

Synthesis and *In Silico* Studies of Certain Benzo[f]quinoline-based Heterocycles as Antitumor Agents

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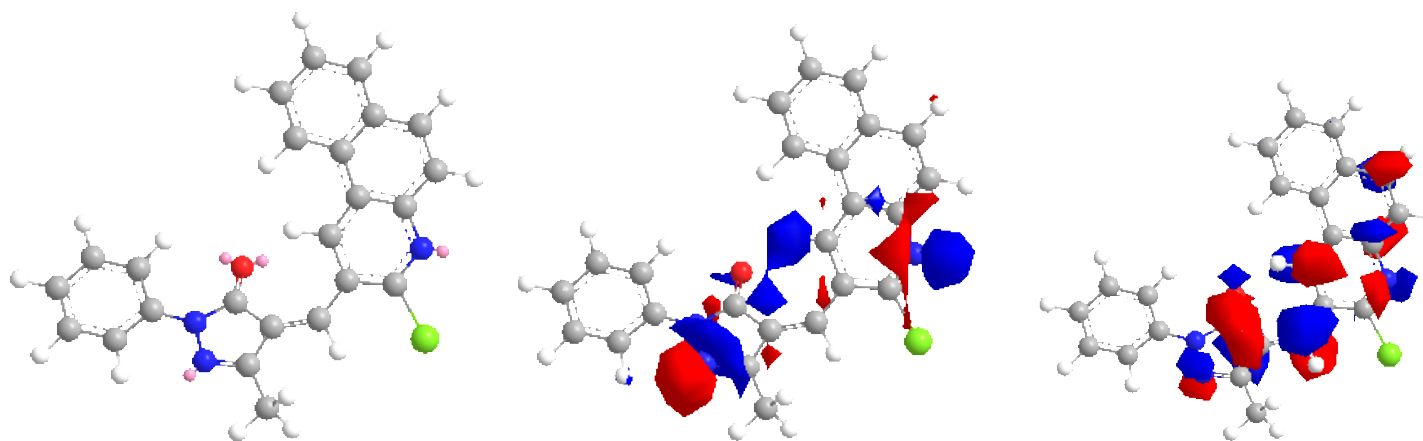
² Chemistry Department, Faculty of Science, Helwan University, Ain-Helwan, Cairo, Egypt

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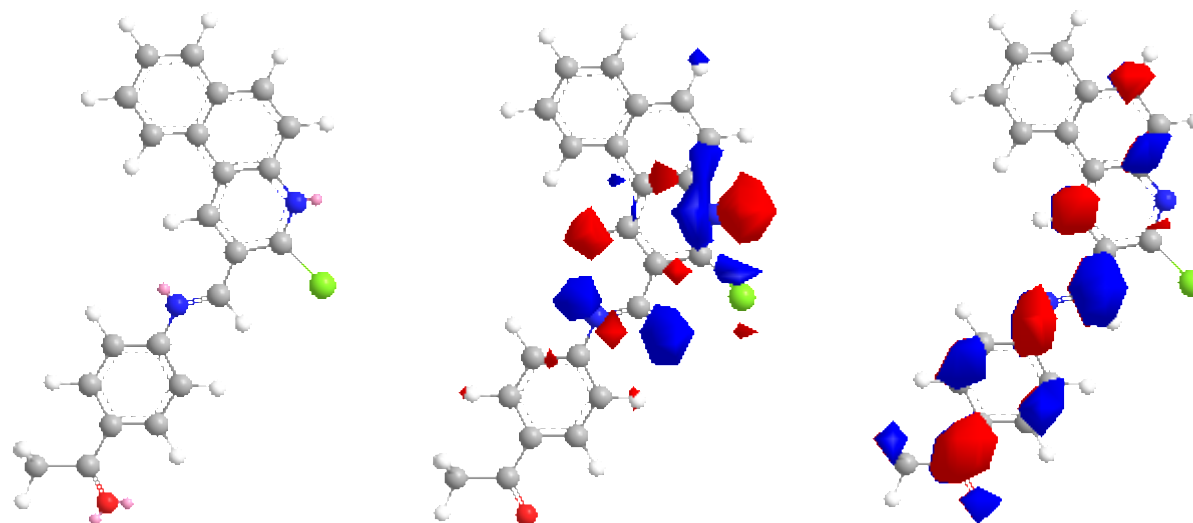
*E-mail: sayed.karam2008@sci.asu.edu.eg

Supporting information:

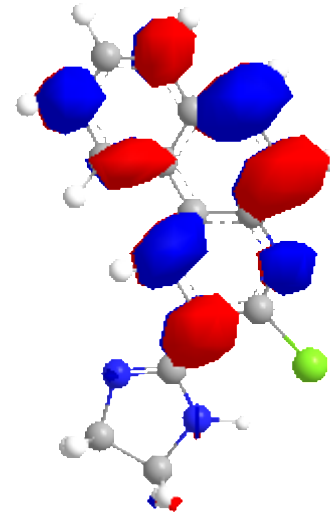
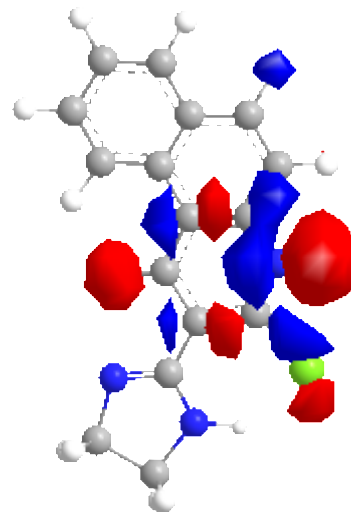
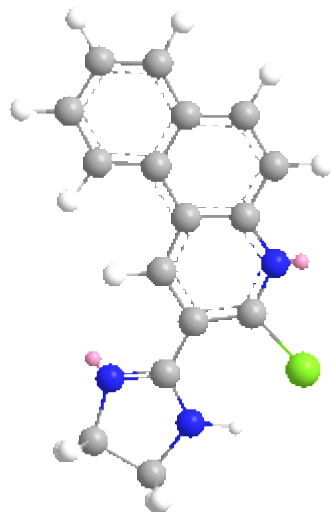
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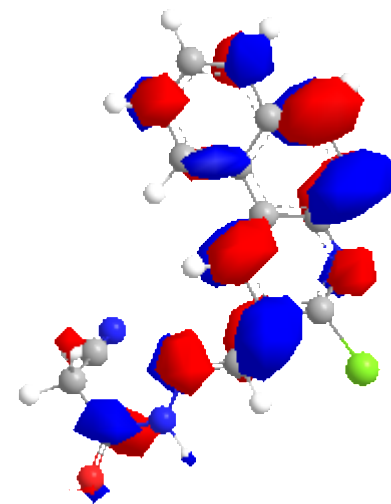
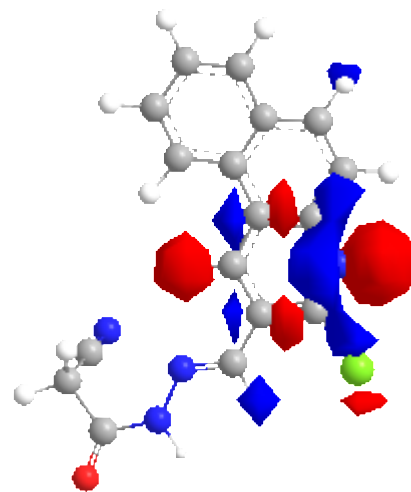
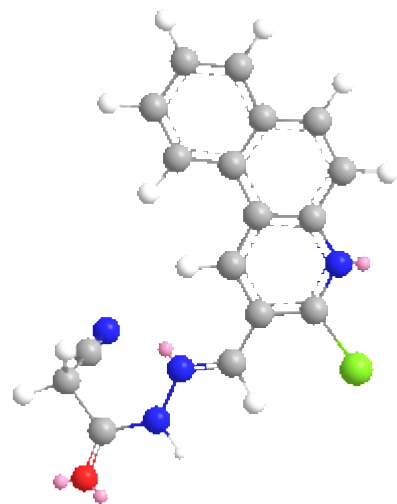
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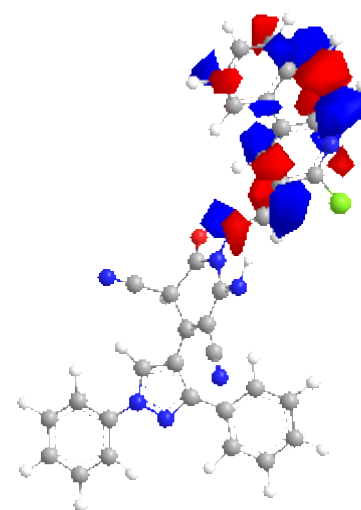
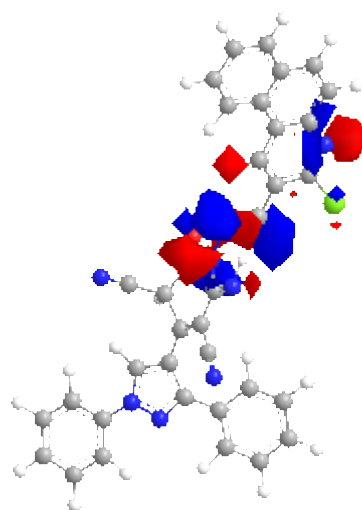
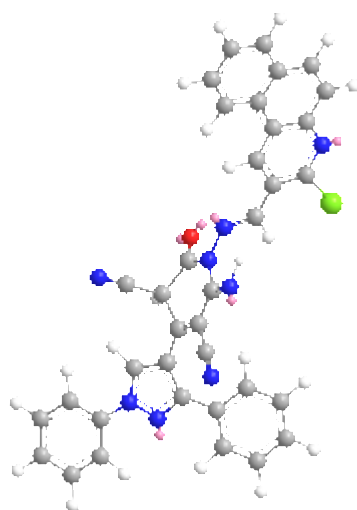
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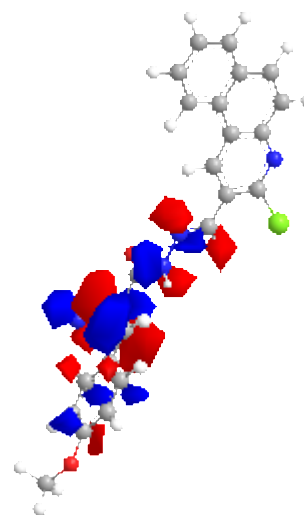
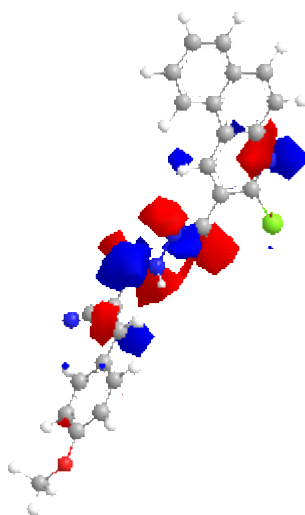
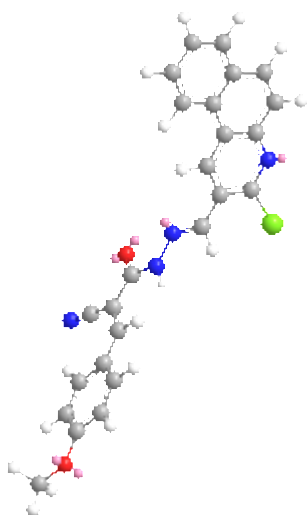
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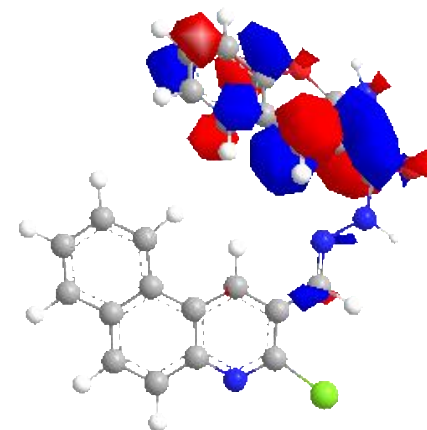
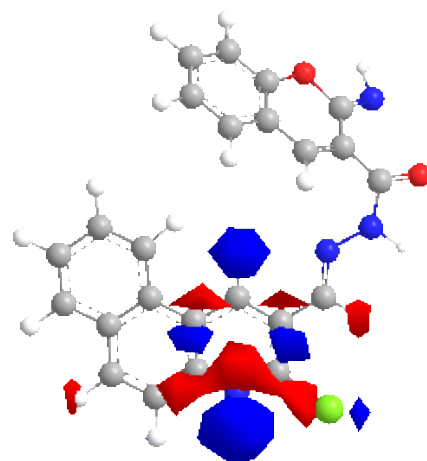
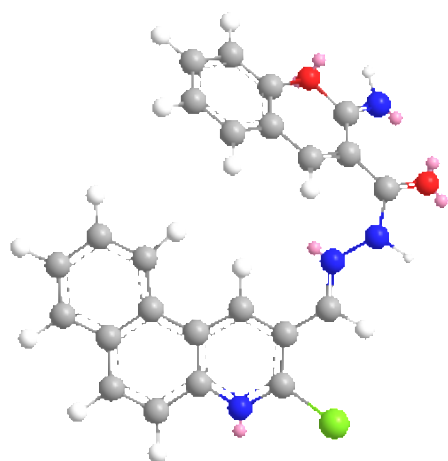
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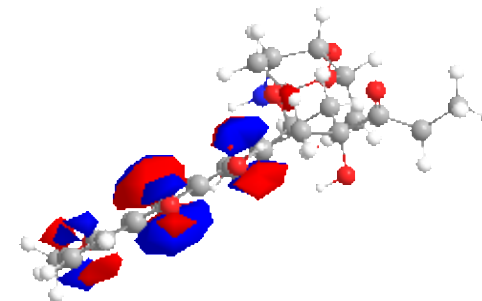
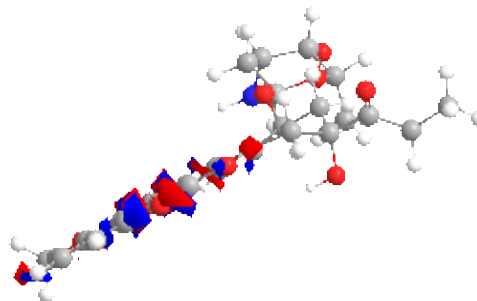
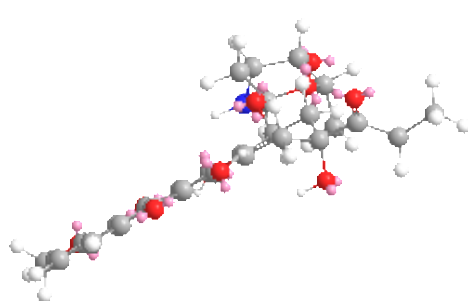
Compound 7



Compound 8



Compound 9



Doxorubicin

Supplementary Figure 1. Optimized structures (left), HOMO (middle), and LUMO (right) for compounds 2-13.

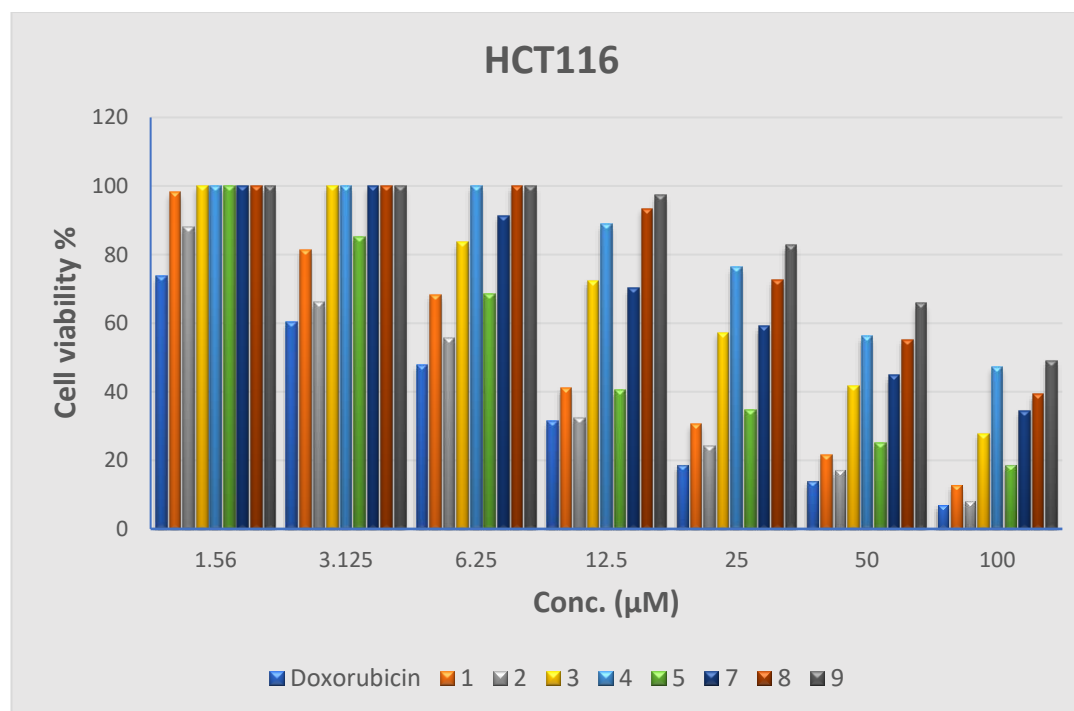
Atom color index: Grey C, White H, Blue N, Red O, Yellow S, and Green Cl.

Supplementary Table 1. Average relative viability of cells (%).*

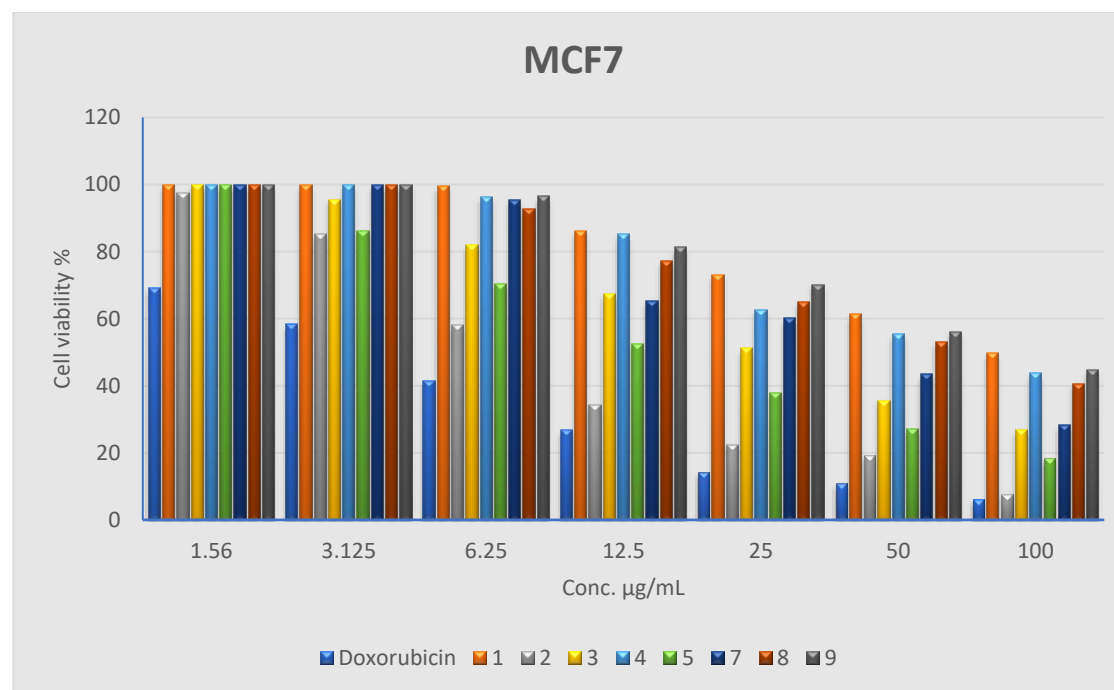
Conc. (μM)	HCT116	MCF7	Conc. (μM)	HCT116	MCF7
Doxorubicin			Compound 7		
100	7.1±1.1	6.2±1.2	100	34.5±0.2	28.2±1.4
50	13.9±1.4	10.9±1.4	50	44.9±1.1	43.5±0.9
25	18.7±1.3	14.3±1.5	25	59.2±0.8	60.2±1.1
12.5	31.4±1.5	26.9±1.1	12.5	70.3±0.5	65.3±0.7
6.25	47.9±1.7	41.5±1.3	6.25	91.4±0.4	95.5±0.3
3.125	60.5±1.9	58.4±1.1	3.125	100	100
1.56	73.8±1.6	69.1±1.9	1.56	100	100
Compound 1			Compound 8		
100	12.8±1.5	49.7±1.9	100	39.3±0.6	40.6±1.2
50	21.7±1.4	61.3±1.4	50	55.2±0.9	53.2±1.5
25	30.6±2.6	73.1±1.1	25	72.5±1.4	65.1±1.1
12.5	41.1±1.3	86.2±1.8	12.5	93.4±1.7	77.3±0.9
6.25	68.3±1.9	99.6±1.6	6.25	100	92.6±1.3
3.125	81.4±1.1	100	3.125	100	100
1.56	98.2±1.4	100	1.56	100	100
Compound 2			Compound 9		
100	8.3±0.7	7.8±0.9	100	49.1±1.3	44.8±1.2
50	17.2±1.3	19.4±1.1	50	65.8±1.4	56.2±0.8
25	24.1±1.6	22.5±0.8	25	82.9±0.9	70.2±1.4
12.5	32.4±1.2	34.2±1.2	12.5	97.3±0.6	81.4±0.5
6.25	55.7±1.1	58.1±1.8	6.25	100	96.6±1.1
3.125	66.2±1.9	85.3±1.4	3.125	100	100
1.56	88.1±1.3	97.6±0.7	1.56	100	100
Compound 3			Compound 11		
100	27.8±1.3	26.7±1.1	100	25.2±0.8	23.3±1.2
50	41.7±0.9	35.6±0.7	50	36.4±1.3	35.3±1.5
25	57.3±1.5	51.2±1.2	25	50.2±1.1	47.6±0.9

12.5	72.4±1.7	67.3±0.9	12.5	65.9±0.5	58.4±0.4
6.25	83.6±0.8	82.0±1.4	6.25	80.3±0.9	71.9±1.1
3.125	100	95.5±1.1	3.125	96.5±0.7	90.4±0.6
1.56	100	100	1.56	100	100
Compound 4			Compound 12		
100	47.2±1.2	43.8±1.3	100	54.4±0.7	53.3±0.3
50	56.3±1.5	55.3±1.4	50	71.9±0.4	72.9±0.4
25	76.4±0.8	62.7±1.1	25	84.6±0.6	84.6±0.7
12.5	88.9±1.2	85.2±1.5	12.5	99.7±0.3	98.8±0.2
6.25	100	96.3±1.3	6.25	100	100
3.125	100	100	3.125	100	100
1.56	100	100	1.56	100	100
Compound 5					
100	18.6±1.1	18.4±0.9			
50	25.2±0.9	27.1±0.6			
25	34.7±0.6	37.8±1.1			
12.5	40.5±0.5	52.4±1.3			
6.25	68.4±0.7	70.5±0.7			
3.125	85.3±0.3	86.2±0.8			
1.56	100	100			

* Data were displayed as mean ± SEM ($n = 3$) and $p < 0.05$.



