

**Practical Synthesis of a Potent Bradykinin B₁ Antagonist via Enantioselective
Hydrogenation of a Pyridyl *N*-Acyl Enamide**

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General Information. All reactions were carried out under a nitrogen atmosphere and using mechanical agitation. All reagents and solvents were commercial products and used without further purification. Analytically pure samples were obtained by chromatography on silica gel. Melting points are uncorrected. All NMR spectra were acquired and processed with standard software.

Experimental Procedures

2-Bromo-4,6-dichlorophenol (11). Toluene (40 L) was charged to a 100 L round-bottom flask covered with aluminum foil and degassed with N₂. The solvent was cooled to –50 °C under N₂ atmosphere and Br₂ (1.05 L, 20.51 mol) was added over 5 min. A solution of 2,4-dichlorophenol (3.04 kg, 18.64 mol) in degassed toluene (6 L) was added over 10 min. *t*-BuNH₂ (3.92 L, 37.28 mol) was then added dropwise over 40 min. The internal temperature rose to –30 °C. HPLC analysis at the end of the addition of *t*-BuNH₂ revealed that the reaction was complete. The reaction was quenched at –50 °C with a degassed aqueous solution of NaHSO₃ (38% w/w, 15 L). The biphasic mixture was warmed to rt and after separation of the aqueous layer, the organic layer was successively washed with degassed 3N NaOH (12.5 L, 37.3 and 8.3 L, 24.8 mol). The combined aqueous layers were added to a cooled (12 °C) and vigorously stirred solution of 2N HCl (37.3 L, 74.6 mol) and MTBE (60 L). After aging for 20 min at rt, the layers were cut and the organic layer was washed with water (2 x 9 L), concentrated under reduced pressure and flushed with fresh toluene (8 L) to afford by HPLC assay 4.4 kg (98% yield) of **11** as a white solid: mp 70-71 °C; ¹H NMR (500 MHz, acetone *d*₆) δ 8.9 (s, 1H), 7.54 (d, 1H, *J* = 2.5 Hz), 7.44 (d, 1H, *J* = 2.5 Hz); ¹³C NMR (125 MHz, acetone *d*₆) δ 150.2, 131.9, 129.5, 125.5, 122.9, 112.3; HRMS calcd for C₆H₃BrCl₂O (M – H) 238.8666, found 238.8663; IR (KBr, cm^{–1}) 3410, 3079; 2920, 2850, 1565, 1462, 1390, 1323, 1265, 1230, 1218, 1167, 855; HPLC: Zorbax Eclipse XDB-C8 4.6 mm x 25 cm column; eluants: A 0.1% aqueous H₃PO₄; B acetonitrile; 1.8 mL/min; gradient: A/B 90:10 to 10:90 over 15 min; λ = 220 nm; temperature 35 °C; *t*_R: **11** = 11.2 min.

2,2-Difluoroethyl methanesulfonate (12). A mixture of 2,2-difluoroethanol (2.95 kg, 36.01 mol) in CH₂Cl₂ (29.5 L) was cooled to 0 °C and methanesulfonyl chloride (3.01 L, 39.62 mol) was added. Et₃N (6.0 L, 43.21 mol) was added dropwise to the reaction mixture over 1 h. The internal temperature rose to 20 °C during the addition. The cooling bath was removed and the suspension was aged at rt for 15 min. The organic layer was washed with H₂O (2 x 21 L), concentrated under reduced pressure and flushed with fresh toluene (12 L) to afford 5.5 kg (95% yield) of **12** as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 6.01 (tt, 1H, *J* = 3.8 Hz, *J* = 54.5 Hz), 4.38 (td, 2H, *J* = 3.8 Hz, *J* = 13.1 Hz), 3.12 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 111.9 (t, *J* = 242 Hz), 66.1 (t, *J* = 30 Hz), 37.7; ¹⁹F NMR (377 MHz, CDCl₃) δ –126.2; HRMS calcd for C₃H₆F₂O₃S (M + Li)⁺ 167.0166, found 167.0168; IR (neat, cm^{–1}) 3660, 3570, 3015, 2947, 1350, 1270, 1175, 1150, 1070, 1030, 970, 933, 902, 820.

1-Bromo-3,5-dichloro-2-(2,2-difluoroethoxy)benzene (13). Using a mechanical stirrer, bromophenol **11** (3.75 kg, 15.51 mol), mesylate **12** (2.73 kg, 17.06 mol), K₂CO₃ (4.3 kg, 31.02 mol) and DMF (40 L) were mixed together at rt. The slurry was degassed by bubbling N₂ through for 15 min prior to heating to 90 °C for 16 h. The milky mixture was cooled to 21 °C, H₂O (37.5 L), MTBE (7.5 L) and heptane (30 L) were added. The organic layer was washed

with 1N HCl (9.4 L) followed by H₂O (4 x 10 L). The organic layer was concentrated under reduced pressure and the residue was flushed with toluene (12 L) to yield by HPLC assay 4.4 kg (93%) of **13** as a white solid: mp 60-61 °C; ¹H NMR (500 MHz, acetone *d*₆) δ 7.68 (d, 1H, *J* = 2.5 Hz), 7.59 (d, 1H, *J* = 2.5 Hz), 6.36 (tt, 1H, *J* = 3.9 Hz, *J* = 54.7 Hz), 4.34 (td, 2H, *J* = 4.0 Hz, *J* = 13.8 Hz); ¹³C NMR (125 MHz, acetone *d*₆) δ 151.5, 132.7, 131.4, 120.5, 130.2, 119.2, 114.6 (t, *J* = 242 Hz), 72.3 (t, *J* = 113 Hz); ¹⁹F NMR (470 MHz, acetone *d*₆) δ -130.7 (dt, *J* = 15 Hz, *J* = 53 Hz); anal calcd for C₈H₅BrCl₂F₂O: C, 31.41%; H, 1.65%; found C, 31.39%; H, 1.68%; IR (KBr, cm⁻¹) 2975, 1500, 1410, 1395, 1330, 1210, 1090, 1030, 875, 850, 818, 803, 751, 718; HPLC: Zorbax Eclipse XDB-C8 4.6 mm x 25 cm column; eluants: A 0.1% aqueous H₃PO₄; B acetonitrile; 1.8 mL/min; gradient: A/B 90:10 to 10:90 over 15 min; λ = 220 nm; temperature 35 °C; *t*_R: **13** = 13.8 min.

[3,5-Dichloro-2-(2,2-difluoroethoxy)phenyl]boronic acid (6). To a solution of aryl bromide **13** (4.4 kg, 14.39 mol) in toluene (41 L) at 0 °C was added *i*-PrMgCl (2.08M in THF, 7.6 L, 15.82 mol). The solution was aged at 0 °C for 1 hr prior to the addition of B(O*i*Pr)₃ (4.63 L, 20.14 mol). The slurry was aged at 0 °C for 3 h at which point 4N HCl (9.4 L, 43.16 mol) was added dropwise. The reaction mixture was warmed to rt and aged for 30 min. The layers were cut and the organic layer was washed with H₂O (2 x 13 L), concentrated and flushed twice with toluene. The crude residue was taken up in heptane (10 L) and H₂O (366 mL, 20.37 mol) was added. The slurry was mechanically agitated at rt for 3.5 h, cooled to 0 °C and aged for 2 h. The slurry was filtered and the solid was washed with precooled (5 °C) heptane (2 x 1.5 L) to afford 3.5 kg (90%) of **6** as a white powder: mp 97-98 °C; ¹H NMR (400 MHz, acetone *d*₆) δ 7.60-7.50 (dd, 1H, *J* = 2.5 Hz, *J* = 14 Hz), 7.45 (1H, s), 6.48-6.11 (tt, 1H, *J* = 3.7 Hz, *J* = 55 Hz), 4.33 (td, 2H, *J* = 3.7 Hz, *J* = 14.2 Hz); ¹³C NMR (125 MHz, acetone *d*₆) δ 157.6, 134.7, 134.6, 132.3, 130.4, 128.4, 114.9 (t, *J* = 240 Hz), 73.1 (*J* = 27 Hz); ¹⁹F NMR (470 MHz, acetone *d*₆) δ -127.2 (dt, *J* = 3.2 Hz, *J* = 54.5 Hz); HRMS calcd for C₈H₇BCl₂F₂O₃ (M - H) 268.9755, found 268.9758; IR (KBr, cm⁻¹) 3480, 3375, 1445, 1402, 1375, 1325, 1225, 1135, 1082, 1005, 932, 902, 873, 799; HPLC: Zorbax Eclipse XDB-C8 4.6 mm x 25 cm column; eluants: A 0.1% aqueous H₃PO₄; B acetonitrile; 1.8 mL/min; gradient: A/B 90:10 to 10:90 over 15 min; λ = 220 nm; temperature 35 °C; *t*_R: **6** = 10.4 min.

2,5-dibromo-3-nitropyridine (14). 5-Bromo-3-nitropyridin-2-ol **10** (4.50 kg, 20.55 mol) was suspended in toluene (11.25 L) and the mixture was stirred for 5 min to partially dissolve the material. With stirring, DMF (158.8 mL, 2.05 mol) was added. The nitrogen outlet of the reaction apparatus was connected to a scrub column containing aqueous NaOH. The reaction mixture was protected from light with aluminum foil and heated to 90 °C. A solution of phosphorus oxybromide (7.07 kg, 24.66 mol) in toluene (11.25 L) was added to the solution of **10** over 1.5 h. The reaction mixture was stirred at 90 °C for 15 h and then cooled to rt. Toluene (22.5 L) and H₂O (45 L) were added and the layers were separated. The organic layer was washed with aqueous 1N NaOH (2 x 45 L) and H₂O (22.5 L). The batch was concentrated under reduced pressure (45 °C), flushed with toluene (2 x 4.5 L), flushed with propionitrile (9 L) and concentrated to a yellow solid. HPLC assay indicated 5.31 kg of dibromopyridine **14**, 92% yield: mp: 95-97 °C; ¹H NMR (400 MHz, acetone-*d*₆) δ 8.86 (d, 1H, *J* = 2.2 Hz), 8.70 (d, 1H, *J* = 2.2 Hz); ¹³C NMR (100 MHz, acetone-*d*₆) δ 154.6, 148.3, 137.2, 131.9, 120.3; HRMS (ES) calcd for C₅H₂Br₂N₂O₂ (M + Ag⁺) 386.7534, found 386.7550; IR (NaCl thin film, cm⁻¹) 3120,

3072, 1566, 1547, 1522, 1422, 1367, 1349, 1335, 1226, 1051; HPLC: Zorbax Rx-C8 4.6 mm x 25.0 cm column; eluents: A 0.1% aqueous H₃PO₄; B acetonitrile; 2 mL/min; gradient: A/B 70:30 to 5:95 over 25 min; λ = 220 nm; temperature 35 °C; t_R : hydroxy pyridine **10** = 2.24 min; dibromopyridine **14** = 8.58 min.

5-bromo-3-nitropyridine-2-carbonitrile (15). 2,5-Dibromo-3-nitropyridine **14** (5.92 assay kg, 20.99 mol) was suspended in propionitrile (17.4 L, starting material contained 3.6 L of solvent by ¹H NMR analysis) and copper cyanide (2.07 kg, 23.09 mol) was added. The reaction mixture was stirred at 90 °C for 17 h and cooled to rt. IPAc (60 L) and saturated aqueous sodium chloride (40 L, 26 wt%) was added. The mixture was stirred for 15 min and the layers were separated. The organic layer was washed with saturated aqueous sodium chloride (26 wt%, 3 x 30 L, 1 x 20 L) and half saturated aqueous sodium chloride (13 wt%, 30 L). For each wash the mixture was stirred for 15 min and the emulsions were kept in the aqueous layer. The batch was concentrated under reduced pressure, flushed with IPAc (10 L) and flushed with DMF (5.9 L) to yield a dark brown solution. HPLC analysis indicated 4.51 assay kg of **15**, 94% yield. An analytically pure sample was obtained by following chromatography: mp 110-112 °C; ¹H NMR (400 MHz, acetone-*d*₆) δ 9.27 (d, 1H, J = 1.9 Hz), 9.11 (d, 1H, J = 2.0 Hz); ¹³C NMR (125 MHz, acetone-*d*₆) δ 156.0, 147.0, 136.2, 126.5, 124.6, 114.2; HRMS (ES) calcd for C₆H₂BrN₃O₂ (M + Ag⁺) 333.8381, found 333.8372; IR (NaCl thin film, cm⁻¹) 3113, 3076, 2247, 1589, 1551, 1529, 1434, 1380, 1351, 1111, 1100; HPLC: Zorbax Rx-C8 4.6 mm x 25.0 cm column; eluents: A 0.1% aqueous H₃PO₄; B acetonitrile; 2 mL/min; gradient: A/B 70:30 to 5:95 over 25 min; λ = 220 nm; temperature 35 °C; t_R : **15** = 6.14 min.

N-((1R)-1-{5-[3,5-dichloro-2-(2,2-difluoroethoxy)phenyl]-3-fluoropyridin-2-yl}ethyl)acetamide (26). A 50 L round-bottom flask was charged with bromo pyridine **7** (2.57 kg, 9.8 mol) and THF (13 L). The solution was degassed with N₂. Boronic acid **6** (3.73 kg, 13.8 mol), triphenylphosphine (165.2 g, 0.63 mol) and palladium acetate trimer (70.7 g, 0.315 mol) were added. The solution was aged for 15 min under a nitrogen atmosphere. A pre-degassed 2M K₃PO₄ solution (6.15 L, 12.5 mol) was added to the mixture. The biphasic solution was heated to reflux (67 °C) under N₂ atmosphere and maintained at this temperature for 50 min. HPLC analysis indicated >99.9% conversion to the biaryl amide **26**. The mixture was cooled to 25 °C, the layers separated and the organic layer was washed with a ¾ saturated NaCl solution (13 L). The THF solution of biaryl amide was used directly in the hydrolysis step. The HPLC assay yield of biaryl amide **26** was 3.87 kg (96.6%): mp 100.8-101.6 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.43 (s, 1 H), 7.57 (d, 1H, J = 10.0 Hz), 7.42 (d, 1H, J = 2.3 Hz), 7.23 (d, 1H, J = 2.4 Hz), 7.02 (d, 1H, J = 7.1 Hz), 5.75 (tt, 1H, J = 3.8, 54.8 Hz), 5.50-5.46 (m, 1 H), 3.86-3.80 (td, 2H, J = 3.9, 13.3 Hz); 2.02 (s, 3 H); 1.43 (d, 3H, J = 6.7 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 169.0, 155.3 (d, J = 259 Hz), 150.0, 149.0 (d, J = 16 Hz), 144.0 (d, J = 4.9 Hz), 132.6, 131.7 (d, J = 3.8 Hz), 130.7, 130.4, 129.2, 128.8, 123.7 (d, J = 20 Hz), 112.6 (t, J = 242 Hz), 71.4 (t, J = 29 Hz), 44.0, 23.2, 21.2; ¹⁹F NMR (377 MHz, CDCl₃) δ -130.8 (dt, J = 13.4, 54.8 Hz), -131.2 (d, J = 7.0 Hz); HRMS calcd for C₁₇H₁₆Cl₂F₃N₂O₂ (M + H⁺) 407.0541, found 407.0539; IR (neat, cm⁻¹) 3405, 3289, 3065, 2984, 2938, 1660, 1517, 1448, 1374, 1073; $[\alpha]_D^{20}$ +0.91° (c 0.01, MeOH); HPLC: Zorbax Rx-SB-C8 4.6 mm x 25 cm column; eluants: A 0.1% aqueous H₃PO₄; B acetonitrile; 1.8 mL/min; gradient: A/B 90:10 to 10:90 over 15 min; λ = 220 nm; temperature 35 °C; t_R : **26** = 11.3 min.

((1R)-1-{5-[3,5-dichloro-2-(2,2-difluoroethoxy)phenyl]-3-fluoropyridin-2-yl}ethyl)amine (2).

A 50 L round-bottom flask was charged with crude biaryl amide **26** (3.87 kg, 9.5 mol) as a solution in THF (13 L). With stirring, 6N HCl (7.9 L, 47.4 mol) was added over a period of 5 min. The solution was heated to reflux (67 °C) under a nitrogen atmosphere and maintained at this temperature for 15 h, to give 99.8% conversion to amine **2** by HPLC. The mixture was cooled to 25 °C. The THF was removed under reduce pressure and the residue was dissolved in water (48 L) and heptane/MTBE (1/1 v/v, 40 L). The layers were separated and the aqueous layer was washed with heptane/MTBE (1/1 v/v, 20 L). 2-Methyl-THF (40 L) was added to the aqueous layer and the pH was adjusted to 12.5 using 10N NaOH. The layers were separated and the aqueous layer was back extracted with 2-methyl-THF (20 L). The organic layers were combined and concentrated under reduce pressure. The HPLC assay yield of biaryl amine **2** was 3.30 kg (95.2%) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1 H), 7.39 (d, 1H, *J* = 10.5 Hz), 7.24 (d, 1H, *J* = 2.3 Hz), 7.09 (d, 1H, *J* = 2.3 Hz), 5.62 (tt, 1H, *J* = 3.9, 55.1 Hz), 4.27 (q, 1H, *J* = 6.5 Hz), 3.67 (td, 2H, *J* = 2.0, 13.2 Hz), 1.66 (s, 2 H); 1.24 (d, 3H, *J* = 6.7 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 155.2 (d, *J* = 257 Hz), 153.3 (d, *J* = 14.8 Hz), 149.8, 143.9 (d, *J* = 4.8 Hz), 132.6, 130.6 (d, *J* = 3.8 Hz), 130.2, 129.7, 128.8, 128.5, 122.8 (d, *J* = 20.7 Hz), 112.4 (t, *J* = 242 Hz), 71.0 (t, *J* = 28.9 Hz), 45.8, 23.0; ¹⁹F NMR (377 MHz, CDCl₃) δ -130.3 (dt, *J* = 13.2, 54.9 Hz), -131.9 (d, *J* = 10.3 Hz); HRMS (FAB⁺) calcd for C₁₅H₁₄Cl₂F₃N₂O (M + H) 365.0435, found 365.0434; IR (neat, cm⁻¹) 3372, 3297, 2976, 2938, 1552, 1448, 1409, 1378, 1073; [α]_D²⁰ +1.4° (c 0.0101, CH₂Cl₂); HPLC: Zorbax Rx-SB-C8 4.6 mm x 25 cm column; eluants: A 0.1% aqueous H₃PO₄; B acetonitrile; 1.8 mL/min; gradient: A/B 90:10 to 10:90 over 15 min; λ = 220 nm; temperature 35 °C; *t*_R: **2** = 7.55 min.

((1R)-1-{5-[3,5-Dichloro-2-(2,2-difluoroethoxy)phenyl]-3-fluoropyridin-2-yl}ethyl)ammonium (S)-mandelate (27).

A 50 L round-bottom flask was charged with (S)-mandelic acid (1.45 kg, 9.5 mol), 2-propanol (9 L) and water (900 mL). The batch was heated to 75 °C and a solution of amine **2** (3.30 kg, 9.03 mol) in 2-propanol (9 L) and water (900 mL) was added over 60 min. The batch was heated at 75 °C for 30 min after which the slurry was allowed cool to rt over 16 h. The slurry was filtered and the solids were washed with 2-propanol / water (2 x 9 L, 10:1 v/v) and MTBE (2 x 9 L). The solids were dried on the frit for 6 h. Mandelate salt **27** was obtained as tan needles. HPLC assay : 3.84 kg, 82% yield: mp 183-184 °C, ¹H NMR (400 MHz, CD₃OD) δ 8.65 (d, 1H, *J* = 1.2 Hz), 7.92 (dd, 1H, *J* = 1.6, 10.8 Hz), 7.67 (d, 1H, *J* = 2.4 Hz), 7.46-7.51 (m, 3H), 7.28-7.32 (m, 2H), 7.21-7.25 (m, 1H), 5.90 (tt, 1H, *J* = 3.6, 51.2 Hz), 4.91 (m, 1H), 4.89 (m, 1H), 3.97 (td, 2H, *J* = 1.6, 12 Hz), 3.33, (m, 1H), 1.63 (d, 3H, *J* = 6.8 Hz); ¹³C NMR (125 MHz, CD₃OD) δ 179.3, 157.1 (*J* = 256 Hz), 152.0, 146.5 (*J* = 5.2 Hz), 146.3, 143.4, 135.1 (*J* = 4.2 Hz), 134.2, 131.9 (*J* = 5.1 Hz), 130.6 (*J* = 3.3 Hz), 129.0, 128.3, 127.9, 125.9 (*J* = 19.7 Hz), 114.7 (*J* = 239 Hz), 76.1, 72.8, 47.0, 19.5; ¹⁹F NMR (450 MHz, CD₃OD) δ -125.2, -126.1; HRMS calcd for C₁₅H₁₃Cl₂F₃N₂O [M + H]⁺ 365.0435, found 365.0437; IR (cm⁻¹) 3421, 3062, 2980, 1615, 1445, 1374, 1234, 1061; [α]_D²⁰ + 17.8 (c = 1.07, MeOH); HPLC: Zorbax Rx-SB-C8 4.6 mm x 25.0 cm column; eluents: A 0.1% aqueous H₃PO₄; B acetonitrile; 2 mL/min; gradient: A/B 90:10 to 10:90 over 15 min; λ = 220 nm; temperature 35 °C; *t*_R: mandelic acid 3.95 min; *t*_R: amine **2** = 7.55 min.

3-Methoxyisoxazole-5-carboxylic acid (32). A 20 L round-bottom flask was charged with methyl 3-hydroxyisoxazole-5-carboxylate **30** (2.0 kg, 13.98 mol) and DMF (6 L). The batch was cooled to -5 °C and K₂CO₃ (2.12 kg, 15.37 mol) was added in portions over 15 min to minimize

foaming. Dimethyl sulfate (1.47 L, 15.37 mol) was added over 30 min. The batch was let stir at $-5\text{ }^{\circ}\text{C}$ for 1 h. *An unexpected and potentially hazardous exotherm was observed after addition of dimethyl sulfate.* The internal temperature rose from -5 to $41\text{ }^{\circ}\text{C}$ in 15 min.. This exotherm was never observed on 20 g scale. Typically the internal temperature went from $-5\text{ }^{\circ}\text{C}$ to $5\text{ }^{\circ}\text{C}$ at most. The ratio of *O*- vs *N*- alkylation was 85:15. HPLC showed 99% conversion to methyl 3-methoxyisoxazole 5-carboxylate **31**. A pure sample (solid) was obtained by chromatography: mp $78\text{--}79\text{ }^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 6.55 (s, 1H), 4.10 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.9, 160.2, 157.0, 100.5, 57.4, 52.7; HRMS (ES) calcd for $\text{C}_6\text{H}_8\text{NO}_4$ $[\text{M} + \text{H}]^+$ 158.0453, found 158.0448; IR (thin film, cm^{-1}) 3141, 1753, 1611, 1520, 1415, 1317, 1231. HPLC: Zorbax Rx-C8 4.6 mm x 25 cm column; eluants: A 0.1% aqueous H_3PO_4 ; B acetonitrile; 1.8 mL/min; gradient: A/B 70:30 to 5:95 over 25 min; $\lambda = 220\text{ nm}$; temperature $35\text{ }^{\circ}\text{C}$; t_{R} : N-Me = 1.9 min; t_{R} : **31** O-Me = 4.2 min.

