Electronic Supplementary Material (ESI) for RSC Advances.

Design, Synthesis, Docking Studies of Novel Pyrazole-based Scaffolds and Their Evaluation as VEGFR2 Inhibitors in the Treatment of Prostate Cancer.

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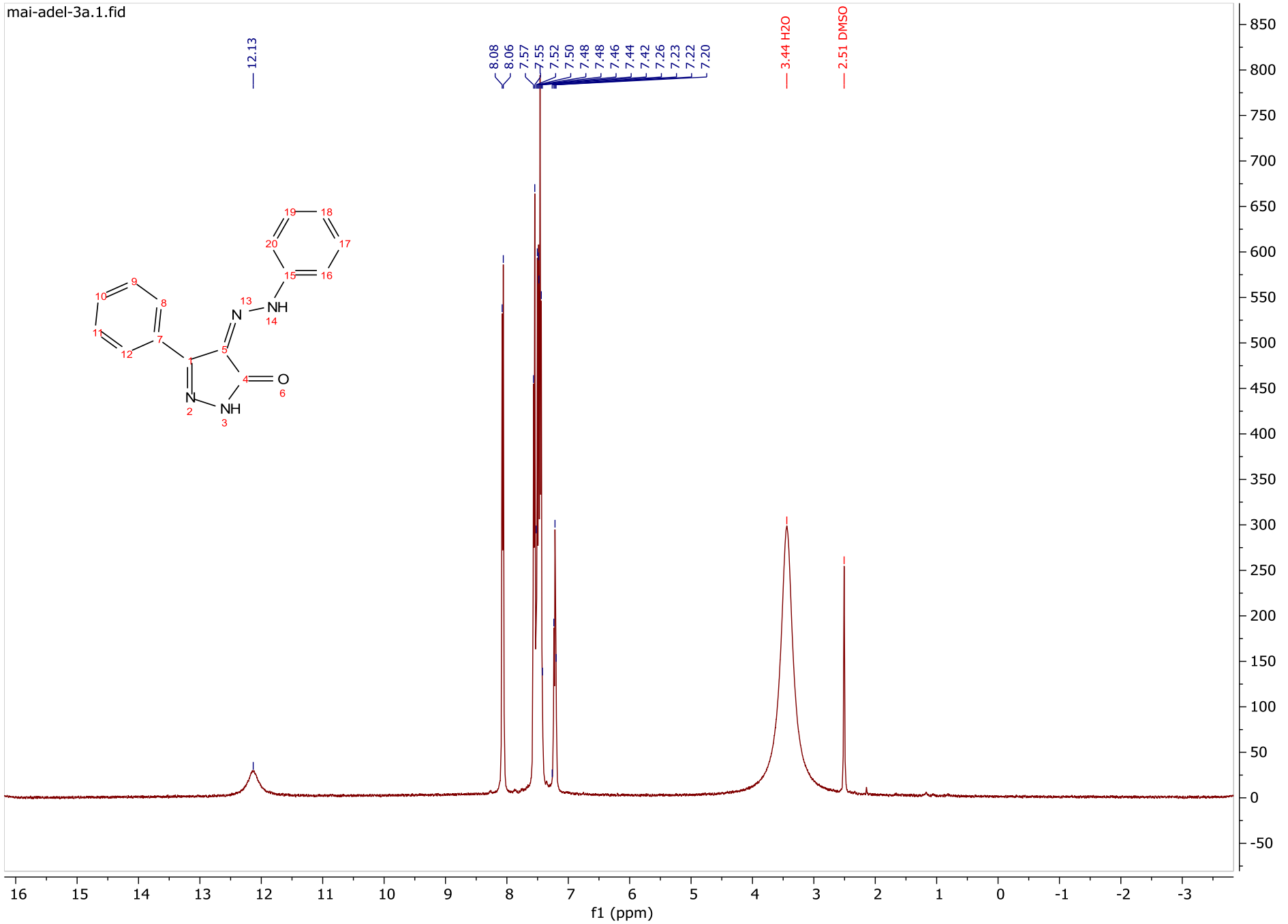
List of supplementary

#	Content
1	Supplementary characterization for the tested compounds NMR, IR, Mass
2	Figure S1 & S2 (Docking part)
3	Detailed methodology for the in vivo experiment.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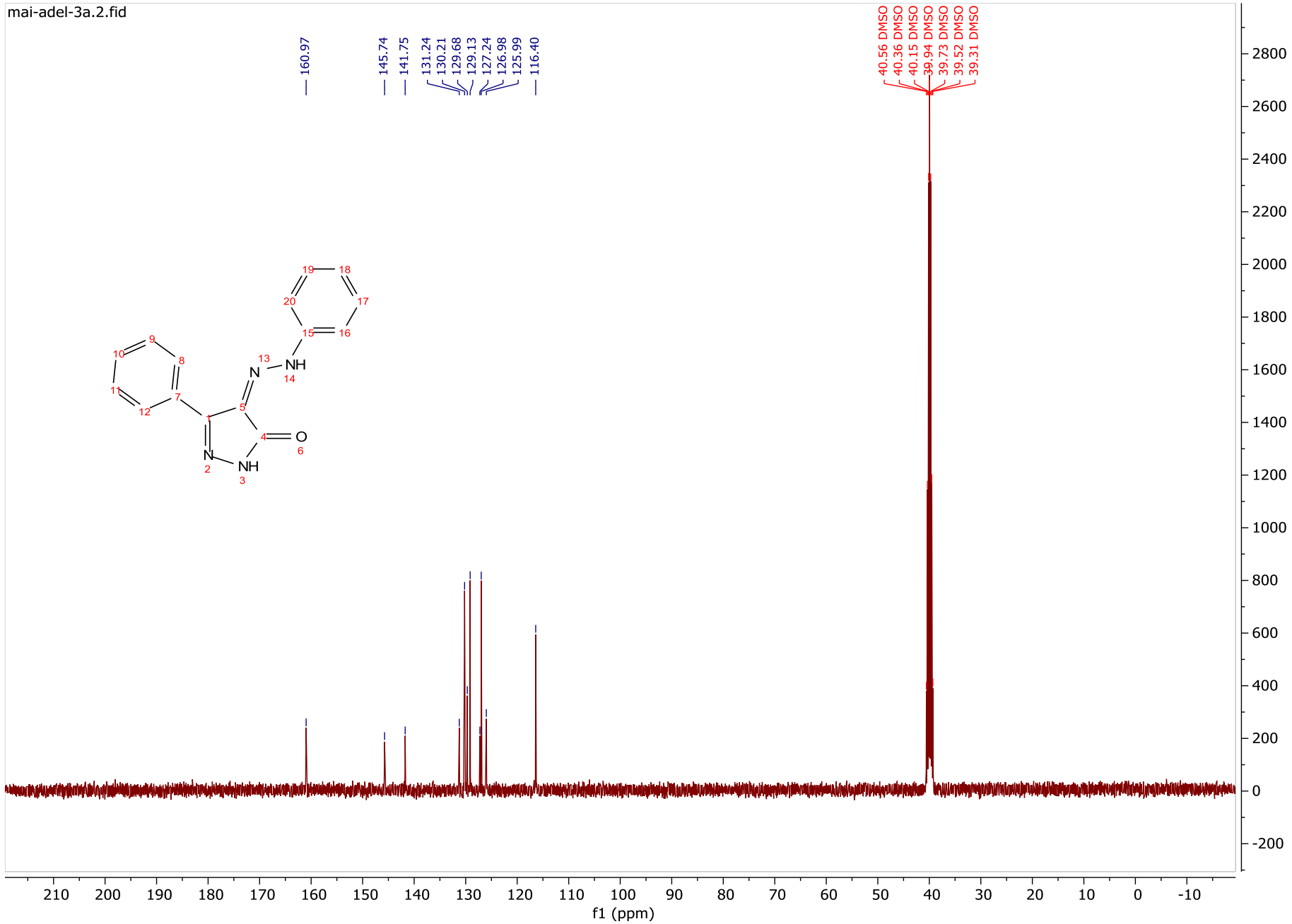
8.08
8.06
7.57
7.55
7.52
7.50
7.48
7.48
7.46
7.44
7.42
7.26
7.23
7.22
7.20
3.44 H2O
2.51 DMSO
f1 (ppm)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129.13
127.24
126.98
125.99
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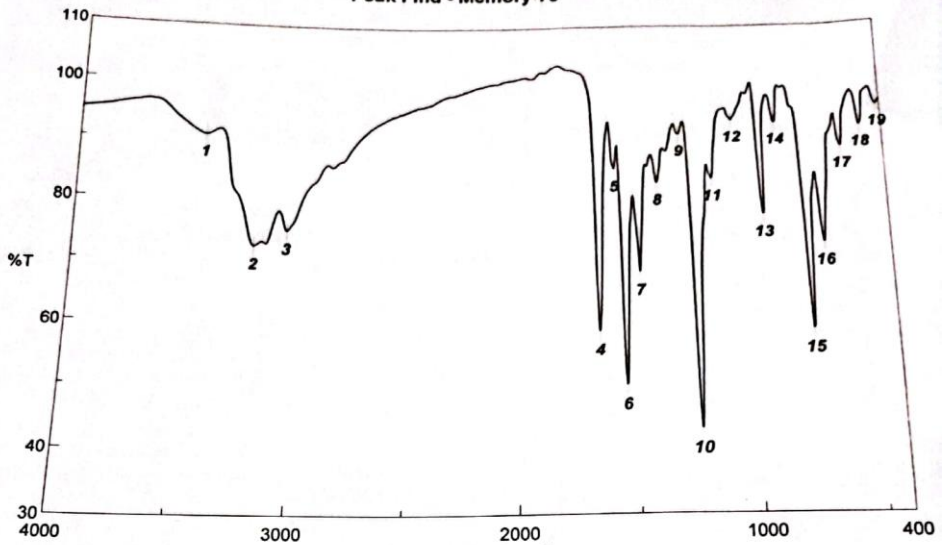
40.56 DMSO
40.36 DMSO
40.15 DMSO
39.94 DMSO
39.73 DMSO
39.52 DMSO
39.31 DMSO
f1 (ppm)

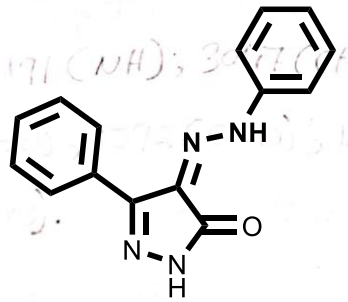


[Comments]

Sample name	MSD4
Comment	12/12/2012
User	IR
Division	IR
Company	Micro Analytical Center

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3432.67	90.8127	2	3191.61	72.1035	3	3047.94	74.5817
4	1662.34	57.6248	5	1592.91	84.2517	6	1550.49	49.1939
7	1486.85	66.992	8	1405.85	81.722	9	1304.61	90.1484
10	1243.86	42.4676	11	1164.79	82.2924	12	1066.44	92.5169
13	943.985	76.2029	14	873.596	92.0836	15	755.959	57.5298
16	686.534	71.4918	17	585.29	87.8236	18	496.58	91.4794
19	416.549	95.0176						



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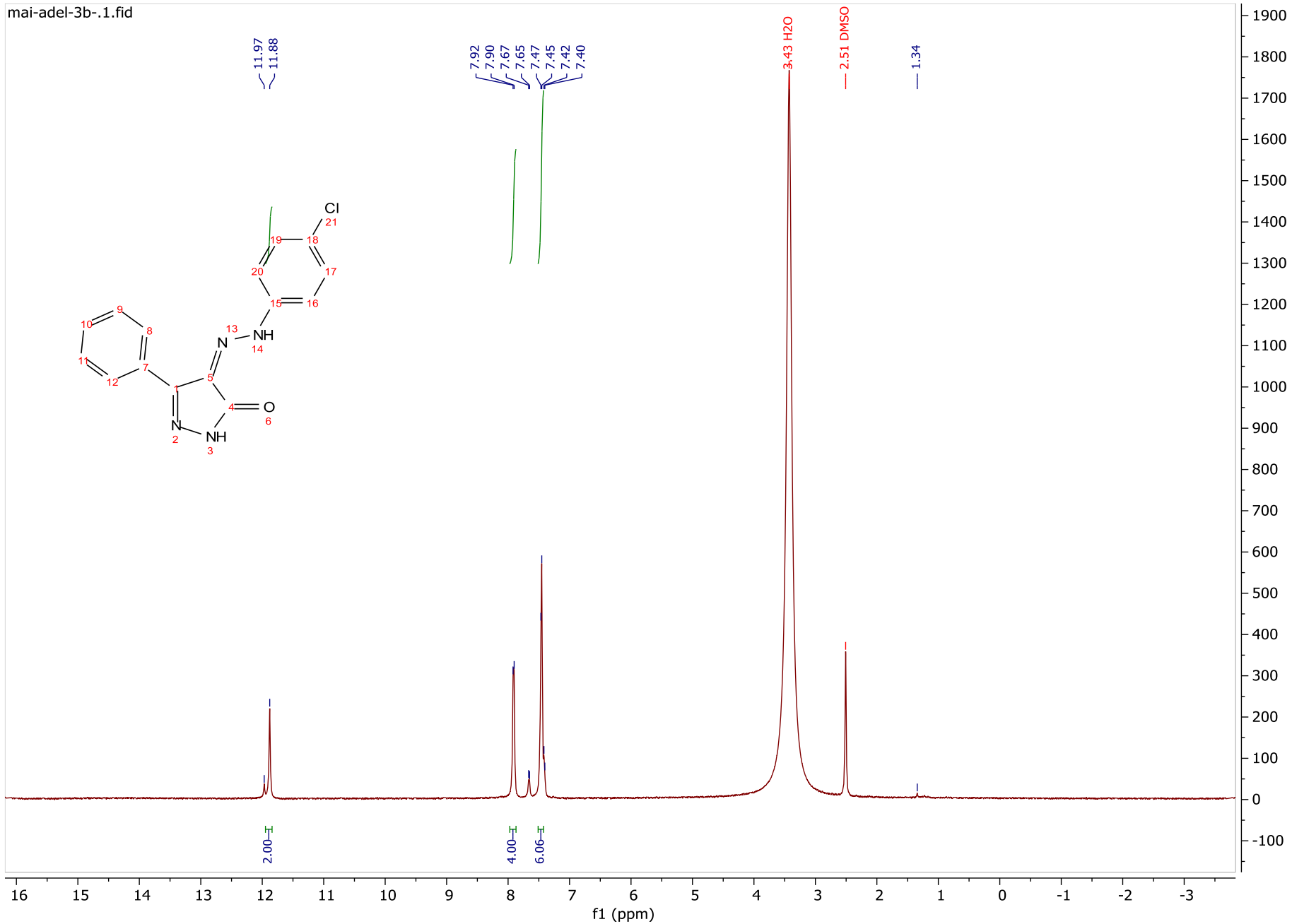
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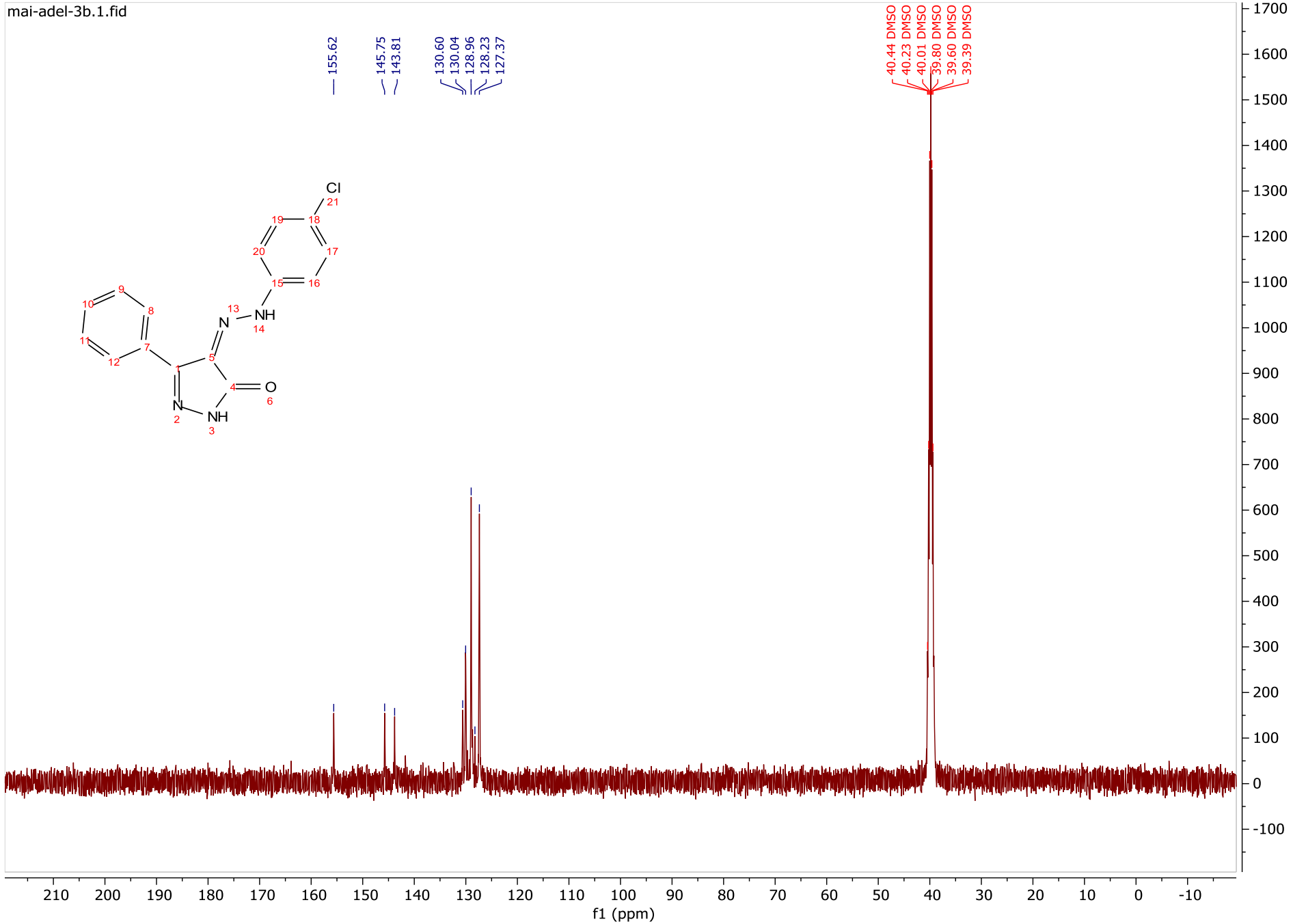
11.88
7.92
7.90
7.67
7.65
7.47
7.45
7.42
7.40
3.43 H2O
2.51 DMSO
1.34
Cl
21
19
18
20
17
15
16
9
10
8
13
N
NH
14
11
7
12
5
1
4
O
6
N
2
NH
3
2.00
4.00
6.06
f1 (ppm)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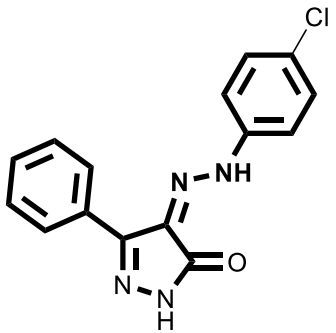
143.81
130.60
130.04
128.96
128.23
127.37
40.44 DMSO
40.23 DMSO
40.01 DMSO
39.80 DMSO
39.60 DMSO
39.39 DMSO
Cl
21
19
18
20
17
15
16
13
N
NH
14
10
9
8
11
12
7
5
1
4
O
6
N
2
NH
3
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



