Electronic Supplementary Material (ESI) for RSC Advances.

Phenylalanyl tRNA synthetase (PheRS) substrate mimics: Design, synthesis, molecular dynamics and antimicrobial evaluation

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Electronic supplementary information

1. Microbiological evaluation results:

Table. S1| MIC (µg/mL) for the synthesised compounds (5a-b), (6a-e), (7a-d) and (9a-e)

Compound	*S. aureus* ATCC 29213	*E. faecalis* ATCC 29212	*P. aeruginosa* ATCC 29853	*E. coli* ATCC 25922	*K. pneumoniae* ATCC 700603
5a	>128	128	128	>128	>128
5b	>128	128	128	>128	128
6a	128	128	128	>128	128
6b	128	128	128	>128	128
6c	128	128	128	>128	128
6d	128	128	128	>128	128
6e	128	128	128	128	128
7a	128	128	128	128	128
7b	128	128	128	>128	128
7c	>128	128	128	>128	128
7d	128	128	128	128	128
9a	128	128	128	>128	128
9b	128	64	128	>128	128
9c	128	128	128	>128	>128
9d	128	64	128	>128	128
9e	64	32	128	>128	128
ciprofloxacin	0.25	1	0.5	0.008	0.25

Table. S2| MIC (µg/mL) for the synthesised compounds (16a-c)

Compound	*S. aureus* ATCC 29213	MRSA NCTC 12493	*E. faecalis* ATCC 29212	*E. faecium* 16568
16a	128	64	64	32
16b	128	64	128	64
16c	128	64	32	32
ciprofloxacin	0.25	0.5	0.5	1

2. Computational studies supplementary information:

2.1. Flexible alignment studies:

Flexible alignment and docking studies were performed using MOE 2015.10 software[1]. Flexible alignment was performed using MMFF94 forcefield, flexible alignment mode and the resulted conformations were examined according to their grand alignment score (S). The latter is the sum of the similiraity measure of configuration (F) and the average strain energy of the molecules in the alignment in kcal/mol (U). The lower S value indicates better alignment.

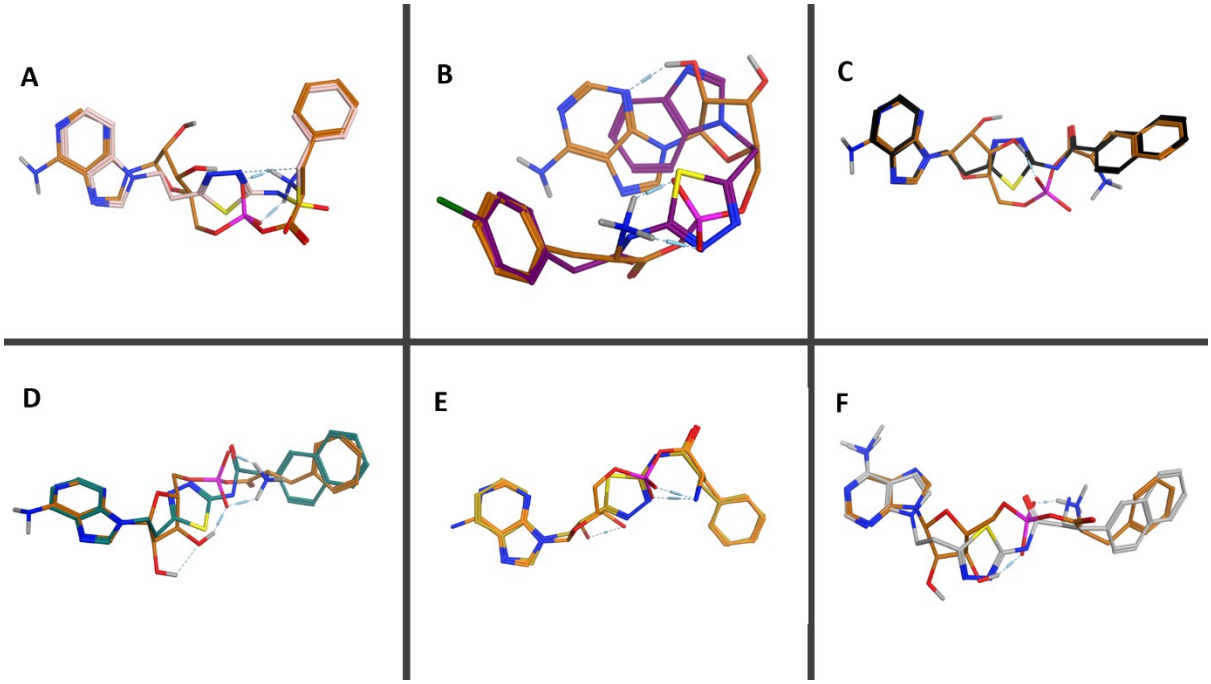


Fig. S1. 3D molecular alignment results. Phe-AMP is presented in orange colour. (A) **5a** (pink colour) S= -170.1604, (B) **6c** (purple colour) S= -154.4615, (C) **6e** (black colour) S= -159.4926, (D) **7d** (green colour) S= -162.6272, (E) **9a** (yellow colour) S= -190.7823 and (F) **16c** (grey colour) S= -206.69

2.2. Multiple sequence alignment:

Fig. S2. Multiple sequence alignment[2] of PheRS α subunit amino acid sequences from *P. aeruginosa* (Q9I0A3), *K. pneumoniae* (A6TAI3), *E. coli* (P08312), *S. aureus* (P68849) and *E. faecalis* (Q836J6). Yellow boxes show residues responsible for hydrophobic interactions. While green boxes show residues responsible for hydrophilic interaction. A high level of conservation among sequences could be observed.

2.3. Homology model evaluation:

2.3.1. Ramachandran plot:

Almost 98% of the amino acids are in the allowed region with only 3 amino acids observed in the outlier region which are Asp 185, Leu 191 and Gly 273 and all of them are not a part of the enzyme's active site.

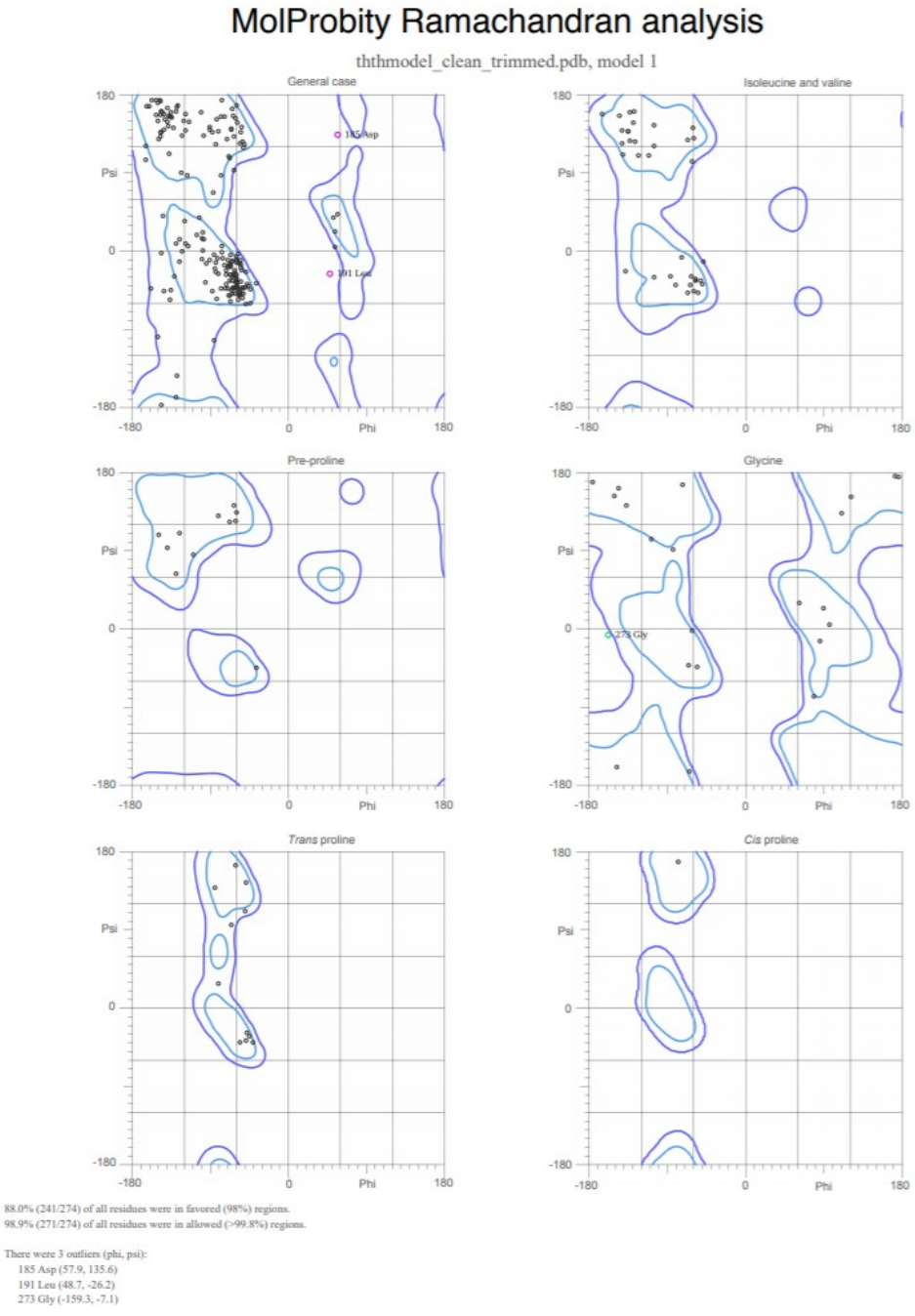
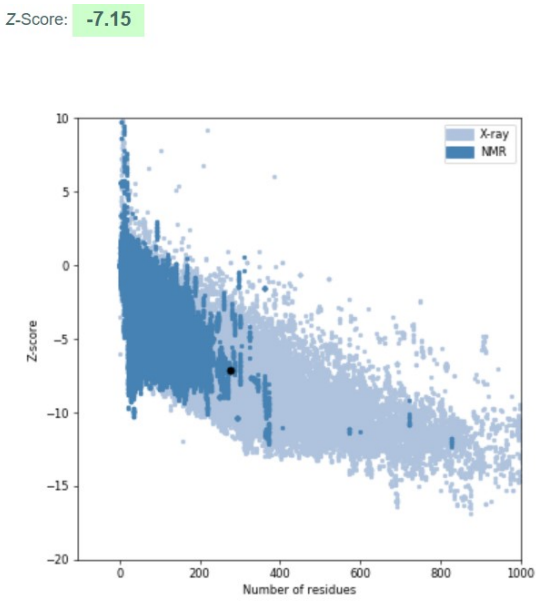
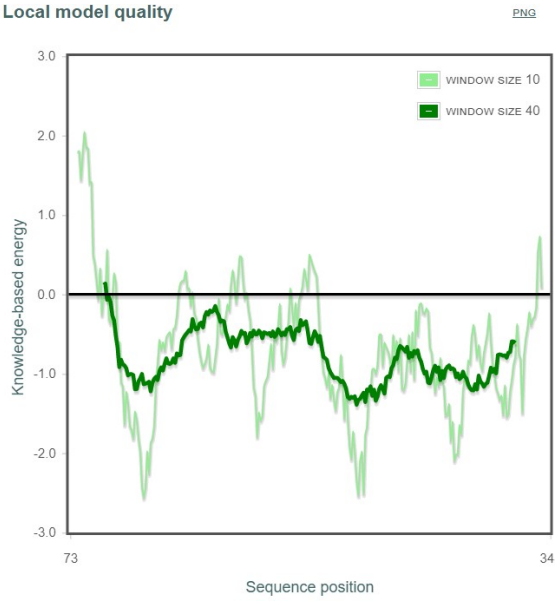


Fig. S3| Ramachandran plot of *E. faecalis* model.[3]

2.3.2. ProSA analysis:

ProSA analysis revealed good quality model as its Z-score is among the same sized solved protein structures and equal to -7.15 and the internal energy of each amino acid in the protein 3D structure is with negative value (Table. S3).

Table. S3| ProSA analysis results of *E. faecalis* model. [4, 5]

Overall model quality	**Local model quality**
	

2.3.3. Verify 3D:

The newly constructed model passed the 3D verification as 86.32% of its amino acids have scored more than or equal to 0.2.

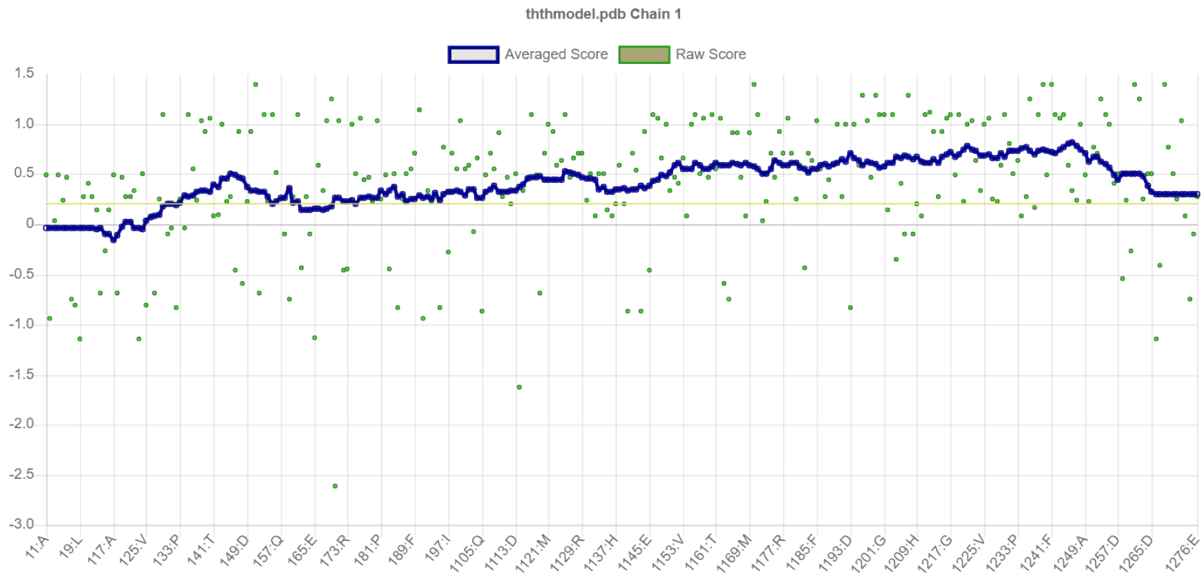


Fig. S4| 3D profile of *E. faecalis* model. [6]

3. Chemistry supplementary information:

3.1. Preparation methods for compounds 3,4 and 12:

3.1.1. *3-(1H-Benzo[d]imidazol-1-yl) propanehydrazide* (**3**) [7, 8]

To a solution of the methyl propanoate ester (**2**) (3 g, 14.69 mmol) in EtOH (125 mL) was added hydrazine monohydrate (10 equivalents) and the reaction mixture was stirred at room temperature overnight. The formed solid was collected by filtration and recrystallised from EtOAc and petroleum ether to give the pure hydrazide compound (**3**) as white crystals; yield 2.5 g (84%); m.p. 105-110 °C; TLC CH_2Cl_2-MeOH 9:1 v/v, R_f = 0.29; ^{1}H NMR (DMSO-d_6) δ: 2.60 (t, J = 6.7 Hz, 2H, CH_2CO), 4.19 (s, 2H, NH_2), 4.47 (t, J = 6.6 Hz, 2H, $C\underline{H_2}CH_2$), 7.21 (t, J = 7.2 Hz, 1H, Ar), 7.26 (t, J = 8.1 Hz, 1H, Ar), 7.58 (d, J = 8.00 Hz, 1H, Ar), 7.62 (d, J = 7.9 Hz, 1H, Ar), 8.11 (s, 1H, H-imidazole), 9.06 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 34.1 ($\underline{C}H_2CO$), 40.9 (NCH_2CH_2), 110.9 (CH), 119.8 (CH), 122.1 (CH), 122.9 (CH), 134.0 (C), 143.6 (C), 144.4 (CH-imidazole), 169.5 (CO).

3.1.2. *5-(2-(1H-Benzo[d]imidazol-1-yl)ethyl)-1,3,4-thiadiazol-2-amine* (**4**) [7]

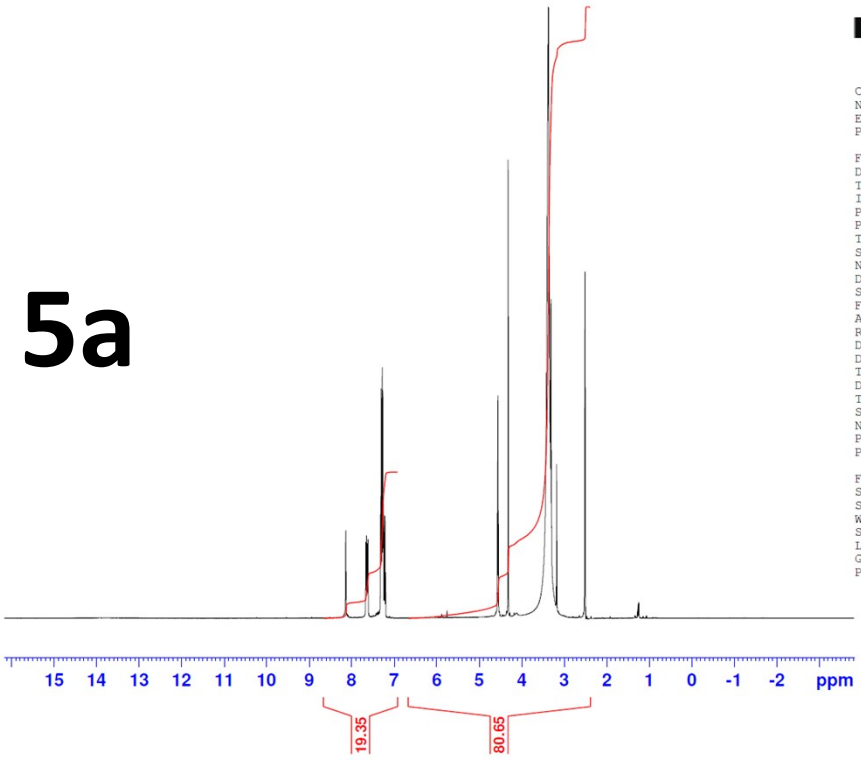
To a stirred mixture of the hydrazide (0.5 g, 2.45 mmol) in dry IPA (20 mL), was added (trimethylsilyl)isothiocyanate (TMSNCS) (1.38mL, 9.8 mmol), then the mixture was heated under reflux overnight. The solvent was then concentrated under vacuum and c.H_2SO_4 (10 mL) was added, and the reaction stirred at room temperature for 2 h. The reaction was poured into crushed ice and neutralised using NH_4OH in -70°C dry ice/acetone bath. The resulting solid was collected by filtration, washed with H_2O and petroleum ether and dried *in vacuo* at 40 °C to afford the product as a yellow solid. Yield 0.3 g (53%); m.p. 208- 210°C (Lit. m.p. 182-184[2]); TLC CH_2Cl_2-MeOH 9:1 v/v, R_f 0.49. ^{1}H NMR (DMSO-d_6) δ: CH_2 signal is obscured by DMSO-d_6 signal, 4.59 (t, J = 6.8 Hz, 2H, $C\underline{H_2}CH_2$), 7.03 (s, 2H, NH_2), 7.21 (t, J = 7.3 Hz, 1H, Ar), 7.26 (t, J = 7.6 Hz, 1H, Ar), 7.63 (t, J = 8.6 Hz, 2H, Ar), 8.15 (s, 1H, H-imidazole). ^{13}C NMR (DMSO-d_6) δ: 30.3 ($NCH_2\underline{C}H_2$), 43.7 ($N\underline{C}H_2$), 110.9 (CH), 119.9 (CH), 122.0 (CH), 122.8 (CH), 134.1 (C), 143.9 (C), 144.6 (CH-imidazole), 154.7 (C), 169.1 (C).

