Synthesis, Biological Evaluation and Molecular Modeling of 2-Hydroxyisoquinoline-1,3-dione Analogues as Inhibitors of HIV Reverse Transcriptase Associated Ribonuclease H and Polymerase

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Table of Contents

Additional docking to NNRTI binding pocket

PDB Structure	Co-crystallized NNRTI	Compound **8c**		Compound **9c**	
		Docking score	Main Side Chain Contacts	Docking score	Side Chain Contacts
3LP1	Nevirapine	-8.32		-7.44	
3V81	Nevirapine	-8.65		-7.24	
1KLM	Delavirdine	-9.64	Asn103, Tyr181, Tyr188, Trp229	-9.91	Asn103, Tyr181, Tyr188, Trp229
2YNG	GSK560	-9.38		-9.78	

LID for best docked poses at RNase H active site

A

Docking Score -7.59 kcal/mol

B

Docking Score -6.80 kcal/mol
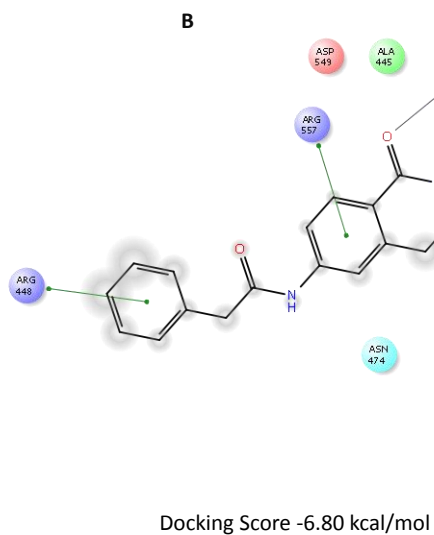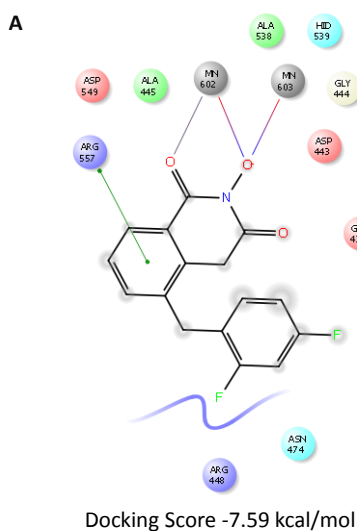
Fig. S1. Ligand Interaction Diagram for best poses of **8c** and **9c** docked into RNase H active center: A) Compound **8c** B) Compound **9c**; LID legend: red – charged (negative) residues; blue – charged (positive) residues; cyan – polar residues; green – hydrophobic residue.
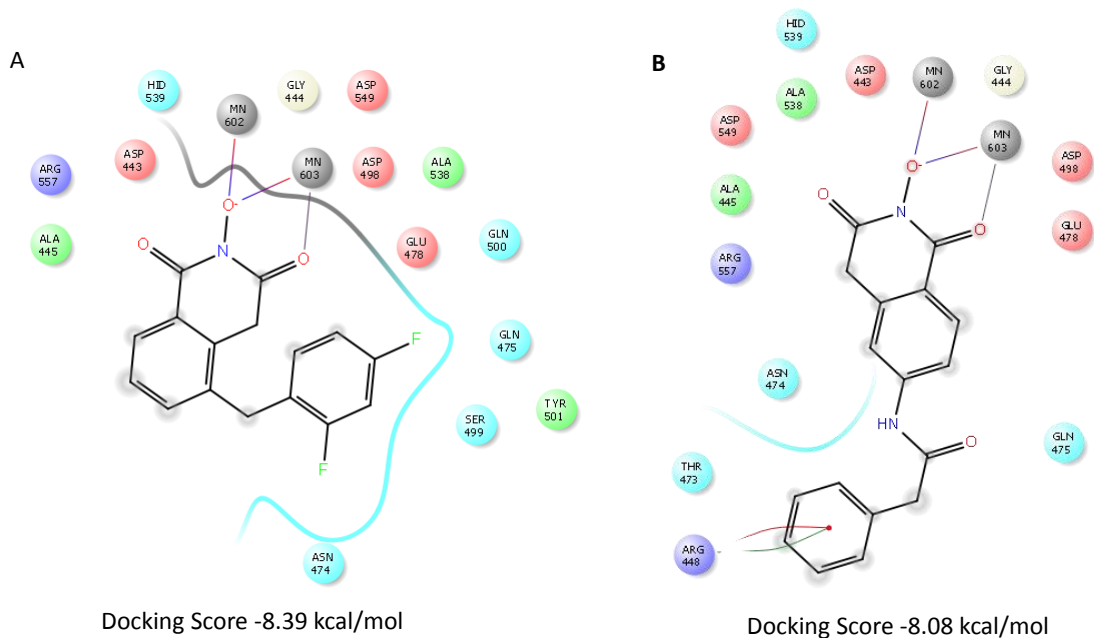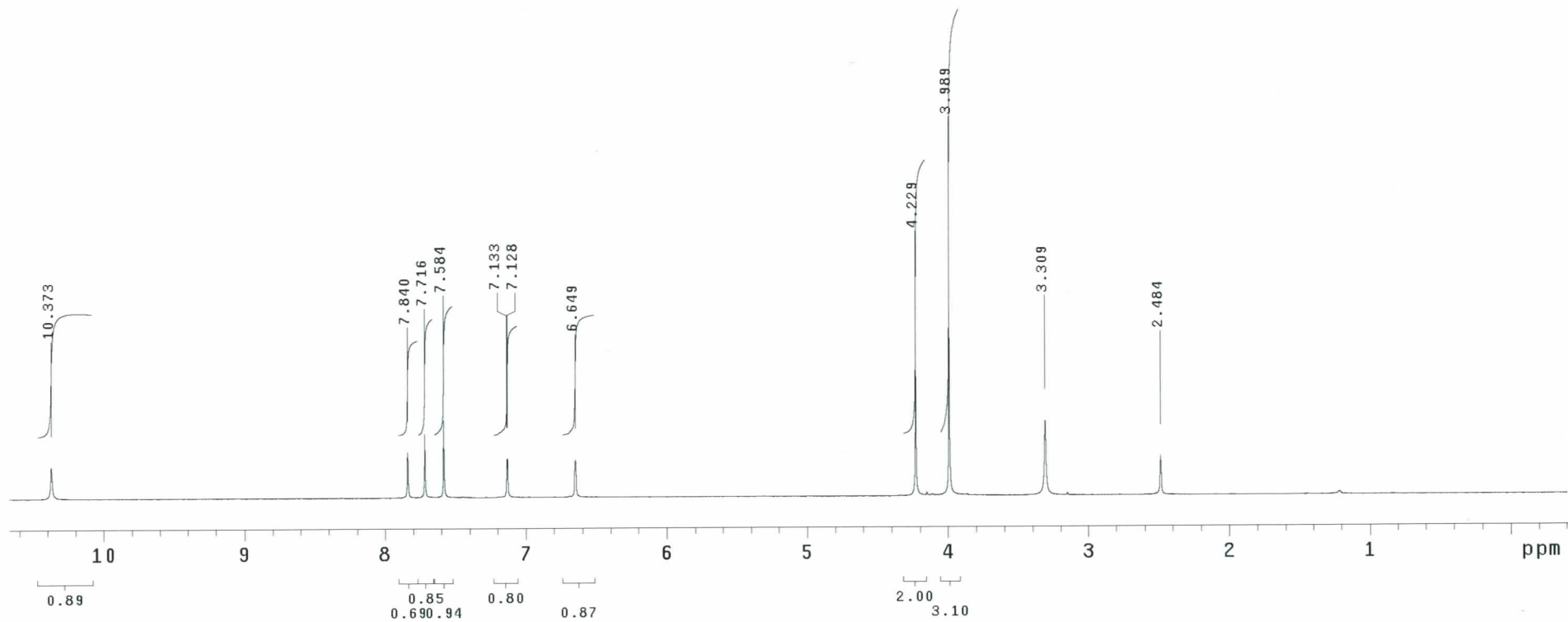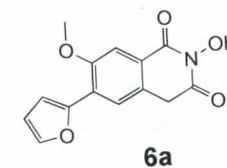

Docking Score -8.08 kcal/mol

Docking Score -7.68 kcal/mol
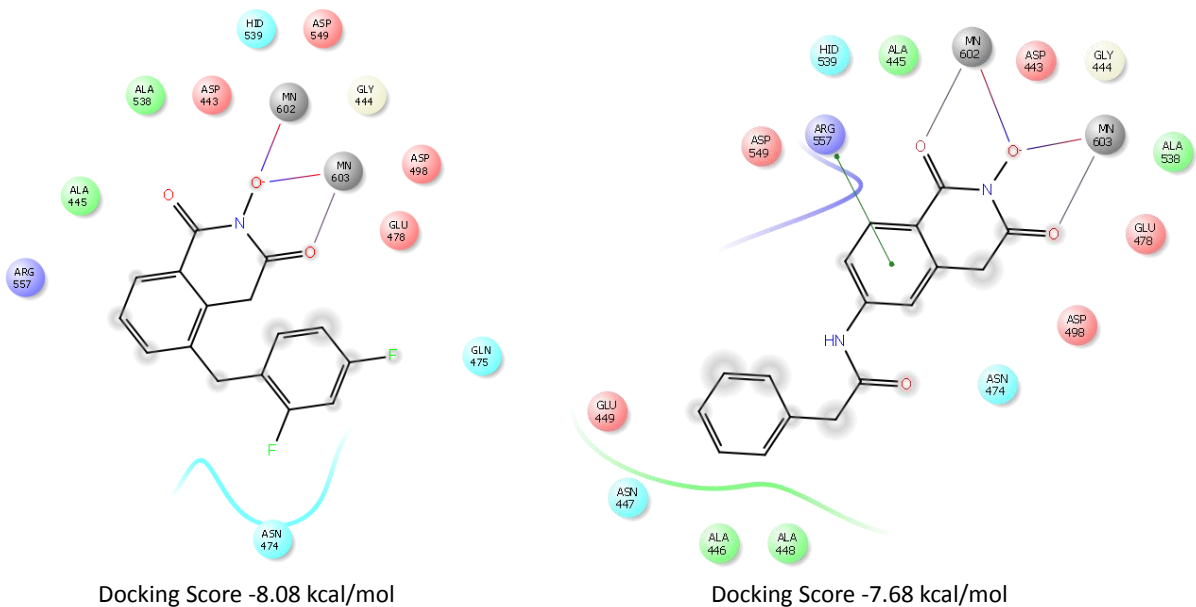
Fig. S2. Ligand Interaction Diagram for best poses of **8c** and **9c** docked into RNase H active center with R448A mutation: A) Compound **8c** B) Compound **9c**; LID legend: red – charged (negative) residues; blue – charged (positive) residues; cyan – polar residues; green – hydrophobic residue.

A

Docking Score -8.39 kcal/mol

B

Docking Score -8.08 kcal/mol

Fig. S3. Ligand Interaction Diagram for best poses of **8c** and **9c** docked into RNase H active center with flexible Arg448 side chain: A) Compound **8c** B) Compound **9c**; LID legend: red – charged (negative) residues; blue – charged (positive) residues; cyan – polar residues; green – hydrophobic residue.

6a

10.373   7.840   7.716   7.584   7.133   7.128   6.649   4.229   3.989   3.309   2.484

0.89   0.85   0.80   0.87   2.00
         0.69 0.94   3.10

10   9   8   7   6   5   4   3   2   1   ppm

6a

Peak labels: 166.923, 161.863, 154.220, 148.508, 144.039, 127.464, 124.467, 124.329, 124.122, 113.626, 112.936, 109.709, 56.373, 40.512, 40.397, 40.259, 40.113, 39.975, 39.837, 39.699, 39.561, 36.724

