

Supporting Information

Cp*Co^{III}-Catalyzed Directed C-H Trifluoromethylthiolation of 2-Phenylpyridines and 6-Arylpurines

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Experimental Section

General: Reported melting points were uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-5300 spectrophotometer and absorbance bands are reported in wave numbers (cm⁻¹). NMR spectra were recorded on JEOL JNM-ECS400 spectrometers operating at 391.78 MHz for ¹H NMR and 98.52 MHz for ¹³C NMR, JOEL JNM-ECX400 spectrometers, operating at 395.88 MHz for ¹H NMR, 99.55 MHz for ¹³C NMR, and 372.48 MHz for ¹⁹F NMR, and JNM-ECA500 spectrometers, operating at 500.16 MHz for ¹H NMR, 125.77 MHz for ¹³C NMR, and 470.59 MHz for ¹⁹F NMR. Chemical shifts were reported in the scale relative to TMS (0.00 ppm for ¹H NMR), CHCl₃ (7.26 ppm for ¹H NMR), CDCl₃ (77.16 ppm for ¹³C NMR), and PhCF₃ (-63.72 ppm for ¹⁹F NMR) as an internal reference, respectively. GC-MS analysis was performed on Shimadzu GC-MS QP2010 Ultra using capillary column (DB-5ms, 30 m x 0.25 mm, 0.25 μm), and the GC-MS yields were calculated based on TIC area values (EI-mode) by fitting with a calibration curve (internal standard: dodecane). ESI mass spectra were measured on JEOL JMS-T100LCP spectrometer. Silica gel column chromatography was performed with Kanto Silica gel 60 N (40-50 mesh) or Yamazen YFLC AI-580 using Universal Column SiOH.

1,2-Dichloroethane (CaH₂), 1,1,1,3,3,3-hexafluoropropan-2-ol (molecular sieves 3A), and 2,2,2-trifluoroethanol (CaSO₄ and NaHCO₃) were distilled from the indicated reagents, purged with argon for over 30 min, and stored over activated molecular sieves 3A or 4A under argon atmosphere before use. Toluene was purified by Glass Contour solvent purification system and stored over activated molecular sieves 4A under argon atmosphere. Cp*Co(CO)I₂^[1] and [Cp*Co(CH₃CN)₃](SbF₆)₂^[2] were synthesized according to the literatures. *N*-Trifluoromethylthiosaccharin **2a**^[3] and *N*-Trifluoromethylthiodibenzenesulfonimide **2b**^[4] were synthesized according to the literatures. 2-Phenylpyridine derivatives that are not commercially available were synthesized via Suzuki-Miyaura cross-coupling using the reported procedures.^[5] 6-Arylpurines **5** were prepared from commercially available 6-chloropurine according to the literature.^[6] All other reagents were commercially available and used as received.

- [1] Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Adv. Synth. Catal.* **2014**, *356*, 1491.
- [2] Yu, D.-G.; Gensch, T.; de Azambuja, F.; Vásquez-Céspedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722.
- [3] Xu, C.; Ma, B.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 9316.
- [4] Zhang, P.; Li, M.; Xue, X.-S.; Xu, C.; Zhao, Q.; Liu, Y.; Wang, H.; Guo, Y.; Lu, L.; Shen, Q. *J. Org. Chem.* **2016**, *81*, 7486.
- [5] (a) Liu, C.; Yang, W. *Chem. Commun.* **2009**, *45*, 6267; (b) Liu, C.; Han, N.; Song, X.; Qiu, J. *Eur. J. Org. Chem.* **2010**, 5548.
- [6] Havelková, M.; Dvořák, D.; Hocek, M. *Synthesis* **2001**, 1704.

Note: The reagent **2b** was often obtained as a highly viscous oil, and thus it was added to a reaction mixture as a HFIP solution (see below). In case **2b** was obtained as a solid, it was directly added to a reaction mixture. Both procedures afforded almost same results.

General procedure of Cp*Co^{III} catalyzed C–H trifluoromethylthiolation of 2-phenylpyridines (for solid substrates: **1b, **1c**, **1d**, **1e**, **1g**)**

In a glovebox, **2b** (238 mg, 0.60 mmol) was added into a pressure reaction tube, and dissolved in HFIP (3 mL). To this solution were successively added [Cp*Co(CH₃CN)₃](SbF₆)₂ (31.6 mg, 0.040 mmol), activated molecular sieves 3A (80 mg), AgSbF₆ (0.020 mmol, 6.9 mg), HFIP (3 mL), and **1** (0.40 mmol). To this mixture was added HFIP (2 mL), and the reaction tube was capped and heated at 80 °C for 12 h with stirring. After the mixture was cooled to room temperature, saturated aqueous EDTA·2Na was added, and extracted with AcOEt three times. The combined organic layers were washed with saturated aqueous NaHCO₃, brine, and dried over Na₂SO₄. After filtration and evaporation, the residue was dissolved in AcOEt and filtered through a short pad of silica gel. The obtained crude mixture was purified by silica gel column chromatography to afford **3**.

General procedure of Cp*Co^{III} catalyzed C–H trifluoromethylthiolation of 2-phenylpyridines (for liquid substrates: **1a, **1f**, **1h**)**

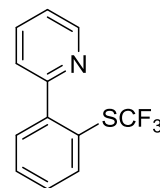
In a glovebox, **2b** (238 mg, 0.60 mmol) was added into a pressure reaction tube, and dissolved in HFIP (3 mL). To this solution were successively added [Cp*Co(CH₃CN)₃](SbF₆)₂ (31.6 mg, 0.040 mmol), activated molecular sieves 3A (80 mg), AgSbF₆ (0.020 mmol, 6.9 mg), HFIP (2 mL). A solution of **1** (0.40 mmol) in HFIP (0.5 mL) was added to the reaction mixture, and the vial was washed with HFIP (0.5 mL). To the reaction mixture was added HFIP (2 mL), and the reaction tube was capped and heated at 80 °C for 12 h with stirring. After the mixture was cooled to room temperature, saturated aqueous EDTA·2Na was added, and extracted with AcOEt three times. The combined organic layers were washed with saturated aqueous NaHCO₃, brine, and dried over Na₂SO₄. After filtration and evaporation, the residue was dissolved in AcOEt and filtered through a short pad of silica gel. The obtained crude mixture was purified by silica gel column chromatography

to afford **3**.

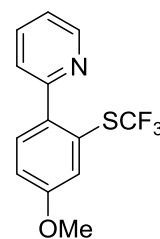
Compounds **3a-g** and **3i** were reported in the literatures,^[7] and the obtained ¹H and ¹³C NMR spectra were in good agreement with the reported spectra.

[7] (a) Xu, C; Shen, Q. *Org. Lett.* **2014**, *16*, 2046; (b) Yin, W.; Wang Z.; Huang, Y. *Adv. Synth. Catal.* **2014**, *356*, 2998.

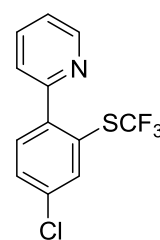
2-(2-((trifluoromethyl)thio)phenyl)pyridine (3a): purified by silica gel column chromatography (hexane/AcOEt = 8/1 to 4/1); a brown oil; ¹H NMR (CDCl₃, 400 MHz) δ : 8.71 (ddd, *J* = 5.0, 1.9, 1.0 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.79 (ddd, *J* = 7.7, 7.6, 1.9 Hz, 1H), 7.60 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.56-7.50 (m, 2H), 7.46 (ddd, *J* = 7.6, 7.5, 1.8 Hz, 1H), 7.32 (ddd, *J* = 7.6, 5.0, 1.1 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ : 157.8, 149.0, 145.2, 136.4, 135.9, 130.8, 130.2, 129.7 (q, ¹*J*_{CF} = 310 Hz), 129.3, 124.3 (q, *J* = 1.9 Hz), 124.2, 122.5.



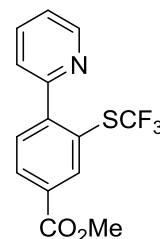
2-(4-methoxy-2-((trifluoromethyl)thio)phenyl)pyridine (3b): purified by silica gel column chromatography (CH₂Cl₂/AcOEt = 40/1); a colorless solid; ¹H NMR (CDCl₃, 400 MHz) δ : 8.68 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.76 (ddd, *J* = 8.0, 7.6, 1.8 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.50 (ddd, *J* = 8.0, 1.1, 0.9 Hz, 1H), 7.35 (d, *J* = 2.7 Hz, 1H), 7.27 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 7.06 (dd, *J* = 8.6, 2.7 Hz, 1H), 3.88 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ : 159.7, 157.5, 148.9, 137.4, 136.3, 131.7, 129.8 (q, ¹*J*_{CF} = 308 Hz), 125.5 (q, *J* = 2.4 Hz), 124.0, 122.1, 120.3, 115.9, 55.7.



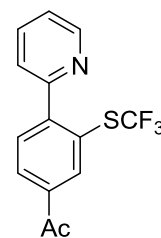
2-(4-chloro-2-((trifluoromethyl)thio)phenyl)pyridine (3c): purified by silica gel column chromatography (hexane/CH₂Cl₂/AcOEt = 40/40/1); an orange oil; ¹H NMR (CDCl₃, 500 MHz) δ : 8.71-8.68 (m, 1H), 7.83-7.77 (m, 2H), 7.57-7.48 (m, 3H), 7.33 (ddd, *J* = 7.4, 4.6, 1.1 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ : 156.6, 149.1, 143.1, 136.6, 135.0, 134.6, 131.7, 130.2, 129.5 (q, ¹*J*_{CF} = 308 Hz), 126.3 (q, *J* = 2.4 Hz), 124.0, 122.8.



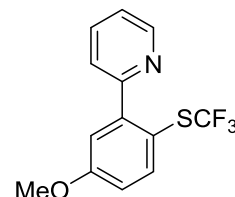
methyl 4-(pyridin-2-yl)-3-((trifluoromethyl)thio)benzoate (3d): purified by silica gel column chromatography (CH₂Cl₂/AcOEt = 30/1); a pale orange solid; ¹H NMR (CDCl₃, 400 MHz) δ : 8.73 (ddd, *J* = 5.0, 1.8, 0.9 Hz, 1H), 8.50 (s, 1H), 8.18 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.83 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.56 (ddd, *J* = 7.7, 1.0, 0.9 Hz, 1H), 7.36 (ddd, *J* = 7.7, 5.0, 1.0 Hz, 1H), 3.98 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ : 165.8, 156.7, 149.1, 148.9, 136.7, 136.5, 131.06, 131.04, 130.9, 129.5 (q, ¹*J*_{CF} = 308 Hz), 125.2 (q, ³*J*_{CF} = 2.4 Hz), 124.2, 123.1, 52.6.



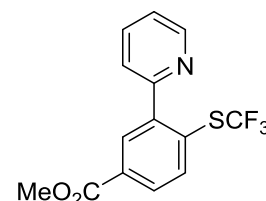
1-(4-(pyridin-2-yl)-3-((trifluoromethyl)thio)phenyl)ethan-1-one (3e): purified by silica gel column chromatography (CH₂Cl₂/AcOEt = 20/1); a pale brown solid; ¹H NMR (CDCl₃, 400 MHz) δ : 8.74 (d, *J* = 5.2 Hz, 1H), 8.40 (s, 1H), 8.10 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.84 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.36 (ddd, *J* = 7.7, 5.2, 0.9 Hz, 1H), 2.68 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ : 196.5, 156.6, 149.1, 148.8, 137.5, 136.6, 135.4, 131.0, 129.6, 129.5 (q, ¹*J*_{CF} = 388 Hz), 125.5 (q, ³*J*_{CF} = 2.4 Hz), 124.1, 123.1, 26.7.



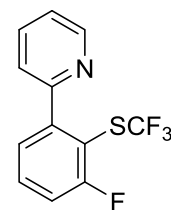
2-(5-methoxy-2-((trifluoromethyl)thio)phenyl)pyridine (3f): purified by silica gel column chromatography (hexane/AcOEt = 85/15 to 70/30); an orange oil; ¹H NMR (CDCl₃, 500 MHz) δ : 8.71-8.68 (m, 1H), 7.78 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.32 (ddd, *J* = 7.7, 5.2, 1.1 Hz, 1H), 7.12 (d, *J* = 2.9 Hz, 1H), 7.00 (dd, *J* = 8.9, 2.9 Hz, 1H), 3.88 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ : 161.5, 157.9, 149.2, 148.1, 139.2, 136.1, 129.6 (q, ¹*J*_{CF} = 308 Hz), 124.6, 122.6, 116.2, 115.4, 113.8 (q, ³*J*_{CF} = 2.4 Hz), 55.6.



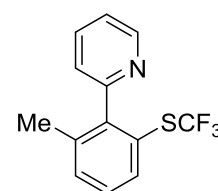
methyl 3-(pyridin-2-yl)-4-((trifluoromethyl)thio)benzoate (3g): purified by silica gel column chromatography (CH₂Cl₂/AcOEt = 40/1); an orange oil; ¹H NMR (CDCl₃, 500 MHz) δ : 8.72 (d, *J* = 4.0 Hz, 1H), 8.27 (d, *J* = 1.7 Hz, 1H), 8.09 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.84 (ddd, *J* = 8.0, 8.0, 1.7 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.37-7.32 (m, 1H), 3.95 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ : 166.1, 156.7, 148.9, 143.5, 136.9, 133.5 (2C), 131.3, 130.9, 129.9, 129.5 (q, ¹*J*_{CF} = 309 Hz), 123.7, 123.0, 52.6.



2-(3-fluoro-2-((trifluoromethyl)thio)phenyl)pyridine (3h): purified by silica gel column chromatography (hexane/AcOEt = 10/1 to 5/1); an orange solid; IR (KBr) ν 1575, 1455, 1248, 1163, 1118, 893, 809, 784, 752 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ : 8.71 (ddd, *J* = 5.1, 1.9, 0.9 Hz, 1H), 7.80 (ddd, *J* = 7.7, 7.4, 1.9 Hz, 1H), 7.59 (ddd, *J* = 8.2, 7.6, 5.6 Hz, 1H), 7.48 (brd, *J* = 7.4 Hz, 1H), 7.41 (brd, *J* = 7.6 Hz, 1H), 7.34 (ddd, *J* = 7.7, 5.1, 1.2 Hz, 1H), 7.28 (ddd, *J* = 8.4, 8.2, 1.2 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ : 163.7 (d, ¹*J*_{CF} = 250 Hz), 156.8 (d, ³*J*_{CF} = 2.4 Hz), 149.2, 149.0, 136.1, 133.0 (d, ³*J*_{CF} = 8.4 Hz), 128.9 (q, ¹*J*_{CF} = 312 Hz), 126.5 (d, ⁴*J*_{CF} = 3.6 Hz), 124.6, 122.7, 116.3 (d, ²*J*_{CF} = 23.9 Hz), 110.9-110.7 (m); ¹⁹F NMR (CDCl₃, 471 MHz) δ : -42.83 (d, ⁵*J*_{FF} = 7.1 Hz), -102.3-102.5 (m); HRMS (ESI): *m/z* calculated for C₁₂H₈NF₄S⁺ [M+H⁺]: 274.0308, found: 274.0309.



2-(2-methyl-6-((trifluoromethyl)thio)phenyl)pyridine (3i): purified by silica gel column chromatography (CH₂Cl₂/AcOEt = 40/1); a yellow oil; ¹H NMR (CDCl₃, 400 MHz) δ : 8.72-8.69 (m, 1H), 7.79 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.41-7.25 (m, 4H), 2.12 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ : 158.1, 149.5, 146.2,



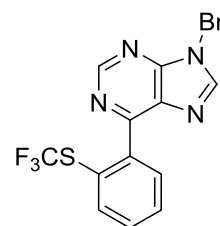
138.2, 136.3, 134.5, 132.8, 129.6 (q, $^1J_{CF} = 306$ Hz), 128.9, 124.9, 124.0 (q, $^3J_{CF} = 2.4$ Hz), 122.5, 20.7.

General procedure of Cp*Co^{III} catalyzed C–H trifluoromethylthiolation of 6-arylpurines

To a pressure reaction tube equipped with a stirring bar were added **4** (0.40 mmol), [Cp*Co(CH₃CN)₃](SbF₆)₂ (31.6 mg, 0.040 mmol), AgOAc (6.7 mg, 0.040 mmol), Gd(OTf)₃ (72.5 mg, 0.12 mmol) activated molecular sieves 3A (80 mg), and HFIP (1 mL). To another vial was added **2b** (159 mg, 0.40 mmol) and dissolved in HFIP (1 mL). This solution was transferred to the reaction tube using additional HFIP (1 mL x 2). The reaction tube was capped and heated at 80 °C for 12 h with stirring. After the mixture was cooled to room temperature, an aliquot of the mixture was transferred to a vial containing additional **2b** (159 mg, 0.40 mmol). This solution was added to the reaction tube, and the vial was washed with a small amount of HFIP. The reaction tube was capped and heated at 80 °C for 12 h with stirring. After the mixture was cooled to room temperature, saturated aqueous EDTA·2Na was added, and extracted with CH₂Cl₂ three times. The combined organic layers were dried over Na₂SO₄. After filtration and evaporation, the residue was dissolved in AcOEt and filtered through a short pad of silica gel. The obtained crude mixture was purified by silica gel column chromatography to afford **5**.

9-benzyl-6-(2-((trifluoromethyl)thio)phenyl)-9H-purine (5a): purified by silica gel

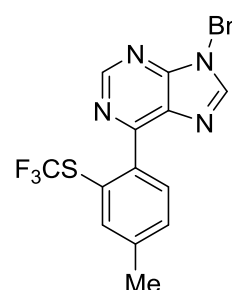
column chromatography (hexane/AcOEt = 70/30 to 50/50); an orange solid; IR (KBr) ν 1574, 1110 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ : 9.12 (s, 1H), 8.10 (s, 1H), 8.03 (dd, $J = 7.4, 1.7$ Hz, 1H), 7.91 (d, $J = 7.7$ Hz, 1H), 7.61 (ddd, $J = 7.5, 7.4, 1.4$ Hz, 1H), 7.56 (ddd, $J = 7.7, 7.5, 1.7$ Hz, 1H), 7.41-7.35 (m, 5H), 5.51 (s, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ :



155.7, 152.1, 145.0, 139.5, 135.2, 135.0, 131.99, 131.96, 130.5, 129.9, 129.6 (q, $^1J_{CF} = 308$ Hz), 129.3, 128.8, 128.0, 125.8 (q, $^3J_{CF} = 2.4$ Hz), 47.5, one of the aromatic ¹³C signal is missing probably due to overlap; ¹⁹F NMR (CDCl₃, 372 MHz) δ : -42.78; HRMS (ESI): m/z calculated for C₁₉H₁₃N₄F₃NaS⁺ [M+Na⁺]: 409.0705, found: 409.0706.

9-benzyl-6-(4-methyl-2-((trifluoromethyl)thio)phenyl)-9H-purine (5b): purified by

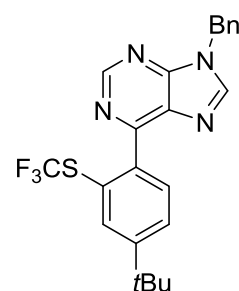
silica gel column chromatography (hexane/AcOEt 4/1 to 3/1); a colorless solid; IR (KBr) ν 1573, 1504, 1455, 1319, 1121, 1092, 799, 728, 699, 649 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ : 9.10 (s, 1H), 8.08 (s, 1H), 7.94 (d, $J = 7.7$ Hz, 1H), 7.71 (brs, 1H), 7.42-7.33 (m, 6H), 5.50 (s, 2H), 2.47 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ : 155.8, 152.0, 151.9, 144.6, 140.9, 136.5, 135.6, 134.9, 131.8, 131.7, 130.6, 129.5 (q, $J_{CF} = 308$ Hz),



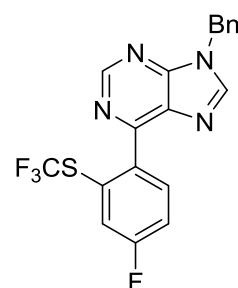
129.1, 128.6, 127.9, 125.5-125.3 (m), 47.4, 21.3; ¹⁹F NMR (CDCl₃, 372 MHz) δ : -42.75; HRMS (ESI): m/z calculated for C₂₀H₁₆N₄F₃S⁺ [M+H⁺]: 401.1042, found: 401.1046.

9-benzyl-6-(4-(tert-butyl)-2-((trifluoromethyl)thio)phenyl)-9H-purine (5c): purified by silica gel column

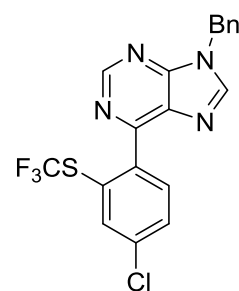
chromatography (hexane/AcOEt = 90/10 to 60/40); an orange oil; IR (neat) ν 2966, 1735, 1581, 1504, 1455, 1329, 1213, 1115, 1049, 727 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ : 9.10 (s, 1H), 8.08 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.63 (dd, J = 8.0, 1.5 Hz, 1H), 7.42–7.35 (m, 5H), 5.51 (s, 2H), 1.38 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ : 155.9, 154.1, 152.2, 152.0, 144.8, 136.7, 135.1, 132.9, 132.0, 131.6, 129.8 (q, $^1J_{\text{CF}}$ = 307.6 Hz), 129.3, 128.7, 128.1, 127.2, 125.2 (q, $^3J_{\text{CF}}$ = 2.4 Hz), 47.5, 35.0, 31.1; $^{19}\text{F NMR}$ (CDCl_3 , 470 MHz) δ : -42.86; HRMS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{15}\text{O}_2\text{N}_4\text{F}_3\text{NaS}^+$ [$\text{M}+\text{Na}^+$]: 443.1512, found: 443.1515.



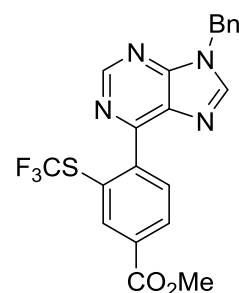
9-benzyl-6-(4-fluoro-2-((trifluoromethyl)thio)phenyl)-9H-purine (5d): purified by silica gel column chromatography (hexane/AcOEt = 70/30 to 50/50); a pale brown solid; IR (KBr) ν 1577, 1500, 1329, 1225, 1153, 1112, 855, 729, 697, 646 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ : 9.10 (s, 1H), 8.22 (dd, J = 8.4, 5.6 Hz), 8.11 (s, 1H), 7.63 (dd, J = 8.8, 2.0 Hz), 7.33–7.43 (m, 5H), 7.31–7.27 (m, 1H), 5.51 (s, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ : 163.2 (d, $^1J_{\text{CF}}$ = 254.9 Hz), 154.4, 152.3, 151.9, 145.0, 135.0, 134.5 (d, $^4J_{\text{CF}}$ = 2.9 Hz), 134.0 (d, $^3J_{\text{CF}}$ = 8.7 Hz), 131.7, 129.4 (q, $^1J_{\text{CF}}$ = 311.4 Hz), 129.4, 129.2 (dq, $^3J_{\text{CF}}$ = 8.6 Hz, $^3J_{\text{CF}}$ = 1.9 Hz), 128.9, 128.1, 120.8 (d, $^2J_{\text{CF}}$ = 22.9 Hz), 116.6 (d, $^2J_{\text{CF}}$ = 22.0 Hz), 47.7; $^{19}\text{F NMR}$ (CDCl_3 , 370 MHz) δ : -42.61, -109.47 (dd, J = 13.7, 7.0 Hz); HRMS (ESI): m/z calculated for $\text{C}_{19}\text{H}_{13}\text{N}_4\text{F}_4\text{S}^+$ [$\text{M}+\text{H}^+$]: 405.0792, found: 405.0802.



9-benzyl-6-(4-chloro-2-((trifluoromethyl)thio)phenyl)-9H-purine (5e): purified by silica gel column chromatography (hexane/AcOEt = 80/20 to 50/50); a pale brown solid; IR (KBr) ν 1569, 1500, 1454, 1322, 1120, 800, 728, 700, 647 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ : 9.11 (s, 1H), 8.11 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.90 (brs, 1H), 7.58 (dd, J = 8.4, 2.0 Hz, 1H), 7.43–7.33 (m, 5H), 5.51 (2H, s); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ : 154.4, 152.3, 152.0, 145.1, 137.1, 136.6, 134.9, 133.9, 133.2, 131.8, 129.8, 129.6 (q, $^1J_{\text{CF}}$ = 311.4 Hz), 129.4, 128.9, 128.3 (q, $^3J_{\text{CF}}$ = 2.8 Hz), 128.1, 47.7; $^{19}\text{F NMR}$ (CDCl_3 , 370 MHz) δ : -42.55; HRMS (ESI): m/z calculated for $\text{C}_{19}\text{H}_{13}\text{N}_4\text{ClF}_3\text{S}^+$ [$\text{M}+\text{H}^+$]: 421.0496, found: 425.0507.



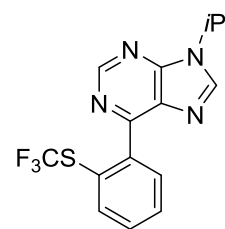
methyl 4-(9-benzyl-9H-purin-6-yl)-3-((trifluoromethyl)thio)benzoate (5f): purified by silica gel column chromatography (hexane/AcOEt = 4/1 to 3/1); a colorless solid; IR (KBr) ν 1717, 1576, 1293, 1271, 1124, 1093, 728 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ : 9.14 (s, 1H), 8.58 (brs, 1H), 8.25 (brd, J = 8.1 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.12 (s, 1H), 7.44–7.34 (m, 5H), 5.52 (s, 2H), 3.99 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ : 165.5, 154.5, 152.1, 152.0, 145.2, 143.1, 135.9, 134.7, 132.0, 131.9, 131.8, 130.6, 129.3 (q, J_{CF} = 308 Hz), 129.2, 128.7, 127.9, 126.6, 52.6, 47.5; $^{19}\text{F NMR}$ (CDCl_3 , 369 MHz) δ -42.66; HRMS (ESI):



m/z calculated for $C_{21}H_{15}O_2N_4F_3NaS^+[M+Na^+]$: 467.0760, found: 467.0762.

9-isopropyl-6-(2-((trifluoromethyl)thio)phenyl)-9H-purine (5g): purified by silica gel

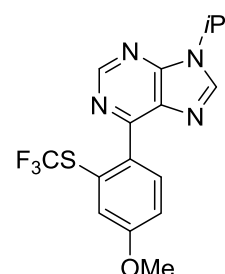
column chromatography (hexane/AcOEt = 70/30 to 50/50); an orange oil; IR (neat) ν 2981, 1580, 1107 cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz) δ : 9.07 (s, 1H), 8.18 (s, 1H), 8.02 (dd, $J = 7.4, 1.7$ Hz, 1H), 7.92 (d, $J = 7.7$ Hz, 1H), 7.61 (ddd, $J = 7.4, 7.4, 1.1$ Hz, 1H), 7.56 (ddd, $J = 7.7, 7.4, 1.7$ Hz, 1H), 5.01 (sept, $J = 6.8$ Hz, 1H), 1.71 (d, $J = 6.8$ Hz,



6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ : 155.6, 151.7, 151.5, 142.9, 139.7, 135.2, 132.5, 131.9, 130.5, 129.9, 129.6 (q, $^1J_{CF} = 308$ Hz), 125.8 (q, $^3J_{CF} = 2.4$ Hz), 47.7, 22.6; ^{19}F NMR ($CDCl_3$, 372 MHz) δ : -42.77; HRMS (ESI): m/z calculated for $C_{15}H_{14}N_4F_3S^+[M+H^+]$: 339.0886, found: 339.0887.