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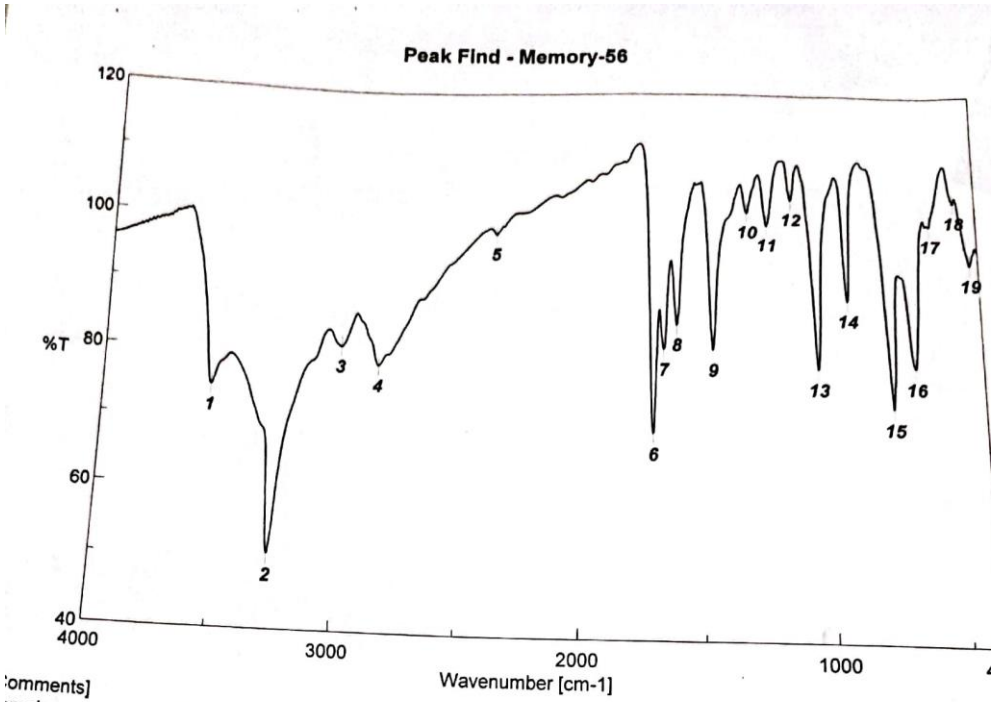


omments]
mple name MD8
mment 12/12/2012
er IR
ision IR
mpany Micro Analytical Center

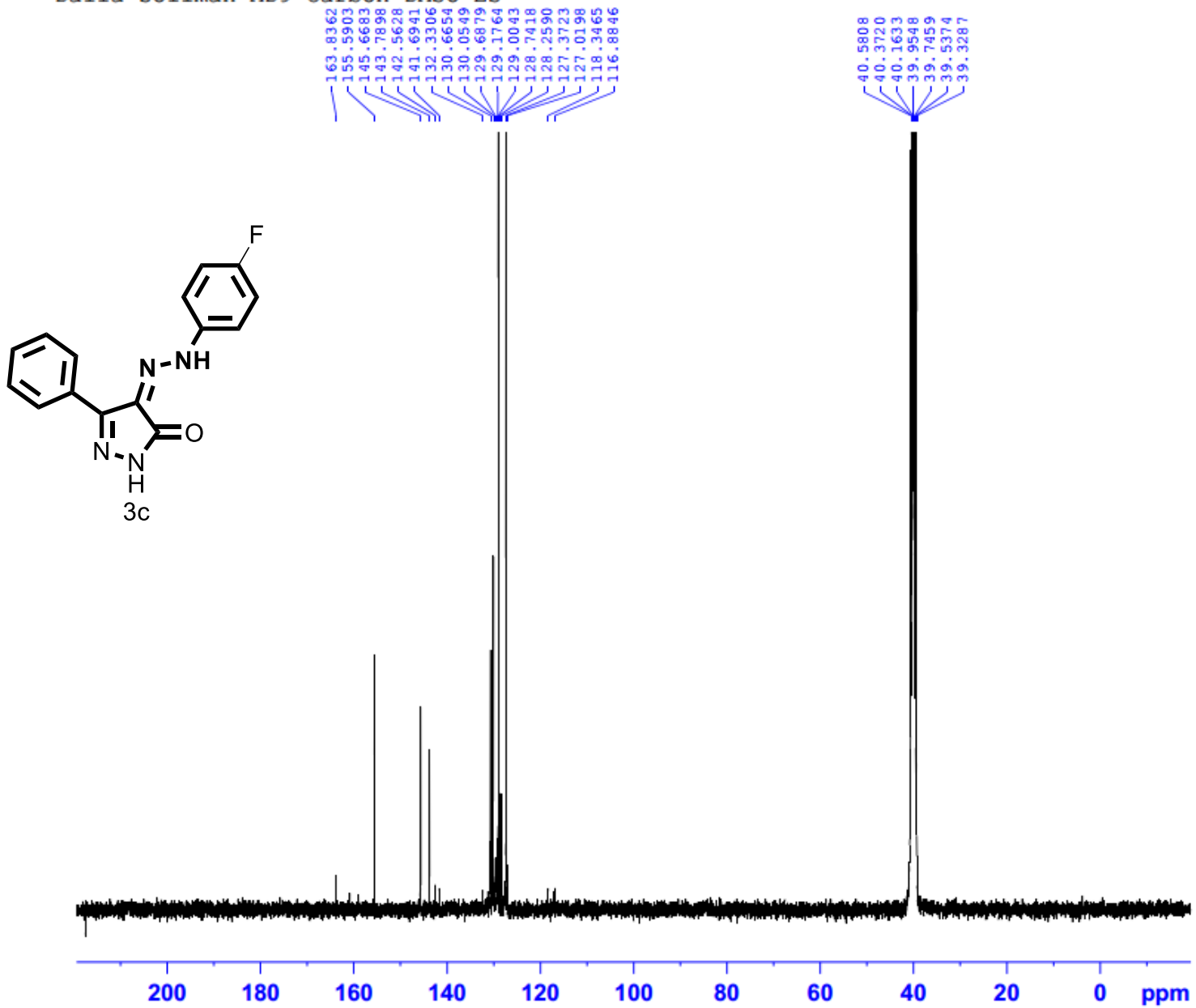
sult of Peak Picking]

Position	Intensity
3543.56	74.371
2848.35	77.8252
1671.02	80.2547
1333.53	100.875
1056.8	77.4236
669.178	77.8957
433.905	93.5379

No.	Position	Intensity
2	3267.79	50.4431
5	2369.12	97.3773
8	1618.95	83.8268
11	1253.5	98.9569
14	932.414	87.636
17	589.147	99.3488

No.	Position	Intensity
3	3007.44	80.5939
6	1711.51	68.1974
9	1474.31	80.1612
12	1153.22	103.023
15	762.709	71.977
18	487.902	103.053

Dalia soliman-MD9-Carbon-DMSO-ES



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Current Data Parameters
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PROCNO                 1

F2 - Acquisition Parameters
Date_              20220511
Time                  0.31 h
INSTRUM              spect
PROBHD    Z108618_0945 (
PULPROG            zgpg30
TD                  65536
SOLVENT              DMSO
NS                   2200
DS                      4
SWH             24038.461 Hz
FIDRES          0.733596 Hz
AQ              1.3631488 sec
RG                 197.77
DW                20.800 usec
DE                 6.50 usec
TE                295.9 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1          100.6404331 MHz
NUC1                  13C
P1                  10.00 usec
PLW1          47.00000000 W
SFO2          400.2016008 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2              90.00 usec
PLW2          13.00000000 W
PLW12          0.29249999 W
PLW13          0.14713000 W

F2 - Processing parameters
SI                  32768
SF            100.6303700 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
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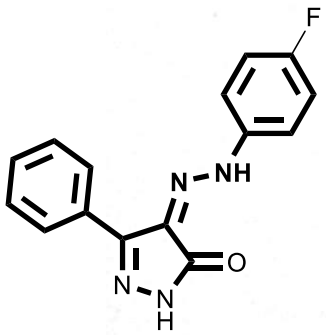
Dr.DaliaSoliman-MDS-H1-DMSO-Main.Defence.Chemical.Laboratory

Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
GEMINI-300BB "NMR"

Relax. delay 1.000 sec
Pulse 39.4 degrees
Acq. time 1.998 sec
Width 8000.0 Hz
36 repetitions
OBSERVE H1, 300.0117449 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 37 sec



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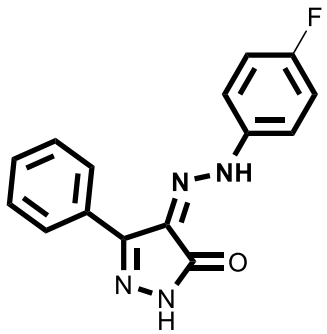

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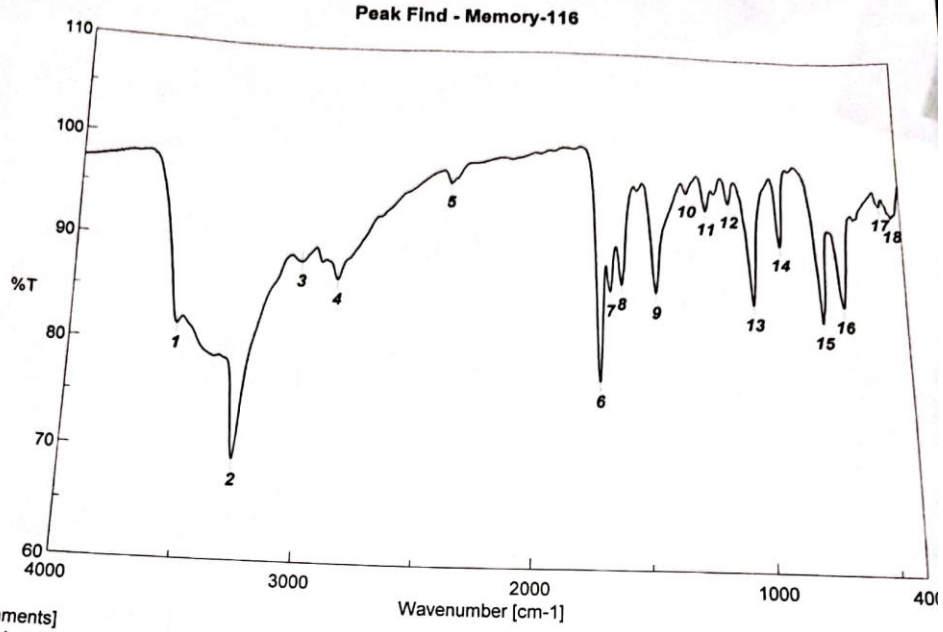
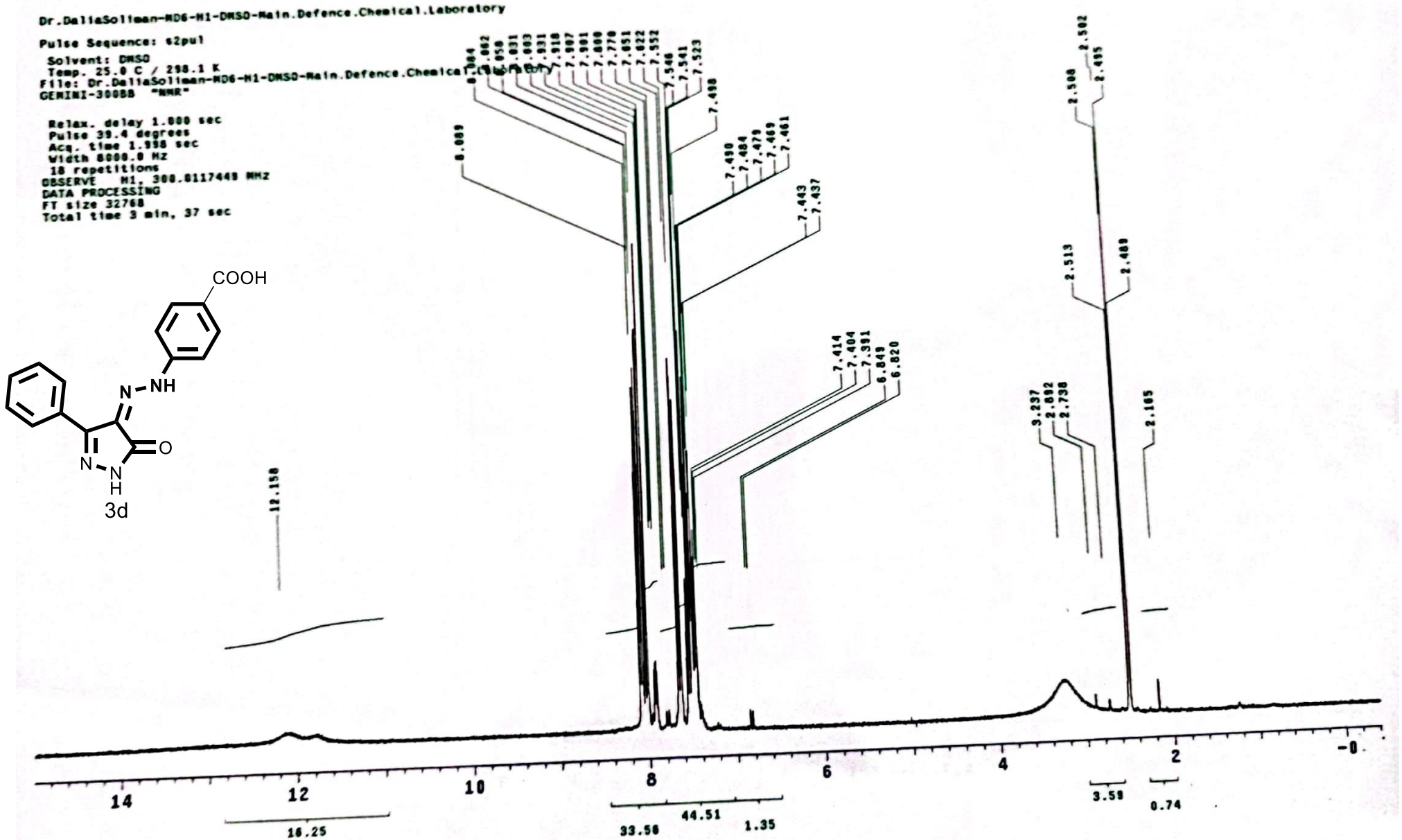


