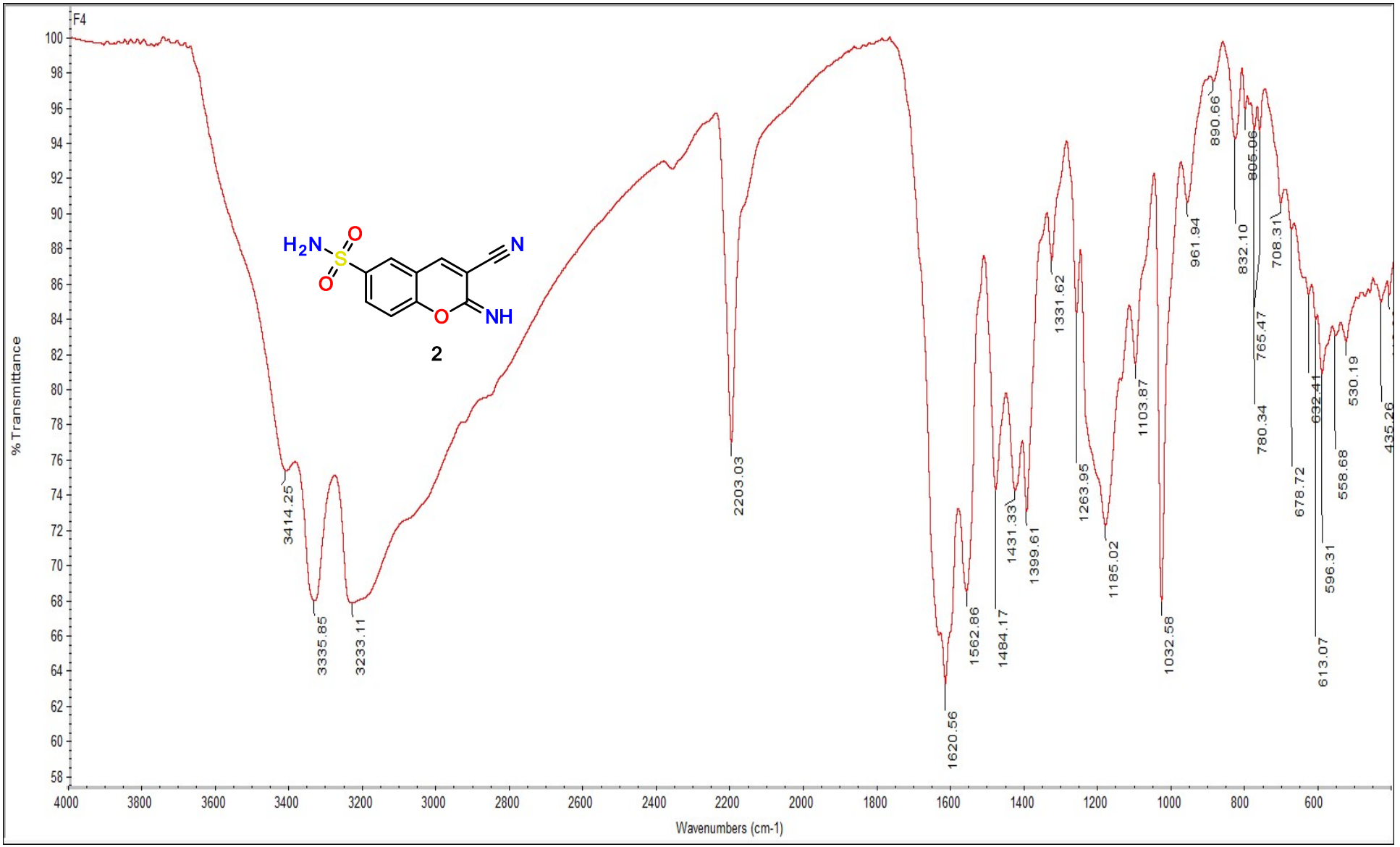
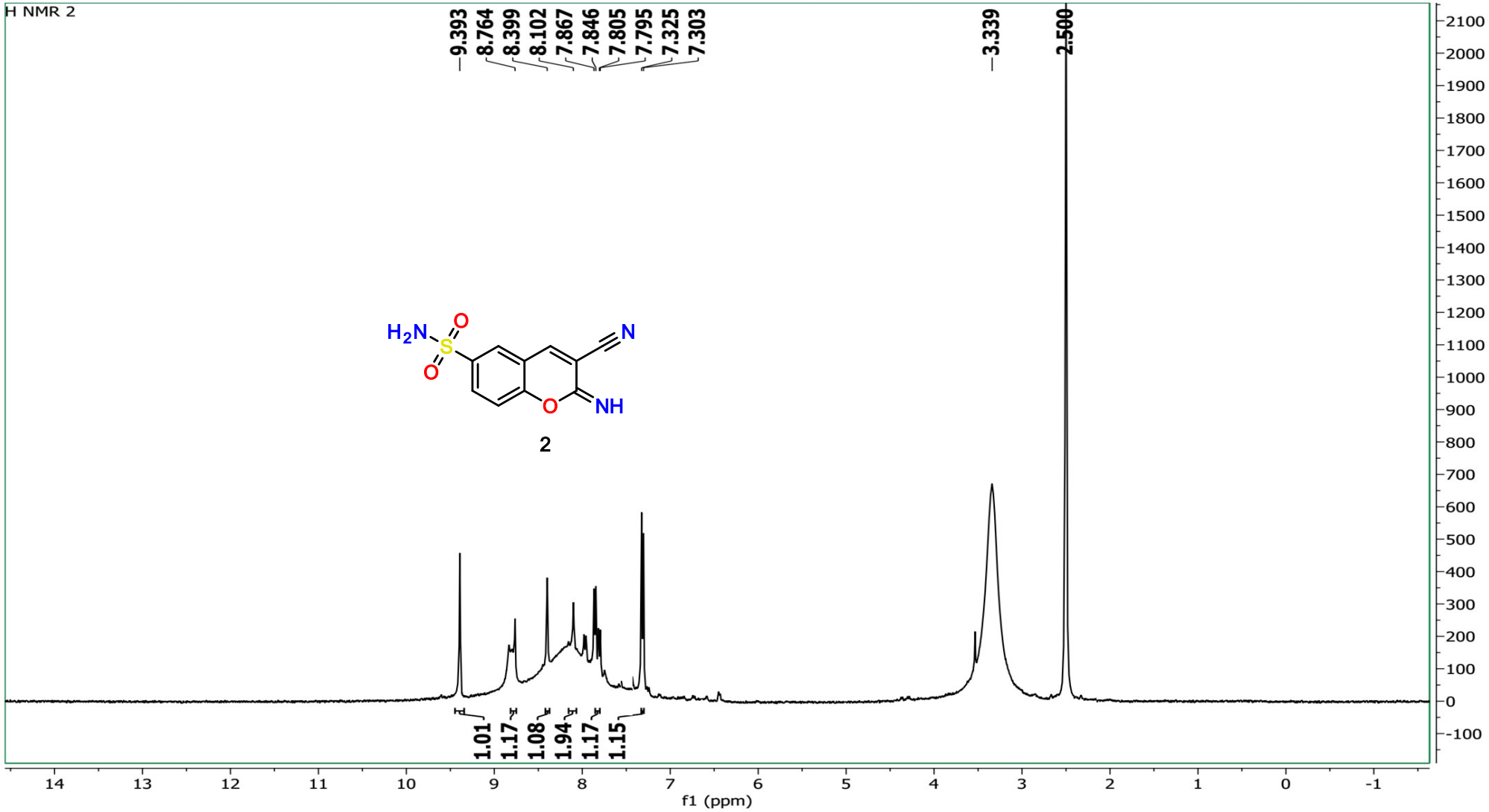
Electronic Supplementary Material (ESI) for RSC Advances.

