

New quinoxaline-2(1*H*)-ones as potential VEGFR-2 inhibitors: Design, synthesis, molecular docking, ADMET profile and anti-proliferative evaluations

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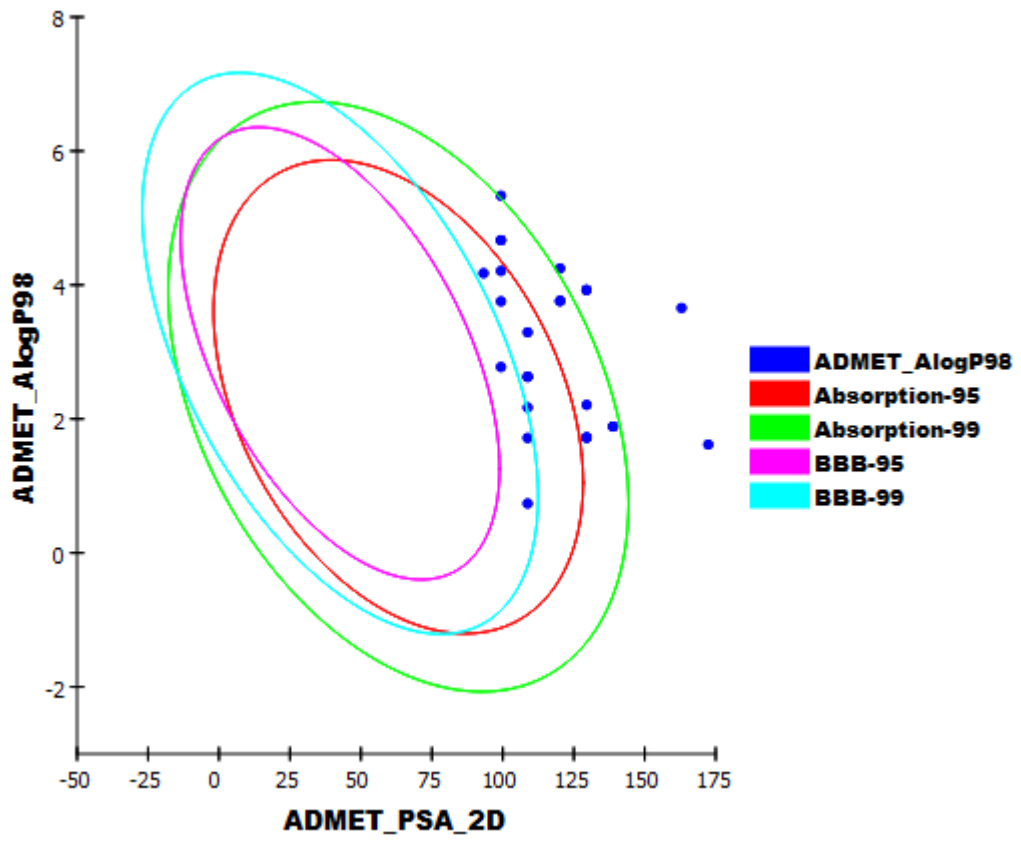
Email: Ibrahimeissa@azhar.edu.eg

Khaled El-Adl

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Emails: eladlkhaled74@yahoo.com; eladlkhaled74@azhar.edu.eg; khaled.eladl@hu.edu.eg

The expected ADMET study



Predicted ADMET for the designed compounds and reference drug

Comp.	BBB level ^a	Solubility level ^b	Absorption level ^c	CYP2D6 prediction ^d	PPB prediction ^e
11a	3	3	0	FALSE	TRUE
11b	4	2	0	FALSE	TRUE
11c	4	2	0	FALSE	TRUE
11d	4	2	0	FALSE	TRUE
11e	4	3	1	FALSE	TRUE
11f	4	3	2	FALSE	TRUE
11g	4	2	2	FALSE	TRUE
12	4	3	1	FALSE	TRUE
13	4	3	0	FALSE	FALSE
14	4	3	0	FALSE	TRUE
15	3	3	0	FALSE	TRUE
Sorafenib	4	1	0	FALSE	TRUE

^a BBB level, blood brain barrier level, 0 = very high, 1 = high, 2 = medium, 3 = low, 4 = very low.

^b Solubility level, 1 = very low, 2 = low, 3 = good, 4 = optimal.

^c Absorption level, 0 = good, 1 = moderate, 2 = poor, 3 = very poor.

^d CYP2D6, cytochrome P2D6, TRUE = inhibitor, FALSE = non inhibitor.

^e PBB, plasma protein binding, FALSE means less than 90%, TRUE means more than 90%

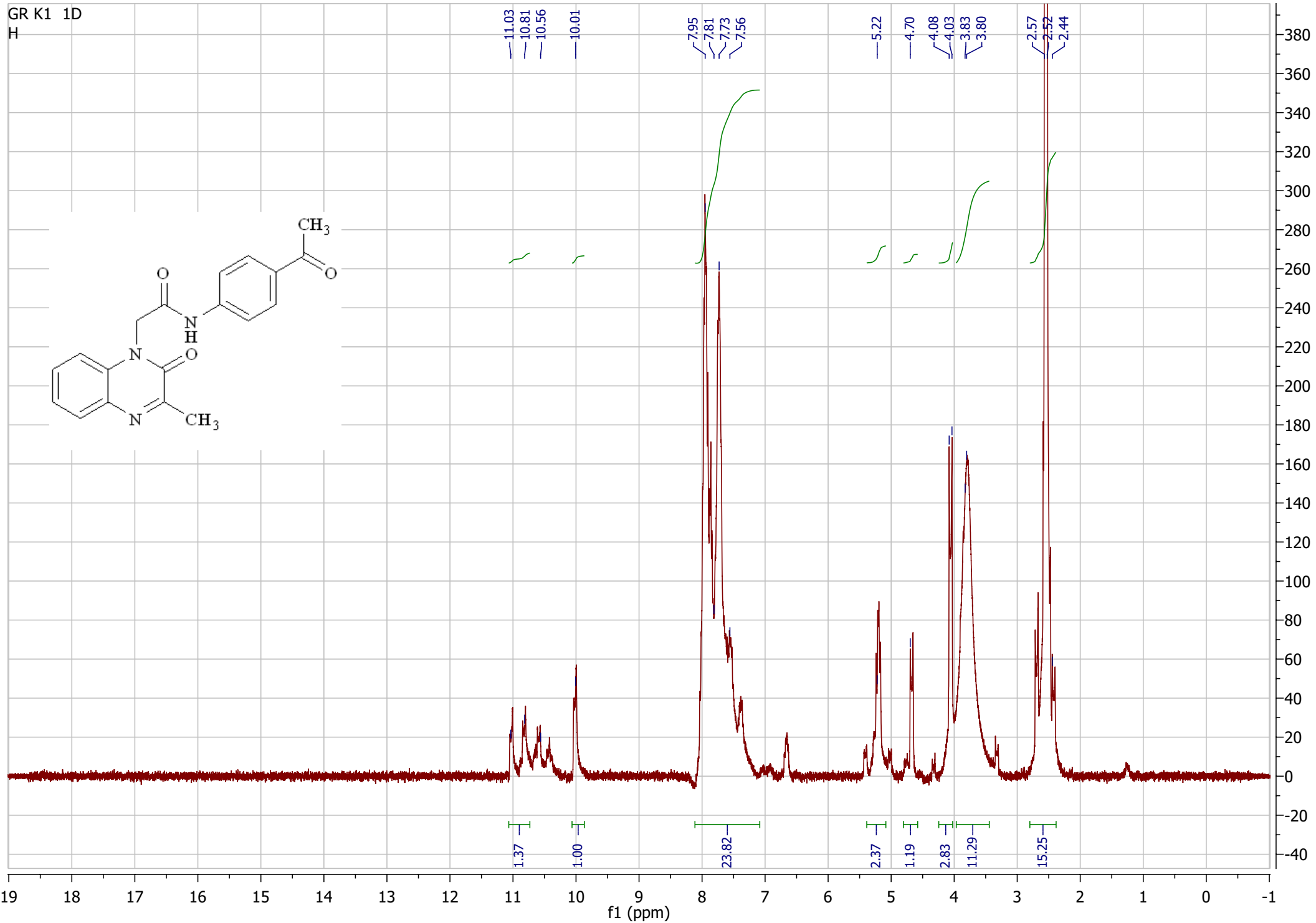
Toxicity properties of the synthesized compounds

Comp.	FDA Rodent Carcinogenicity (Mouse-Female)	Carcinogenic Potency TD ₅₀ (Rat) ^a	Rat Maximum Tolerated Dose (Feed) ^b	Developmental Toxicity Potential	Rat Oral LD ₅₀ ^b	Rat Chronic LOAEL ^b	Ocular Irritancy	Skin Irritancy
11a	Non-Carcinogen	23.443	0.067	Non-Toxic	2.730	0.244	Irritant	Non-Irritant
11b	Non-Carcinogen	6.212	0.081	Non-Toxic	4.841	0.264	Irritant	Non-Irritant
11c	Non-Carcinogen	5.977	0.081	Non-Toxic	2.881	0.155	Irritant	Non-Irritant
11d	Non-Carcinogen	5.977	0.081	Non-Toxic	2.478	0.144	Irritant	Non-Irritant
11e	Non-Carcinogen	51.481	0.220	Non-Toxic	2.539	0.347	Irritant	Non-Irritant
11f	Non-Carcinogen	4.715	0.049	Non-Toxic	5.090	0.186	Irritant	Non-Irritant
11g	Non-Carcinogen	2.964	0.059	Non-Toxic	5.866	0.098	Irritant	Non-Irritant
12	Non-Carcinogen	32.462	0.087	Non-Toxic	0.936	0.212	Irritant	Non-Irritant
13	Non-Carcinogen	42.027	0.087	Non-Toxic	0.656	0.227	Irritant	Non-Irritant
14	Non-Carcinogen	12.449	0.054	Non-Toxic	4.518	0.220	Irritant	Non-Irritant
15	Non-Carcinogen	46.537	0.161	Non-Toxic	3.627	0.391	Irritant	Non-Irritant
Sorafenib	Single-Carcinogen	14.244	0.089	Toxic	0.823	0.005	Irritant	Non-Irritant

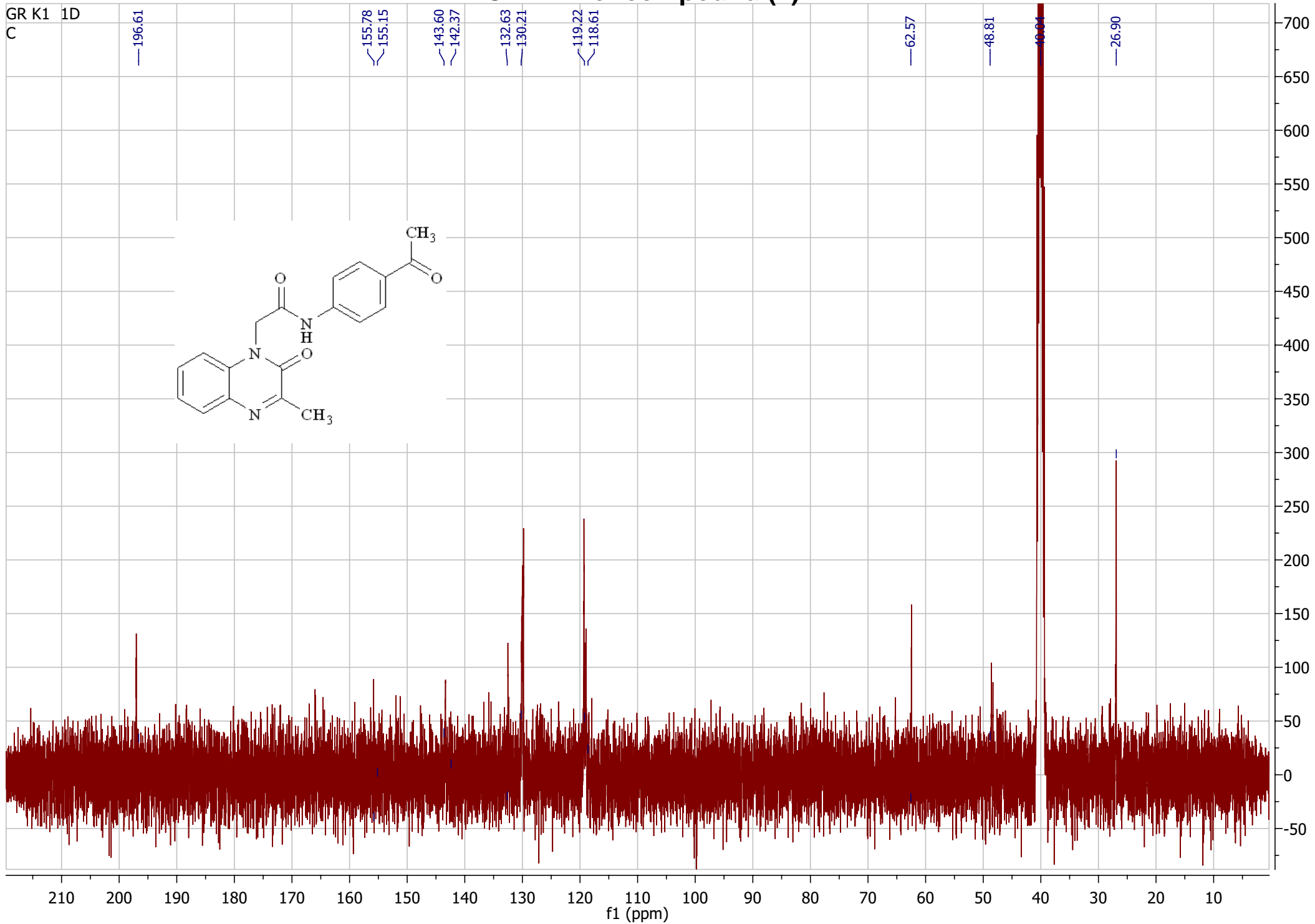
^a Unit: mg/kg body weight/day

^b Unit: g/kg body weight

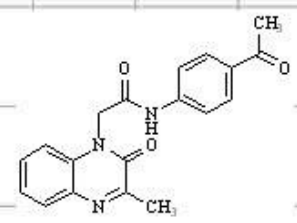
H¹NMR of compound (7)



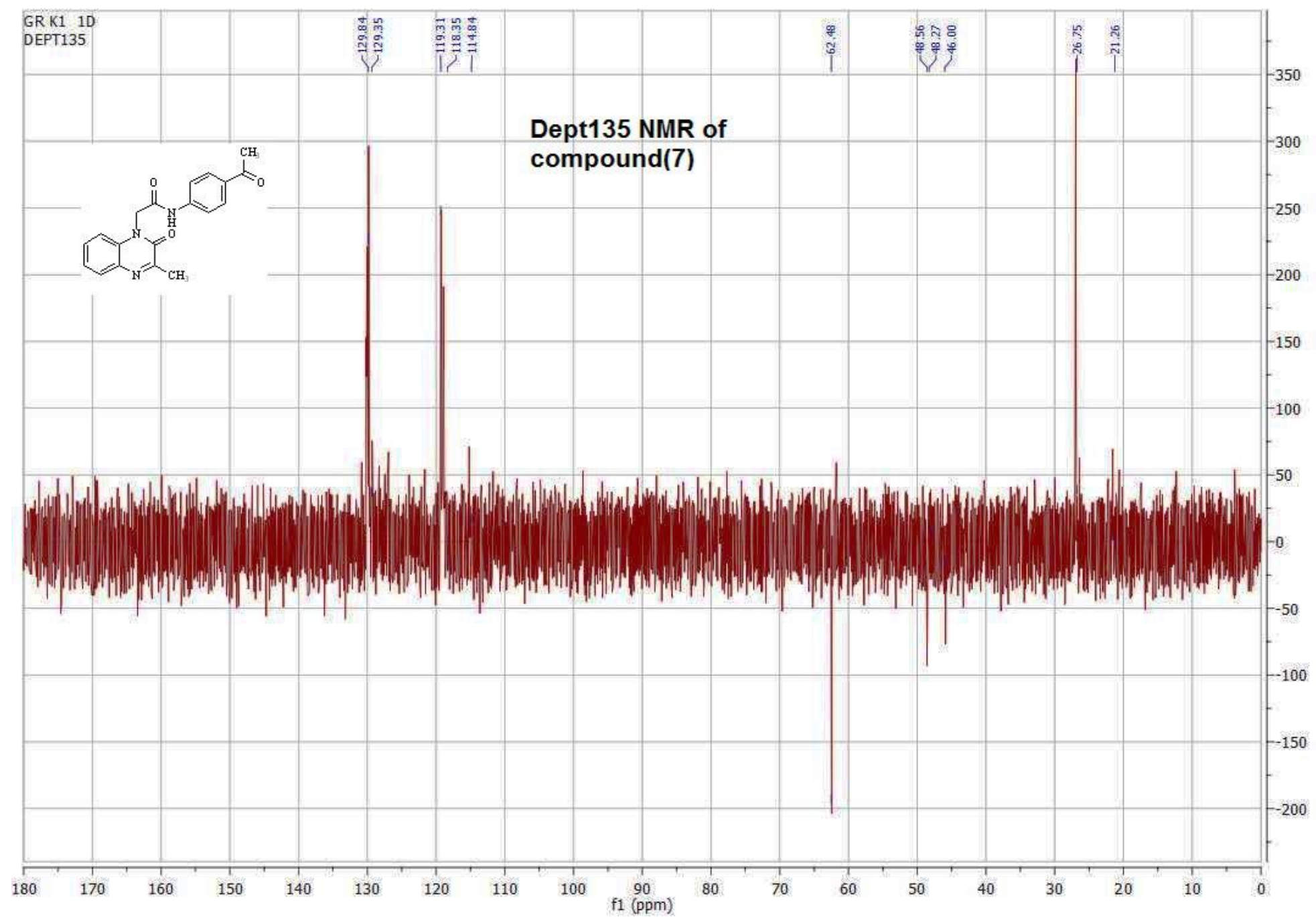
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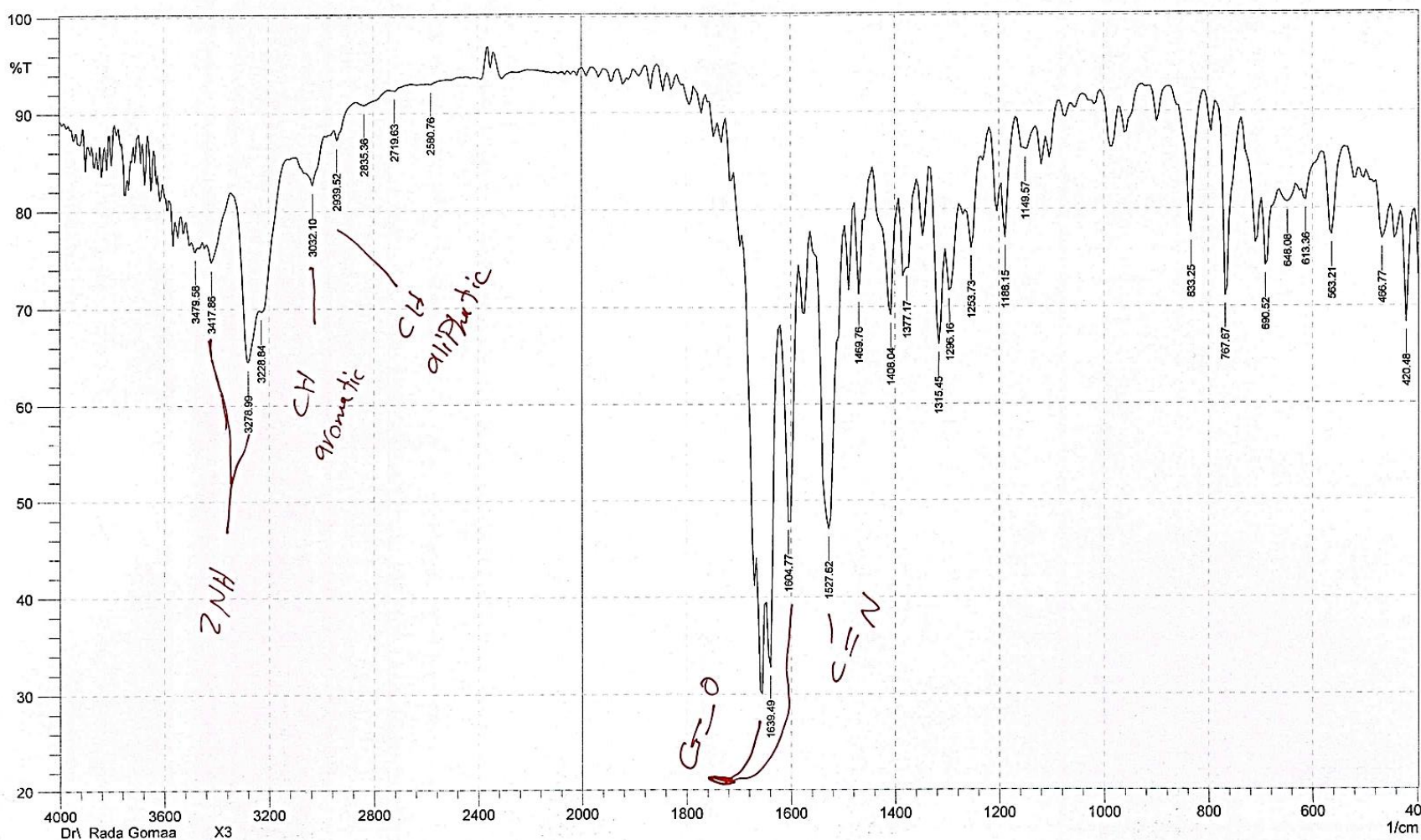
GR K1 1D
DEPT135



Dept135 NMR of compound(7)



IR of compound 11a



Comment;

Dr\ Rada Gomaa X3

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Resolution; 8 [1/cm]

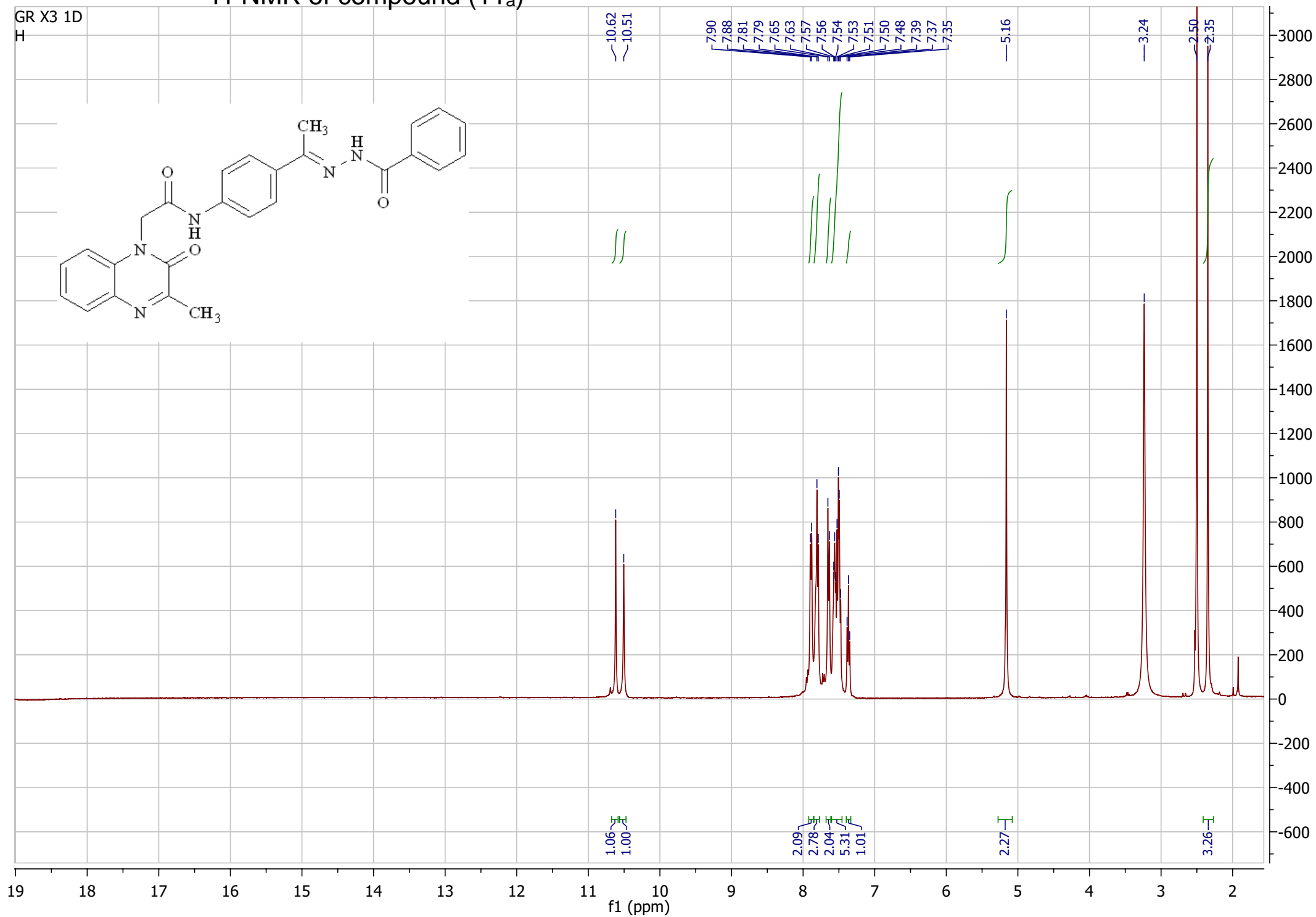
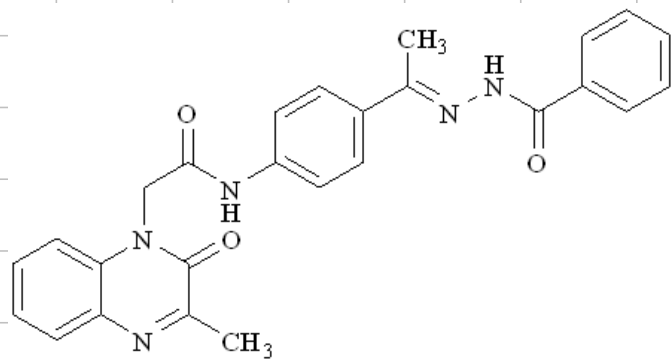
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User; usama

