Electronic Supplementary Material (ESI) for Green Chemistry

Supporting information

Tin-free radical reactions under mimimal solvent conditions for the synthesis of substituted chromones and coumarins

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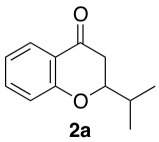
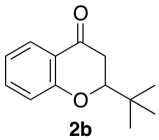
General Methods: All chromones, coumarins, Lewis acids, alkyl iodides, triethylborane, and solvents (dichloromethane and tetrahydrofuran) were purchased from Aldrich chemicals and used without further purification.

^{1}H-NMR were recorded on a Varian Gemini 200 MHz instrument. Chemical shifts are reported in parts per million (ppm) down field from TMS, using residual $CDCl_3$ (7.27 ppm) as an internal standard. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, bs = broad singlet), coupling constant and integration. ^{13}C-NMR was recorded on a Varian Gemini 200 MHz (50 MHz) instrument using broadband proton decoupling. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using the middle resonance of $CDCl_3$ (77.0) as an internal standard. Infrared spectra were recorded on Thermofisher IR100 FTIR instrument using NaCl pellets. Absorptions are given in wavenumbers (cm^{-1}).



2a

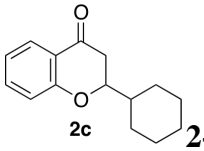
2-isopropylchroman-4-one (2a): 95% yield; IR (cm^{-1}) 2964, 2876, 1691, 1605, 1577, 1463, 1304, 1229, 1115; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.87 (dd, *J* = 1.8, 4.2 Hz, 1H), 7.52-7.42 (m, 1H), 7.04-6.94 (m, 2H), 4.26-4.11 (m, 1H), 2.70 (d, J = 7.2 Hz, 1H), 266 (s, 1H), 2.15-1.93 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 193.4, 162.1, 136.2, 127.1, 121.3, 121.2, 118.1, 82.7, 40.3, 32.4, 18.1; (CI/MS) *m/z* Calcd for $C_{12}H_{15}O_2$ [M+H]: 191.1; found: 191.0.



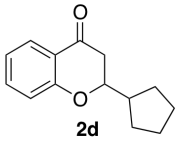
2b

2-(*tert*-butyl)chroman-4-one (2b): 97% yield, Known compound. ^{1}H NMR, ^{13}C NMR and HRMS are consistent with literature value.[1]

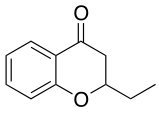
1. Bergdahl, M.; Eriksson, M.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1993**, *58*, 7238-7244.



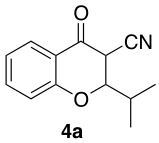
2c **2-cyclohexylchroman-4-one (2c)**: 85% yield; IR (cm^{-1}) 2927, 2853, 1692, 1607, 1577, 1463, 1306, 1228, 1148; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.90-7.83 (m, 1H), 7.51-7.41 (m, 1H), 7.05-6.93 (m, 2H), 4.26-4.12 (m, 1H), 2.77-2.64 (m, 2H), 1.99 (d, *J* = 10.4 Hz, 1H), 1.98-1.62 (m, 5H), 1.42-0.96 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 193.4, 162.1, 136.1, 127.1, 121.2, 118.1, 82.2, 42.0, 40.5, 28.5, 28.4, 26.5, 26.2, 26.1; (CI/MS) *m/z* Calcd for $C_{15}H_{19}O_2$ [M+H]: 231.1; found: 231.1.



2d **2-cyclopentylchroman-4-one (2d)**: 82% yield; IR (cm^{-1}) 2953, 2868, 1691, 1607, 1576, 1463, 1304, 1228, 1147; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.91-7.82 (m, 1H), 7.52-7.40 (m, 1H), 7.04-6.92 (m, 2H), 4.29-4.14 (m, 1H), 2.74-2.67 (m, 2H), 2.30-2.15 (m, 1H), 2.03-1.45 (m, 6H), 1.43-1.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 193.1, 162., 136.2, 127.1, 121.3, 118.2, 81.9, 44.3, 42.4, 29.0, 28.6, 25.8, 25.6; (CI/MS) *m/z* Calcd for $C_{14}H_{17}O_2$ [M + Na]: 217.1; found: 217.1.



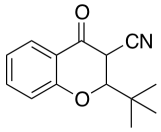
2e **2-ethylchroman-4-one (2e)**: 80% yield; Known compound. ^{1}H NMR, ^{13}C NMR and MS are consistent with literature value.[2]



4a **2-isopropyl-4-oxochroman-3-carbonitrile (4a)**: 98% yield; 2.1:1 inseparable mixture of diastereomers, IR (cm^{-1}) 2968, 2879, 1702, 1606, 1579, 1464, 1307, 1228, 1150; ^{1}H NMR ($CDCl_3$, 200 MHz) δ major diastereomer: 7.94-7.86 (m, 1H), 7.63-7.51 (m, 1H), 7.15-7.99 (m, 2H), 4.48-4.39 (dd, *J* = 2.5, 12.1 Hz, 1H), 3.93 (d, *J* = 12.1 Hz, 1H), 2.48-2.23 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H); minor diasteromer: 7.94-7.86 (m, 1H), 7.63-7.51 (m, 1H), 7.15-7.99 (m, 2H), 4.03-3.99 (dd, *J* = 2.5, 12.1 Hz, 1H), 3.71 (d, *J* = 12.1 Hz, 1H), 2.48-2.23 (m, 1H), 1.24 (d, *J* = 6.8

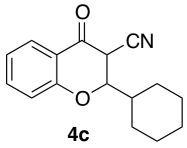
2 . Albrecht, U.; Lalk, M.; Langer, P. Bioorg. Med. Chem. **2005**, *13*, 1531-1536.

Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 183.6, 182.8, 161.6, 161.2, 137.8, 137.5, 128.4, 128.0, 122.7, 122.6, 119.0, 118.7, 118.5, 118.3, 113.7, 113.2, 83.2, 82.4, 43.5, 41.3, 31.3, 30.8, 19.3, 19.1, 18.1, 15.0; *m/z* Calcd for $C_{13}H_{14}NO_2$ [M+H]: 216.1; found: 216.1.



4b

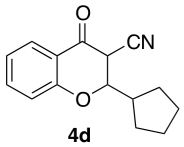
2-(*tert*-butyl)-4-oxochroman-3-carbonitrile (4b): 97% yield; 2:1 inseparable mixture of diastereomers, IR (cm^{-1}) 2968, 2879, 1702, 1606, 1579, 1464, 1307, 1228, 1150; ^{1}H NMR ($CDCl_3$, 200 MHz) δ major diastereomer: 7.90 (d, *J* = 7.4 Hz, 1H), 7.63-7.49 (m, 1H), 7.12-6.95 (m, 2H), 4.26 (dd, *J* = 1.0, 10.5 Hz, 1H), 3.87 (dd, *J* = 1.0, 10.5 Hz, 1H), 1.23 (s, 9H); minor diastereomer: 7.90 (d, *J* = 7.4 Hz, 1H), 7.63-7.49 (m, 1H), 7.12-6.95 (m, 2H), 3.97 (dd, *J* = 1.0, 2.0 Hz, 1H), 3.63 (dd, *J* = 1.0, 2.0 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 183.7, 183.3, 162.0, 161.3, 137.6, 137.5, 128.6, 127.9, 122.7, 118.8, 118.5, 118.4, 118.2, 114.9, 114.2, 85.7, 85.1, 45.8, 39.1, 36.1, 35.4, 26.4, 26.3, 25.6; HRMS Exact mass calcd for $C_{14}H_{15}NO_2Na$ $[M + Na]^+$: 252.1000; Found: 252.0993.



4c

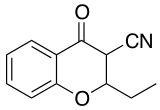
2-cyclohexyl-4-oxochroman-3-carbonitrile (4c): 94% yield; 1.3:1 inseparable mixture of diastereomers; The reaction was done following the general procedure listed in the paper. Additionally, the silica bed was first washed with 15 mL hexane to remove non-volatile cyclohexyl iodide followed by ether; IR (cm^{-1}) 2930, 2855, 1703, 1607, 1579, 1465, 1307, 1227, 1148; ^{1}H NMR ($CDCl_3$, 200 MHz) δ major diasteromer: 7.94-7.86 (m, 1H), 7.62-7.50 (m, 1H), 7.14-6.99 (m, 2H), 4.41 (dd, *J* = 2.3, 11.9 Hz, 1H), 3.98 (d, *J* = 11.9 Hz, 1H), 2.43-2.26 (m, 1H), 2.21-1.58 (m, 6H), 1.56-0.90 (m, 4H); minor diastereomer: 7.94-7.86 (m, 1H), 7.62-7.50 (m, 1H), 7.14-6.99 (m, 2H), 4.06 (dd, *J* = 2.7, 9.4 Hz, 1H), 3.96 (d, *J* = 2.5 Hz, 1H), 2.43-2.26 (m, 1H), 2.21-1.58 (m, 6H), 1.56-0.90 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 183.8, 182.9, 161.6, 161.2, 137.7, 137.5, 128.3, 128.0, 122.7, 122.6, 119.1, 118.8, 118.5, 118.3, 113.8, 113.3, 82.3, 82.2,

42.8, 40.9, 40.2, 40.0, 30.3, 29.6, 29.3, 28.0, 26.3, 26.1, 25.9, 25.6, 25.5, 25.4, 23.9; *m/z* Calcd for $C_{16}H_{18}NO_2$ [M+H]: 256.1; found: 256.2.



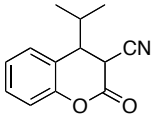
4d

2-cyclopentyl-4-oxochroman-3-carbonitrile (4d): 96% yield; 1.1:1 inseparable mixture of diastereomers; the reaction was done following the general procedure listed in the paper. Additionally, the silica bed was first washed with 15 mL hexane to remove non-volatile cyclopentyl iodide followed by ether; IR (cm^{-1}) 2954, 2870, 1702, 1607, 1578, 1464, 1306, 1226, 1148; ^{1}H NMR ($CDCl_3$, 200 MHz) δ major diasteromer: 7.93-7.86 (m, 1H), 7.63-7.50 (m, 1H), 7.14-6.98 (m, 2H), 4.58 (dd, *J* = 3.9, 11.4 Hz, 1H), 3.87 (d, *J* = 11.5 Hz, 1H), 2.69-2.45 (m, 1H), 2.21-1.77 (m, 4H), 1.75-1.44 (m, 4H); minor diasteromer: 7.93-7.86 (m, 1H), 7.63-7.50 (m, 1H), 7.14-6.98 (m, 2H), 4.15-4.07 (m, 1H), 3.66 (d, *J* = 2.5 Hz, 1H), 2.69-2.45 (m, 1H), 2.21-1.77 (m, 4H), 1.75-1.44 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 183.4, 182.8, 161.5, 161.1, 137.7, 137.5, 128.3, 128.0, 122.7, 122.6, 119.1, 118.9, 118.5, 118.4, 114.0, 113.4, 82.4, 80.6, 44.6, 42.5, 42.4, 42.3, 30.0, 28., 28.6, 26.0, 26.0, 25.9, 25.5, 25.4; *m/z* Calcd for $C_{15}H_{16}NO_2$ [M+H]: 242.1; found: 242.0.