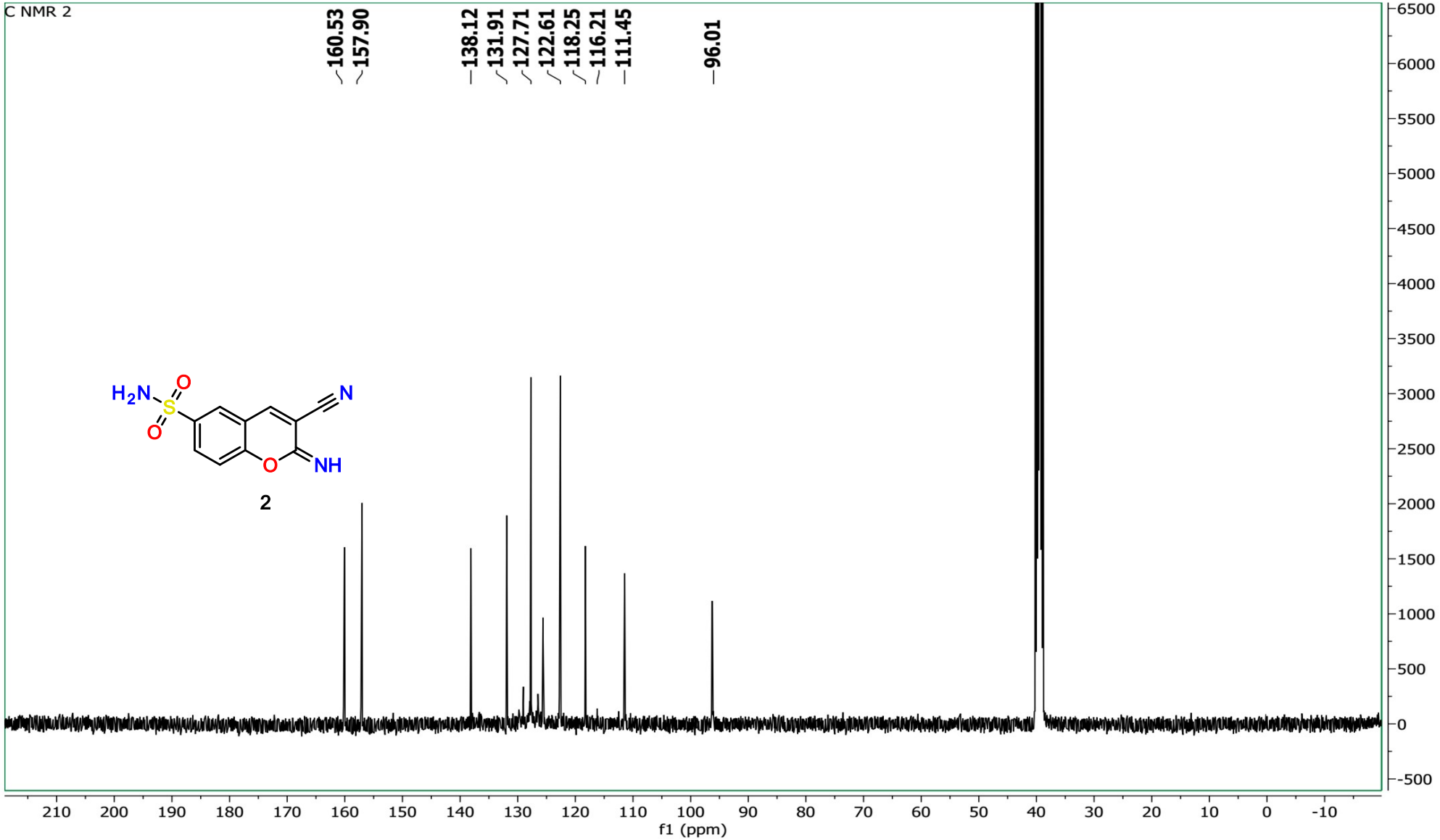
Innovation of 6-sulfonamide-2*H*-chromene as antidiabetic agents targeting α-amylase, α-glycosidase, and PPAR-γ inhibitors with *in-silico* molecular docking simulation

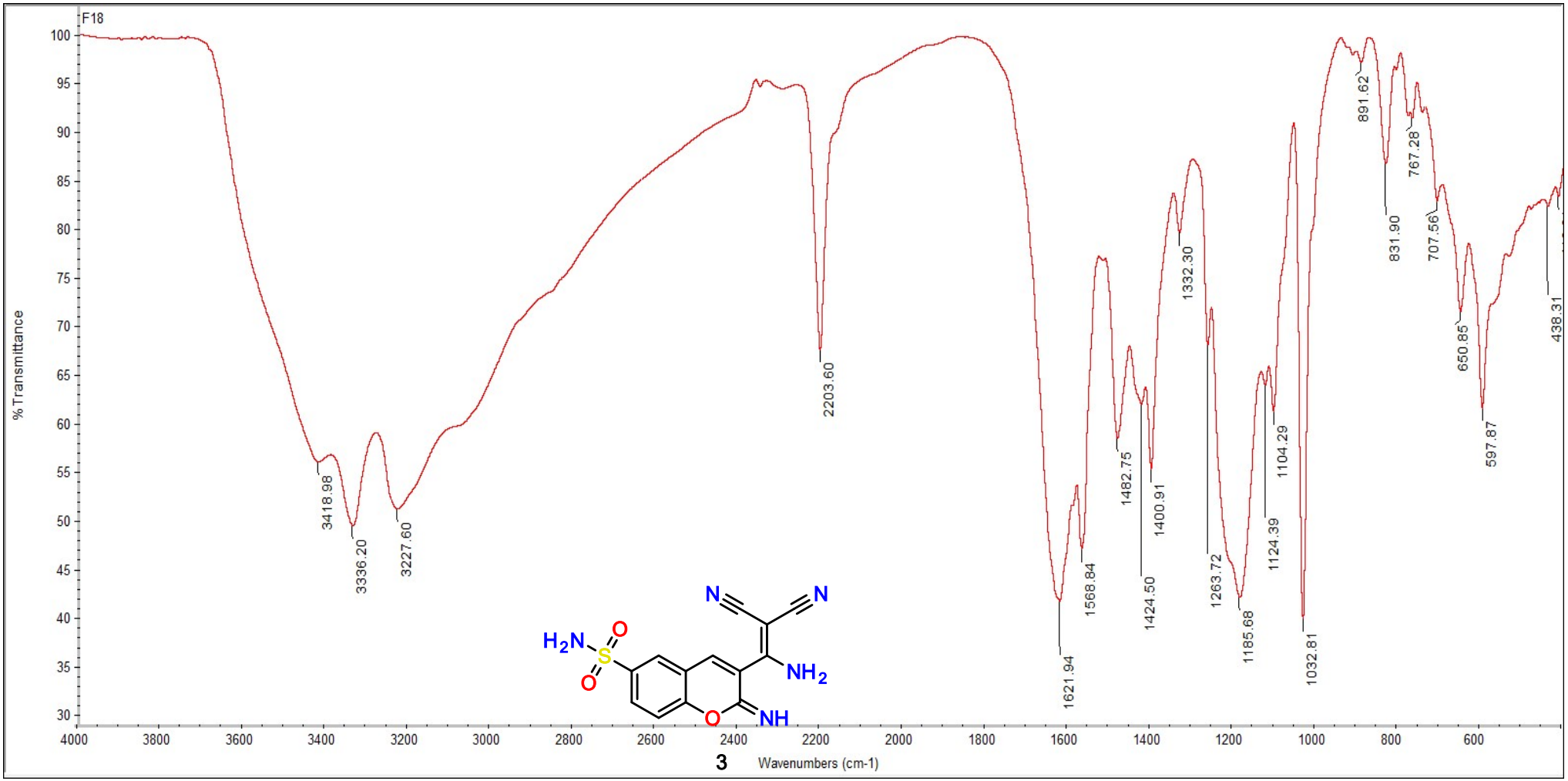
Hamdy Khamees Thabet[1,*], Ahmed Ragab[2,*], Mohd Imran[3], Mohamed Hamdy Helal[1], Saleh Ibrahim Alaqel[3], Ahmed Alshehri[4,5], Abida Ash Mohd[3], Saleh Saad Alshammari[1], Yousry A. Ammar[2,] Moustafa S. Abusaif [2]

[1] Department of Chemistry, College of Sciences and Arts, Northern Border University, Rafha, 91911, Saudi Arabia.
[2] Department of Chemistry, Faculty of Science (Boys), Al-Azhar University, Nasr City, 11884, Cairo, Egypt.
[3] Department of Pharmaceutical Chemistry, College of Pharmacy, Northern Border University, Rafha 91911, Saudi Arabia.
[4] Department of Pharmacology and Toxicology, College of Pharmacy, Northern Border University, Rafha 91911, Saudi Arabia.