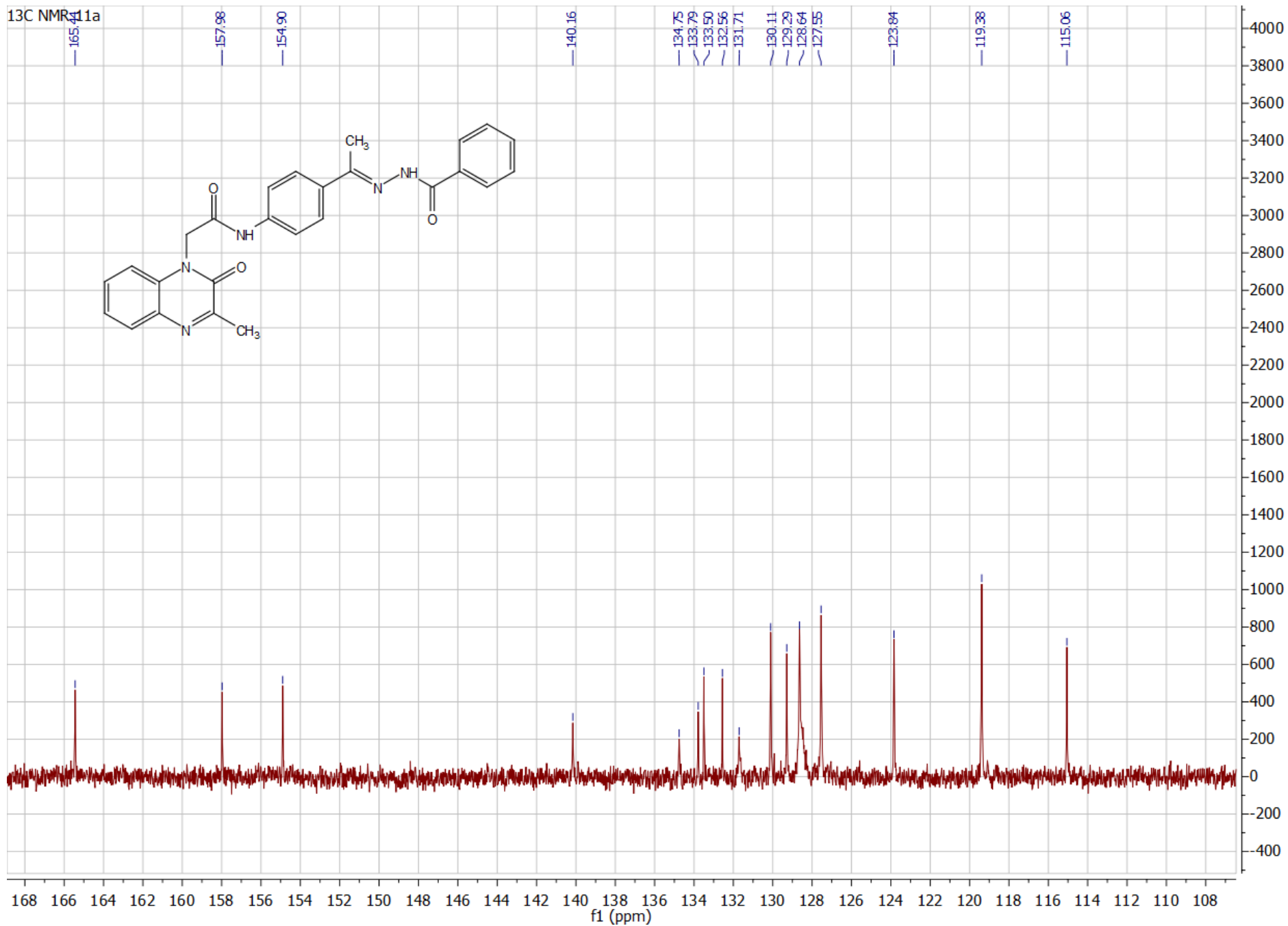
H¹NMR of compound (11a)

GR X3 1D

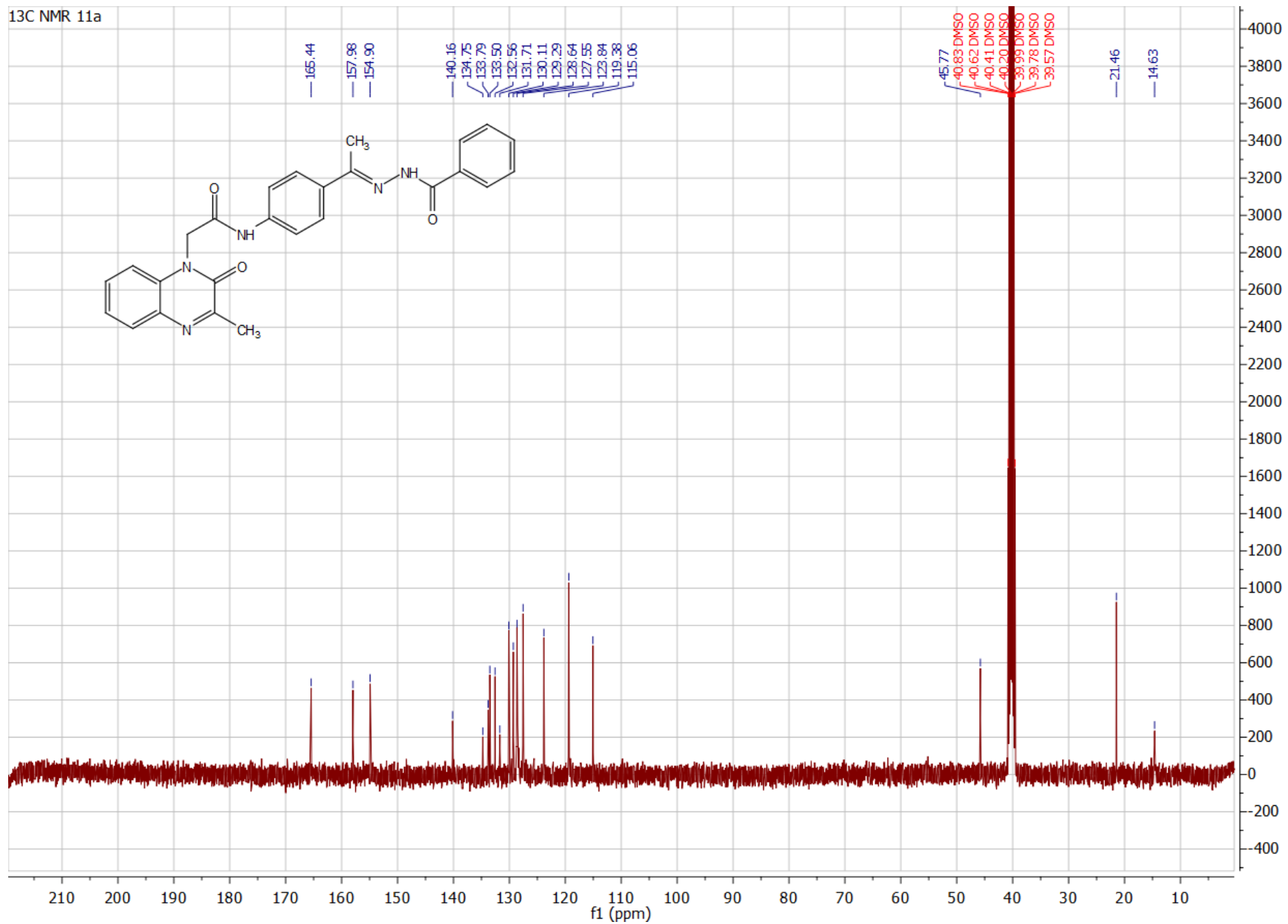
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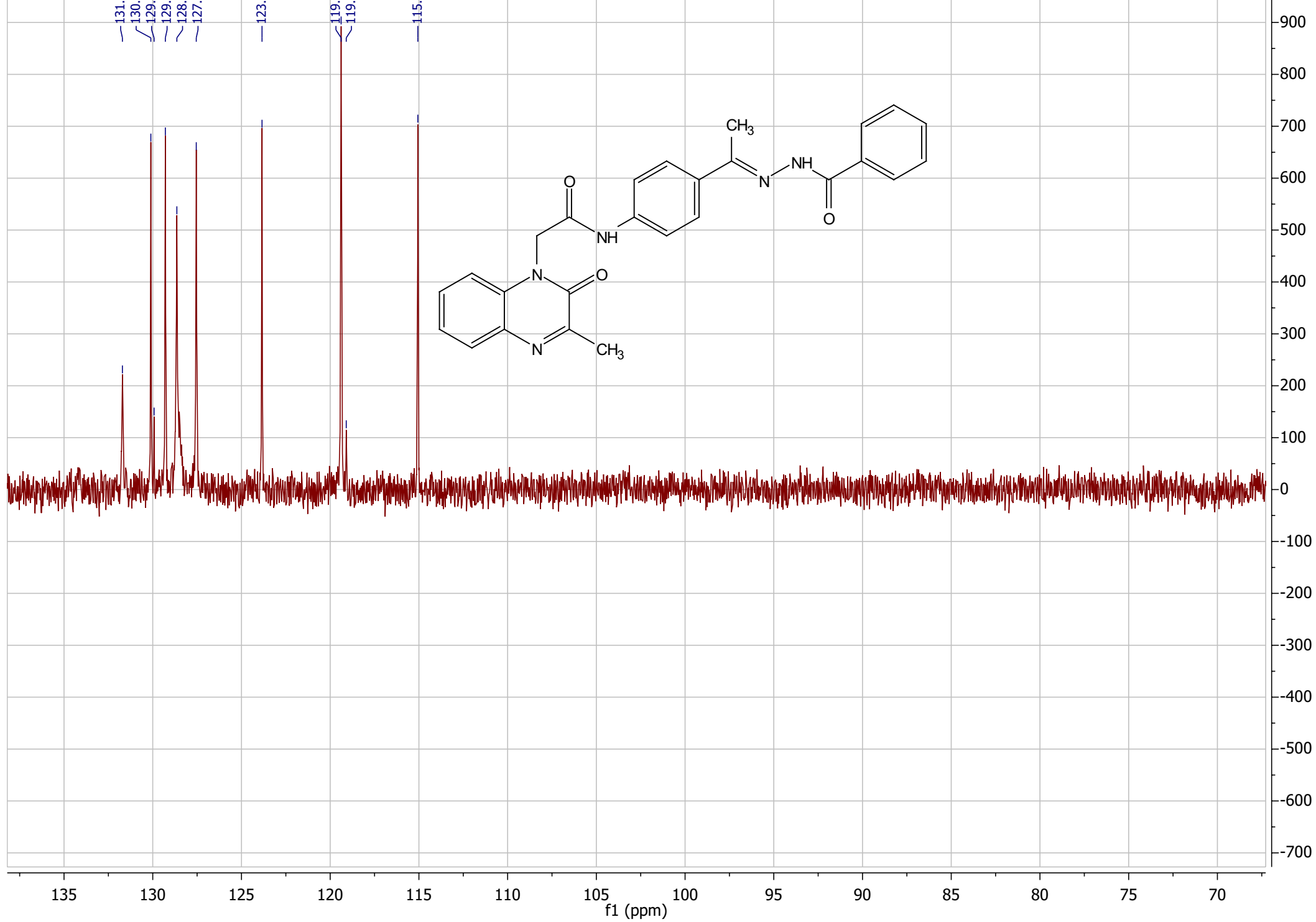
¹³C NMR 11a



¹³C NMR 11a

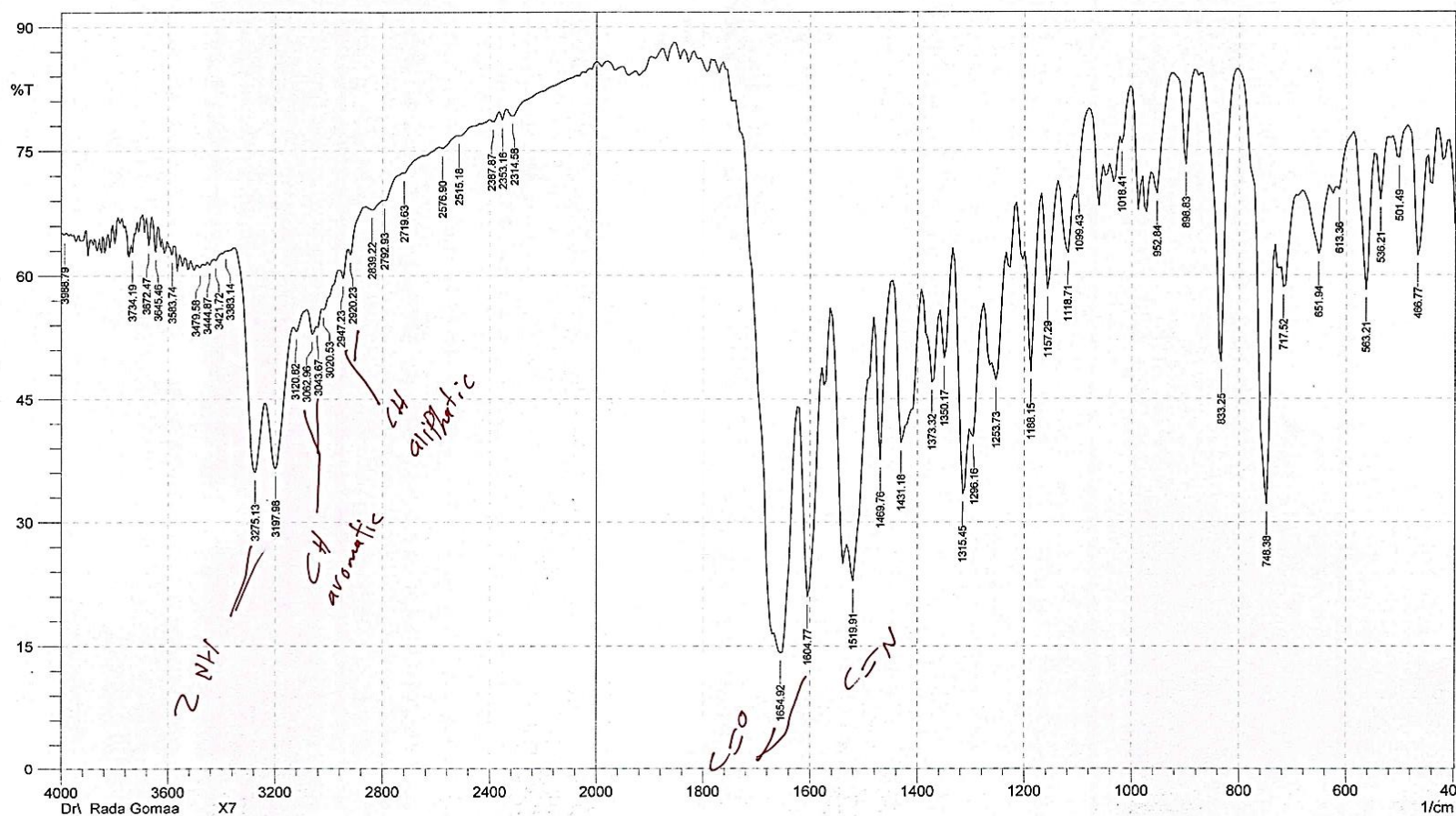


DEPT NMR 11a



IR of compound 11b

SHIMADZU



Comment;

Dr/ Rada Gornaa X7

No. of Scans; 8

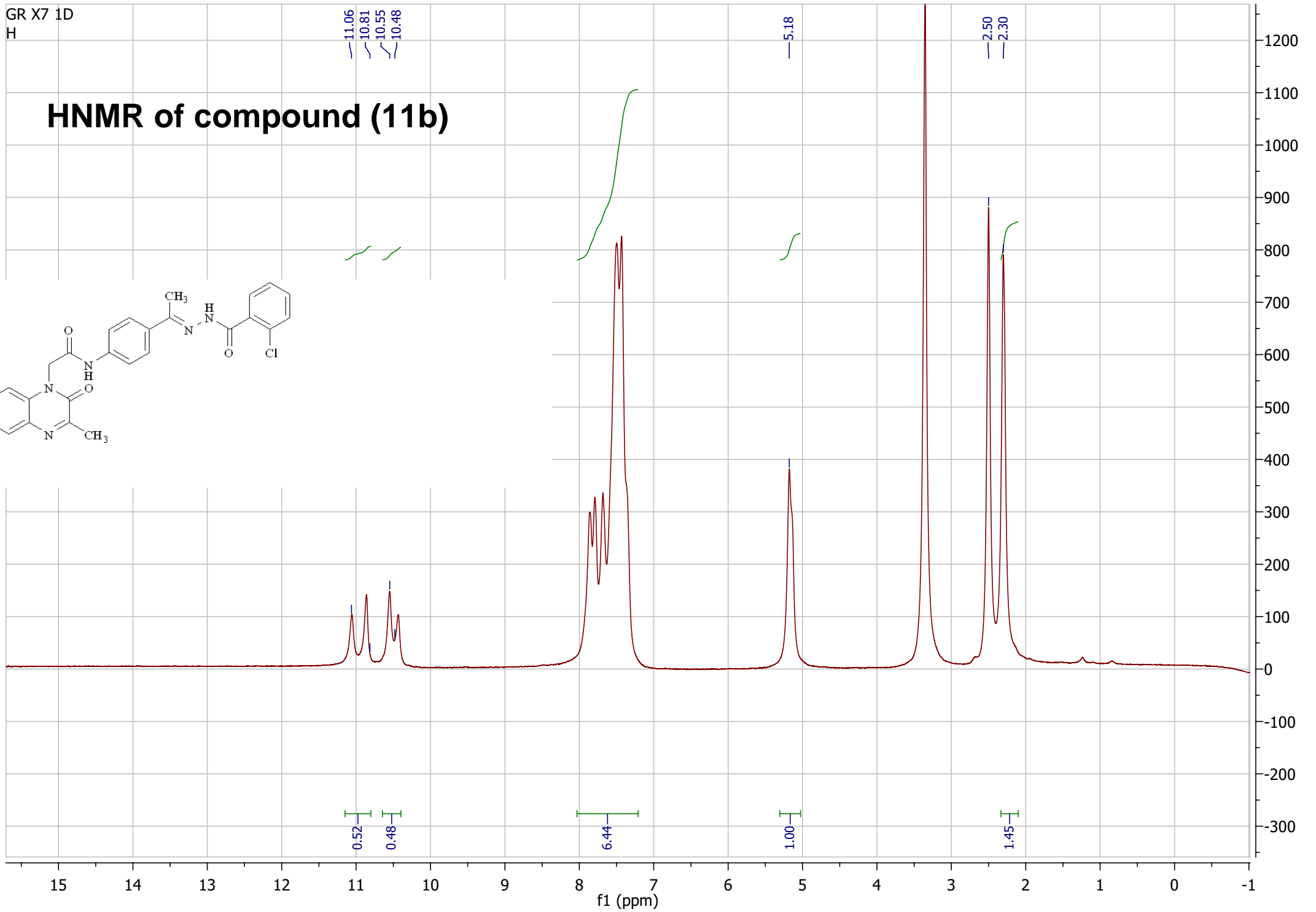
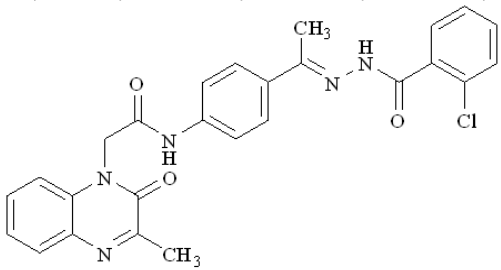
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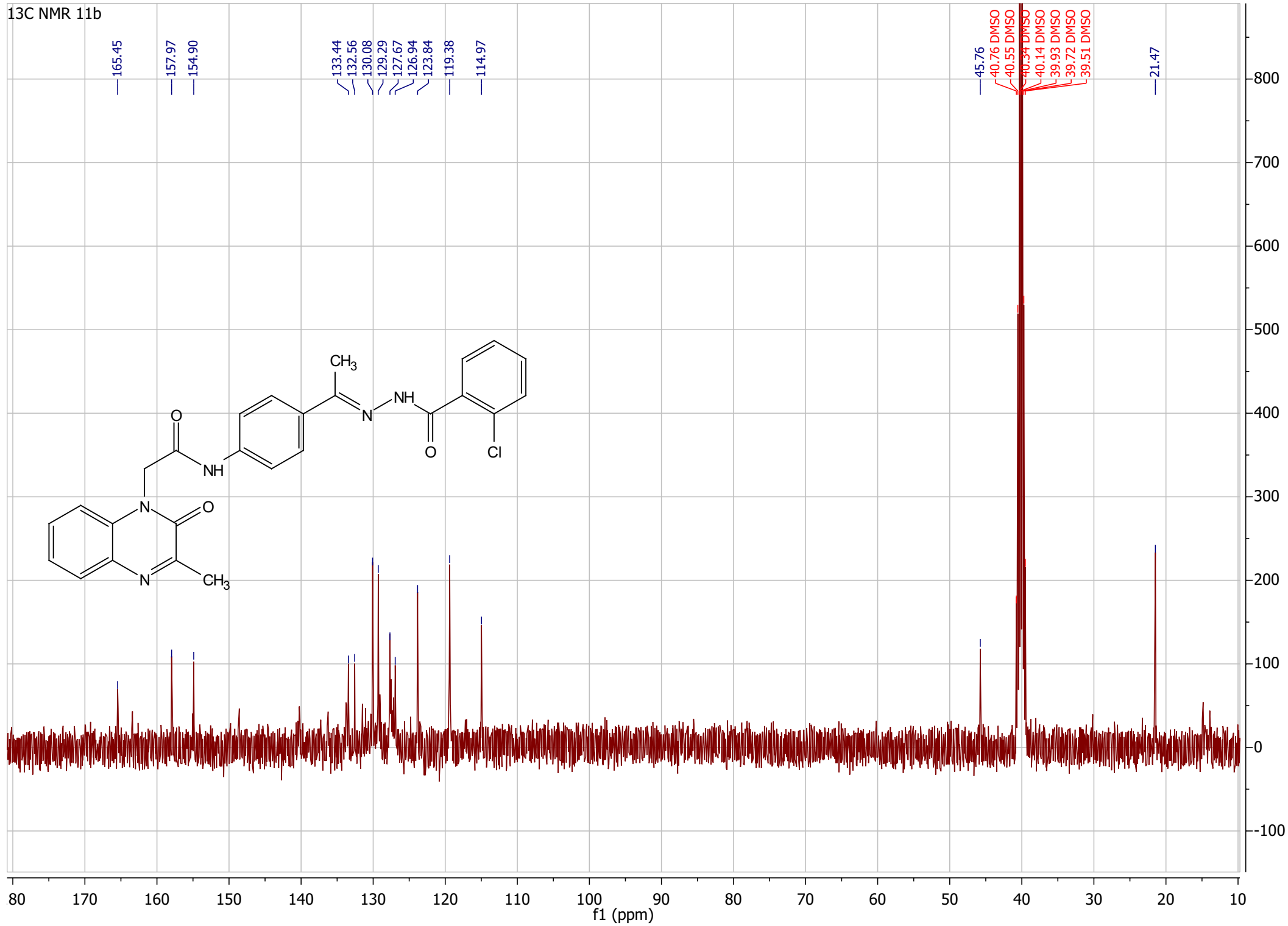
User; usama