9-isopropyl-6-(4-methoxy-2-((trifluoromethyl)thio)phenyl)-9H-purine (5h): purified

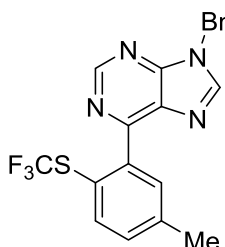
by silica gel column chromatography (hexane/AcOEt = 60/40 to 40/60); an orange oil; IR (neat) ν 1577, 1109 cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz) δ : 9.03 (s, 1H), 8.17 (s, 1H), 8.14 (d, $J = 8.6$ Hz, 1H), 7.43 (d, $J = 2.0$ Hz, 1H), 7.11 (dd, $J = 8.6, 2.0$ Hz, 1H), 5.00 (sept, $J = 7.0$ Hz, 1H), 3.91 (s, 3H), 1.70 (d, $J = 7.0$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ : 160.8, 155.1, 151.6, 151.3, 142.5, 133.4, 132.1, 131.1, 129.7 (q, $^1J_{CF} = 308$ Hz),



127.9 (q, $^3J_{CF} = 2.4$ Hz), 119.5, 115.0, 55.6, 47.6, 22.5; ^{19}F NMR ($CDCl_3$, 470 MHz) δ : -42.58; HRMS (ESI): m/z calculated for $C_{16}H_{16}ON_4F_3S^+[M+H^+]$: 369.0991, found: 369.0990.

9-benzyl-6-(5-methyl-2-((trifluoromethyl)thio)phenyl)-9H-purine (5i): purified by

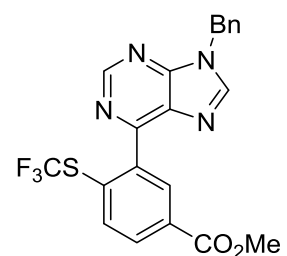
silica gel column chromatography (hexane/AcOEt 4/1 to 3/1); an orange solid; IR (KBr) ν 1585, 1496, 1327, 1099, 815, 727, 651 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) δ : 9.11 (s, 1H), 8.08 (s, 1H), 7.79 (d, $J = 8.1$ Hz, 1H), 7.75 (brd, $J = 1.3$ Hz, 1H), 7.43-7.34 (m, 6H), 5.51 (s, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ : 156.1, 152.1, 151.8, 144.8, 140.7, 140.0, 136.1, 134.9, 132.2, 132.0, 131.3, 129.5 (q, $J = 307$ Hz), 129.1,



128.6, 127.9, 121.7-121.6 (m), 47.4, 21.2; ^{19}F NMR ($CDCl_3$, 372 MHz) δ : -43.28; HRMS (ESI): m/z calculated for $C_{20}H_{15}N_4F_3NaS^+[M+Na^+]$: 423.0862, found: 423.0865.

methyl 3-(9-benzyl-9H-purin-6-yl)-4-((trifluoromethyl)thio)benzoate (5j):

purified by silica gel column chromatography (CH_2Cl_2 /AcOEt = 95/5 to 90/10); a pale brown solid; IR (K Br) ν 1711, 1572, 1277, 1199, 1148, 1115, 1046, 759, 726, 696 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) δ : 9.12 (s, 1H), 8.84 (d, $J = 1.5$ Hz, 1H), 8.18 (dd, $J = 8.0, 2.0$ Hz, 1H), 8.14 (s, 1H), 7.97 (d, $J = 8.5$ Hz, 1H), 7.42-7.36 (m, 5H), 5.52 (s, 2H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 165.9, 154.4, 152.4,



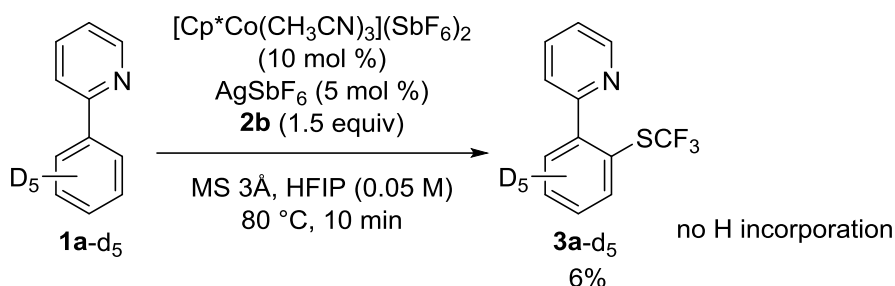
151.9, 145.3, 138.2, 135.0, 133.3, 133.2, 132.5 (q, $^3J_{CF} = 2.4$ Hz), 131.8, 131.2, 130.8, 129.40 (q, $^1J_{CF} = 308.9$

Hz), 129.38, 128.9, 128.1, 52.6, 47.7; ¹⁹F NMR (CDCl₃, 370 MHz) δ : -42.12; HRMS (ESI): *m/z* calculated for C₂₁H₁₅O₂N₄F₃NaS [M+Na⁺]: 467.0760, found: 467.0767.

Gram-scale reaction of **4c**

To a 50 mL autoclave vessel equipped with a stirring bar were added [Cp*Co(CH₃CN)₃](SbF₆)₂ (237 mg, 0.30 mmol), Gd(OTf)₃ (544 mg, 0.90 mmol), **4c** (1.03 g, 3.0 mmol), activated molecular sieves 3A (600 mg), **2b** (1.19 g, 3.0 mmol), and HFIP (30 mL) in a glovebox. The vessel was closed and heated at 85 °C (oil bath) for 12 h with stirring. The mixture was cooled, and **2b** (1.19 g, 3.0 mmol) was added in a glovebox. The mixture was again heated at 85 °C (oil bath) for 12 h with stirring. After the mixture was cooled to room temperature, most of the solvent was removed by evaporation. To the residue was added saturated aqueous EDTA·2Na, and the mixture was extracted with CH₂Cl₂ three times. The combined organic layers were dried over Na₂SO₄. After filtration and evaporation, the residue was filtered through a short pad of silica gel (hexane/AcOEt = 1/1). The obtained crude mixture was purified by silica gel column chromatography (CH₂Cl₂/AcOEt = 99/1 to 95/5) to afford **5c** (0.817 g, 62% yield).

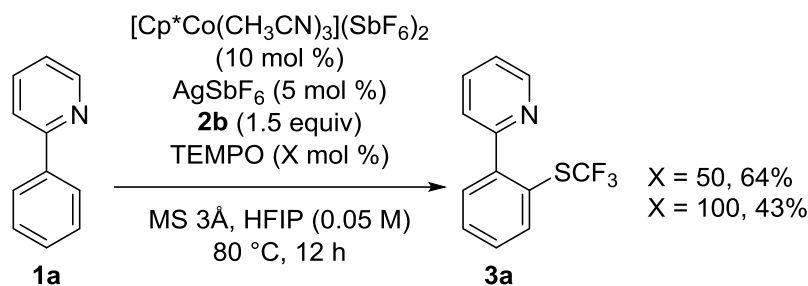
Reaction using deuterated substrate **1a-d₅**



To a screw-capped vial equipped with a stirring bar were successively added [Cp*Co(CH₃CN)₃](SbF₆)₂ (15.8 mg, 0.020 mmol), AgSbF₆ (3.4 mg, 0.010 mmol), activated molecular sieves 3A (40 mg), **2b** (119 mg, 0.30 mmol), HFIP (4 mL), and **1a-d₅**^[8] (29 μL, 0.20 mmol). The vial was capped and heated at 80 °C for 10 min with stirring. The mixture was immediately cooled, and saturated aqueous EDTA·2Na was added. The mixture was then extracted with CH₂Cl₂ three times, and the combined organic layers were dried over Na₂SO₄. After filtration and evaporation, the residue was dissolved in AcOEt and filtered through a short pad of silica gel. The obtained crude mixture was purified by silica gel column chromatography (hexane/AcOEt = 10/1 to 8/1) to afford **3a** (2.9 mg, 6% yield), and **1a** was partially recovered. The ¹H NMR analysis revealed only negligible incorporation of ¹H from HFIP to the phenyl moiety of **3a** and **1a**. This result indicated that the C-H activation step is irreversible under the optimal reaction conditions and trifluoromethylthiolation with **2b** is faster than protonation of the metallacycle intermediate.

[8] Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Lett.* **2008**, *10*, 3409.

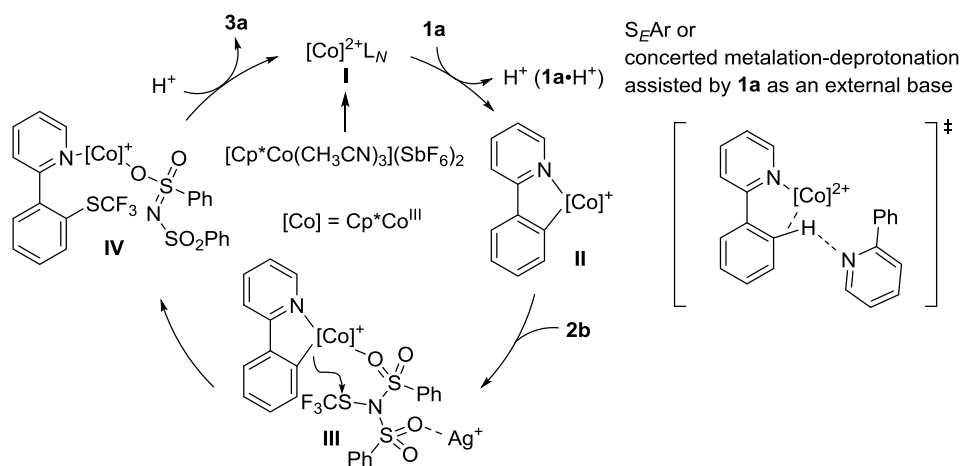
Reactions in the presence of TEMPO



To a screw-capped vial equipped with a stirring bar were successively added $[\text{Cp}^*\text{Co}(\text{CH}_3\text{CN})_3](\text{SbF}_6)_2$ (7.9 mg, 0.010 mmol), AgSbF_6 (1.7 mg, 0.005 mmol), activated molecular sieves 3A (20 mg), **2b** (60 mg, 0.15 mmol), TEMPO (50 or 100 mol %), HFIP (2 mL), and **1a** (14 μL , 0.10 mmol). The vial was capped and heated at 80 °C for 12 h with stirring. The mixture was cooled to room temperature, and saturated aqueous $\text{EDTA} \cdot 2\text{Na}$ was added. The mixture was then extracted with CH_2Cl_2 three times, and the combined organic layers were dried over Na_2SO_4 . After filtration and evaporation, the yield of **3a** was determined by ^1H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. Because the reaction proceeded in moderate yield even in the presence of TEMPO, a radical pathway including addition reaction of trifluoromethylthio radical to the phenyl moiety of the substrate is not dominant under the optimal conditions.

Proposed catalytic cycle for trifluoromethylthiolation of **1a**

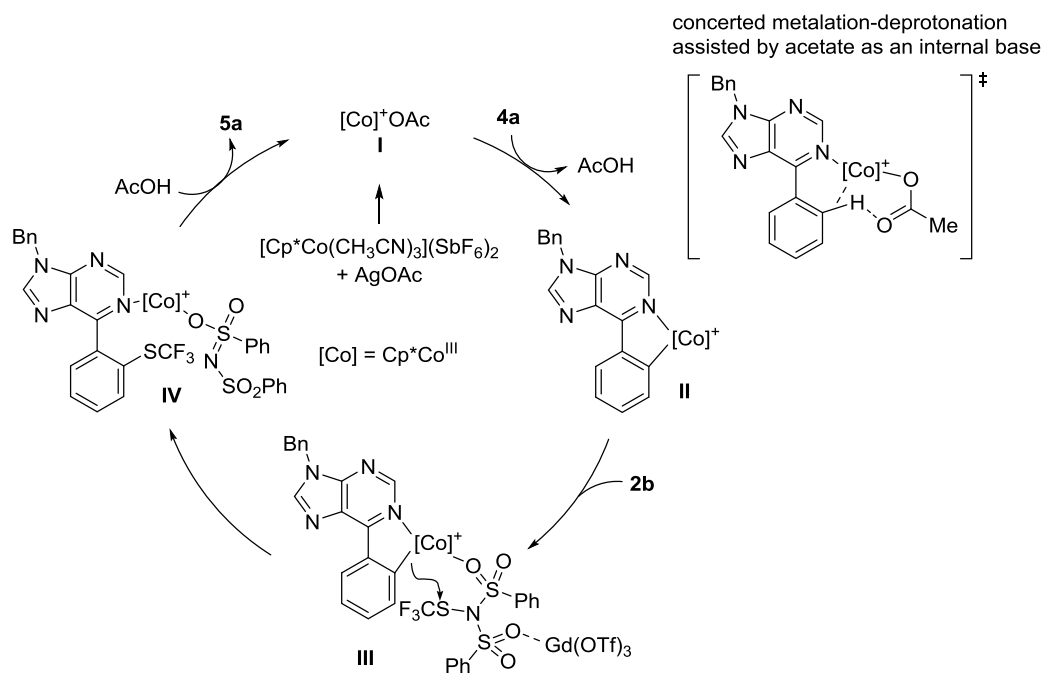
The C-H metalation step is assumed to proceed via aromatic electrophilic substitution ($\text{S}_{\text{E}}\text{Ar}$) or concerted metalation-deprotonation assisted by another **1a** as an intermolecular base.^[9]



[9] An intermolecular base-assisted concerted mechanism was proposed in Ru^{II} catalysis: Flegeau, E. F.; Bruneau, C.; Dixnerf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161.

Proposed catalytic cycle for trifluoromethylthiolation of **4a**

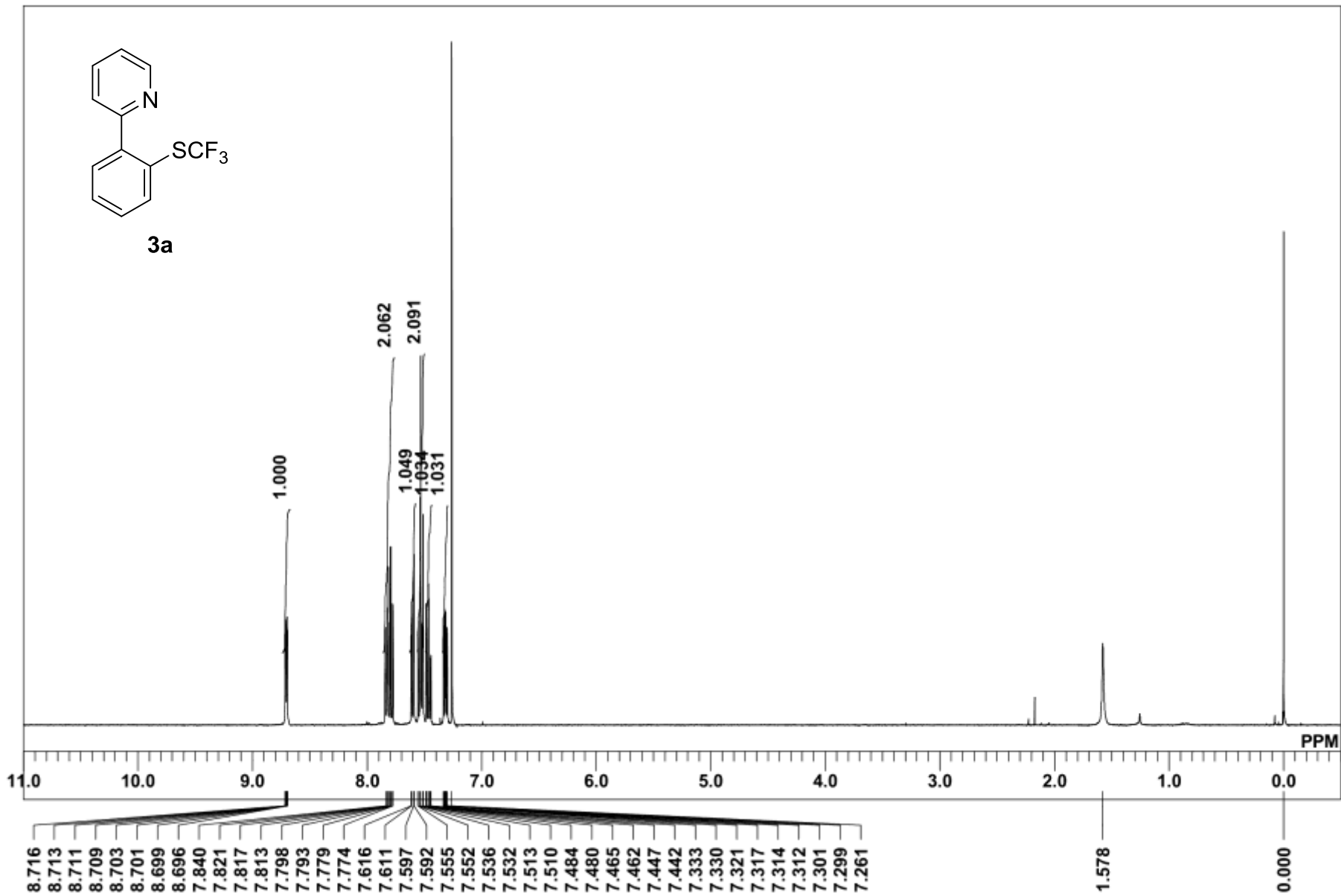
The C-H metalation step is assumed to proceed via concerted metalation-deprotonation assisted by acetate as an intramolecular base.^[10]

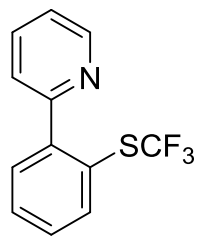


[10] (a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118; (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

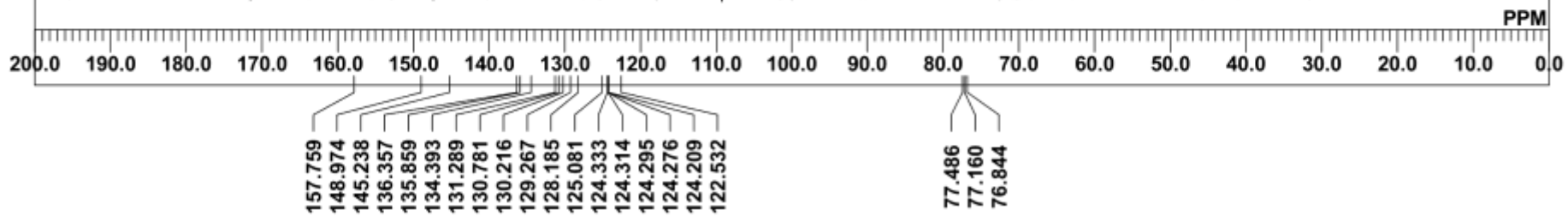


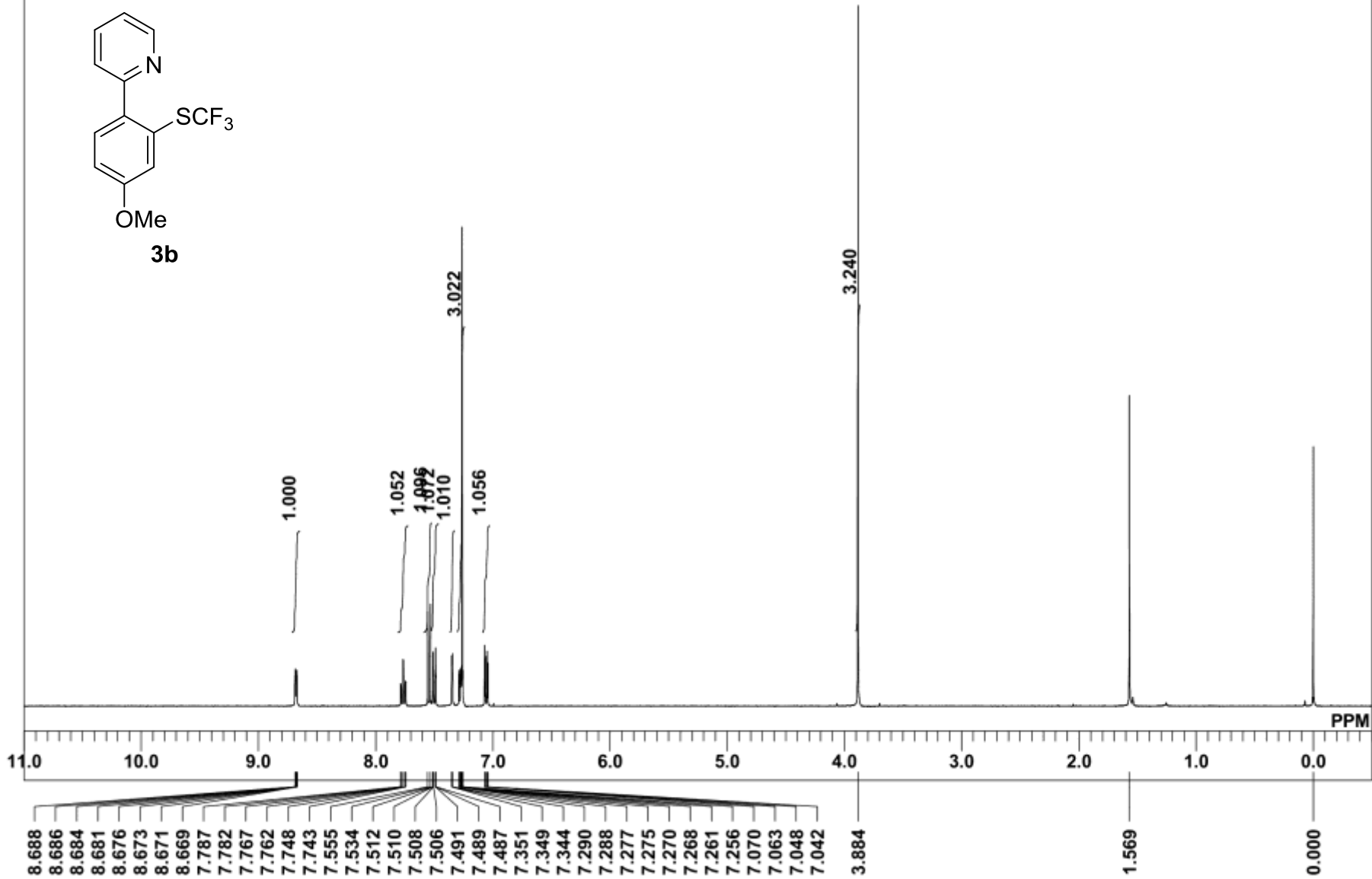
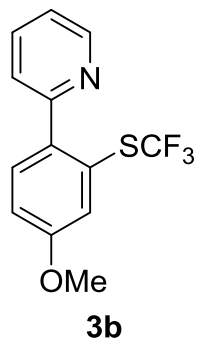
3a

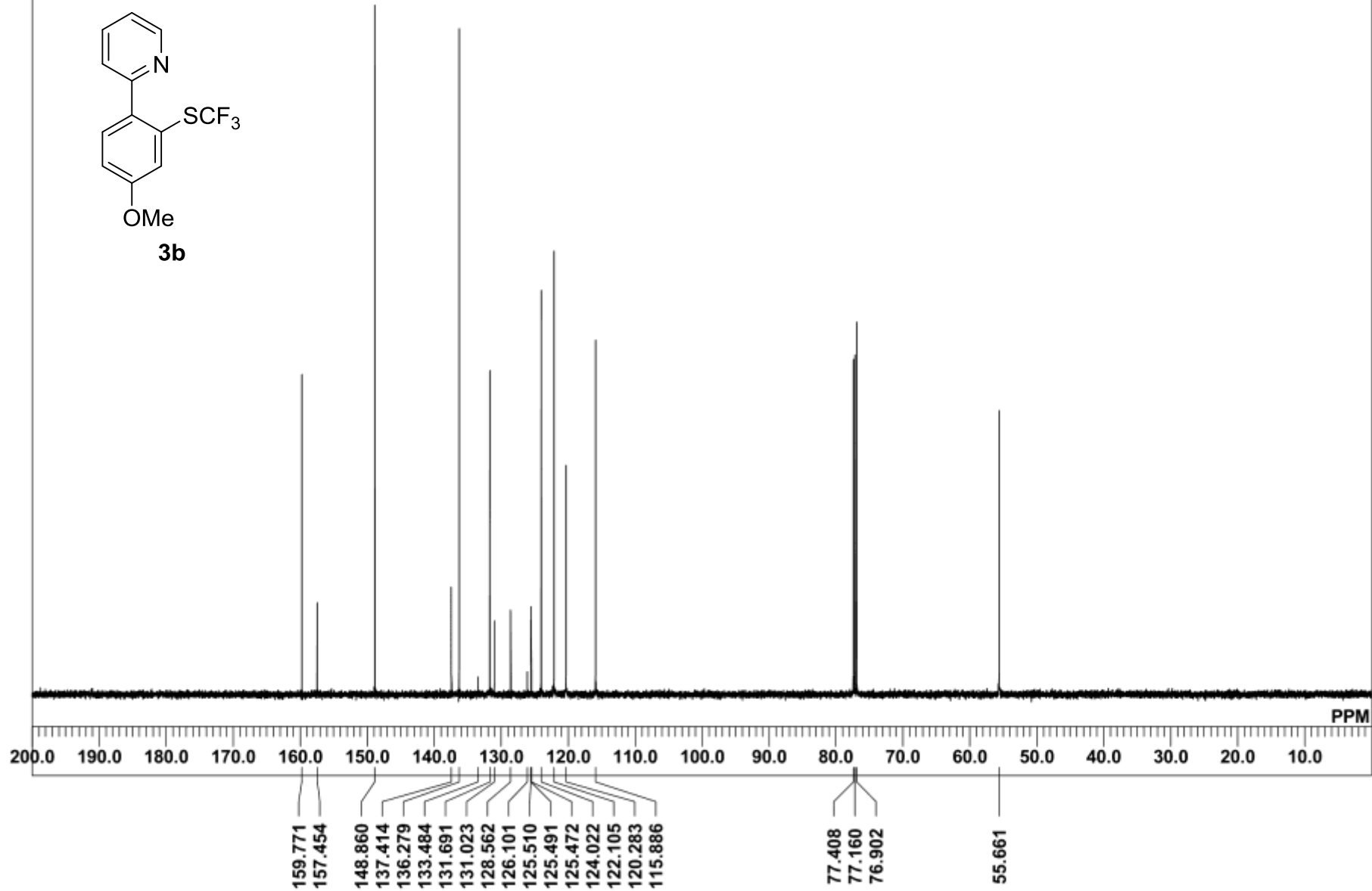
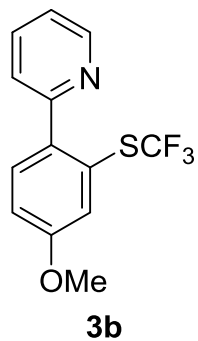


