

Design, Synthesis and *In Silico* Studies of New Quinazolinone Derivatives as Antitumor PARP-1 Inhibitors

Sayed K. Ramadan^a, Eman Z. Elrazaz^b, Khaled A. M. Abouzid^{b,c,*}, Abeer M. El-Naggar^{a,*}

^a *Department of Chemistry, Faculty of Science, Ain Shams University, Abbassia, 11566 Cairo, Egypt*

^b *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ain Shams University, Abbassia, 11566 Cairo, Egypt*

^c *Department of Organic and Medicinal Chemistry, Faculty of Pharmacy, University of Sadat City, Sadat City, Egypt*

Supporting information

*** Corresponding authors:**

Khaled A. M. Abouzid

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ain Shams University, Abbassia, 11566 Cairo, Egypt

Email: khaled.abouzid@pharma.asu.edu.eg

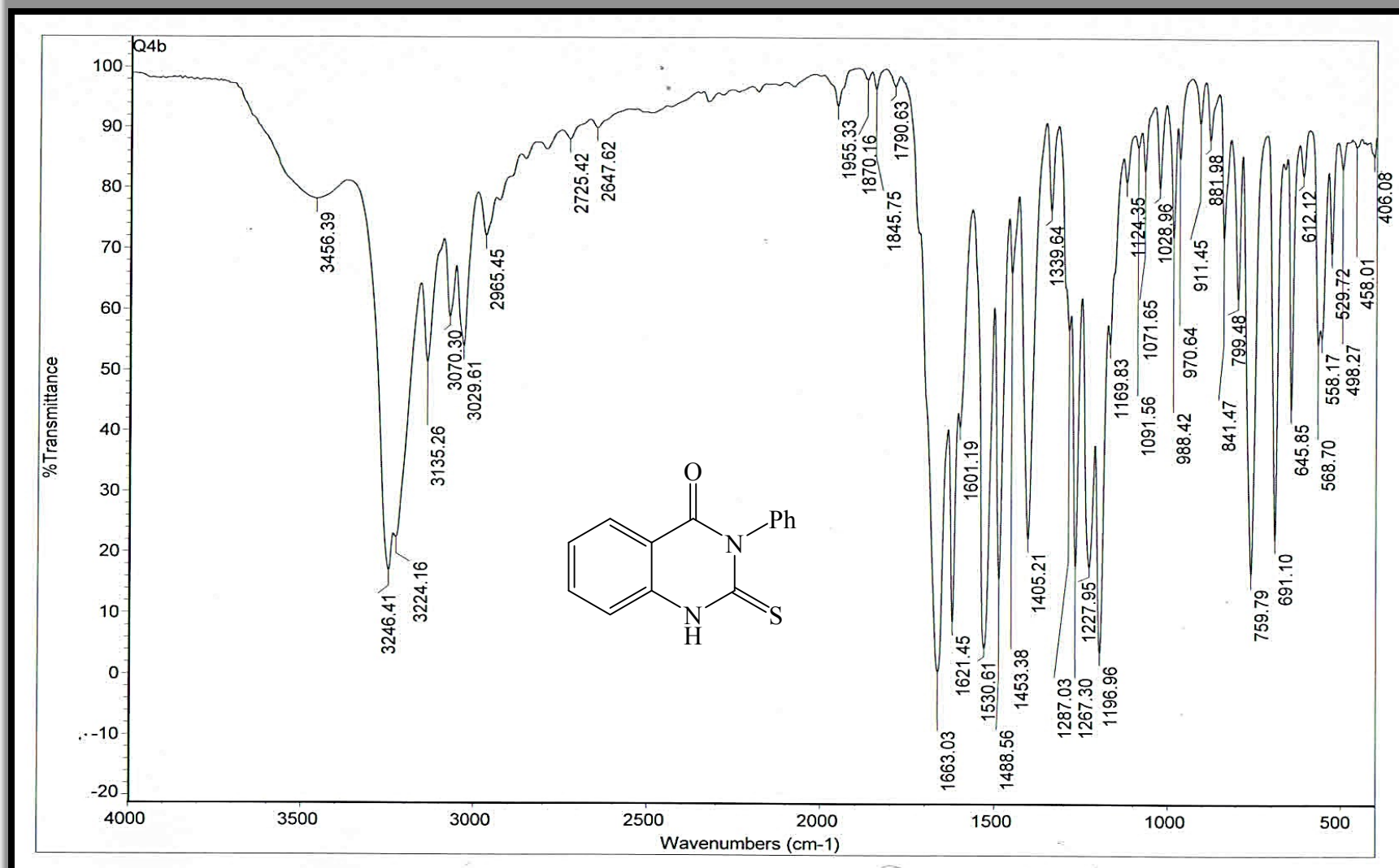
Abeer M. El-Naggar

Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo-11566, Egypt.

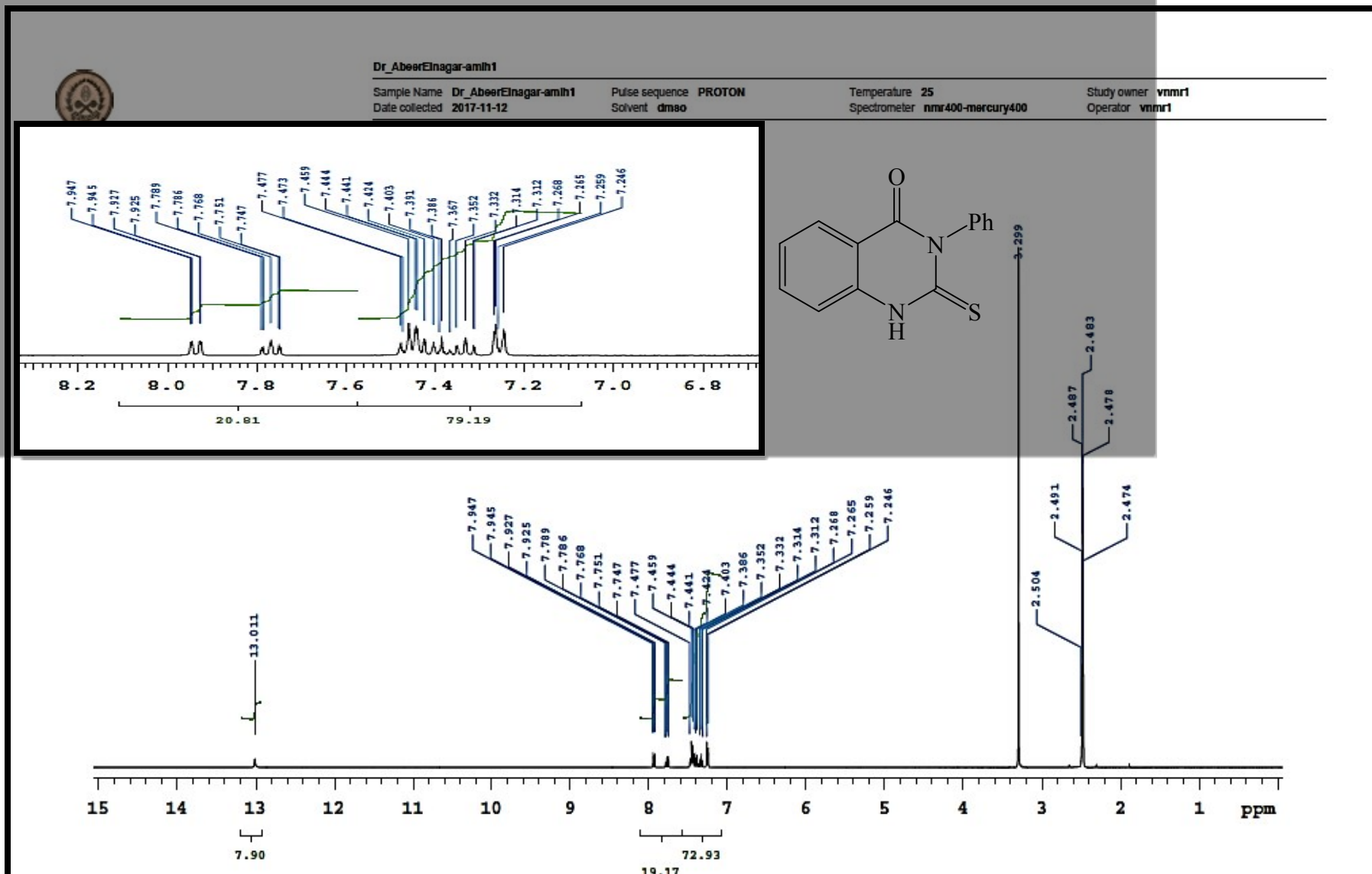
E-mail: elsayedam@sci.asu.edu.eg

3-Phenyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3).

IR



HNMR



HNMR-D2O

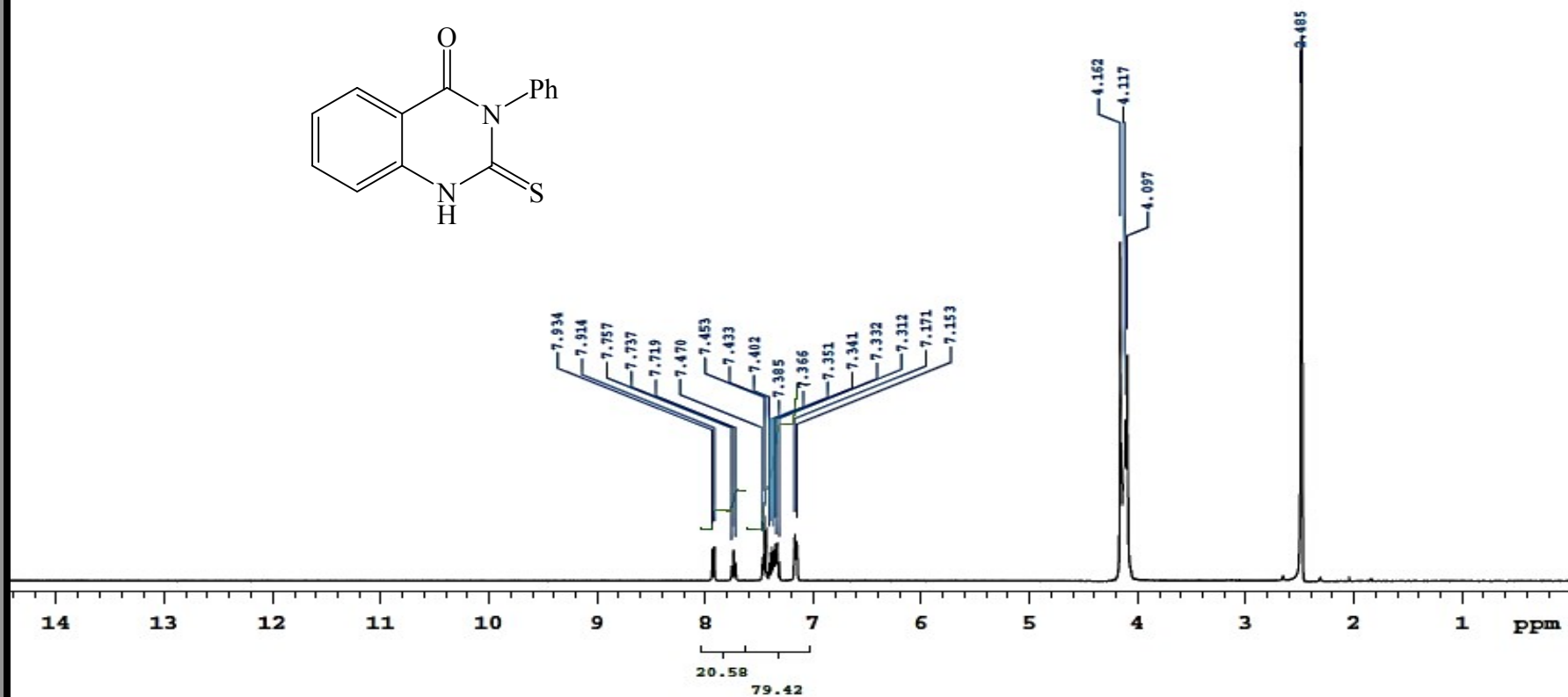
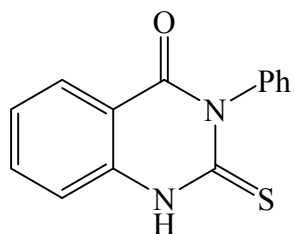
Dr_AbeerElnagar-amih1-D2O

Sample Name **Dr_AbeerElnagar-amih1-D2O** Pulse sequence **PROTON**
Date collected **2017-11-13** Solvent **dms**

Temperature **25**
Spectrometer **nmr400-mercury400**

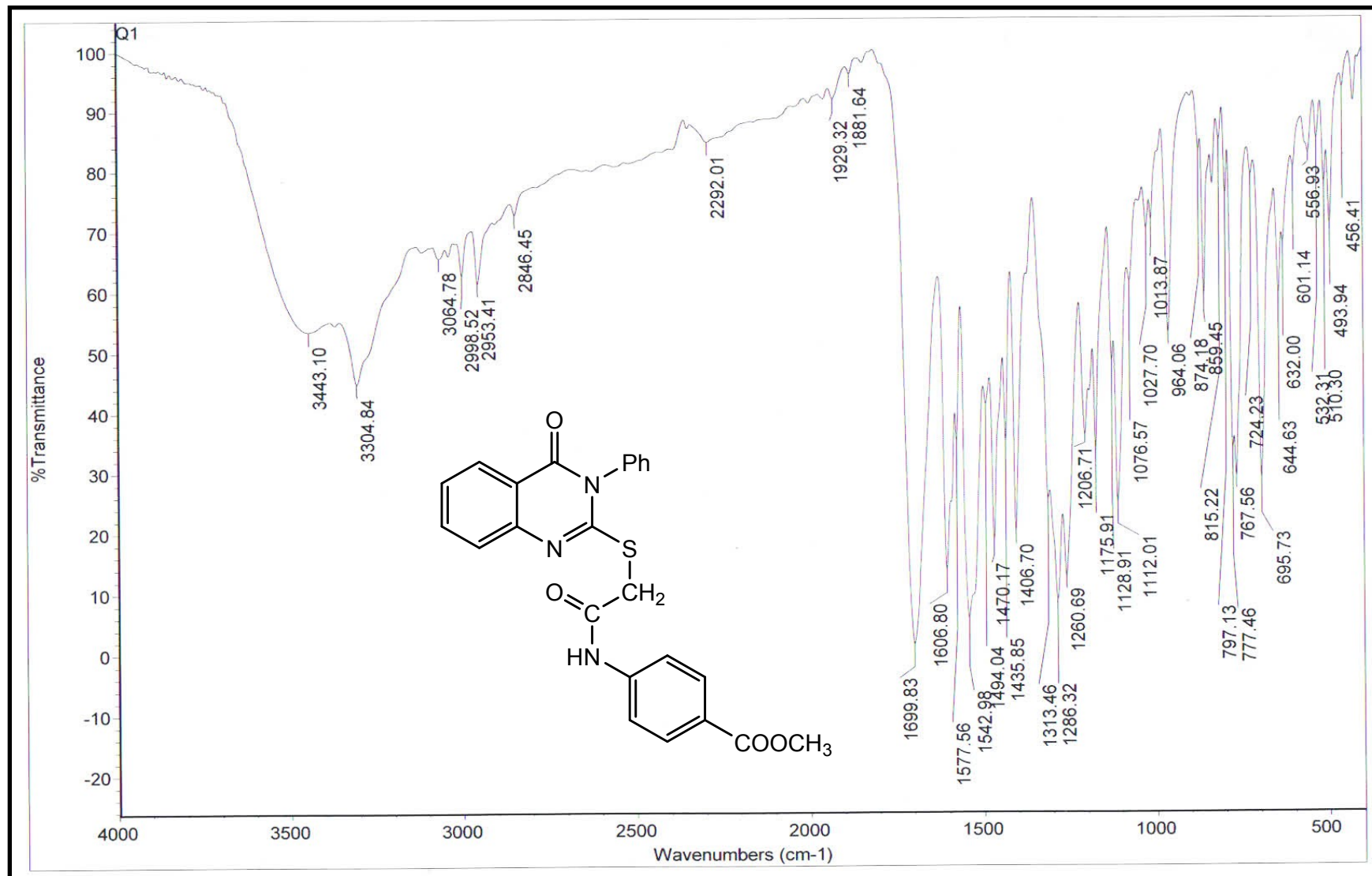
Study owner **vnmr1**
Operator **vnmr1**

agar-amih1-D2O

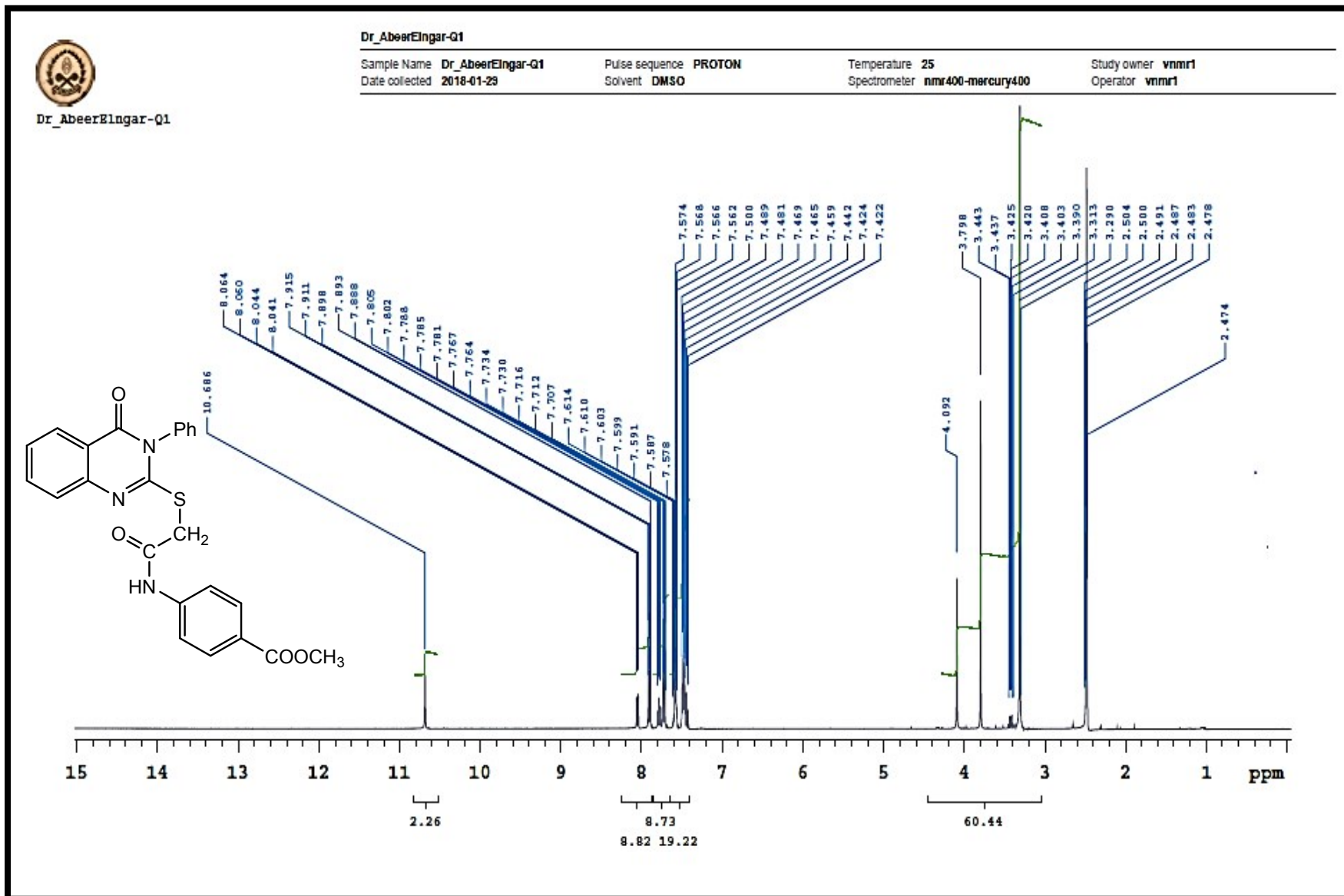


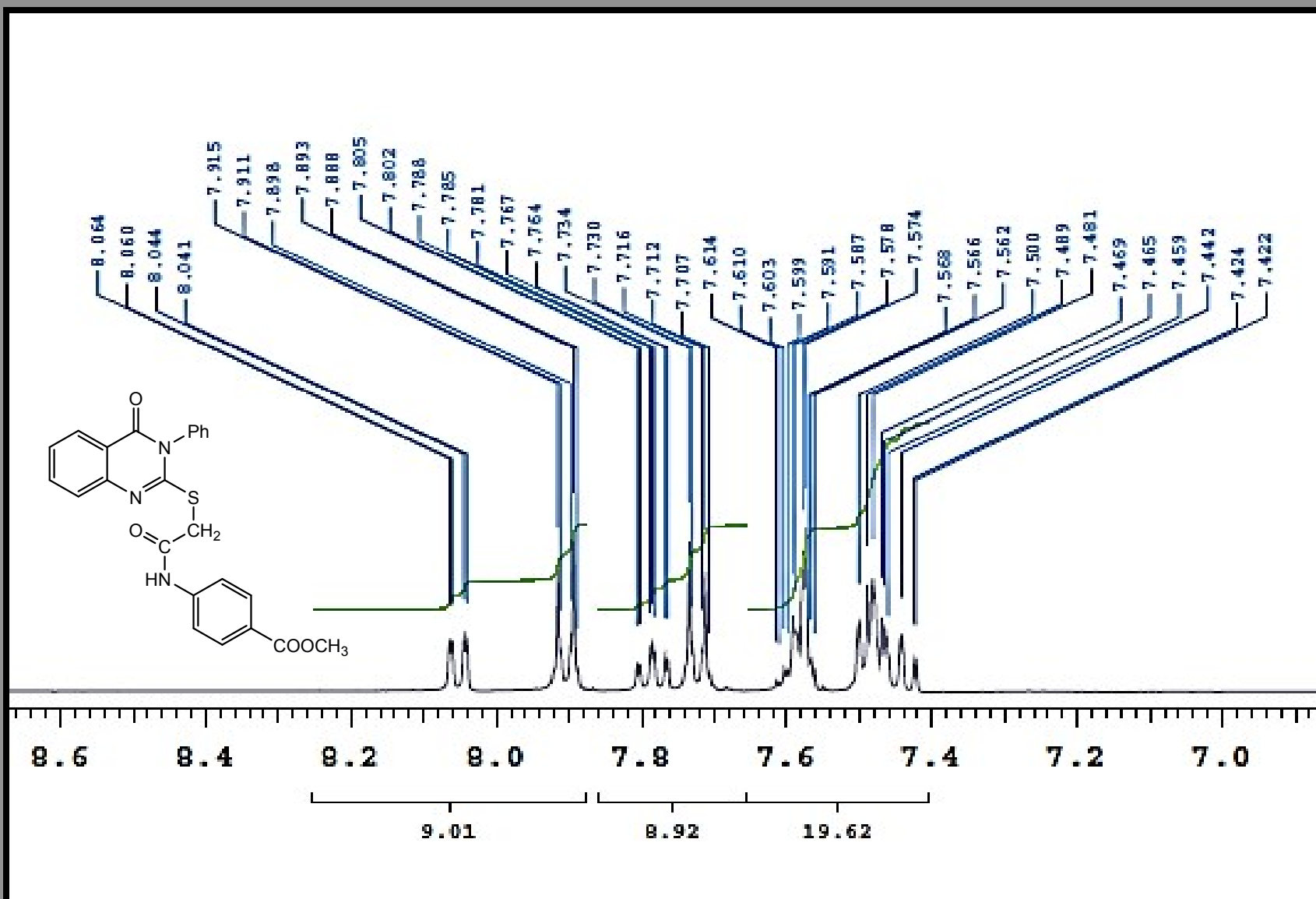
Methyl 4-(2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio)acetamido)benzoate (5a).

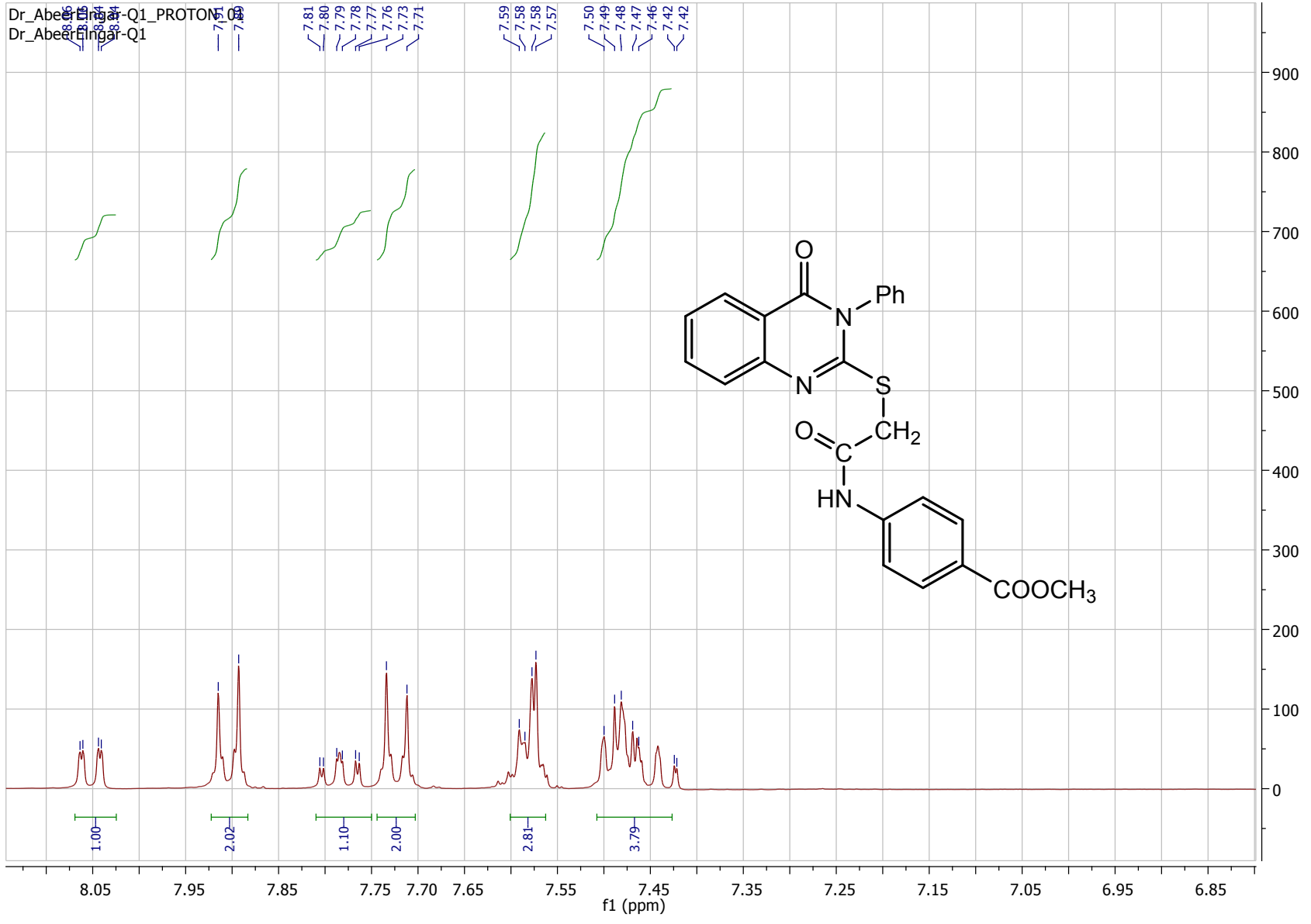
IR



¹H NMR







D20



Dr_AbeerEingar-Q1-D20

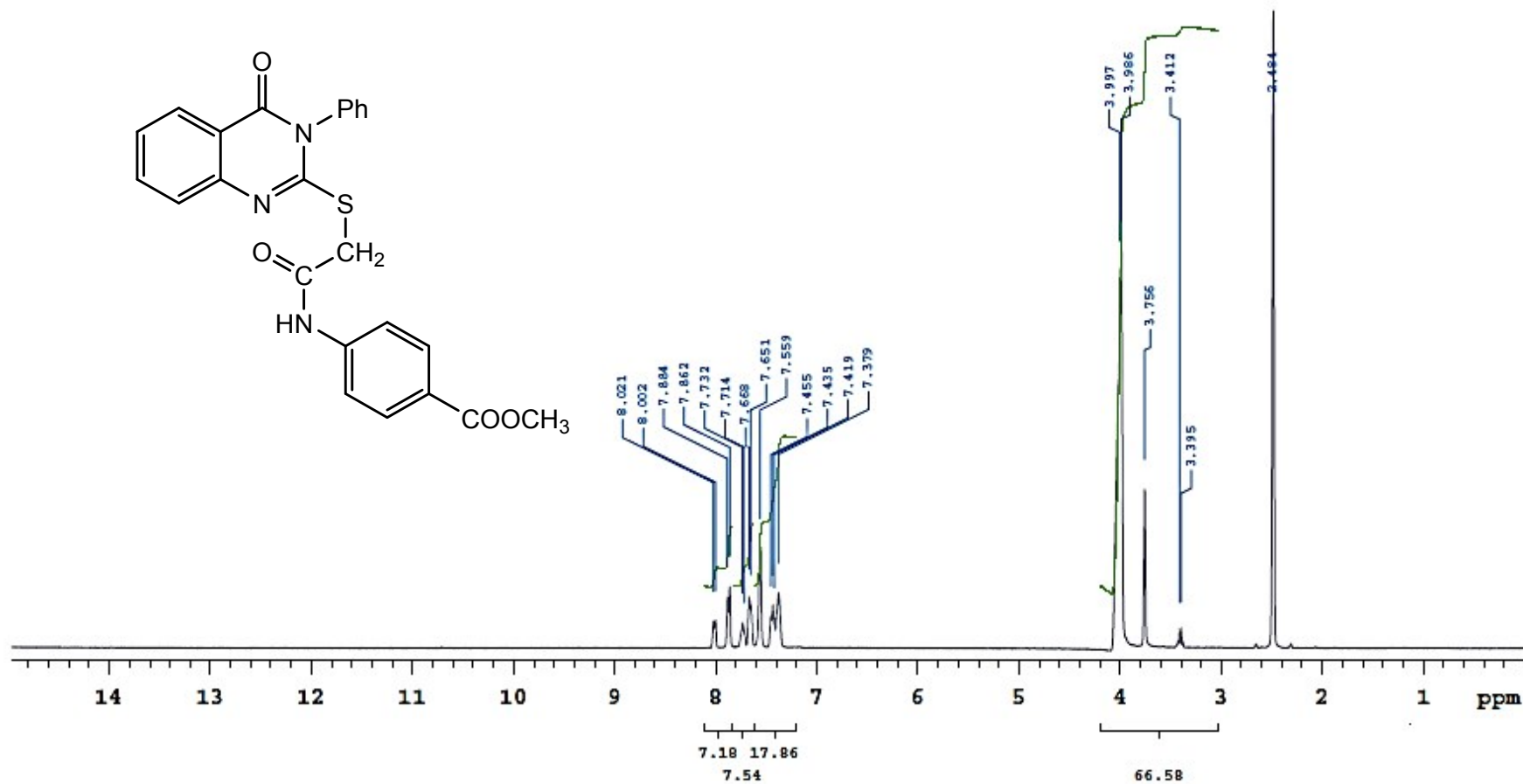
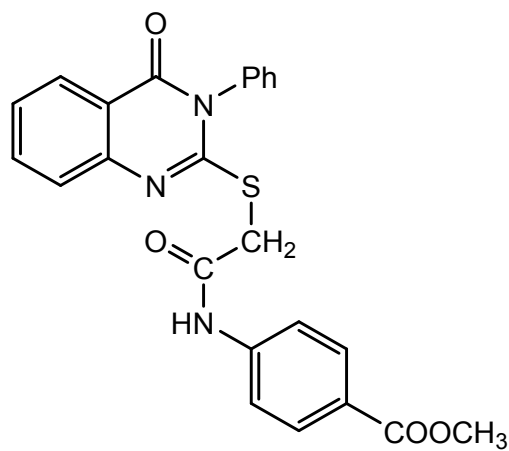
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Date collected 2018-01-30

Pulse sequence PROTON
Solvent DMSO

Temperature 25
Spectrometer nmr400-mercury400

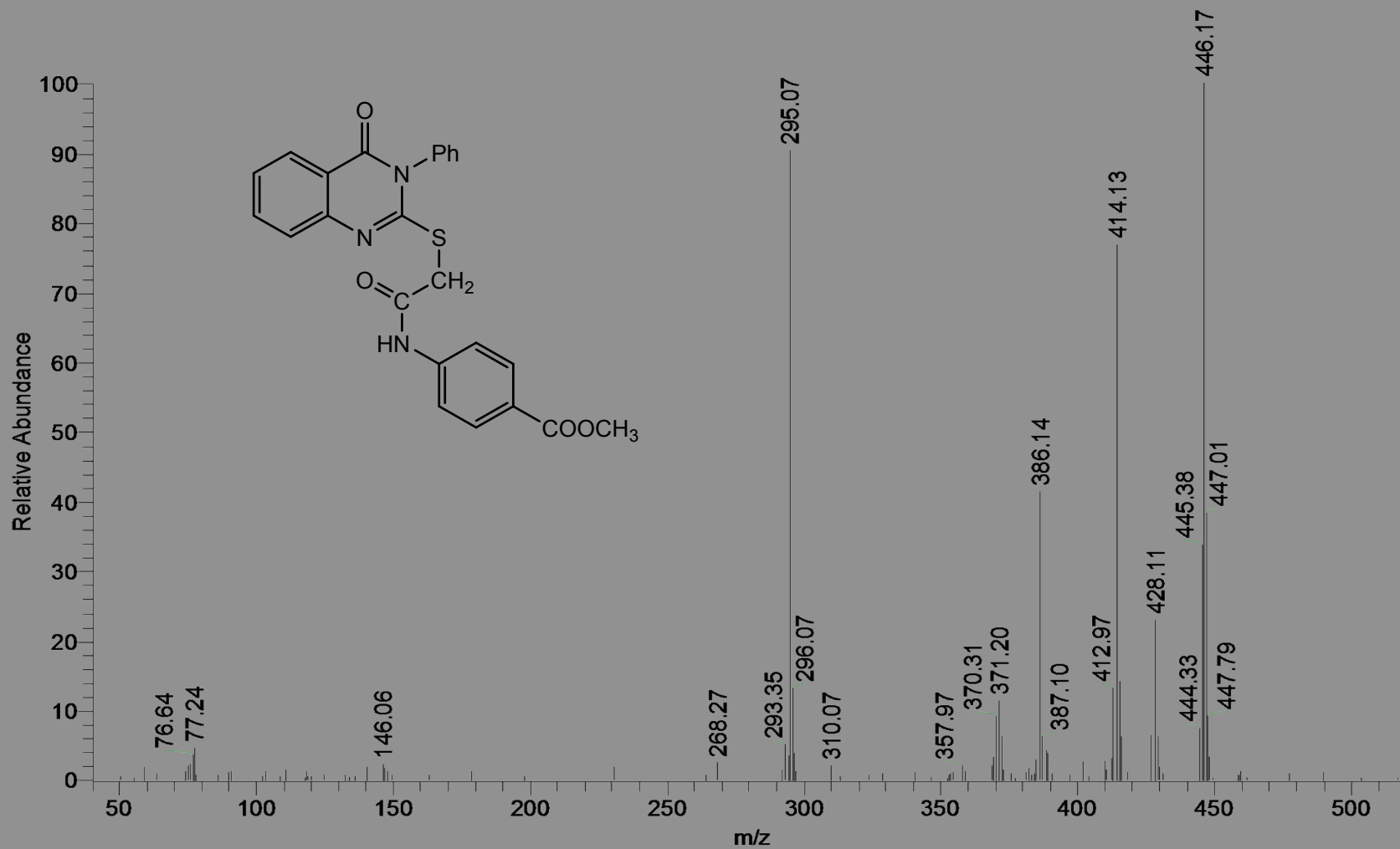
Study owner vnmr1
Operator vnmr1

Dr_AbeerEingar-Q1-D20



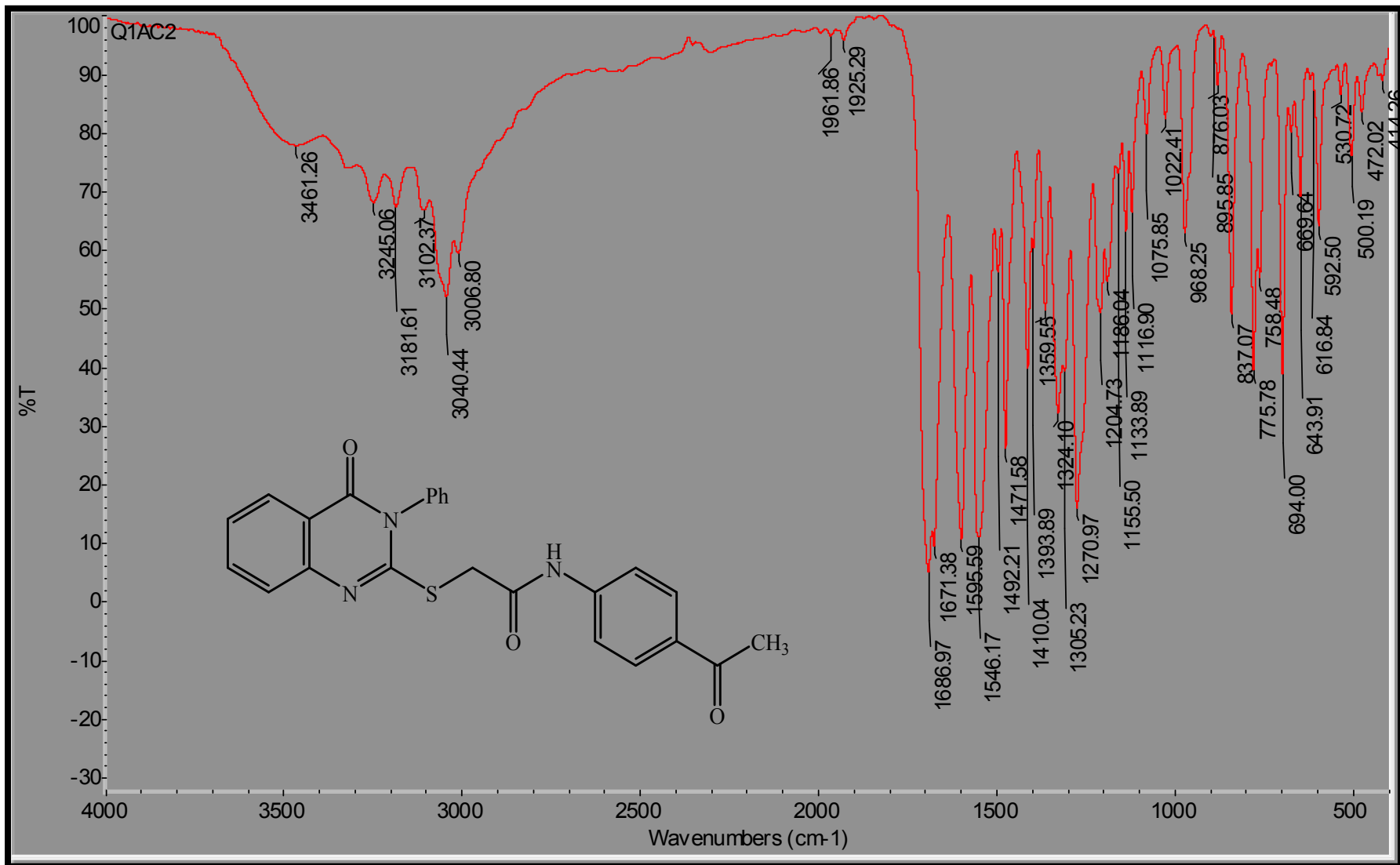
Mass

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

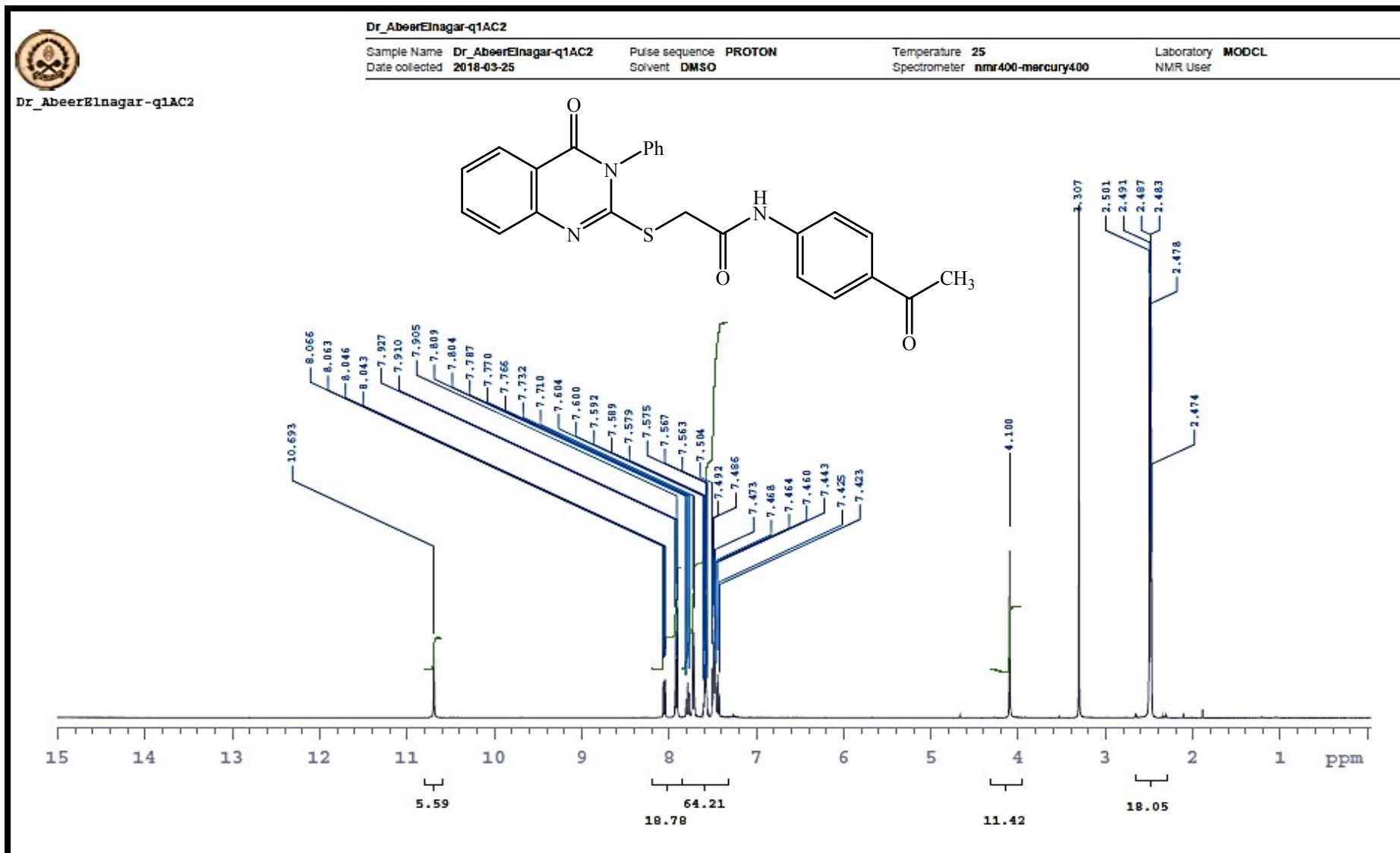


N-(4-acetylphenyl)-2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio)acetamide (5b).

IR



HNMR

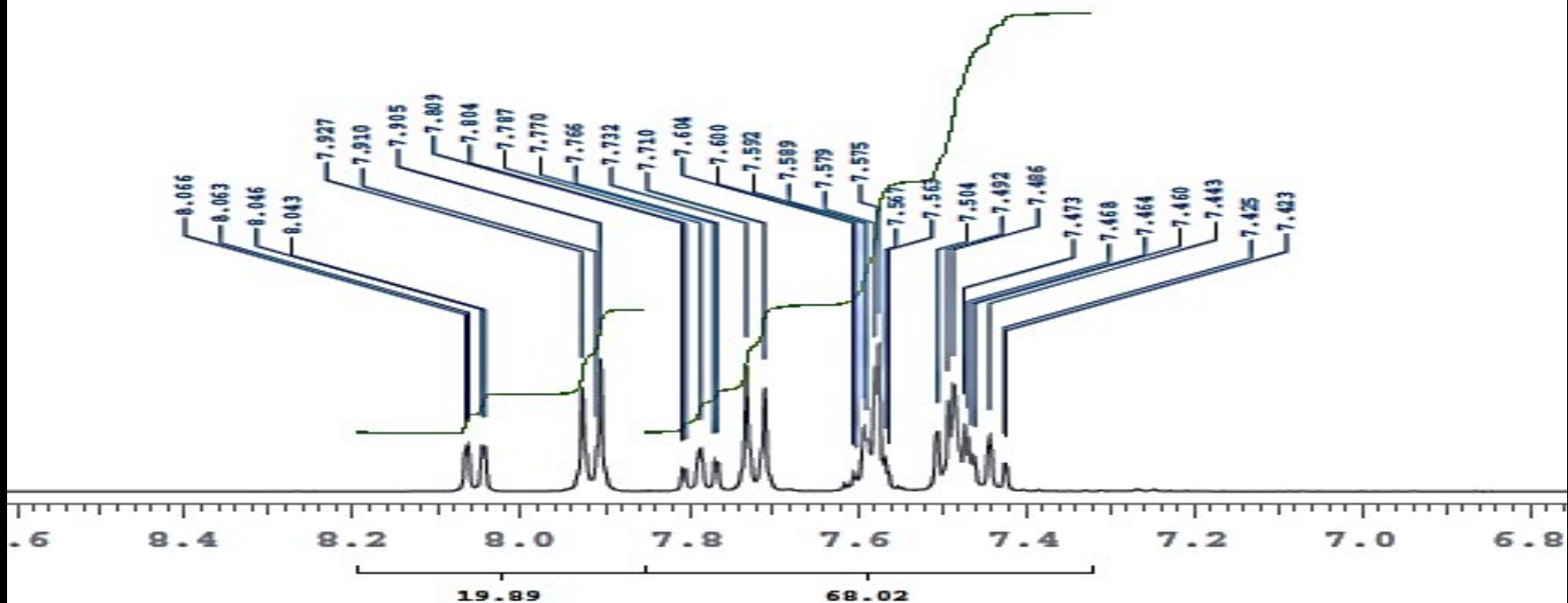


Dr_AbeerElnagar-q1AC2

Sample Name **Dr_AbeerElnagar-q1AC2**
Date collected **2018-03-25**

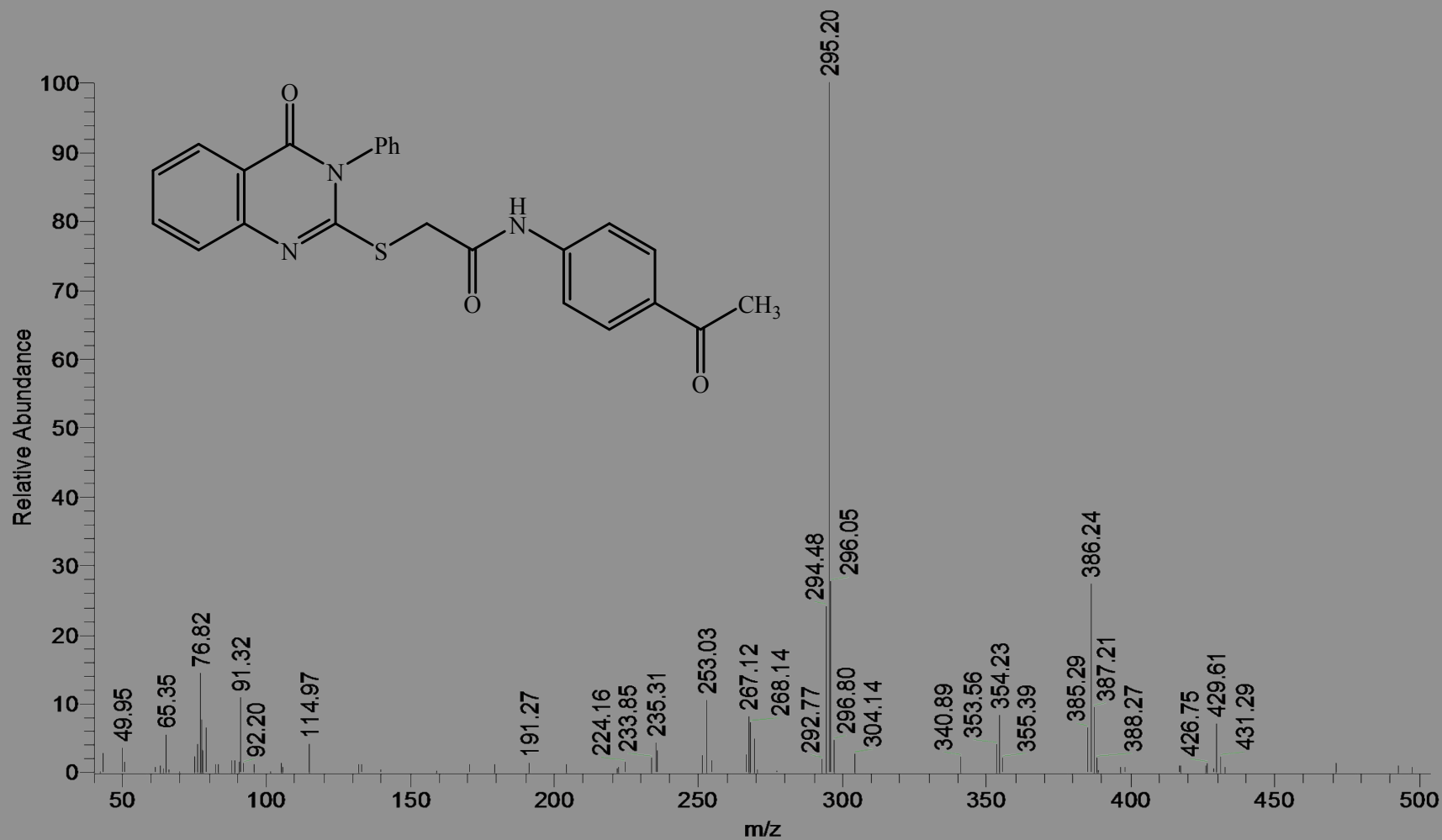
Pulse sequence **PROTON**
Solvent **DMSO**

Temperature **25**
Spectrometer **nmr400-**



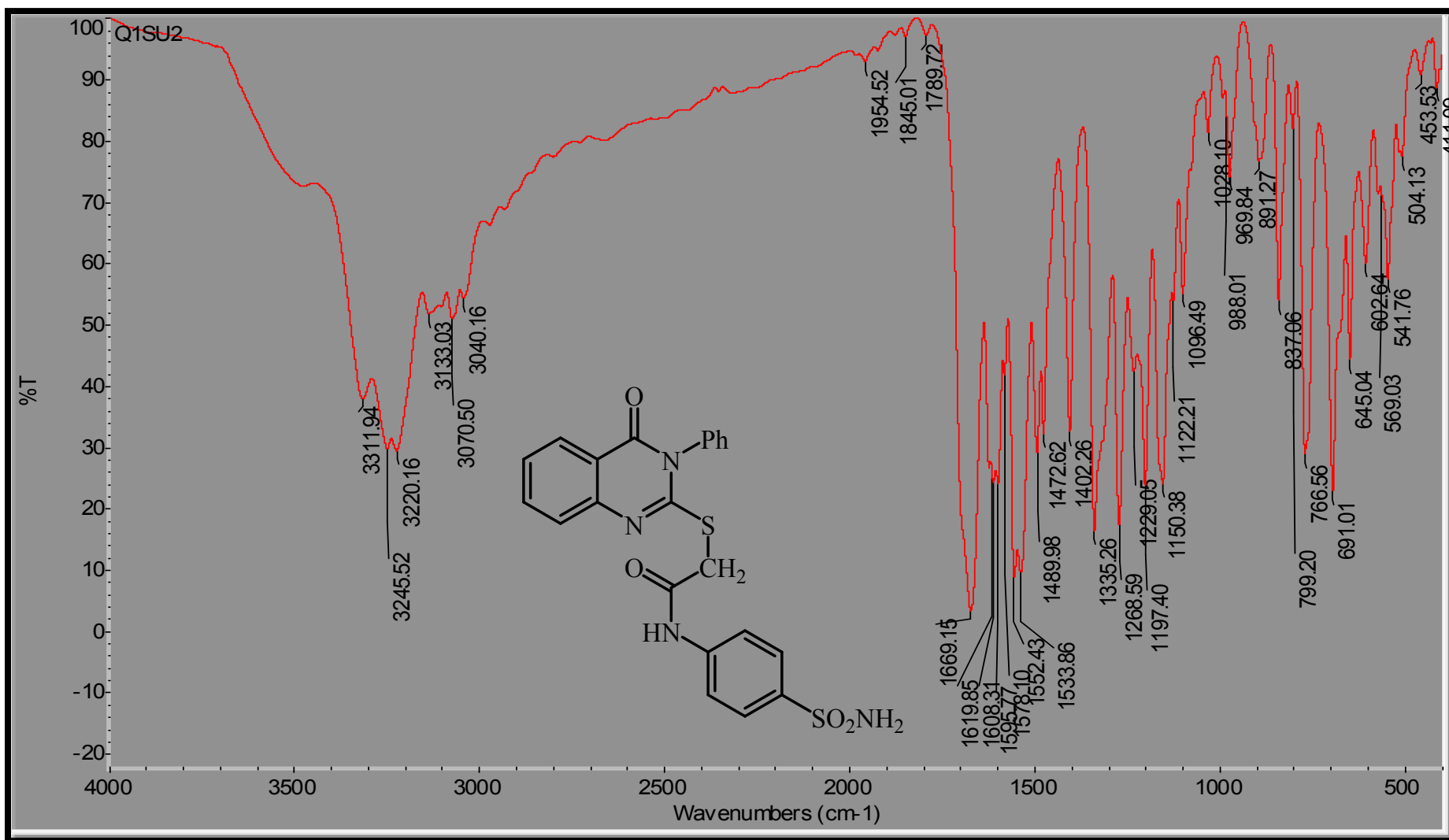
Mass

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



2-((4-Oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio)-N-(4-sulfamoylphenyl)acetamide (5c).