3.1.3. *Methyl 3-(4-(dimethylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propanoate* **(12)** [9]

Prepared using *N,N*-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (11) (2 g, 12.33 mmol). The product was pure enough to be used in next steps with any further purification needed and separated as yellow low melting solid. Yield: 2.54 g, 83%; m.p. 52-54 °C; TLC: CH_2Cl_2-MeOH

9:1 v/v, R_f 0.75. ^{1}H NMR (DMSO-d_6) δ: 2.85 (t, J = 7.0 Hz, 2H, CH_2CO), 3.28 (s, 6H, $N(CH_3)_2$), 3.58 (s, 3H, OCH_3), 4.38 (t, J = 7.0 Hz, 2H, NCH_2), 6.62 (d, J = 3.6 Hz, 1H, Ar), 7.18 (d, J =3.7 Hz, 1H, Ar), 8.14 (s, 1H, Ar). ^{13}C NMR (DMSO-d_6) δ: 34.6 ($\underline{C}H_2CO$), 39.1 ($N(CH_3)_2$), CH_2 peak is obscured by DMSO-d_6 peak , 52.0 (OCH3), 101.7 (CH), 102.9 (C), 124.2 (CH), 150.5 (C), 151.2 (CH), 157.4 (C), 171.7 (CO).

3.2. NMR Charts for compounds (5a-b), (6a-e), (7a-d), (9a-e) and (16a-c)

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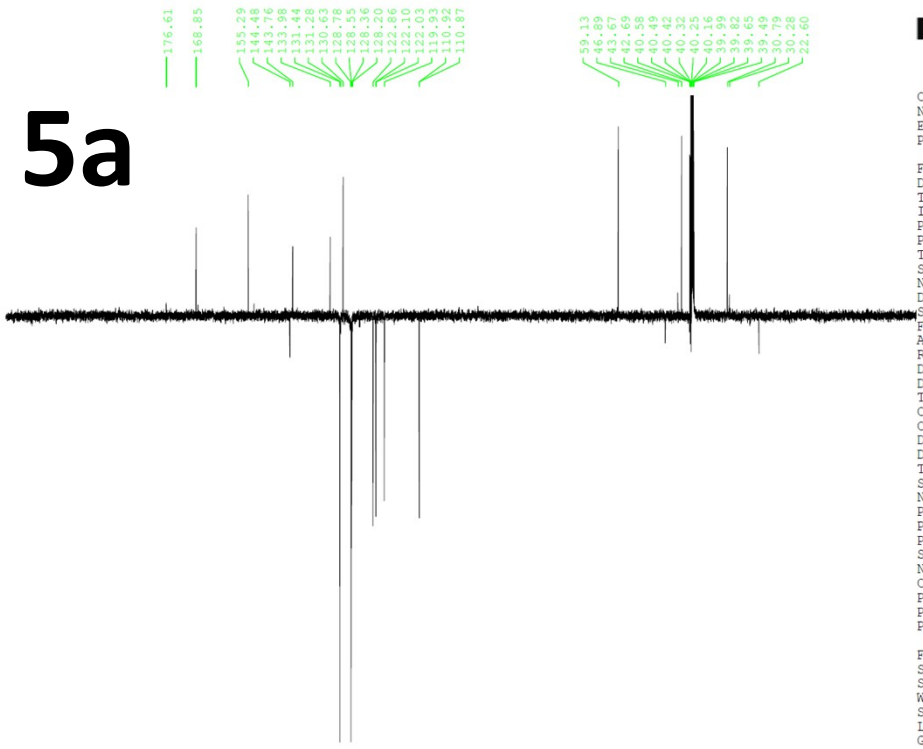


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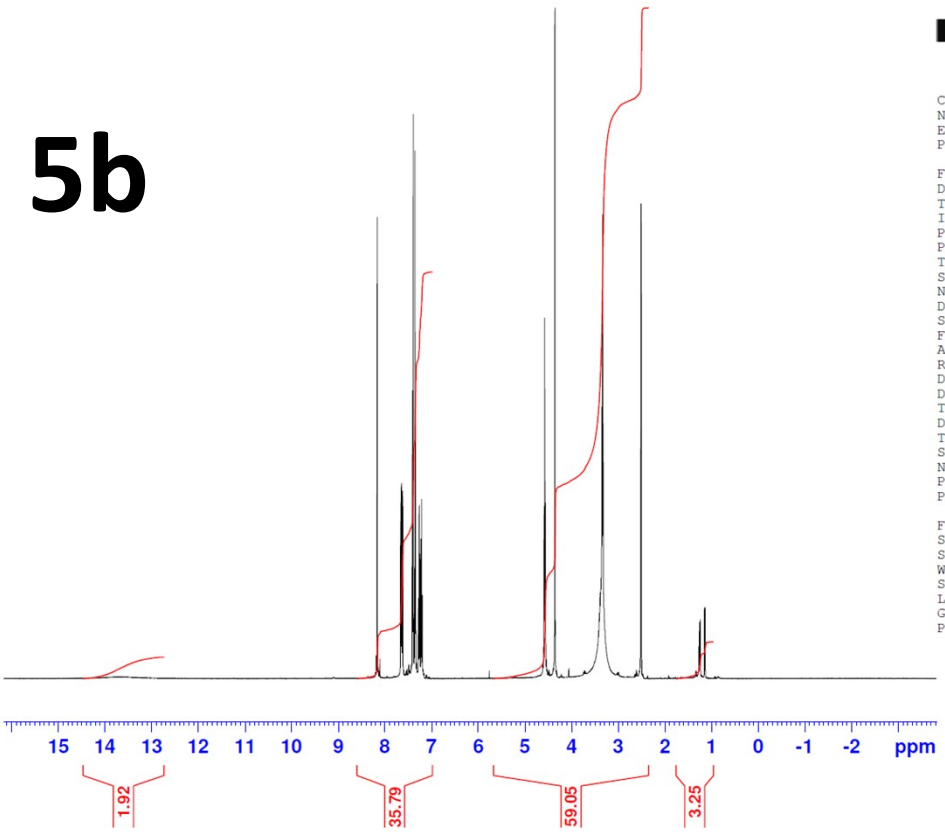
5b



BRUKER

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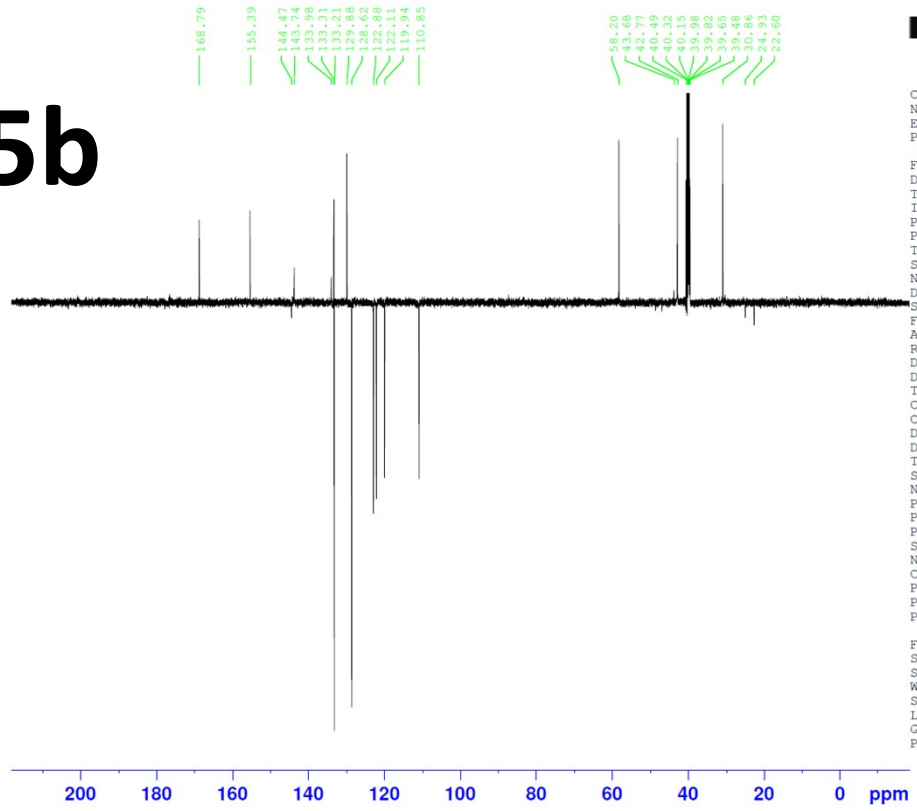
5b



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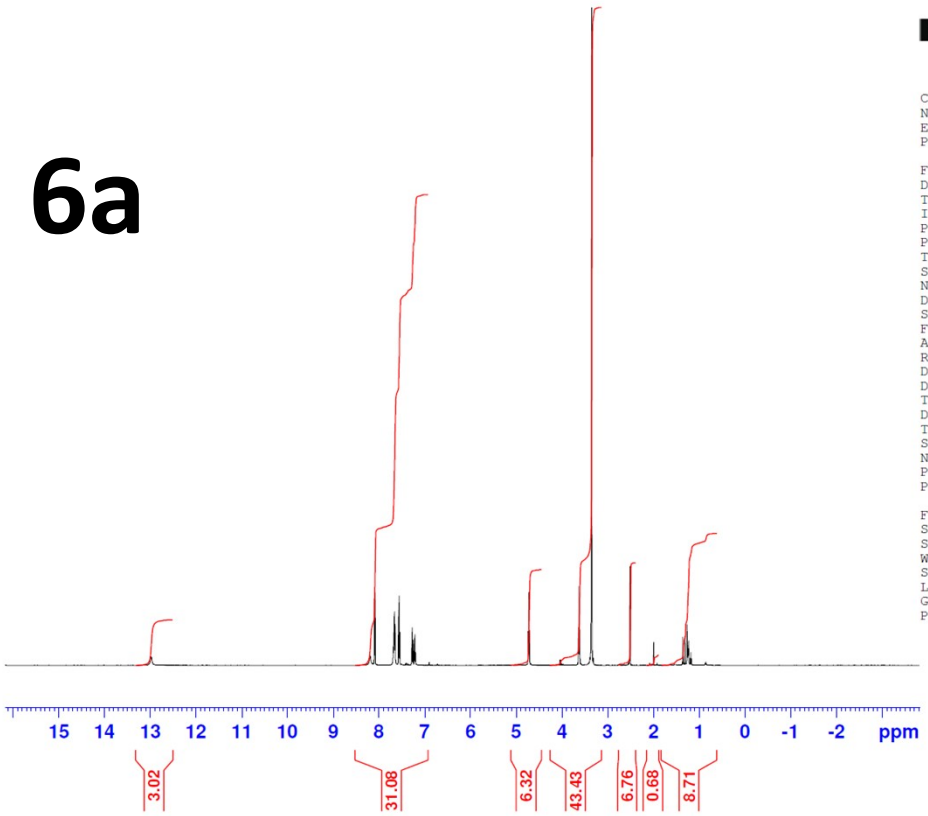


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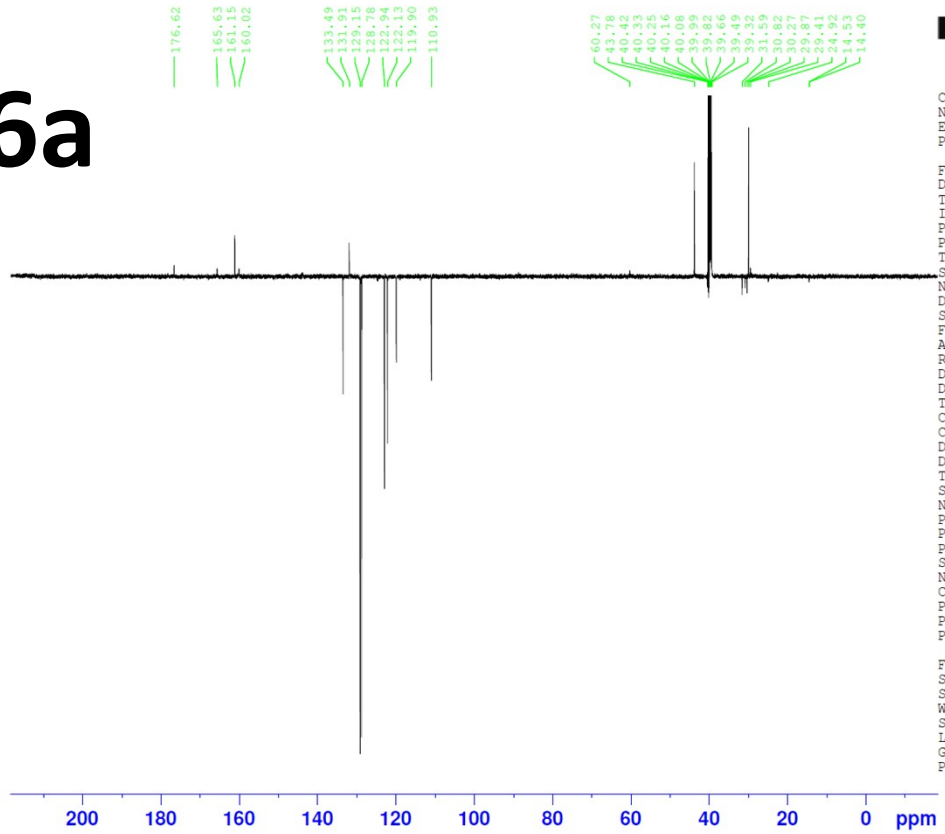


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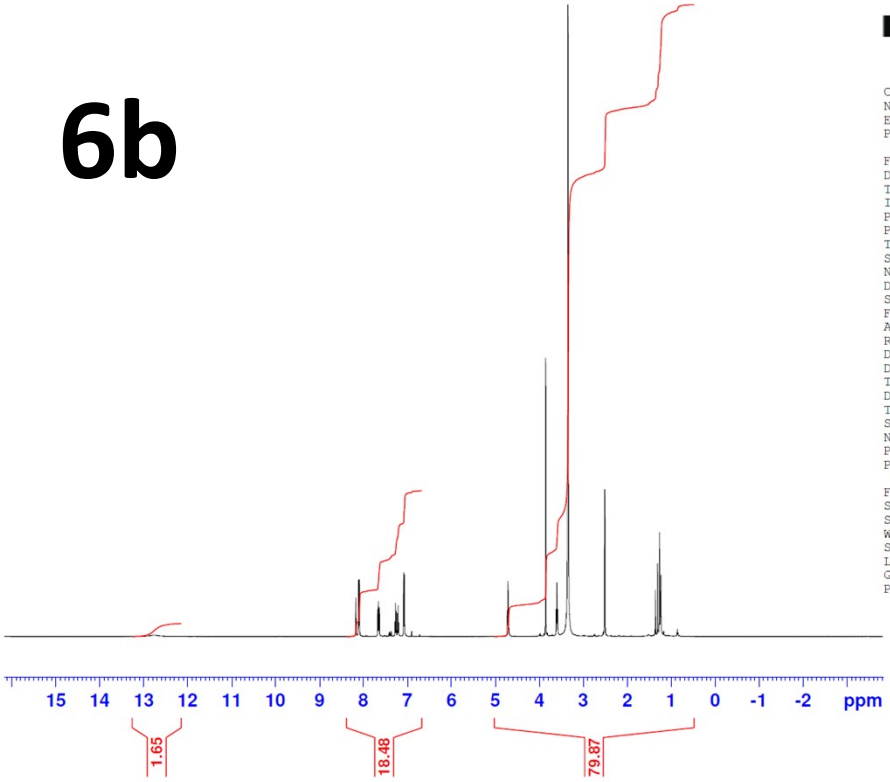
6b

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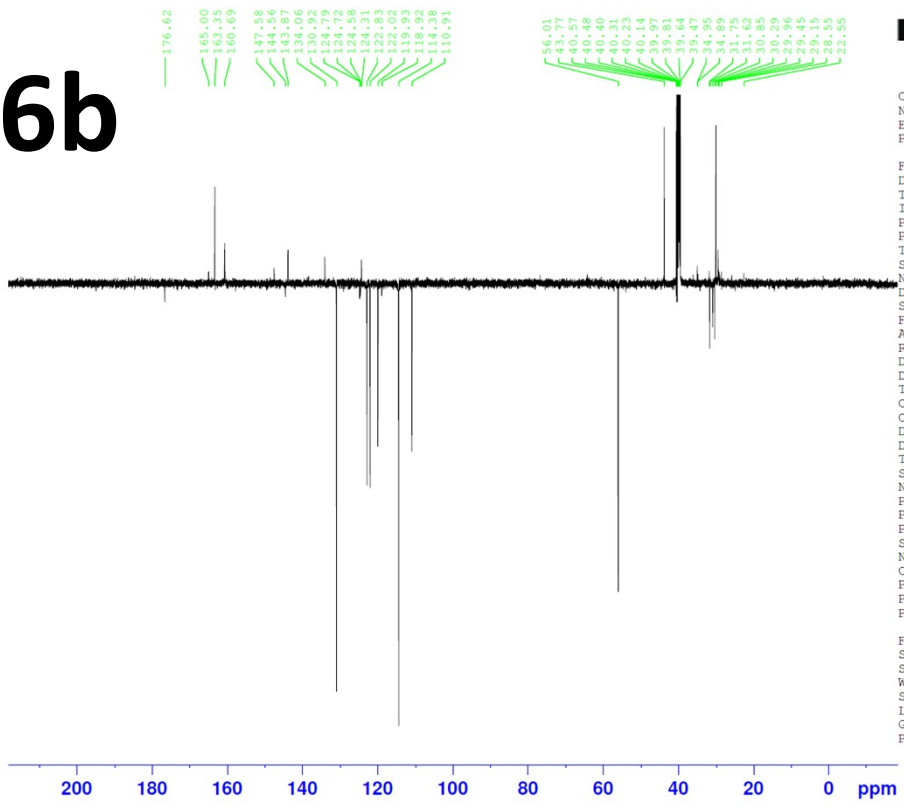


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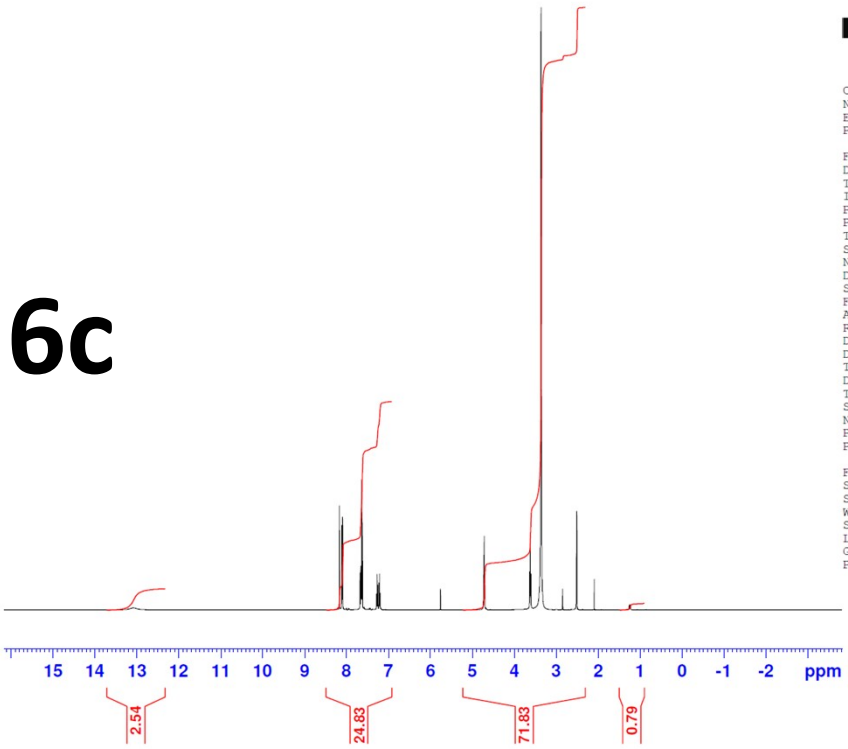