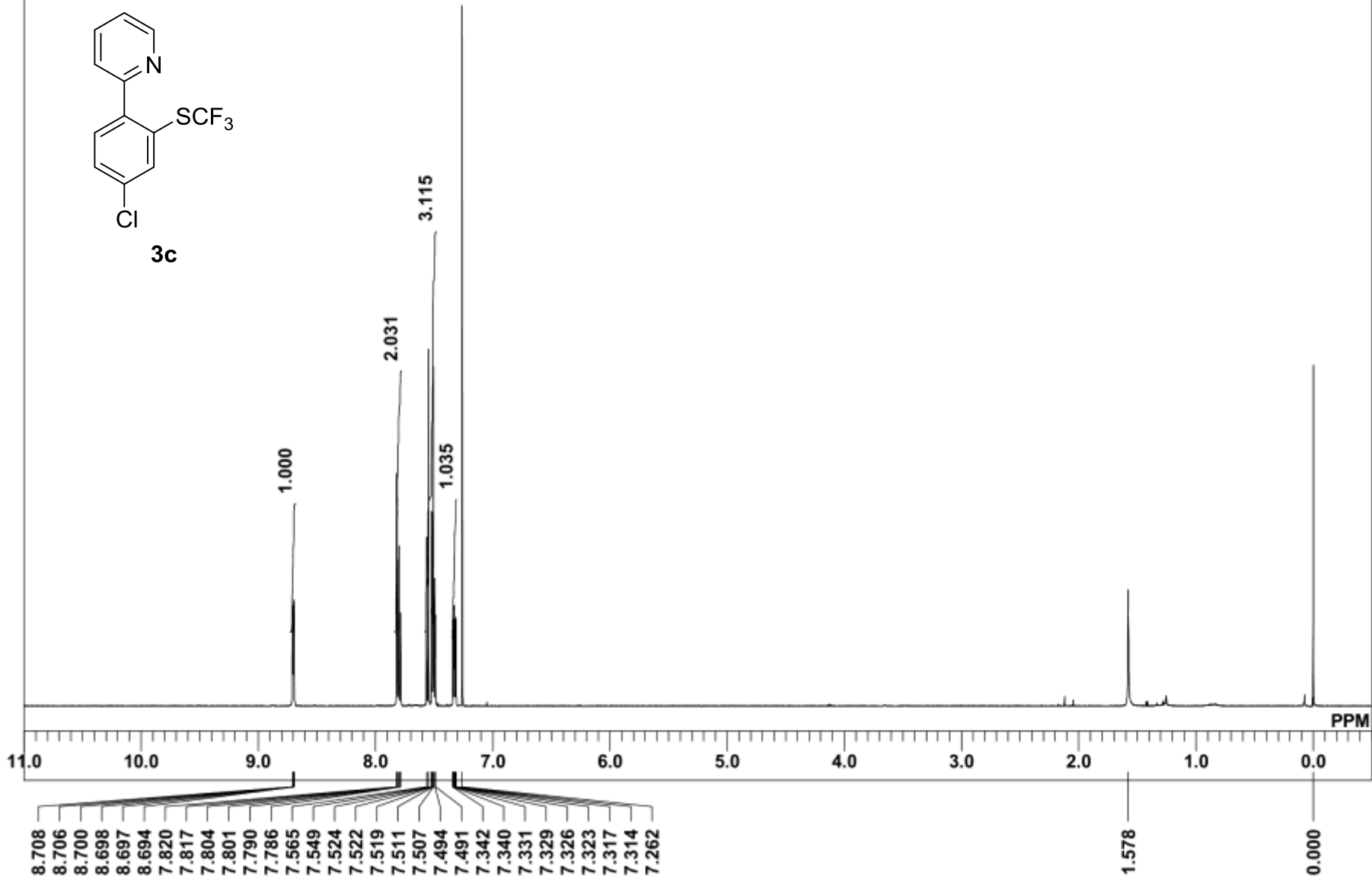
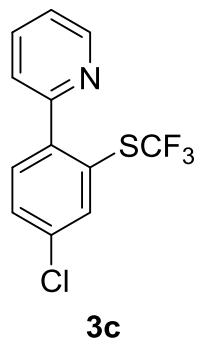


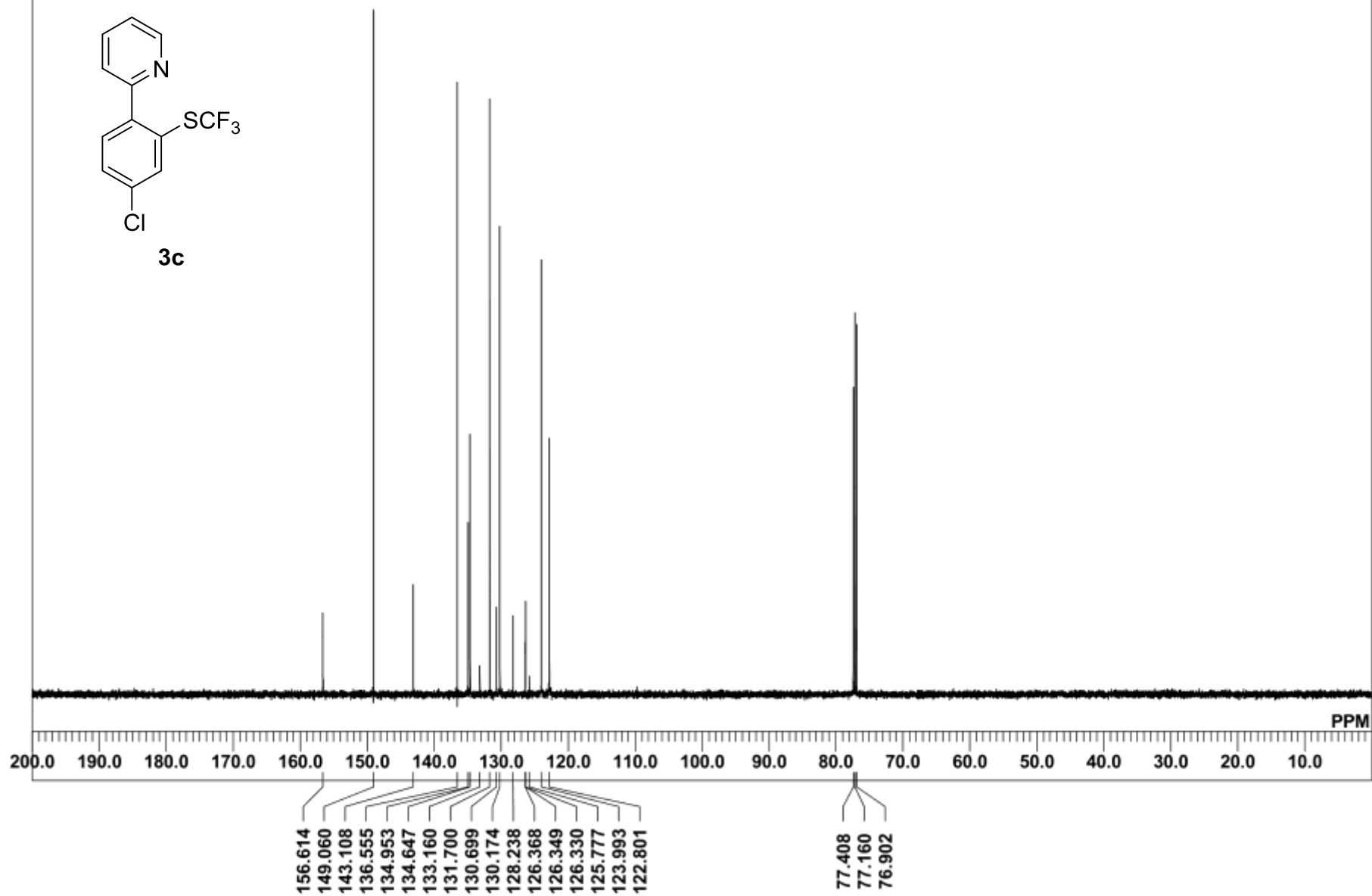
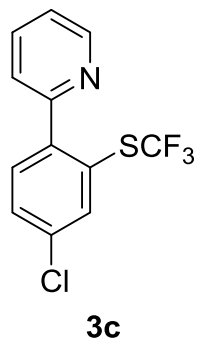
3a

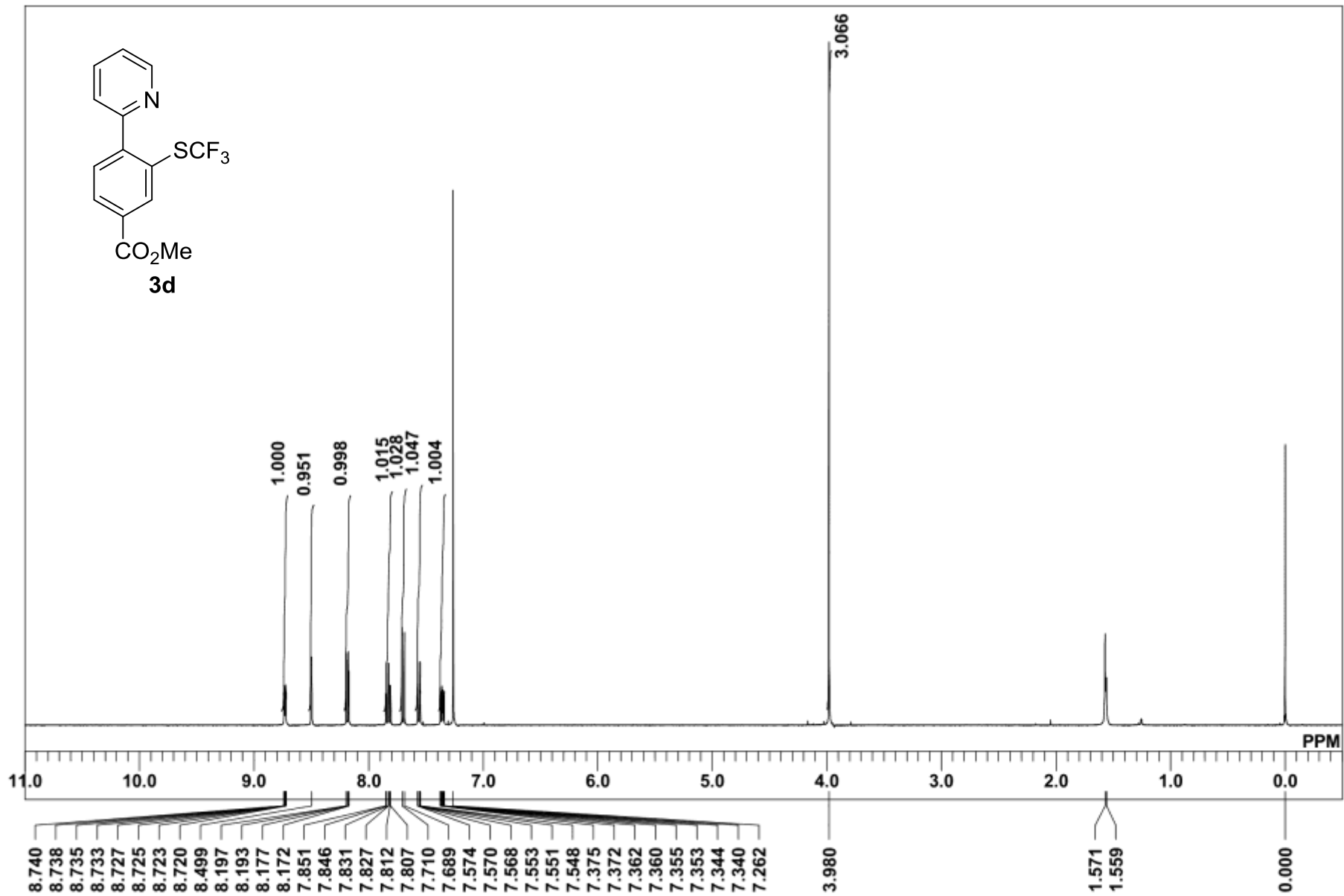
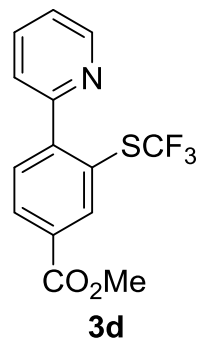


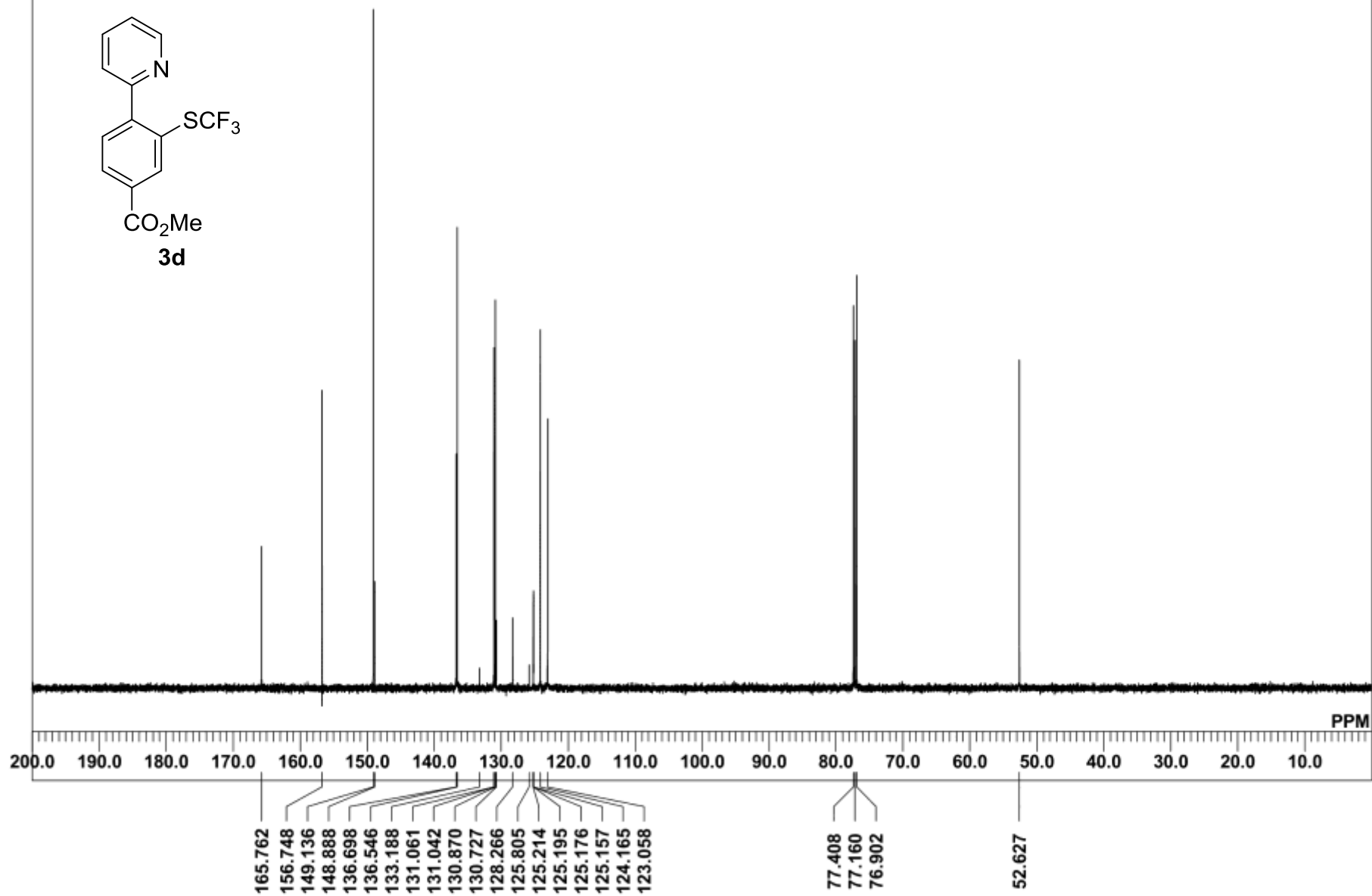
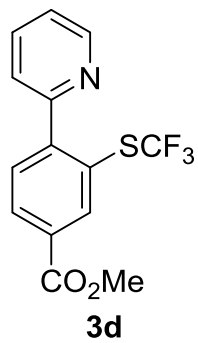


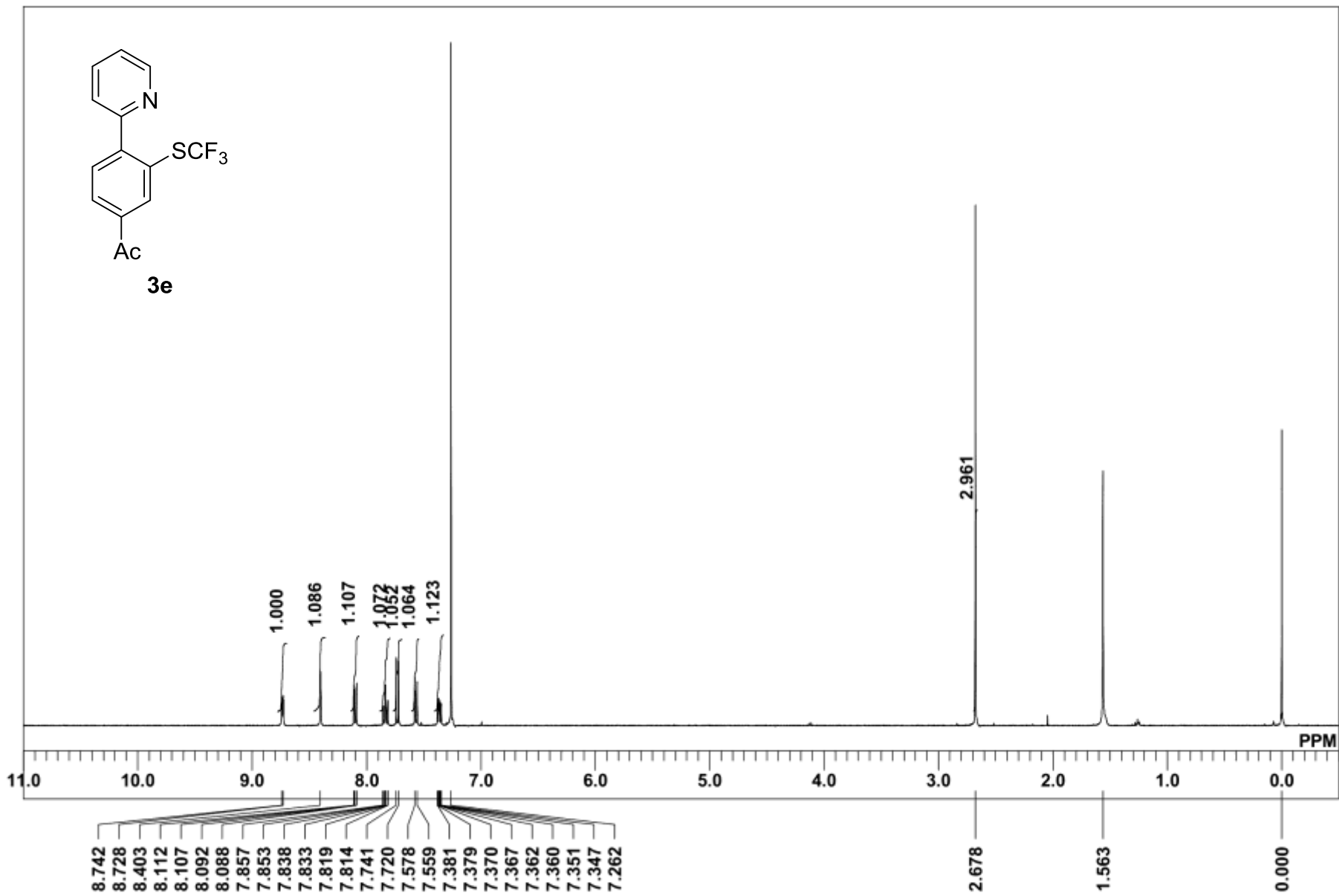
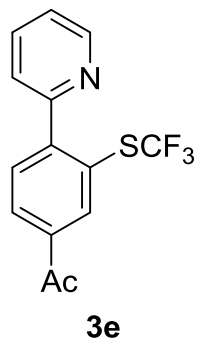


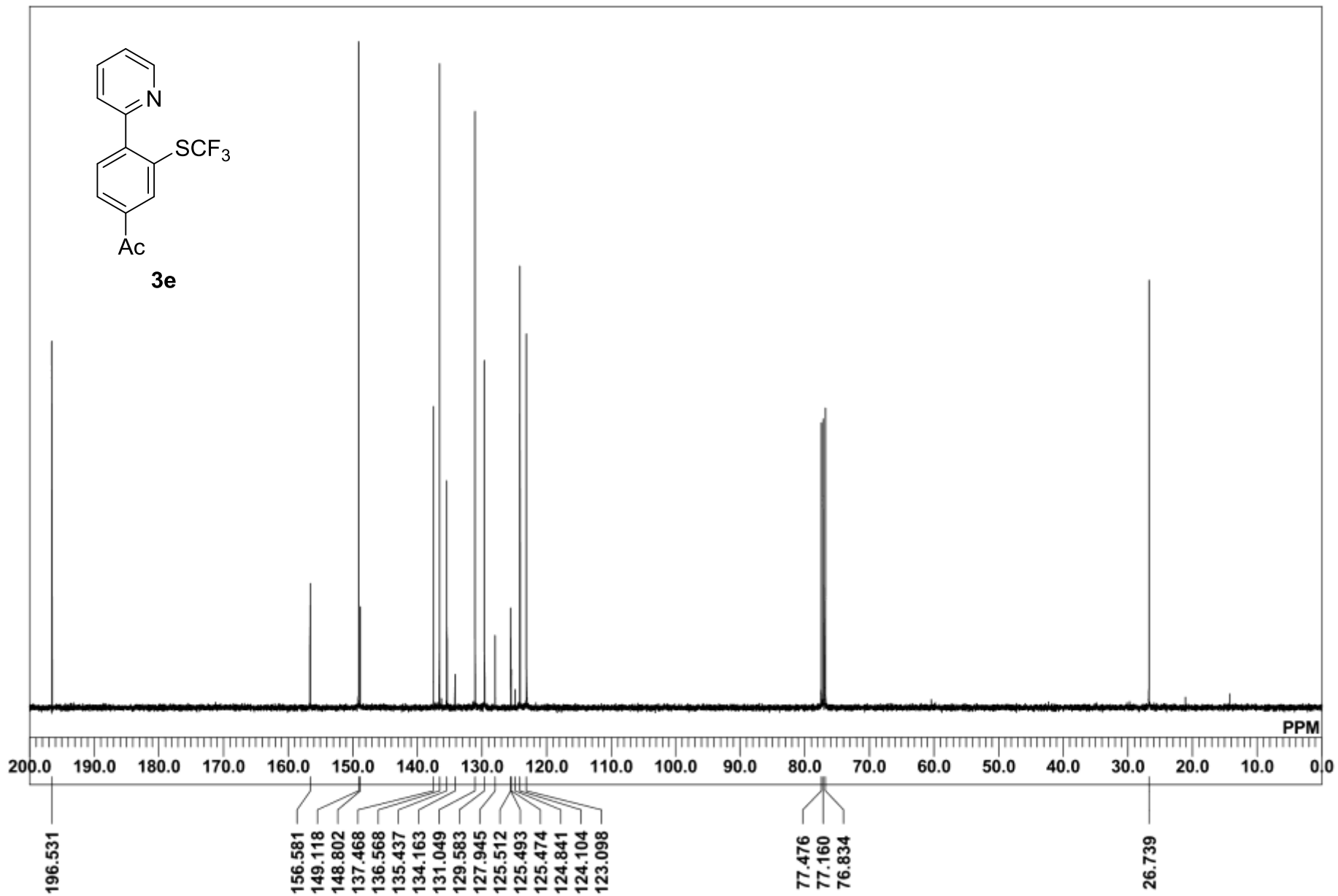
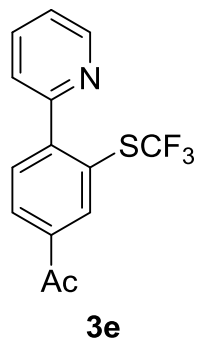


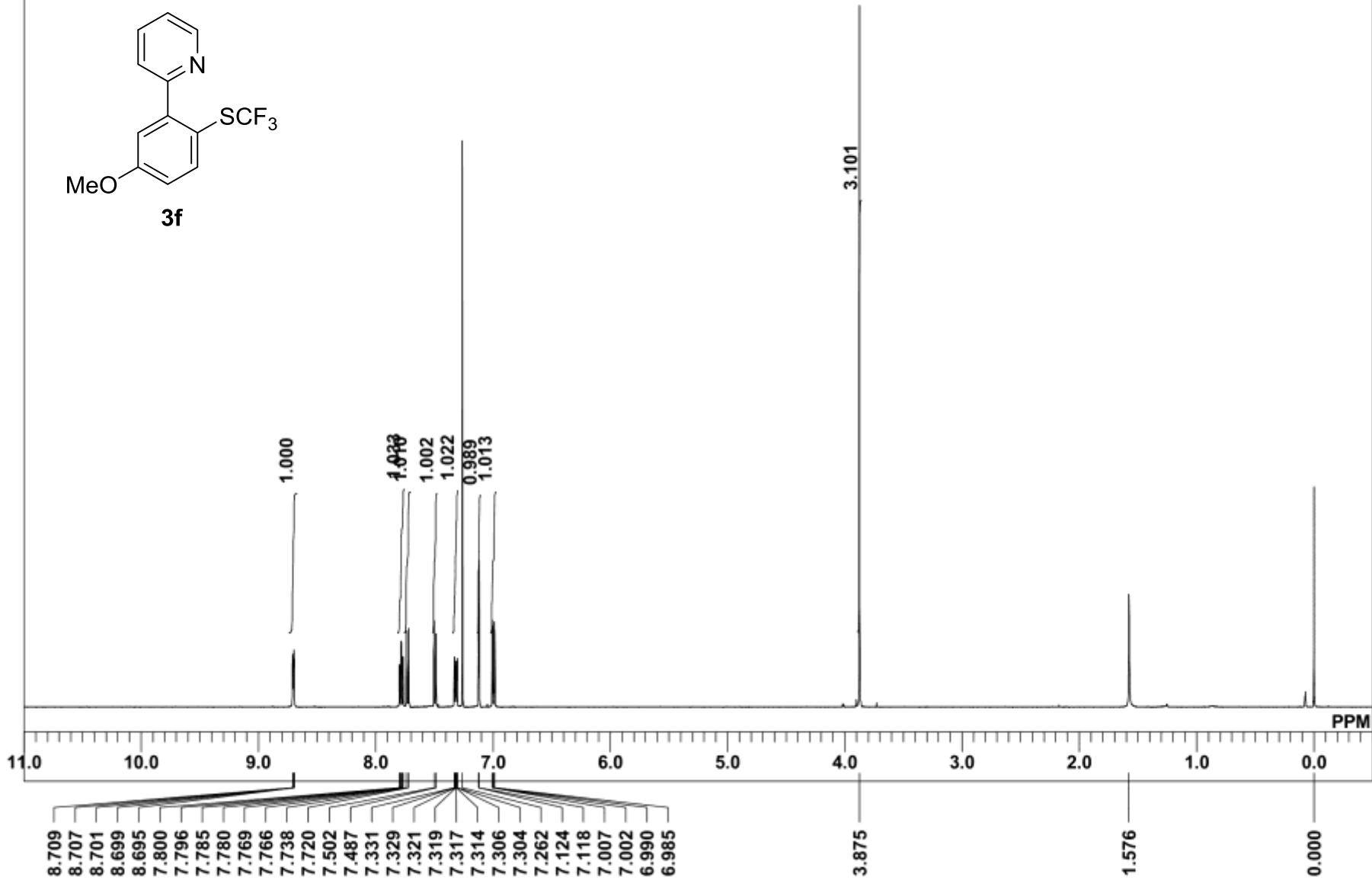
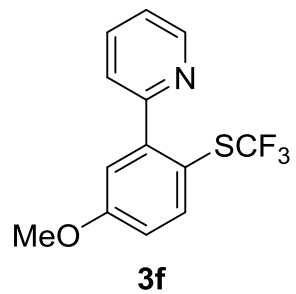


