

Supporting Information

Inhibition of N-Type Calcium Channels by Phenoxyaniline and Sulfonamide Analogues

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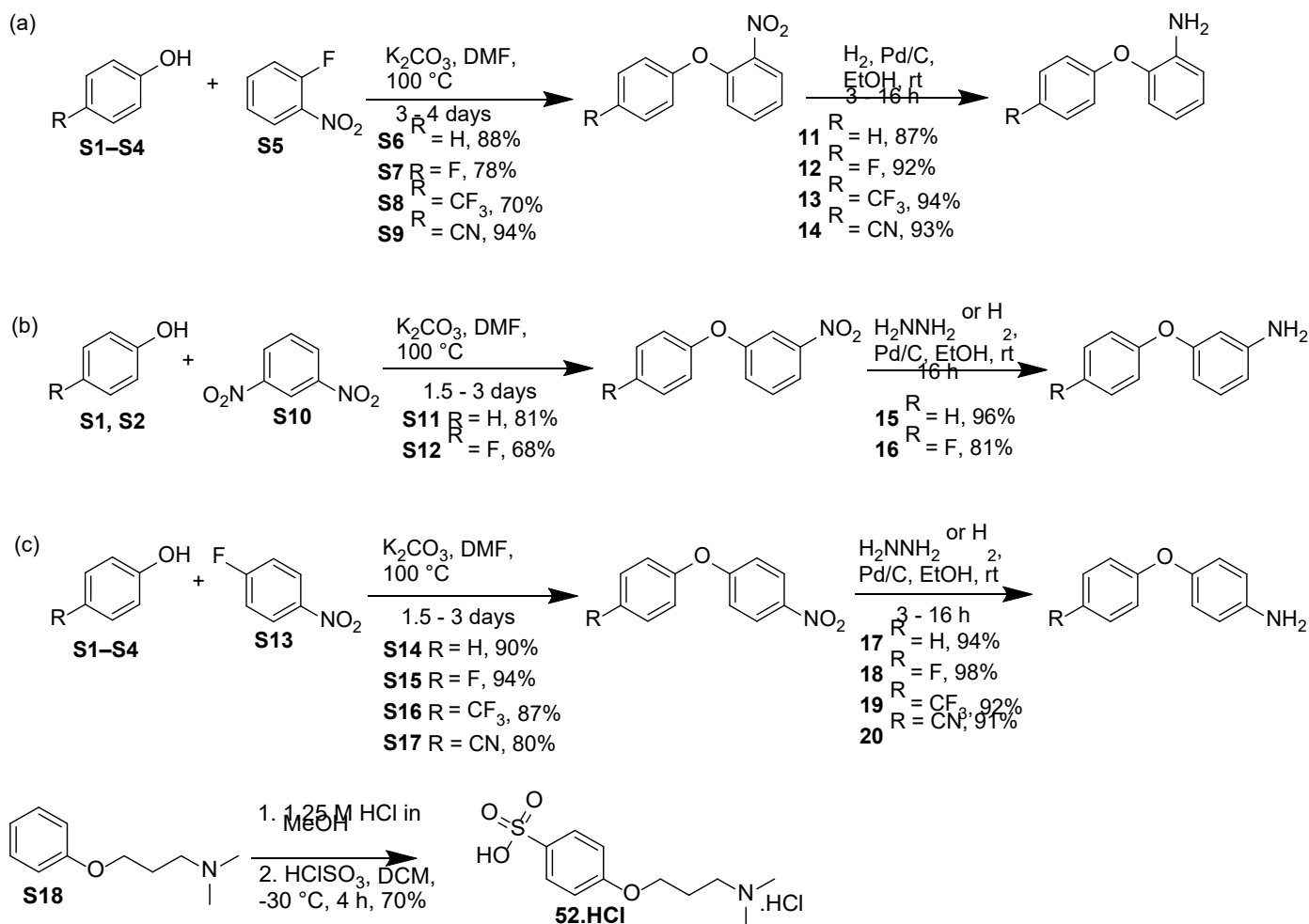
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1.1. Chemistry



1-Nitro-2-phenoxybenzene (S6)

A mixture of phenol **S1** (2.78 g, 29.6 mmol), K_2CO_3 (17.0 g, 123 mmol) and dry DMF (30 mL) was stirred under N_2 for 15 min at rt. 1-Fluoro-2-nitrobenzene **S5** (4.21 g, 29.9 mmol) was added and the reaction mixture heated at 100 °C 4 days. The mixture was cooled to rt, poured into cold water (100 mL) and the crude product **S6** extracted with DCM (3 × 80 mL). The combined organic layers were washed with water (4 × 80 mL) followed by brine (80 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The title compound **S6** was obtained as an orange oil (5.59 g, 88%) after purification by column chromatography.

Rf: 0.25 (5% EtOAc:95% Petroleum Benzene); IR (neat, cm^{-1}): 3070, 1586, 1522, 1475, 1347, 1238, 1194, 881, 710; 1H NMR (400 MHz, $CDCl_3-d$) δ 7.95 (dd, $J=8.4, 1.7$ Hz, 1H), 7.50 (ddd, $J=8.4, 7.4, 1.7$ Hz, 1H), 7.44 – 7.33 (m, 2H), 7.24 – 7.14 (m, 2H), 7.09 – 7.03 (m, 2H), 7.01 (dd, $J=8.4, 1.7$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.65, 150.36, 141.17, 134.13, 129.93, 125.44, 124.41, 123.15, 120.38, 118.94; HRMS (APCI): m/z calcd for $C_{12}H_{10}O_3N$ [$M+H$] $^+$ 216.0655, found, 216.0655.

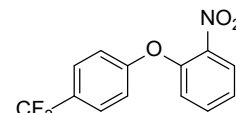
1-(4-Fluorophenoxy)-2-nitrobenzene (S7)

A mixture of 4-fluorophenol **S2** (3.28 g, 29.2 mmol), K_2CO_3 (16.4 g, 119 mmol) and DMF (30 mL) and was stirred under N_2 for 10 min at rt. 1-Fluoro-2-nitrobenzene **S5** (4.15 g, 29.3 mmol) was added and the reaction mixture heated at 100 °C for 3 days. The mixture was cooled to rt,

poured into cold water (100 mL) and the crude product **S7** extracted with DCM (3 × 60 mL). The organic layers were combined, washed with water (4 × 100 mL), dried over Na₂SO₄ and the solvent removed *in vacuo*. The title compound **S7** was obtained as an orange oil (5.38 g, 79%) after purification by column chromatography.

R_f: 0.25 (5% EtOAc:95% Petroleum Benzine); IR (neat, cm⁻¹): 3077, 1602, 1524, 1497, 1476, 1347, 1218, 1184, 1088, 813; ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.93 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.50 (ddd, *J* = 8.4, 7.4, 1.7 Hz, 1H), 7.23 – 7.15 (m, 1H), 7.14 – 6.99 (m, 4H), 6.96 (dd, *J* = 8.4, 1.2 Hz, 1H), ¹³C NMR (101 MHz, CDCl₃-*d*) δ 159.48 (d, *J* = 243.6 Hz), 151.57 (d, *J* = 2.7 Hz), 150.88, 141.13, 134.28, 125.82, 123.25, 120.93 (d, *J* = 8.4 Hz), 119.94, 116.77 (d, *J* = 23.6 Hz); ¹⁹F NMR (CDCl₃-*d*): δ -118.67; HRMS (APCI): *m/z* calcd for C₁₂H₈O₃NF [M]⁺ 233.0483 found 233.0484 and C₁₂H₉O₃NF [M+H]⁺ 234.0561 found 234.0561.

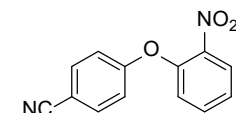
1-Nitro-2-(4-(trifluoromethyl)phenoxy)benzene (**S8**)



A mixture of 4-trifluoromethylphenol **S3** (2.15 g, 13.2 mmol), K₂CO₃ (9.24 g, 66.8 mmol) and DMF (30 mL) and was stirred under N₂ for 10 min at rt. 1-Fluoro-2-nitrobenzene **S5** (1.69 g, 12.0 mmol) was added and the reaction mixture heated at 100 °C for 3 days. The mixture was cooled to rt, poured into cold water (100 mL) and the crude product **S8** extracted with DCM (3 × 60 mL). The organic layers were combined, washed with water (4 × 100 mL), dried over Na₂SO₄ and the solvent removed *in vacuo*. The title compound **S8** obtained as an orange oil (2.37 g, 70%) after purification by column chromatography.

R_f: 0.21 (5% EtOAc:95% Petroleum Benzine); IR (neat, cm⁻¹): 1598, 1527, 1512, 1478, 1321, 1241, 1104, 1063, 838, 736; ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.99 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.65 – 7.55 (m, 3H), 7.32 (ddd, *J* = 8.3, 7.5, 1.3 Hz, 1H), 7.14 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.11 – 7.03 (m, 2H); ¹³C NMR (101 MHz, CDCl₃-*d*) δ 159.30, 148.77, 142.05, 134.65, 127.38 (q, *J* = 3.8 Hz), 125.98 (q, *J* = 32.9 Hz), 125.93, 124.97, 124.02 (q, *J* = 271.6 Hz), 122.41, 117.96; ¹⁹F NMR (377 MHz, CDCl₃) δ -62.47; HRMS (APCI): *m/z* calcd for C₁₃H₈O₃NF₃ [M]⁺ 283.0451 found 283.0450 and C₁₃H₉O₃NF₃ [M+H]⁺ 284.0529 found 283.0527.

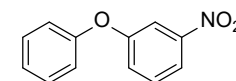
4-(2-Nitrophenoxy)benzonitrile (**S9**)



A mixture of 4-cyanophenol **S4** (1.47 g, 12.3 mmol), K₂CO₃ (1.52 g, 12.7 mmol) and DMF (30 mL) and was stirred under N₂ for 10 min at rt. 1-Fluoro-2-nitrobenzene **S5** (1.74 g, 12.3 mmol) was added and the reaction mixture heated at 100 °C for 3 days. The reaction mixture was cooled to rt, poured into cold water (100 mL) and, upon standing, a yellow precipitate was formed. The mixture was filtered and the solid washed with cold water to remove excess DMF. The crude product **S9** was obtained as a pale yellow solid (2.77 g, 94%). The crude **S9** product was sufficiently pure by ¹H NMR analysis and was used without purification.

R_f: 0.31 (20% EtOAc:80% Petroleum Benzine); mp: 110 – 113 °C; IR (neat, cm⁻¹): 3096, 2227, 1588, 1522, 1492, 1353, 1236, 1160, 839, 783; ¹H NMR (400 MHz, CDCl₃-*d*) δ 8.09 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.78 – 7.65 (m, 3H), 7.45 (ddd, *J* = 8.2, 7.5, 1.3 Hz, 1H), 7.25 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.14 – 7.05 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 160.40, 147.86, 142.30, 134.82, 134.34, 126.16, 125.75, 123.24, 118.44, 117.94, 107.22; HRMS (APCI): *m/z* calcd for C₁₃H₉O₃N₂ [M+H]⁺ 241.0608 found 241.0608.

1-Nitro-3-phenoxybenzene (**S11**)

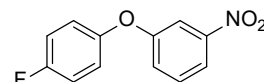


A mixture of phenol **S1** (2.97 g, 31.6 mmol), K₂CO₃ (17.1 g, 124 mmol) and dry DMF (30 mL) and was stirred under N₂ for 15 min at rt. 1,3-Dinitrobenzene **S10** (5.31 g, 31.6 mmol) was added and the reaction mixture heated at 100 °C for 4 days. The mixture was cooled to rt, poured into cold water (100

mL) and the crude product **S11** extracted with DCM (3 × 80 mL). The combined organic layers were washed with water (4 × 80 mL), brine (80 mL), dried over Na₂SO₄ and the solvent removed *in vacuo*. The title compound **S11** was obtained as a yellow oil (5.54 g, 81%) after purification column chromatography.

R_f: 0.32 (5% EtOAc:95% Petroleum Benzine); IR (neat, cm⁻¹): 3080, 3039, 1739, 1585, 1522, 1488, 1473, 1351, 1275, 1230, 1022, 939, 837, 735; ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.92 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 7.79 (t, *J* = 2.3 Hz, 1H), 7.47 (t, *J* = 8.2 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.32 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.10 – 7.02 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 158.61, 155.60, 149.37, 130.38, 124.90, 124.20, 119.84, 117.67, 112.89; HRMS (APCI): *m/z* calcd for C₁₂H₁₀O₃N [M+H]⁺ 216.0655, found, 216.0655.

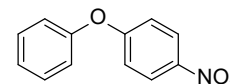
1-(4-Fluorophenoxy)-3-nitrobenzene (**S12**)



A mixture of 4-fluorophenol **S2** (2.24 g, 20.0 mmol), Cs₂CO₃ (17.8 g, 54.5 mmol) and DMF (15 mL) and was stirred under N₂ for 10 min at rt. 1,3-Dinitrobenzene **S10** (3.40 g, 20.3 mmol) was added and the reaction mixture heated at 70 °C for 3 days. The mixture was cooled to rt, poured into cold water (100 mL) and the crude product **S12** extracted with DCM (6 x 60 mL). The organic layers were combined, washed with water (4 x 100 mL), dried over MgSO₄ and the solvent removed *in vacuo*. The title compound **S12** was obtained as a pale yellow oil (3.16 g, 68%) after purification column chromatography.

R_f: 0.16 (3% EtOAc:97% Petroleum Benzine); IR (neat, cm⁻¹): 3082, 1526, 1498, 1473, 1351, 1276, 1212; ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.93 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 7.74 (t, *J* = 2.3 Hz, 1H), 7.48 (t, *J* = 8.2 Hz, 1H), 7.29 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 7.15 – 7.07 (m, 2H), 7.07 – 7.01 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 161.01, 158.96, 158.58, 151.31 (d, *J* = 2.8 Hz), 149.44, 130.52, 123.78, 121.65 (d, *J* = 8.4 Hz), 117.75, 117.18, 116.95, 112.42, 77.48, 77.36, 77.16, 76.84; ¹⁹F NMR (CDCl₃-*d*): δ -118.16. HRMS (APCI): *m/z* calcd for C₁₂H₉O₃NF [M+H]⁺ 234.0561 found 234.0559.

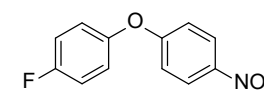
1-Nitro-4-phenoxybenzene (**S14**)



A mixture of phenol **S1** (2.43 g, 25.9 mmol), K₂CO₃ (18.3 g, 132.6 mmol) and dry DMF (40 mL) was stirred under N₂ for 15 min. 1-Fluoro-4-nitrobenzene **S13** (3.65 g, 25.8 mmol) was added and the reaction mixture heated at 100 °C for 3 days. The reaction mixture was cooled to rt, poured into cold water (100 mL) and, upon standing, a yellow precipitate was formed. The mixture was filtered and the solid washed with cold water. The title compound **S14** was obtained as a pale yellow solid (5.01 g, 90%) after purification by column chromatography.

R_f: 0.36 (5% EtOAc:95% Petroleum Benzine); mp: 58 – 60 °C; IR (neat, cm⁻¹): 3104, 3075, 3018, 1610, 1591, 1580, 1481, 1457, 1420, 1329, 1236, 1196, 1110; ¹H NMR (400 MHz, CDCl₃-*d*) δ 8.19 (d, *J* = 9.2 Hz, 2H), 7.49 – 7.37 (m, 2H), 7.26 (dt, *J* = 7.5, 1.1 Hz, 1H), 7.14 – 7.05 (m, 2H), 7.01 (d, *J* = 9.2 Hz, 2H)., ¹³C NMR (101 MHz, CDCl₃) δ 163.38, 154.76, 142.68, 130.36, 125.94, 125.45, 120.56, 117.14; HRMS (APCI): *m/z* calcd for C₁₂H₁₀O₃N [M+H]⁺ 216.0655, found, 216.0654.

Fluoro-4-(4-nitrophenoxy)benzene (**S15**)



A mixture of 4-fluorophenol **S2** (3.00 g, 26.8 mmol), K₂CO₃ (14.8 g, 107 mmol) and dry DMF (30 mL) was stirred under N₂ for 15 min. 1-Fluoro-4-nitrobenzene **S13** (4.15 g, 29.4 mmol) was added and the reaction mixture heated at 100 °C for 3 days. The reaction mixture was cooled to rt, poured into cold water (100 mL) and, upon standing, a yellow precipitate was formed. The mixture

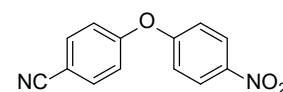
was filtered and the solid washed with water. The title compound **S15** was obtained as a pale yellow solid (5.84 g, 94%) after purification by column chromatography.

R_f: 0.32 (5% EtOAc:95% Petroleum Benzine); mp: 73 – 74.6 °C; IR (neat, cm⁻¹): 3077, 1602, 1524, 1497, 1476, 1347, 1252, 1218, 1184, 1088, 839, 813 770, 738; ¹H NMR (400 MHz, CDCl₃-*d*) δ 8.25 – 8.10 (m, 2H), 7.19 – 7.02 (m, 4H), 7.02 – 6.90 (m, 2H); ¹³C NMR (101 MHz, CDCl₃-*d*) δ 163.54, 160.05 (d, *J* = 244.6 Hz), 150.58 (d, *J* = 2.8 Hz), 142.80, 126.08, 122.26 (d, *J* = 8.4 Hz), 117.11 (d, *J* = 23.5 Hz), 116.87; ¹⁹F NMR (CDCl₃-*d*): δ -117.38; HRMS (APCI): *m/z* calcd for C₁₂H₈O₃NF [M]⁺ 233.0483 found 233.0484 and C₁₂H₉O₃NF [M+H]⁺ 234.0561 found 234.0560.

1-Nitro-4-(4-(trifluoromethyl)phenoxy)benzene (S16)

A mixture of 4-(trifluoromethyl)phenol **S3** (1.87 g, 11.5 mmol), K₂CO₃ (7.09 g, 51.3 mmol) and DMF (30 mL) and was stirred under N₂ for 10 min at rt. 1-Fluoro-4-nitrobenzene **S13** (1.63 g, 11.5 mmol) was added and the reaction mixture heated at 100 °C for 1.5 days. The reaction mixture was cooled to rt, poured into cold water (100 mL) and, upon standing, a yellow precipitate was formed. The mixture was filtered and the solid washed with cold water. The crude product **S16** was obtained as a yellow solid (2.83 g, 87%). The crude product **S16** was sufficiently pure by ¹H NMR analysis and was used without purification.

R_f: 0.32 (5% EtOAc:95% Petroleum Benzine); mp: 58.4 – 62.8 °C; IR (neat, cm⁻¹): 3120, 1609, 1586, 1509, 1489, 1325, 1240, 1101, 1062, 843, 747; ¹H NMR (400 MHz, CDCl₃-*d*) δ 8.25 (d, *J* = 9.3 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 9.3 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃-*d*) δ 162.00, 157.98, 143.59, 127.79 (q, *J* = 3.7 Hz), 127.30 (q, *J* = 32.8, 0.0 Hz), 124.41 (q, *J* = 270.0, 0.0 Hz), 120.18, 118.29; ¹⁹F NMR (377 MHz, CDCl₃-*d*) δ -62.63; HRMS (APCI): *m/z* calcd for C₁₃H₉O₃NF₃ [M+H]⁺ 284.0529 found 283.0526.



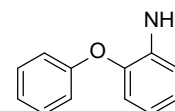
4-(4-Nitrophenoxy)benzonitrile (S17)

A mixture of 4-cyanophenol **S4** (0.78 g, 6.52 mmol), K₂CO₃ (4.88 g, 35.3 mmol) and DMF (30 mL) and was stirred under N₂ for 10 min at rt. 1-Fluoro-4-nitrobenzene **S13** (0.92 g, 6.52 mmol) was added and the reaction mixture heated at 100 °C for 2 days. The reaction mixture was cooled to rt, poured into cold water (100 mL) and, upon, standing a yellow precipitate was formed. The mixture was filtered and the solid washed with cold water. The crude product **S17** was obtained as a yellow solid (1.26 g, 80%). The crude product **S17** was sufficiently pure by ¹H NMR analysis and was used without purification.

R_f: 0.25 (15% EtOAc:85% Petroleum Benzine); mp: 159.9 – 160.7 °C; IR (neat, cm⁻¹): 3103, 2225, 1582, 1509, 1499, 1482, 1342, 1246, 1100, 839, 754, 688; ¹H NMR (400 MHz, CDCl₃-*d*) δ 8.28 (d, *J* = 9.1 Hz, 2H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.20 – 7.07 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 161.04, 159.15, 144.15, 134.79, 126.38, 120.14, 119.10, 118.30, 108.57; HRMS (APCI): *m/z* calcd for C₁₃H₉O₃N₂ [M+H]⁺ 241.0608 found 241.0607.

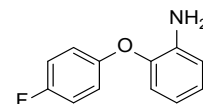
2-Phenoxyaniline (11)

A mixture of the nitro compound **S6** (1.85 g, 8.60 mmol), EtOH (50 mL) and Pd/C (188 mg) was deoxygenated by bubbling with N₂ for 30 min. The mixture was placed under H₂ and stirred overnight at rt. The reaction progress was monitored by TLC analysis. The mixture was filtered through celite, which was subsequently washed with EtOH (3 × 30 mL), and solvent removed *in vacuo*. The title compound **11** was obtained as a pale brown oil (1.38 g, 87%) after purification by column chromatography.



R_f: 0.32 (15% EtOAc:85% Petroleum Benzine); IR (neat, cm⁻¹): 3433, 3355, 3049, 1619, 1582, 1487, 1191, 1166, 877, 741, 692; ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.36 – 7.27 (m, 2H), 7.10 – 7.03 (m, 1H), 7.02 – 6.94 (m, 3H), 6.88 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.72 (ddd, *J* = 8.0, 7.3, 1.6 Hz, 1H), 3.80 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 157.63, 143.20, 138.87, 129.82, 125.02, 122.75, 120.39, 118.88, 117.24, 116.59.

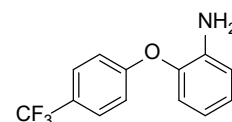
2-(4-Fluorophenoxy)aniline (12)



A mixture of the nitro compound **S7** (1.30 g, 5.57 mmol), Pd/C (183 mg) and EtOH (50 mL) was deoxygenated by bubbling with N₂ for 30 min. The mixture was placed under H₂ and stirred overnight at rt. The reaction progress was monitored by TLC analysis. The mixture was filtered through celite, which was subsequently washed with EtOH (3 × 30 mL), and the solvent removed *in vacuo*. The title compound **12** was obtained as a yellow oil (1.04 g, 92%) after purification by column chromatography.

R_f: 0.24 (15% EtOAc:85% Petroleum Benzine); ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.06 – 6.91 (m, 5H), 6.83 (dd, *J* = 7.9, 1.6 Hz, 2H), 6.72 (td, *J* = 7.9, 1.6 Hz, 1H), 3.81 (s, 2H); ¹³C NMR (101 MHz, CDCl₃-*d*) δ 158.53 (d, *J* = 240.8 Hz), 153.38 (d, *J* = 2.4 Hz), 143.73, 138.57, 124.91, 119.63, 118.89, 118.75 (d, *J* = 8.2 Hz), 116.59, 116.28 (d, *J* = 23.3 Hz); ¹⁹F NMR (377 MHz, CDCl₃) δ -121.71; HRMS (APCI): *m/z* calcd for C₁₂H₁₀ONF [M]⁺ 203.0743 found 203.0743 and C₁₂H₁₁ONF [M]⁺ 203.0741, found 203.0742.

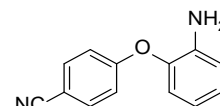
2-(4-(Trifluoromethyl)phenoxy)aniline (13)



A mixture of the nitro compound **S8** (1.79 g, 6.32 mmol), Pd/C (172 mg) and EtOH (50 mL) was deoxygenated by bubbling with N₂ for 30 min. The mixture was placed under H₂ and stirred overnight at rt. The reaction progress was monitored by TLC analysis. The mixture was filtered through celite, which was subsequently washed with EtOH (3 × 30 mL), and the solvent removed *in vacuo*. The title compound **13** was obtained as a brown oil (1.50 g, 94%) after purification by column chromatography.

R_f: 0.31 (10% EtOAc:90% Petroleum Benzine); IR (neat, cm⁻¹): 3455, 3364, 1609, 1449, 1323, 1222, 1165, 1102, 1066, 831, 743; ¹H NMR (600 MHz, CDCl₃-*d*) δ 7.61 – 7.52 (m, 2H), 7.06 (td, *J* = 7.6, 1.5 Hz, 1H), 7.03 (dd, *J* = 9.1, 2.5 Hz, 2H), 6.93 (dt, *J* = 8.2, 1.8 Hz, 1H), 6.86 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.77 (td, *J* = 7.6, 1.6 Hz, 1H), 3.72 (s, 2H); ¹³C NMR (151 MHz, CDCl₃-*d*) δ 160.48, 141.79, 139.07, 127.28 (q, *J* = 3.6 Hz), 126.13, 124.69 (q, *J* = 32.8 Hz), 124.36 (q, *J* = 271.4 Hz), 121.28, 119.15, 116.96, 116.57; ¹⁹F NMR (377 MHz, CDCl₃) δ -62.24; HRMS (APCI): *m/z* calcd for C₁₃H₁₀O₃NF₃ [M]⁺ 253.0709 found 253.0709 and C₁₃H₁₁O₃NF₃ [M+H]⁺ 254.0787 found 254.0786.

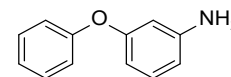
4-(2-Aminophenoxy)benzotrile (14)



A mixture of the nitro compound **S9** (790 mg, 3.29 mmol), Pd/C (99 mg) and EtOH (50 mL) was deoxygenated by bubbling with N₂ for 30 min. The mixture was placed under H₂ and stirred for 3 h at rt. The reaction progress was monitored by TLC analysis. The mixture was filtered through celite, which was subsequently washed with EtOH (3 × 30 mL), and the solvent removed *in vacuo*. The title compound **14** was obtained as a brown solid (641 mg, 93%) after purification by column chromatography.

R_f: 0.29 (20% EtOAc:80% Petroleum Benzine); ¹H NMR (600 MHz, CDCl₃-*d*) δ 7.60 – 7.49 (m, 2H), 7.11 – 7.01 (m, 1H), 7.01 – 6.95 (m, 2H), 6.91 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.79 – 6.71 (m, 1H), 3.79 (s, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 161.25, 140.75, 139.06, 134.09, 126.43, 121.36, 118.88, 118.86, 116.90, 116.77, 105.44; HRMS (APCI): *m/z* calcd for C₁₃H₁₀ON₂ [M]⁺ 210.0789, found, 210.0789.

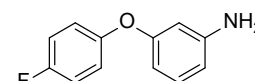
3-Phenoxyaniline (15)



A mixture of the nitro compound **S11** (1.81 g, 8.46 mmol), EtOH (50 mL) and Pd/C (180 mg) was deoxygenated by bubbling with N₂ for 30 min. The reaction mixture was placed under H₂ and stirred overnight at rt. The reaction progress was monitored by TLC analysis. The mixture was filtered through celite, which was subsequently washed with EtOH (3 × 30 mL), and the solvent removed *in vacuo*. The title compound **15** was obtained as a brown oil (1.50 g, 96%) after purification by column chromatography.

R_f: 0.34 (20% EtOAc:80% Petroleum Benzine); ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.38 – 7.28 (m, 2H), 7.15 – 7.05 (m, 2H), 7.06 – 6.97 (m, 2H), 6.46 – 6.36 (m, 2H), 6.33 (t, *J* = 2.3 Hz, 1H), 3.67 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 158.43, 157.19, 148.10, 130.37, 129.69, 123.18, 119.10, 110.11, 108.83, 105.52.

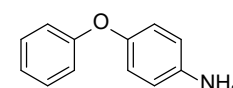
3-(4-Fluorophenoxy)aniline (16)



A mixture of 1-(4-fluorophenoxy)-3-nitrobenzene **S12** (1.86 g, 7.96 mmol), EtOH (50 mL) and Pd/C (217 mg) was deoxygenated by bubbling with N₂. Hydrazine monohydrate (2.4 mL, 49.48 mmol) was added and the mixture stirred overnight at rt. The mixture was filtered through celite, which was subsequently washed with EtOH (3 × 30 mL), and the solvent removed *in vacuo*. DCM (30 mL) was added and the organic layer was washed with water (3 × 15 mL), dried over MgSO₄ and the solvent removed *in vacuo*. The title compound **16** was obtained as a brown oil (1.31 g, 81%) after purification by column chromatography.

R_f: 0.22 (20% EtOAc:80% Petroleum Benzine); IR (neat, cm⁻¹): 3387, 3010, 1601, 1584, 1486, 1193. ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.08 (t, *J* = 8.1 Hz, 1H), 7.05 – 6.96 (m, 4H), 6.41 (ddd, *J* = 8.1, 2.2, 0.9 Hz, 1H), 6.34 (ddd, *J* = 8.1, 2.2, 0.9 Hz, 1H), 6.28 (t, *J* = 2.2 Hz, 1H), 3.69 (s, 2H); ¹³C NMR (101 MHz, CDCl₃-*d*) δ 159.16, 159.07 (d, *J* = 241.4 Hz), 153.06 (d, *J* = 2.7 Hz), 148.29, 130.67, 120.99 (d, *J* = 8.2 Hz), 116.45 (d, *J* = 23.2 Hz), 110.24, 108.52, 105.18; ¹⁹F NMR (376 MHz, CDCl₃-*d*) δ -120.80; HRMS (APCI): *m/z* calcd for C₁₂H₁₁ONF [M+H]⁺ 204.0819 found 204.0819.

4-Phenoxyaniline (17)

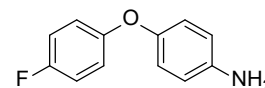


A mixture of the nitro compound **S14** (1.98 g, 9.25 mmol), EtOH (50 mL) and Pd/C (200 mg) was deoxygenated by bubbling with N₂ for 30 min. The reaction mixture was placed under H₂ and stirred overnight at rt. The reaction progress was monitored by TLC analysis. The mixture was filtered through celite, which was subsequently washed with EtOH (3 × 30 mL), and the solvent removed *in vacuo*. The title compound **17** was obtained as a pale brown solid (1.61 g, 94%) after purification by column chromatography.

R_f: 0.22 (20% EtOAc:80% Petroleum Benzine); IR (neat, cm⁻¹): 3391, 3316, 3223, 1589, 1502, 1483, 1220, 812, 700; ¹H NMR (600 MHz, CDCl₃-*d*) δ 7.31 – 7.26 (m, 2H), 7.01 (td, *J* = 7.5, 1.0 Hz, 1H), 6.95 – 6.91 (m, 2H), 6.89 – 6.85 (m, 2H), 6.71 – 6.65 (m, 2H), 3.57 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 158.97, 148.61, 142.81, 129.59, 122.14, 121.17, 117.30, 116.29; HRMS (APCI): *m/z* calcd for C₁₂H₁₁ONF [M]⁺ 185.0835 found 185.0843.

4-(4-Fluorophenoxy)aniline (18)

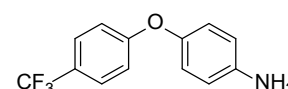
A mixture of the nitro compound **S15** (1.98 g, 8.50 mmol), Pd/C (212 mg) and EtOH (50 mL) was deoxygenated by bubbling with N₂ for 30 min. The mixture was placed under H₂ and stirred overnight at rt. The reaction progress was monitored by TLC analysis. The mixture was filtered through celite, which was subsequently washed with EtOH (3 × 30 mL), and the solvent removed *in vacuo*. The title compound **18** was obtained as a reddish-brown solid (1.68 g, 98%) after purification by column chromatography.



R_f: 0.24 (25% EtOAc:75% Petroleum Benzine); ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.01 – 6.92 (m, 2H), 6.92 – 6.86 (m, 2H), 6.86 – 6.80 (m, 2H), 6.70 – 6.62 (m, 2H), 3.57 (s, 2H); ¹³C NMR (101 MHz, CDCl₃-*d*) δ 156.81, 154.65 (d, *J* = 2.3 Hz), 154.04 (d, *J* = 1037.4 Hz), 142.78, 120.56, 118.60 (d, *J* = 8.1 Hz), 116.17, 115.93 (d, *J* = 23.2 Hz); ¹⁹F NMR (CDCl₃-*d*): δ -124.48; HRMS (APCI): *m/z* calcd for C₁₂H₁₁ONF [M+H]⁺ 204.0819 found 204.0825.

4-(4-(Trifluoromethyl)phenoxy)aniline (19)

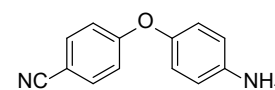
A mixture of the nitro compound **S16** (2.83 g, 10.0 mmol), EtOH (50 mL) and Pd/C (283 mg) was deoxygenated. Hydrazine monohydrate (3 mL, 61.5 mmol) was added and the mixture stirred overnight at rt. The mixture was filtered through celite, which was subsequently washed with EtOH (3 × 30 mL), and the solvent removed *in vacuo*. DCM (30 mL) was added and the organic layer was washed with water (3 × 15 mL), dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude product **120** was obtained as a cream solid (2.33 g, 92%). The crude product **19** was sufficiently pure by ¹H NMR analysis and was used without purification.



R_f: 0.26 (15% EtOAc:85% Petroleum Benzine); IR (neat, cm⁻¹): 3488, 3401, 1603, 1504, 1313, 1239, 1027, 1063, 834; ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.52 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 3.64 (s, 2H); ¹³C NMR (151 MHz, CDCl₃-*d*) δ 161.98, 147.41, 143.49, 127.08 (q, *J* = 3.8 Hz), 124.45 (q, *J* = 271.3 Hz), 124.06 (q, *J* = 32.6 Hz), 121.80, 116.71, 116.53; ¹⁹F NMR (377 MHz, CDCl₃) δ -62.17; HRMS (APCI): *m/z* calcd for C₁₃H₁₀O₃NF₃ [M]⁺ 253.0709 found 253.0710 and C₁₃H₁₁O₃NF₃ [M+H]⁺ 254.0787 found 254.0785.

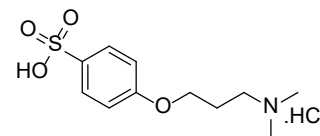
4-(4-Aminophenoxy)benzonitrile (20)

A mixture of the nitro compound **S17** (620 mg, 2.17 mmol), EtOH (50 mL) and Pd/C (52 mg) was deoxygenated by bubbling with N₂ for 30 min. The mixture was placed under H₂ and stirred for 3h at rt. The reaction progress was monitored by TLC analysis. The mixture was filtered through celite, which was subsequently washed with EtOH (3 × 30 mL), and the solvent removed *in vacuo*. The crude product **20** was obtained as a cream solid (494 mg, 91%). The crude product **121** was sufficiently pure by ¹H NMR analysis and was used without purification.



R_f: 0.30 (30% EtOAc:80% Petroleum Benzine); ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.58 – 7.53 (m, 2H), 6.97 – 6.91 (m, 2H), 6.90 – 6.84 (m, 2H), 6.74 – 6.69 (m, 2H), 3.67 (s, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 162.83, 146.18, 144.13, 134.00, 121.79, 119.11, 116.93, 116.26, 104.79; HRMS (APCI): *m/z* calcd for C₁₃H₁₀ON₂ [M]⁺ 210.0789, found, 210.0788.

4-(3-(Dimethylamino)propoxy)benzenesulfonic acid hydrochloride (**52.HCl**)

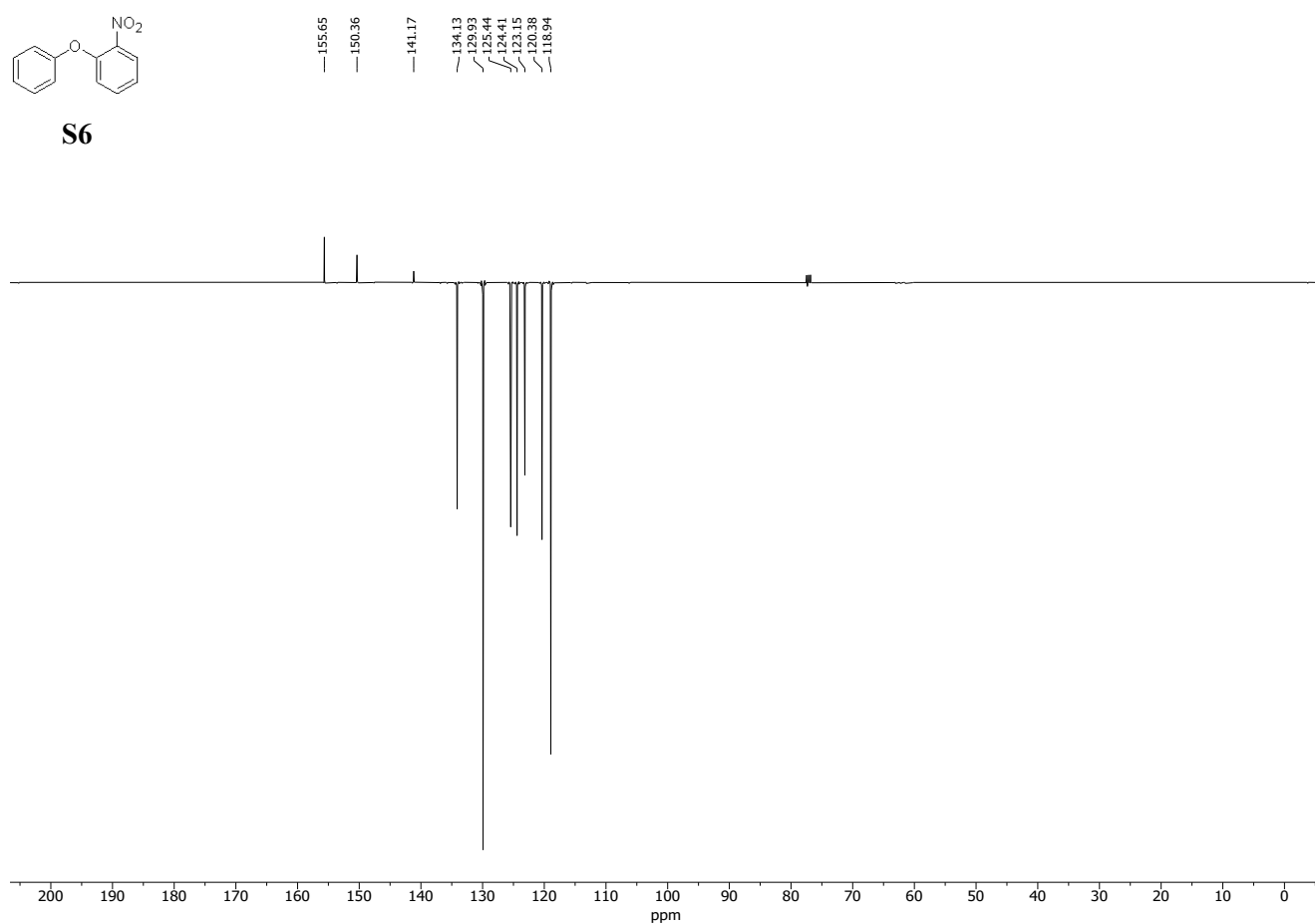
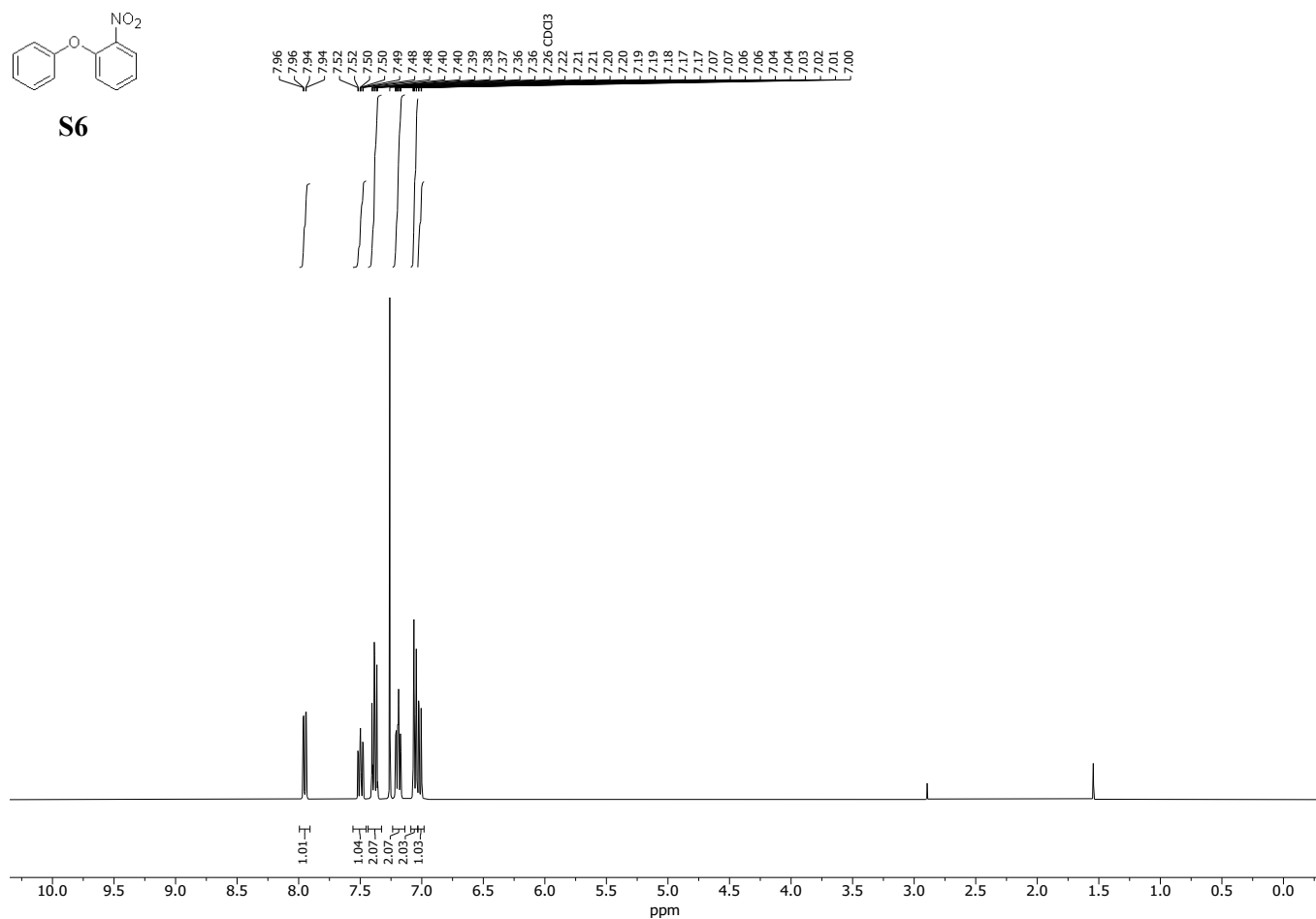


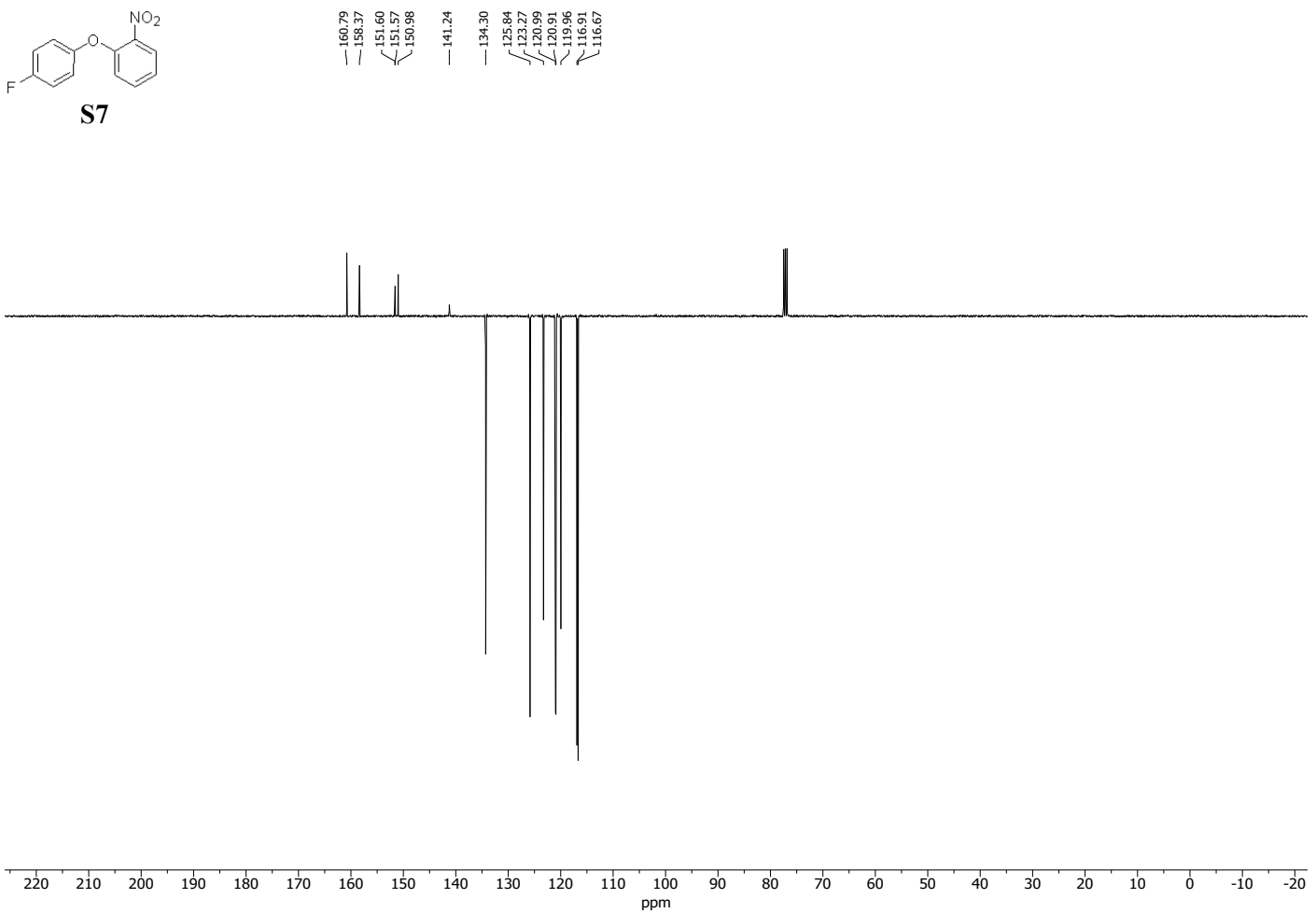
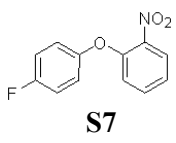
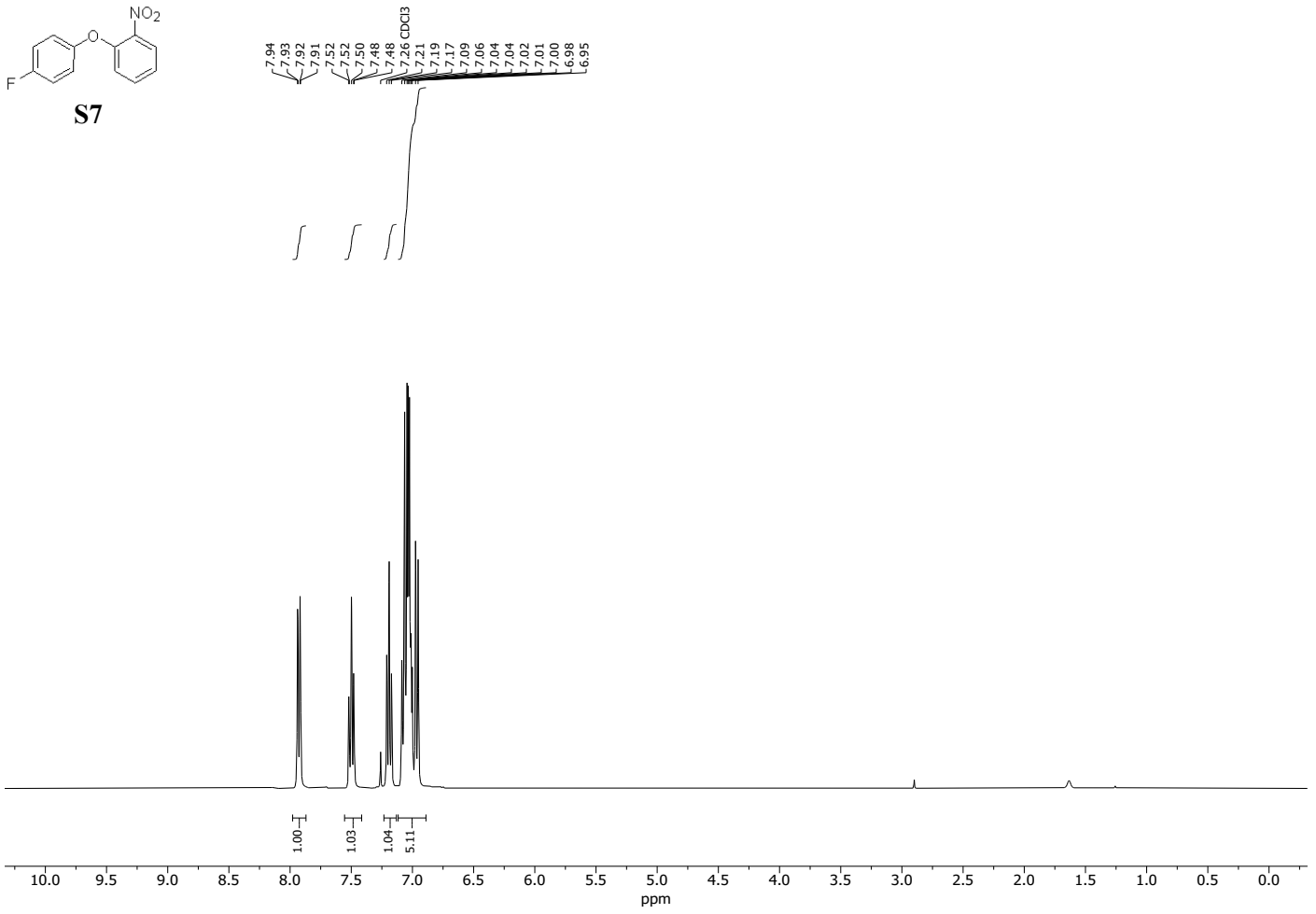
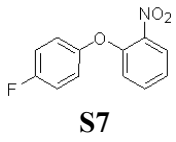
The benzenesulfonic acid **52** was prepared using a modified procedure reported by Payne *et al.*² The HCl salt of **S18** (8.26 g, 0.038 mol) was dissolved in DCM (60 mL) and the solution cooled to $-30\text{ }^{\circ}\text{C}$ in an acetone/dry ice bath. A solution of chlorosulfonic acid (6.0 mL, 0.09 mol) in DCM (30 mL) was added to the stirred flask dropwise over 1 h while the temperature was maintained at $-30\text{ }^{\circ}\text{C}$. The reaction was stirred for an additional 3 h at $-30\text{ }^{\circ}\text{C}$. The aqueous layer was collected and the product was recrystallised from MeOH to give the title compound **52** as a white solid (7.97 g, 70%). The crude product was sufficiently pure to proceed to the next step in the reaction sequence based on the ^1H NMR analysis.

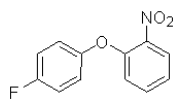
IR (neat, cm^{-1}): 3012, 2698, 1599, 1487, 1219, 1157, 1119, 1102, 1017, 995, 831, 700 ; ^1H NMR (400 MHz, Deuterium Oxide): δ 7.70 (d, $J = 8.4$ Hz, 2H), 6.98 (d, $J = 7.3$ Hz, 2H), 4.12 – 4.00 (m, 2H), 3.28 (t, $J = 7.8$ Hz, 2H), 2.88 (s, 6H), 2.23 – 2.06 (m, 2H); ^{13}C NMR* (101 MHz, D_2O): δ 161.02, 136.69, 128.35, 115.54, 66.18, 56.43, 43.80, 24.91; HRMS (APCI): m/z calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_4\text{S} [\text{M}]^-$ 258.0800, found, 258.0806.

* - Referenced against MeOD (added to NMR sample)

1.2. Spectra of intermediate compounds



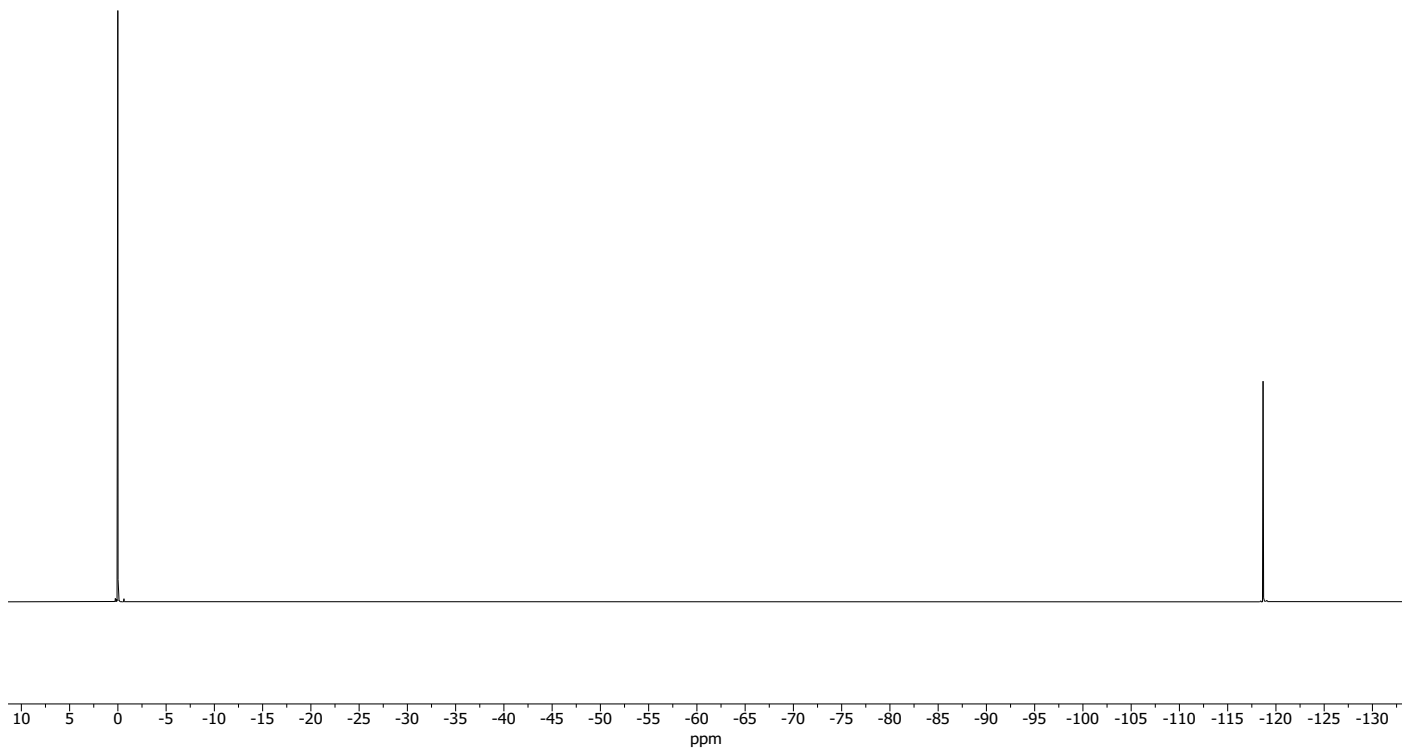


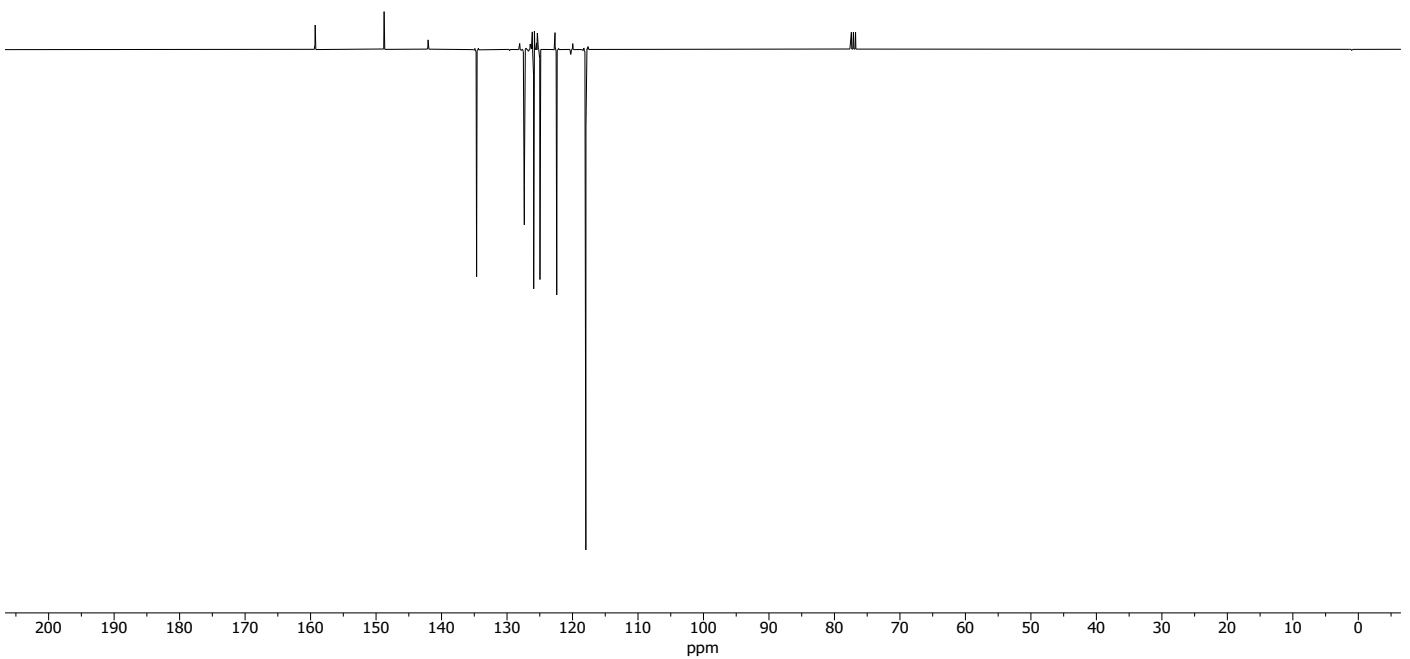
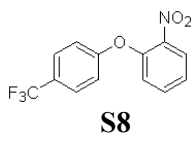
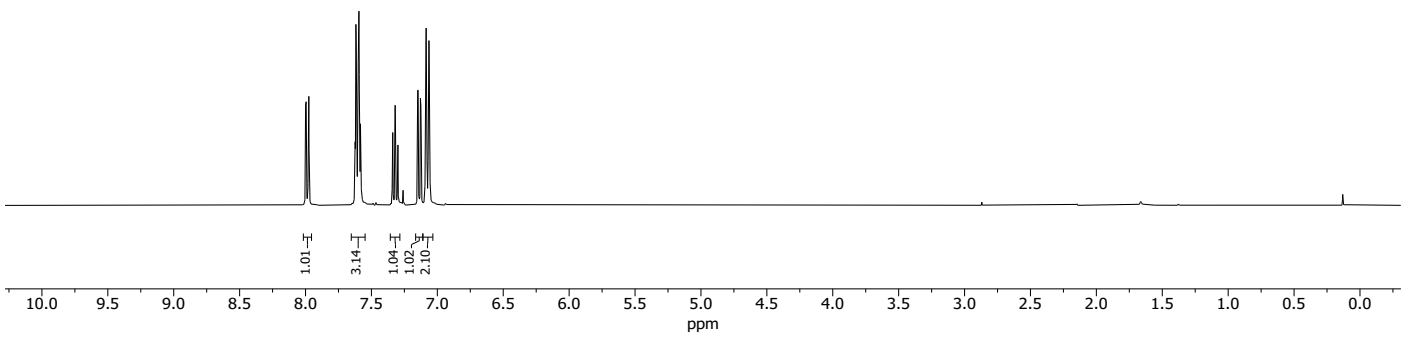
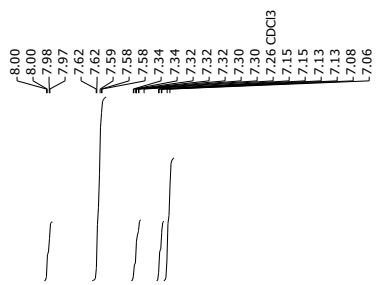
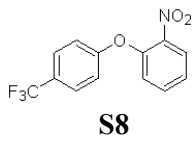


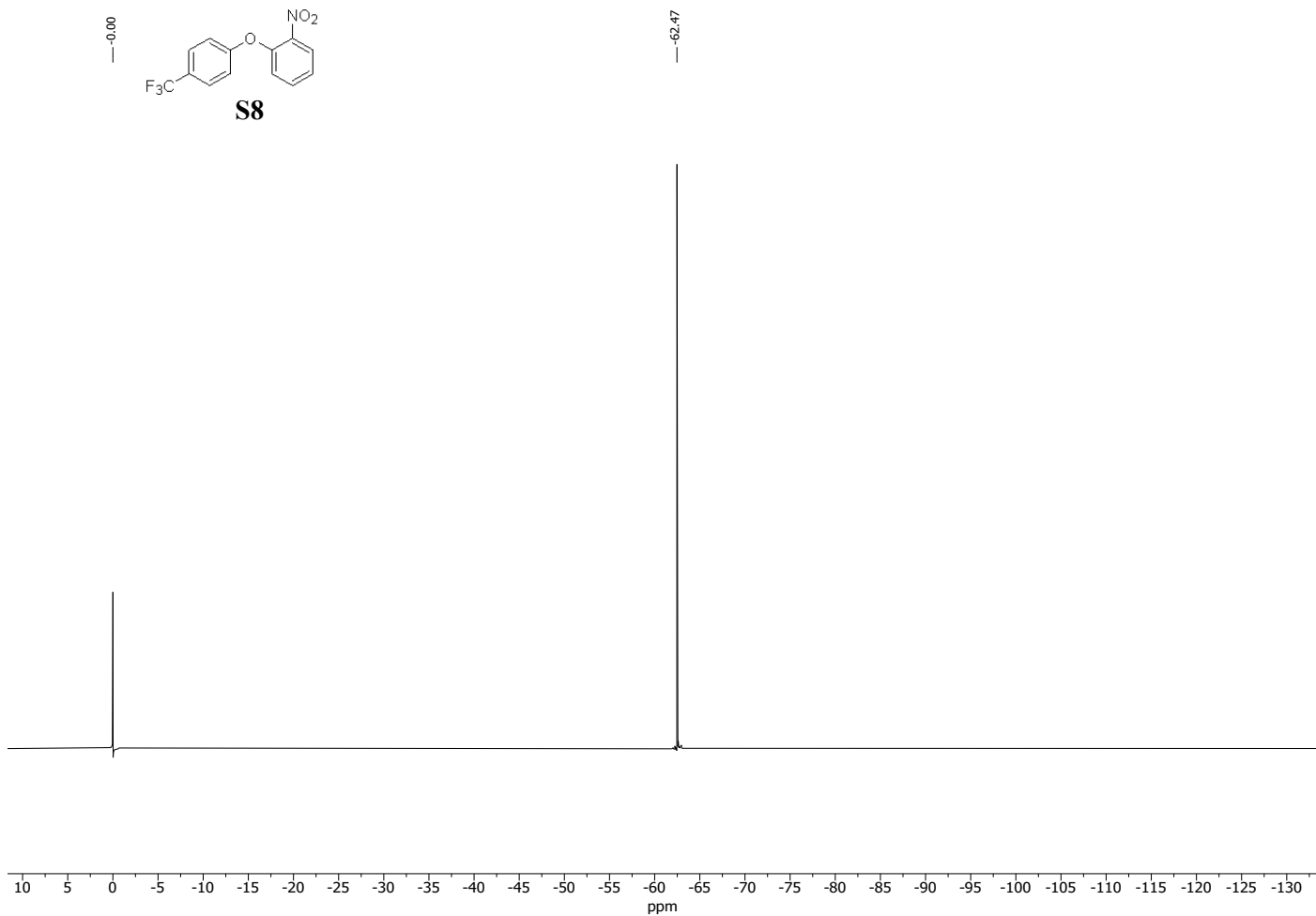
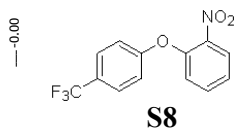
S7

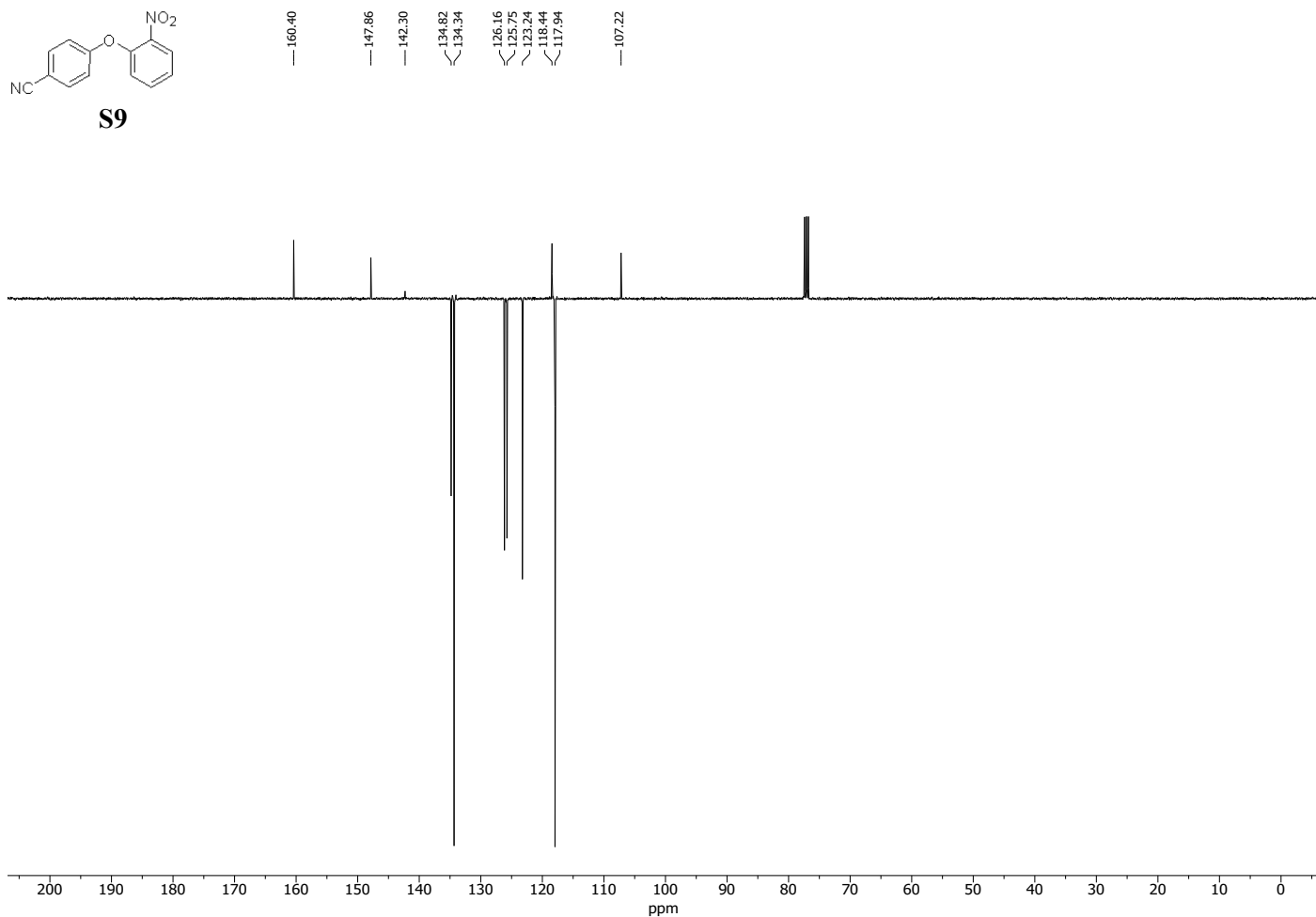
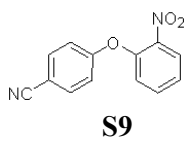
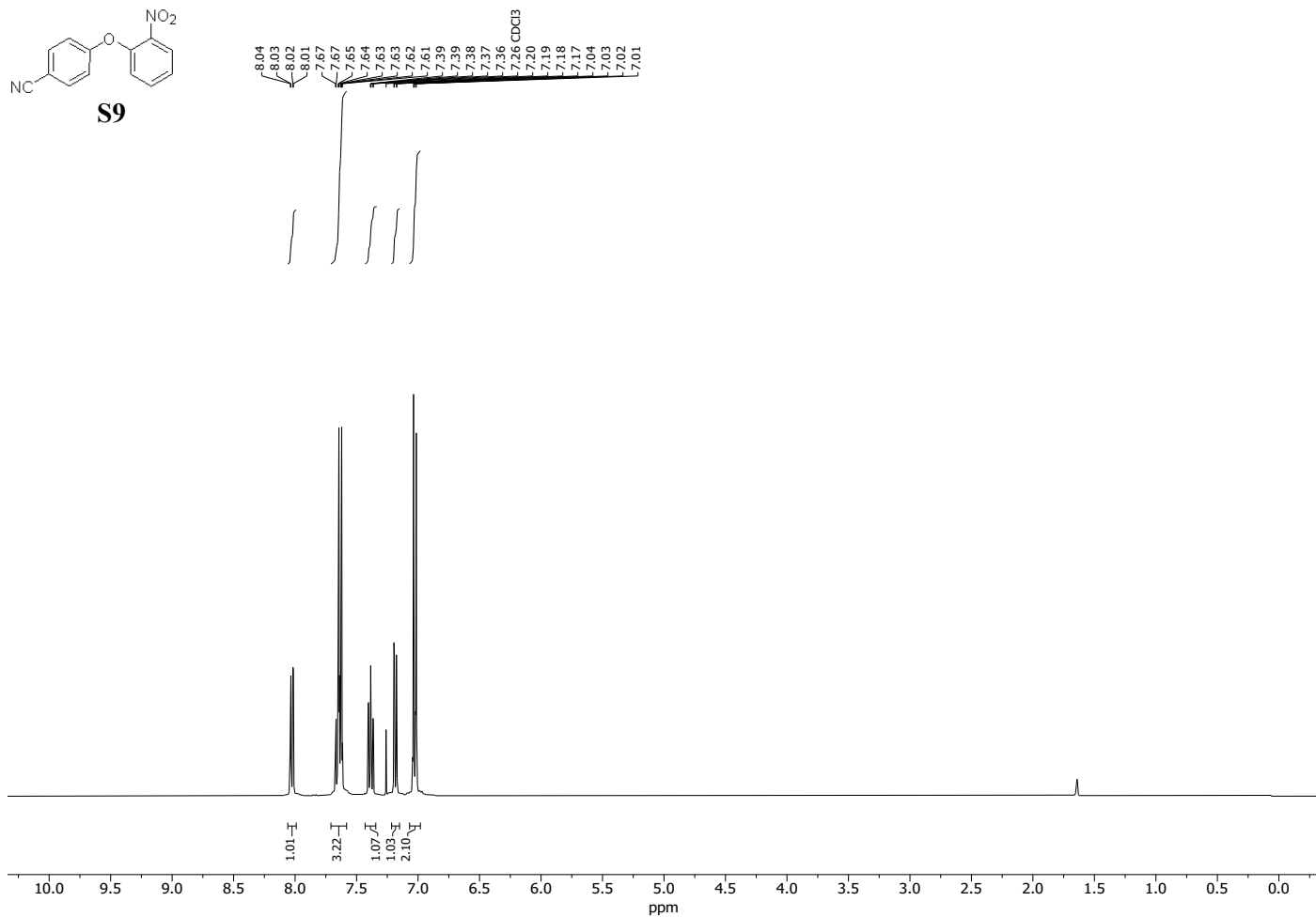
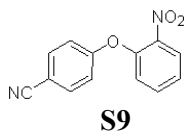
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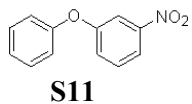
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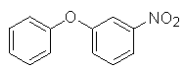
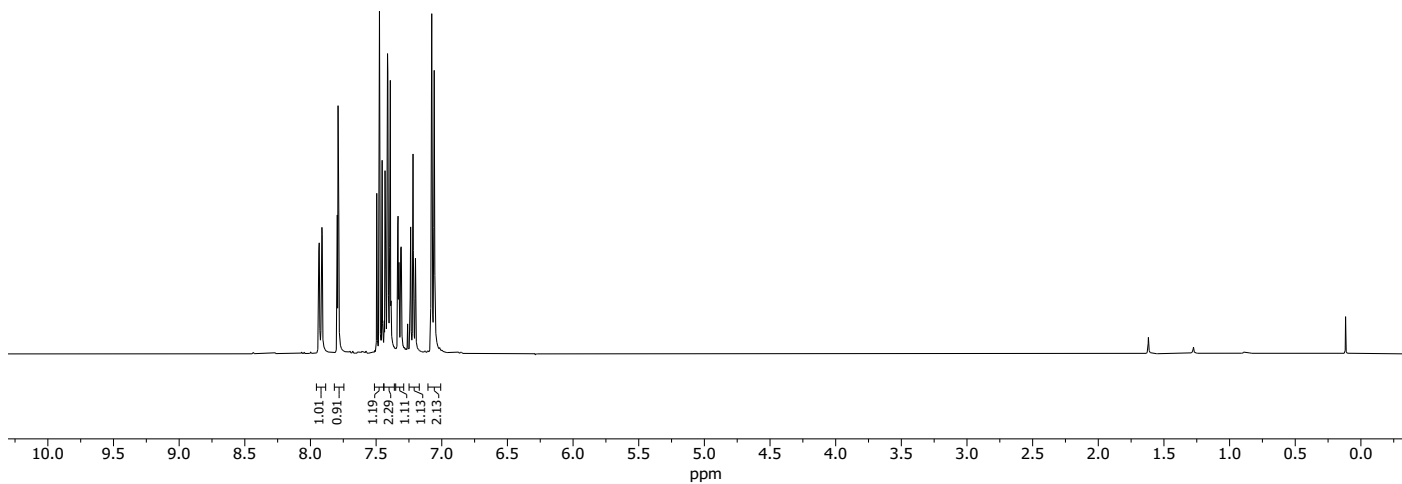
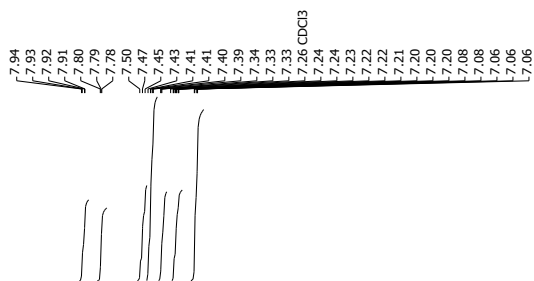




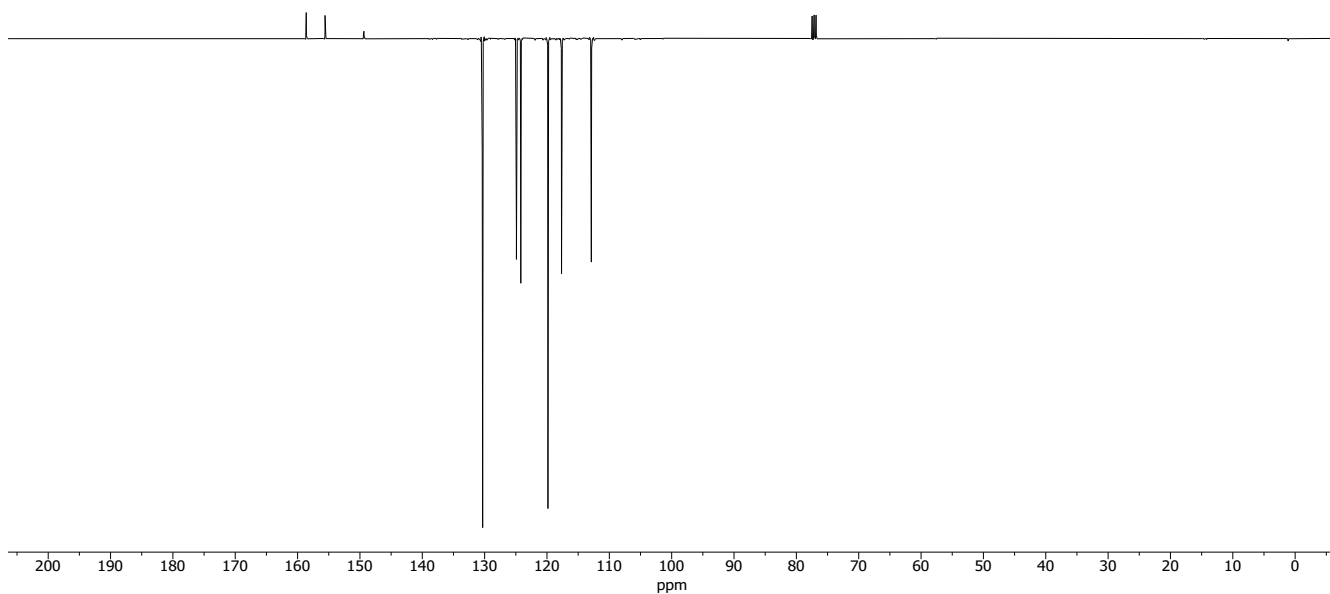


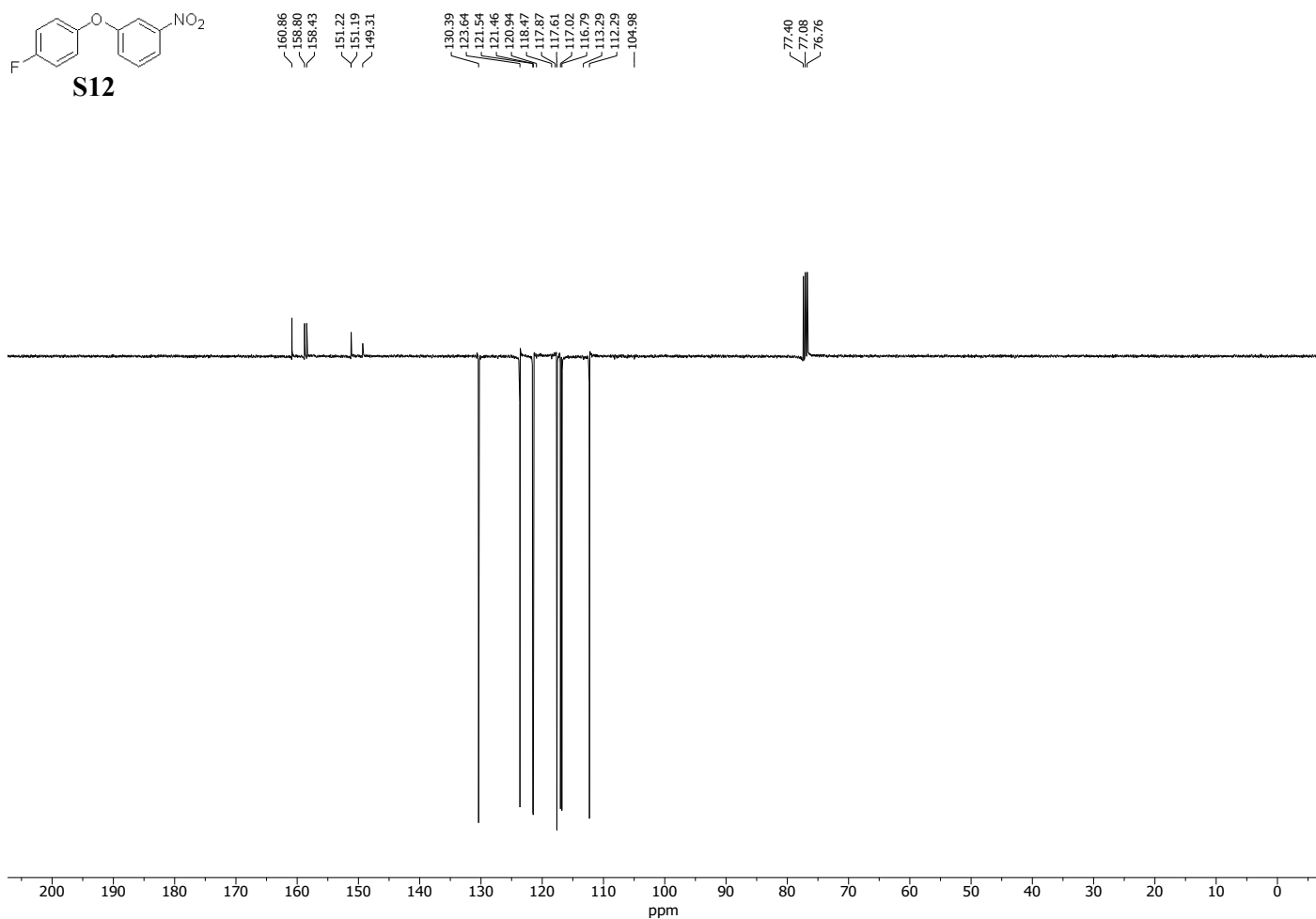
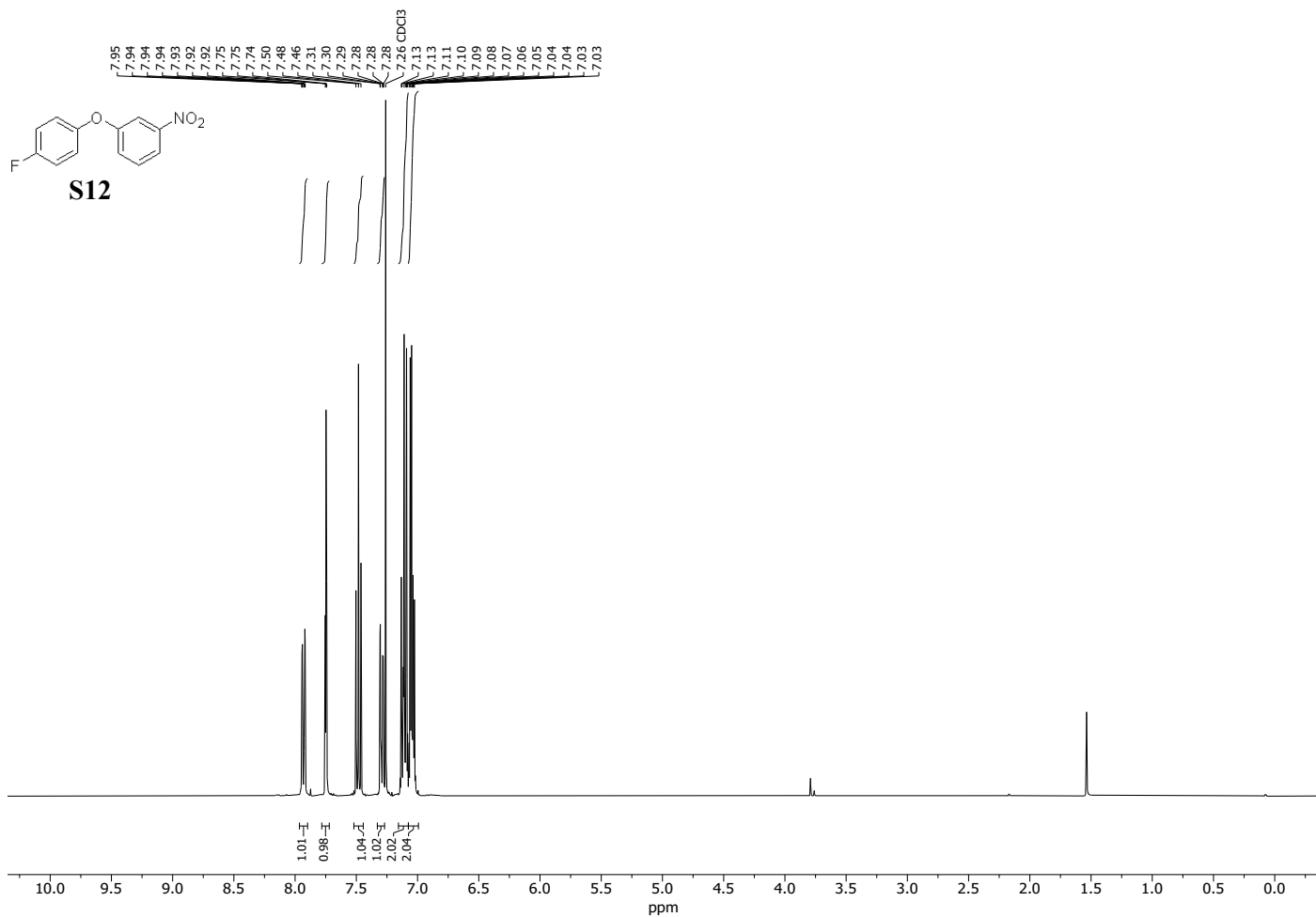


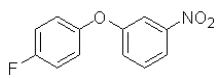
S11



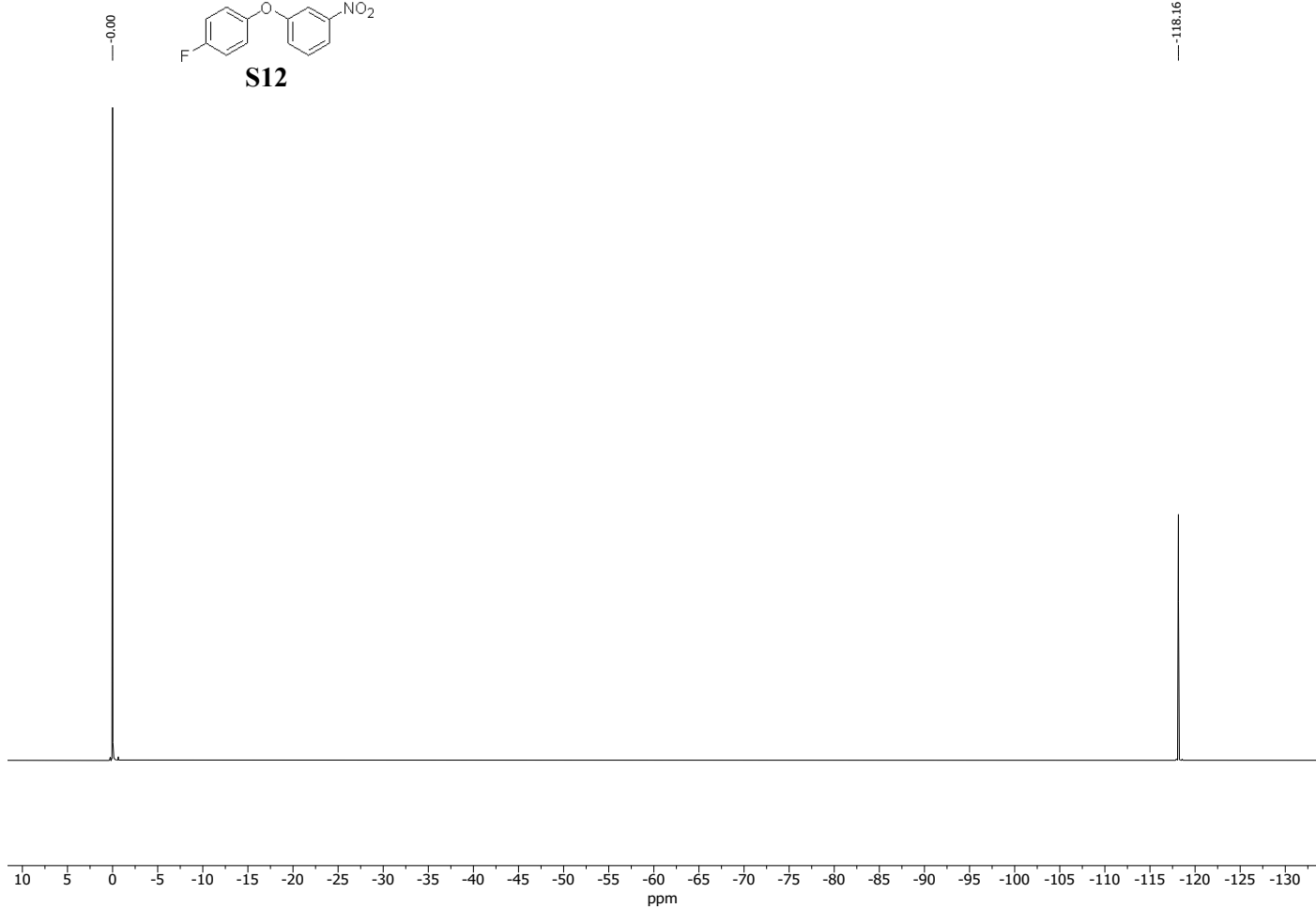
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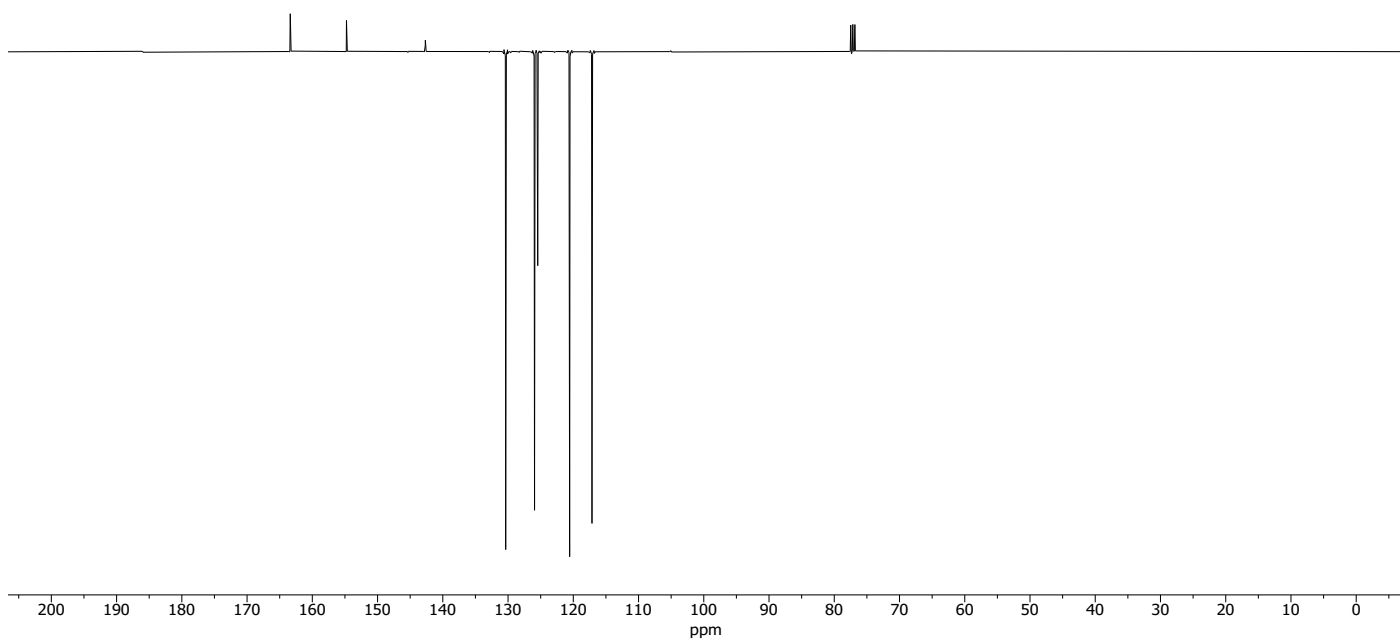
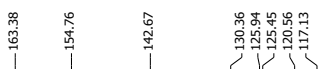
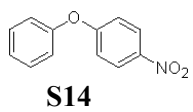
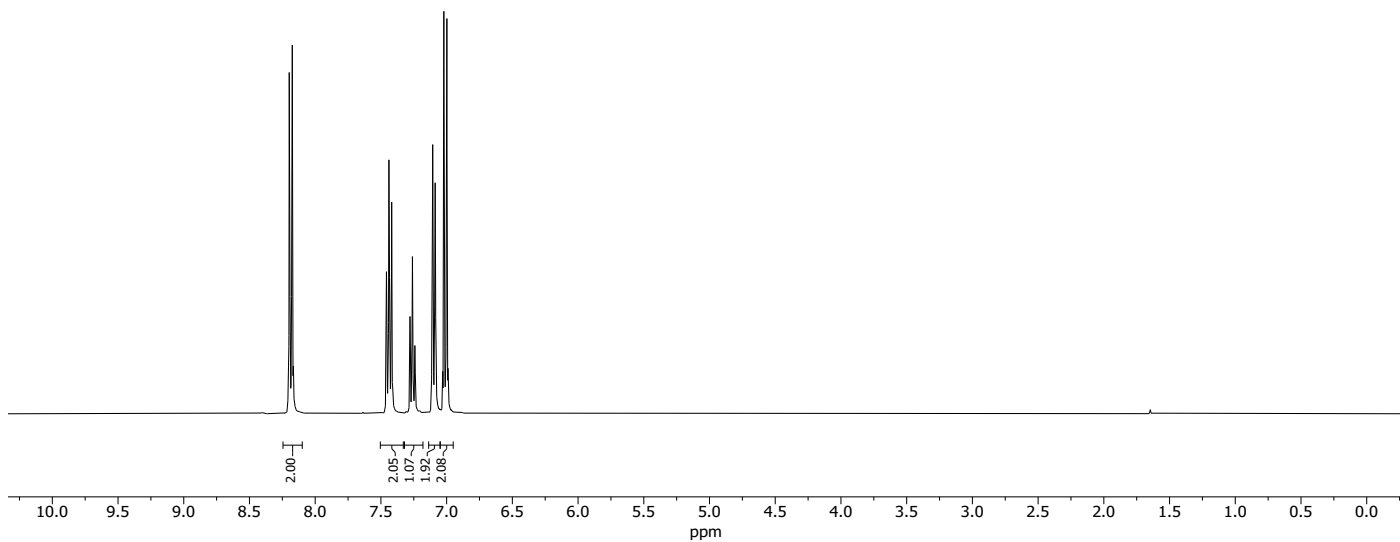
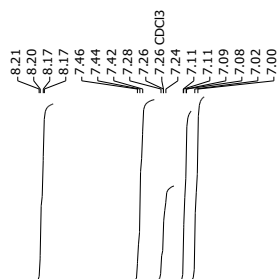
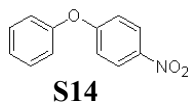


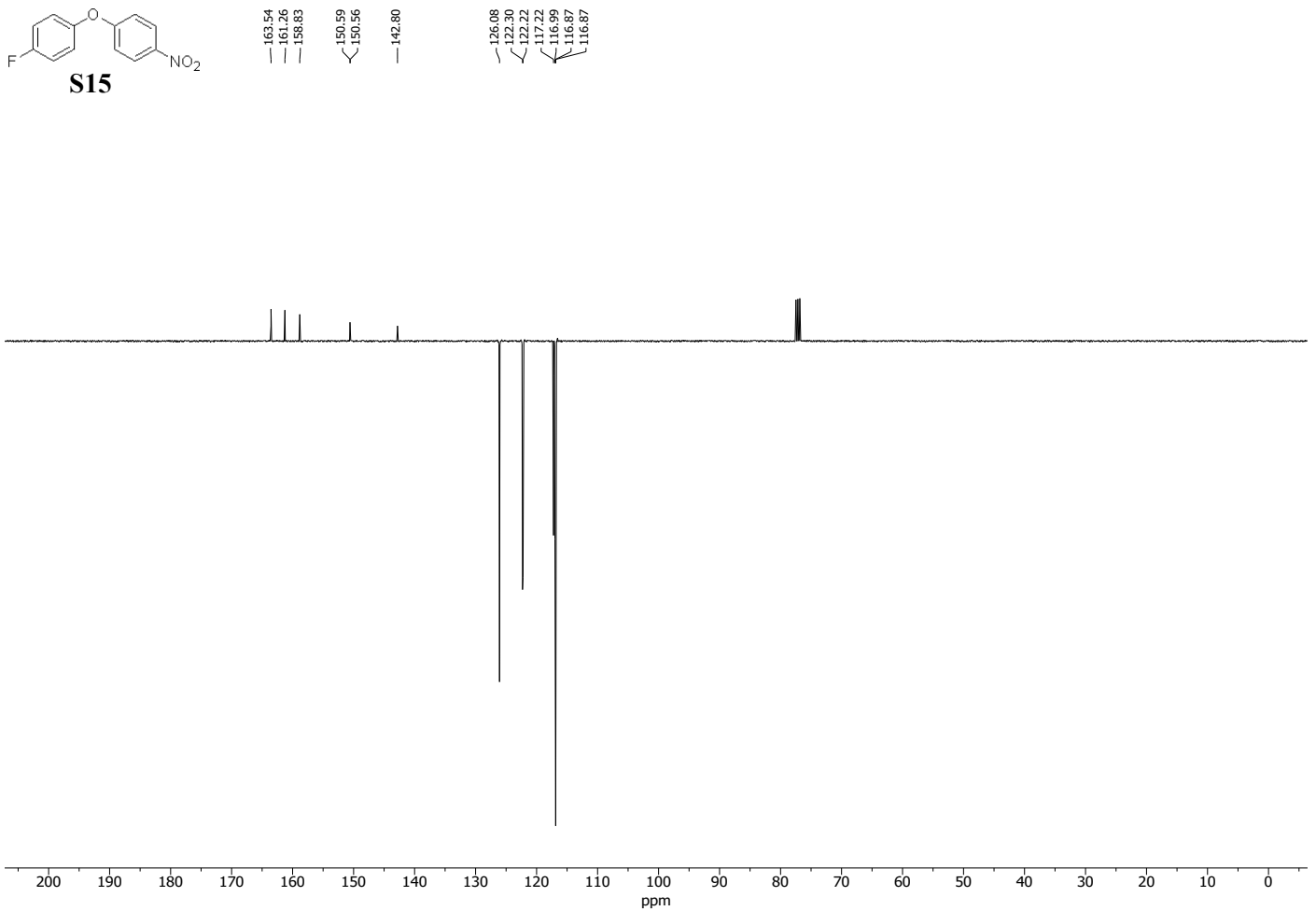
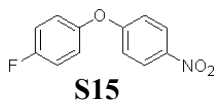
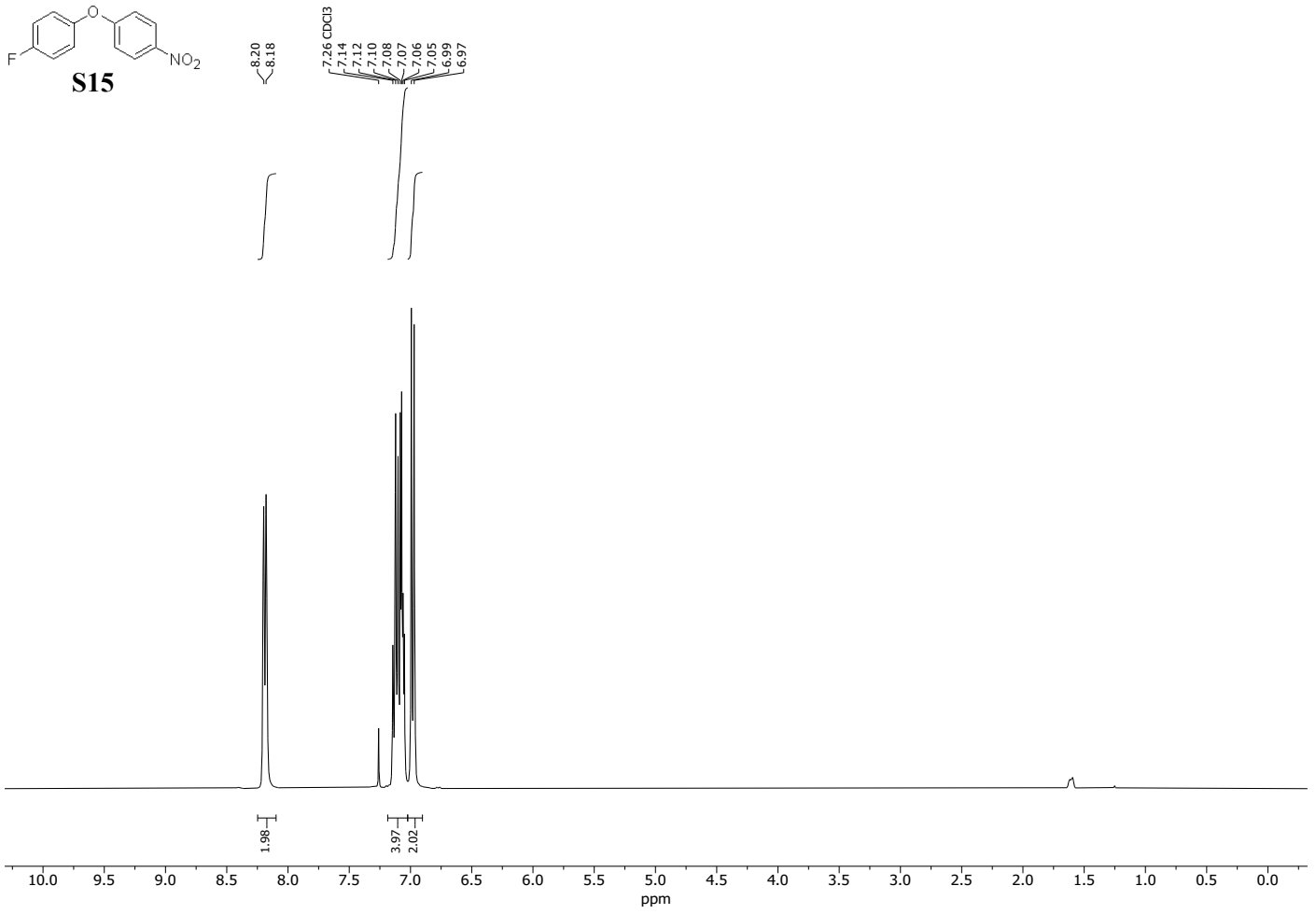
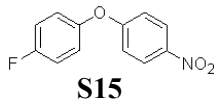


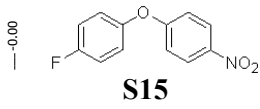


S12

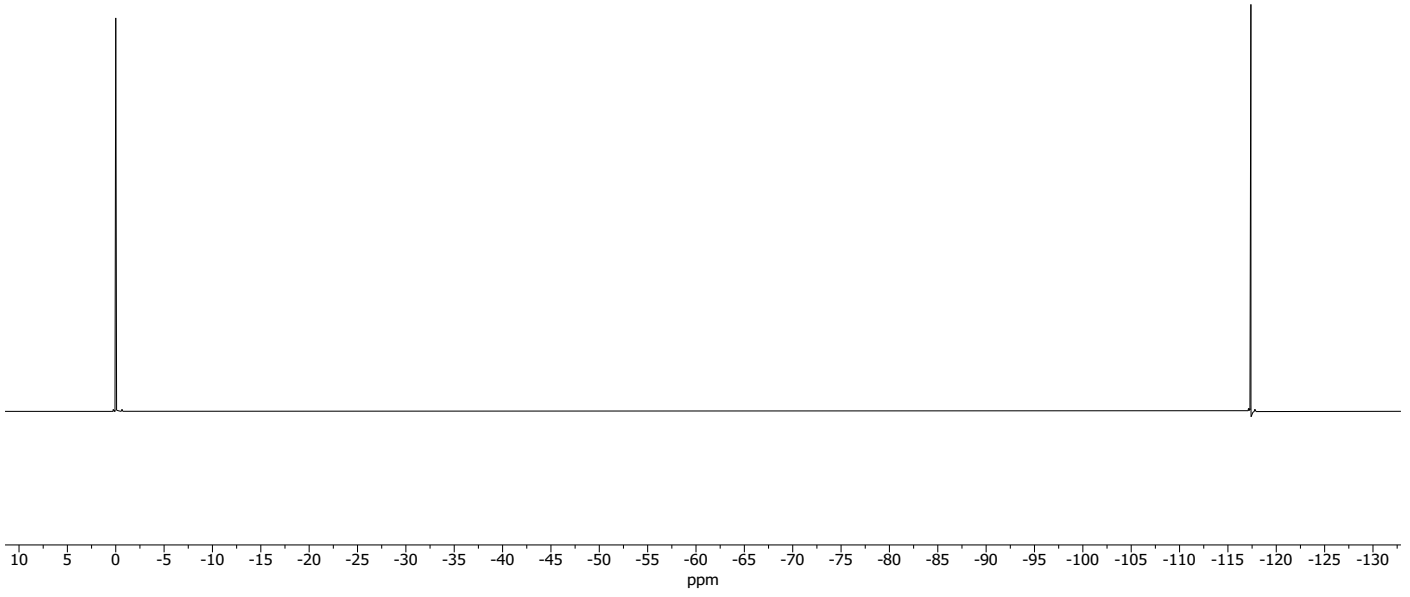


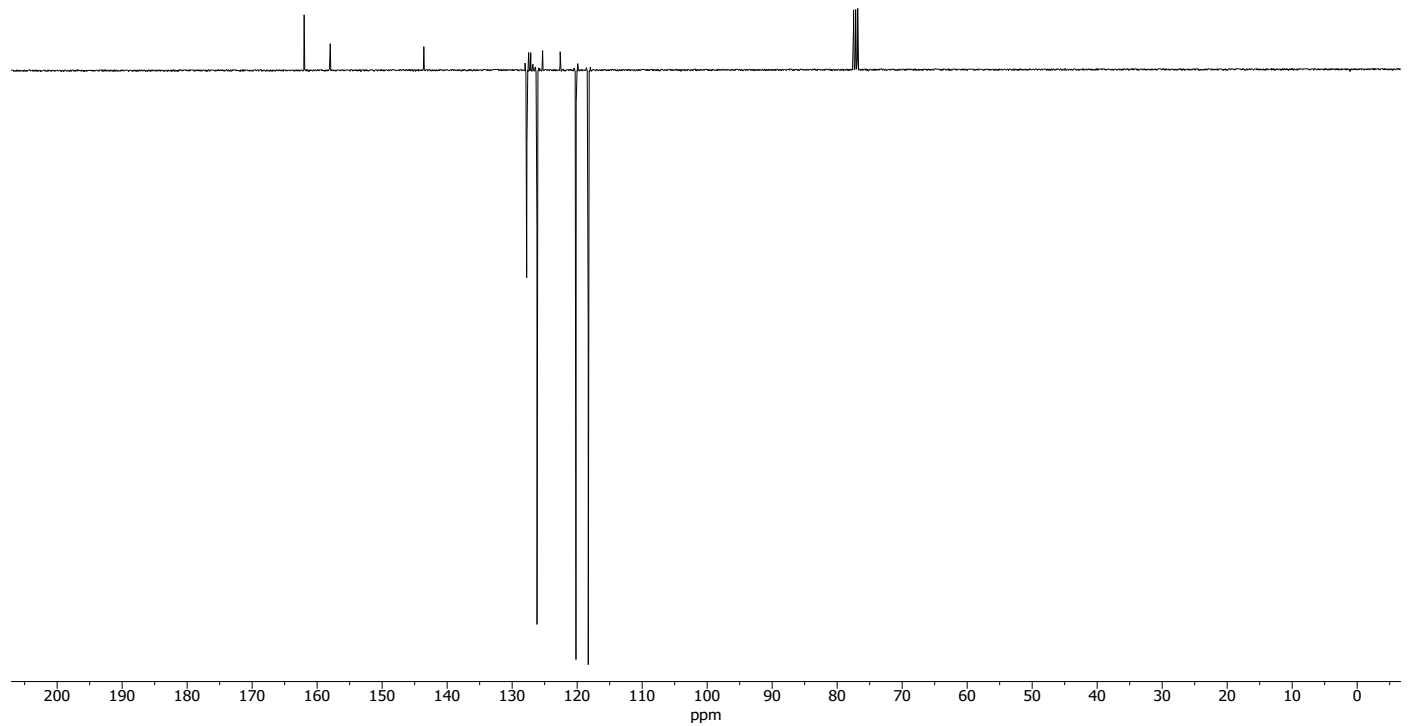
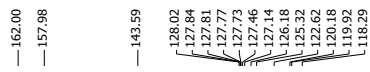
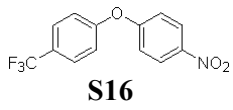
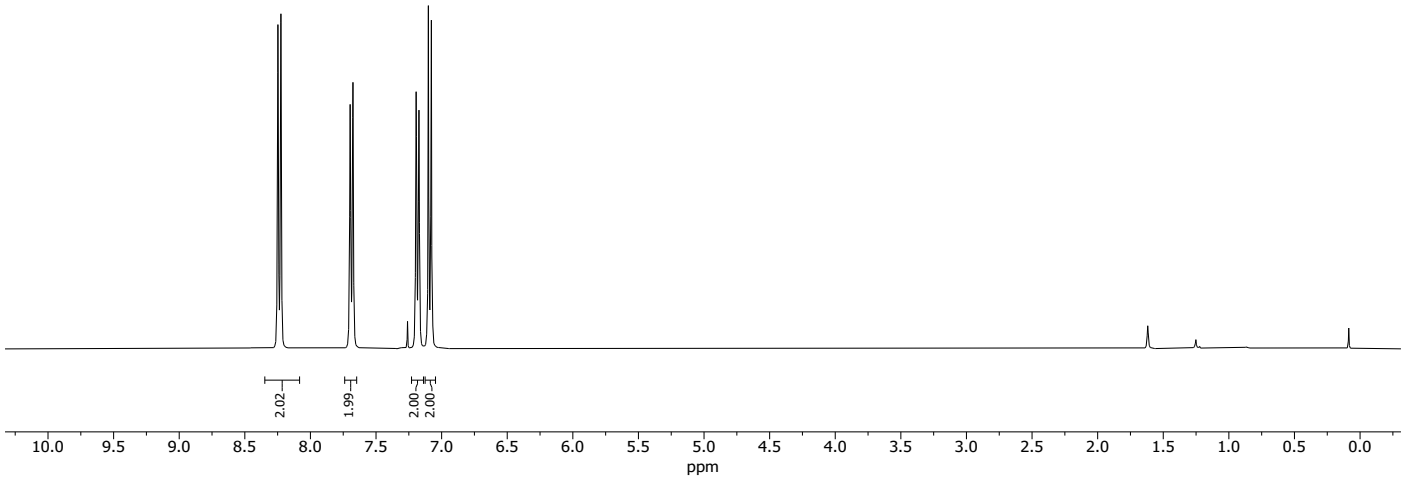
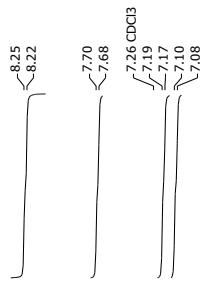
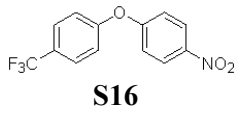


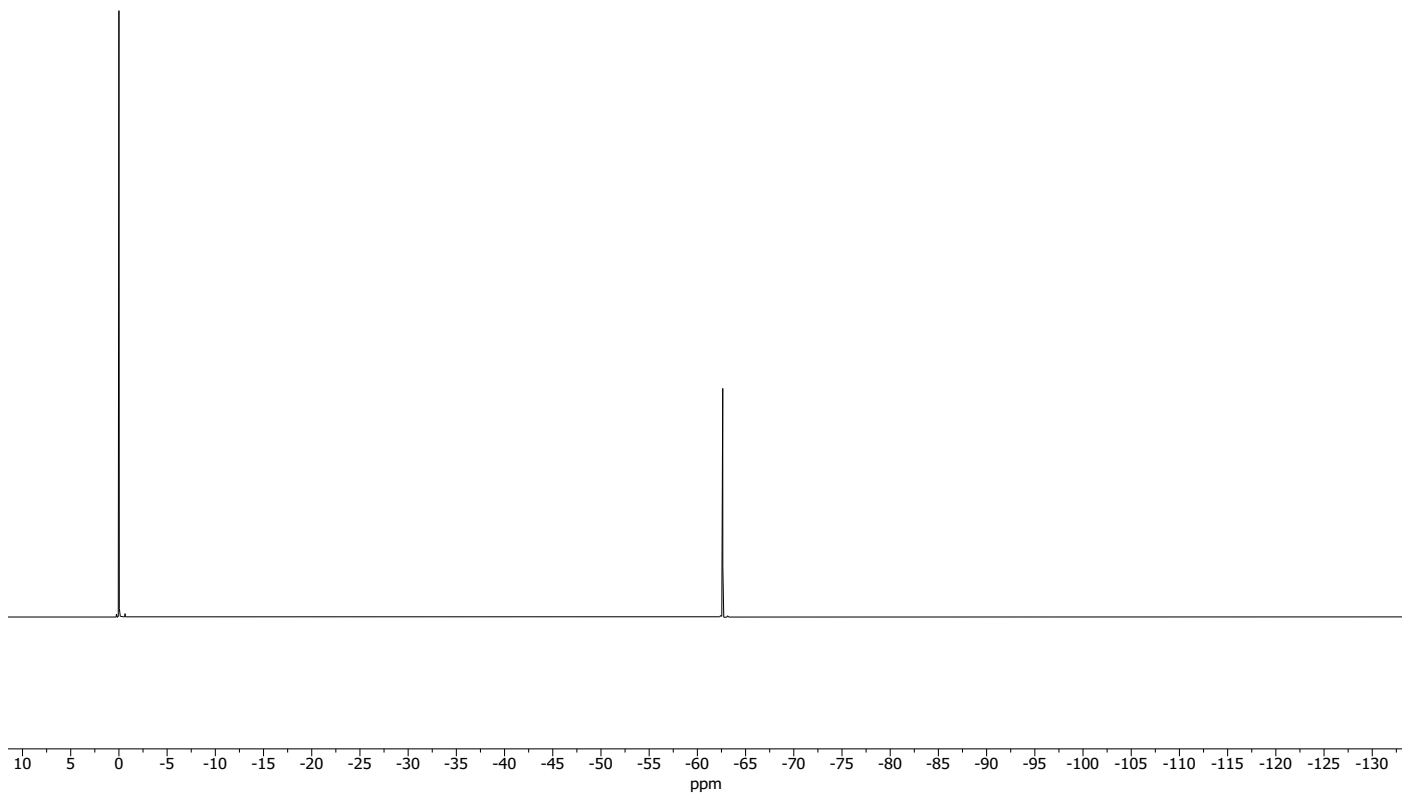
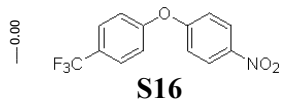


