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Synthesis, Computational Chemical Study, Antiproliferative Activity Screening, and Molecular Docking of Some Thiophene-Based Oxadiazole, Triazole, and Thiazolidinone Derivatives

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Supporting information:

Figures:

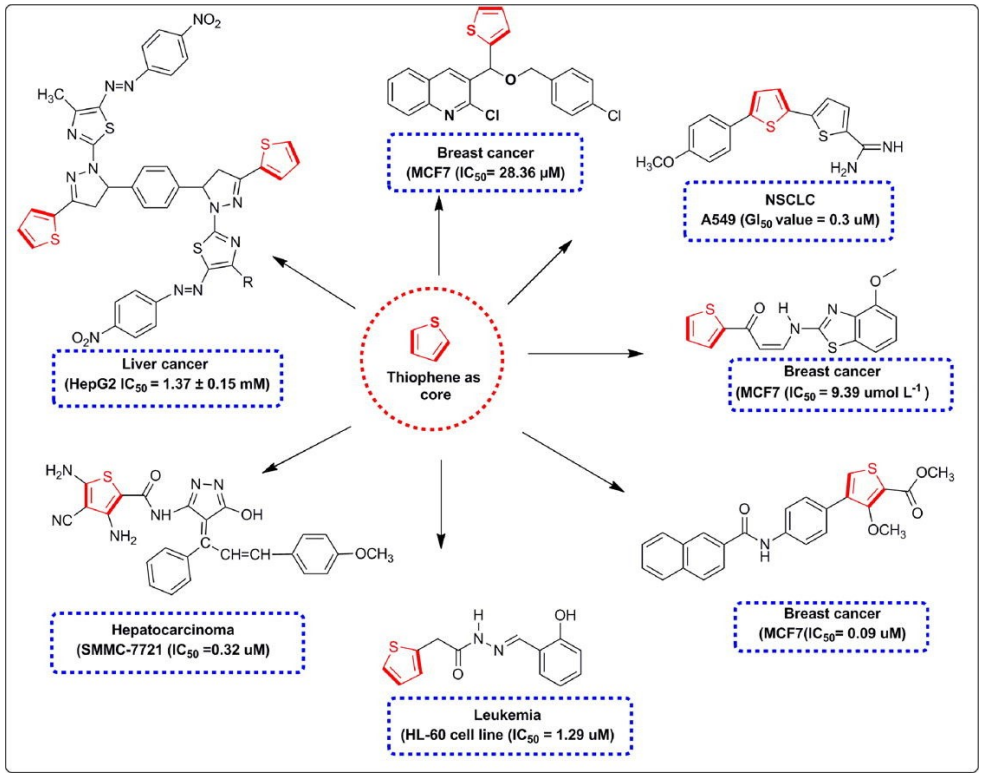


Fig. 1. Some clinical drugs bearing thiophene scaffolds as anticancer agents.

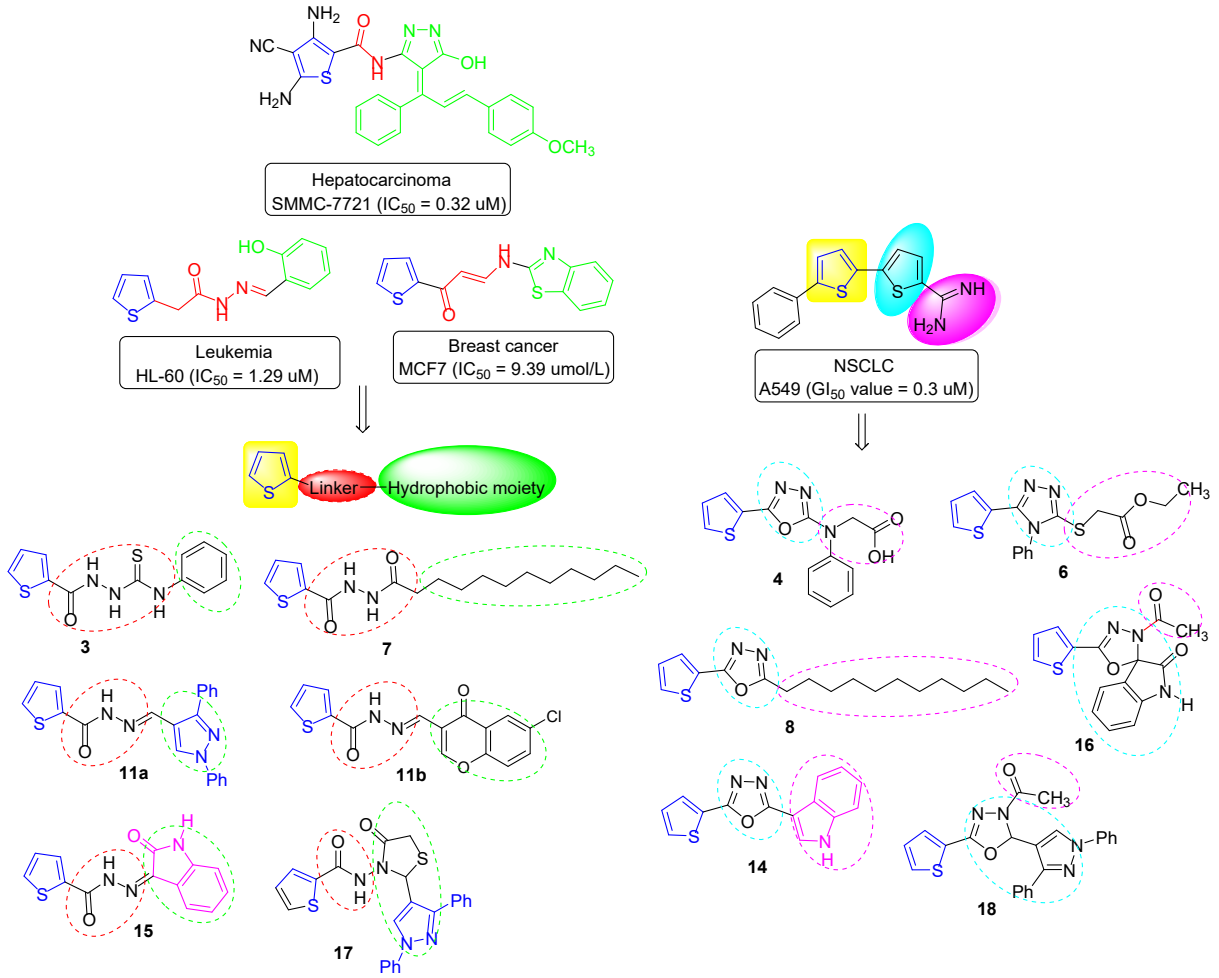
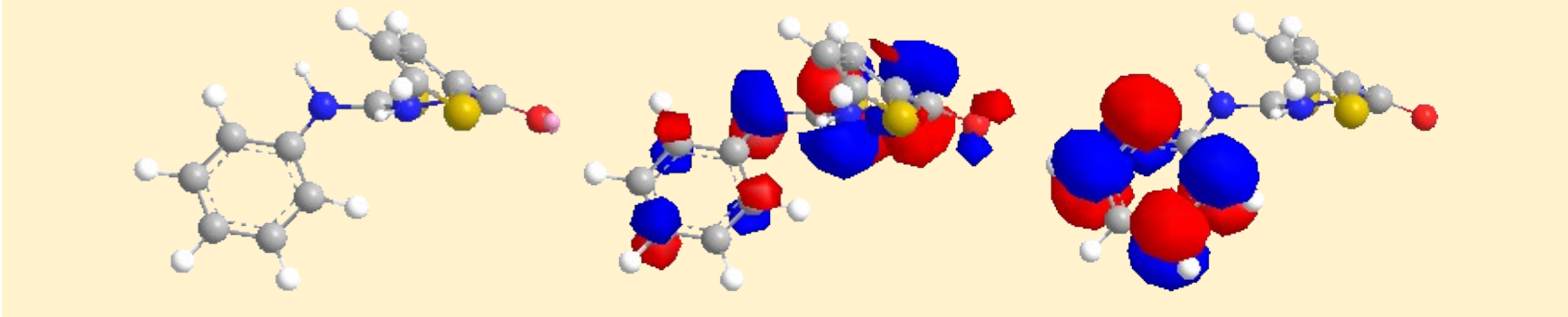
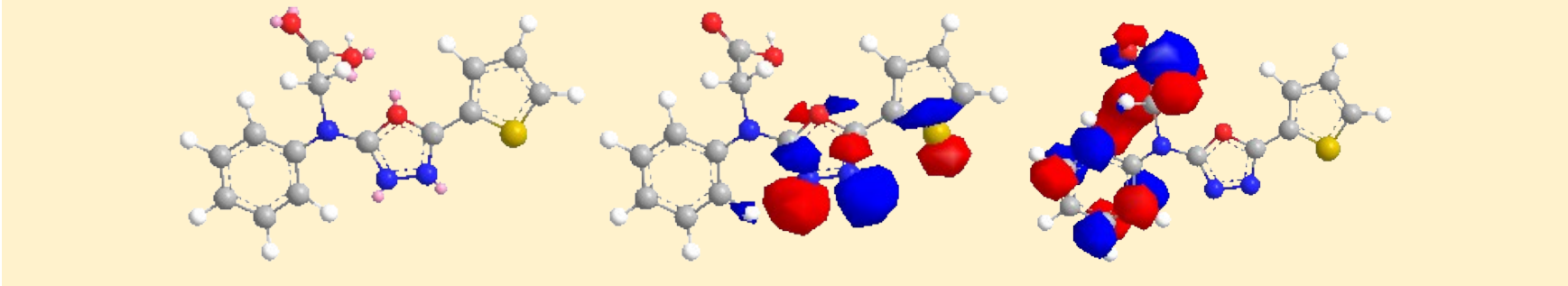


Fig. 2. Rationale and design of the chemical structures of some anticancer agents (bearing thiophene nucleus) and the target derivatives.



Compound 3



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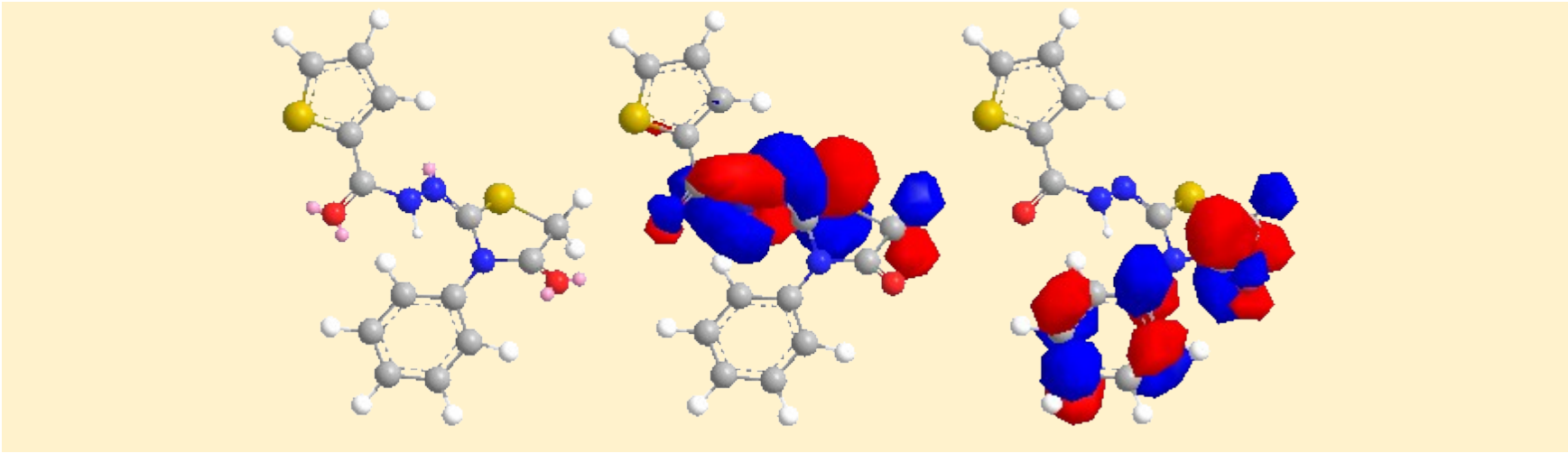

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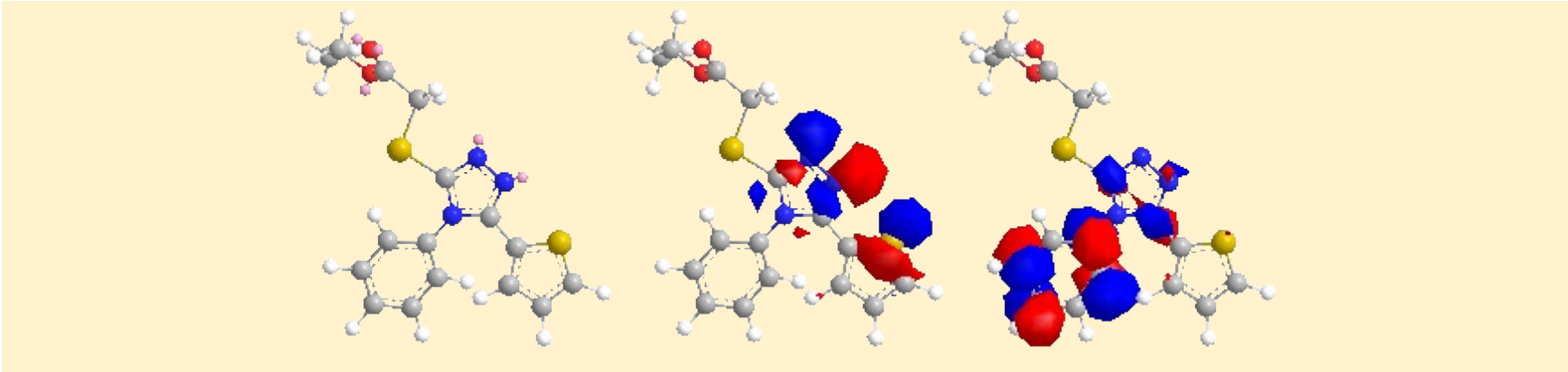

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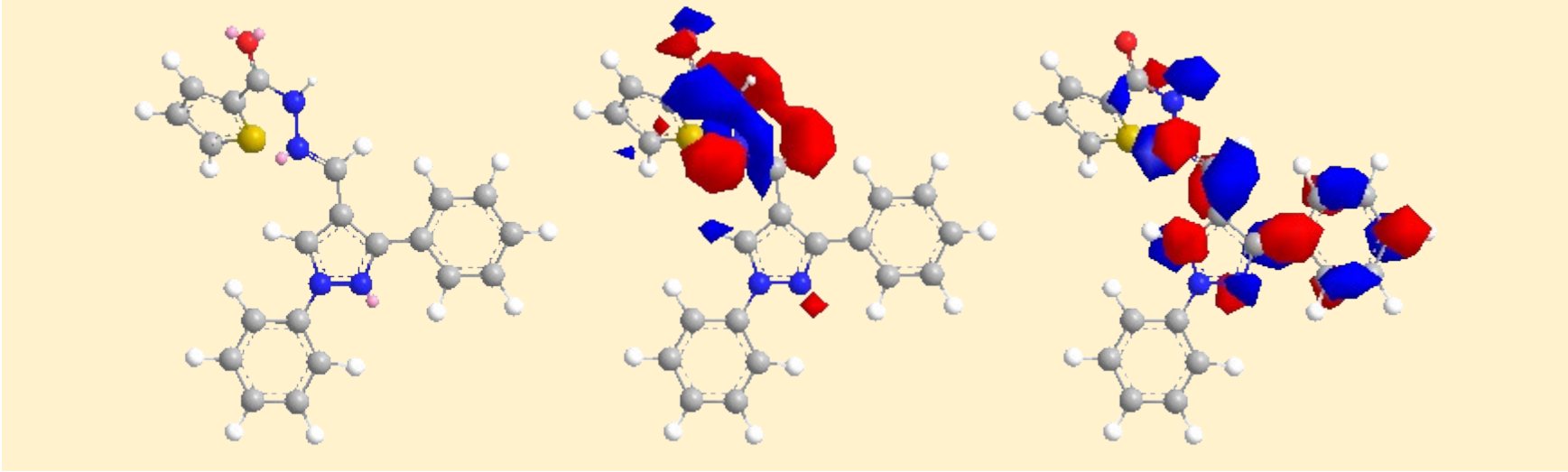
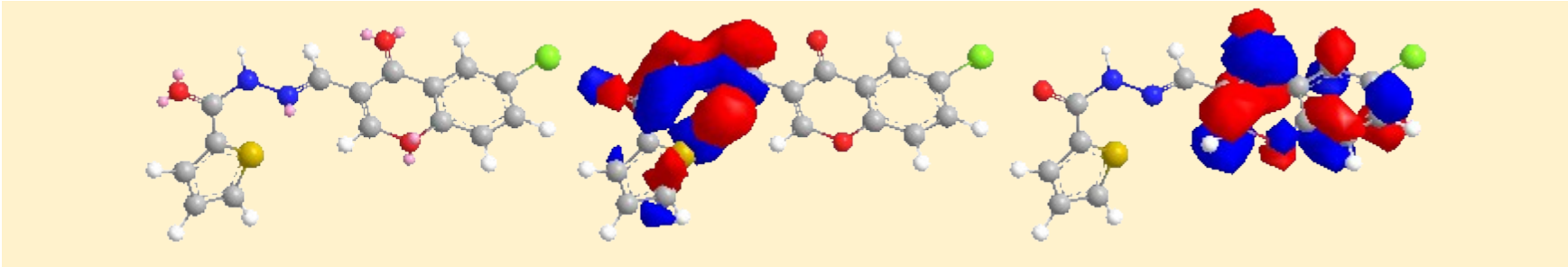
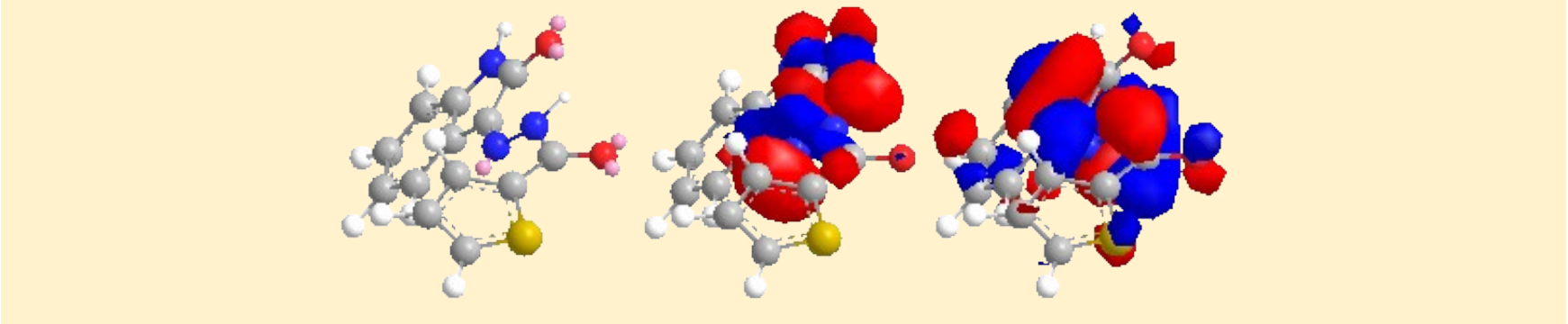


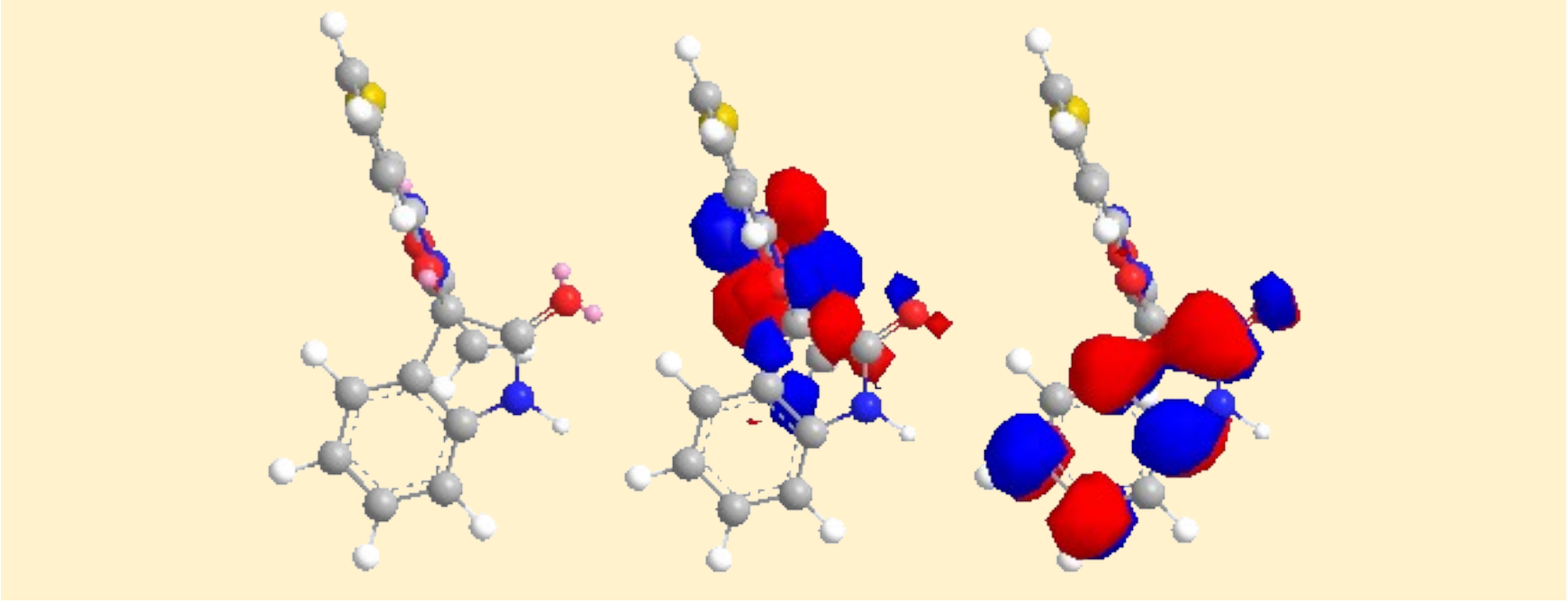
Compound 11a



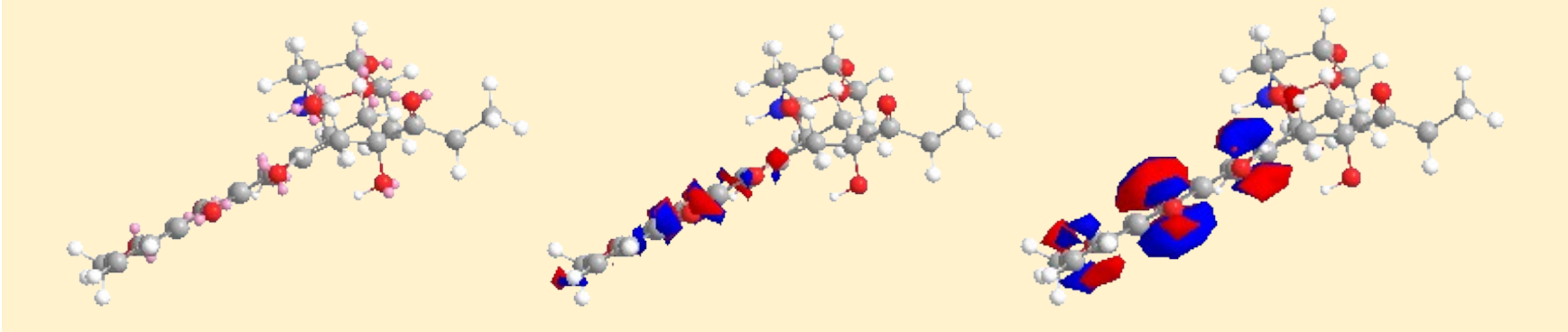
Compound 11b



Compound 15



Compound 16



Doxorubicin

Fig. 3. Optimized structures (left), HOMO (middle), and LUMO (right) for substances **3-18** and Doxorubicin.
Atom color index: Grey C, White H, Blue N, Red O, Yellow S, and Green Cl.