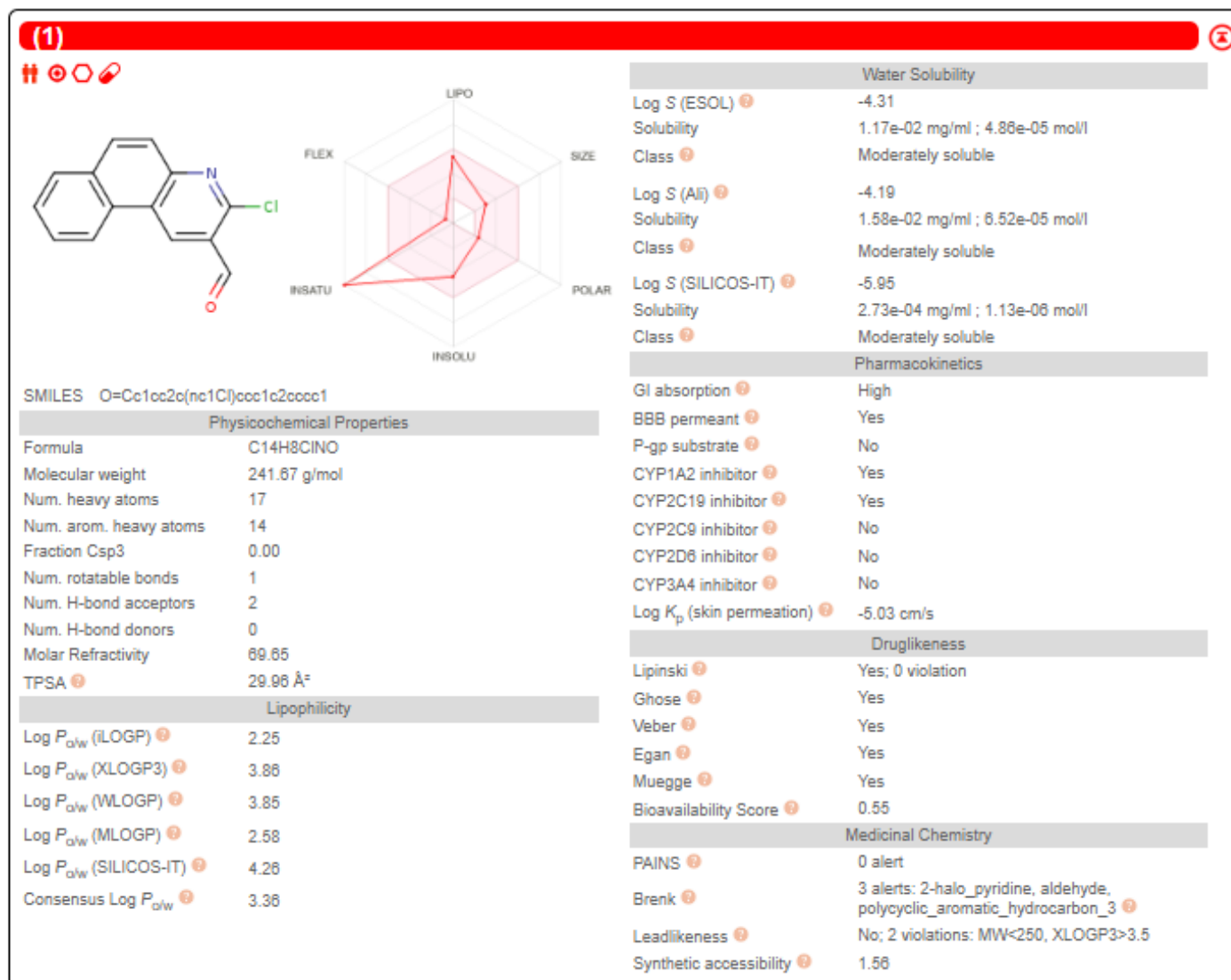
Supplementary Figure 2. Effect of the tested compounds on the cell viability of colon cancer cell line using different concentrations (1.56 to 100 µM) for each compound after treatment for 48 h compared to untreated cells.



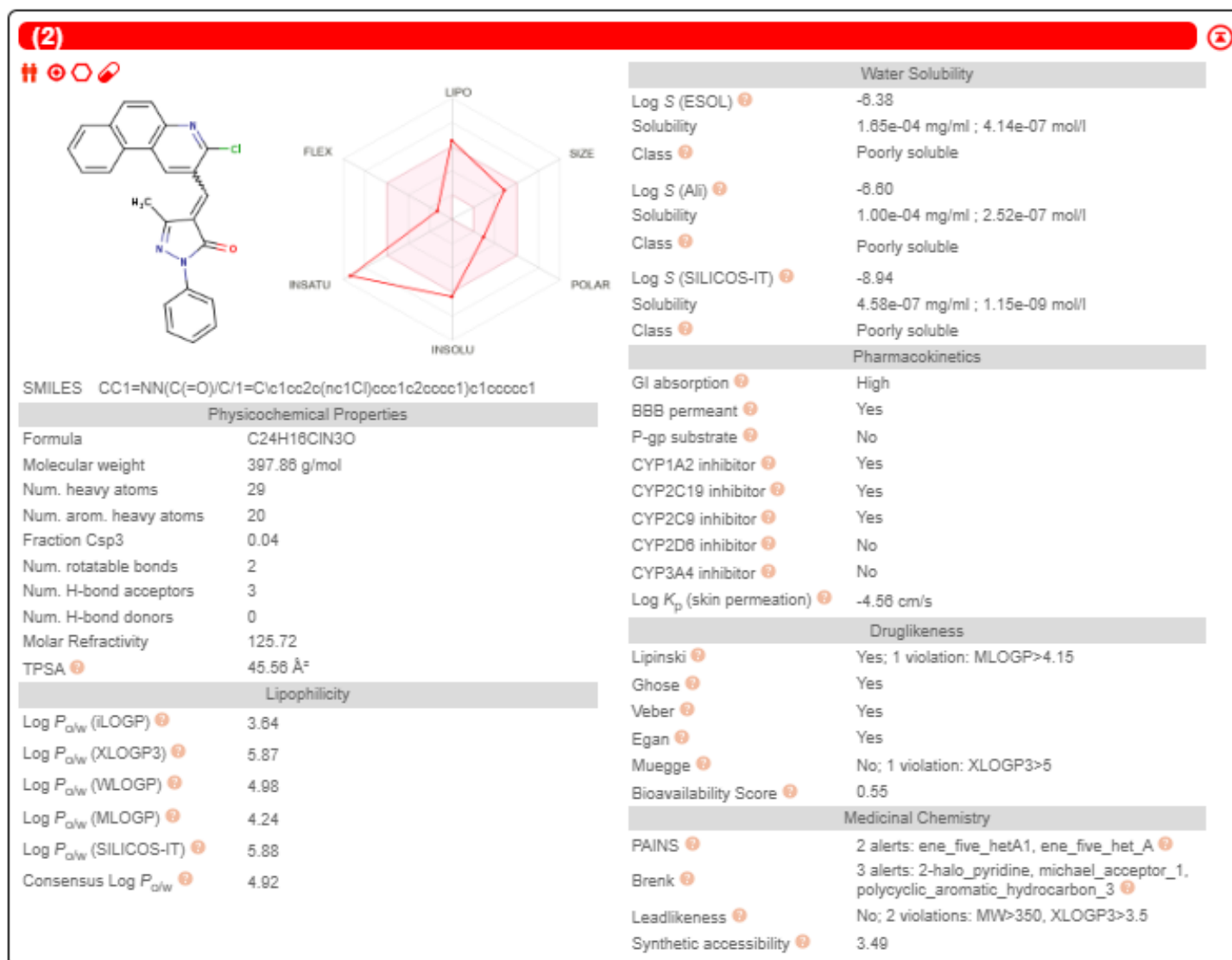
Supplementary Figure 3. Effect of the tested compounds on the cell viability of breast cancer cell line using different concentrations (1.56 to 100 μM) for each compound after treatment for 48 h compared to untreated cells.

Supplementary Table 2. ADME characteristics of compounds **1**, **2**, and **5**.

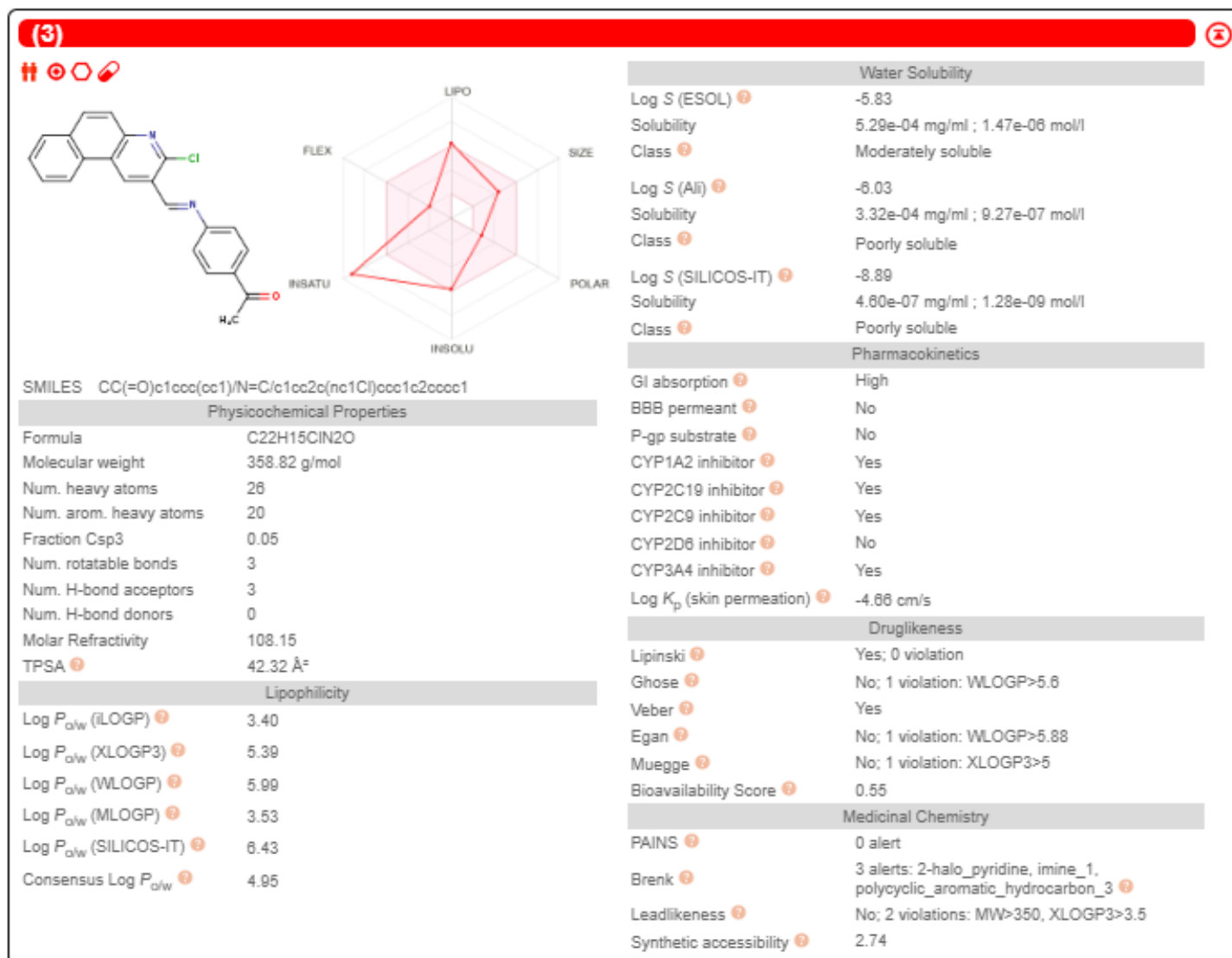
Entry	Compounds		
	1	2	5
Physicochemical Properties / Lipophilicity / Drug-likeness			
Molecular weight (g/mol)	241.67	397.86	322.75
Num. heavy atoms	17	29	23
Num. arom. Heavy atoms	14	20	14
Fraction Csp3	0.00	0.04	0.06
Num. rotatable bonds	1	2	4
Num. H-bond acceptor	2	3	4
Num. H-bond donors	0	0	1
Molar Refractivity	69.65	125.72	90.08
TPSA (Å ²)	29.96	45.56	78.14
Consensus Log P _{o/w}	3.36	4.92	2.97
Lipinski's Rule	Yes	Yes	Yes
Bioavailability Score	0.55	0.55	0.55
Pharmacokinetics			
GI absorption	High	High	High
BBB permeant	Yes	Yes	Yes
P-gp substrate	No	No	No
CYP1A2 inhibitor	Yes	Yes	Yes
CYP2C19 inhibitor	Yes	Yes	Yes
CYP2C9 inhibitor	No	Yes	Yes
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	No	No	No
Log K _p (cm/s)	-5.03	-4.56	-5.76



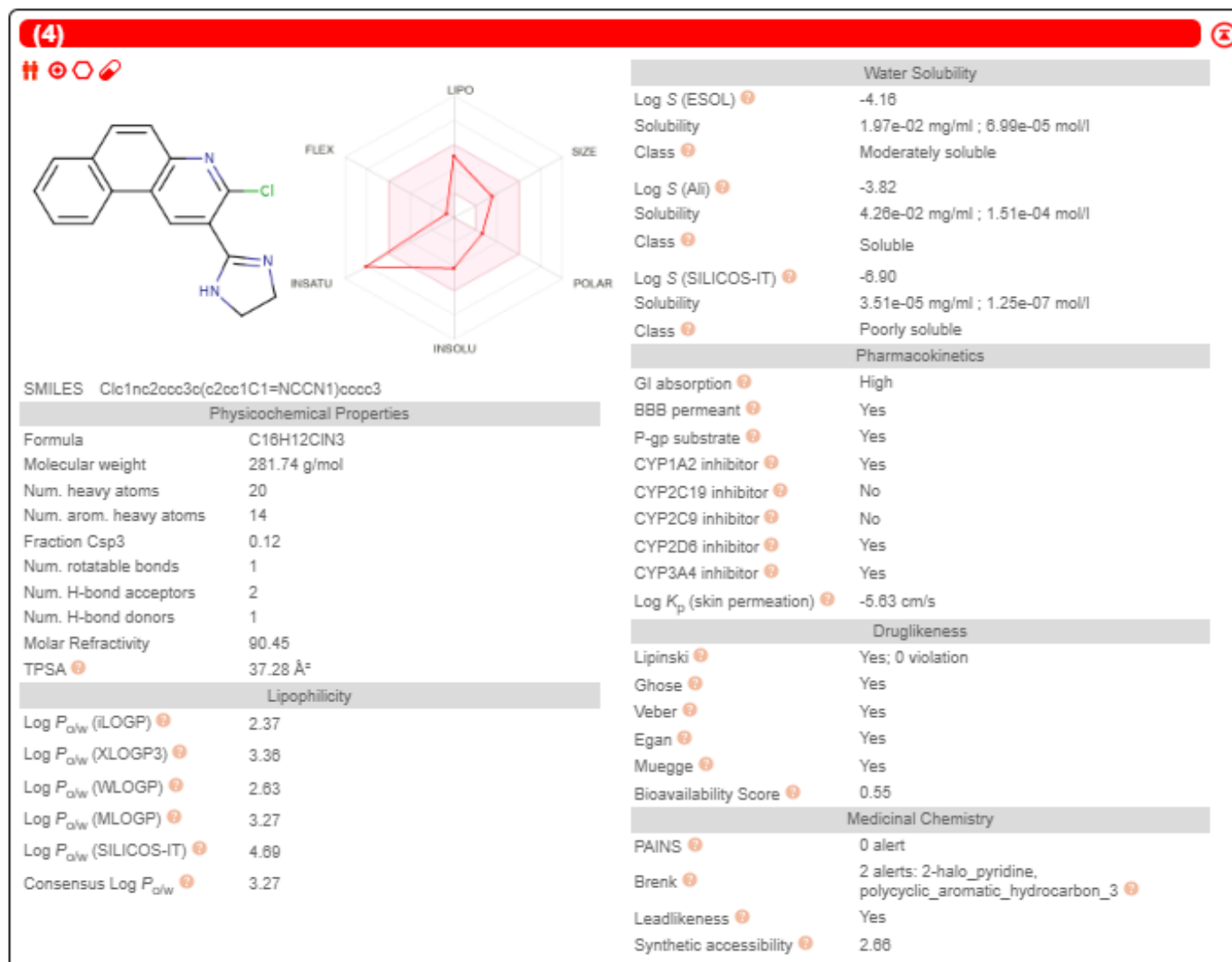
Supplementary Figure 4. ADME of compound 1.



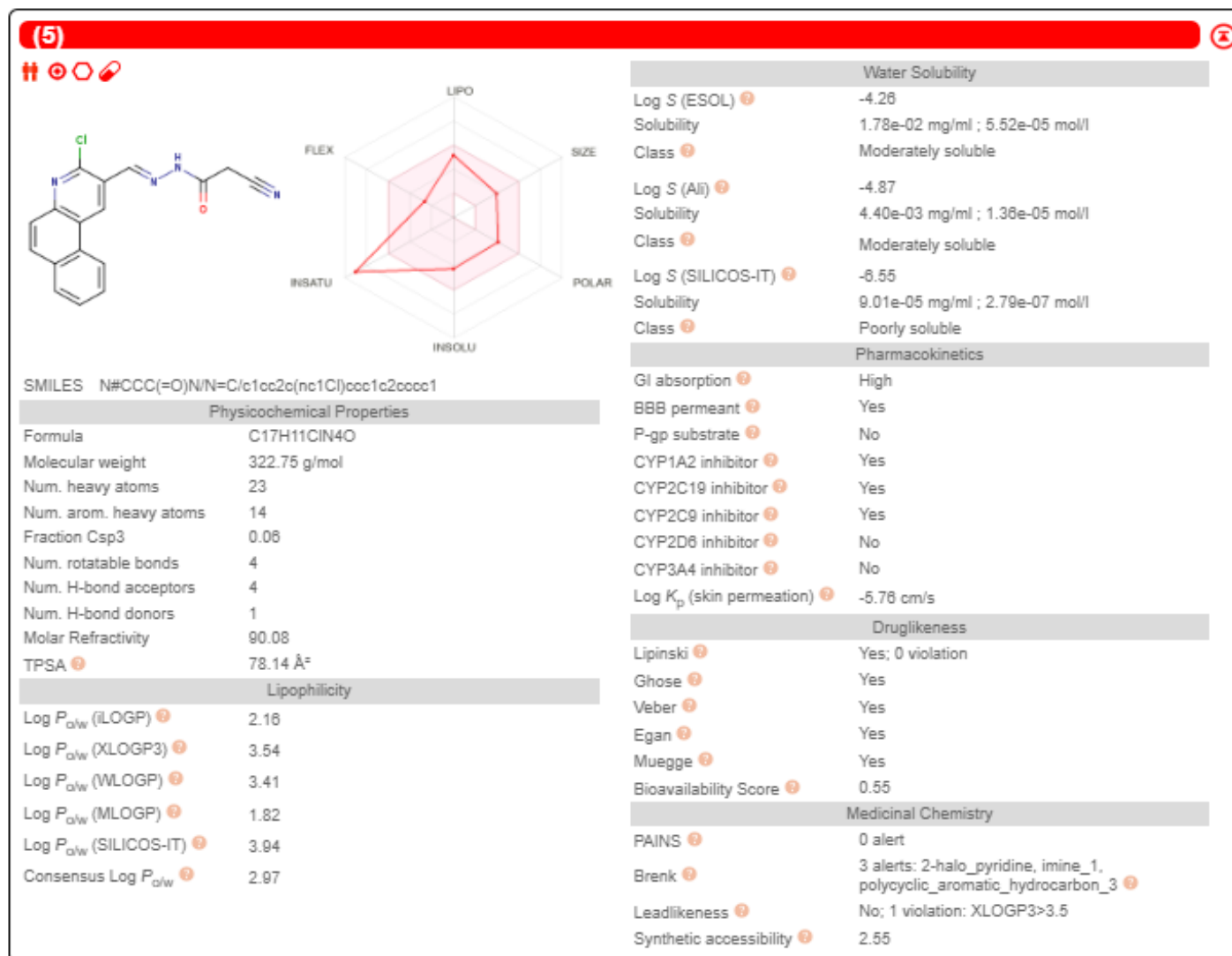
Supplementary Figure 5. ADME of compound 2.



