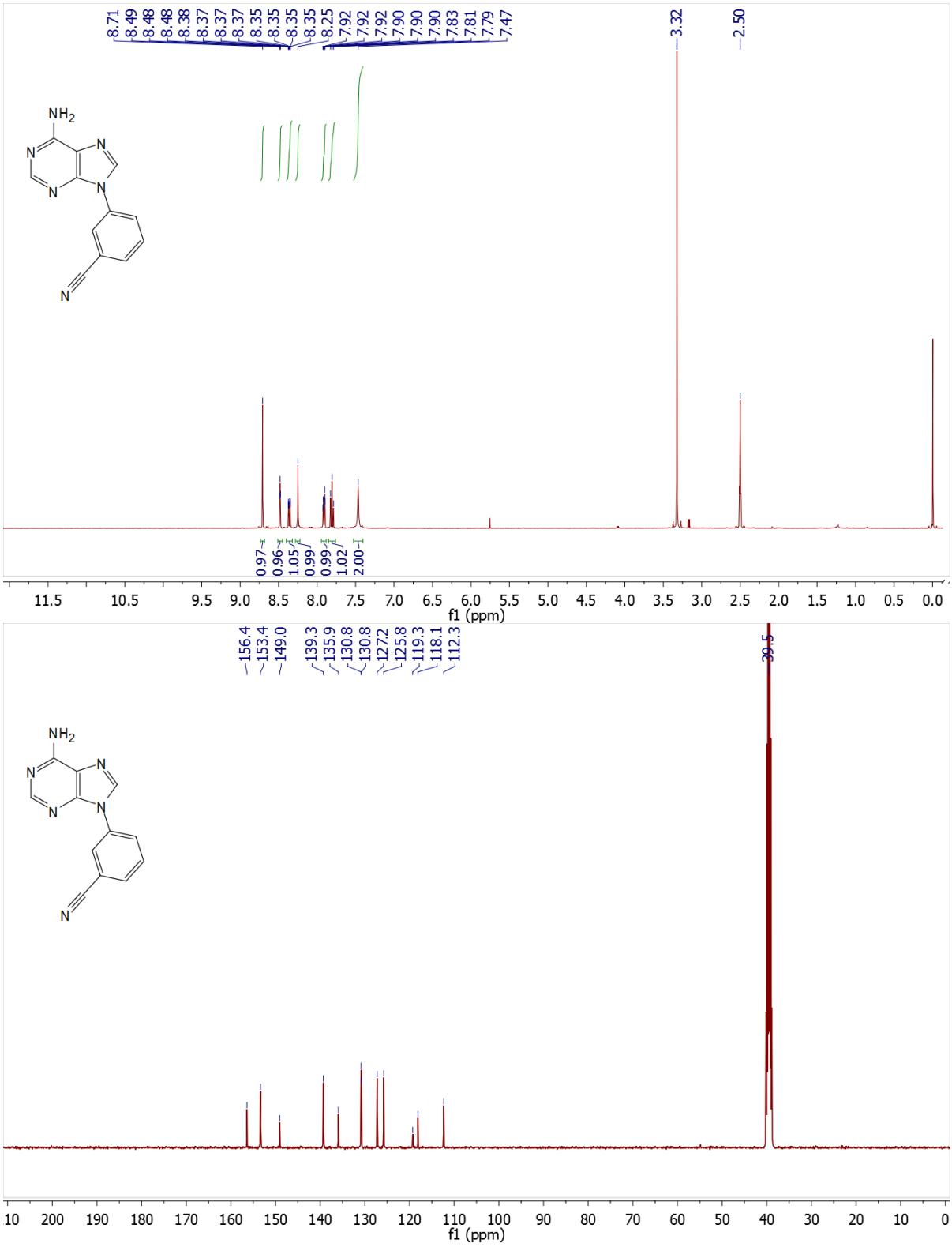
9-(4-Aminophenyl)purin-6-amine (3b)



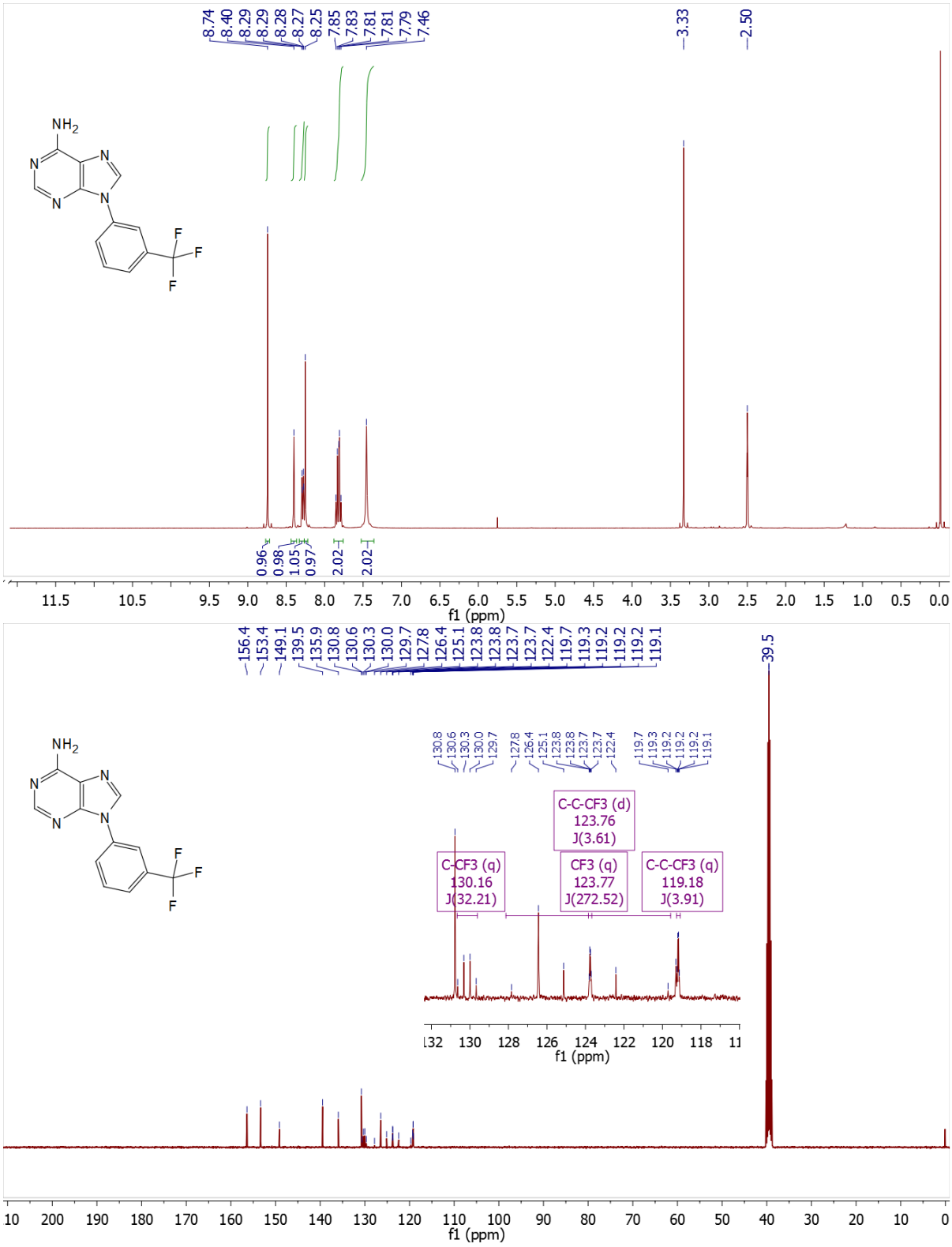
3-(6-Aminopurin-9-yl)benzoic acid (3c)



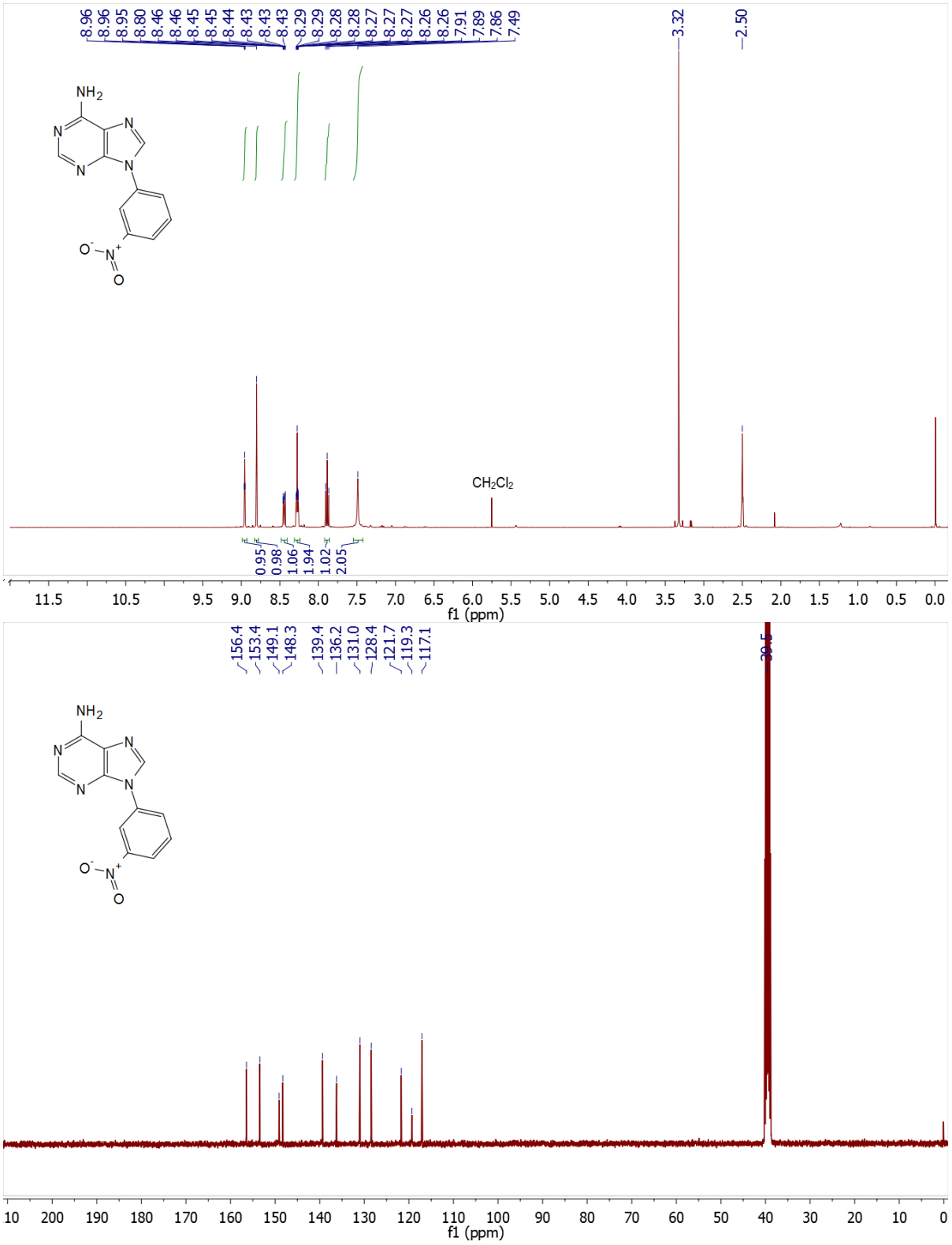
3-(6-Aminopurin-9-yl)benzonitrile (3d)



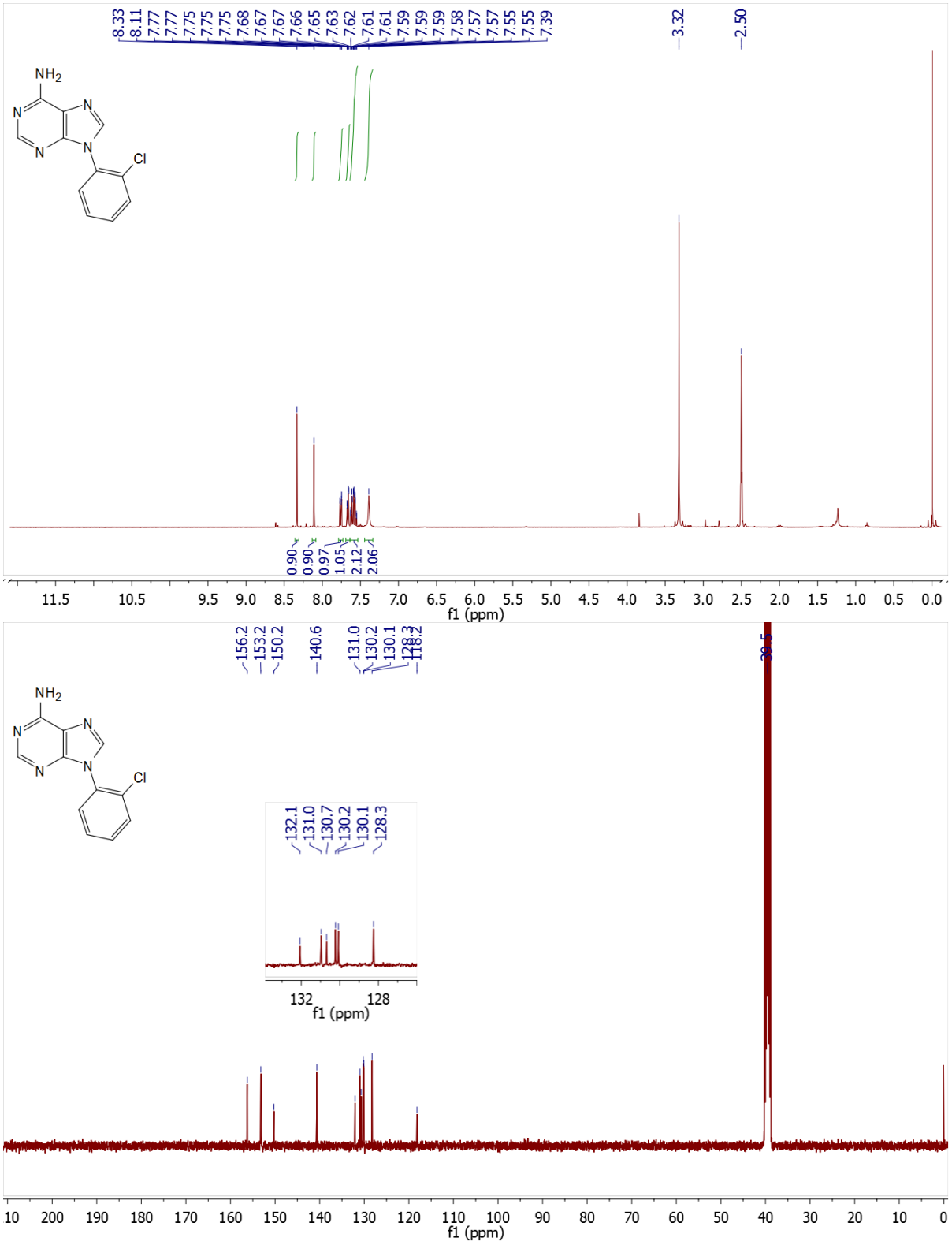
9-(3-(Trifluoromethyl)phenyl)purin-6-amine (3e)



