Selective Amidation of 2,6-Dihalogenopurines: Application to the Synthesis of New 2,6,9-Trisubstituted Purines

Sandrine Piguel[†, ‡] *and Michel Legraverend*[‡*]

[†]Univ Paris-Sud, Orsay, F-91405

[‡]UMR 176, Institut Curie, Bât. 110-112, Centre Universitaire, 91405 Orsay France

Supporting information

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General Experimental Methods

Commercially available reagents and solvents were used without further purification unless otherwise stated. Yields refer to isolated and purified products. Reactions were monitored by thin-layer chromatography carried out on silica gel plates (60F-254) visualized under UV light and using 5% ethanolic phosphomolybdic acid and heat as a developing agent. Column chromatography was performed on silica gel 60, 40-63 μm. Chemical shifts of ^{1}H NMR and ^{13}C NMR were reported in ppm (δ units) and residual non deuterated solvent was used as internal reference[1]. The following abbreviations were used to designate the multiplicities: s = singlet, d = doublet, t = triplet, bs = broad singlet, bd = broad doublet, m = multiplet, sept = septuplet.

[1] Gottlieb, H.G.; Kotlyar, V.; Nudelman, A. NMR chemical shifts of common laboratory solvents as trace impurities *J. Org. Chem.* **1997**, *62*, 7512-7515.

6-chloro-2-iodo-9-isopropyl-9*H*-purine 1. This compound was prepared according to the literature [2] and copies of ^{1}H and ^{13}C spectra are included in the supporting information page S14.

Procedure (A): **General Procedure for the Pd-Catalyzed Couplings of 2,6-Dihalogenopurines and Amides As Illustrated by the Synthesis of *N*-(6-Chloro-9-isopropyl-9*H*-purin-2-yl)-benzamide (2a).** A Schlenk tube was charged with 6-chloro-2-iodo-9-isopropyl-9*H*-purine **1** (155 mg, 0.48 mmol), benzamide (65 mg, 0.53 mmol), cesium carbonate (224 mg, 0.68 mmol), Pd_2dba_3 (8.8 mg, 0.01 mmol) and Xantphos (16.5 mg, 0.028 mmol). The Schlenk tube was fitted with a condenser and capped with a rubber septum, evacuated and backfilled with argon. This evacuation/backfill was repeated twice. Then, 1,4-dioxane (2.5 mL) was added through the septum. The mixture was stirred for 30 min at 100 °C. The reaction mixture was then cooled to room temperature and partitioned between H_2O/CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The yellow solid was purified by flash chromatography on silica gel (1-5 % $EtOH/CH_2Cl_2$) to afford the title compound **2a** (114 mg, 75 %) as a pale yellow amorphous solid: mp 180-182 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (d, J = 6.8 Hz, 6H), 4.96 (sept, J = 6.8 Hz, 1H), 7.53 (m, 2H), 7.60 (m, 1H), 7.96 (d, J = 7.1 Hz, 2H), 8.10 (s, 1H), 8.71 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23, 48.3, 127.9, 129.1, 132.9, 134.4, 143, 151.3, 152.1, 152.8, 165.1. MS (electrospray) m/z (%) 316.4 (30) $[M+H]^+$, 318.5 (10) $[M+H]^+$, 338.4 (100) $[M+Na]^+$, 340.5 (36) $[M+Na]^+$. Anal. Calcd. for $C_{15}H_{14}ClN_5O$, 0.5 H_2O: C, 55.47; H, 4.66; N, 21.56. Found: C, 55.33; H, 4.26; N, 21.62.

Compound **(2a)** was also obtained by using procedure **B** (0 °C for 4h) along with compound **(4a)** in a ratio 58 : 15.

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[2] Legraverend, M.; Ludwig, O.; Bisagni, E.;Meijer, L.; Giocanti, N.; Sadri, R.; Favaudon, V. *Bioorg. Med. Chem.* **1999**, *7*, 1281-1293.

4-Chloro-*N*-(6-chloro-9-isopropyl-9*H*-purin-2-yl)-benzamide (2b). Same procedure as above with 6-chloro-2-iodo-9-isopropyl-9*H*-purine **1** (101 mg, 0.31 mmol), 4-chlorobenzamide (55 mg, 0.35 mmol), cesium carbonate (151 mg, 0.46 mmol), Pd_2dba_3 (6.6 mg, 0.007 mmol), Xantphos (11.1 mg, 0.019 mmol) and dioxane (2 mL) at 110 °C for 1 h. The residue was purified by flash chromatography on silica gel (1-2 % EtOH/CH_2Cl_2) to afford the title compound **2b** (74 mg, 67 %) as a yellow amorphous solid: mp 148-150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (d, *J* = 6.8 Hz, 6H), 4.94 (sept, *J* = 6.8 Hz, 1H), 7.49 (d, *J* = 9 Hz, 2H), 7.89 (d, *J* = 9 Hz, 2H), 8.10 (s, 1H), 8.64 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 48, 128.9, 129.1, 132.4, 138.9, 142.7, 151, 151.5, 152.3, 163.7. HRMS (ESI) calcd for $C_{15}H_{13}Cl_2N_5ONa$ [$(M+Na)^+$] 372.0389, found 372.0398.

Compound **(2b)** was also obtained by using procedure **B** (0 °C for 4h) along with compound **(4b)** in a ratio 58 : 11.

***N*-(6-Chloro-9-isopropyl-9*H*-purin-2-yl)-4-methoxy-benzamide (2c).** Same procedure as above with 6-chloro-2-iodo-9-isopropyl-9*H*-purine **1** (204.5 mg, 0.634 mmol), 4-methoxybenzamide (104 mg, 0.68 mmol), cesium carbonate (294 mg, 0.9 mmol), Pd_2dba_3 (12 mg, 0.013 mmol), Xantphos (22 mg, 0.038 mmol) and dioxane (4 mL). The residue was purified by flash chromatography on silica gel (1 % EtOH/CH_2Cl_2) to afford the title compound **2c** (175 mg, 80 %) as an off-white amorphous solid. An analytical sample was obtained by recrystallization from hot heptane as a white solid (46 %): mp 121-124 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (d, *J* = 6.9 Hz, 6H), 3.89 (s, 3H), 4.95 (sept, *J* = 6.8 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 2H), 8.09 (s, 1H), 8.64 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 47.9, 55.5, 114, 126.1, 128.6, 129.5, 142.4, 150.8, 151.9, 152.4, 163, 164. MS (electrospray) m/z (%) 368 (100) $[M+Na]^+$, 370 (36) $[M+Na]^+$. Anal. Calcd. for $C_{16}H_{16}ClN_5O_2$: C, 55.58; H, 4.66. Found: C, 55.66; H, 4.87.

***N*-(6-Chloro-9-isopropyl-9*H*-purin-2-yl)-3-methyl-butyramide (2d).** Same procedure as above with 6-chloro-2-iodo-9-isopropyl-9*H*-purine **1** (198 mg, 0.61 mmol), isovaleramide (66 mg, 0.65 mmol),

cesium carbonate (280 mg, 0.86 mmol), Pd_2dba_3 (12.4 mg, 0.013 mmol), Xantphos (21.2 mg, 0.036 mmol) and dioxane (4 mL) at 110 °C for 1 h. The resulting solid was purified by flash chromatography on silica gel (0-3 % EtOH/CH_2Cl_2) to afford the title compound **2d** (140 mg, 77 %) as a pale yellow amorphous solid: mp 175-177 °C. An analytical sample was obtained by trituration with Et_2O as a white solid (72 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05, (d, *J* = 6.7 Hz, 6H), 1.64 (d, *J* = 6.8 Hz, 6H), 2.27 (sept, *J* = 6.7 Hz, 1H), 2.65 (bd, *J* = 6.7 Hz, 2H), 4.85 (sept, *J* = 6.8 Hz, 1H), 8.05 (bs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 22.5, 25.5, 46.3, 47.9, 128.3, 142.3, 150.9, 151.5, 152.2, 171.9. MS (electrospray) m/z (%) 296.1 (45) $[M+H]^+$, 298.1 (10) $[M+H]^+$, 318.1 (100) $[M+Na]^+$, 320.1 (30) $[M+Na]^+$. Anal. Calcd. for $C_{13}H_{18}ClN_5O$: C, 52.79; H, 6.13; N, 23.68. Found: C, 52.69; H, 6.33; N, 23.59.

Compound **(2d)** was also obtained by using procedure **B** (0 °C for 2h) in 30 % yield.

6-chloro-2-fluoro-9-isopropyl-9*H*-purine 3. To a stirred solution of PPh_3 (4.3 g, 16.35 mmol) in dry THF (28 mL), cooled at – 50 °C, was added dropwise DIAD (3.2 mL, 16.25 mmol) . The suspension was stirred for 10 min. Then, isopropanol (1.3 mL, 17 mmol) was added. After stirring at – 50 °C for 15 min, a solution of 6-chloro-2-fluoro-purine[3] (2.17 g, 12.57 mmol) in THF (38 mL) was introduced and the reaction mixture was then allowed to warm up overnight. After evaporation of the solvent, the resulting yellow solid was purified by flash chromatography on silica gel (0-30 % AcOEt/Cyclohexane) to afford the title compound **3** (2.08 g, 77 %) as a white solid: mp 158-161 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (d, *J* = 6.8 Hz, 6H), 4.84 (sept, *J* = 6.8 Hz, 1H), 8.15 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 48.4, 130.6, 143.6, 152.5 (d, *J* = 15 Hz), 153.1 (d, *J* = 15 Hz), 155.8/158.4 (d, *J* = 195 Hz). MS (electrospray) m/z (%) 213.3 (100) $[M-H]^+$, 215.3 (35) $[M-H]^+$. Anal. Calcd. for $C_8H_8ClFN_4$: C, 44.77; H, 3.76; N, 26.10. Found: C, 44.99; H, 3.69; N, 25.84.

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[3] Gray, N.S.; Kwon, S.; Schultz, P.G. *Tetrahedron Lett*. **1997**, *38*, 1161-1164.

***N*-(2-Fluoro-9-isopropyl-9*H*-purin-6-yl)-benzamide (4a).** Same procedure as above with 6-chloro-2-fluoro-9-isopropyl-9*H*-purine **3** (473 mg, 2.20 mmol), benzamide (289 mg, 2.39 mmol), cesium carbonate (1 g, 3.08 mmol), Pd_2dba_3 (40.3 mg, 0.044 mmol), Xantphos (78.2 mg, 0.135 mmol) and dioxane (7 mL) at 110 °C for 15 min. The residue was purified by flash chromatography on silica gel (1-2 % MeOH/CH_2Cl_2) to afford the title compound **4a** (562 mg, 85 %) as a pale yellow amorphous solid: mp 160-162 °C. ^{1}H NMR (300 MHz, Aceton-d_6) δ 1.56 (d, *J* = 6.8 Hz, 6H), 4.76 (sept, *J* = 6.8 Hz, 1H), 7.47 (m, 2H), 7.57 (m, 1H), 8.01 (d, *J* = 7.1 Hz, 2H), 8.28 (s, 1H), 10 (bs, 1H). ^{13}C NMR (75 MHz, Aceton-d_6) δ 22.7, 49.1, 124.1, 129.7, 129.9, 133.9, 135.2, 143.6, 153.2 (d, *J* = 19 Hz), 155 (d, *J* = 19 Hz), 159 (d, *J* = 207 Hz), 166.1. MS (electrospray) m/z (%) 322.5 (100) $[M+Na]^+$. Anal. Calcd. for $C_{15}H_{14}FN_5O$, H_2O: C, 56.78; H, 5.08; N, 22.07. Found: C, 56.69; H, 4.95; N, 21.81.

4-Chloro-*N*-(2-fluoro-9-isopropyl-9*H*-purin-6-yl)-benzamide (4b). Same procedure as above with 6-chloro-2-fluoro-9-isopropyl-9*H*-purine **3** (400 mg, 1.86 mmol), 4-chlorobenzamide (321 mg, 2.06 mmol), cesium carbonate (832 mg, 2.55 mmol), Pd_2dba_3 (36.6 mg, 0.040 mmol), Xantphos (64.7 mg, 0.112 mmol) and dioxane (8 mL) at 110 °C for 1h30. The residue was triturated with CH_2Cl_2/pentane to afford the title compound **4b** (488 mg, 78 %) as an off-white amorphous solid: mp decomposition. ^{1}H NMR (300 MHz, Aceton-d_6) δ 1.63 (d, *J* = 6.8 Hz, 6H), 4.85 (sept, *J* = 6.8 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 8.11 (d, *J* = 8.5 Hz, 2H), 8.36 (s, 1H), 10.3 (bs, 1H). ^{13}C NMR (75 MHz, Aceton-d_6) δ 21.7, 48.1, 123.1, 128.9, 130.5, 132.9, 138.4, 142.7, 151.9 (d, *J* = 19 Hz), 154.1 (d, *J* = 18 Hz), 157.9 (d, *J* = 208 Hz), 164.3. HRMS (ESI) calcd for $C_{15}H_{13}ClFN_5ONa$ $[(M+Na)^+]$ 356.0685, found 356.0693.

***N*-(2-Fluoro-9-isopropyl-9*H*-purin-6-yl)-4-methoxy-benzamide (4c).** Same procedure as above with 6-chloro-2-fluoro-9-isopropyl-9*H*-purine **3** (206 mg, 0.96 mmol), 4-methoxybenzamide (161 mg, 1.06 mmol), cesium carbonate (438 mg, 1.35 mmol), Pd_2dba_3 (18.6 mg, 0.020 mmol), Xantphos (33.7 mg, 0.058 mmol) and dioxane (4 mL) at 110 °C for 2h. The orange solid was purified by flash chromatography on silica gel (1 % MeOH/CH_2Cl_2) to afford the title compound **4c** (220 mg, 69 %) as a

pale yellow amorphous solid. An analytical sample can be obtained by recrystallization from hot *iso*-propanol as a white solid (81 %): mp 156-158 °C. ^{1}H NMR (300 MHz, Aceton-d_6) δ 1.63 (d, *J* = 6.8 Hz, 6H), 3.90 (s, 3H), 4.84 (sept, *J* = 6.8 Hz, 1H), 7.07 (d, *J* = 8.9 Hz, 2H), 8.09 (d, *J* = 8.9 Hz, 2H), 8.34 (s, 1H), 9.94 (bs, 1H). ^{13}C NMR (75 MHz, Aceton-d_6) δ 22.7, 49, 56.3, 115, 123.9, 127.2, 131.7, 143.4, 153.4 (d, *J* = 19 Hz), 154.9 (d, *J* = 19 Hz), 159 (d, *J* = 208 Hz), 164.6, 165.3. MS (electrospray) m/z (%) 352.5 (100) $[M+Na]^+$. Anal. Calcd. for $C_{16}H_{16}FN_5O_2$, H_2O: C, 55.33; H, 5.22; N, 20.16. Found: C, 55.31; H, 5.14; N, 20.06.

***N*-(2-Fluoro-9-isopropyl-9*H*-purin-6-yl)-2-hydroxy-benzamide (4d)**. Same procedure as above with 6-chloro-2-fluoro-9-isopropyl-9*H*-purine **3** (404 mg, 1.88 mmol), salicylamide (283 mg, 2.07 mmol), cesium carbonate (863 mg, 2.65 mmol), Pd_2dba_3 (35.5 mg, 0.038 mmol), Xantphos (68.8 mg, 0.119 mmol) and dioxane (8 mL) at 110 °C for 2h. The residue was purified by flash chromatography on silica gel (1 % MeOH/CH_2Cl_2) to afford the title compound **4d** (441 mg, 74 %) as an off-white solid: mp 219-221 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (d, *J* = 6.7 Hz, 6H), 4.67 (sept, *J* = 6.7 Hz, 1H), 6.4 (t, *J* = 6 Hz, 1H), 6.54 (d, *J* = 8 Hz, 1H), 7.08 (t, *J* = 6.7 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 8.26 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.3, 47, 113, 119.8, 119.9, 122.5, 129.9, 132.7, 140.6, 151.8 (d, *J* = 20 Hz), 156.2 (d, *J* = 19 Hz), 158.3 (d, *J* = 203 Hz), 167.8, 167.9. HRMS (ESI) calcd for $C_{15}H_{14}FN_5O_2Na$ $[(M+Na)^+]$ 338.1024, found 338.1026.

***N*-(2-Fluoro-9-isopropyl-9*H*-purin-6-yl)-3-methyl-butyramide (4e).** Same procedure as above with 6-chloro-2-fluoro-9-isopropyl-9*H*-purine **3** (198 mg, 0.920 mmol), isovaleramide (101 mg, 1 mmol), cesium carbonate (421 mg, 1.29 mmol), Pd_2dba_3 (17.5 mg, 0.019 mmol), Xantphos (32.1 mg, 0.055 mmol) and dioxane (5.5 mL). The residue was purified by flash chromatography on silica gel (1 % EtOH/CH_2Cl_2) to afford the title compound **4e** (181 mg, 70 %) as a yellow solid. An analytical sample was obtained by recrystallization from hot heptane as off-white crystals: mp 156-158 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05, (d, *J* = 6.7 Hz, 6H), 1.62 (d, *J* = 6.8 Hz, 6H), 2.28 (m, 1H), 2.83 (bd, *J* = 6.7 Hz,

2H), 4.81 (sept, *J* = 6.8 Hz, 1H), 8.07 (s, 1H), 8.97 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 22.5, 25.5, 46.6, 47.89, 120.2, 141.1, 150.7 (d, *J* = 19 Hz), 152.6 (d, *J* = 18 Hz), 157.8 (d, *J* = 212 Hz), 172.9. MS (electrospray) m/z (%) 302 (100) $[M+Na]^+$, 280 (30) $[M+H]^+$. Anal. Calcd. for $C_{13}H_{18}FN_5O$: C, 55.90; H, 6.50; N, 25.07. Found: C, 55.53; H, 6.35; N, 25.06.

Procedure (B): **General Procedure for Amidation of 2,6-dihalogenopurines with Amides using NaH As Illustrated by the Synthesis of *N*-(2-Iodo-9-isopropyl-9*H*-purin-6-yl)-benzamide (5a).** To a suspension of NaH (60 % in mineral oil, 42 mg, 1 mmol) in anhydrous DMF (2.5 mL) was added at once benzamide (115 mg, 0.95 mmol) and the mixture was stirred at room temperature for 1.5 h. To the resultant thick white suspension cooled to 0 °C was added dropwise a solution of 6-chloro-2-iodo-9-isopropyl-9*H*-purine **1** (102 mg, 0.32 mmol) in anhydrous DMF (1.1 mL). The reaction mixture was allowed to warm up to room temperature overnight. The DMF was evaporated off after quenching with a few drops of water. The resulting crude mixture was partitioned between H_2O/CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The yellow solid was purified by flash chromatography on silica gel (0-1 % $EtOH/CH_2Cl_2$) to afford the title compound **5a** (69 mg, 50 %) as a yellow amorphous solid. An analytical sample was obtained by trituration with Et_2O as a white solid (53 %): mp 181-184 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (d, *J* = 6.6 Hz, 6H), 4.93 (sept, *J* = 6.6 Hz, 1H), 7.52 (m, 2H), 7.60 (m, 1H), 8 (m, 3H), 8.74 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23, 47.9, 118, 124.1, 128.4, 129.2, 133.3, 133.4, 141.1, 149.5, 153.6, 164.8. MS (electrospray) m/z (%) 408.3 (70) $[M+H]^+$, 430.3 (100) $[M+Na]^+$. Anal. Calcd. for $C_{15}H_{14}IN_5O$, H_2O: C, 42.37; H, 3.79; N, 16.47. Found: C, 42.77; H, 3.56; N, 16.61.