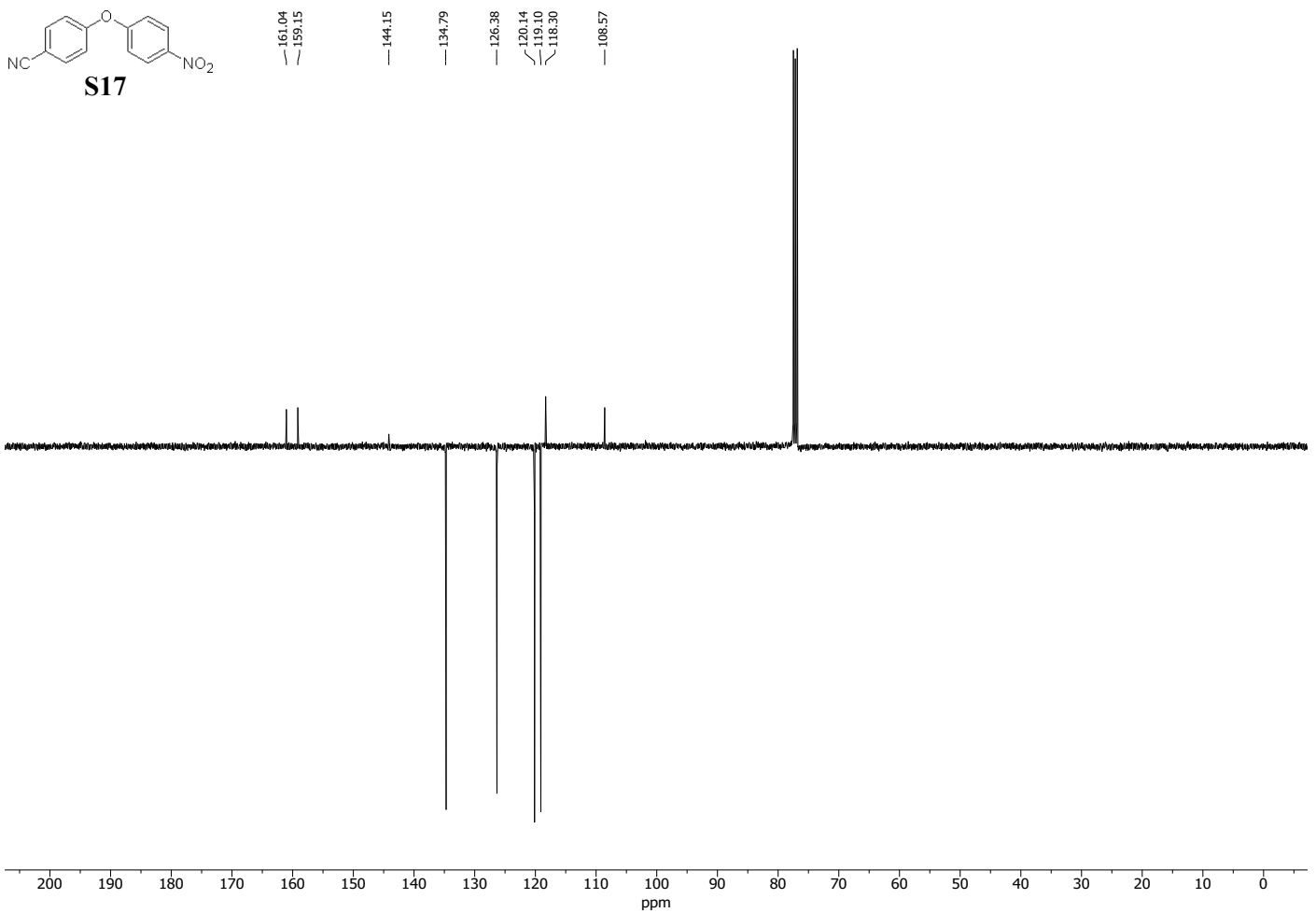
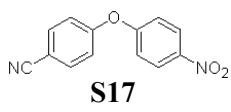
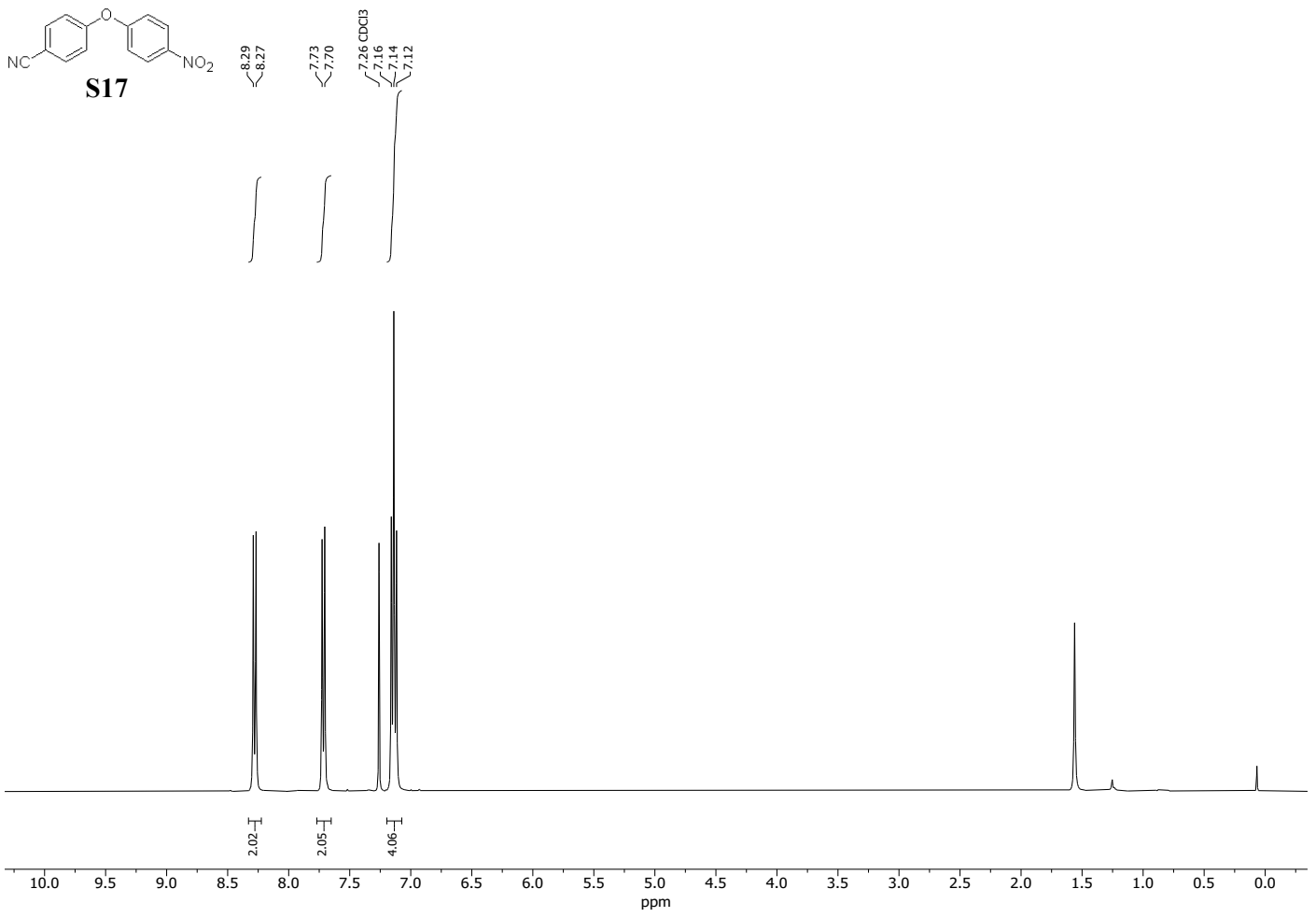
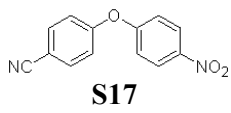


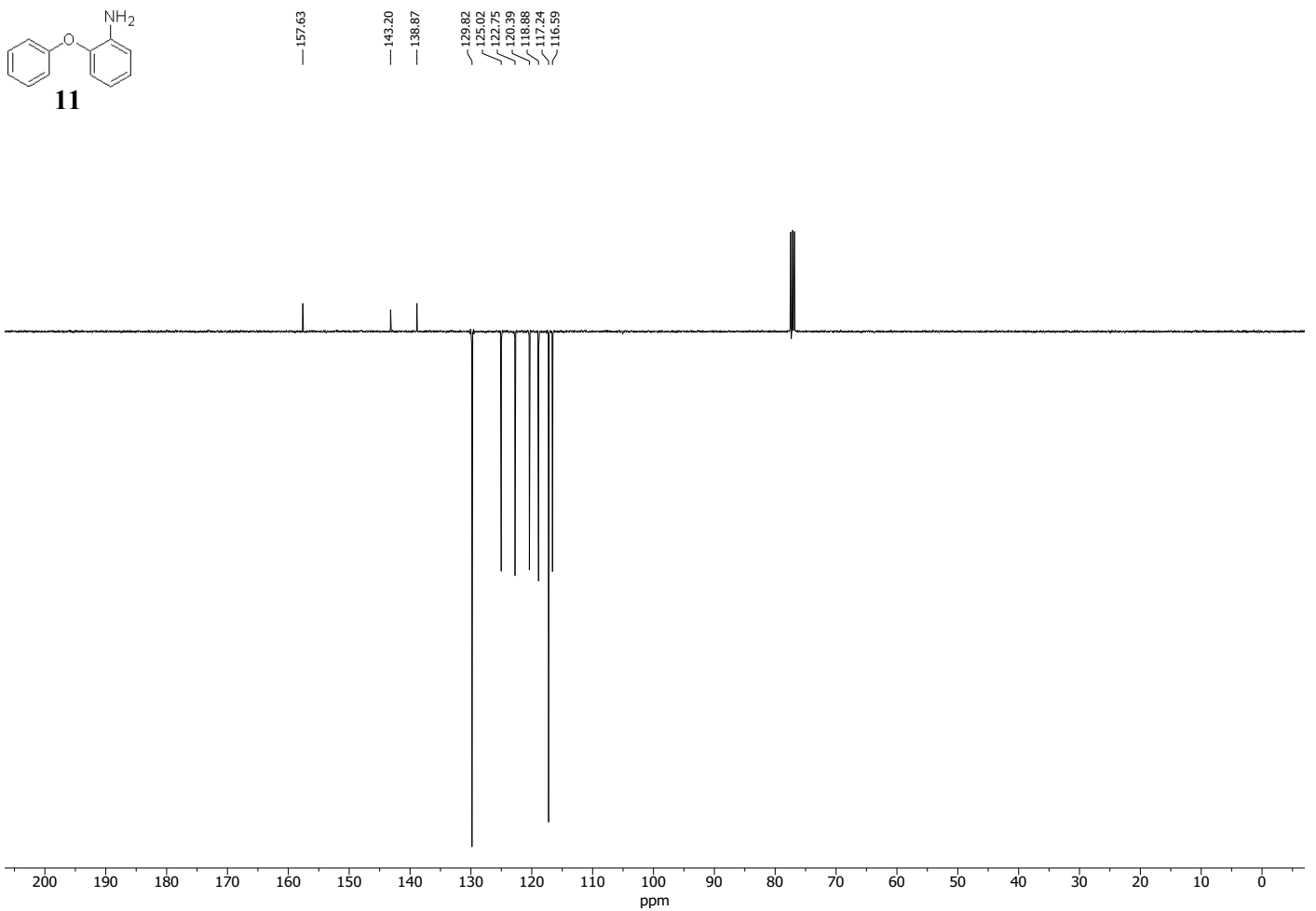
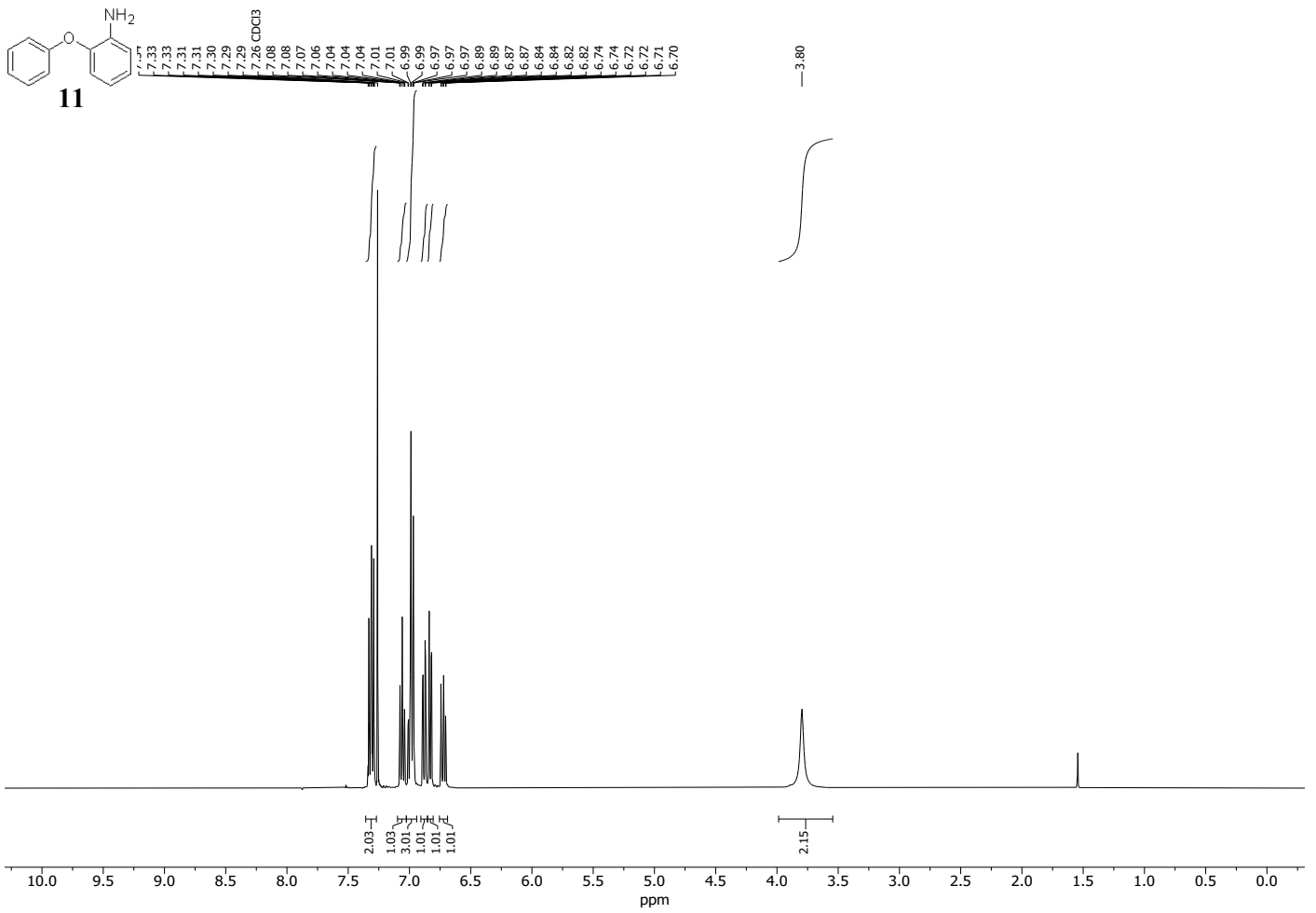
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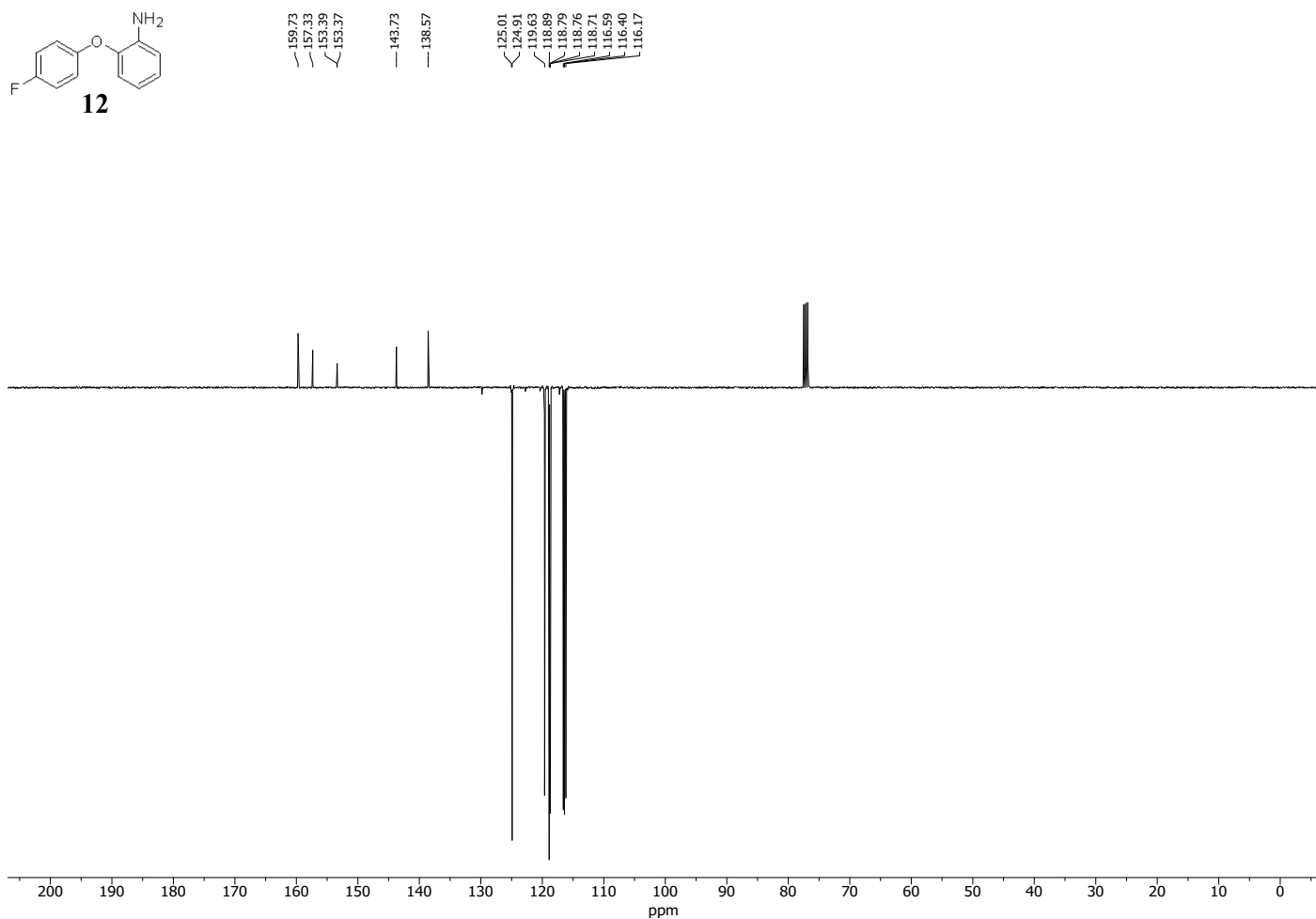
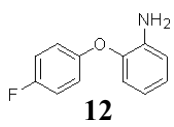
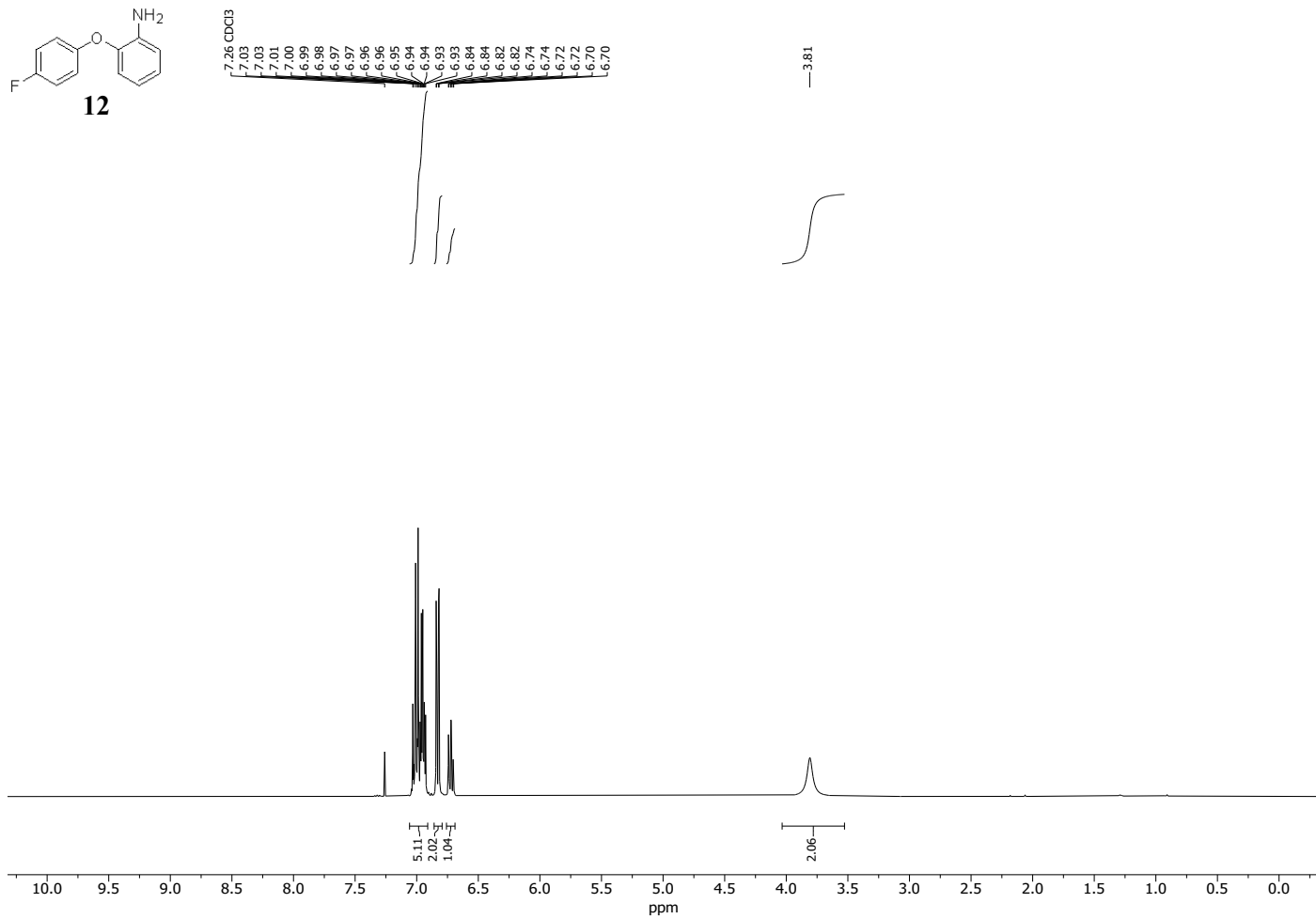
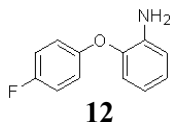


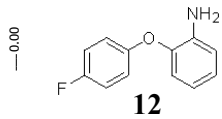




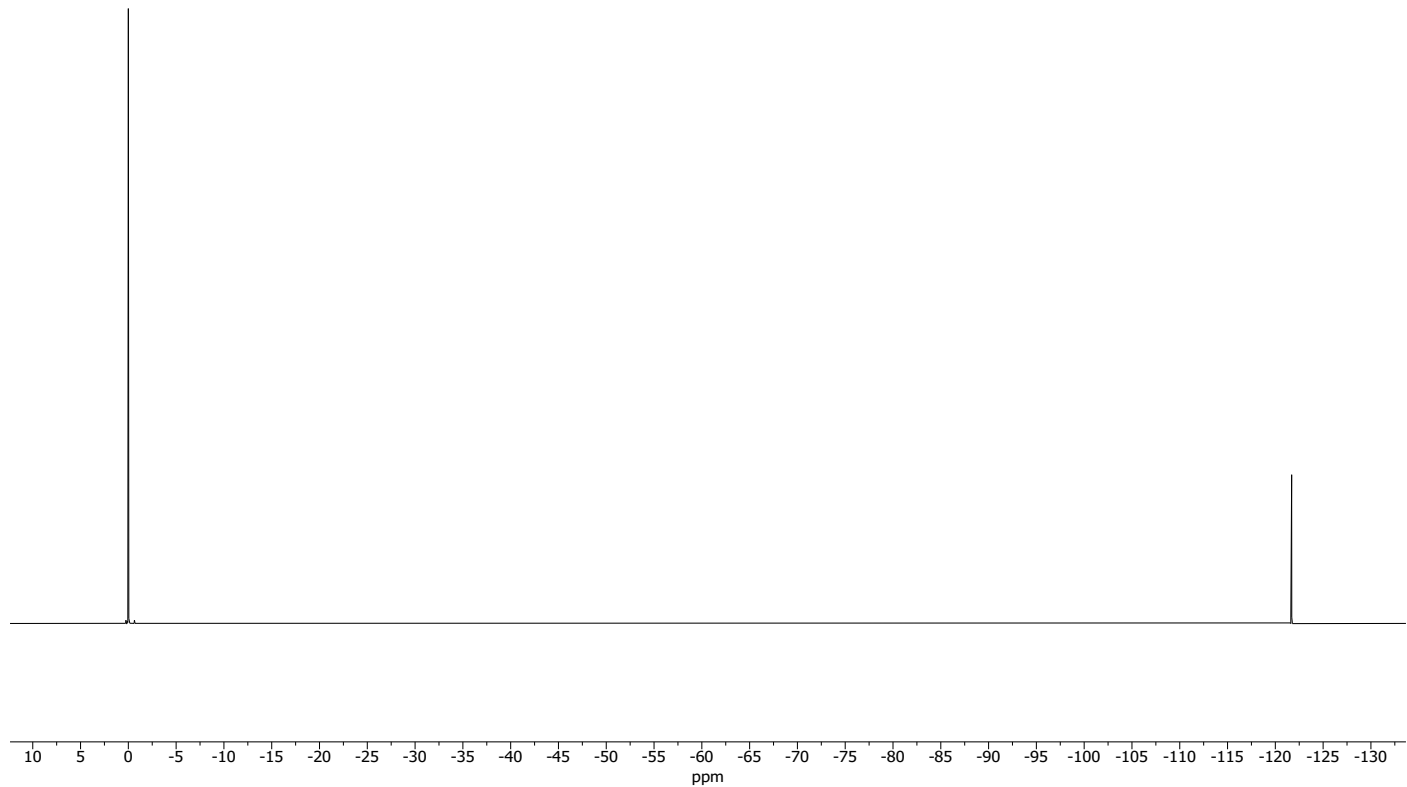


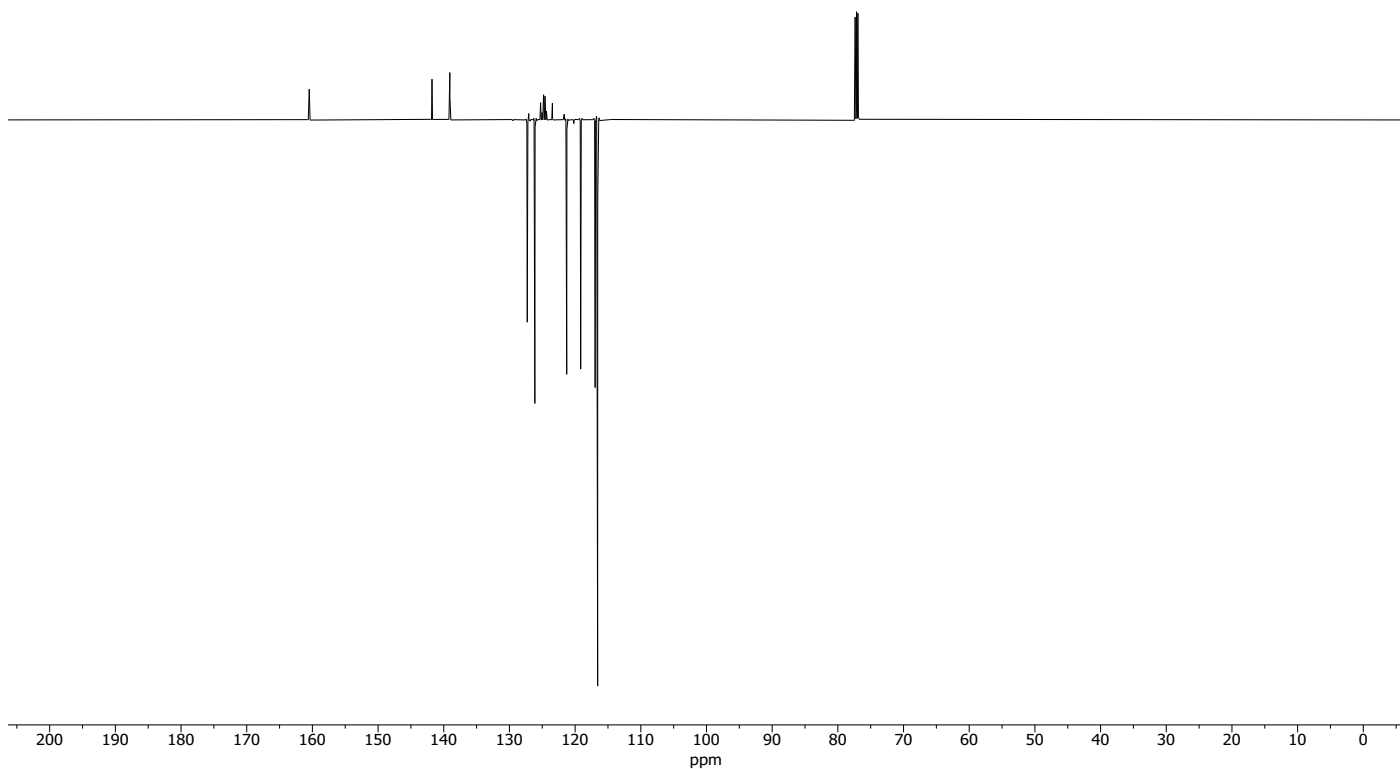
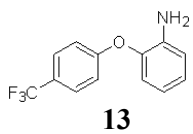
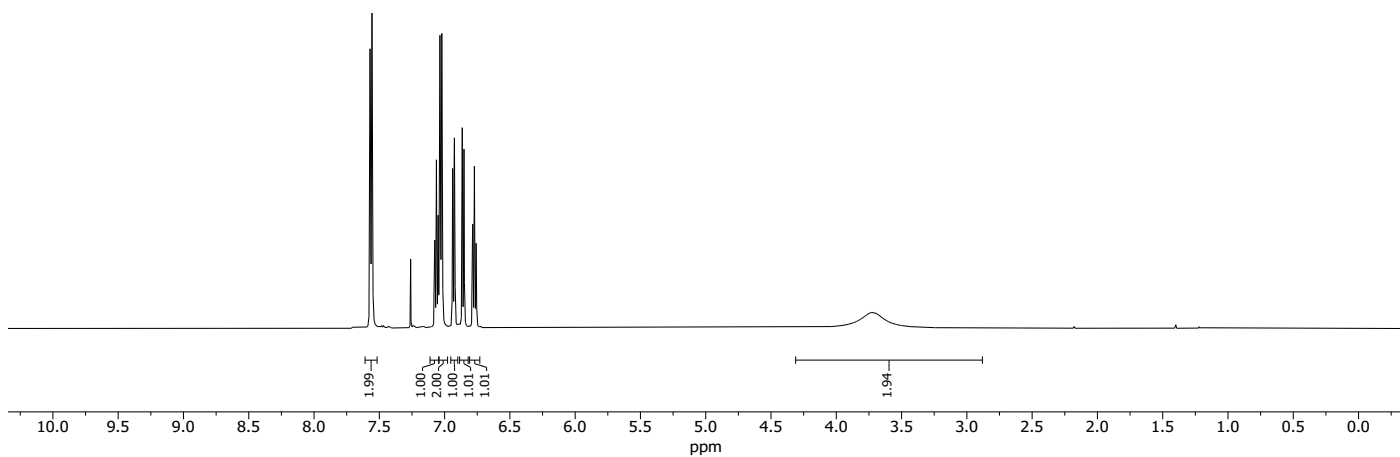
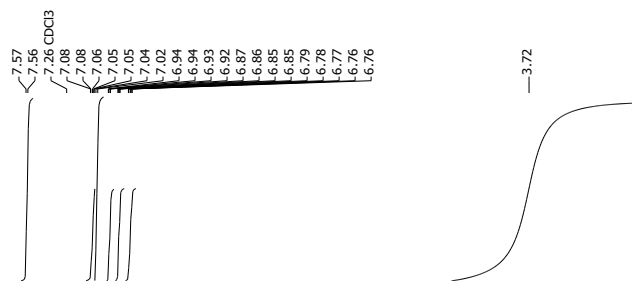
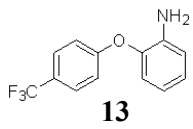


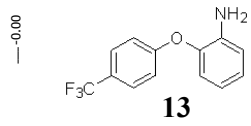




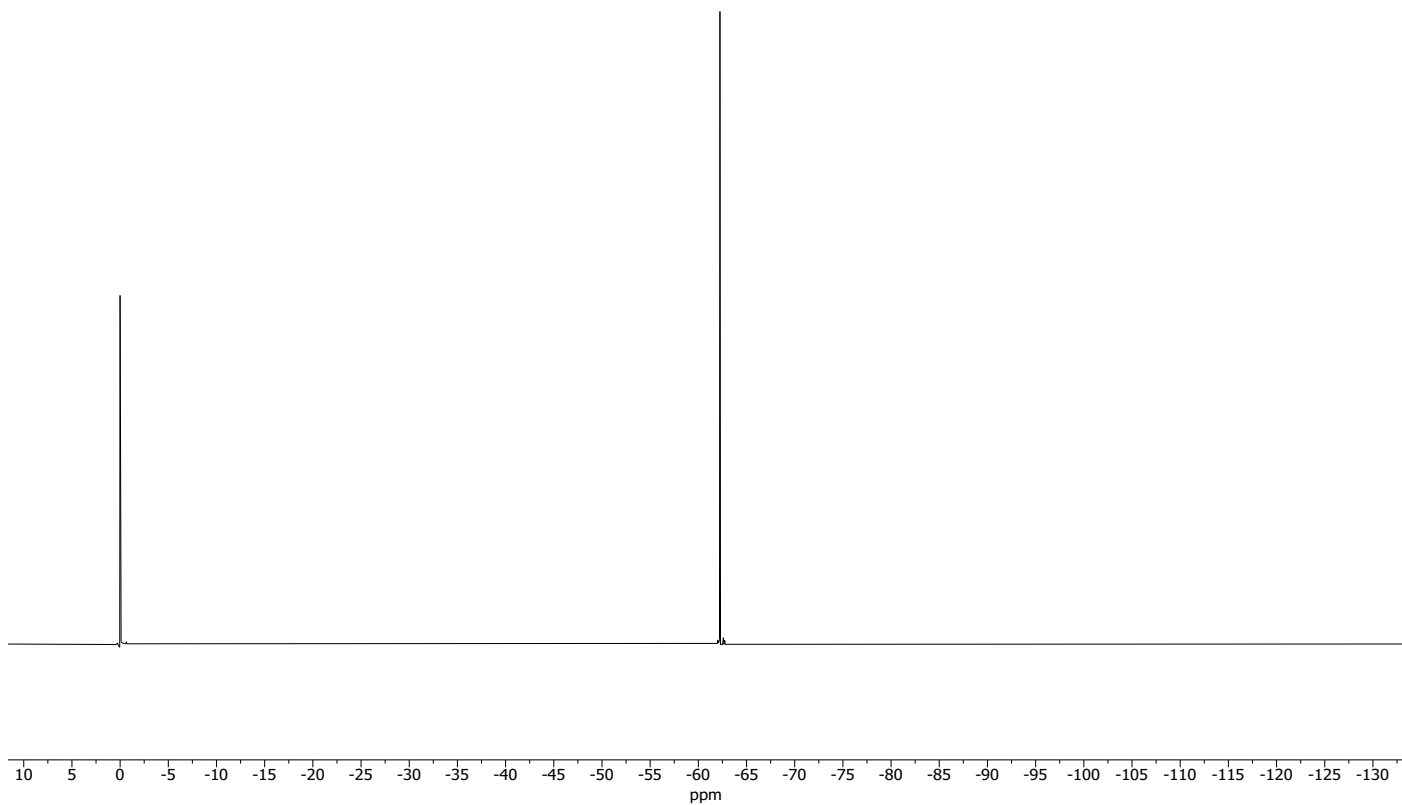
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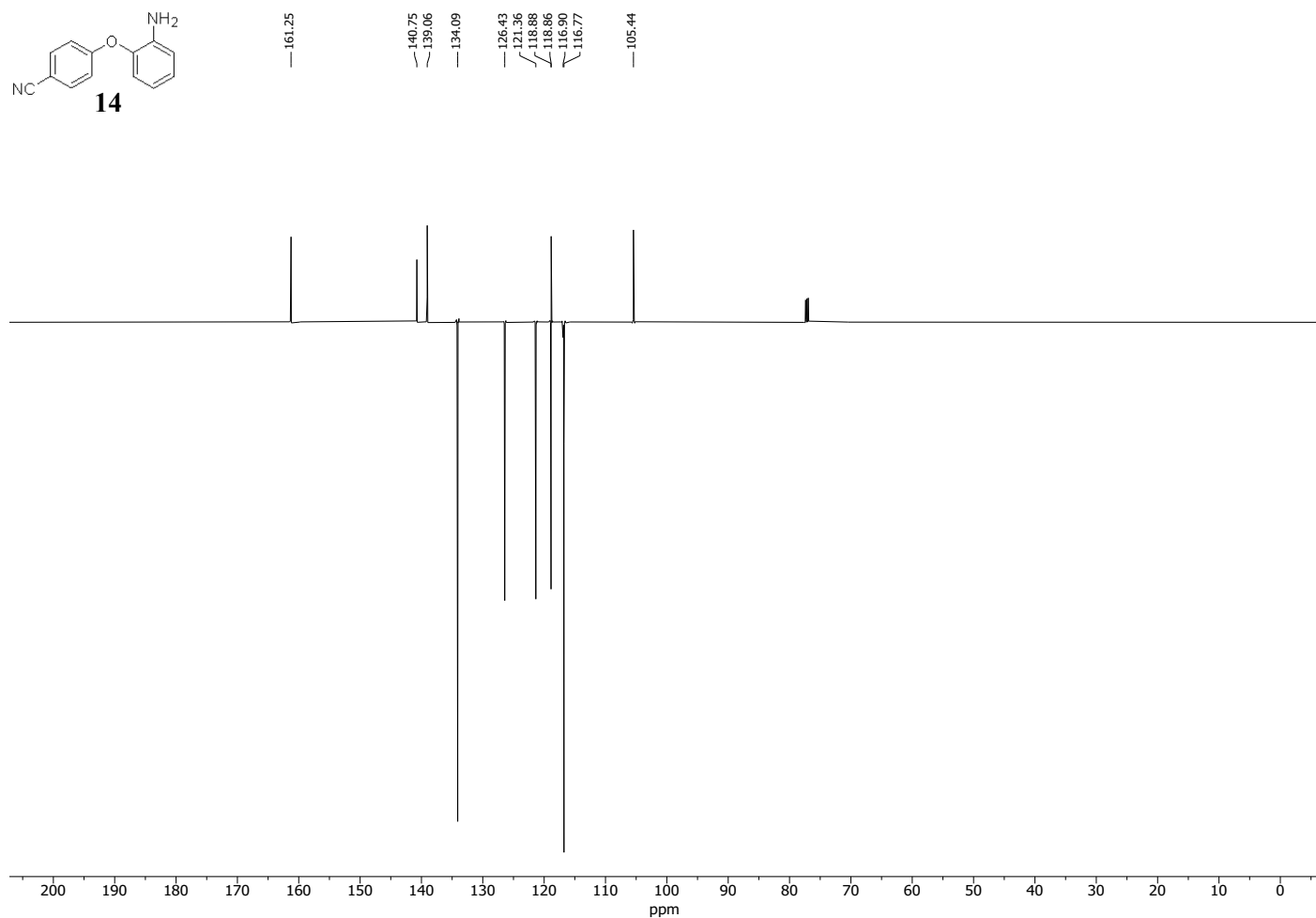
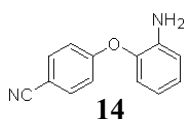
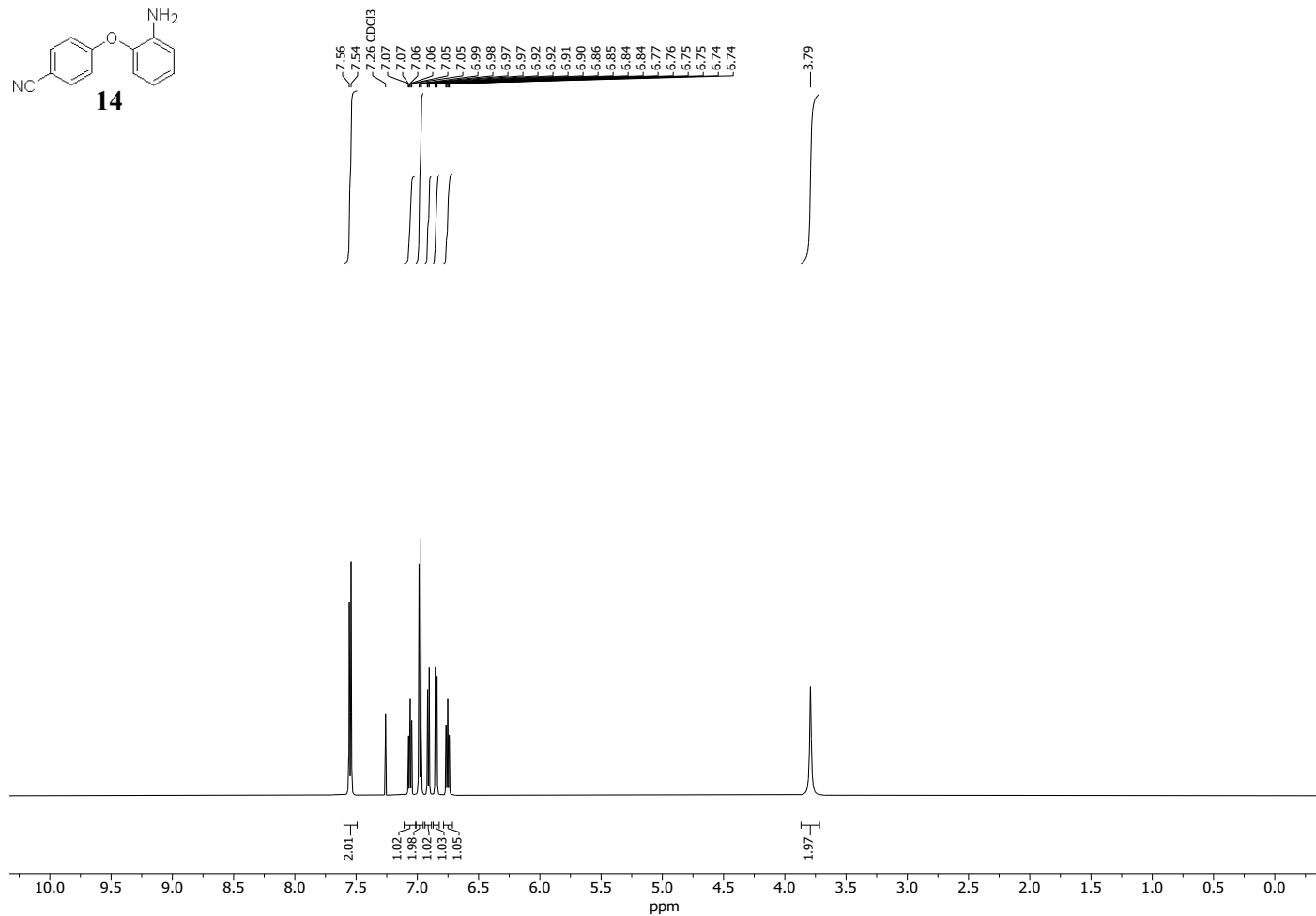
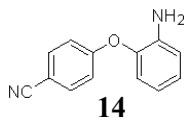


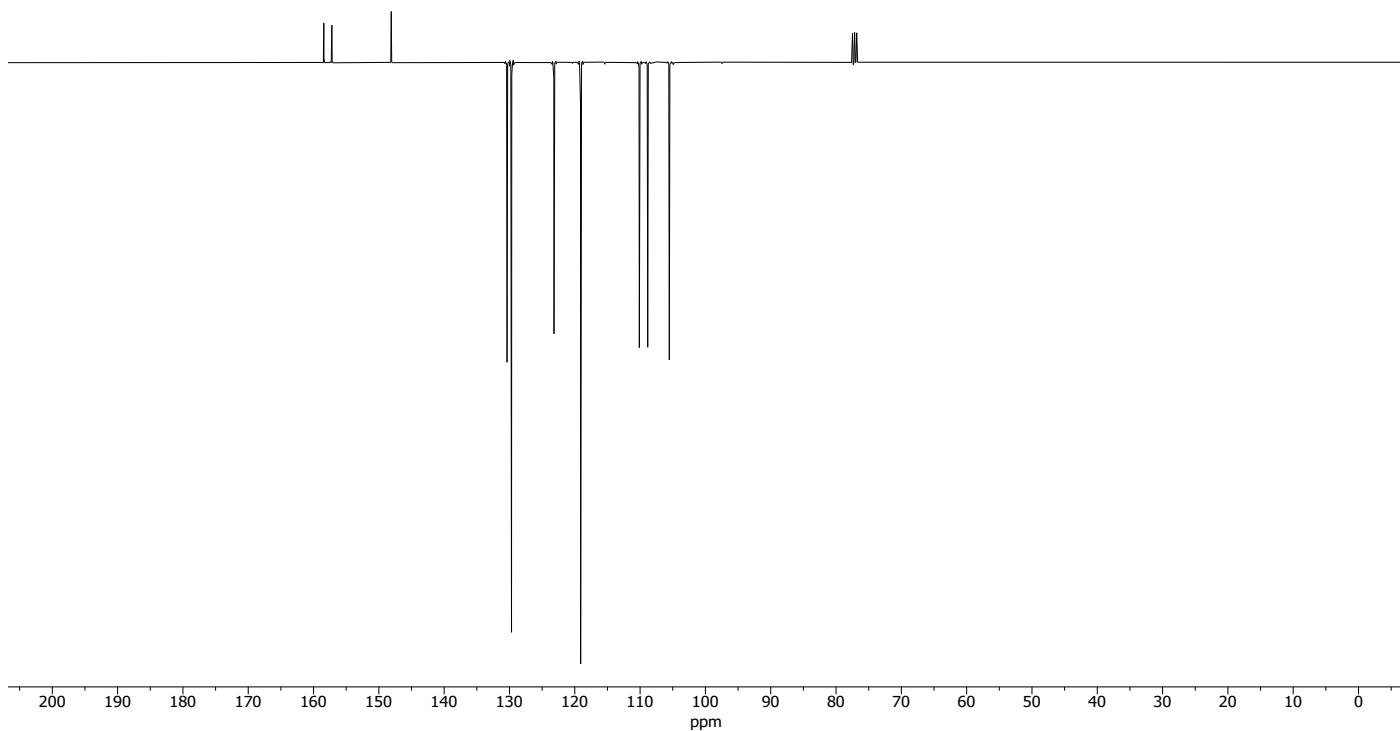
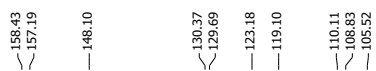
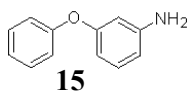
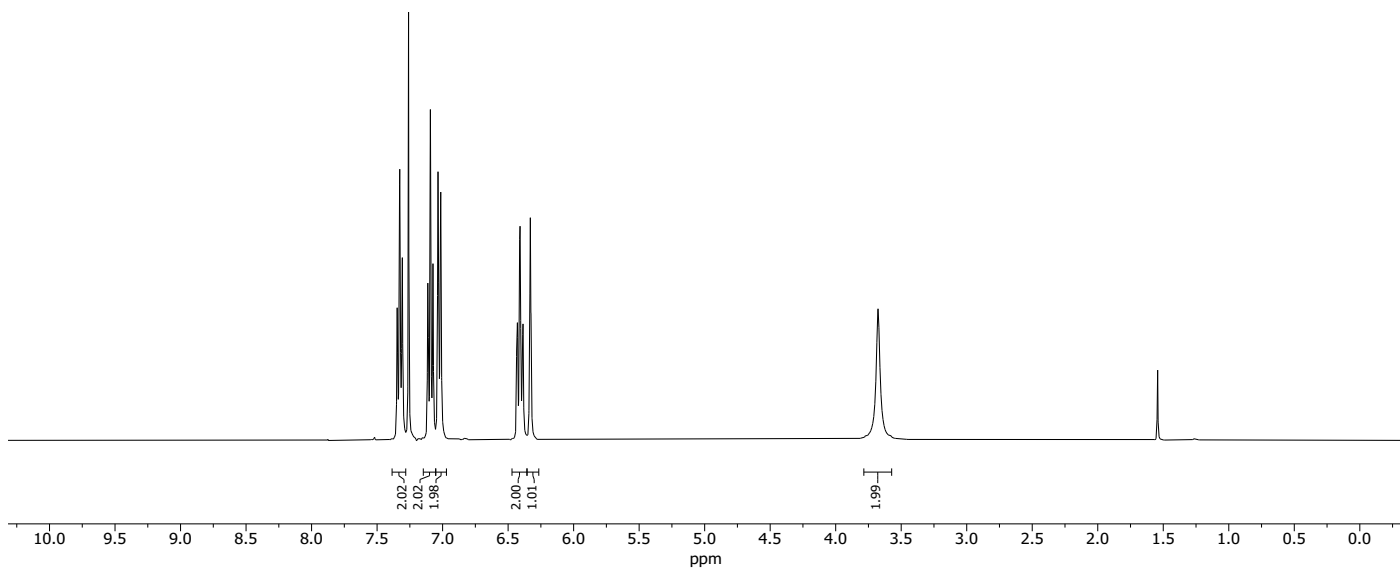
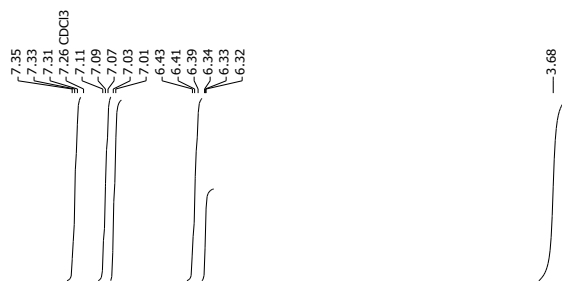
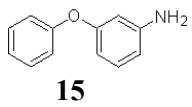


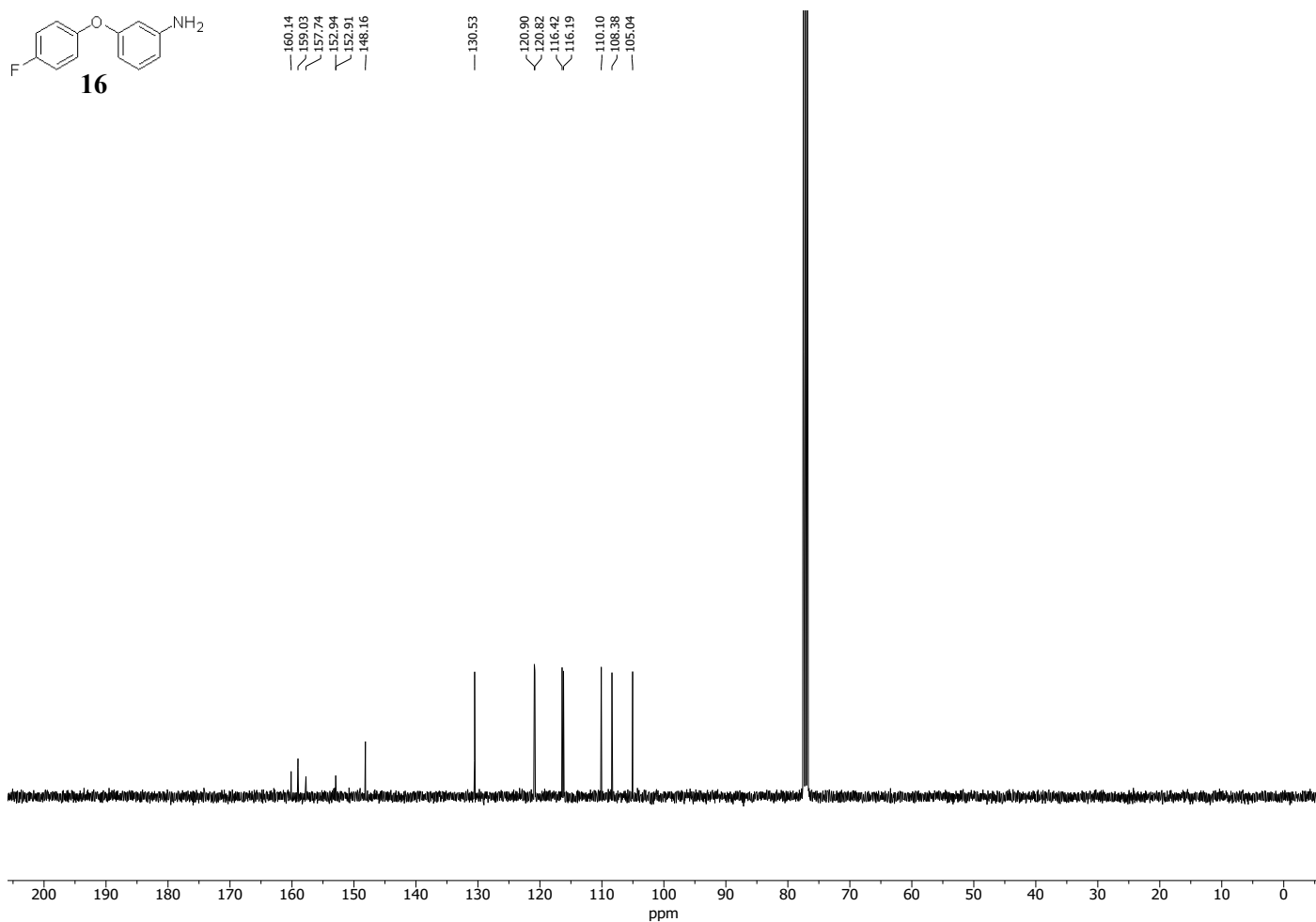
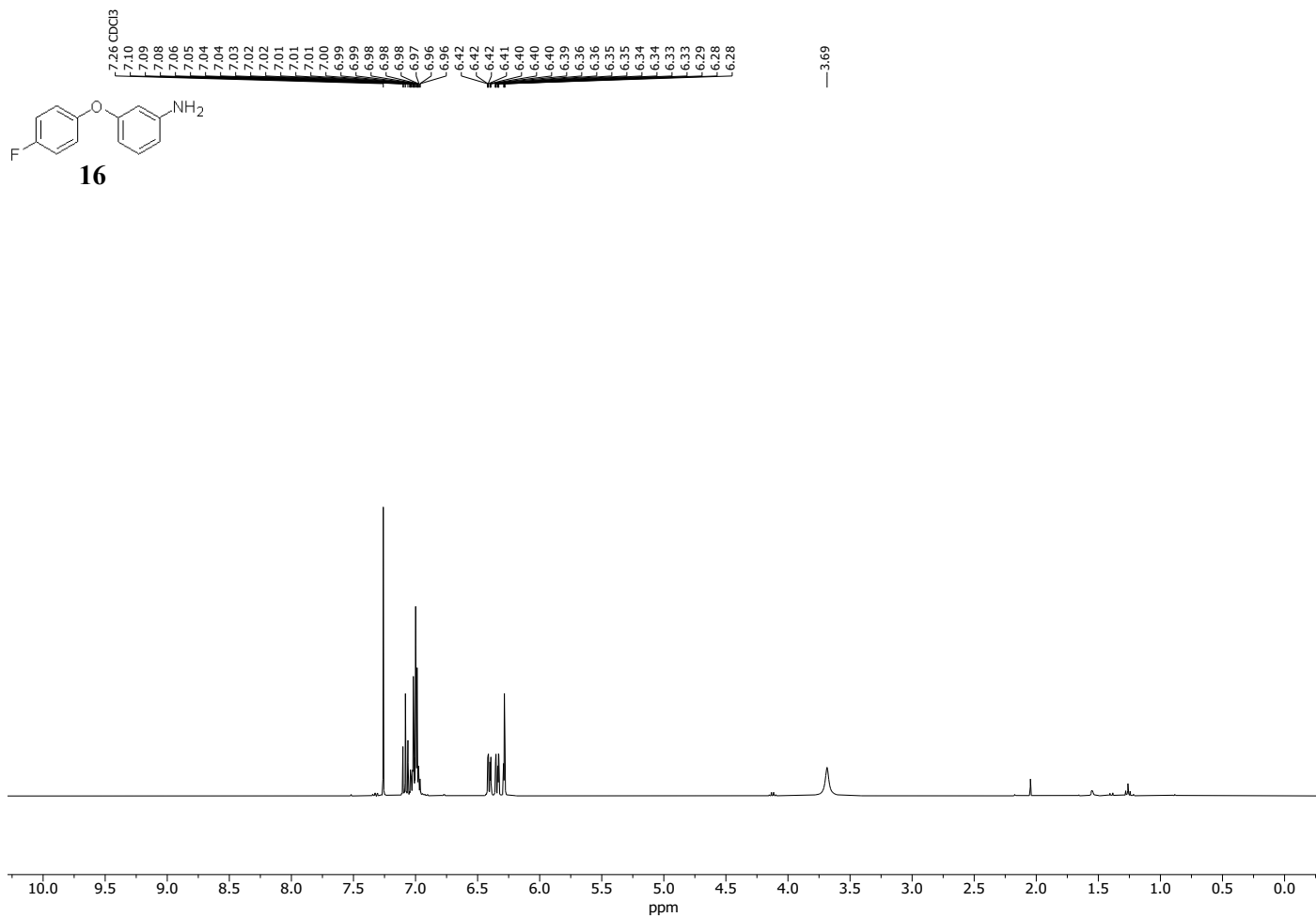


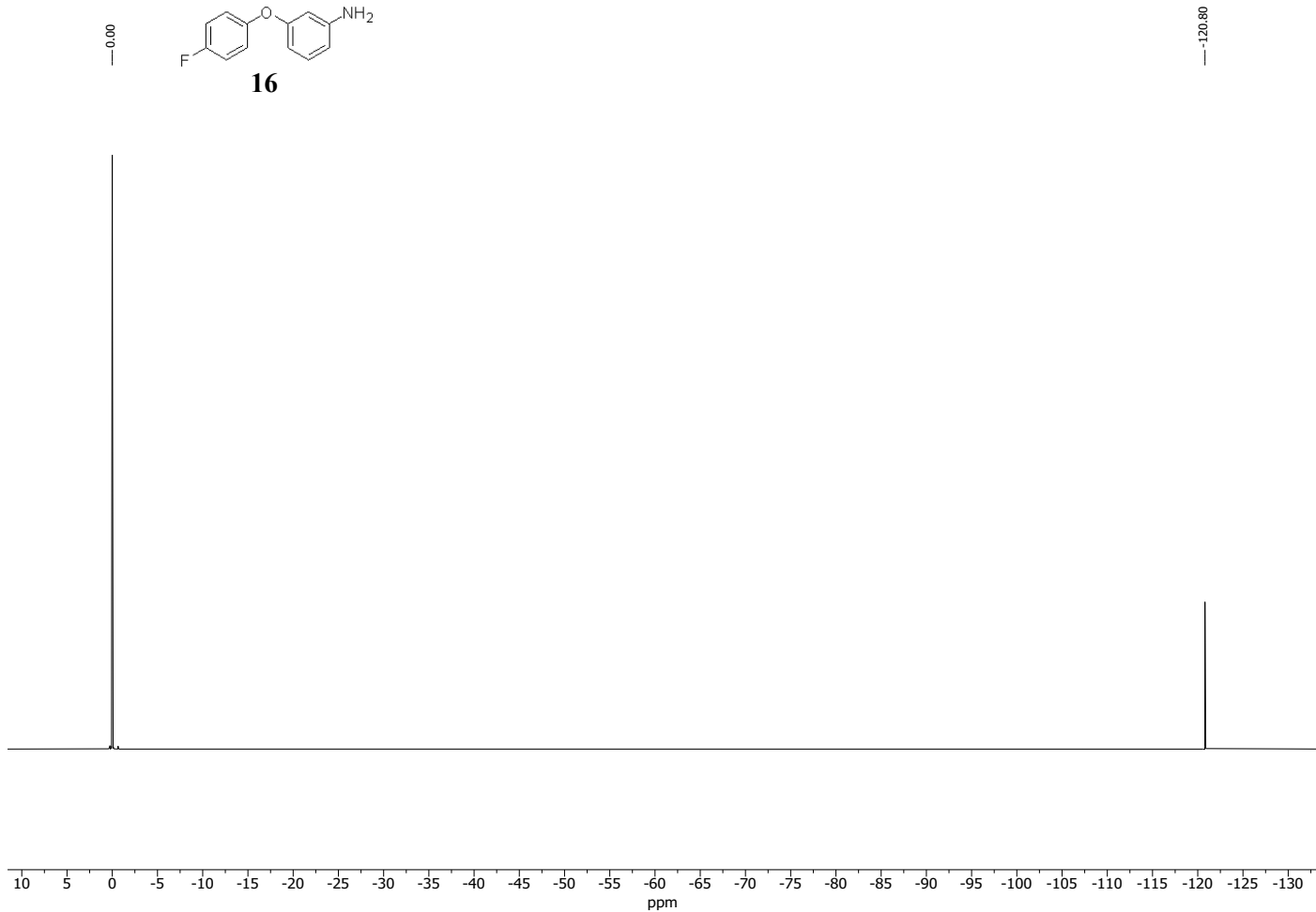
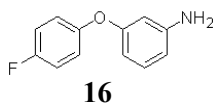
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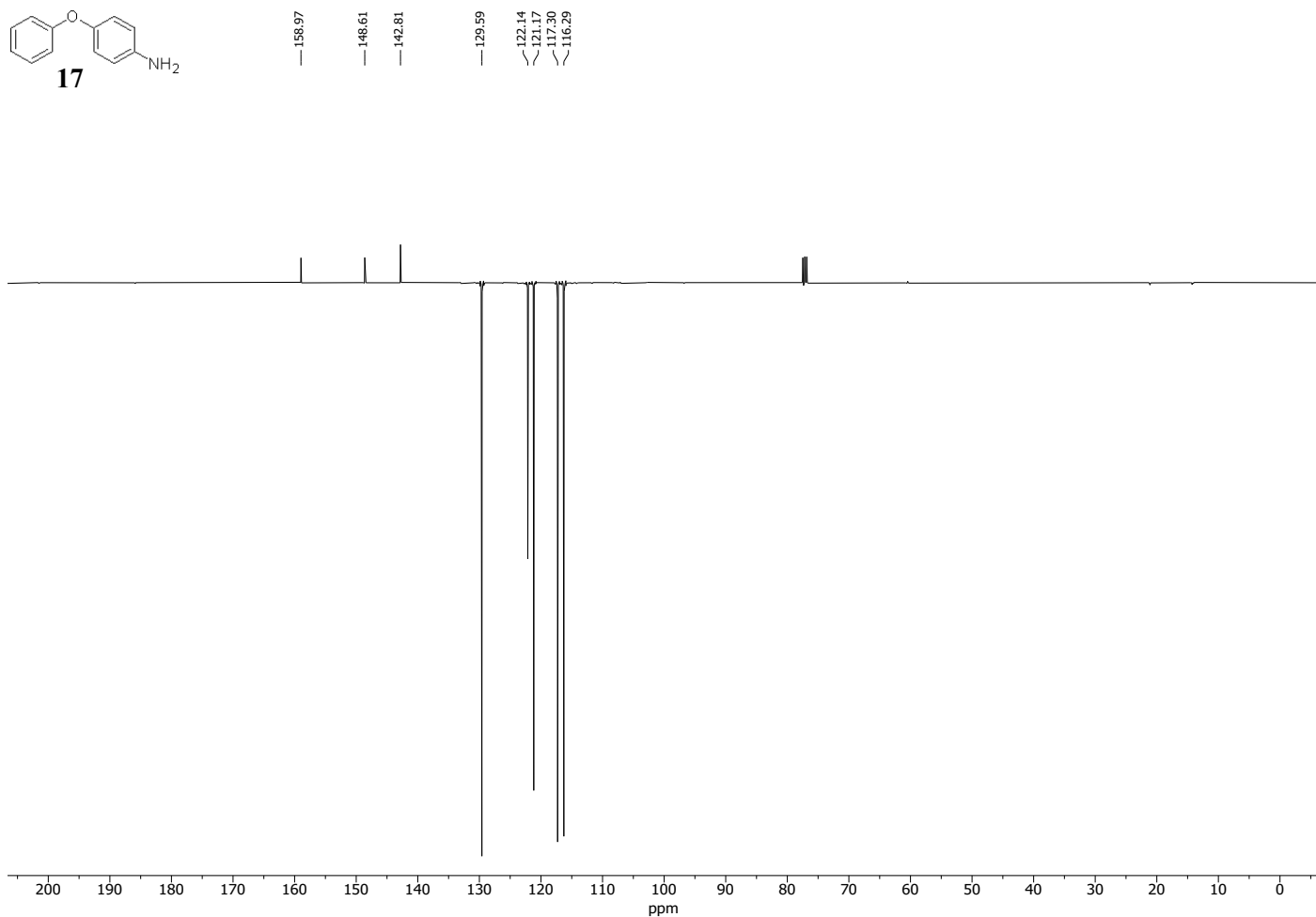
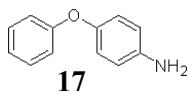
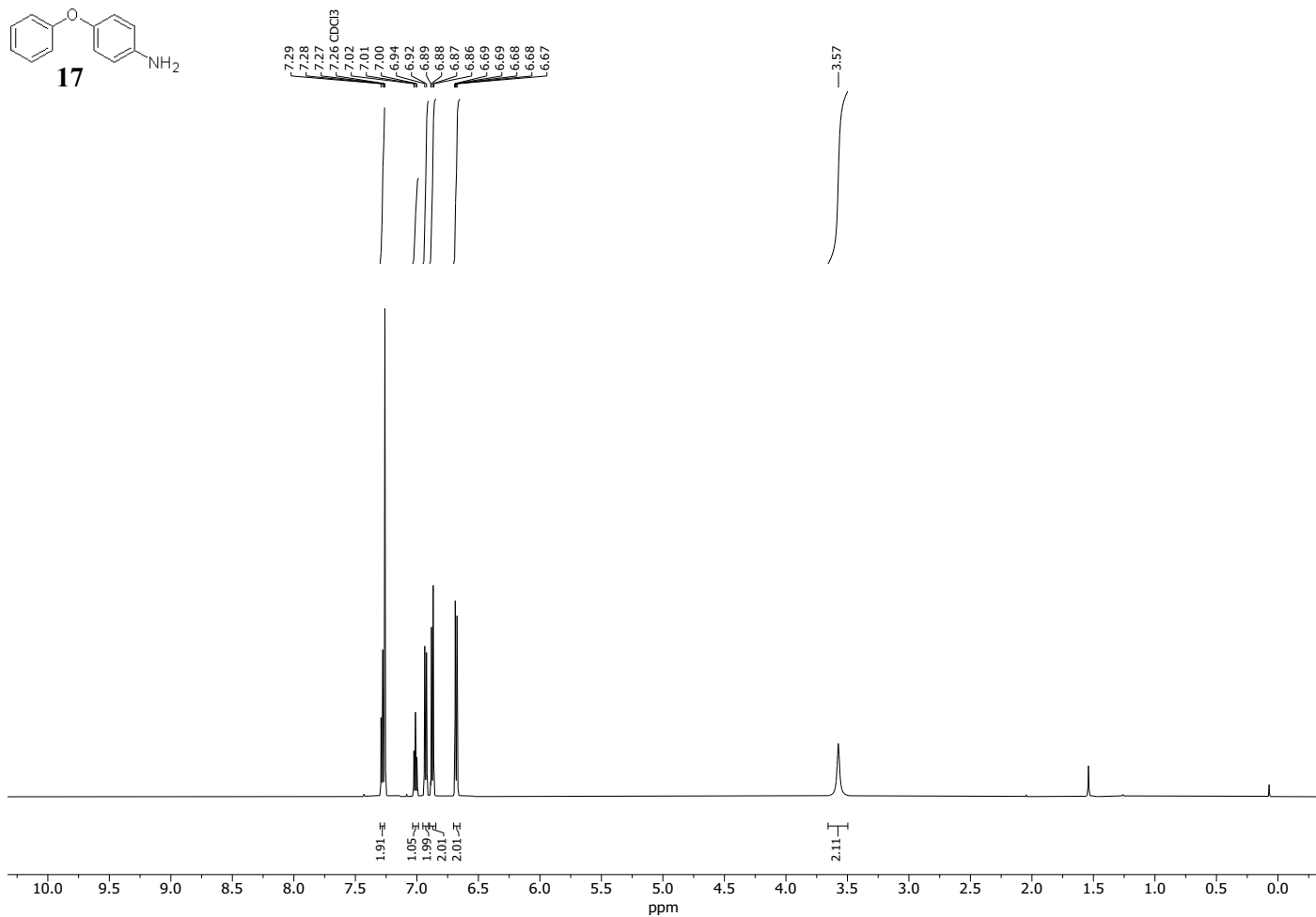
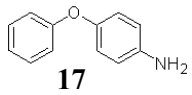


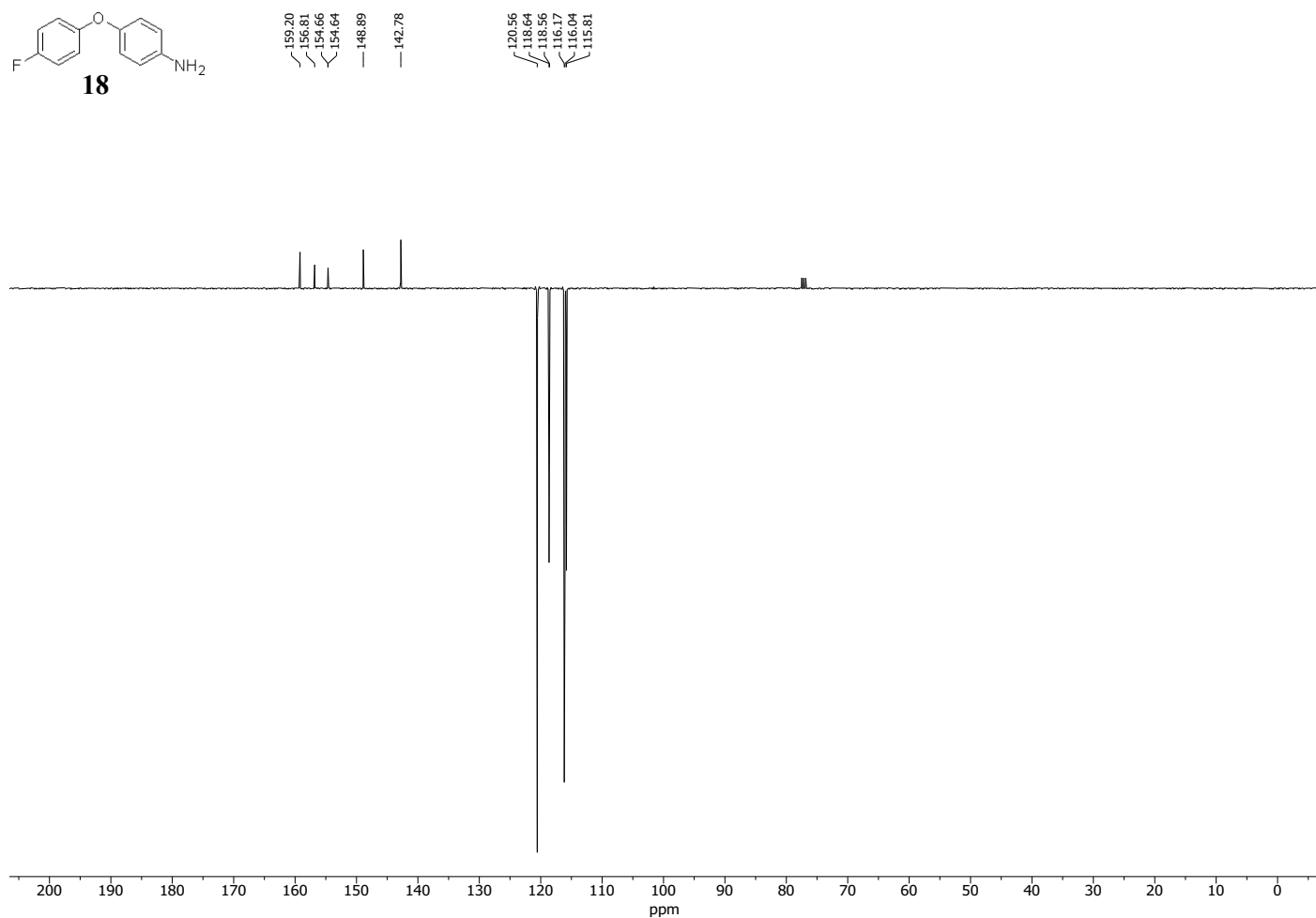
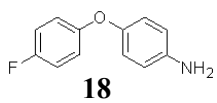
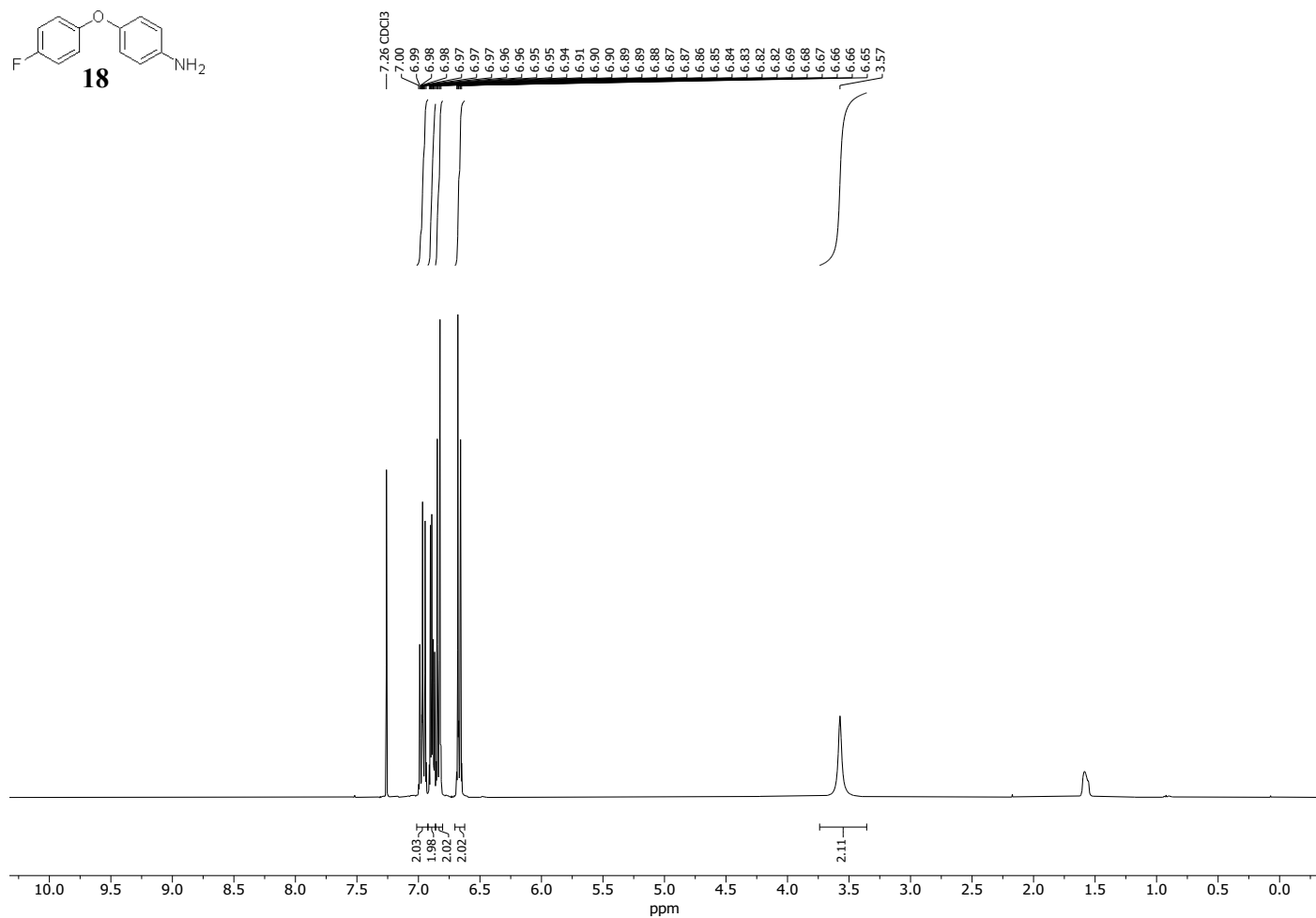
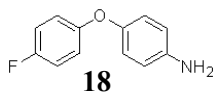


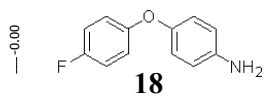




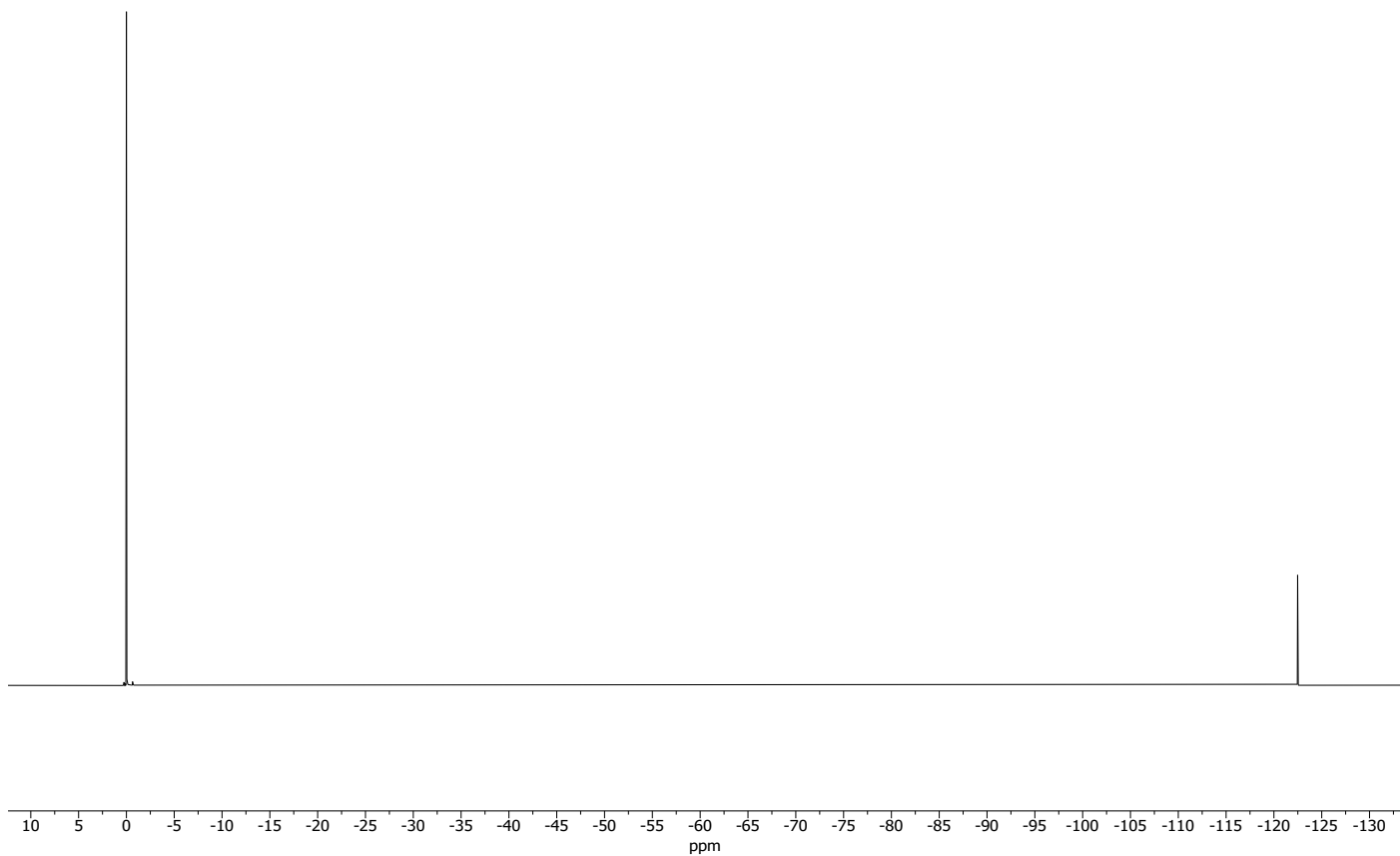


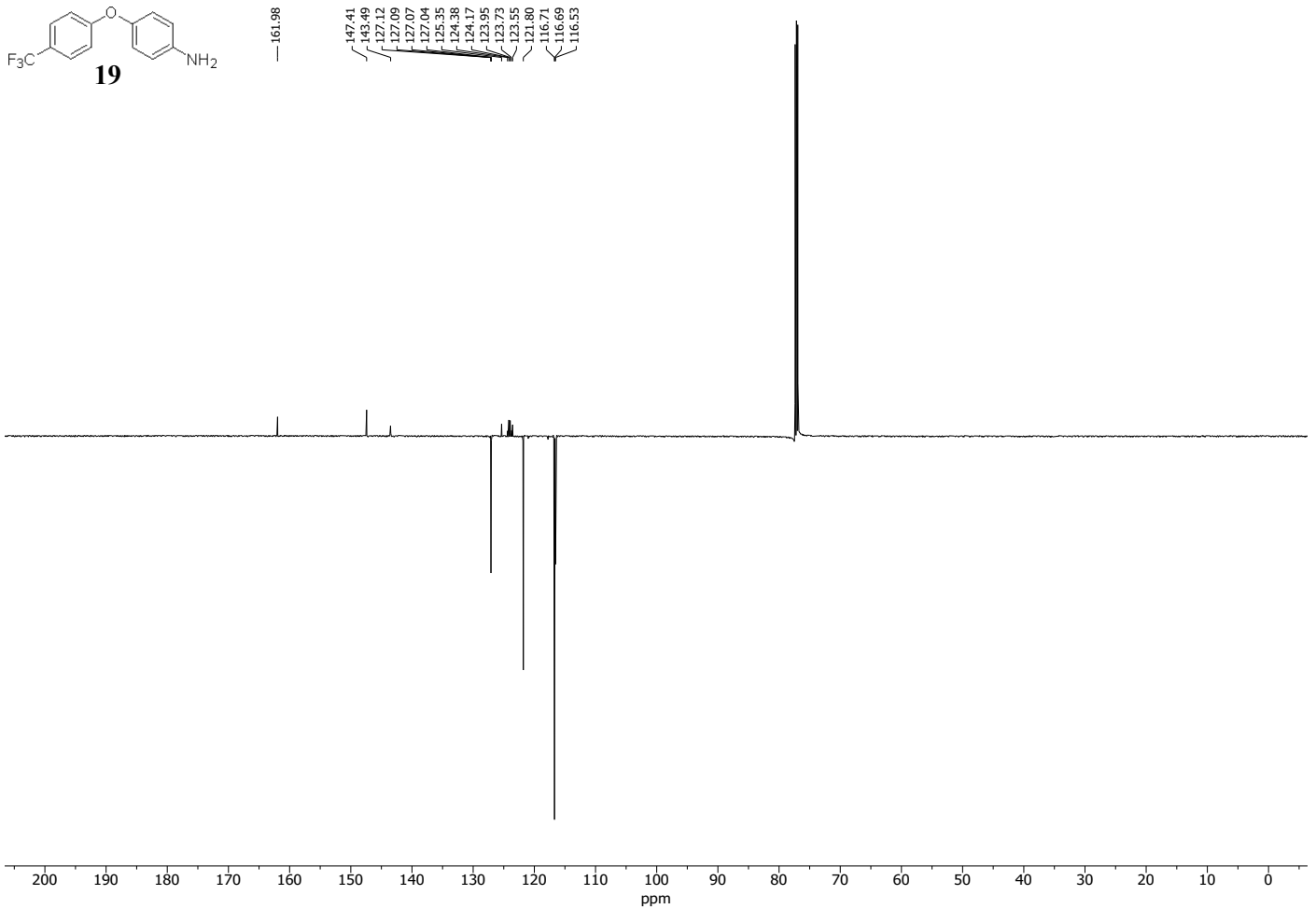
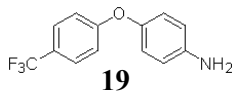
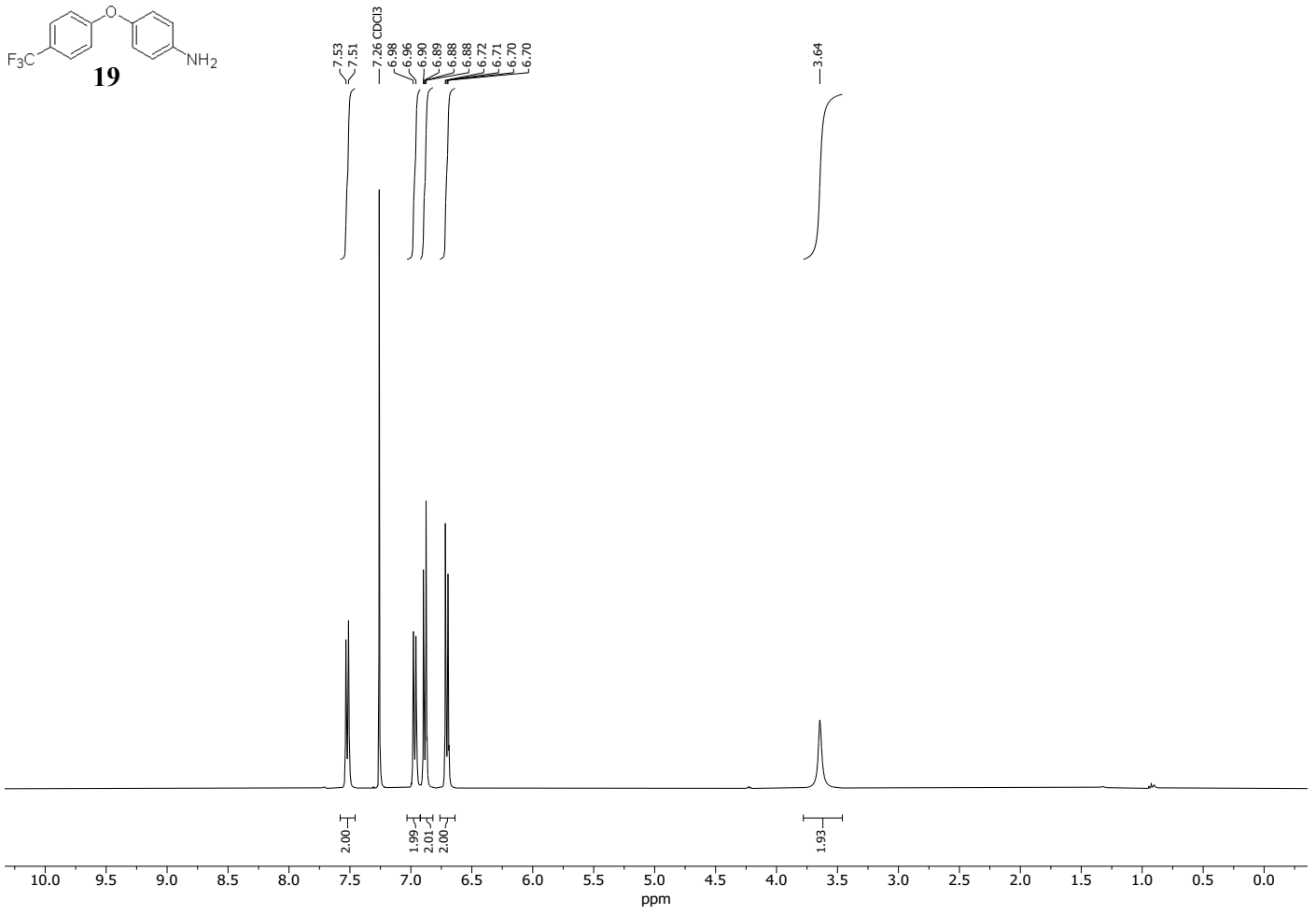
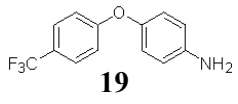


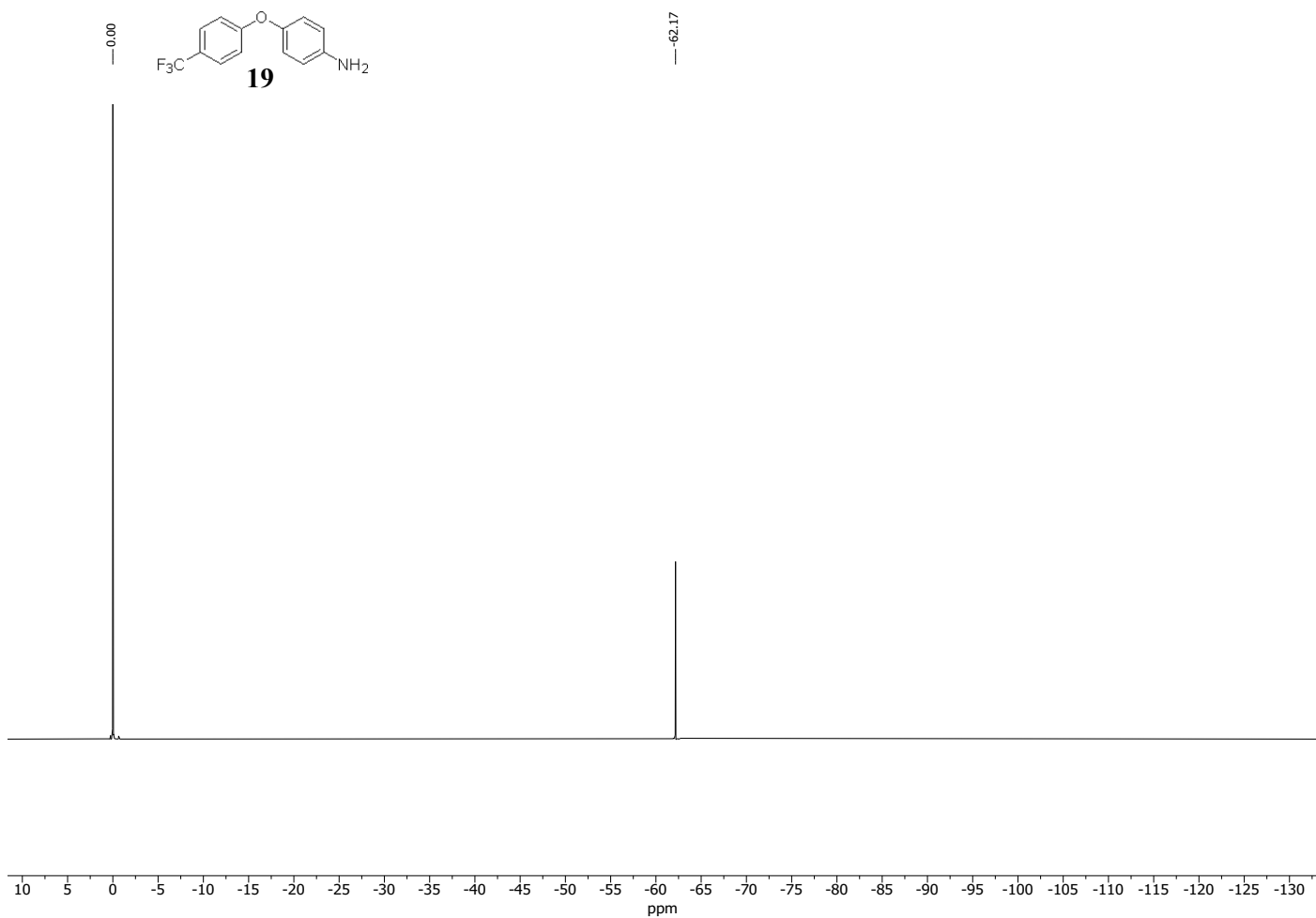
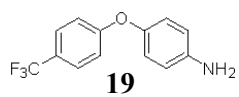


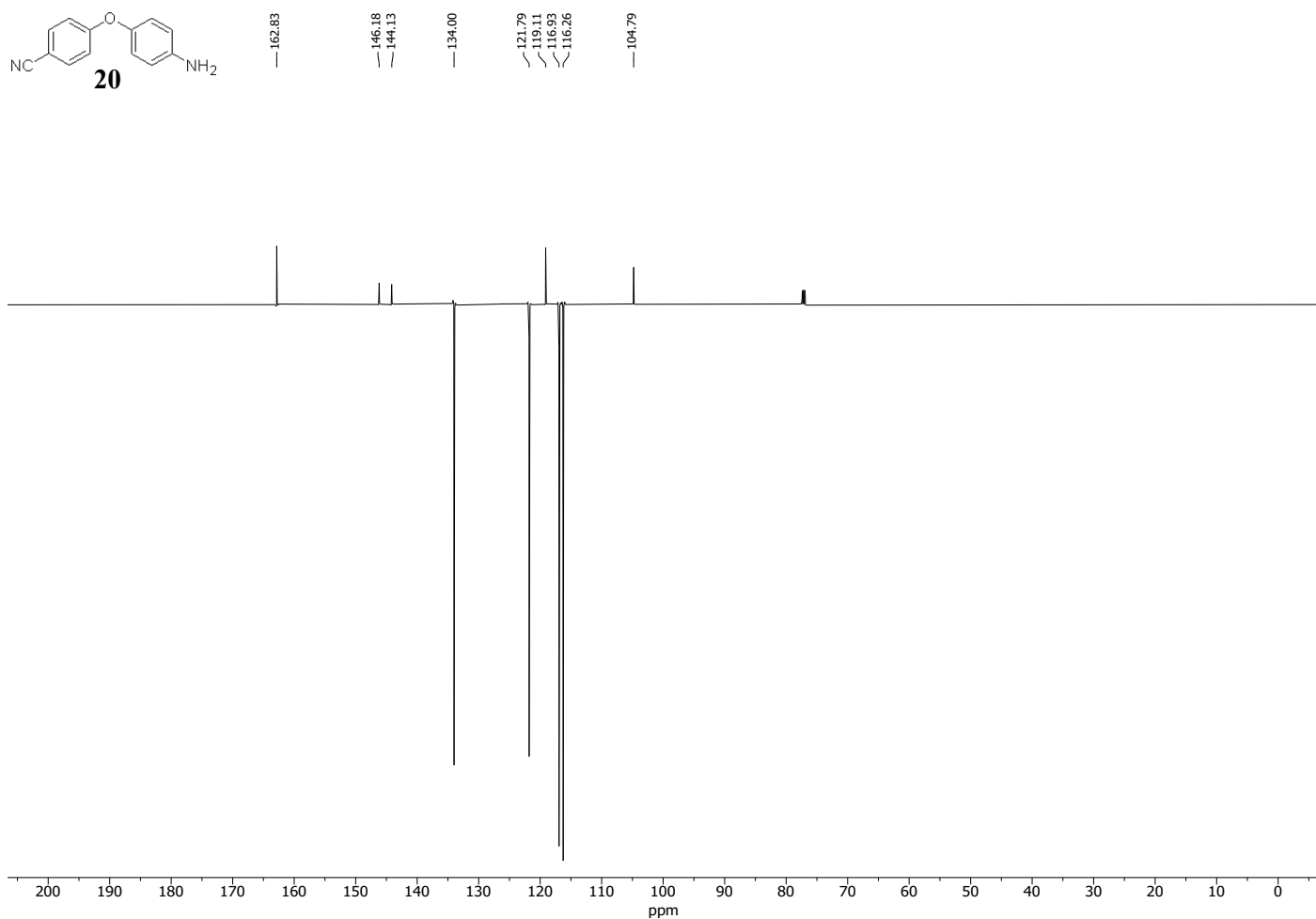
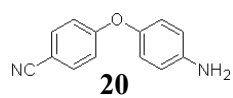
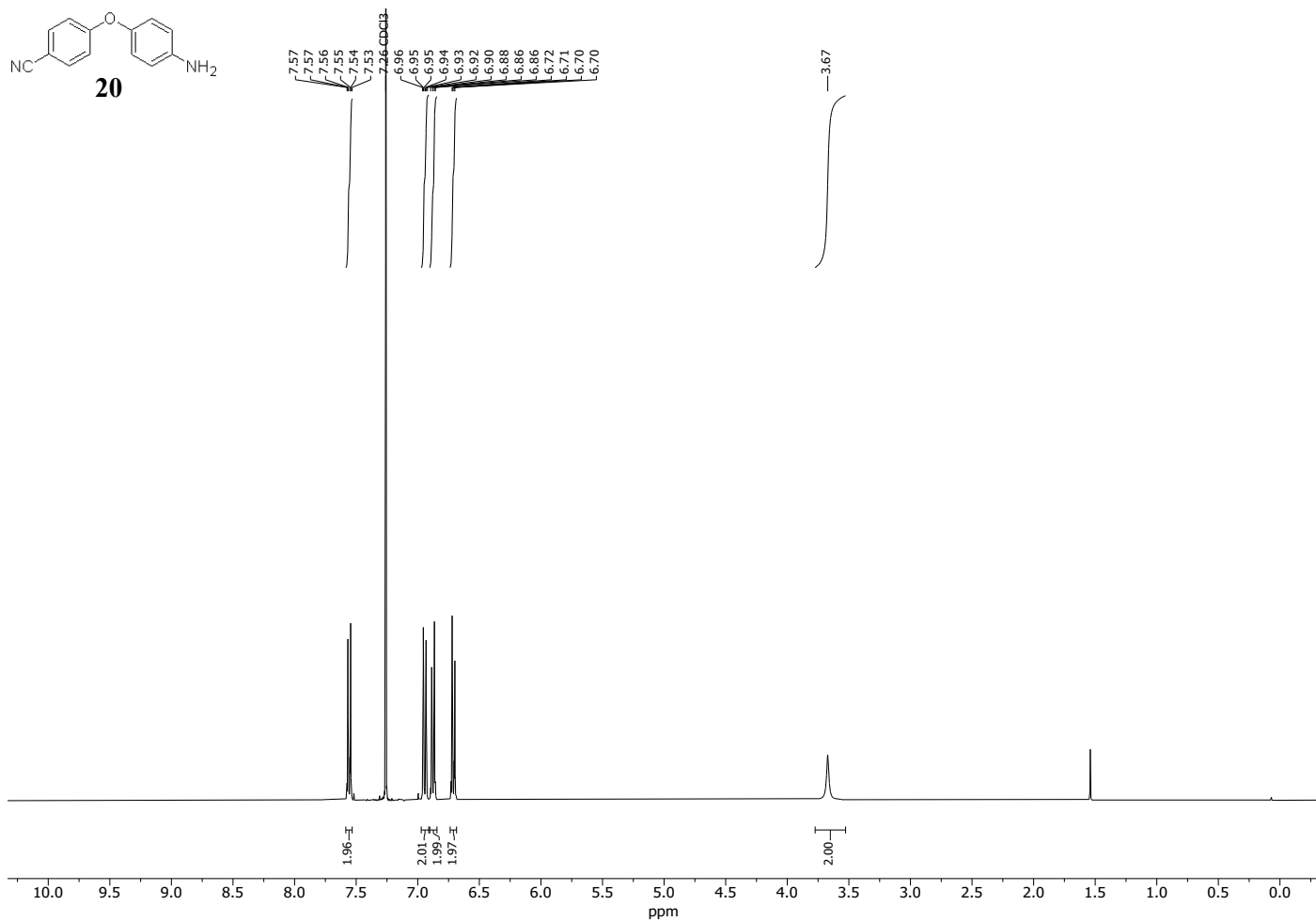
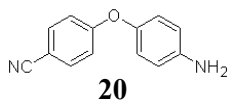


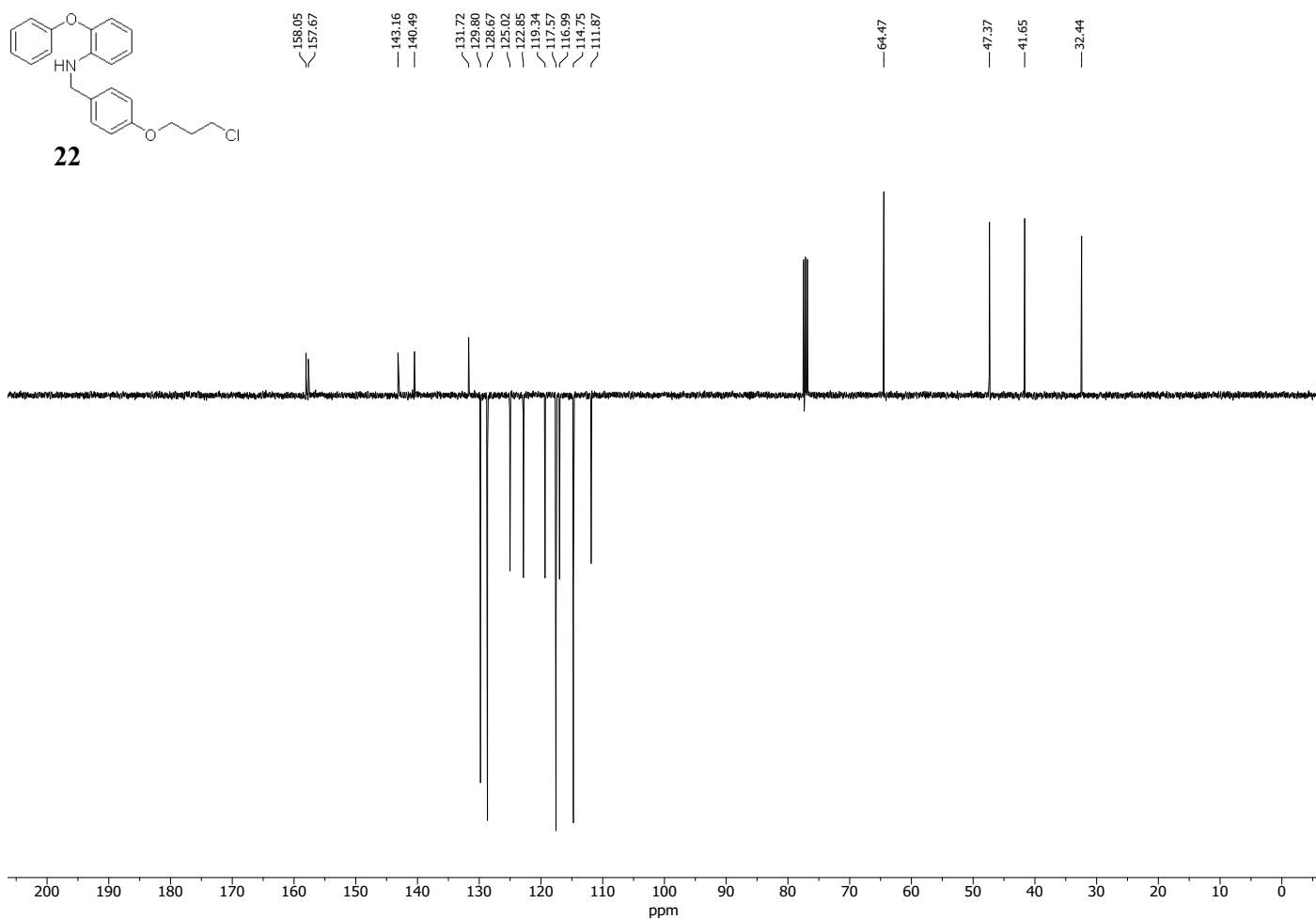
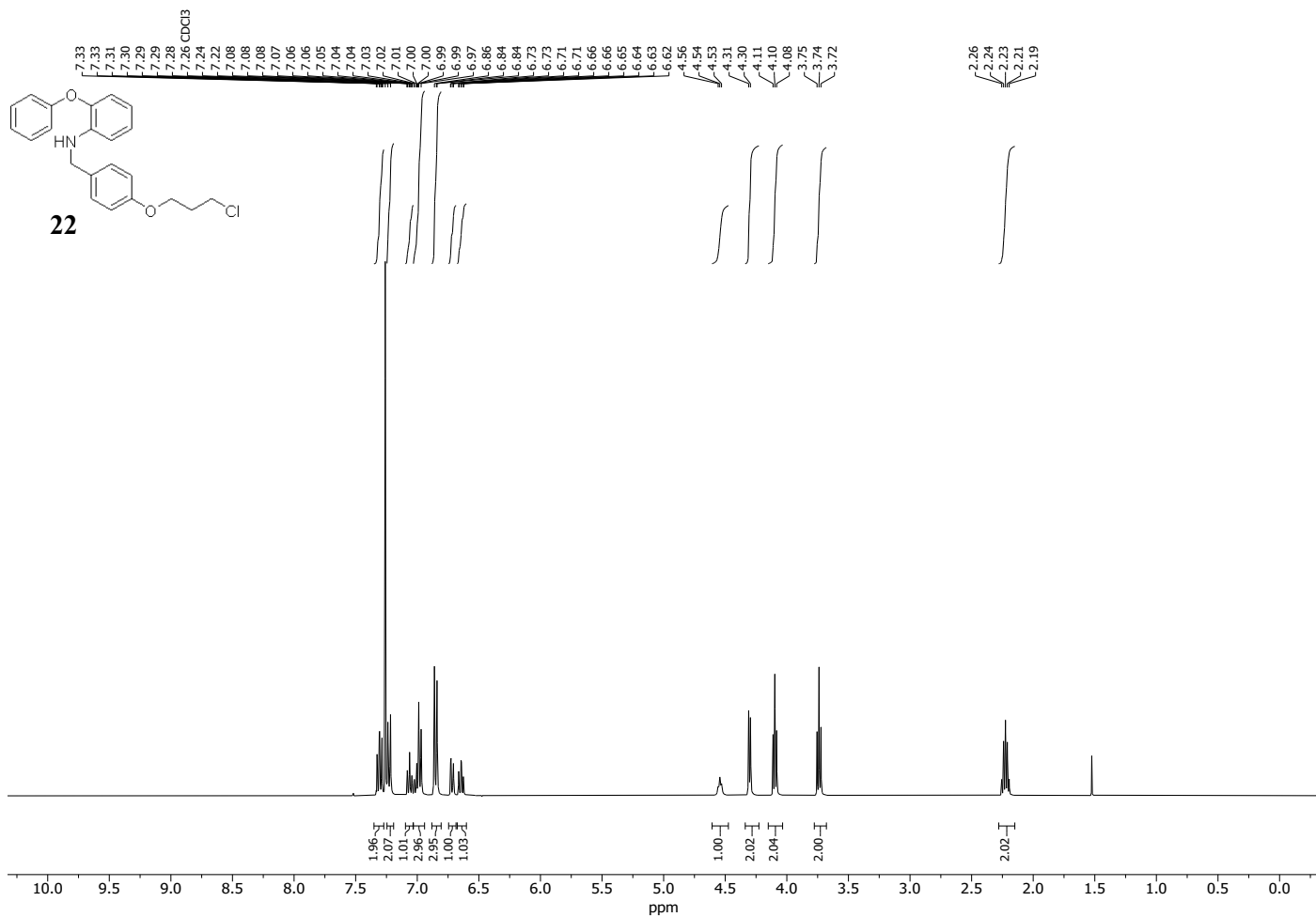
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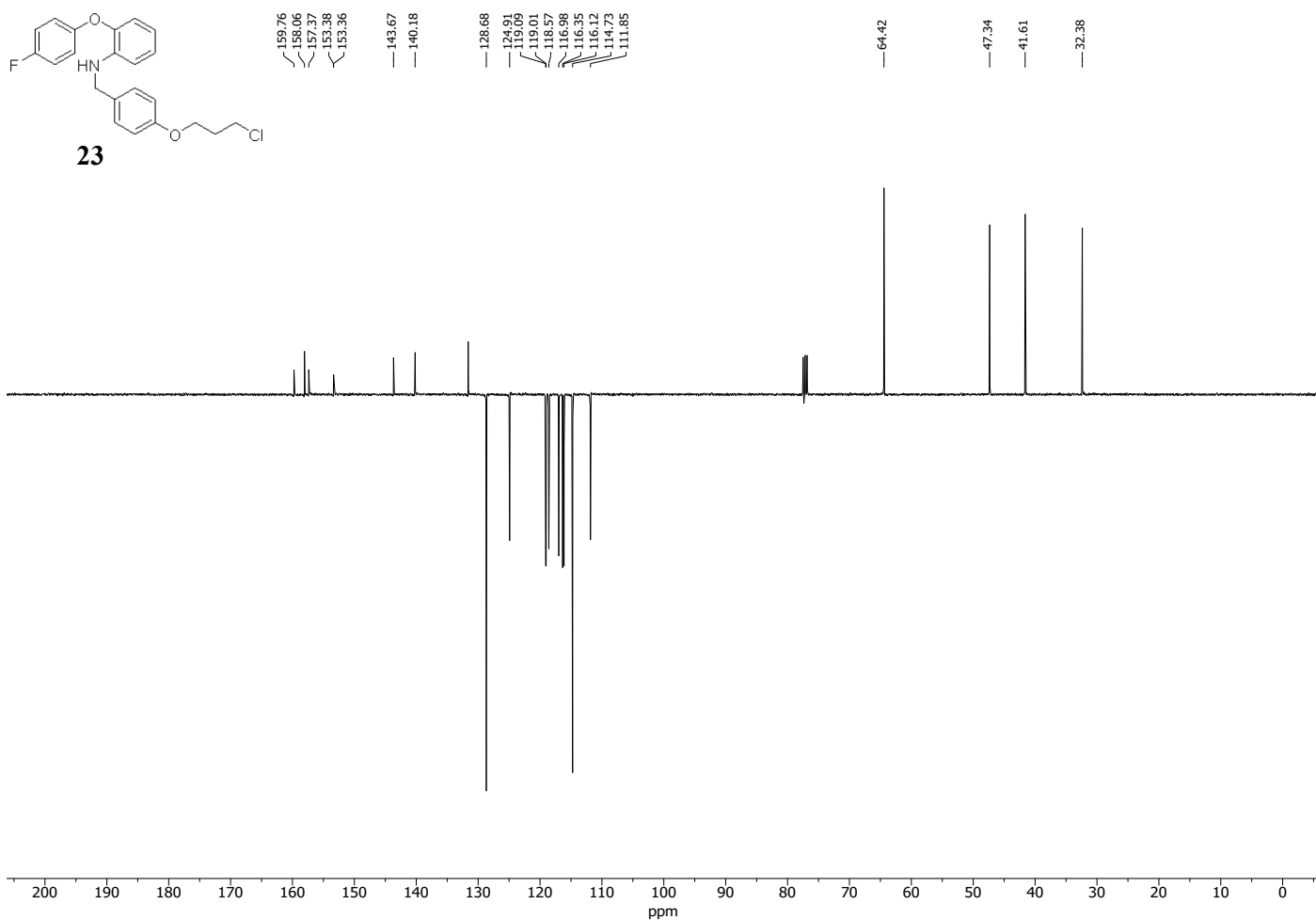
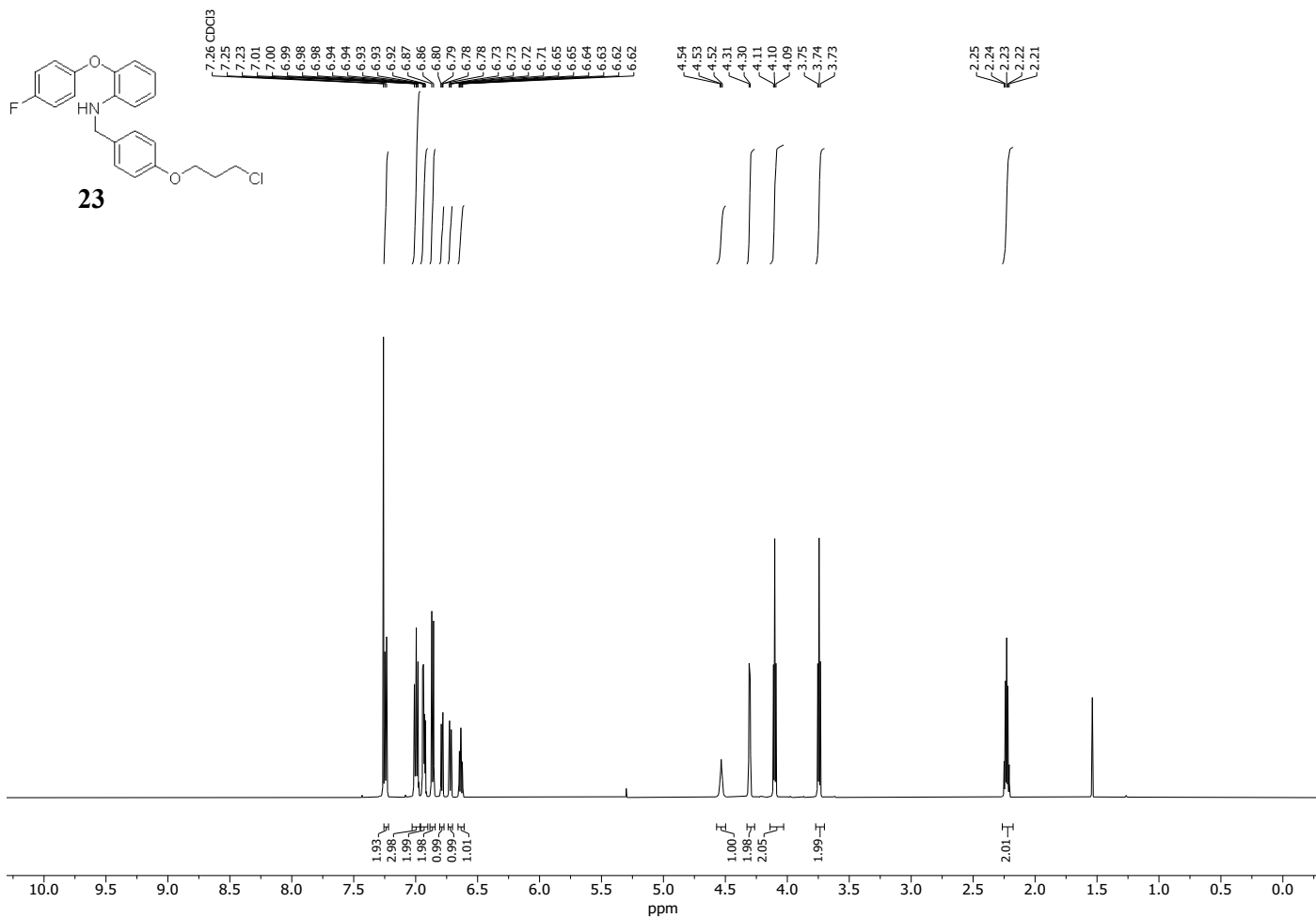


