

Atropisomerism in 3-arylthiazolidine-2-thiones. A combined Dynamic NMR and Dynamic HPLC Study.

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SUPPORTING INFORMATION

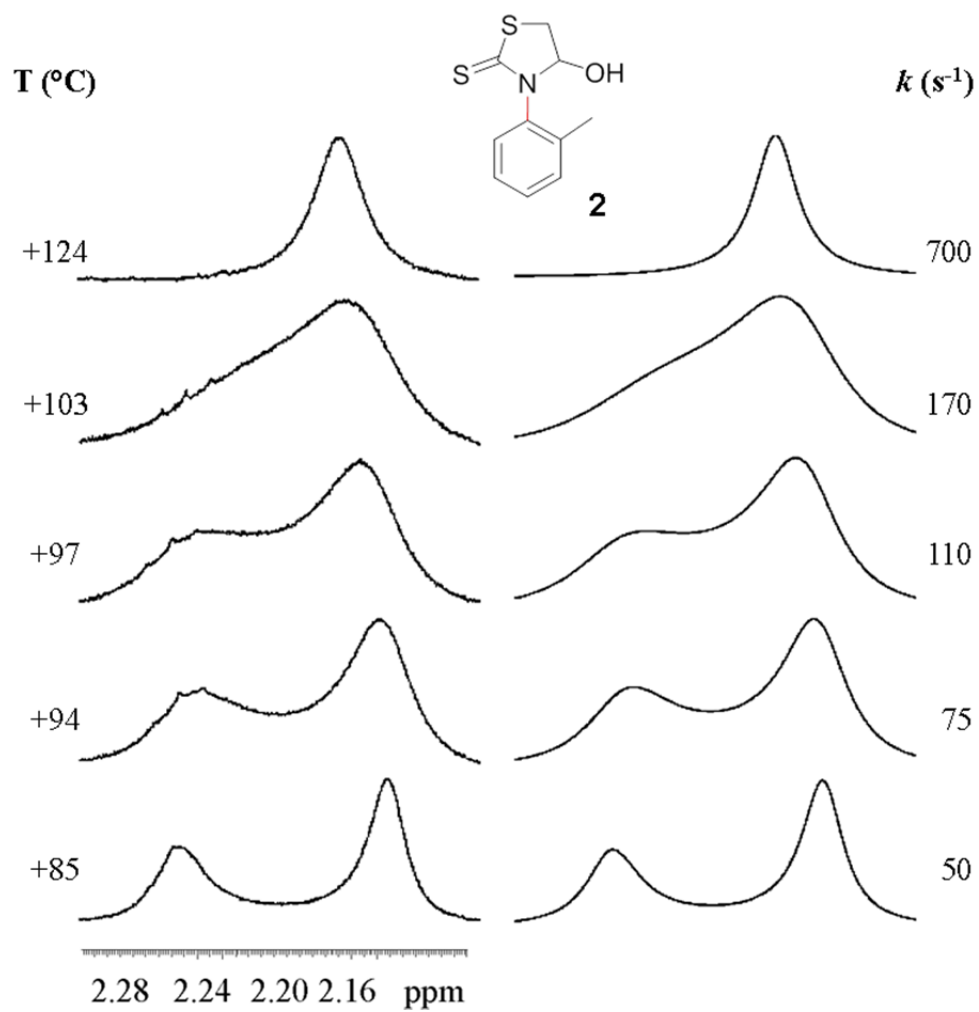


Figure S1. Left: ^1H methyl signals at different temperatures of compound **2** (^1H -NMR 600 MHz in DMSO). Right: line shape simulation obtained with the rate constants reported (from the less stable to the more stable conformation).

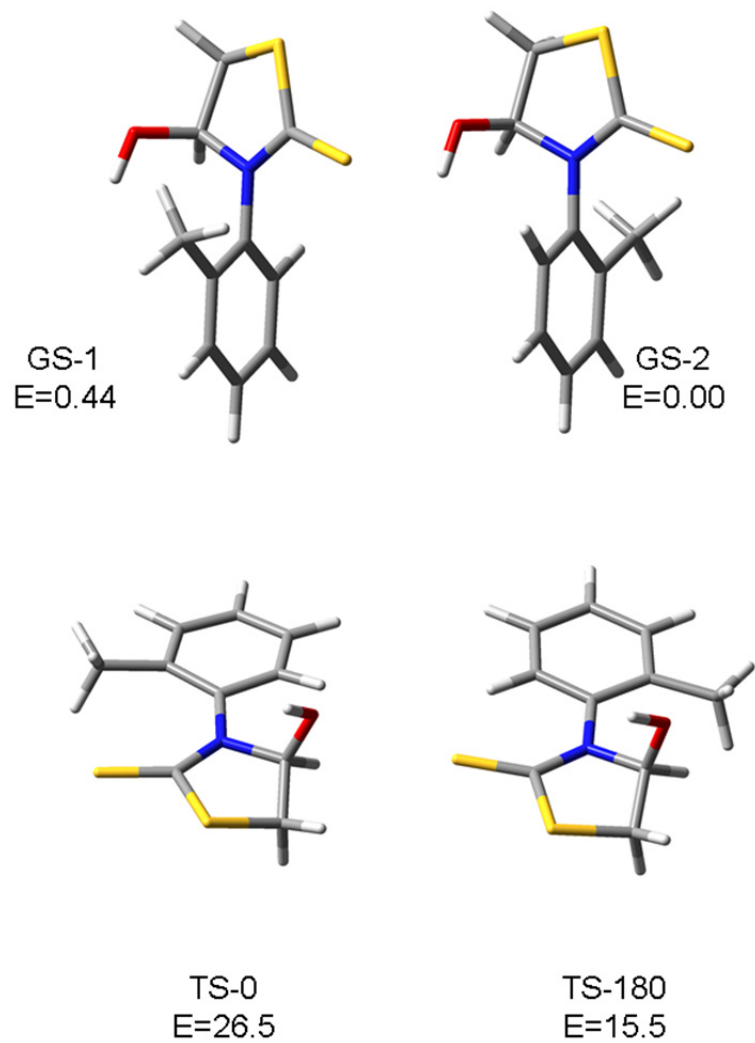


Figure S2. Calculated ground state and transition states for aryl rotation in compound **2**. Calculation at the B3LYP/6-31++G(d,p), energies in kcal/mol.

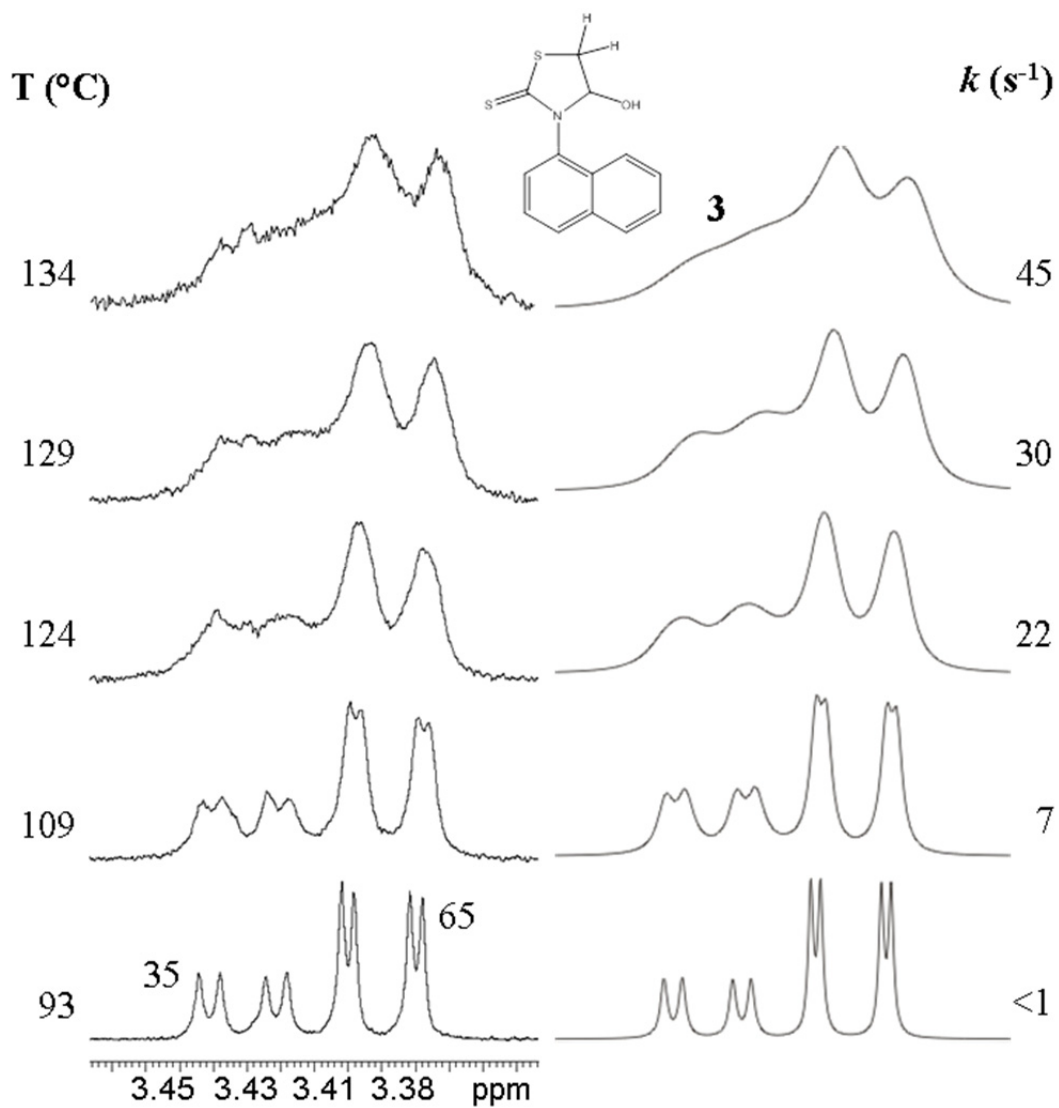


Figure S3. VT-NMR of compound **3**. On the left the experimental spectra (^1H NMR 600 MHz in DMSO- d_6). On the right the lineshape simulations with the relative rate constants (from the less stable to the more stable conformation).

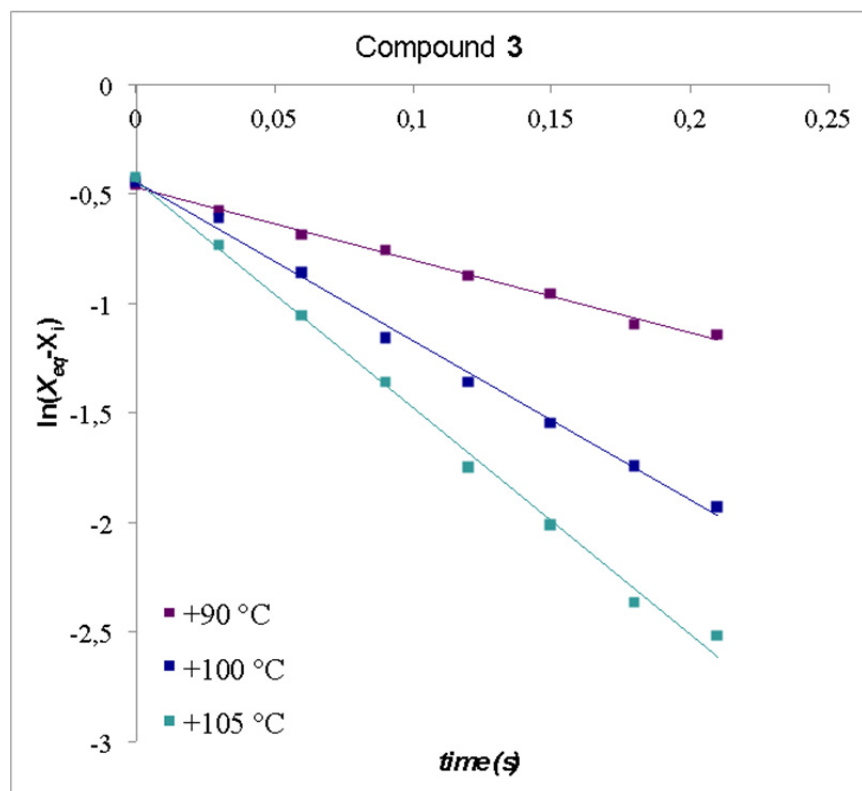
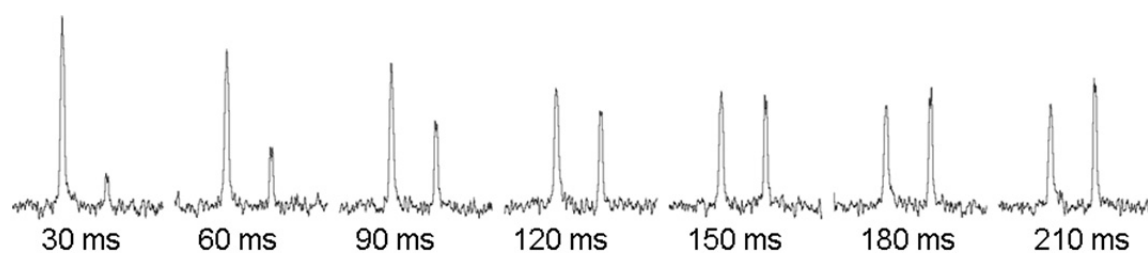


Figure S4. Kinetic study by 1D-EXSY of compound **3** at different temperatures. NMR spectra at top are relative to +100 °C. The signal is that of the stereogenic CH.

Table S1. Free energy of interconversion ΔG^\ddagger of compound **3** obtained at each temperature.