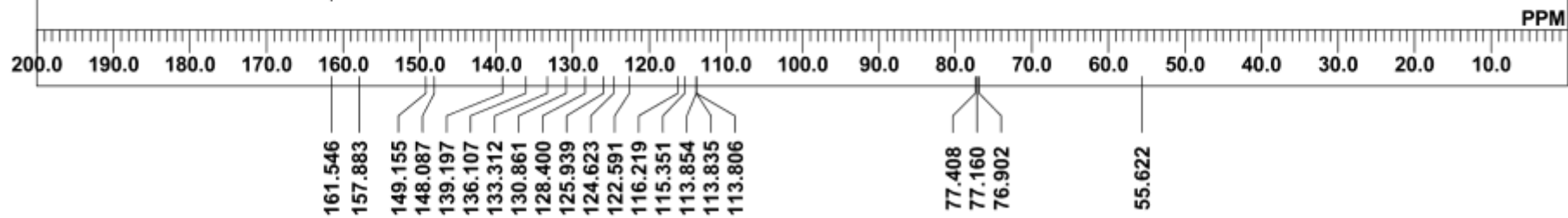
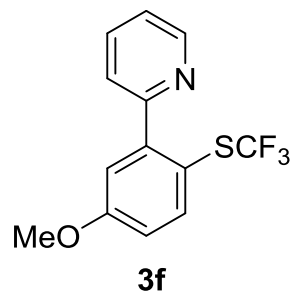


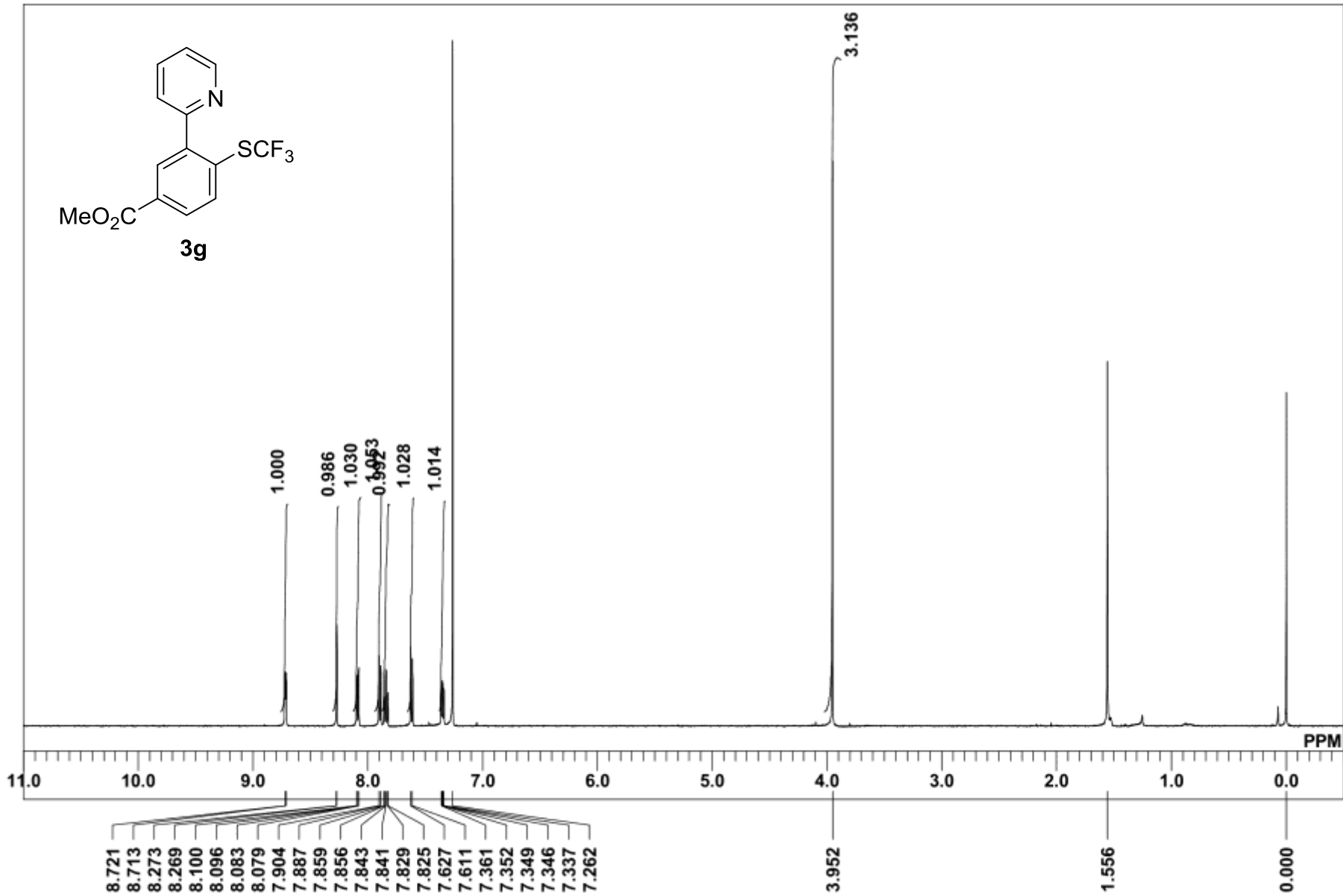
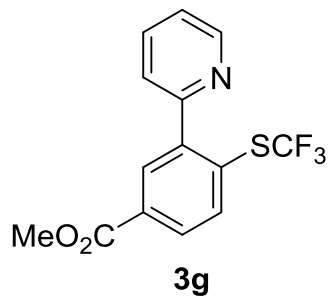


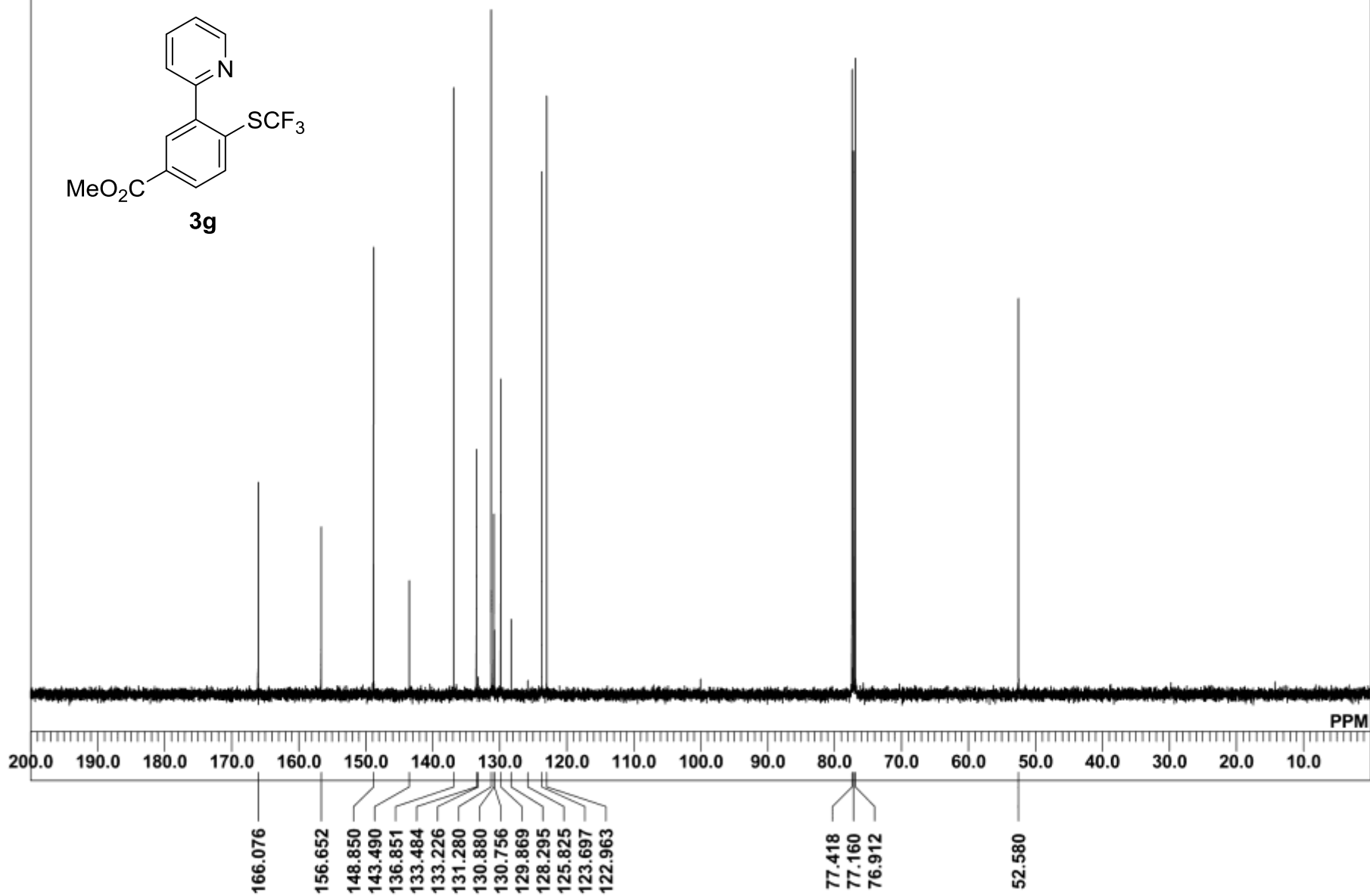
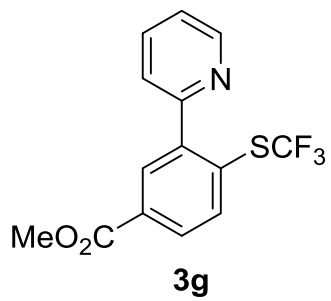


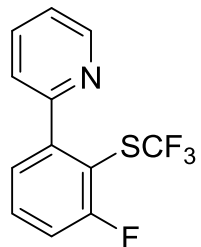




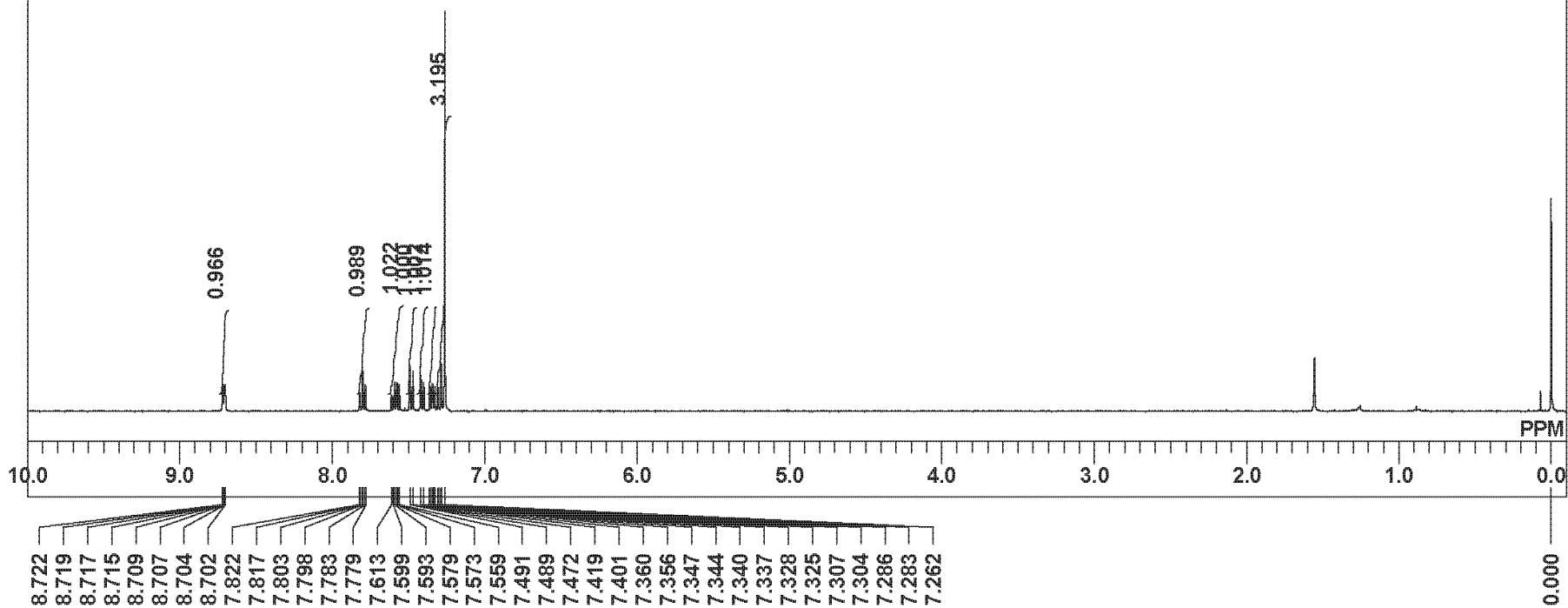


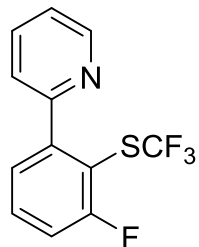




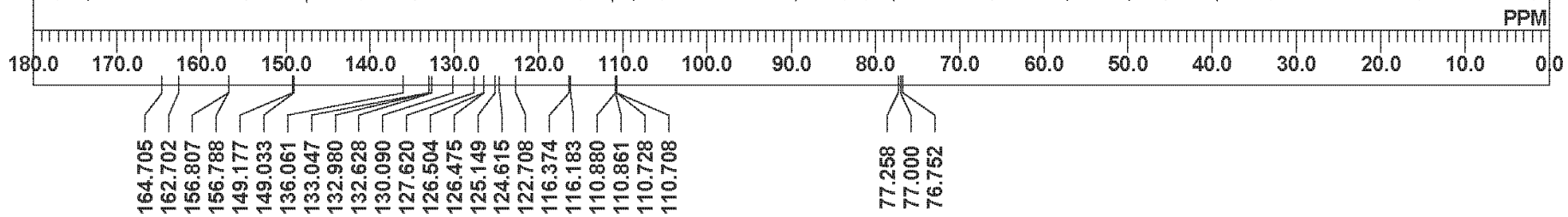


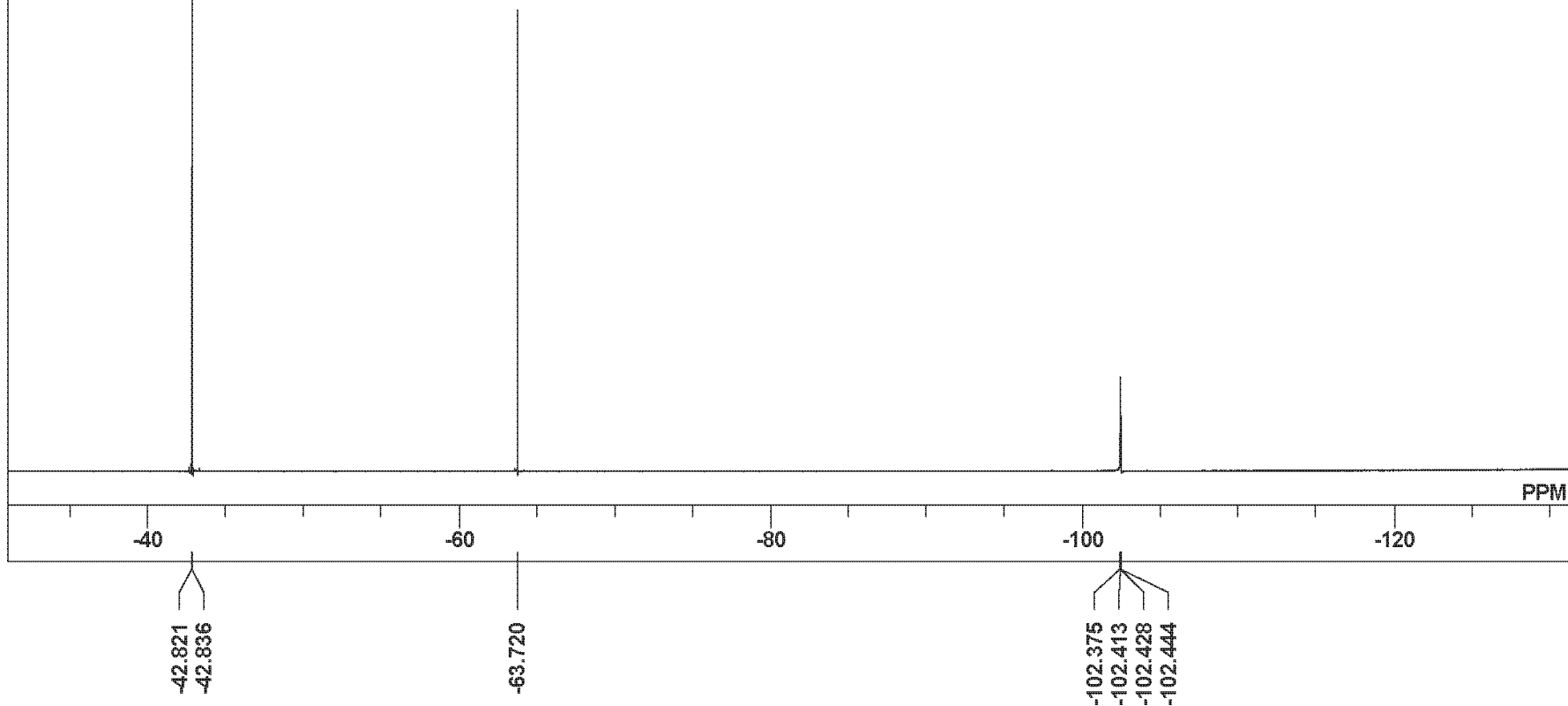
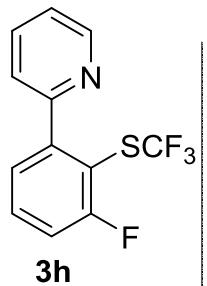
3h

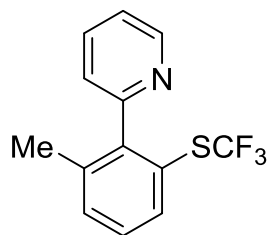




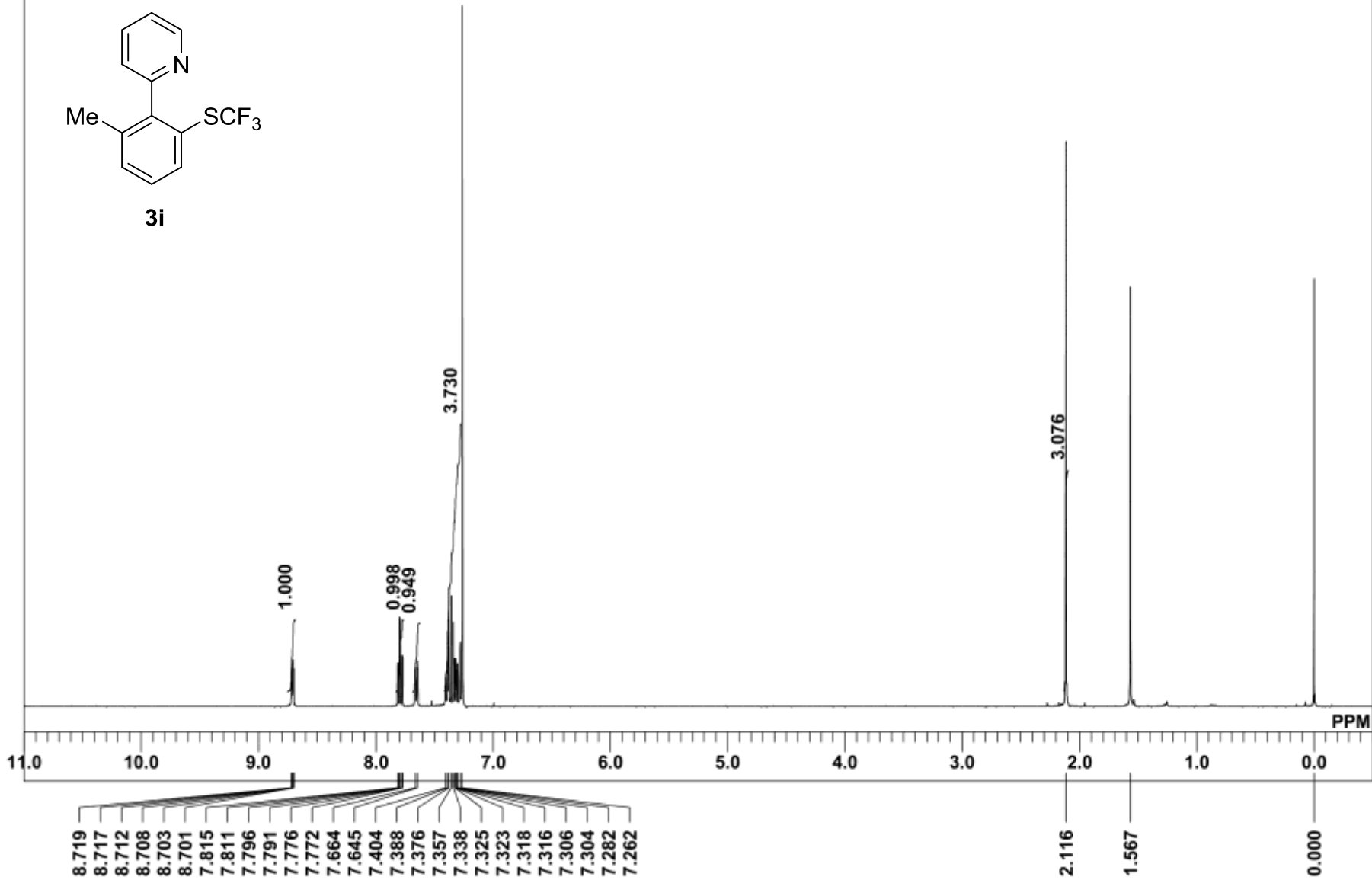
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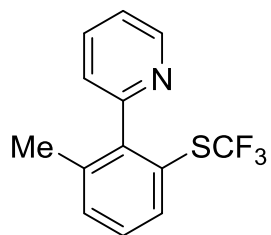




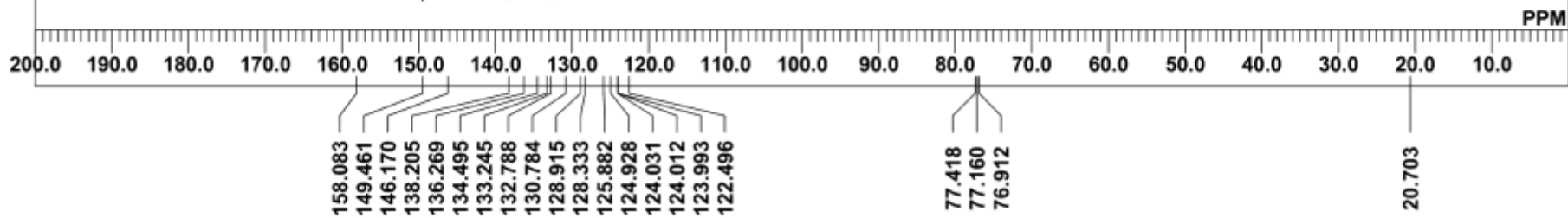


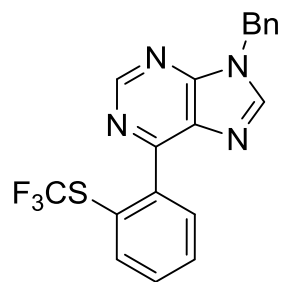
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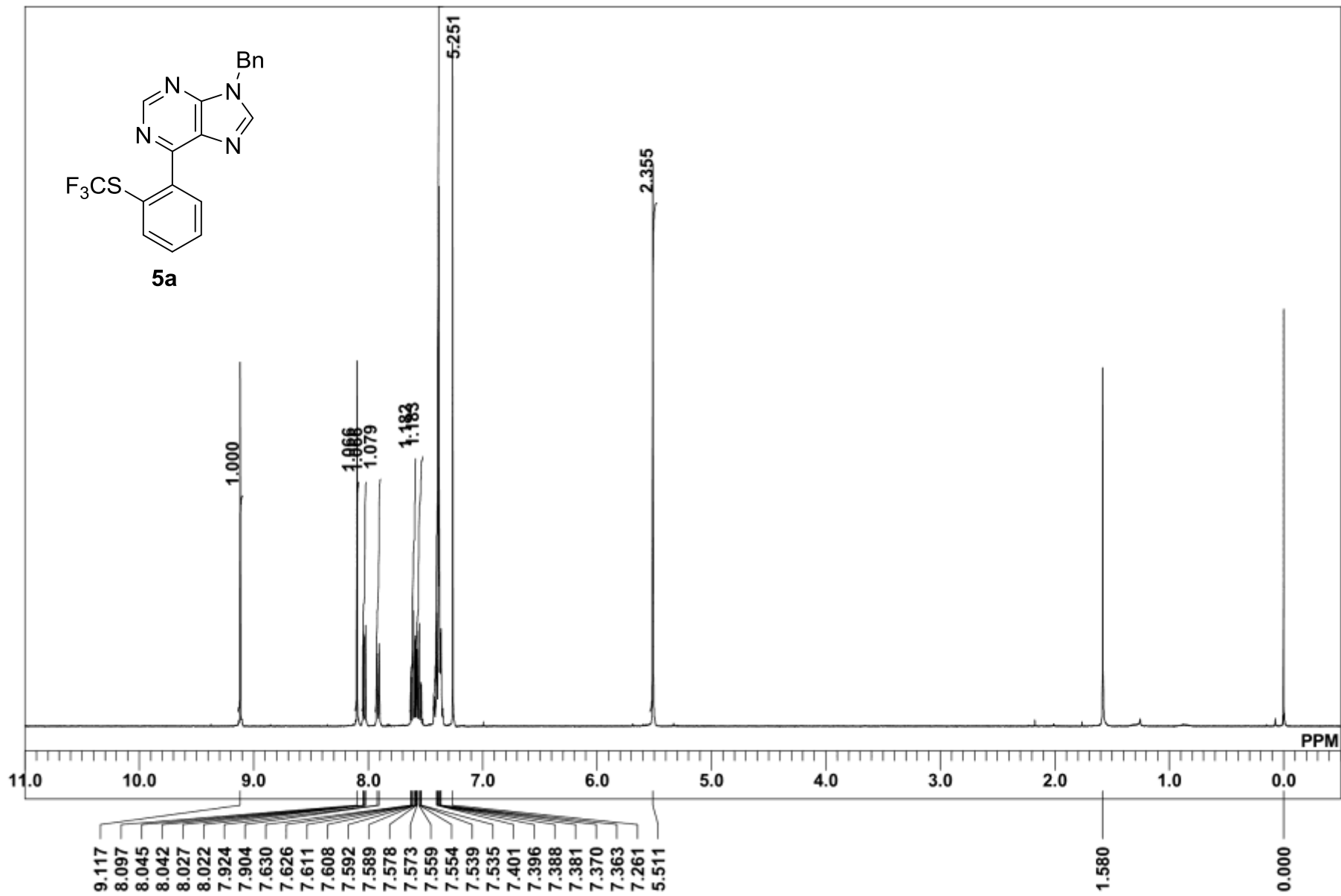