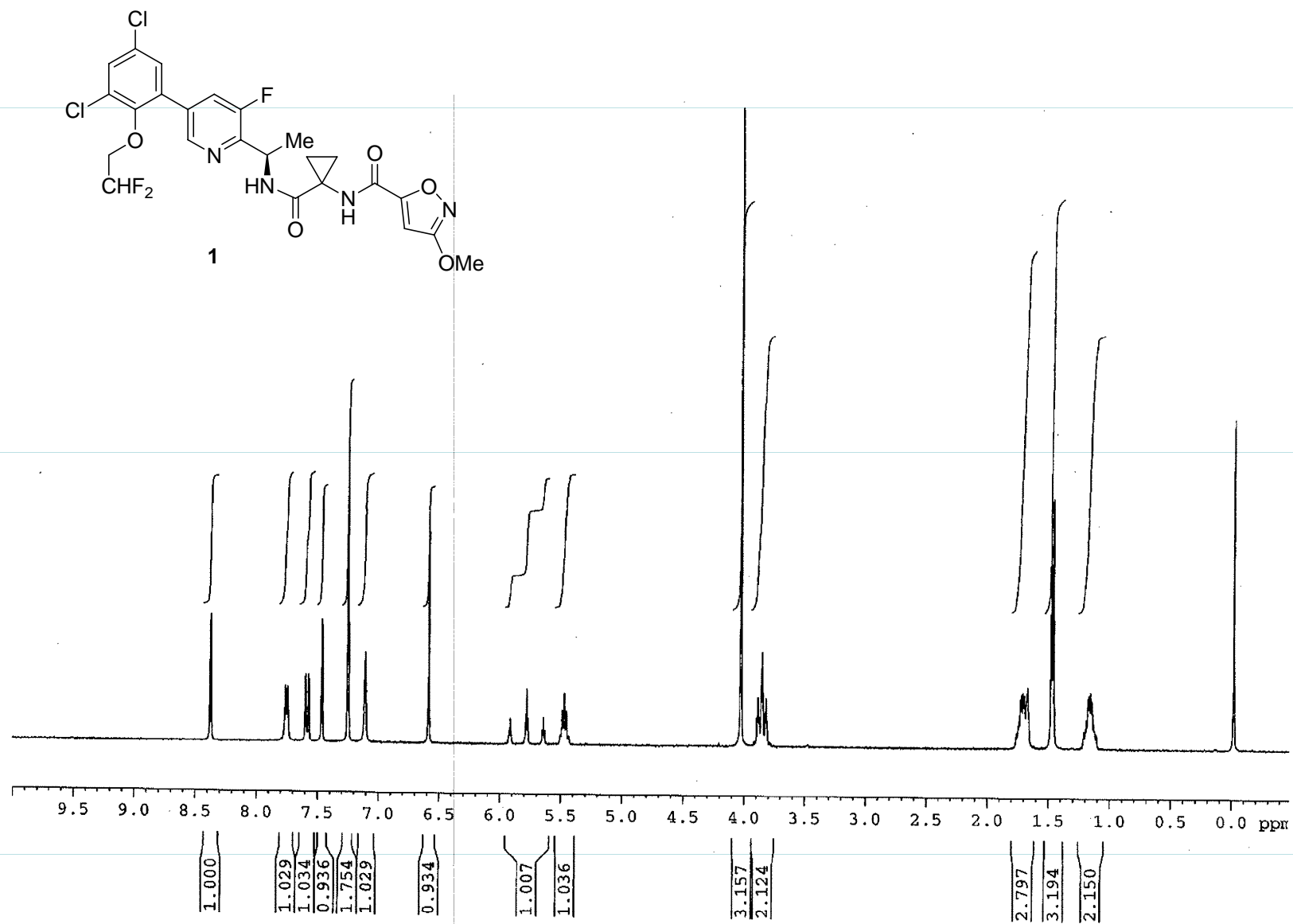
2N NaOH (10.48 L, 20.97 mol) was added to the DMF solution of **31** over 30 min. The batch was let stir at rt for 2 h after which time HPLC analysis indicated >99% conversion to acid salt. The batch was quenched into aqueous 2N HCl (13.98 L) over 30 min during which time gas evolution was observed. The batch was diluted with MTBE (20 L) and NaCl (2 kg) added. The layers were cut and the aqueous layer was extracted with MTBE (2 x 20 L). The batch was concentrated and flushed with toluene (5 L). HPLC assay yield **32**: 1.64 kg, 82% (over 2 steps). A pure sample (solid) was obtained by chromatography: mp $134\text{--}136\text{ }^{\circ}\text{C}$; ^1H NMR (400 MHz, acetone- d_6) δ 11.75 (s, 1H), 6.72 (s, 1H), 3.98 (s, 3H); ^{13}C NMR (125 MHz, acetone- d_6) δ 173.2, 162.0, 157.6, 101.0, 57.9; HRMS (ES) calcd for $\text{C}_5\text{H}_6\text{NO}_4$ $[\text{M} + \text{H}]^+$: 144.0299, found 144.0293; IR (thin film, cm^{-1}) 3418, 1734, 1612, 1525, 1414, 1316, 1238; HPLC: Zorbax Rx-C8 4.6 mm x 25.0 cm column; eluents: A 0.1% aqueous H_3PO_4 ; B acetonitrile; 2 mL/min; gradient: A/B 70:30 to 5:95 over 25 min; $\lambda = 220\text{ nm}$; temperature $35\text{ }^{\circ}\text{C}$; t_{R} : 3-methoxyisoxazole-5-carboxylic acid **32** = 1.85 min; t_{R} : ethyl-3-methoxyisoxazole-5-carboxylate **31**: = 4.24 min.

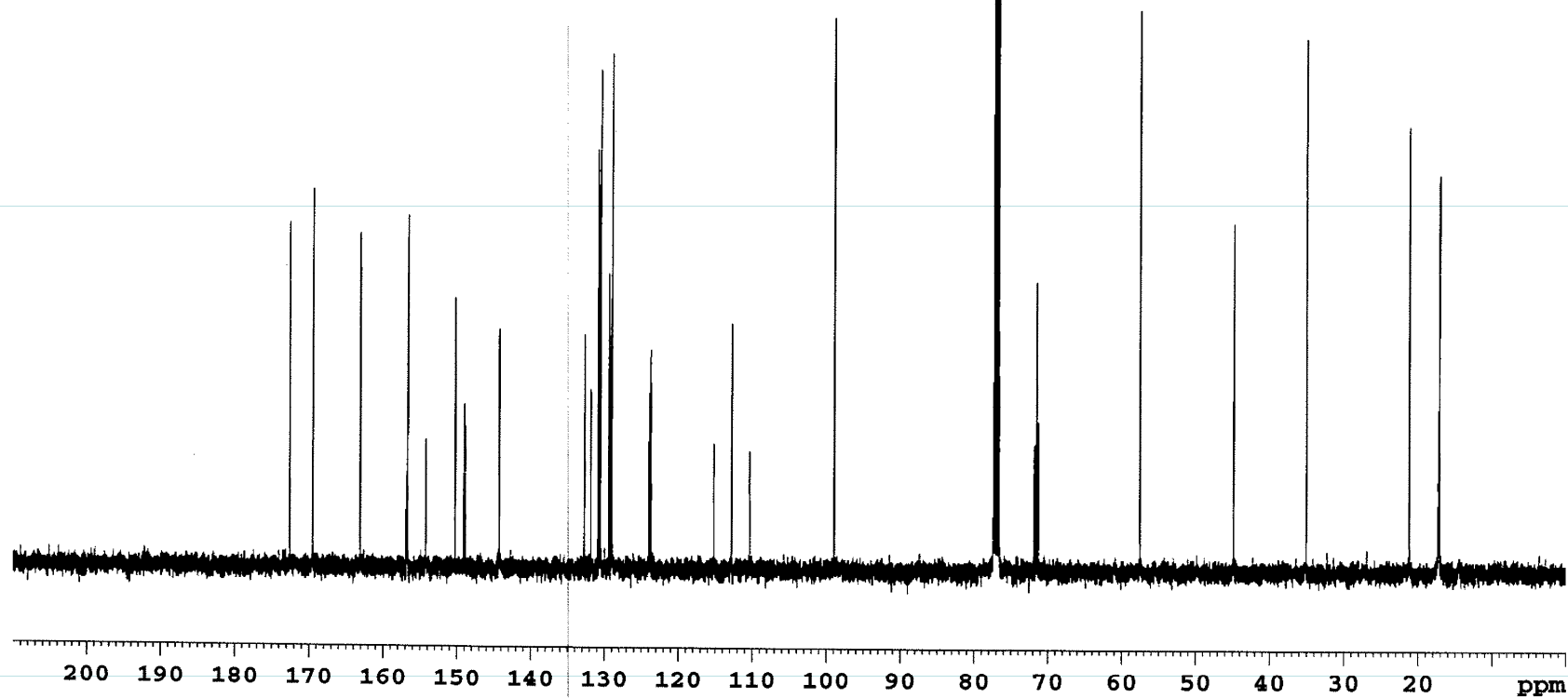
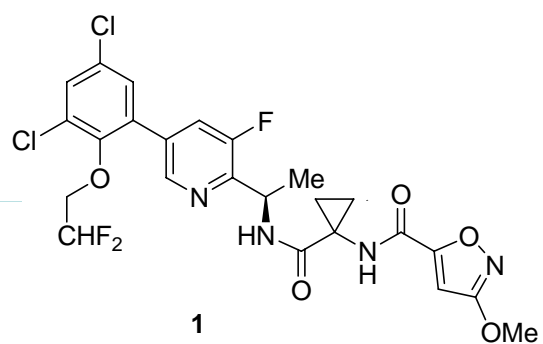
1-[(3-Methoxyisoxazol-5-yl)carbonyl]amino}cyclopropanecarboxylic acid (34**).** A 20 L round-bottom flask was charged with isoxazole acid **32** (900 g, 6.67 kg @ 13.5wt% in MTBE/toluene) and MTBE (3 L). Oxalyl chloride (649 mL, 6.92 mol) was added over 30 min and the batch was let stirred at rt for 1 h. HPLC showed > 99.8% conversion to acid chloride (monitored by quenching aliquot into anhydrous MeOH). In a separate 50 L round-bottom flask equipped with a mechanical stirrer, a thermocouple, a dropping funnel and a nitrogen inlet was charged K_2CO_3 (1.74 kg, 12.6 mol) and water (4.50 L). The solution was cooled to $0\text{--}5\text{ }^{\circ}\text{C}$ and amine hydrochloride **33** (1.15 kg, 7.56 mol) was added. The solution of acid chloride in MTBE was added over 1 h. HPLC showed > 99% conversion to dipeptide ester **34**. The batch was diluted with MeOH (1 L) to dissolve all materials, concentrated to remove volatiles and flushed with heptane (10 L) to remove residual MeOH. The slurry was filtered and the solids washed with water (2 x 2.5 L). Dipeptide ester **34** was obtained as an off-white solid. HPLC analysis showed 1.41 kg, 88% yield; mp $104.5\text{--}105.6\text{ }^{\circ}\text{C}$; ^1H NMR (400 MHz, acetone- d_6) δ 8.53 (bs, 1H), 6.59 (s, 1H), 4.1 (q, 2H, $J = 7.2\text{ Hz}$), 3.96 (s, 3H), 1.50 (dd, 2H, $J = 4.6, 8.2\text{ Hz}$), 1.25 (dd, 2H, $J = 4.6, 8.2\text{ Hz}$), 1.16 (t, 3H, $J = 7.2\text{ Hz}$); ^{13}C NMR (125 MHz, acetone- d_6) δ 173.4, 172.2, 165.1, 157.3, 98.1, 61.7, 57.8, 33.9, 17.4, 14.4; HRMS (ES) calcd for $\text{C}_{11}\text{H}_{15}\text{N}_2\text{O}_5$ $[\text{M} + \text{H}]^+$ 255.0981, found 255.0977; IR (thin film, cm^{-1}) 3293, 3167, 2984, 1727, 1666, 1528, 1186. HPLC: Zorbax Rx-C8 4.6 mm x 25 cm column; eluents: A 0.1% aqueous H_3PO_4 ; B acetonitrile;

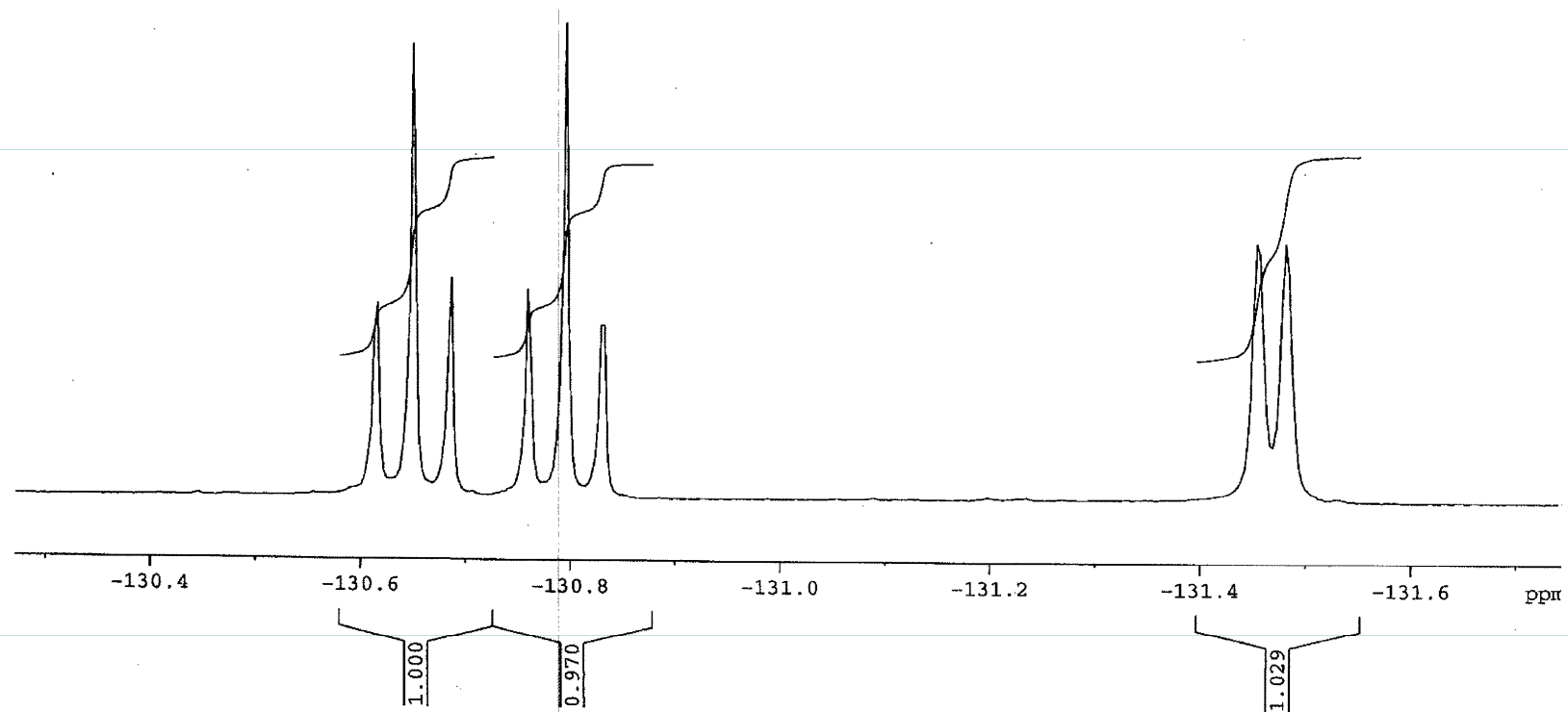
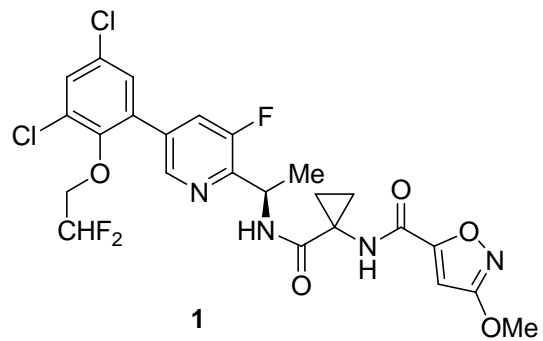
1.8 mL/min; gradient: A/B 70:30 to 5:95 over 25 min; λ = 220 nm; temperature 35 °C; t_R : **34** = 3.8 min.

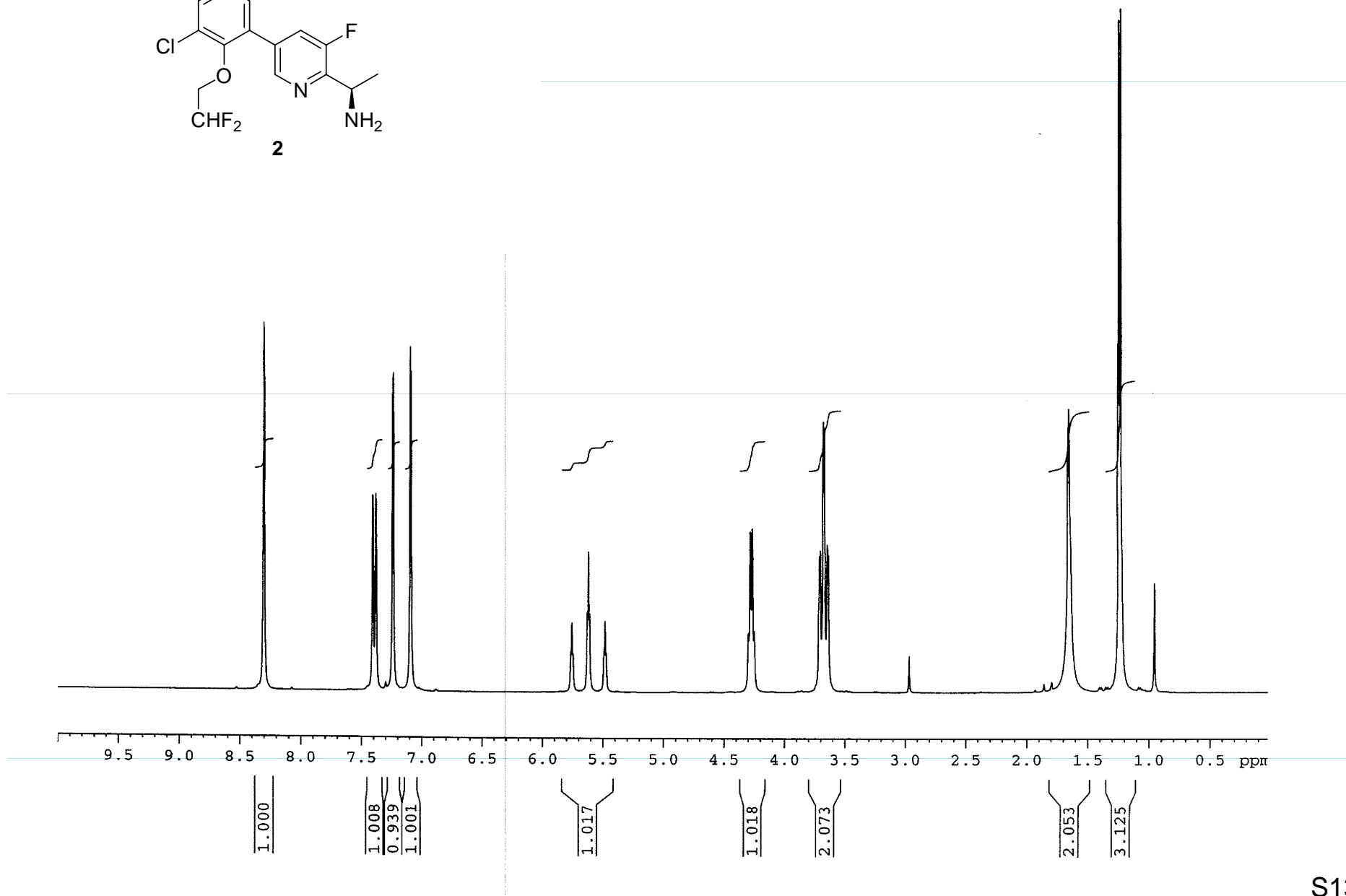
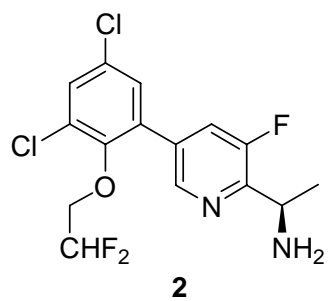
Solid **34** (1.41 kg, 1.55 kg @ 90.8wt%, 5.54 mol) was charged into a 20 L round-bottom flask. Methanol (7 L) was added, followed by 2N aqueous NaOH (4.2 L, 8.31 mol). The batch was stirred at rt for 2 h after which time HPLC indicated >99% conversion to dipeptide acid **3**. The batch was concentrated and flushed with heptane (10 L) to remove residual MeOH. The batch was acidified with aqueous 2N HCl (11.1 L, 2 eq) and the solids were filtered and washed with water (2 x 10 L). The batch was dried under vacuum at 30 °C for 24 h. Dipeptide acid **3** was obtained as a white solid. HPLC assay yield: 1.05 kg, 84% yield, 99.7wt%; mp 228-229 °C; ^1H NMR (400 MHz, acetone- d_6) δ 8.55 (bs, 1H), 8.04 (s, 1H), 6.63 (s, 1H), 4.0 (s, 3H), 1.57 (m, 2H), 1.31 (m, 2H); ^{13}C NMR (125 MHz, acetone- d_6) δ 173.1, 165.0, 157.2, 97.9, 79.0, 57.6, 33.3, 17.2; HRMS (ES) calcd for $\text{C}_9\text{H}_{11}\text{N}_2\text{O}_5$ $[\text{M} + \text{H}]^+$: 227.0668, found 227.0672; IR (thin film, cm^{-1}) 3314, 3108, 3092, 1702, 1666, 1534, 1446, 1331, 1209, 1109; HPLC: Zorbax Rx-C8 4.6 mm x 25.0 cm column; eluents: A 0.1% aqueous H_3PO_4 ; B acetonitrile; 2 mL/min; gradient: A/B 70:30 to 5:95 over 25 min; λ = 220 nm; temperature 35 °C; t_R : dipeptide acid **3** = 2.0 min, dipeptide ester **34** = 3.8 min.