4-chloro-*N*-(2-Iodo-9-isopropyl-9*H*-purin-6-yl)-benzamide (5b). Same procedure as above with 6-chloro-2-iodo-9-isopropyl-9*H*-purine **1** (149 mg, 0.46 mmol) in anhydrous DMF (3 mL), NaH (60 % in mineral oil, 61 mg, 1.52 mmol) in anhydrous DMF (3.4 mL) and 4-chlorobenzamide (217 mg, 1.39

mmol). The yellow solid was purified by flash chromatography on silica gel (0-1 % EtOH/CH_2Cl_2) to afford the title compound **5b** (115 mg, 56 %) as a white amorphous solid. An analytical sample was obtained by recrystallization from hot EtOH as white needles (53 %): mp 208-210 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (d, *J* = 6.8 Hz, 6H), 4.93 (sept, *J* = 6.8 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 8.5 Hz, 2H), 8.03 (s, 1H), 8.71 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 47.5, 117.5, 123.6, 129.1, 129.5, 131.3, 139.4, 140.7, 148.9, 153.2, 163.5. HRMS (ESI) calcd for $C_{15}H_{13}ClIN_5ONa$ [$(M+Na)^+$] 463.9751, found 463.9753.

***N*-(2-Iodo-9-isopropyl-9*H*-purin-6-yl)-3-methyl-butyramide (5c).** Same procedure as above with 6-chloro-2-iodo-9-isopropyl-9*H*-purine **1** (101 mg, 0.313 mmol) in anhydrous DMF (3 mL), NaH (60 % in mineral oil, 43.3 mg, 1.08 mmol) in anhydrous DMF (2.3 mL) and isovaleramide (95.3 mg, 0.942 mmol). The residue was purified by flash chromatography on silica gel (0-3 % EtOH/CH_2Cl_2) to afford the title compound **5c** (43 mg, 35 %) as a white solid: mp 158-160 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.7 Hz, 6H), 1.61 (d, *J* = 6.8 Hz, 6H), 2.27 (m, 1H), 2.82 (bd, *J* = 7 Hz, 2H), 4.88 (sept, *J* = 6.8 Hz, 1H), 7.95 (s, 1H), 8.39 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 22.6, 25.6, 46.4, 47.5, 117.4, 121.8, 140.4, 148.4, 152, 172.7. HRMS (ESI) calcd for $C_{13}H_{18}IN_5ONa$ [$(M+Na)^+$] 410.0454, found 410.0468.

General Procedure for Couplings of Compounds 4a-d and (R)-(-)-2-pyrrolidinemethanol As Illustrated by the Synthesis of *N*-[2-((R)-(-)-2-Hydroxymethyl-pyrrolidin-1-yl)-9-isopropyl-9*H*-purin-6-yl]-benzamide (6a). To a solution of compound 4a (147 mg, 0.49 mmol) in anhydrous DMF (2 mL) was successively added *N*,*N*-diisopropylethylamine (257 μL, 1.5 mmol), (R)-(-)-2-pyrrolidinemethanol (97 μL, 0.98 mmol). The mixture was stirred overnight at room temperature. The DMF was then evaporated off and the residue was purified by flash chromatography on silica gel (0-1.5 % MeOH/CH_2Cl_2) to give a yellow solid which was further triturated with Et_2O to afford the title compound **6a** (118 mg, 64 %) as an off-white solid: mp 188-190 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59

(d, *J* = 6.7 Hz, 6H), 1.72 (m, 1H), 1.89-2.17 (m, 3H), 3.63-3.87 (m, 4H), 4.45 (m, 1H), 4.70 (sept, *J* = 6.7 Hz, 1H), 7.49 (m, 2H), 7.58 (m, 1H), 7.68 (s, 1H), 8 (d, *J* = 7.3 Hz, 2H), 9 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 22.2, 24, 29.7, 46.9, 48.6, 61, 68.9, 116, 127.8, 128.6, 132.4, 134, 137.2, 148.9, 153.1, 158.2, 164.8. HRMS (ESI) calcd for $C_{20}H_{24}N_6O_2Na$ [$(M+Na)^+$] 403.1853, found 403.1863.

4-Chloro-*N*-[2-((R)-(-)-2-hydroxymethyl-pyrrolidin-1-yl)-9-isopropyl-9*H*-purin-6-yl]-benzamide (6b). Same procedure as above with compound **4b** (131 mg, 0.39 mmol), *N*,*N*-diisopropylethylamine (210 μL, 1.2 mmol), (R)-(-)-2-pyrrolidinemethanol (80 μL, 0.81 mmol) in 2 mL anhydrous DMF. The residue was purified by flash chromatography on silica gel (0-1 % MeOH/CH_2Cl_2) to give a pale yellow solid which was further triturated with Et_2O to afford the title compound **6b** (104 mg, 64 %) as a white solid: mp 205-208 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (d, *J* = 6.7 Hz, 6H), 1.72 (m, 1H), 1.91-2.14 (m, 3H), 3.61-3.87 (m, 4H), 4.42 (m, 1H), 4.69 (sept, *J* = 6.7 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.67 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 9.1 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 22.2, 24, 29.7, 46.9, 48.6, 61, 68.7, 116, 128.6, 129.3, 132.4, 137.4, 138.7, 148.8, 153.2, 158.1, 164. HRMS (ESI) calcd for $C_{20}H_{23}ClN_6O_2Na$ [$(M+Na)^+$] 437.1463, found 437.1472.

***N*-[2-((R)-(-)-2-Hydroxymethyl-pyrrolidin-1-yl)-9-isopropyl-9*H*-purin-6-yl]-4-methoxy-benzamide (6c).** Same procedure as above with compound **4c** (87 mg, 0.26 mmol), *N*,*N*-diisopropylethylamine (125 μL, 0.72 mmol), (R)-(-)-2-pyrrolidinemethanol (50 μL, 0.50 mmol) in 1.5 mL anhydrous DMF. The resulting yellow solid was purified by flash chromatography on silica gel (1-2 % MeOH/CH_2Cl_2) to afford the title compound **6c** (85 mg, 78 %) as a colorless oil which crystallizes upon standing: mp 154-156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (d, *J* = 6.7 Hz, 6H), 1.71 (m, 1H), 1.89-2.13 (m, 3H), 3.62-3.87 (m, 7H), 4.44 (m, 1H), 4.68 (sept, *J* = 6.7 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.65 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 9.1 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 22.3, 24, 29.8, 46.9, 48.7, 55.5, 61, 69, 113.9, 116, 126.2, 129.9, 137, 149.2, 153, 158.3, 163, 164.1. HRMS (ESI) calcd for $C_{21}H_{26}N_6O_3Na$ [$(M+Na)^+$] 433.1959, found 433.1962.

2-Hydroxy-*N*-[2-((R)-(-)-2-hydroxymethyl-pyrrolidin-1-yl)-9-isopropyl-9*H*-purin-6-yl]-benzamide (6d). Same procedure as above with compound **4d** (129.5 mg, 0.41 mmol), *N*,*N*-diisopropylethylamine (210 μL, 1.2 mmol), (R)-(-)-2-pyrrolidinemethanol (85 μL, 0.92 mmol) in 2 mL anhydrous DMF. The resulting red oil was purified by flash chromatography on silica gel (1-2 % MeOH/CH_2Cl_2) to give a white solid which was further triturated with Et_2O to afford the title compound **6d** (114 mg, 70 %) as a yellow solid: mp 178-180 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (d, *J* = 6.7 Hz, 6H), 1.81 (m, 1H), 1.99-2.19 (m, 3H), 3.68-3.90 (m, 4H), 4.41 (m, 1H), 4.68 (sept, *J* = 6.7 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.74 (s, 1H), 7.86 (d, *J* = 8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 22.2, 24, 29.4, 47, 48.5, 61, 69, 116.1, 117, 117.9, 118.9, 128.9, 134.6, 137.9, 150, 152.9, 160.8. MS (electrospray) m/z (%) 397.2 (45) $[M+H]^+$, 419.2 (100) $[M+Na]^+$. Anal. Calcd. for $C_{20}H_{24}N_6O_3$: C, 60.59; H, 6.10; N, 21.20. Found: C, 60.36; H, 6.07; N, 21.25.

General Procedure for Couplings of Compounds 4a-c and (R)-(-)-2-aminobutan-1-ol As Illustrated by the Synthesis of *N*-[2-((R)-(-)-1-Hydroxymethyl-propylamino)-9-isopropyl-9*H*-purin-6-yl]-benzamide (7a). To a solution of compound 4a (70 mg, 0.234 mmol) in anhydrous DMF (1.5 mL) was successively added *N*,*N*-diisopropylethylamine (110 μL, 0.631 mmol), (R)-(-)-2-aminobutan-1-ol (25 μL, 0.264 mmol). The mixture was stirred for 6 h at 110 °C. The DMF was then evaporated off and the residue was purified by flash chromatography on silica gel (1-3 % EtOH/CH_2Cl_2) to give the title compound 7a (38 mg, 44 %) as a yellow pale oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1 (t, *J* = 7.5 Hz, 3H), 1.53-1.67 (m, 8H), 3.64-3.89 (m, 2H), 4 (m, 1H), 4.65 (sept, *J* = 6.7 Hz, 1H), 5.59 (bs, 1H), 7.46 (m, 2H), 7.55 (m, 1H), 7.70 (s, 1H), 7.99 (d, *J* = 7.3 Hz, 2H), 9.3 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.7, 22.1, 22.2, 24.7, 46.8, 55.4, 66, 116.4, 127.8, 128.5, 132.3, 134, 137.2, 149.6, 153, 159.3, 165.2. HRMS (ESI) calcd for $C_{19}H_{24}N_6O_2Na$ $[(M+Na)^+]$ 391.1853, found 391.1859.

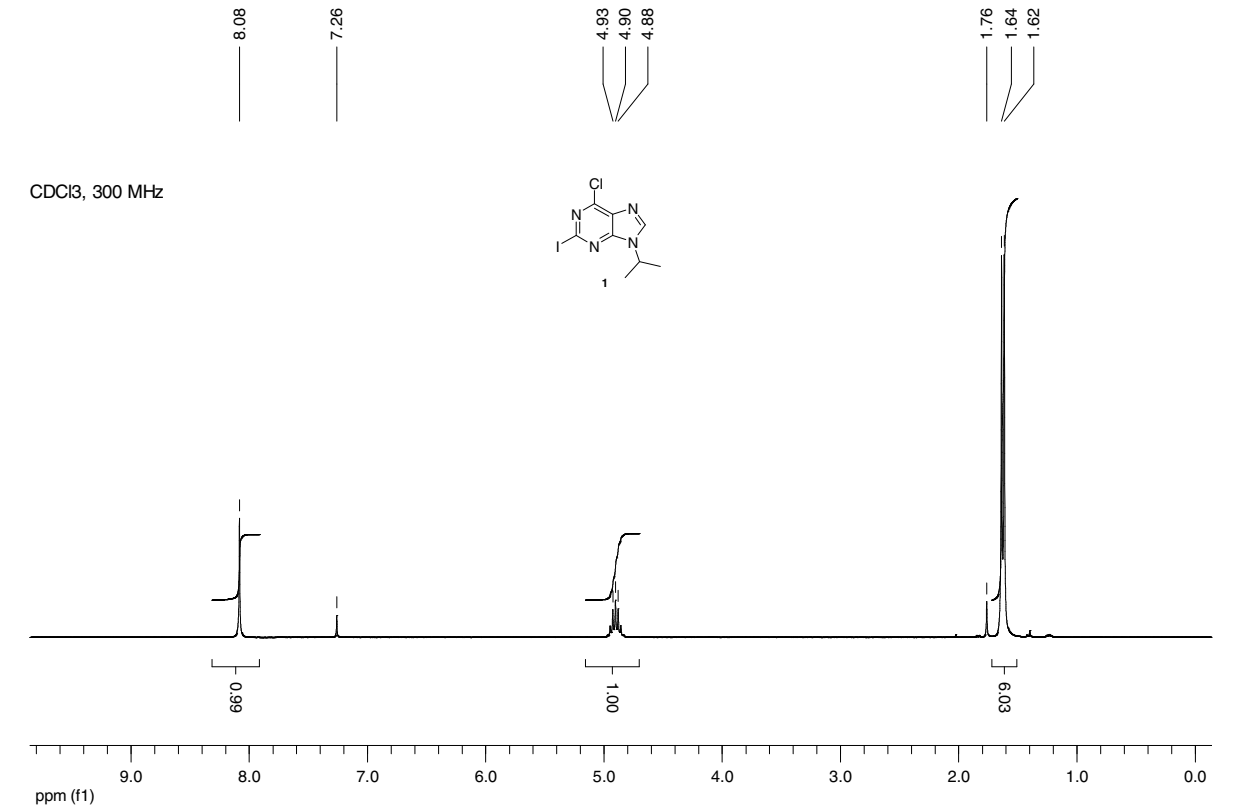
4-Chloro-*N*-[2-((R)-(-)-1-hydroxymethyl-propylamino)-9-isopropyl-9*H*-purin-6-yl]-benzamide

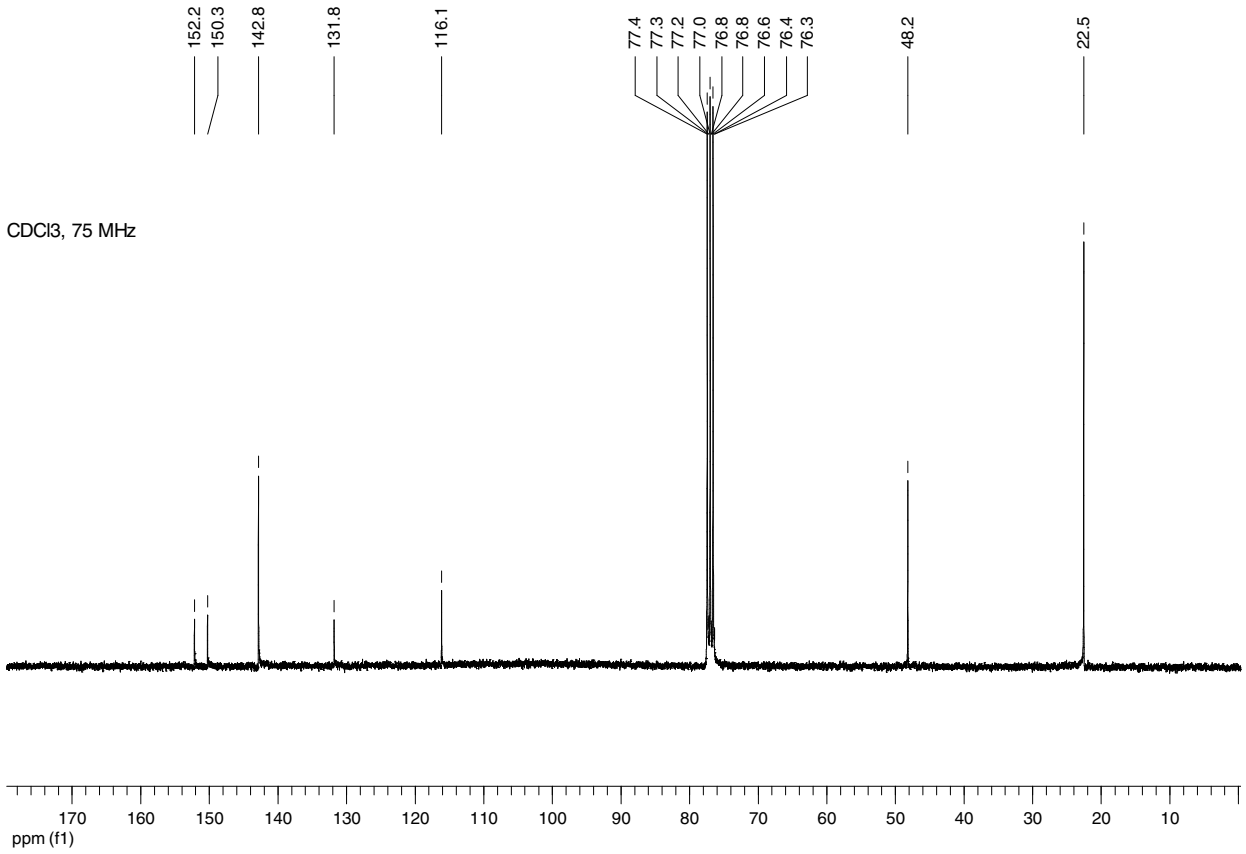
(7b). Same procedure as above with compound **4b** (109 mg, 0.327 mmol), *N*,*N*-diisopropylethylamine (150 μL, 0.861 mmol), (R)-(-)-2-aminobutan-1-ol (34 μL, 0.359 mmol) in DMF (2.5 mL). The residue was purified by flash chromatography on silica gel (1-3 % EtOH/CH_2Cl_2) to give the title compound **7b** (51 mg, 38 %) as a white solid: mp 173-176 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.5 Hz, 3H), 1.55-1.70 (m, 8H, CH_2), 3.63-3.90 (m, 2H), 3.99 (m, 1H), 4.67 (sept, *J* = 6.7 Hz, 1H), 5.39 (bs, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.70 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 2H), 9.18 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 22.2, 22.3, 24.8, 46.8, 55.7, 66.6, 116.6, 128.9, 129.3, 132.4, 137.4, 138.8, 149.5, 153.1, 159.4, 164. HRMS (ESI) calcd for $C_{19}H_{23}ClN_6O_2Na$ [$(M+Na)^+$] 425.1463, found 425.1465.

***N*-[2-((R)-(-)-1-Hydroxymethyl-propylamino)-9-isopropyl-9*H*-purin-6-yl]-4-methoxy-benzamide (7c).** Same procedure as above with compound **4c** (131 mg, 0.40 mmol), *N*,*N*-diisopropylethylamine (175 μL, 1 mmol), (R)-(-)-2-aminobutan-1-ol (42 μL, 0.44 mmol) in DMF (2.5 mL). The residue was purified by flash chromatography on silica gel (1-3 % EtOH/CH_2Cl_2) to give the title compound **7c** (78 mg, 49 %) as a yellow pale solid. An analytical sample was obtained by trituration with acetone as a white solid (42 %): mp decomposition. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, *J* = 7.5 Hz, 3H), 1.56-1.70 (m, 8H), 3.64 (m, 1H), 3.87 (bs, 4H), 4.01 (m, 1H), 4.66 (sept, *J* = 6.7 Hz, 1H), 5.42 (bs, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 7.68 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 9.1 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 22.2, 22.3, 24.8, 46.8, 55.4, 55.8, 66.7, 113.8, 116.4, 126.2, 130, 137, 149.8, 152.9, 159.5, 162.9, 164.4. MS (electrospray) m/z (%) 399.2 (100) $[M+H]^+$, 421.2 (60) $[M+Na]^+$. Anal. Calcd. for $C_{20}H_{26}N_6O_3$, H_2O: C, 57.68; H, 6.78; N, 20.18. Found: C, 57.66; H, 6.42; N, 20.34.