I.R





Dr_AbeerElnagar-q1su2

Sample Name Dr_AbeerElnagar-q1su2

Pulse sequence PROTON

Temperature 25

Laboratory MODCL

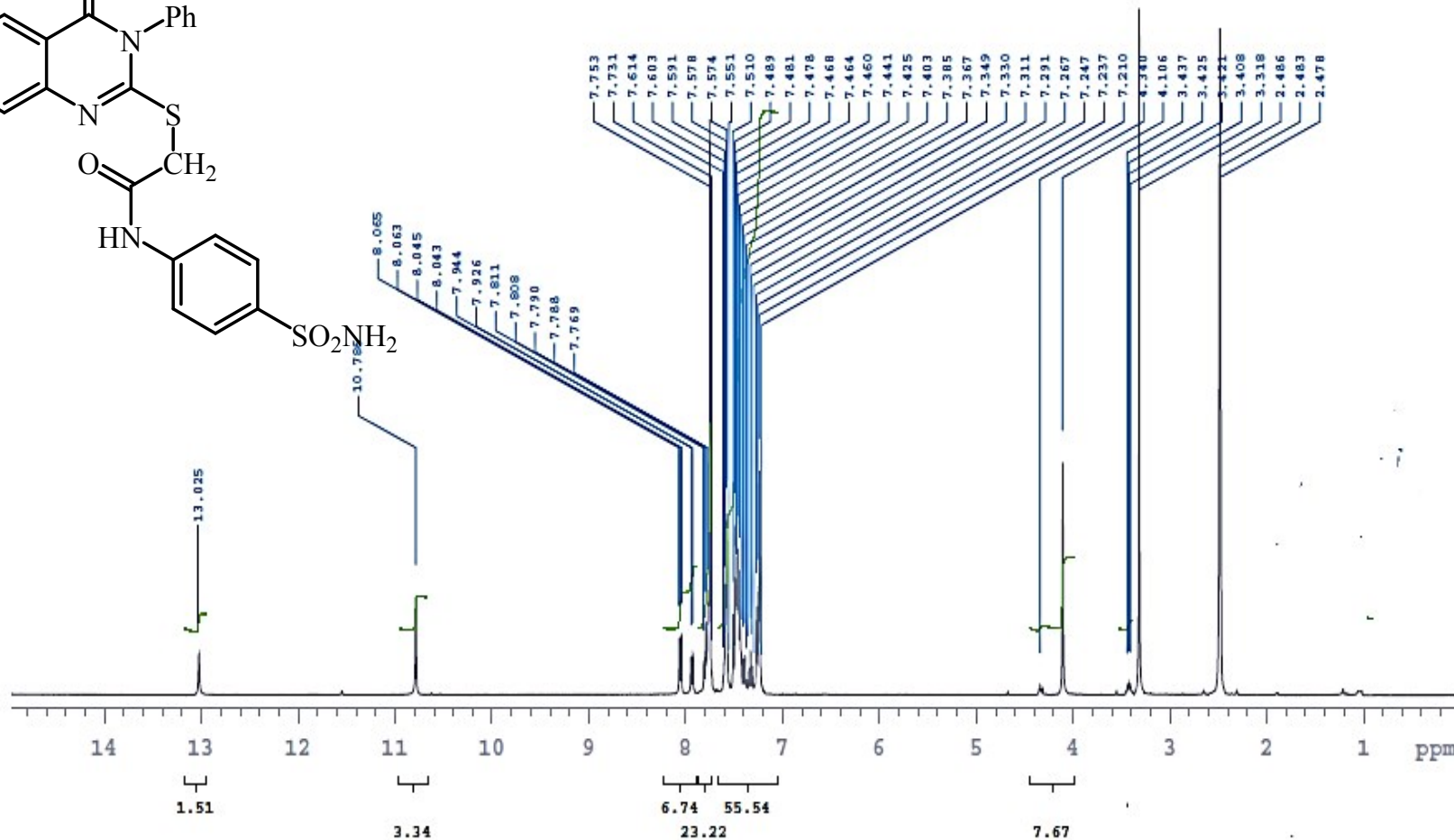
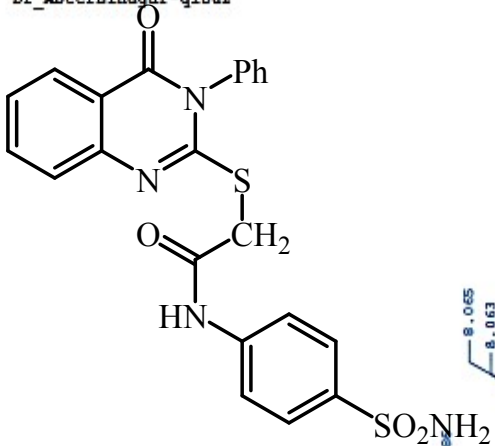
Date collected 2018-03-25

Solvent DMSO

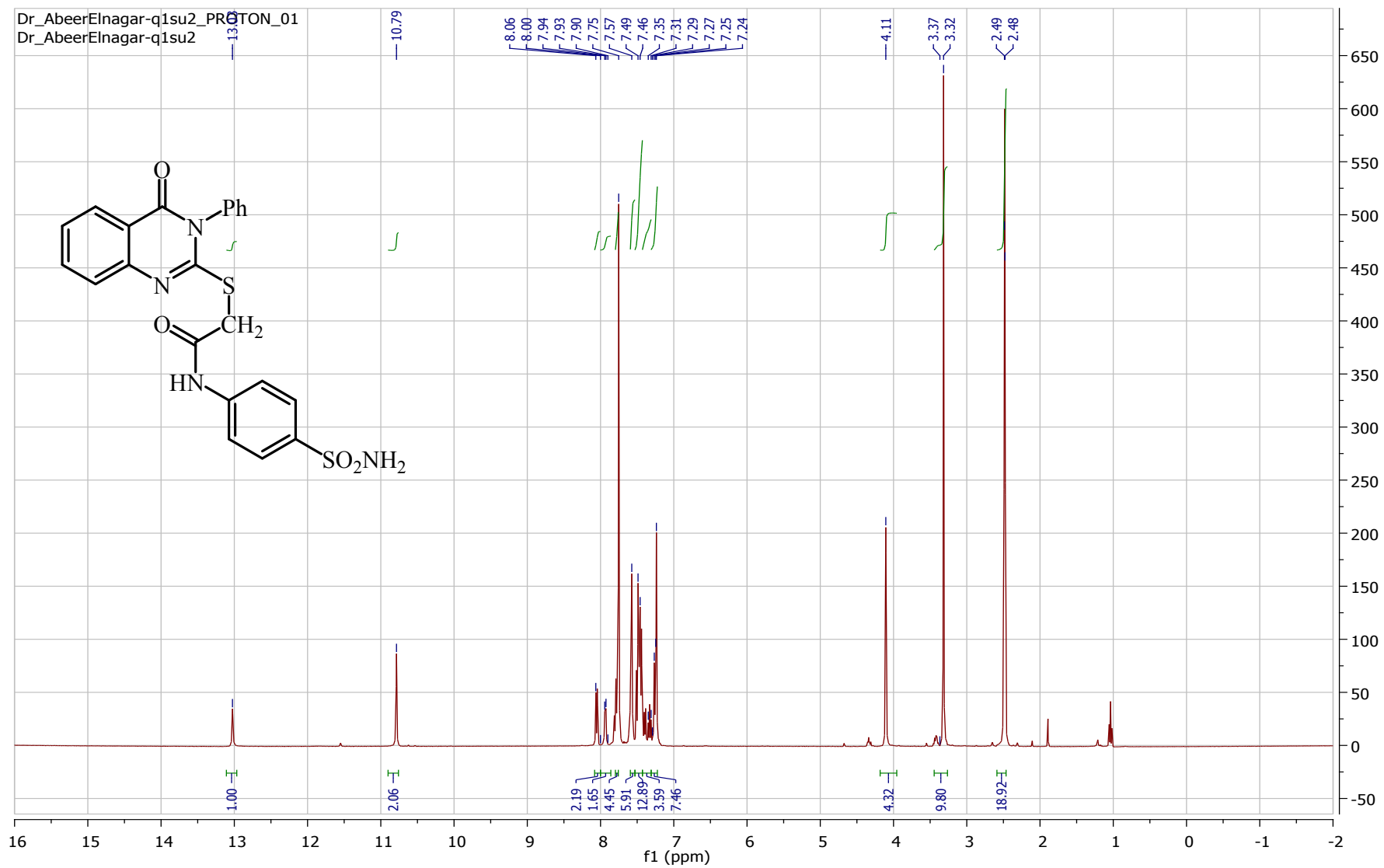
Spectrometer nmr400-mercury400

NMR User sameeh_Albadauy

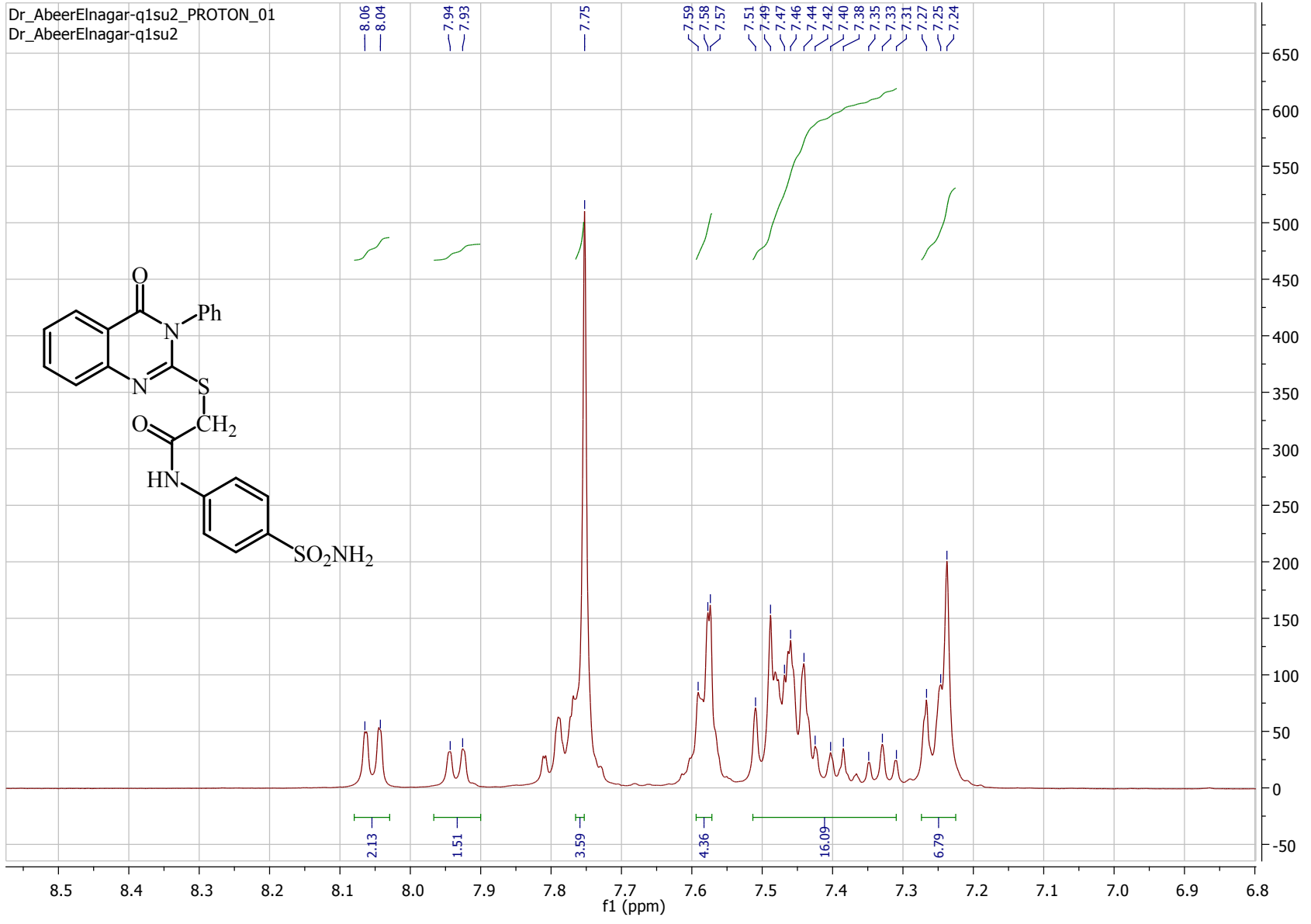
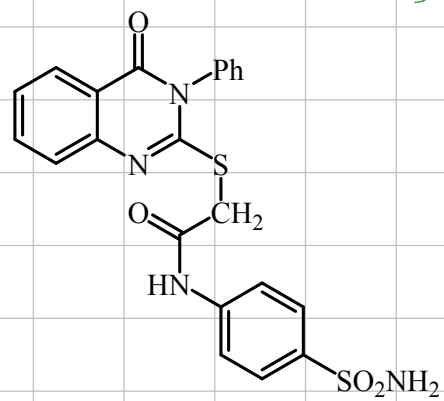
Dr_AbeerElnagar-q1su2



HNMR

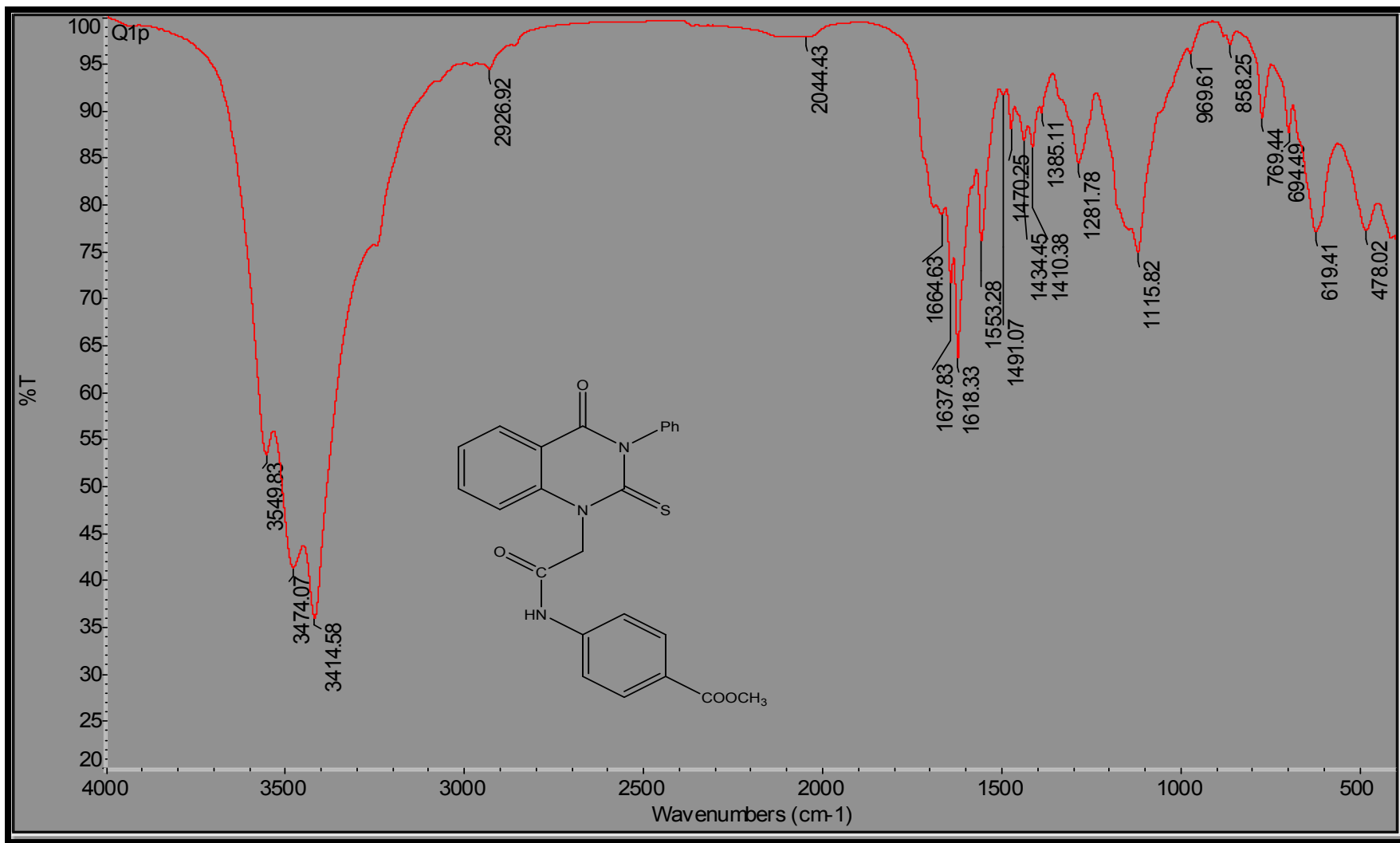


Dr_AbeerElnagar-q1su2_PROTON_01
Dr_AbeerElnagar-q1su2

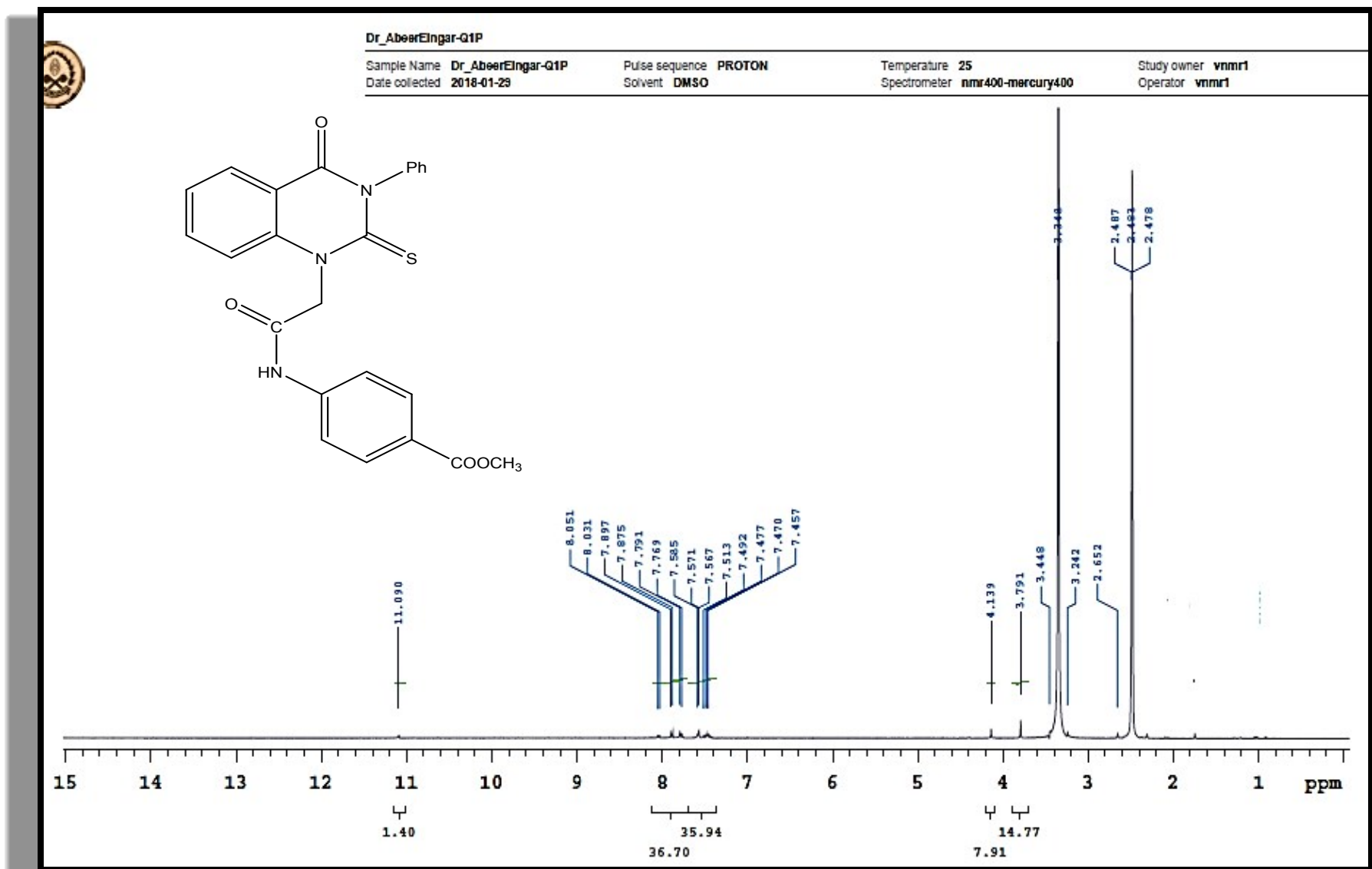


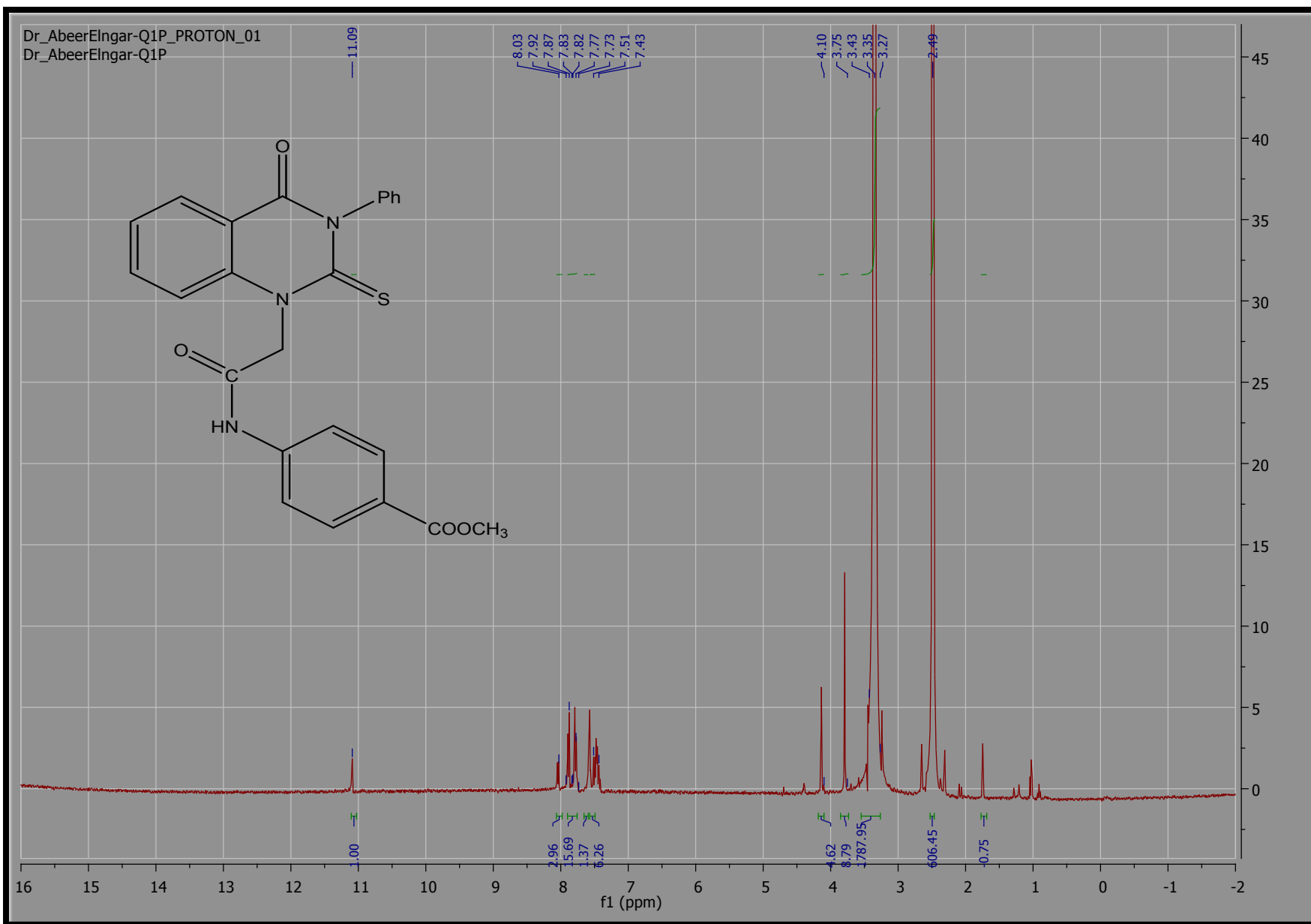
Methyl 4-(2-(4-oxo-3-phenyl-2-thioxo-3,4-dihydroquinazolin-1(2H)-yl)acetamido)benzoate (6a).

IR

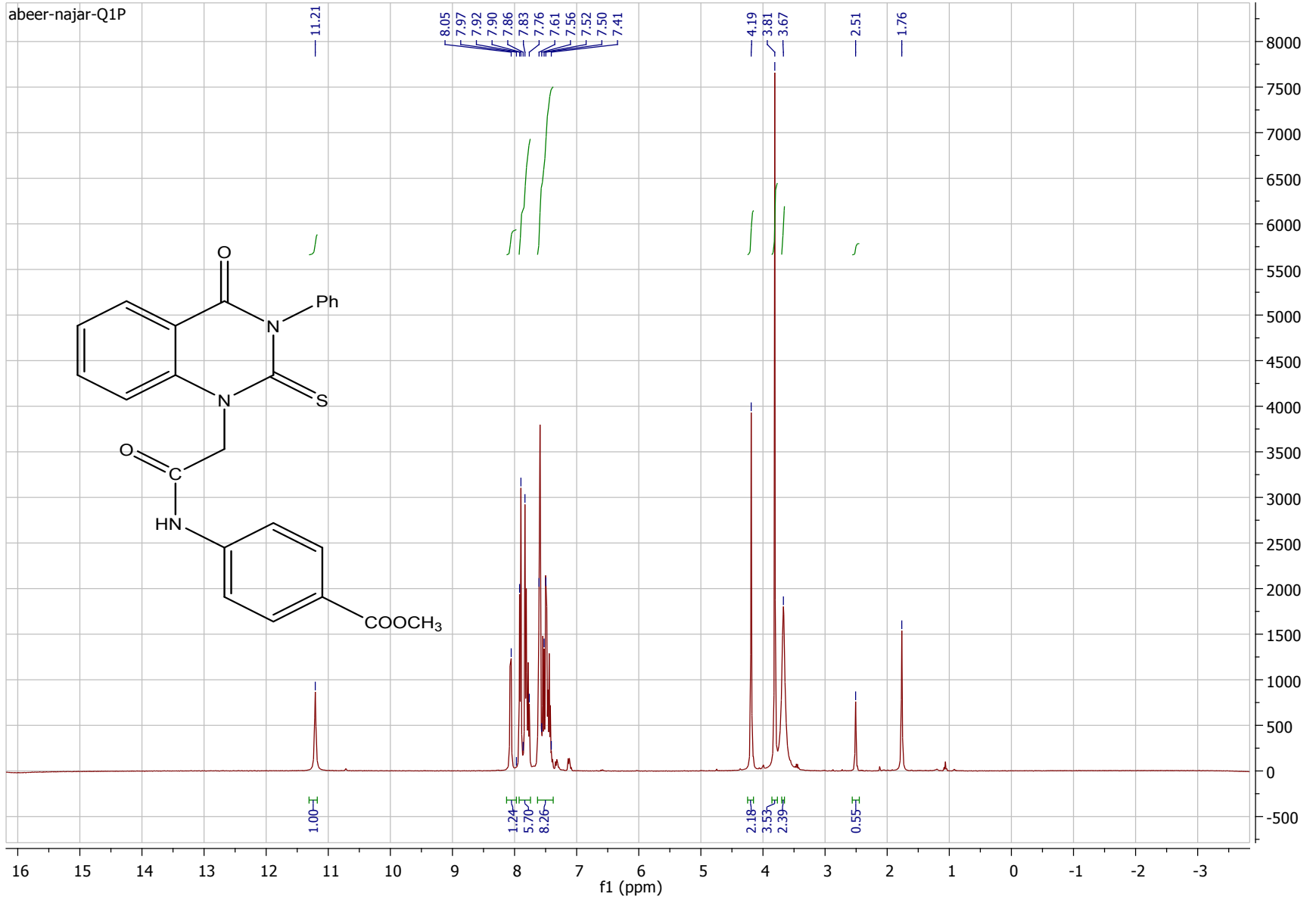


HNMR

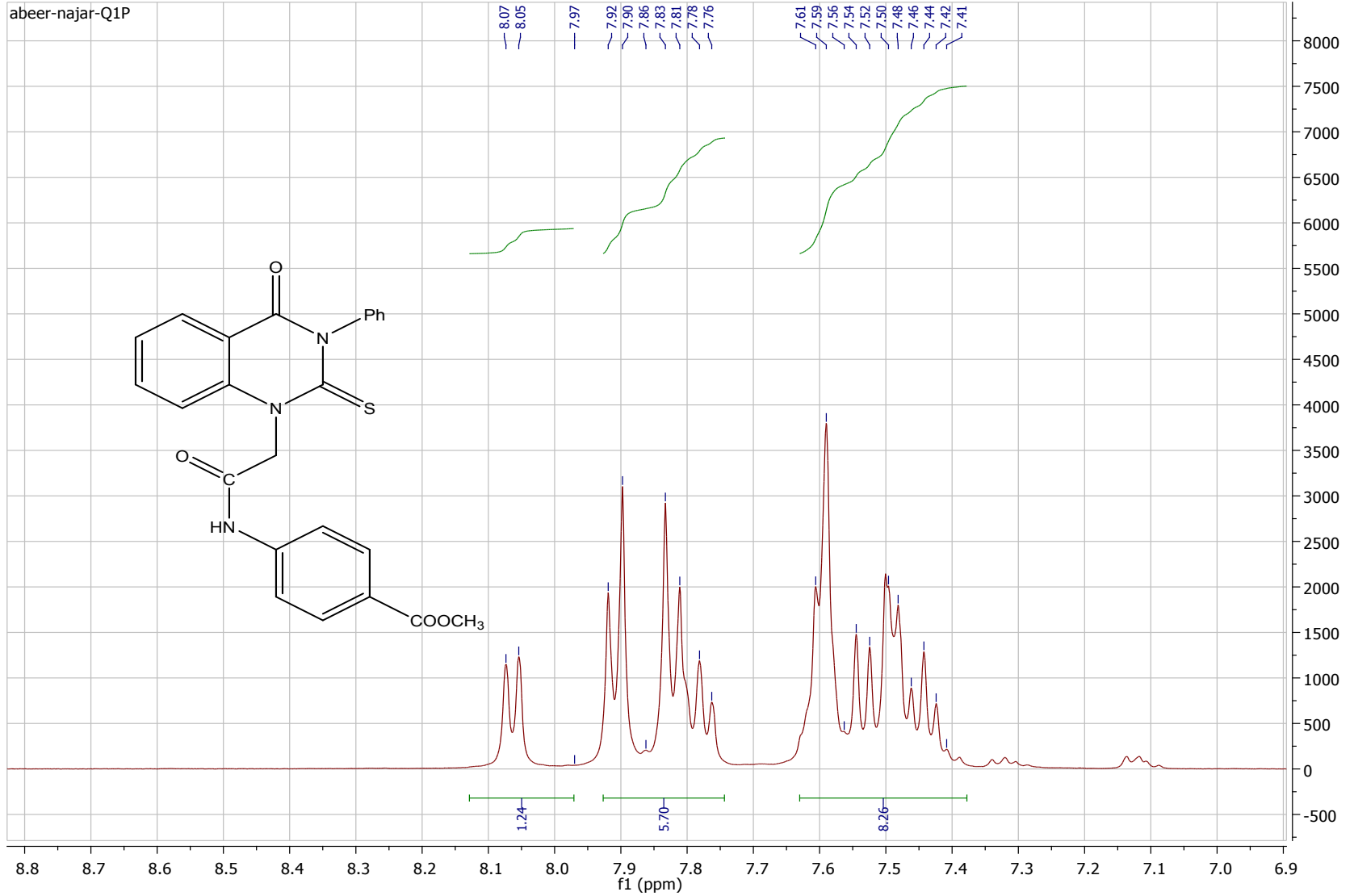




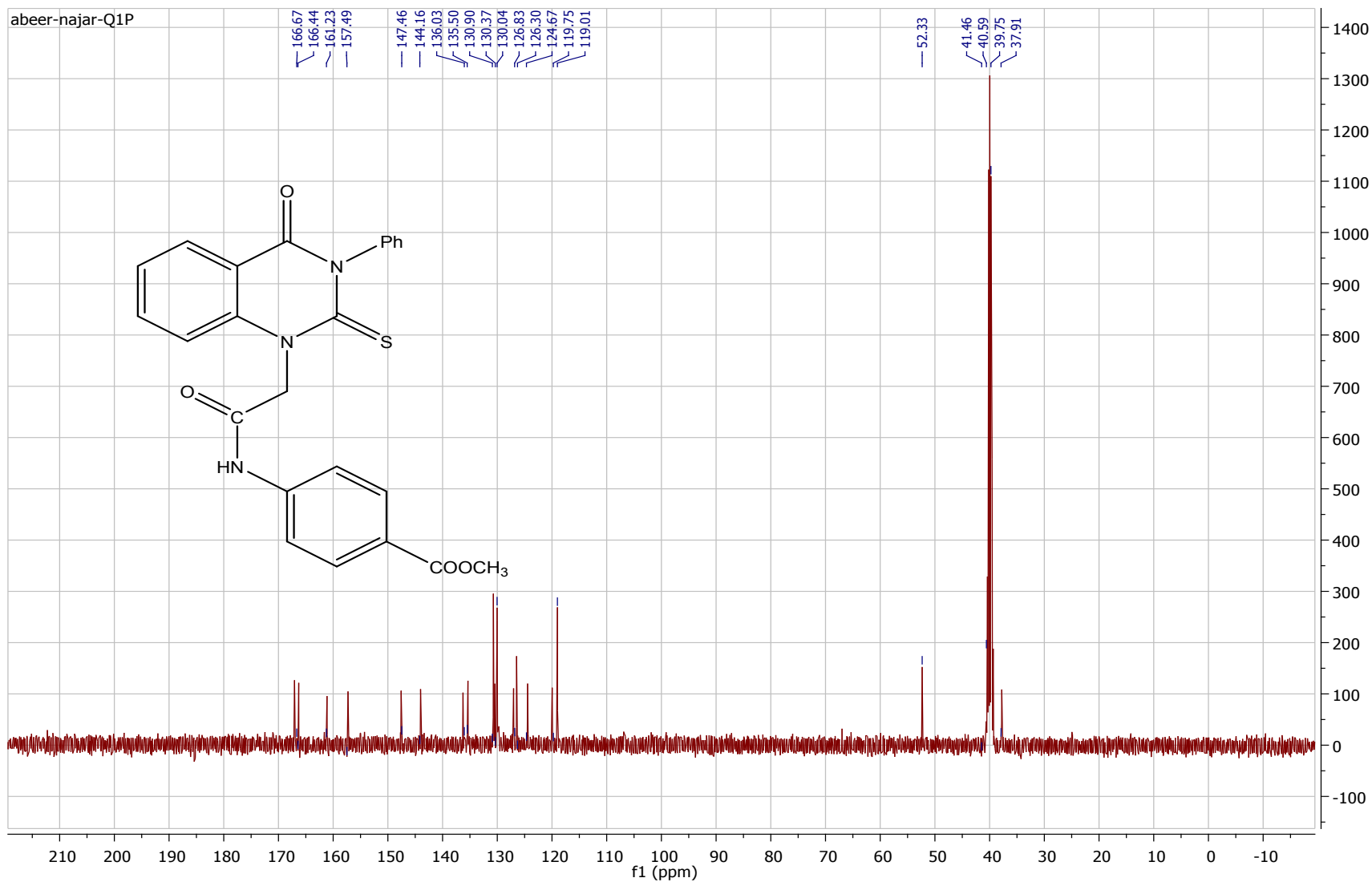
abeer-najar-Q1P



abeer-najar-Q1P

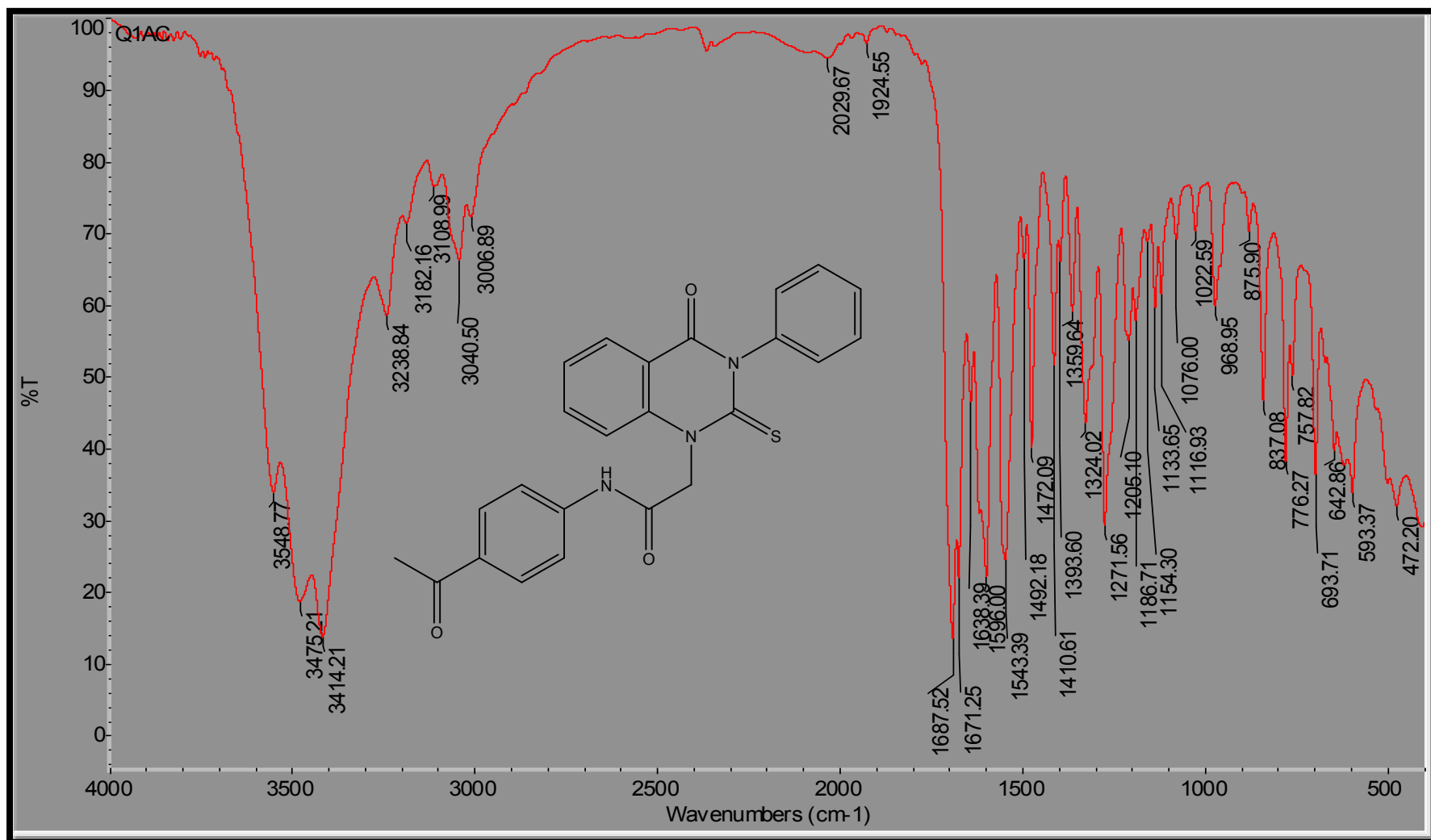


¹³C NMR



N-(4-acetylphenyl)-2-(4-oxo-3-phenyl-2-thioxo-3,4-dihydroquinazolin-1(2H)-yl)acetamide (6b).