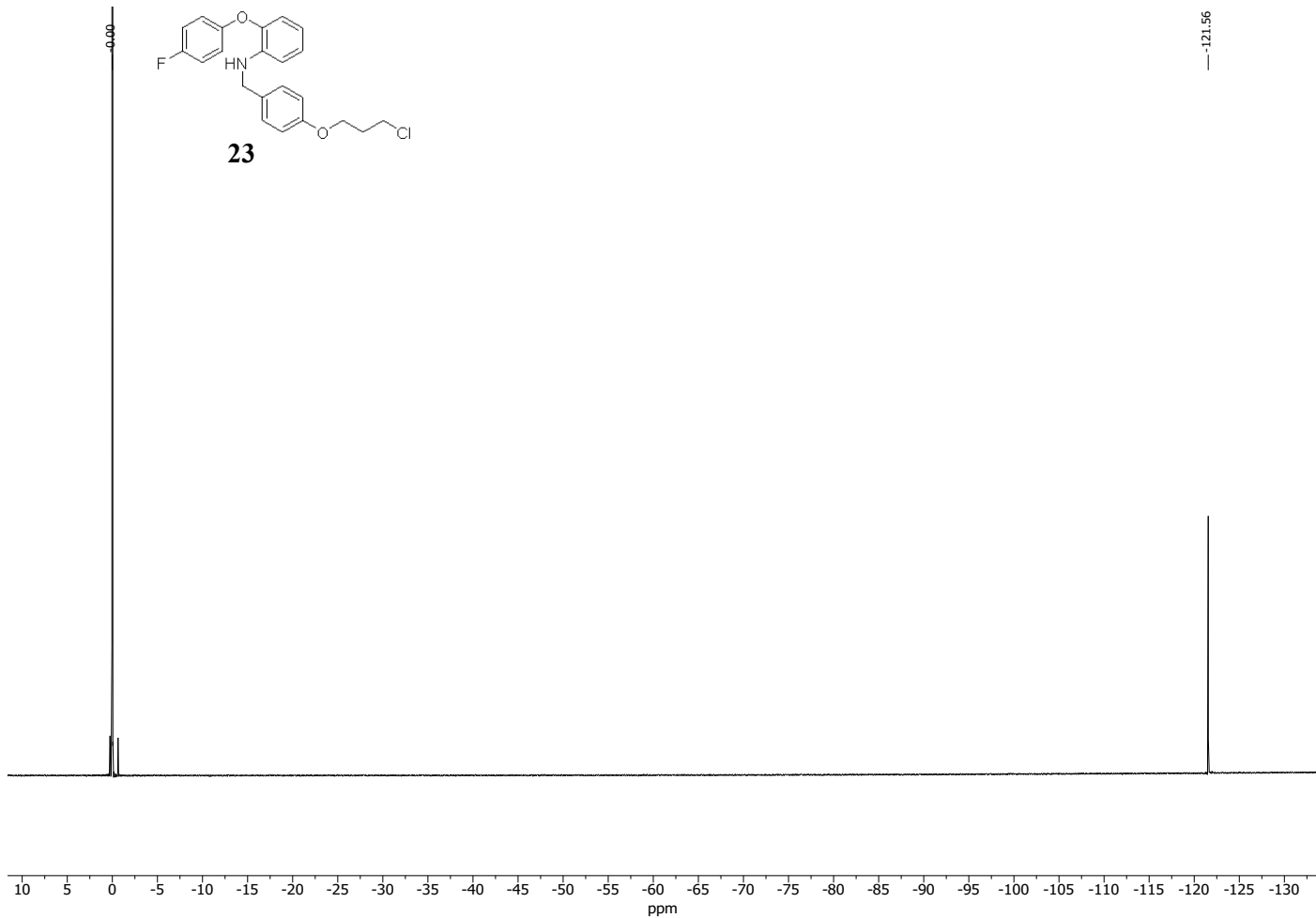
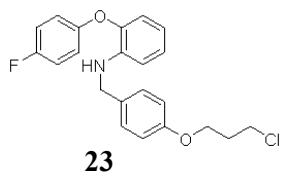


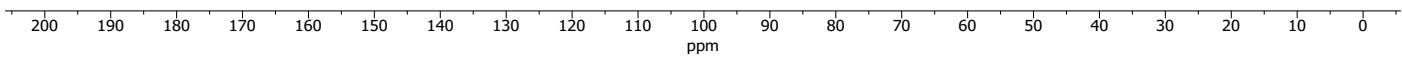
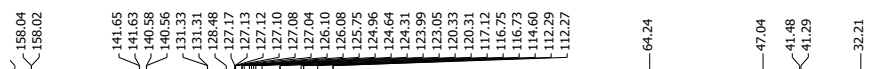
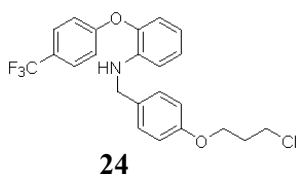
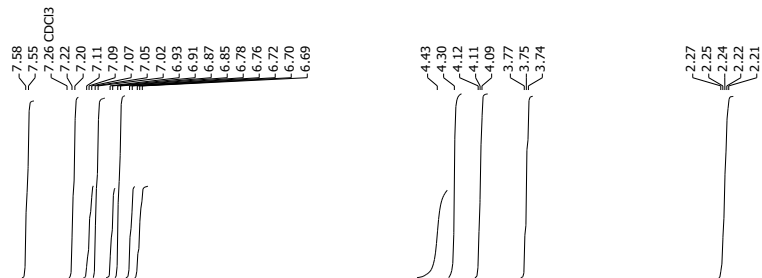
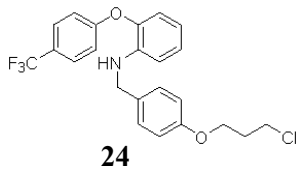


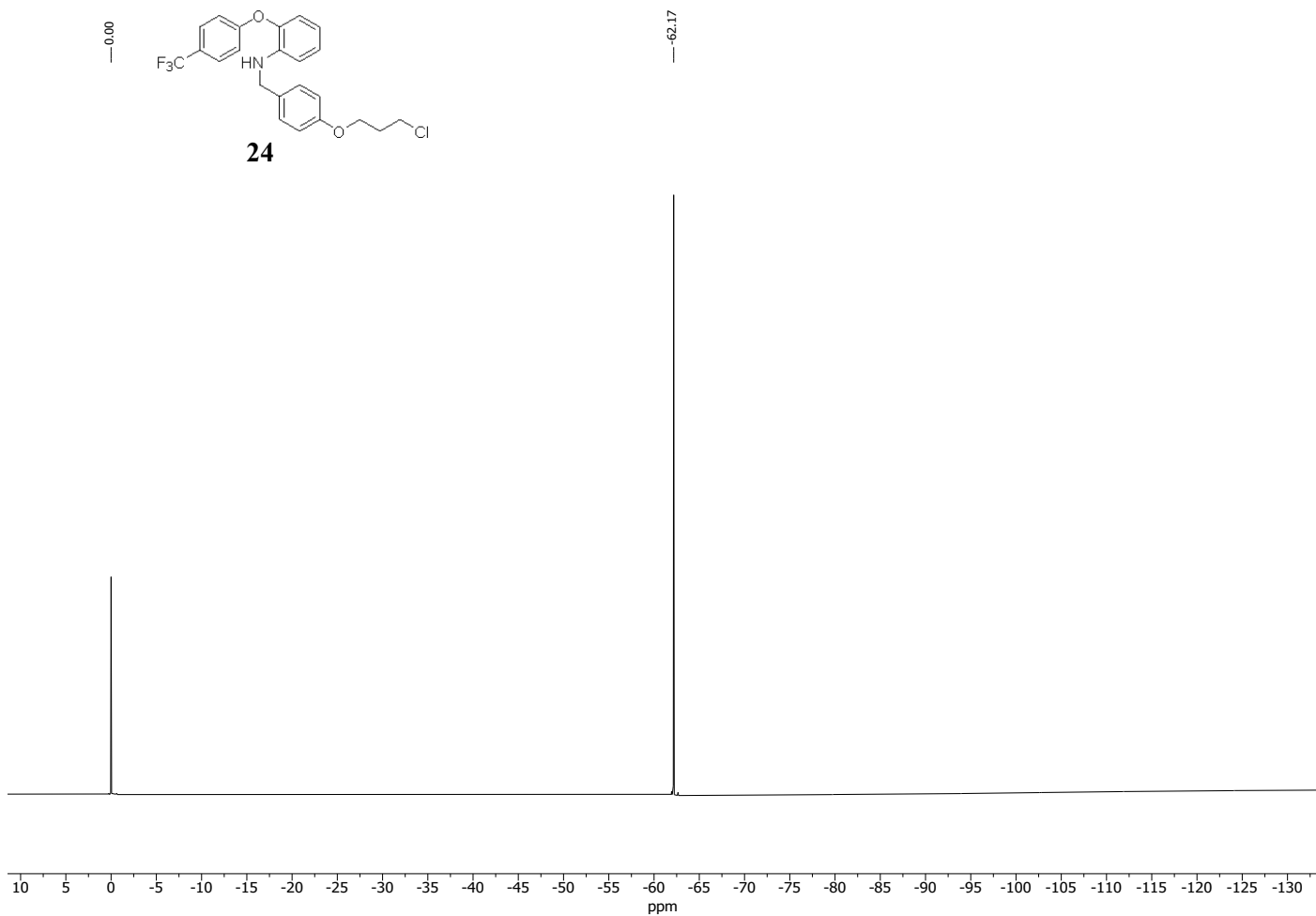
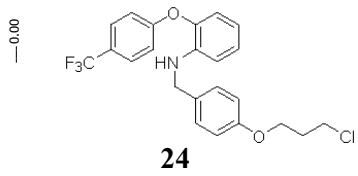


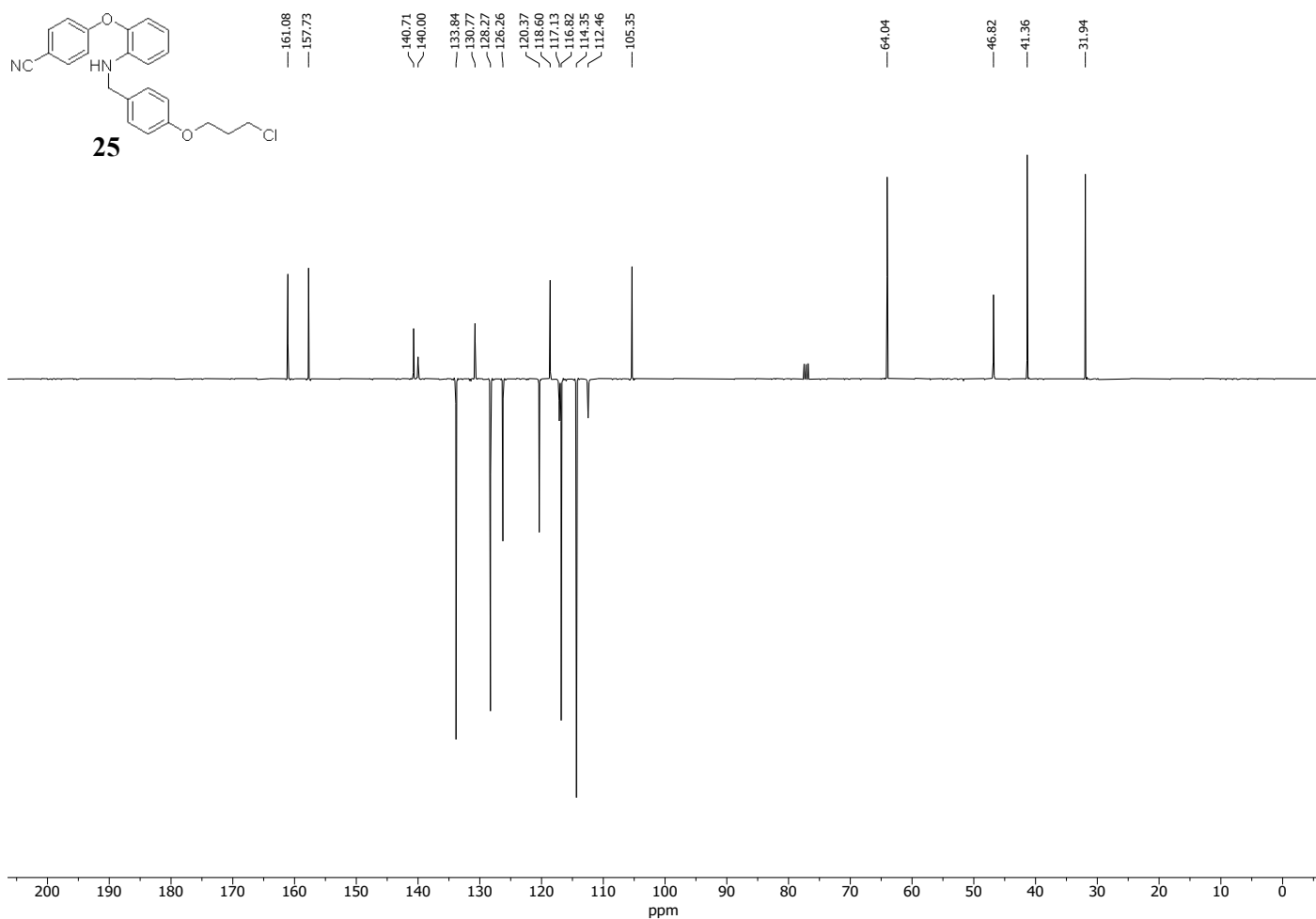
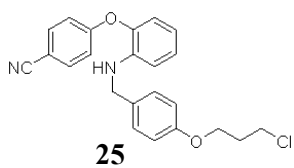
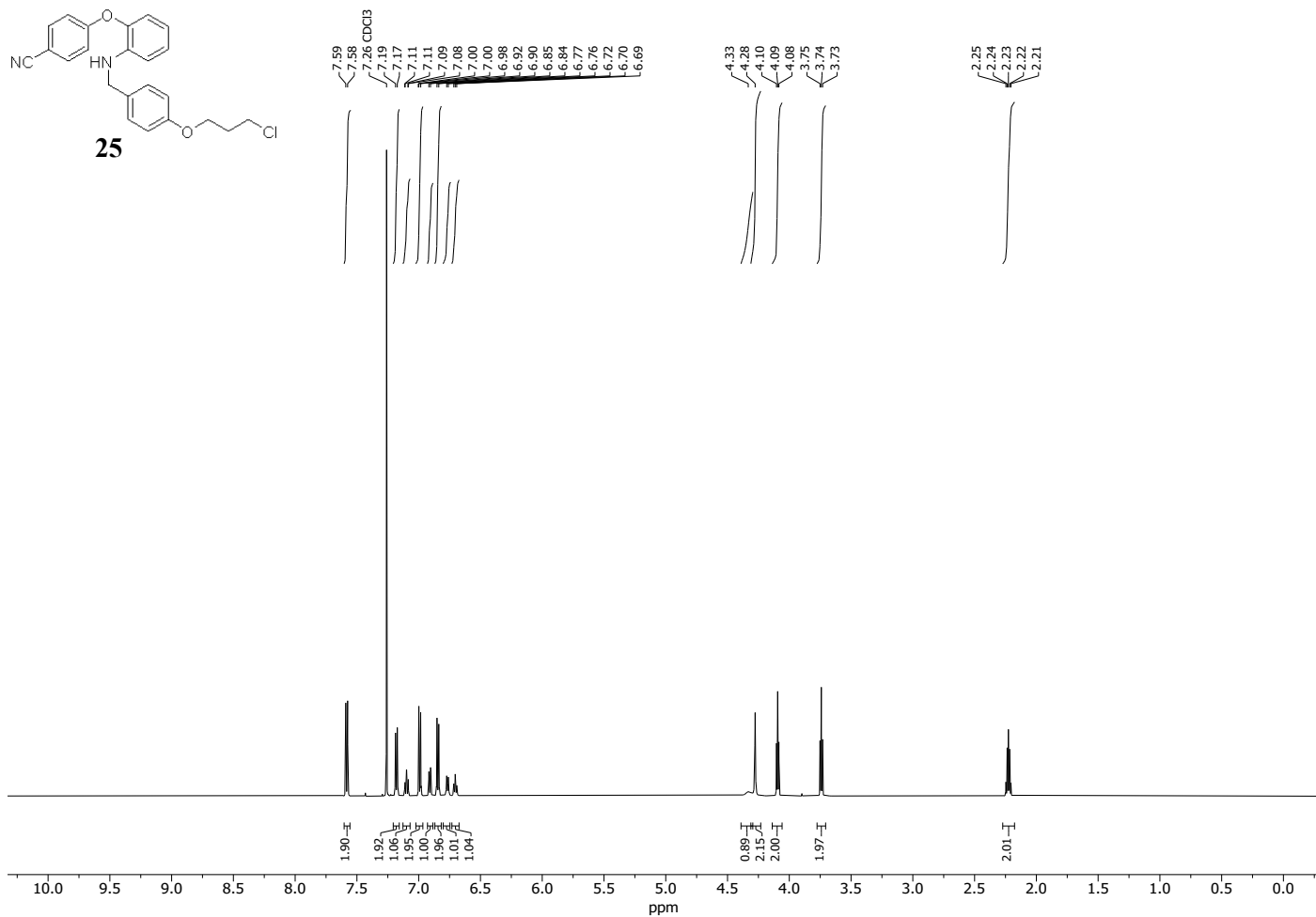
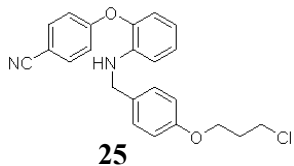


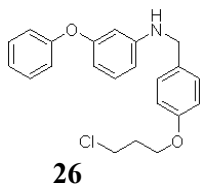




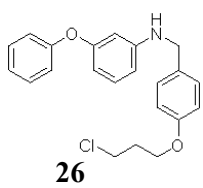
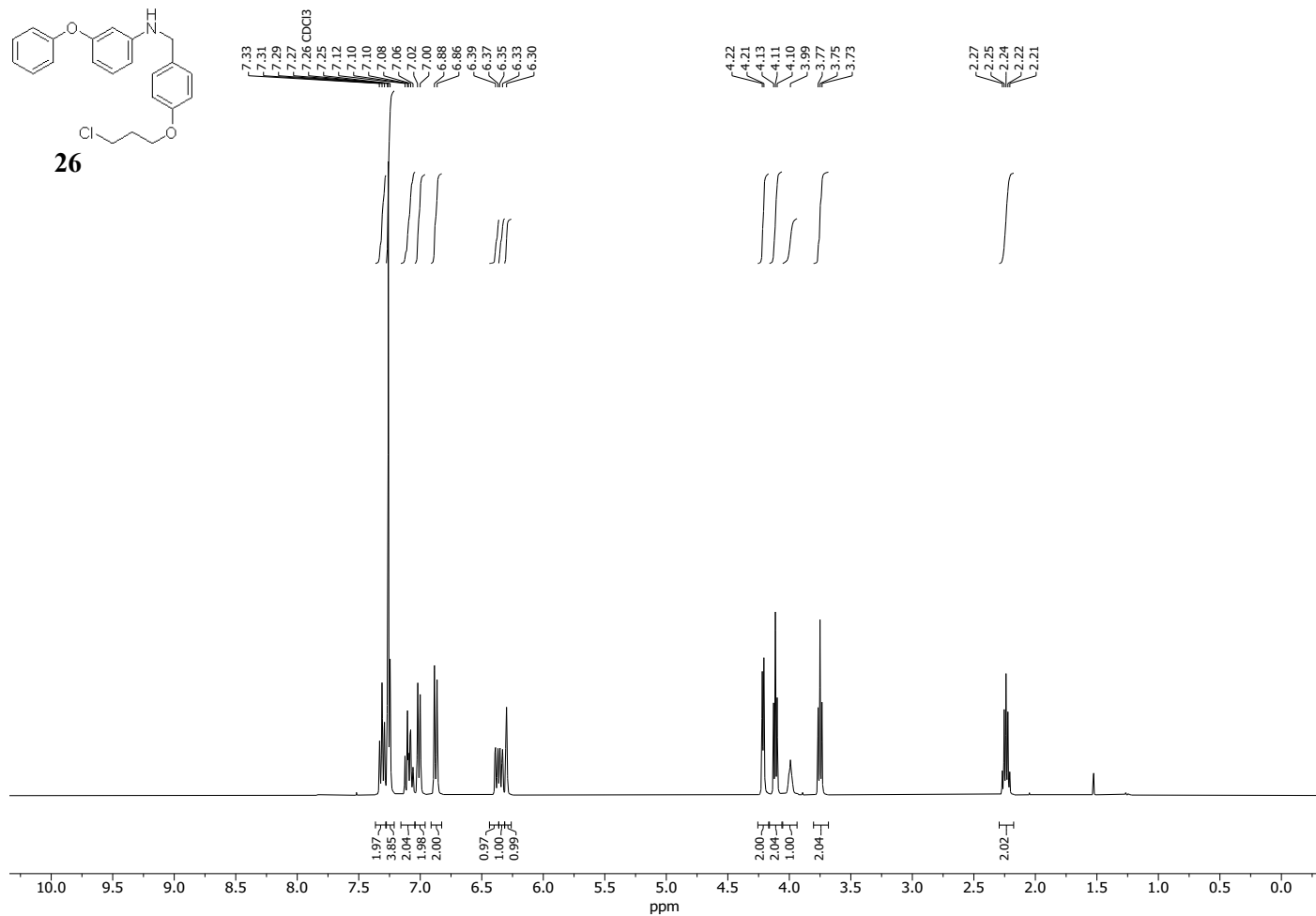




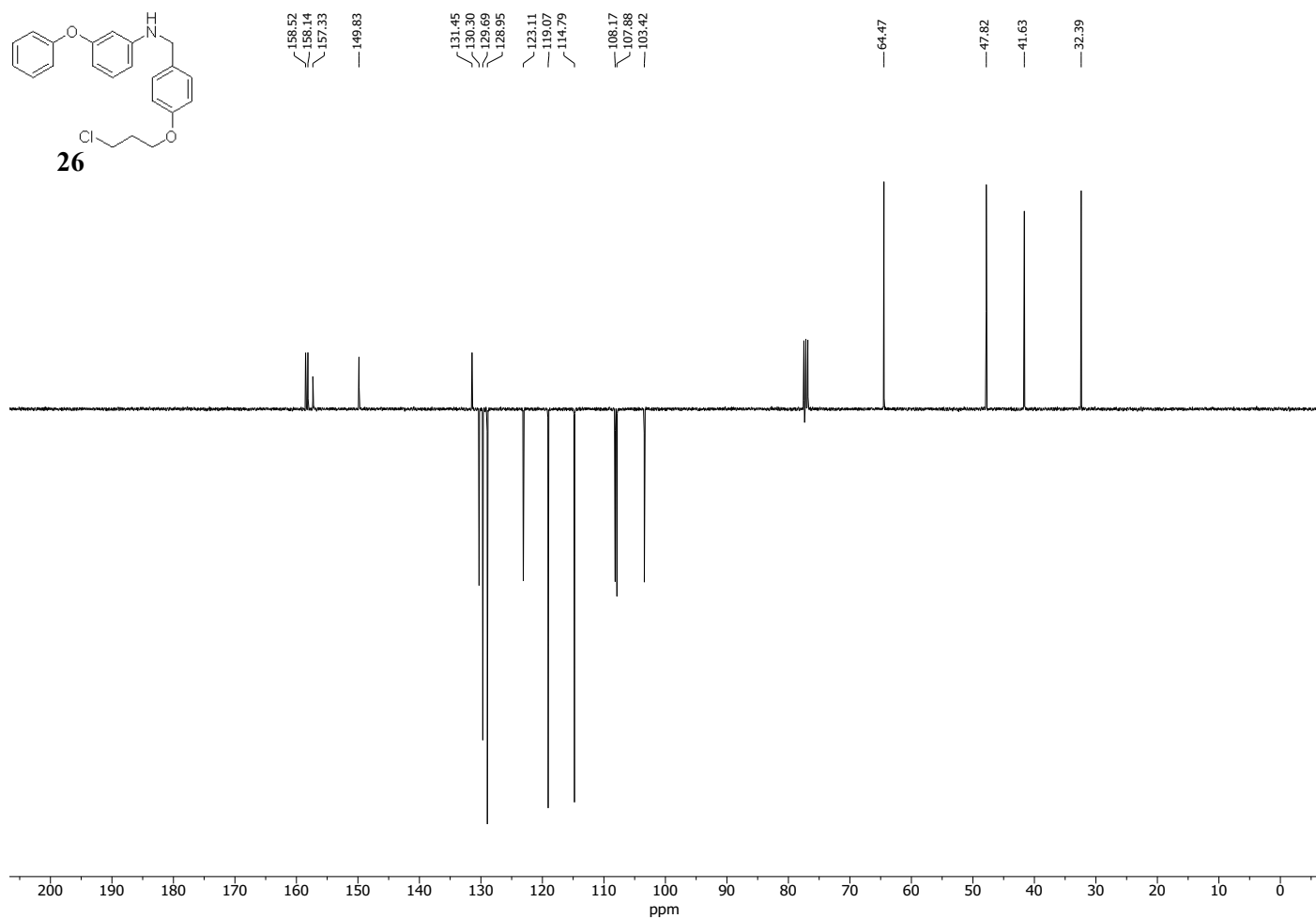


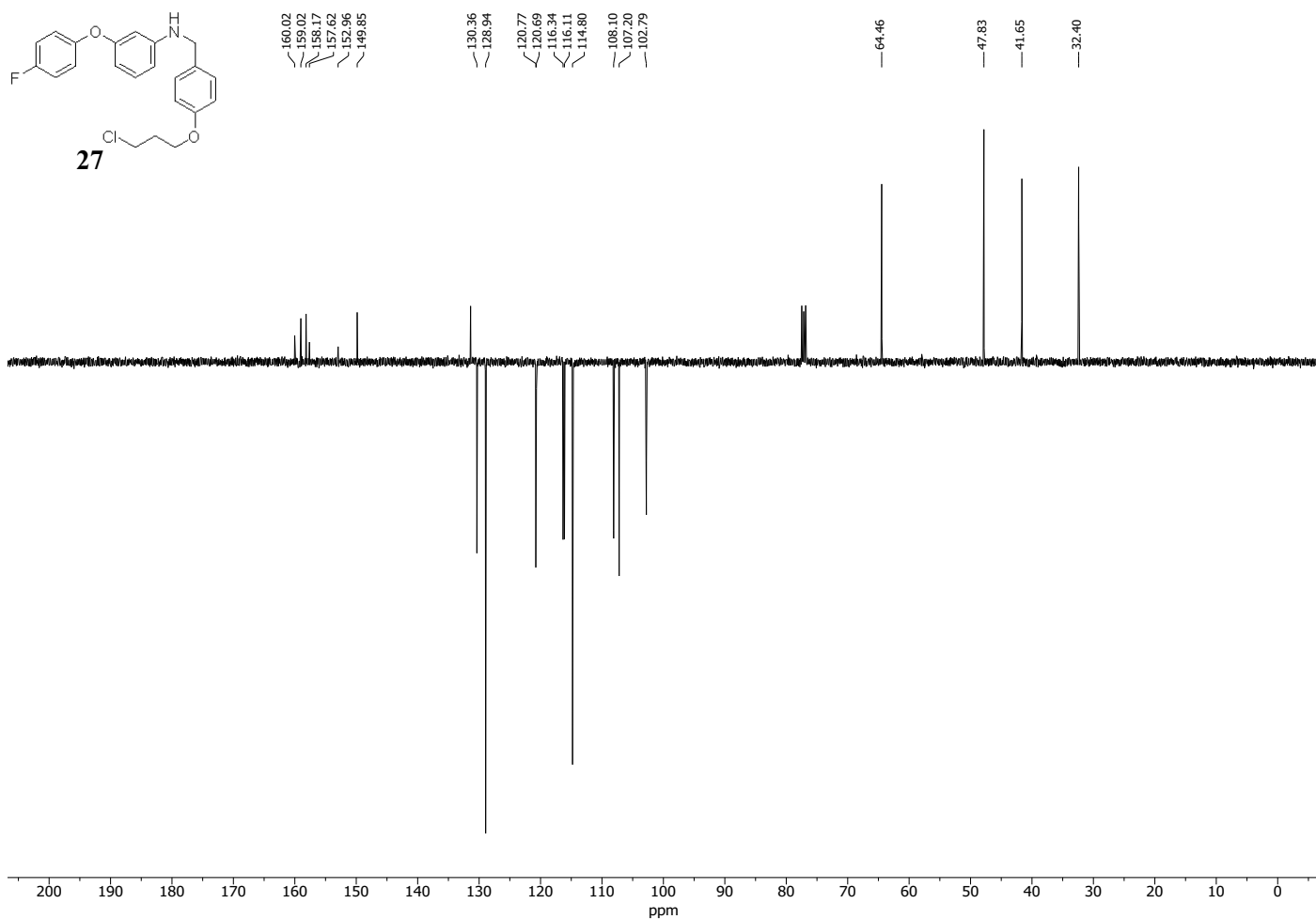
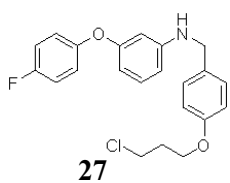
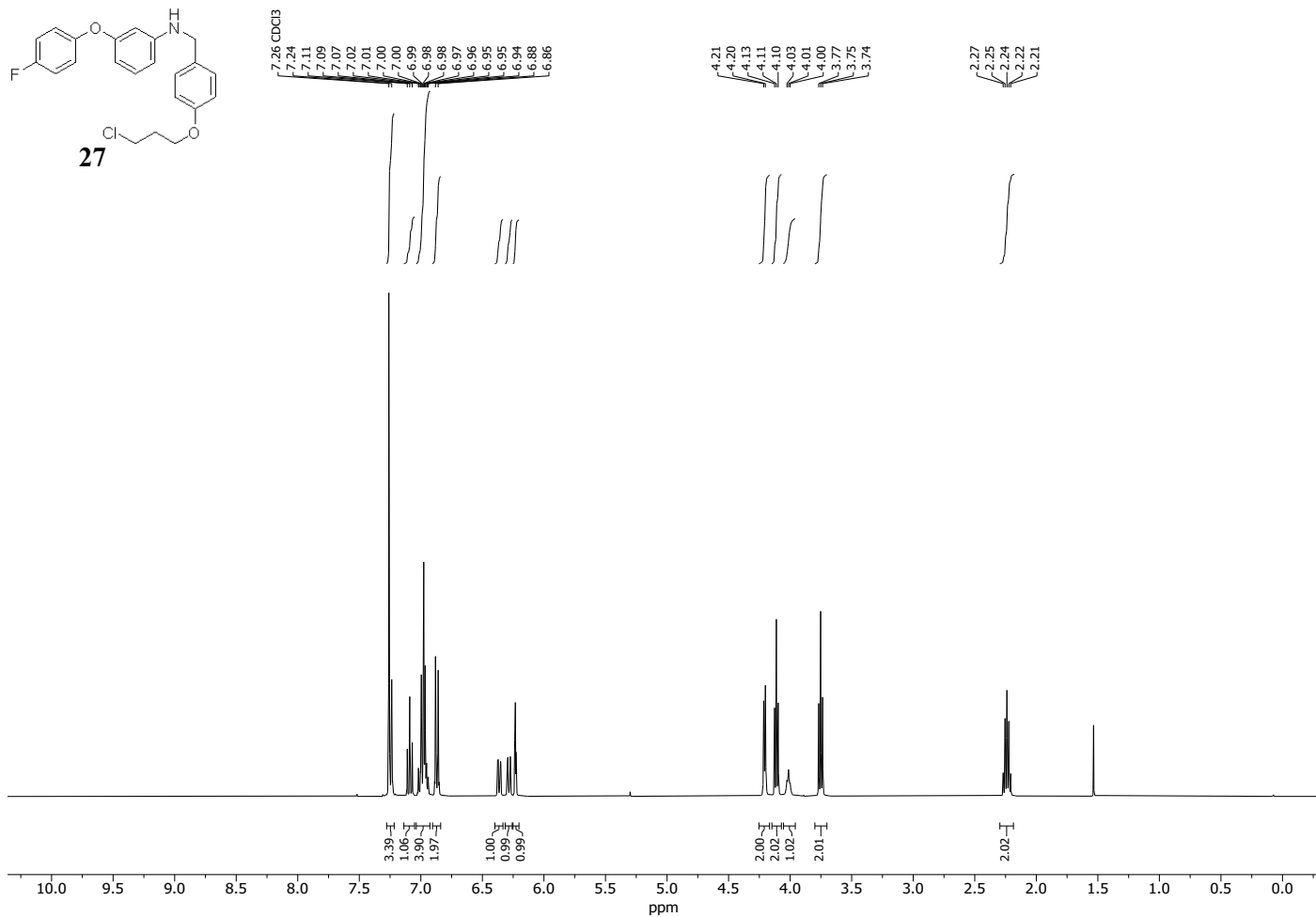
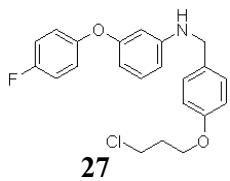


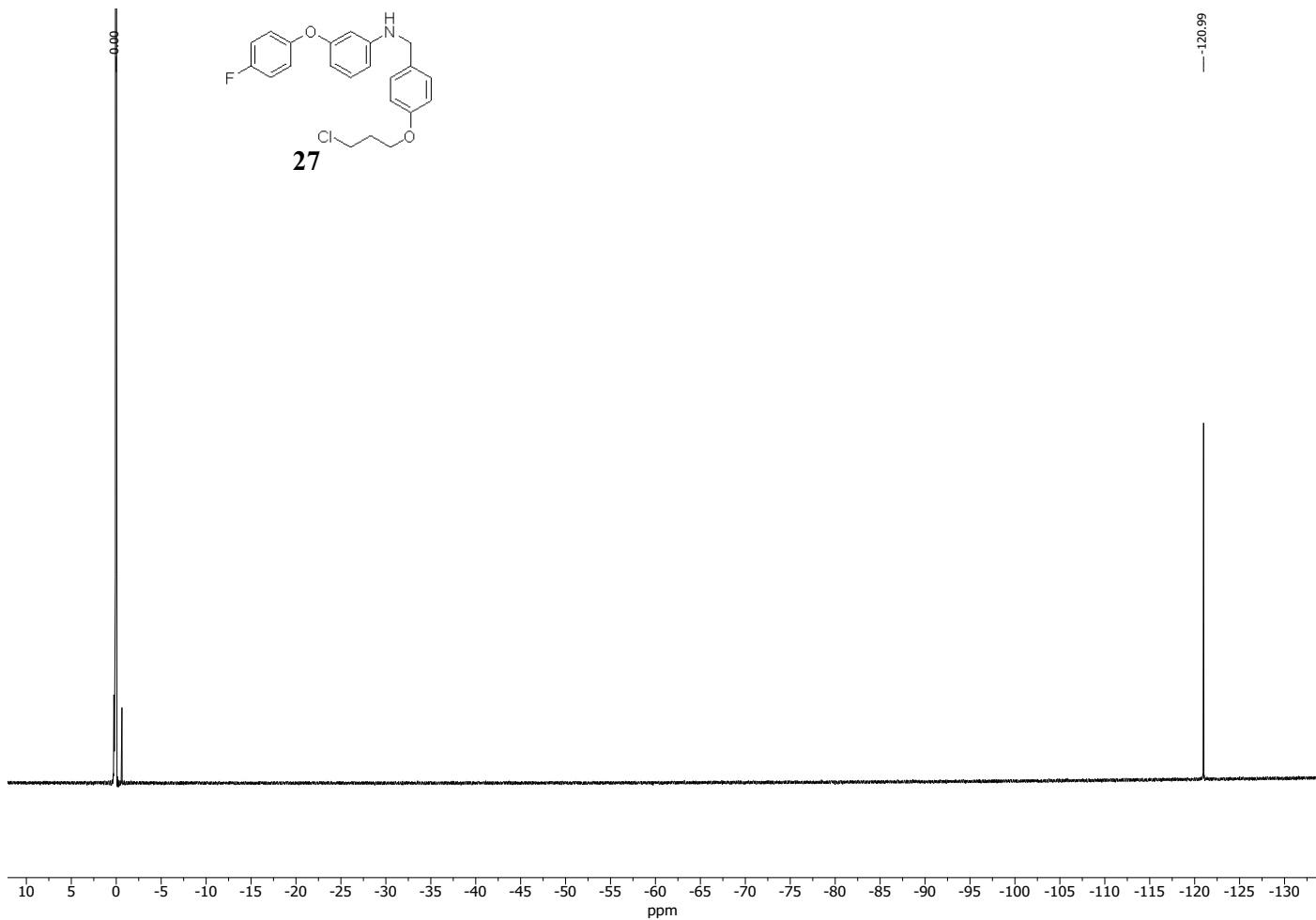
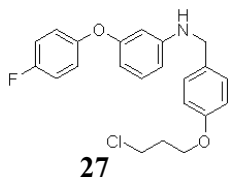
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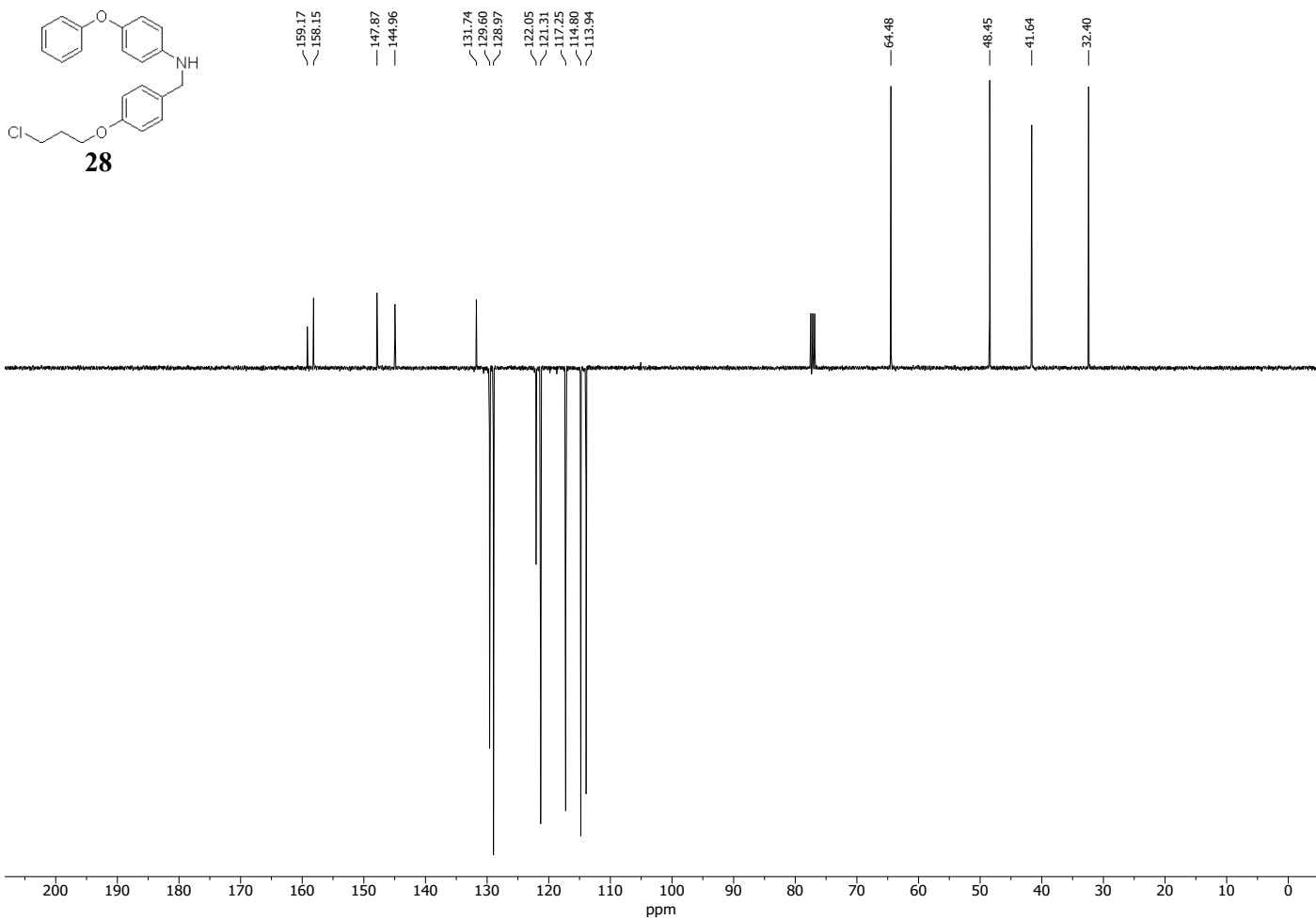
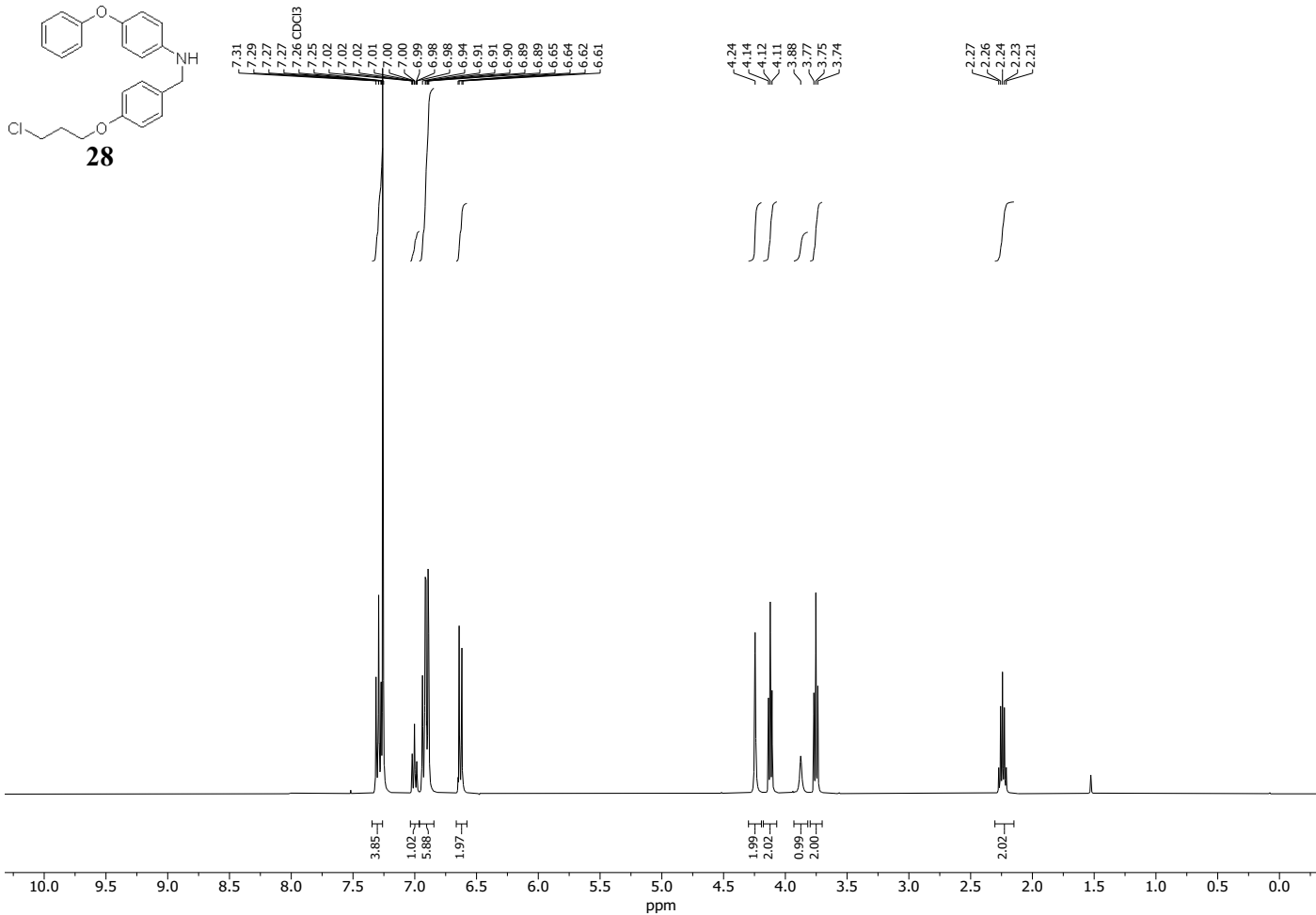


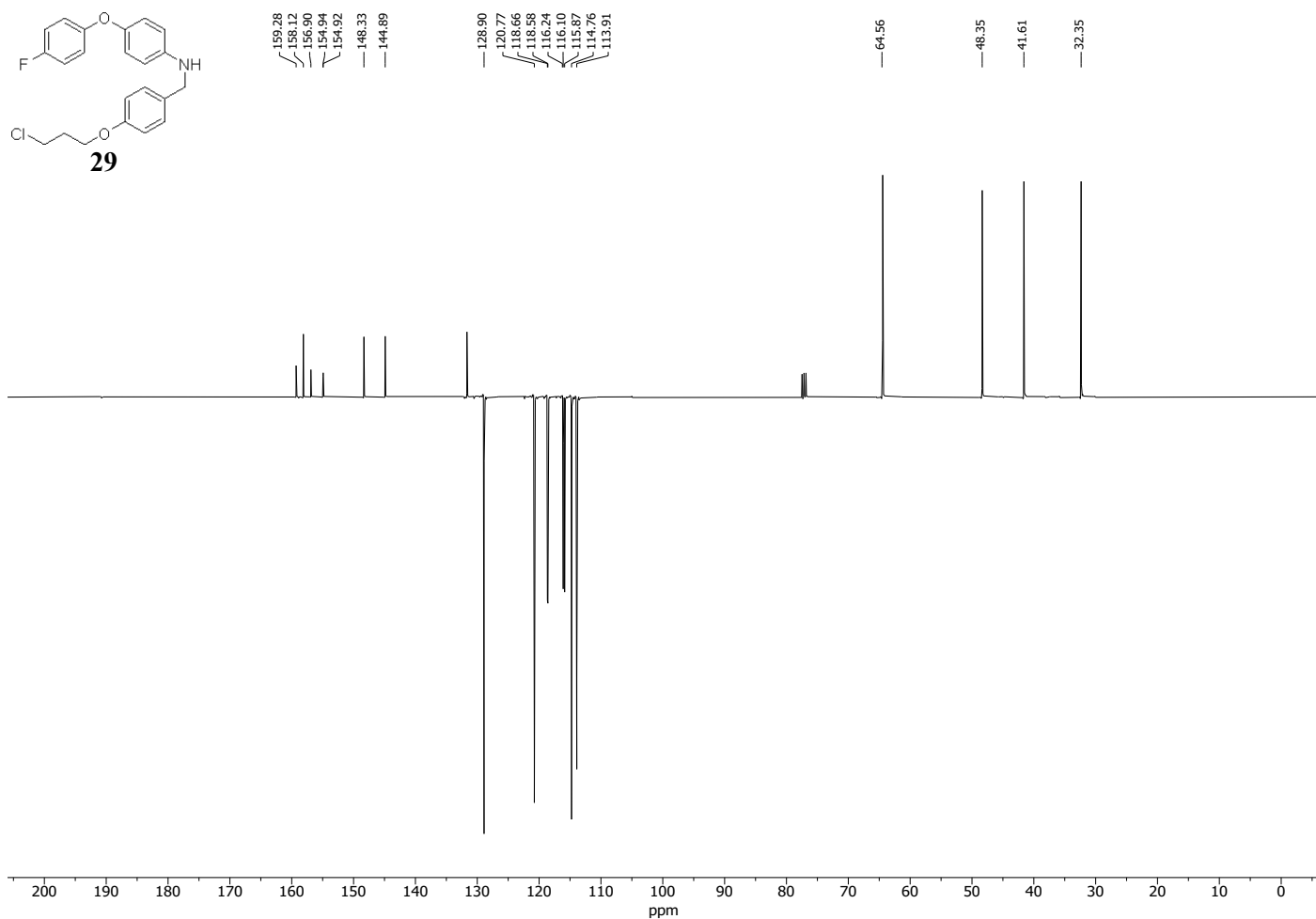
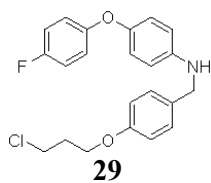
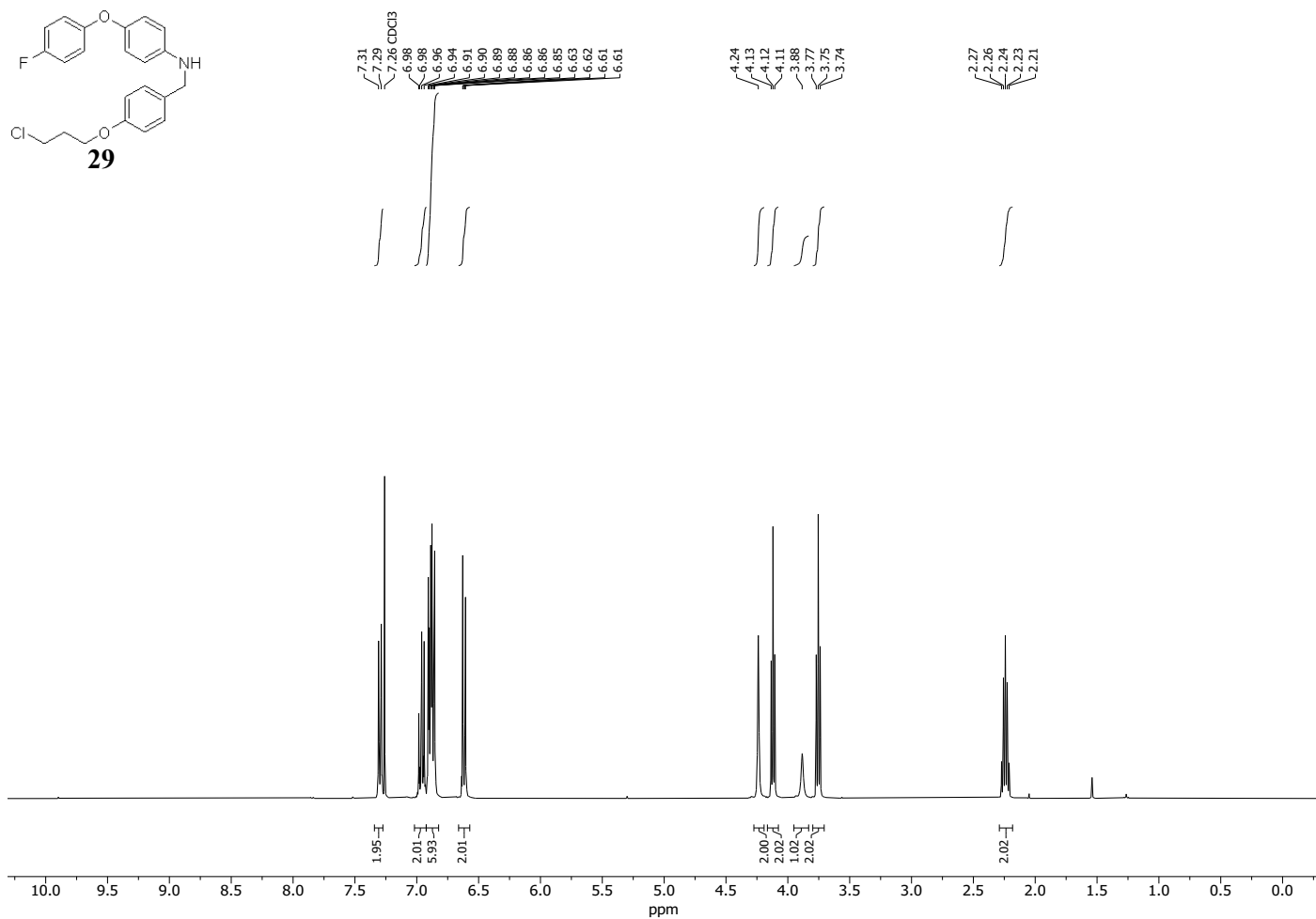
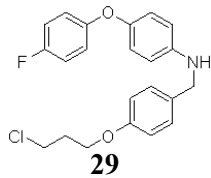
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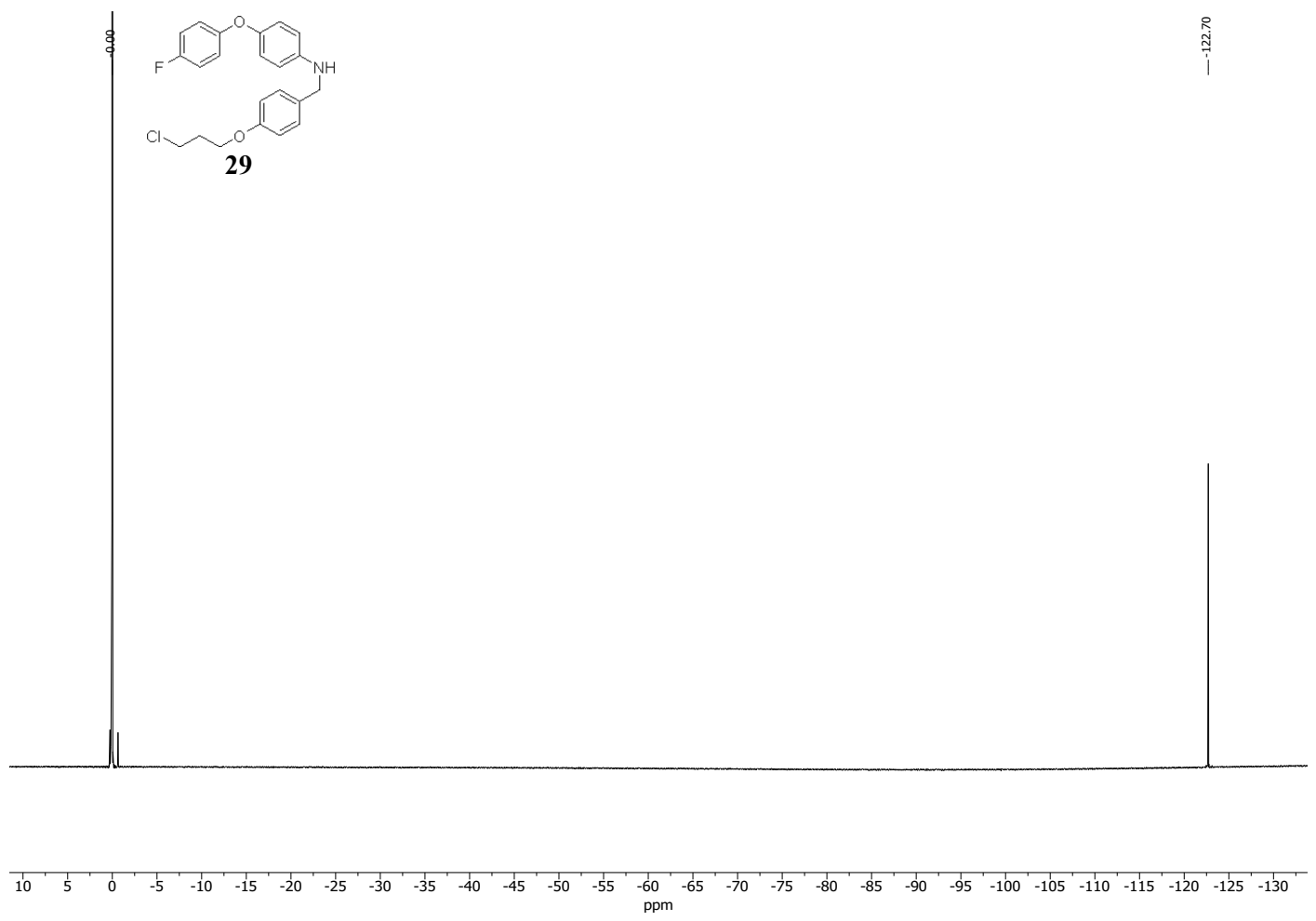
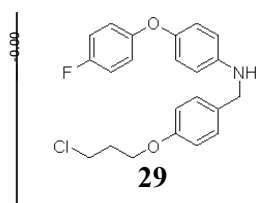


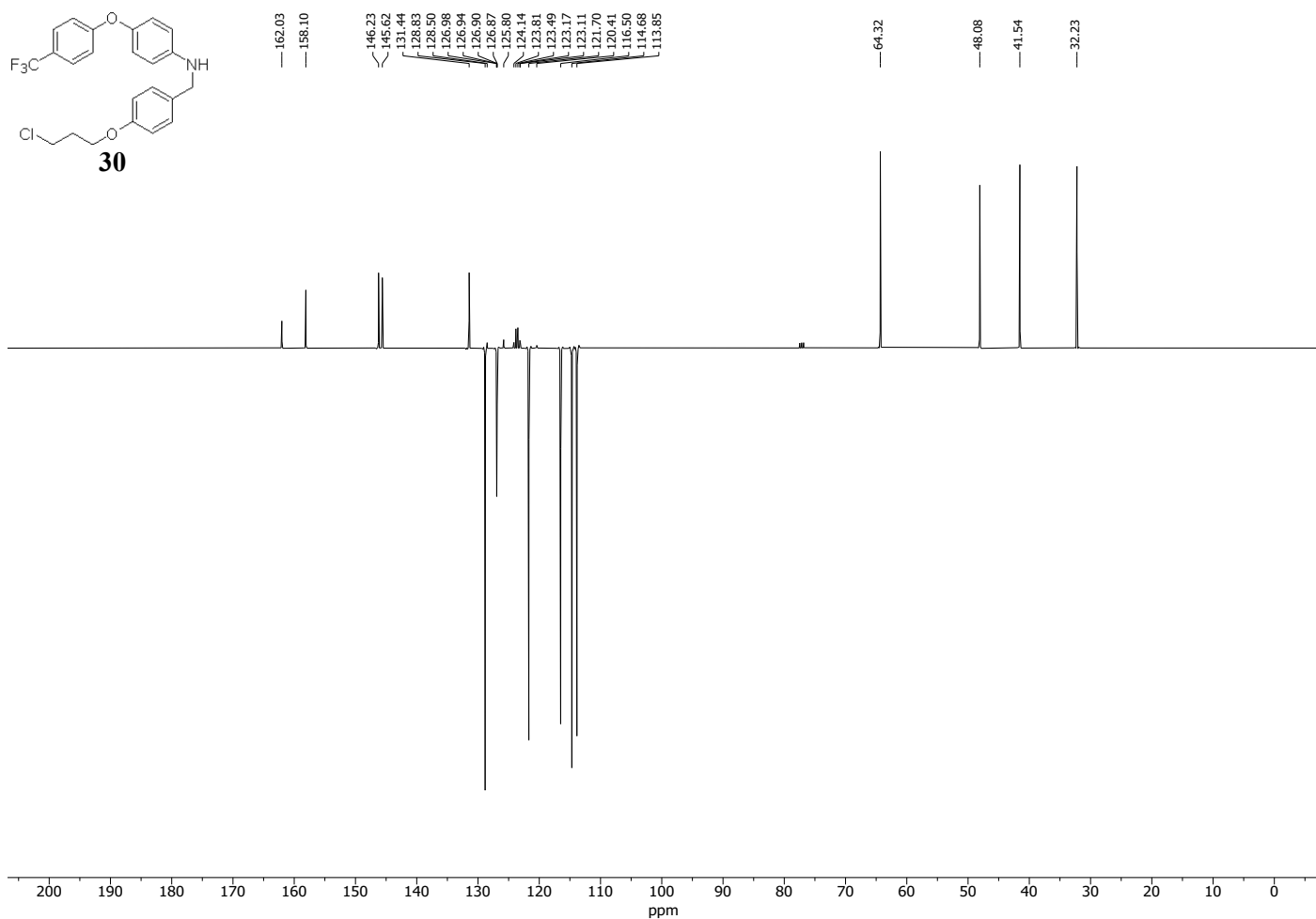
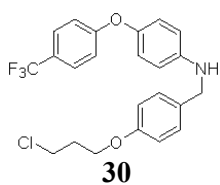
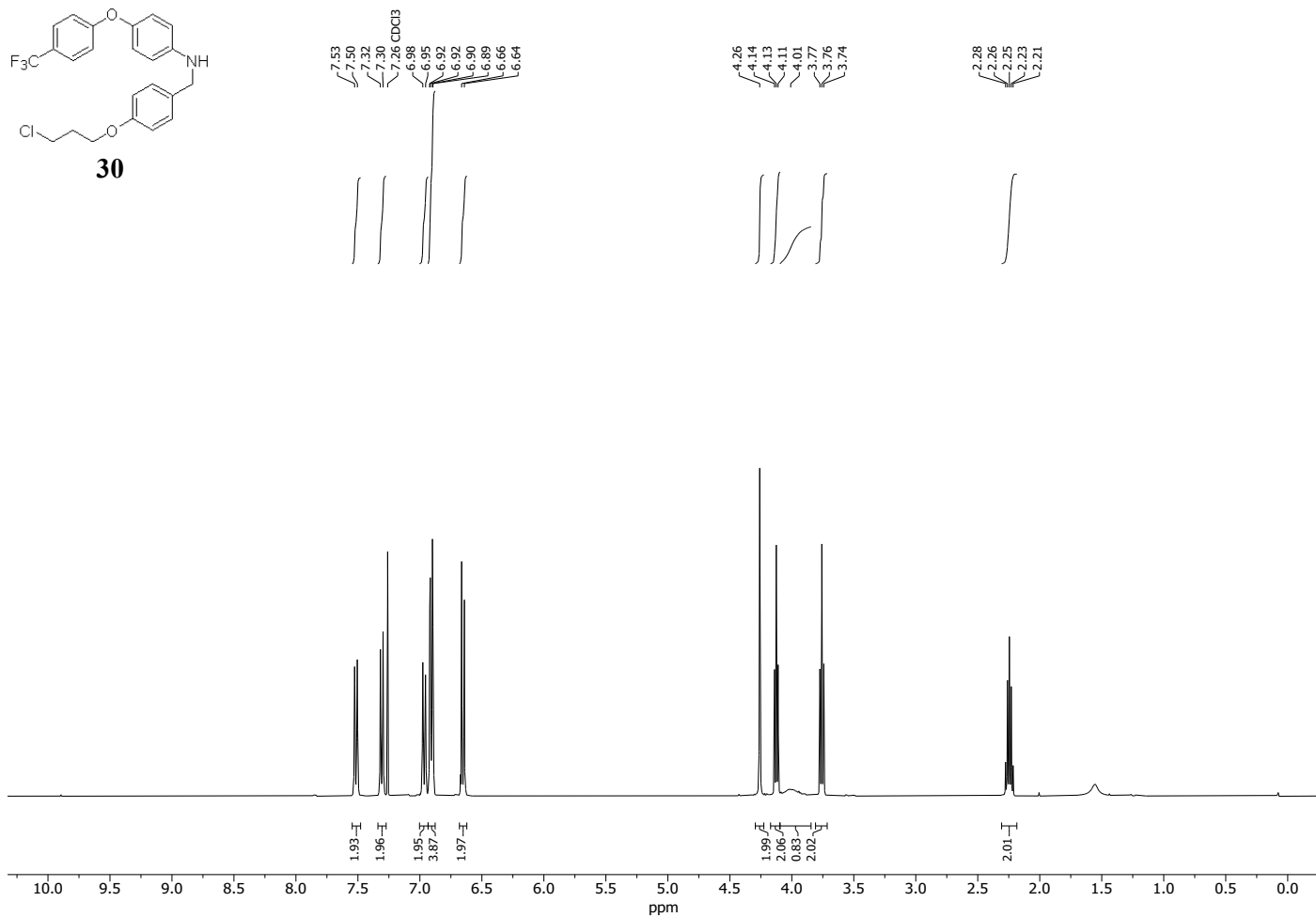
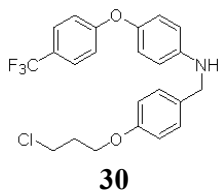


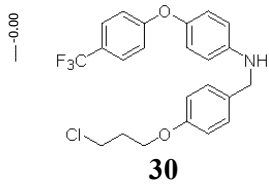




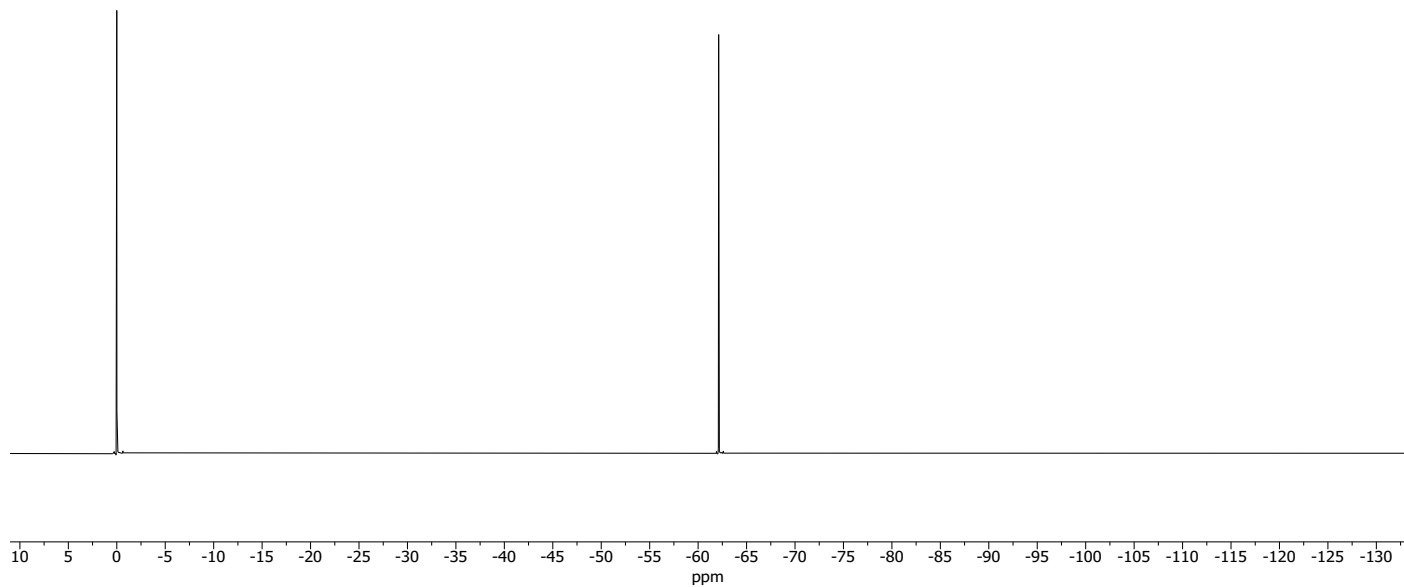


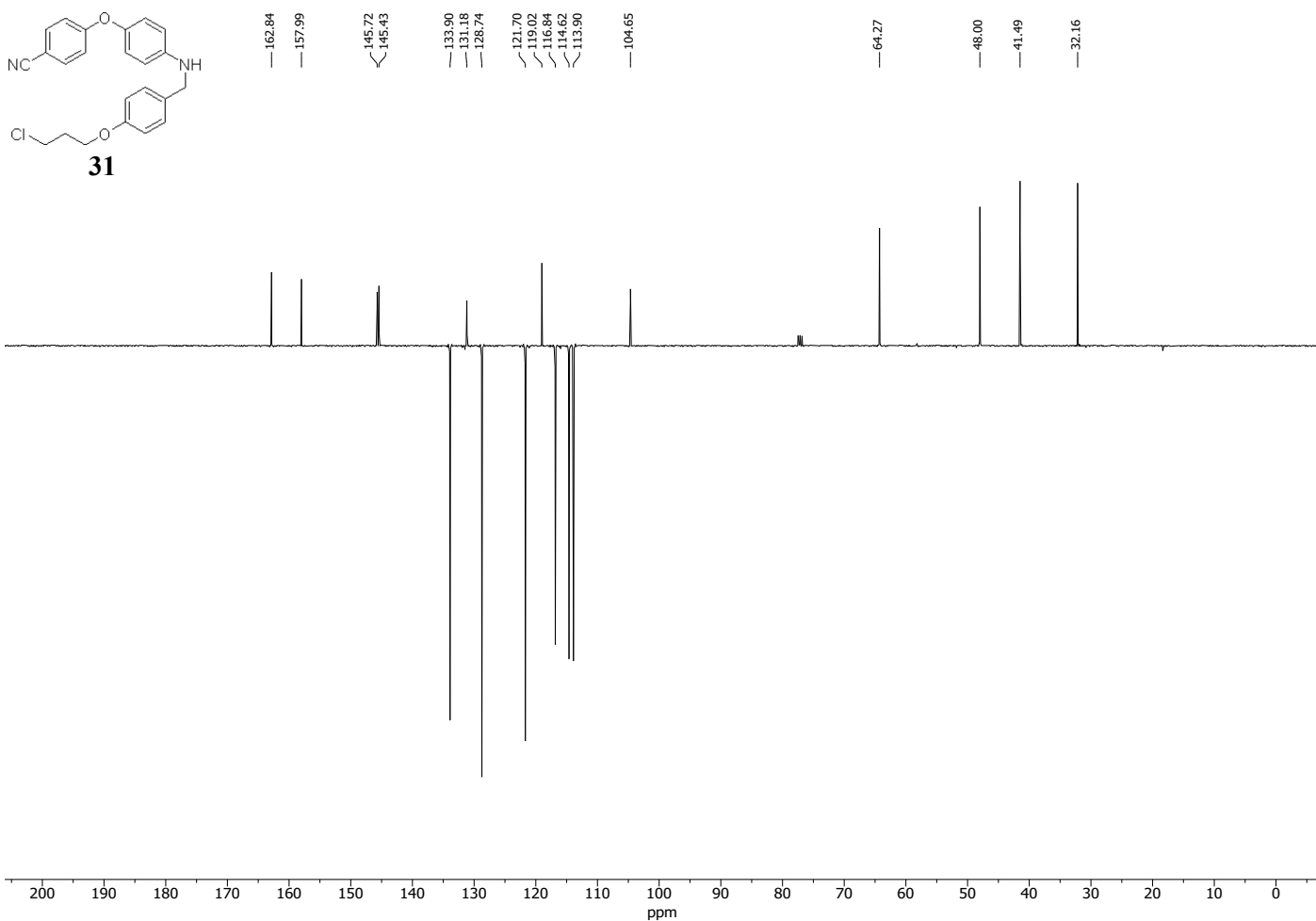
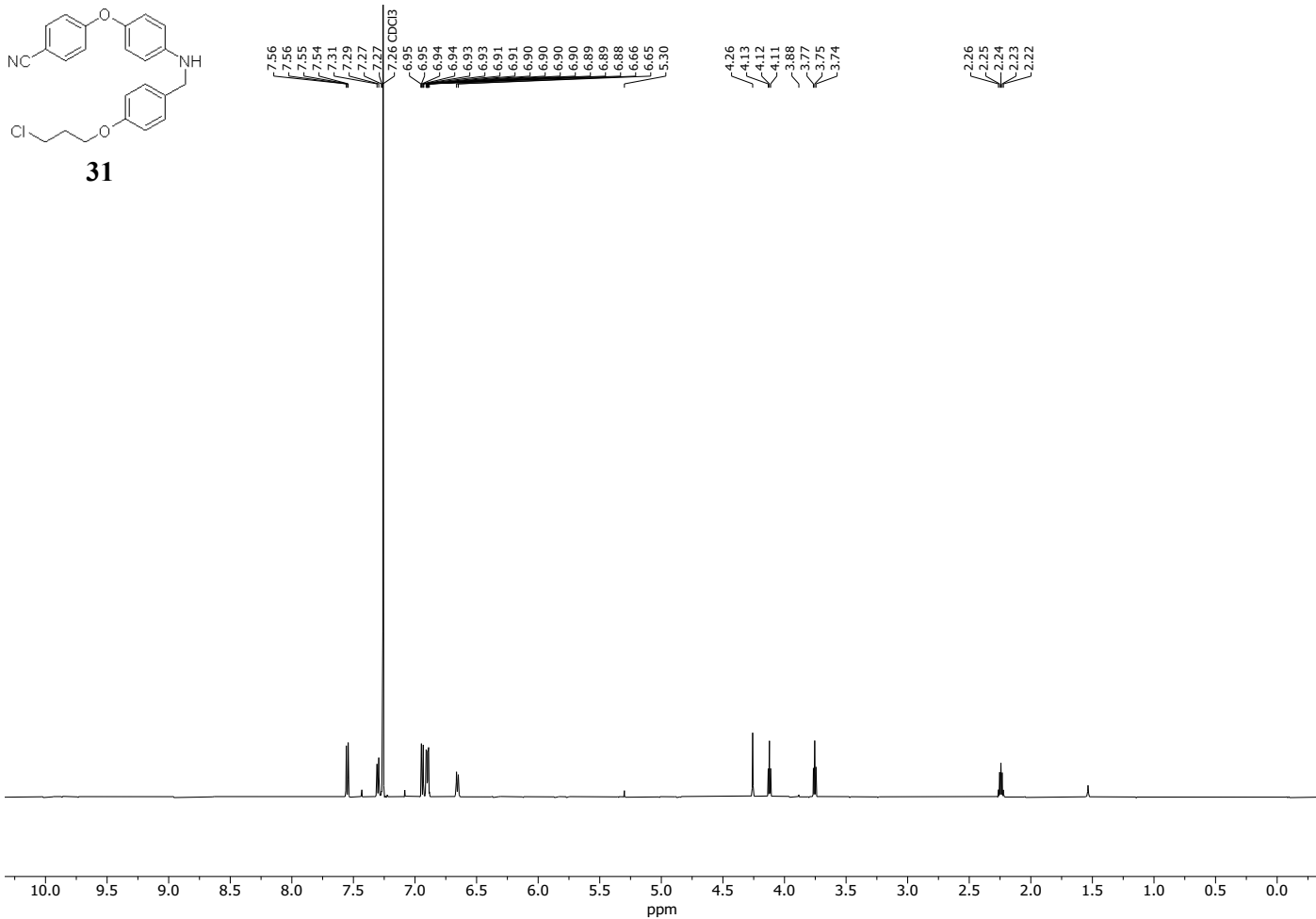


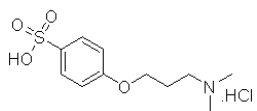




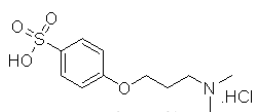
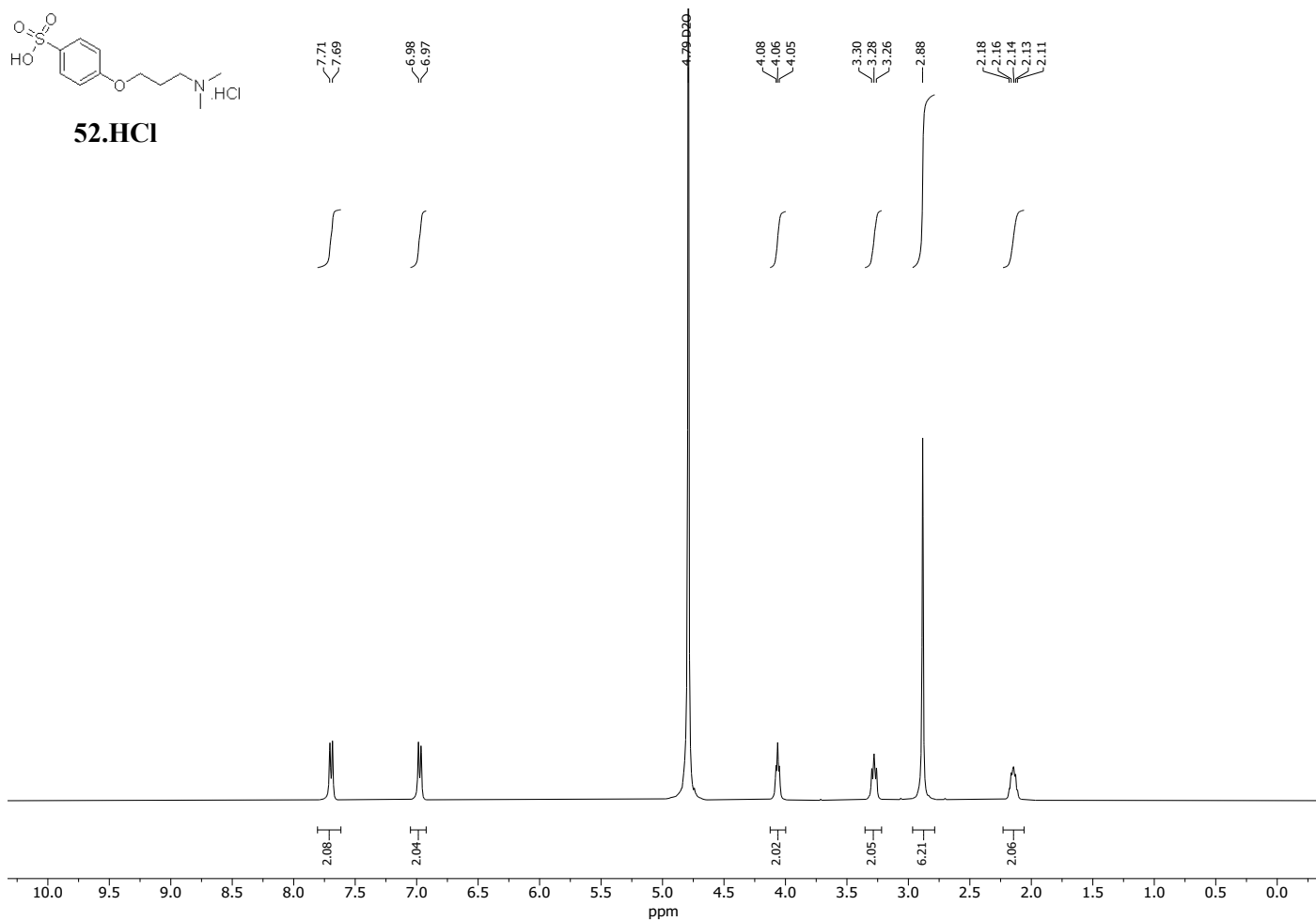
— -62.12



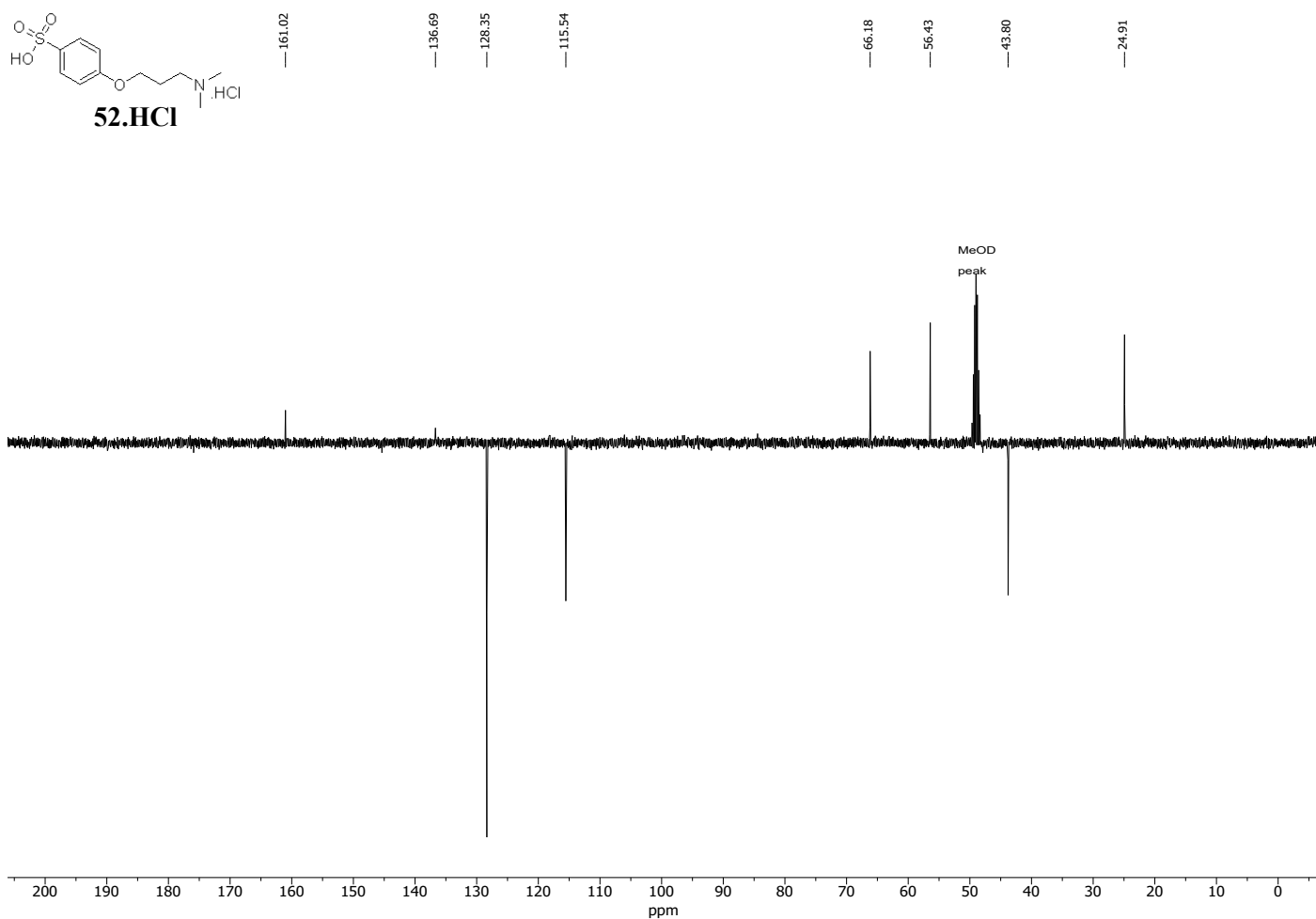




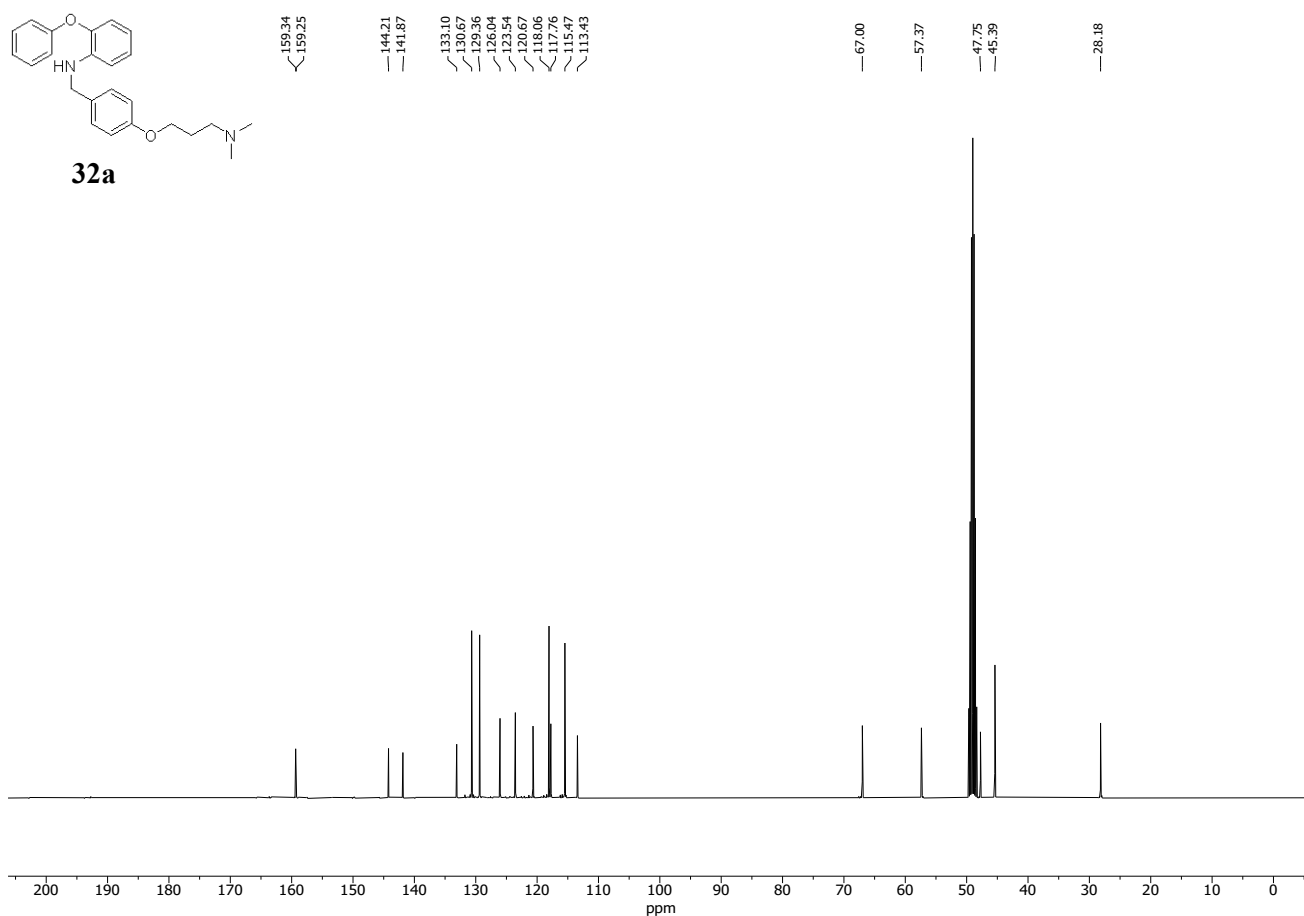
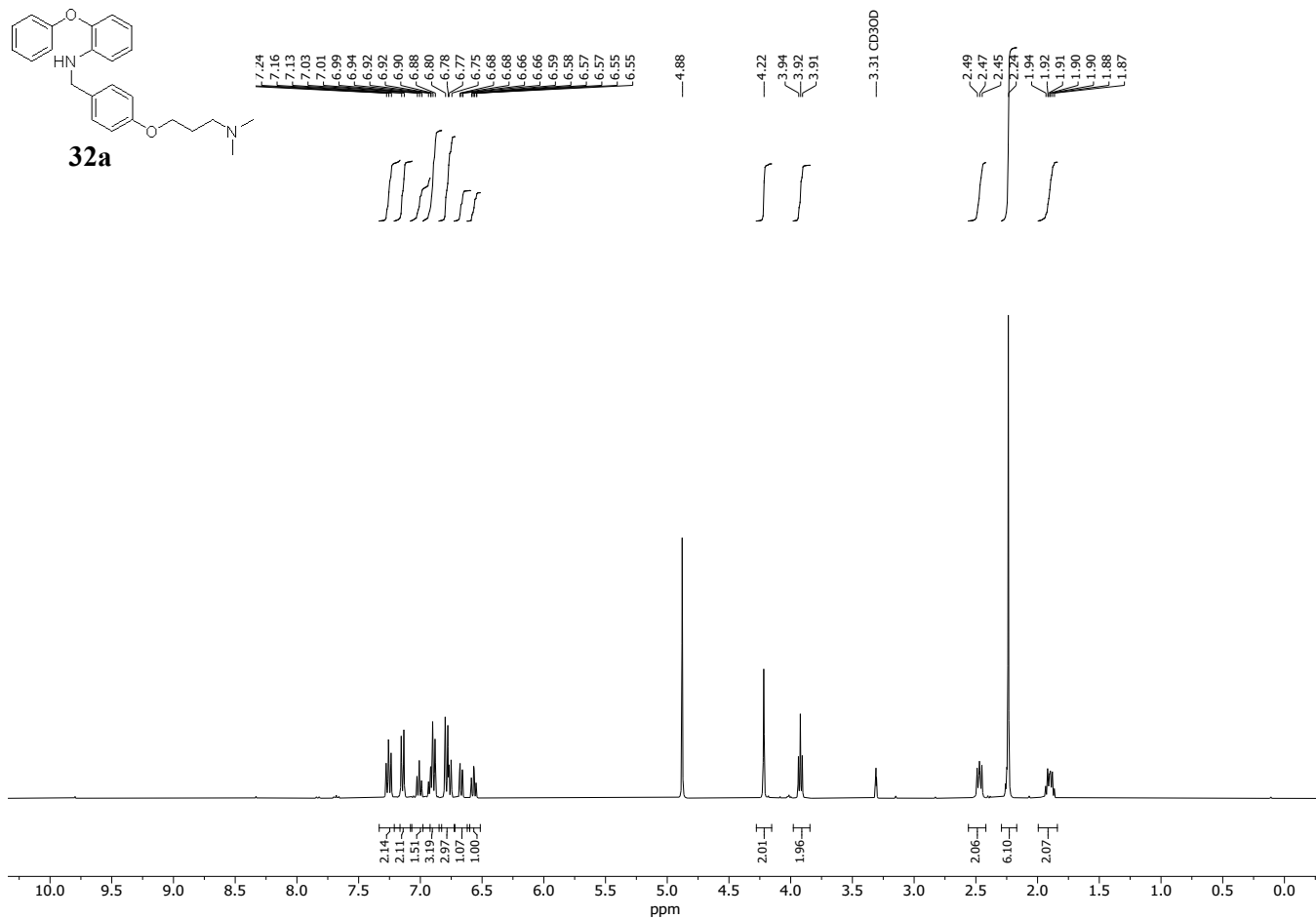
52.HCl

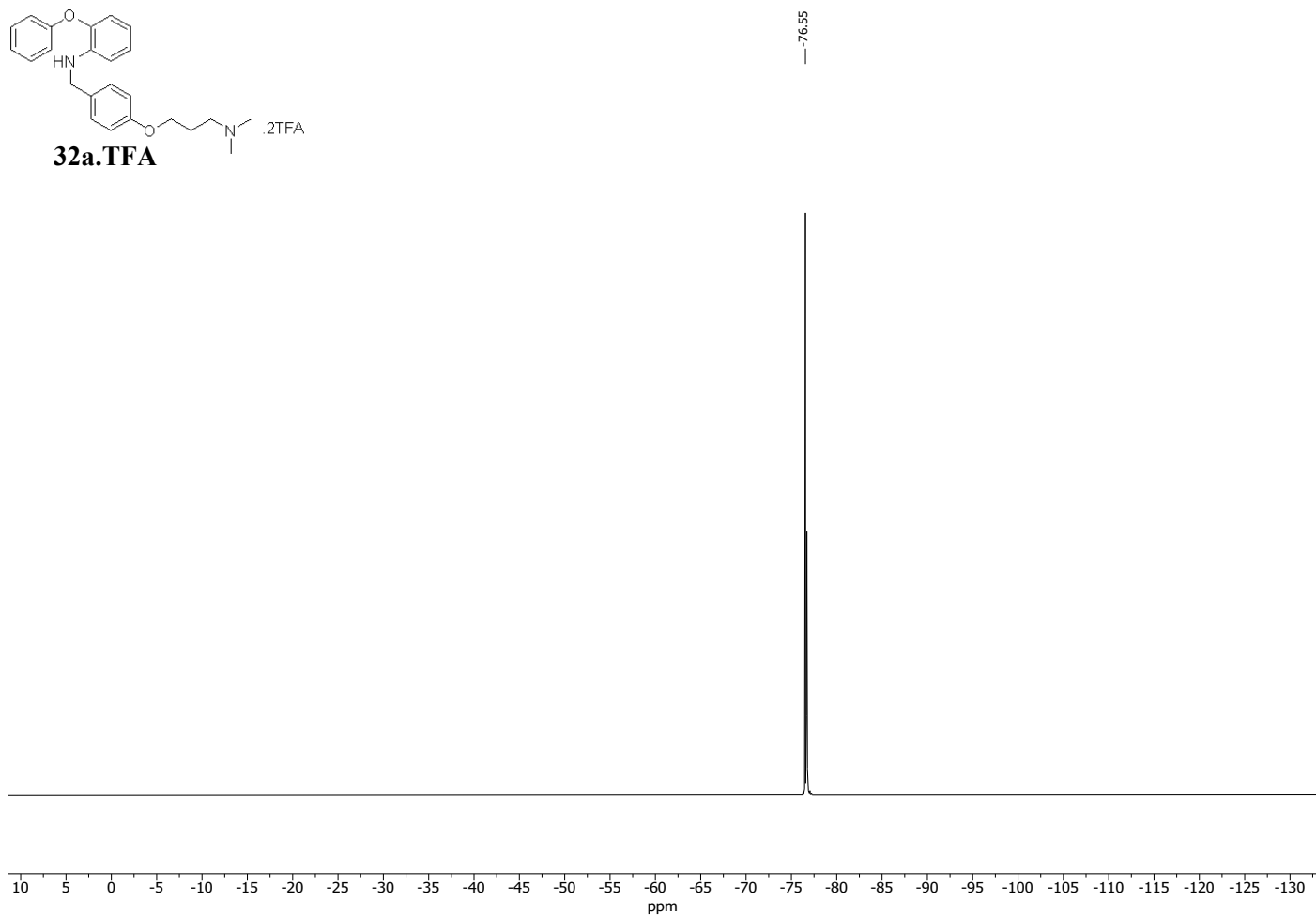
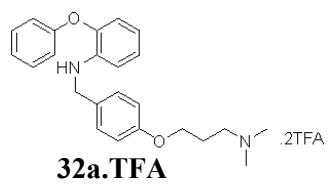


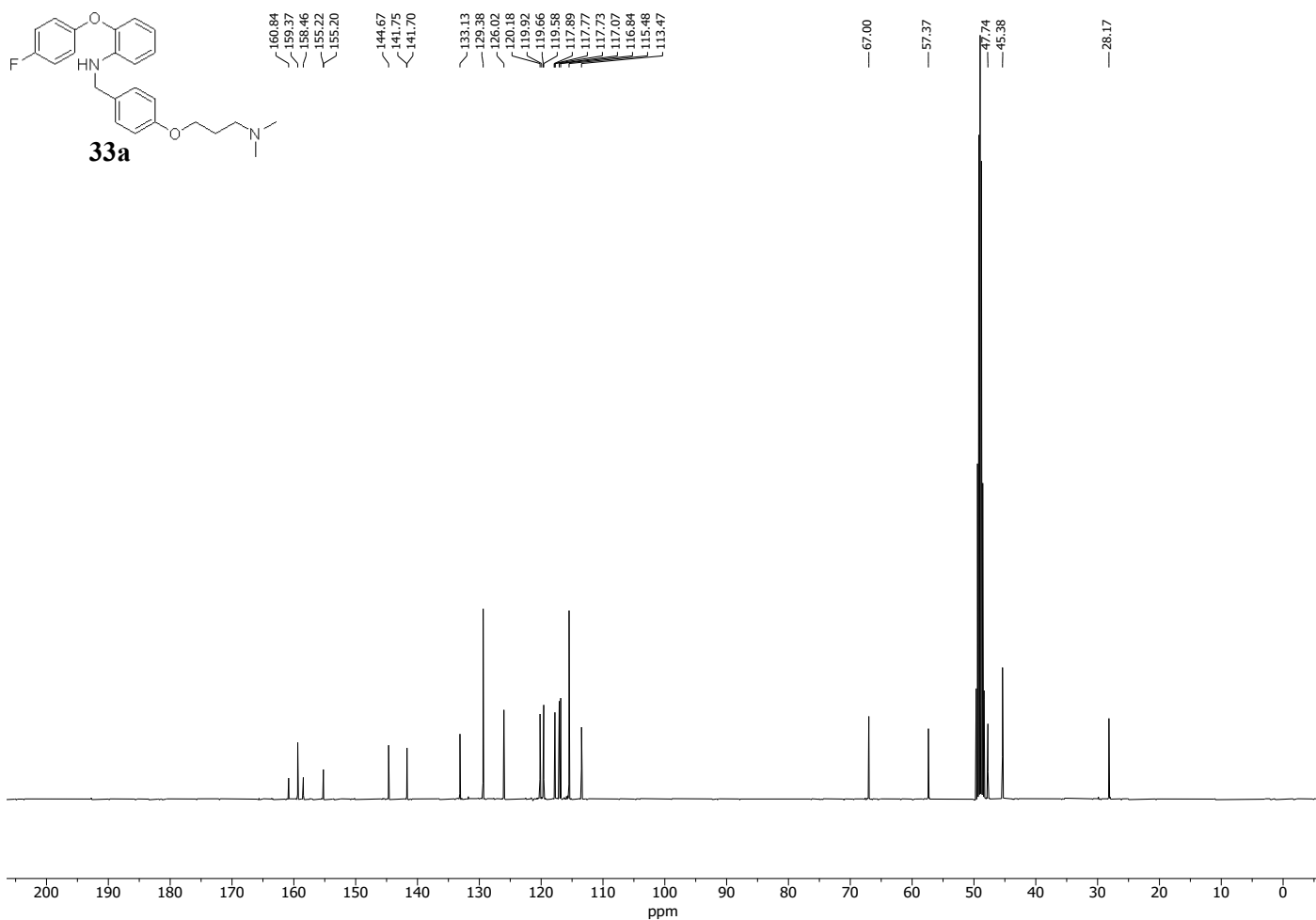
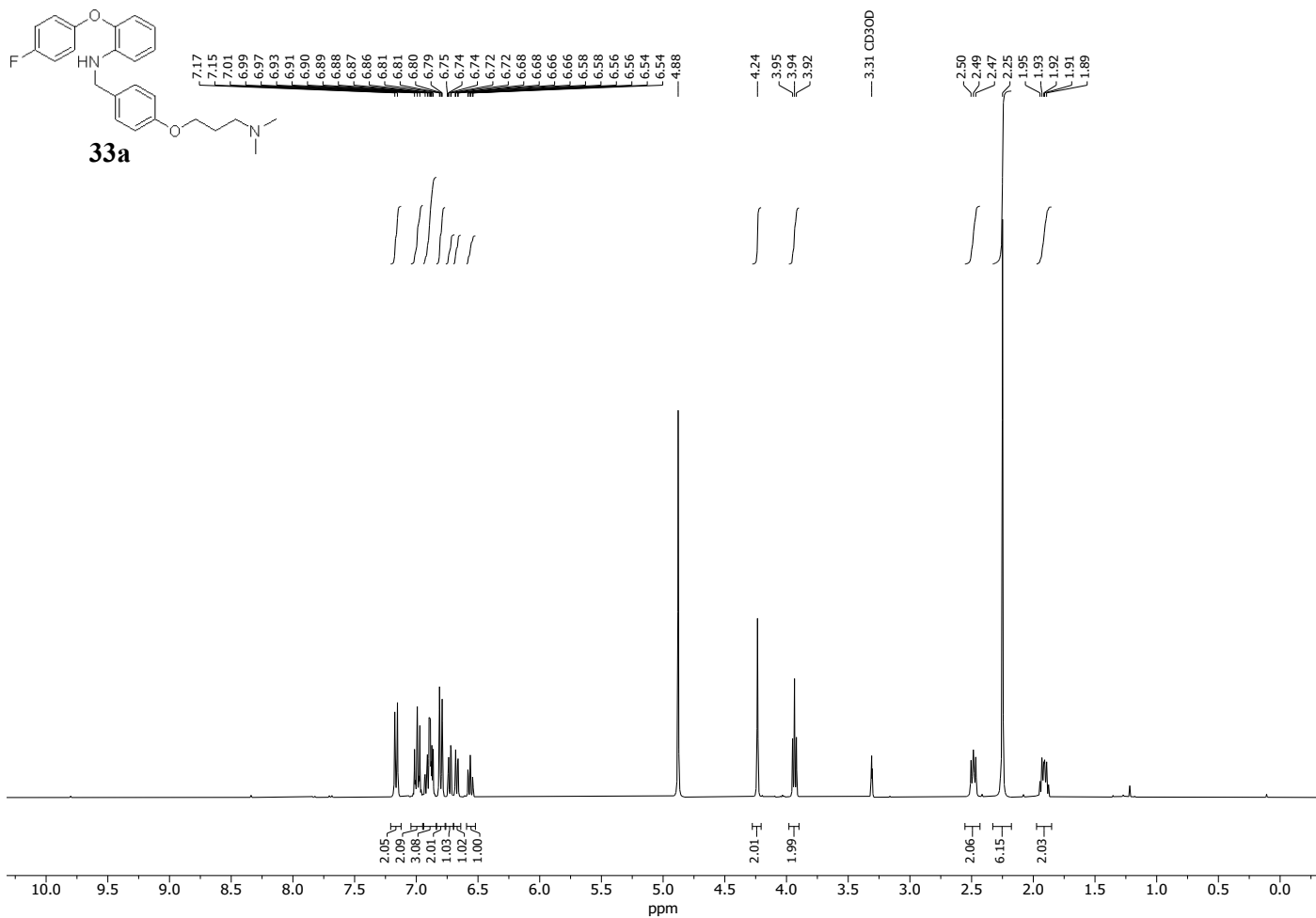
52.HCl

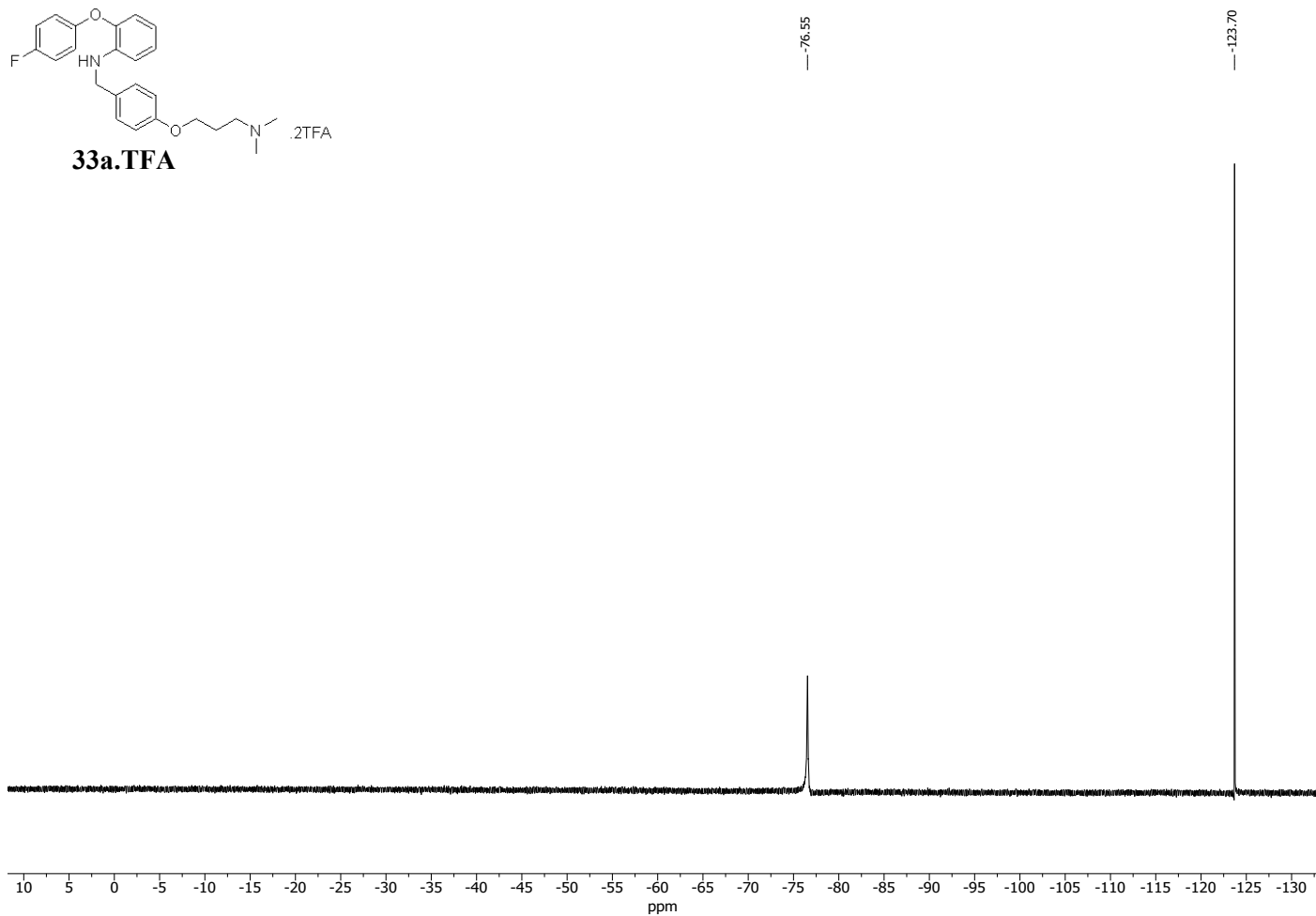
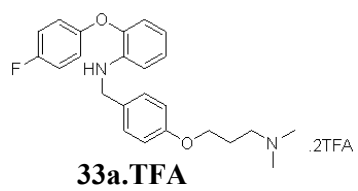


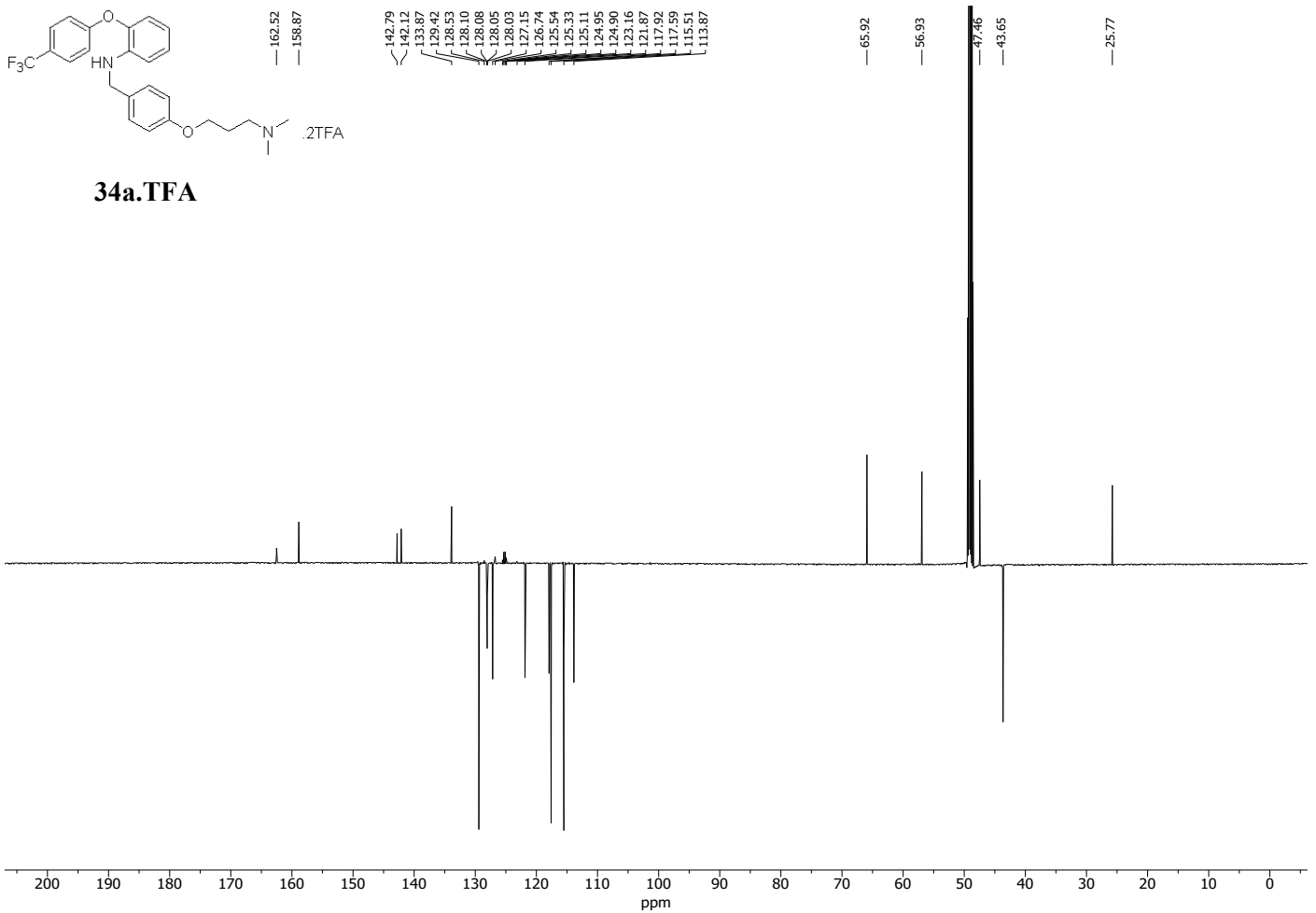
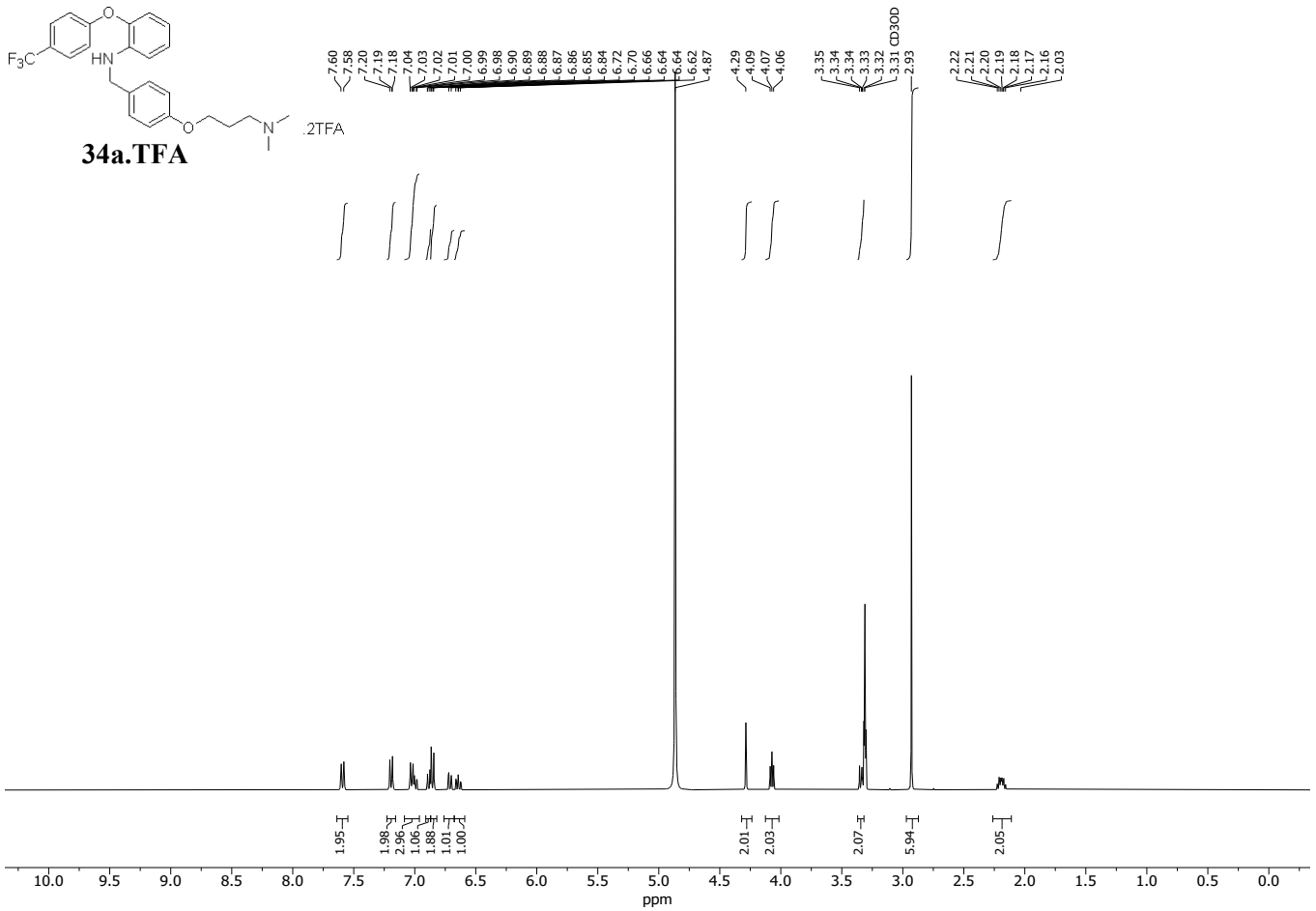
1.3. Spectra of novel phenoxyaniline compounds