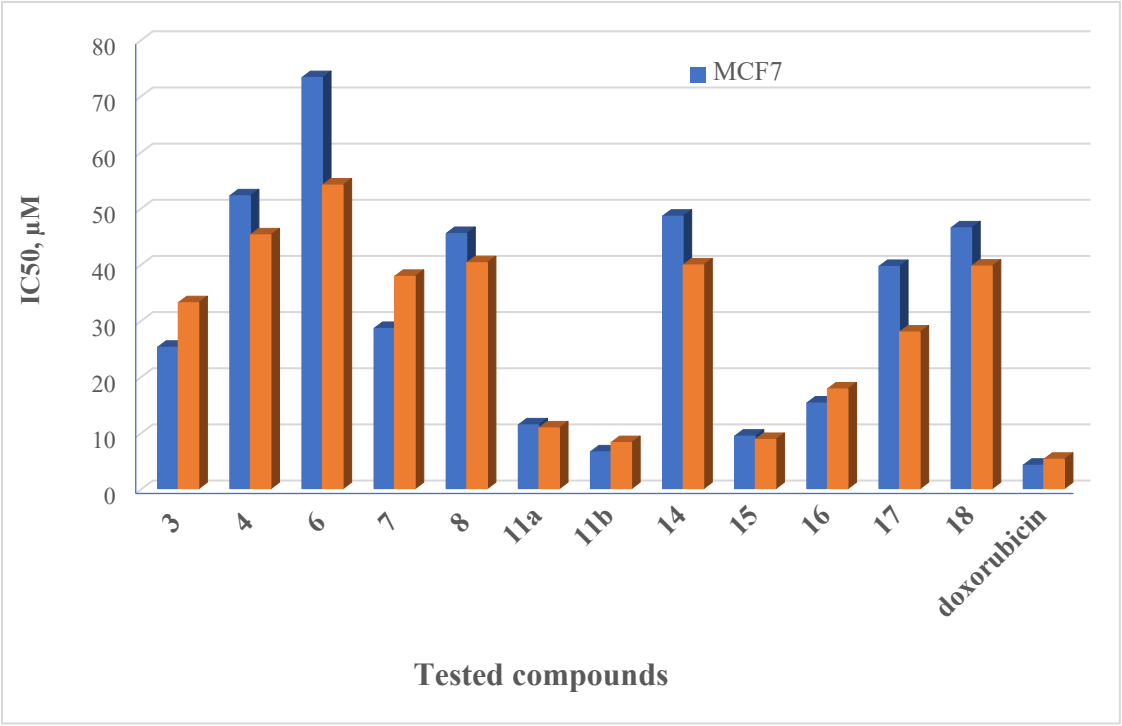


Fig. 4. IC_{50} values of the tested compounds against MCF7 and HCT116 cell lines.

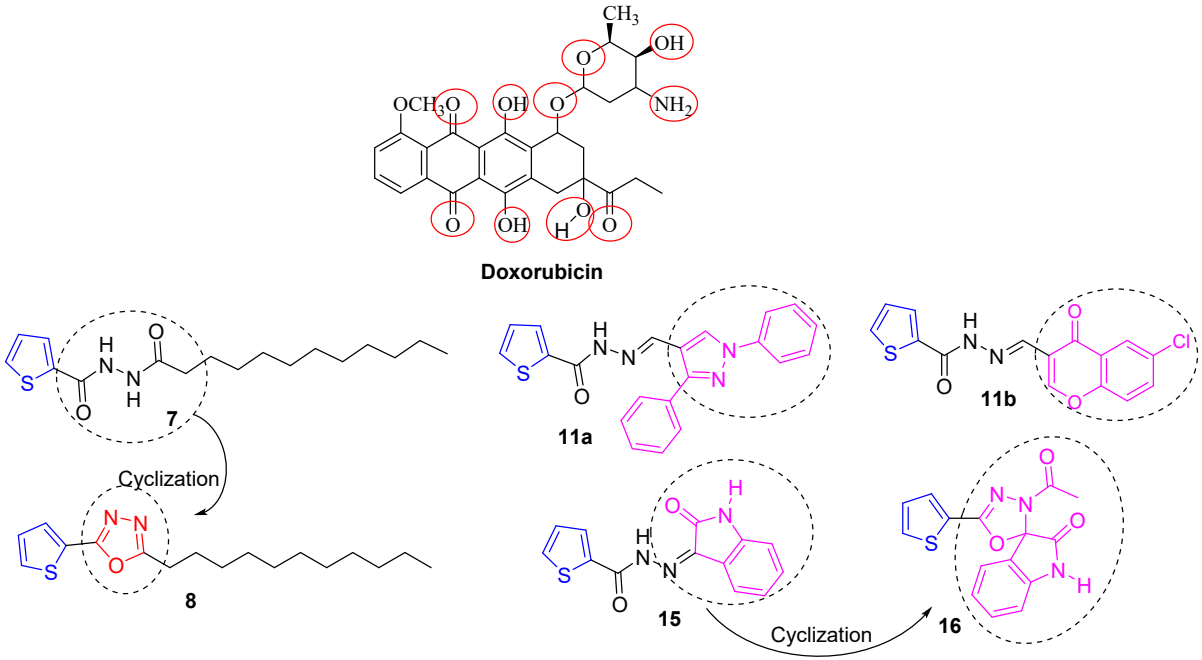
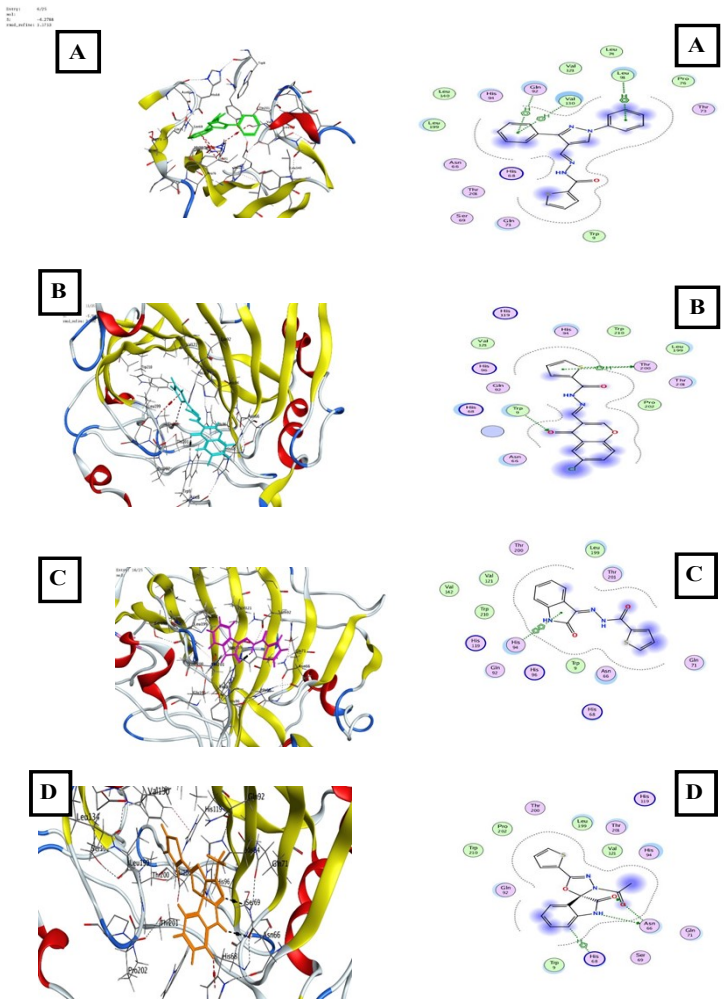


Fig. 5. SAR of compounds **7, 8, 11a,b, 15**, and **16**.



*Hydrogen bonds are illustrated as arrows; C atoms are colored gray, N blue, and O red

Fig. 6. 2D and 3D-interactions of compounds **11a, 11b, 15**, and **16** with CA IX protein binding pockets.

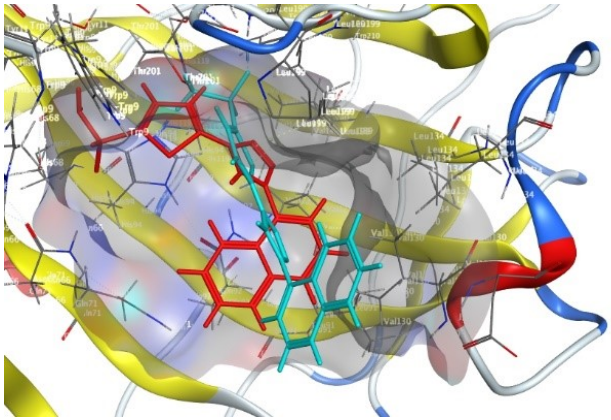


Fig. 7. 3D diagram displays the overlay of the native co-crystallized ligand, Etoposide (in cyan), with the redocked co-crystallized ligand (in red) within the CA IX protein target.

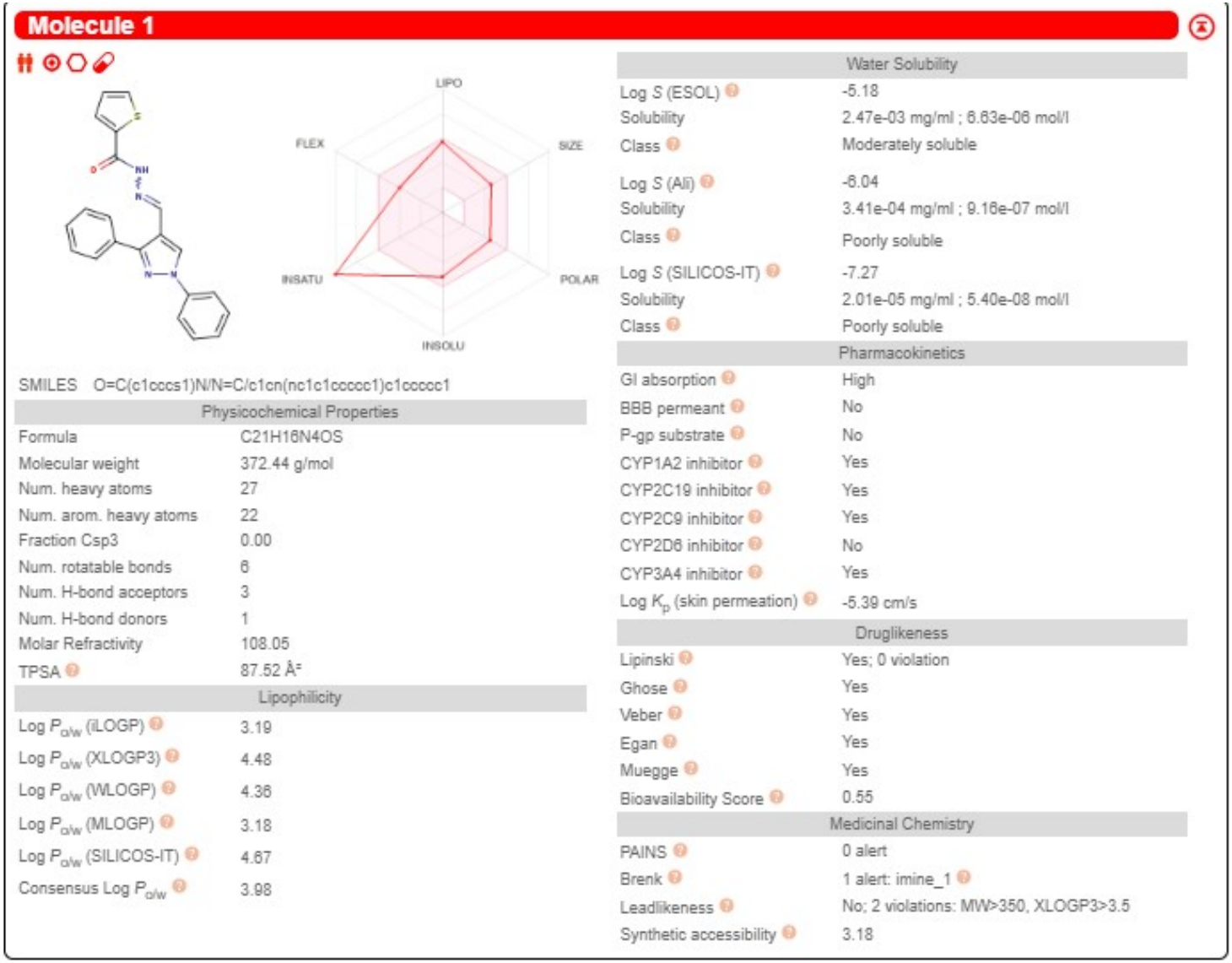


Fig. 8. ADME prediction of compound **11a**.

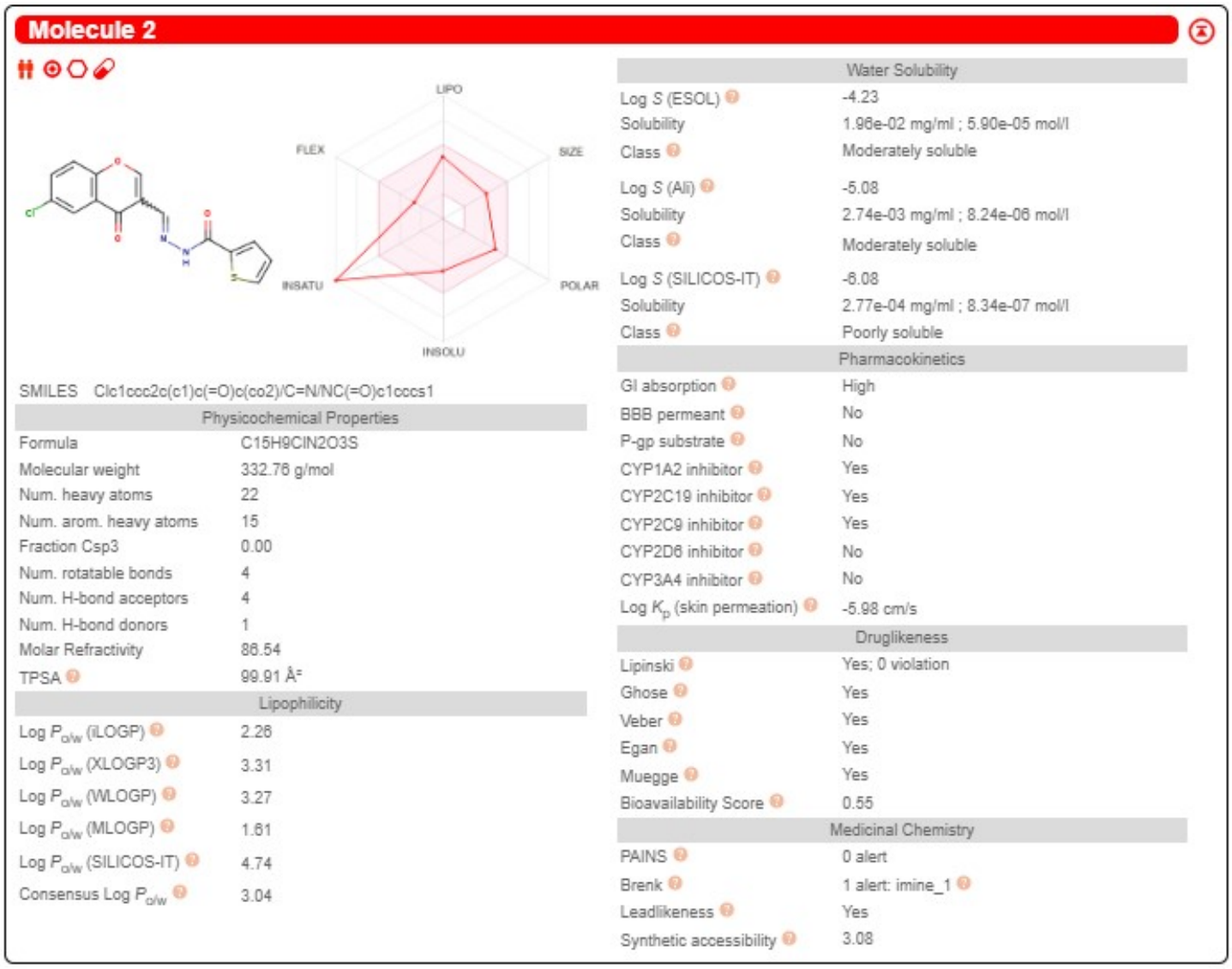


Fig. 9. ADME prediction of compound **11b**.

