Benzothiazole Derivatives Endowed with Antiproliferative Activity in Paraganglioma and Pancreatic Cancer Cells: Structure-Activity Relationship Studies and Target Prediction Analysis.

Rosa Amoroso[1,#], Laura De Lellis[1,2,#], Rosalba Florio[1], Nazaret Moreno Rodriguez[3], Mariangela Agamennone[1], Barbara De Filippis[1], Letizia Giampietro[1], Cristina Maccallini[1], Inmaculada Fernández[3], Rocío Recio[3], Alessandro Cama[1,2], Marialuigia Fantacuzzi[1,*], Alessandra Ammazzalorso[1,*]

1 Department of Pharmacy, "G. d'Annunzio" University of Chieti-Pescara, Via Dei Vestini 31, 66100 Chieti, Italy; rosa.amoroso@unich.it (R.A.); laura.delellis@unich.it (L.D.L.); rosalba.florio@unich.it (R.F.); mariangela.agamennone@unich.it (M.A.); barbara.defilippis@unich.it (B.D.F.); letizia.giampietro@unich.it (L.G.); cristina.maccallini@unich.it (C.M.); alessandro.cama@unich.it (A.C.).

2 Center for Advanced Studies and Technology CAST, Via Luigi Polacchi 11; 66100 Chieti, Italy.

3 Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, C/Profesor García González, 2, 41012, Sevilla, Spain; nmoreno4@us.es (N.M.R.); inmaff@us.es (I.F.F.); rrecioj@us.es (R. R.).

# These authors contributed equally to the work

Correspondence: alessandra.ammazzalorso@unich.it (A.A.); marialuigia.fantacuzzi@unich.it (M.F.).

*Corresponding authors: Dr. Alessandra Ammazzalorso, Department of Pharmacy, "G. d'Annunzio" University, Via dei Vestini 31, 66100 Chieti, Italy; Ph. +39 0871 3554682; alessandra.ammazzalorso@unich.it;

Dr. Marialuigia Fantacuzzi, Department of Pharmacy, "G. d'Annunzio" University, Via dei Vestini 31, 66100 Chieti, Italy; Ph. +39 0871 3554684; marialuigia.fantacuzzi@unich.it.

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Supplementary Table S1. Selectivity index (SI) values for compounds **2b**, **4d**, **4e**, **4f**, **4h**, **4i**, **4j** and **4m**. SI values were calculated for each compound as follows: IC_{50} in normal (HFF-1) fibroblast cells/IC_{50} in pancreatic (AsPC-1, BxPC-3 and Capan-2), or paraganglioma (PTJ64i, PTJ86i) cancer cells (see IC_{50} values in **Table 2** of the main text).

	Selectivity index (SI) values				
	Pancreatic cancer			Paraganglioma	
	AsPC-1	**BxPC-3**	**Capan-2**	**PTJ64i**	**PTJ86i**
2b	1.72	1.43	1.09	2.52	1.28
4d	1.20	2.31	1.03	1.36	0.74
4e	1.31	1.56	1.18	1.70	0.88
4f	0.65	0.35	0.33	0.53	0.51
4h	0.95	0.96	0.65	1.59	0.70
4i	1.01	0.81	0.53	1.74	1.28
4j	1.90	1.30	0.75	1.62	1.04
4m	1.22	1.05	0.77	1.32	0.52

Supplementary Figure S1. Effect of combined treatments with compound **4k** and gemcitabine on the viability of pancreatic cancer (AsPC-1, BxPC-3 and Capan-2) and normal (HFF-1) fibroblast cells. Cell viability was assessed by MTT assays after a 72-h incubation of cells with **4k** and gemcitabine at the indicated concentrations, as single agents or in combination. Histograms represent the means ±SD of two independent experiments with quintuplicate determinations. Combination indexes (CIs) were calculated by CompuSyn software. Combinations assessed as synergistic by CIs < 1 are indicated.
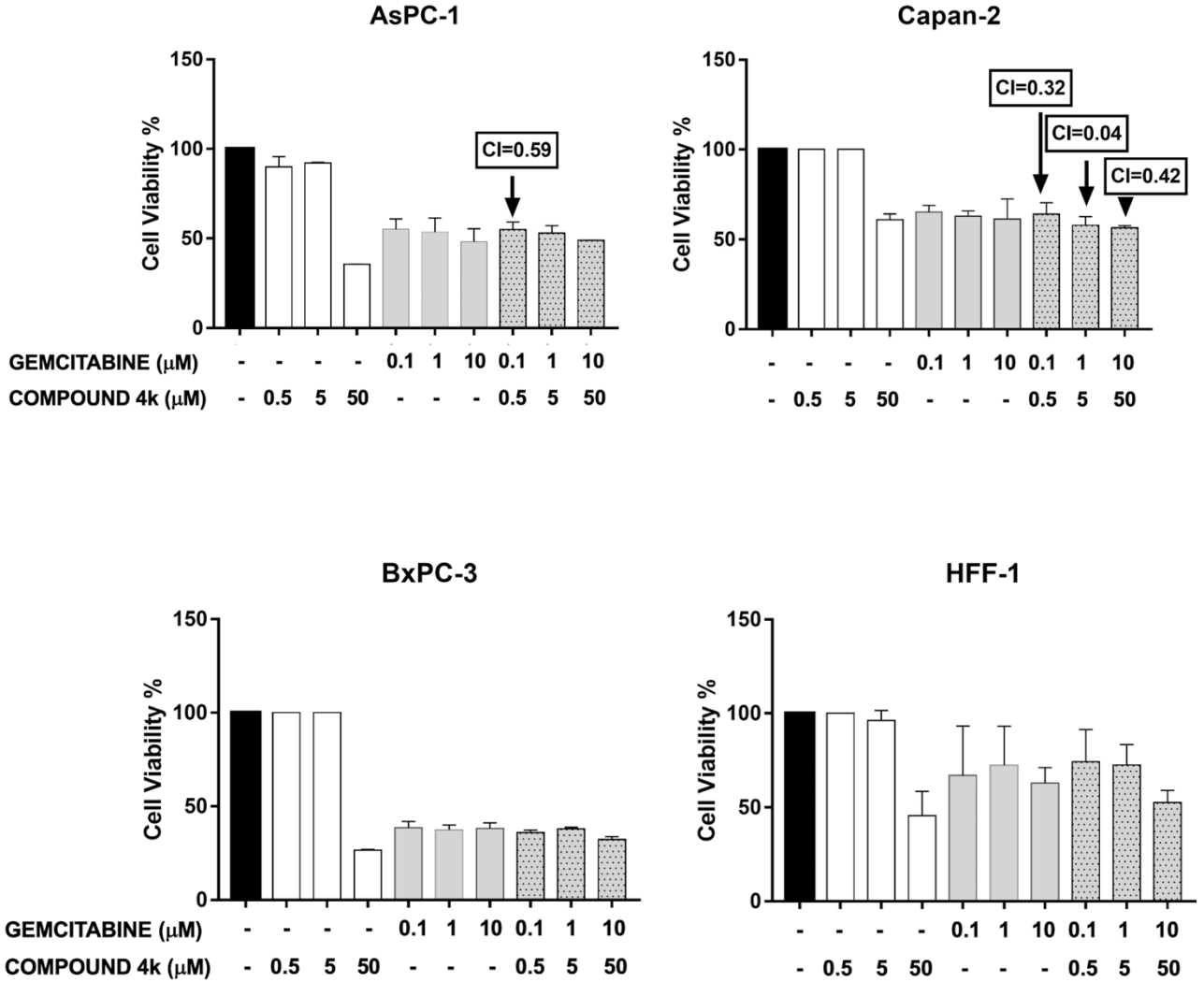
Supplementary Figure S2. Interaction diagram of compounds **2b**, **4a-p** in the catalytic site of CBR1 (PDB:6KPG).
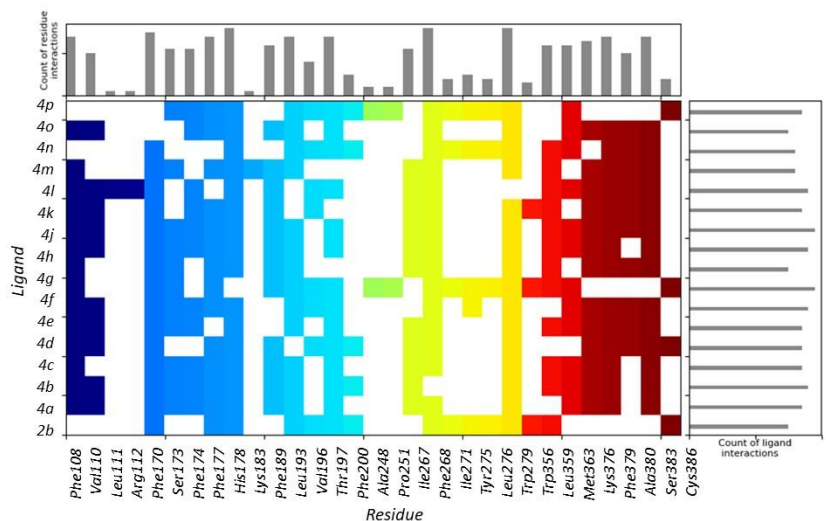
Supplementary Figure S3. Interaction diagram of compounds **2b**, **4a-p** in the catalytic site of the chimera SENP2-loop1 of SENP6 (PDB:3ZO5).

4a

5.44   5.36 11.25 6.5537.48 11.05   5.67   17.19

4a

Gradient Shimming

4b

6.85

6.48
13.18
14.02
45.66
6.84

6.96

13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 ppm

Gradient Shimming

Sample Name:
AA948A
Data Collected on:
m300-mercury300
Archive directory:
/home/ammazza/vnmrsys/data
Sample directory:
MF255_20150422_01
FidFile: AA948A_C13

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Sep 28 2020

Operator: ammazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 18867.9 Hz
1080 repetitions
OBSERVE C13, 75.4847602 MHz
DECOUPLE H1, 300.1991980 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 16 hr, 6 min