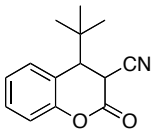


4e

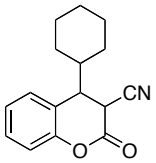
2-ethyl-4-oxochroman-3-carbonitrile (4e): 87% yield; 2:1 inseparable mixture of diastereomers, IR (cm^{-1}) 2973, 2937, 2882, 1701, 1607, 1578, 1464, 1310, 1226, 1150, 1120; ^{1}H NMR ($CDCl_3$, 200 MHz) δ major diasteromer: 7.97-7.84 (m, 1H), 7.66-7.51 (m, 1H), 7.16-6.96 (m, 2H), 4.57-4.35 (m, 1H), 3.85 (d, *J* = 12.1 Hz, 1H), 2.29-1.79 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H); minor diasteromer: 7.97-7.84 (m, 1H), 7.66-7.51 (m, 1H), 7.16-6.96 (m, 2H), 4.57-4.35 (m, 1H), 3.74 (d, *J* = 3.1 Hz, 1H), 2.29-1.79 (m, 2H), 1.13 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 183.3, 182.5, 161.1, 160.9, 137.8, 137.5, 128.2, 128.0, 122.7, 119.1, 119.0, 118.6, 118.3, 113.8, 113.3, 79.5, 79.1, 44.7, 43.0, 27.0, 25.4, 9.7, 8.9; (CI/MS) *m/z* Calcd for $C_{12}H_{12}NO_2$ [M+H]: 202.1; found: 202.0.



6a **4-isopropyl-2-oxochroman-3-carbonitrile (6a)**: 94% yield; 2.3:1 inseparable mixture of diasteromers, IR (cm^{-1}) 2967, 2879, 1766, 1614, 1588, 1488, 1456, 1367, 1239, 1213, 1164, 1118, 762; ^{1}H NMR ($CDCl_3$, 200 MHz) δ major diastereomer: 7.41-7.07 (m, 4H), 4.09 (d, *J* = 6.3 Hz, 1H), 3.32-3.27 (dd, *J* = 3.9, 6.3 Hz, 1H), 2.95-2.34 (m, 1H), 1.06 (d, *J* = 7.0, 3H), 0.91 (d, *J* = 7.0 Hz, 3H); minor diastereomer: 7.41-7.07 (m, 4H), 4.02 (d, *J* = 2.0 Hz, 1H), 3.03-2.98 (dd, *J* = 2.0, 8.2 Hz, 1H), 1.87-1.69 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.2, 160.2, 151.2, 150.6, 130.3, 130.0, 129.9, 125.6, 125.2, 121.8, 120.3, 117.6, 117.6, 114.2, 47.6, 44.6, 38.3, 25.4, 32.0, 30.8, 21.7, 20.3, 19.8, 16.7; (CI/MS) *m/z* Calcd for $C_{13}H_{14}NO_2$ [M+H]: 216.1; found: 216.1.

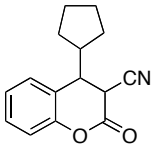


6b **4-*tert*-butyl-2-oxochroman-3-carbonitrile (6b)**: 96% yield; 1.6:1 IR (cm^{-1}) 2964, 2871, 1755, 1615, 1487, 1457, 1371, 1349, 1280, 1255, 1221, 1171, 1112, 1046, 908; ^{1}H NMR ($CDCl_3$, 200 MHz) δ major diastereomer: 7.43-7.13 (m, 4H), 4.18 (d, *J* = 5.5 Hz, 1H), 3.22 (d, *J* = 5.5 Hz, 1H), 1.10 (s, 9H); minor diastereomer: 7.43-7.13 (m, 4H), 3.74-3.77 (m, 1H), 3.05 (s, 1H), 0.97 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.8, 151.1, 131.6, 130.1, 126.3, 119.8, 117.7, 114.8, 51.5, 35.2, 34.0, 28.6, 27.3; (CI/MS) *m/z* Calcd for $C_{14}H_{16}NO_2$ [M+H]: 230.1; found: 230.0.

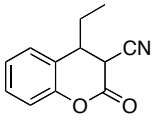


6c **4-cyclohexyl-2-oxochroman-3-carbonitrile (6c)**: 81% yield; 2.7:1 inseparable mixture of diasteromers; The reaction was done following the general procedure listed in the paper. Additionally, the silica bed was first washed with 15 mL hexane to remove non-volatile cyclohexyl iodide followed by ether; IR (cm^{-1}) 2929, 2855, 1770, 1487, 1455, 1360, 1225, 1161, 1115, 1002, 762; ^{1}H NMR ($CDCl_3$) δ major diastereomer: 7.42-7.08 (m, 4H), 4.06 (d, *J* = 7.4 Hz, 1H), 3.29-3.23 (dd, *J* = 3.9, 6.3 Hz,

1H), 3.05-3.00 (dd, *J* = 2.0, 8.2 Hz, 1H), 2.12-0.63 (m, 11H); minor diastereomer: 7.42-7.08 (m, 4H), 4.06 (d, *J* = 7.4 Hz, 1H), 3.05-3.00 (dd, *J* = 2.0, 8.2 Hz, 1H), 2.12-0.63 (m, 11H)**;** ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.3, 160.2, 151.1, 150.6, 130.3, 129.9, 129.8, 129.8, 121.8, 121.2, 117.6, 117.5, 114.6, 114.2, 46.9, 44.6, 41.1, 40.5, 38.0, 35.1, 31.6, 30.6, 30.1, 27.2, 26.4, 26.1, 26.0, 25.9, 25.8; (CI/MS) *m/z* Calcd for $C_{16}H_{18}NO_2$ [M+H]: 256.1; found: 256.0.