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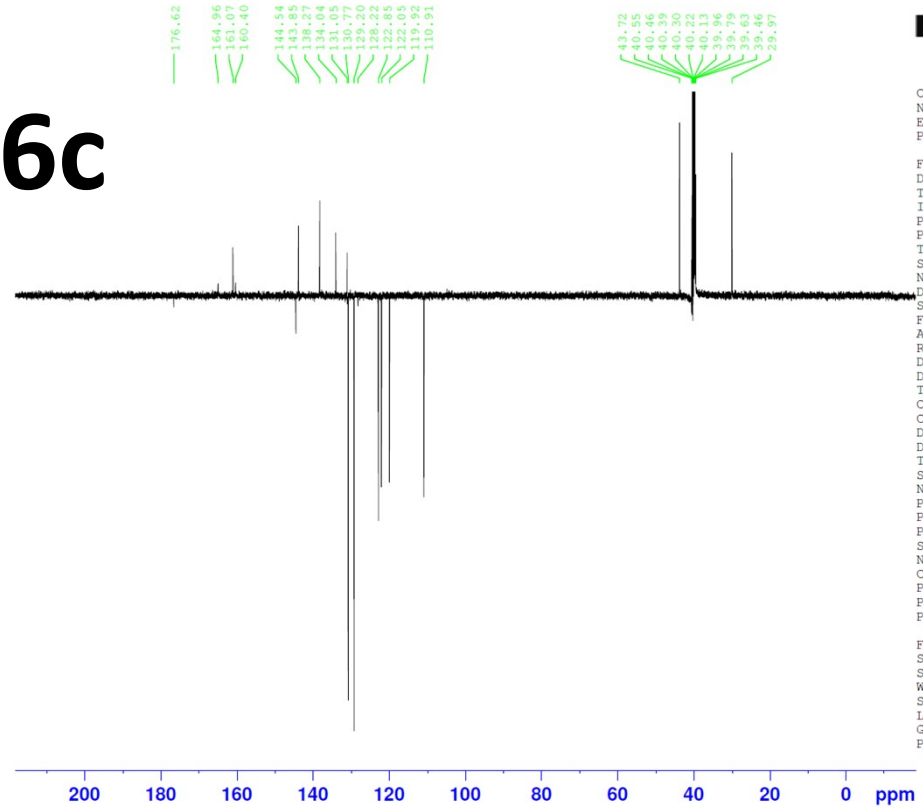


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DE                     6.50 usec
TE                    298.1 K
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CNST11           1.0000000
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D20              0.00689655 sec
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NUC2                   1H
CPDPRG[2           waltz16
PCPD2                 80.00 usec
PLW2            21.07600021 W
PLW12            0.32931000 W

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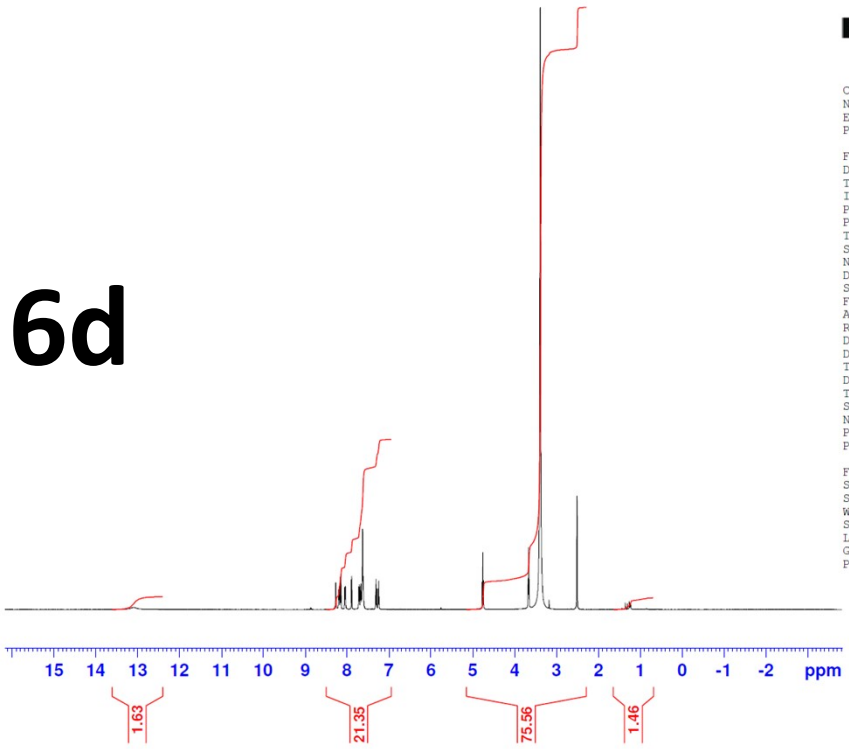
```

6d

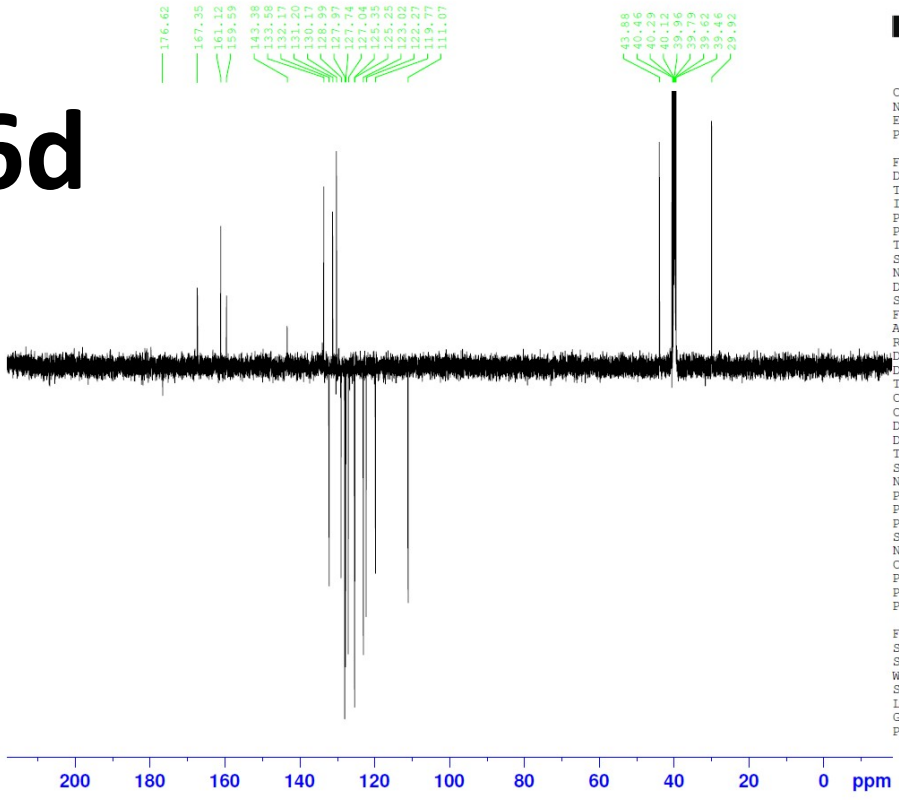



```
Current Data Parameters
NAME                  NA122
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20190910
Time                 11.06 h
INSTRUM              spect
PROBHD    Z113652_0266 (
PULPROG               zg30
TD                   65536
SOLVENT               DMSO
NS                      16
DS                       2
SWH            10000.000 Hz
FIDRES             0.305176 Hz
AQ                 3.2767999 sec
RG                    85.54
DW                   50.000 usec
DE                   13.50 usec
TE                   298.2 K
D1              1.00000000 sec
TD0                      1
SFO1          500.1330883 MHz
NUC1                    1H
P1                   10.00 usec
PLW1          21.07600021 W

F2 - Processing parameters
SI                   65536
SF            500.1300000 MHz
WDW                     EM
SSB       0
LB                    0.30 Hz
GB        0
PC                    1.00
```

6d

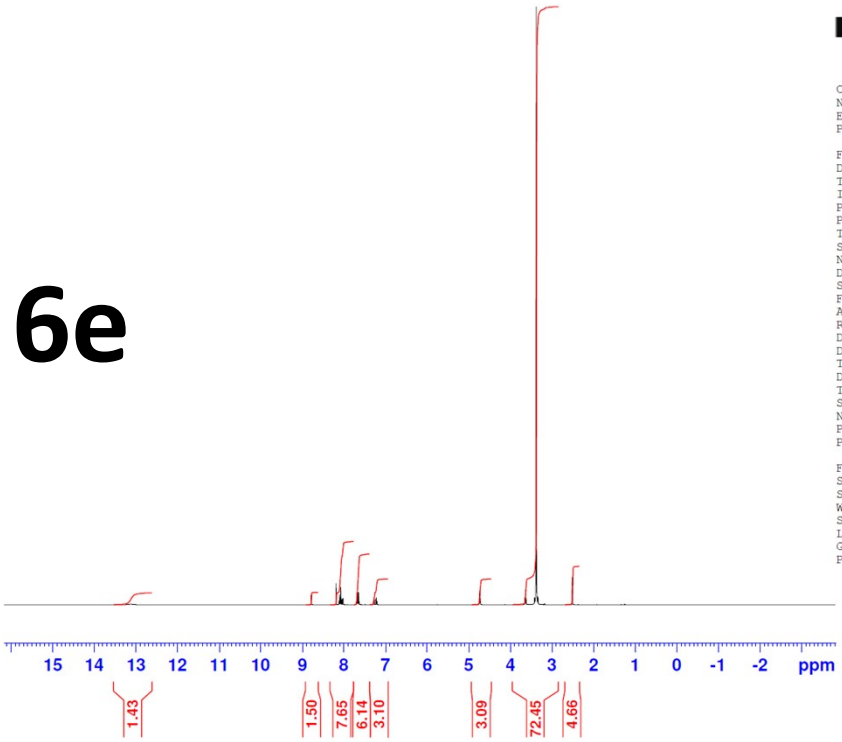



```
Current Data Parameters
NAME                  NA122
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20190912
Time                  5.36 h
INSTRUM              spect
PROBHD    Z113652_0266 (
PULPROG               jmod
TD                   65536
SOLVENT               DMSO
NS                      512
DS                        4
SWH            29761.904 Hz
FIDRES             0.908261 Hz
AQ                 1.1010048 sec
RG                   189.93
DW                   16.800 usec
DE                    6.50 usec
TE                   298.1 K
CNST2         145.0000000
CNST11          1.0000000
D1              2.00000000 sec
D20             0.00689655 sec
TD0                      1
SFO1          125.7703643 MHz
NUC1                   13C
P1                   10.00 usec
P2                   20.00 usec
PLW1          74.02700043 W
SFO2          500.1320005 MHz
NUC2                    1H
CPDPRG[2          waltz16
PCPD2                80.00 usec
PLW2          21.07600021 W
PLW12          0.32931000 W

F2 - Processing parameters
SI                   32768
SF            125.7577885 MHz
WDW                     EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    1.40
```

6e



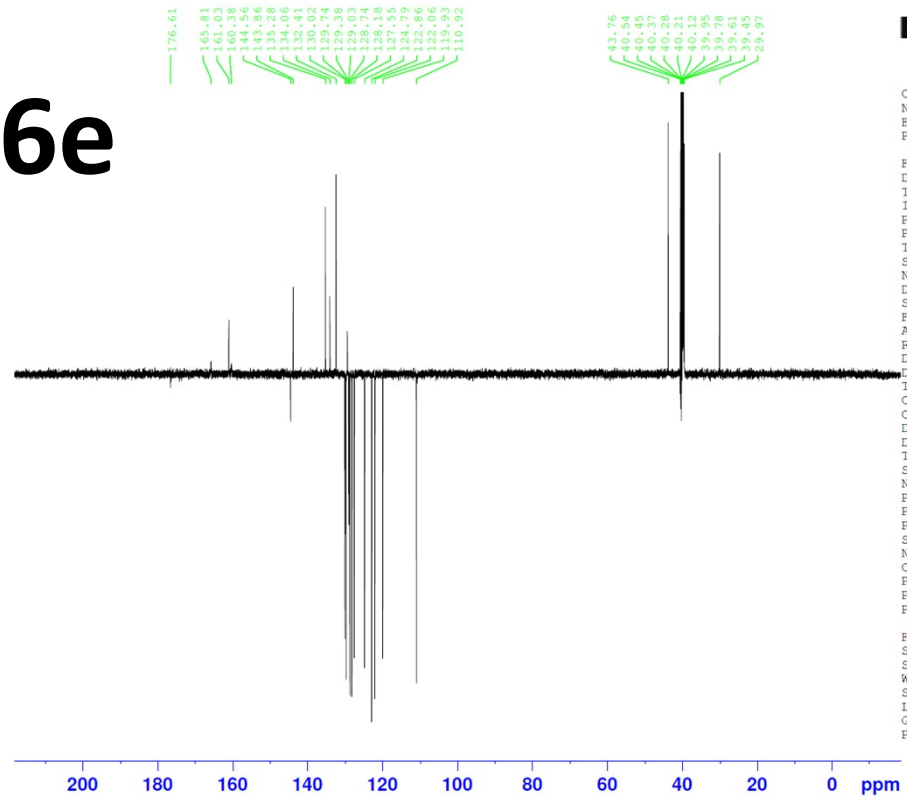
BRUKER

```
Current Data Parameters
NAME                  NA121
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20190910
Time                  11.01 h
INSTRUM               spect
PROBHD    Z113652_0266 (
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH             10000.000 Hz
FIDRES              0.305176 Hz
AQ                3.2767999 sec
RG                    85.54
DW                  50.000 usec
DE                  13.50 usec
TE                  298.1 K
D1              1.00000000 sec
TD0                       1
SFO1           500.1330883 MHz
NUC1                   1H
P1                  10.00 usec
PLW1           21.07600021 W

F2 - Processing parameters
SI                    65536
SF              500.1300000 MHz
WDW                     EM
SSB          0
LB                   0.30 Hz
GB           0
PC                    1.00
```

6e



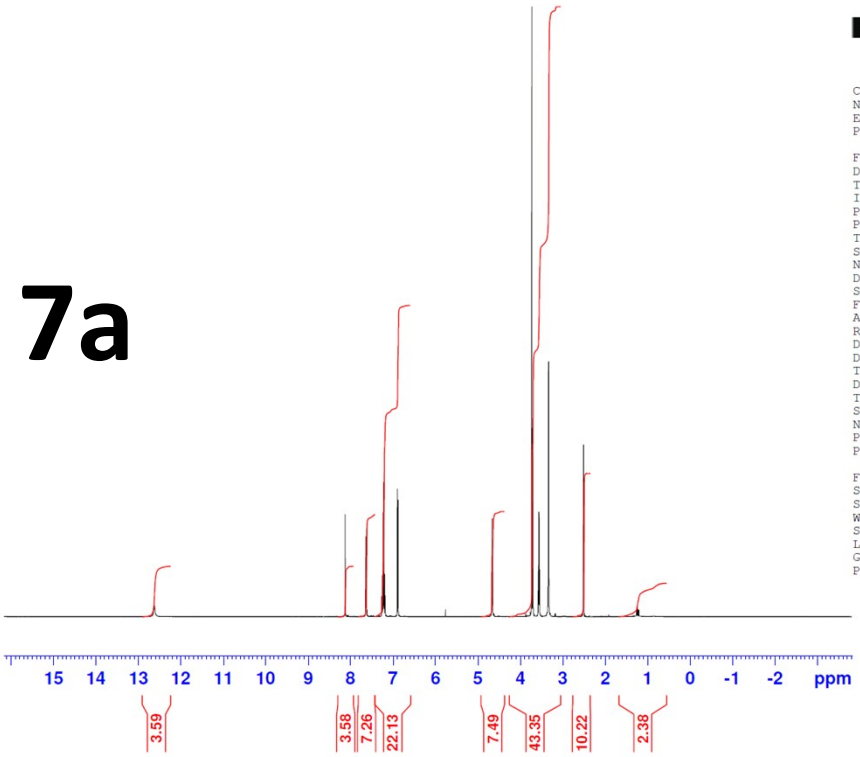
BRUKER

```
Current Data Parameters
NAME                  NA121
EXPNO                     3
PROCNO                    1

F2 - Acquisition Parameters
Date_              20190919
Time                   2.05 h
INSTRUM               spect
PROBHD    Z113652_0266 (
PULPROG                jmod
TD                    65536
SOLVENT                DMSO
NS                     3072
DS                        4
SWH             29761.904 Hz
FIDRES              0.908261 Hz
AQ                1.1010048 sec
RG                   189.93
DW                  16.800 usec
DE                   6.50 usec
TE                  298.1 K
CNST2          145.0000000
CNST11           1.0000000
D1               2.00000000 sec
D20              0.00689655 sec
TD0                       1
SFO1           125.7703643 MHz
NUC1                   13C
P1                  10.00 usec
P2                  20.00 usec
PLW1           74.02700043 W
SFO2           500.1320005 MHz
NUC2                   1H
CPDPRG[2            waltz16
PCPD2               80.00 usec
PLW2           21.07600021 W
PLW12           0.32931000 W

F2 - Processing parameters
SI                    32768
SF              125.7577885 MHz
WDW                     EM
SSB          0
LB                   1.00 Hz
GB           0
PC                    1.40
```

7a

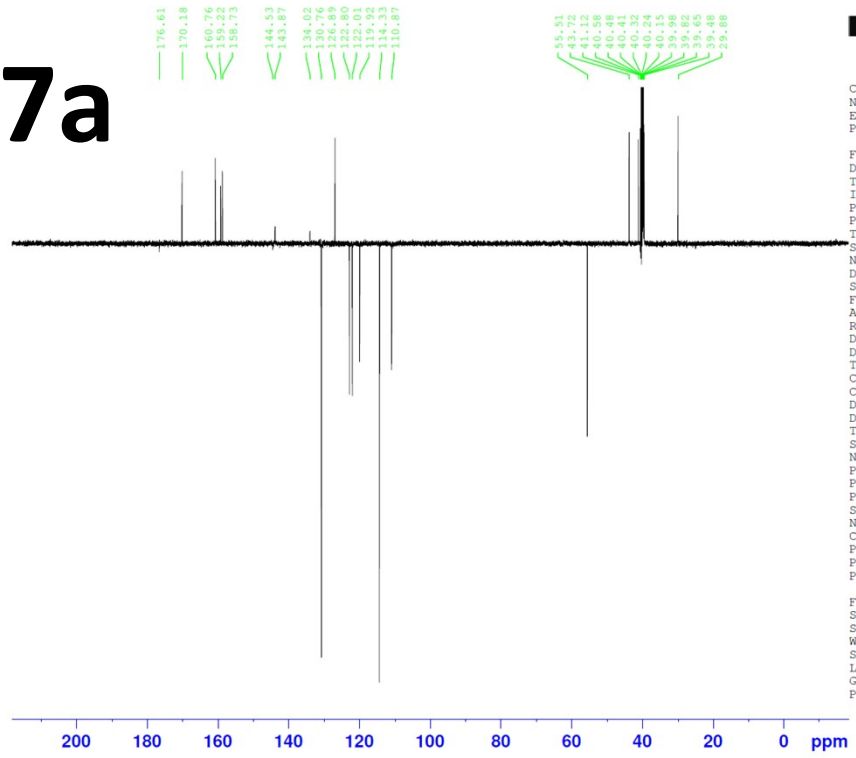



```
Current Data Parameters
NAME                  NA124
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20190920
Time                 16.38 h
INSTRUM               spect
PROBHD    Z113652_0266 (
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH              10000.000 Hz
FIDRES               0.305176 Hz
AQ                3.2767999 sec
RG                   118.43
DW                   50.000 usec
DE                    13.50 usec
TE                    298.1 K
D1               1.00000000 sec
TD0                       1
SFO1            500.1330883 MHz
NUC1                    1H
P1                    10.00 usec
PLW1            21.07600021 W

F2 - Processing parameters
SI                    65536
SF              500.1300000 MHz
WDW                     EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