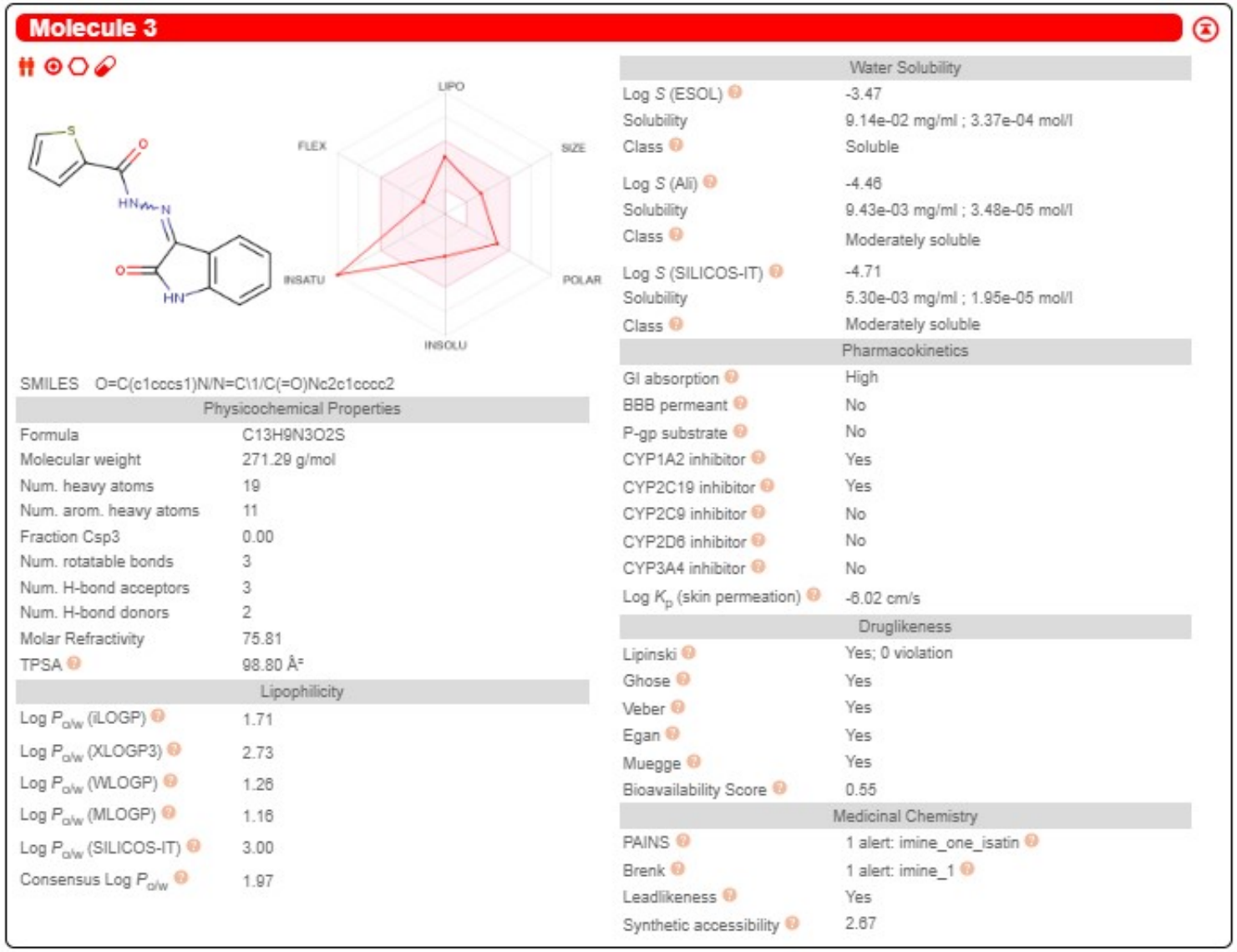


Fig. 10. ADME prediction of compound **15**.

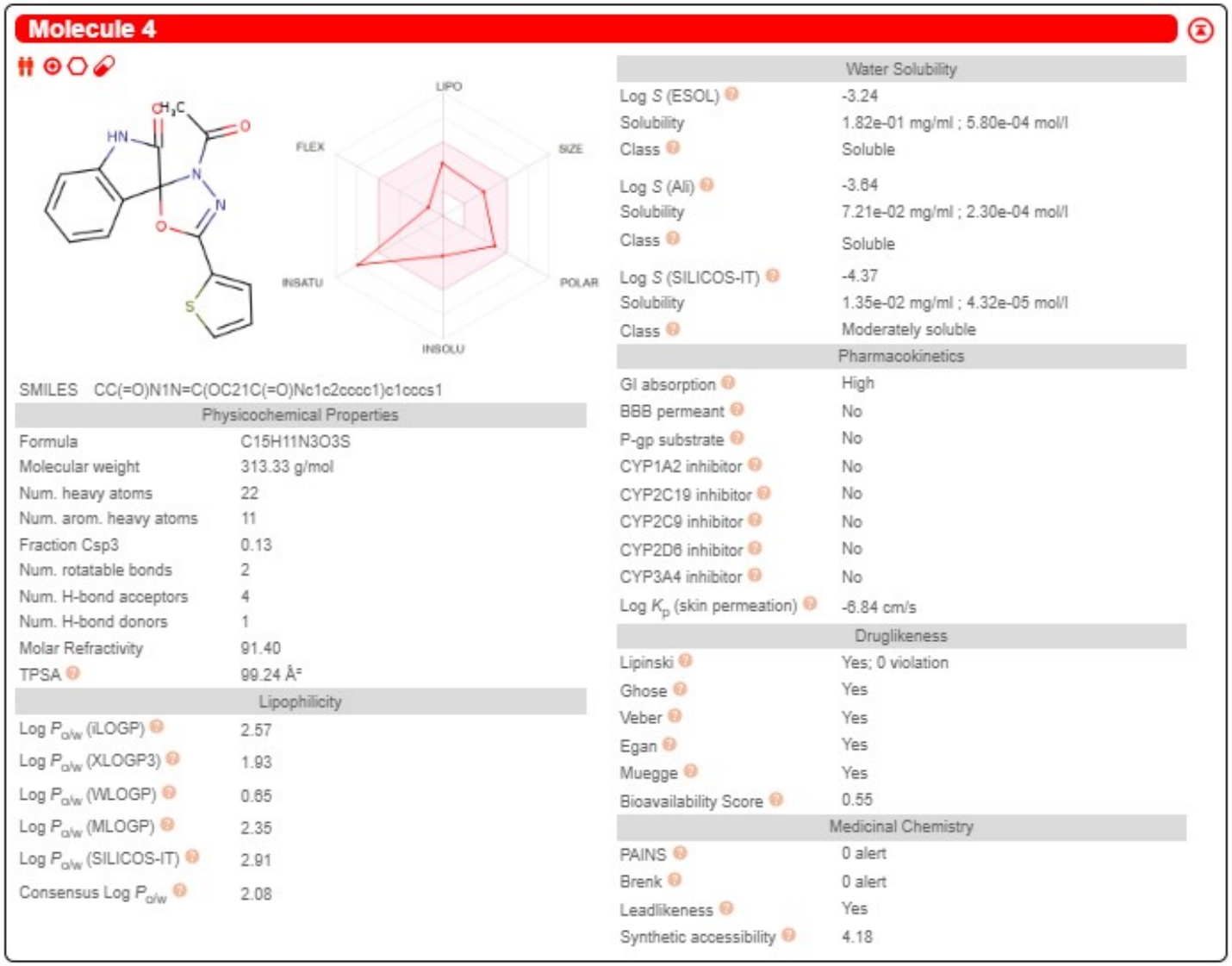


Fig. 11. ADME prediction of compound **16**.

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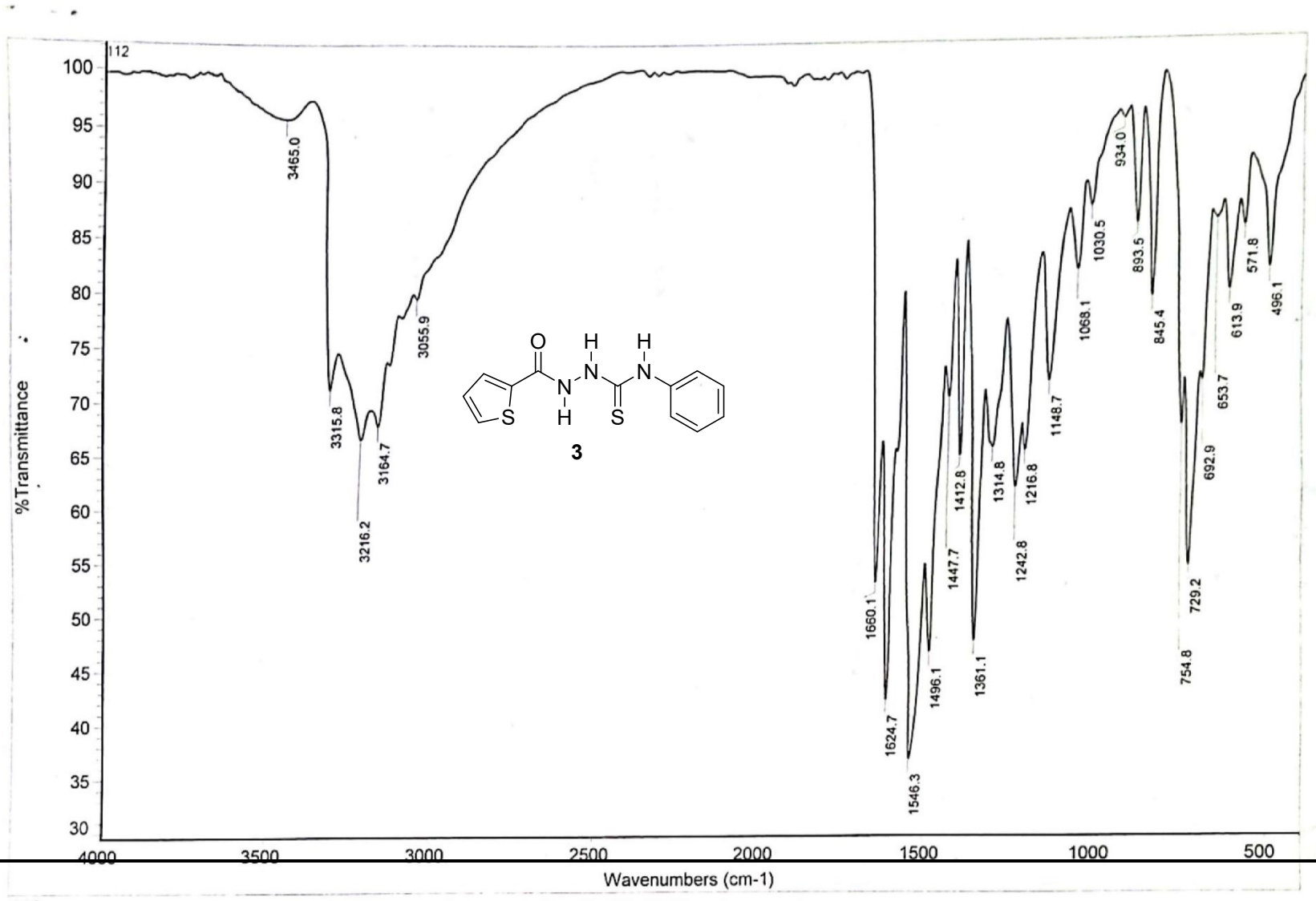
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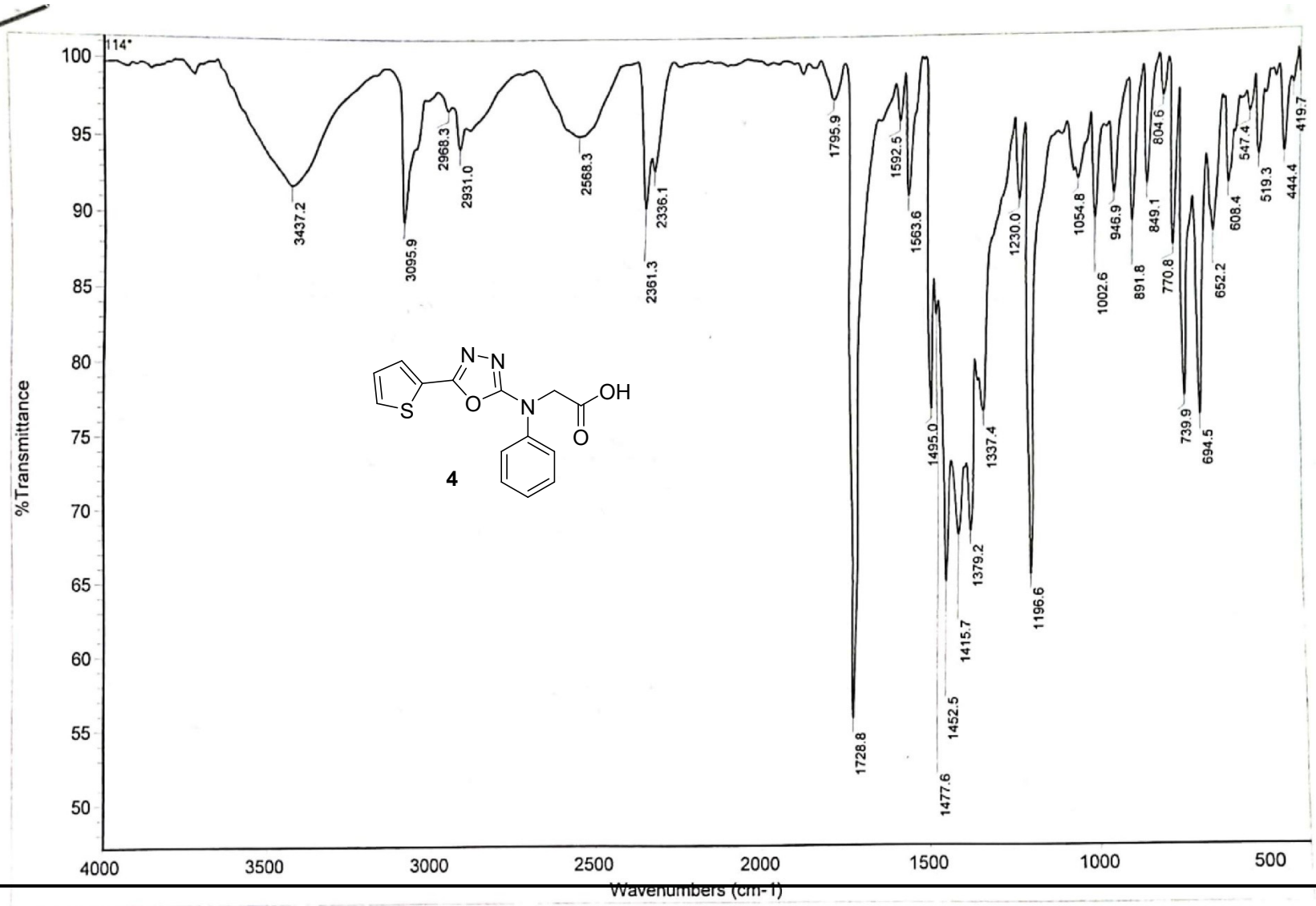
3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4