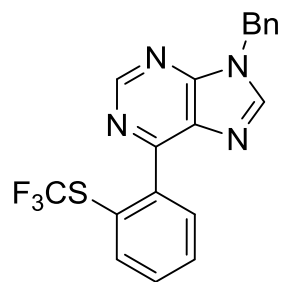
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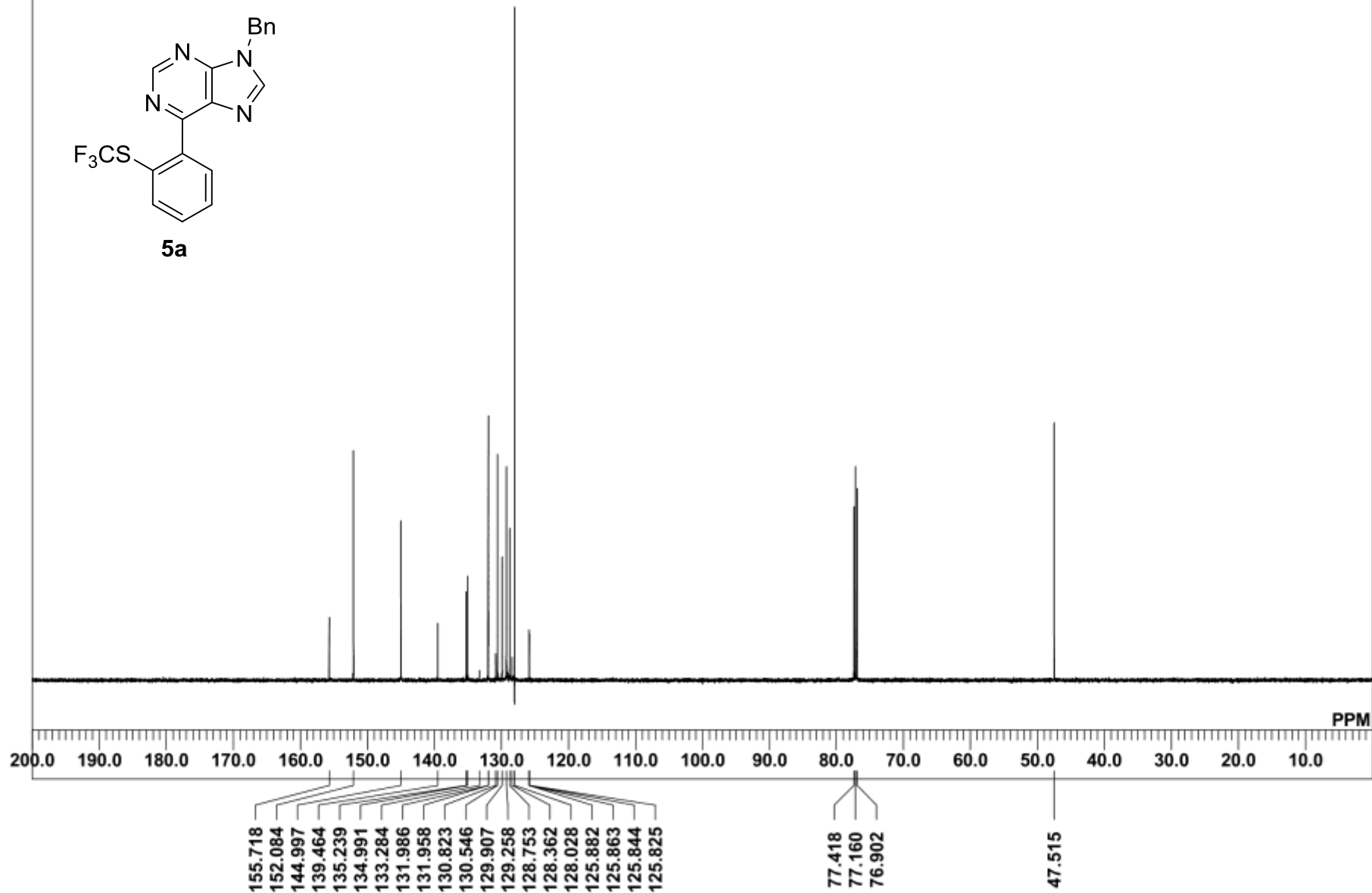


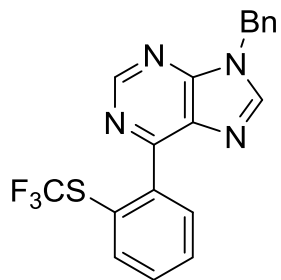
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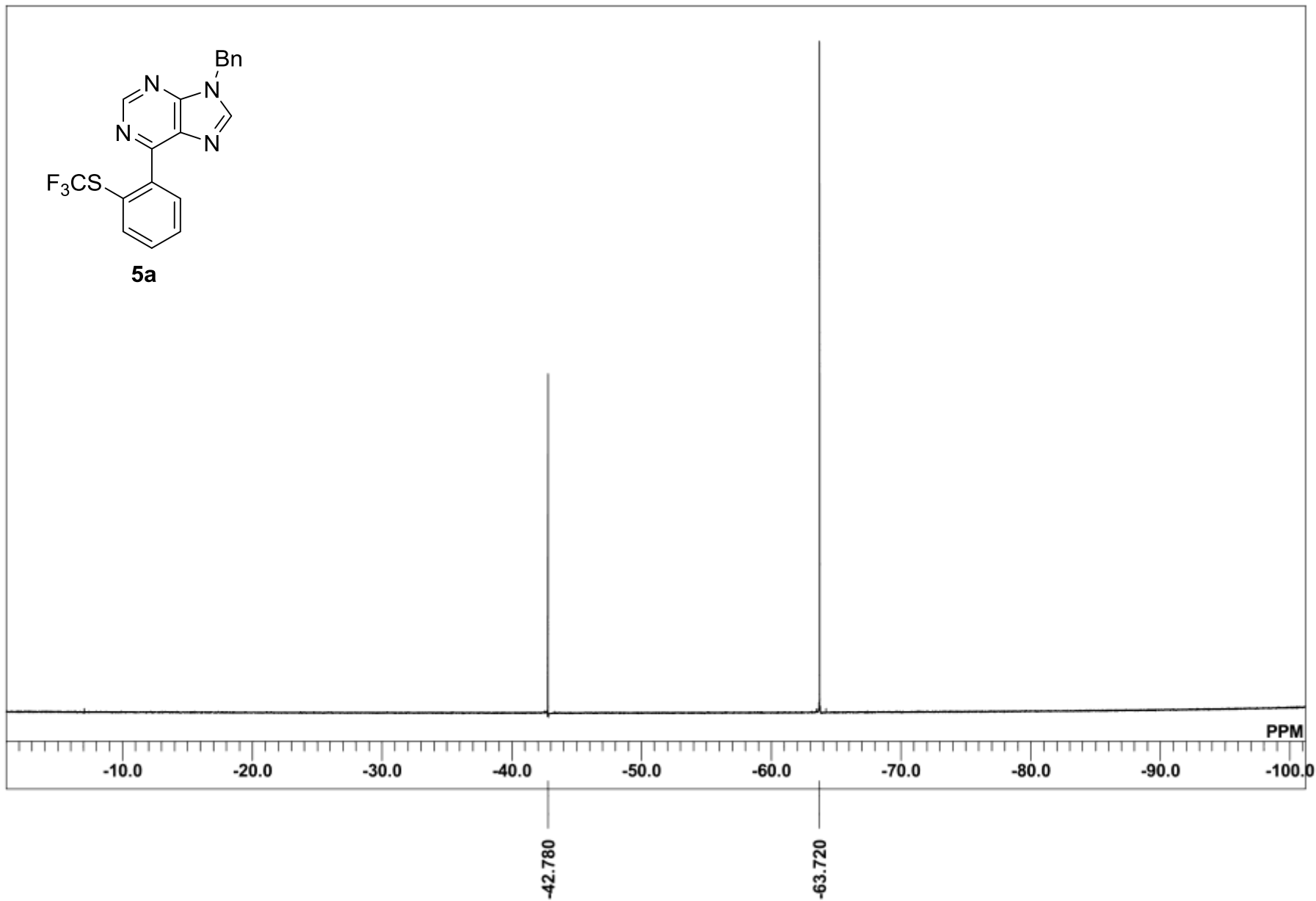


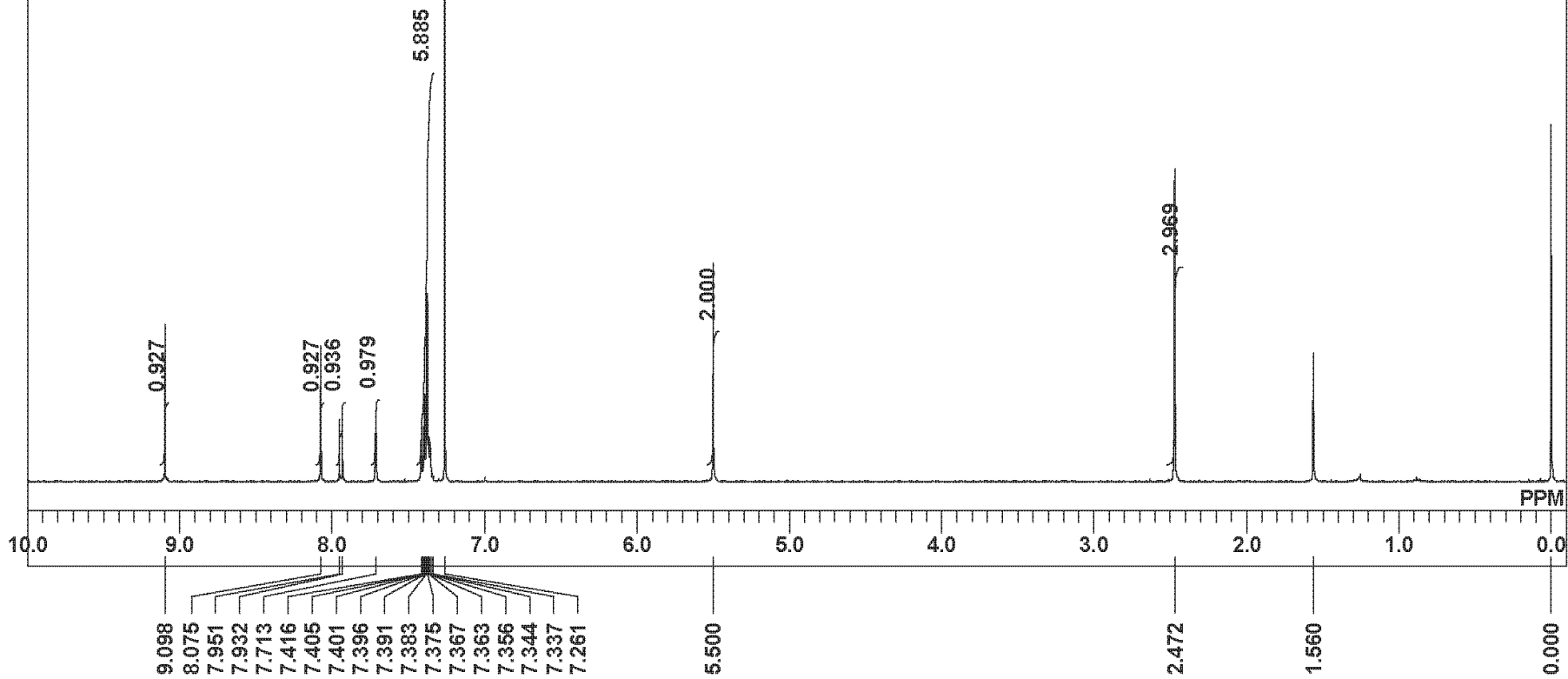
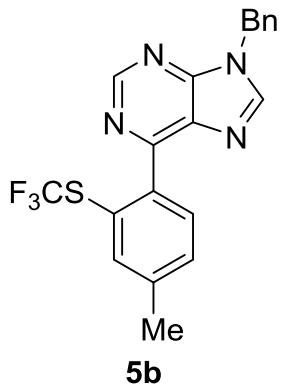
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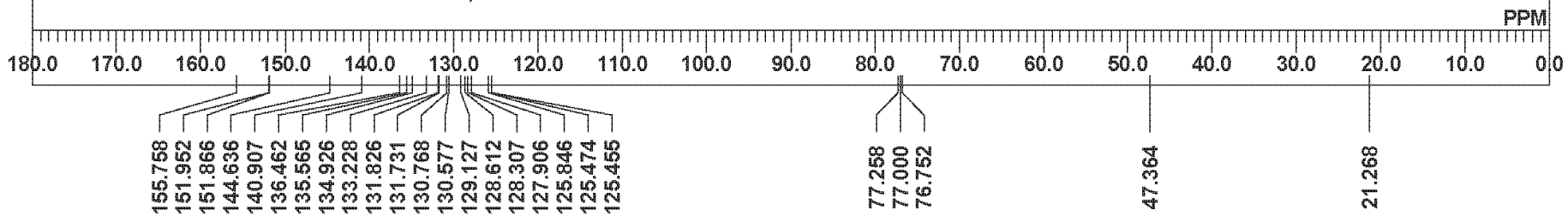
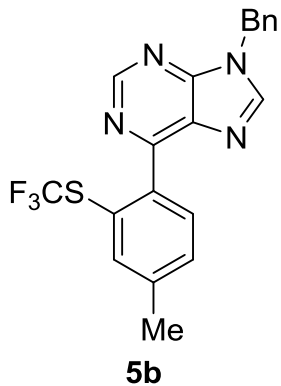


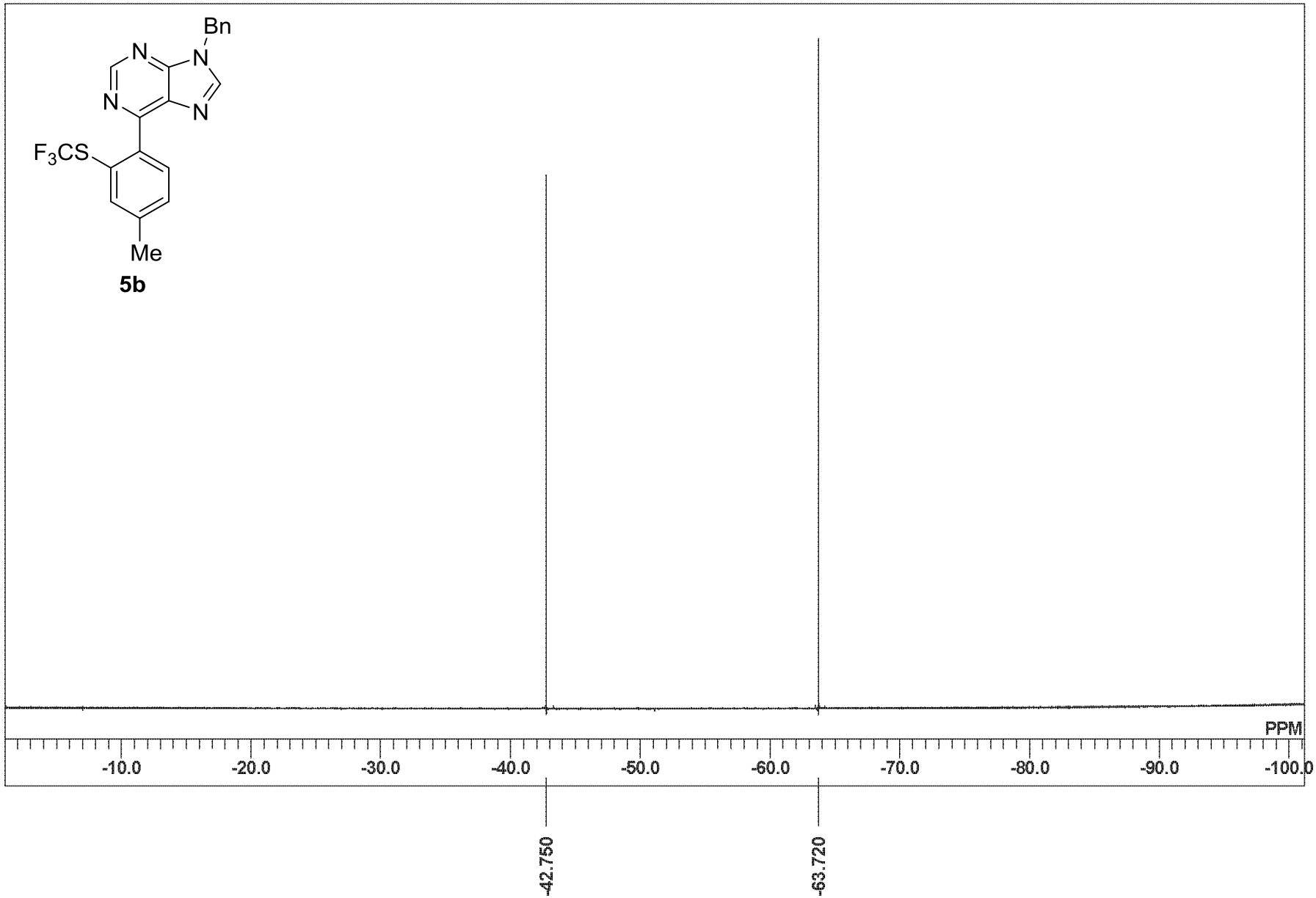
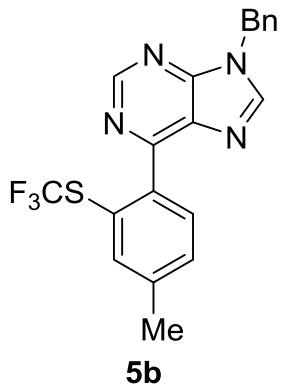


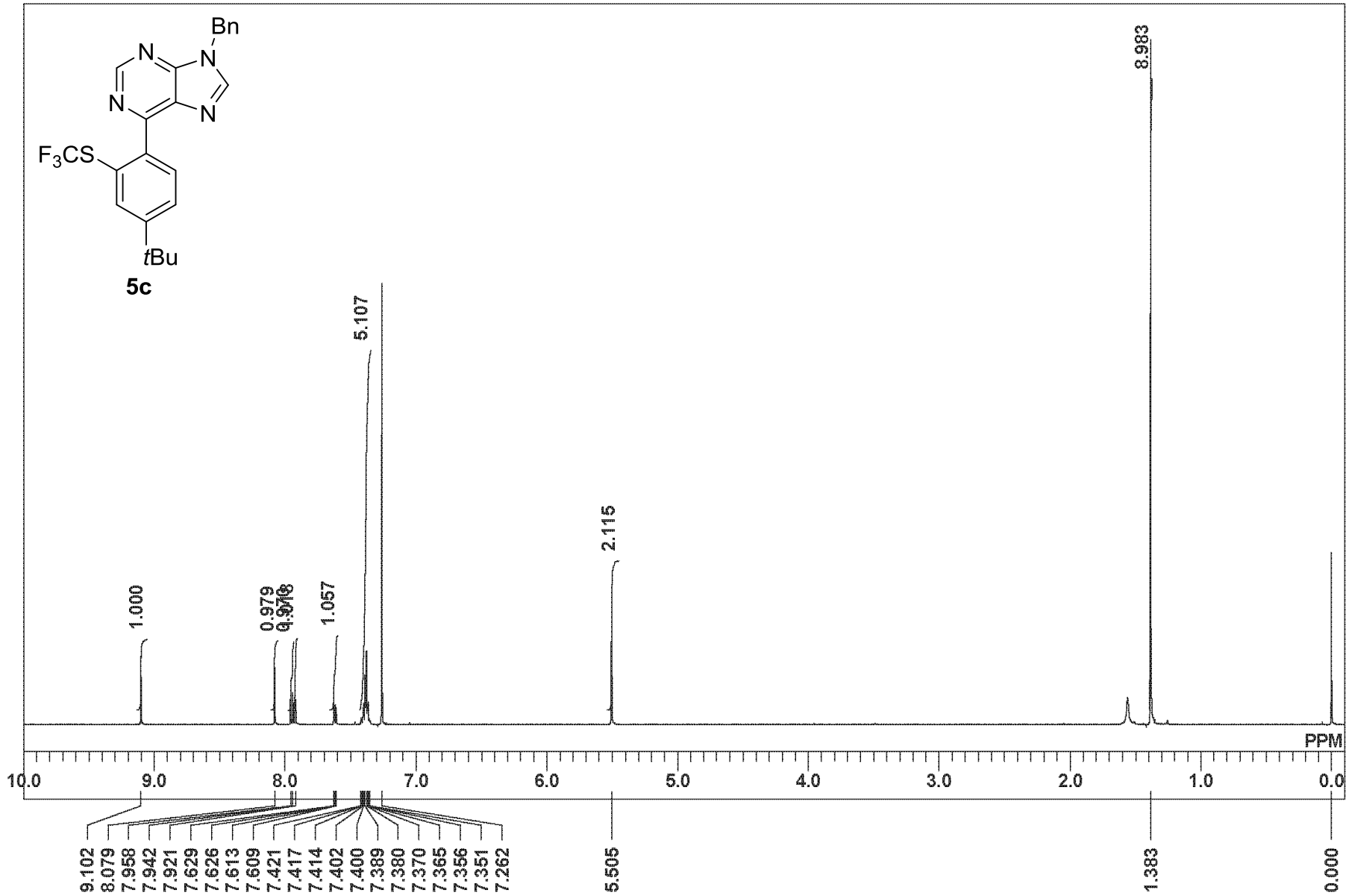
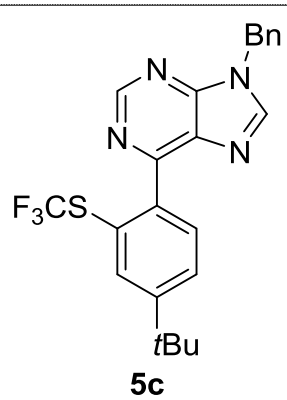
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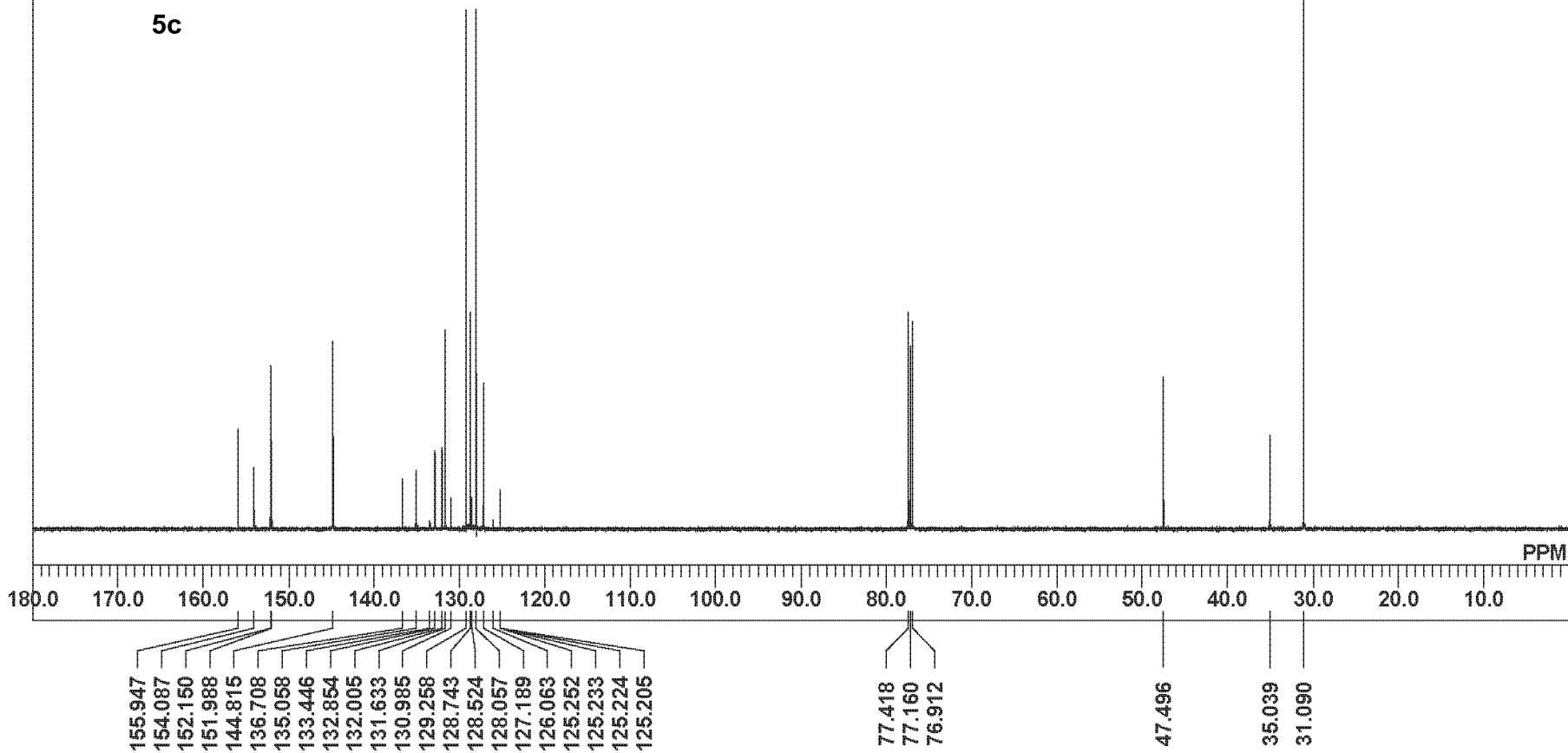
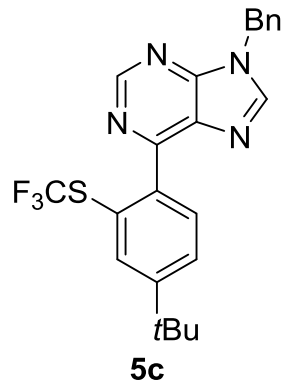