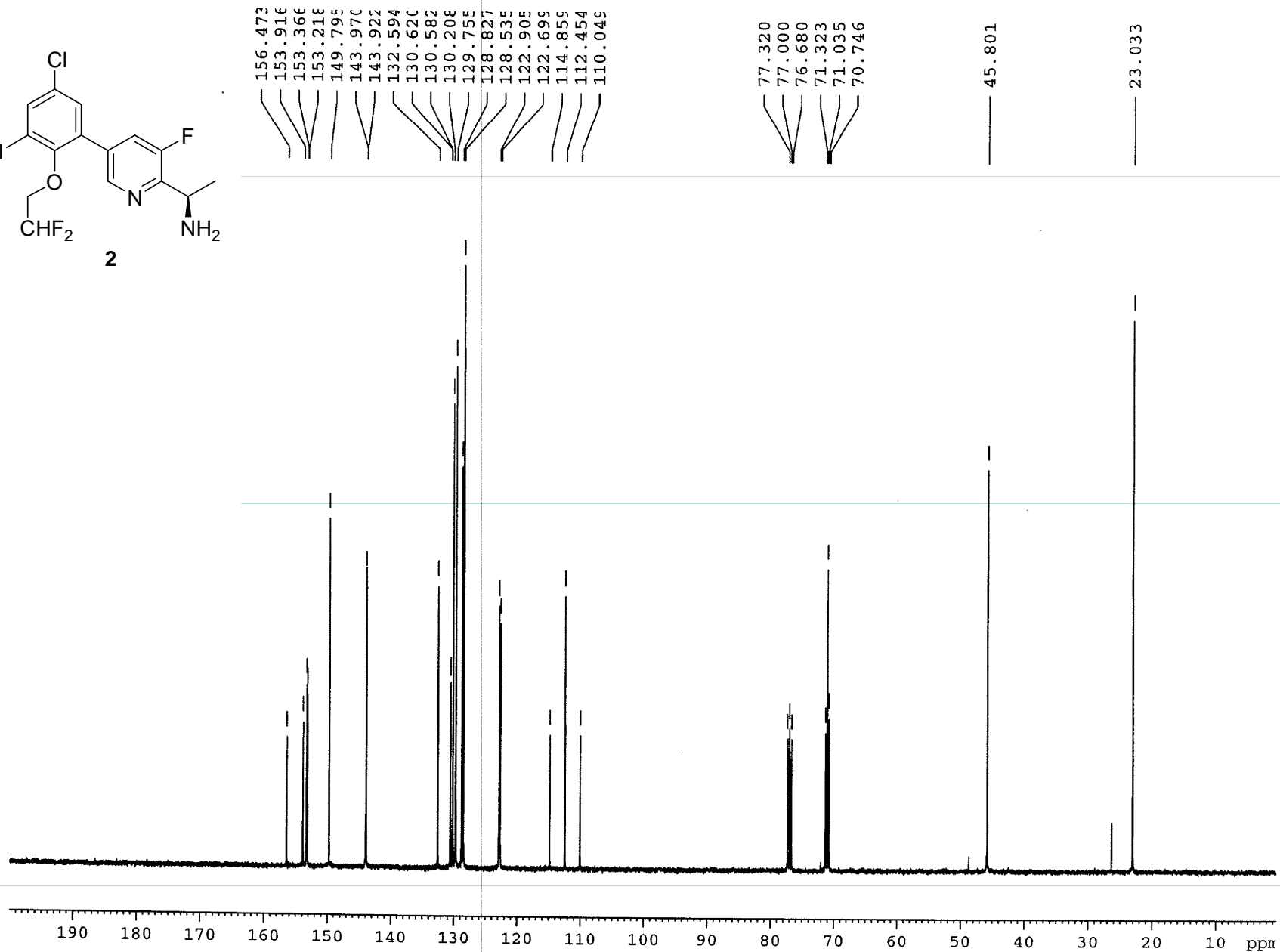
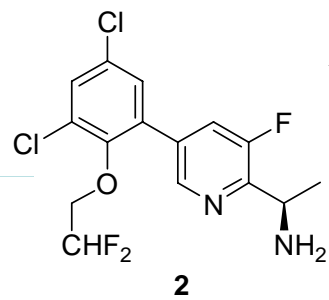
***N*-(1-[[[(1*R*)-1-{5-[3,5-dichloro-2-(2,2-difluoroethoxy)phenyl]-3-fluoropyridin-2-yl]ethyl]amino]carbonyl]cyclopropyl)-3-methoxyisoxazole-4-carboxamide (1).** Biaryl amine **2** (1.58 kg, 4.33 mol) was dissolved in DMF (7 L) and transferred to a 50 L round bottomed flask. DMF (3 x 100 mL) was used to rinse. The dipeptide acid **3** (1.03 kg, 4.55 mol) was added, followed by HOBT· H_2O (59.0 g, 0.433 mol) and *N*-methyl morpholine (0.501 L, 4.55 mol) giving an internal temperature of 24 °C. The reaction flask was placed in an ice water bath to control an exotherm as EDC·HCl (0.833 kg, 4.33 mol) was added in portions over 30 min maintaining the temperature below 32 °C. After aging 45 min, HPLC analysis indicated 100% conversion. Water (9.5 L) was added over 80 min with the mixture warming to 28 °C. After cooling to 20 °C over 30 min, the suspension was filtered and the cake was washed with DMF/water (5 x 4 L, 1:1 v/v) followed by water (3 x 8 L). The solids were dried under vacuum at 35 °C for 72 h to afford **1** as a solid, 2.39 kg, 96% yield, 99.9 wt%, >99.9% ee by HPLC: mp 200.1 – 200.9 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.35 (s, 1 H), 7.77 (d, 1 H, J = 7.4 Hz), 7.56 (dd, 1 H, J = 1.6, 10.1 Hz), 7.43 (d, 1 H, J = 2.5 Hz), 7.35 (s, 1 H), 7.22 (d, 1 H, J = 2.5 Hz), 6.55 (s, 1 H), 5.75 (tt, 1 H, J = 4.0, 55.0 Hz), 5.44 (quin, 1 H, J = 7.0 Hz), 3.99 (s, 3 H), 3.83 (tt, 2 H, J = 3.0, 13.6 Hz), 1.73-1.67 (m, 2 H), 1.43 (d, 3 H, J = 6.8 Hz), 1.19-1.09 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.6, 169.5, 163.1, 156.7, 155.5 (d, J = 259 Hz), 150.2, 148.92 (d, J = 15.8 Hz), 144.2 (d, J = 4.9 Hz), 132.7, 131.8 (d, J = 3.9 Hz), 130.9, 130.5, 129.4, 129.0, 123.8 (d, J = 20 Hz), 112.8 (t, J = 241 Hz), 99.0, 71.5 (t, J = 29.6 Hz), 57.5, 44.9, 35.1, 21.2, 17.2, 17.1; ^{19}F NMR (377 MHz, CDCl_3) δ -130.6 (t, 1F, J = 14.4 Hz), -130.8 (t, 1F, J = 14.4 Hz), -131.47 (d, 1F, J = 10.0 Hz); anal calcd for $\text{C}_{24}\text{H}_{21}\text{Cl}_2\text{F}_3\text{N}_4\text{O}_5$: C, 50.28; H, 3.69; N, 9.77, found: C, 50.03; H, 3.46; N, 9.72; HRMS (ESI) $[\text{M} + \text{H}]^+$ $\text{C}_{24}\text{H}_{21}\text{Cl}_2\text{F}_3\text{N}_4\text{O}_5$ 573.0913, found 573.0919; IR (film, cm^{-1}) 3431, 3202, 3059, 1683, 1650, 1513, 1442, 1409, 1374, 1068, 1024; $[\alpha]_D^{20}$ (c = 1.1, CHCl_3) = -26.0; HPLC: Ace-5-C18 4.6 mm x 25.0 cm column; eluents: A 0.1% aqueous H_3PO_4 ; B acetonitrile; 1 mL/min; gradient: A/B 65:45 to 10:90 over 30 min; λ = 210 nm; temperature 35 °C; t_R : **1** = 15.4 min.

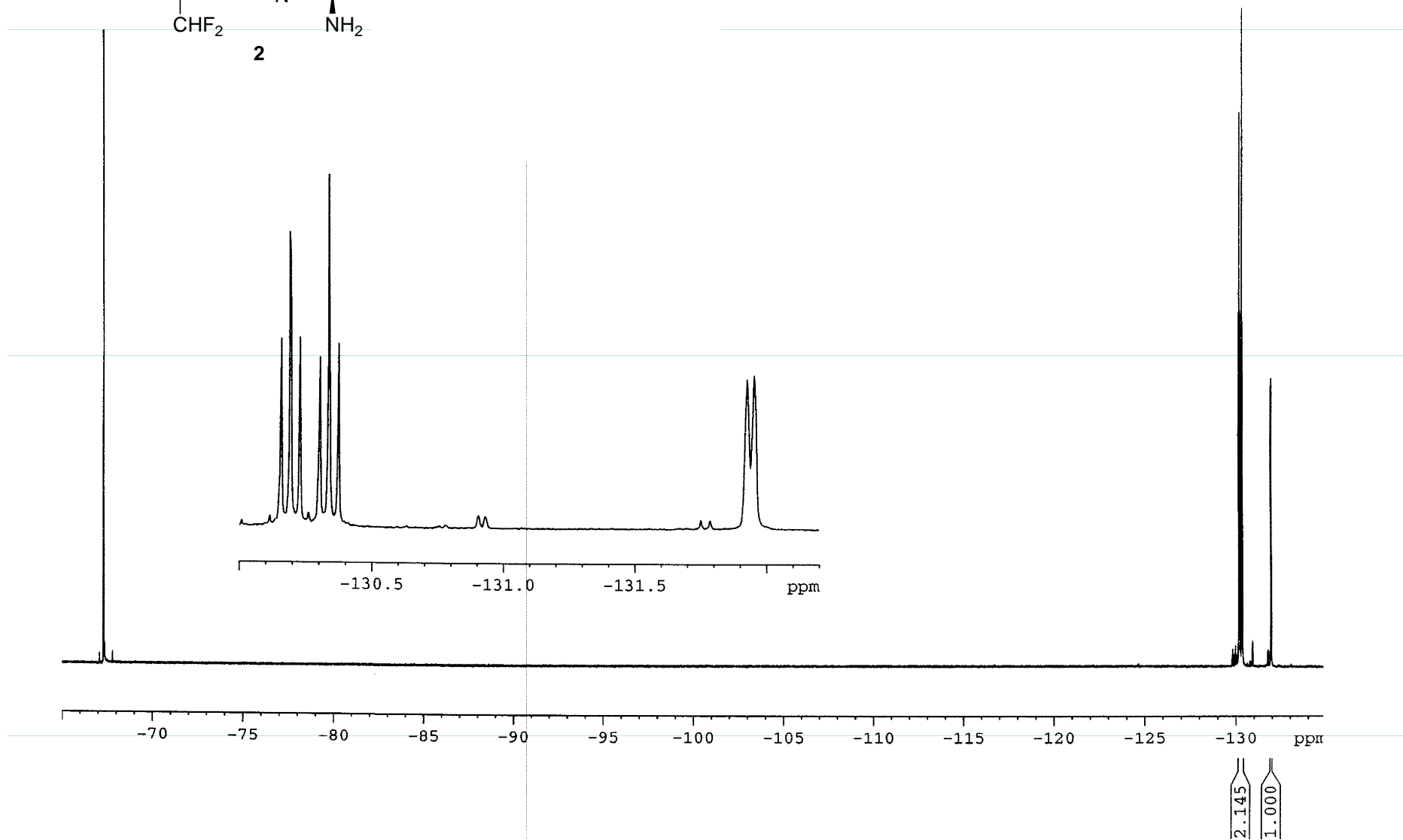
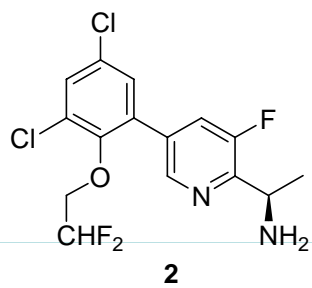


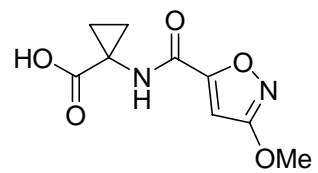




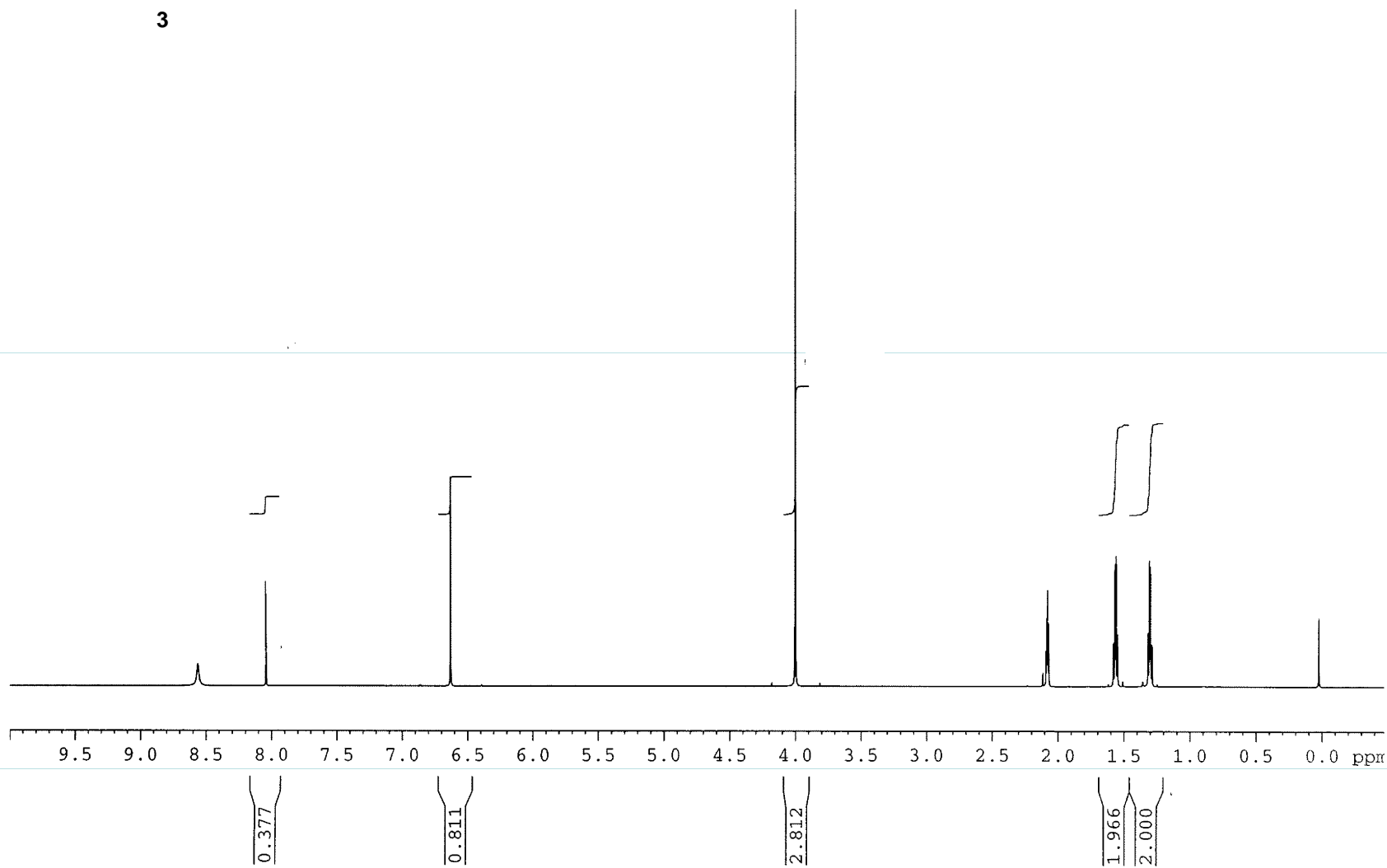


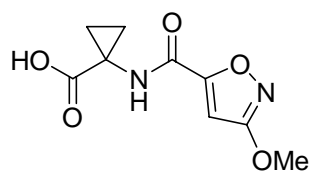




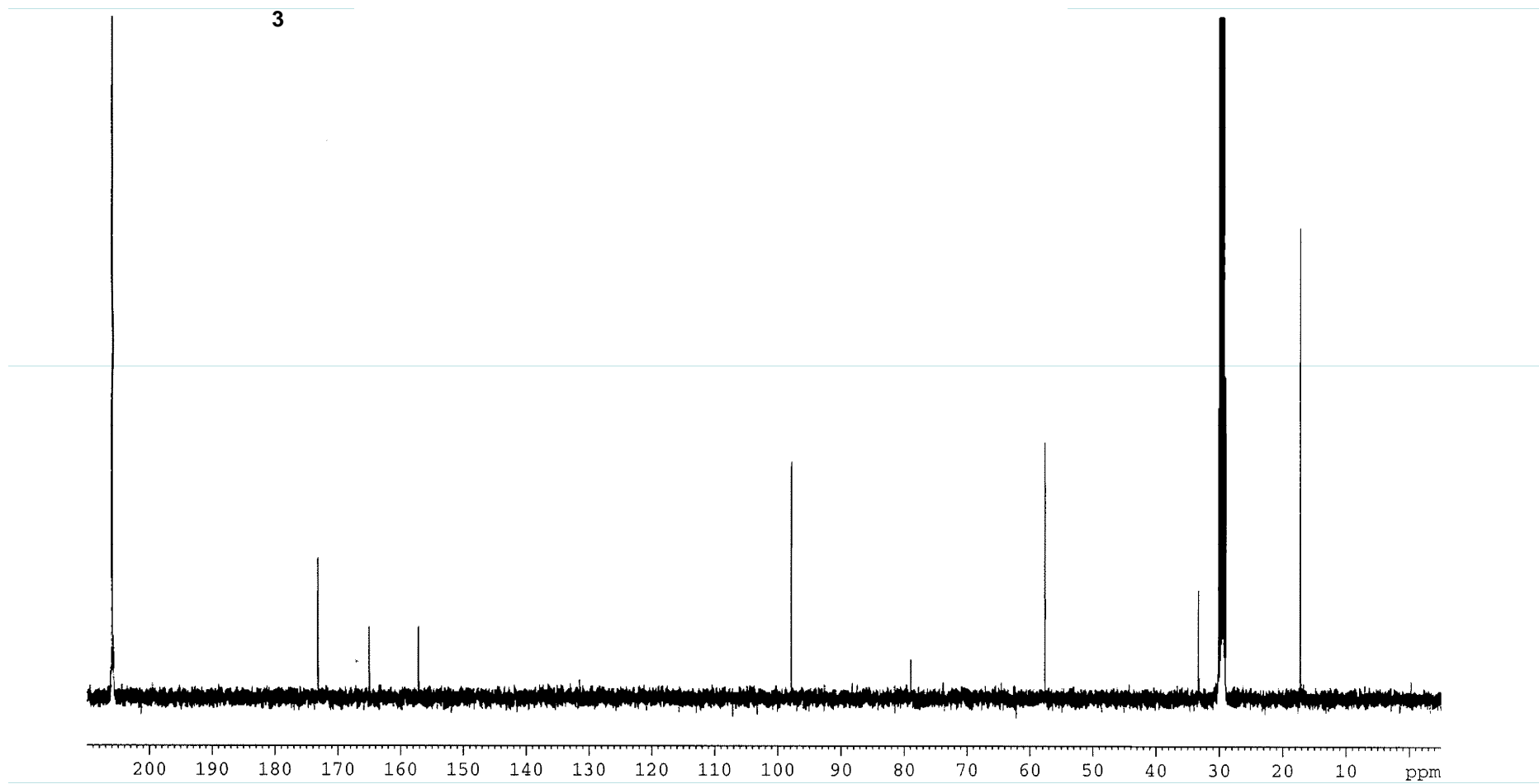


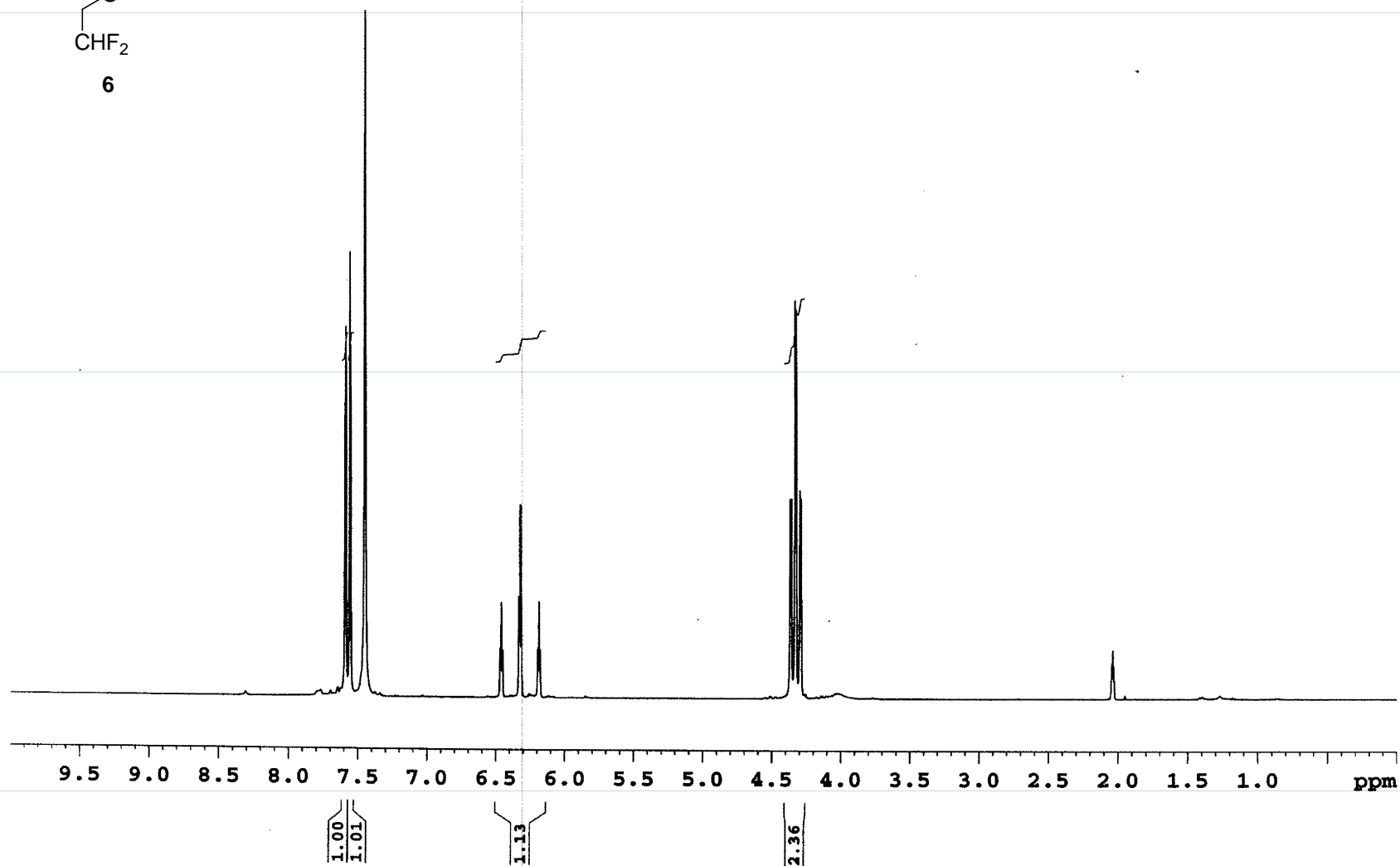
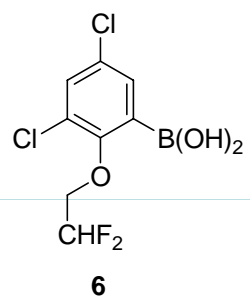
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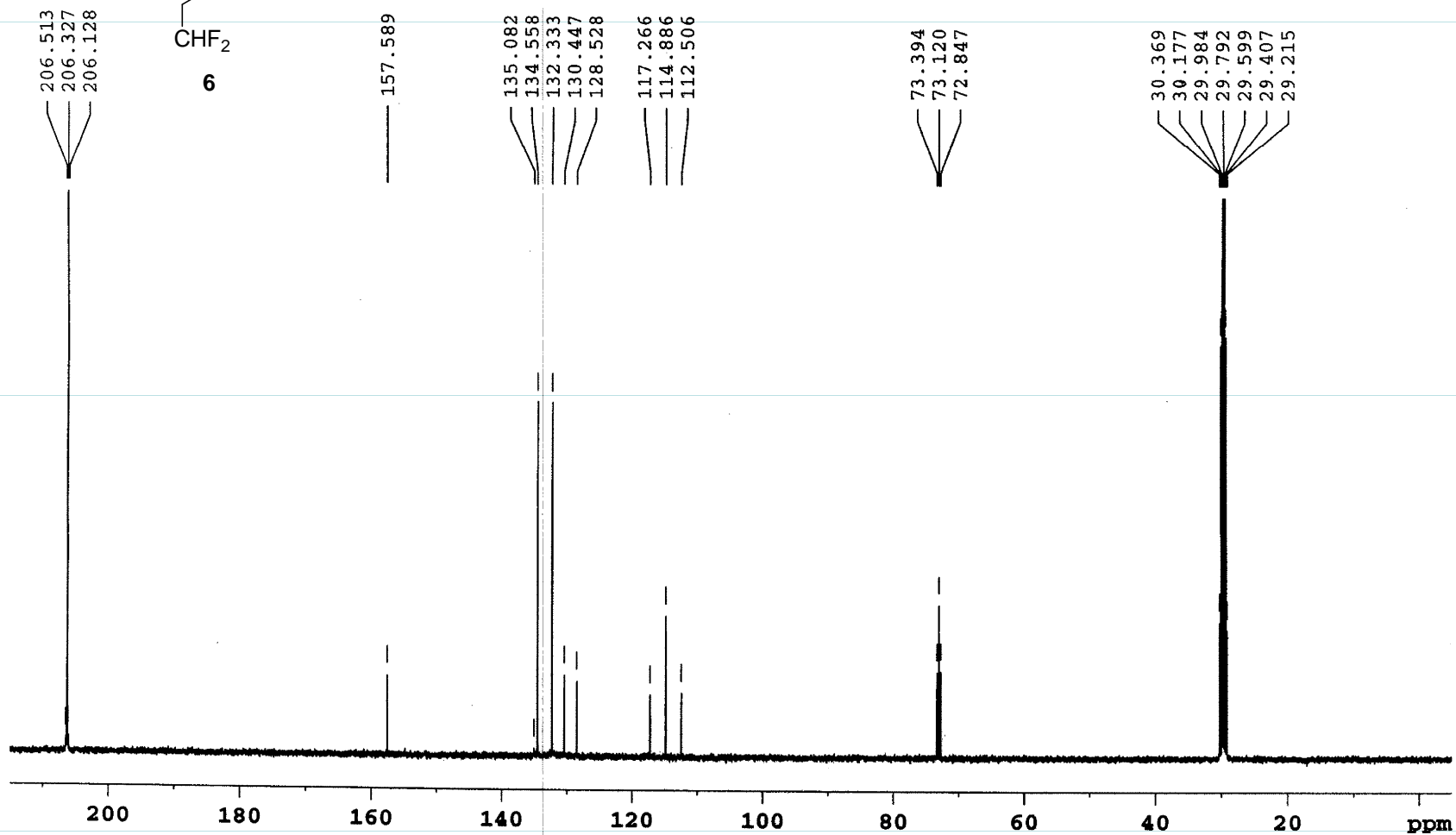
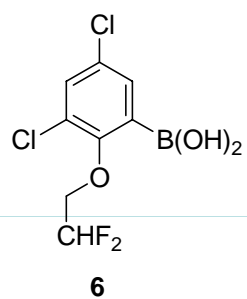


