Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Chemoselective Nitration of Aromatic Sulfonamides with *tert*-Butyl Nitrite

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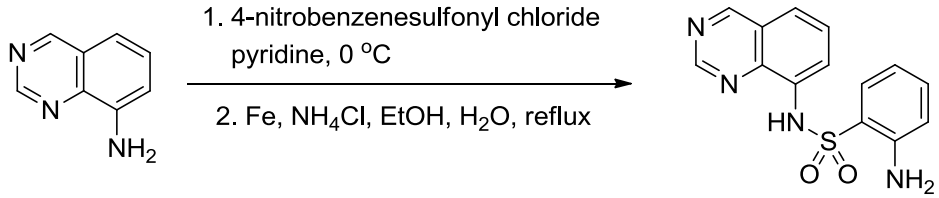
General: Reactions were run in dry glassware and no special precautions were taken to exclude air unless otherwise noted. Solvents and reagents were used as supplied and were not purified prior to use. Reactions were monitored by TLC using EMD TLC silica gel 60 F_{254} aluminum backed plates (UV visualization), and by analytical HPLC-MS using a Waters 2695 Separations Module, a Waters 996 Photodiode Array Detector and a Waters Micromass ZQ mass spectrometer. Purifications were performed using a Biotage Isolera One flash chromatography system equipped with Biotage SNAP KP-Sil silica gel cartridges. NMR spectra were recorded on a Bruker Avance III 400 Mhz spectrometer, a Bruker Avance III 500 MHz spectrometer or a Bruker Avance II TCI 600 MHz spectrometer, as noted in the characterization data for each compound.

2-amino-N-(quinazolin-8-yl)benzenesulfonamide (1)



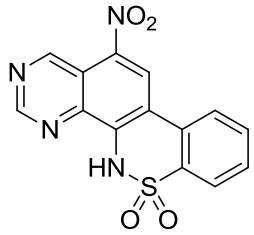
1

Quinazolin-8-amine[1] (200 mg, 1.38 mmol, 1.0 eq) was dissolved in pyridine (14 mL, 0.1 M), cooled to 0 °C and treated with 4-nitrobenzenesulfonyl chloride (397 mg, 1.79 mmol, 1.3 eq). The reaction immediately turned dark orange. After 0.5 h the reaction was warmed to room temperature and stirred for 18 h, after which the pyridine was evaporated. The resulting red oil was taken up in EtOAc (50 mL) and water was added (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2

× 20 mL). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography to afford 2-nitro-N-(quinazolin-8-yl)benzenesulfonamide (226 mg, 0.684 mmol, 50 %) as an orange solid.

2-nitro-N-(quinazolin-8-yl)benzenesulfonamide (226 mg, 0.684 mmol, 1.0 eq) was suspended in EtOH/H_2O (7 mL/1.5 mL, 0.08 M) and treated with NH_4Cl (366 mg, 6.84 mmol, 10.0 eq) and iron powder (286 mg, 5.13 mmol, 7.5 eq). The mixture was stirred and heated to reflux for 30 minutes, after which the reaction was complete. The reaction mixture was hot filtered through a pad of Celite to give a clear orange solution. The filter cake was washed with hot EtOH until the filtrate was colorless. The resulting EtOH solution was concentrated, and the residue was taken up in EtOAc (25 mL). The EtOAc solution was washed with $NaHCO_3$ (25 mL, saturated, aqueous). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to give compound **1** (132 mg, 0.440 mmol, 64 %) as a light brown solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ = 10.42 (bs, 1H), 9.57 (s, 1H), 9.31 (s, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.74 (dd, J = 7.8, 1.1 Hz, 1H), 7.67 (dd, J = 8.1, 1.5 Hz, 1H), 7.63 (dd, J = 8.0, 8.0 Hz, 1H), 7.20 (dd, J = 7.6, 7.6 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.55 (dd, J = 7.5, 7.5 Hz, 1H), 6.24 (bs, 2H). ^{13}C NMR (150 MHz, d_6-DMSO) δ = 160.7 (CH), 154.0 (CH), 146.6 (C_4), 140.5 (C_4), 134.2 (CH), 133.7 (C_4), 129.6 (CH), 128.1 (CH), 124.8 (C_4), 121.3 (C_4), 119.3 (CH), 118.1 (CH), 116.9 (CH), 114.6 (CH).

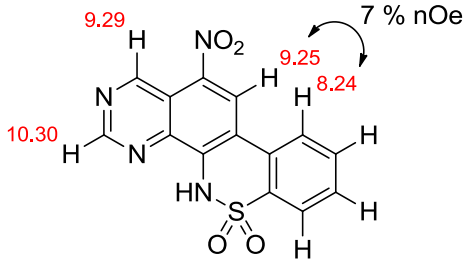
4-nitro-7-phenylquinazoline-2',8-sultam (3)



Aniline **1** (50 mg, 0.166 mmol, 1.0 eq) was suspended in AcOH (3 mL, 0.06 M) and dissolved by heating with a heat gun. This solution was placed in an oil bath pre-heated to 45 °C. Once the internal temperature of the solution was stabilized at 45 °C it was treated with tert-butyl nitrite (30 µL, 0.255 mmol, 1.5 eq) dropwise over 3 minutes. The reaction was stirred for 30 minutes after which it was cooled to 0 °C whereupon an orange precipitate formed. Water (5 mL) was added to further encourage precipitation, and the solid was isolated by suction filtration. This crude product was purified by flash chromatography to afford **3** (R_f = 0.2 in 10 % MeOH/DCM, 20 mg, 36 %) as a yellow solid along with a trace amount of compound **2**. ^{1}H NMR (400 MHz, d_6-DMSO) δ = 10.30 (s, 1H), 9.29 (s, 1H), 9.25 (s, 1H), 8.24 (d, J = 8.1 Hz, 1H), 7.88 (dd, J = 7.8, 1.2 Hz, 1H), 7.72-7.67 (m, 1H), 7.63-7.58 (m, 1H). N-H proton not observed. ^{13}C NMR (150 MHz, d_6-DMSO) δ = 155.4 (CH), 153.7 (CH), 152.4 (C_4), 145.6

(C_4), 131.6 (C_4), 131.4 (C_4), 130.4 (CH), 128.0 (CH), 127.9 (C_4), 125.5 (CH), 123.2 (CH), 122.9 (CH), 119.8 (C_4), 112.7 (C_4).

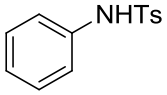
Regiochemical assignment of compound 3



no nOE's observed for 10.30 or 9.29

H (10.30), H (9.29), H (9.25) and H (8.24) were identified by a series of COSY, HSQC and HMBC NMR experiments. A strong NOE of 7 % between H (9.25) and H (8.24) confirms the *para* relationship between the nitro group and the sulfonamide. Were the nitro group *meta* with the sulfonamide, this NOE would not be observed, and one would be expected between H (9.29) and H (9.25).

4-methyl-N-phenylbenzenesulfonamide (4)

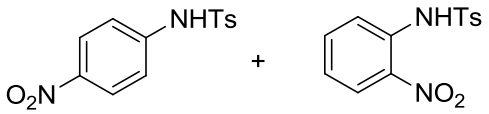


Aniline hydrochloride (5.00 g, 38.6 mmol, 1.0 eq) was dissolved in pyridine (200 mL, 0.19 M) and treated with tosyl chloride (7.44 g, 39.0 mmol, 1.0 eq) in portions over 5 minutes. The mixture was heated at reflux for 16 h, after which it was cooled to room temperature and the pyridine was evaporated. The crude product was taken up in EtOAc (300 mL) and this solution was washed with HCl (1 M, 100 mL), water (100 mL) and brine (100 mL). The organic solution was then dried over Na_2SO_4, filtered and concentrated to give **4** (9.26 g, 37.4 mmol, 96 % yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ = 10.20 (s, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.23-7.19 (m, 2H), 7.09-7.06 (m, 2H), 7.02-6.98 (m, 1H), 2.32 (s, 3H).

4-methyl-N-(4-nitrophenyl)benzenesulfonamide (5a) and

4-methyl-N-(2-nitrophenyl)benzenesulfonamide (5b)

Optimized reaction conditions, Table 1, entry 14



5a **5b**

Sulfonamide **4** (247 mg, 1.00 mmol, 1.0 eq) was dissolved in acetonitrile (10mL, 0.1M) and heated to 45 °C. The reaction was treated with tert-butyl nitrite (177 µL, 1.49 mmol, 1.5 eq) while stirring at 45 °C. After 6 h the sulfonamide **4** had been consumed (TLC and analytical HPLC-MS analysis), and the reaction was cooled to room temperature. Volatiles were removed *in vacuo*, and the resulting crude products were purified using flash chromatography to yield pure **5a** (135 mg, 0.462 mmol, 46 %) and **5b** (115 mg, 0.394 mmol, 39 %).

5a: Yellow solid. R_f = 0.24, 30 % EtOAc/hexanes. ^{1}H NMR (400 MHz, d_6-DMSO) δ = 11.20 (s, 1H), 8.13 (d, J = 9.3 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 9.3 Hz, 2H), 2.34 (m, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ = 144.3 (C_4), 144.1 (C_4), 142.5 (C_4), 136.0 (C_4), 130.0 (2 × CH), 126.8 (2 × CH), 125.4 (2 × CH), 117.9 (2 × CH), 21.0 (CH_3).

5b: Yellow solid. R_f = 0.47, 30 % EtOAc/hexanes. ^{1}H NMR (400 MHz, d_6-DMSO) δ = 10.22 (s, 1H), 7.92 (dd, J = 8.2, 1.5 Hz, 1H), 7.64-7.59 (m, 3H), 7.38-7.34 (m, 3H), 7.26 (dd, J = 8.2, 1.2 Hz, 1H), 2.36 (m, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ = 143.8 (C_4), 143.1 (C_4), 136.3 (C_4), 134.2 (CH), 130.3 (C_4), 129.8 (2 × CH), 126.8 (2 × CH), 126.2 (CH), 125.5 (CH), 125.3 (CH), 21.0 (CH_3).

General procedure for the sulfonylation of substituted anilines – Table 2 starting materials

The aniline (1.0 eq) was dissolved in pyridine (0.2 M) and treated with the appropriate sulfonyl chloride (1.0 eq) in portions over 5 minutes. The mixture was heated at reflux until the reaction was complete (as determined by TLC and/or analytical HPLC-MS analysis), after which it was cooled to room temperature and the pyridine was evaporated. The crude product was taken up in EtOAc and this solution was washed with HCl (1 M), water and brine. The organic solution was then dried over Na_2SO_4, filtered and concentrated to give a crude product that was purified by flash chromatography.

The following sulfonylated anilines have been previously described in the literature:

Table 2, entry 1, starting material: N-(4-methoxyphenyl)-4-methylbenzenesulfonamide[2]

Table 2, entry 2, starting material: 4-methyl-N-p-tolylbenzenesulfonamide[2]

Table 2, entry 3, starting material: N-(4-chlorophenyl)-4-methylbenzenesulfonamide[3]

Table 2, entry 4, starting material: ethyl 4-(4-methylphenylsulfonamido)benzoate[4]

Table 2, entry 5, starting material: N-(4-cyanophenyl)-4-methylbenzenesulfonamide[4]

Table 2, entry 6, starting material: 4-methyl-N-(4-(trifluoromethyl)phenyl)benzenesulfonamide[5]

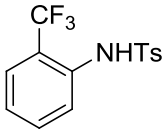
Table 2, entry 7, starting material: 4-methyl-N-(4-nitrophenyl)benzenesulfonamide[4]

Table 2, entry 8, starting material: N-phenylmethanesulfonamide[5]

Table 2, entry 9, starting material: 4-nitro-N-phenylbenzenesulfonamide[6]

Table 2, entry 10, starting material

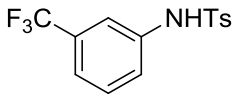
4-methyl-N-(2-(trifluoromethyl)phenyl)benzenesulfonamide



Brown solid. R_f = 0.53, 30% ethyl acetate/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.83 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.54 – 7.48 (m, 2H), 7.25 – 7.17 (m, 3H), 6.86 (s, 1H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 144.4 (C_4), 135.7 (C_4), 134.5 (C_4), 133.1 (CH), 129.6 (CH), 127.3 (CH), 126.5 (q, $^3J_{C-F}$ = 5.5 Hz, CH), 124.7 (CH), 123.6 (q, $^1J_{C-F}$ = 272.9 Hz, CF_3), 122.9 (CH), 120.6 (q, $^2J_{C-F}$ = 29.7, C_4), 21.6 (CH_3). MS (ESI$^-$): M-H$^+$ = 314.0 Calculated at 314.1.

Table 2, entry 11, starting material

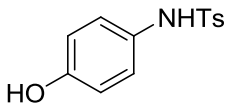
4-methyl-N-(3-(trifluoromethyl)phenyl)benzenesulfonamide



White solid. R_f = 0.35, 30% ethyl acetate/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.70 (d, J = 8.5 Hz, 2H), 7.39 – 7.22 (m, 7H), 2.39 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ =144.4 (C_4), 137.3 (C_4), 135.6 (C_4), 131.8 (q, $^2J_{C-F}$ = 32.7 Hz, C_4), 129.9$_3$ (CH), 129.8$_5$ (CH), 127.3 (CH), 124.0 (CH), 123.5 (q, $^1J_{C-F}$ = 272.5 Hz, CF_3), 121.7 (q, $^3J_{C-F}$ = 3.6 Hz, CH), 117.5 (q, $^3J_{C-F}$ = 3.6 Hz, CH), 21.5 (CH_3). MS (ESI$^-$): M-H$^+$ = 314.0 Calculated at 314.1.

Competition experiment # 3 starting material

4-(((4-methylphenyl)sulfonyl)methyl)phenol



Brown solid. R_f = 0.50, 10% Methanol/dichloromethane. ^{1}H NMR (500 MHz, d_6-DMSO) δ = 9.65 (s, 1H), 9.29 (s, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 6.59 (d, J = 8.9 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, d_6-DMSO) δ = 155.2 (C_4), 143.3 (C_4), 131.2 (C_4), 129.9

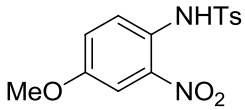
(CH), 129.1 (C_4), 127.2 (CH), 124.4 (CH), 116.0 (CH), 21.4 (CH_3) MS (ESI$^-$): M-H$^+$ = 264.2 Calculated at 362.3.

General procedure for the nitration of sulfonamides using *tert*-butyl nitrite

The sulfonamide (1.0 eq) was dissolved in acetonitrile (0.1 M) and heated to 45 °C. The reaction was treated with *tert*-butyl nitrite (1.5 eq) while continuing to be stirred at 45 °C. When the reaction was complete (as determined by TLC and/or analytical HPLC-MS analysis) the reaction was cooled to room temperature and the volatiles were removed by evaporation under reduced pressure. The resulting crude products(s) were purified by flash chromatography.

Table 2, entry 1

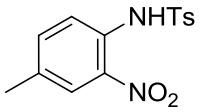
N-(4-methoxy-2-nitrophenyl)-4-methylbenzenesulfonamide



Yellow solid. R_f = 0.61, 30% EtOAc/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.26 (s, 1H), 7.80 (d, J = 9.2 Hz,1H), 7.61 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 3.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.2 (dd, J = 9.2, 3.0 Hz, 1H), 3.82 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 156.2 (C_4), 144.5 (C_4), 139.0 (C_4), 135.5 (C_4), 129.8 (CH), 127.1 (CH), 126.6 (CH), 124.8 (C_4), 123.0 (CH), 109.0 (CH), 56.0 (CH_3), 21.6 (CH_3). MS (ESI$^-$): M-H$^+$ = 321.1. Calculated at 321.1.

Table 2, entry 2

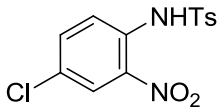
4-methyl-*N*-(4-methyl-2-nitrophenyl)benzenesulfonamide



Yellow solid. R_f = 0.64, 30% ethyl acetate/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.63 (s, 1H), 7.88 (d, J = 2.1 Hz,1H), 7.74 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.39 (dd, J = 8.5, 2.1 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 2.38 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 144.6 (C_4), 137.3 (C_4), 136.7 (CH), 135.7 (C_4), 134.45 (C_4), 131.2 (C_4), 129.9 (CH), 127.2 (CH), 125.9 (CH), 121.6 (CH), 21.5 (CH_3), 20.4 (CH_3). MS (ESI$^-$): M-H$^+$ = 305.1. Calculated at 305.1.

Table 2, entry 3

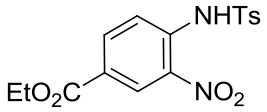
***N*-(4-chloro-2-nitrophenyl)-4-methylbenzenesulfonamide**



Yellow solid. R_f = 0.74, 30% ethyl acetate/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.75 (s, 1H), 8.12 (d, J = 2.5 Hz, 1H), 7.85 (d, J = 9.2 Hz, 1H), 7.74 (d, J = 8.6 Hz, 2H), 7.56 (dd, J = 8.9, 2.5 Hz, 1H), 7.30 (d, J = 8.6 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 145.1 (C_4), 137.1 (C_4), 135.8 (CH), 135.4 (C_4), 132.6 (C_4), 130.1 (CH), 129.3 (C_4), 127.2 (CH), 125.8 (CH), 122.3 (CH), 21.6 (CH_3). MS (ESI$^-$): M-H$^+$ = 325.1 and 326.9. Calculated at 325.0 and 327.0.

Table 2, entry 4

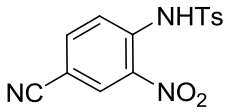
ethyl 4-(4-methylphenylsulfonylamido)-3-nitrobenzoate



Yellow solid. R_f = 0.60, 30% ethyl acetate/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 10.19 (s, 1H), 8.80 (d, J = 2.1 Hz, 1H), 8.19 (dd, J = 8.9, 2.1 Hz, 1H), 7.88 (d, J = 8.9 Hz, 1H), 7.80 (d, J = 8.5, 2H), 7.30 (d, J = 8.5 Hz, 2H), 4.38 (q, 7.1 Hz ,2H), 2.40 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.9 (C_4), 145.3 (C_4), 137.5 (C_4), 136.3 (CH), 135.6 (C_4), 135.4 (C_4), 130.1 (CH), 127.9 (CH), 127.4 (CH), 125.5 (C_4), 119.4 (CH), 61.8 (CH_2), 21.6 (CH_3), 14.2 (CH_3). MS (ESI$^-$): M-H$^+$ = 363.1. Calculated at 363.1.

Table 2, entry 5

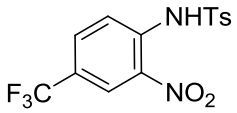
***N*-(4-cyano-2-nitrophenyl)-4-methylbenzenesulfonamide**



Yellow solid. R_f = 0.54, 30% ethyl acetate/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 10.24 (s, 1H), 8.48 (d, J = 1.8 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 8.5 Hz, 2H), 7.79 (dd, J = 8.7, 1.8 Hz, 1H), 7.34 (d, J = 8.5 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 145.7 (C_4), 138.2 (CH), 137.9 (C_4), 135.3 (C_4), 135.1 (C_4), 130.7 (CH), 130.3 (CH), 127.4 (CH), 120.0 (CH), 116.2 (C_4), 106.8 (C_4), 21.64 (CH_3). MS (ESI$^-$): M-H$^+$ = 316.2. Calculated at 316.0.

Table 2, entry 6

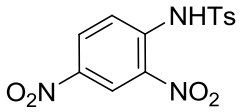
4-methyl-*N*-(2-nitro-4-(trifluoromethyl)phenyl)benzenesulfonamide



Yellow solid. R_f = 0.72, 30% ethyl acetate/hexanes. ^{1}H NMR (500 MHz, d_6-DMSO) δ = 10.72 (s, 1H), 8.27 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 8.7, 1.8 Hz, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, d_6-DMSO) δ = 144.3 (C_4), 141.0 (C_4), 136.0 (C_4), 134.4 (C_4), 130.8 (q, $^3J_{C-F}$ = 2.7 Hz, CH), 130.0 (CH), 127.0 (CH), 125.0 (q, $^2J_{C-F}$ = 33.6, C_4), 123.9 (CH), 123.2 (q, $^3J_{C-F}$ = 3.6, CH), 122.9 (q, $^1J_{C-F}$ = 272.5 Hz, CF_3), 21.0 (CH_3). MS (ESI$^-$): M-H$^+$ = 359.0. Calculated at 359.0.

Table 2, entry 7

***N*-(2,4-dinitrophenyl)-4-methylbenzenesulfonamide**

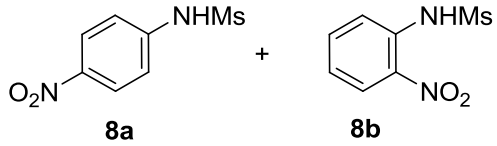


Yellow solid. R_f = 0.56, 30% ethyl acetate/hexanes. ^{1}H NMR (500 MHz, d_6-DMSO) δ = 8.65 (d, J = 2.5 Hz, 1H), 8.40 (dd, J = 9.2, 2.5 Hz, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 9.2 Hz, 1H), 7.42 (d, J = 8.5 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (125 MHz, d_6-DMSO) δ = 144.4 (C_4), 139.7 (C_4), 130.0 (CH), 128.8 (CH), 127.1 (CH), 122.2 (CH), 121.7 (CH), 21.0 (CH_3). MS (ESI$^-$): M-H$^+$ = 336.1. Calculated at 336.0.

Table 2, entry 8

***N*-(4-nitrophenyl)methanesulfonamide (8a) and**

***N*-(2-nitrophenyl)methanesulfonamide (8b)**



8a **8b**

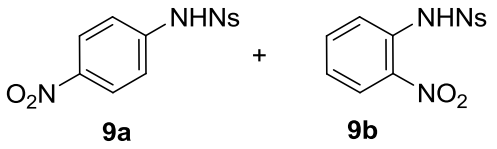
8a: Yellow solid. R_f = 0.18, 50% ethyl acetate/hexanes. ^{1}H NMR (500 MHz, d_6-DMSO) δ = 10.74 (s, 1H), 8.22 (d, J = 9.2, 2H), 7.36 (d, J = 9.2 Hz, 2H), 3.18 (s, 3H). ^{13}C NMR (125 MHz, d_6-DMSO) δ = 145.0(C_4), 142.2 (C_4), 125.5 (CH), 117.5 (CH), 40.2 (CH_3). MS (ESI$^-$): M-H$^+$ = 215.2. Calculated at 215.0

8b: Yellow Solid. R_f = 0.36, 50% ethyl acetate/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.77 (s, 1H), 8.28 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.70 (t, J = 8.5 Hz, 1H), 7.25 (t, J = 8.5 Hz, 1H), 3.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 136.2 (CH), 134.3 (C_4), 126.6 (CH), 123.6 (CH), 119.5 (CH), 40.7 (CH_3). MS (ESI$^-$): M-H$^+$ = 215.2. Calculated at 215.0.

Table 2, entry 9

4-nitro-*N*-(4-nitrophenyl)benzenesulfonamide (9a) and

4-nitro-*N*-(2-nitrophenyl)benzenesulfonamide (9b)



9a **9b**

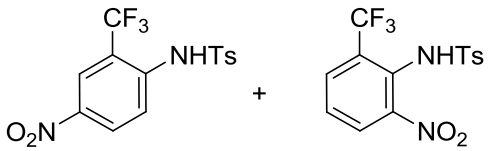
9a: Yellow Solid. R_f = 0.30, 10% ethyl acetate/toluene. ^{1}H NMR (500 MHz, d_6-DMSO) δ = 11.57 (s, 1H), 8.40 (d, 8.9 Hz, 2H), 8.15 (9.4 Hz, 2H), 8.11 (d, J = 9.2 Hz, 2H), 7.34 (d, J = 9.2 Hz, 2H). ^{13}C NMR (125 MHz, d_6-DMSO) δ = 150.2 (C_4), 144.2 (C_4), 143.4 (C_4), 143.1 (C_4), 128.3 (CH), 125.5 (CH), 125.0 (CH), 119.6 (CH). MS (ESI$^-$): M-H$^+$ = 322.2. Calculated at 322.0.

9b: White Solid. R_f = 0.70, 10% ethyl acetate/toluene. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.93 (s, 1H), 8.33 (d, J = 8.9 Hz, 2H), 8.15 (dd, J = 8.5, 1.6 Hz, 1H), 8.05 (d, J = 8.9 Hz, 2H), 7.87 (dd, J = 8.5, 1.4 Hz, 1H), 7.66 (m, 1H), 7.26 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 144.3 (C_4), 136.1 (CH), 132.7 (C_4), 128.5 (CH), 126.4 (CH), 124.92 (CH), 124.6 (CH), 121.4 (CH). MS (ESI$^-$): M-H$^+$ = 322.2. Calculated at 322.0.

Table 2, entry 10

4-methyl-*N*-[4-nitro-2-(trifluoromethyl)phenyl]benzenesulfonamide (10a) and

4-methyl-*N*-[2-nitro-6-(trifluoromethyl)phenyl]benzenesulfonamide (10b)



10a **10b**

10a: Yellow solid. R_f = 0.31, 30% ethyl acetate/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.41 (d, J = 2.8 Hz, 1H), 8.35 (dd, J = 9.2, 2.8 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.76 (d, J = 8.5 Hz, 2H), 7.32 – 7.27 (m, 3H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 145.5 (C_4), 143.0 (C_4), 140.4 (q, $^3J_{C\text{-}F}$ = 1.8 Hz, C_4), 134.8 (C_4), 130.1 (CH), 128.3 (CH), 127.4 (CH), 122.9 (q, $^3J_{C\text{-}F}$ = 6.4 Hz, CH), 122.5 (q, $^1J_{C\text{-}F}$ = 274.0 Hz, C_4), 120.7 (CH), 119.3 (q, $^2J_{C\text{-}F}$ = 31.8 Hz, C_4), 21.6 (CH_3). MS (ESI$^-$): M-H$^+$ = 359.0. Calculated at 359.0

10 b: White solid. R_f = 0.16, 30% ethyl acetate/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.06 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 7.97 (dd, J = 8.0, 1.4 Hz, 1H), 7.62 (dd, J = 8.01, 8.01 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ =148.1 (C_4), 144.9 (C_4), 135.4 (C_4), 132.3 (q, $^3J_{C\text{-}F}$ = 4.5 Hz, CH), 131.1 (q, $^2J_{C\text{-}F}$ = 30.9 Hz, C_4), 129.9 (CH), 128.6 (CH), 128.4 (CH),

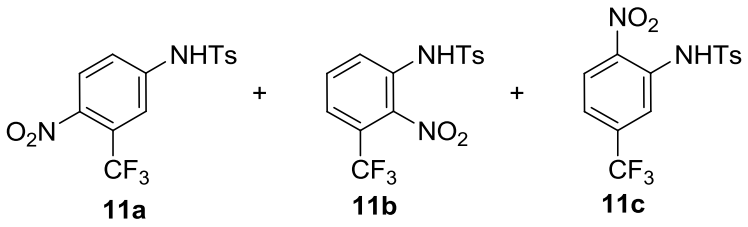
127. 9 (C_4), 127.3 (CH), 122.4 (q, $^1J_{C-F}$ = 275.2, CF_3), 21.6 (CH_3). MS (ESI$^-$): M-H$^+$ = 359.0. Calculated at 359.0.

Table 2, entry 11

4-methyl-*N*-[4-nitro-3-(trifluoromethyl)phenyl]benzenesulfonamide (11a) and

4-methyl-*N*-[2-nitro-3-(trifluoromethyl)phenyl]benzenesulfonamide (11b) and

4-methyl-*N*-[2-nitro-5-(trifluoromethyl)phenyl]benzenesulfonamide (11c)



11a: White solid. R_f = 0.12, dichloromethane. ^{1}H NMR (500 MHz, d_6-DMSO) δ = 11.48 (s, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.60 – 7.54 (m, 2H), 7.41 (d, J = 8.5 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, d_6-DMSO) δ = 144.4 (C_4), 142.8 (C_4), 141.5 (q, $^3J_{C-F}$ = 1.8 Hz, C_4), 135.7 (C_4), 130.1 (CH), 128.3 (CH), 126.8 (CH), 123.4 (q, $^2J_{C-F}$ = 33.6 Hz, C_4), 121.7 (q, $^1J_{C-F}$ = 273.4 Hz, CF_3), 121.1 (CH), 116.3 (q, $^3J_{C-F}$ = 6.4 Hz, CH), 21.0 (CH_3). MS (ESI$^-$): M-H$^+$ = 359.0 Calculated at 359.0.

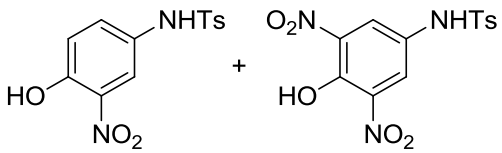
11b: White solid. R_f = 0.23, dichloromethane. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.05 (dd, J = 8.24, 0.8 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.56 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 7.49 (s, 1H), 7.27 (d, J = 8.5 Hz, 2H) 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 145.2, (C_4), 135.1 (C_4), 132.1 (CH), 130.6 (C_4), 130.2 (CH), 128.5 (CH), 127.0 (CH), 124.4 (q, $^2J_{C-F}$ = 34.5 Hz, C_4), 124.1 (q, $^3J_{C-F}$ = 5.5 Hz, CH), 121.5 (q, $^1J_{C-F}$ = 274.3 Hz, CF_3), 21.6 (CH_3). MS (ESI$^-$): M-H$^+$ = 359.0 Calculated at 359.0.