7a

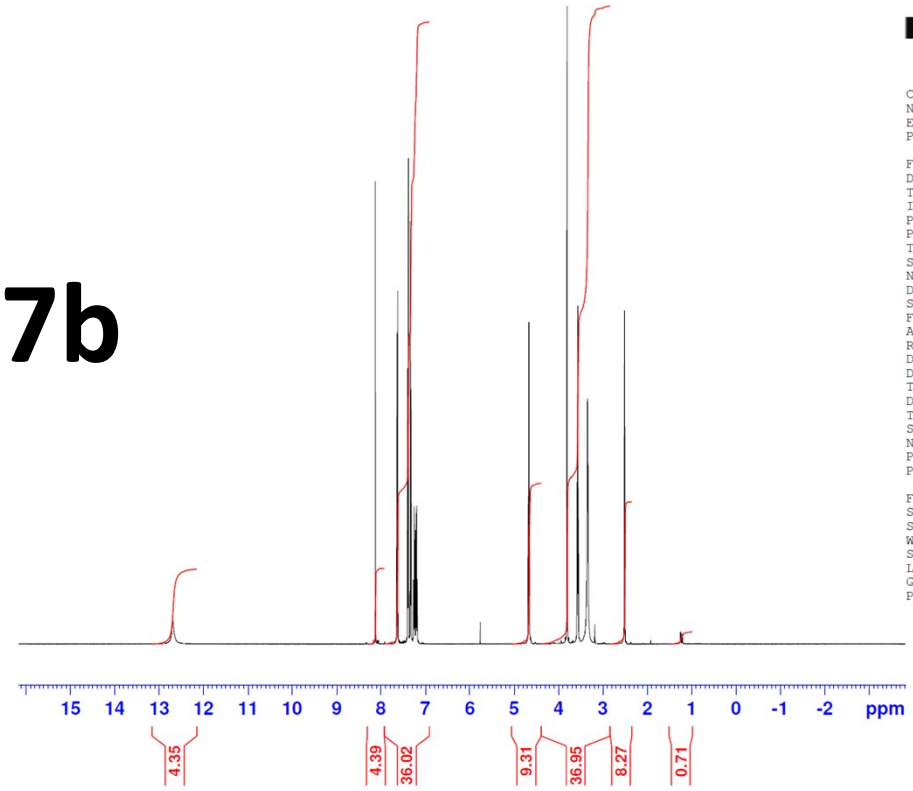



```
Current Data Parameters
NAME                  NA124
EXPNO                     3
PROCNO                    1

F2 - Acquisition Parameters
Date_              20191007
Time                 22.47 h
INSTRUM               spect
PROBHD    Z113652_0266 (
PULPROG                jmod
TD                    65536
SOLVENT                DMSO
NS                     2048
DS                        4
SWH              29761.904 Hz
FIDRES               0.908261 Hz
AQ                1.1010048 sec
RG                   189.93
DW                   16.800 usec
DE                     6.50 usec
TE                    298.2 K
CNST2           145.0000000
CNST11            1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                       1
SFO1            125.7703643 MHz
NUC1                    13C
P1                    10.00 usec
P2                    20.00 usec
PLW1            74.02700043 W
SFO2            500.1320005 MHz
NUC2                    1H
CPDPRG[2             waltz16
PCPD2                 80.00 usec
PLW2            21.07600021 W
PLW12            0.32931000 W

F2 - Processing parameters
SI                    32768
SF              125.7577885 MHz
WDW                     EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

7b



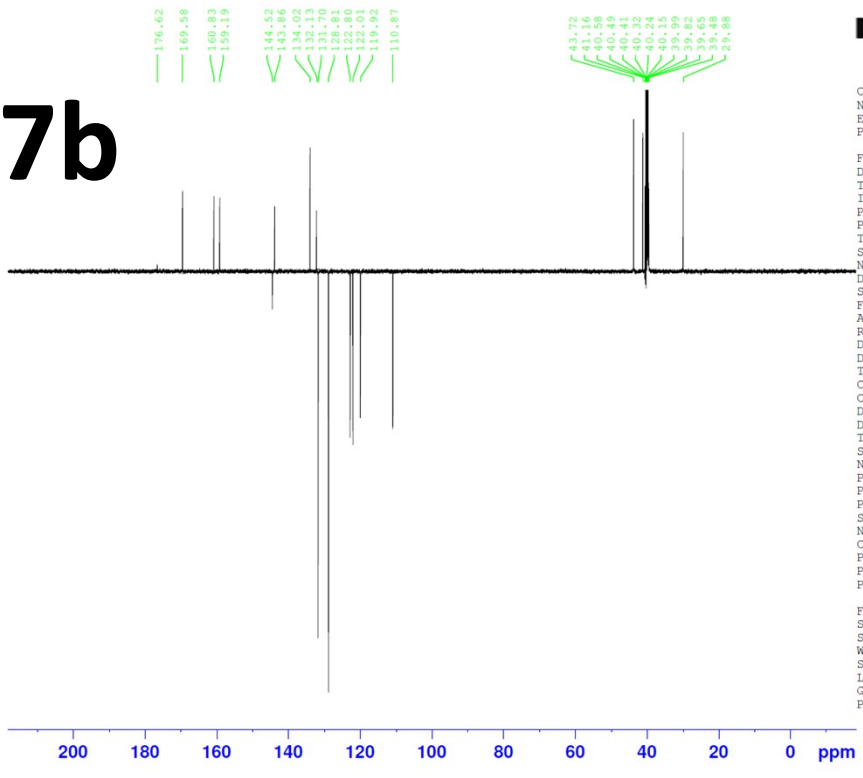
BRUKER

```
Current Data Parameters
NAME                  NA123
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20190920
Time                 15.54 h
INSTRUM              spect
PROBHD    Z113652_0266 (
PULPROG               zg30
TD                   65536
SOLVENT               DMSO
NS                      16
DS                       2
SWH             10000.000 Hz
FIDRES              0.305176 Hz
AQ                3.2767999 sec
RG                   118.43
DW                   50.000 usec
DE                   13.50 usec
TE                   298.1 K
D1               1.00000000 sec
TD0                       1
SFO1            500.1330883 MHz
NUC1                    1H
P1                   10.00 usec
PLW1            21.07600021 W

F2 - Processing parameters
SI                    65536
SF              500.1300000 MHz
WDW                     EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

7b



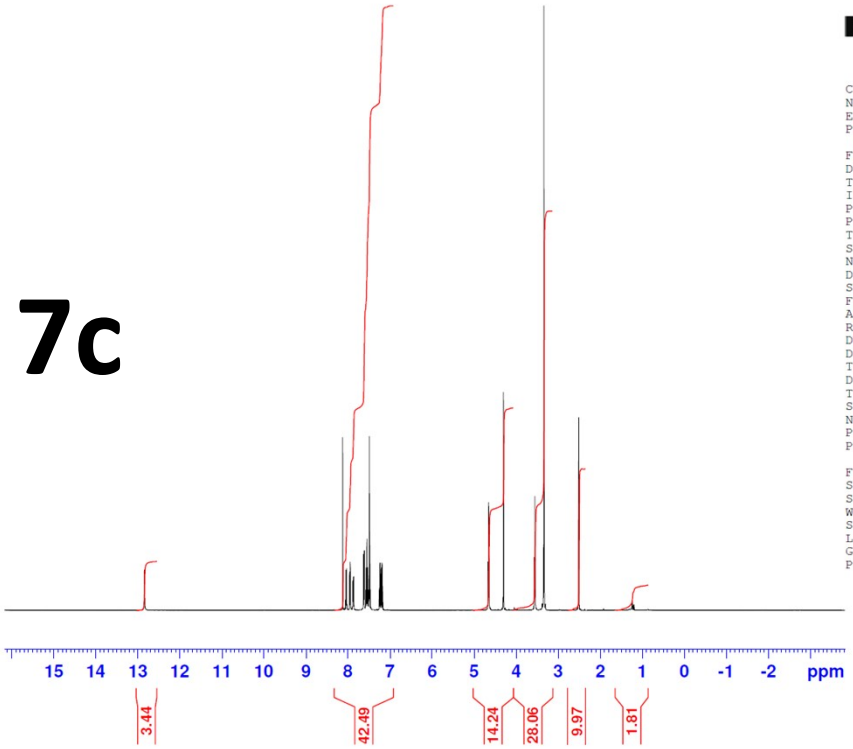
BRUKER

```
Current Data Parameters
NAME                  NA123
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20191001
Time                 23.45 h
INSTRUM              spect
PROBHD    Z113652_0266 (
PULPROG               jmod
TD                   65536
SOLVENT               DMSO
NS                    2048
DS                       4
SWH             29761.904 Hz
FIDRES              0.908261 Hz
AQ                1.1010048 sec
RG                   189.93
DW                   16.800 usec
DE                    6.50 usec
TE                   298.1 K
CNST2           145.0000000
CNST11            1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                       1
SFO1            125.7703643 MHz
NUC1                   13C
P1                   10.00 usec
P2                   20.00 usec
PLW1            74.02700043 W
SFO2            500.1320005 MHz
NUC2                    1H
CPDPRG[2            waltz16
PCPD2                80.00 usec
PLW2            21.07600021 W
PLW12            0.32931000 W

F2 - Processing parameters
SI                    32768
SF              125.7577885 MHz
WDW                     EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

7c

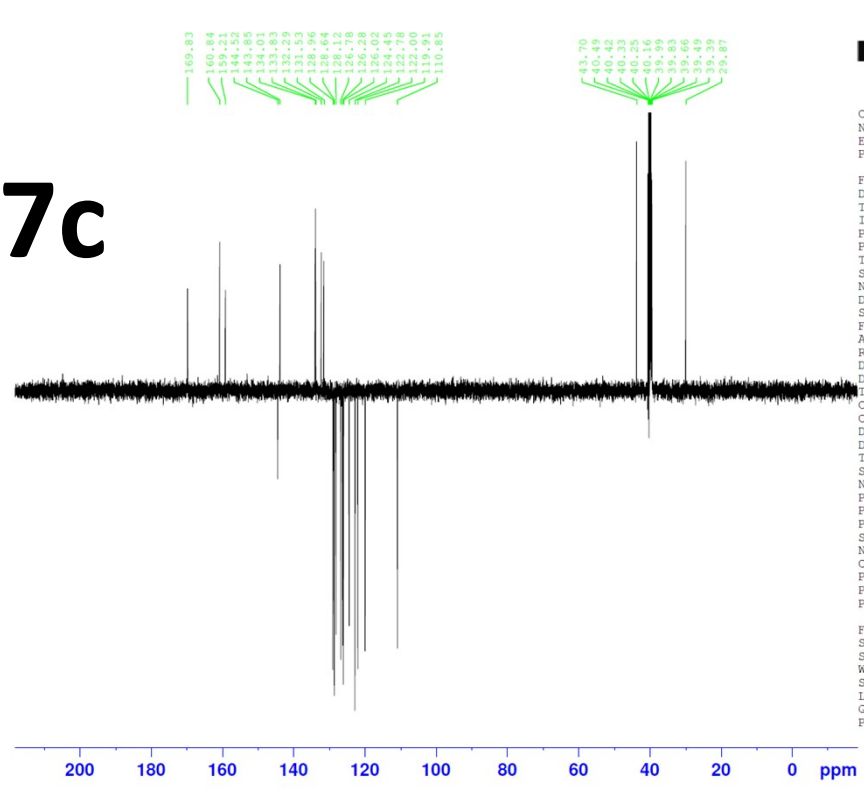



```
Current Data Parameters
NAME                  NA126
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20191016
Time                 15.50 h
INSTRUM              spect
PROBHD     Z113652_0266 (
PULPROG               zg30
TD                   65536
SOLVENT               DMSO
NS                       16
DS                        2
SWH              10000.000 Hz
FIDRES           0.305176 Hz
AQ               3.2767999 sec
RG                  118.43
DW                  50.000 usec
DE                  13.50 usec
TE                  298.1 K
D1              1.00000000 sec
TD0                       1
SFO1           500.1330883 MHz
NUC1                    1H
P1                  10.00 usec
PLW1           21.07600021 W

F2 - Processing parameters
SI                    65536
SF             500.1300000 MHz
WDW                      EM
SSB         0
LB                   0.30 Hz
GB          0
PC                   1.00
```

7c

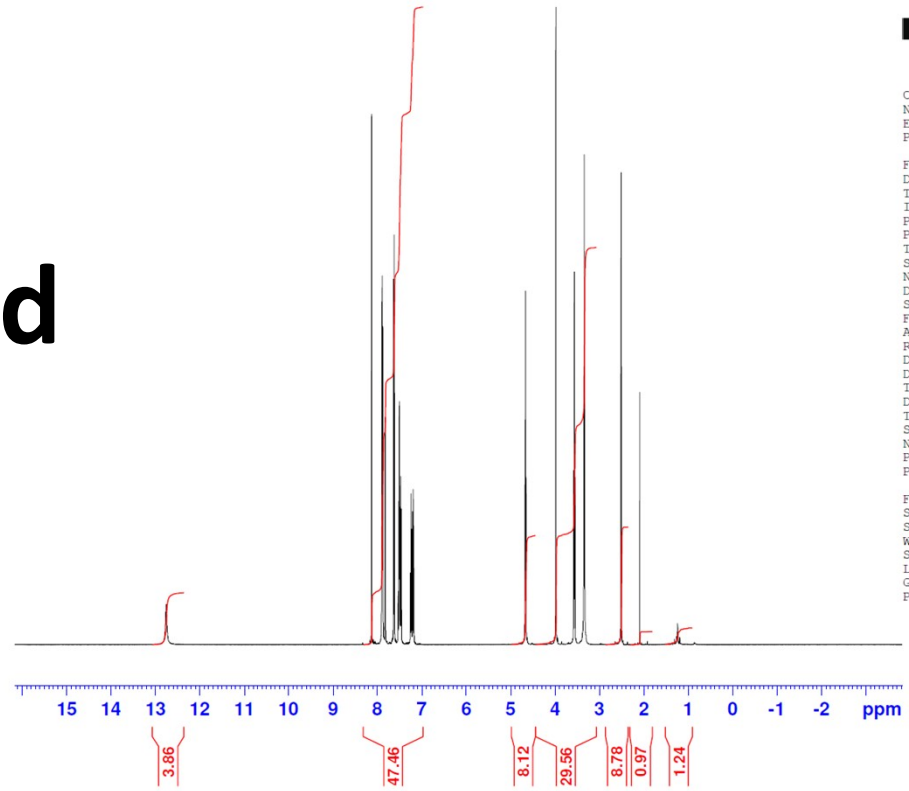



```
Current Data Parameters
NAME                  NA126
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20191016
Time                 20.02 h
INSTRUM              spect
PROBHD     Z113652_0266 (
PULPROG              jmod
TD                   65536
SOLVENT               DMSO
NS                      512
DS                        4
SWH              29761.904 Hz
FIDRES           0.908261 Hz
AQ               1.1010048 sec
RG                  189.93
DW                  16.800 usec
DE                   6.50 usec
TE                  298.2 K
CNST2          145.0000000
CNST11           1.0000000
D1               2.00000000 sec
D20              0.00689655 sec
TD0                       1
SFO1           125.7703643 MHz
NUC1                    13C
P1                  10.00 usec
P2                  20.00 usec
PLW1           74.02700043 W
SFO2           500.1320005 MHz
NUC2                    1H
CPDPRG[2          waltz16
PCPD2               80.00 usec
PLW2           21.07600021 W
PLW12           0.32931000 W

F2 - Processing parameters
SI                    32768
SF             125.7577885 MHz
WDW                      EM
SSB         0
LB                   1.00 Hz
GB          0
PC                   1.40
```

7d

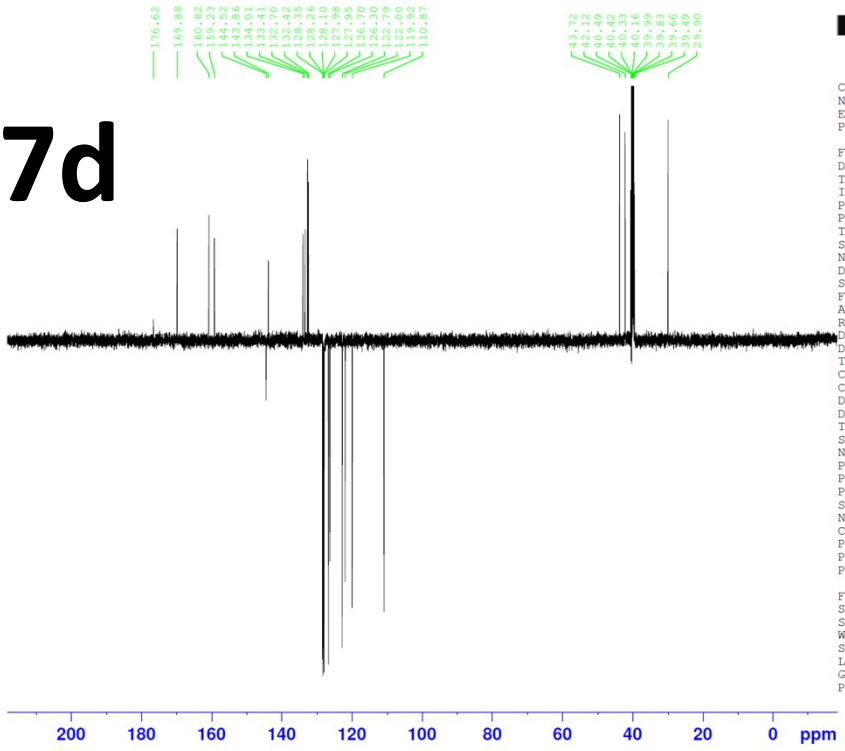



```
Current Data Parameters
NAME                  NA125
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20191016
Time                  15.35 h
INSTRUM                spect
PROBHD    Z113652_0266 (
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH              10000.000 Hz
FIDRES               0.305176 Hz
AQ                3.2767999 sec
RG                   118.43
DW                   50.000 usec
DE                   13.50 usec
TE                   298.1 K
D1              1.00000000 sec
TD0                       1
SFO1           500.1330883 MHz
NUC1                     1H
P1                   10.00 usec
PLW1           21.07600021 W

F2 - Processing parameters
SI                    65536
SF             500.1300000 MHz
WDW                      EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

7d

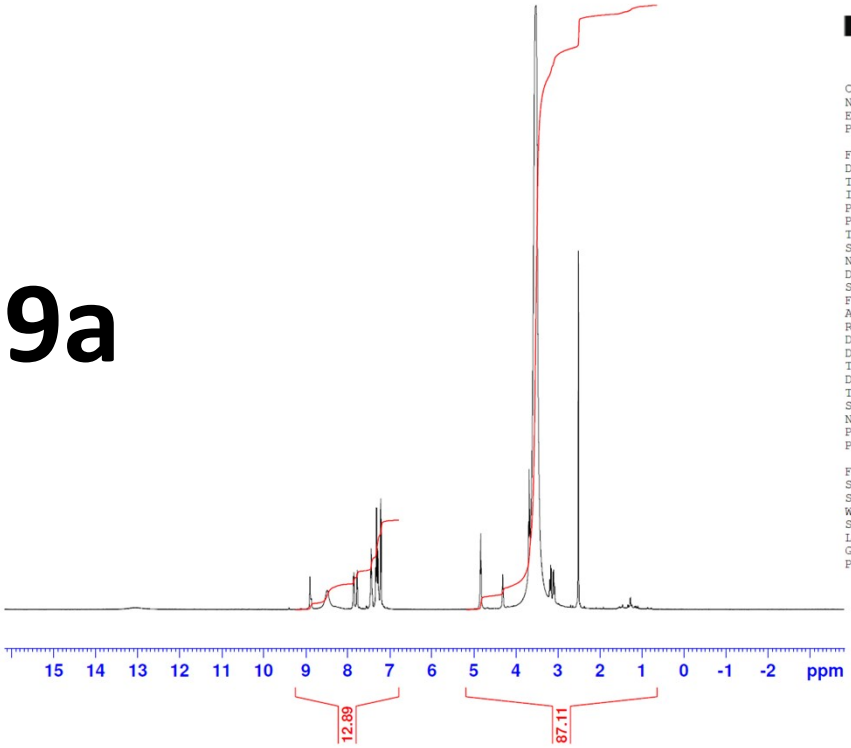



```
Current Data Parameters
NAME                  NA125
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20191016
Time                  19.32 h
INSTRUM                spect
PROBHD    Z113652_0266 (
PULPROG              jmod
TD                    65536
SOLVENT                DMSO
NS                       512
DS                        4
SWH              29761.904 Hz
FIDRES               0.908261 Hz
AQ                1.1010048 sec
RG                   189.93
DW                   16.800 usec
DE                    6.50 usec
TE                   298.2 K
CNST2          145.0000000
CNST11           1.0000000
D1               2.00000000 sec
D20              0.00689655 sec
TD0                       1
SFO1           125.7703643 MHz
NUC1                    13C
P1                   10.00 usec
P2                   20.00 usec
PLW1           74.02700043 W
SFO2           500.1320005 MHz
NUC2                     1H
CPDPRG[2             waltz16
PCPD2                80.00 usec
PLW2           21.07600021 W
PLW12            0.32931000 W

F2 - Processing parameters
SI                    32768
SF             125.7577885 MHz
WDW                      EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

9a

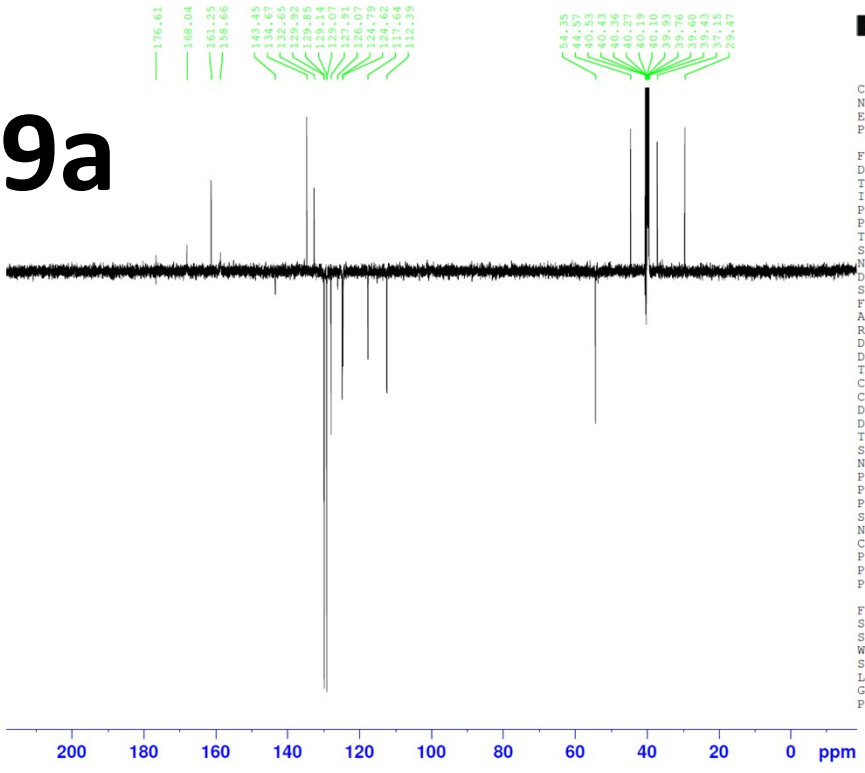