GR X7 1D
H

HNMR of compound (11b)

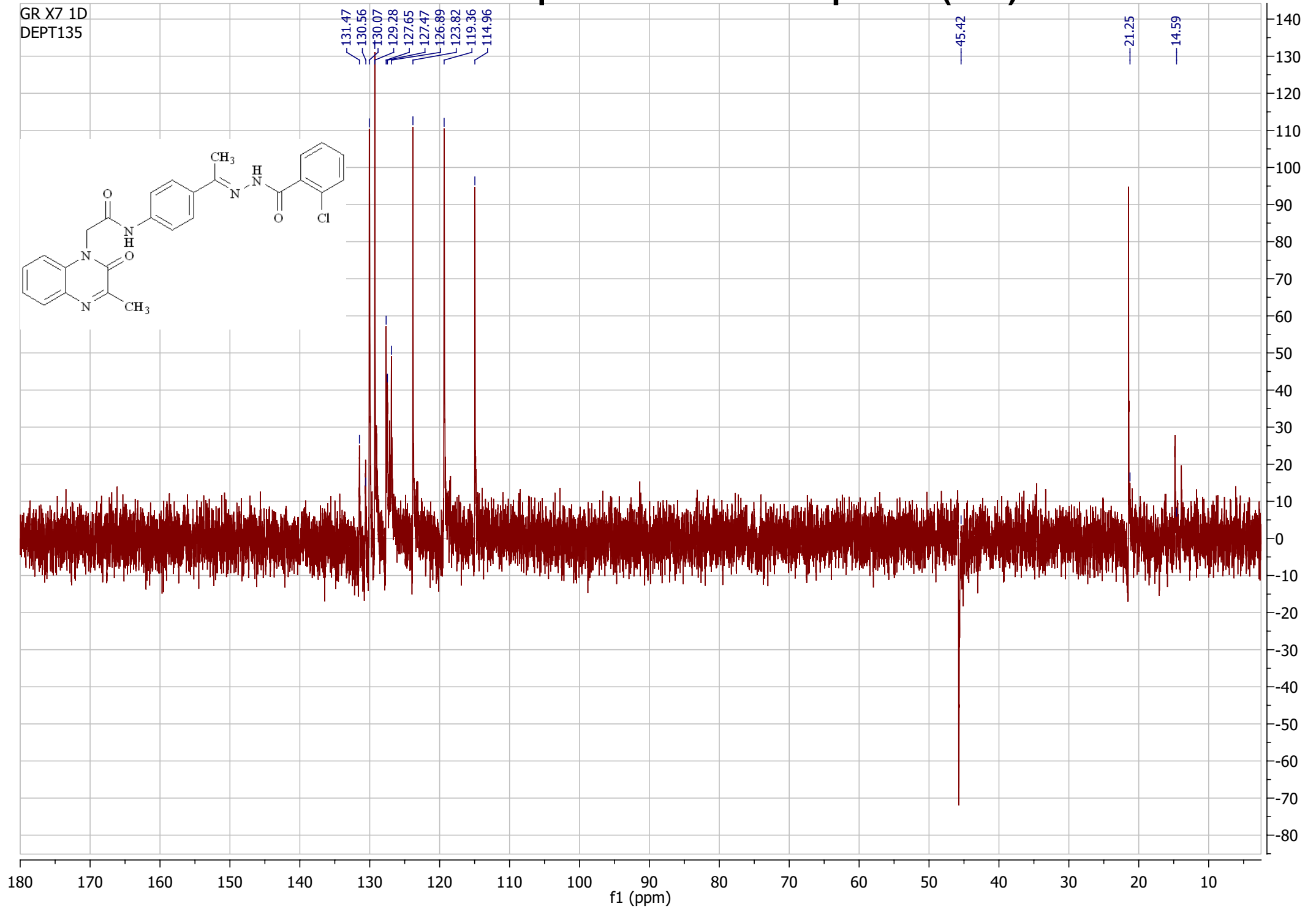
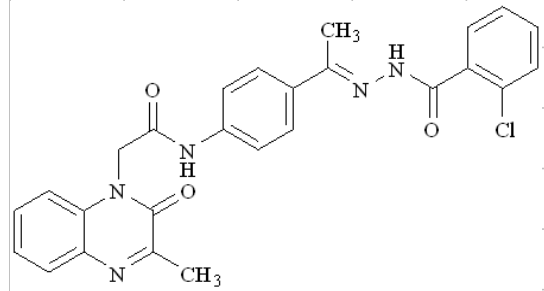


¹³C NMR 11b



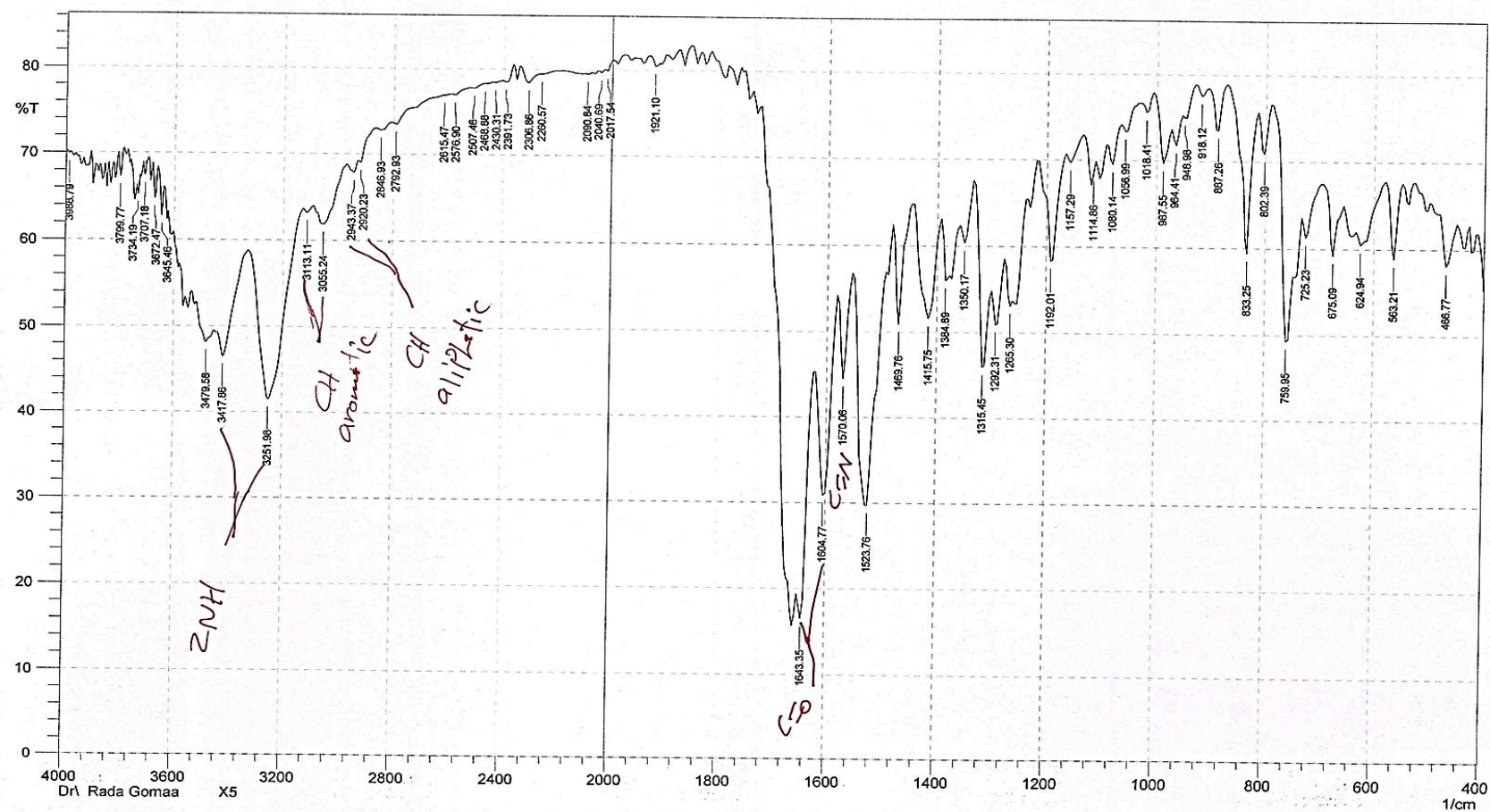
Dept 135 NMR of compound (11b)

GR X7 1D
DEPT135



IR of compound 11c

SHIMADZU



Comment;

Dr Rada Goma X5

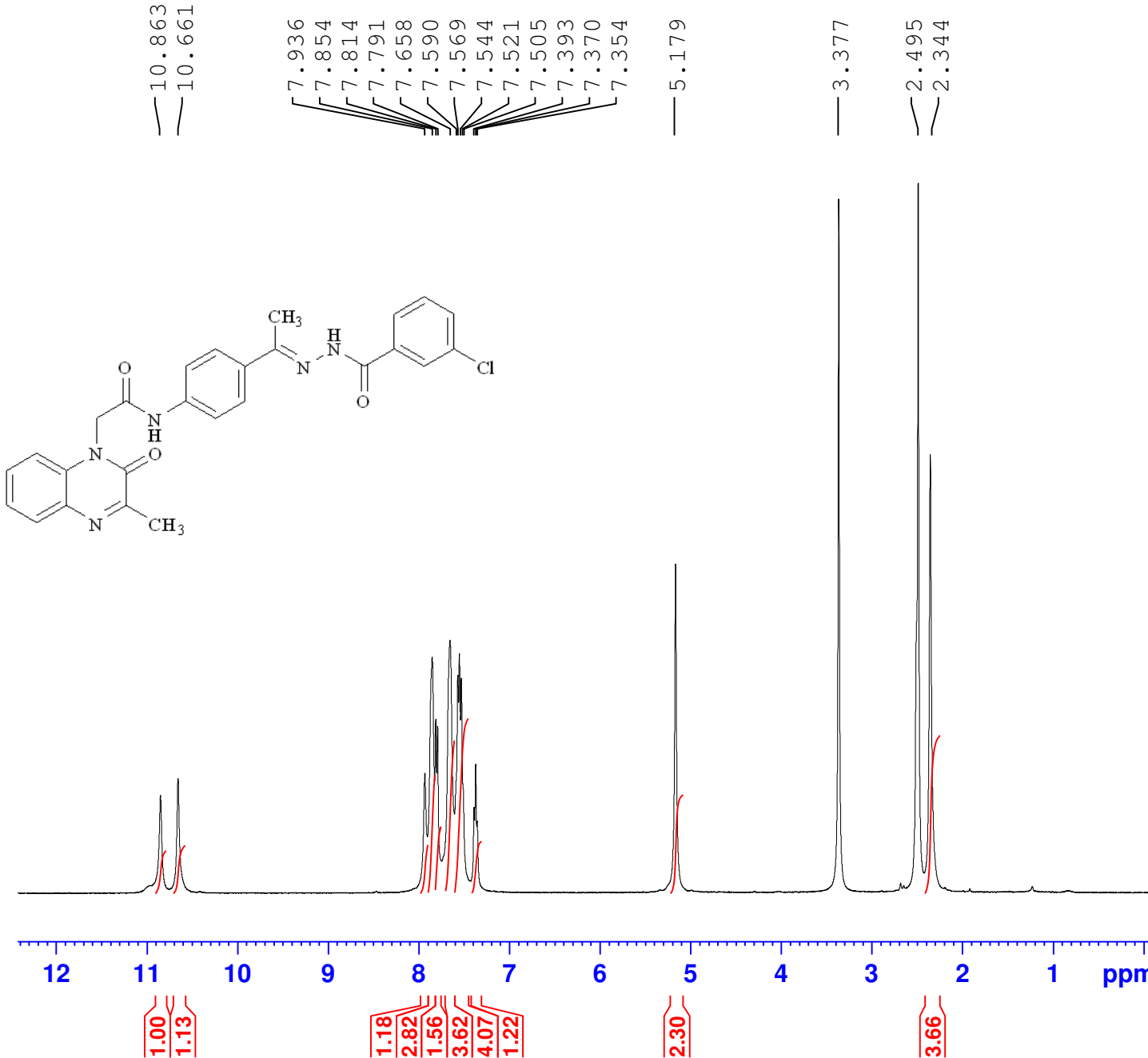
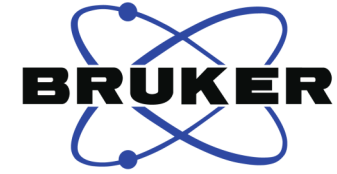
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^1H NMR of compound (11c)



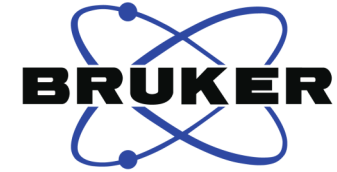
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PROCNO 1

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PULPROG zg30
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SOLVENT DMSO
NS 50
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 205.37
DW 62.400 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1

==== CHANNEL f1 =====
SFO1 400.1524711 MHz
NUC1 1H
P1 12.00 usec
PLW1 18.00000000 W

F2 - Processing parameters
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WDW EM
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H¹NMR of compound (11c)

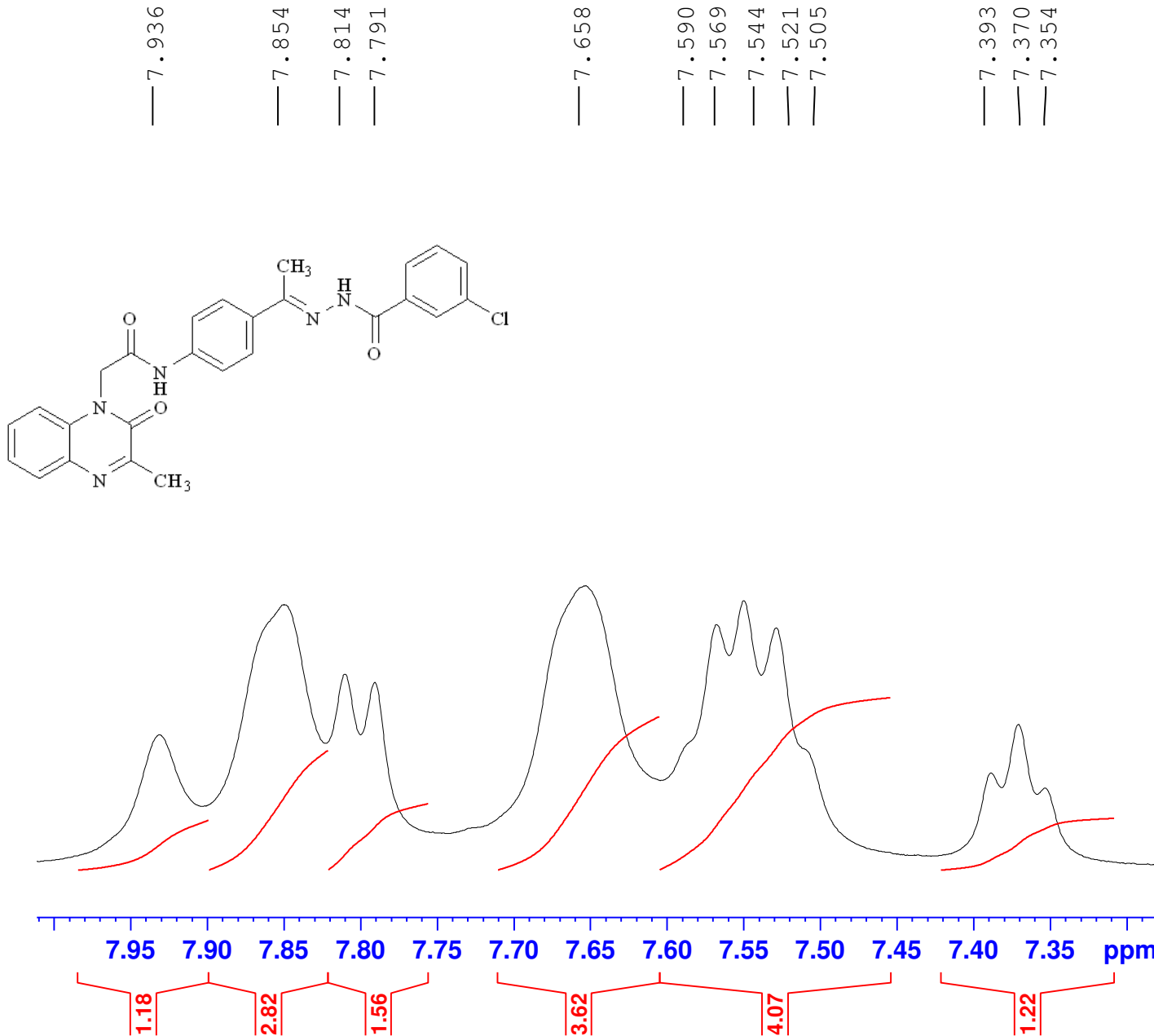


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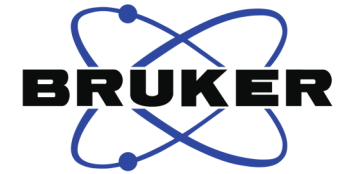
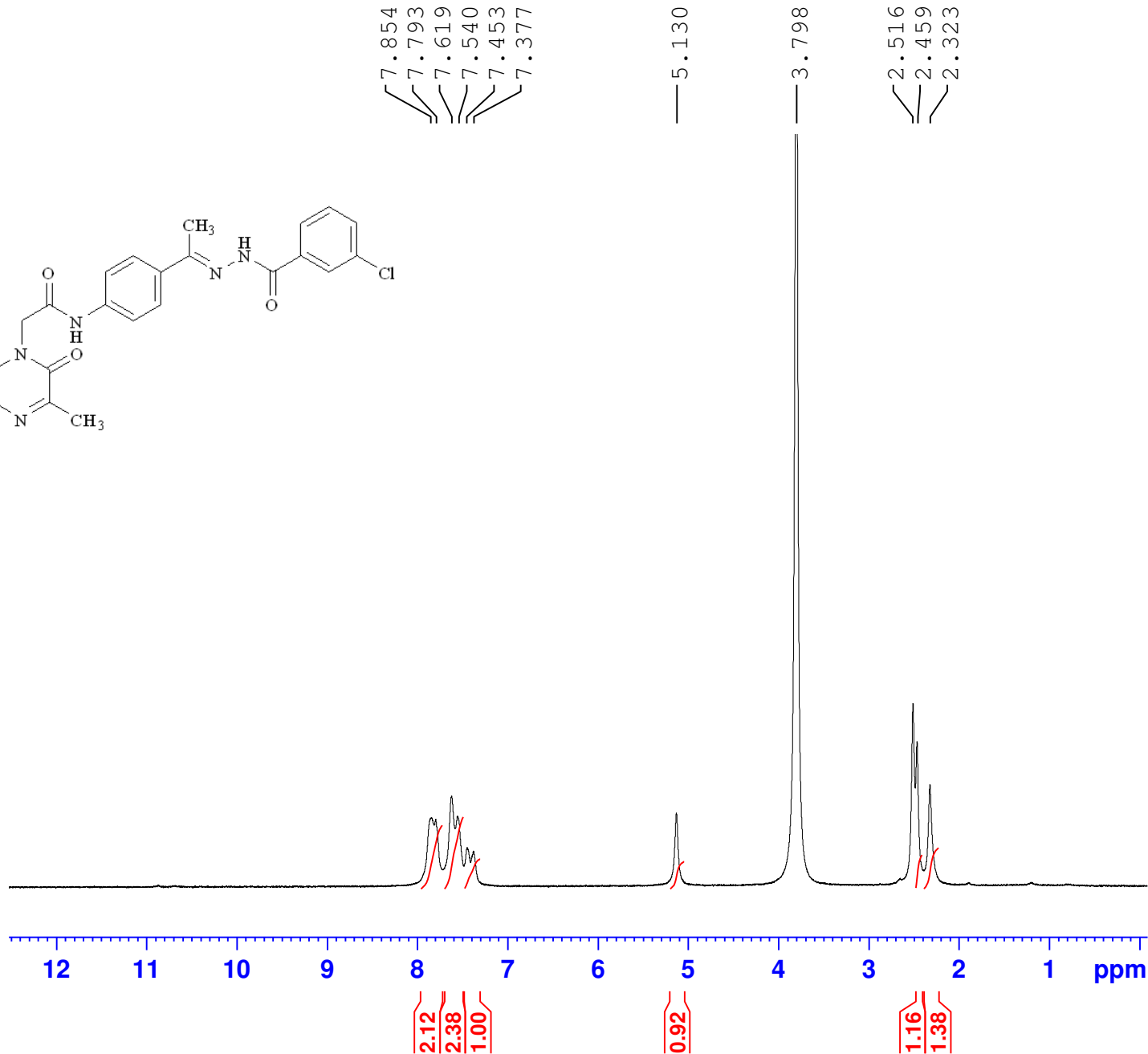
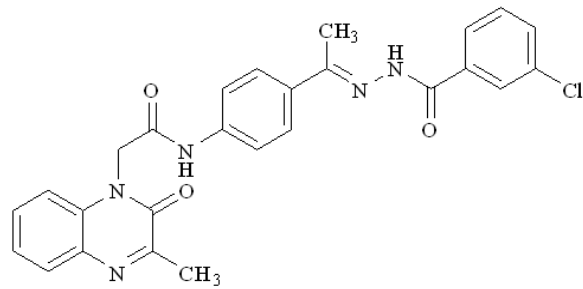
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SOLVENT DMSO
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FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 205.37
DW 62.400 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1

==== CHANNEL f1 =====
SFO1 400.1524711 MHz
NUC1 1H
P1 12.00 usec
PLW1 18.00000000 W

F2 - Processing parameters
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PC 1.00



H¹NMR (D₂O) of compound (11c)



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EXPNO 1
PROCNO 1

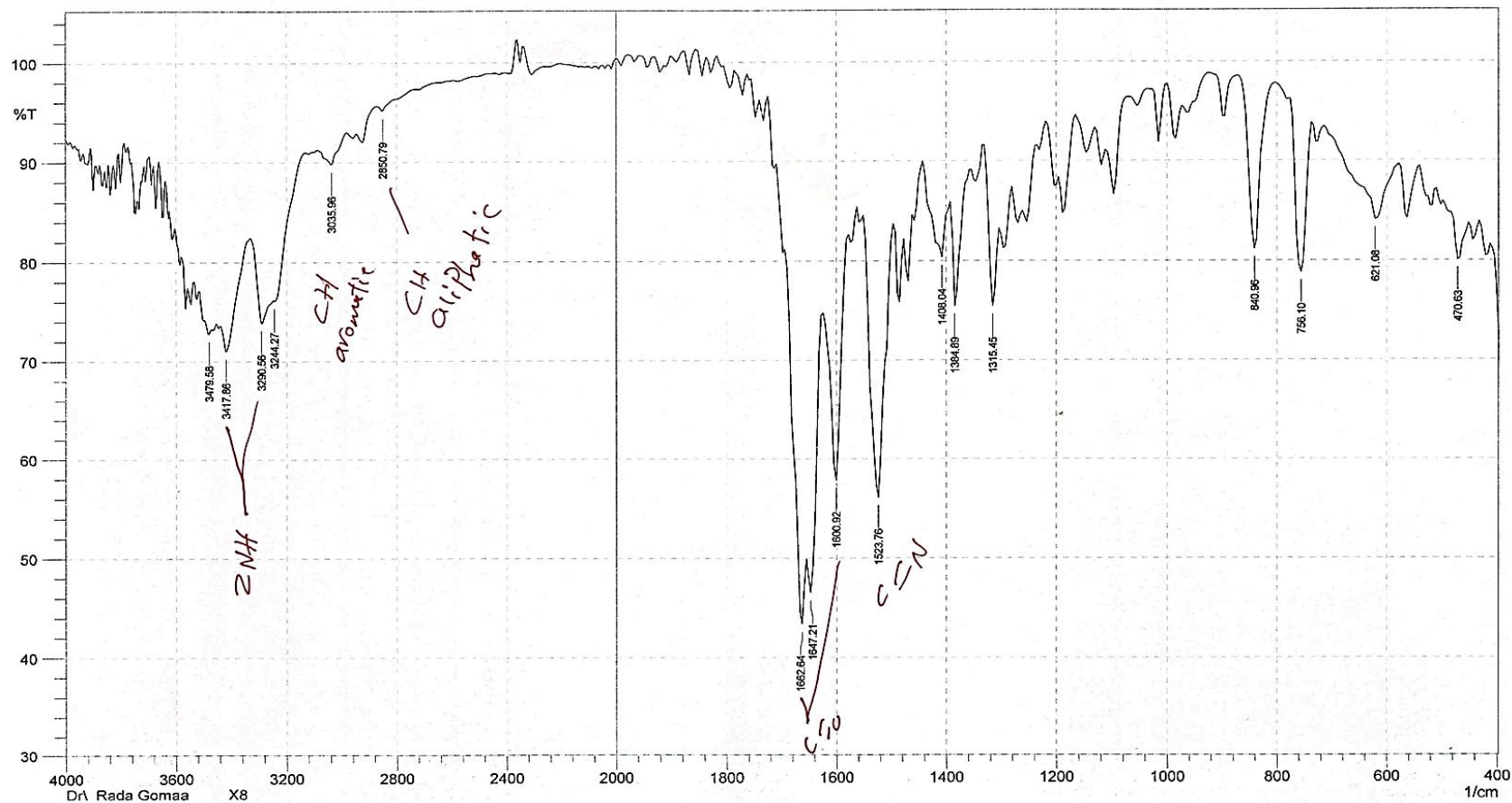
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RG 205.37
DW 62.400 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1