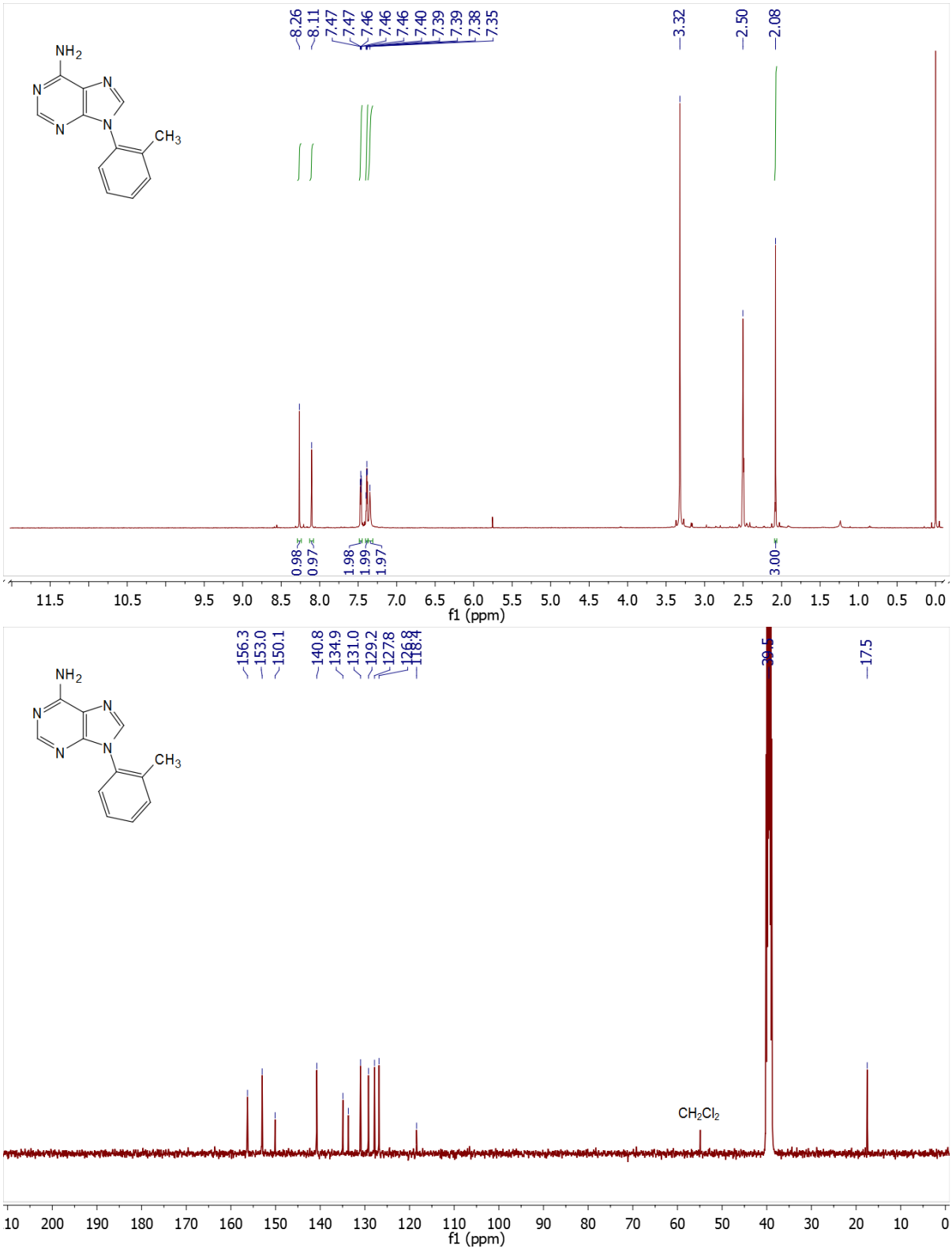
9-(3-Nitrophenyl)purin-6-amine (3f)



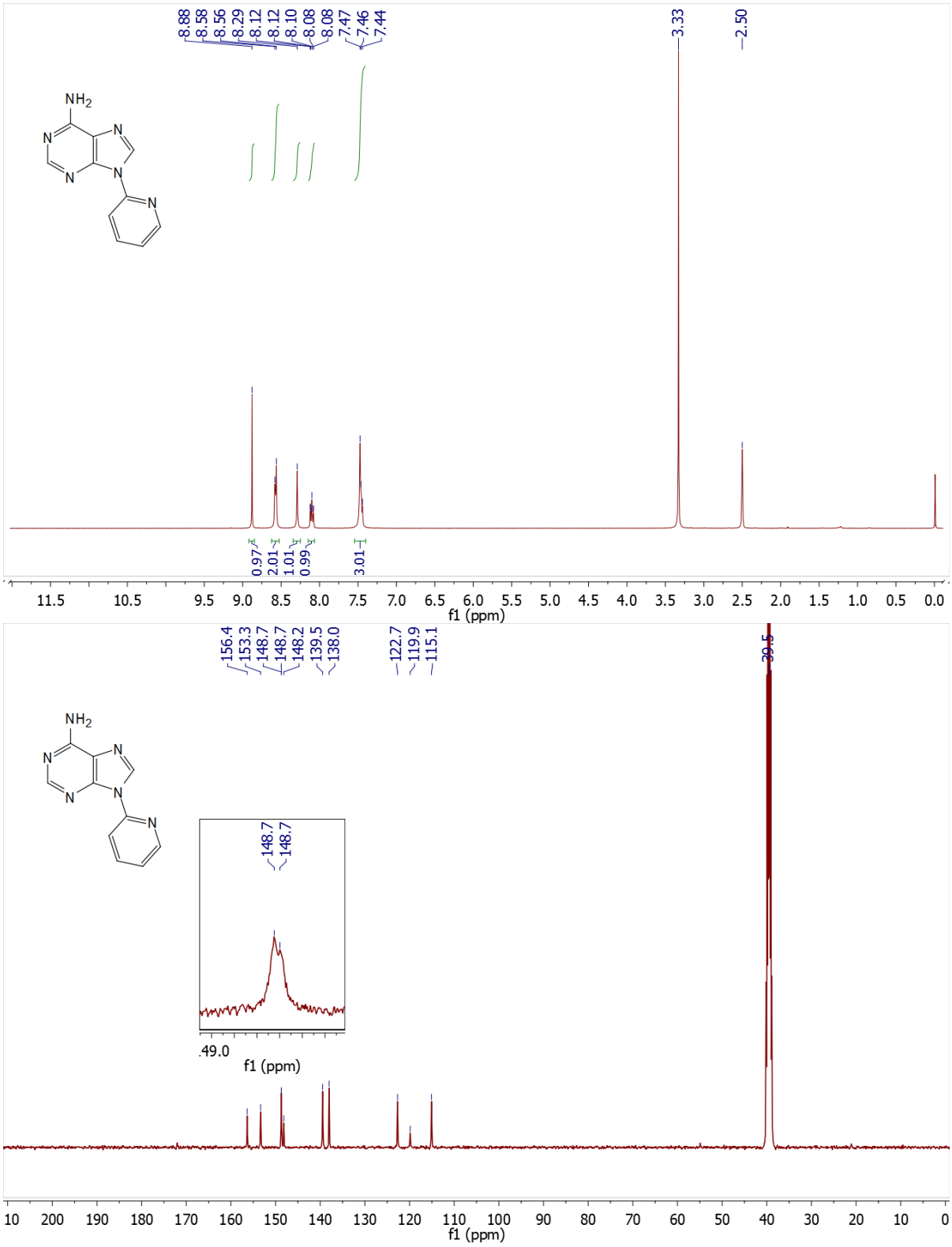
9-(2-Chlorophenyl)purin-6-amine (3g)



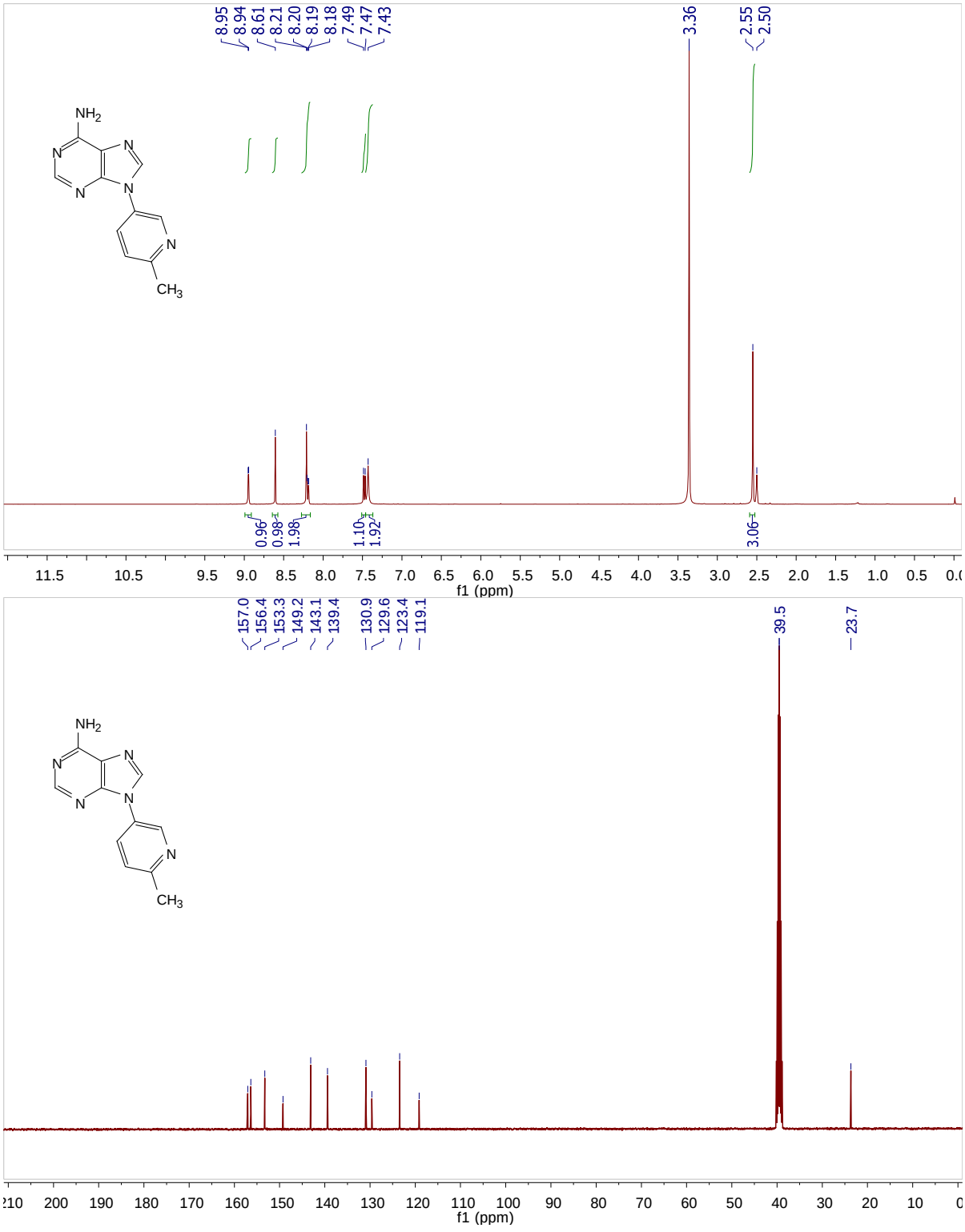
9-(*o*-Tolyl)purin-6-amine (3h)



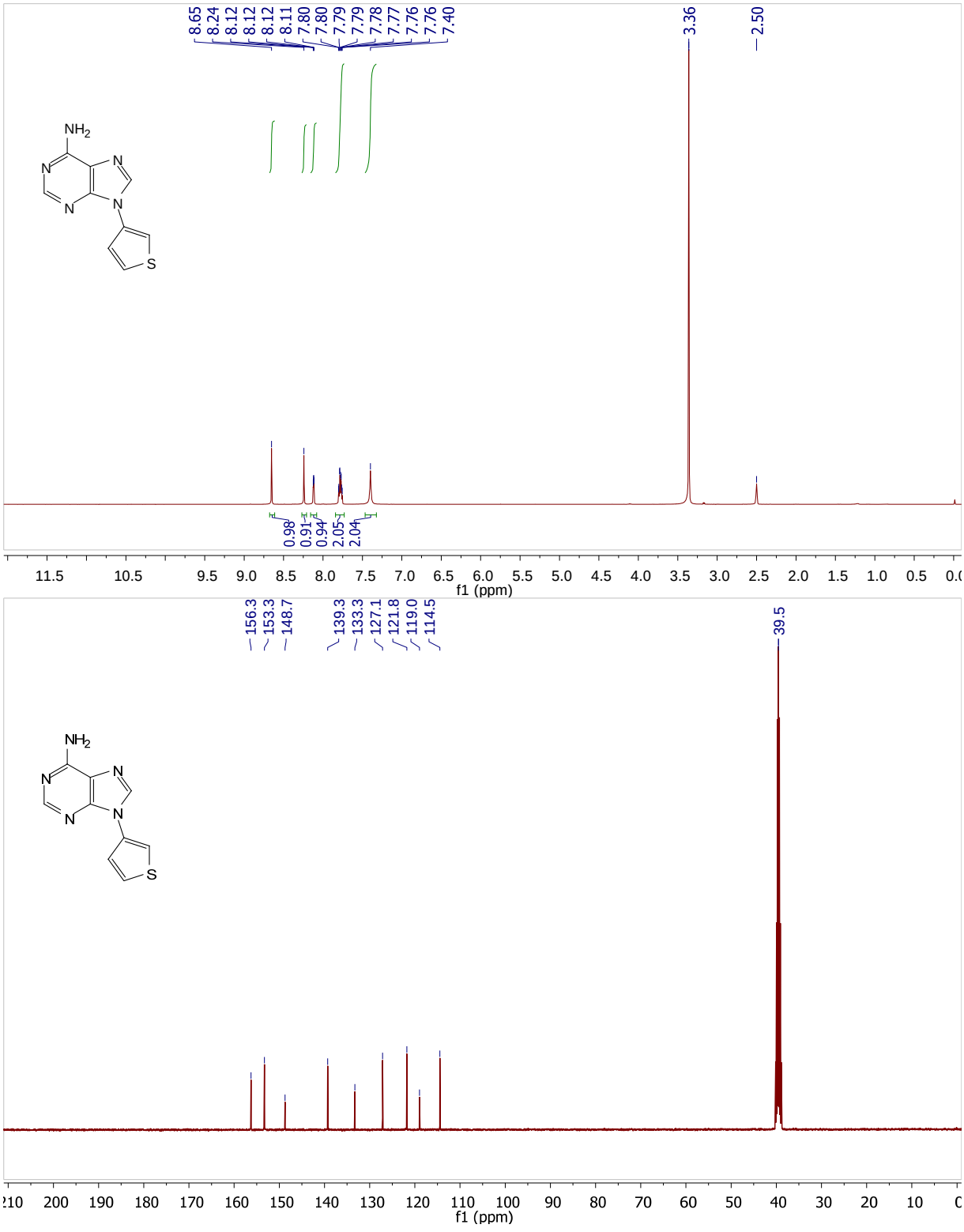
9-(Pyridin-2-yl)purin-6-amine (3i)