```
Current Data Parameters
NAME        NA110 melted
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20190809
Time             11.27 h
INSTRUM           spect
PROBHD    Z113652_0266 (
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                   16
DS                    2
SWH          10000.000 Hz
FIDRES           0.305176 Hz
AQ             3.2767999 sec
RG                  76.2
DW                50.000 usec
DE                13.50 usec
TE                298.1 K
D1            1.00000000 sec
TD0                   1
SFO1         500.1330883 MHz
NUC1                  1H
P1                10.00 usec
PLW1         21.07600021 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

9a

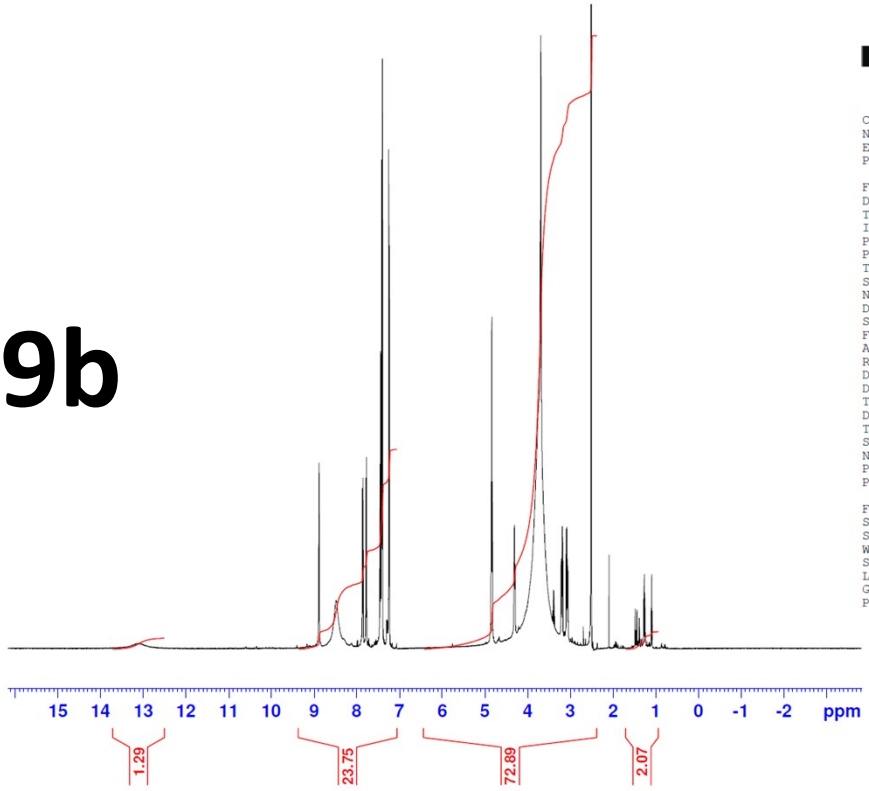



```
Current Data Parameters
NAME                 NA110
EXPNO                    5
PROCNO                   1

F2 - Acquisition Parameters
Date_           20190821
Time              1.03 h
INSTRUM            spect
PROBHD    Z113652_0266 (
PULPROG             jmod
TD                 65536
SOLVENT             DMSO
NS                  3072
DS                     4
SWH           29761.904 Hz
FIDRES            0.908261 Hz
AQ              1.1010048 sec
RG                 189.93
DW                16.800 usec
DE                 6.50 usec
TE                 298.1 K
CNST2         145.0000000
CNST11          1.0000000
D1            2.00000000 sec
D20           0.00689655 sec
TD0                    1
SFO1          125.7703643 MHz
NUC1                  13C
P1                10.00 usec
P2                20.00 usec
PLW1          74.02700043 W
SFO2          500.1320005 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2             80.00 usec
PLW2          21.07600021 W
PLW12          0.32931000 W

F2 - Processing parameters
SI                 32768
SF           125.7577885 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

9b



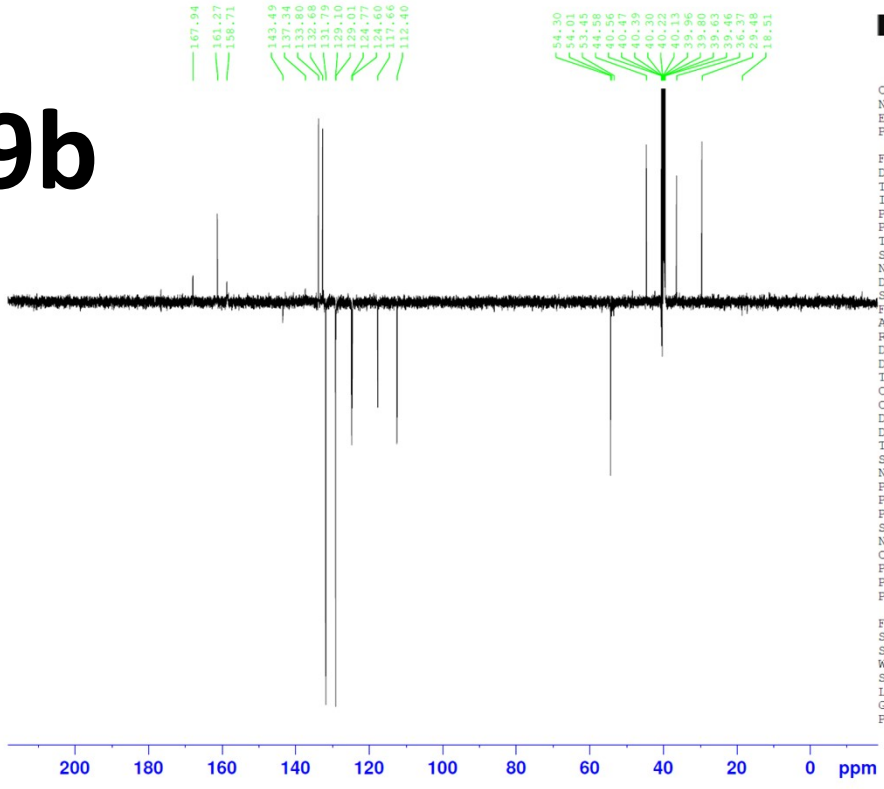
BRUKER

```
Current Data Parameters
NAME                  NA118
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20190904
Time                 16.53 h
INSTRUM               spect
PROBHD    Z113652_0266 (
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH              10000.000 Hz
FIDRES           0.305176 Hz
AQ               3.2767999 sec
RG                  104.67
DW                  50.000 usec
DE                  13.50 usec
TE                  298.1 K
D1              1.00000000 sec
TD0                       1
SFO1           500.1330883 MHz
NUC1                    1H
P1                  10.00 usec
PLW1           21.07600021 W

F2 - Processing parameters
SI                    65536
SF               500.1300000 MHz
WDW                      EM
SSB          0
LB                  0.30 Hz
GB           0
PC                  1.00
```

9b



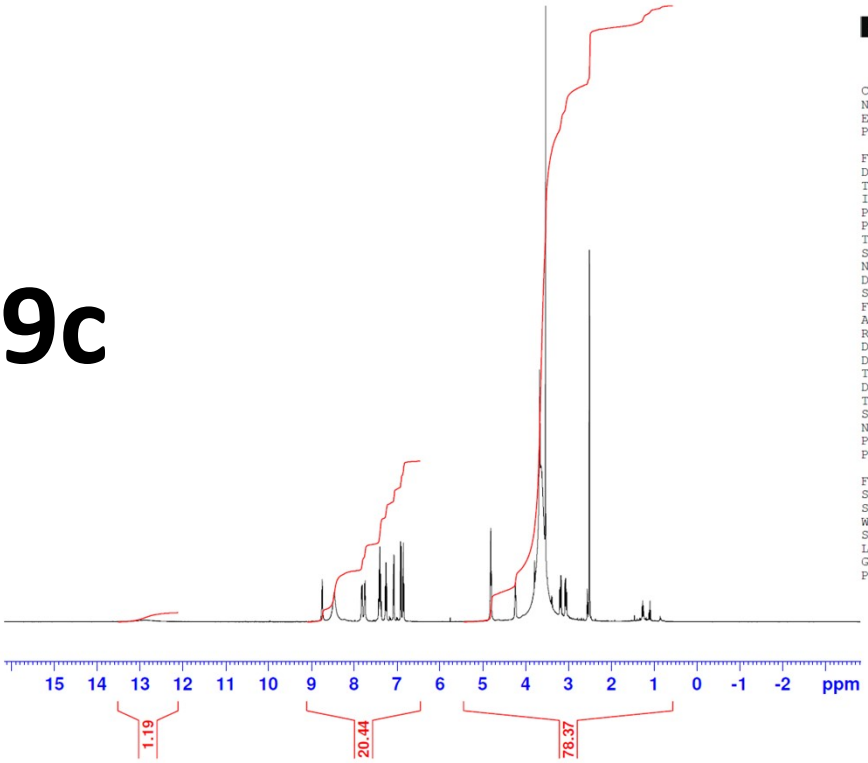
BRUKER

```
Current Data Parameters
NAME                  NA118
EXPNO                     5
PROCNO                    1

F2 - Acquisition Parameters
Date_              20190914
Time                  3.47 h
INSTRUM               spect
PROBHD    Z113652_0266 (
PULPROG                jmod
TD                    65536
SOLVENT                DMSO
NS                     3072
DS                        4
SWH              29761.904 Hz
FIDRES           0.908261 Hz
AQ               1.1010048 sec
RG                  189.93
DW                  16.800 usec
DE                   6.50 usec
TE                  298.2 K
CNST2          145.0000000
CNST11           1.0000000
D1               2.00000000 sec
D20              0.00689655 sec
TD0                       1
SFO1           125.7703643 MHz
NUC1                   13C
P1                  10.00 usec
P2                  20.00 usec
PLW1           74.02700043 W
SFO2           500.1320005 MHz
NUC2                    1H
CPDPRG[2            waltz16
PCPD2               80.00 usec
PLW2           21.07600021 W
PLW12           0.32931000 W

F2 - Processing parameters
SI                    32768
SF               125.7577885 MHz
WDW                      EM
SSB          0
LB                  1.00 Hz
GB           0
PC                  1.40
```

9c

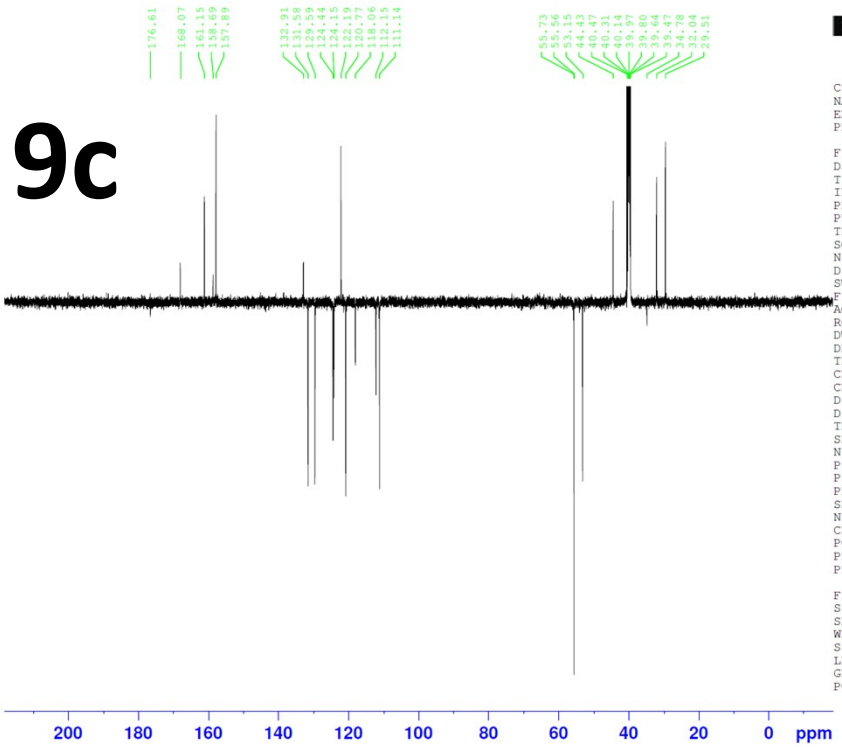



```
Current Data Parameters
NAME                  NA119
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20190910
Time                 10.49 h
INSTRUM              spect
PROBHD    Z113652_0266 (
PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                     16
DS                      2
SWH             10000.000 Hz
FIDRES              0.305176 Hz
AQ                3.2767999 sec
RG                    91.87
DW                   50.000 usec
DE                   13.50 usec
TE                   298.1 K
D1               1.00000000 sec
TD0                     1
SFO1            500.1330883 MHz
NUC1                   1H
P1                   10.00 usec
PLW1            21.07600021 W

F2 - Processing parameters
SI                  65536
SF              500.1300000 MHz
WDW                    EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

9c

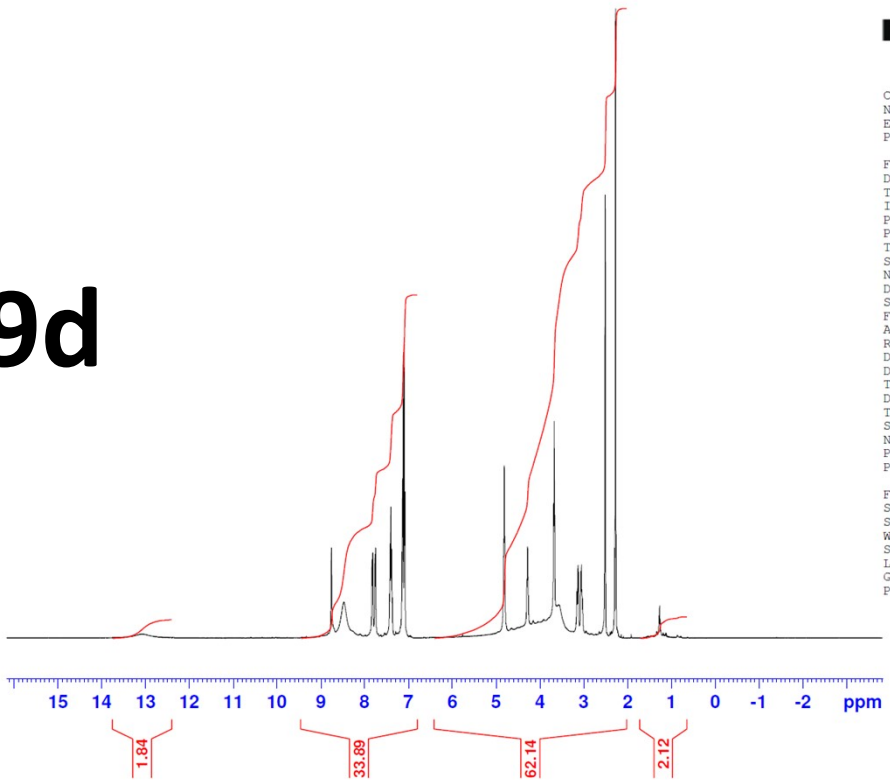



```
Current Data Parameters
NAME                  NA119
EXPNO                     3
PROCNO                    1

F2 - Acquisition Parameters
Date_              20190918
Time                  1.36 h
INSTRUM              spect
PROBHD    Z113652_0266 (
PULPROG              jmod
TD                  65536
SOLVENT              DMSO
NS                   3072
DS                      4
SWH             29761.904 Hz
FIDRES              0.908261 Hz
AQ                1.1010048 sec
RG                   189.93
DW                   16.800 usec
DE                    6.50 usec
TE                   298.2 K
CNST2           145.0000000
CNST11            1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                     1
SFO1            125.7703643 MHz
NUC1                   13C
P1                   10.00 usec
P2                   20.00 usec
PLW1            74.02700043 W
SFO2            500.1320005 MHz
NUC2                   1H
CPDPRG[2            waltz16
PCPD2                80.00 usec
PLW2            21.07600021 W
PLW12            0.32931000 W

F2 - Processing parameters
SI                  32768
SF              125.7577885 MHz
WDW                    EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

9d

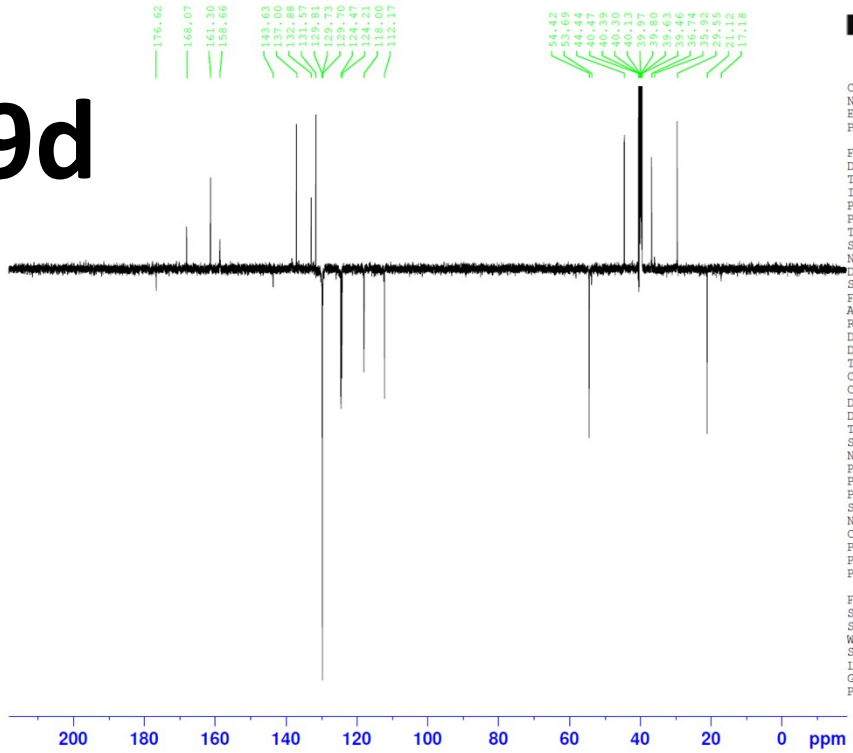