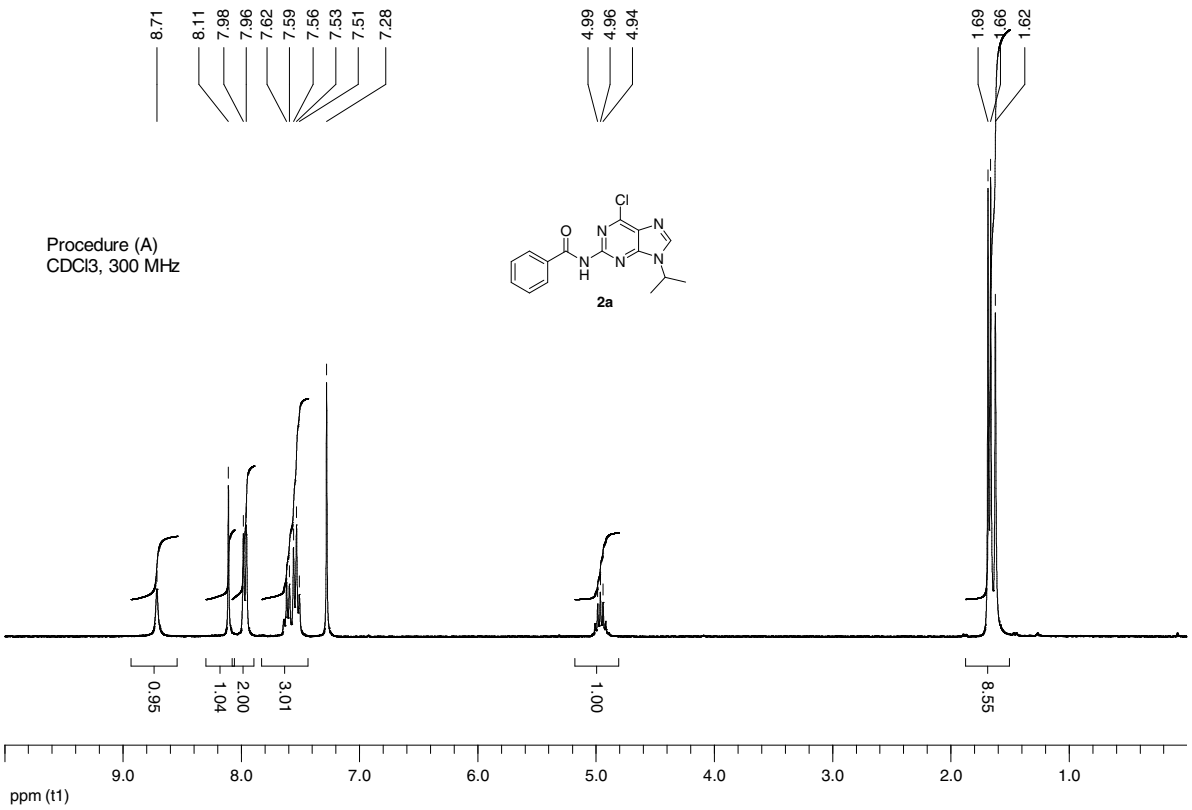
(R)-(-)-2-(6-Amino-9-isopropyl-9*H*-purin-2-ylamino)-butan-1-ol (8). White foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.5 Hz, 3H), 1.47-1.66 (m, 8H, CH_2), 3.60-3.91 (m, 3H), 4.60 (sept, *J* = 6.7 Hz, 1H), 5.04 (bd, 1H), 5.65 (bs, 2H), 7.55 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 22.3, 22.4, 24.8, 46.5, 55.8, 67.3, 114.2, 135.1, 151, 155.6, 159.7. HRMS (ESI) calcd for $C_{12}H_{21}N_6O$ [$(M+H)^+$] 265.1771, found 265.1772.

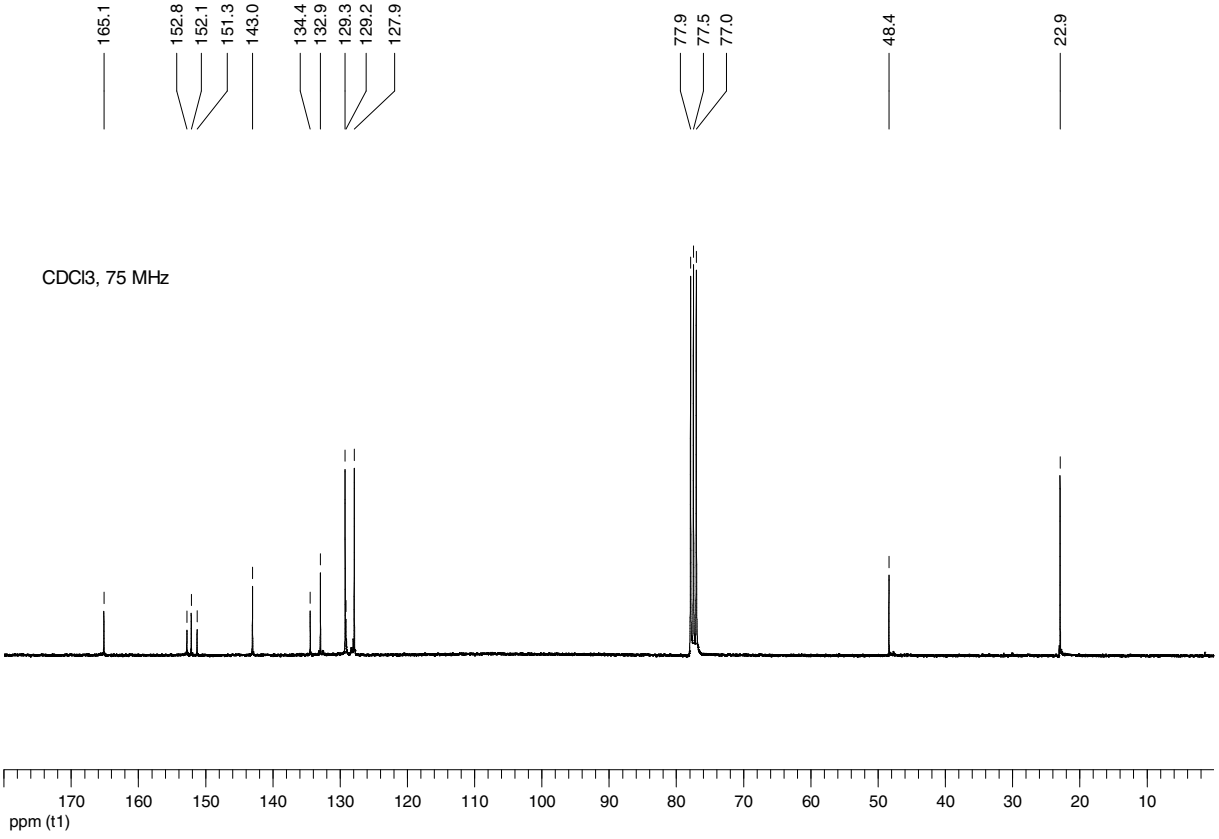
6-chloro-2-iodo-9-isopropyl-9*H*-purine 1



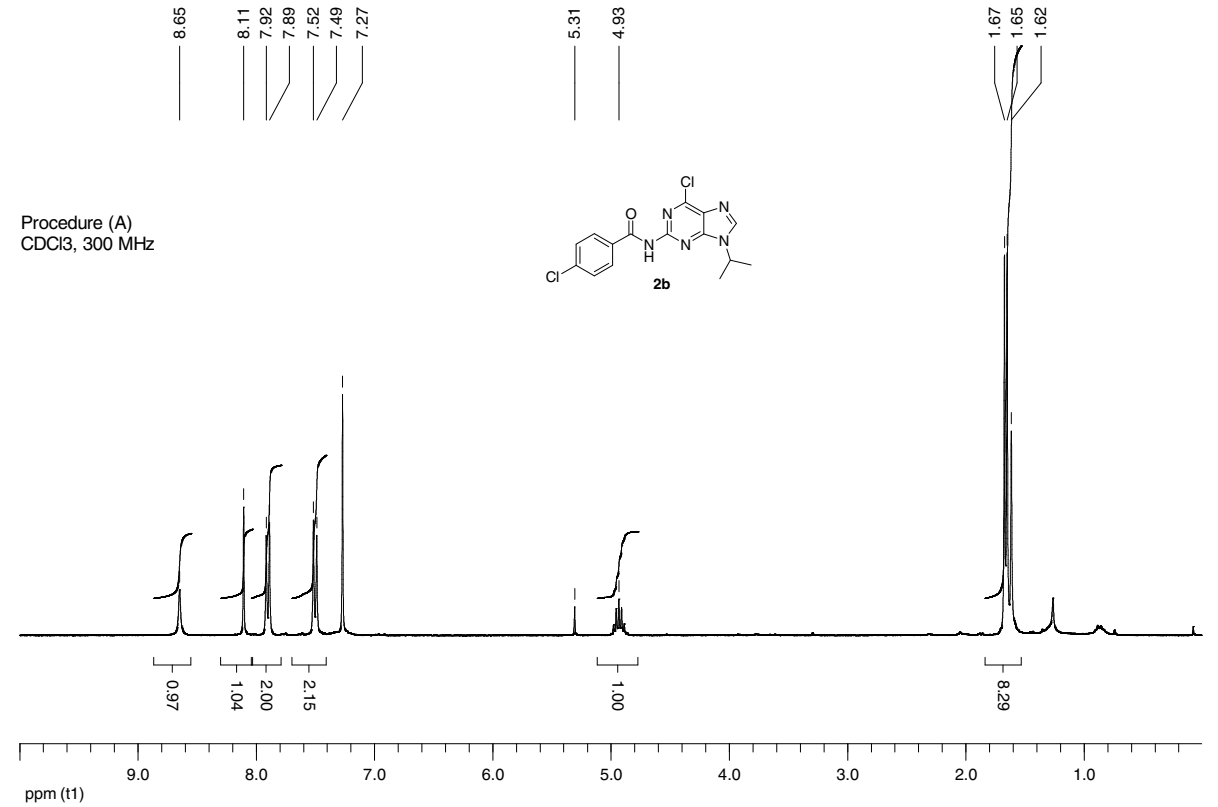


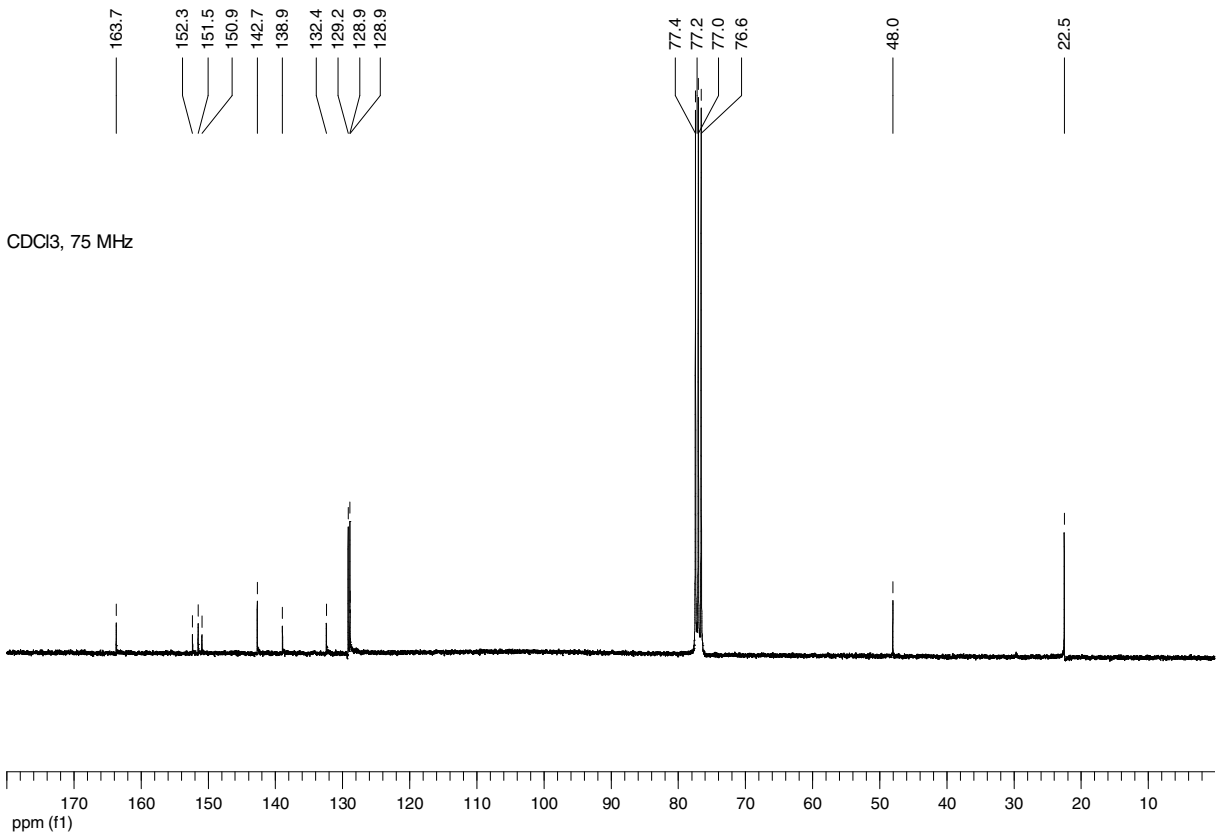
N-(6-Chloro-9-isopropyl-9*H*-purin-2-yl)-benzamide (2a)



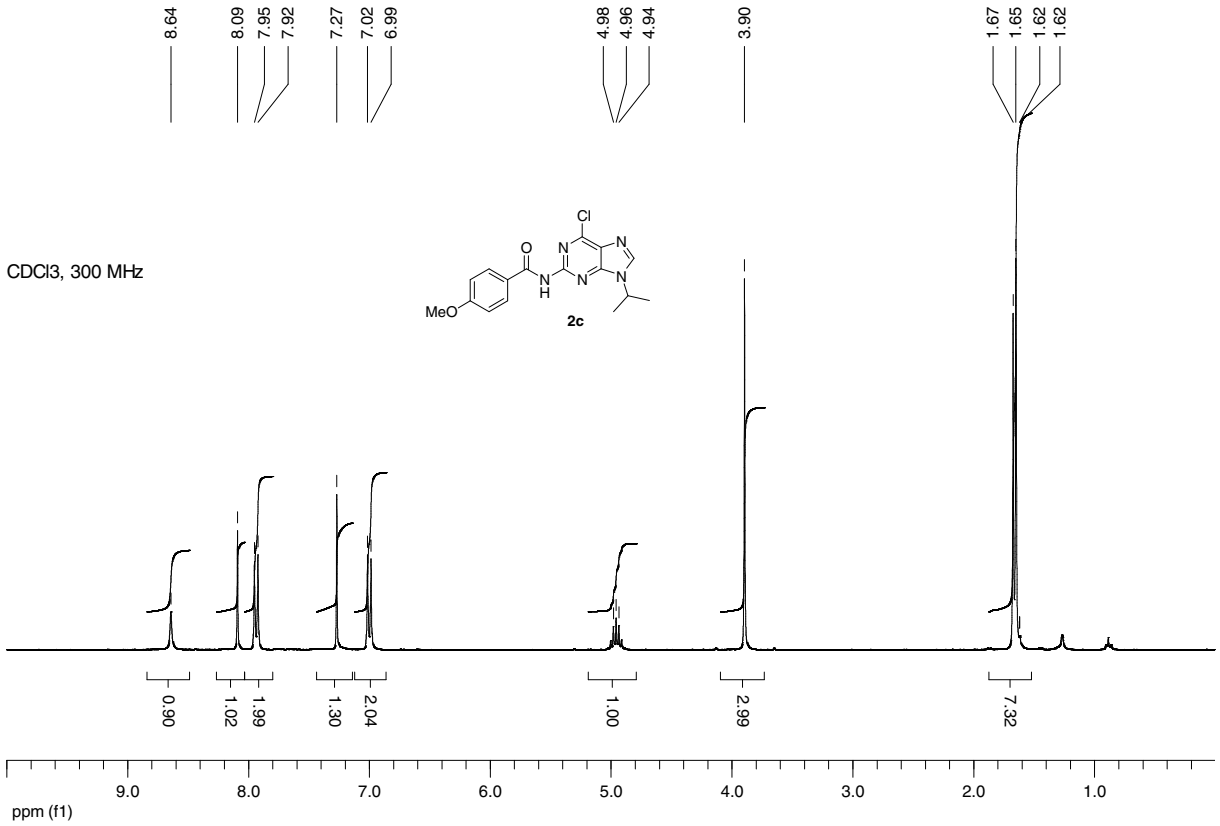


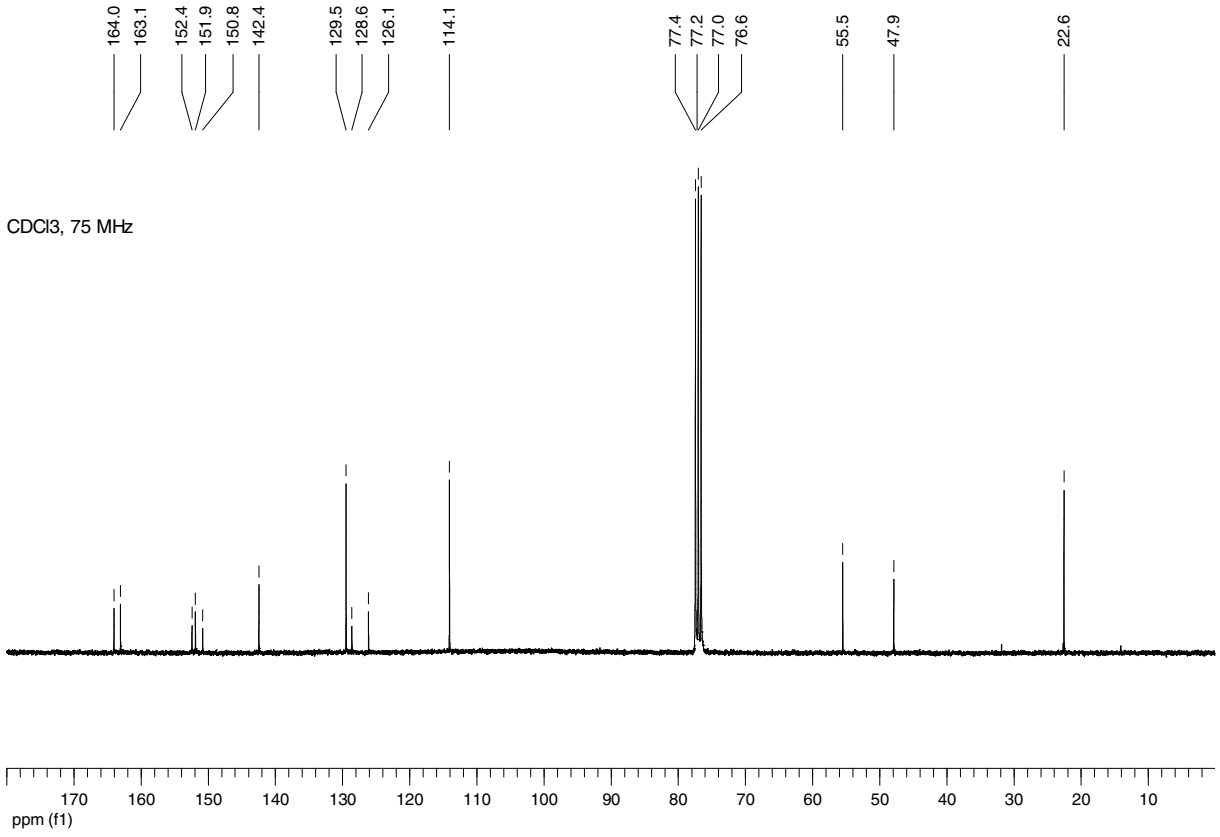
4-Chloro-*N*-(6-chloro-9-isopropyl-9*H*-purin-2-yl)-benzamide (2b)