4b

180   160   140   120   100   80   60   40   20   ppm
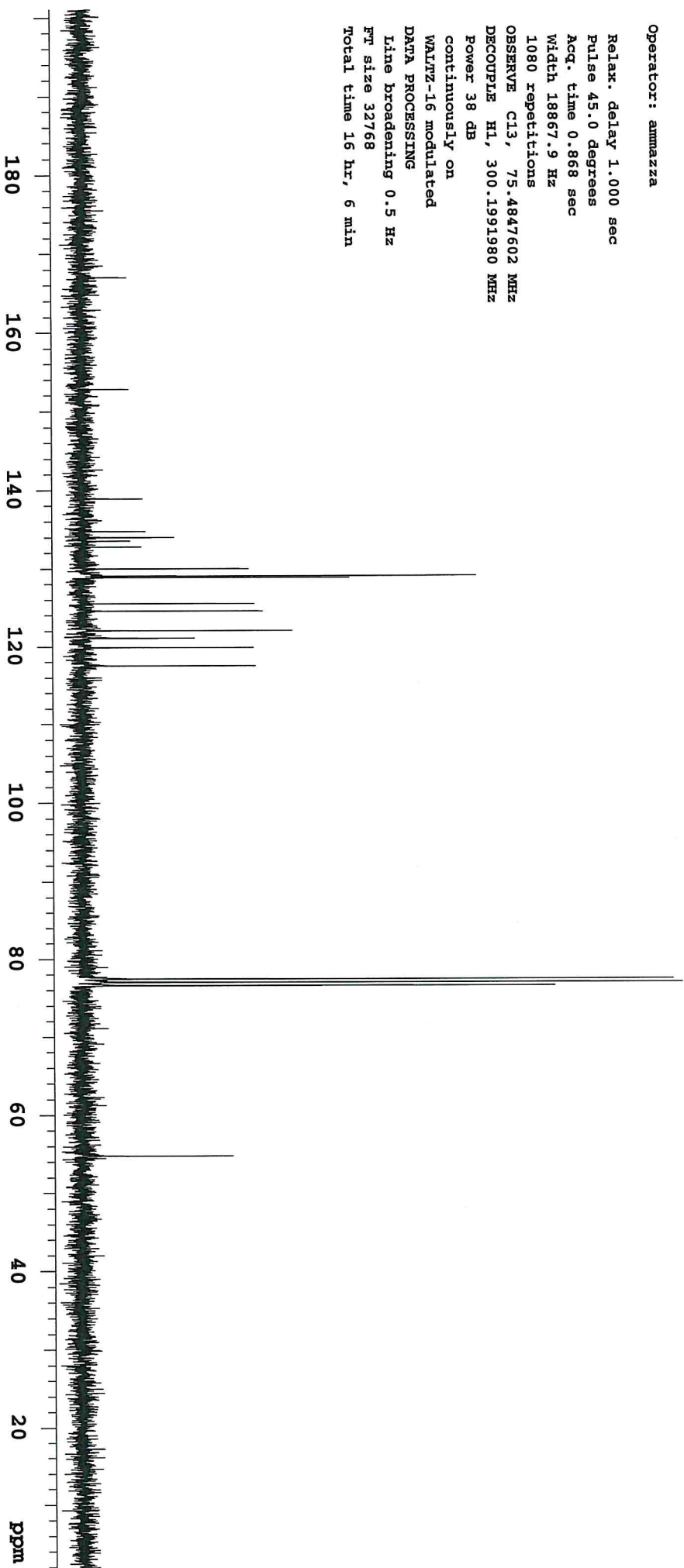
Sample Name:
    AA701A
Data Collected on:
    m300-mercury300
Archive directory:
    /export/home/chempack/vnmrsys/data
Sample directory:

    FidFile: AA701A

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 19 2015

Temp. 18.0 C / 291.1 K
Operator: ammazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.706 sec
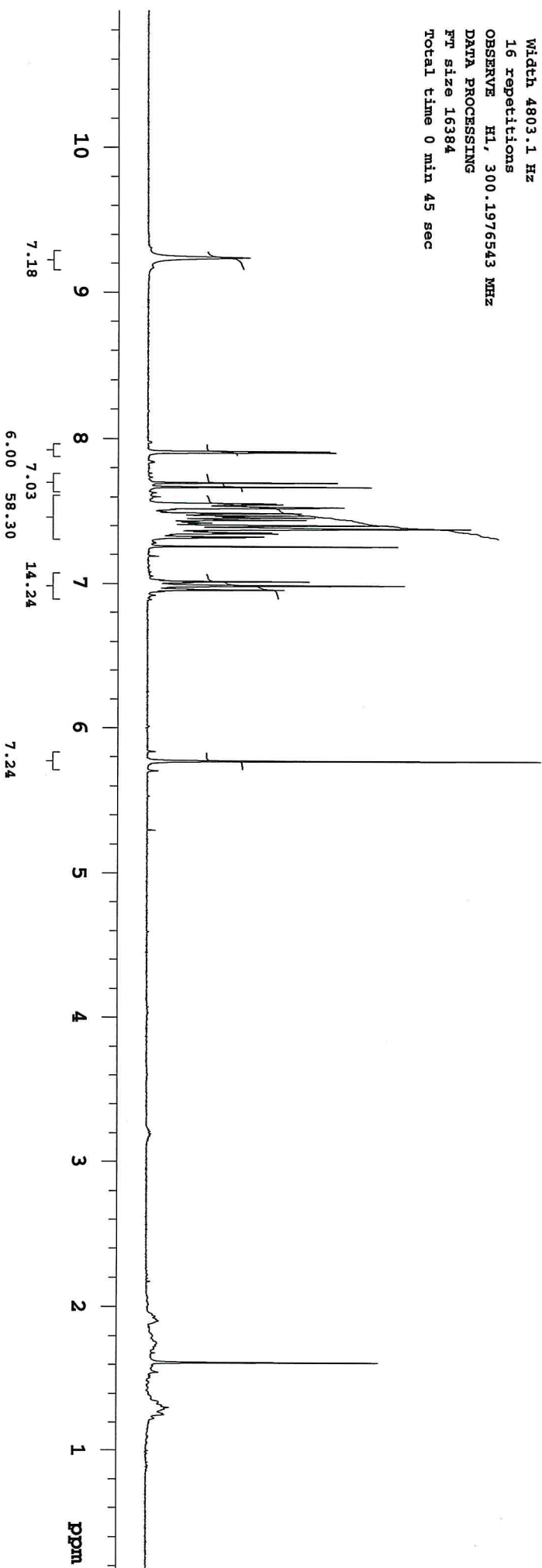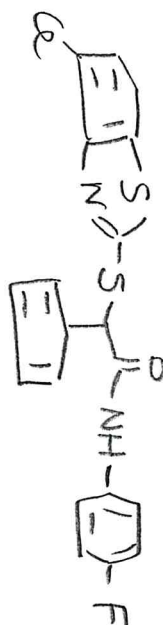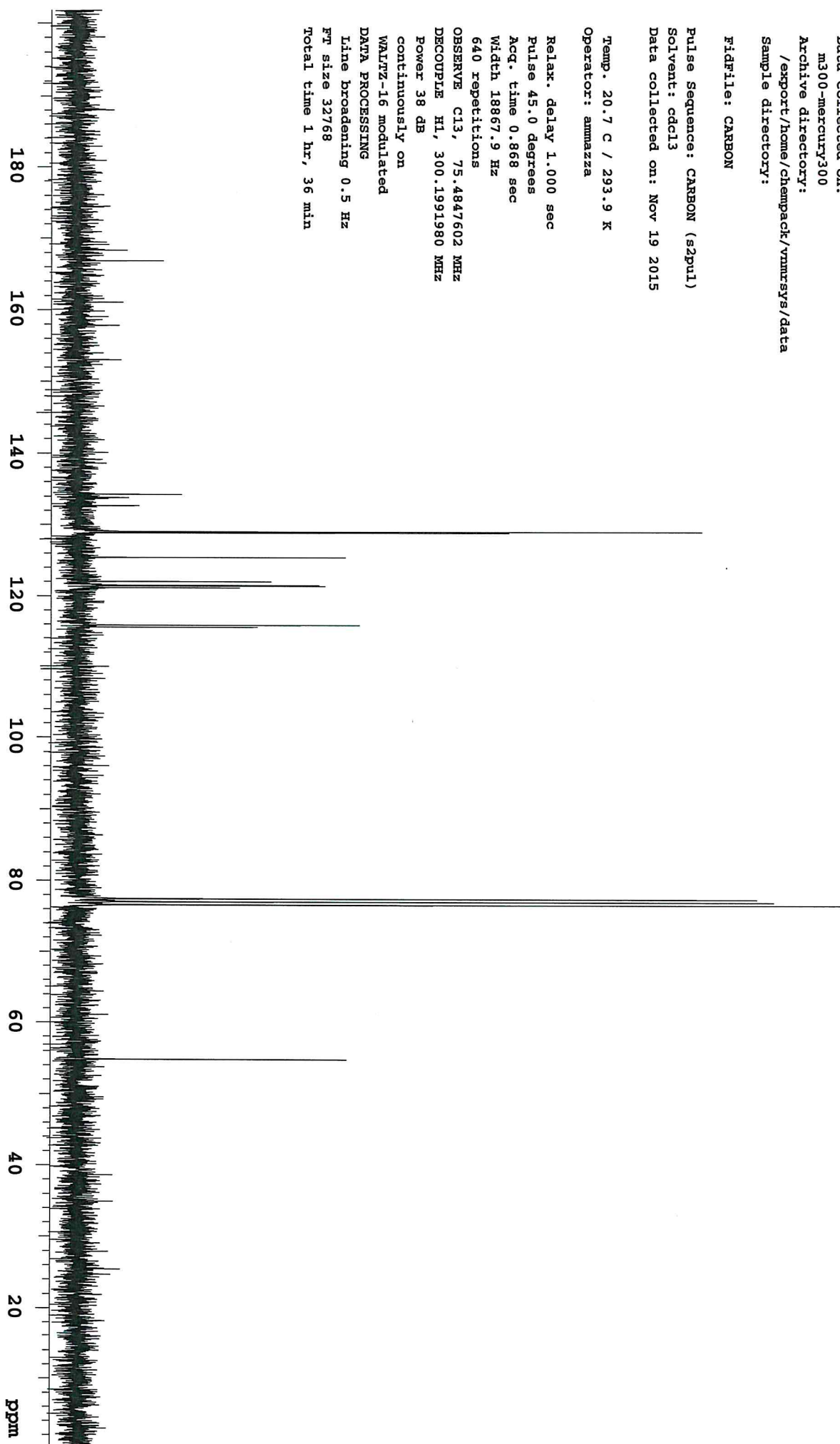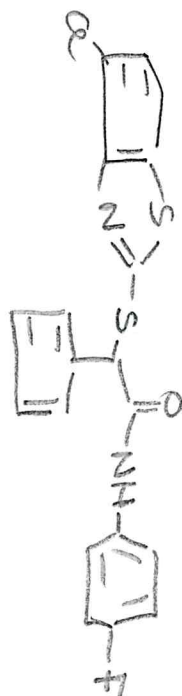Width 4803.1 Hz
16 repetitions
OBSERVE   H1, 300.1976543 MHz
DATA PROCESSING
FT size 16384
Total time 0 min 45 sec

4c

7.18

6.00 7.03   14.24   7.24
     58.30

10   9   8   7   6   5   4   3   2   1   ppm

Gradient Shimming

Sample Name:
Data Collected on:
m300-mercury300
Archive directory:
/export/home/chempack/vnmrsys/data
Sample directory:

FidFile: CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 19 2015

Temp. 20.7 C / 293.9 K
Operator: ammazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 18867.9 Hz
640 repetitions
OBSERVE C13, 75.4847602 MHz
DECOUPLE H1, 300.1991980 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 1 hr, 36 min

4C

180   160   140   120   100   80   60   40   20   ppm

401

6.80

21.2229.57
6.70 28.50

7.21

11   10   9   8   7   6   5   4   3   2   1   ppm

Gradient Shimming

Sample Name:
AA955A
Data Collected on:
m300-mercury300
Archive directory:
/home/ammazza/vnmrsys/data
Sample directory:
MF255_20150422_01
FidFile: CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 11 2020