11c: Yellow-brown solid. R_f = 0.56, 30% ethyl acetate/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.89 (s, 1H), 8.24 (d, J = 8.7 Hz, 1H), 8.15 (d, J = 1.4 Hz, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.38 (dd, J = 8.7, 1.6 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 145.4 (C_4), 137.0 (q, $^2J_{C-F}$ = 33.6 Hz, C_4), 135.1 (C_4), 134.6 (C_4), 130.2 (CH), 127.4 (CH), 127.1 (CH), 122.4 (q, $^1J_{C-F}$ = 273.4, CF_3), 119.9 (q, $^3J_{C-F}$ = 3.6 Hz, CH), 117.8 (q, $^3J_{C-F}$ = 3.6 Hz, CH), 21.6 (CH_3). MS (ESI$^-$): M-H$^+$ = 359.0 Calculated at 359.0.

Competition experiment #3 products

4-{[(4-methylphenyl)sulfonyl]methyl}-2-nitrophenol and

4-{[(4-methylphenyl)sulfonyl]methyl}-2,6-dinitrophenol



a **b**

a: Yellow solid. R_f = 0.70, 10% Methanol/dichloromethane. ^{1}H NMR (500 MHz, d_6-DMSO) δ = 10.85 (s, 1H), 10.19 (s, 1H), 7.59 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 2.7 Hz, 1H) 7.35 (d, J = 8.6 Hz, 2H), 7.24 (dd, J = 9.0, 2.7 Hz, 1H), 7.02 (d, J = 9.0 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 149.5 (C_4), 143.5 (C_4), 136.2 (C_4), 136.0 (C_4), 129.8 (CH), 129.2 (C_4), 129.0 (CH), 126.8 (CH), 120.2 (CH), 117.3 (CH), 21.0 (CH_3) MS (ESI$^-$): M-H$^+$ = 307.2 Calculated at 307.3.

b: Orange solid. R_f = 0.1, 10% Methanol/dichloromethane. ^{1}H NMR (500 MHz, d_6-DMSO) δ = 10.18 (s, 1H), 7.69 (s, 2H), 7.62 (d, J = 8.2 Hz, 2H) 7.37 (d, J = 8.2 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 149.1 (C_4), 143.7 (C_4), 140.9 (C_4), 136.0 (C_4), 129.9 (C_4), 126.9 (CH), 123.9 (CH), 122.9(CH), 21.0 (CH_3). MS (ESI$^-$): M-H$^+$ = 352.2 Calculated at 352.3

^{1}H, ^{13}C, and ^{15}N NMR assignment of N-(4-methoxy-2-nitrophenyl)-4-methylbenzenesulfonamide (Table 2, entry 1) and *N*-(4-chloro-2-nitrophenyl)-4-methylbenzenesulfonamide (Table 2, entry 3)

The ^{1}H, ^{13}C, and ^{15}N chemical shifts for *N*-(4-chloro-2-nitrophenyl)-4-methylbenzenesulfonamide and N-(4-methoxy-2-nitrophenyl)-4-methylbenzenesulfonamide were obtained on a Bruker AVIII NMR Spectrometer at a magnetic field strength of 9.4 T (^{1}H frequency of 400 MHz) using a combination of 1D and 2D NMR experiments: ^{1}H and ^{13}C 1D, ^{1}H,^{13}C-HSQC (heteronuclear single quantum correlation), ^{1}H,^{13}C-HMBC (heteronuclear multiple bond correlation) optimized for long-range coupling constants of 7.7 Hz, ^{1}H,^{15}N-HSQC, and ^{1}H,^{15}N-HMBC optimized for 10 Hz couplings. In addition, 1D selective NOE experiments with mixing times of 300 ms were recorded (see below for details). ^{1}H and ^{13}C chemical shifts were referenced to the residual solvent signal ($CDCl_3$).

The regiochemistry (the position of the nitro group) for *N*-(4-chloro-2-nitrophenyl)-4-methylbenzenesulfonamide and N-(4-methoxy-2-nitrophenyl)-4-methylbenzenesulfonamide was confirmed using correlations from H3 and H6 to the nitro-nitrogen (see figure A). For N-(4-methoxy-2-nitrophenyl)-4-methylbenzenesulfonamide, an NOE was observed between the methyl protons of the methoxy group and H3 (see figure B).

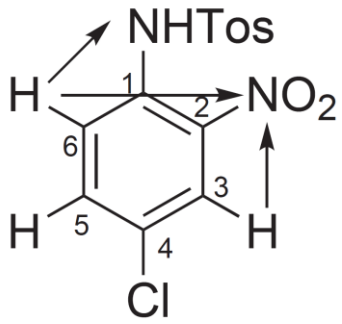


Figure A: Correlations observed in a $^{1}H,^{15}N$-HMBC experiment for *N*-(4-chloro-2-nitrophenyl)-4-methylbenzenesulfonamide, indicated by arrows.

Table A: Chemical shifts for *N*-(4-chloro-2-nitrophenyl)-4-methylbenzenesulfonamide

Position	Nucleus	Chemical Shift (ppm)
1	C	132.7
1	N	119.7
1	HN	9.7
Tos1	C	135.4
2	C	137.2
2	N	-32.9
Tos2	C	127.2
Tos2	H	7.7
3	C	125.8
3	H	8.1
Tos3	C	130.1
Tos3	H	7.3
TosCH3	C	21.6
TosCH3	H	2.4
4	C	129.3
Tos4	C	145.1
5	C	135.8
5	H	7.5
6	C	122.4
6	H	7.8

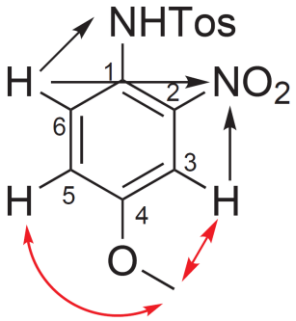


Figure B: Correlations observed in a $^{1}H,^{15}N$-HMBC experiment (black arrows) and in 1D selective NOE experiments (red arrows) for N-(4-methoxy-2-nitrophenyl)-4-methylbenzenesulfonamide.

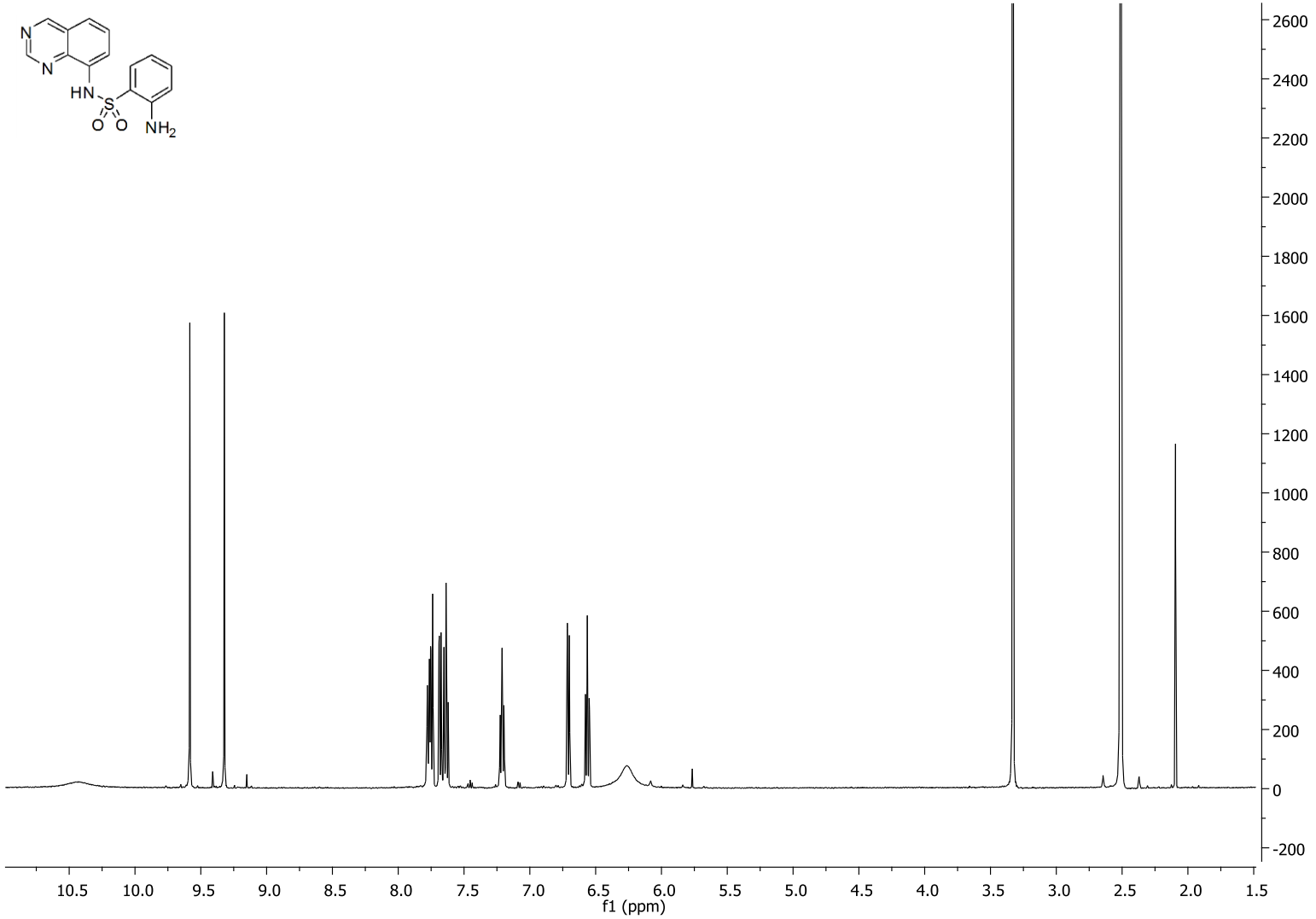
Table B: Chemical shifts for *N*-(4-methoxy-2-nitrophenyl)-4-methylbenzenesulfonamide

Position	Nucleus	Chemical Shift (ppm)
OMe	C	55.9
OMe	H	3.8
1	C	126.5
1	N	116.2
1	HN	9.2
Tos1	C	135.5
2	C	138.9
2	N	-30.8
Tos2	C	127.0
Tos2	H	7.6
3	C	108.9
3	H	7.5
Tos3	C	129.8
Tos3	H	7.2
TosCH3	C	21.5
TosCH3	H	2.4
4	C	156.1
Tos4	C	144.5
5	C	123.0
5	H	7.2
6	C	124.7