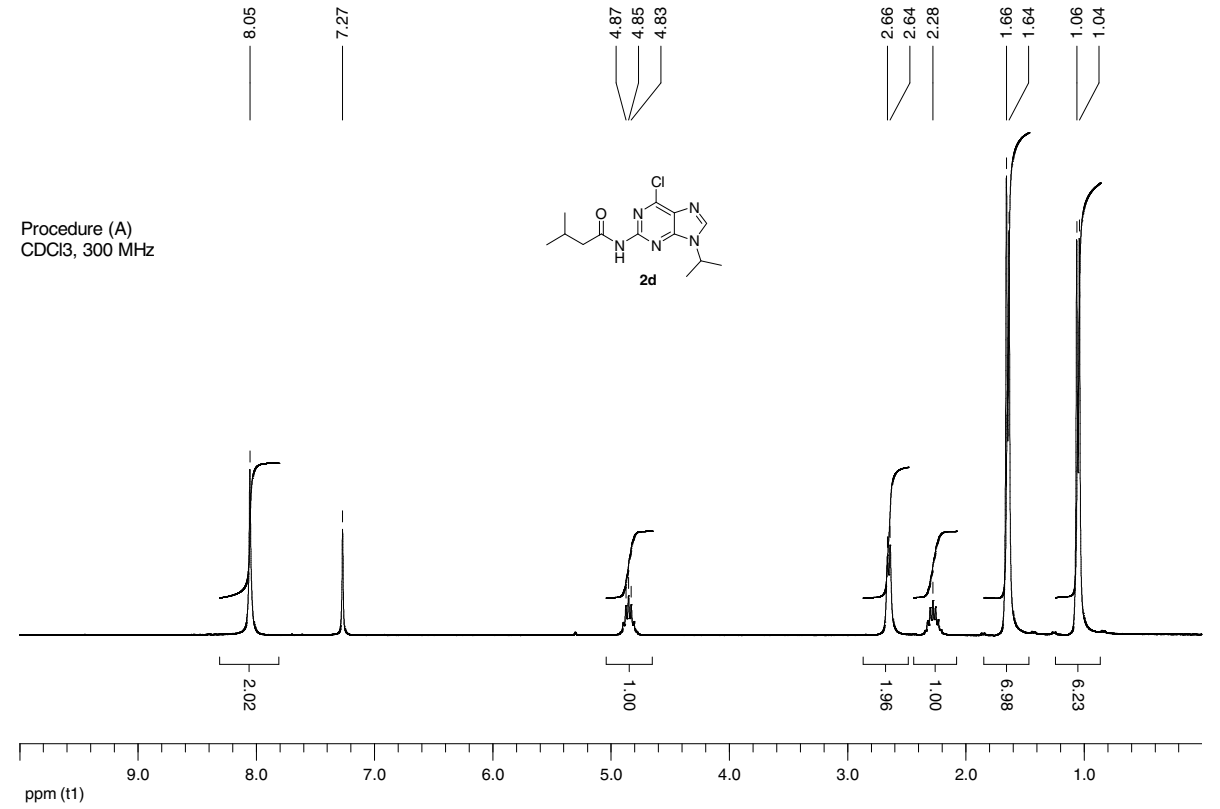


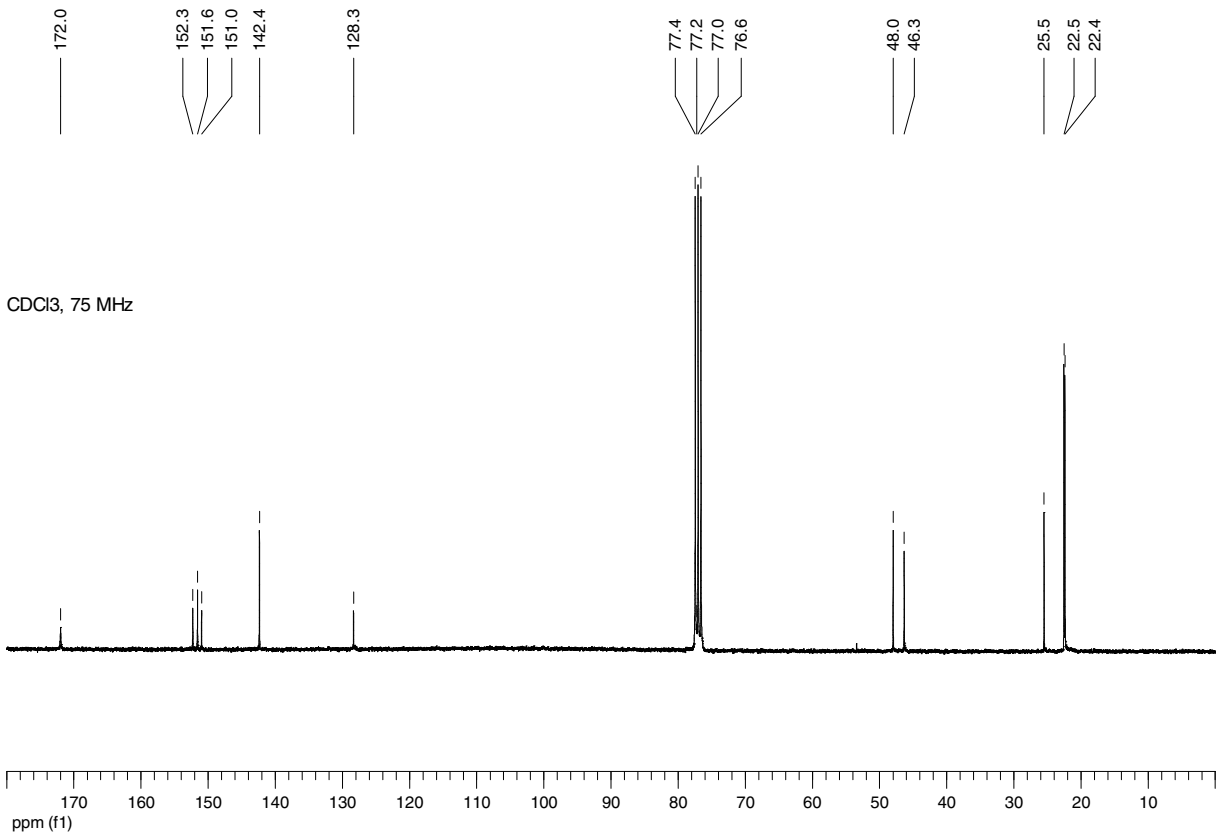
N-(6-Chloro-9-isopropyl-9*H*-purin-2-yl)-4-methoxy-benzamide (2c)



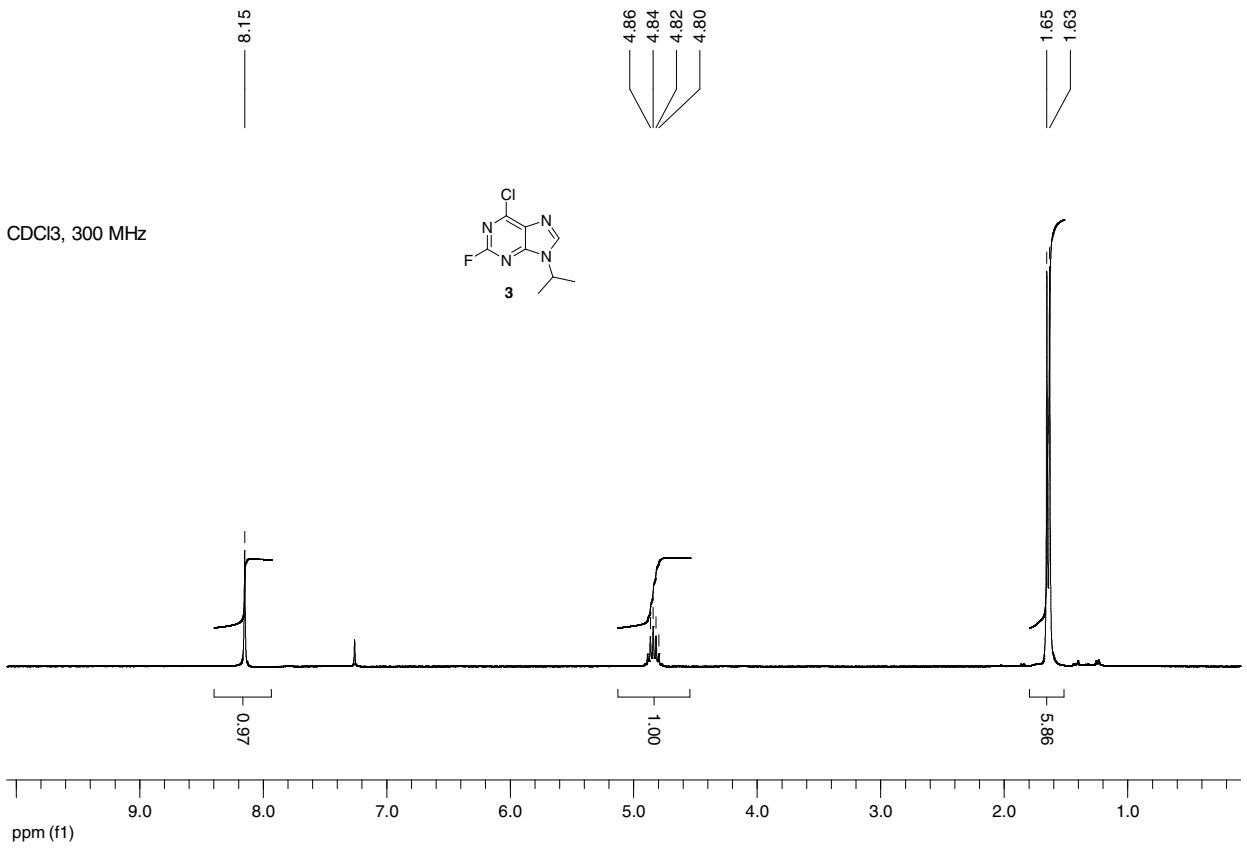


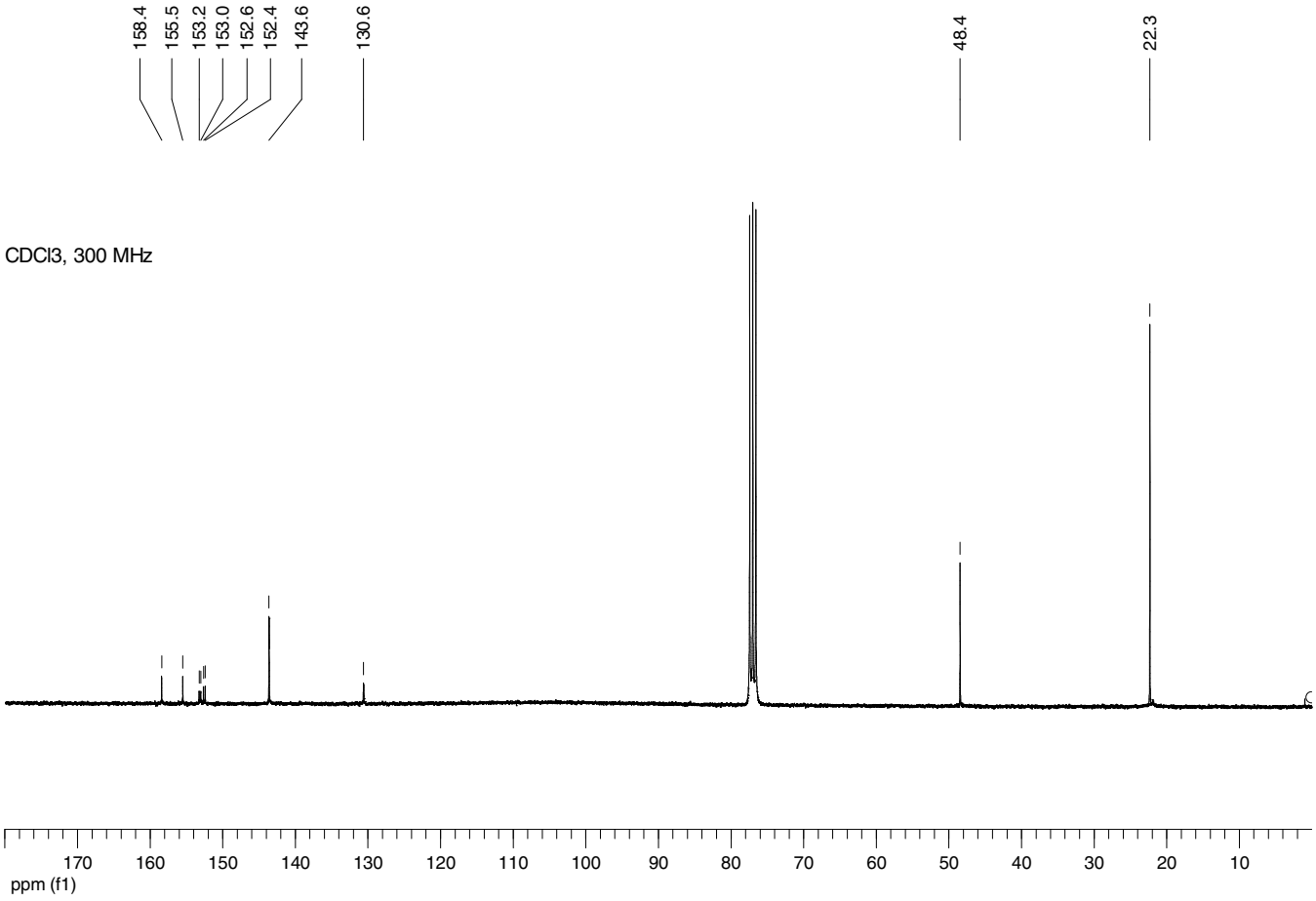
N-(6-Chloro-9-isopropyl-9*H*-purin-2-yl)-3-methyl-butyramide (2d)



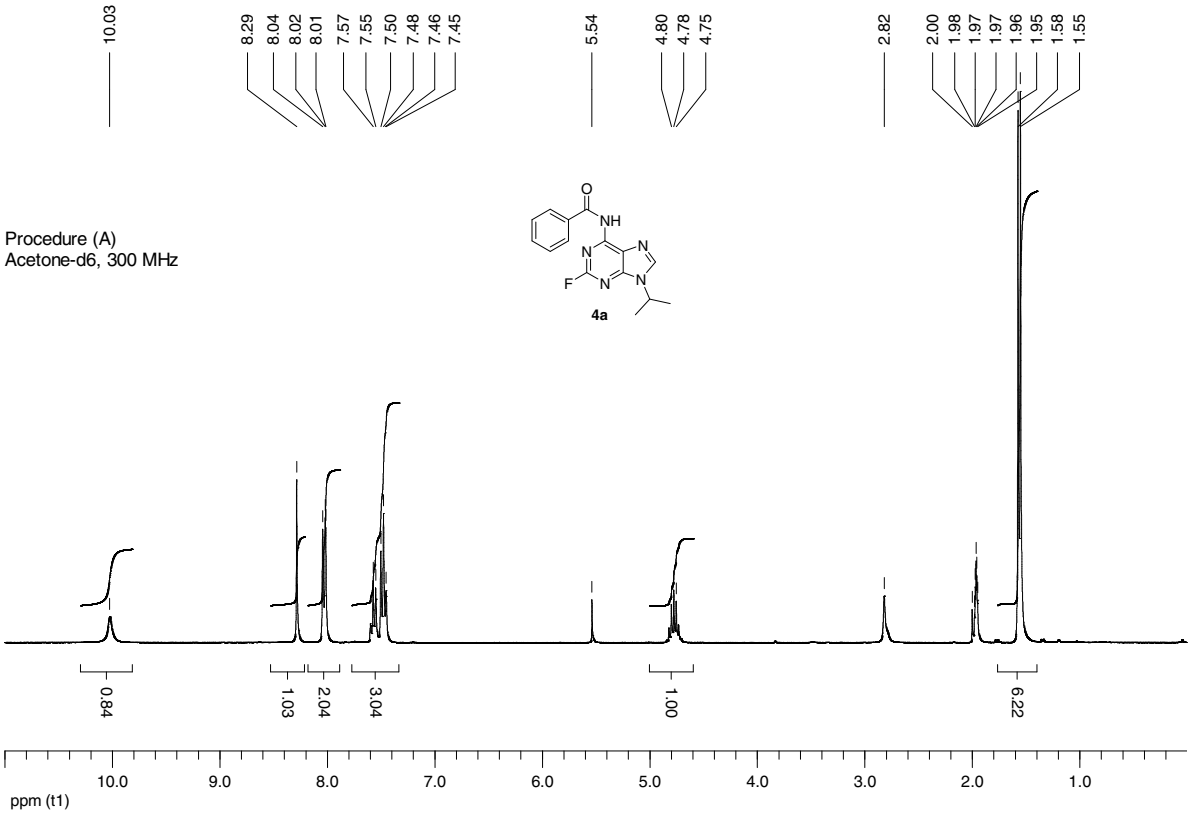


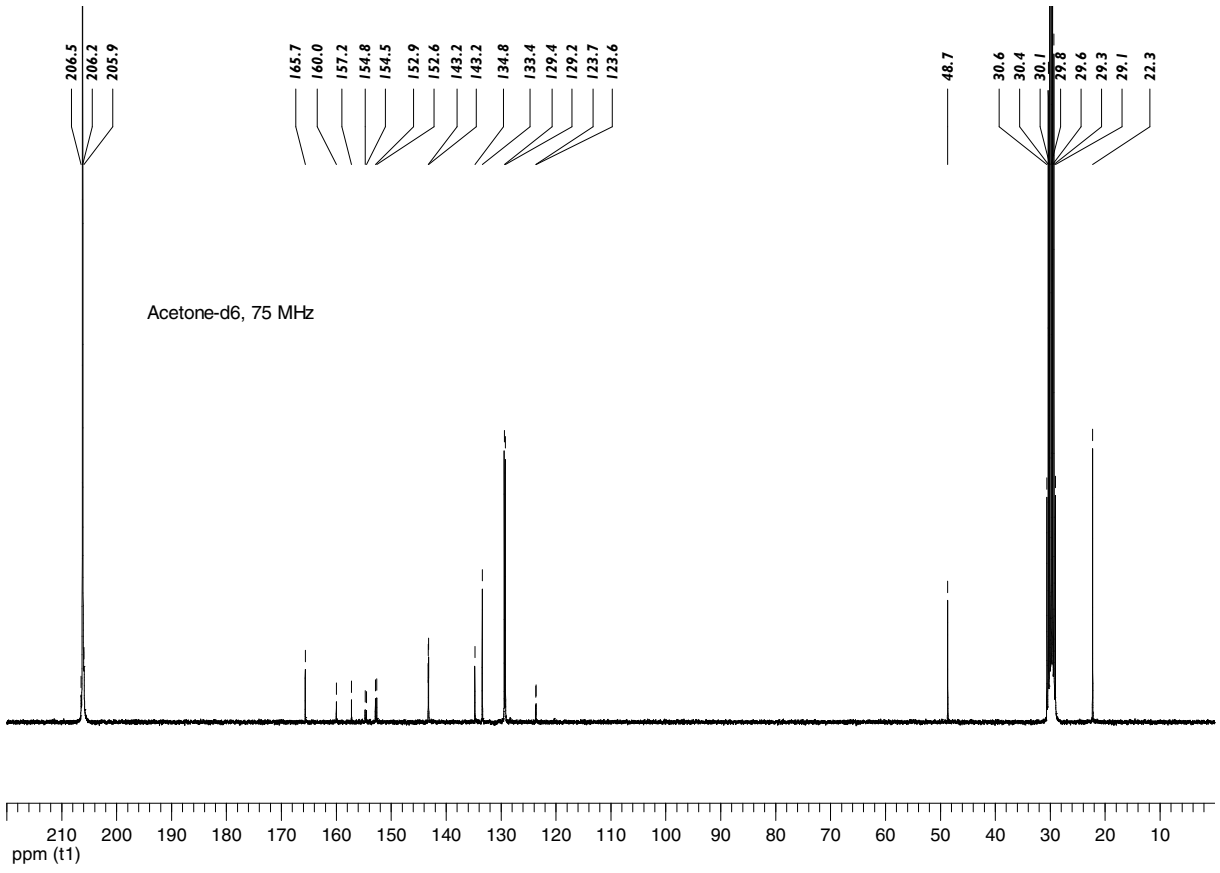
6-chloro-2-fluoro-9-isopropyl-9*H*-purine 3