==== CHANNEL f1 =====
SFO1 400.1524711 MHz
NUC1 1H
P1 12.00 usec
PLW1 18.00000000 W

F2 - Processing parameters
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SF 400.1500000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

IR of compound 11d

SHIMADZU



Comment;
Dr\ Rada Gomaa X8

No. of Scans; 8
Resolution; 8 [1/cm]

Date/Time; 11/11/2018 11:22:06 AM
User; usama

H¹NMR of compound (11d)



Current Data Parameters
NAME reda-X8
EXPNO 1
PROCNO 1

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SOLVENT DMSO
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DS 2
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FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 205.37
DW 62.400 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1

==== CHANNEL f1 =====
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NUC1 1H
P1 12.00 usec
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PC 1.00

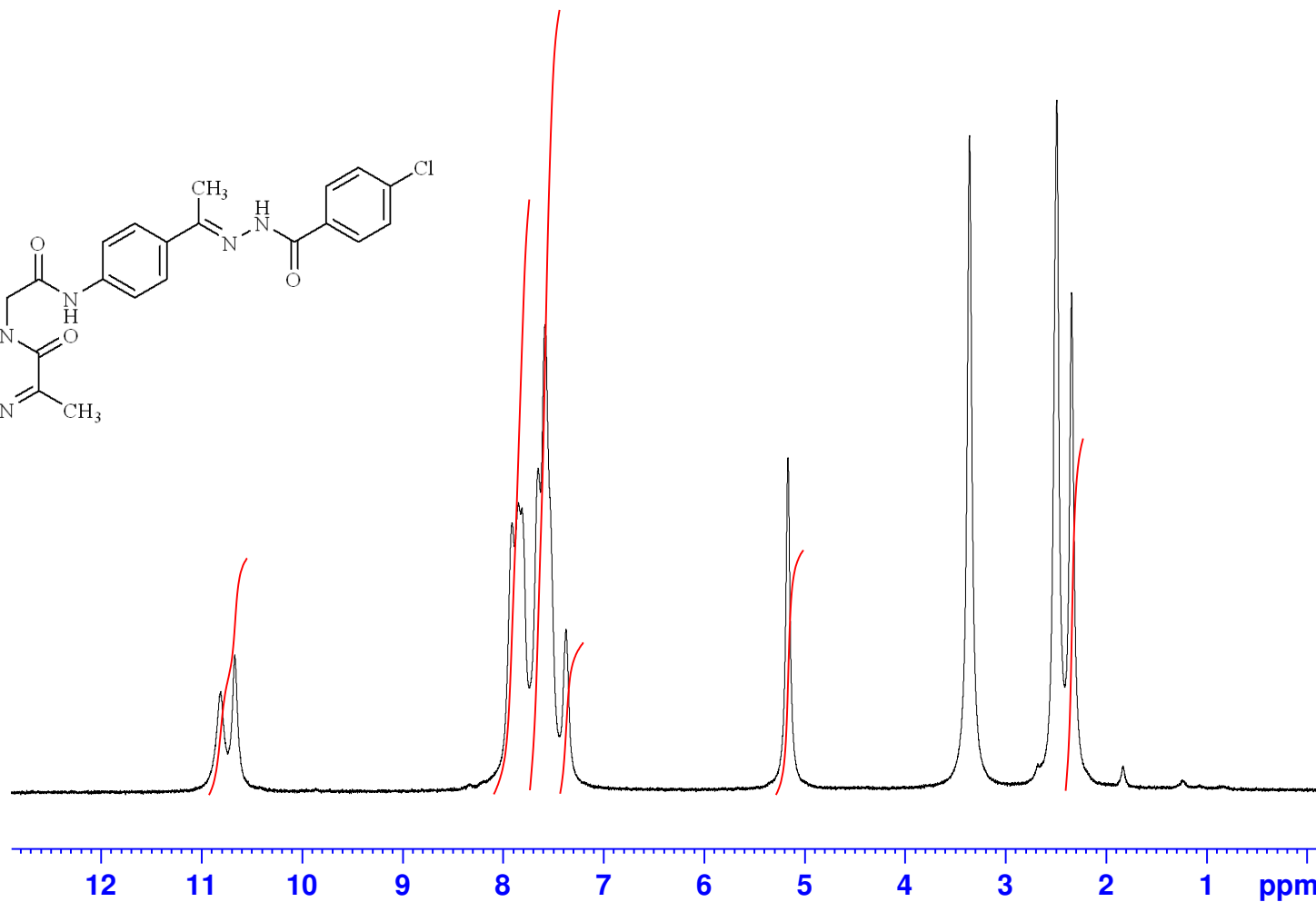
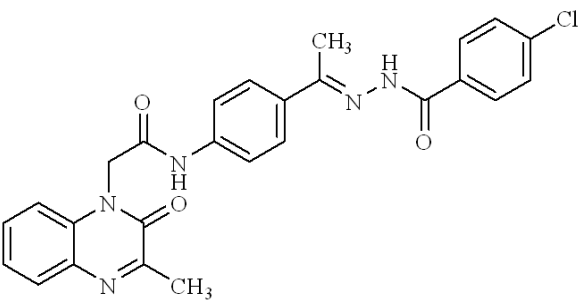
10.807
10.667

7.915
7.846
7.801
7.650
7.576
7.361

5.205

3.352

2.483
2.357



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

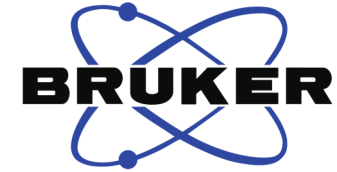
1.00

2.52
3.32
0.65

1.04

1.51

H¹NMR of compound (11e)

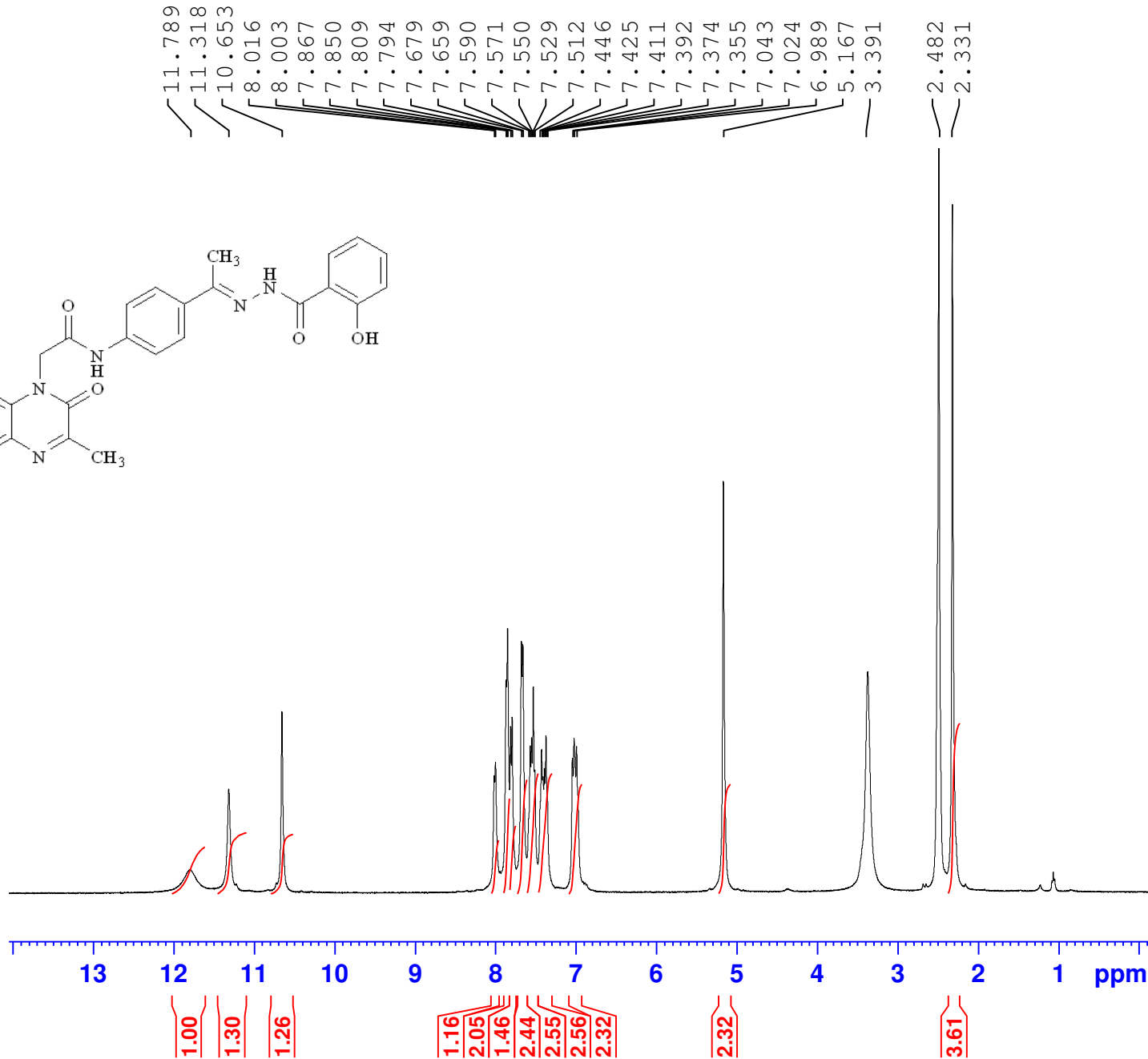
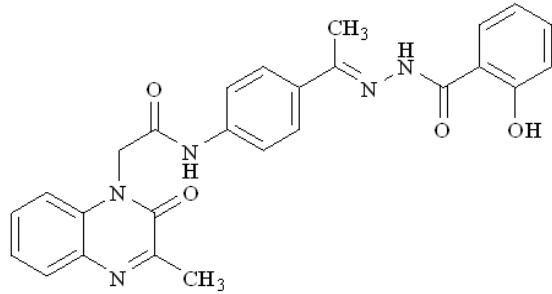


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 SOLVENT DMSO
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 FIDRES 0.122266 Hz
 AQ 4.0894465 sec
 RG 205.37
 DW 62.400 usec
 DE 6.50 usec
 TE 298.0 K
 D1 1.00000000 sec
 TD0 1

==== CHANNEL f1 =====
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 NUC1 1H
 P1 12.00 usec
 PLW1 18.00000000 W

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^1H NMR of compound (11e)

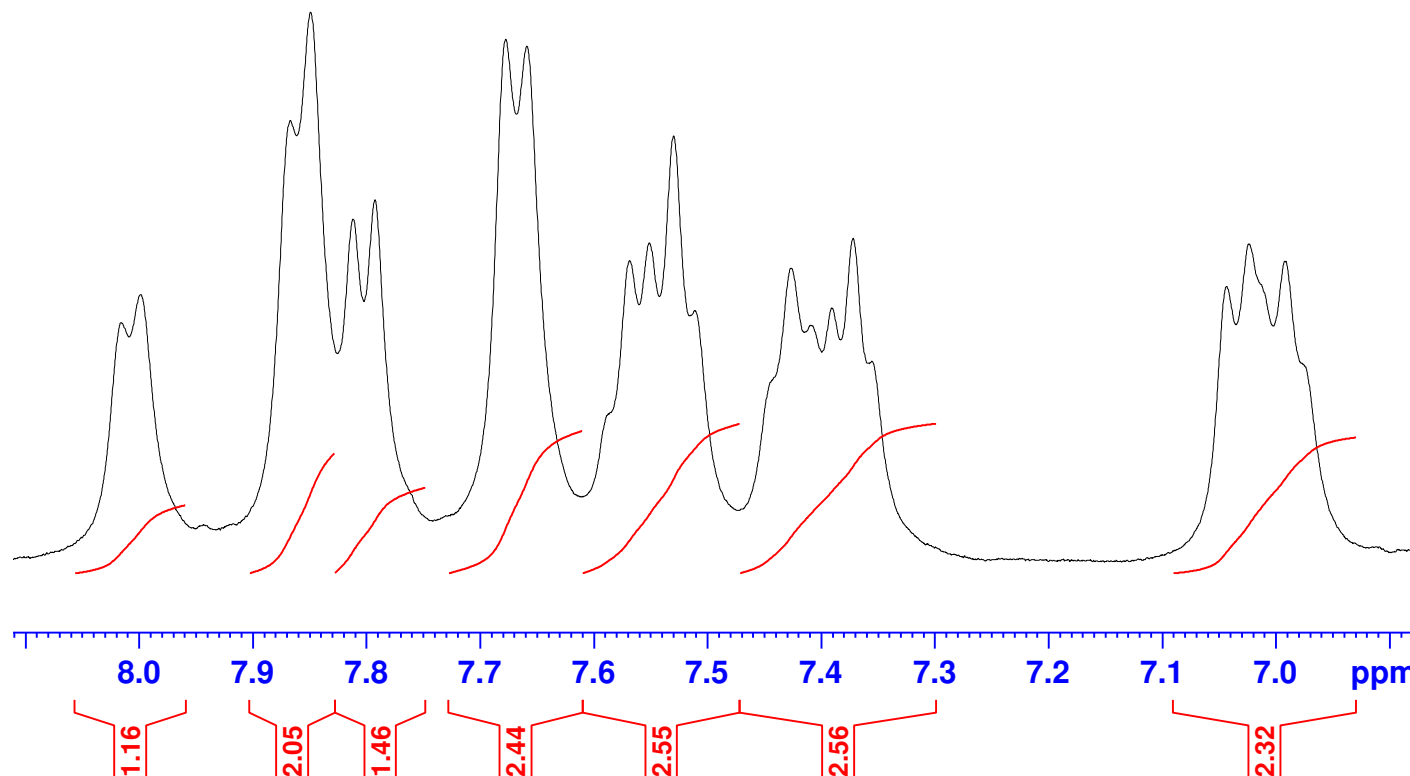
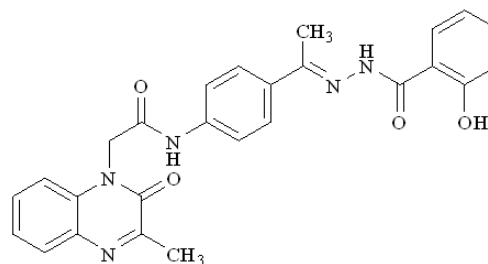


8.016
8.003

7.867
7.850
7.809
7.794

7.679
7.659
7.590
7.571
7.550
7.529
7.512
7.446
7.425
7.411
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7.374
7.355

7.043
7.024
6.989



Current Data Parameters
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EXPNO 1
PROCNO 1

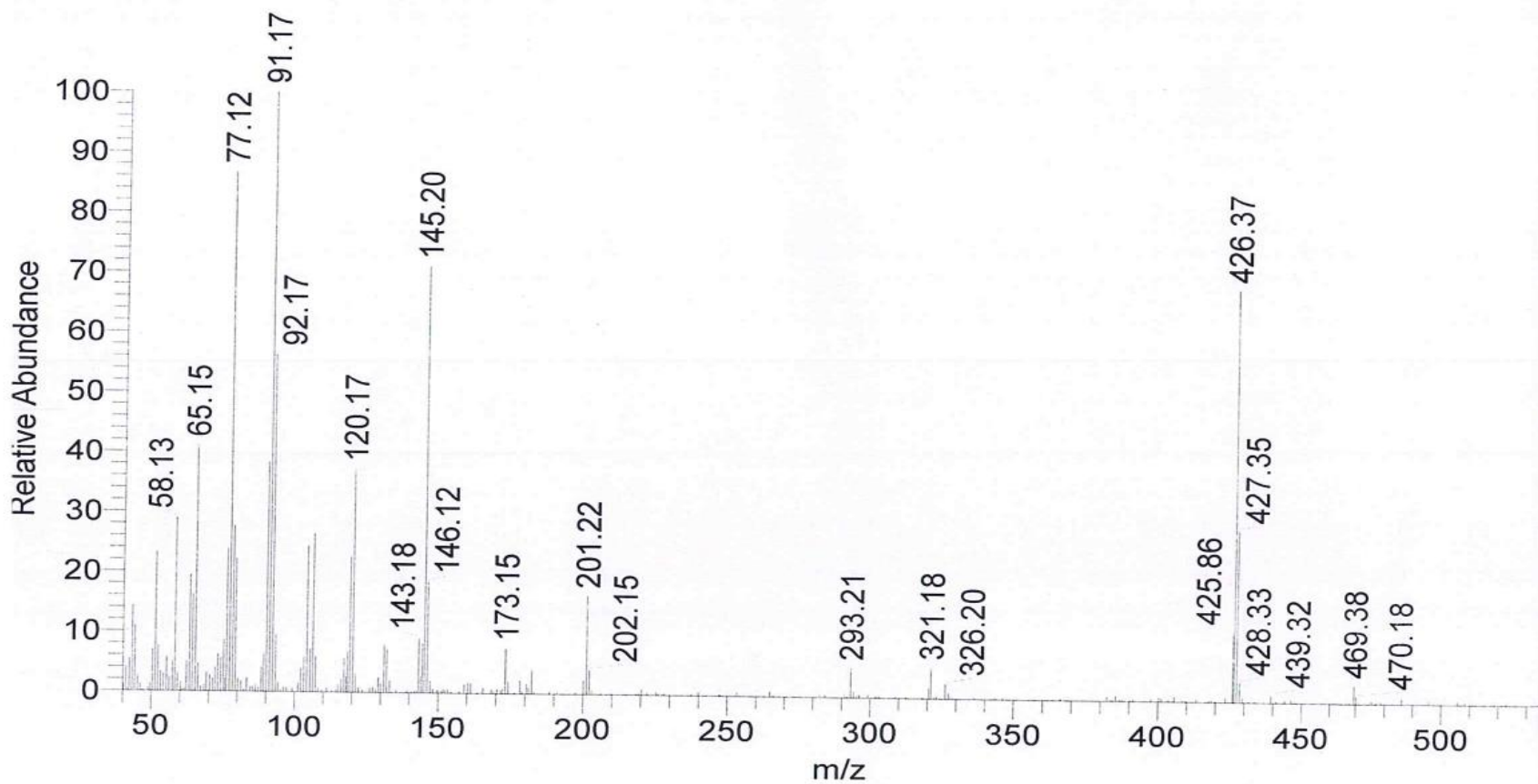
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SOLVENT DMSO
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DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 205.37
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1

==== CHANNEL f1 =====
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NUC1 1H
P1 12.00 usec
PLW1 18.00000000 W

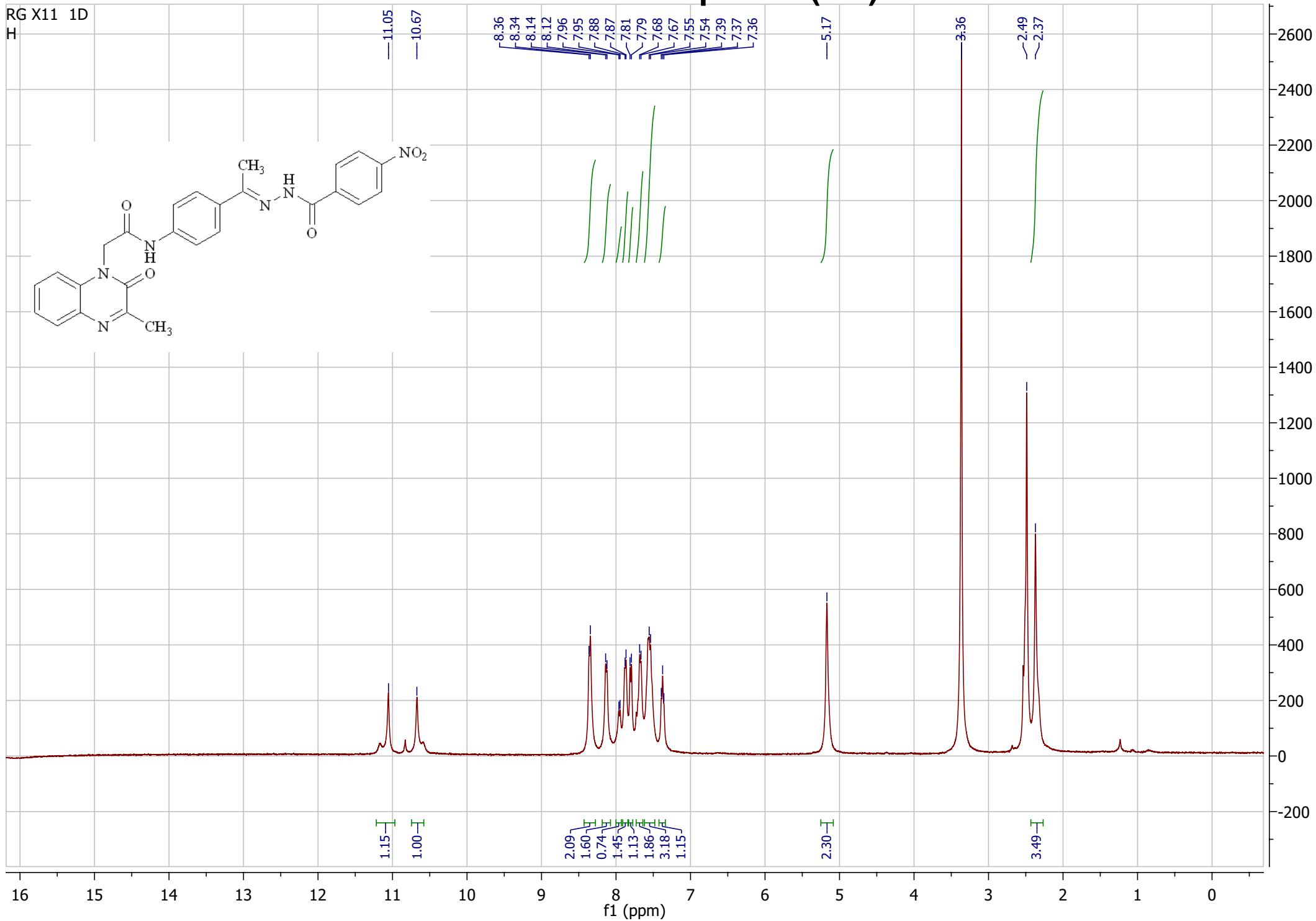
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Mass spec. of compound 11e

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: {0,0} + c EI Full ms [40.00-1000.00]