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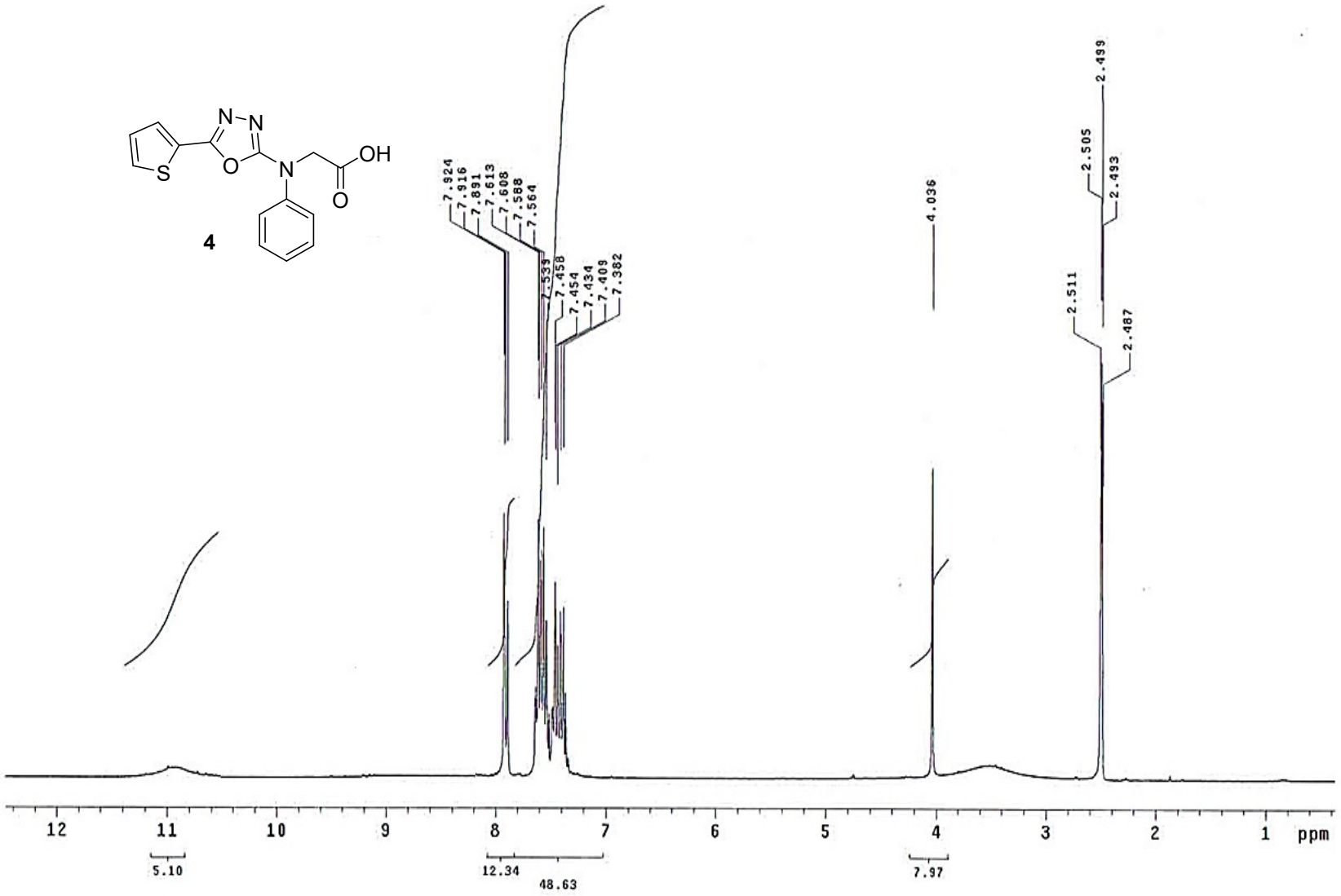
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7.382
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2.493
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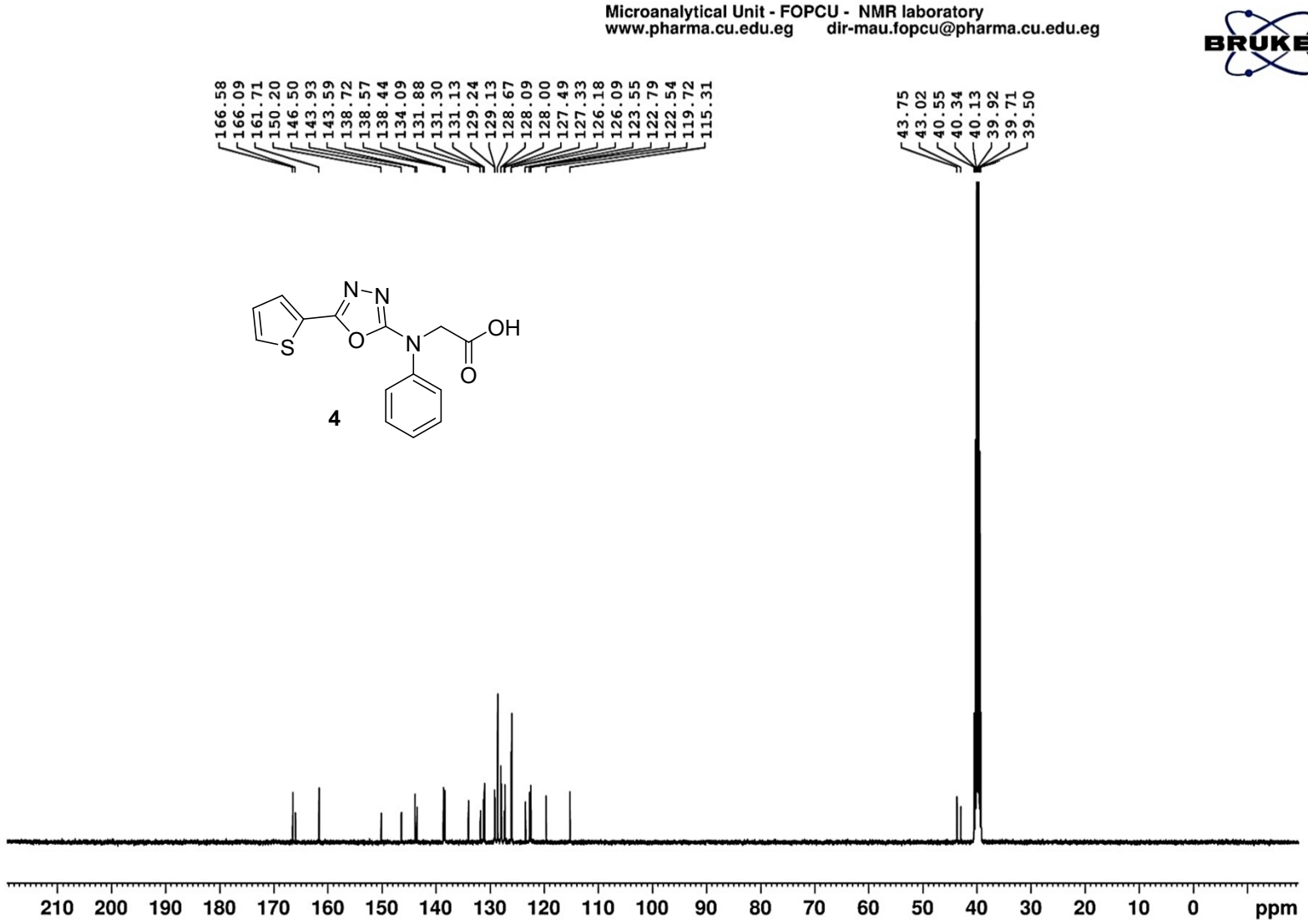
Microanalytical Unit - FOPCU - NMR laboratory
www.pharma.cu.edu.eg dir-mau.fopcu@pharma.cu.edu.eg
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122.79
122.54
119.72
115.31
43.75
43.02
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40.13
39.92
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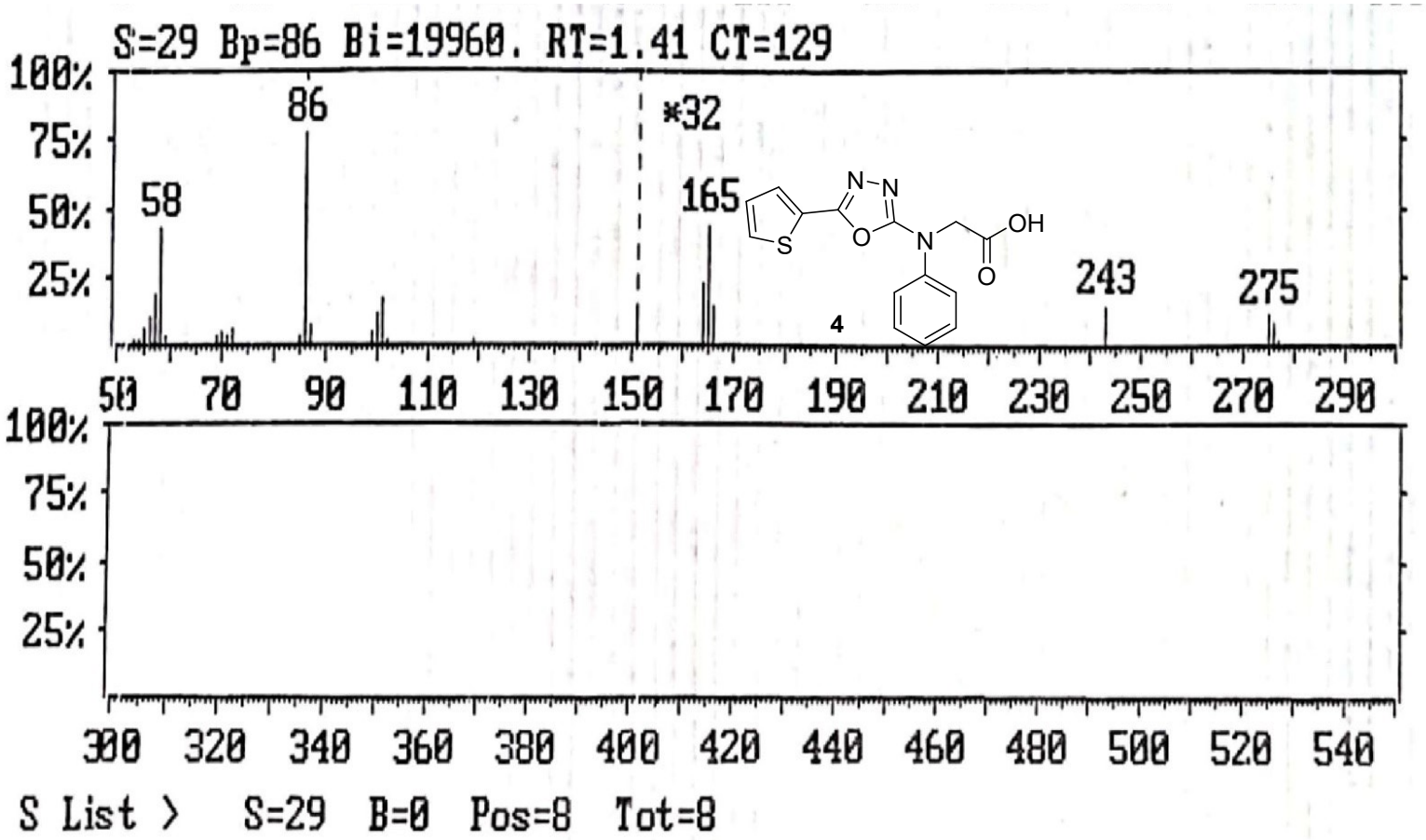
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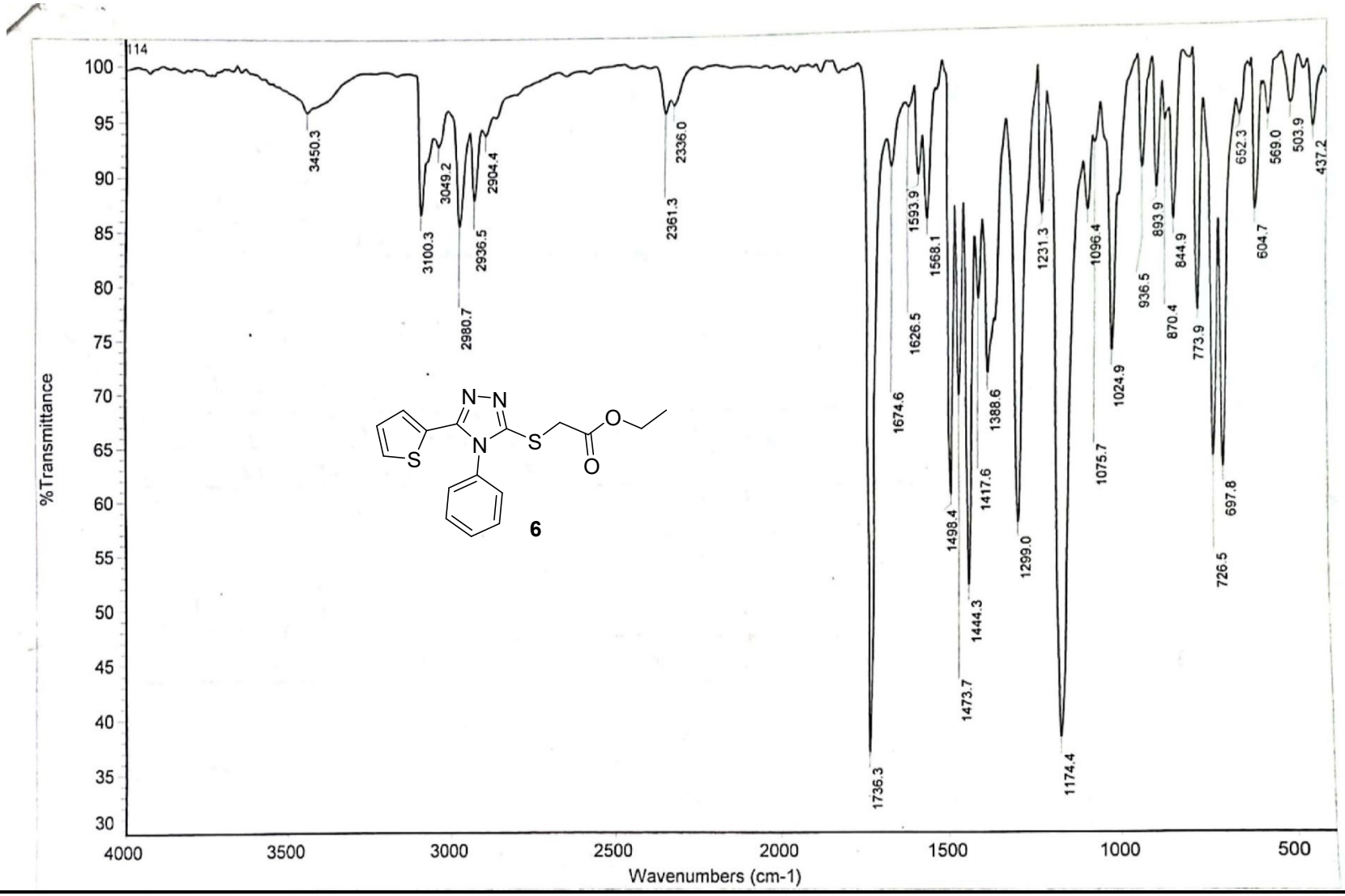
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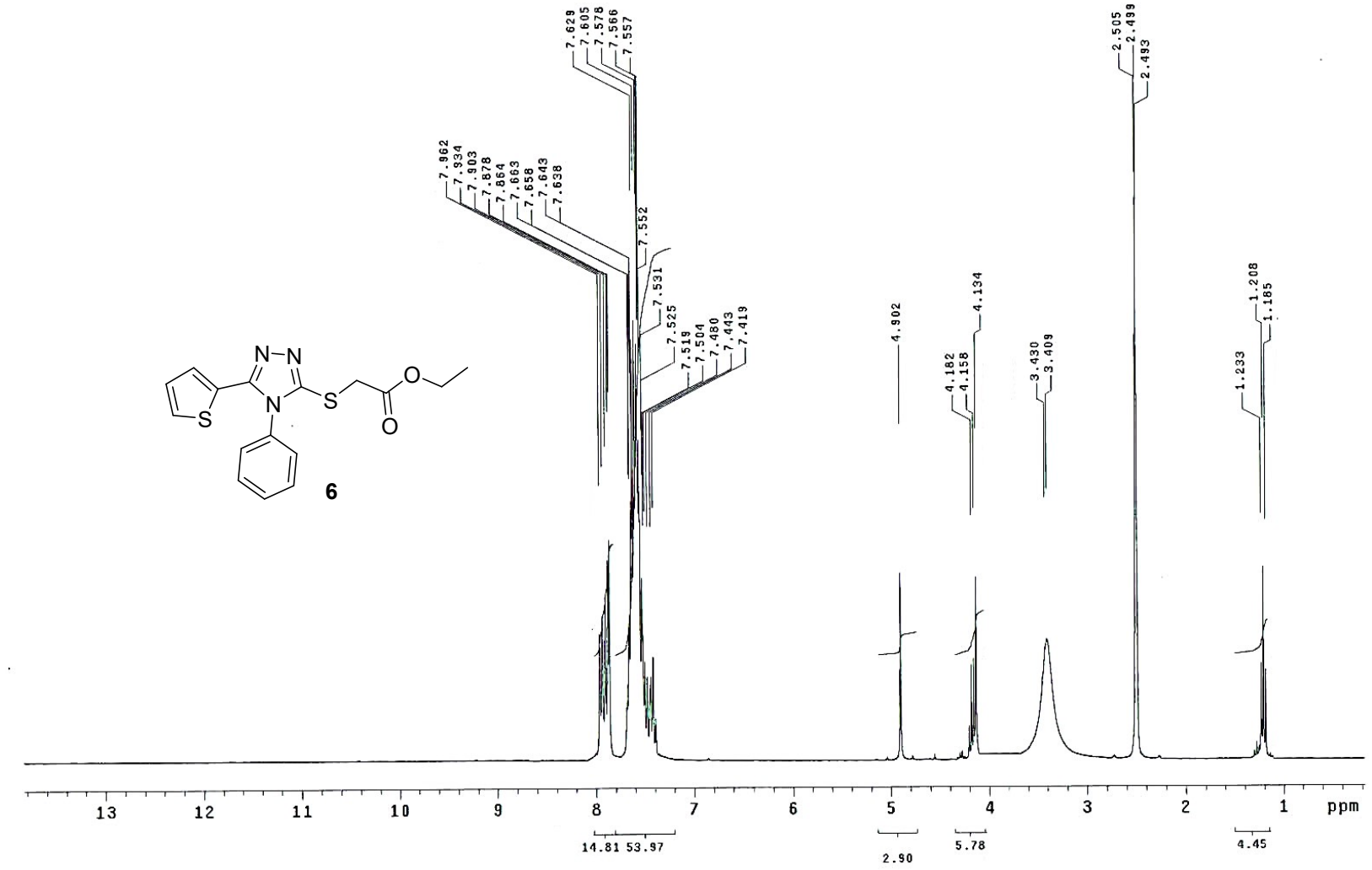
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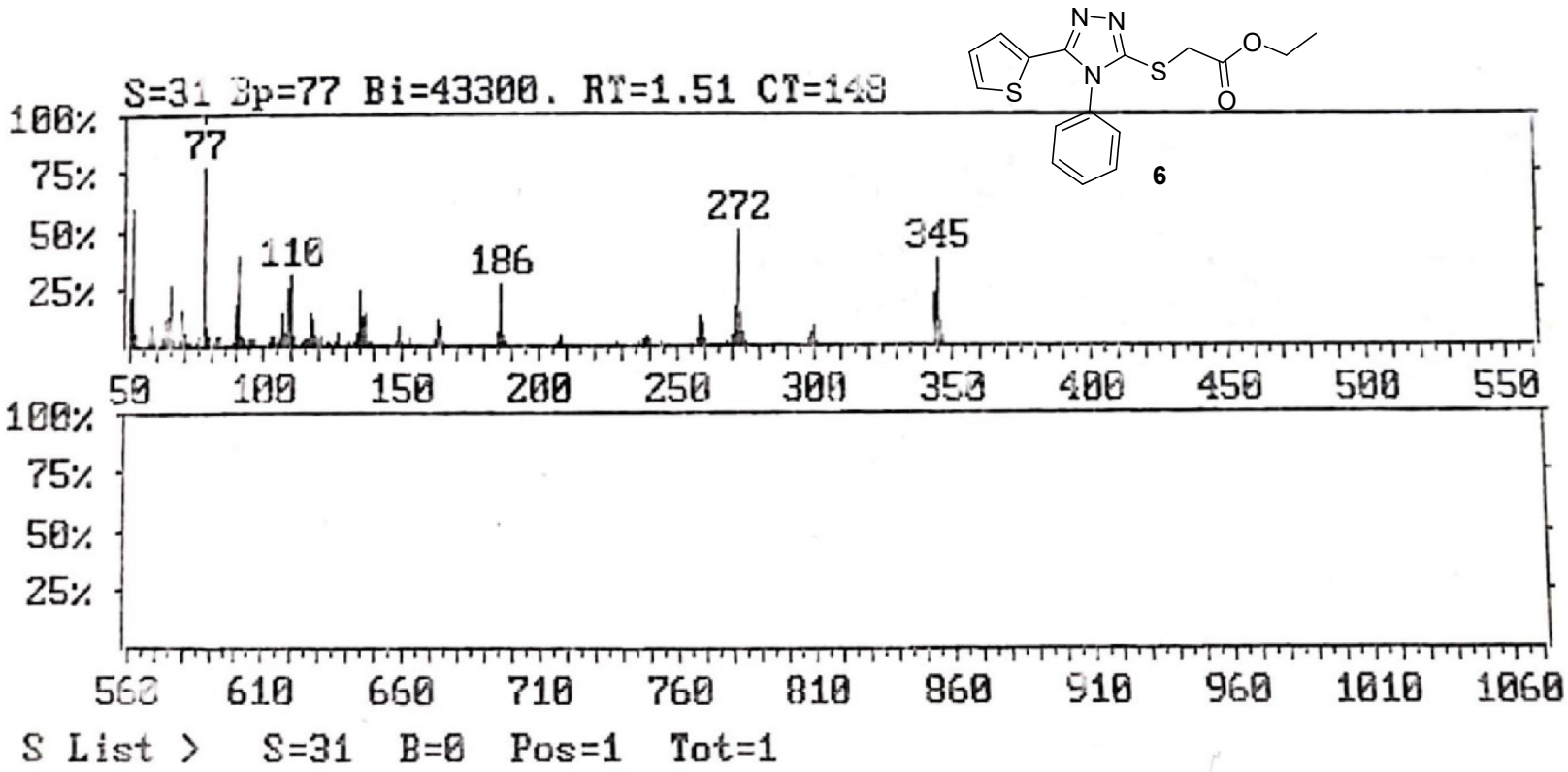
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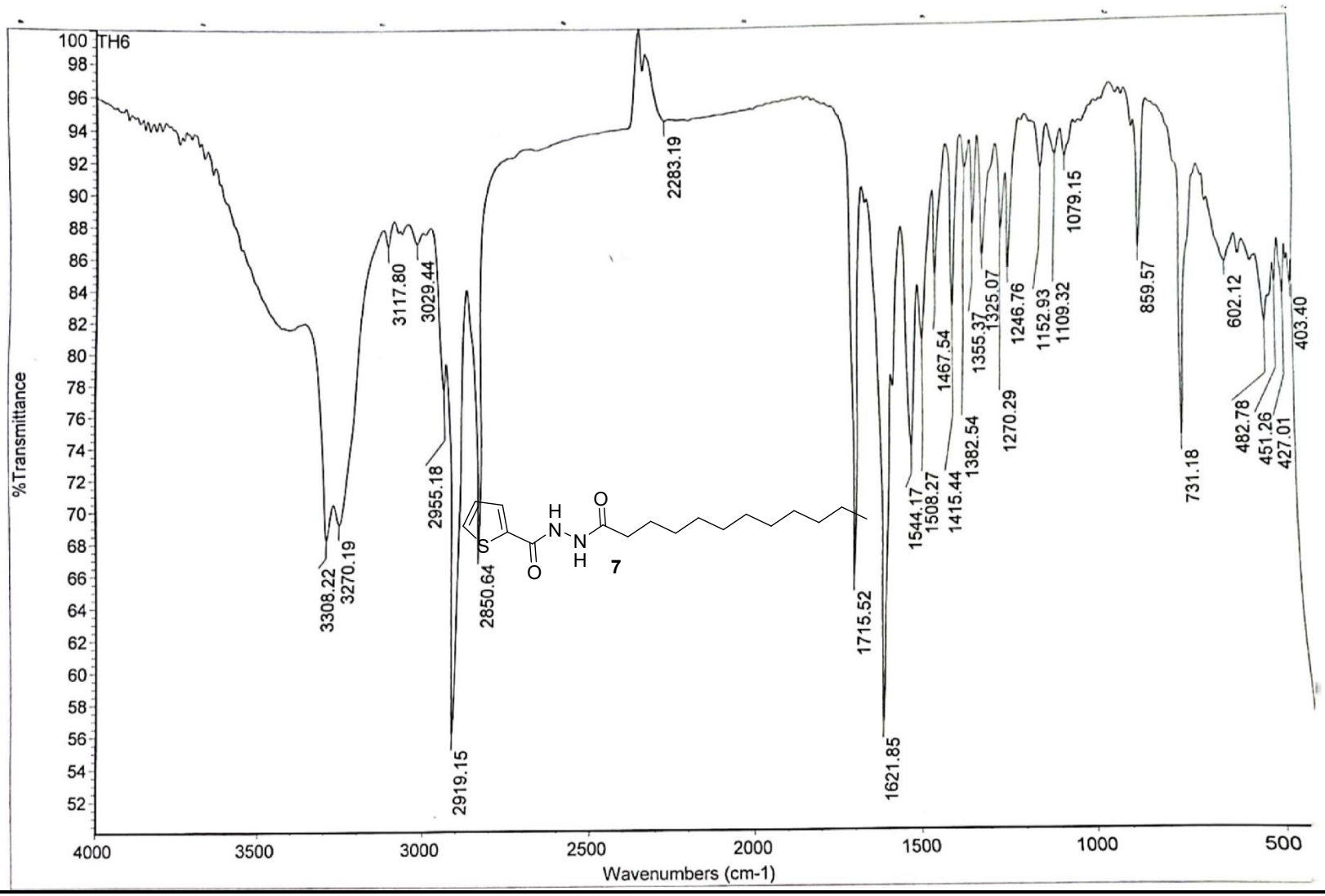
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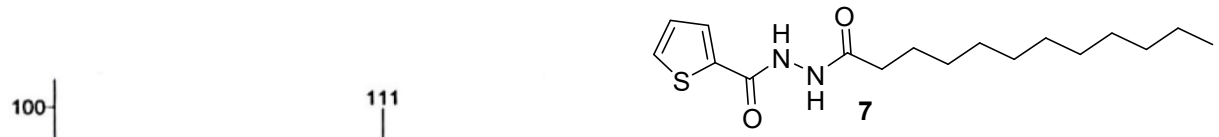
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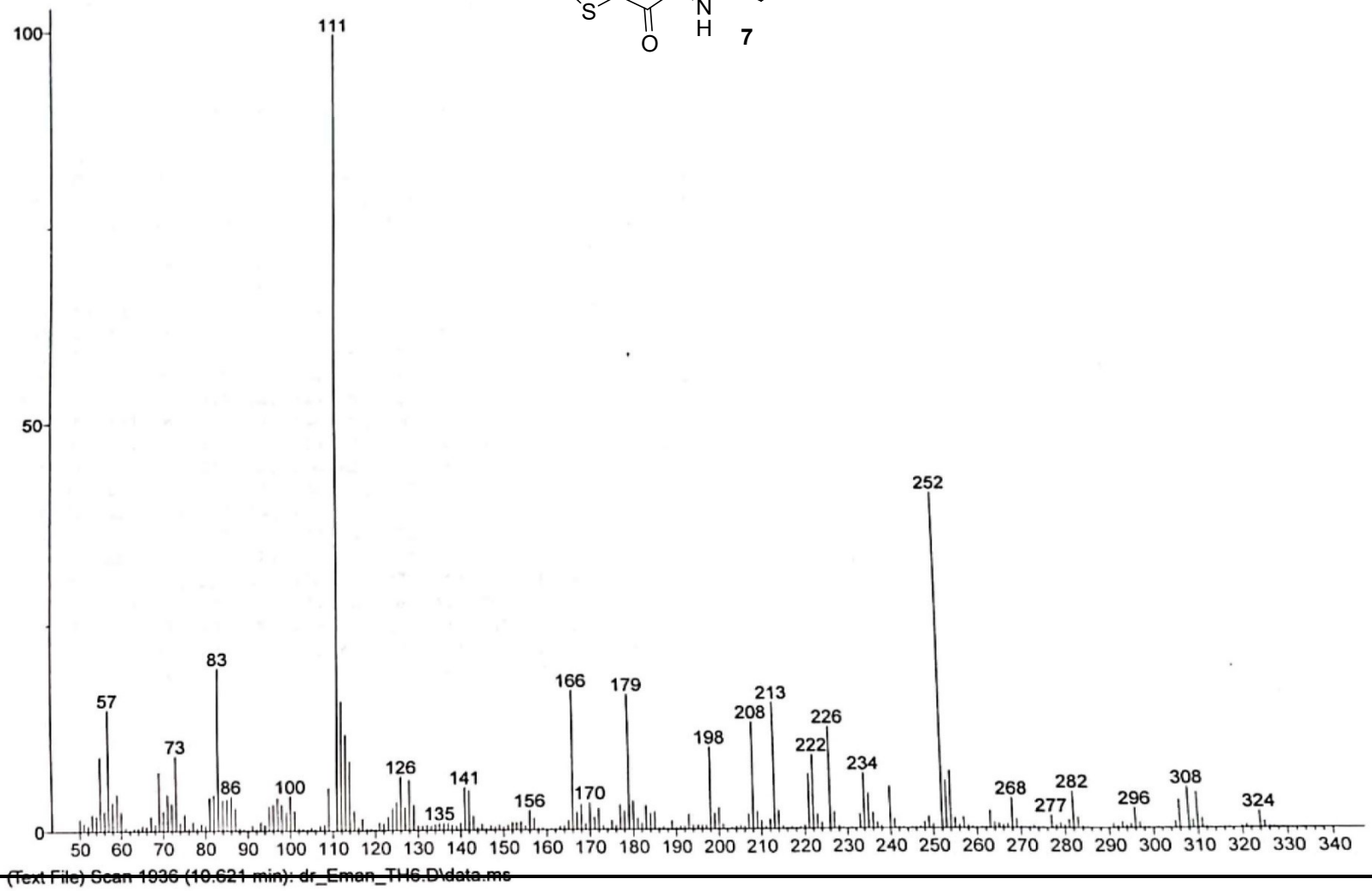
N
H
O
O