```
Current Data Parameters
NAME                  NA128
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20190920
Time                 16.44 h
INSTRUM               spect
PROBHD    Z113652_0266 (
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH               10000.000 Hz
FIDRES                0.305176 Hz
AQ                 3.2767999 sec
RG                    104.67
DW                    50.000 usec
DE                    13.50 usec
TE                    298.1 K
D1              1.00000000 sec
TD0                       1
SFO1           500.1330883 MHz
NUC1                     1H
P1                    10.00 usec
PLW1           21.07600021 W

F2 - Processing parameters
SI                    65536
SF             500.1300000 MHz
WDW                      EM
SSB         0
LB                    0.30 Hz
GB          0
PC                    1.00
```

9d

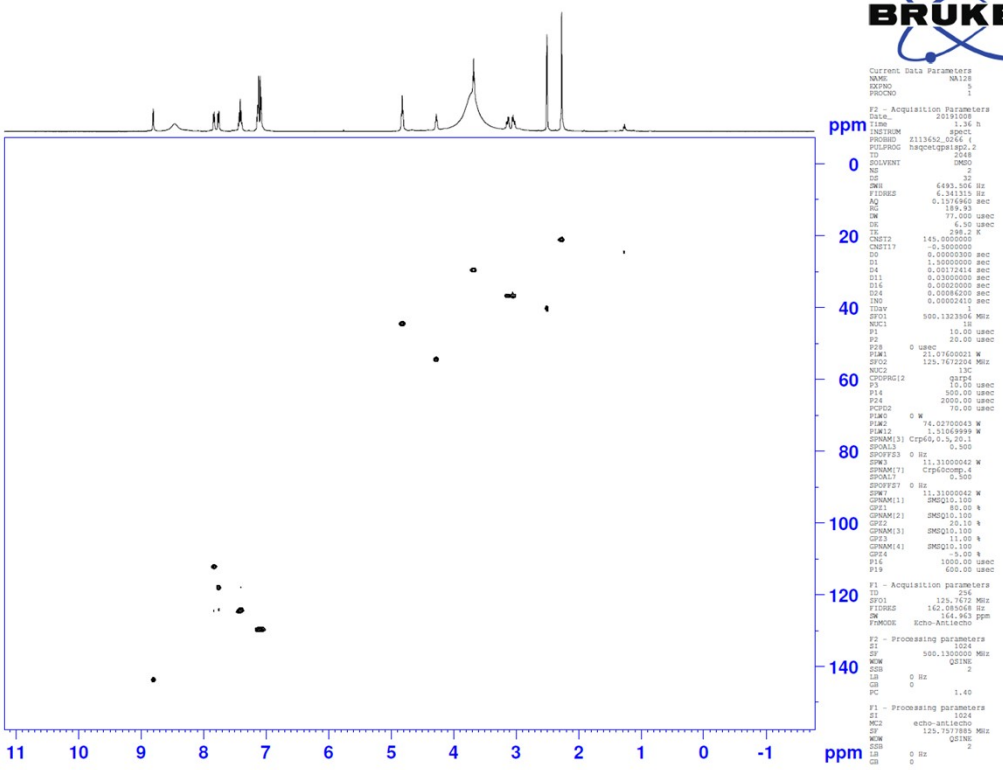



```
Current Data Parameters
NAME                  NA128
EXPNO                     3
PROCNO                    1

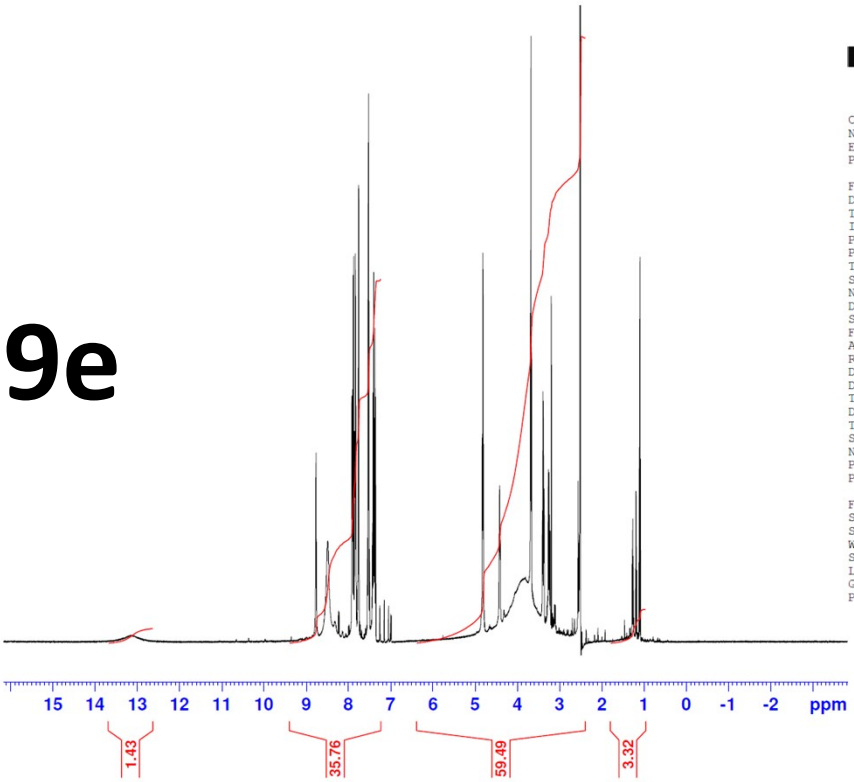
F2 - Acquisition Parameters
Date_              20191008
Time                  1.33 h
INSTRUM               spect
PROBHD    Z113652_0266 (
PULPROG                jmod
TD                    65536
SOLVENT                DMSO
NS                     3072
DS                        4
SWH              29761.904 Hz
FIDRES                0.908261 Hz
AQ                 1.1010048 sec
RG                    189.93
DW                    16.800 usec
DE                    6.50 usec
TE                    298.1 K
CNST2          145.0000000
CNST11           1.0000000
D1               2.00000000 sec
D20              0.00689655 sec
TD0                       1
SFO1           125.7703643 MHz
NUC1                     13C
P1                    10.00 usec
P2                    20.00 usec
PLW1           74.02700043 W
SFO2           500.1320005 MHz
NUC2                     1H
CPDPRG[2           waltz16
PCPD2                 80.00 usec
PLW2           21.07600021 W
PLW12           0.32931000 W

F2 - Processing parameters
SI                    32768
SF             125.7577885 MHz
WDW                      EM
SSB         0
LB                    1.00 Hz
GB          0
PC                    1.40
```

9d



9e

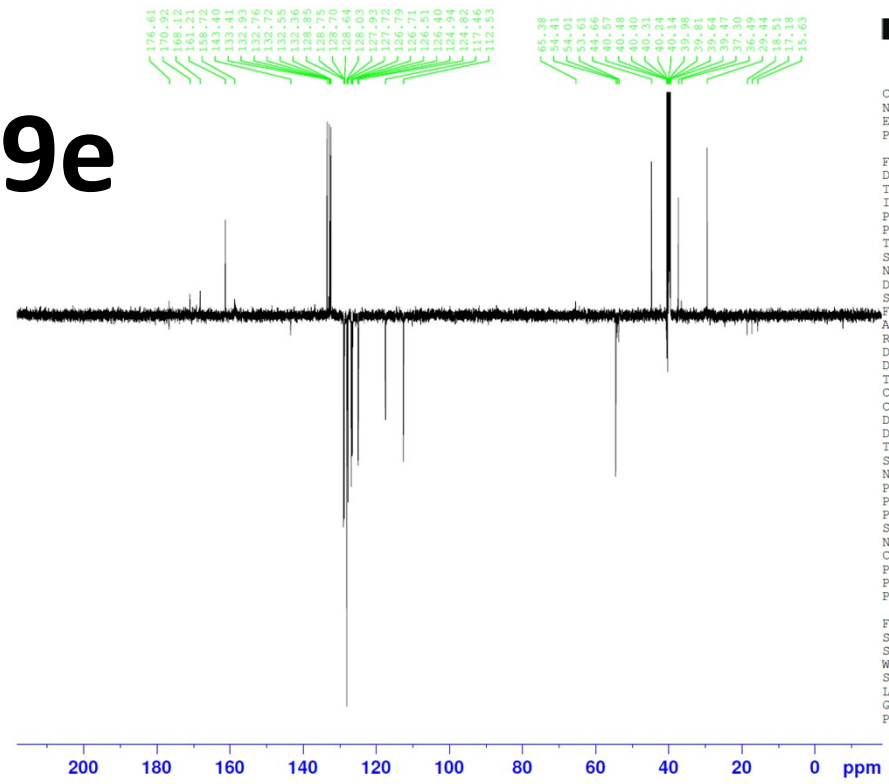



```
Current Data Parameters
NAME          NA120 repeat
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20200219
Time                 18.16 h
INSTRUM                spect
PROBHD    Z113652_0266 (
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH              10000.000 Hz
FIDRES               0.305176 Hz
AQ                3.2767999 sec
RG                     133.44
DW                   50.000 usec
DE                   13.500 usec
TE                   298.1 K
D1               1.00000000 sec
TD0                       1
SFO1           500.1330883 MHz
NUC1                     1H
P1                   10.00 usec
PLW1           21.07600021 W

F2 - Processing parameters
SI                    65536
SF              500.1300000 MHz
WDW                      EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

9e

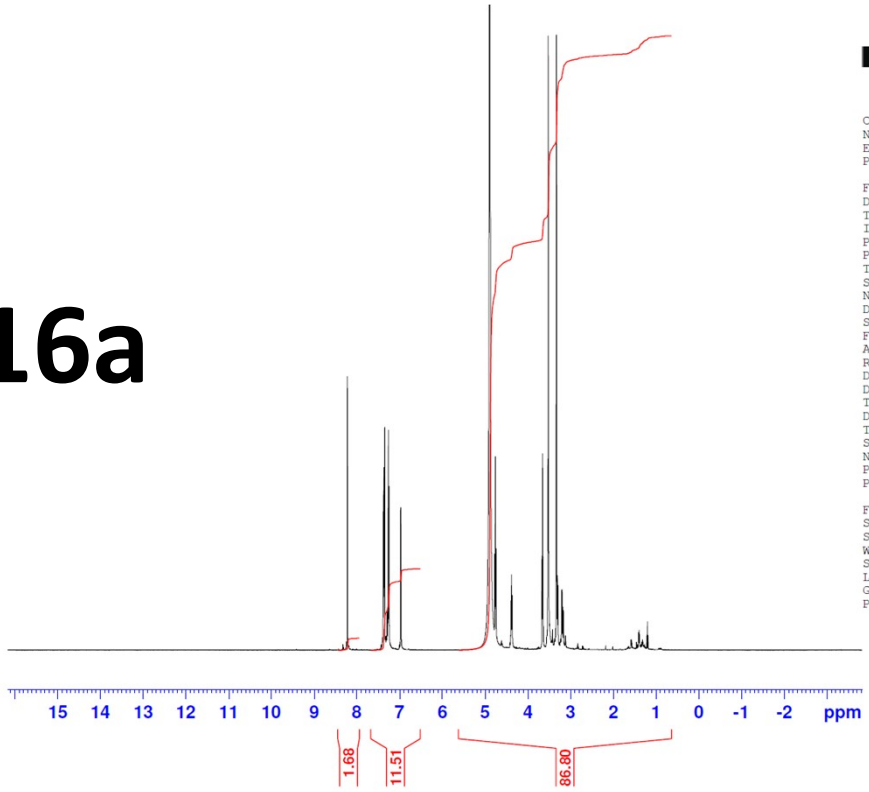



```
Current Data Parameters
NAME                   NA120
EXPNO                      3
PROCNO                     1

F2 - Acquisition Parameters
Date_              20190918
Time                  4.21 h
INSTRUM                spect
PROBHD    Z113652_0266 (
PULPROG                jmod
TD                    65536
SOLVENT                DMSO
NS                     3072
DS                        4
SWH              29761.904 Hz
FIDRES               0.908261 Hz
AQ                1.1010048 sec
RG                     189.93
DW                   16.800 usec
DE                    6.50 usec
TE                   298.2 K
CNST2           145.0000000
CNST11            1.0000000
D1             2.00000000 sec
D20            0.00689655 sec
TD0                       1
SFO1           125.7703643 MHz
NUC1                     13C
P1                   10.00 usec
P2                   20.00 usec
PLW1           74.02700043 W
SFO2           500.1320005 MHz
NUC2                     1H
CPDPRG[2             waltz16
PCPD2                80.00 usec
PLW2           21.07600021 W
PLW12           0.32931000 W

F2 - Processing parameters
SI                    32768
SF             125.7577885 MHz
WDW                      EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

16a

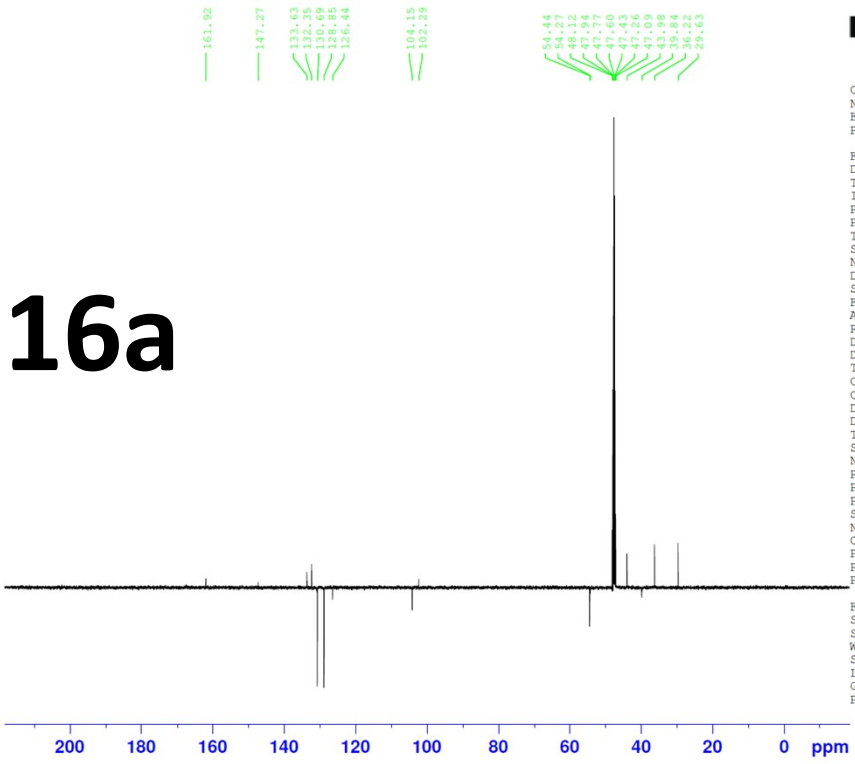



```
Current Data Parameters
NAME         NA1111 MeOD
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_           20200226
Time              16.13 h
INSTRUM            spect
PROBHD   Z113652_0266 (
PULPROG             zg30
TD                 65536
SOLVENT             MeOD
NS                    16
DS                     2
SWH           10000.000 Hz
FIDRES        0.305176 Hz
AQ            3.2767999 sec
RG                 91.87
DW                50.000 usec
DE                13.50 usec
TE                298.1 K
D1            1.00000000 sec
TD0                    1
SFO1          500.1330883 MHz
NUC1                  1H
P1                 10.00 usec
PLW1          21.07600021 W

F2 - Processing parameters
SI                 65536
SF            500.1300000 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

16a

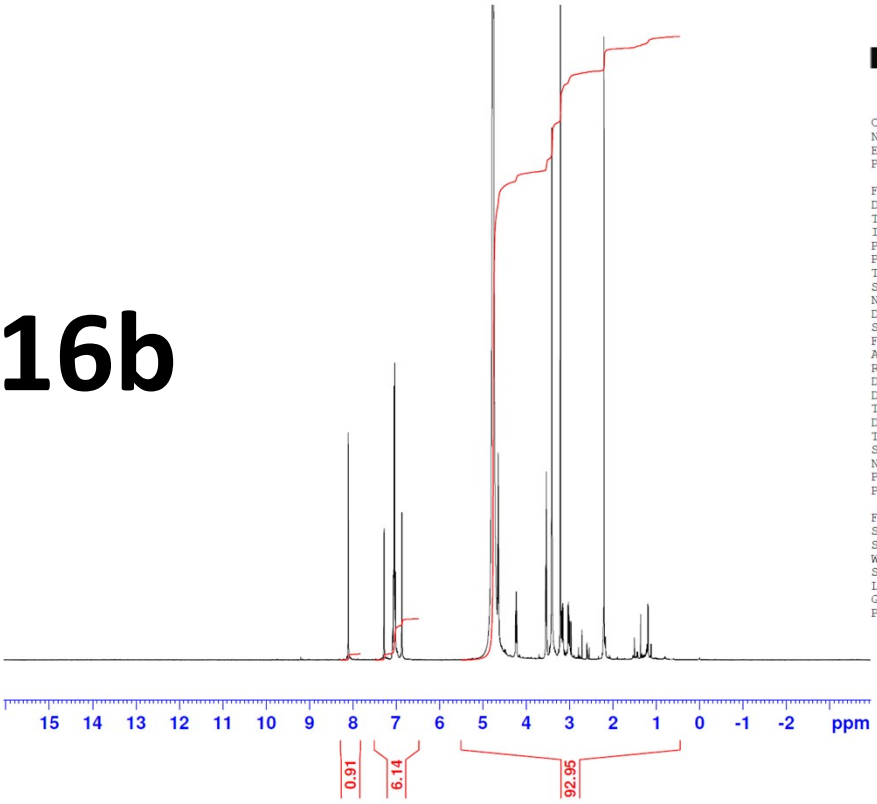



```
Current Data Parameters
NAME         NA1111 MeOD
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_           20200226
Time              22.49 h
INSTRUM            spect
PROBHD   Z113652_0266 (
PULPROG             jmod
TD                 65536
SOLVENT             MeOD
NS                  1024
DS                     4
SWH           29761.904 Hz
FIDRES        0.908261 Hz
AQ            1.1010048 sec
RG                189.93
DW                16.800 usec
DE                 6.50 usec
TE                298.1 K
CNST2         145.0000000
CNST11          1.0000000
D1            2.00000000 sec
D20           0.00689655 sec
TD0                    1
SFO1          125.7703643 MHz
NUC1                  13C
P1                 10.00 usec
P2                 20.00 usec
PLW1          74.02700043 W
SFO2          500.1320005 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2              80.00 usec
PLW2          21.07600021 W
PLW12          0.32931000 W

F2 - Processing parameters
SI                 32768
SF            125.7577885 MHz
WDW                   EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

16b

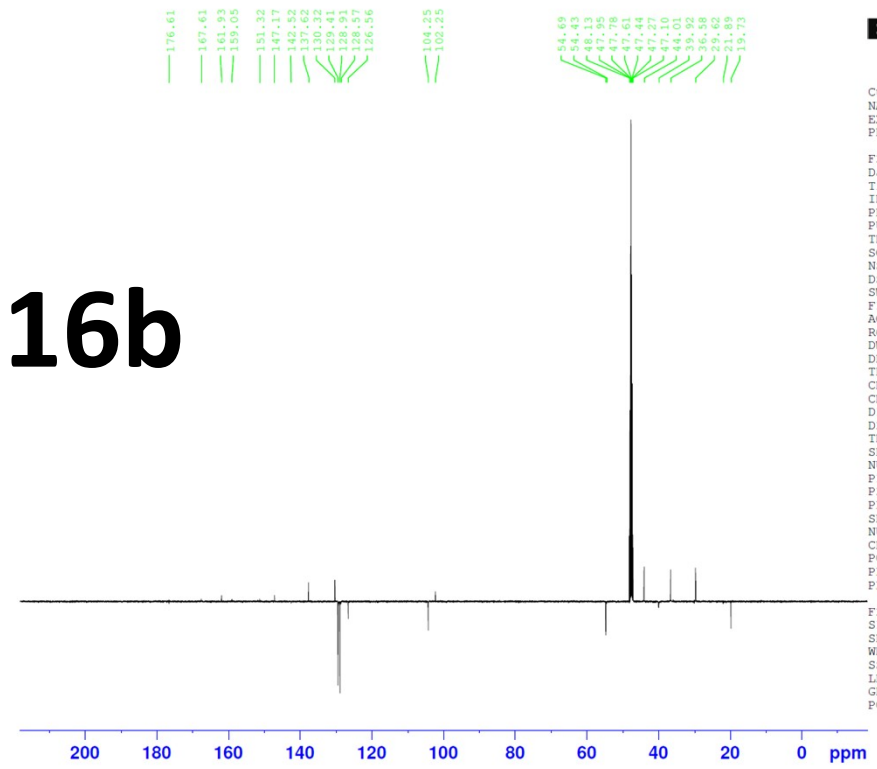