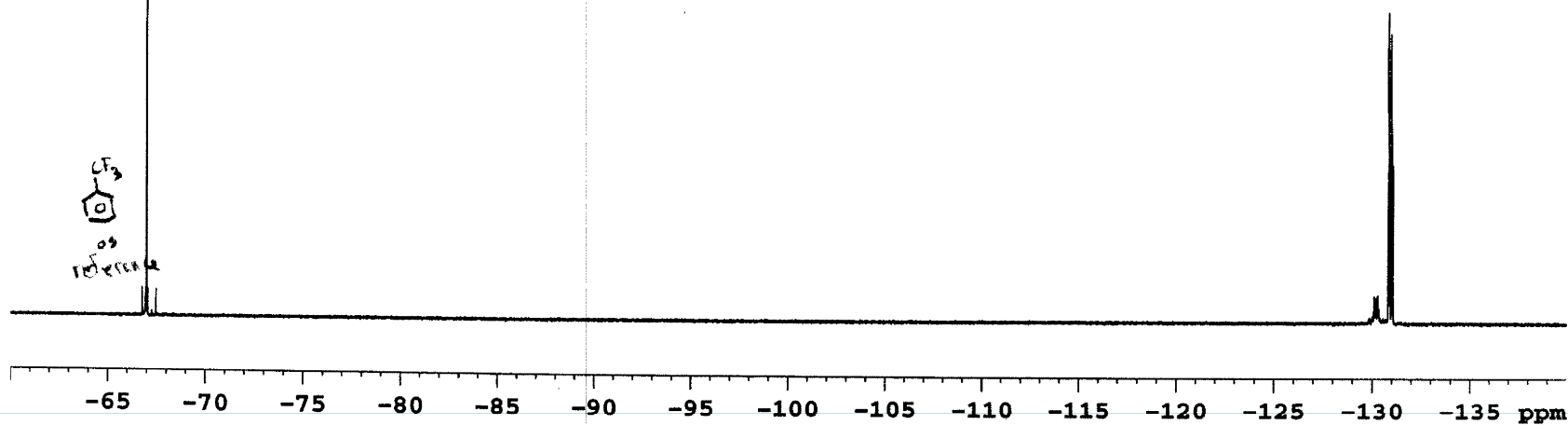
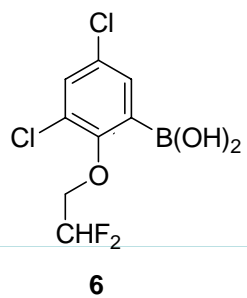


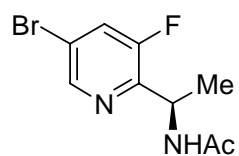
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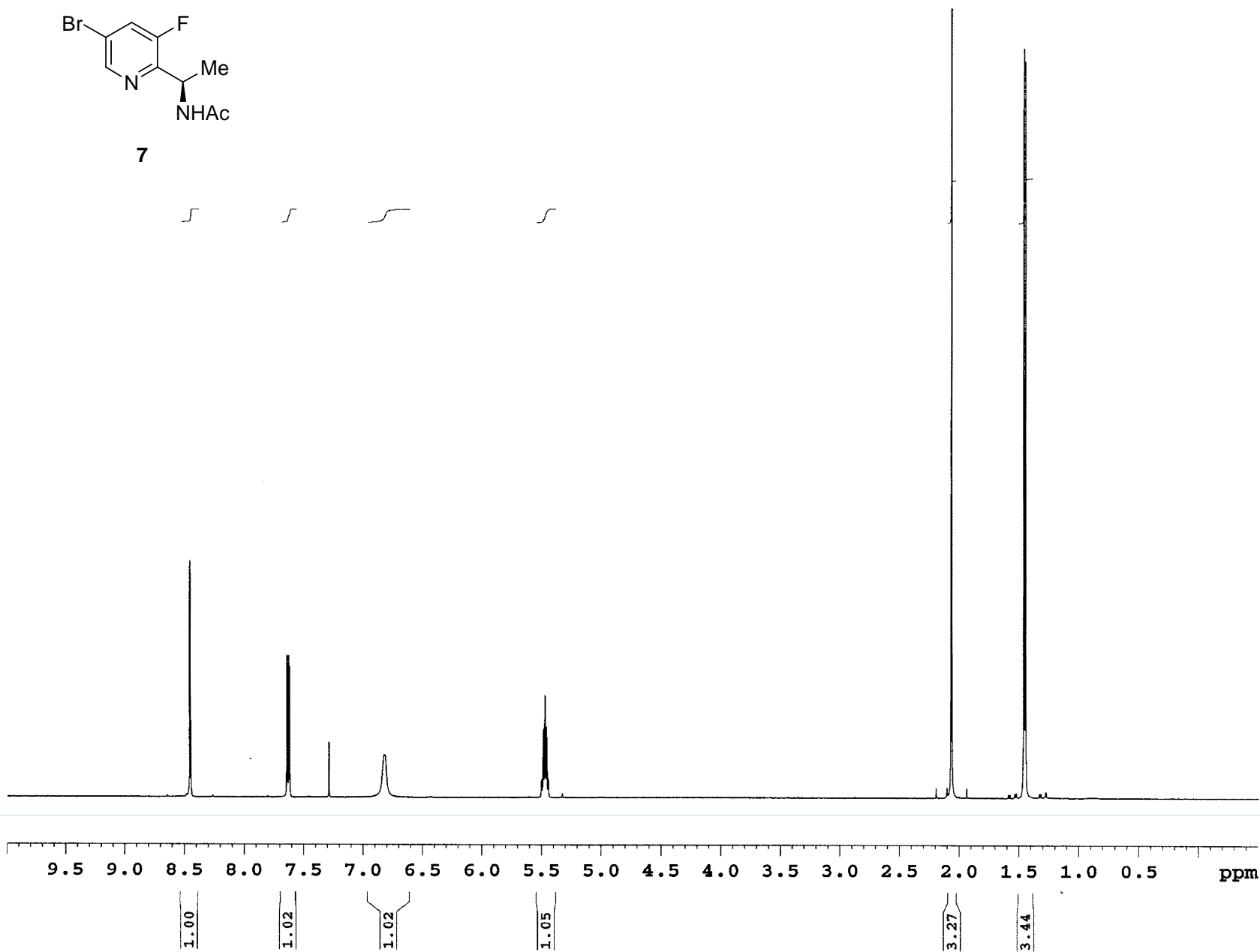


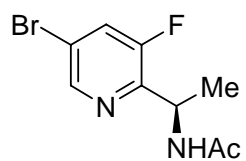




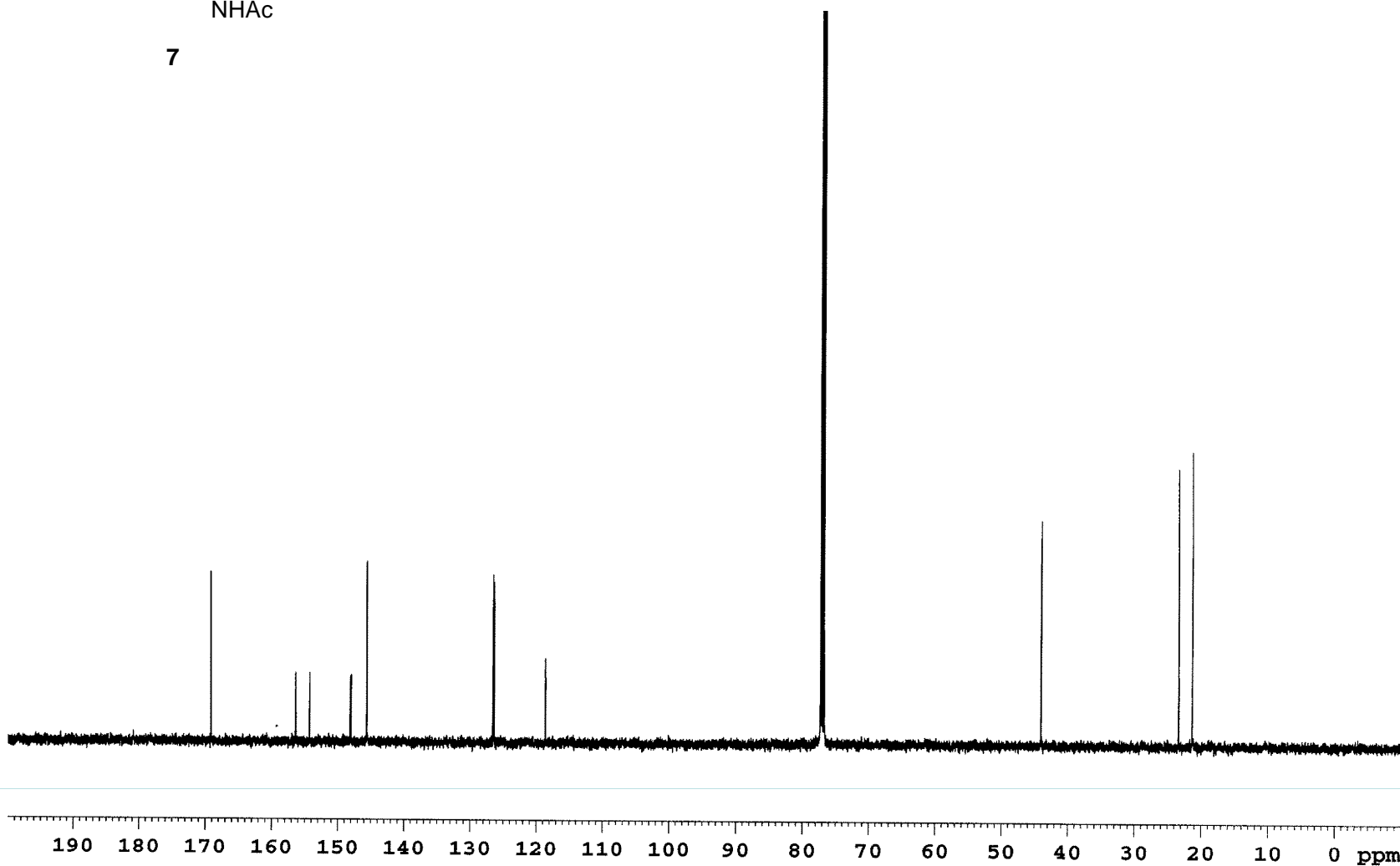


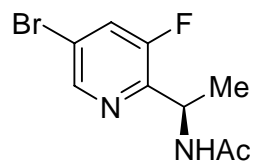
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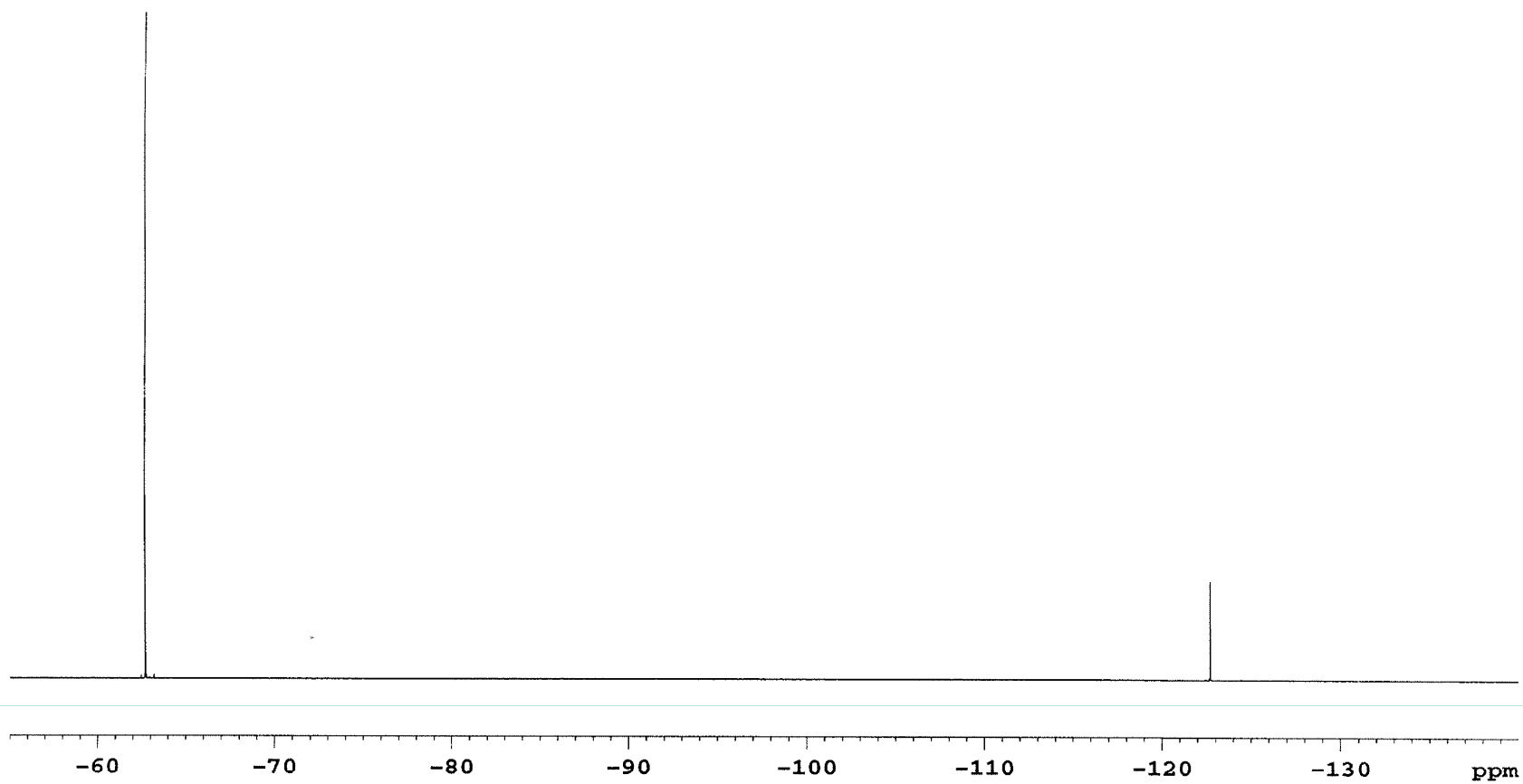


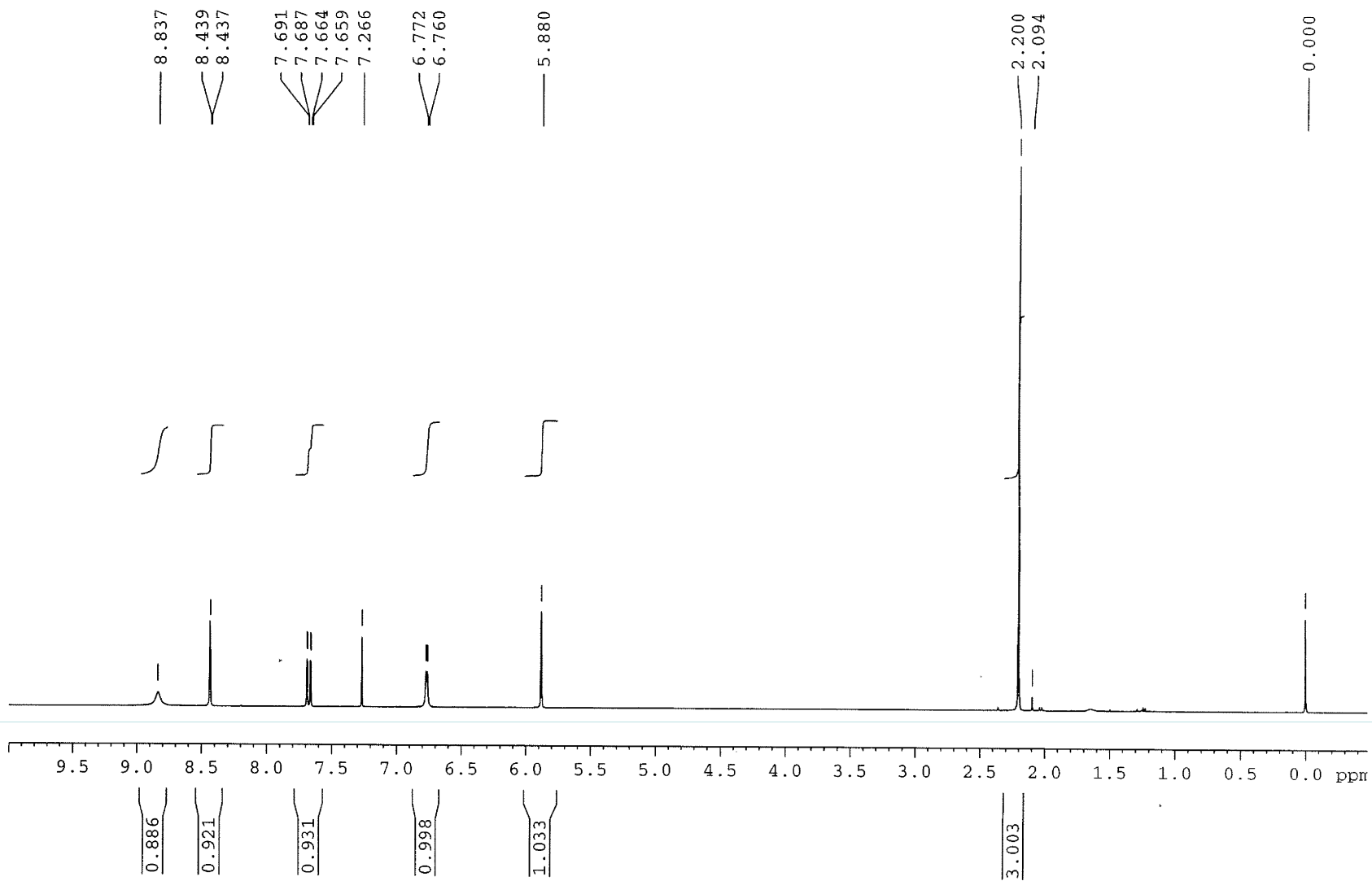
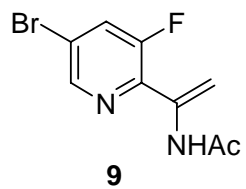
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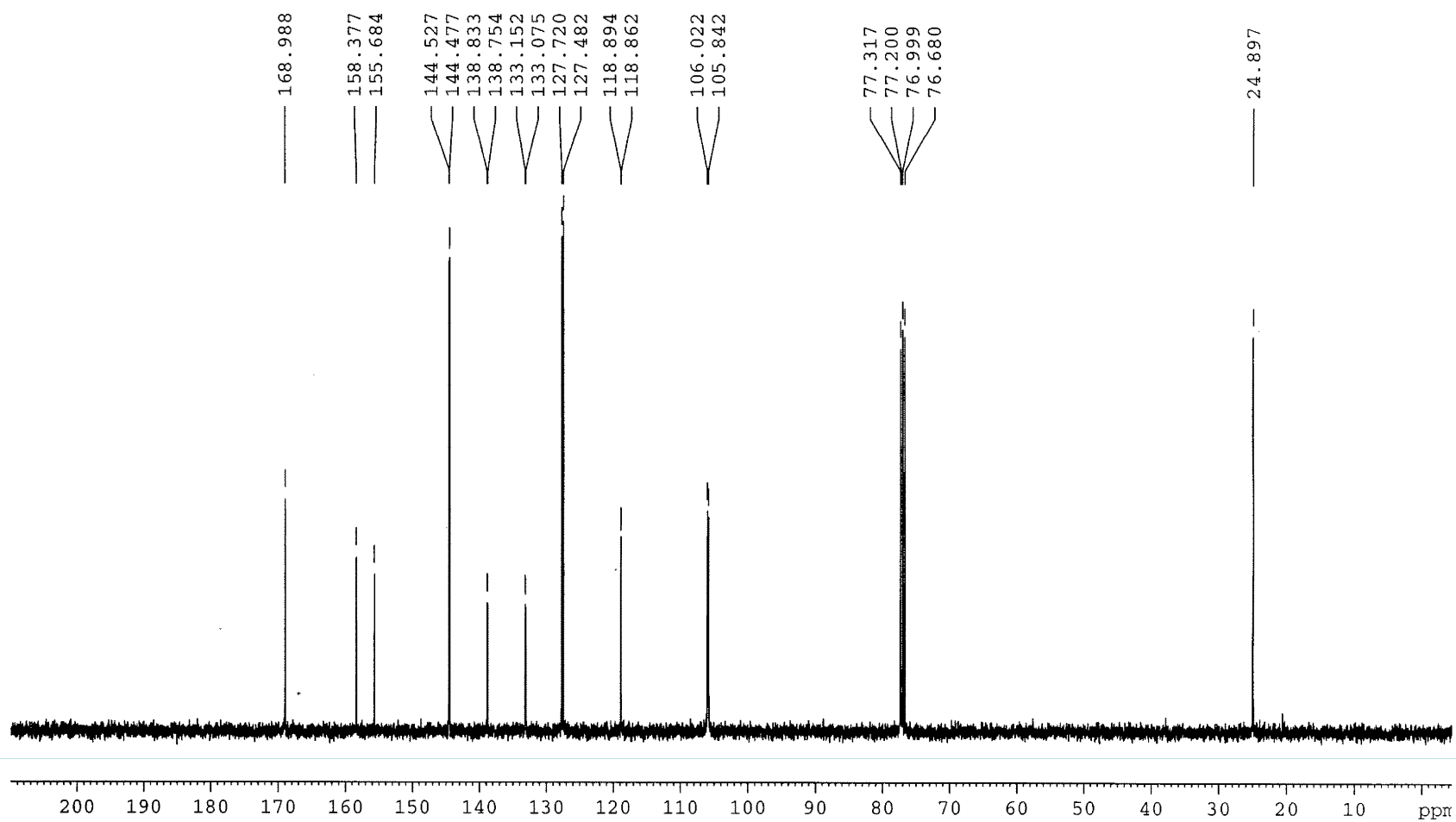
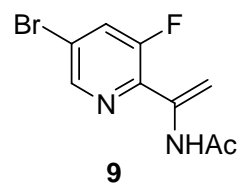


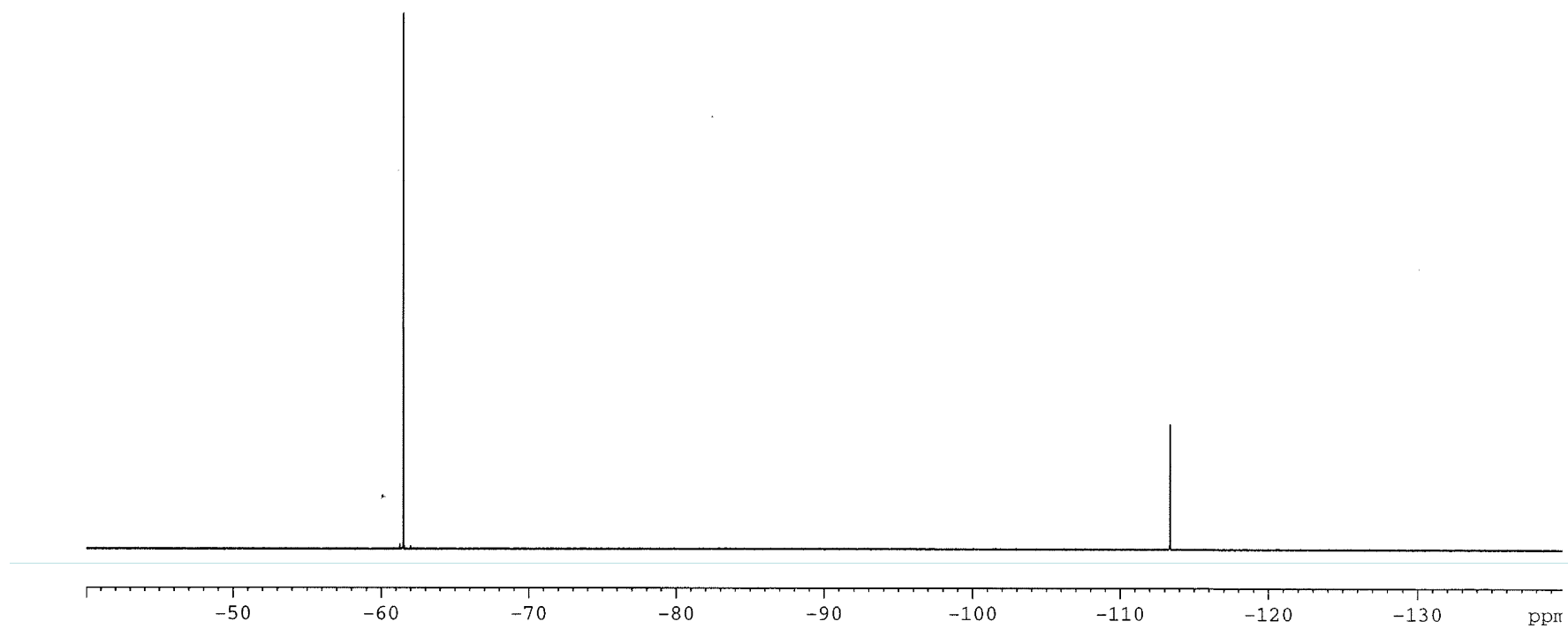
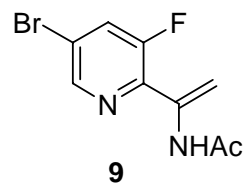