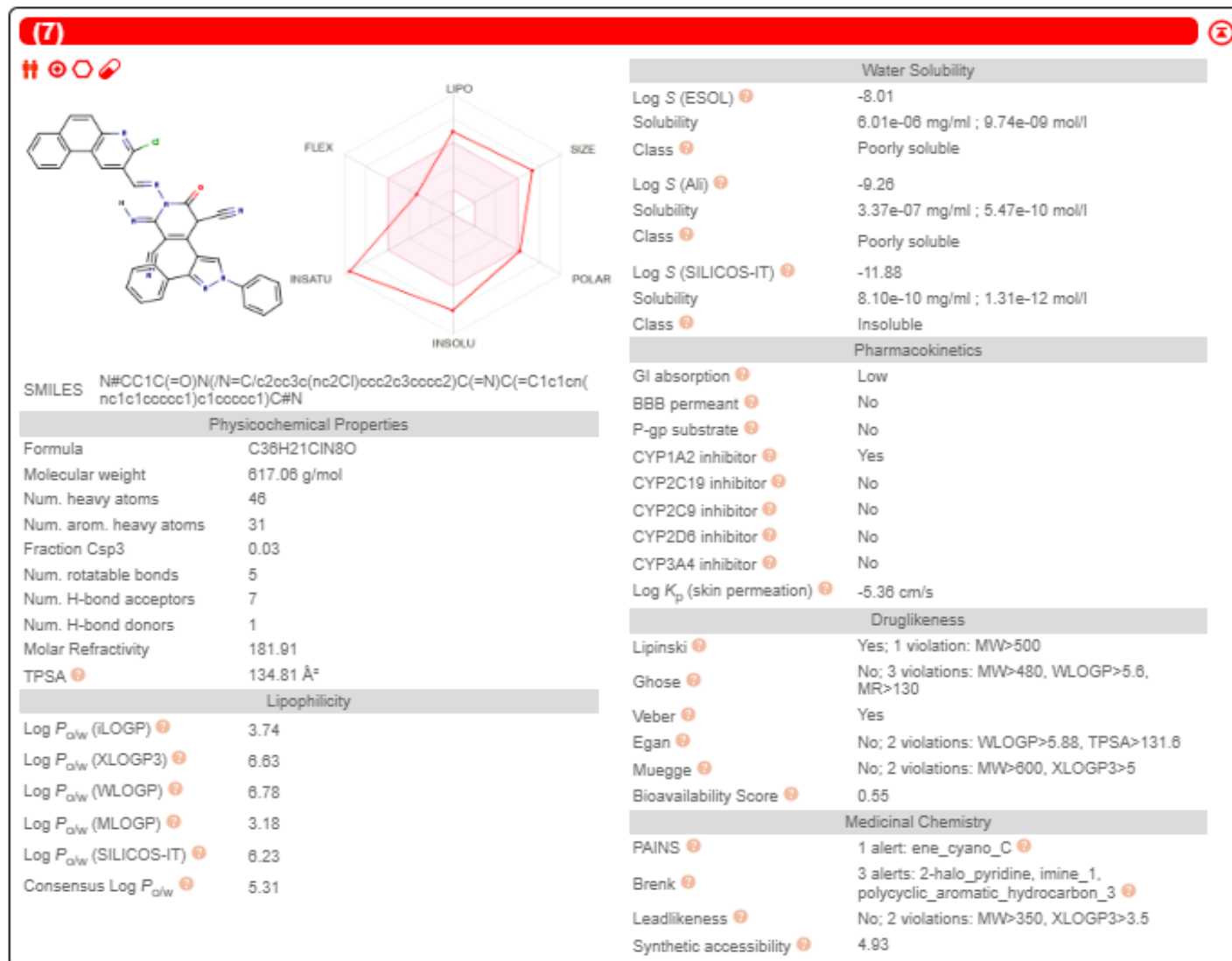
Supplementary Figure 6. ADME of compound 3.



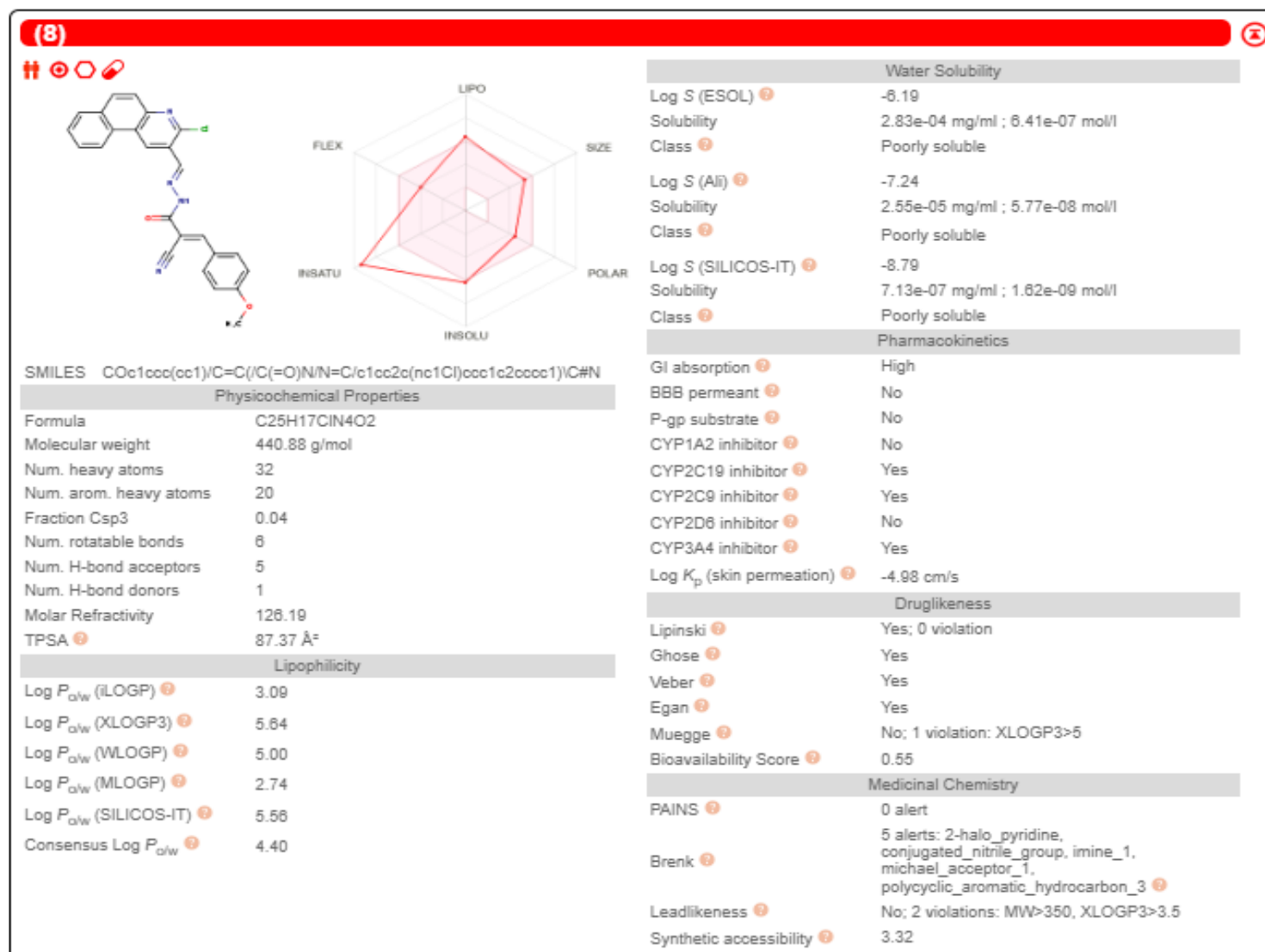
Supplementary Figure 7. ADME of compound 4.



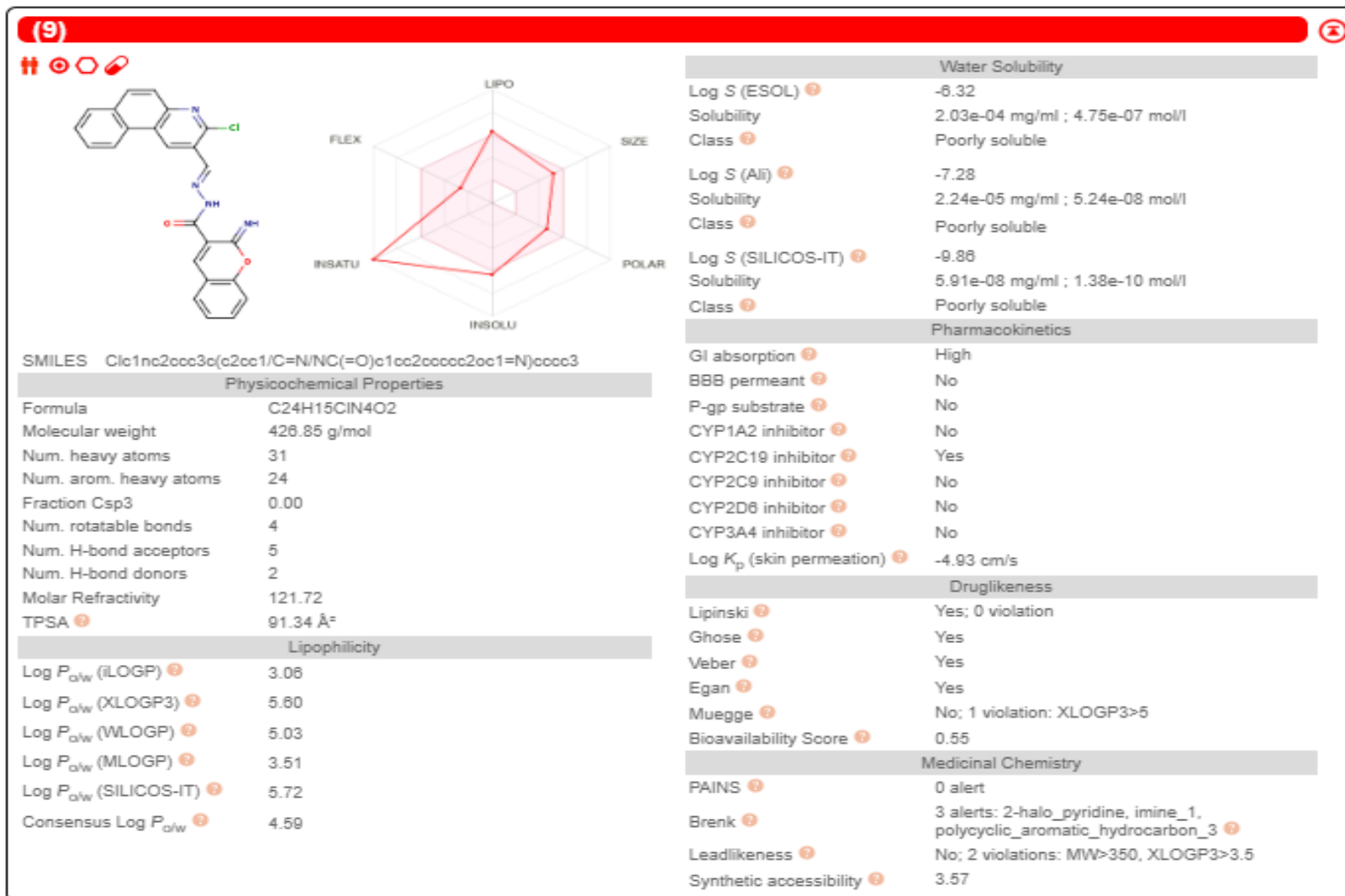
Supplementary Figure 8. ADME of compound 5.



Supplementary Figure 9. ADME of compound 7.



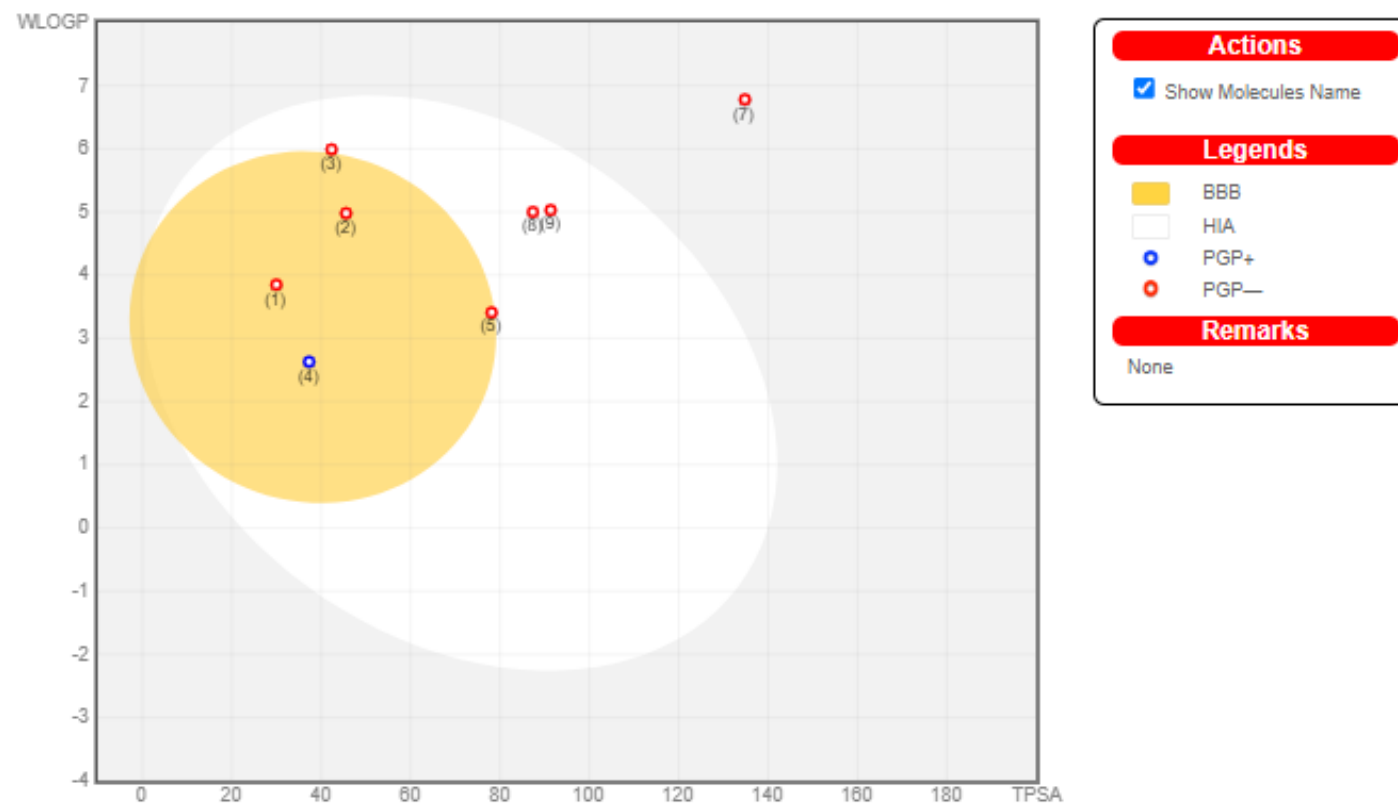
Supplementary Figure 10. ADME of compound 8.



Supplementary Figure 11. ADME of compound 9.

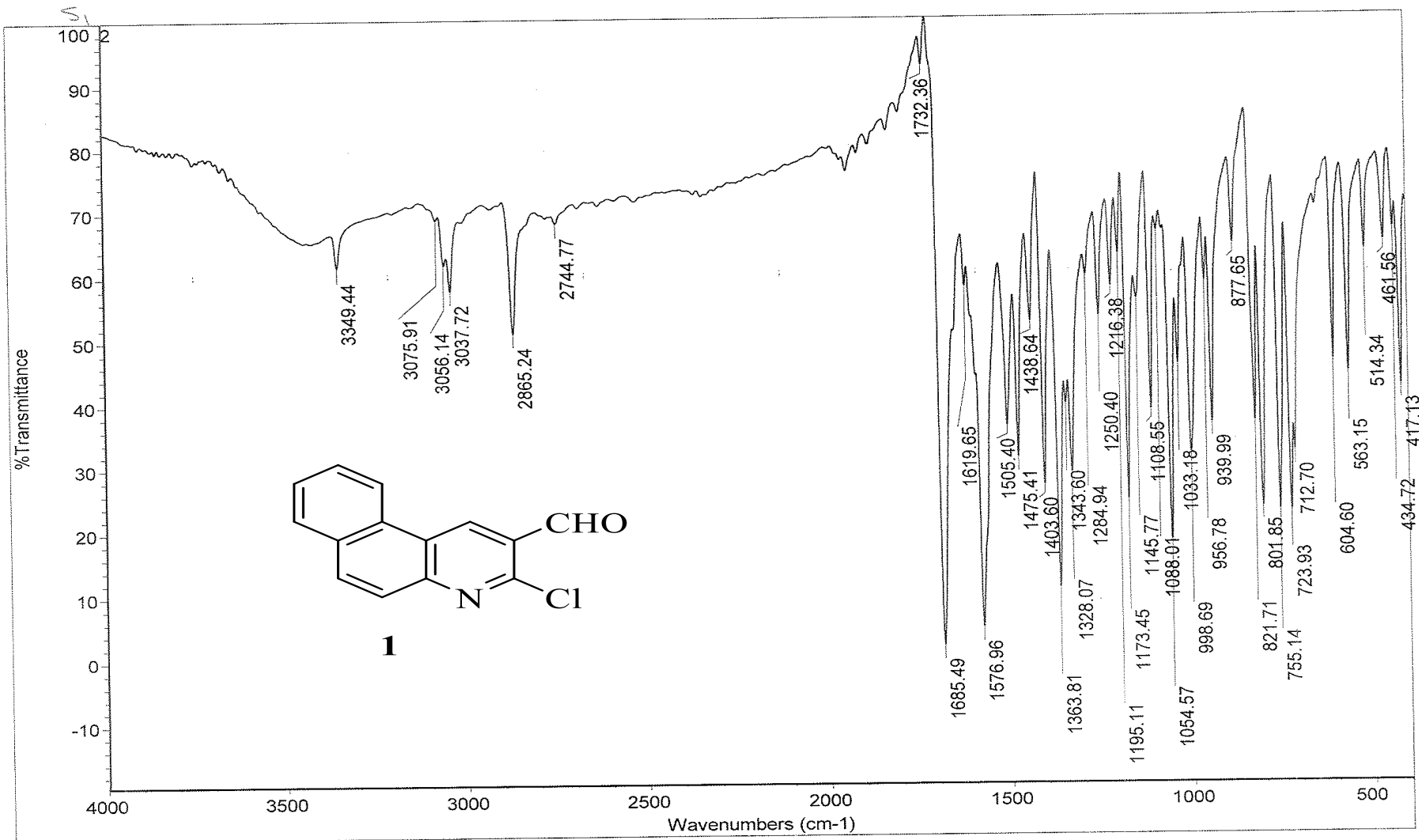
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Supplementary Figure 12. BOILED-EGG chart of the synthesized substrates **1-9**.