[Comments]

Sample name	MD9
Comment	12/12/2012
User	IR
Division	IR
Company	Micro Analytical Center

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
	3540.67	81.5317	2	3268.75	69.0422	3	3012.27	87.8988
	2853.17	86.1914	5	2365.26	95.9361	6	1713.44	76.7895
	1670.05	85.3349	8	1621.84	85.9855	9	1475.28	85.2198
	1337.39	95.3479	11	1254.47	93.5837	12	1154.19	94.4152
	1057.76	84.2929	14	934.342	90.2879	15	761.744	82.8141
	668.214	84.4367	17	487.902	94.8503	18	438.726	93.6942


Dr.DaliaSolieman-MD6-H1-DMSO-Main.Defence.Chemical.Laboratory
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
File: Dr.DaliaSolieman-MD6-H1-DMSO-Main.Defence.Chemical.Laboratory
GEMINI-300BB "NMR"
Relax. delay 1.000 sec
Pulse 39.4 degrees
Acq. time 1.998 sec
Width 6000.0 Hz
16 repetitions
OBSERVE H1, 300.0117448 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 37 sec
COOH
N
NH
O
N
N
H
3d
12.158
8.089
8.084
8.062
8.058
8.031
8.003
7.931
7.918
7.907
7.901
7.800
7.770
7.651
7.622
7.552
7.546
7.541
7.523
7.498
7.490
7.484
7.479
7.469
7.461
7.443
7.437
7.414
7.404
7.391
6.849
6.820
2.508
2.502
2.495
2.513
2.488
3.237
2.882
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16.25
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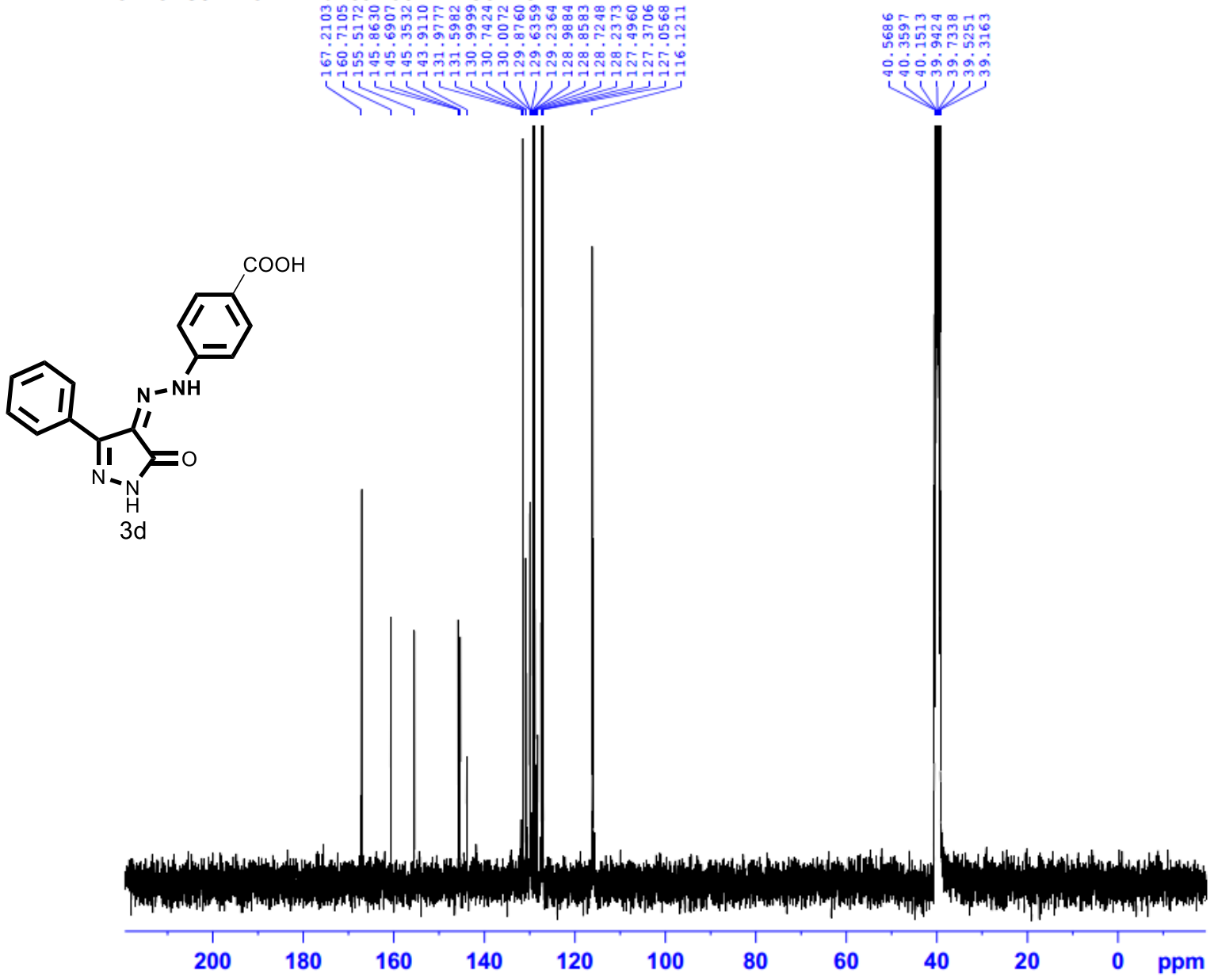
44.51
1.35
3.59
0.74

Dalia soliman-MD6-Carbon-DMSO-ES



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```
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EXPNO                 10
PROCNO                 1

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Date_           20220513
Time               9.48 h
INSTRUM            spect
PROBHD   Z108618_0945 (
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                 2200
DS                    4
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ             1.3631488 sec
RG                197.77
DW                20.800 usec
DE                 6.50 usec
TE                294.1 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                   1
SFO1         100.6404331 MHz
NUC1                 13C
P1                 10.00 usec
PLW1          47.00000000 W
SFO2         400.2016008 MHz
NUC2                 1H
CPDPRG[2          waltz16
PCPD2              90.00 usec
PLW2          13.00000000 W
PLW12          0.29249999 W
PLW13          0.14713000 W

F2 - Processing parameters
SI                 32768
SF           100.6303700 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
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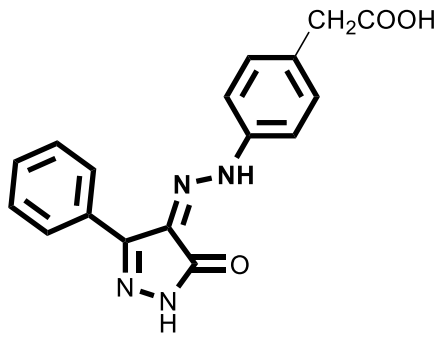
Dalia soliman-MD11-Carbon-DMSO-ES



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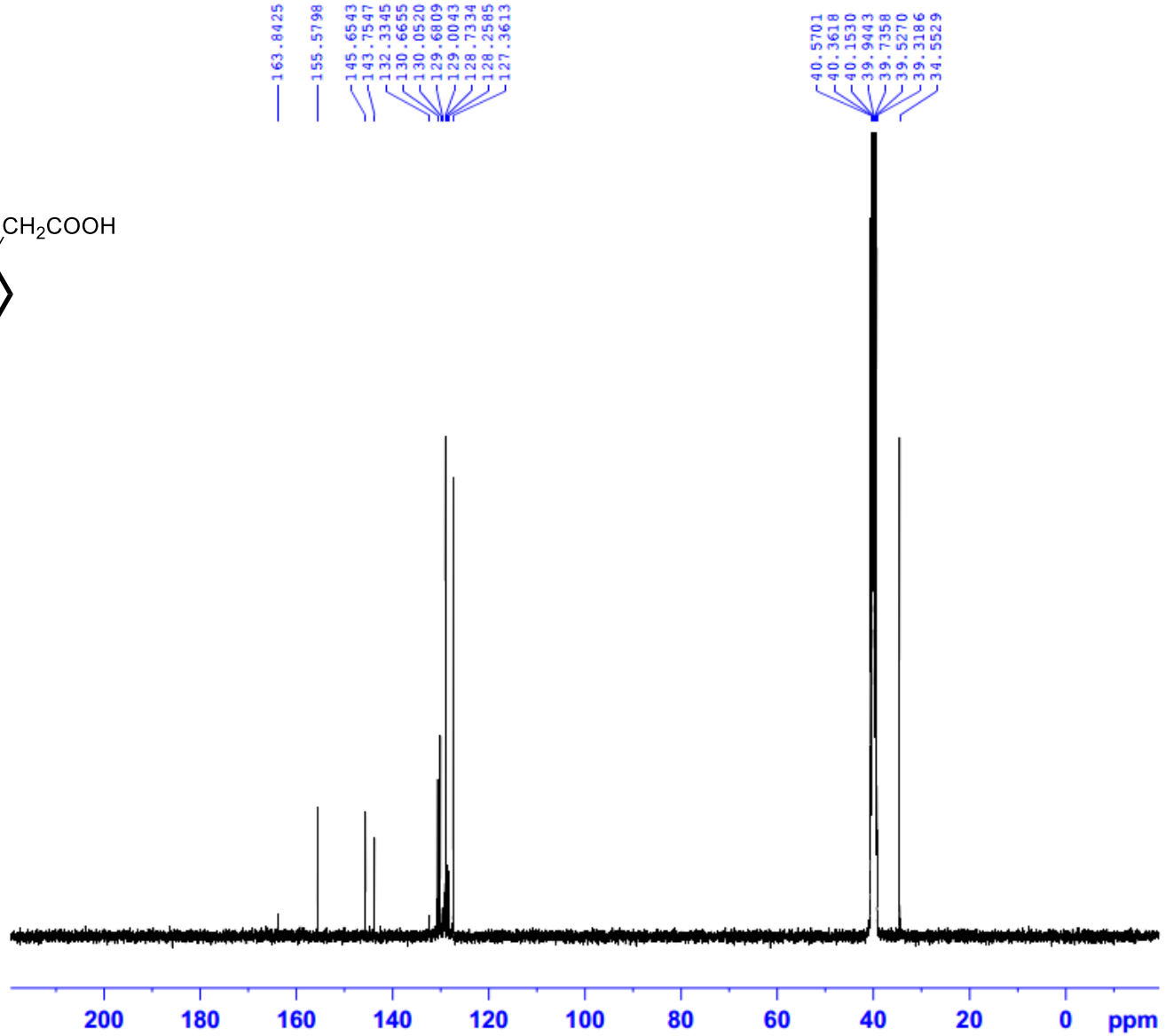

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EXPNO              10
PROCNO              1

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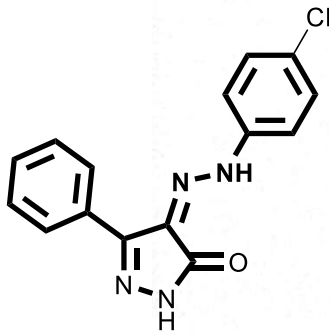
Date_          20220510
Time              22.21 h
INSTRUM             spect
PROBHD   Z108618_0945 (
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                  2200
DS                     4
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ             1.3631488 sec
RG                197.77
DW                20.800 usec
DE                 6.50 usec
TE                295.8 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1
SFO1         100.6404331 MHz
NUC1                13C
P1                 10.00 usec
PLW1          47.00000000 W
SFO2         400.2016008 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2              90.00 usec
PLW2          13.00000000 W
PLW12          0.29249999 W
PLW13          0.14713000 W

F2 - Processing parameters
SI                 32768
SF           100.6303700 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

Dr.DaliaSoliman-ND11-H1-DMSO-Main.Defence.Chemical.Laboratory

Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
GEMINI-300BB "NMR"

Relax. delay 1.000 sec
Pulse 39.4 degrees
Acq. time 1.998 sec
Width 6000.0 Hz
42 repetitions
OBSERVE H1, 300.0117449 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 37 sec



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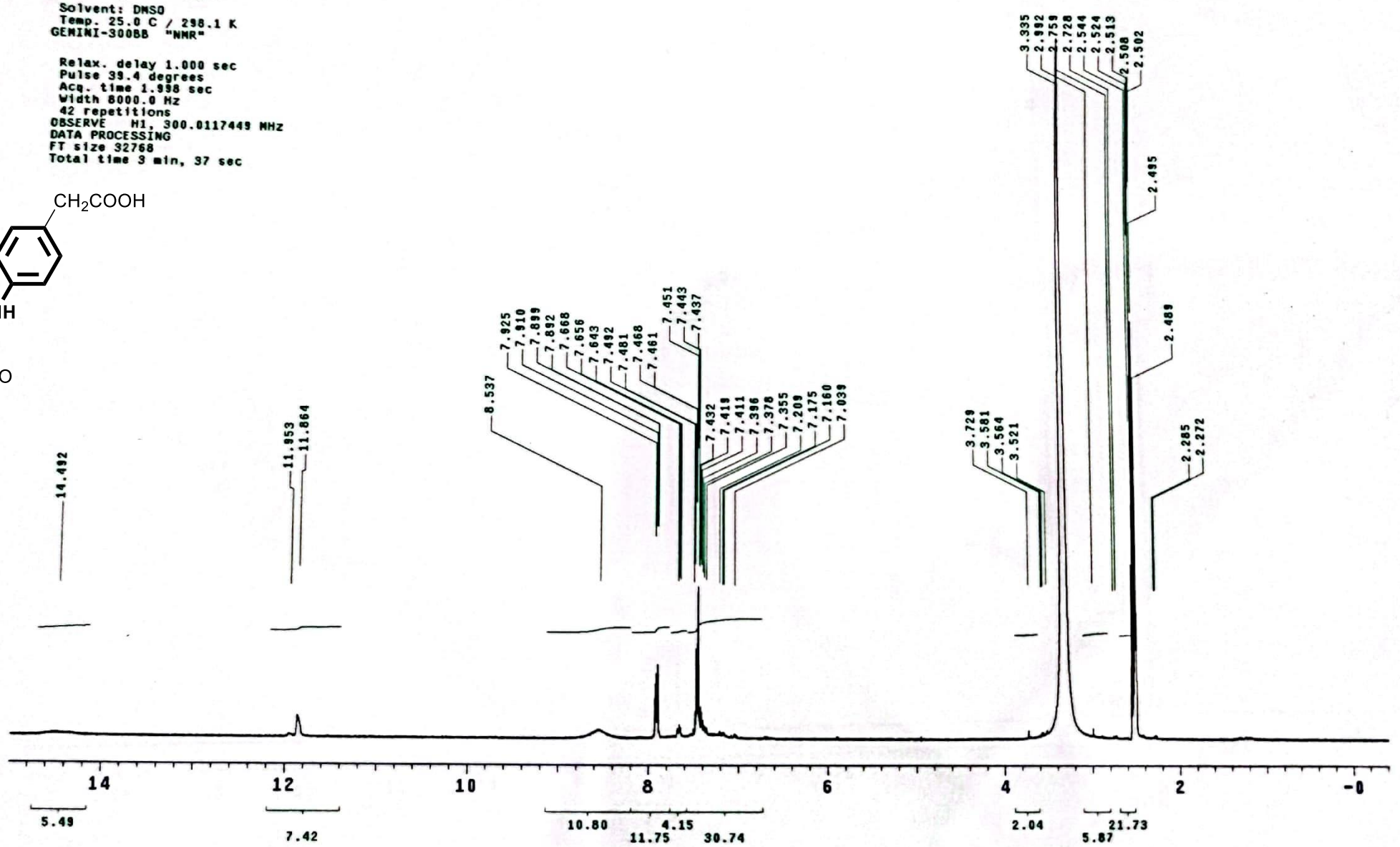