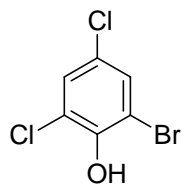
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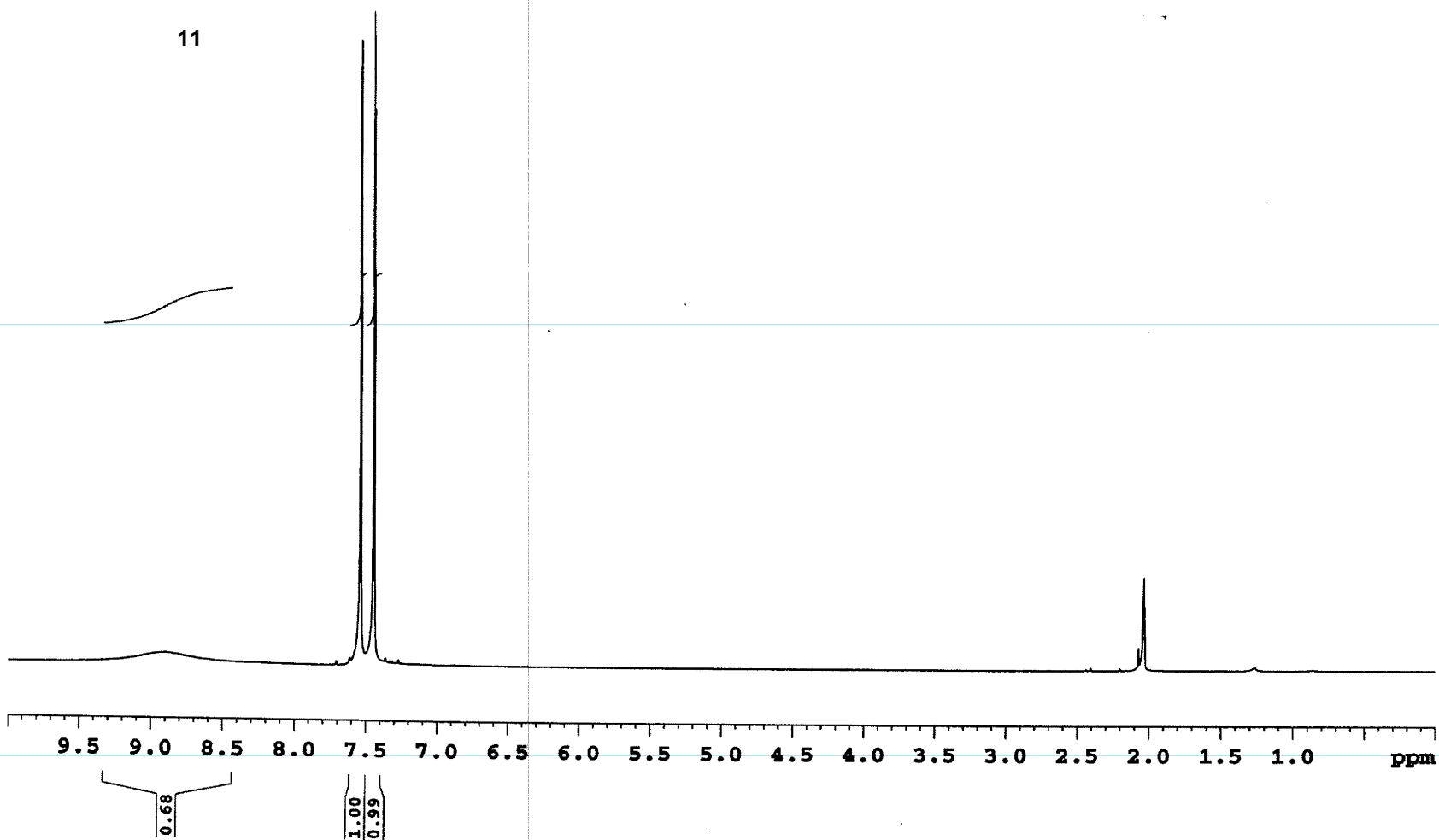


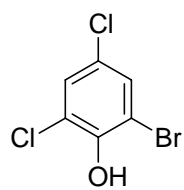




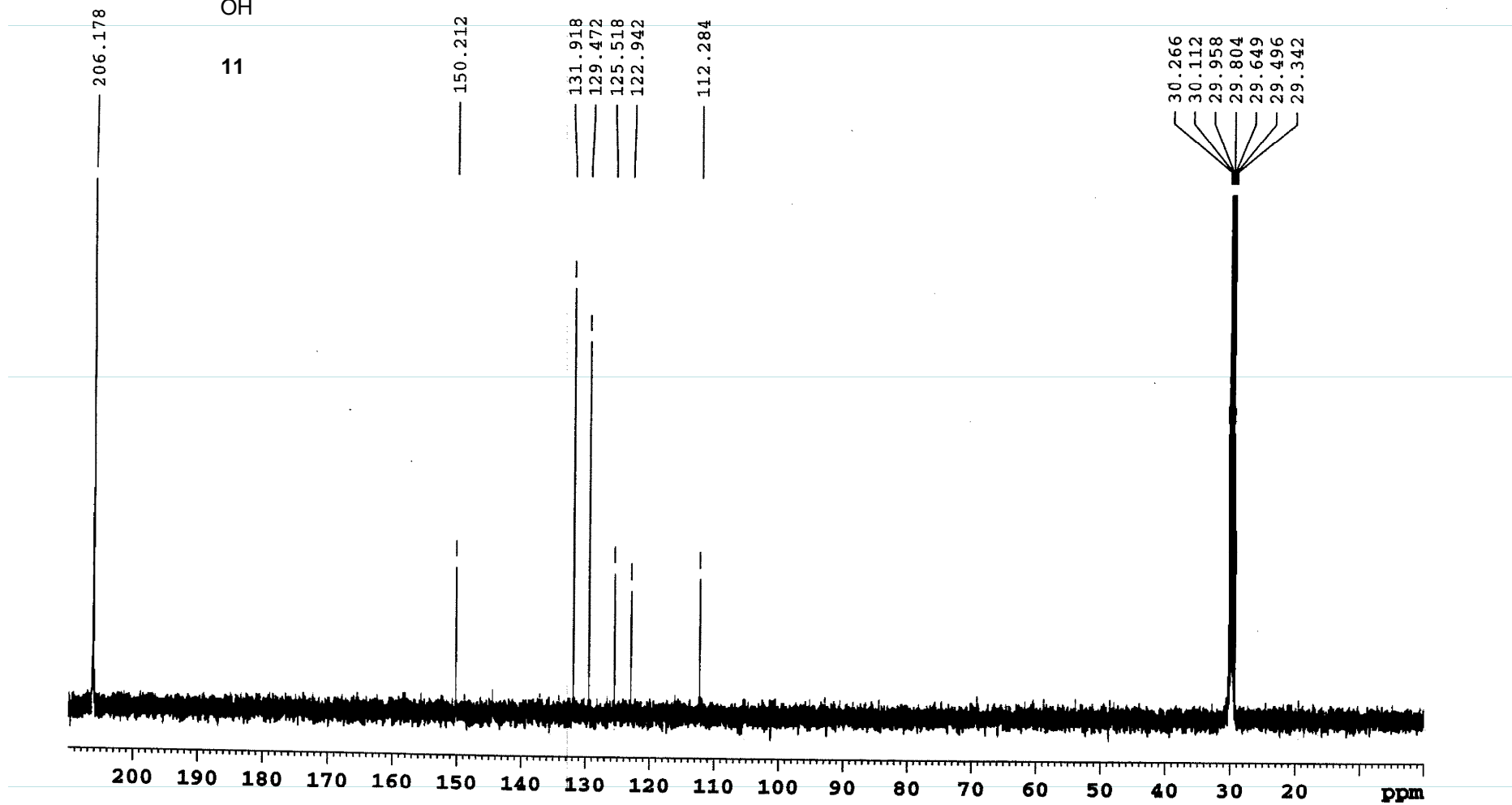


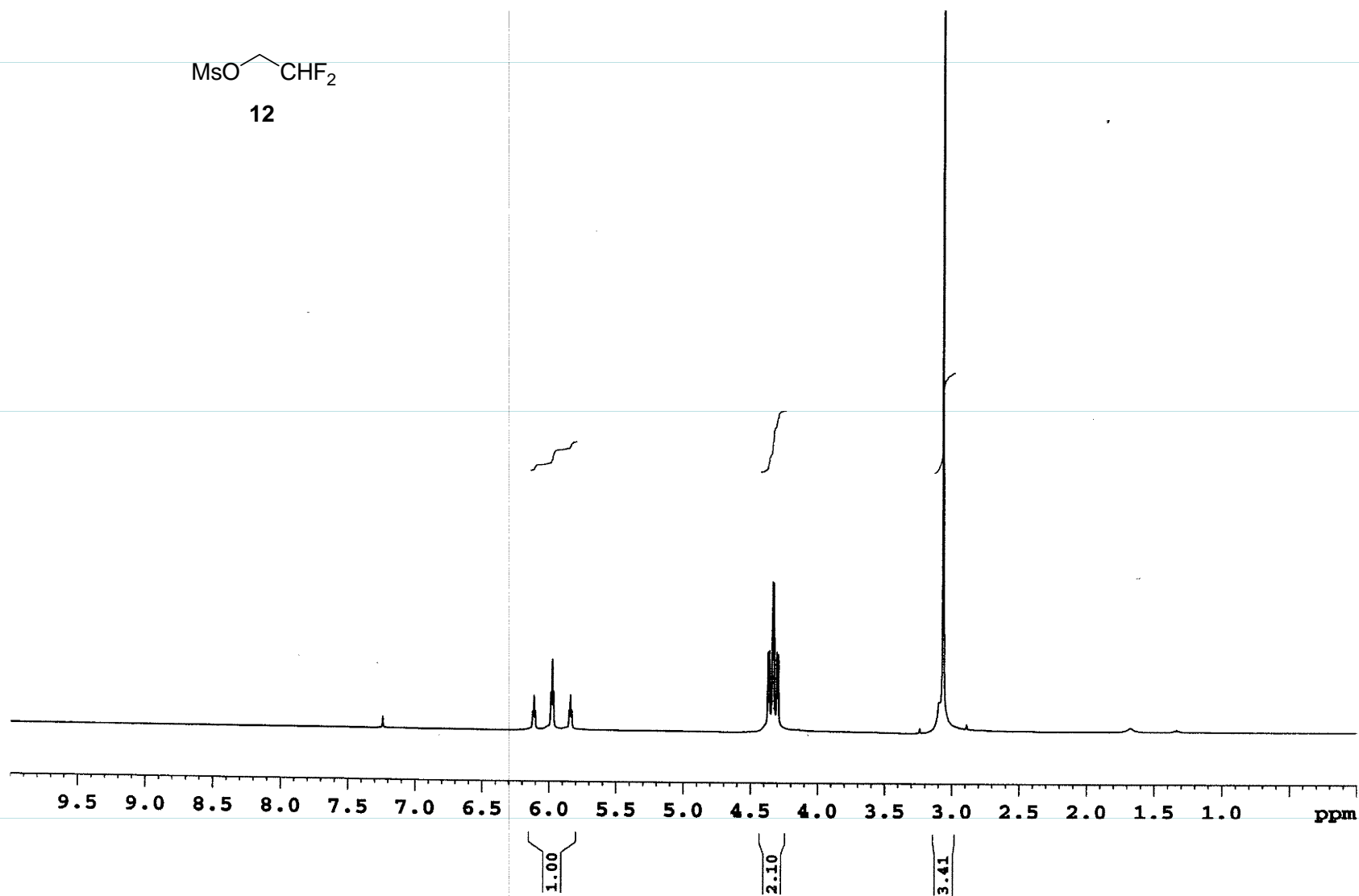
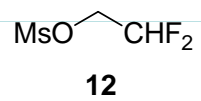
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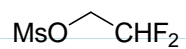




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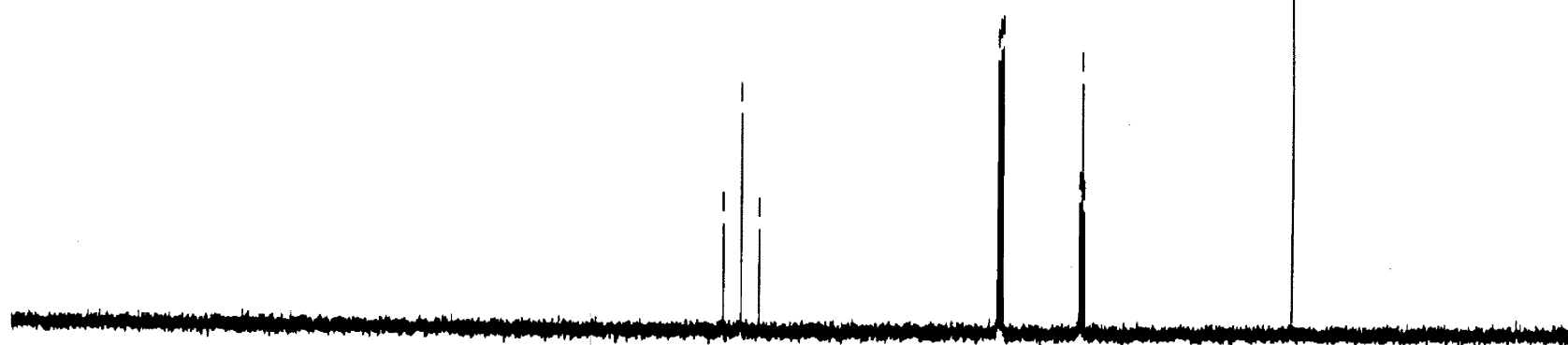


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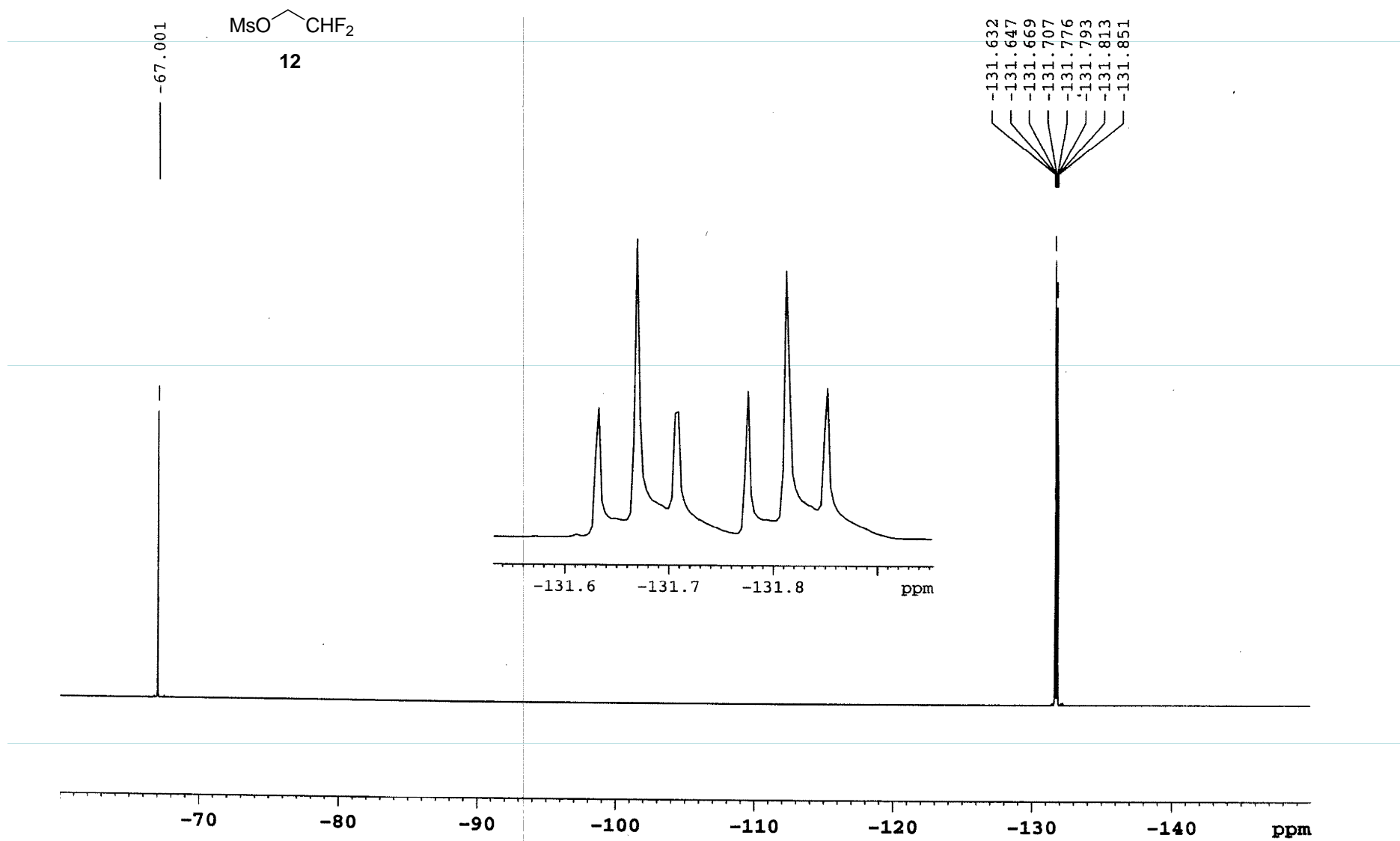
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111.932
109.523

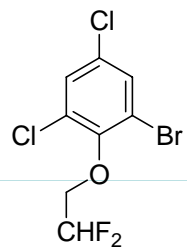
77.317
76.998
76.681
66.310
66.011
65.713

37.804

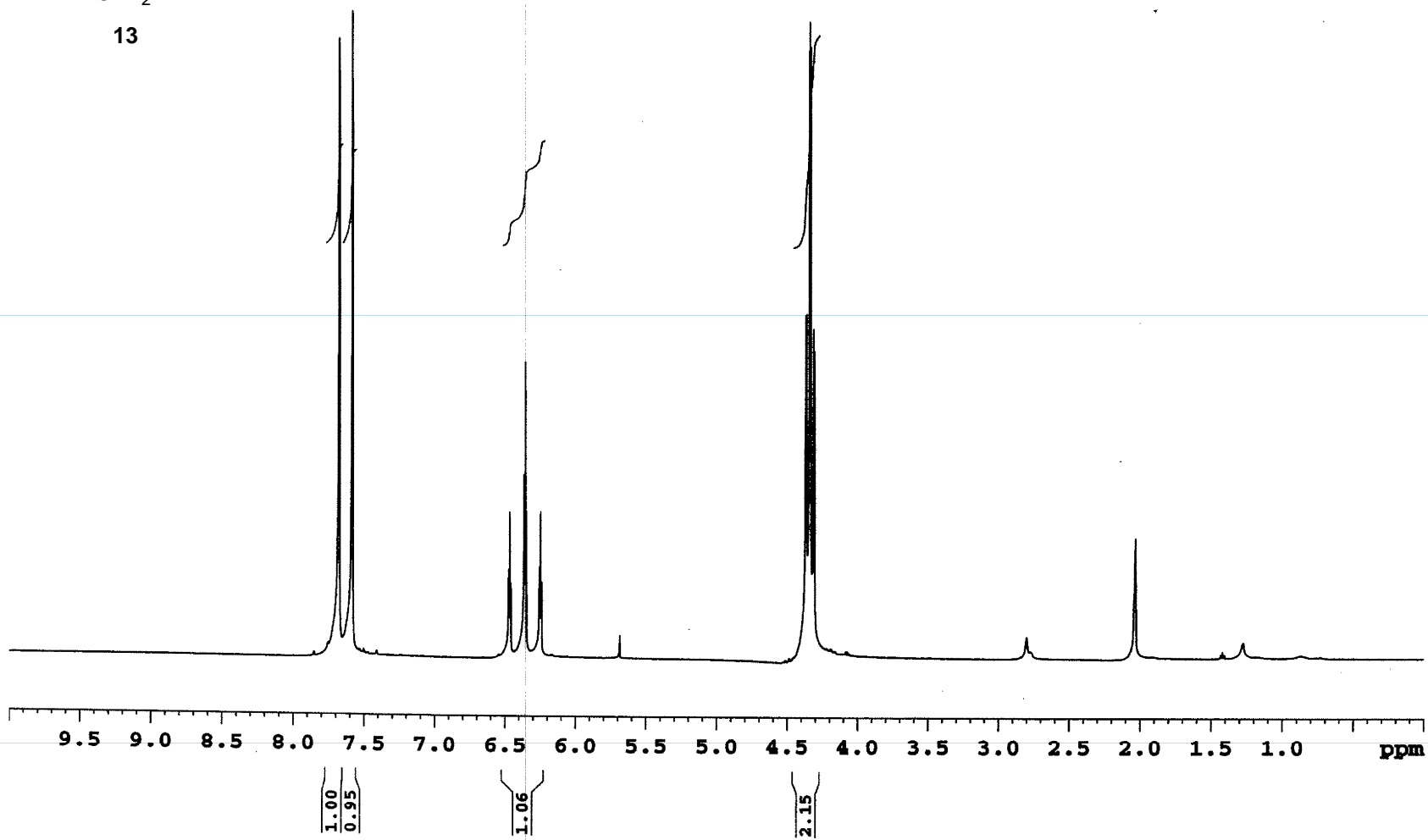


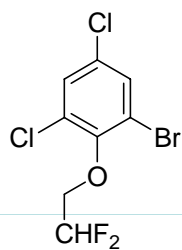
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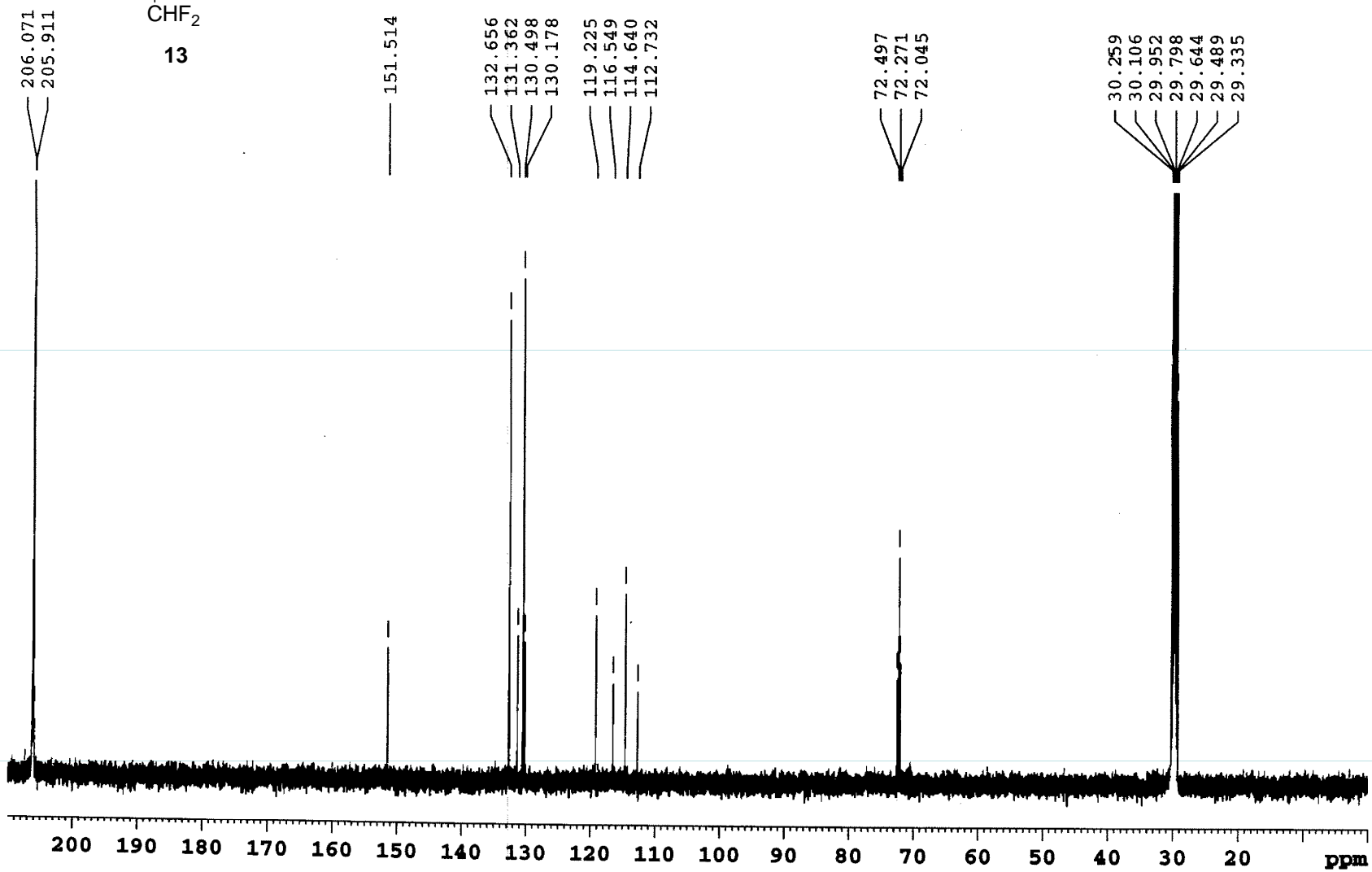