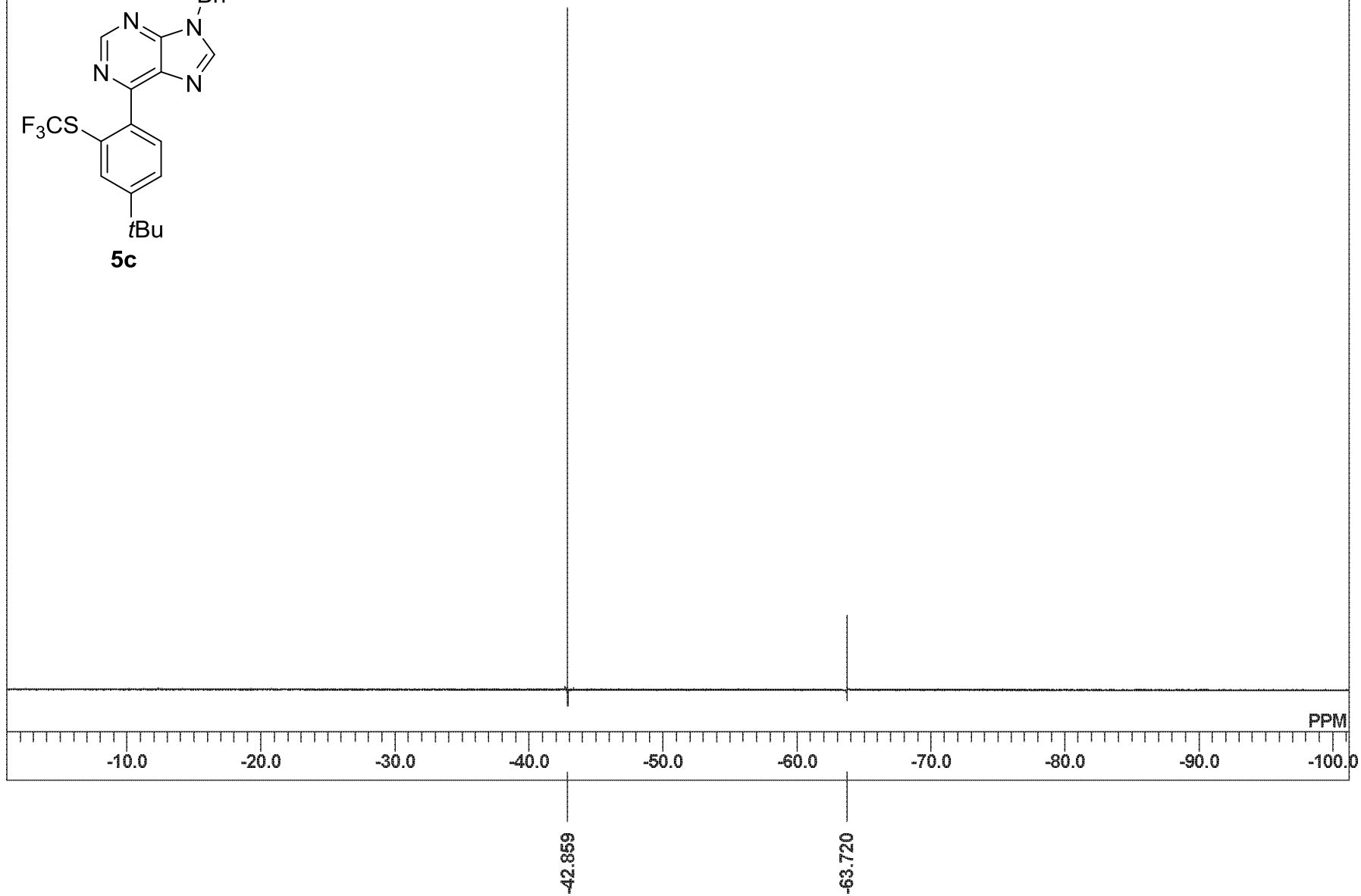
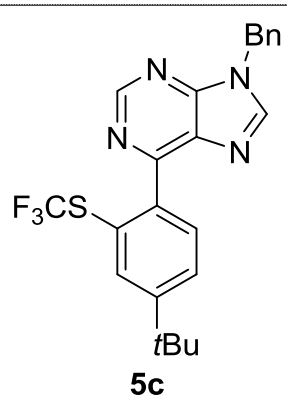


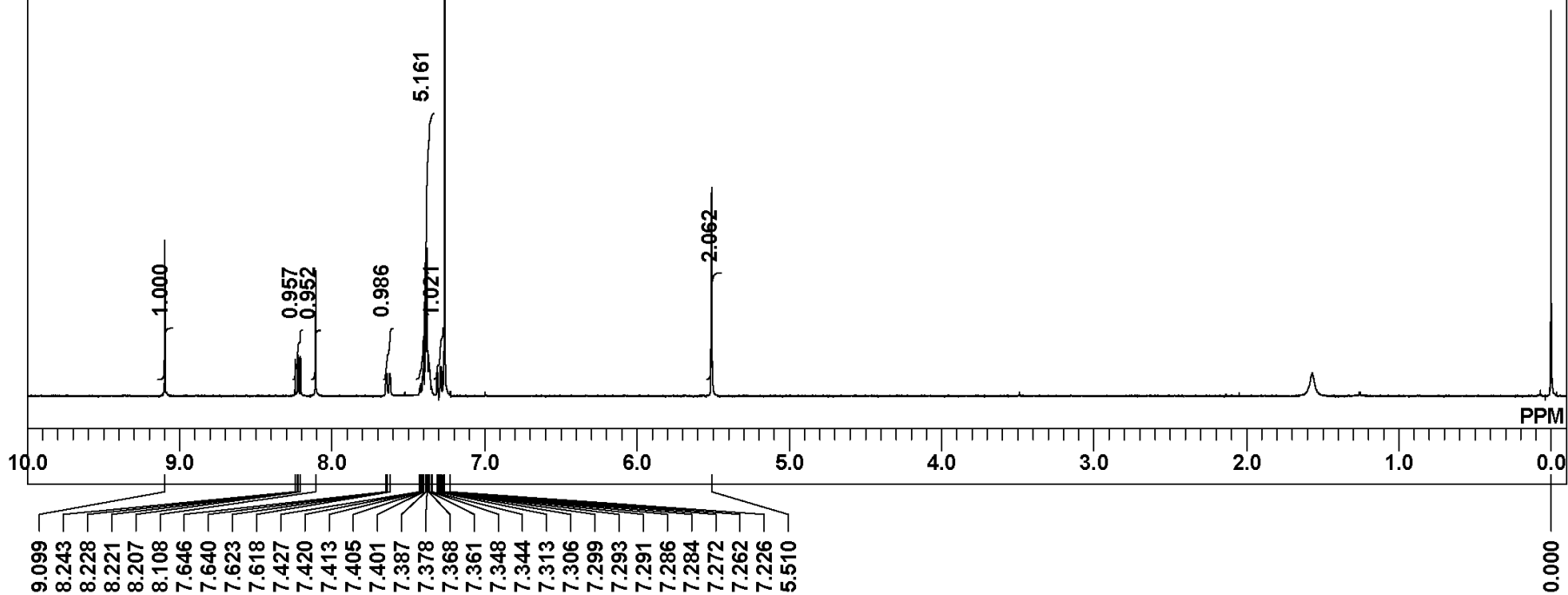
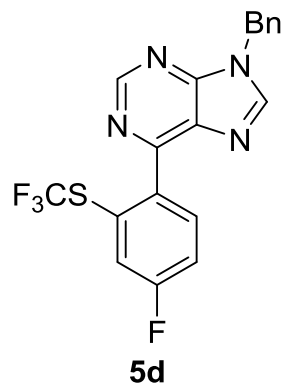


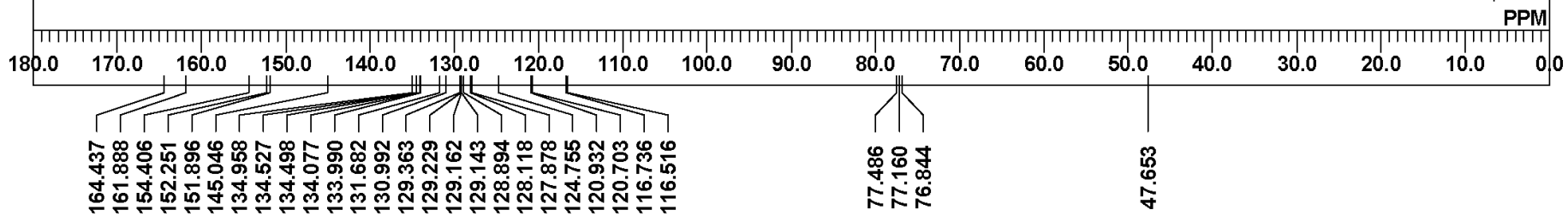
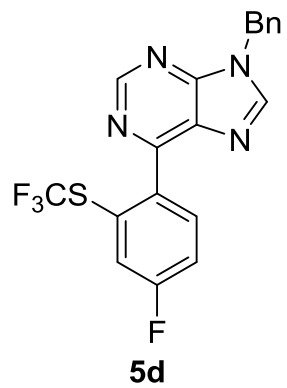


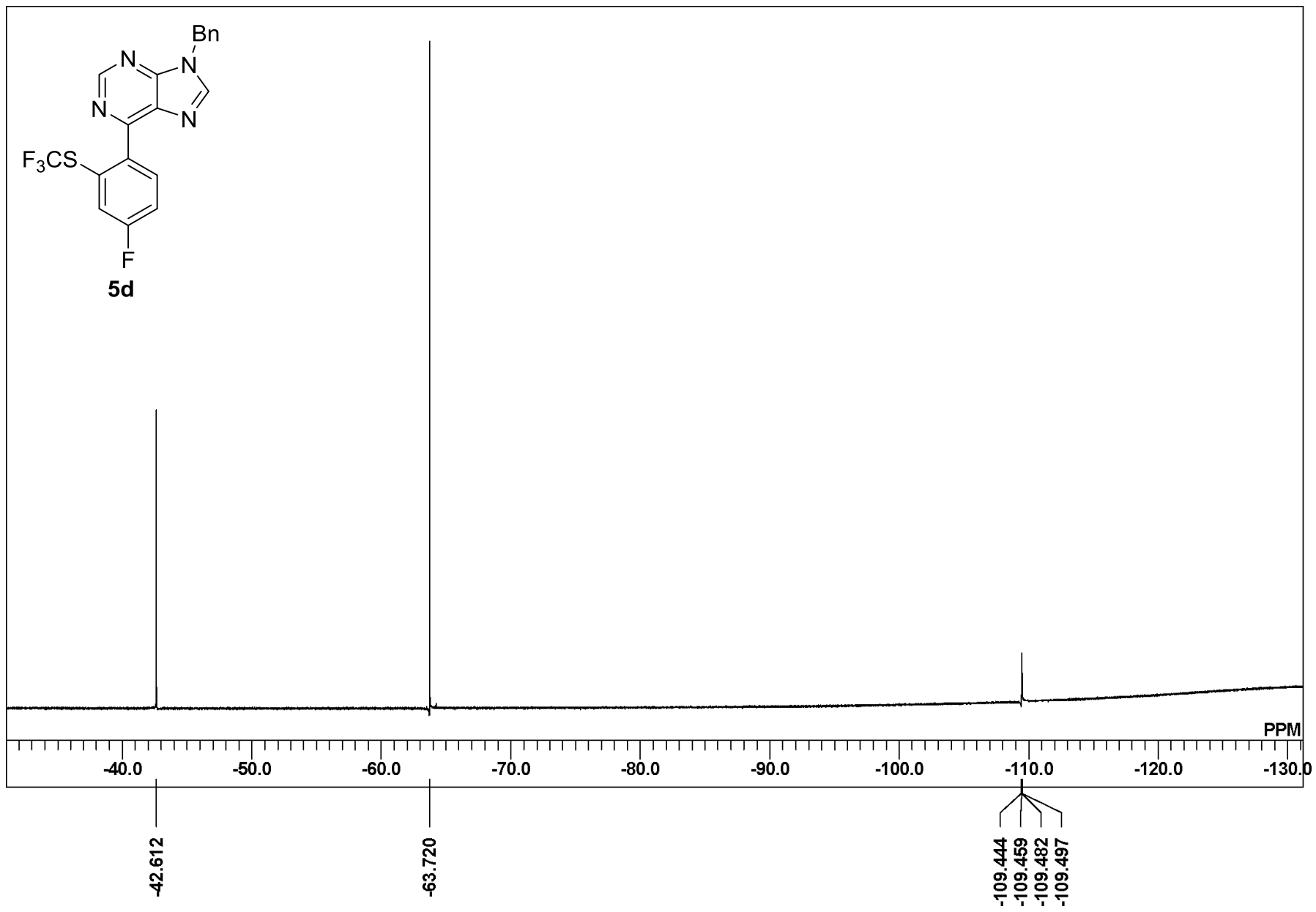


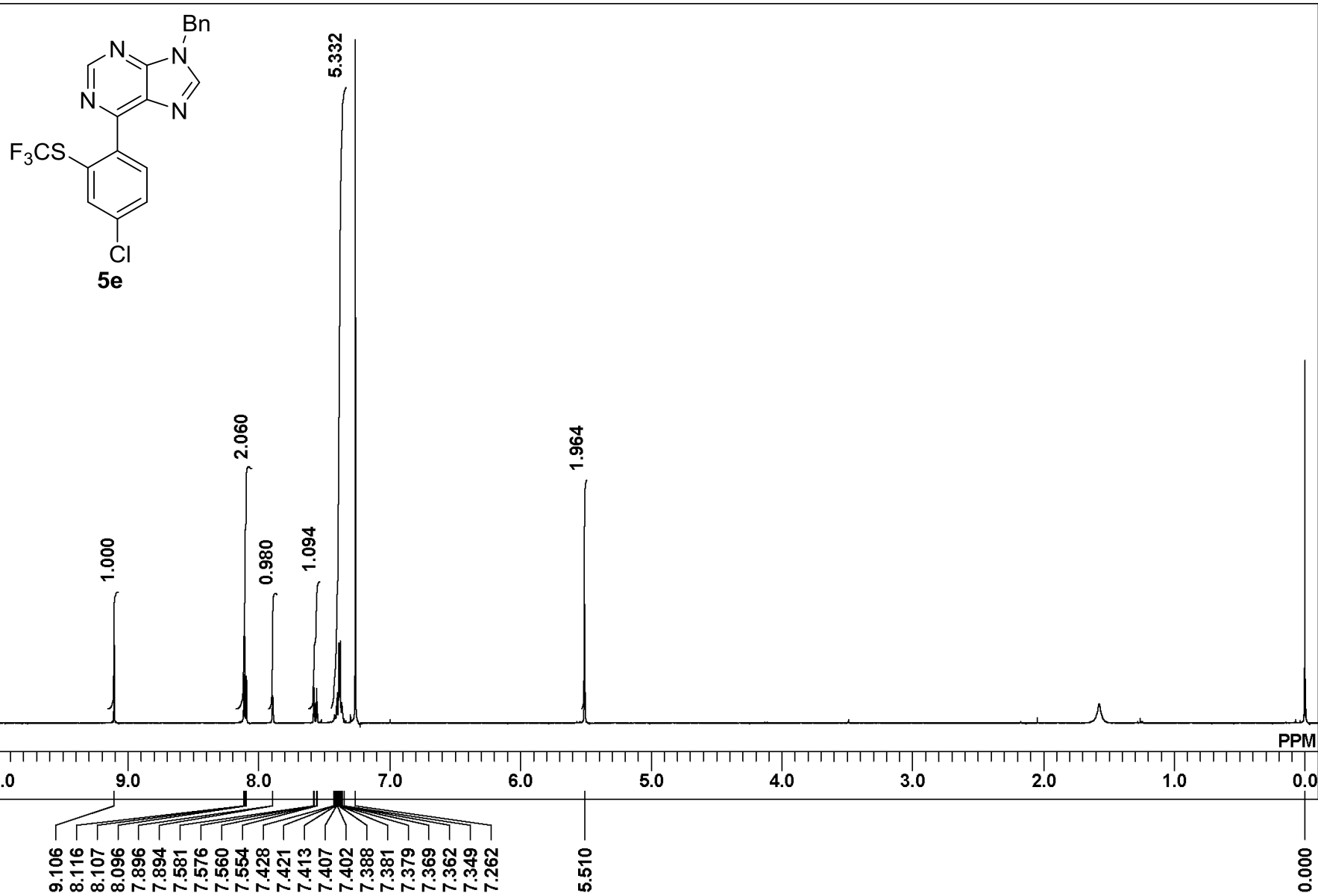


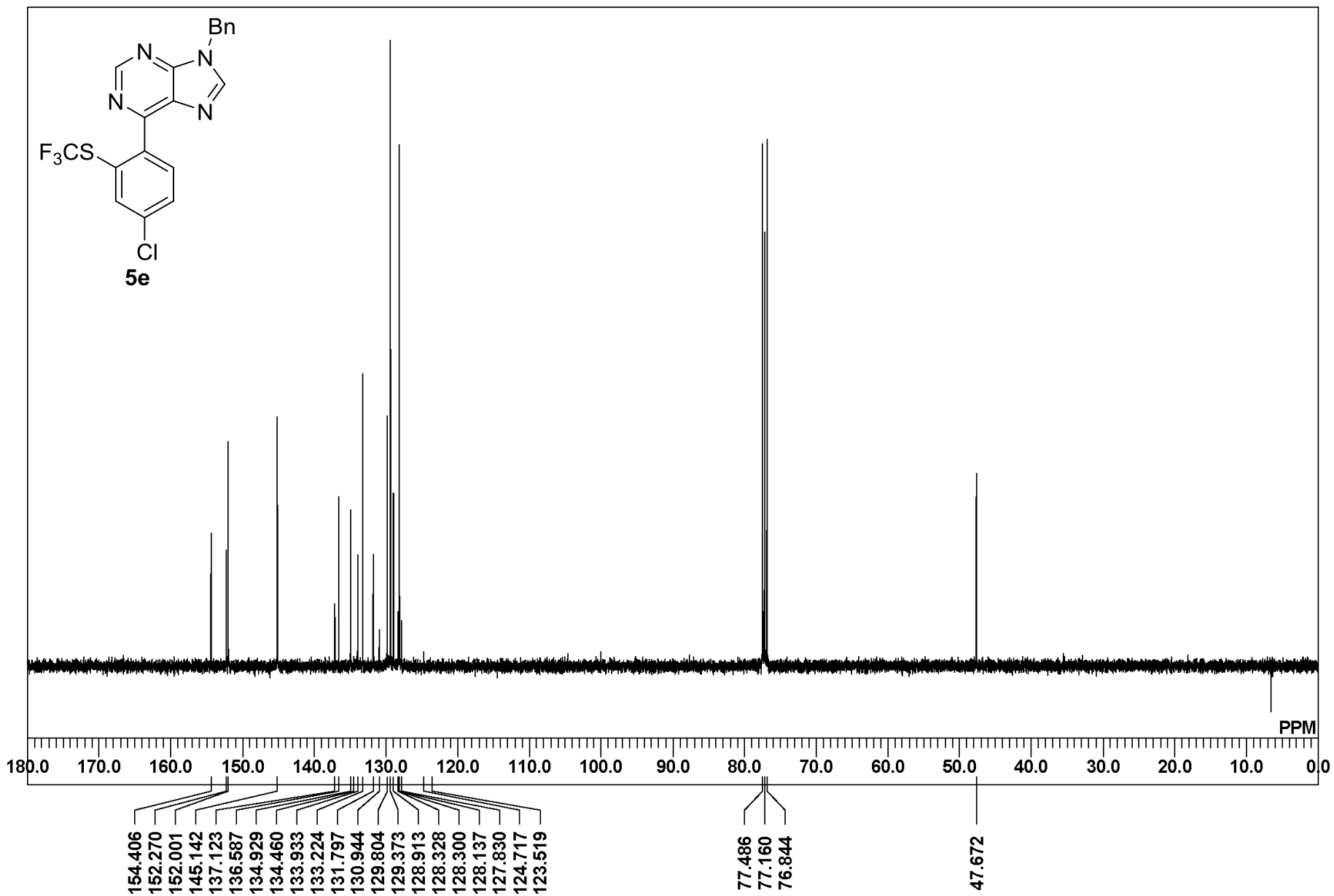
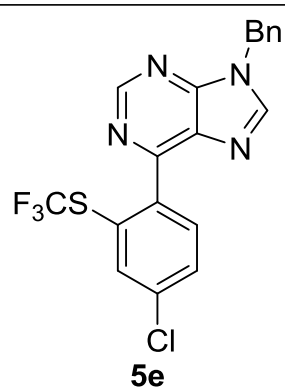


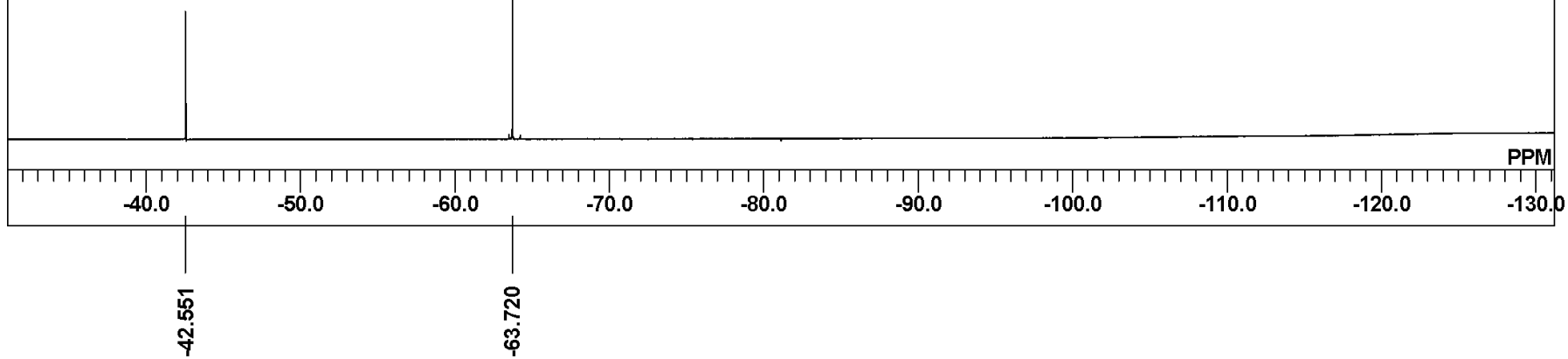
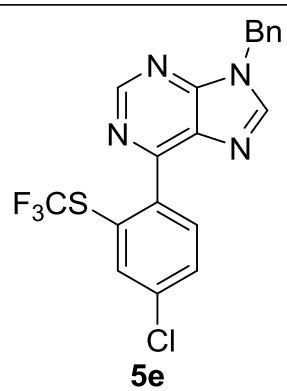


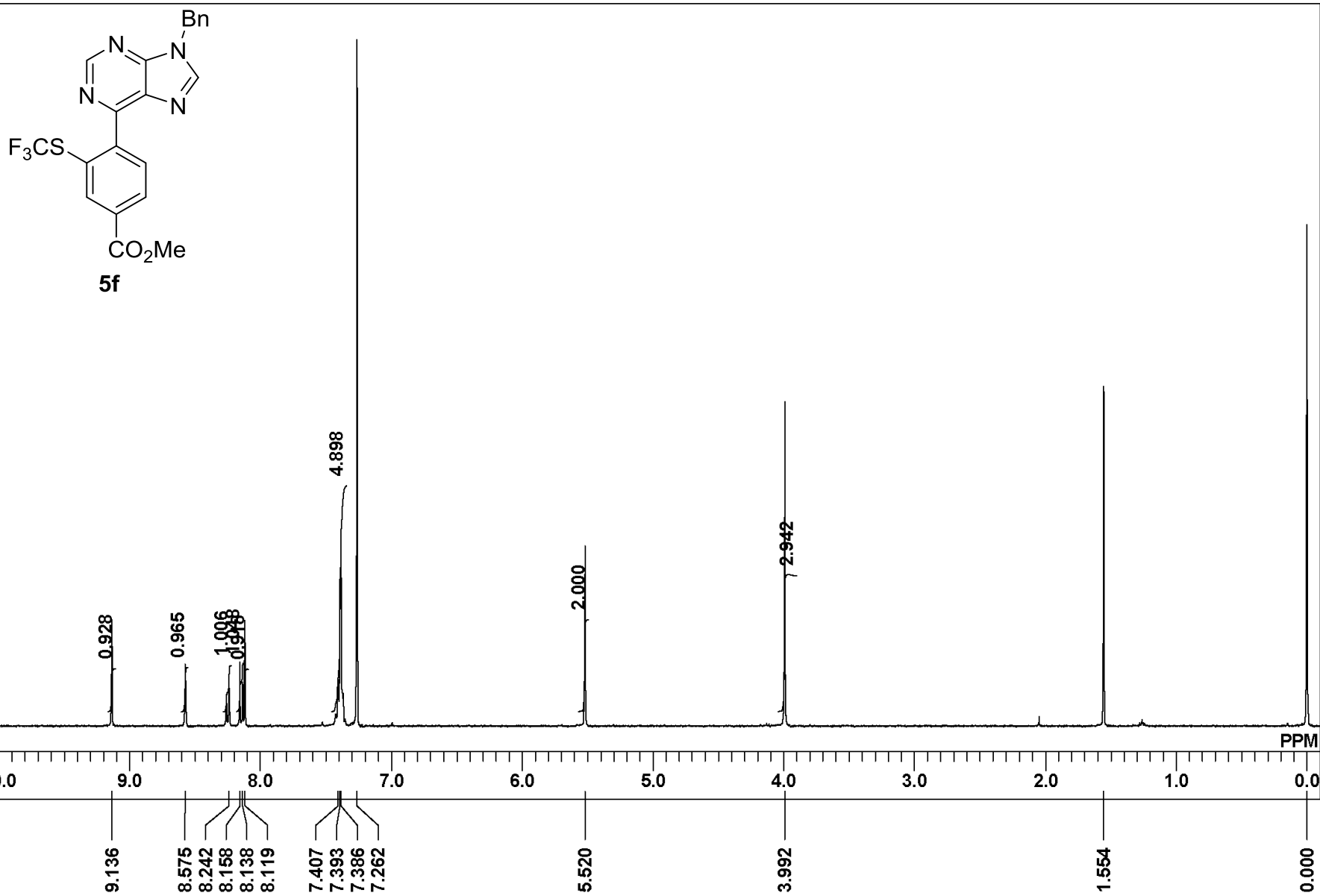


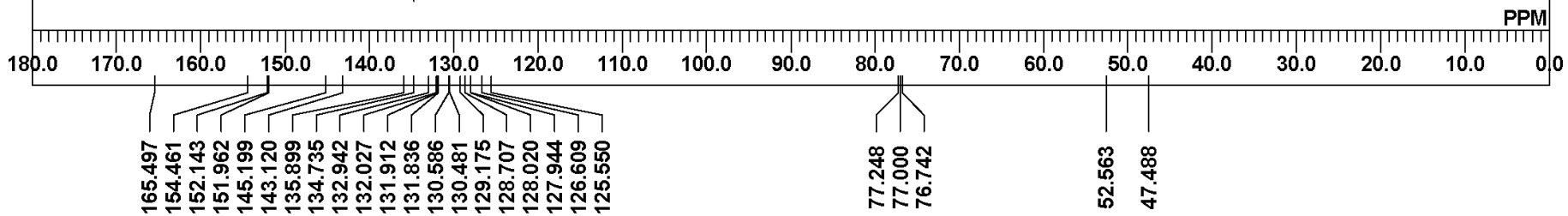
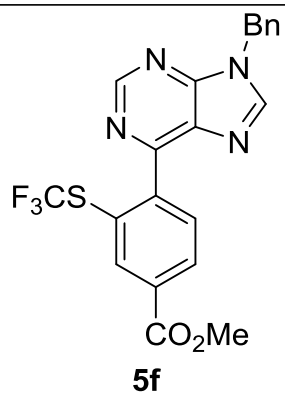