<i>Temperature (°C)</i>	<i>k₁ (s⁻¹)</i>	<i>ΔG[‡] (kcal/mol)</i>
+90	1.91	21.0
+100	4.05	21.1
+105	5.42	21.2

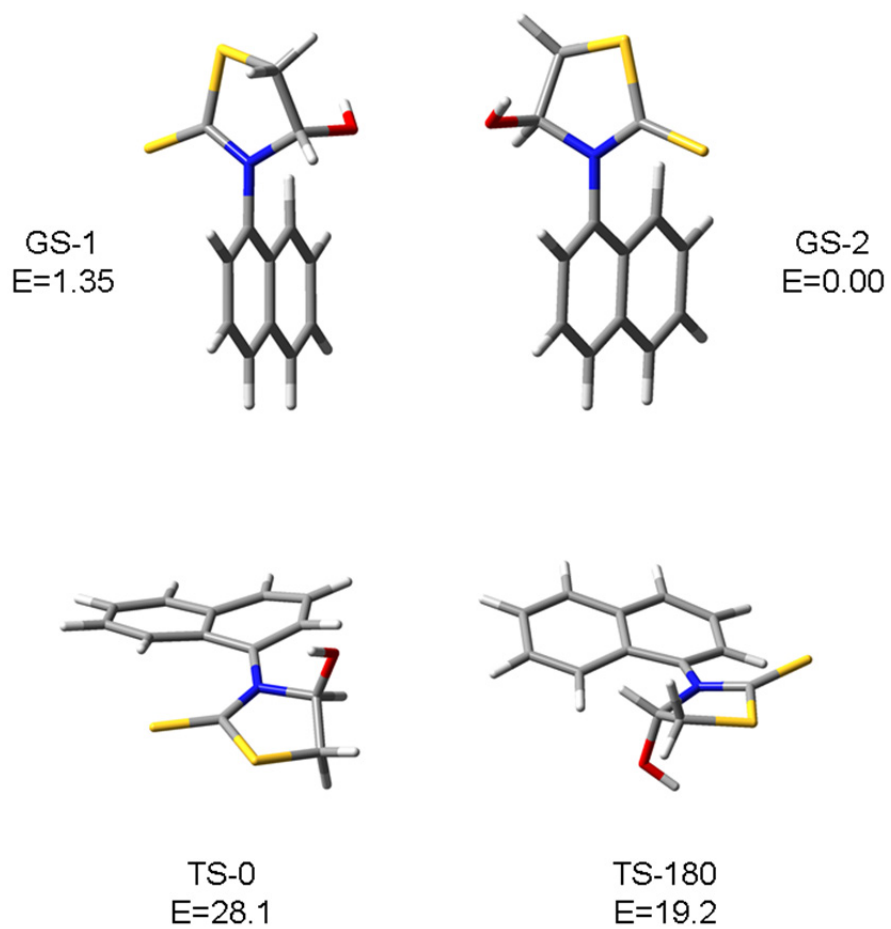


Figure S5. Calculated ground state and transition states for aryl rotation in compound **3**. Calculation at the B3LYP/6-31++G(d,p), energies in kcal/mol.

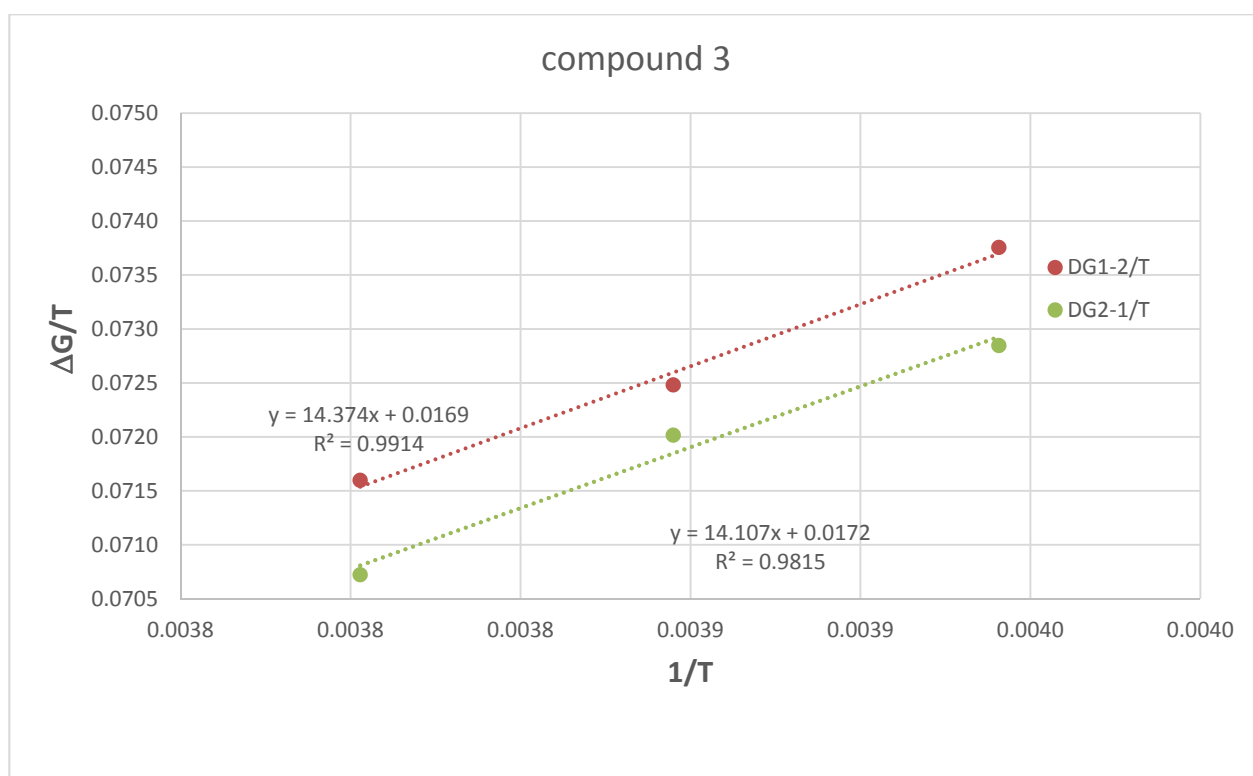


Figure S6. Van't Hoff analysis of the free activation energy in function of temperature in compound **3**.

Table S2. Calculated Values of ΔG^\ddagger (kcal/mol) for diastereomerization process in compound **3**.

<i>T</i> (K)	<i>1/T</i>	ΔG_{1-2}	ΔG_{2-1}	<i>T</i> (°C)
263	0,0038	18,83	18,60	-10
258	0,0039	18,70	18,58	-15
253	0,0040	18,66	18,43	-20

$$\frac{\Delta G}{T} = \frac{\Delta H}{T} - \Delta S$$

$$\Delta S_{2-1} = -0.0172 = -17 \text{ u.e.}$$

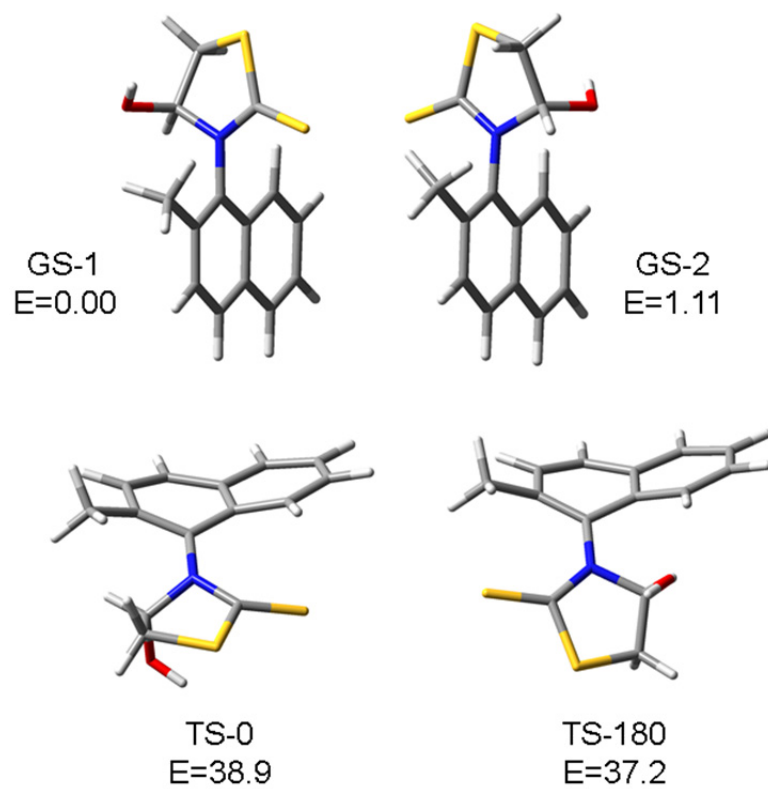


Figure S7. Calculated ground state and transition states for aryl rotation in compound **4**. Calculation at the B3LYP/6-31++G(d,p), energies in kcal/mol.

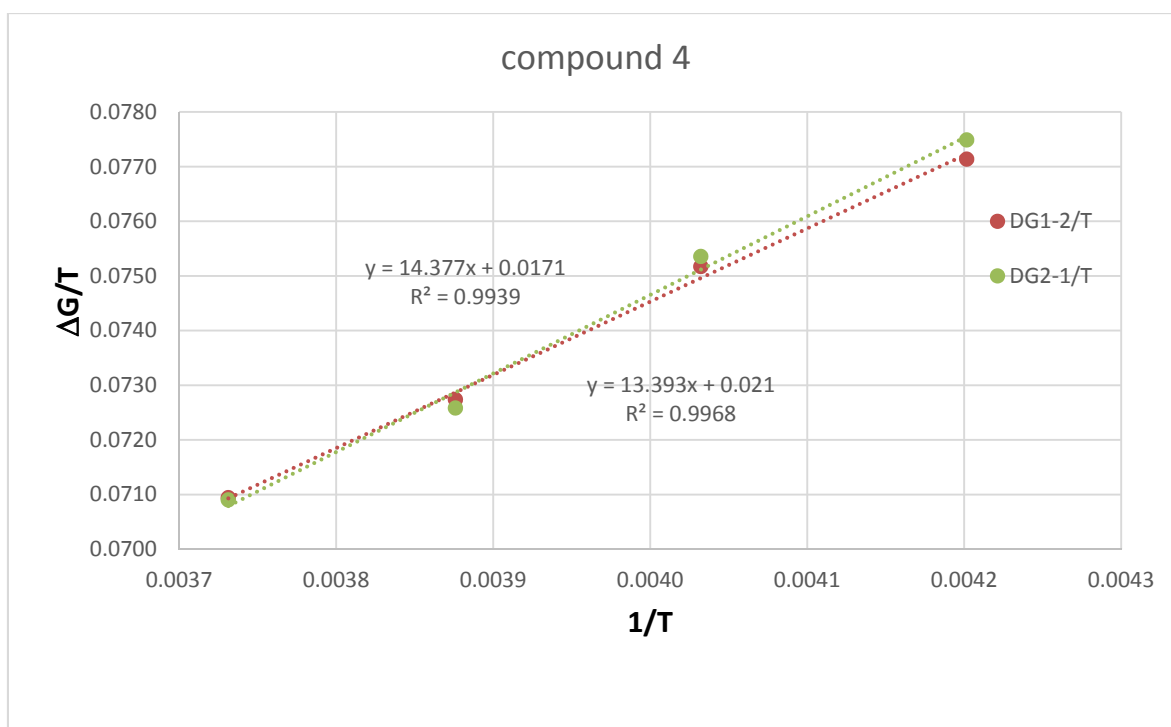


Figure S8. Van't Hoff analysis of free activation energy in function of temperature in compound **4**.

Table S3: Calculated Values of ΔG^\ddagger (kcal/mol) for diastereomerization process in compound **4**.

<i>T</i> (K)	<i>1/T</i>	ΔG_{1-2}	ΔG_{2-1}	<i>T</i> (°C)
288	0,0035	21,503	21,575	+ 15
302	0,0033	21,516	21,579	+ 29
308	0,0032	21,529	21,599	+ 35
313	0,0032	21,670	21,739	+ 40

$$\frac{\Delta G}{T} = \frac{\Delta H}{T} - \Delta S$$

$$\Delta S_{2-1} = -0.017 = -17 \text{ u.e.}$$

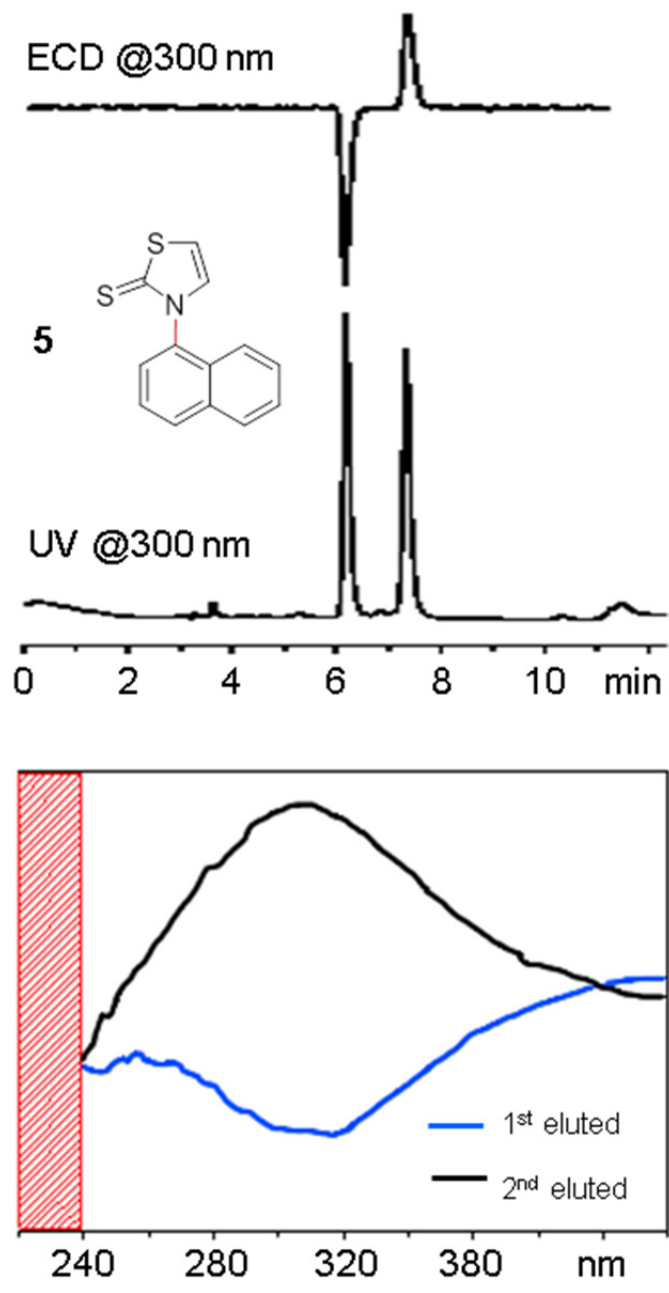


Figure S9. Top: CD and UV chromatograms of compound **5** recorded at +2 °C. Analytical condition: (*R,R*)-Whelk-O1 column, 250 x 4.6 mm I.D. 5 μ m; eluent: hexane/dichloromethane, 70:30 +2% MeOH ; flow rate: 1 mL/min; UV and CD @ 300 nm. Bottom: Stopped-flow On-line ECD spectra of the two conformational enantiomers.