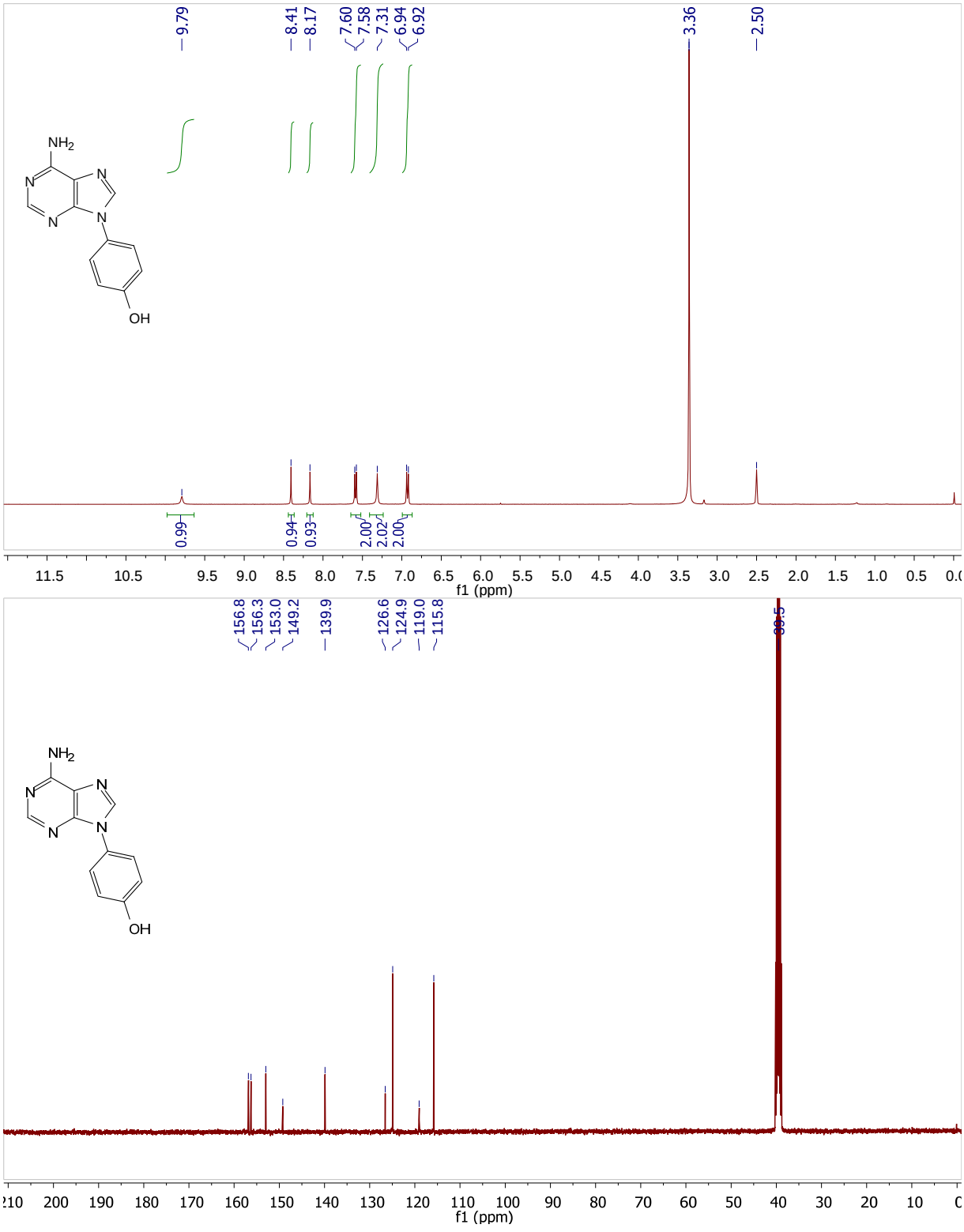
9-(6-Methylpyridin-3-yl)purin-6-amine (3j)



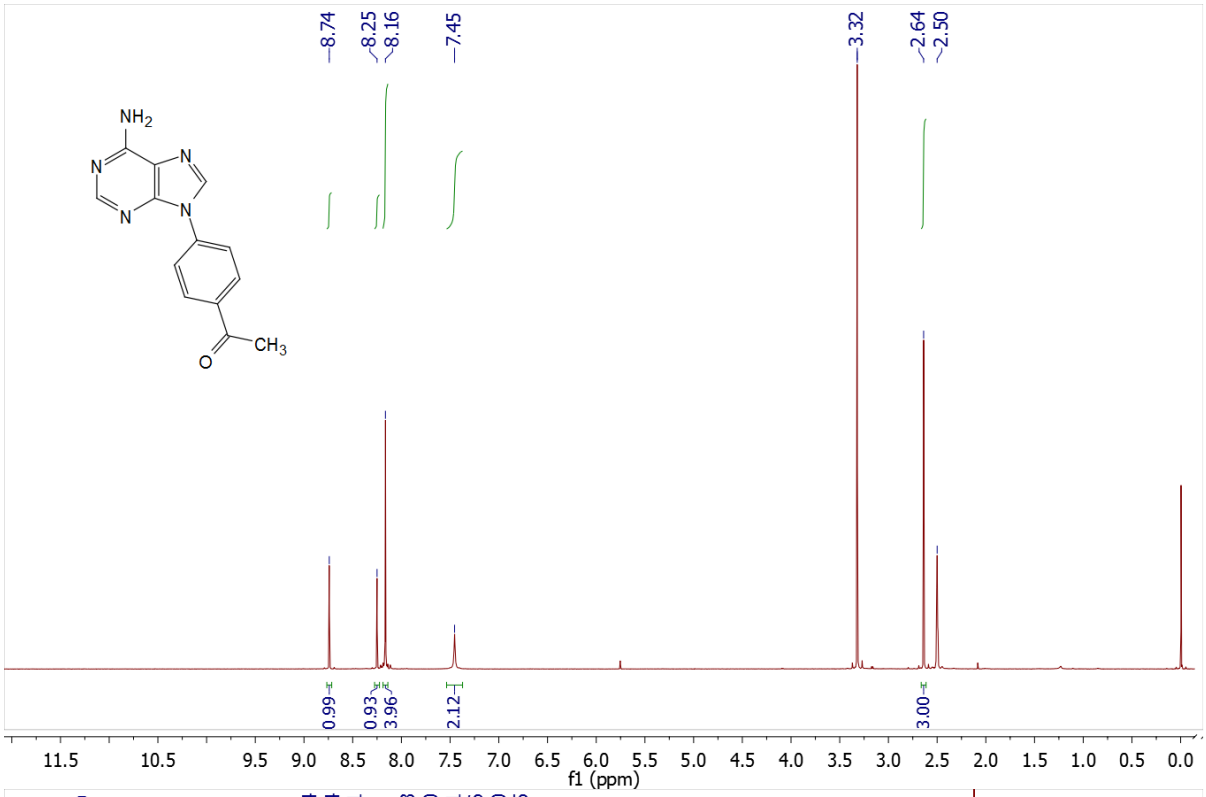
9-(Thiophen-3-yl)purin-6-amine (3k)

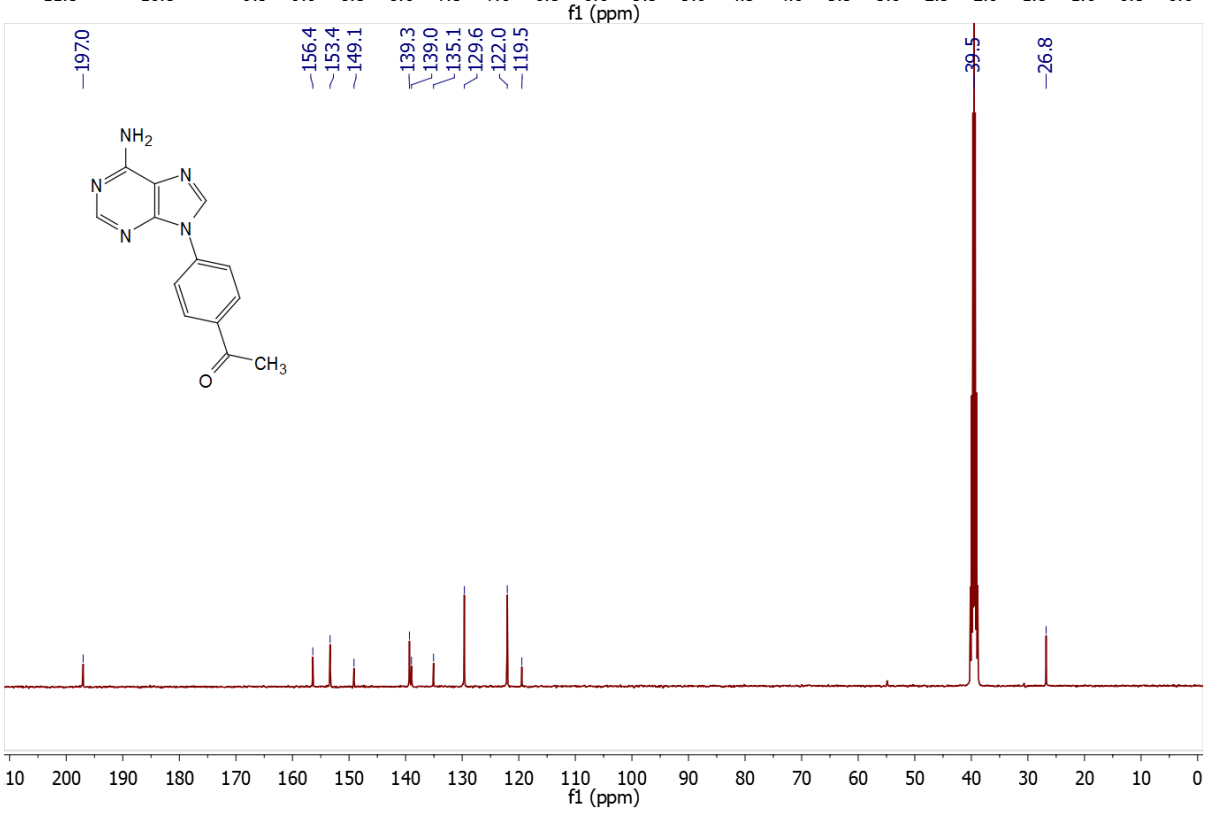


4-(6-Aminopurin-9-yl)phenol (3l)

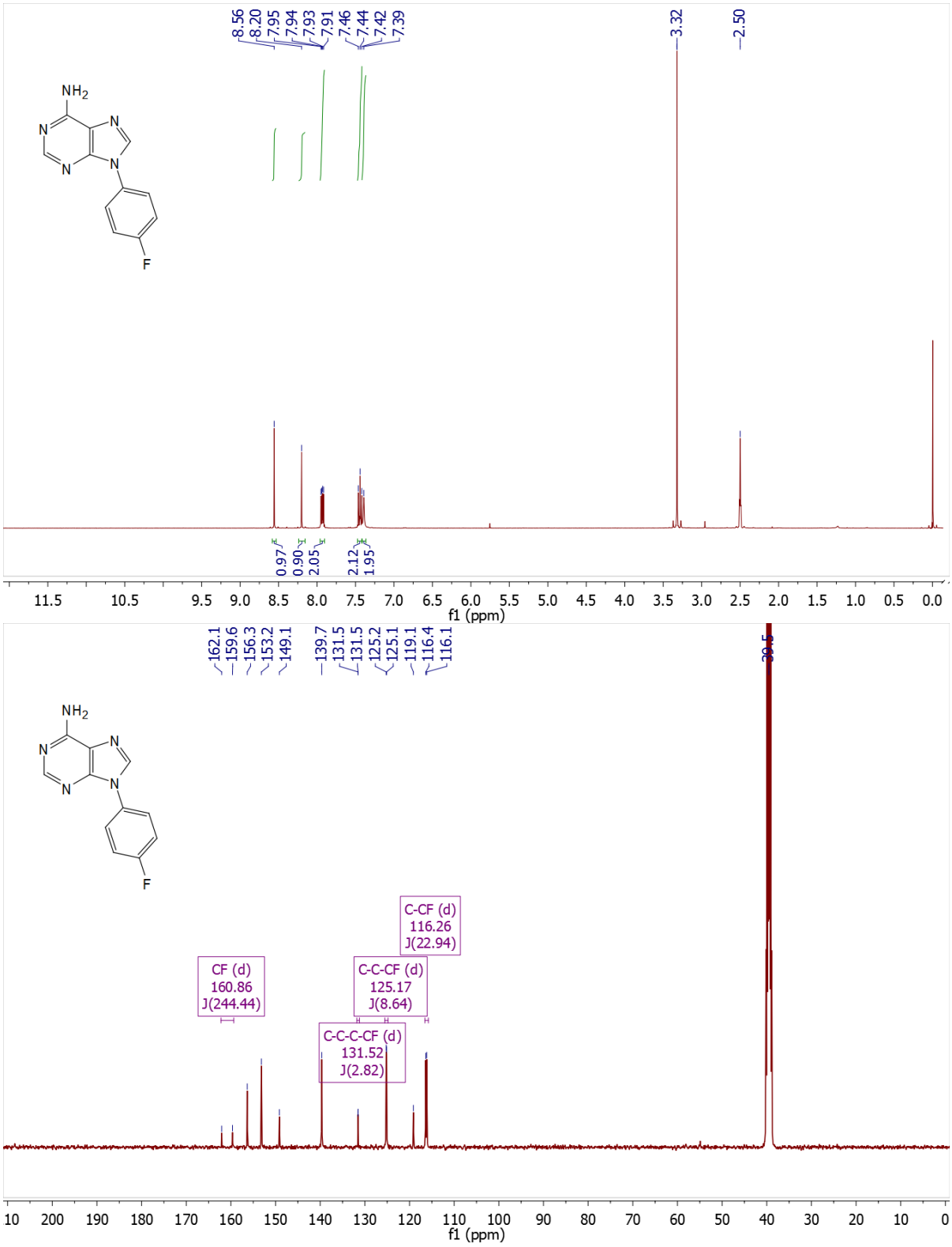


1-(4-(6-Aminopurin-9-yl)phenyl)ethan-1-one (3m)