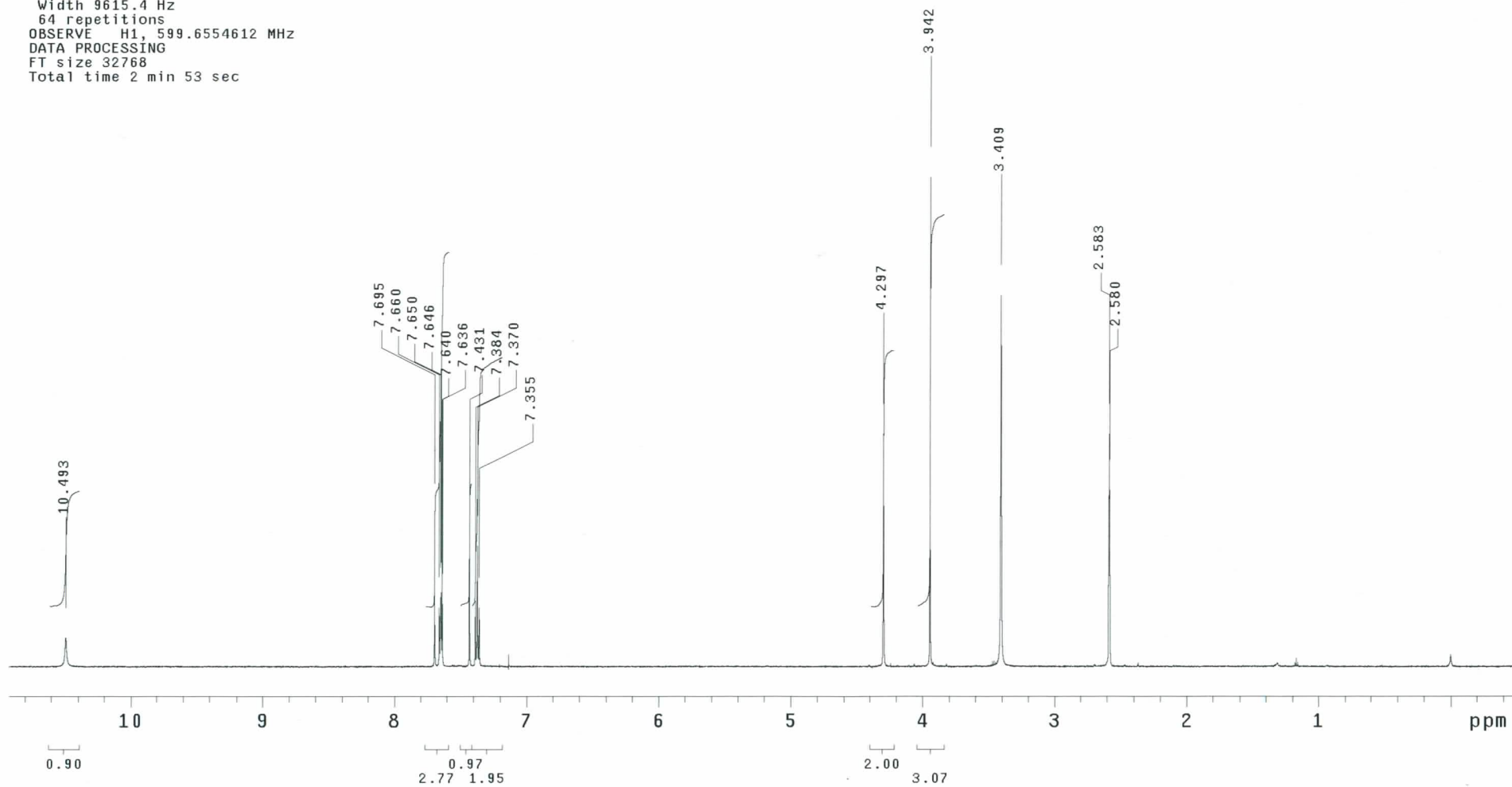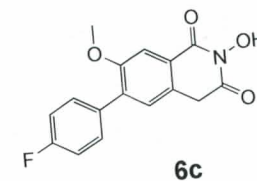ppm axis: 160, 140, 120, 100, 80, 60, 40, 20, ppm
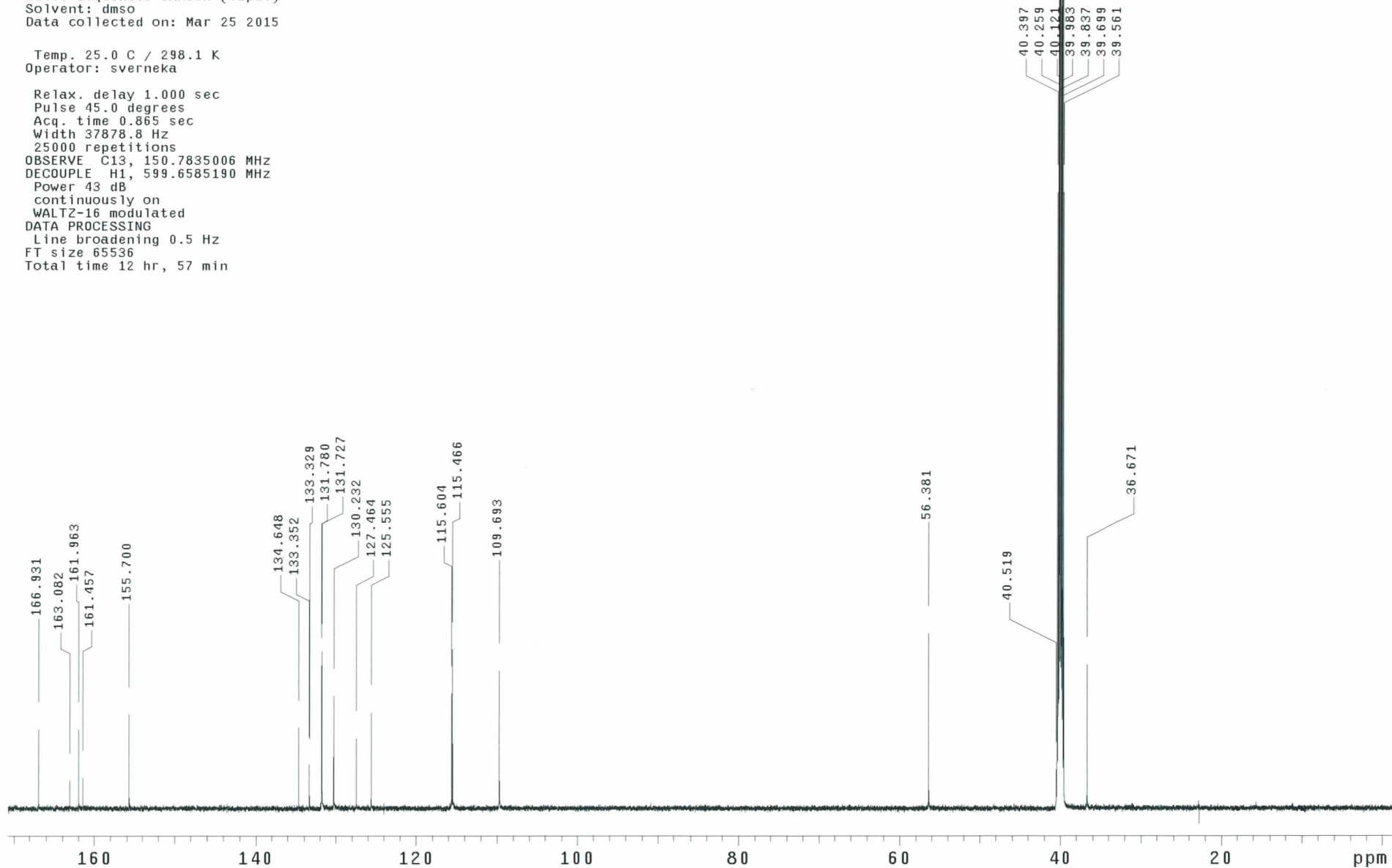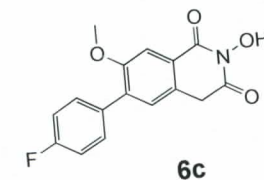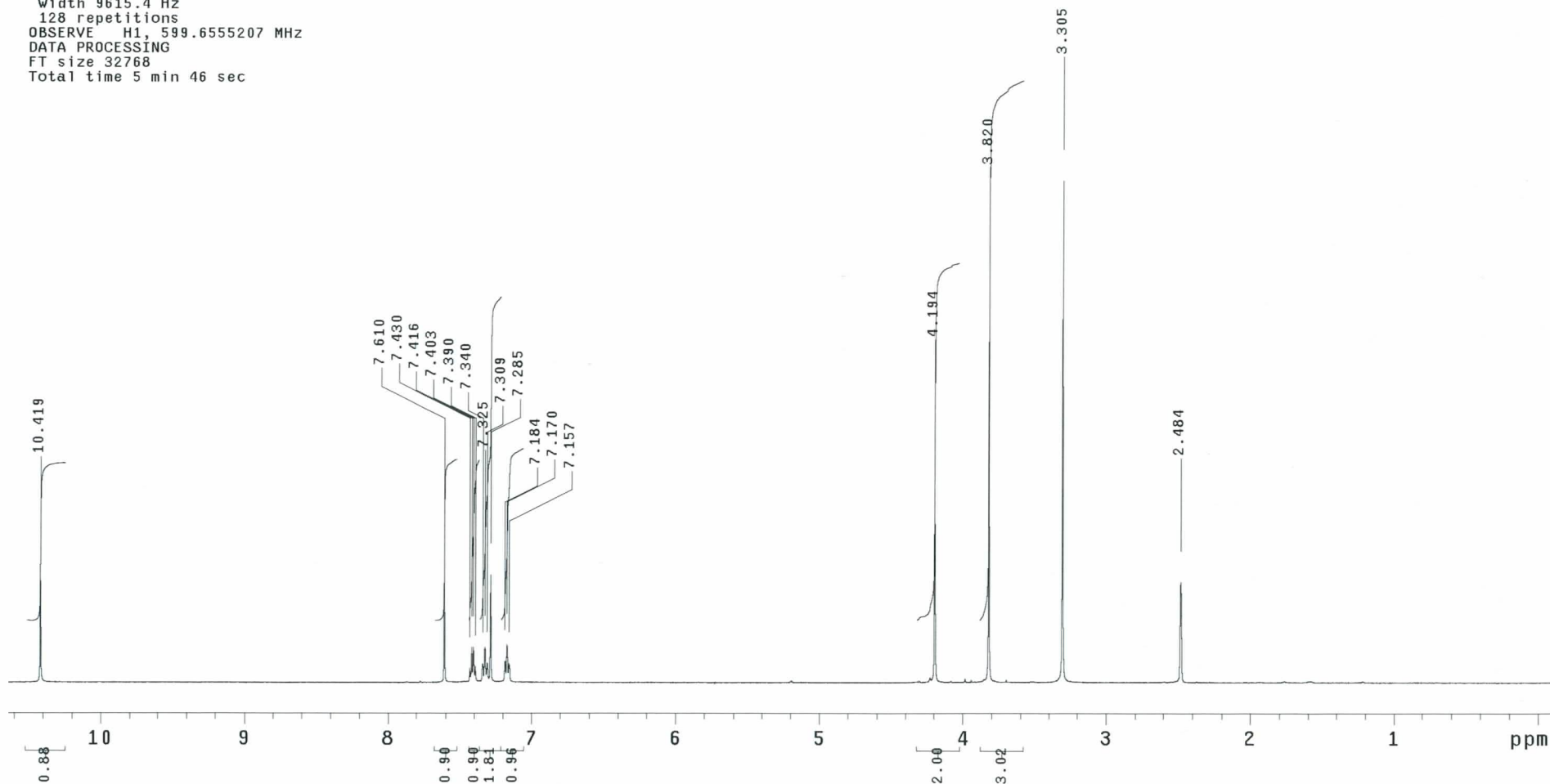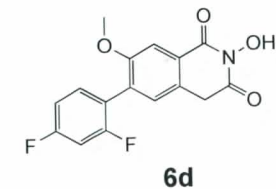
sv-7-263-carb

Sample Name:
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Data Collected on:
 nmr6003-vnmrs600
Archive directory:
 /data/sverneka
Sample directory:
 20150326_sv-7-263-carb_01
FidFile: sv-7-263-carb_PROTON_02

Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Mar 27 2015

 Temp. 25.0 C / 298.1 K
Operator: sverneka

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.704 sec
 Width 9615.4 Hz
 64 repetitions
OBSERVE   H1, 599.6555207 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 53 sec