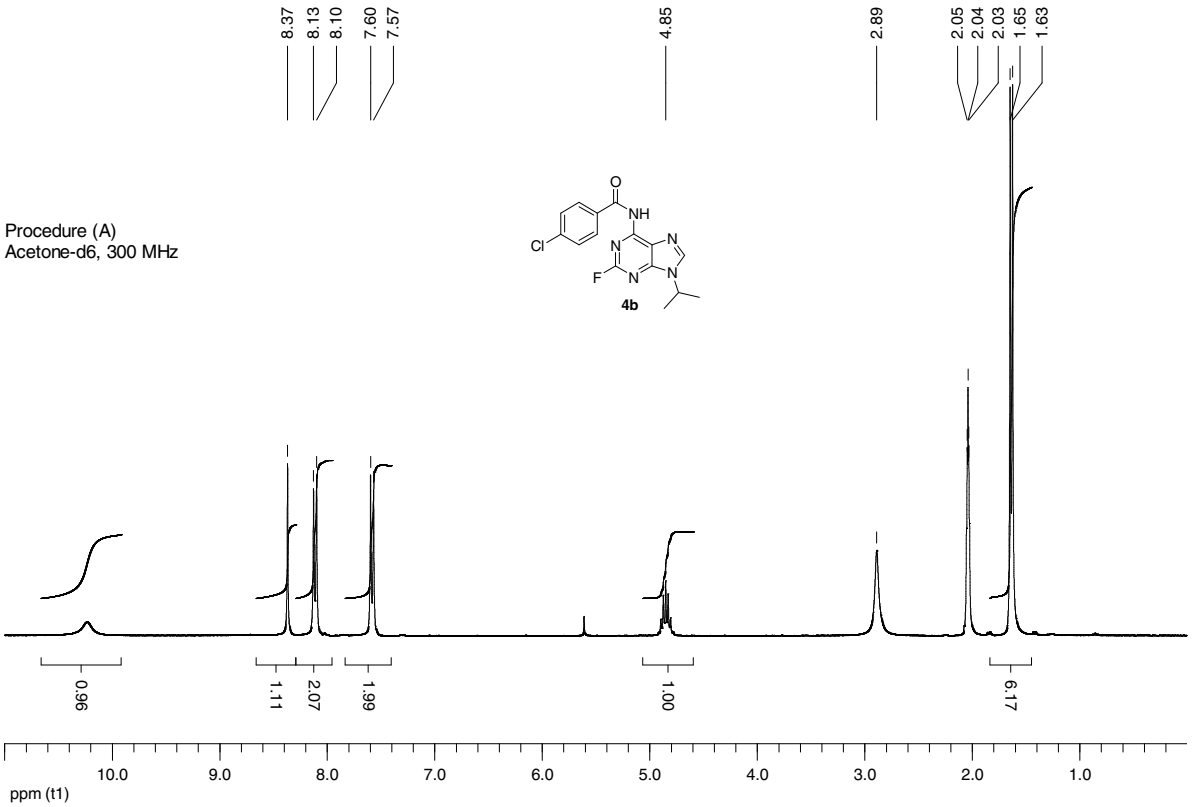


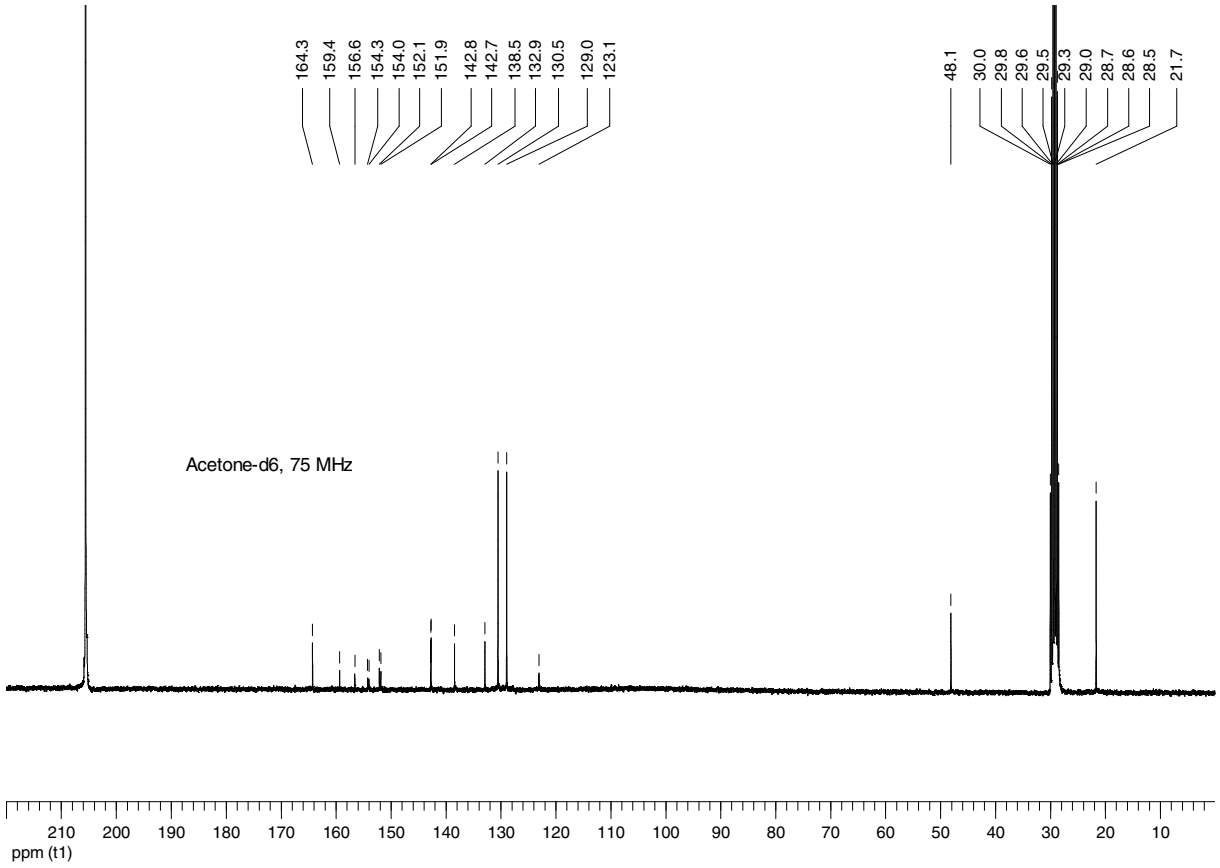
N-(2-Fluoro-9-isopropyl-9*H*-purin-6-yl)-benzamide (4a)



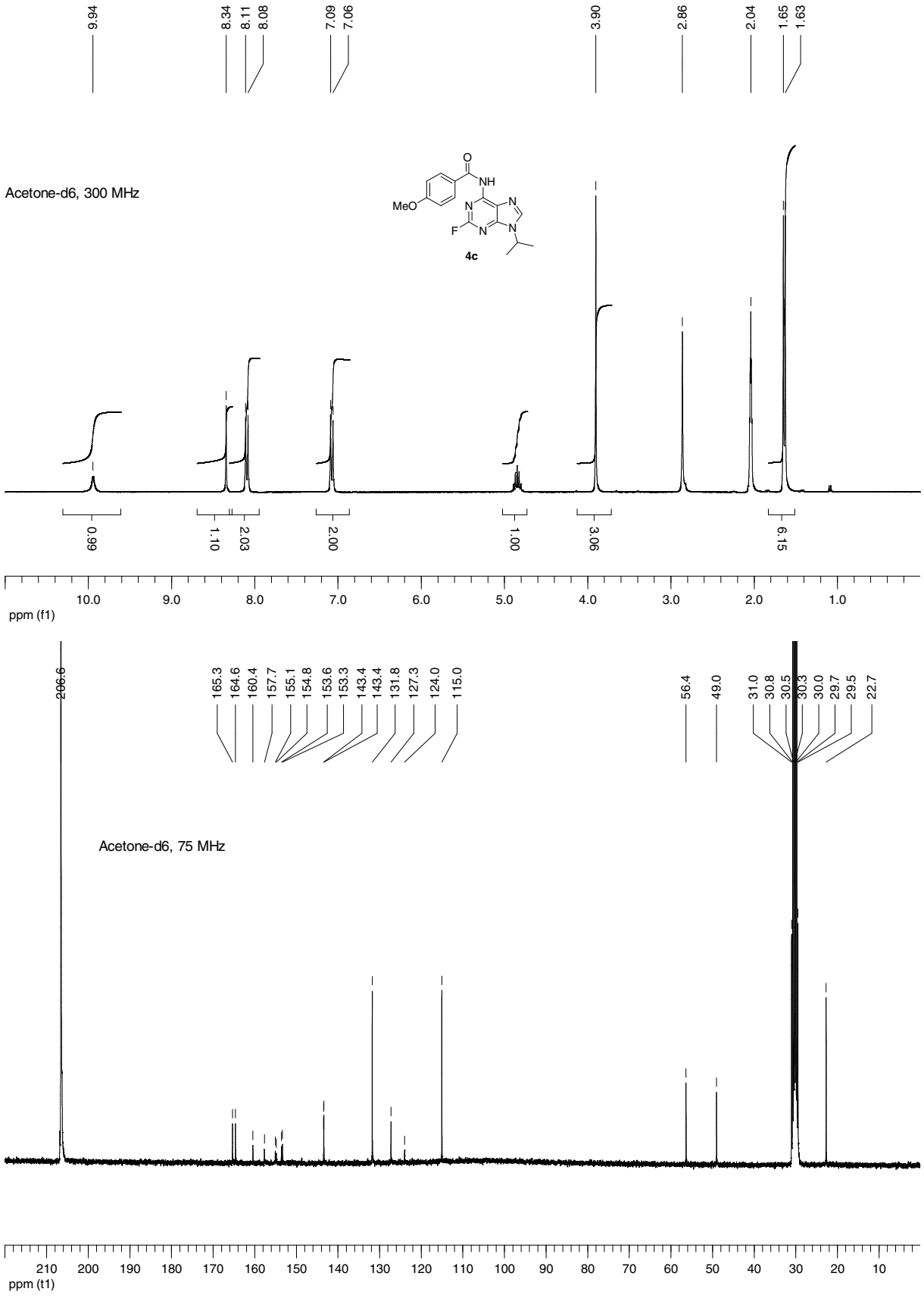


4-Chloro-*N*-(2-fluoro-9-isopropyl-9*H*-purin-6-yl)-benzamide (4b)

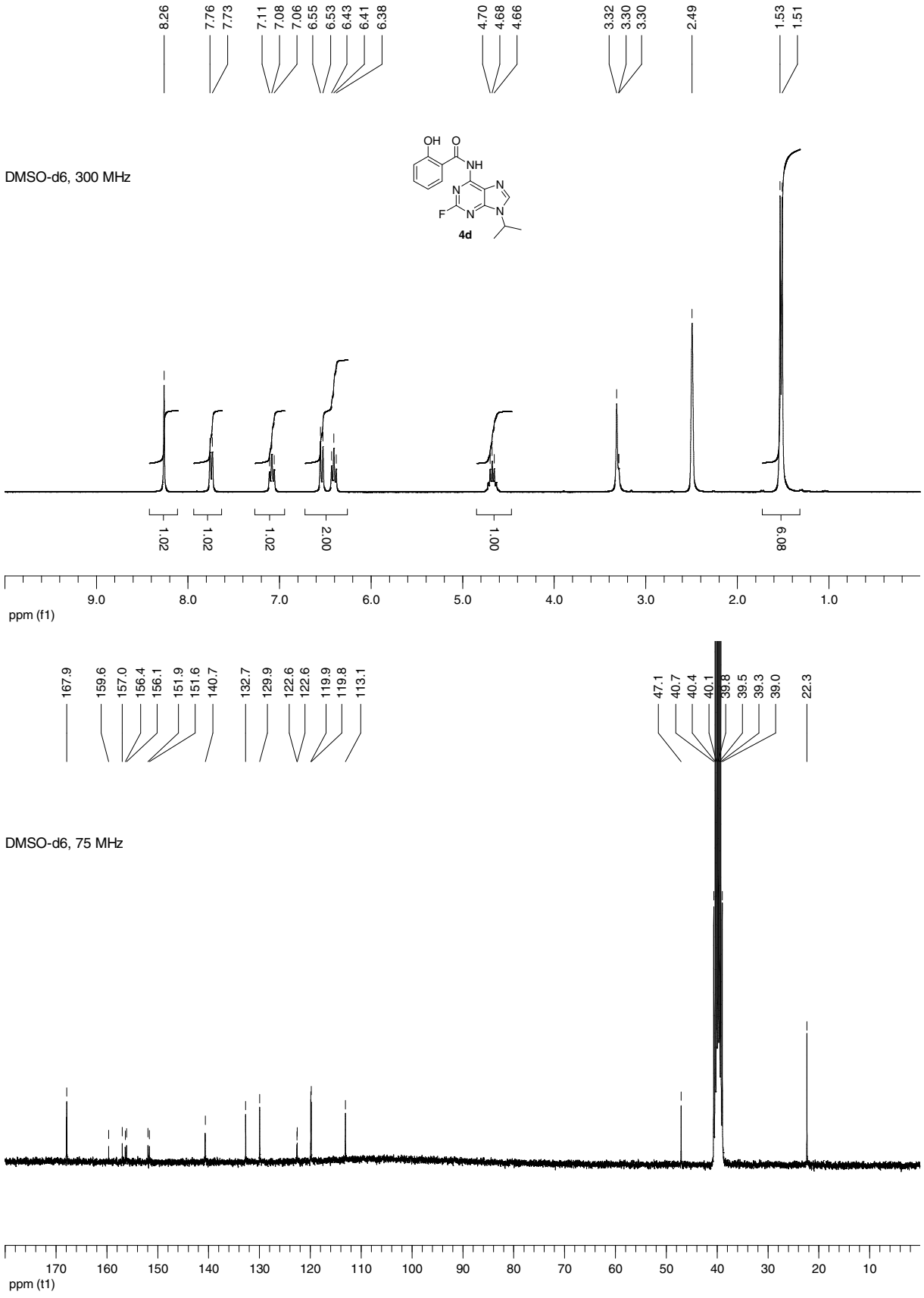




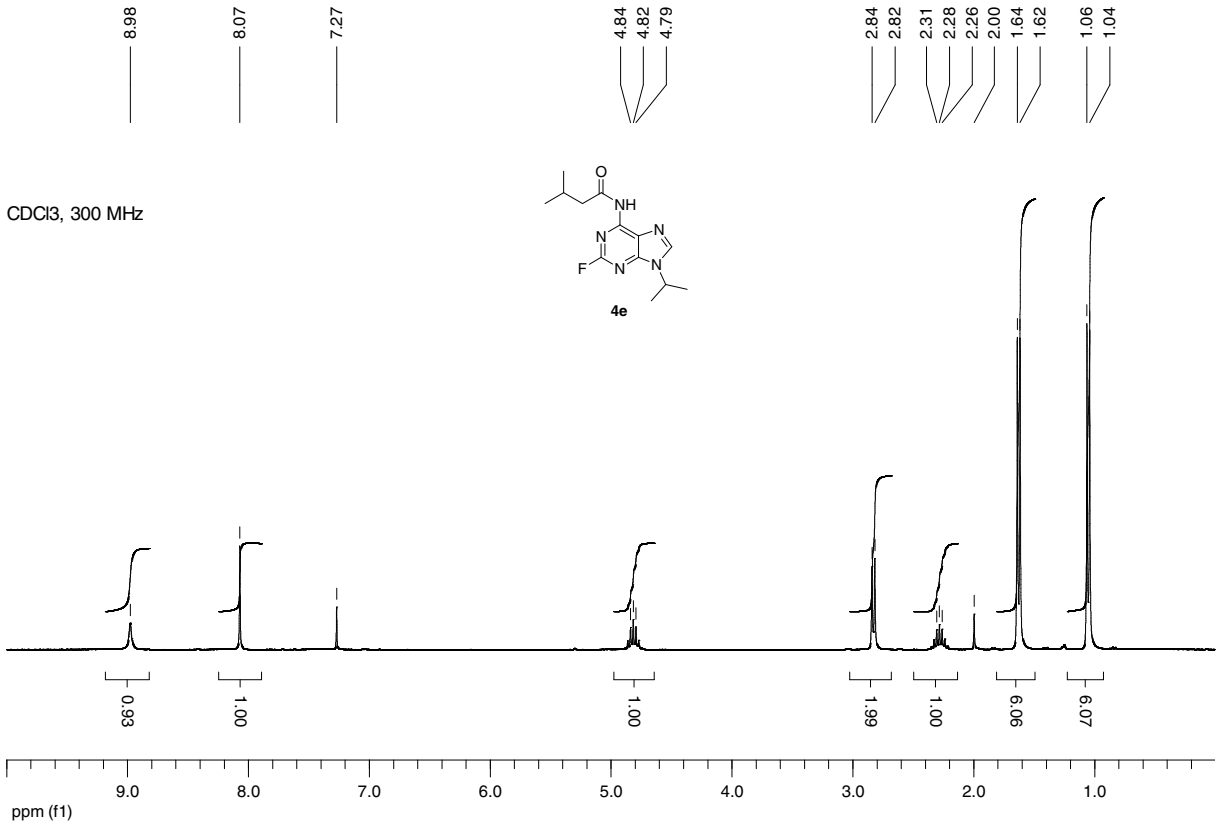
N-(2-Fluoro-9-isopropyl-9*H*-purin-6-yl)-4-methoxy-benzamide (4c)