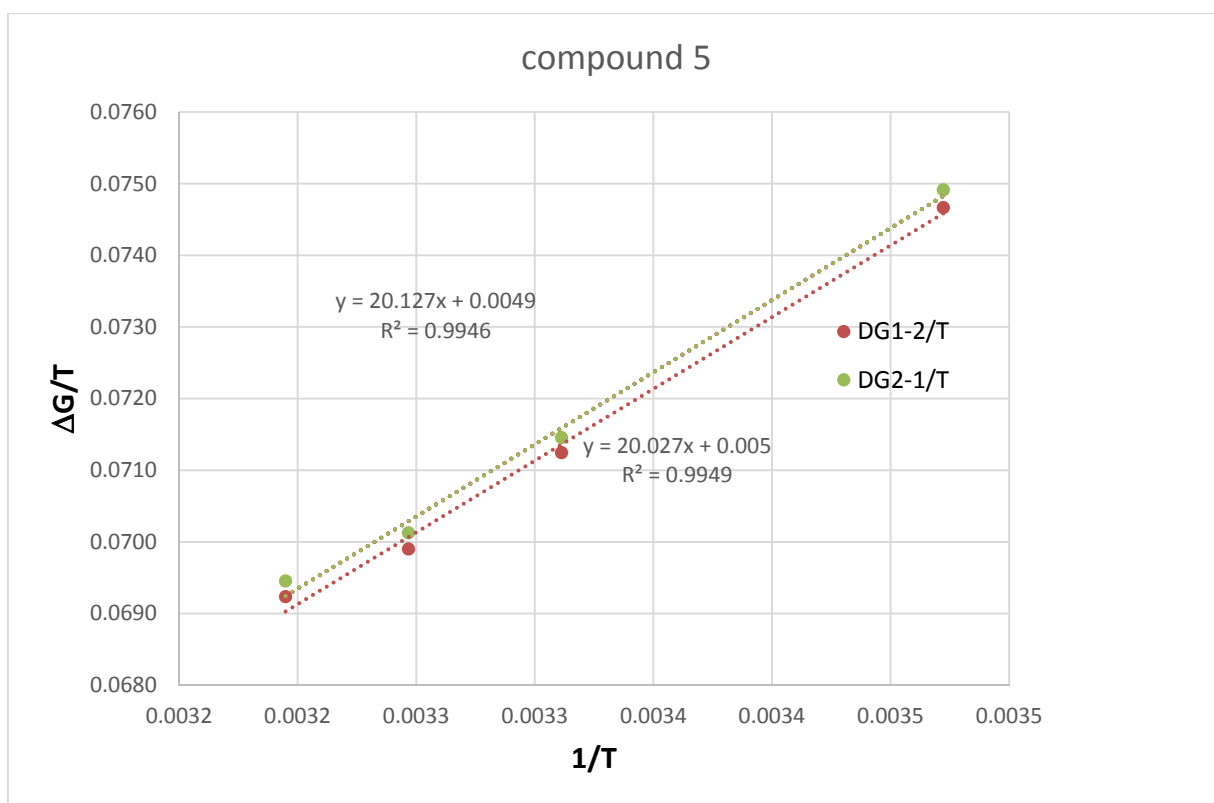


Figure S10. Van't Hoff analysis of free activation energy in function of temperature in compound 5.

Table S4: Calculated Values of ΔG^\ddagger (kcal/mol) for diastereomerization process in compound 5.

T (K)	$1/T$	ΔG_{1-2}	ΔG_{2-1}	T ($^{\circ}\text{C}$)
288	0,0035	21,503	21,575	+15
302	0,0033	21,516	21,579	+29
308	0,0032	21,529	21,599	+35
313	0,0032	21,670	21,739	+40

$$\frac{\Delta G}{T} = \frac{\Delta H}{T} - \Delta S$$

$$\Delta S = -0.0049 = -5 \text{ u.e.}$$

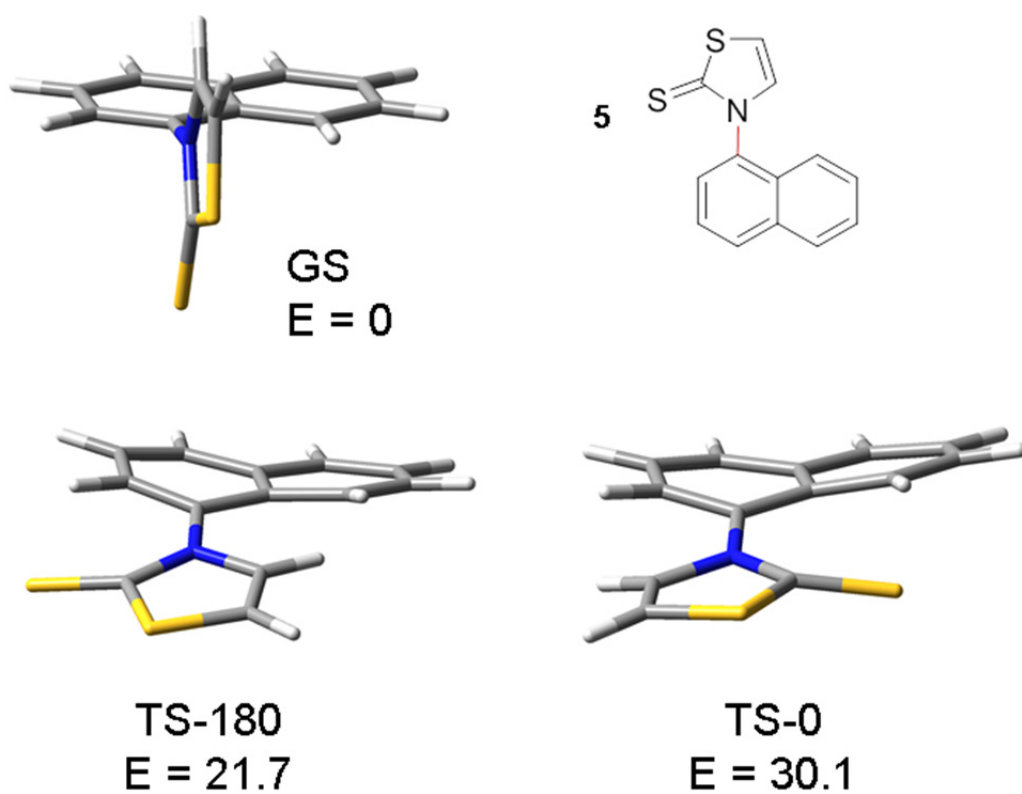


Figure S11. Calculated ground state and transition states for aryl rotation in compound **5**. Calculation at the B3LYP/6-31++G(d,p), energies in kcal/mol.

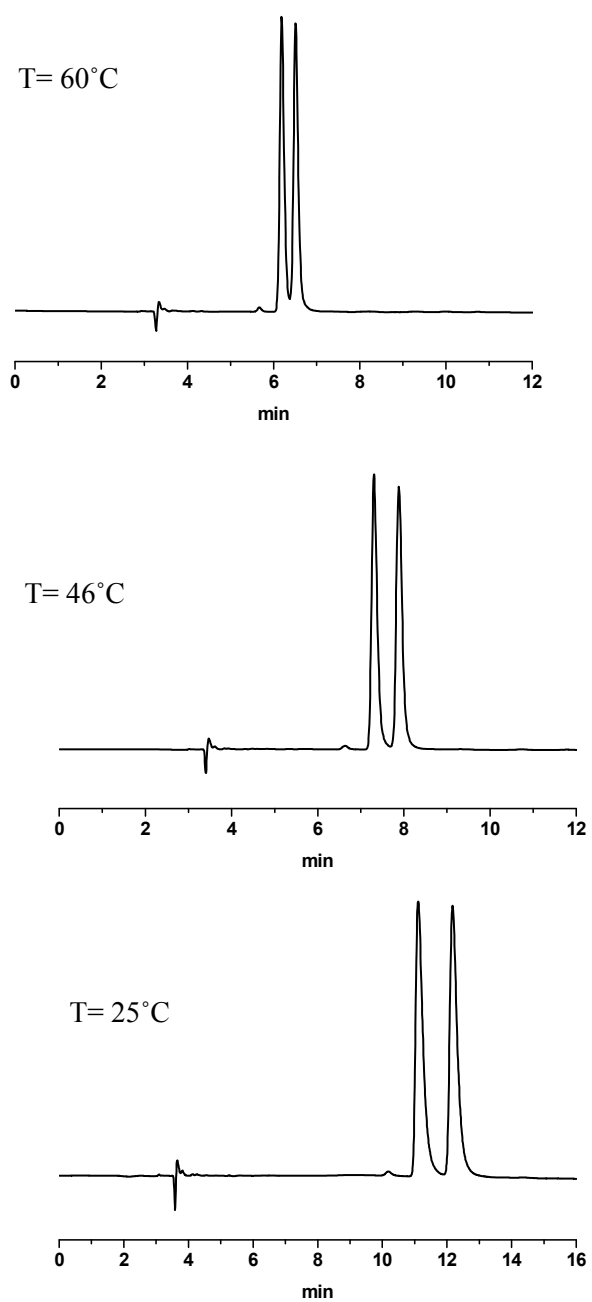


Figure S12. Experimental chromatographic profiles of the compound **6**, at different temperatures. Analytical conditions: Column: Chiralpak IB 250 x 4.6 mm *I.D.* 5 μm ; Mobile phase hexane/IPA, 80:20; Flow: 1 mL/min; Detector: UV@ 254 nm.

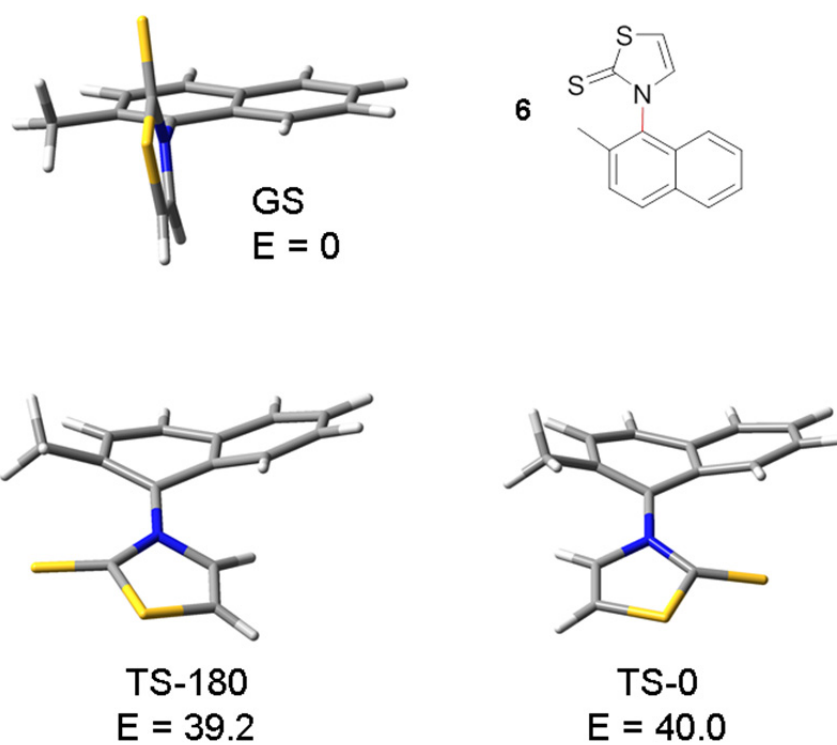
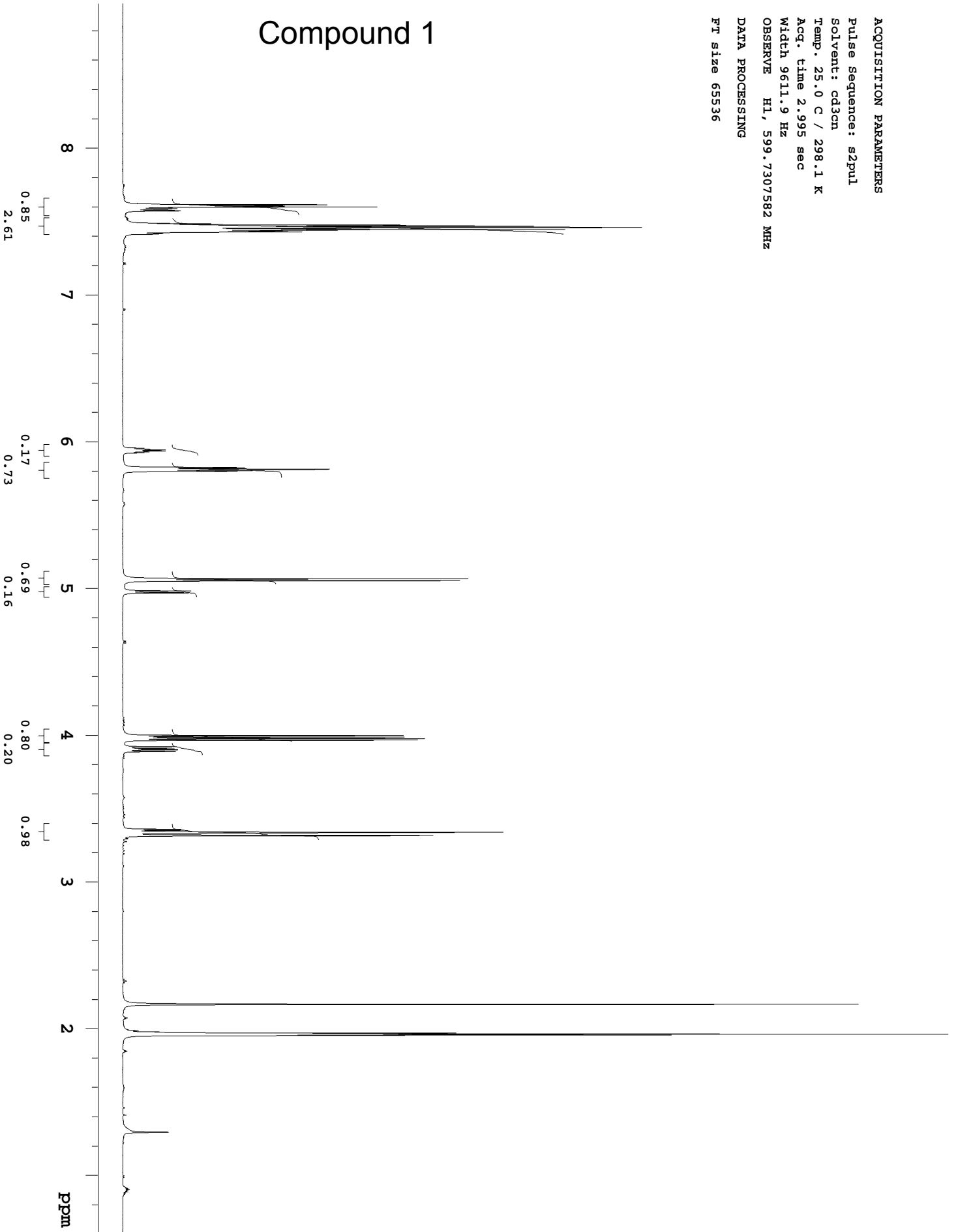


Figure S13. Calculated ground state and transition states for aryl rotation in compound **6**. Calculation at the B3LYP/6-31++G(d,p), energies in kcal/mol.