Spectral data



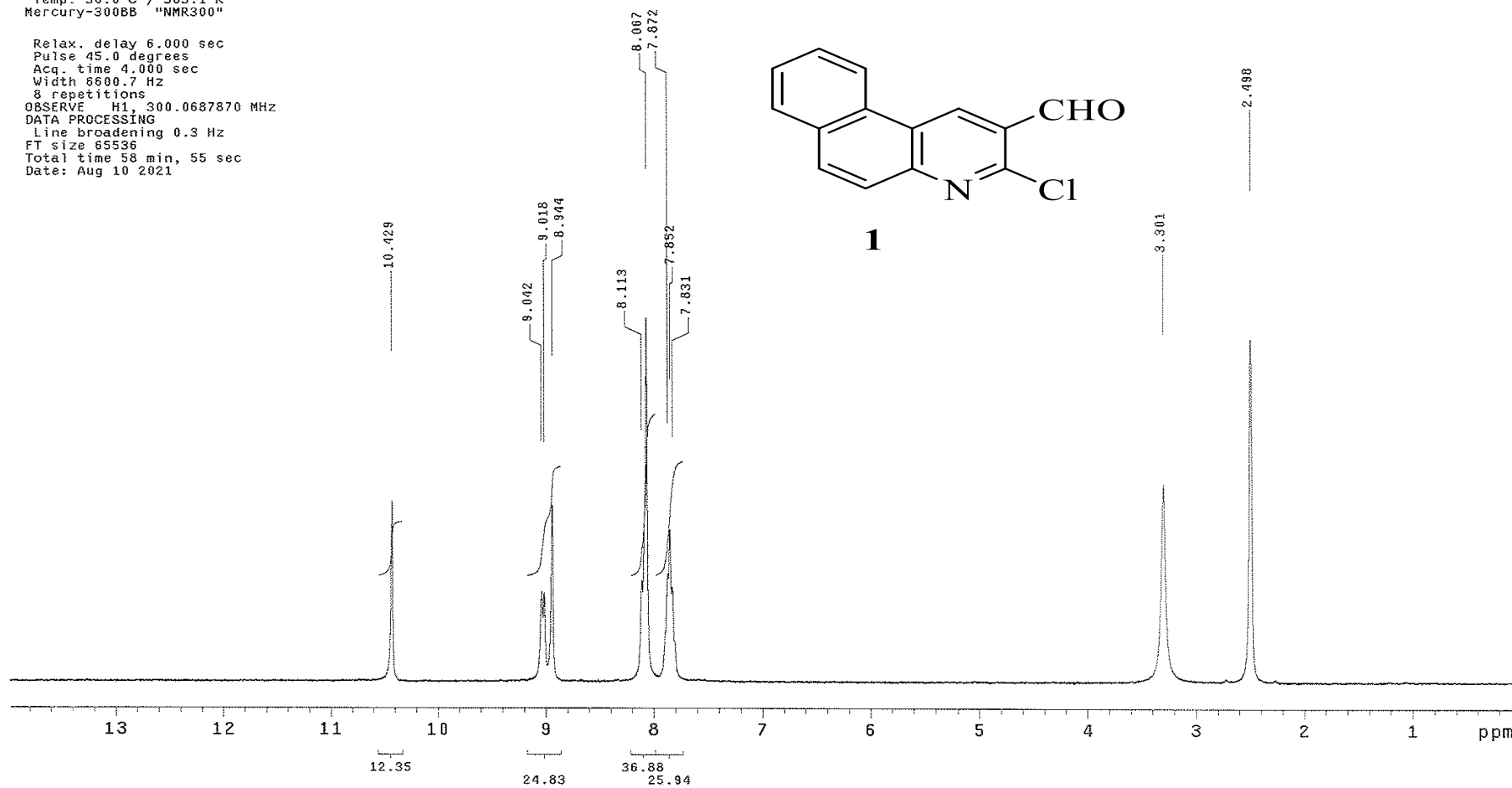
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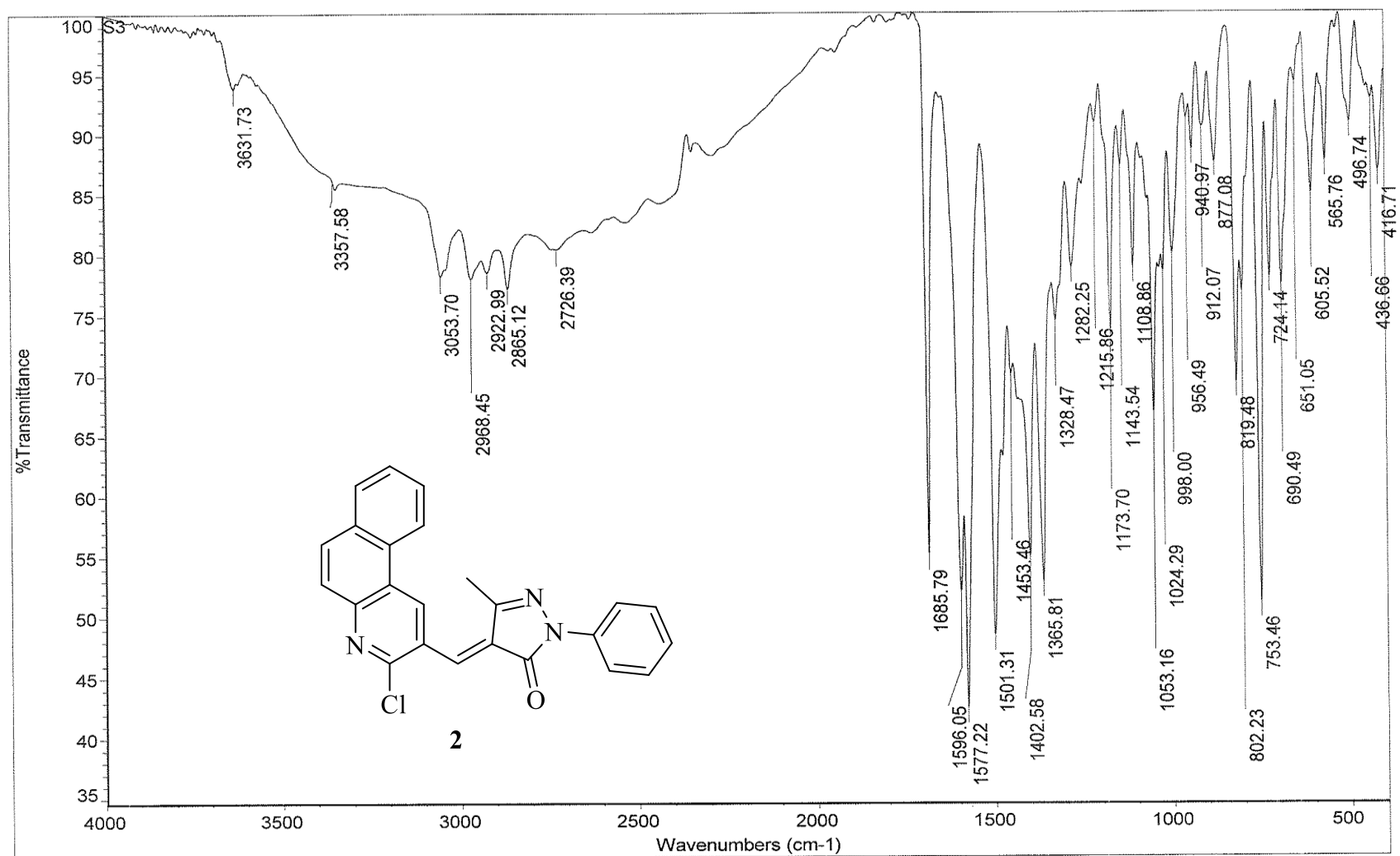
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Mercury-300BB "NMR300"

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Acq. time 4.000 sec
Width 6600.7 Hz
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DATA PROCESSING
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FT size 65536
Total time 58 min, 55 sec
Date: Aug 10 2021





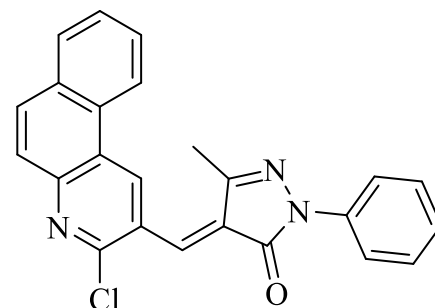
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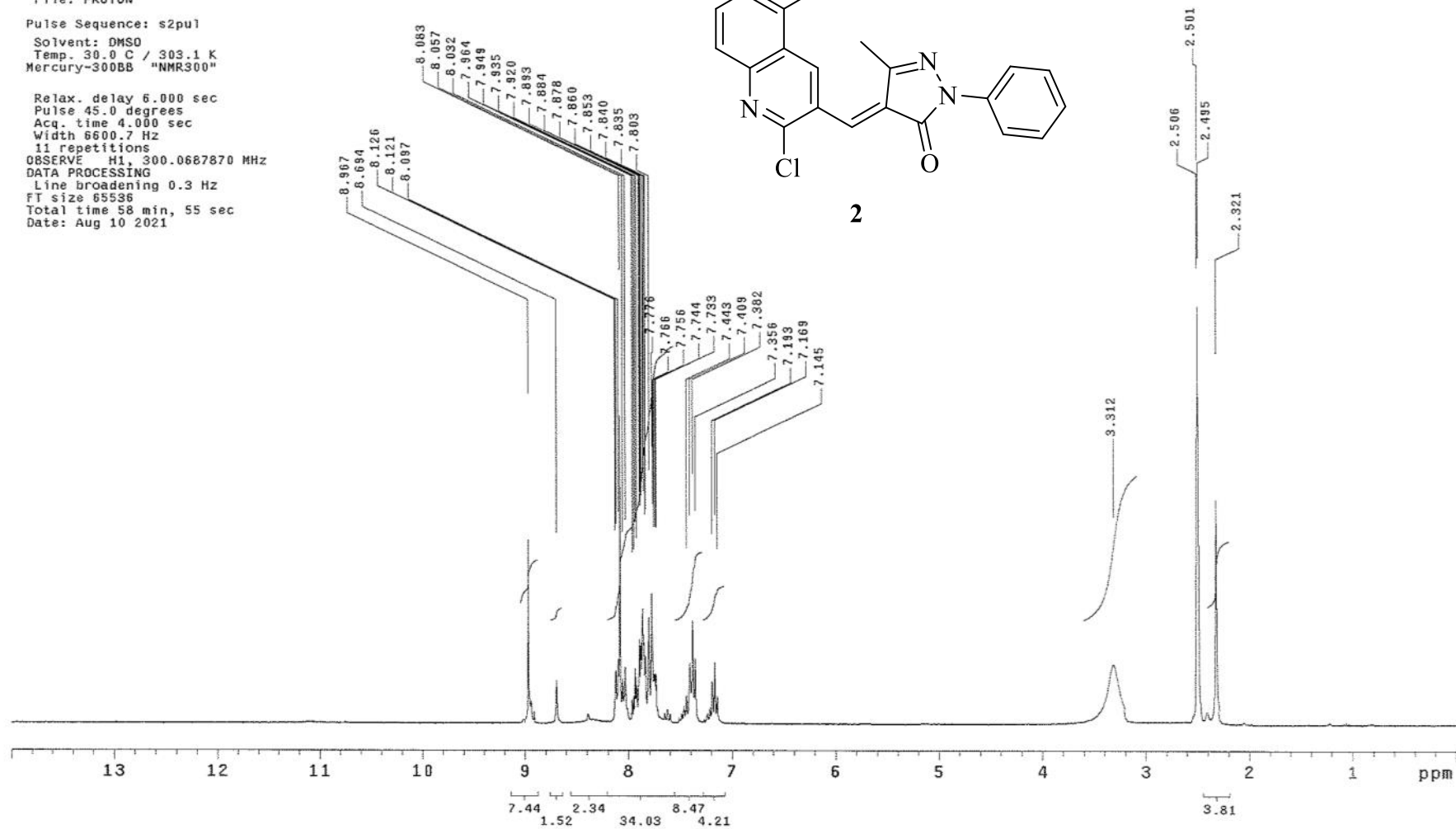
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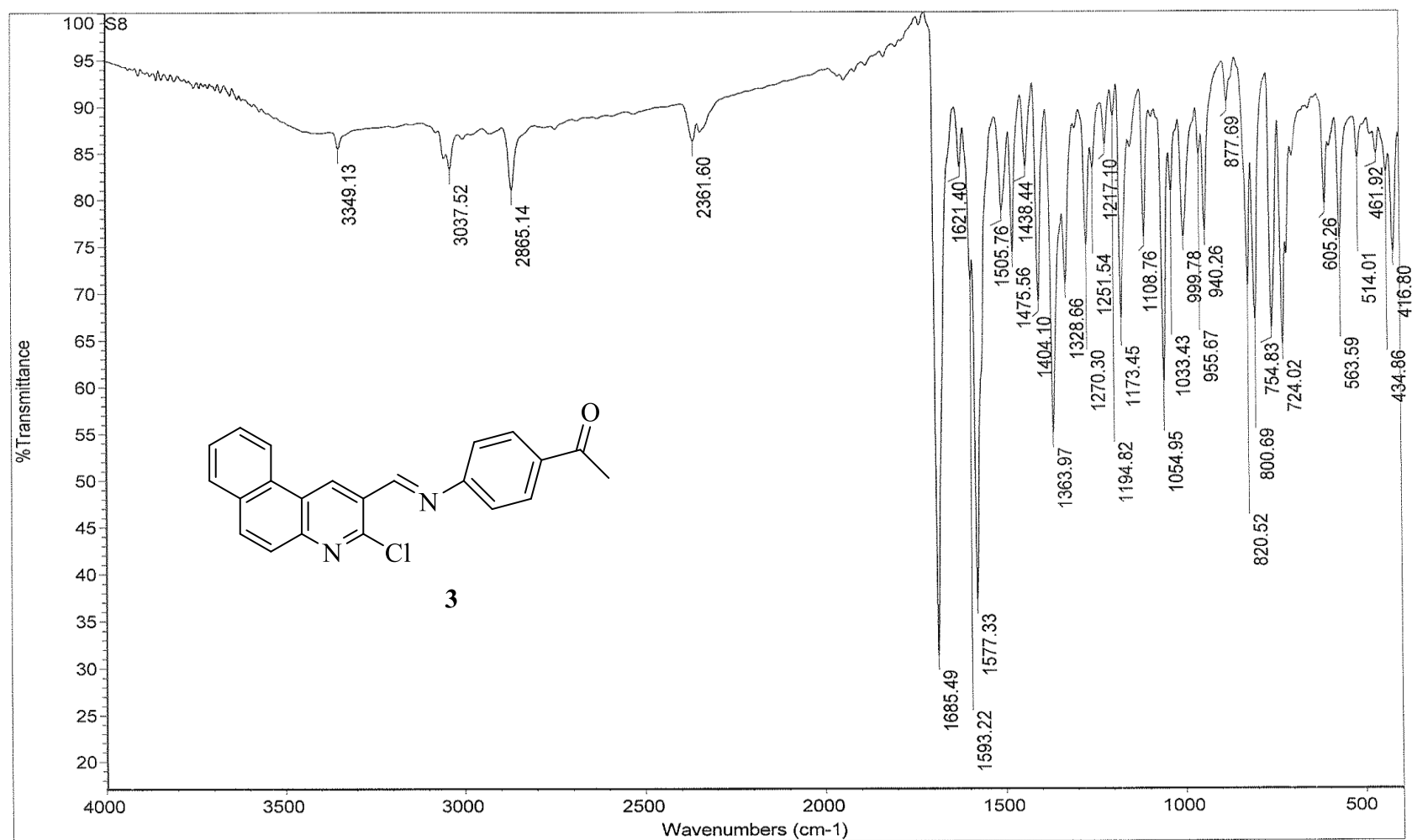
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2





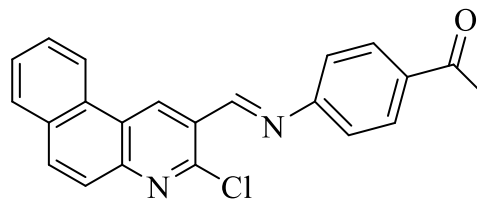
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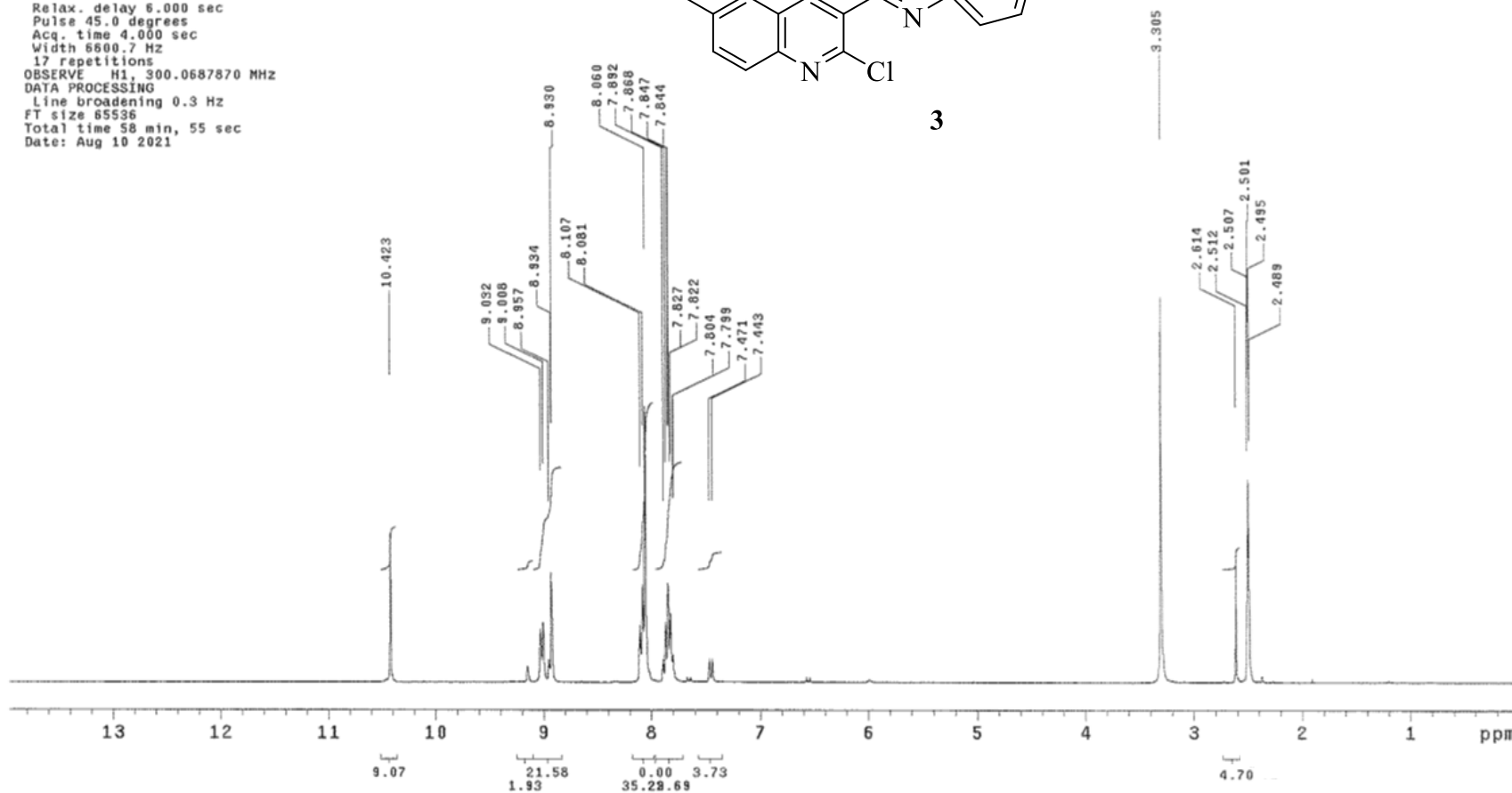
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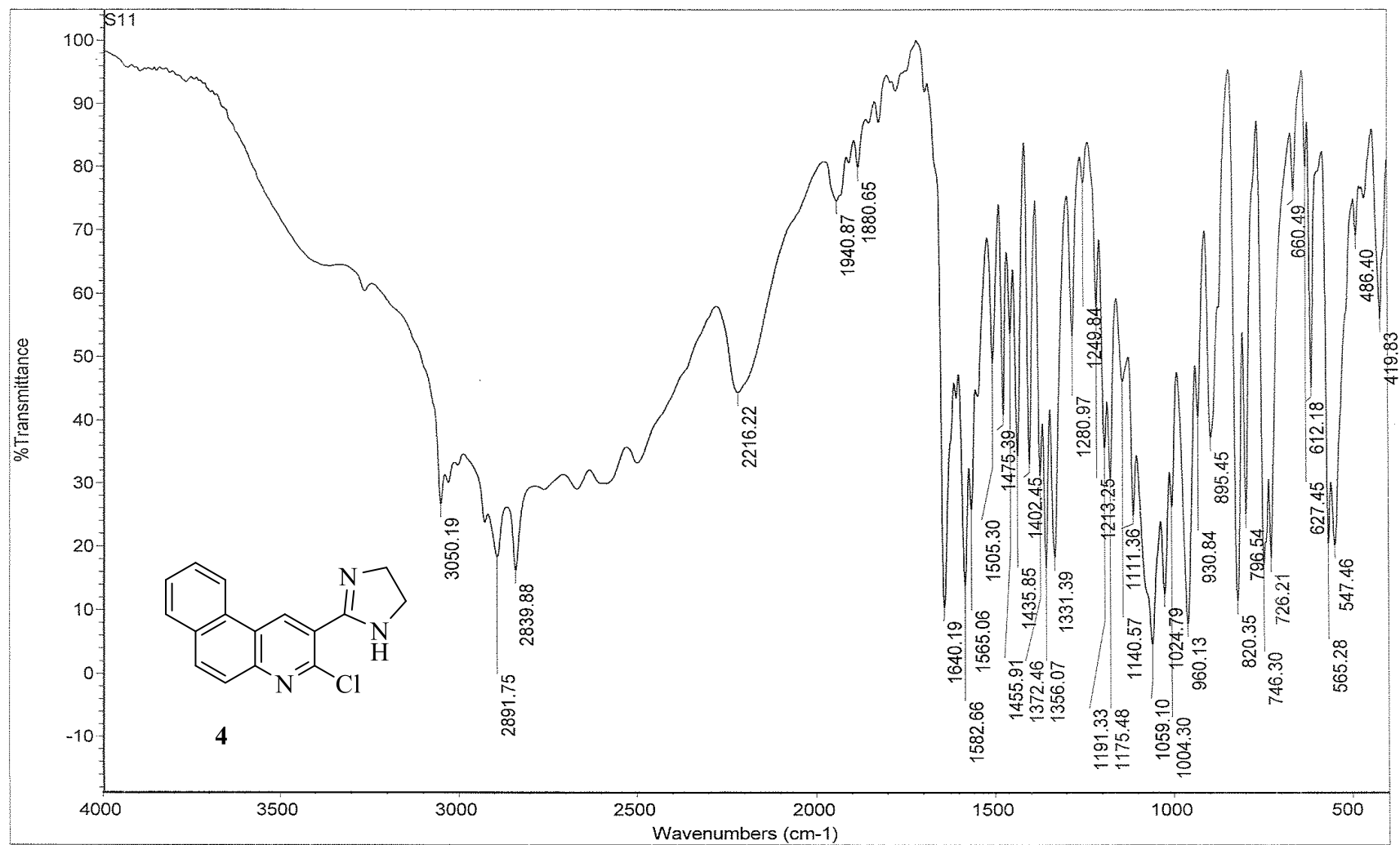
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3