IR



¹HNMR



Dr_AbeerElnagar-q1AC

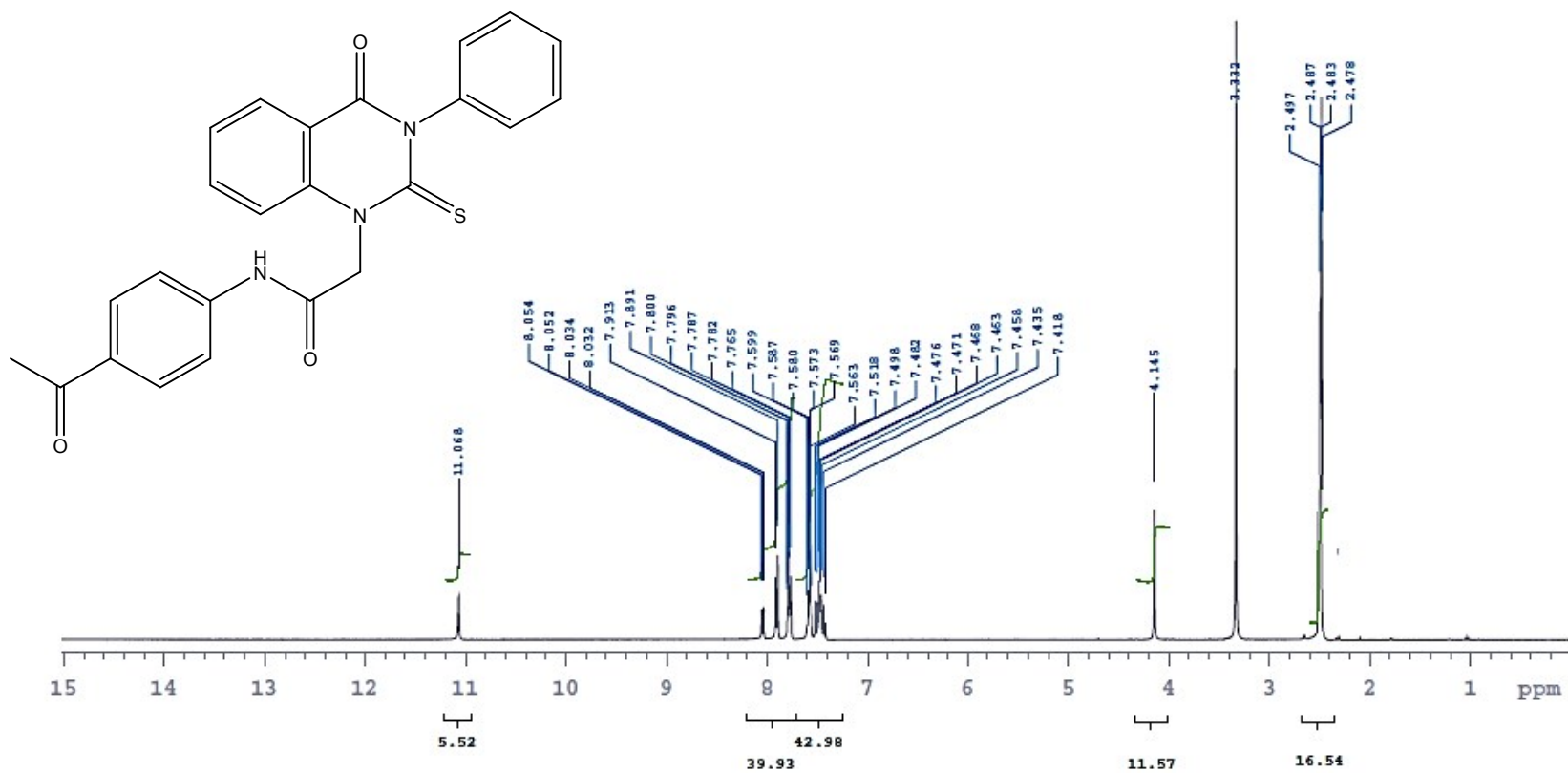
Dr_AbeerElnagar-q1AC

Sample Name Dr_AbeerElnagar-q1AC
Date collected 2018-03-25

Pulse sequence PROTON
Solvent DMSO

Temperature 25
Spectrometer nmr400-mercury400

Laboratory MODCL
NMR User sameeh_Albadowy





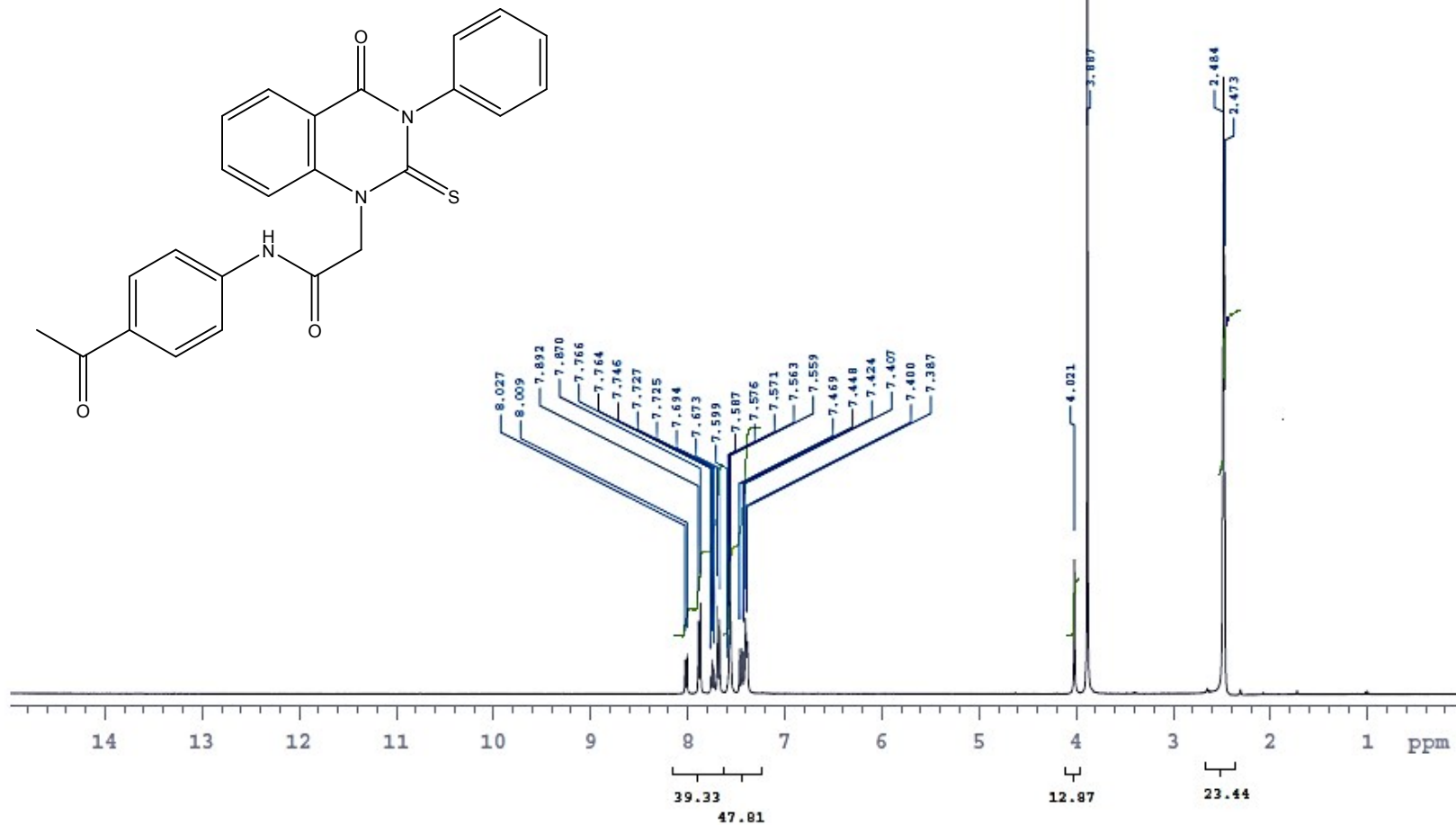
Dr_AbeerElmagar-q1AC-D2O

Dr_AbeerElmagar-q1AC-D2O

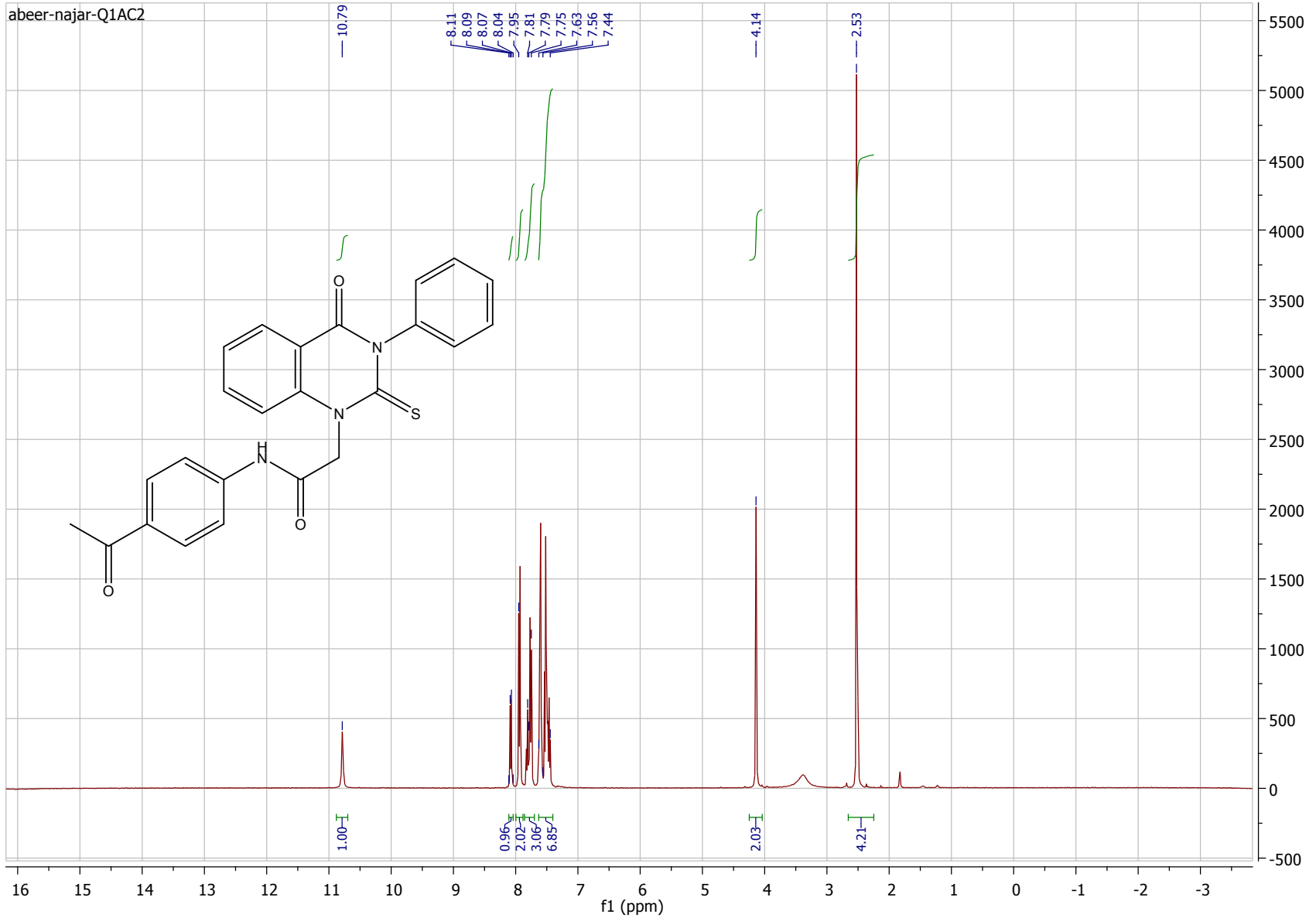
Sample Name **Dr_AbeerElmagar-q1AC-D2O** Pulse sequence **PROTON**
Date collected **2018-03-26** Solvent **DMSO**

Temperature **25**
Spectrometer **nmr400-mercury400**

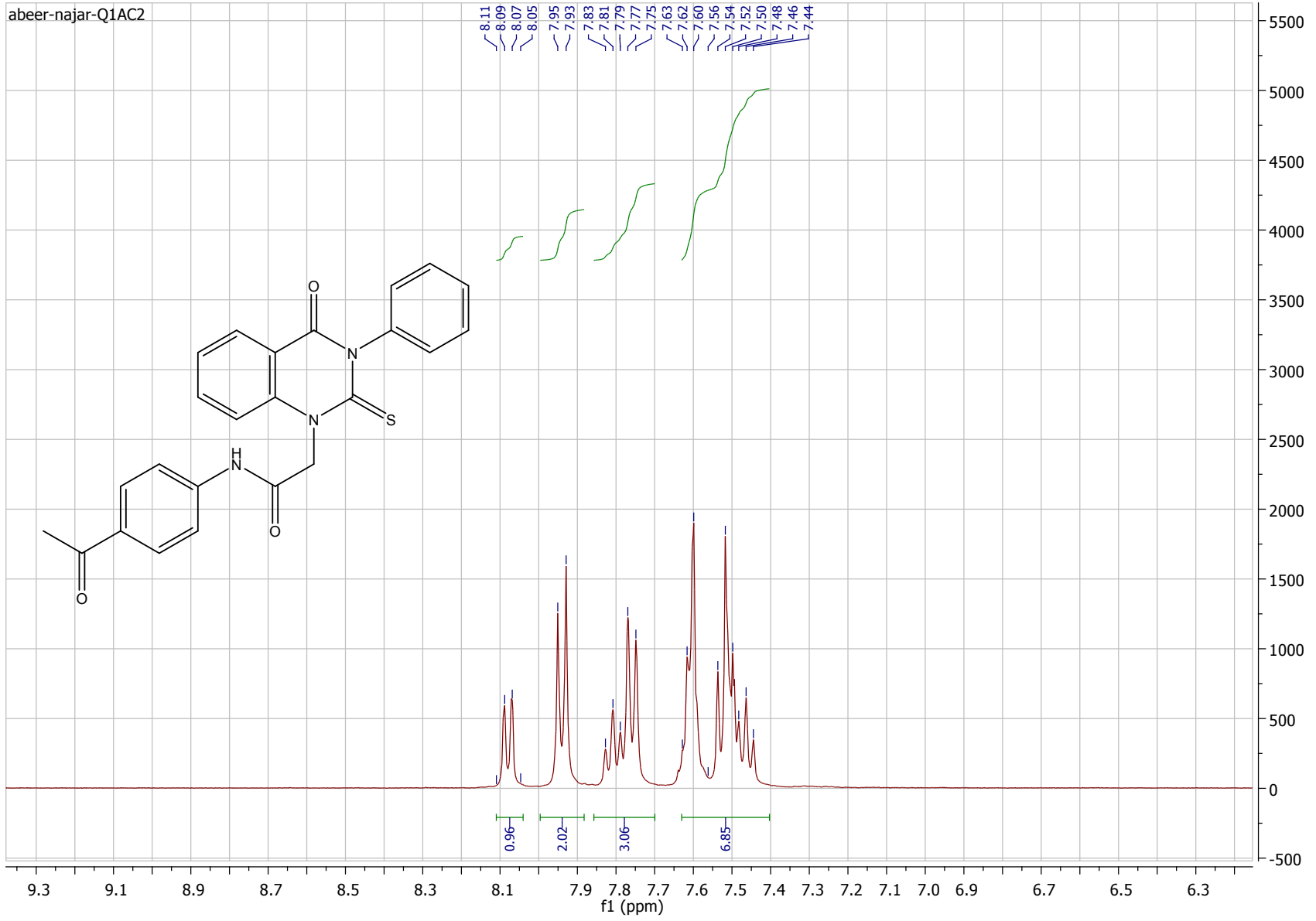
Laboratory **MODCL**
NMR User **sameeh_Albadauy**



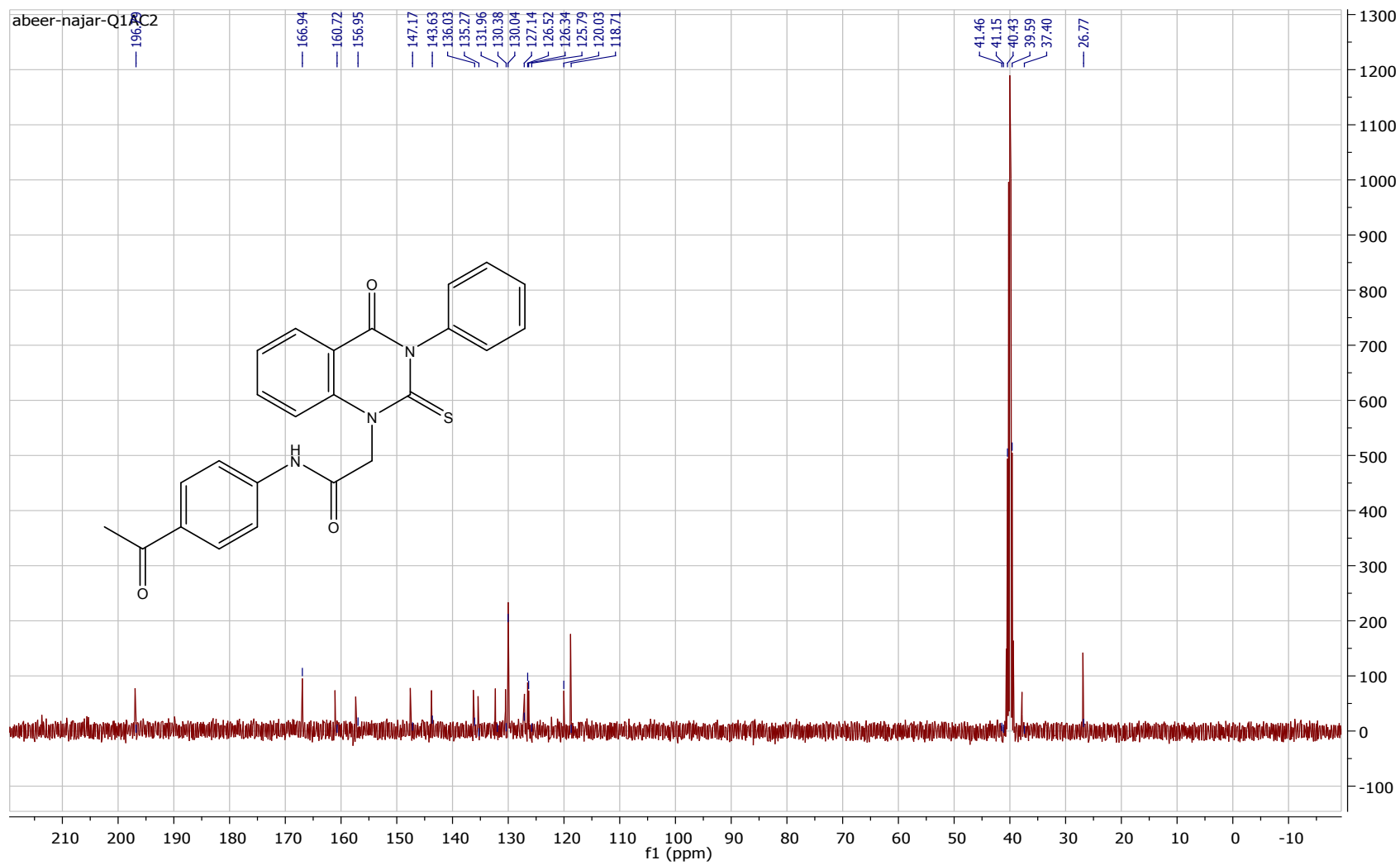
abeer-najar-Q1AC2



abeer-najar-Q1AC2

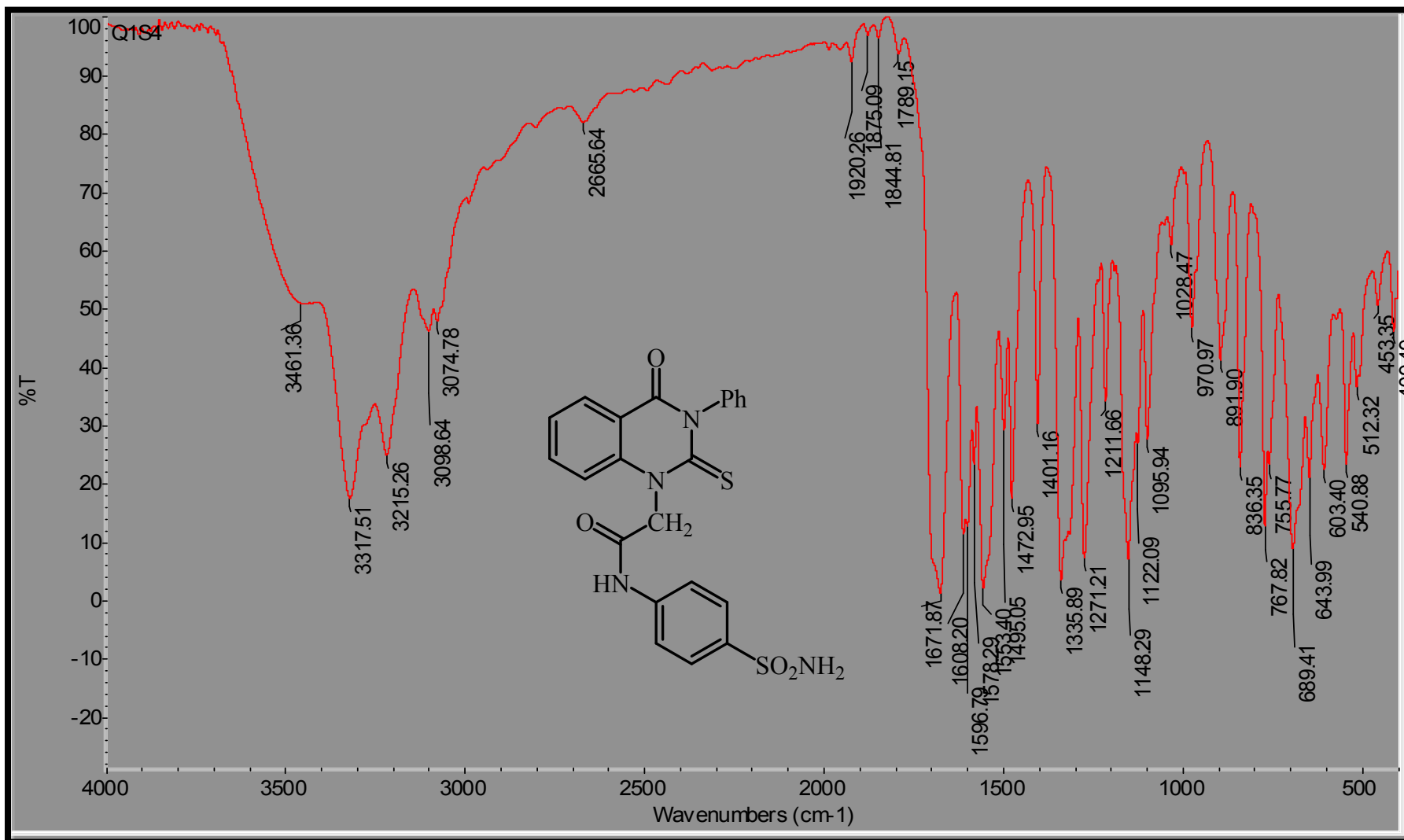


¹³C NMR

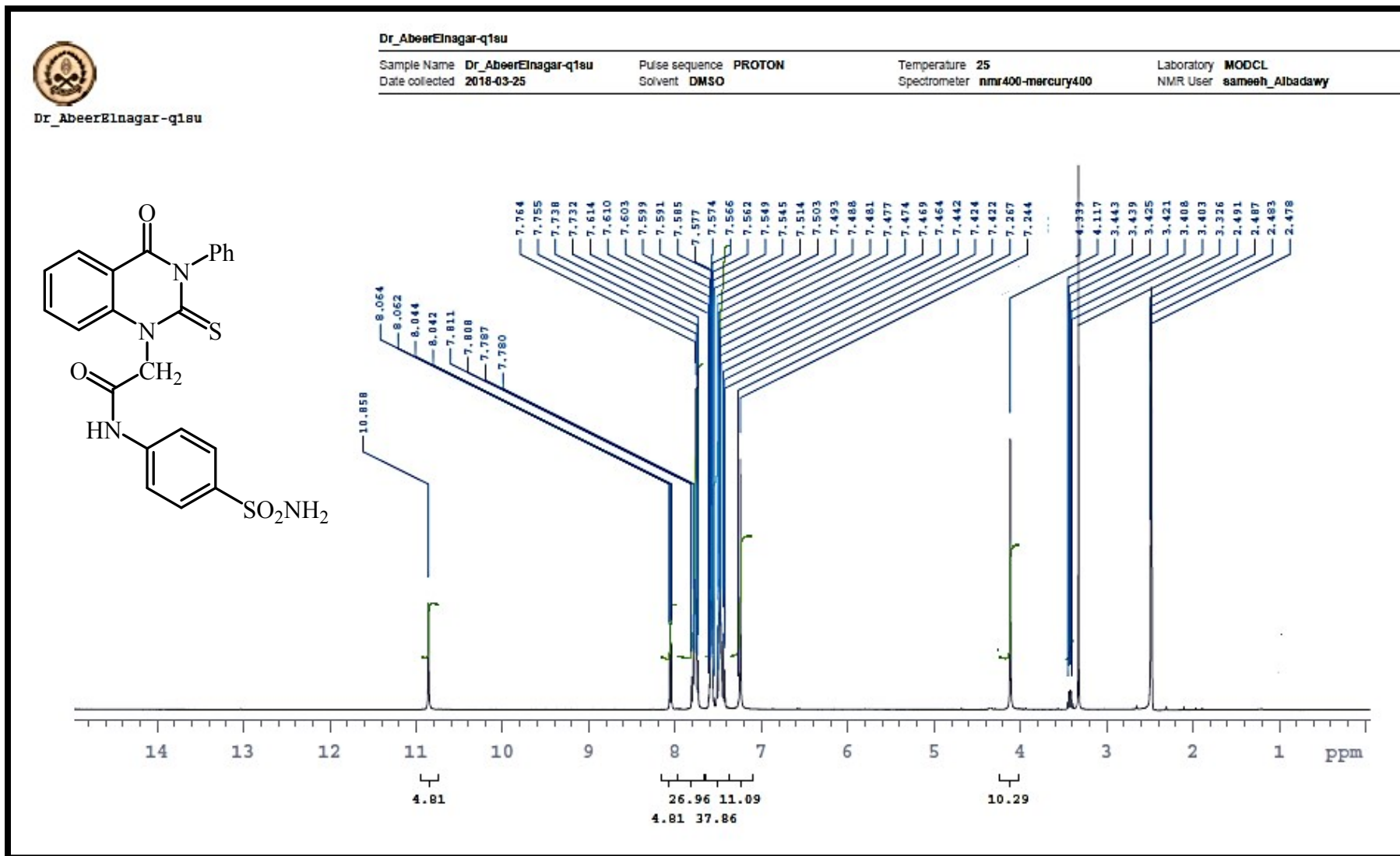


2-(4-Oxo-3-phenyl-2-thioxo-3,4-dihydroquinazolin-1(2H)-yl)-N-(4-sulfamoylphenyl) acetamide (6c).

IR



HNMR





Dr_AbeerElnagar-q1su

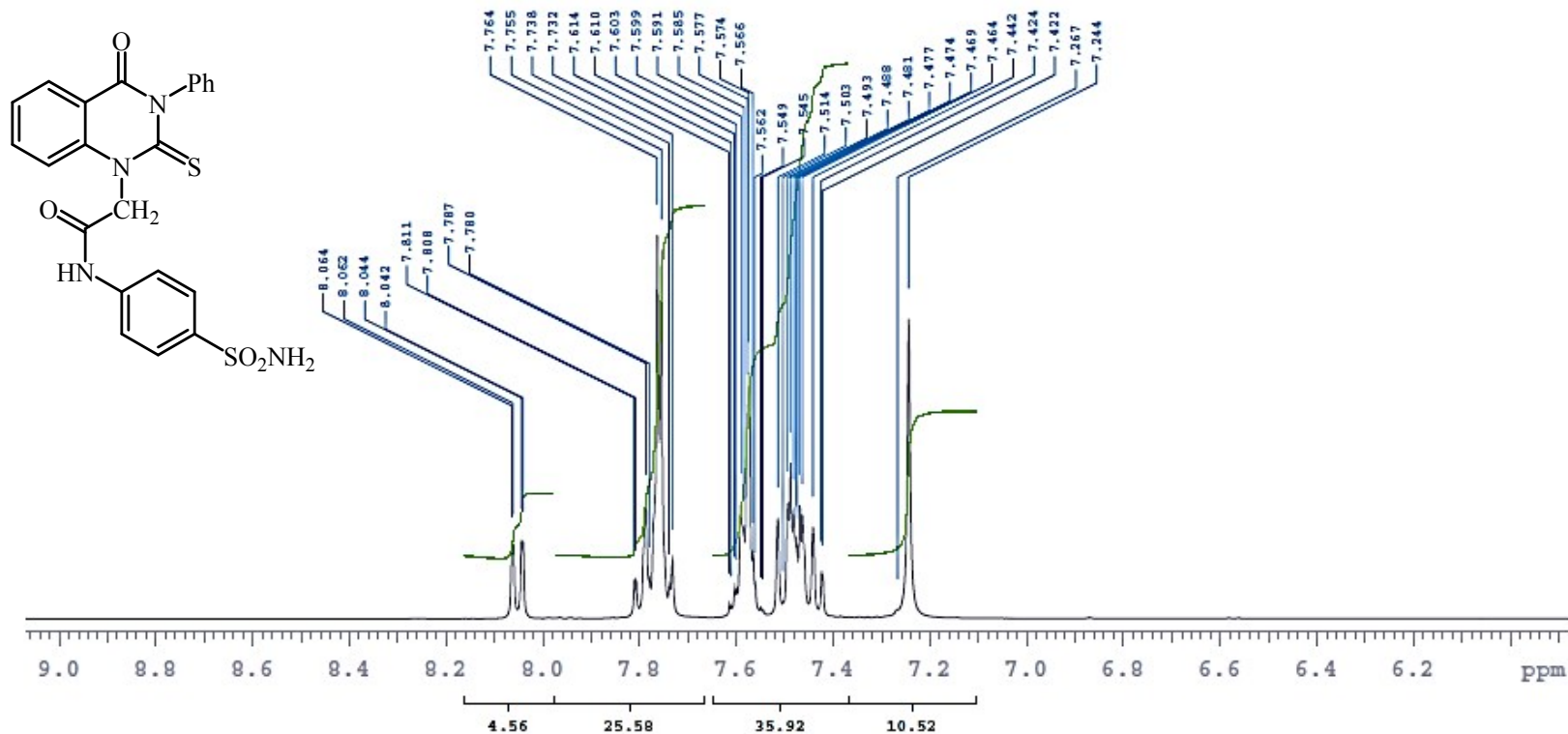
Dr_AbeerElnagar-q1su

Sample Name Dr_AbeerElnagar-q1su
Date collected 2018-03-25

Pulse sequence PROTON
Solvent DMSO

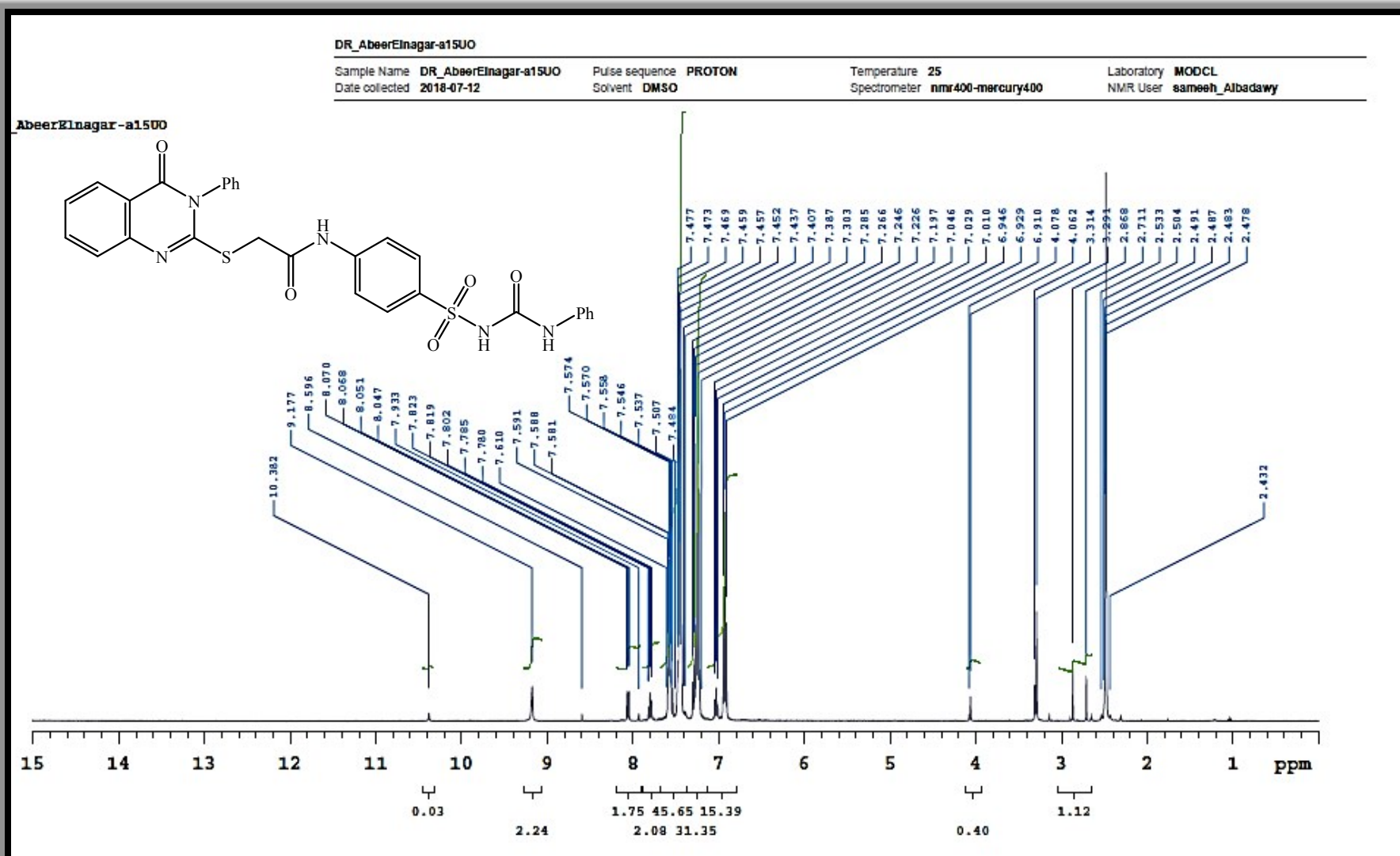
Temperature 25
Spectrometer nmr400-mercury400

Laboratory MODCL
NMR User sameeh_Albadawy

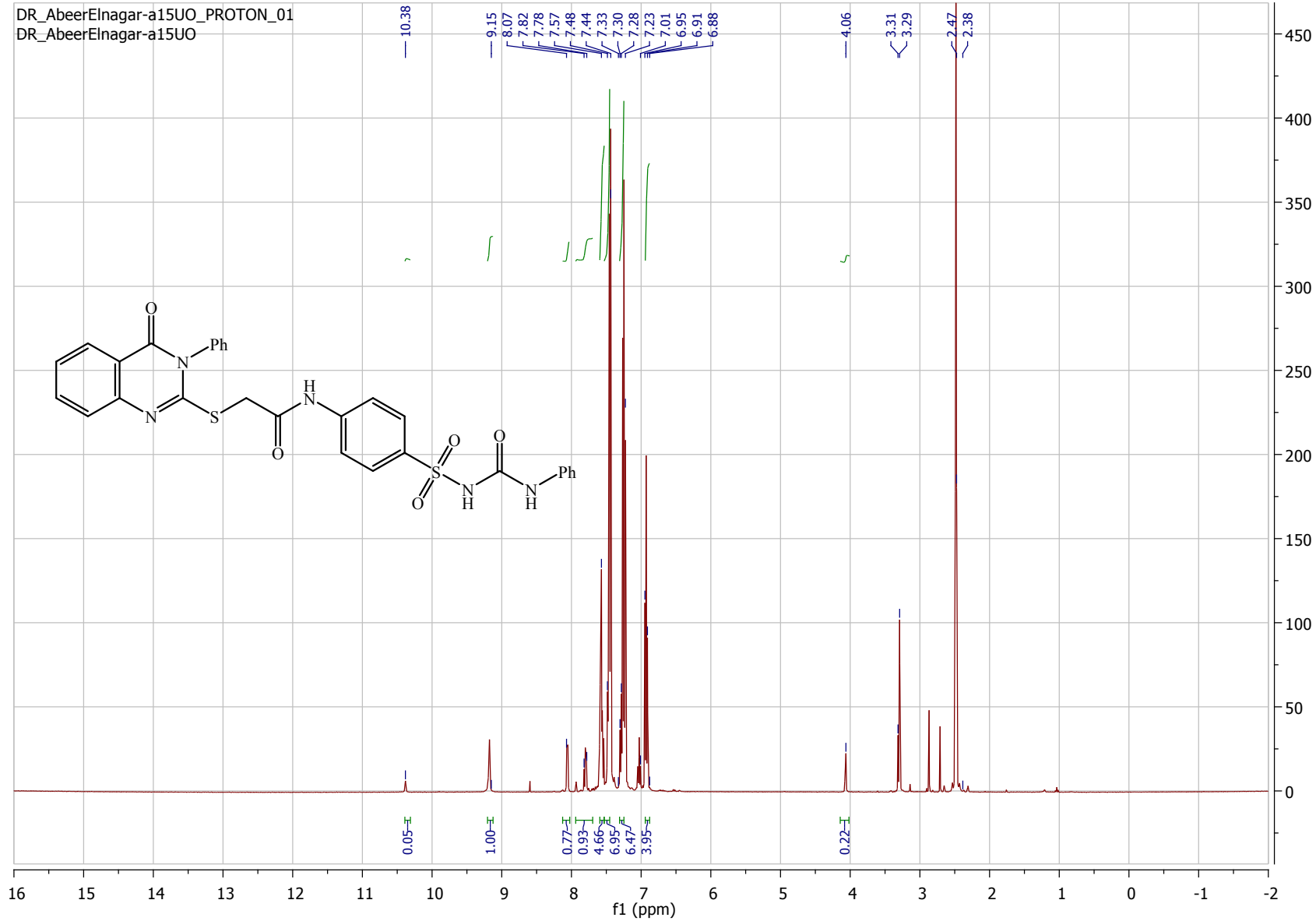


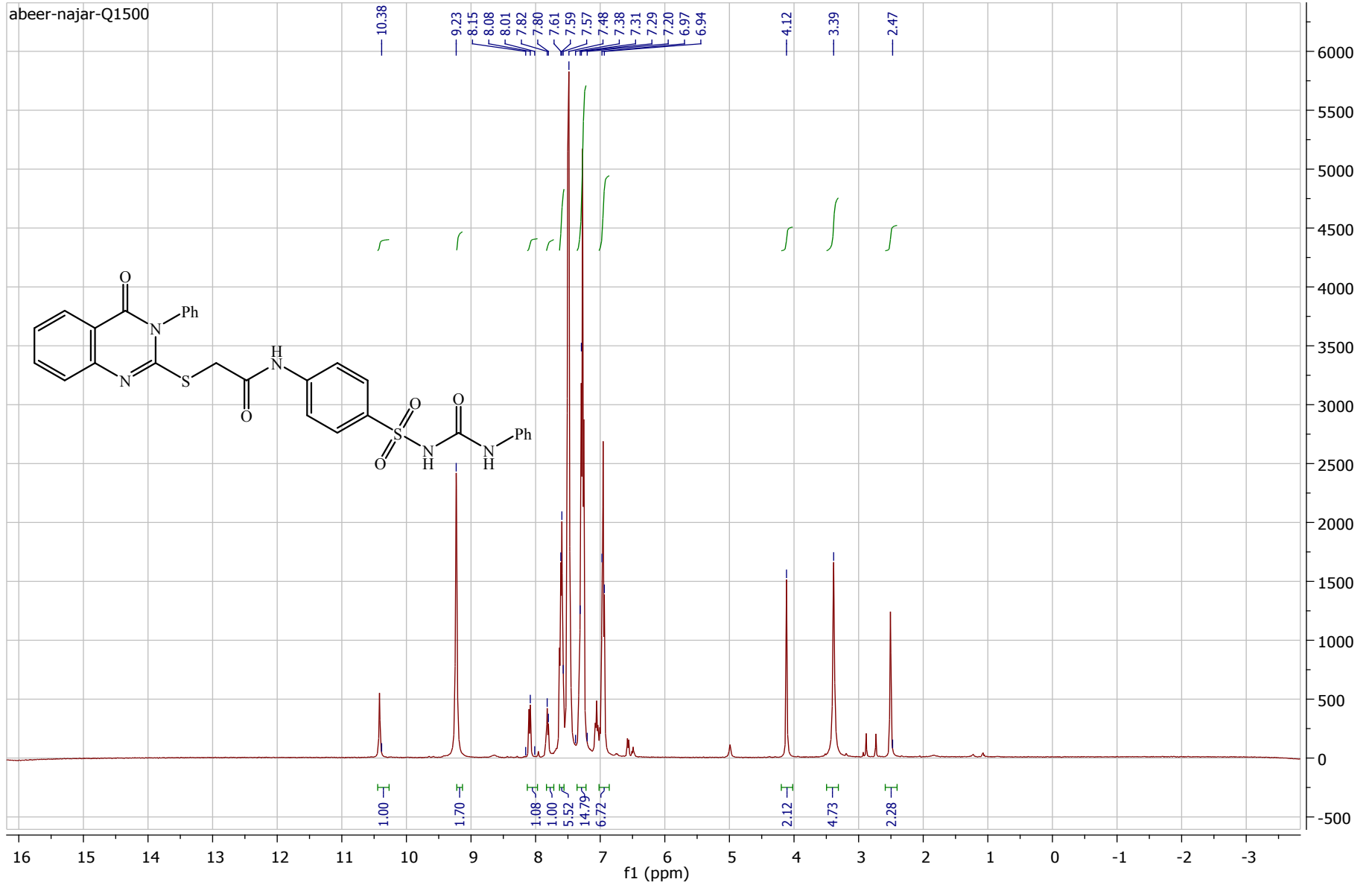
2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio)-N-(4-(N-(phenylcarbamoyl) sulfamoyl) phenyl)acetamide (7a).

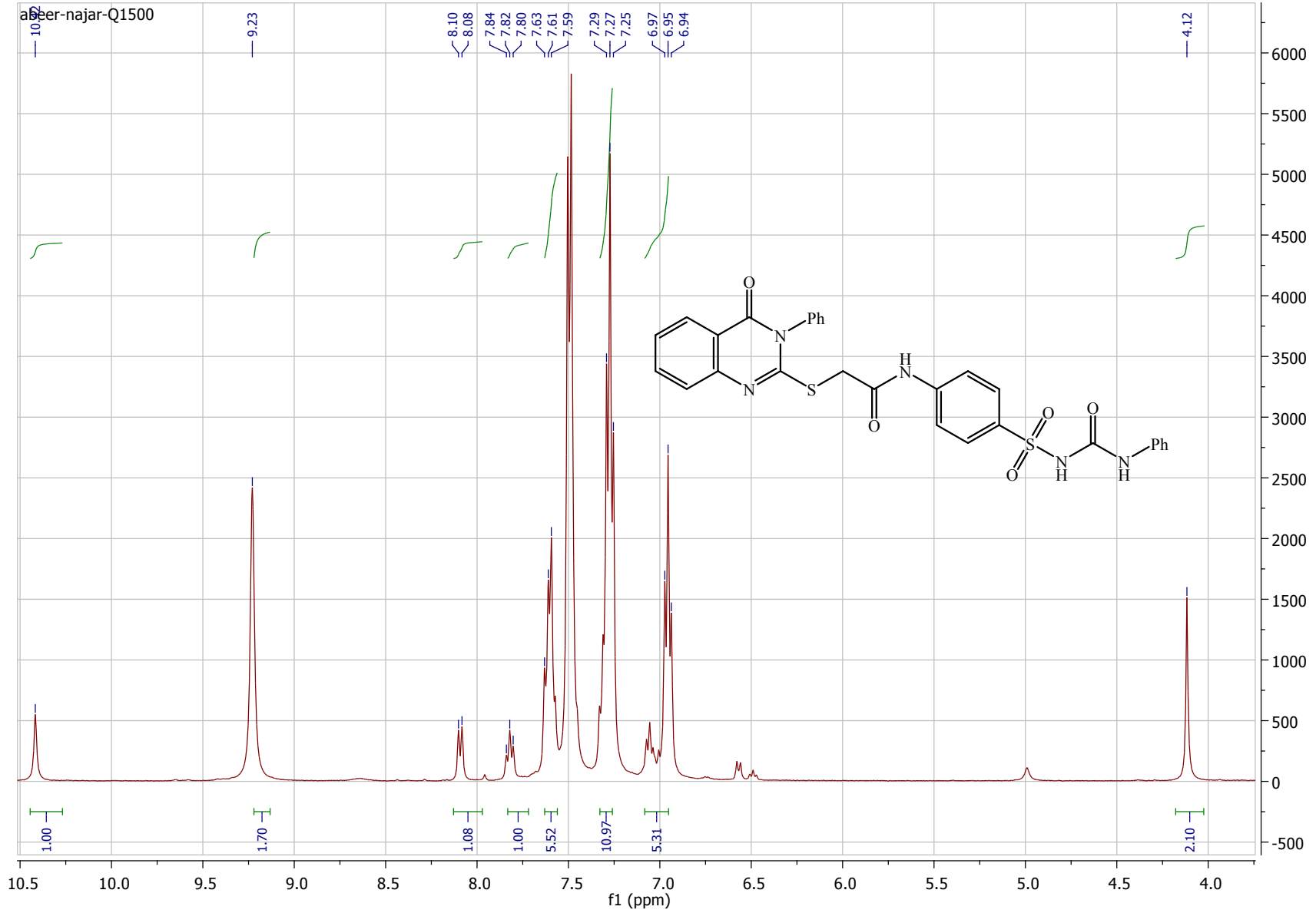
HNMR



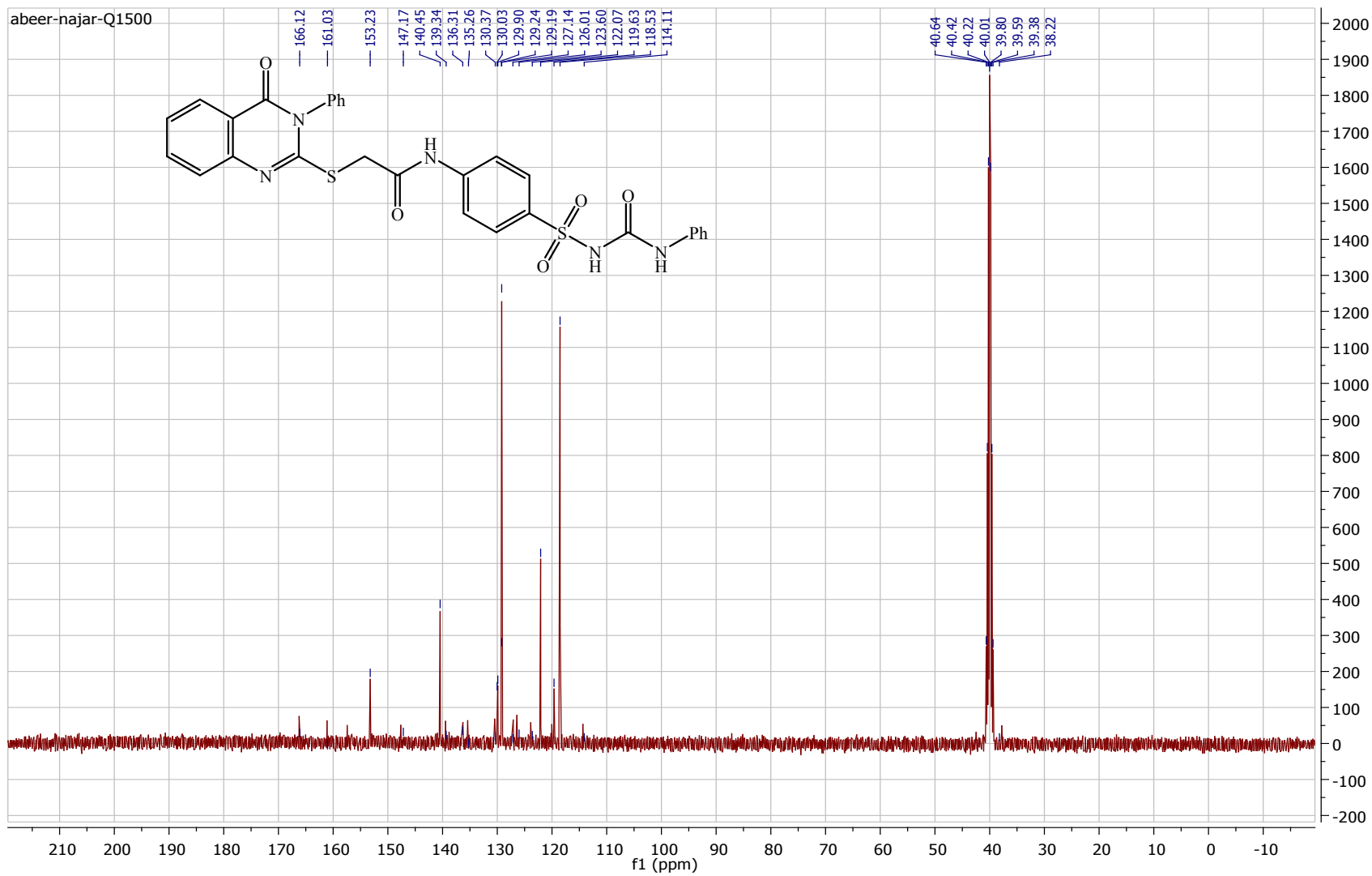
DR_AbeerElnagar-a15UO_PROTON_01
DR_AbeerElnagar-a15UO