6b

Peaks: 7.598, 7.502, 7.490, 7.434, 7.324, 4.203, 3.838, 3.307, 2.483

Integrations: 1.01, 2.0218, 1.03.1020, 2.00, 3.22

6b

Peaks: 166.961, 162.001, 155.776, 137.078, 135.805, 130.278, 129.649, 128.622, 128.277, 127.456, 125.456, 109.663, 56.335, 40.512, 40.397, 40.259, 40.121, 39.983, 39.837, 39.699, 39.561, 36.686
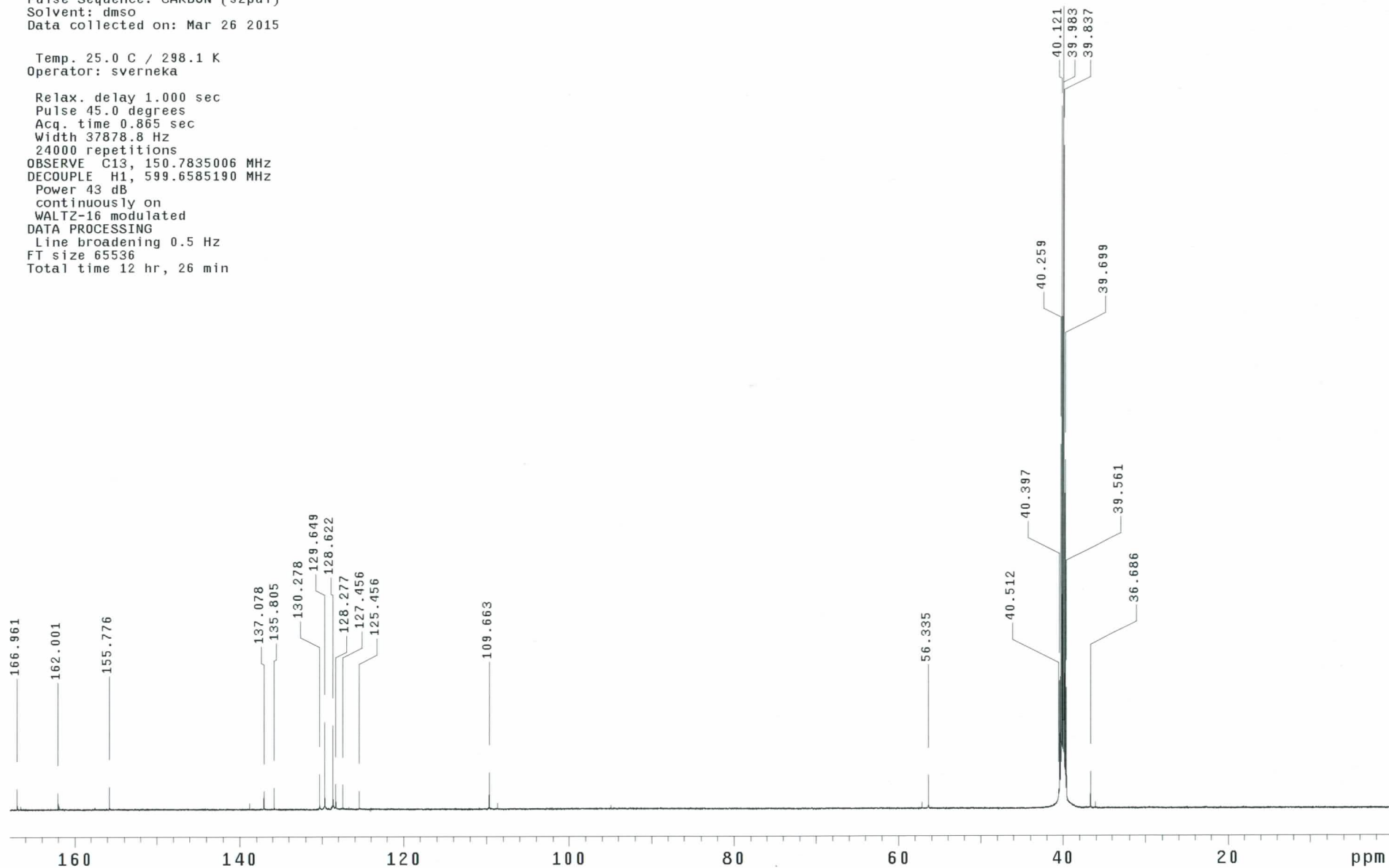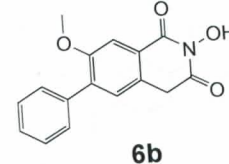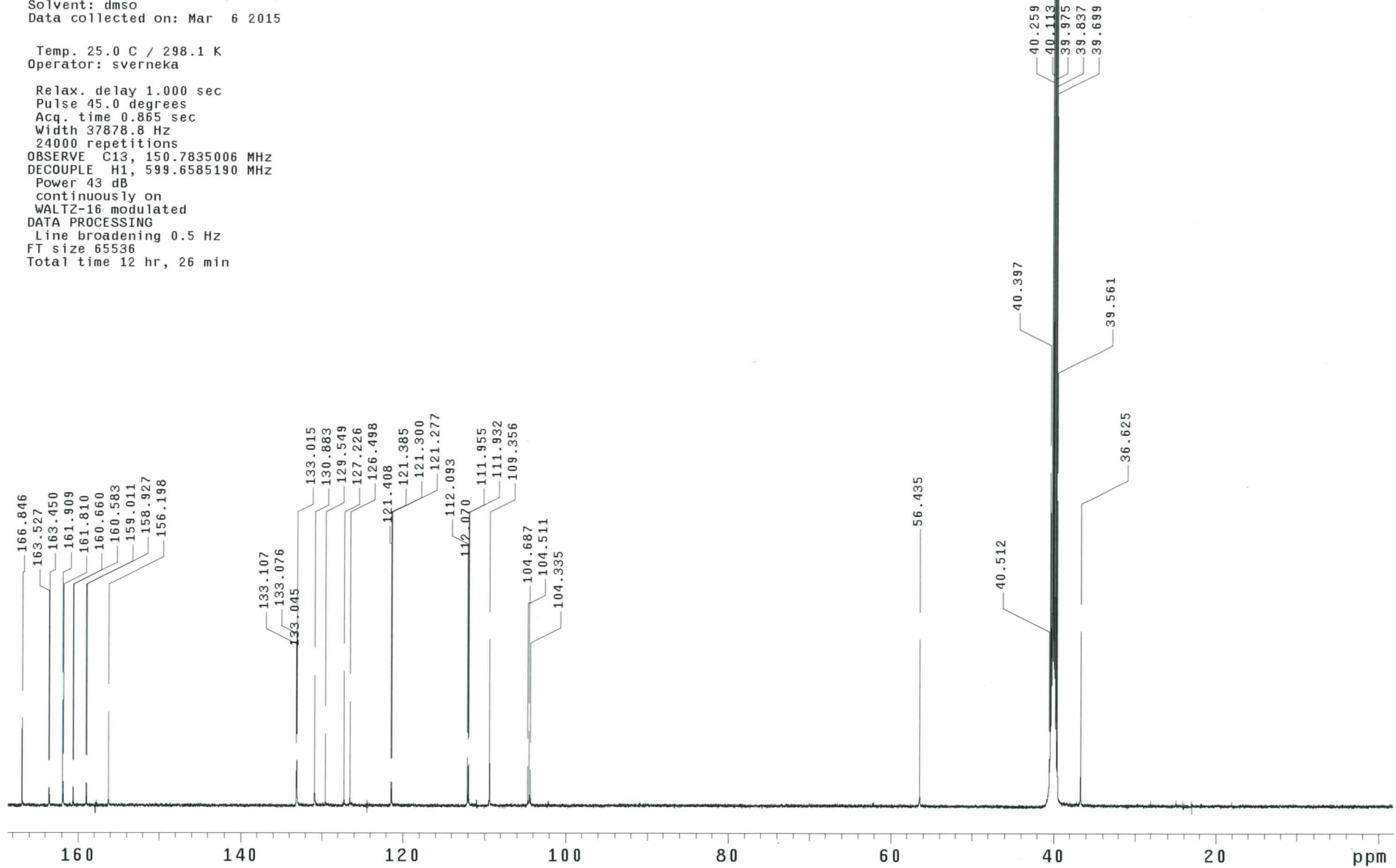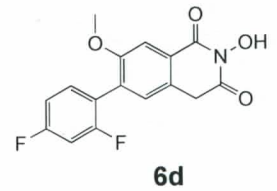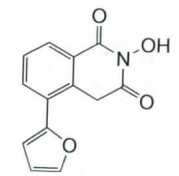
sv-7-261-carb

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Data Collected on:
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Archive directory:
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Sample directory:
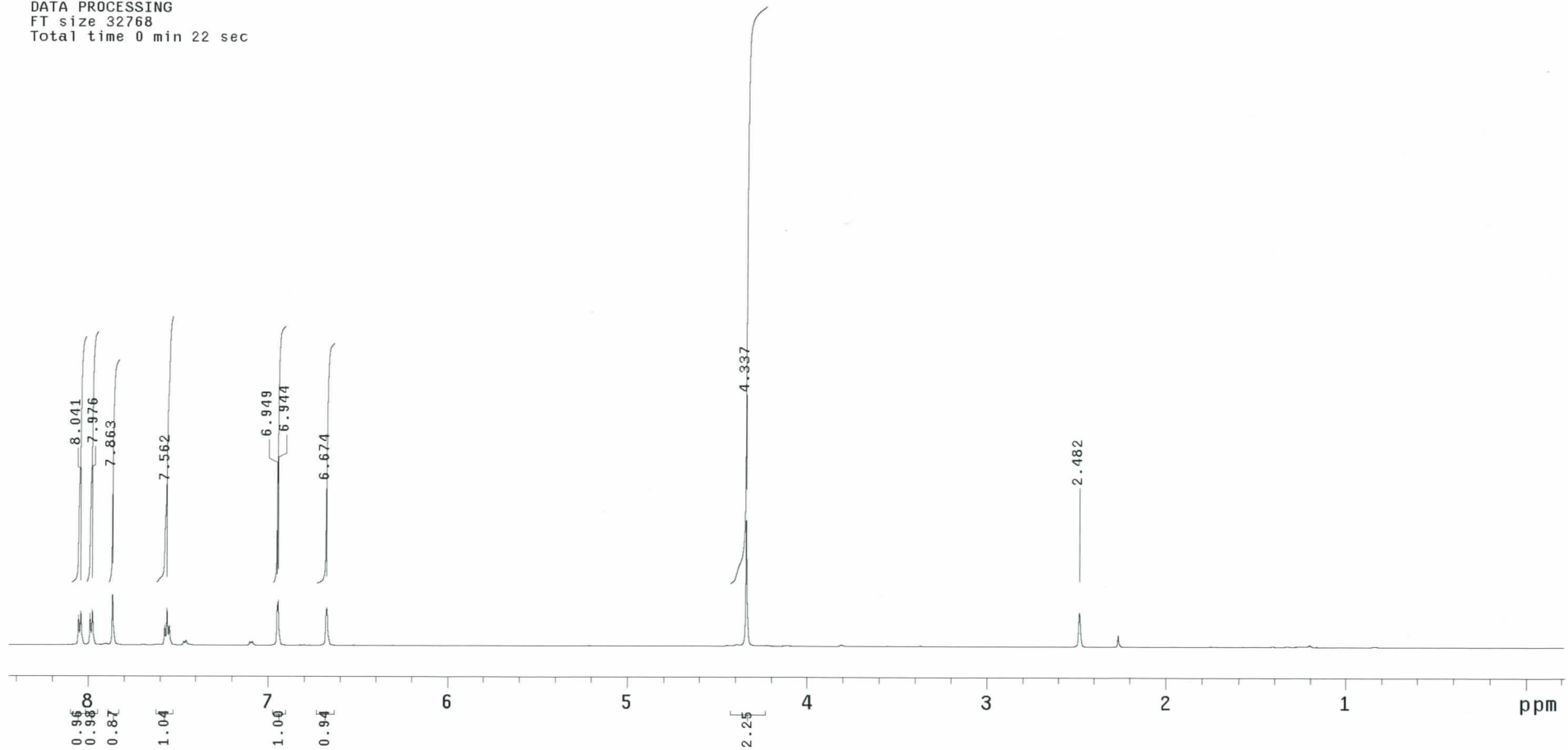 20150325_sv-7-261-carb_01
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Solvent: dmso
Data collected on: Mar 25 2015

 Temp. 25.0 C / 298.1 K
Operator: sverneka

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.704 sec
 Width 9615.4 Hz
 64 repetitions
 OBSERVE   H1, 599.6554612 MHz
 DATA PROCESSING
 FT size 32768
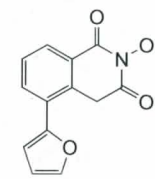 Total time 2 min 53 sec

6c

Peak labels (ppm): 10.493, 7.695, 7.660, 7.650, 7.646, 7.640, 7.636, 7.431, 7.384, 7.370, 7.355, 4.297, 3.942, 3.409, 2.583, 2.580