Temp. 17.6 C / 290.8 K
Operator: ammazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 18867.9 Hz
2688 repetitions
OBSERVE C13, 75.4847602 MHz
DECOUPLE H1, 300.1991980 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 2 hr, 8 min
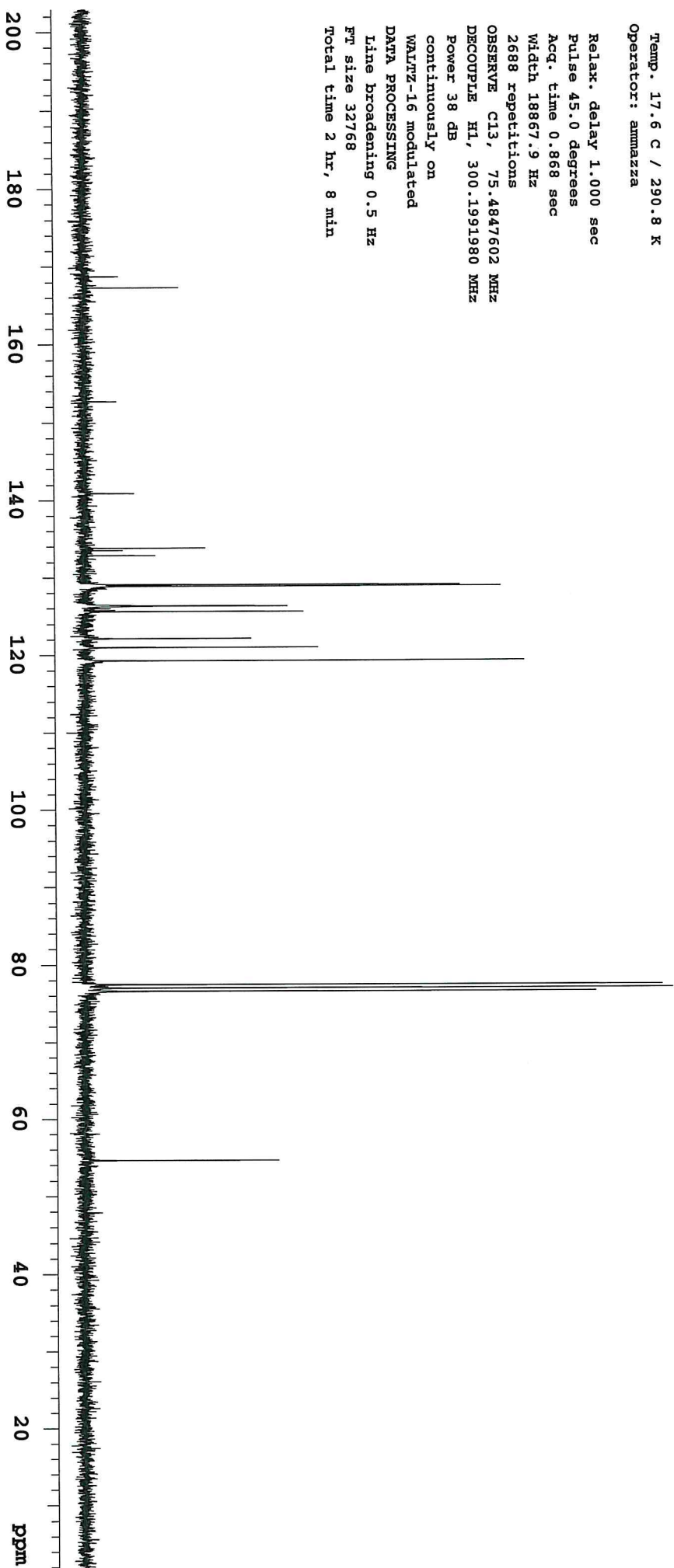
42

Sample Name:
    AA952A
Data Collected on:
    m300-mercury300
Archive directory:
    /home/ammazza/vnmrsys/data
Sample directory:
    MF255_20150422_01
FidFile: AA952A

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 7 2020

Operator: ammazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.706 sec
Width 4803.1 Hz
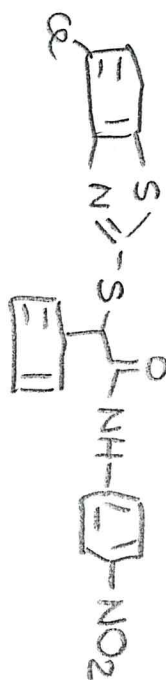16 repetitions
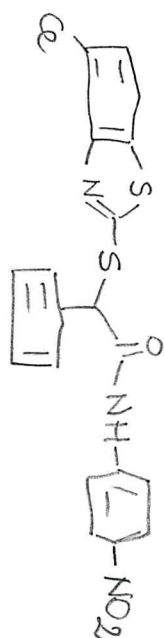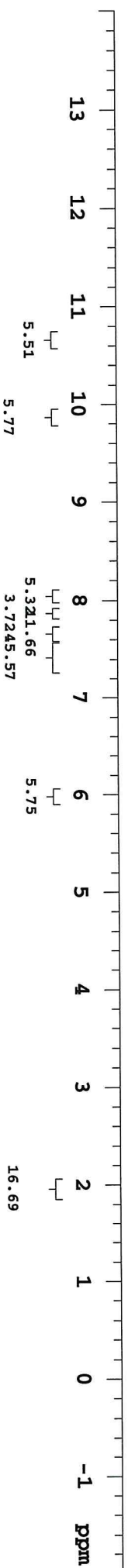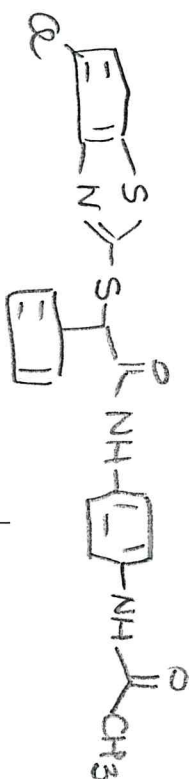OBSERVE H1, 300.1976543 MHz
DATA PROCESSING
FT size 16384
Total time 0 min 45 sec

4e

5.68

6.51 18.4925.43
12.56.97 12.89

6.25

6.21

10   9   8   7   6   5   4   3   2   1   ppm

4e
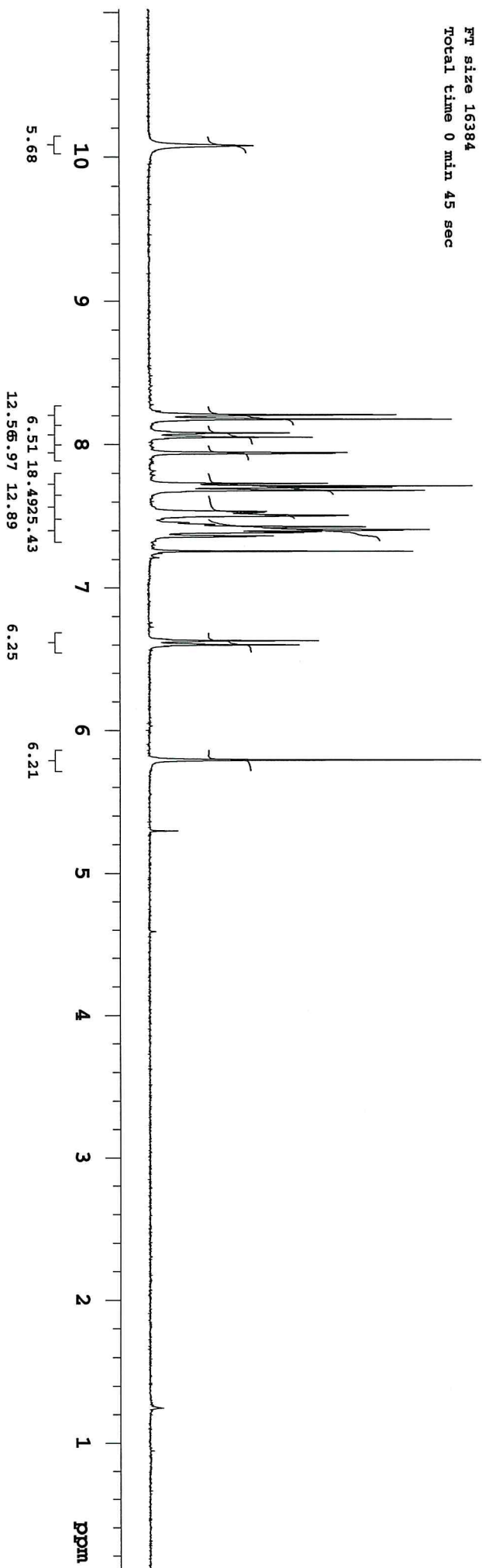
Gradient Shimming

Sample Name:
AA952A

Data Collected on:
m300-mercury300

Archive directory:
/home/anmazza/vnmrsys/data

Sample directory:
MF255_20150422_01

FidFile: CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 8 2020

Temp. 18.7 C / 291.9 K
Operator: anmazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 18867.9 Hz
4032 repetitions
OBSERVE C13, 75.4847602 MHz
DECOUPLE H1, 300.1991980 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 3 hr, 13 min
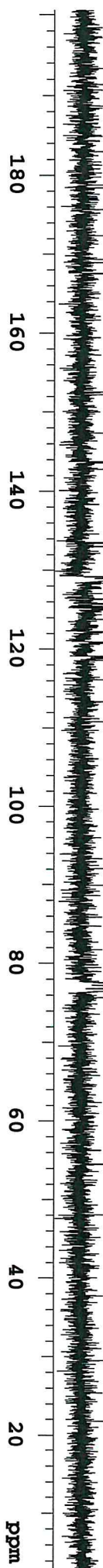
Gradient Shimming

Sample Name:
AA675ppt
Data Collected on:
m300-mercury300
Archive directory:
/export/home/chempack/vnmrsys/data
Sample directory:

FidFile: AA675ppt

Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Oct 27 2014

Operator: ammazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.706 sec
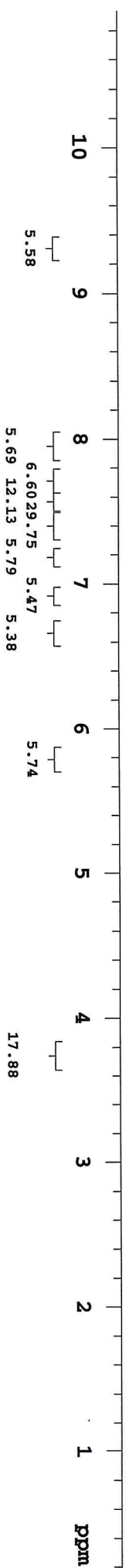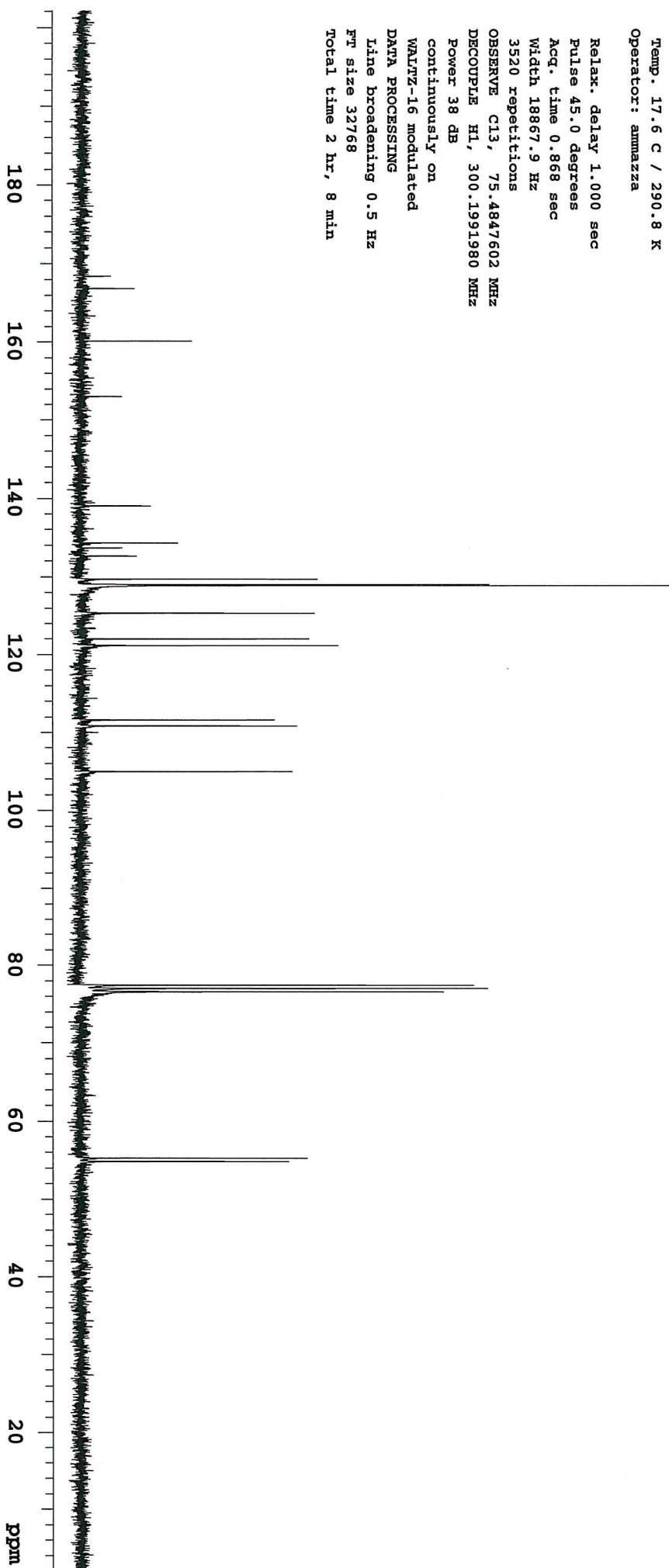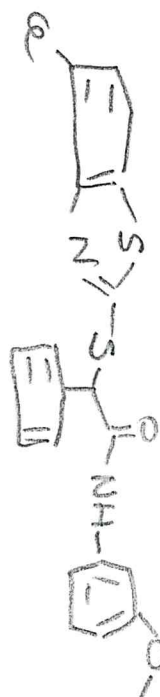Width 4803.1 Hz
16 repetitions
OBSERVE   H1, 300.1990802 MHz
DATA PROCESSING
FT size 16384
Total time 0 min 45 sec

4 f

13   12   11   10   9   8   7   6   5   4   3   2   1   0   -1   ppm

5.51   5.77   5.32 5.75   5.75   16.69
                    21.66
                    3.72
                    45.57

Gradient Shimming

Sample Name:
AA675ppt
Data Collected on:
m300-mercury300
Archive directory:
/export/home/chempack/vnmrsys/data
Sample directory:

FidFile: CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Oct 27 2014

Temp. 20.1 C / 293.2 K
Operator: ammazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 18867.9 Hz
576 repetitions
OBSERVE C13, 75.4851188 MHz
DECOUPLE H1, 300.2006240 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 1 hr, 4 min

4f

180   160   140   120   100   80   60   40   20   ppm
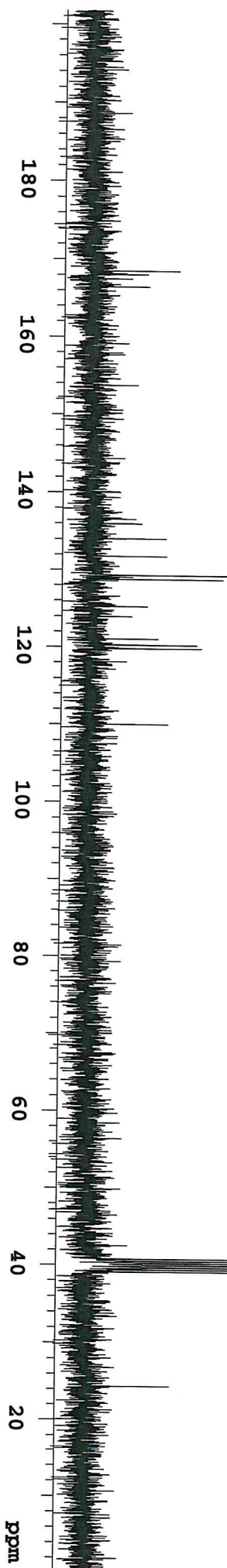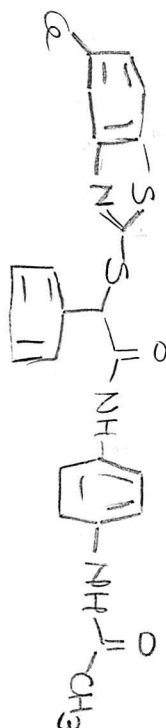
Gradient Shimming

Sample Name:
AA1009A
Data Collected on:
m300-mercury300
Archive directory:
/home/ammazza/vnmrsys/data
Sample directory:
AA1008A_20210409_01
FidFile: AA1009A

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 9 2021

Operator: ammazza

Relax. delay 1.000 sec
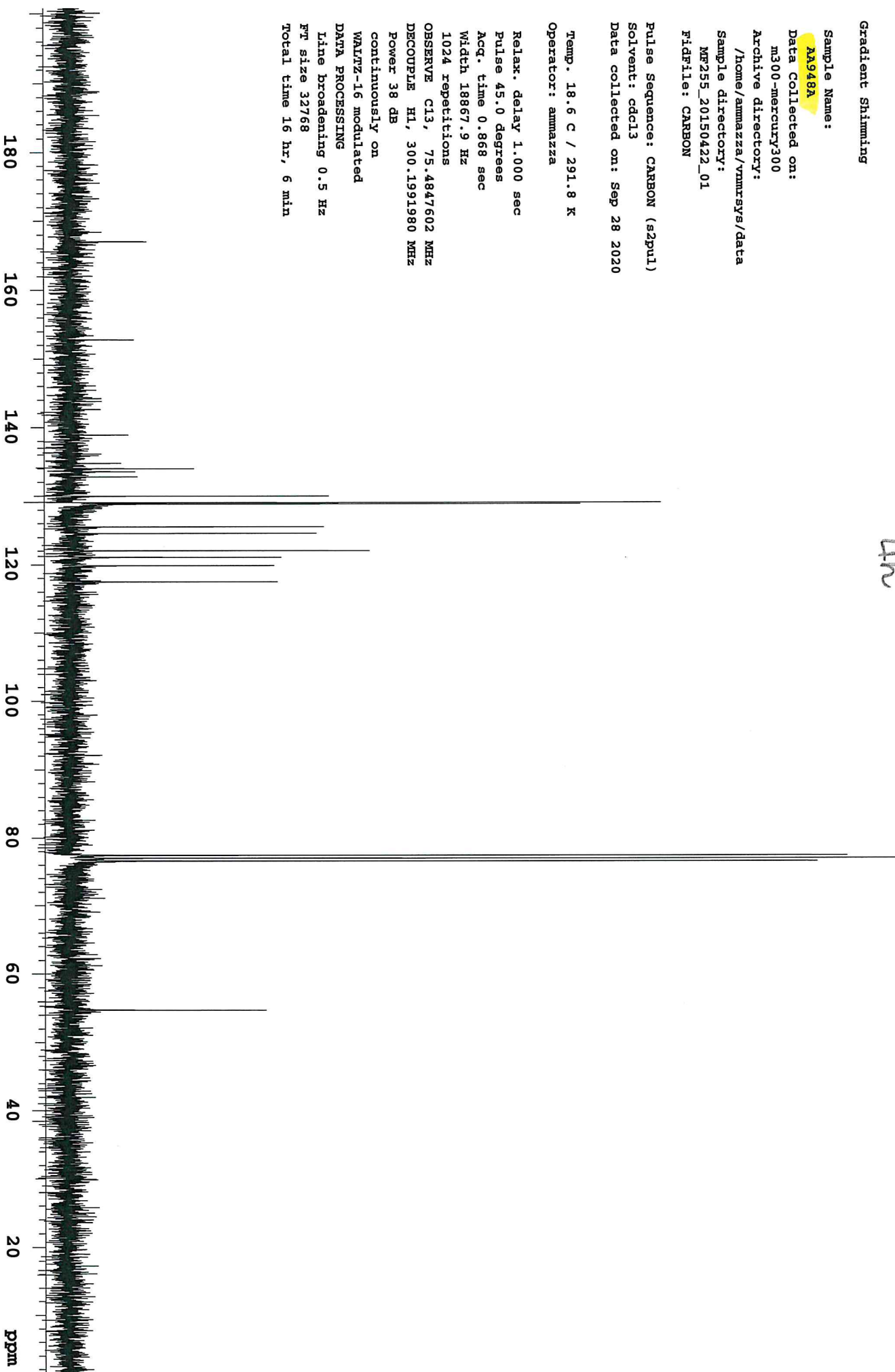Pulse 45.0 degrees
Acq. time 1.706 sec
Width 4803.1 Hz
16 repetitions
OBSERVE H1, 300.1976543 MHz
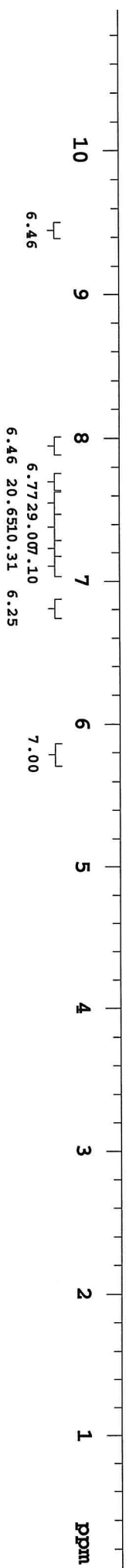DATA PROCESSING
FT size 16384
Total time 0 min 45 sec