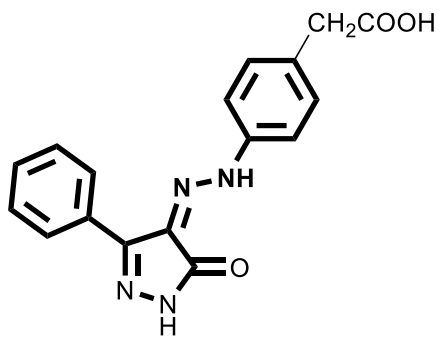

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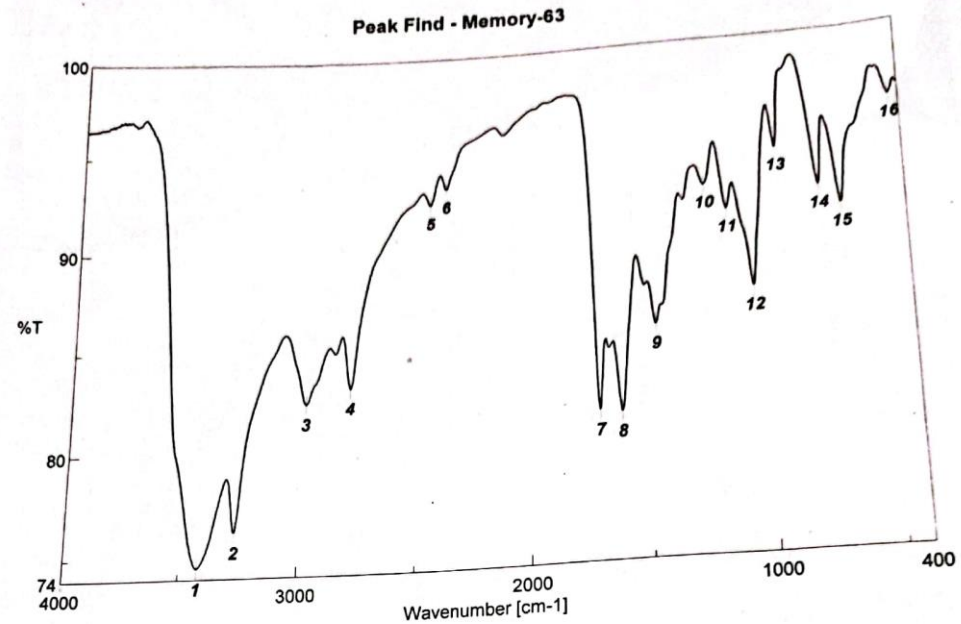


[Comments]

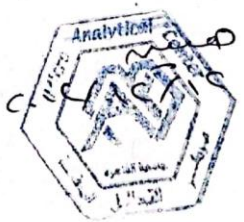
Sample name	MD 11
Comment	12/12/2012
User	IR
Division	IR
Company	Micro Analytical Center

[Result of Peak Picking]

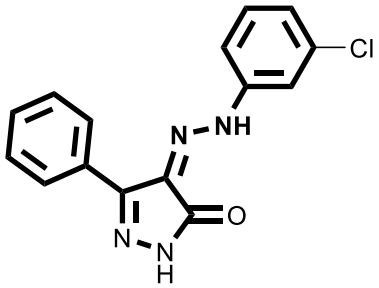
No.	Position	Intensity
1	3421.1	74.534
4	2782.78	82.9325
7	1709.59	81.1071
10	1247.72	92.0117
13	935.306	93.7165
16	439.69	96.0167

No.	Position	Intensity
2	3268.75	76.1832
5	2439.51	92.0784
8	1617.98	80.9596
11	1156.12	90.6488
14	759.816	91.5939

No.	Position	Intensity
3	2973.7	82.2455
6	2369.12	92.8806
9	1470.46	85.0764
12	1055.84	86.6001
15	669.178	90.5794



Soha Ramadan-MD12-Cnmr



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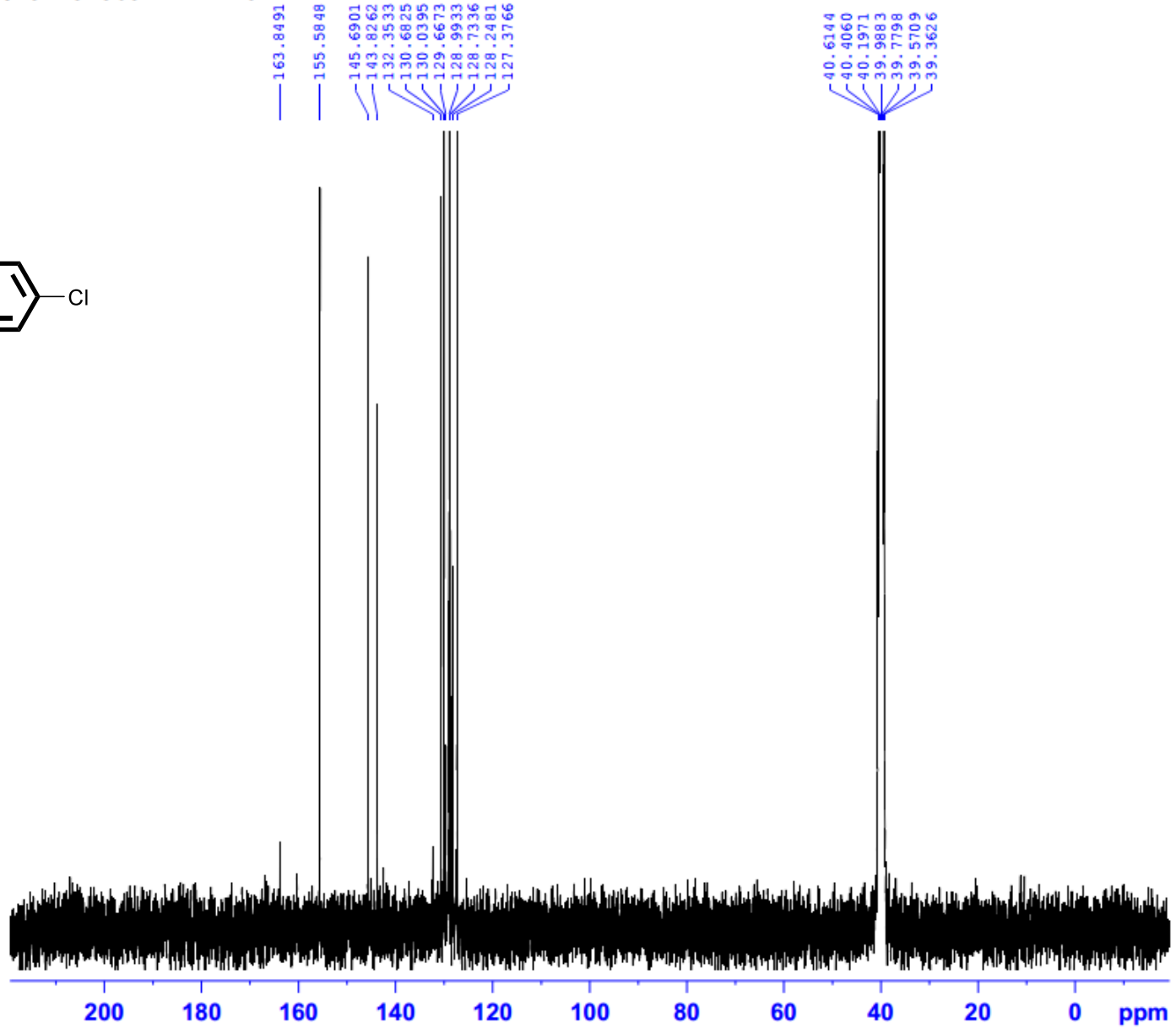


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Current Data Parameters
NAME      Soha Ramadan-MD12-Cnmr-ow
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PROCNO                 1

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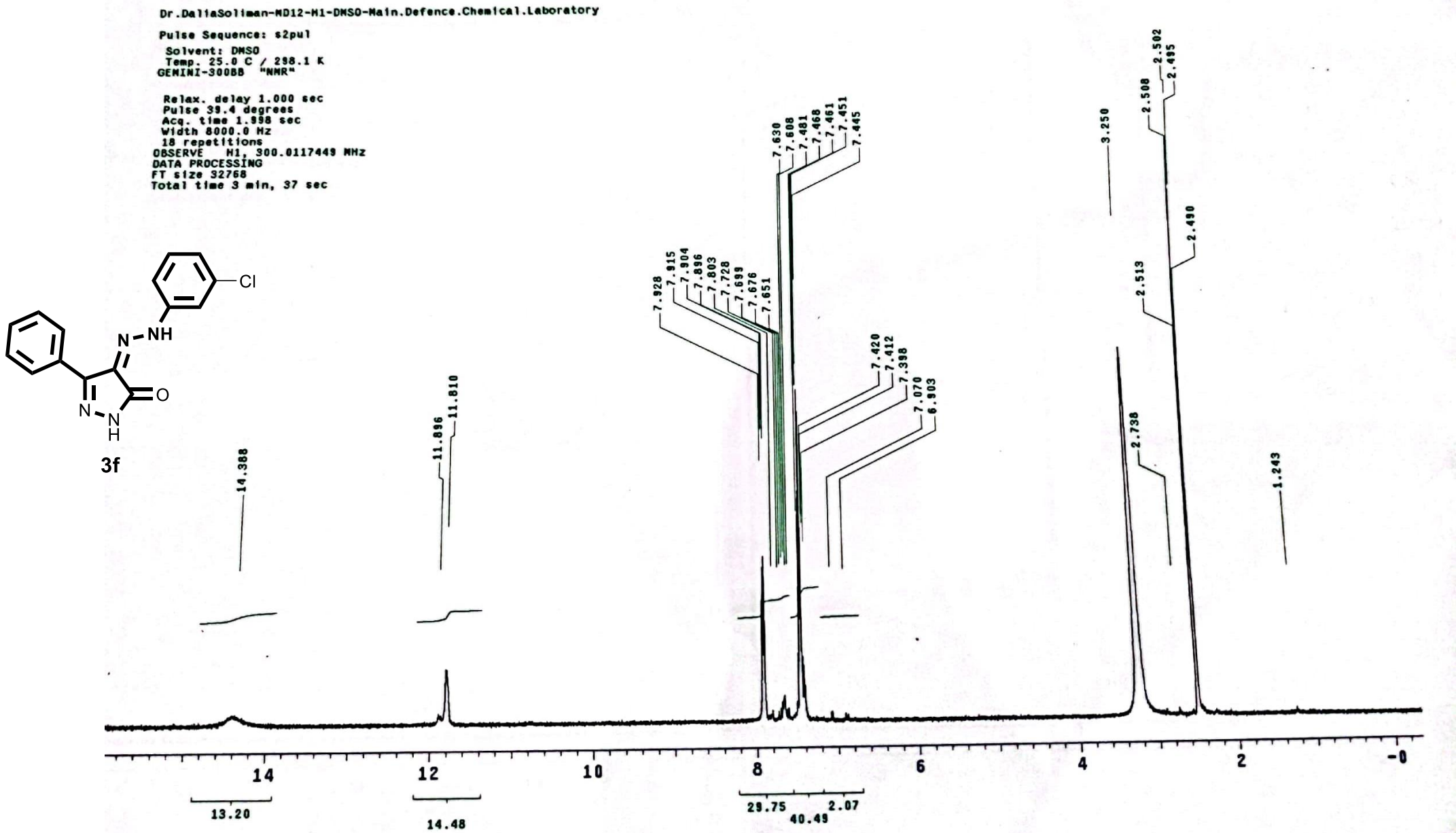
Time              18.23 h
INSTRUM             spect
PROBHD    Z108618_0945 (
PULPROG           zgpg30
TD                65536
SOLVENT             DMSO
NS                 2200
DS                    4
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ             1.3631488 sec
RG               197.77
DW              20.800 usec
DE               6.50 usec
TE              300.1 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1
SFO1         100.6404331 MHz
NUC1                13C
P1               10.00 usec
PLW1         47.00000000 W
SFO2         400.2016008 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2            90.00 usec
PLW2         13.00000000 W
PLW12         0.29249999 W
PLW13         0.14713000 W

F2 - Processing parameters
SI                32768
SF           100.6303700 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```


Dr.DaliaSoliman-MD12-H1-DMSO-Main.Defence.Chemical.Laboratory
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
GEMINI-300BB "NMR"
Relax. delay 1.000 sec
Pulse 39.4 degrees
Acq. time 1.998 sec
Width 8000.0 Hz
18 repetitions
OBSERVE H1, 300.0117449 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 37 sec
Cl
N-NH
O
N
N
H
3f
14.388
11.896
11.810
7.928
7.915
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7.676
7.651
7.630
7.608
7.481
7.468
7.461
7.451
7.445
7.420
7.412
7.398
7.070
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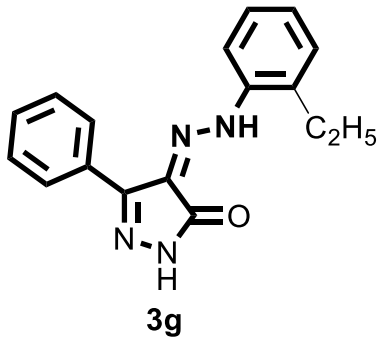
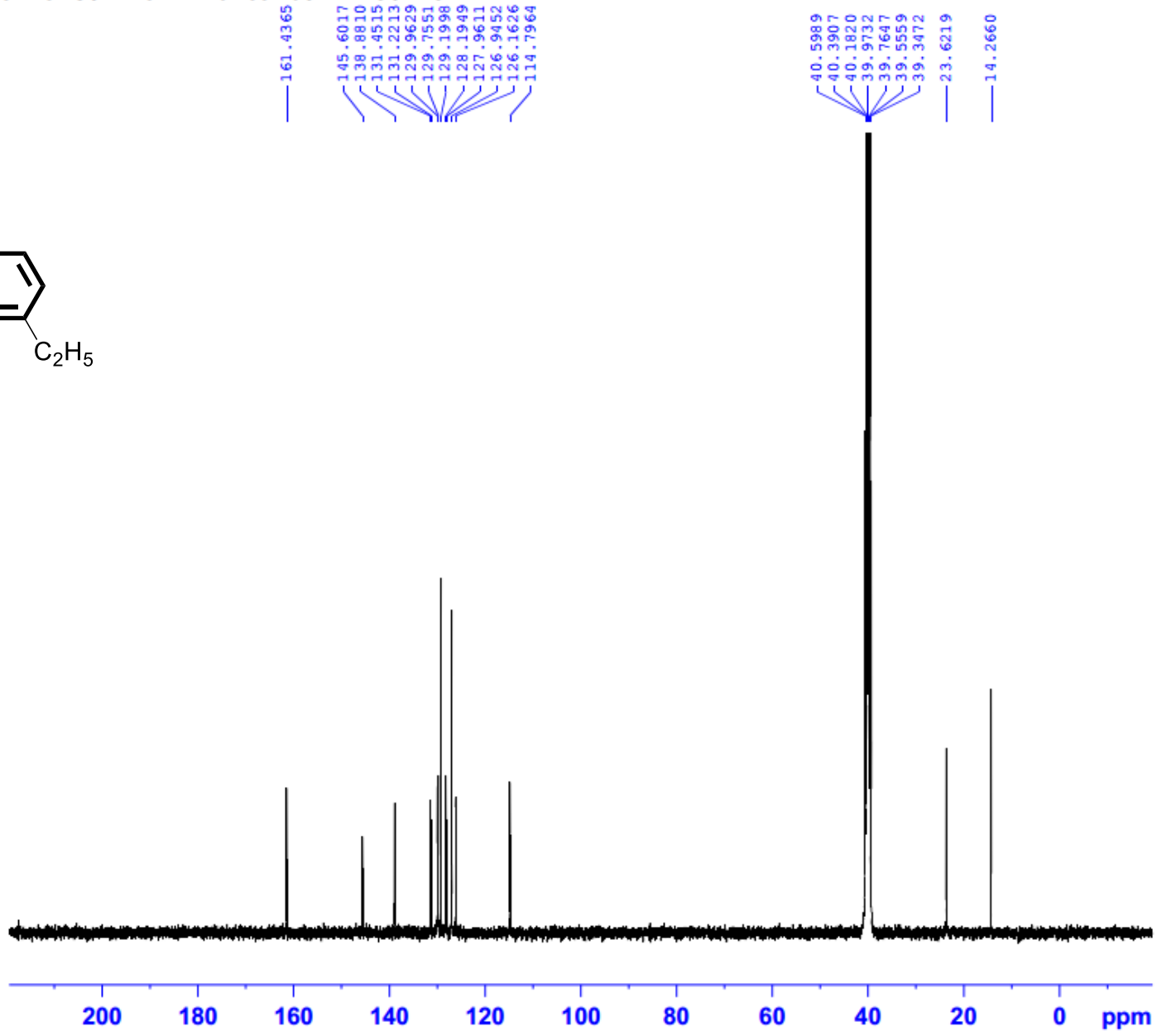
3.250
2.513
2.502
2.495
2.490
2.508
2.738
1.243
14
12
10
8
6
4
2
-0
13.20
14.48
29.75
2.07
40.49