6	H	7.8

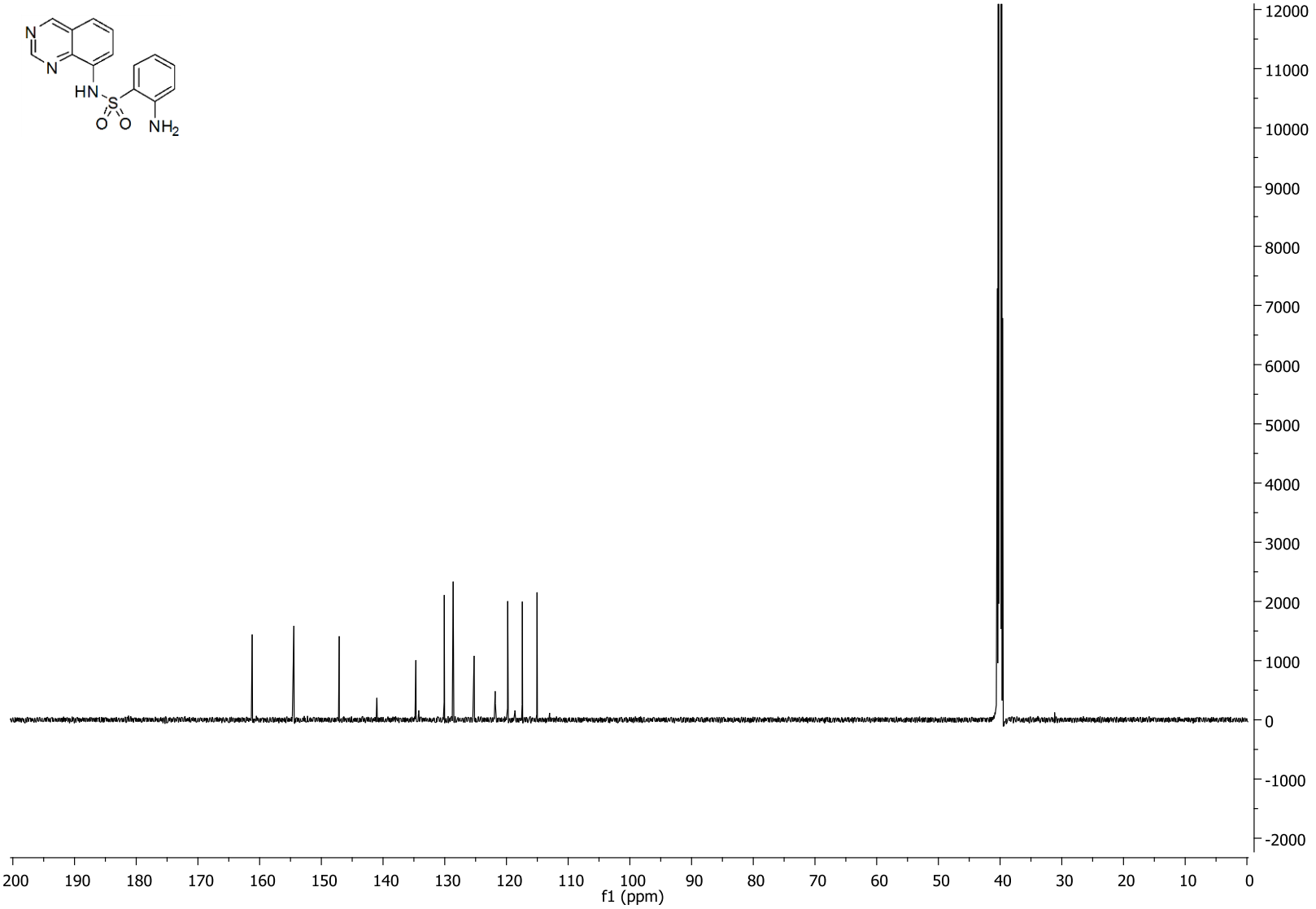
Compound 1

d_6-DMSO, ^{1}H NMR, 400 MHz



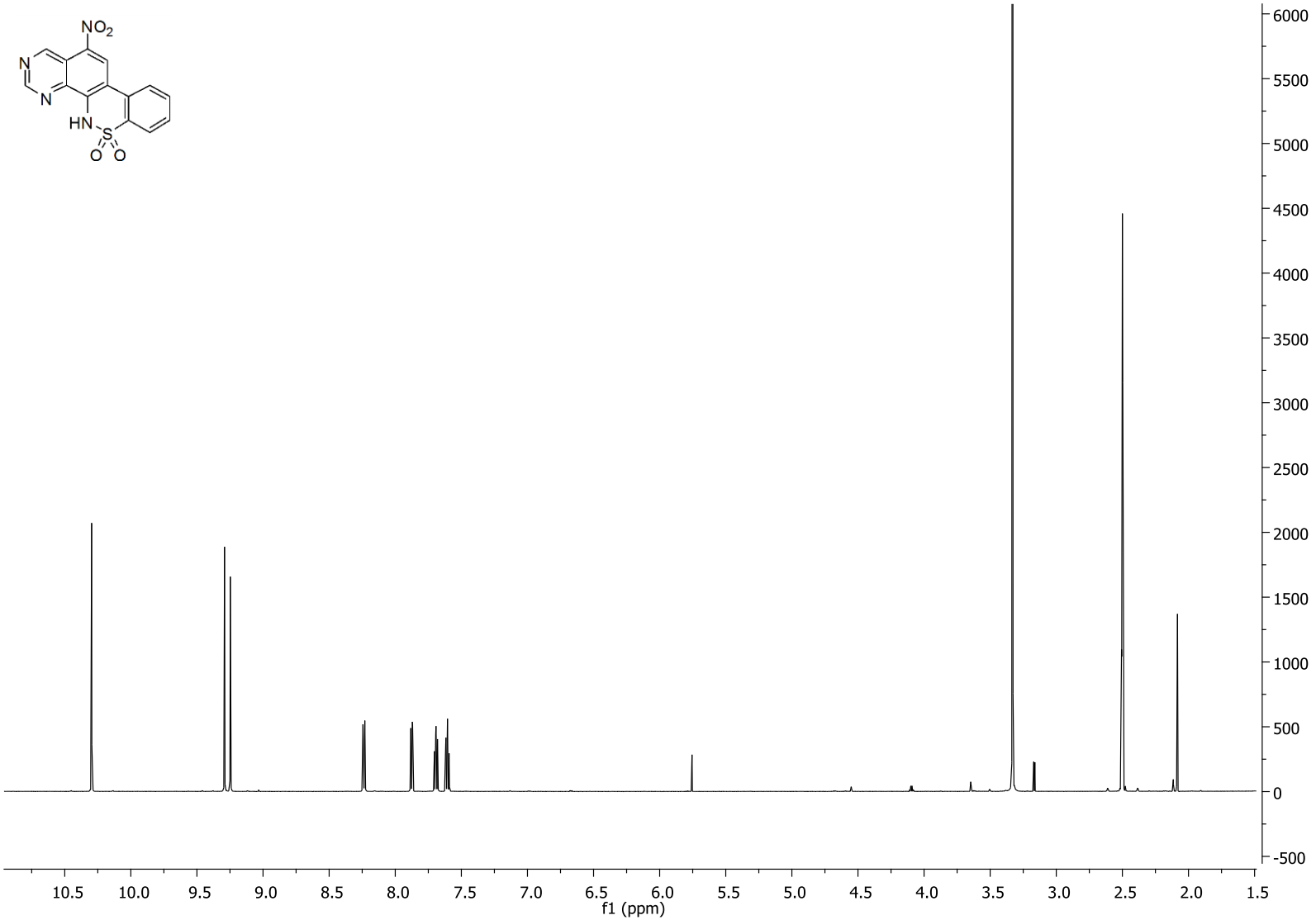
Compound 1

d_6-DMSO, ^{13}C NMR, 150 MHz



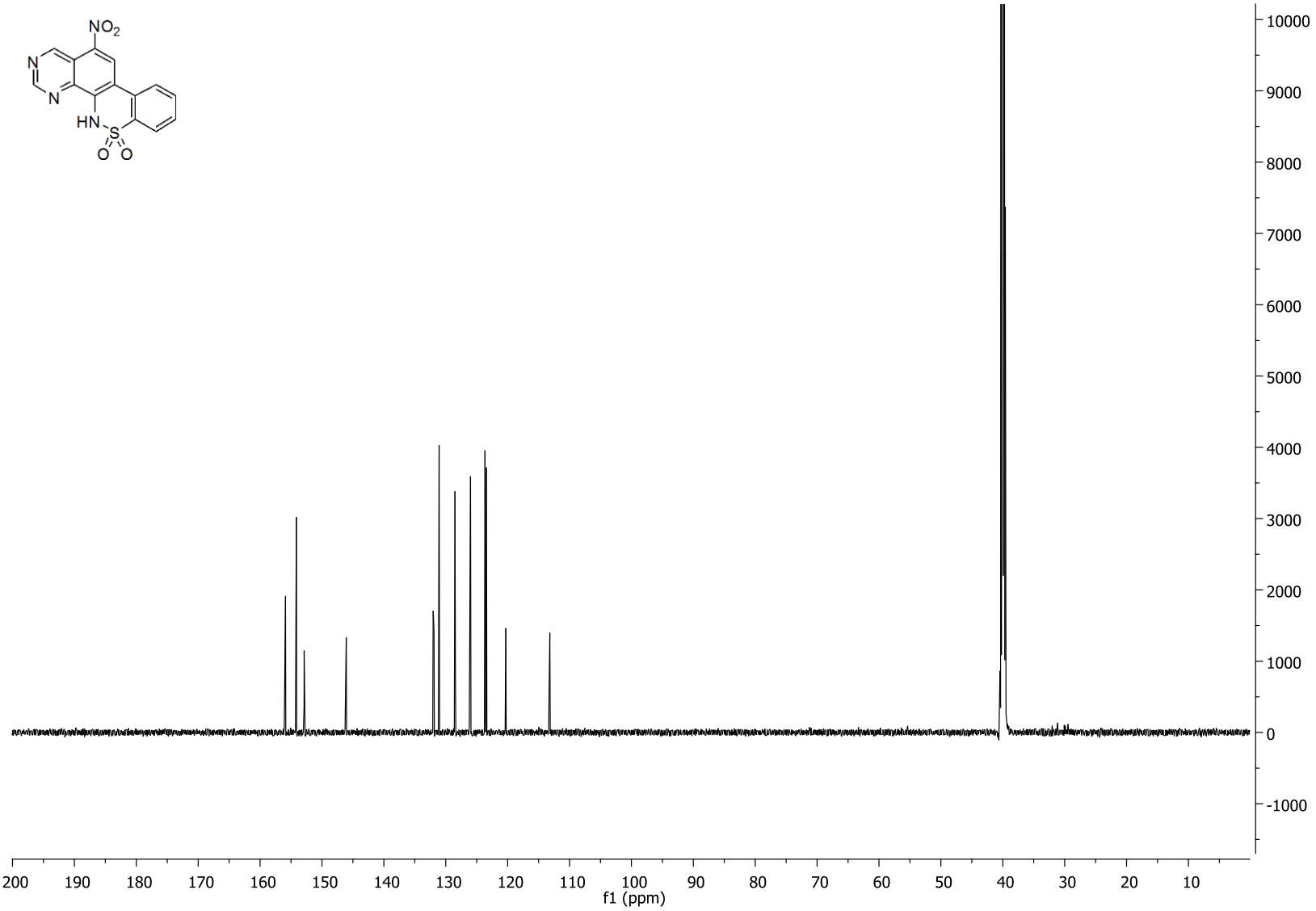
Compound 3

d_6-DMSO, ^{1}H NMR, 400 MHz



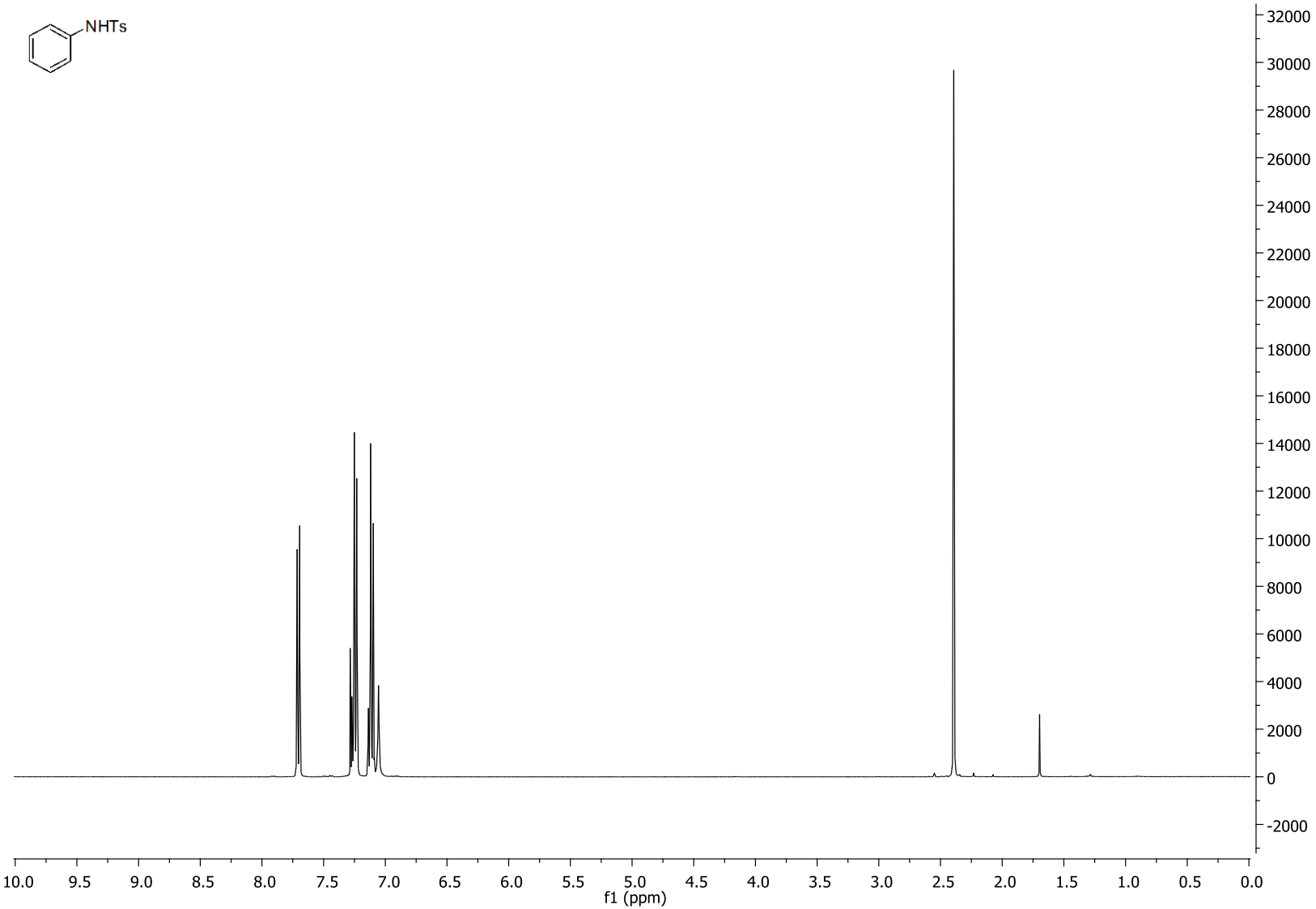
Compound 3

d_6-DMSO, ^{13}C NMR, 150 MHz



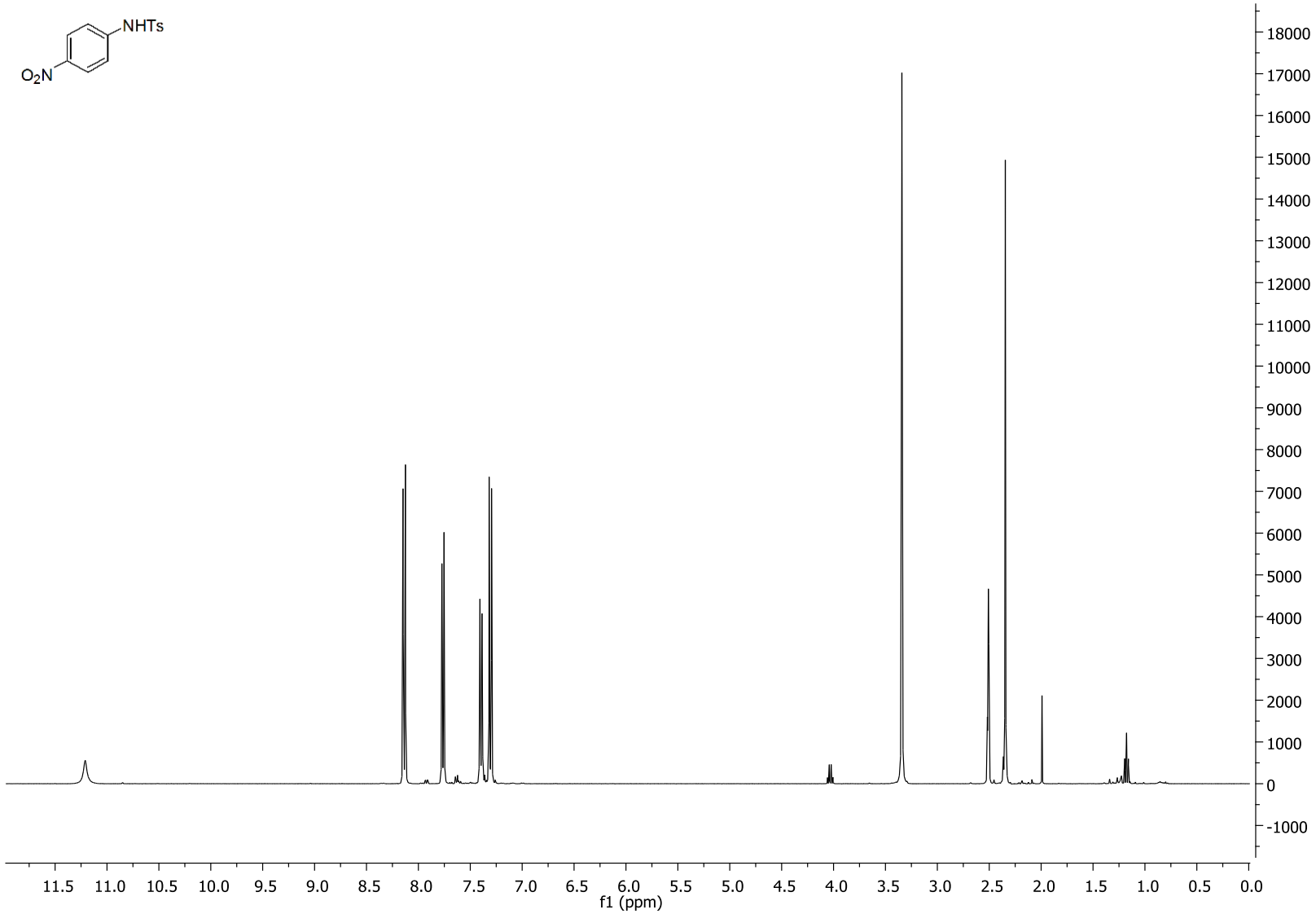
Compound 4

d_6-DMSO, ^{1}H NMR, 400 MHz



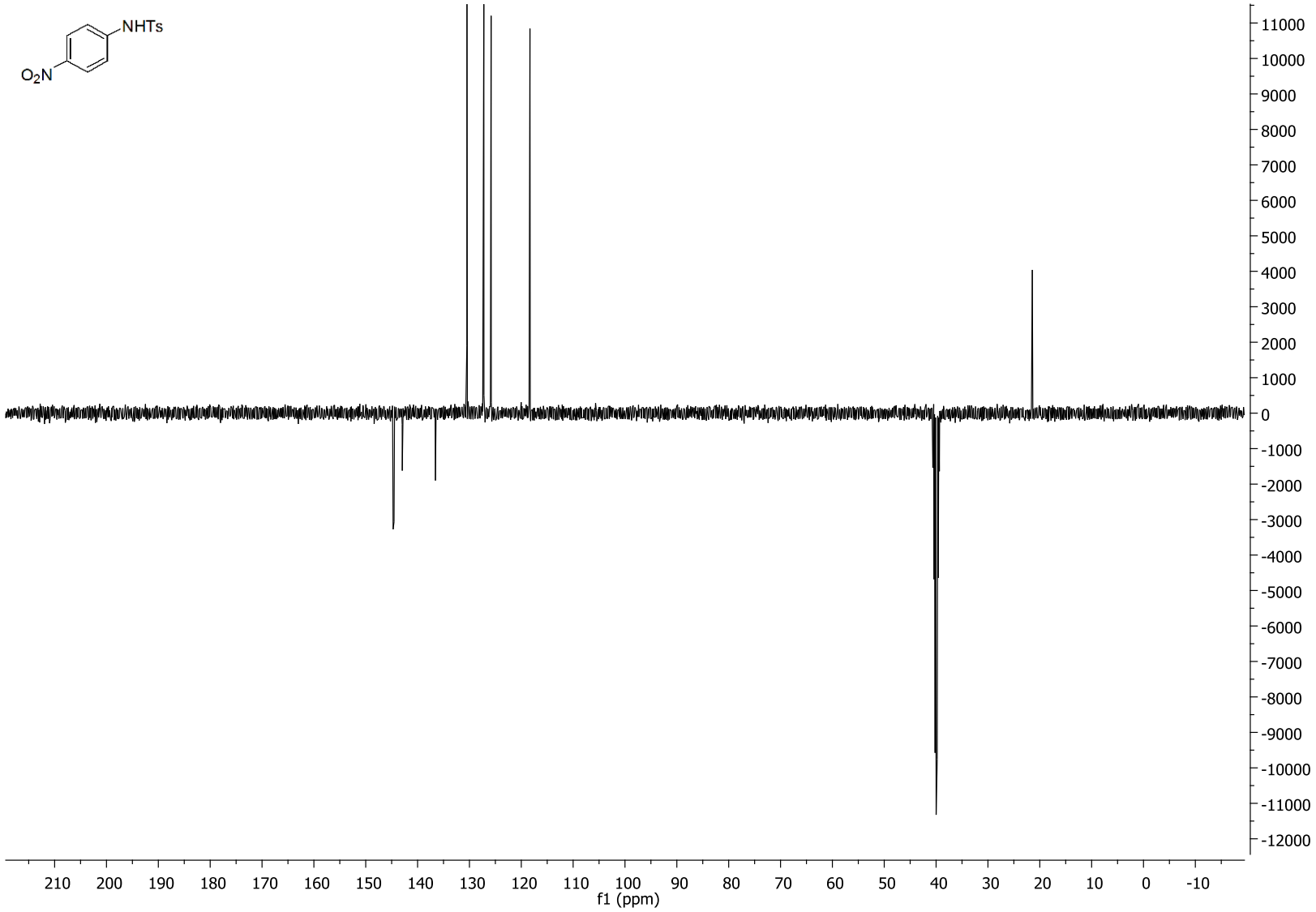
Compound 5a

d_6-DMSO, ^{1}H NMR, 400 MHz



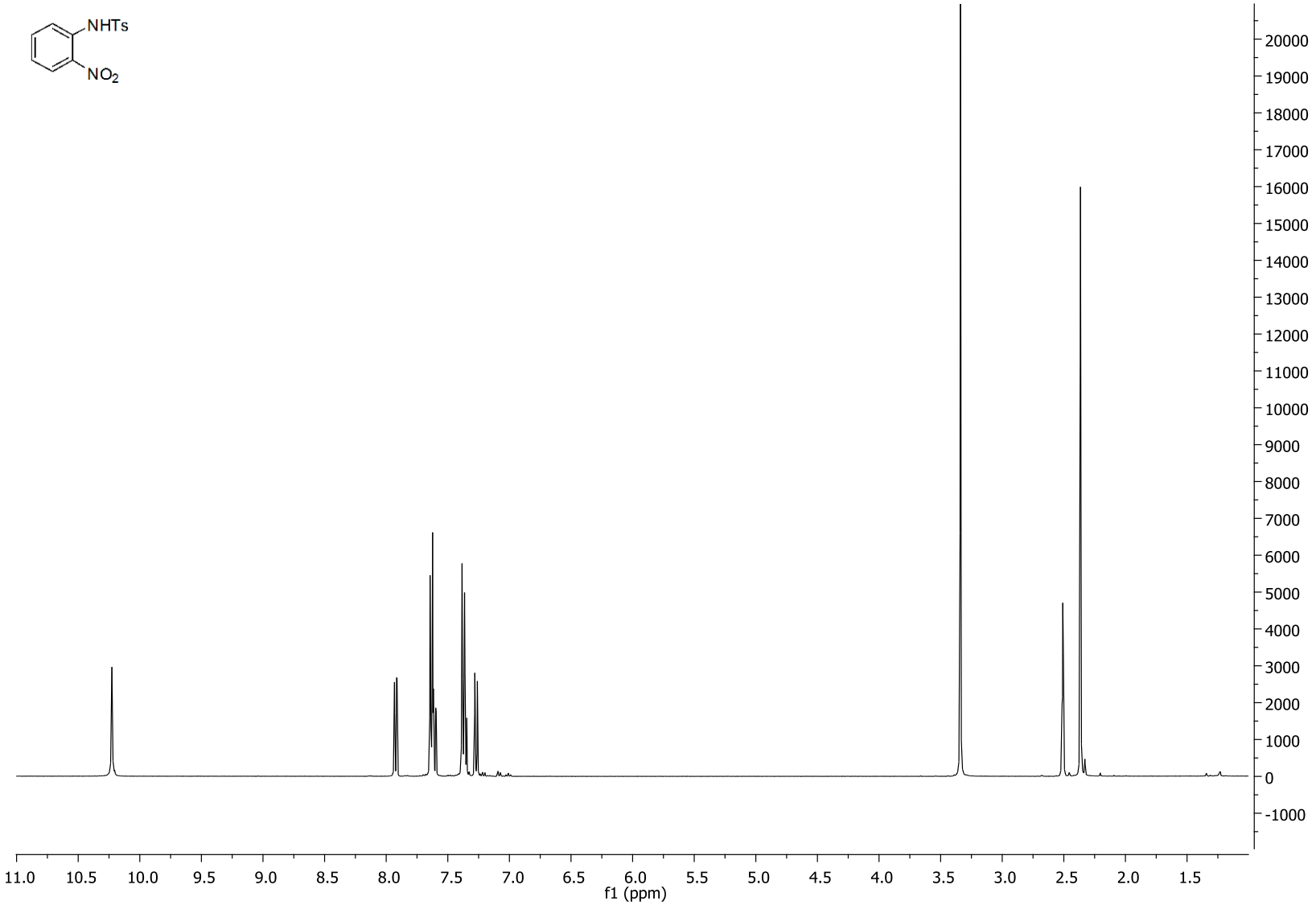
Compound 5a

d_6-DMSO, ^{13}C APT, 100 MHz



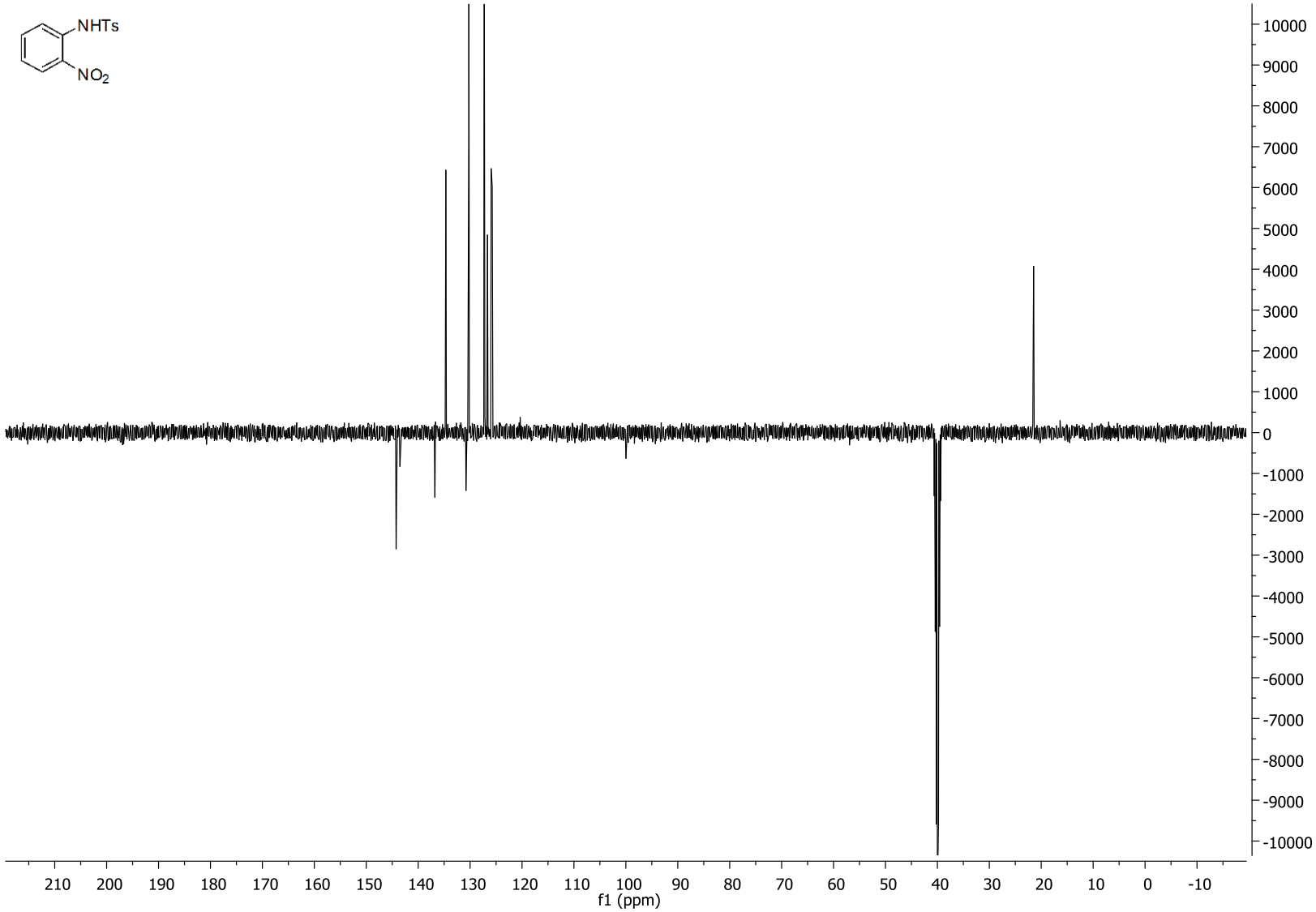
Compound 5b

d_6-DMSO, ^{1}H NMR, 400 MHz



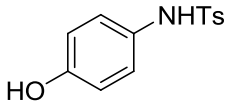
Compound 5b

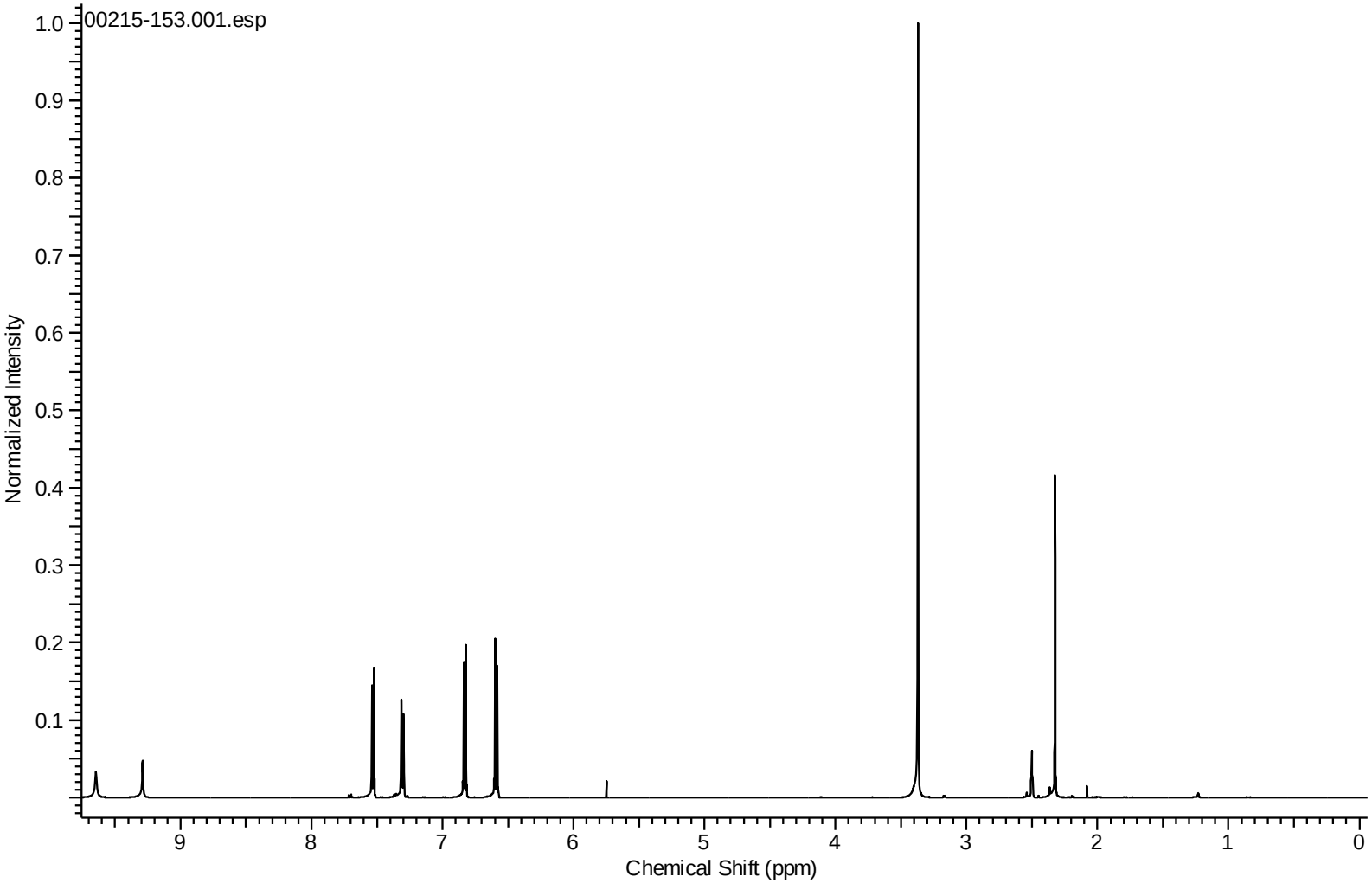
d_6-DMSO, ^{13}C APT, 100 MHz



Competition experiment #3 starting material

d_6-DMSO ^{1}HNMR, 500 MHz





Competition experiment #3 starting material

d_6-DMSO ^{13}CNMR, 125 MHz

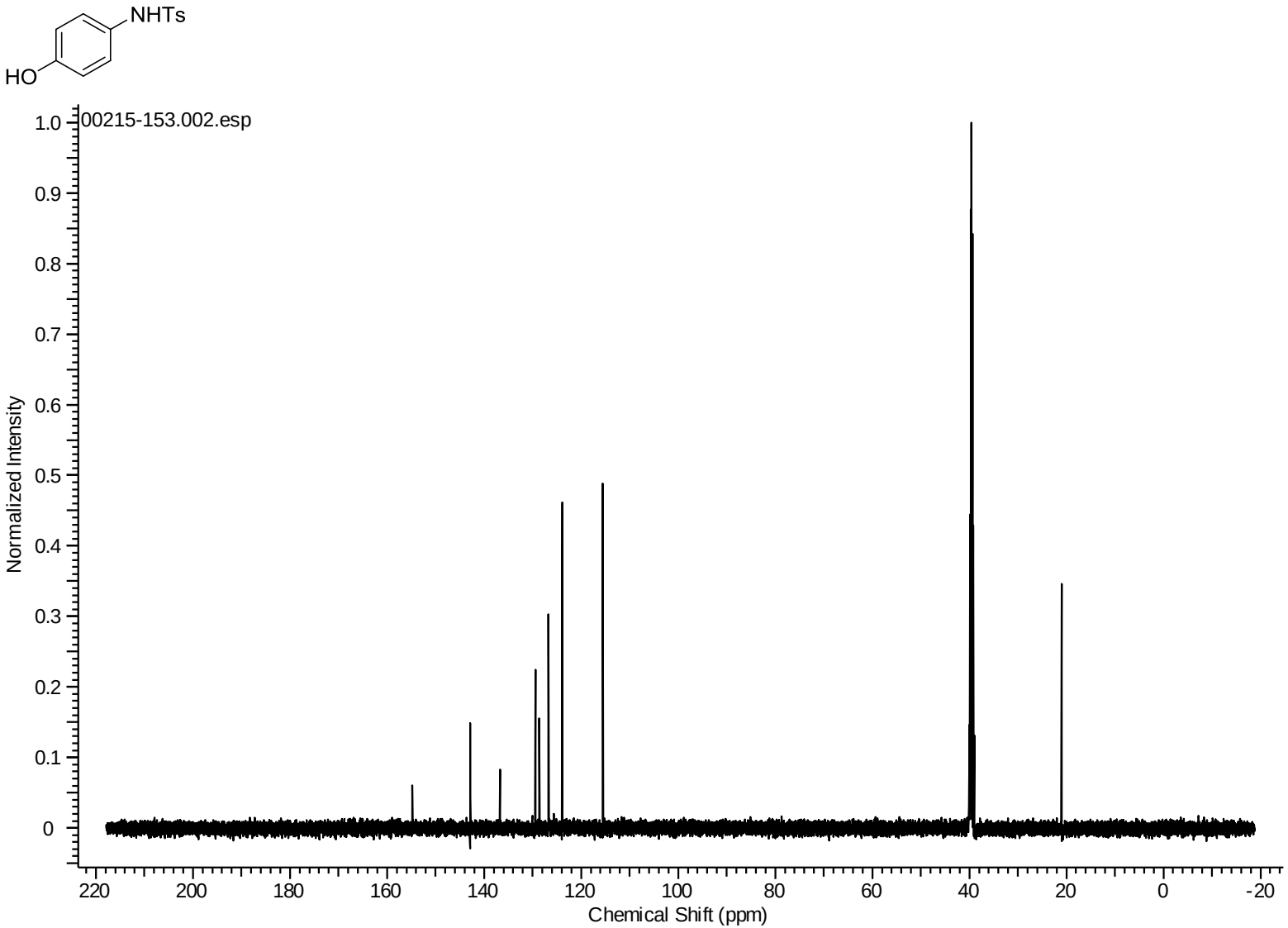
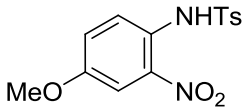


Table 2, entry 1

$CDCl_3$, ^1H NMR 500 MHz



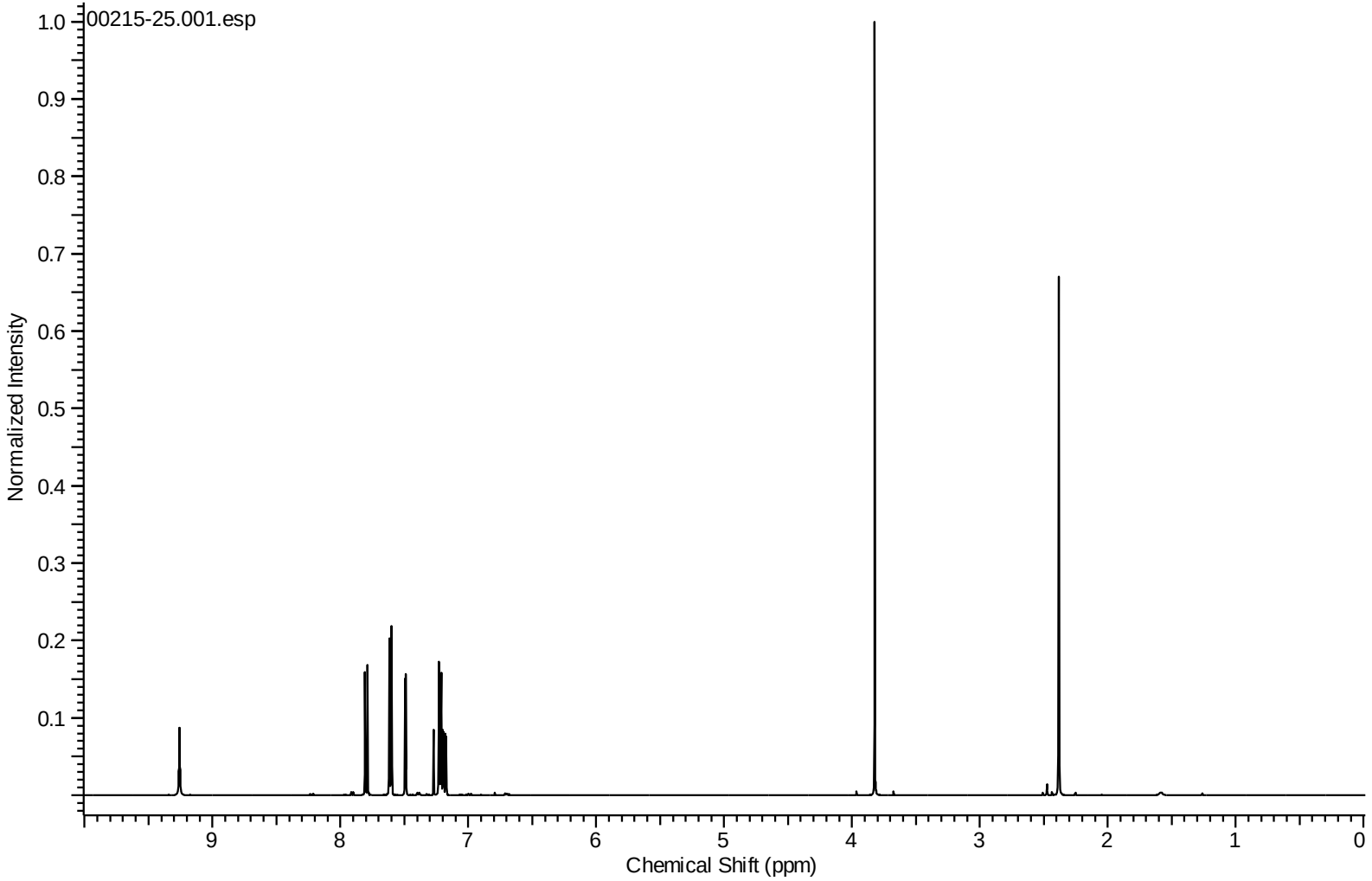


Table 2, entry 1:

$CDCl_3$, ^{13}C NMR 125 MHz

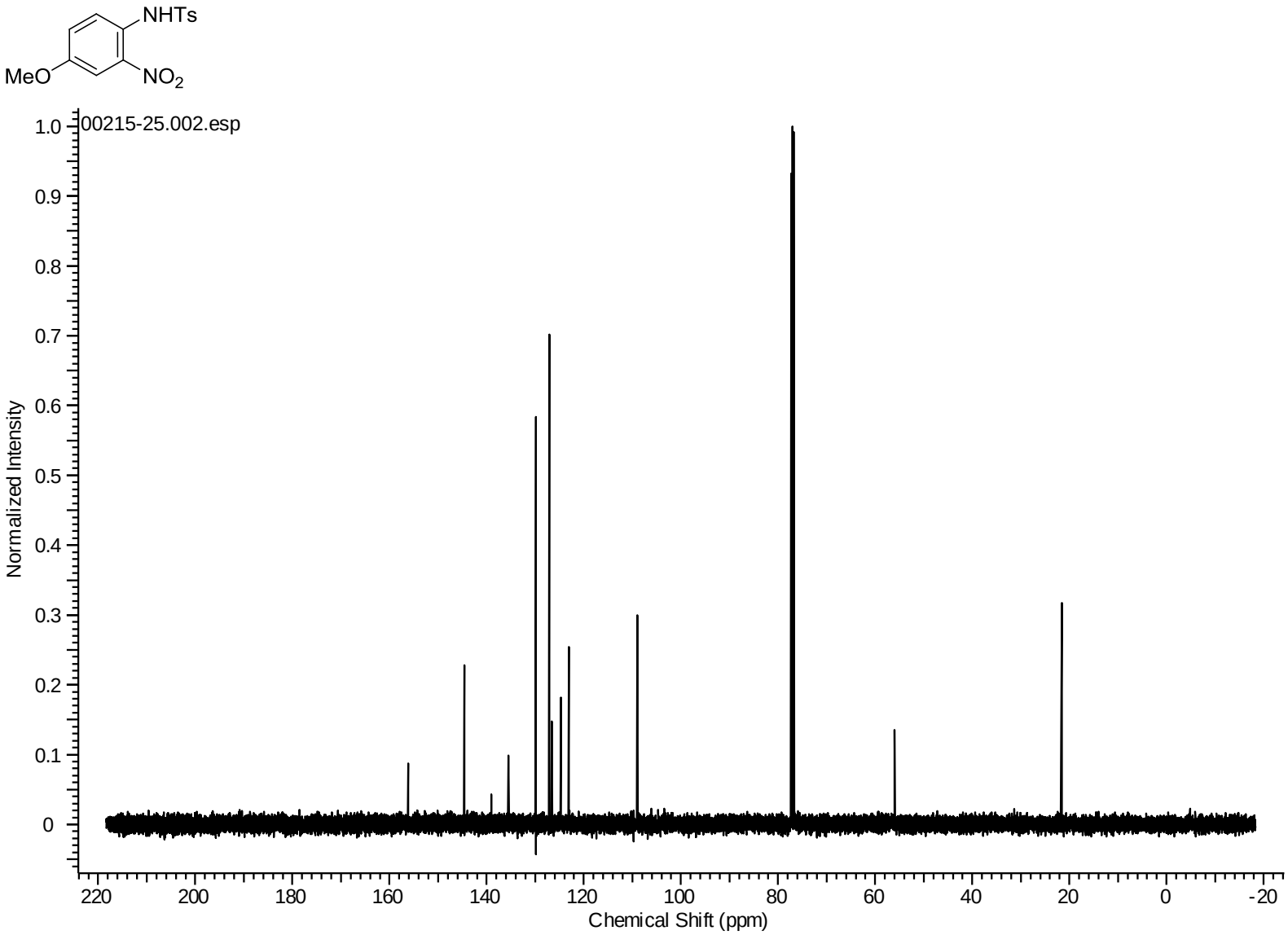
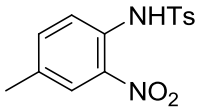


Table 2, entry 2

$CDCl_3$, ^1H NMR 500 MHz



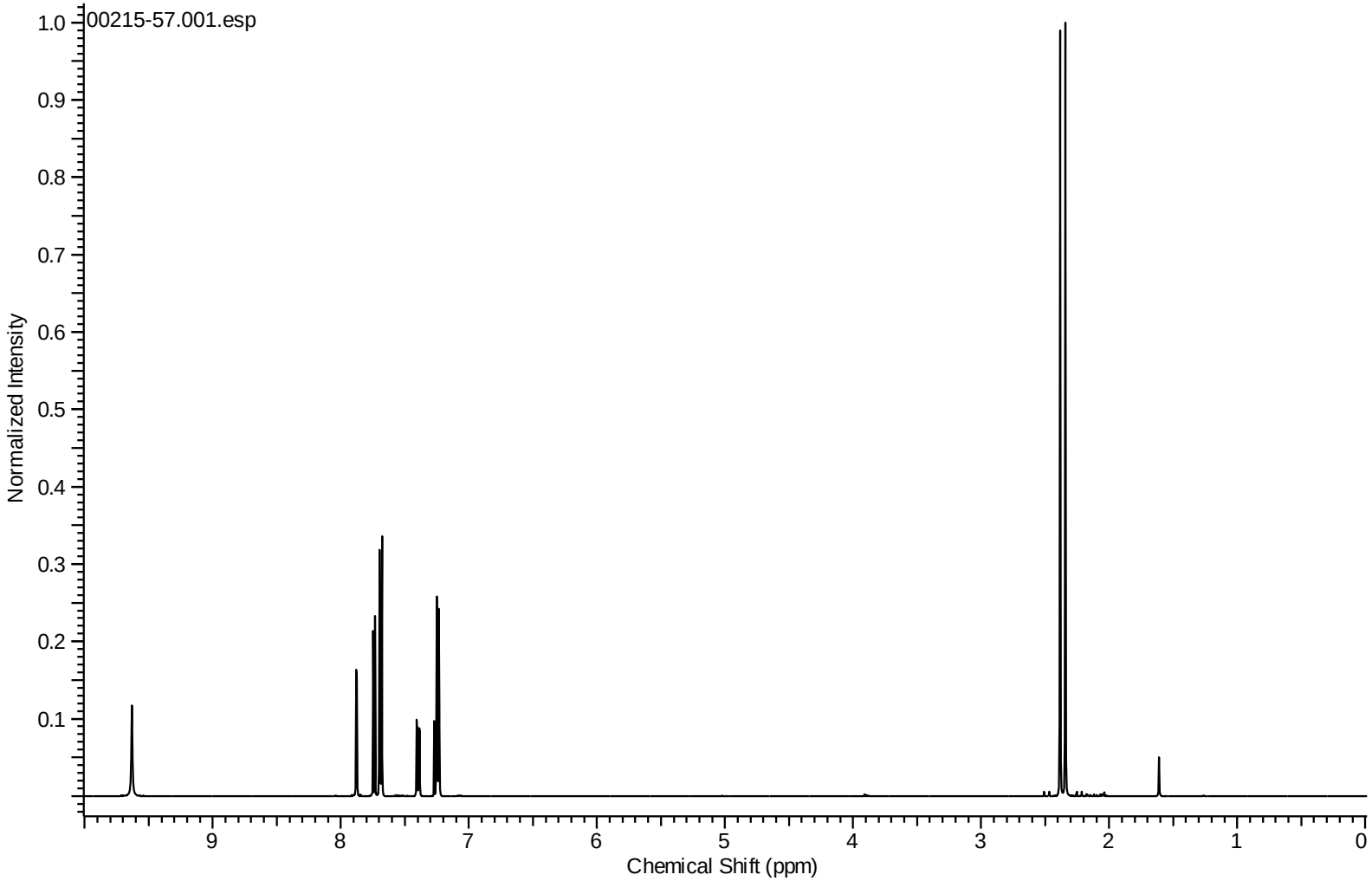
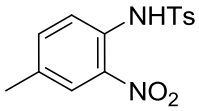