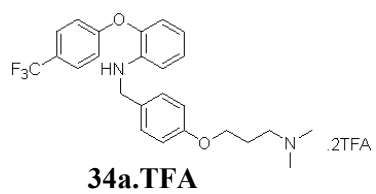






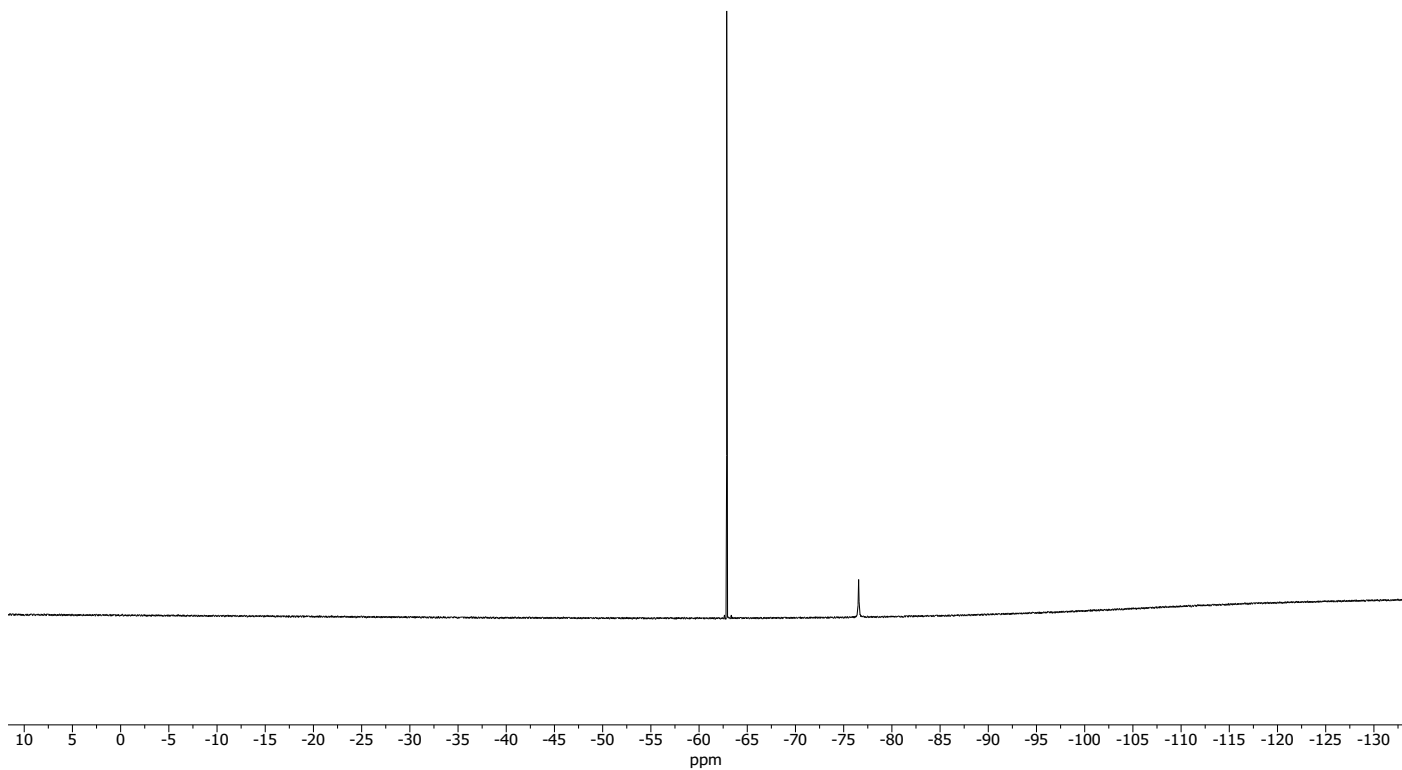


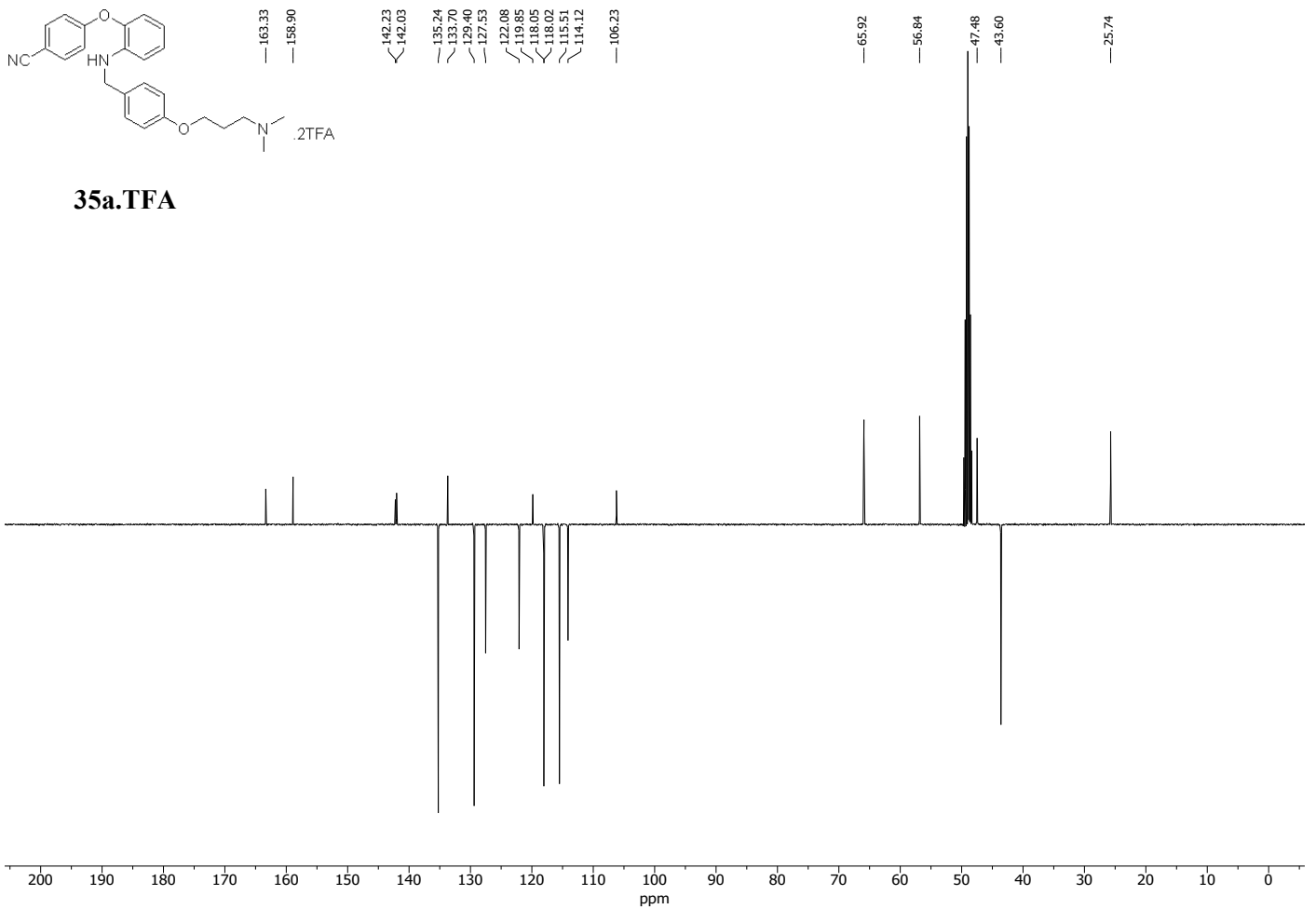
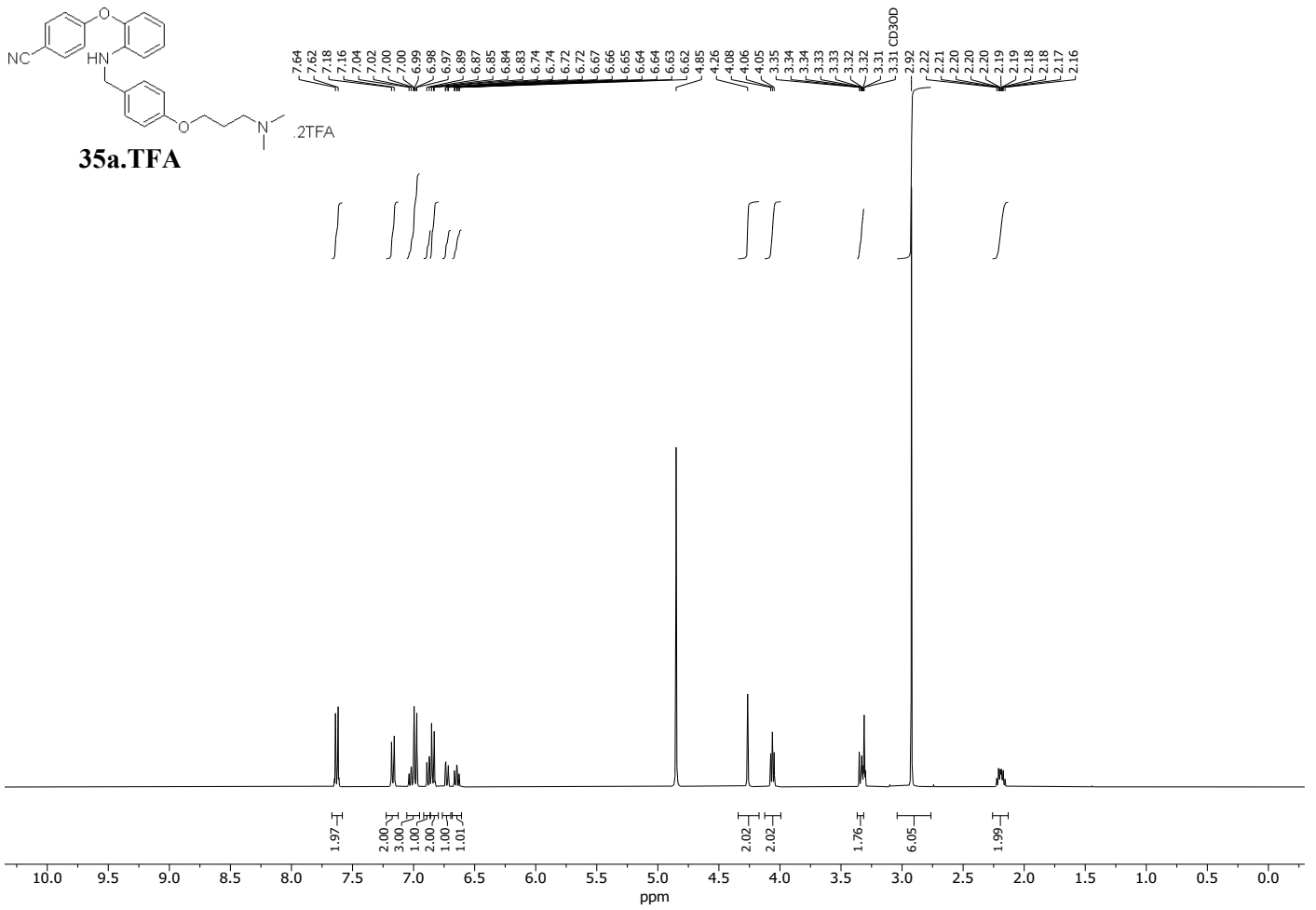


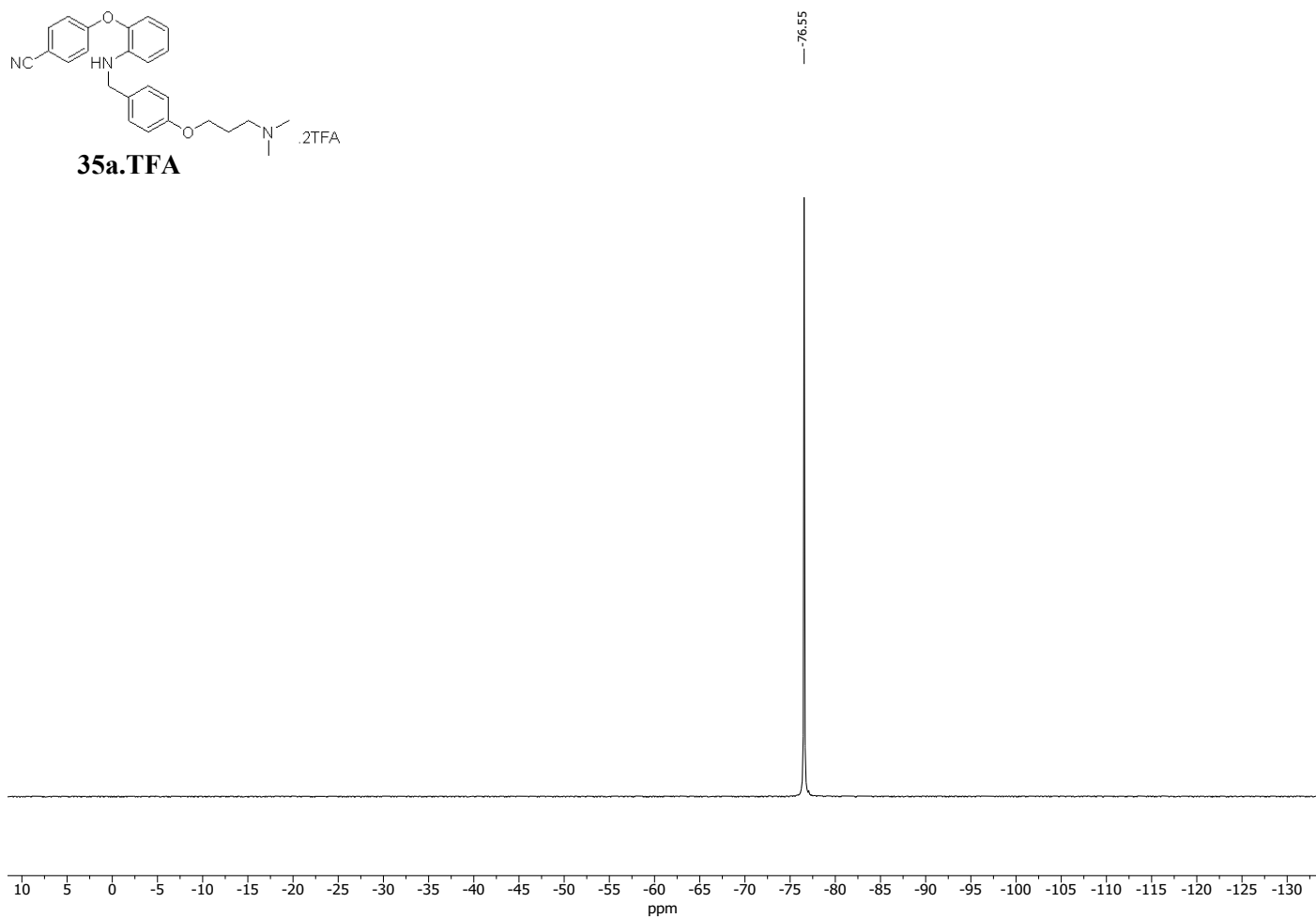
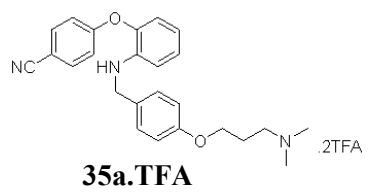


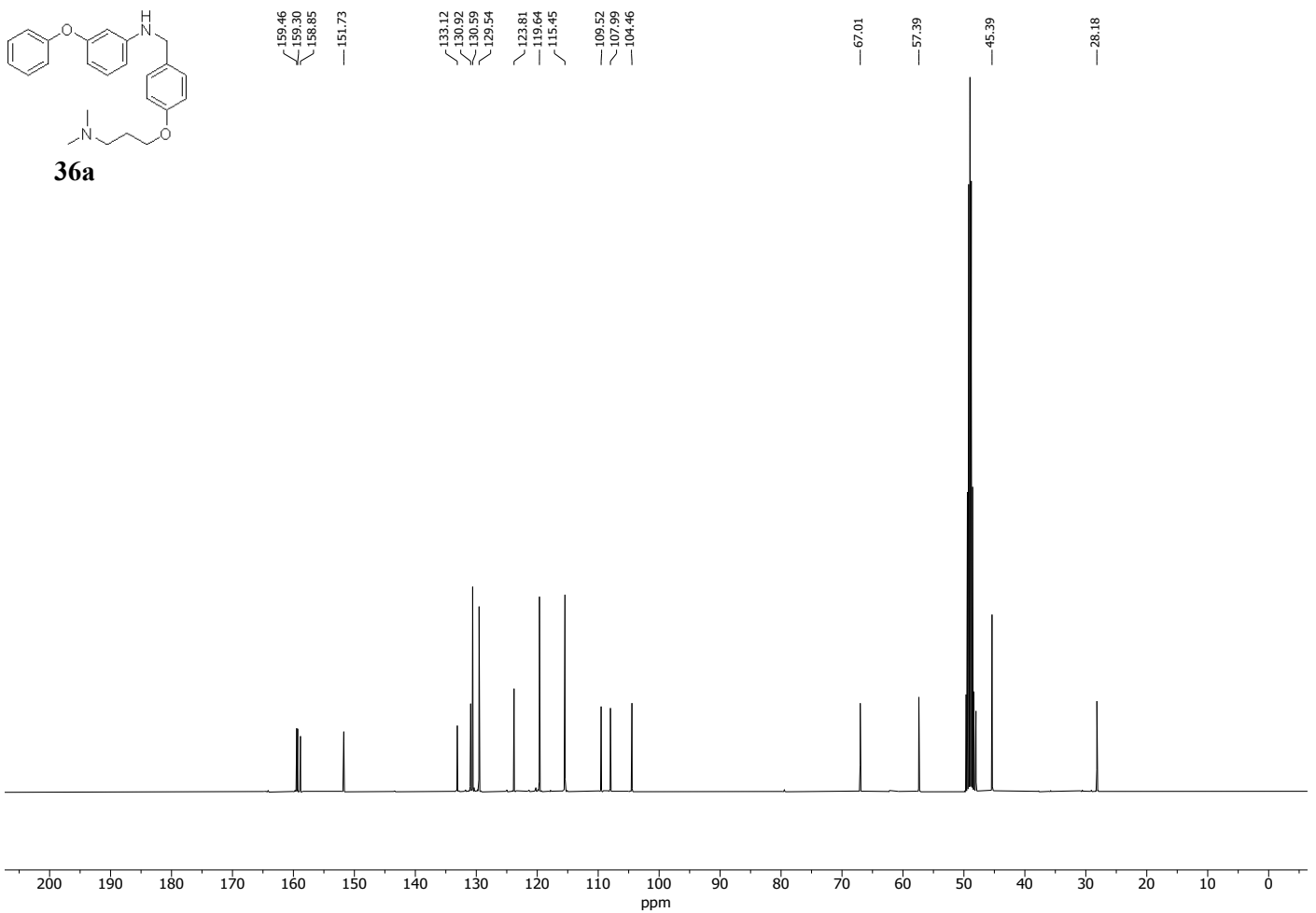
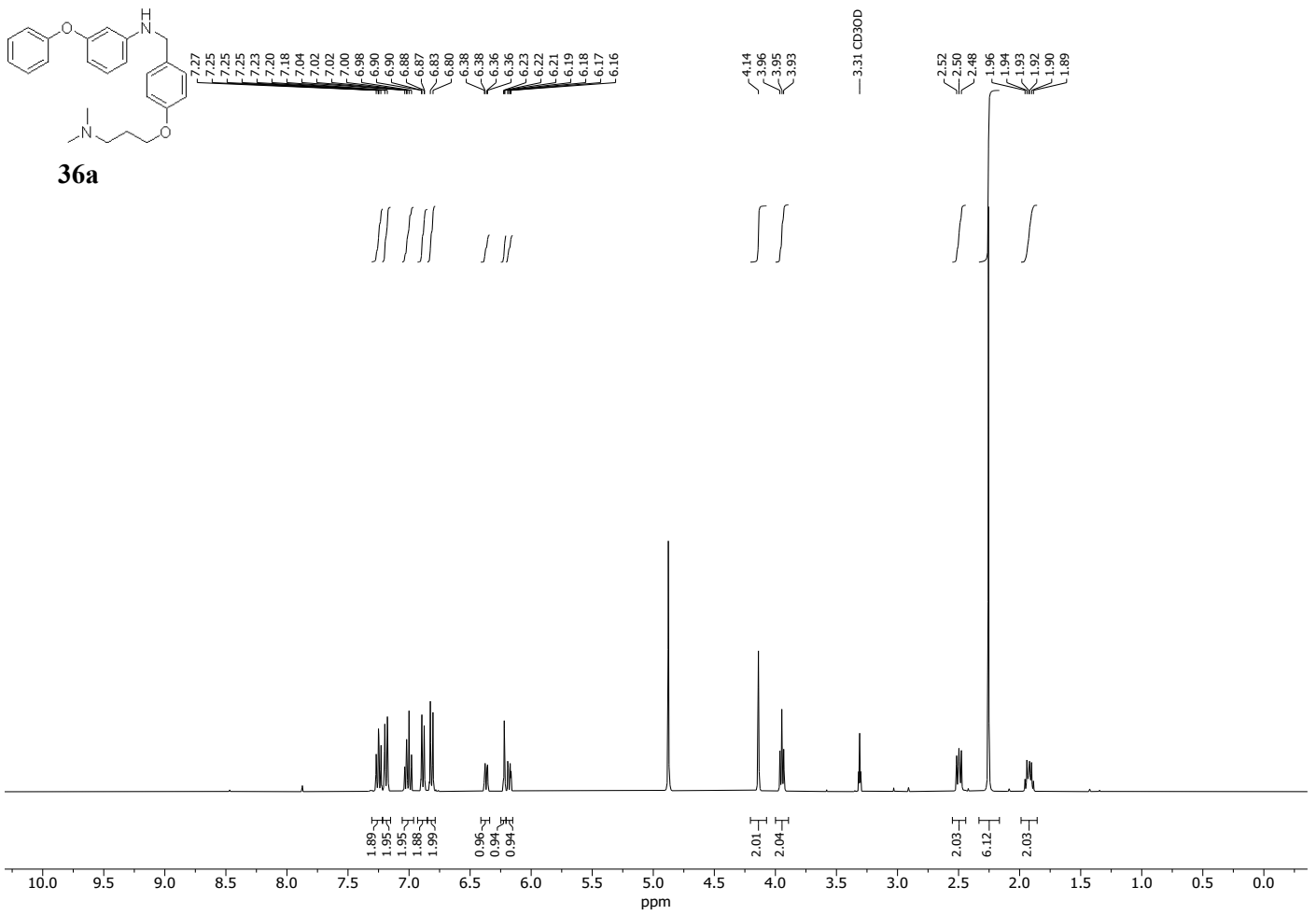
—62.87

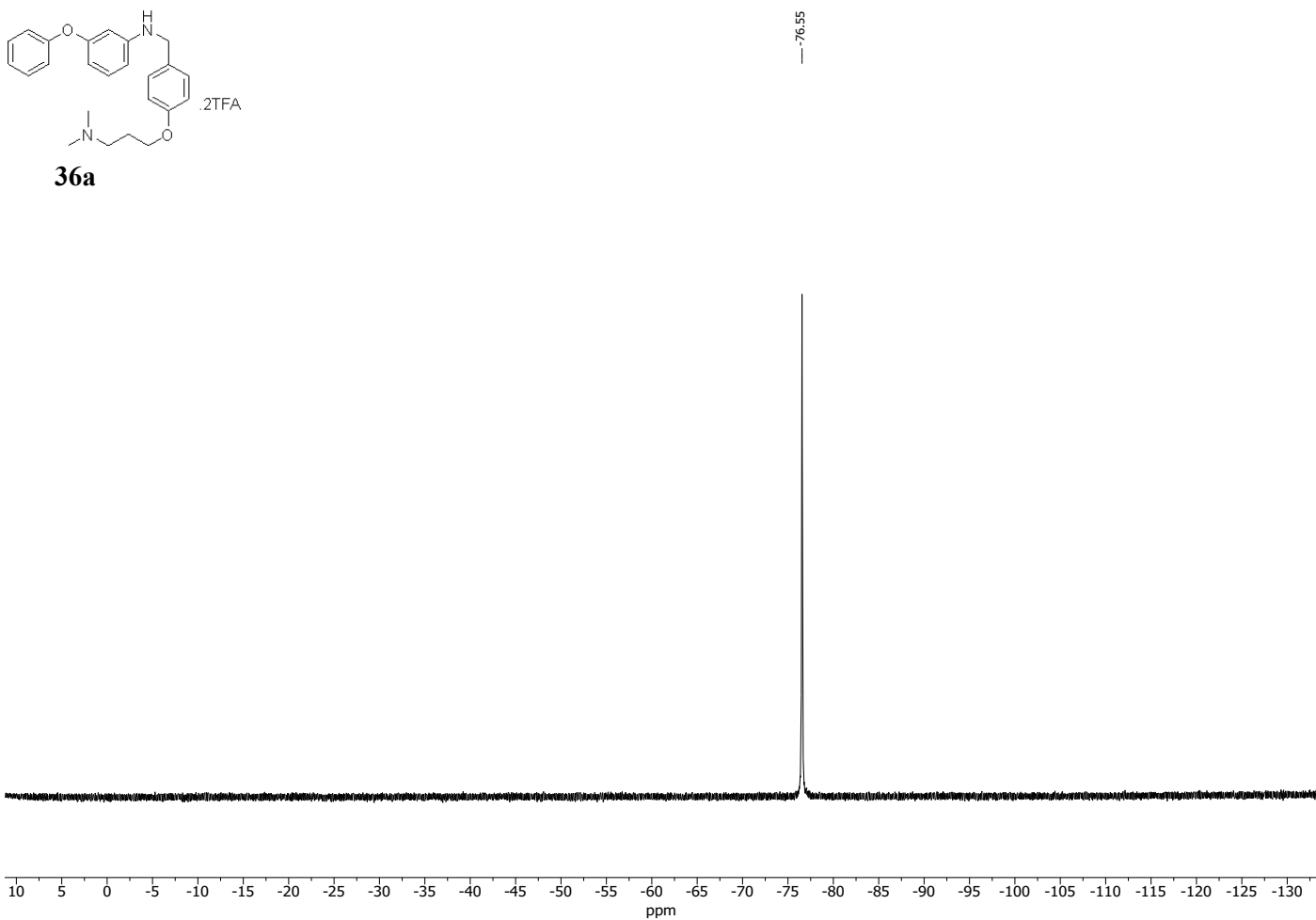
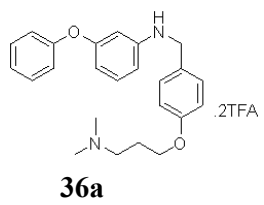
—76.55

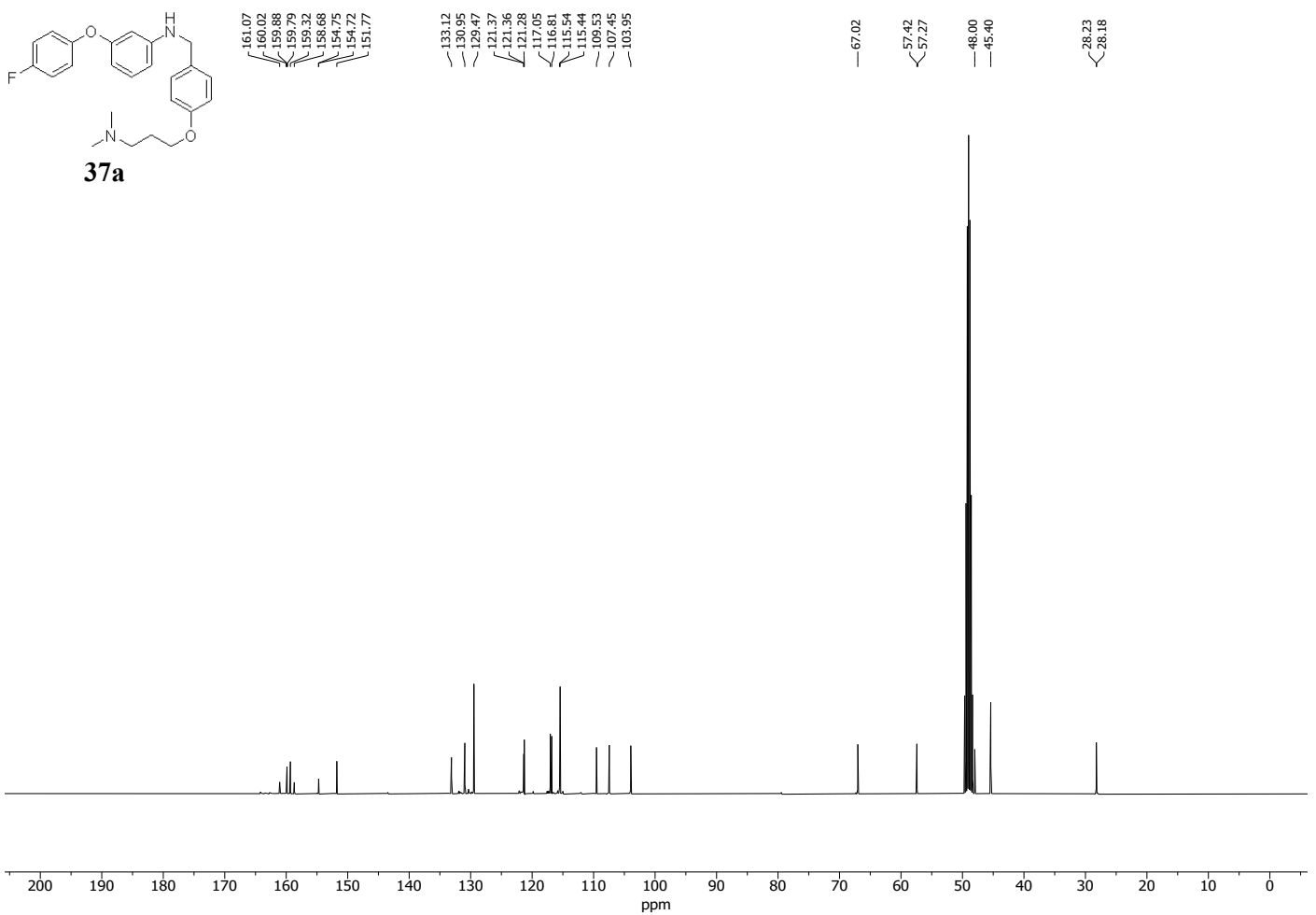
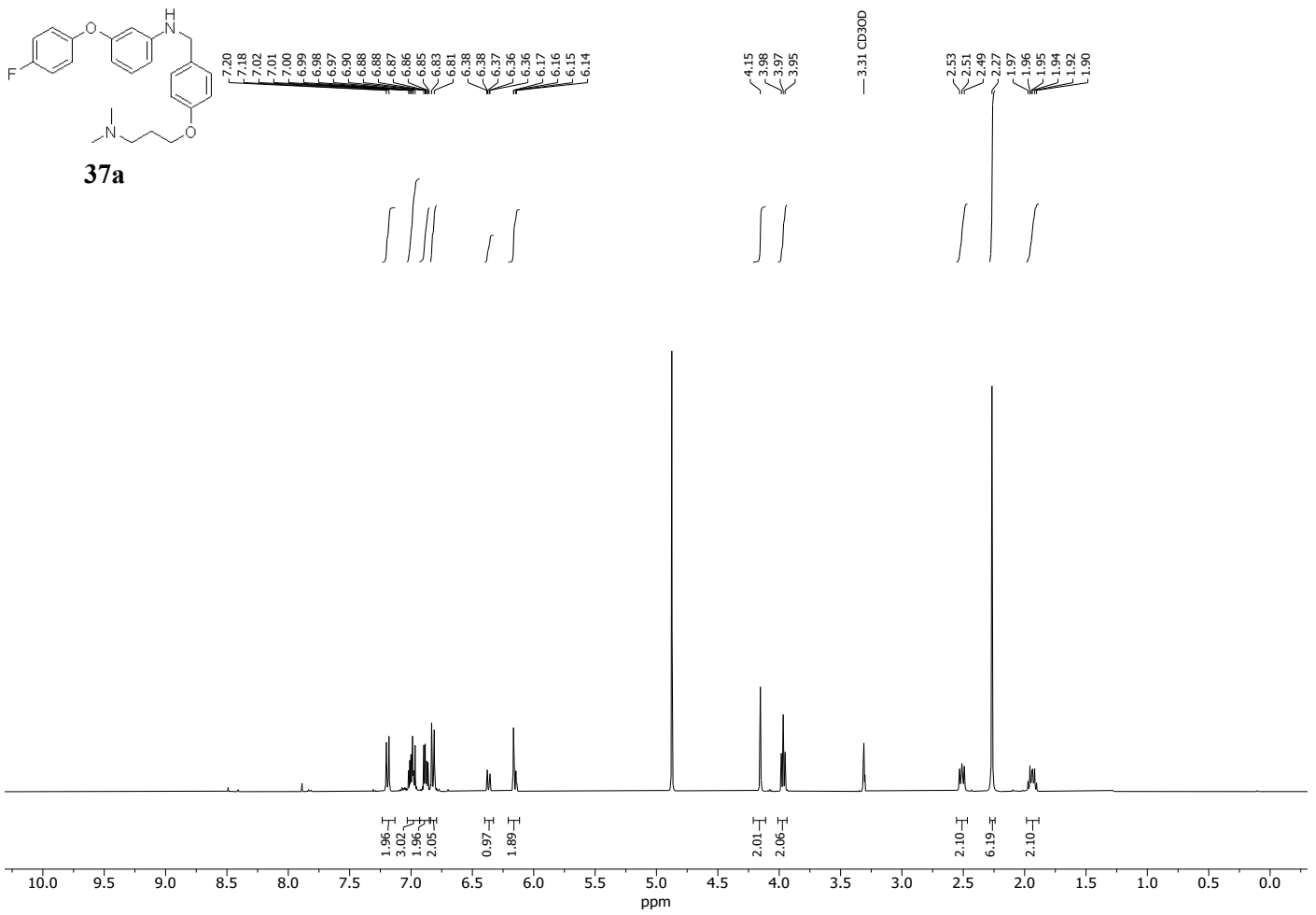


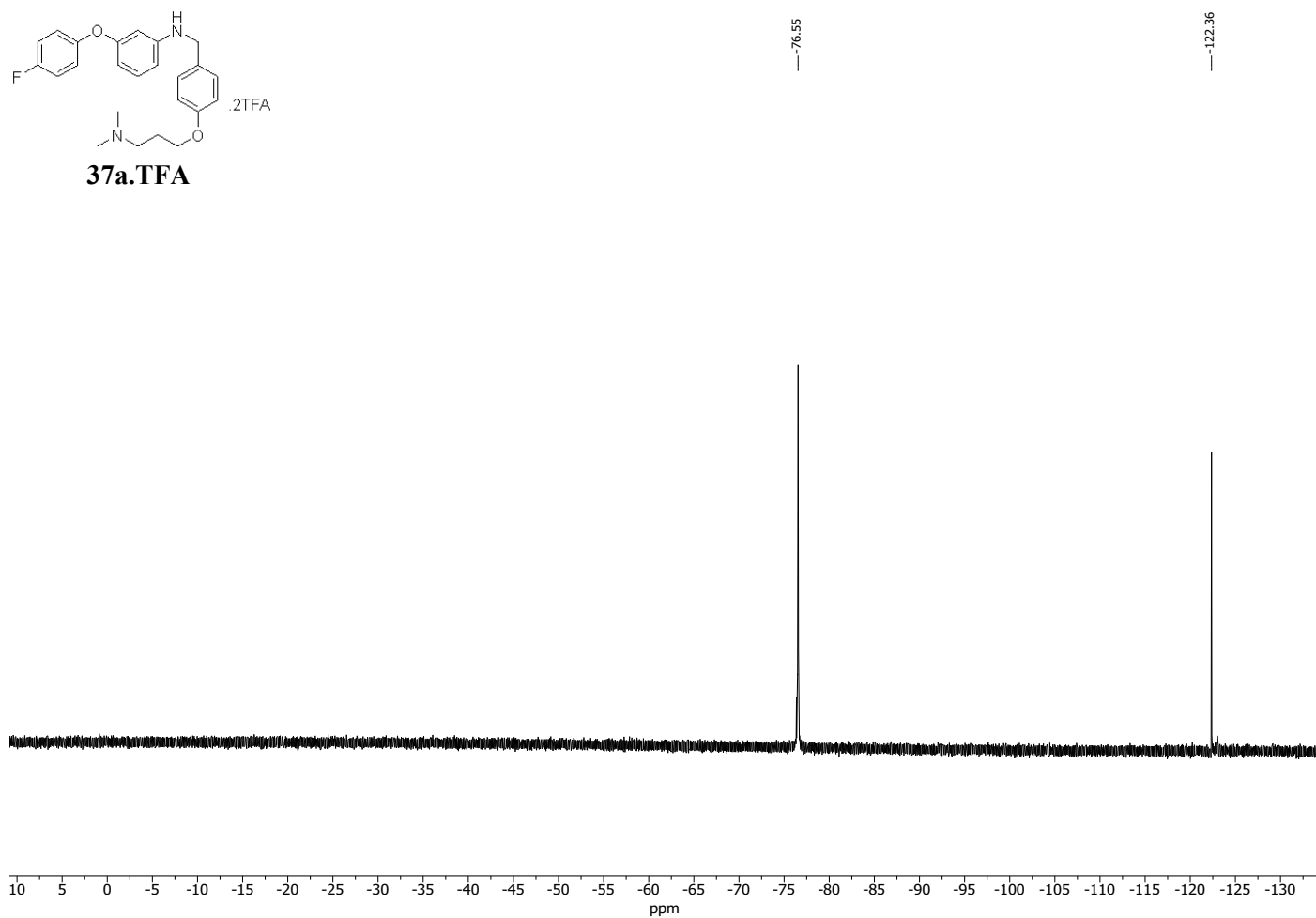
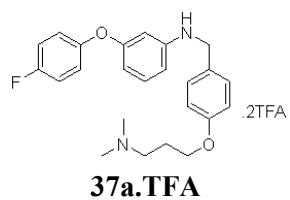


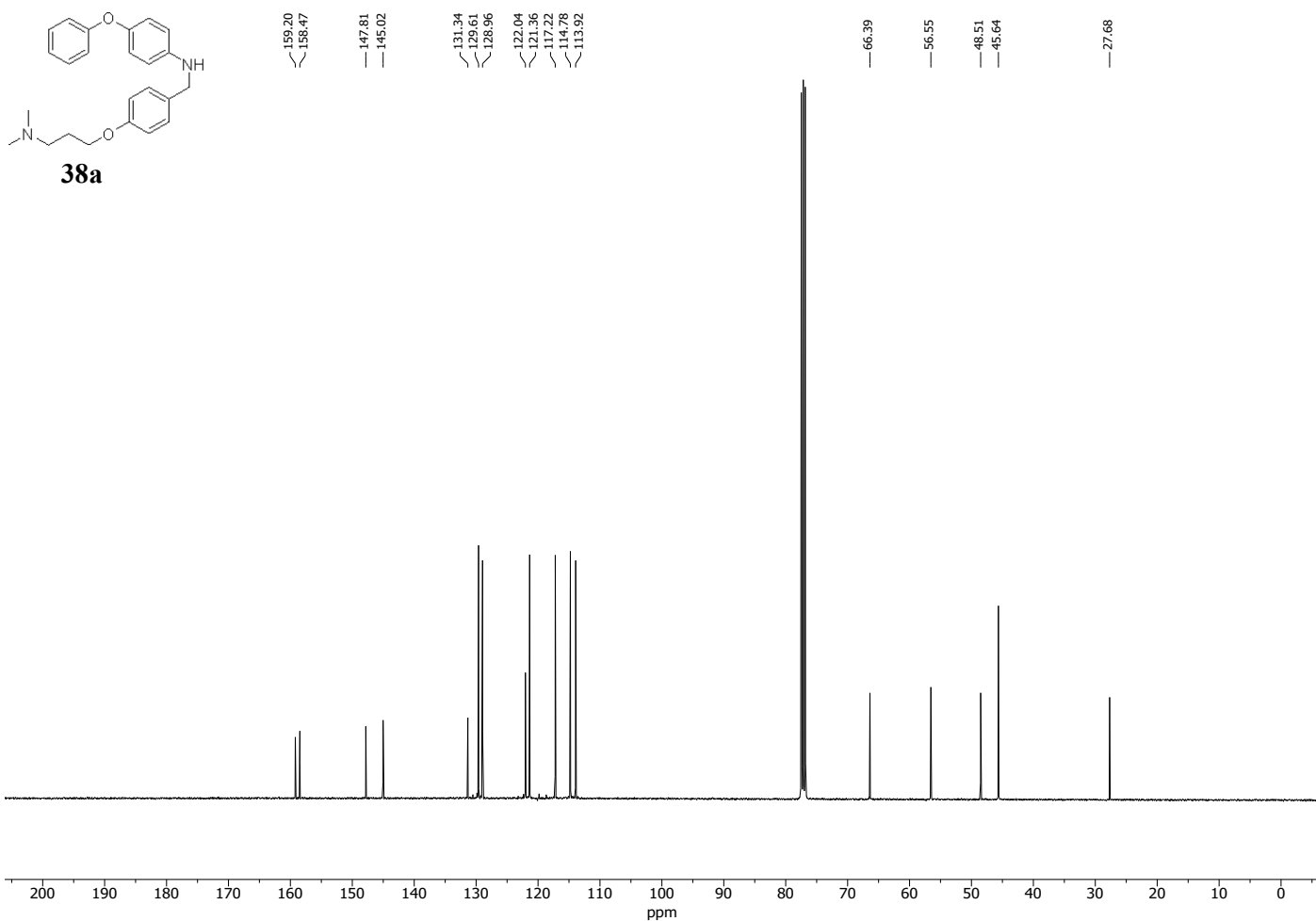
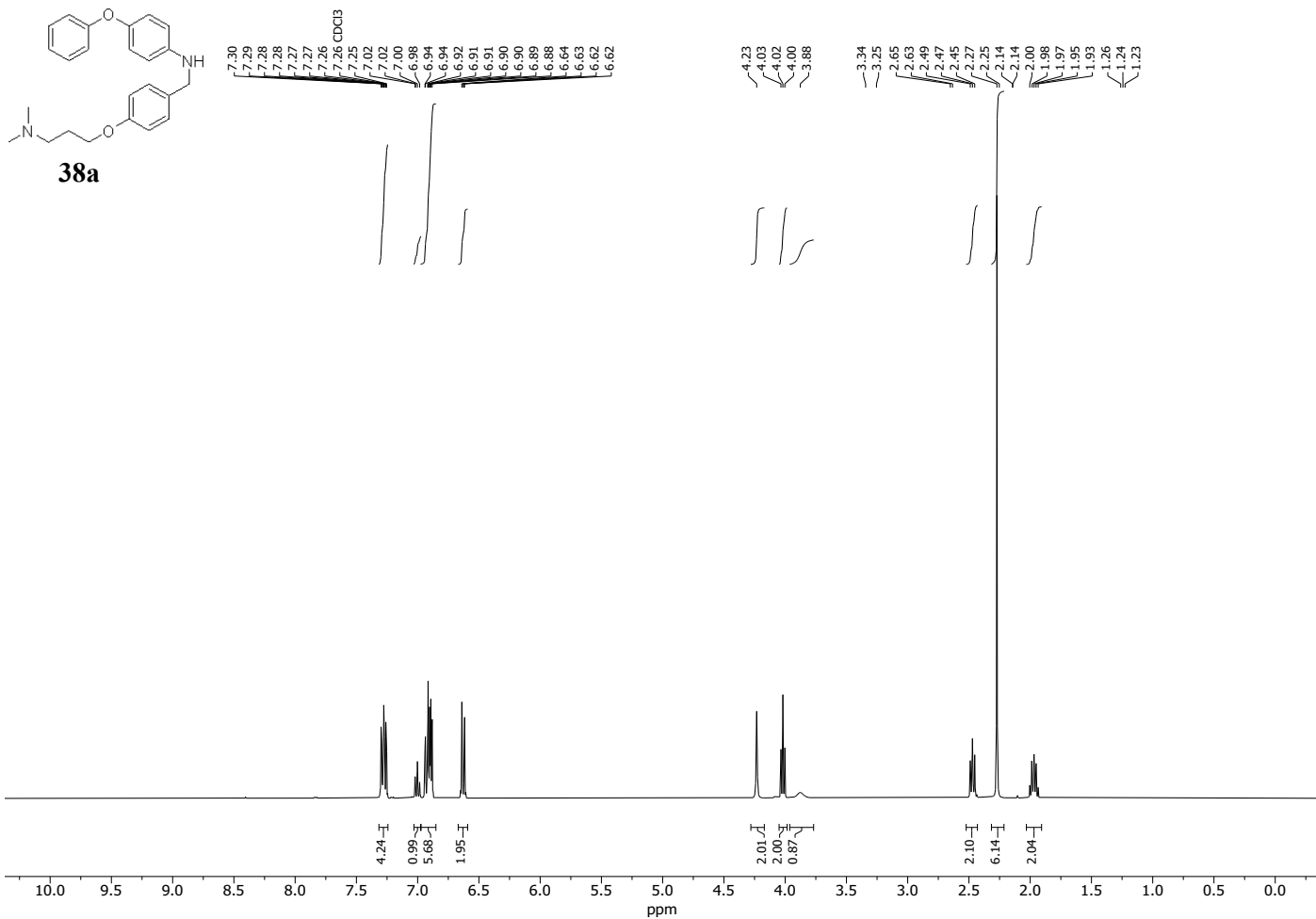


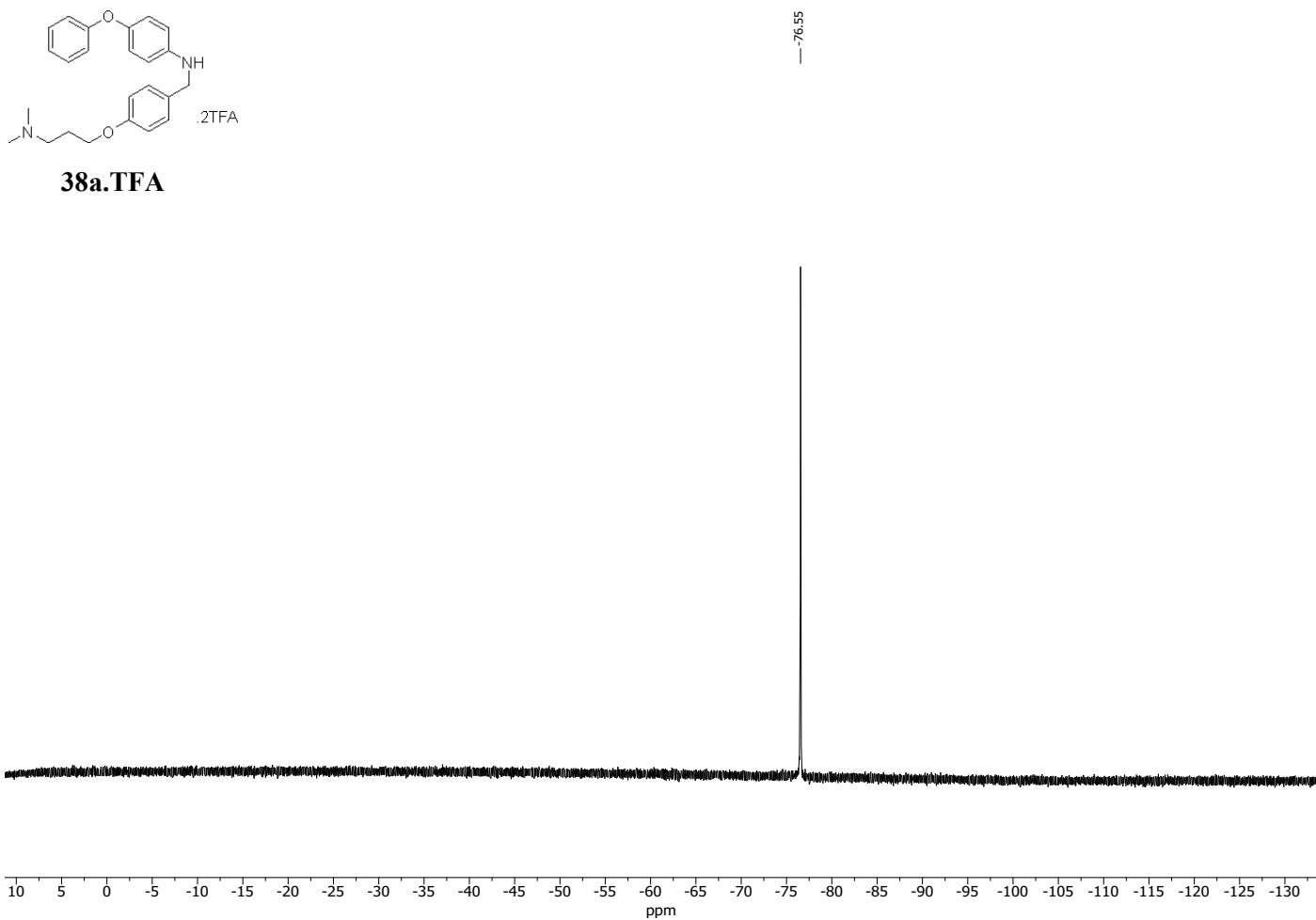
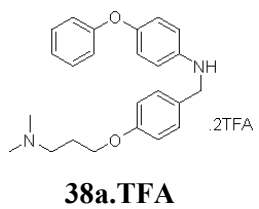


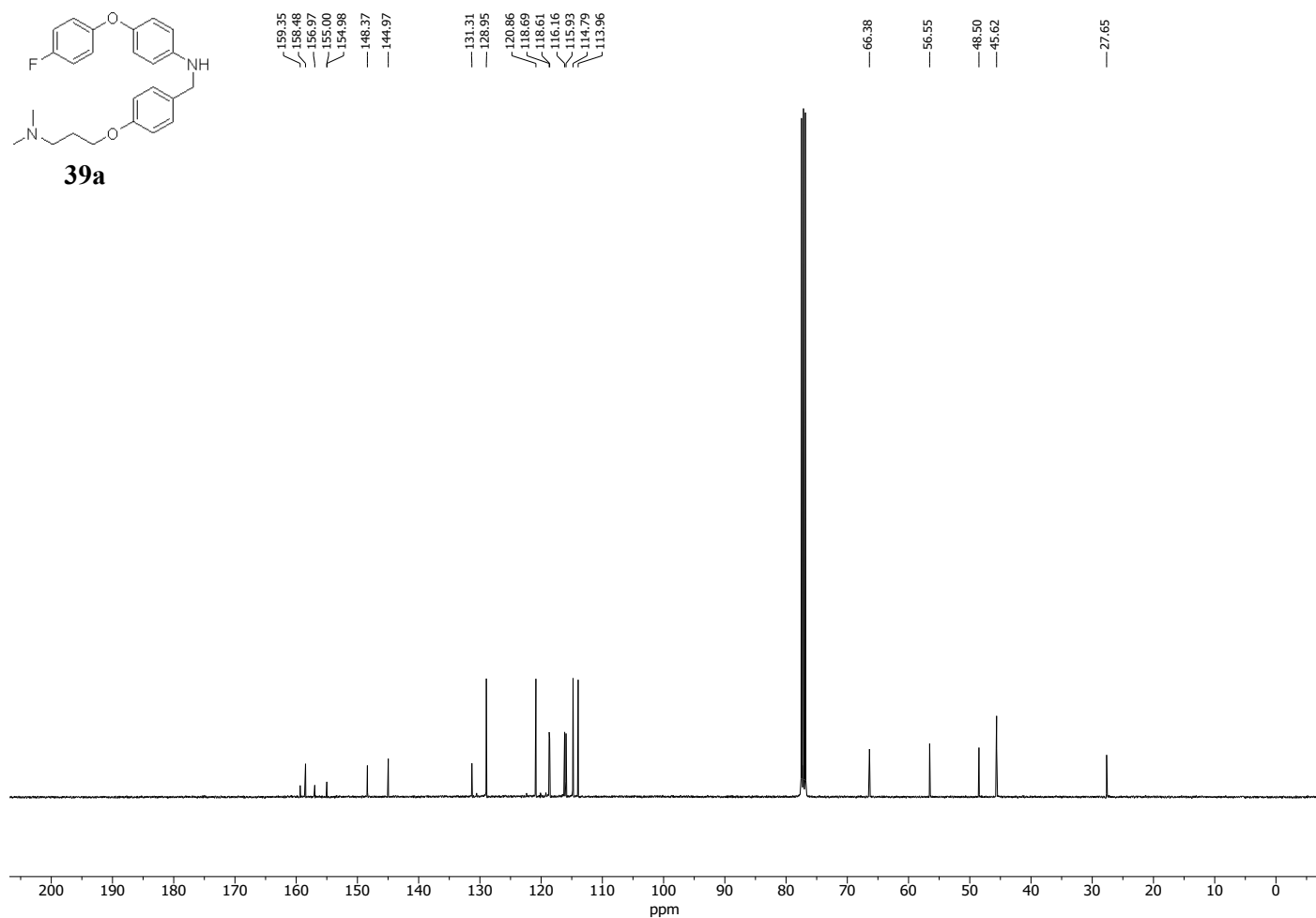
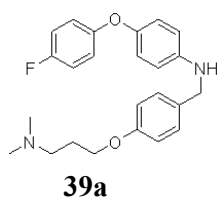
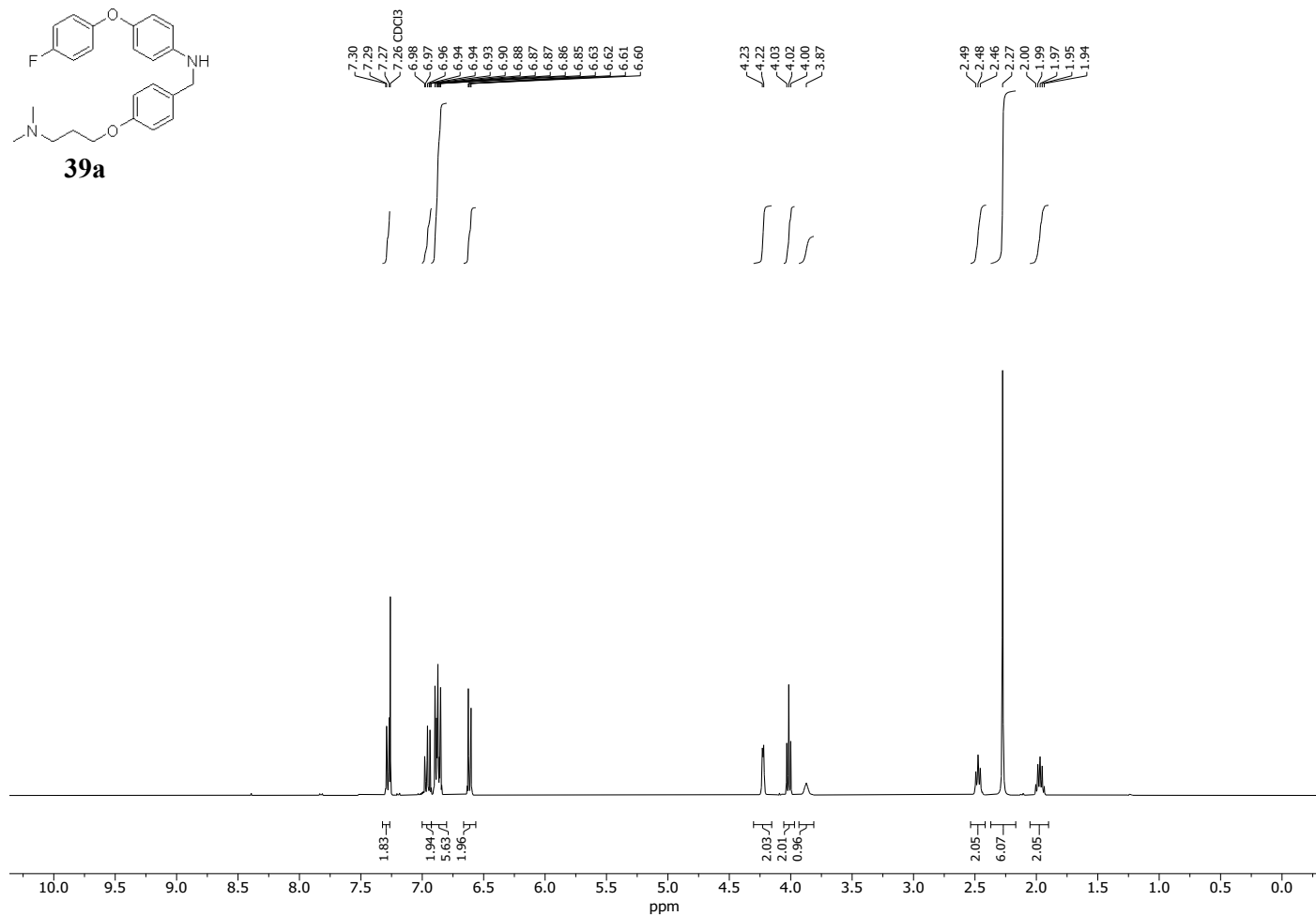
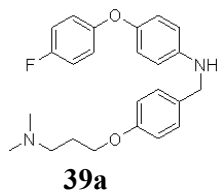


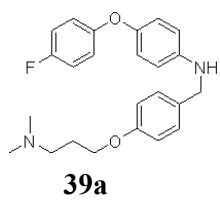




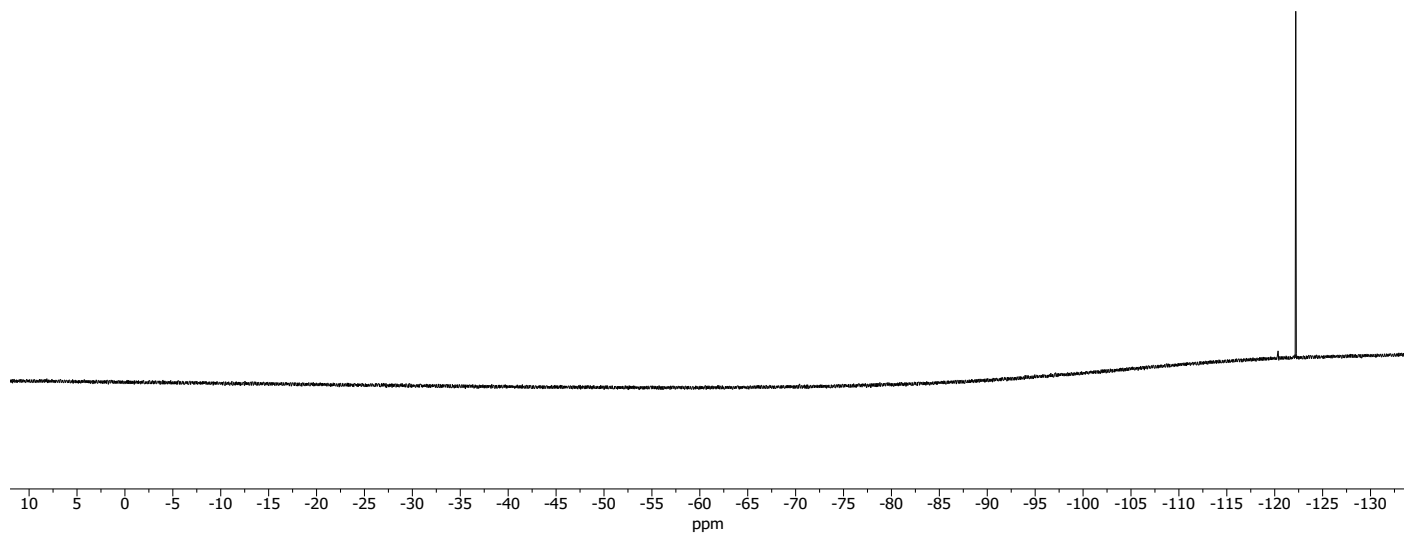


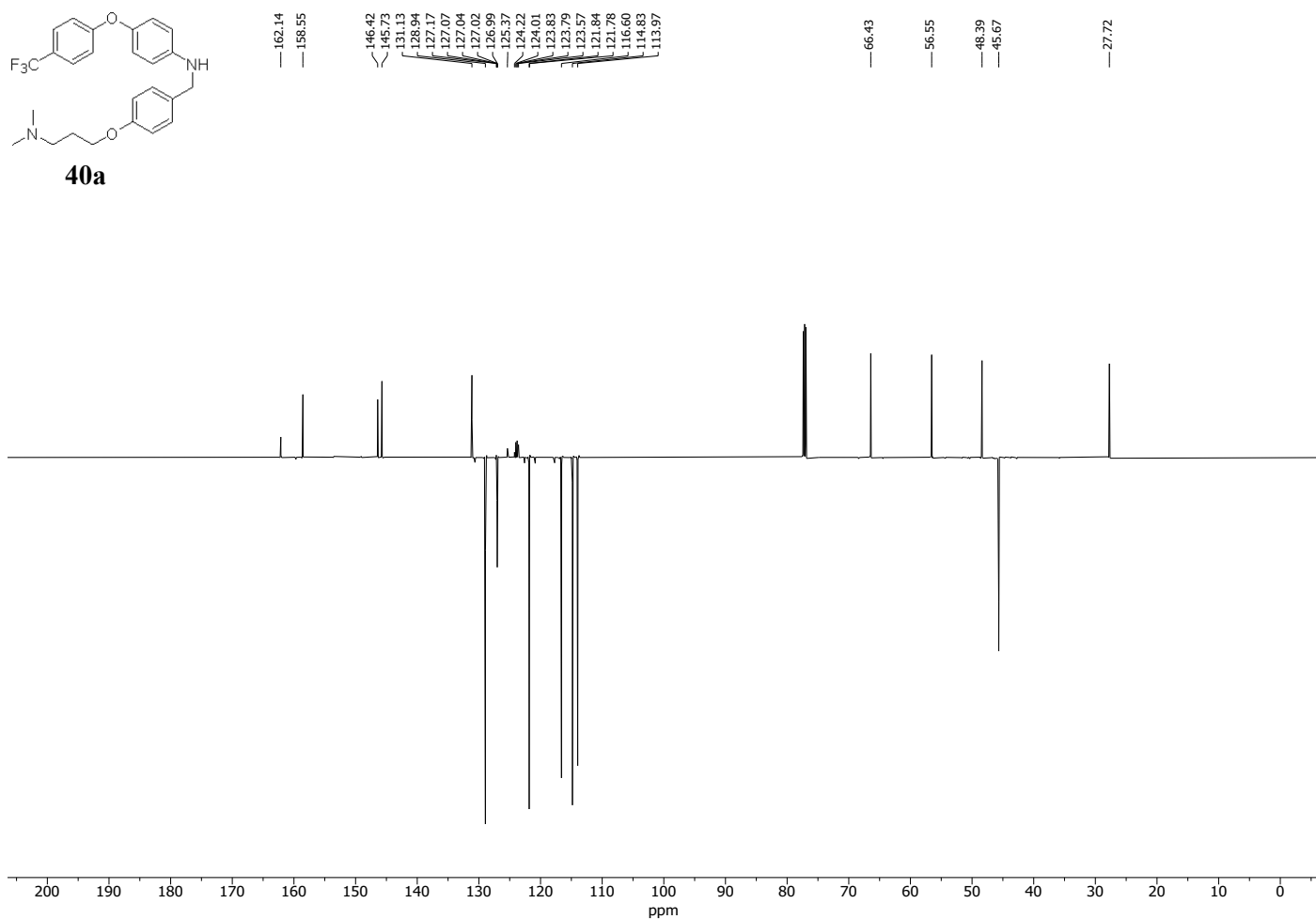
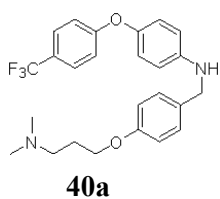
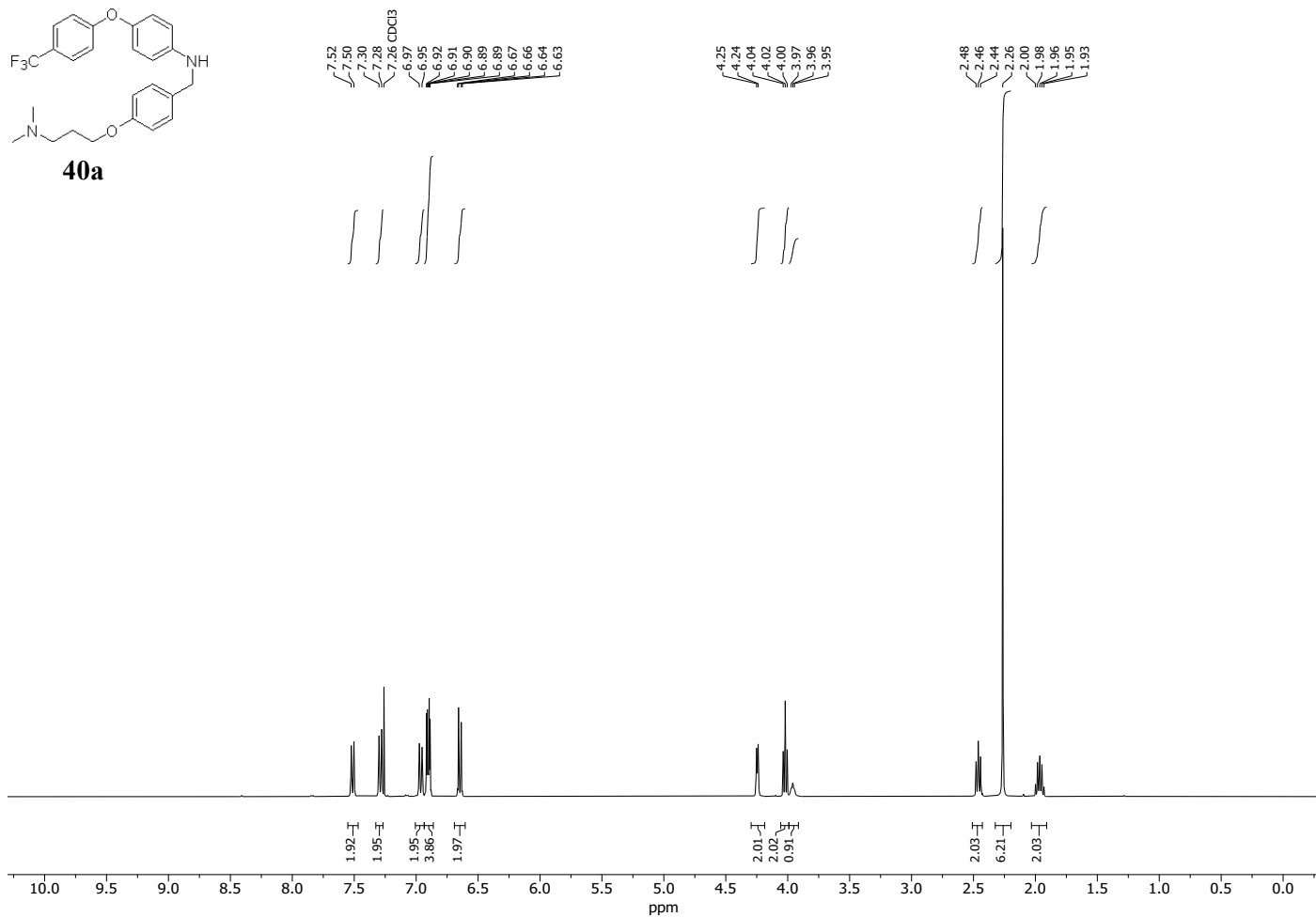
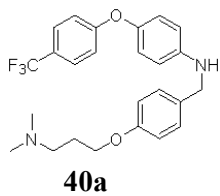


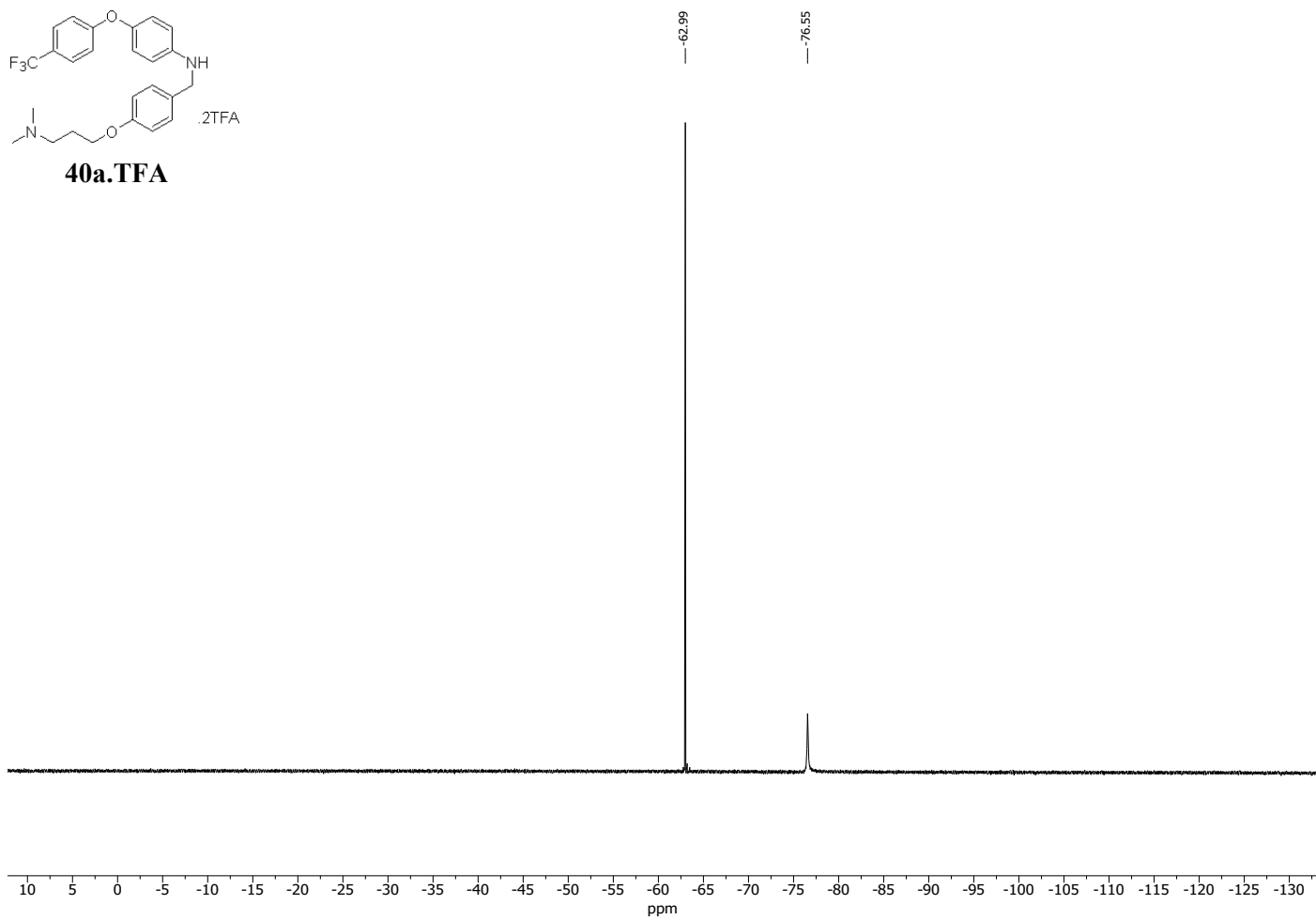
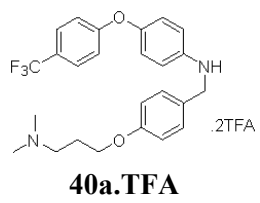


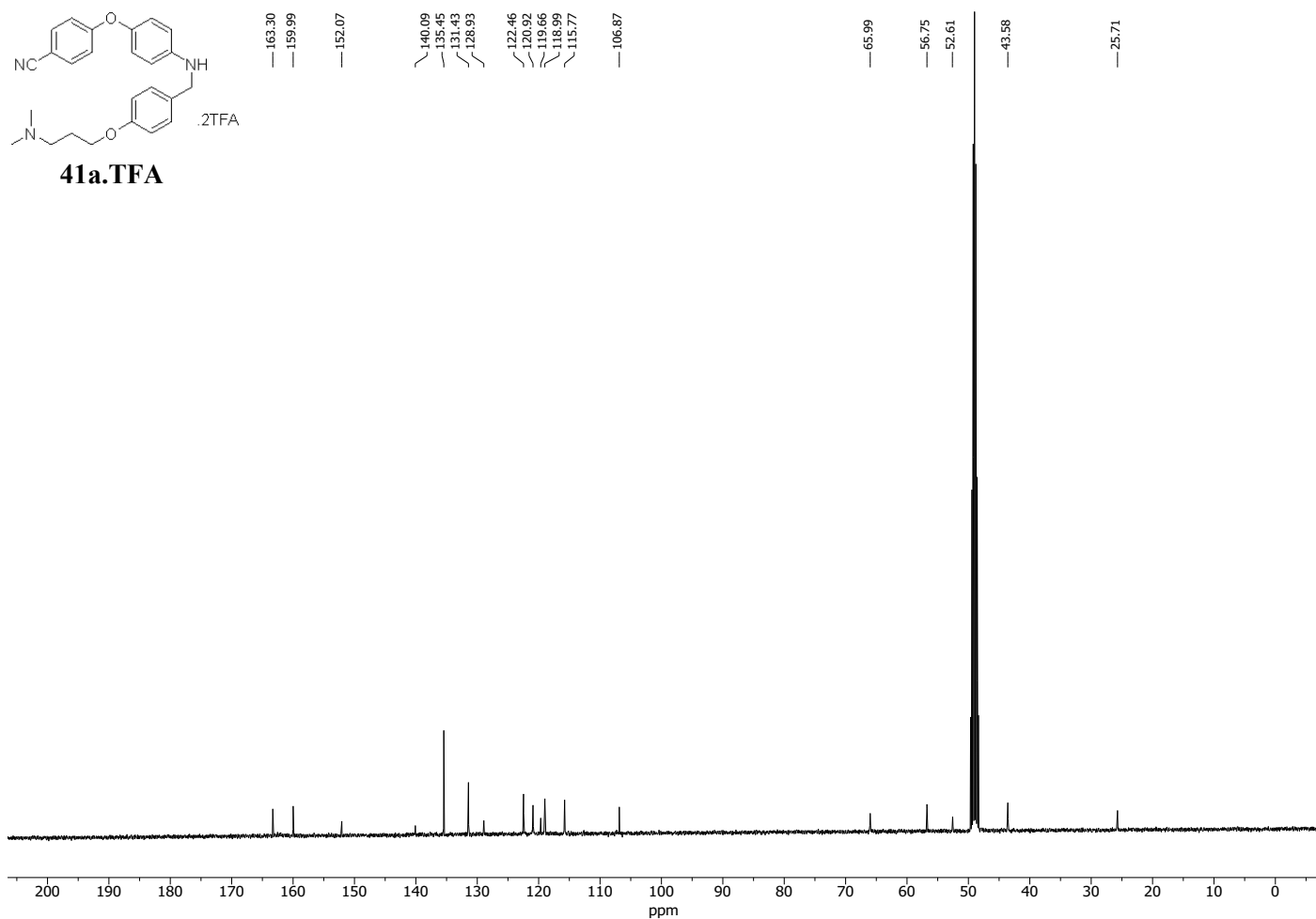
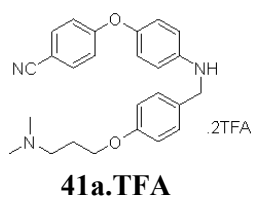
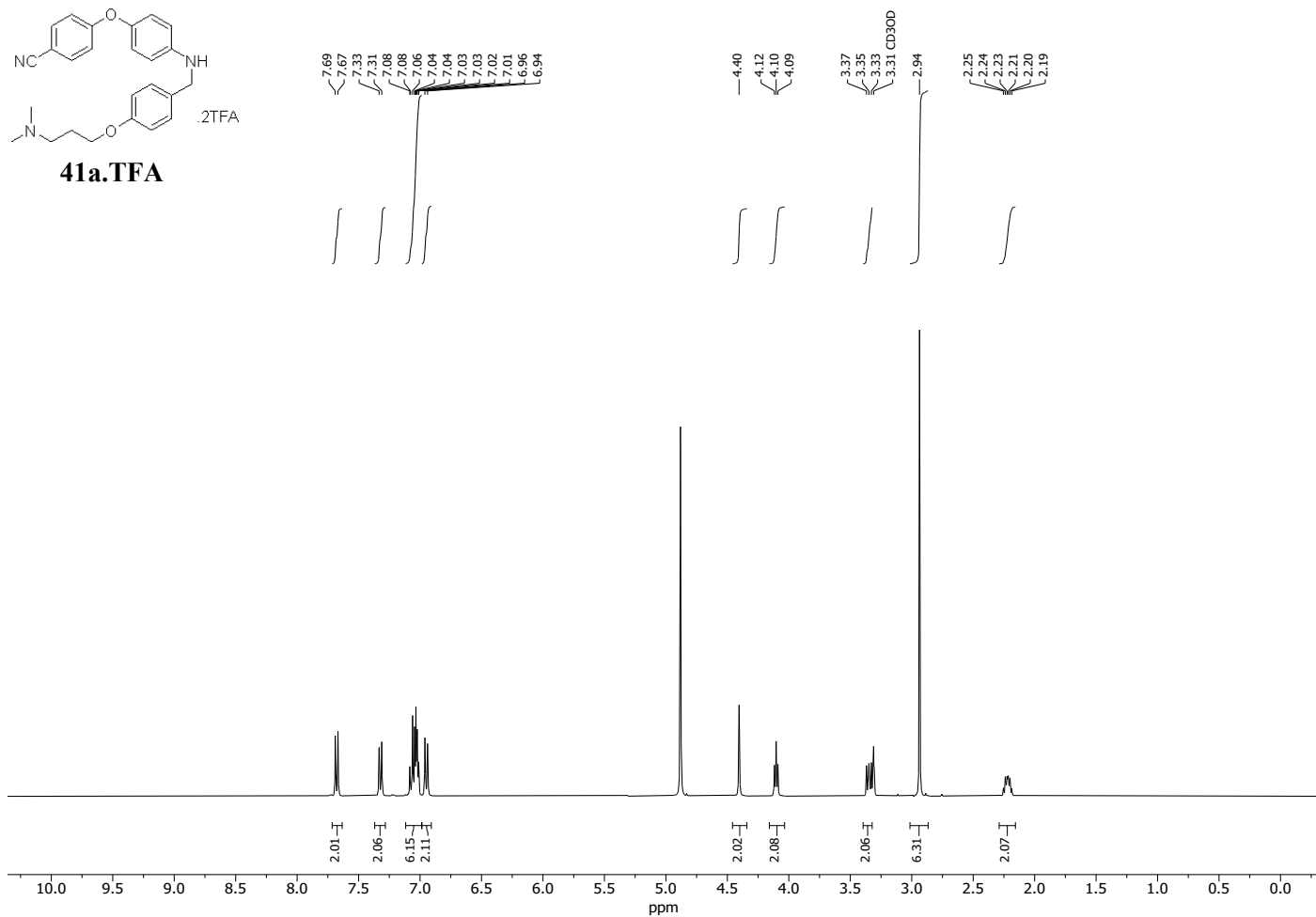
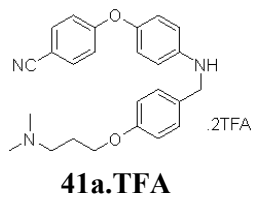


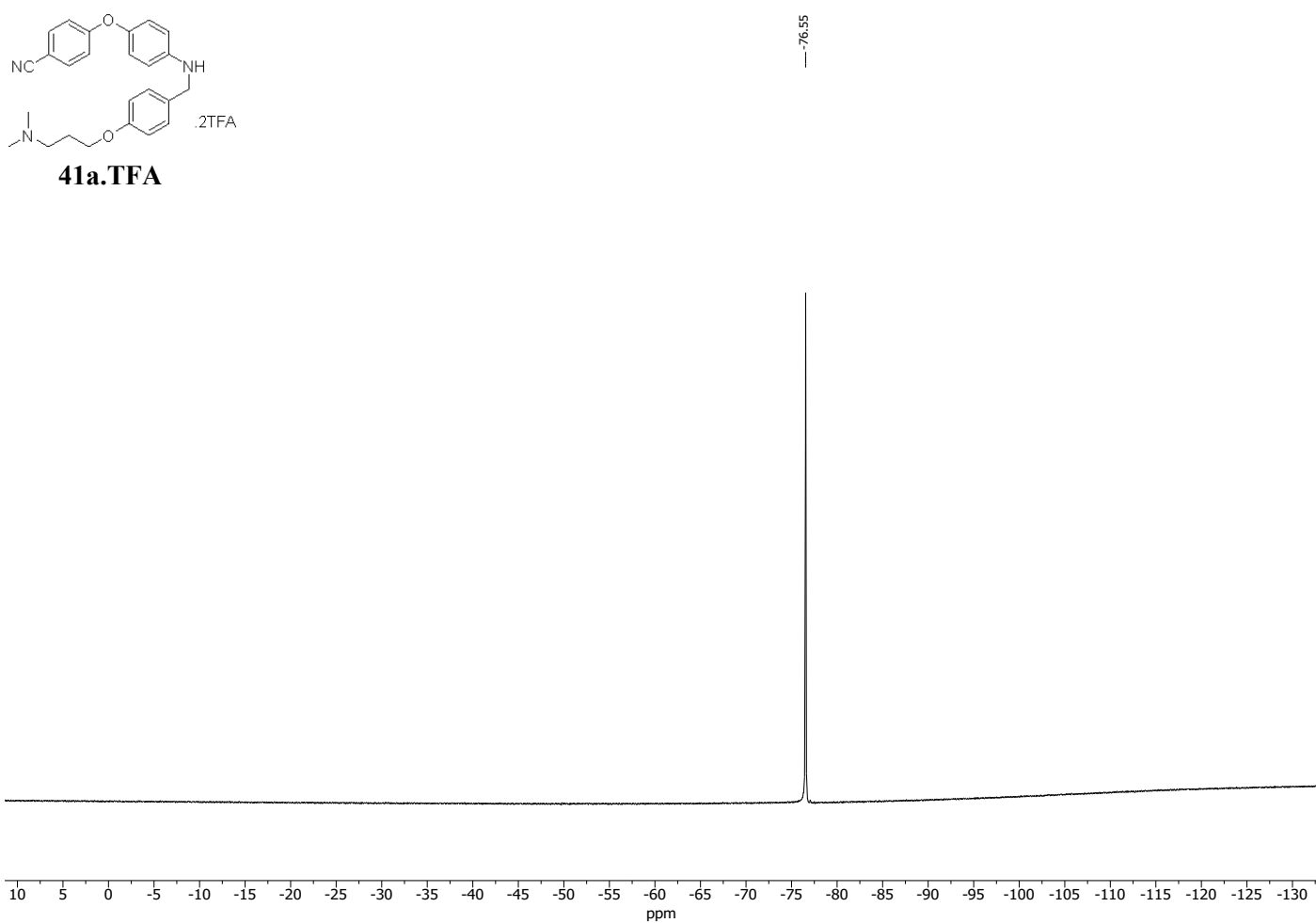
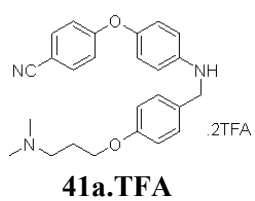
—122.20

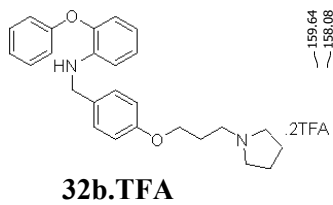












159.64
158.08

147.12

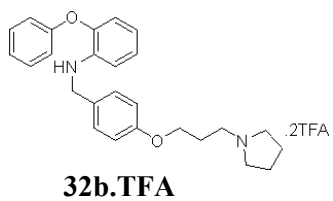
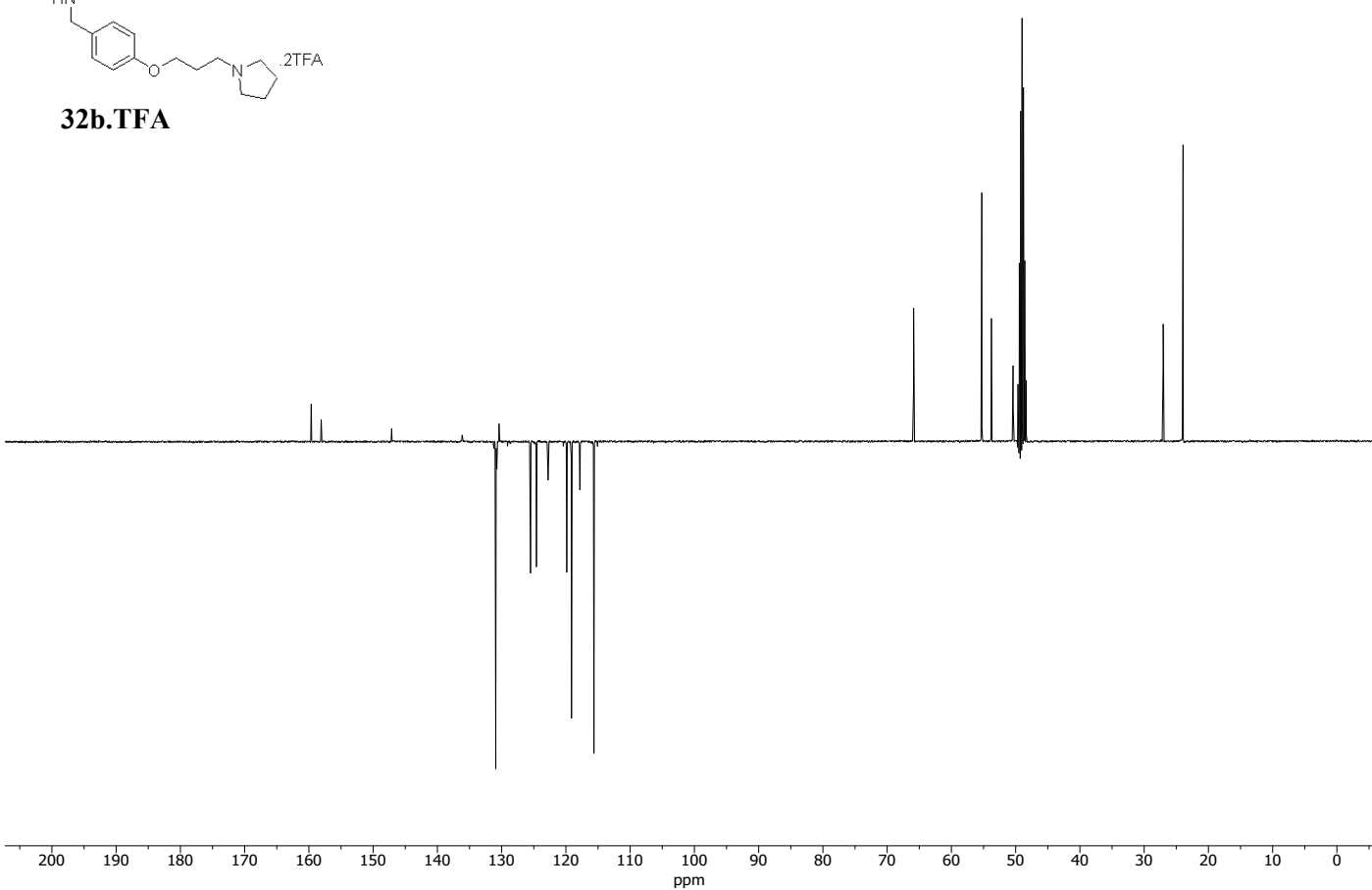
136.15
130.91
130.78
130.41
125.50
124.89
122.77
119.87
119.83
117.83
115.64

65.88

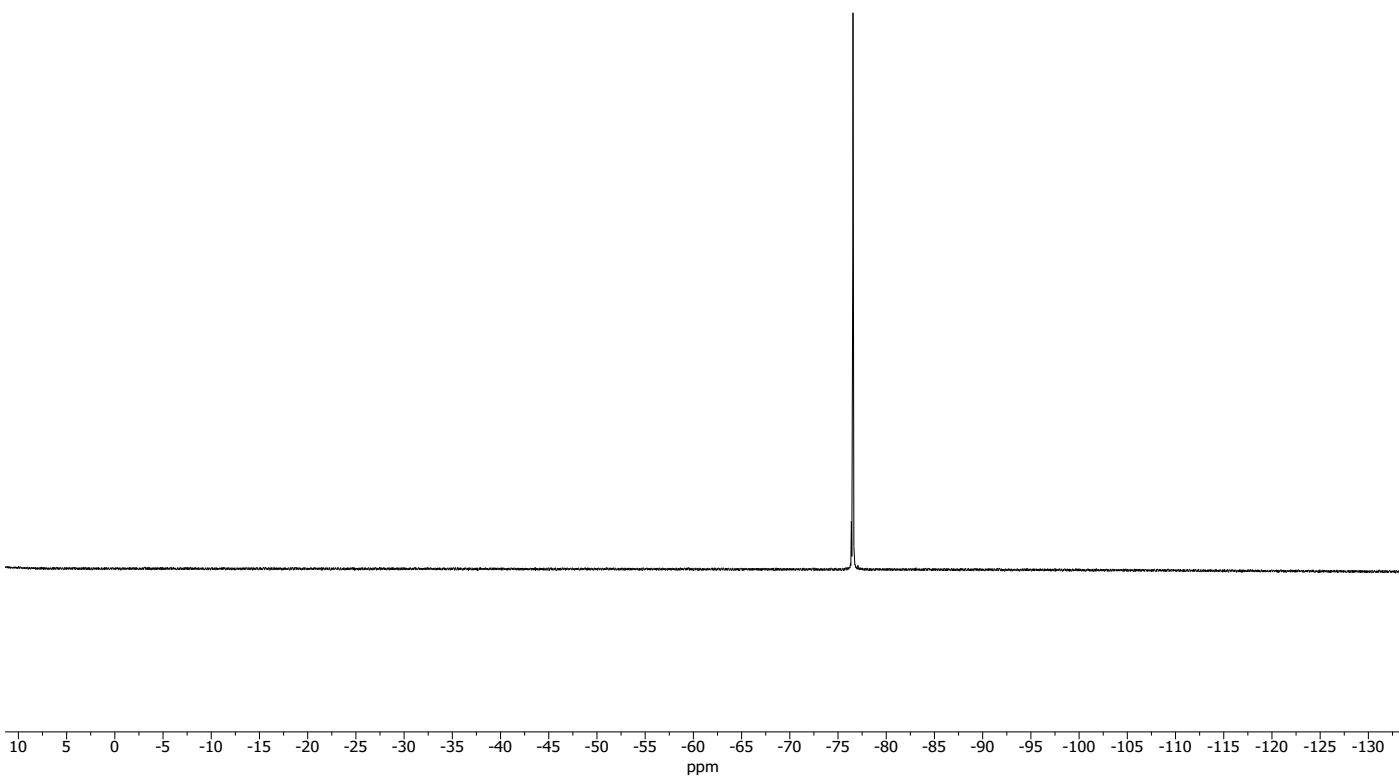
55.27
53.77

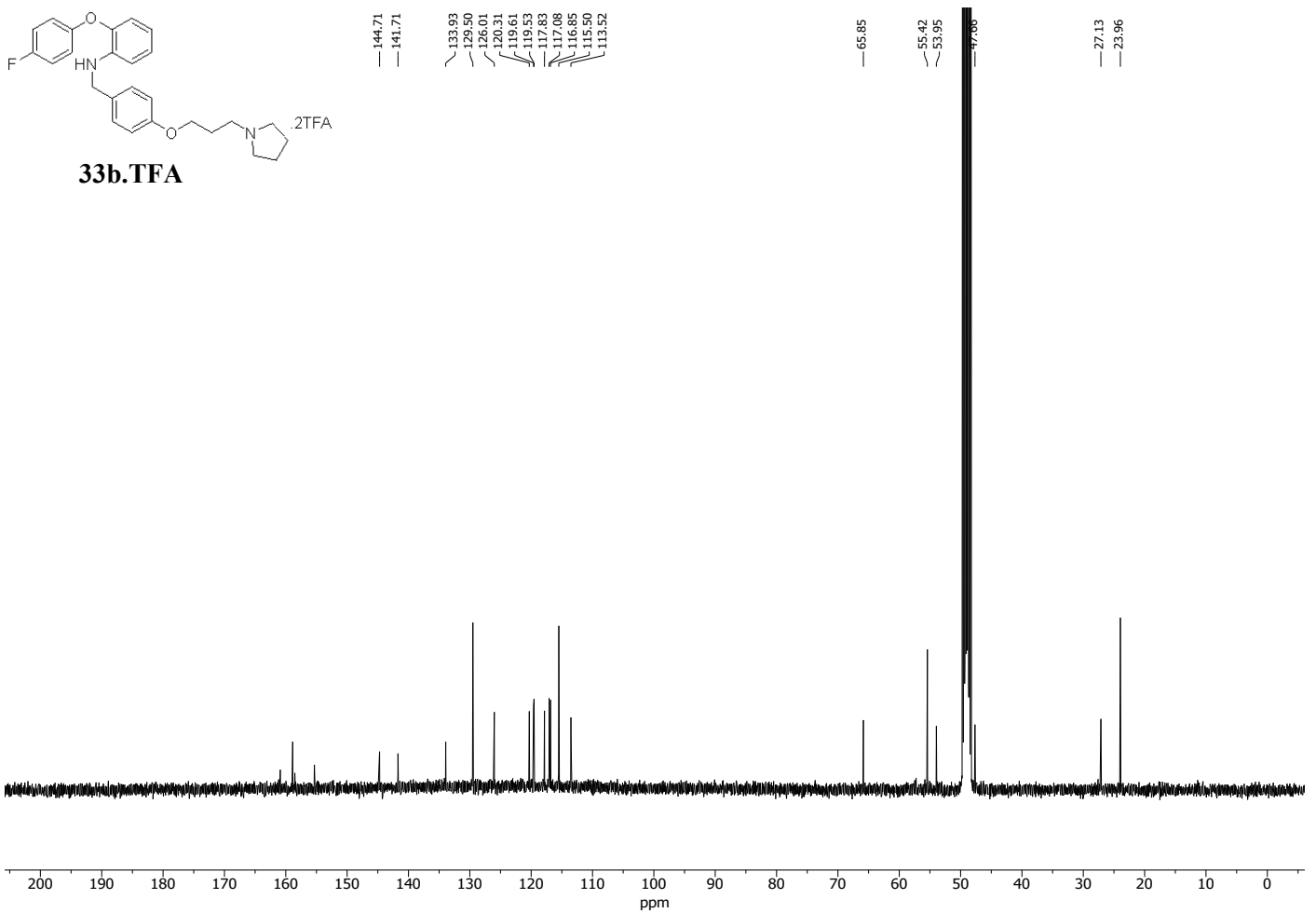
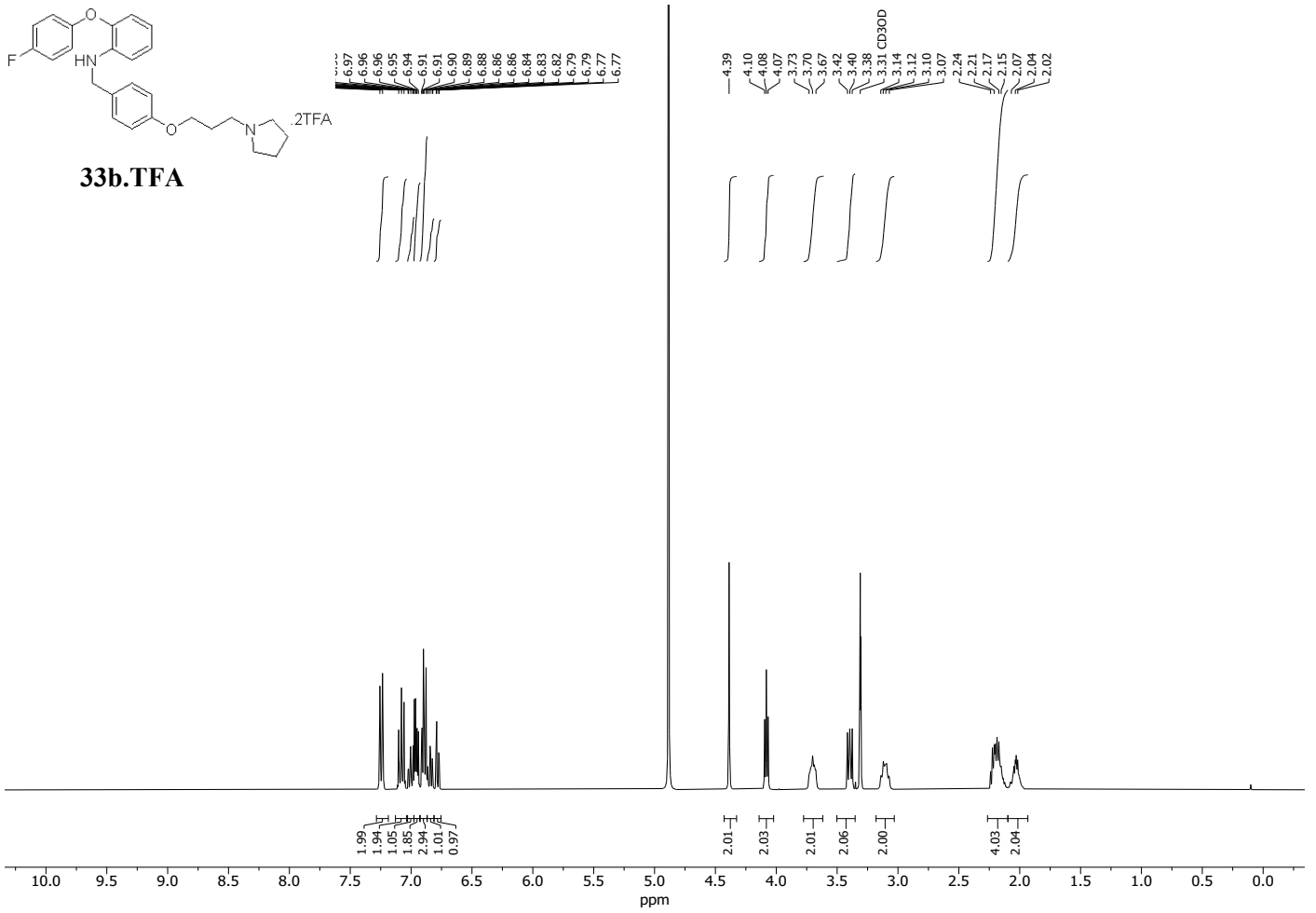
50.40

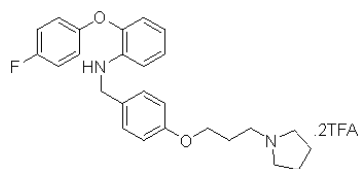
27.03
23.95



-76.55



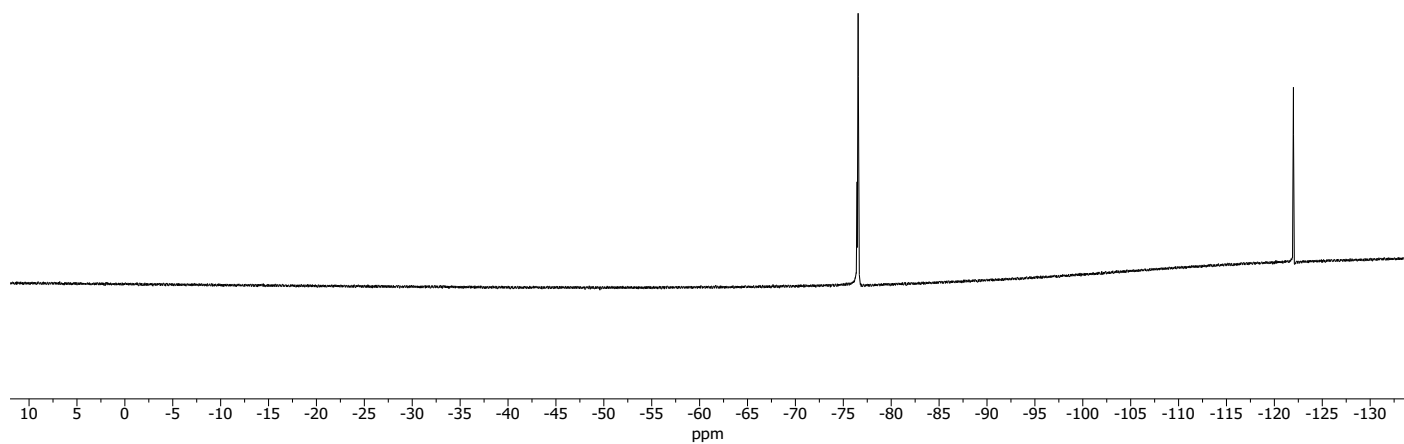


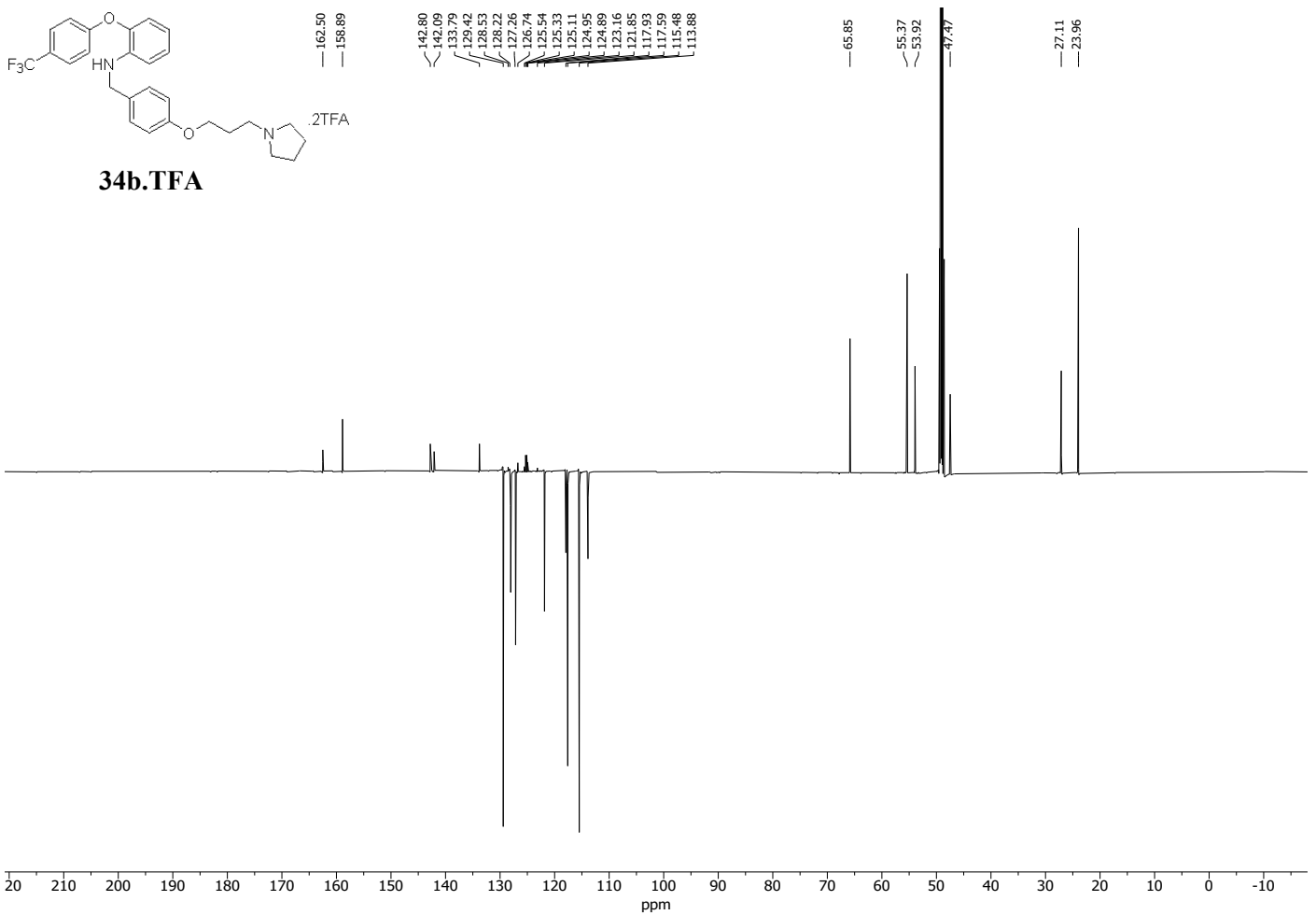
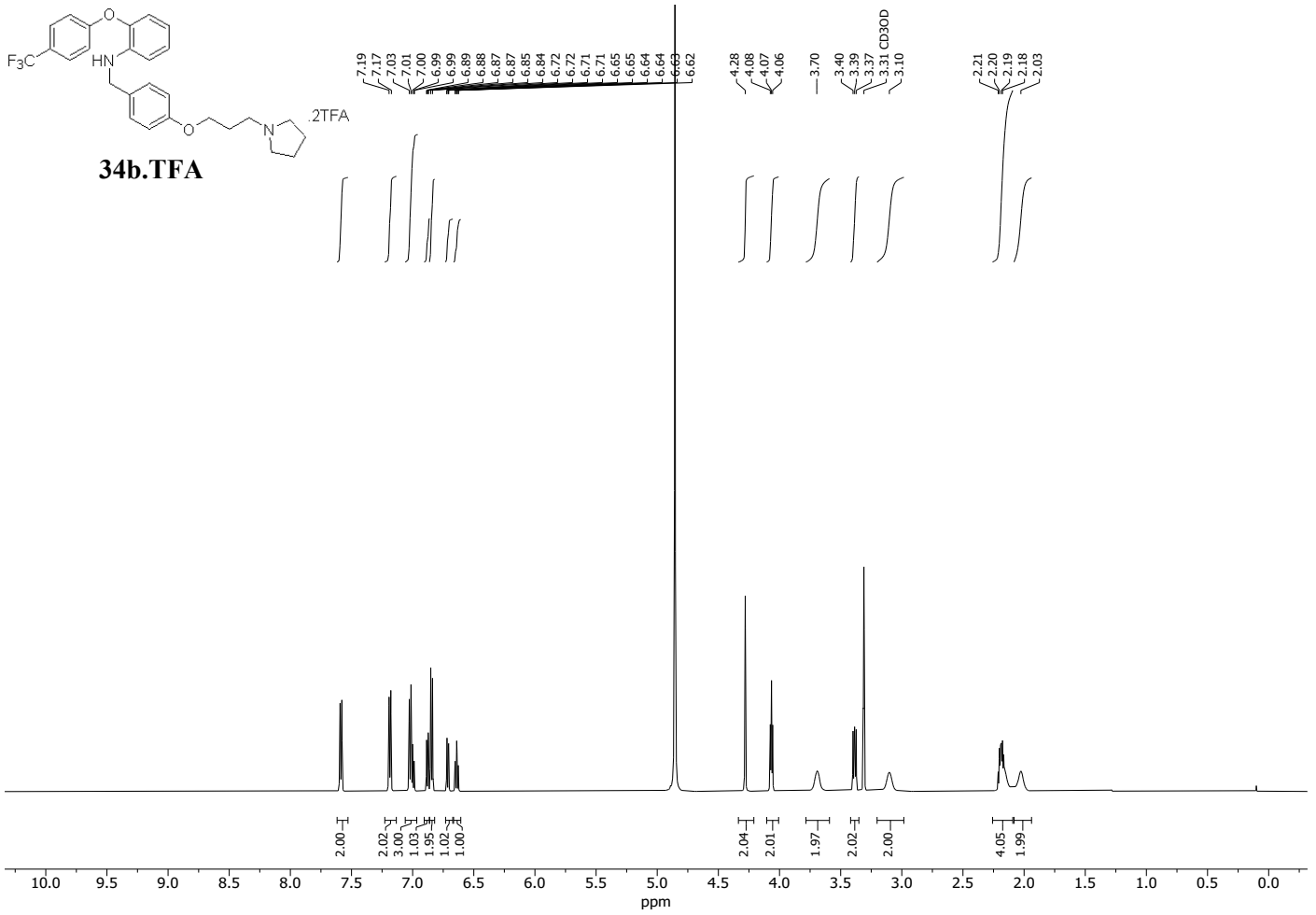


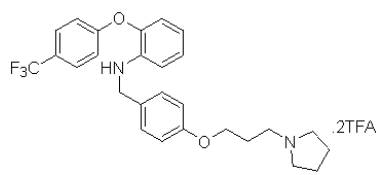
33b.TFA

—76.55

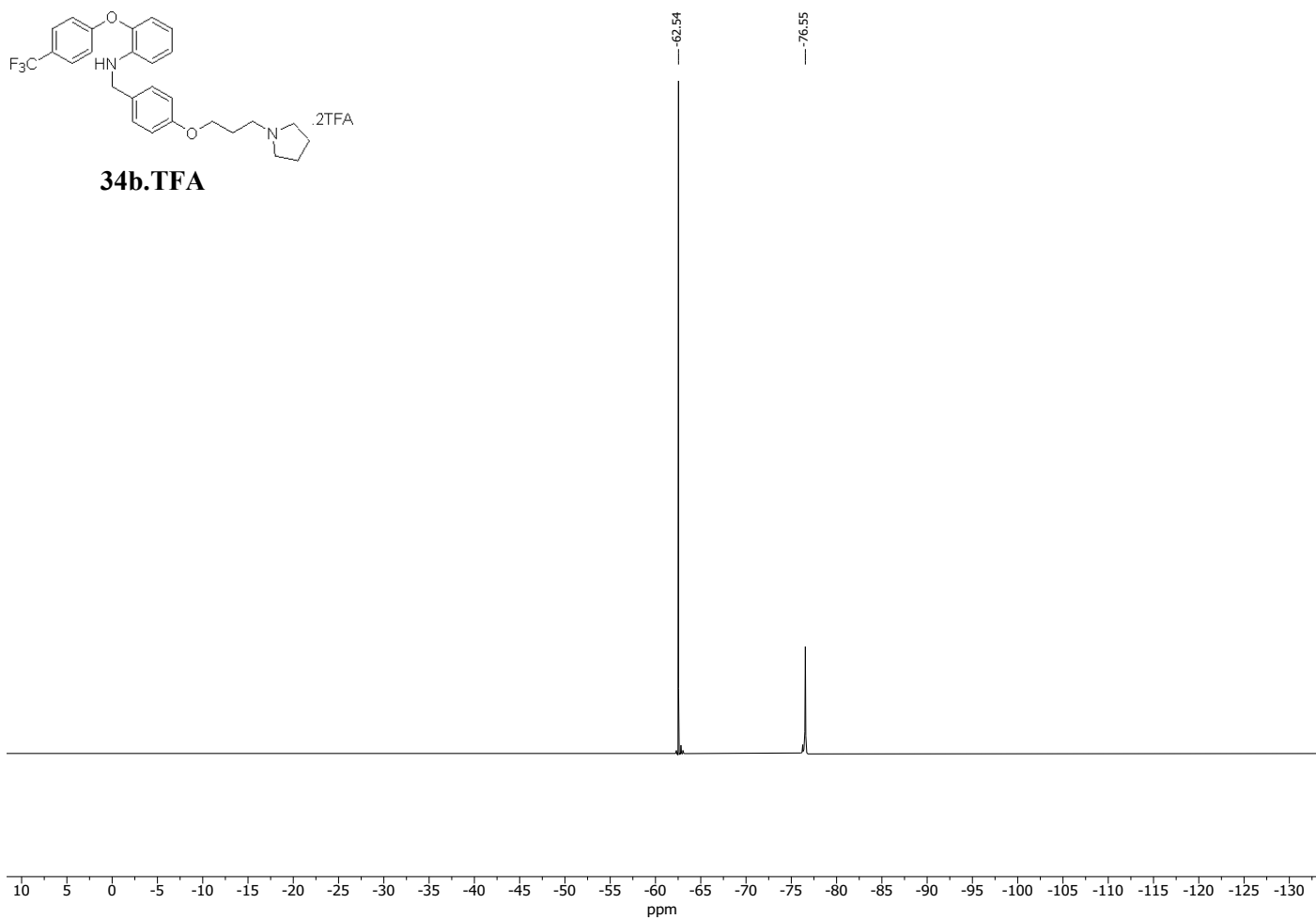
—121.99

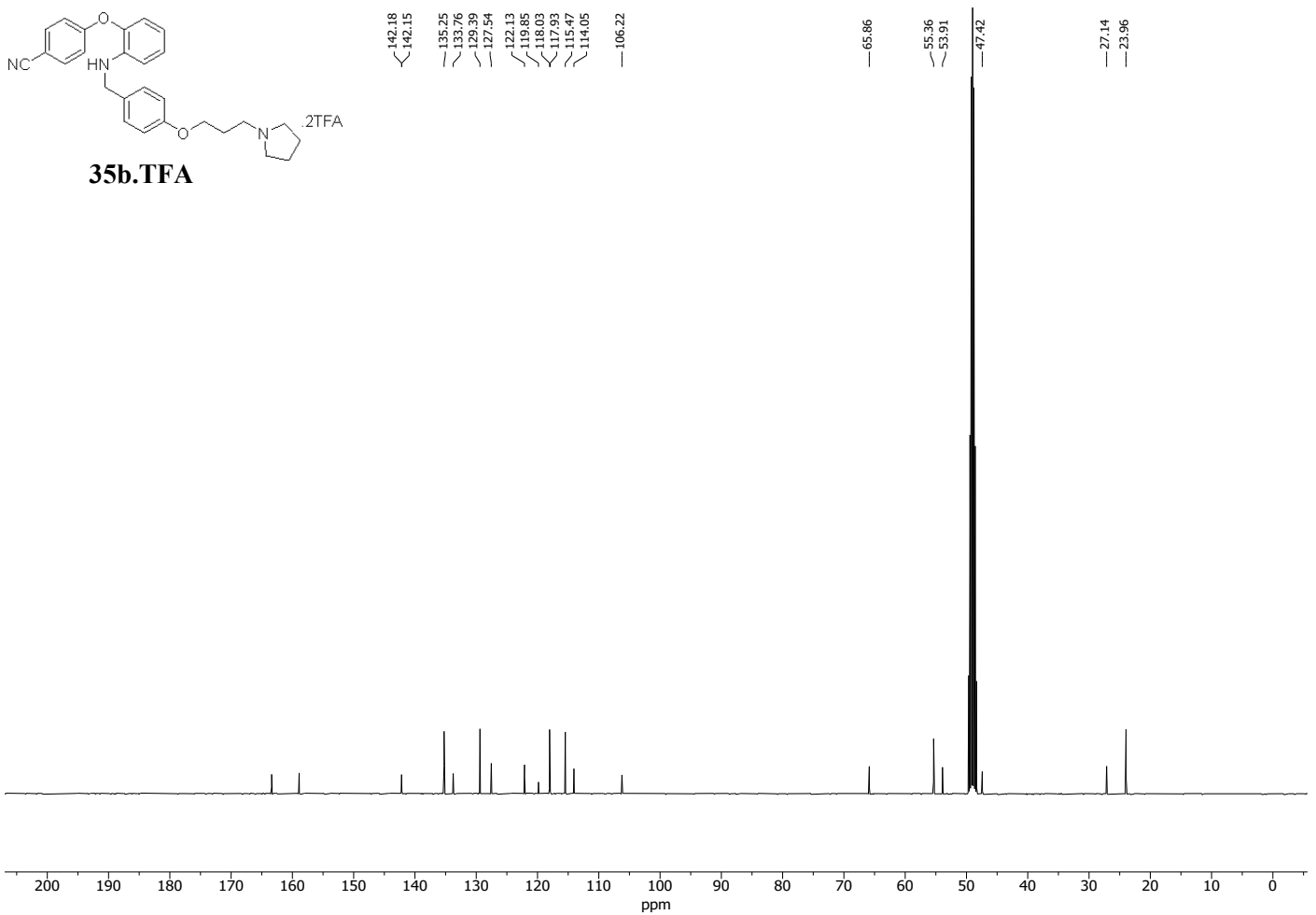
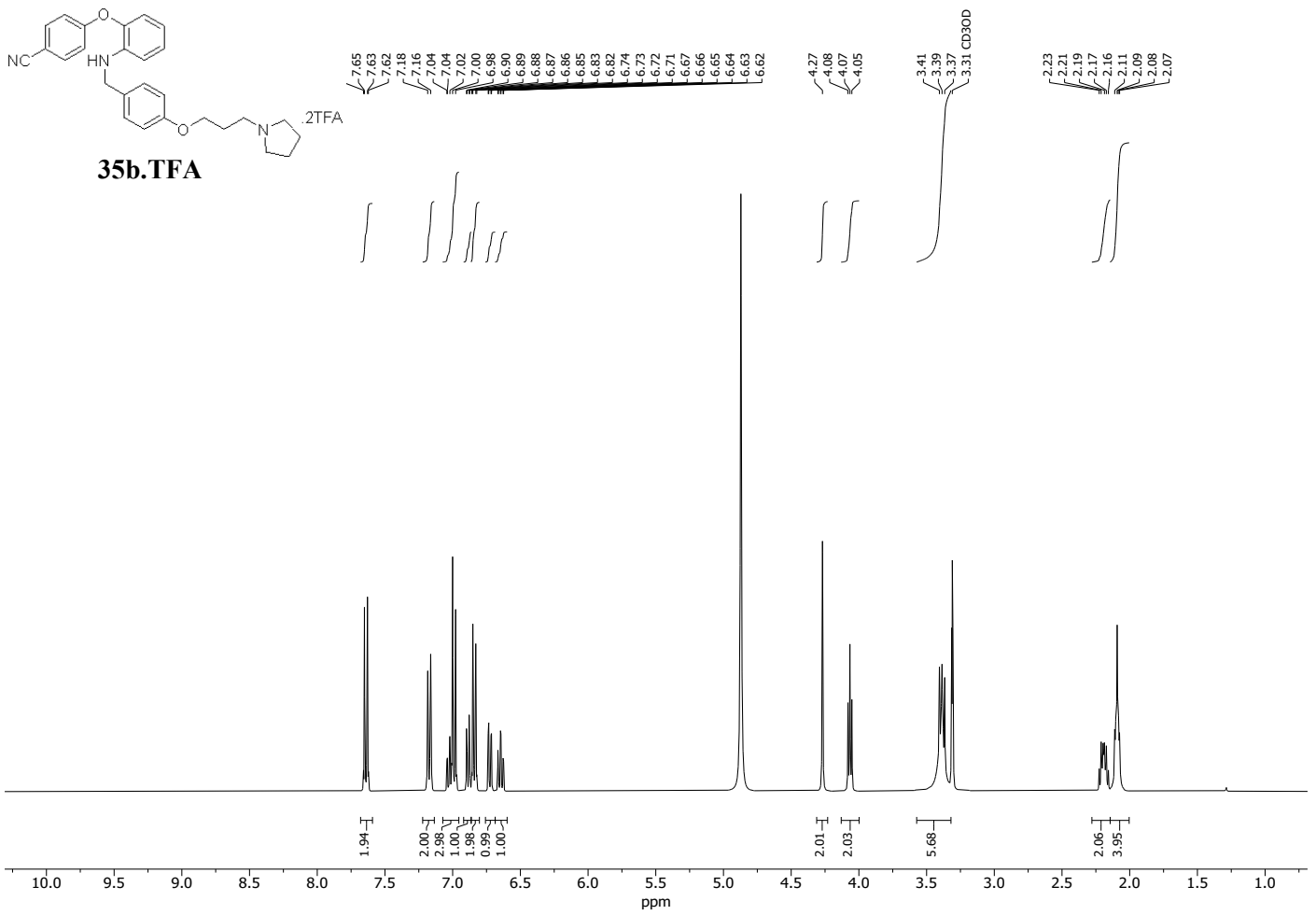