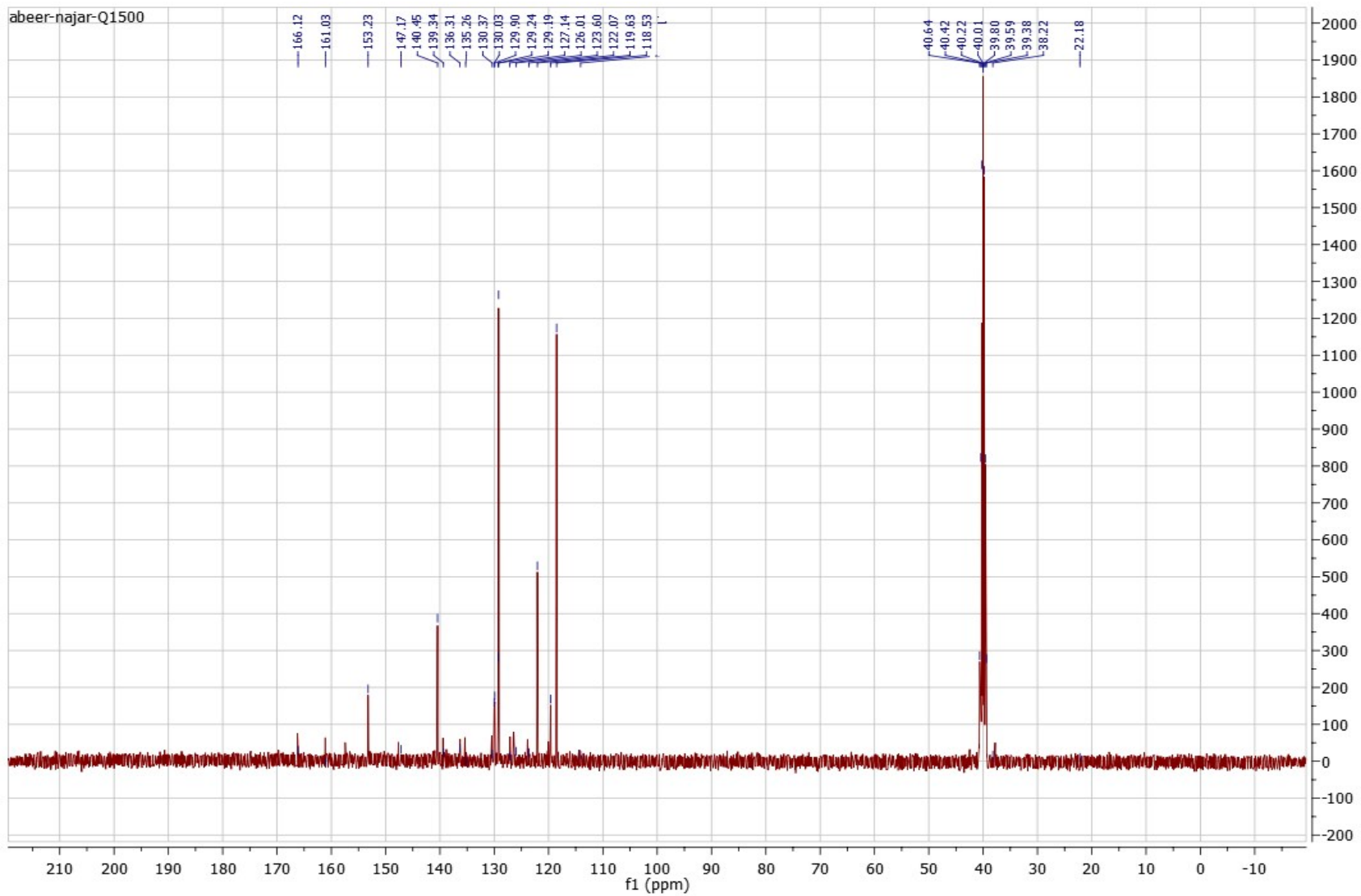


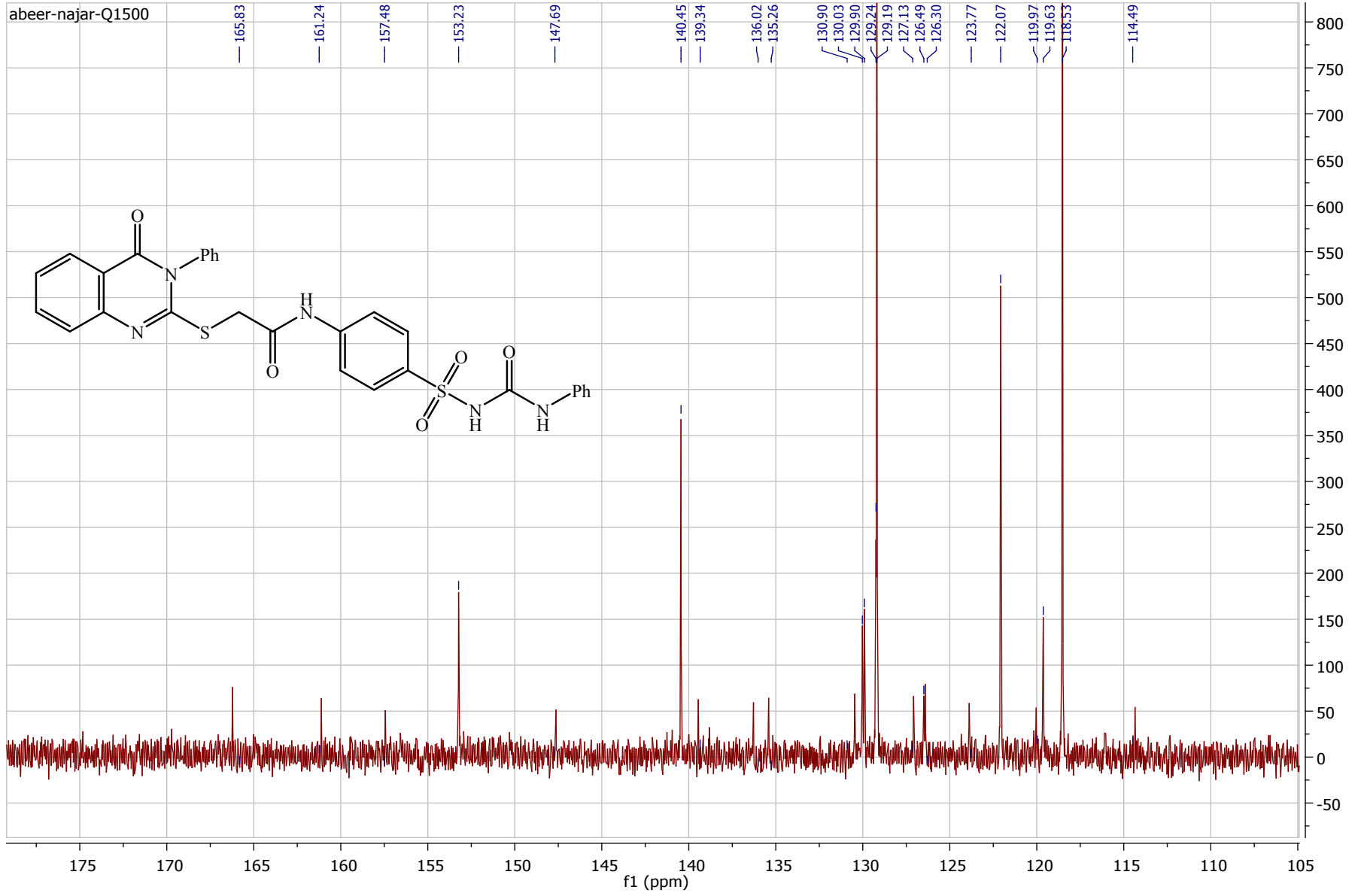




¹³C NMR

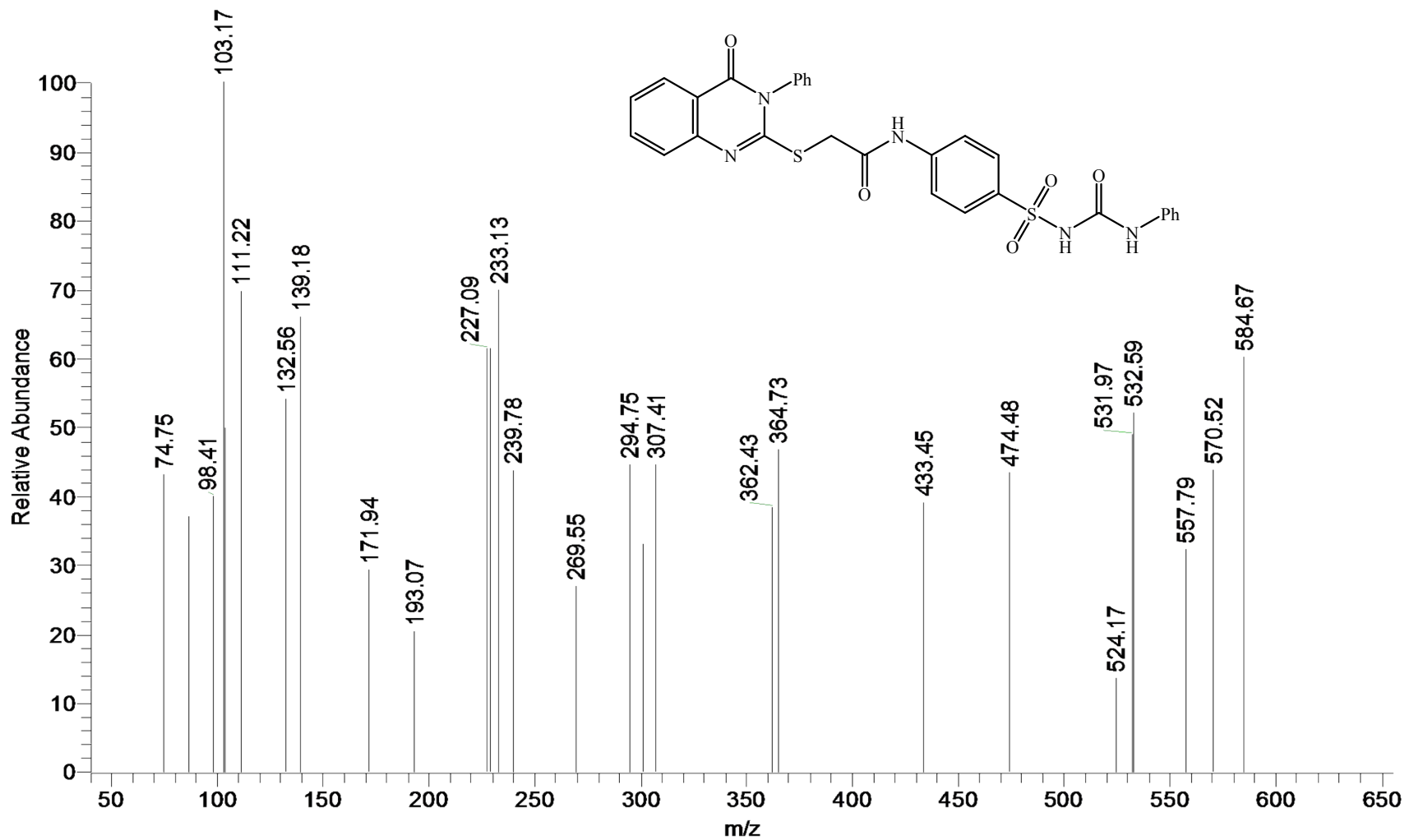






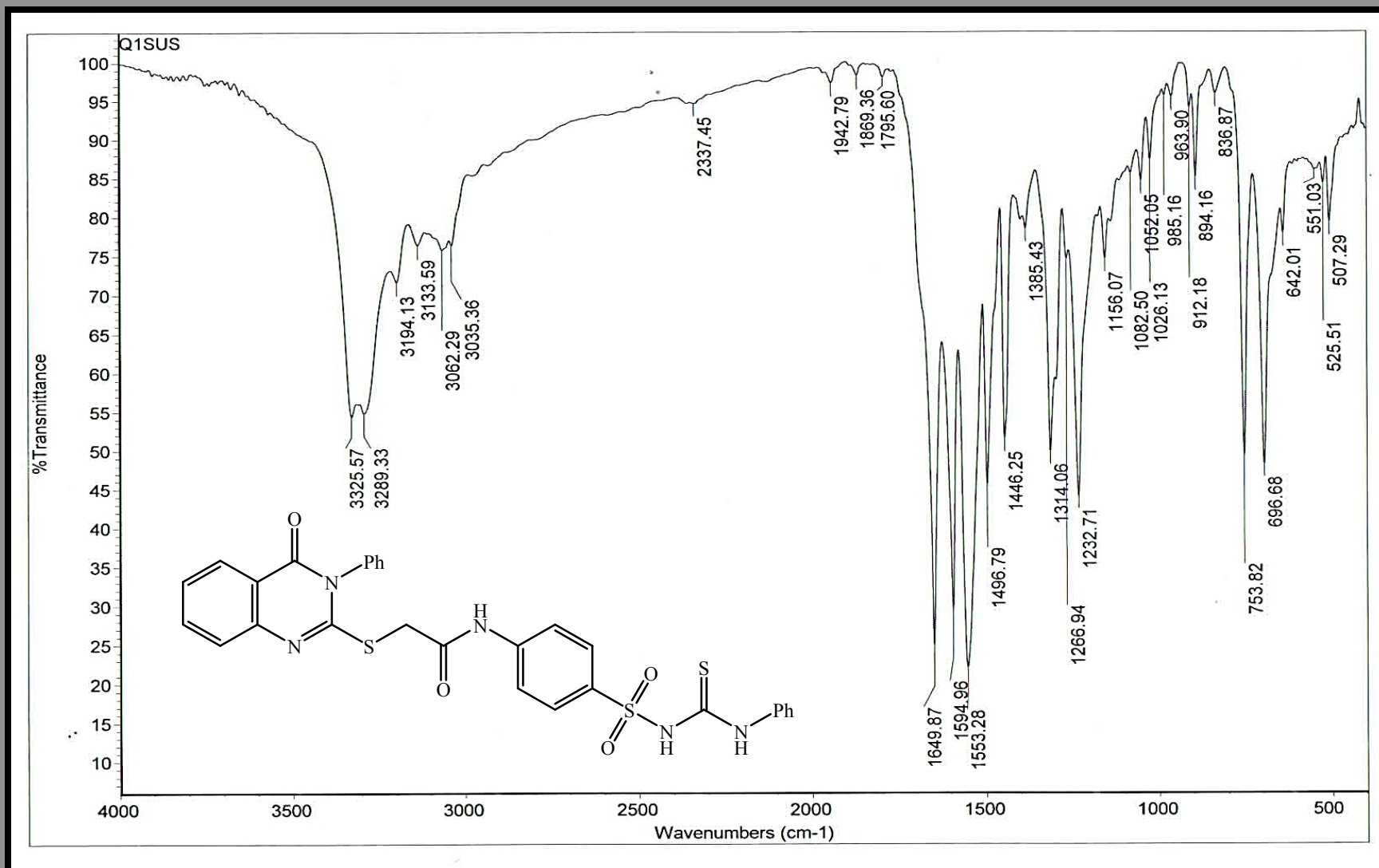
Mass

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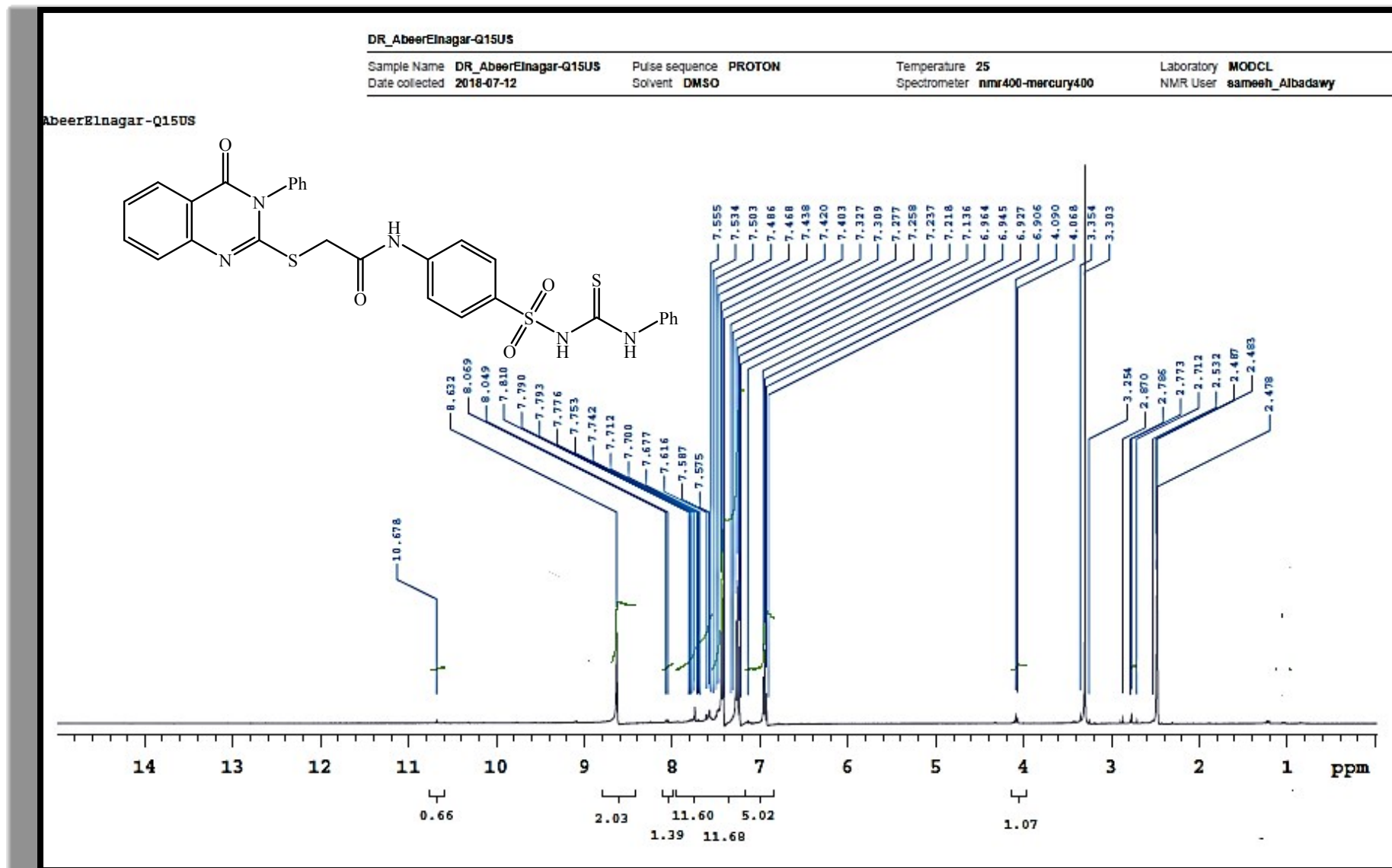


2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio)-N-(4-(N-(phenylcarbamothioyl) sulfamoyl) phenyl)acetamide (7b).

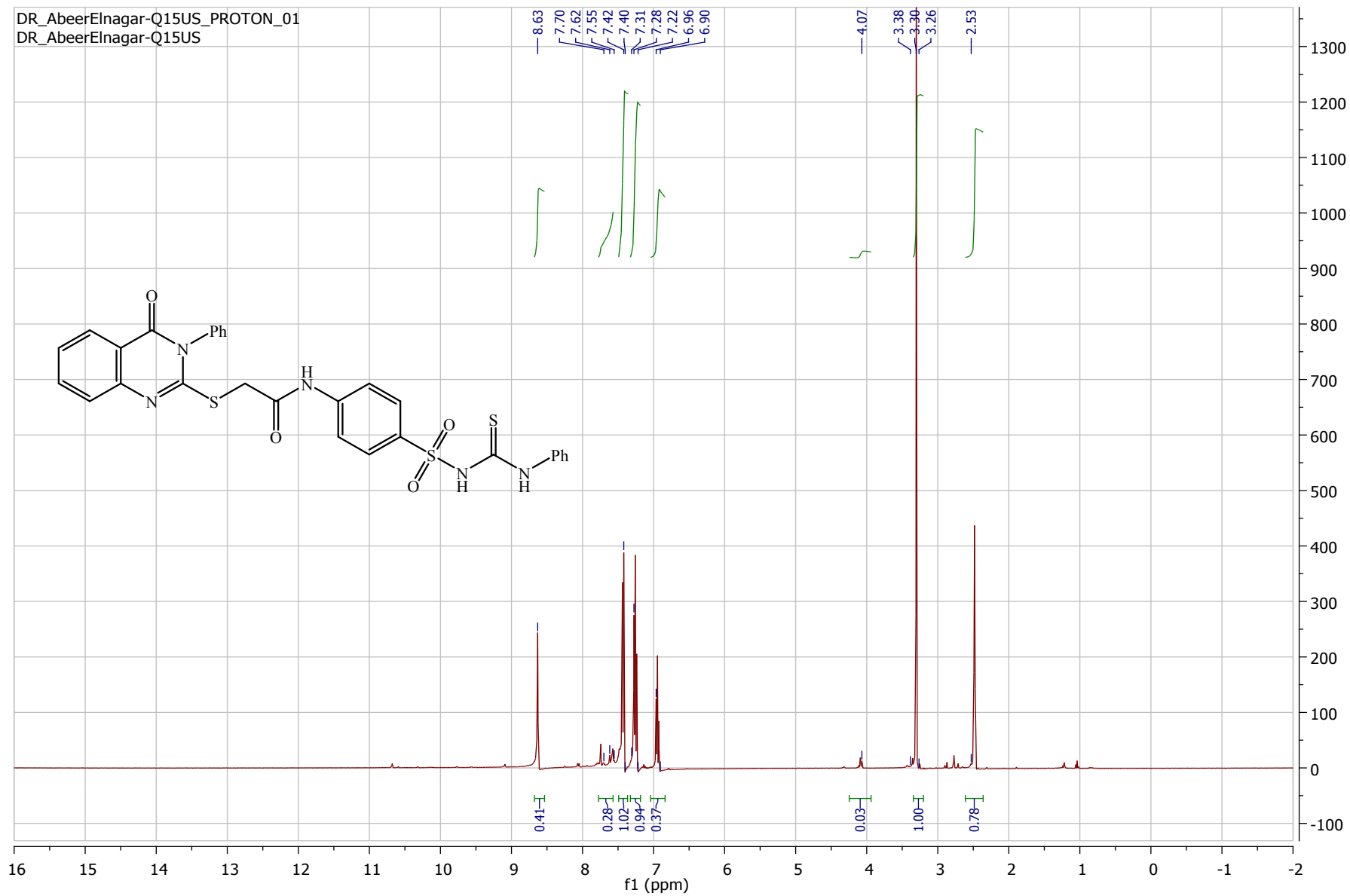
IR



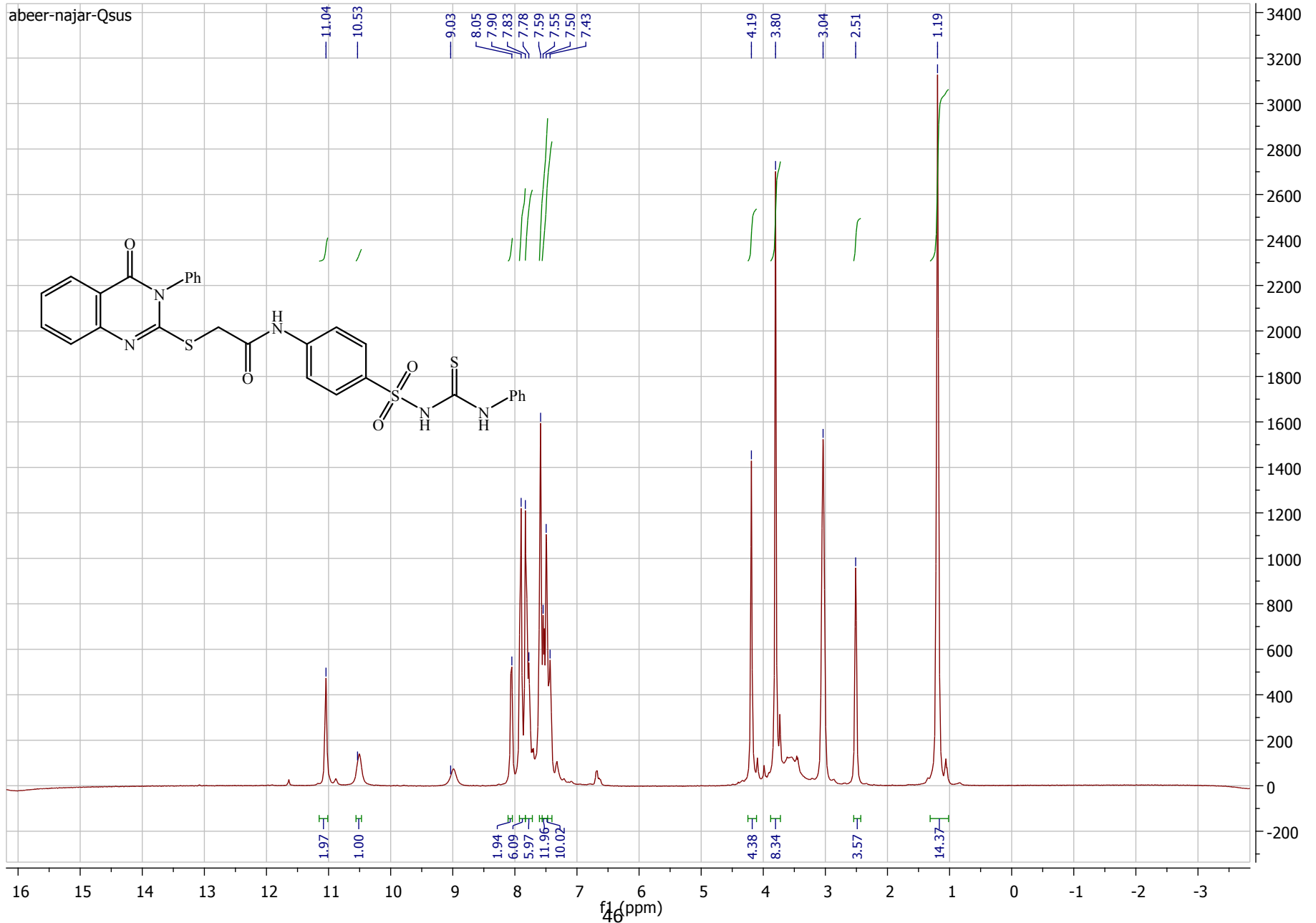
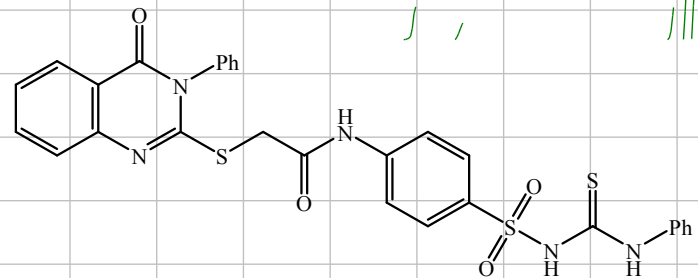
HNMR



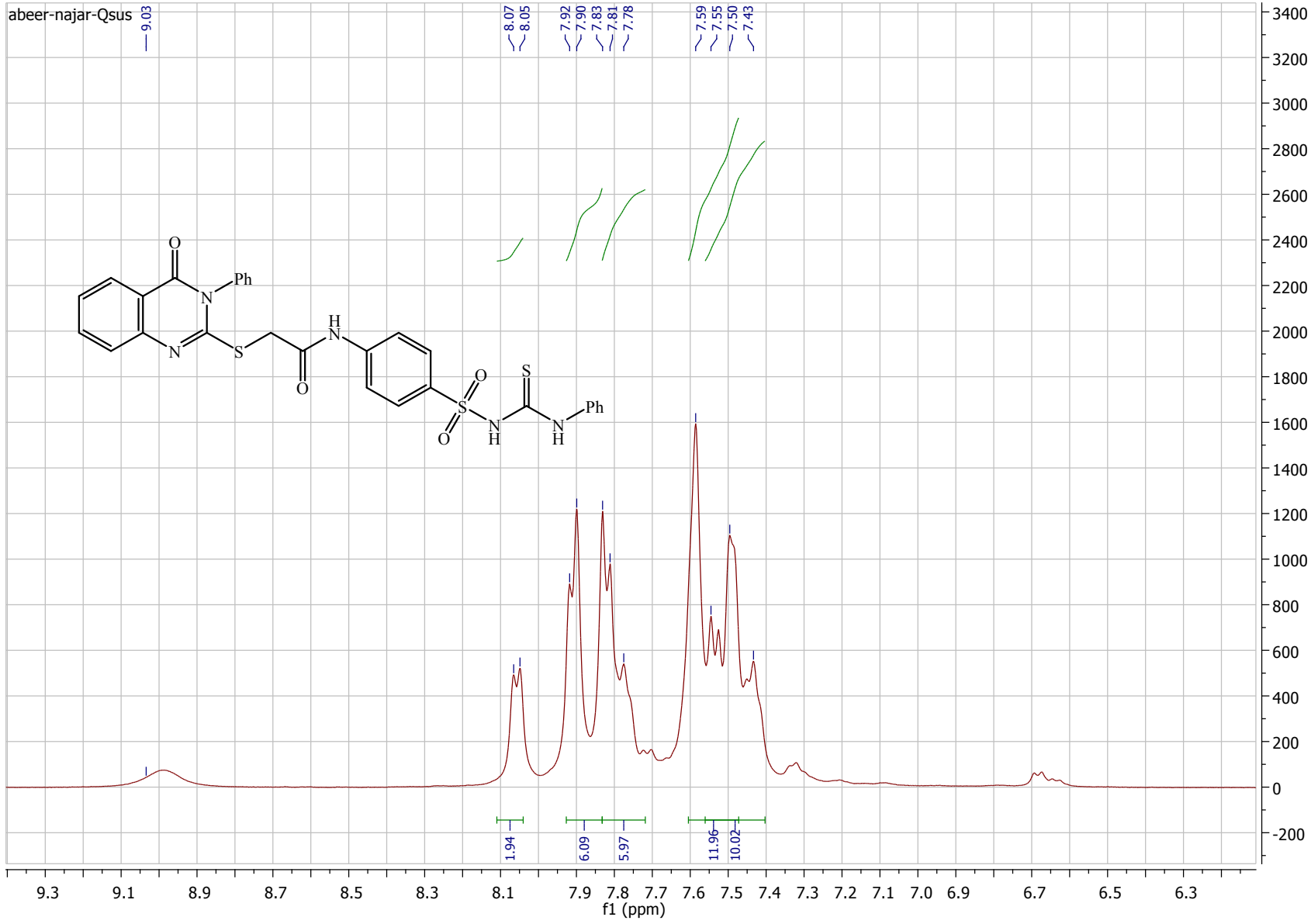
DR_AbeerElnagar-Q15US_PROTON_01
DR_AbeerElnagar-Q15US



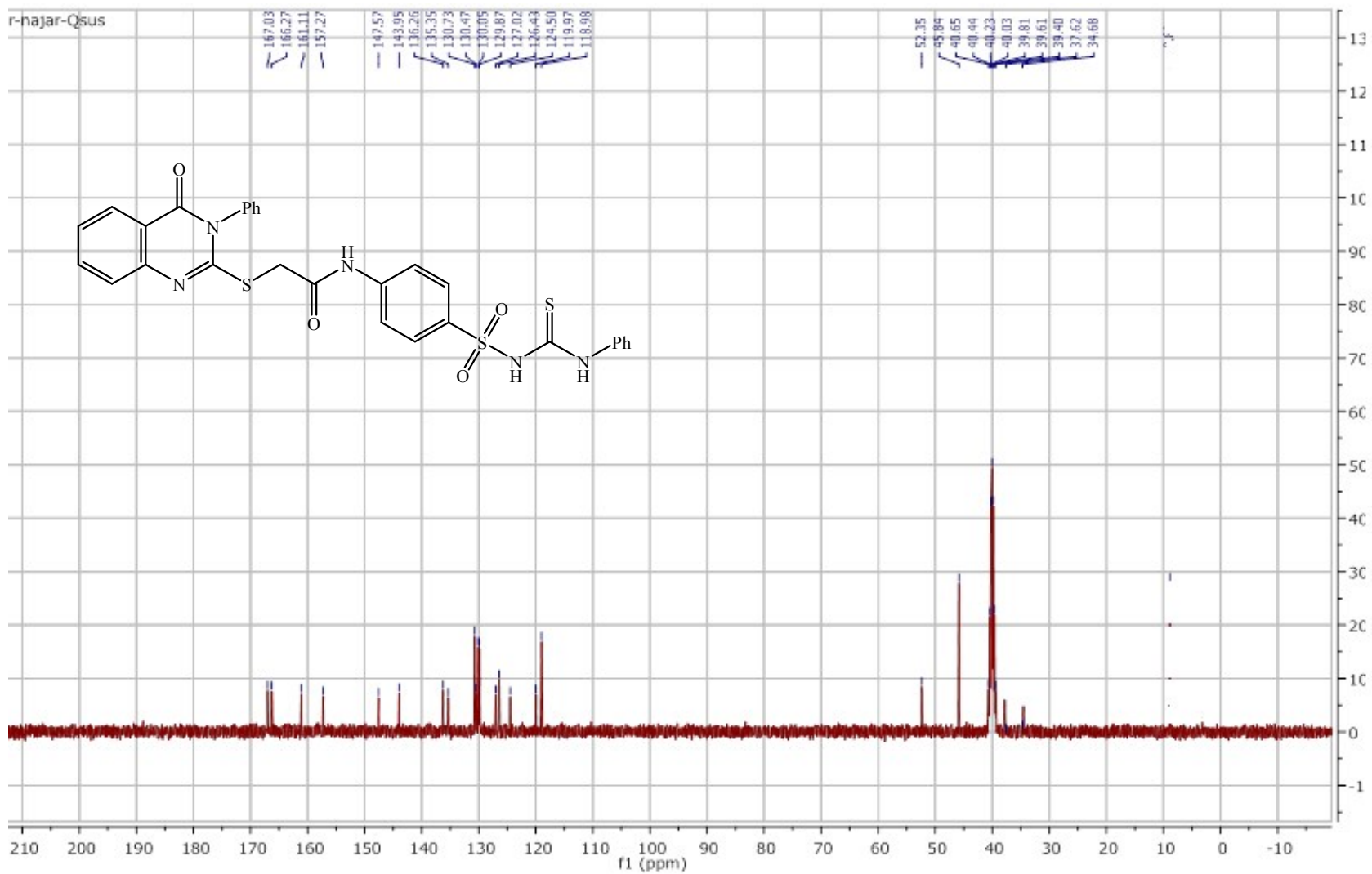
abeer-najar-Qsus



f1 (ppm)

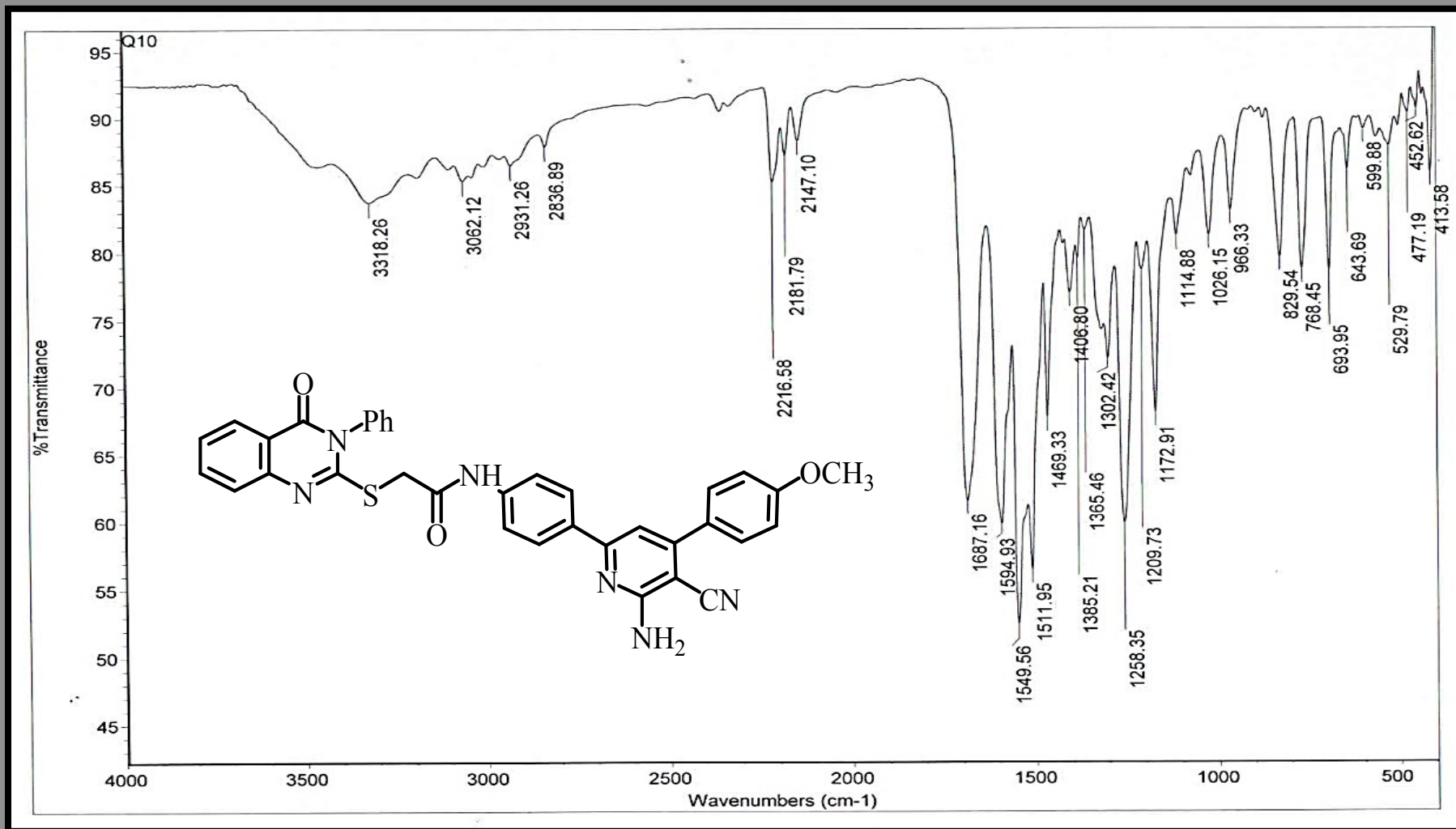


¹³C NMR

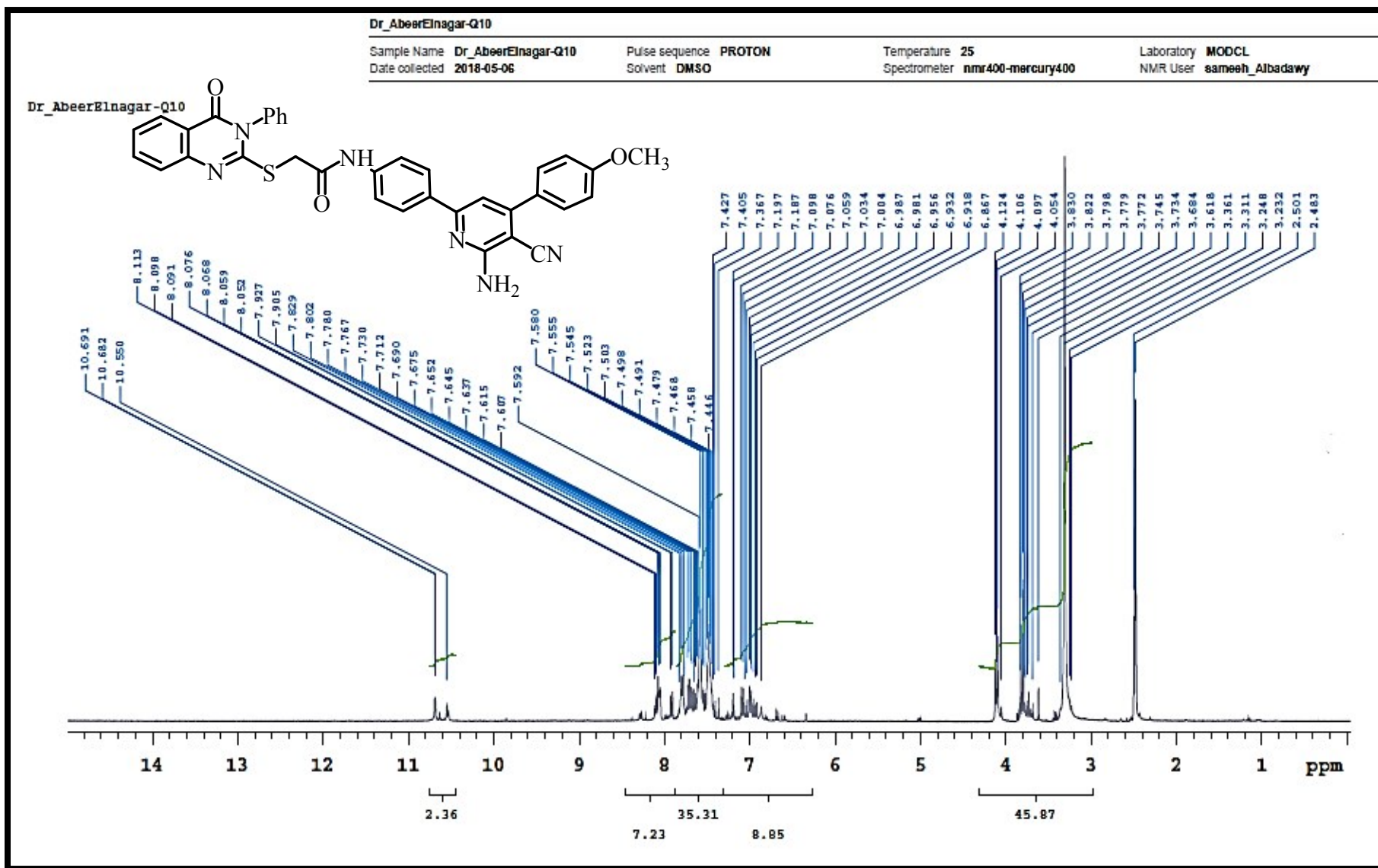


N-(4-(6-Amino-5-cyano-4-(4-methoxyphenyl)pyridin-2-yl)phenyl)-2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio)acetamide (8a).

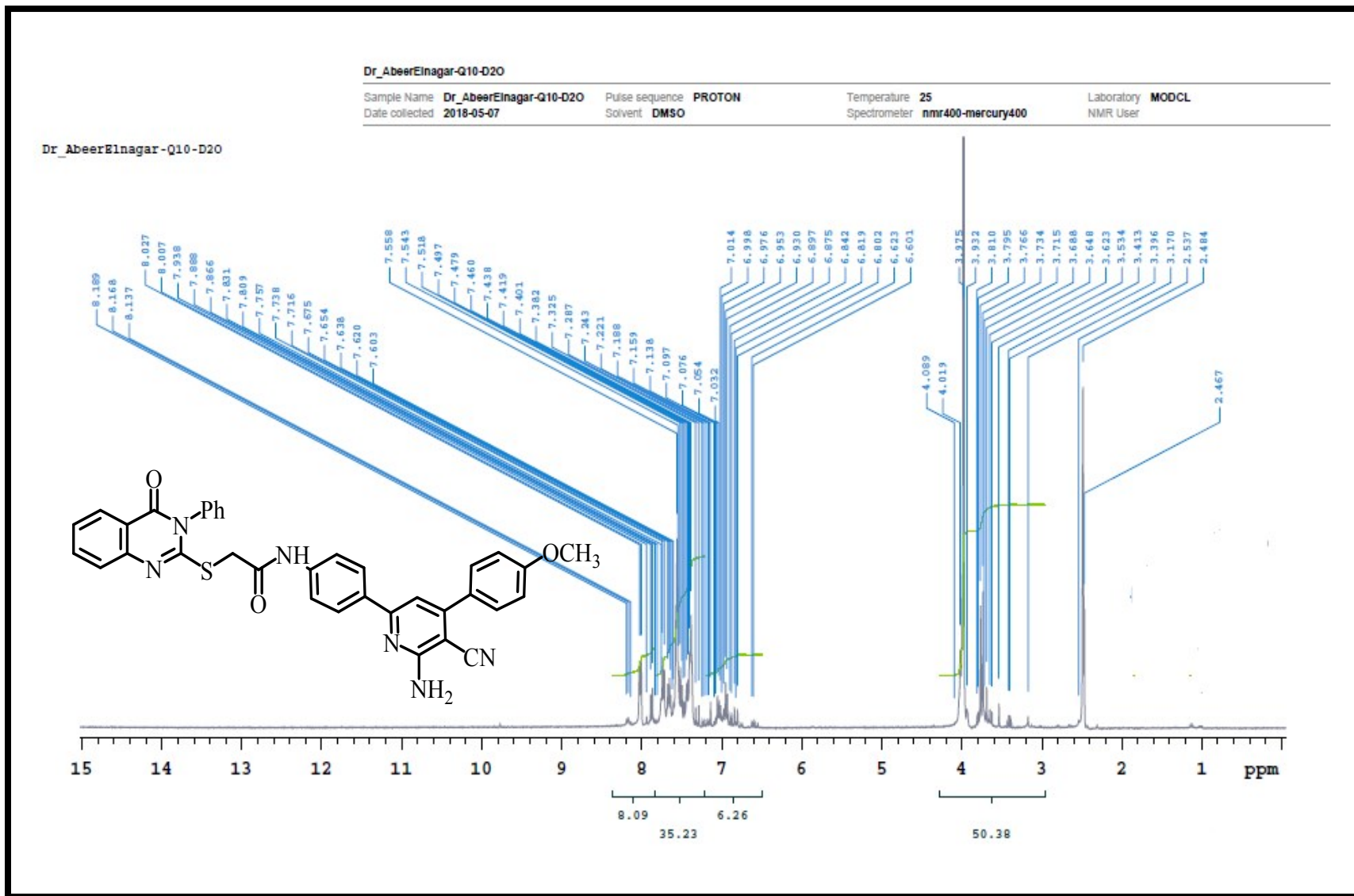
IR



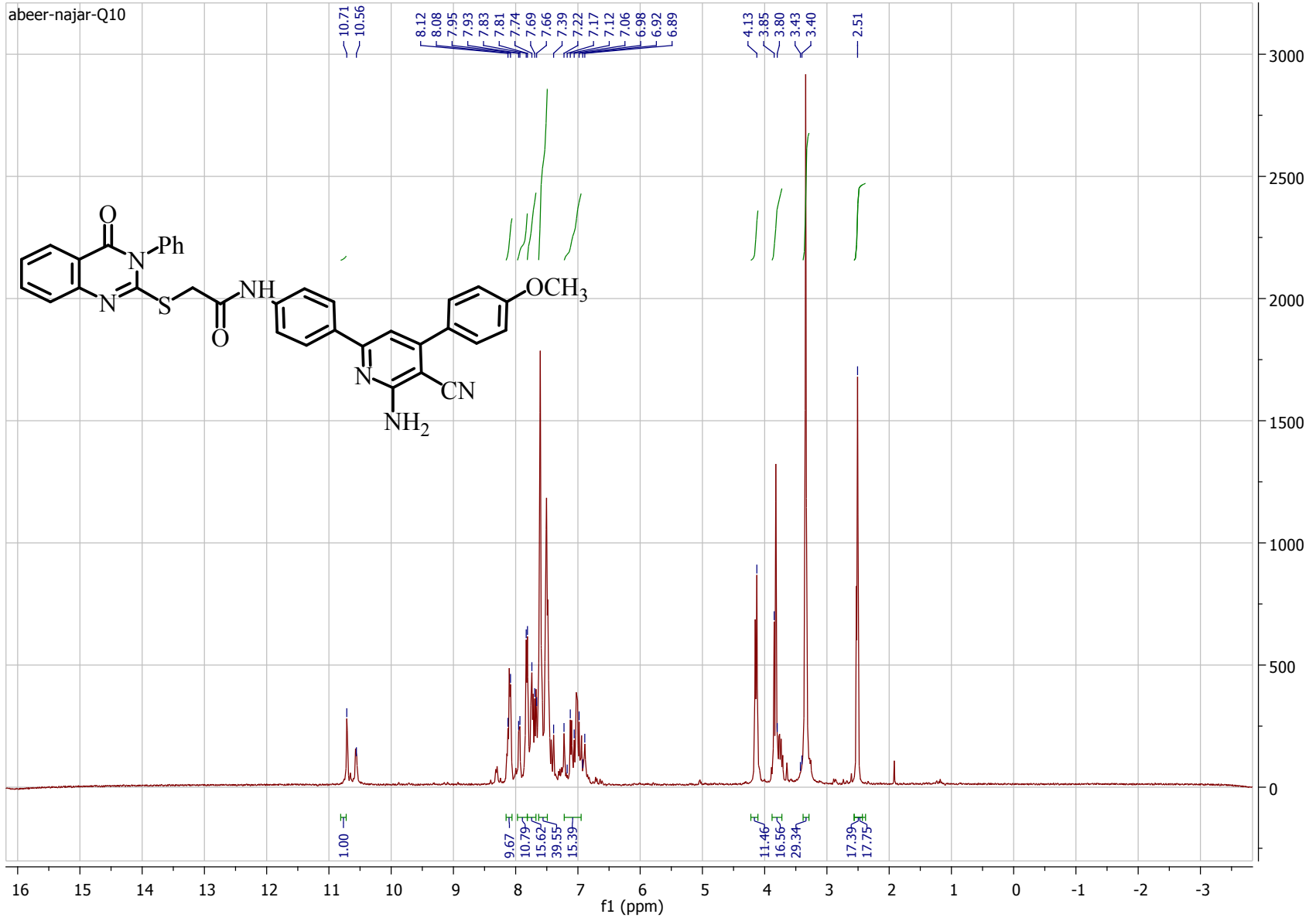
HNMR



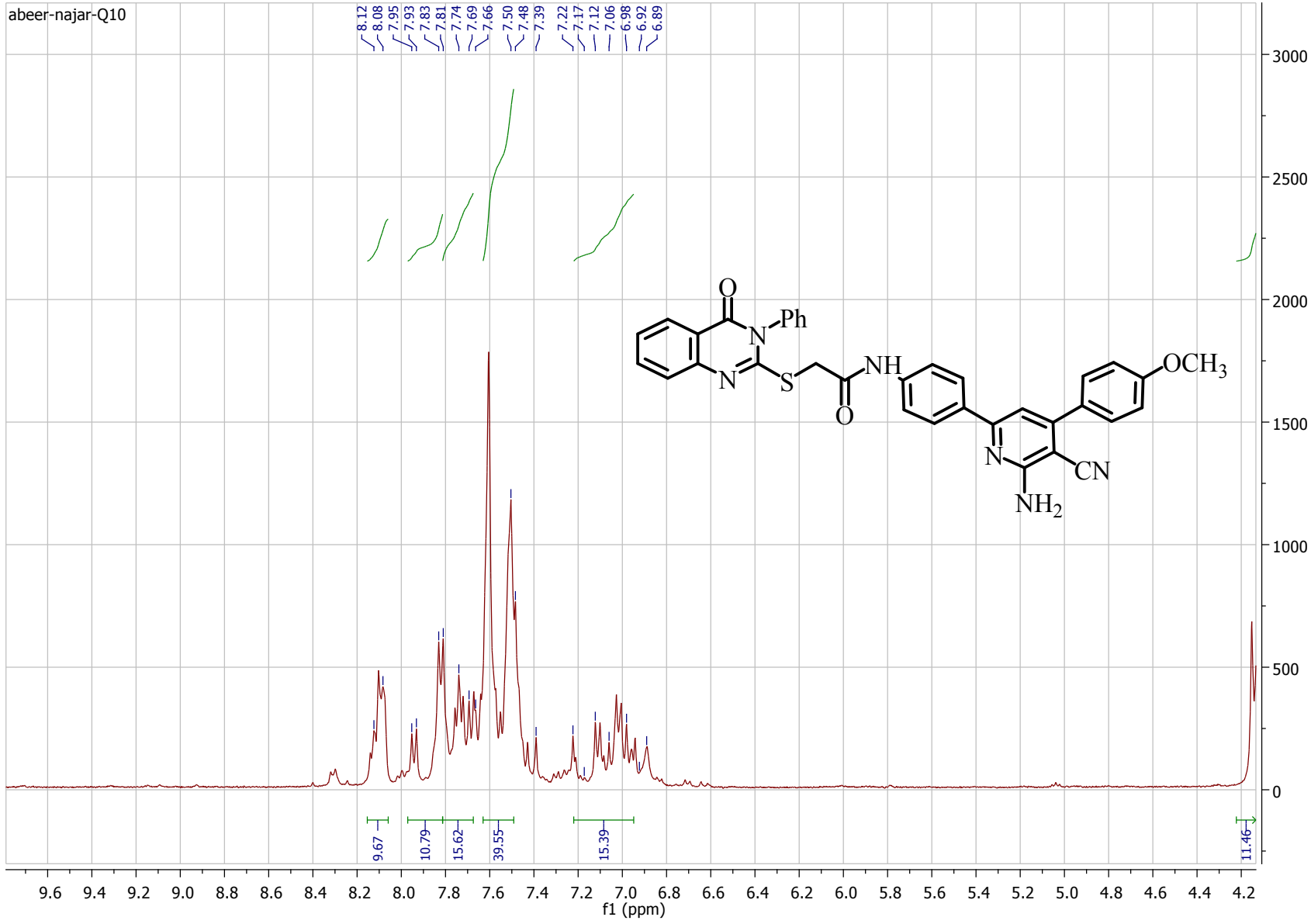
D2O



abeer-najar-Q10



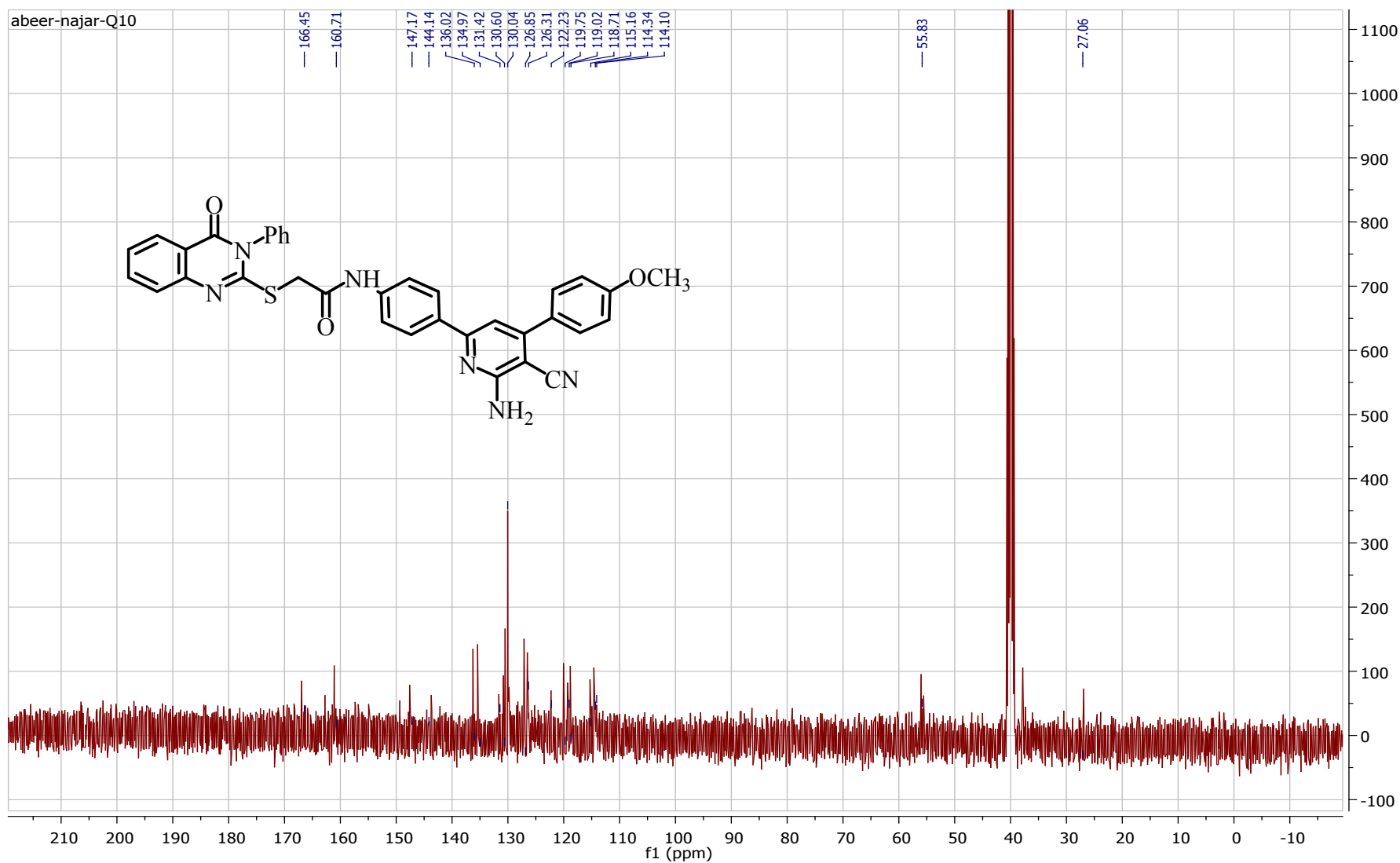
abeer-najar-Q10



- 8.12
- 8.08
- 7.95
- 7.93
- 7.83
- 7.81
- 7.74
- 7.69
- 7.66
- 7.50
- 7.48
- 7.39
- 7.22
- 7.17
- 7.12
- 7.06
- 6.98
- 6.92
- 6.89