```
Current Data Parameters
NAME                  NA1112
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_              20200225
Time                 15.44 h
INSTRUM              spect
PROBHD    Z113652_0266 (
PULPROG                zg30
TD                    65536
SOLVENT                MeOD
NS                       16
DS                        2
SWH              10000.000 Hz
FIDRES               0.305176 Hz
AQ                3.2767999 sec
RG                     76.2
DW                  50.000 usec
DE                  13.50 usec
TE                   298.1 K
D1              1.00000000 sec
TD0                       1
SFO1           500.1330883 MHz
NUC1                     1H
P1                    10.00 usec
PLW1           21.07600021 W

F2 - Processing parameters
SI                    65536
SF               500.1300594 MHz
WDW                      EM
SSB         0
LB                    0.30 Hz
GB          0
PC                    1.00
```

16b

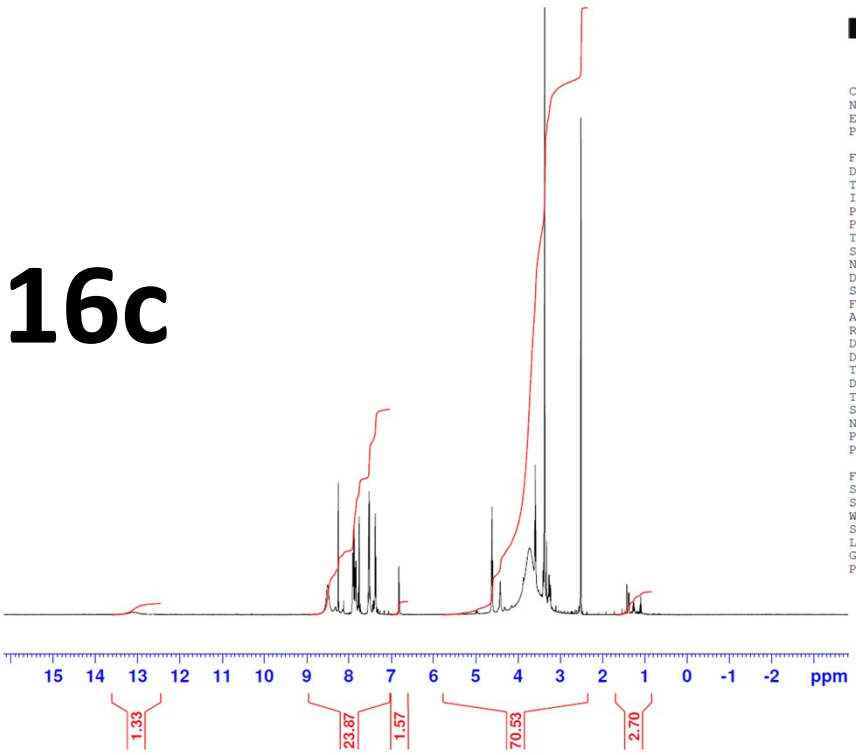



```
Current Data Parameters
NAME                  NA1112
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_              20200226
Time                  0.40 h
INSTRUM              spect
PROBHD    Z113652_0266 (
PULPROG                jmod
TD                    65536
SOLVENT                MeOD
NS                     3072
DS                        4
SWH              29761.904 Hz
FIDRES               0.908261 Hz
AQ                1.1010048 sec
RG                     189.93
DW                  16.800 usec
DE                   6.50 usec
TE                   298.1 K
CNST2          145.0000000
CNST11           1.0000000
D1              2.00000000 sec
D20             0.00689655 sec
TD0                       1
SFO1           125.7703643 MHz
NUC1                     13C
P1                    10.00 usec
P2                    20.00 usec
PLW1           74.02700043 W
SFO2           500.1320005 MHz
NUC2                     1H
CPDPRG[2            waltz16
PCPD2                 80.00 usec
PLW2           21.07600021 W
PLW12           0.32931000 W

F2 - Processing parameters
SI                    32768
SF               125.7577885 MHz
WDW                      EM
SSB         0
LB                    1.00 Hz
GB          0
PC                    1.40
```

16c

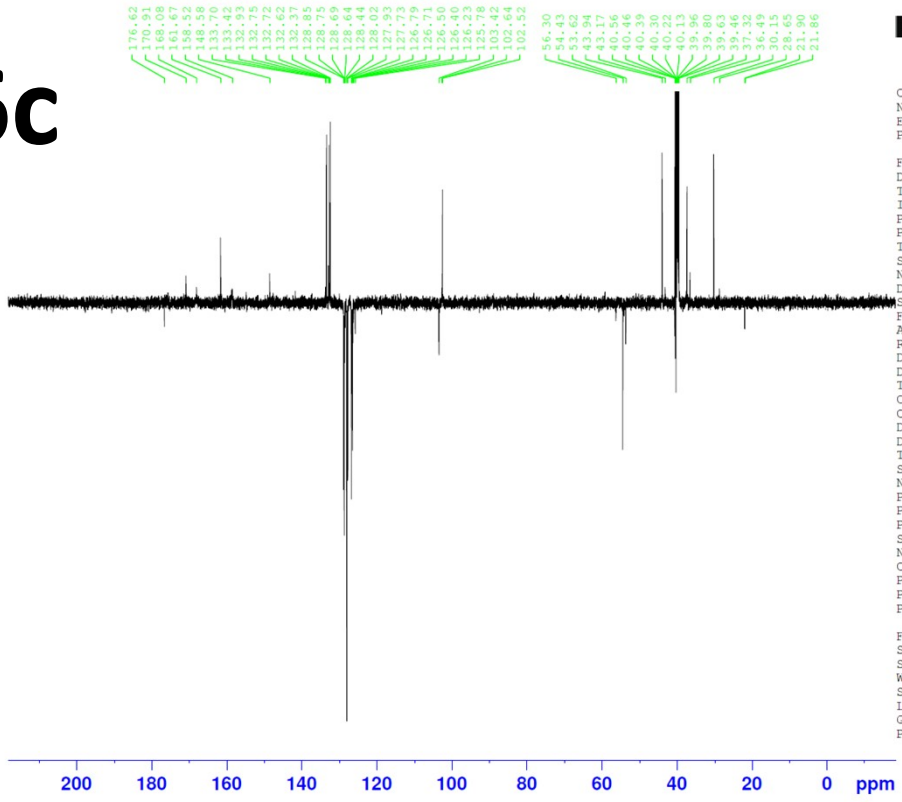



```
Current Data Parameters
NAME                  NA1107
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_              20200210
Time                 18.03 h
INSTRUM                spect
PROBHD    Z113652_0266 (
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH              10000.000 Hz
FIDRES               0.305176 Hz
AQ                3.2767999 sec
RG                   104.67
DW                   50.000 usec
DE                   13.500 usec
TE                   298.2 K
D1               1.00000000 sec
TD0                        1
SFO1           500.1330883 MHz
NUC1                      1H
P1                   10.00 usec
PLW1           21.07600021 W

F2 - Processing parameters
SI                    65536
SF             500.1300000 MHz
WDW                      EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