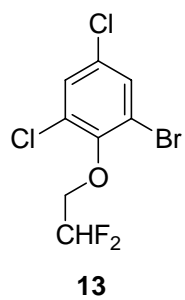
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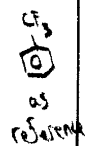


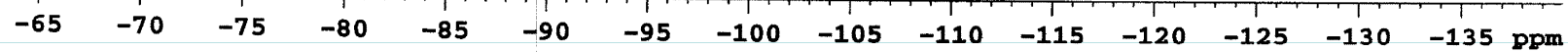
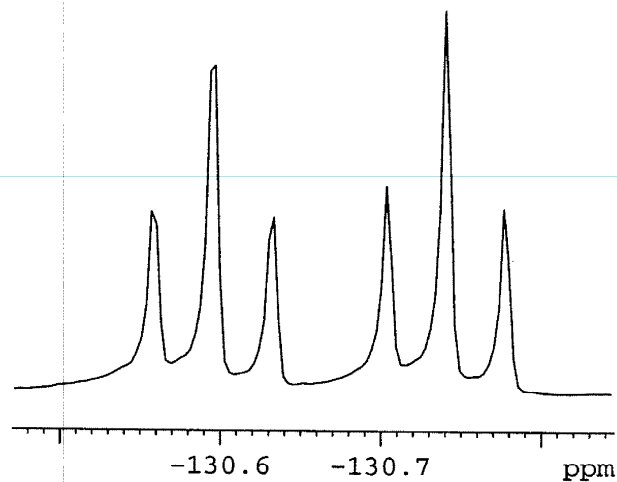


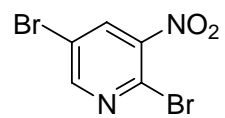
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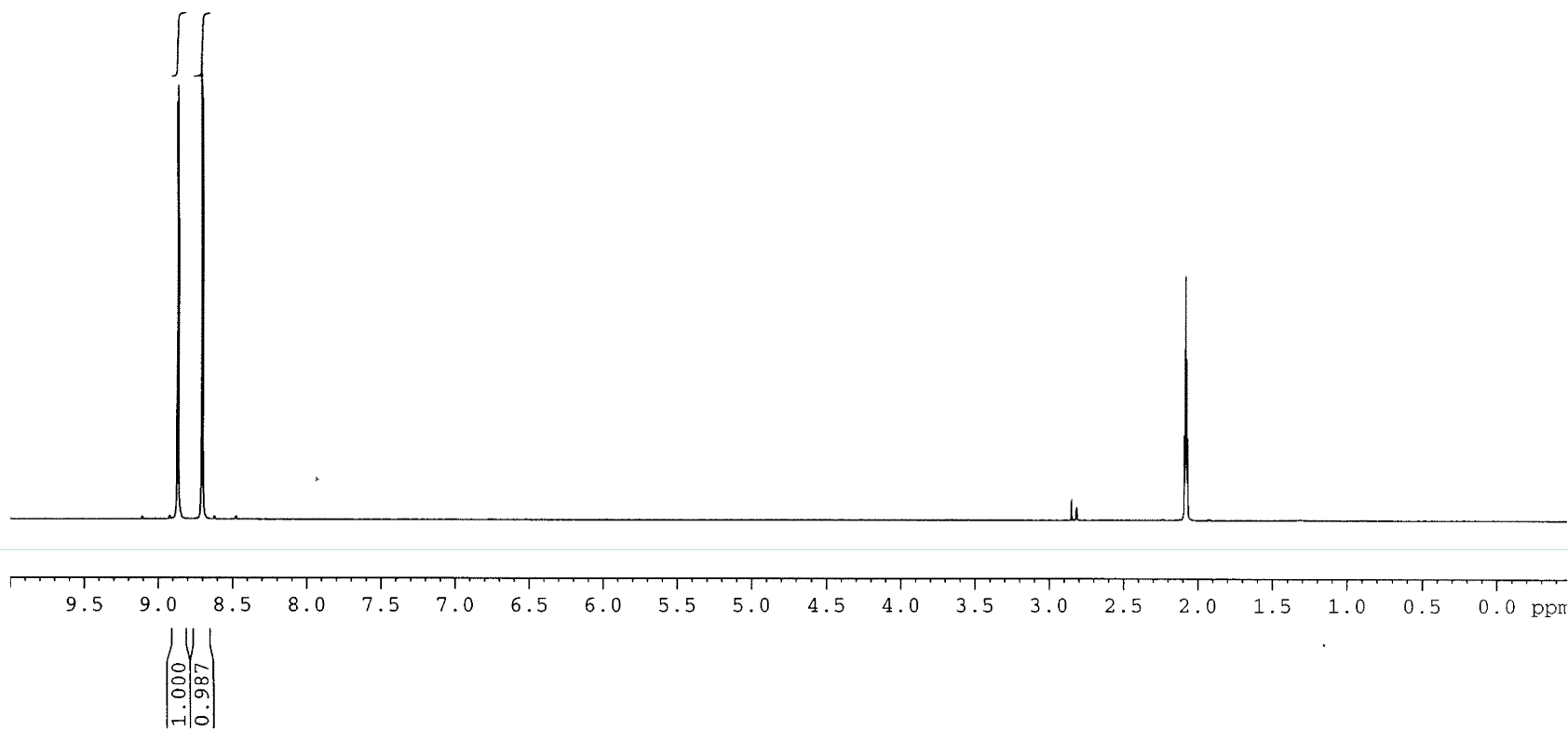


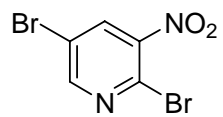

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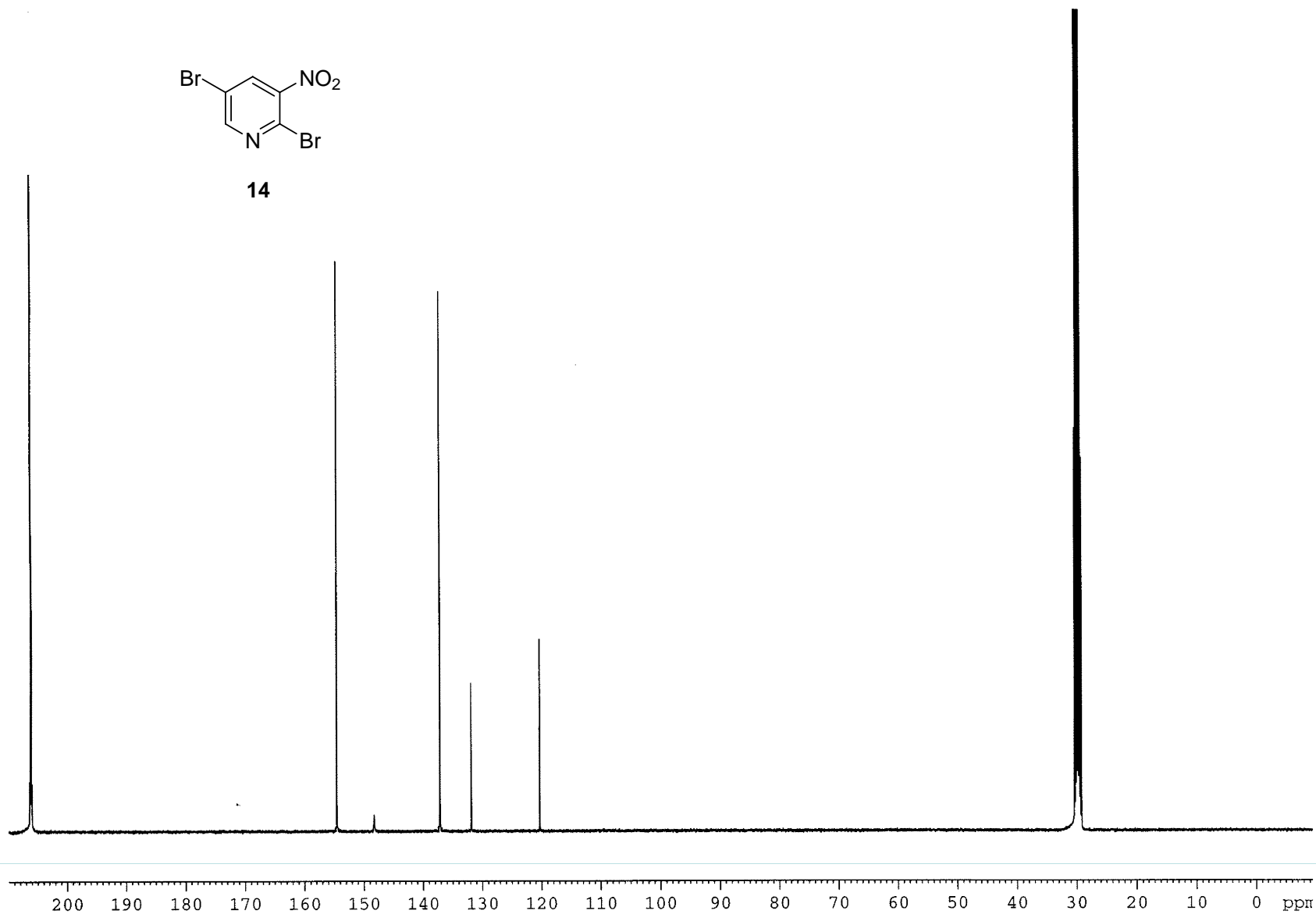


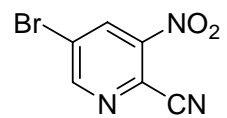
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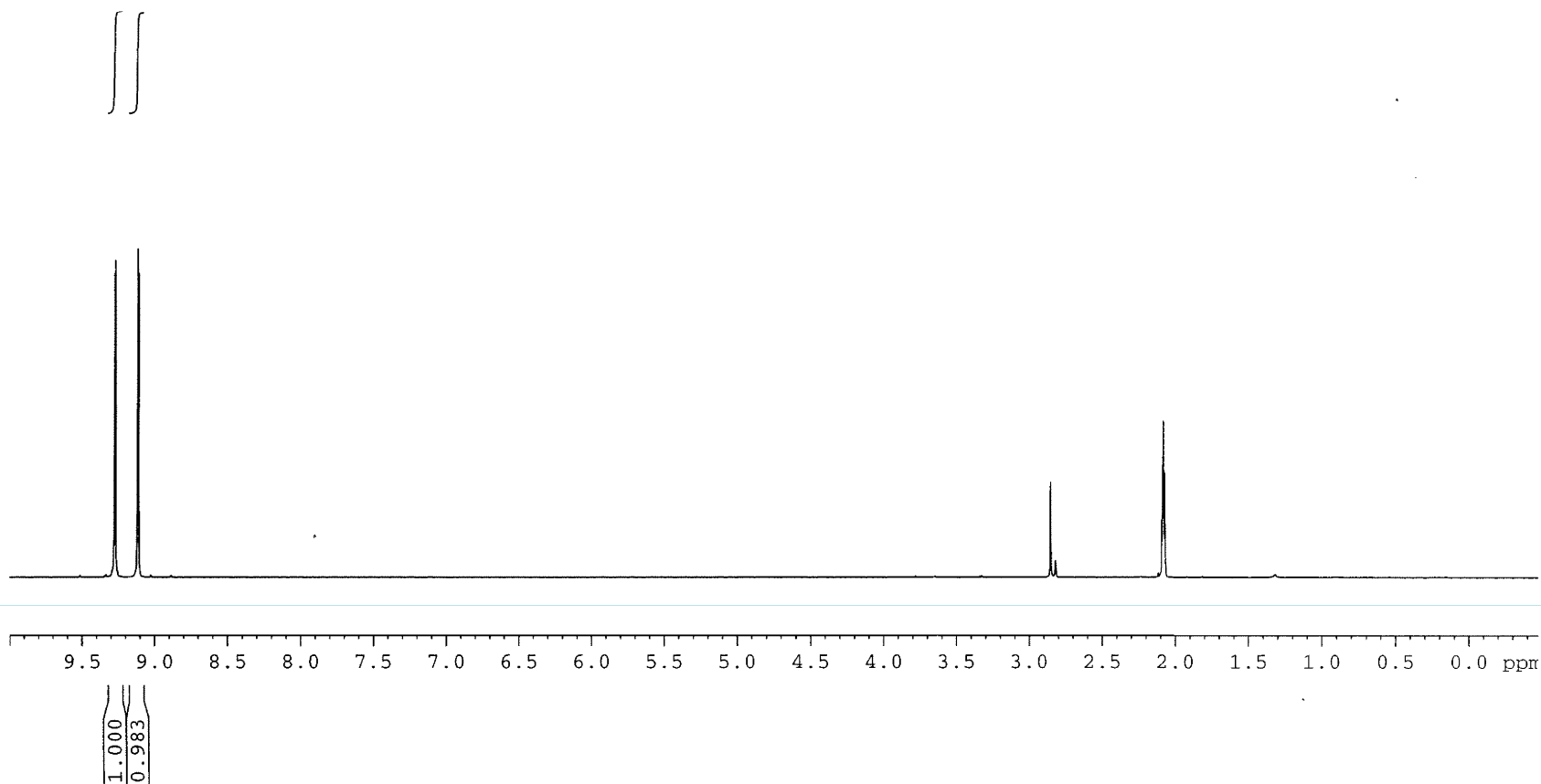


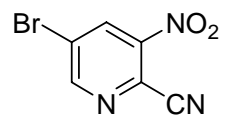
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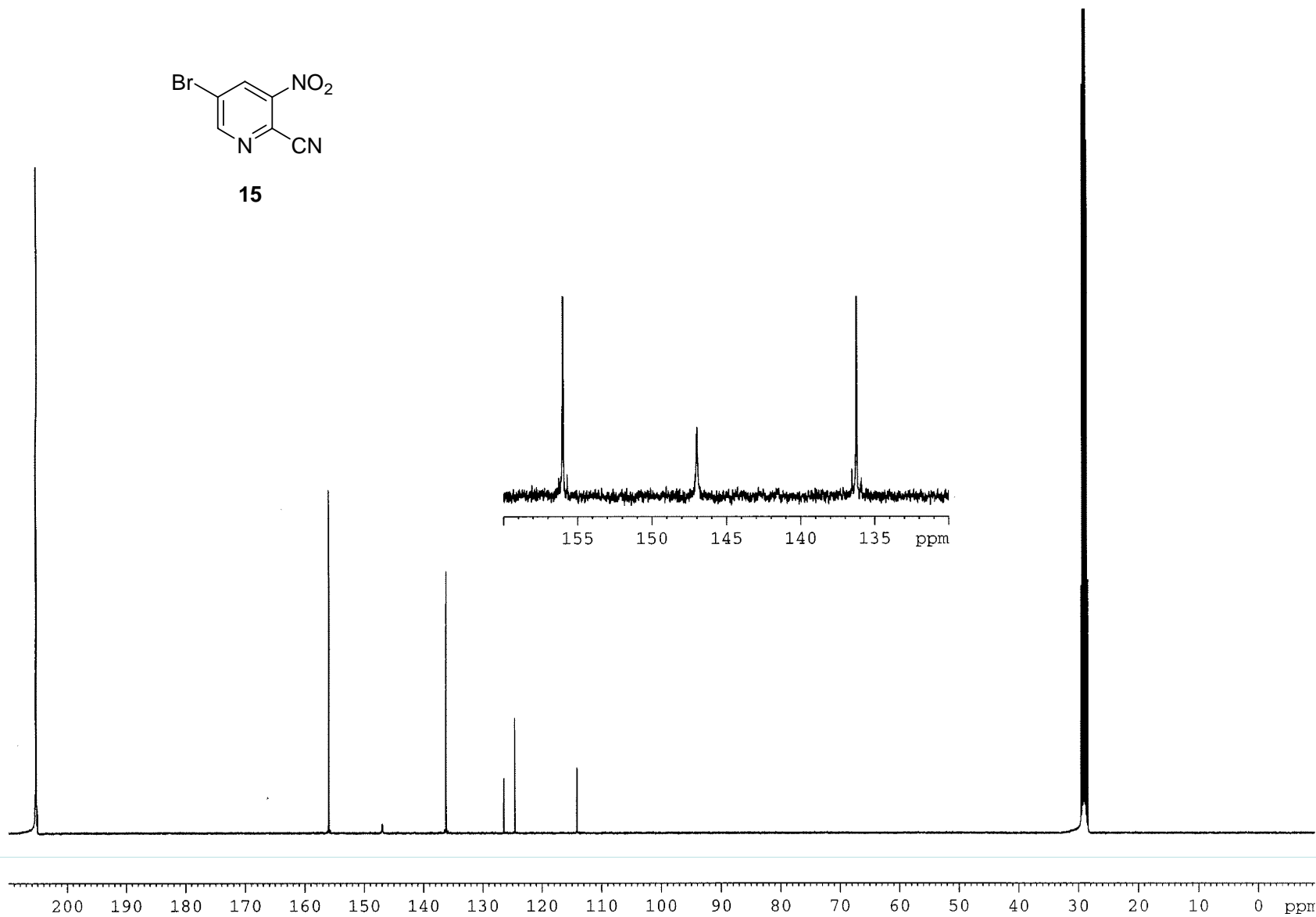


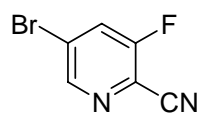
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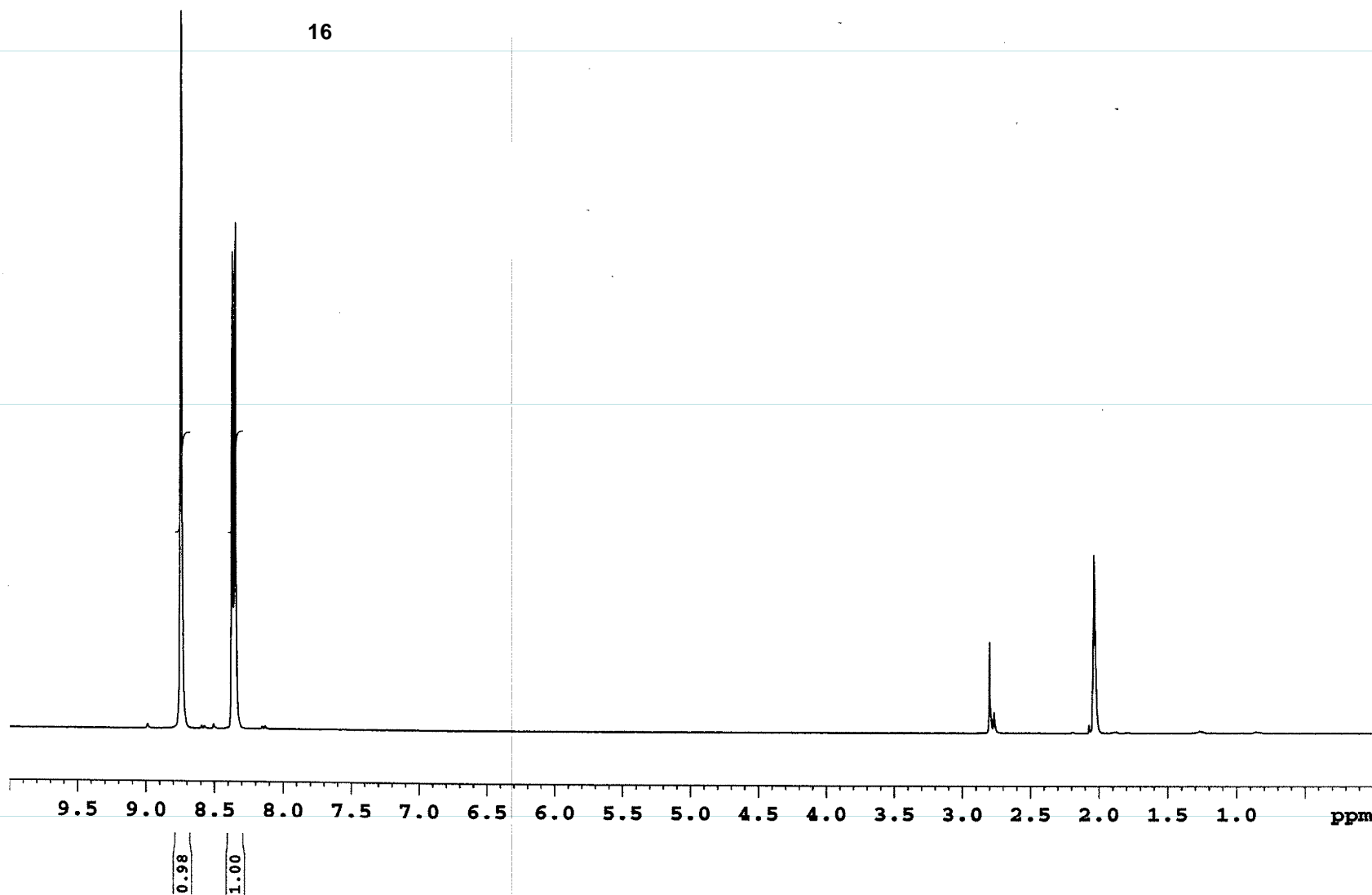


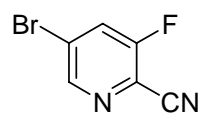
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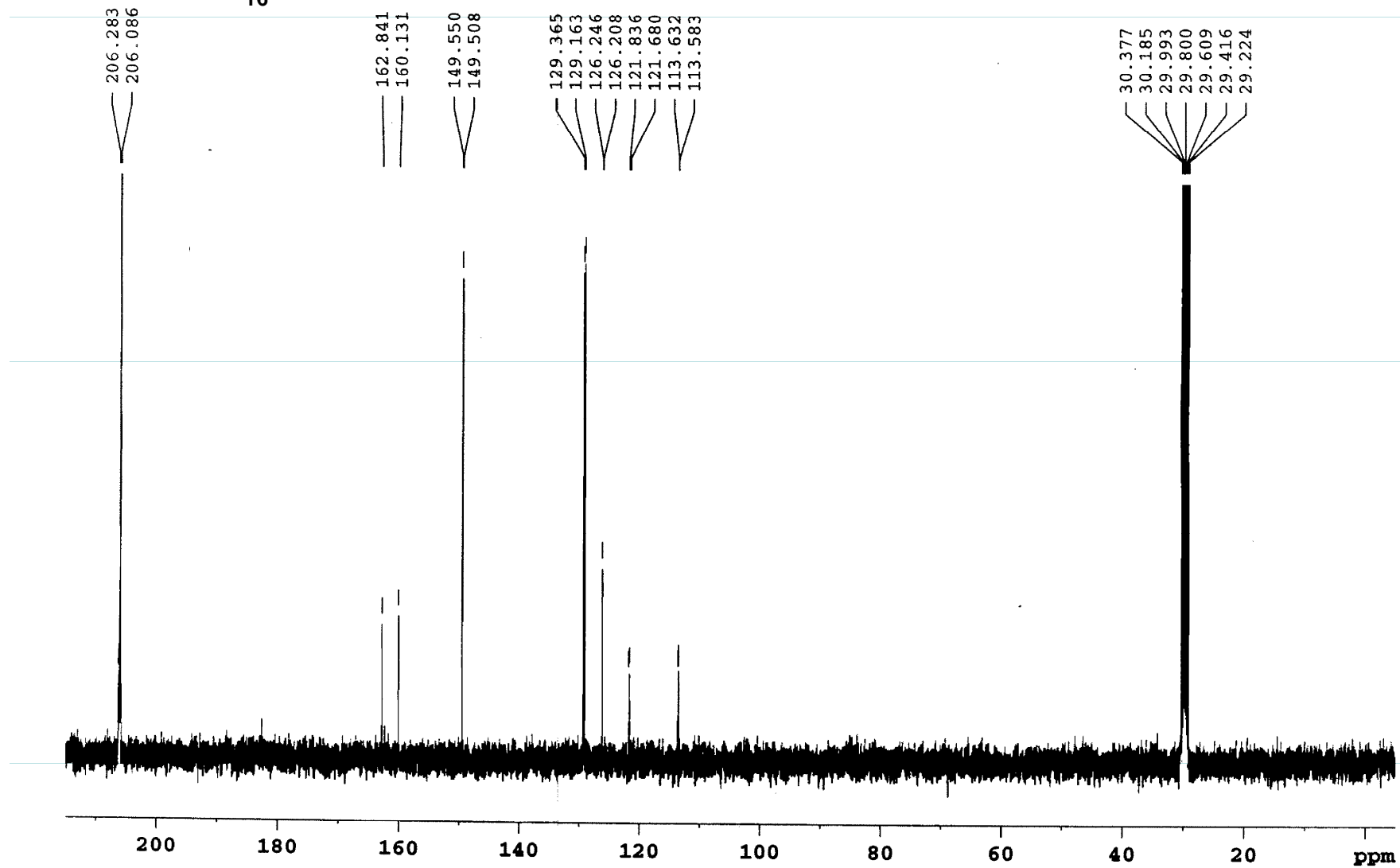