Dalia soliman-MD5-Carbon-DMSO-ES



3g



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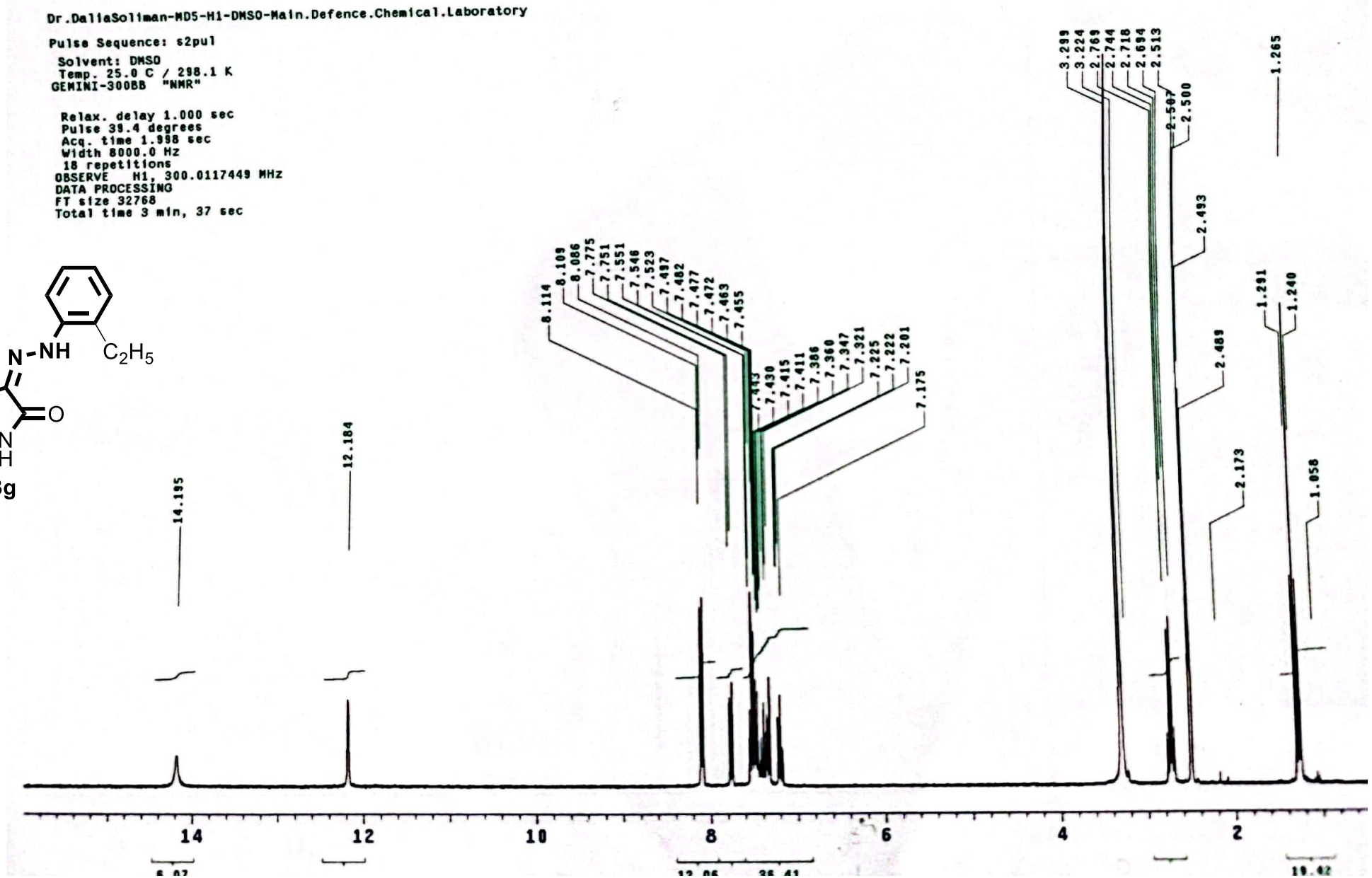
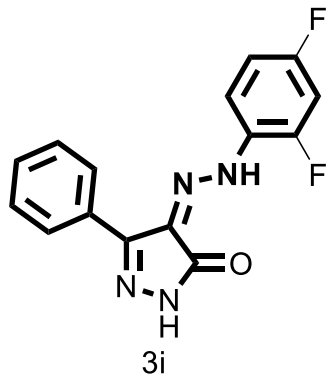
```
Current Data Parameters
NAME      Dalia soliman-MD5-Carbon-DMSO-ES
EXPNO                  10
PROCNO                  1

F2 - Acquisition Parameters
Date_            20220511
Time                9.07 h
INSTRUM             spect
PROBHD   Z108618_0945 (
PULPROG          zgpg30
TD                 65536
SOLVENT             DMSO
NS                  2200
DS                     4
SWH            24038.461 Hz
FIDRES          0.733596 Hz
AQ              1.3631488 sec
RG                 197.77
DW                20.800 usec
DE                 6.50 usec
TE                295.8 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1
SFO1          100.6404331 MHz
NUC1                  13C
P1                  10.00 usec
PLW1          47.00000000 W
SFO2          400.2016008 MHz
NUC2                   1H
CPDPRG[2          waltz16
PCPD2              90.00 usec
PLW2          13.00000000 W
PLW12          0.29249999 W
PLW13          0.14713000 W

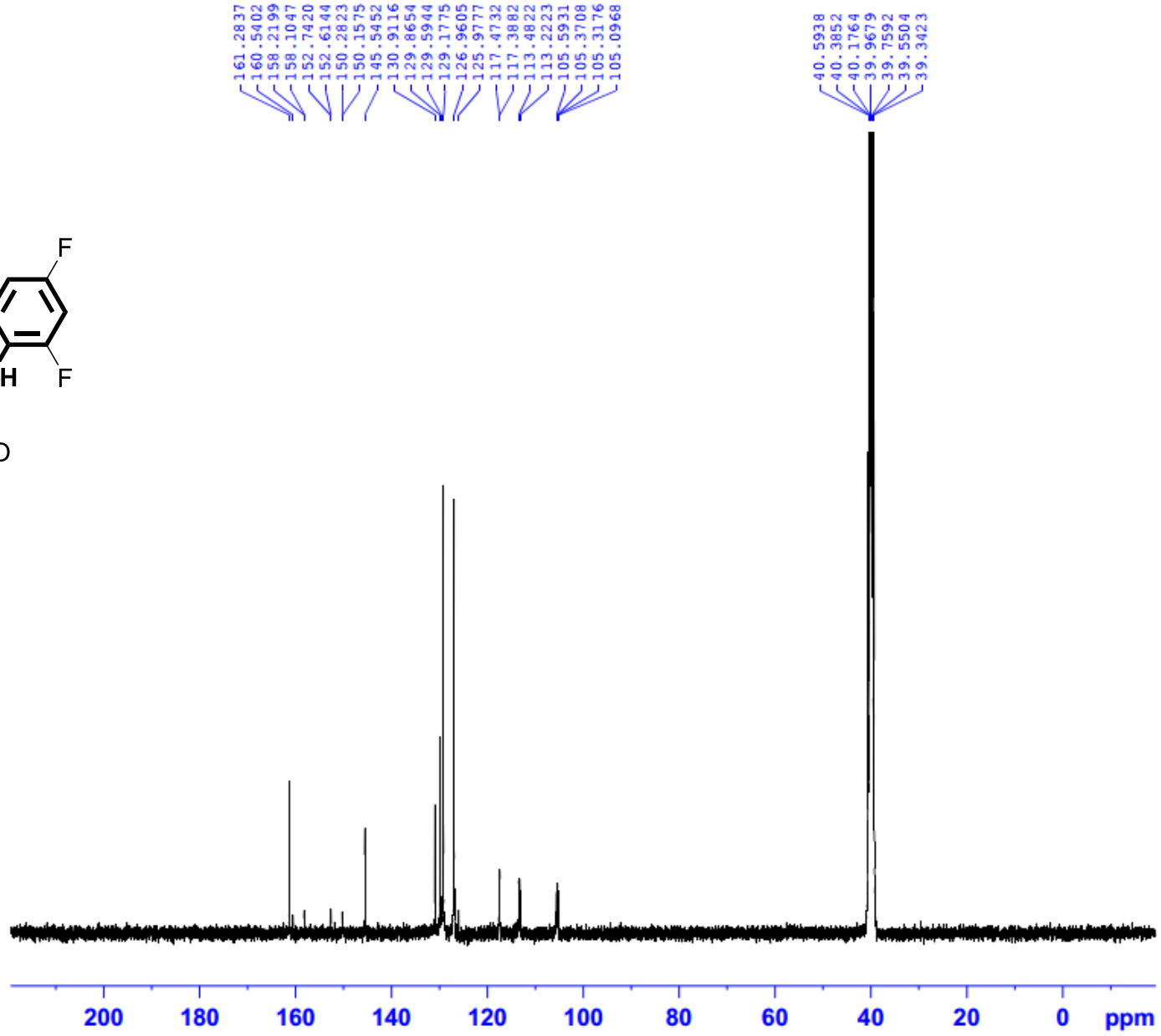
F2 - Processing parameters
SI                  32768
SF            100.6303700 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```


Dr.DaliaSoliman-MD5-H1-DMSO-Main.Defence.Chemical.Laboratory
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
GEMINI-300BB "NMR"
Relax. delay 1.000 sec
Pulse 39.4 degrees
Acq. time 1.998 sec
Width 8000.0 Hz
18 repetitions
OBSERVE H1, 300.0117449 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 37 sec
N-NH
C2H5
O
N
N
H
3g
14.195
12.184
8.114
8.103
8.086
7.775
7.751
7.551
7.548
7.523
7.487
7.482
7.477
7.472
7.463
7.455
7.430
7.415
7.411
7.386
7.360
7.347
7.321
7.225
7.222
7.201
7.175
3.299
3.224
2.769
2.744
2.718
2.694
2.513
2.507
2.500
2.493
2.483
2.173
1.291
1.265
1.240
1.058
14
12
10
8
6
4
2
19.42

Dalia soliman-MD1-Carbon-DMSO-ES



3i



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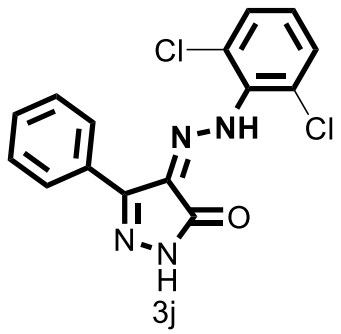
```
Current Data Parameters
NAME      Dalia soliman-MD1-Carbon-DMSO-ES
EXPNO                10
PROCNO                1

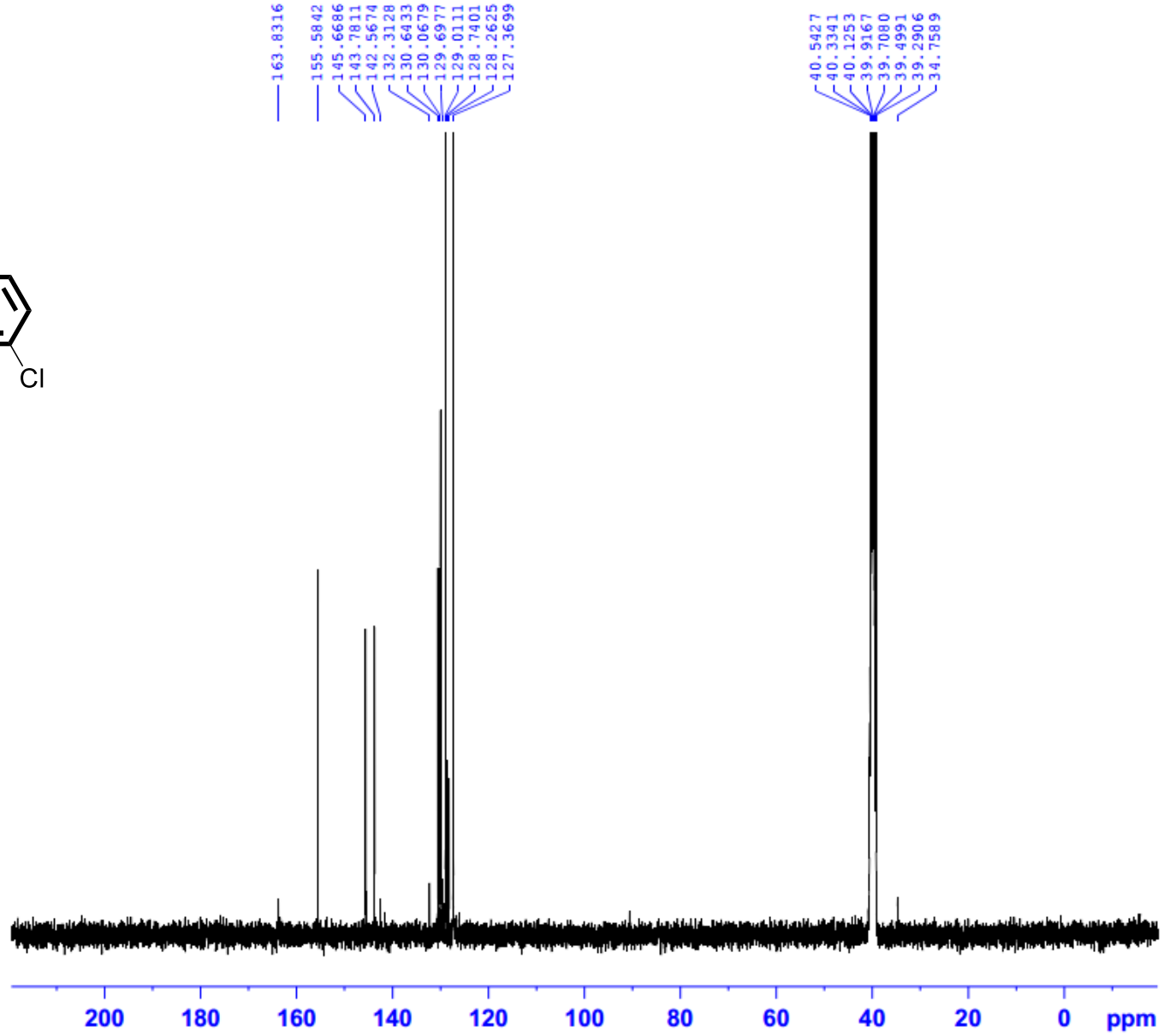
F2 - Acquisition Parameters
Date_              20220511
Time                2.40 h
INSTRUM             spect
PROBHD   Z108618_0945 (
PULPROG             zgpg30
TD                  65536
SOLVENT               DMSO
NS                    2200
DS                       4
SWH             24038.461 Hz
FIDRES          0.733596 Hz
AQ              1.3631488 sec
RG                 197.77
DW                 20.800 usec
DE                  6.50 usec
TE                296.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1          100.6404331 MHz
NUC1                  13C
P1                  10.00 usec
PLW1          47.00000000 W
SFO2          400.2016008 MHz
NUC2                  1H
CPDPRG[2           waltz16
PCPD2               90.00 usec
PLW2          13.00000000 W
PLW12          0.29249999 W
PLW13          0.14713000 W