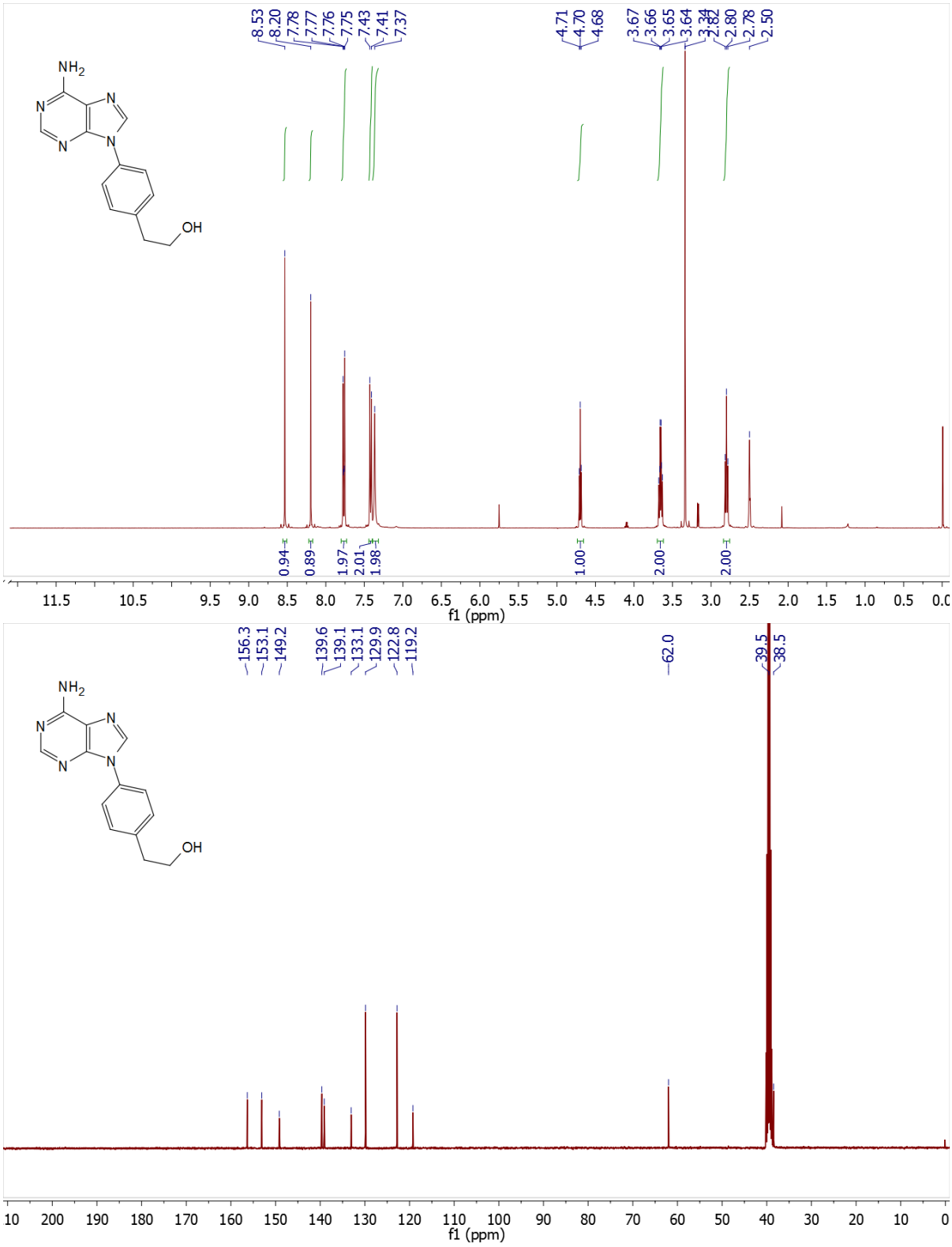




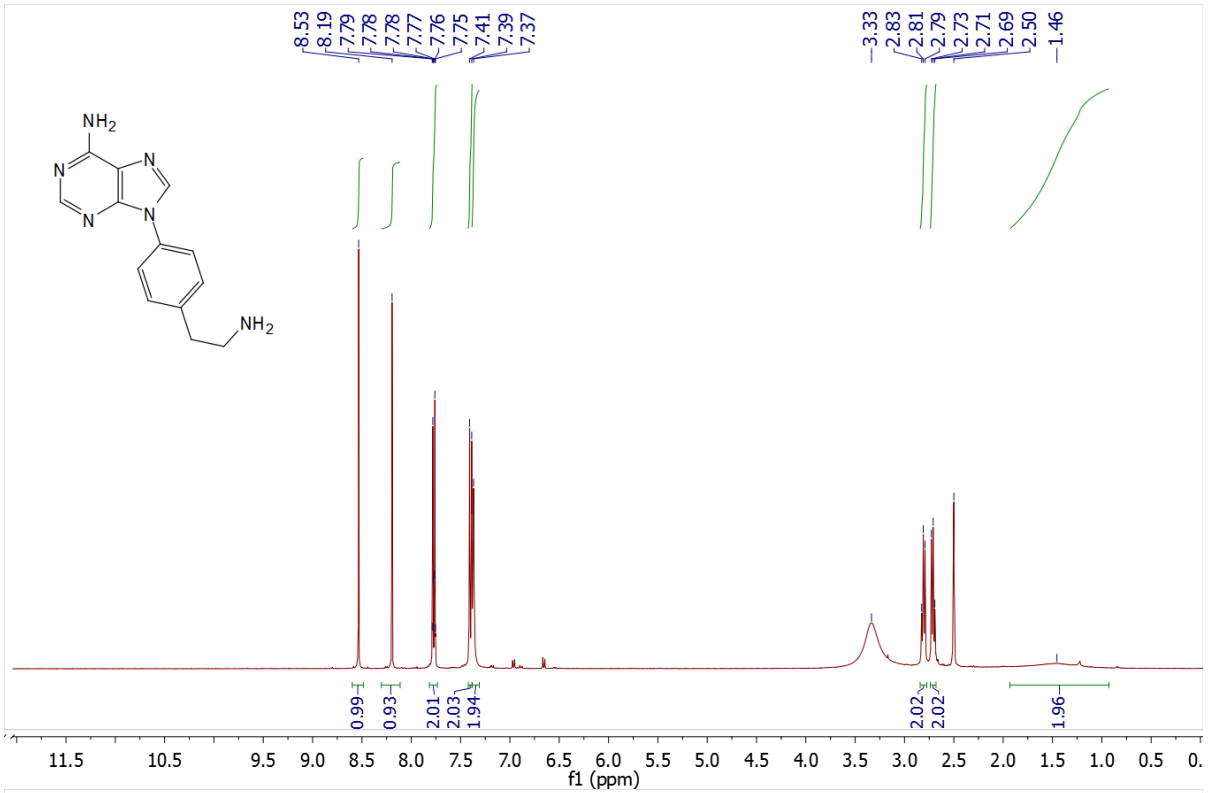
9-(4-Fluorophenyl)purin-6-amine (3n)

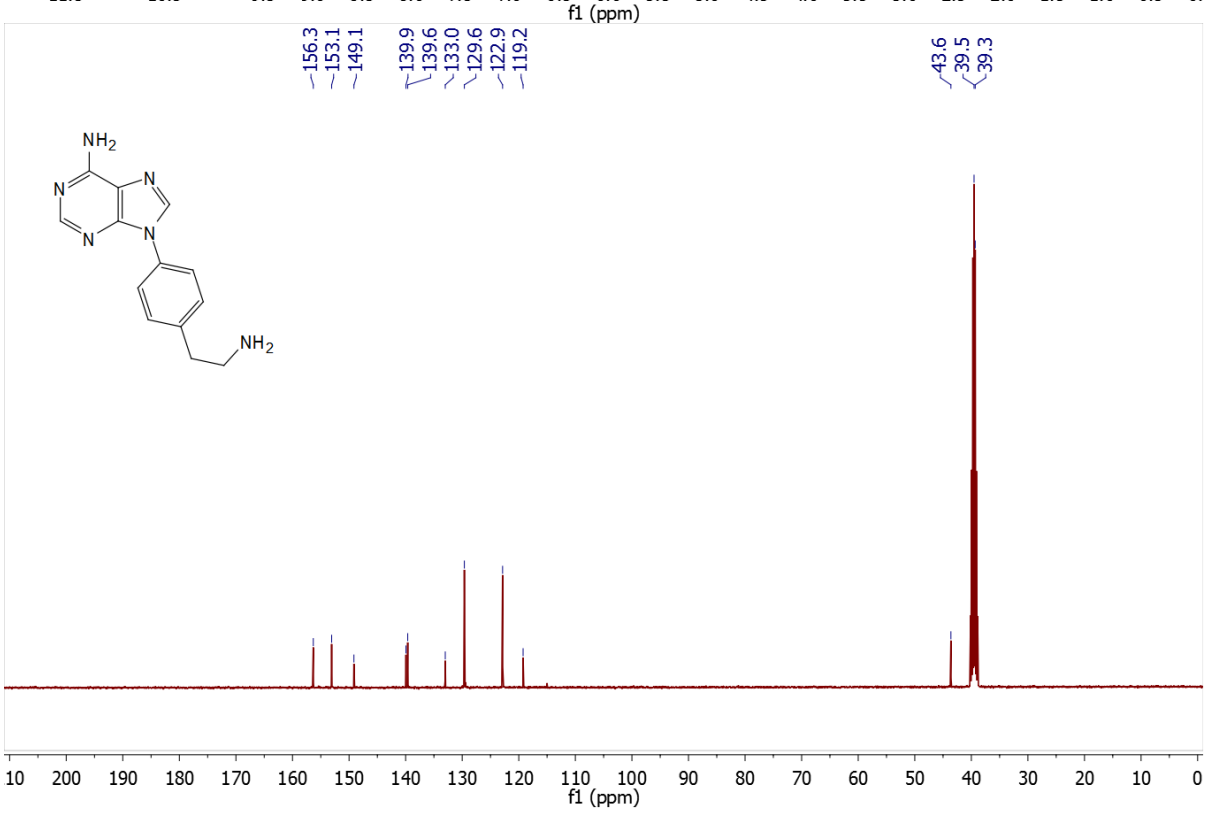


2-(4-(6-Aminopurin-9-yl)phenyl)ethan-1-ol (3o)

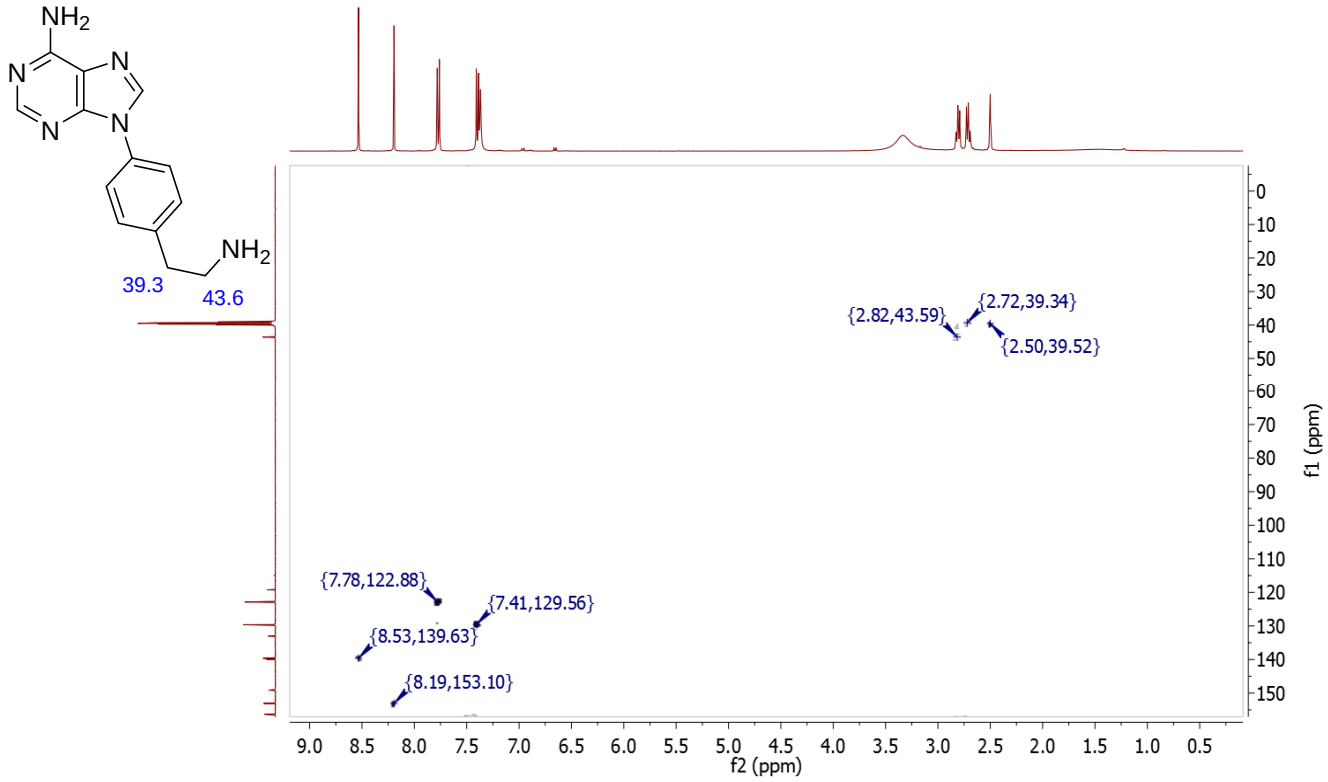


9-(4-(2-Aminoethyl)phenyl)purin-6-amine (3p)

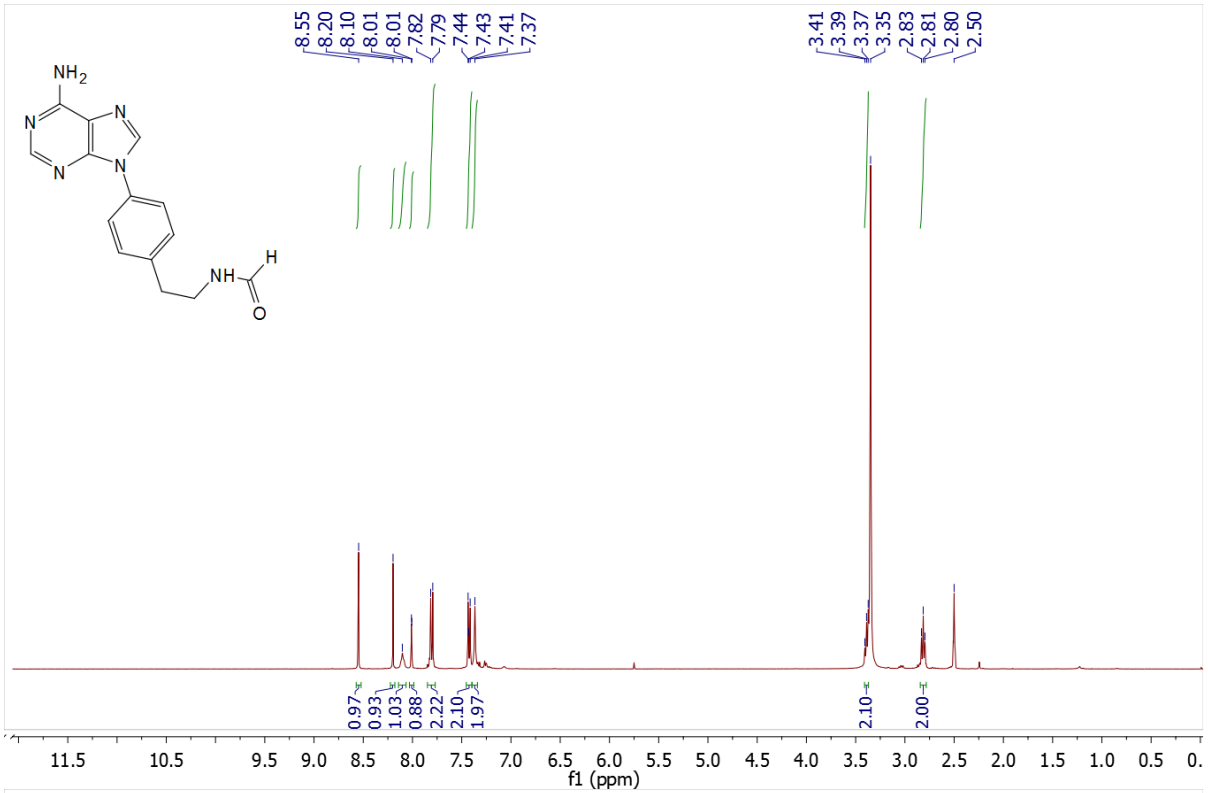


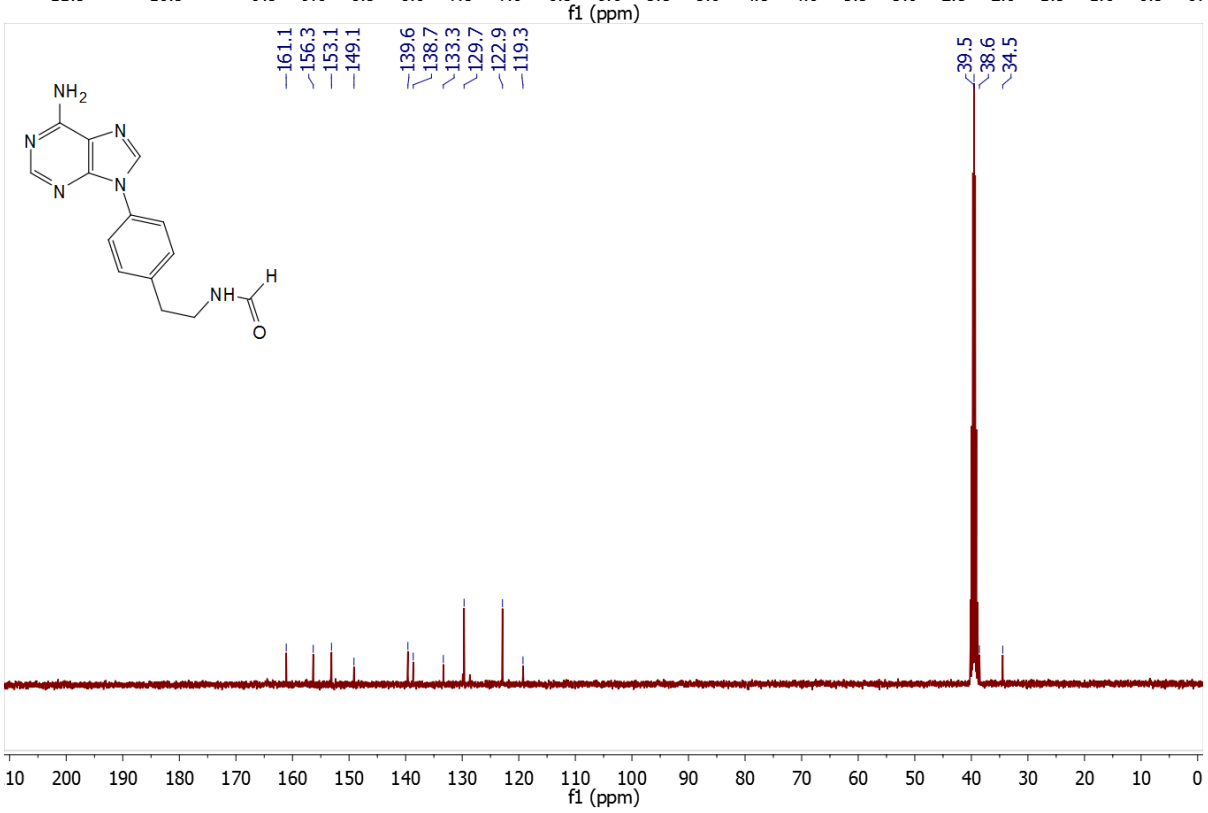


HSQC of **3p**:

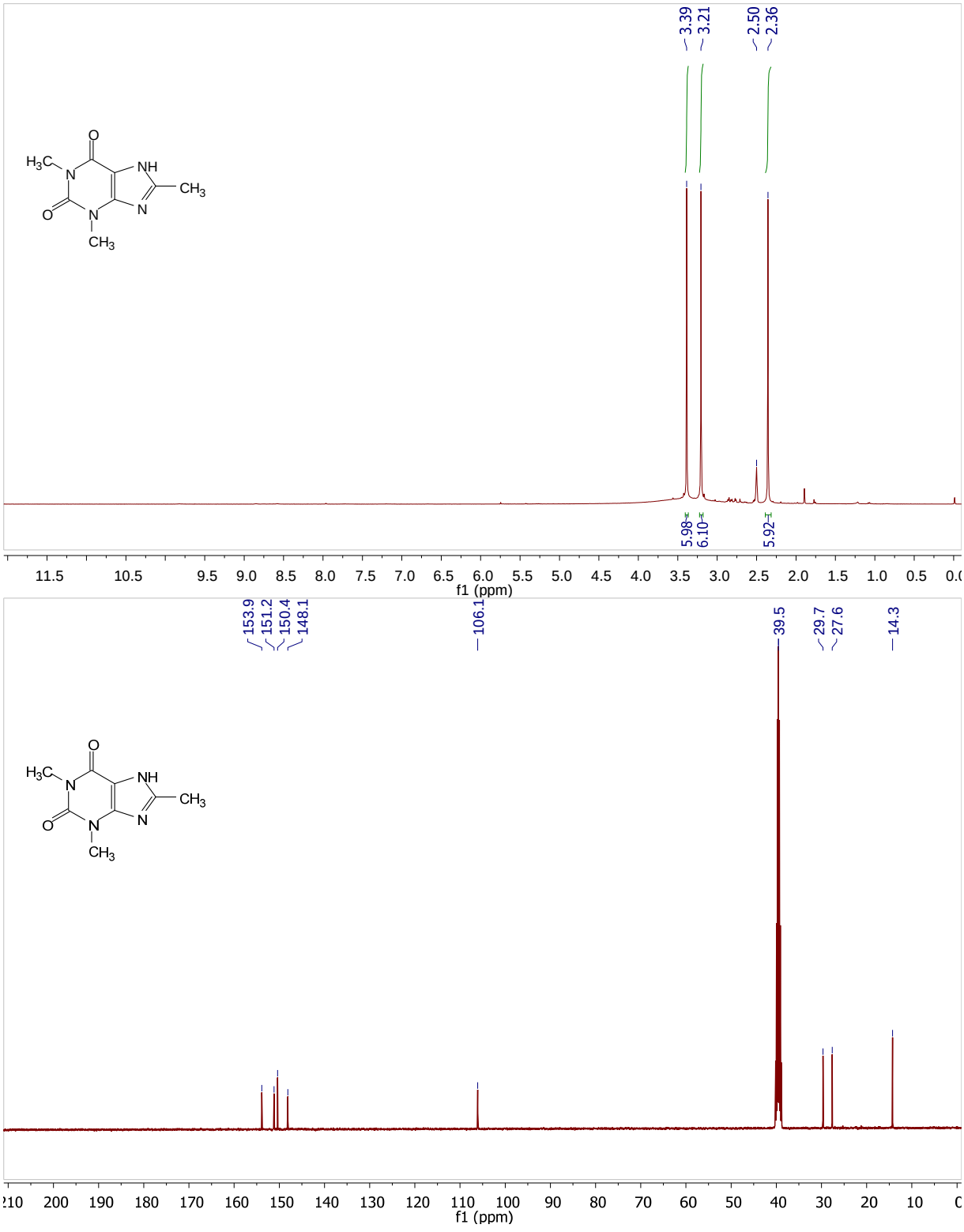

NH2
N
N
N
N
NH2
39.3
43.6
{2.82,43.59}
{2.72,39.34}
{2.50,39.52}
{7.78,122.88}
{7.41,129.56}
{8.53,139.63}
{8.19,153.10}
f1 (ppm)
f2 (ppm)

_N_-(4-(6-Aminopurin-9-yl)phenethyl)formamide

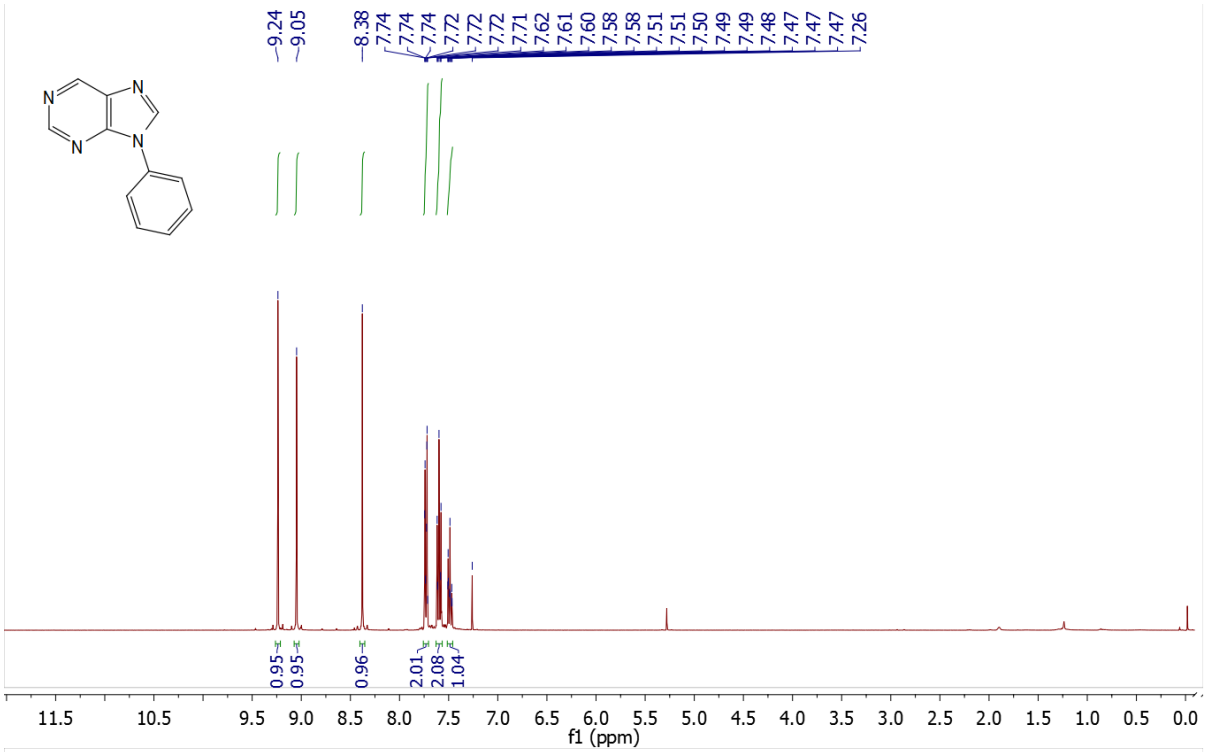


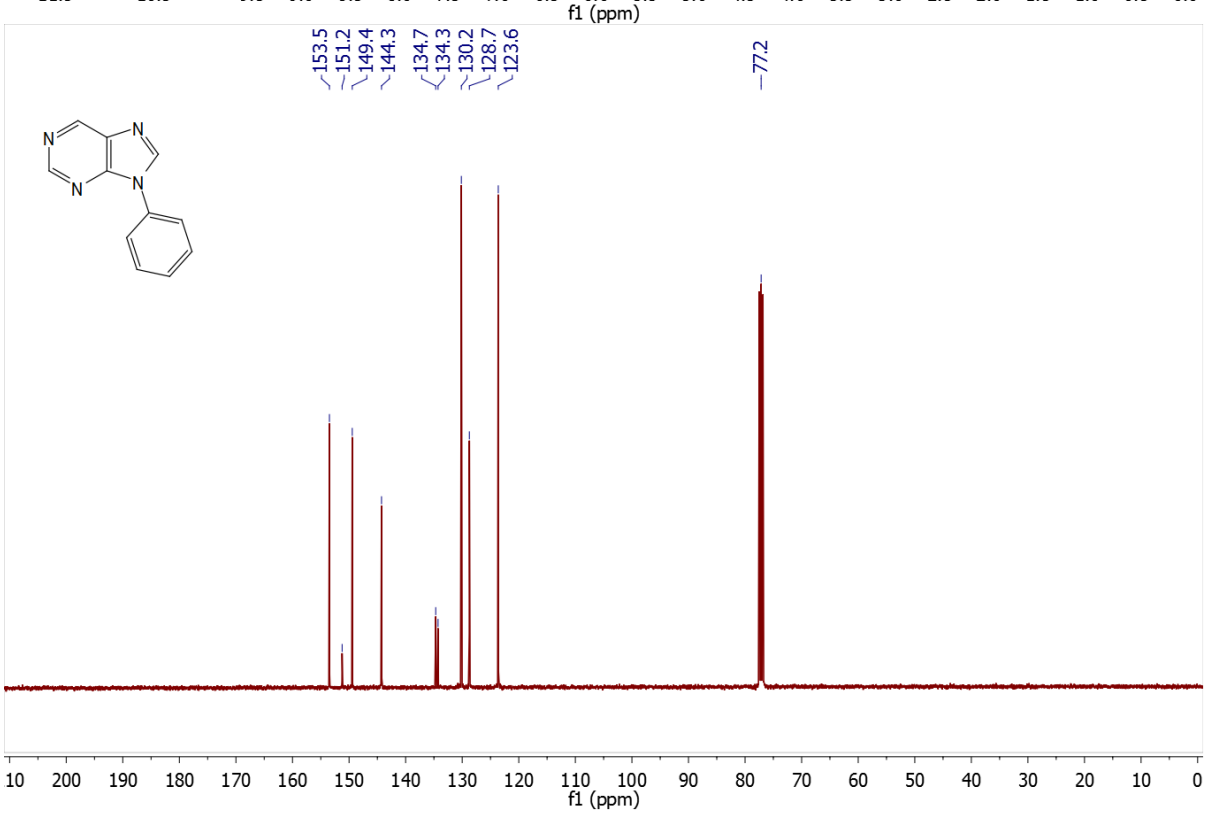


8-Methyltheophylline (4d)

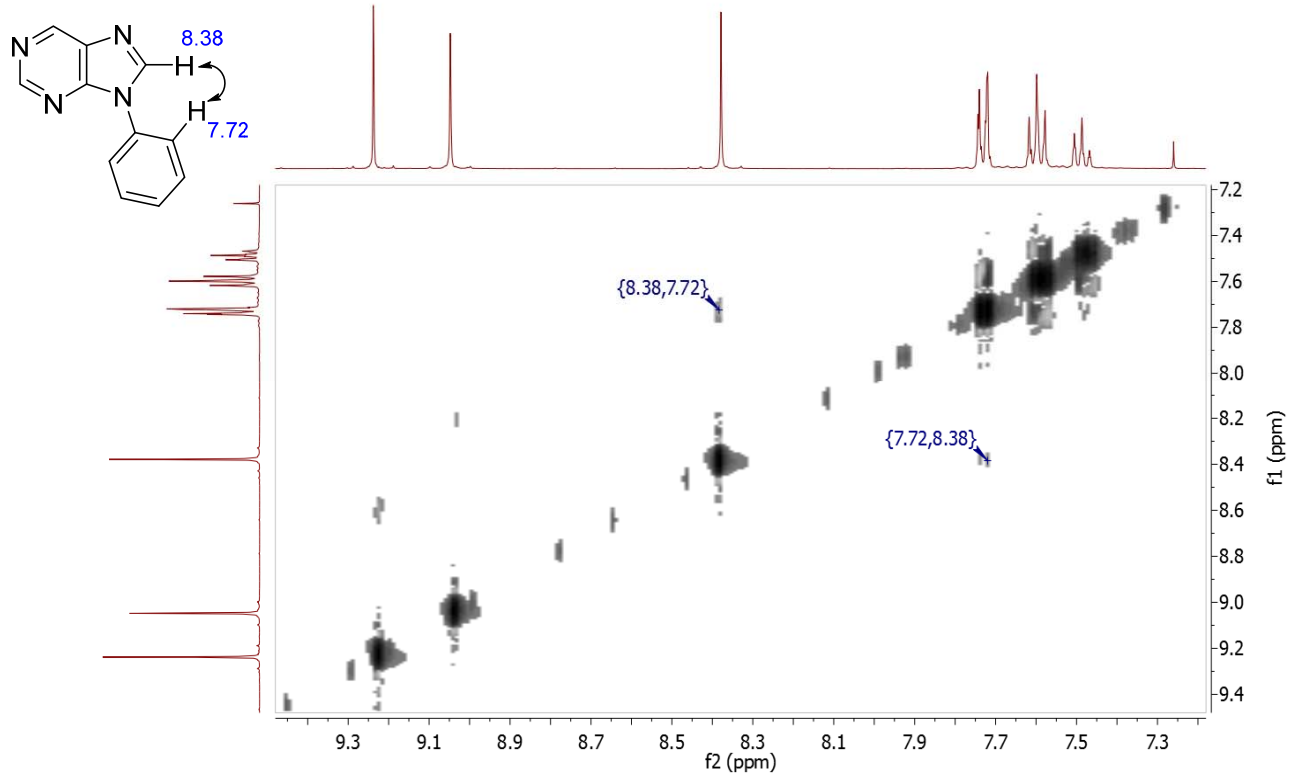


9-Phenylpurine (5a)