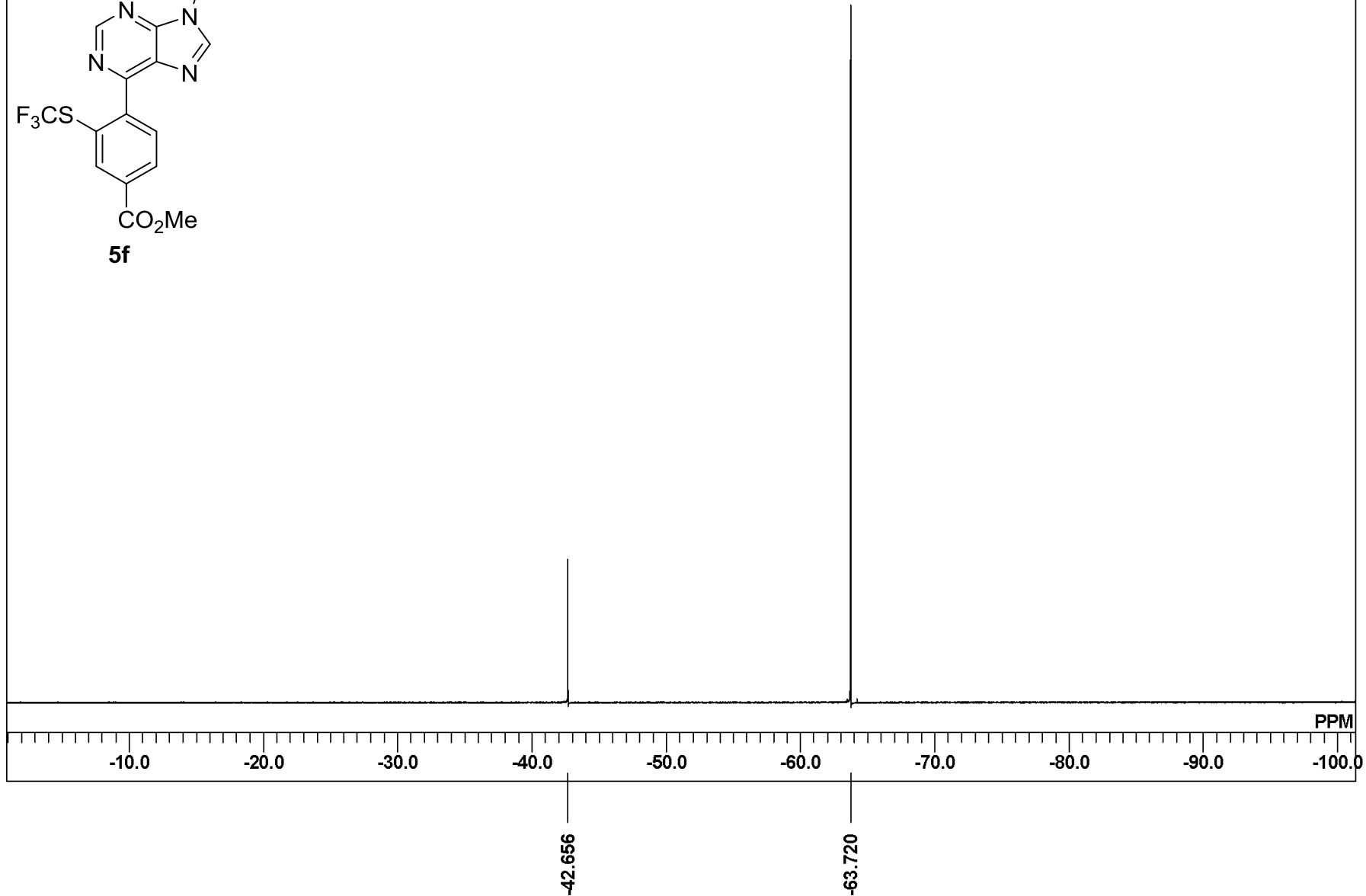
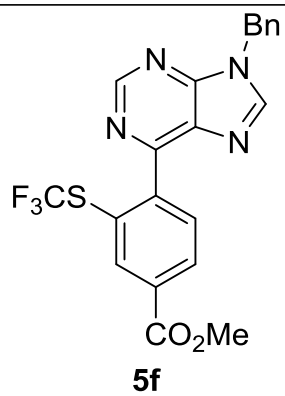


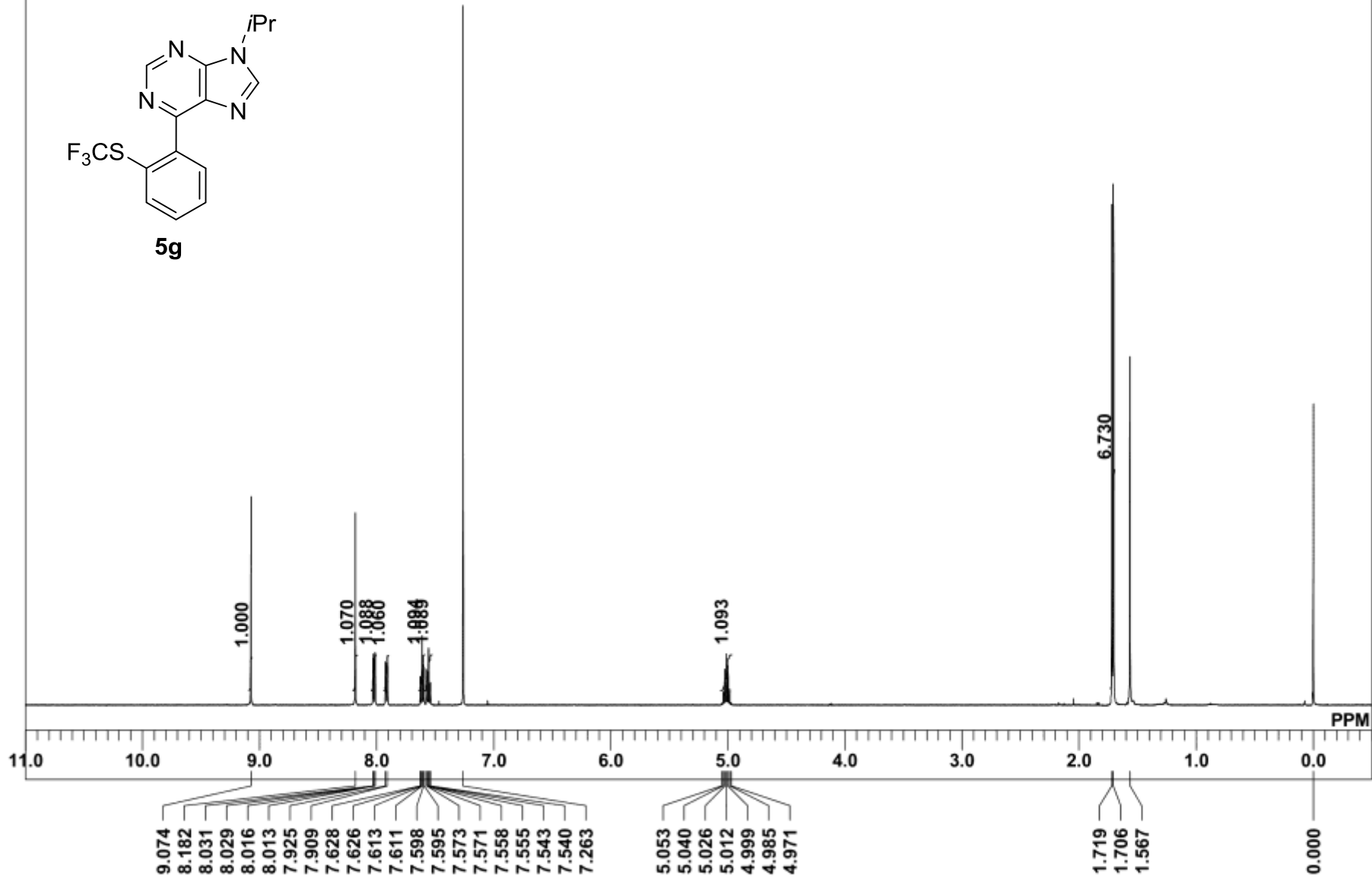
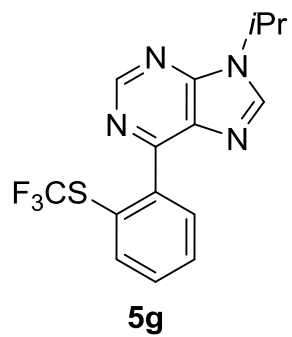


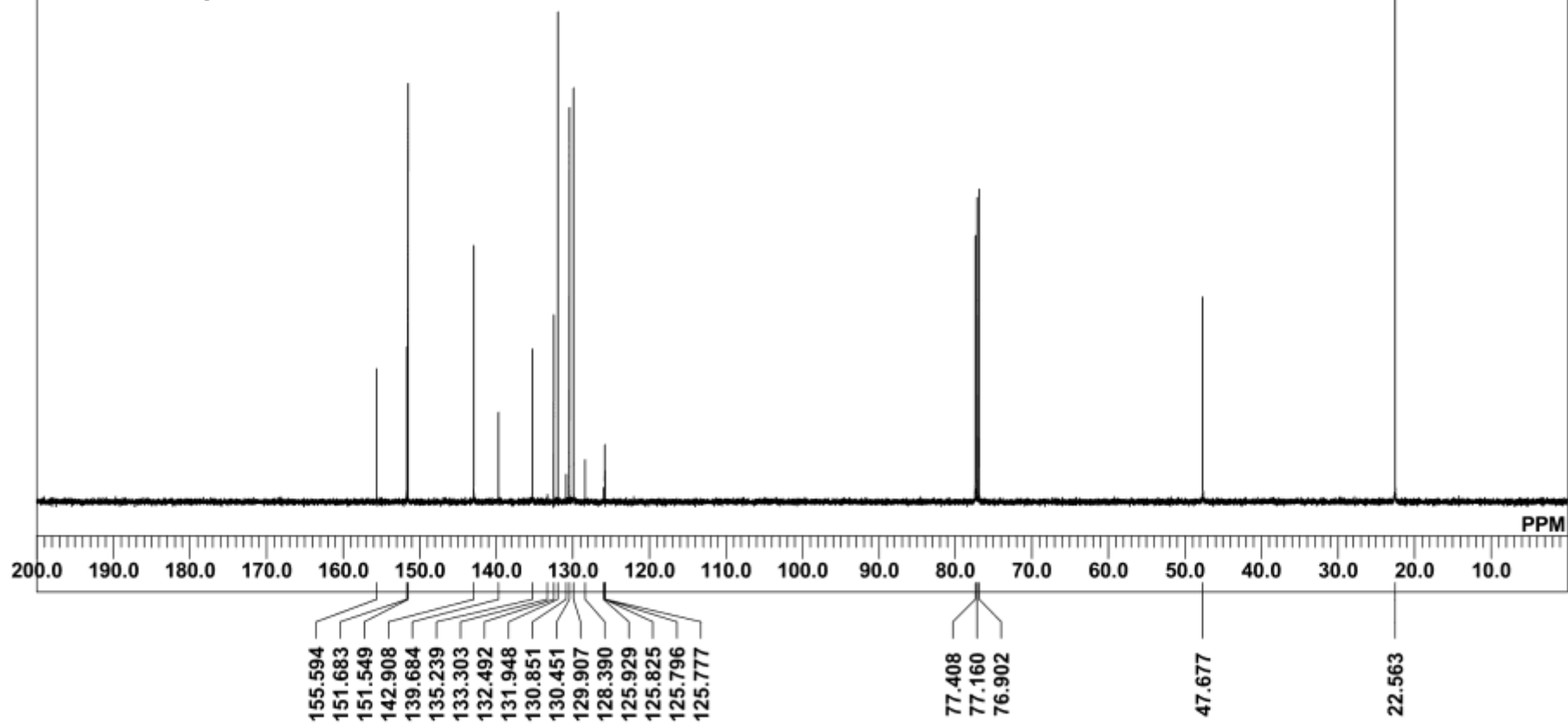
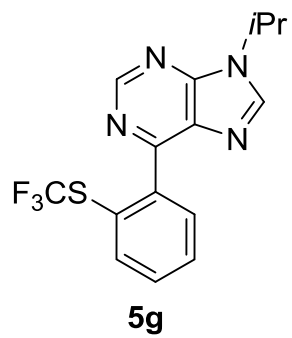


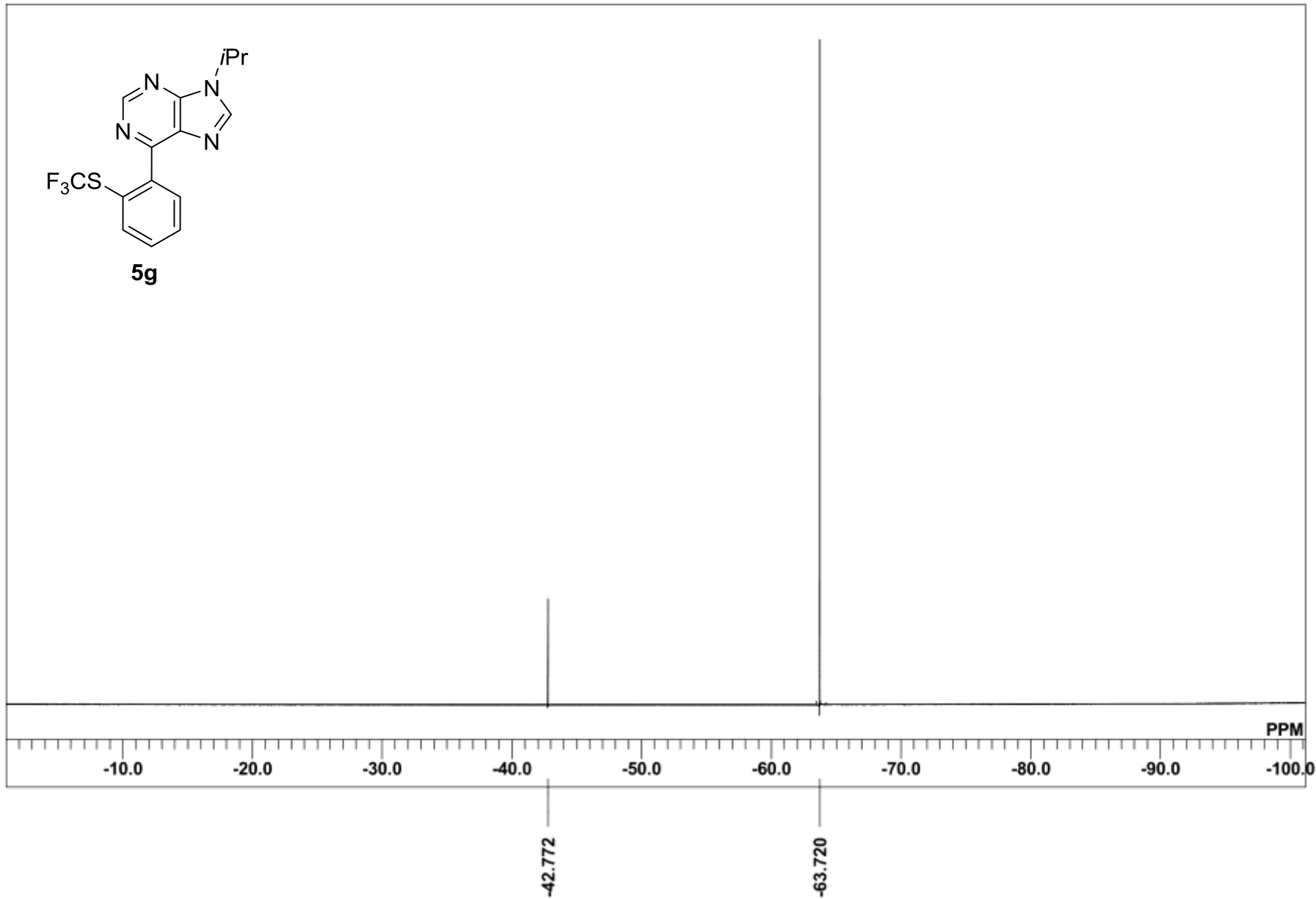
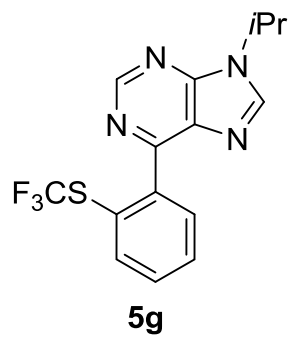


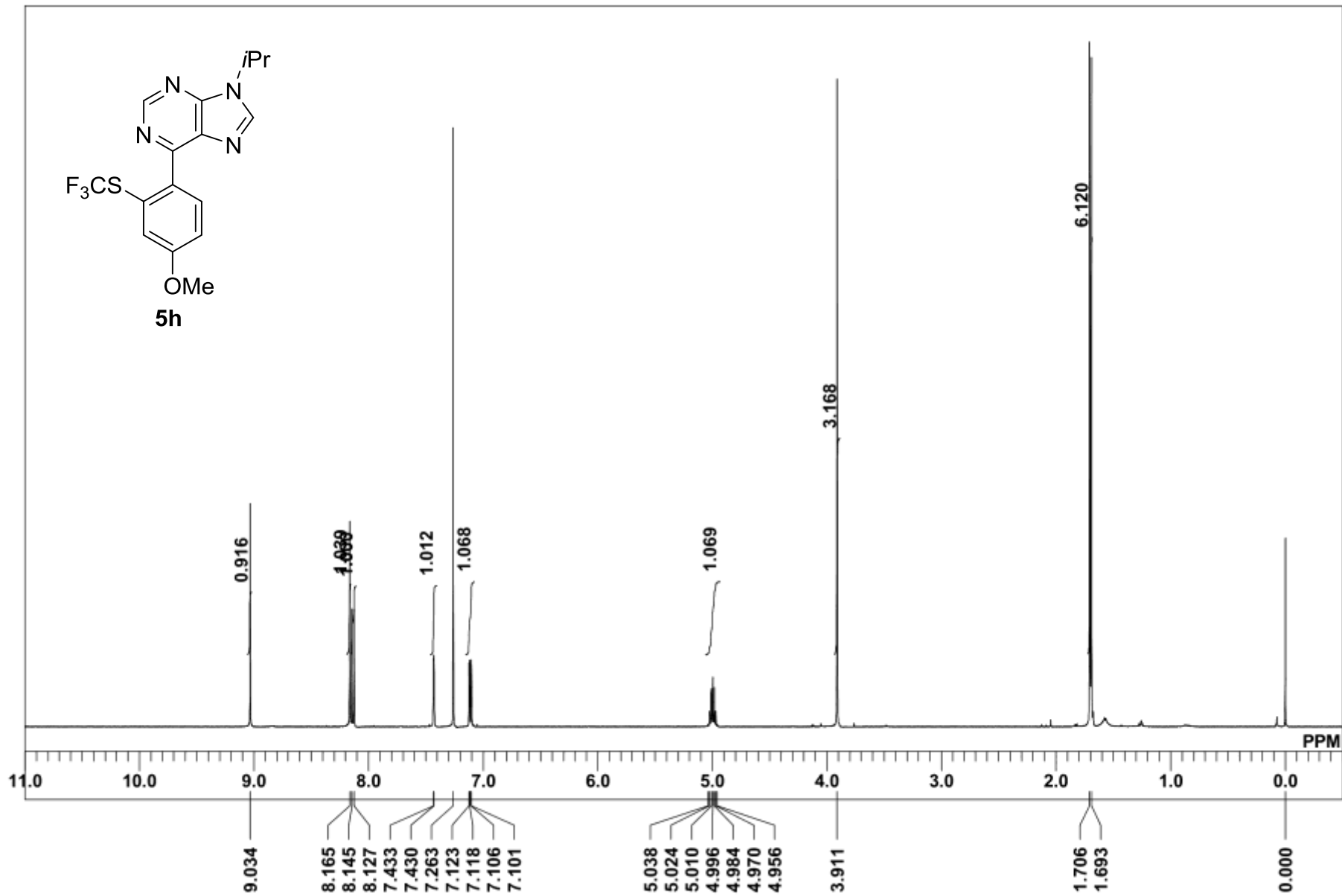
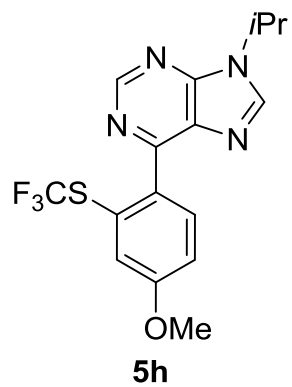


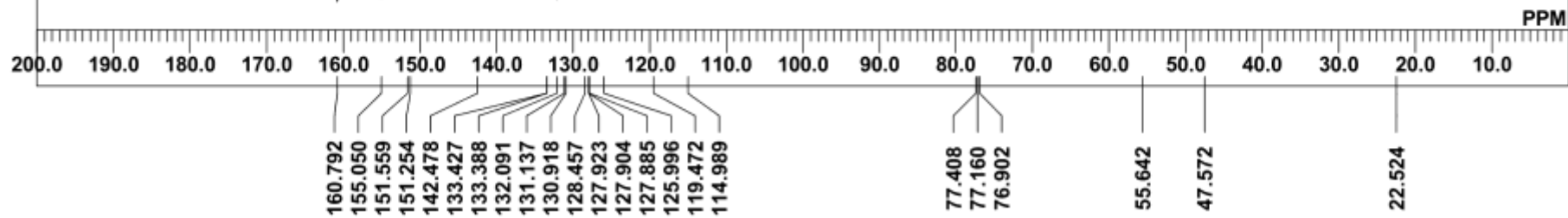
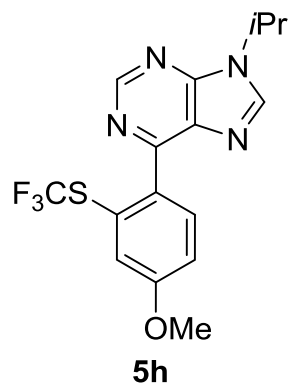


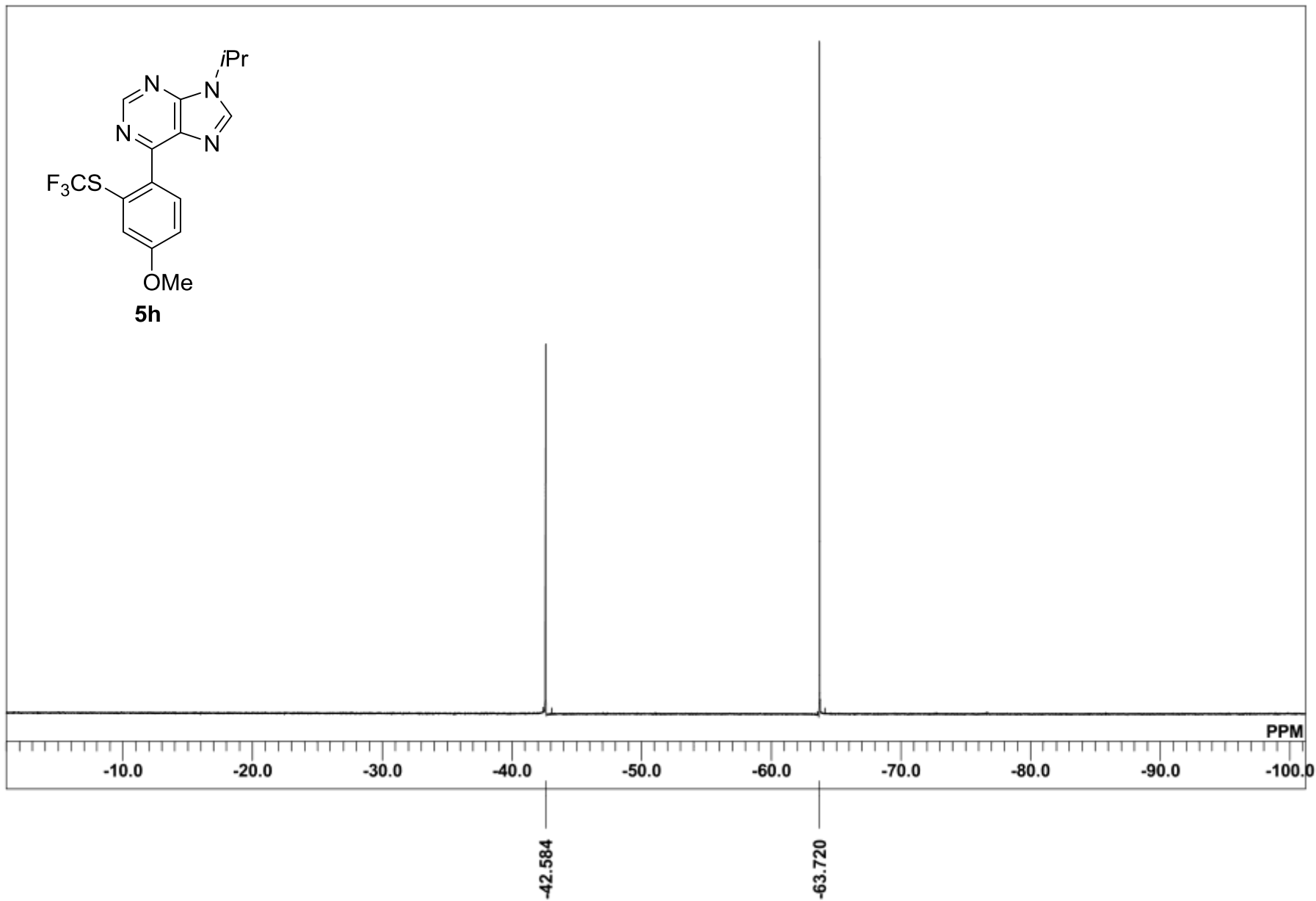
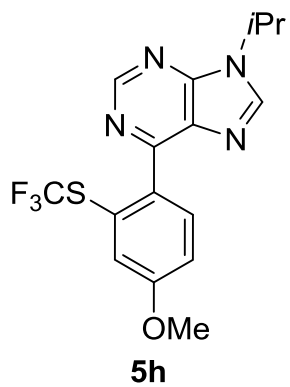