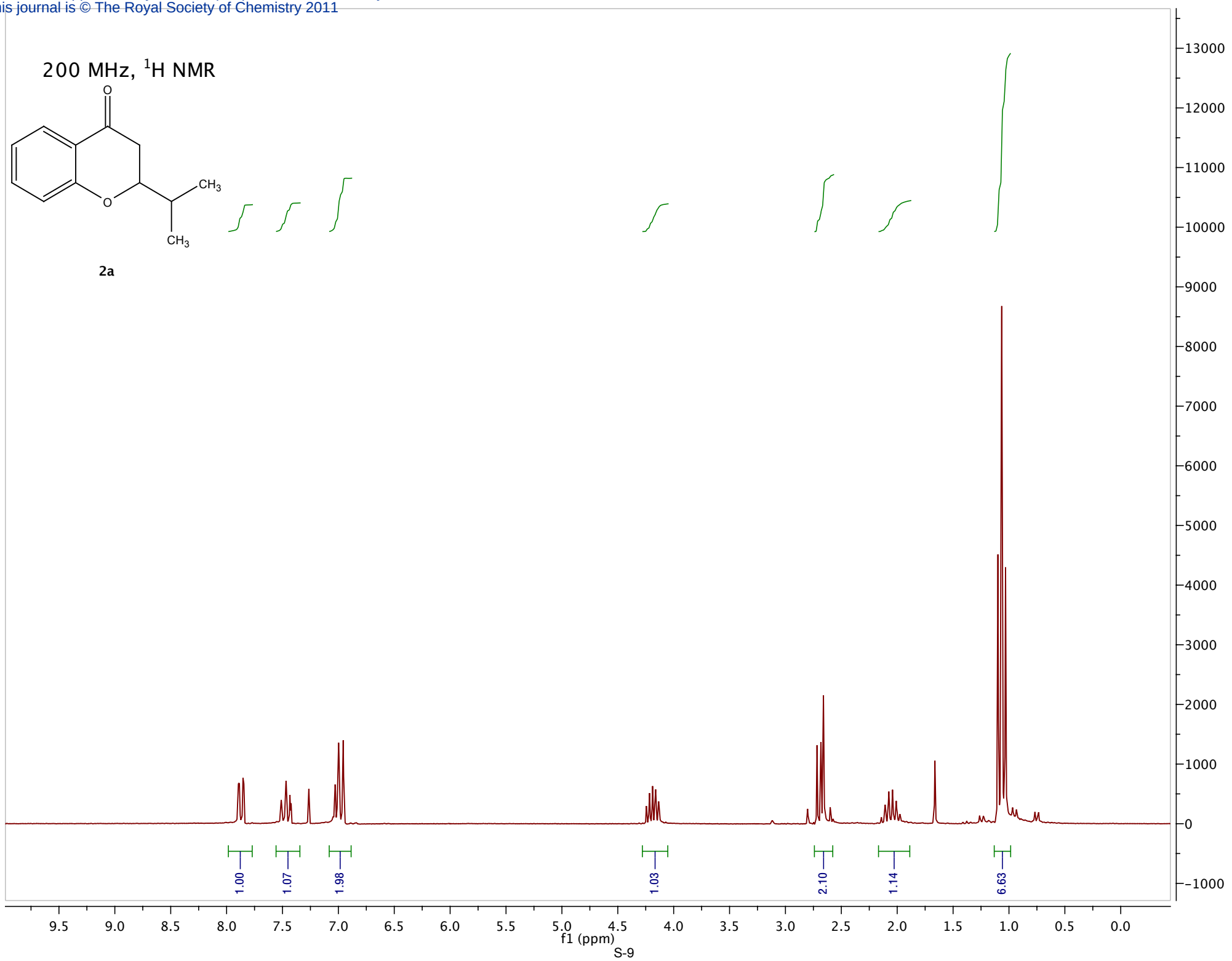


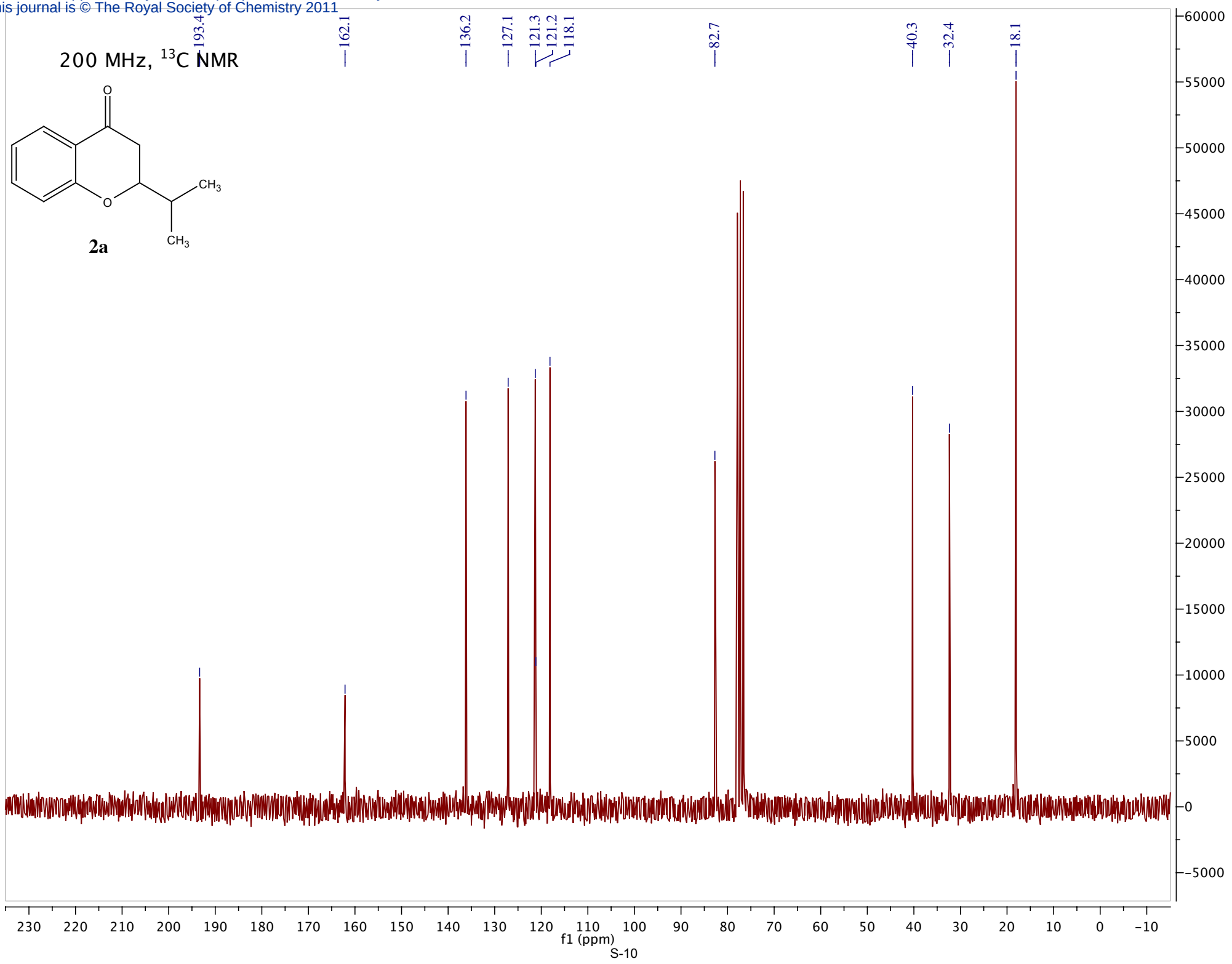
6d **4-cyclopentyl-2-oxochroman-3-carbonitrile (6d)**: 83% yield; 1.8:1 inseparable mixture of diasteromers; The reaction was done following the general procedure listed in the paper. Additionally, the silica bed was first washed with 15 mL hexane to remove non-volatile cyclopentyl iodide followed by ether; IR (cm^{-1}) 2957, 2872, 1778, 1614, 1588, 1487, 1456, 1350, 1238, 1214, 1163, 1110, 1013, 911, 762; ^{1}H NMR ($CDCl_3$, 200 MHz) δ major diasteromer: 7.38-7.07 (m, 4H), 4.08 (d, *J* = 5.5 Hz, 1H), 3.43-3.37 (t, *J* = 5.9 Hz, 1H), 2.38-0.86 (m, 9H); minor diastereomer: 7.38-7.07 (m, 4H), 3.97 (d, *J* = 1.6 Hz, 1H), 3.09-3.04 (dd, *J* = 1.6, 9.4 Hz, 1H), 2.38-0.86 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.0, 160.0, 150.9, 150.4, 129.8, 129.8, 129.7, 129.6, 125.6, 125.3, 122.8, 122.5, 117.6, 117.6, 46.3, 43.8, 42.7, 42.7, 39.1, 36, 9, 31.2, 30.9, 30.6, 28.5, 24.9, 24.8, 24.4, 24.2; (CI/MS) *m/z* Calcd for $C_{15}H_{16}NO_2$ [M+H]: 242.1; found: 242.0.

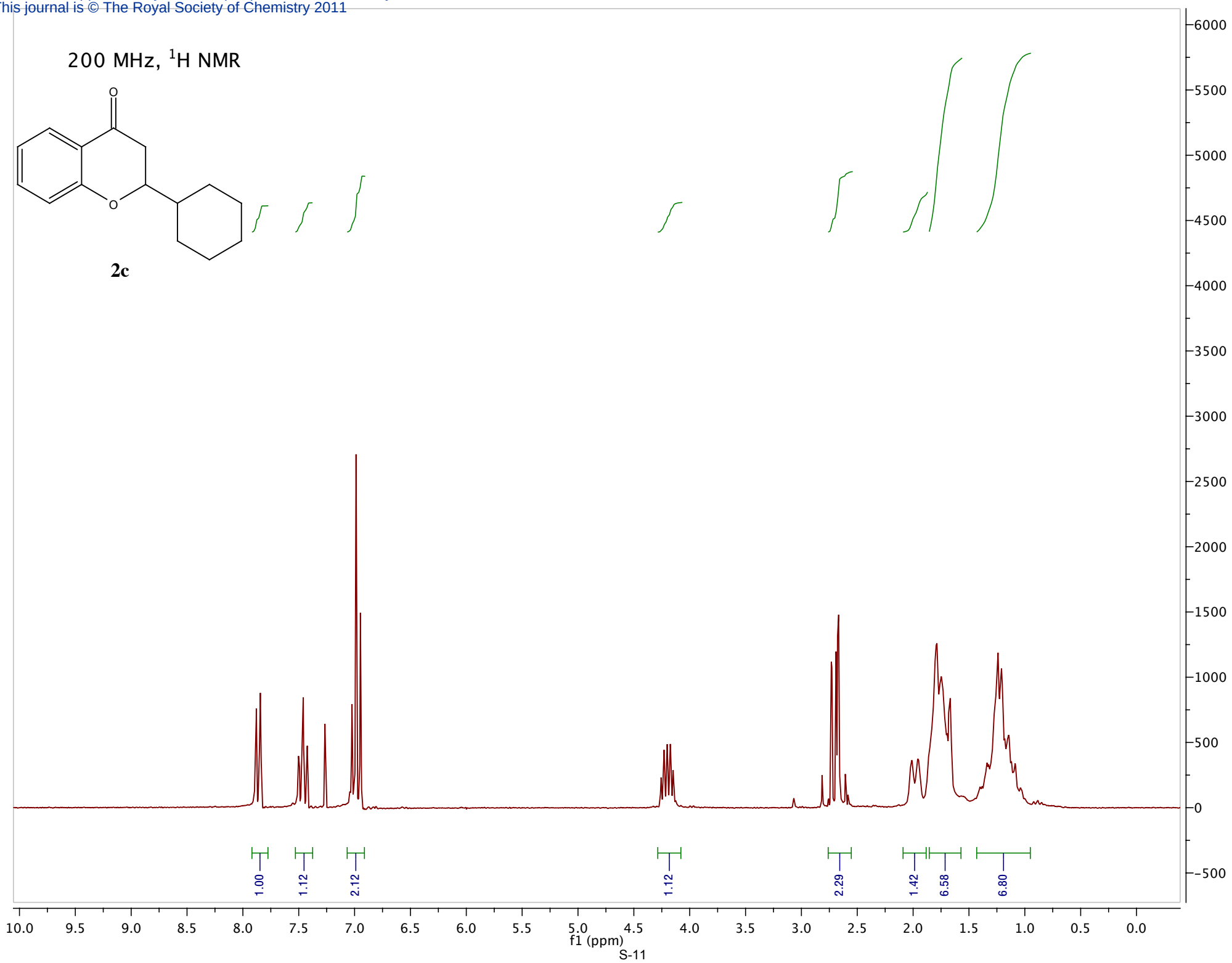


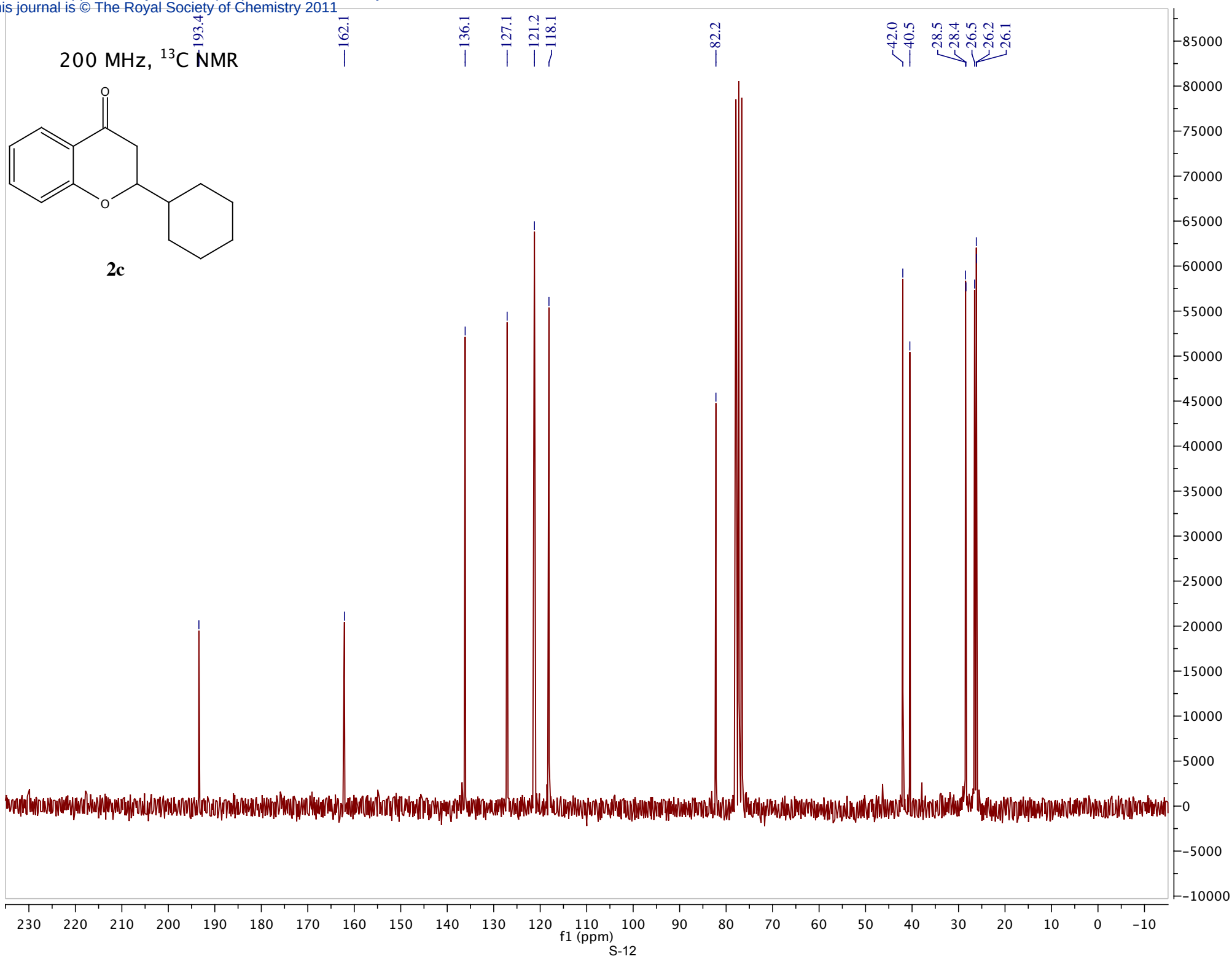
6e **4-ethyl-2-oxochroman-3-carbonitrile (6e):** 91% yield; 3:1 inseparable mixture of diasteromers, IR (cm^{-1}) 2970, 2936, 1770, 1613, 1588, 1487, 1455, 1360, 1204, 1163, 1119, 1020, 761; ^{1}H NMR ($CDCl_3$) δ major diastereomer: 7.40-6.93 (m, 4H), 3.99 (d, *J* = 5.5 Hz, 1H), 3.22-3.10 (m, 1H), 2.10-1.92 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H); minor diastereomer: 7.40-6.93 (m, 4H), 3.77 (d, *J* = 4.6 Hz, 1H), 3.31-3.17 (m, 1H), 2.10-1.92 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 150.4, 129.9, 129.8, 129.6, 128.9, 128.4, 127.0, 125.8, 125.5, 125.4, 123.4, 118.1, 117.8, 42.2, 40.8, 39.3,