10   9   8   7   6   5   4   3   2   1   ppm

5.58

5.69   6.60 5.47   5.74   17.88
12.13 29.75
       5.79
       5.38

Gradient Shimming

409

180 160 140 120 100 80 60 40 20 ppm

Sample Name:
AA948A
Data Collected on:
m300-mercury300
Archive directory:
/home/ammazza/vnmrsys/data
Sample directory:
MF255_20150422_01
FidFile: AA948A

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 28 2020

Operator: ammazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.706 sec
Width 4803.1 Hz
16 repetitions
OBSERVE   H1, 300.1976543 MHz
DATA PROCESSING
FT size 16384
Total time 0 min 45 sec

6.69

13.328.22 6.62
6.49 14.0517.72
6.88

10   9   8   7   6   5   4   3   2   1   ppm
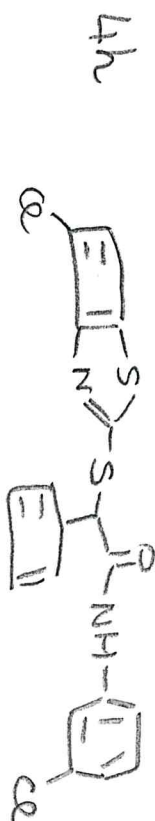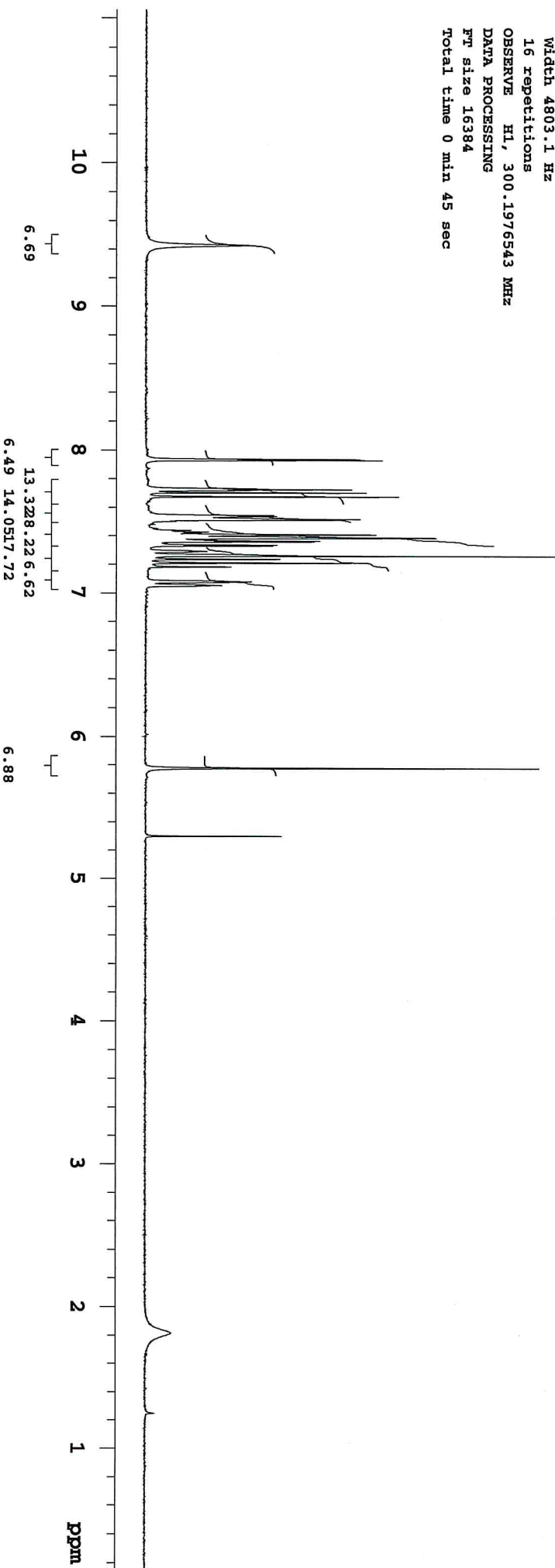
Gradient Shimming

Sample Name:
AA948A

Data Collected on:
m300-mercury300
Archive directory:
/home/ammazza/vnmrsys/data
Sample directory:
MF255_20150422_01
FidFile: CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Sep 28 2020

Temp. 18.6 C / 291.8 K
Operator: ammazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 18867.9 Hz
1024 repetitions
OBSERVE C13, 75.4847602 MHz
DECOUPLE H1, 300.1991980 MHz
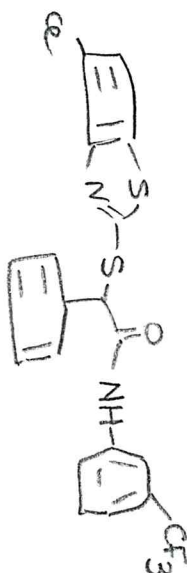Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 16 hr, 6 min

4h

4i

6.46
6.46 20.6510.31 6.25
6.7729.007.10
7.00

Gradient Shimming

Data Collected on:
m300-mercury300
Archive directory:
/export/home/chempack/vnmrsys/data
Sample directory:

FidFile: CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 19 2015

Temp. 20.7 C / 293.9 K
Operator: ammazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 18867.9 Hz
192 repetitions
OBSERVE C13, 75.4847602 MHz
DECOUPLE H1, 300.1991980 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 1 hr, 36 min

4i
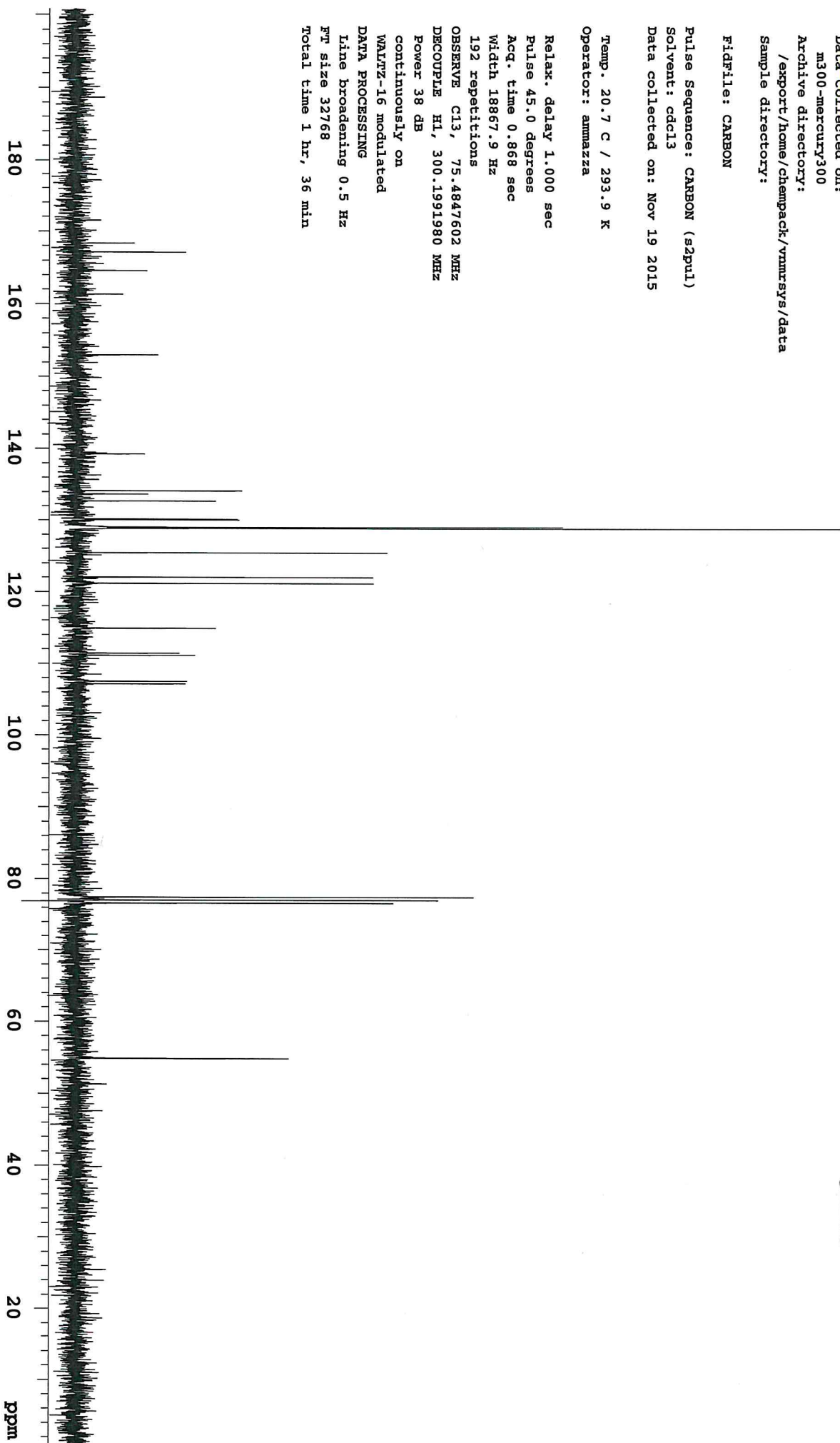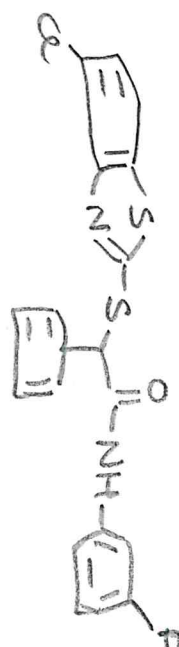
180   160   140   120   100   80   60   40   20   ppm

Gradient Shimming

Sample Name:
AA993B

Data Collected on:
m300-mercury300

Archive directory:
/home/ammazza/vnmrsys/data
Sample directory:
MF255_20150422_01
FidFile: AA993B2