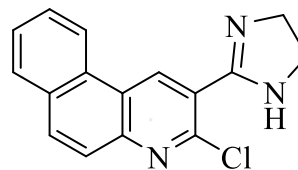
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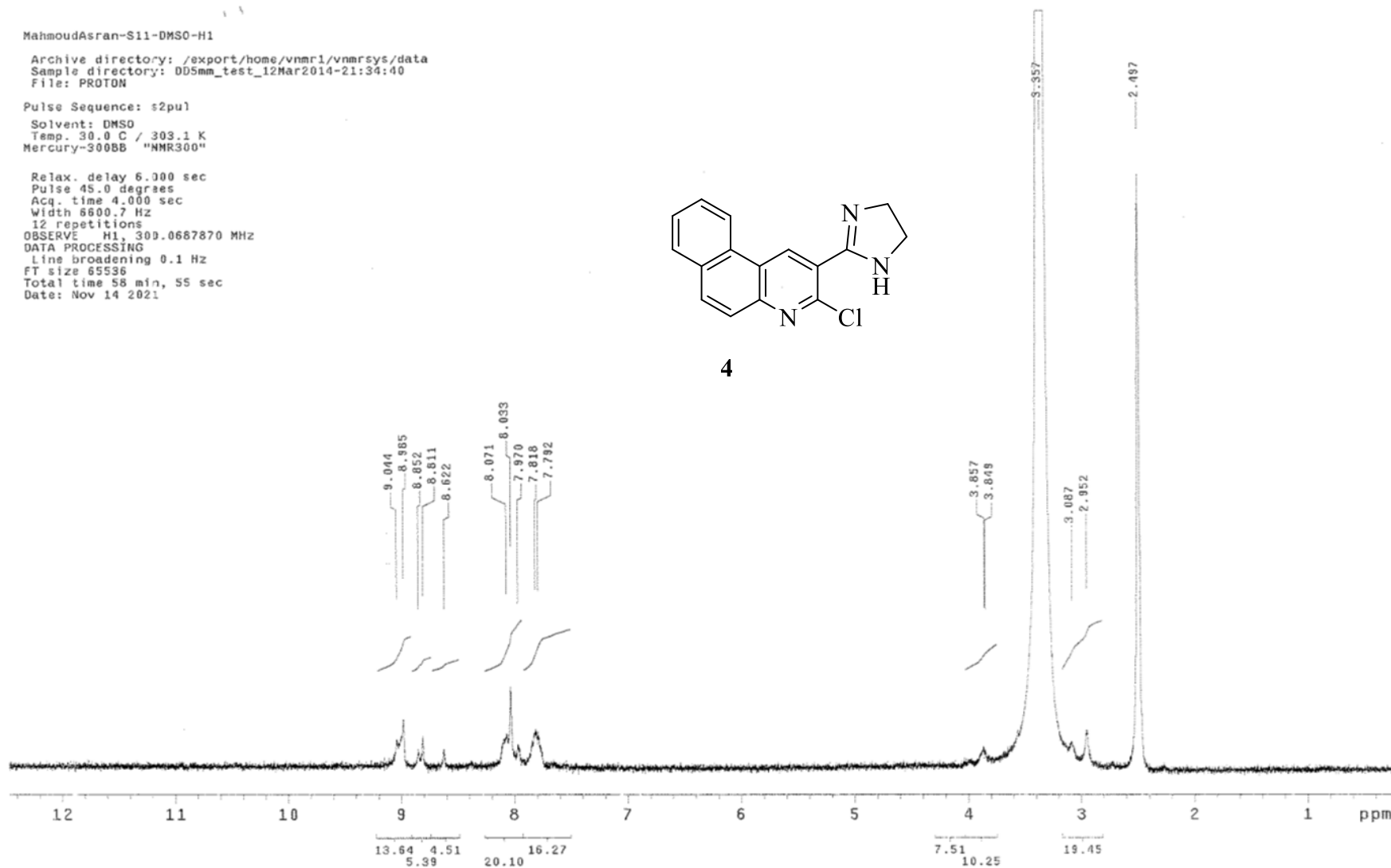
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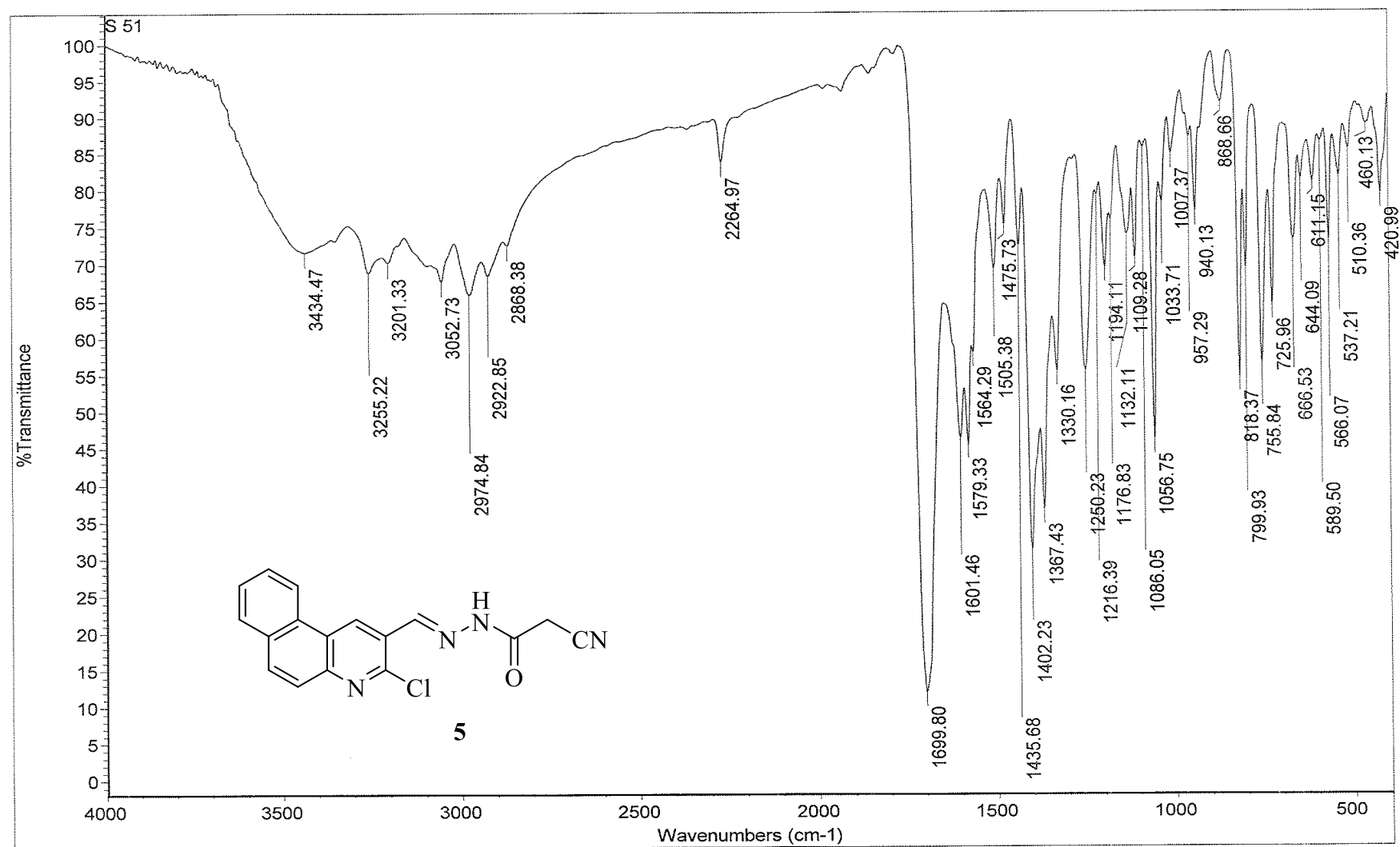
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4





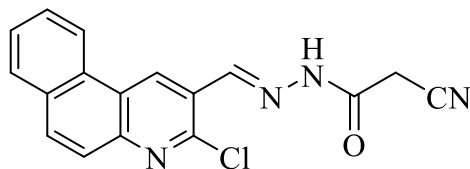
MahmoudAsran-S51-DMSO-H1

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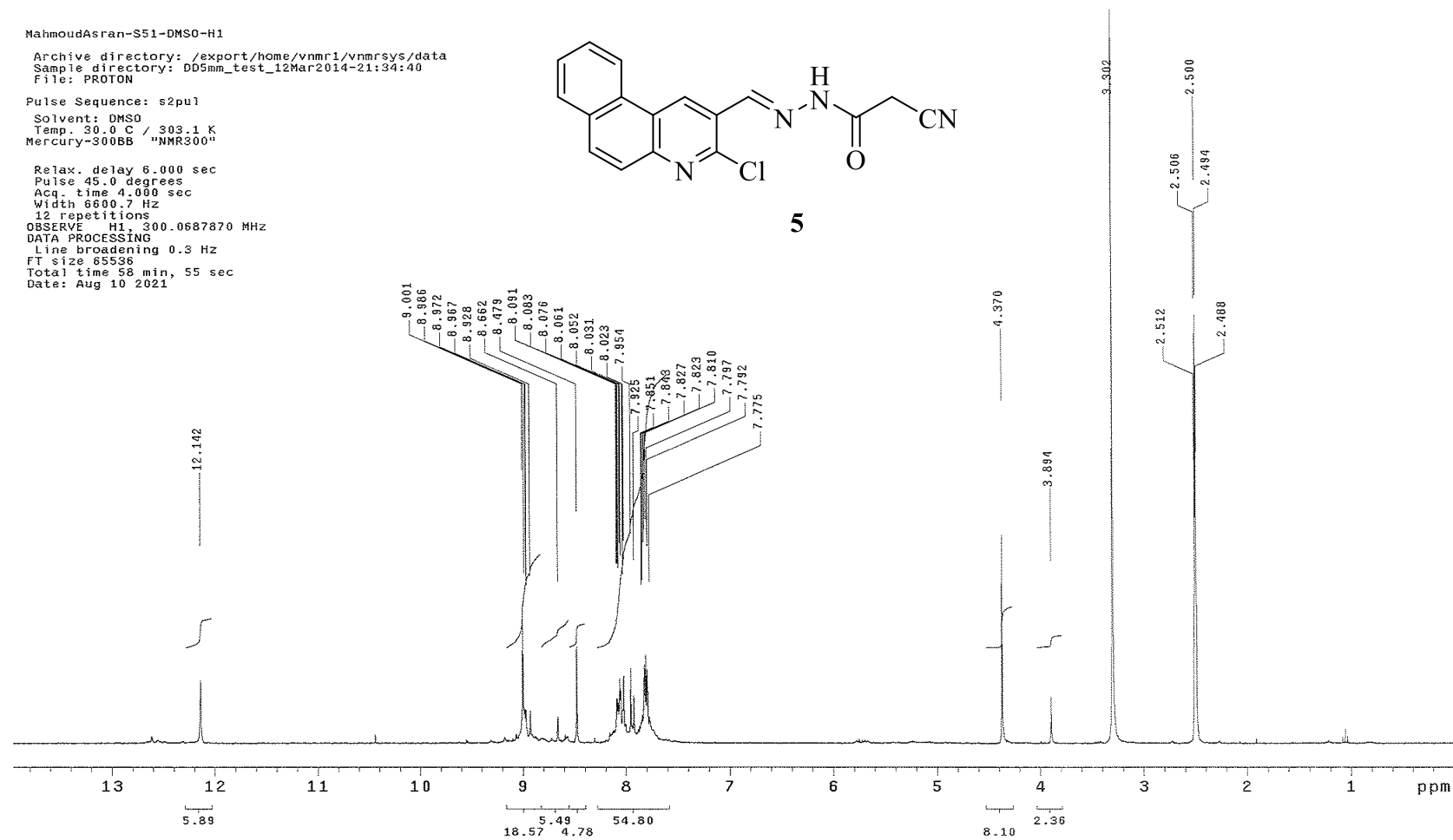
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5



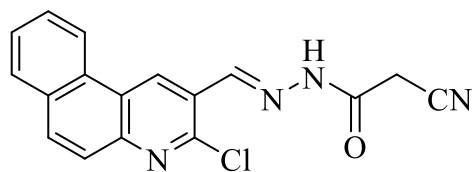
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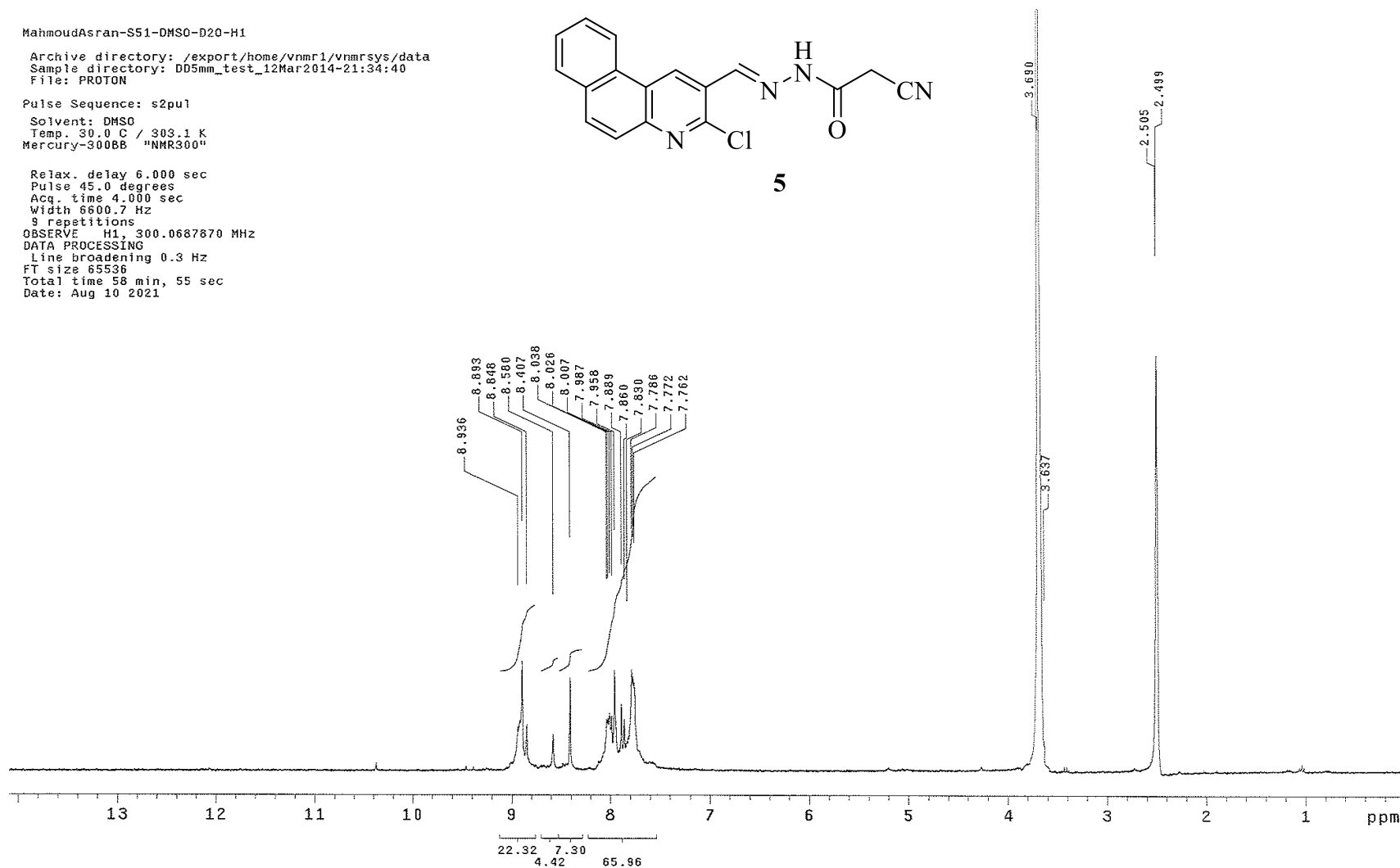
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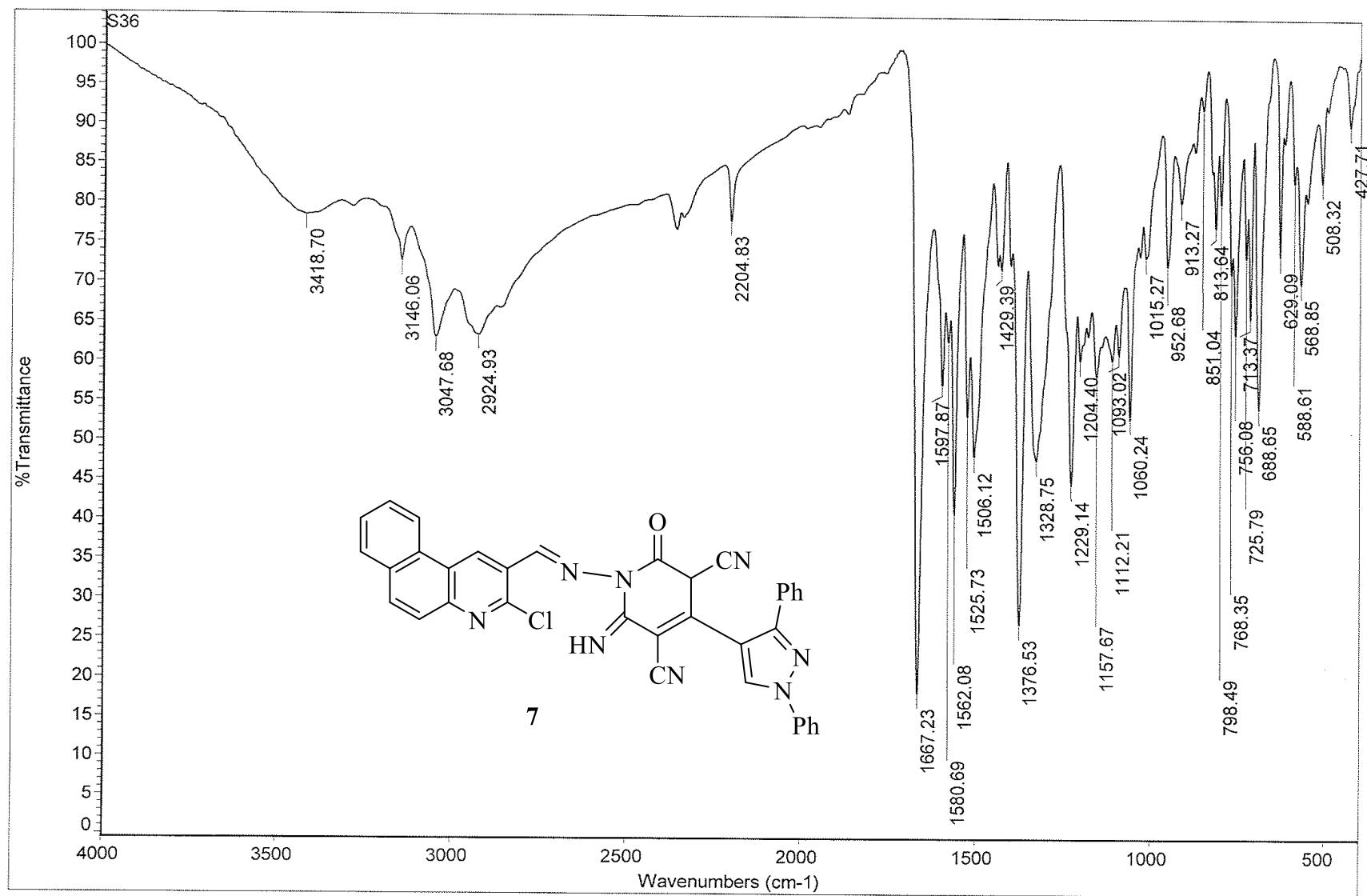
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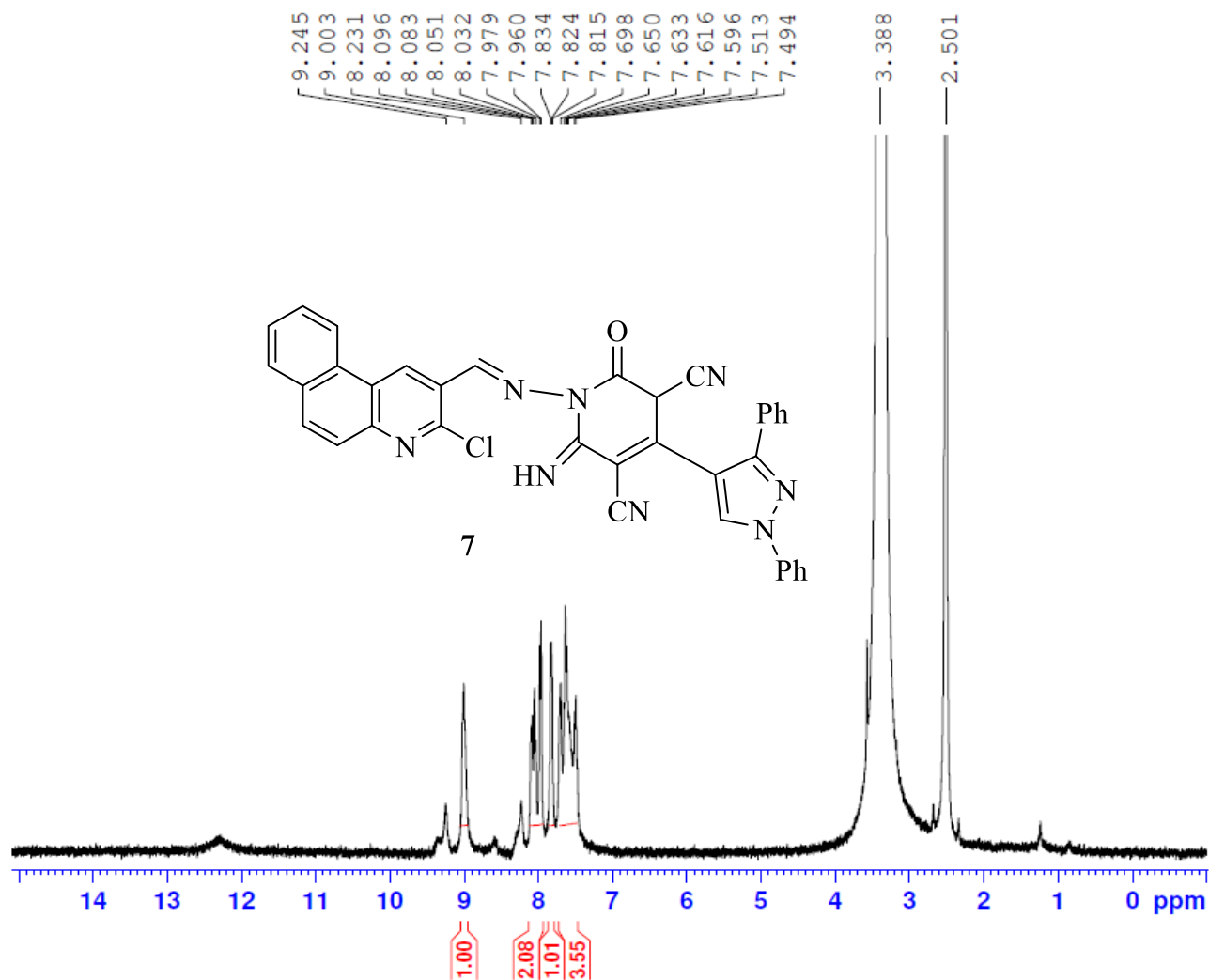
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FT size 65536
Total time 58 min, 55 sec
Date: Aug 10 2021