Table 2, entry 2

$CDCl_3$, ^{13}C NMR 125 MHz



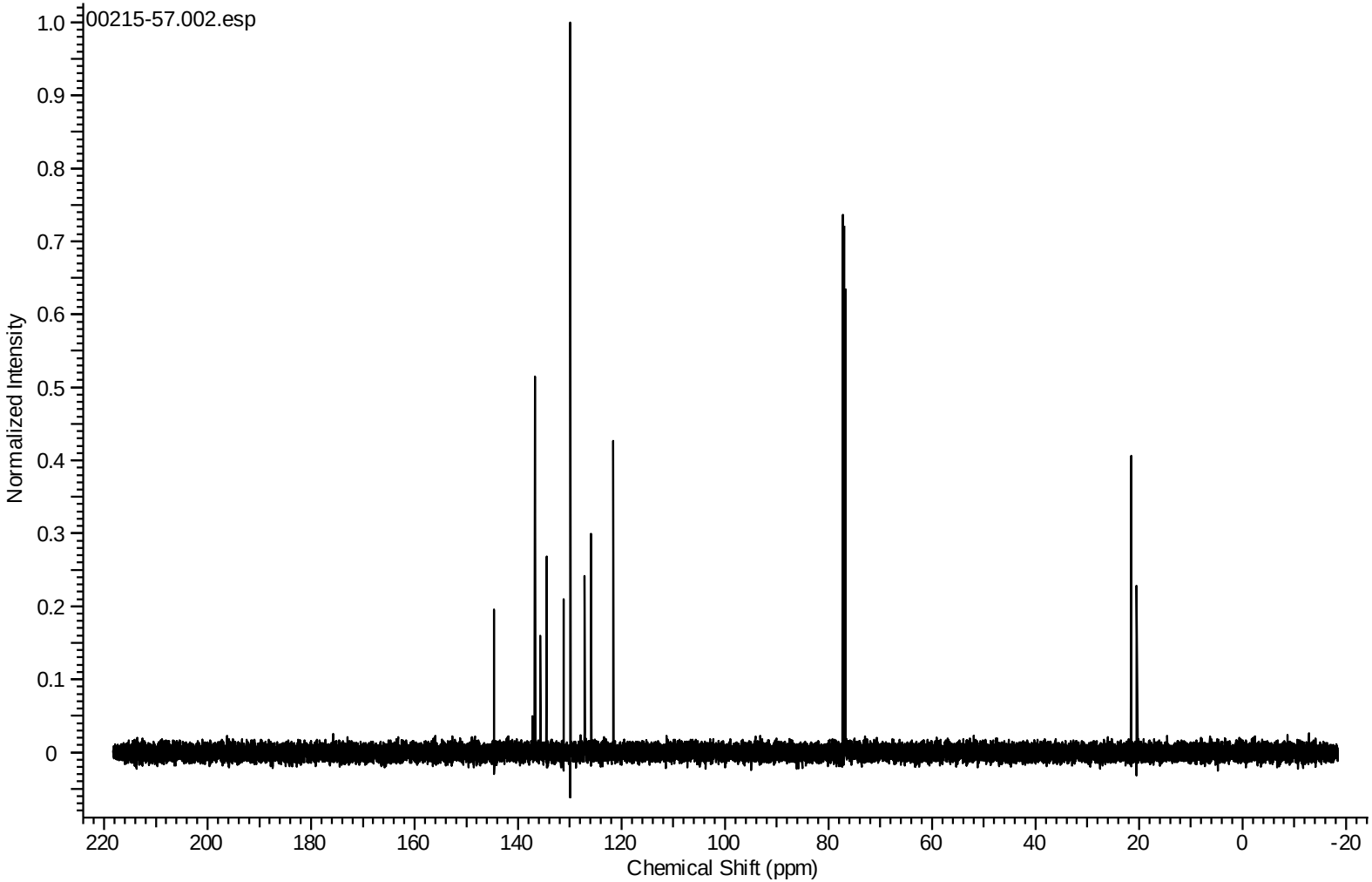
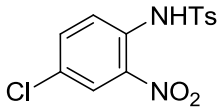


Table 2, entry 3:

$CDCl_3$, ^1H NMR 500MHz



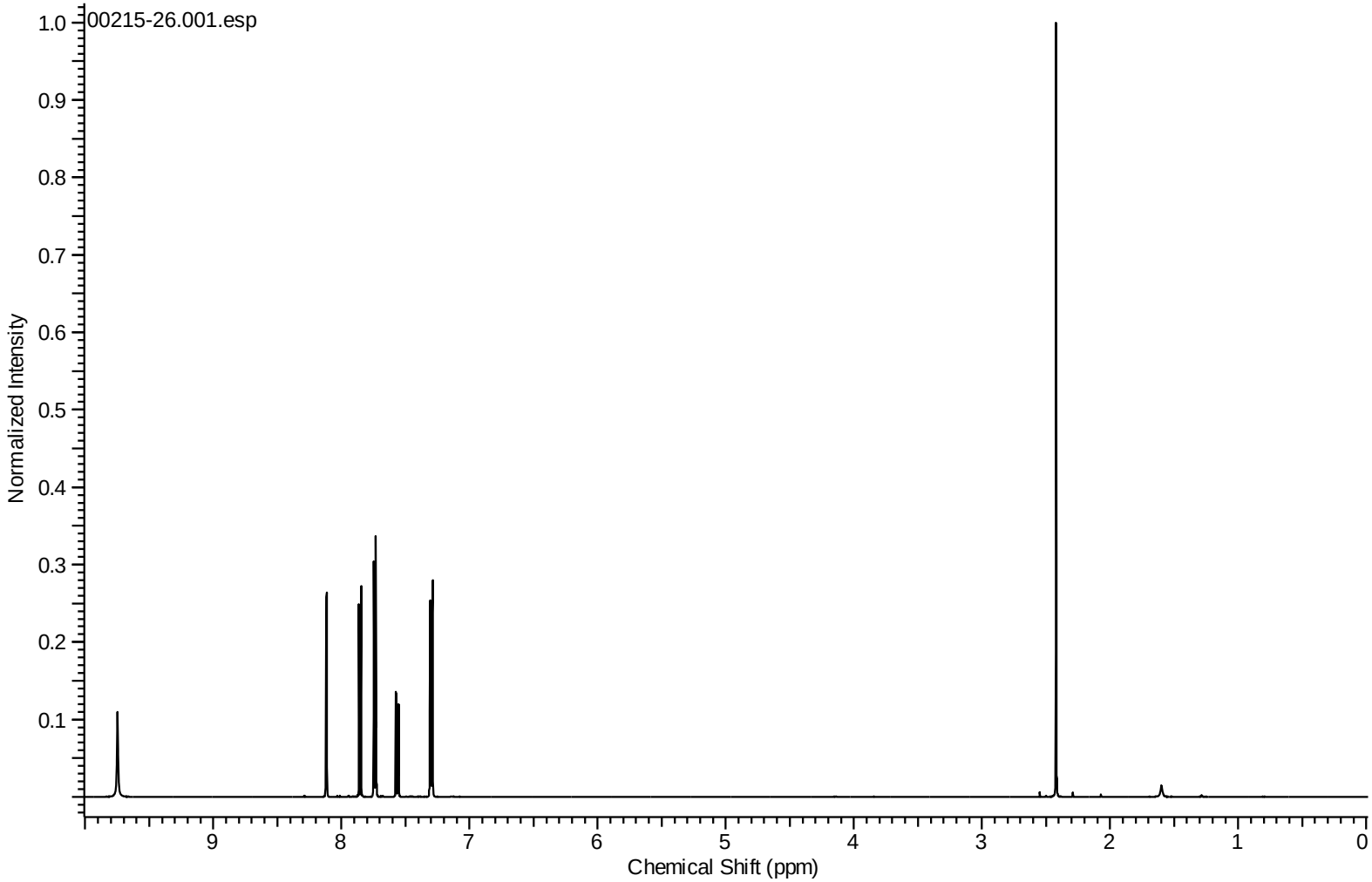


Table 2, entry 3:

$CDCl_3$, ^{13}CNMR 125 MHz

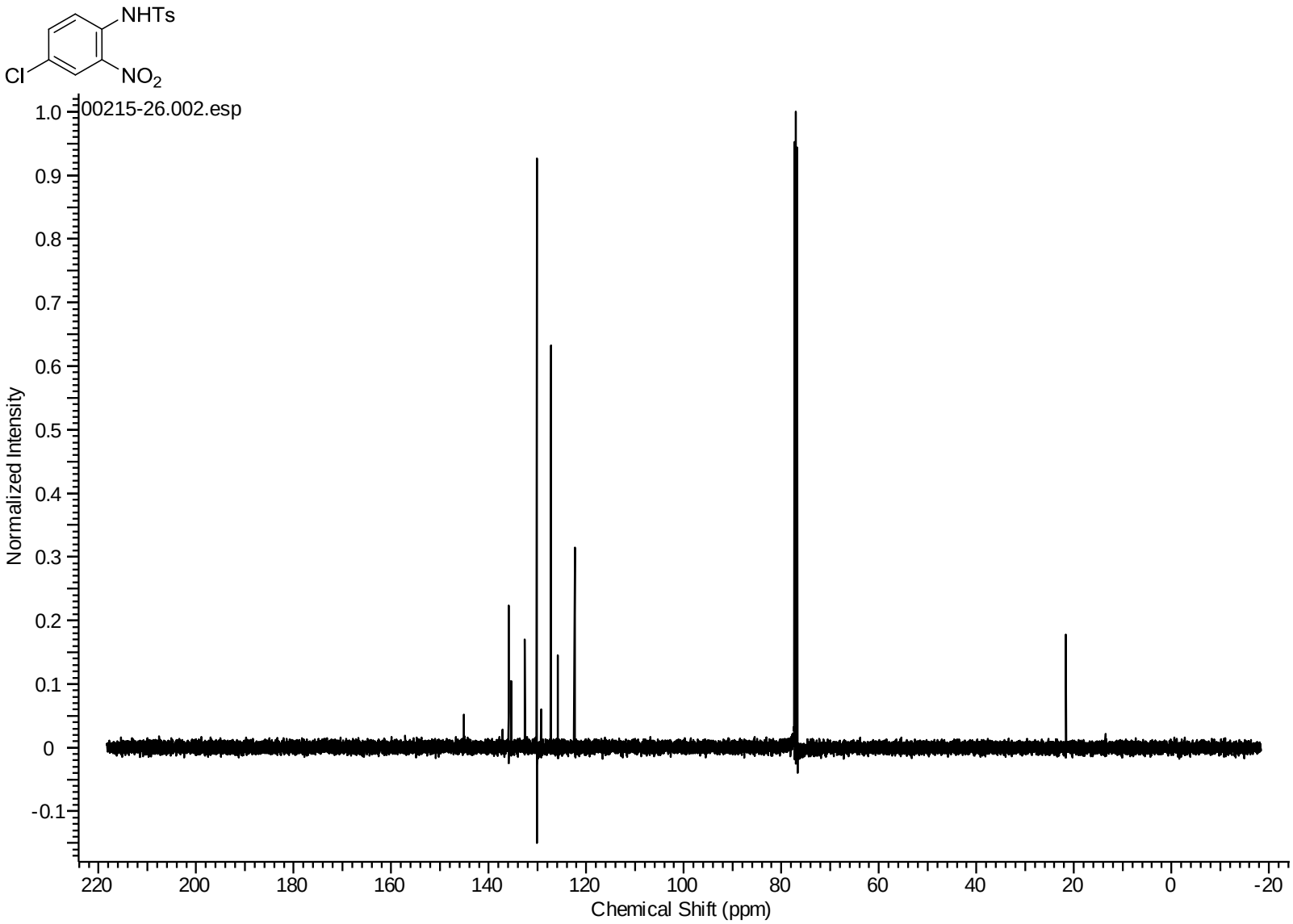
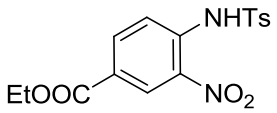


Table 2, entry 4:

$CDCl_3$, ^1H NMR 500 MHz



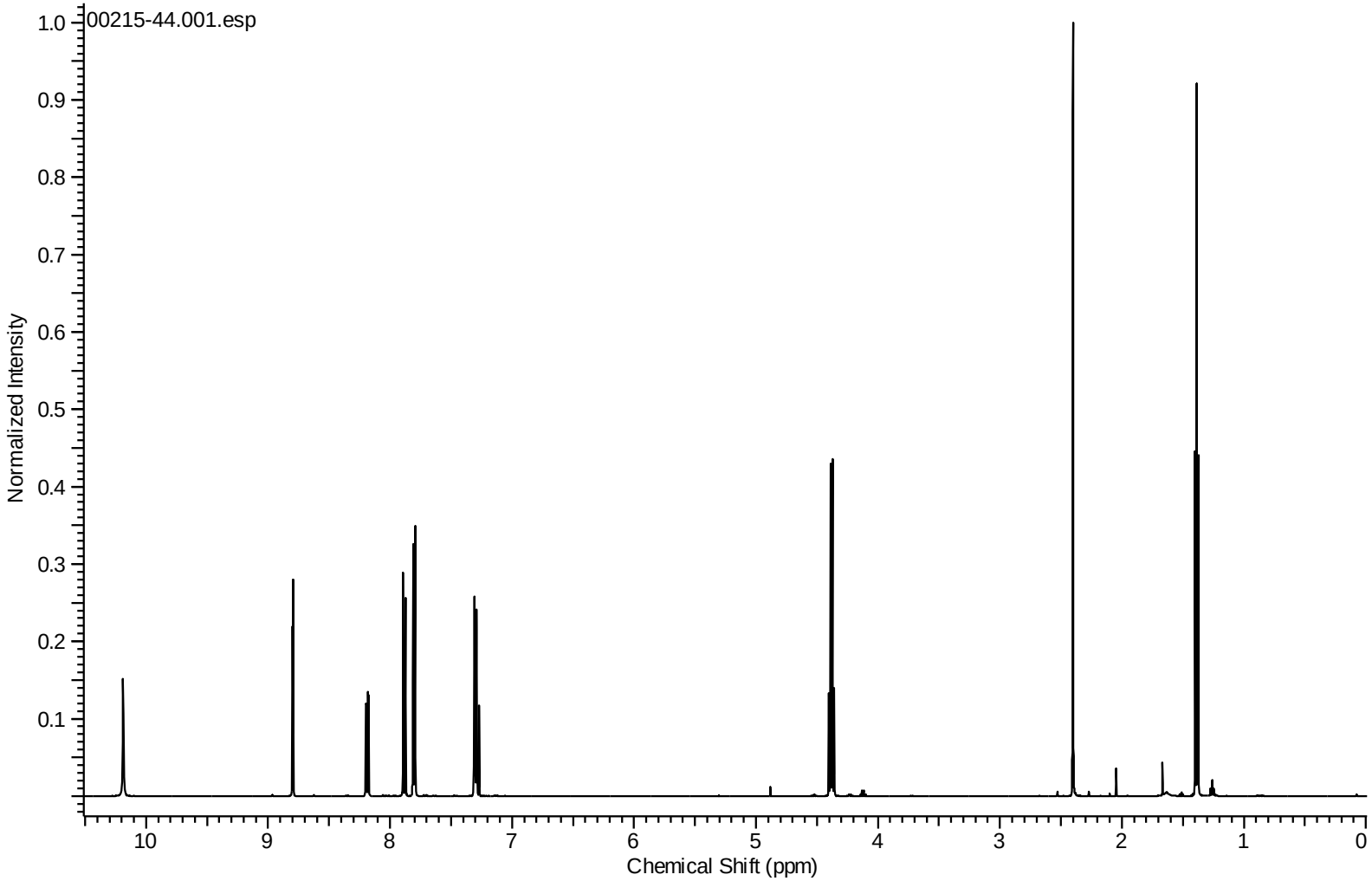
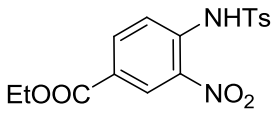


Table 2, entry 4:

$CDCl_3$, ^{13}C NMR 125 MHz



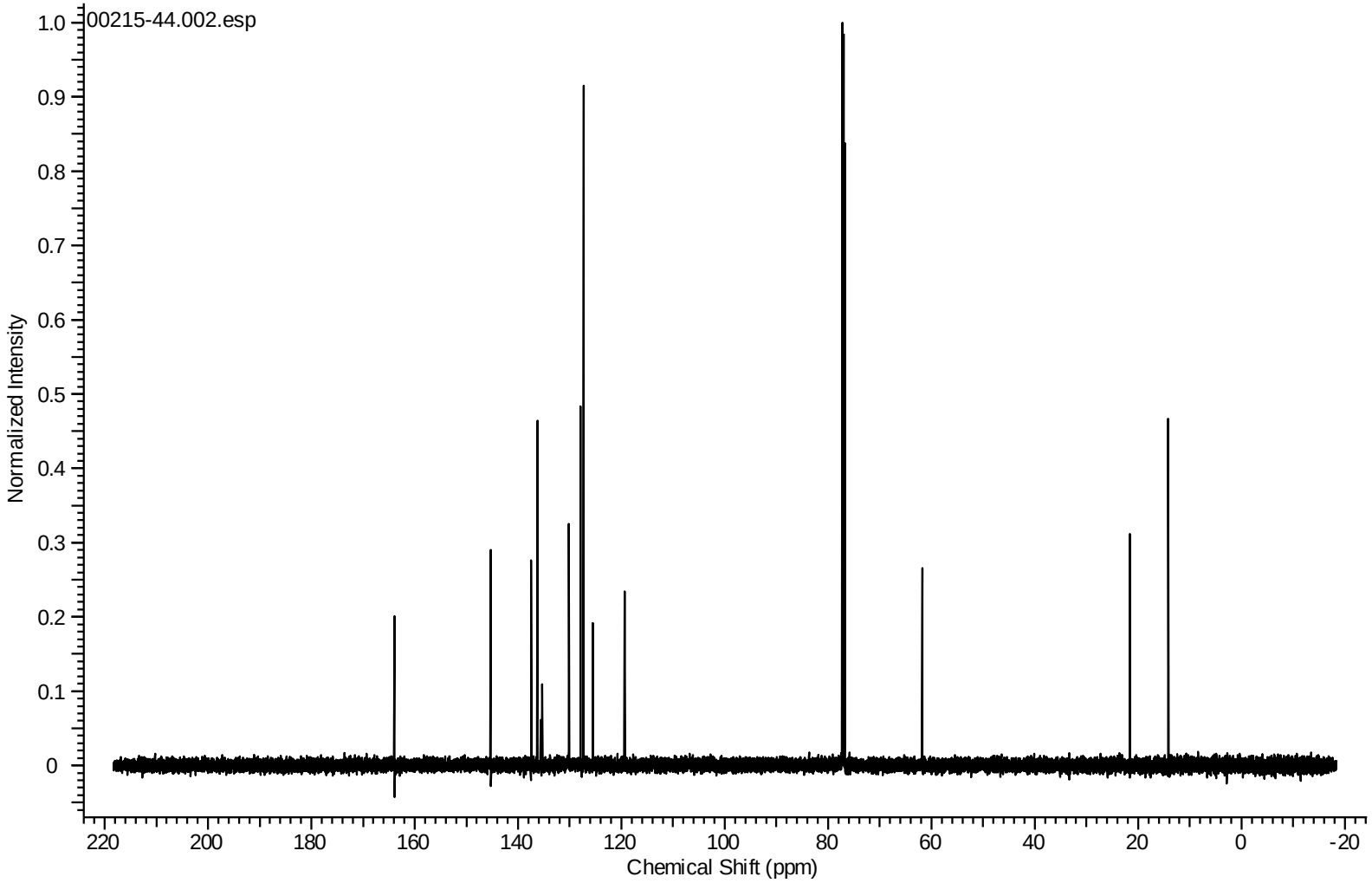
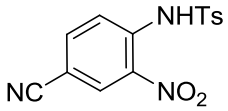


Table 2, entry 5:

$CDCl_3$, ^1H NMR 500 MHz



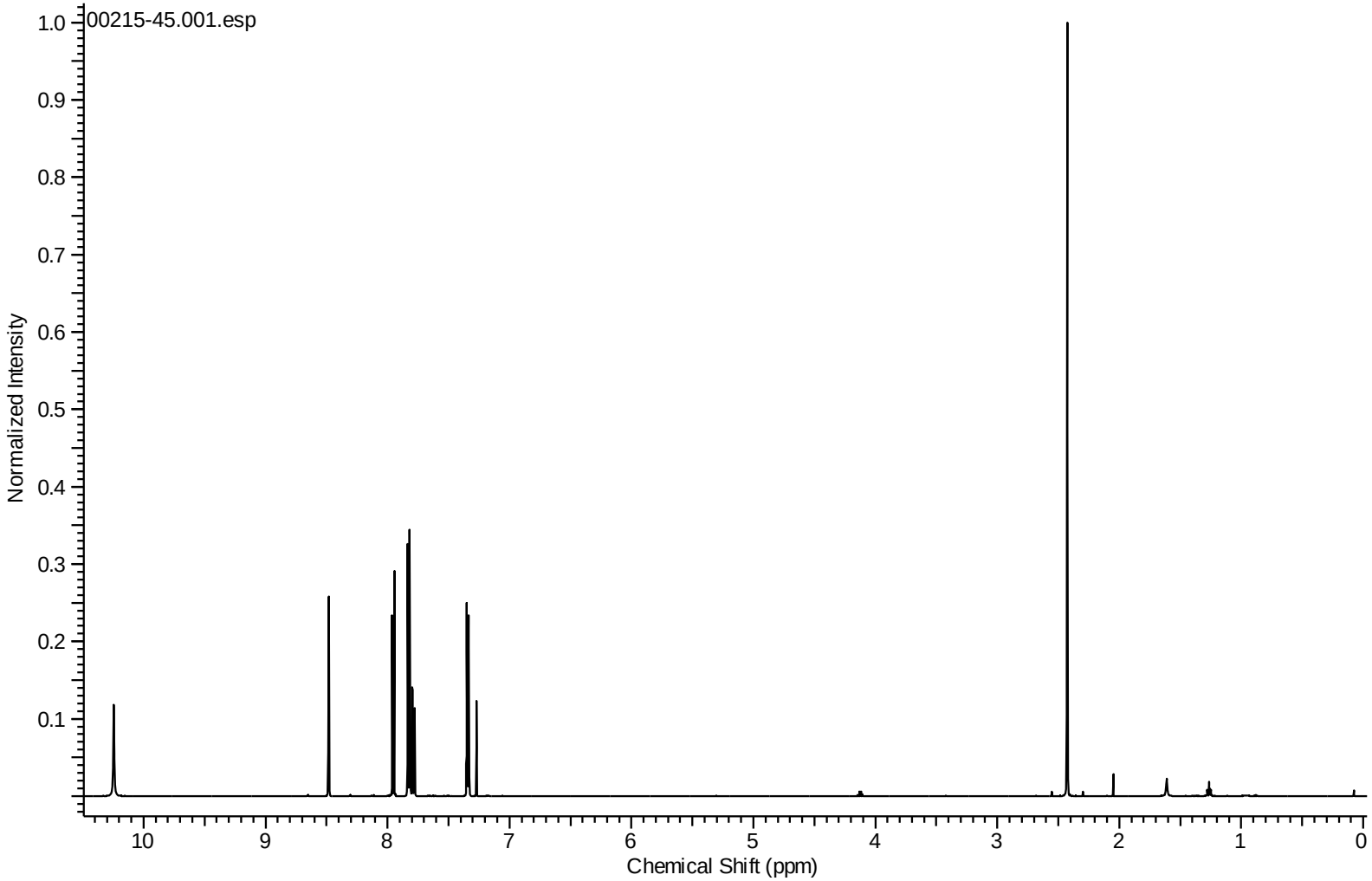
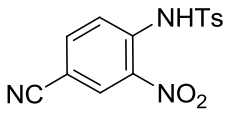


Table 2, entry 5:

$CDCl_3$, ^{13}C NMR 125 MHz



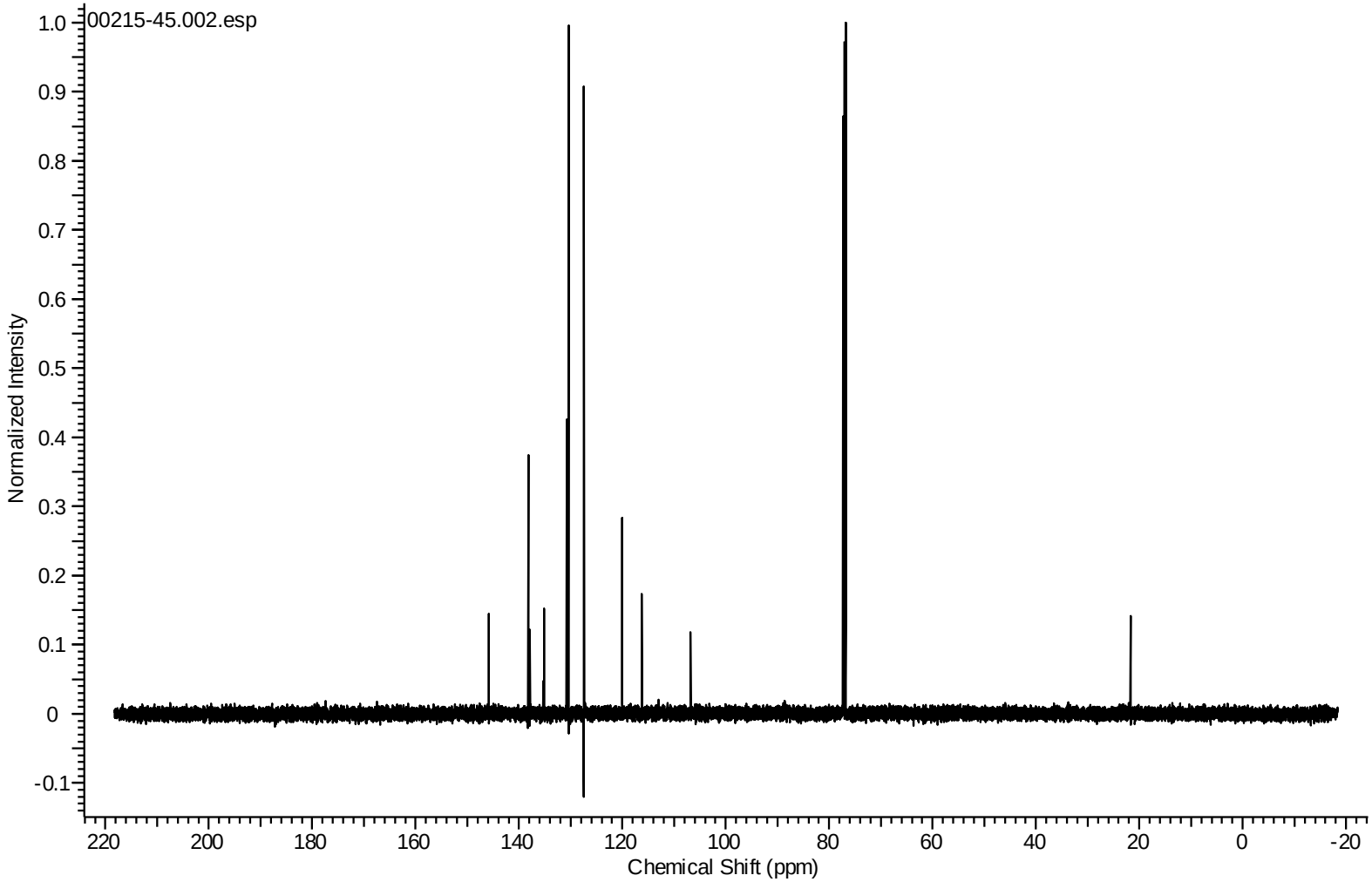


Table 2, entry 6:

d_6-DMSO, ^{1}H NMR 500 MHz

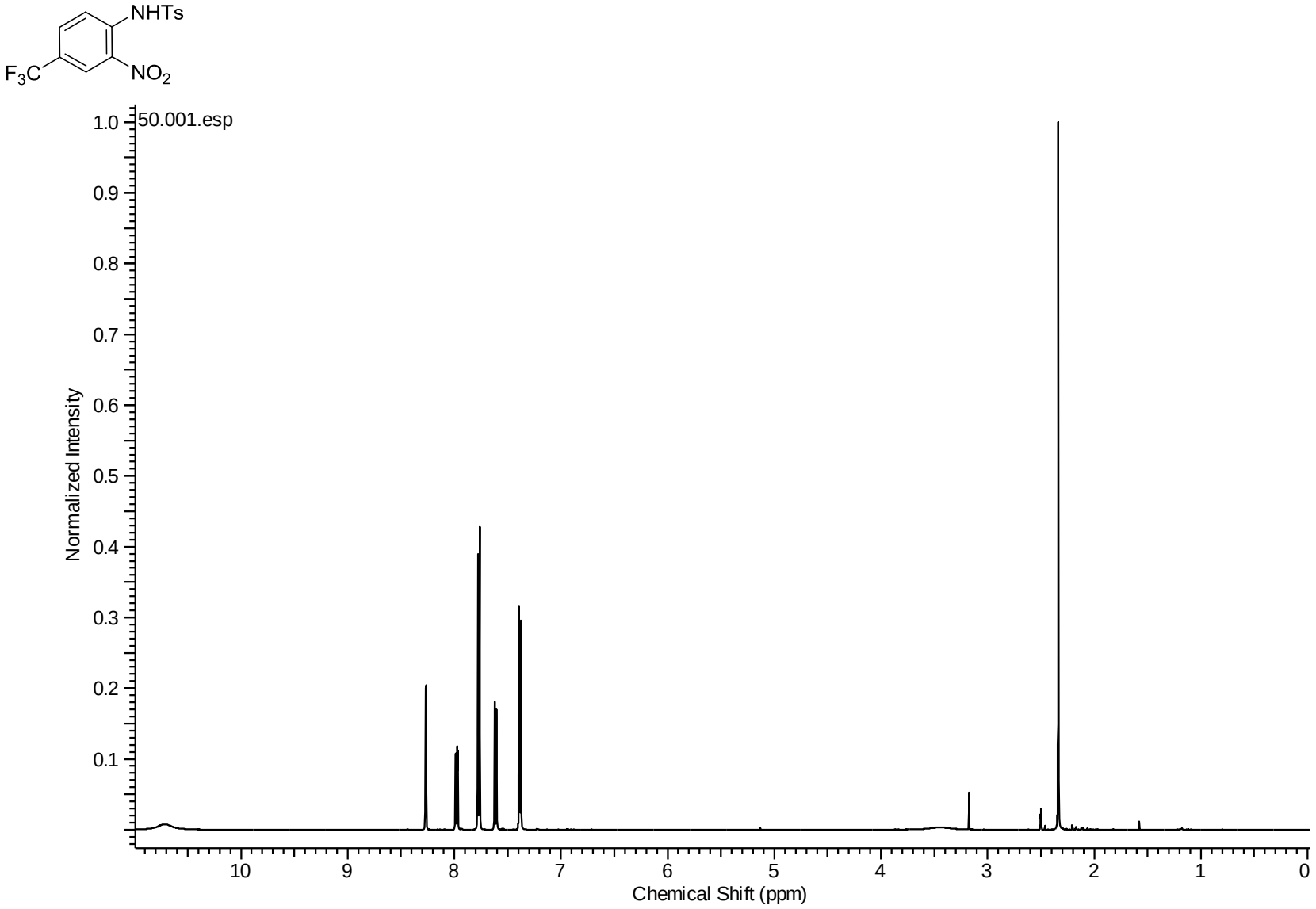
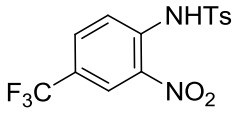