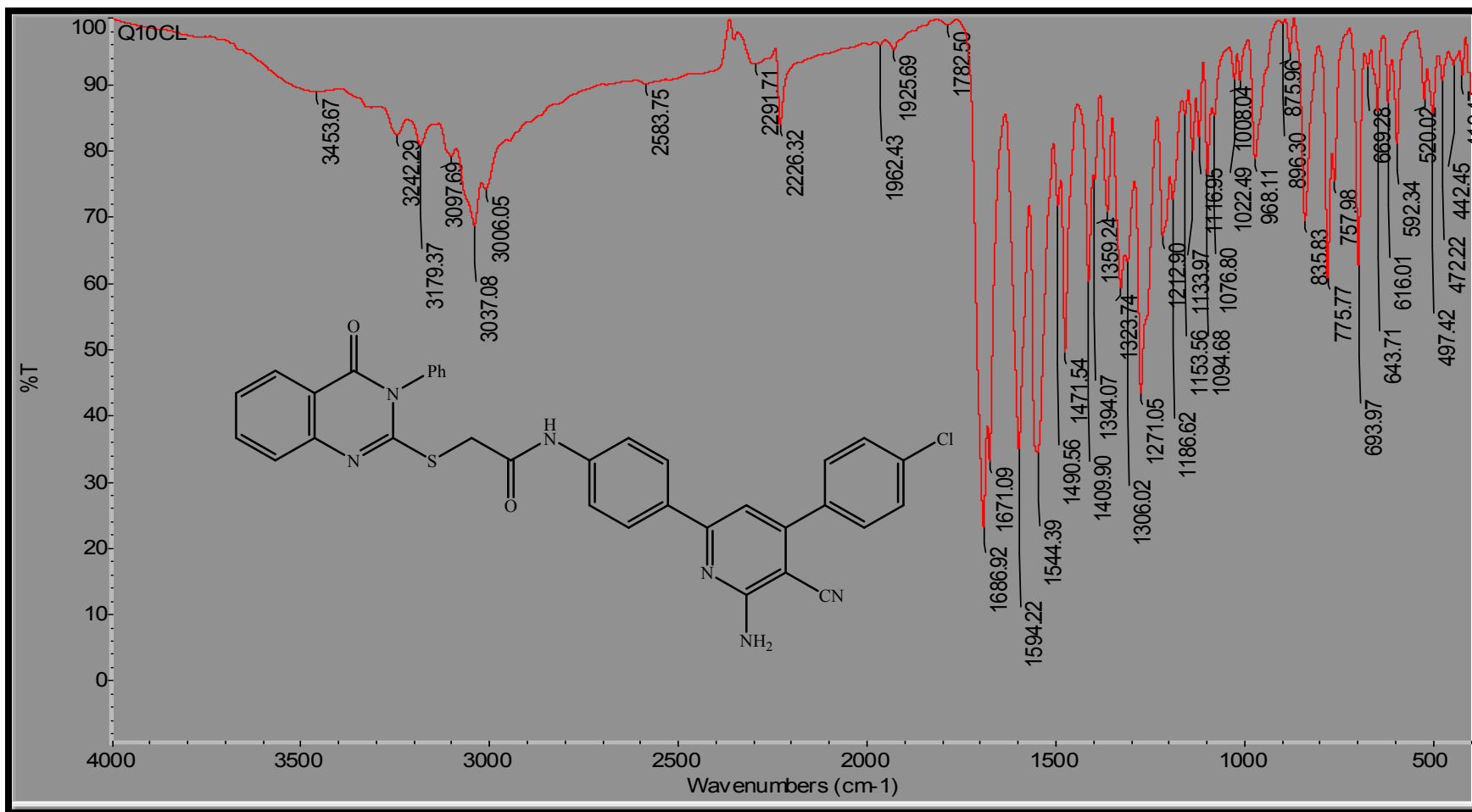
- 9.67
- 10.79
- 15.62
- 39.55
- 15.39
- 11.46

¹³C NMR

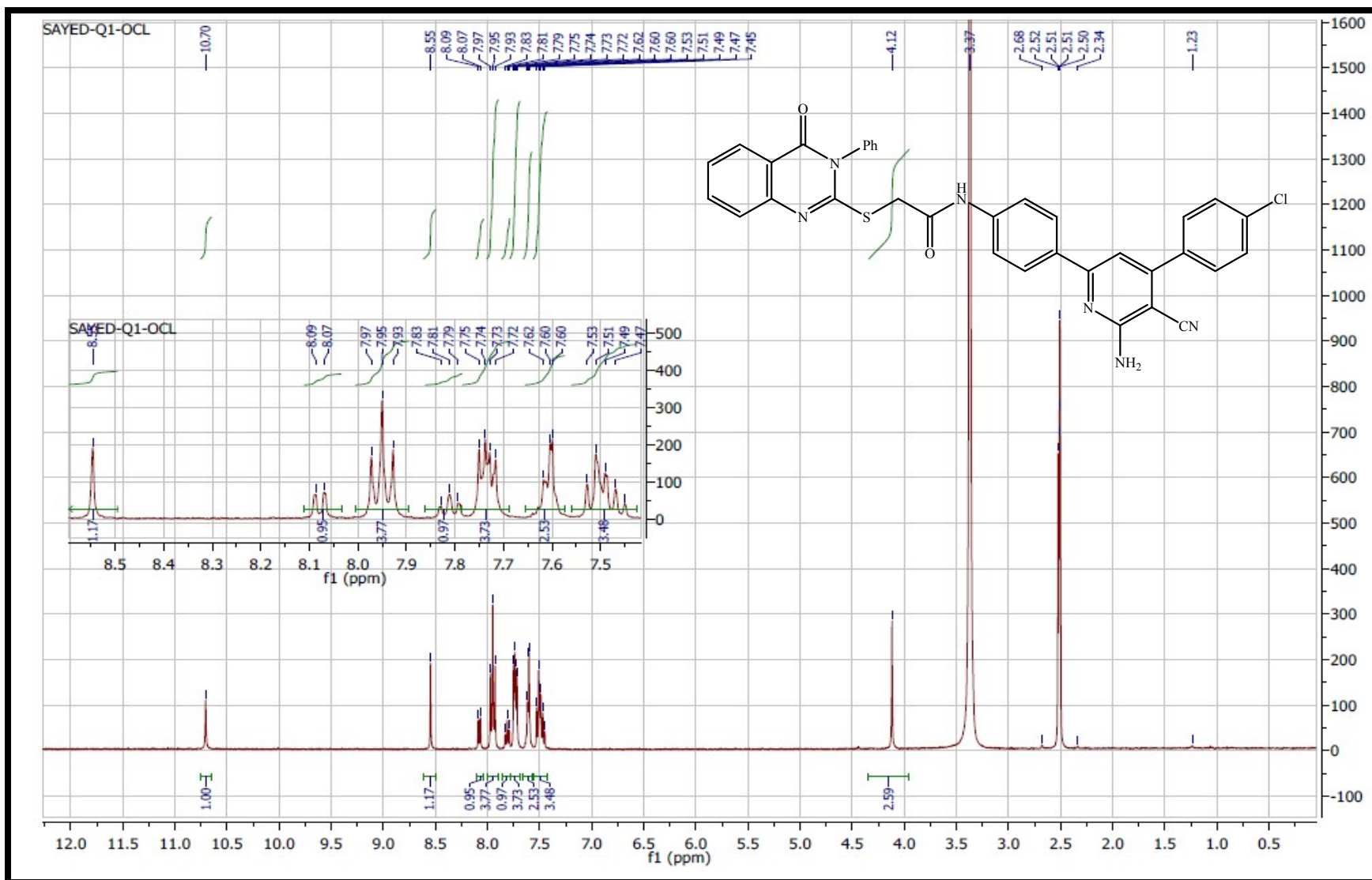


N-(4-(6-amino-4-(4-chlorophenyl)-5-cyanopyridin-2-yl)phenyl)-2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio)acetamide (8b).

IR

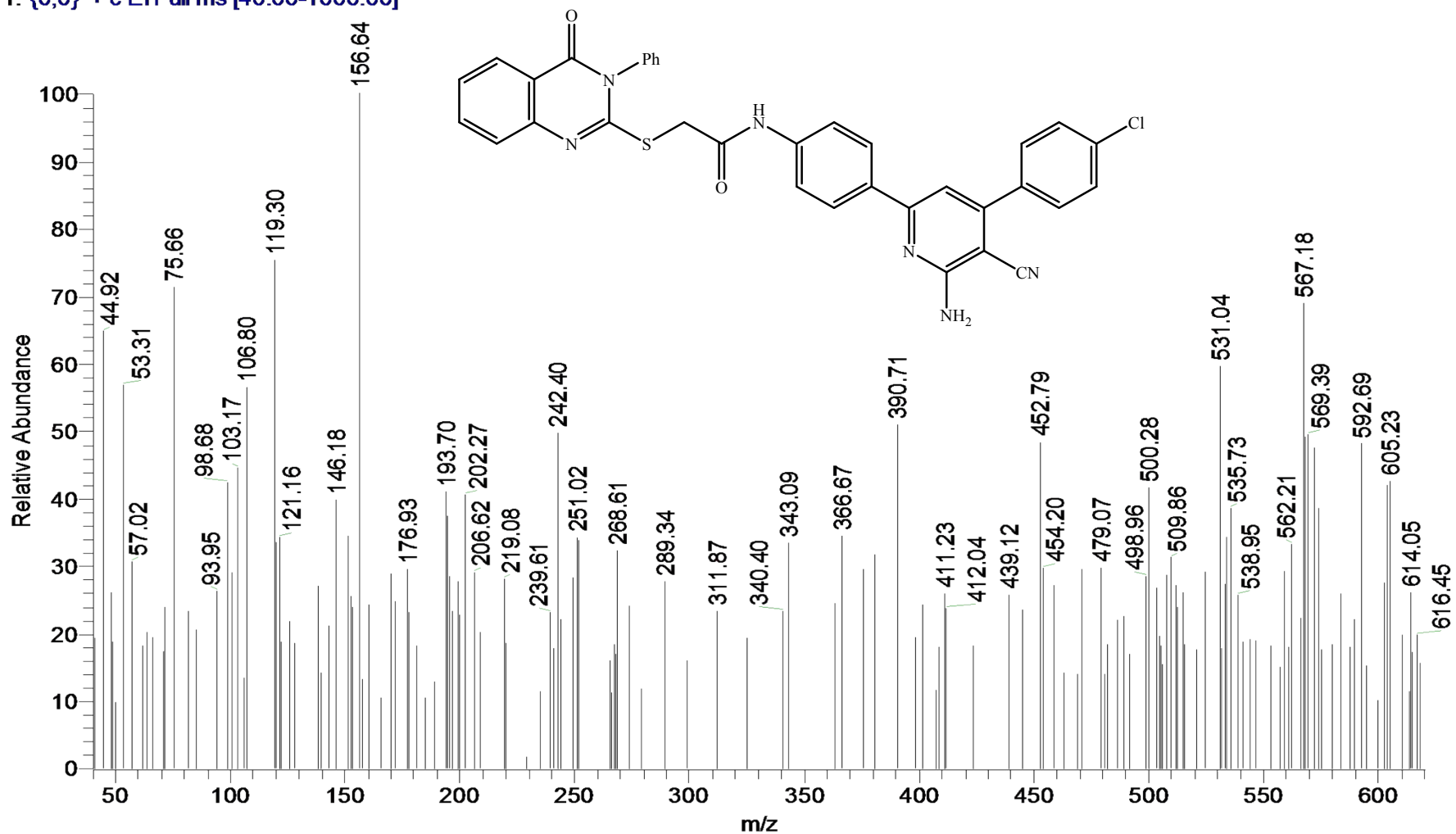


HNMR



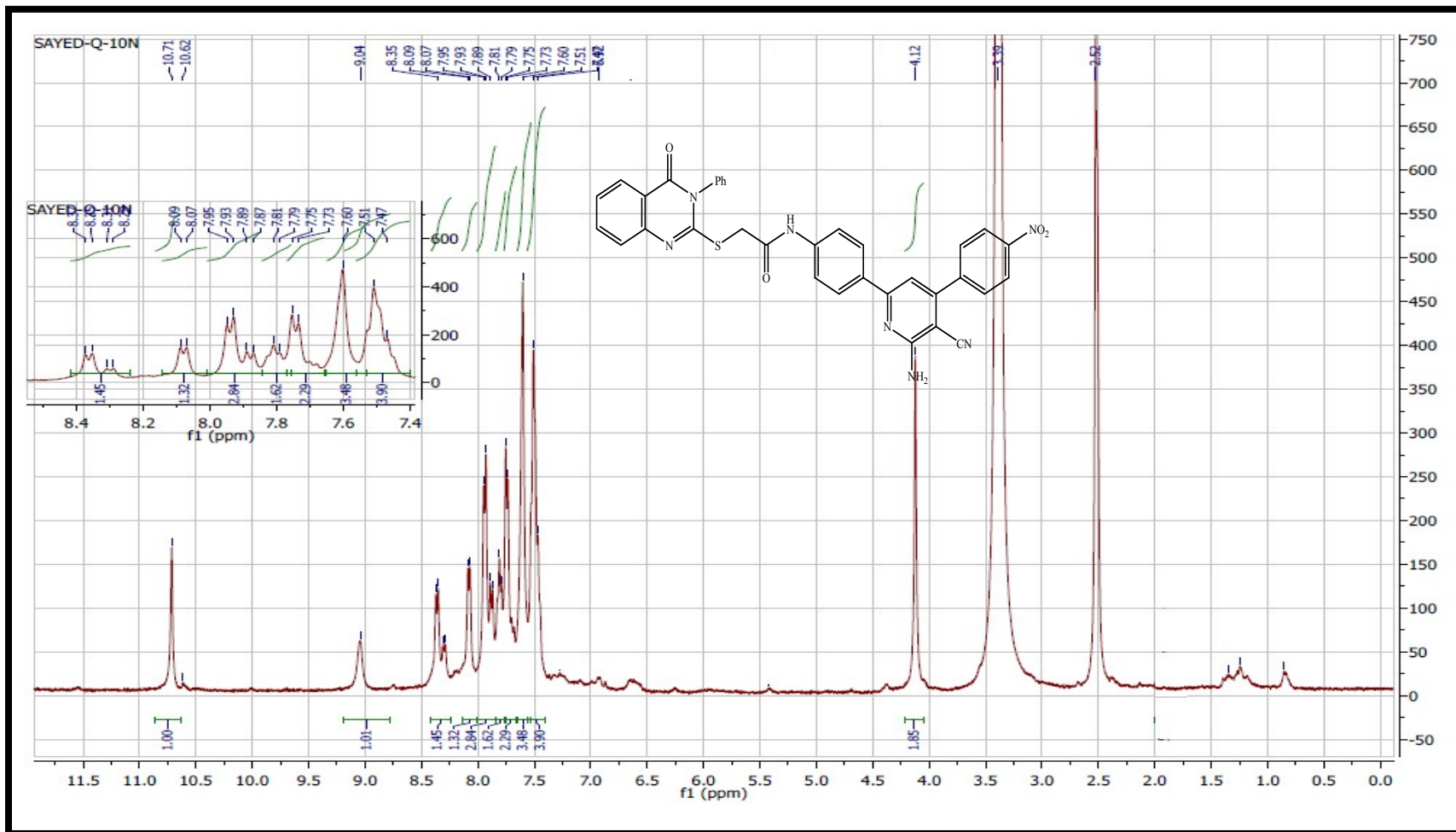
Mass

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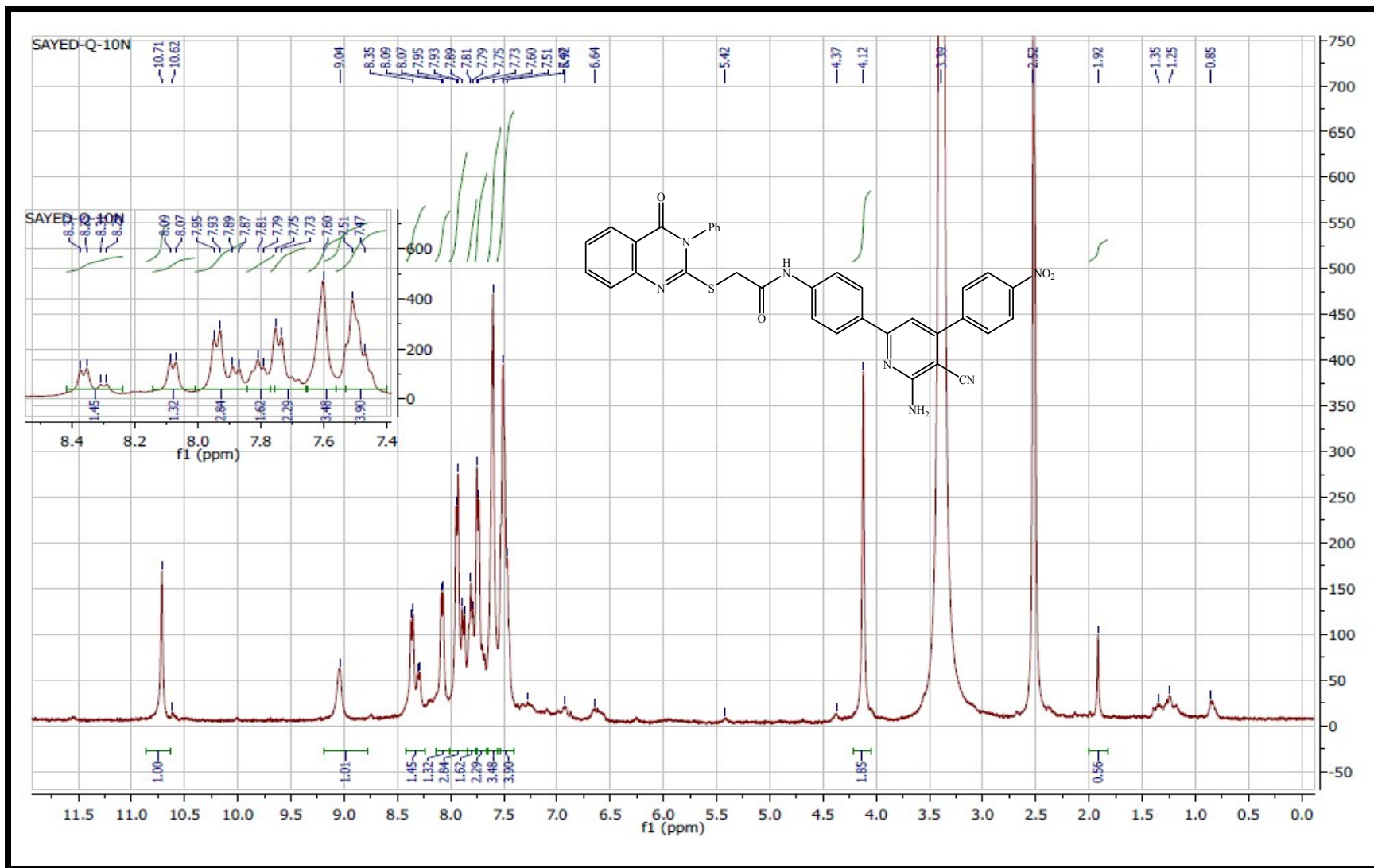


N-(4-(6-amino-5-cyano-4-(4-nitrophenyl)pyridin-2-yl)phenyl)-2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio)acetamide (8c).

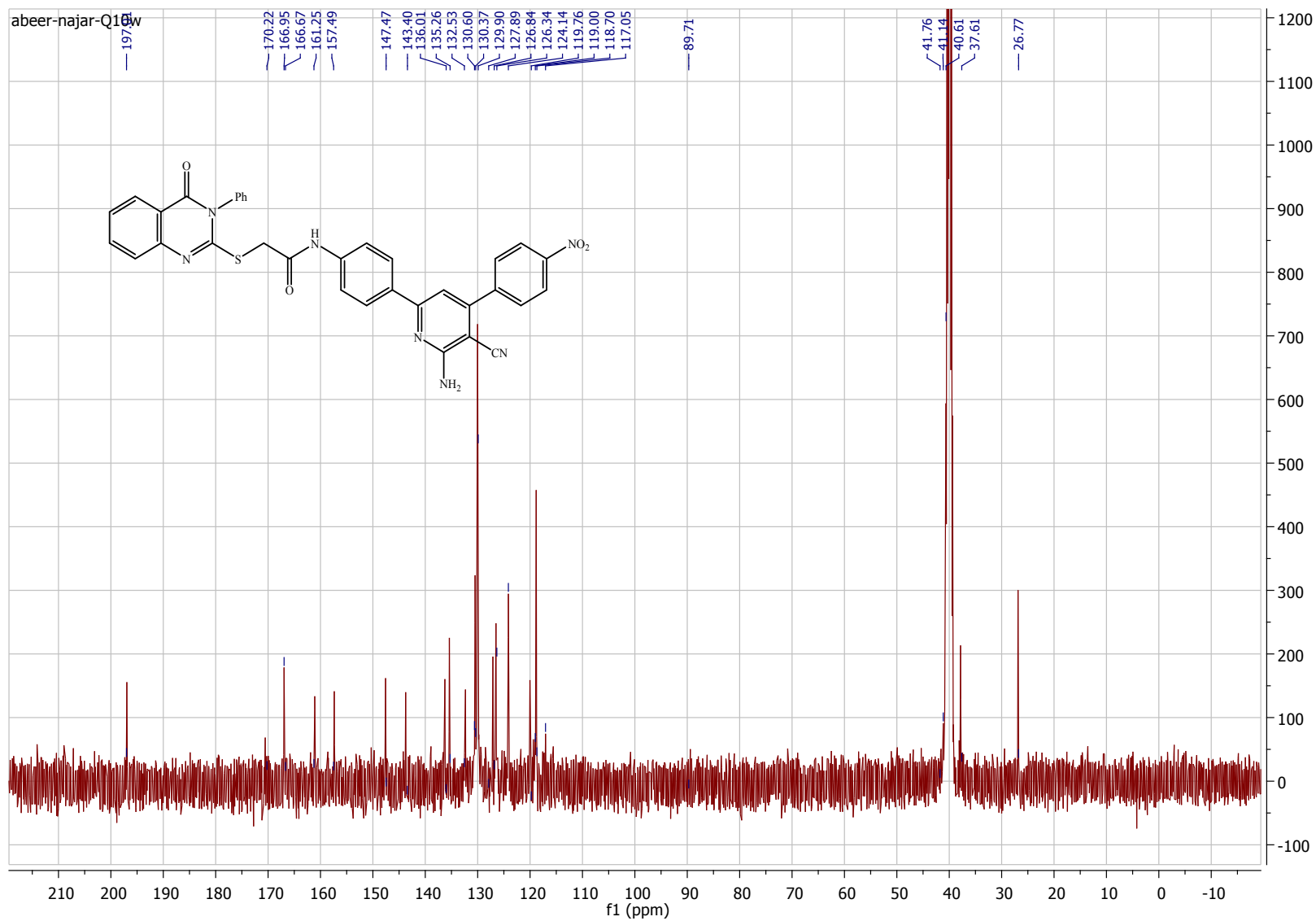
IR



HNMR

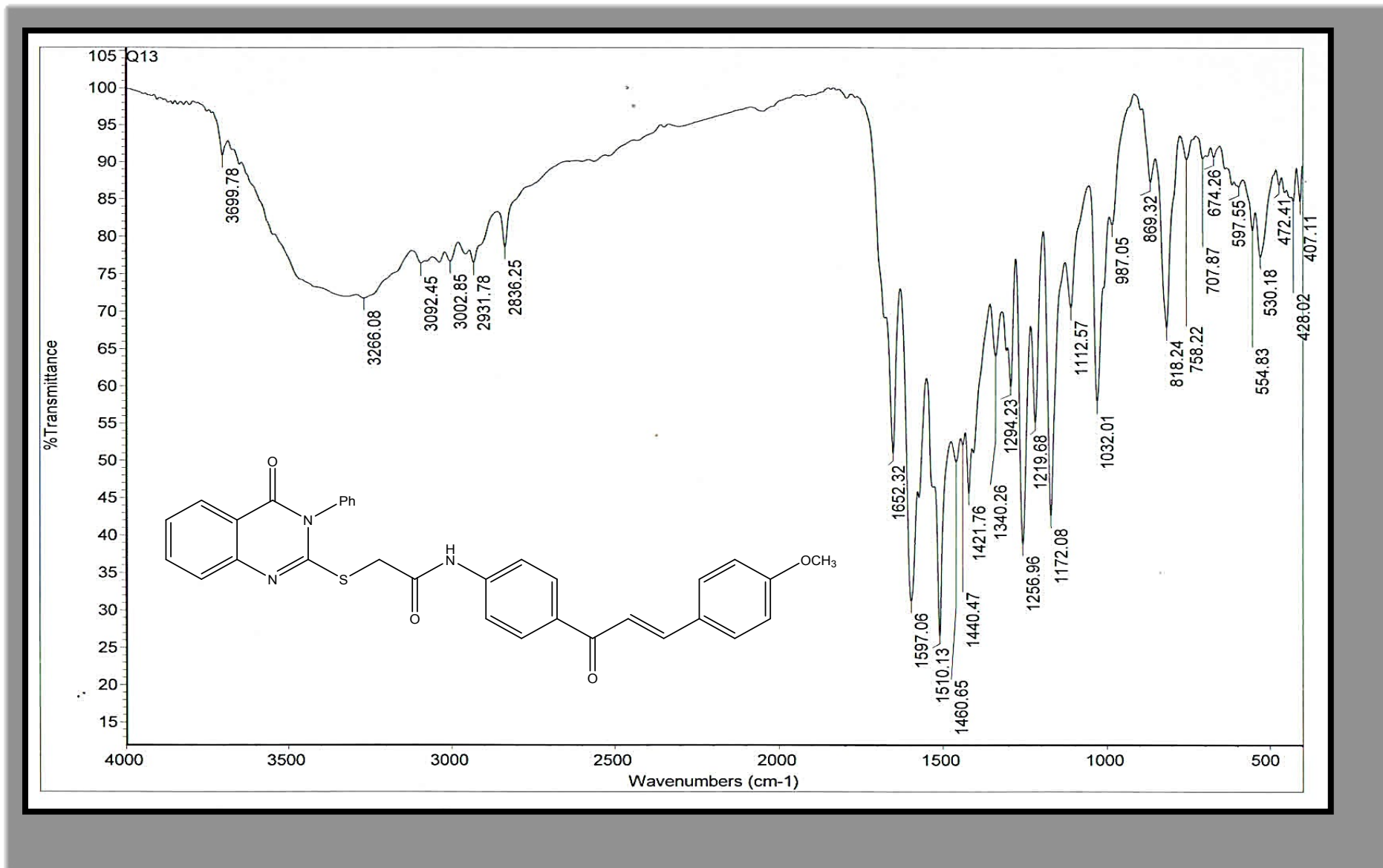


¹³C NMR

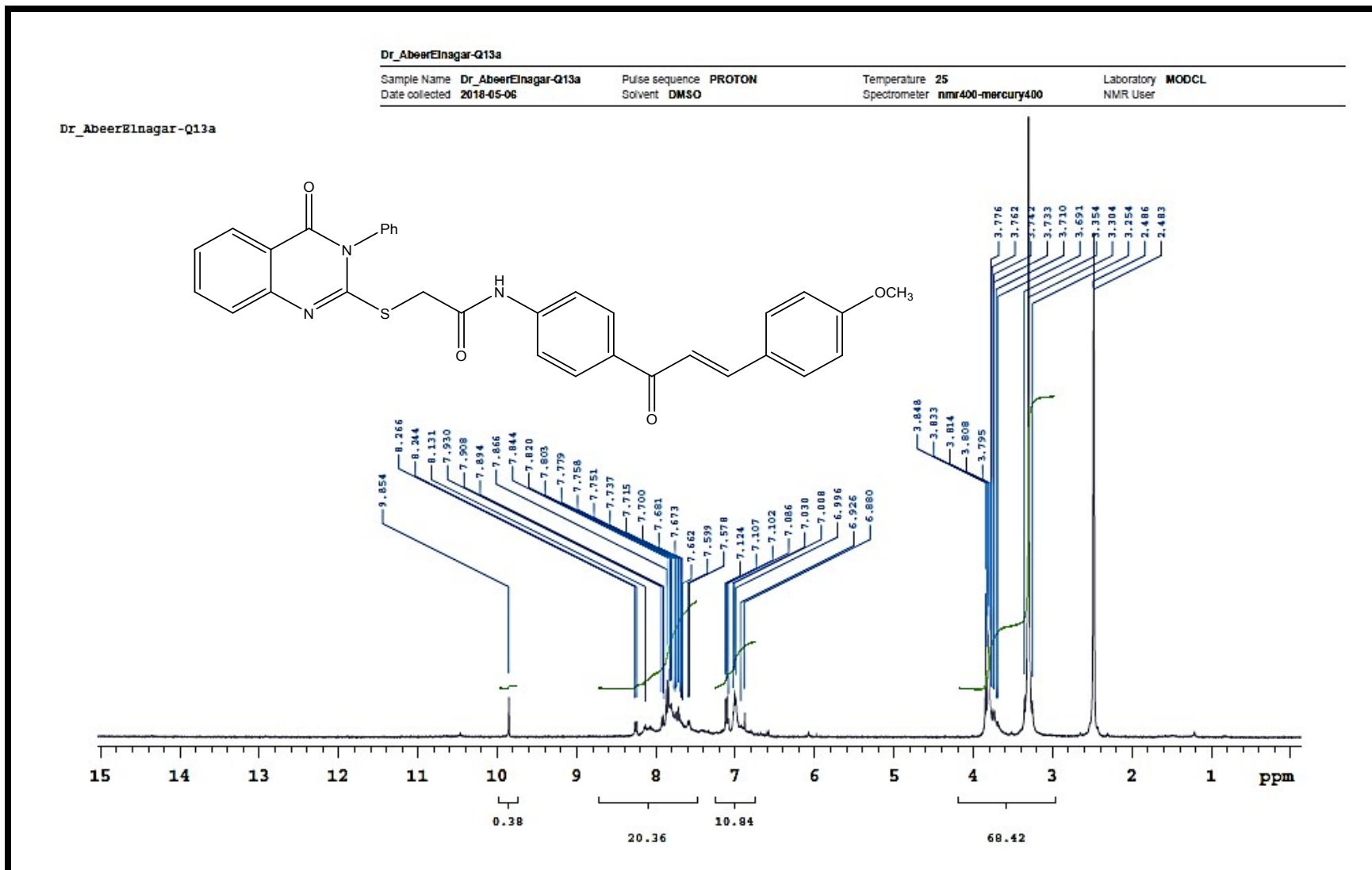


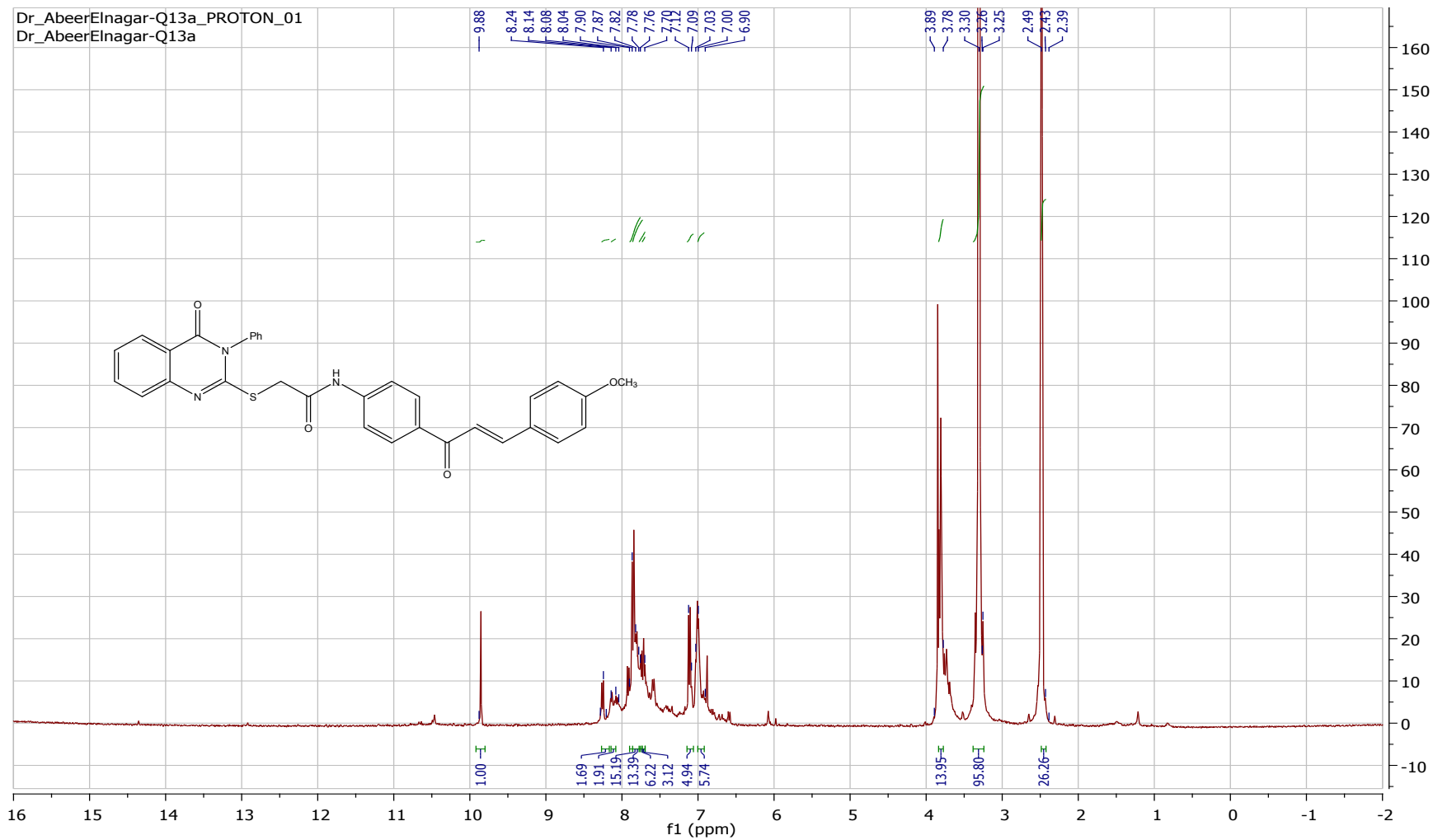
N-(4-(3-(4-methoxyphenyl)acryloyl)phenyl)-2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio)acetamide (9a).

IR



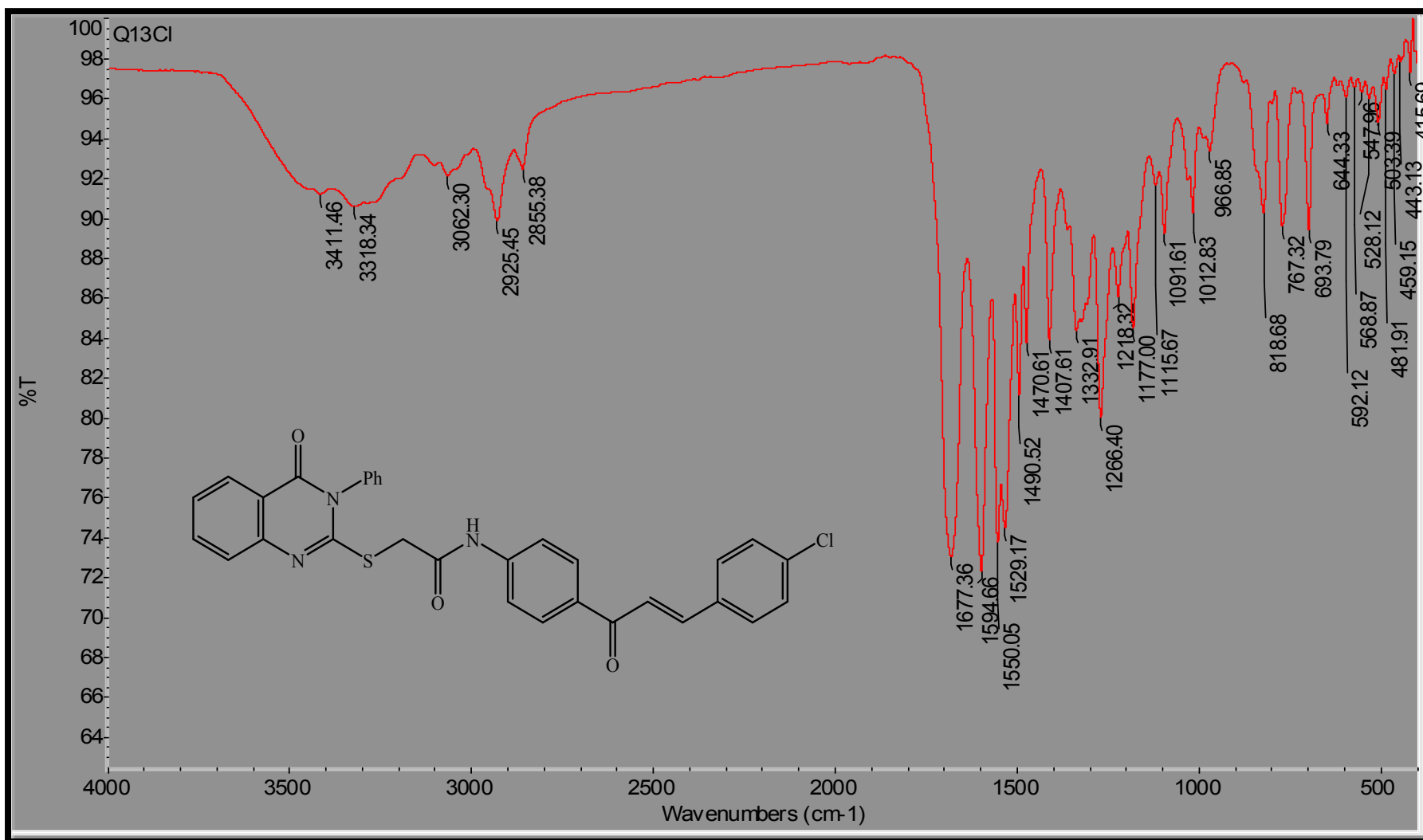
HNMR



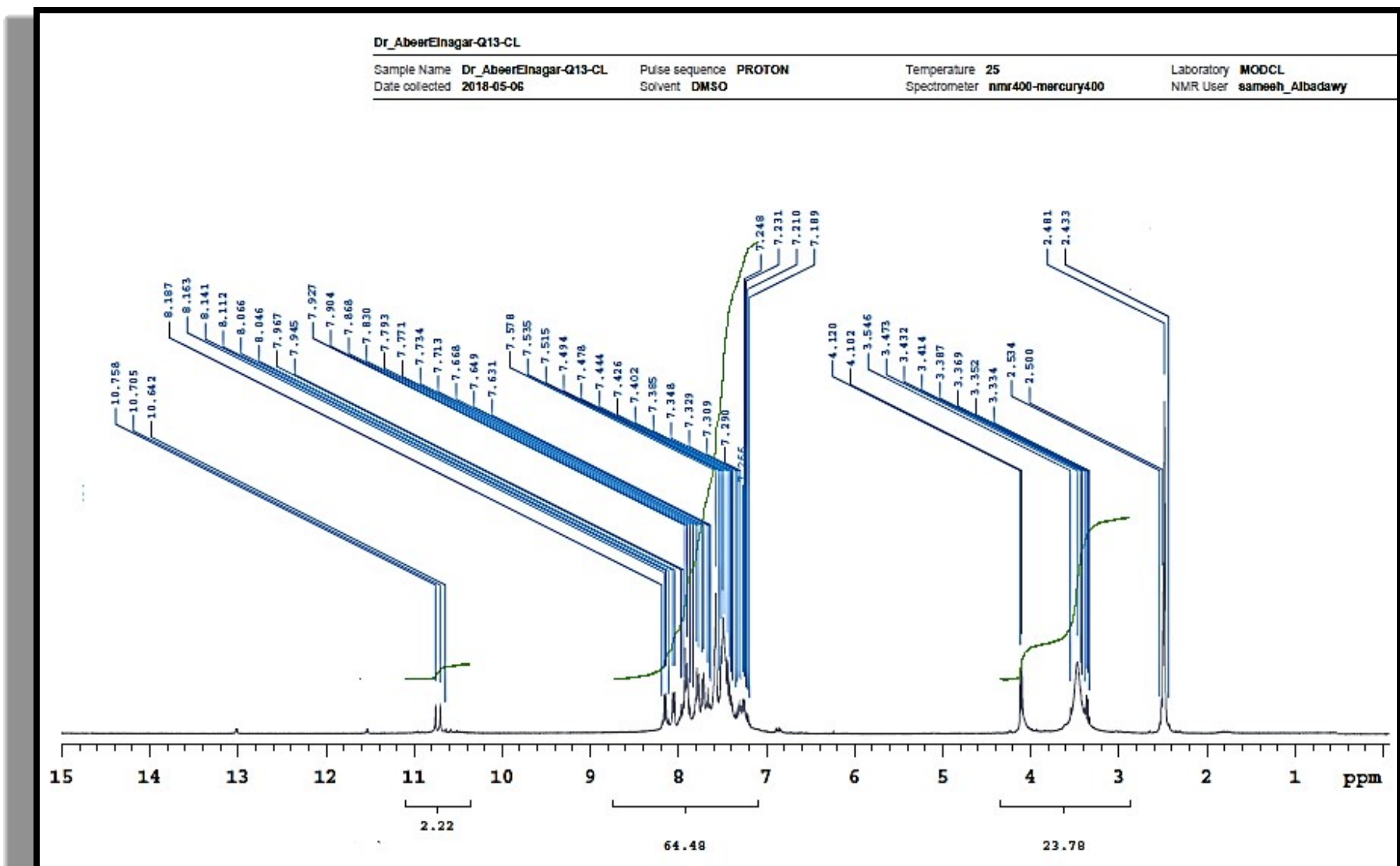


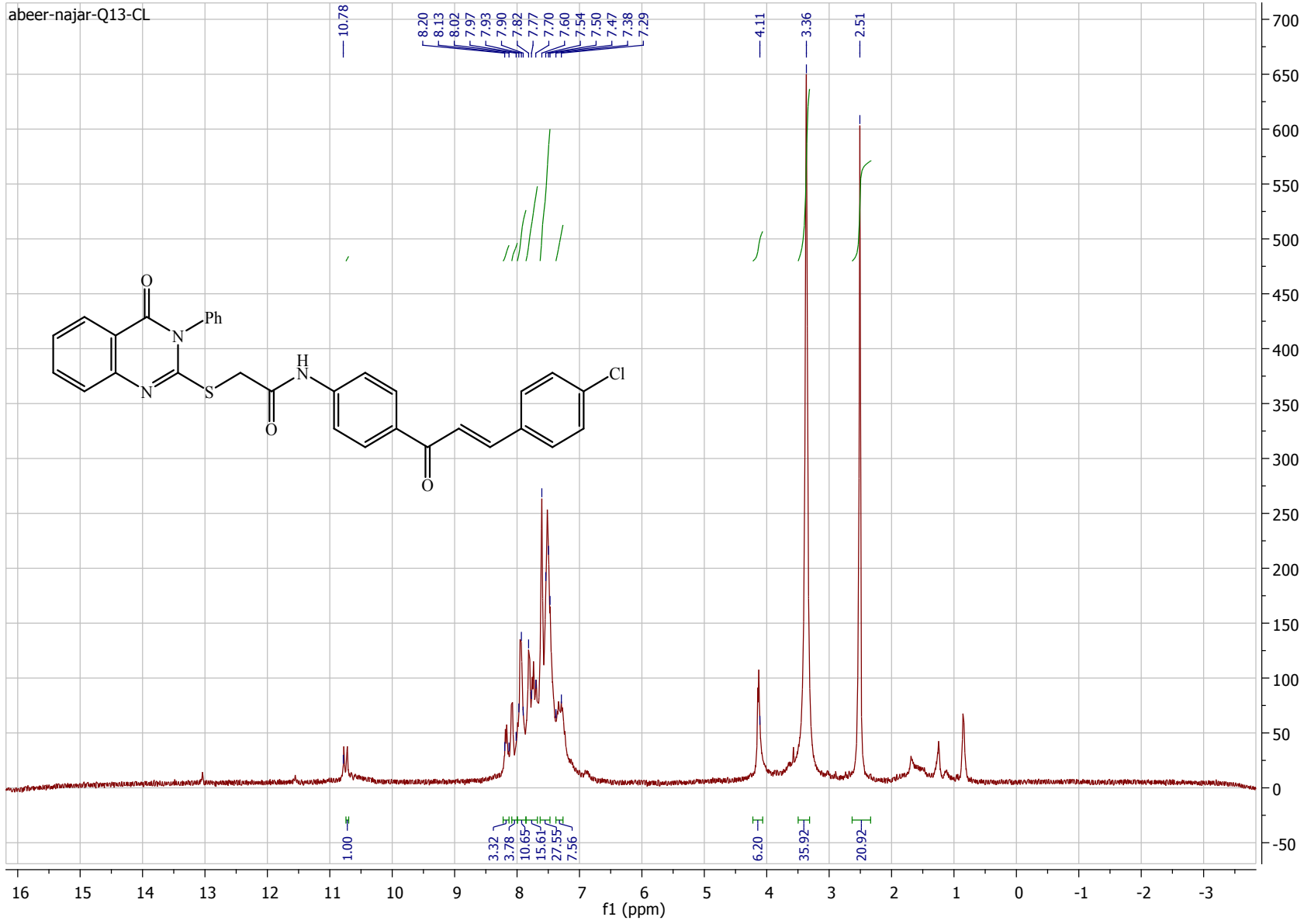
N-(4-(3-(4-chlorophenyl)acryloyl)phenyl)-2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio)acetamide (9b).