7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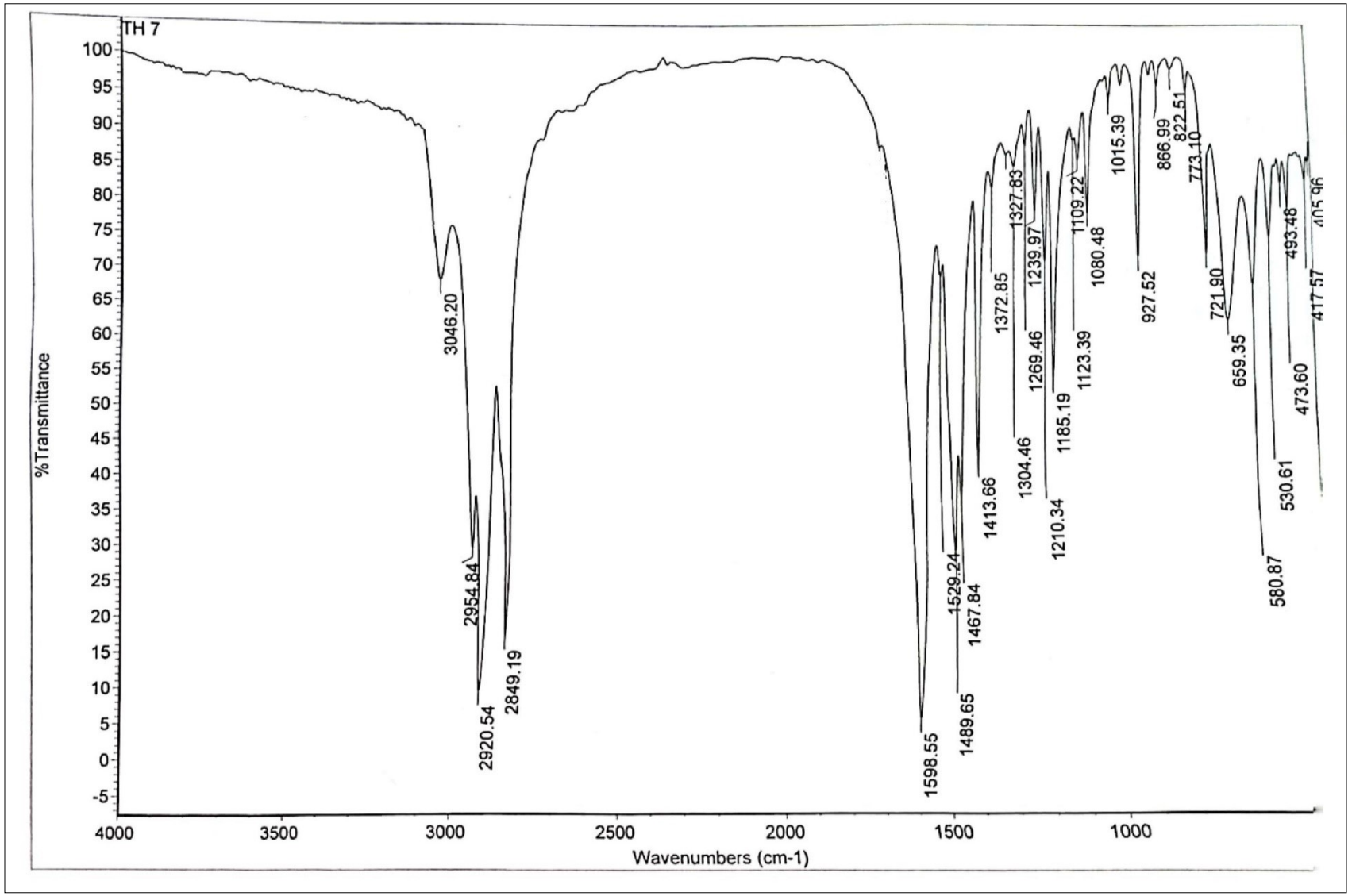
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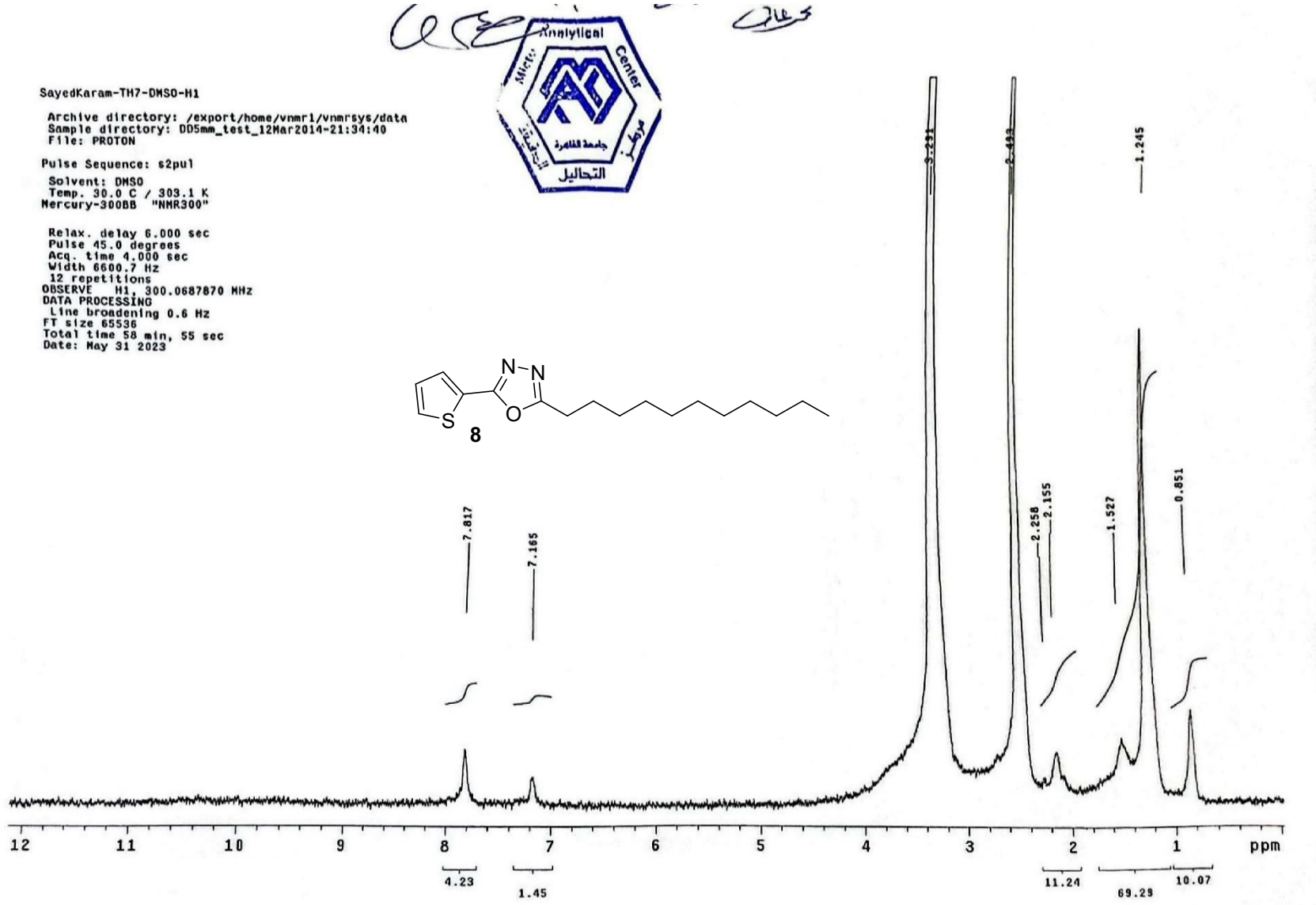
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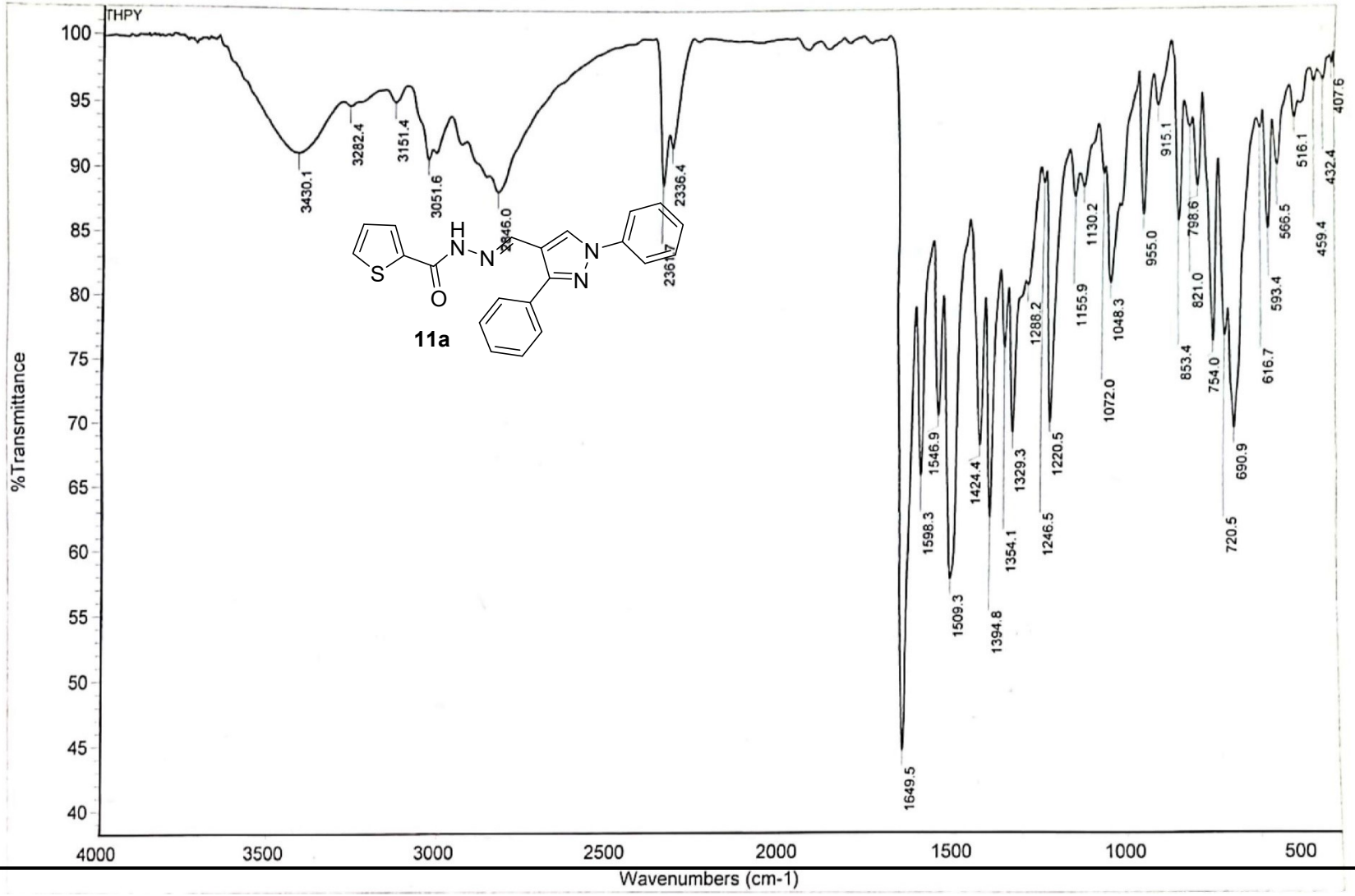
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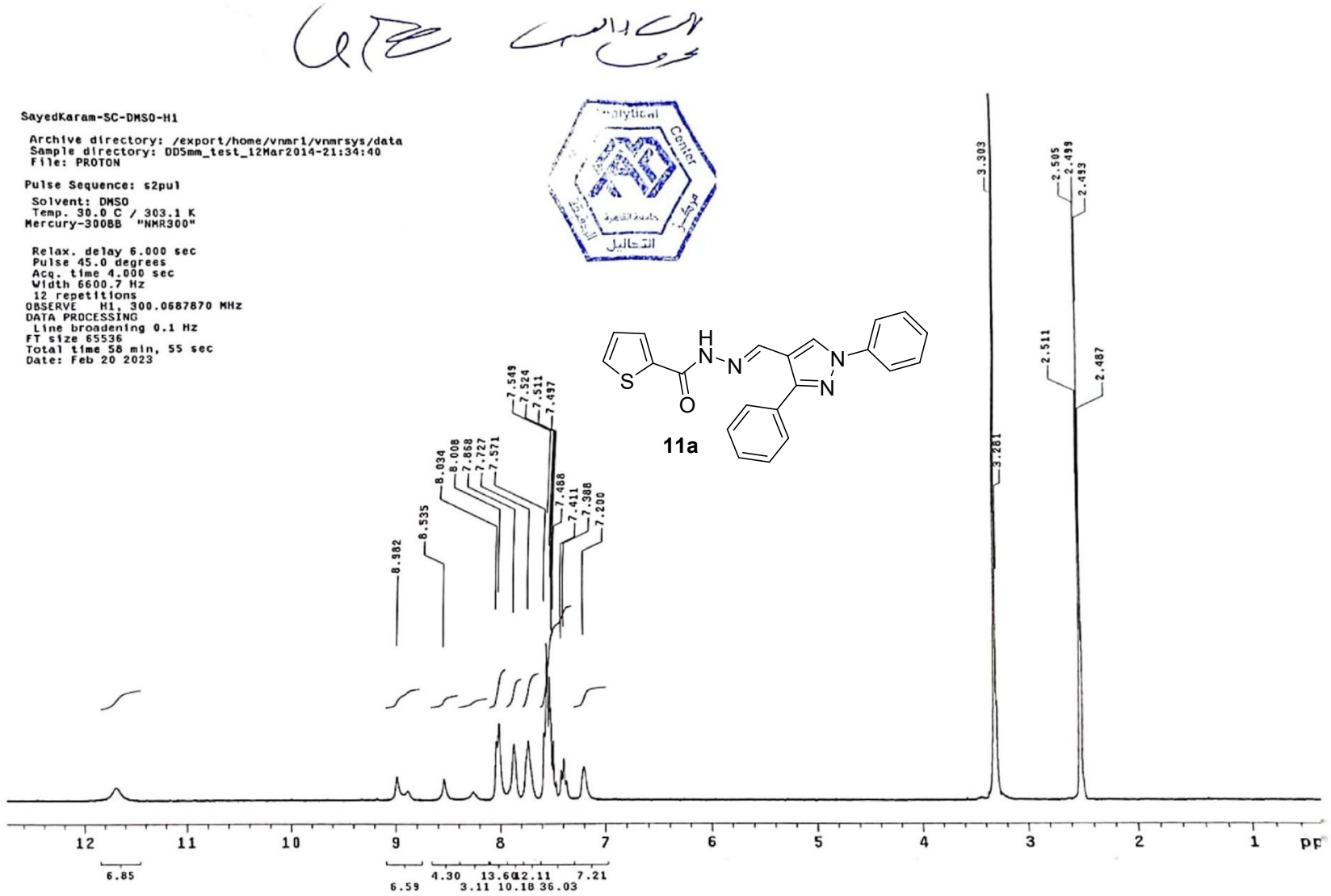
11a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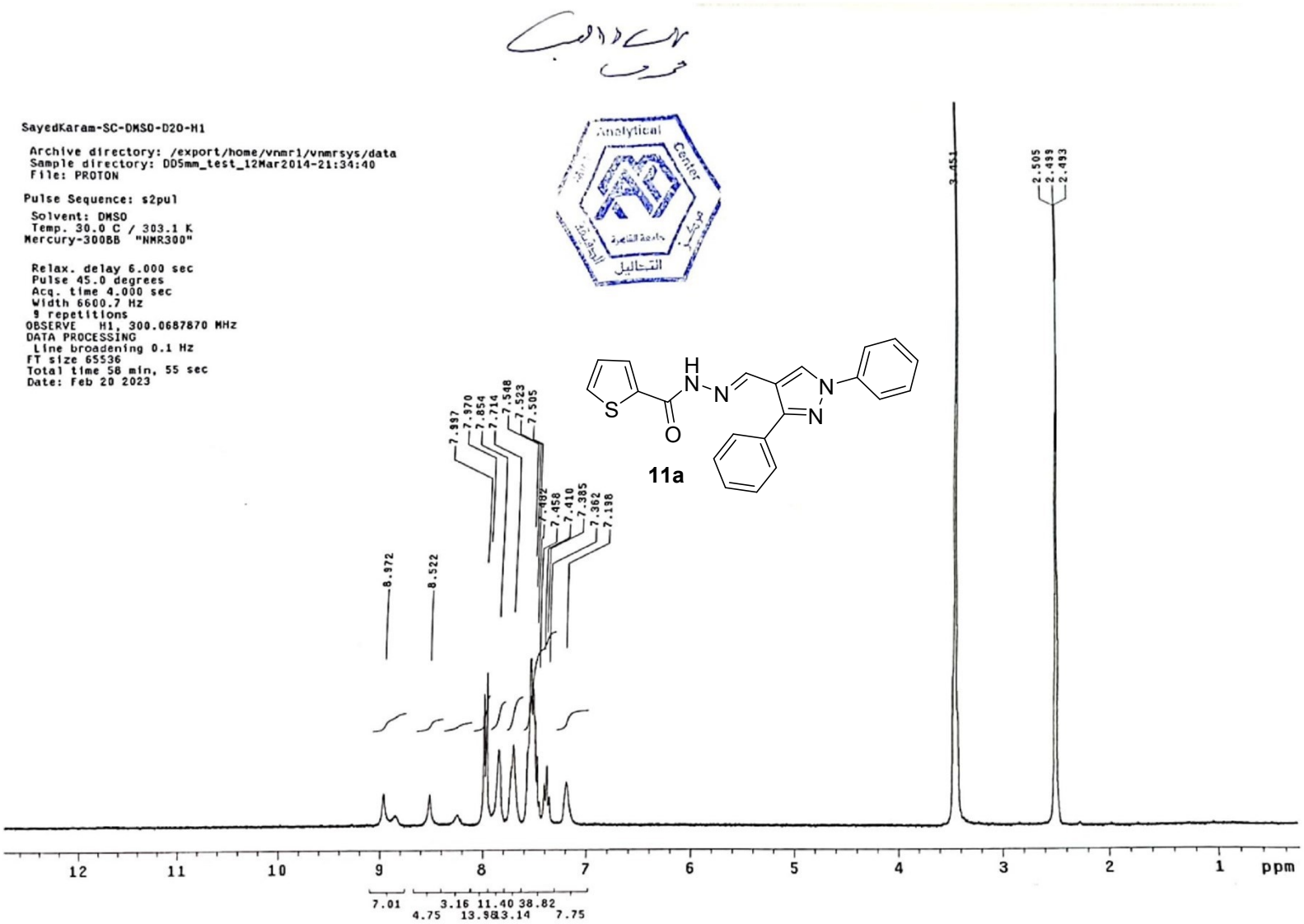
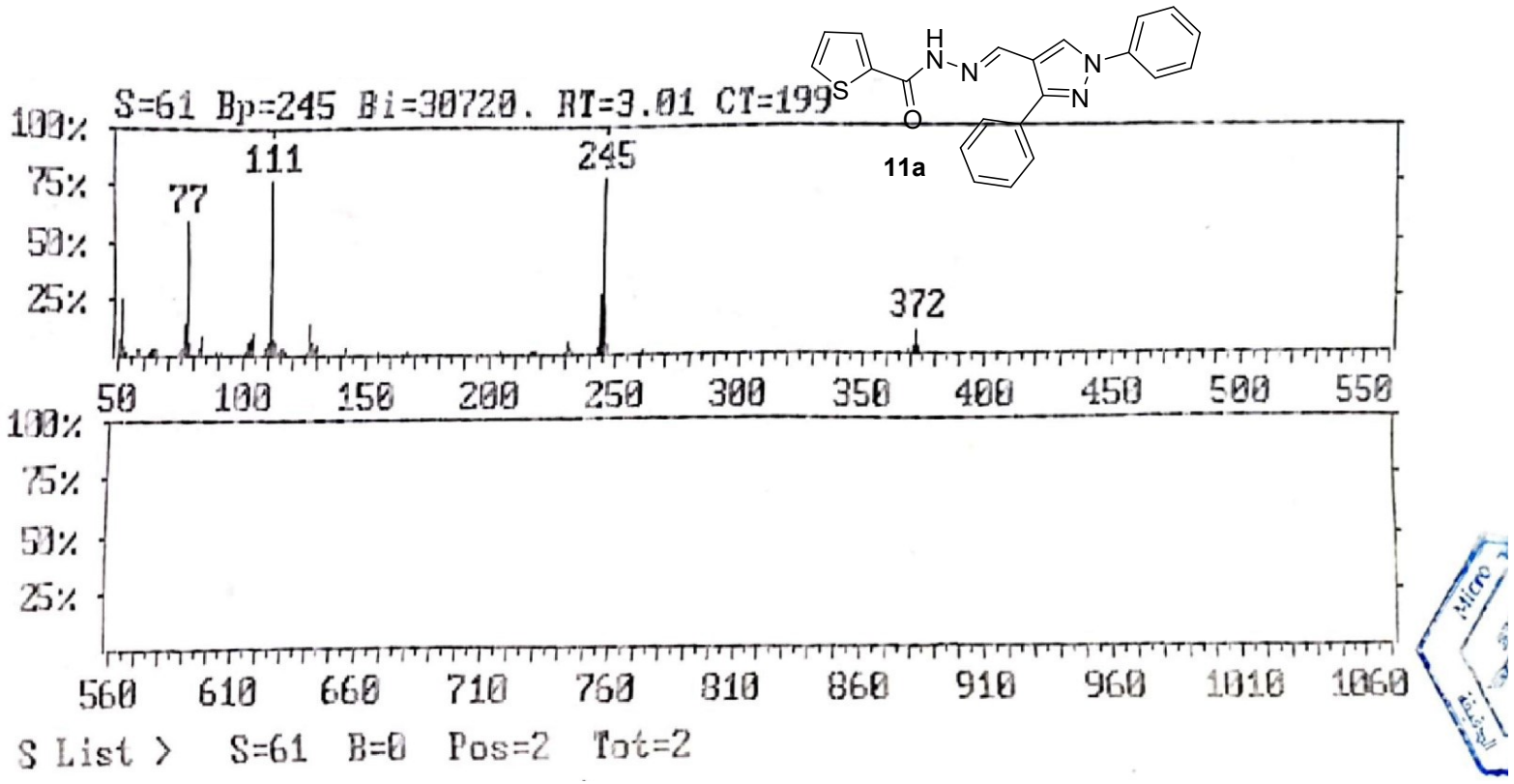
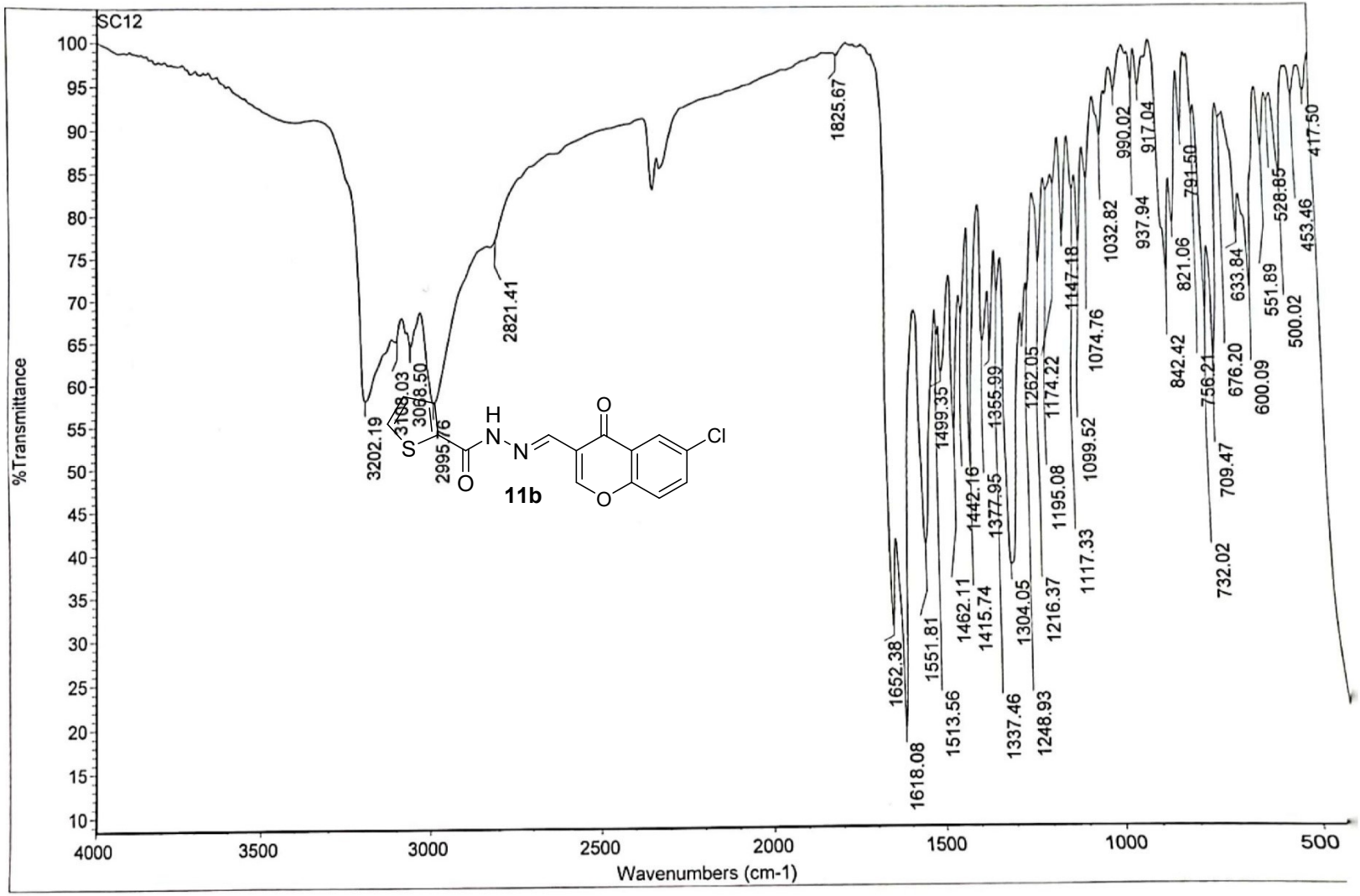
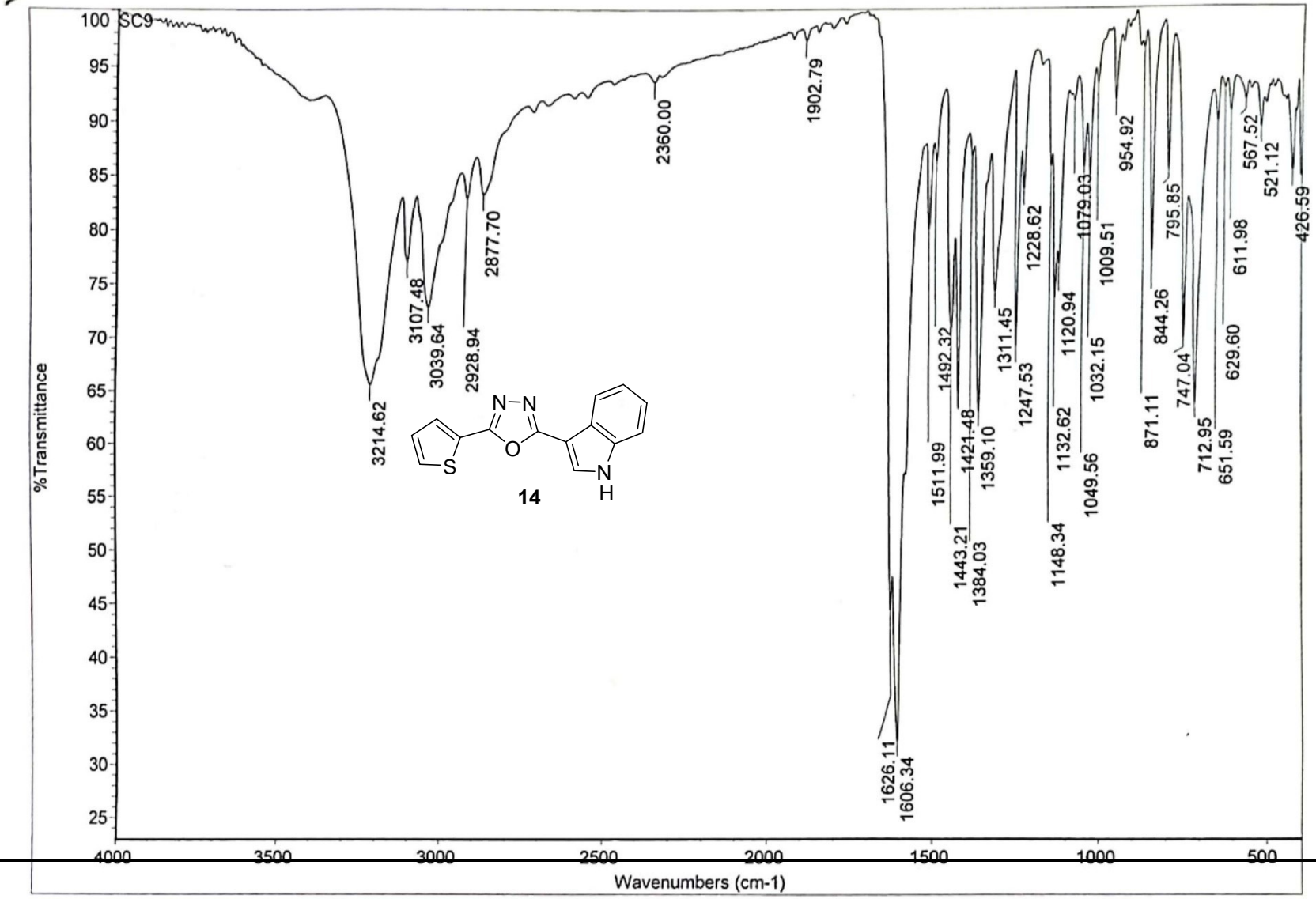
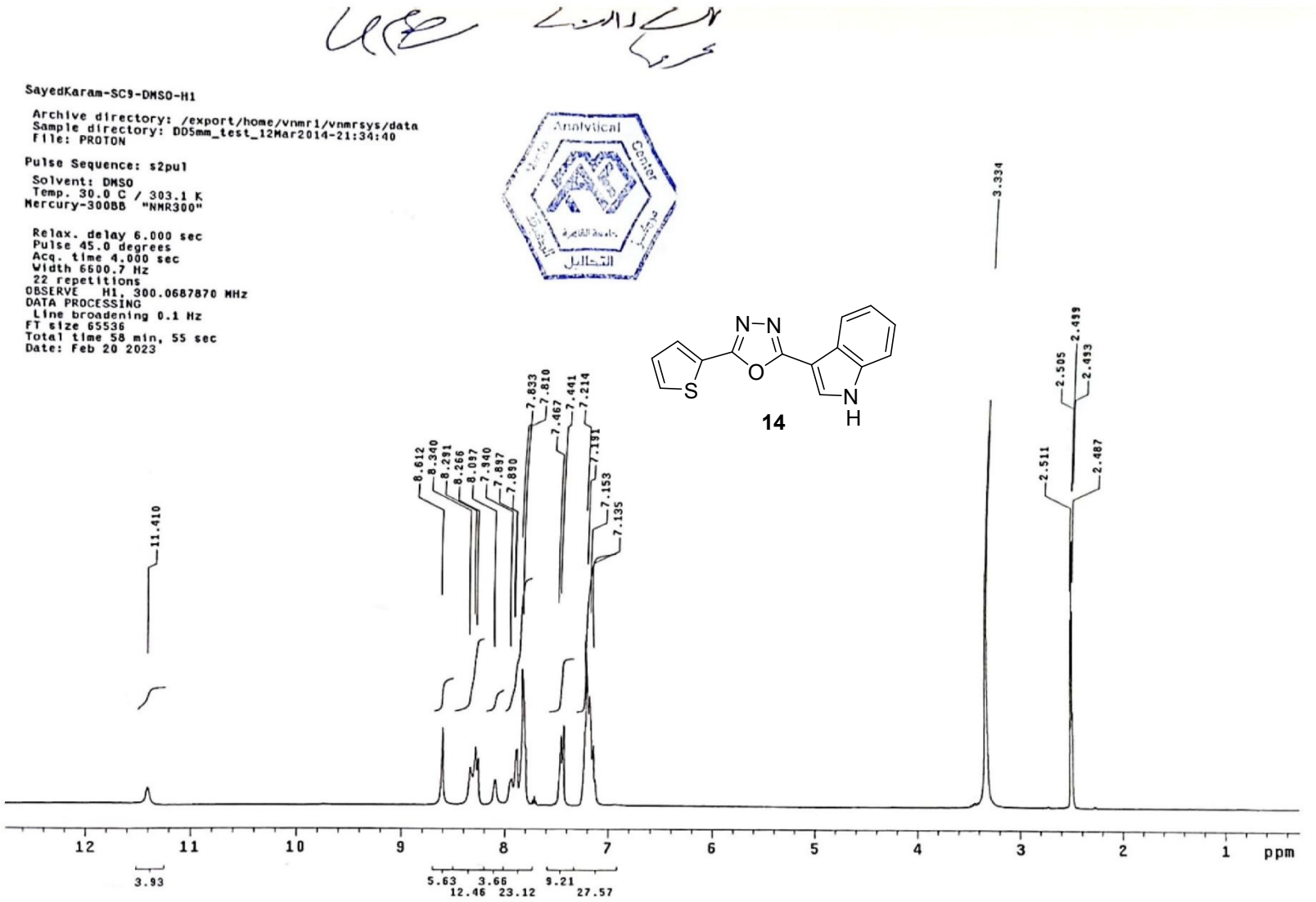
Temp. 30.0 C / 303.1 K
Mercury-300BB "NMR300"
Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 4.000 sec
Width 6600.7 Hz
12 repetitions
OBSERVE H1, 300.0687870 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 58 min, 55 sec
Date: Feb 20 2023
11a
8.982
8.535
8.034
8.008
7.858
7.727
7.571
7.549
7.524
7.511
7.497
7.488
7.411
7.388
7.200
3.303
3.261
2.505
2.499
2.493
2.511
2.487
12
11
10
9
8
7
6
5
4
3
2
1
ppm
6.85
6.59
4.30
3.11
13.60
10.18
12.11
36.03
7.21