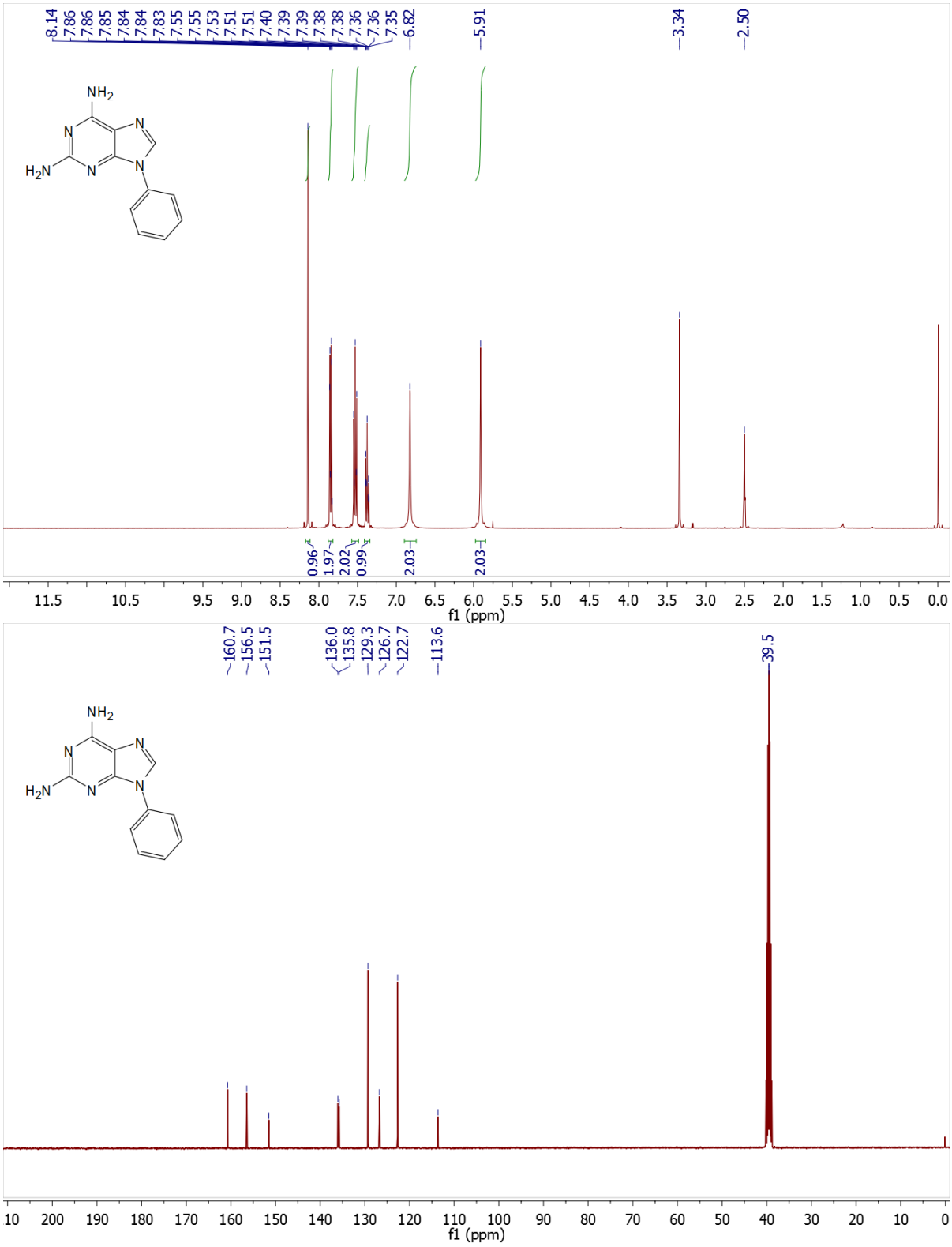




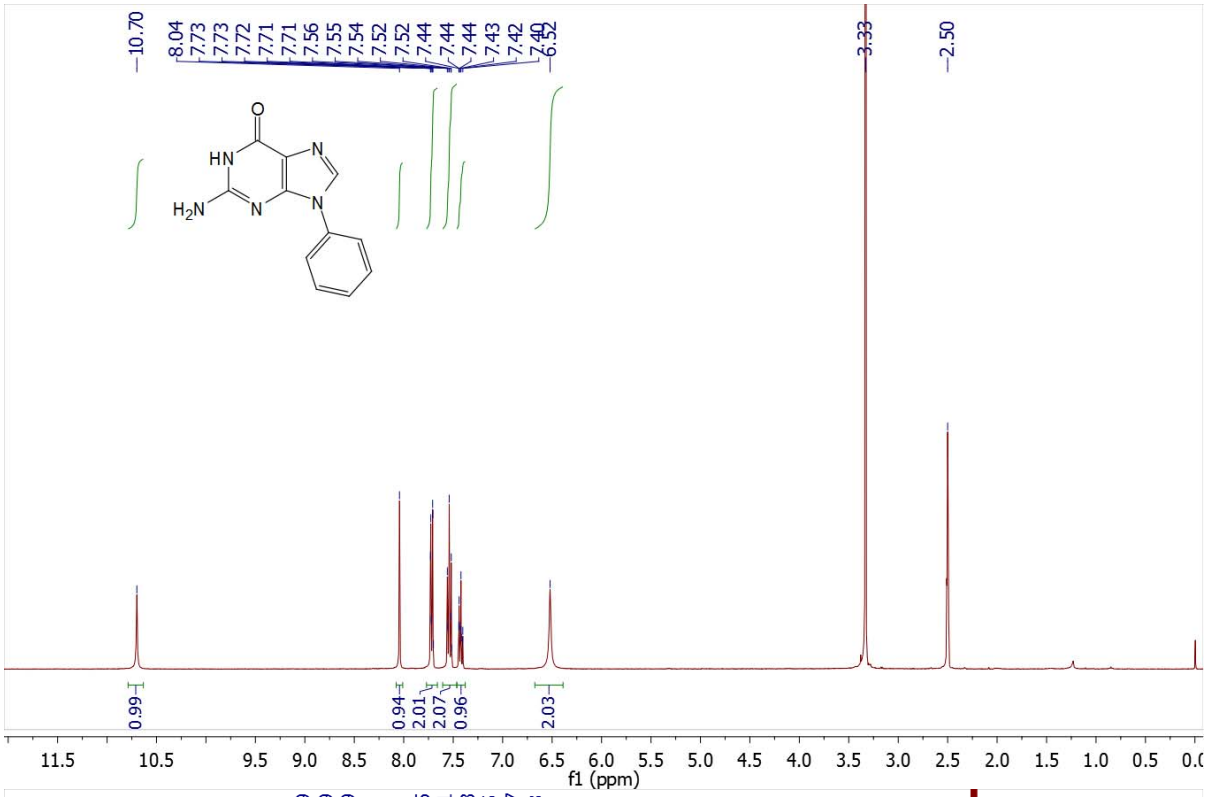
NOESY of **5a**

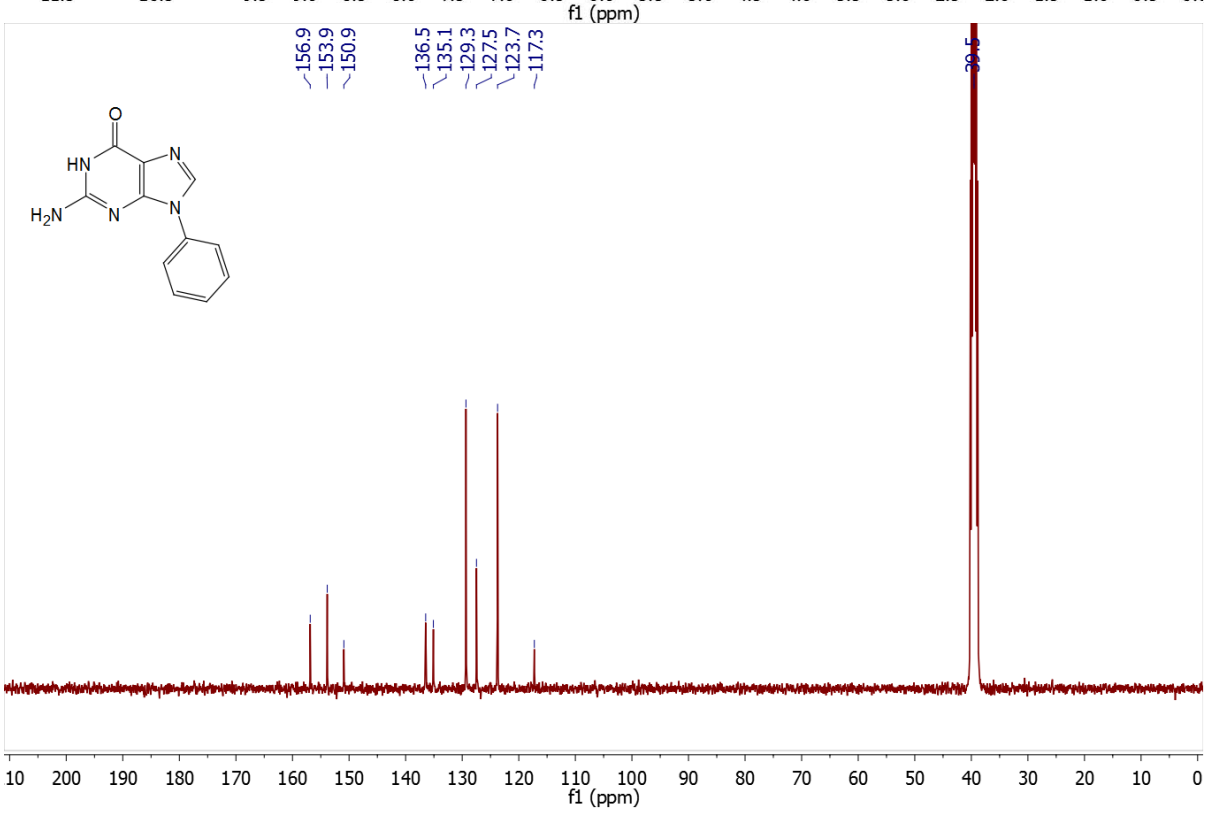


9-Phenylpurine-2,6-diamine (5b)

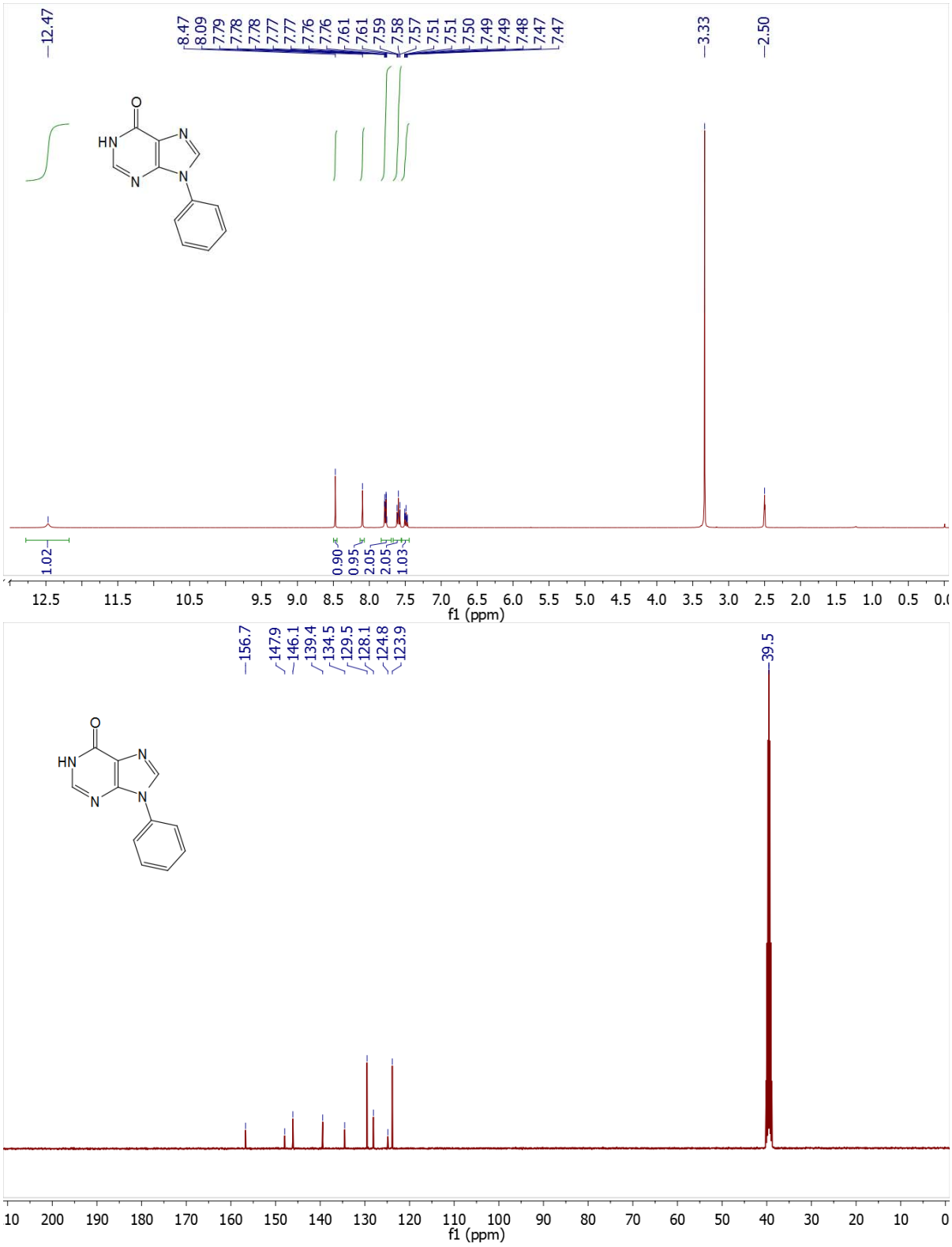


9-Phenylguanine (5e)

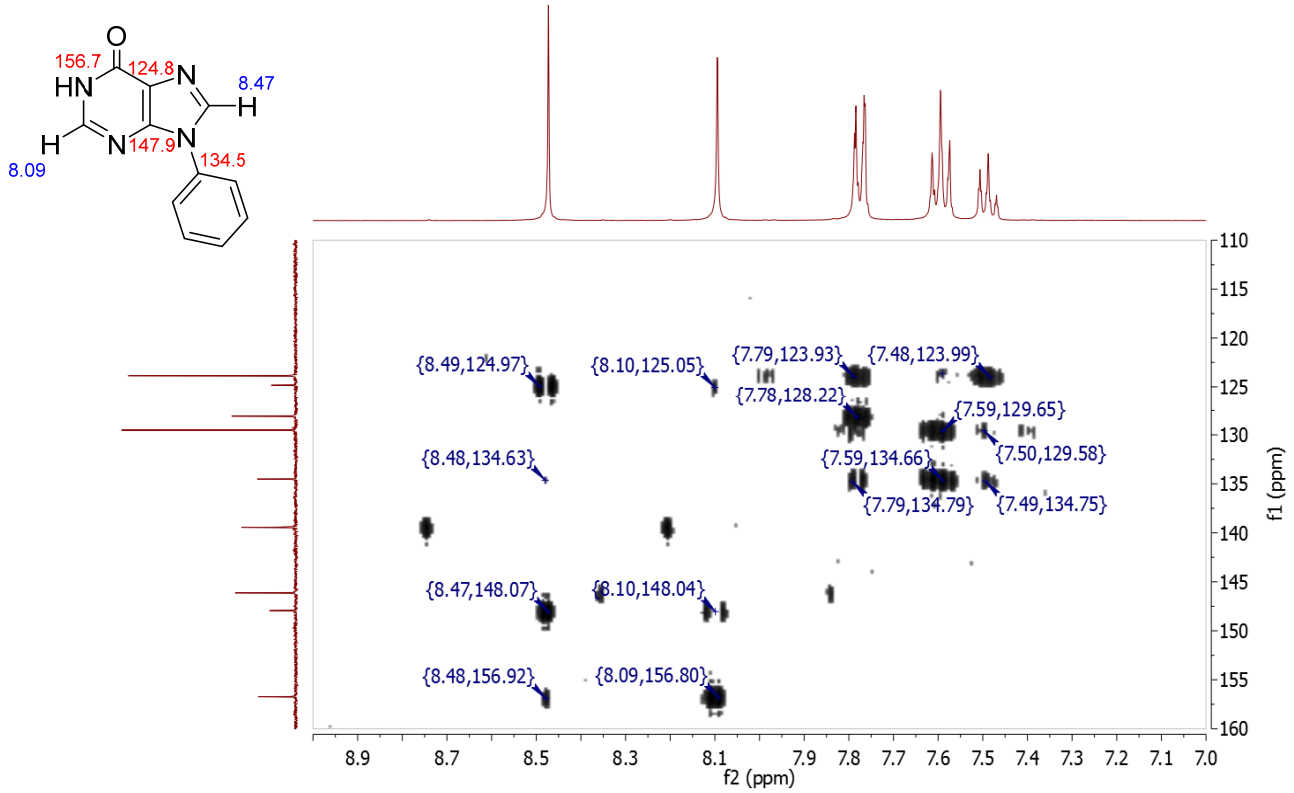




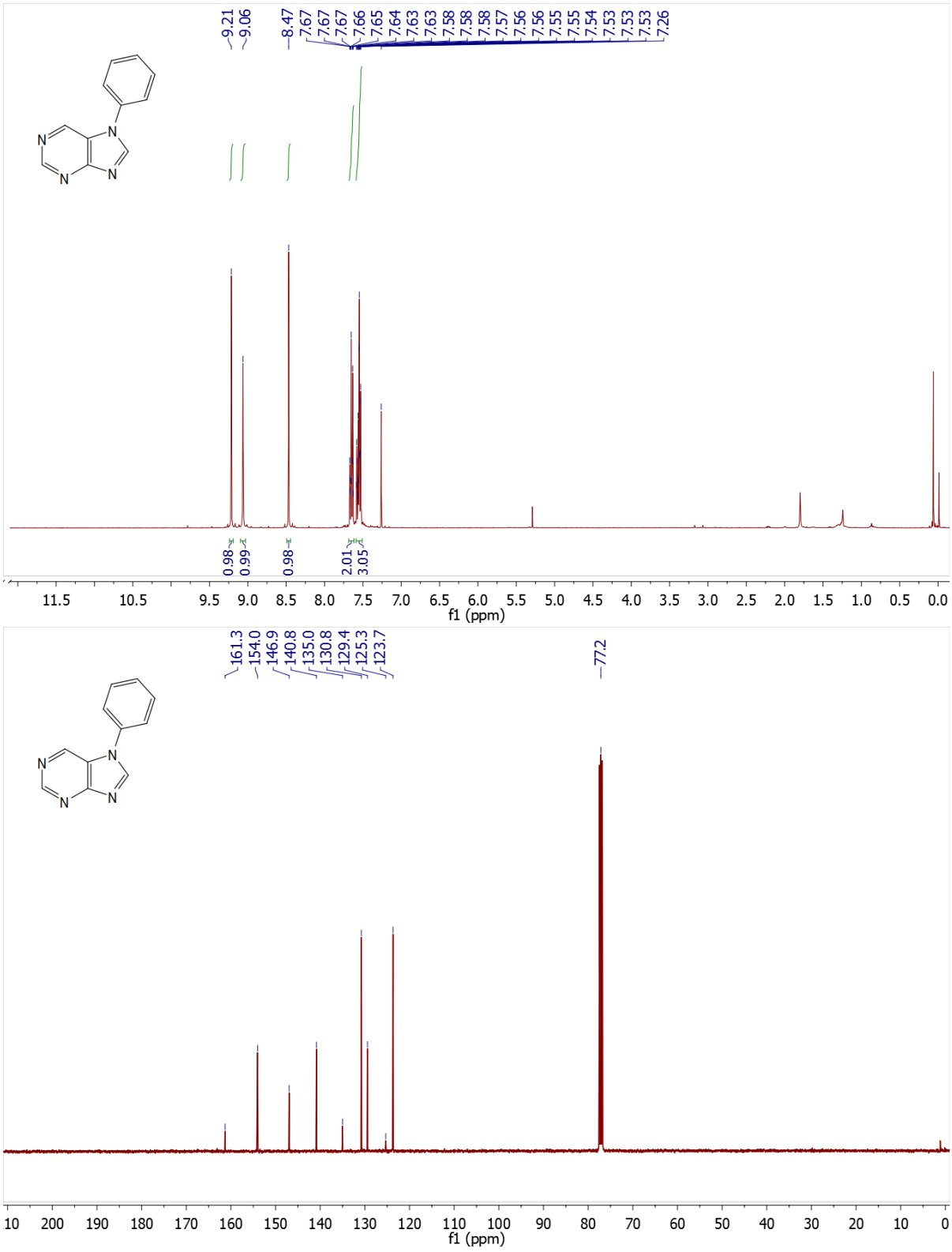
9-Phenylhypoxanthine (5f)