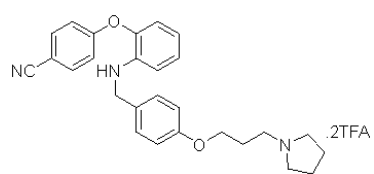




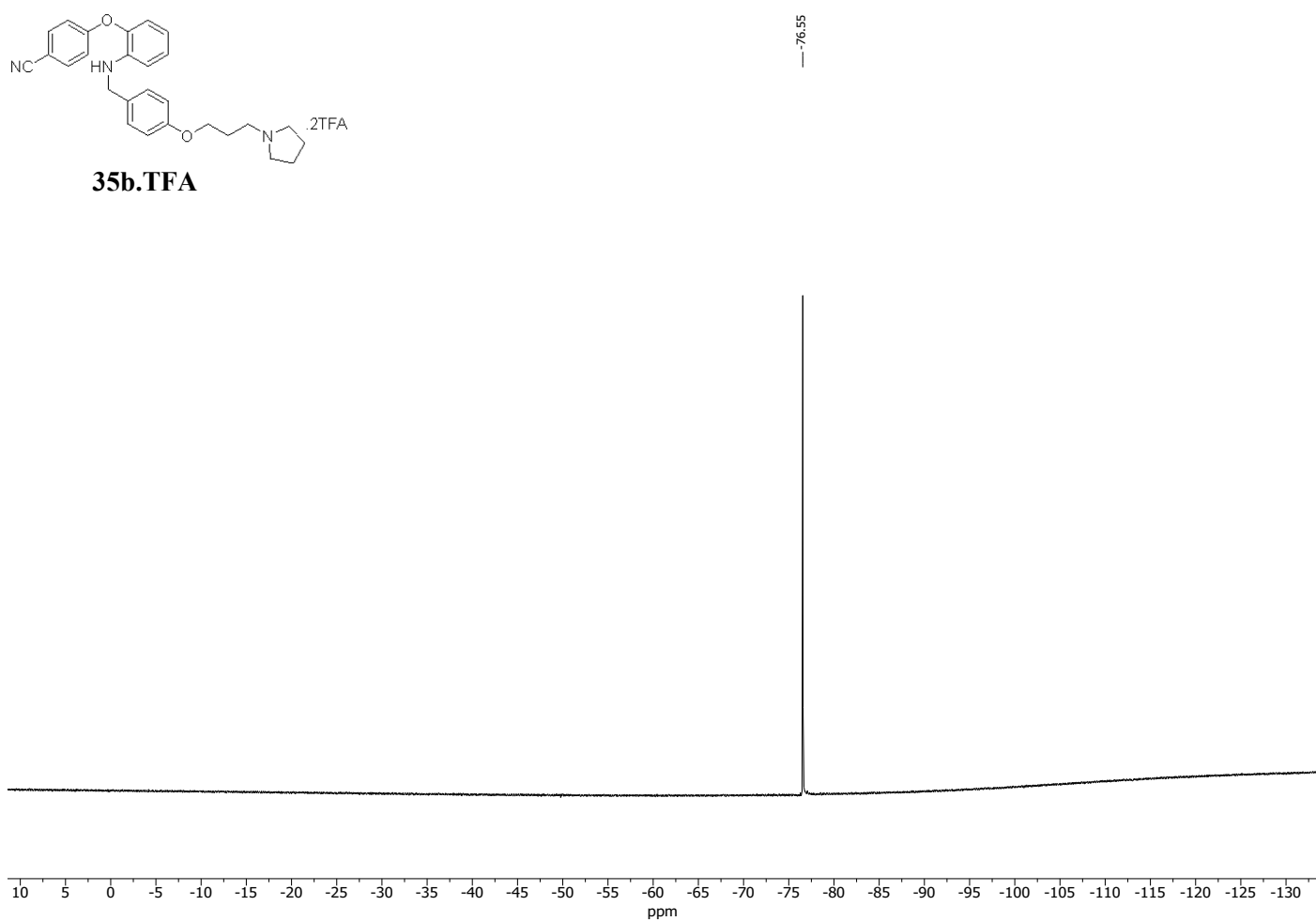
34b.TFA

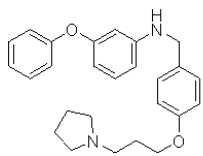




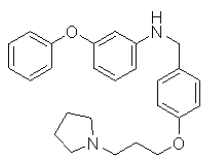
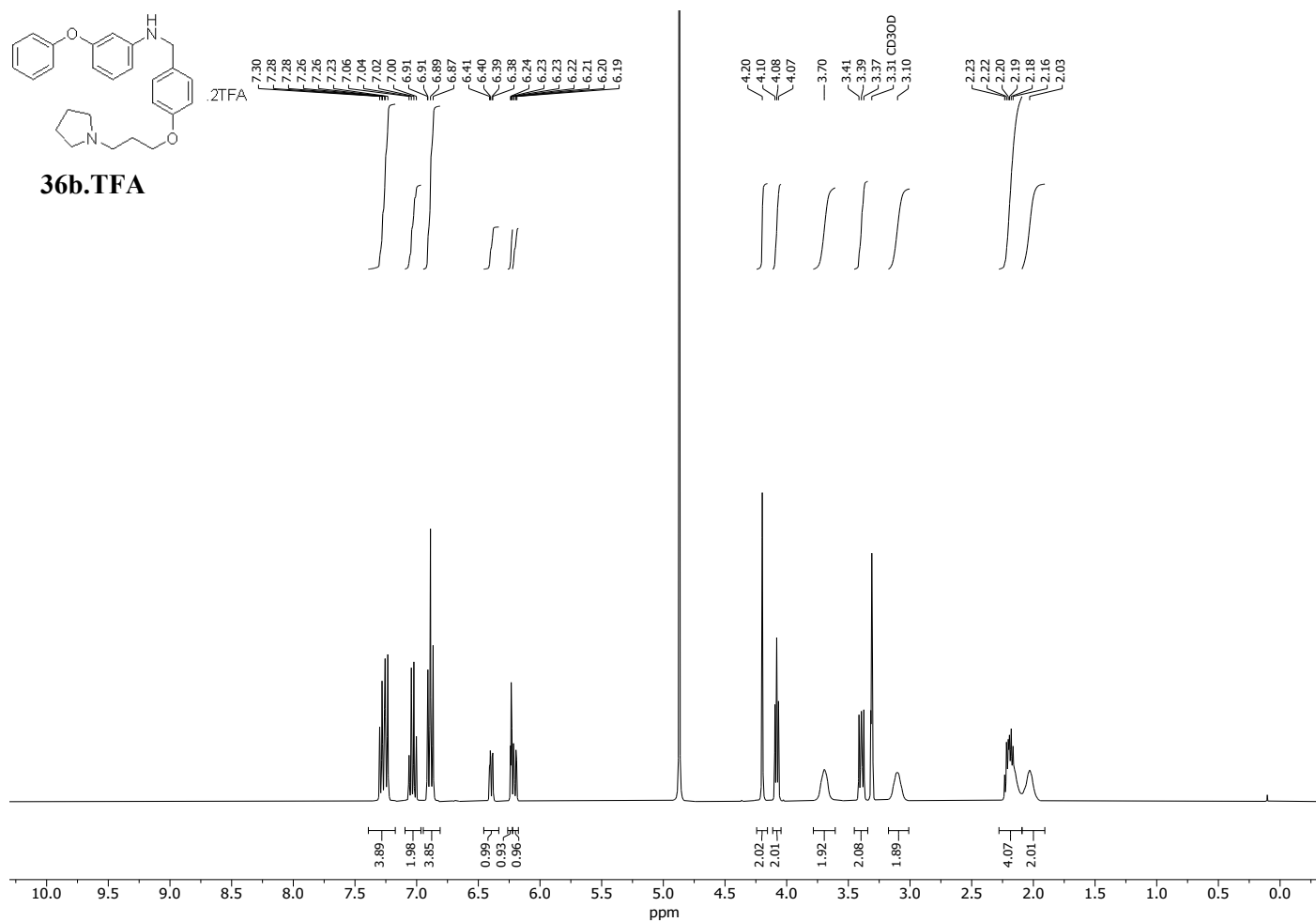


35b.TFA

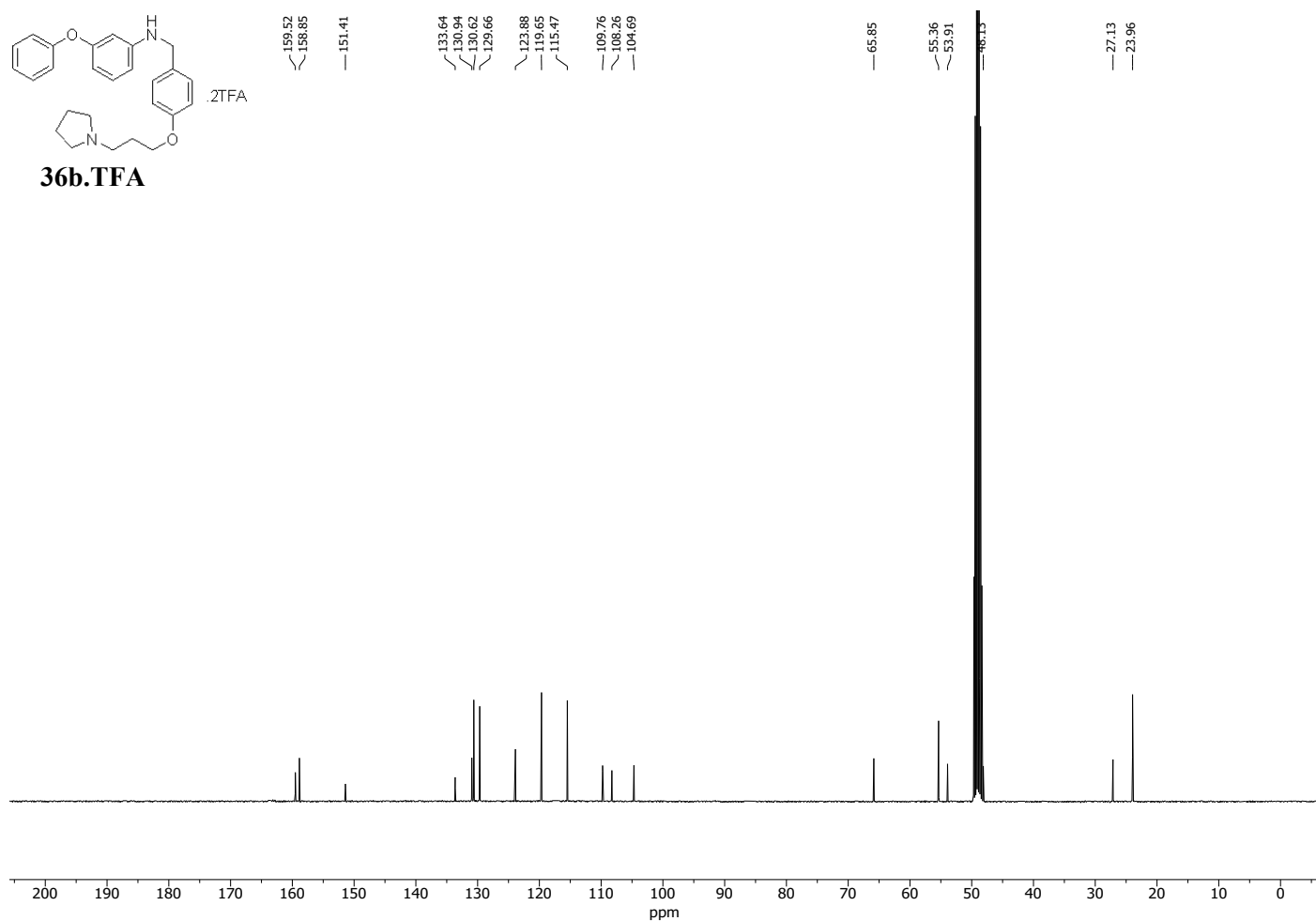


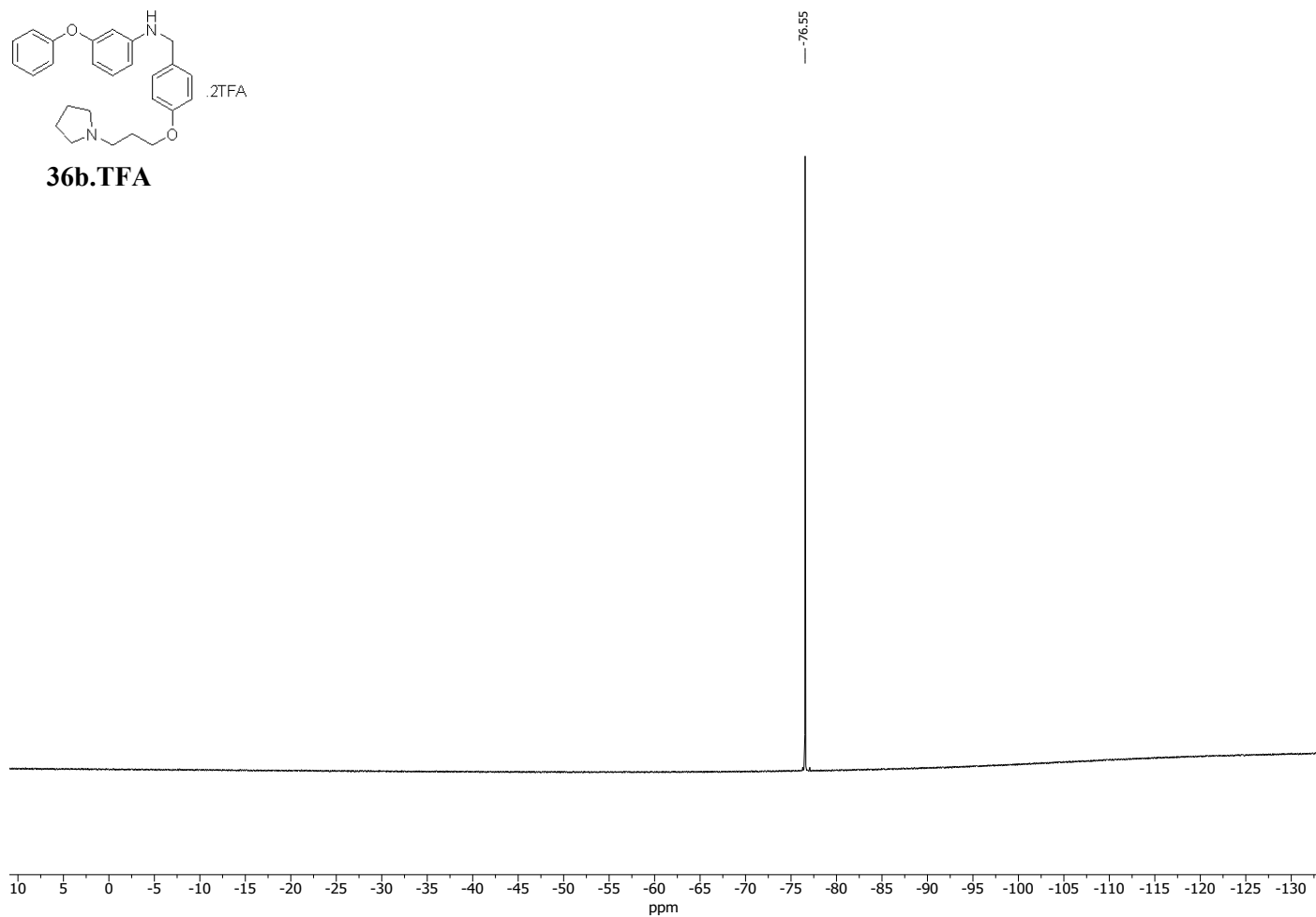
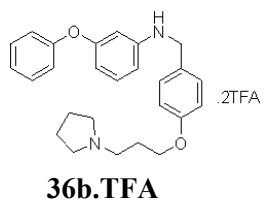


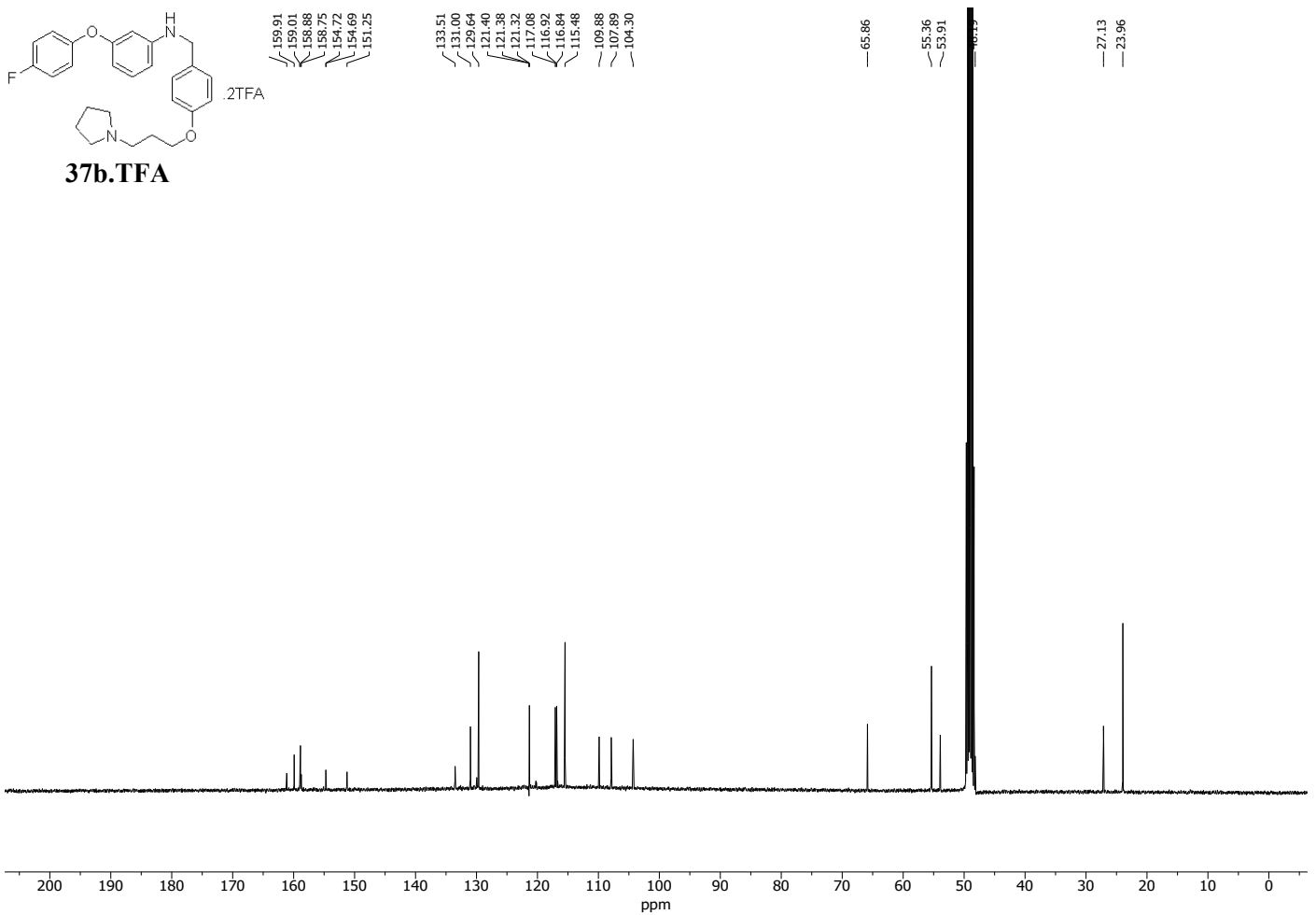
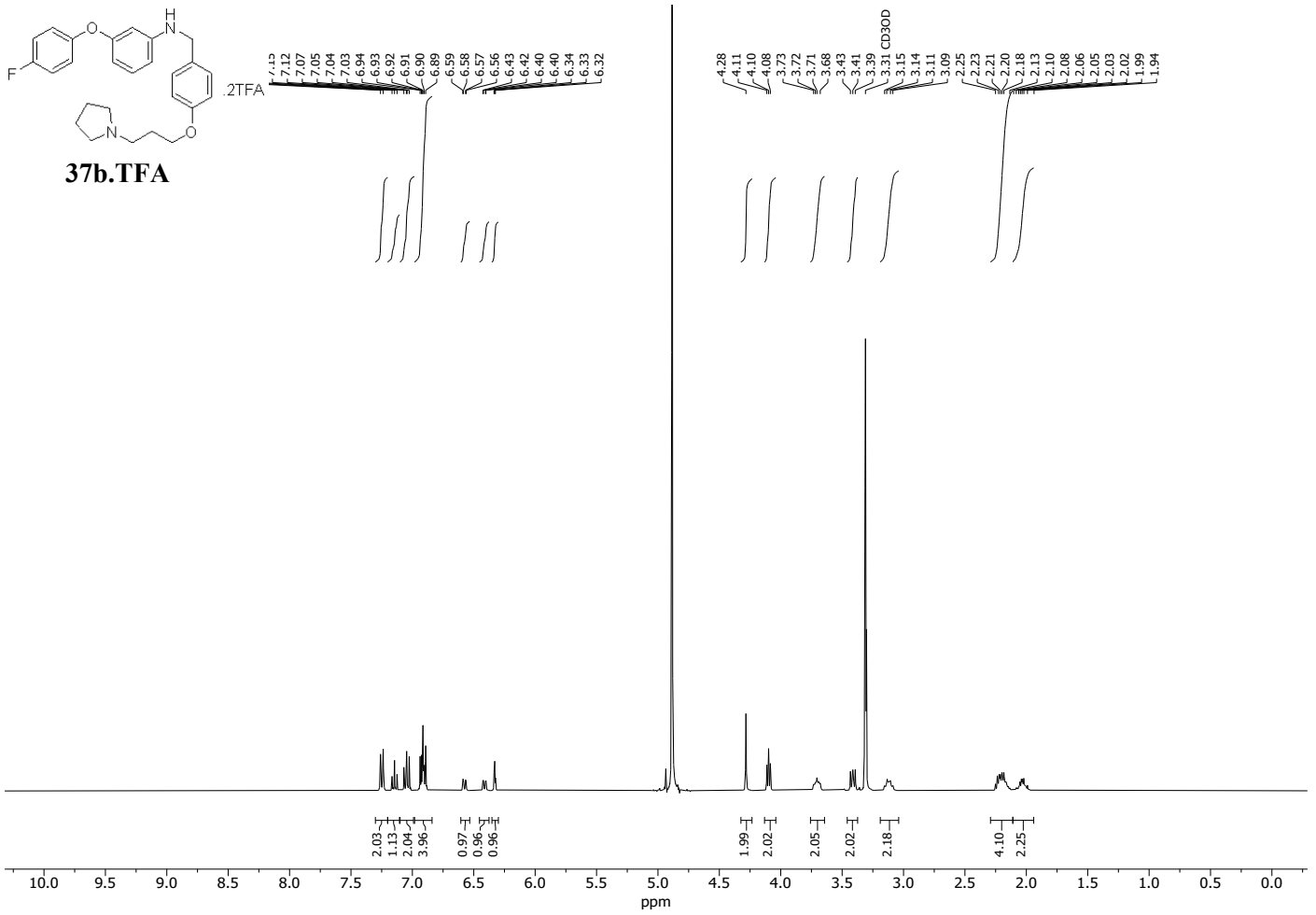
36b.TFA

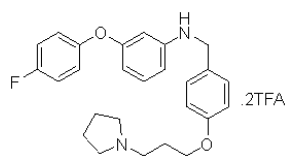


36b.TFA

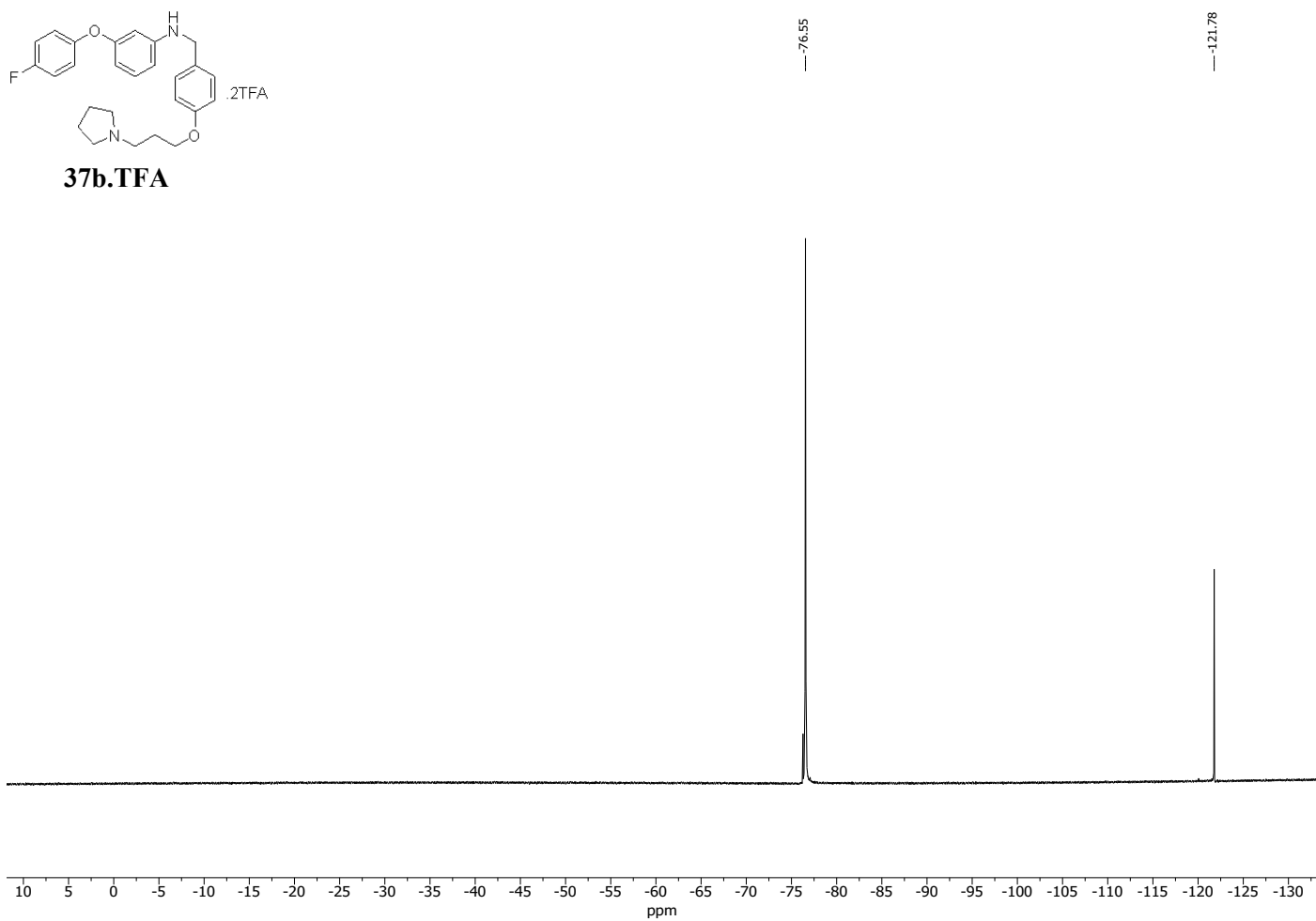


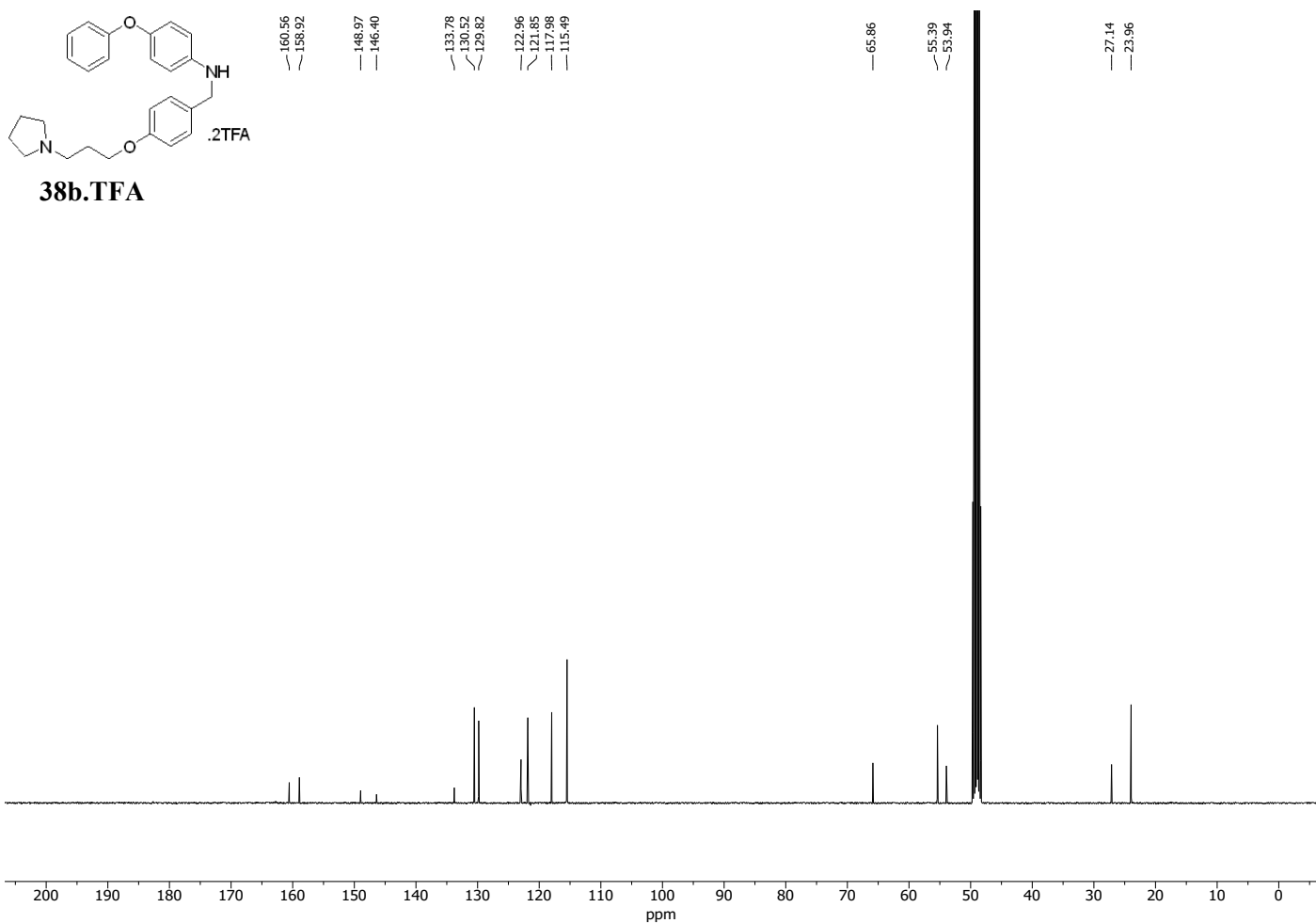
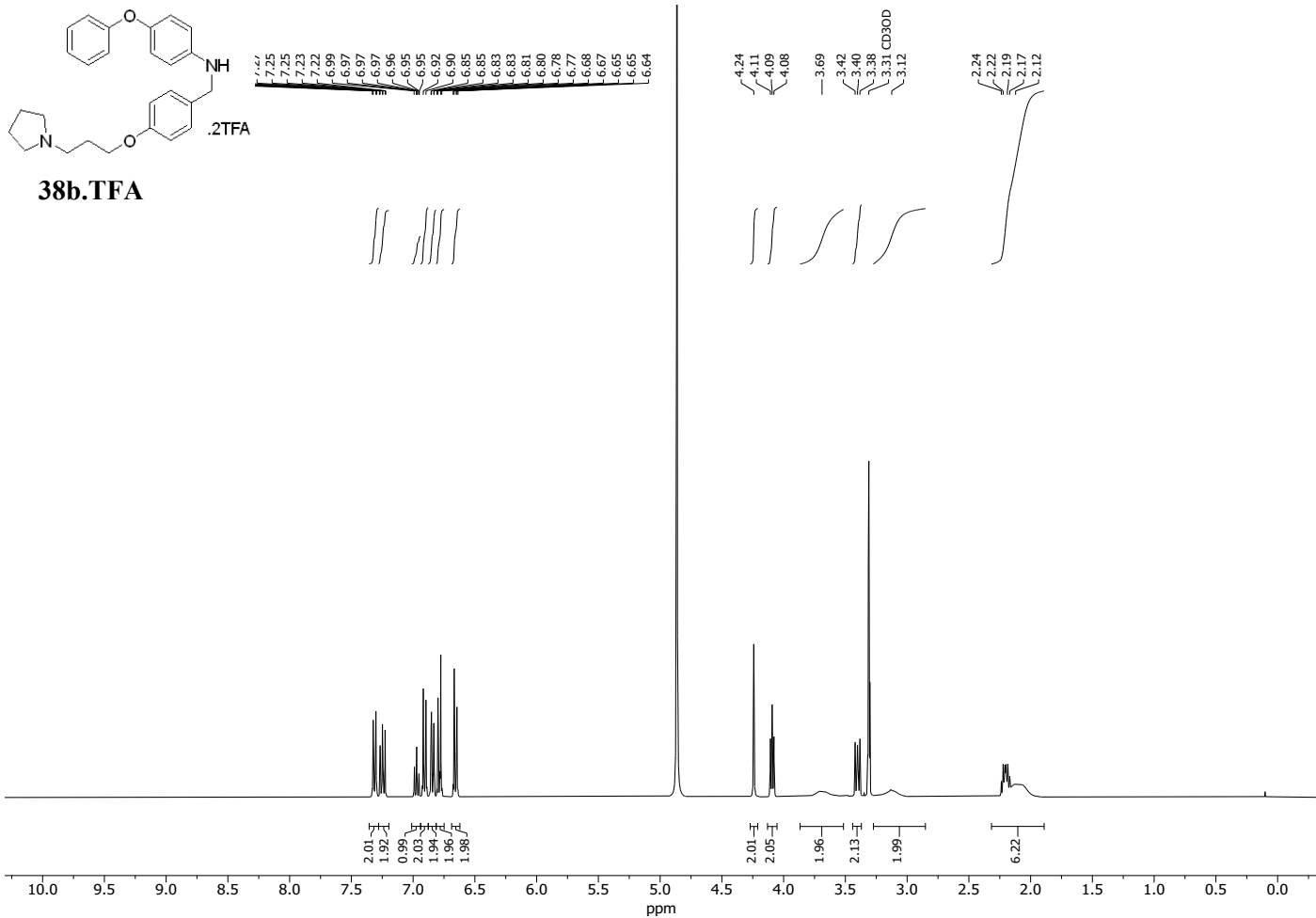


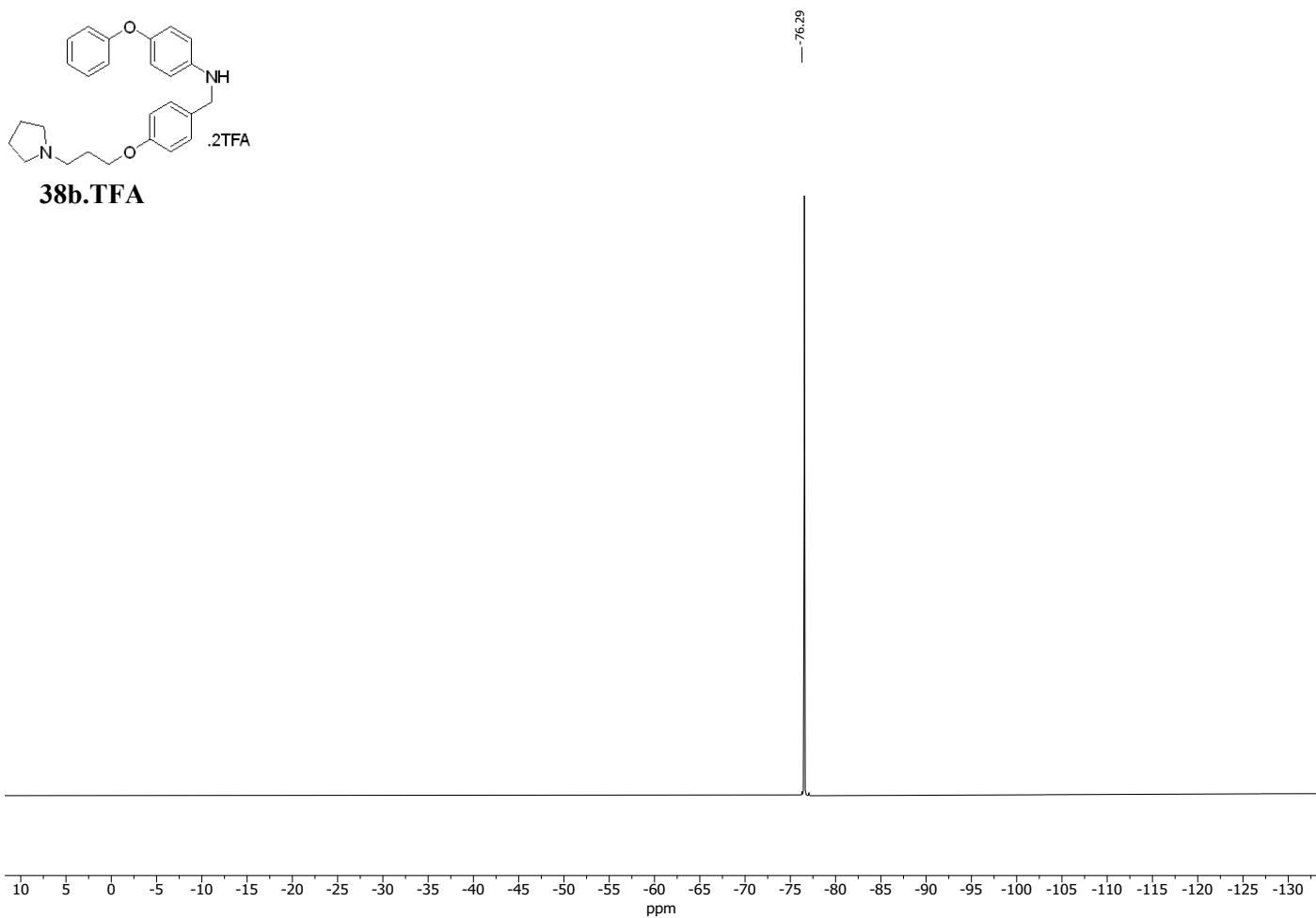
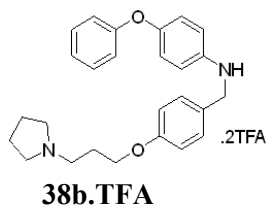


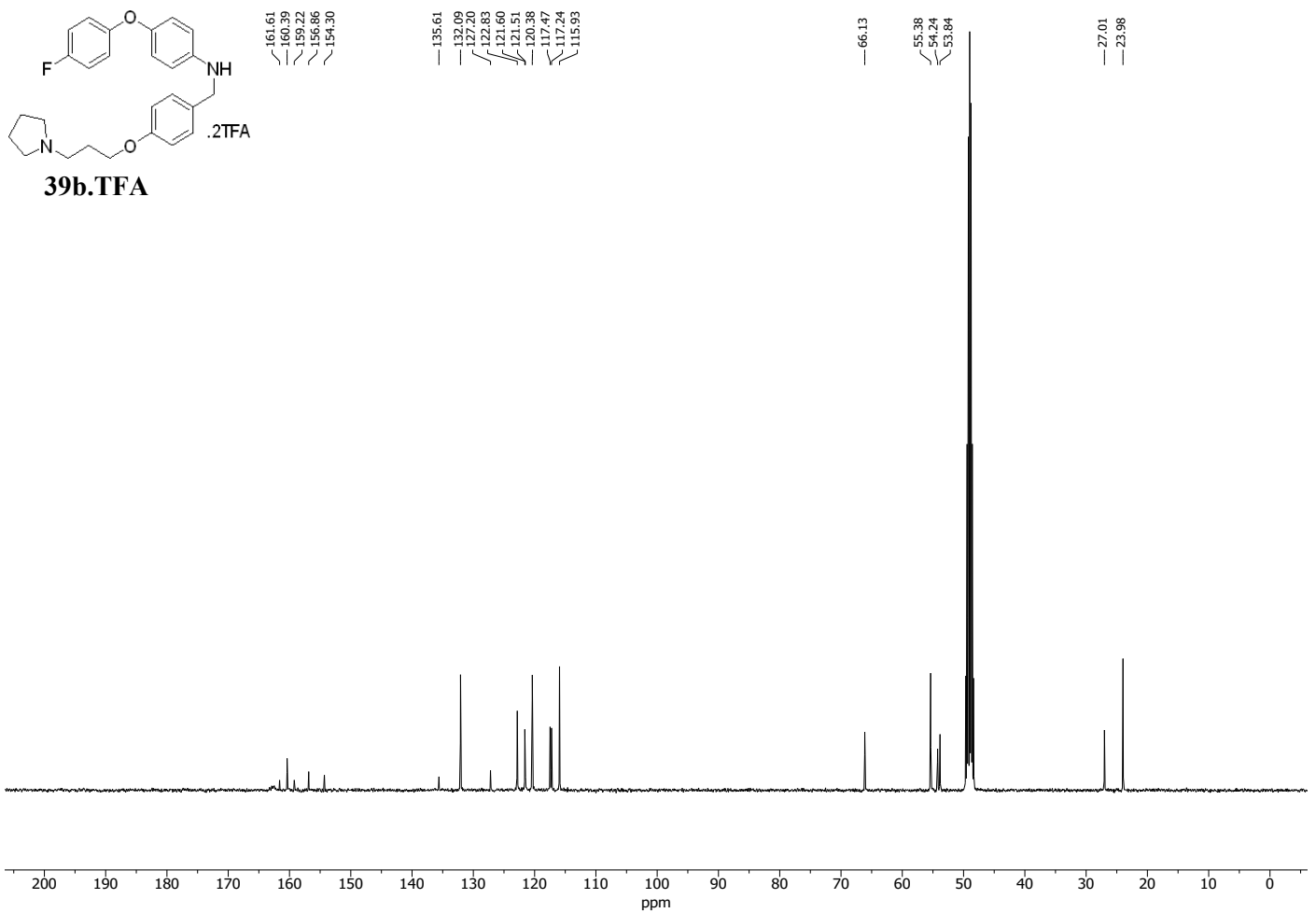
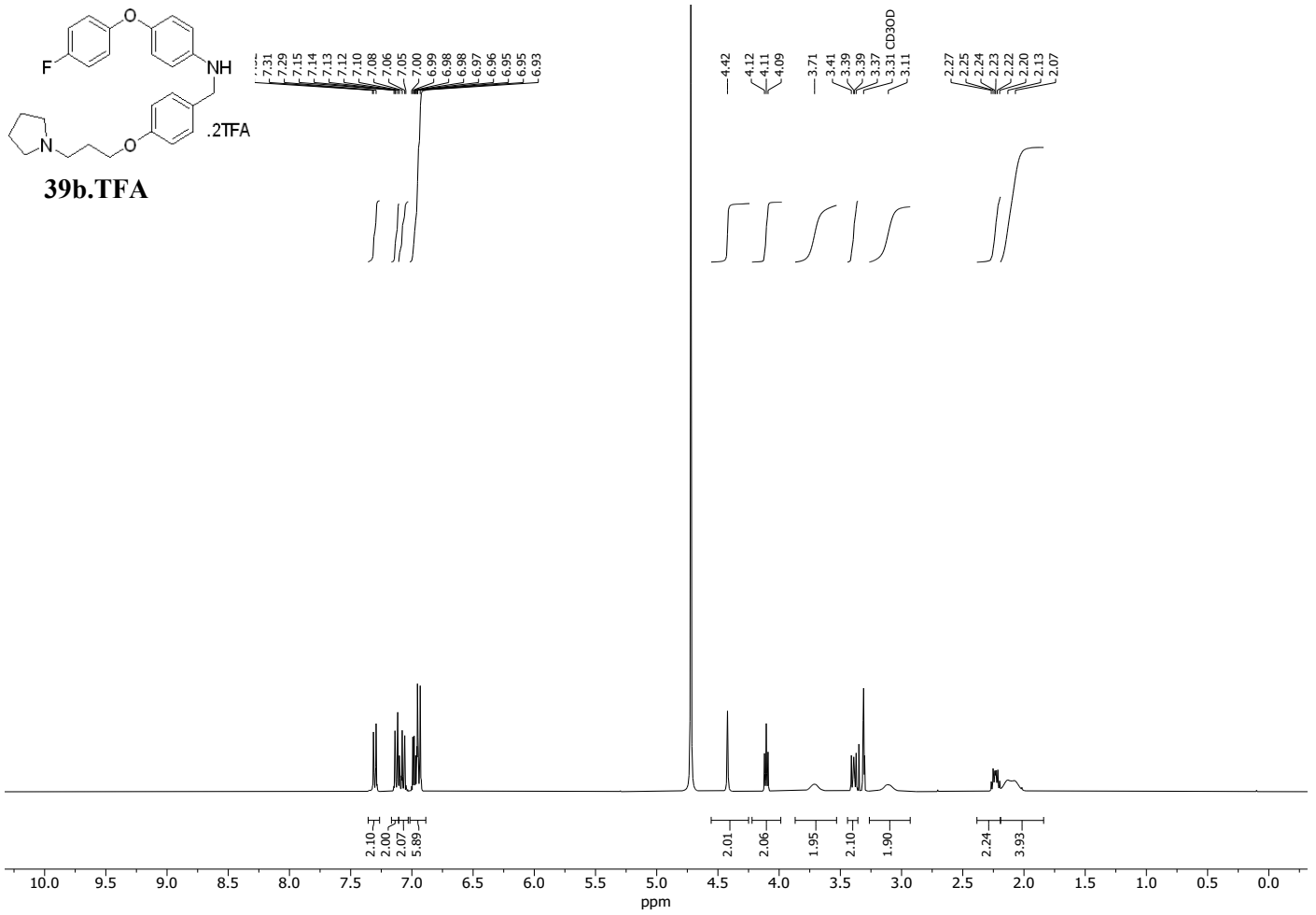


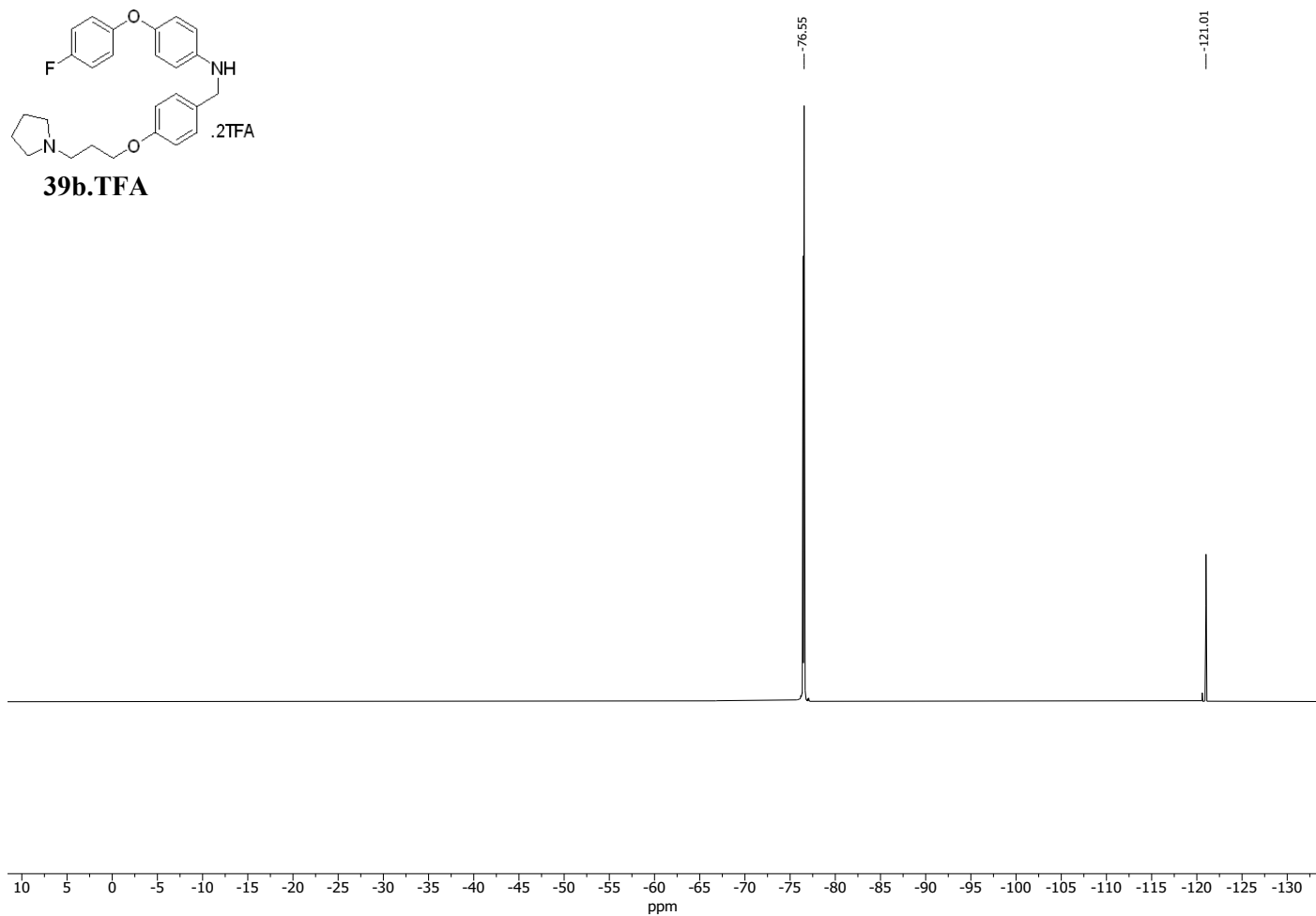
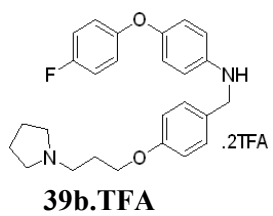
37b.TFA

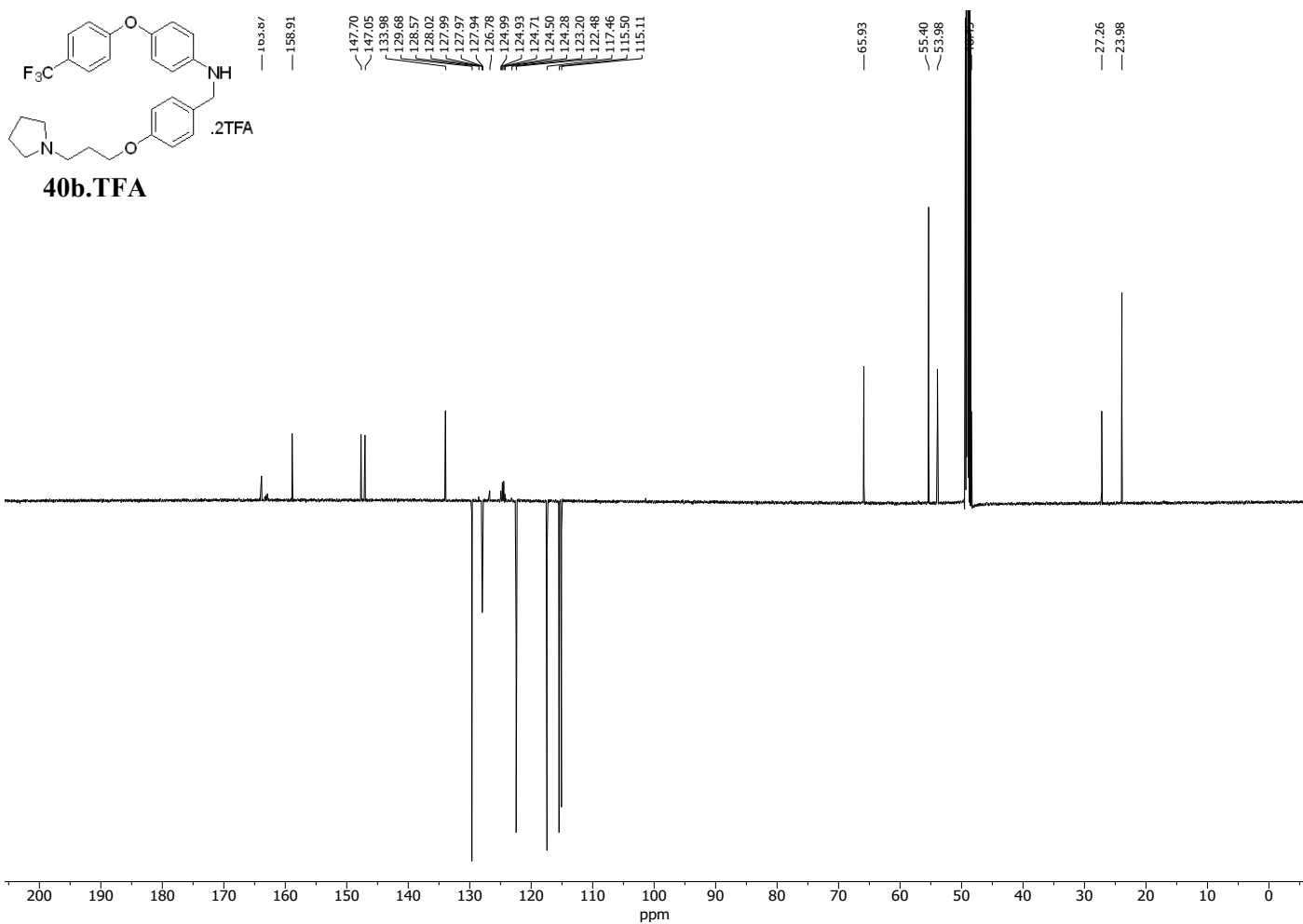
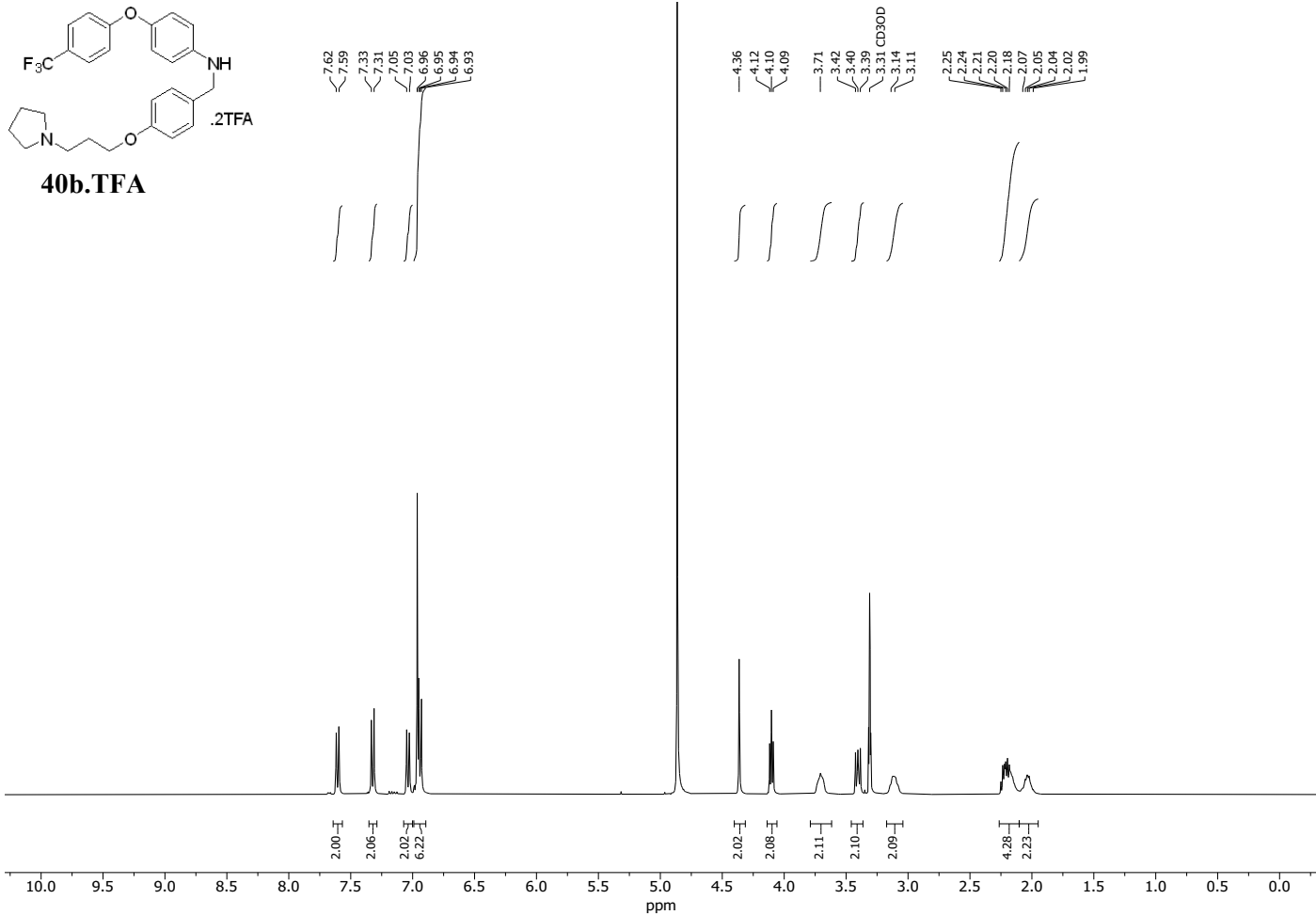


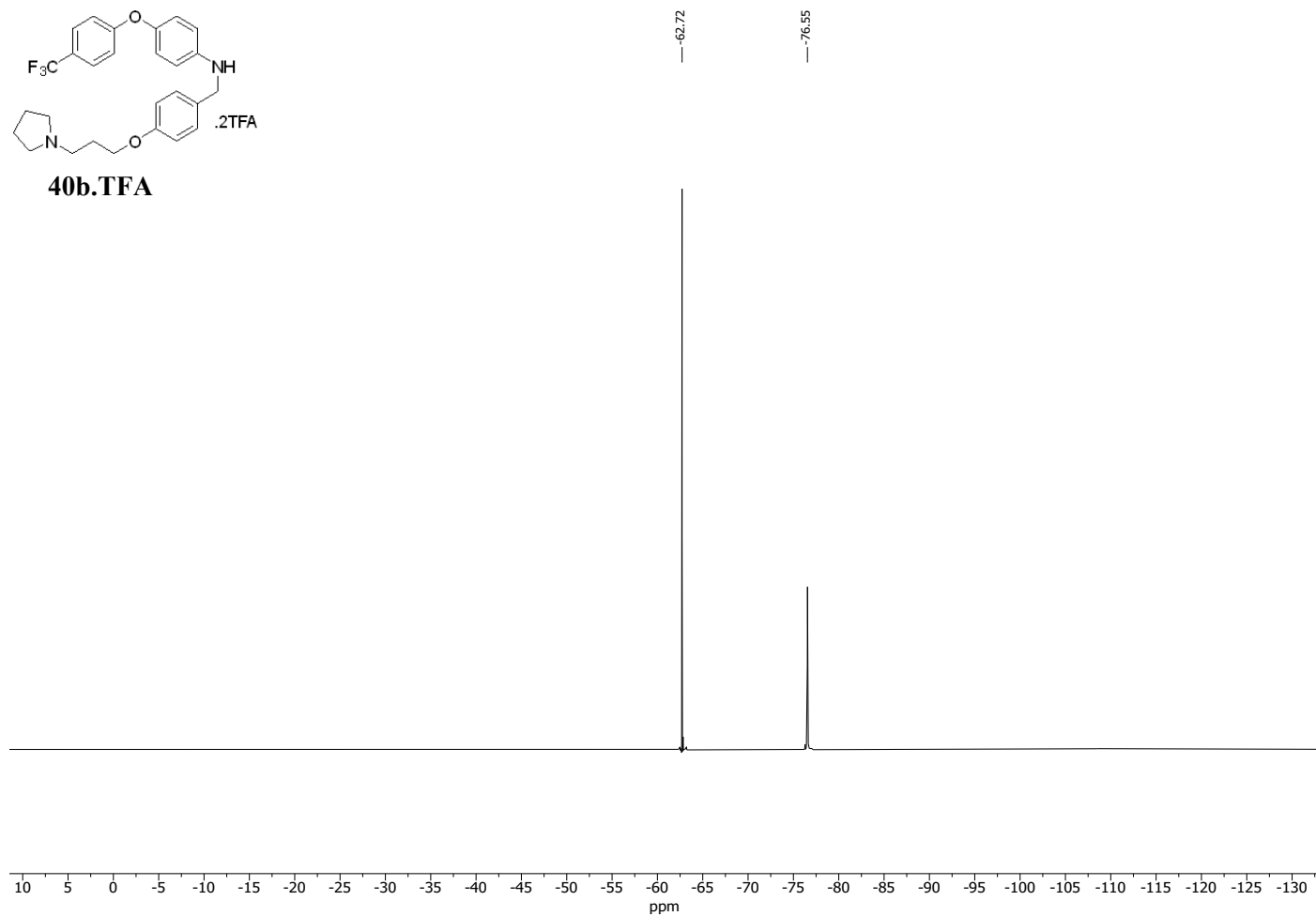
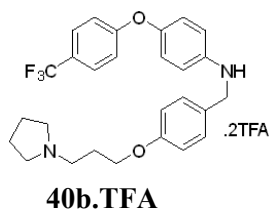


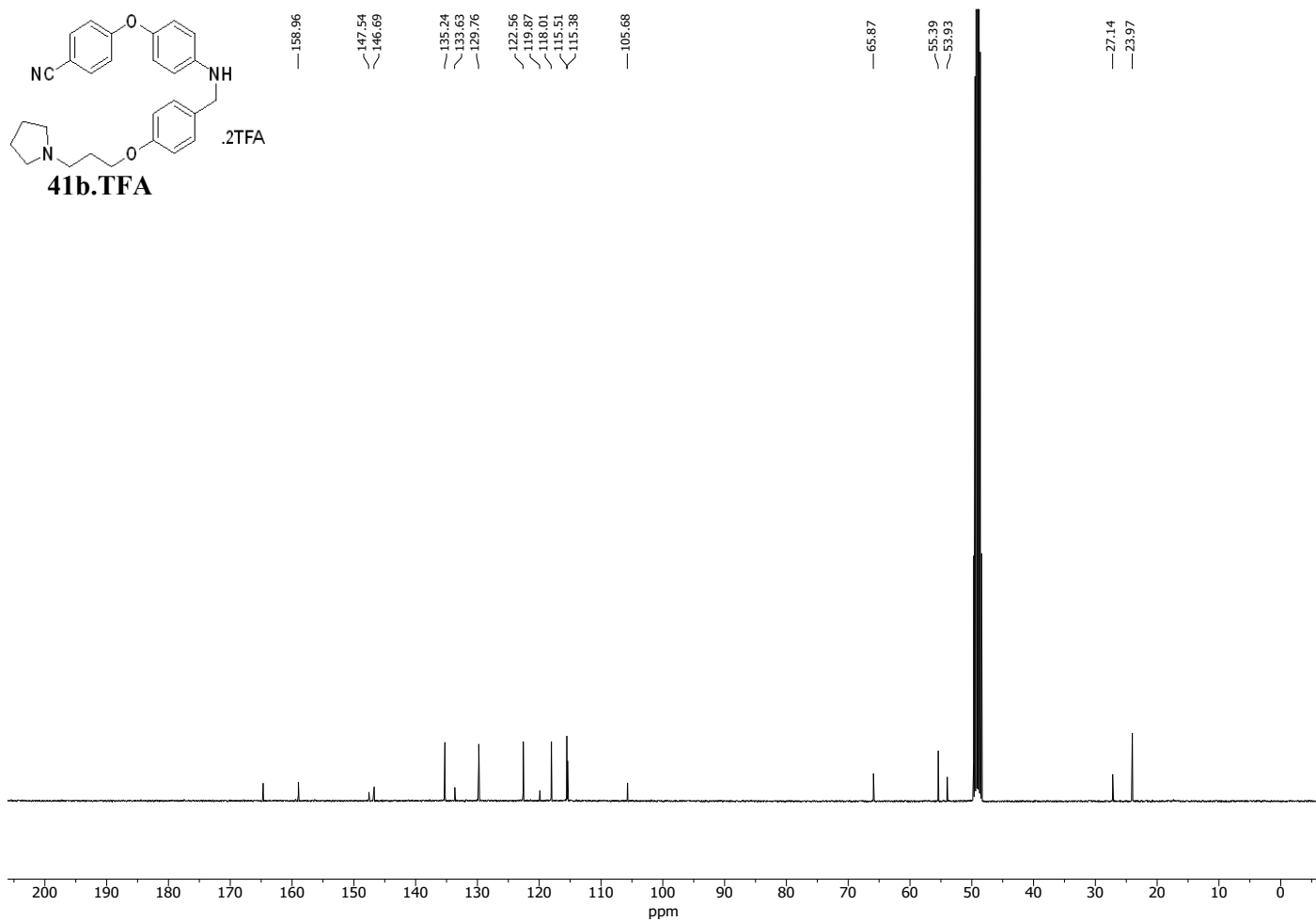
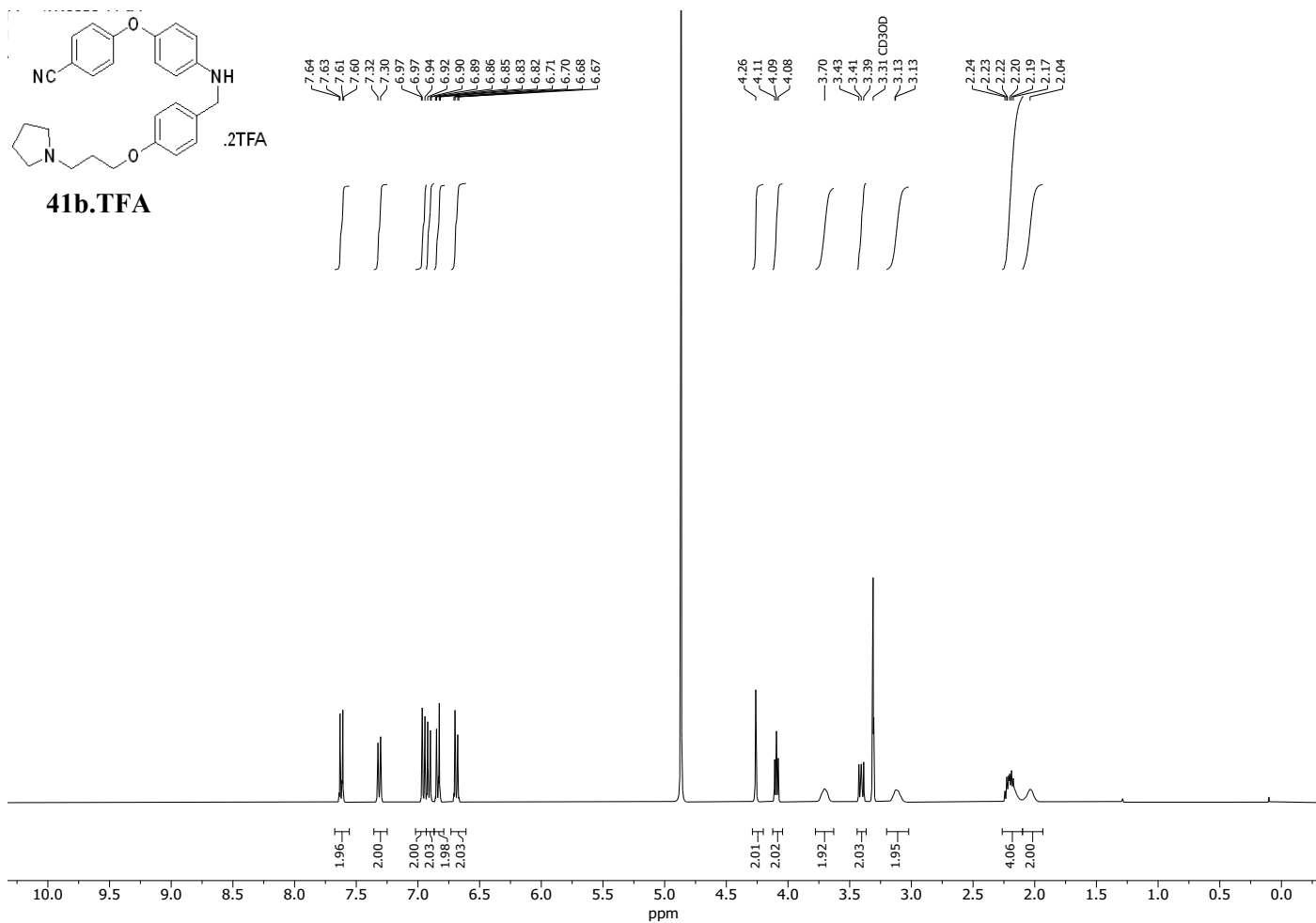


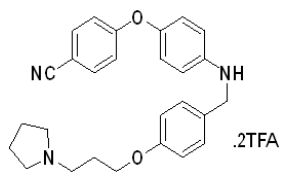




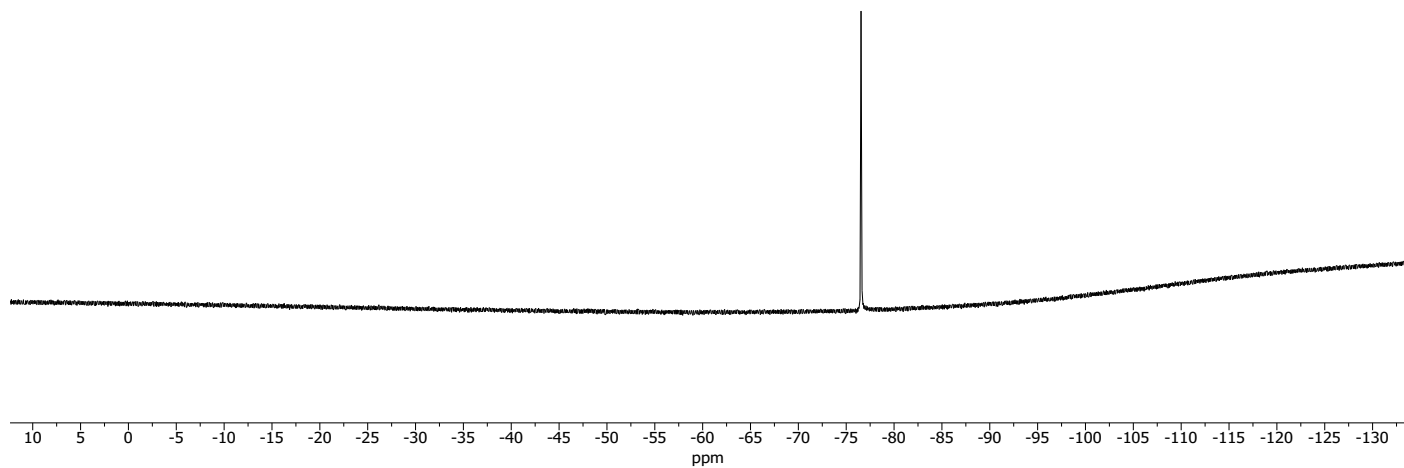


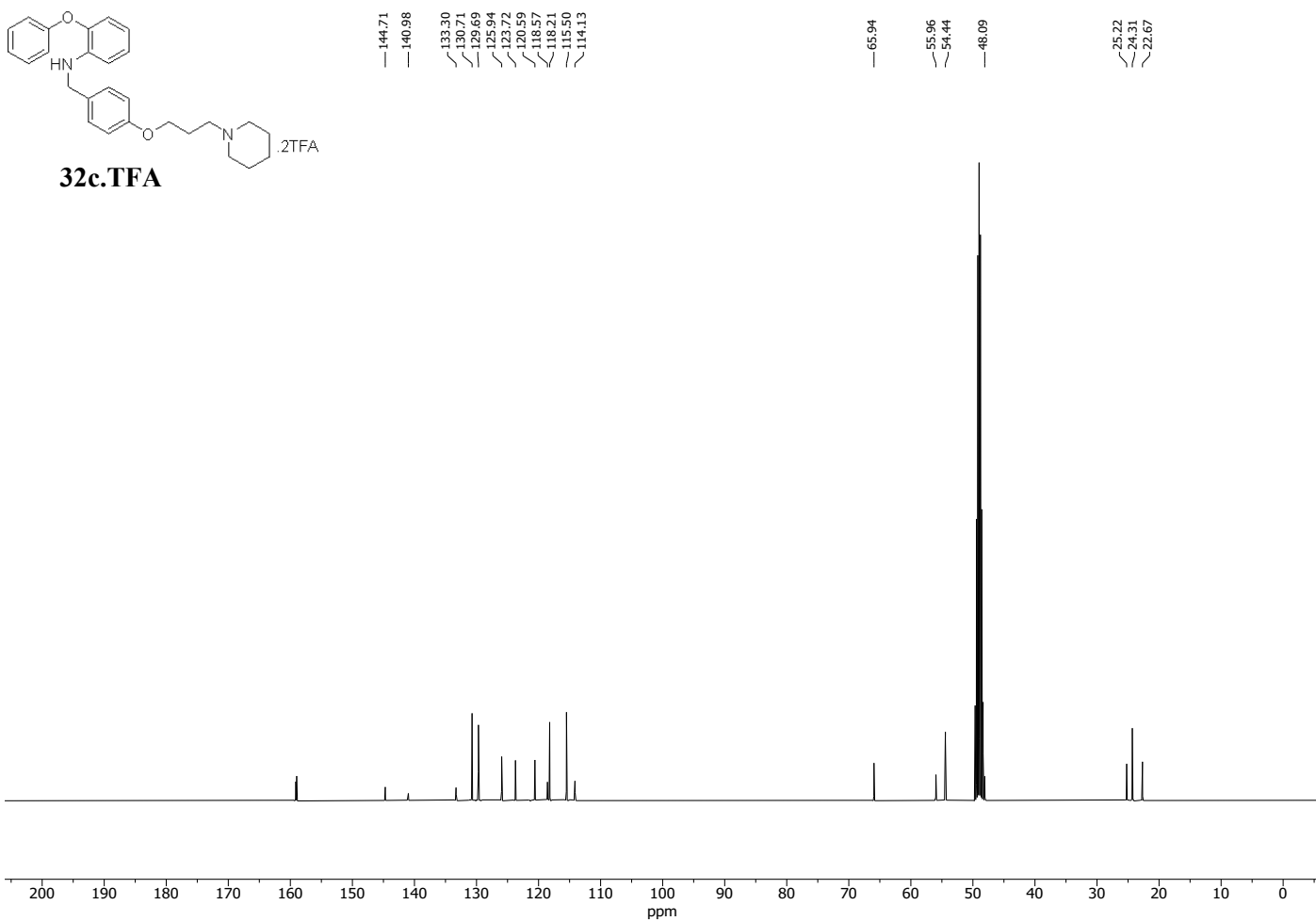
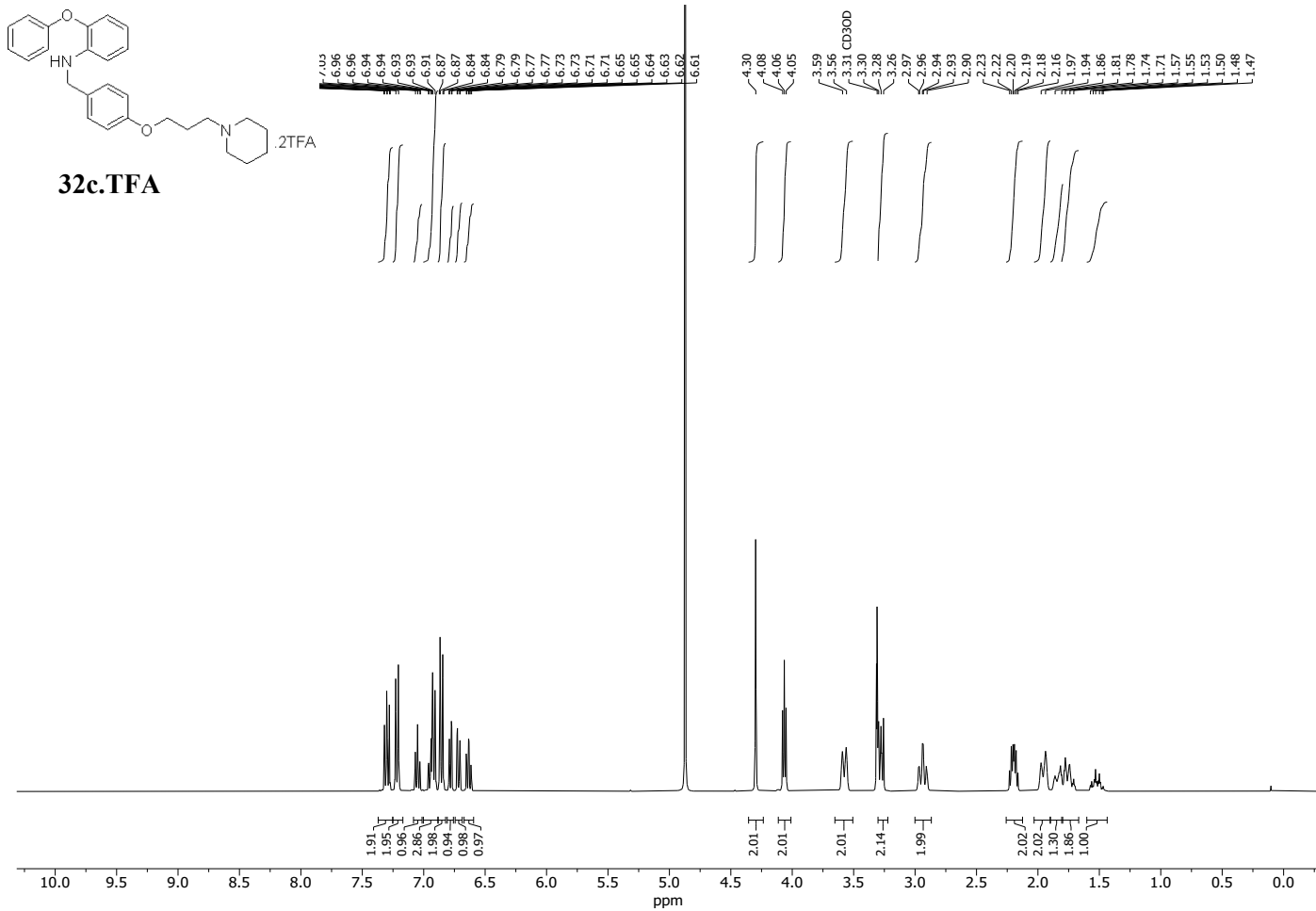


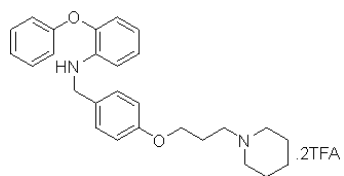




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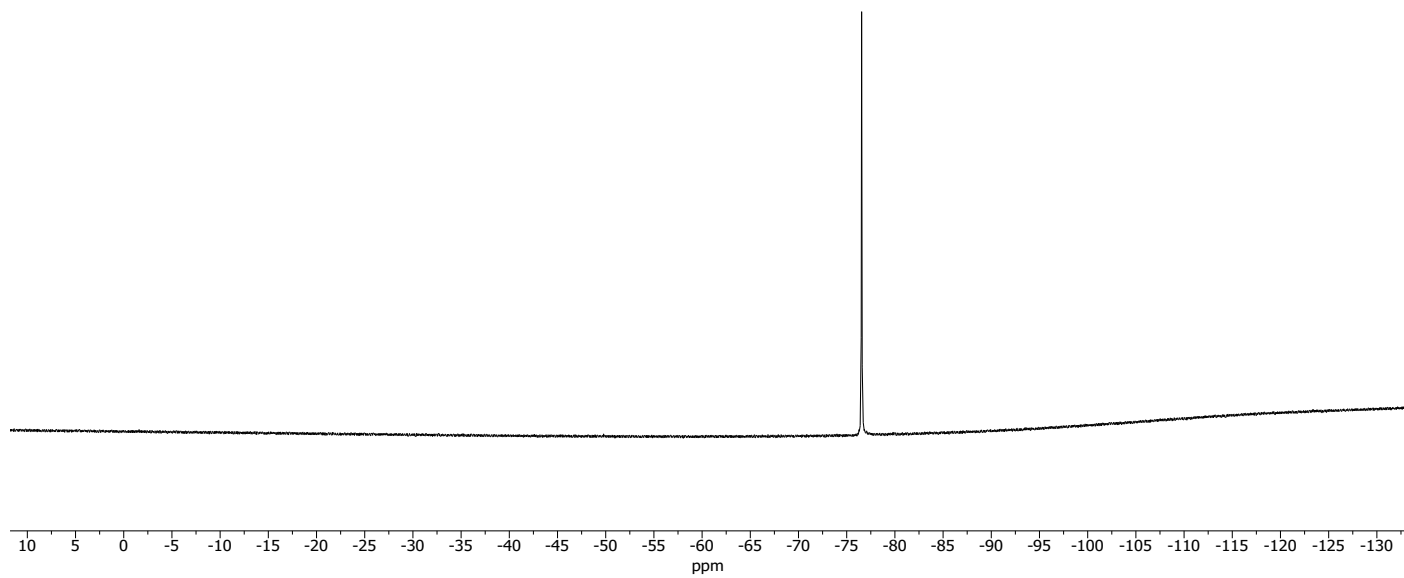


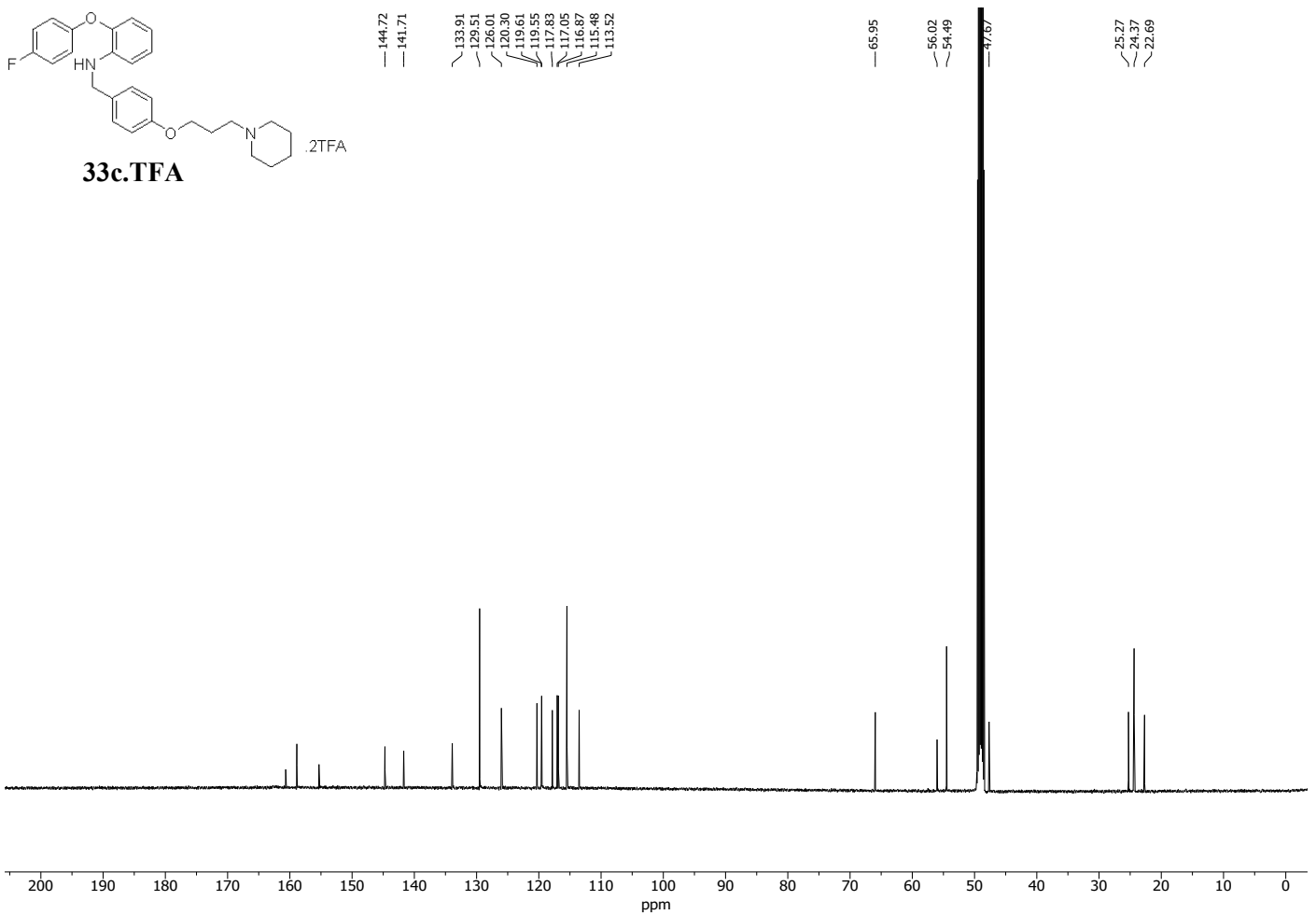
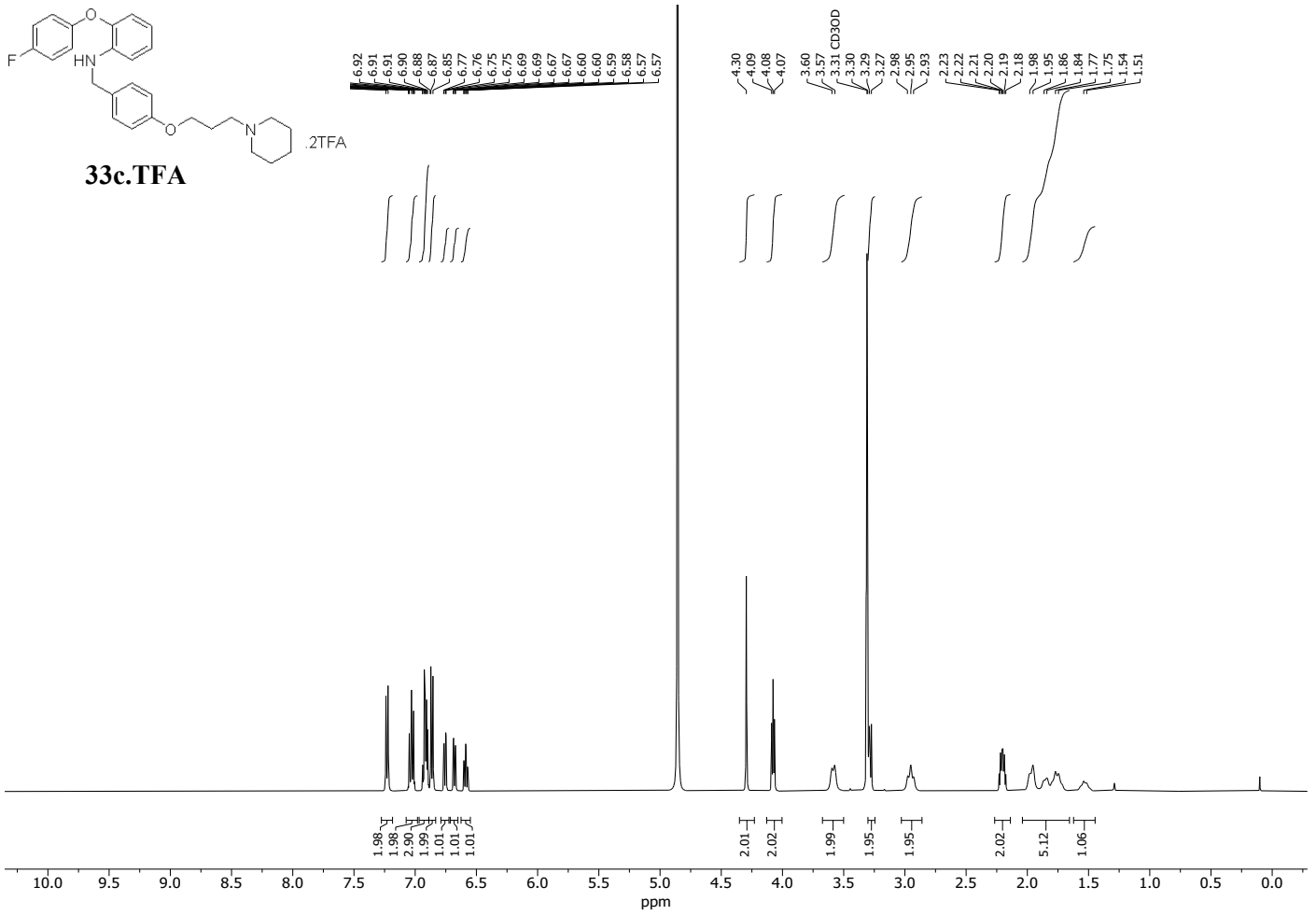


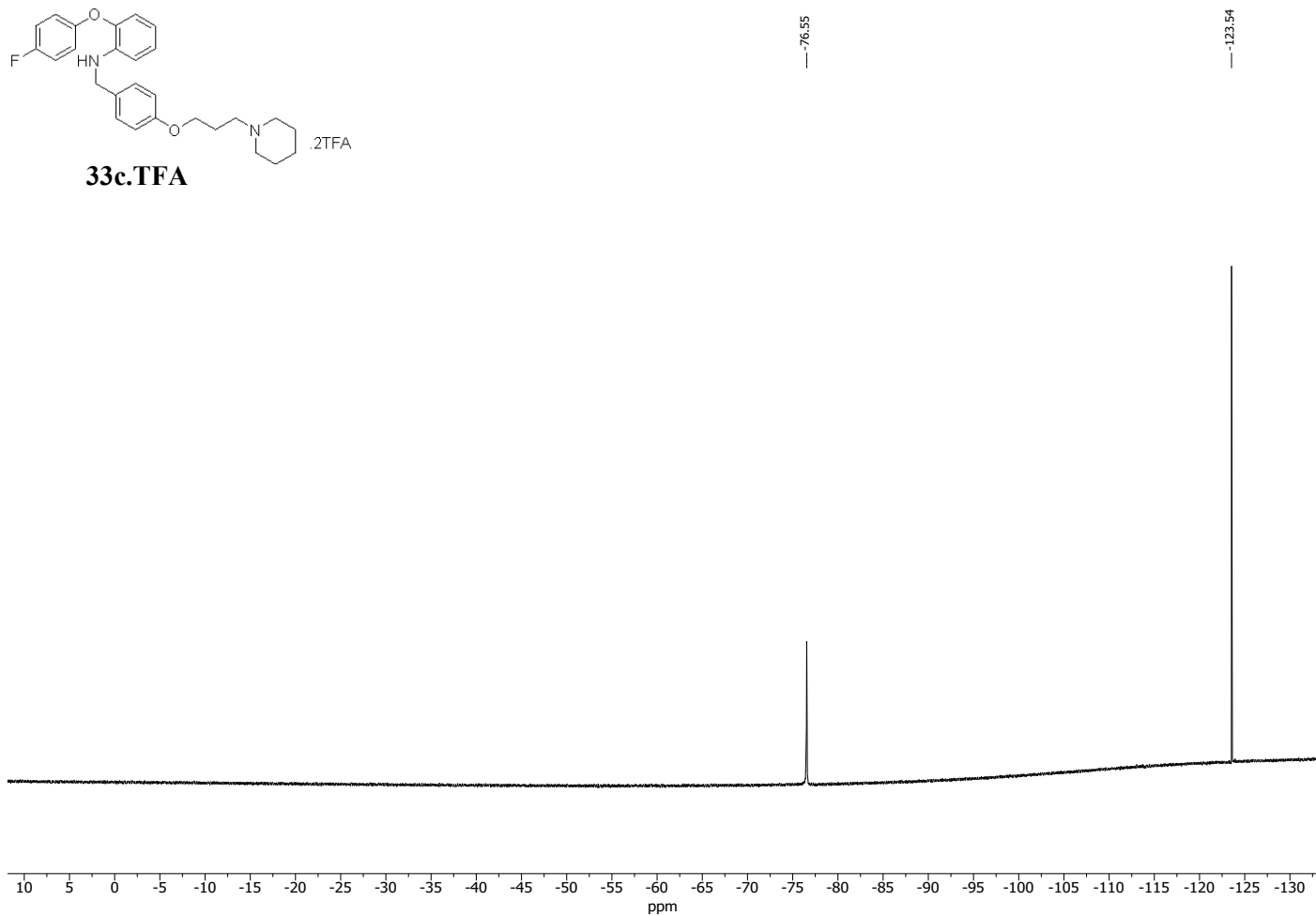
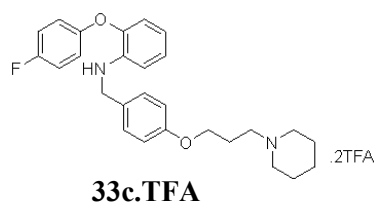


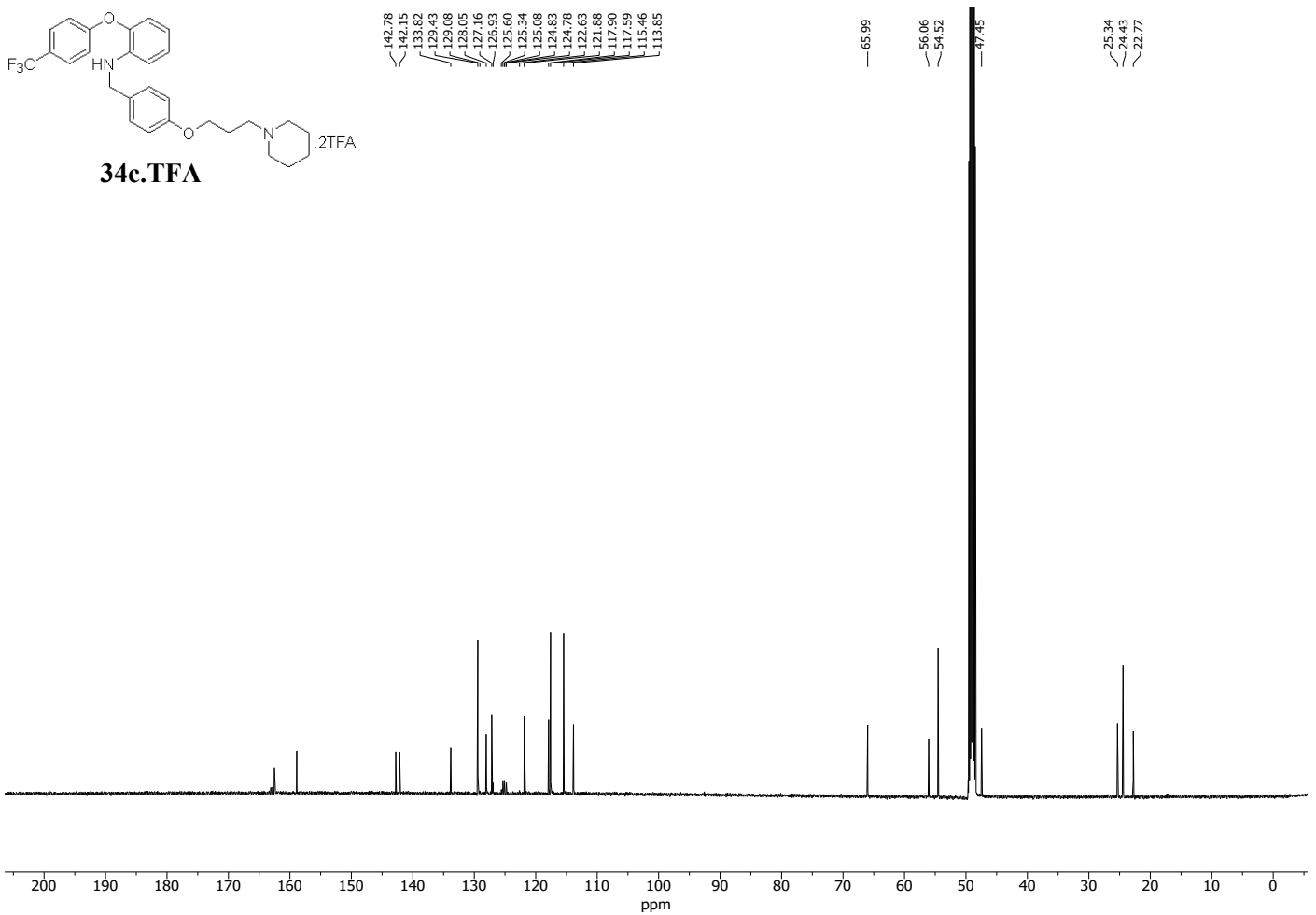
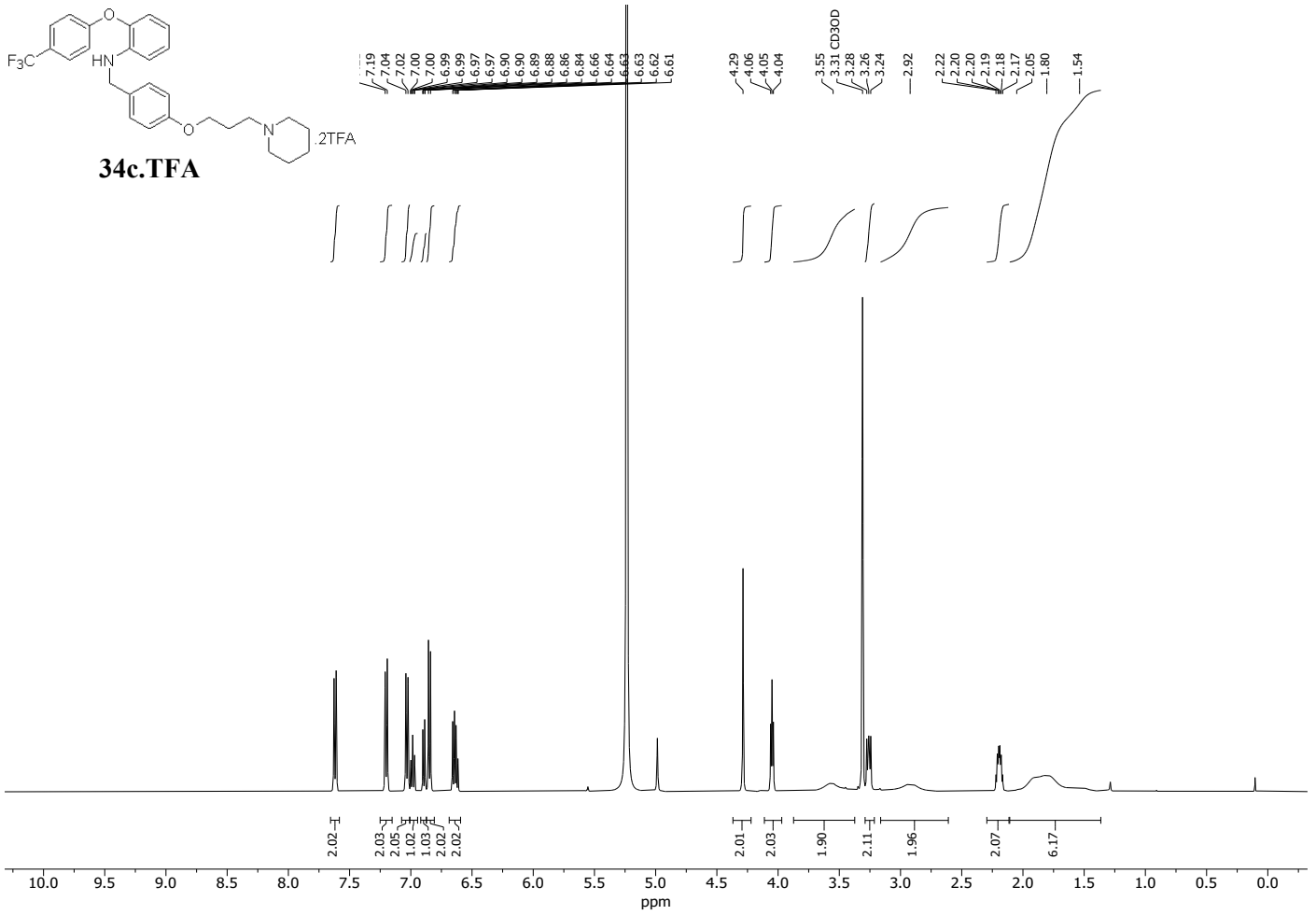
32c.TFA

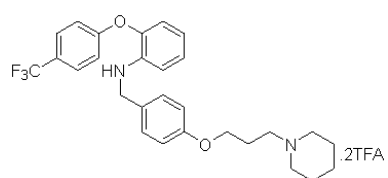
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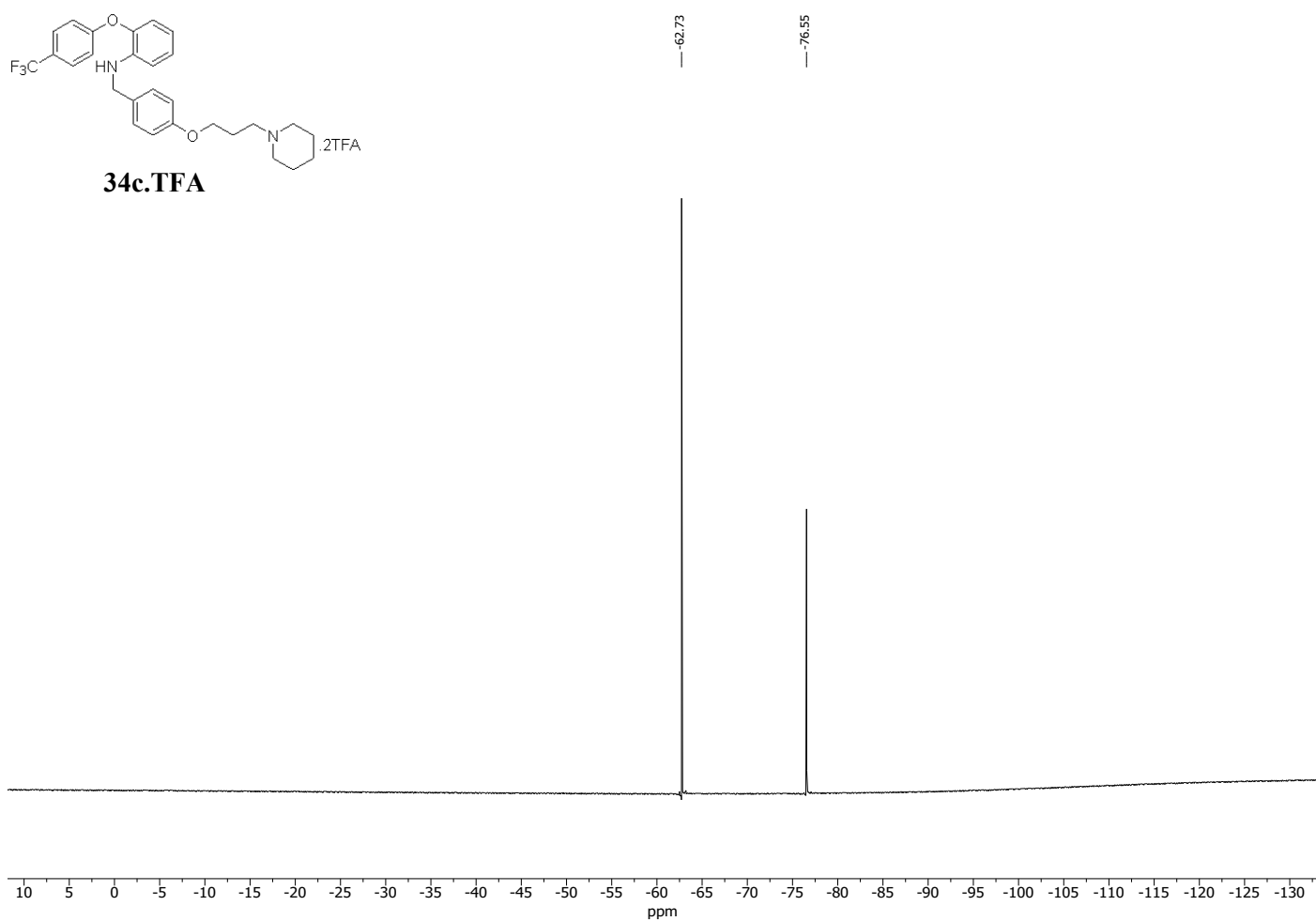


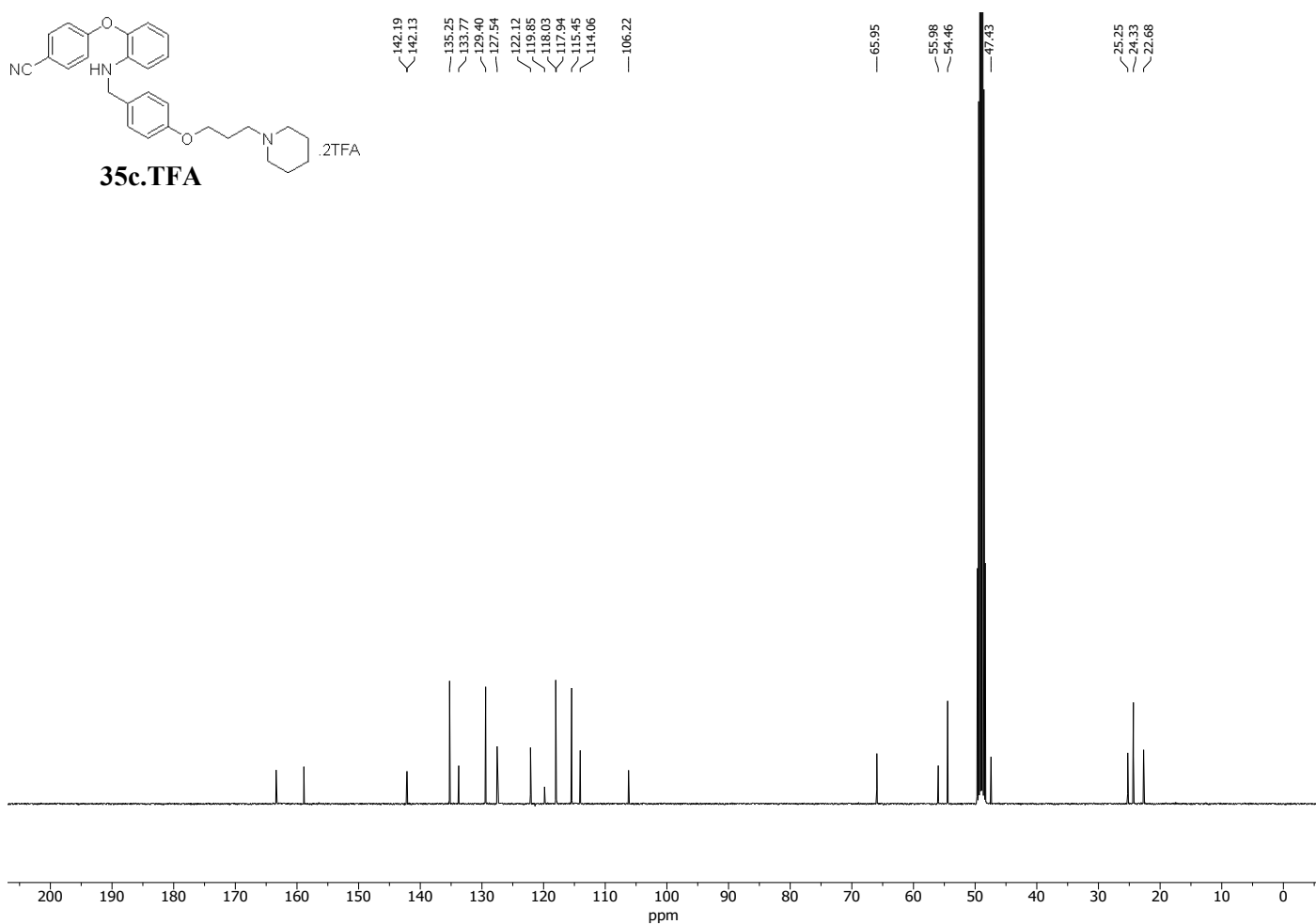
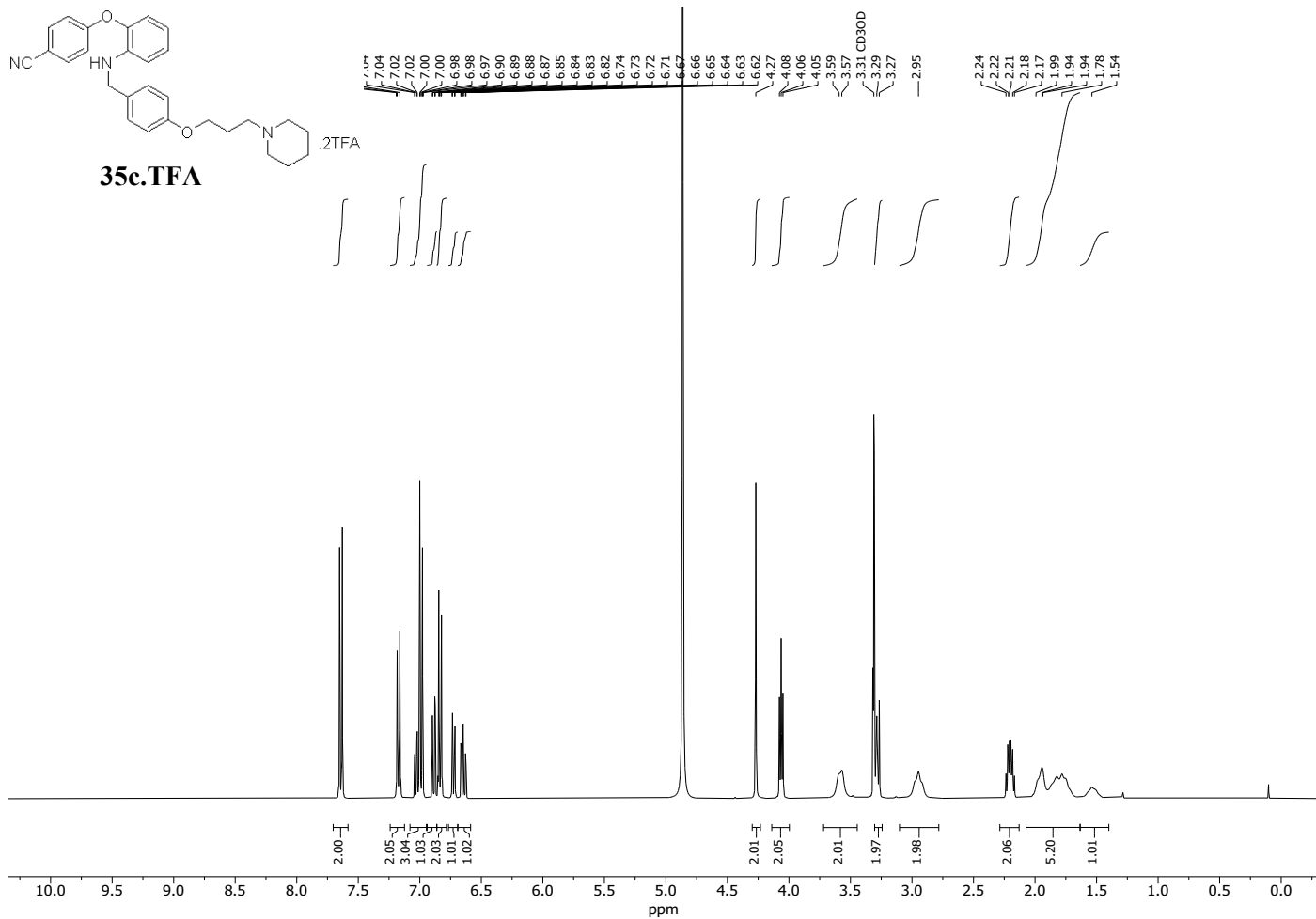


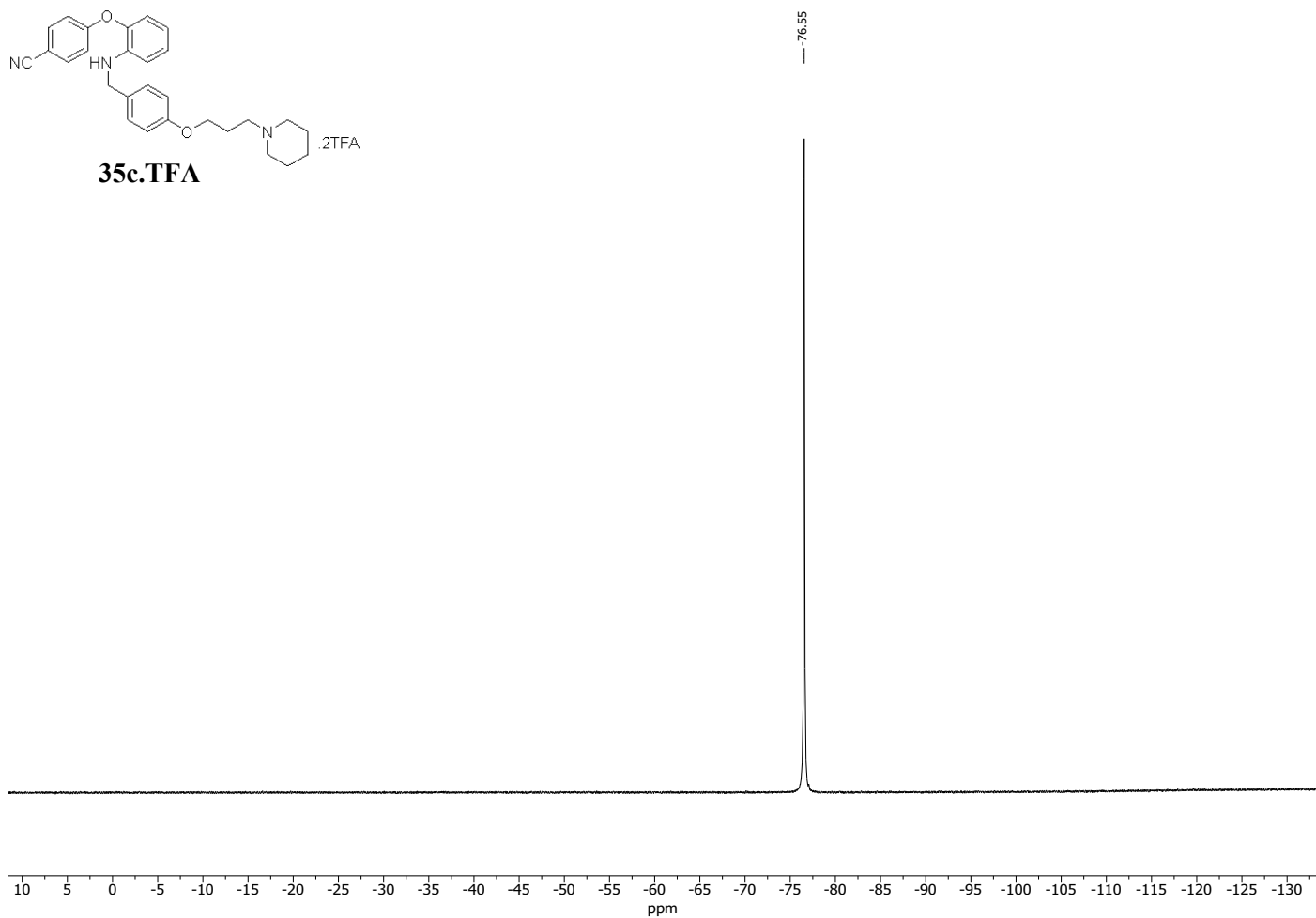
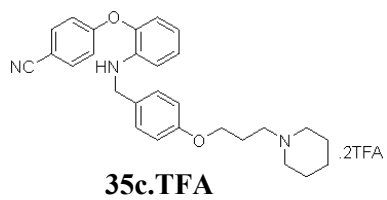