ACQUISITION PARAMETERS

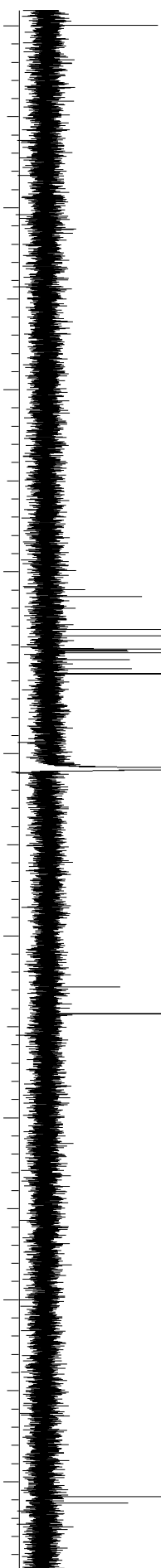
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DATA PROCESSING
F1 size 65536

Compound 1



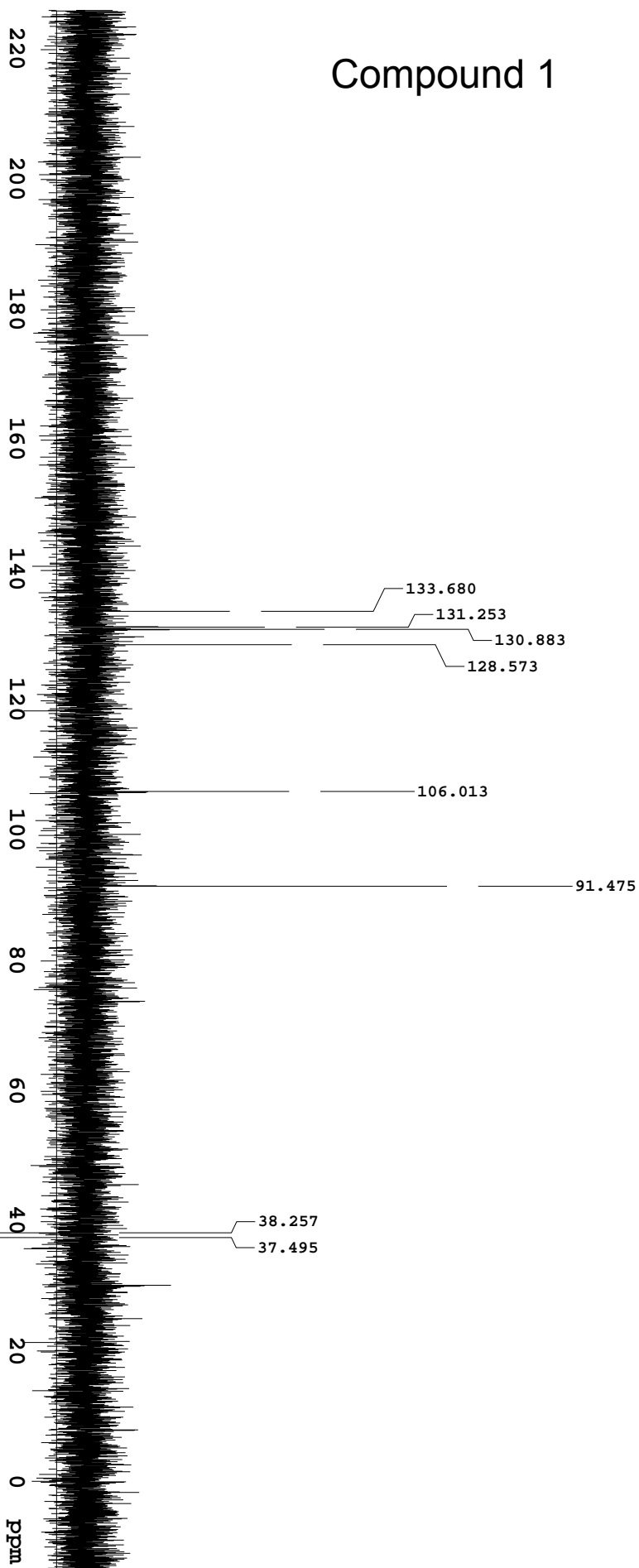
Compound 1

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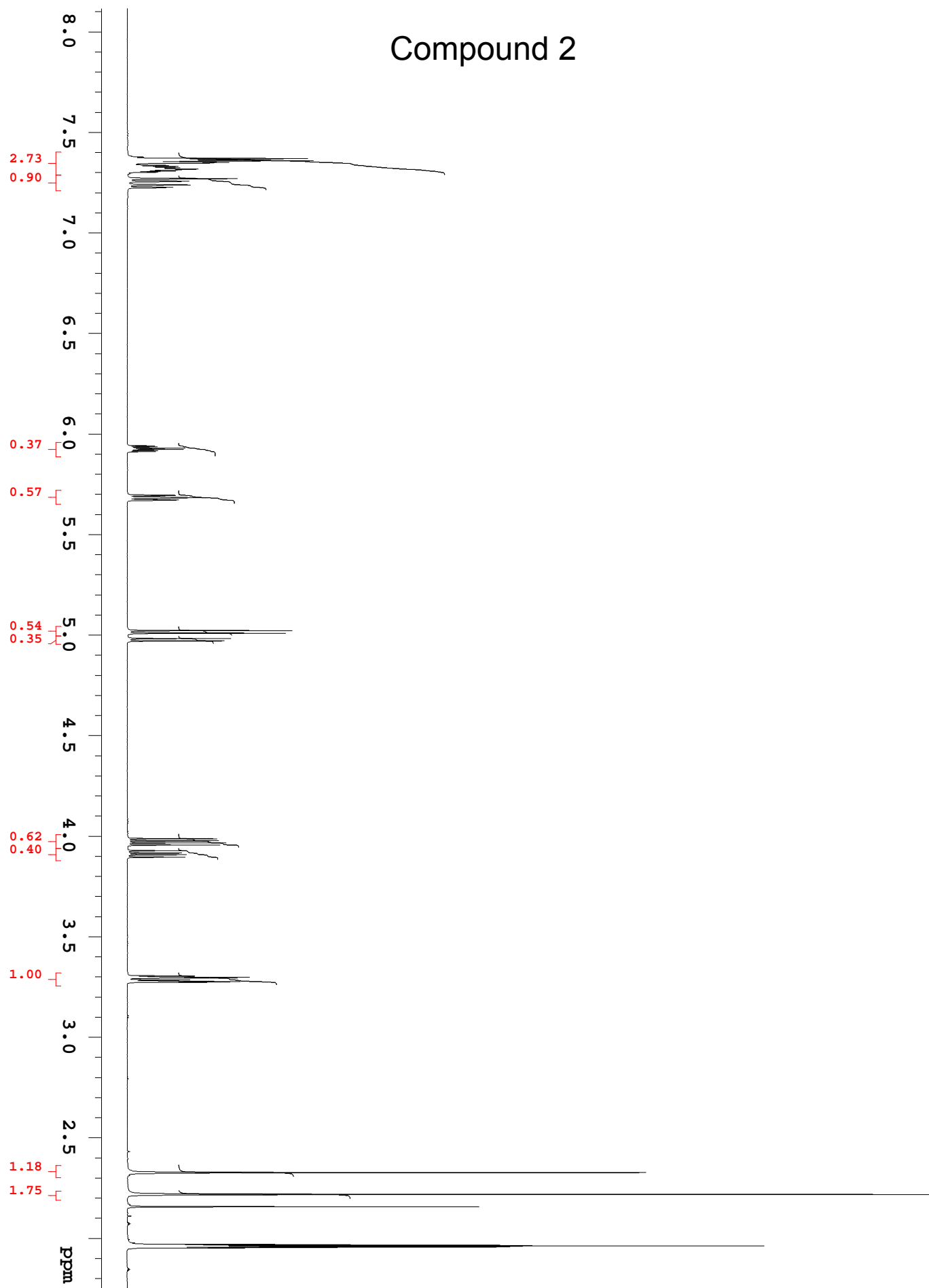


INDEX	FREQUENCY	PPM	HEIGHT
1	30165.6	200.034	17.1
2	20695.9	137.239	14.6
3	20153.8	133.644	79.0
4	20043.9	132.915	19.9
5	19830.2	131.498	72.0
6	19806.0	131.337	12.2
7	19793.8	131.257	12.4
8	19762.9	131.052	71.4
9	19654.7	130.334	12.6
10	19497.9	129.294	13.0
11	19417.8	128.763	77.4
12	17839.9	118.300	941.5
13	14226.4	94.338	11.1
14	13783.6	91.402	67.7
15	5779.2	38.323	73.8
16	5674.8	37.631	12.3