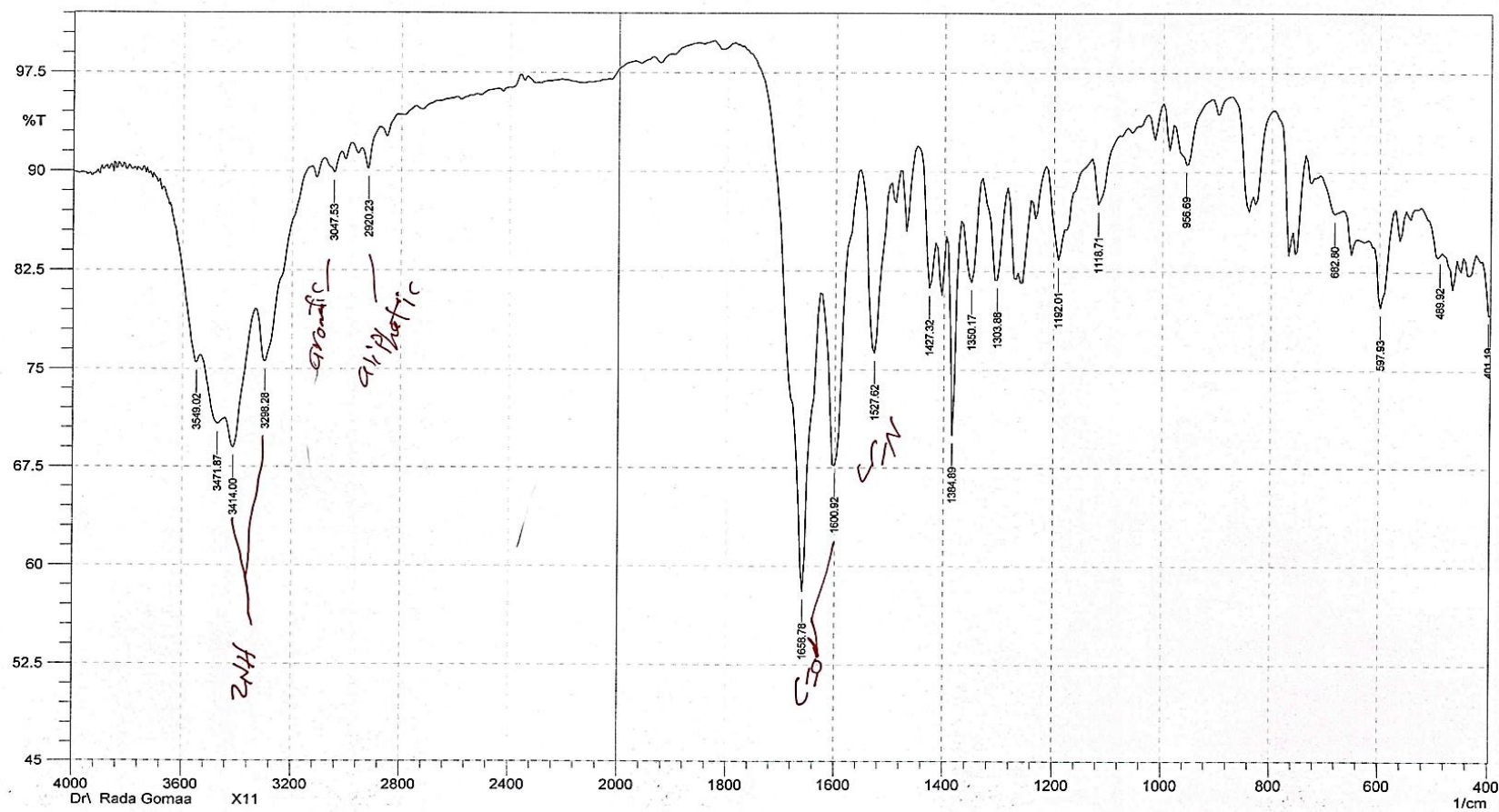


H¹NMR of compound (11f)



IR of compound 11f

SHIMADZU



Comment;

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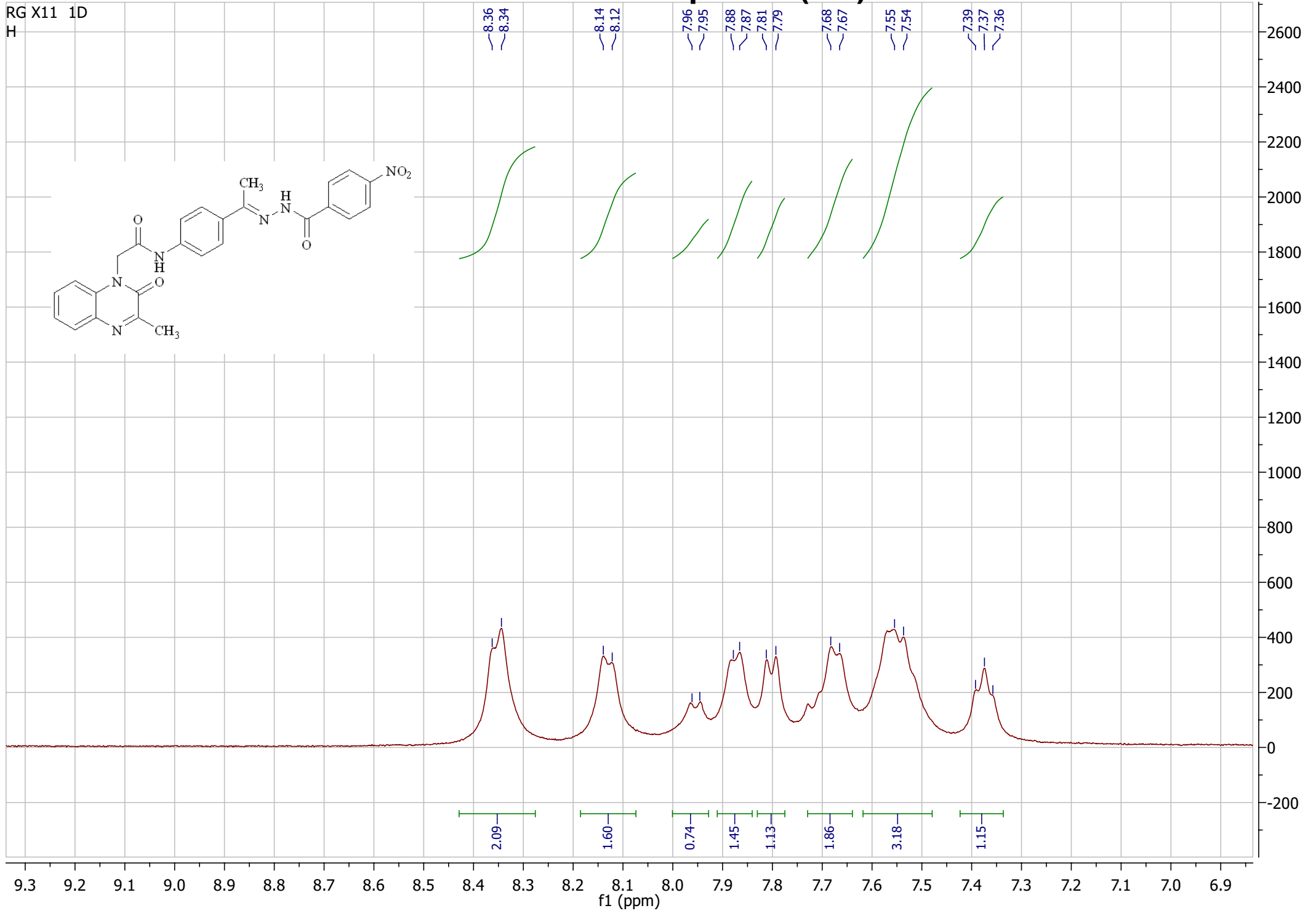
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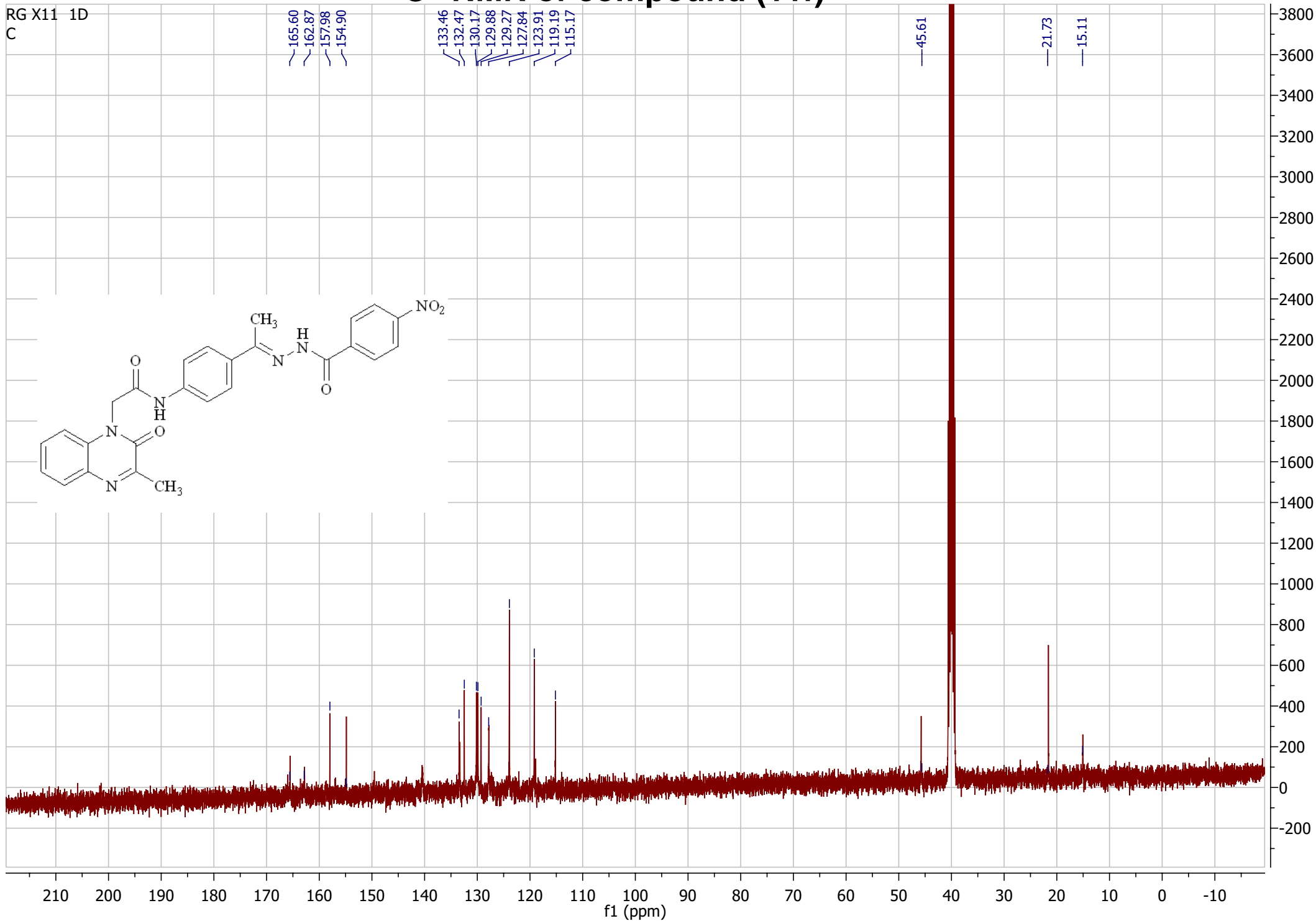
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User; usama

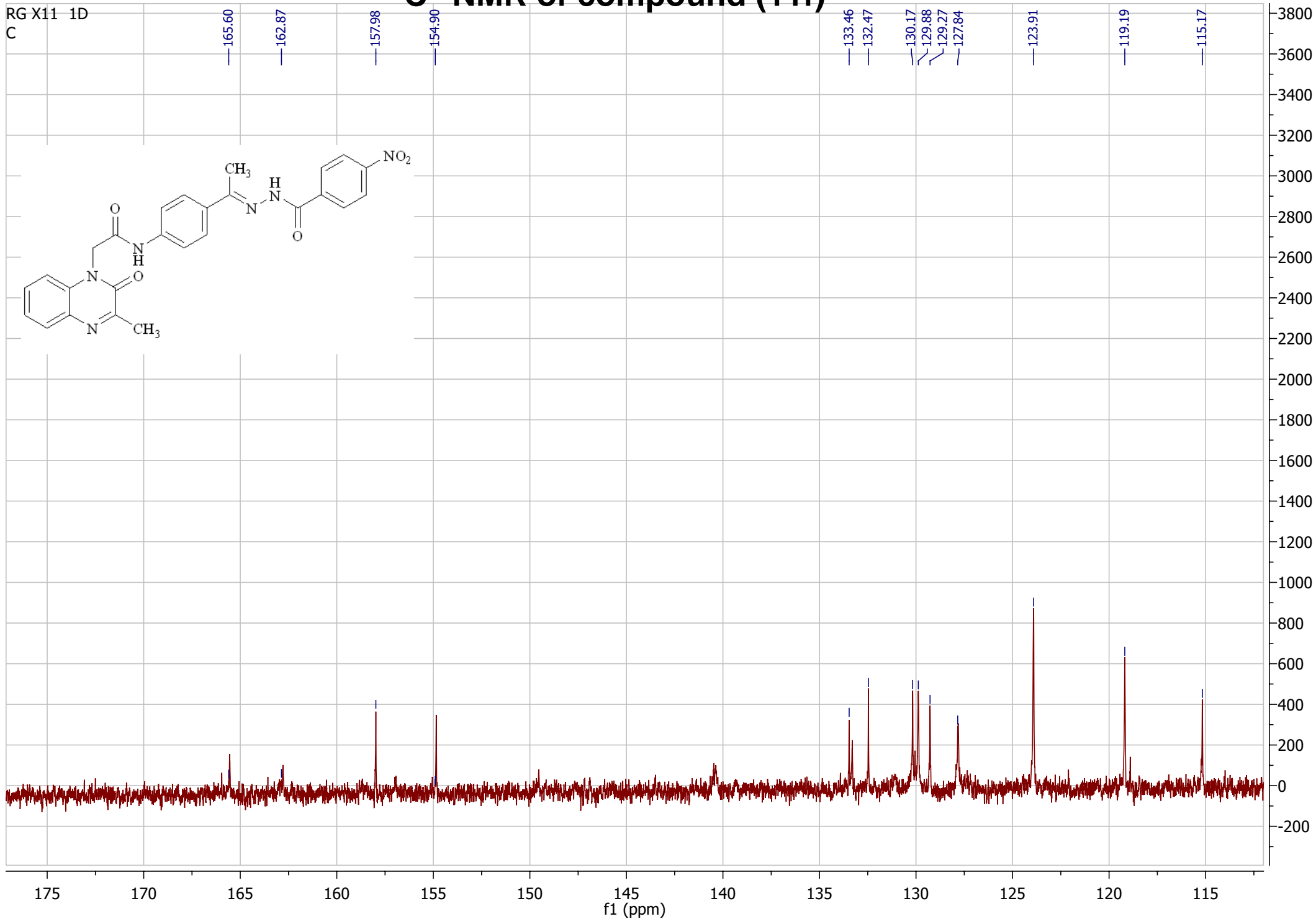
H¹NMR of compound (11f)



C¹³NMR of compound (11f)



C¹³NMR of compound (11f)



Dept135 NMR of compound (11f)

RG X11 1D
DEPT135

130.17
129.87
129.27
127.82
123.91

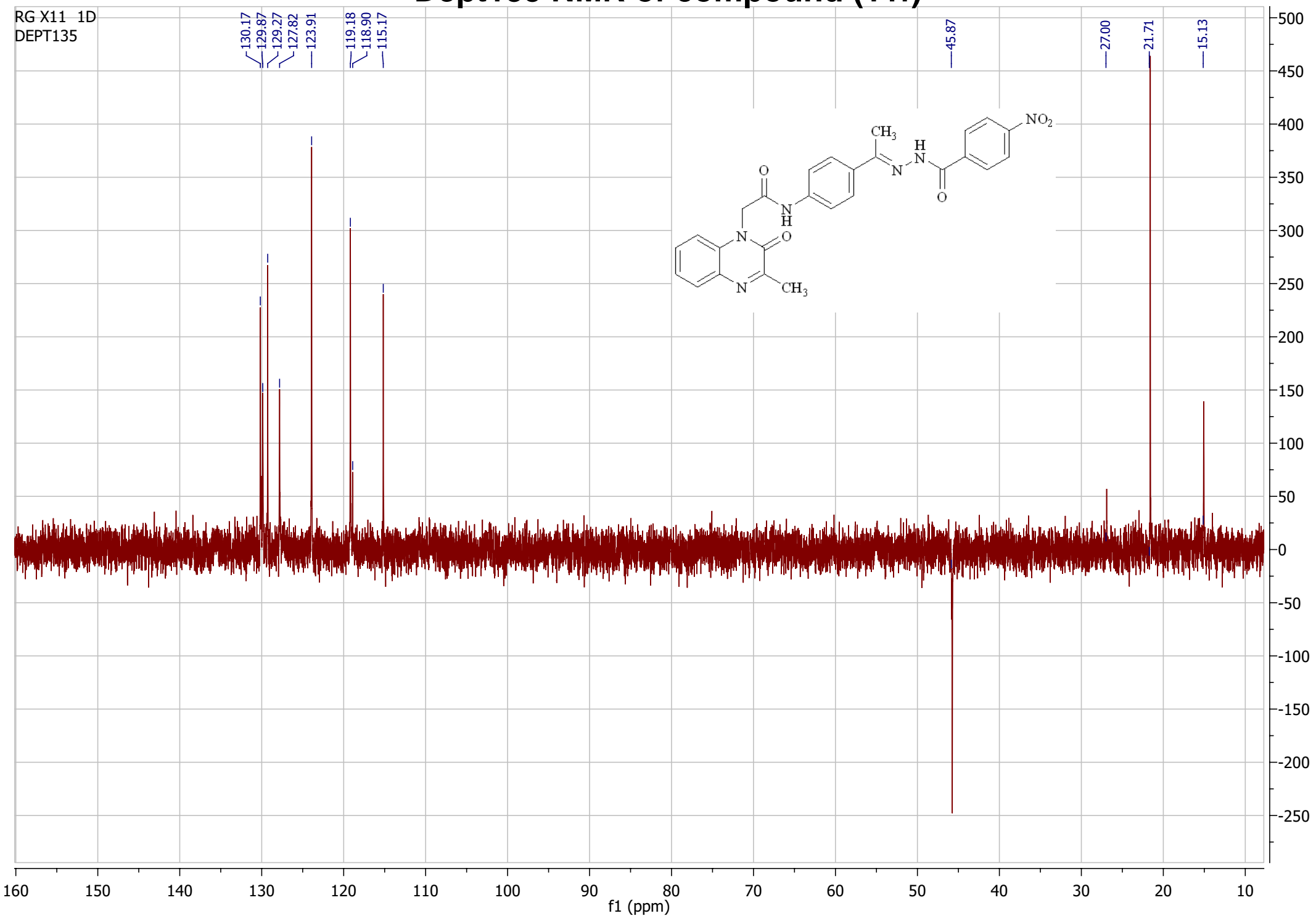
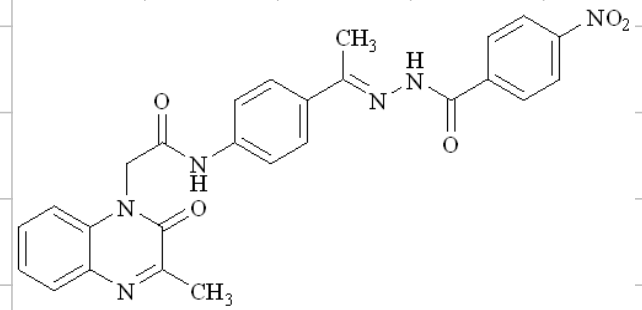
119.18
118.90
115.17

45.87

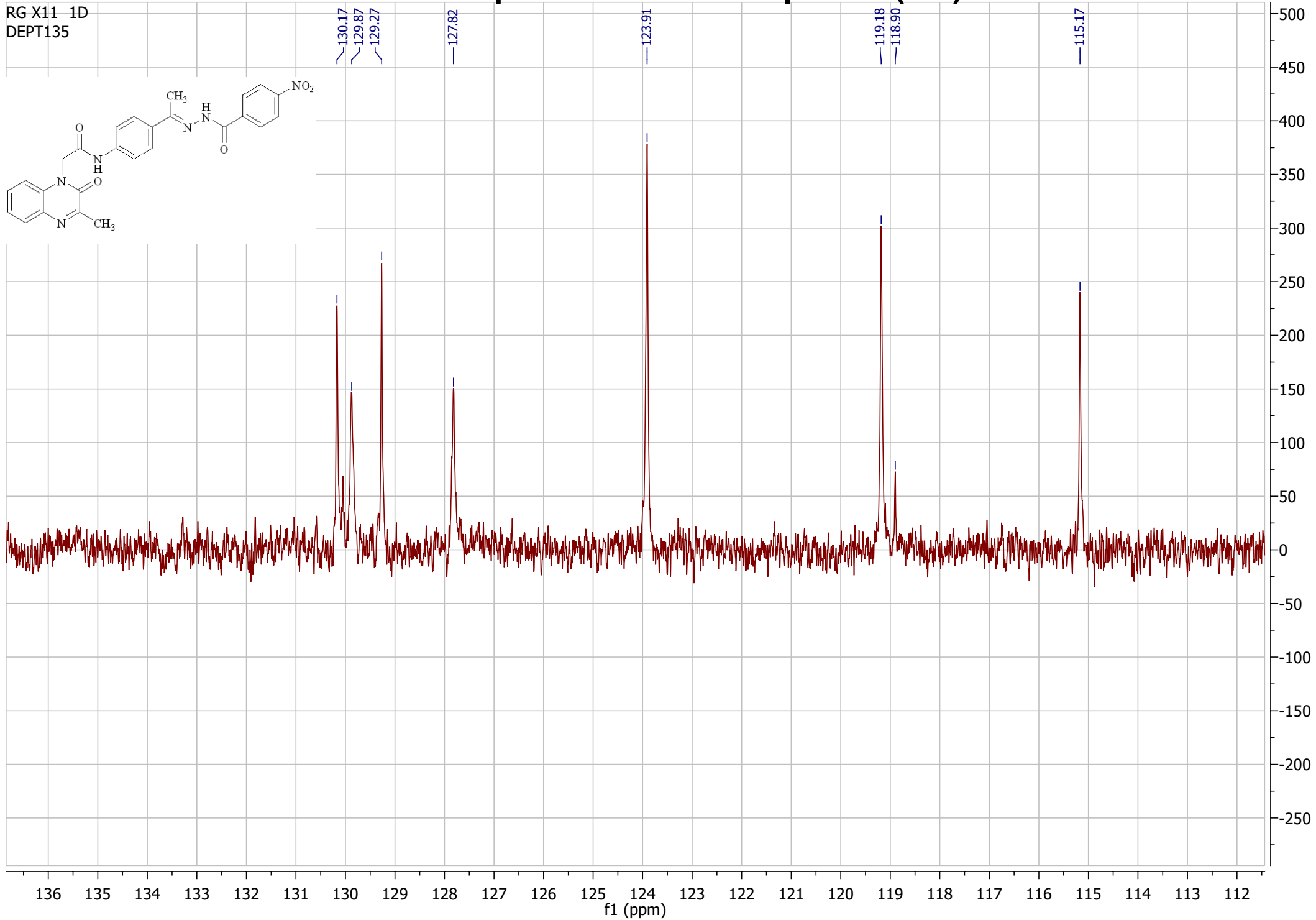
27.00

21.71

15.13

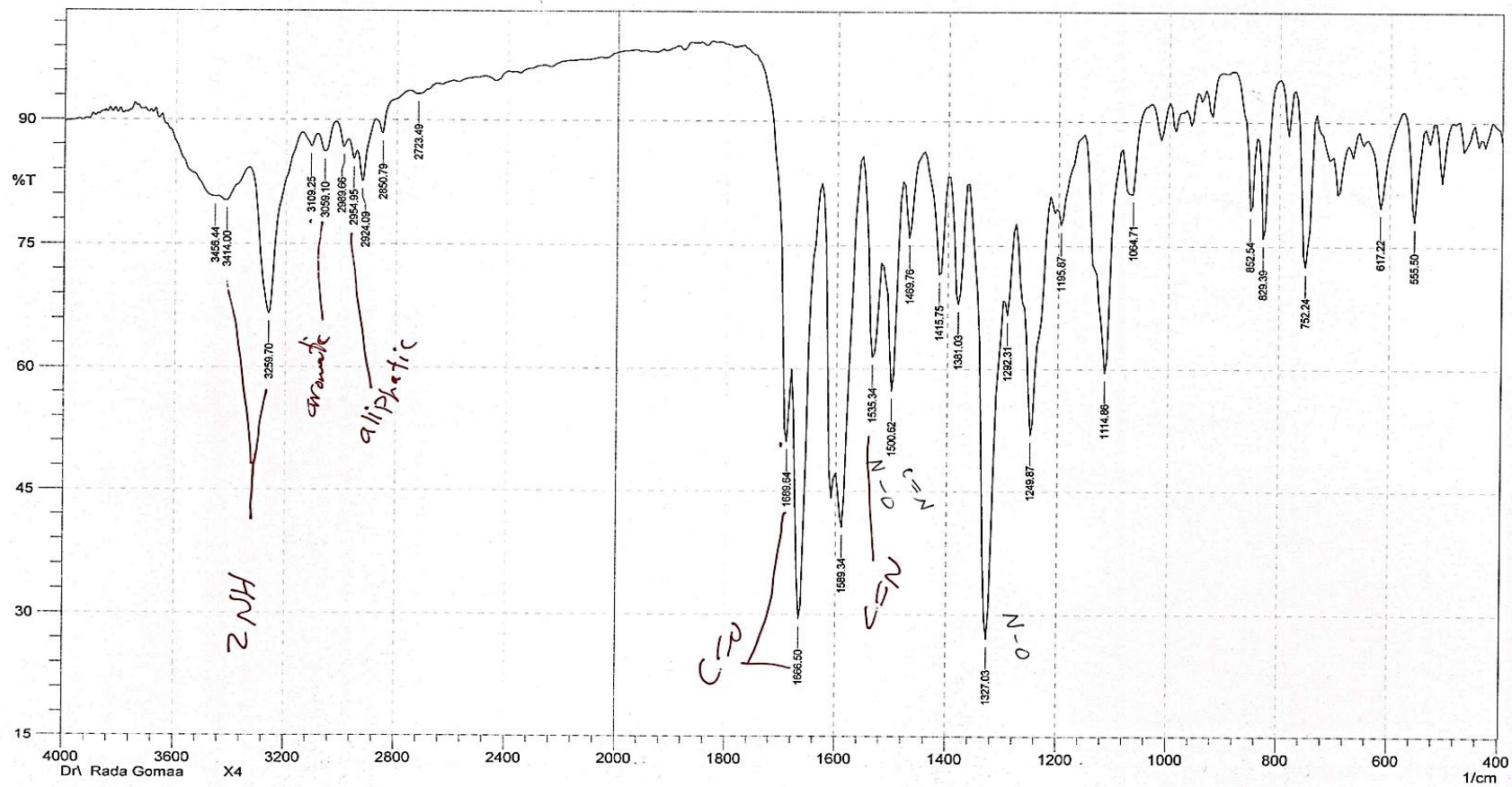


Dept135 NMR of compound (11f)