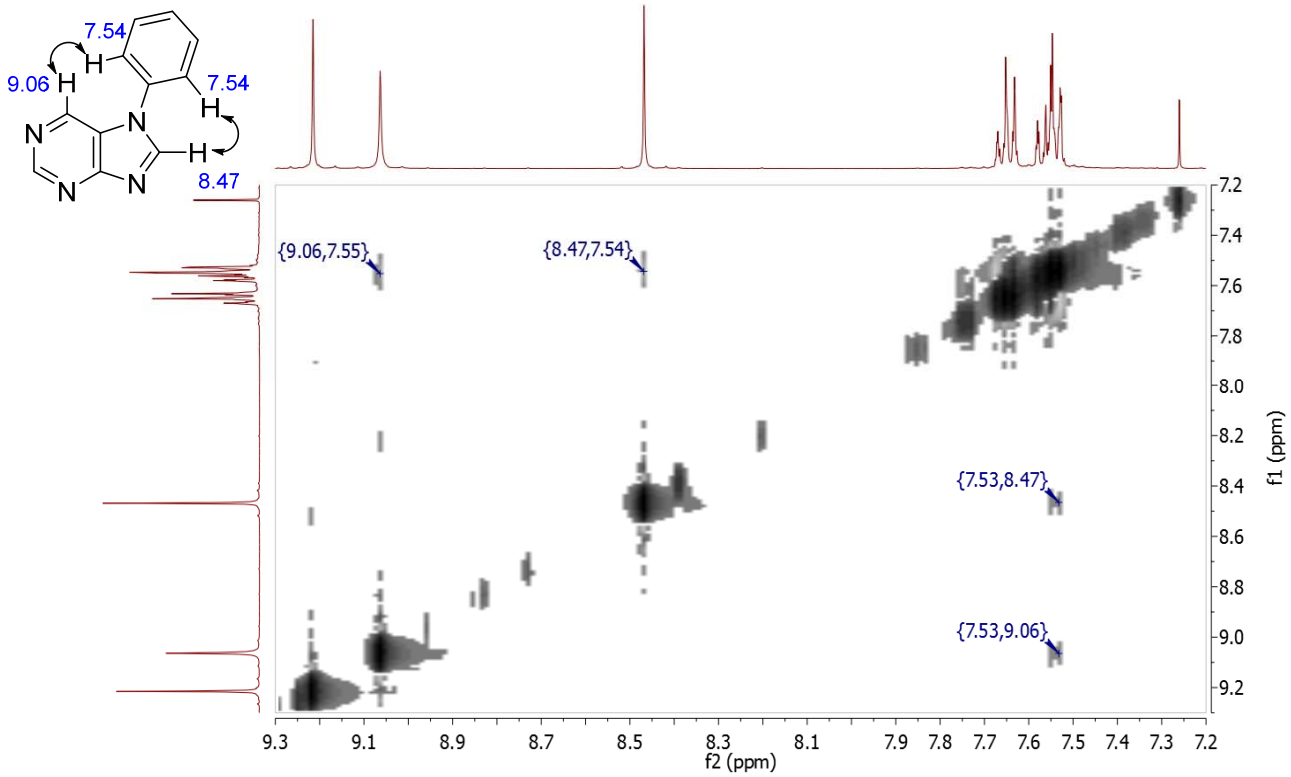
HMBC of **5f**


O
156.7
124.8
HN
N
8.47
H
H
N
147.9
N
134.5
8.09
{8.49,124.97}
{8.10,125.05}
{7.79,123.93}
{7.48,123.99}
{7.78,128.22}
{7.59,129.65}
{8.48,134.63}
{7.59,134.66}
{7.50,129.58}
{7.79,134.79}
{7.49,134.75}
{8.47,148.07}
{8.10,148.04}
{8.48,156.92}
{8.09,156.80}
f1 (ppm)
f2 (ppm)

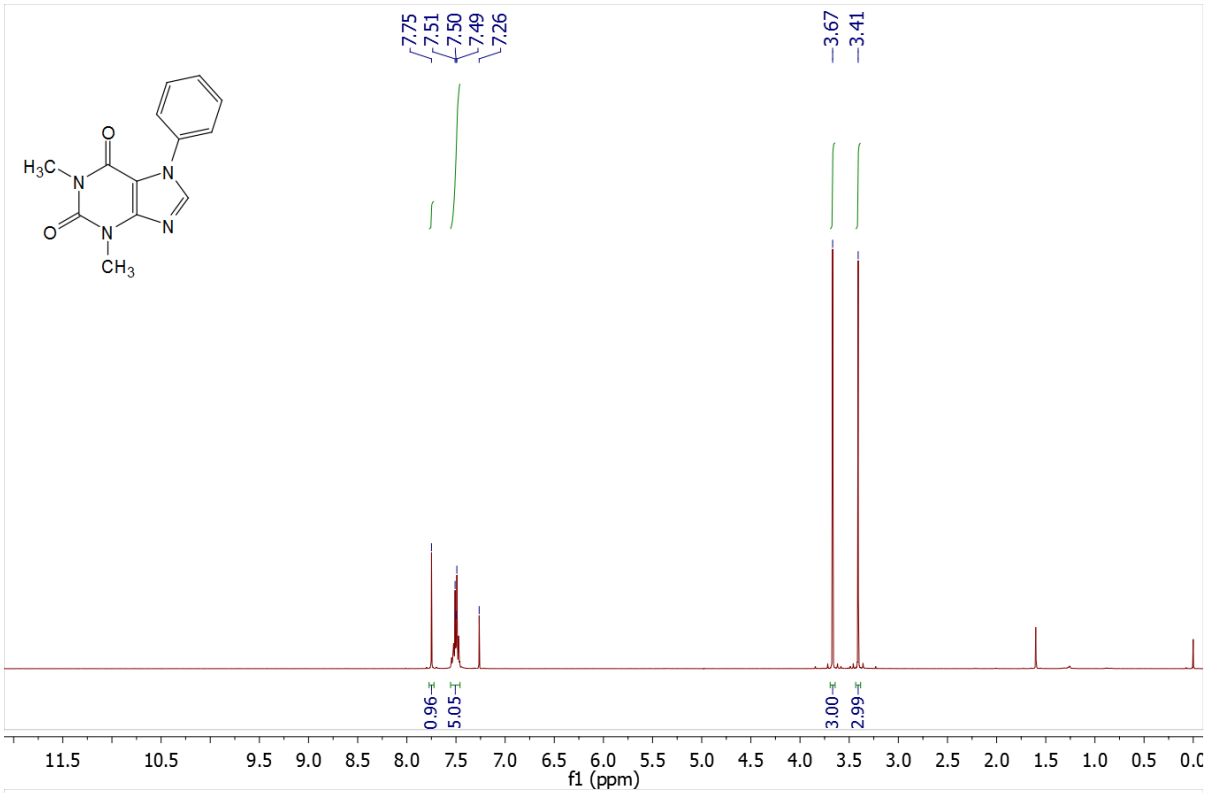
7-Phenylpurine (6a)

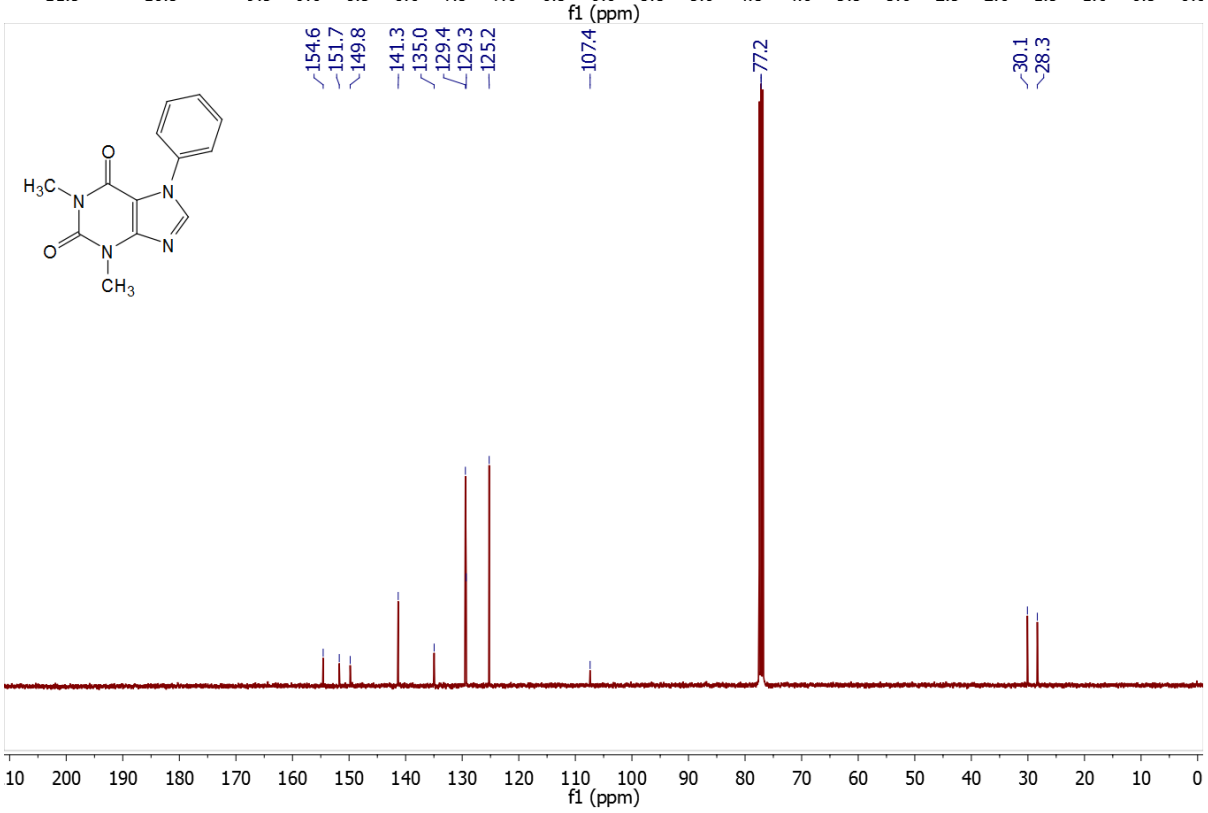


NOESY of **6a**

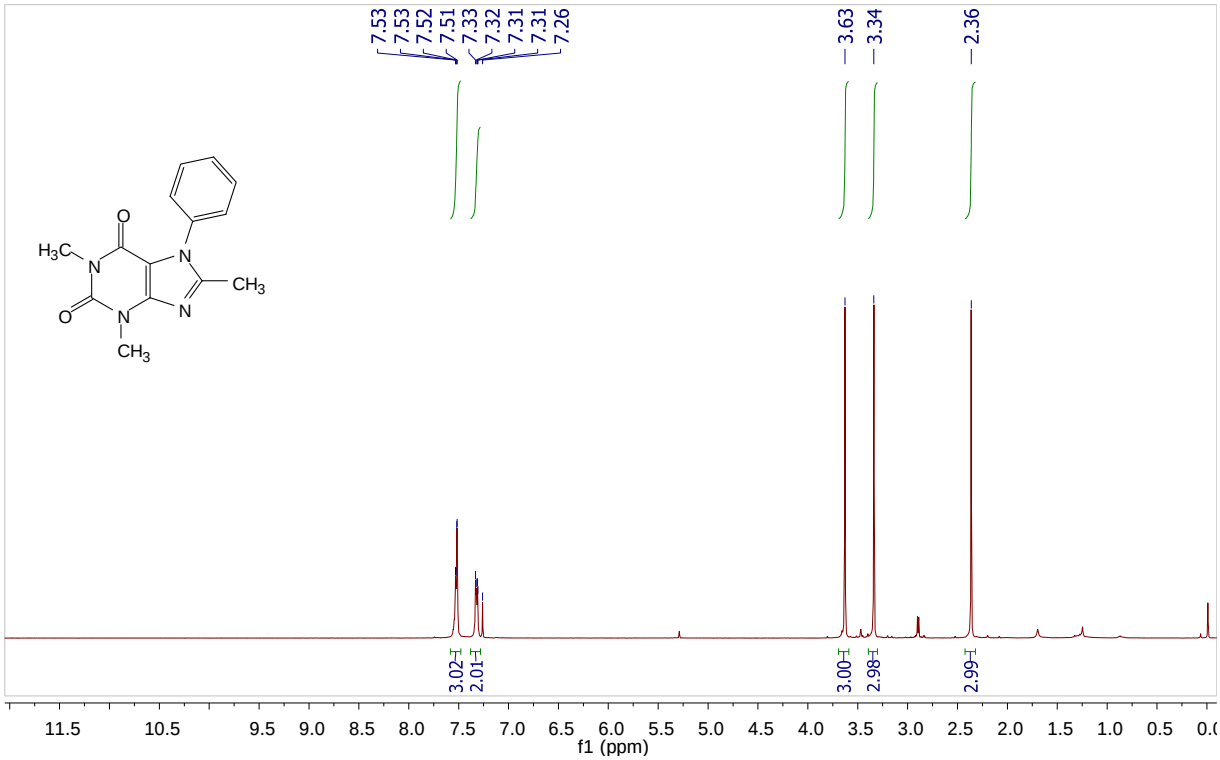


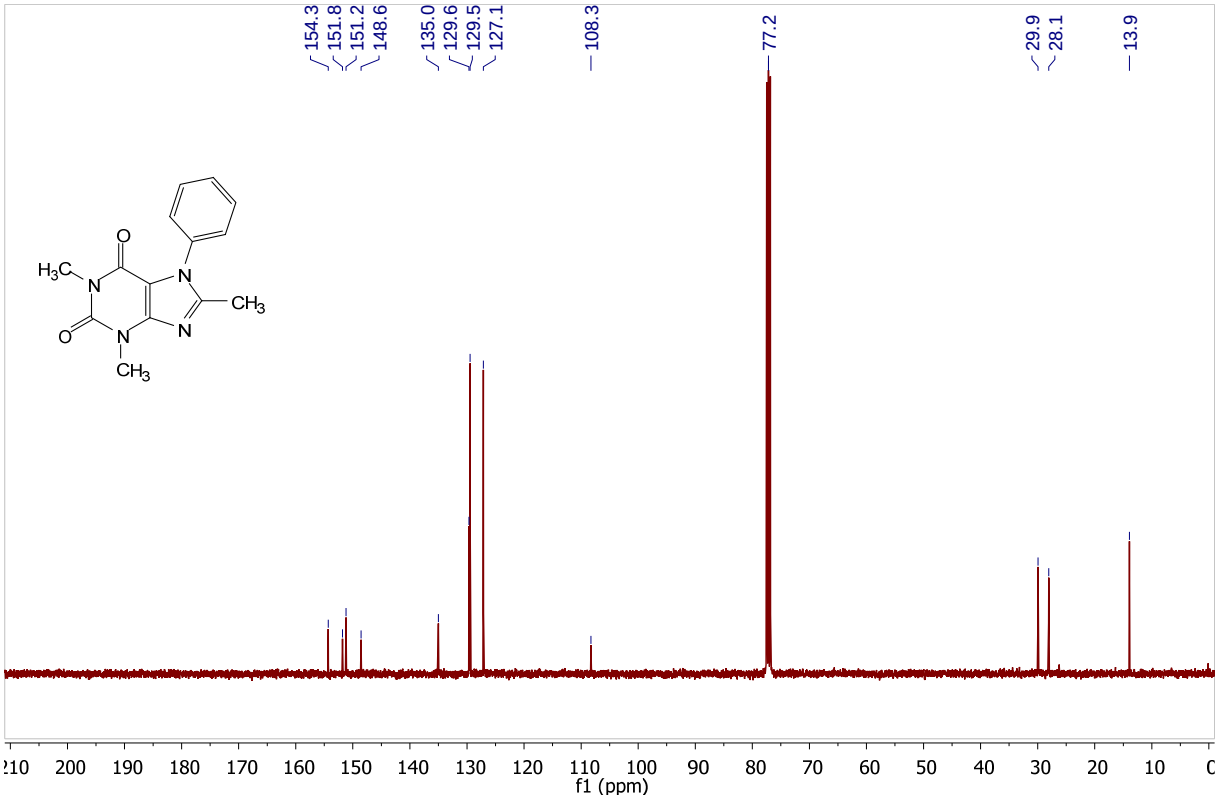
7-Phenyltheophylline (6c)