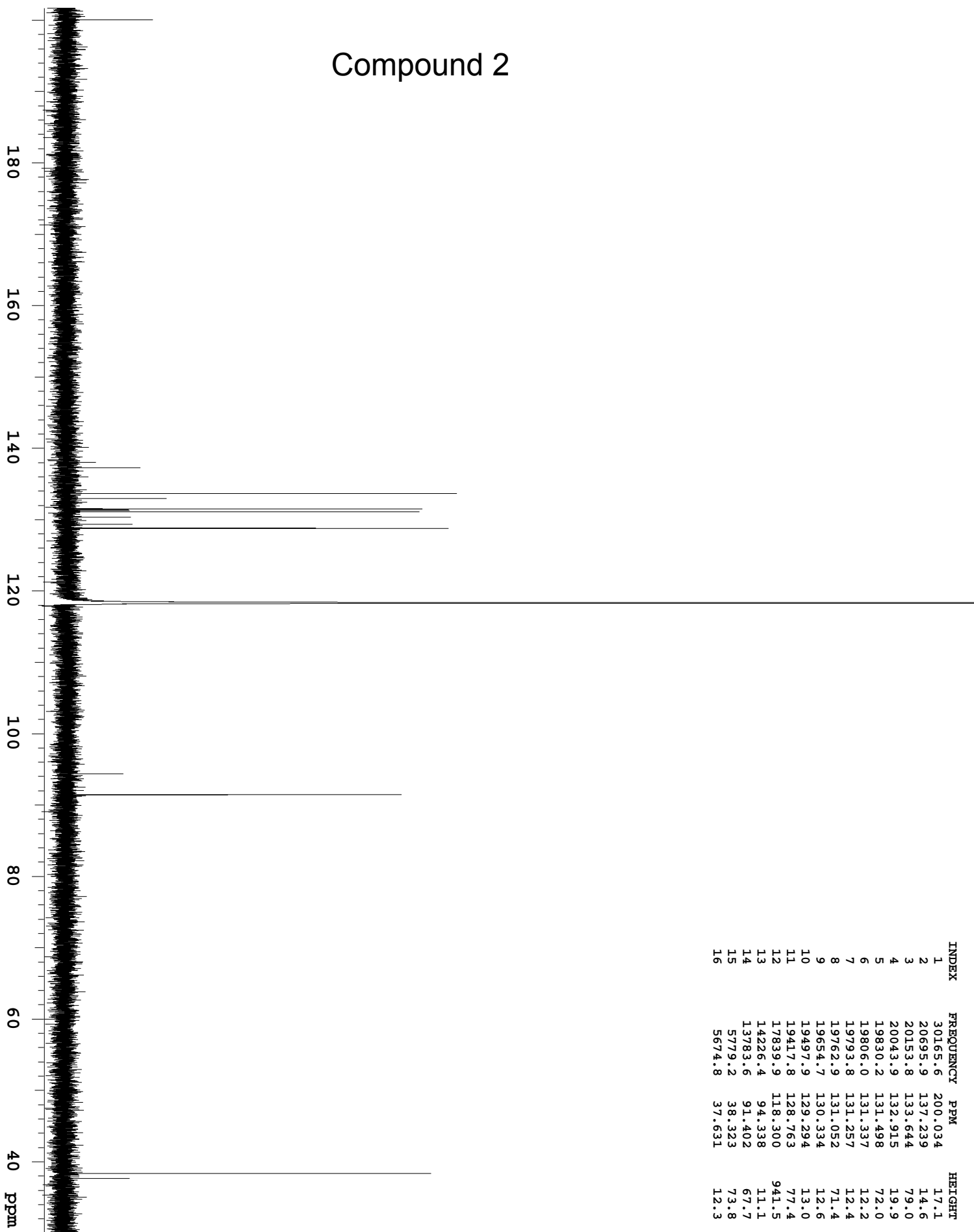
Compound 1



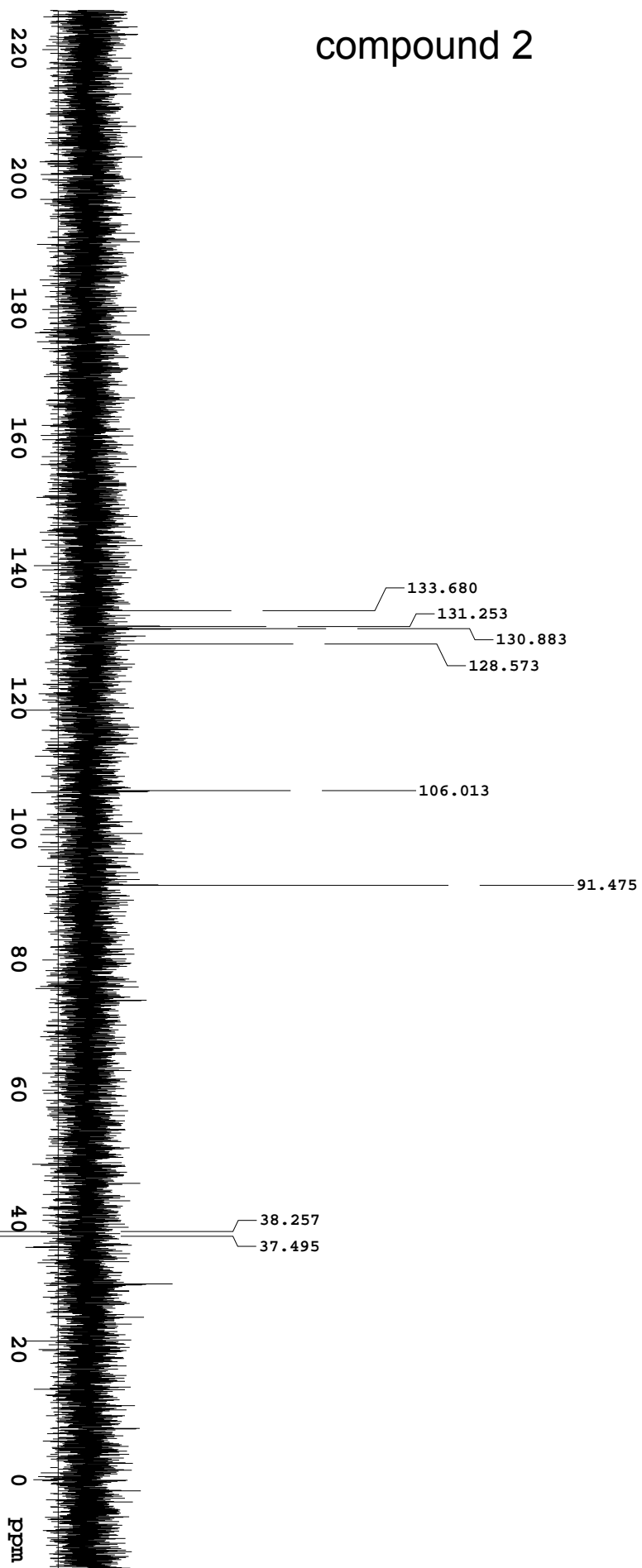
Compound 2



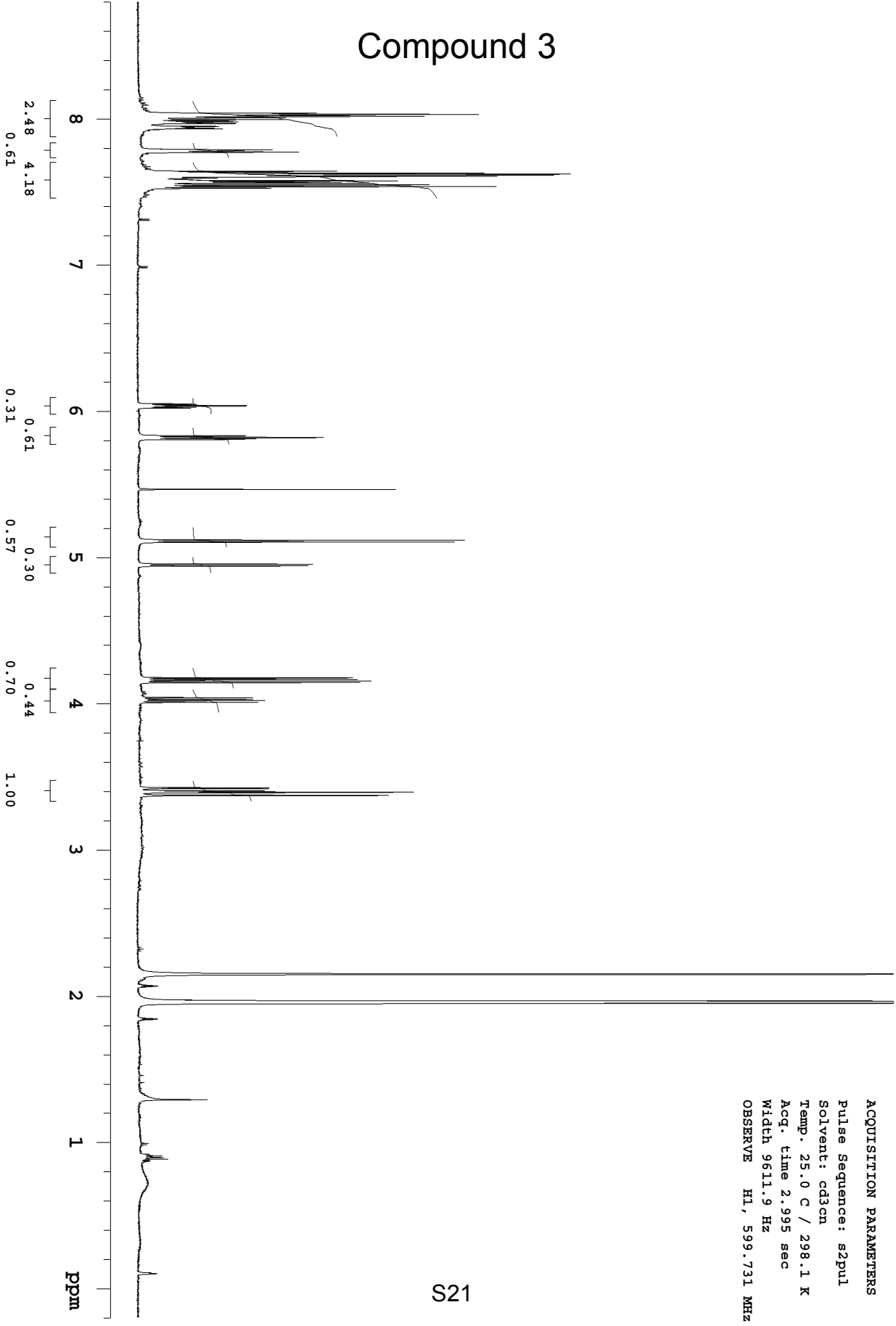
Compound 2



compound 2



Compound 3



ACQUISITION PARAMETERS
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Solvent: cd3cn
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Width 9611.9 Hz
OBSERVE H1, 599.731 MHz

ACQUISITION PARAMETERS

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DECOUPLE H1, 599.734 MHz
Power 45 dB
continuously on
WALTZ-16 modulated

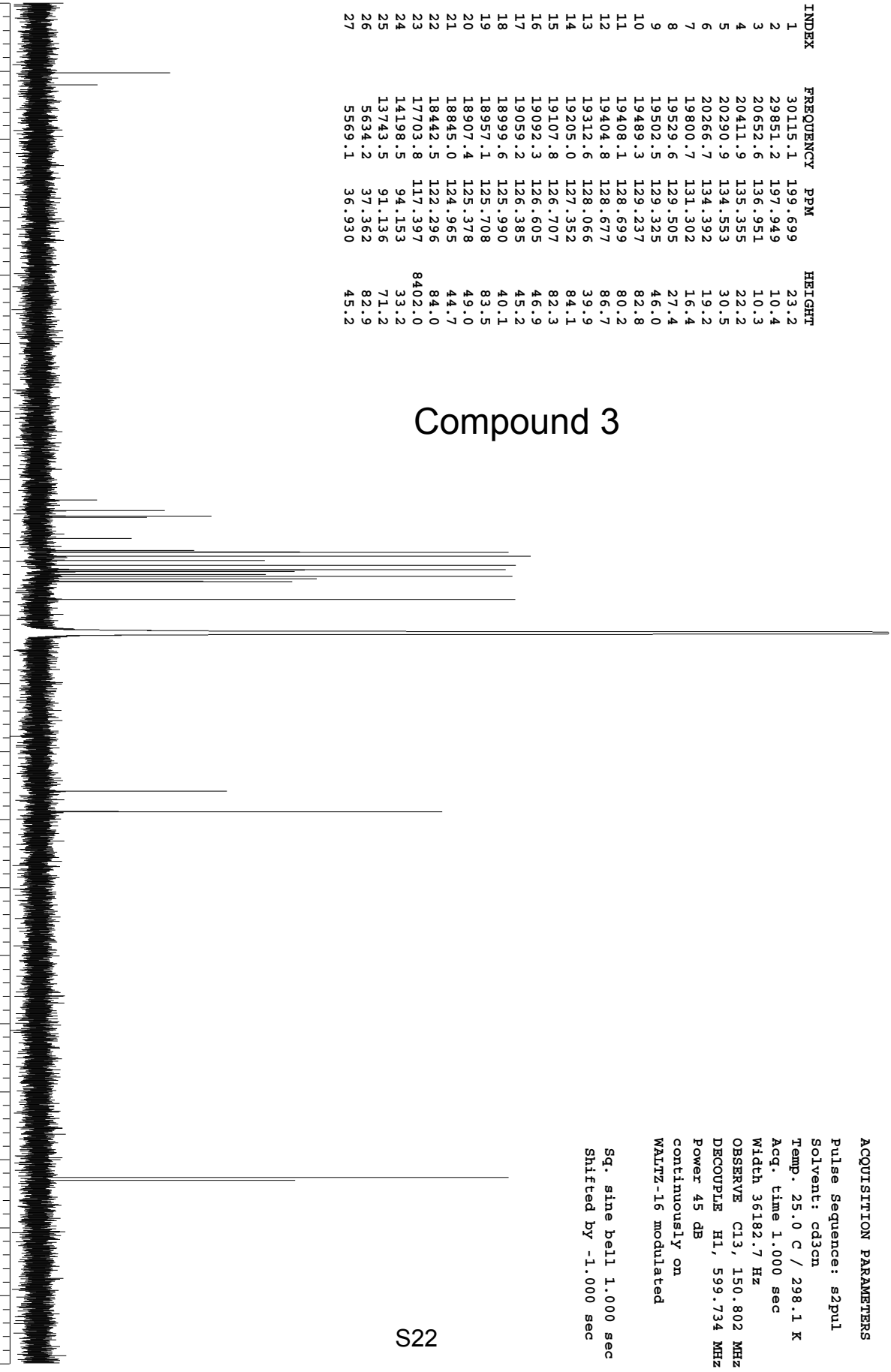
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Compound 3

INDEX	FREQUENCY	PPM	HEIGHT
1	30115.1	199.699	23.2
2	29851.2	197.949	10.4
3	20652.6	136.951	10.3
4	20411.9	135.355	22.2
5	20290.9	134.553	30.5
6	20266.7	134.392	19.2
7	19800.7	131.302	16.4
8	19529.6	129.505	27.4
9	19502.5	129.325	46.0
10	19489.3	129.237	82.8
11	19408.1	128.699	80.2
12	19404.8	128.677	86.7
13	19312.6	128.066	39.9
14	19205.0	127.352	84.1
15	19107.8	126.707	82.3
16	19092.3	126.605	46.9
17	19059.2	126.385	45.2
18	18999.6	125.990	40.1
19	18957.1	125.708	83.5
20	18907.4	125.378	49.0
21	18845.0	124.965	44.7
22	18442.5	122.296	84.0
23	17703.8	117.397	8402.0
24	14198.5	94.153	33.2
25	13743.5	91.136	71.2
26	5634.2	37.362	82.9
27	5569.1	36.930	45.2

S22

200 180 160 140 120 100 80 60 40 ppm



ACQUISITION PARAMETERS

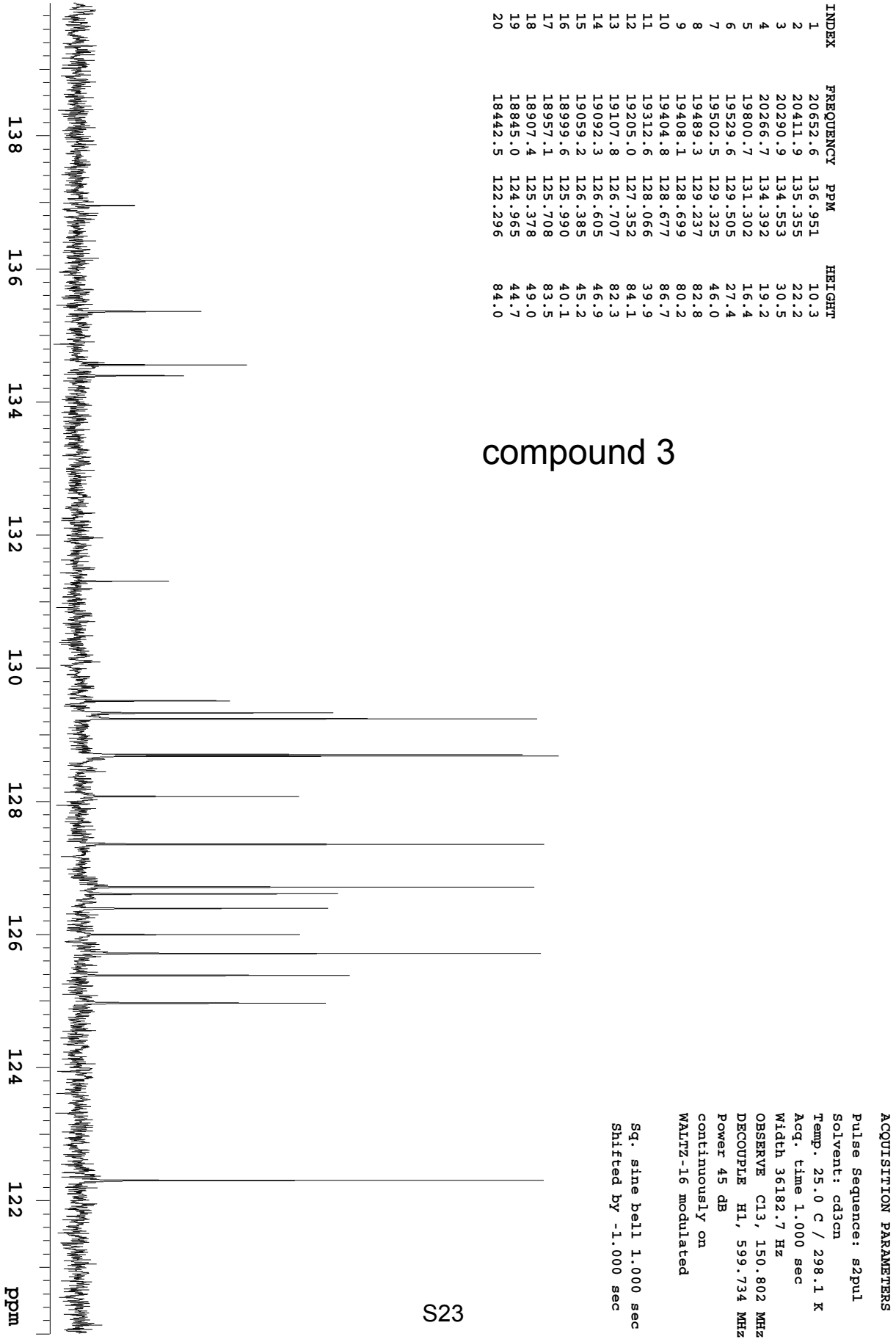
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DECOUPLE H1, 599.734 MHz
Power 45 dB
continuously on
WALTZ-16 modulated