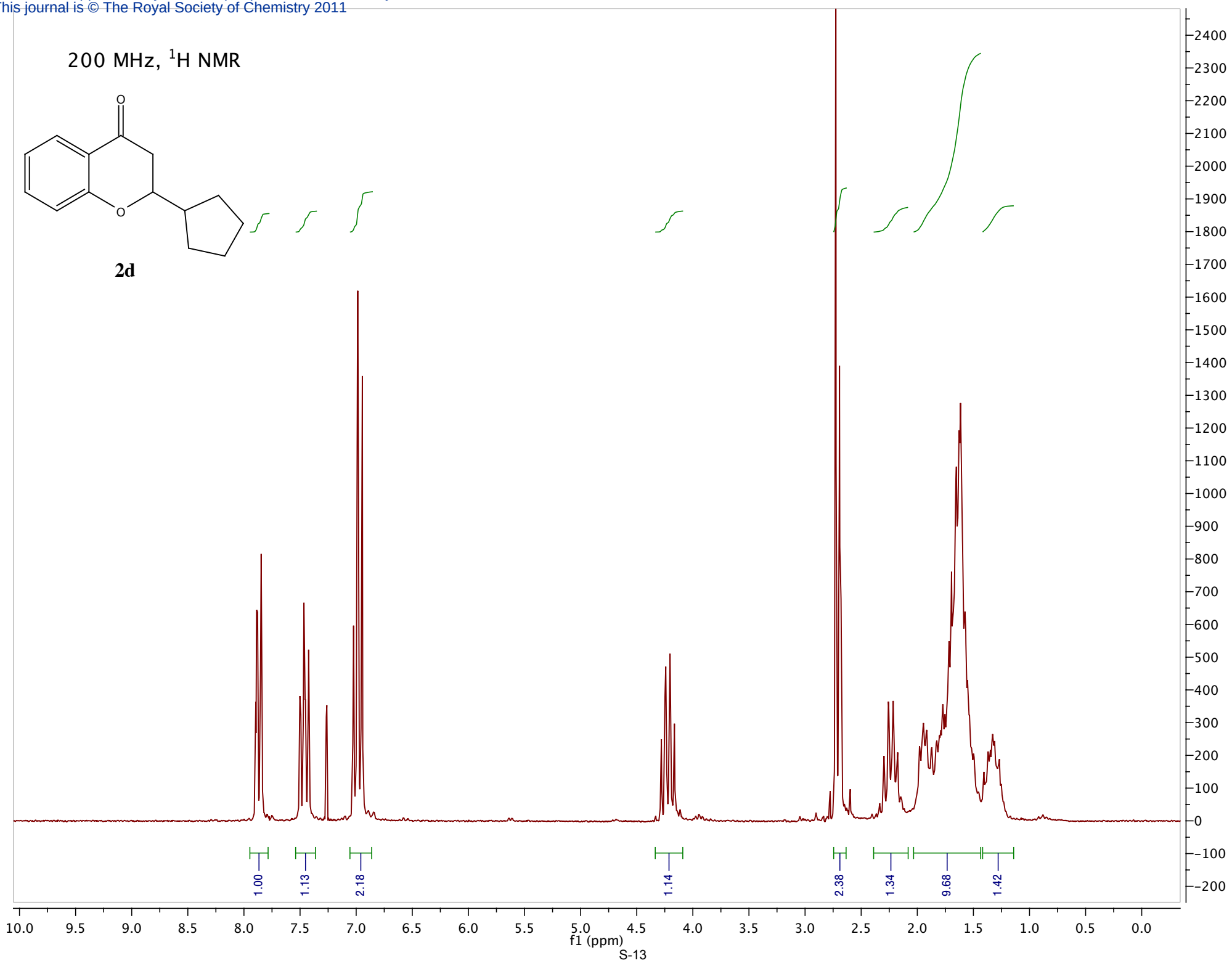
37.2, 30.9, 26.0, 25.3, 24.9, 11.1; (CI/MS) *m/z* Calcd for $C_{12}H_{12}NO_2$ [M+H]: 202.1.1; found: 202.1.