Integrations: 0.90, 2.77, 0.97, 1.95, 2.00, 3.07

ppm scale: 10, 9, 8, 7, 6, 5, 4, 3, 2, 1

6c

sv-7-251-carb

Sample Name:
  sv-7-251-carb
Data Collected on:
  nmr6003-vnmrs600
Archive directory:
  /data/sverneka
Sample directory:
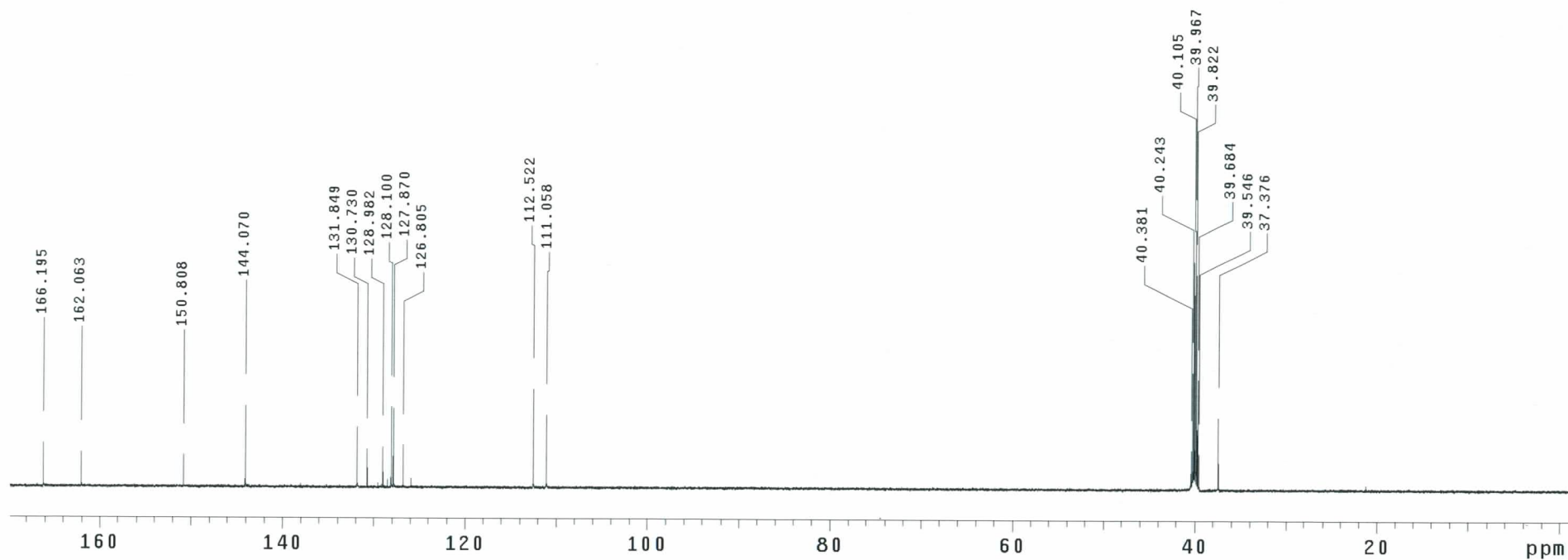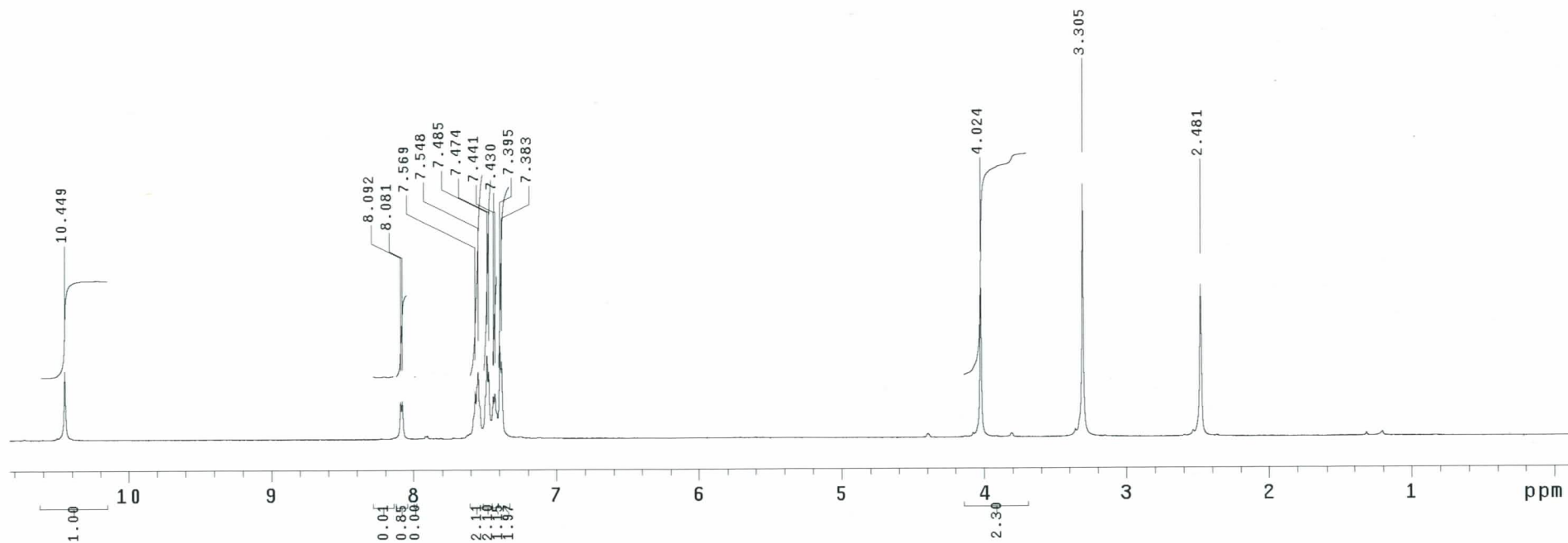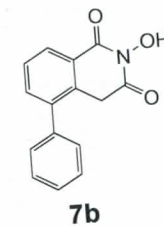 20150306_sv-7-251-carb_01
FidFile: sv-7-251-carb_PROTON_02

Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Mar 7 2015

Temp. 25.0 C / 298.1 K
Operator: sverneka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.704 sec
Width 9615.4 Hz
128 repetitions
OBSERVE   H1, 599.6555207 MHz
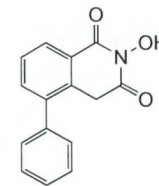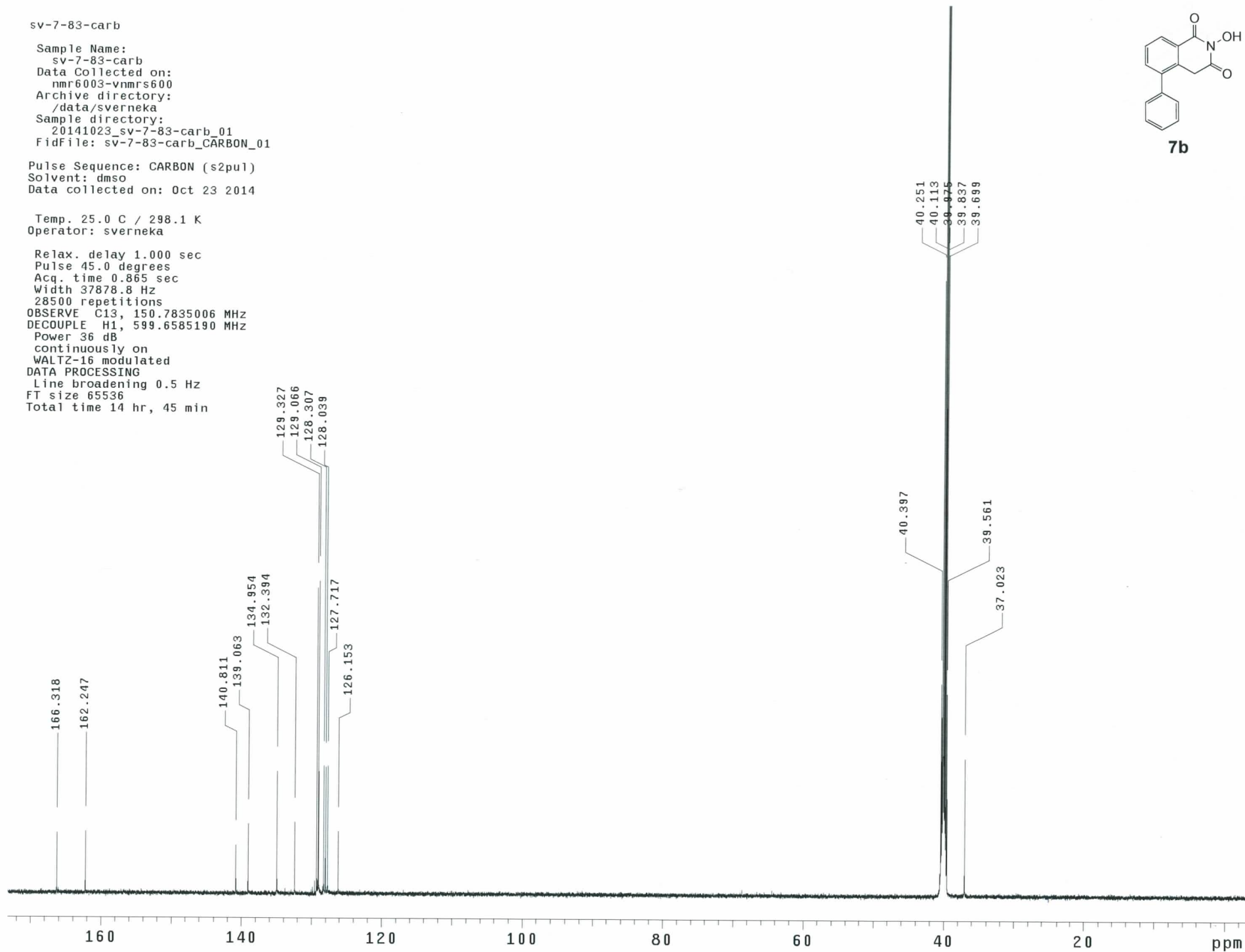DATA PROCESSING
FT size 32768
Total time 5 min 46 sec

6d

Peak labels: 10.419; 7.610; 7.430; 7.416; 7.403; 7.390; 7.340; 7.325; 7.309; 7.285; 7.184; 7.170; 7.157; 4.194; 3.820; 3.305; 2.484

Integrations: 0.88; 0.90; 0.90; 1.81; 0.96; 2.00; 3.02

ppm scale: 10 9 8 7 6 5 4 3 2 1 ppm

sv-7-251-carb

6d

Peak labels:
166.846, 163.527, 163.450, 161.909, 161.810, 160.660, 160.583, 159.011, 158.927, 156.198
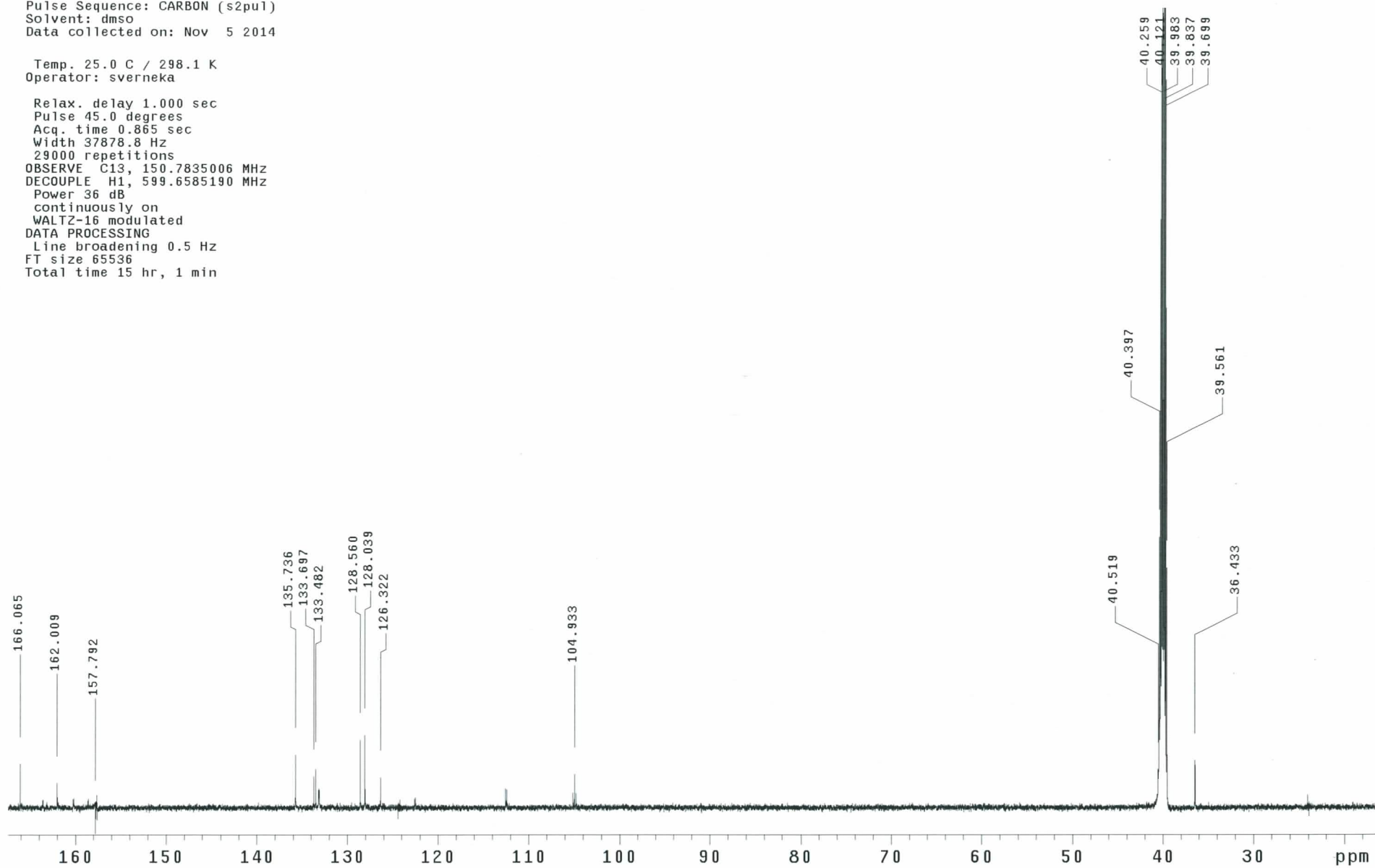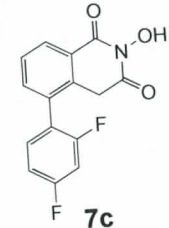133.107, 133.076, 133.045, 133.015, 130.883, 129.549, 127.226, 126.498, 121.408, 121.385, 121.300, 121.277, 112.093, 112.070, 111.955, 111.932, 109.356, 104.687, 104.511, 104.335
56.435
40.512, 40.397, 40.259, 40.113, 39.975, 39.837, 39.699, 39.561, 36.625

160   140   120   100   80   60   40   20   ppm

sv-7-111

7a

8.041
7.976
7.863
7.562
6.949
6.944
6.674
4.337
2.482

8   7   6   5   4   3   2   1   ppm

0.96
0.98
0.87
1.04
1.00
0.94
2.25

7a

Peaks (ppm): 166.195, 162.063, 150.808, 144.070, 131.849, 130.730, 128.982, 128.100, 127.870, 126.805, 112.522, 111.058, 40.381, 40.243, 40.105, 39.967, 39.822, 39.684, 39.546, 37.376