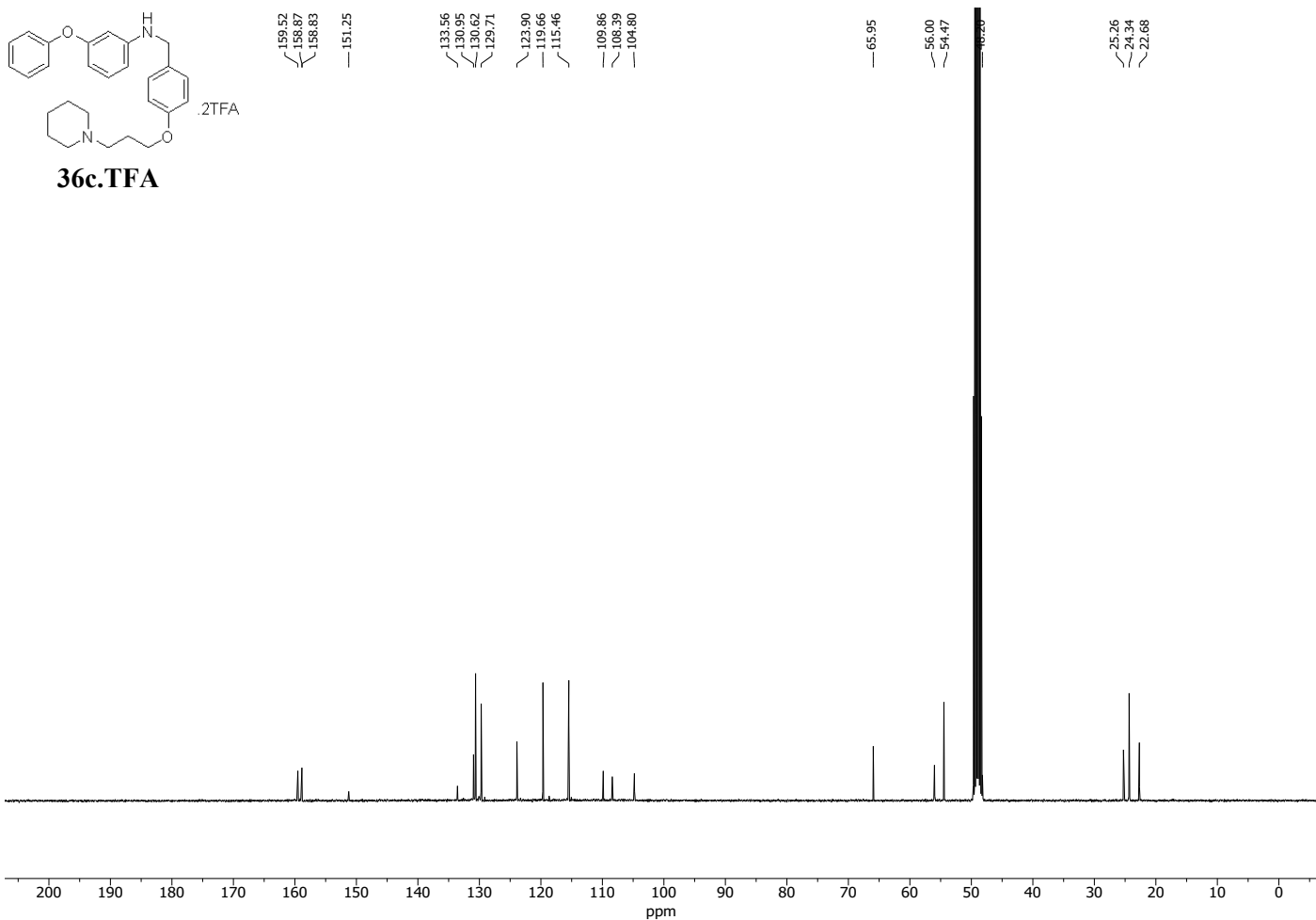
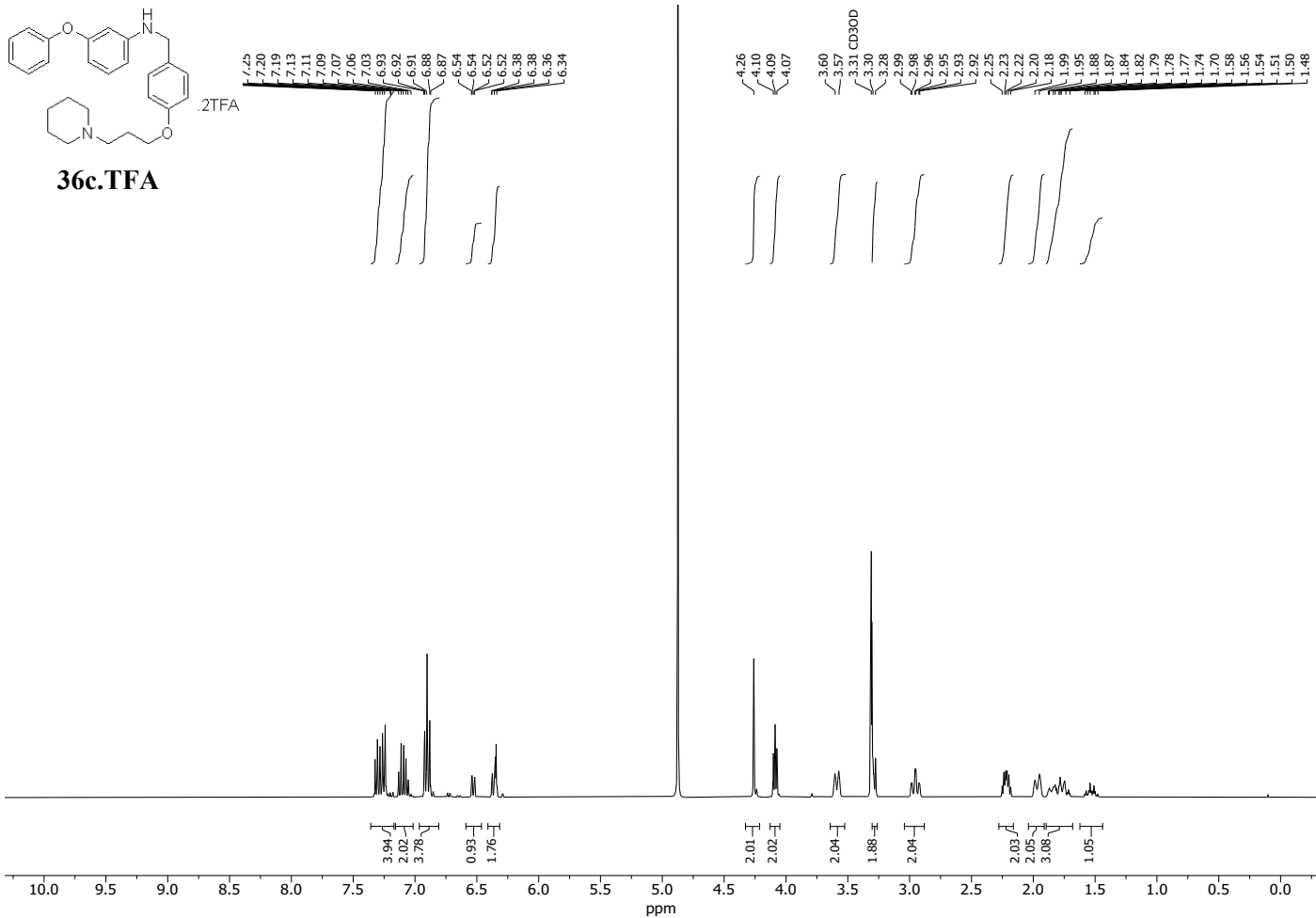


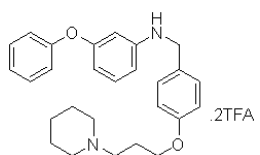
34c.TFA





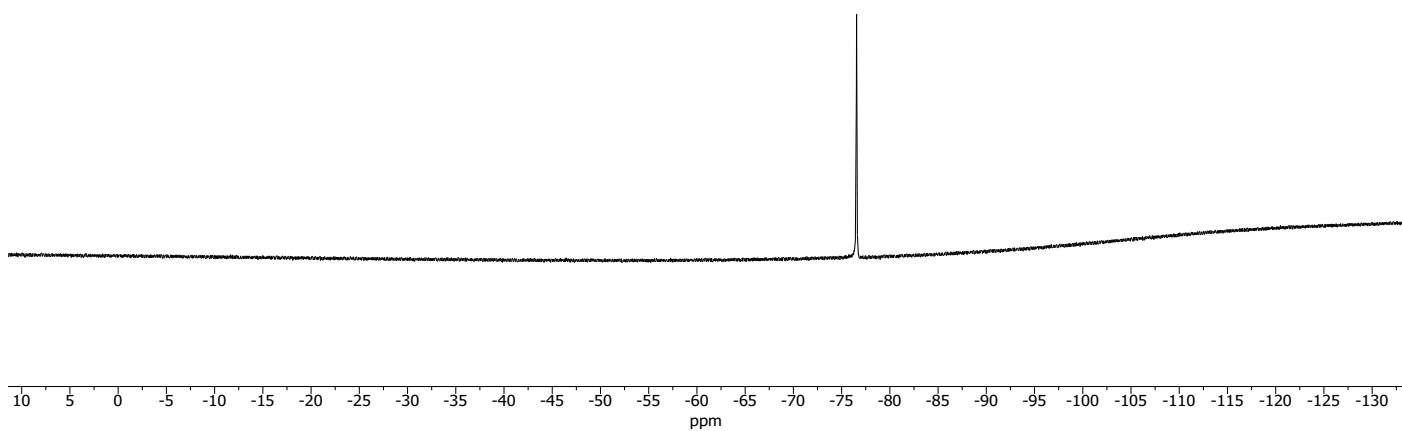


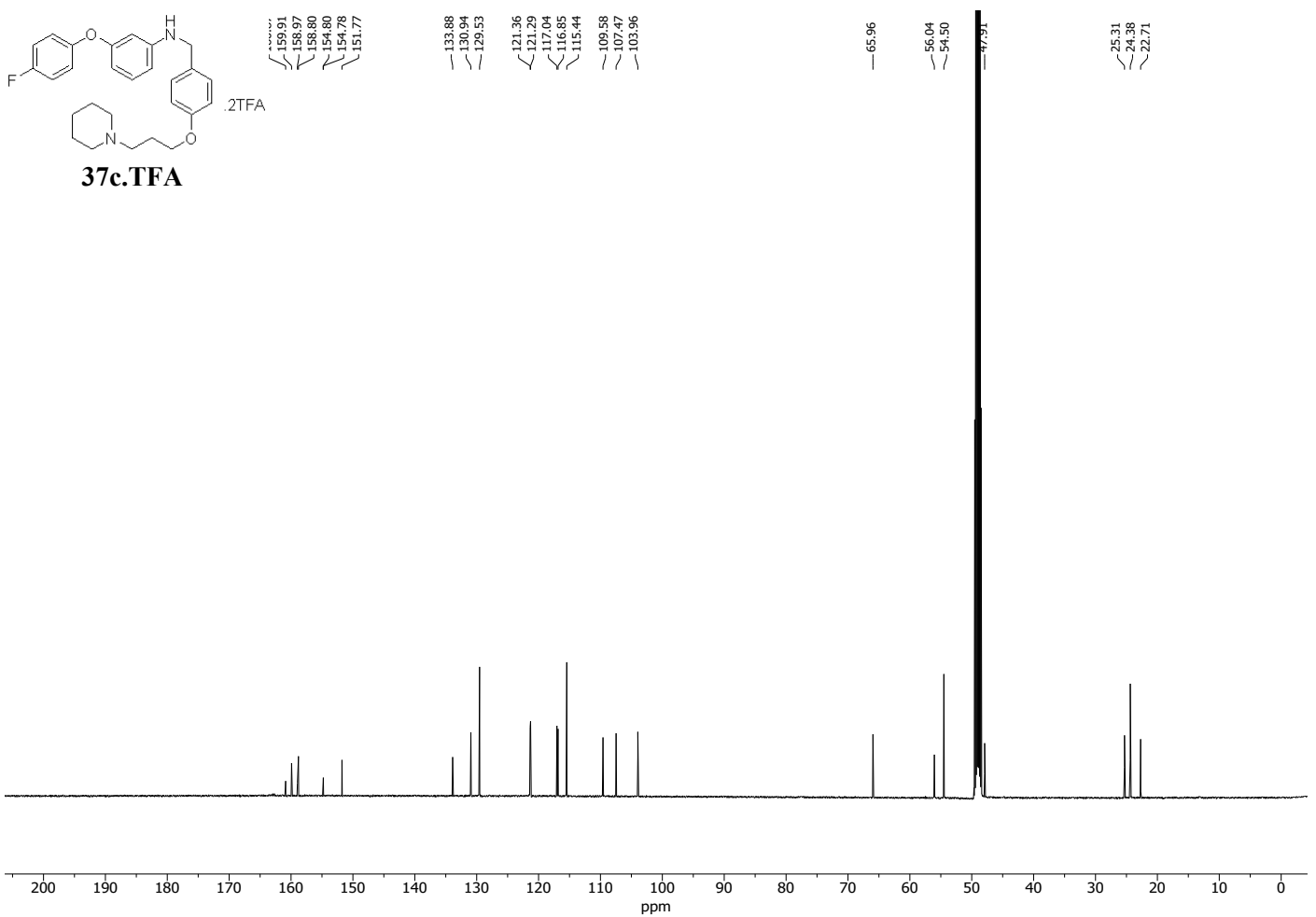
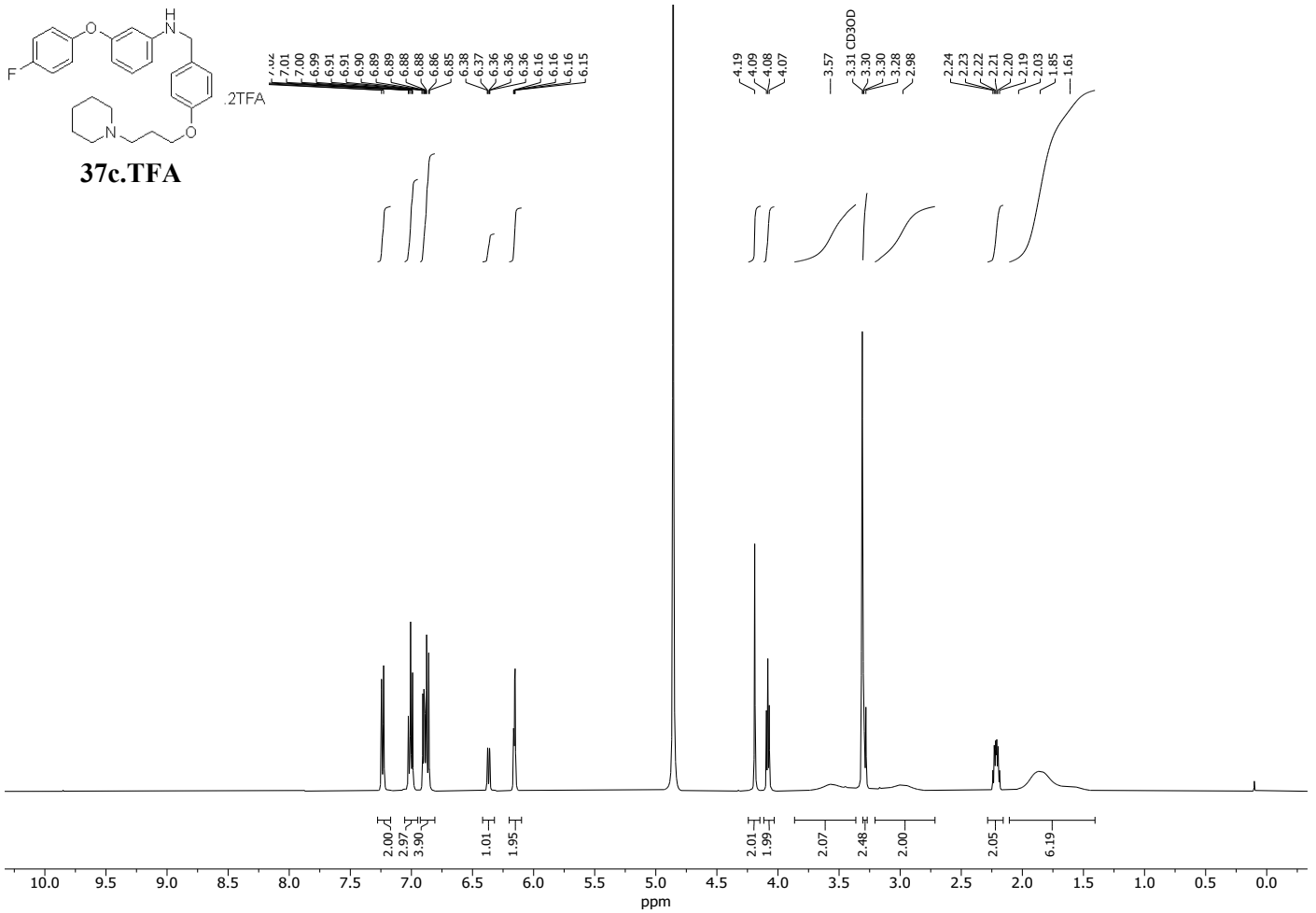


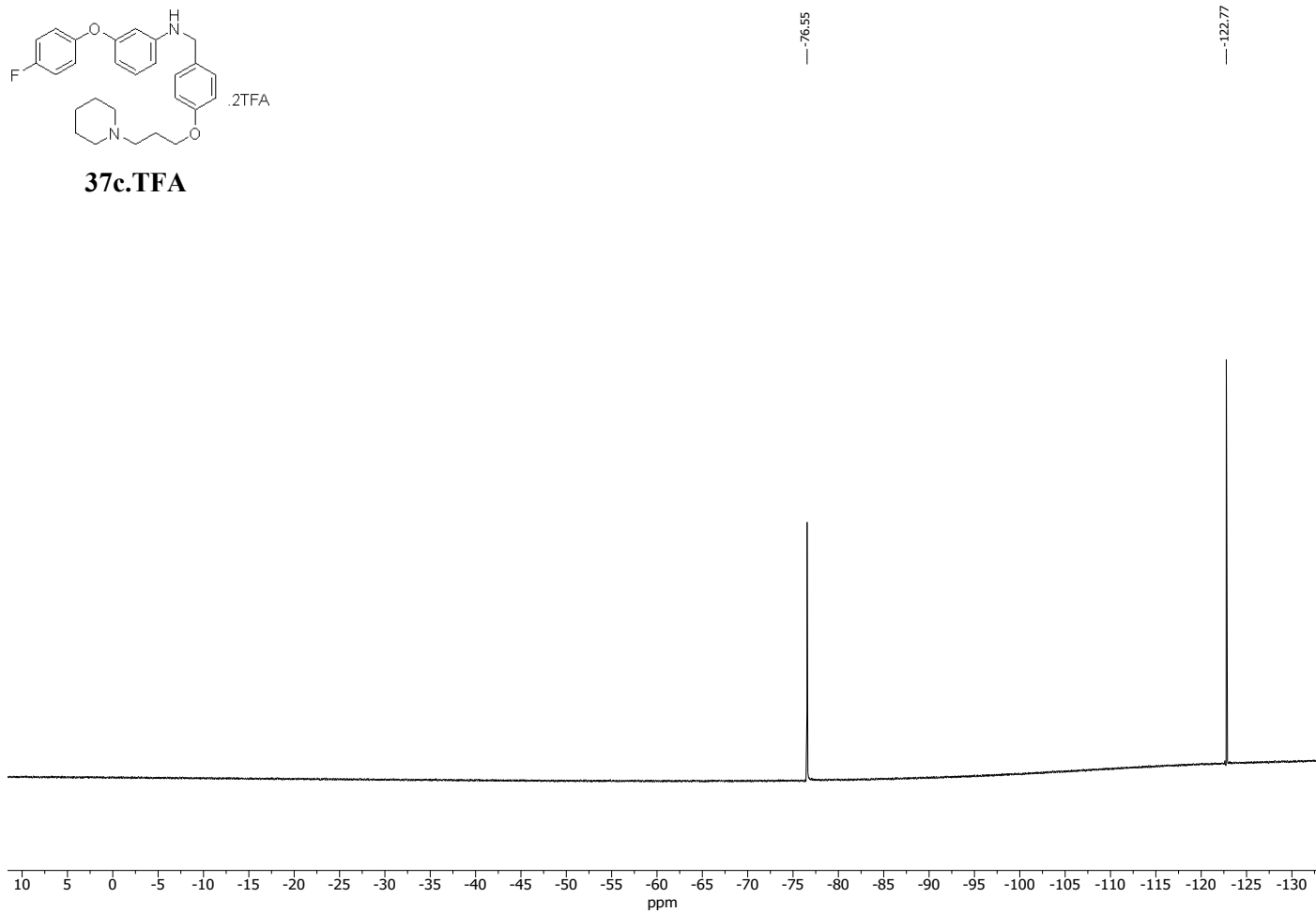
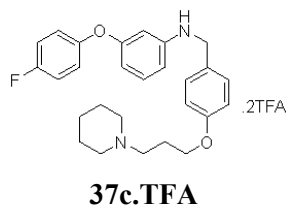


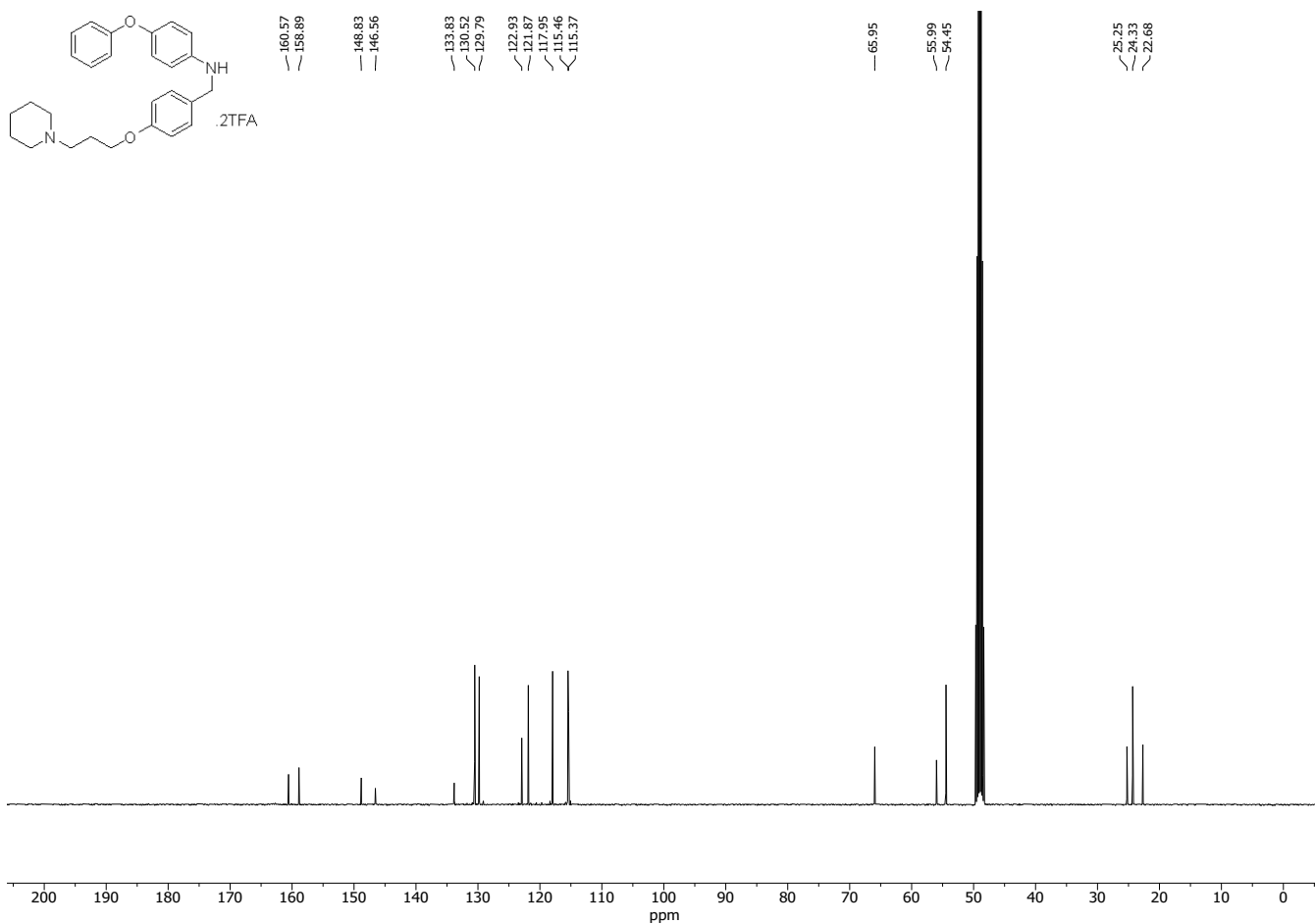
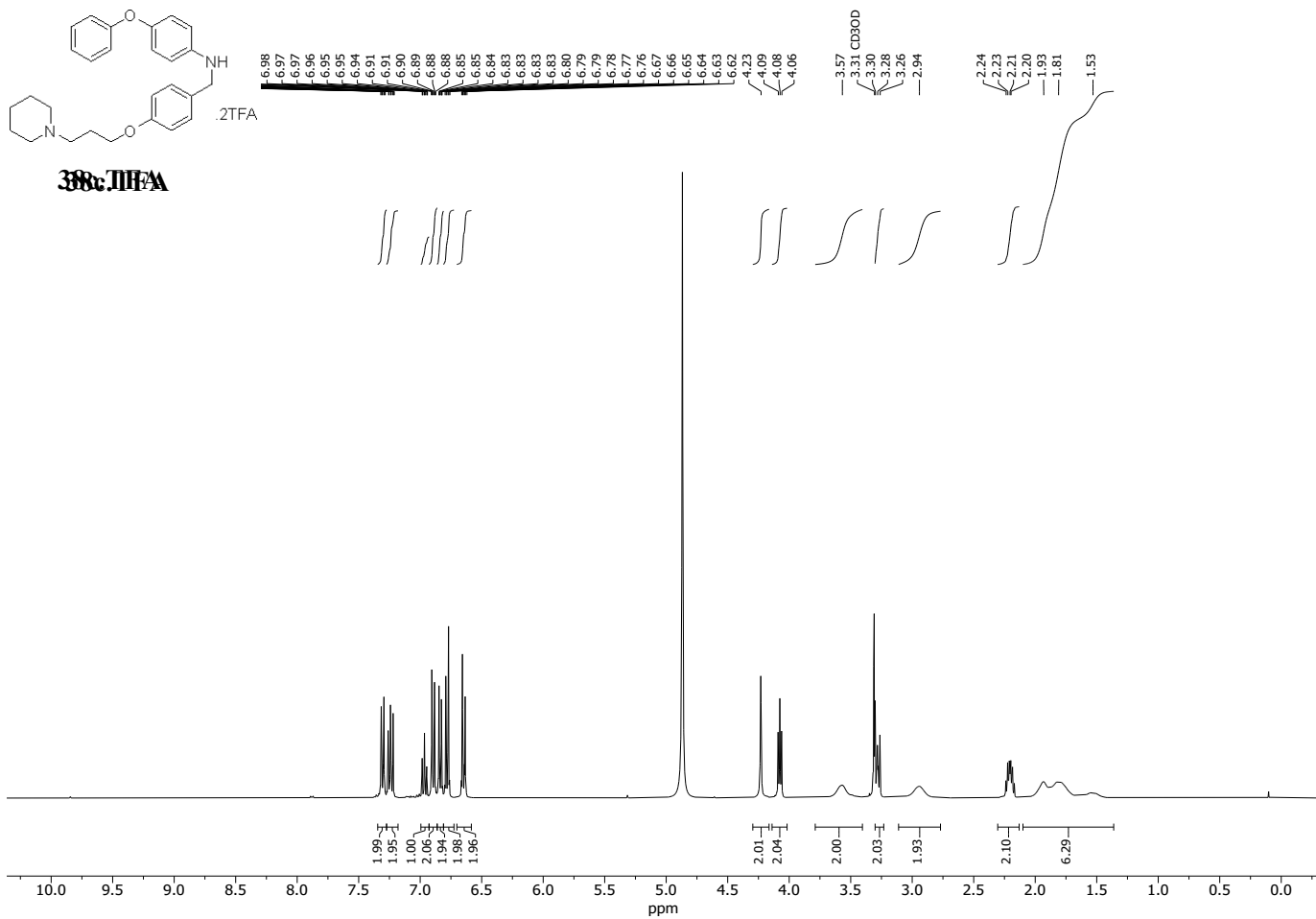
36c.TFA

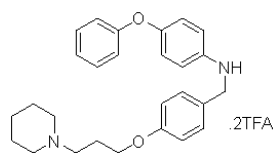
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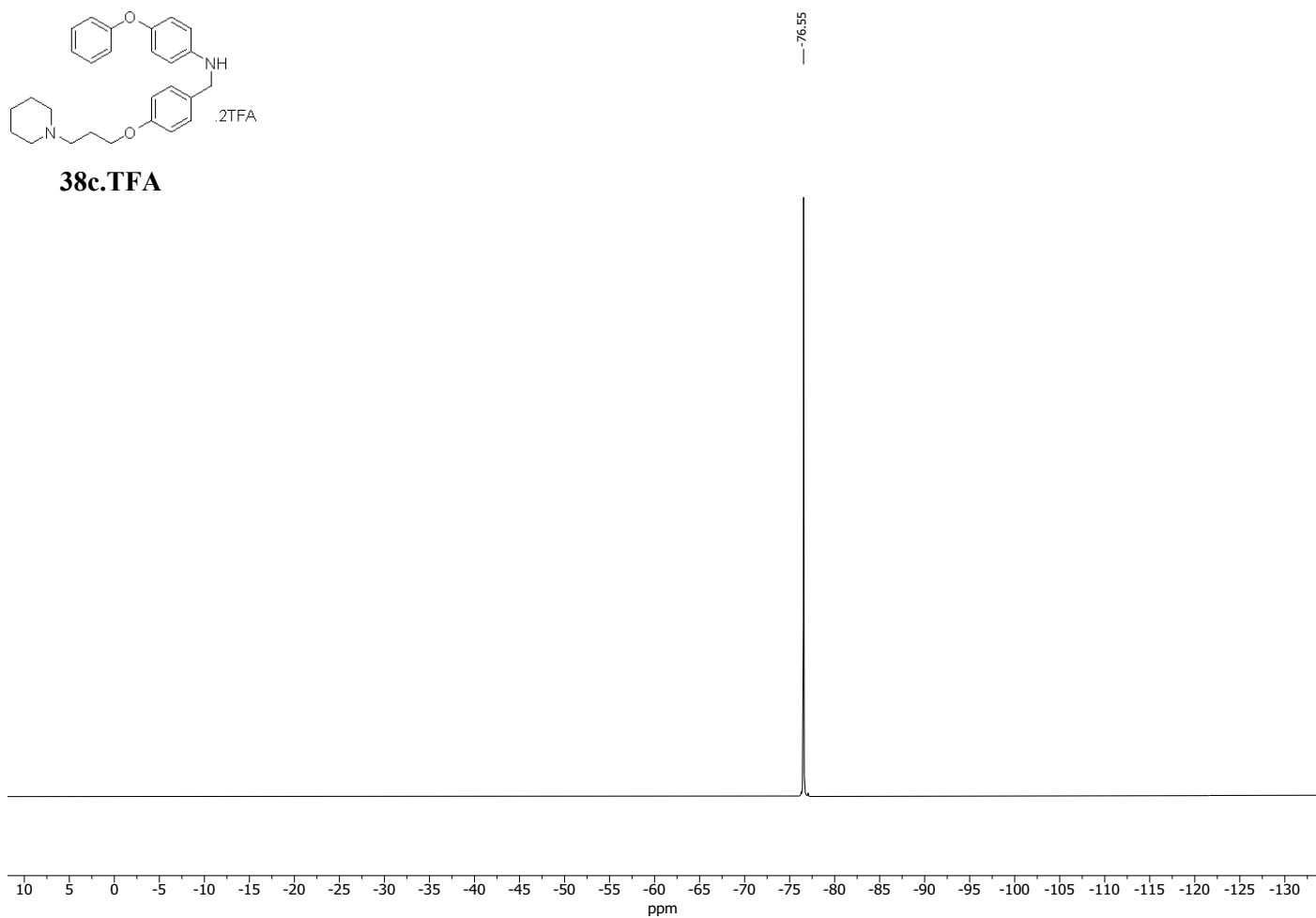


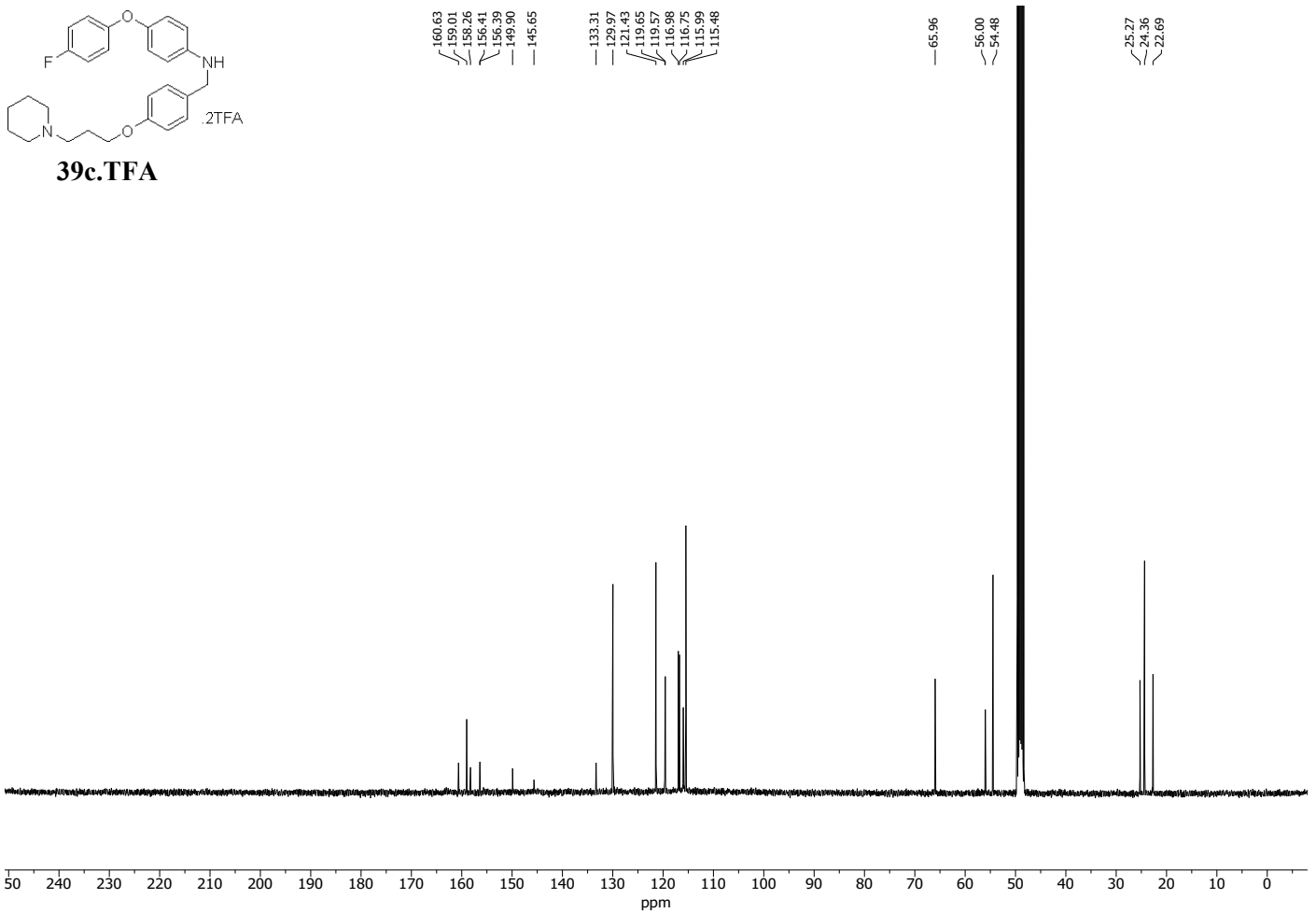
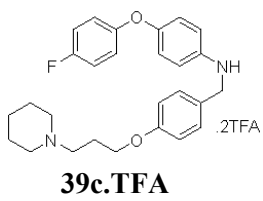
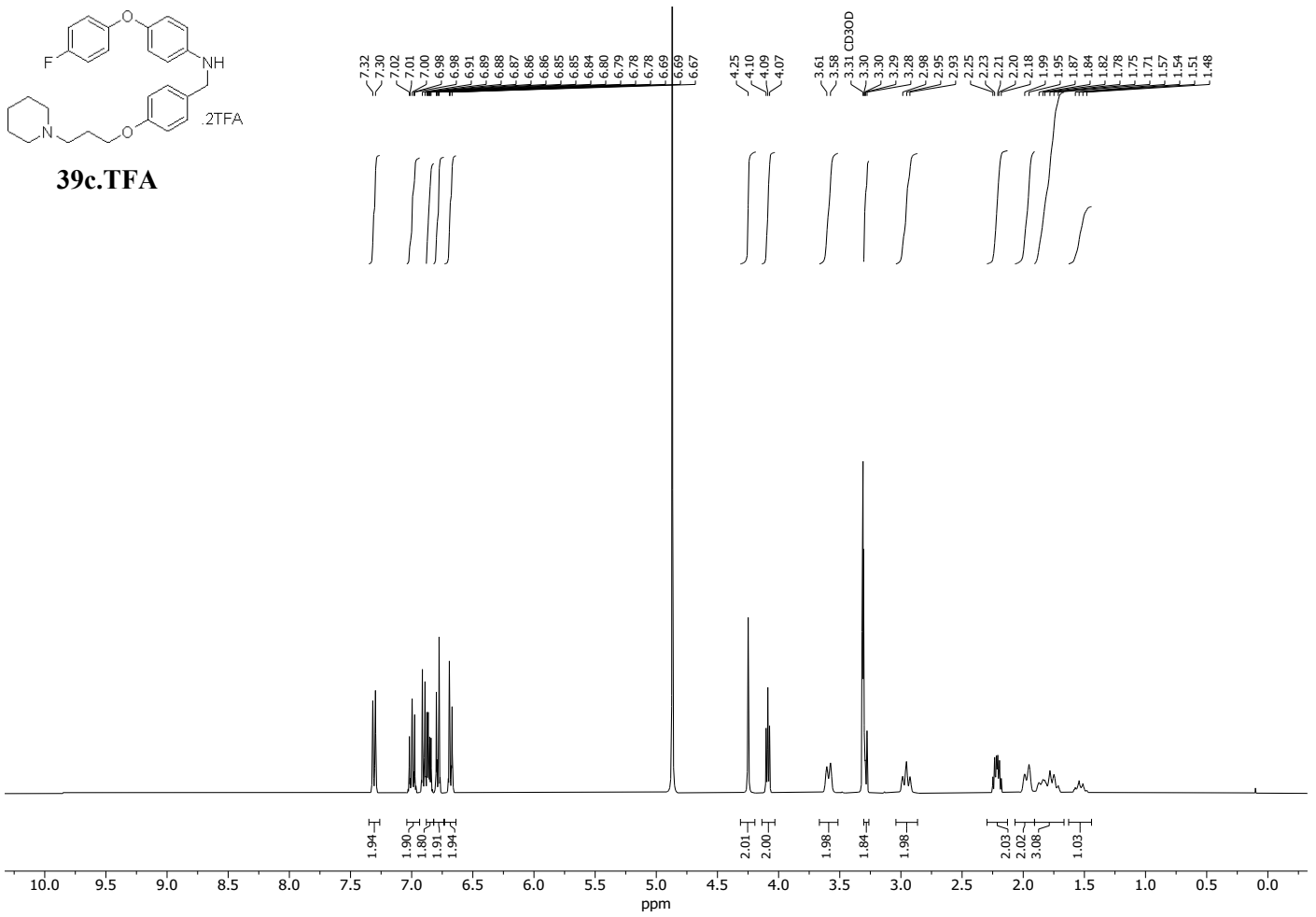
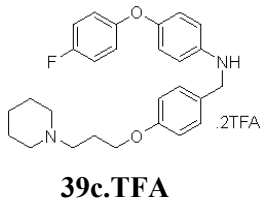


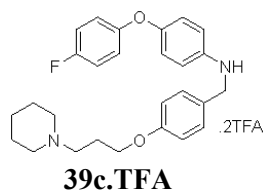




38c.TFA

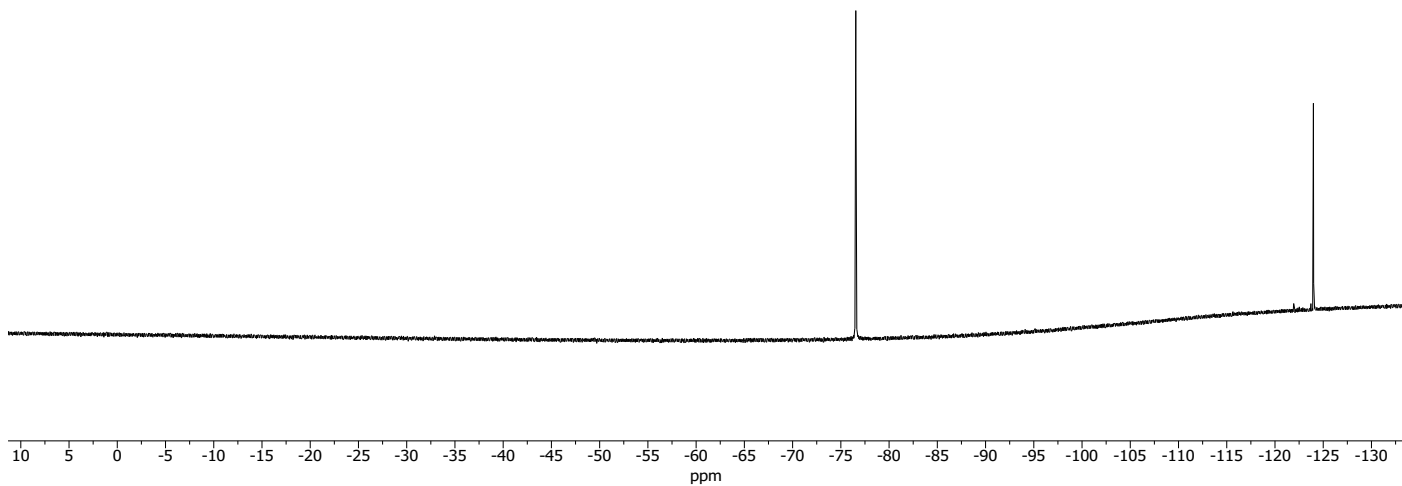


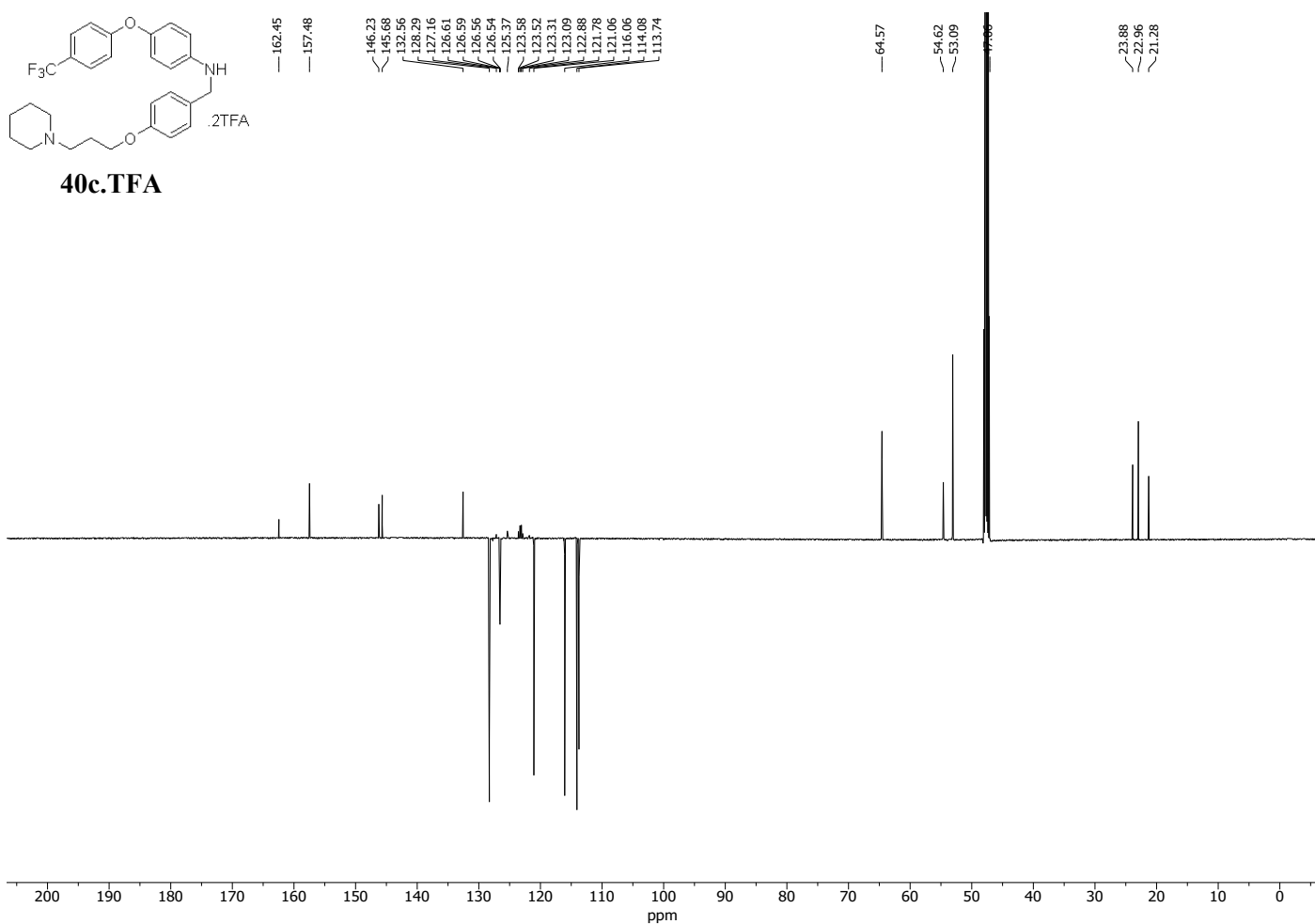
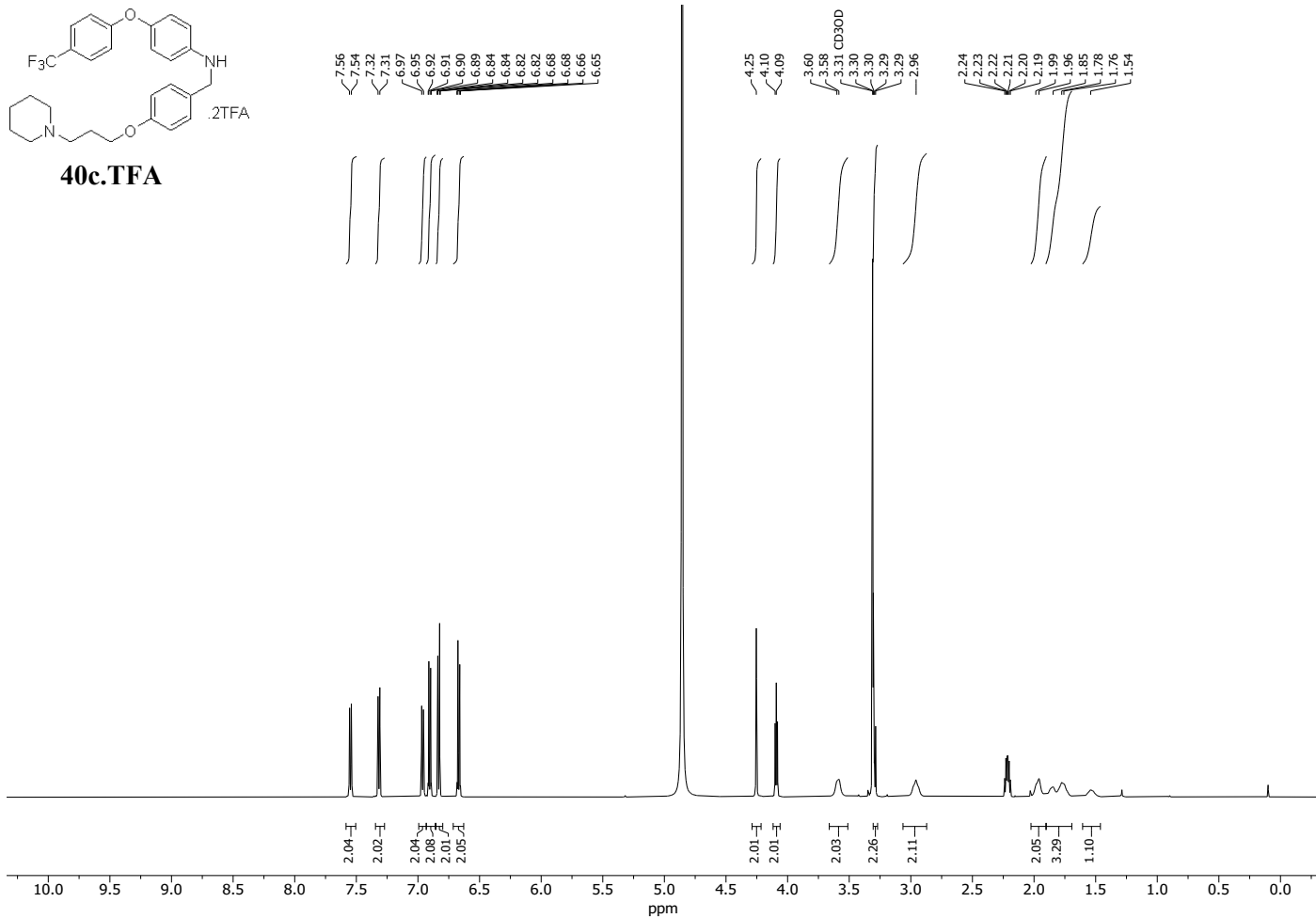


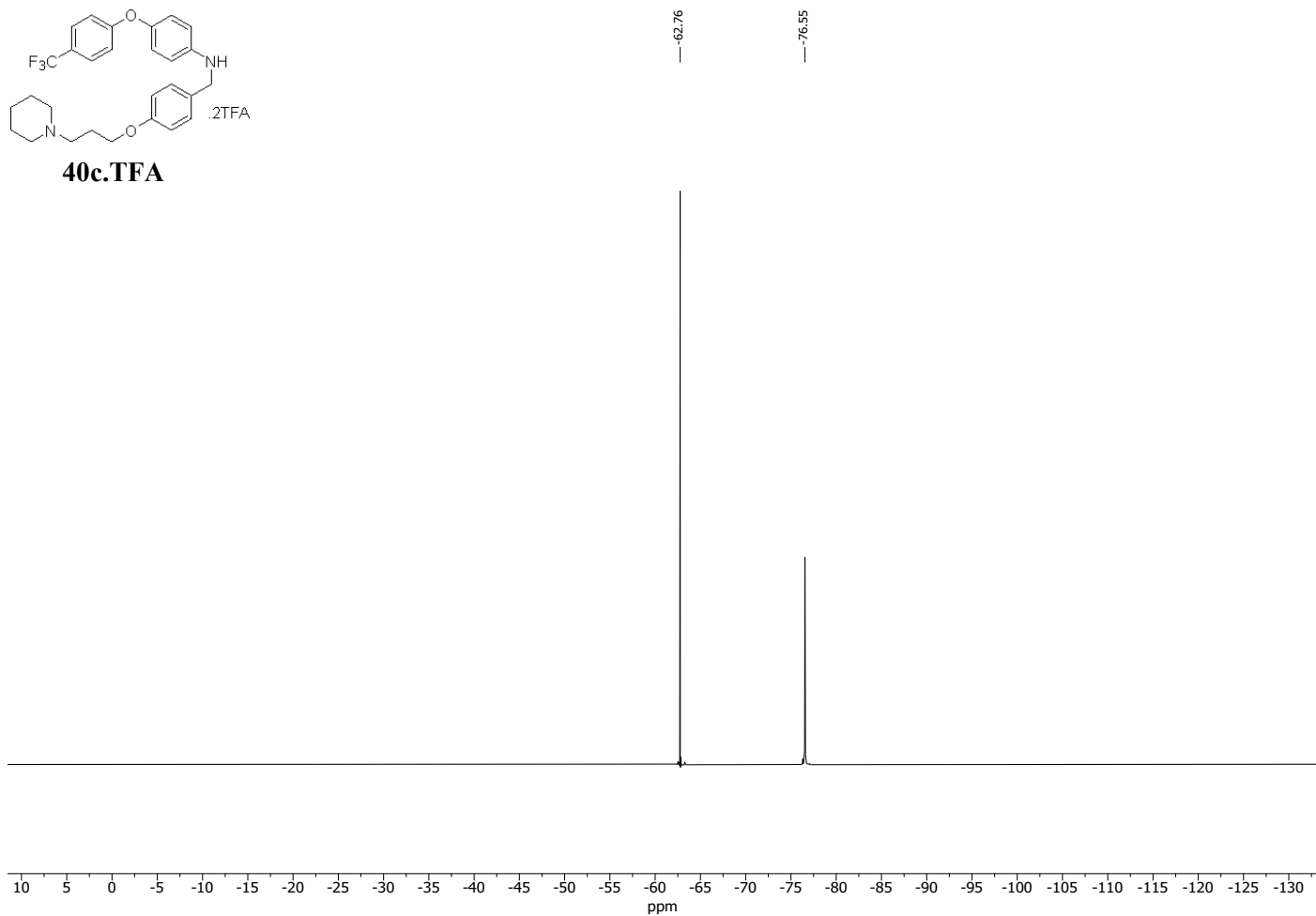
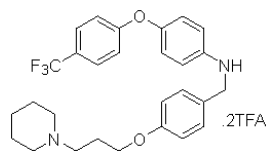


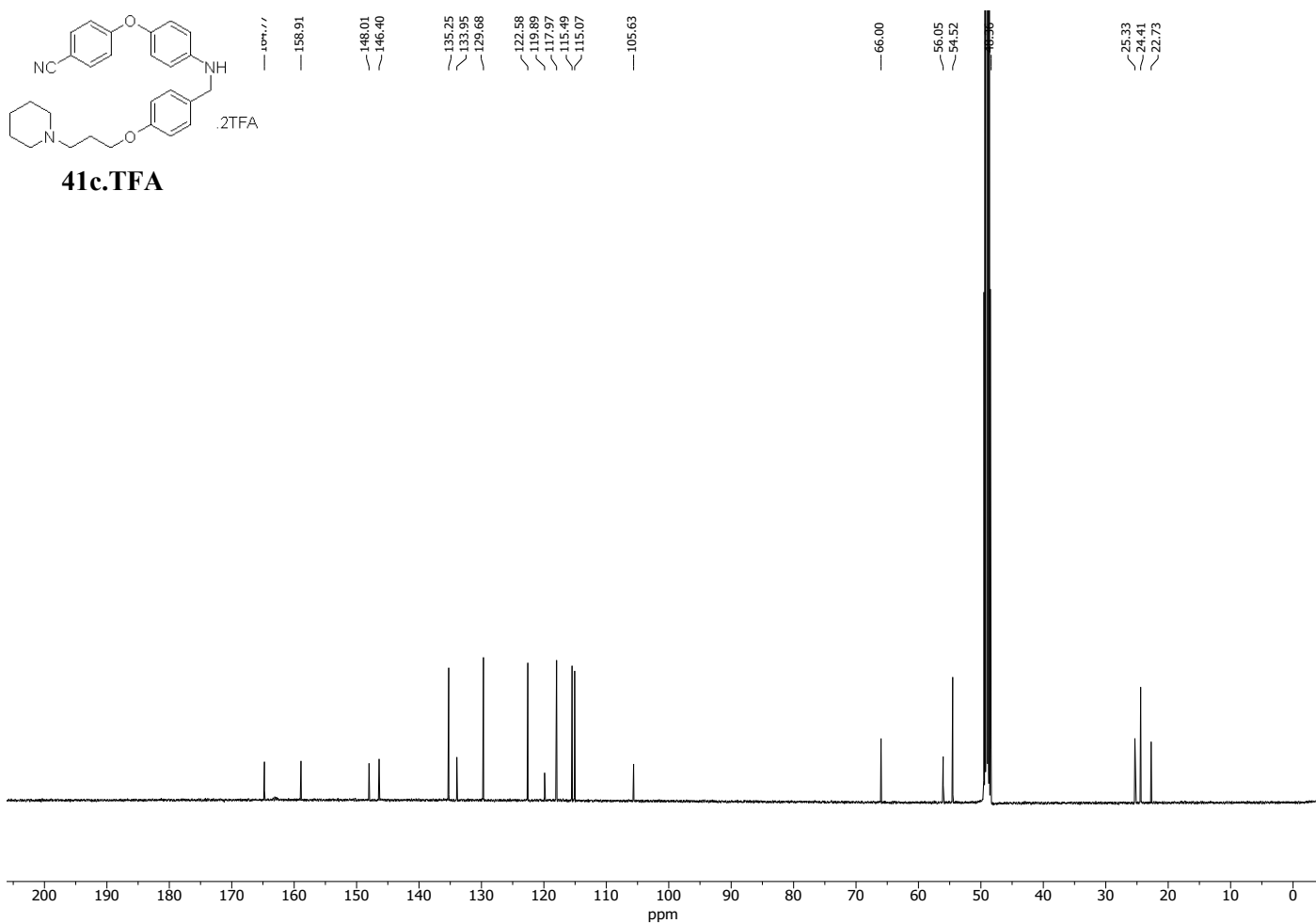
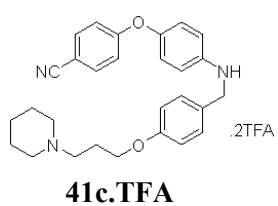
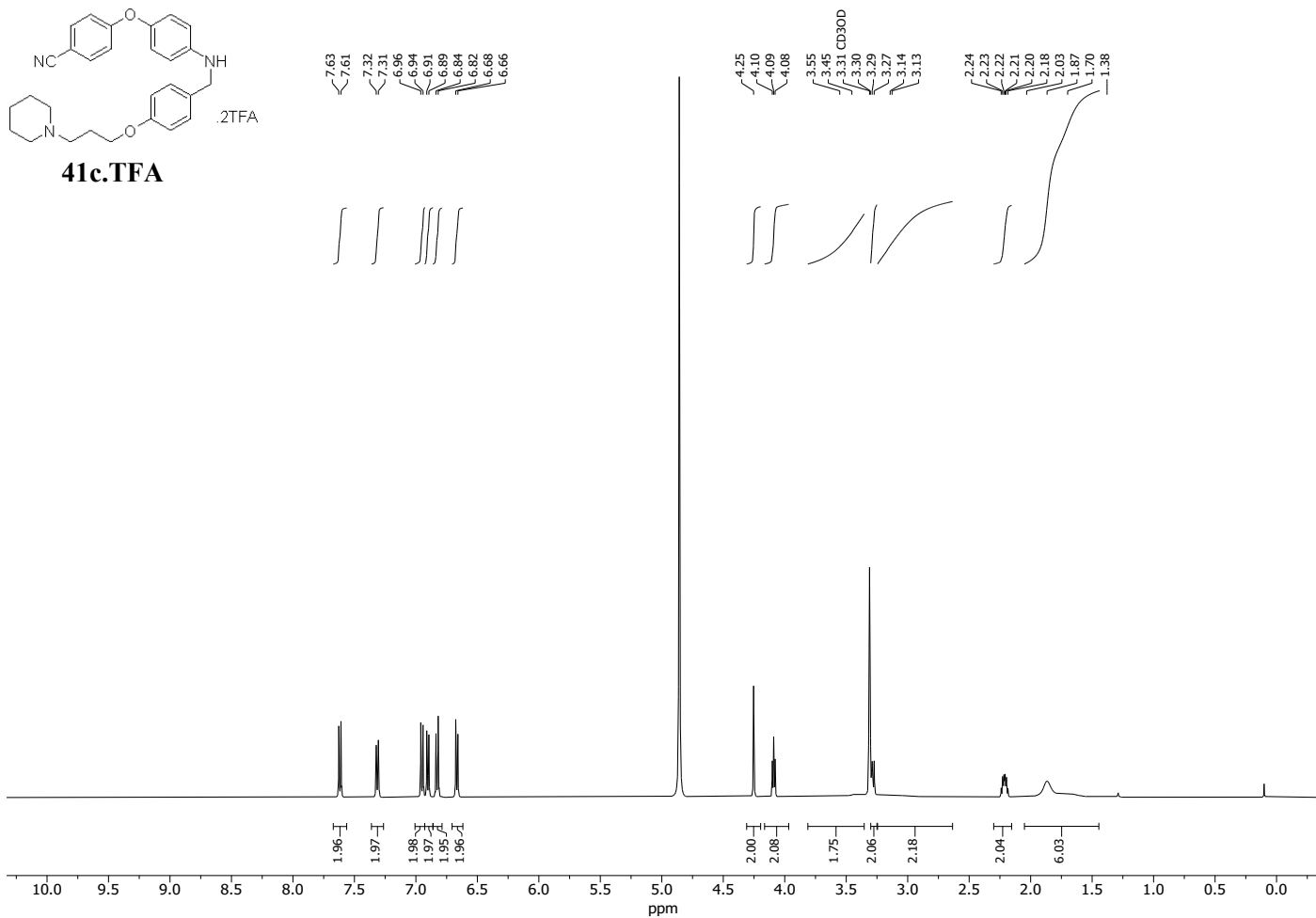
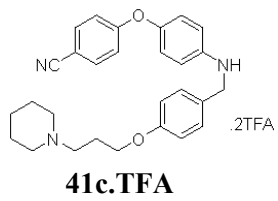
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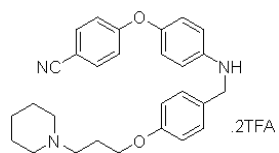
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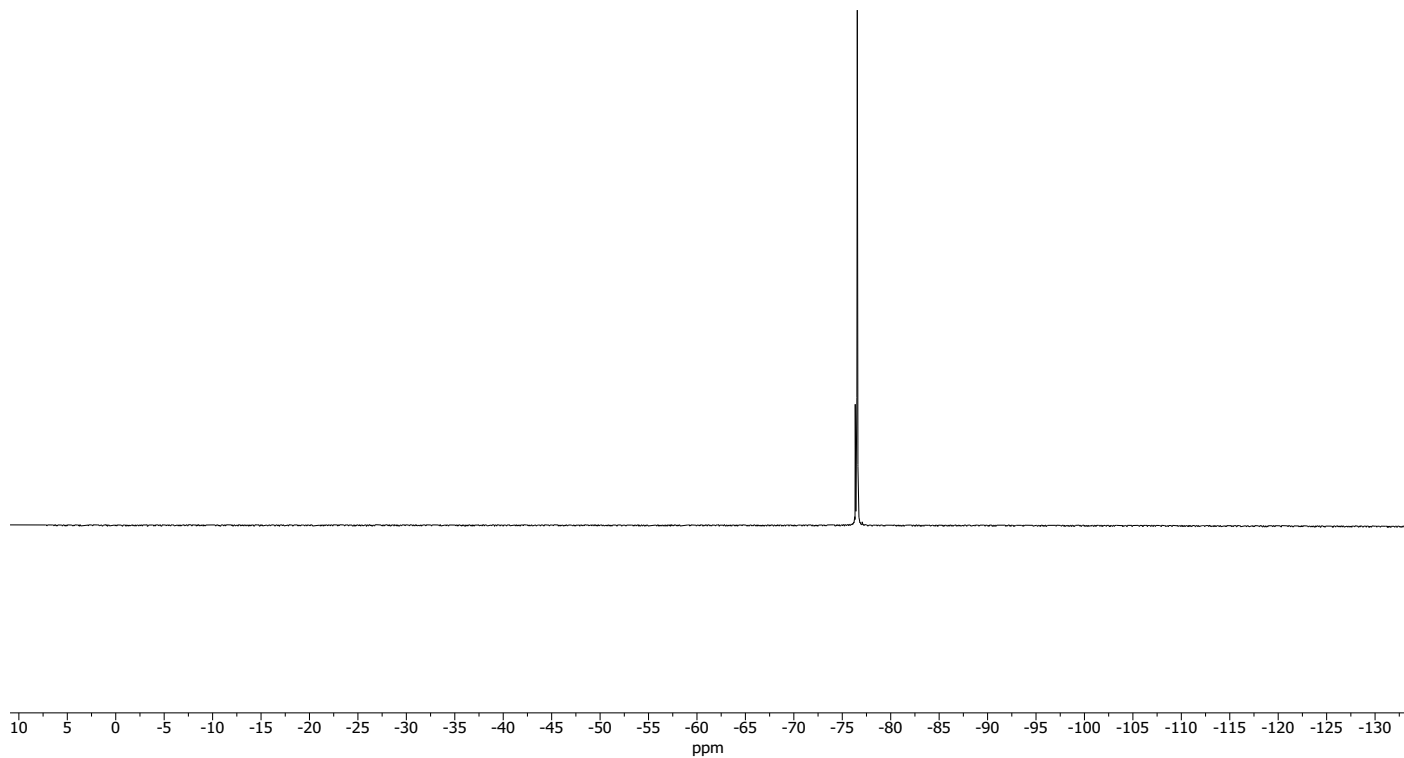


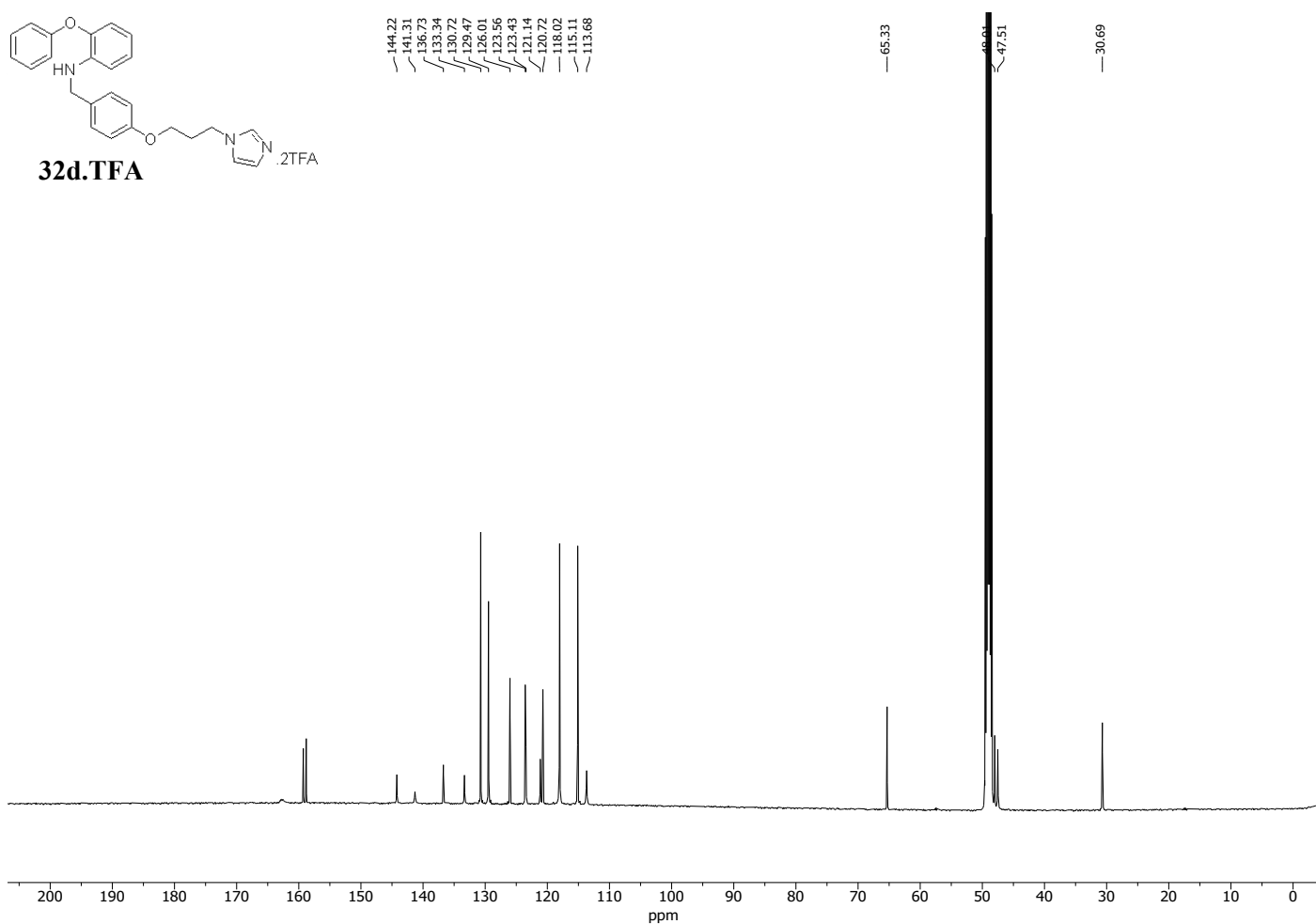
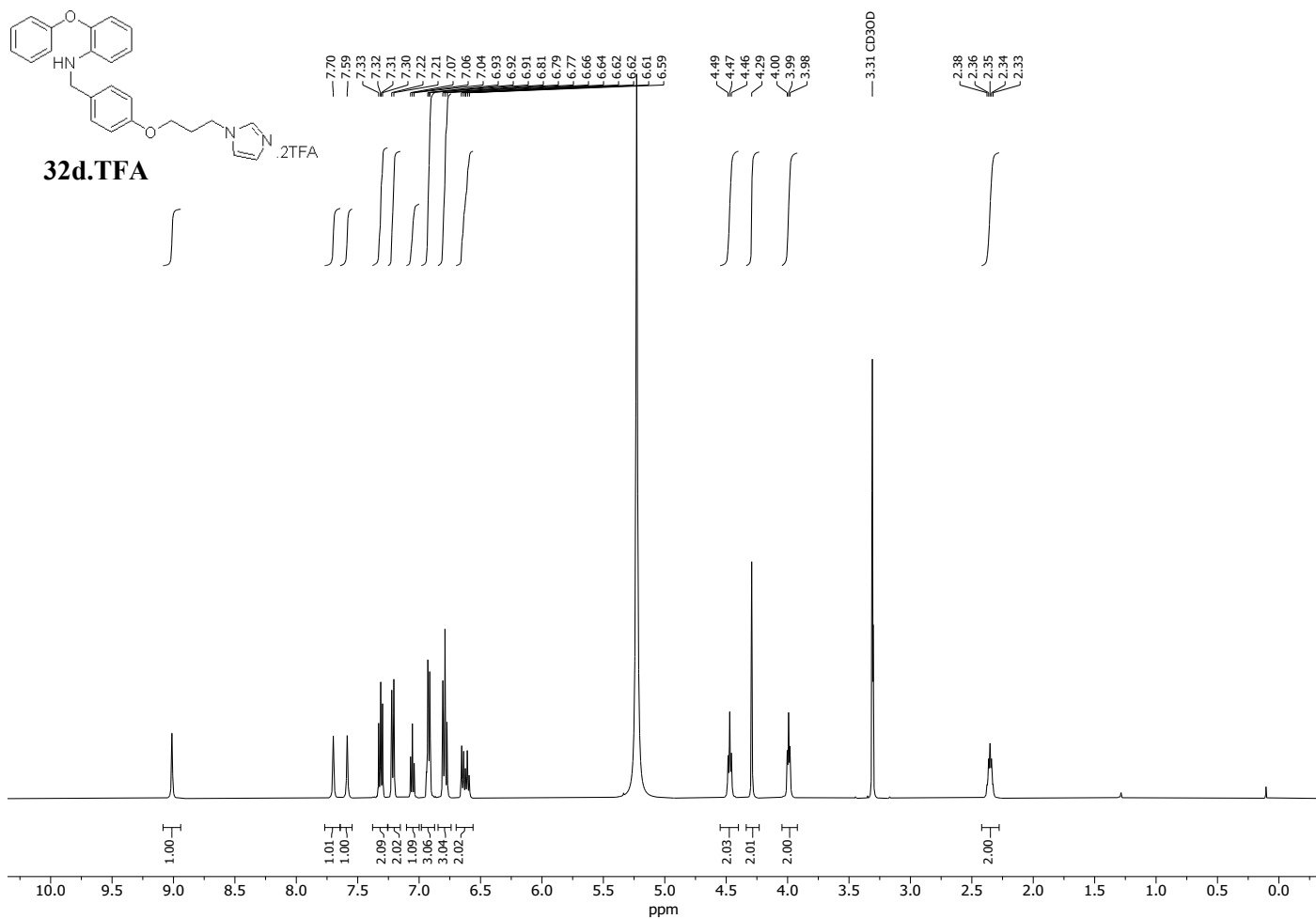


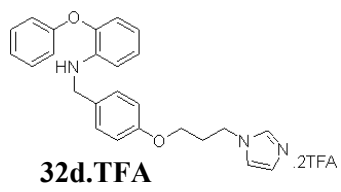




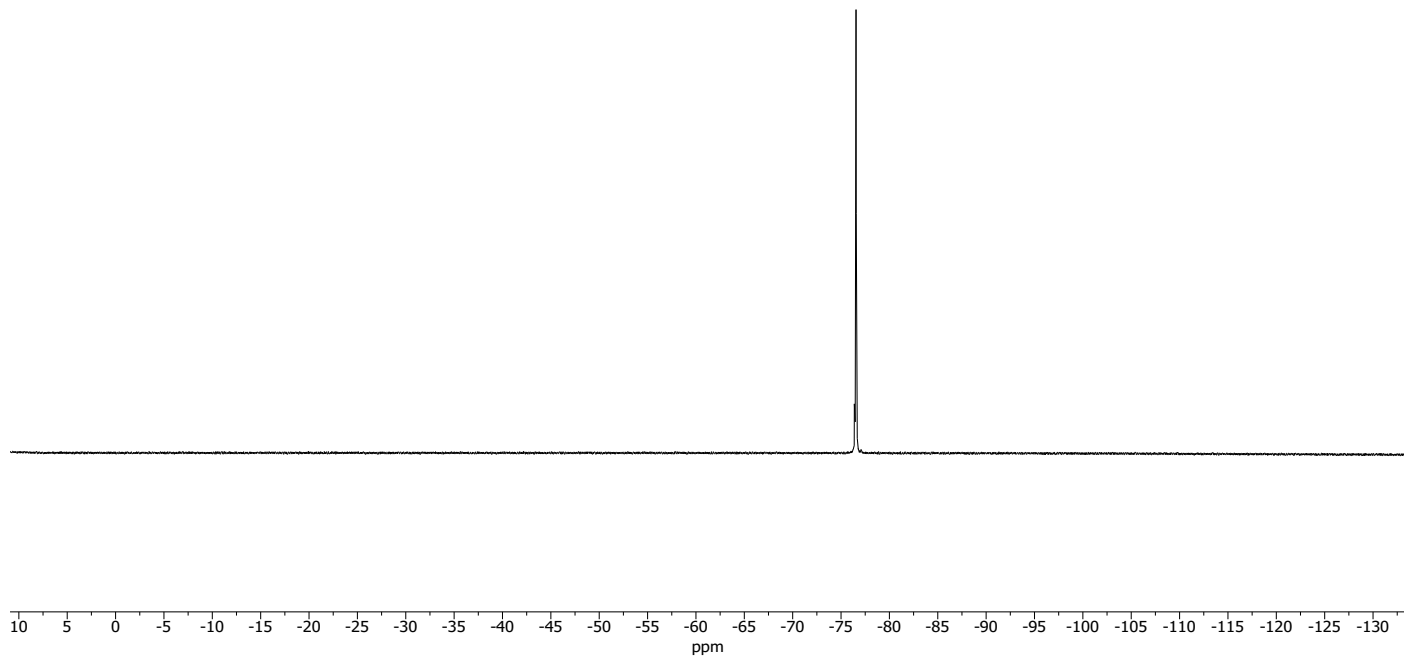
41c.TFA

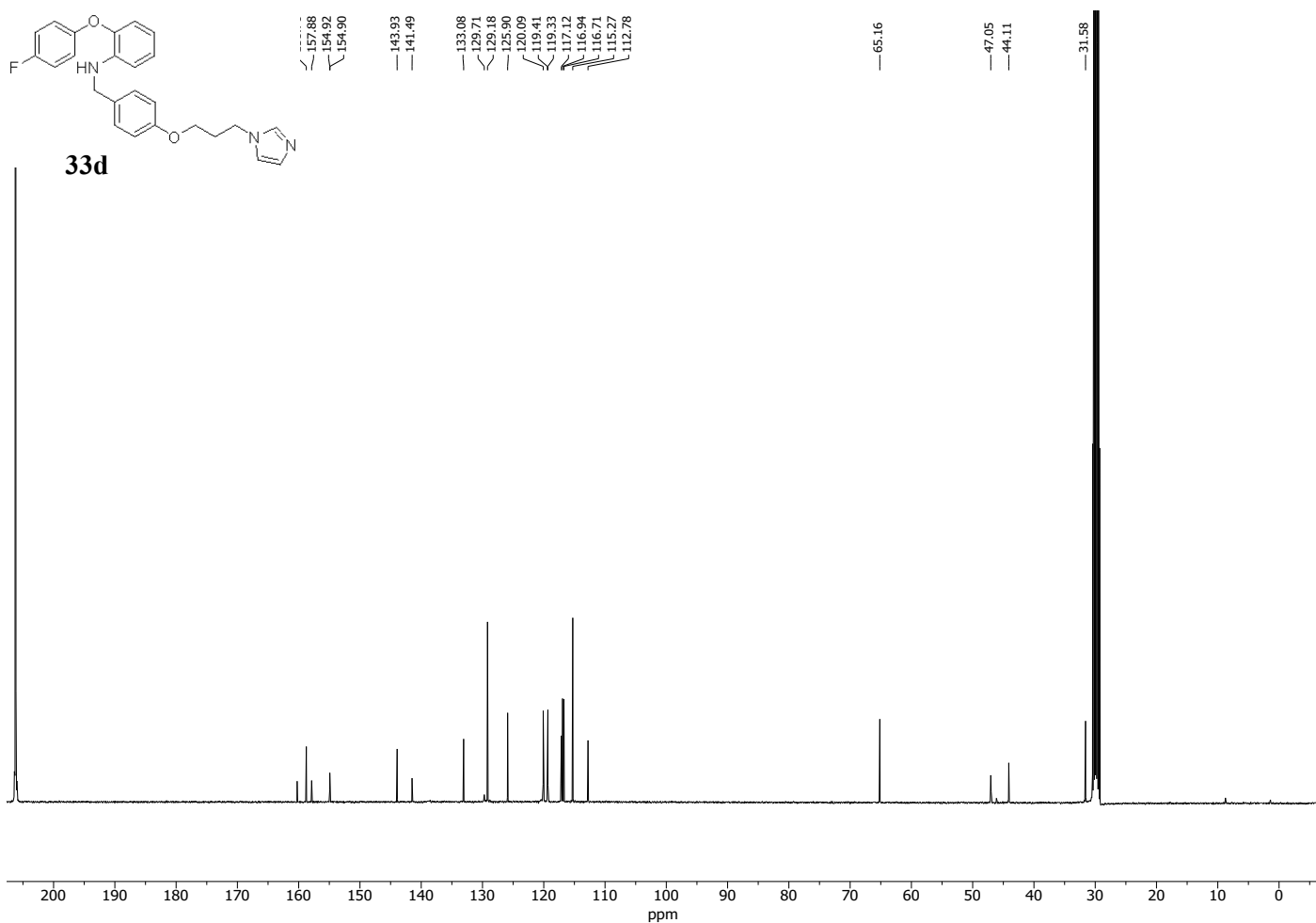
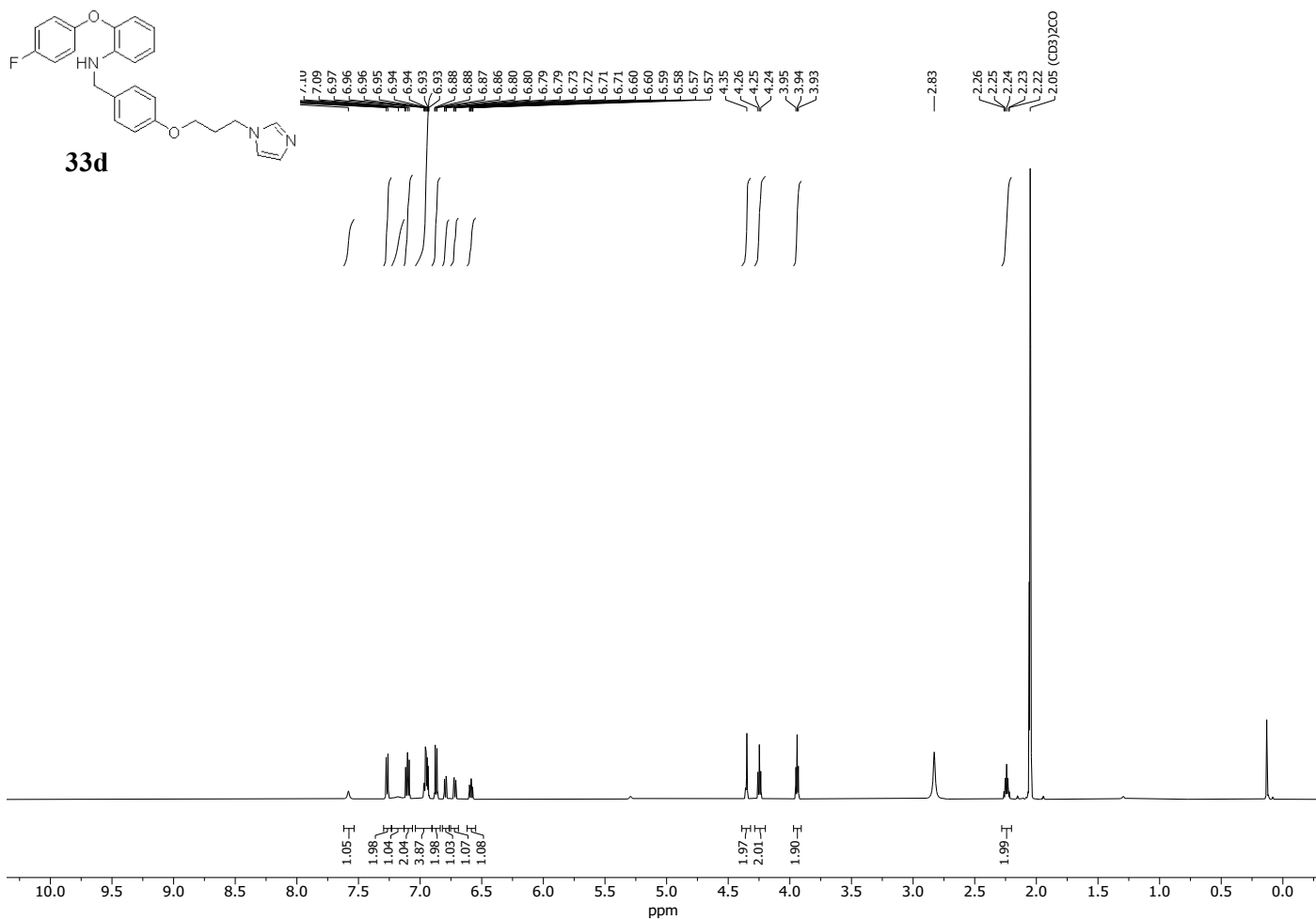


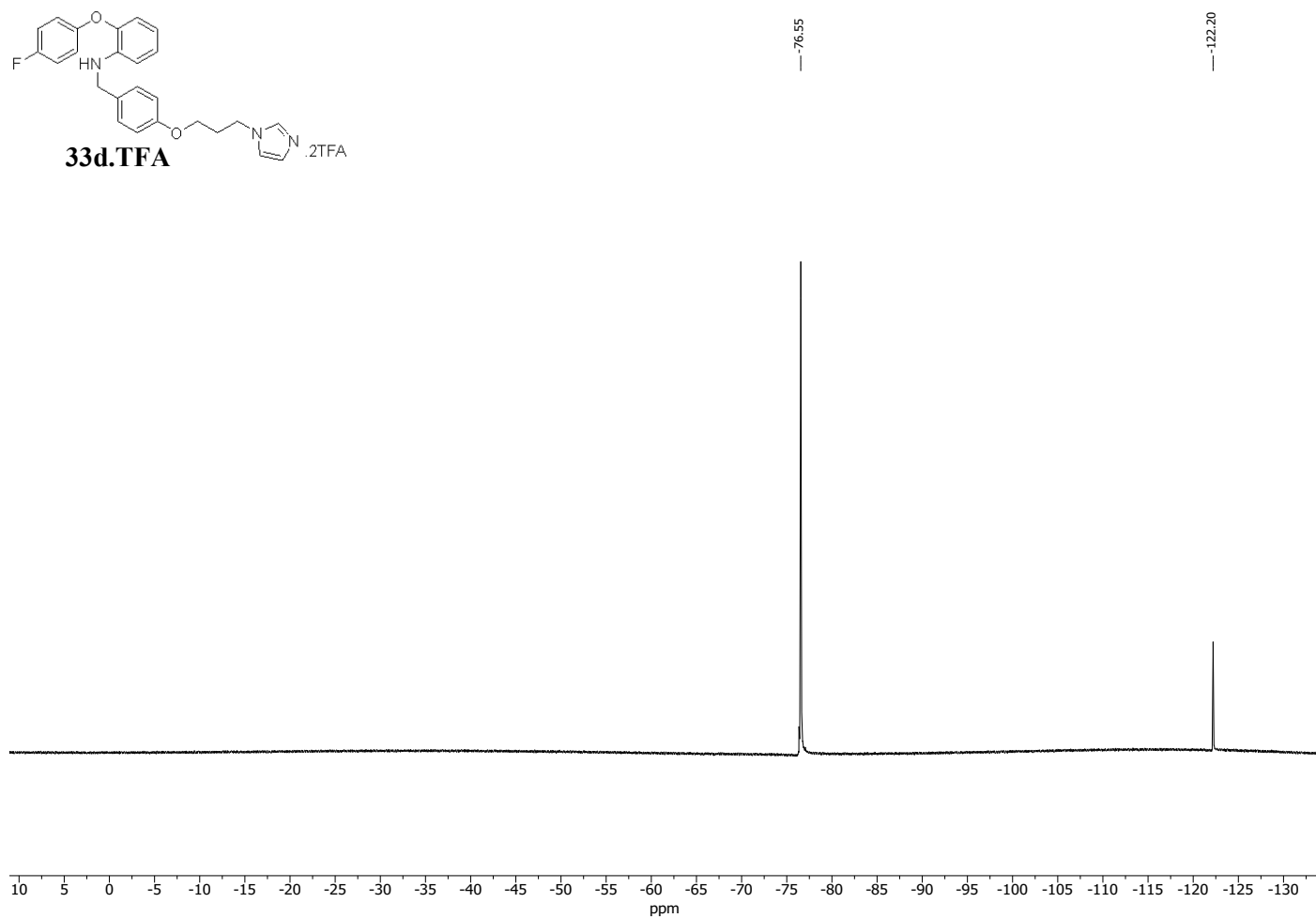
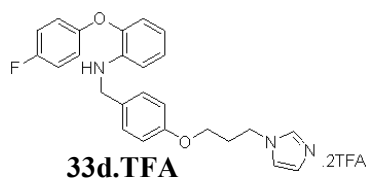


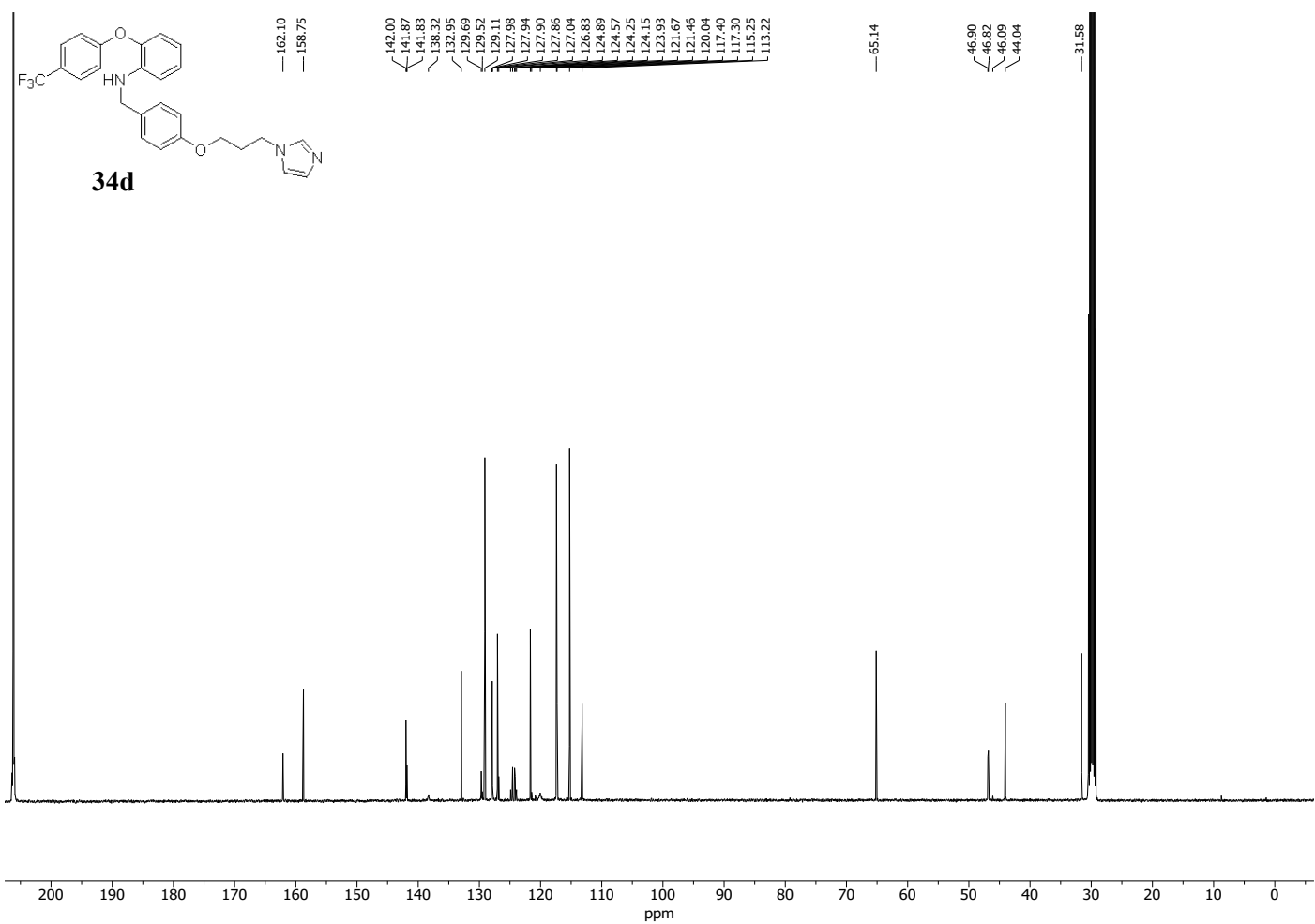
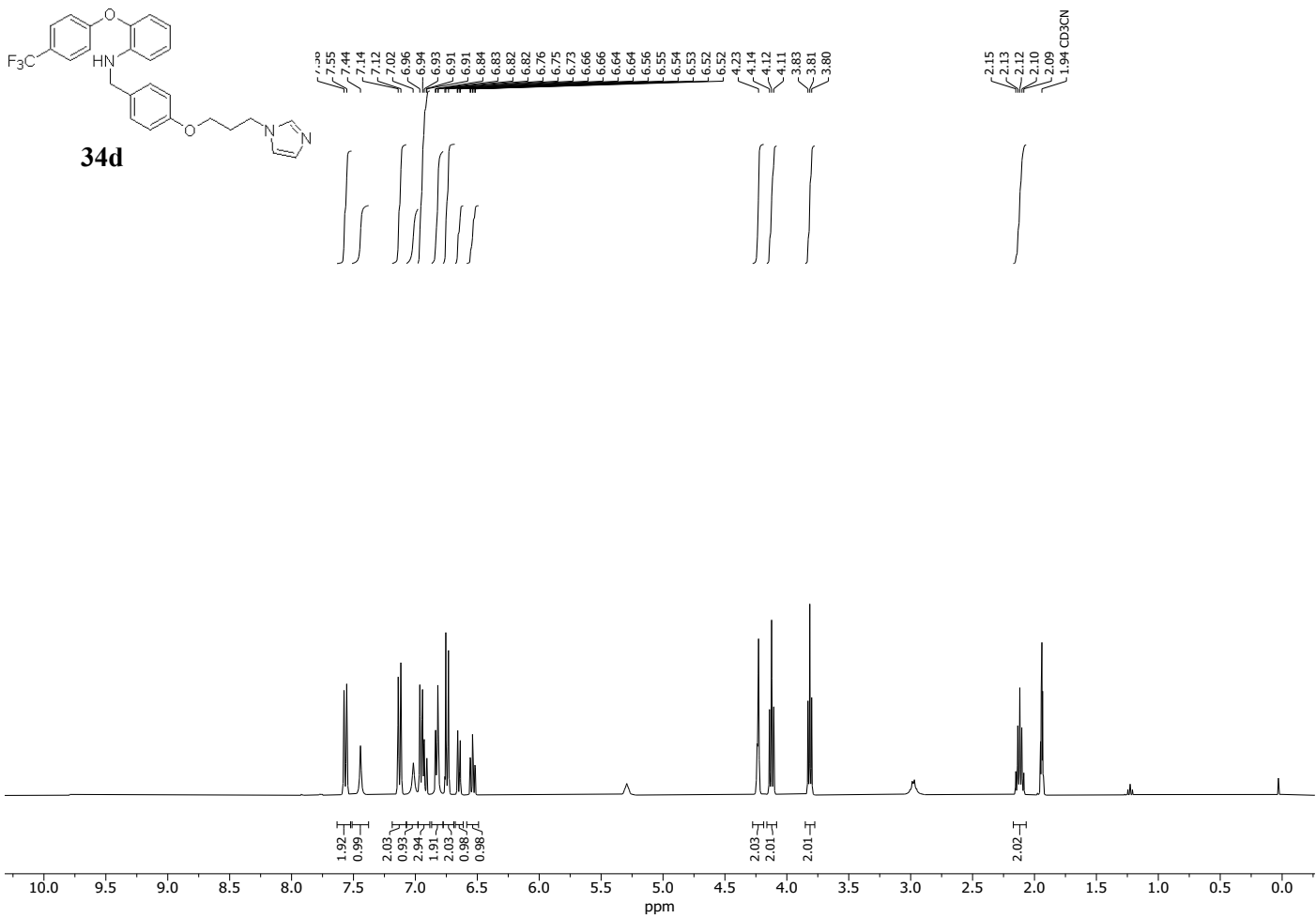


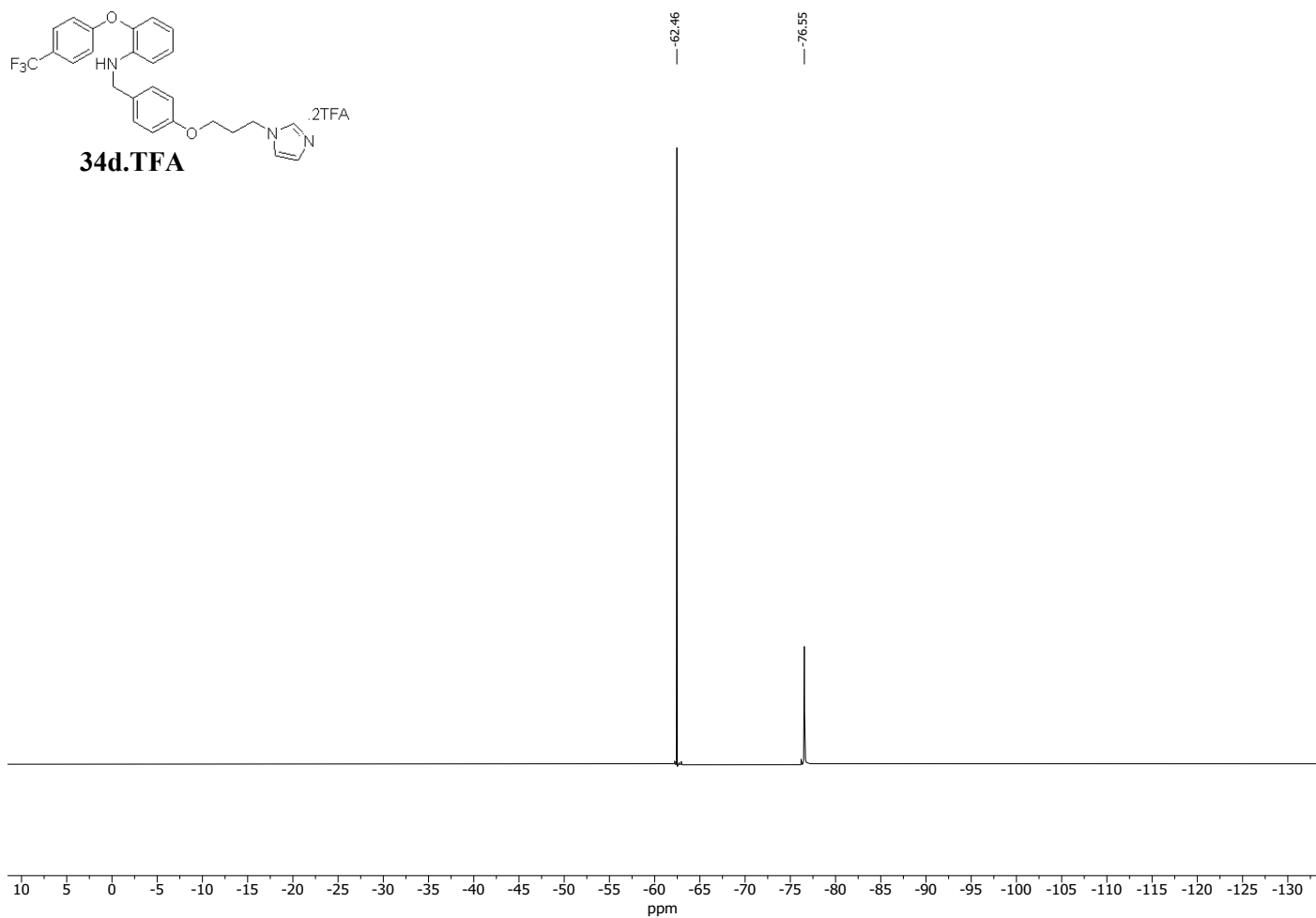
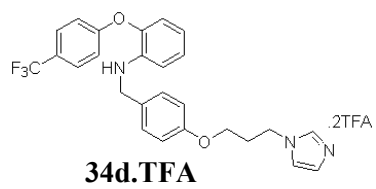
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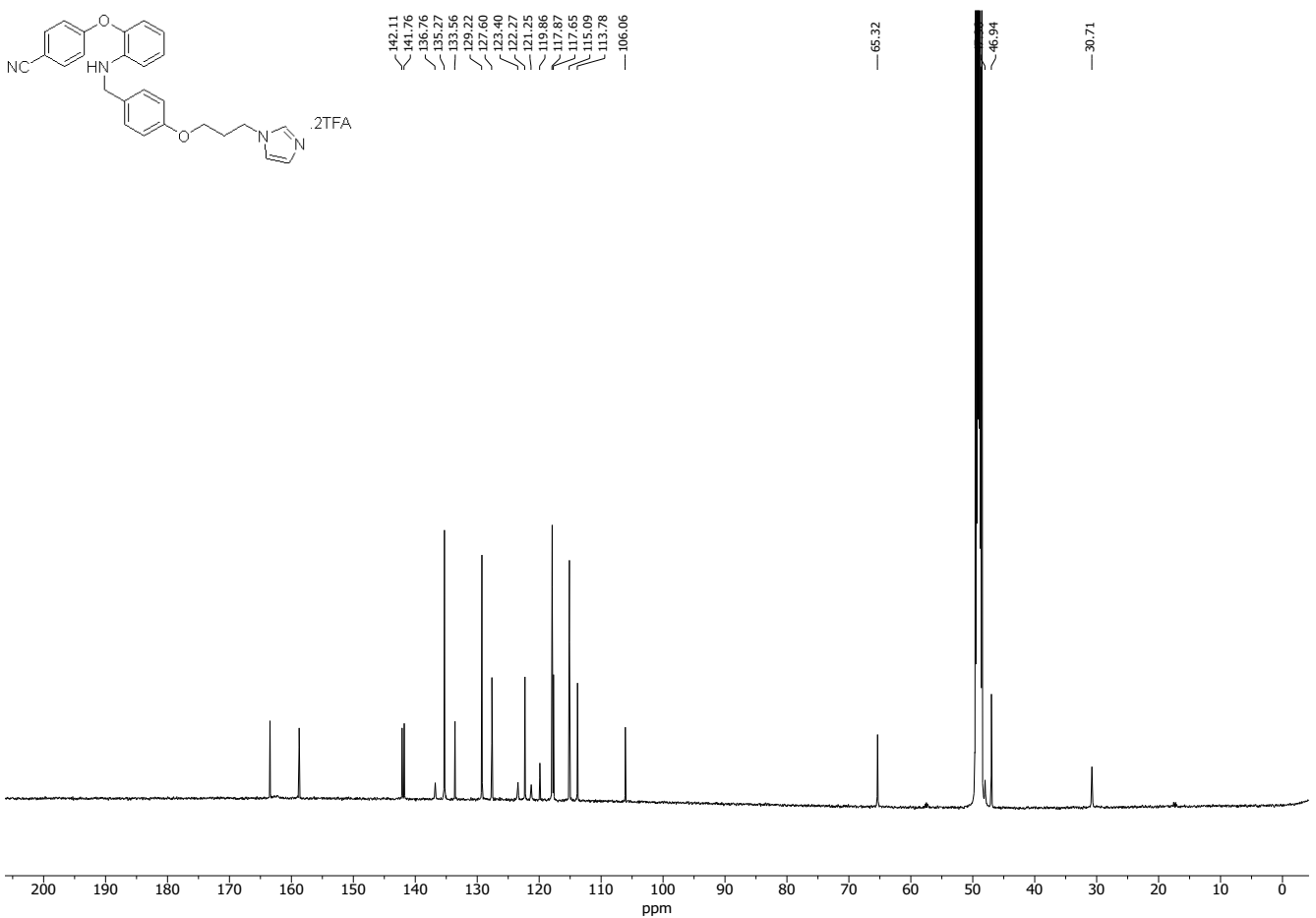
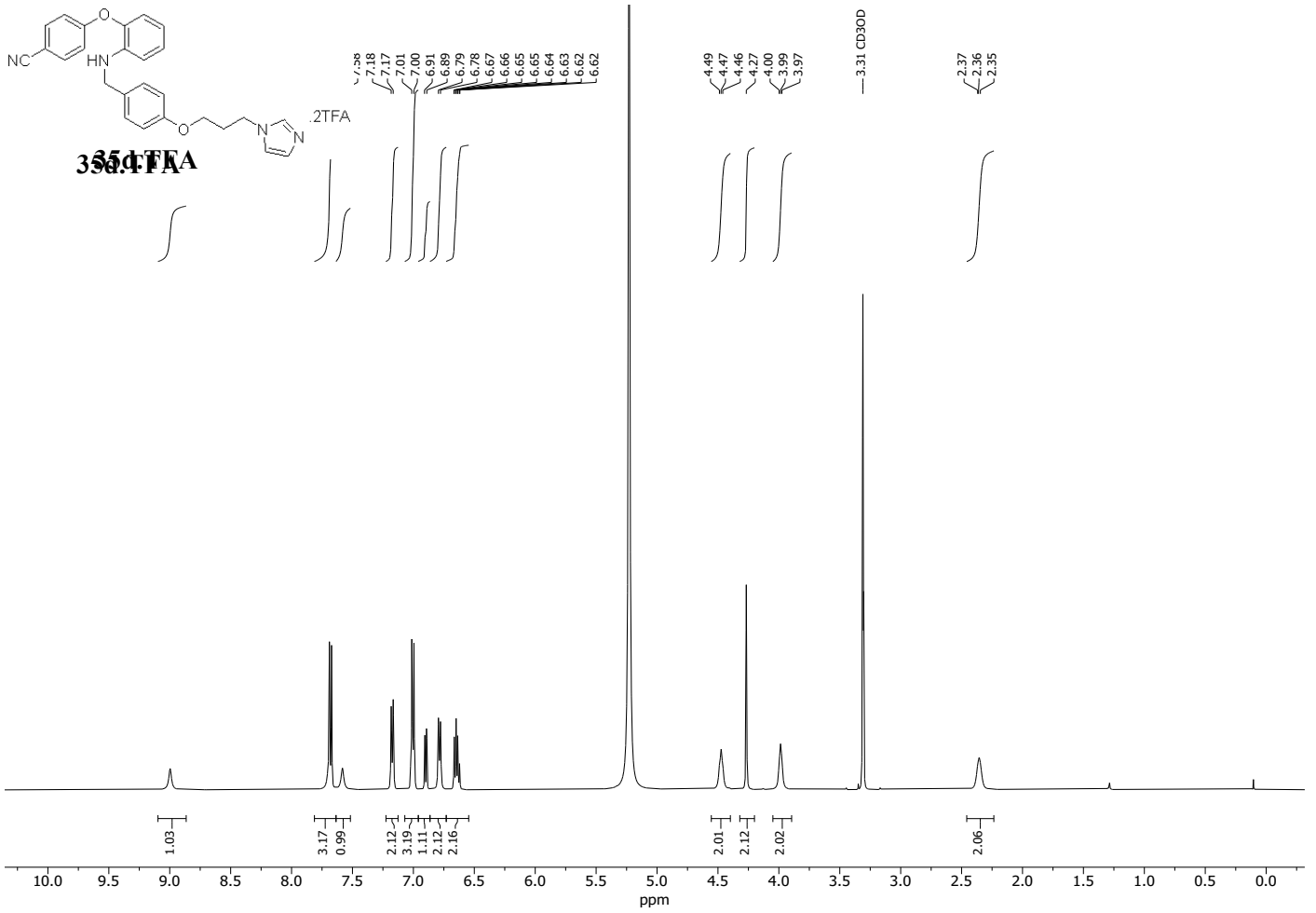


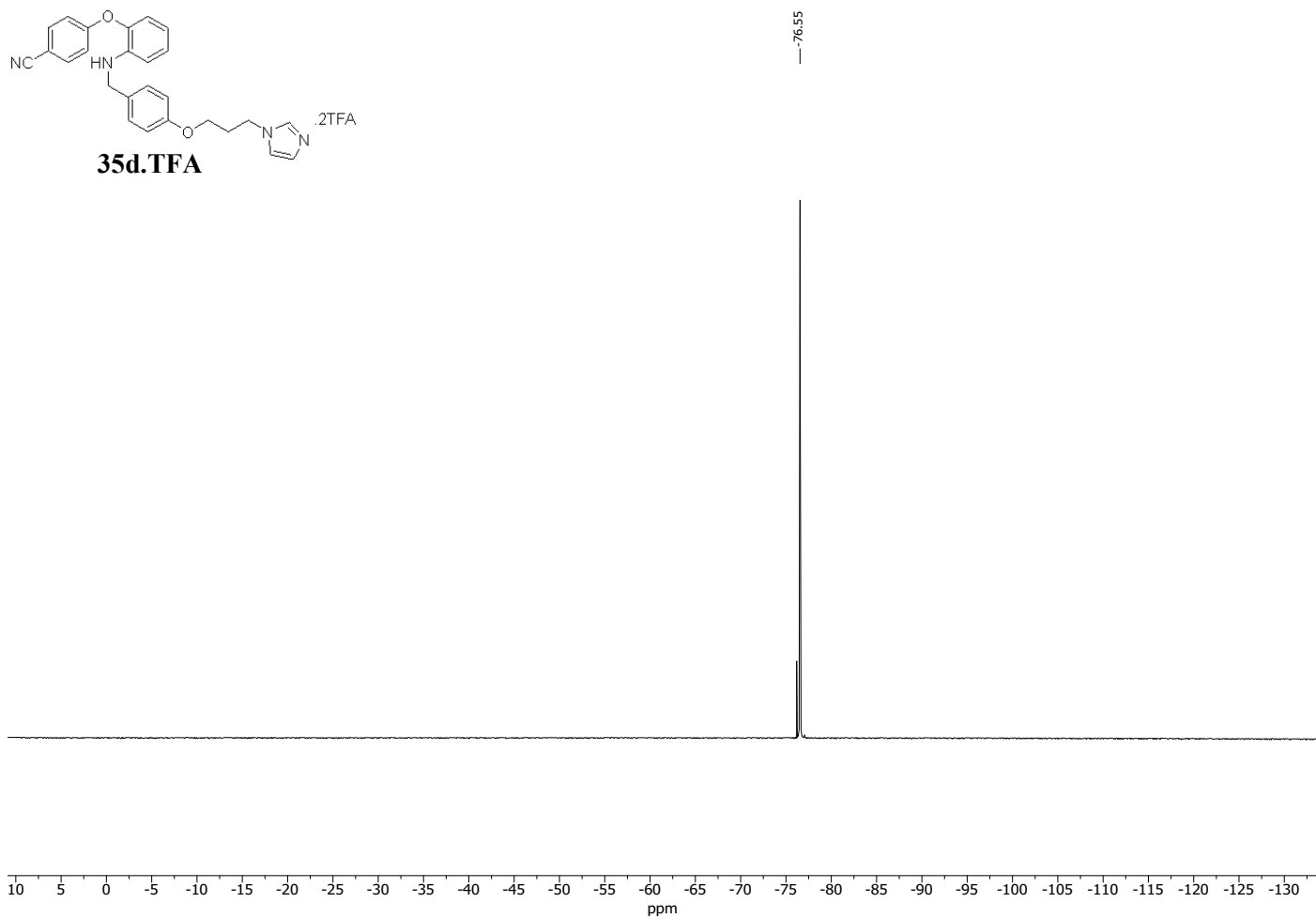
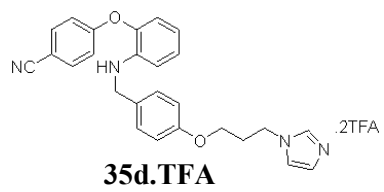


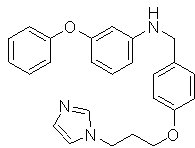




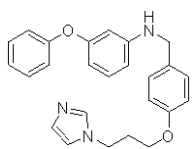
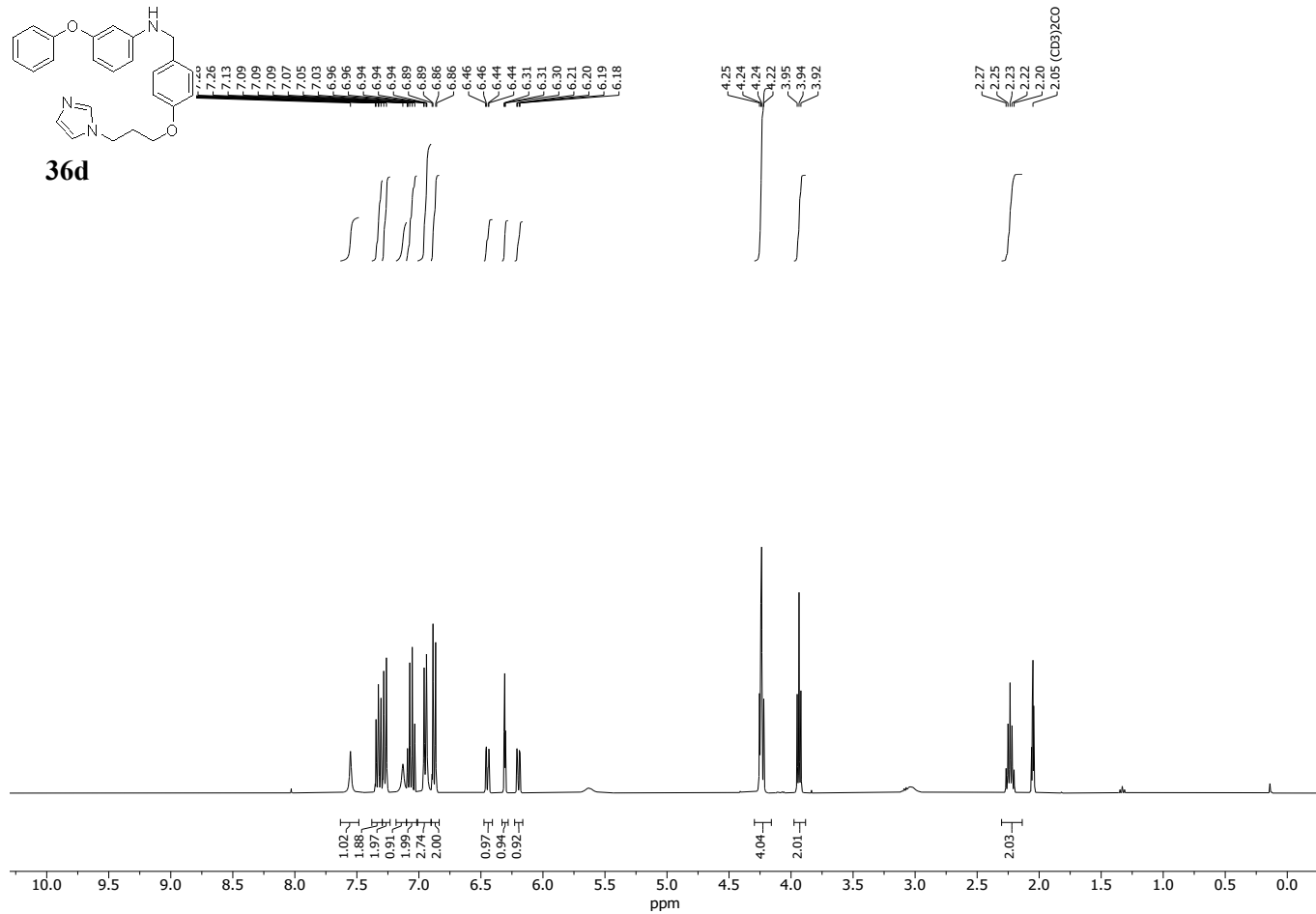