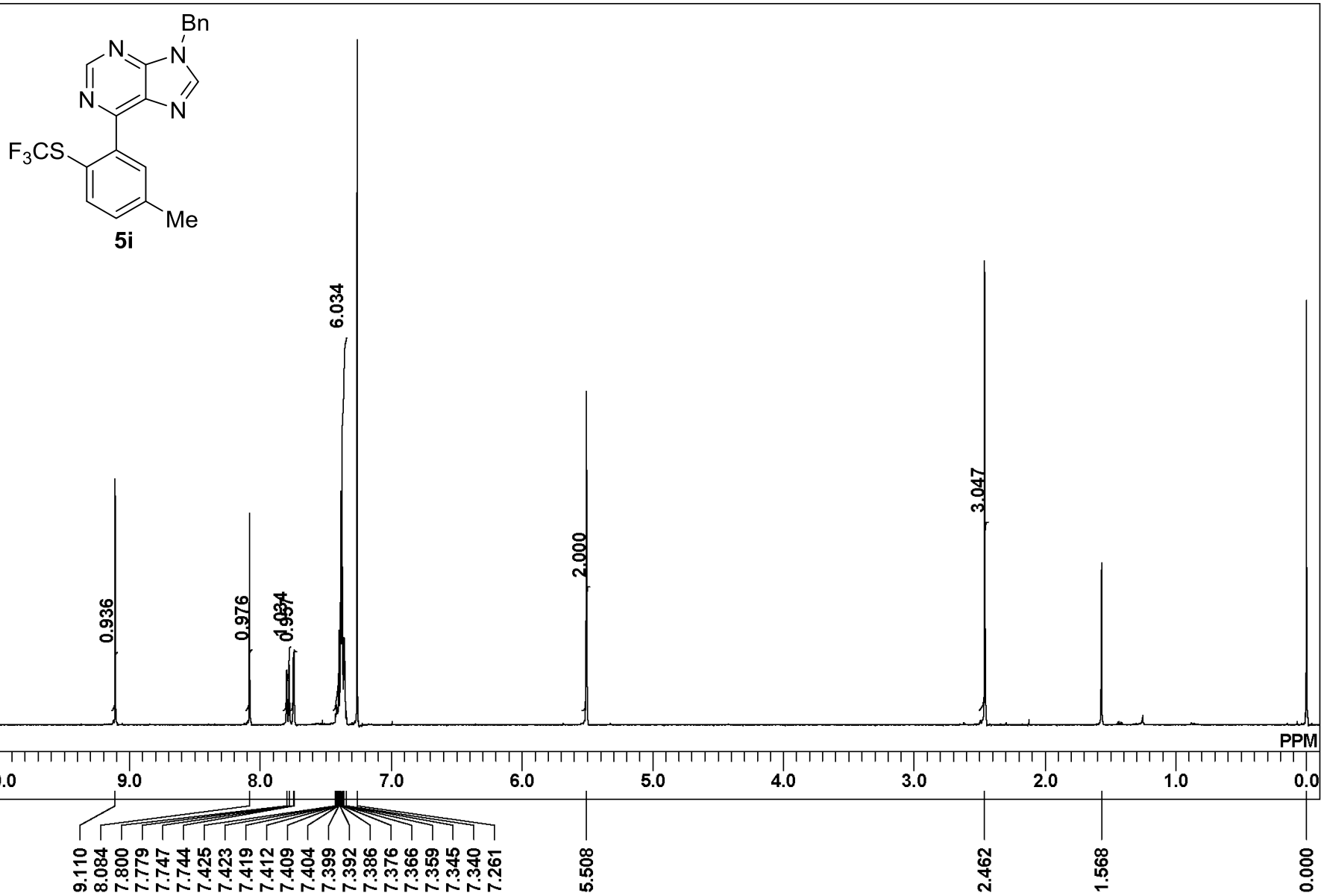


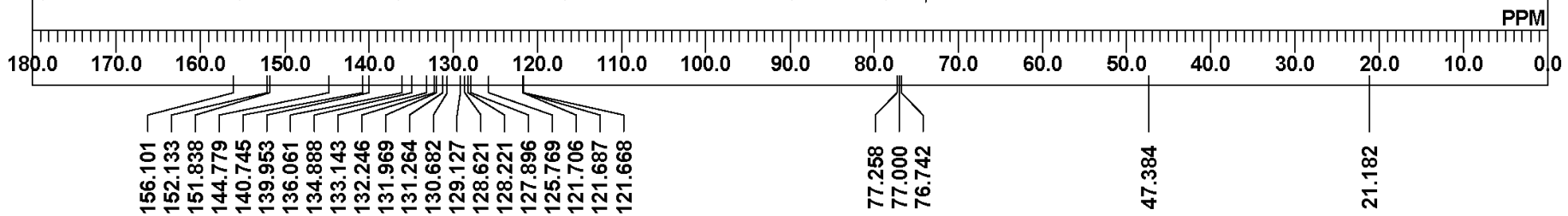
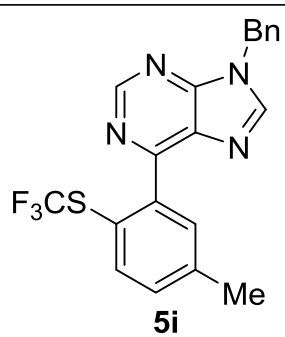


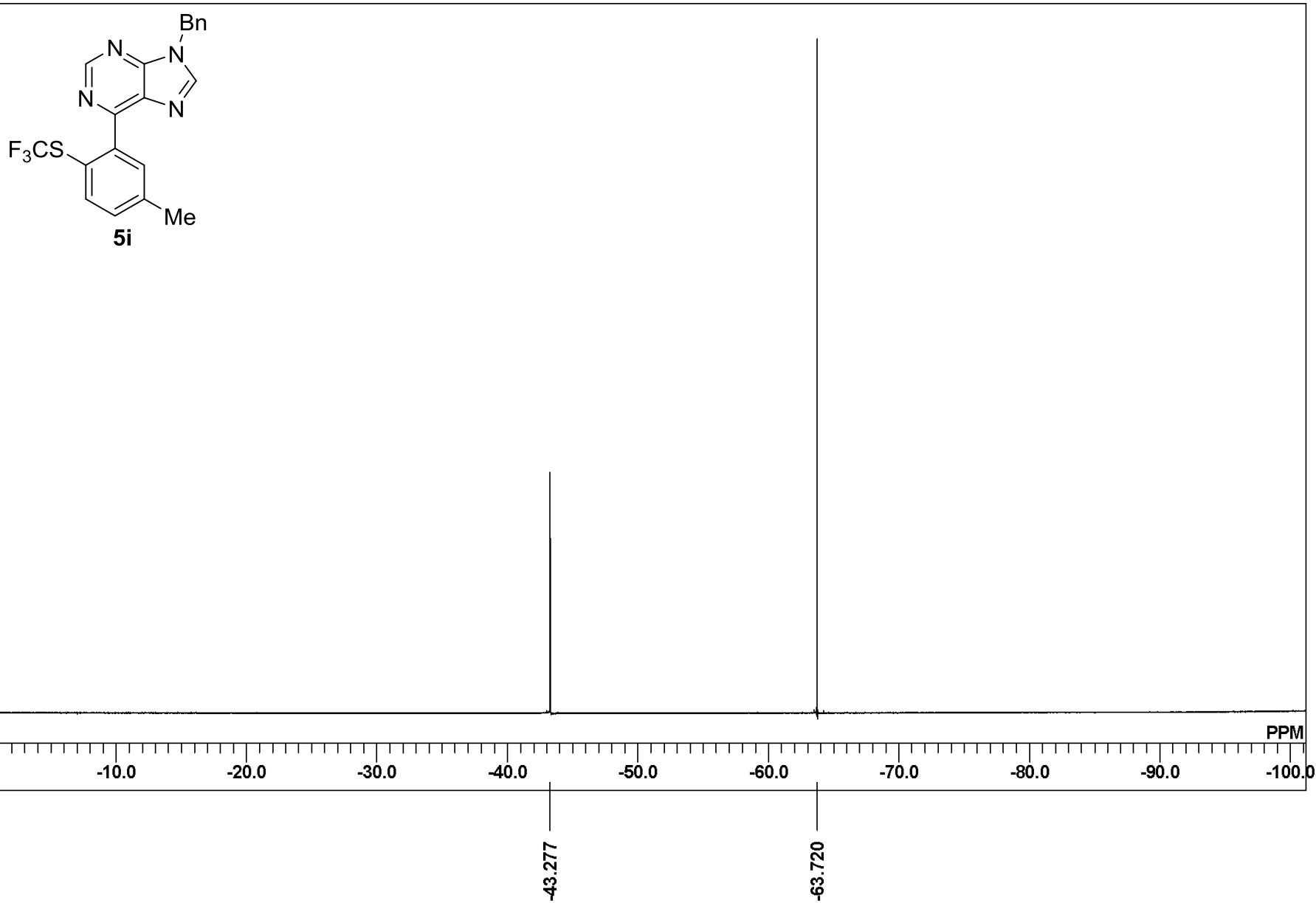


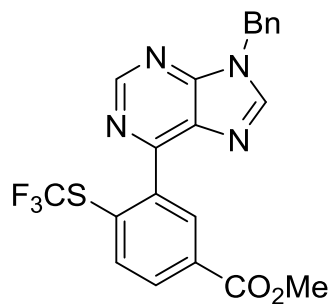




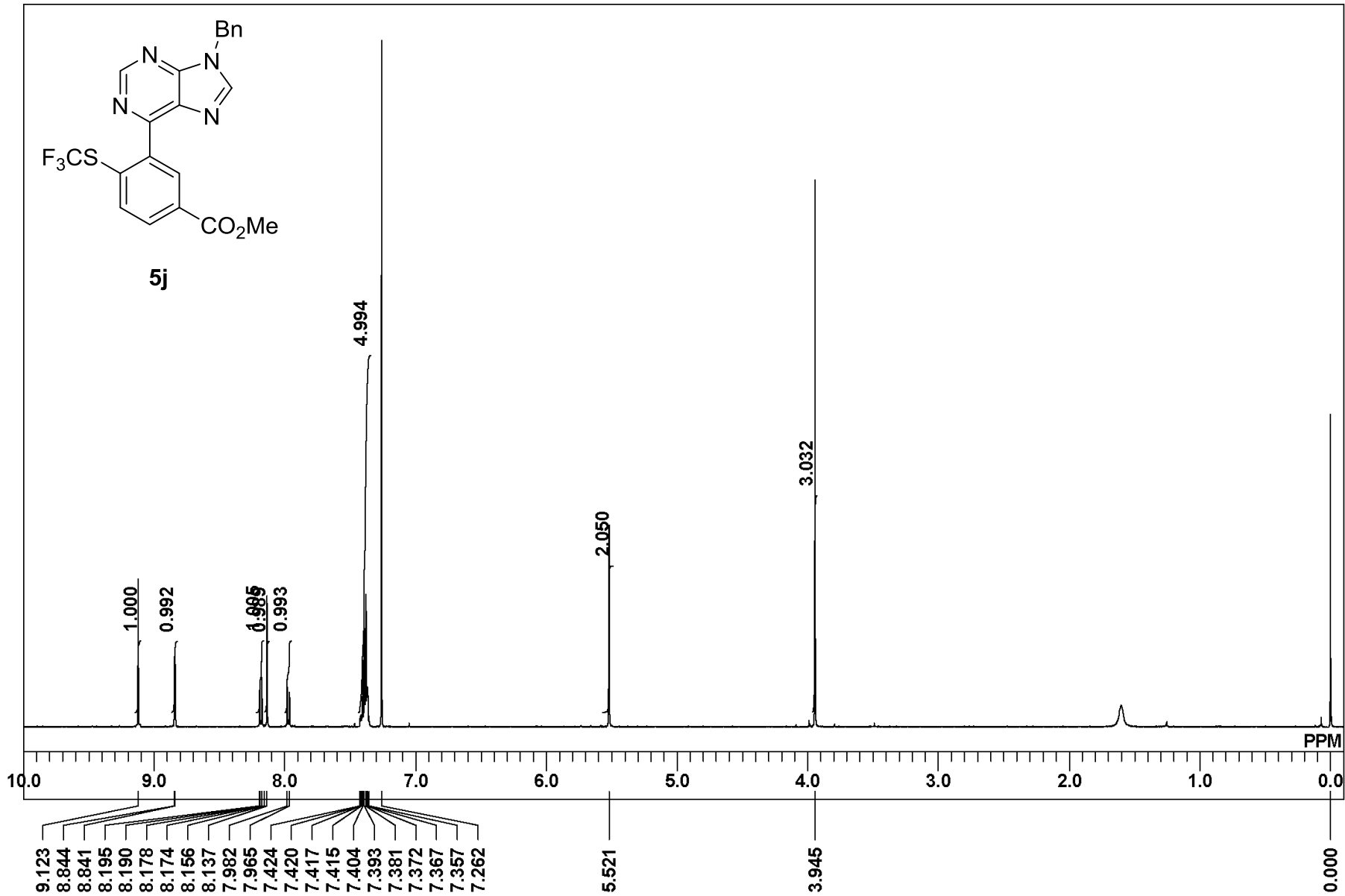


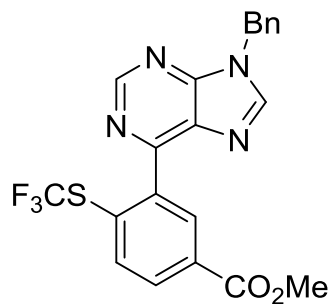




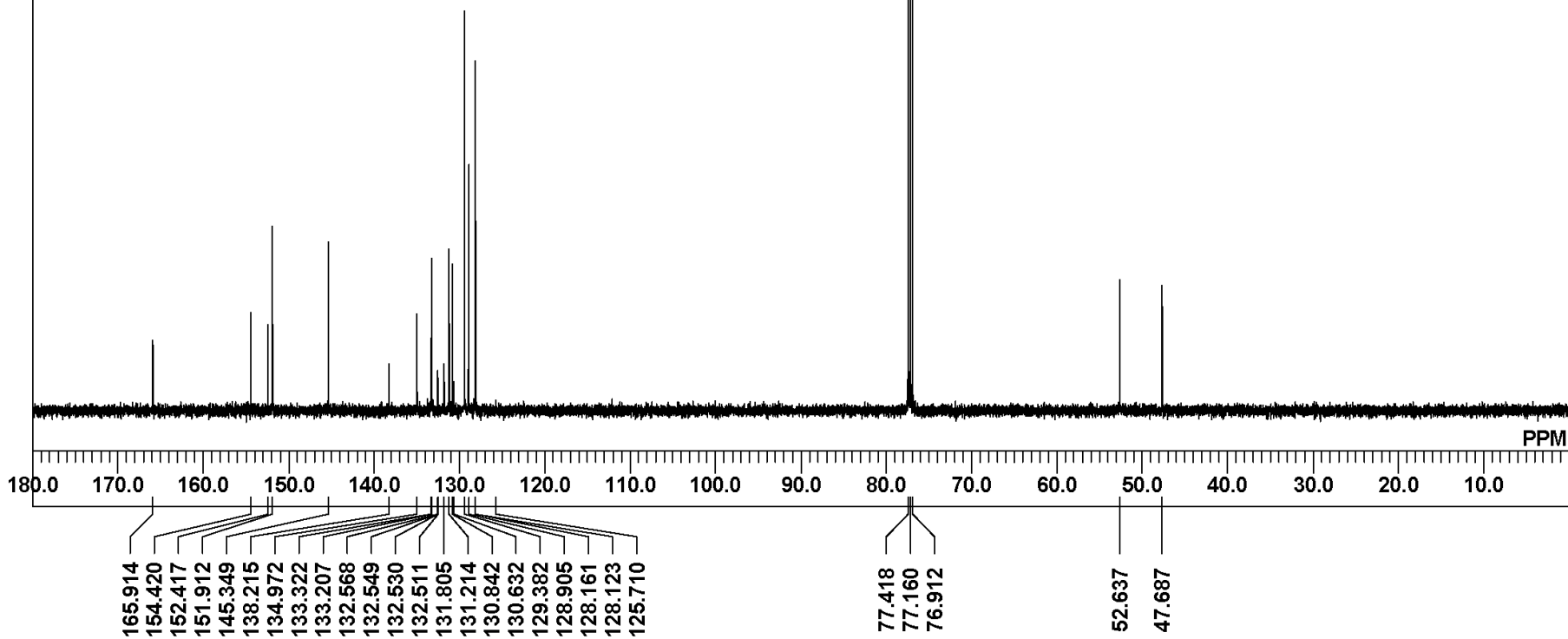


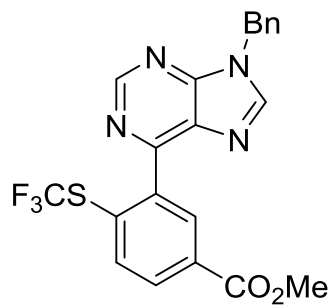
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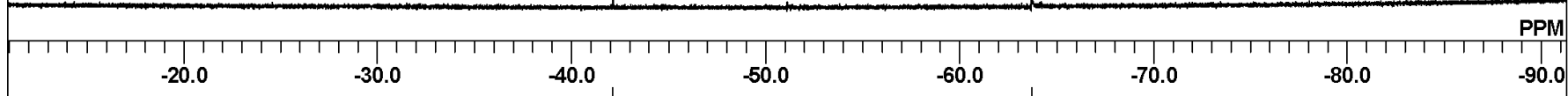


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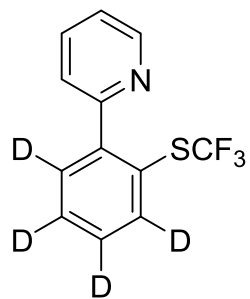


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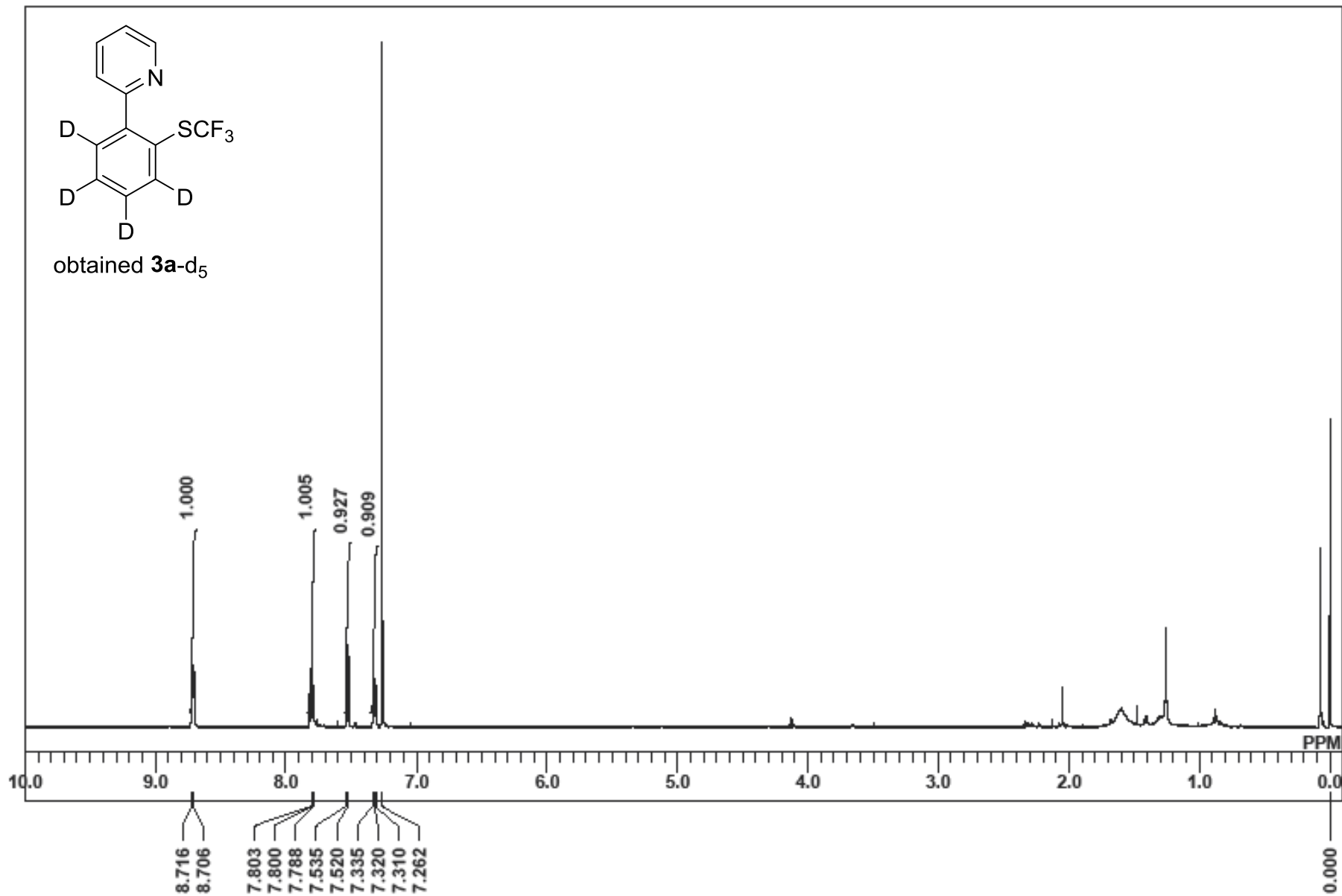


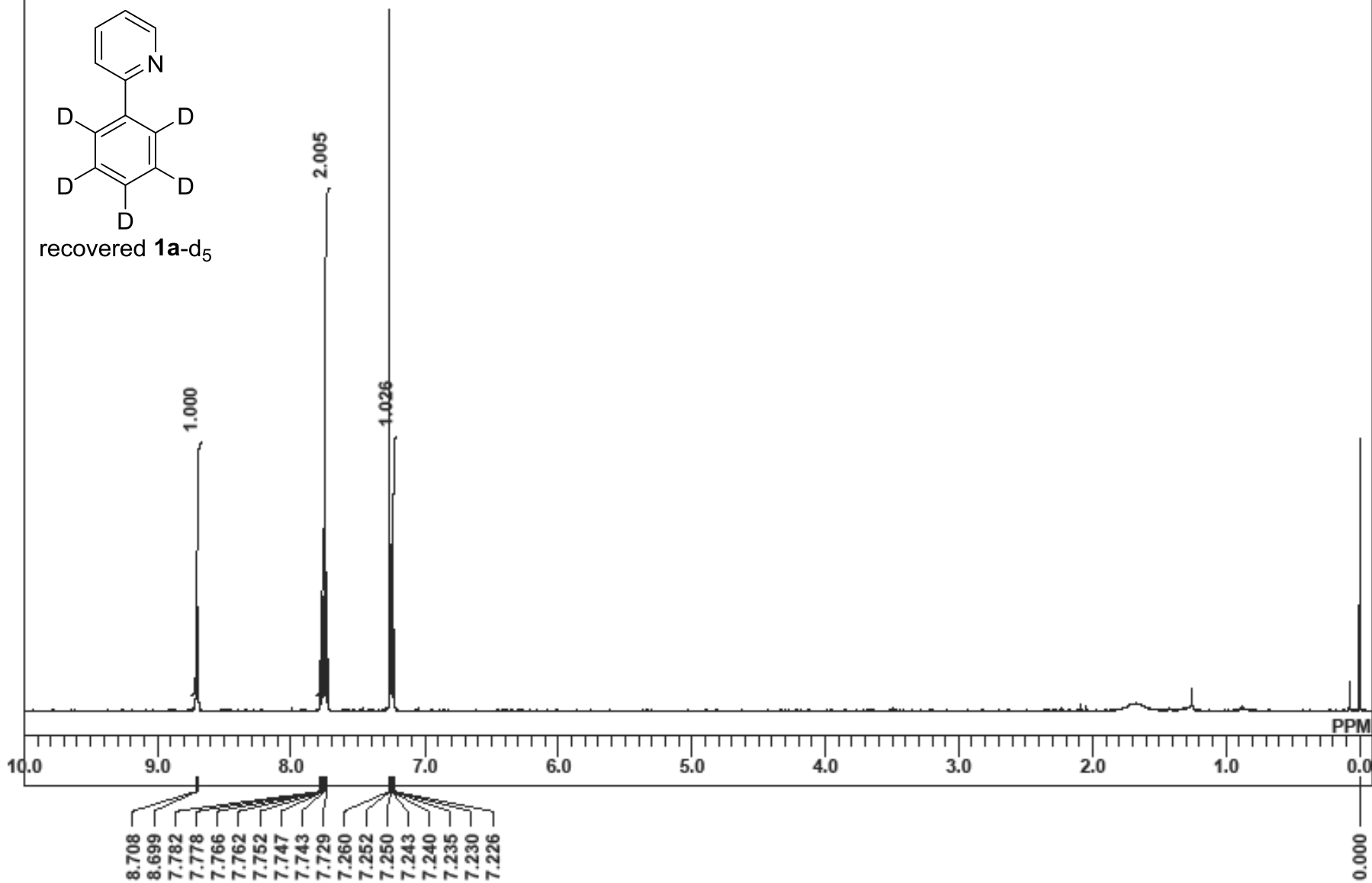
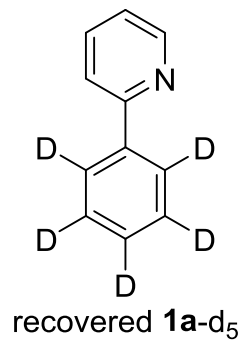
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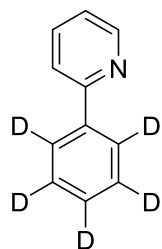
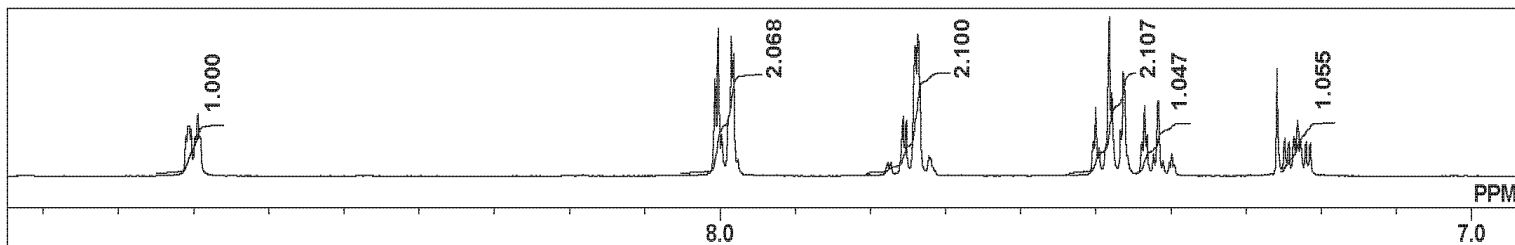


obtained **3a-d₅**

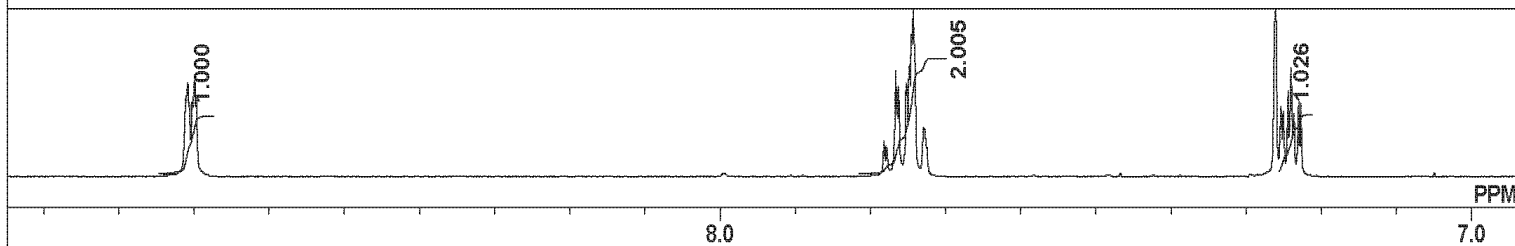




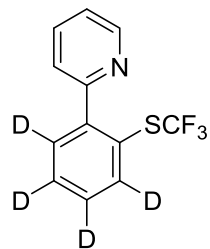
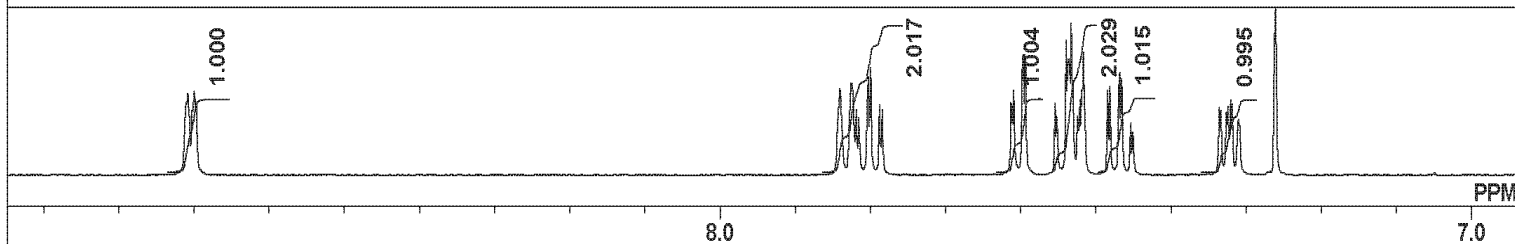
1a



recovered **1a-d₅**



3a



obtained **3a-d₅**