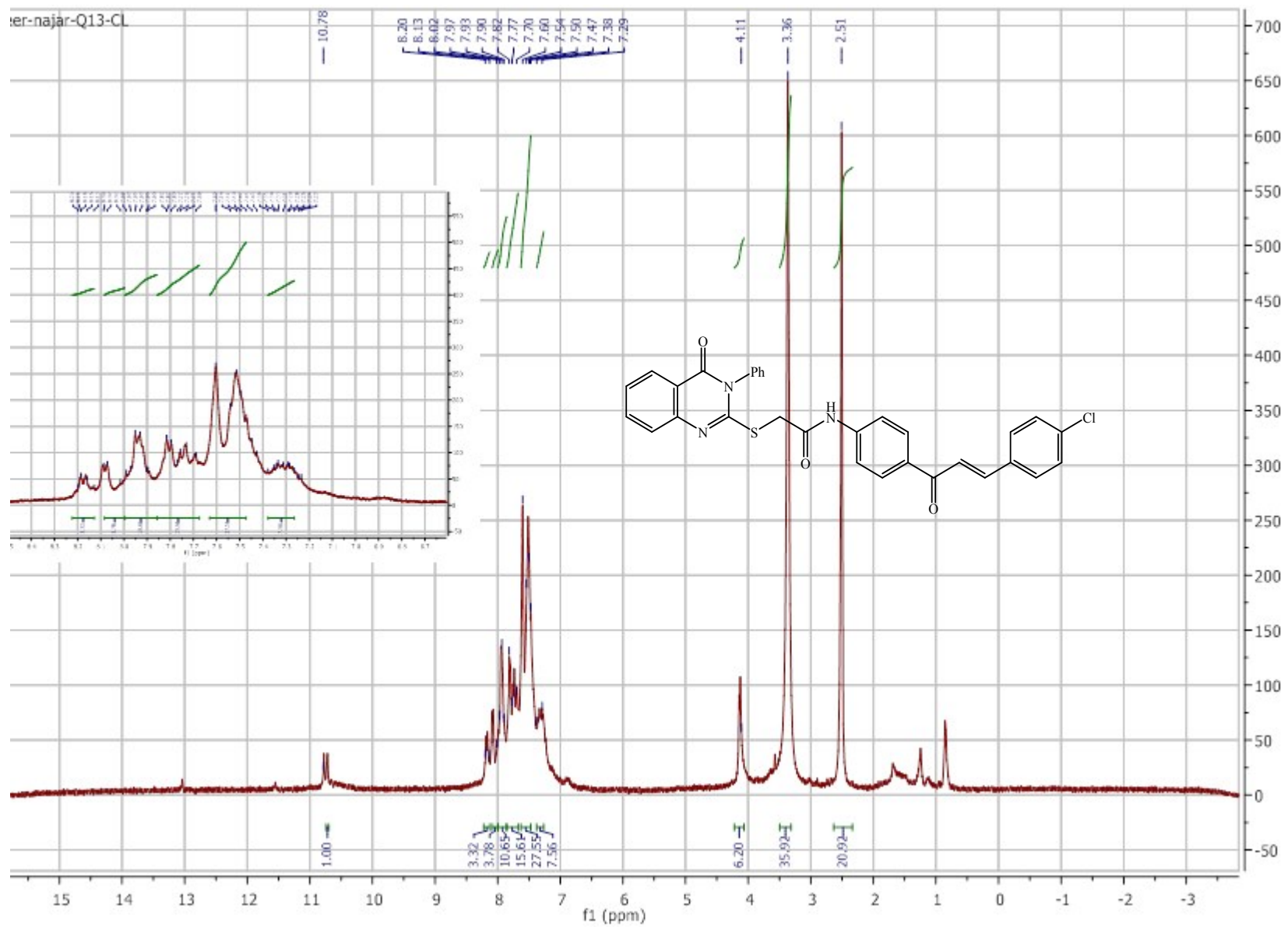
IR



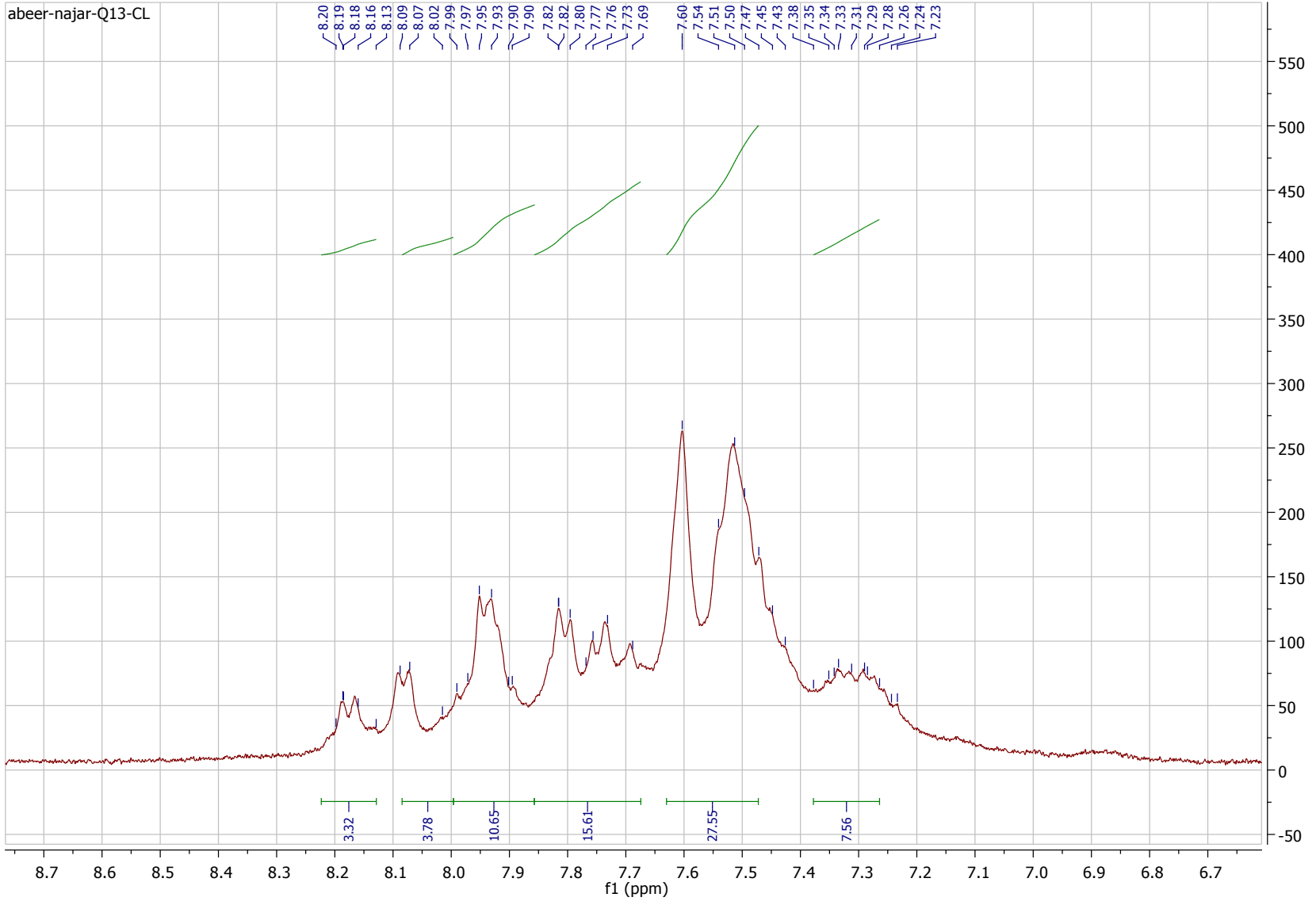
HNMR





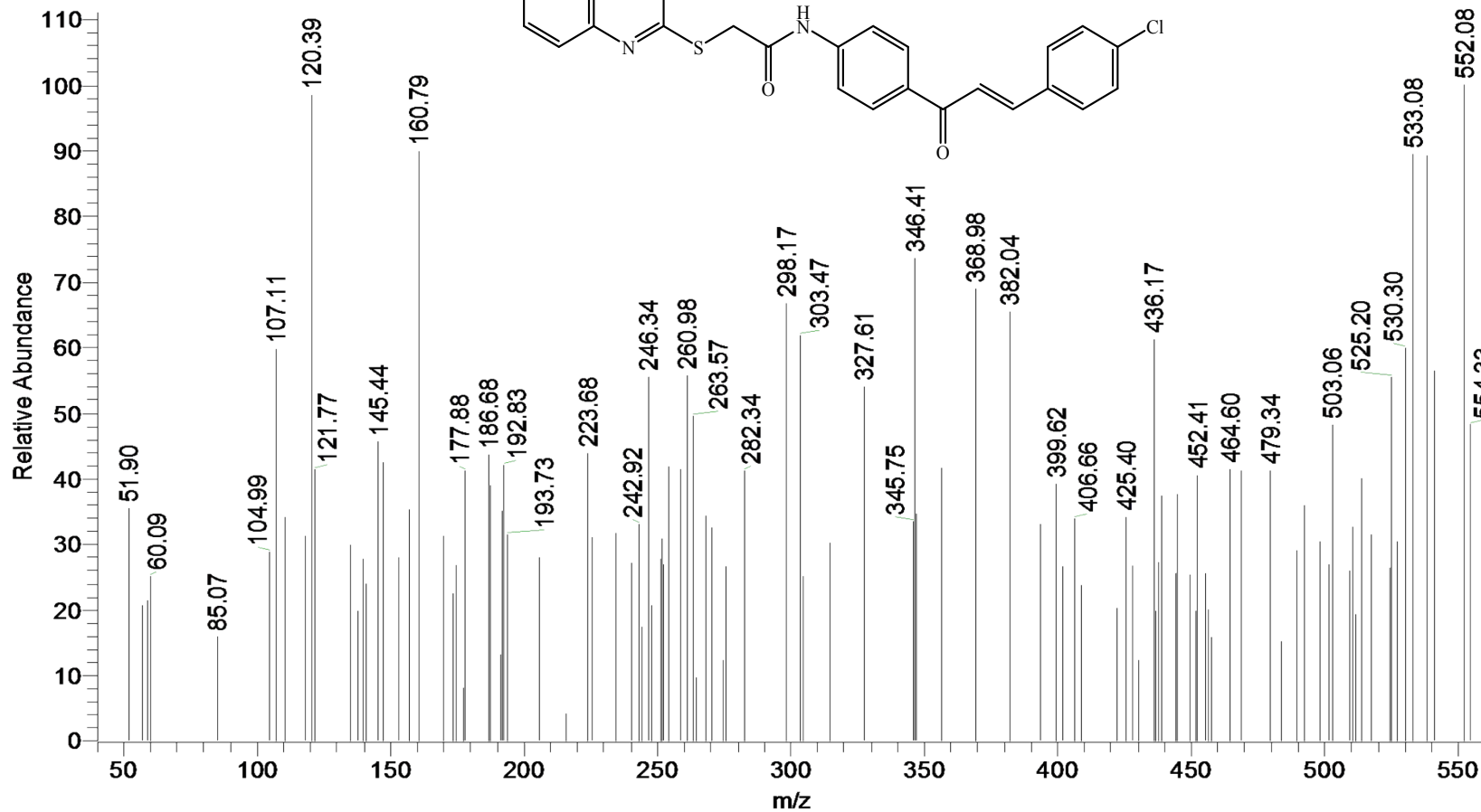
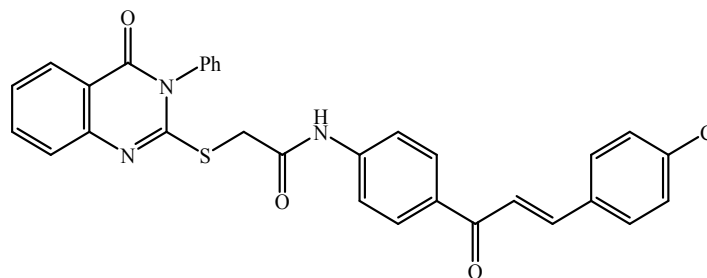


abeer-najar-Q13-CL



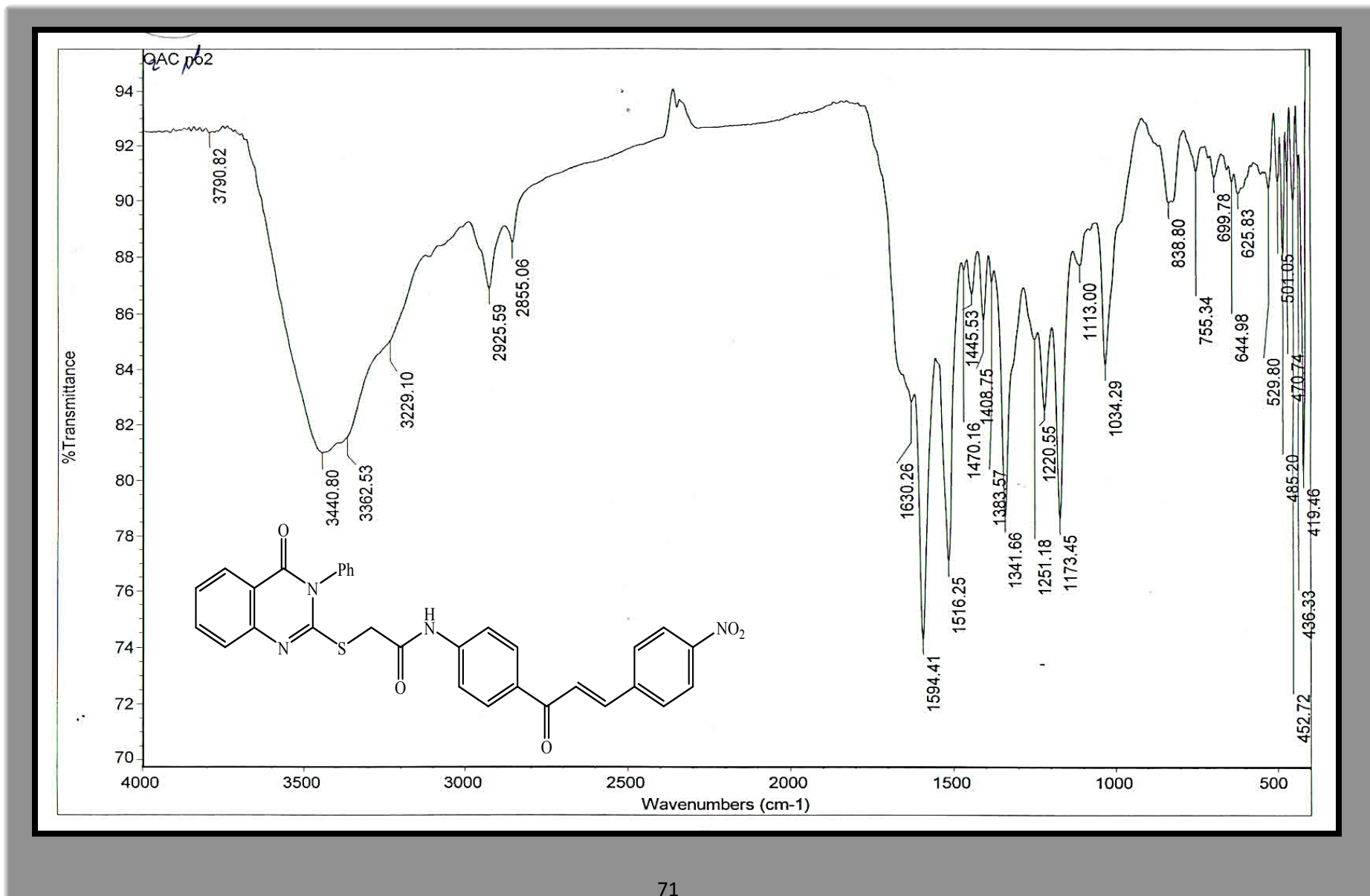
Mass

sayed-karam-Q13CL #172 RT: 2.90 AV: 1 SB: 2 4.55 , 4.59 NL: 3.14E2
T: {0,0} + c EI Full ms [40.00-1000.00]



N-(4-(3-(4-nitrophenyl)acryloyl)phenyl)-2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio)acetamide (9c).

HNMR



DR_AbeerElnagar-q13N

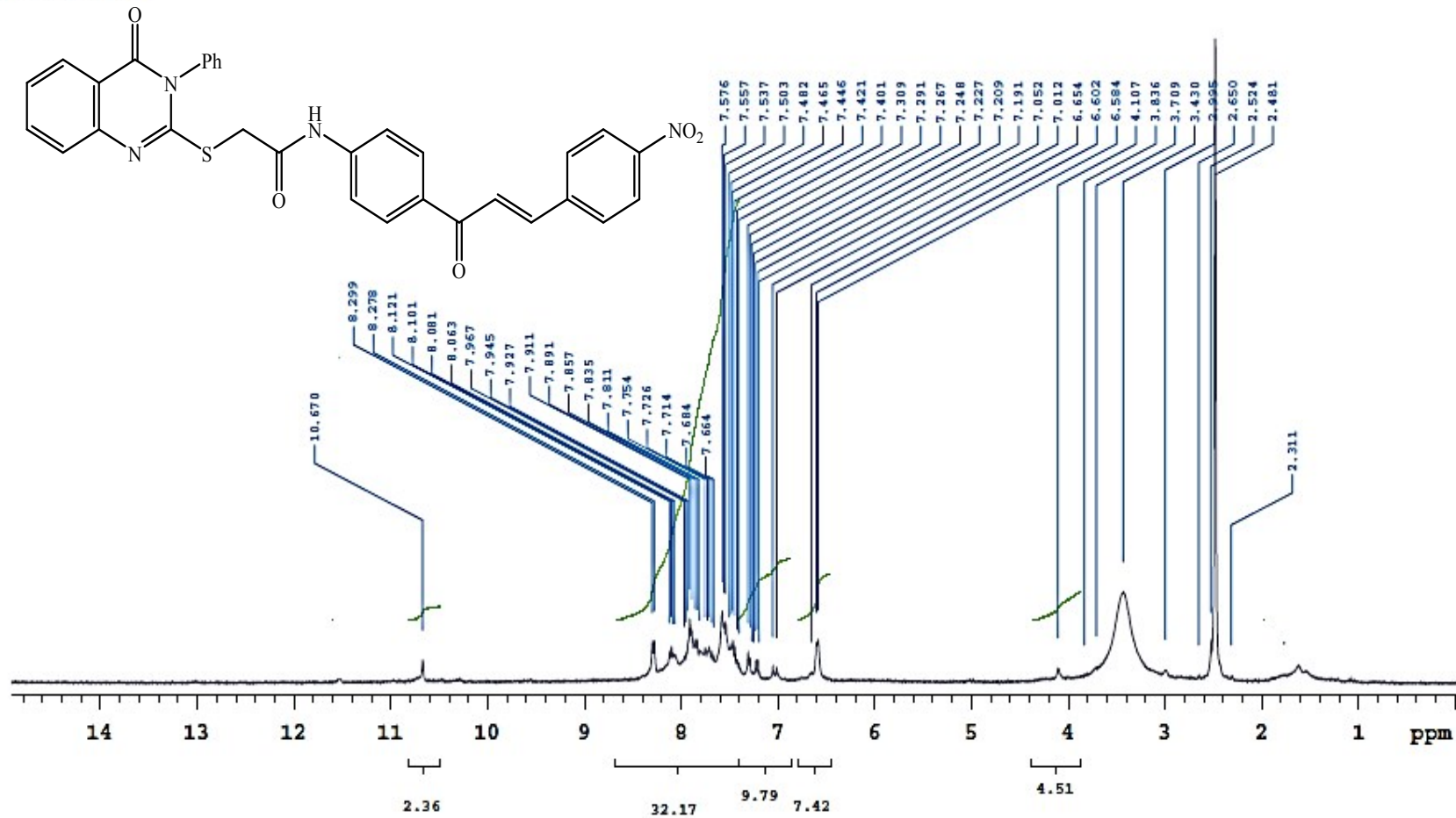
Sample Name DR_AbeerElnagar-q13N
Date collected 2018-07-12

Pulse sequence PROTON
Solvent DMSO

Temperature 25
Spectrometer nmr400-mercury400

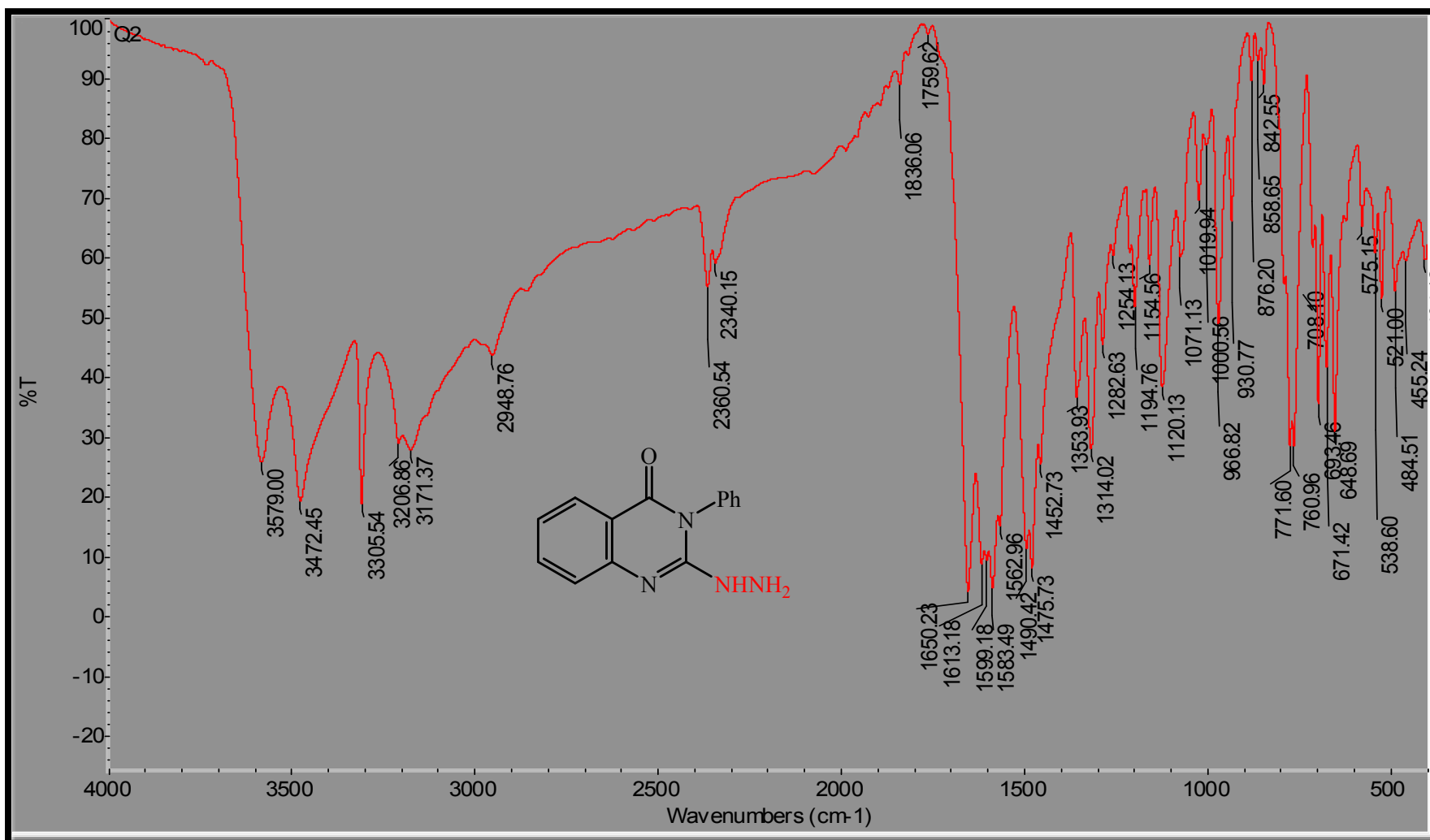
Laboratory MODCL
NMR User sameeh_Abdawy

DR_AbeerElnagar-q13N



2-Hydrazinyl-3-phenylquinazolin-4(3H)-one (11).

IR





Dr_AbeerElnagar-q2

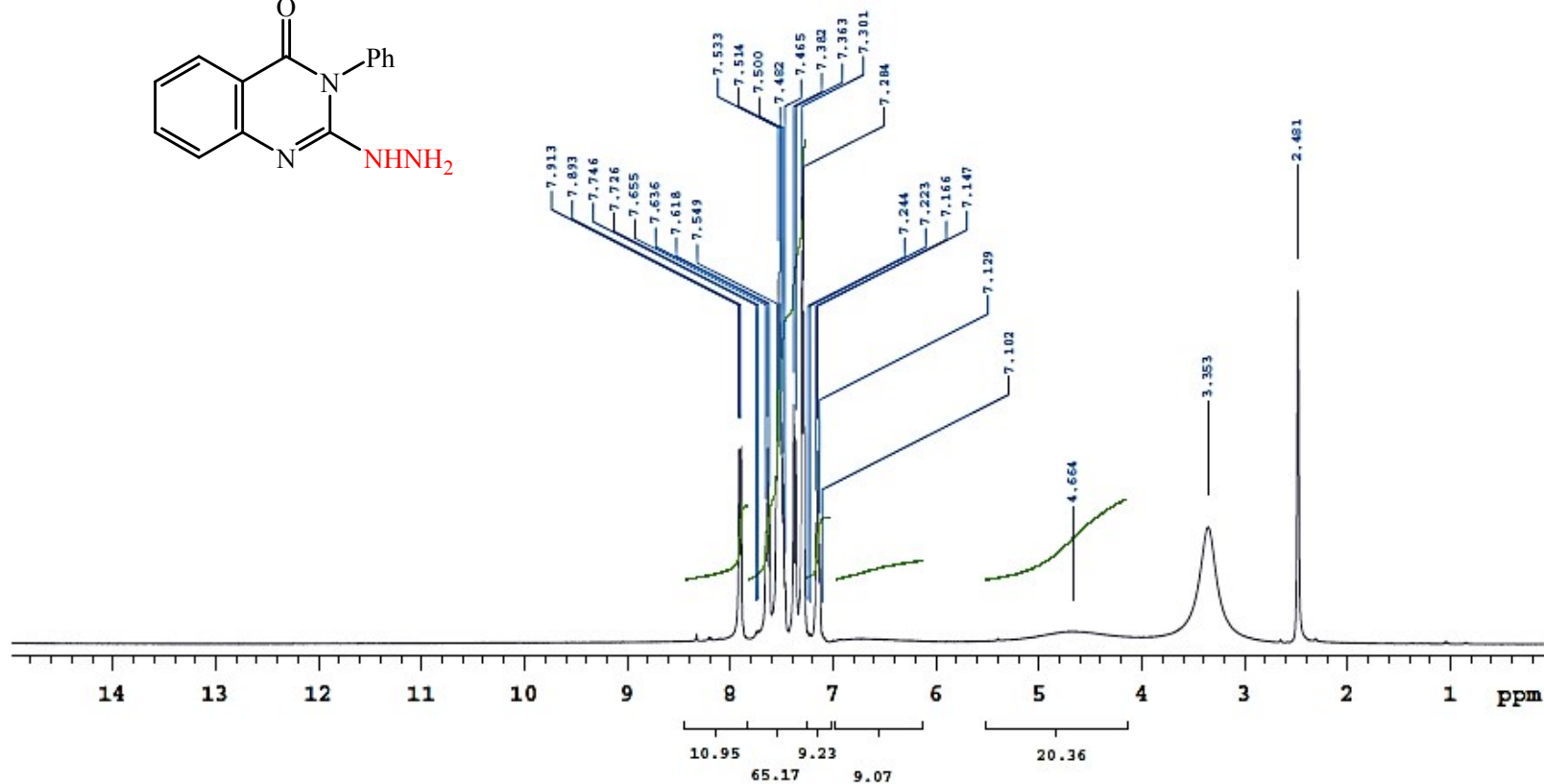
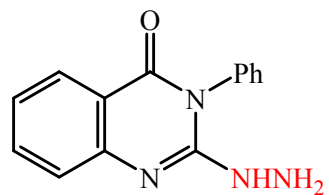
Dr_AbeerElnagar-q2

Sample Name Dr_AbeerElnagar-q2
Date collected 2018-02-26

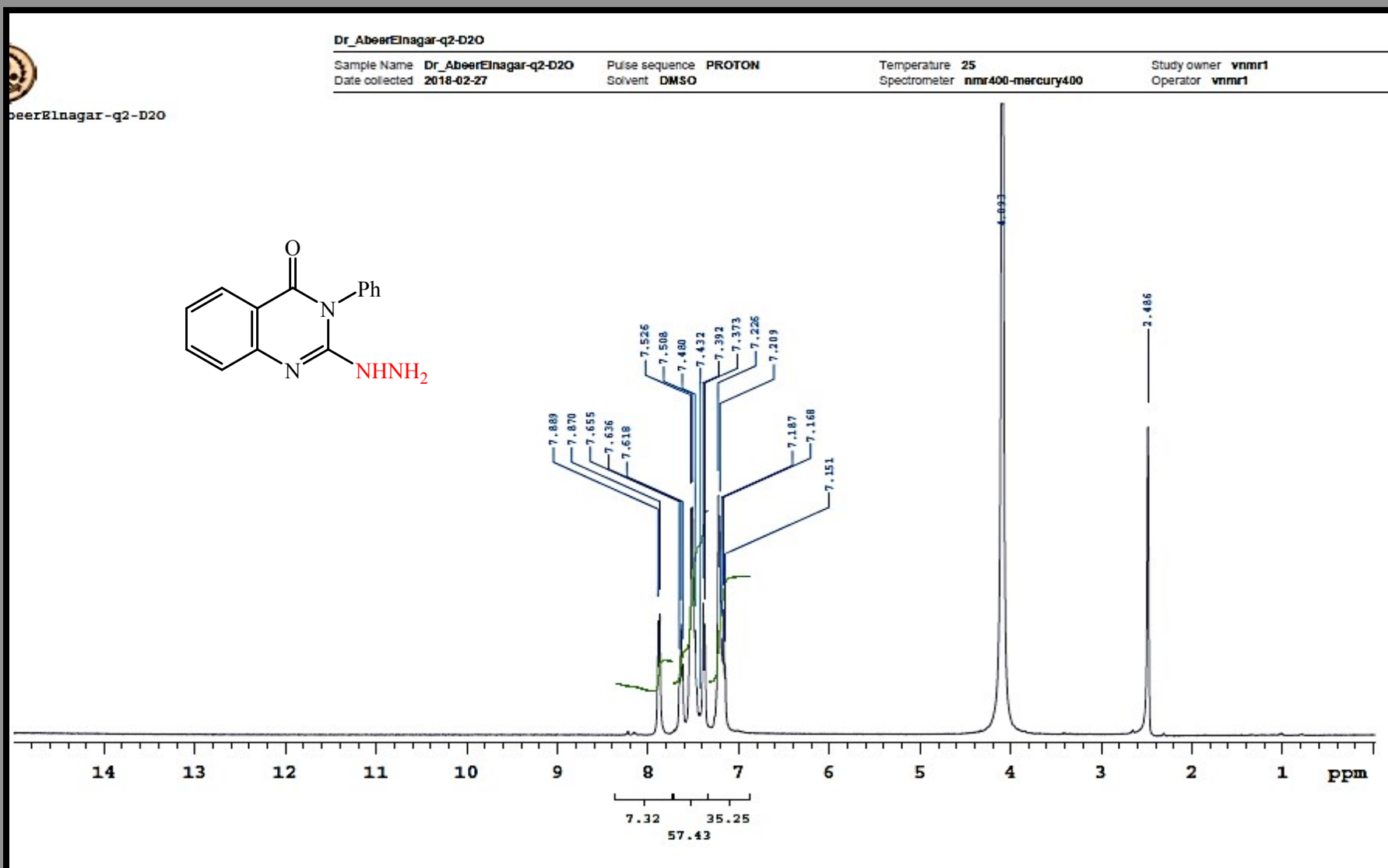
Pulse sequence PROTON
Solvent DMSO

Temperature 25
Spectrometer nmr400-mercury400

Study owner vnmr1
Operator vnmr1

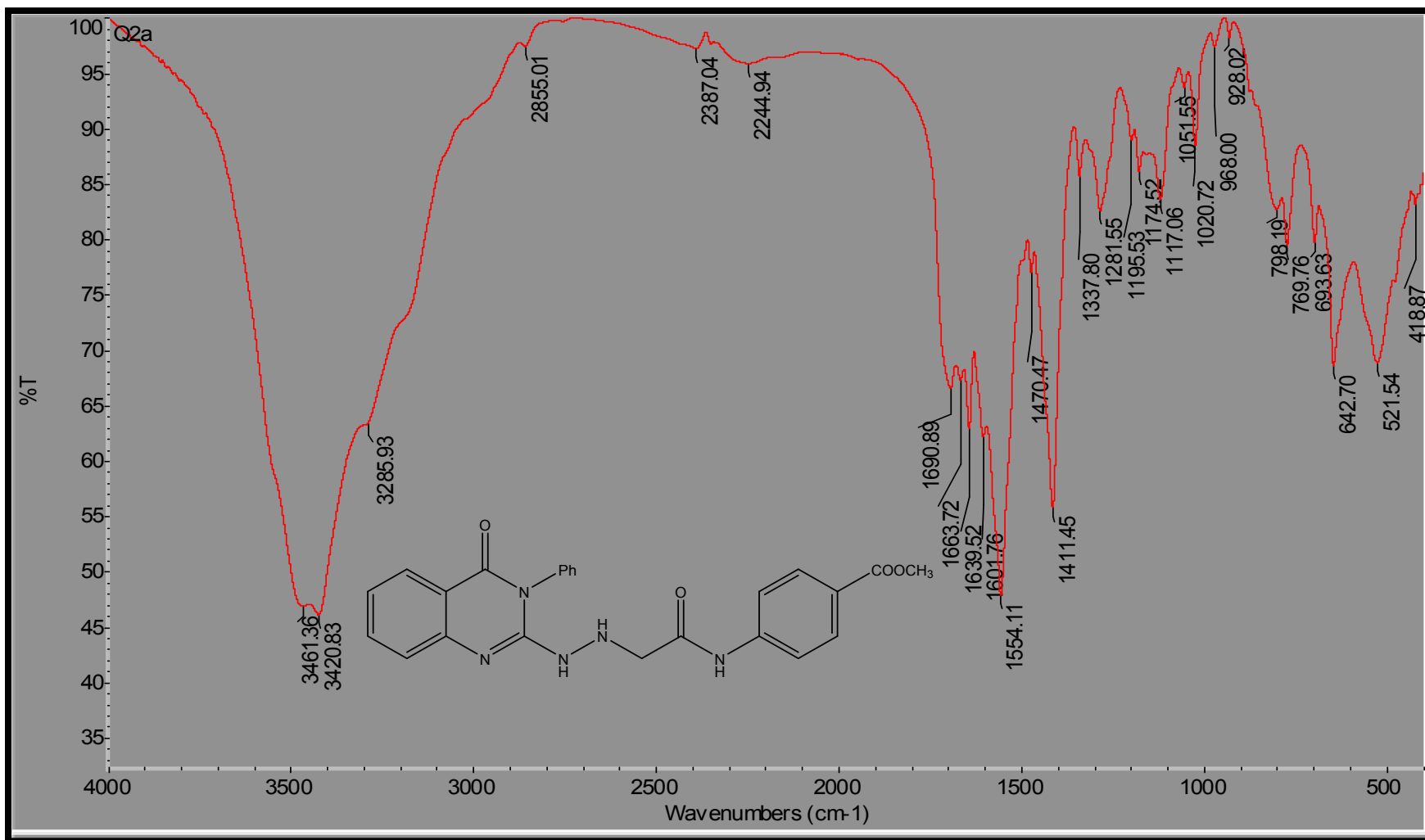


D20

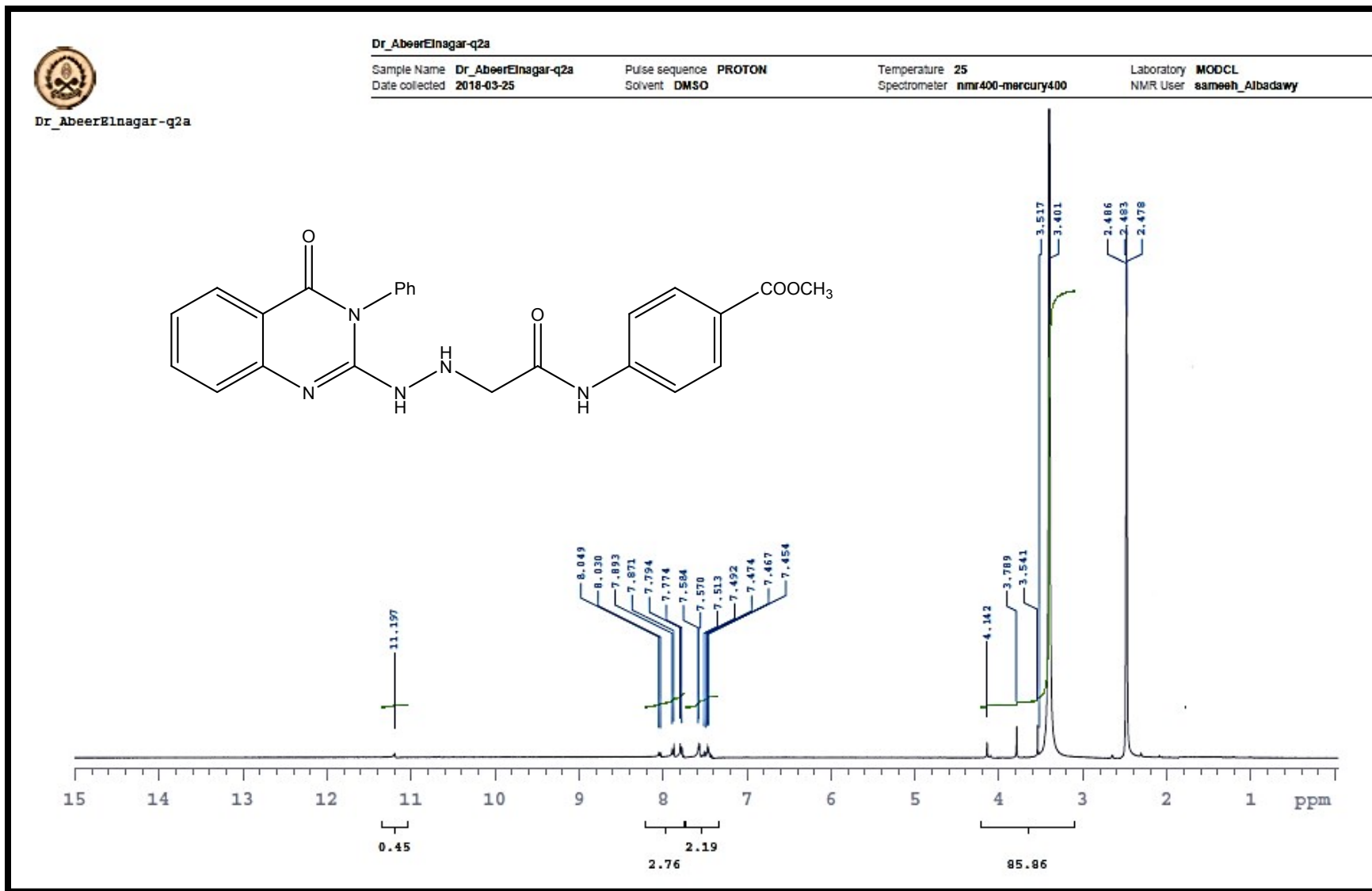


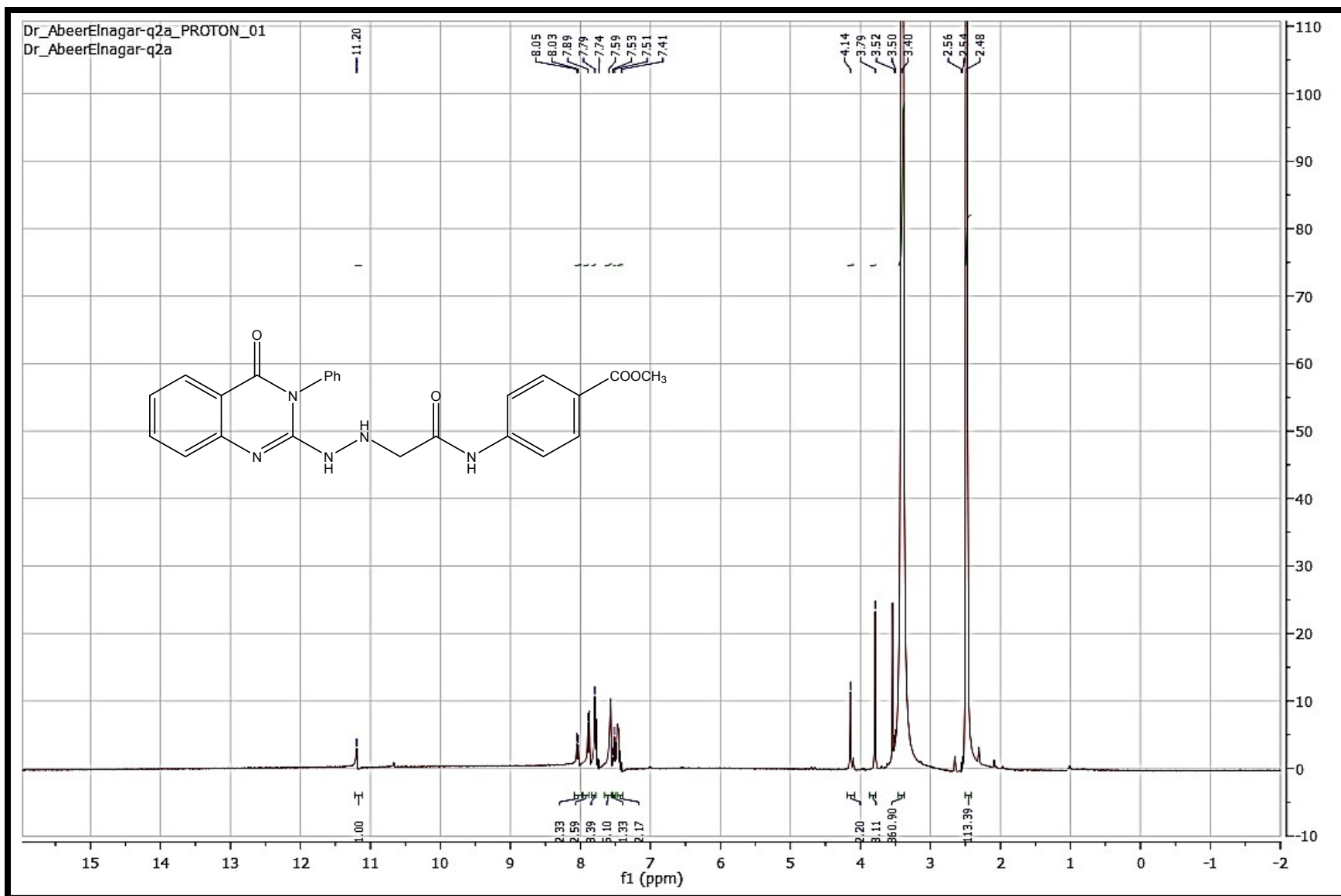
Methyl 4-(2-(2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)hydrazinyl)acetamido)benzoate (12a).