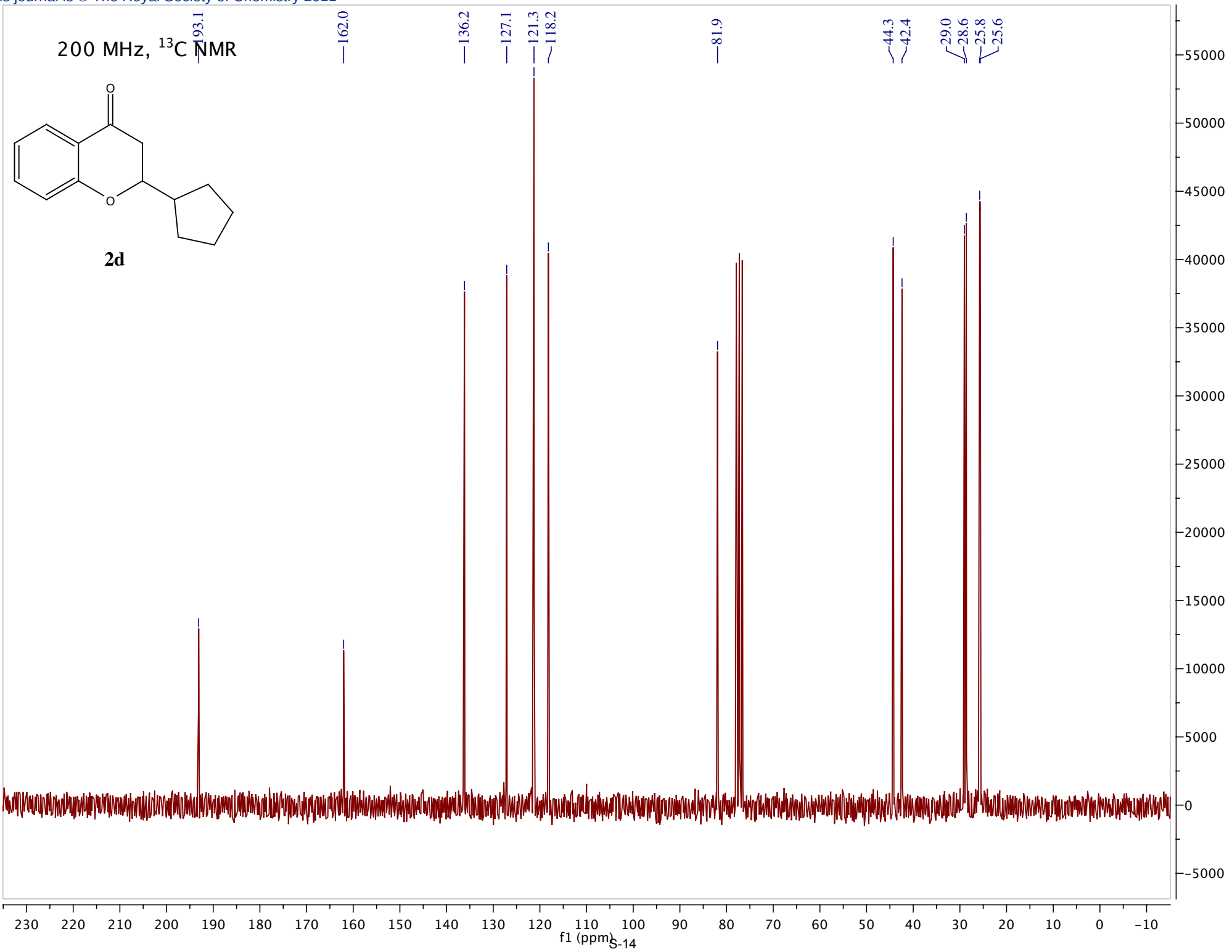


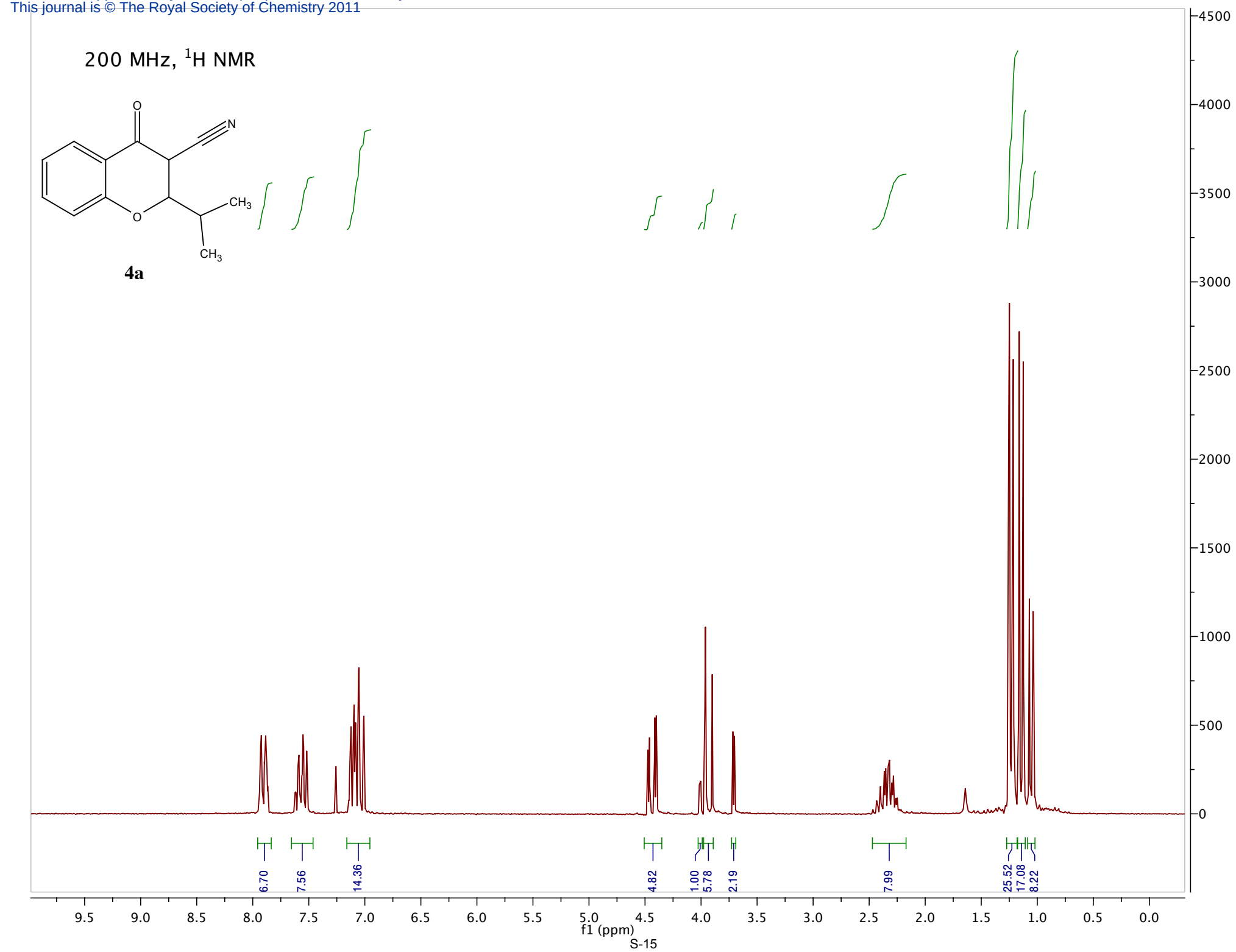












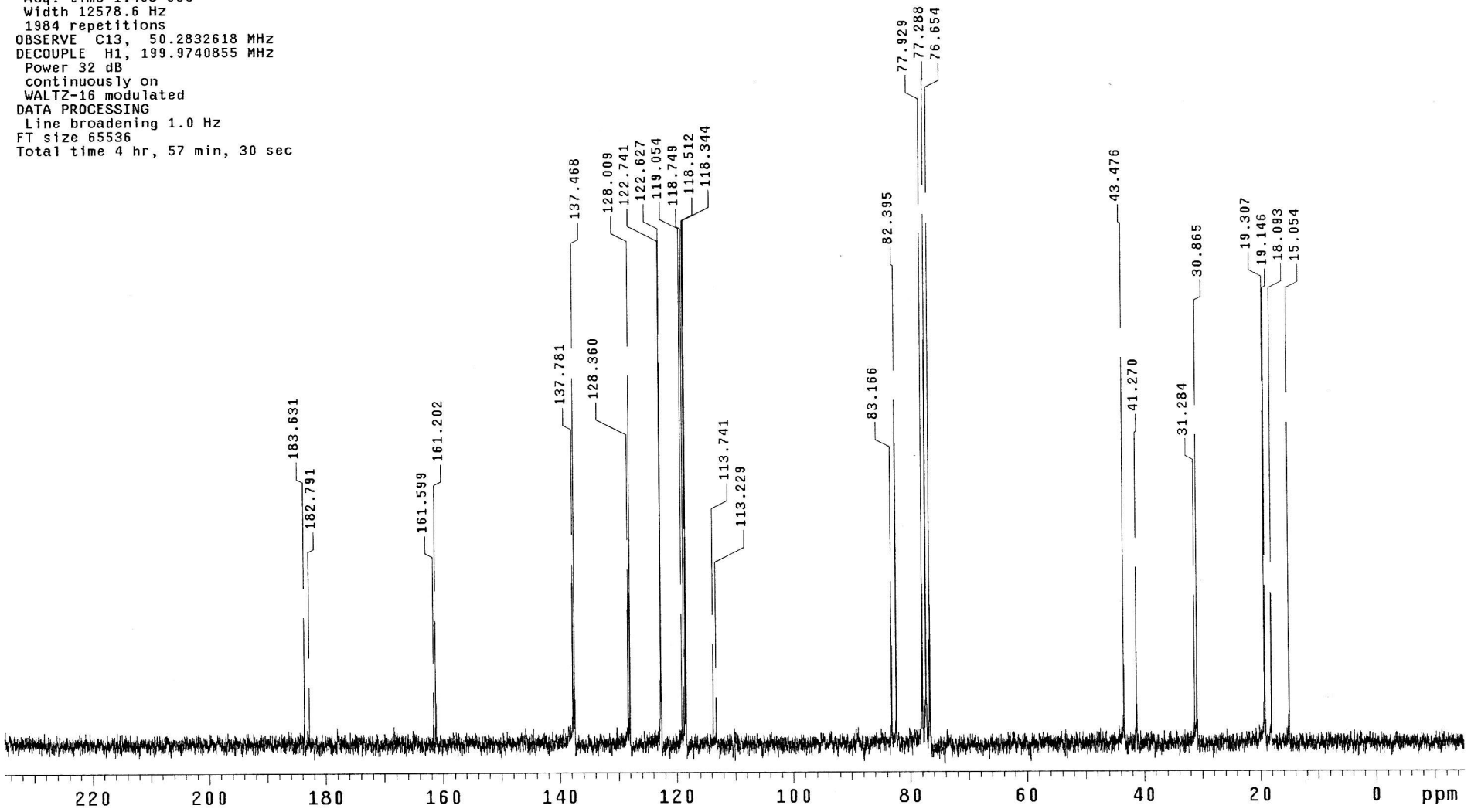
87a

Archive directory: /export/home/jzimm/vnmrsys/data
Sample directory: 87A_18May2011
File: CARBON

Pulse Sequence: s2pul

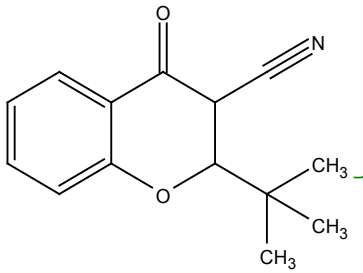
Date: May 18 2011
Solvent: CDCl3
Ambient temperature
Mercury-200 "chemsun"

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.498 sec
Width 12578.6 Hz
1984 repetitions
OBSERVE C13, 50.2832618 MHz
DECOUPLE H1, 199.9740855 MHz
Power 32 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 4 hr, 57 min, 30 sec