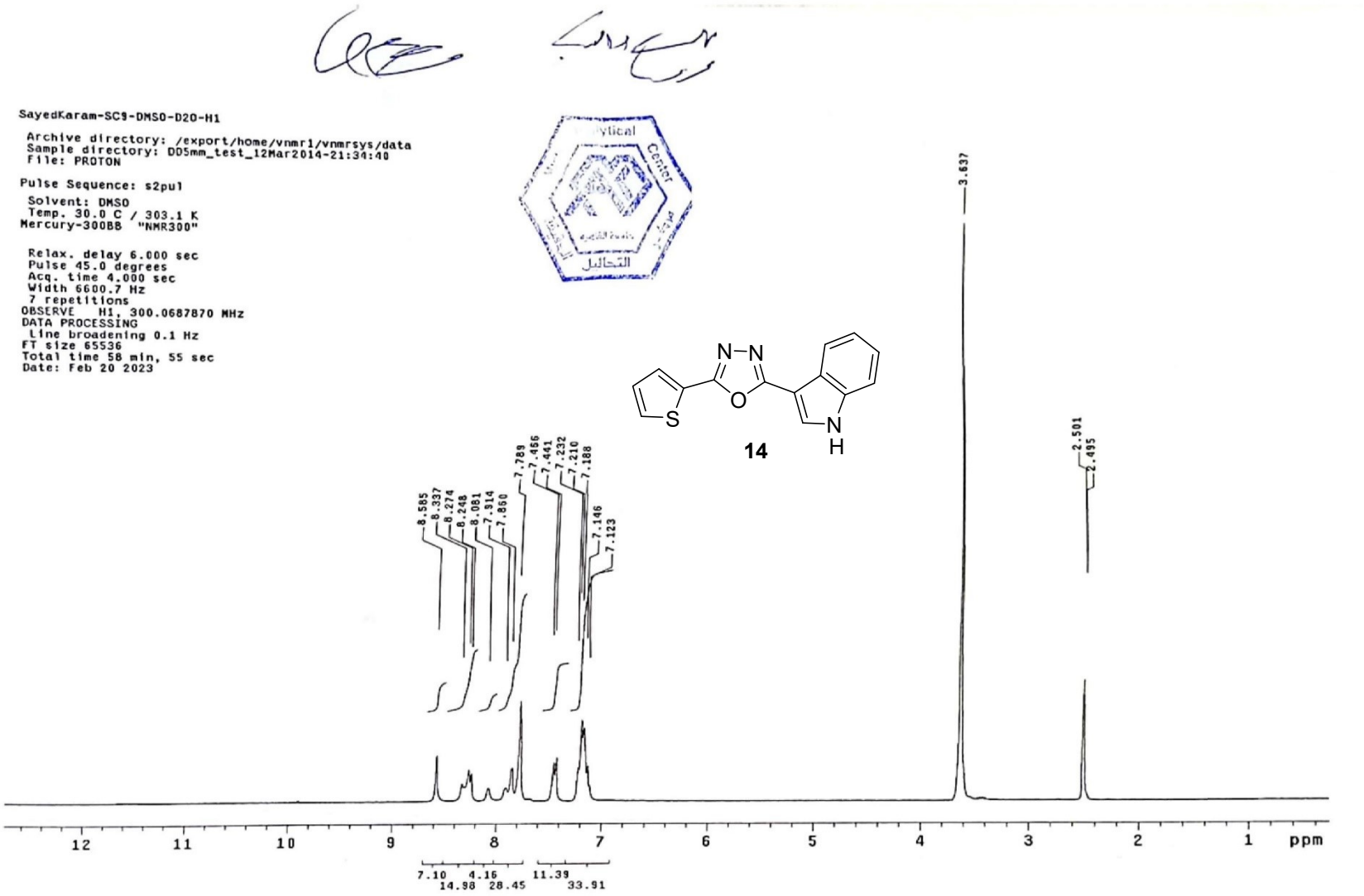

SayedKaram-SC-DMSO-D2O-H1
Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 30.0 C / 303.1 K
Mercury-300BB "NMR300"
Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 4.000 sec
Width 6600.7 Hz
9 repetitions
OBSERVE H1, 300.0687870 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 58 min, 55 sec
Date: Feb 20 2023
Analytical Center
11a
8.972
8.522
7.997
7.970
7.854
7.714
7.548
7.523
7.505
7.482
7.458
7.410
7.385
7.362
7.198
3.451
2.505
2.499
2.493
12
11
10
9
8
7
6
5
4
3
2
1
ppm
7.01
4.75
3.16
13.98
11.40
3.14
38.82
7.75