IR

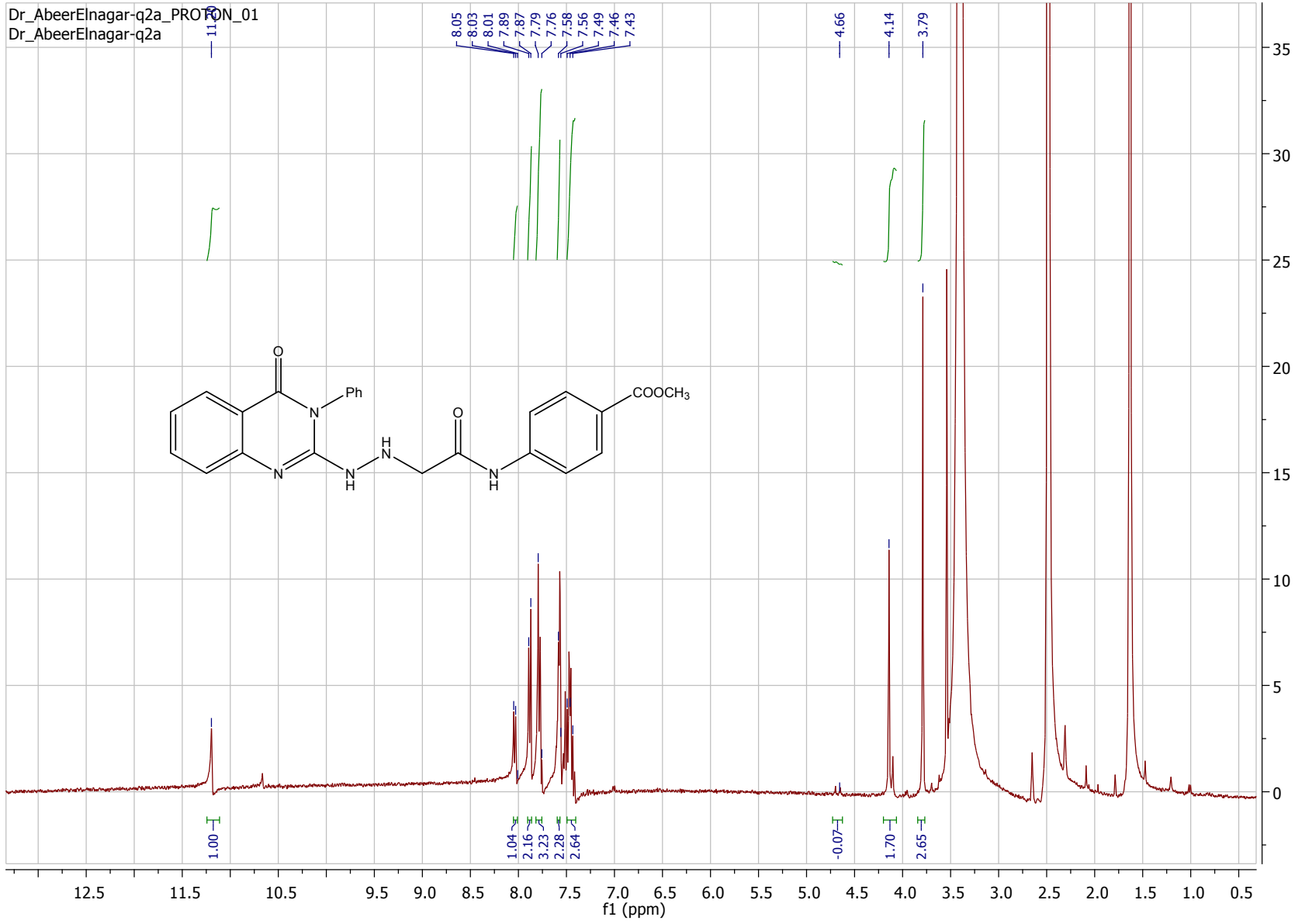


HNMR

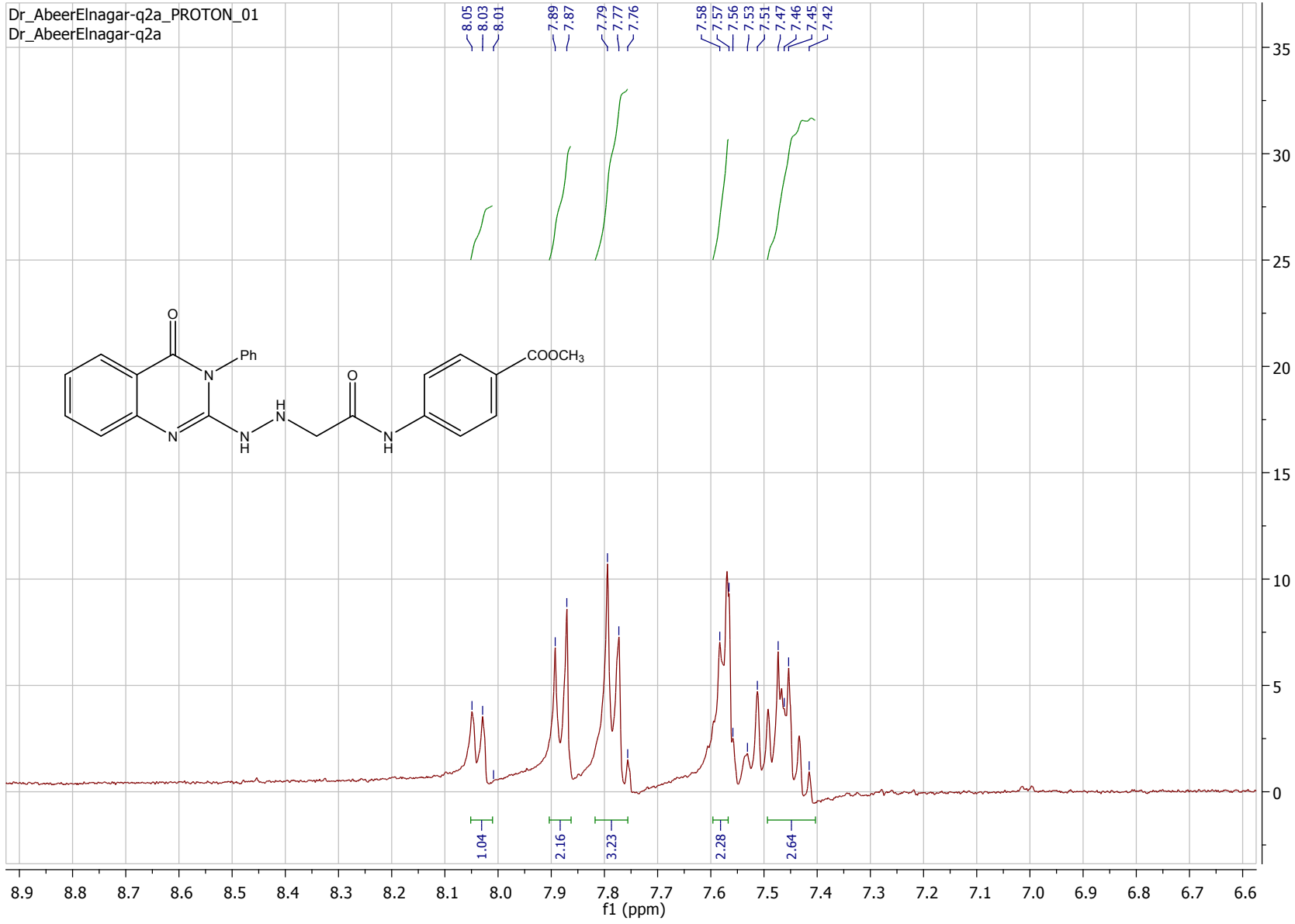




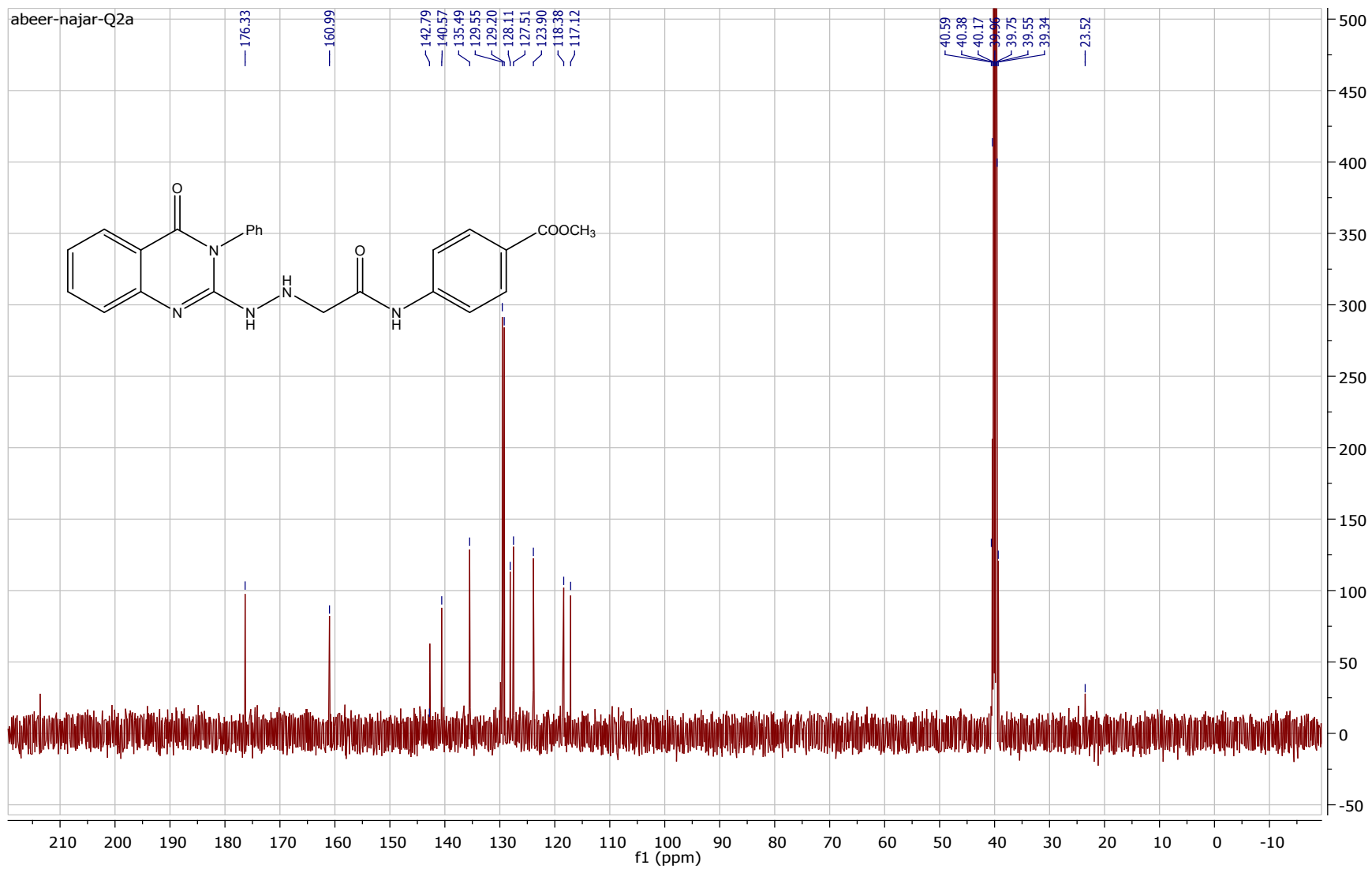
Dr_AbeerElnagar-q2a_PROTON_01
Dr_AbeerElnagar-q2a



Dr_AbeerElnagar-q2a_PROTON_01
Dr_AbeerElnagar-q2a

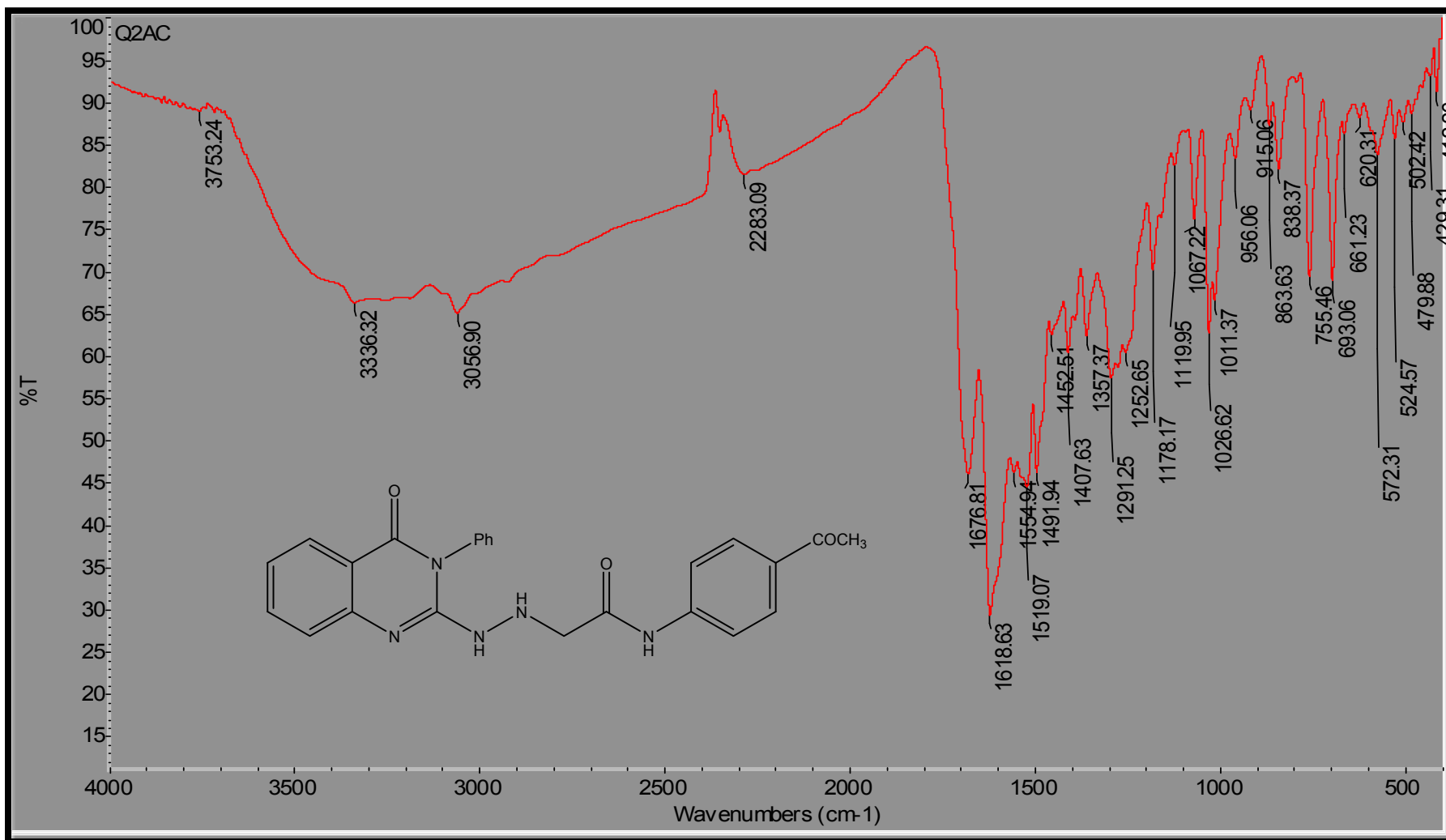


¹³C NMR

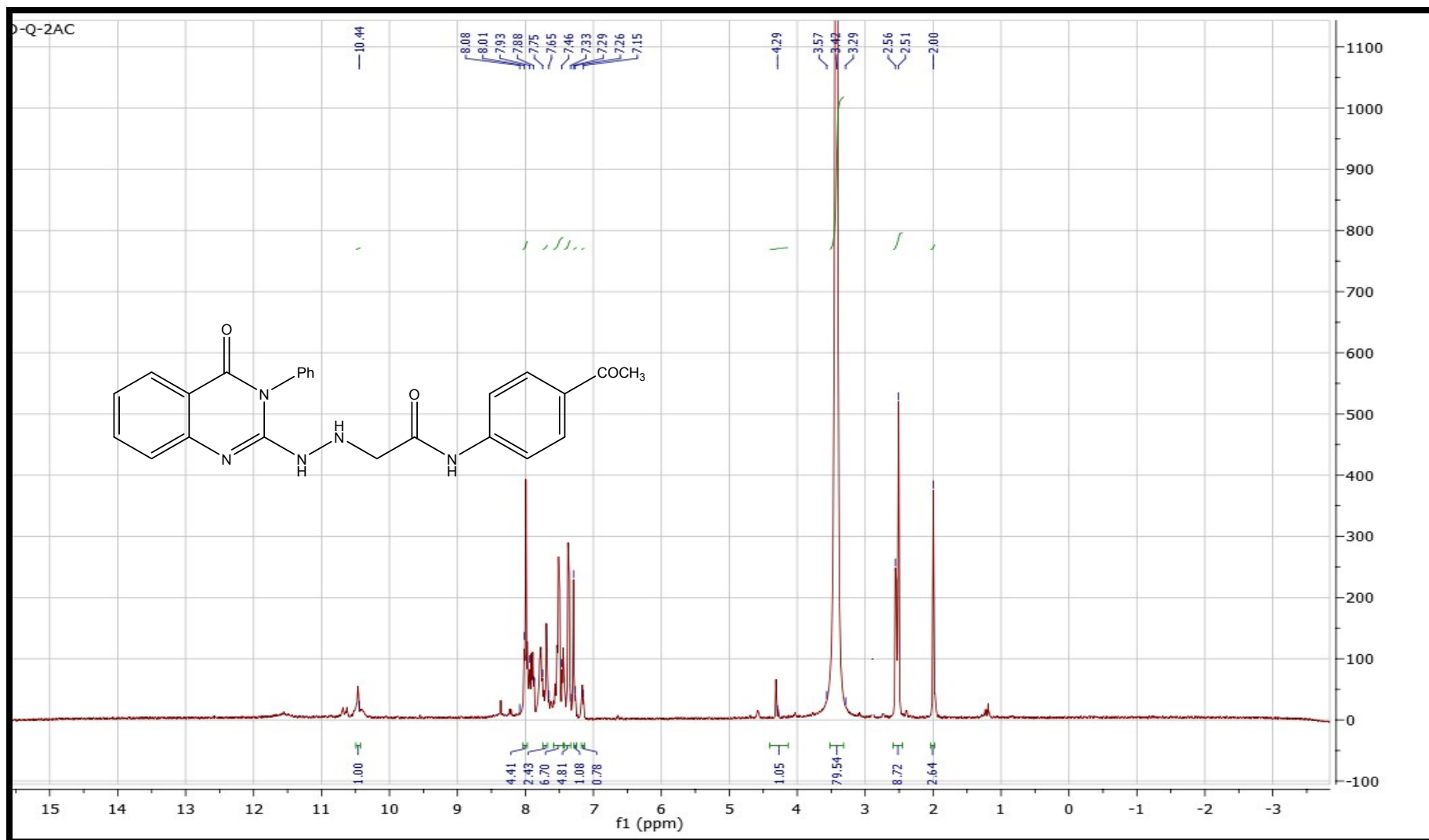


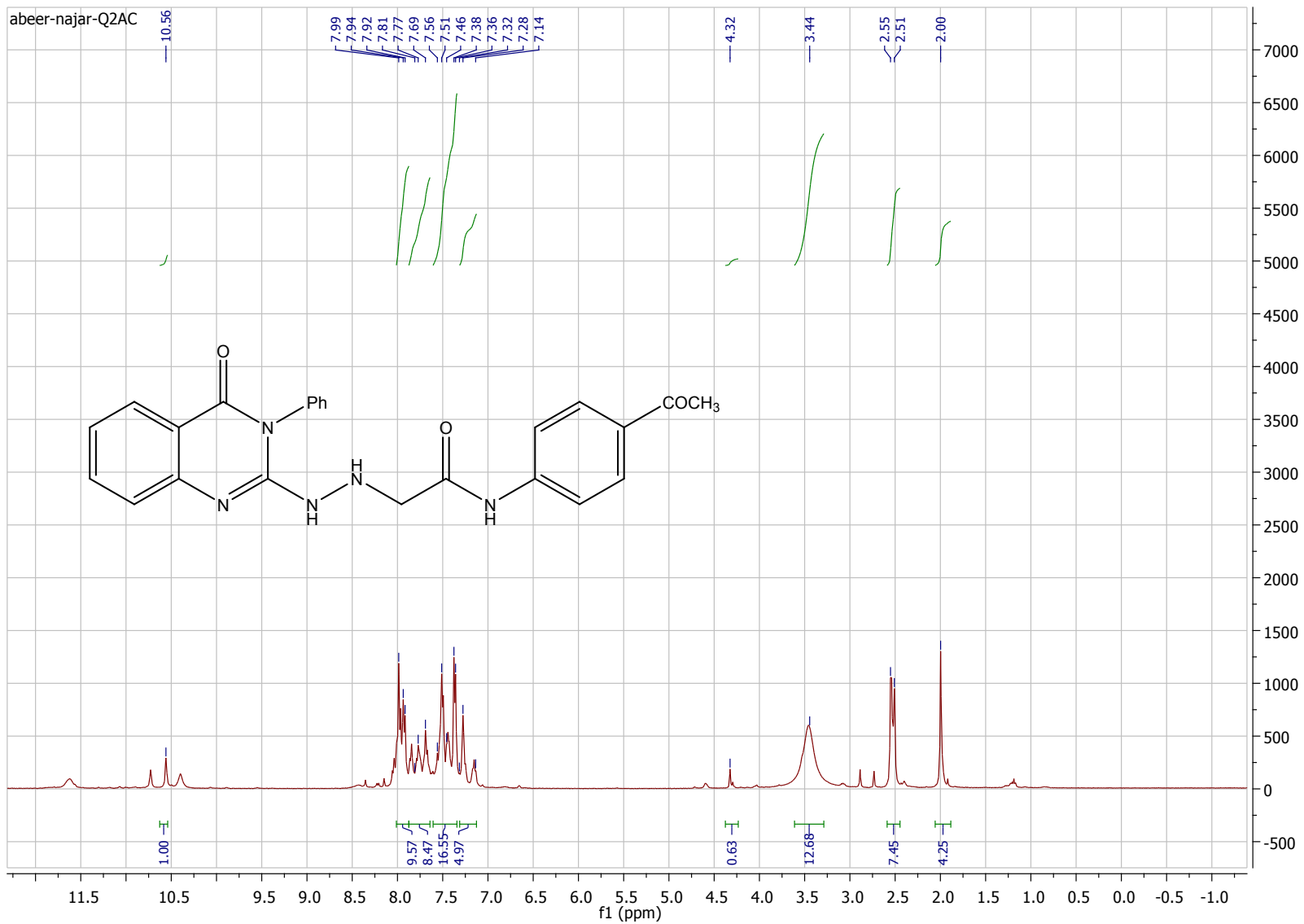
N-(4-Acetylphenyl)-2-(2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)hydrazinyl)acetamide (12b).

IR



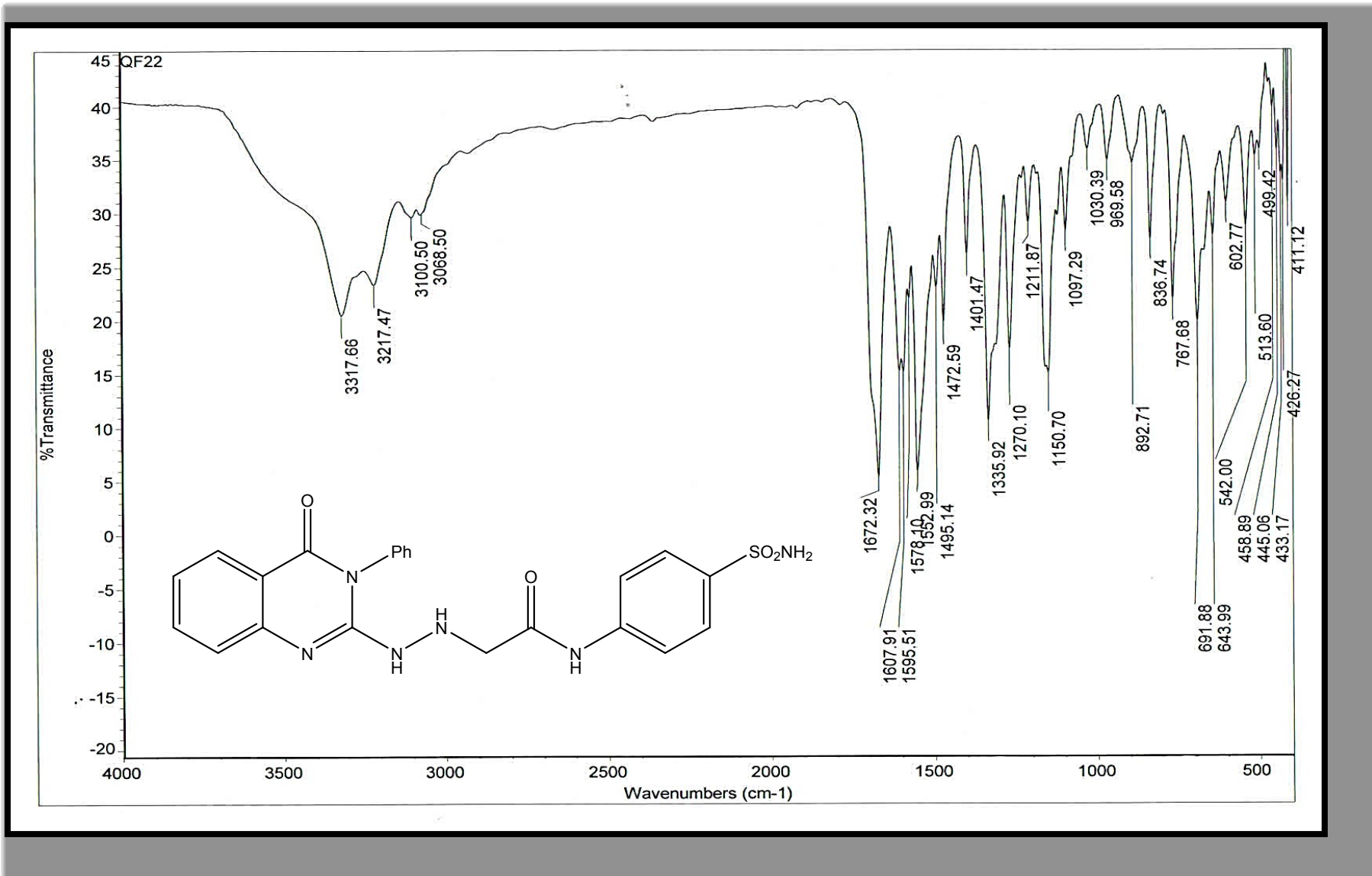
HNMR



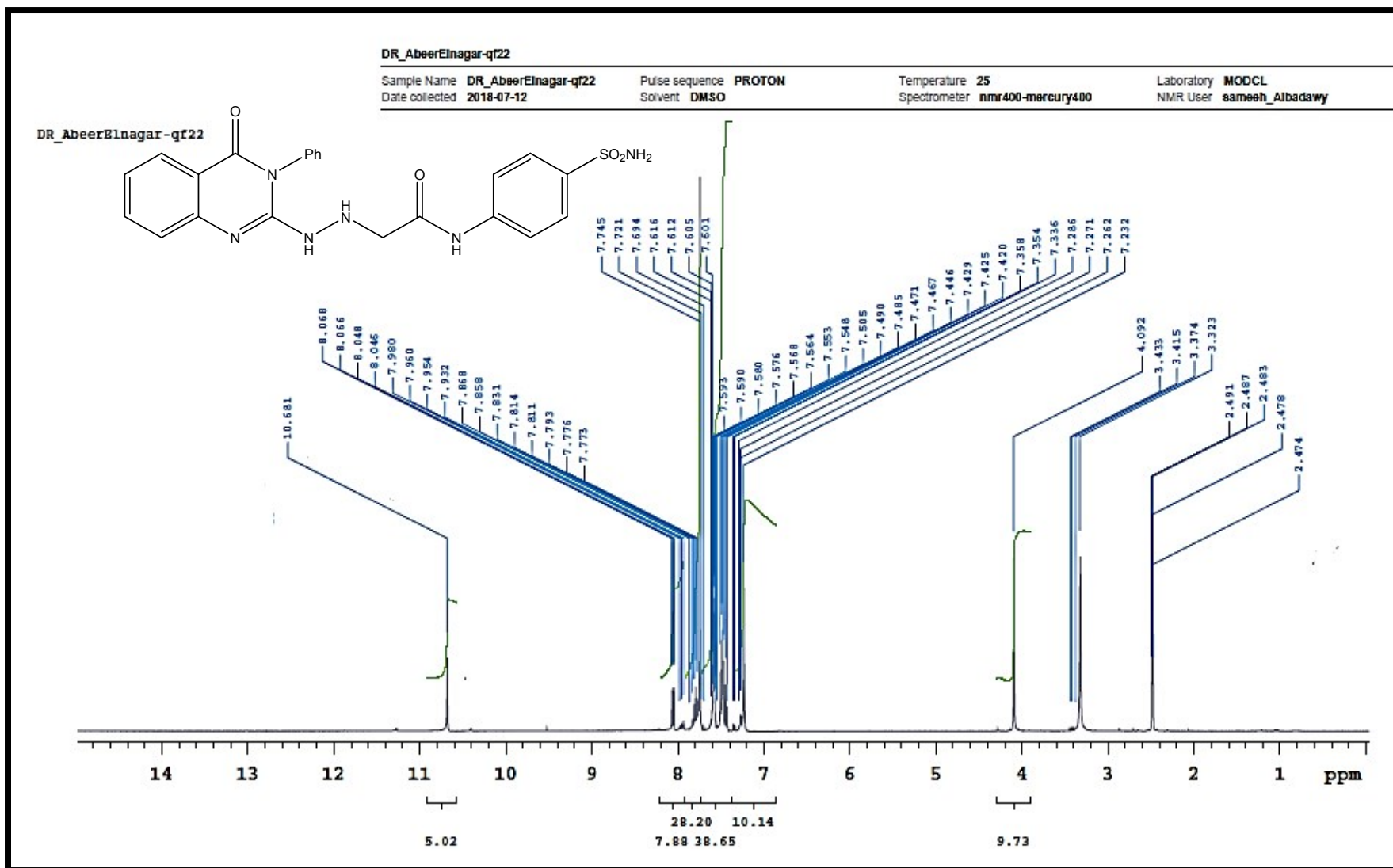


2-(2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)hydrazinyl)-N-(4-sulfamoylphenyl)acetamide (12c).

IR



HNMR



DR_AbeerElmagar-qf22

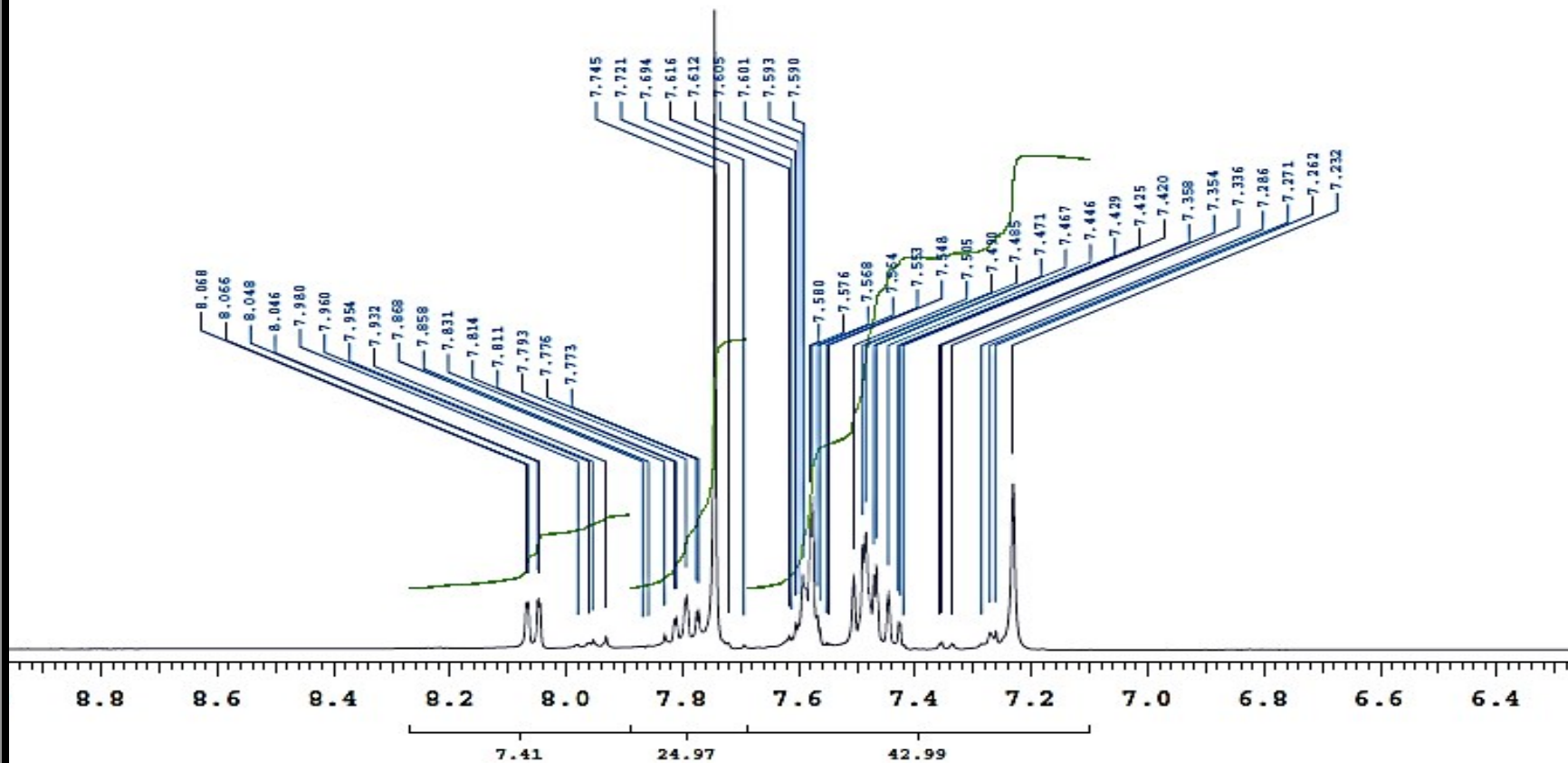
Sample Name DR_AbeerElmagar-qf22
Date collected 2018-07-12

Pulse sequence PROTON
Solvent DMSO

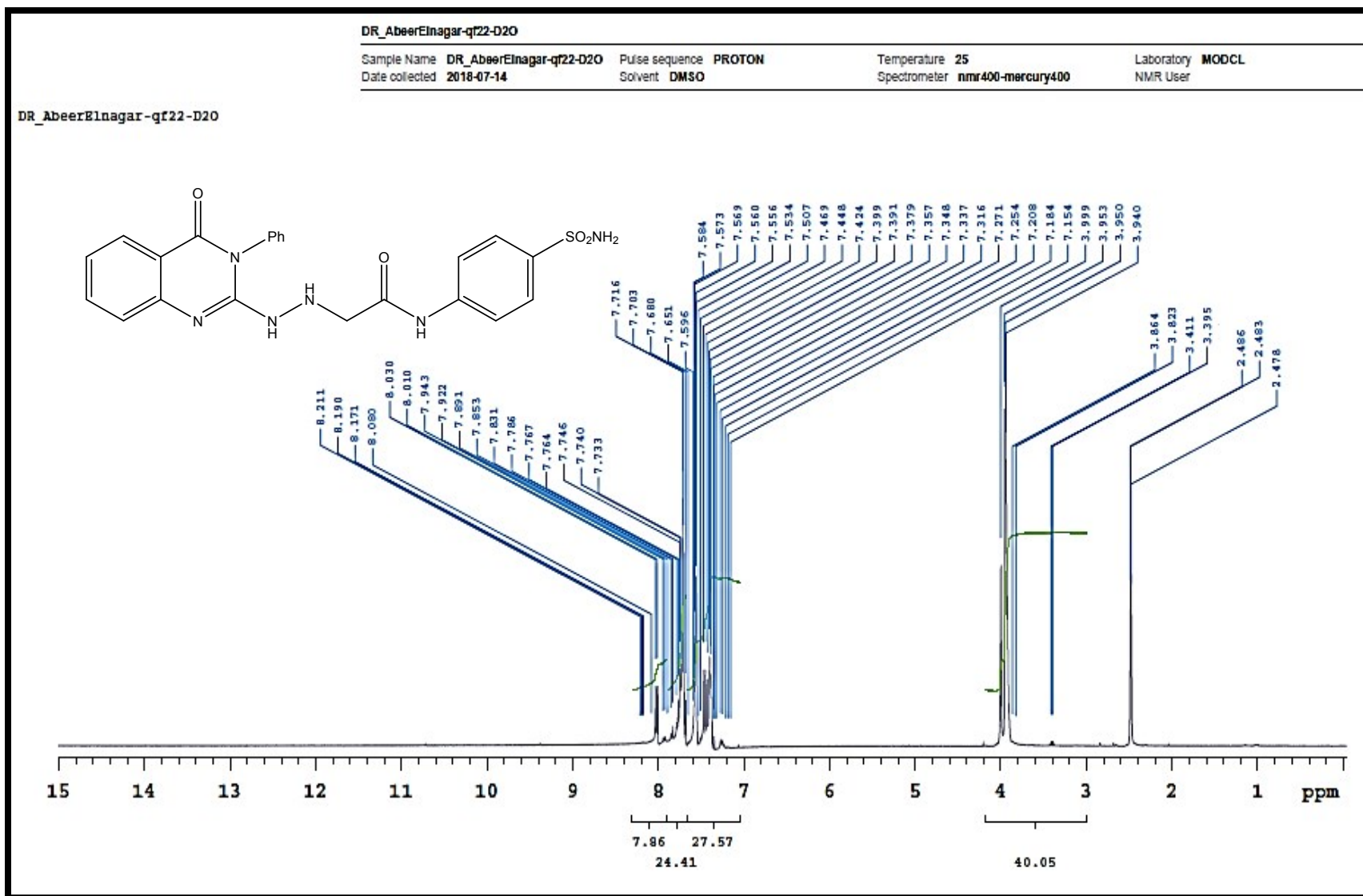
Temperature 25
Spectrometer nmr400-mercury400

Laboratory MODCL
NMR User sameeh

r-qf22



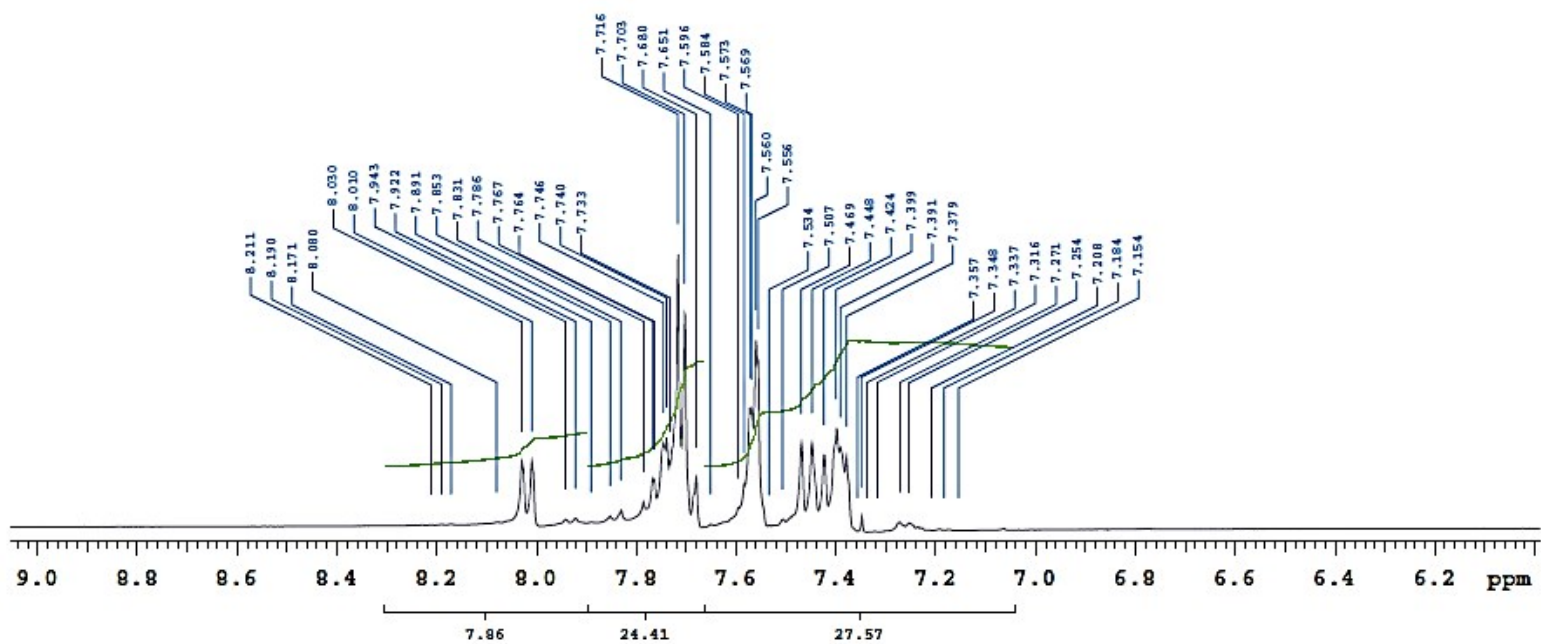
D2O

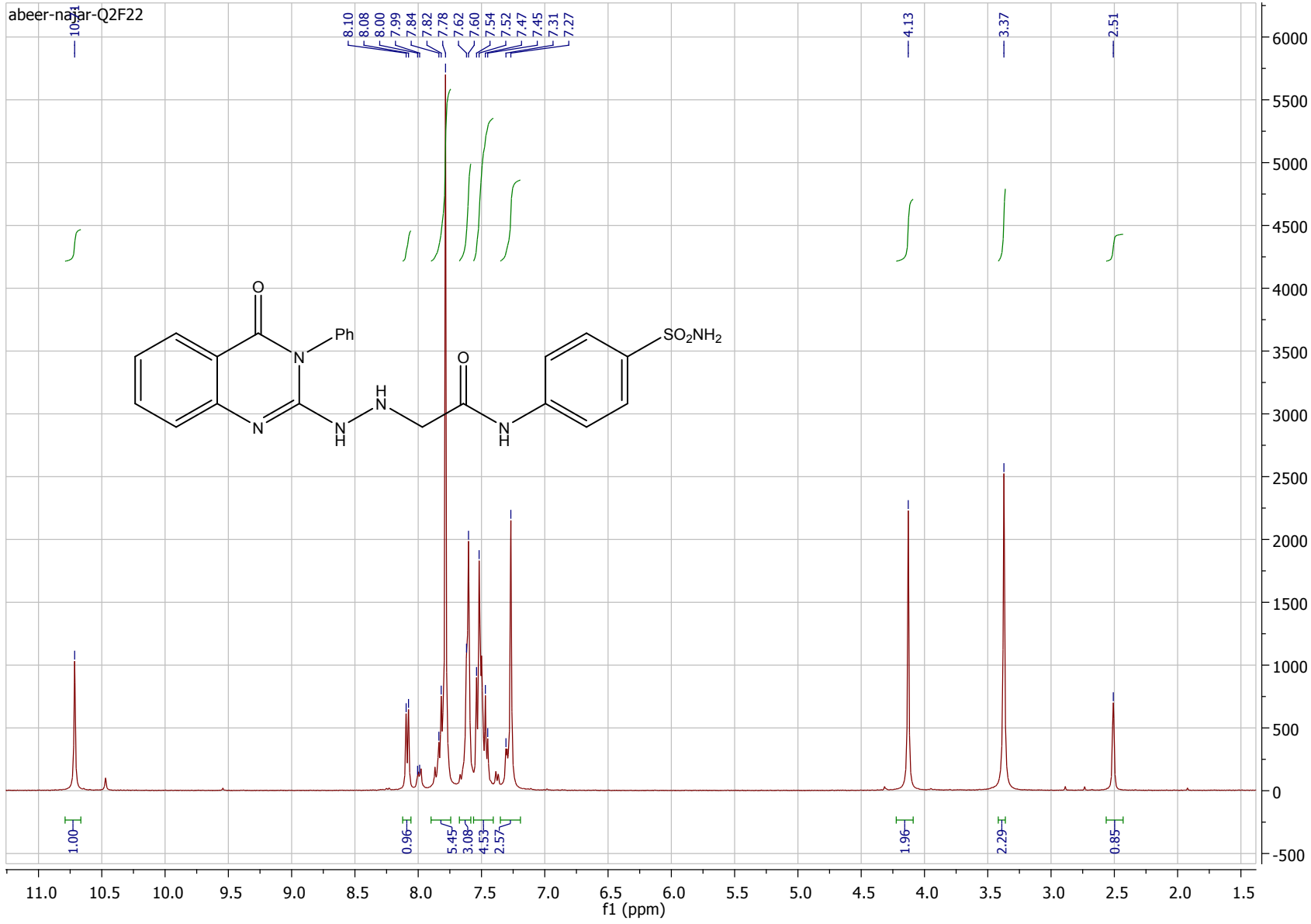


DR_AbeerElnagar-qt22-D2O

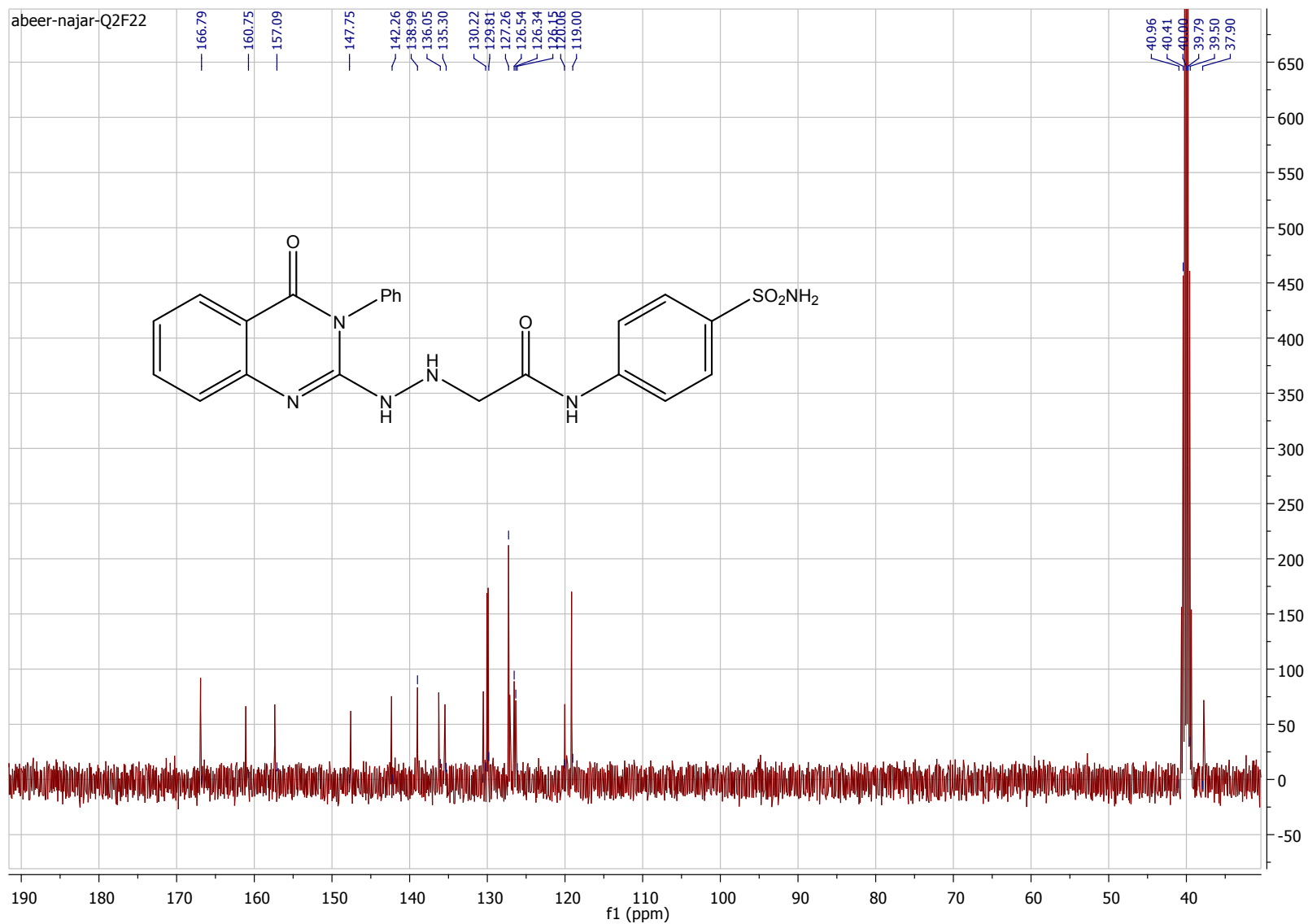
Sample Name	DR_AbeerElnagar-qt22-D2O	Pulse sequence	PROTON	Temperature	25	Laboratory	MODCL
Date collected	2018-07-14	Solvent	DMSO	Spectrometer	nmr400-mercury400	NMR User	