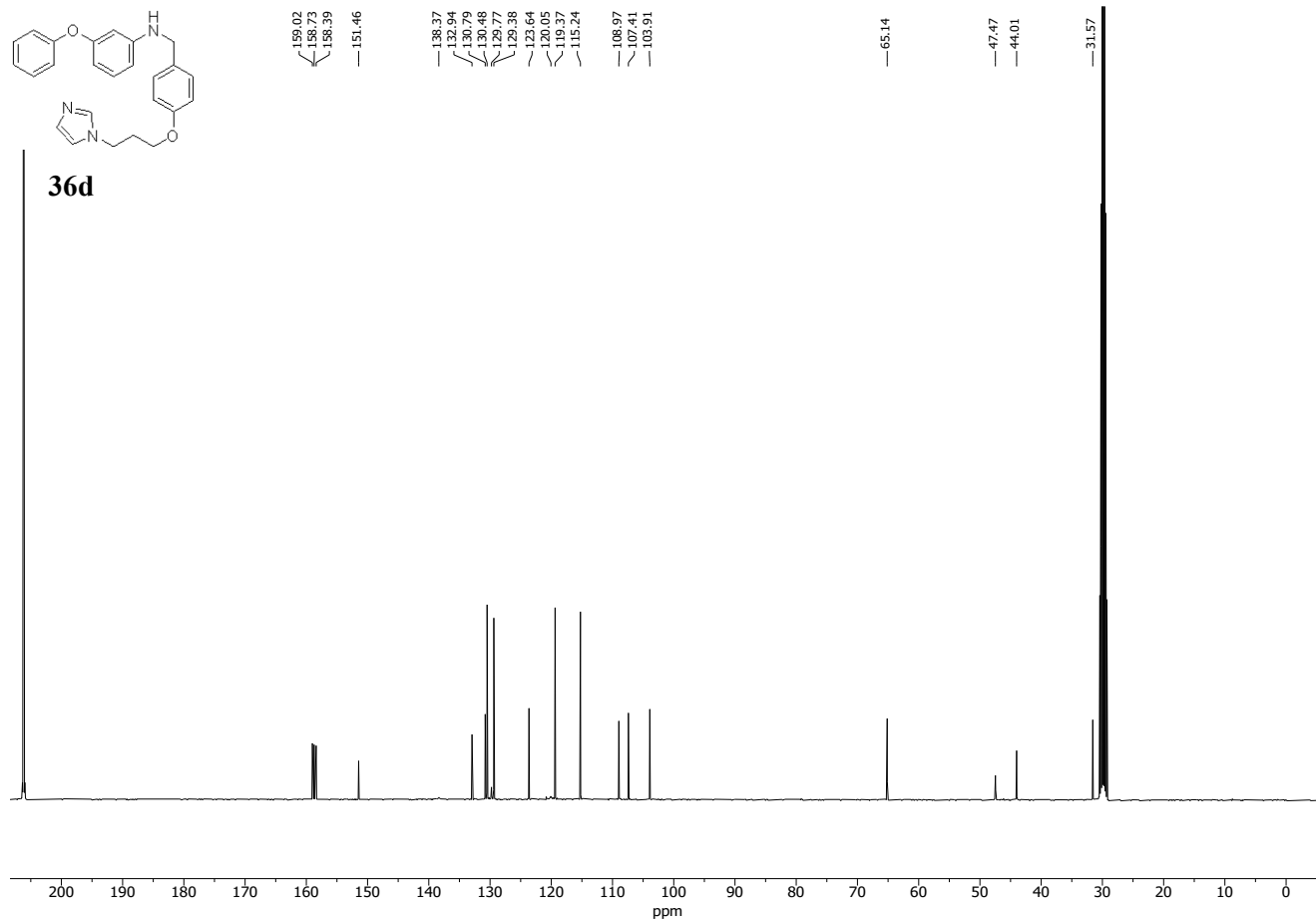


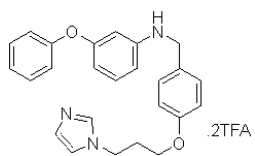


36d



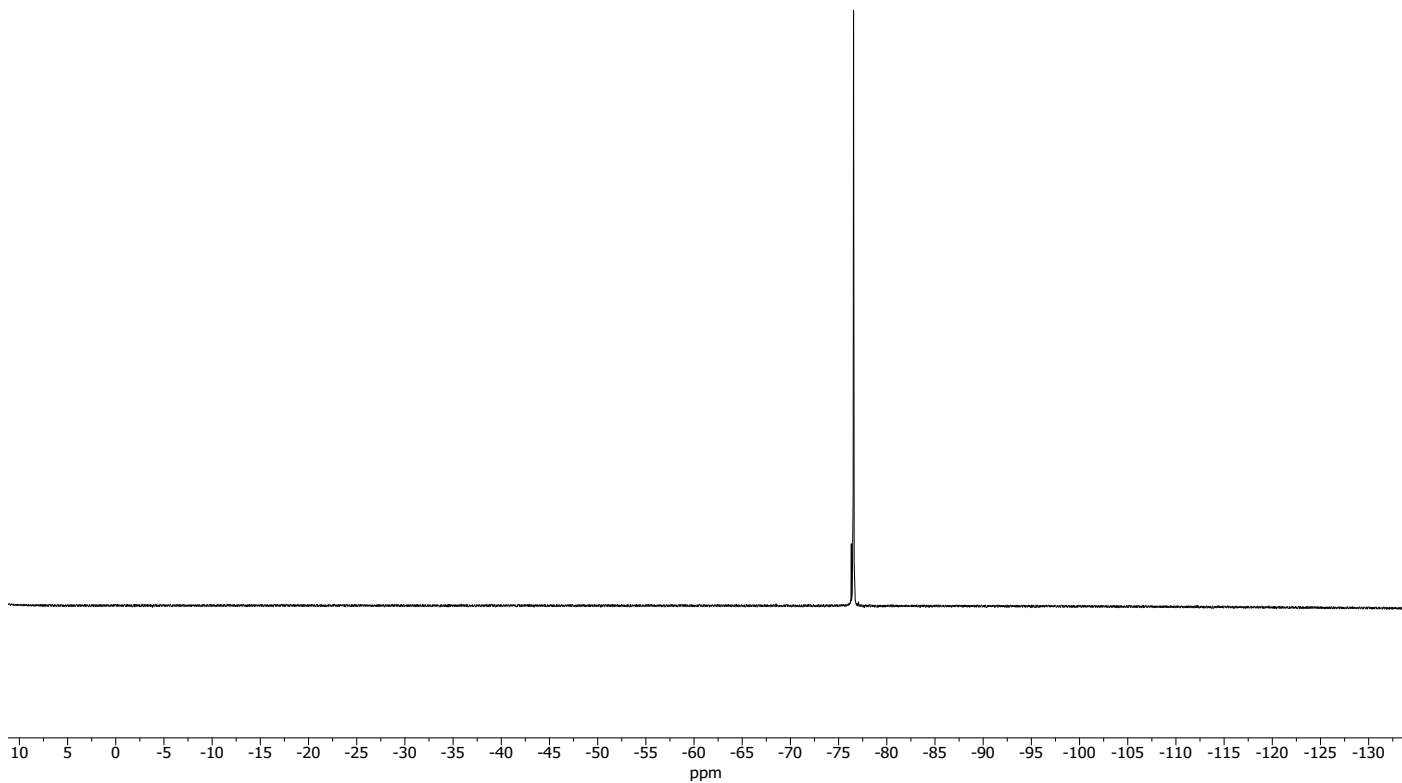
36d

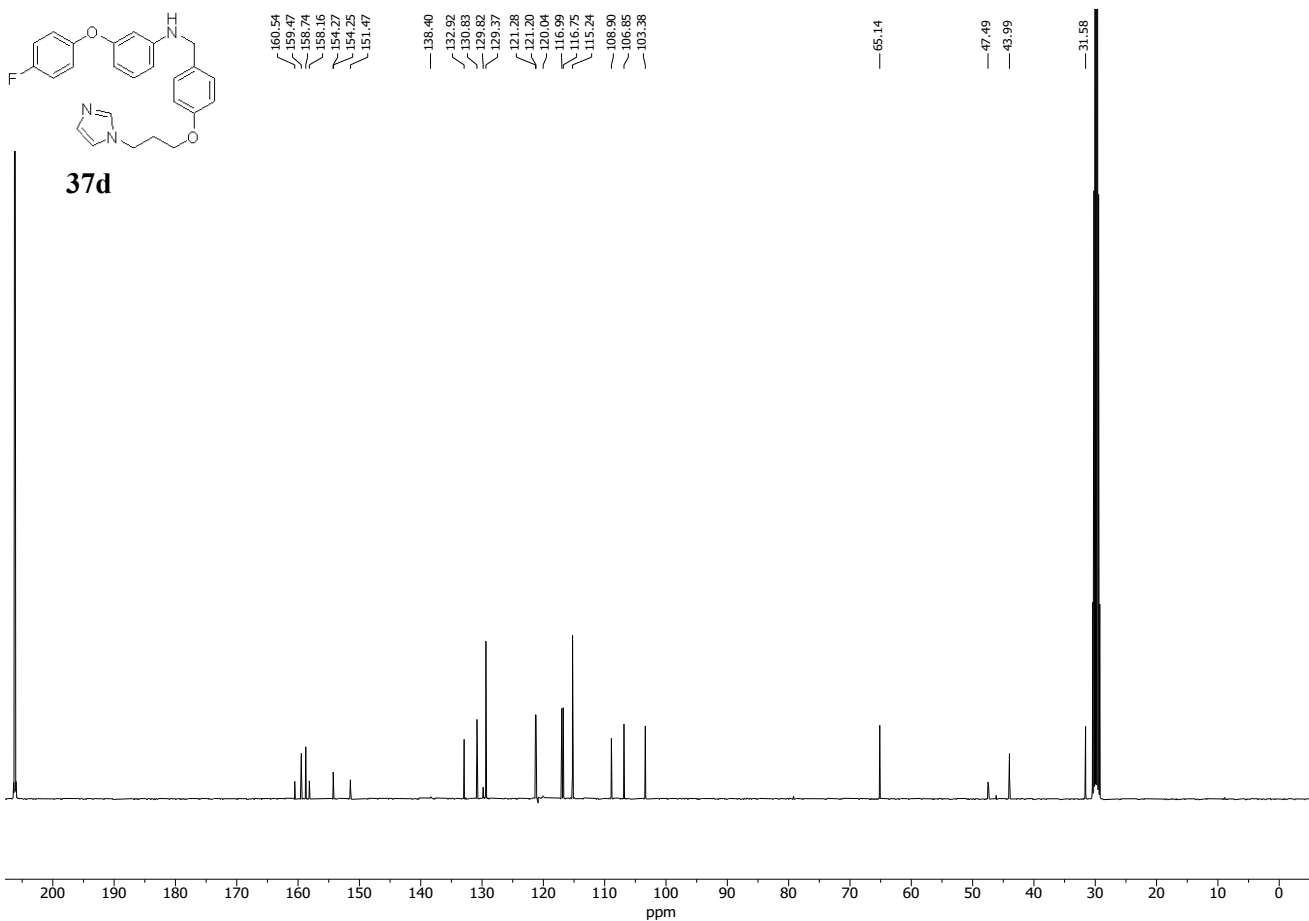
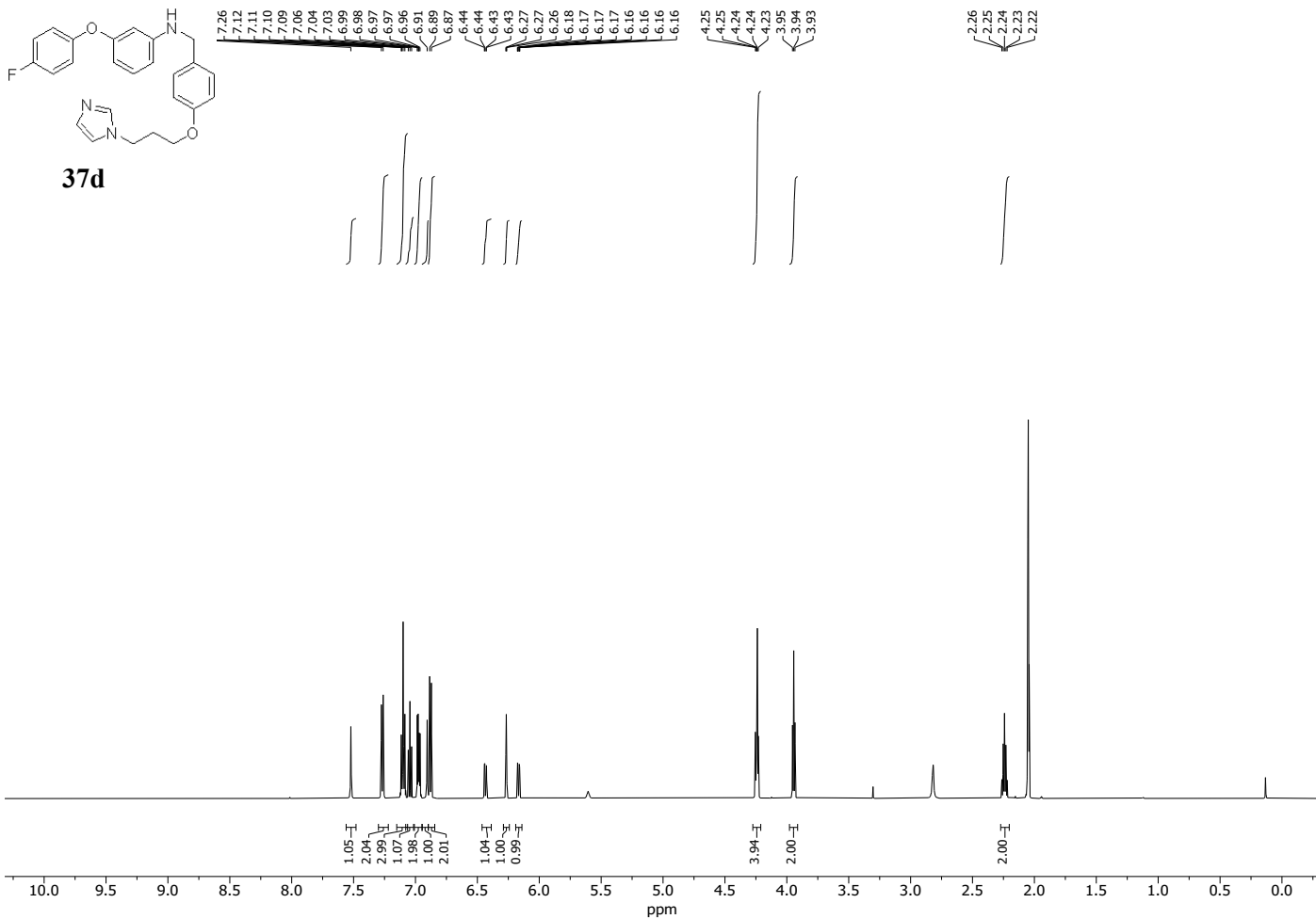


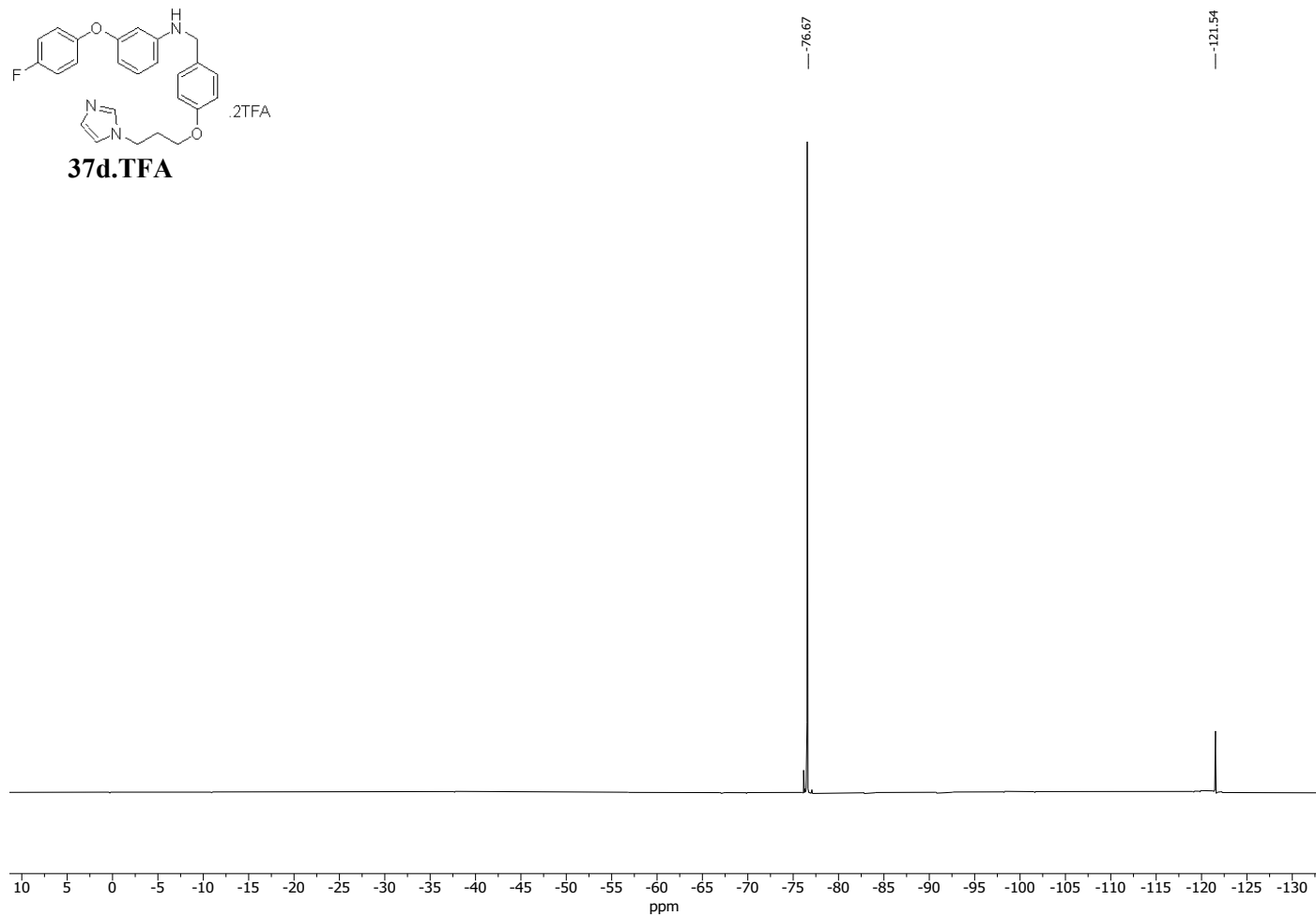
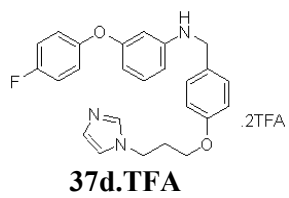


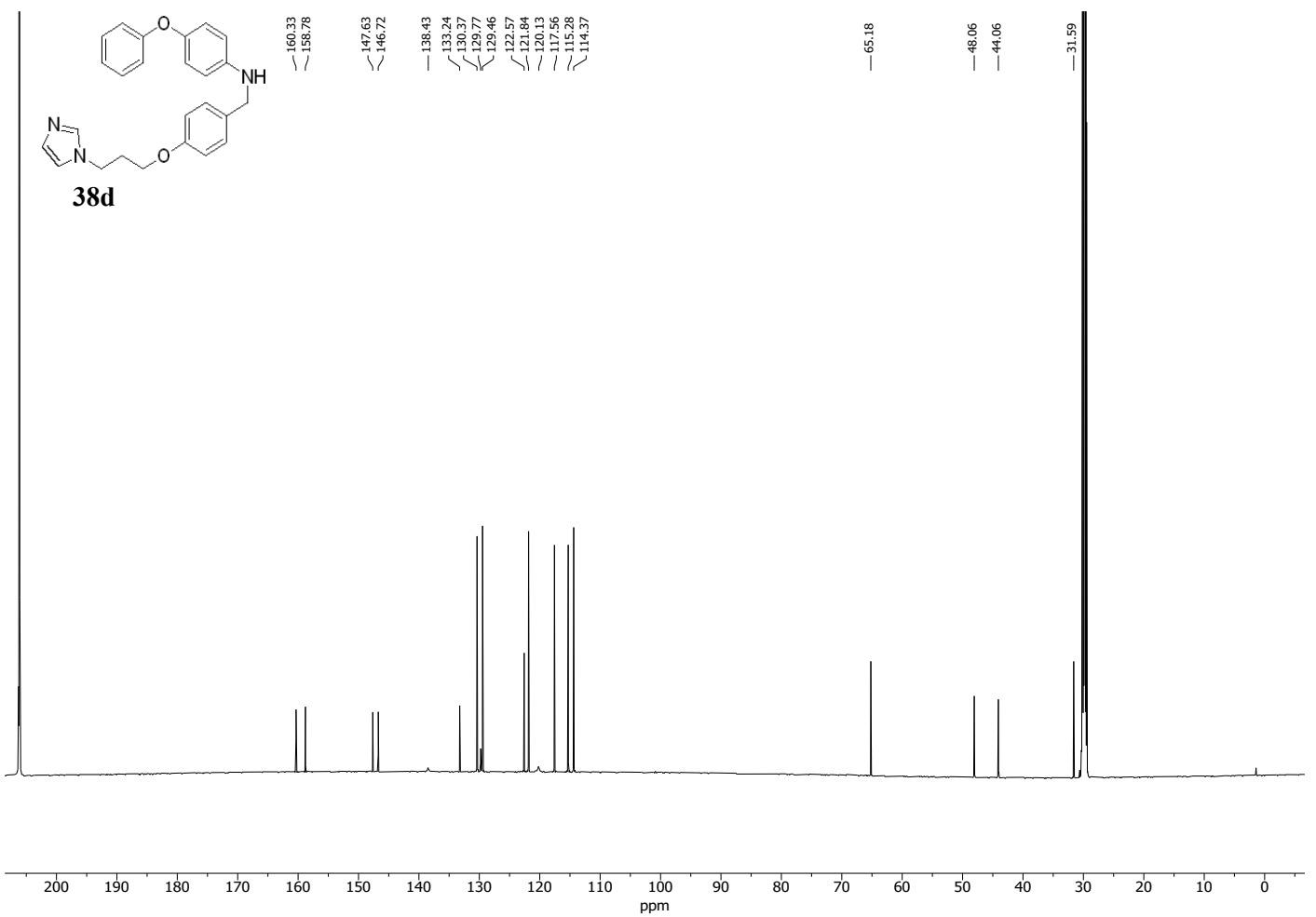
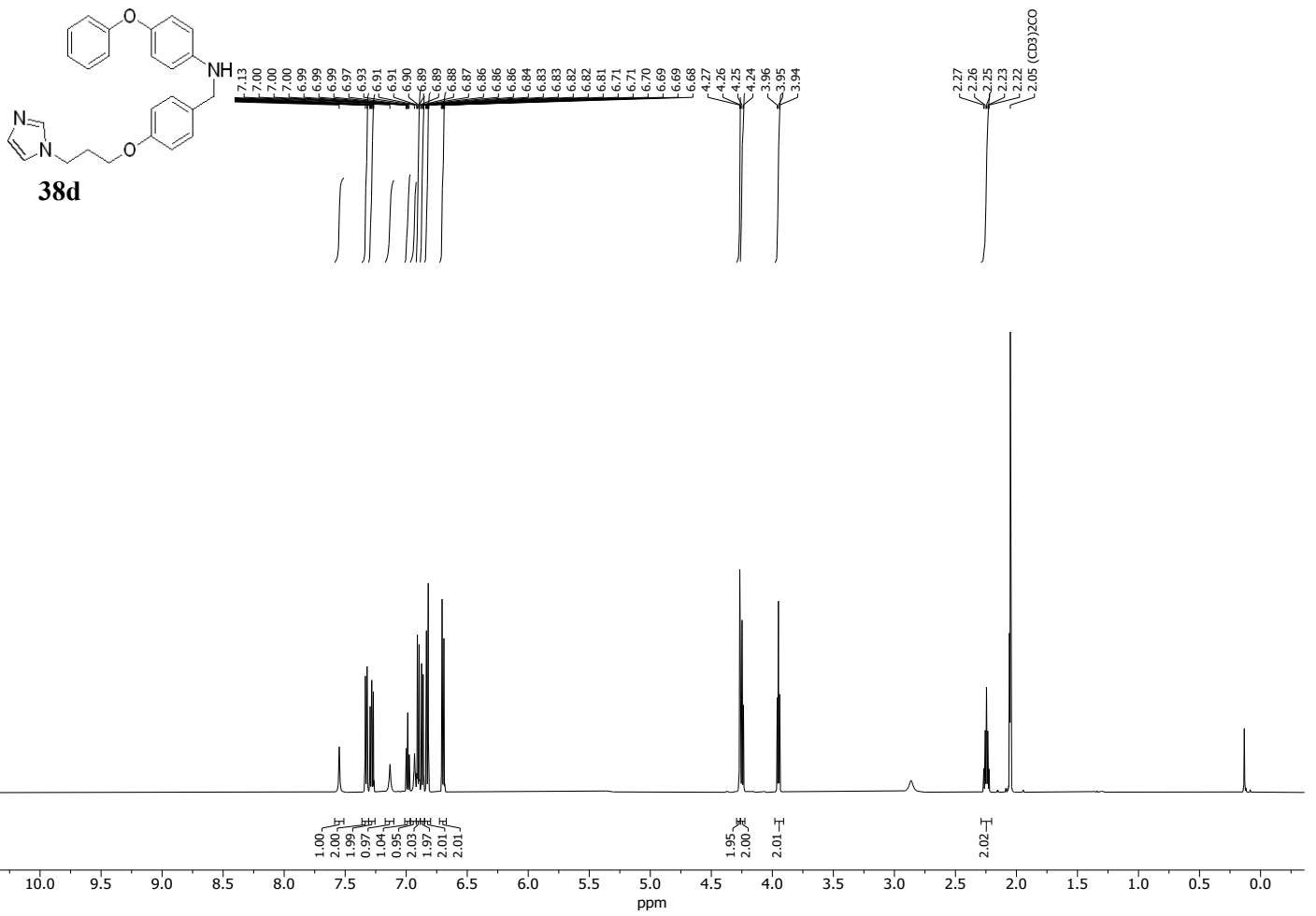
36d.TFA

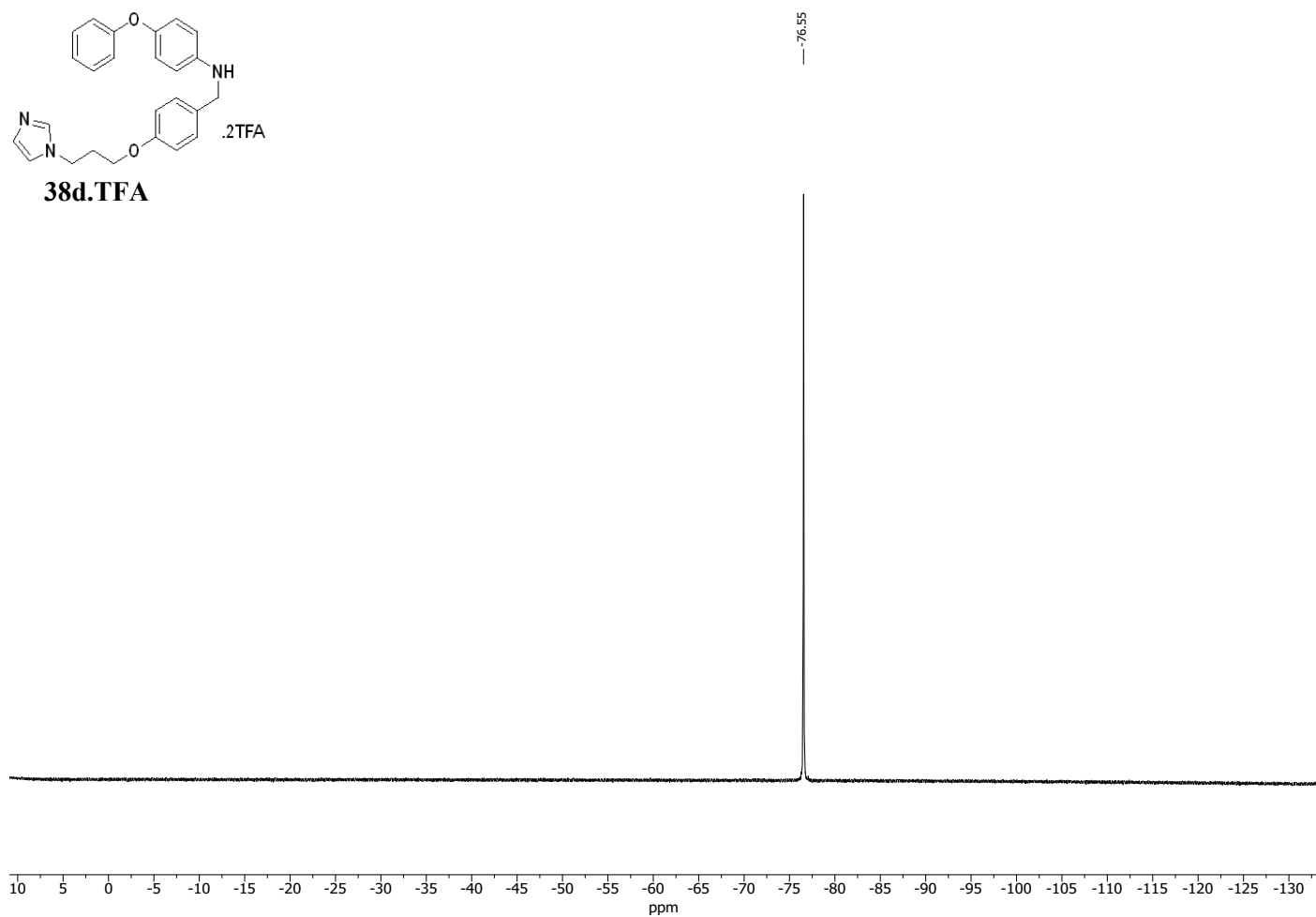
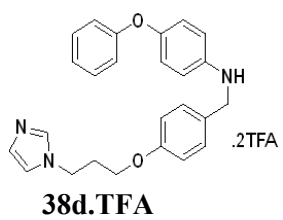
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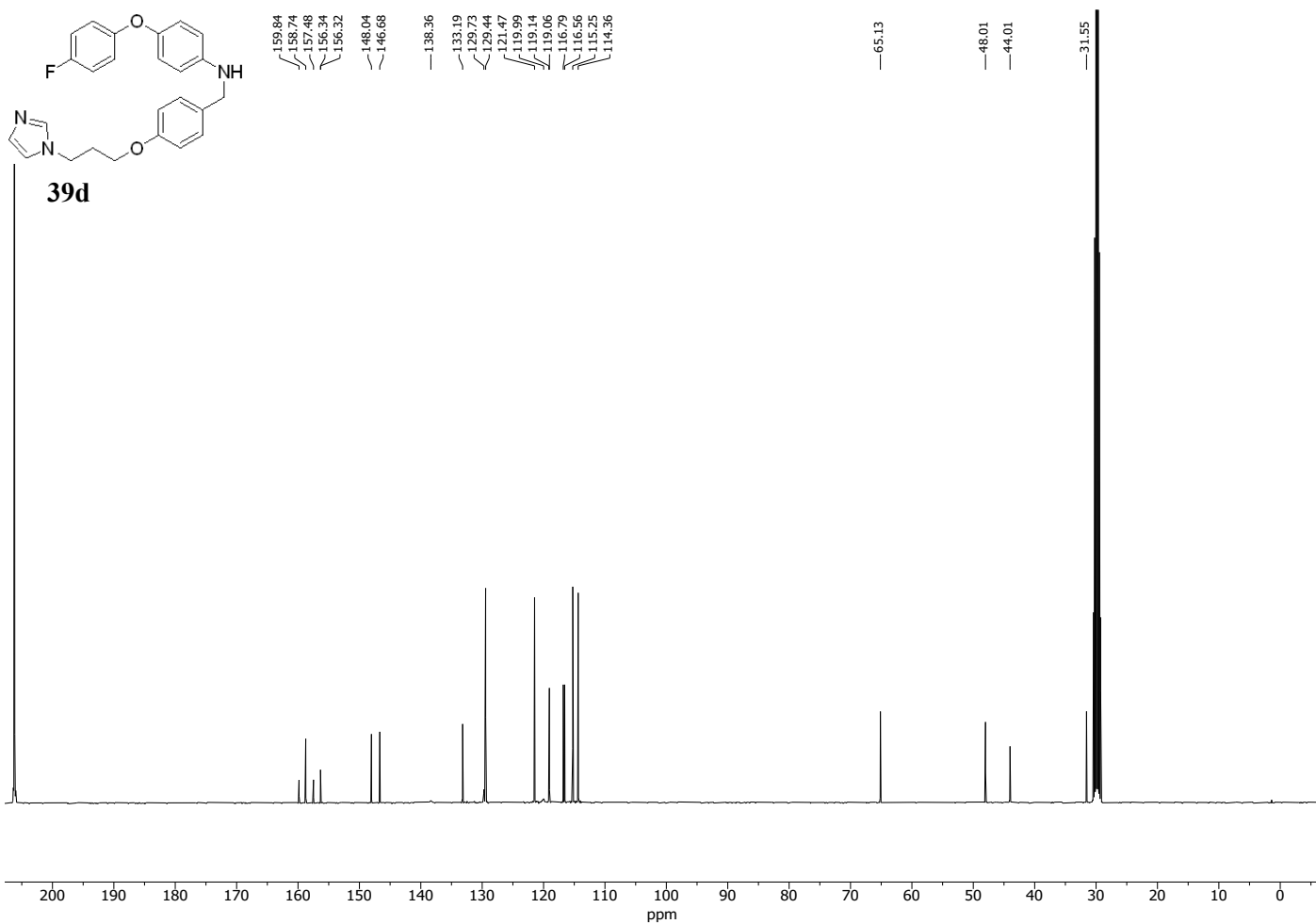
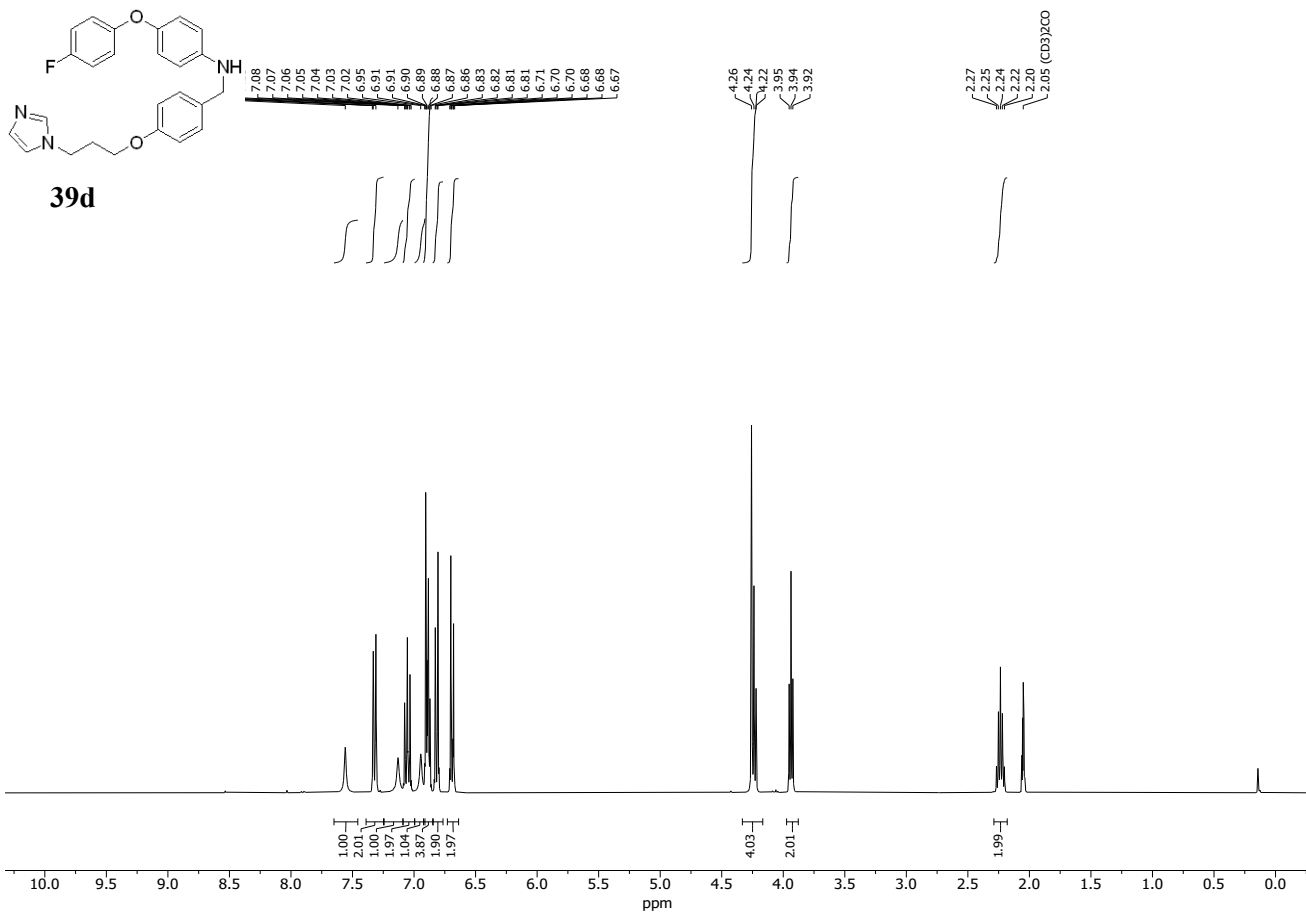


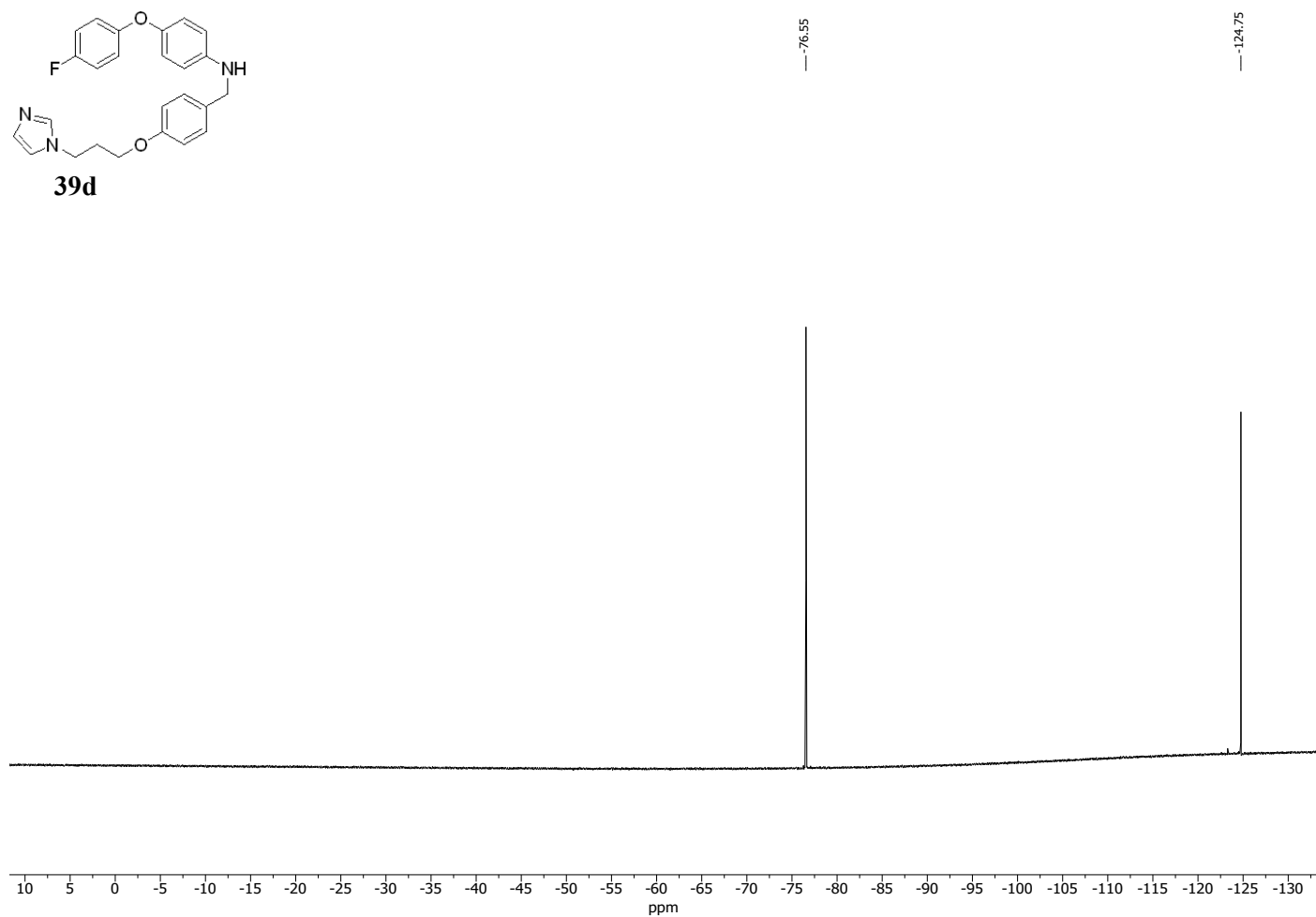
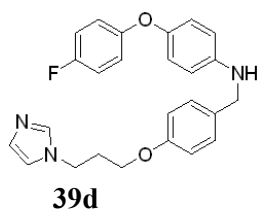


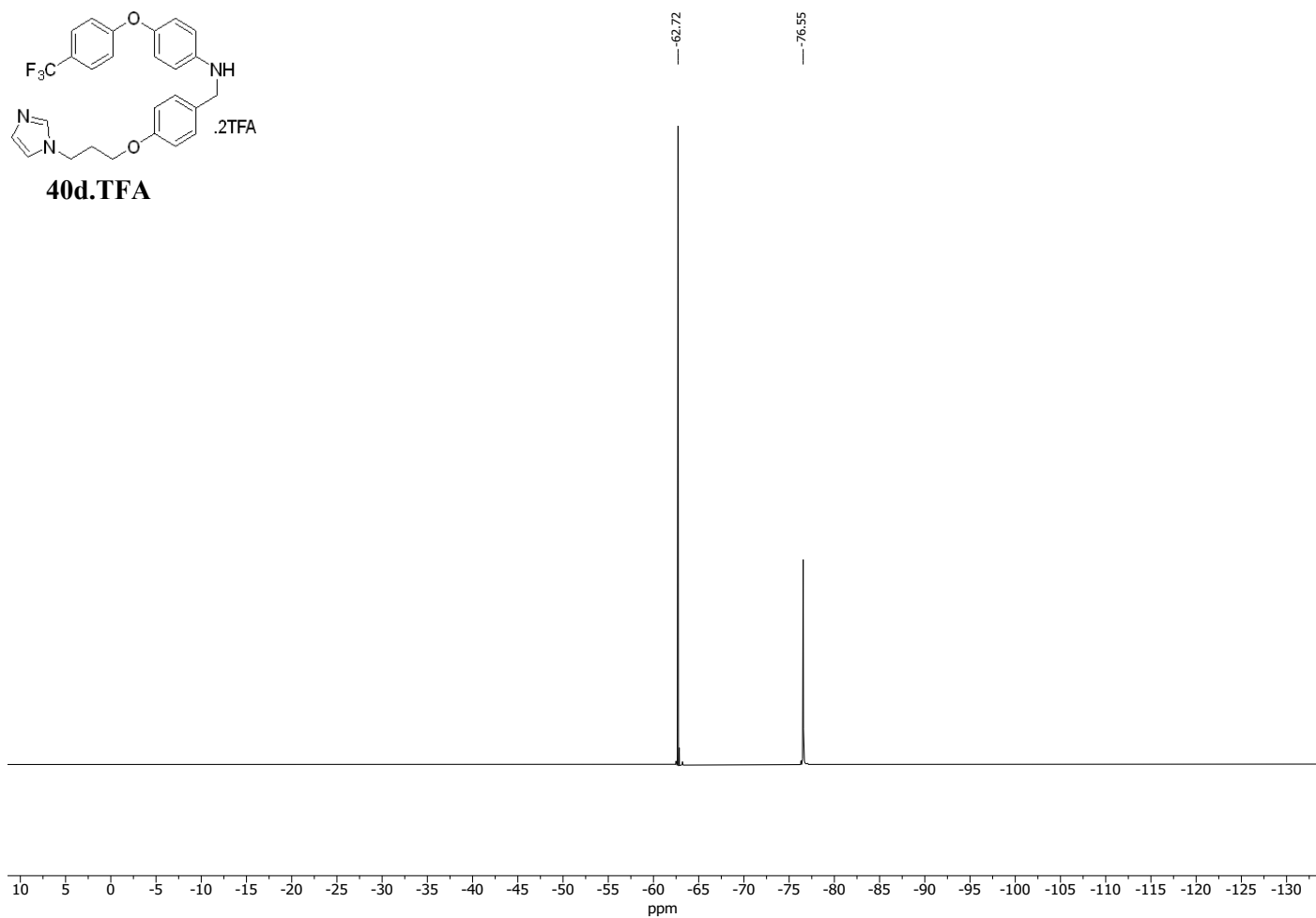
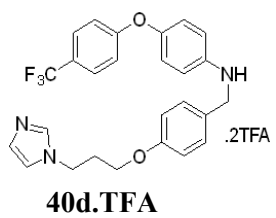


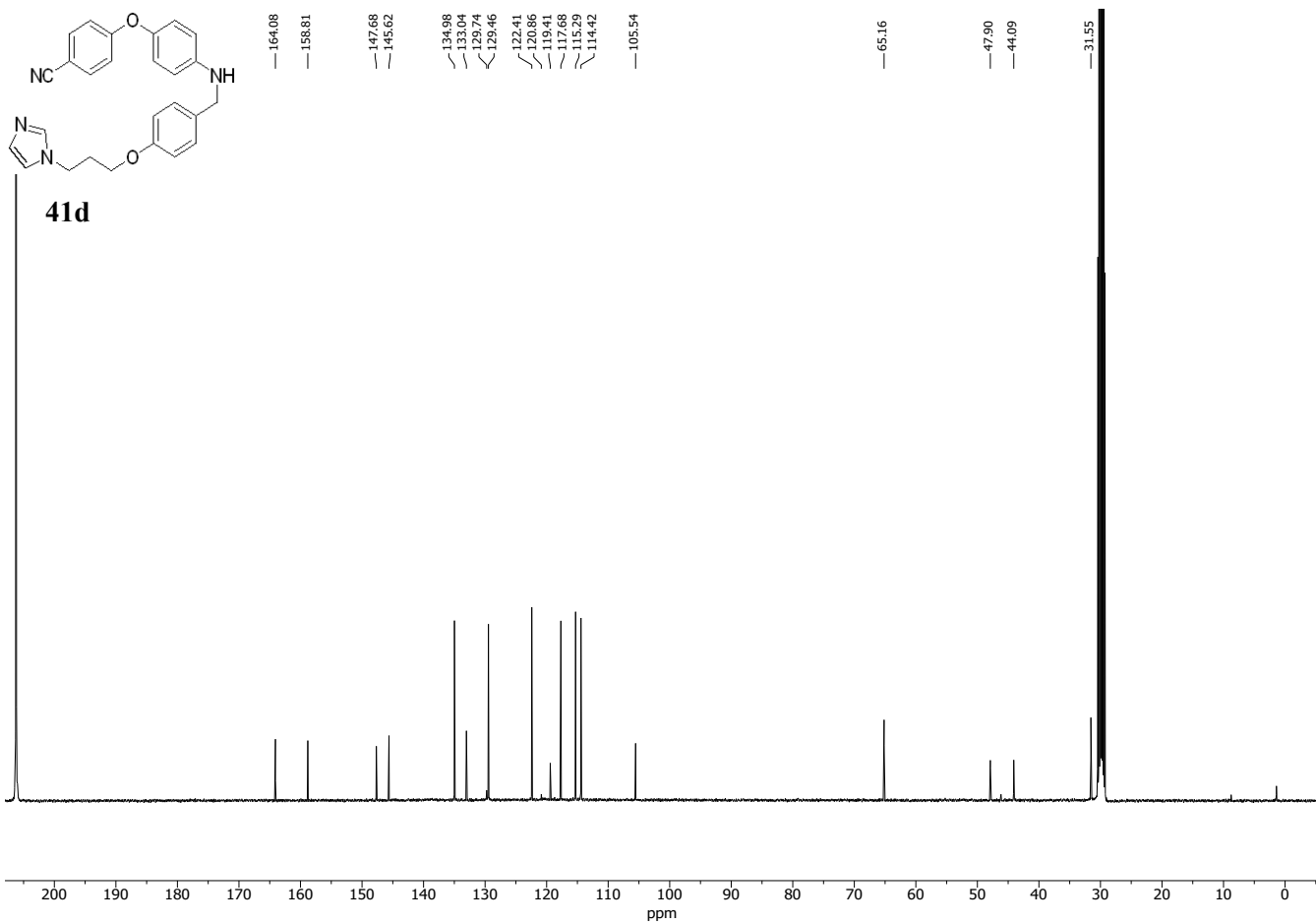
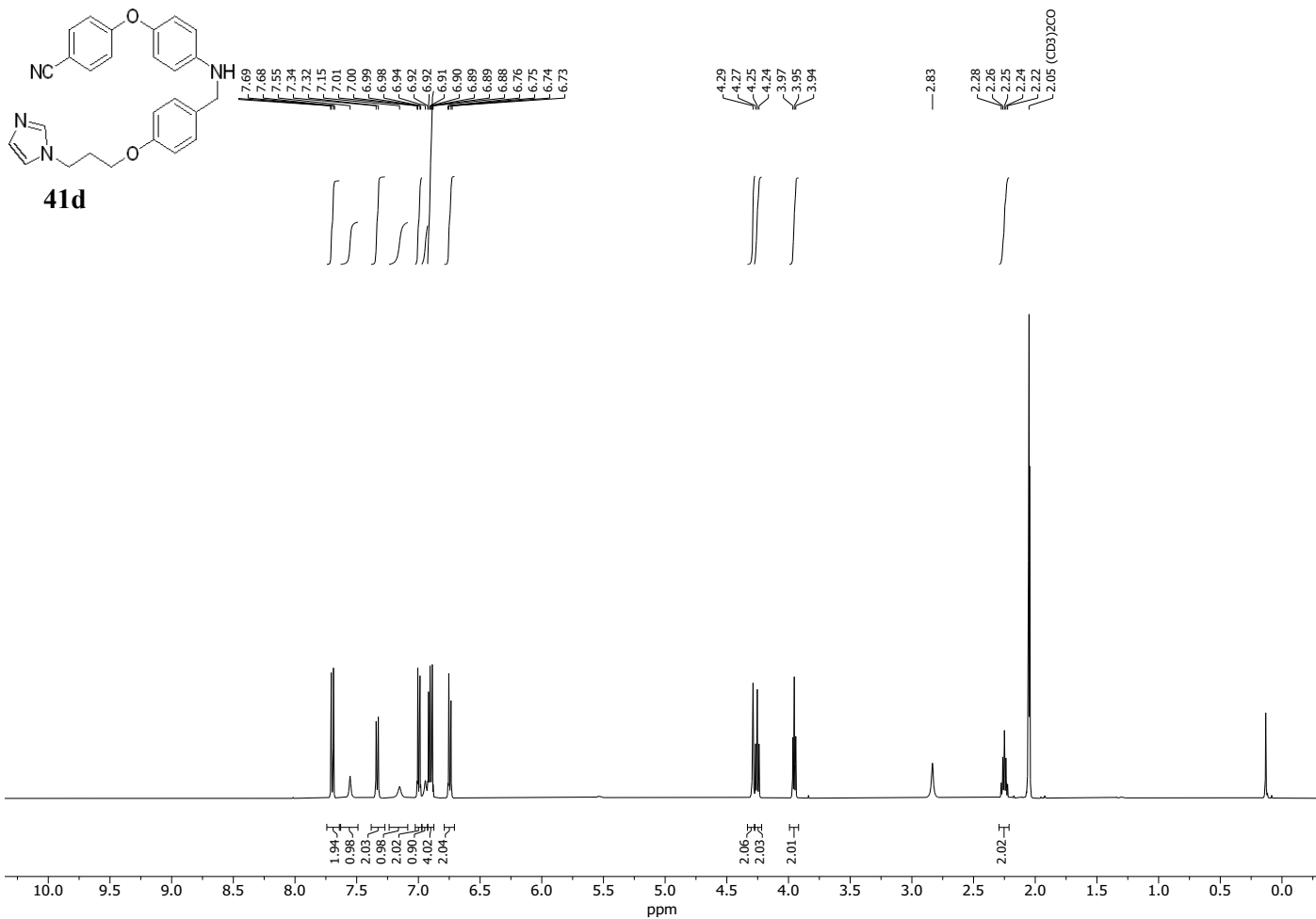


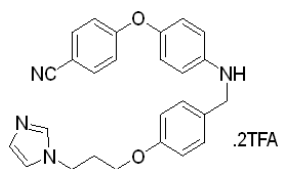










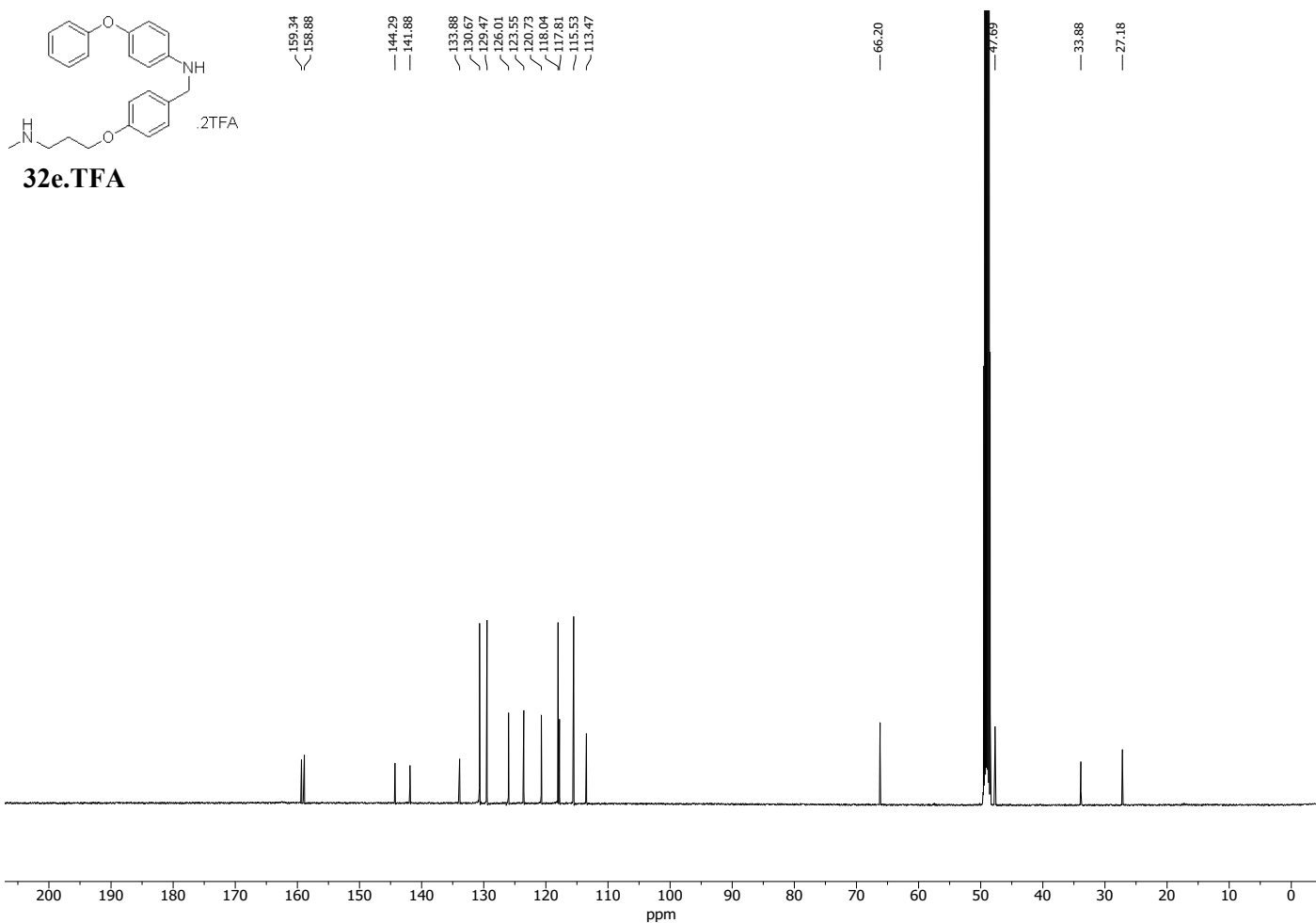
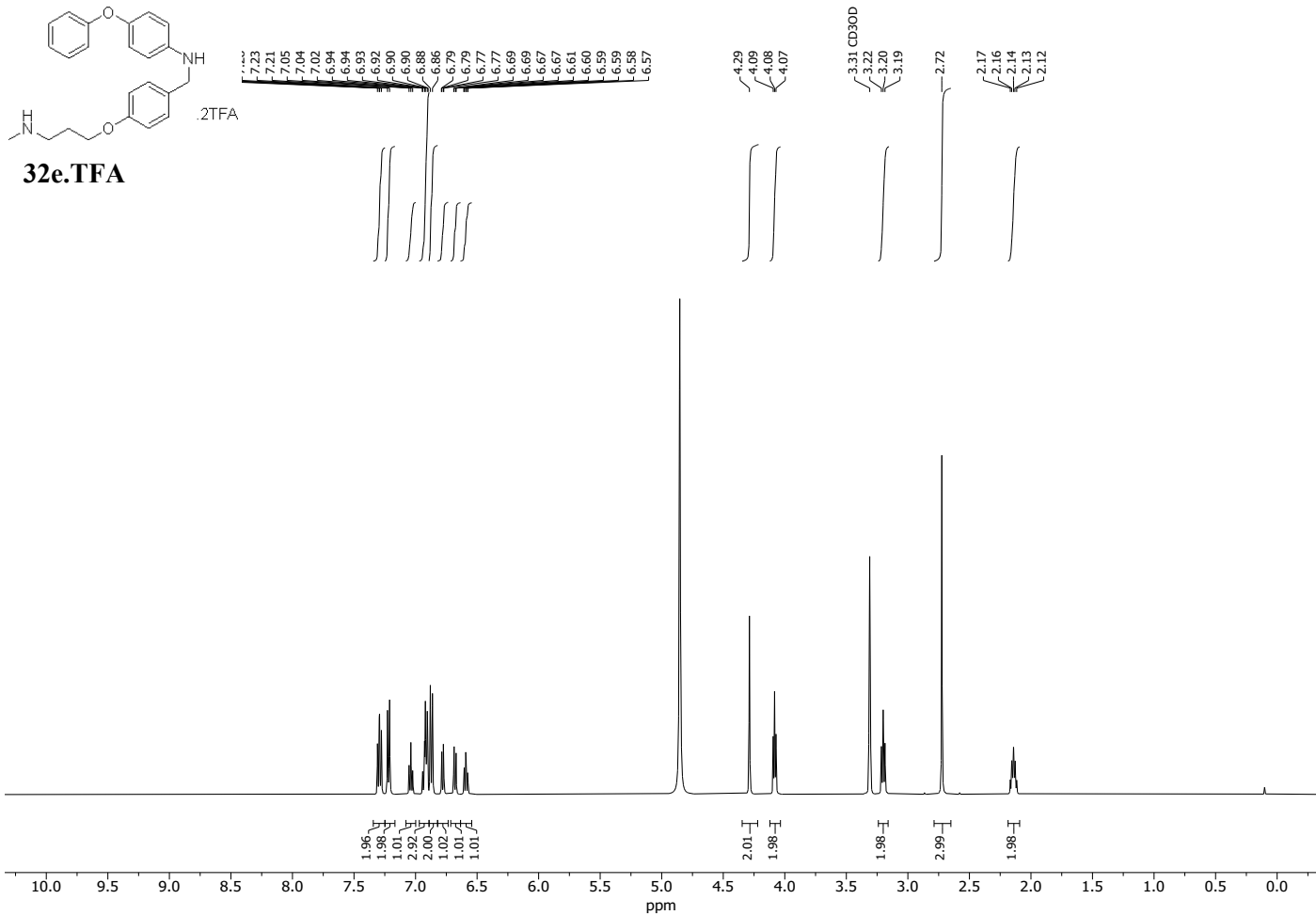


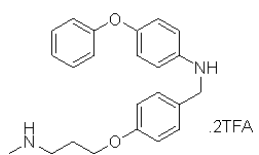
41d.TFA

—76.55

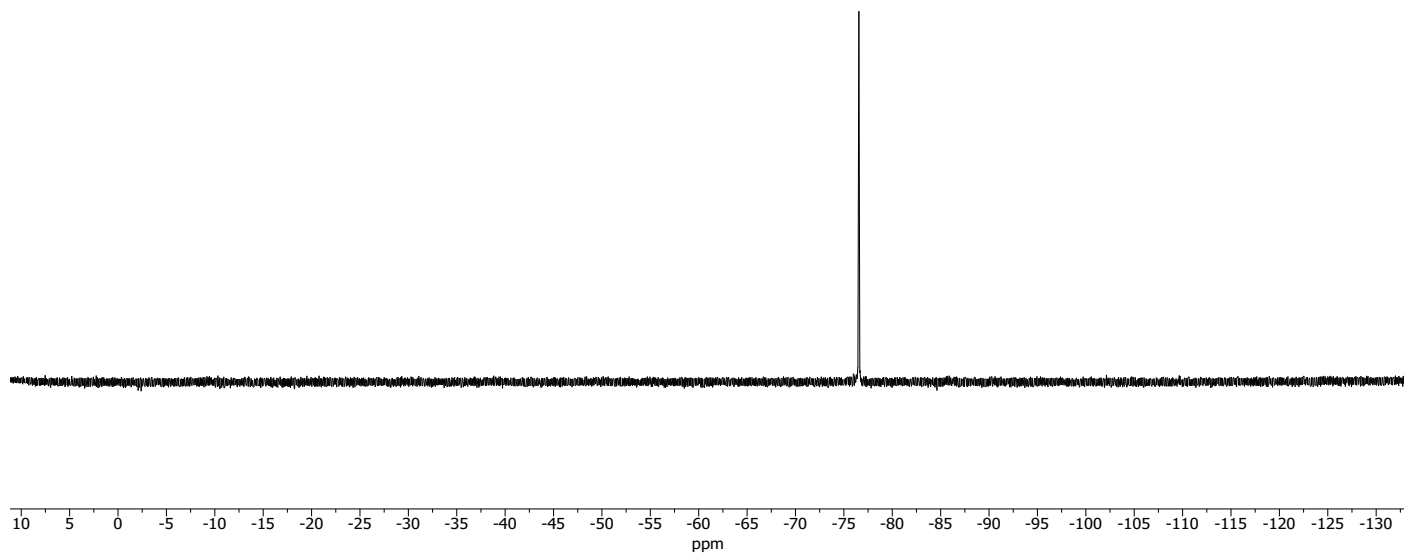


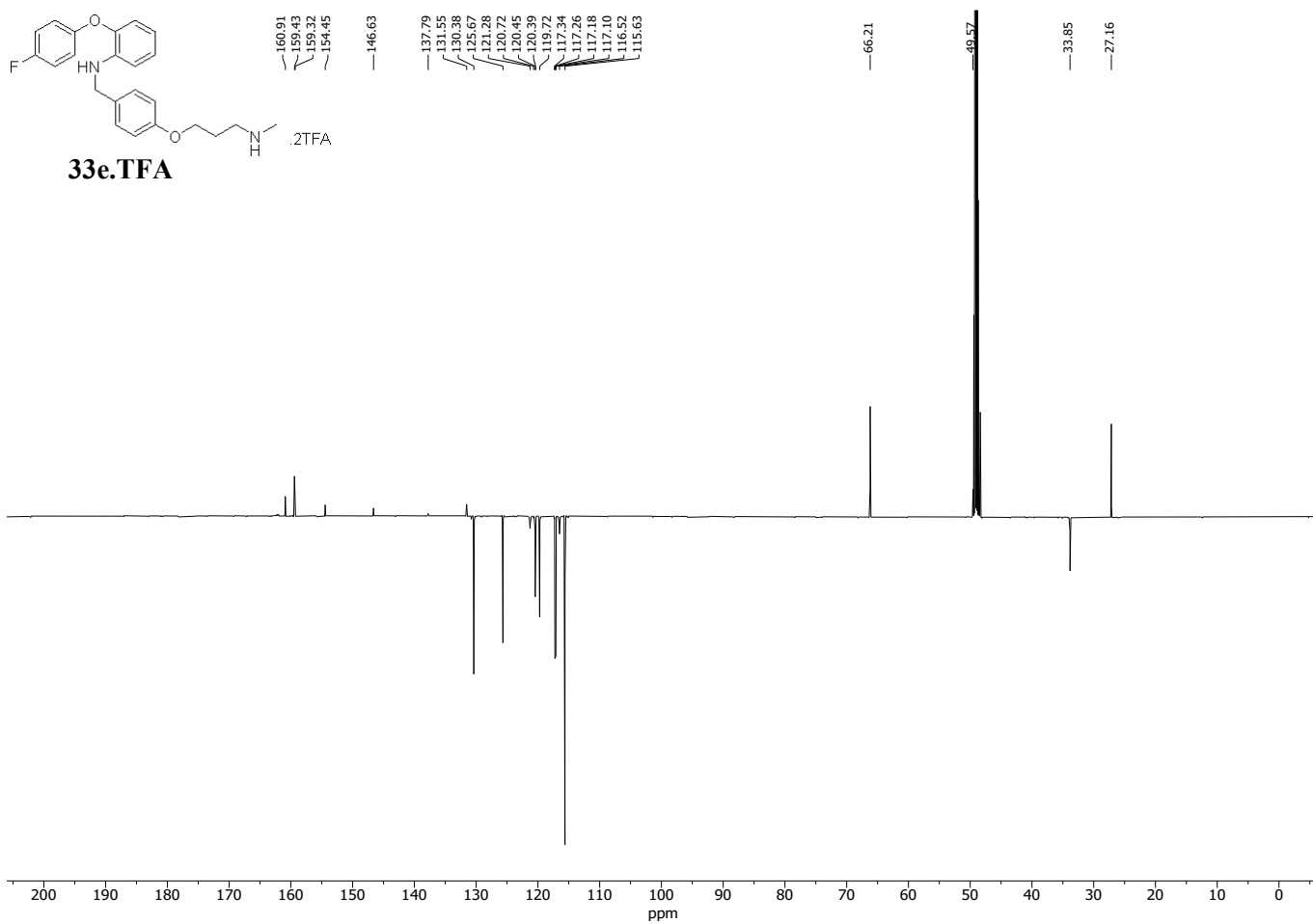
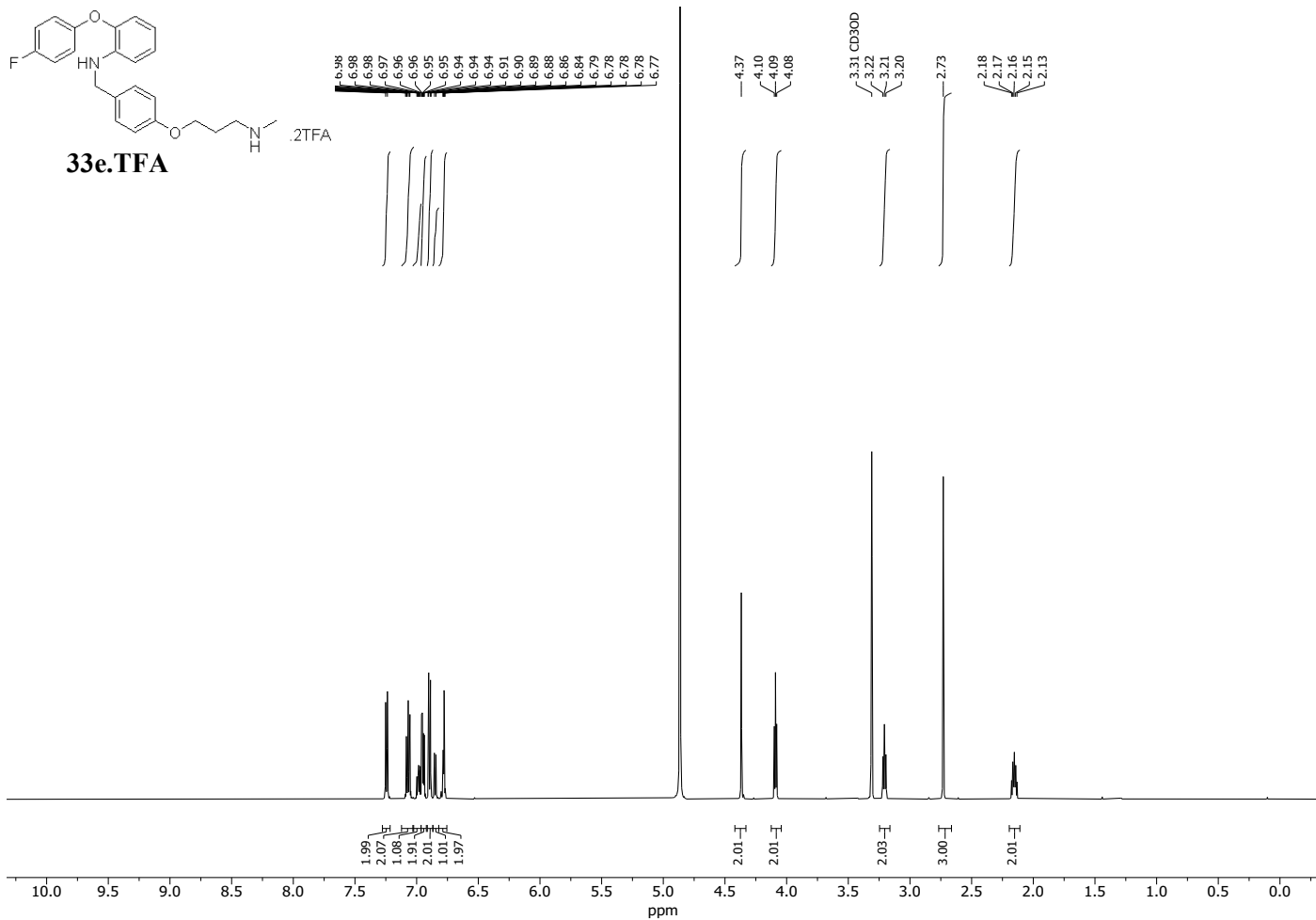
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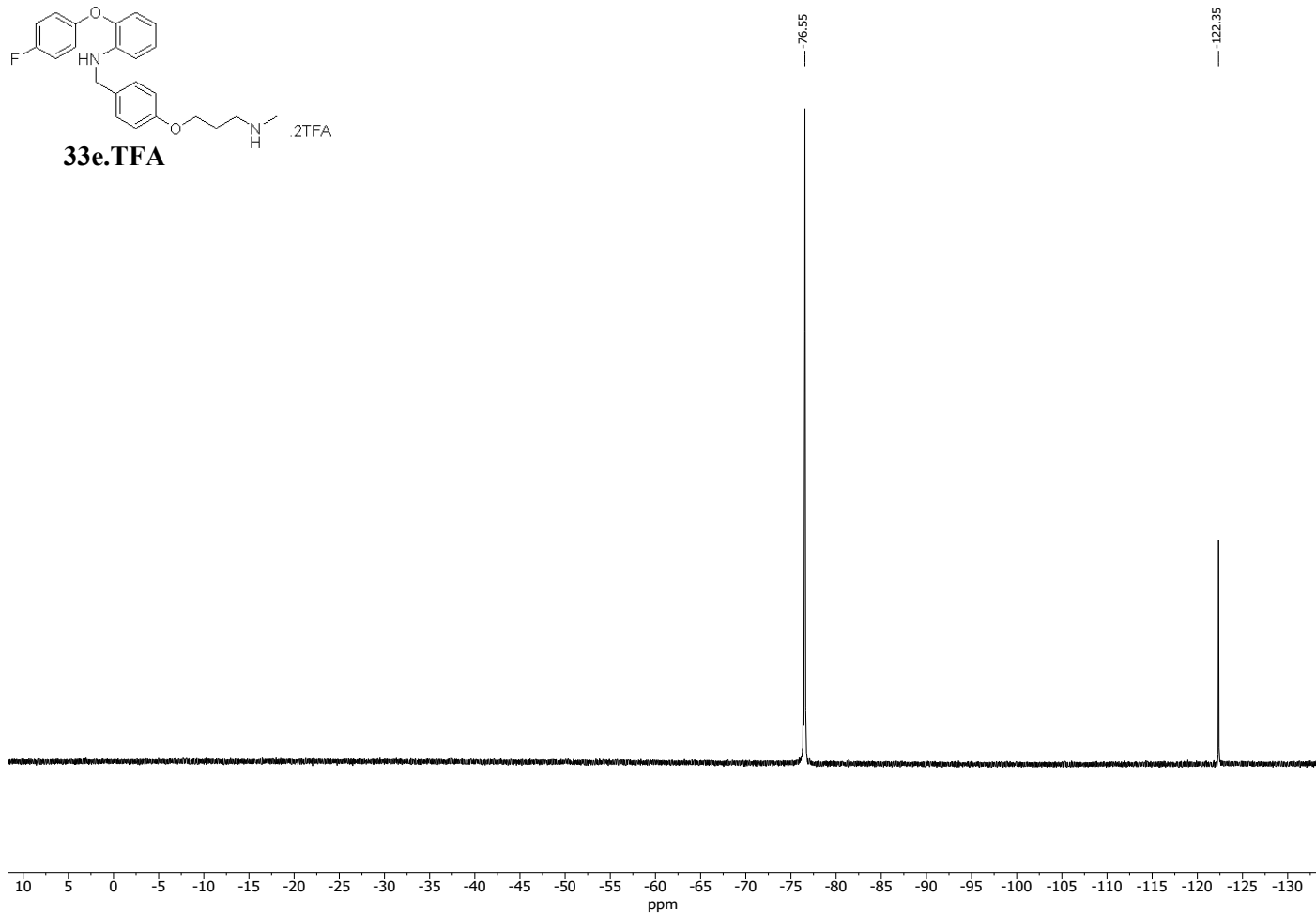
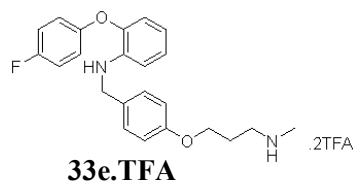


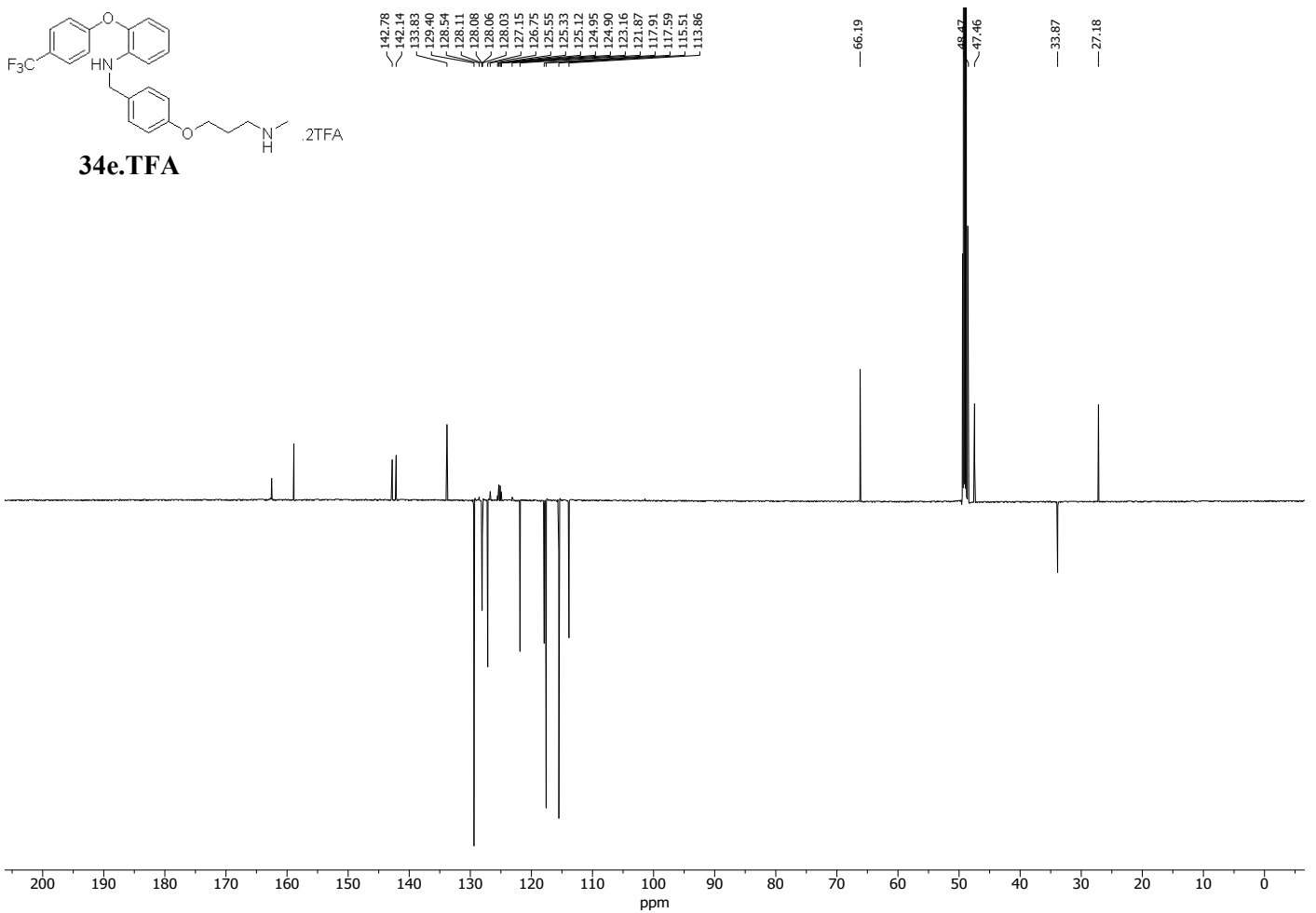
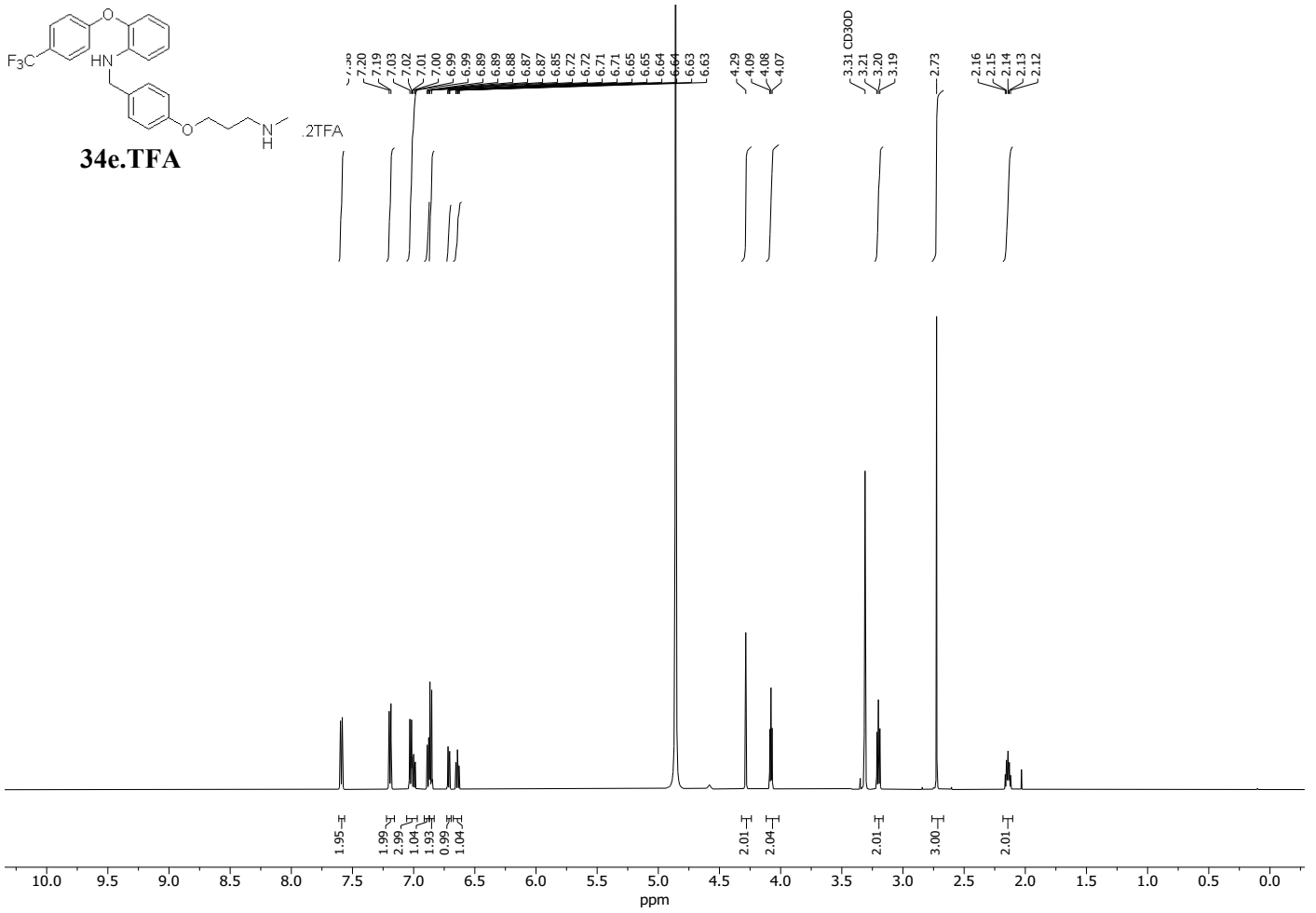


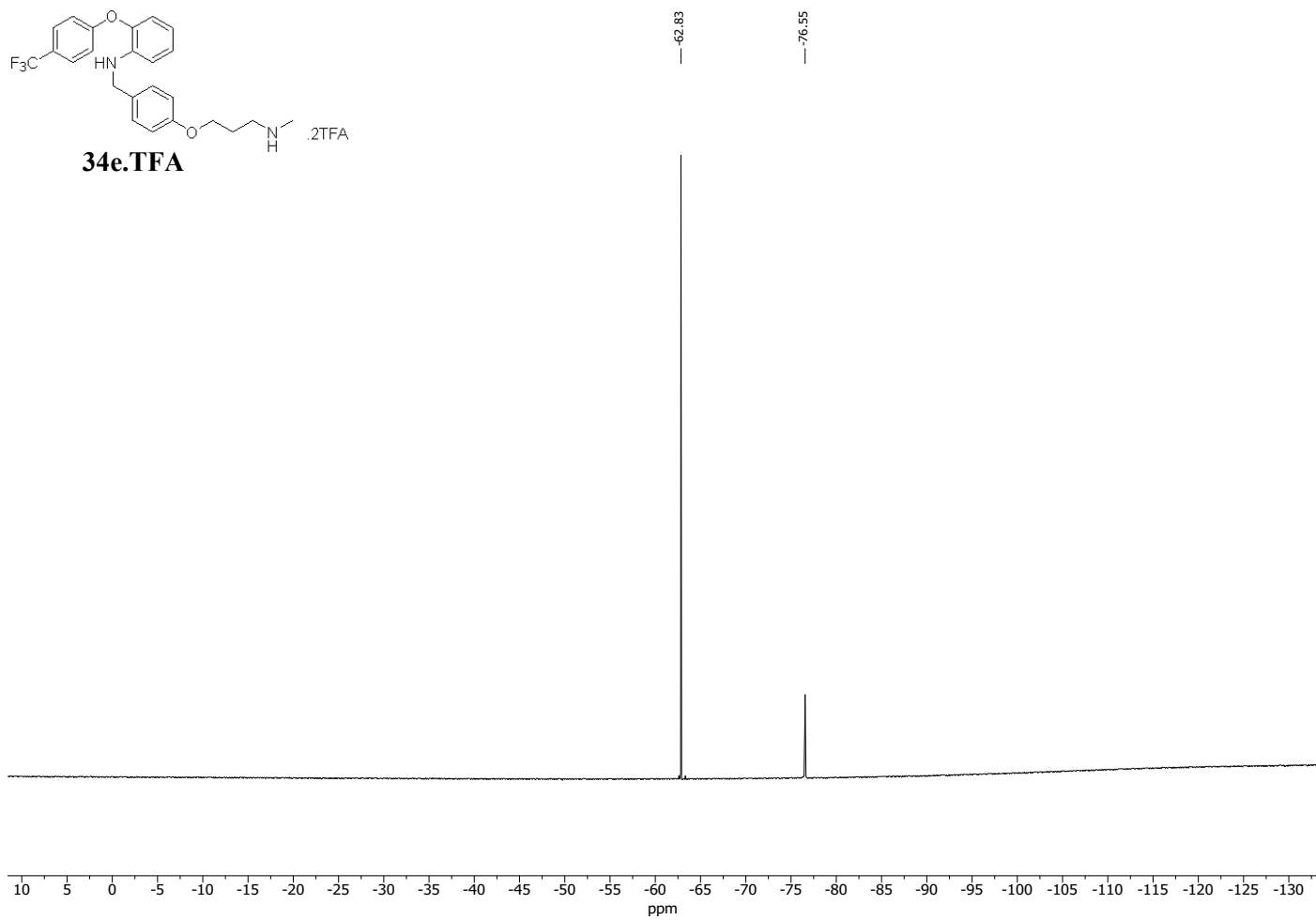
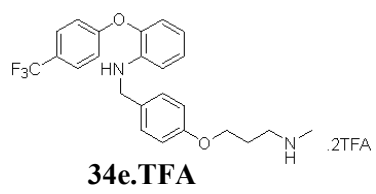
32e.TFA

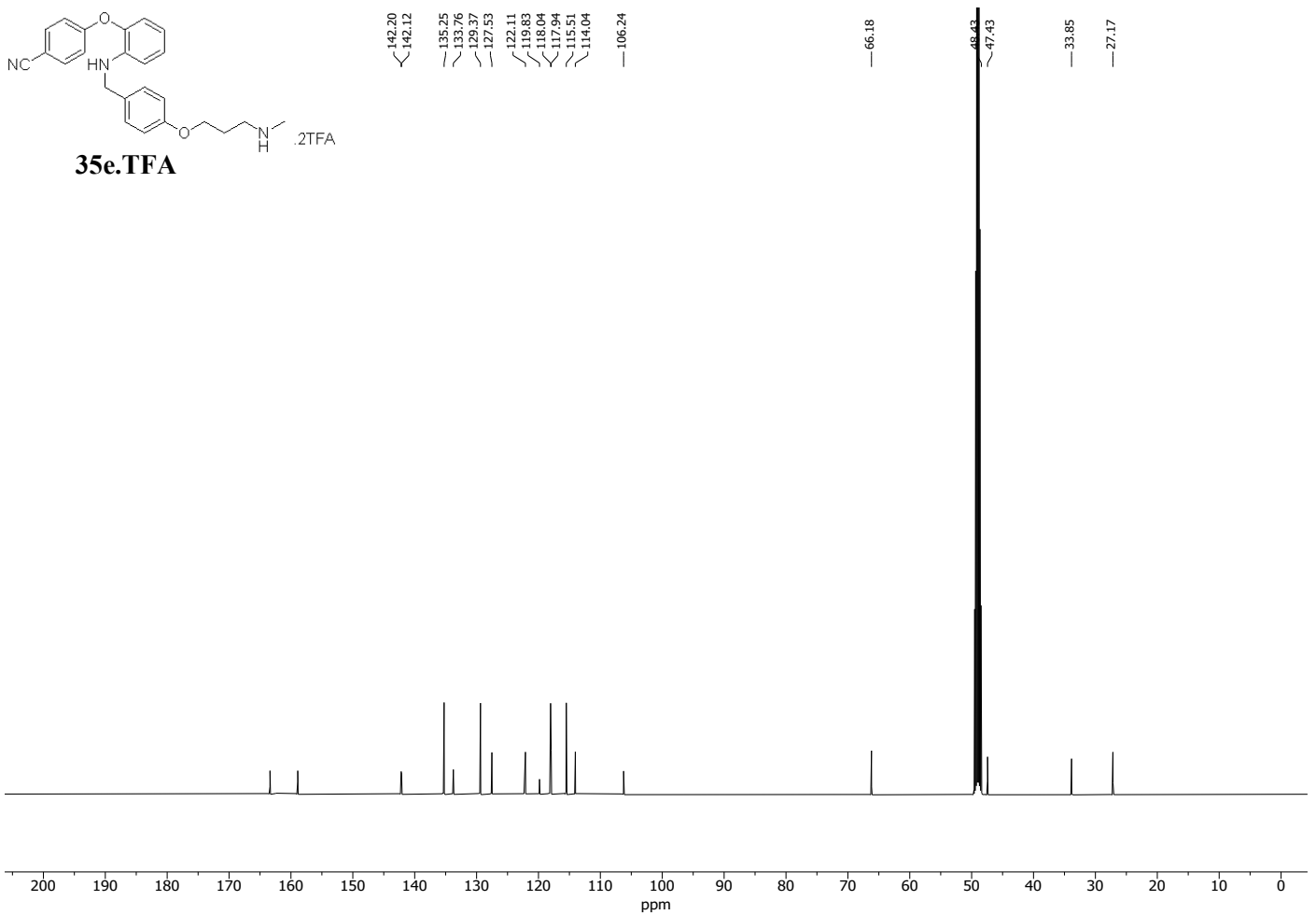
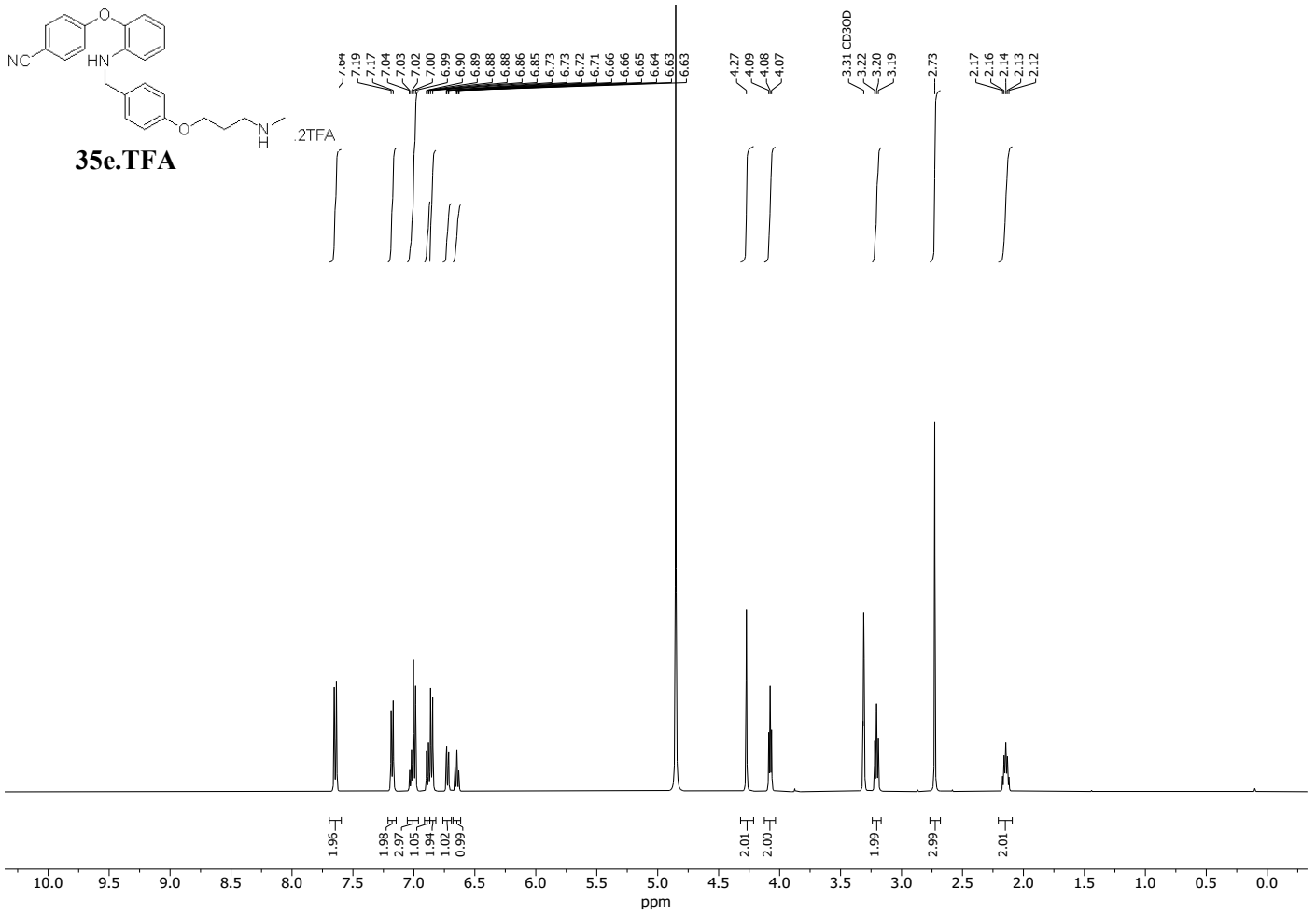


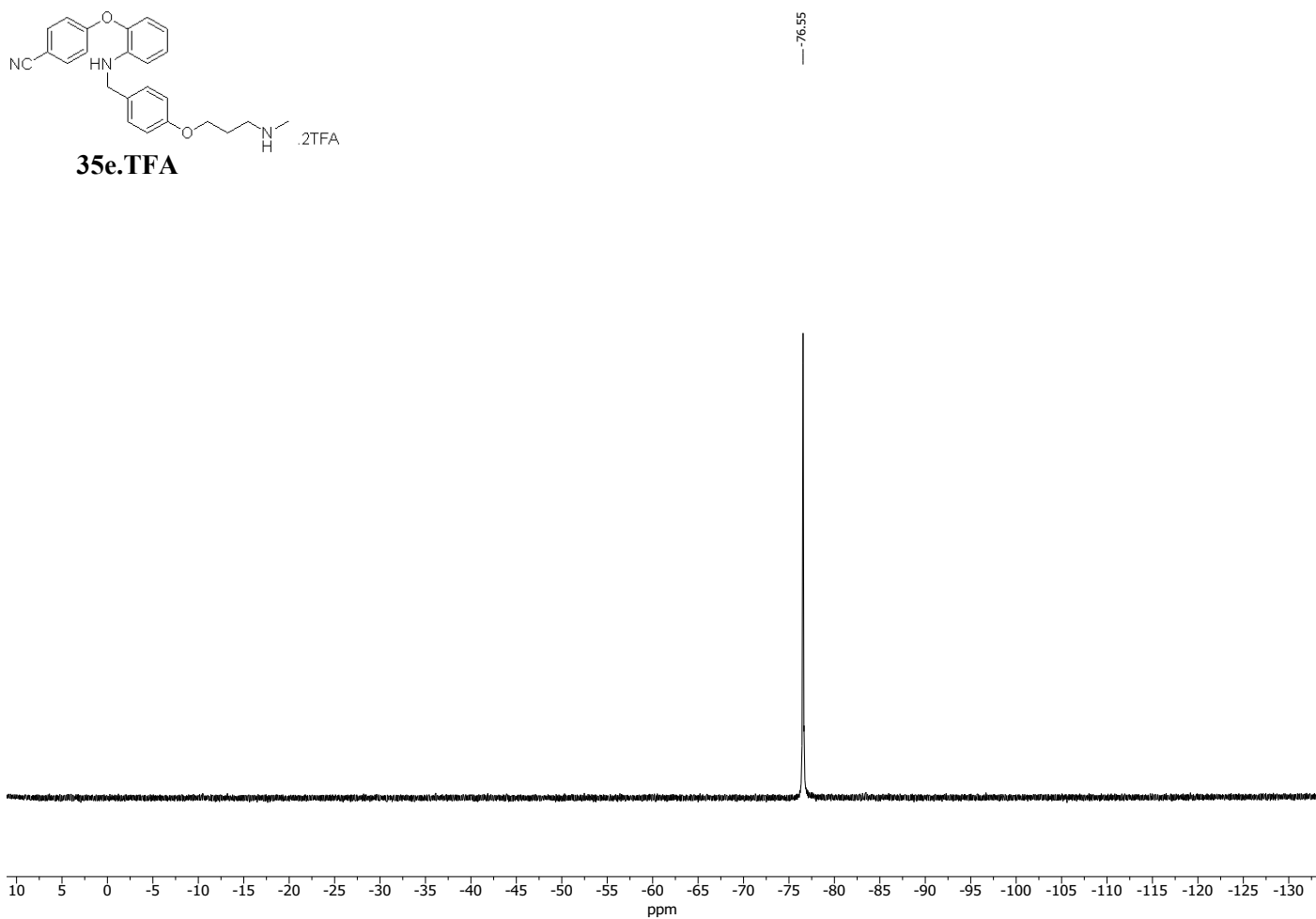
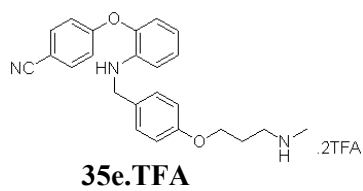




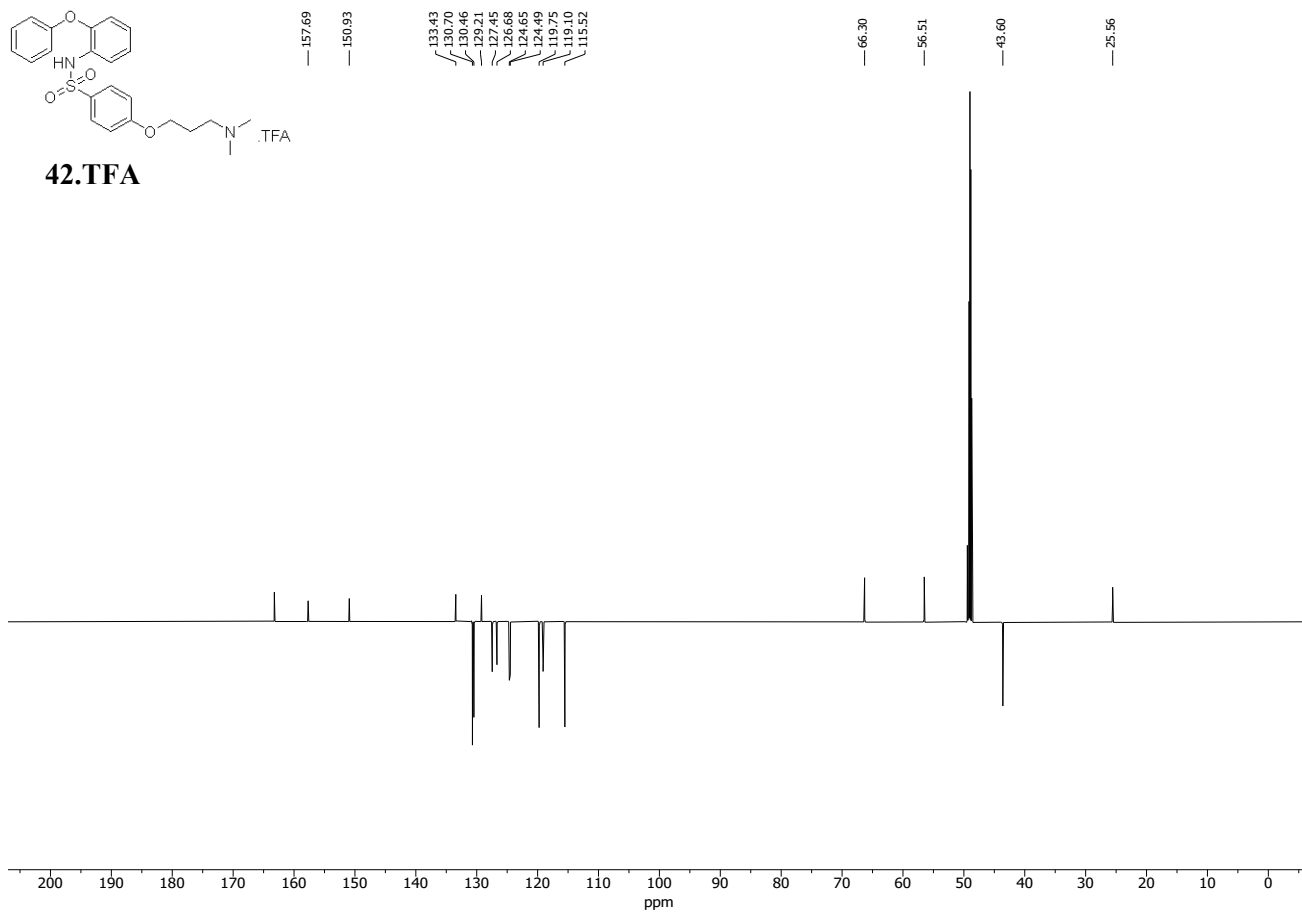
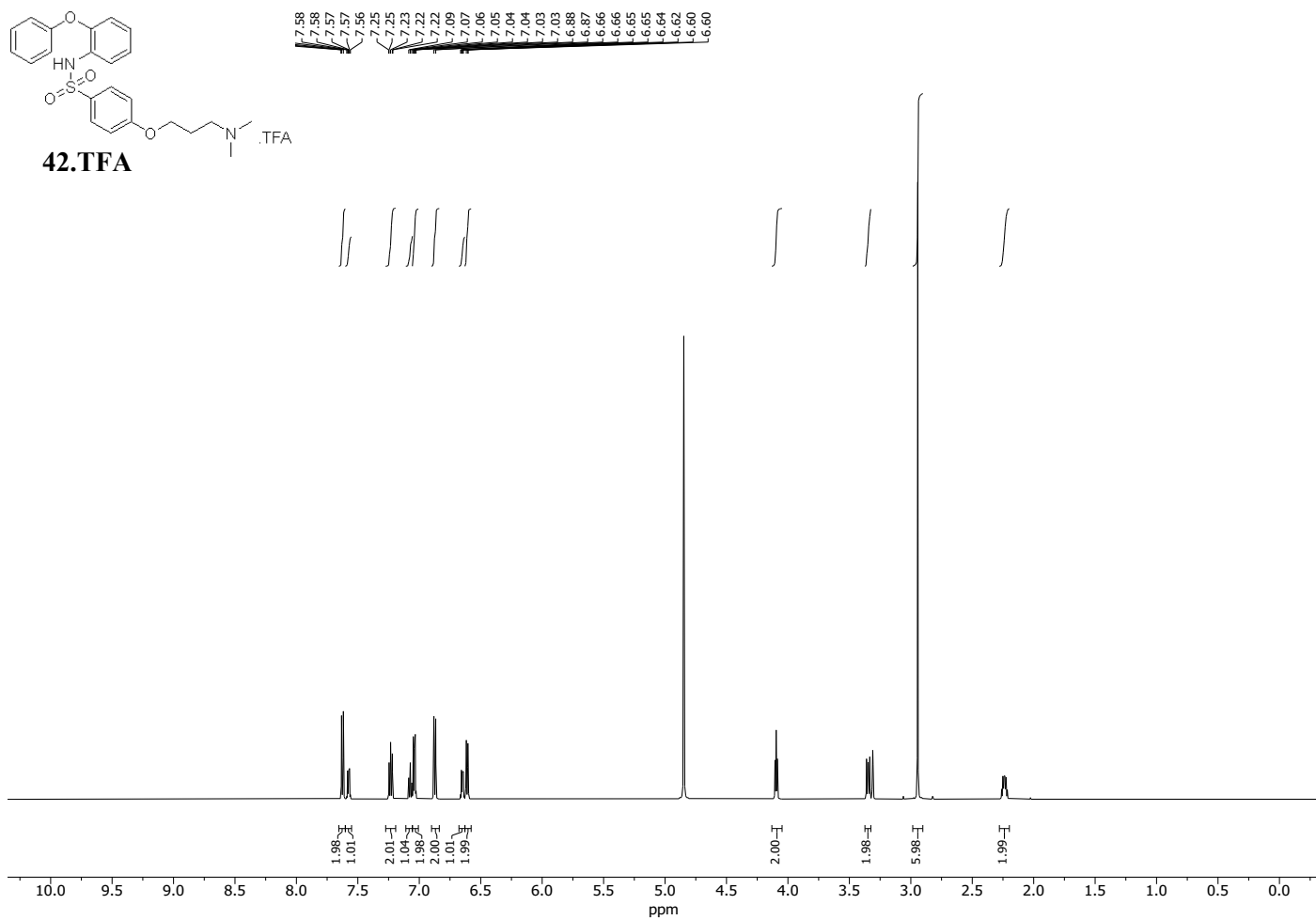


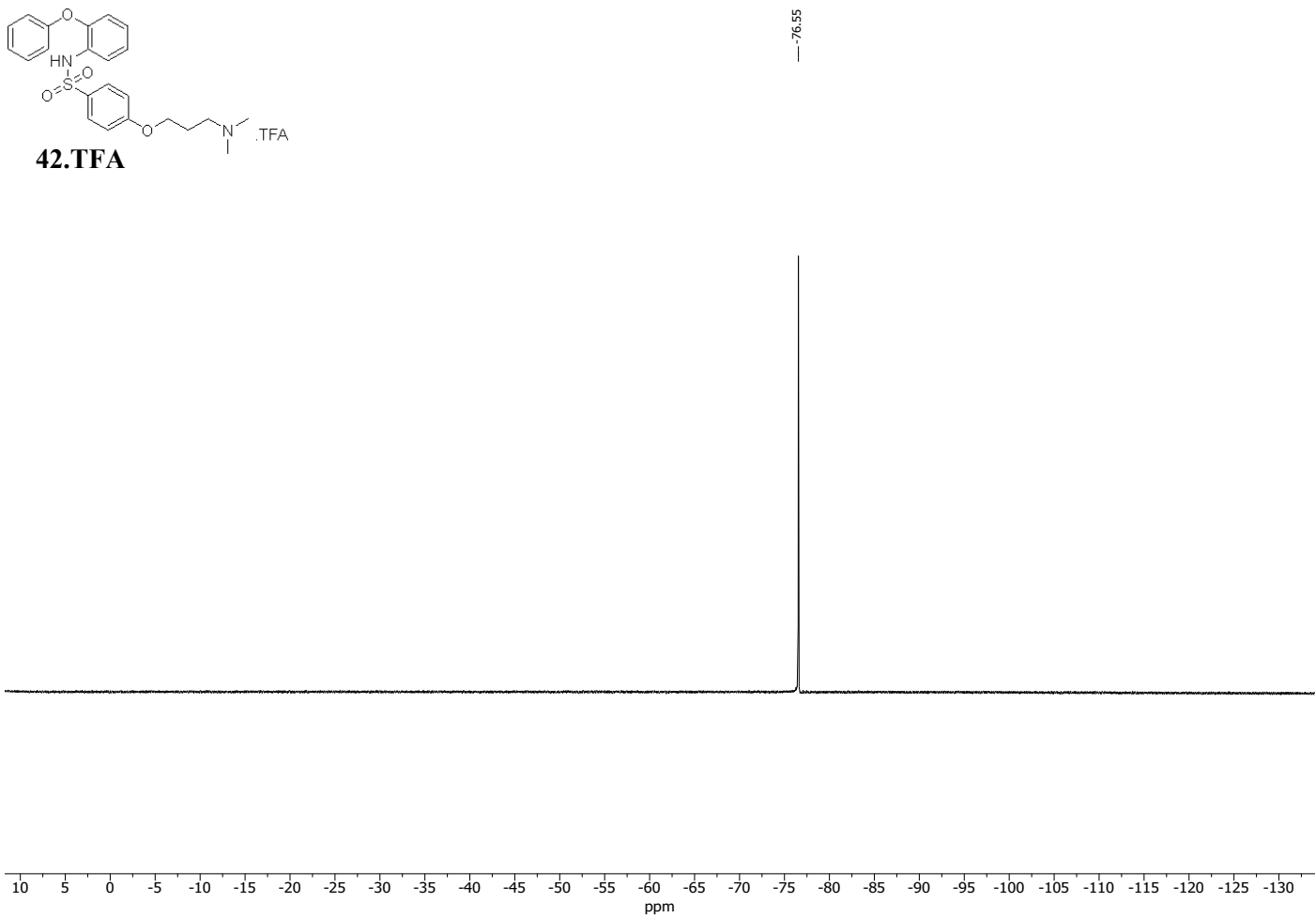
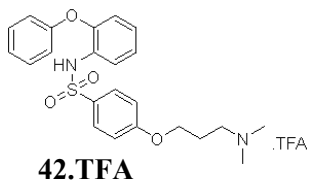


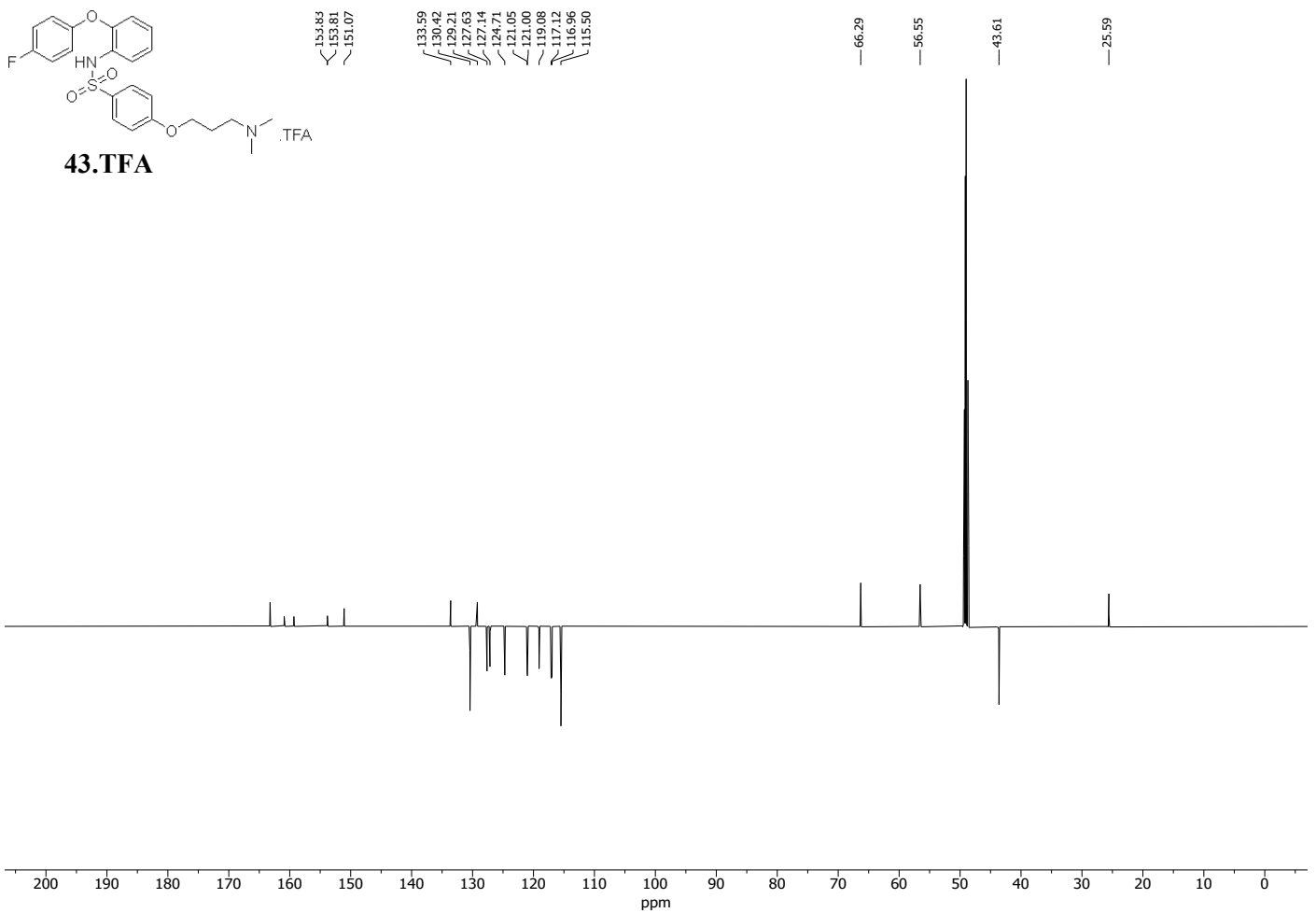
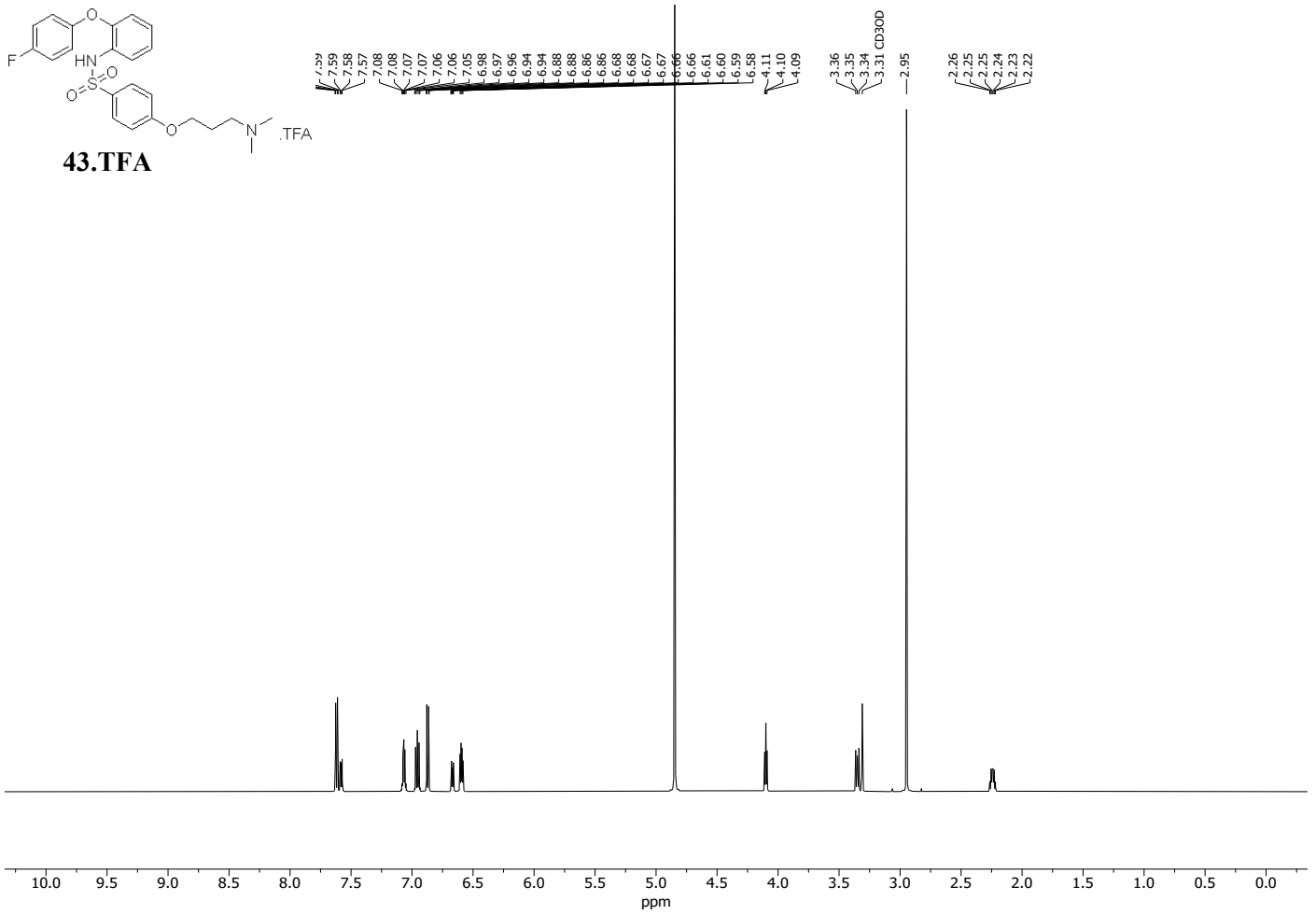