7b

10.449

8.092
8.081
7.569
7.548
7.485
7.474
7.441
7.430
7.395
7.383

4.024

3.305

2.481

1.00

0.01
0.85
0.00

2.11
2.00
1.07

2.30

ppm   10   9   8   7   6   5   4   3   2   1

sv-7-83-carb

7b

166.318
162.247
140.811
139.063
134.954
132.394
129.327
129.066
128.307
128.039
127.717
126.153
40.397
40.251
40.113
39.875
39.837
39.699
39.561
37.023

160   140   120   100   80   60   40   20   ppm

7c

10.478

8.154
8.143

7.598
7.479
7.467
7.453
7.435
7.419
7.258
7.247
7.233

3.904

3.339

2.498

1.232

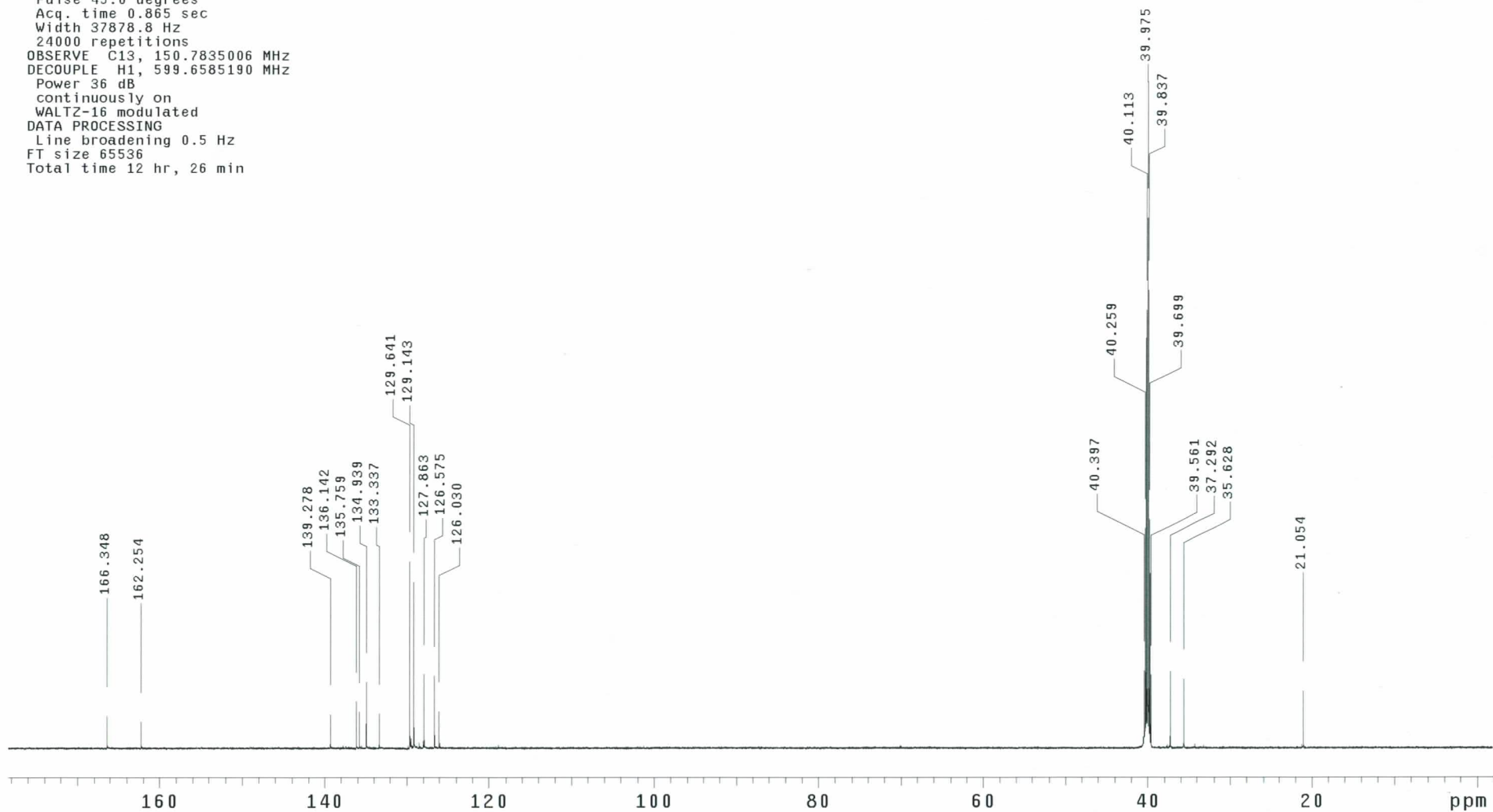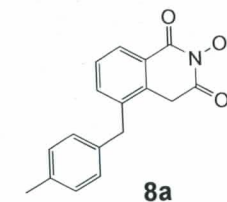10   9   8   7   6   5   4   3   2   1   ppm

sv-7-77-carbon

Sample Name:
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Archive directory:
   /data/sverneka
Sample directory:
   20141105_sv-7-77-carbon_01
FidFile: sv-7-77-carbon_CARBON_01

Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Nov 5 2014

Temp. 25.0 C / 298.1 K
Operator: sverneka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.865 sec
Width 37878.8 Hz
29000 repetitions
OBSERVE C13, 150.7835006 MHz
DECOUPLE H1, 599.6585190 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
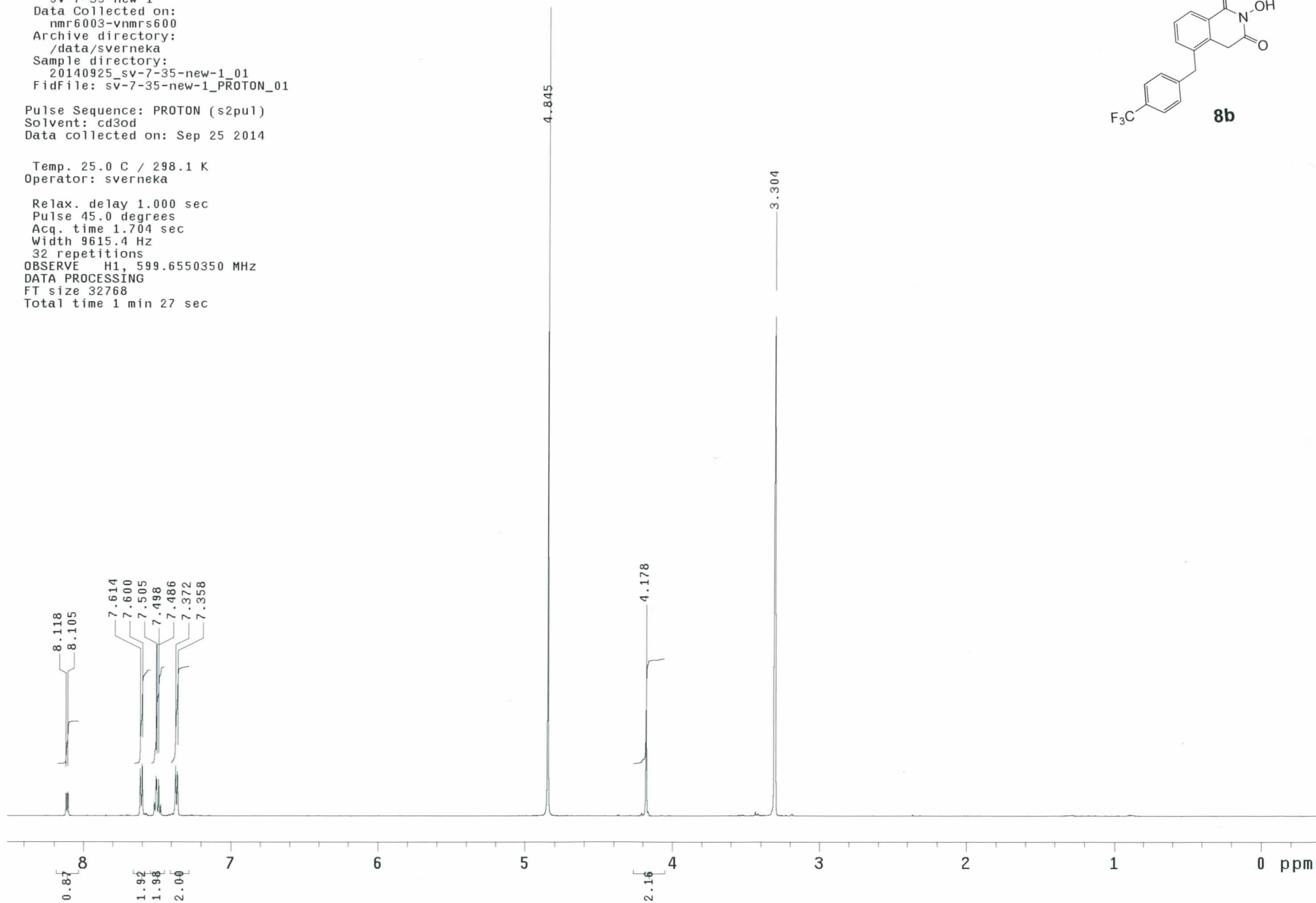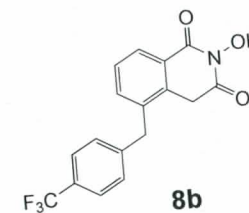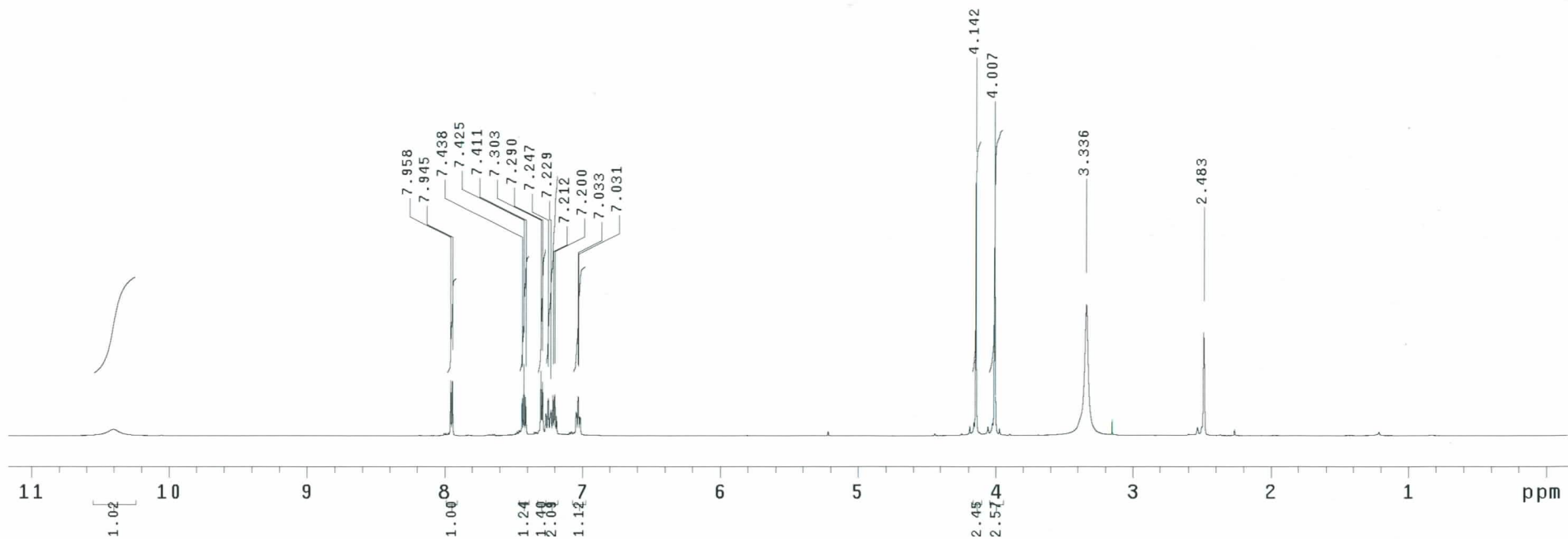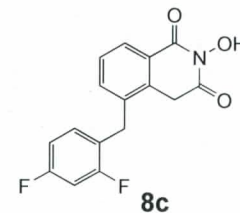Line broadening 0.5 Hz
FT size 65536
Total time 15 hr, 1 min