5







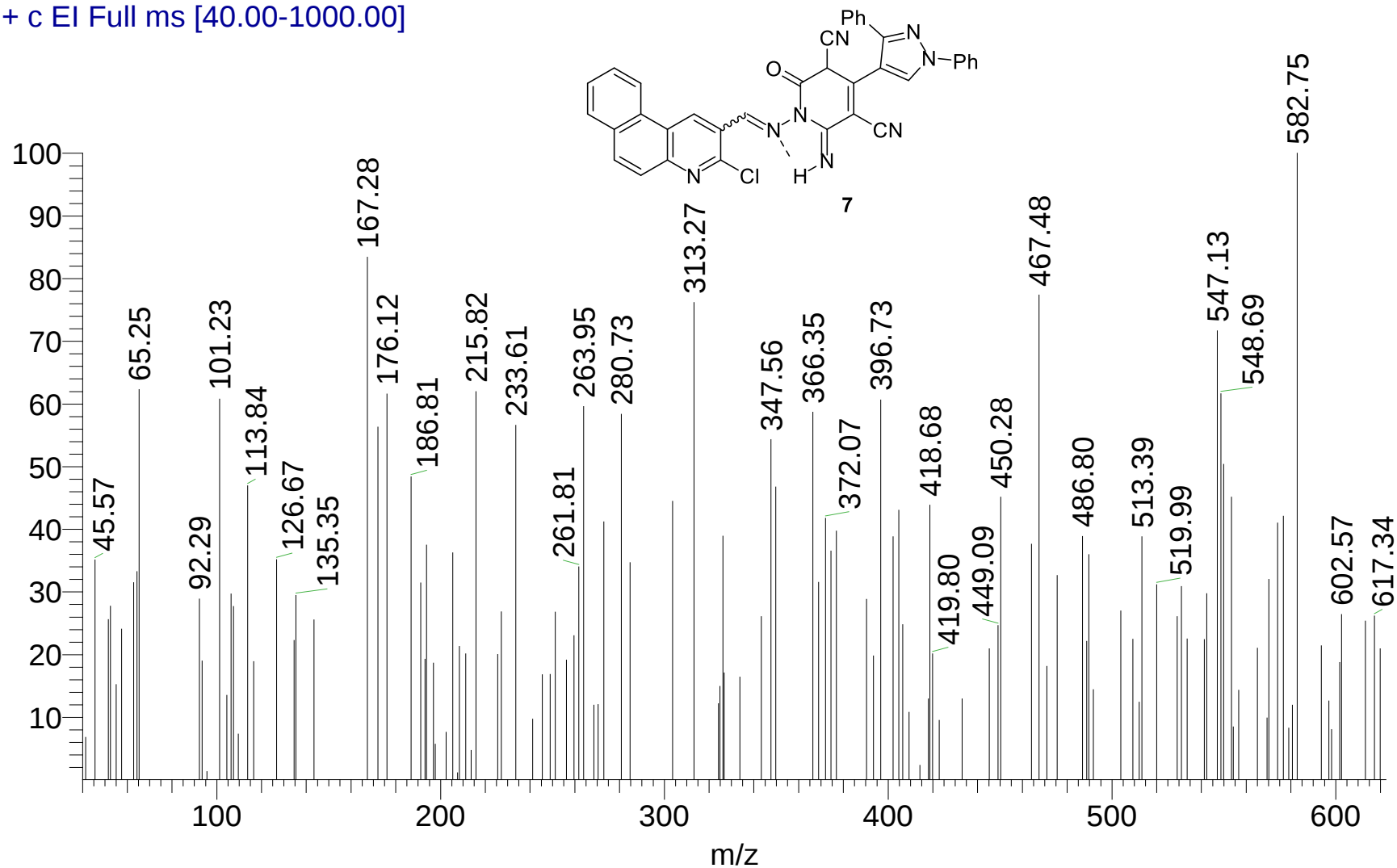
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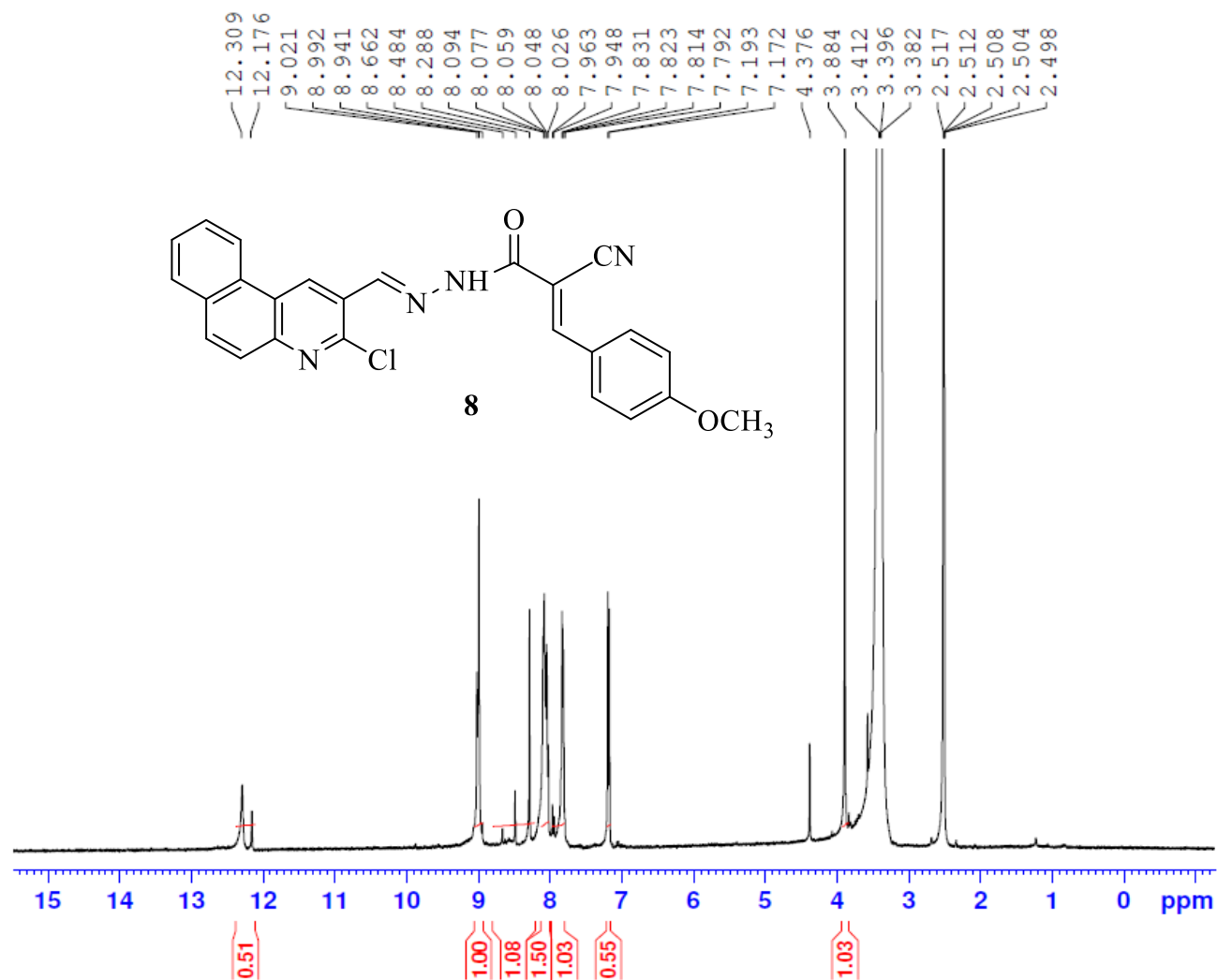
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 SOLVENT DMSO
 NS 128
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.122266 Hz
 AQ 4.0894465 sec
 RG 205.37
 DW 62.400 usec
 DE 6.50 usec
 TE 300.0 K
 D1 1.00000000 sec
 TD0 1

===== 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

Mahmoud-asran-S36 #212-223 RT: 3.56-3.75 AV: 12 SB: 26 1.21-1.34 , 0.87-1.14 NL: 2.90E1
T: + c EI Full ms [40.00-1000.00]



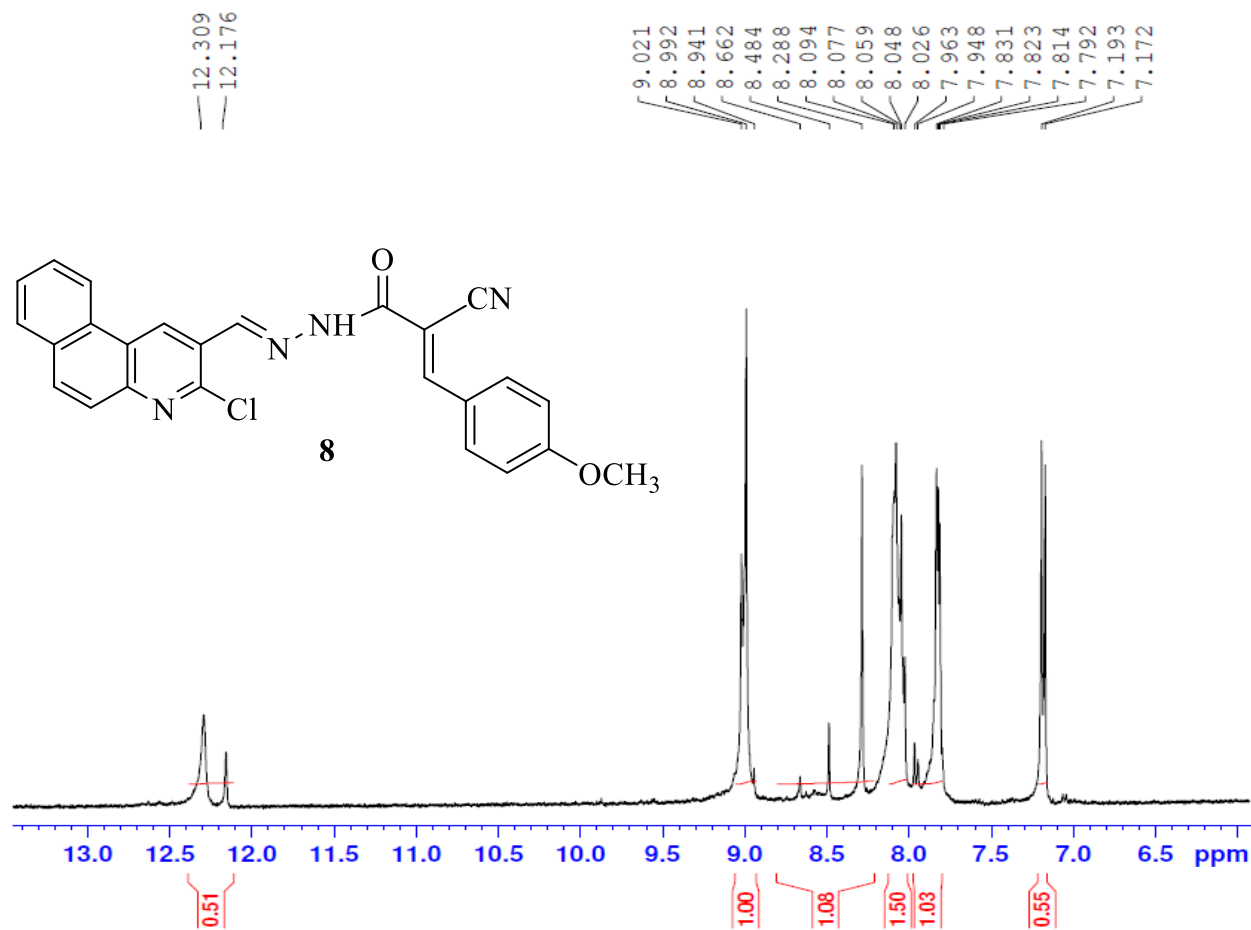


Current Data Parameters
 NAME mahmoud-S34
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220929
 Time 13.41
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zg30
 TD 65536
 SOLVENT DMSO
 NS 128
 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 300.0 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

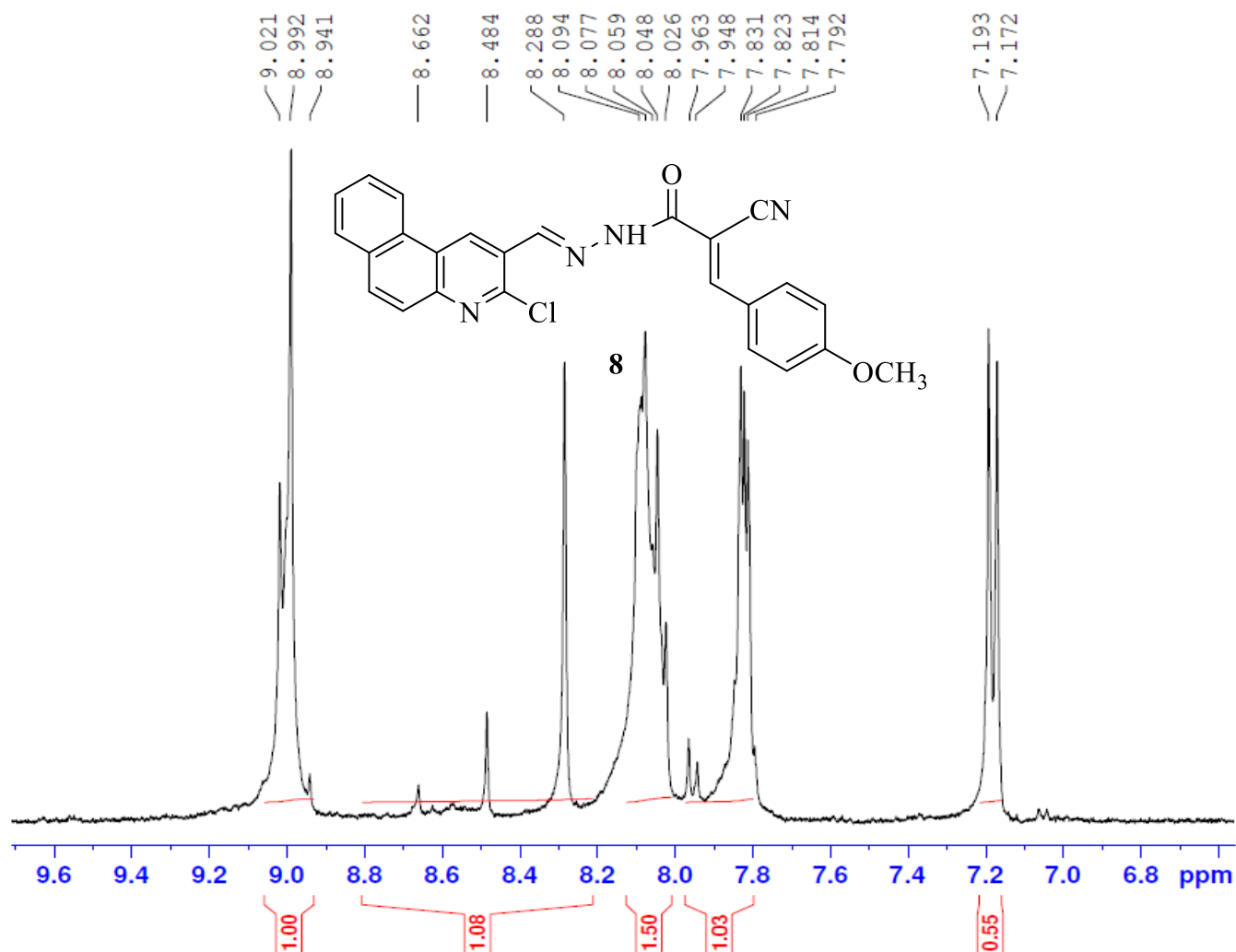


Current Data Parameters
 NAME mahmoud-S34
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220929
 Time 13.41
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zg30
 TD 65536
 SOLVENT DMSO
 NS 128
 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 300.0 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

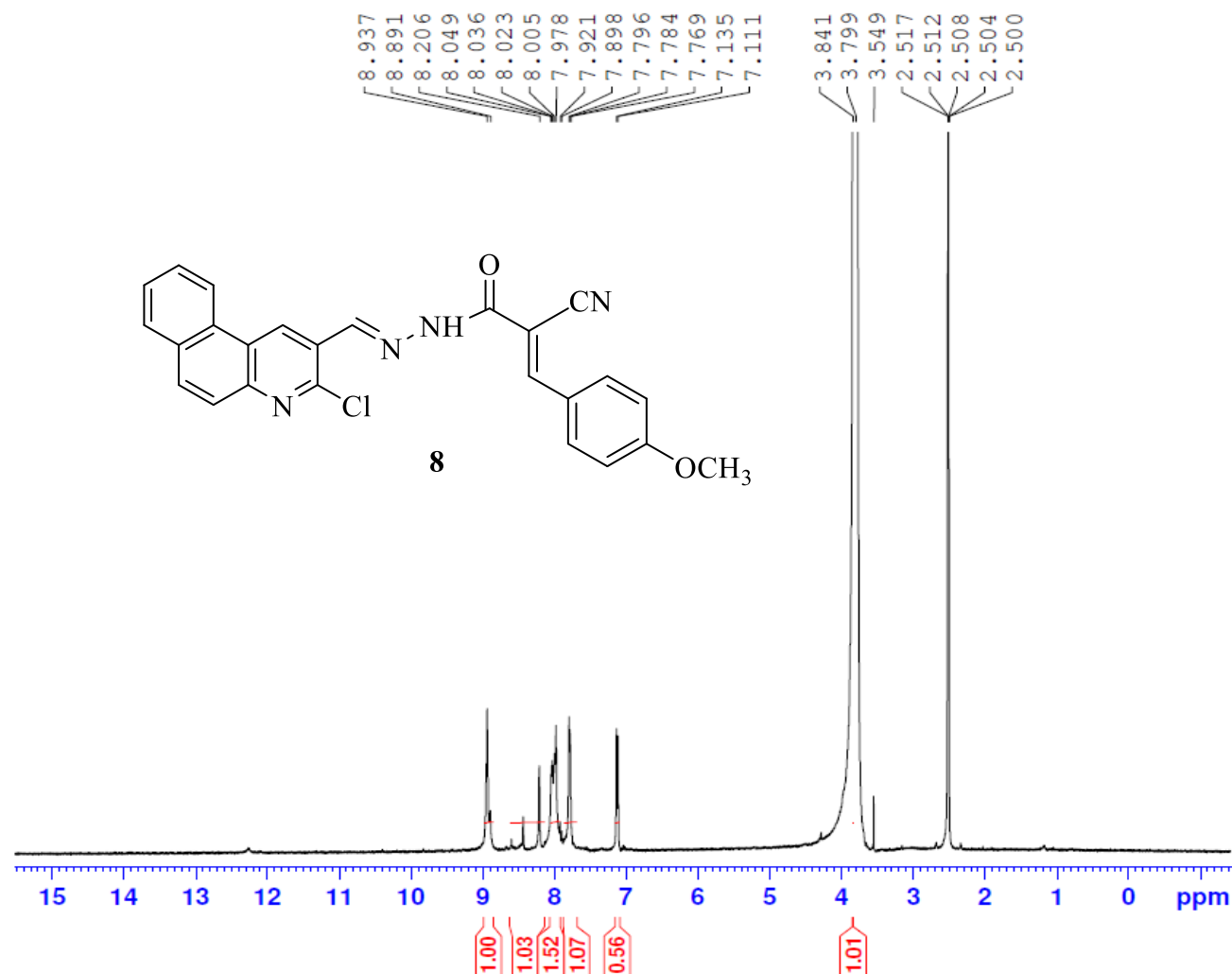


Current Data Parameters
 NAME mahmoud-S34
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220929
 Time 13.41
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zg30
 TD 65536
 SOLVENT DMSO
 NS 128
 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 300.0 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