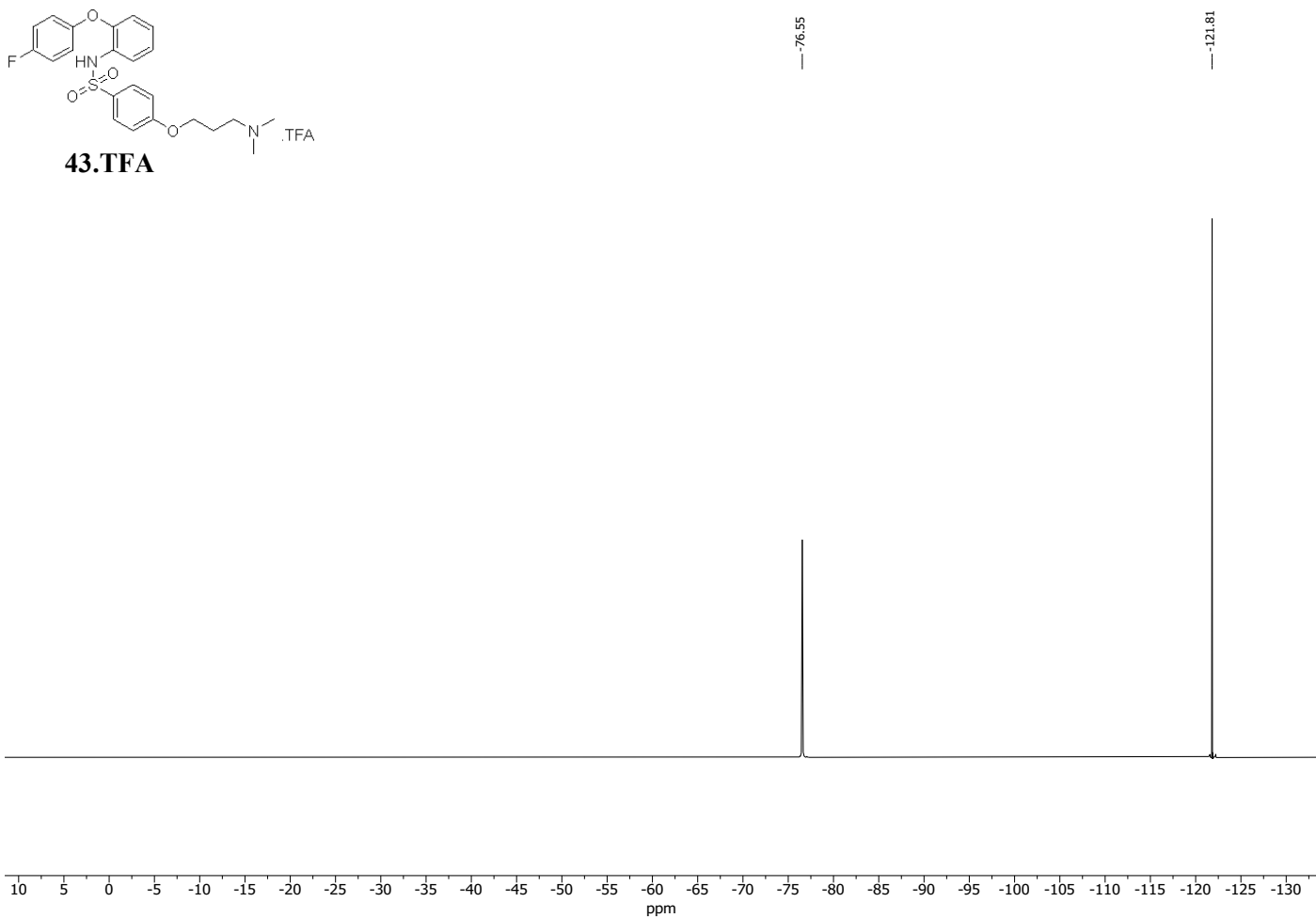
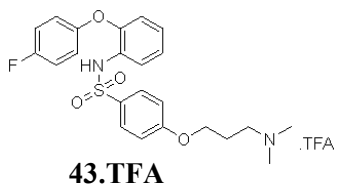


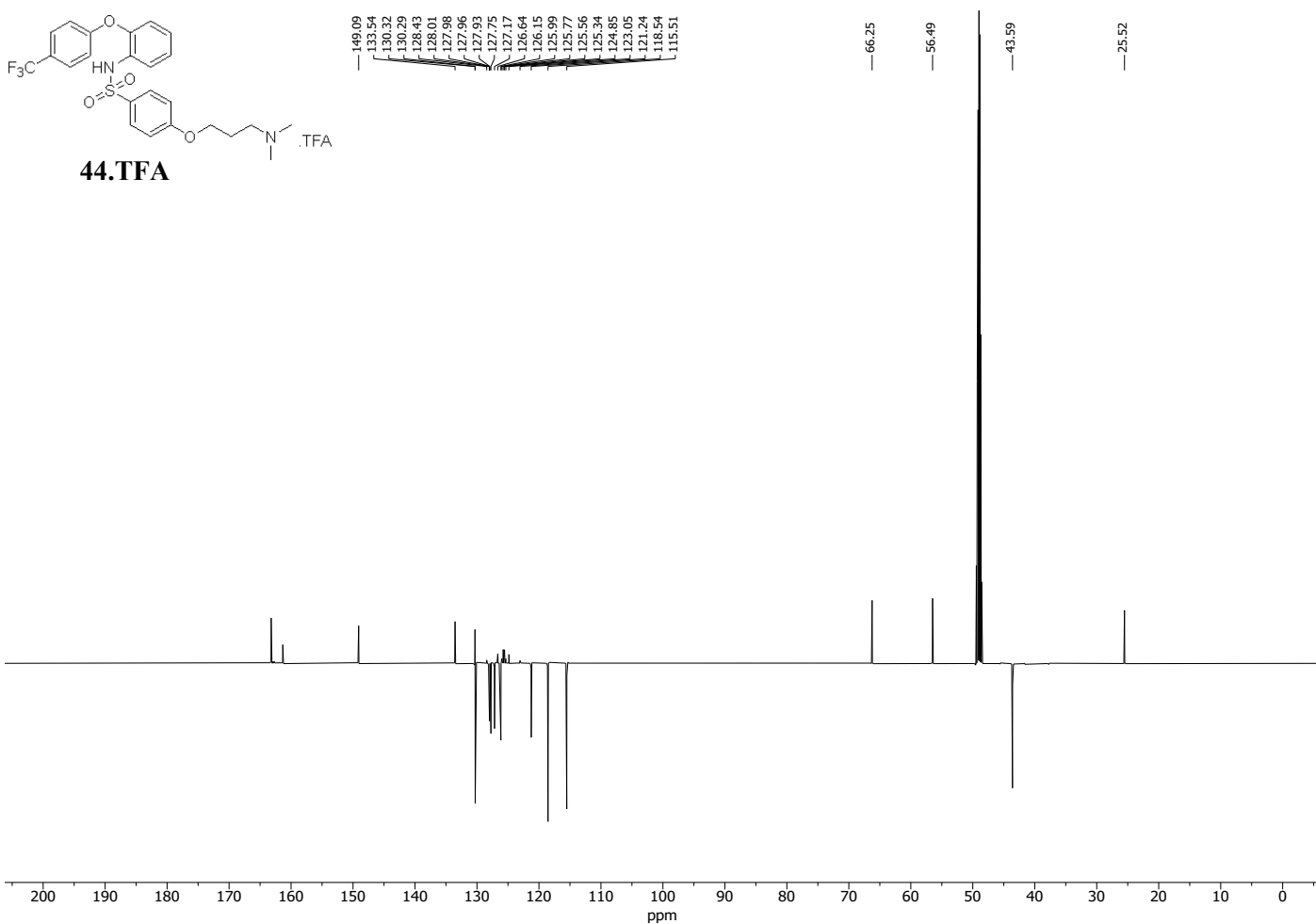
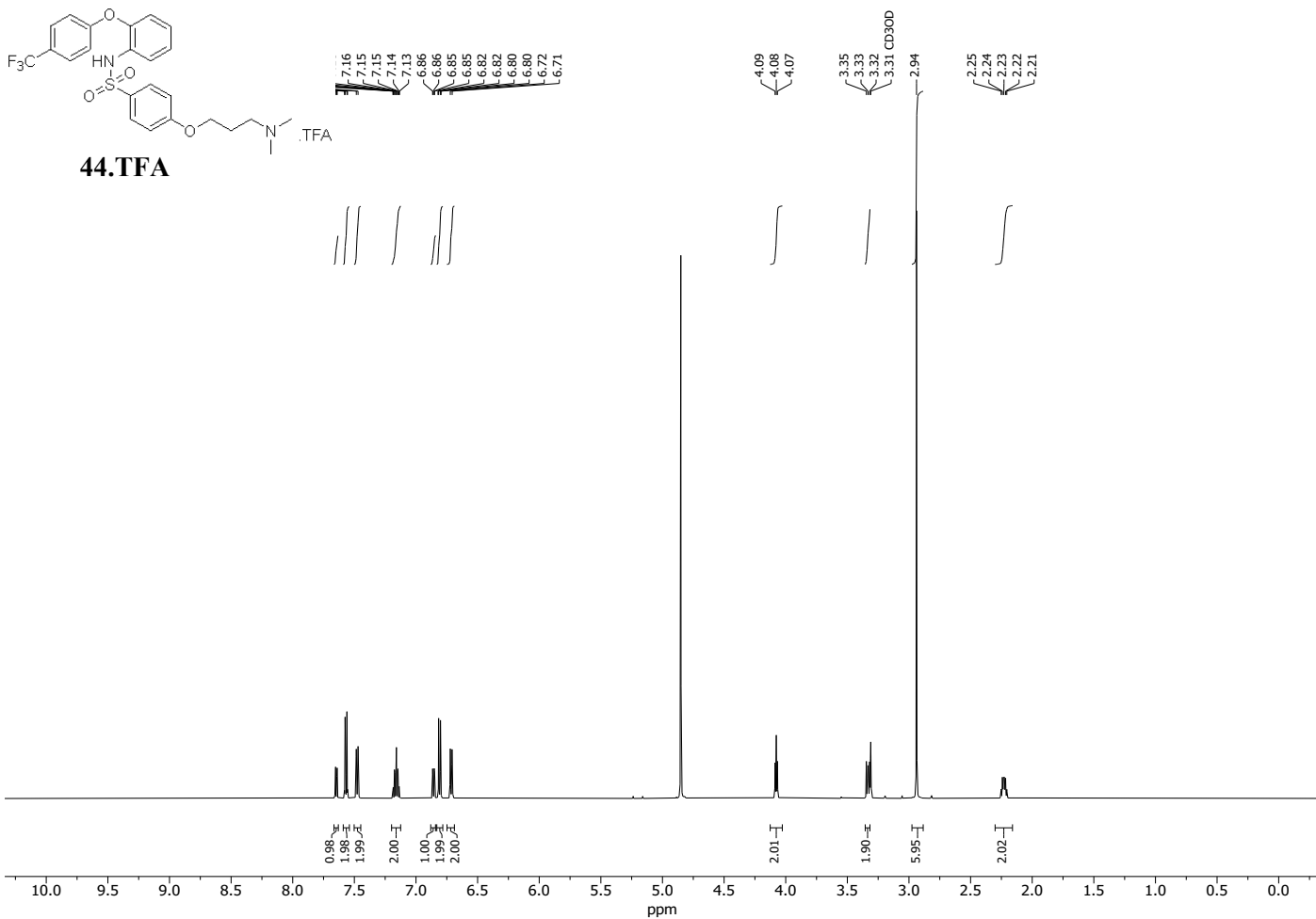
1.5. Spectra of novel sulfonamide compounds

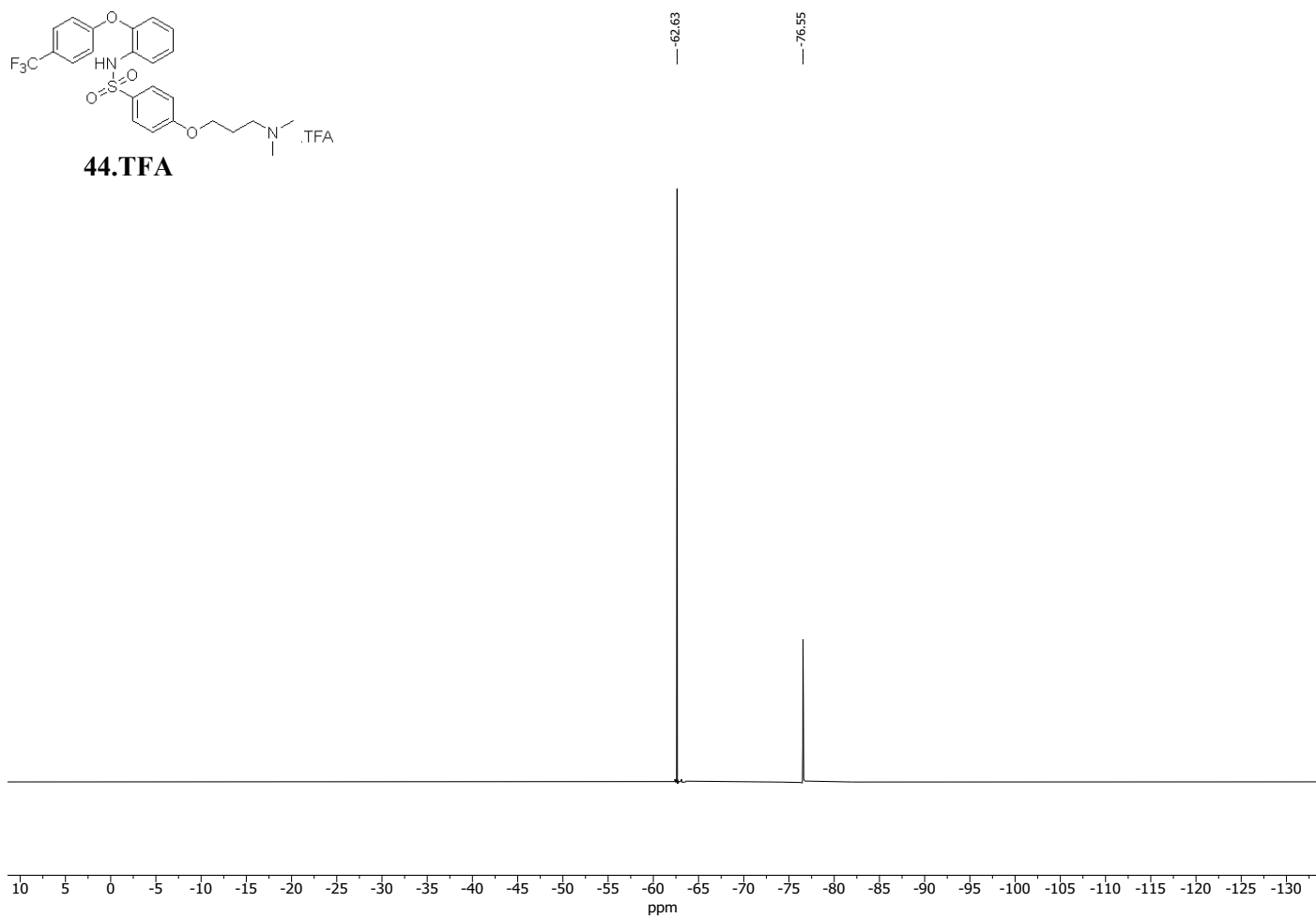
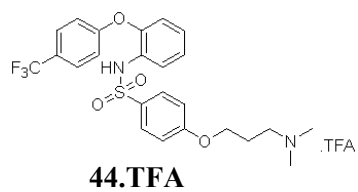


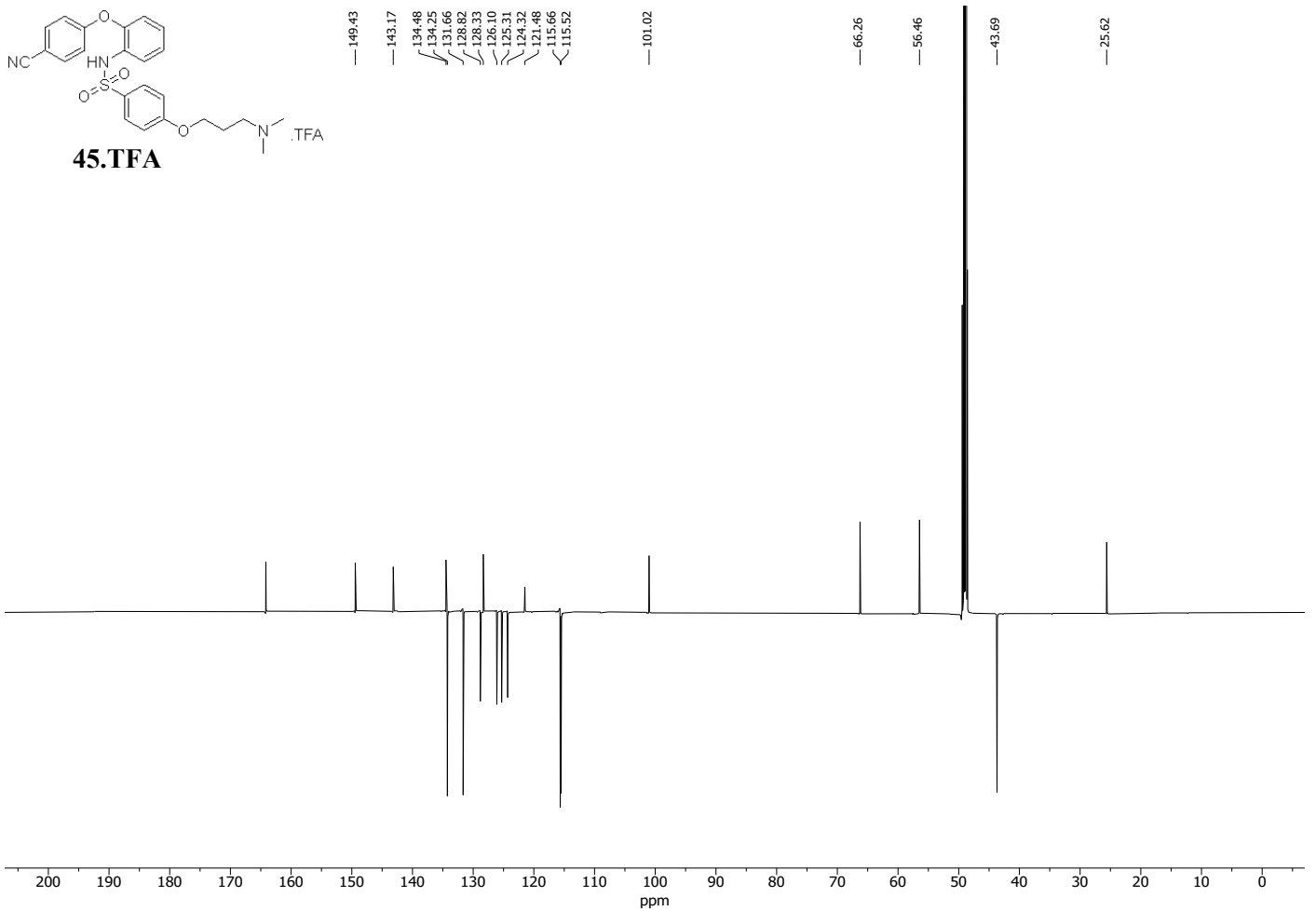
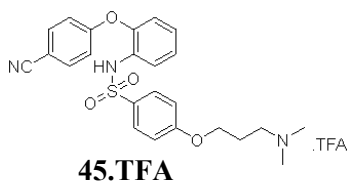
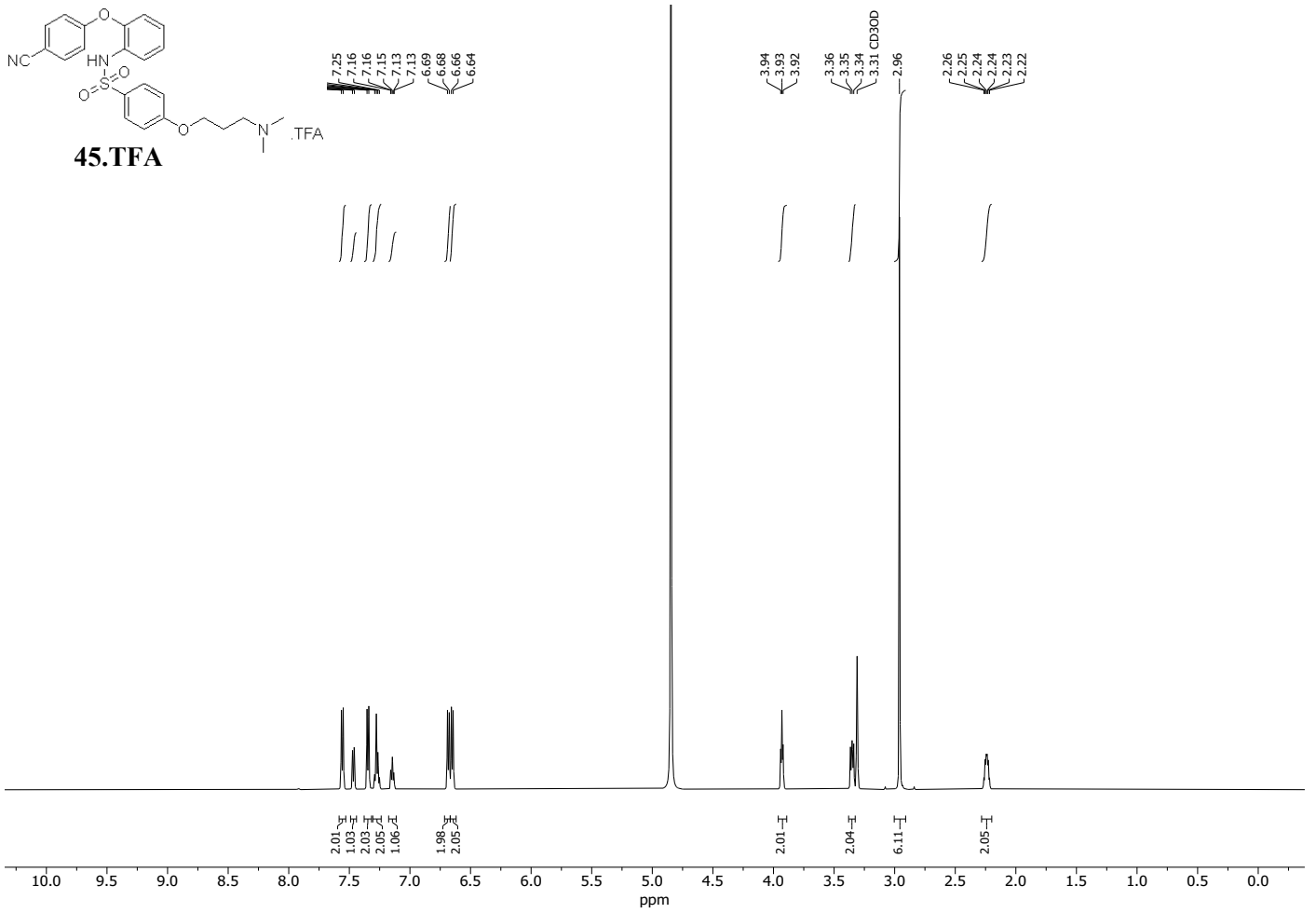
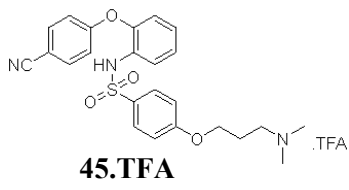


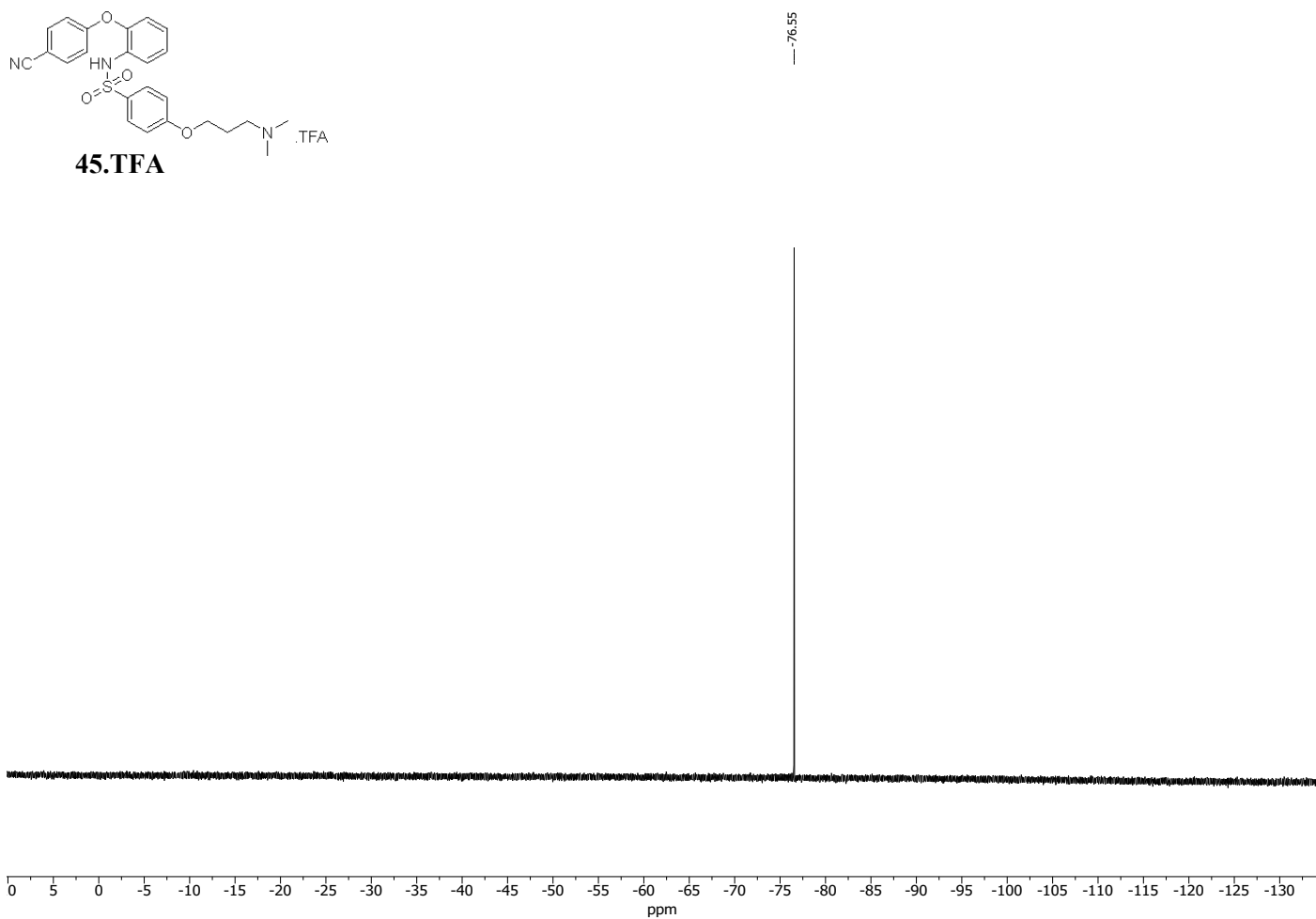
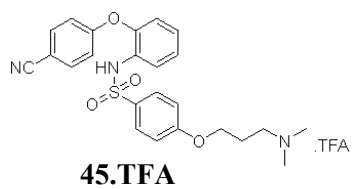


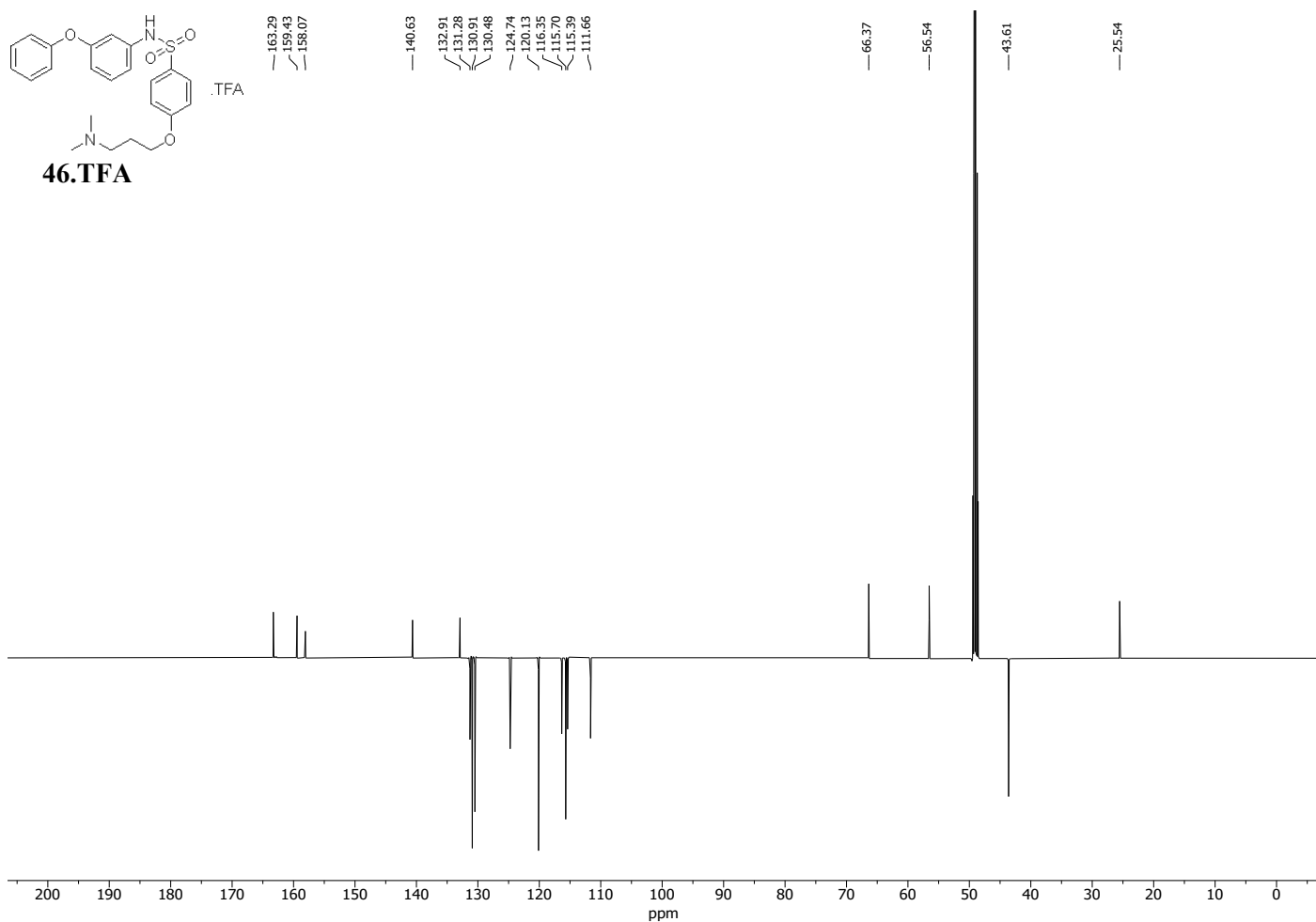
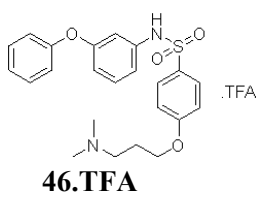
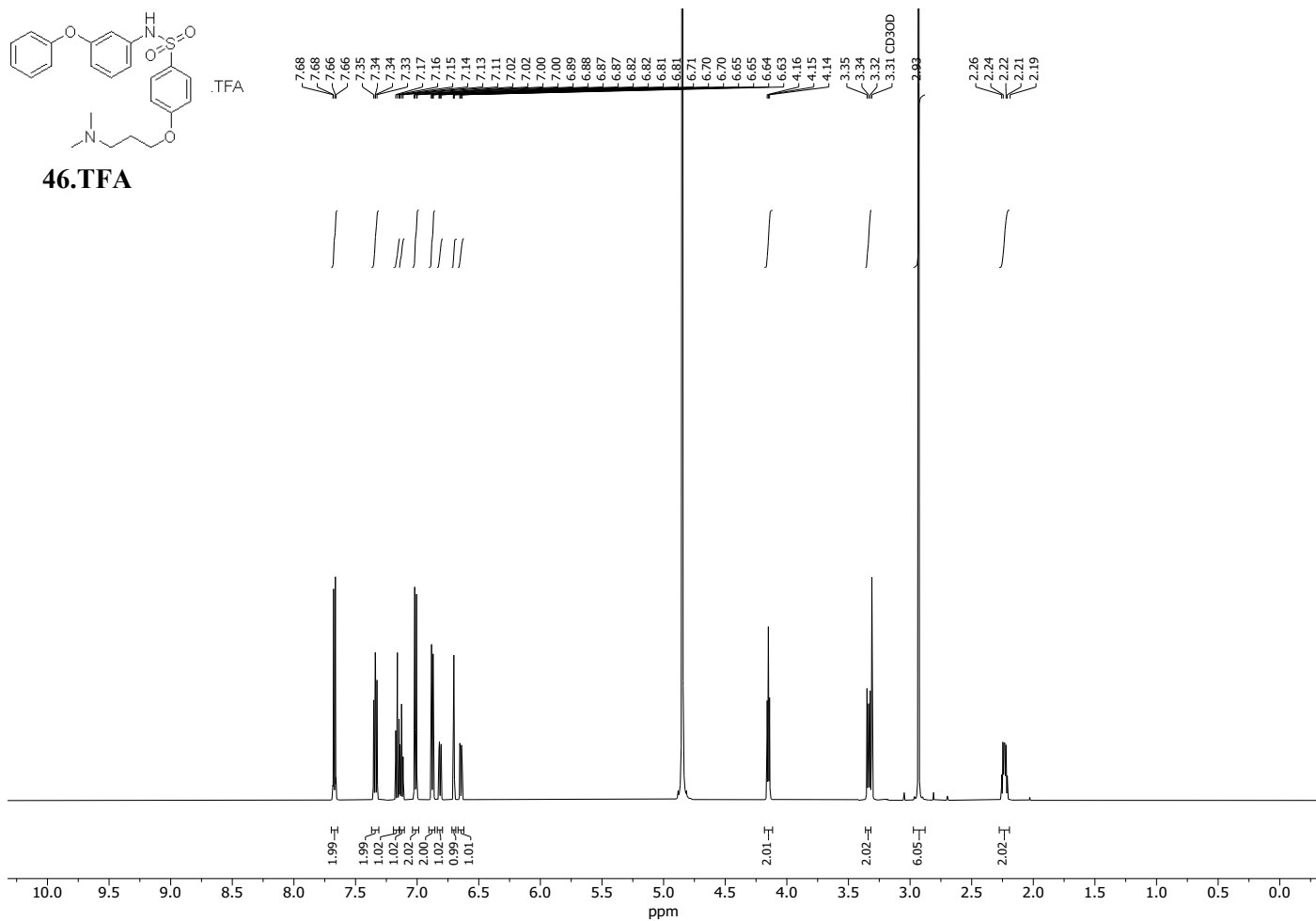
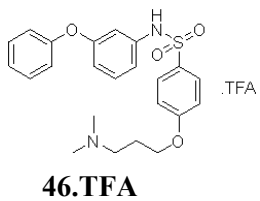


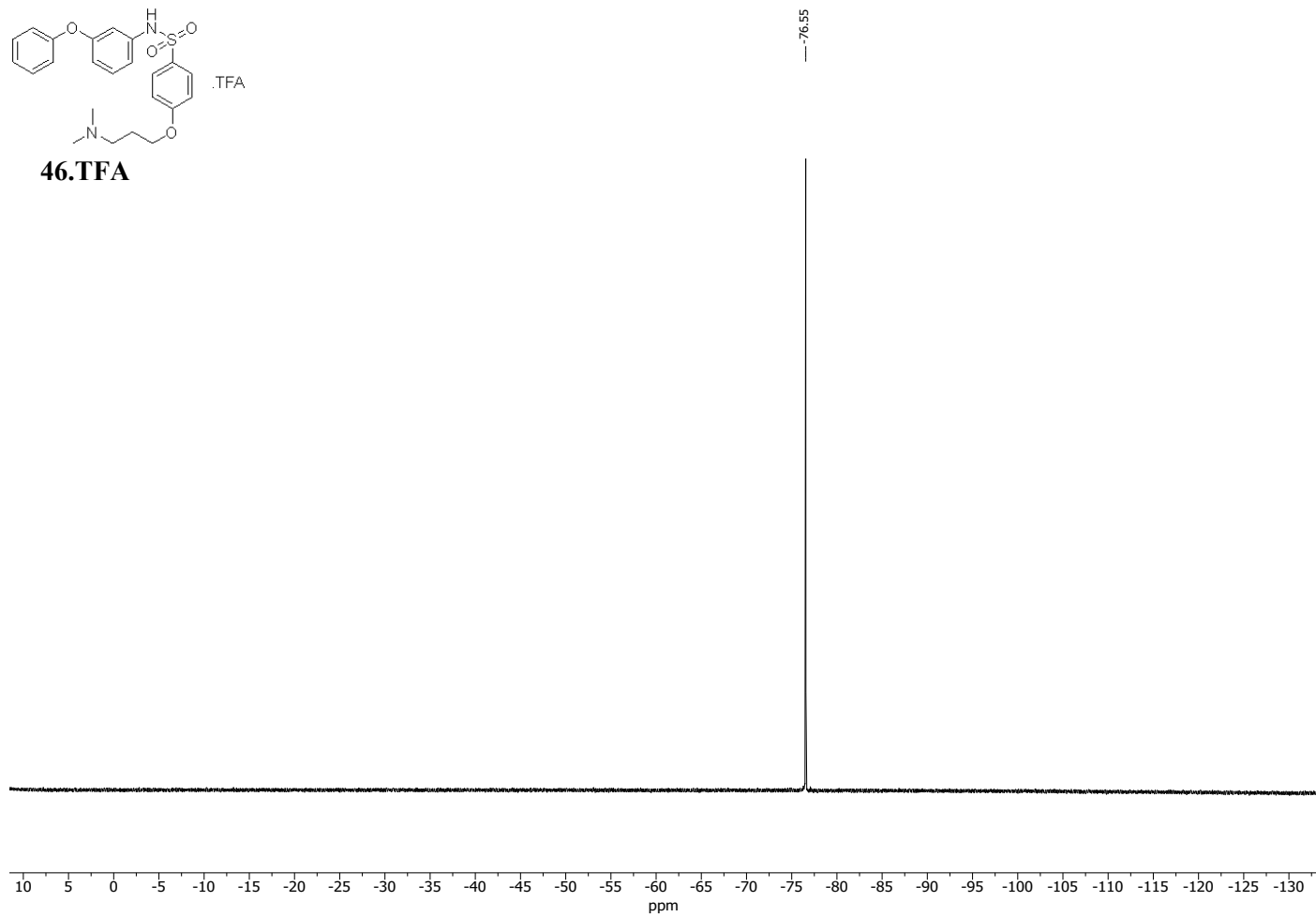
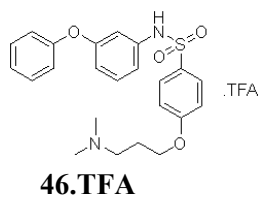


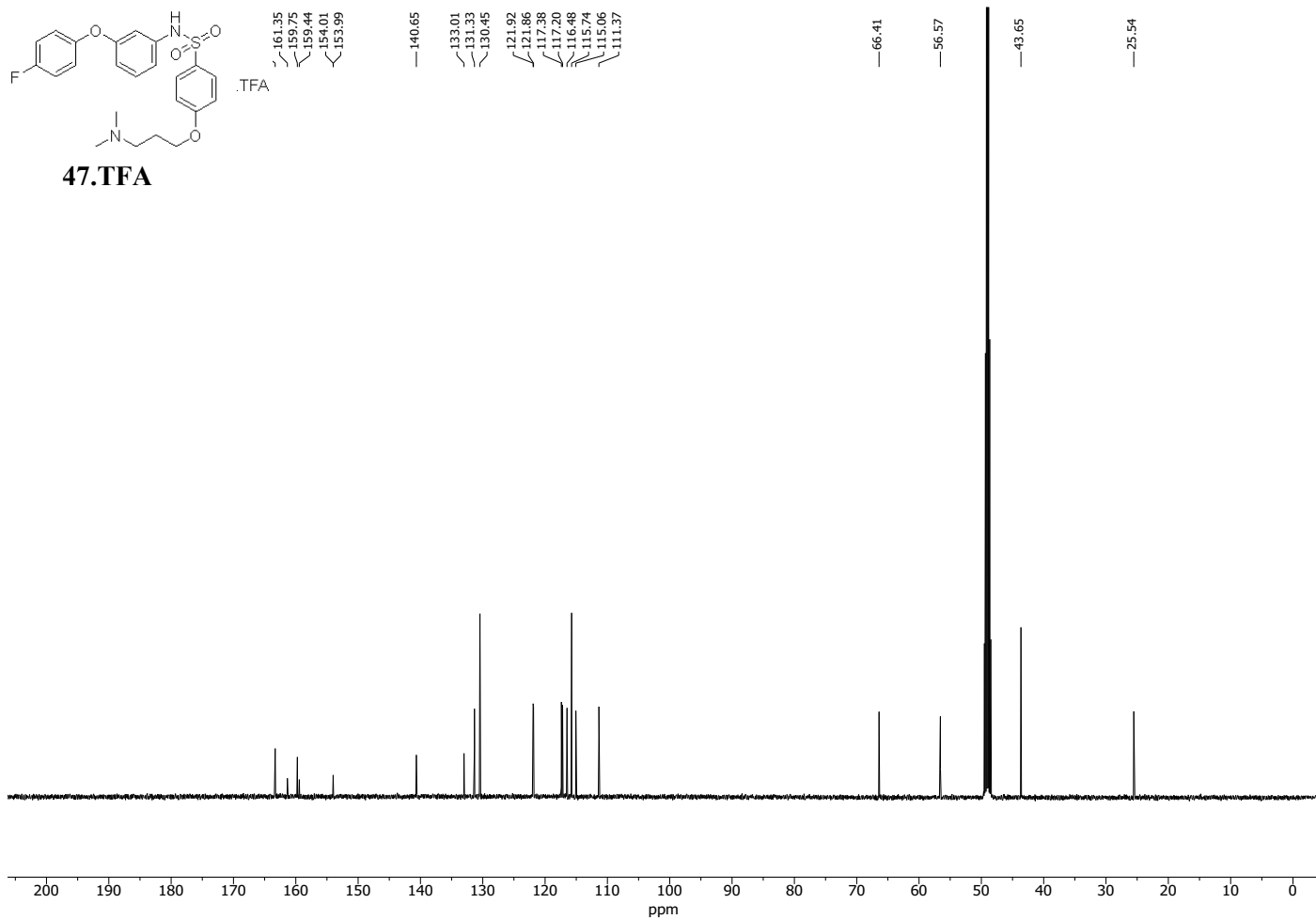
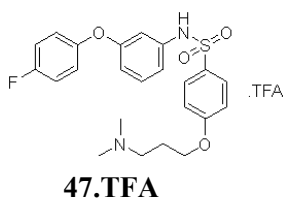
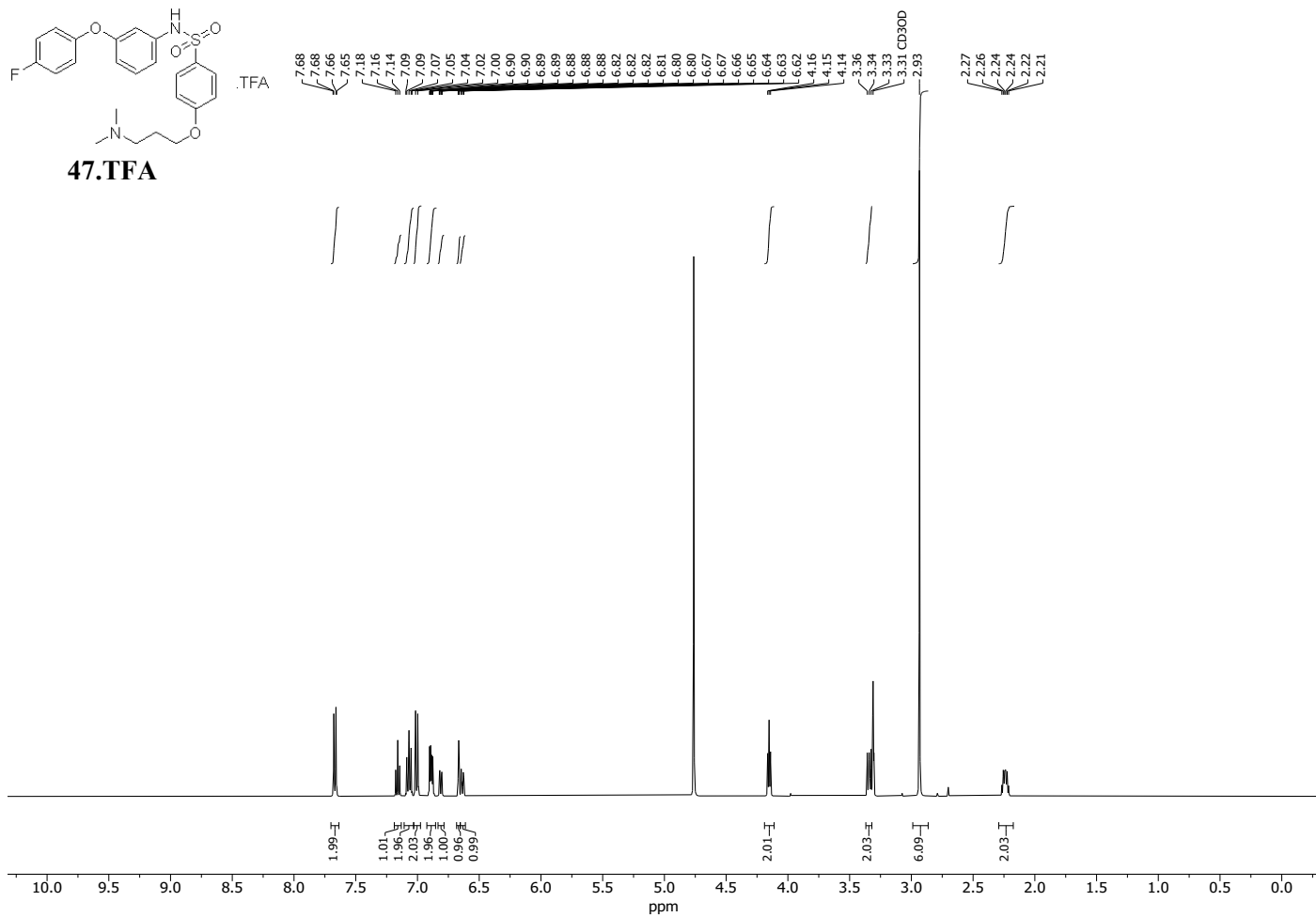
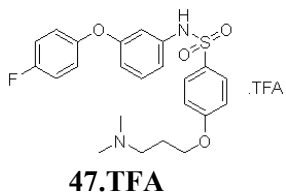


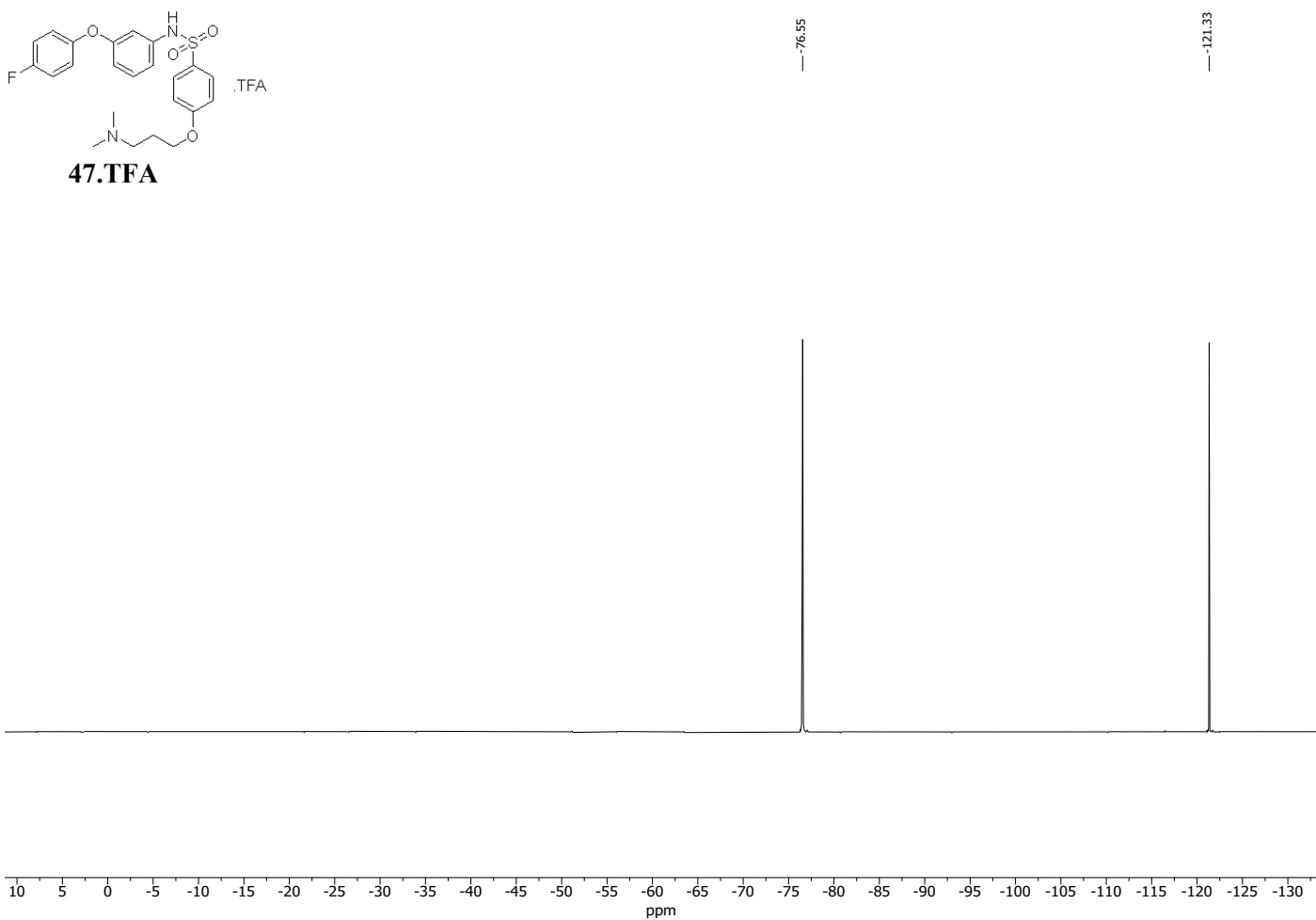
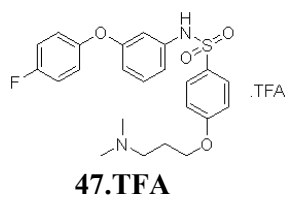


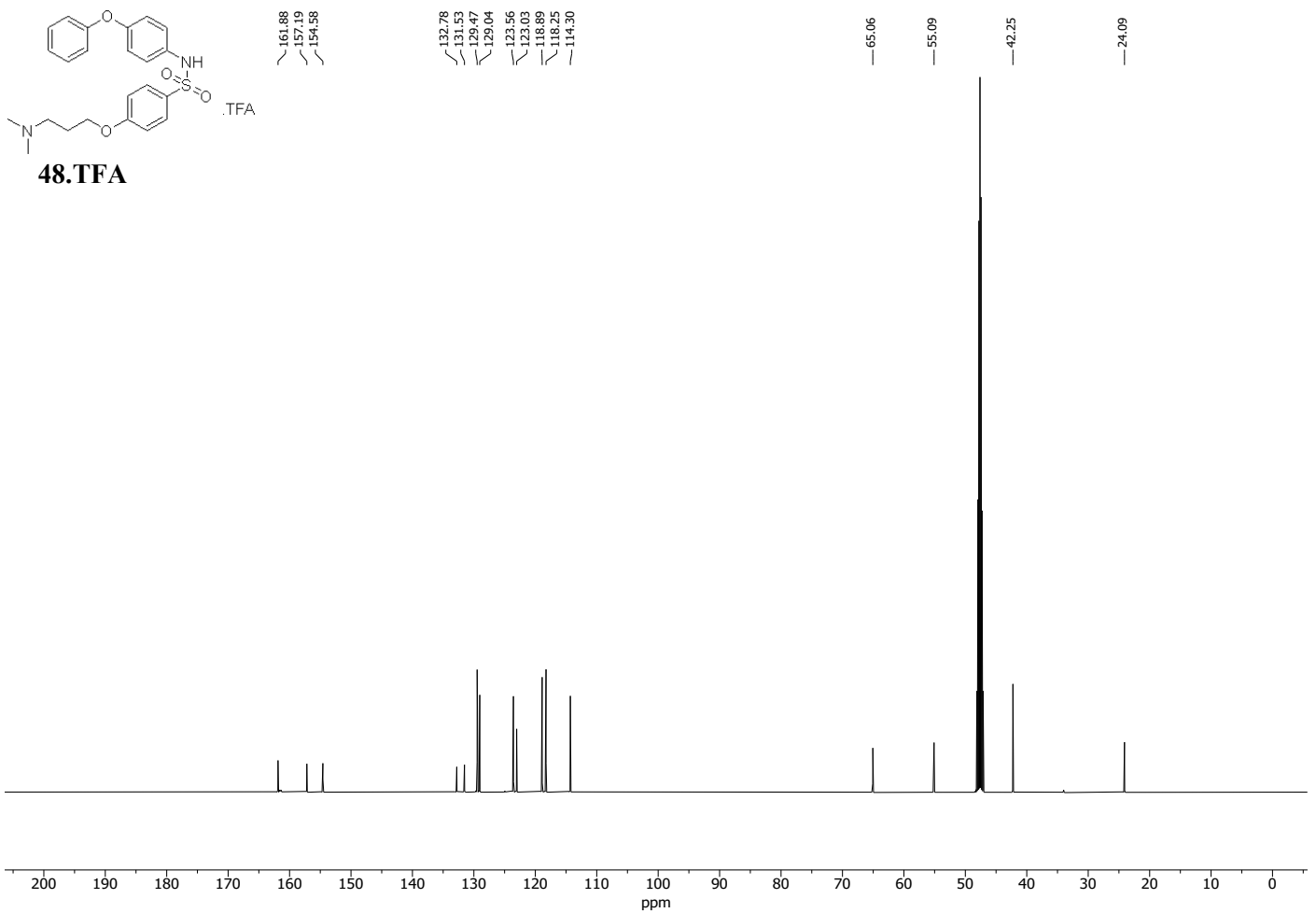
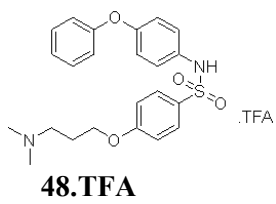
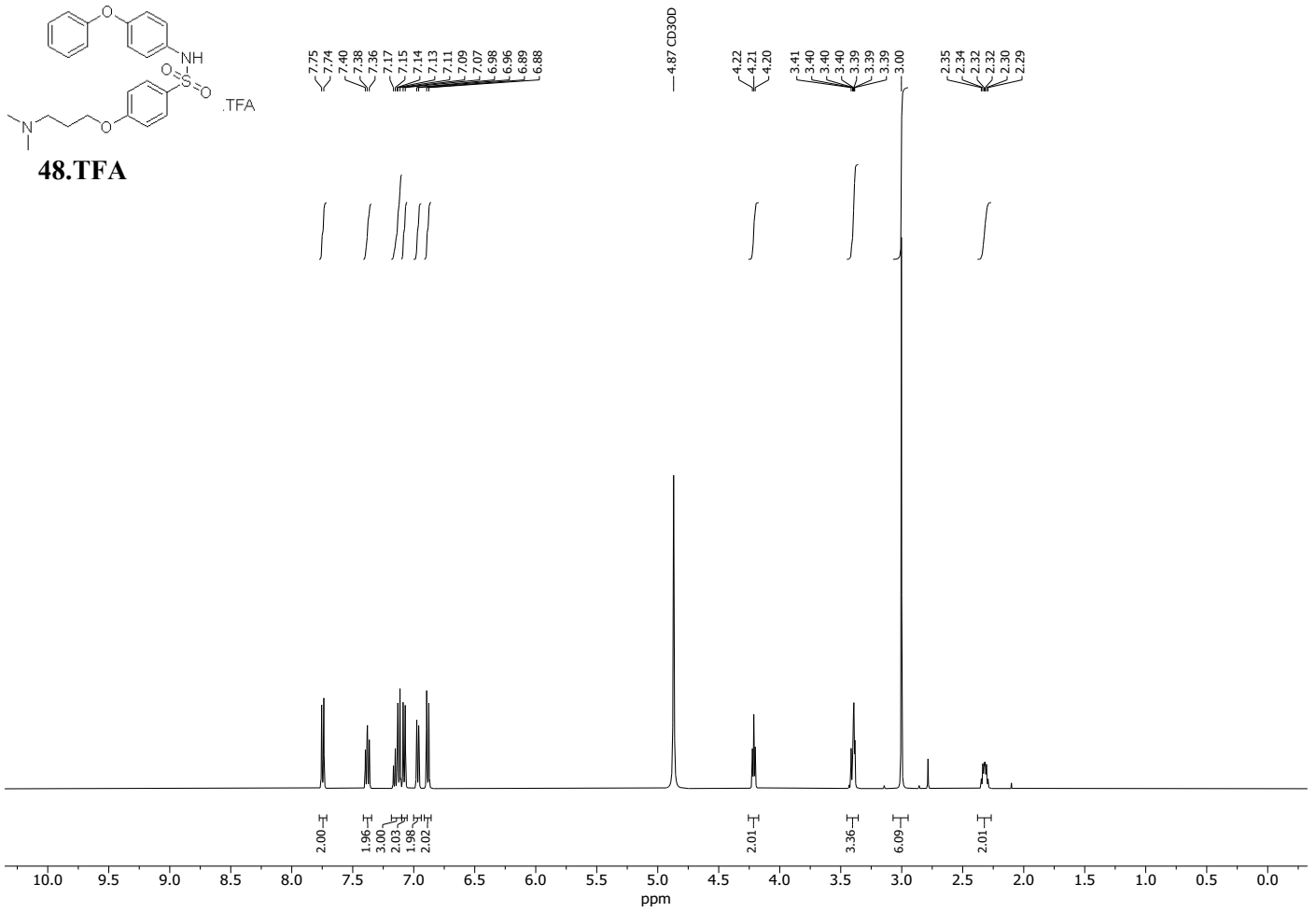
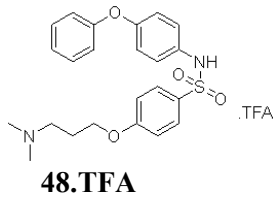


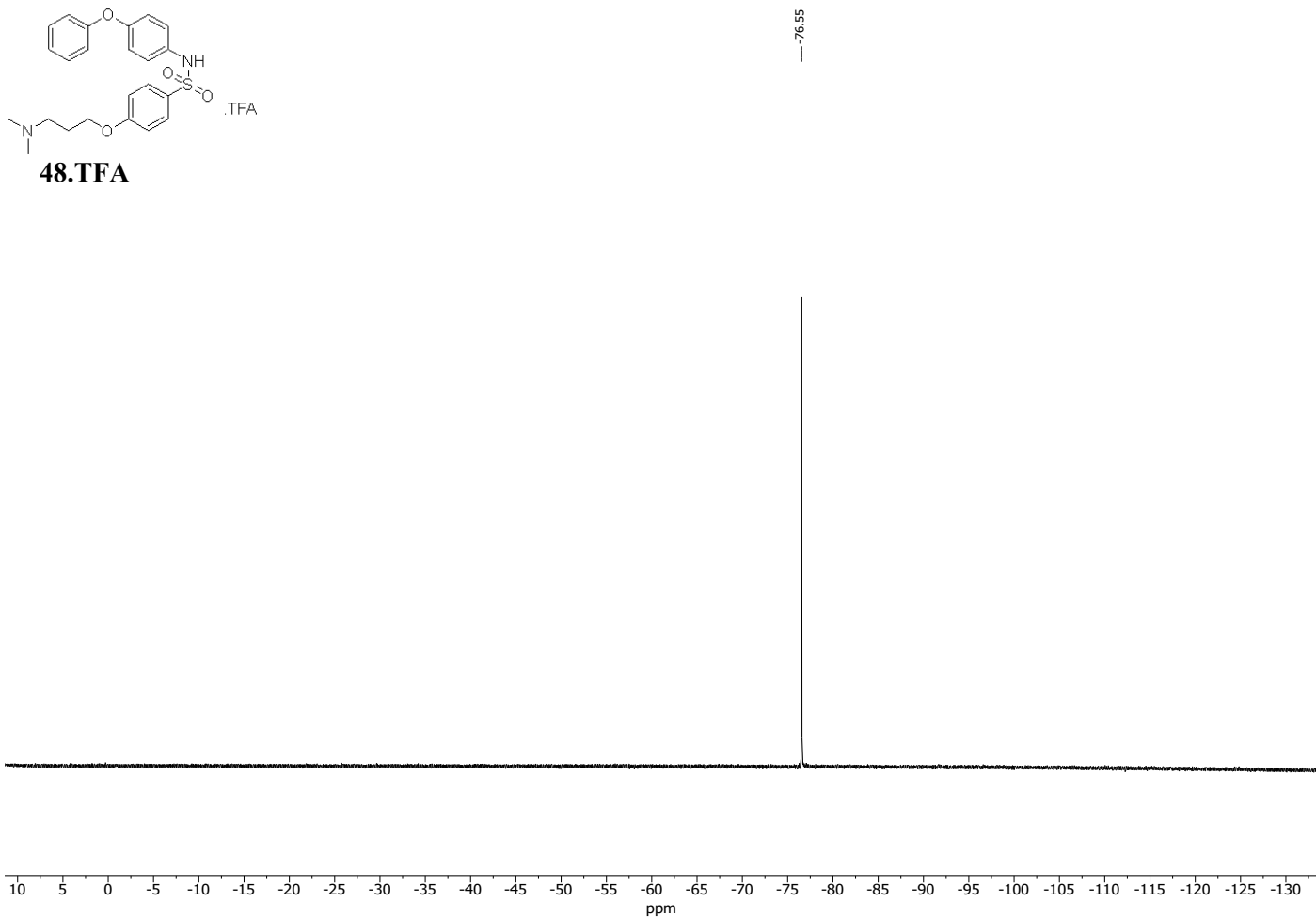
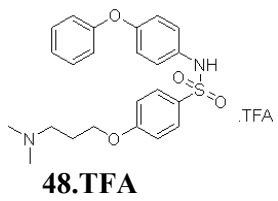


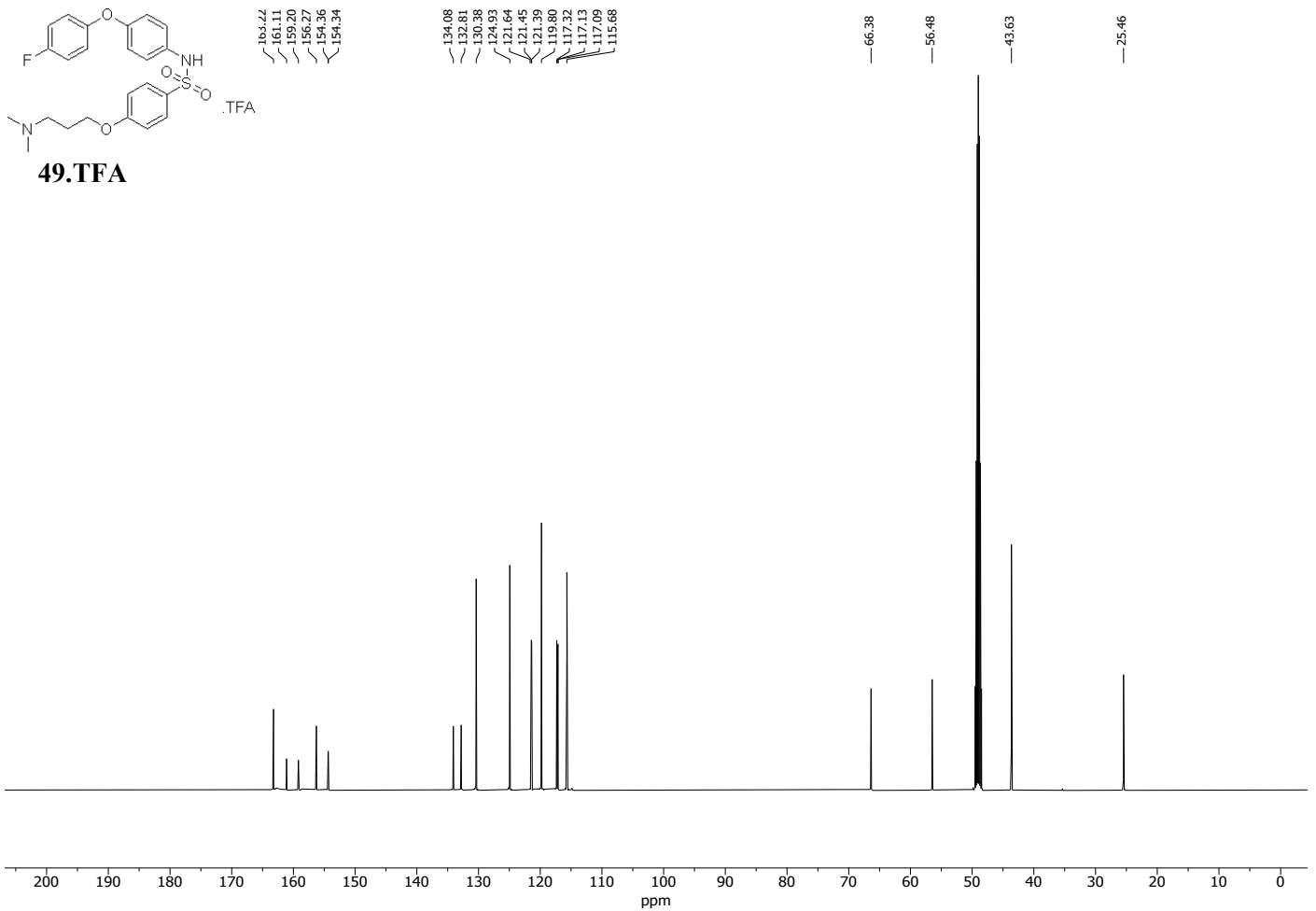
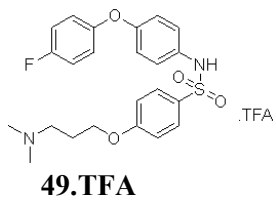
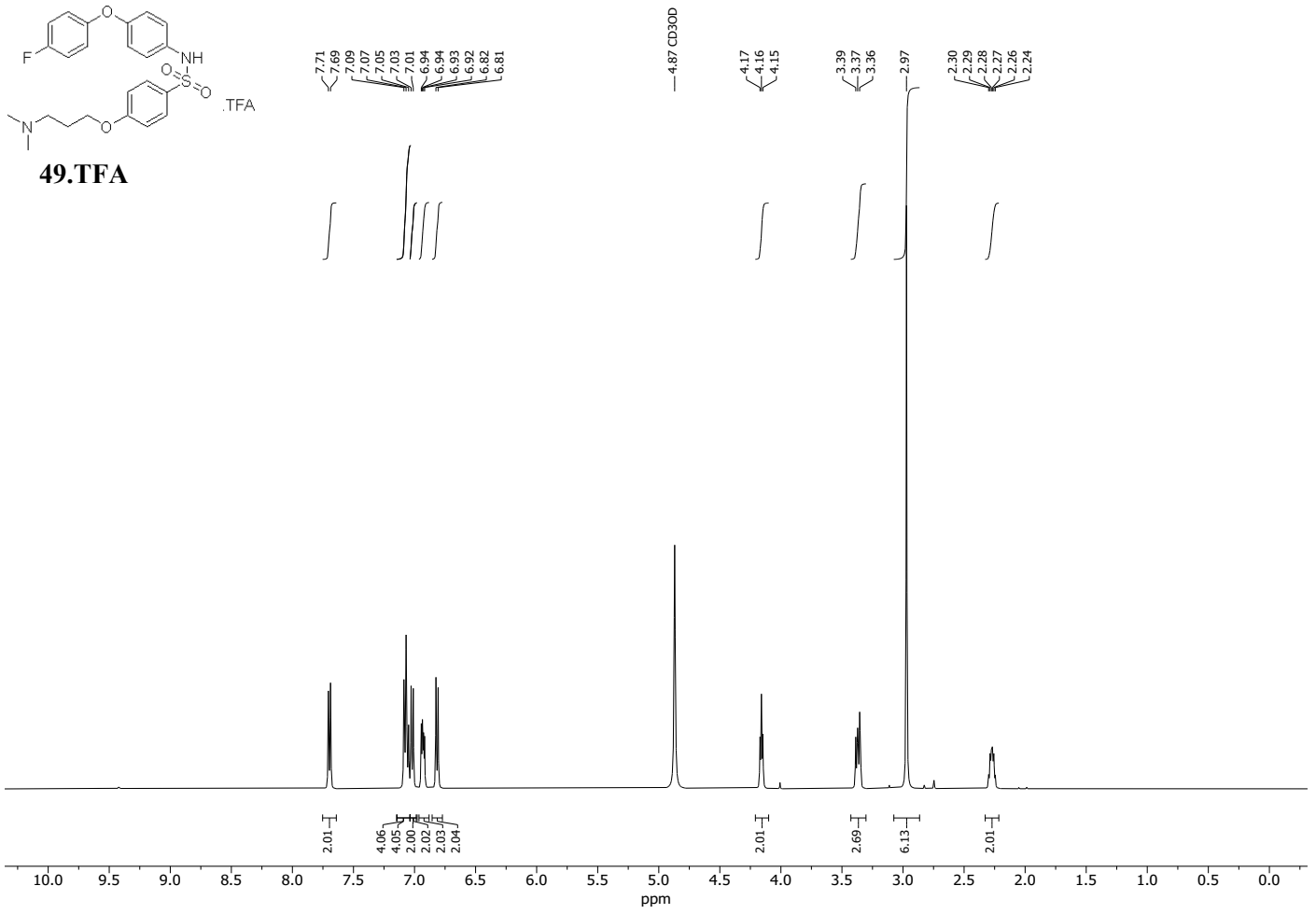
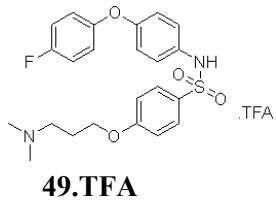


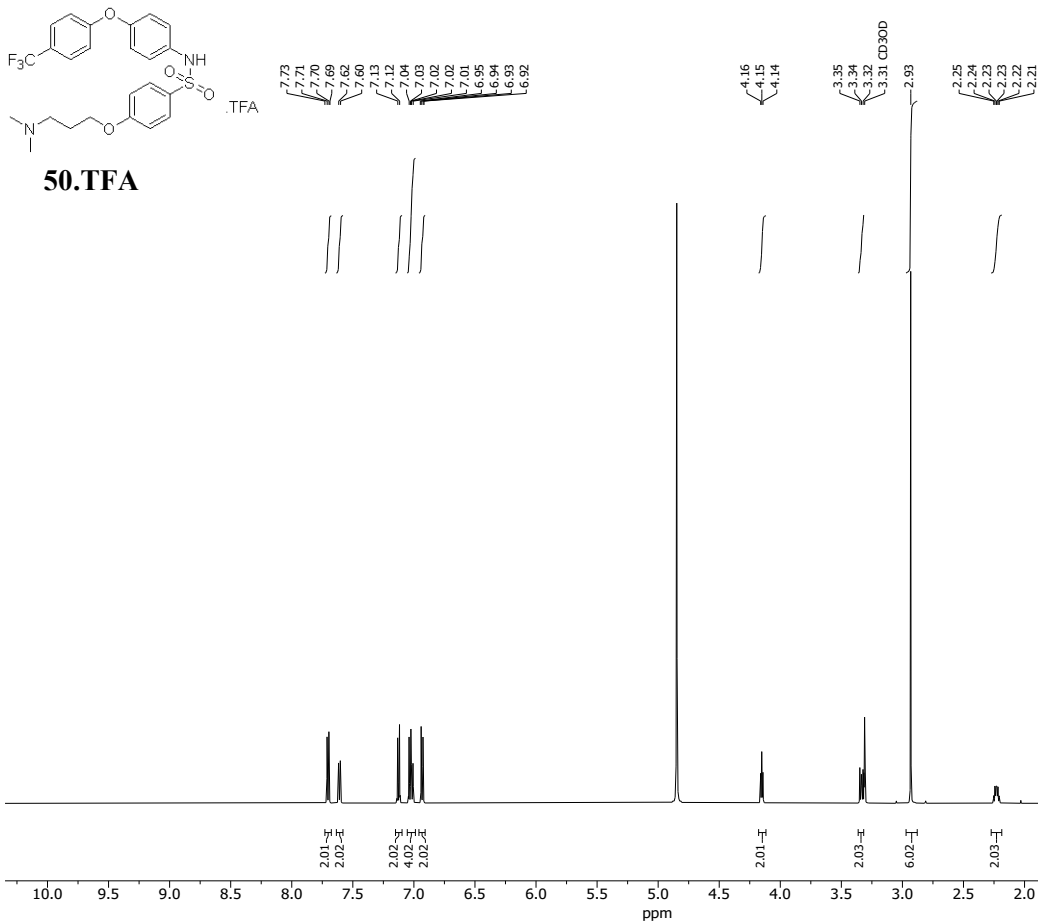
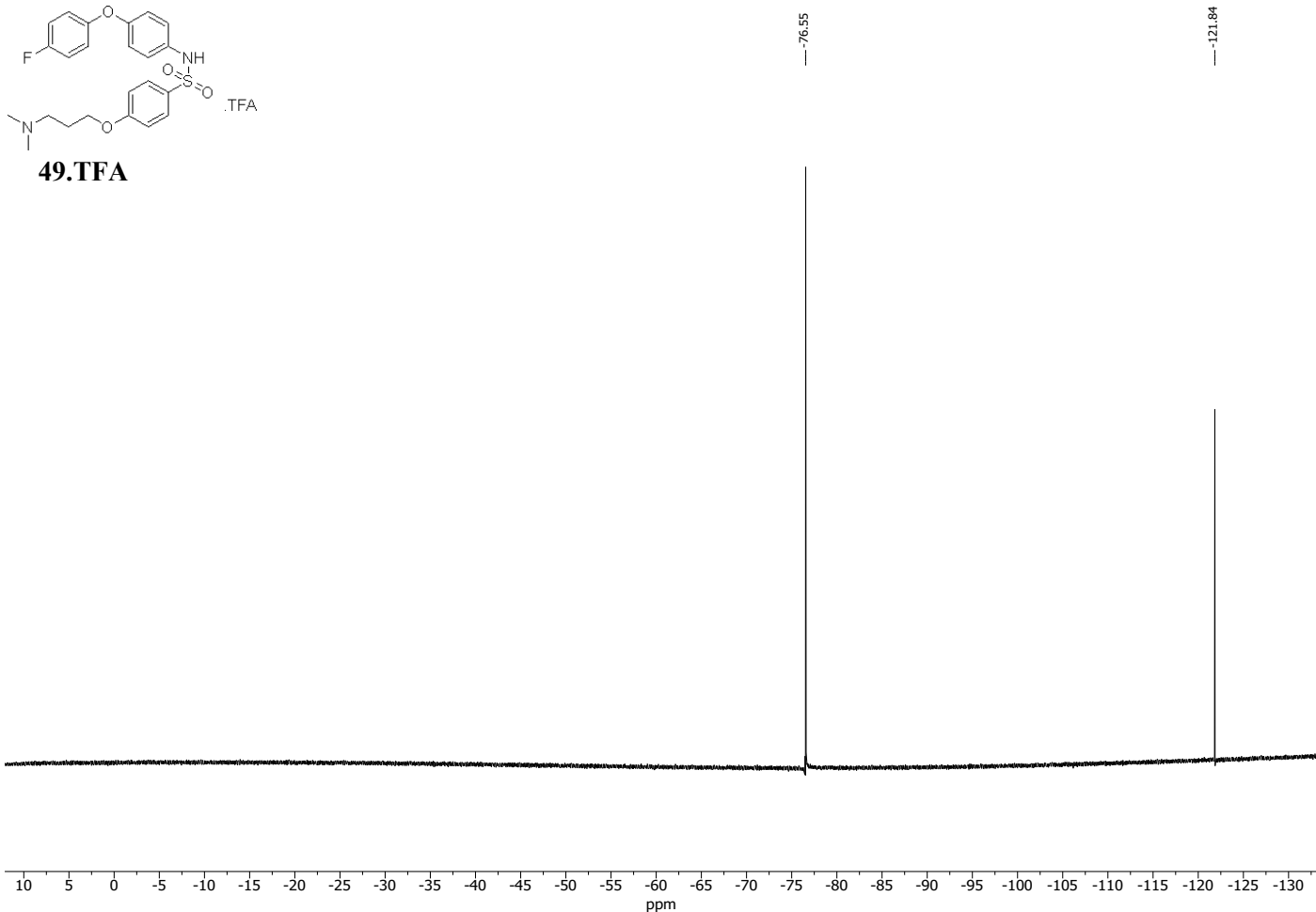
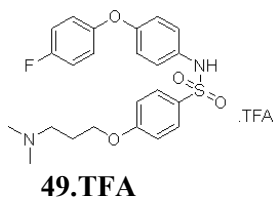


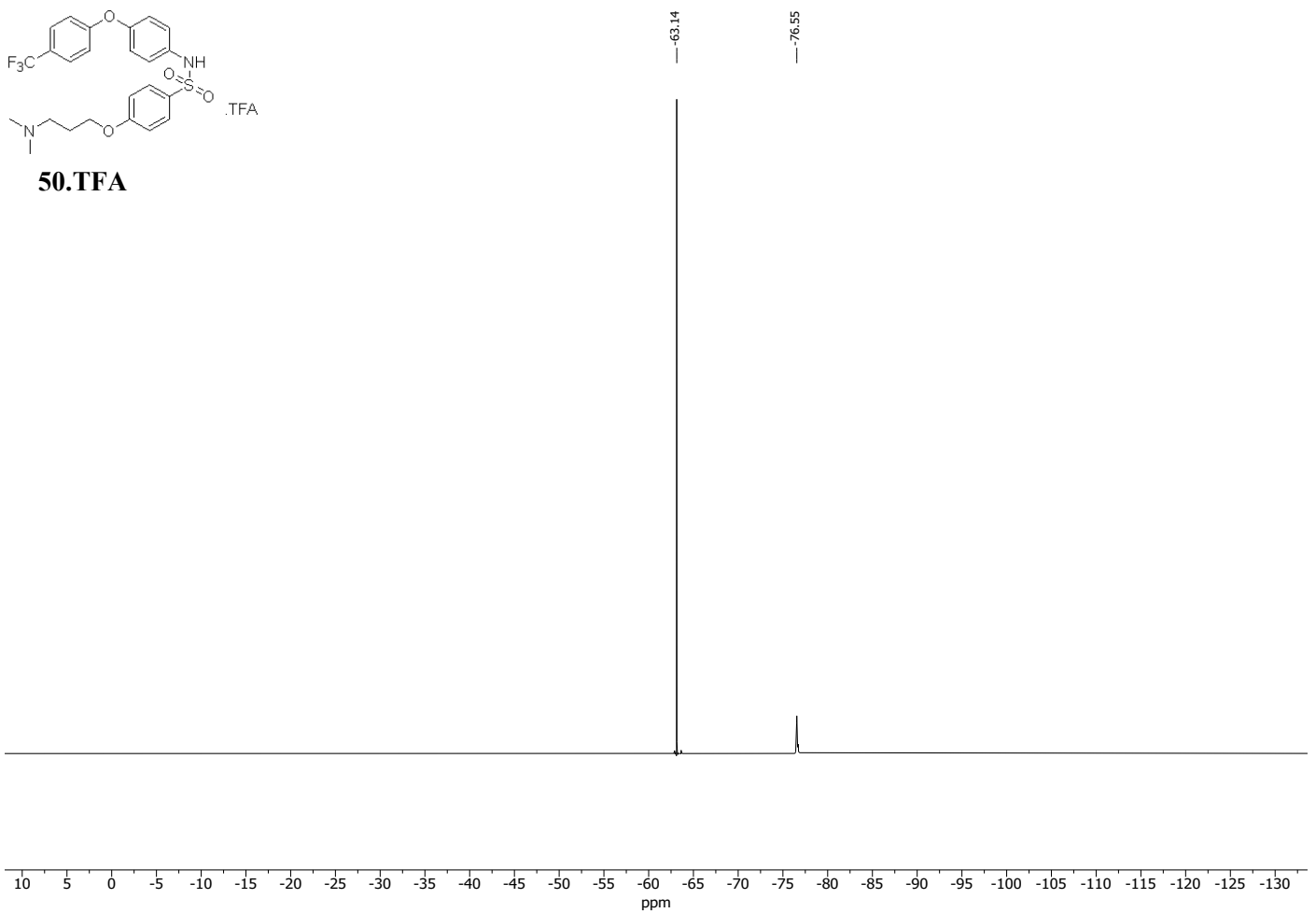
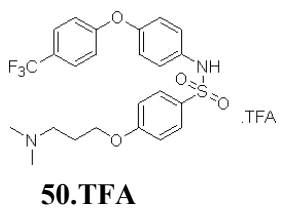
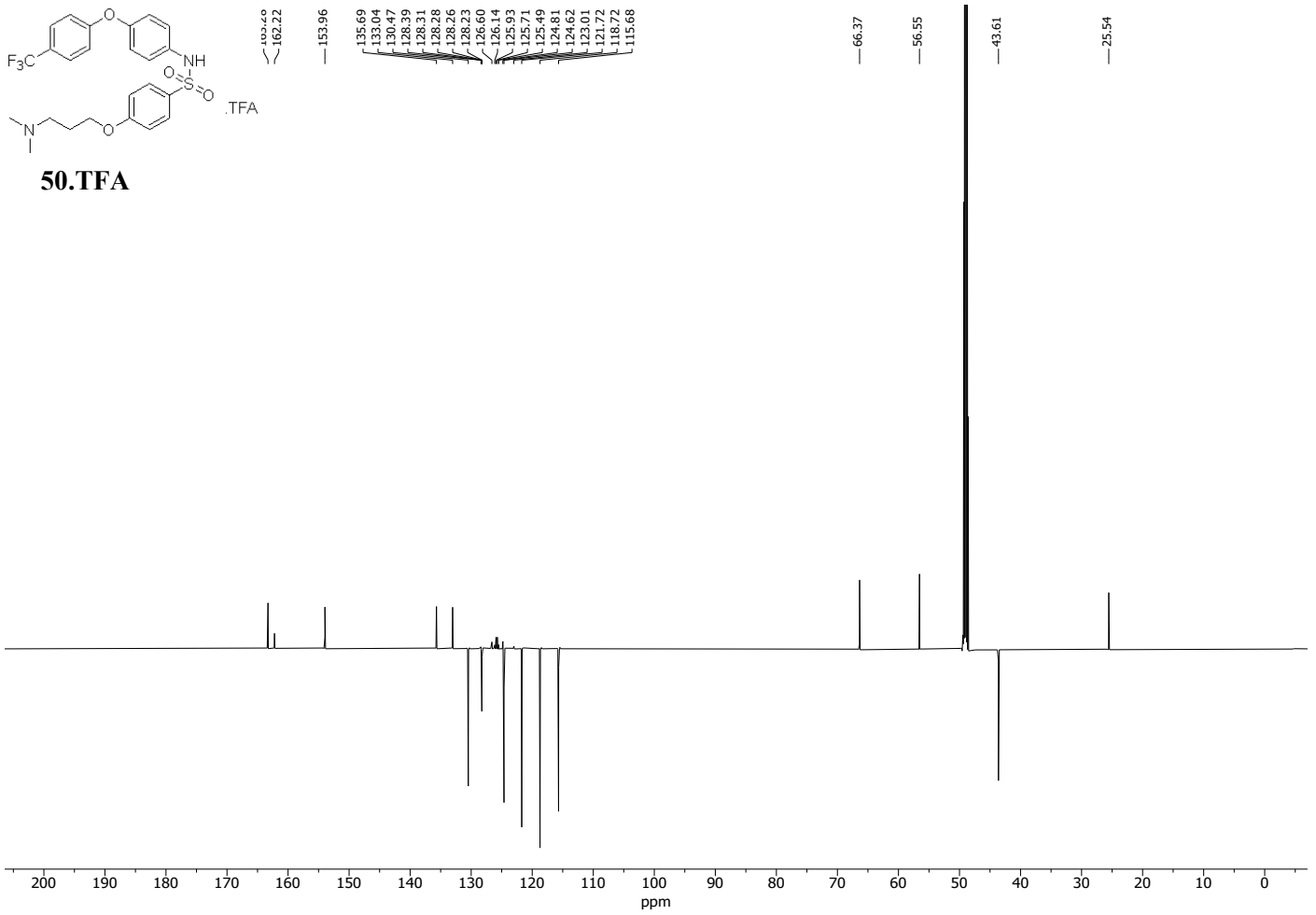
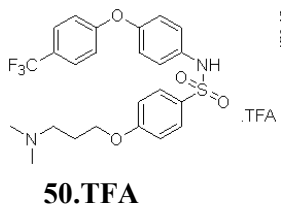


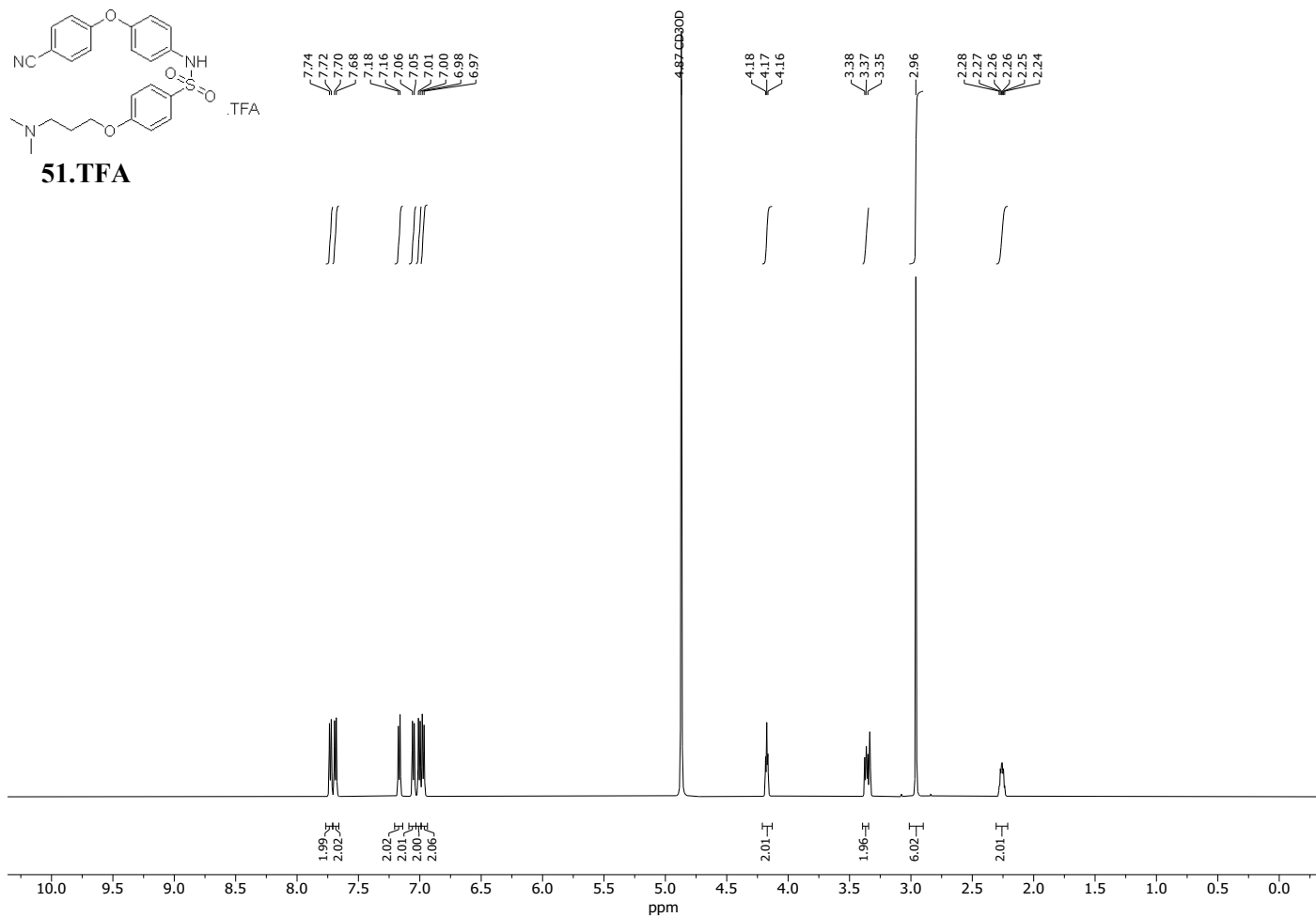
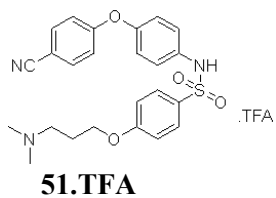


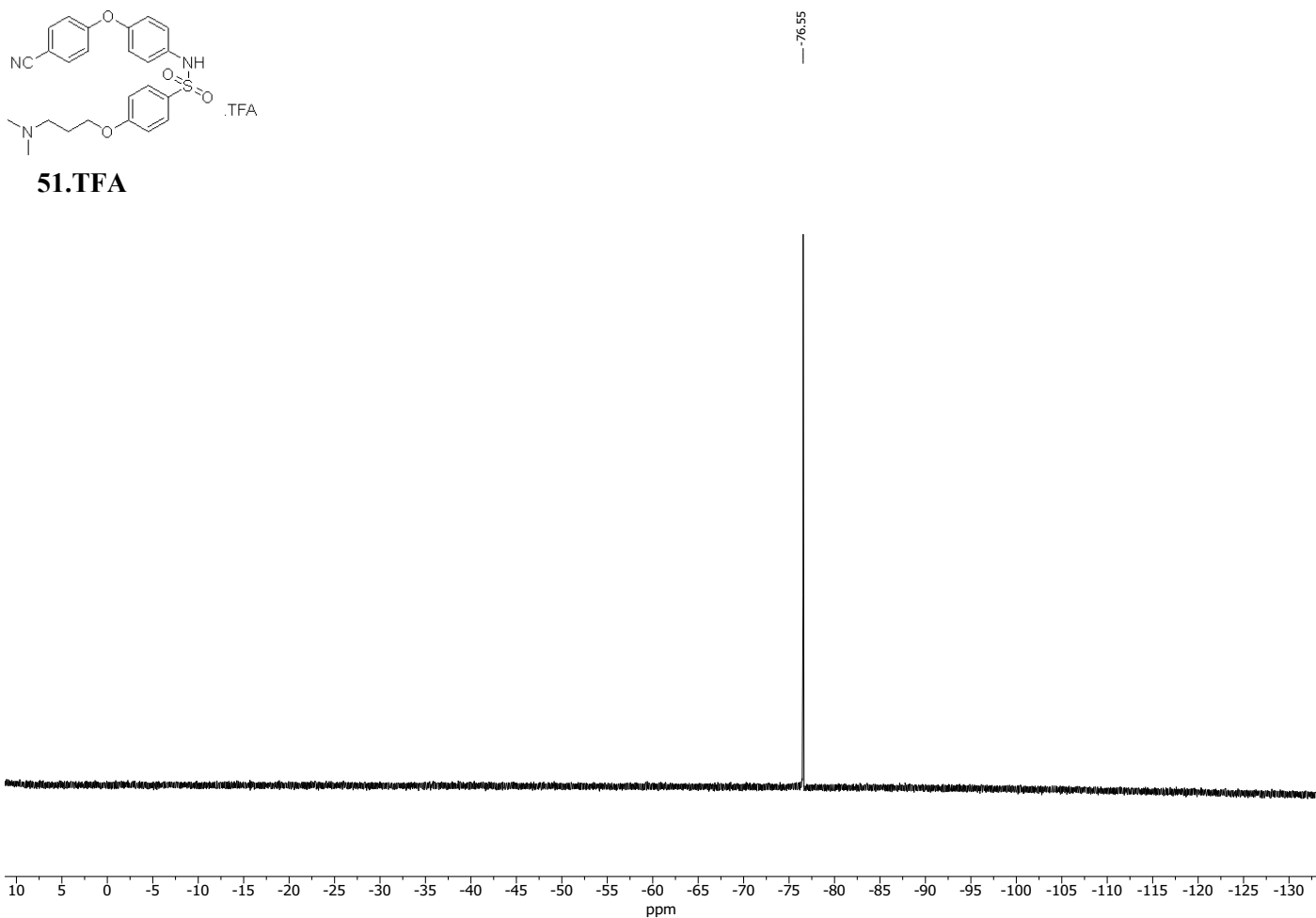
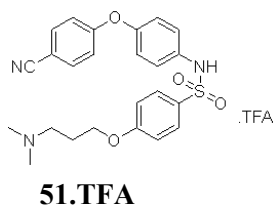
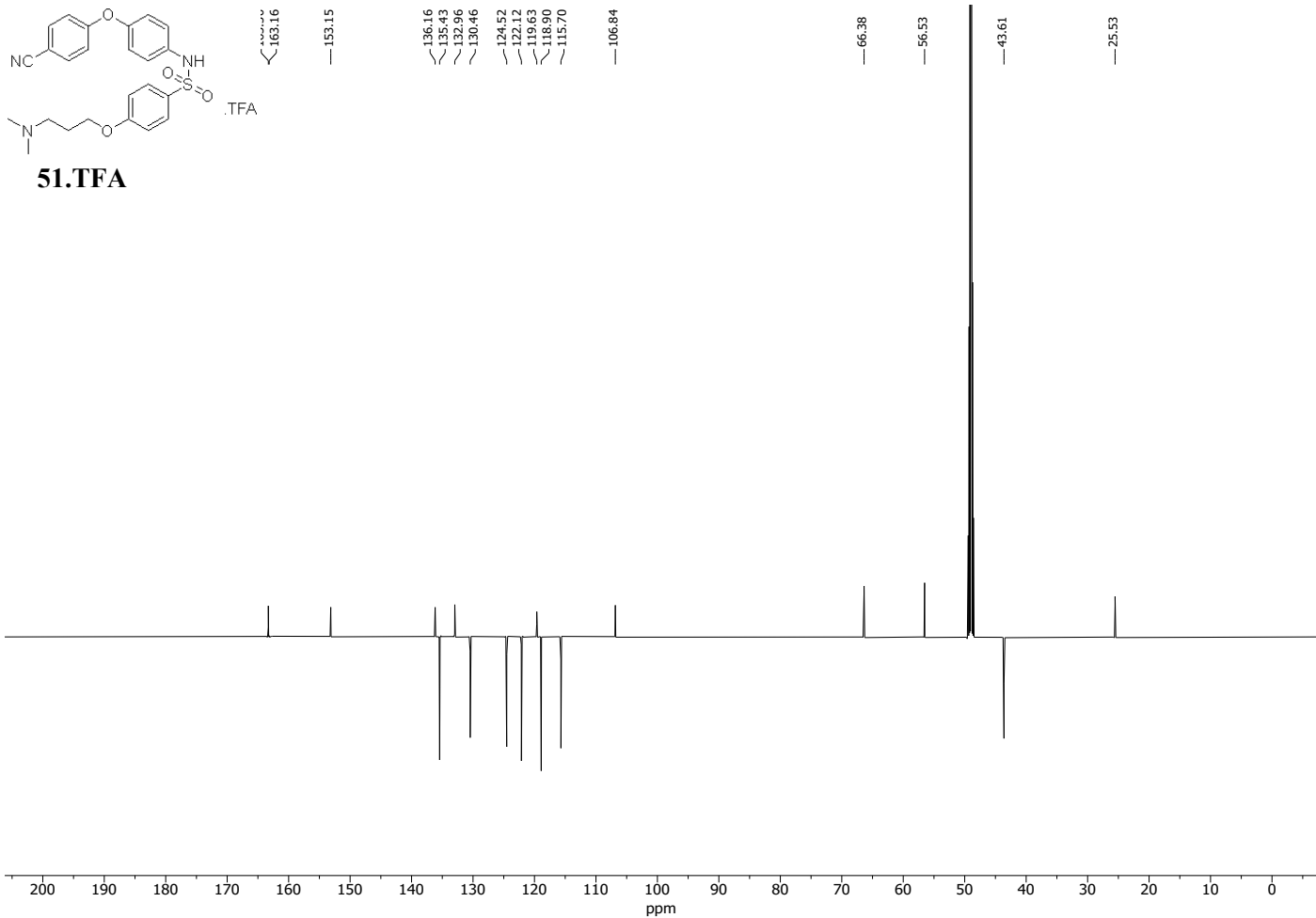
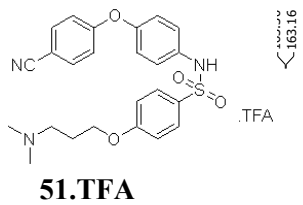












2.1. Dose response curves

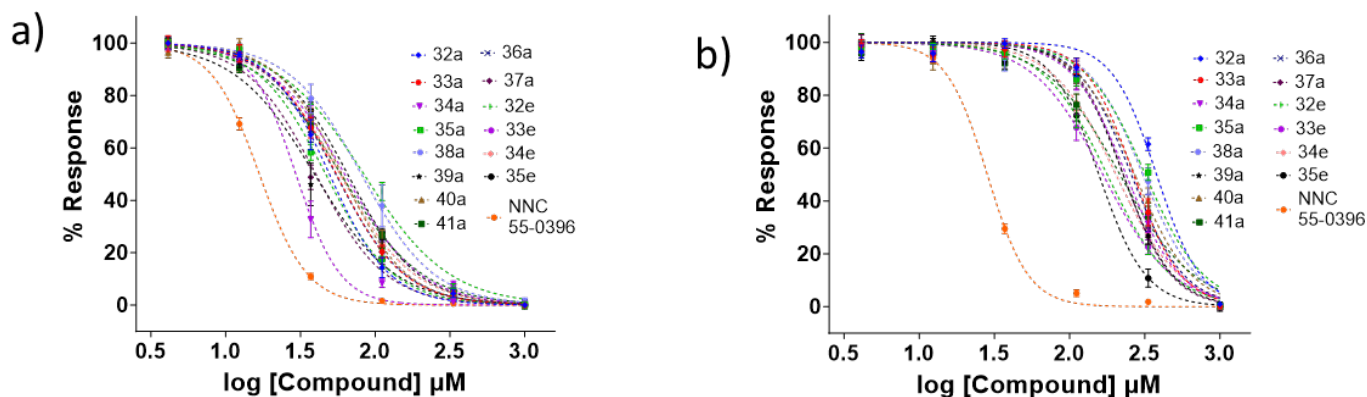


Figure S1: Dose response curves, determined by calcium influx fluorescence-imaging assays of the dimethylated anilines **32a–41a** and mono methylated anilines **32e–35e** in a) hCav2.2 and b) hCav3.2 channels. Data are presented as mean \pm SEM from $n = 3–5$ independent experiments.

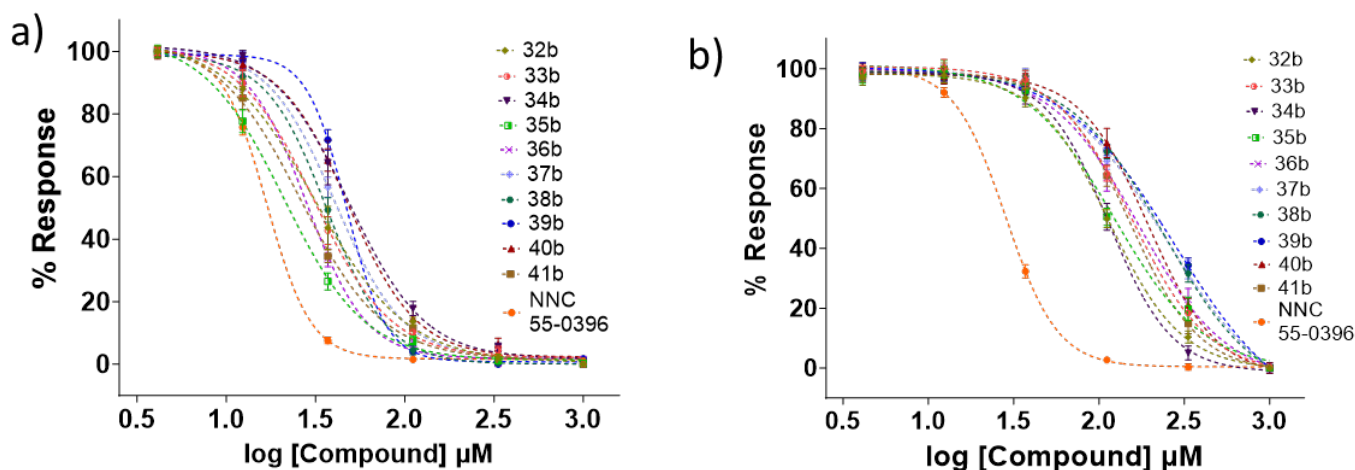


Figure S2: Dose response curves, determined by calcium influx fluorescence-imaging assays of the pyrrolidine- and piperidine-based phenoxyaniline analogues **32b–41b** a) hCav2.2 and b) hCav3.2 channels. Data are presented as mean \pm SEM from $n = 3–5$ independent experiments.

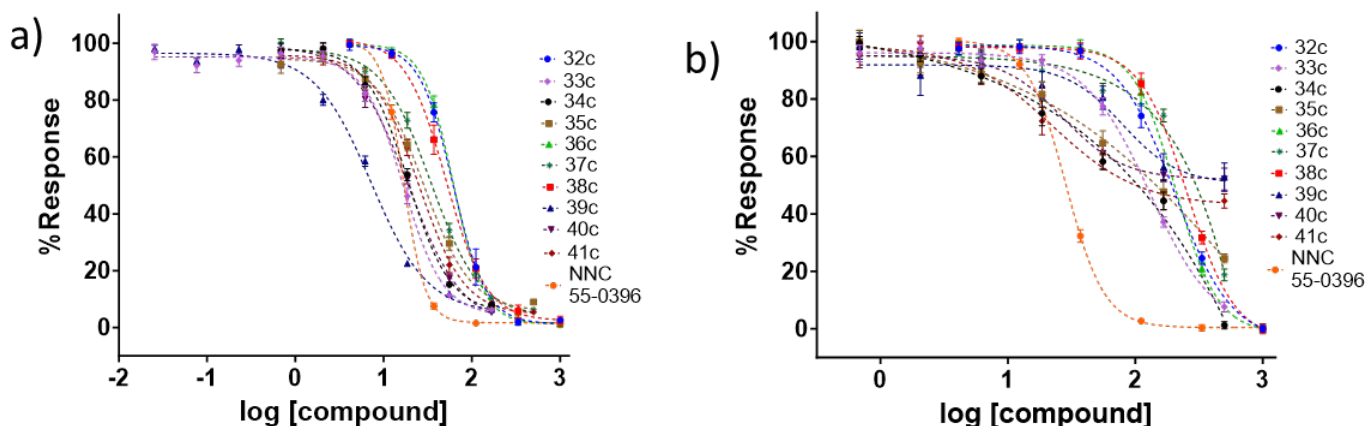


Figure S3: Dose response curves, determined by calcium influx fluorescence-imaging assays of the pyrrolidine- and piperidine-based phenoxyaniline analogues **32c–41c** in a) hCav2.2 and b) hCav3.2 channels. Data are presented as mean \pm SEM from $n = 3–5$ independent experiments.

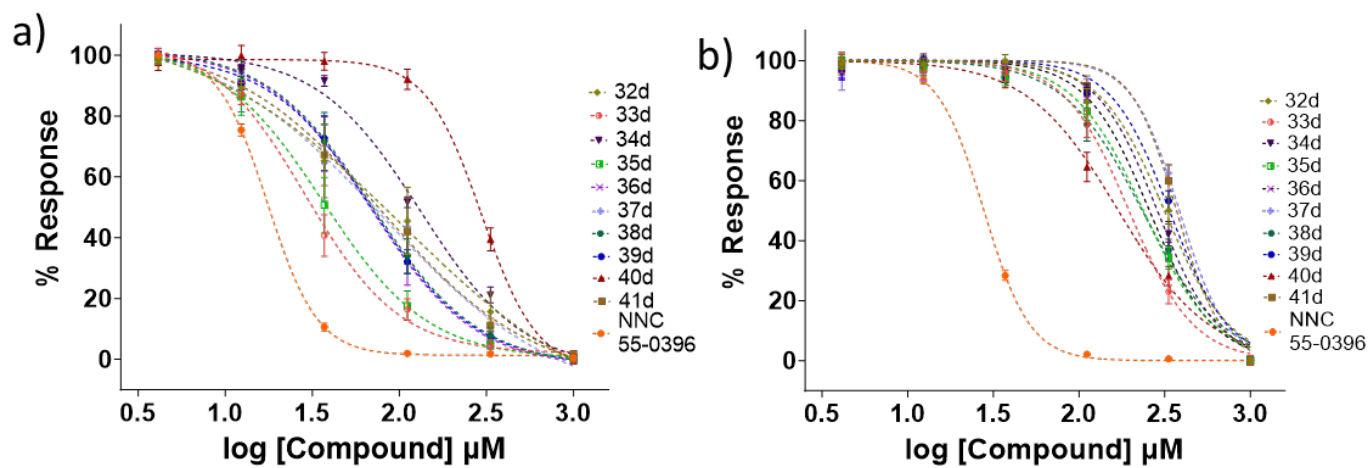


Figure S4: Dose response curves, determined by calcium influx fluorescence-imaging assays of the imidazole-based phenoxyanilines **32d–41d** in a) hCav2.2 and b) hCav3.2 channels. Data are presented as mean \pm SEM from $n = 3–5$ independent experiments.

2.2. Plasma stability studies

The stability of the compounds in rat plasma was performed by incubating the desired compound and internal standard, diazepam, at 37 °C in rat plasma with a final concentration of 150 µM of test compound/control and 125 µM of diazepam (total volume 1 mL). The aliquots collected at different time points over the course of 24 h were analysed by analytical HPLC. The ratio of the peak area of test compound/control to diazepam was calculated for each time point analysed (n=3, ± SD). The ratios obtained were normalised such that the ratio of peak area of test compound/control to diazepam test compound/control at time = 0 mins is equivalent to 100% of test compound. A plot of % compound remaining versus time (mins) was plotted using GraphPad Prism 8.0.2 and the half-lives of phenoxyaniline analogues (**33a**, **34b**, **33c**, **35d**, **32e**) sulfonamide derivatives (**44**, **47**, **48**) and the positive control, diltiazem, were determined using a one phase decay least squares curve fitting analysis. Shown below are the plots obtained over the course of 0 to 3600 mins for the compounds investigated.

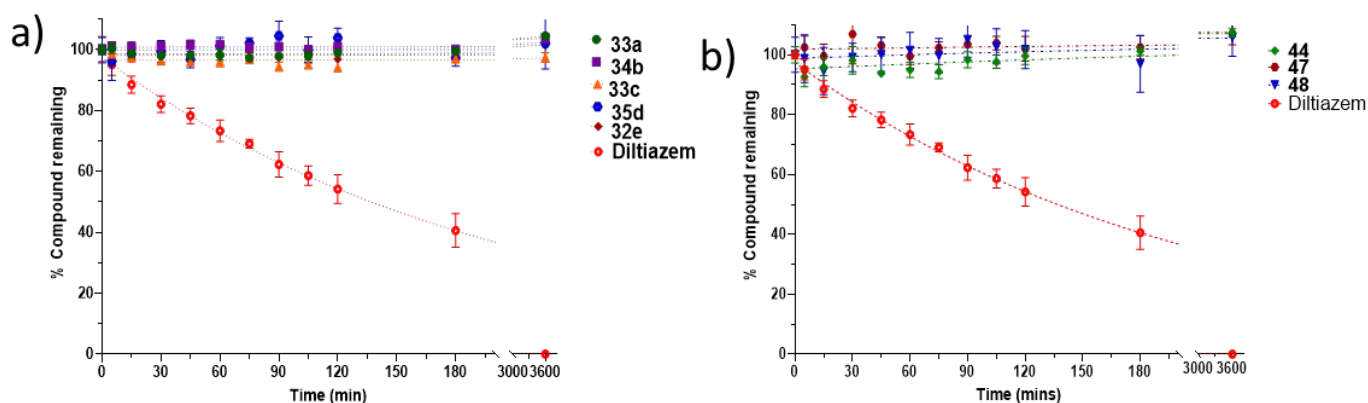


Figure S5: Rat plasma stability assessment plots; (a) phenoxyaniline analogues and (b) sulfonamide derivatives (n = 3, ± SD) along with the positive control diltiazem ($t_{1/2} = 143 \pm 17$ mins).

2.3. Cytotoxicity studies

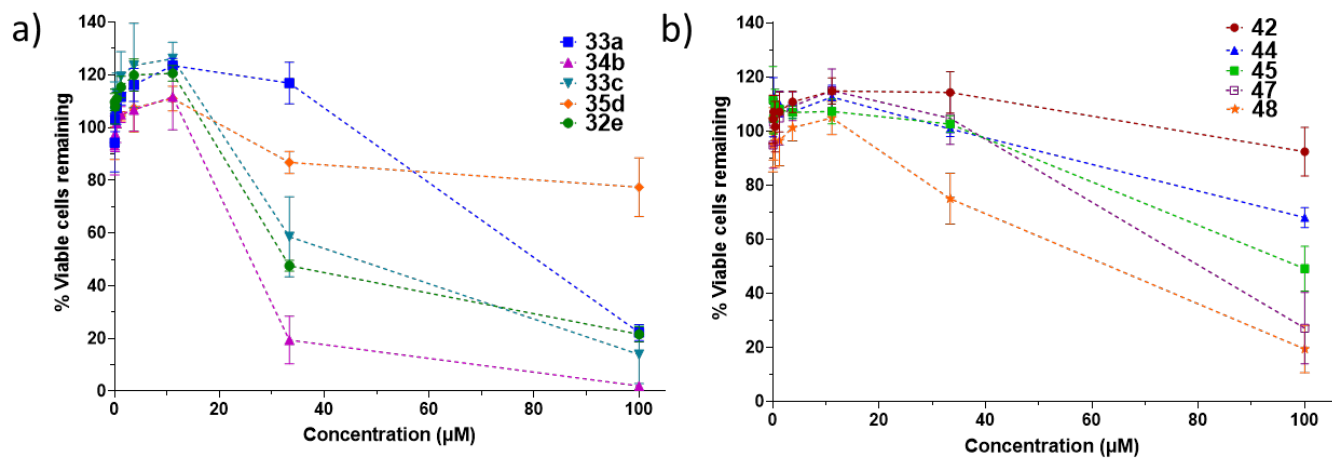


Figure S6: Dose-response curves obtained for the (a) phenoxyaniline compounds **33a**, **34b**, **33c**, **35d**, **32e** and (b) sulfonamide compounds **42**, **44**, **45**, **47**, **48** at concentrations ranging from 0.05 to 100 μM. The experiments were conducted in triplicate in two independent runs ($n=2$).

2.4. CNS MPO scores

The central nervous system multiparameter optimization (CNS MPO) desirability tool, which was developed by researchers at Pfizer Pharma Therapeutics^{1, 2}, was used to evaluate the likelihood of the compounds penetrating the CNS based on the total score calculated. The estimated values for the topological surface area (TPSA) and molecular weight (MW) were obtained from ChemDraw Professional Version 20.1.1.125 whilst the predicted values for pK_a, lipophilicity (cLogP) and the distribution coefficient (cLogD) at pH 7 were obtained from MarvinSketch 20.1.0-11077. The CNS MPO values for the phenoxyaniline and the sulfonamide derivatives were calculated and the results shown below in Tables T1 and T2. An example of the calculation is shown in Figure S7.

CNS MPO Calculator		
Property	Value	T0
ClogP	4.85	0.075
ClogD	2.85	0.575
TPSA	57.52	1.000
MW	427.226	0.520
HBD	1	0.833
pKa	9.4	0.300
CNS MPO		3.3

35b

Figure S7: Calculation of CNS MPO desirability score for phenoxyaniline **35d**. The individual transformed value, T0, for each parameter is colour coded; green implies a very good value, yellow moderate and red indicates a very low contribution to the overall score.

Table T1: CNS MPO Scores for phenoxyaniline analogues

Compound	Substitution on central ring	R ¹	CNS MPO Score				
			R ²				
			a	b	c	d	e
32	<i>ortho</i>	H	3.6	3.0	2.7	3.8	3.9
33	<i>ortho</i>	F	3.3	2.8	2.5	3.6	3.7
34	<i>ortho</i>	CF ₃	2.5	2.1	2.0	3.1	2.8
35	<i>ortho</i>	CN	3.9	3.3	2.9	3.7	3.8
36	<i>meta</i>	H	3.6	3.0	2.7	3.8	-
37	<i>meta</i>	F	3.3	2.8	2.5	3.6	-
38	<i>para</i>	H	3.6	3.0	2.7	3.8	-
39	<i>para</i>	F	3.3	2.8	2.5	3.6	-
40	<i>para</i>	CF ₃	2.5	2.1	2.0	3.1	-
41	<i>para</i>	CN	3.9	3.3	2.9	3.7	-

Table T2: CNS MPO Scores for sulfonamide analogues

Sulfonamide Analogue	R	Substitution on central ring	CNS MPO Score
42	H	<i>ortho</i>	4.3
43	F	<i>ortho</i>	4.1
44	CF ₃	<i>ortho</i>	3.1
45	CN	<i>ortho</i>	4.1
46	H	<i>meta</i>	4.3
47	F	<i>meta</i>	4.1
48	H	<i>para</i>	4.3
49	F	<i>para</i>	4.0
50	CF ₃	<i>para</i>	2.9
51	CN	<i>para</i>	4.1

References

- 1 T. T. Wager, X. Hou, P. R. Verhoest and A. Villalobos, *ACS Chem. Neurosci.*, 2010, **1**, 435-449.
- 2 T. T. Wager, X. Hou, P. R. Verhoest and A. Villalobos, *ACS Chem. Neurosci.*, 2016, **7**, 767-775.