Sq. sine bell 1.000 sec
Shifted by -1.000 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	20652.6	136.951	10.3
2	20411.9	135.355	22.2
3	20290.9	134.553	30.5
4	20266.7	134.392	19.2
5	19800.7	131.302	16.4
6	19529.6	129.505	27.4
7	19502.5	129.325	46.0
8	19489.3	129.237	82.8
9	19408.1	128.699	80.2
10	19404.8	128.677	86.7
11	19312.6	128.066	39.9
12	19205.0	127.352	84.1
13	19107.8	126.707	82.3
14	19092.3	126.605	46.9
15	19059.2	126.385	45.2
16	18999.6	125.990	40.1
17	18957.1	125.708	83.5
18	18907.4	125.378	49.0
19	18845.0	124.965	44.7
20	18442.5	122.296	84.0

compound 3

S23

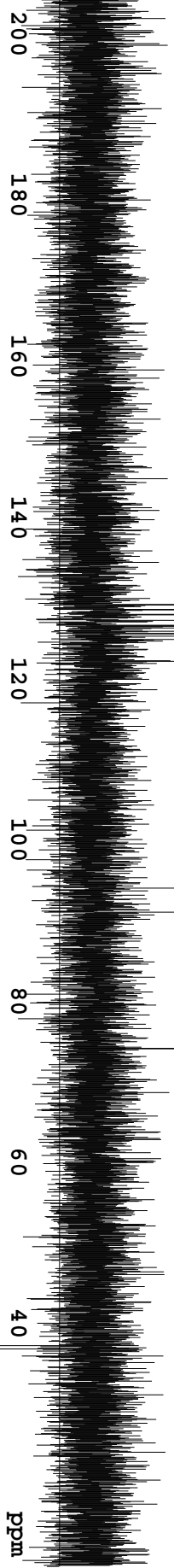


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DECOUPLE H1, 599.734 MHz
power 45 dB
on during acquisition
off during delay
WALTZ-16 modulated

Line broadening 1.0 Hz
Sq. sine bell 1.000 sec
Shifted by -1.000 sec

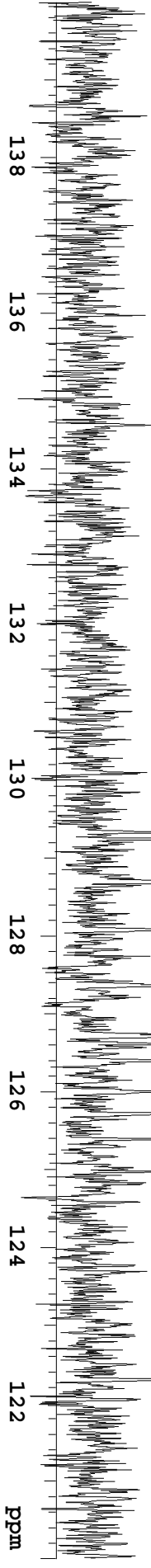
compound 3

INDEX	FREQUENCY	PPM	HEIGHT
1	19503.1	129.329	27.4
2	19489.8	129.241	63.1
3	19408.1	128.699	52.7
4	19405.4	128.681	67.8
5	19313.2	128.069	37.8
6	19205.5	127.355	60.3
7	19108.3	126.711	63.4
8	19092.9	126.609	34.4
9	19059.7	126.389	40.3
10	19000.1	125.993	39.2
11	18957.6	125.712	65.2
12	18907.9	125.382	35.6
13	18845.5	124.968	35.5
14	18443.0	122.299	58.5
15	14198.5	94.153	26.8
16	13743.5	91.136	55.3
17	5634.8	37.365	-63.2
18	5569.6	36.933	-35.8



INDEX	FREQUENCY	PPM	HEIGHT
1	19503.1	129.329	30.7
2	19489.8	129.241	63.7
3	19408.7	128.703	65.3
4	19405.4	128.681	67.2
5	19313.7	128.073	40.1
6	19205.5	127.355	60.6
7	19108.3	126.711	69.4
8	19092.9	126.609	36.1
9	19059.7	126.389	39.0
10	19000.7	125.997	39.5
11	18957.6	125.712	64.5
12	18907.9	125.382	35.1
13	18845.5	124.968	35.9
14	18443.0	122.299	60.9

compound 3



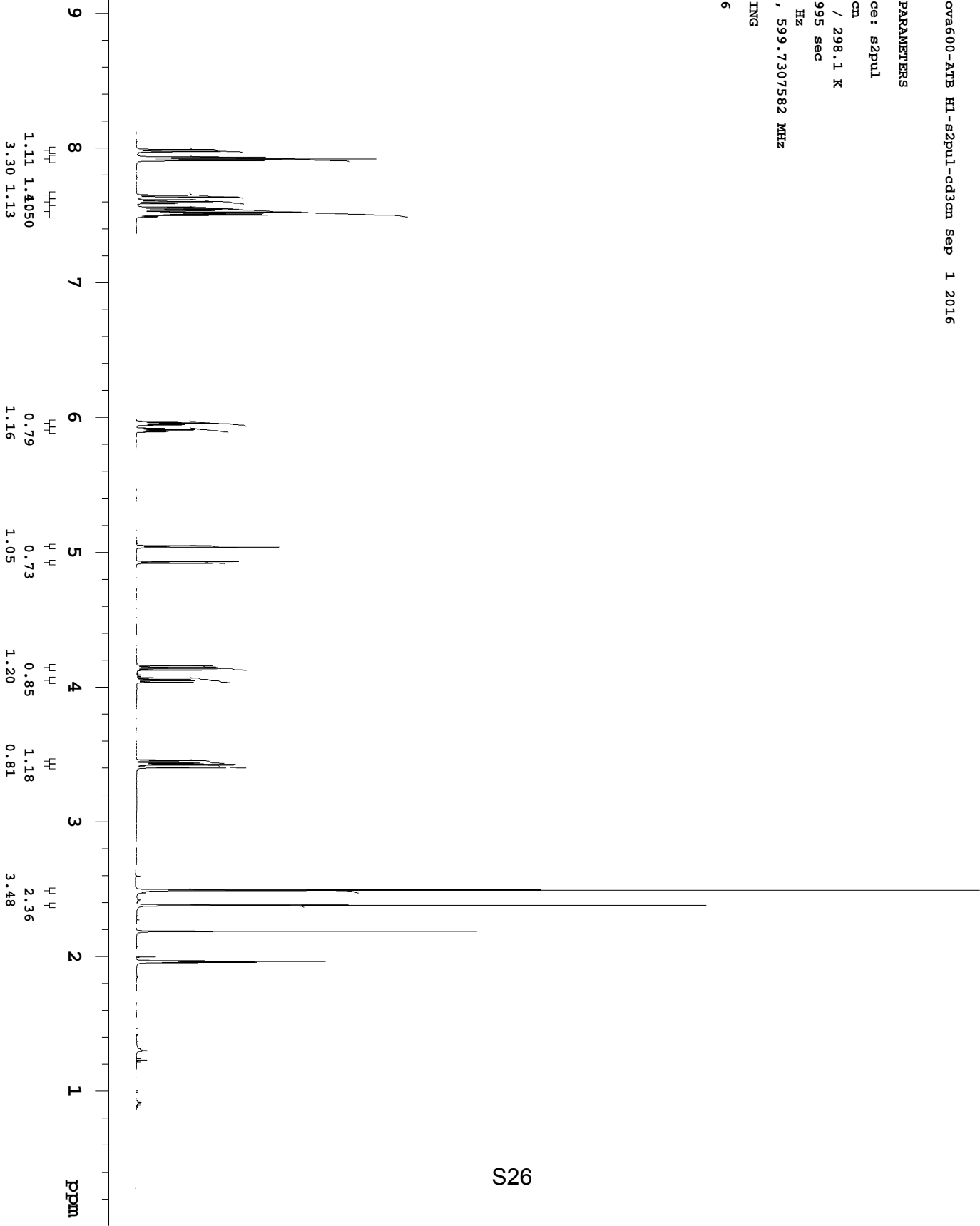
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 Sq. sine bell 1.000 sec
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ACQUISITION PARAMETERS

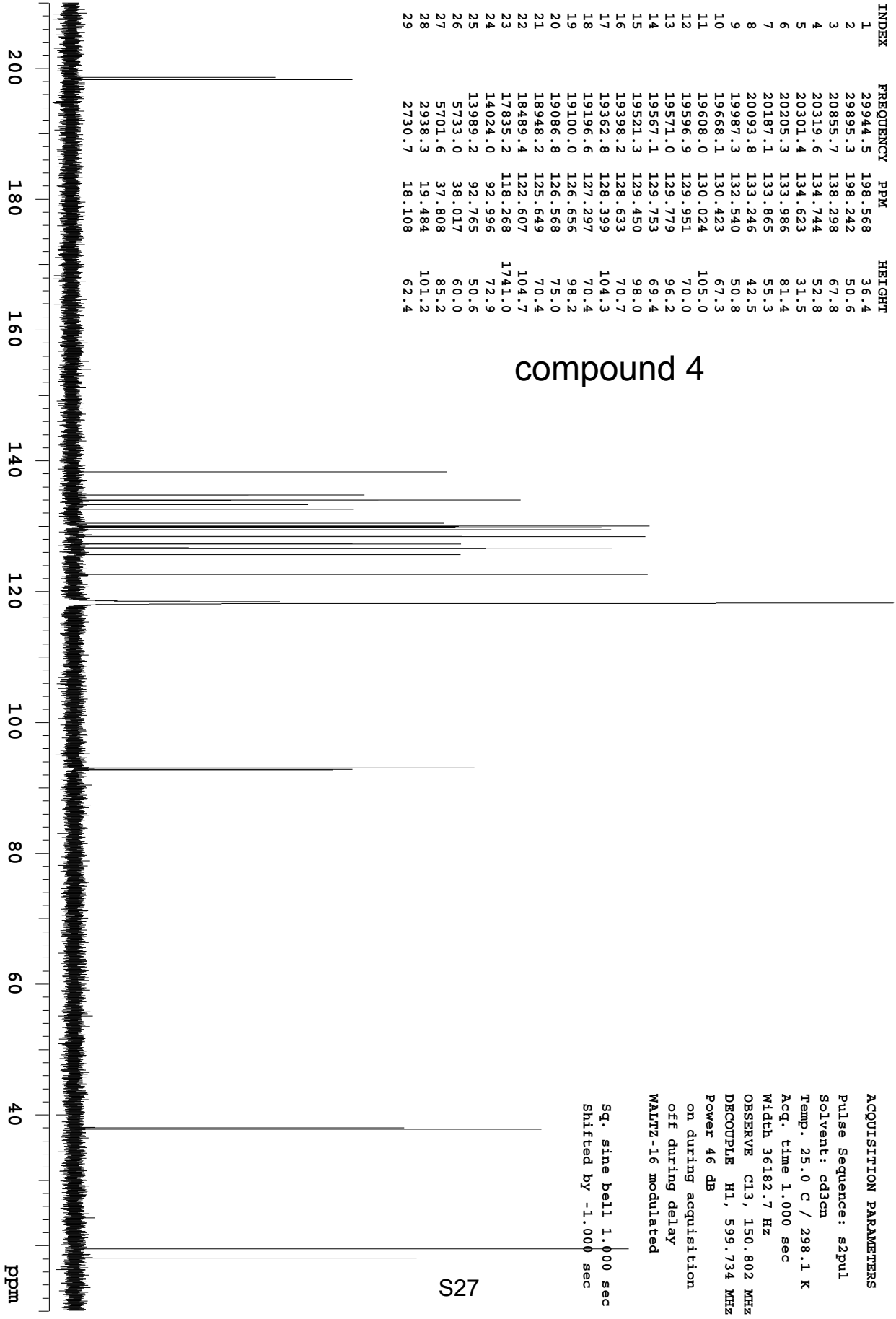
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Solvent: cd3cn
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Width 9611.9 Hz
OBSERVE H1, 599.7307582 MHz
DATA PROCESSING
F1 size 65536

compound 4



INDEX	FREQUENCY	PPM	HEIGHT
1	29944.5	198.568	36.4
2	29895.3	198.242	50.6
3	20855.7	138.298	67.8
4	20319.6	134.744	52.8
5	20301.4	134.623	31.5
6	20205.3	133.986	81.4
7	20187.1	133.865	55.3
8	20093.8	133.246	42.5
9	19987.3	132.540	50.8
10	19668.1	130.423	67.3
11	19608.0	130.024	105.0
12	19596.9	129.951	70.0
13	19571.0	129.779	96.2
14	19567.1	129.753	69.4
15	19521.3	129.450	98.0
16	19398.2	128.633	70.7
17	19362.8	128.399	104.3
18	19196.6	127.297	70.4
19	19100.0	126.656	98.2
20	19086.8	126.568	75.0
21	18948.2	125.649	70.4
22	18489.4	122.607	104.7
23	17835.2	118.268	1741.0
24	14024.0	92.996	72.9
25	13989.2	92.765	50.6
26	5733.0	38.017	60.0
27	5701.6	37.808	85.2
28	2938.3	19.484	101.2
29	2730.7	18.108	62.4

compound 4



ACQUISITION PARAMETERS
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DECOUPLE H1, 599.734 MHz
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on during acquisition
off during delay
WALTZ-16 modulated

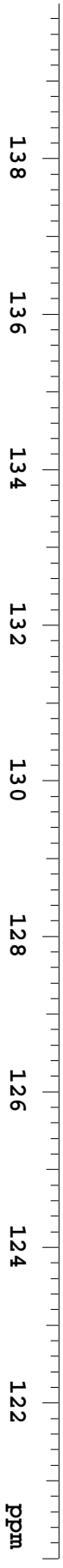
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S27