Table 2, entry 6:

d_6-DMSO, ^{13}C NMR 125 MHz



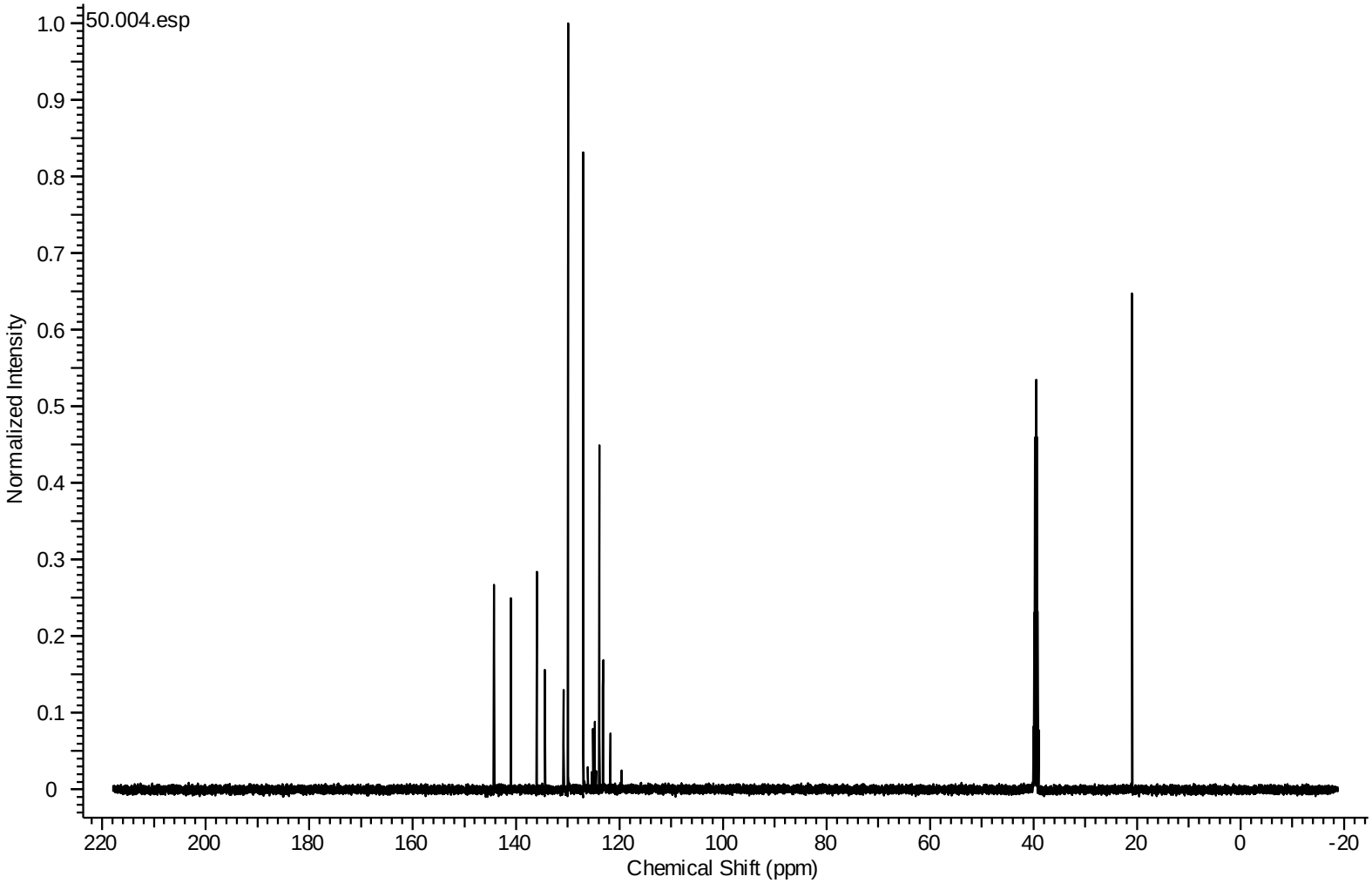
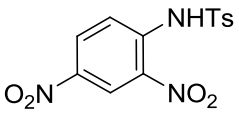


Table 2, entry 7:

d_6-DMSO, ^{1}H NMR 500 MHz



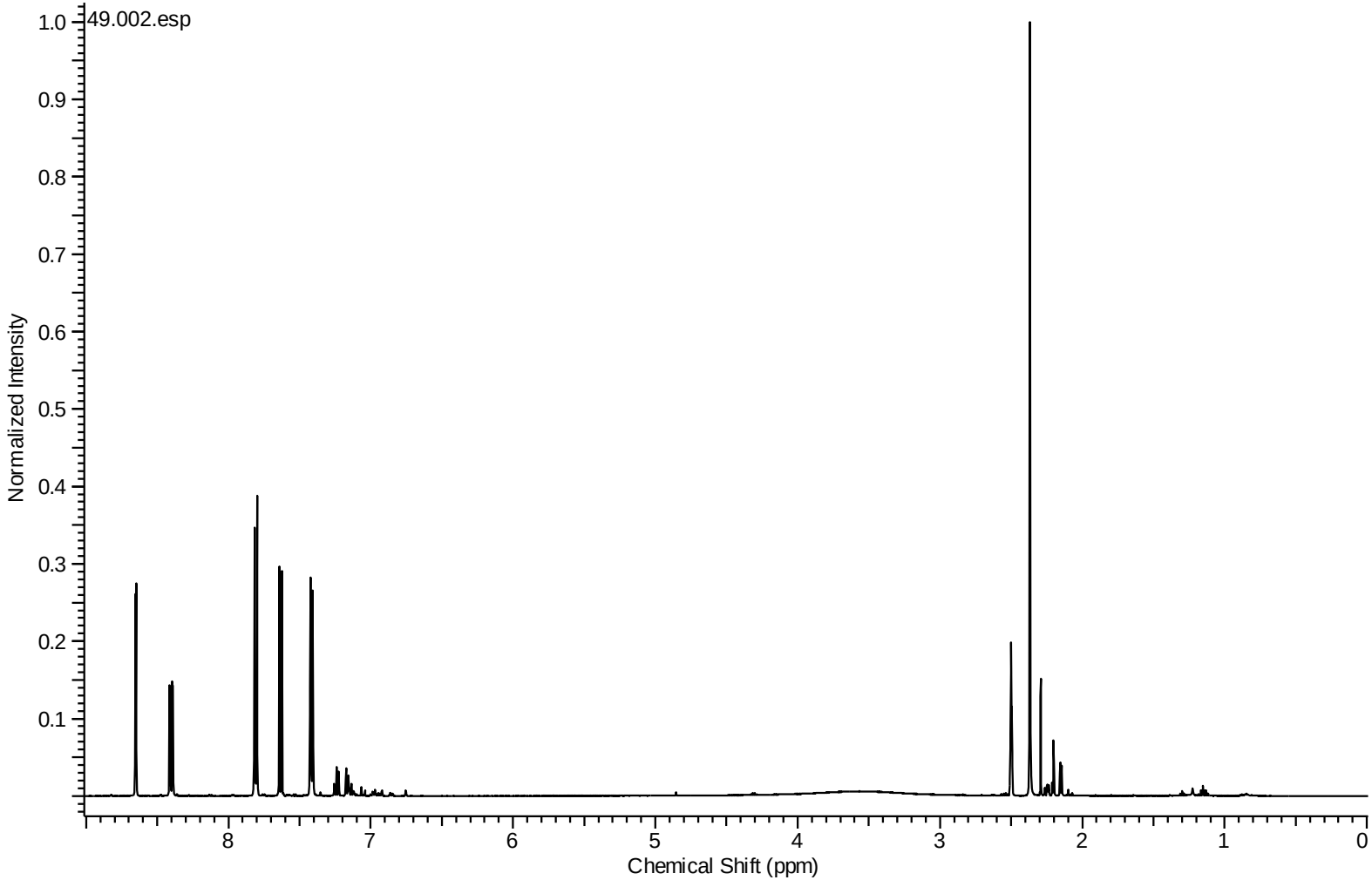
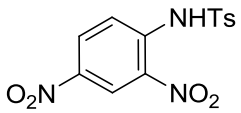


Table 2, entry 7:

d_6-DMSO, ^{13}C NMR 125 MHz



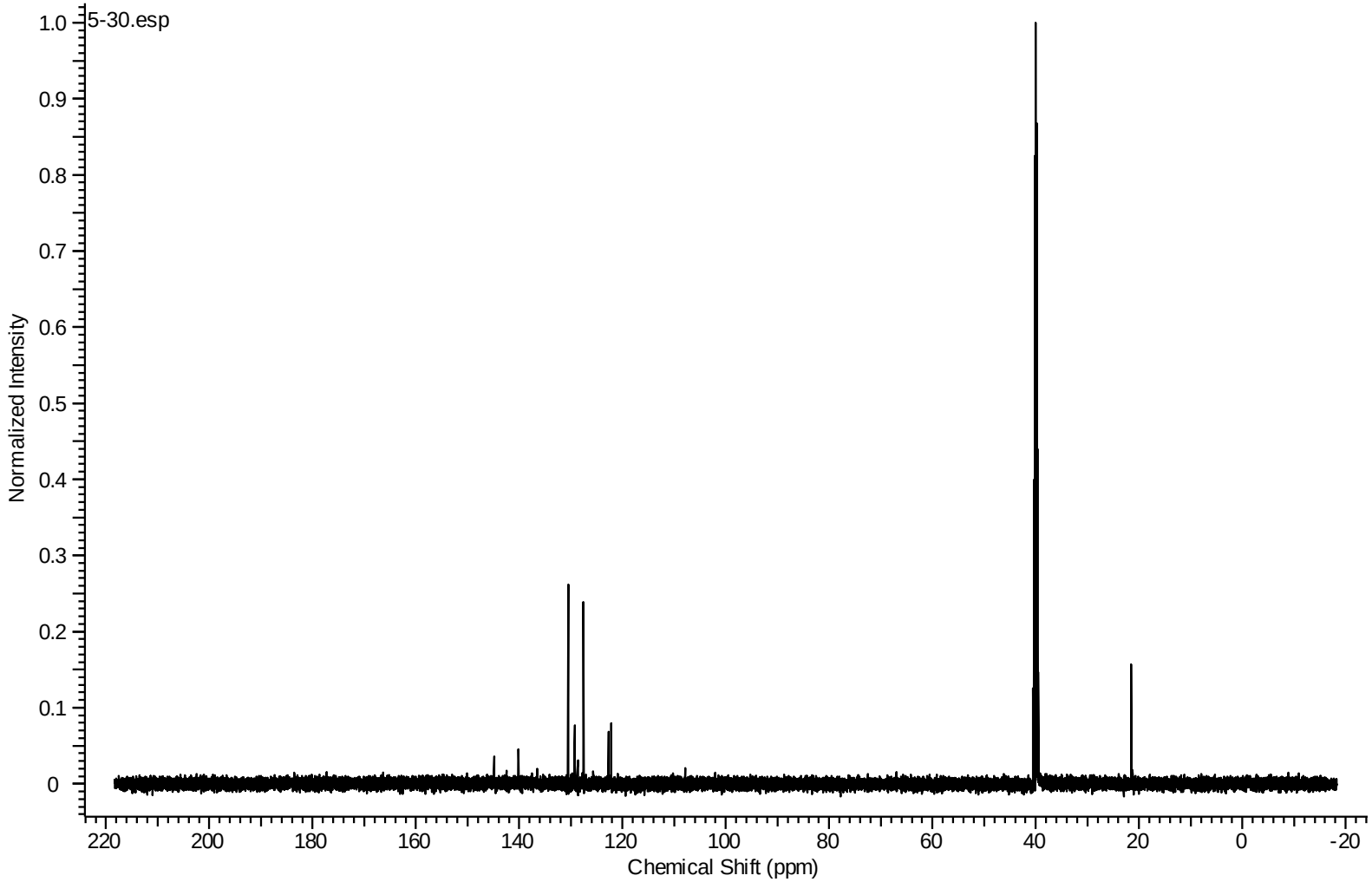
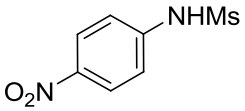


Table 2, entry 8a:

d_6-DMSO, ^{1}H NMR 500 MHz



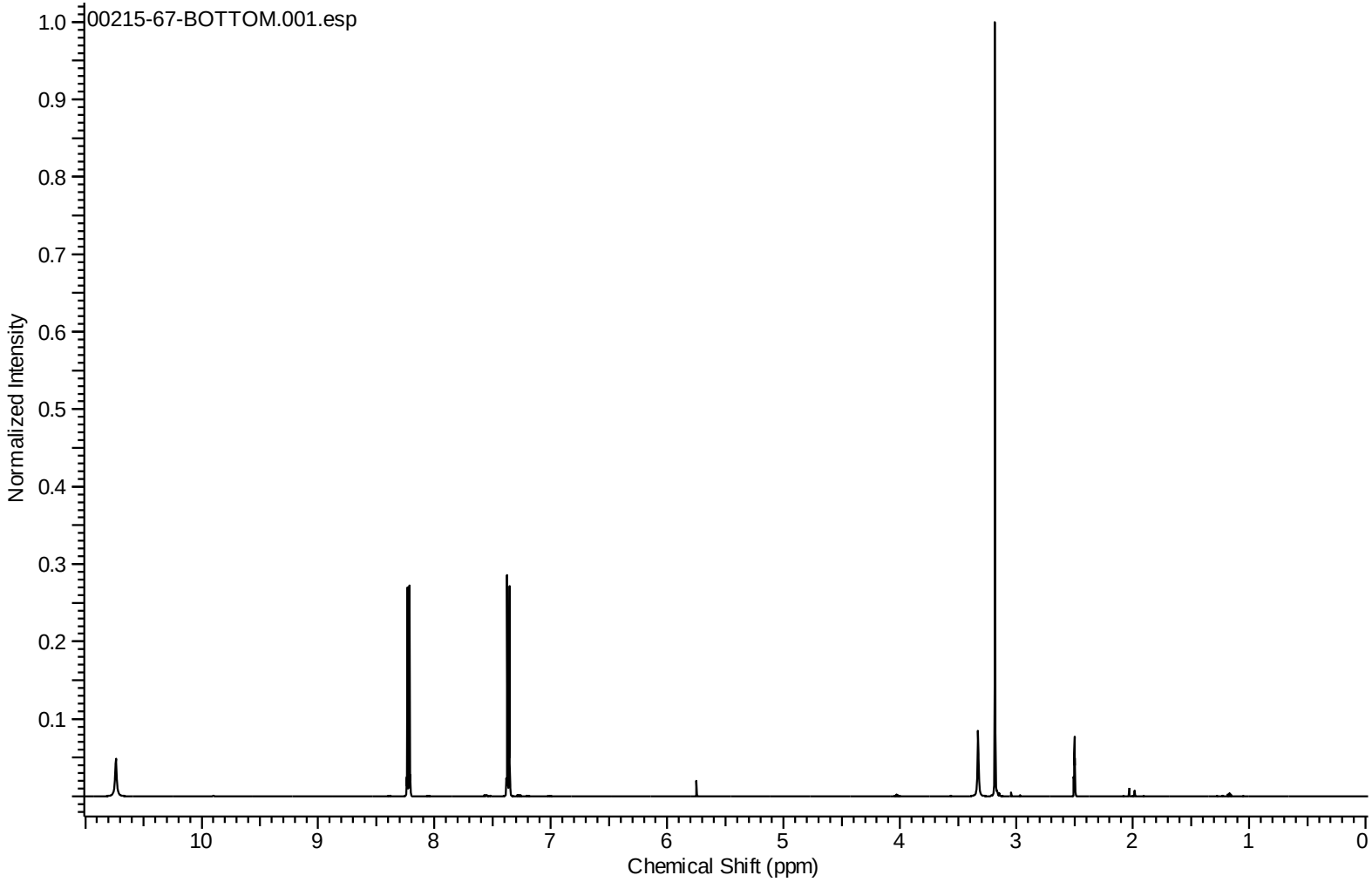
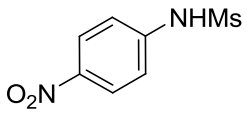


Table 2, entry 8a:

d_6-DMSO, ^{13}C NMR 125 MHz



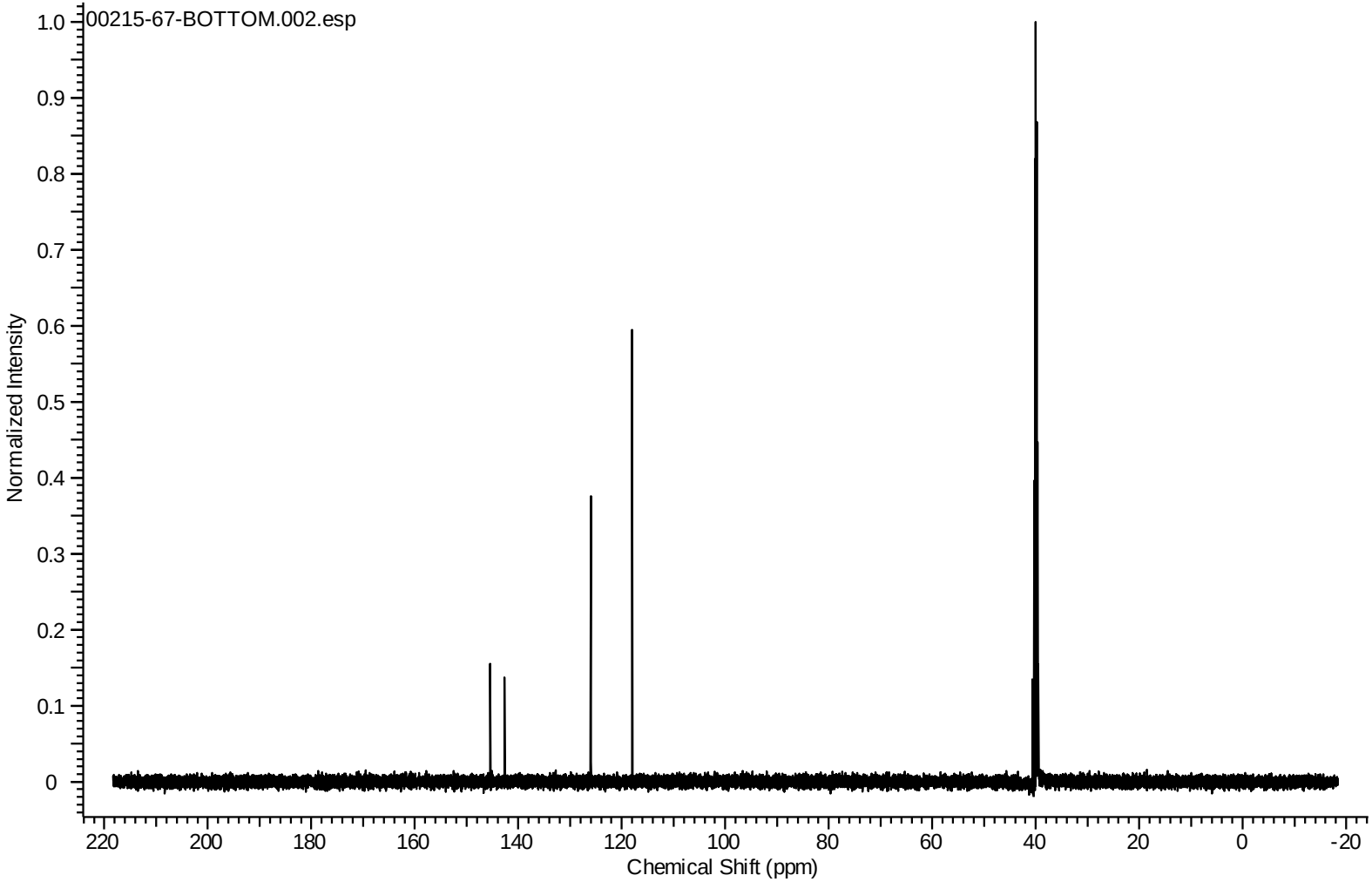
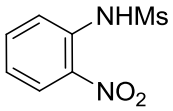


Table 2, entry 8b:

$CDCl_3$, ^1H NMR 500 MHz



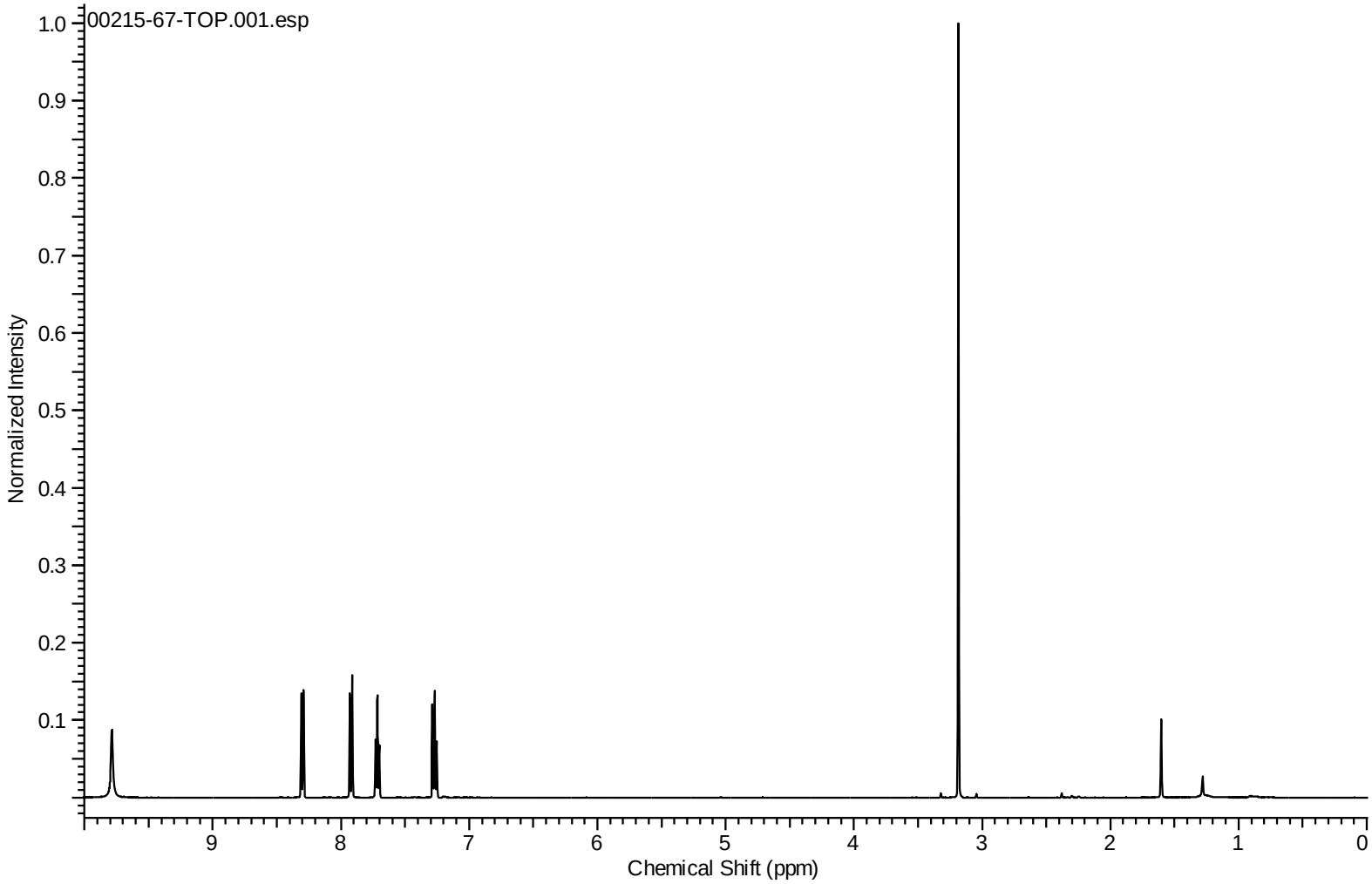
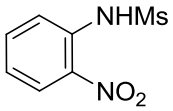


Table 2, entry 8b:

$CDCl_3$, ^{13}C NMR 125 MHz



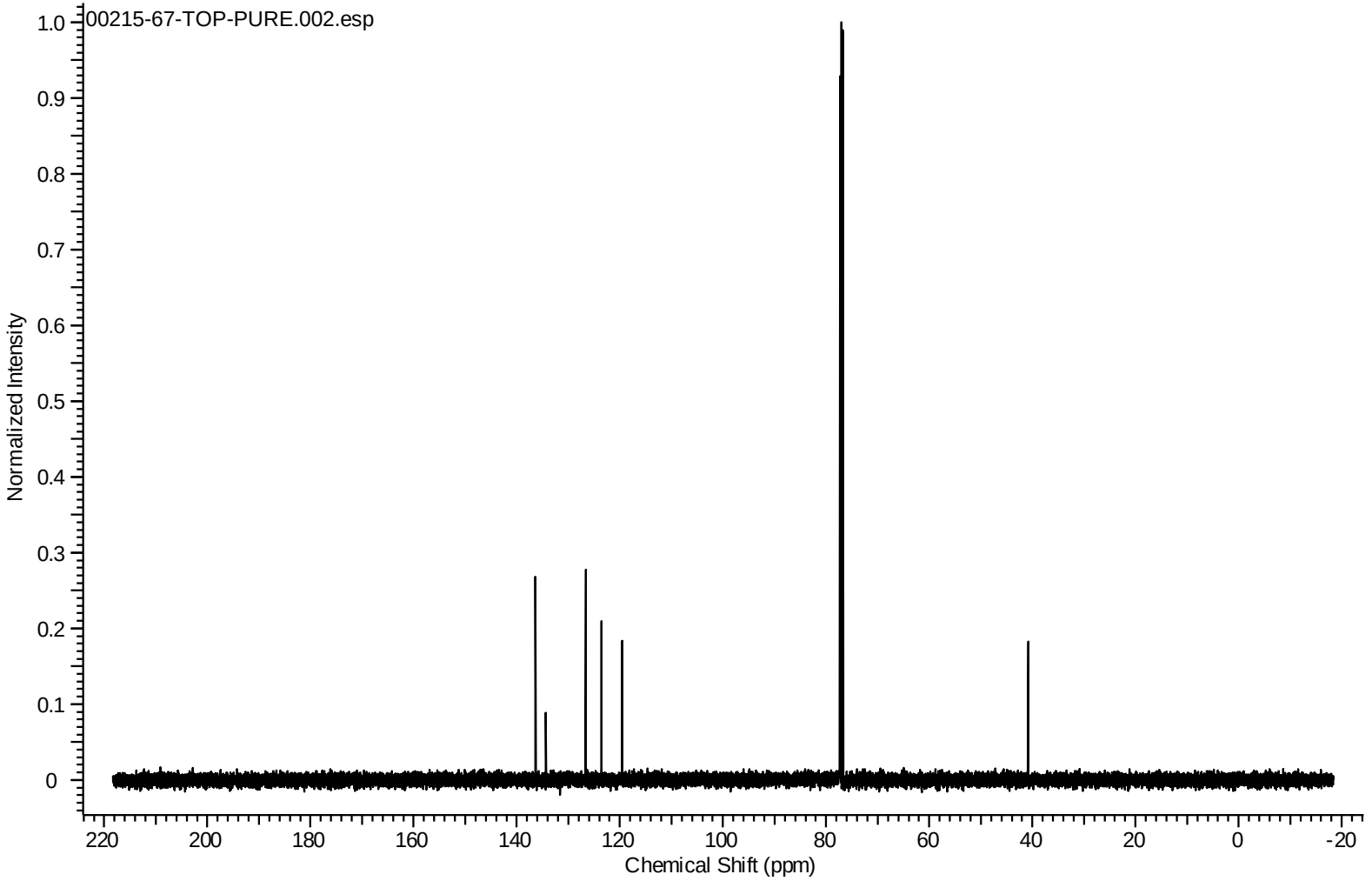
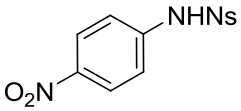