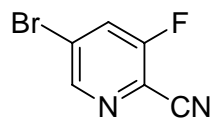
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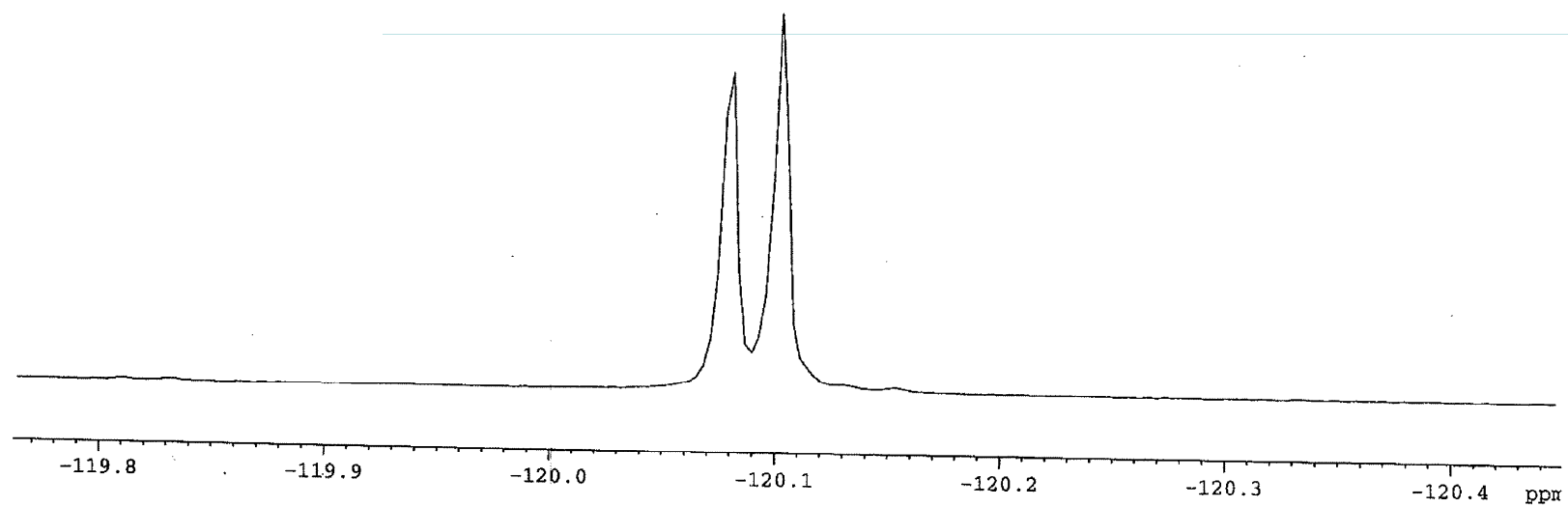


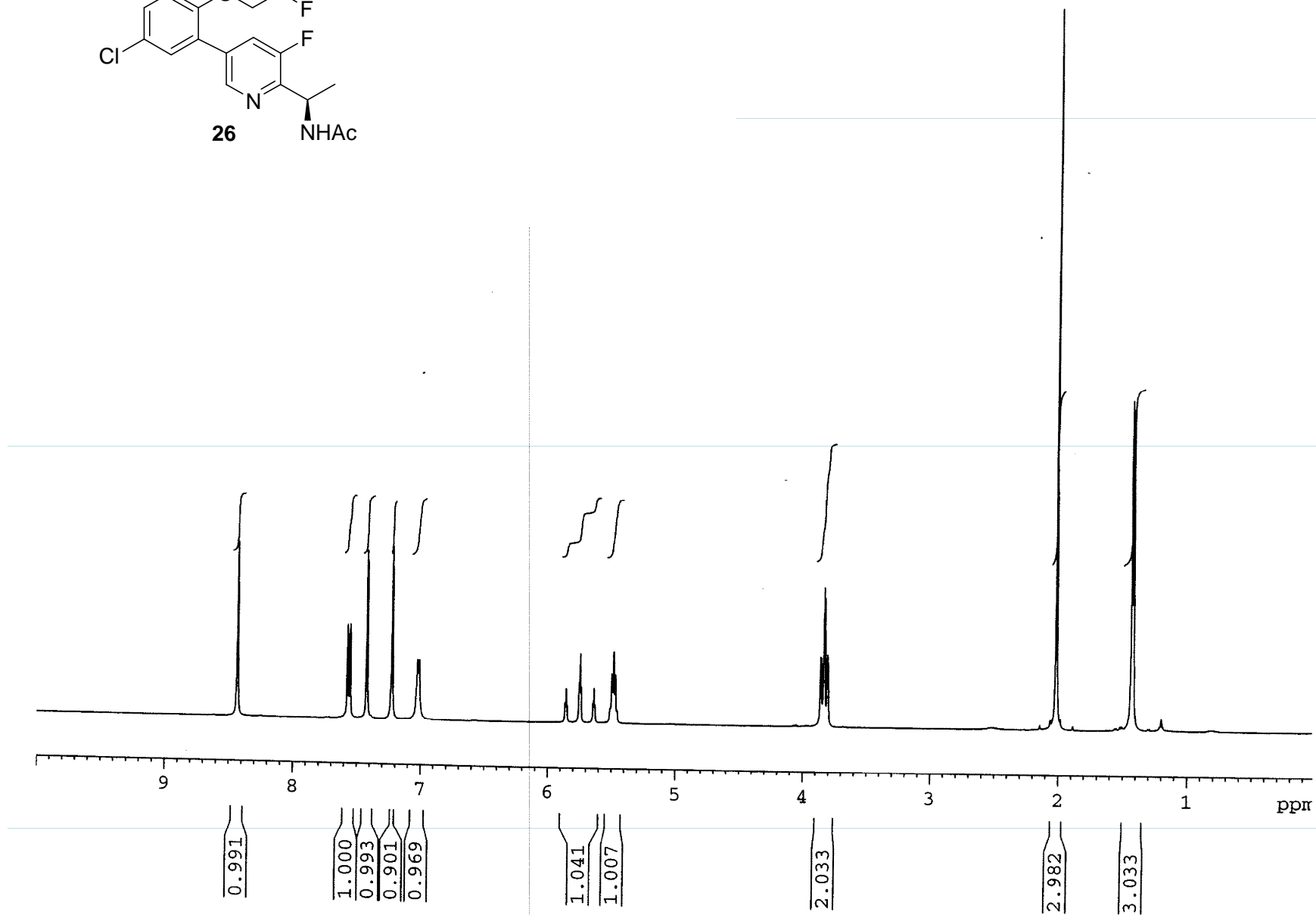
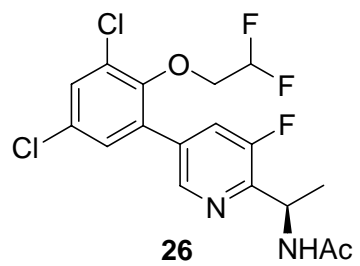
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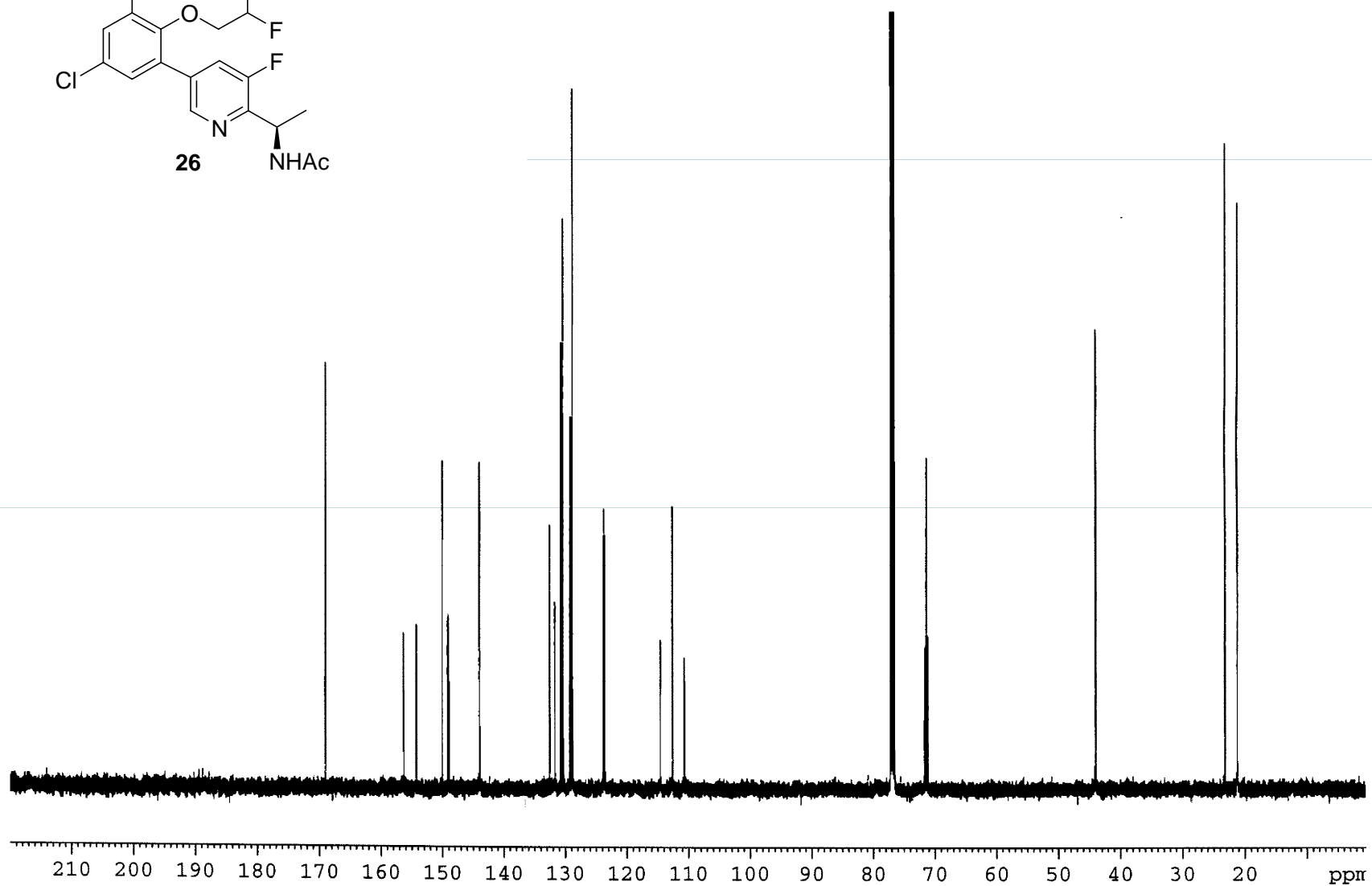
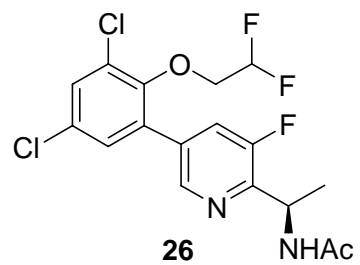


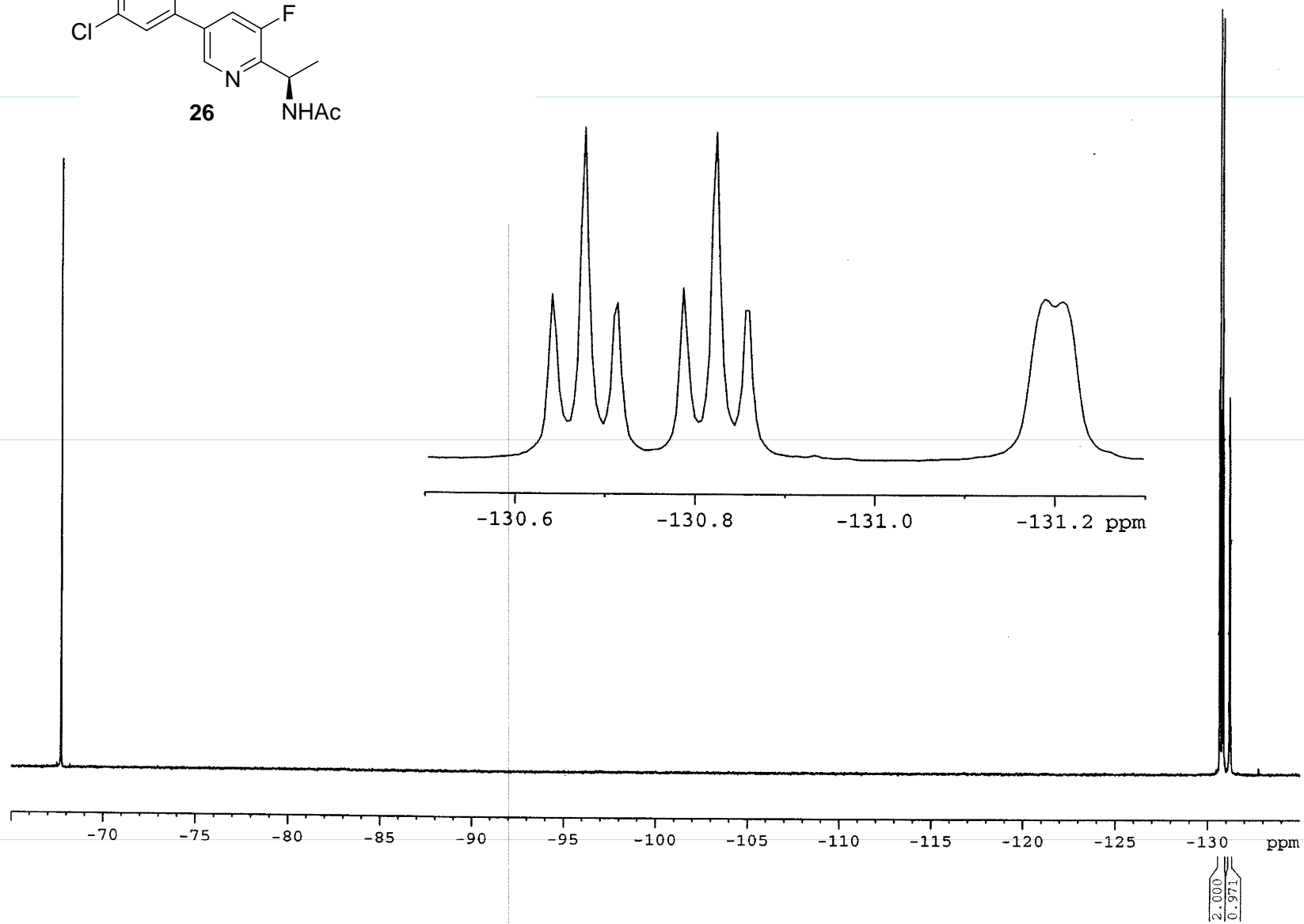
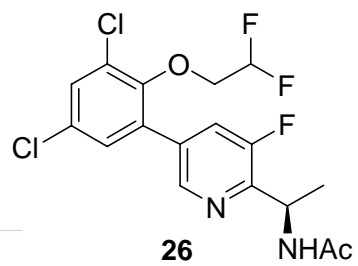


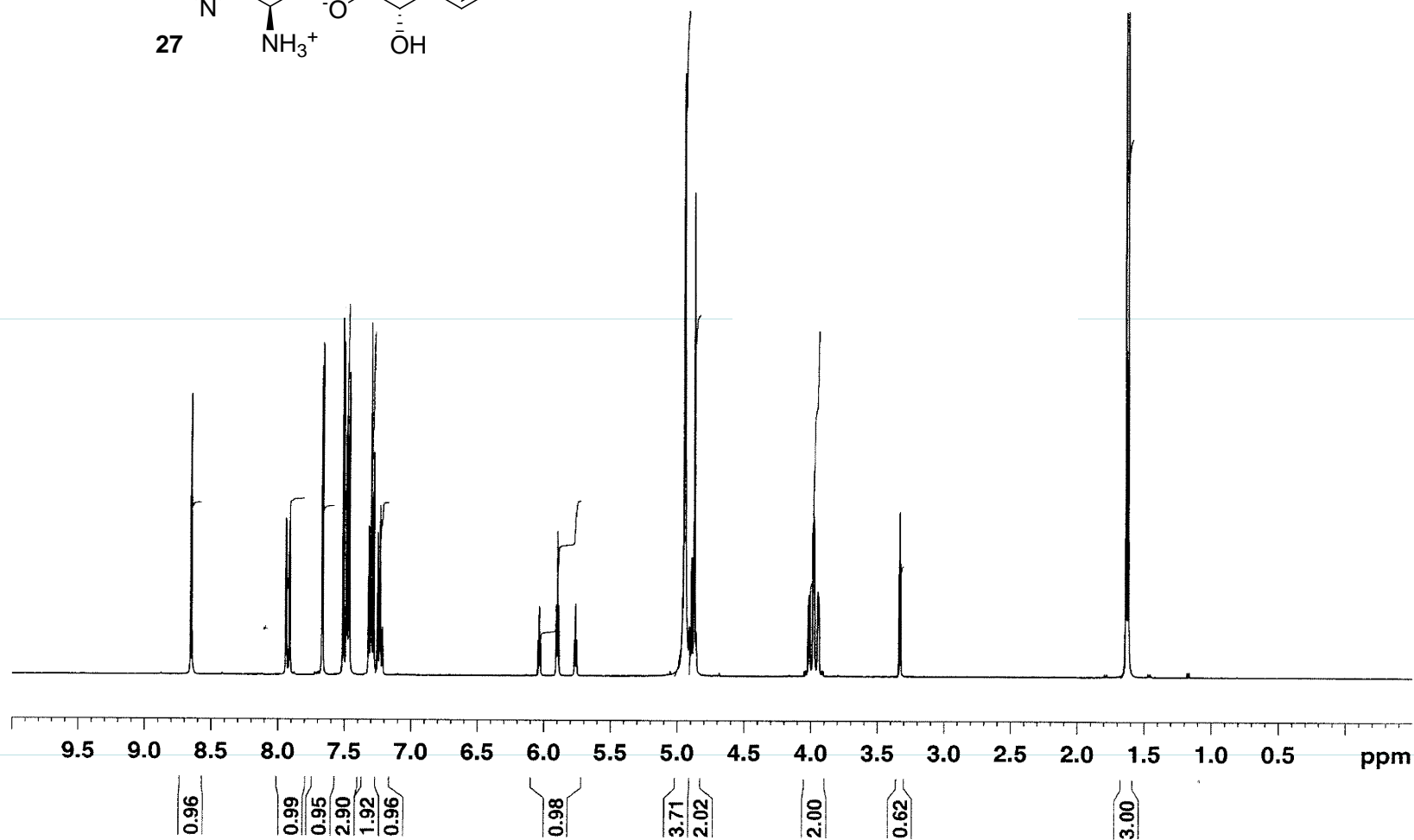
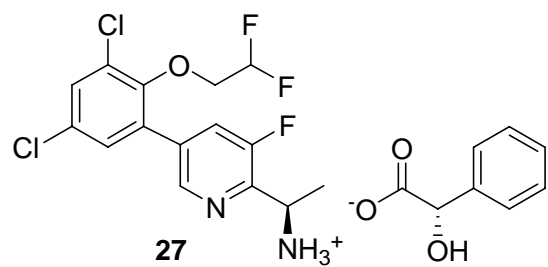
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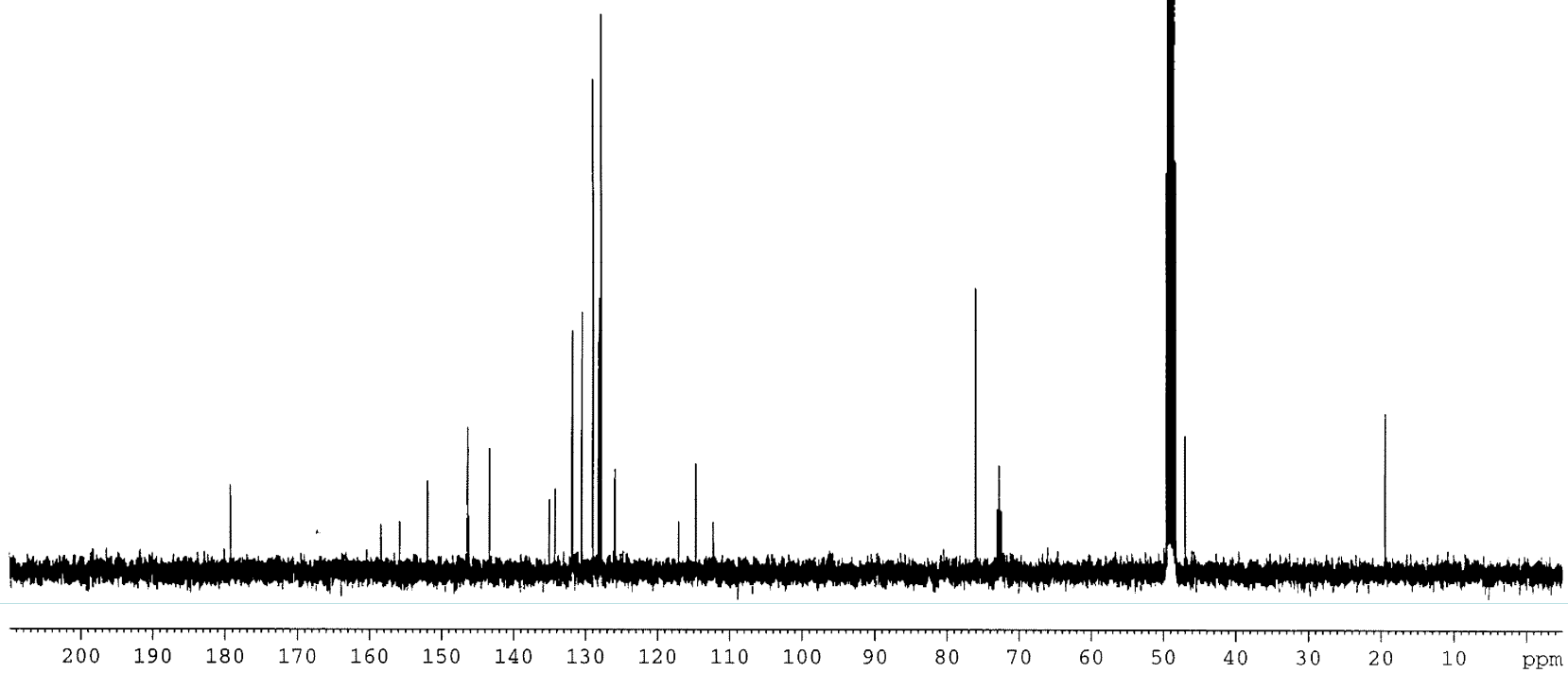
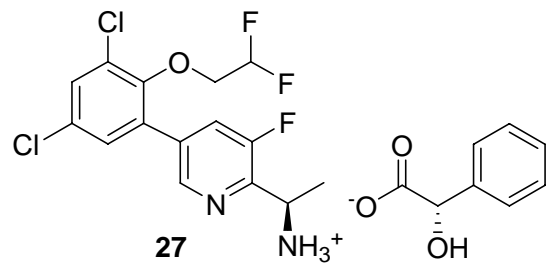