INDEX	FREQUENCY	PPM	HEIGHT
1	20855.7	138.298	67.8
2	20319.6	134.744	52.8
3	20301.4	134.623	31.5
4	20205.3	133.986	81.4
5	20187.1	133.865	55.3
6	20093.8	133.246	42.5
7	19987.3	132.540	50.8
8	19668.1	130.423	67.3
9	19608.0	130.024	105.0
10	19596.9	129.951	70.0
11	19571.0	129.779	96.2
12	19567.1	129.753	69.4
13	19521.3	129.450	98.0
14	19398.2	128.633	70.7
15	19362.8	128.399	104.3
16	19196.6	127.297	70.4
17	19100.0	126.656	98.2
18	19086.8	126.568	75.0
19	18948.2	125.649	70.4
20	18489.4	122.607	104.7

compound 4

ACQUISITION PARAMETERS
Pulse Sequence: s2pul
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OBSERVE C13, 150.802 MHz
DECOUPLE H1, 599.734 MHz
Power 46 dB
on during acquisition
off during delay
WALTZ-16 modulated



INDEX	FREQUENCY	PPM	HEIGHT
1	19608.6	130.028	40.1
2	19597.5	129.955	26.9
3	19571.6	129.783	38.0
4	19568.3	129.761	26.9
5	19521.9	129.454	37.6
6	19398.8	128.637	27.4
7	19363.4	128.403	33.4
8	19197.3	127.301	24.8
9	19101.2	126.664	37.2
10	19087.4	126.572	27.4
11	18948.8	125.653	25.7
12	18490.0	122.611	37.5
13	14024.6	93.000	33.7
14	13989.8	92.769	21.3
15	5733.6	38.021	-33.1
16	5702.2	37.812	-49.6
17	2938.9	19.488	36.1
18	2731.3	18.112	26.3

compound 4



ACQUISITION PARAMETERS
Pulse Sequence: DEPT
Solvent: cd3cn
Temp. 25.0 C / 298.1 K
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Width 36182.7 Hz
OBSERVE C13, 150.802 MHz
DECOUPLE H1, 599.734 MHz
Power 46 dB
off during acquisition
on during delay
WALTZ-16 modulated
Line broadening 1.0 Hz
Sq. sine bell 1.000 sec
Shifted by -1.000 sec

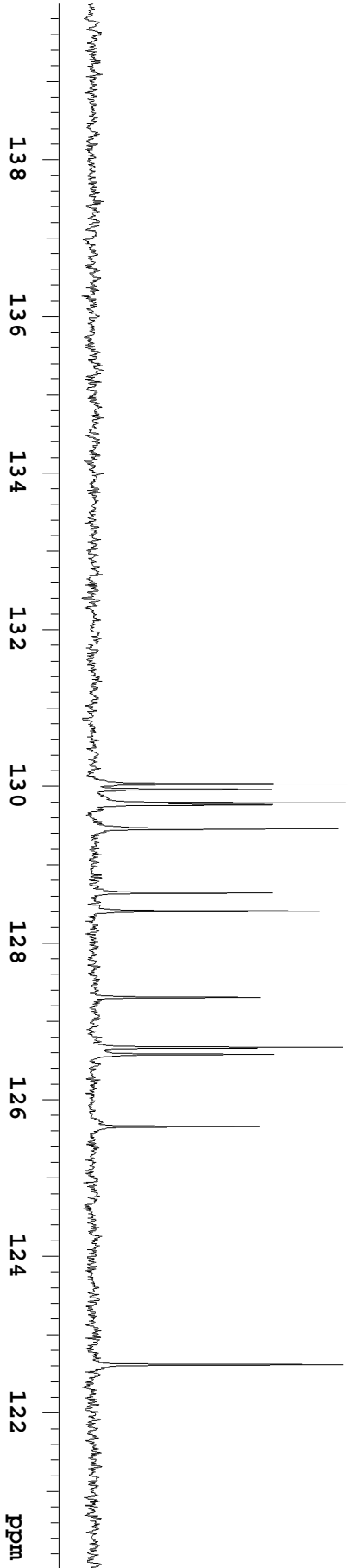
INDEX	FREQUENCY	PPM	HEIGHT
1	19608.6	130.028	39.2
2	19597.5	129.955	27.6
3	19571.6	129.783	39.0
4	19568.3	129.761	27.9
5	19521.9	129.454	37.9
6	19398.8	128.637	27.7
7	19363.4	128.403	35.0
8	19197.3	127.301	25.8
9	19100.6	126.660	38.5
10	19087.4	126.572	28.0
11	18948.8	125.653	25.7
12	18490.0	122.611	38.6

compound 4

ACQUISITION PARAMETERS
Pulse Sequence: DEPT
Solvent: cd3cn
Temp. 25.0 C / 298.1 K
Acq. time 1.001 sec
Width 36182.7 Hz
OBSERVE C13, 150.802 MHz
DECOUPLE H1, 599.734 MHz
Power 46 dB
on during acquisition
off during delay
WALTZ-16 modulated

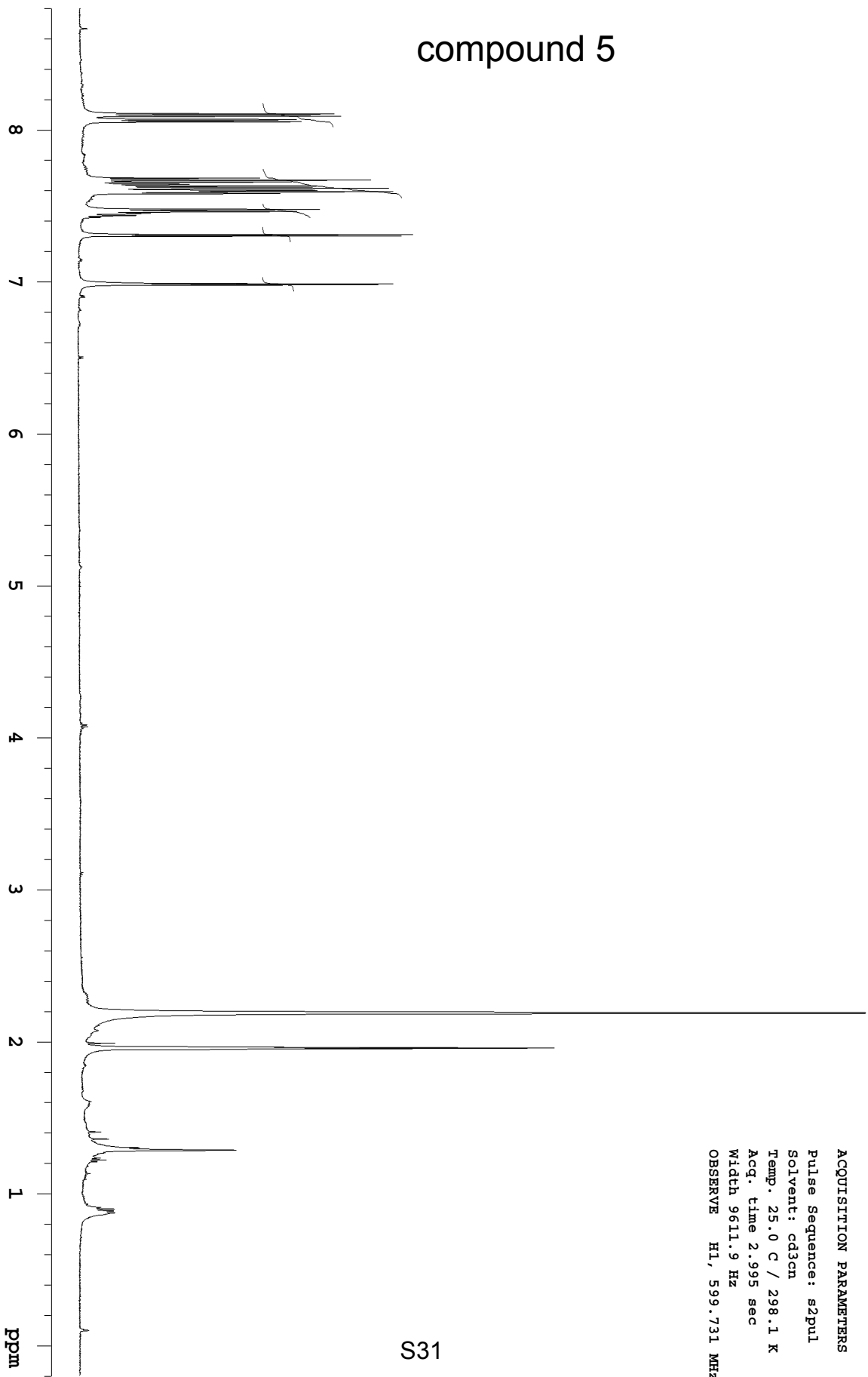
Line broadening 1.0 Hz
Sq. sine bell 1.000 sec
Shifted by -1.000 sec

S30



compound 5

ACQUISITION PARAMETERS
Pulse Sequence: s2pul
Solvent: cd3cn
Temp. 25.0 C / 298.1 K
Acq. time 2.595 sec
Width 9611.9 Hz
OBSERVE H1, 599.731 MHz



S31

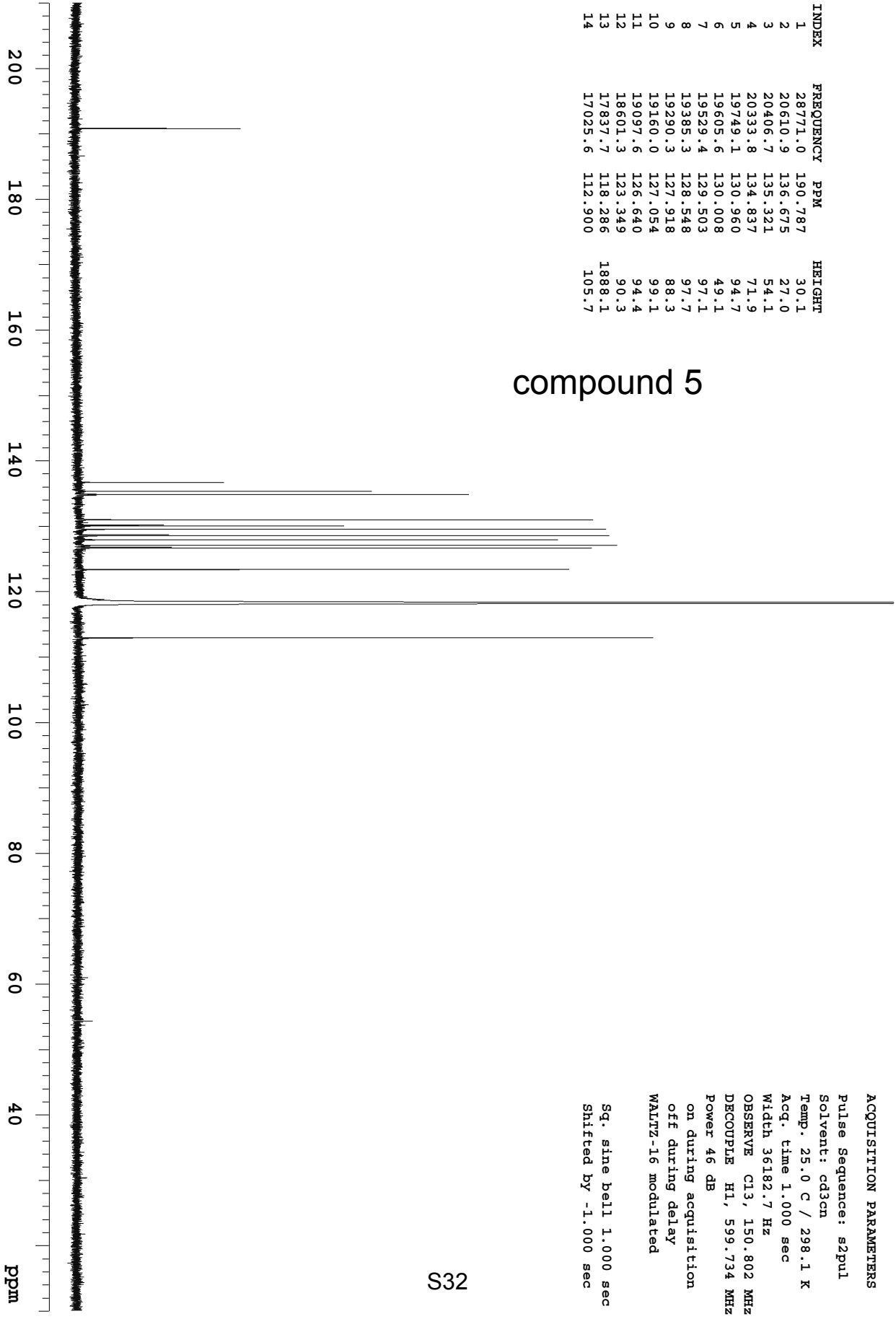
ACQUISITION PARAMETERS

Pulse Sequence: s2pul
Solvent: cd3cn
Temp. 25.0 C / 298.1 K
Acq. time 1.000 sec
Width 36182.7 Hz
OBSERVE C13, 150.802 MHz
DECOUPLE H1, 599.734 MHz
Power 46 dB
on during acquisition
off during delay
WALTZ-16 modulated
Sq. sine bell 1.000 sec
Shifted by -1.000 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	28771.0	190.787	30.1
2	20610.9	136.675	27.0
3	20406.7	135.321	54.1
4	20333.8	134.837	71.9
5	19749.1	130.960	94.7
6	19605.6	130.008	49.1
7	19529.4	129.503	97.1
8	19385.3	128.548	97.7
9	19290.3	127.918	88.3
10	19160.0	127.054	99.1
11	19097.6	126.640	94.4
12	18601.3	123.349	90.3
13	17837.7	118.286	1888.1
14	17025.6	112.900	105.7