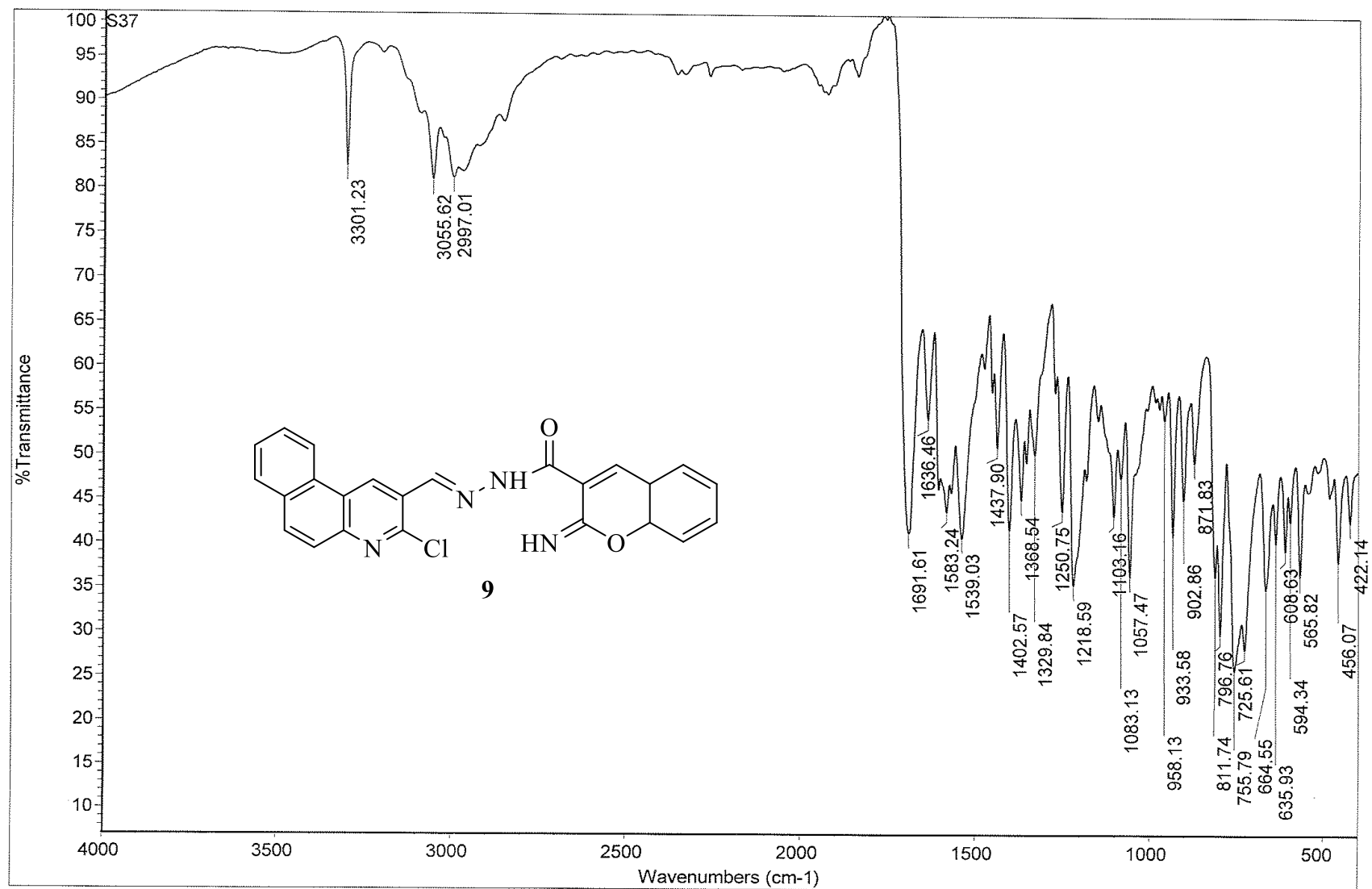


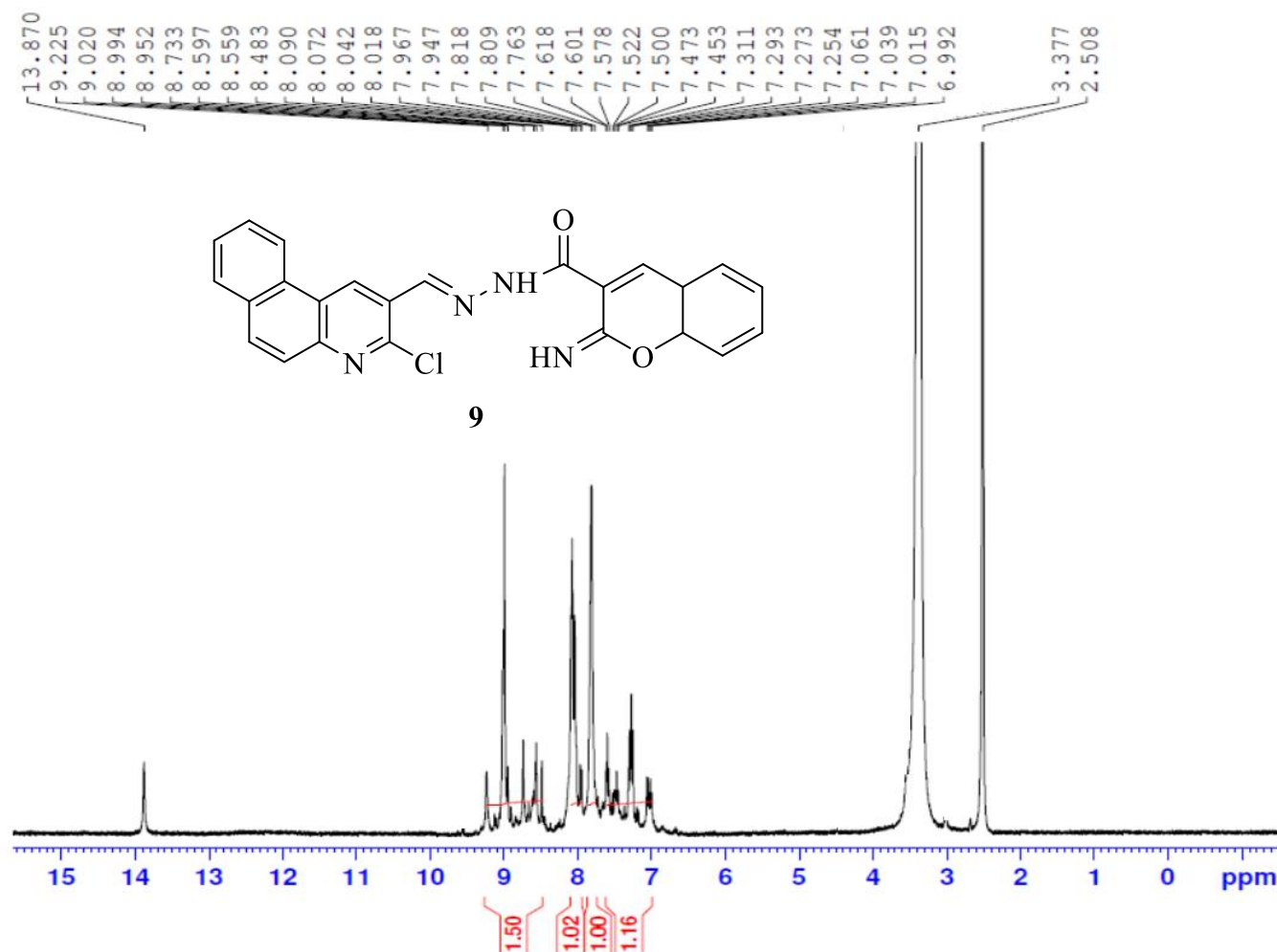
Current Data Parameters
 NAME mahmoud-S34-d2o
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220929
 Time 17.21
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zg30
 TD 65536
 SOLVENT DMSO
 NS 115
 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 300.0 K
 D1 1.00000000 sec
 TDO 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



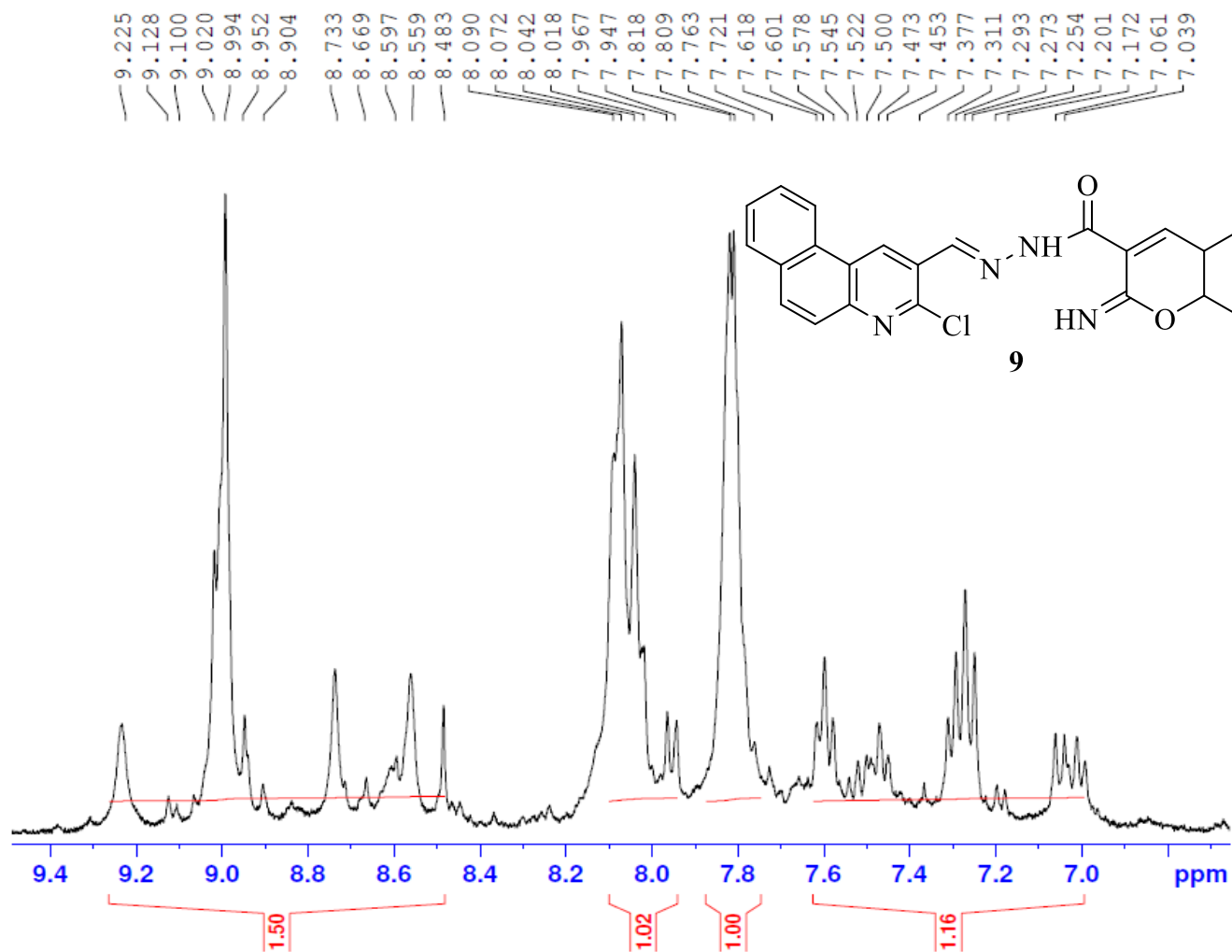


Current Data Parameters
 NAME mahmoud-S37
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220929
 Time 14.17
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zg30
 TD 65536
 SOLVENT DMSO
 NS 128
 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 300.0 K
 D1 1.00000000 sec
 TDO 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

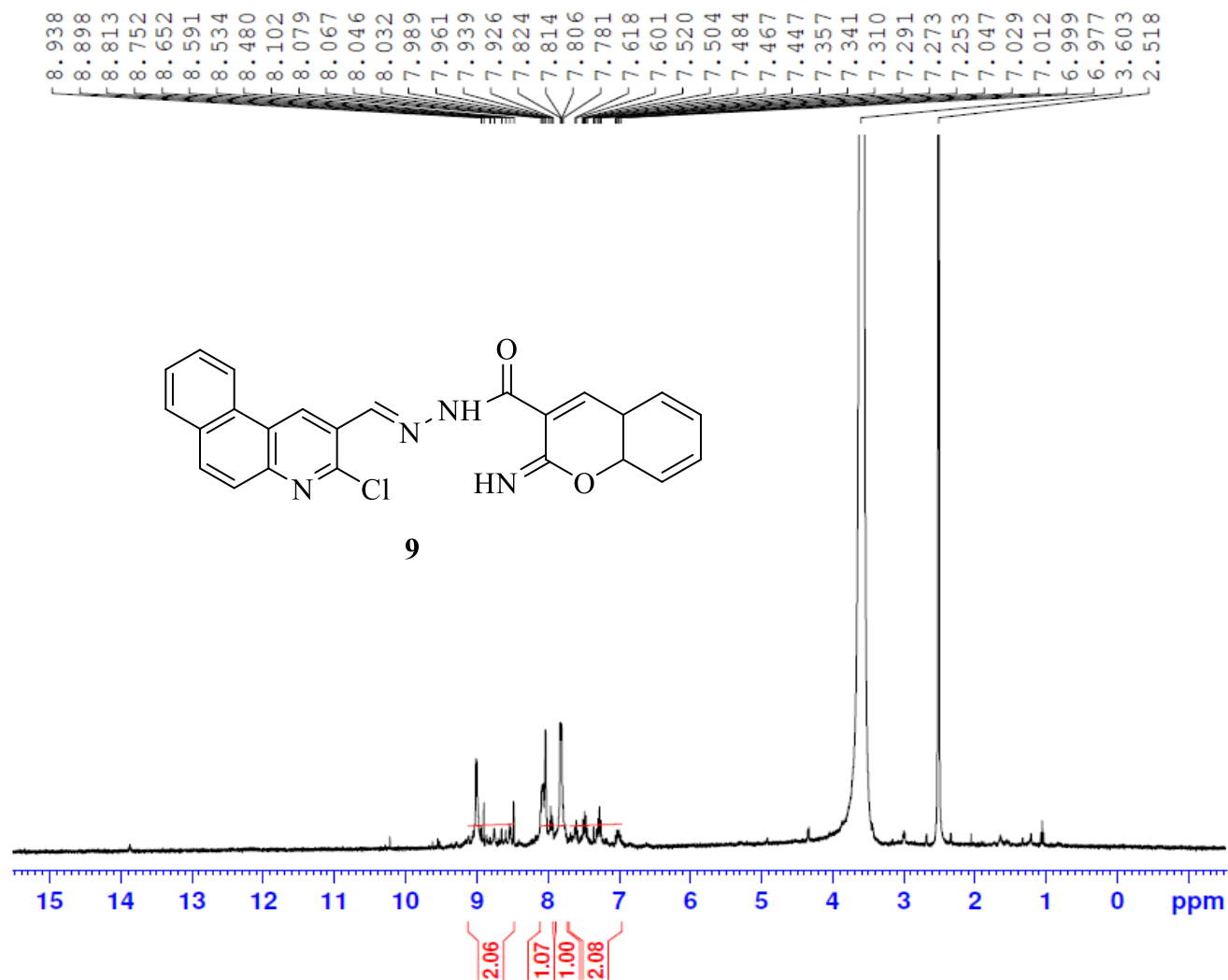


Current Data Parameters
 NAME mahmoud-S37
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220929
 Time 14.17
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zg30
 TD 65536
 SOLVENT DMSO
 NS 128
 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 300.0 K
 D1 1.00000000 sec
 TDO 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



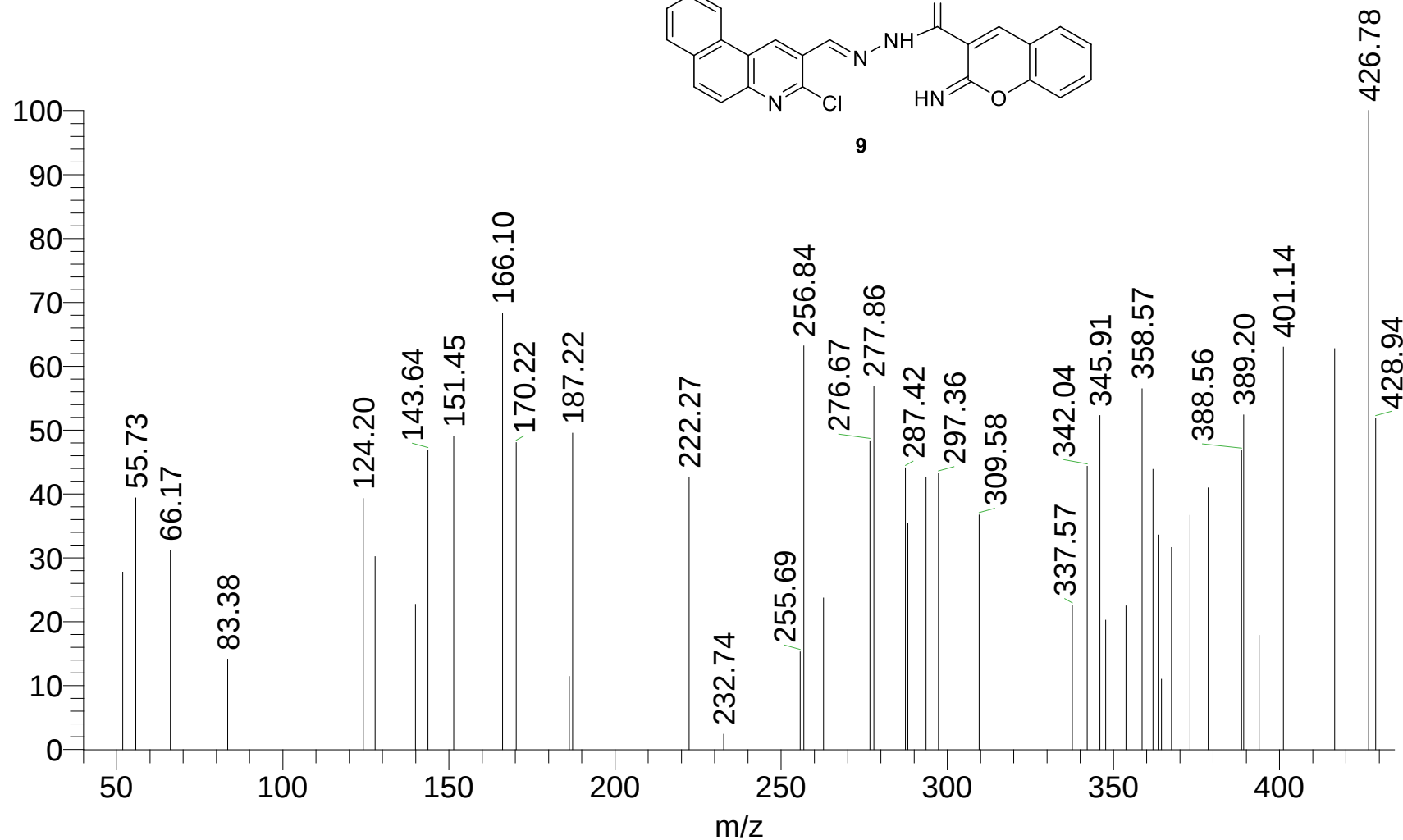
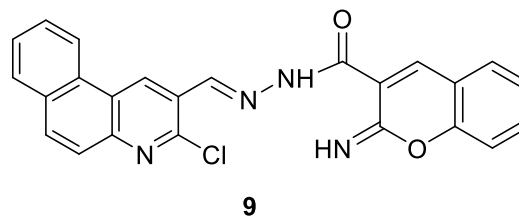
Current Data Parameters
 NAME mahmoud-S37-d20
 EXPNO 3
 PROCNO 1