7c

8a

8a

Peak labels (left to right): 166.348, 162.254, 139.278, 136.142, 135.759, 134.939, 133.337, 129.641, 129.143, 127.863, 126.575, 126.030, 40.397, 40.259, 40.113, 39.975, 39.837, 39.699, 39.561, 37.292, 35.628, 21.054

ppm axis: 160, 140, 120, 100, 80, 60, 40, 20 ppm

8b

4.845

3.304

8.118
8.105

7.614
7.600
7.505
7.498
7.486
7.372
7.358

4.178

0.87   1.92 1.98 2.00   2.16
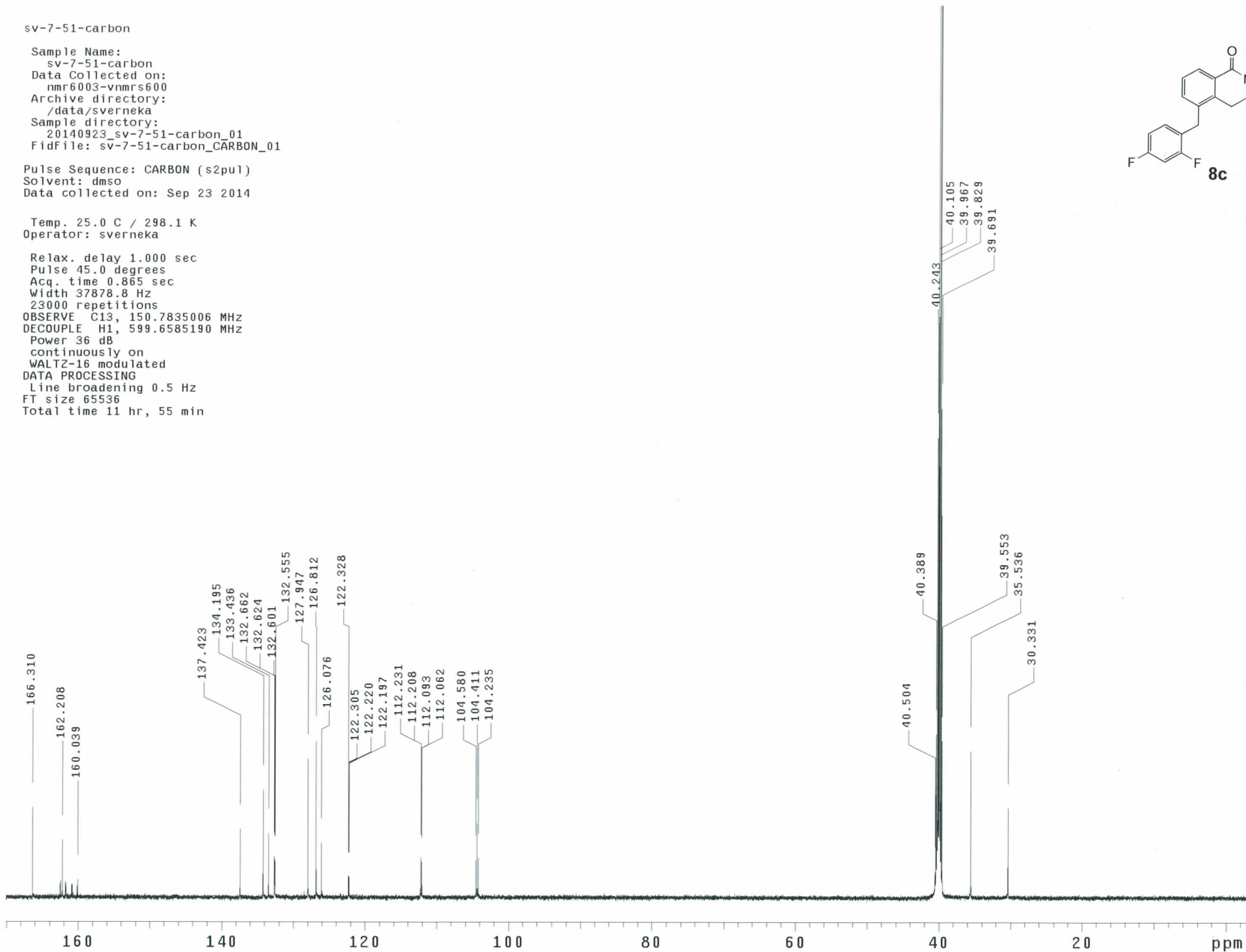
8   7   6   5   4   3   2   1   0 ppm

sv-7-35-carbon-1

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Data Collected on:
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Archive directory:
 /data/sverneka
Sample directory:
 20141007_sv-7-35-carbon-1_01
FidFile: sv-7-35-carbon-1_CARBON_01

Pulse Sequence: CARBON (s2pul)
Solvent: cd3od
Data collected on: Oct 7 2014

Temp. 25.0 C / 298.1 K
Operator: sverneka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.865 sec
Width 37878.8 Hz
25000 repetitions
OBSERVE C13, 150.7833785 MHz
DECOUPLE H1, 599.6580333 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
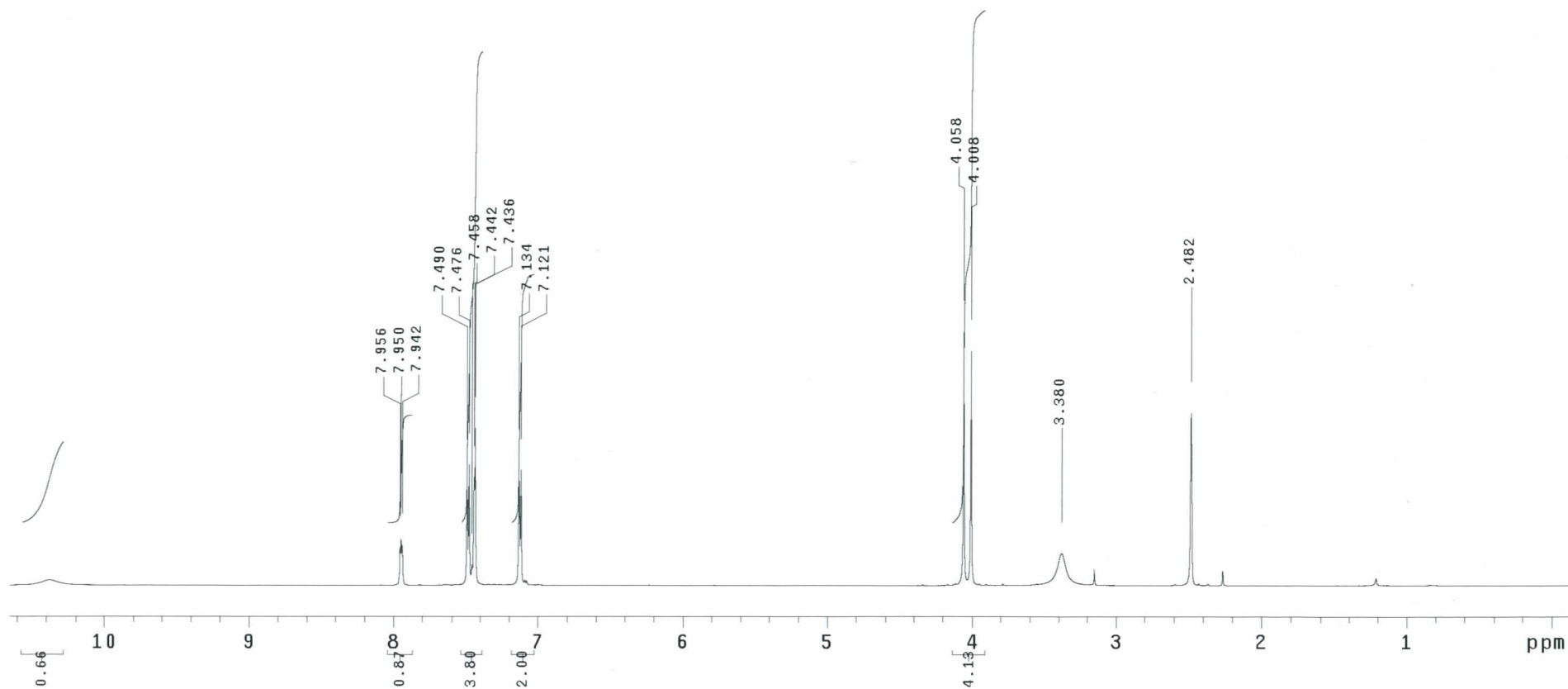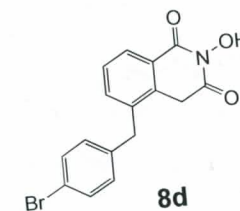FT size 65536
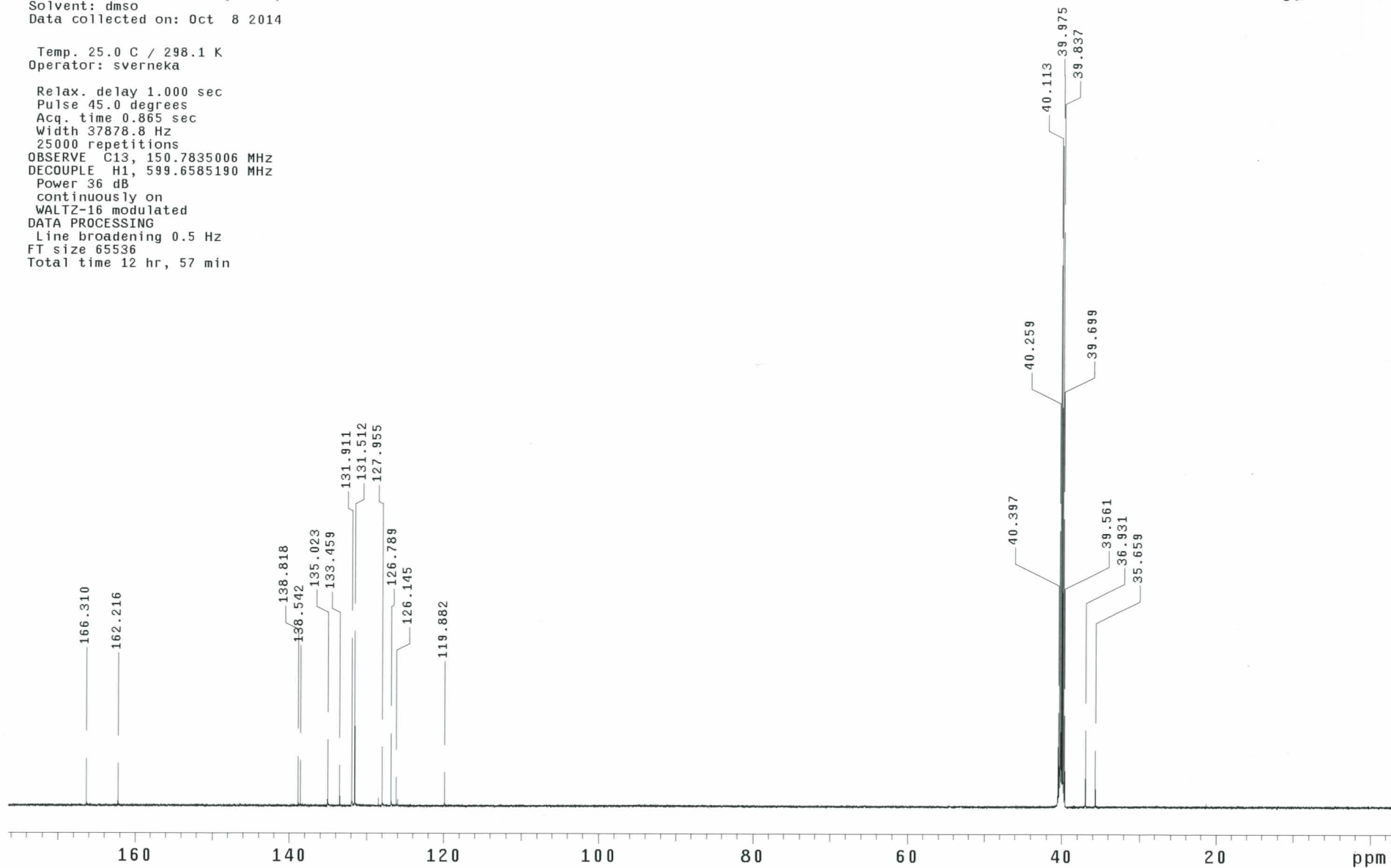Total time 12 hr, 57 min