IR of compound 11g

SHIMADZU



Comment;

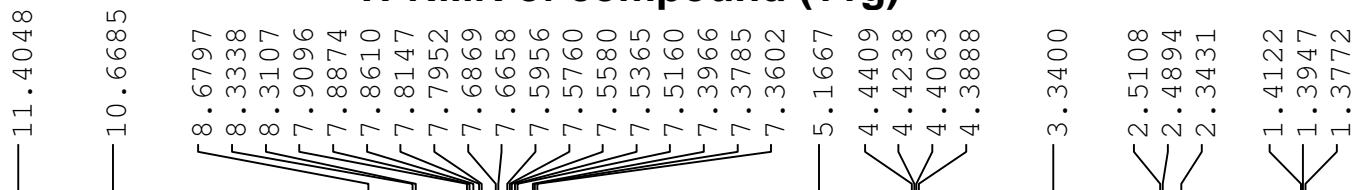
Dr\ Rada Gomaa X4

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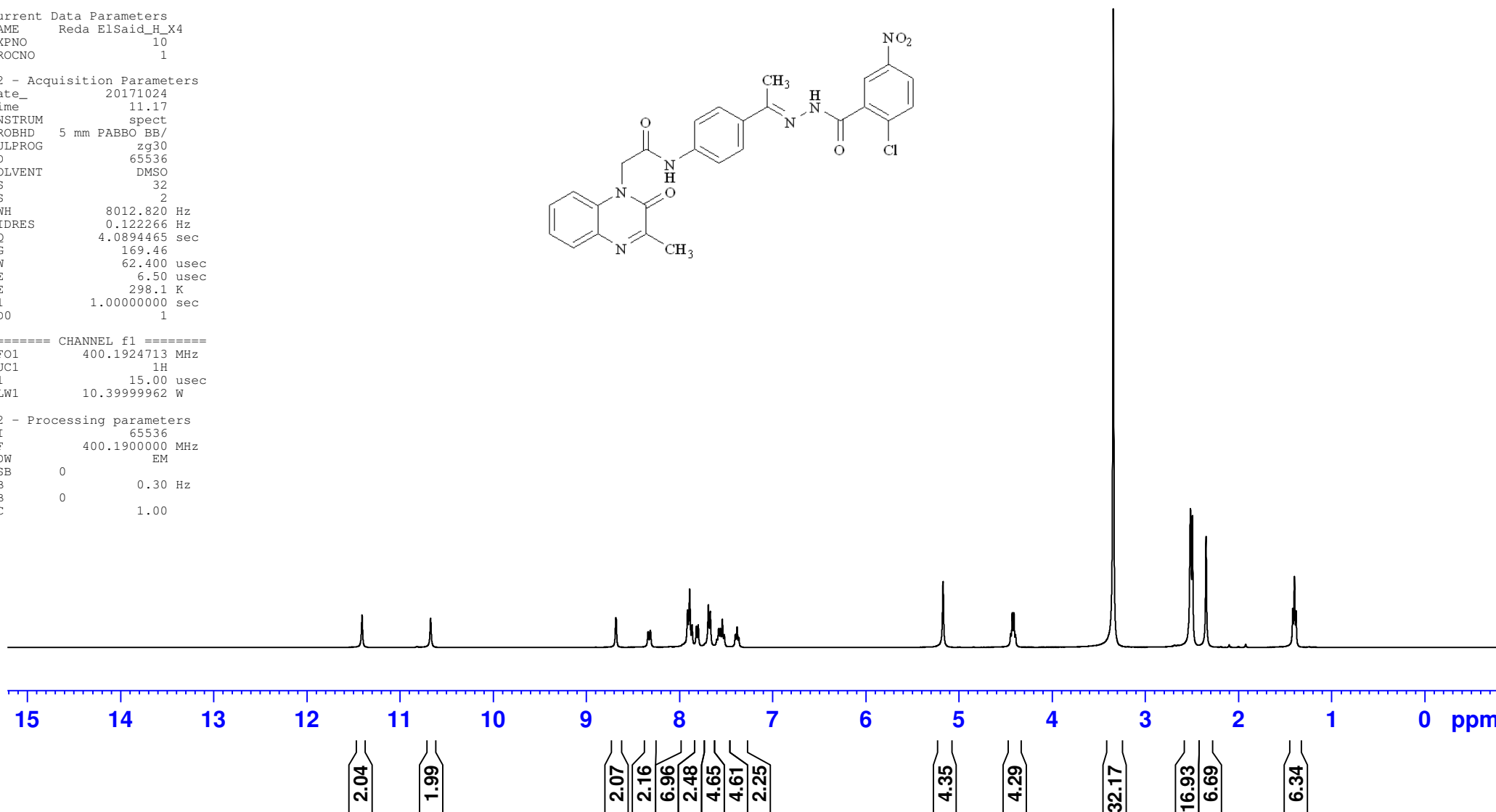
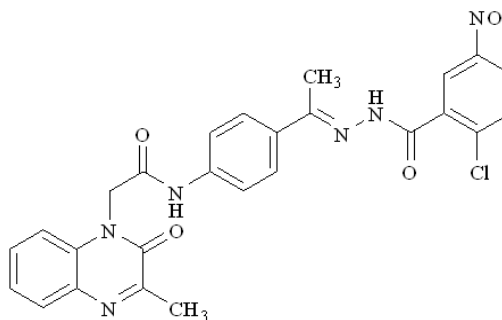
H¹NMR of compound (11g)

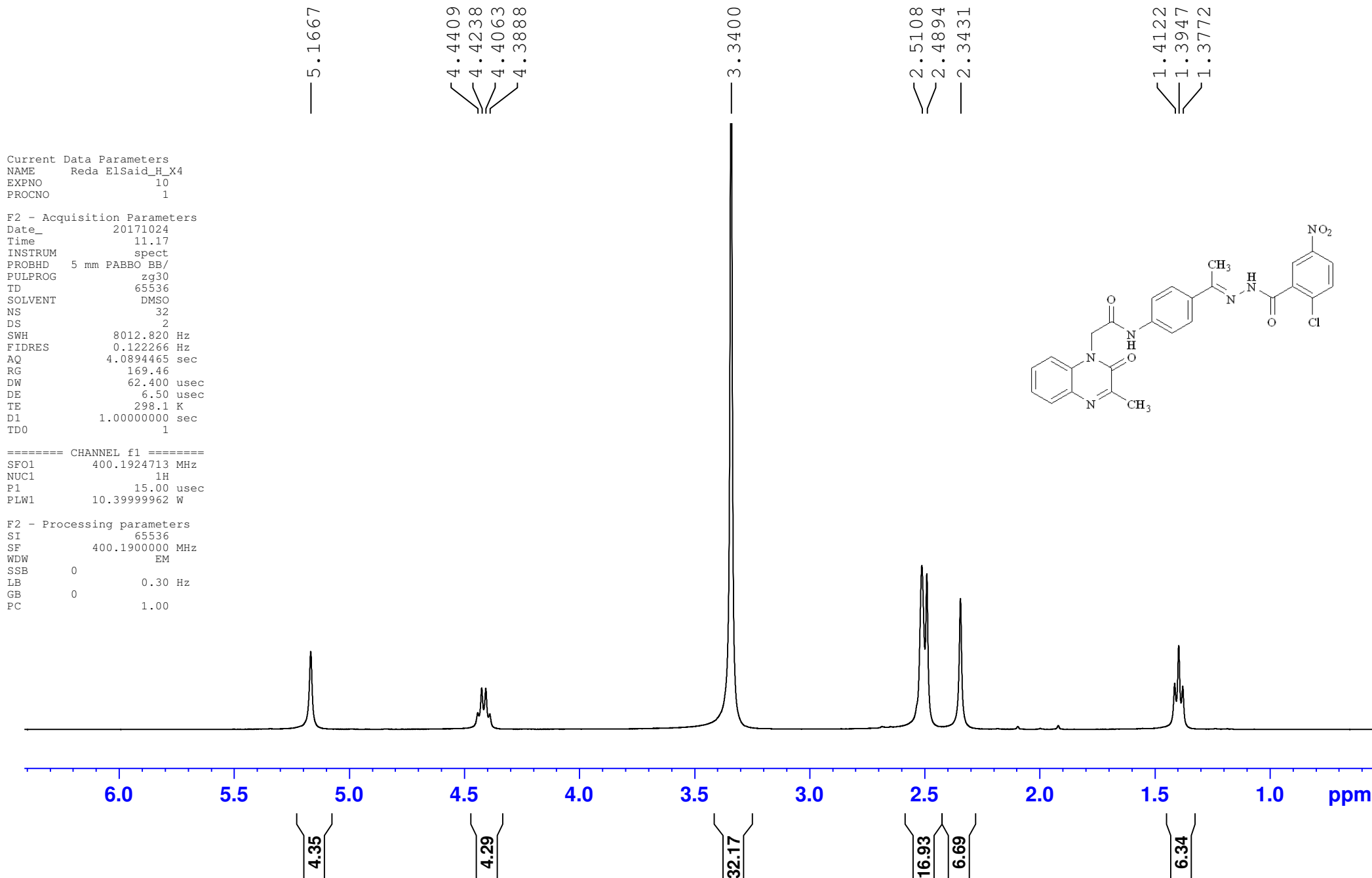
Current Data Parameters
NAME Reda ElSaid_H_X4
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20171024
Time 11.17
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 169.46
DW 62.400 usec
DE 6.50 usec
TE 298.1 K
D1 1.0000000 sec
TD0 1

===== CHANNEL f1 =====
SFO1 400.1924713 MHz
NUC1 1H
P1 15.00 usec
PLW1 10.39999962 W

F2 - Processing parameters
SI 65536
SF 400.1900000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



H¹NMR of compound (11g)

H¹NMR of compound (11g)

— 11.4048

— 10.6685

— 8.6797

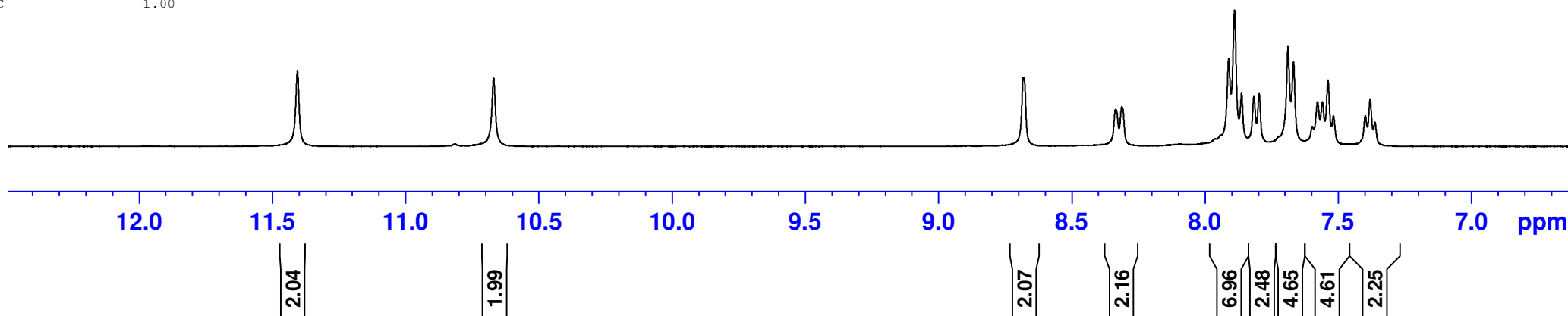
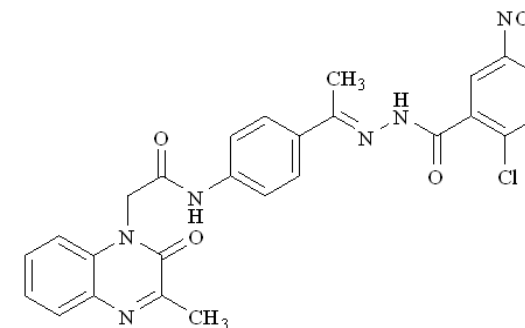
 8.3338
 8.3107
 7.9096
 7.8874
 7.8610
 7.8147
 7.7952
 7.6869
 7.6658
 7.5956
 7.5760
 7.5580
 7.5365
 7.5160
 7.3966
 7.3785
 7.3602

Current Data Parameters
 NAME Reda ElSaid_H_X4
 EXPNO 10
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20171024
 Time 11.17
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zg30
 TD 65536
 SOLVENT DMSO
 NS 32
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.122266 Hz
 AQ 4.0894465 sec
 RG 169.46
 DW 62.400 usec
 DE 6.50 usec
 TE 298.1 K
 D1 1.0000000 sec
 TD0 1

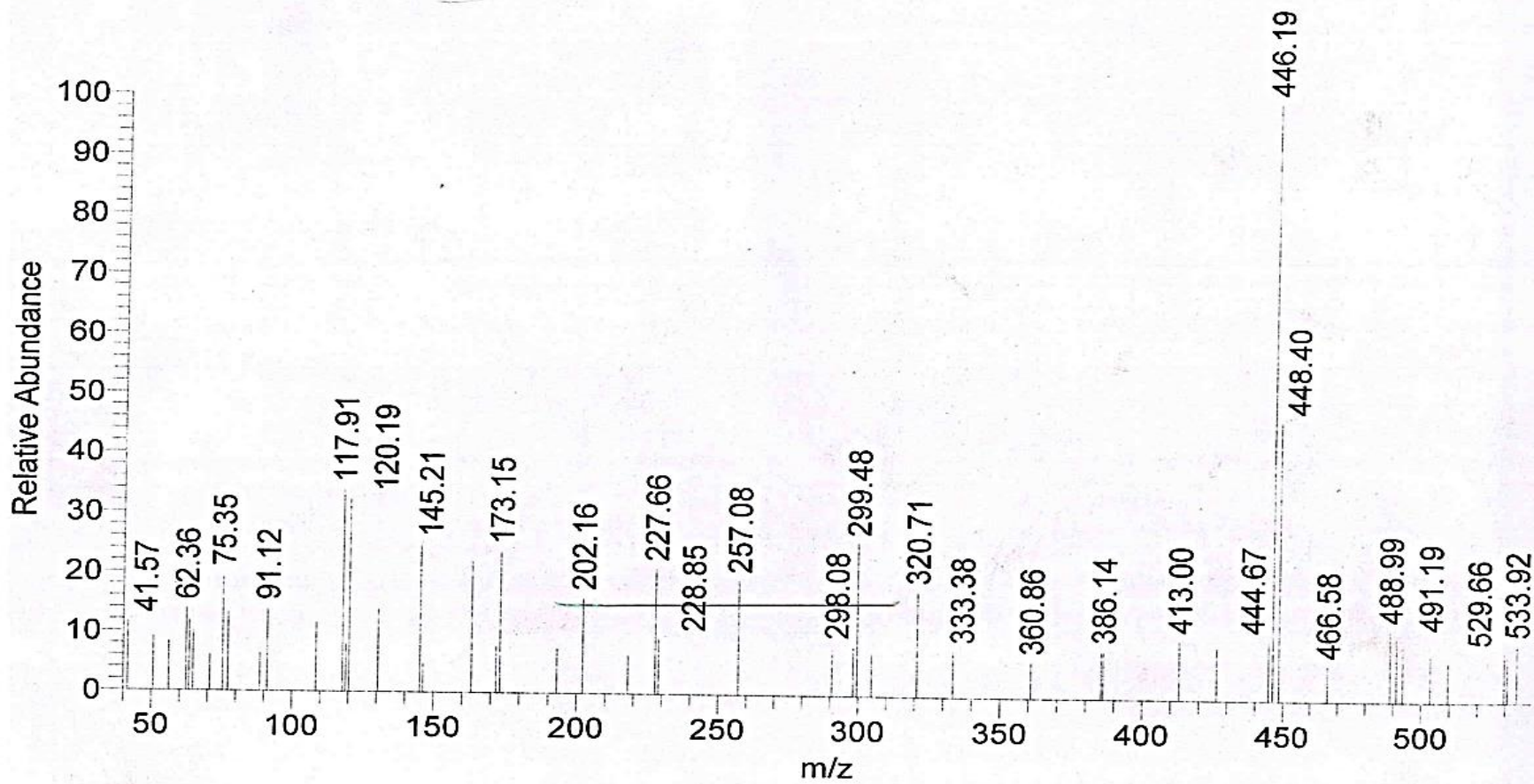
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 SFO1 400.1924713 MHz
 NUC1 1H
 P1 15.00 usec
 PLW1 10.39999962 W

F2 - Processing parameters
 SI 65536
 SF 400.1900000 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00



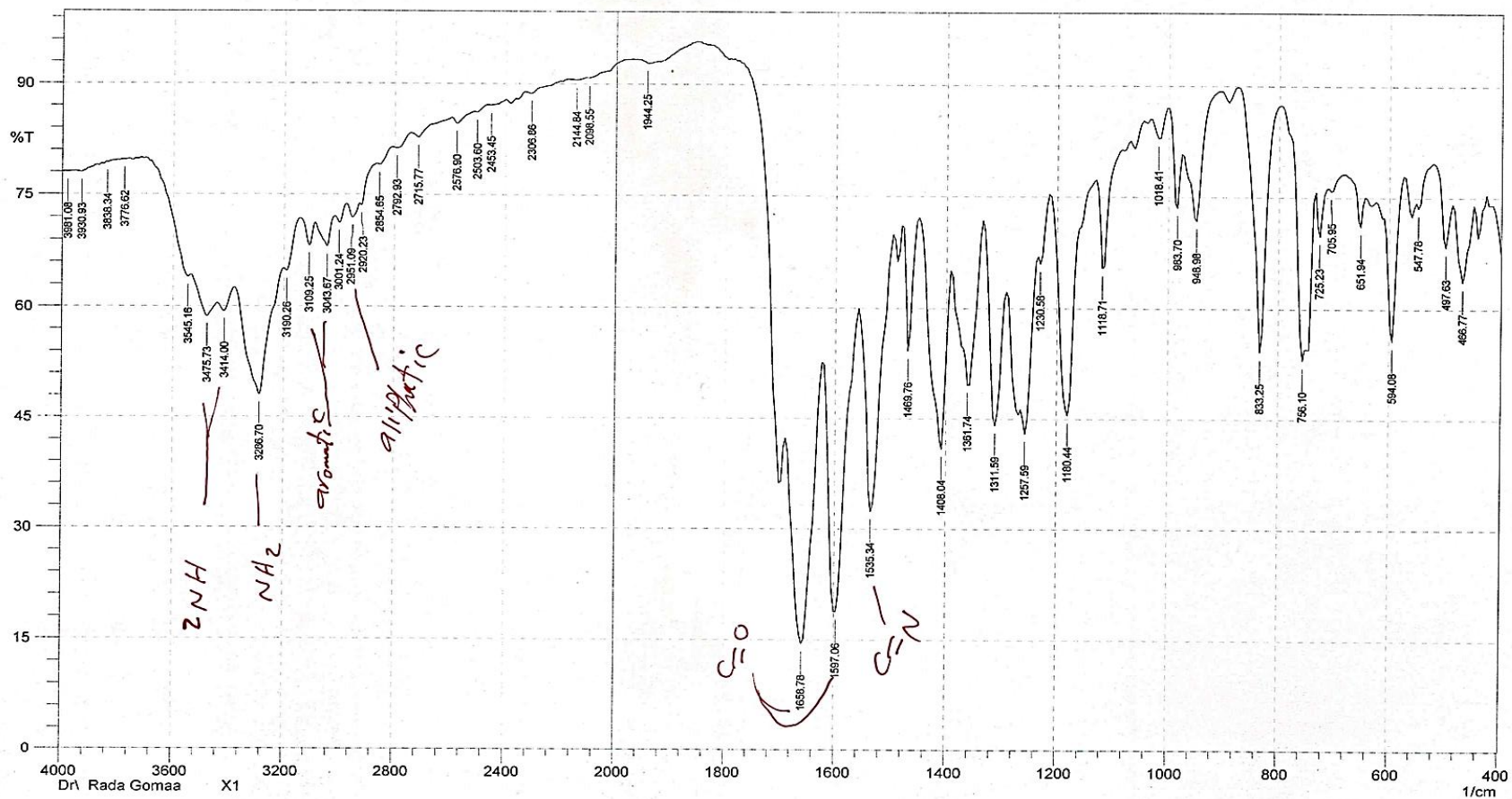
Mass spec. of compound 11g

reda-alsyed-gomaa-rg-x4 #287 RT: 4.82 AV: 1 NL: 1.25E3
T: {0,0} + c EI Full ms [40.00-1000.00]



IR of compound 12

SHIMADZU



Comment;

Dr Rada Gomaa X1

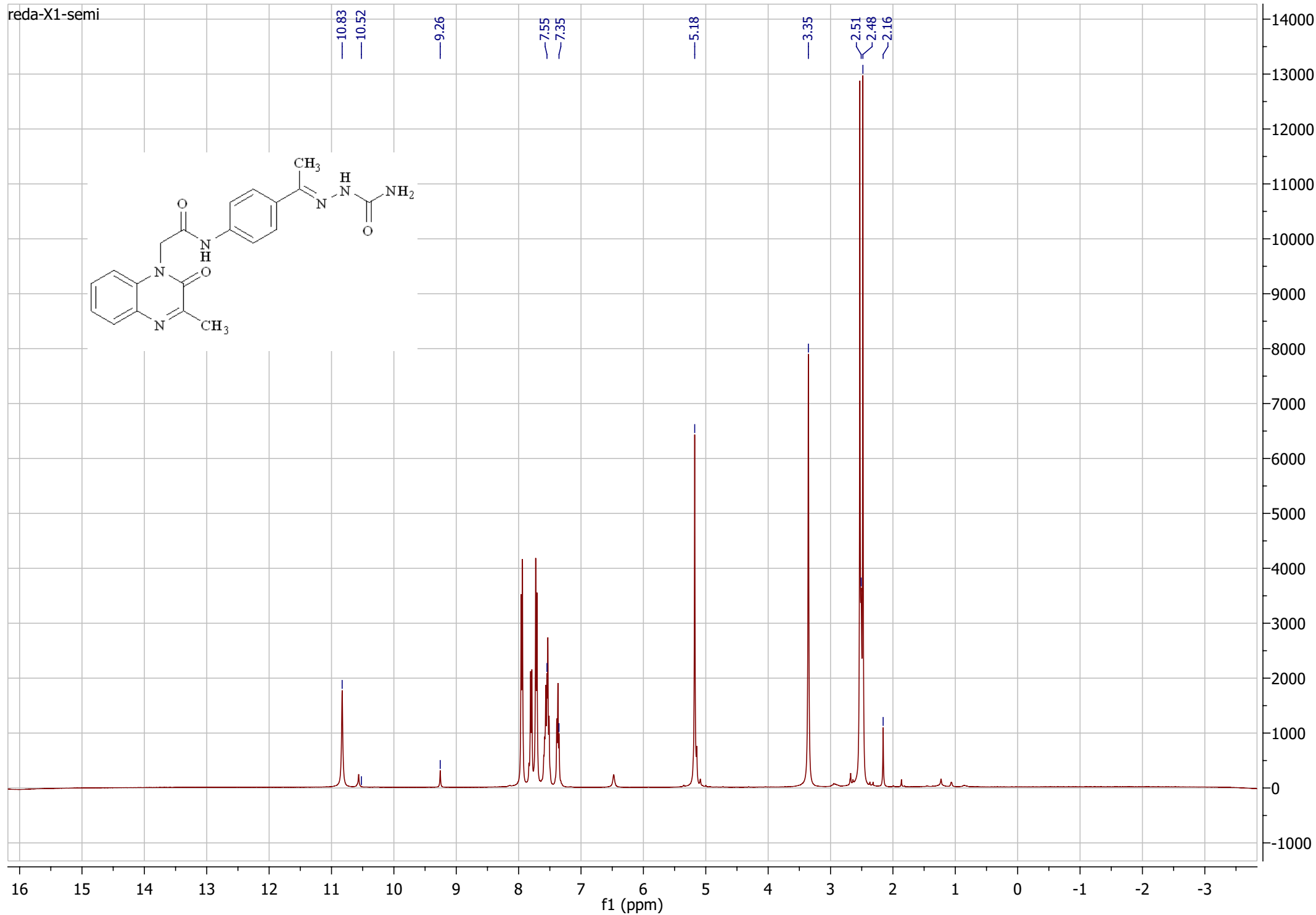
No. of Scans; 8

Resolution; 8 [1/cm]