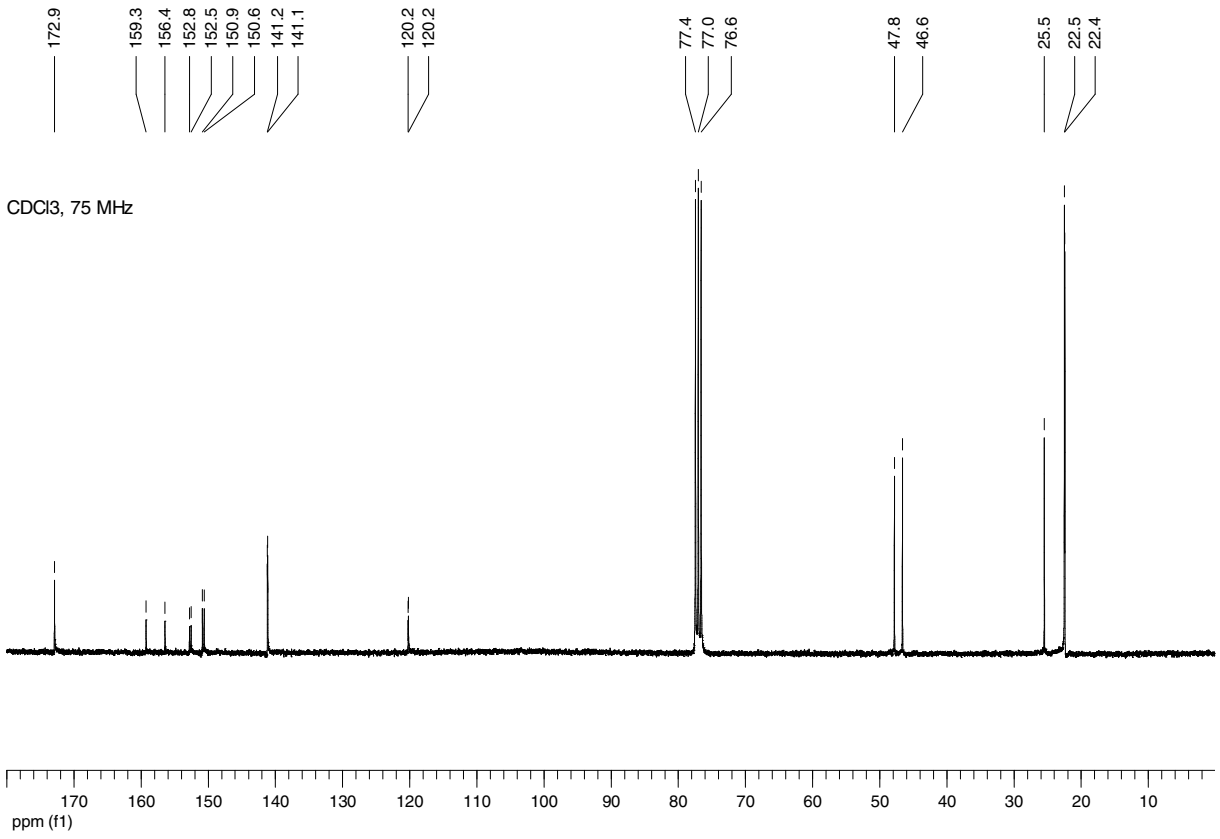


N-(2-Fluoro-9-isopropyl-9*H*-purin-6-yl)-2-hydroxy-benzamide (4d)

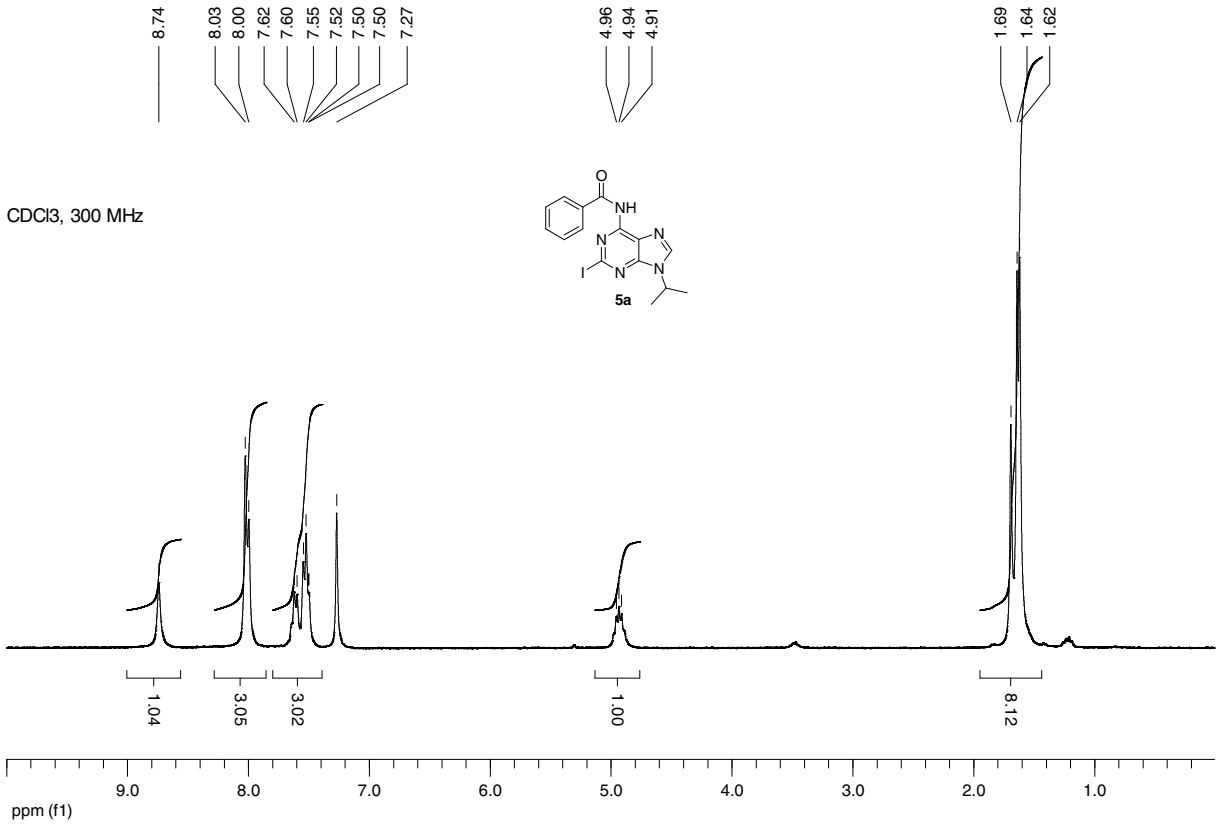


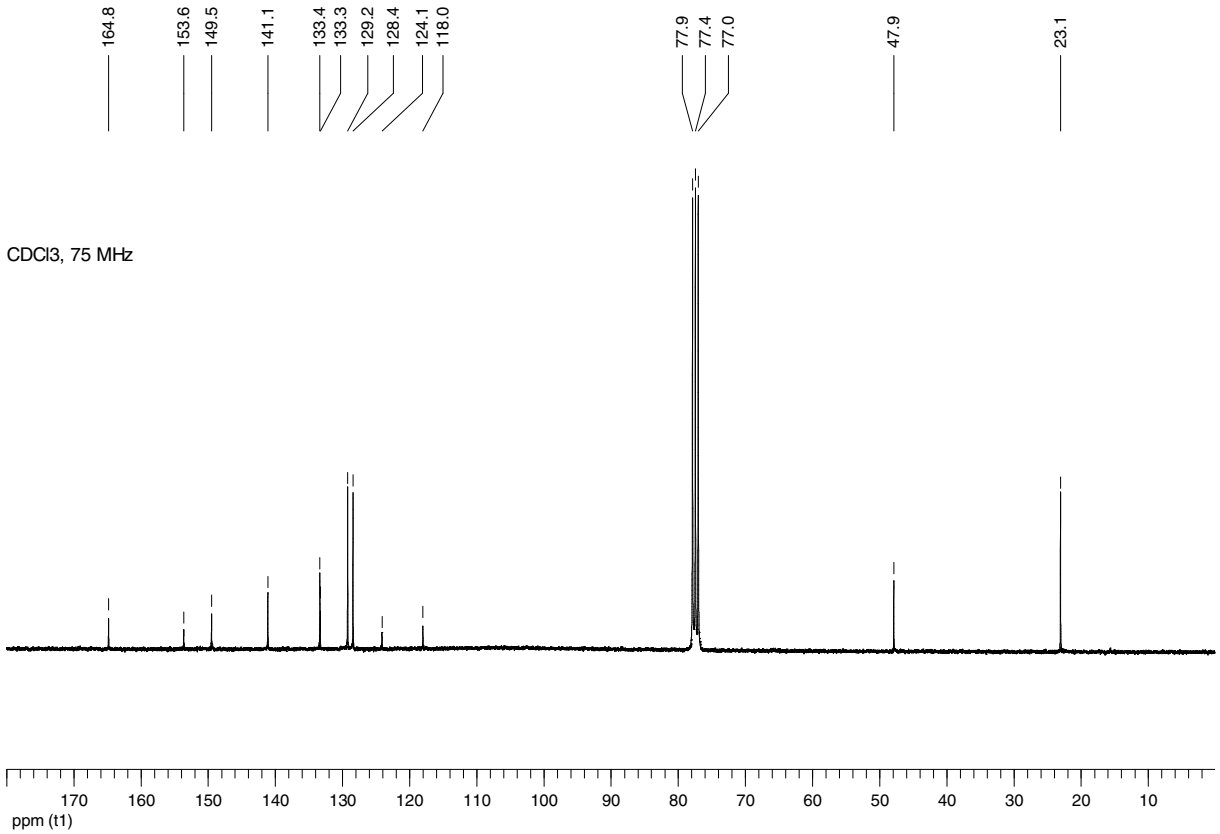
N-(2-Fluoro-9-isopropyl-9*H*-purin-6-yl)-3-methyl-butyramide (4e)



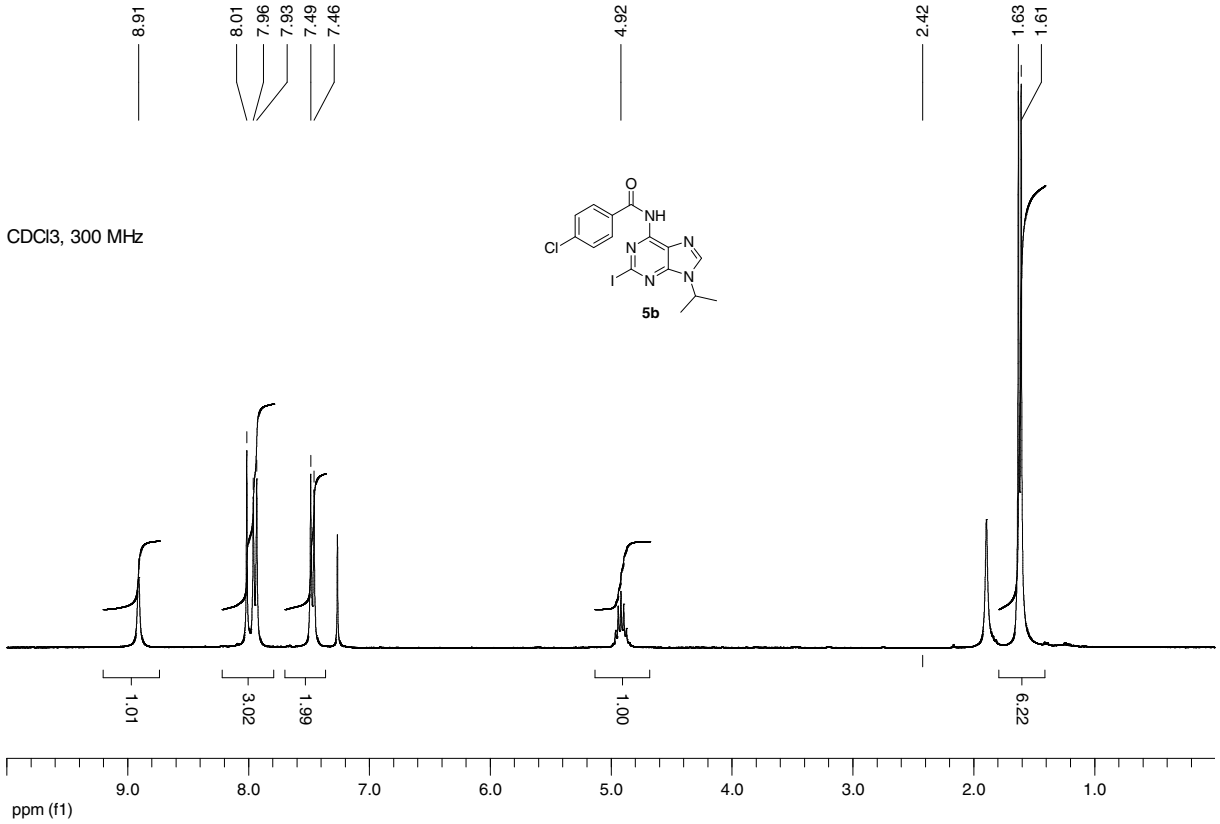


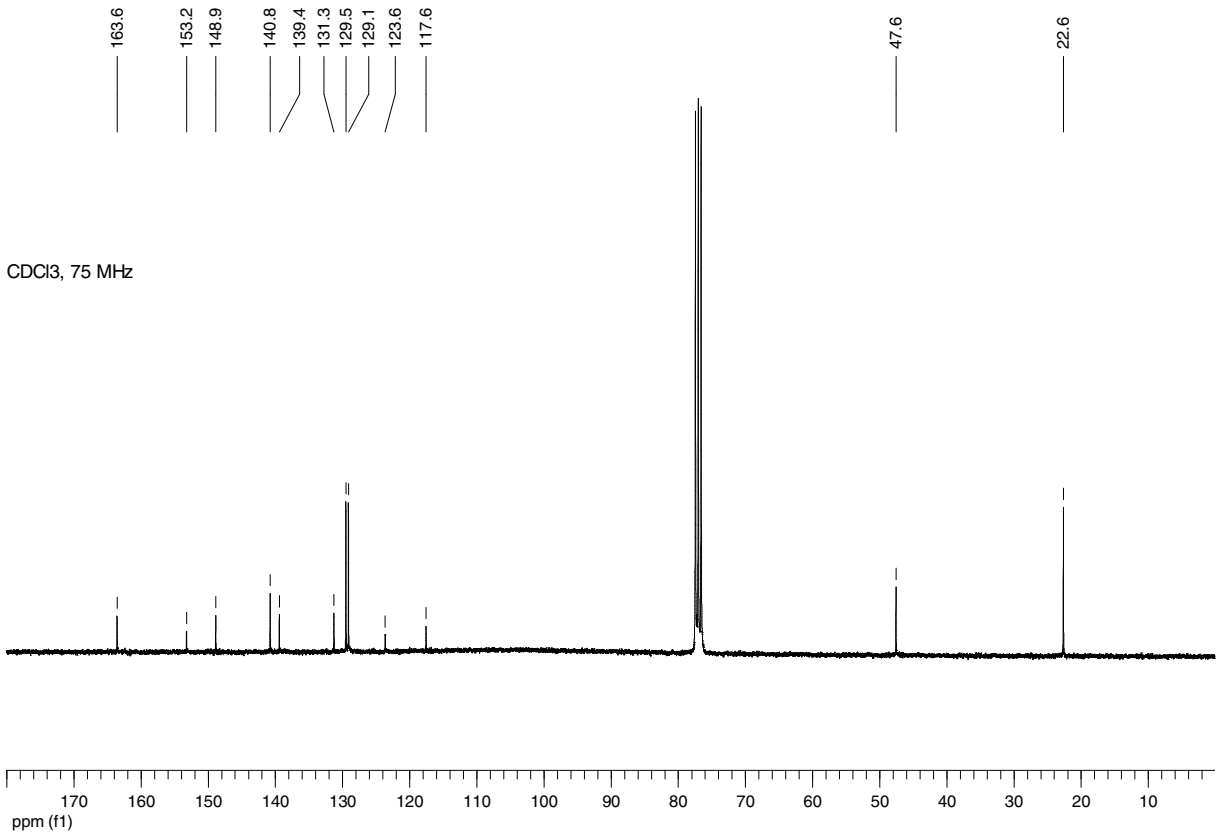
N-(2-Iodo-9-isopropyl-9*H*-purin-6-yl)-benzamide (5a)



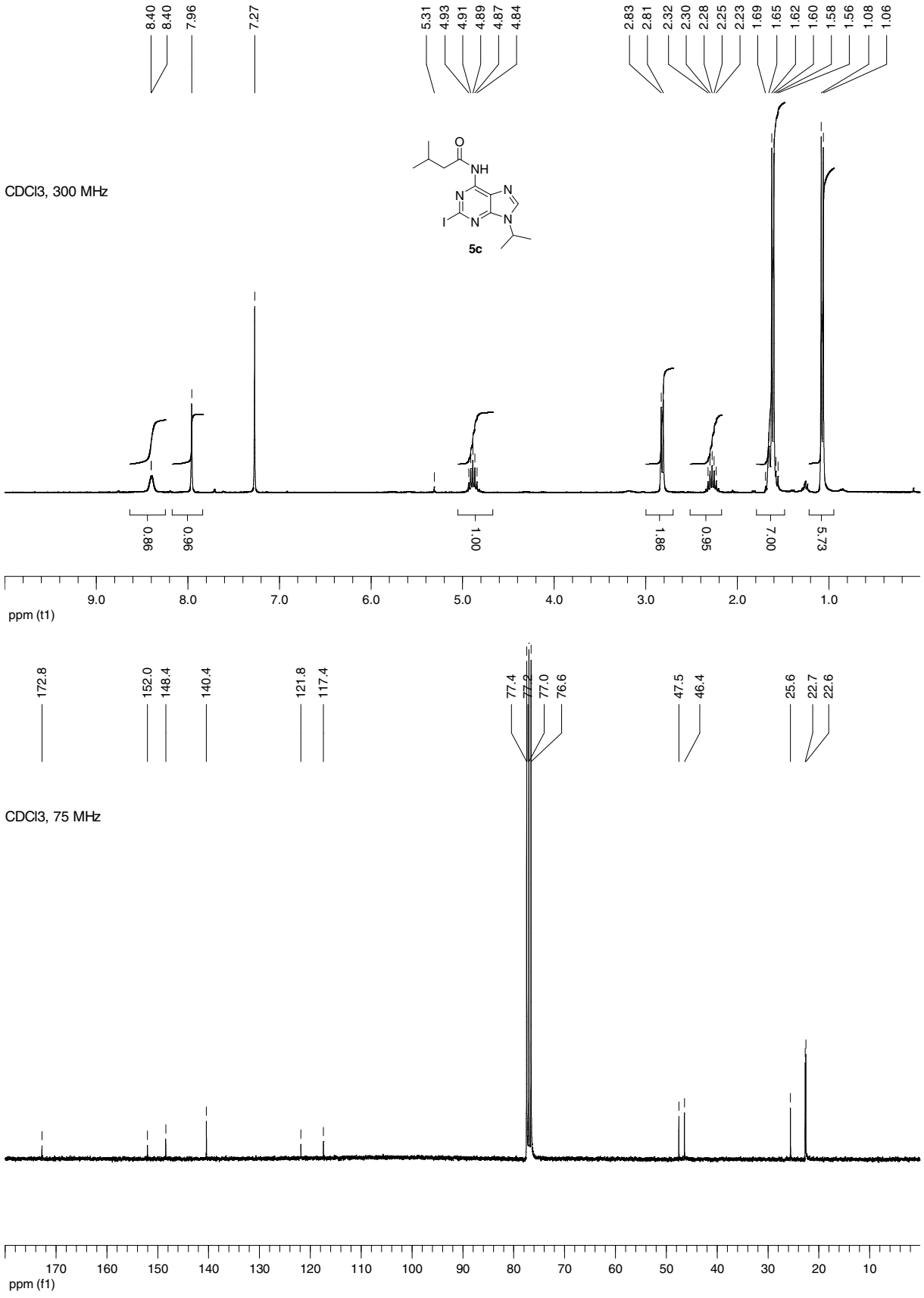


4-chloro-*N*-(2-Iodo-9-isopropyl-9*H*-purin-6-yl)-benzamide (5b)