16c




```
Current Data Parameters
NAME                  NA1107
EXPNO                      4
PROCNO                     1

F2 - Acquisition Parameters
Date_              20200220
Time                 21.45 h
INSTRUM                spect
PROBHD    Z113652_0266 (
PULPROG                jmod
TD                    65536
SOLVENT                DMSO
NS                     3072
DS                        4
SWH              29761.904 Hz
FIDRES               0.908261 Hz
AQ                1.1010048 sec
RG                   189.93
DW                   16.800 usec
DE                    6.50 usec
TE                   298.2 K
CNST2          145.0000000
CNST11           1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                        1
SFO1           125.7703643 MHz
NUC1                      13C
P1                   10.00 usec
P2                   20.00 usec
PLW1           74.02700043 W
SFO2           500.1320005 MHz
NUC2                      1H
CPDPRG[2           waltz16
PCPD2                80.00 usec
PLW2           21.07600021 W
PLW12           0.32931000 W

F2 - Processing parameters
SI                    32768
SF             125.7577885 MHz
WDW                      EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

3.3. HPLC Charts:

5a

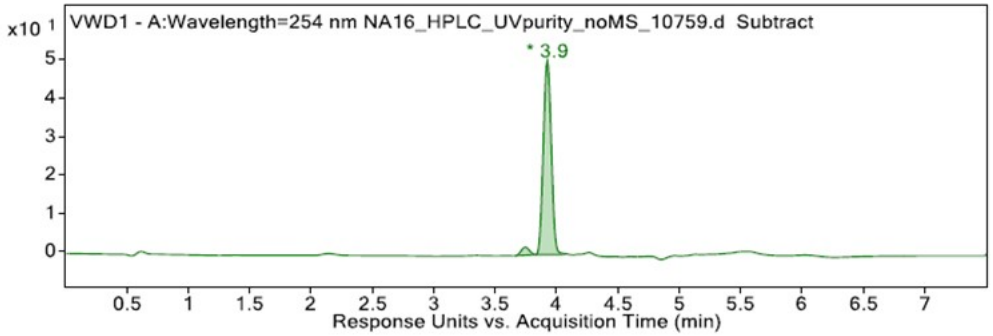


Figure: Base peak or HPLC chromatogram (indicated in left hand corner)

User Chromatogram Peak List

RT (min)	Area	Area %	Area Sum (%)	Symmetry	Width (min)
3.70	9.62	4.21	4.04	1.25	0.200
3.90	228.55	100.00	95.96	1.02	0.200

5b

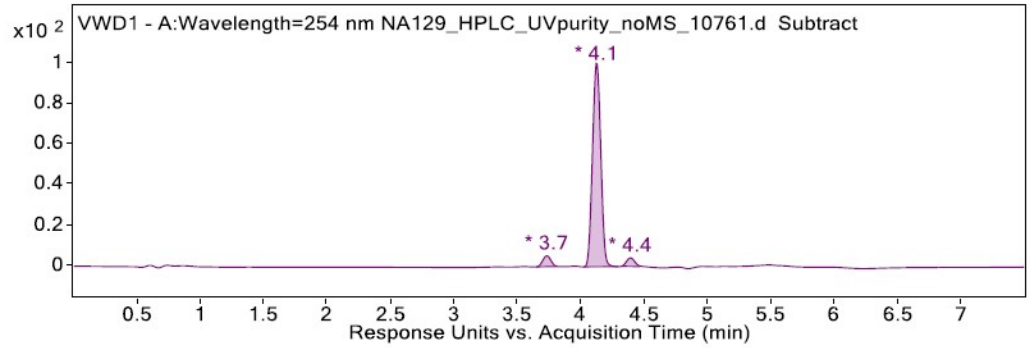
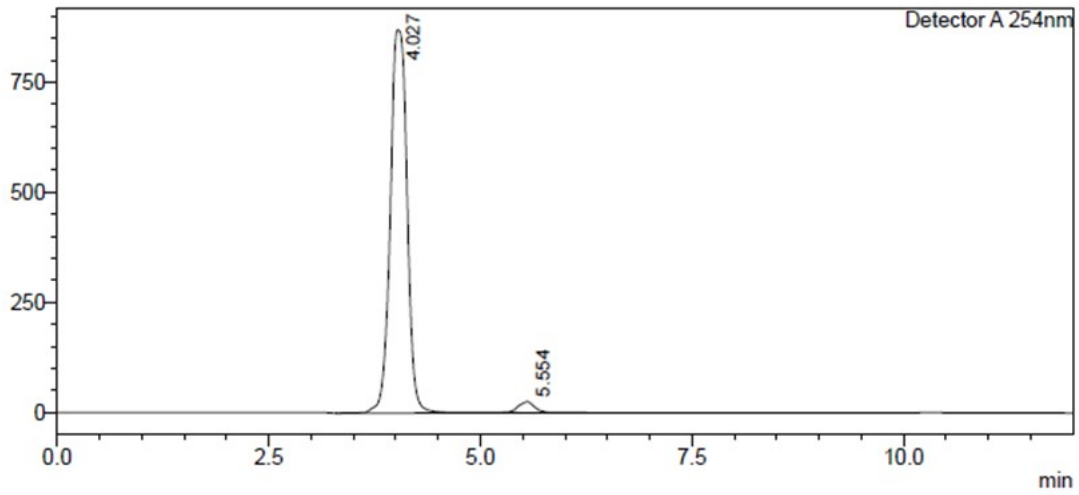


Figure: Base peak or HPLC chromatogram (indicated in left hand corner)

User Chromatogram Peak List

RT (min)	Area	Area %	Area Sum (%)	Symmetry	Width (min)
3.70	23.51	5.17	4.73	1.19	0.200
4.10	454.63	100.00	91.53	1.14	0.300
4.40	18.54	4.08	3.73	1.23	0.100

6a

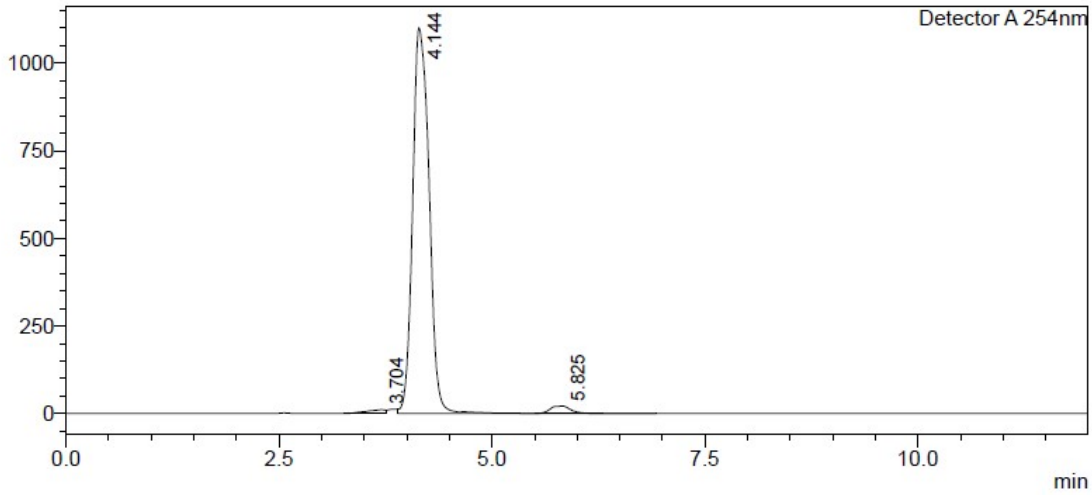


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Unit	Mark
1	4.027	12067622	869684	97.334	97.334		S
2	5.554	330540	24671	2.666	2.666		TV
Total		12398162	894354		100.000		

6b

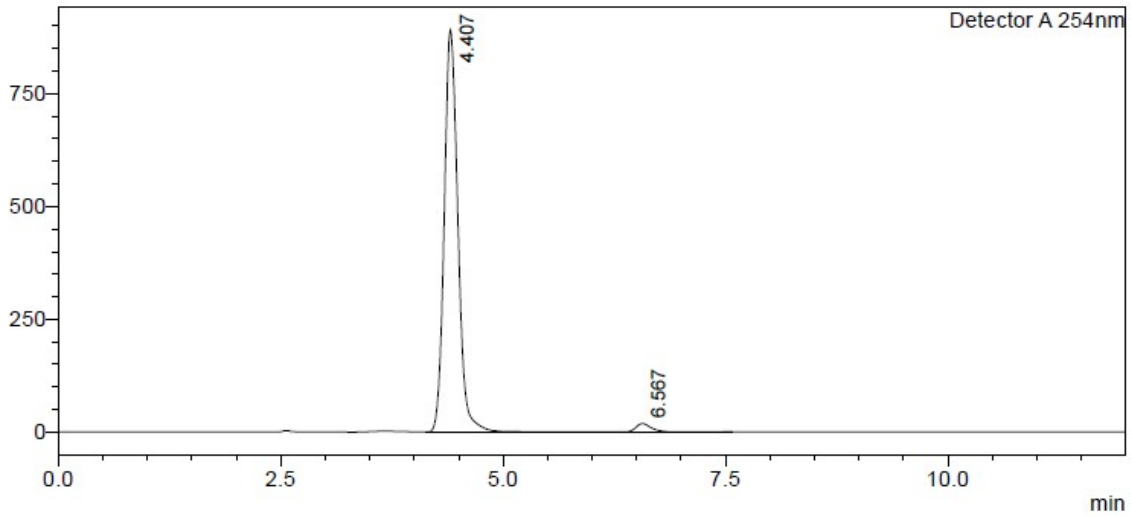


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Unit	Mark
1	3.704	172783	10747	1.123	1.123		
2	4.144	14873977	1100700	96.664	96.664		SV
3	5.825	340571	21063	2.213	2.213		T
Total		15387331	1132510		100.000		

6c

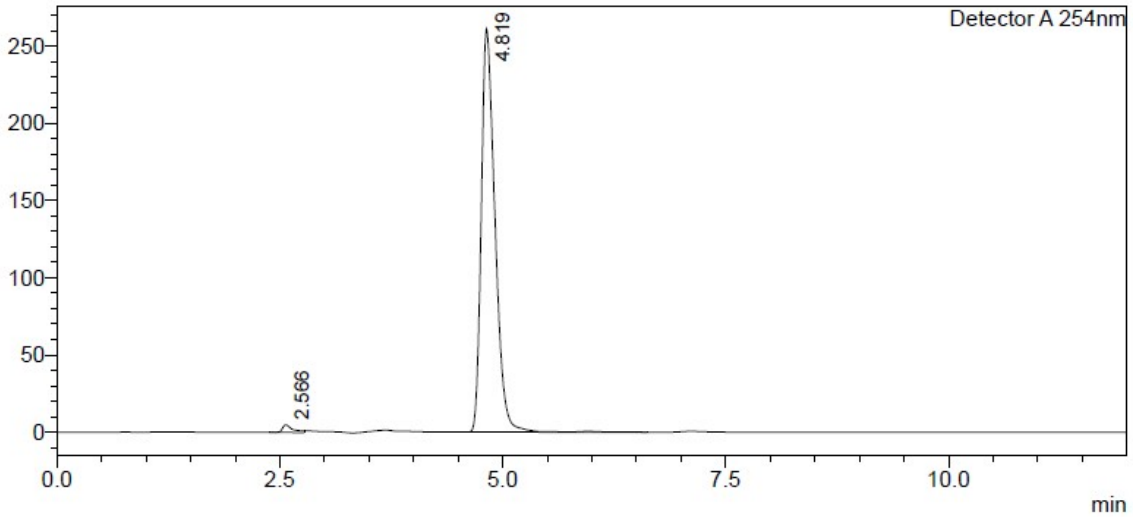


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Unit	Mark
1	4.407	9583264	891048	97.632	97.632		SV
2	6.567	232408	18956	2.368	2.368		T
Total		9815672	910004		100.000		

6d

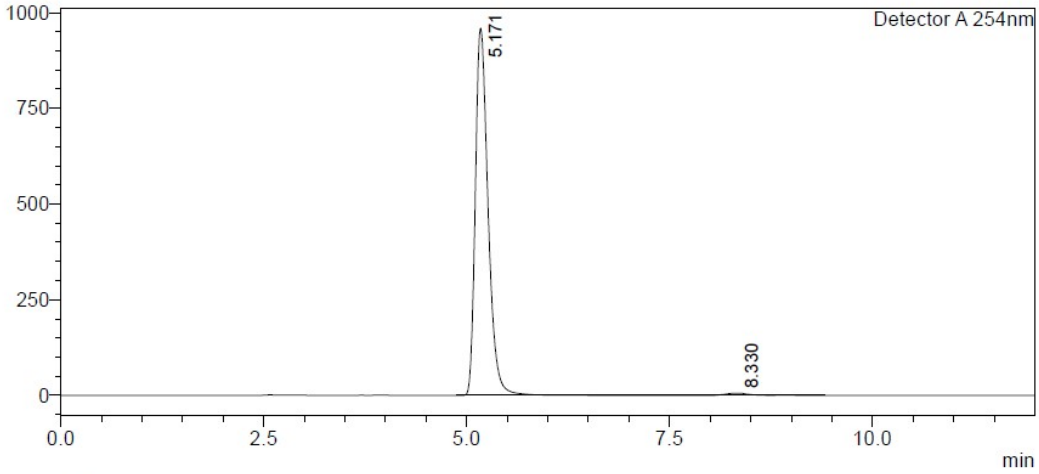


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Unit	Mark
1	2.566	38346	4863	1.353	1.353		
2	4.819	2794845	261036	98.647	98.647		S
Total		2833191	265899		100.000		

6e



<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Unit	Mark
1	5.171	10438829	958772	98.975	98.975		S
2	8.330	108114	5998	1.025	1.025		T
Total		10546943	964770		100.000		

7a

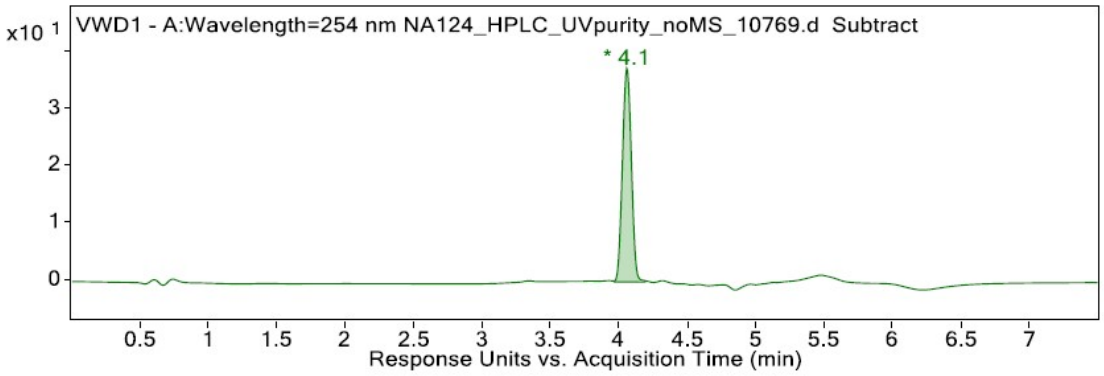


Figure: Base peak or HPLC chromatogram (indicated in left hand corner)

User Chromatogram Peak List

RT (min)	Area	Area %	Area Sum (%)	Symmetry	Width (min)
4.10	169.54	100.00	100.00	1.09	0.200

7b

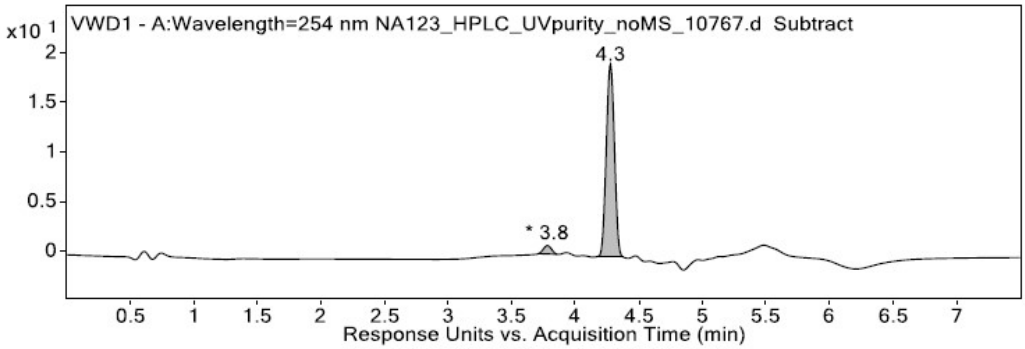


Figure: Base peak or HPLC chromatogram (indicated in left hand corner)

User Chromatogram Peak List

RT (min)	Area	Area %	Area Sum (%)	Symmetry	Width (min)
3.80	3.72	4.30	4.12	1.06	0.100
4.30	86.49	100.00	95.88	0.96	0.200

7c

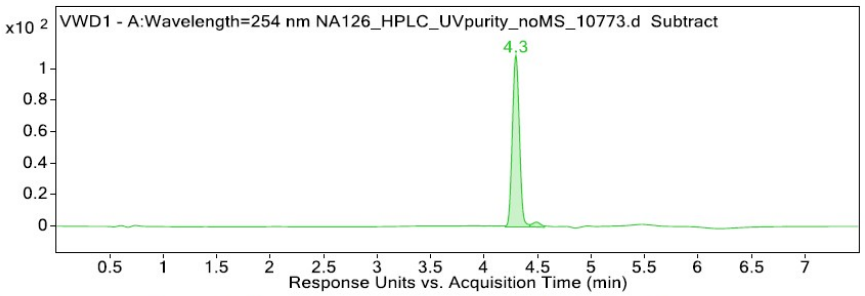


Figure: Base peak or HPLC chromatogram (indicated in left hand corner)

User Chromatogram Peak List

RT (min)	Area	Area %	Area Sum (%)	Symmetry	Width (min)
4.30	500.35	100.00	96.79	1.03	0.200
4.50	16.59	3.32	3.21	1.22	0.100

7d

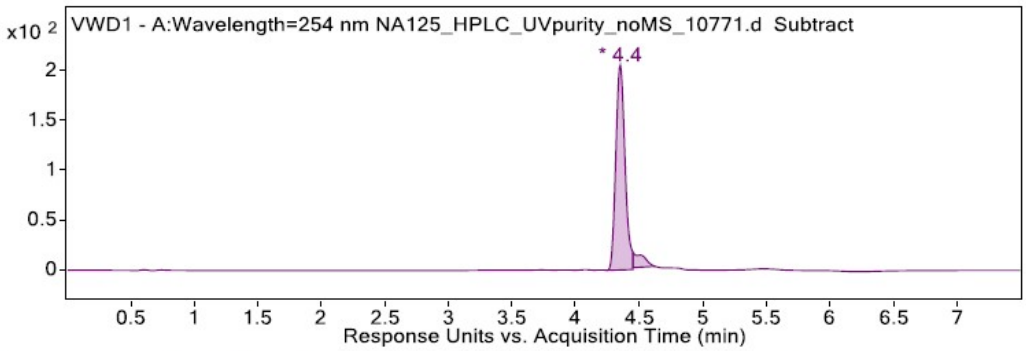
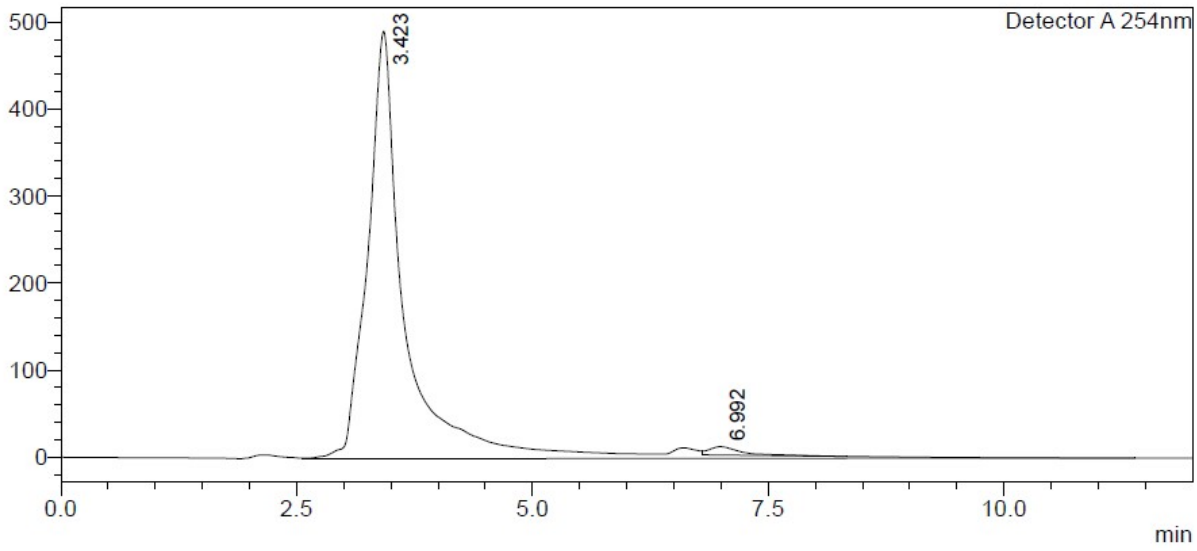


Figure: Base peak or HPLC chromatogram (indicated in left hand corner)

User Chromatogram Peak List

RT (min)	Area	Area %	Area Sum (%)	Symmetry	Width (min)
4.40	1031.23	100.00	92.43	1.36	0.200
4.50	84.51	8.20	7.57	Infinity	0.200

9a

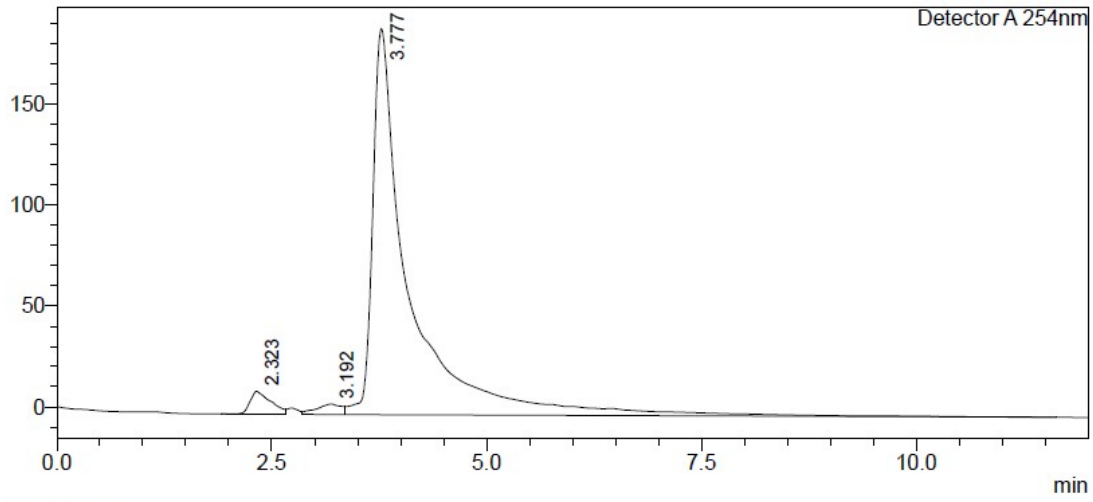


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	3.423	14074909	491002	98.420		SV	
2	6.992	225940	9393	1.580		TV	
Total		14300849	500395				

9b

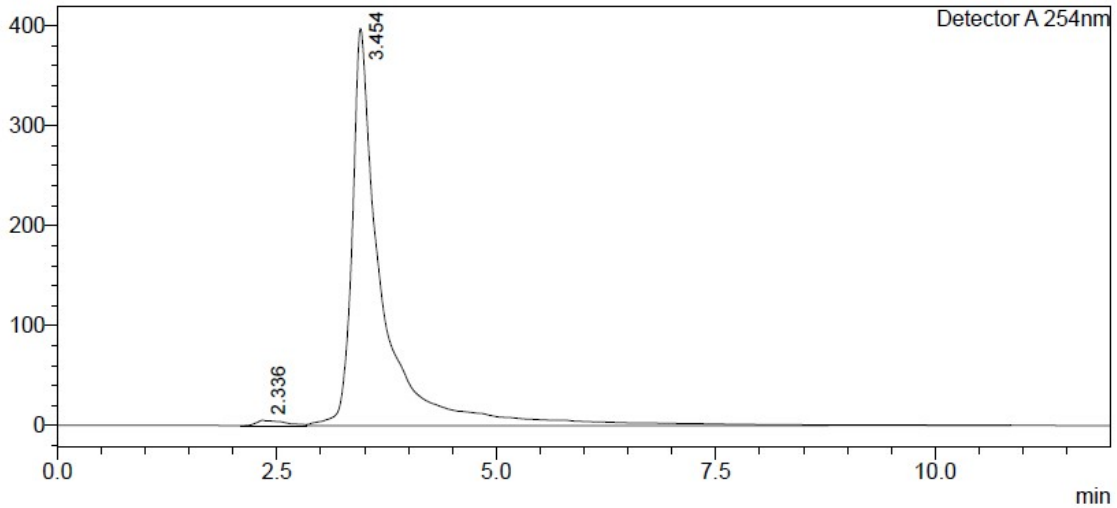


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Unit	Mark
1	2.323	187965	11295	3.135	3.135		
2	3.192	102866	5150	1.716	1.716		V
3	3.777	5705411	190986	95.150	95.150		SV
Total		5996242	207430		100.000		

9c



<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Unit	Mark
1	2.336	115196	5326	1.199	1.199		
2	3.454	9492896	397489	98.801	98.801		SV
Total		9608093	402815		100.000		

9d

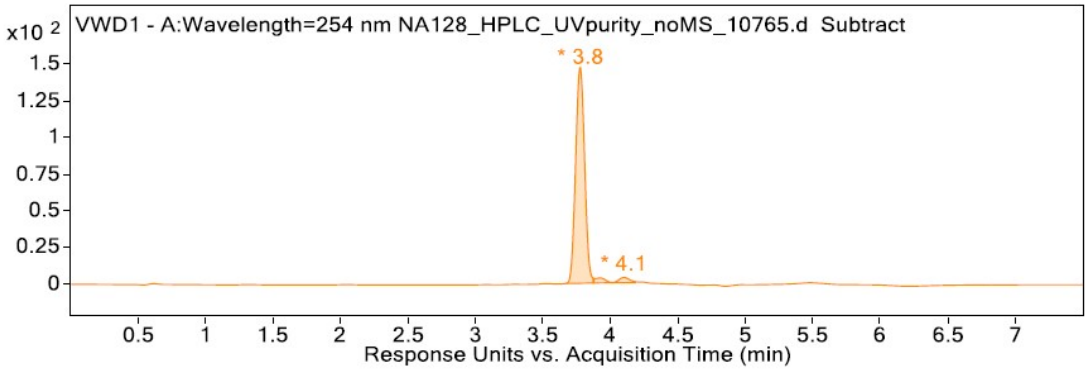


Figure: Base peak or HPLC chromatogram (indicated in left hand corner)

User Chromatogram Peak List

RT (min)	Area	Area %	Area Sum (%)	Symmetry	Width (min)
3.80	684.74	100.00	94.81	0.98	0.200
3.90	17.91	2.62	2.48	1.79	0.100
4.10	19.57	2.86	2.71	1.29	0.200

9e

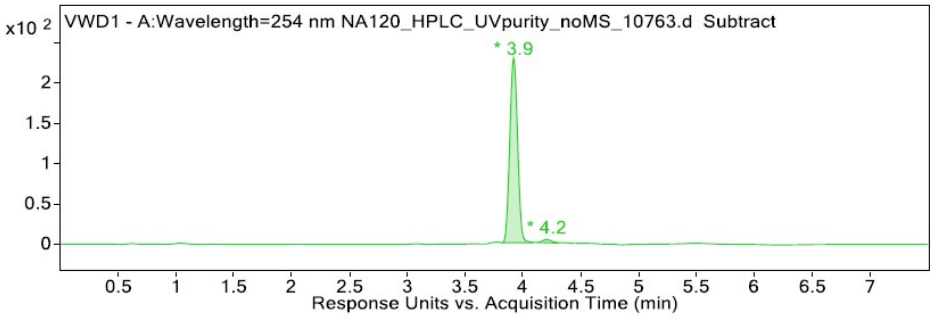


Figure: Base peak or HPLC chromatogram (indicated in left hand corner)

User Chromatogram Peak List

RT (min)	Area	Area %	Area Sum (%)	Symmetry	Width (min)
3.90	1072.78	100.00	97.96	1.09	0.300
4.20	22.36	2.08	2.04	0.95	0.200

16a

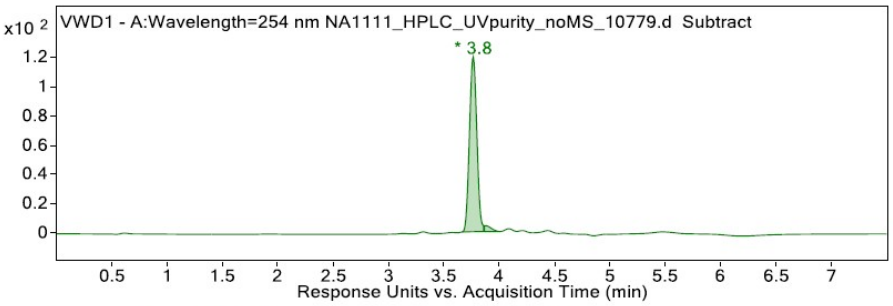


Figure: Base peak or HPLC chromatogram (indicated in left hand corner)

User Chromatogram Peak List

RT (min)	Area	Area %	Area Sum (%)	Symmetry	Width (min)
3.80	552.97	100.00	97.05	1.03	0.200
3.90	16.78	3.04	2.95	Infinity	0.100

16b

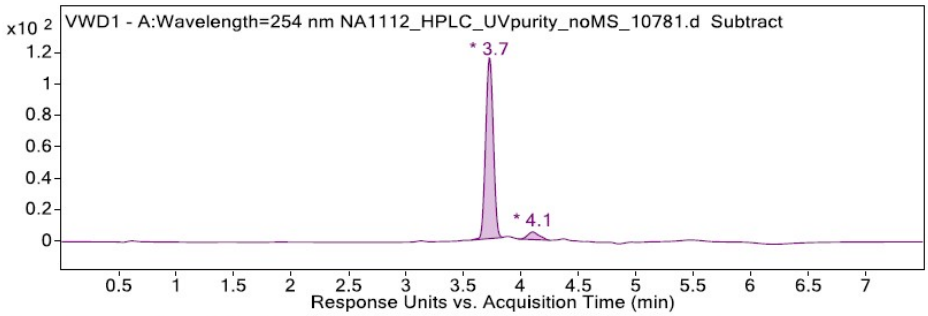


Figure: Base peak or HPLC chromatogram (indicated in left hand corner)

User Chromatogram Peak List

RT (min)	Area	Area %	Area Sum (%)	Symmetry	Width (min)
3.70	532.75	100.00	94.03	1.15	0.300
4.10	33.81	6.35	5.97	1.15	0.300

16c

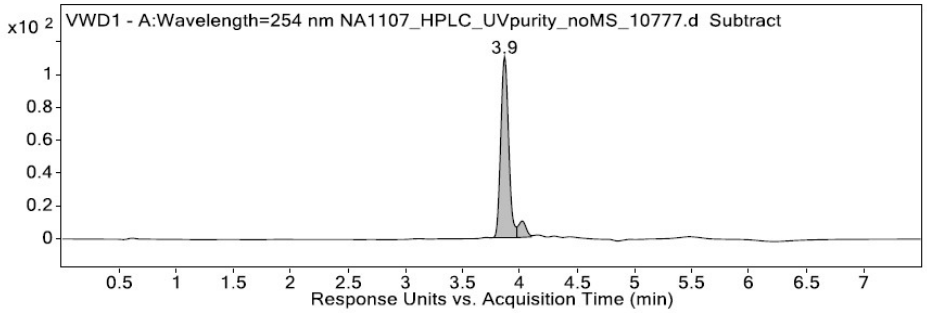


Figure: Base peak or HPLC chromatogram (indicated in left hand corner)

User Chromatogram Peak List

RT (min)	Area	Area %	Area Sum (%)	Symmetry	Width (min)
3.90	528.3	100.00	91.73	1.19	0.200
4.00	47.6	9.01	8.27	1.71	0.100

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