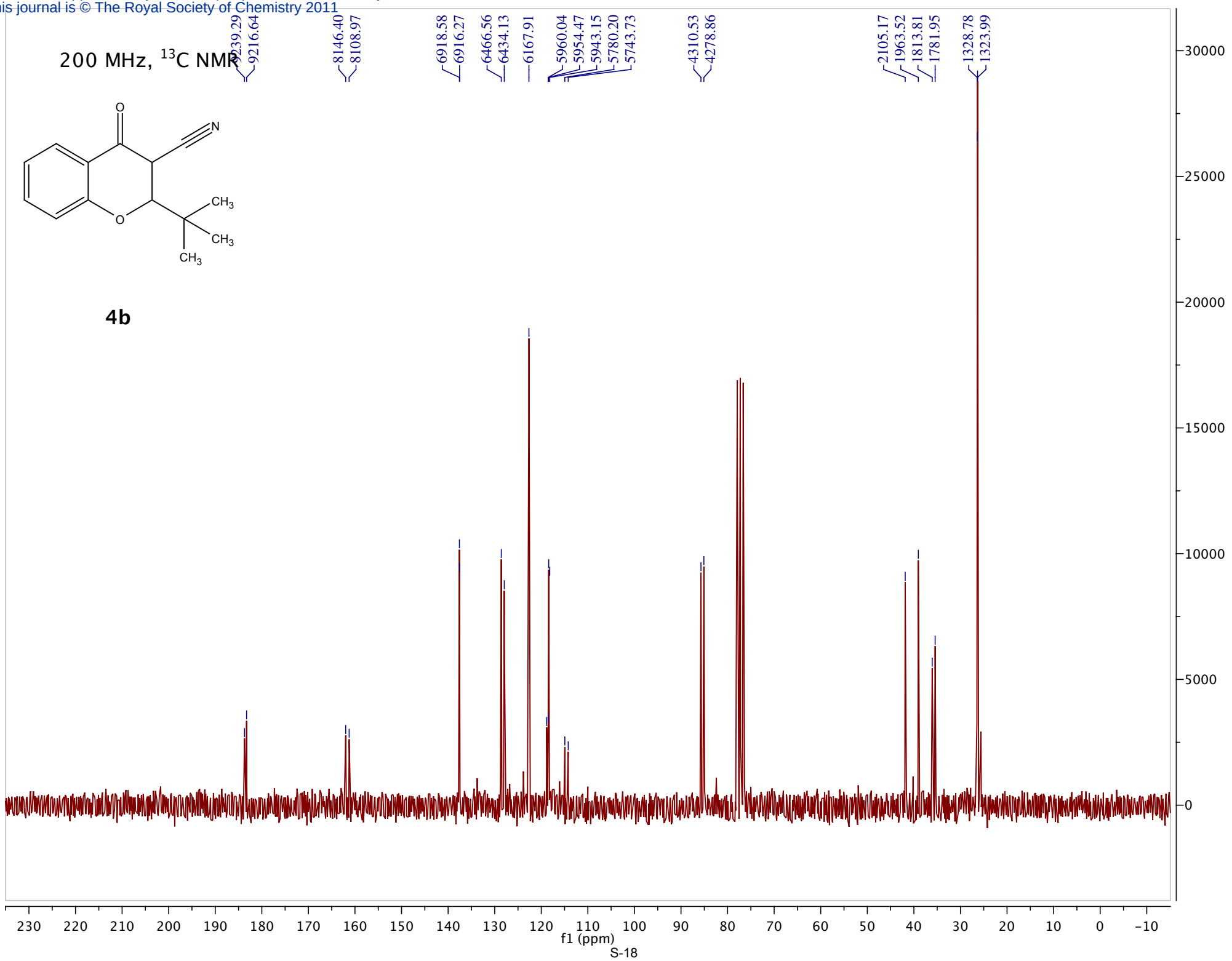


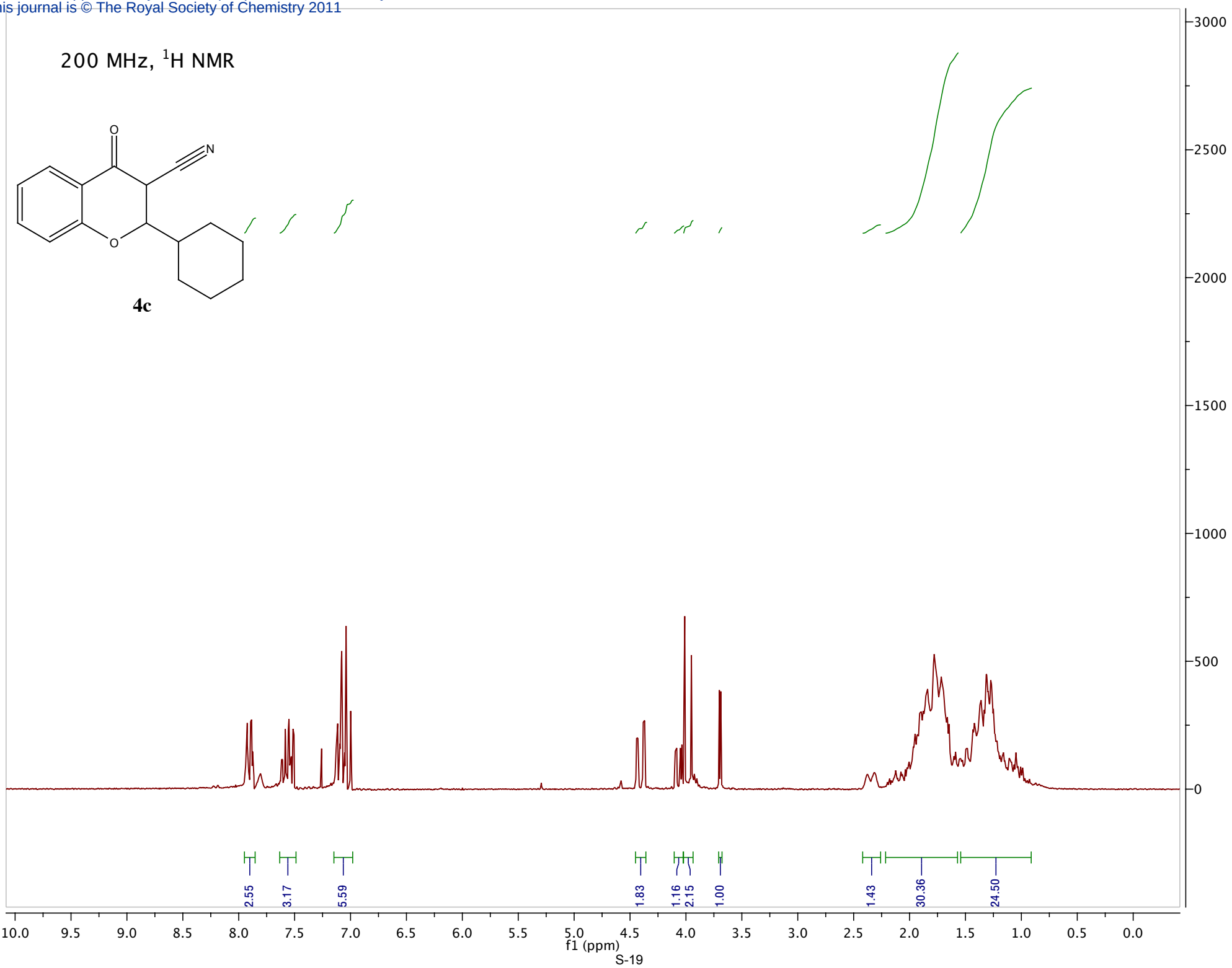
200 MHz, ^{1}H NMR

4b



4b





87b

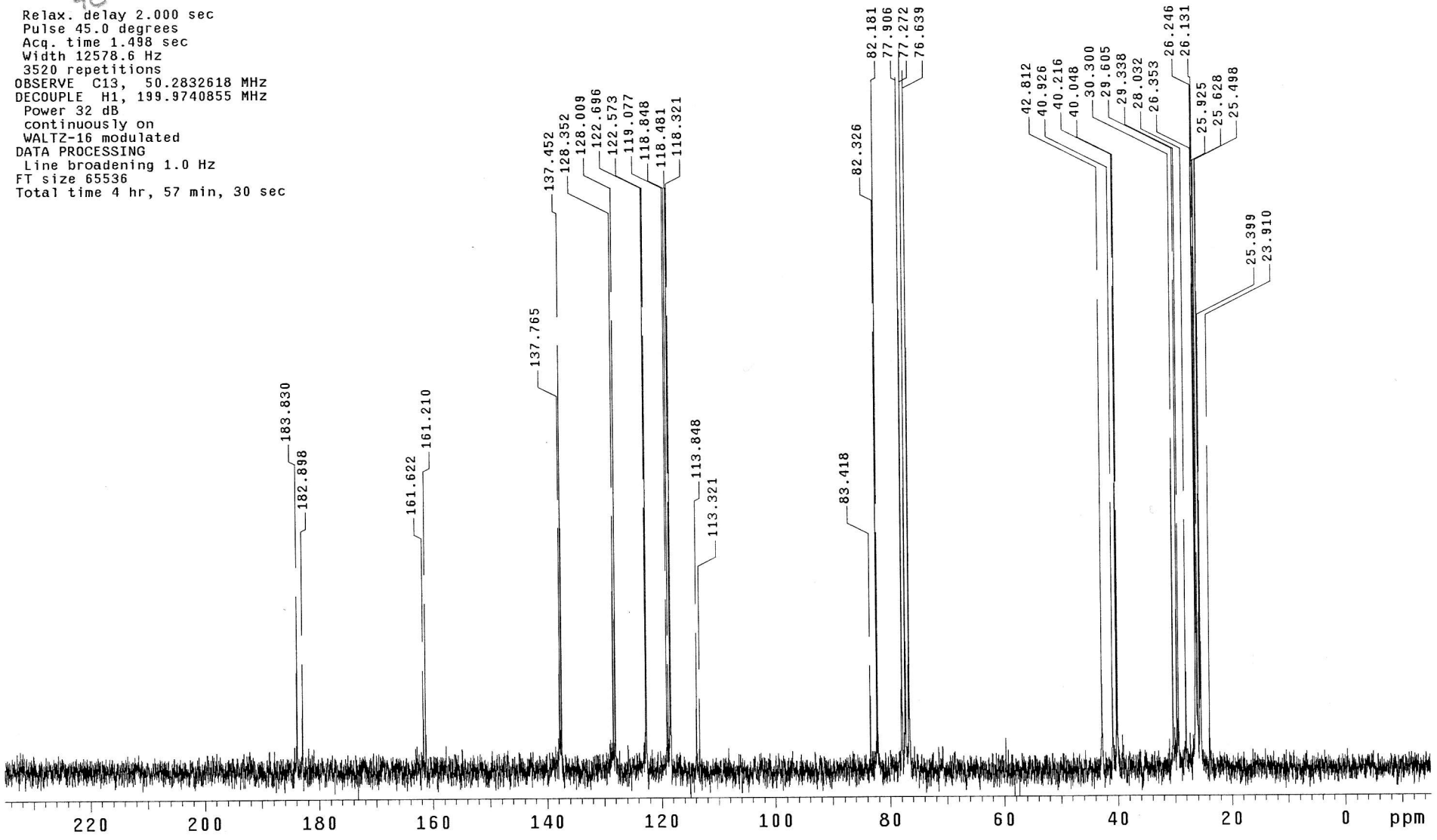
Archive directory: /export/home/jzimm/vnmrsys/data
Sample directory: 87bcarb_18May2011
File: CARBON