DR_AbeerElnagar-qt22-D2O



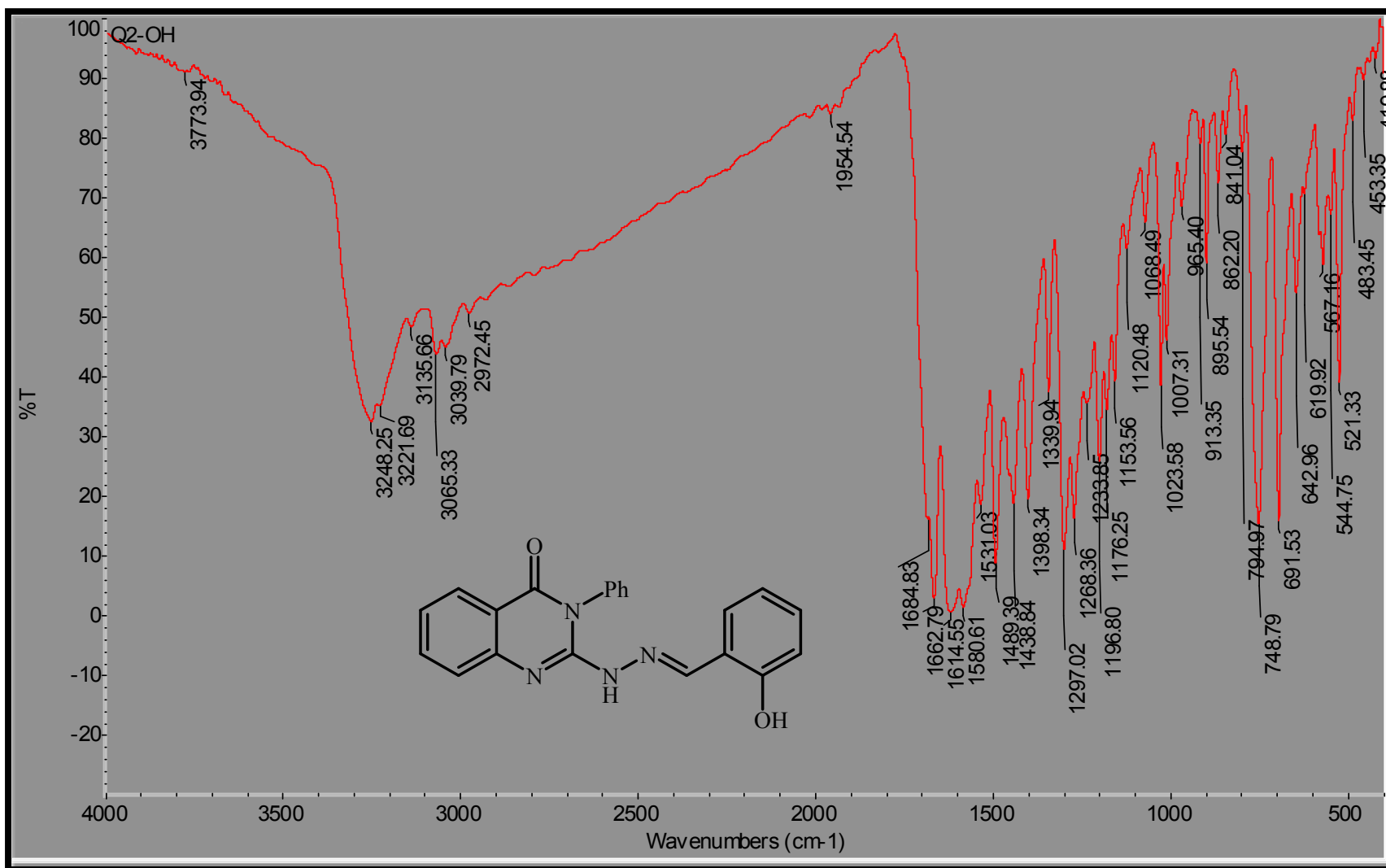


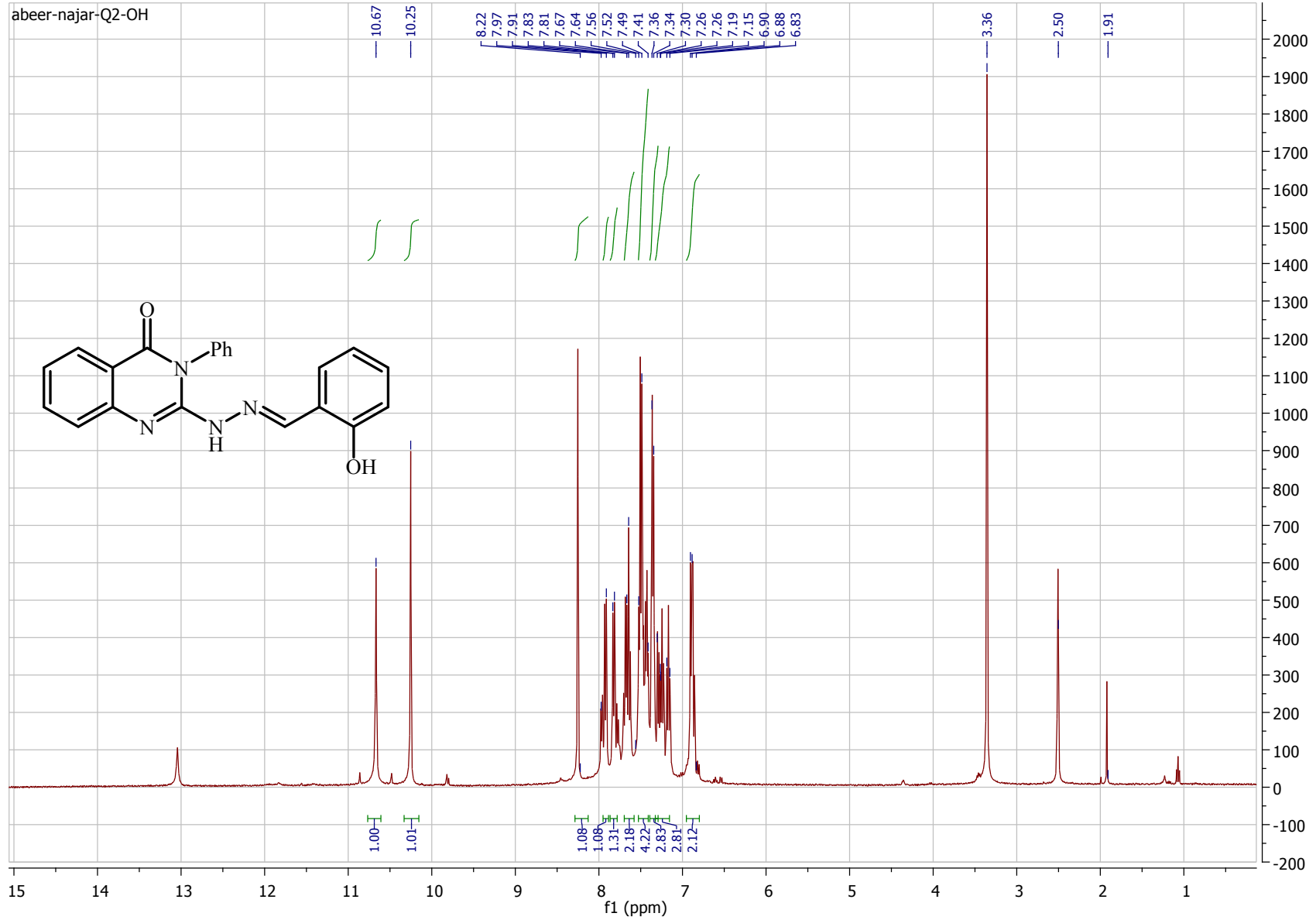
¹³C NMR

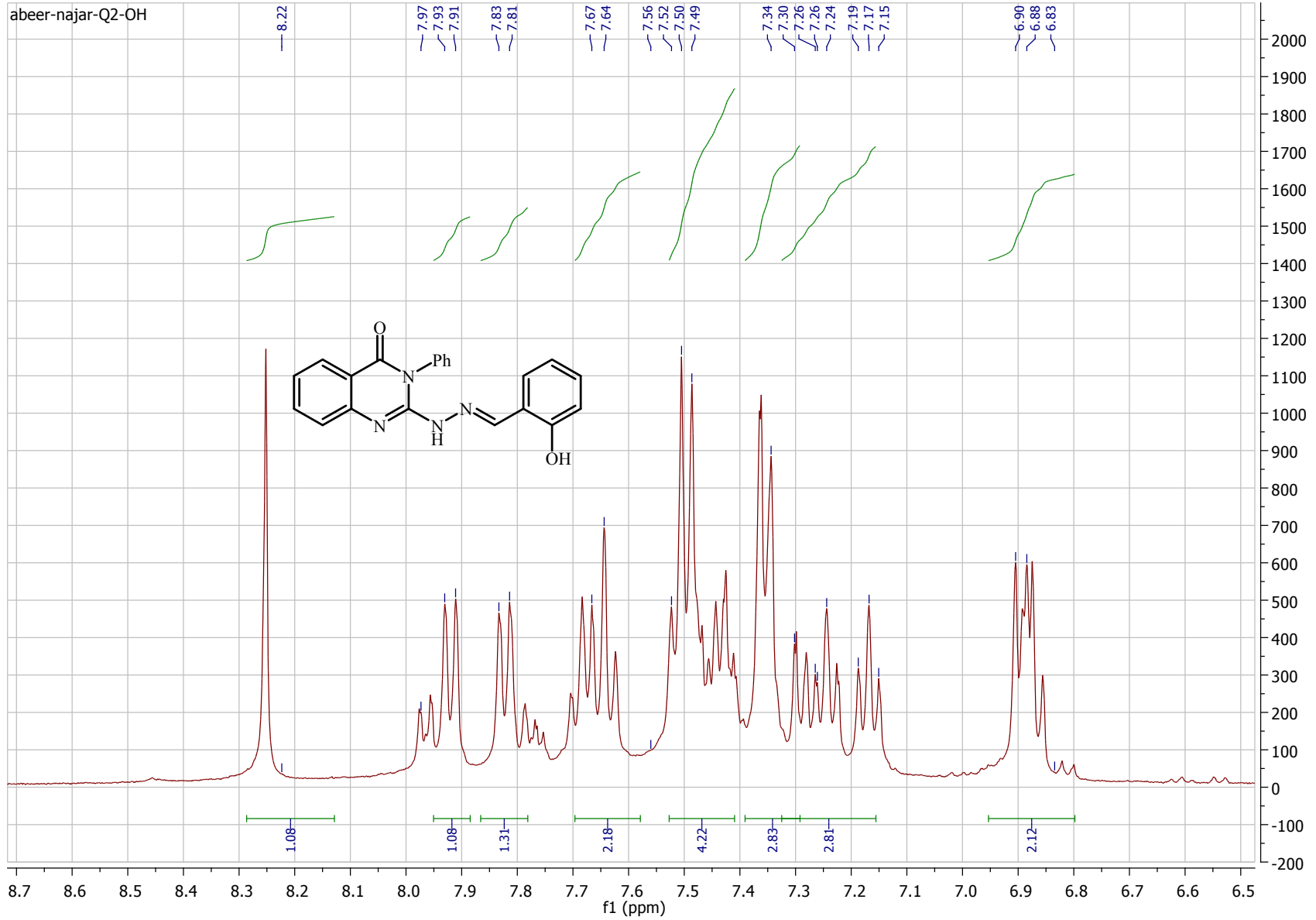


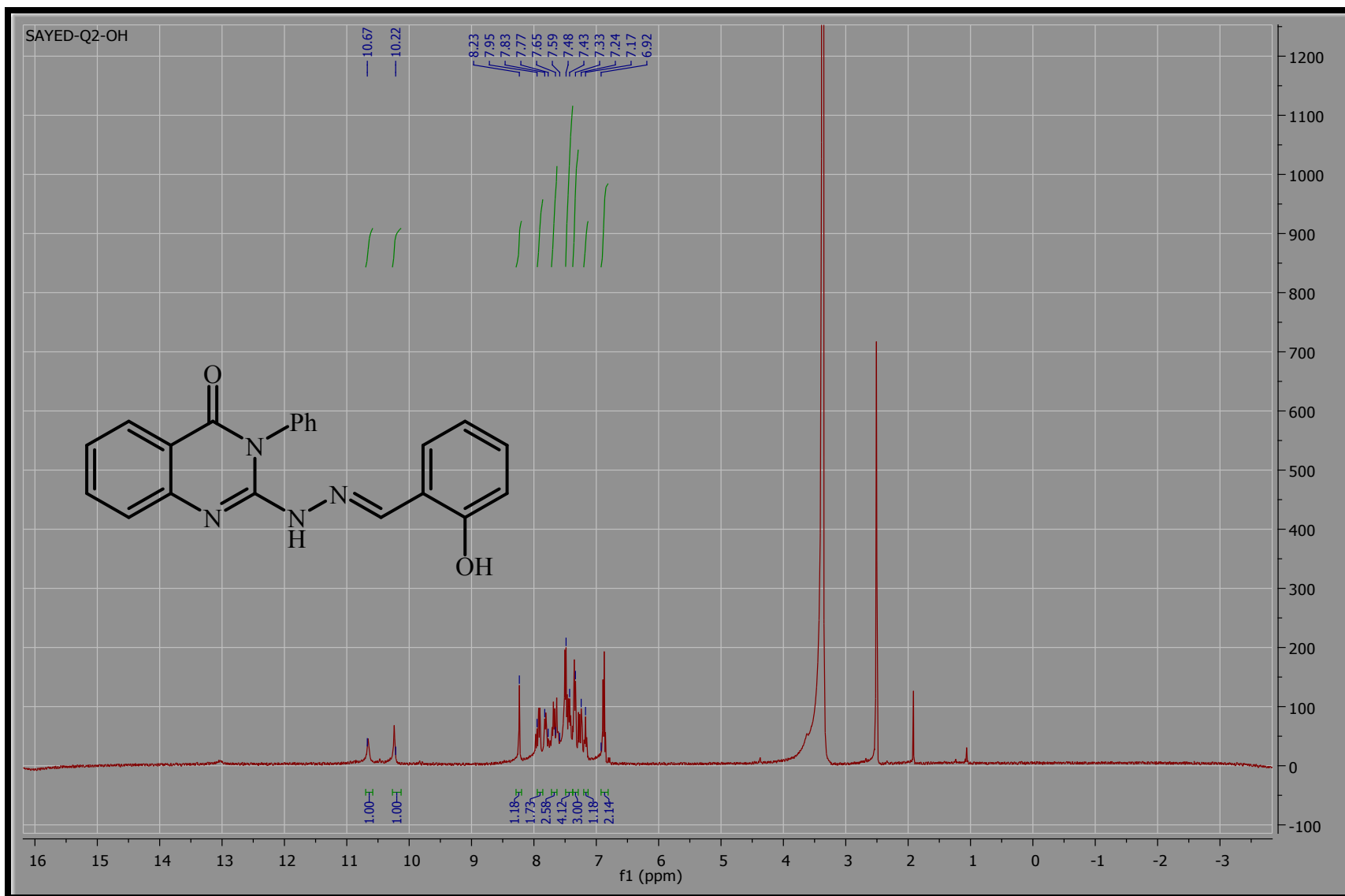
2-(2-(2-Hydroxybenzylidene)hydrazinyl)-3-phenylquinazolin-4(3H)-one (13a).

IR

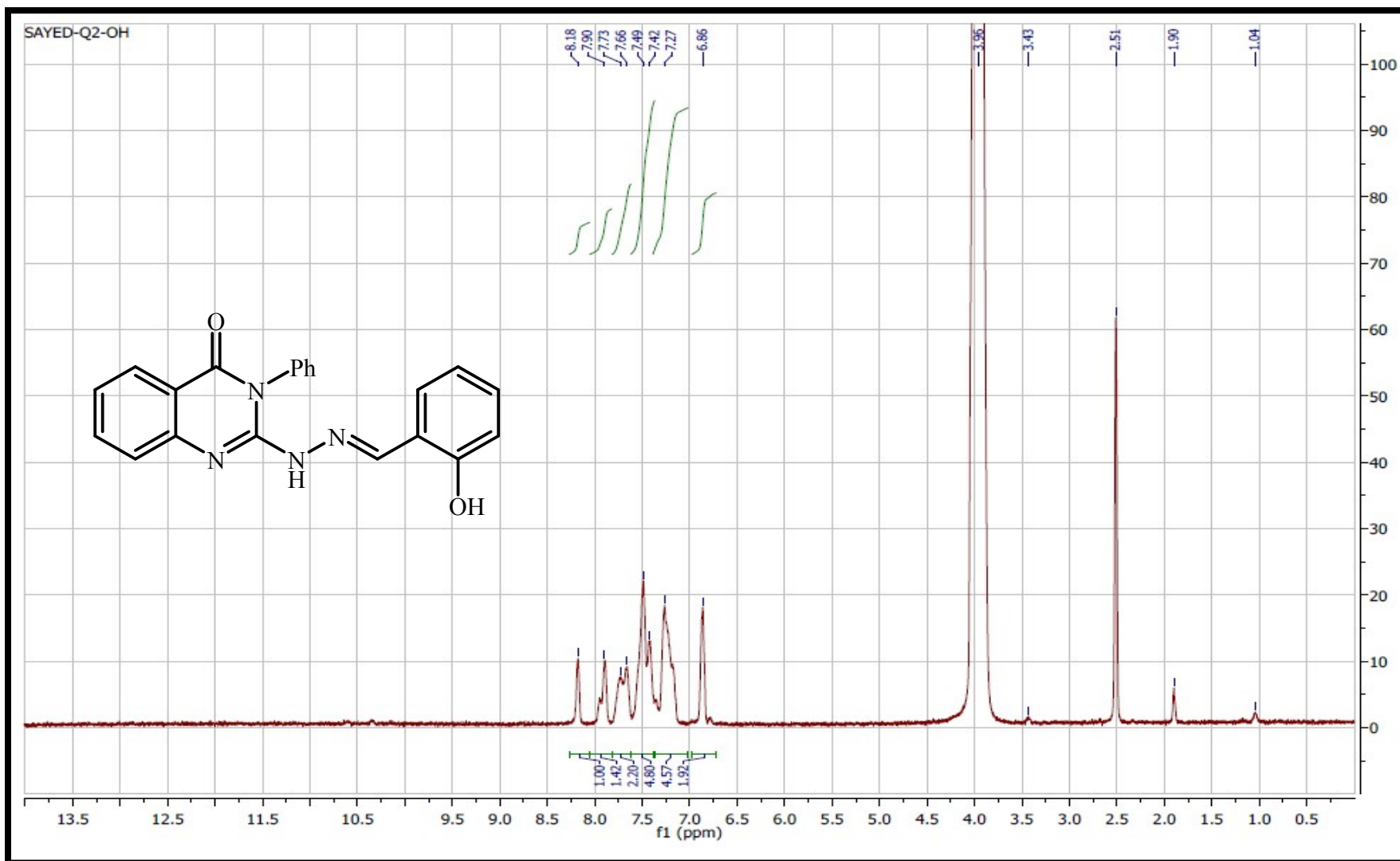




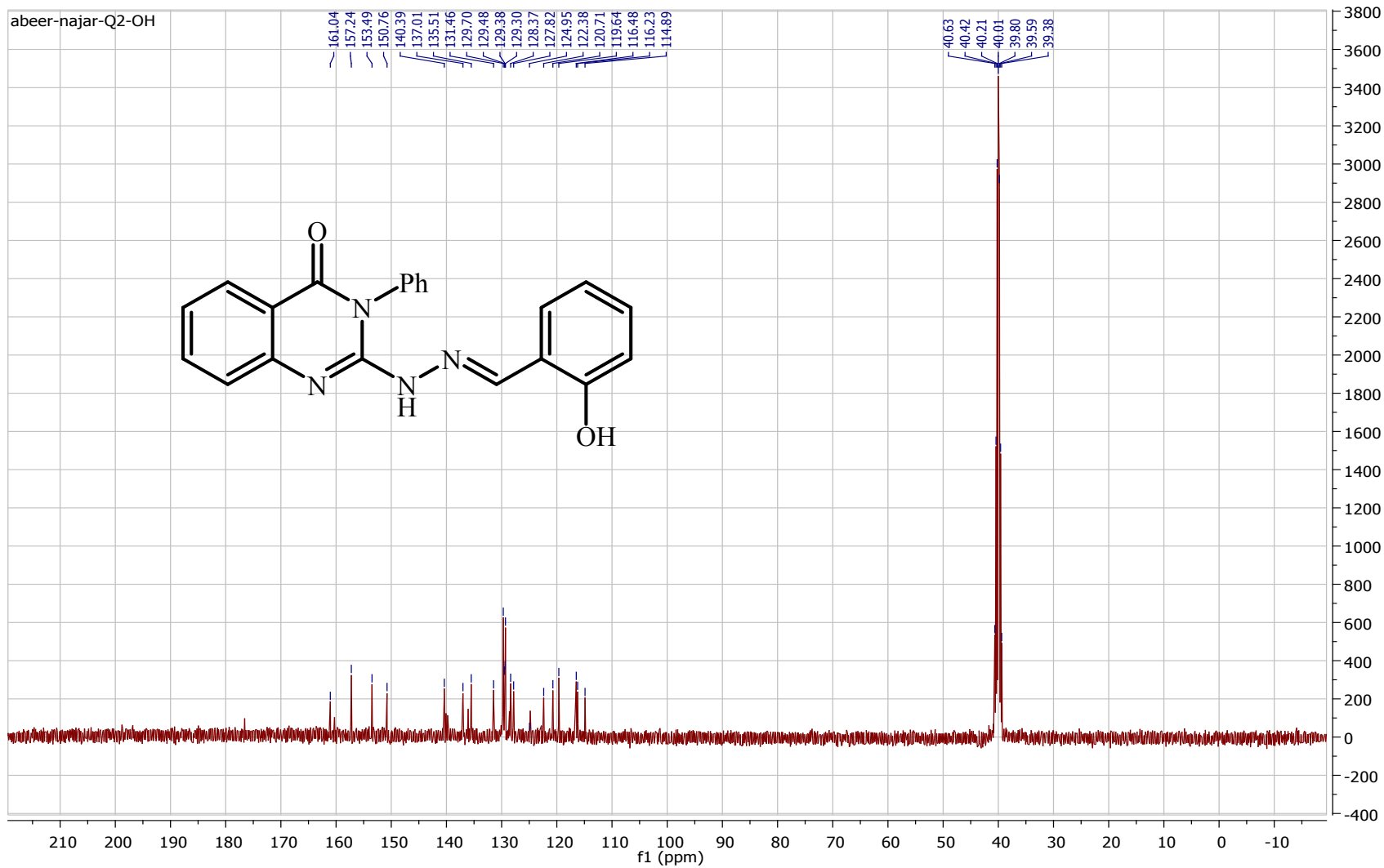




D20

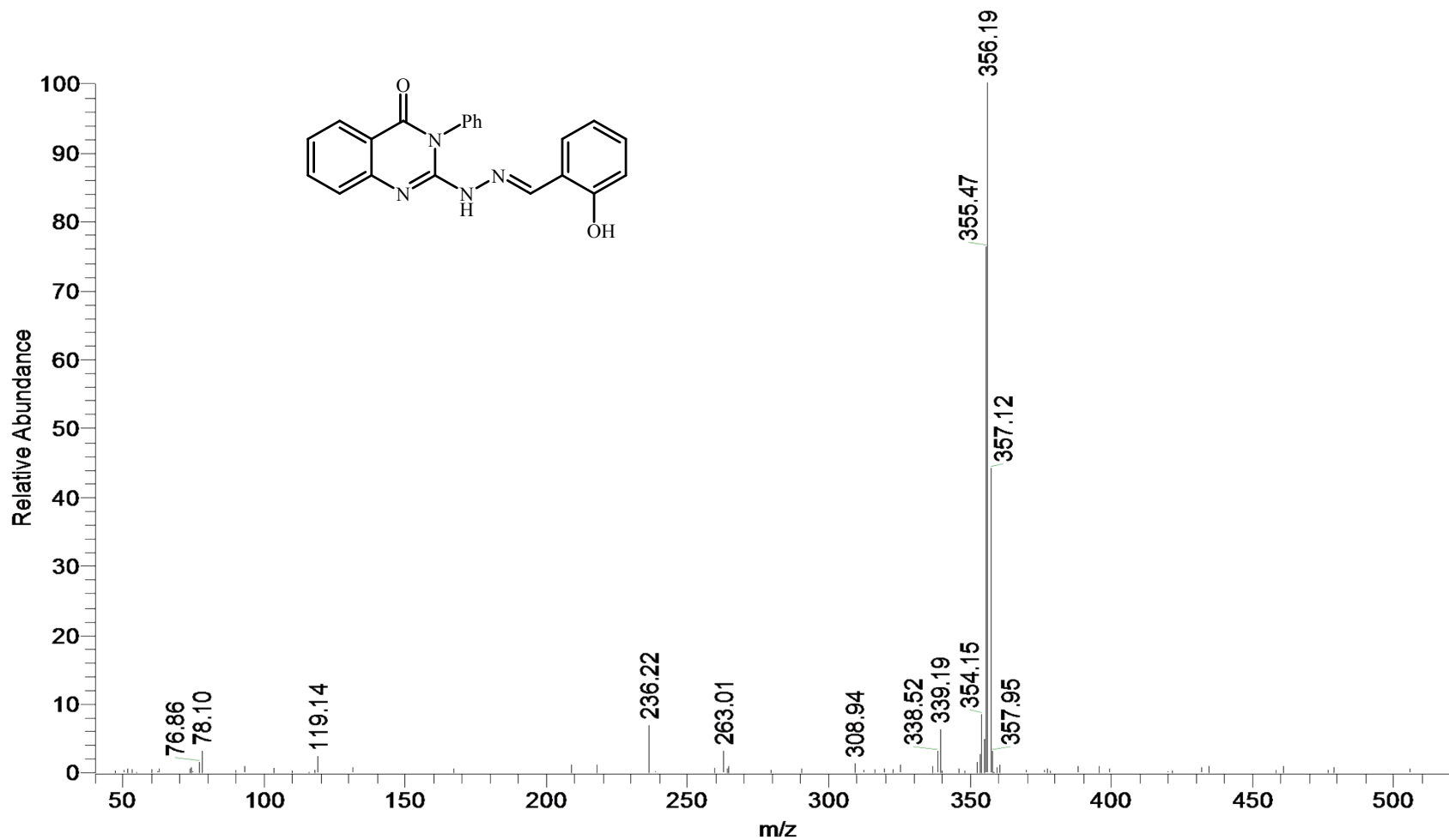


¹³C NMR



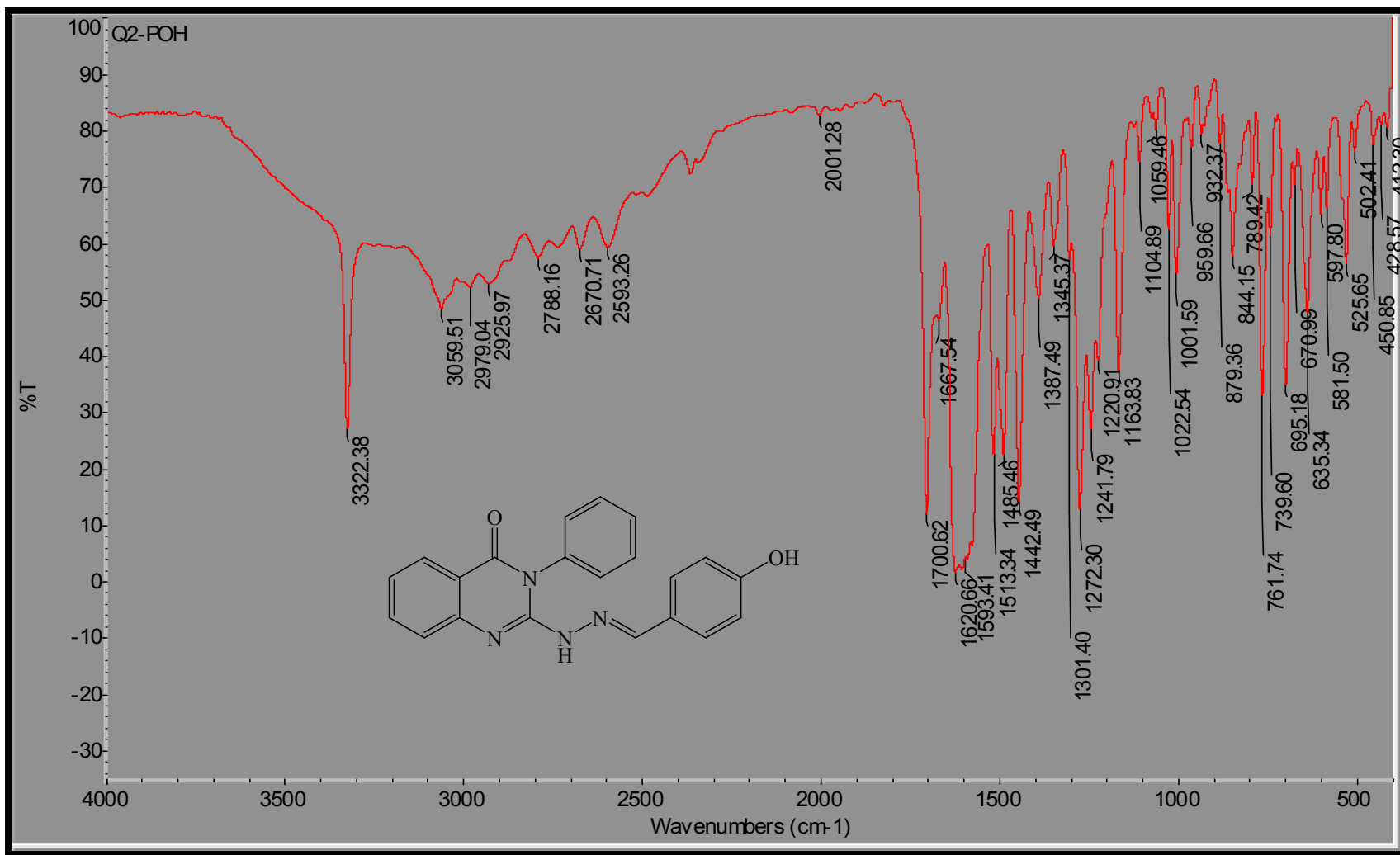
Mass

sayed-karam-Q2-OH#152 RT: 2.56 AV: 1 SB: 2 2.58 , 2.58 NL: 3.46E4
T: {0,0} + c EI Full ms [40.00-1000.00]

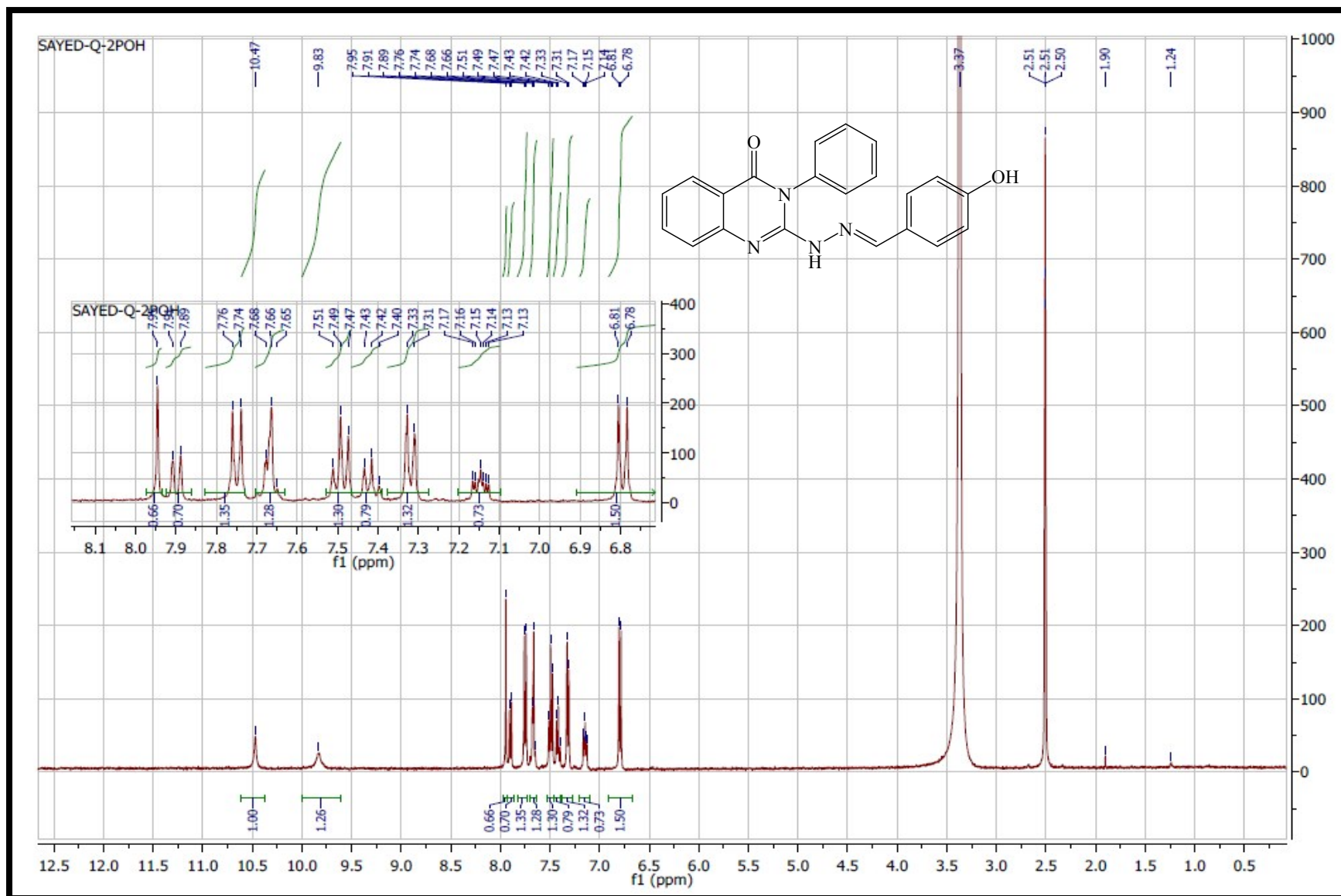


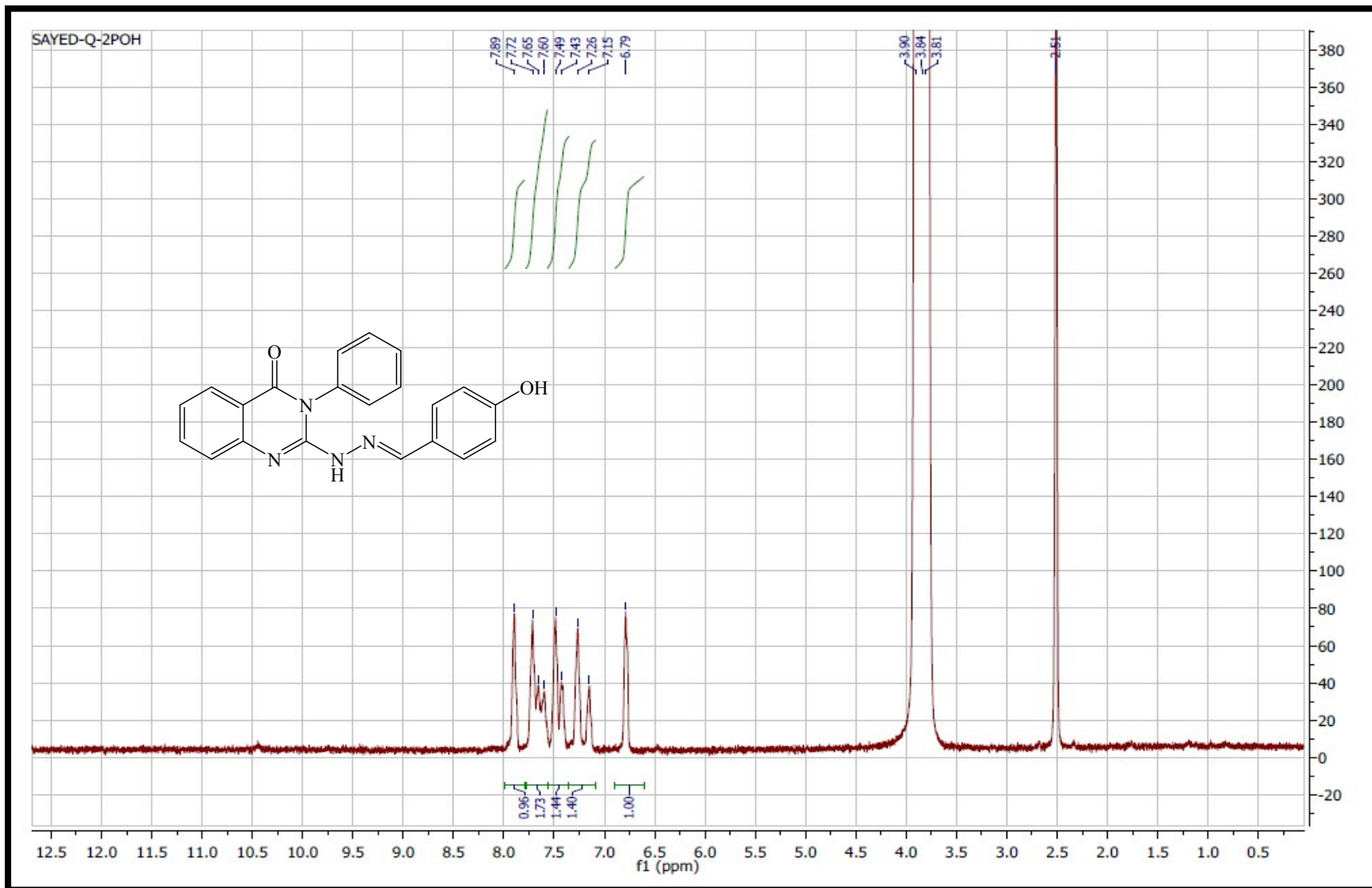
2-(2-(4-Hydroxybenzylidene)hydrazinyl)-3-phenylquinazolin-4(3H)-one (13b).

IR



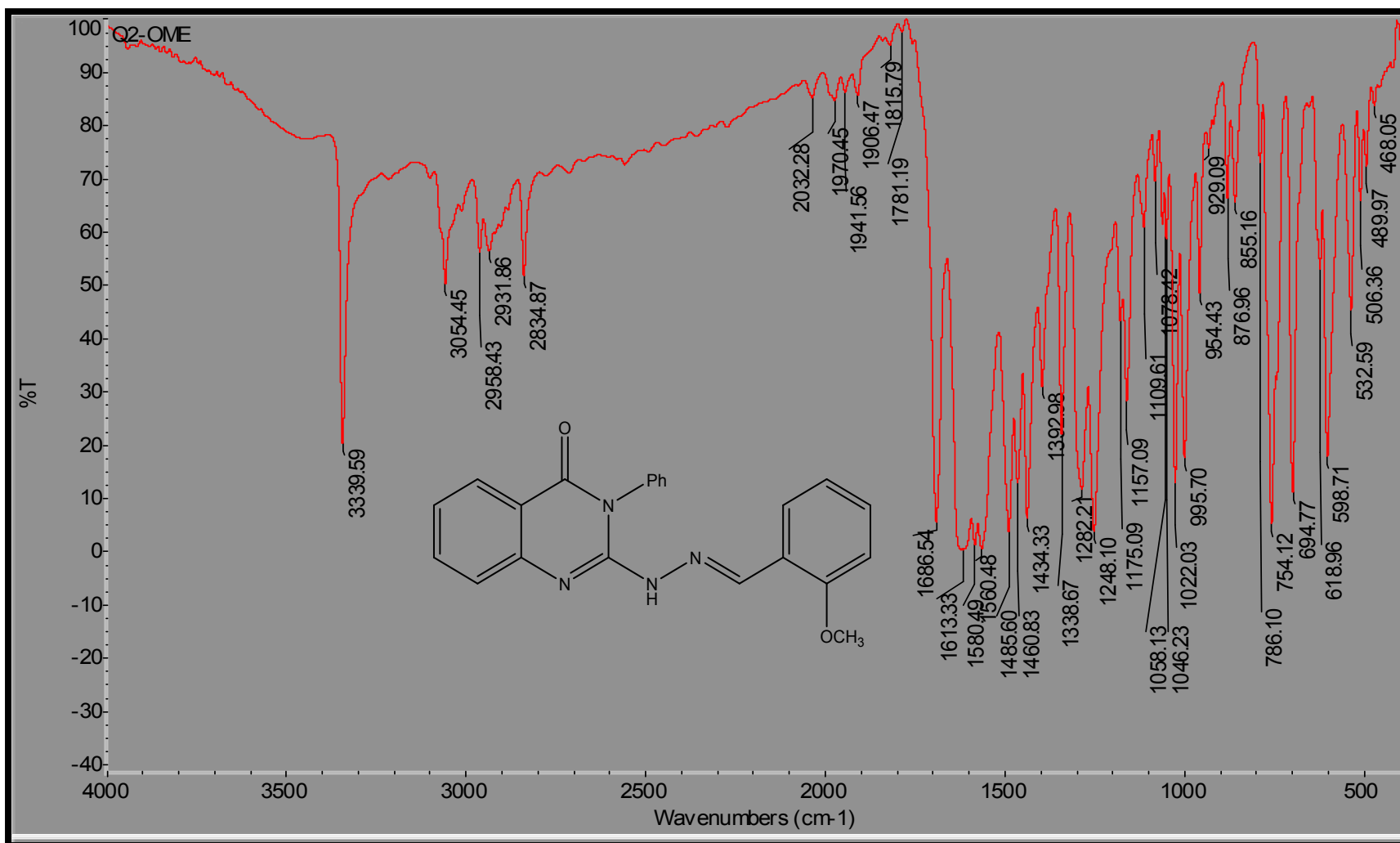
HNMR



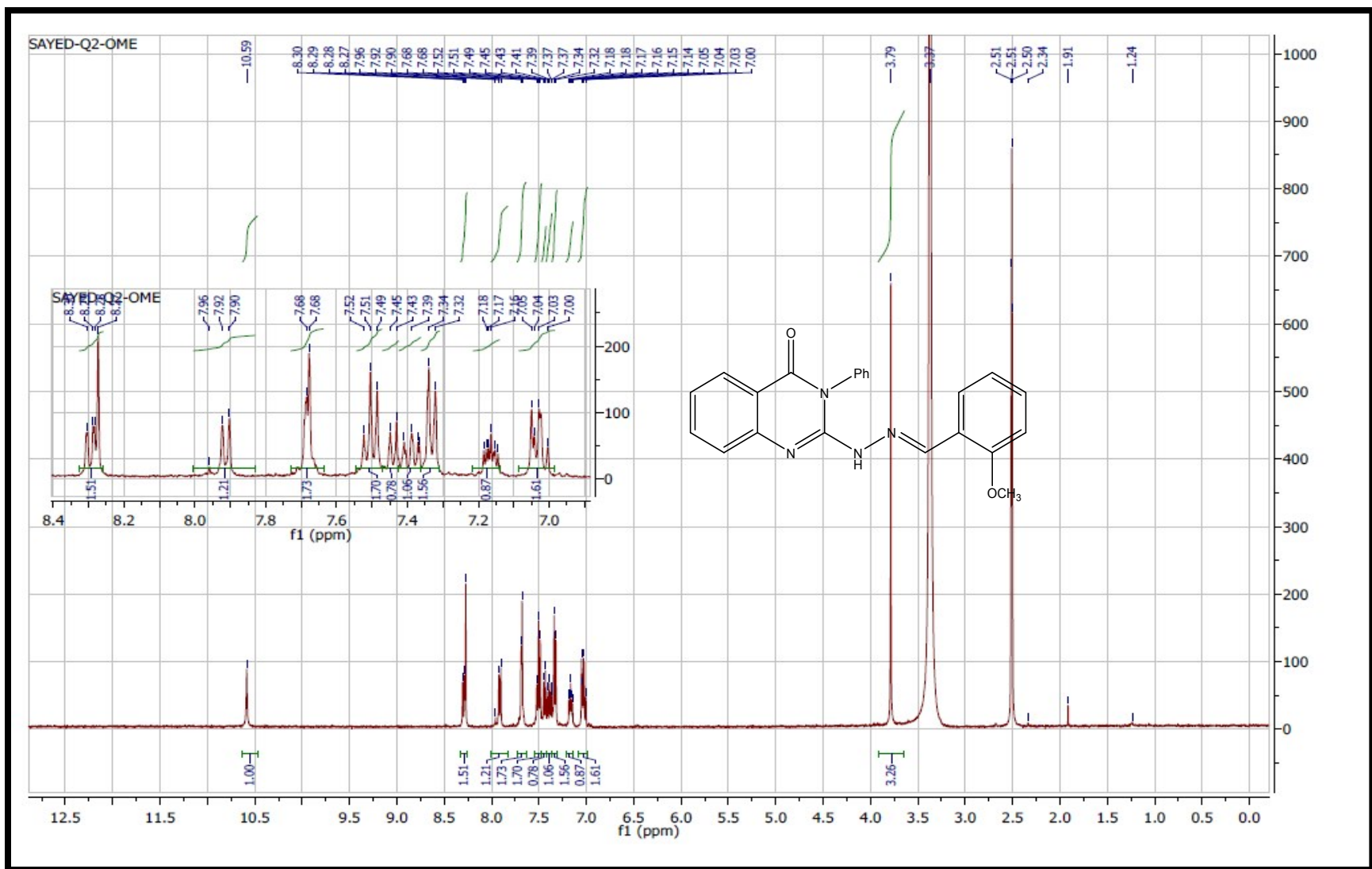


2-(2-(2-Methoxybenzylidene)hydrazinyl)-3-phenylquinazolin-4(3H)-one (13c).

IR

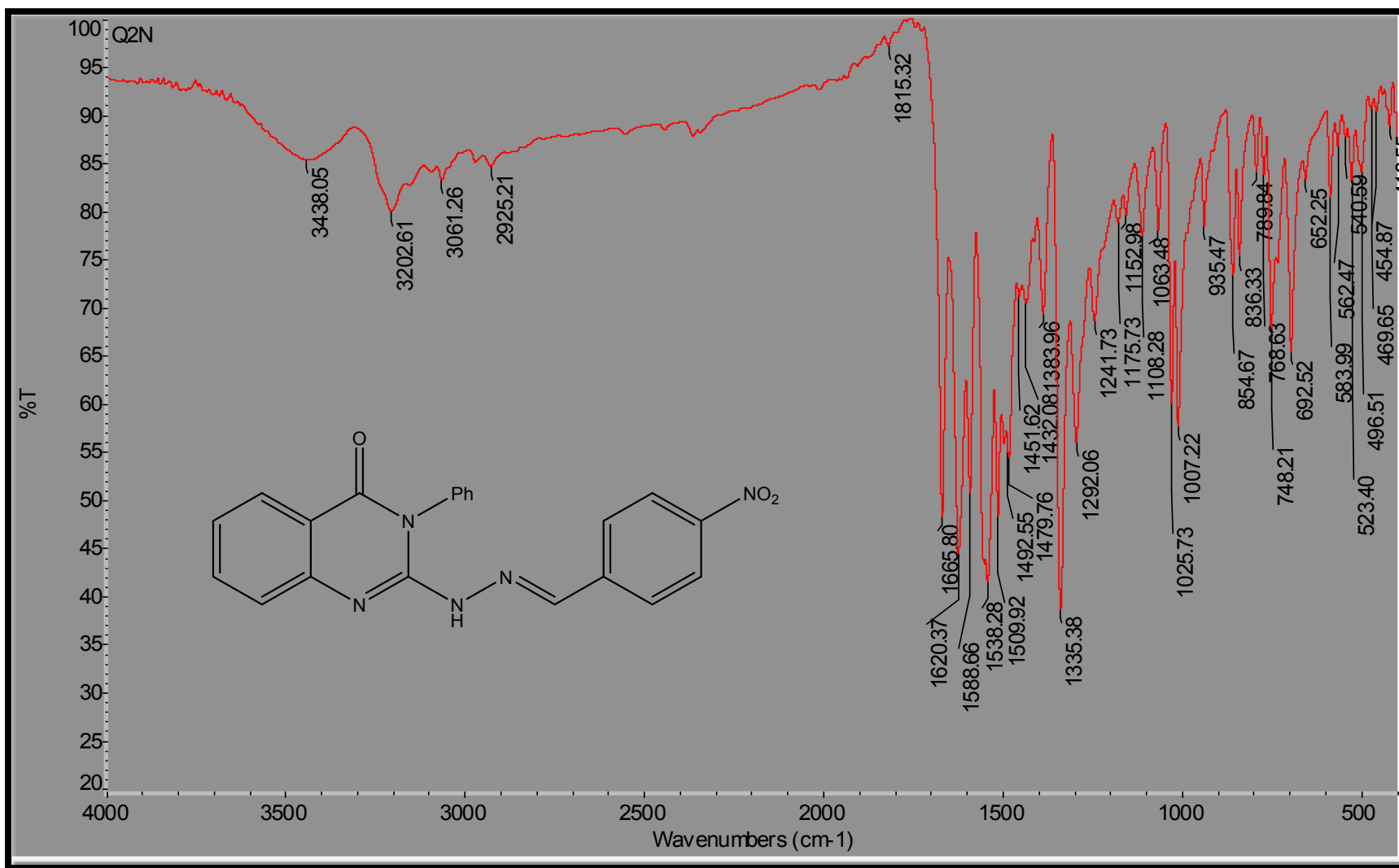


HNMR



2-(2-(4-Nitrobenzylidene)hydrazinyl)-3-phenylquinazolin-4(3H)-one (13d).

IR



HNMR

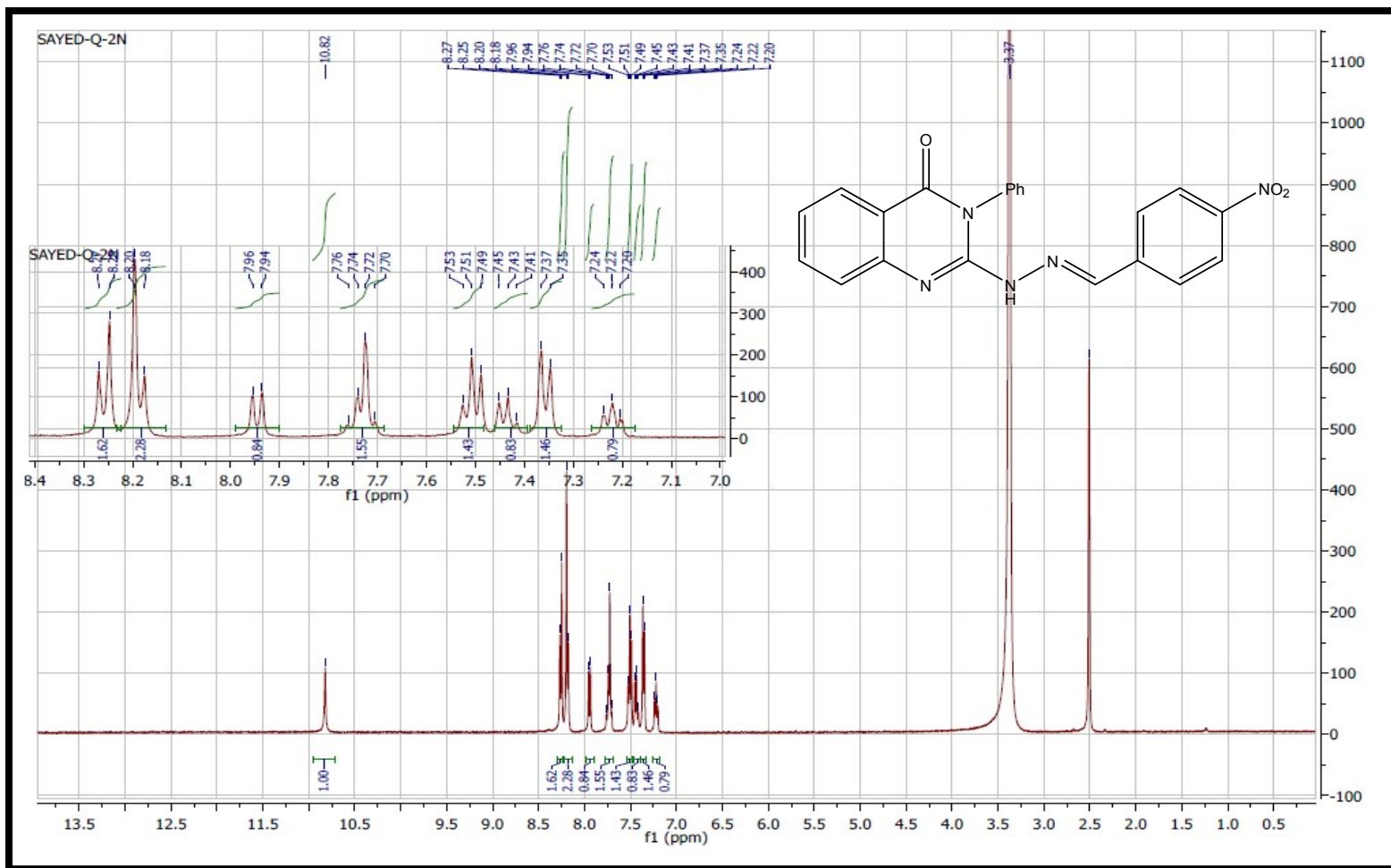


Table 5. The docking binding free energies of the synthesized compounds with PARP-1, forming hydrogen bonding and cationic- π interactions.

Compd.	ΔG		
	kcal/mol	No. of hydrogen bonding	No. of cationic- π interactions
5a	-51.47	4 (TYR907, GLY863, TYR896, ARG878)	3 (TYR907, HIS862, LYS903)
5b	-53.18	4 (TYR907, HIS862, TYR896, ARG878)	3 (TYR907, HIS862, LYS903)
5c	-51.30	6 (TYR907, GLY863, HIS862, TYR896, ARG878, TYR907)	3 (TYR907, HIS862, LYS903)
6a	-57.87	5 (GLY863, HIS862, TYR896, ARG878, ARG878)	3 (TYR907, HIS862, LYS903)
6b	-55.23	5 (TYR907, GLY863, HIS862, TYR896, ARG878)	3 (TYR907, HIS862, LYS903)
7a	-58.20	7 (TYR907, GLY863, HIS862, GLY888, ALA880, ARG878, ARG878)	3 (TYR907, HIS862, ARG878)
7b	-58.43	6 (TYR907, GLY863, HIS862, GLY888, ALA880, ARG878, ARG878)	3 (TYR907, HIS862, ARG878)
8a	-62.52	6 (TYR907, GLY863, HIS862, TYR896, ARG878, ASN868)	3 (TYR907, HIS862, HIS862)
8b	-57.54	5 (TYR907, GLY863, HIS862, TYR896, ARG878)	3 (TYR907, HIS862, HIS862)
8c	-54.18	5 (TYR907, GLY863, HIS862, TYR896, ARG878)	3 (TYR907, HIS862, HIS862)
9a	-61.58	6 (TYR907, GLY863, HIS862, GLY894, ARG878, ASN868)	3 (TYR907, HIS862, LYS903)
9b	-61.10	4 (TYR907, GLY863, GLY894, ARG878)	3 (TYR907, HIS862, LYS903)

9c	-58.25	5 (TYR907, GLY863 , HIS862, GLY894, ARG878)	3 (TYR907, HIS862, LYS903)
12a	-59.61	9 (TYR907, SER904, GLY863, HIS862, GLY888, TYR889, TYR896, ARG878, ARG878)	3 (TYR907, HIS862, LYS903)
12b	-58.01	8 (TYR907, SER904, GLY863, HIS862, GLY888, TYR889, TYR896, ARG878)	3 (TYR907, HIS862, LYS903)
12c	-59.56	8 (TYR907, SER904, GLY863, HIS862, GLY888, TYR889, TYR896, ARG878)	3 (TYR907, HIS862, LYS903)
13a	-53.14	5 (TYR907, TYR907, GLY863, HIS862, GLY888)	3 (TYR907, HIS862, LYS903)
13b	-55.98	6 (TYR907, TYR907, GLY863, HIS862 , ALA880, ARG878)	3 (TYR907, HIS862, LYS903)
13c	-55.01	5 (TYR907, TYR907, GLY863, HIS862, TYR896)	3 (TYR907, HIS862, LYS903)
13d	-50.56	5 (TYR907, TYR907, GLY863, HIS862, TYR889)	3 (TYR907, HIS862, LYS903)
olaparib	-60.60	4 (GLY863, SER904, TYR896, ARG878)	3 (TYR907, HIS862, LYS903, TYR896)