F2 - Processing parameters
SI                   32768
SF            100.6303700 MHz
WDW                     EM
SSB       0
LB                   1.00 Hz
GB        0
PC                   1.40
```

Dalia soliman-MD10-DMSO-C13nmr-A



3j



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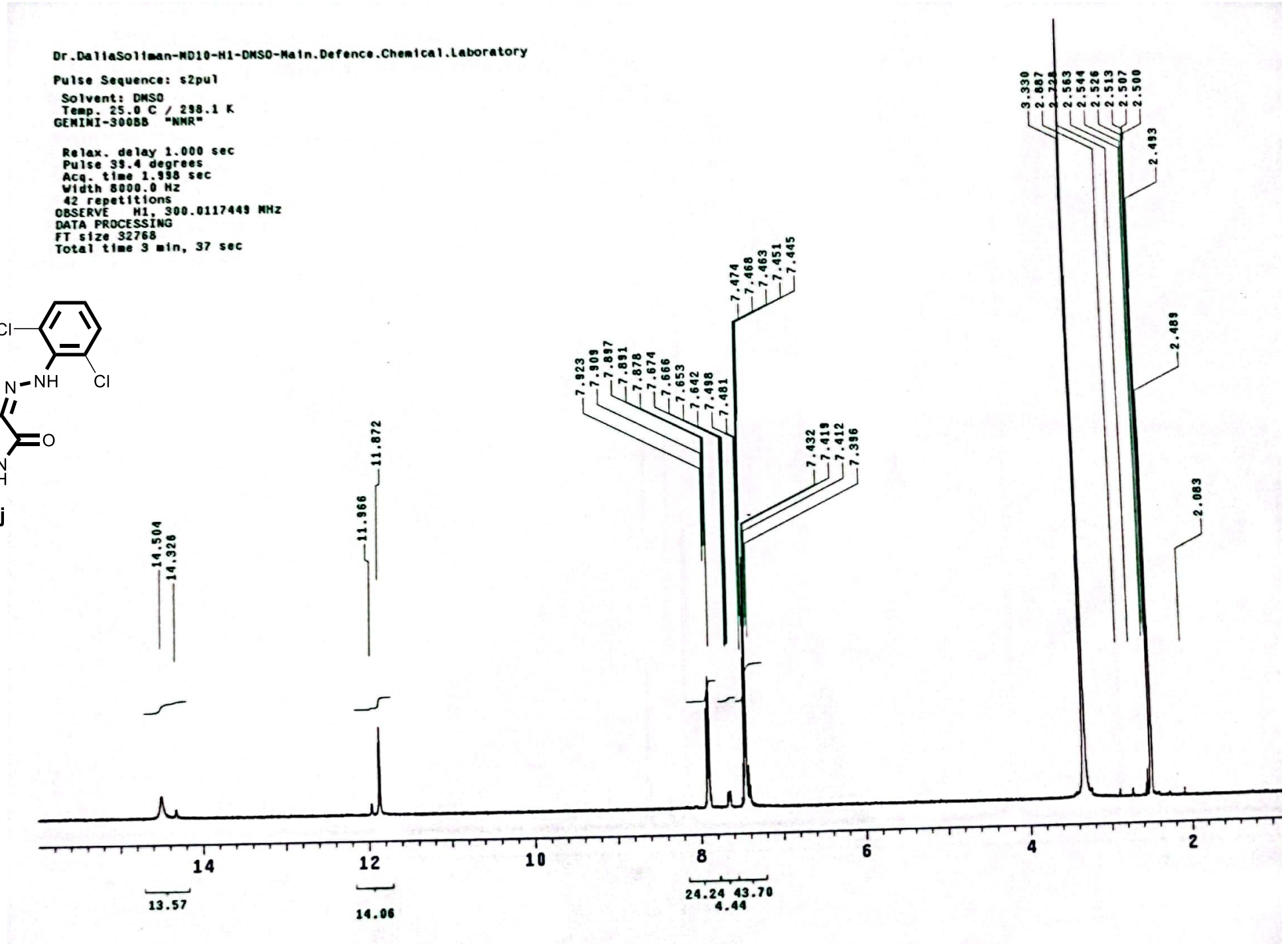
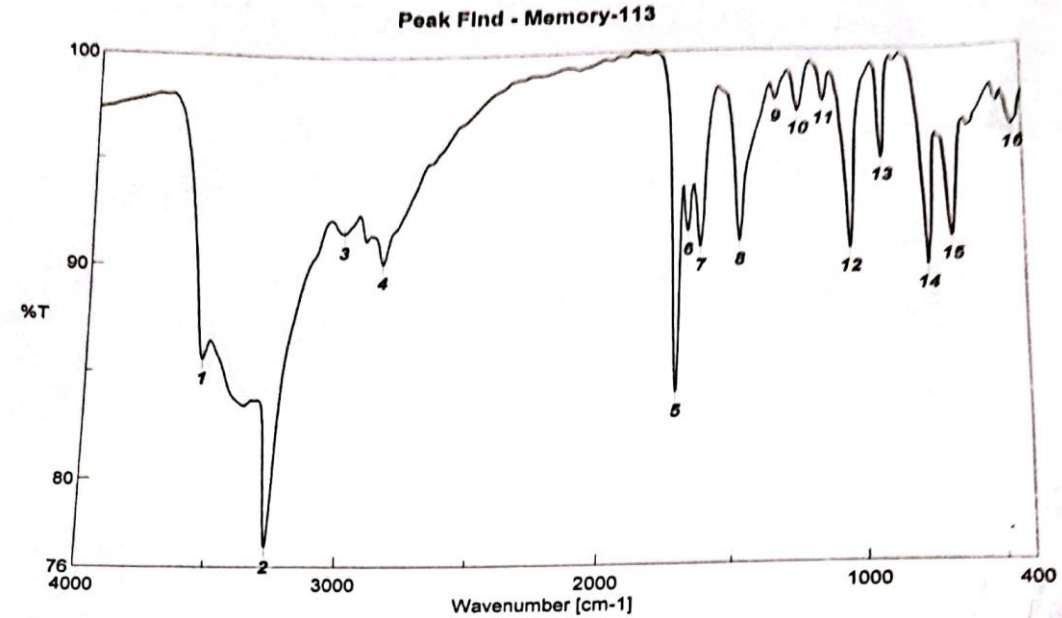
```
Current Data Parameters
NAME      Dalia soliman-MD10-DMSO-C13nmr-A
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_              20220514
Time                  7.06 h
INSTRUM               spect
PROBHD    I108618_0945 (
PULPROG             zgpg30
TD                   65536
SOLVENT               DMSO
NS                    2200
DS                       4
SWH               24038.461 Hz
FIDRES            0.733596 Hz
AQ                1.3631488 sec
RG                   197.77
DW                  20.800 usec
DE                   6.50 usec
TE                  294.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                      1
SFO1          100.6404331 MHz
NUC1                   13C
P1                  10.00 usec
PLW1          47.00000000 W
SFO2          400.2016008 MHz
NUC2                   1H
CPDPRG[2           waltz16
PCPD2               90.00 usec
PLW2          13.00000000 W
PLW12          0.29249999 W
PLW13          0.14713000 W

F2 - Processing parameters
SI                   32768
SF            100.6303700 MHz
WDW                    EM
SSB       0
LB                   1.00 Hz
GB        0
PC                   1.40
```


Dr.DaliaSoliman-MD10-H1-DMSO-Main.Defence.Chemical.Laboratory
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
GEMINI-300BB "NMR"
Relax. delay 1.000 sec
Pulse 39.4 degrees
Acq. time 1.998 sec
Width 8000.0 Hz
42 repetitions
OBSERVE H1, 300.0117449 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 37 sec
Cl
NH
Cl
N
O
N
N
H
3j
14.504
14.326
11.966
11.872
7.923
7.909
7.897
7.891
7.878
7.674
7.666
7.653
7.642
7.498
7.481
7.474
7.468
7.463
7.451
7.445
7.432
7.419
7.412
7.396
3.330
2.887
2.563
2.544
2.526
2.513
2.507
2.500
2.493
2.489
2.083
14
12
10
8
6
4
2
13.57
14.06
24.24
43.70
4.44

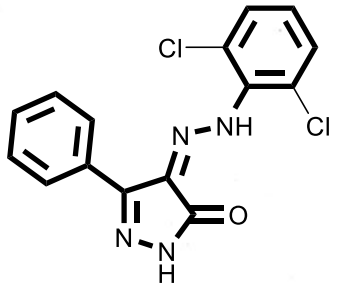


[Comments]

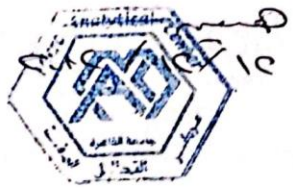
Sample name	MD 10
Comment	12/12/2012
User	IR
Division	IR
Company	Micro Analytical Center

[Result of Peak Picking]

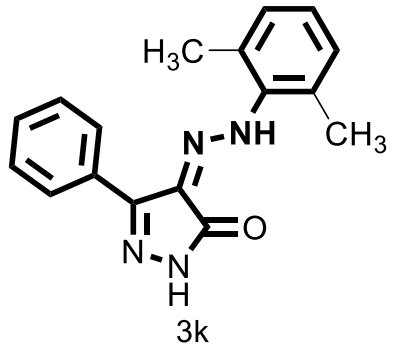
No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3543.56	85.5363	2	3269.72	76.8953	3	3009.37	91.4156
4	2853.17	89.9321	5	1714.41	83.6458	6	1670.05	91.0971
7	1622.8	90.3407	8	1475.28	90.5472	9	1338.36	97.5105
10	1254.47	96.8972	11	1155.15	97.401	12	1057.76	90.1593
13	933.378	94.5632	14	762.709	89.3672	15	669.178	90.7441
16	434.869	96.0791						



3j



Dalia soliman-MD7-Carbon-DMSO-ES



3k

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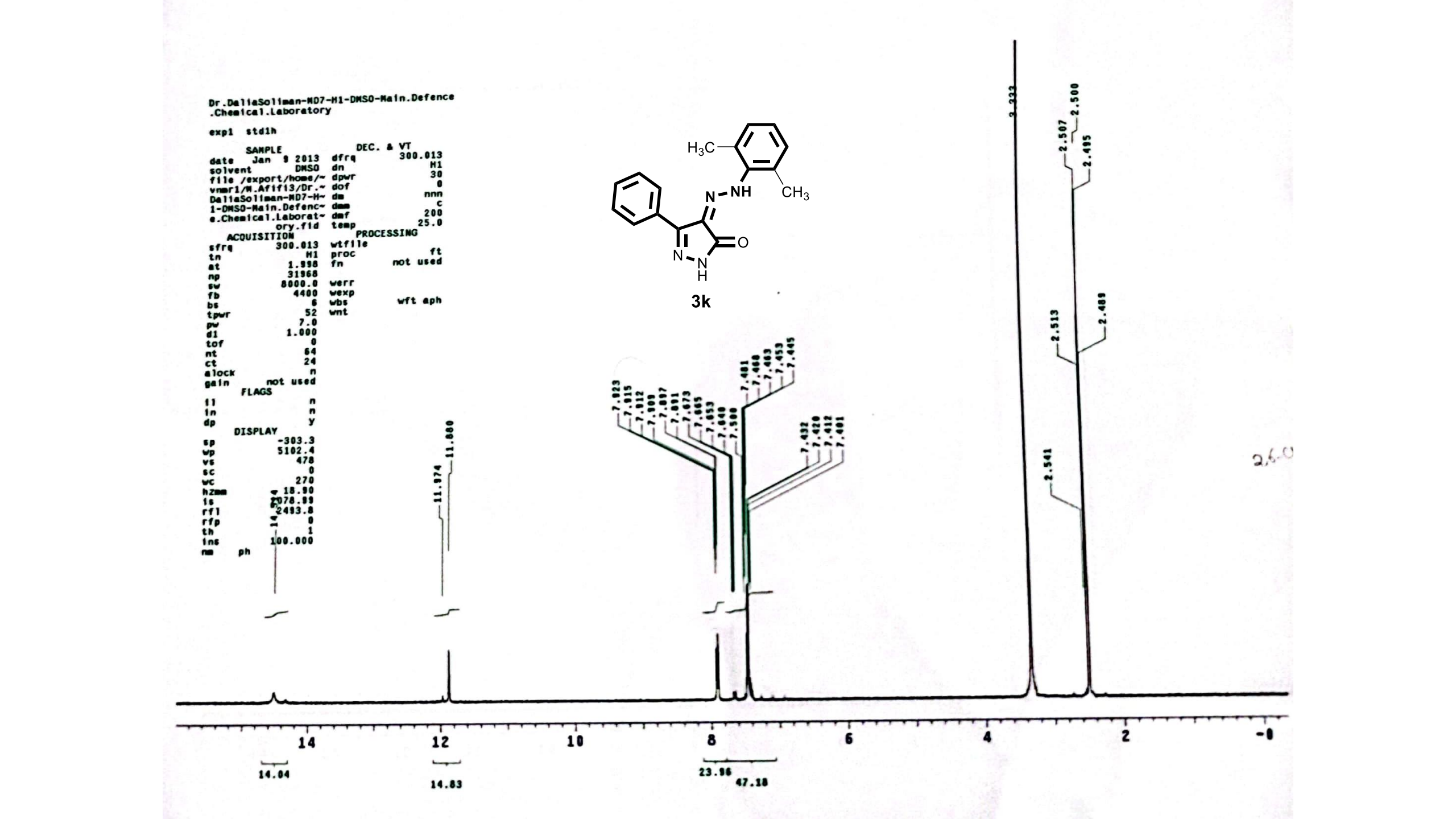
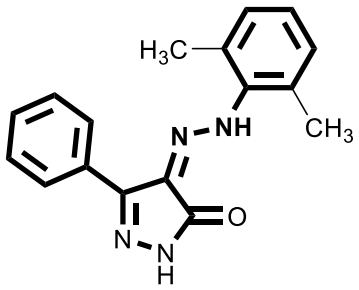
```
Current Data Parameters
NAME      Dalia soliman-MD7-Carbon-DMSO-ES
EXPNO                  10
PROCNO                  1

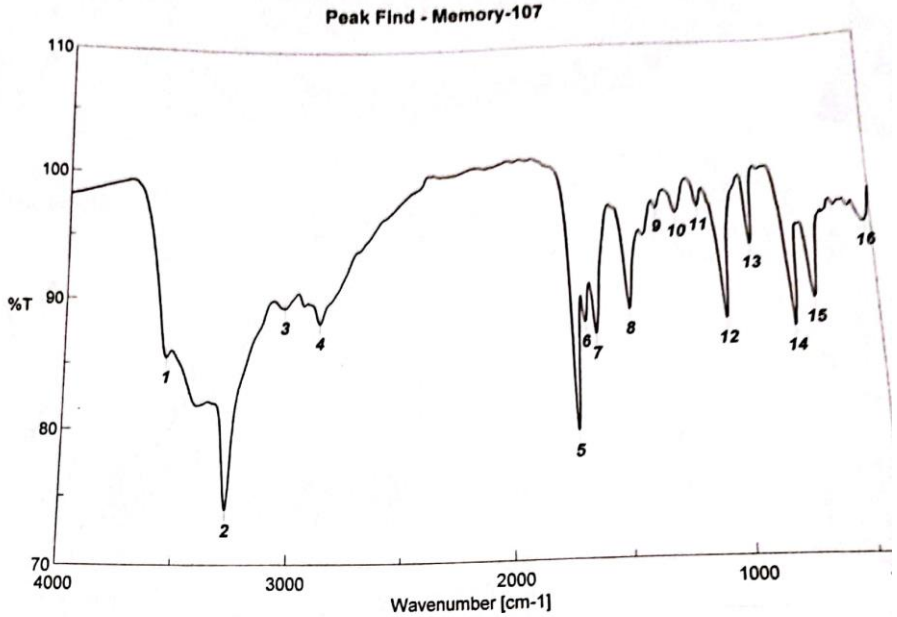
F2 - Acquisition Parameters
Date_            20220511
Time                6.58 h
INSTRUM             spect
PROBHD   Z108618_0945 (
PULPROG             zgpg30
TD                  65536
SOLVENT              DMSO
NS                   2200
DS                      4
SWH              24038.461 Hz
FIDRES           0.733596 Hz
AQ               1.3631488 sec
RG                  197.77
DW                  20.800 usec
DE                   6.50 usec
TE                  295.8 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                     1
SFO1            100.6404331 MHz
NUC1                   13C
P1                   10.00 usec
PLW1            47.00000000 W
SFO2            400.2016008 MHz
NUC2                   1H
CPDPRG[2            waltz16
PCPD2                90.00 usec
PLW2            13.00000000 W
PLW12            0.29249999 W
PLW13            0.14713000 W

F2 - Processing parameters
SI                   32768
SF              100.6303700 MHz
WDW                     EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```


Dr.DaliaSoliman-MD7-H1-DMSO-Main.Defence
.Chemical.Laboratory
exp1 std1h
SAMPLE
date Jan 9 2013
solvent DMSO
file /export/home/~
vnmr1/M.Afif13/Dr.~
DaliaSoliman-MD7-H~
1-DMSO-Main.Defenc~
e.Chemical.Laborat~
ory.fid
ACQUISITION
sfrq 300.013
tn H1
at 1.998
np 31968
sw 8000.0
fb 4400
bs 6
tpwr 52
pw 7.0
d1 1.000
tof 0
nt 64
ct 24
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -303.3
wp 5102.4
vs 478
sc 0
wc 270
hzmm 18.90
is 2078.88
rfl 2493.8
rfp 0
th 1
ins 100.000
nm ph
DEC. & VT
dfrq 300.013
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
temp 25.0
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs wft aph
wnt
H3C
N-NH
CH3
N
O
N
H
3k
11.974
11.880
7.923
7.915
7.912
7.909
7.897
7.891
7.673
7.665
7.653
7.640
7.500
7.481
7.468
7.463
7.453
7.445
7.432
7.420
7.412
7.401
3.333
2.541
2.513
2.507
2.500
2.495
2.488
14
12
10
8
6
4
2
-0
14.04
14.83
23.96
47.18