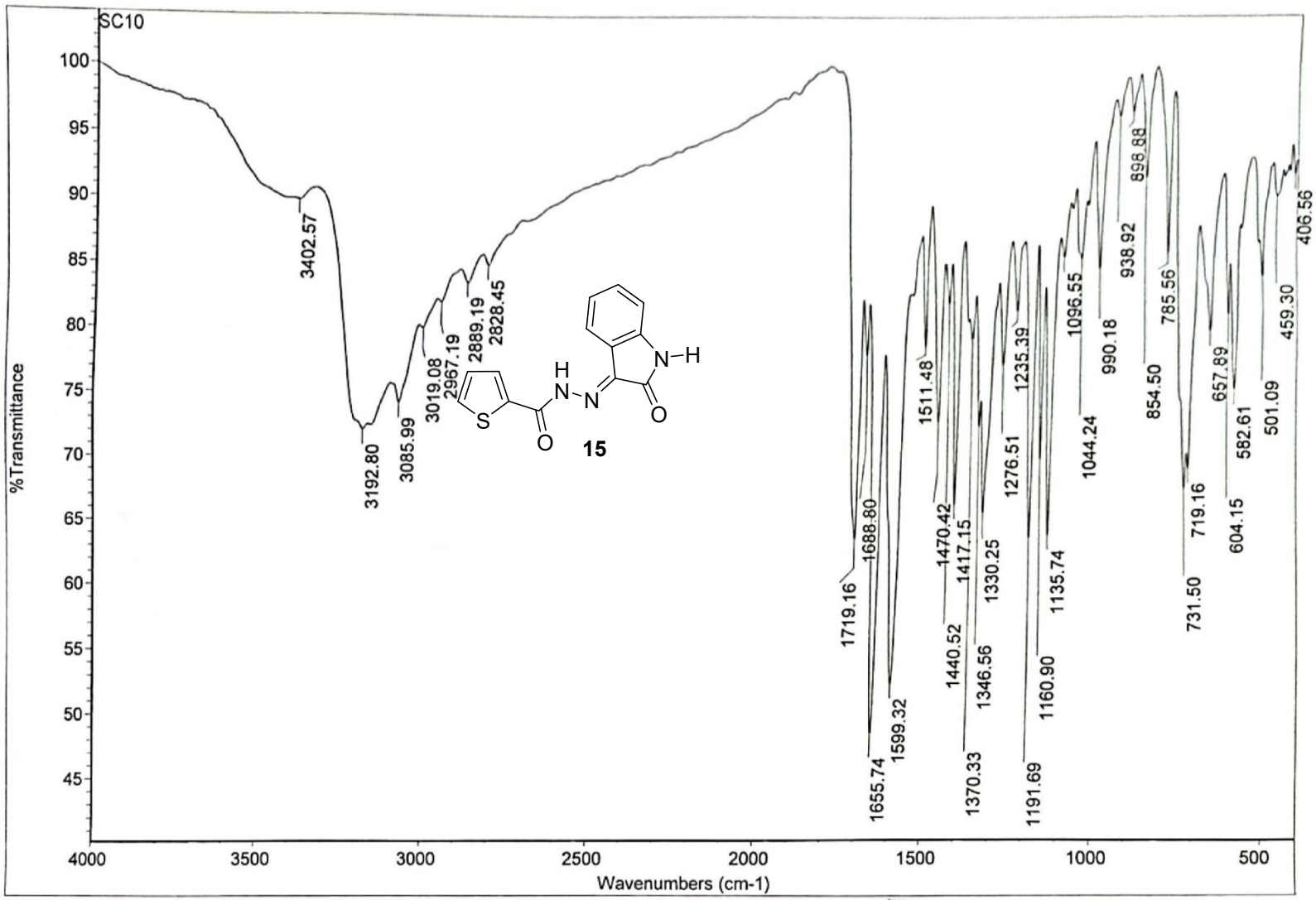

S=61 Bp=245 Bi=30720. RT=3.01 CT=199
100%
75%
50%
25%
111
77
245
372
50 100 150 200 250 300 350 400 450 500 550
560 610 660 710 760 810 860 910 960 1010 1060
S List > S=61 B=0 Pos=2 Tot=2
11a

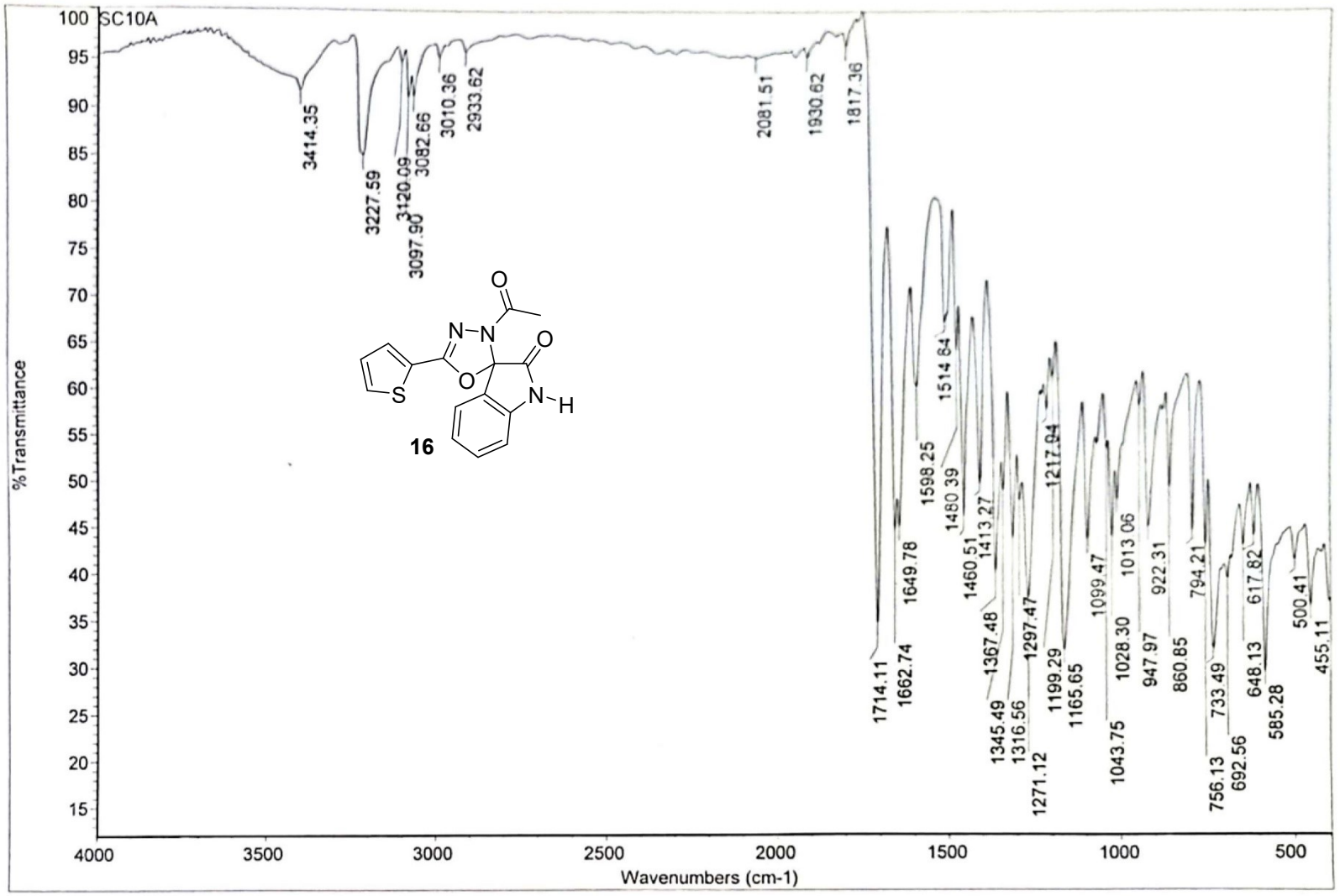

SC12
%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
3202.19
3108.03
3068.50
2995.76
2821.41
1825.67
1652.38
1618.08
1551.81
1513.56
1499.35
1462.11
1442.16
1415.74
1377.95
1355.99
1337.46
1304.05
1262.05
1248.93
1216.37
1195.08
1174.22
1147.18
1117.33
1099.52
1074.76
1032.82
990.02
937.94
917.04
842.42
821.06
791.50
756.21
732.02
709.47
676.20
633.84
600.09
551.89
528.85
500.02
453.46
417.50
H
N
N
O
O
S
O
Cl
11b


SC9
%Transmittance
Wavenumbers (cm-1)
3214.62
3107.48
3039.64
2928.94
2877.70
2360.00
1902.79
1626.11
1606.34
1511.99
1492.32
1443.21
1421.48
1384.03
1359.10
1311.45
1247.53
1228.62
1148.34
1132.62
1120.94
1079.03
1049.56
1032.15
1009.51
954.92
871.11
844.26
795.85
747.04
712.95
651.59
629.60
611.98
567.52
521.12
426.59
N
N
O
S
N
H
14


SayedKaram-SC9-DMSO-H1
Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
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
22 repetitions
OBSERVE H1, 300.0687870 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 58 min, 55 sec
Date: Feb 20 2023
Analytical Center
N
N
O
S
N
H
14
11.410
8.612
8.340
8.291
8.266
8.057
7.940
7.897
7.850
7.833
7.810
7.467
7.441
7.214
7.191
7.153
7.135
3.334
2.511
2.505
2.499
2.493
2.487
12
11
10
9
8
7
6
5
4
3
2
1
ppm
3.93
5.63
3.66
12.46
23.12
9.21
27.57


SayedKaram-SC9-DMSO-D2O-H1
Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
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
7 repetitions
OBSERVE H1, 300.0687870 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 58 min, 55 sec
Date: Feb 20 2023
N–N
O
S
N
H
14
8.585
8.337
8.274
8.248
8.081
7.914
7.850
7.789
7.466
7.441
7.232
7.210
7.188
7.146
7.123
3.637
2.501
2.495
12
11
10
9
8
7
6
5
4
3
2
1
ppm
7.10
14.98
4.16
28.45
11.39
33.91


SC10
%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
100
95
90
85
80
75
70
65
60
55
50
45
3402.57
3192.80
3085.99
3019.08
2967.19
2889.19
2828.45
1719.16
1688.80
1655.74
1599.32
1511.48
1470.42
1440.52
1417.15
1370.33
1346.56
1330.25
1276.51
1235.39
1191.69
1160.90
1135.74
1096.55
1044.24
990.18
938.92
898.88
854.50
785.56
731.50
719.16
657.89
604.15
582.61
501.09
459.30
406.56
N-H
H
N-N
S
O
O
15


SC10A
%Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
500
3414.35
3227.59
3120.09
3097.90
3082.66
3010.36
2933.62
2081.51
1930.62
1817.36
1714.11
1662.74
1649.78
1598.25
1514.84
1480.39
1460.51
1413.27
1367.48
1345.49
1316.56
1297.47
1271.12
1217.84
1199.29
1165.65
1099.47
1043.75
1028.30
1013.06
947.97
922.31
860.85
794.21
756.13
733.49
692.56
648.13
617.82
585.28
500.41
455.11
O
N
N
O
O
S
N
H

16

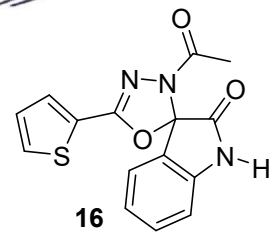
SayedKaram-SC10A-DMSO-H1

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

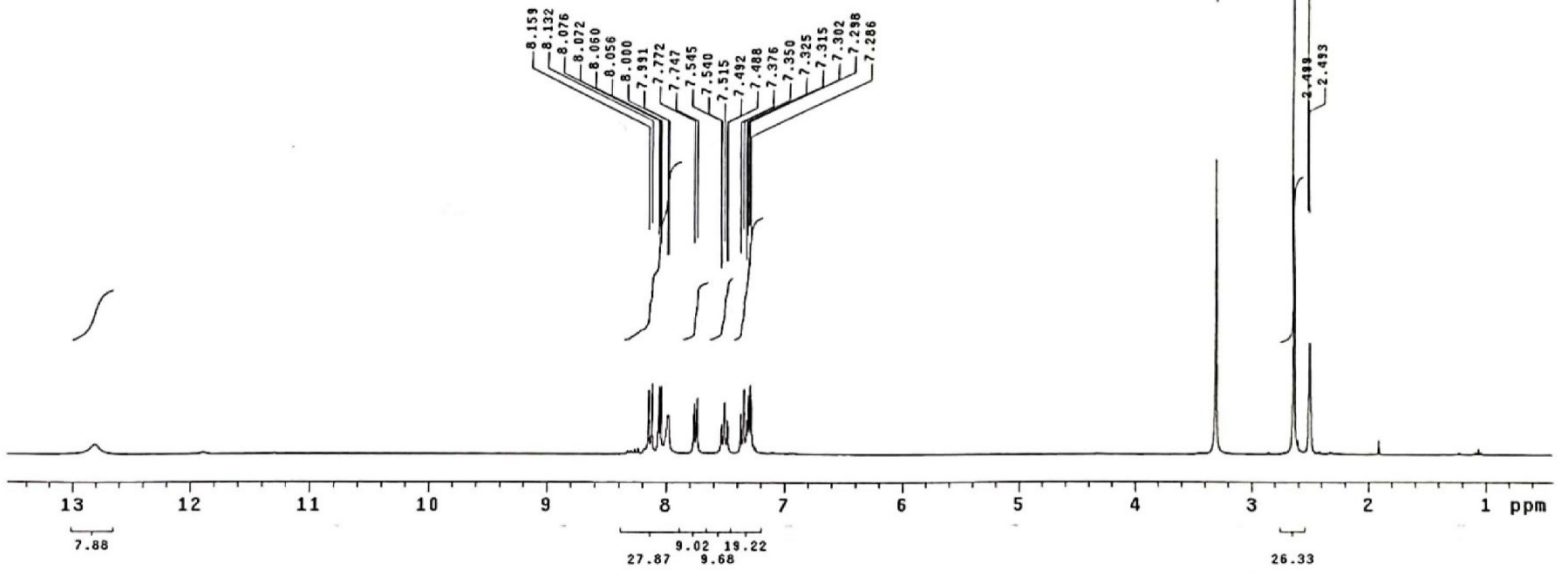
Pulse Sequence: s2pul

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
11 repetitions
OBSERVE H1, 300.0687870 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 58 min, 55 sec
Date: Feb 20 2023



16



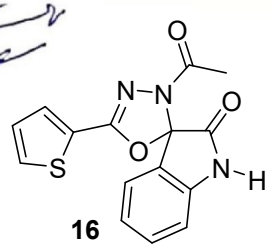
SayedKaram-SC10A-DMSO-D2O-H1

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

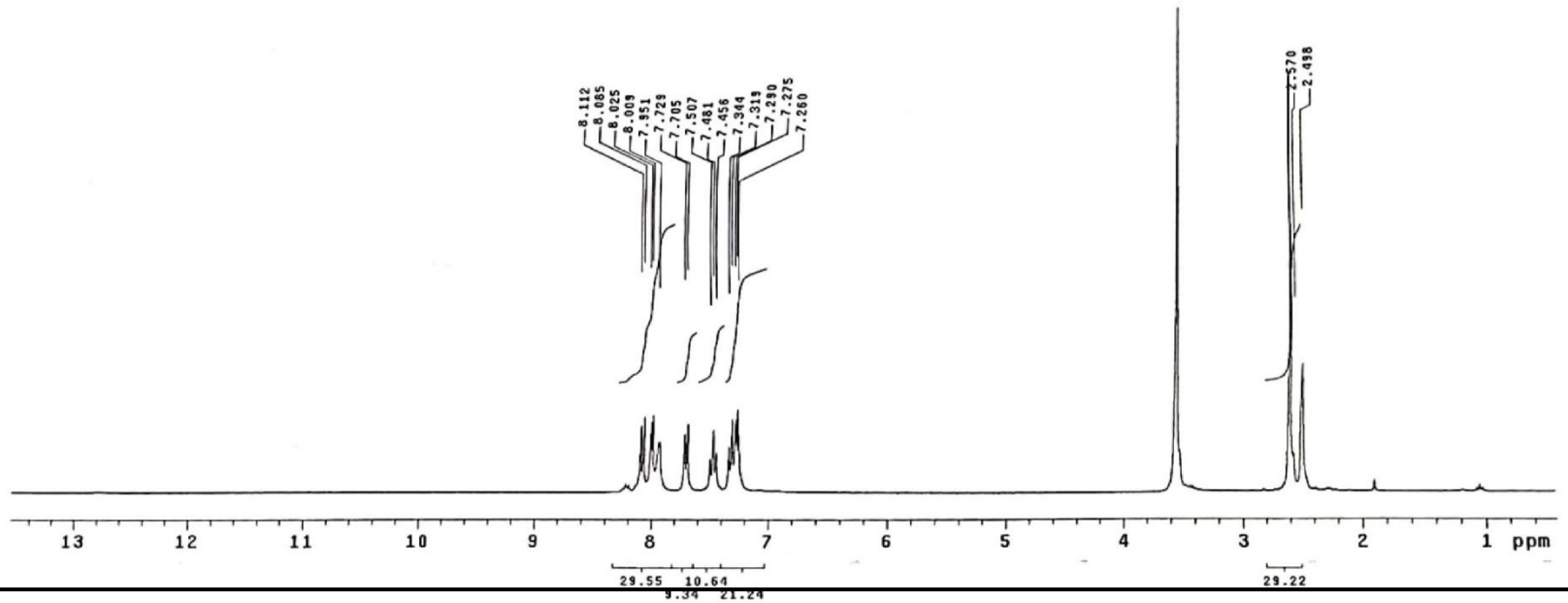
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 30.0 C / 303.1 K
Mercury-300BB "NMR300"

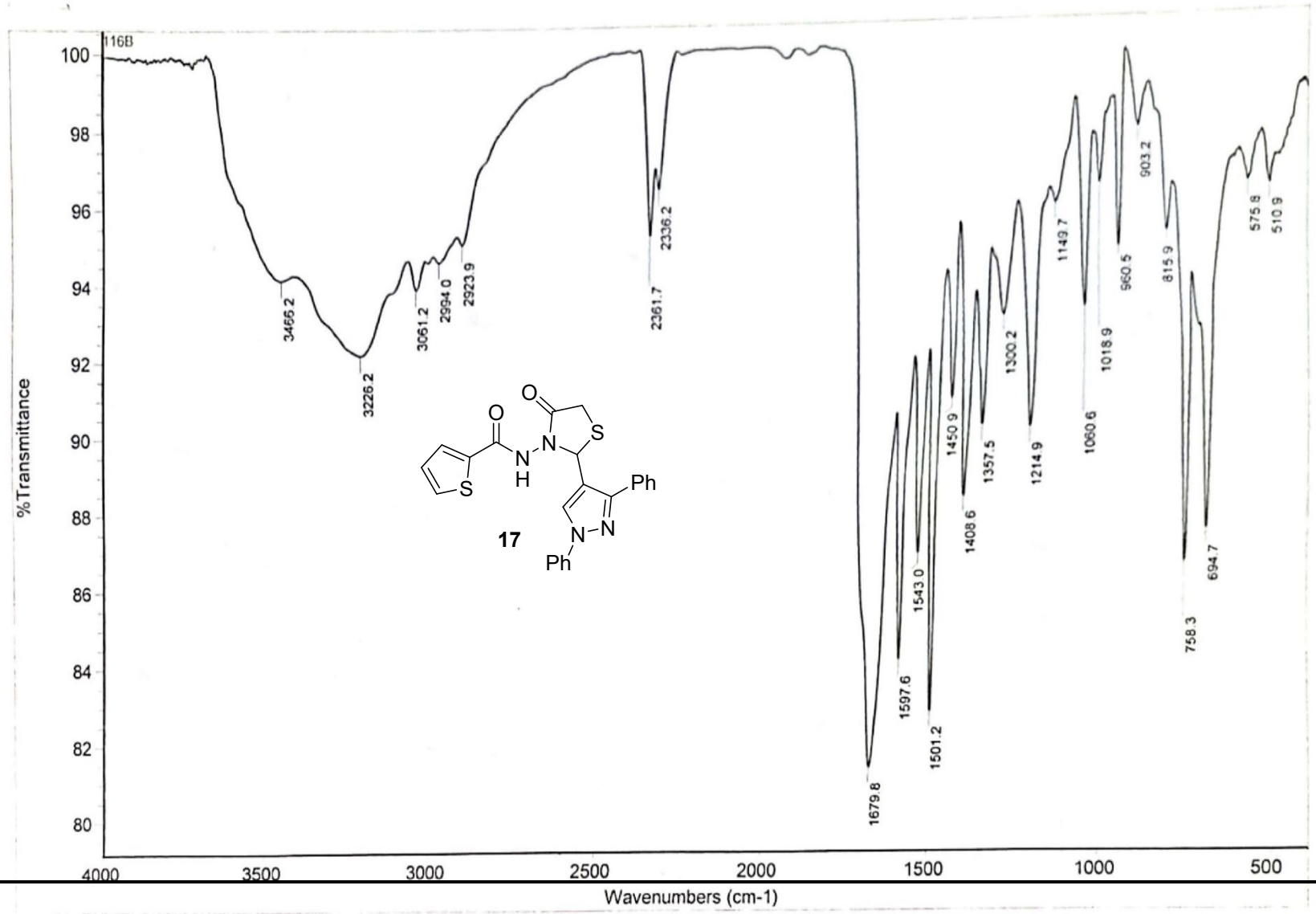
Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 4.000 sec
Width 6600.7 Hz
6 repetitions
OBSERVE H1, 300.0687870 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 58 min, 55 sec
Date: Feb 20 2023