Operator: ammazza

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 22 2021

Relax. delay 1.000 sec
Pulse 45.0 degrees
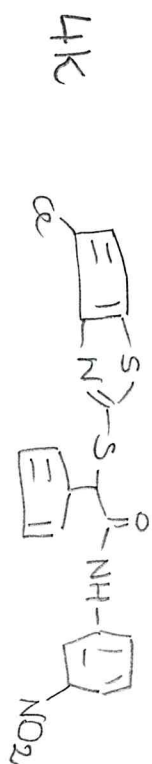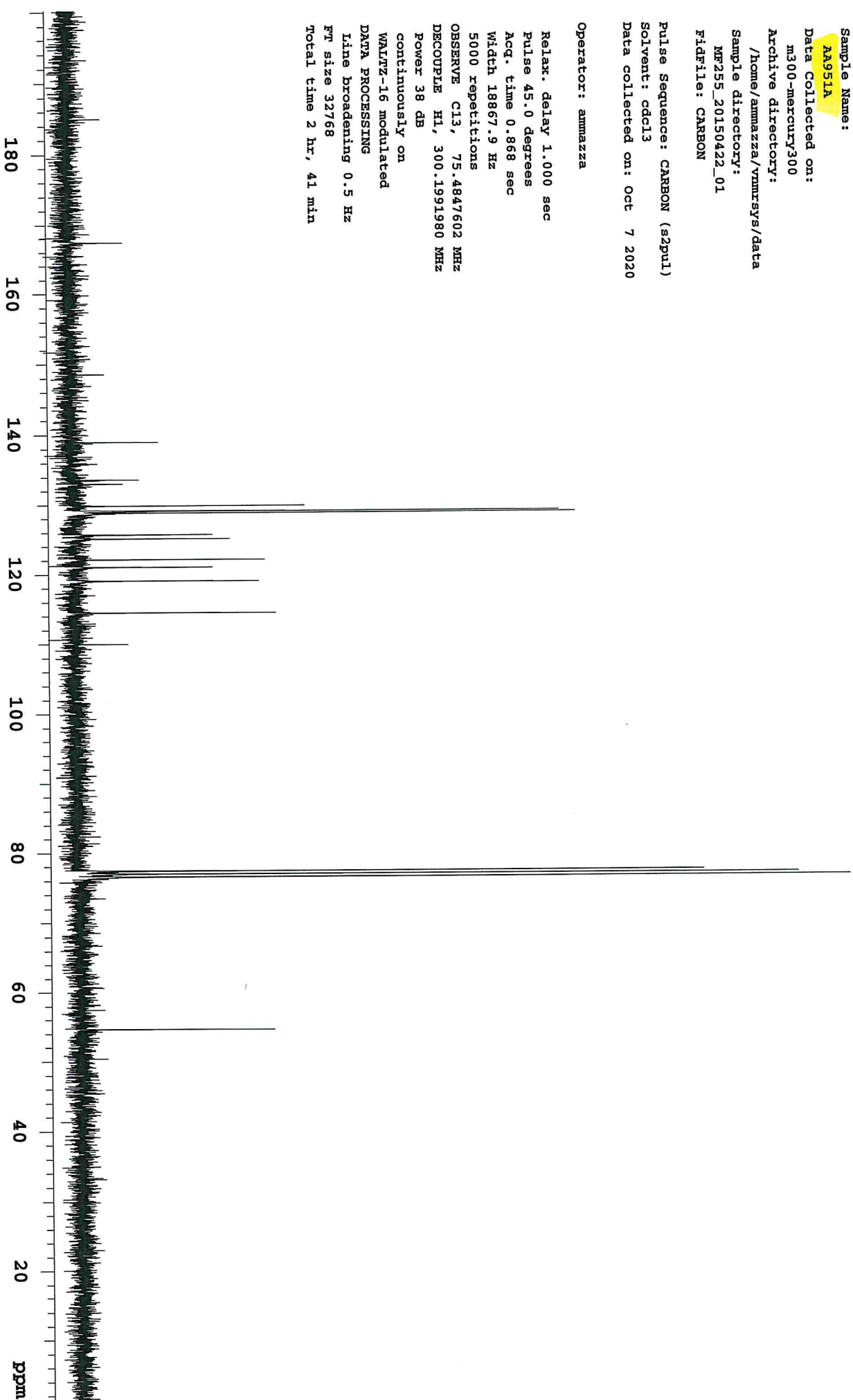Acq. time 1.706 sec
Width 4803.1 Hz
16 repetitions
OBSERVE H1, 300.1976543 MHz
DATA PROCESSING
FT size 16384
Total time 0 min 45 sec

4J

ppm scale markings: 10, 9, 8, 7, 6, 5, 4

6.16

12.42   6.813.74
        7.8345.90

7.14

Gradient Shimming

4J

Gradient Shimming

Sample Name:
  AA951A
Data Collected on:
  m300-mercury300
Archive directory:
  /home/ammazza/vnmrsys/data
Sample directory:
  MF255_20150422_01
FidFile: AA951A

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 7 2020

Operator: ammazza

  Relax. delay 1.000 sec
  Pulse 45.0 degrees
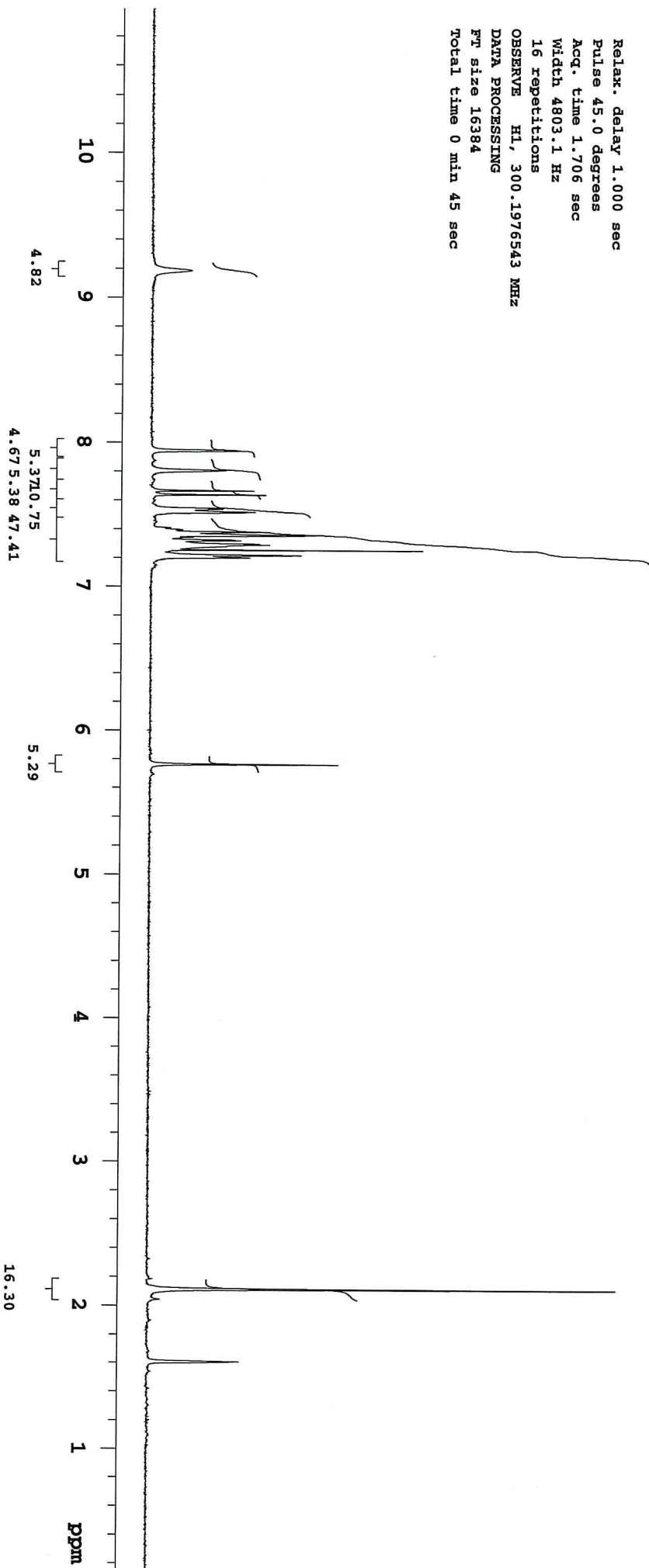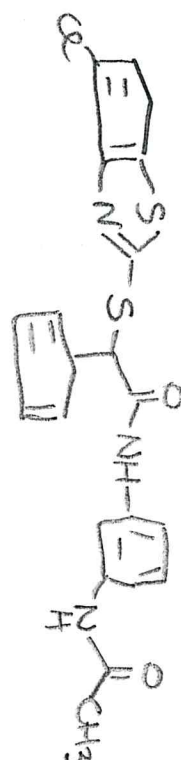 Acq. time 1.706 sec
  Width 4803.1 Hz
  16 repetitions
  OBSERVE   H1, 300.1976543 MHz
  DATA PROCESSING
  FT size 16384
  Total time 0 min 45 sec

4K
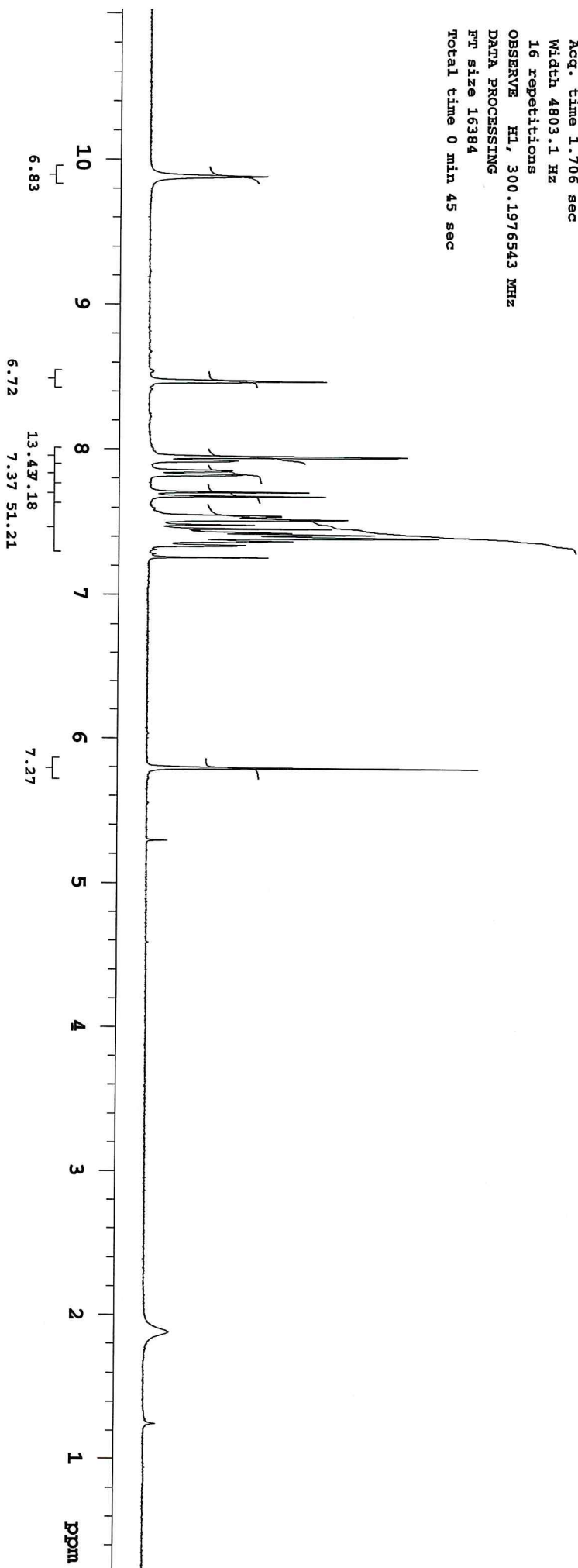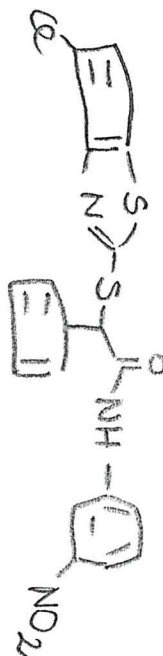
6.83   6.72   13.43 7.18   7.27
              7.37 51.21