Date/Time; 11/11/2018 11:38:35 AM

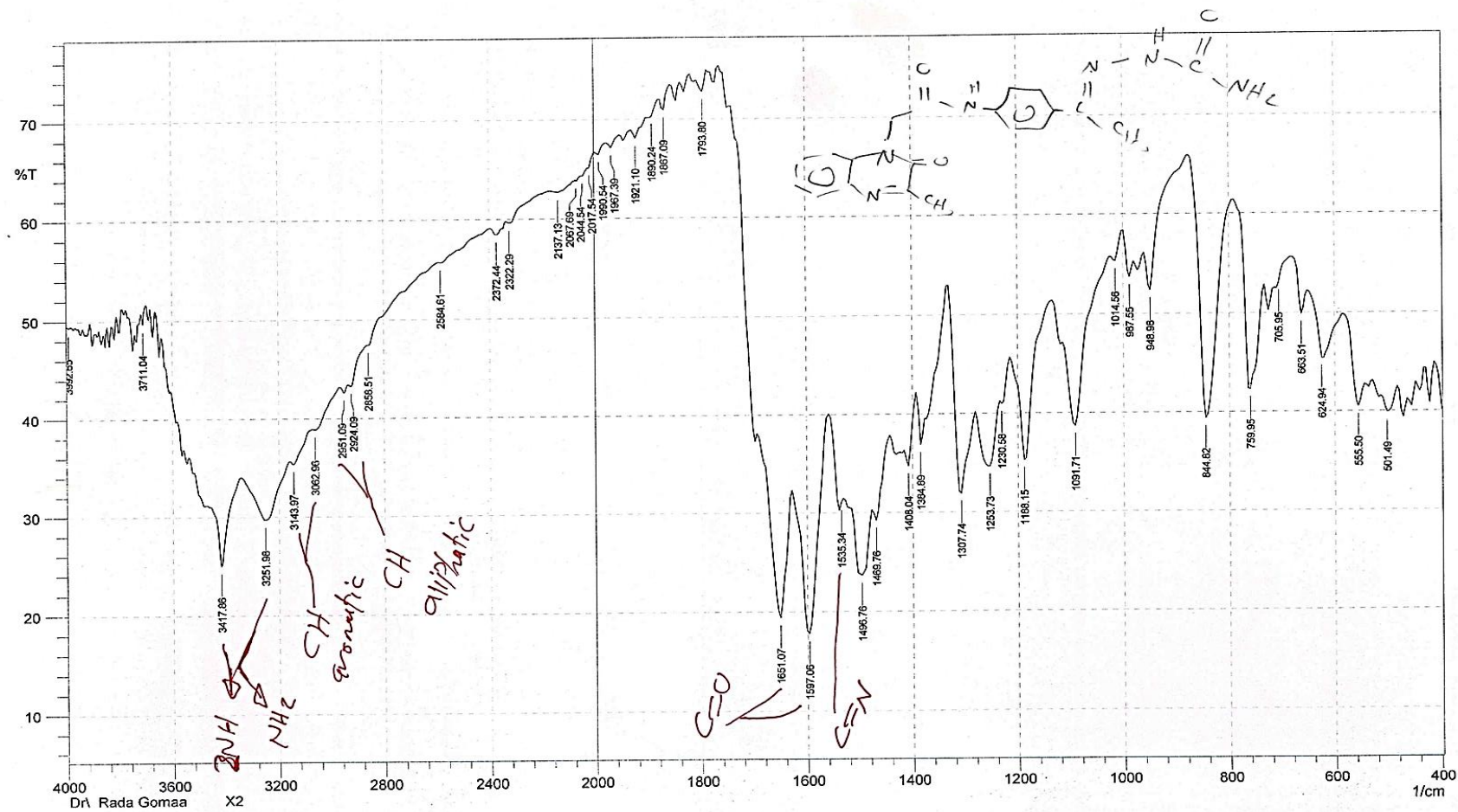
User; usama

^1H NMR of compound (12)



IR of compound 13

SHIMADZU



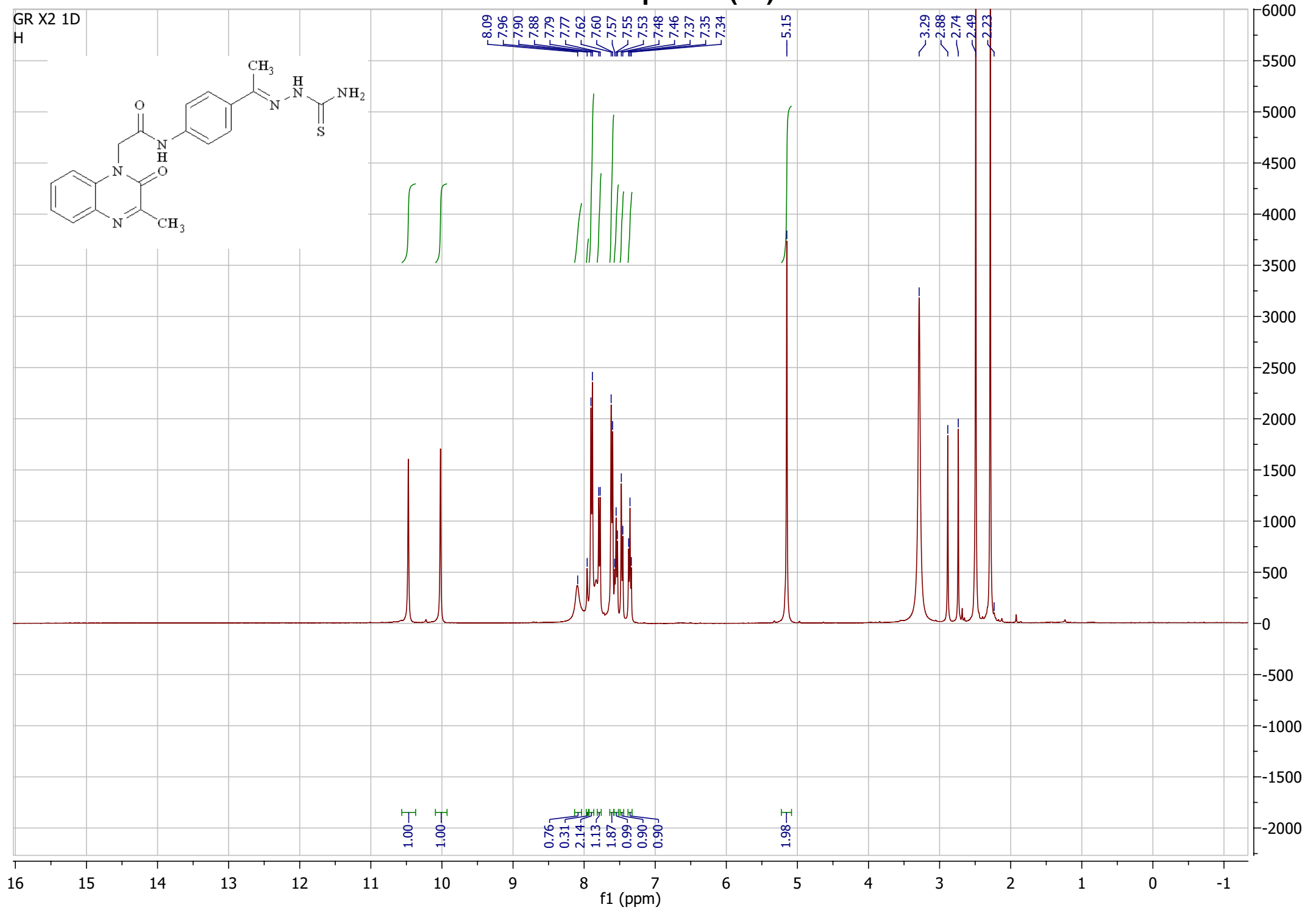
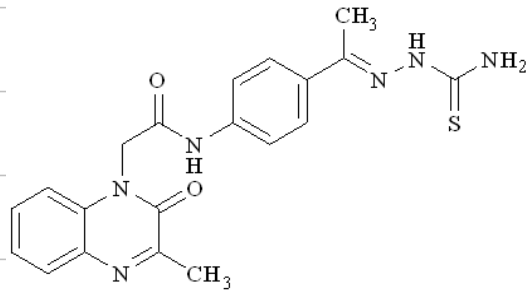
Comment; Dr Rada Gomaa X2

No. of Scans; 8
Resolution; 8 [1/cm]

Date/Time; 11/11/2018 11:04:52 AM
User; usama

H¹NMR of compound (13)

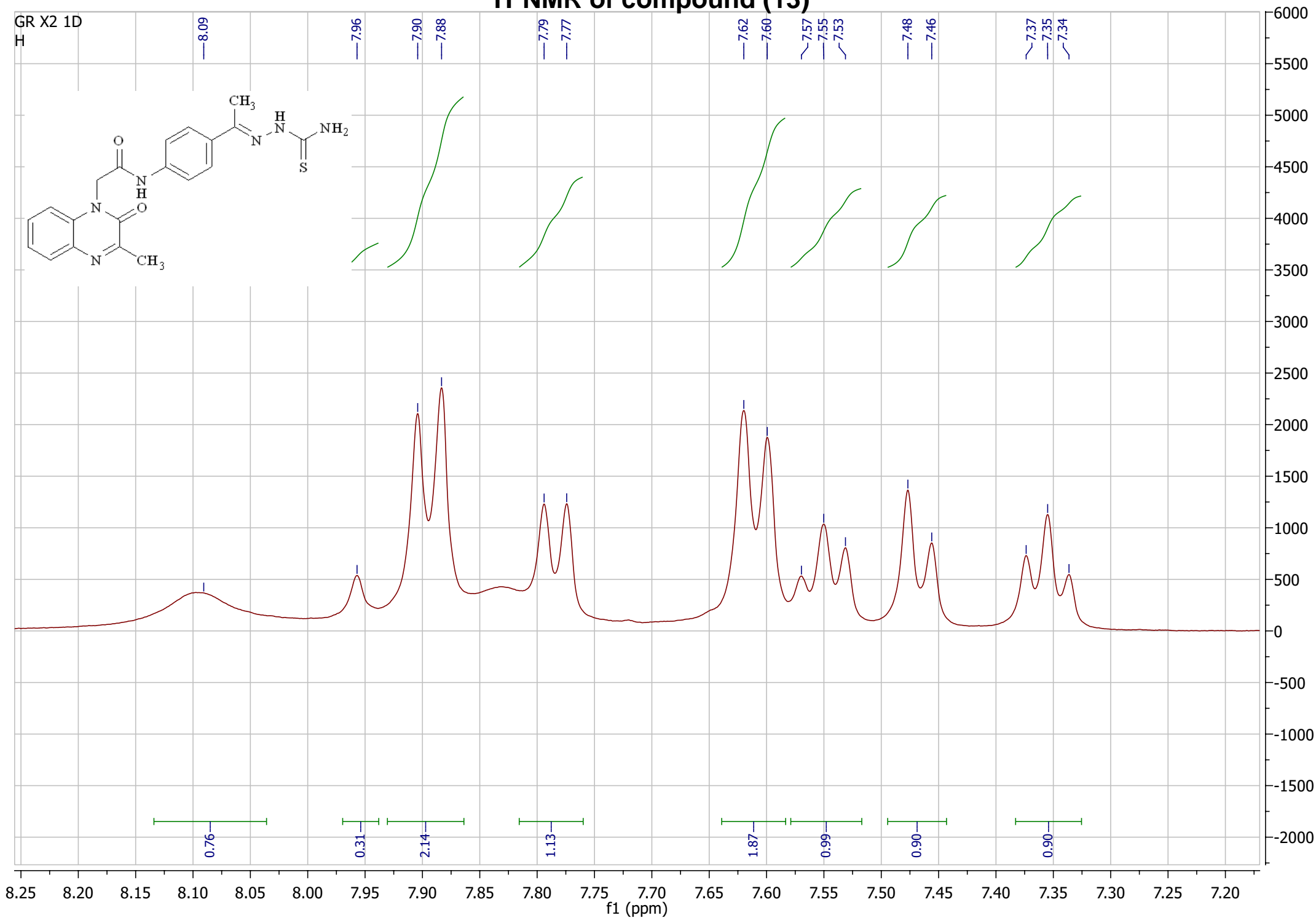
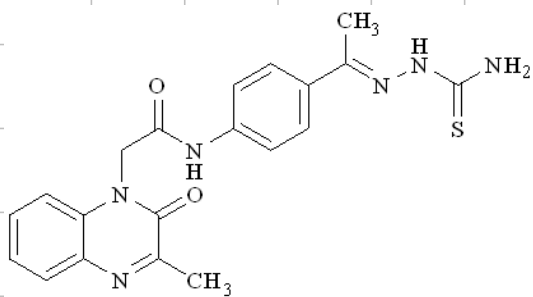
GR X2 1D
H



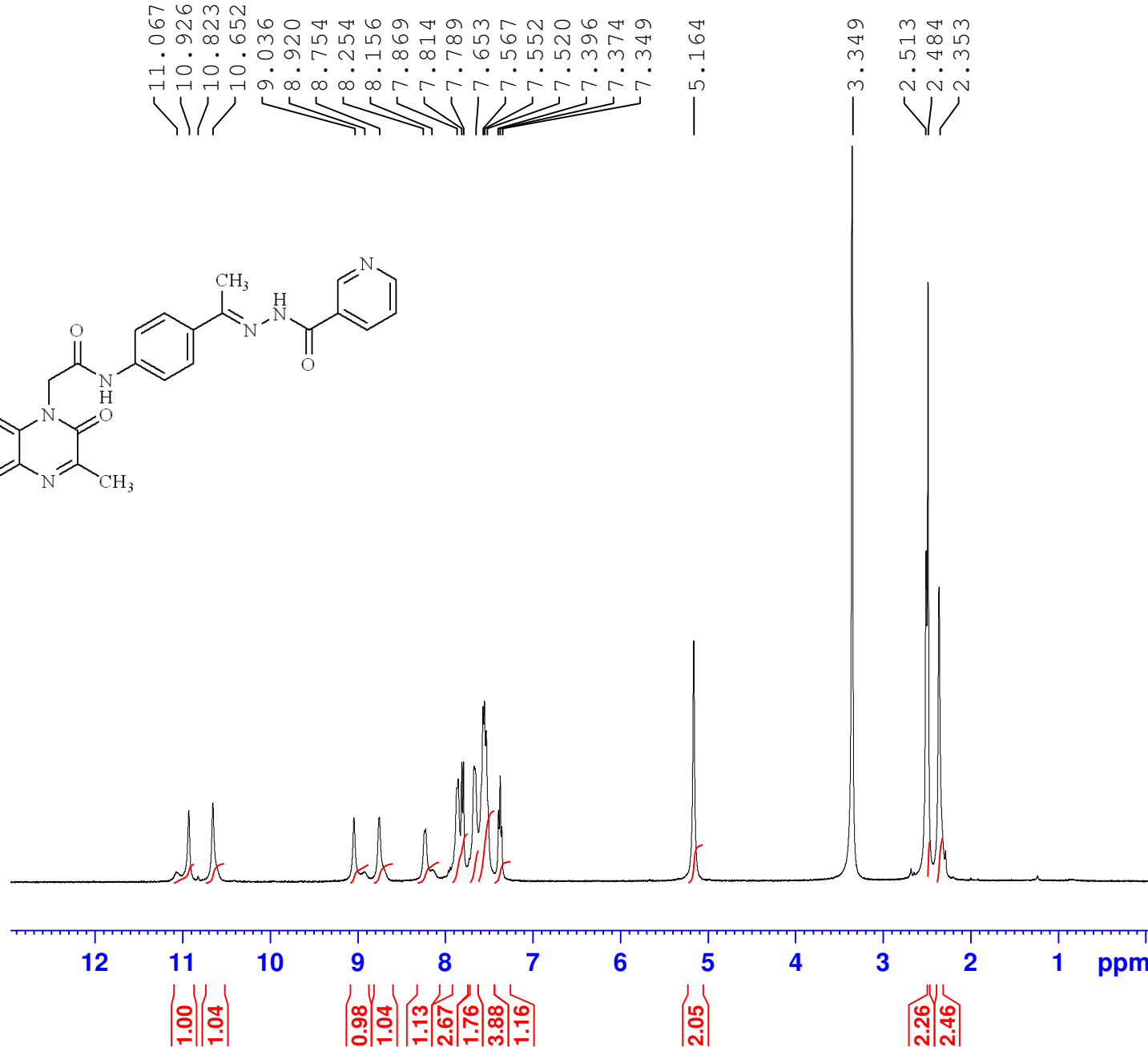
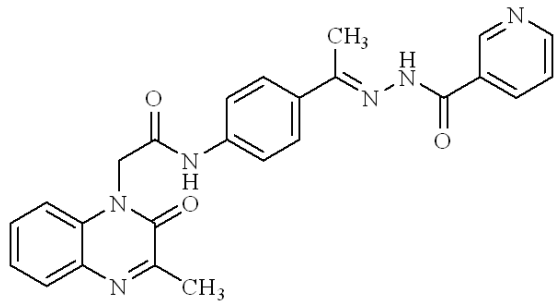
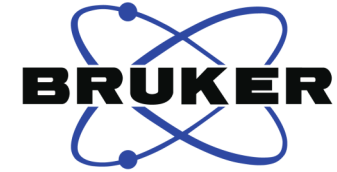
H¹NMR of compound (13)

GR X2 1D

H



H¹NMR of compound (14)



Current Data Parameters
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 EXPNO 1
 PROCNO 1

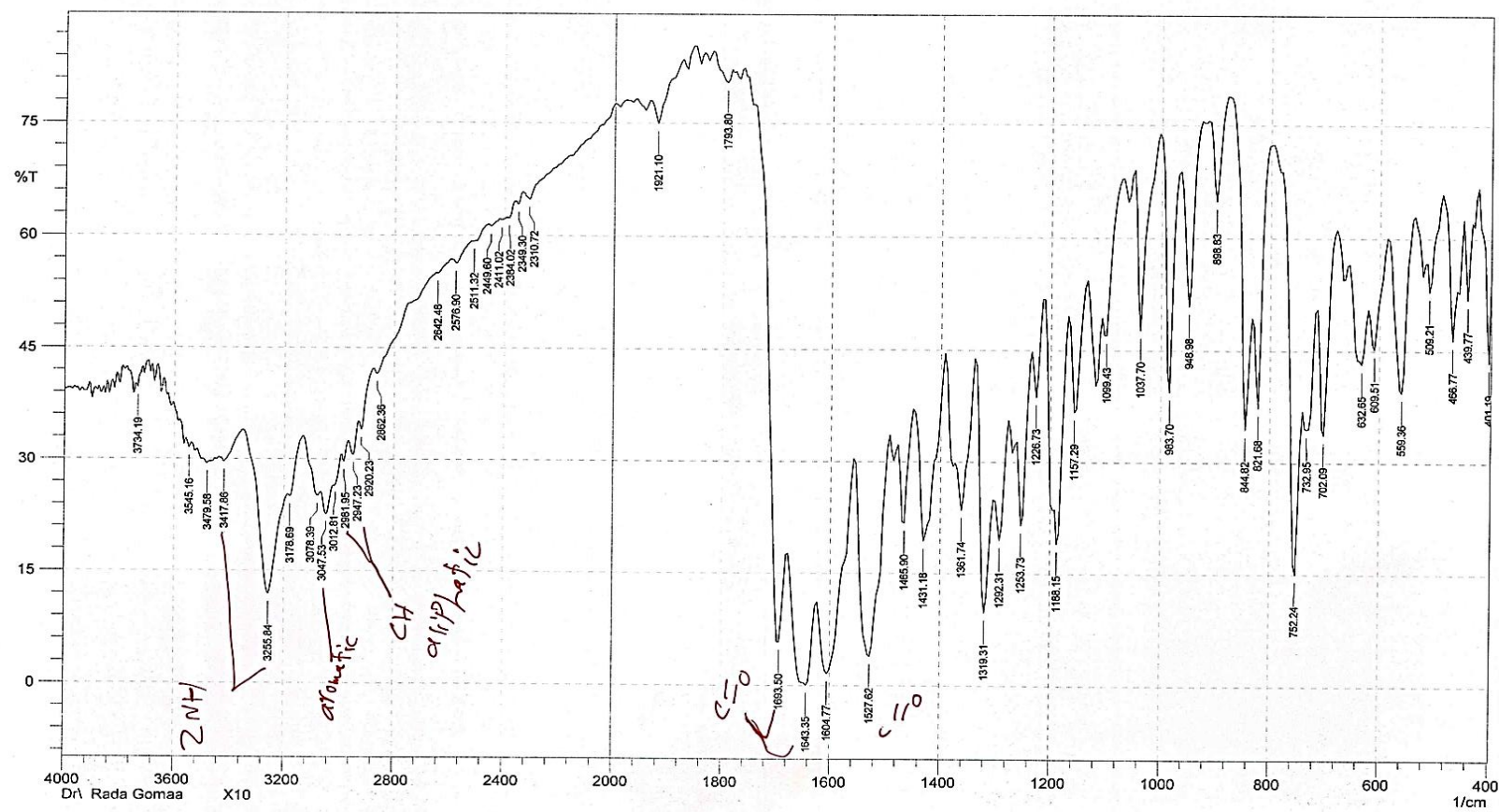
F2 - Acquisition Parameters
 Date_ 20180423
 Time 9.21
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zg30
 TD 65536
 SOLVENT DMSO
 NS 35
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.122266 Hz
 AQ 4.0894465 sec
 RG 205.37
 DW 62.400 usec
 DE 6.50 usec
 TE 298.4 K
 D1 1.00000000 sec
 TD0 1

===== CHANNEL f1 =====
 SFO1 400.1524711 MHz
 NUC1 1H
 P1 12.00 usec
 PLW1 18.00000000 W

F2 - Processing parameters
 SI 65536
 SF 400.1500000 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

IR of compound 14

SHIMADZU



Comment;

Dr Rada Goma X10

No. of Scans; 8

Resolution; 8 [1/cm]

Date/Time; 11/11/2018 11:25:37.AM

User; usama

H¹NMR of compound (14)