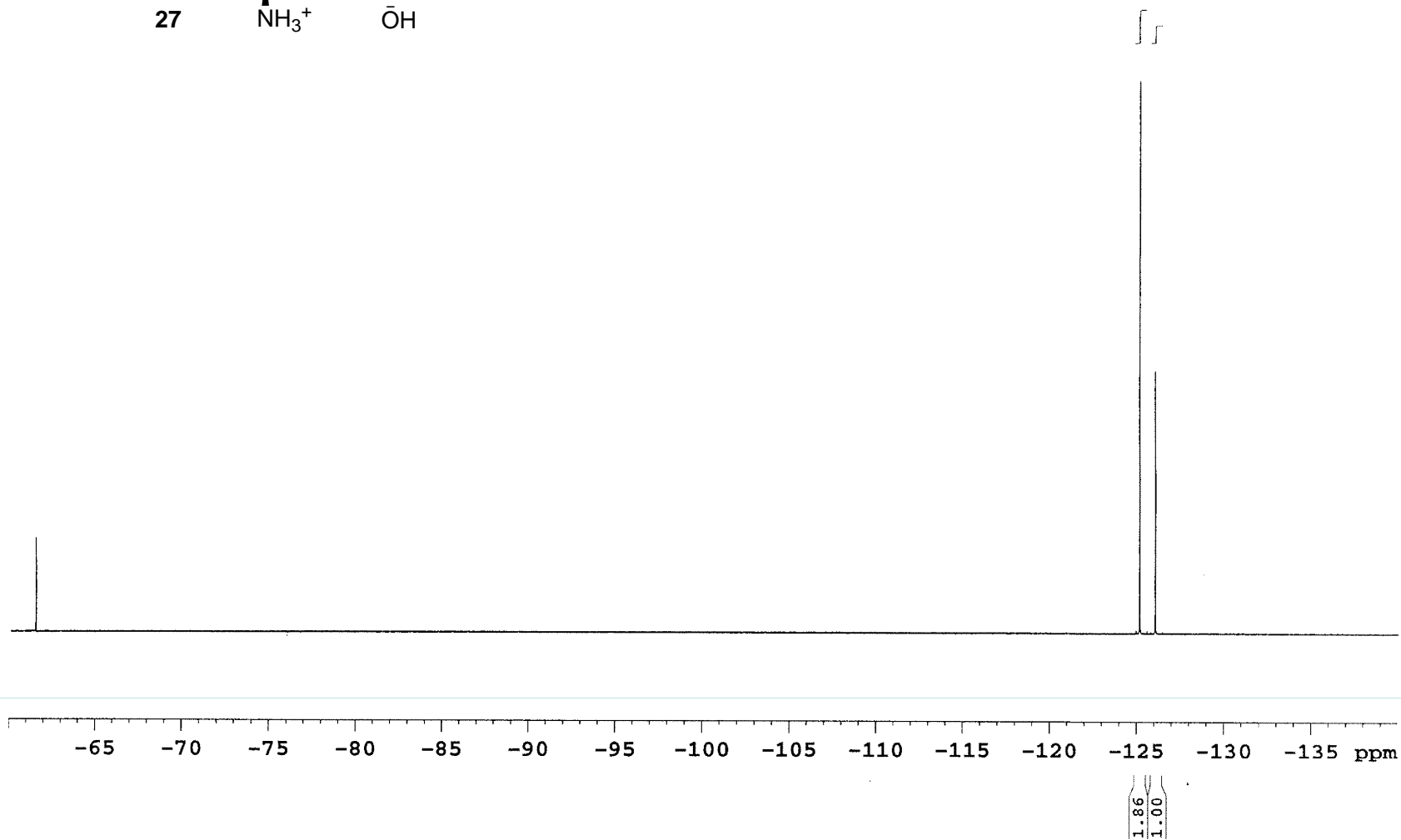
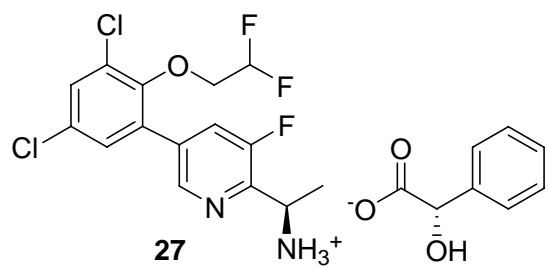


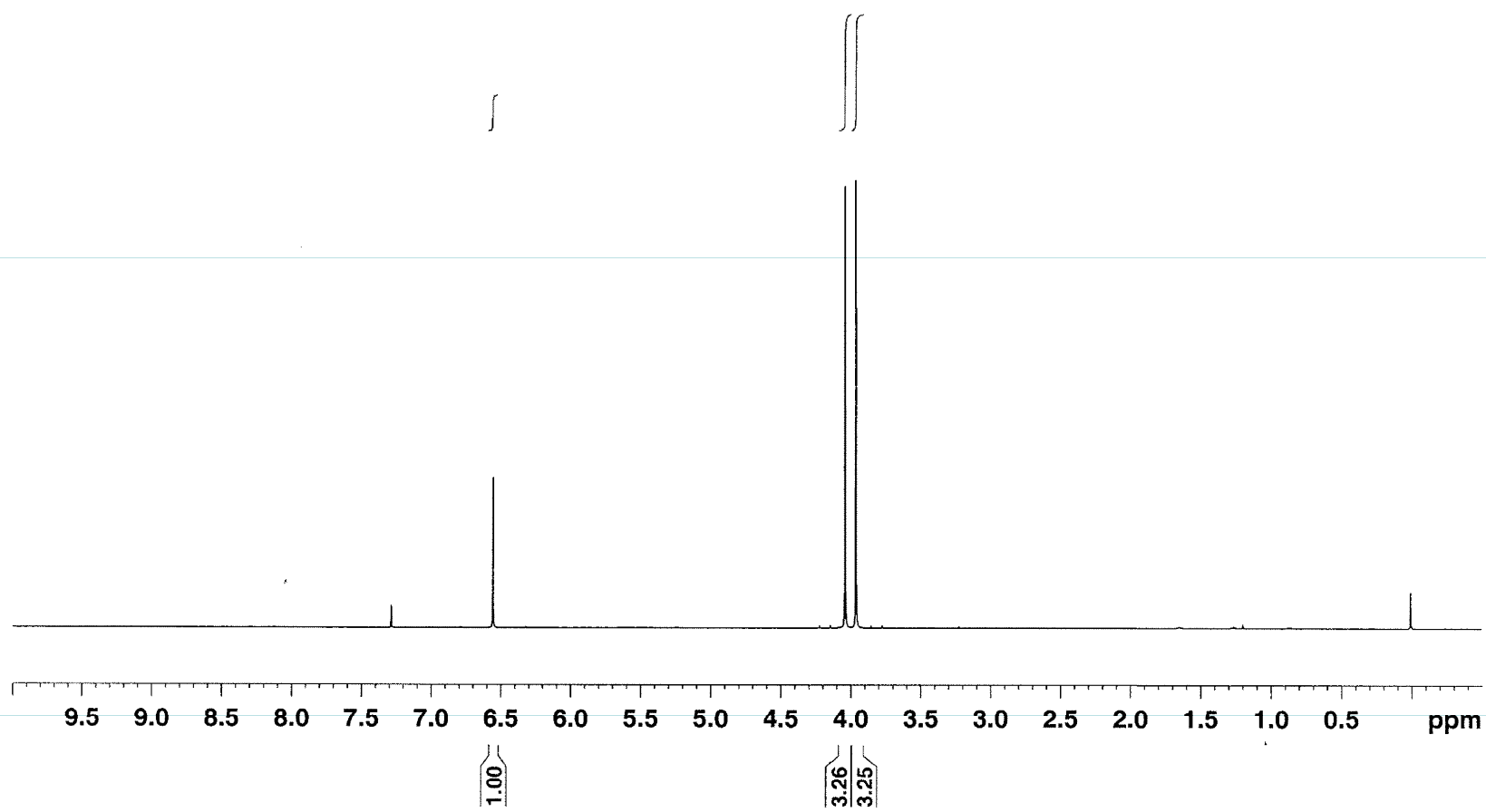
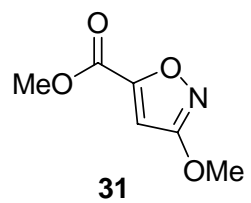


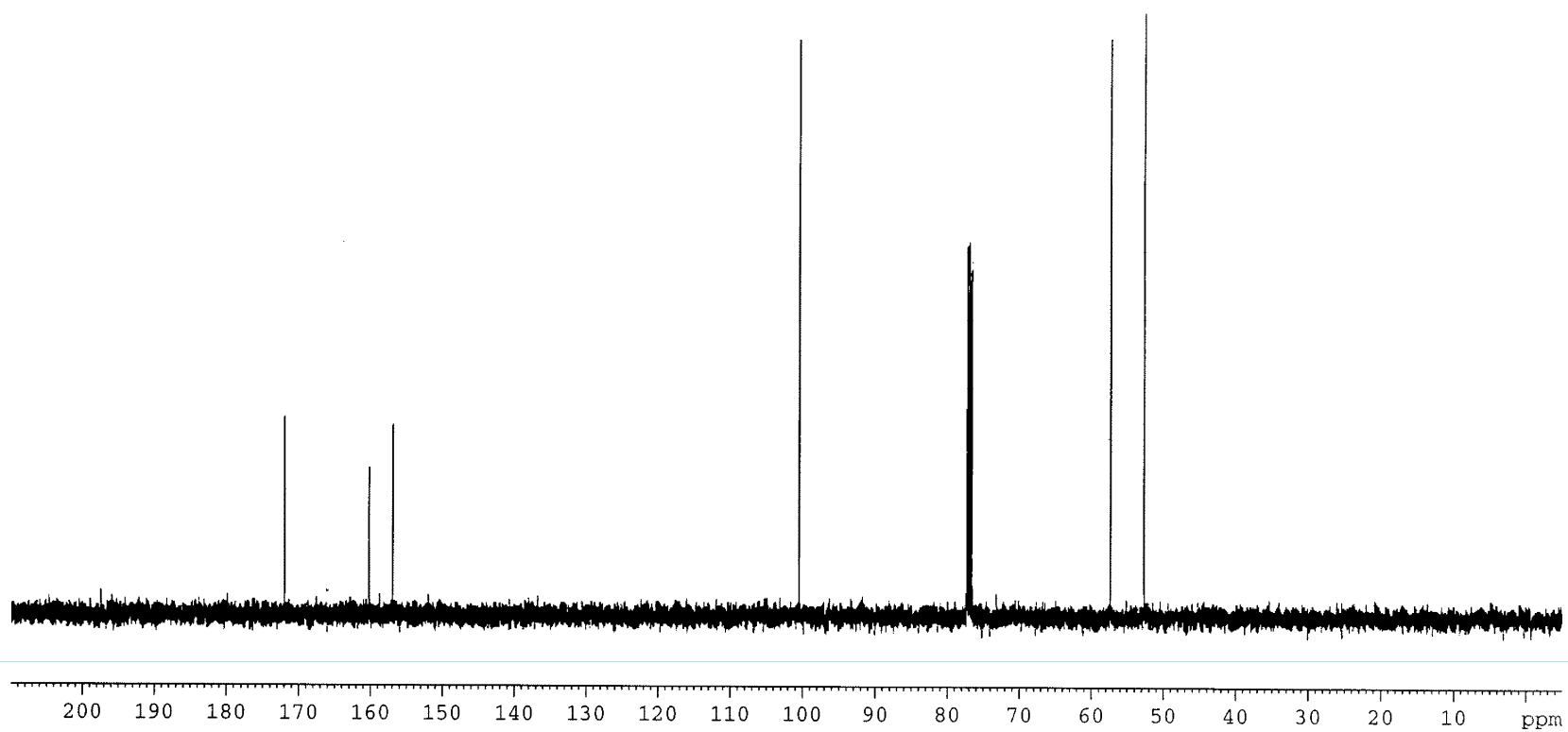
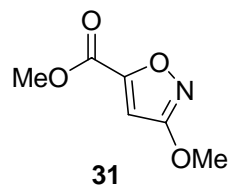


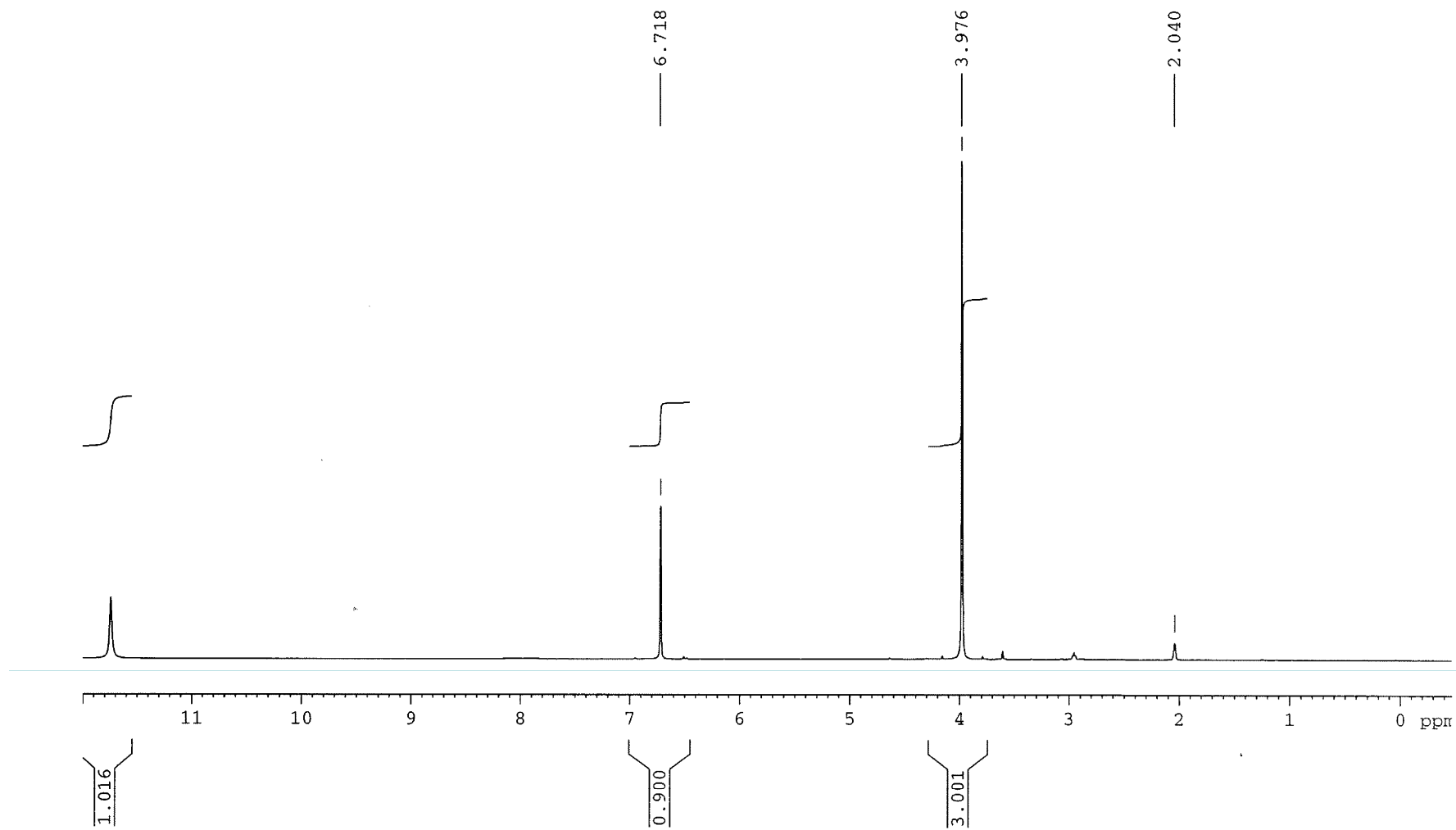
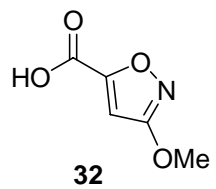


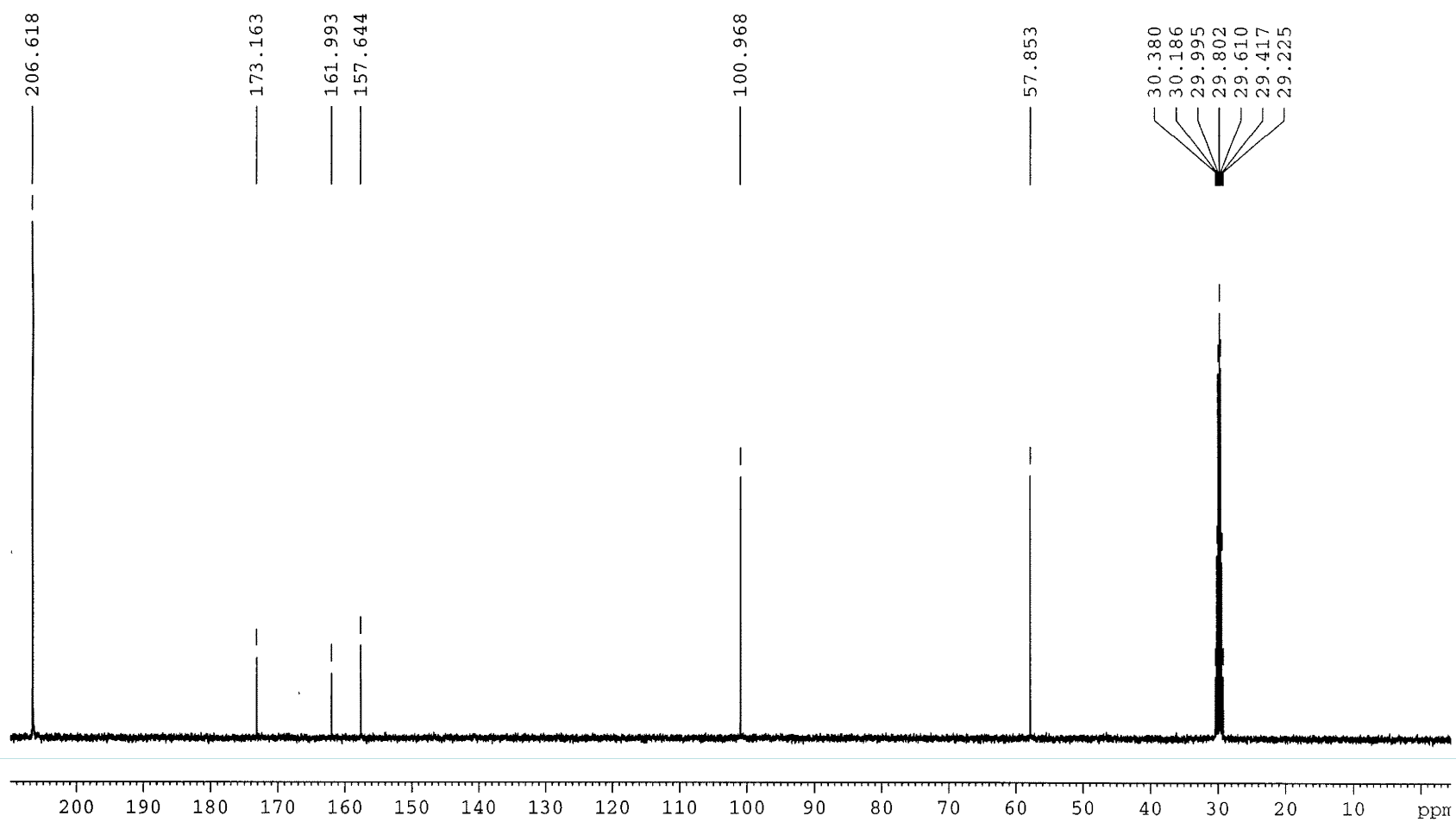
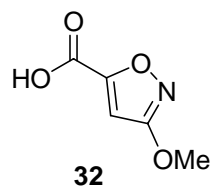


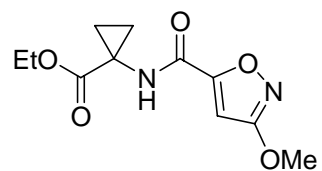




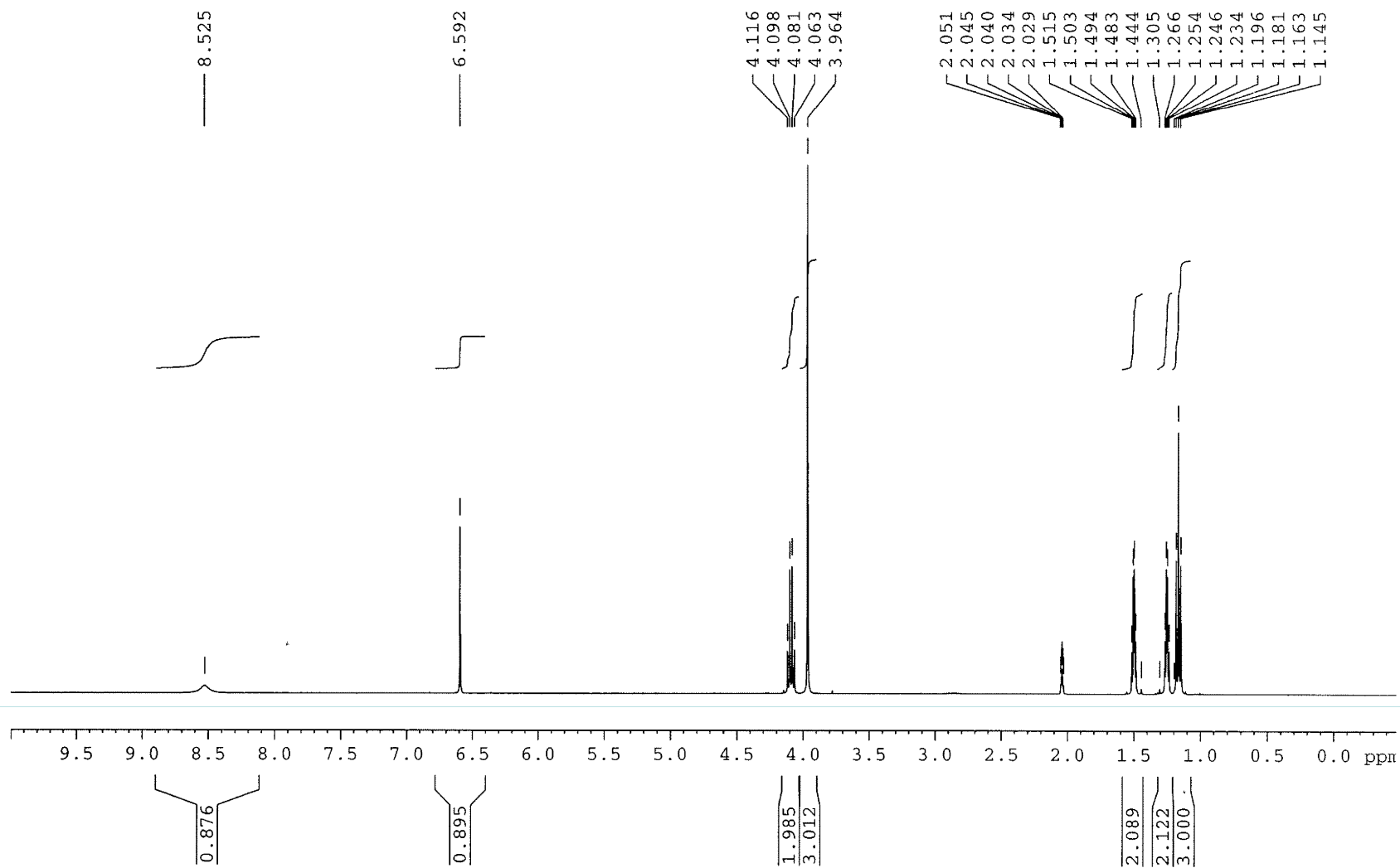


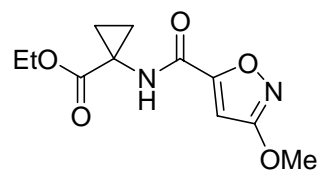






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