8b
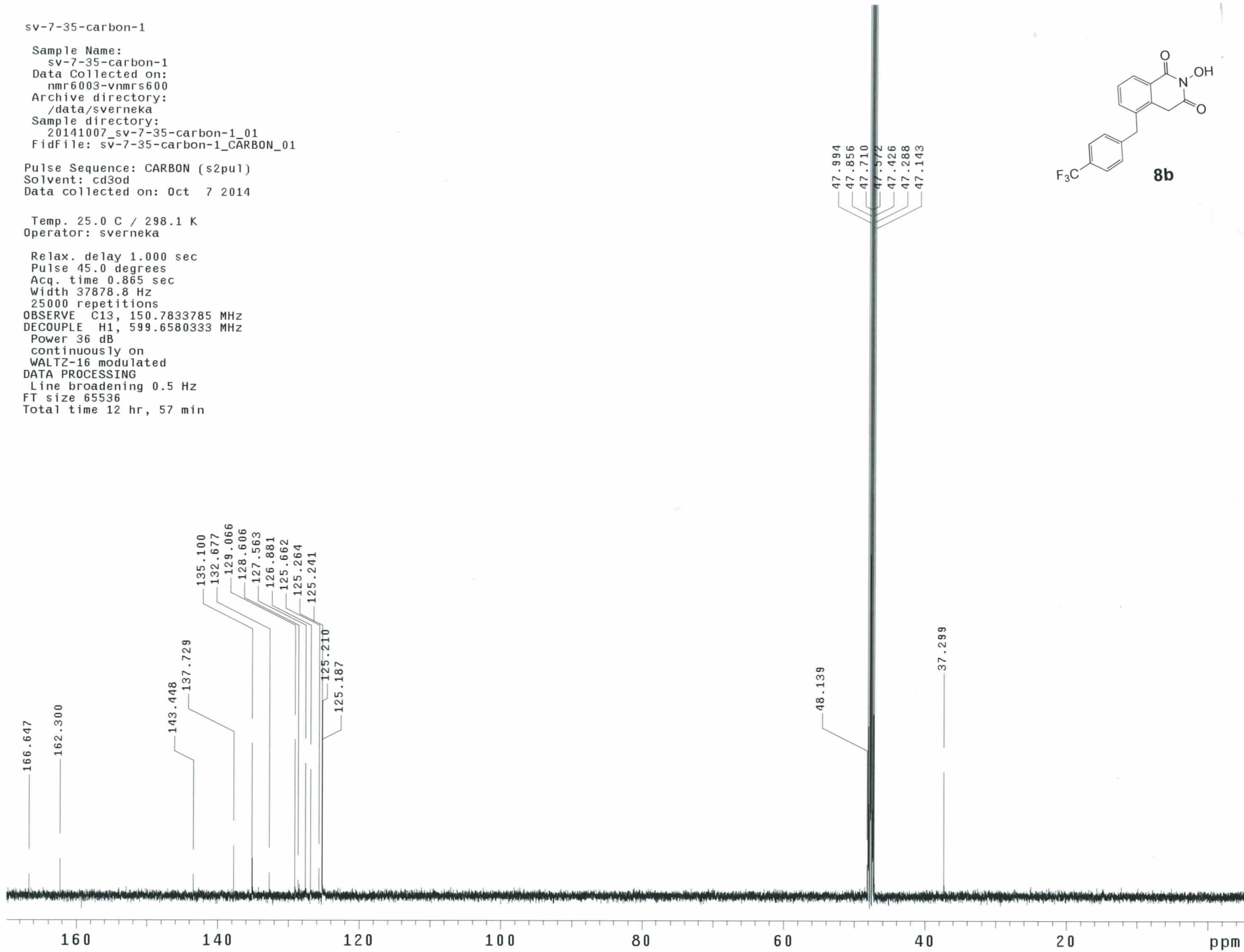
sv-7-51-carbon

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Archive directory:
  /data/sverneka
Sample directory:
  20140923_sv-7-51-carbon_01
FidFile: sv-7-51-carbon_PROTON_01

Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Sep 23 2014

Temp. 25.0 C / 298.1 K
Operator: sverneka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.704 sec
Width 9615.4 Hz
32 repetitions
OBSERVE   H1, 599.6555207 MHz
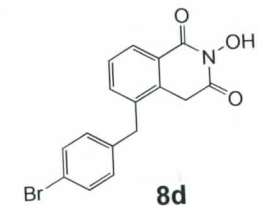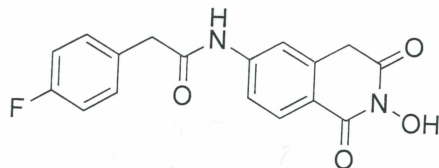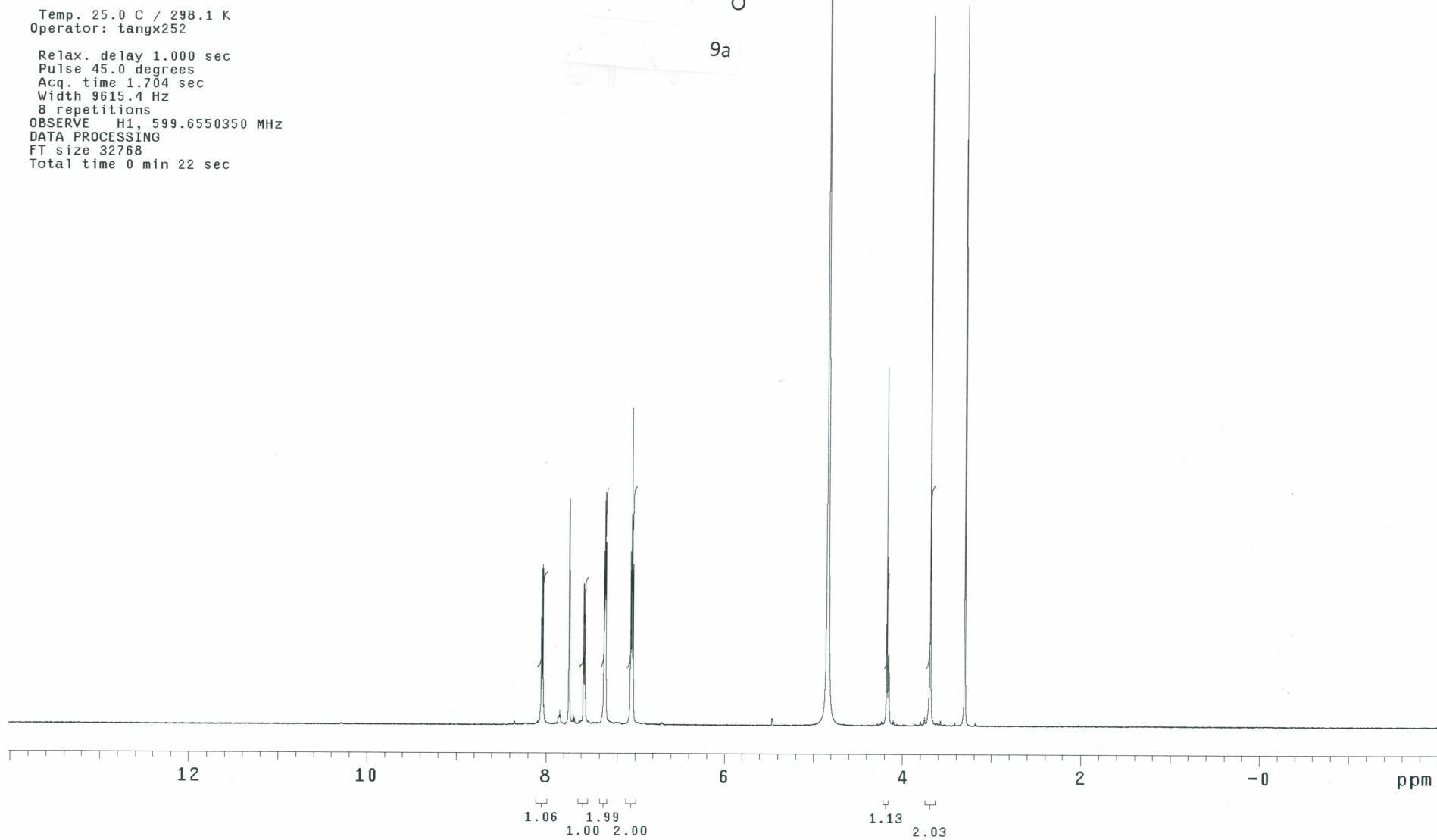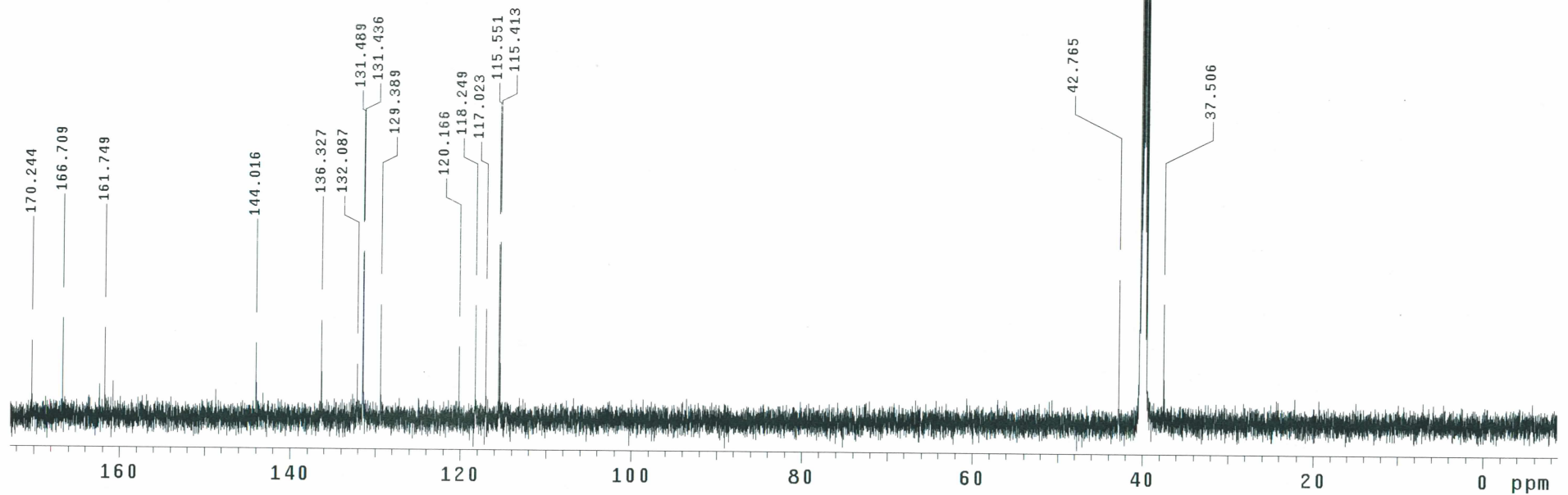DATA PROCESSING
FT size 32768
Total time 1 min 27 sec

8c

Peaks (ppm): 7.958, 7.945, 7.438, 7.425, 7.411, 7.303, 7.290, 7.247, 7.229, 7.212, 7.200, 7.033, 7.031, 4.142, 4.007, 3.336, 2.483

Integrations: 1.02, 1.00, 1.24, 1.40, 2.09, 1.12, 2.45, 2.57

8c

166.310
162.208
160.039
137.423
134.195
133.436
132.662
132.624
132.601
132.555
127.947
126.812
126.076
122.328
122.305
122.220
122.197
112.231
112.208
112.093
112.062
104.580
104.411
104.235
40.504
40.389
40.243
40.105
39.967
39.829
39.691
39.553
39.536
35.536
30.331

8d

Peaks: 7.956, 7.950, 7.942, 7.490, 7.476, 7.458, 7.442, 7.436, 7.134, 7.121, 4.058, 4.008, 3.380, 2.482

Integrations: 0.66, 0.87, 3.80, 2.00, 4.13

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Sample directory:
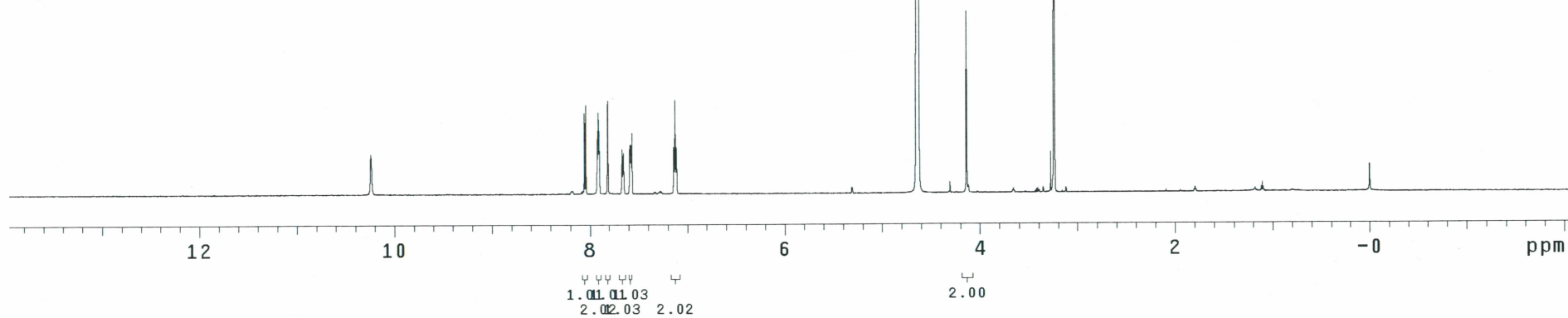 20141008_sv-7-95-carbon_01
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Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Oct 8 2014

 Temp. 25.0 C / 298.1 K
Operator: sverneka

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 0.865 sec
 Width 37878.8 Hz
 25000 repetitions
OBSERVE C13, 150.7835006 MHz
DECOUPLE H1, 599.6585190 MHz
 Power 36 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 12 hr, 57 min

8d

Peaks:
166.310
162.216
138.818
138.542
135.023
133.459
131.911
131.512
127.955
126.789
126.145
119.882
40.397
40.259
40.113
39.975
39.837
39.699
39.561
36.931
35.659