Table 2, entry 9a:

d_6-DMSO, ^{1}H NMR 500 MHz



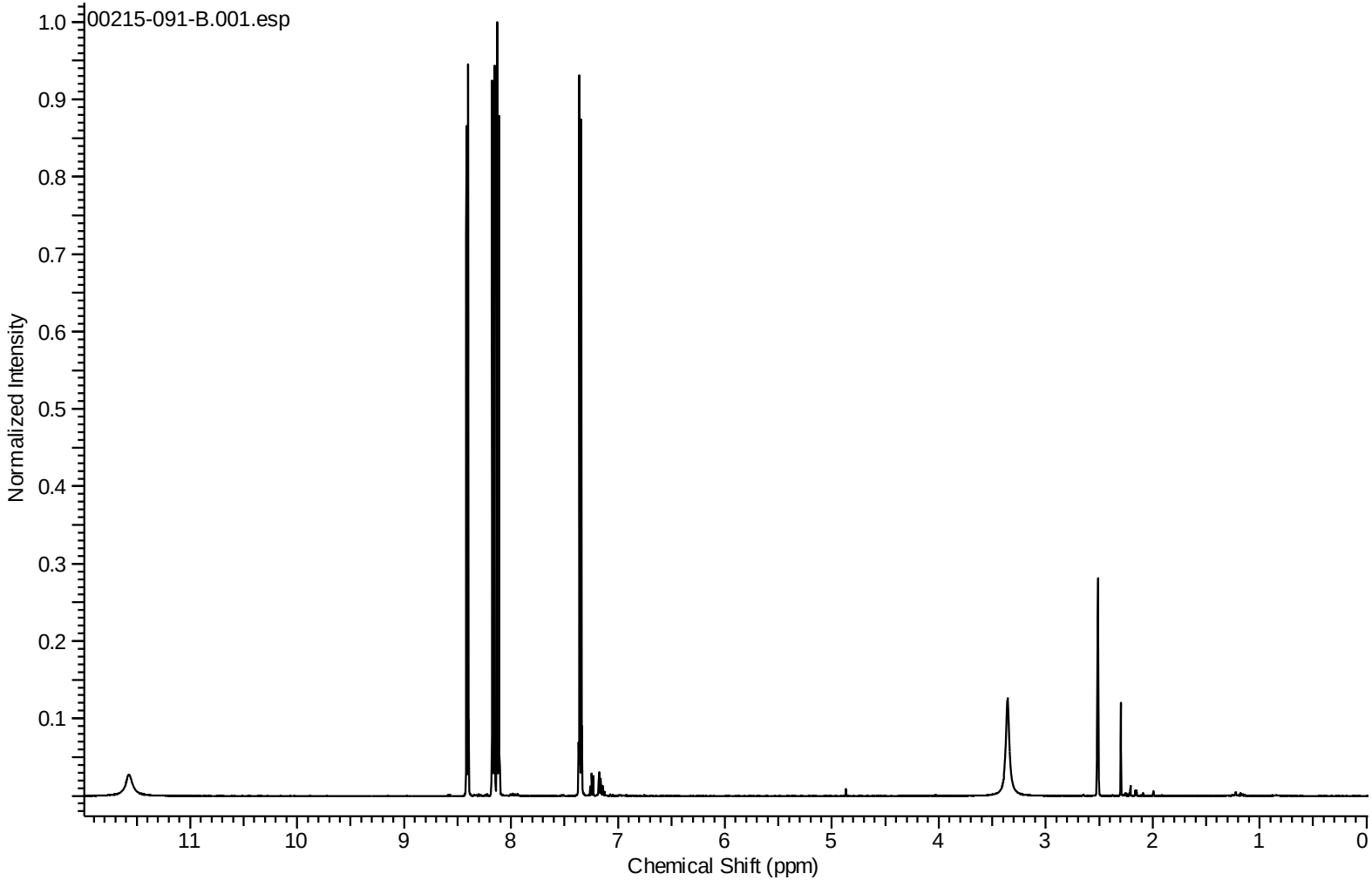
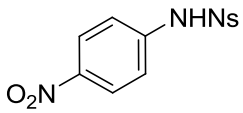


Table 2, entry 9a:

d_6-DMSO, ^{13}C NMR 125 MHz



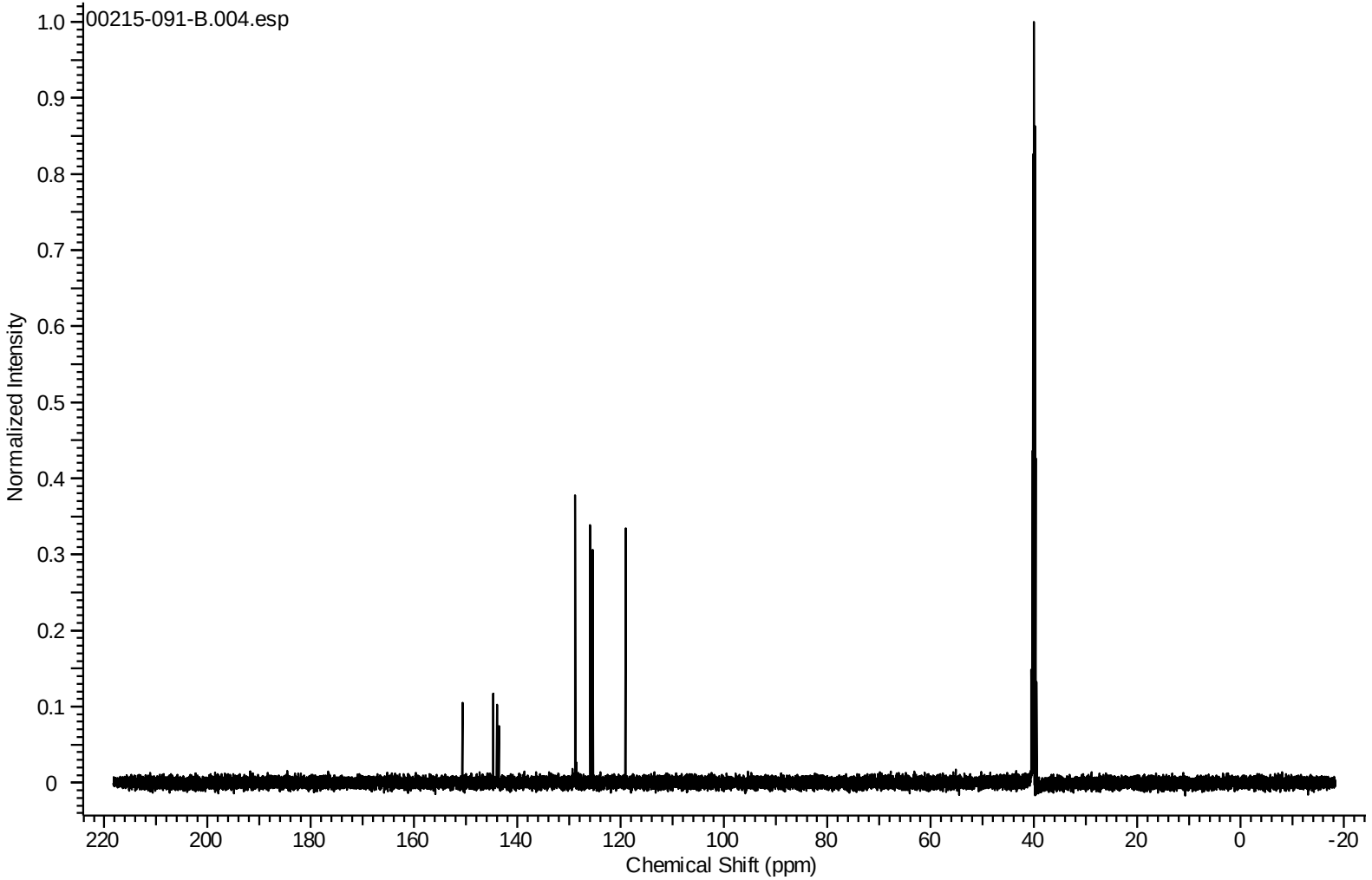
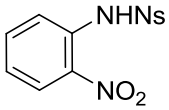


Table 2, entry 9b:

$CDCl_3$, ^1H NMR 500 MHz



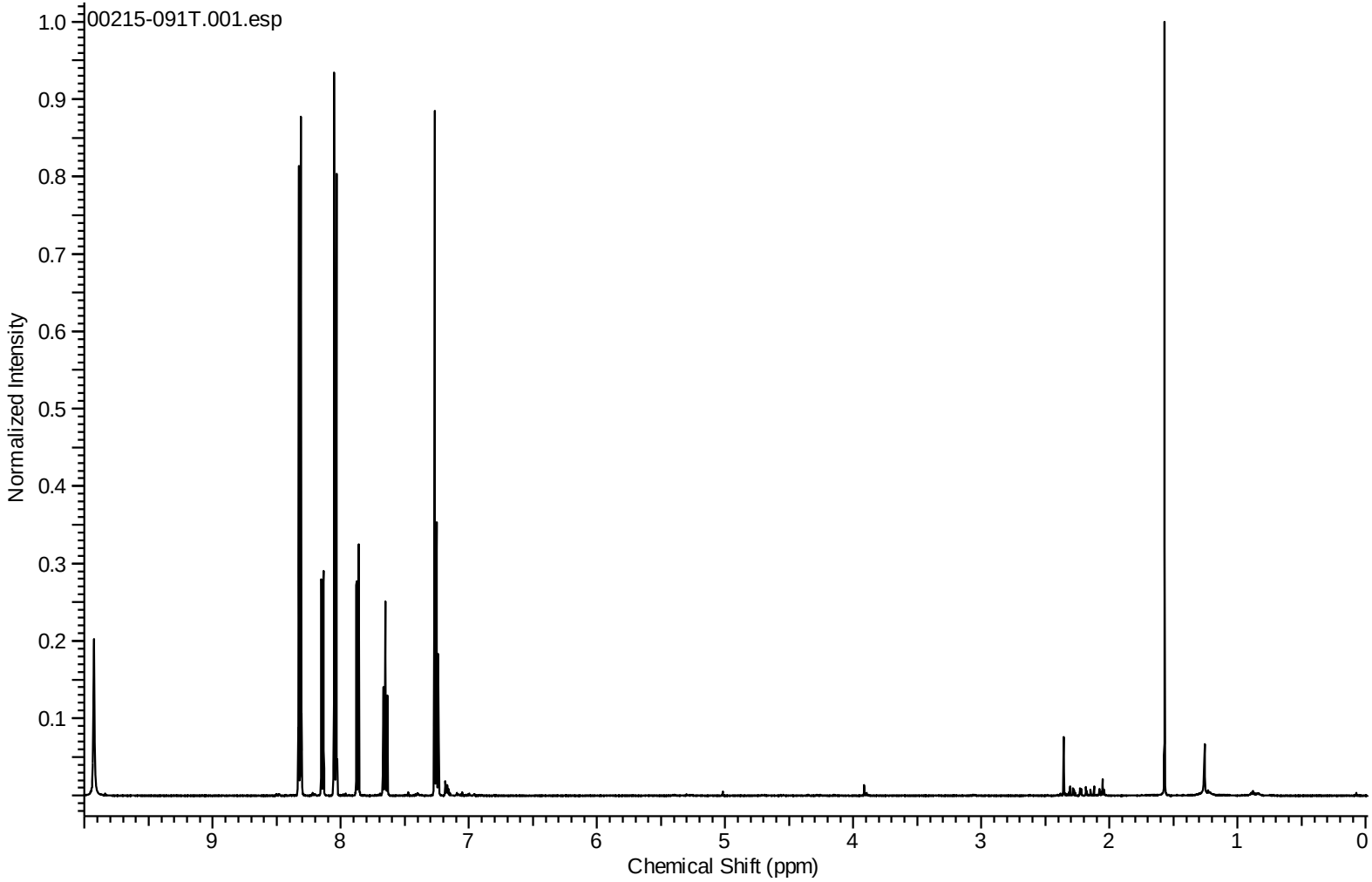
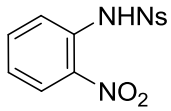


Table 2, entry 9b:

$CDCl_3$, ^{13}C NMR 125 MHz



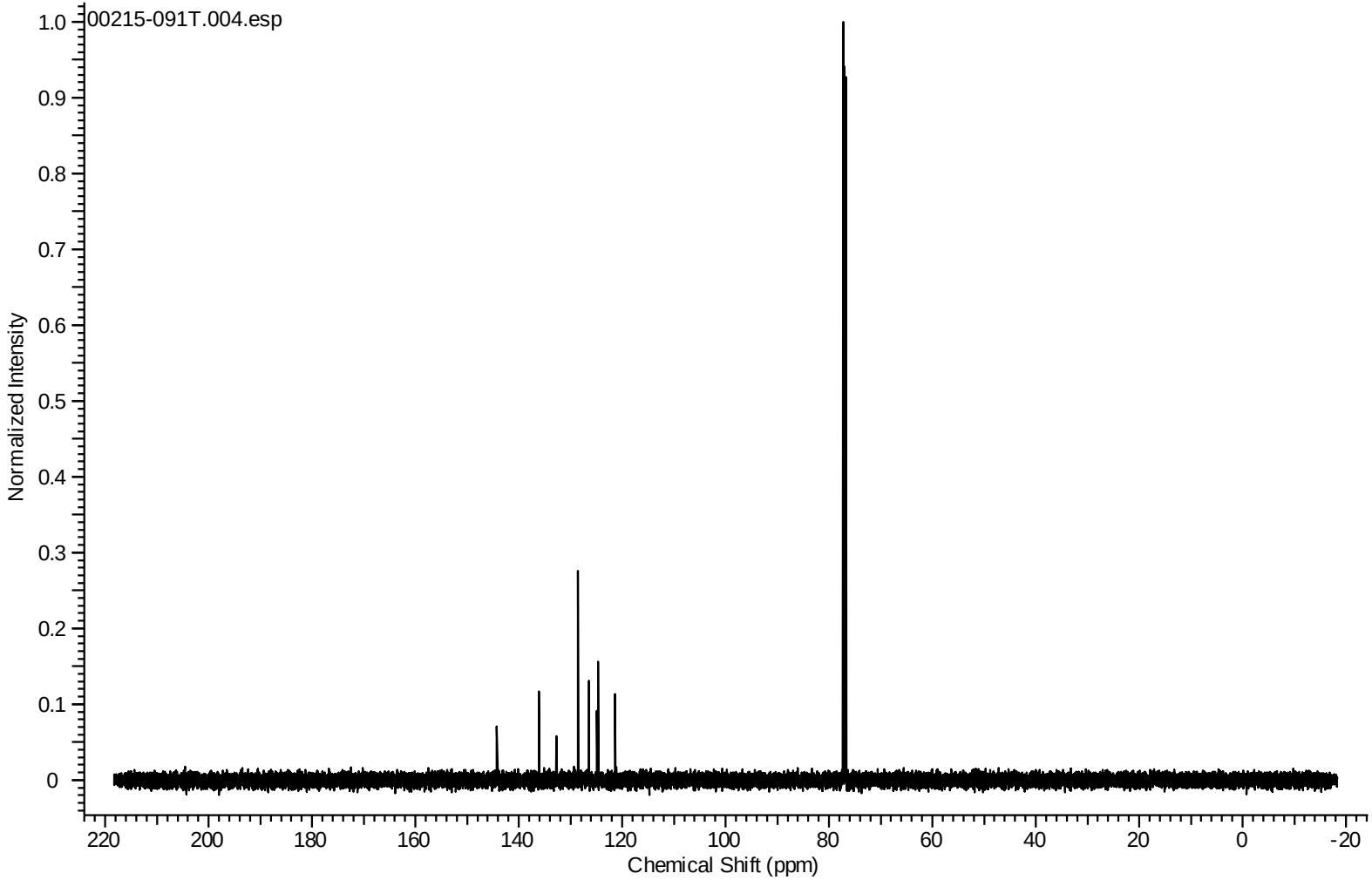
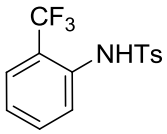


Table 2: entry 10 starting material:

$CDCl_3$, ^1H NMR 500 MHz



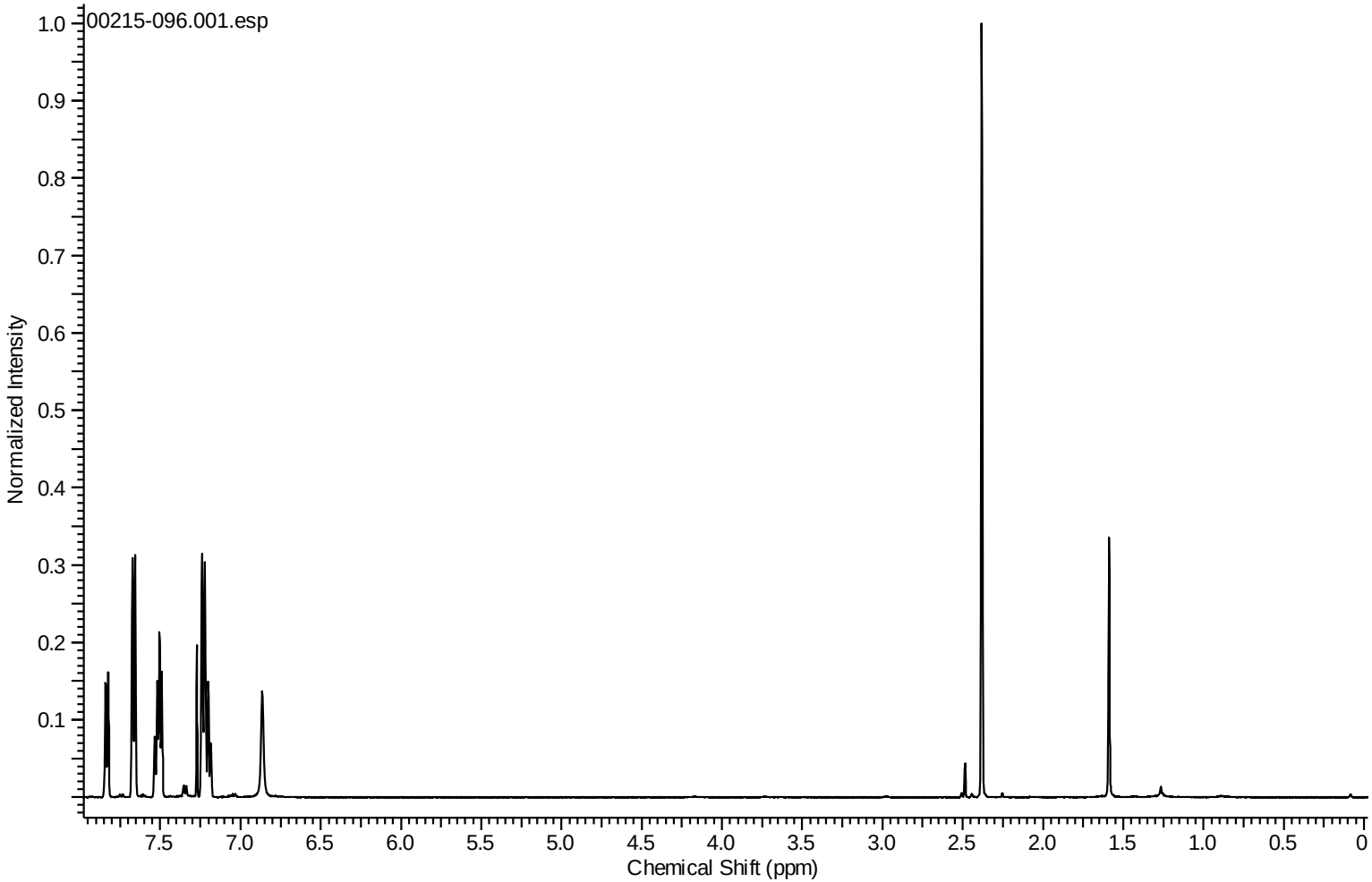
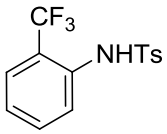


Table 2: entry 10 starting material:

$CDCl_3$, ^{13}C NMR 150 MHz



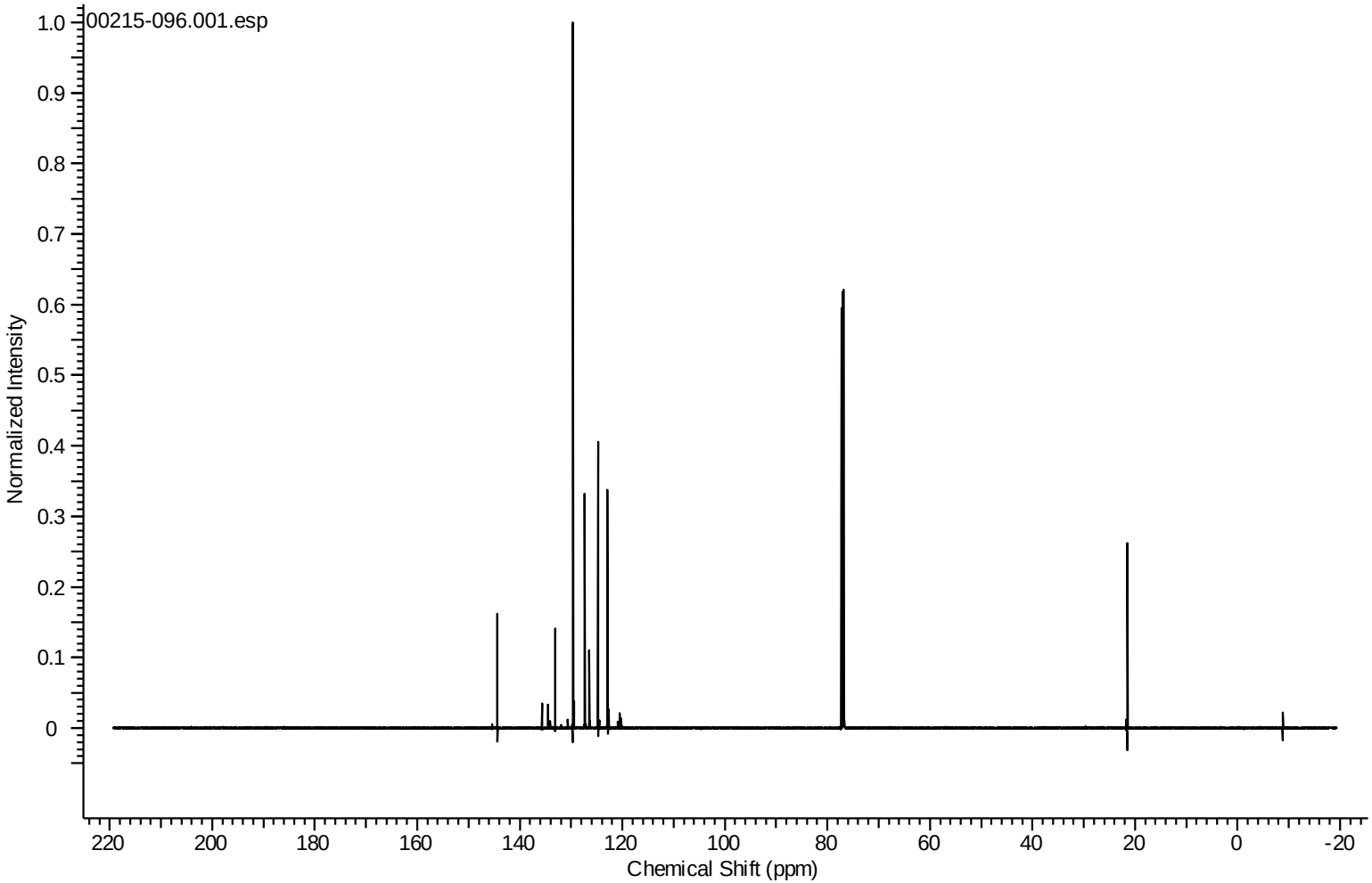
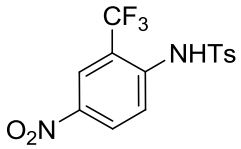


Table 2, entry 10a:

$CDCl_3$, ^1H NMR 500 MHz



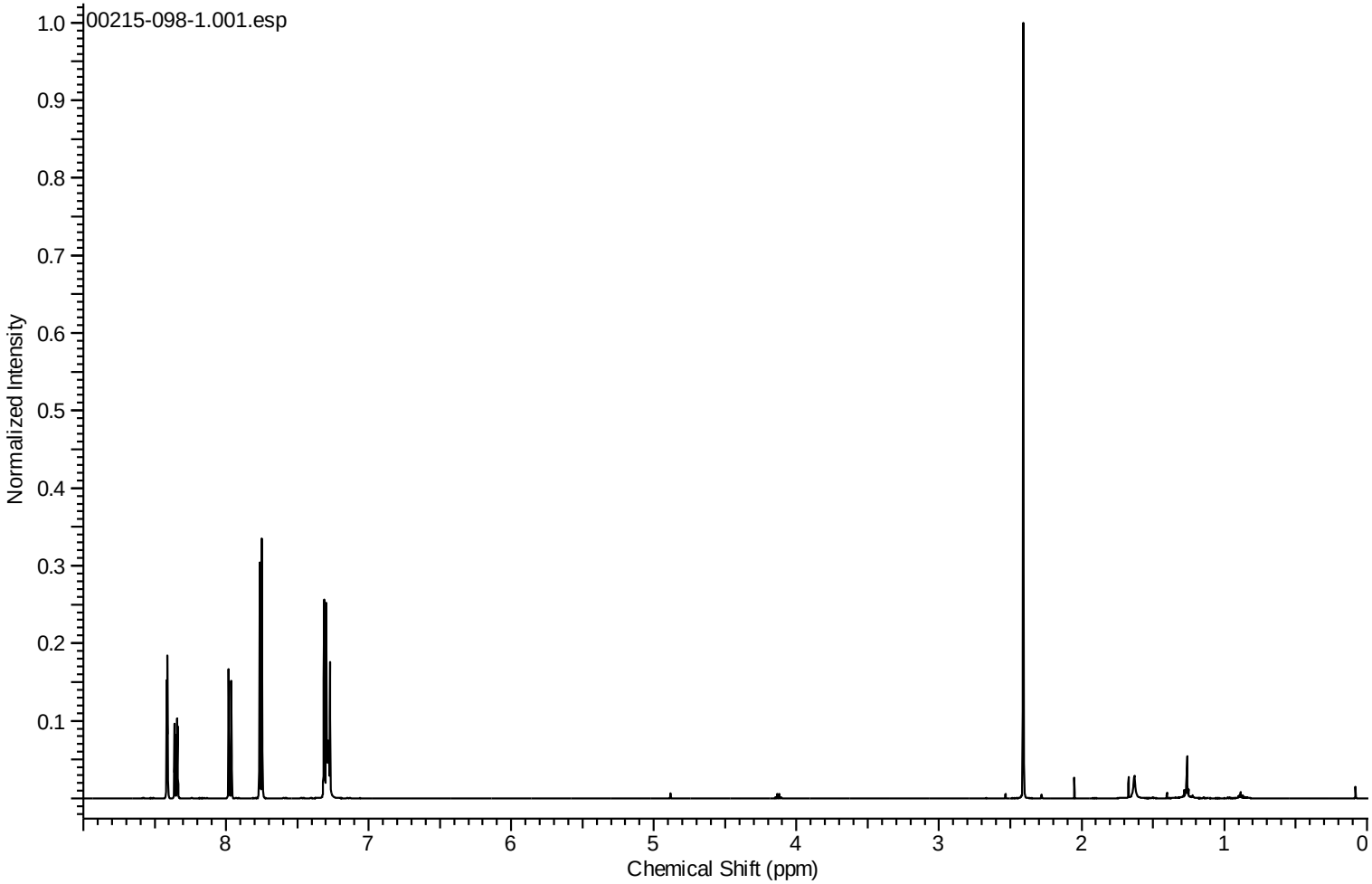


Table 2, entry 10a:

$CDCl_3$, ^{13}C NMR 125 MHz

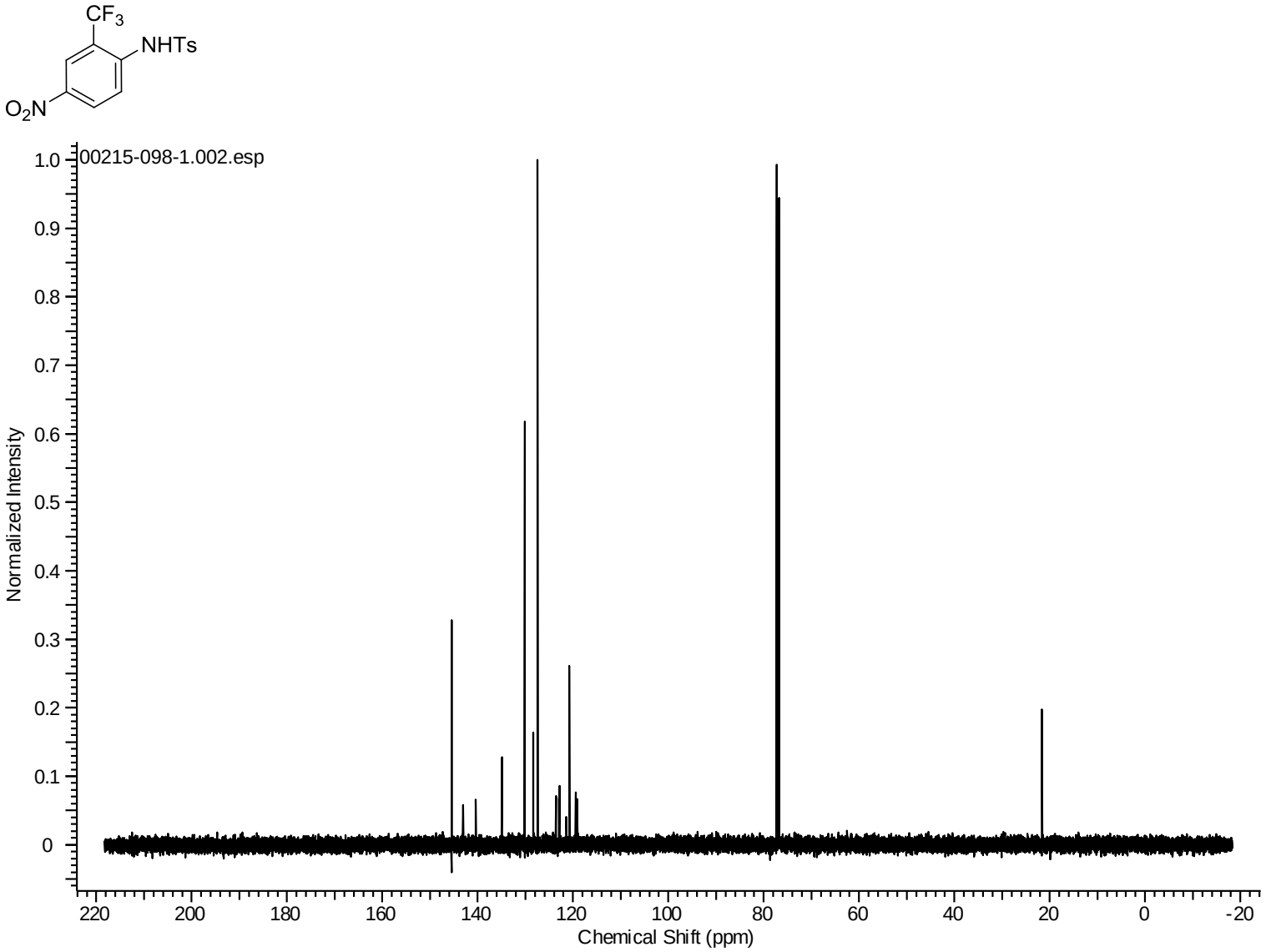
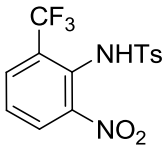


Table 2, entry 10b:

$CDCl_3$, ^1H NMR 500 MHz



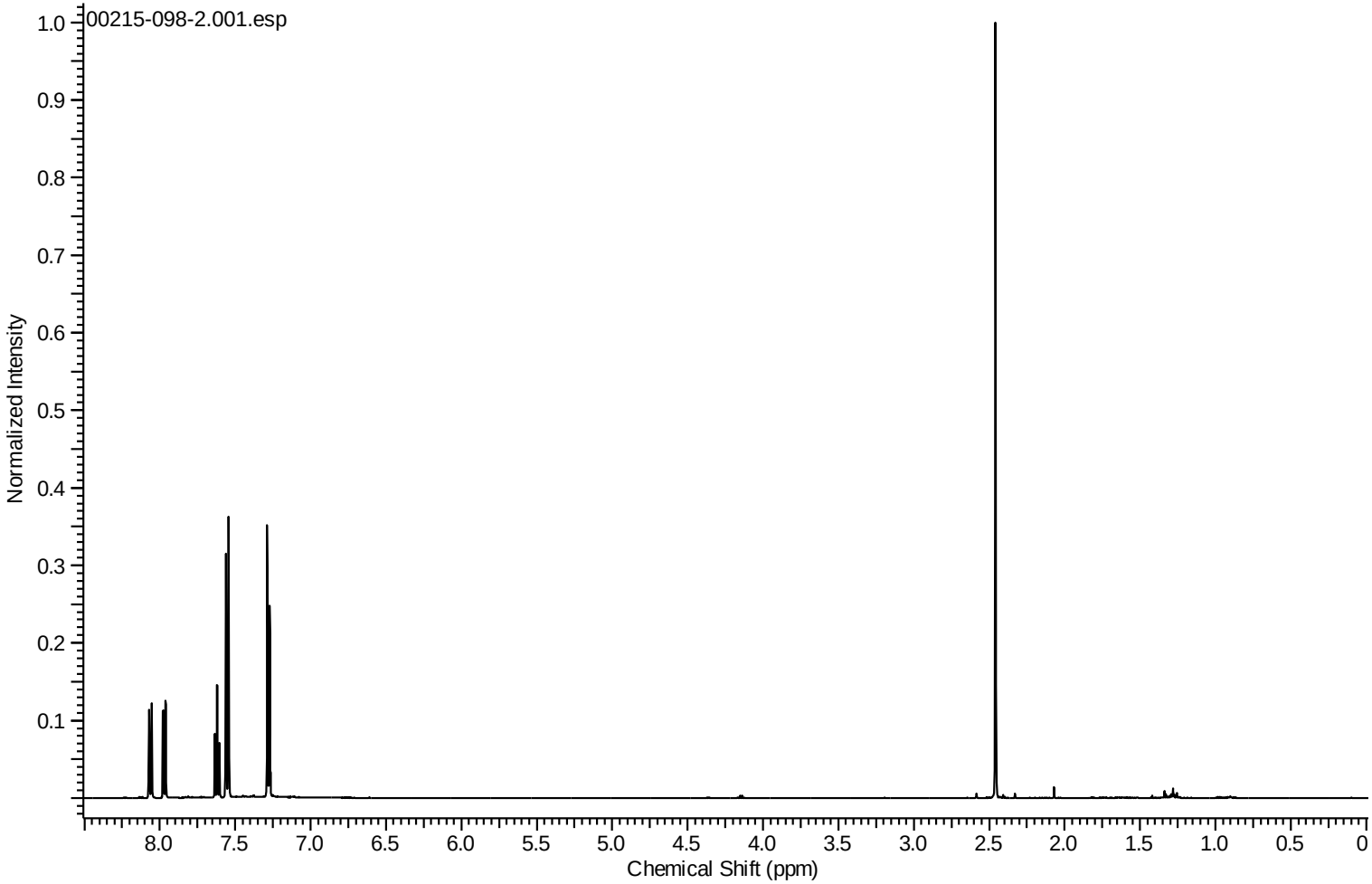
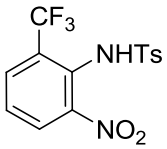


Table 2, entry 10b:

$CDCl_3$, ^{13}C NMR 125 MHz



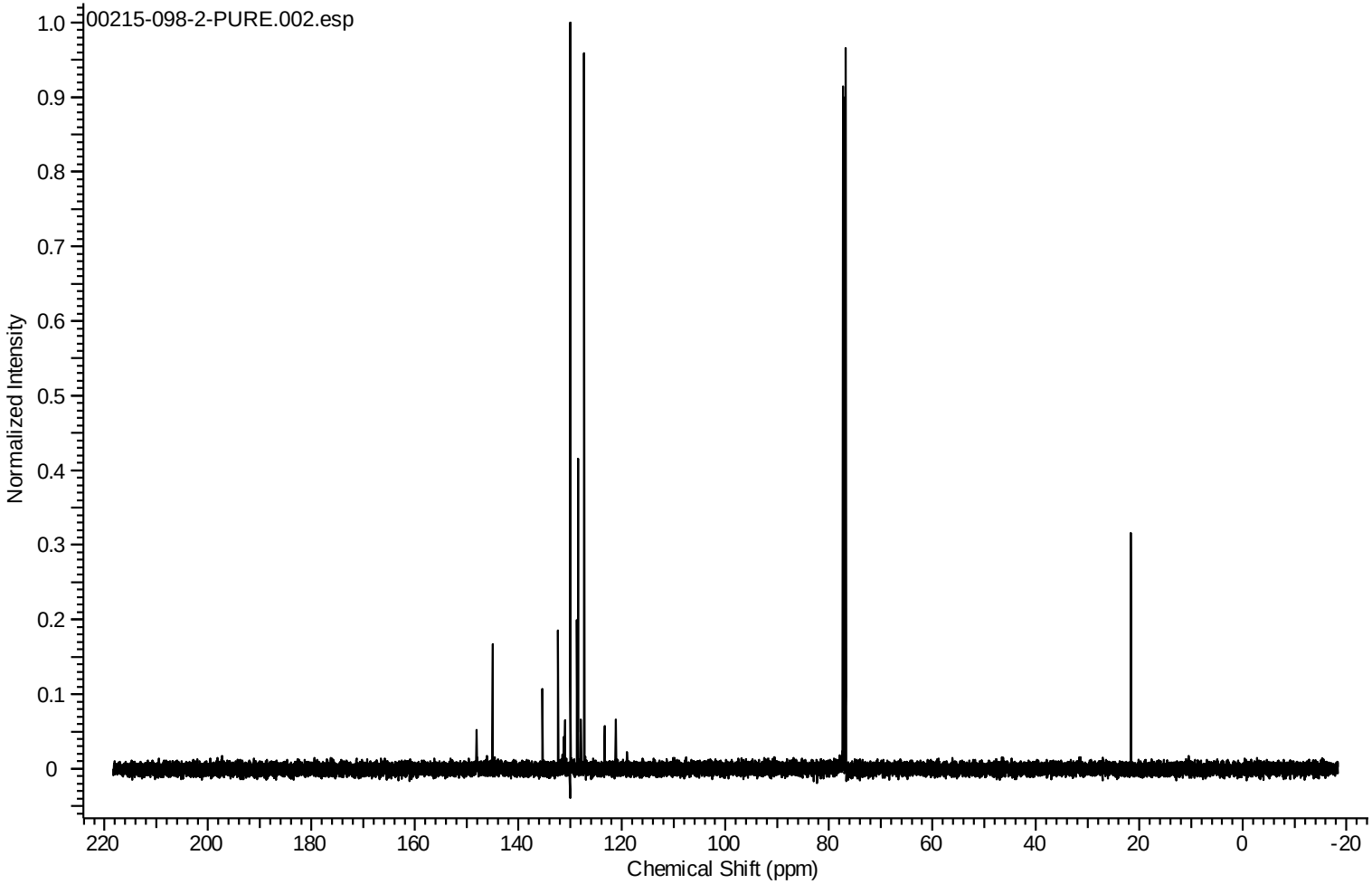
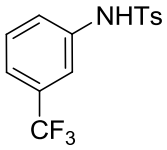


Table 2, entry 11 starting material:

$CDCl_3$, ^1H NMR 500 MHz



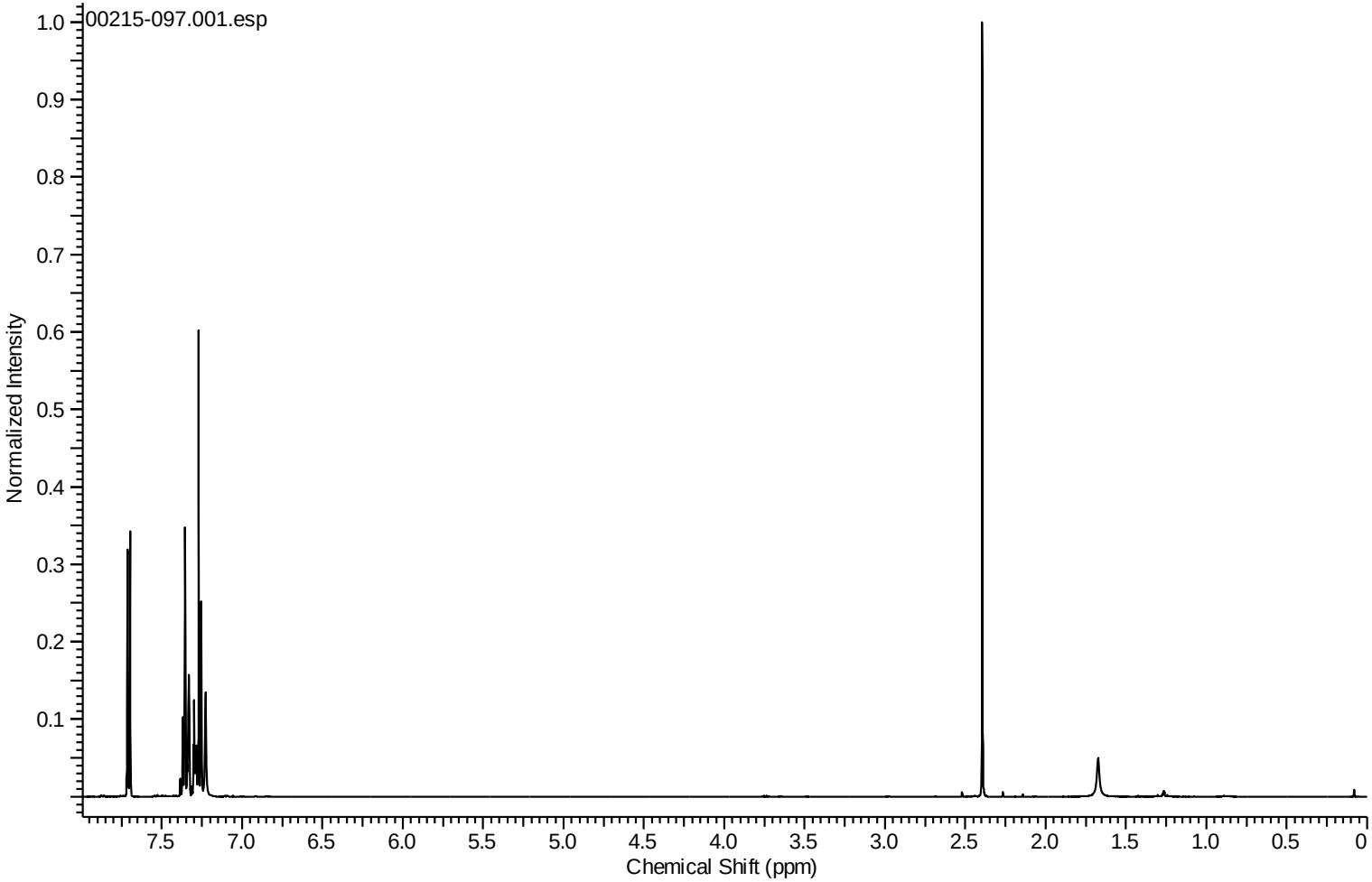
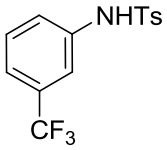


Table 2, entry 11 starting material:

$CDCl_3$, ^{13}C NMR 125 MHz



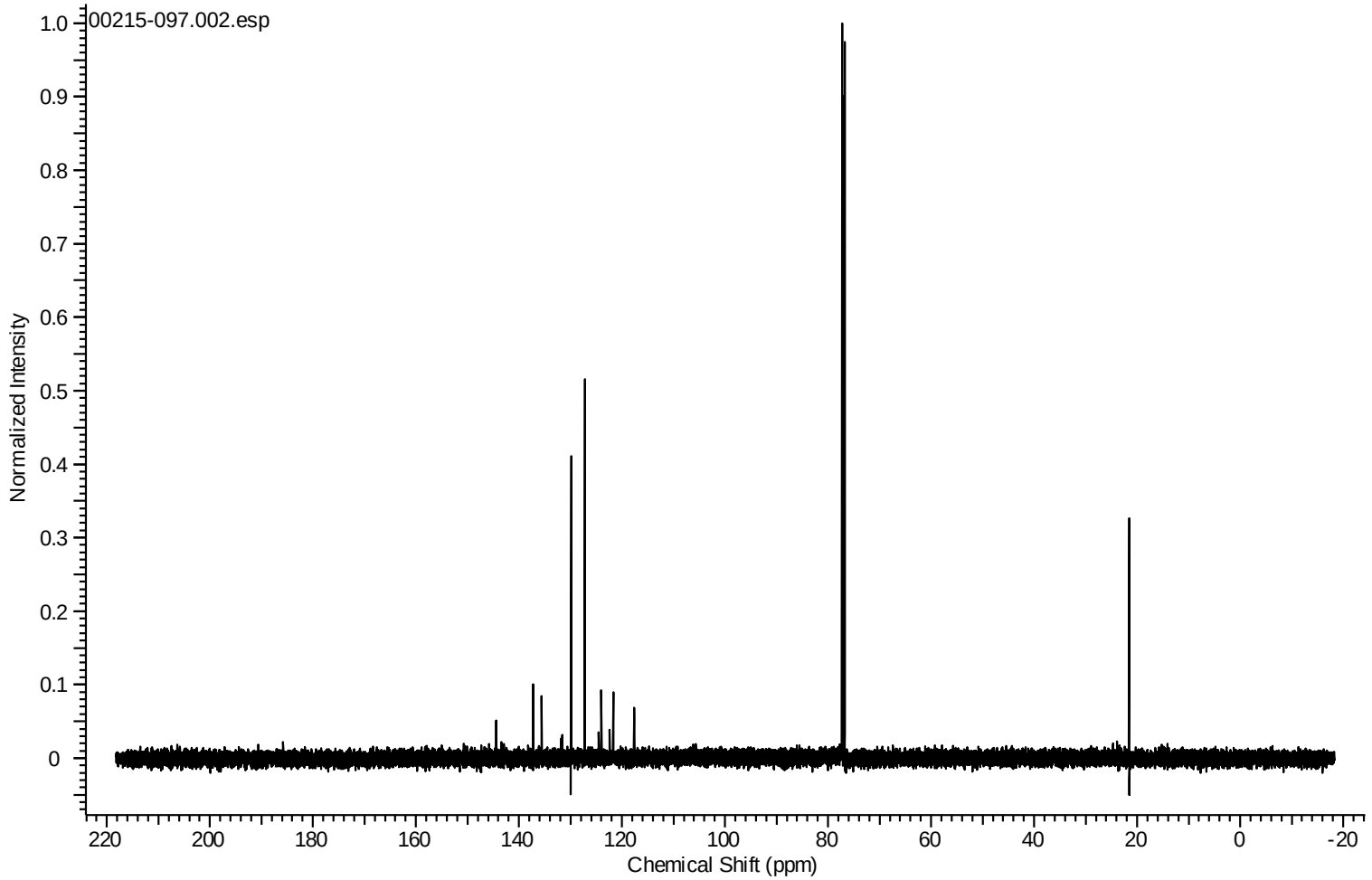
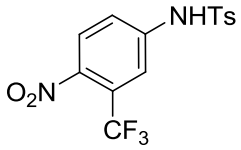


Table 2, entry 11a:

d_6-DMSO, ^{1}H NMR 500 MHz



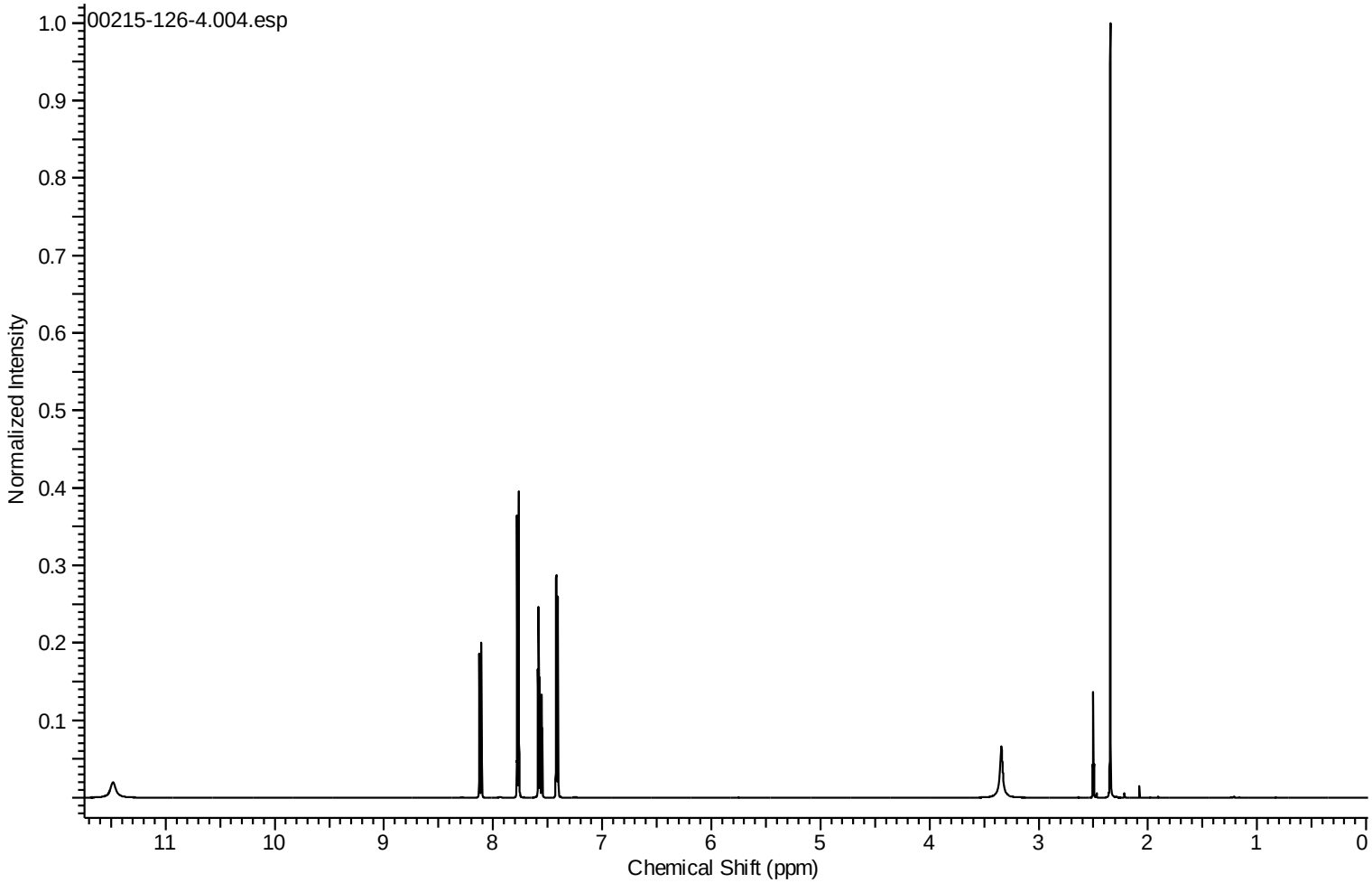
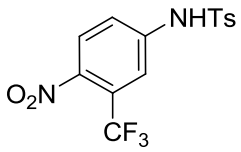


Table 2, entry 11a:

d_6-DMSO, ^{13}C NMR 125 MHz



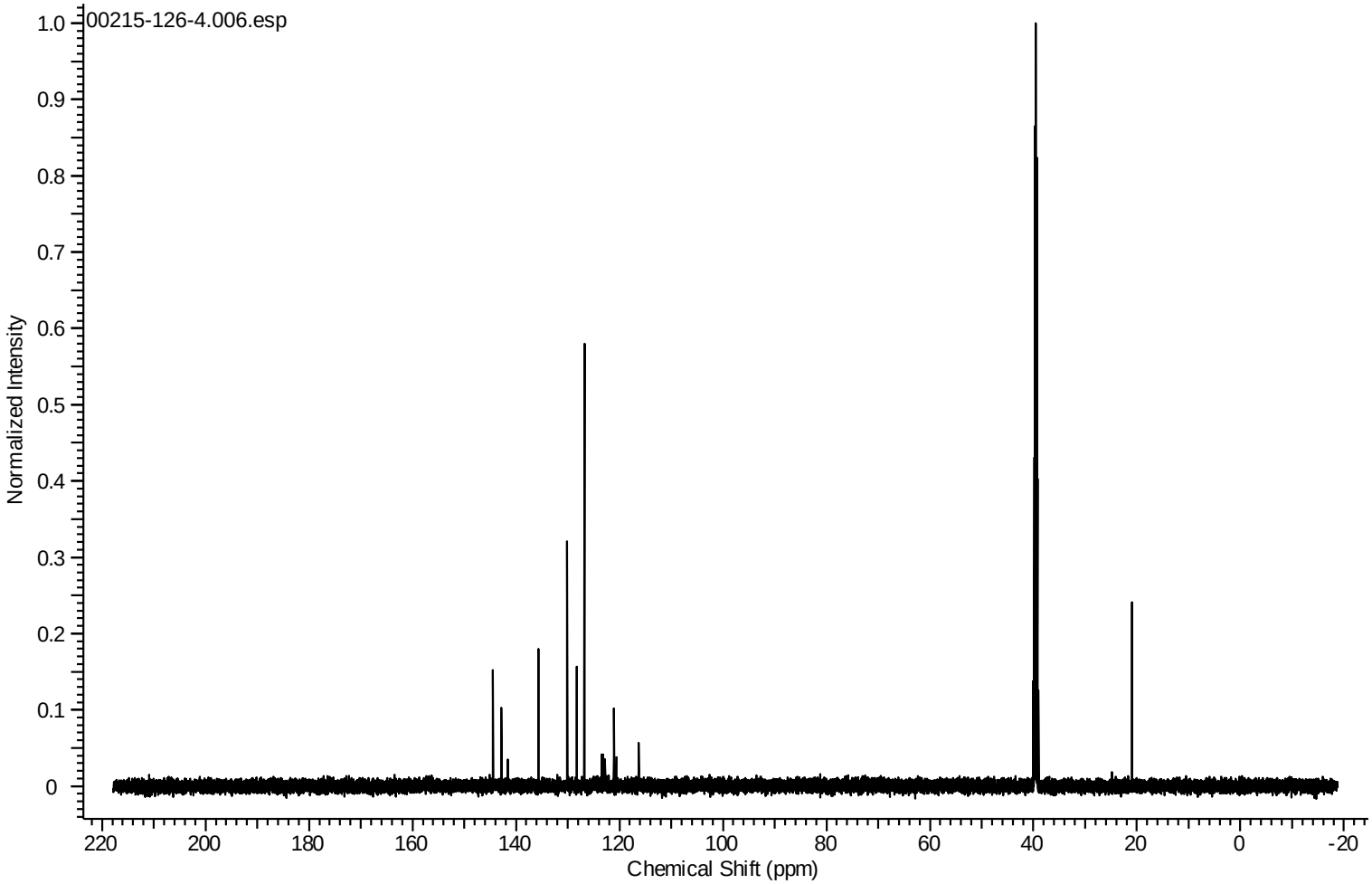
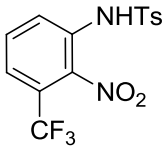


Table 2, entry 11b:

$CDCl_3$, ^1H NMR 500 MHz



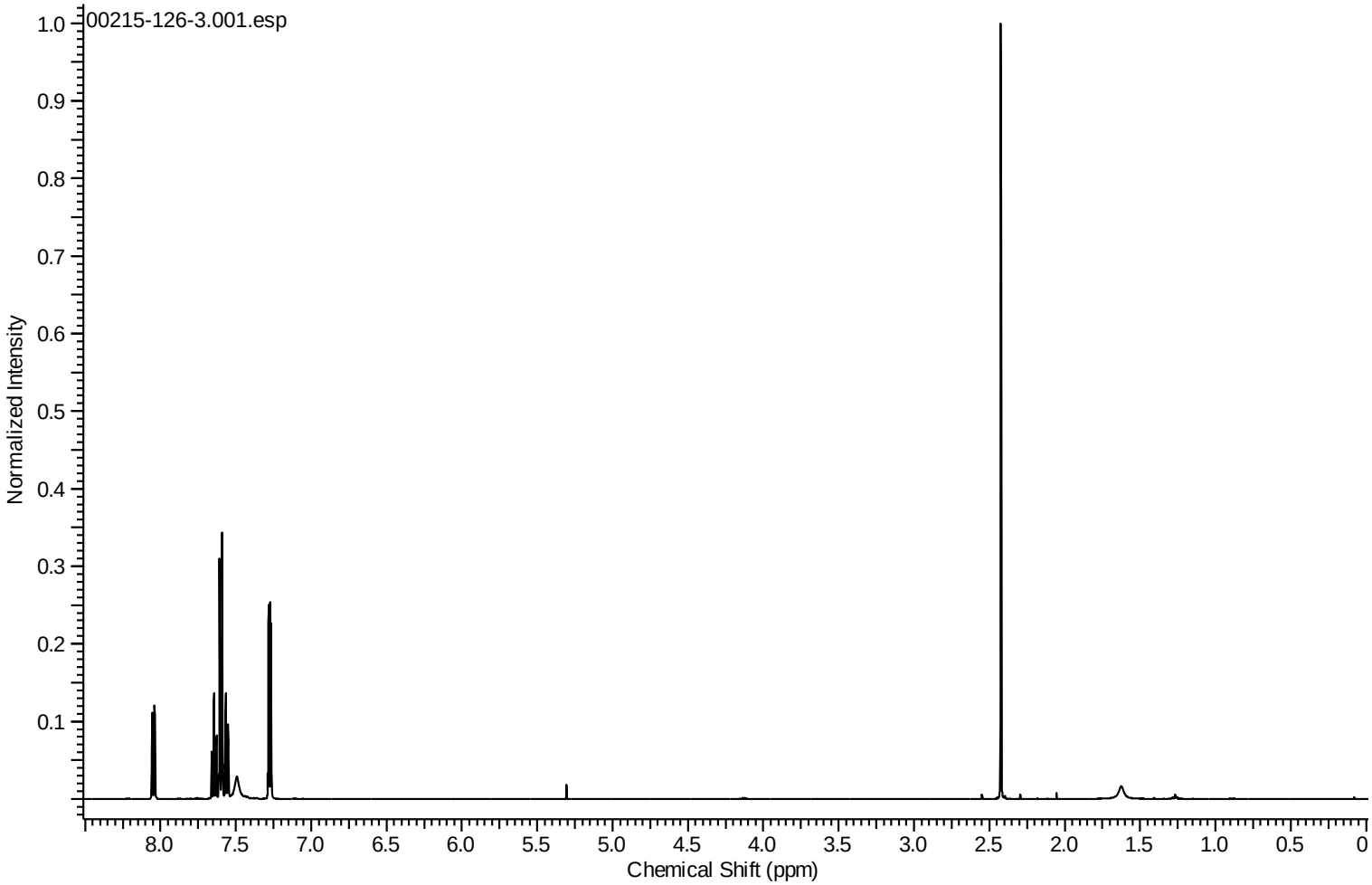
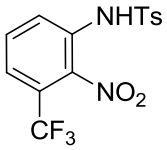