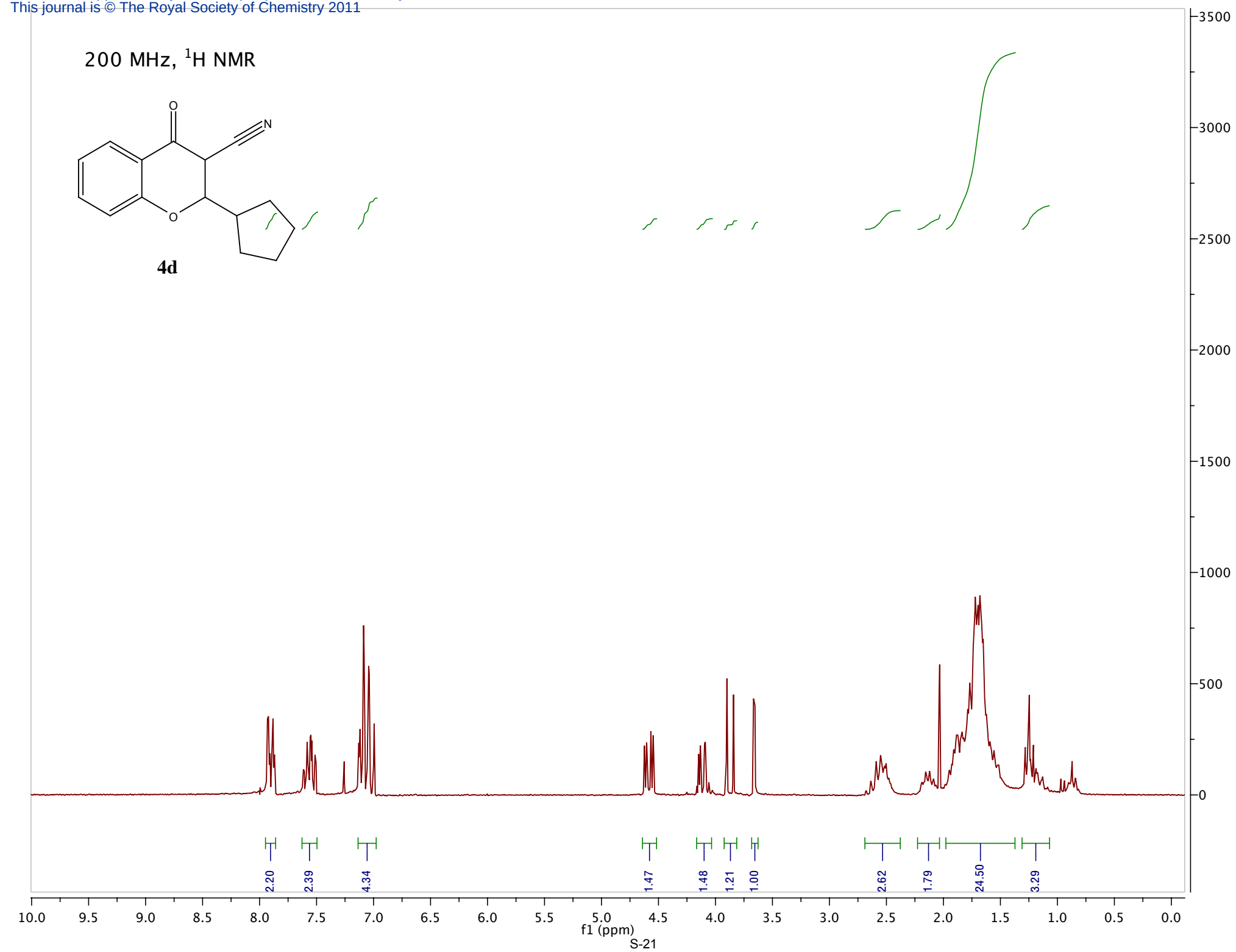
Pulse Sequence: s2pul

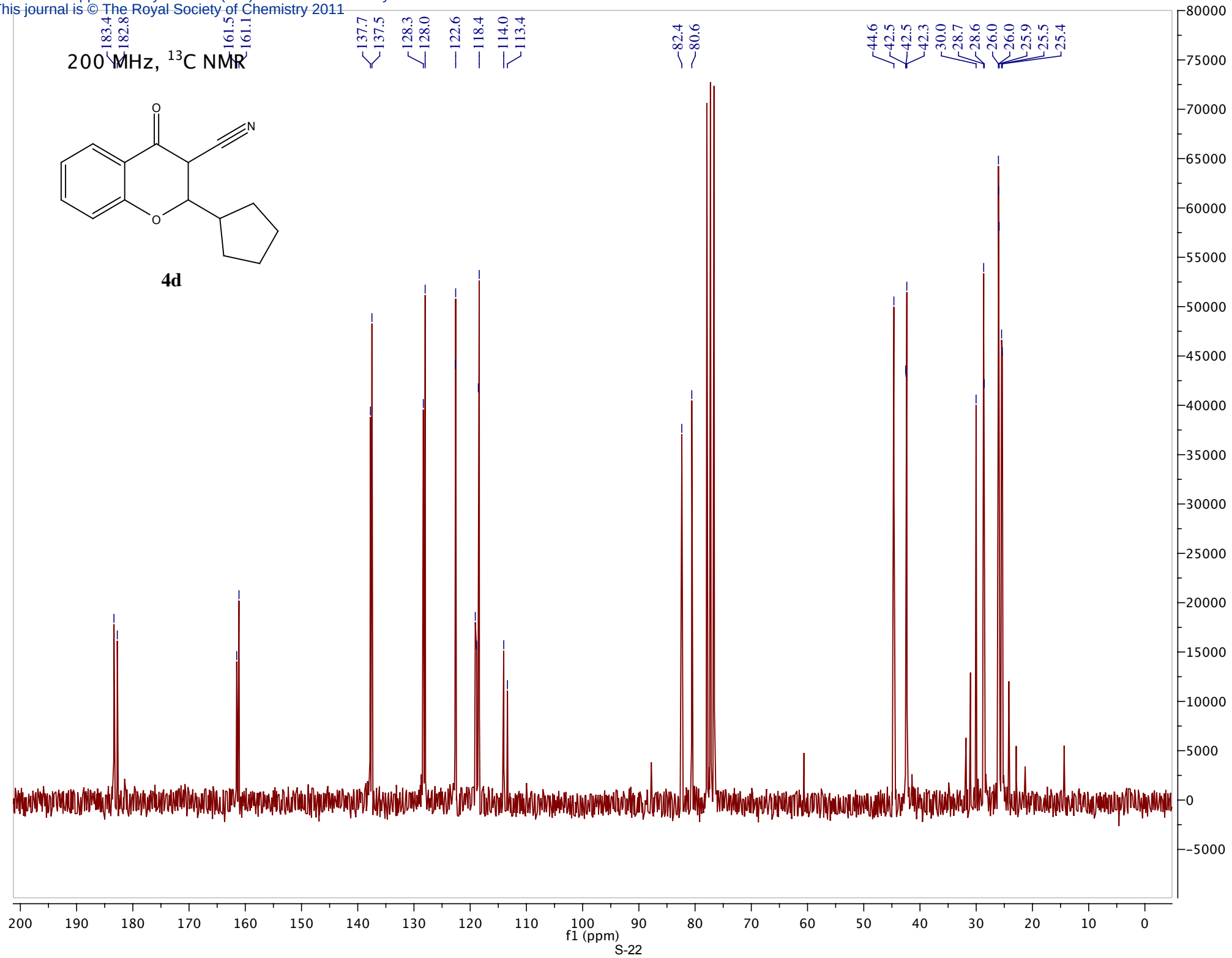
Date: May 18 2011
Solvent: CDCl3
Ambient temperature
Mercury-200 "chemsun"

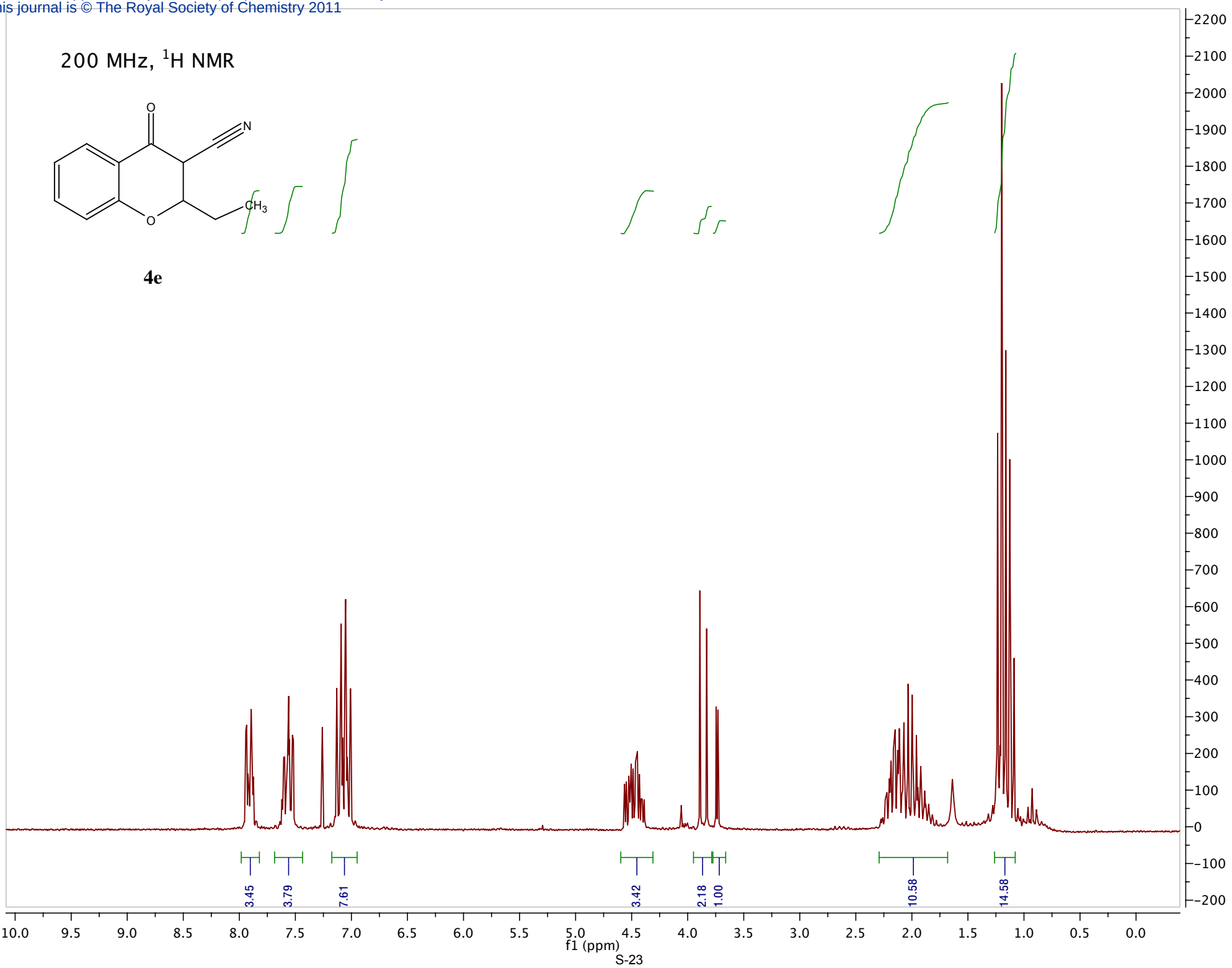
4C

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.498 sec
Width 12578.6 Hz
3520 repetitions
OBSERVE C13, 50.2832618 MHz
DECOUPLE H1, 199.9740855 MHz
Power 32 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 4 hr, 57 min, 30 sec









87d

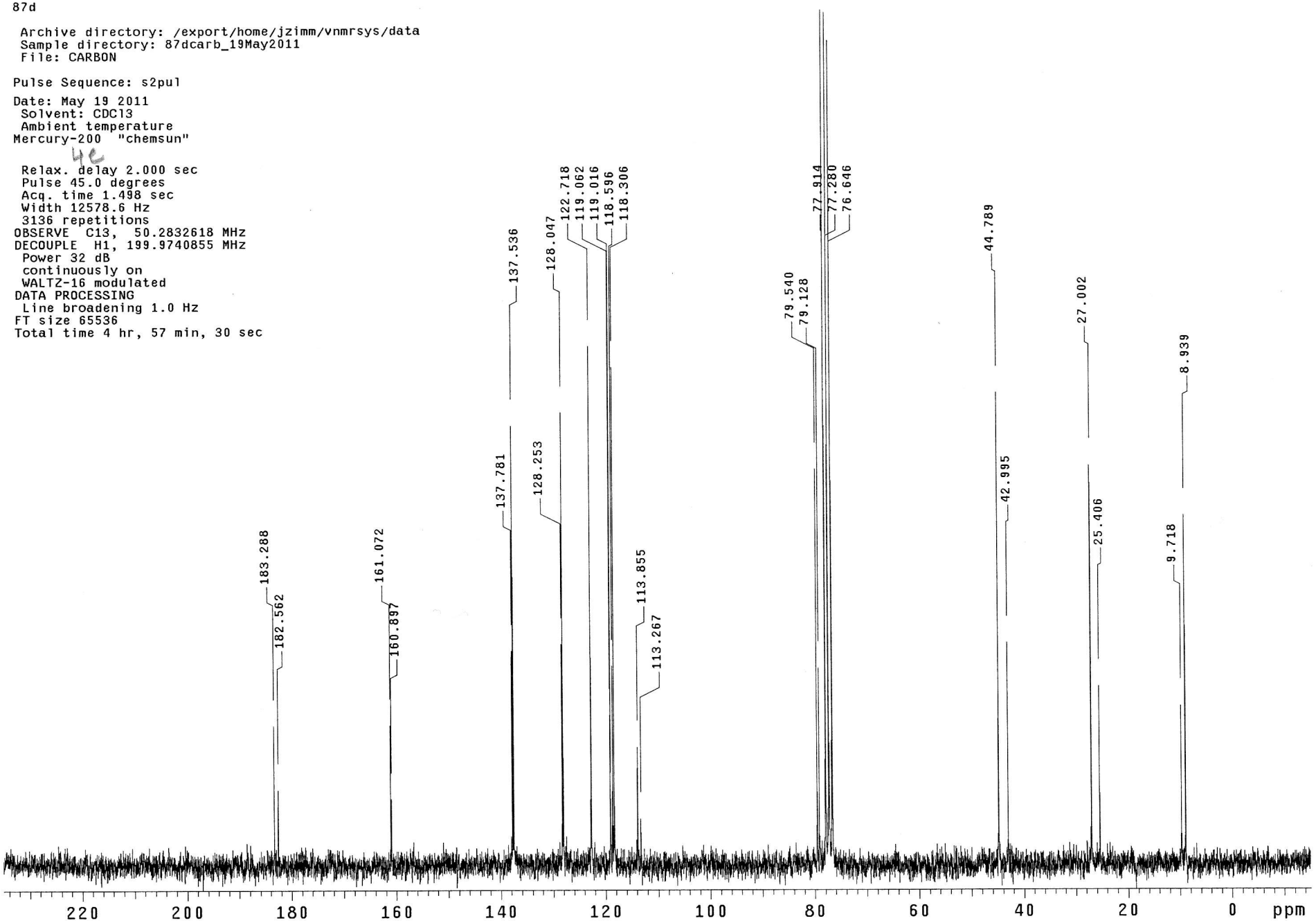
Archive directory: /export/home/jzimm/vnmrsys/data
Sample directory: 87dcarb_19May2011
File: CARBON