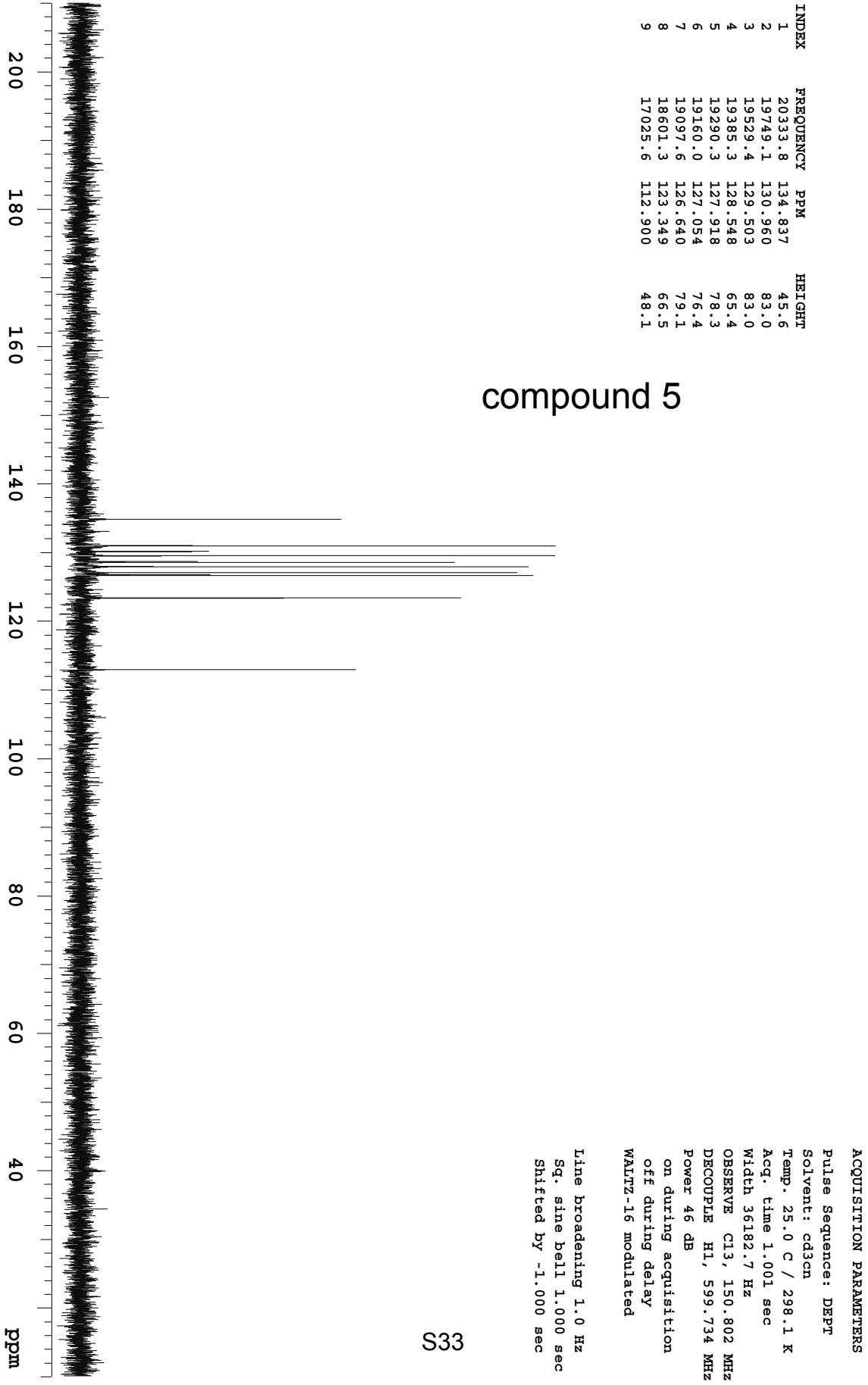
compound 5

S32



INDEX	FREQUENCY	PPM	HEIGHT
1	20333.8	134.837	45.6
2	19749.1	130.960	83.0
3	19529.4	129.503	83.0
4	19385.3	128.548	65.4
5	19290.3	127.918	78.3
6	19160.0	127.054	76.4
7	19097.6	126.640	79.1
8	18601.3	123.349	66.5
9	17025.6	112.900	48.1

compound 5



ACQUISITION PARAMETERS

Pulse Sequence: DEPT
 Solvent: cd3cn
 Temp. 25.0 C / 298.1 K
 Acq. time 1.001 sec
 Width 36182.7 Hz
 OBSERVE C13, 150.802 MHz
 DECOUPLE H1, 599.734 MHz
 Power 46 dB
 on during acquisition
 off during delay
 WALTZ-16 modulated

Line broadening 1.0 Hz
 Sq. sine bell 1.000 sec
 Shifted by -1.000 sec

S33

ppm

ACQUISITION PARAMETERS

Pulse Sequence: s2pul

Solvent: cd3cn

Temp. 25.0 C / 298.1 K

Acq. time 2.995 sec

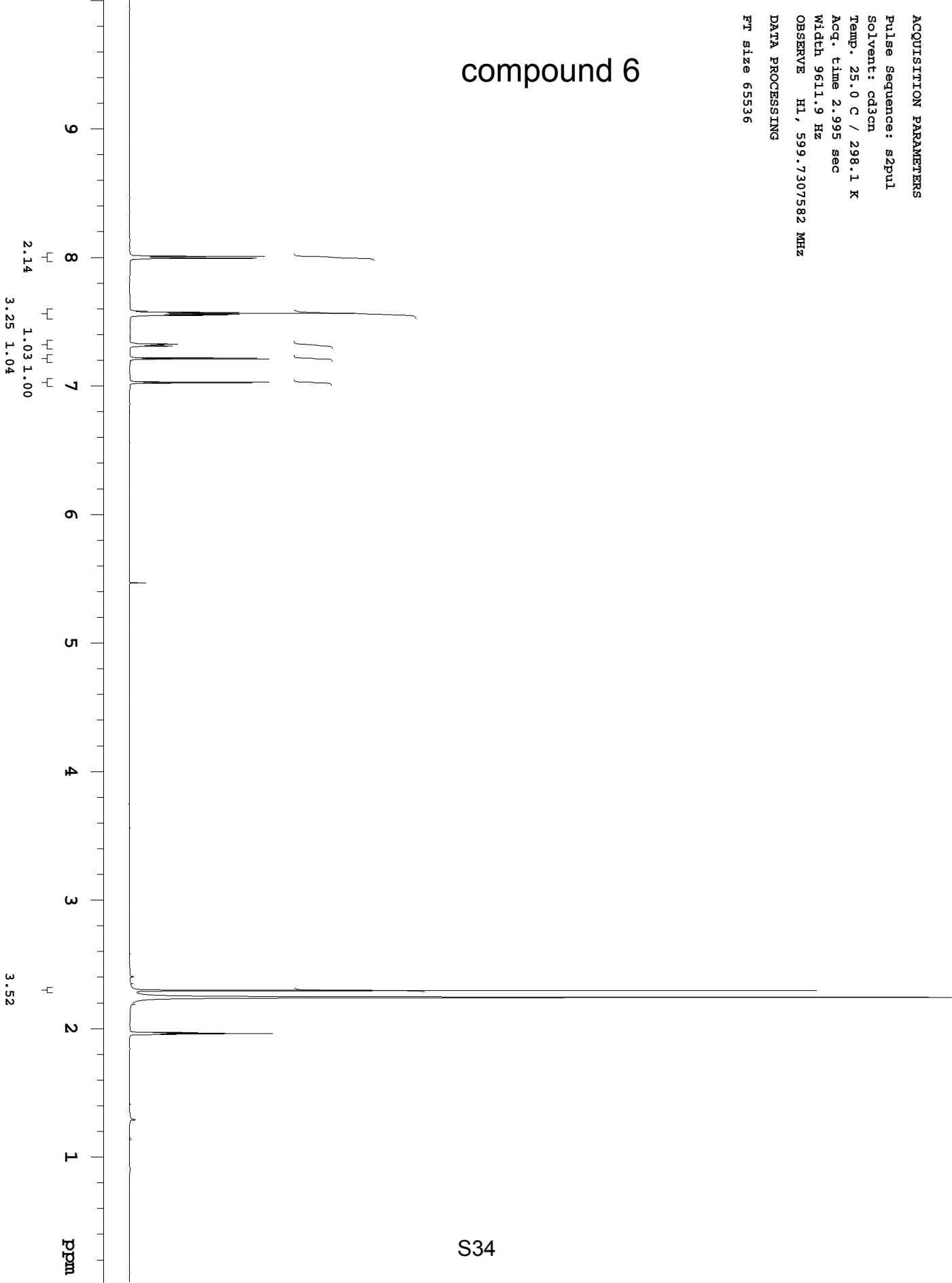
Width 9611.9 Hz

OBSERVE H1, 599.7307582 MHz

DATA PROCESSING

FT size 65536

compound 6

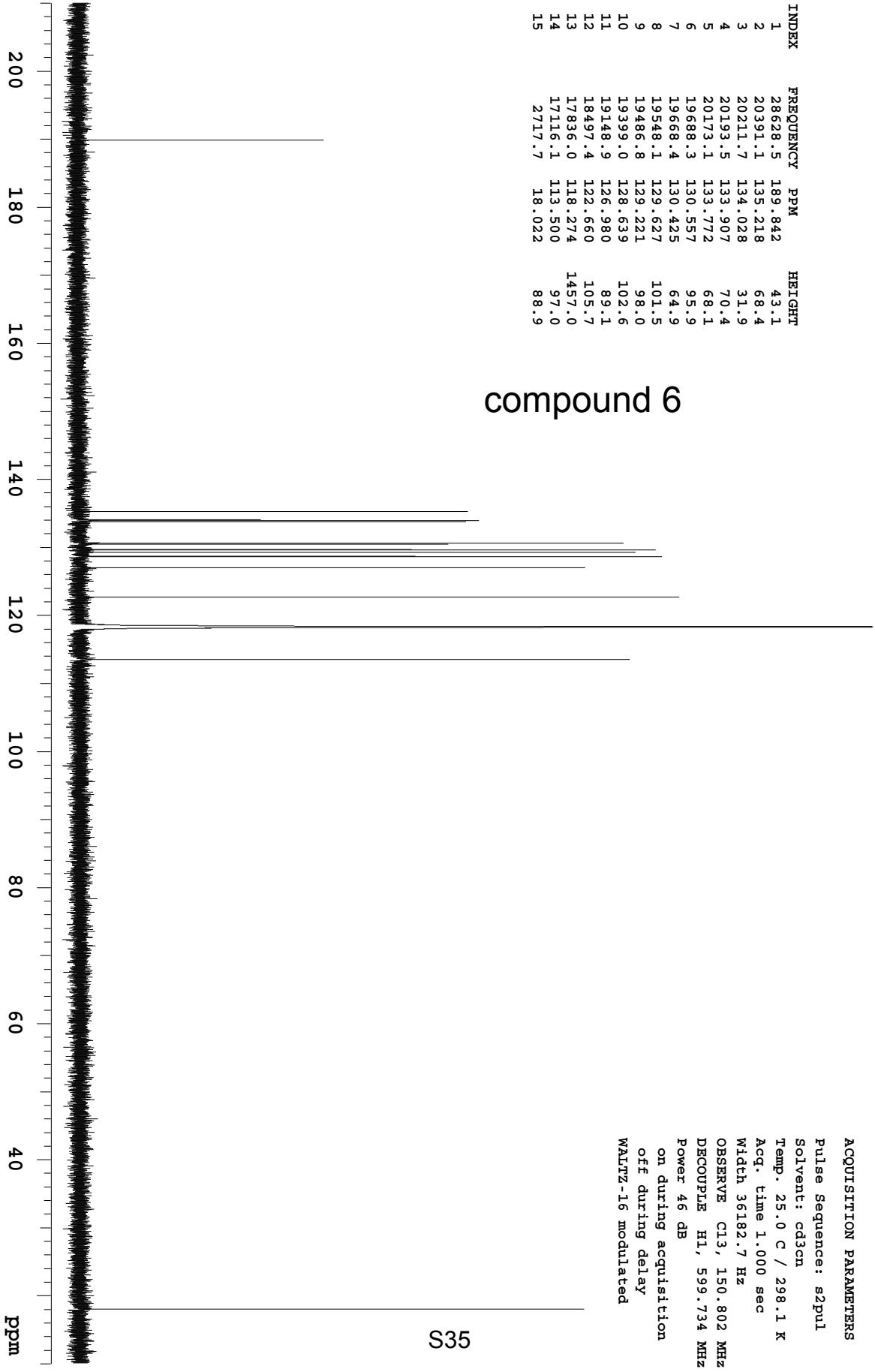


ACQUISITION PARAMETERS

Pulse Sequence: s2pul
 Solvent: cd3cn
 Temp. 25.0 C / 298.1 K
 Acq. time 1.000 sec
 Width 36182.7 Hz
 OBSERVE C13, 150.802 MHz
 DECOUPLE H1, 599.734 MHz
 Power 46 dB
 on during acquisition
 off during delay
 WALTZ-16 modulated

INDEX	FREQUENCY	PPM	HEIGHT
1	28628.5	189.842	43.1
2	20391.1	135.218	68.4
3	20211.7	134.028	31.9
4	20193.5	133.907	70.4
5	20173.1	133.772	68.1
6	19688.3	130.557	95.9
7	19668.4	130.425	64.9
8	19548.1	129.627	101.5
9	19486.8	129.221	98.0
10	19399.0	128.639	102.6
11	19148.9	126.980	89.1
12	18497.4	122.660	105.7
13	17836.0	118.274	1457.0
14	17116.1	113.500	97.0
15	2717.7	18.022	88.9

compound 6



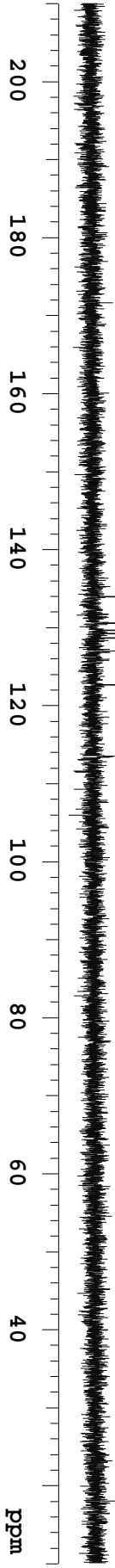
S35

ACQUISITION PARAMETERS

Pulse Sequence: DEPT
Solvent: cd3cn
Temp. 25.0 C / 298.1 K
Acq. time 1.001 sec
Width 36182.7 Hz
OBSERVE C13, 150.802 MHz
DECOUPLE H1, 599.734 MHz
Power 46 dB
on during acquisition
off during delay
WALTZ-16 modulated

INDEX	FREQUENCY	PPM	HEIGHT
1	20193.5	133.907	39.4
2	19688.3	130.557	76.5
3	19548.1	129.627	73.7
4	19486.8	129.221	76.9
5	19399.0	128.639	76.3
6	19148.9	126.980	74.2
7	18497.4	122.660	80.0
8	17116.1	113.500	45.3
9	2717.7	18.022	70.0

compound 6



S36