3k



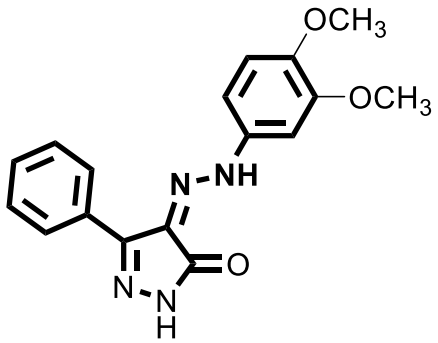
[Comments]

Sample name	MD7
Comment	12/12/2012
User	IR
Division	IR
Company	Micro Analytical Center

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3540.67	85.3871	2	3267.79	73.9667	3	3010.34	89.1254
4	2852.2	87.8833	5	1712.48	79.1504	6	1669.09	87.2955
7	1622.8	86.3832	8	1475.28	88.1398	9	1339.32	96.0209
10	1253.5	95.6034	11	1155.15	96.0779	12	1056.8	87.1685
13	933.378	92.9489	14	762.709	86.4947	15	670.142	88.6502
16	427.155	94.5296						

Dalia soliman-MD2-Carbon-DMSO-ES



3l

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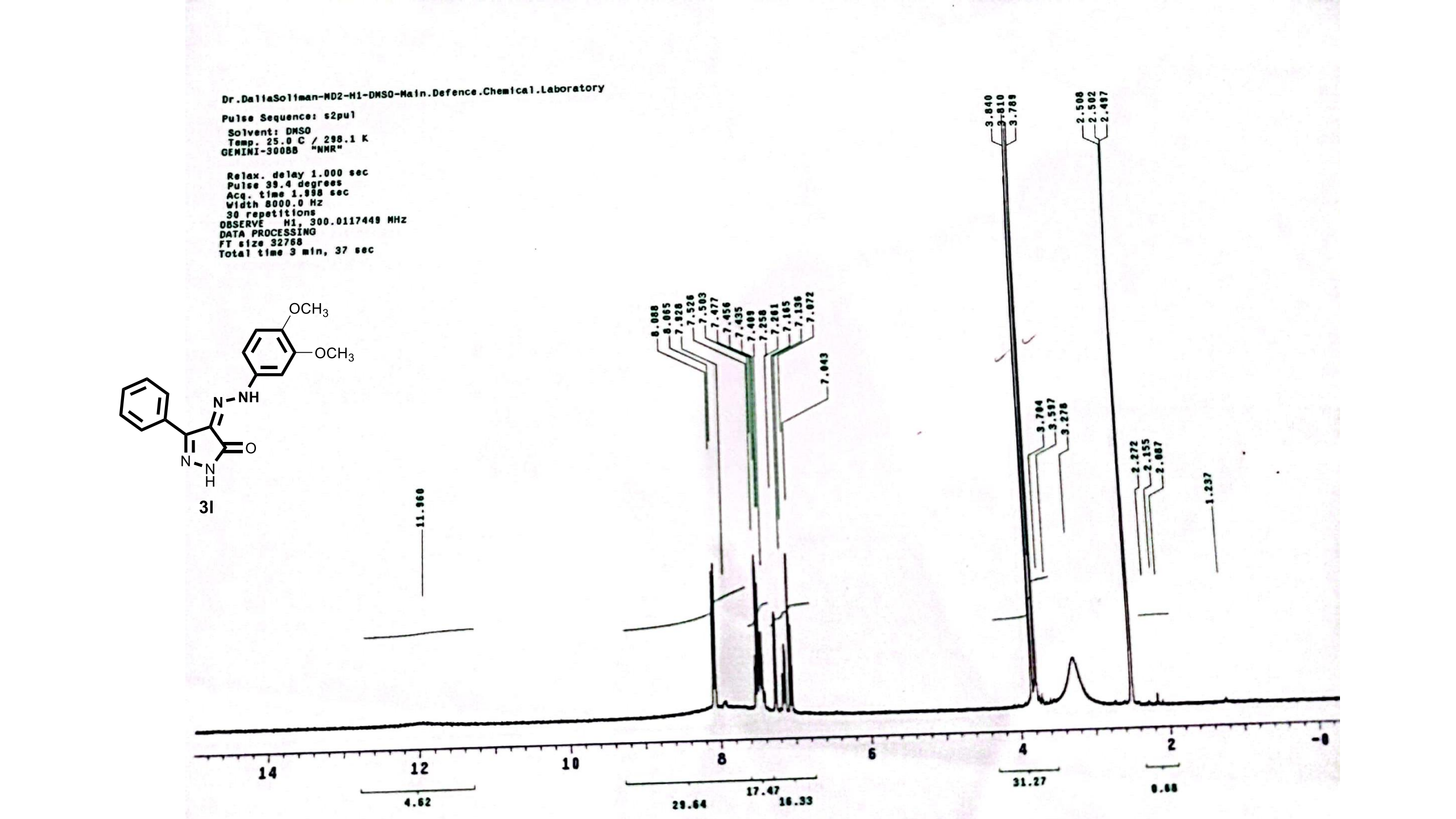
```
Current Data Parameters
NAME      Dalia soliman-MD2-Carbon-DMSO-ES
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20220511
Time                4.49 h
INSTRUM            spect
PROBHD   Z108618_0945 (
PULPROG          zgpg30
TD                65536
SOLVENT             DMSO
NS                   2200
DS                      4
SWH             24038.461 Hz
FIDRES          0.733596 Hz
AQ              1.3631488 sec
RG                 197.77
DW                 20.800 usec
DE                  6.50 usec
TE                295.7 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1
SFO1          100.6404331 MHz
NUC1                  13C
P1                 10.00 usec
PLW1          47.00000000 W
SFO2          400.2016008 MHz
NUC2                  1H
CPDPRG[2           waltz16
PCPD2              90.00 usec
PLW2          13.00000000 W
PLW12          0.29249999 W
PLW13          0.14713000 W

F2 - Processing parameters
SI                   32768
SF            100.6303700 MHz
WDW                     EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```


Dr.DaliaSoliman-MD2-H1-DMSO-Main.Defence.Chemical.Laboratory
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
GEMINI-300BB "NMR"
Relax. delay 1.000 sec
Pulse 39.4 degrees
Acq. time 1.998 sec
Width 8000.0 Hz
30 repetitions
OBSERVE H1, 300.0117449 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 37 sec
OCH3
OCH3
NH
N
O
N
N
H
3l
11.960
8.088
8.065
7.928
7.526
7.503
7.477
7.456
7.435
7.409
7.258
7.201
7.165
7.136
7.072
7.643
3.840
3.810
3.788
3.704
3.597
3.278
2.508
2.502
2.497
2.272
2.155
2.087
1.237
14
12
10
8
6
4
2
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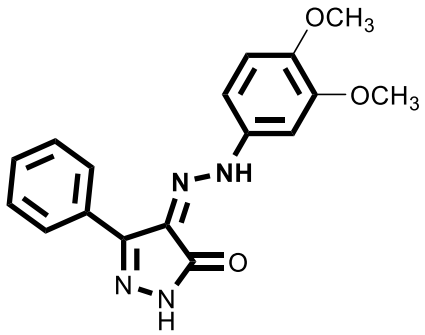
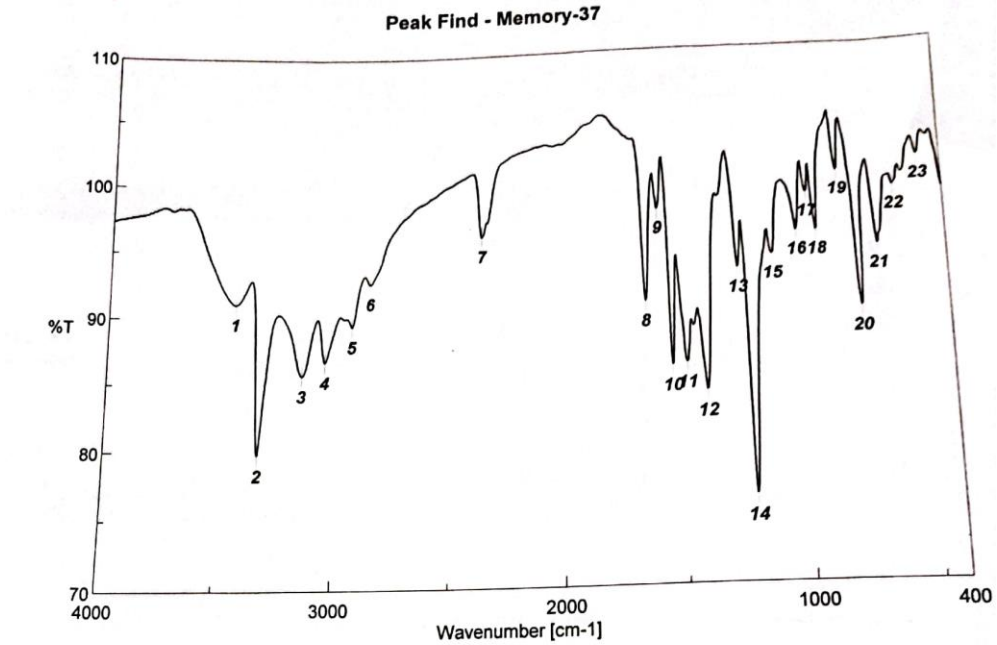
4.62
29.64
17.47
16.33
31.27
0.68



3l

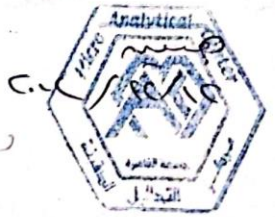


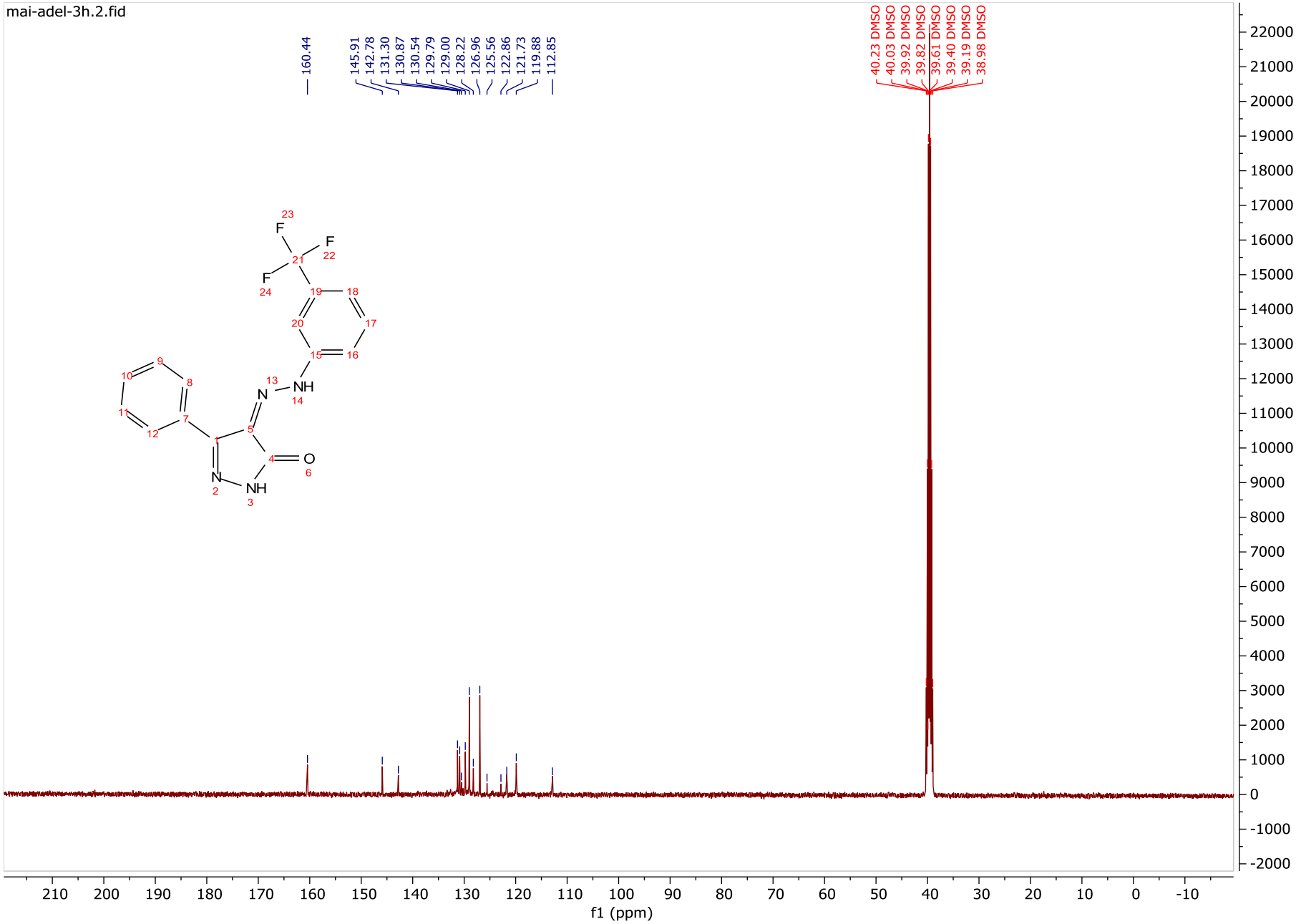
[Comments]

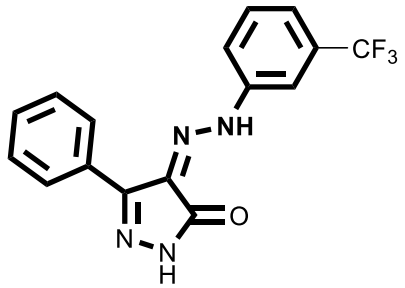
Sample name	M.SD 2
Comment	12/12/2012
User	IR
Division	IR
Company	Micro Analytical Center

[Result of Peak Picking]

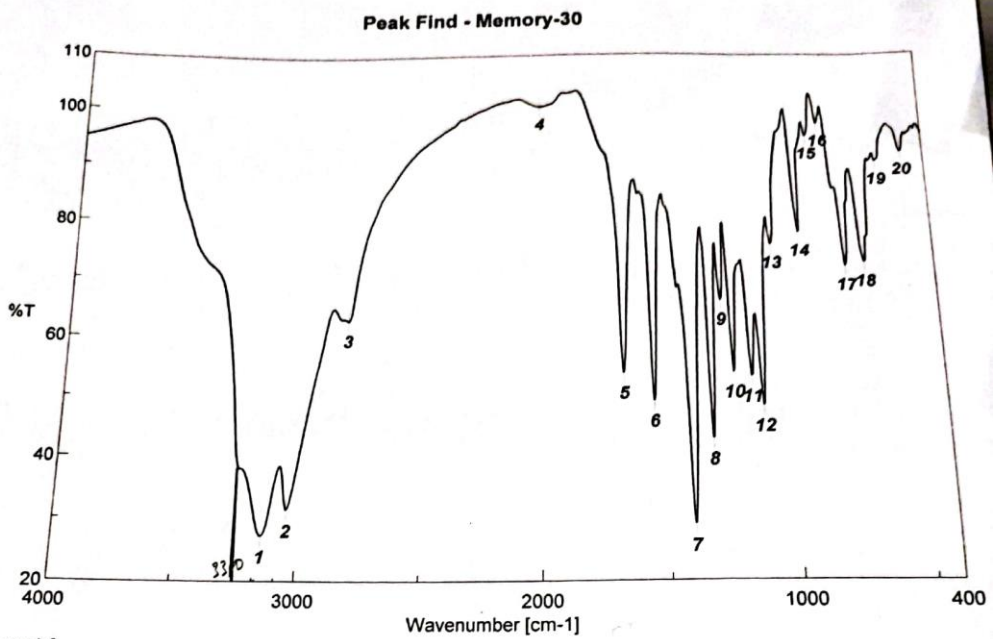
No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3439.42	90.9026	2	3325.64	79.7092	3	3141.47	85.4807
4	3042.16	86.4484	5	2927.41	89.0458	6	2849.31	92.228
7	2360.44	95.4371	8	1658.48	90.0128	9	1604.48	96.9844
10	1550.49	85.2869	11	1490.7	85.4495	12	1409.71	83.3804
13	1273.75	92.2371	14	1221.68	75.9868	15	1127.19	93.2243
16	1021.12	94.9852	17	970.983	97.8989	18	936.271	94.9693
19	836.955	99.5774	20	761.744	89.184	21	680.749	93.833
22	602.646	98.3362	23	493.688	100.607			




mai-adel-3h.2.fid
160.44
145.91
142.78
131.30
130.87
130.54
129.79
129.00
128.22
126.96
125.56
122.86
121.73
119.88
112.85
40.23 DMSO
40.03 DMSO
39.92 DMSO
39.82 DMSO
39.61 DMSO
39.40 DMSO
39.19 DMSO
38.98 DMSO
f1 (ppm)



3h

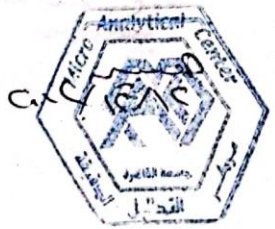


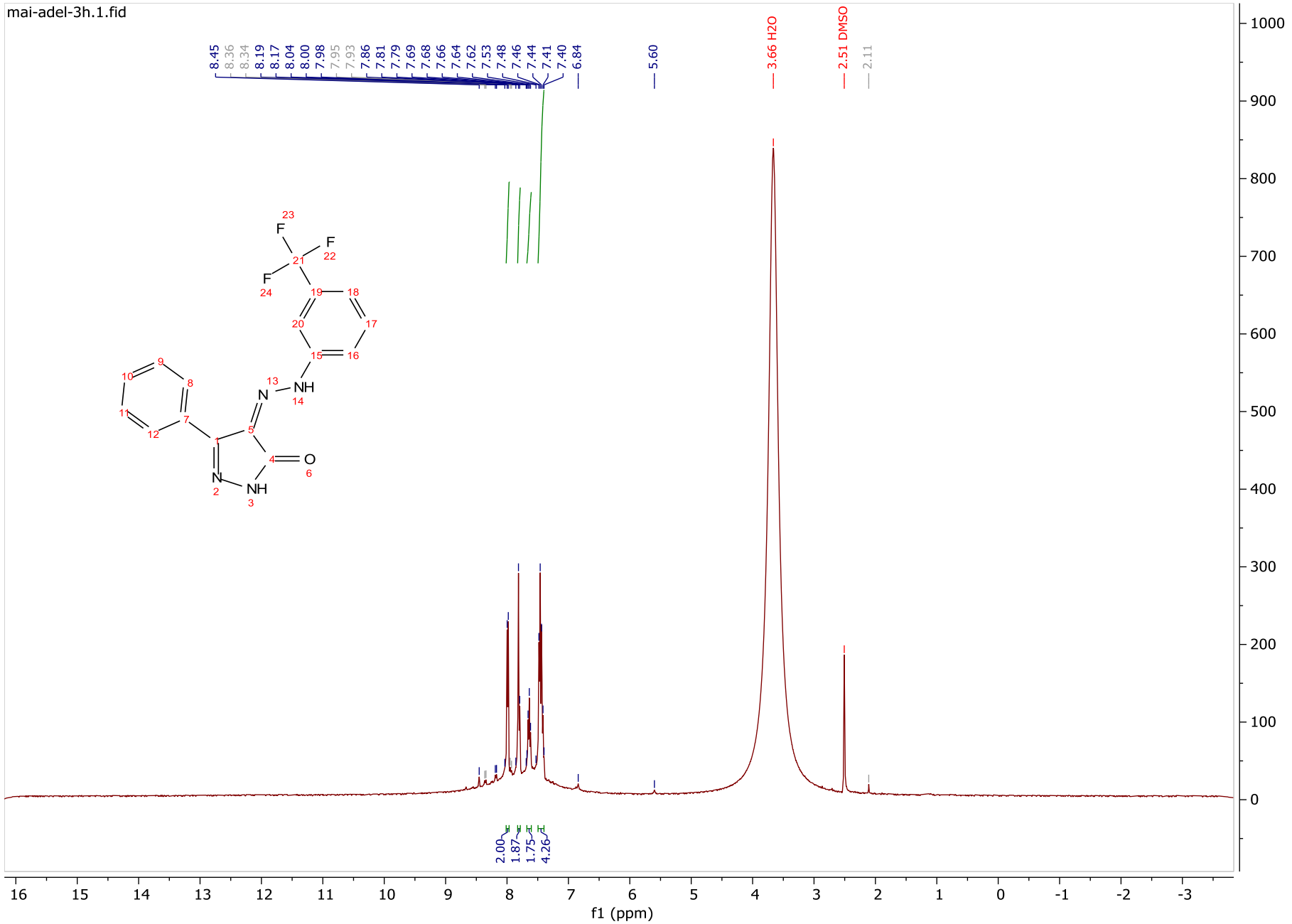
[Comments]

Sample name	MSD3
Comment	12/12/2012
User	IR
Division	IR
Company	Micro Analytical Center

Result of Peak Picking]

No.	Position	Intensity
1	3142.44	27.1806
2	3043.12	31.2856
3	2814.6	62.0183
4	2017.18	99.9552
5	1675.84	52.5383
6	1556.27	47.8968
7	1405.85	28.5557
8	1327.75	41.7668
9	1283.39	64.3712
10	1240	52.4221
11	1168.65	51.6675
12	1126.22	46.9187
13	1066.44	74.0867
14	947.842	76.2686
15	889.023	94.1178
16	836.955	96.529
17	763.673	70.3229
18	683.642	71.0352
19	603.61	89.4393
20	492.723	91.2829




mai-adel-3h.1.fid
8.45
8.36
8.34
8.19
8.17
8.04
8.00
7.98
7.95
7.93
7.86
7.81
7.79
7.69
7.68
7.66
7.64
7.62
7.53
7.48
7.46
7.44
7.41
7.40
6.84
5.60
3.66 H2O
2.51 DMSO
2.11
2.00
1.87
1.75
4.26
f1 (ppm)

Docking study

Automated docking studies were carried out using Glide (SP) scoring function Maestro10.1 Schrodinger, (2015-Release-4).

Ligand Preparation

LigPrep module, was used for geometrical refining of chemical structures. LigPrep is intended to set up premium 3D structures with accurate chiralities. Original states of ionization were retained; tautomers and conformations were generated by the Monte Carlo method as implemented in MacroModel version 9.8, 2010, using OPLS-2005 force field. The generated conformers were subsequently minimized using truncated Newton conjugate gradient (TNCG) minimization up to 500 iterations. The conformers with an energy difference of 30 kcal/mol as compared to the global energy minimum conformer were retained. The conformational searches were carried out for aqueous solution using the generalized born/solvent accessible surface (GB/SA) continuum solvation model.