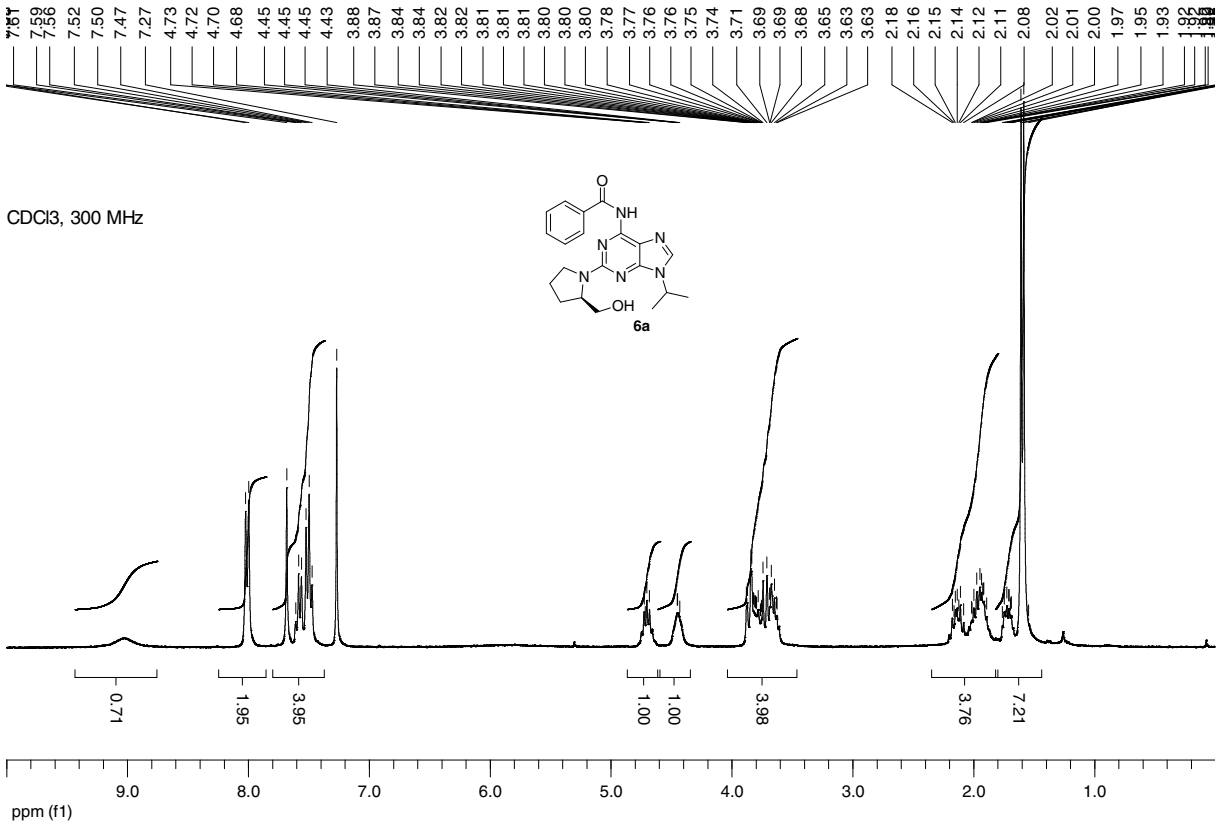


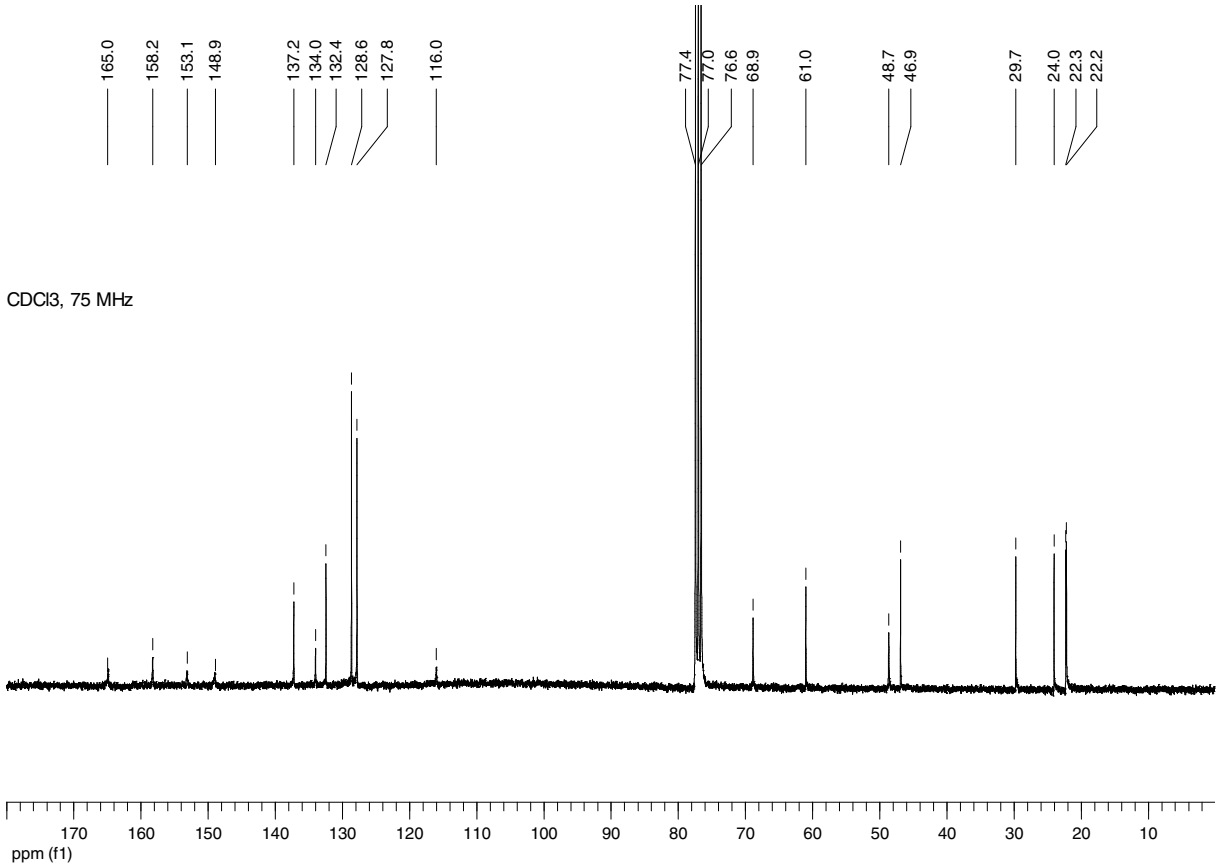


N-(2-Iodo-9-isopropyl-9*H*-purin-6-yl)-3-methyl-butyramide (5c)

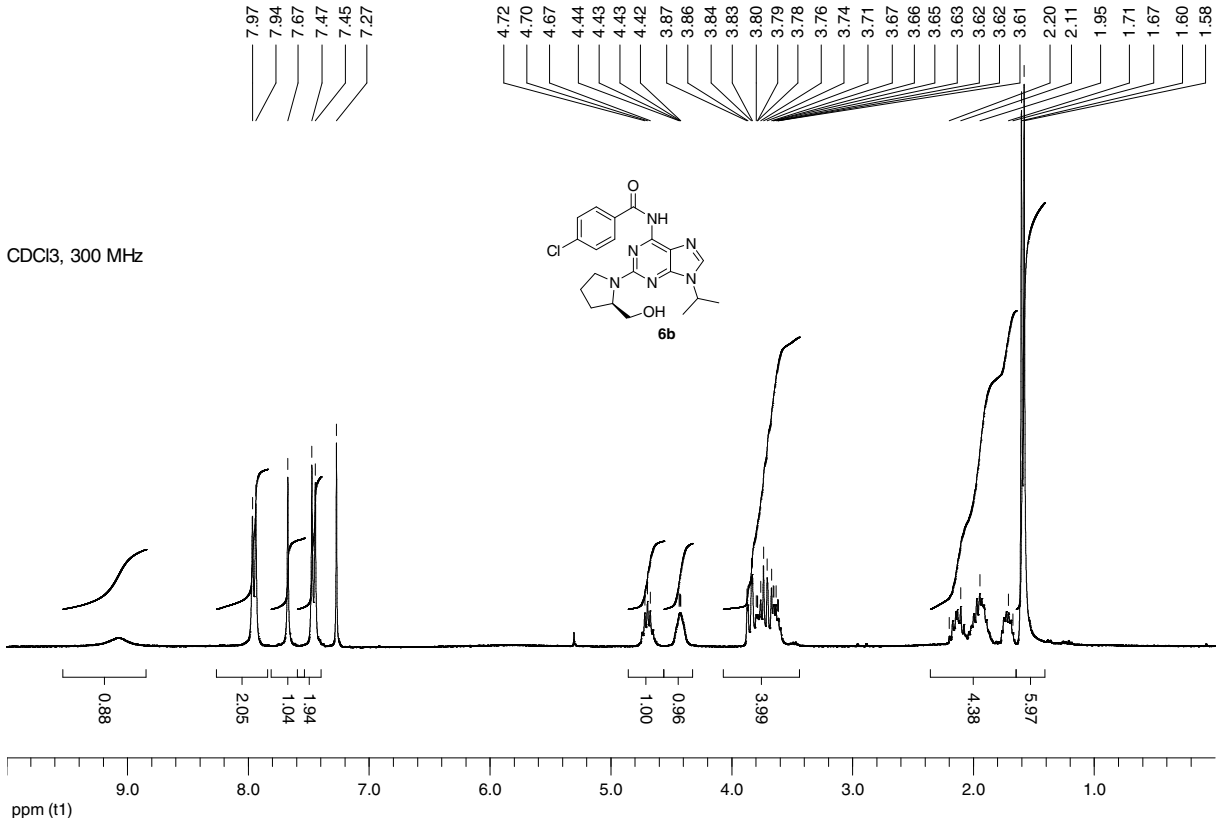


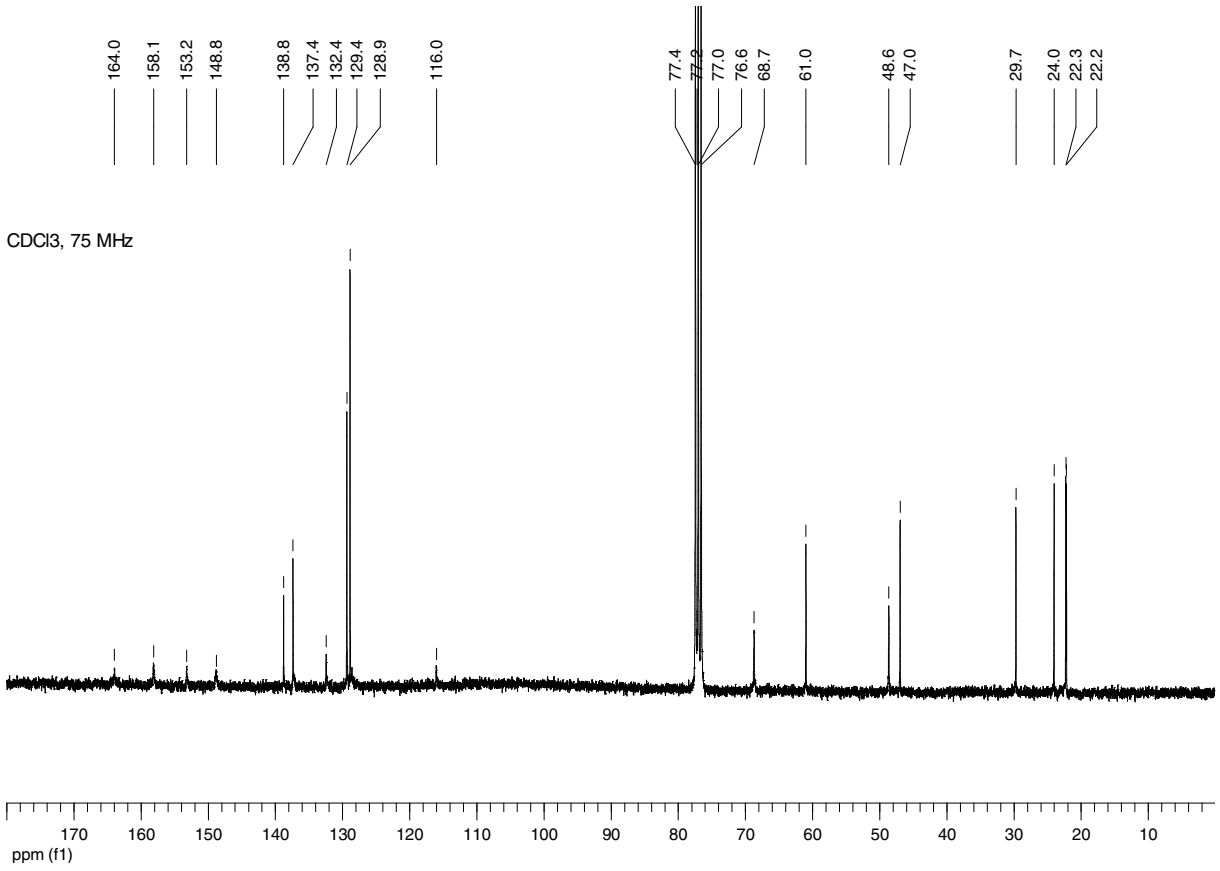
_N_-[2-((_R_)-(-)-2-Hydroxymethyl-pyrrolidin-1-yl)-9-isopropyl-9_H_-purin-6-yl]-benzamide (6a)