Table 2, entry 11b:

$CDCl_3$, ^{13}C NMR 125 MHz



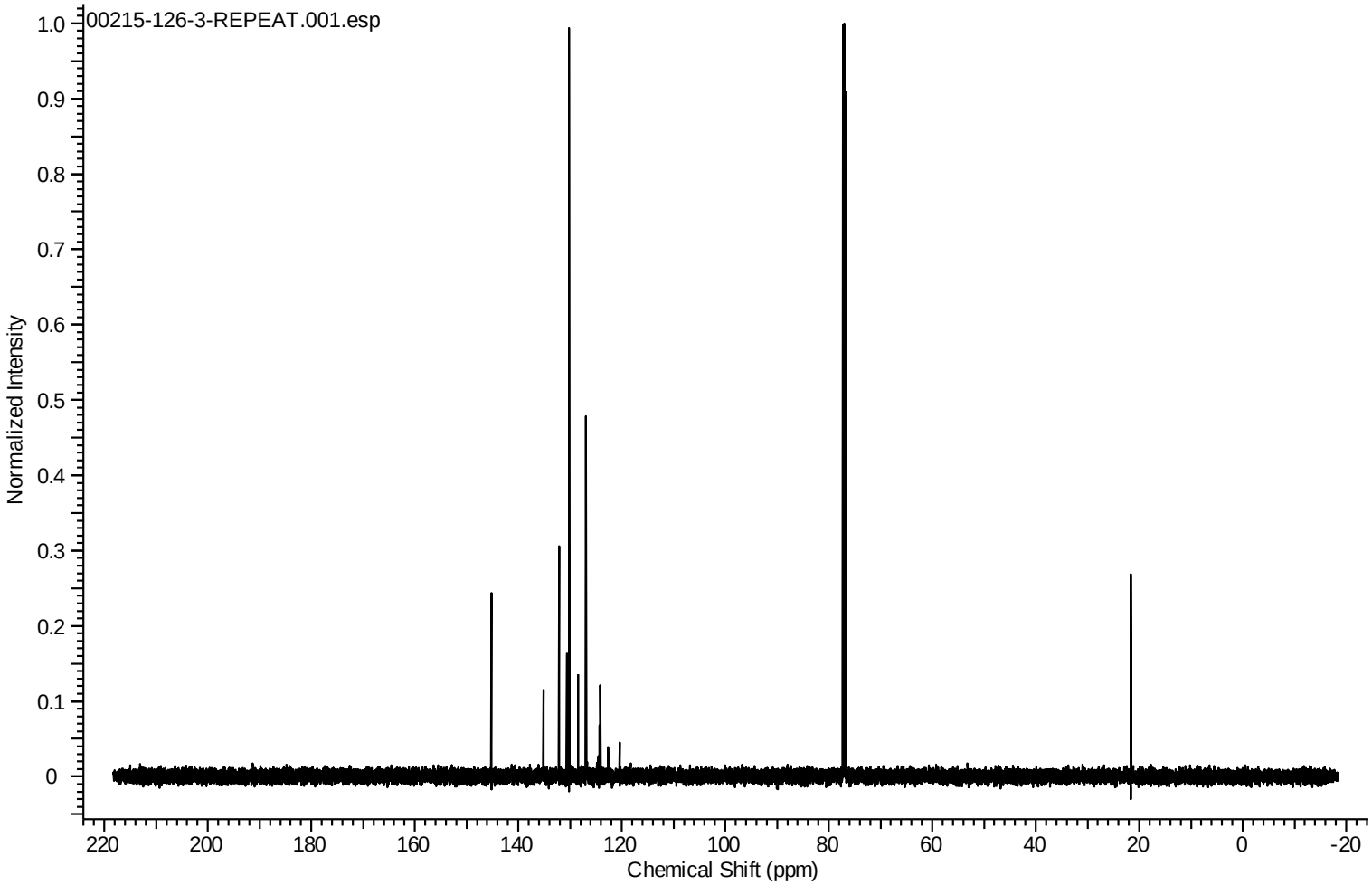
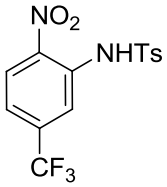


Table 2, entry 11c:

$CDCl_3$, ^1H NMR 500 MHz



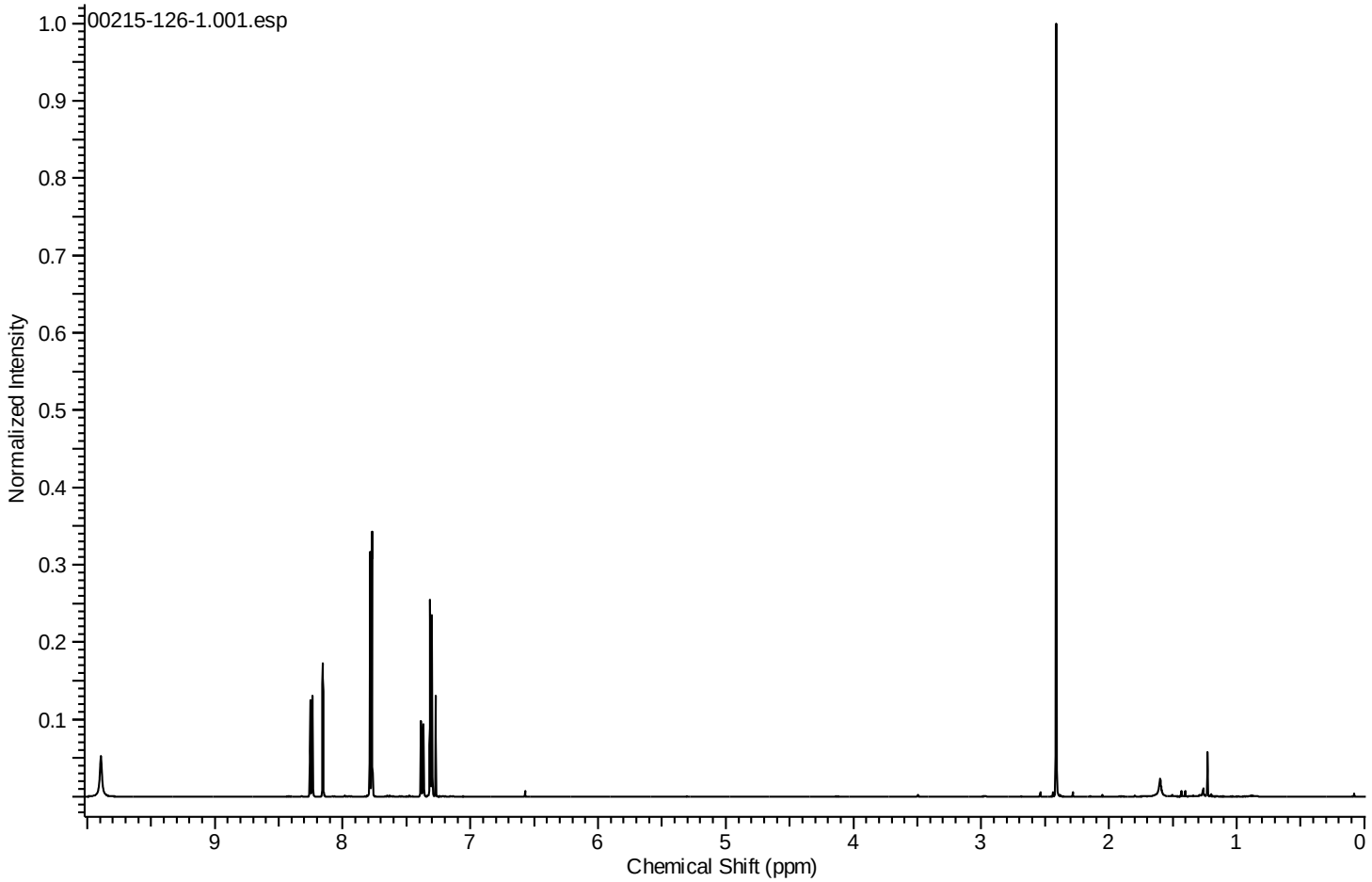
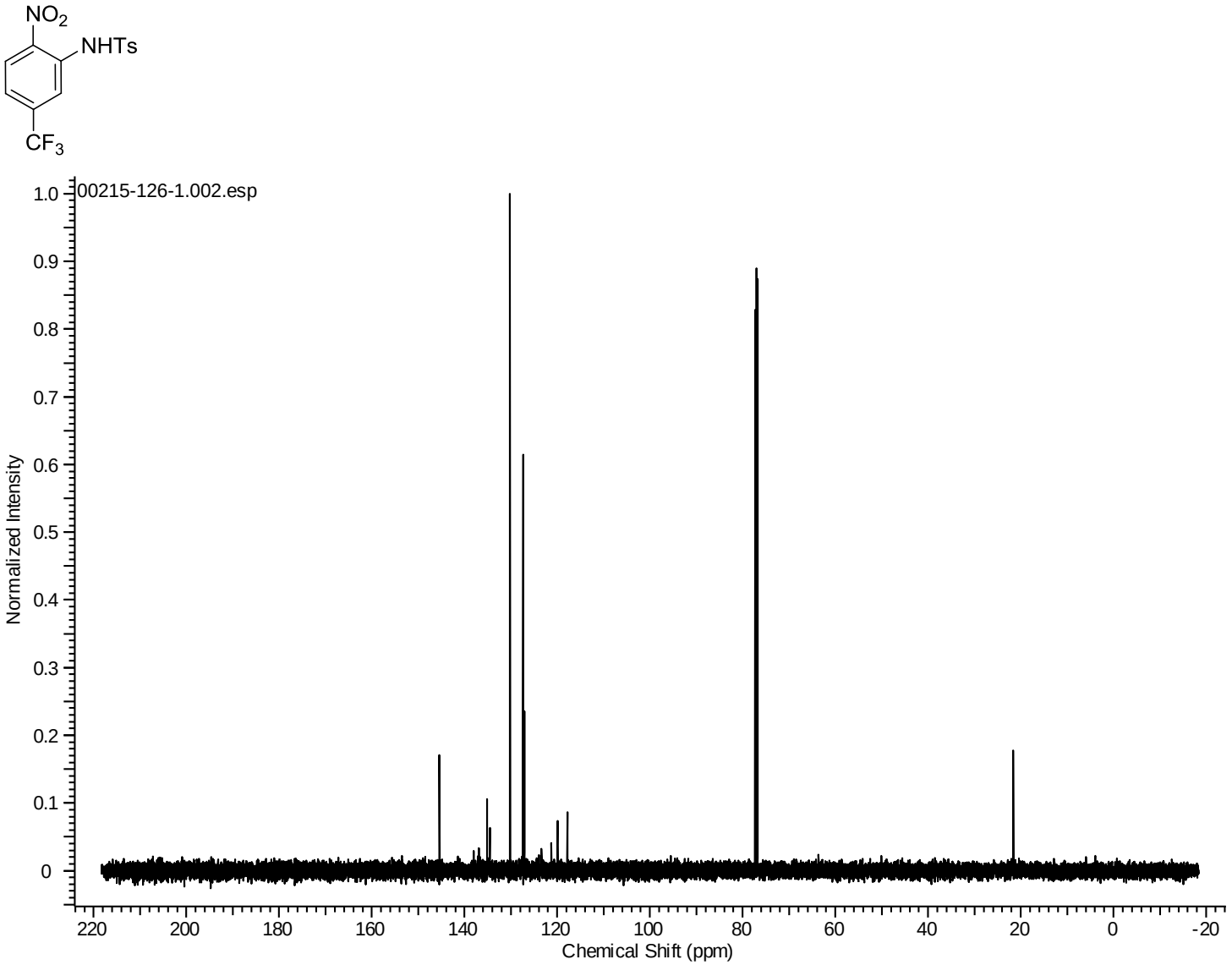


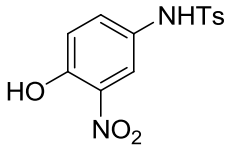
Table 2, entry 11c:

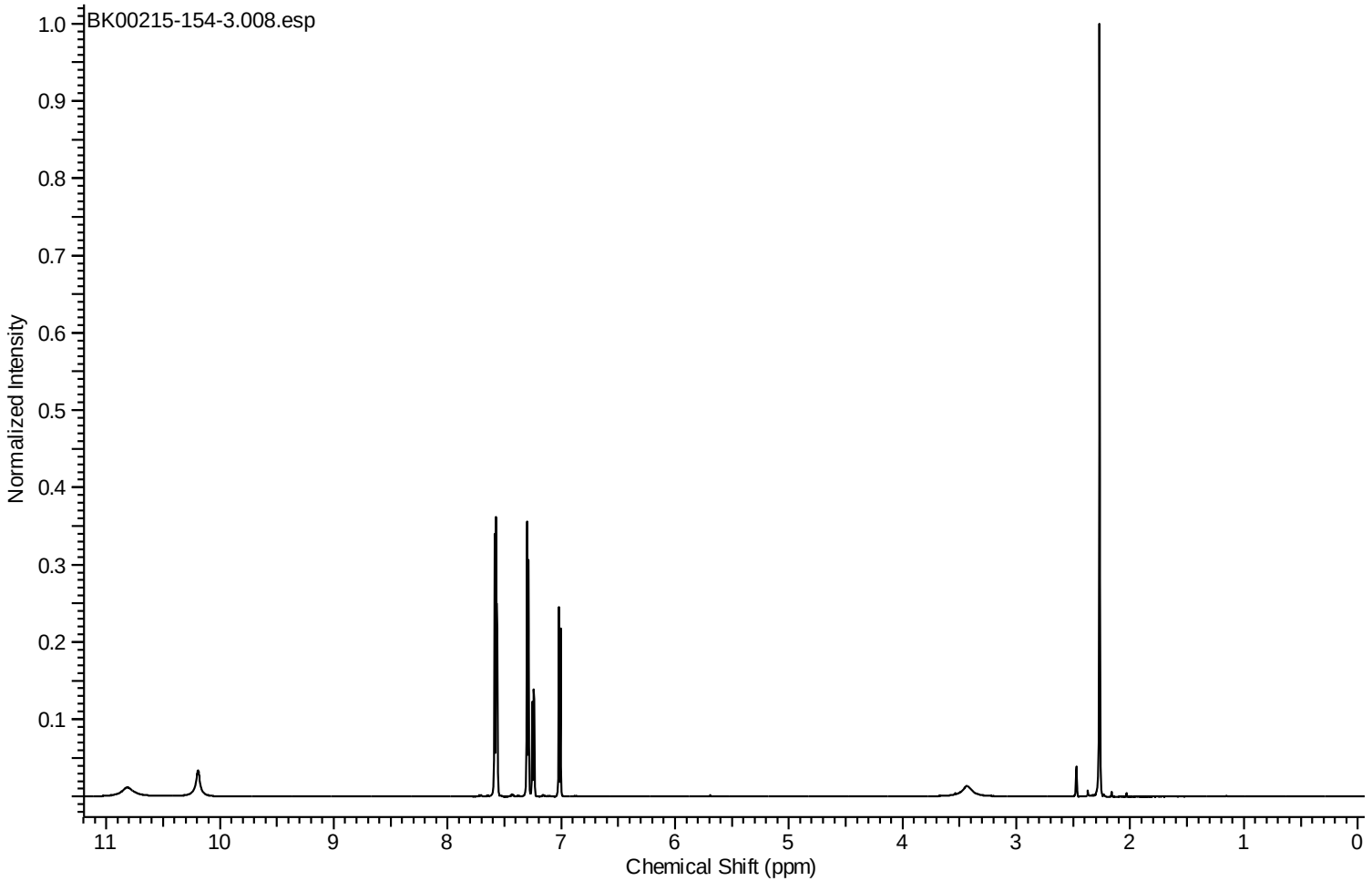
$CDCl_3$, ^{13}C NMR 125 MHz



Competition experiment #3 product a

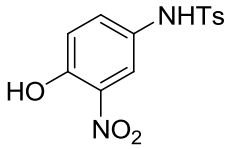
d_6-DMSO, ^{1}HNMR, 500 MHz

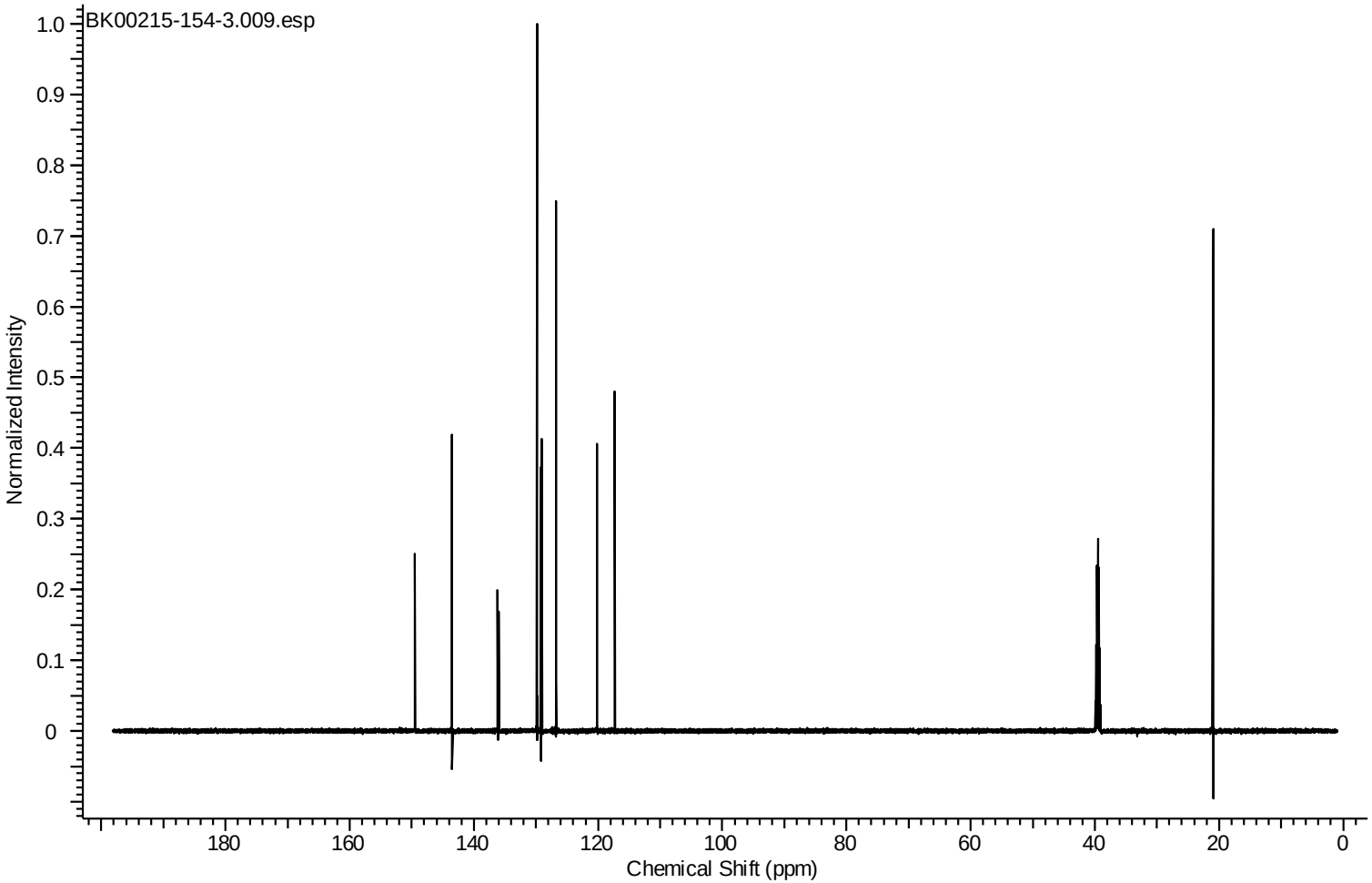




Competition experiment #3 product a

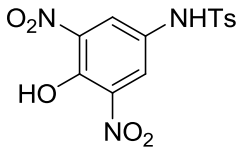
d_6-DMSO, ^{13}CNMR, 150 MHz

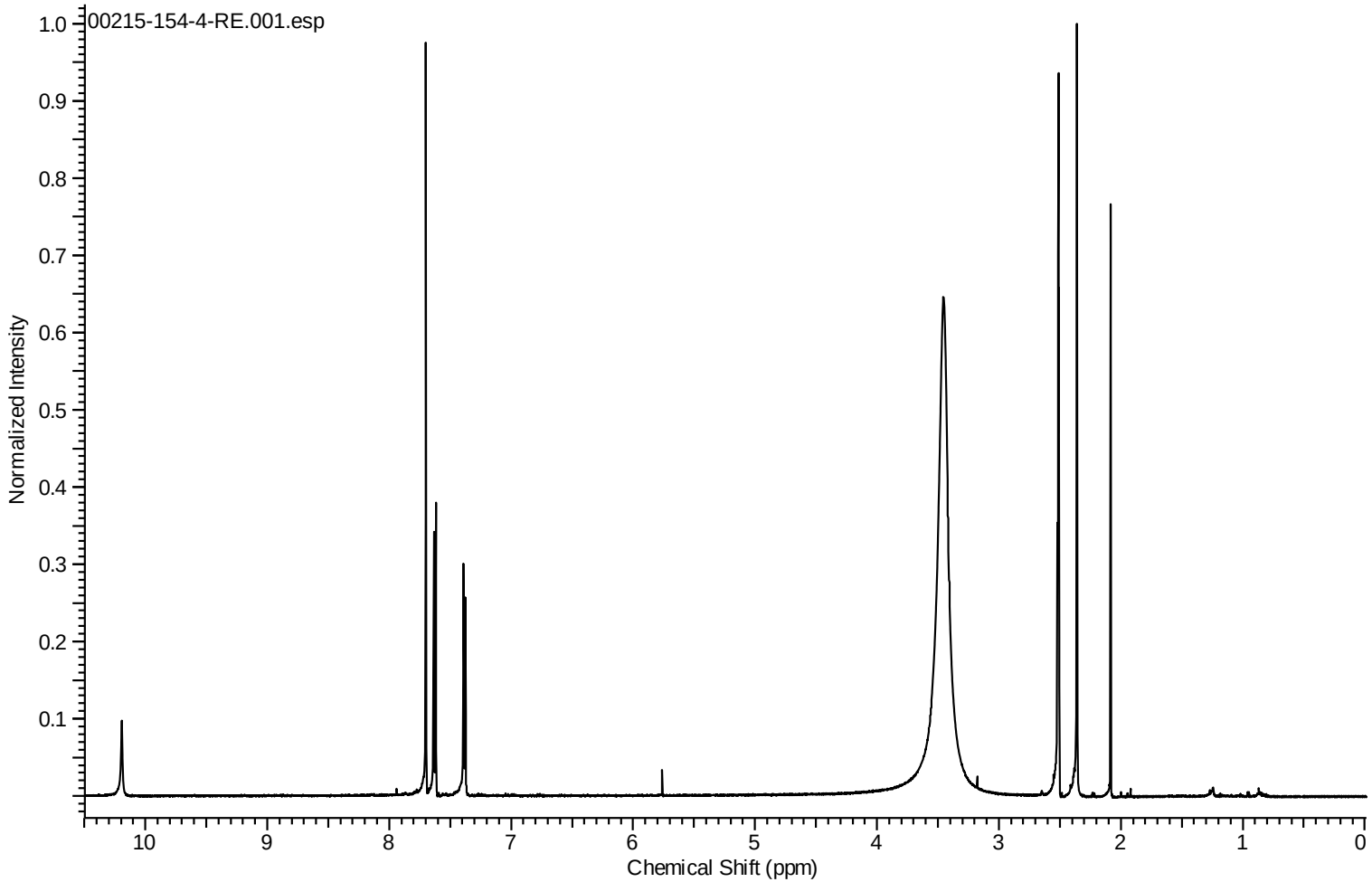




Competition experiment #3 product b

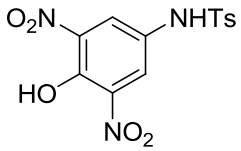
d_6-DMSO, ^{1}HNMR, 500 MHz

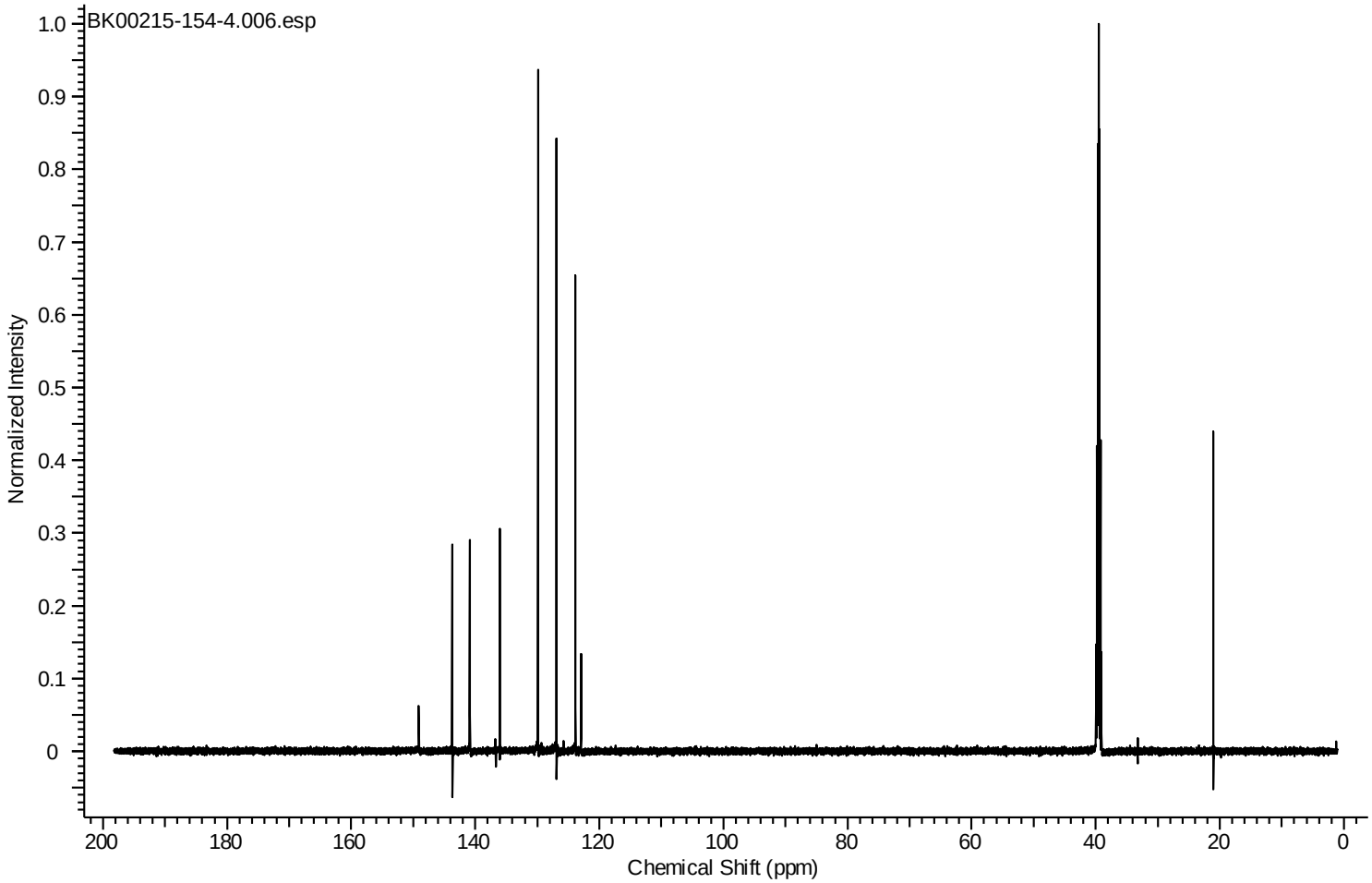




Competition experiment #3 product b

d_6-DMSO, ^{13}CNMR, 150 MHz





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