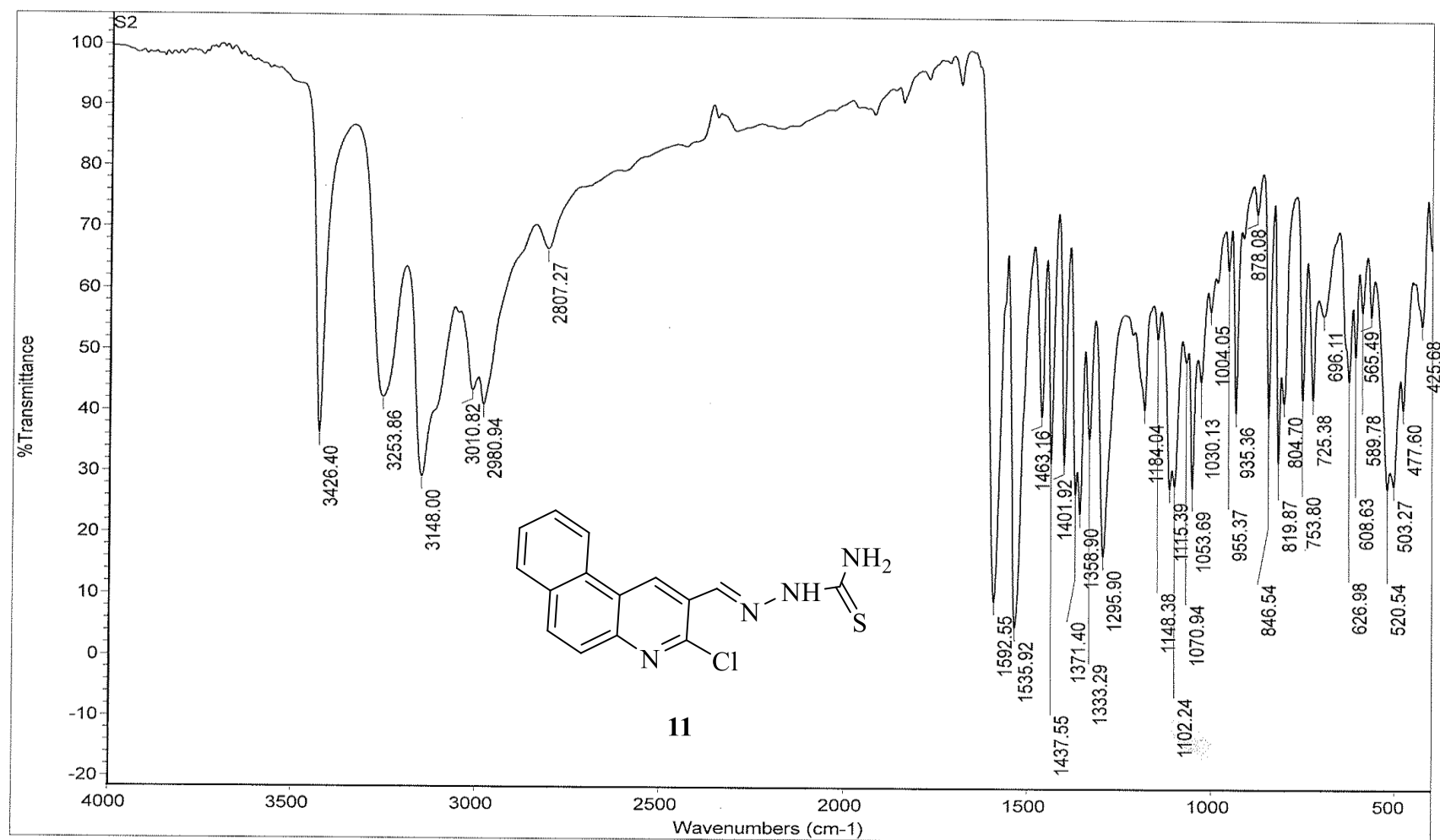
F2 - Acquisition Parameters
 Date_ 20221009
 Time 14.21
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zg30
 TD 65536
 SOLVENT DMSO
 NS 128
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.122266 Hz
 AQ 4.0894465 sec
 RG 205.37
 DW 62.400 usec
 DE 6.50 usec
 TE 300.0 K
 D1 1.00000000 sec
 TD0 1

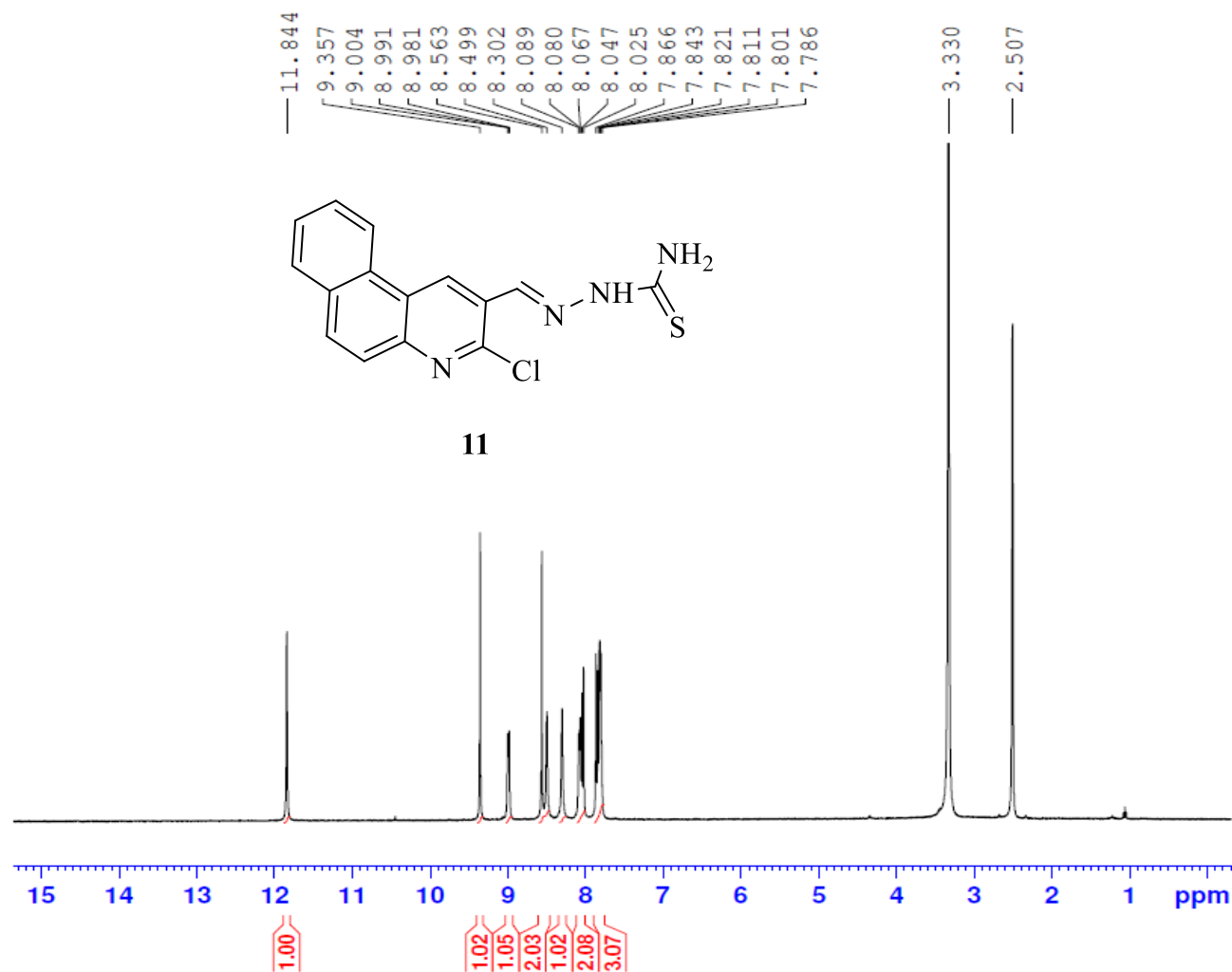
===== CHANNEL f1 =====
 SFO1 400.1524711 MHz
 NUC1 1H
 P1 12.00 usec
 PLW1 18.00000000 W

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

Mahmoud-asran-S37 #164-166 RT: 2.76-2.79 AV: 3 SB: 26 1.21-1.34 , 0.87-1.14 NL: 6.85E1
T: + c EI Full ms [40.00-1000.00]





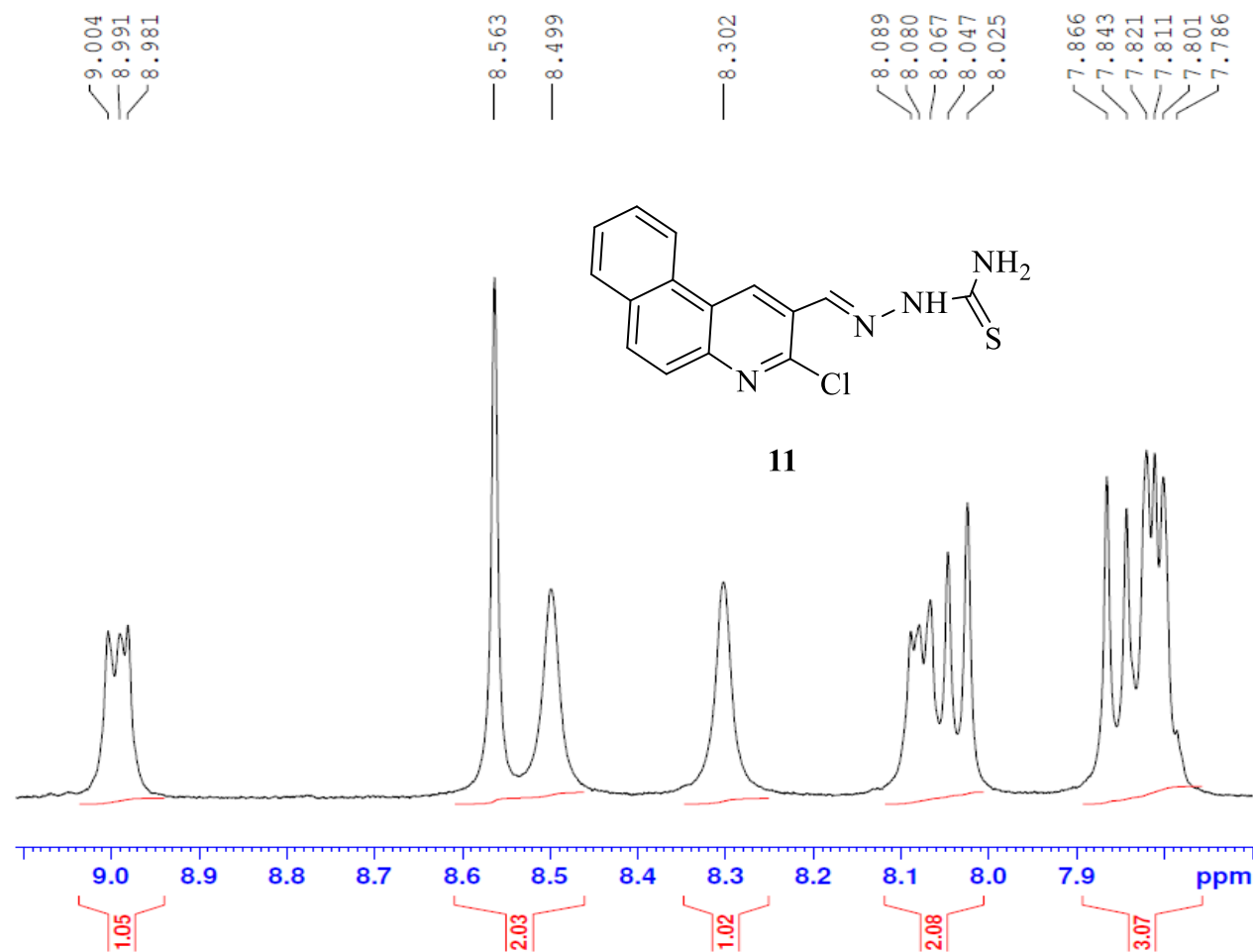


Current Data Parameters
 NAME mahmoud-mohamed-S2
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20221025
 Time 11.35
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zg30
 TD 65536
 SOLVENT DMSO
 NS 81
 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 300.0 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

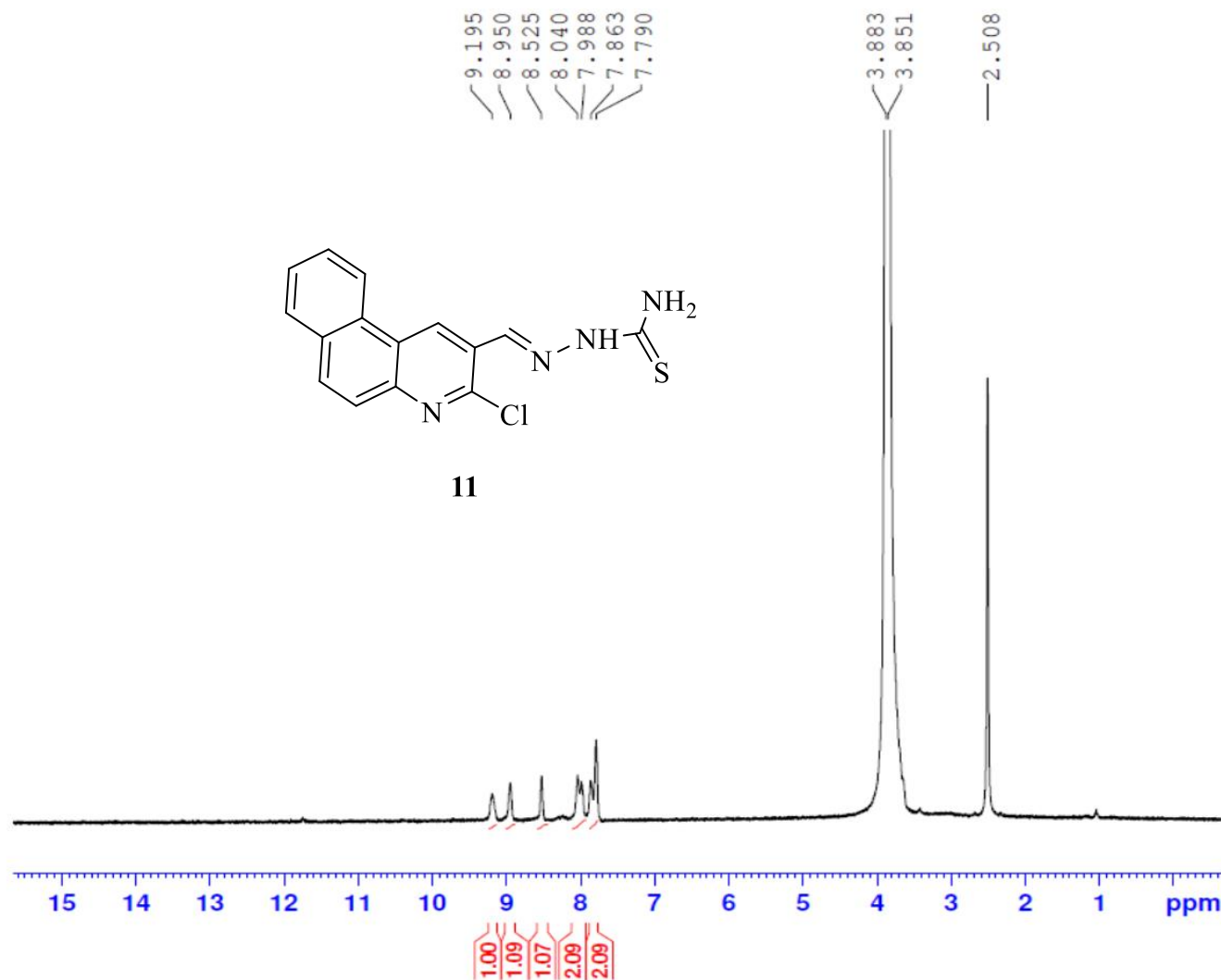


Current Data Parameters
 NAME mahmoud-mohamed-S2
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20221025
 Time 11.35
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zg30
 TD 65536
 SOLVENT DMSO
 NS 81
 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 300.0 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

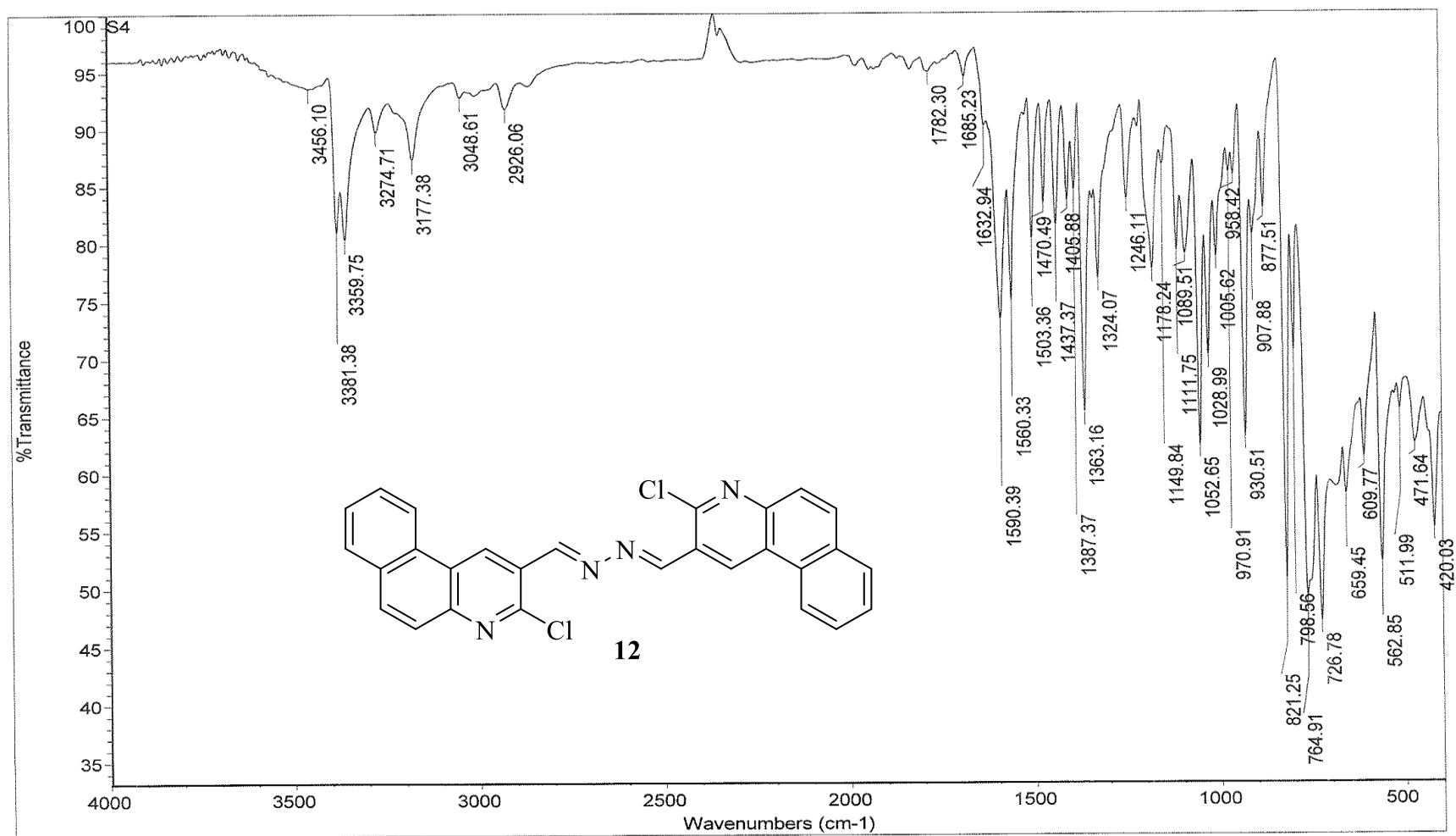


Current Data Parameters
 NAME mahmoud-mohamed-S2-d2o
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20221026
 Time 10.47
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zg30
 TD 65536
 SOLVENT DMSO
 NS 80
 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 300.0 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



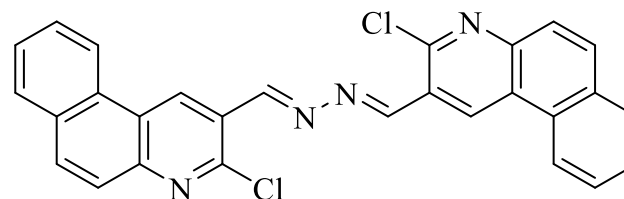
MahmoudAsran-54-DMSO-H1

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON

Pulse Sequence: s2pu1

Solvent: DMSO
Temp. 30.0 C / 303.1 K
Mercury-300BB "NMR300"

Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 4.000 sec
Width 6600.7 Hz
16 repetitions
OBSERVE H1, 300.0687870 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 65536
Total time 58 min, 55 sec
Date: Aug 10 2021



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