160   140   120   100   80   60   40   20   ppm

jt-6-7

9a

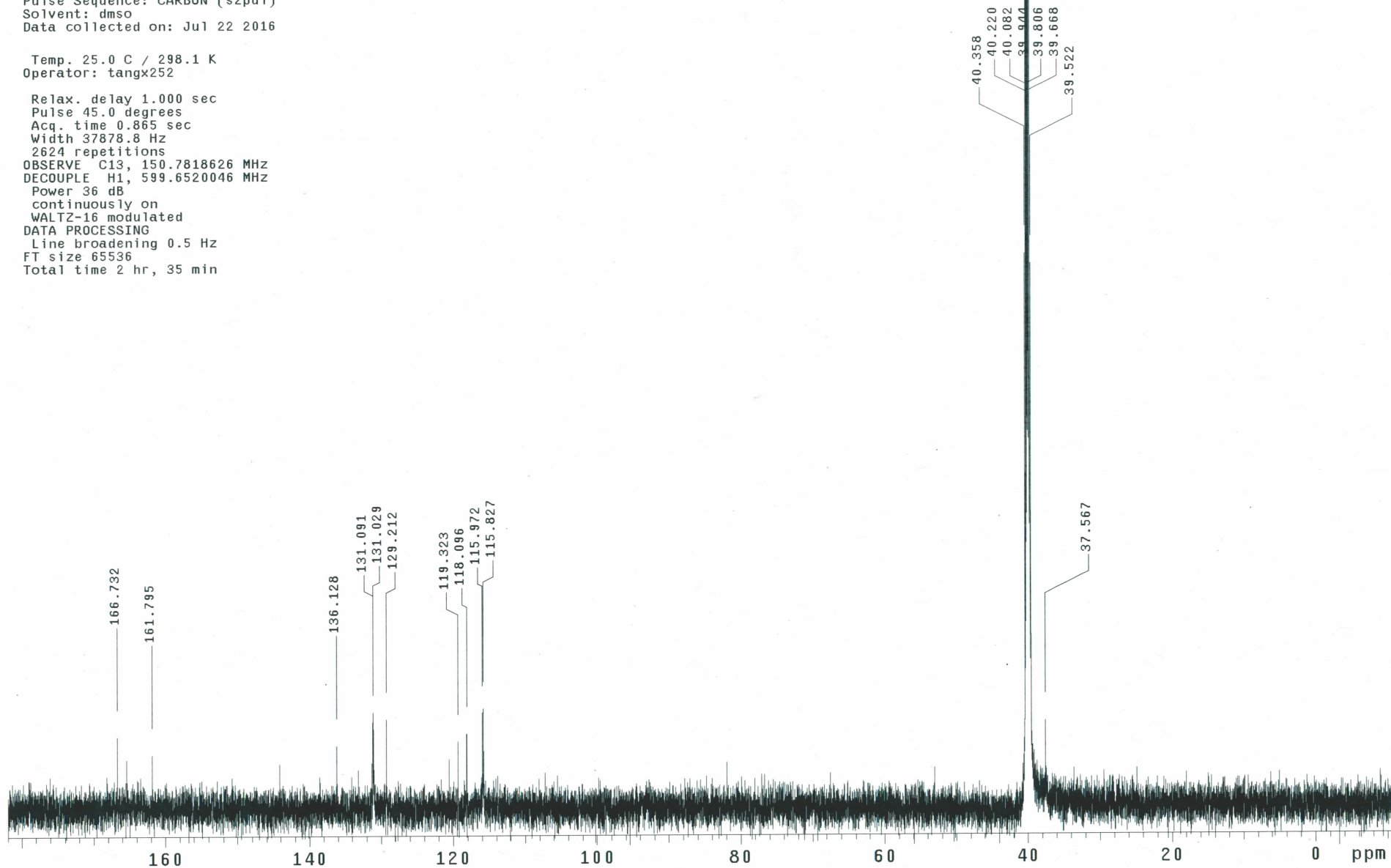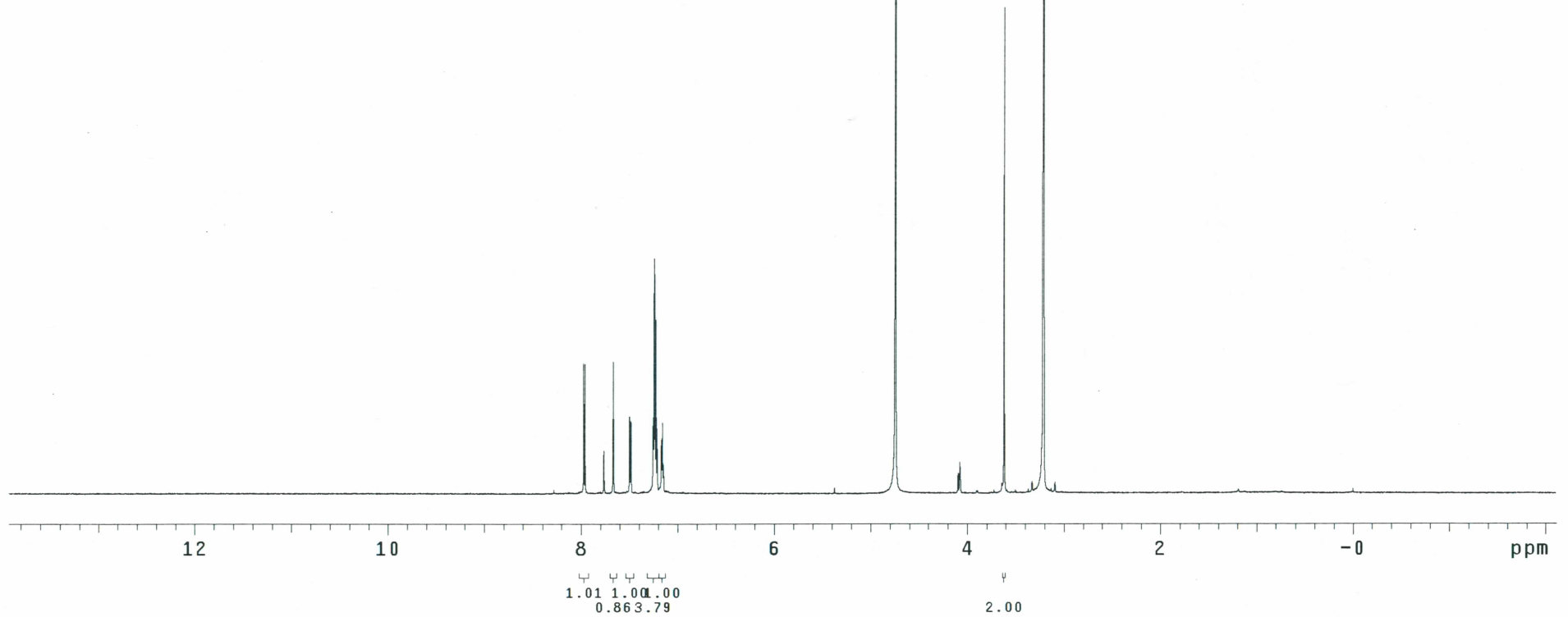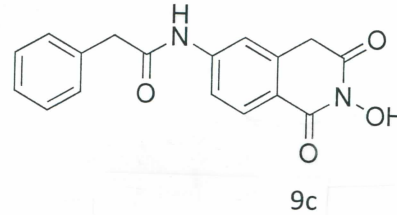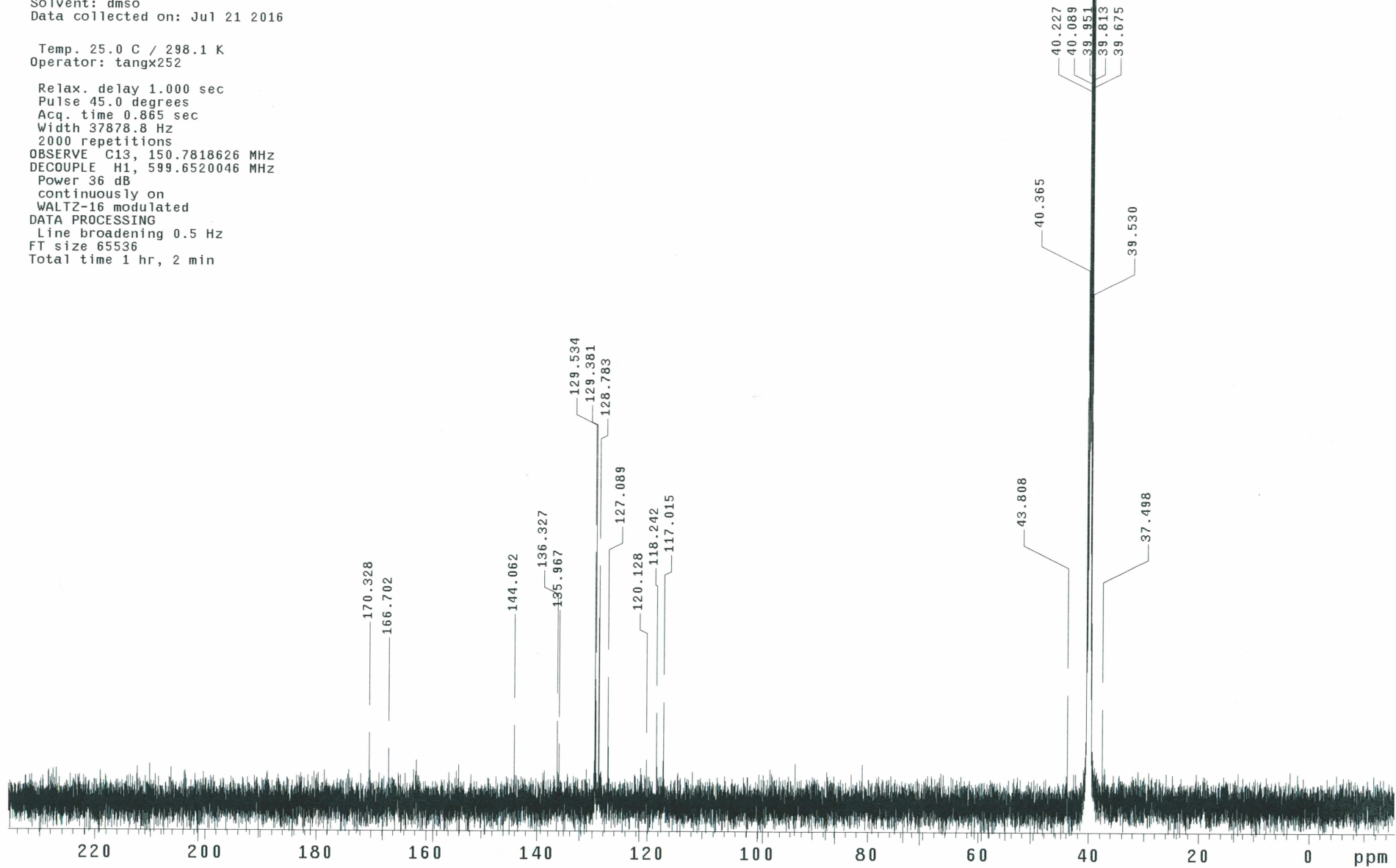1.06   1.99   1.13
   1.00 2.00   2.03

jt-6-7-13C

9a

Sample Name:
 jt-6-11
Data Collected on:
 nmr6003-vnmrs600
Archive directory:
 /data/tangx252
Sample directory:
 20110525_jt-6-11_01
FidFile: jt-6-11_PROTON_01

Pulse Sequence: PROTON (s2pul)
Solvent: cd3od
Data collected on: May 25 2011

Temp. 25.0 C / 298.1 K
Operator: tangx252

Relax. delay 1.000 sec
Pulse 45.0 degrees
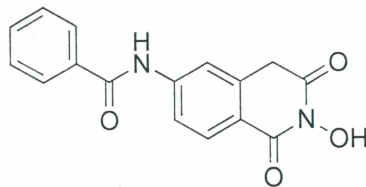Acq. time 1.704 sec
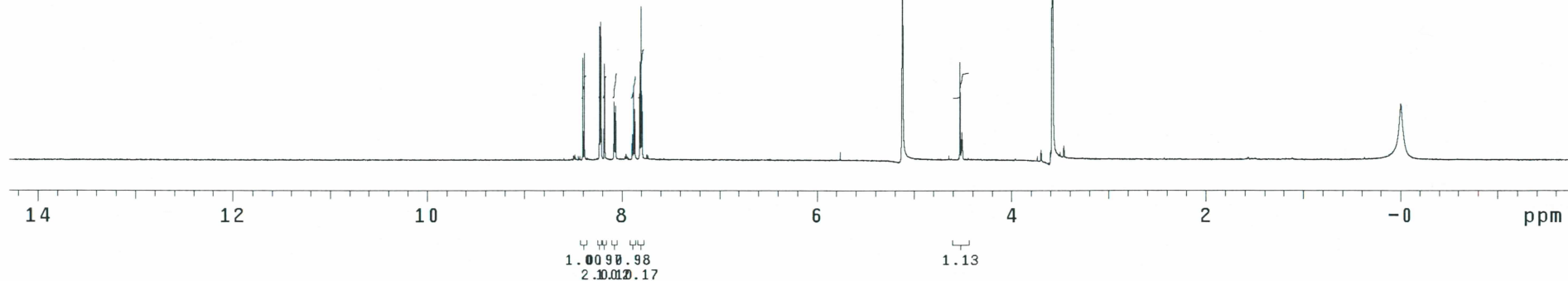Width 9615.4 Hz
32 repetitions
OBSERVE   H1, 599.6811318 MHz
DATA PROCESSING
FT size 32768
Total time 1 min 27 sec

9b

1.01 01 03
2.00 2.03 2.02

2.00

12   10   8   6   4   2   -0   ppm

jt-6-11-13C

9b

9c

1.01 1.00 1.00
   0.86 3.79

2.00

12   10   8   6   4   2   -0   ppm

9c

9d

1.009 0.98
2.10.010.17

1.13

14   12   10   8   6   4   2   −0   ppm

9d