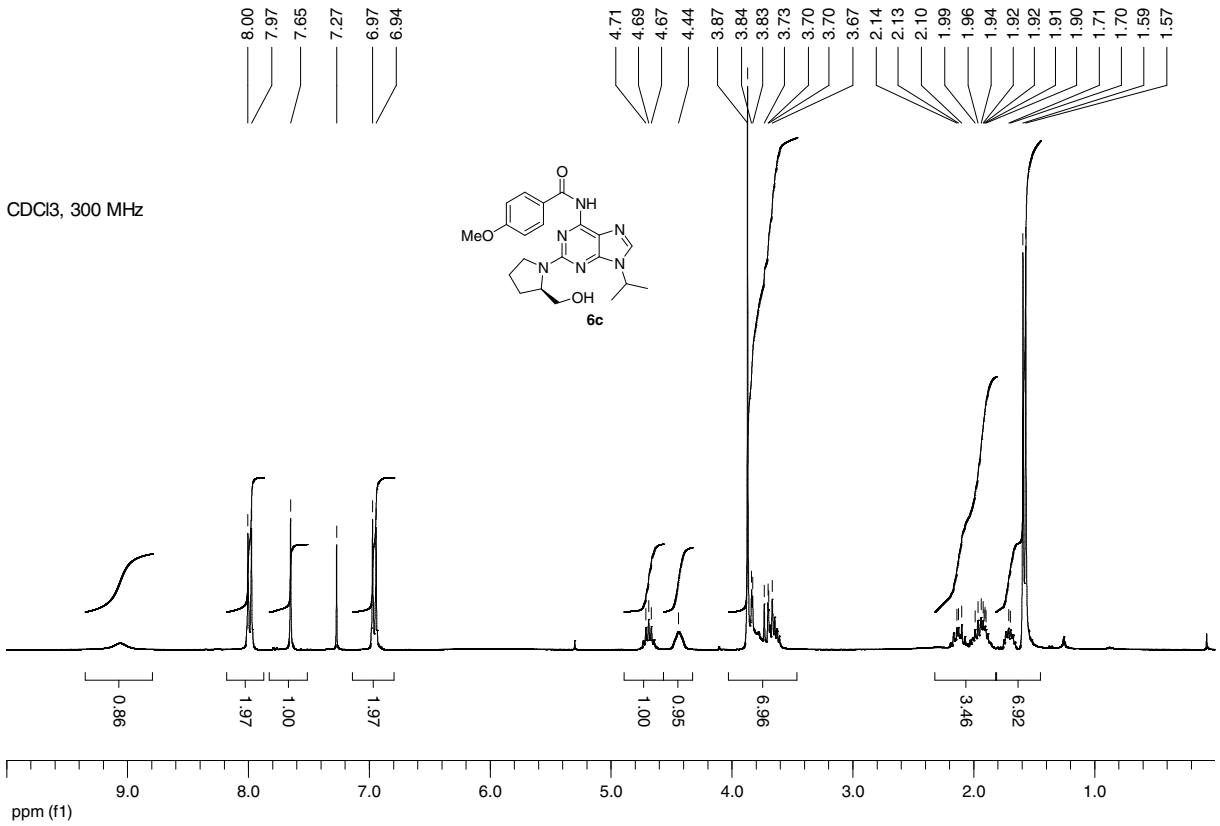


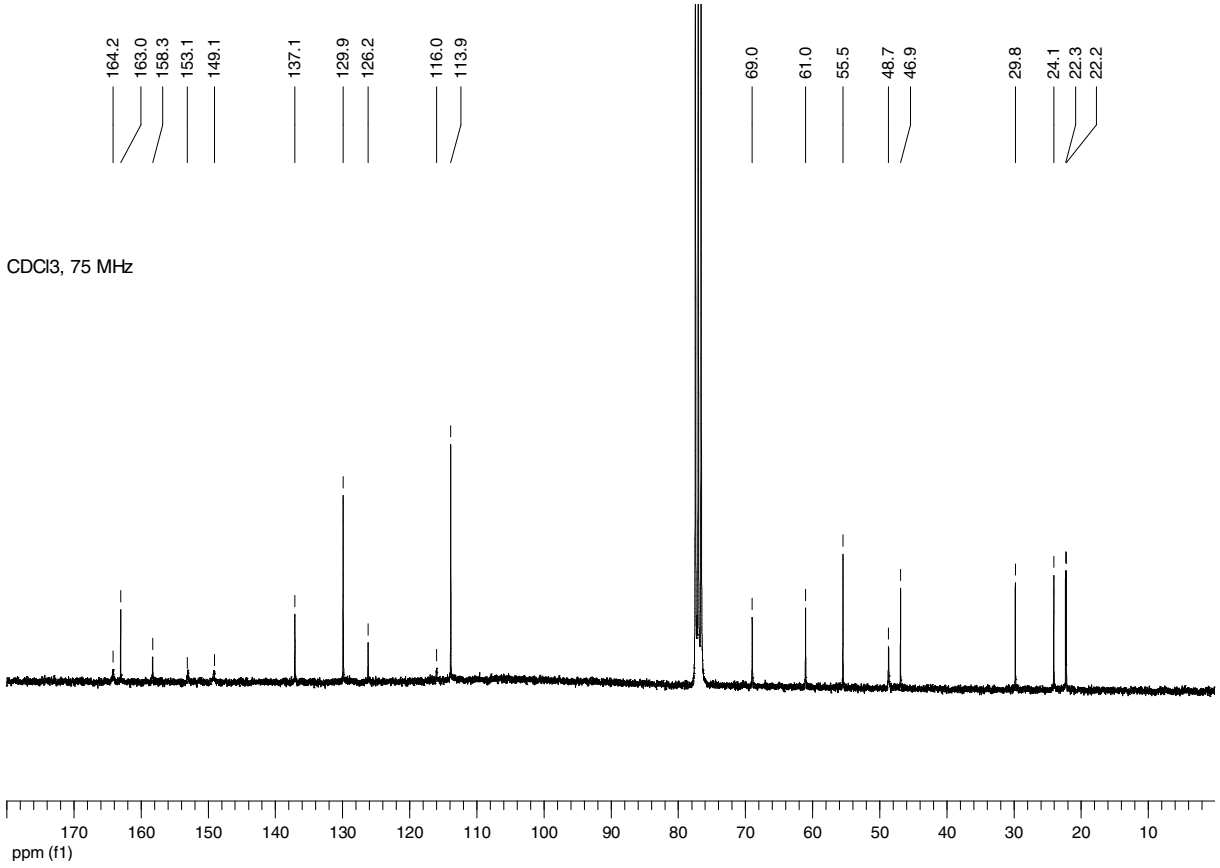
4-Chloro-*N*-[2-((*R*)-(-)-2-hydroxymethyl-pyrrolidin-1-yl)-9-isopropyl-9*H*-purin-6-yl]-benzamide (6b)



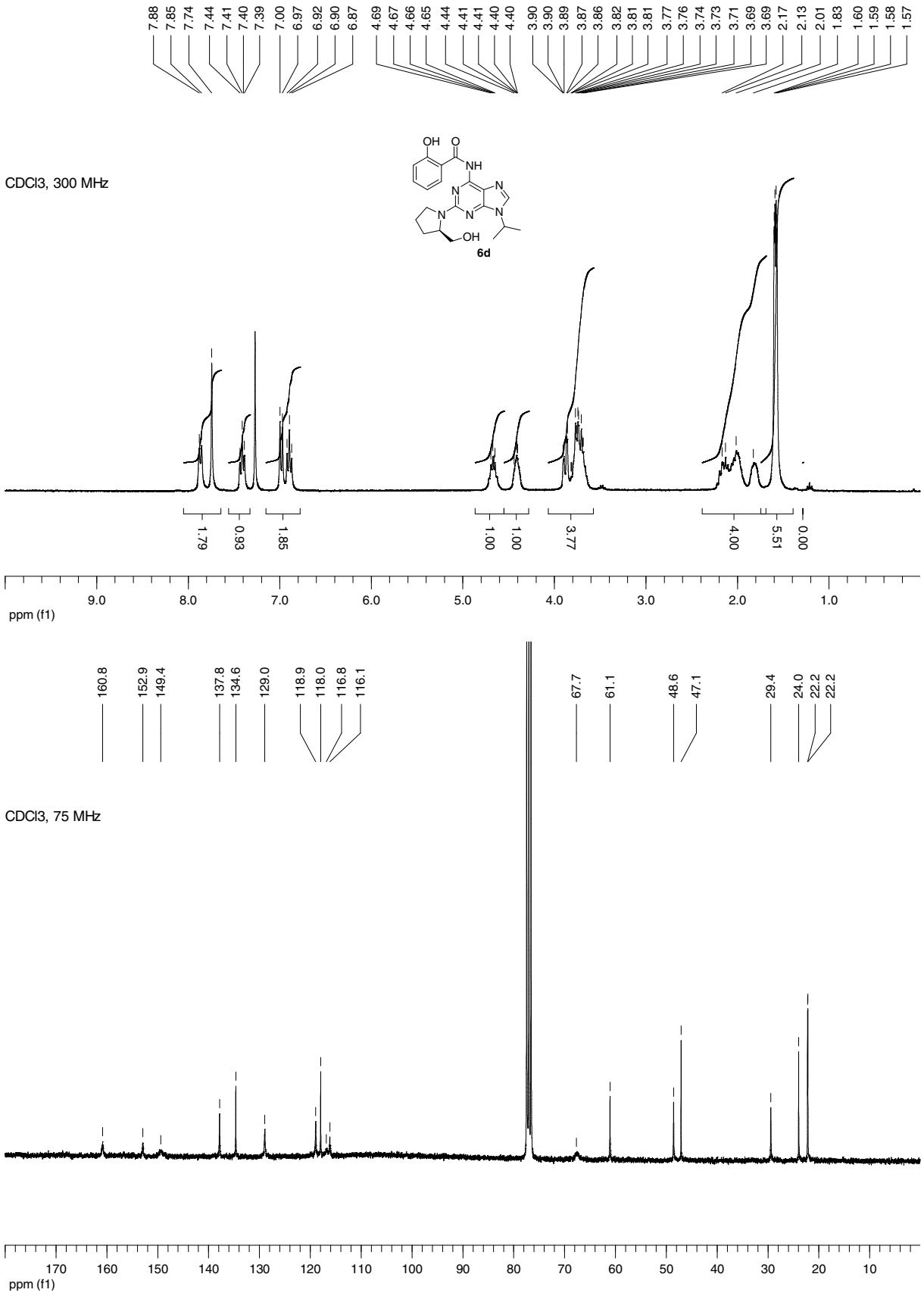


_N_-[2-((_R_)-(-)2-Hydroxymethyl-pyrrolidin-1-yl)-9-isopropyl-9_H_-purin-6-yl]-4-methoxy-benzamide (6c)

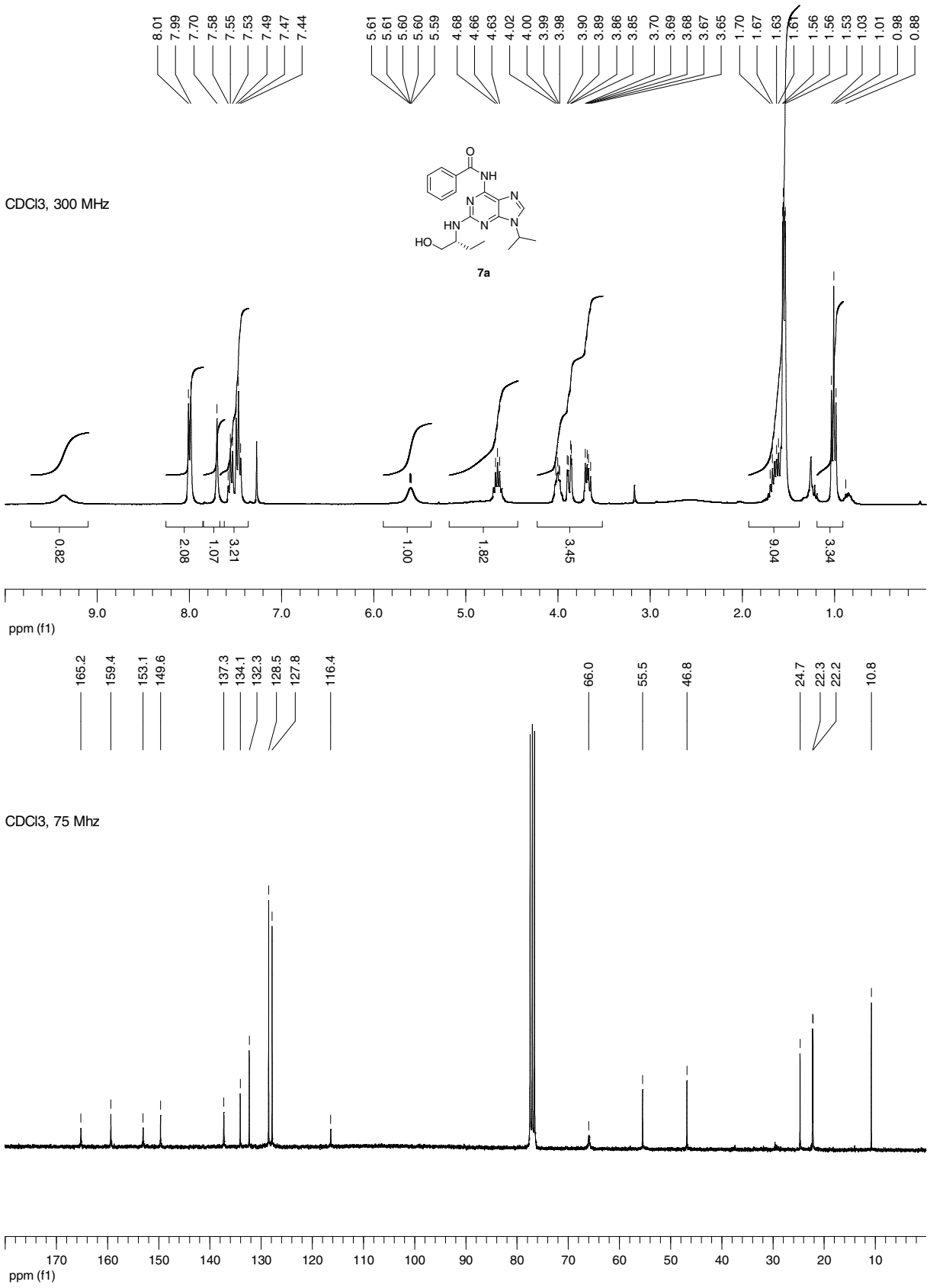




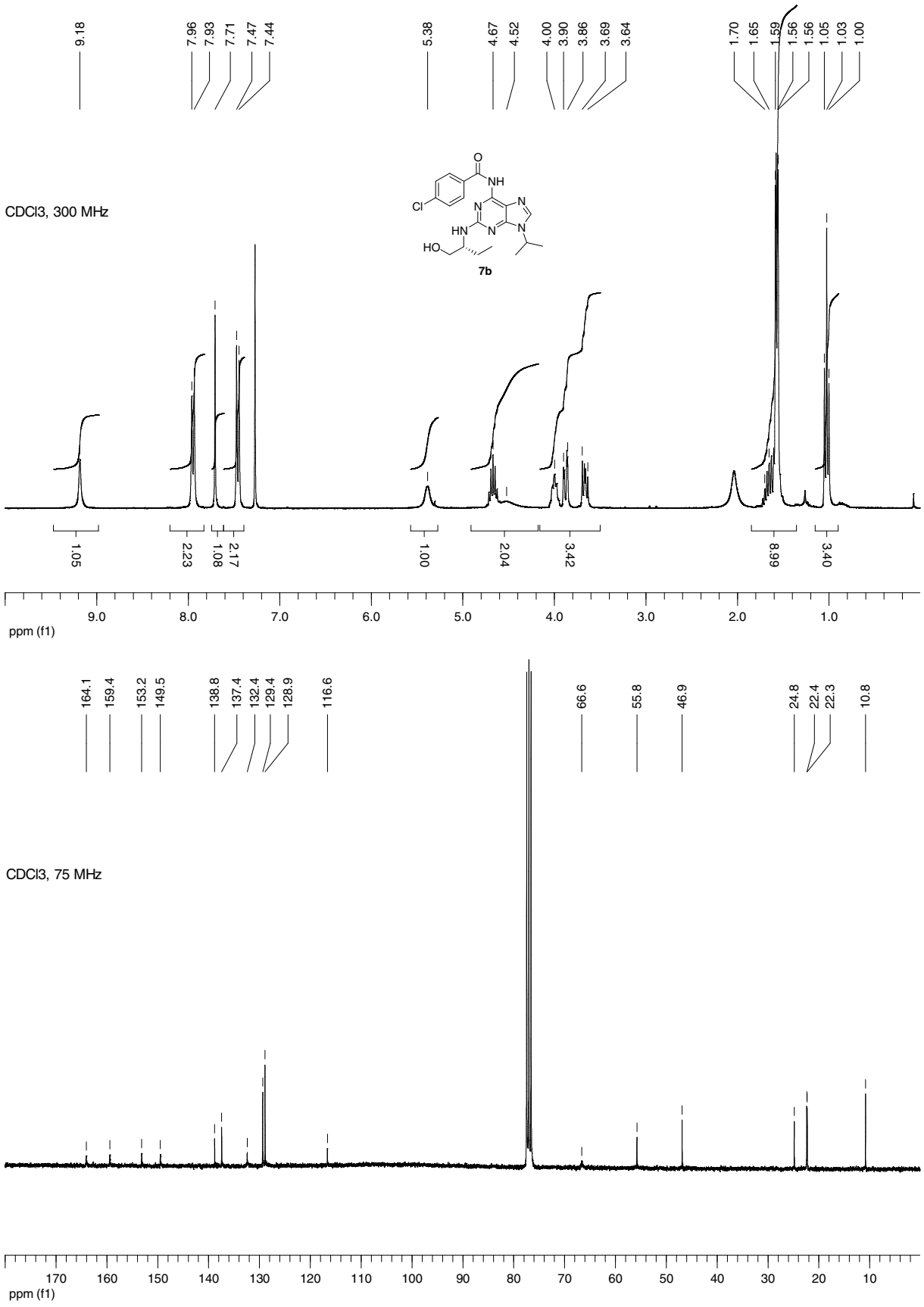
2-Hydroxy-*N*-[2-((*R*)-(-)-2-hydroxymethyl-pyrrolidin-1-yl)-9-isopropyl-9*H*-purin-6-yl]-benzamide (6d)



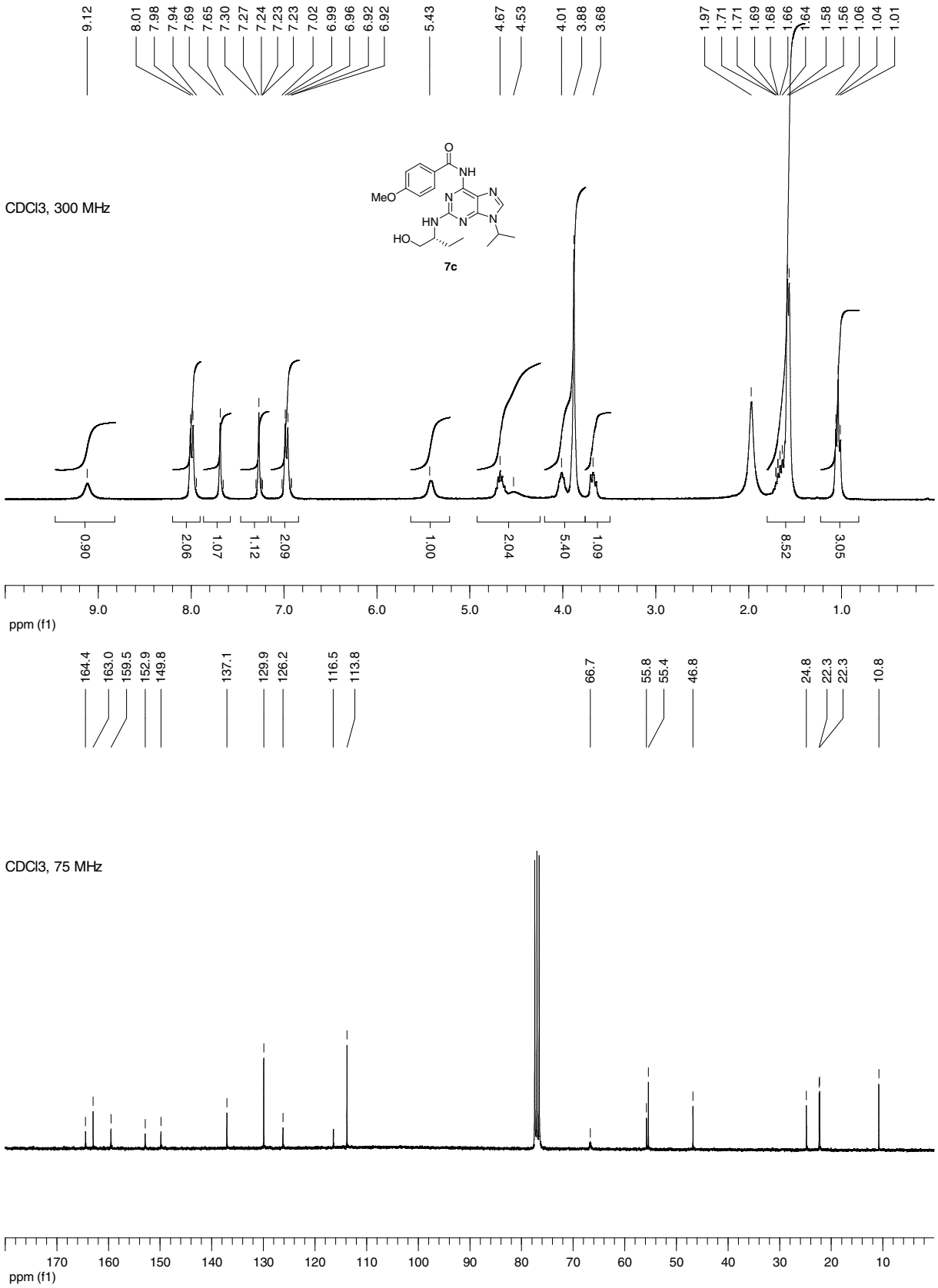
_N_-[2-((_R_)-(-)-1-Hydroxymethyl-propylamino)-9-isopropyl-9_H_-purin-6-yl]-benzamide (7a)



4-Chloro-*N*-[2-((*R*)-(-)-1-hydroxymethyl-propylamino)-9-isopropyl-9*H*-purin-6-yl]-benzamide (7b)



_N_-[2-((_R_)-(-)-1-Hydroxymethyl-propylamino)-9-isopropyl-9_H_-purin-6-yl]-4-methoxy-benzamide (7c)



(*R*)-(-)-2-(6-Amino-9-isopropyl-9*H*-purin-2-ylamino)-butan-1-ol (8)