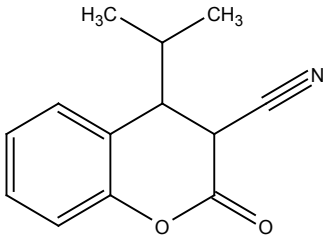
Pulse Sequence: s2pul

Date: May 19 2011
Solvent: CDCl3
Ambient temperature
Mercury-200 "chemsun"

4e

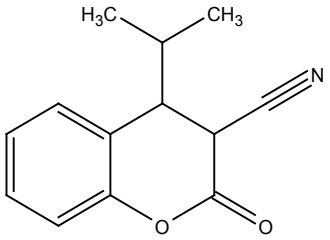
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.498 sec
Width 12578.6 Hz
3136 repetitions
OBSERVE C13, 50.2832618 MHz
DECOUPLE H1, 199.9740855 MHz
Power 32 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 4 hr, 57 min, 30 sec





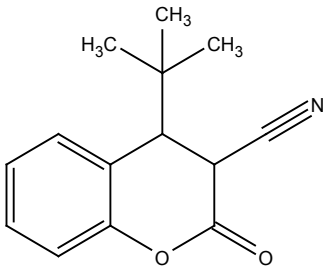
6a

200 MHz ^{1}H NMR



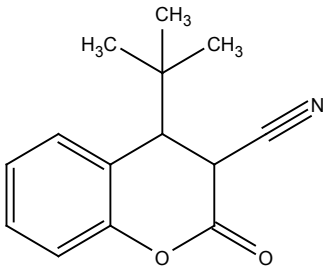
6a

200 MHz ^{13}C NMR



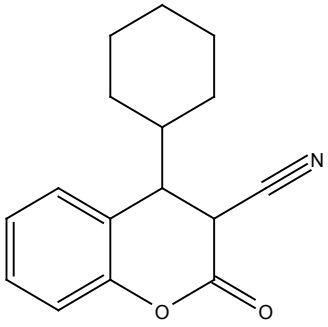
6b

200 MHz ^{1}H NMR



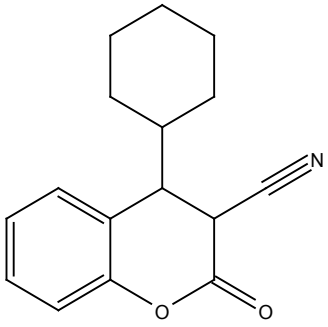
6b

200 MHz ^{13}C NMR



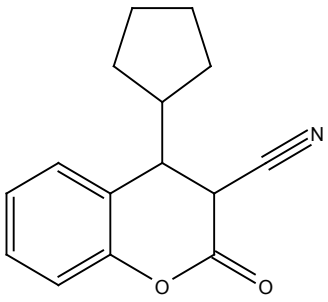
6c

200 MHz ^{1}H NMR



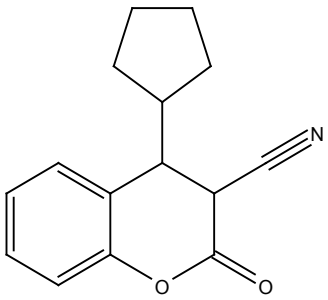
6c

200 MHz ^{13}C NMR



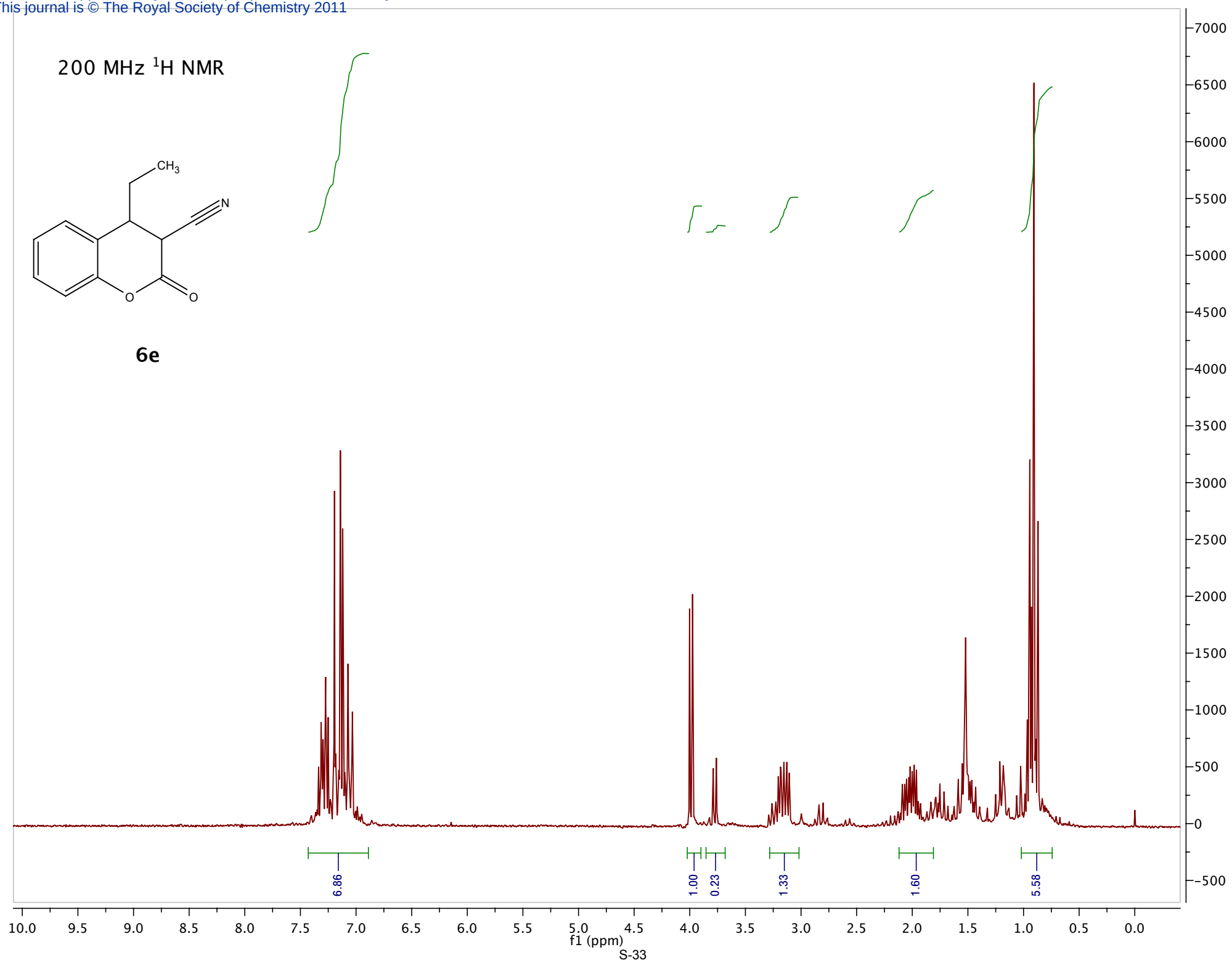
6d

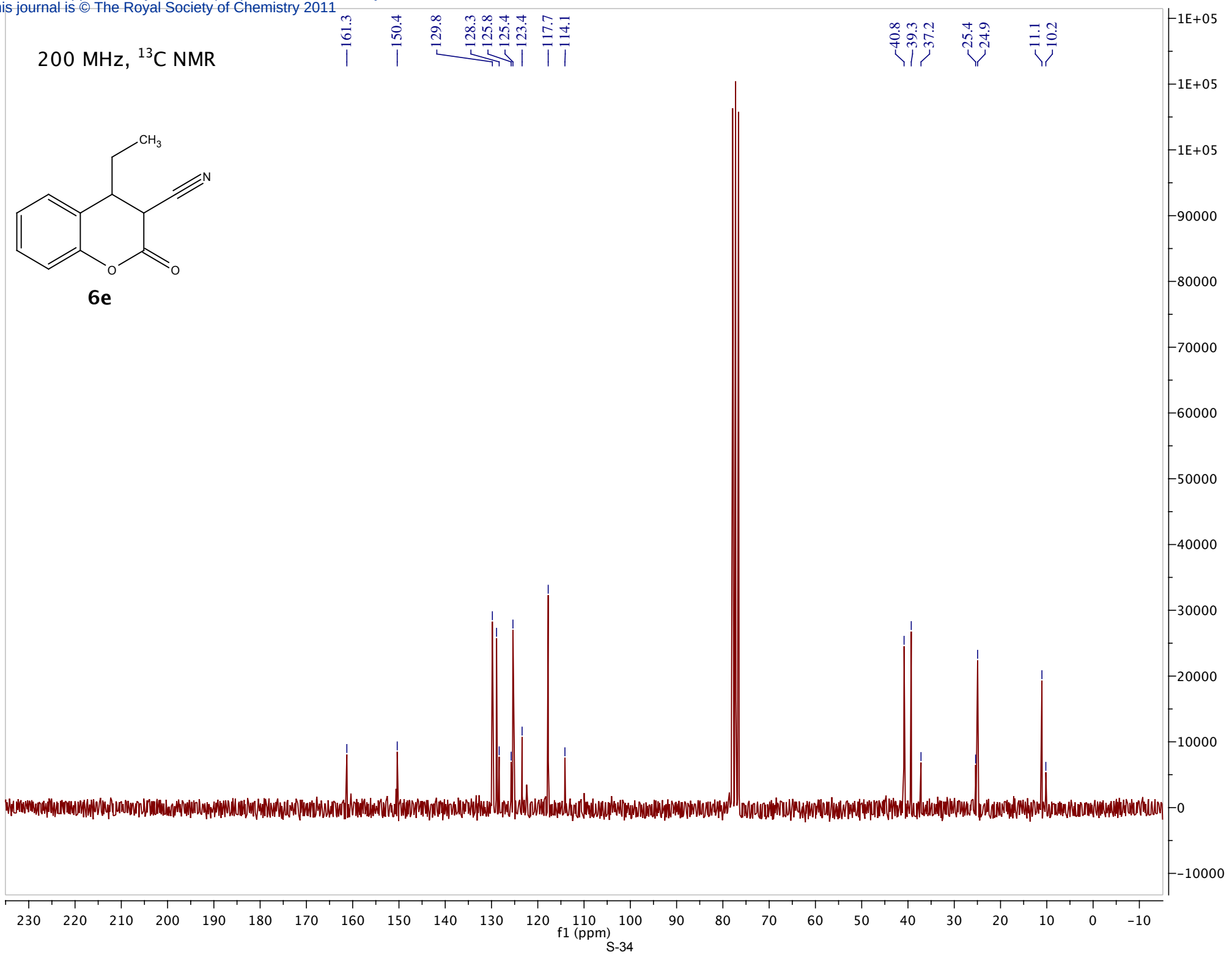
200 MHz ^{1}H NMR

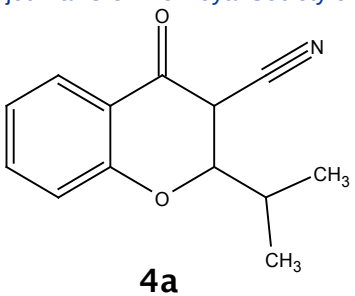


6d

200 MHz ^{13}C NMR







4a

Crude NMR of 1g scale reaction

200 MHz, ^{1}H NMR