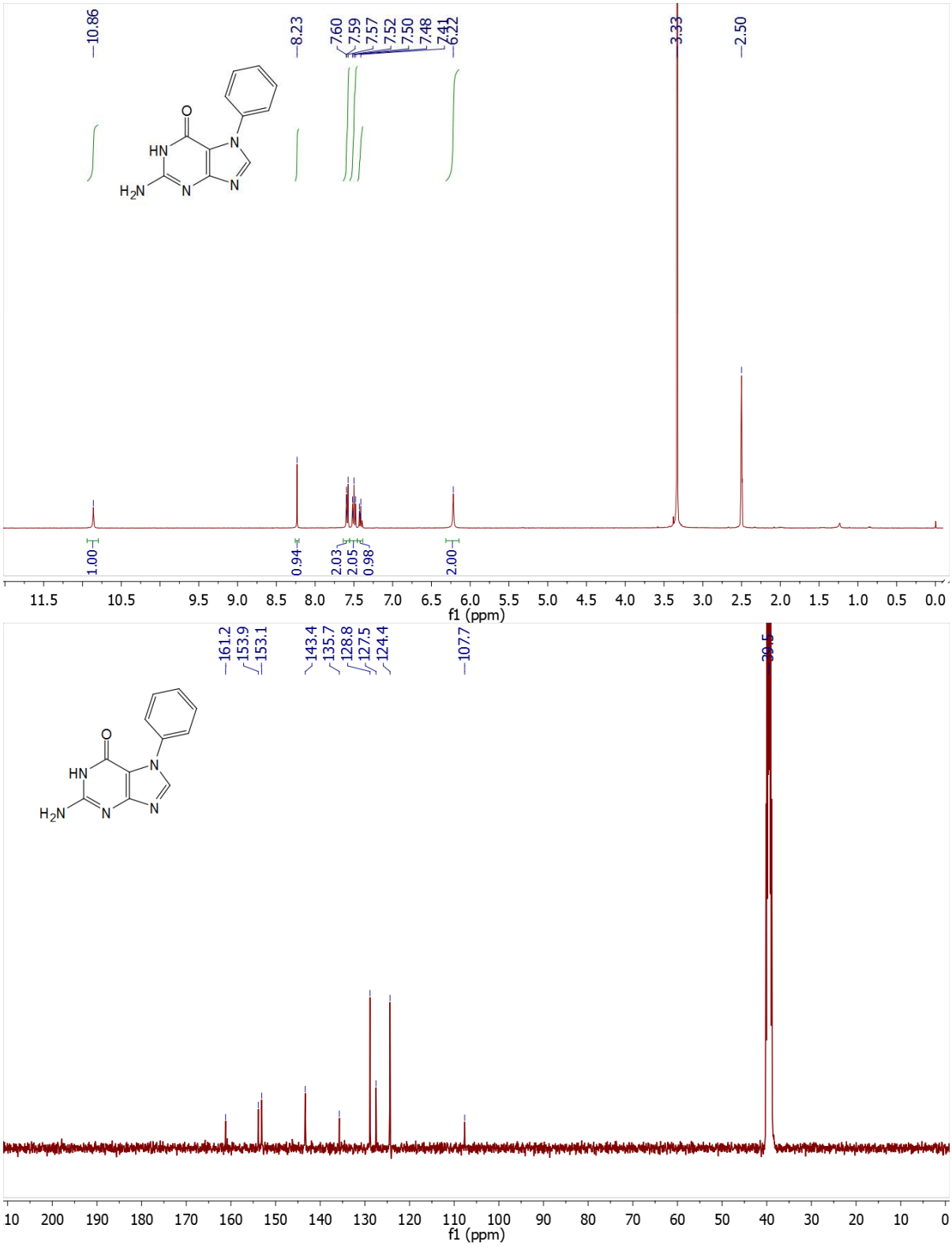


8-methyl-7-phenyltheophylline (6d)

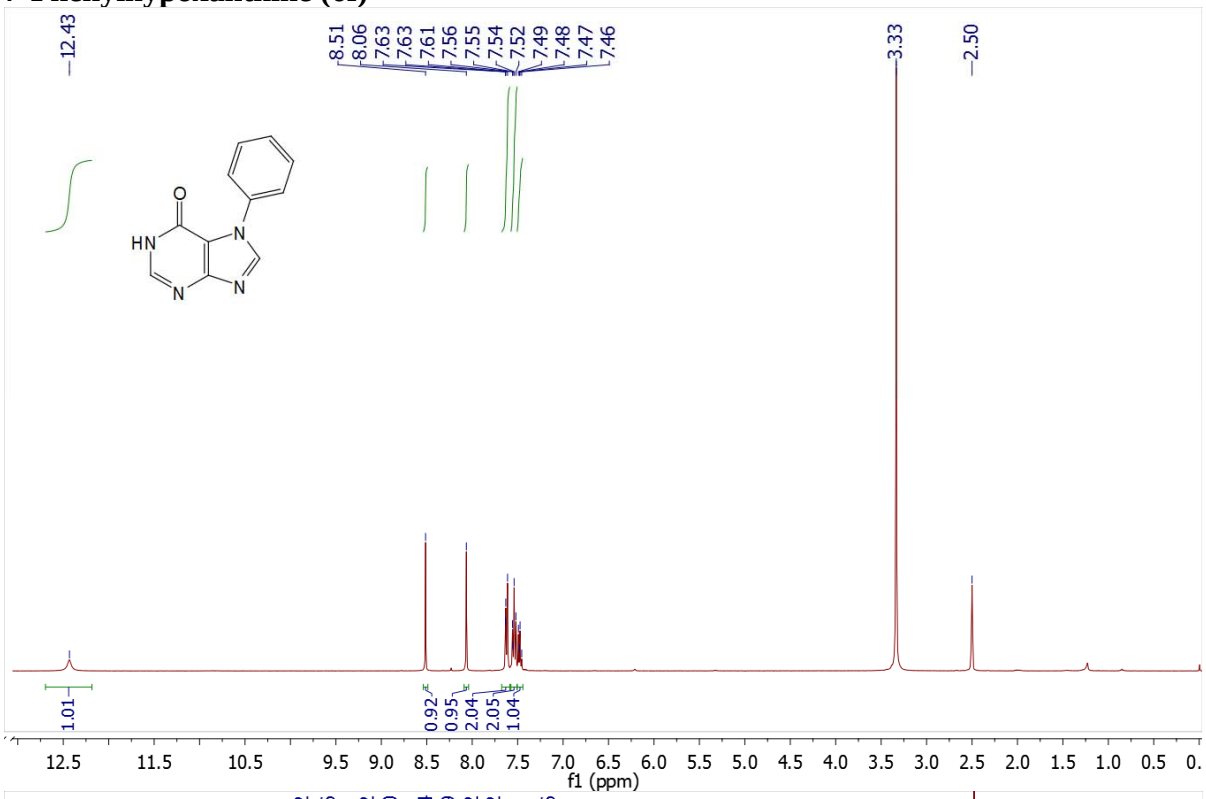


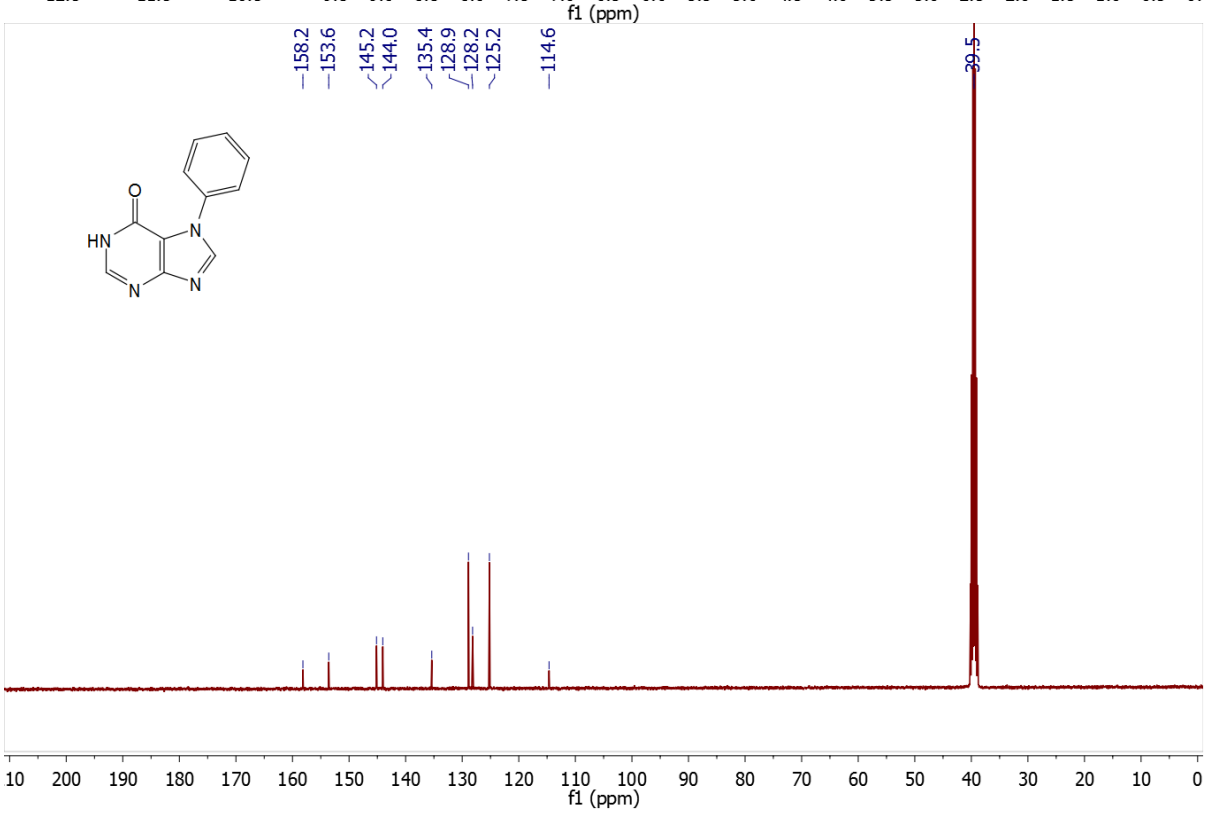


7-phenylguanine (6e)

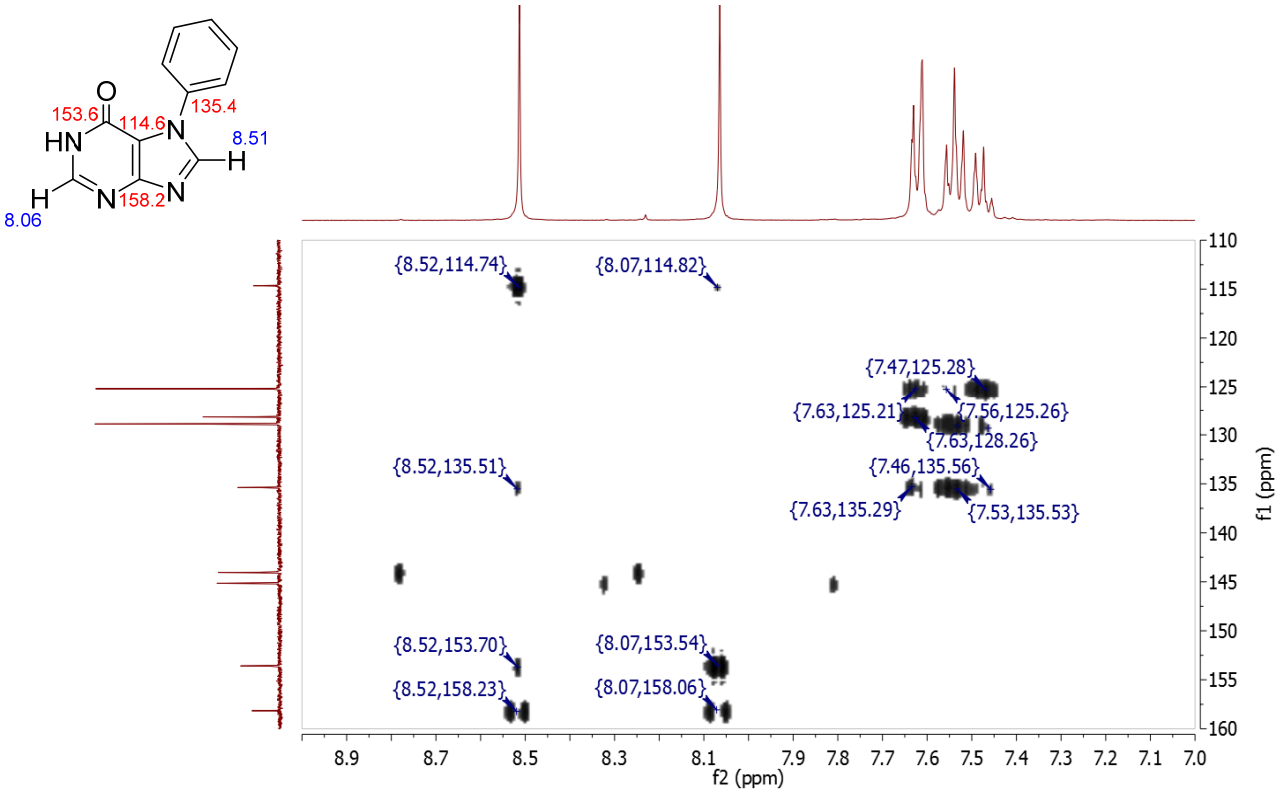


7-Phenylhypoxanthine (6f)





HMBC of **6f**


O
153.6
114.6
135.4
HN
N
8.51
H
H
N
158.2
N
8.06
{8.52,114.74}
{8.07,114.82}
{7.47,125.28}
{7.63,125.21}
{7.56,125.26}
{7.63,128.26}
{8.52,135.51}
{7.46,135.56}
{7.63,135.29}
{7.53,135.53}
{8.52,153.70}
{8.07,153.54}
{8.52,158.23}
{8.07,158.06}
f1 (ppm)
f2 (ppm)