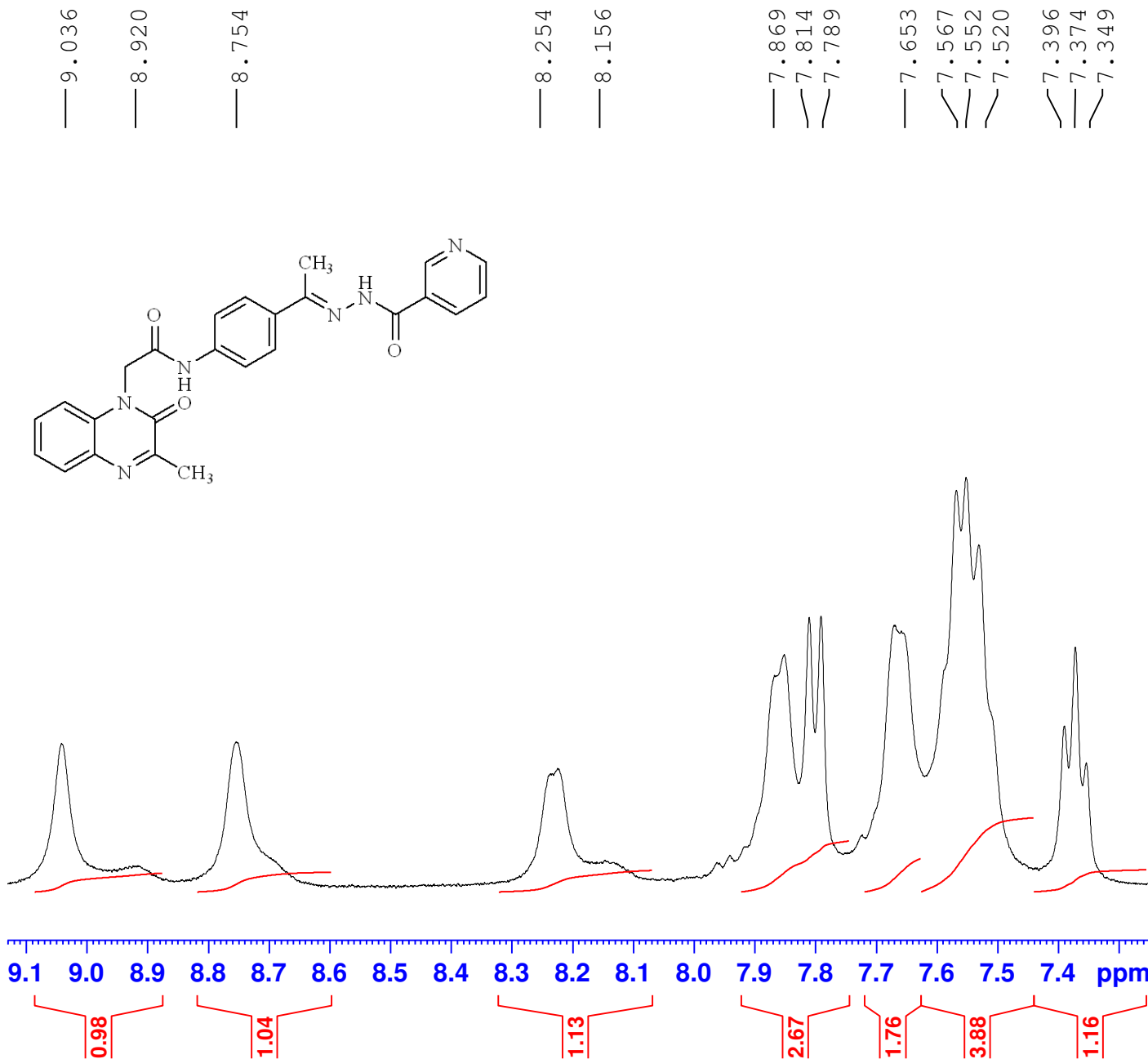


Current Data Parameters
NAME reda-X10
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20180423
Time 9.21
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 35
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 205.37
DW 62.400 usec
DE 6.50 usec
TE 298.4 K
D1 1.00000000 sec
TD0 1

===== CHANNEL f1 =====
SFO1 400.1524711 MHz
NUC1 1H
P1 12.00 usec
PLW1 18.00000000 W

F2 - Processing parameters
SI 65536
SF 400.1500000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



H¹NMR of compound (14)

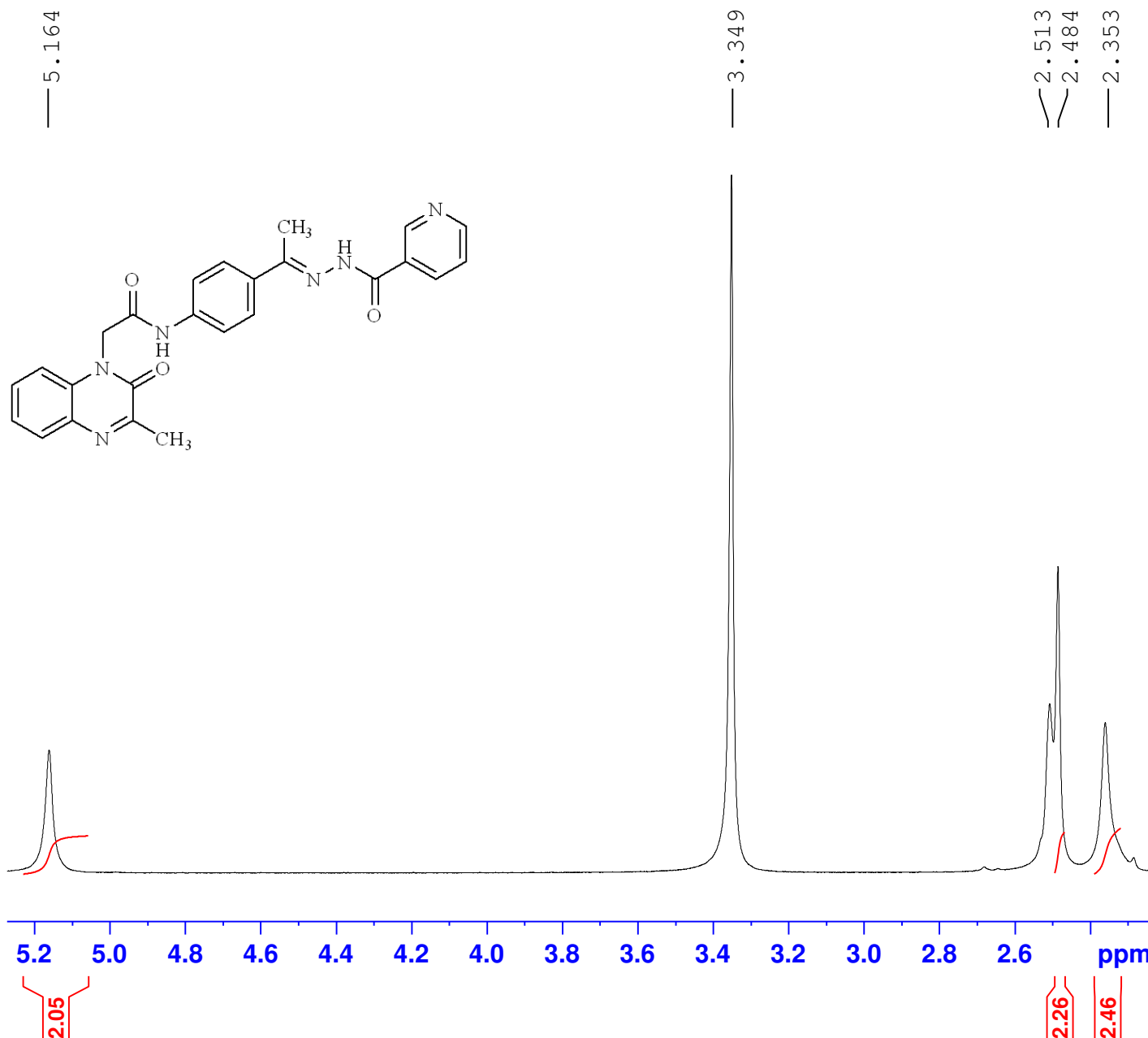


Current Data Parameters
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EXPNO 1
PROCNO 1

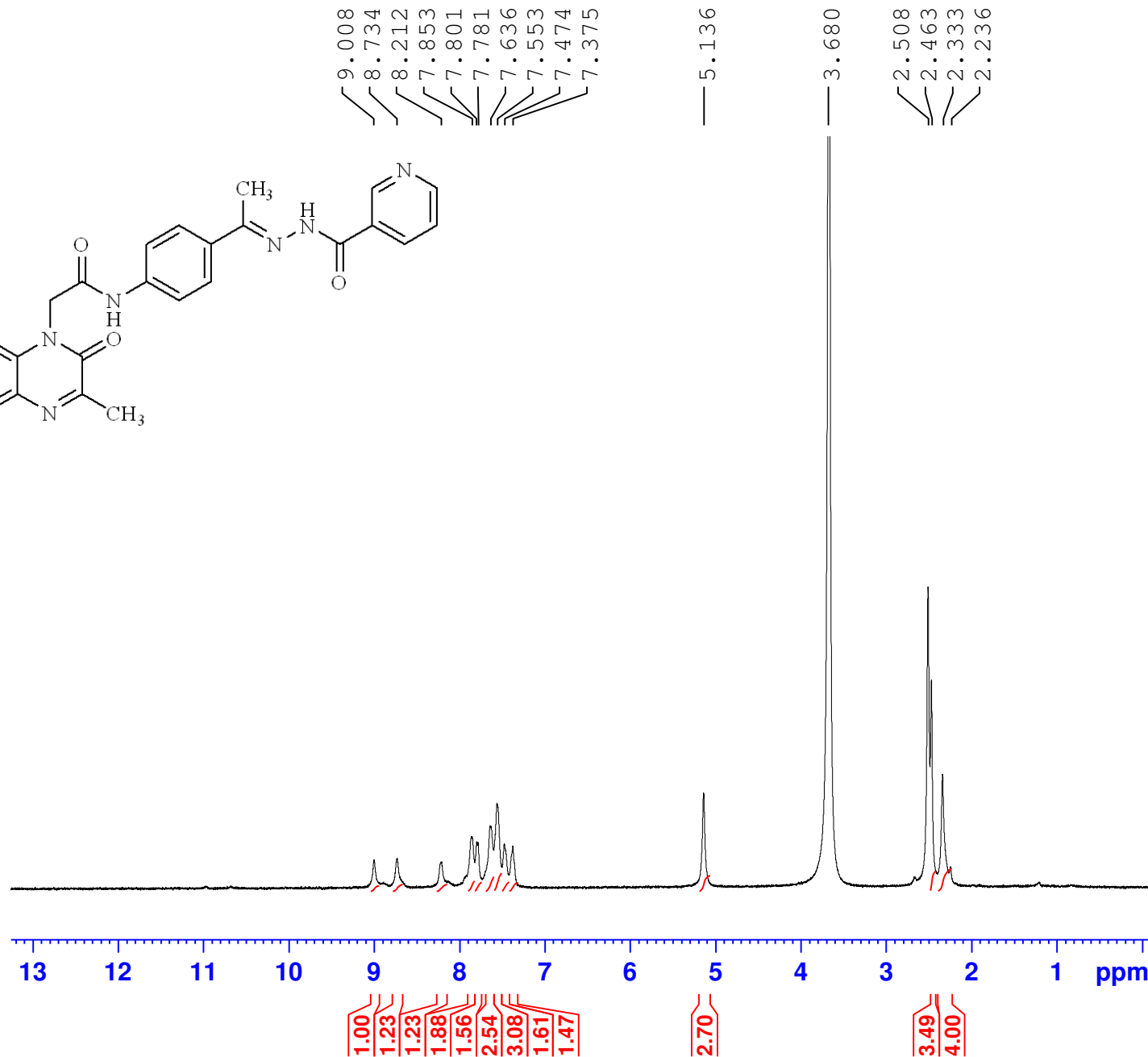
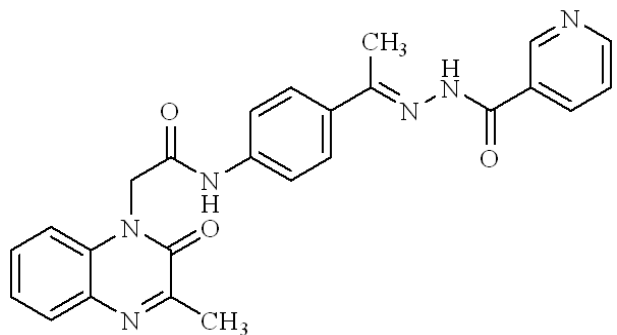
F2 - Acquisition Parameters
Date_ 20180423
Time 9.21
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 35
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 205.37
DW 62.400 usec
DE 6.50 usec
TE 298.4 K
D1 1.00000000 sec
TD0 1

==== CHANNEL f1 =====
SFO1 400.1524711 MHz
NUC1 1H
P1 12.00 usec
PLW1 18.00000000 W

F2 - Processing parameters
SI 65536
SF 400.1500000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



H¹NMR(D₂O) of compound (14)



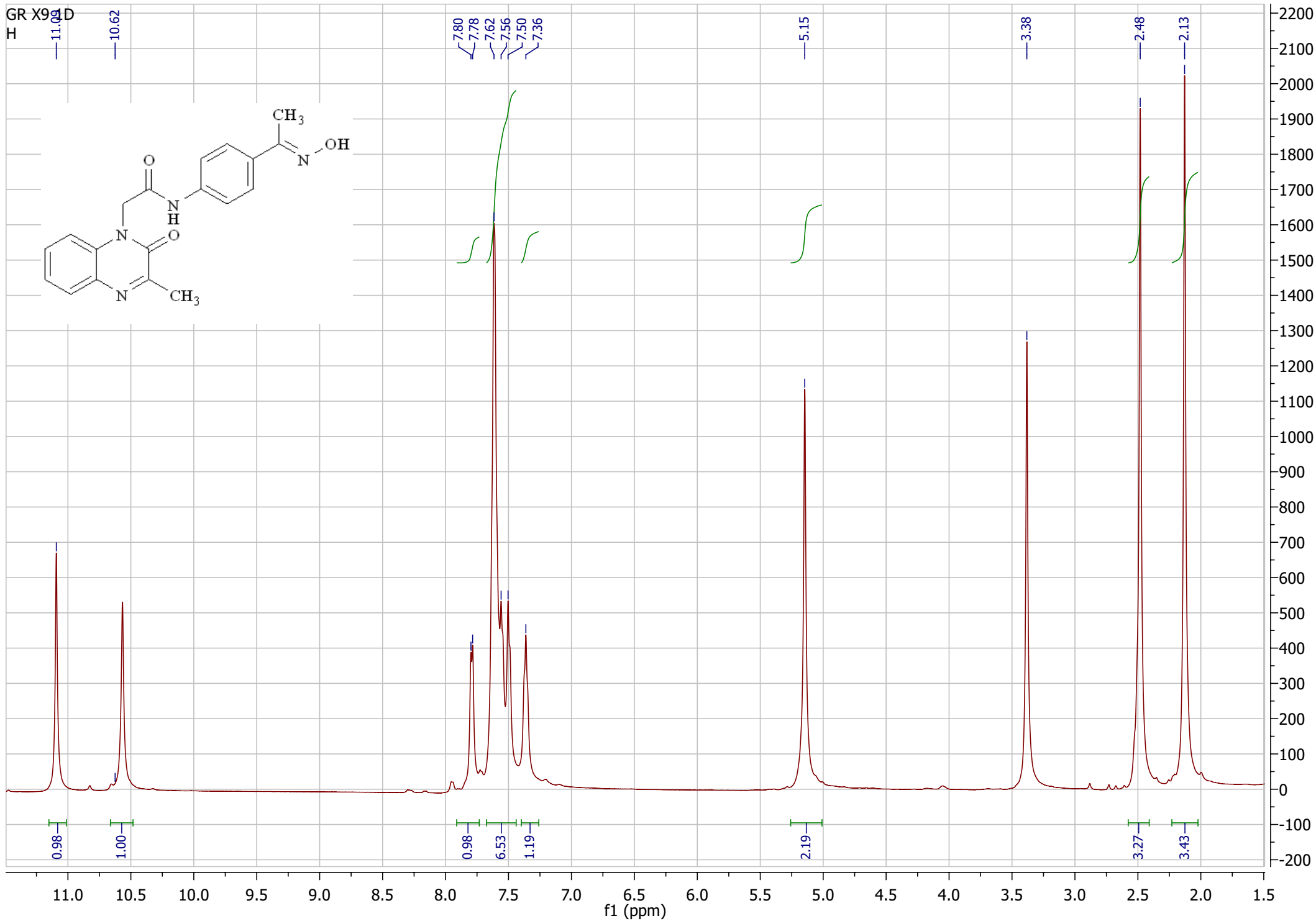
Current Data Parameters
 NAME reda-X10-d2o
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20180423
 Time 9.33
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zg30
 TD 65536
 SOLVENT DMSO
 NS 42
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.122266 Hz
 AQ 4.0894465 sec
 RG 205.37
 DW 62.400 usec
 DE 6.50 usec
 TE 298.2 K
 D1 1.00000000 sec
 TD0 1

==== CHANNEL f1 =====
 SFO1 400.1524711 MHz
 NUC1 1H
 P1 12.00 usec
 PLW1 18.00000000 W

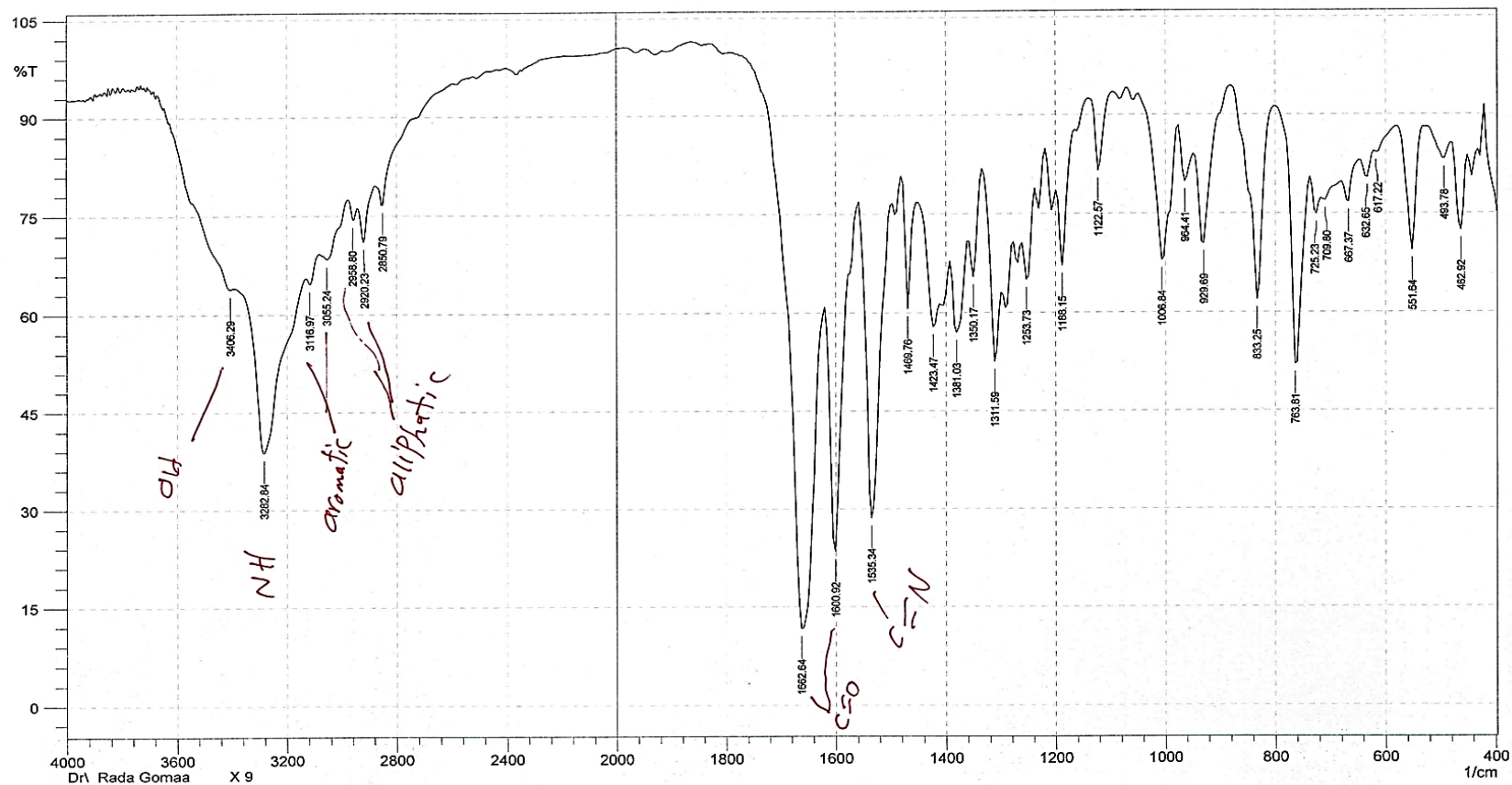
F2 - Processing parameters
 SI 65536
 SF 400.1500000 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

H¹NMR of compound (15)



IR of compound 15

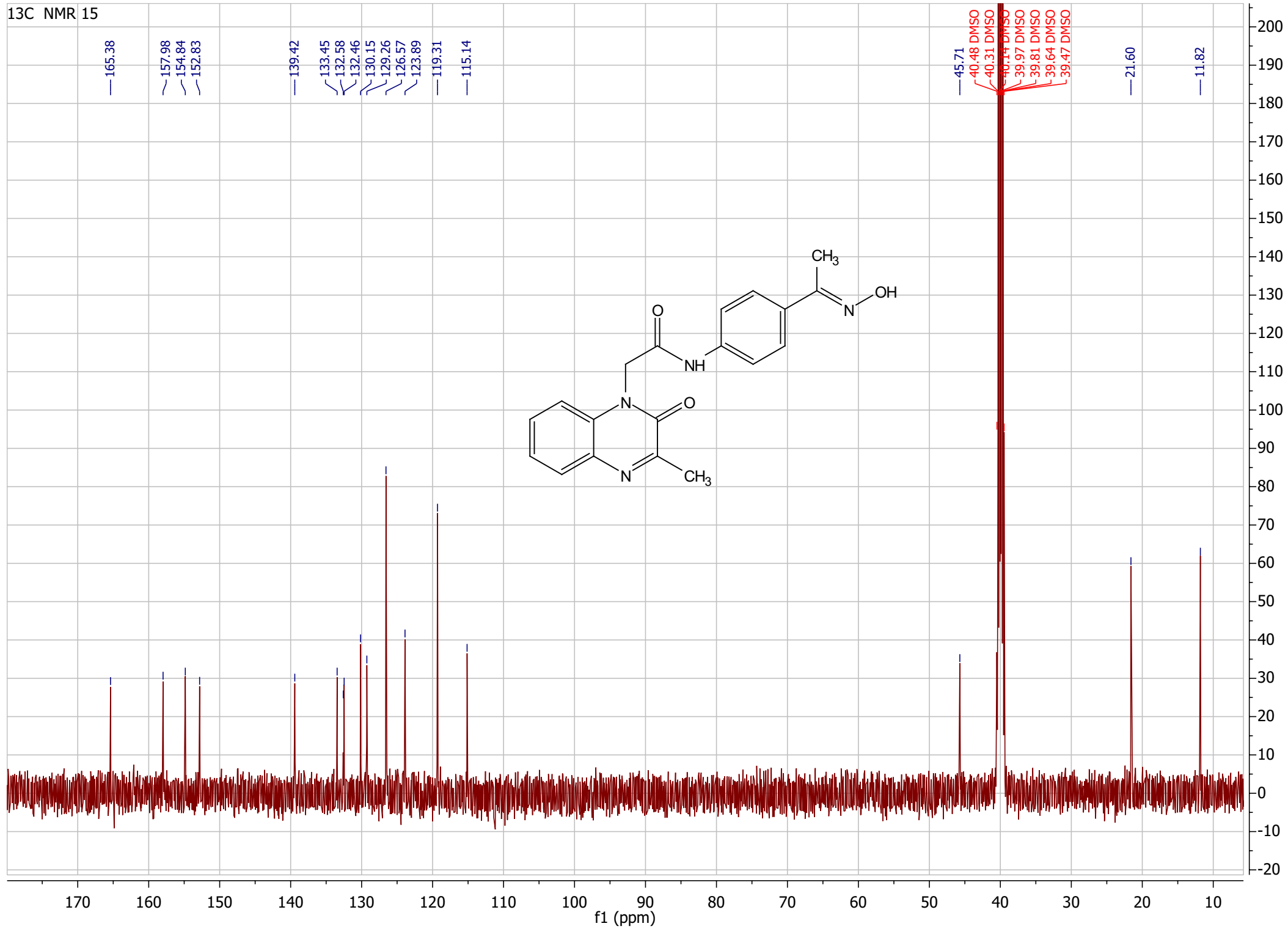
SHIMADZU



Comment;
Dr\ Rada Goma X 9

No. of Scans; 8
Resolution; 8 [1/cm]

Date/Time; 11/11/2018 11:55:23 AM
User; usama



DEPT NMR 15