Gradient Shimming

4K

Sample Name:
AA951A
Data Collected on:
n300-mercury300
Archive directory:
/home/anmazza/vnmrsys/data
Sample directory:
MF255_20150422_01
Fidfile: CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 7 2020

Operator: anmazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 18867.9 Hz
5000 repetitions
OBSERVE C13, 75.4847602 MHz
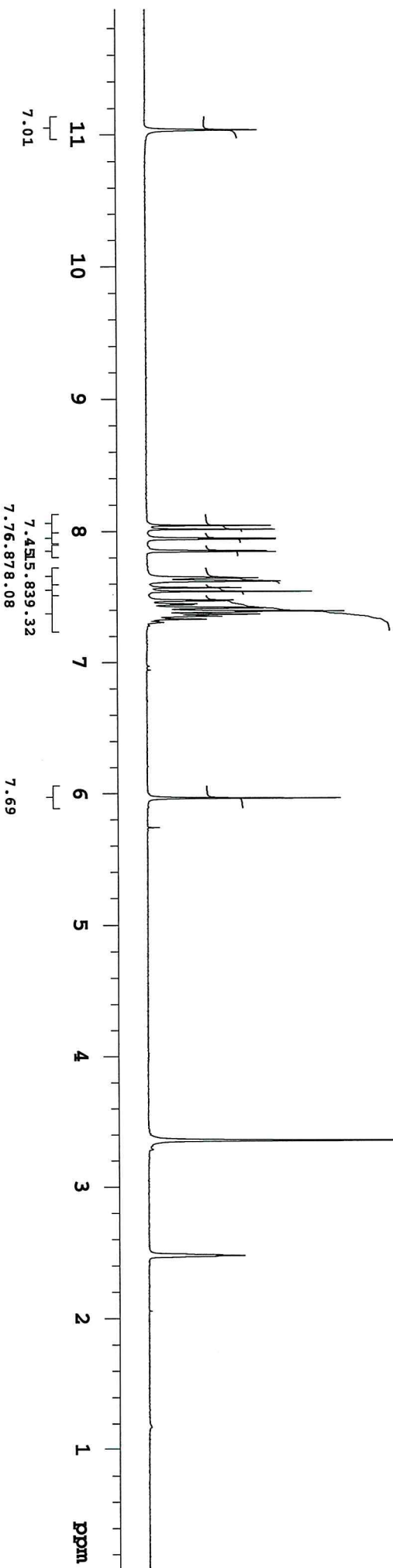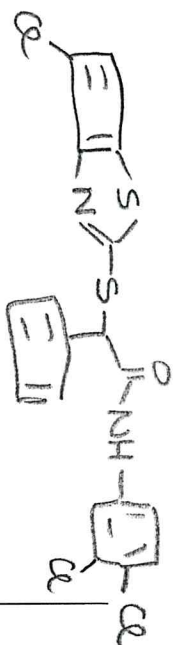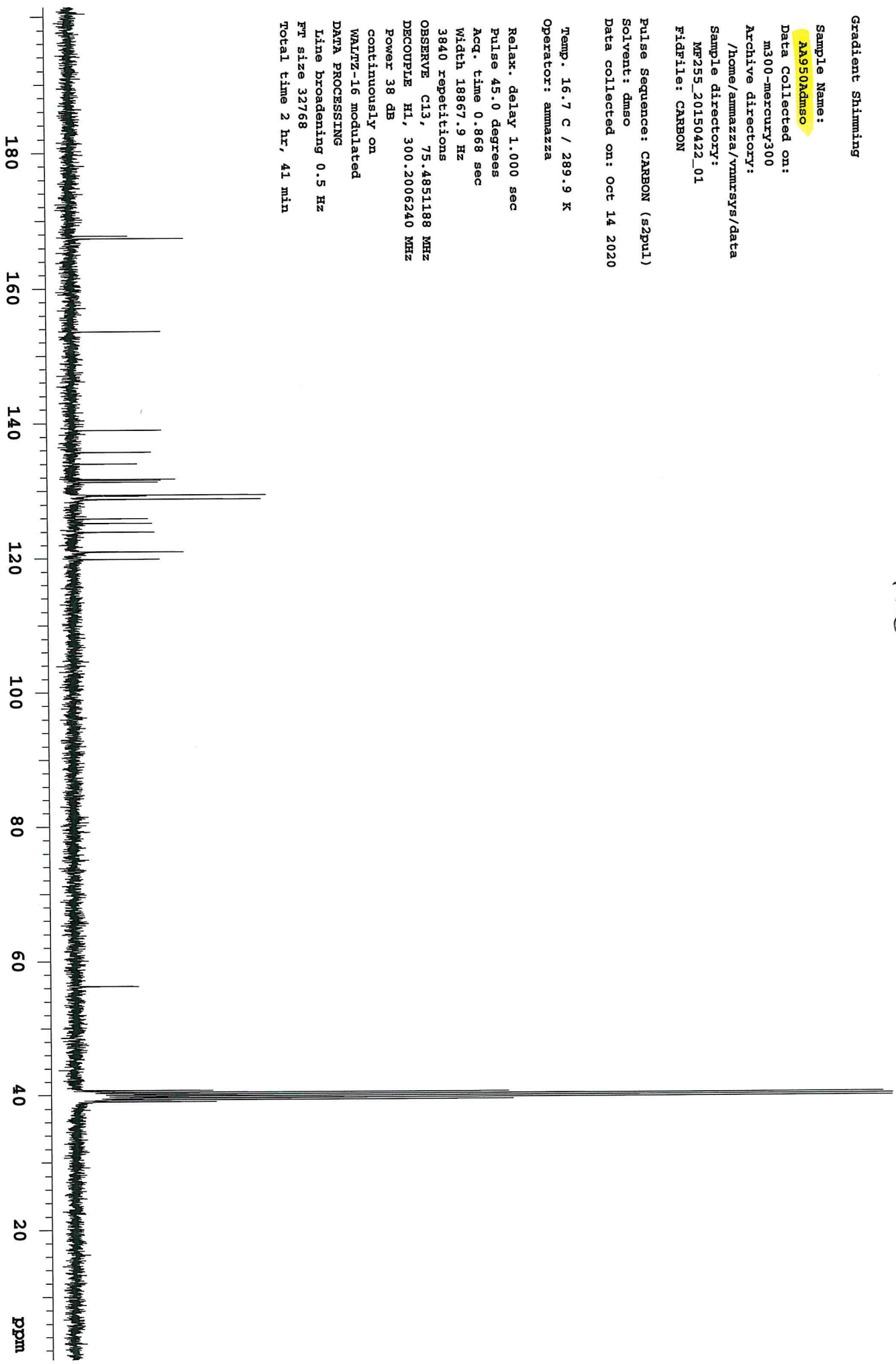DECOUPLE H1, 300.1991980 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 2 hr, 41 min

180 160 140 120 100 80 60 40 20 ppm

Sample Name:
AA1016ppt
Data Collected on:
m300-mercury300
Archive directory:
/home/anmazza/vnmrsys/data
Sample directory:
AA1008A_20210409_01
FidFile: AA1016ppt

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 22 2021

Operator: anmazza

Relax. delay 1.000 sec
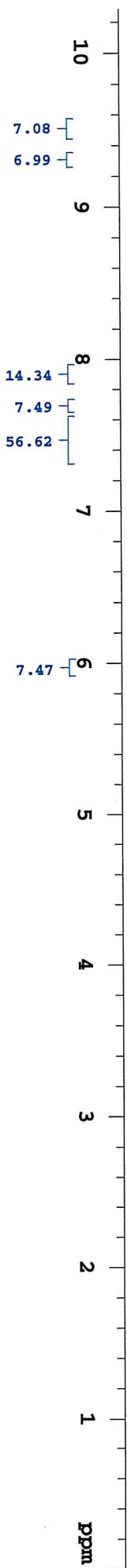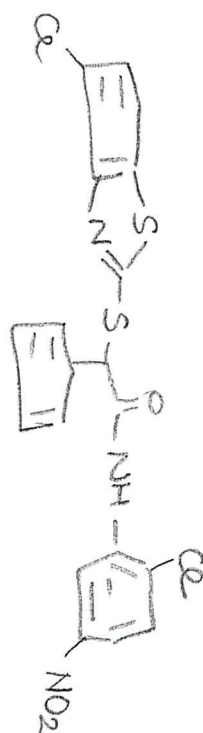Pulse 45.0 degrees
Acq. time 1.706 sec
Width 4803.1 Hz
16 repetitions
OBSERVE   H1, 300.1976543 MHz
DATA PROCESSING
FT size 16384
Total time 0 min 45 sec

42

4.82
5.37 10.75
4.67 5.38 47.41
5.29
16.30

Gradient Shimming

4l
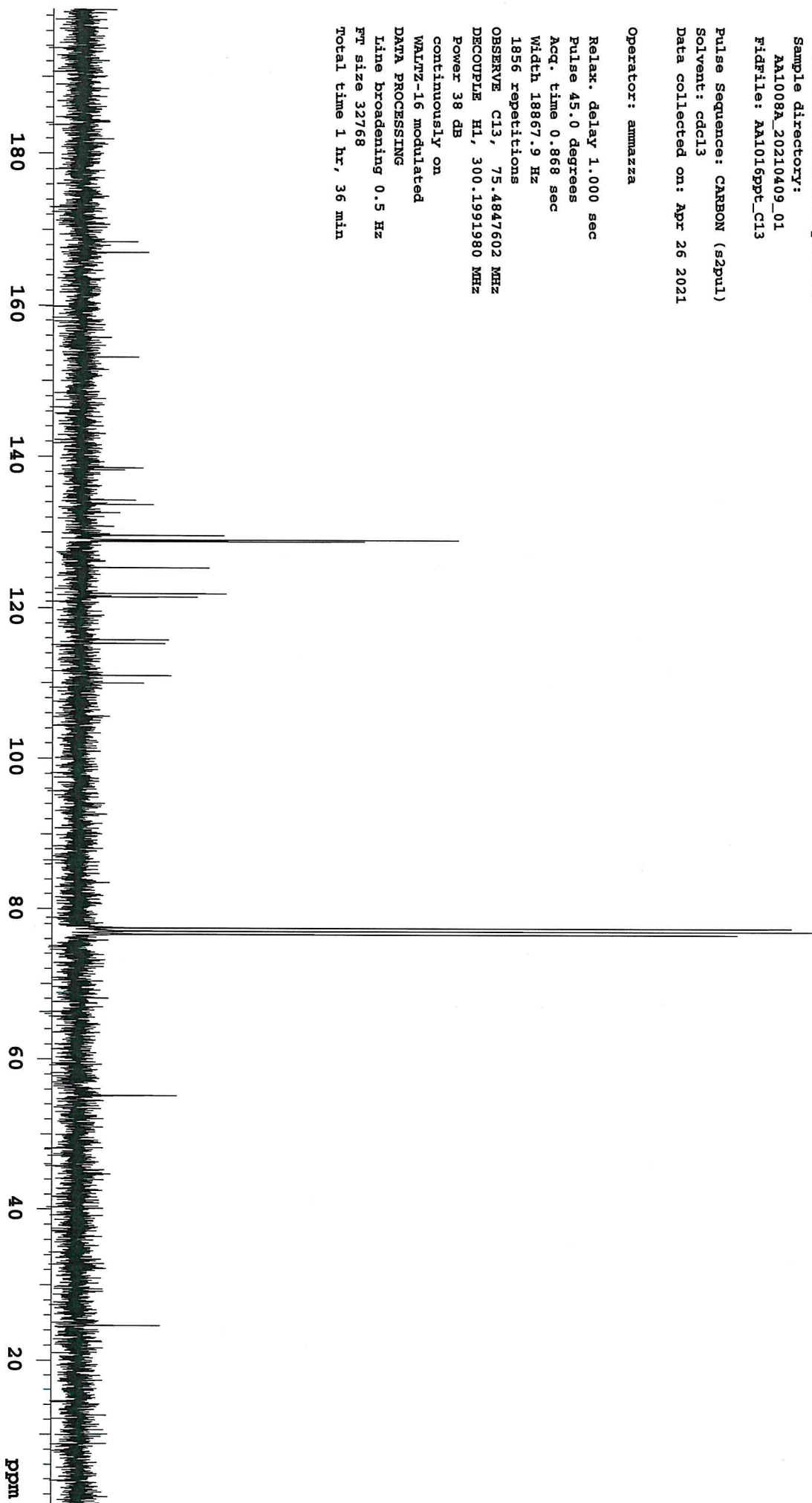
Sample Name:
AA950Admso
Data Collected on:
m300-mercury300
Archive directory:
/home/ammazza/vnmrsys/data
Sample directory:
MF255_20150422_01
FidFile: AA950Admso

Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Oct 14 2020

Operator: ammazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.706 sec
Width 4803.1 Hz
16 repetitions
OBSERVE   H1, 300.1990802 MHz
DATA PROCESSING
FT size 16384
Total time 0 min 45 sec

4 m

7.01

7.4875.839.32
7.76.878.08

7.69

4m

Gradient Shimming

Sample Name:
AA950Admso

Data Collected on:
m300-mercury300

Archive directory:
/home/ammazza/vnmrsys/data

Sample directory:
MF255_20150422_01

FidFile: CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Oct 14 2020

Temp. 16.7 C / 289.9 K
Operator: ammazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 18867.9 Hz
3840 repetitions
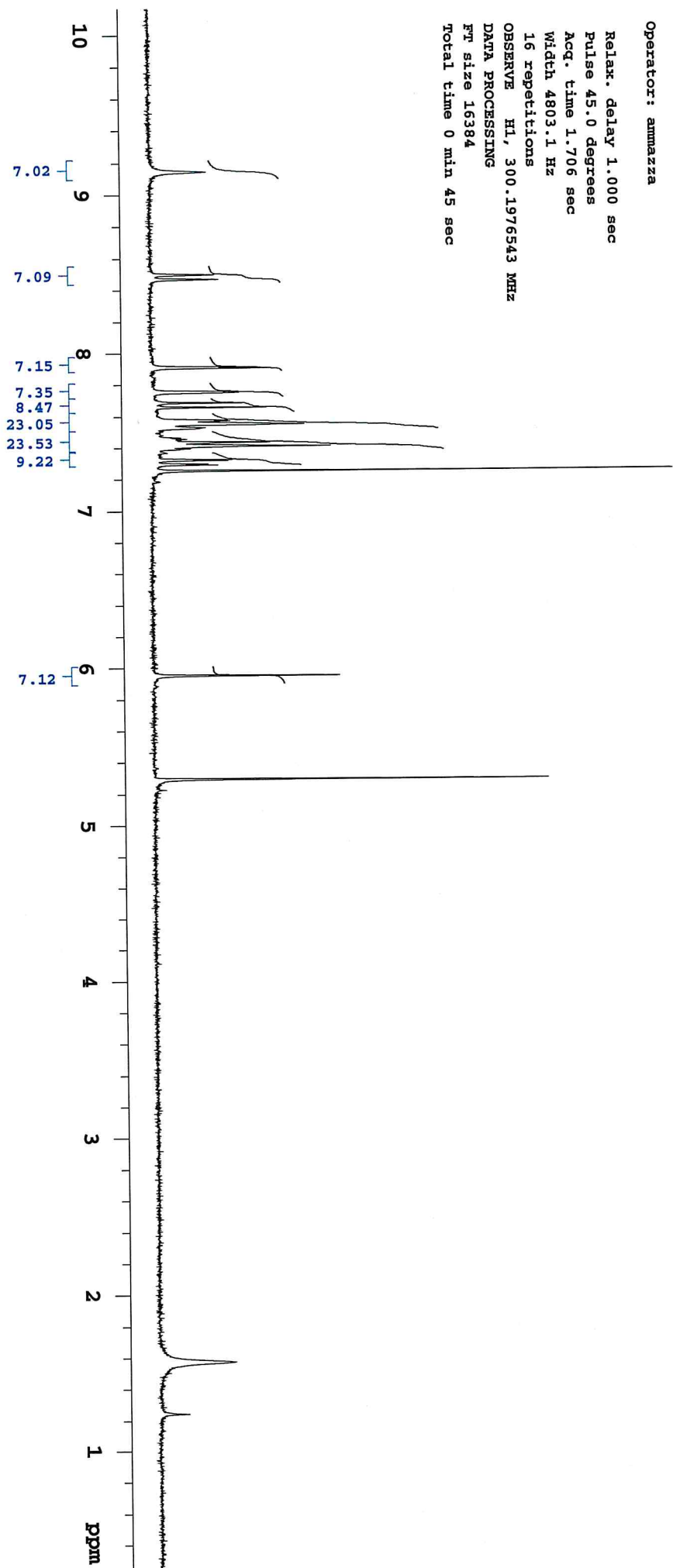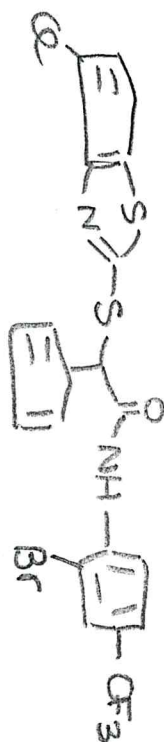OBSERVE C13,   75.4851188 MHz
DECOUPLE H1, 300.2006240 MHz
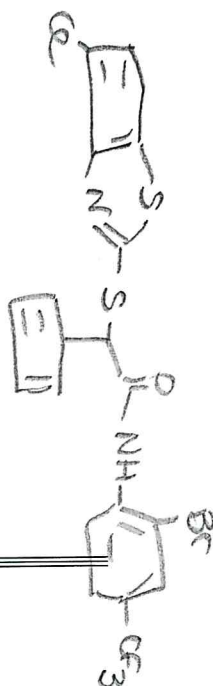Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 2 hr, 41 min

4n

Gradient Shimming

7.08
6.99

14.34
7.49
56.62

7.47

10   9   8   7   6   5   4   3   2   1   ppm

4n

Gradient Shimming

Gradient Shimming

40

10   9   8   7   6   5   4   3   2   1   ppm

7.02
7.09
7.15
7.35
8.47
23.05
23.53
9.22
7.12

Gradient Shimming

40

ppm   180   160   140   120   100   80   60   40   20

Sample Name:
AA962A
Data Collected on:
m300-mercury300
Archive directory:
/home/ammazza/vnmrsys/data
Sample directory:
MF255_20150422_01
FidFile: AA962Acrist

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 24 2021

Operator: ammazza

Relax. delay 1.000 sec
Pulse 45.0 degrees
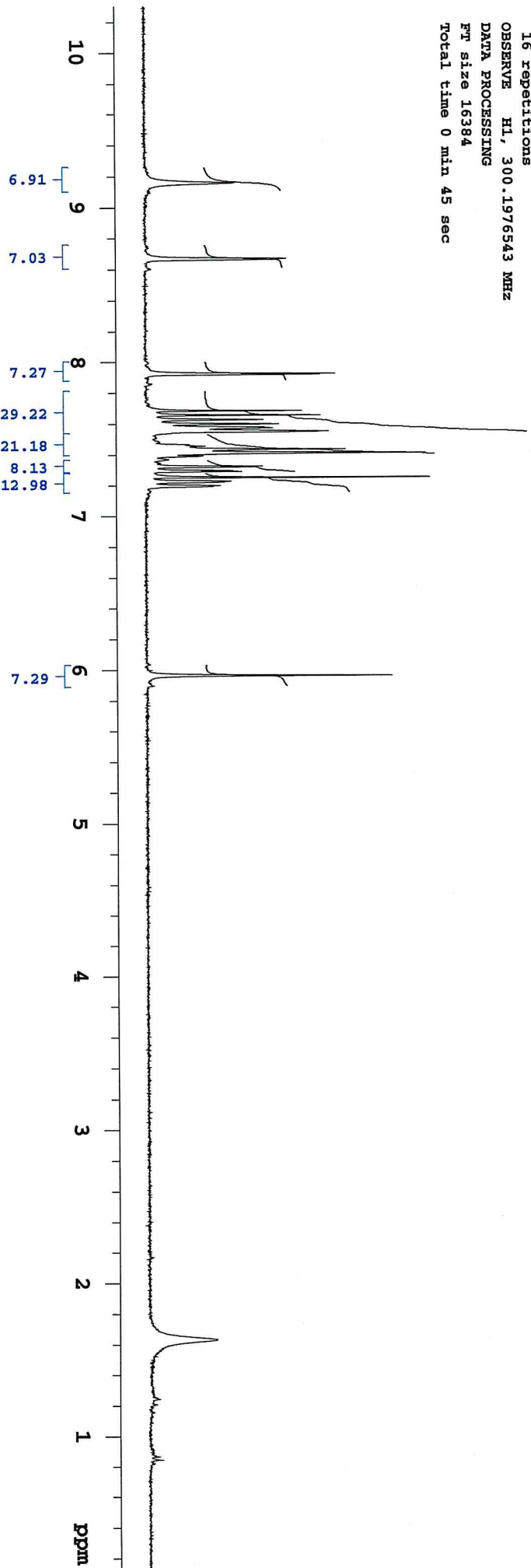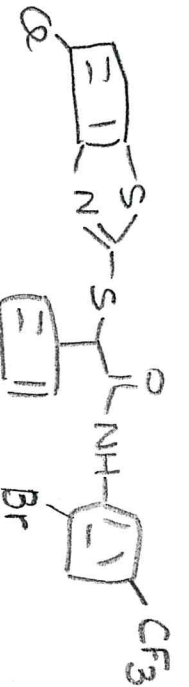Acq. time 1.706 sec
Width 4803.1 Hz
16 repetitions
OBSERVE   H1, 300.1976543 MHz
DATA PROCESSING
FT size 16384
Total time 0 min 45 sec

4p

6.91
7.03
7.27
29.22
21.18
8.13
12.98
7.29

10   9   8   7   6   5   4   3   2   1   ppm

Gradient Shimming

4p