Protein Preparation.

Protein preparation wizard of Maestro software was used for protein preparation. The selected chains were edited for missing hydrogens and for assigning proper bond orders. The H-bonds were optimized using sample orientations. All the polar hydrogens were displayed. All the crystallographic waters without hydrogen bond interactions with protein residues were removed. Finally, the non-hydrogen atoms of the protein structure was minimized to the default Root Mean Square Deviation (RMSD) value of 0.3.

Receptor Grid Generation.

From the defined receptor, the co-crystallized ligand was separated from the active site of receptor chain. The atoms were of size equal to Van der Waals radii of 1.0> while the partial atomic charge was less than 0.25 defaults. The active site represents an enclosing box at the centroid of the workspace ligand. Following this protocol, a grid centered on the ligand was generated using the default Glide settings. All ligands were docked into this grid structure.

Molecular Docking Analysis.

On a defined receptor grid, flexible docking was performed using the precision (SP) feature of Glide module, version 5.6, 2010. The constraints to defined ligand-receptor interactions were not set. The structure output format was set to pose viewer file so as to view the output of the resulting docking studies from pose viewer.

Acknowledgements

In this work, docking studies were carried out using the Glide, Maestro10.1 Schrodinger, (2015-Release-4).

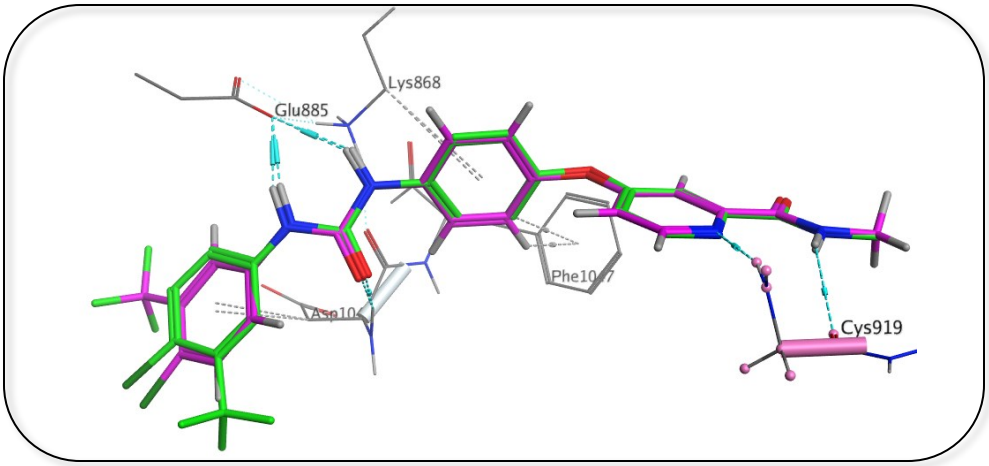


Figure S1 3D Representation of the superimposition of the docking pose (green) and the co-crystallized (purple) of sorafenib in the VEGFR-2 active site with RMSD of 0.21Å.

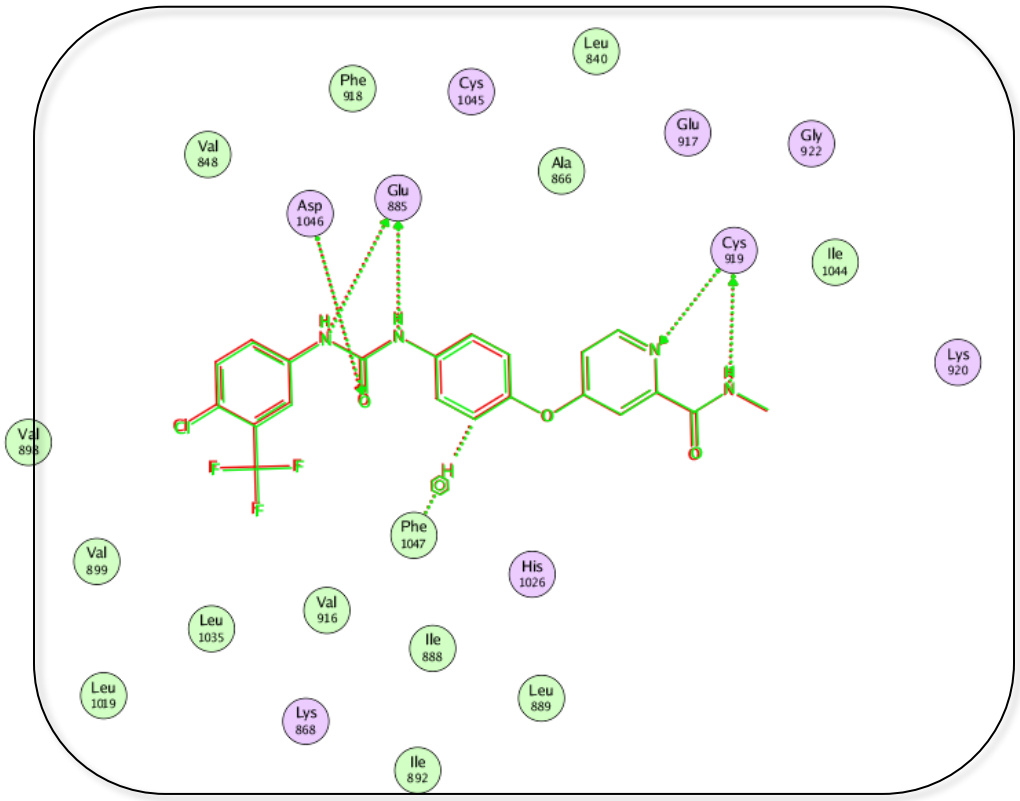


Figure S2 2D Representation of the superimposition of the docking pose (green) and the co-crystallized (purple) of sorafenib in the VEGFR-2 active site with RMSD of 0.21Å.

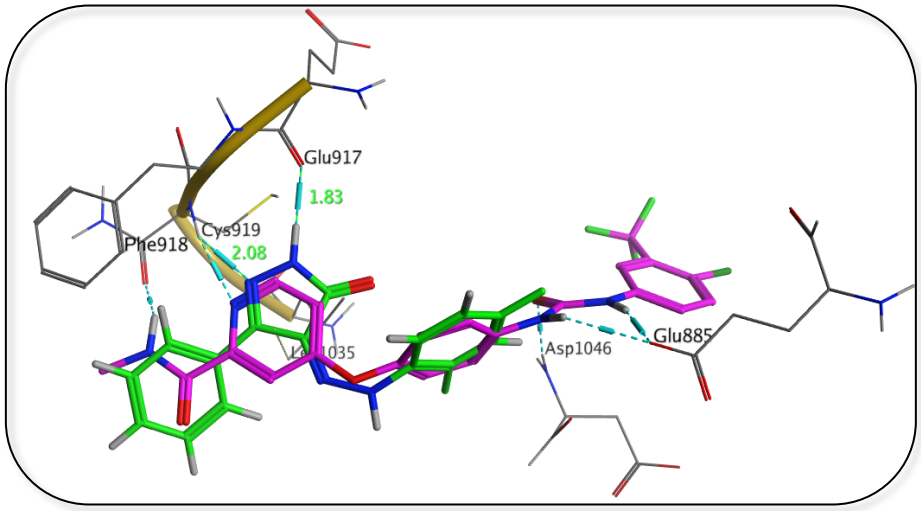


Figure S3 Superimposition of the docking pose of **3i** (green) and the co-crystallized (purple) of sorafenib in the VEGFR-2 active site.

In Vivo Assay

Animals and tumor cell line

Adult female Swiss albino mice purchased from Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt, with an average body weight of (18-23) g was used. Mice were housed under constant conditions of 12 h light/dark cycle in a temperature under conditions of controlled humidity (22 ± 2 °C), with free access to standard laboratory mice food and water .All procedures related to care and maintenance of the animals were performed according to the international guiding principles for animal research and approved by Faculty of Science, Suez Canal University bioethics and animal ethics committee (Approval number REC107/2022).

Solid Ehrlich carcinoma (SEC) were got from the National Cancer Institute (Cairo University, Egypt). The tumor cell line was proliferated in mice through serial intraperitoneal (I.P.) transplantation of a volume of 0.2 mL physiological saline containing 1×10^6 viable cells for 24 h. SEC cells were collected 7 days after I.P. implantation. The harvested cells were diluted with saline to obtain a concentration of 5×10^6 viable SEC cells/mL. A volume of 0.2 mL saline contains 1×10^6 SEC cells that were I.P. implanted into each normal mouse. SEC cells (1×10^6 tumor cells/mouse) were implanted subcutaneously into the right thigh of the hind limb.

The experimental animals were randomly divided into four groups. Group **1** served as the normal saline control. Group **2** served as the SEC control (1×10^6 cells/mouse). Group **3** served as the compound-treated group (6 mg/kg B.Wt., I.P.). Group **4** received the standard anticancer drug of Sorafenib (6 mg/kg BW, I.P.) and is considered as a reference control. Body weight and survival were recorded daily until the 24^{th} day in both treated and control groups. At the end of experiment, anesthetized animals were then sacrificed for evaluation of the antitumor activity and histopathological examination.

Antitumor potentiality

It includes tumor volume, weight, and tumor inhibition ration (TIR%). Time interval measurements of tumor volume using digital Vernier caliper (Tricle Brand, Shanghai, China). Measure tumor length and width using clipper and then calculate tumor volume using formulations V = (L x W x W)/2, where V is tumor volume, W is tumor width, L is tumor length. While TIR% was calculated according to the following equation $\frac{Tumor\ volume\ (Control) - Tumor\ volume\ (treated)}{Tumor\ volume\ (control)} x\ 100$.

Histopathological study

Specimens of liver-sacrificed mice were fixed in 10% saline formalin. The fixed liver specimens were dehydratedin ascending series of ethyl alcohol and embedded in paraffin. Sections at 5 mm thicknesses were stained with hematoxylin and eosin and examined under light microscopy

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