Analytical Center

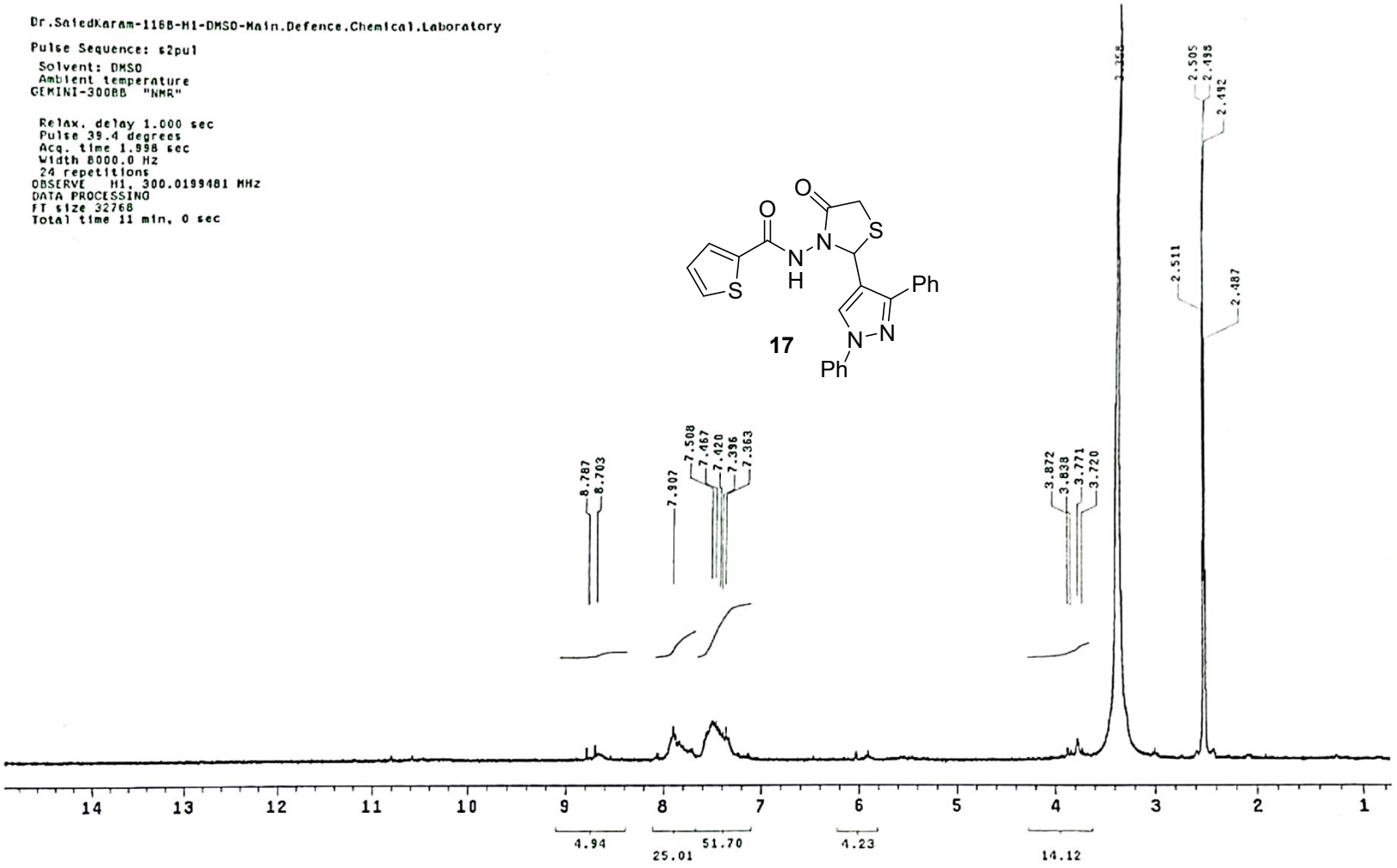


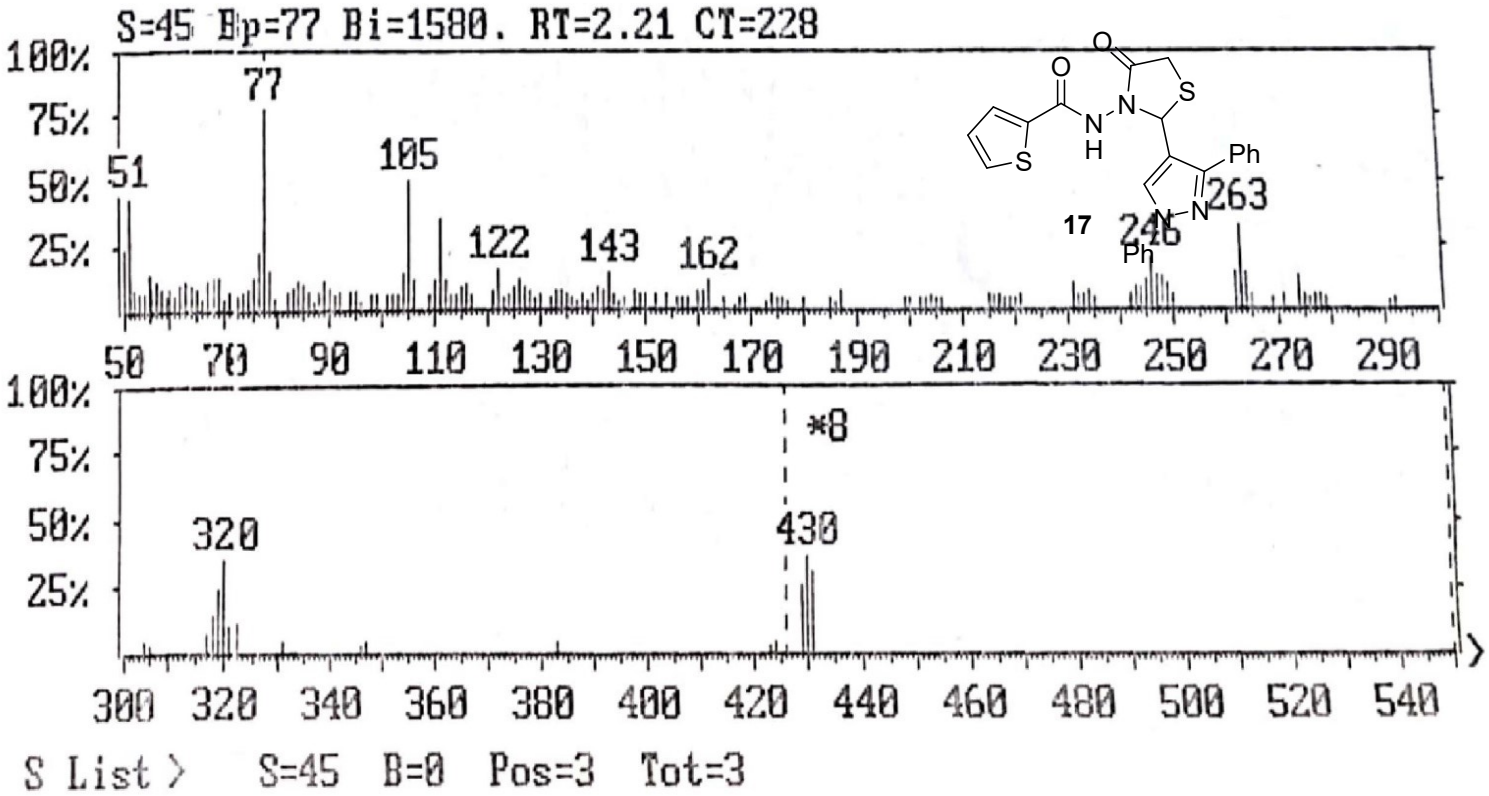
16

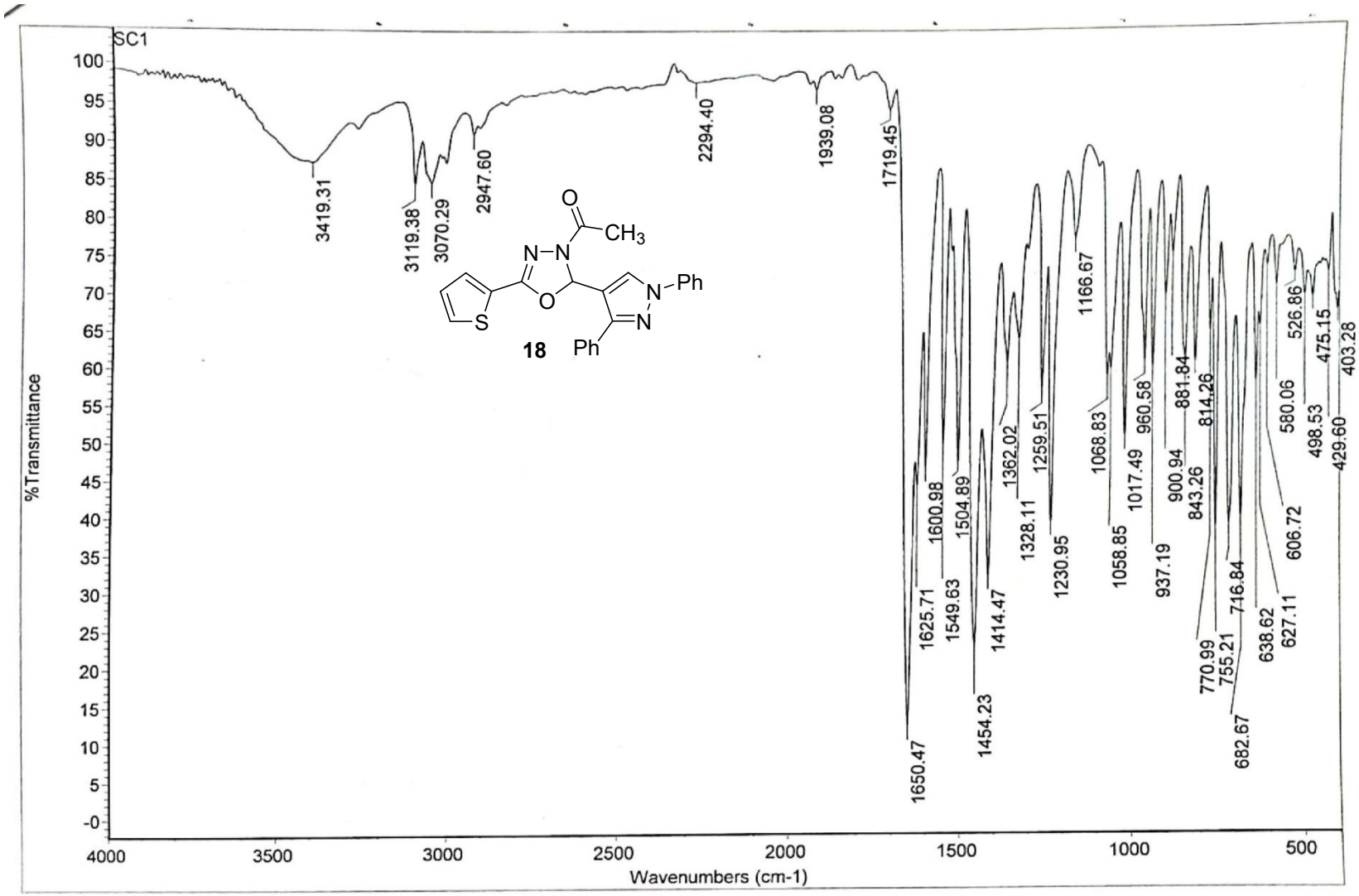


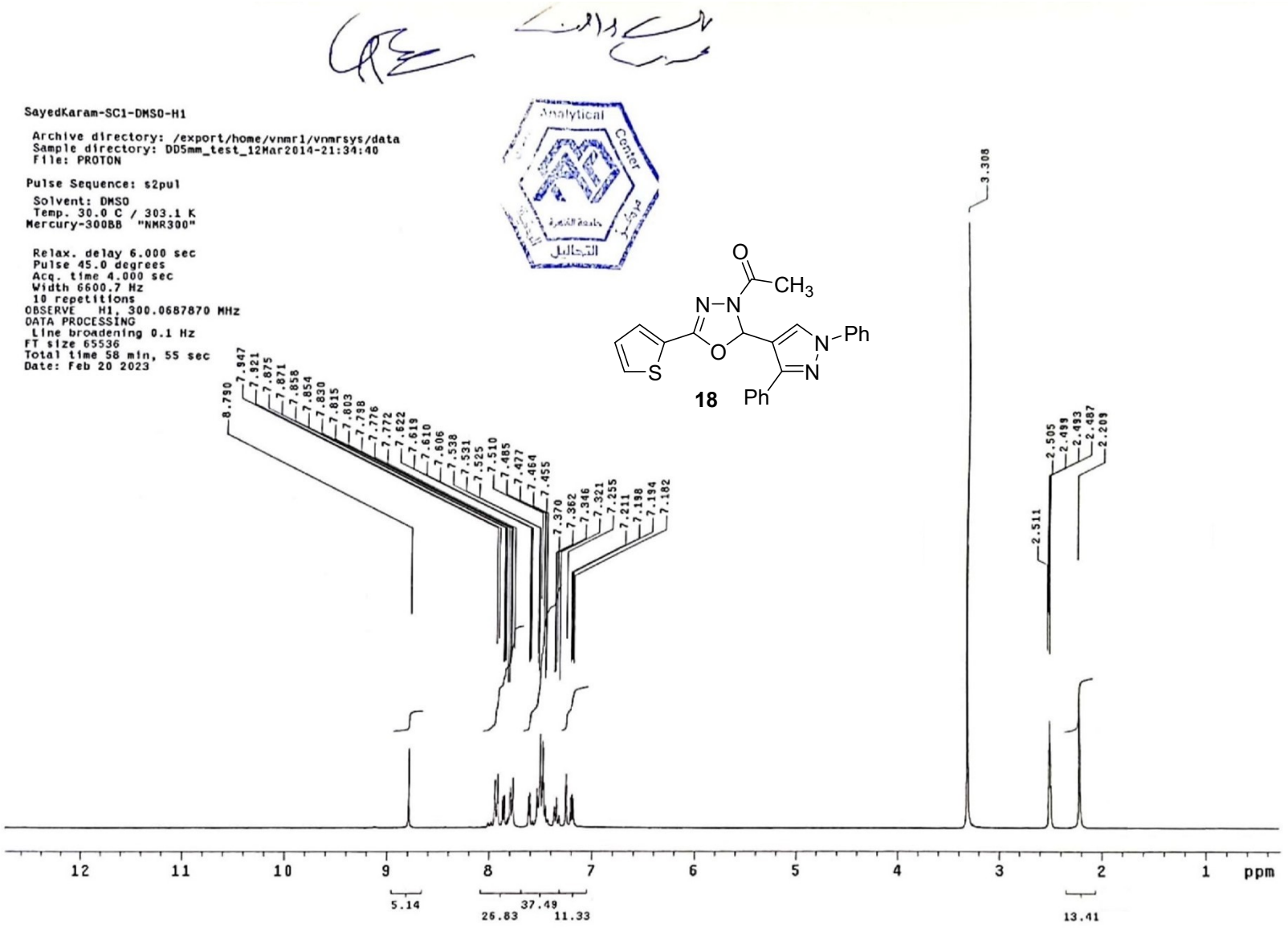

116B
%Transmittance
Wavenumbers (cm-1)
100
98
96
94
92
90
88
86
84
82
80
4000
3500
3000
2500
2000
1500
1000
500
3466.2
3226.2
3061.2
2994.0
2923.9
2361.7
2336.2
1679.8
1597.6
1543.0
1501.2
1450.9
1408.6
1357.5
1300.2
1214.9
1149.7
1060.6
1018.9
960.5
903.2
815.9
758.3
694.7
575.8
510.9
O
O
N
H
N
S
S
Ph
N
N
Ph

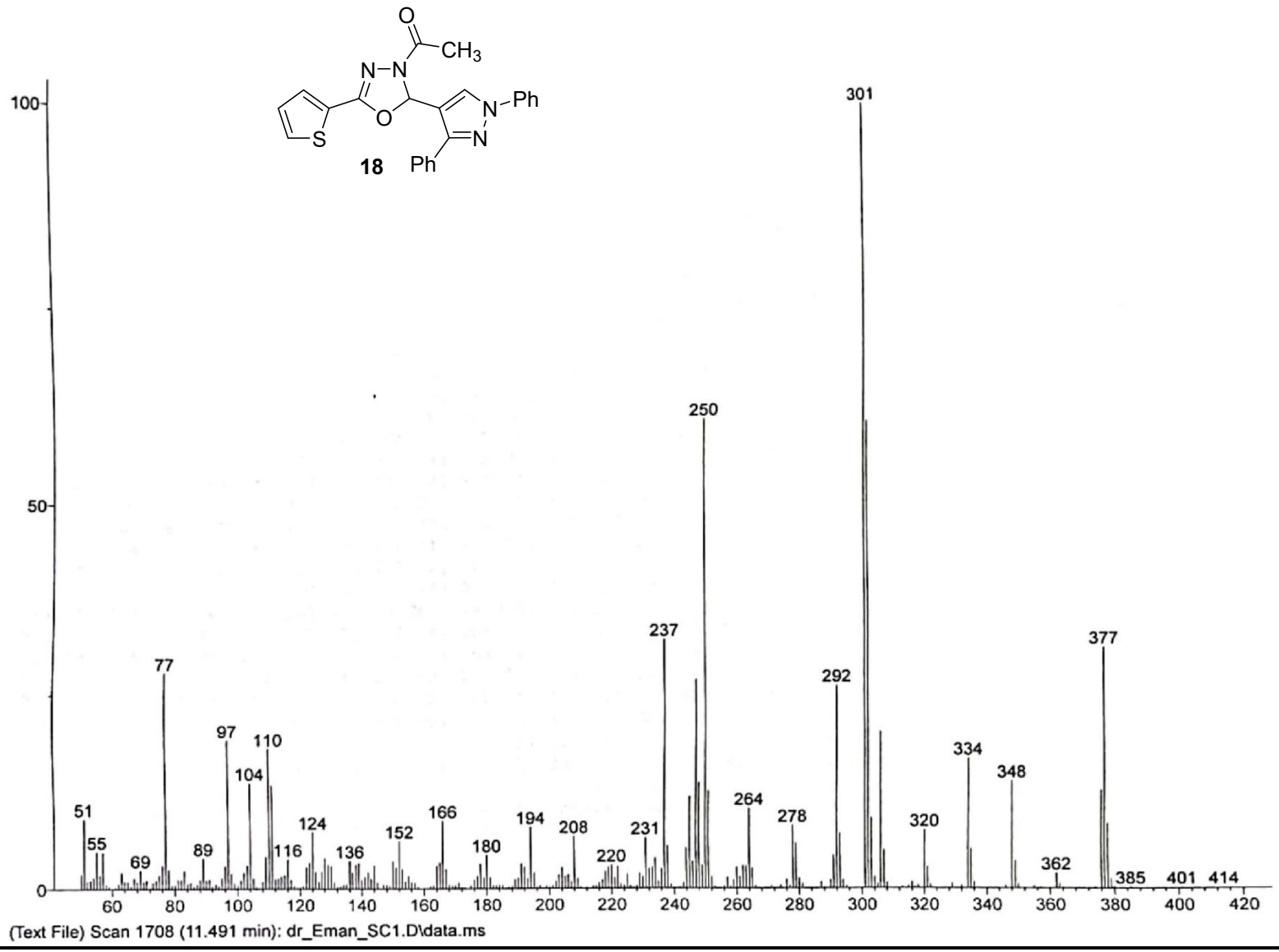
17


Dr.SaiedKaram-116B-H1-DMSO-Main.Defence.Chemical.Laboratory
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
GEMINI-300BB "NMR"
Relax. delay 1.000 sec
Pulse 39.4 degrees
Acq. time 1.998 sec
Width 8000.0 Hz
24 repetitions
OBSERVE H1, 300.0199481 MHz
DATA PROCESSING
FT size 32768
Total time 11 min, 0 sec
17
8.787
8.703
7.907
7.508
7.467
7.420
7.396
7.363
3.872
3.838
3.771
3.720
2.511
2.505
2.498
2.492
2.487
4.94
25.01
51.70
4.23
14.12


S=45 Bp=77 Bi=1580. RT=2.21 CT=228
100%
75%
50%
25%
77
51
105
122
143
162
263
246
Ph
Ph
17
50 70 90 110 130 150 170 190 210 230 250 270 290
100%
75%
50%
25%
*8
320
430
300 320 340 360 380 400 420 440 460 480 500 520 540
S List > S=45 B=0 Pos=3 Tot=3


SC1
%Transmittance
Wavenumbers (cm-1)
3419.31
3119.38
3070.29
2947.60
2294.40
1939.08
1719.45
1650.47
1625.71
1600.98
1549.63
1504.89
1454.23
1414.47
1362.02
1328.11
1259.51
1230.95
1166.67
1068.83
1058.85
1017.49
960.58
937.19
900.94
881.84
843.26
814.26
770.99
755.21
716.84
682.67
638.62
627.11
606.72
580.06
526.86
498.53
475.15
429.60
403.28
O
CH3
N–N
N–Ph
O
S
N
Ph
18


SayedKaram-SC1-DMSO-H1
Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
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
10 repetitions
OBSERVE H1, 300.0687870 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 58 min, 55 sec
Date: Feb 20 2023
Analytical Center
18
Ph
8.790
7.947
7.921
7.875
7.871
7.858
7.854
7.830
7.815
7.803
7.798
7.776
7.772
7.622
7.619
7.610
7.606
7.538
7.531
7.525
7.510
7.485
7.477
7.464
7.455
7.370
7.362
7.346
7.321
7.255
7.211
7.198
7.194
7.182
3.308
2.511
2.505
2.499
2.493
2.487
2.209
12
11
10
9
8
7
6
5
4
3
2
1
ppm
5.14
37.49
26.83
11.33
13.41


O
CH3
N–N
O
S
N–Ph
N
Ph
18
100
50
0
301
250
237
377
292
334
348
264
278
320
362
385
401
414
77
97
110
104
51
55
69
89
124
116
136
152
166
180
194
208
220
231
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
(Text File) Scan 1708 (11.491 min): dr_Eman_SC1.D\data.ms