[5] Department of Pharmacology, College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, King Faisal Road, Dammam 31441, Saudi Arabia

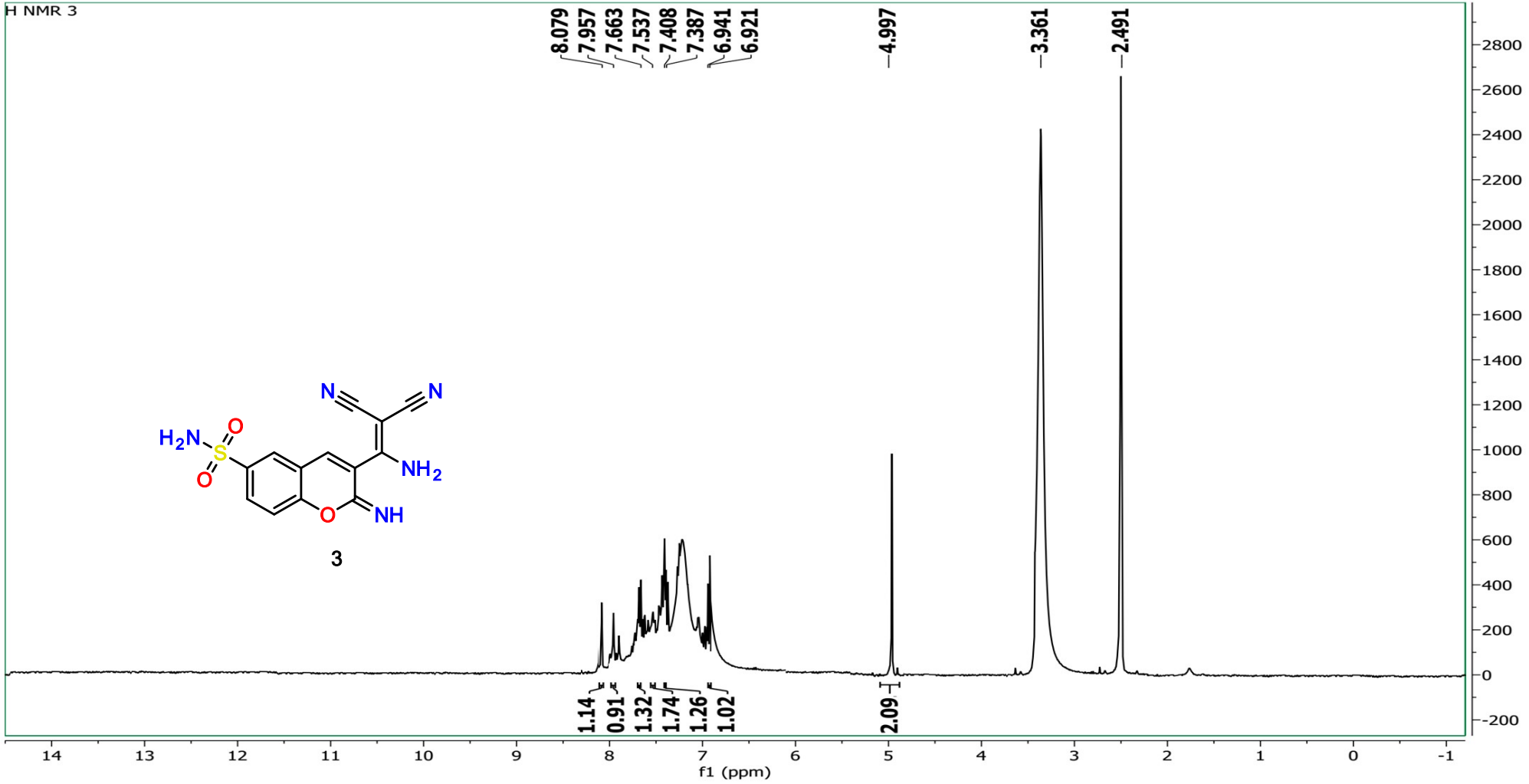

F4
% Transmittance
Wavenumbers (cm-1)
3414.25
3335.85
3233.11
2203.03
1620.56
1562.86
1484.17
1431.33
1399.61
1331.62
1263.95
1185.02
1103.87
1032.58
961.94
890.66
832.10
805.06
780.34
765.47
708.31
678.72
632.41
613.07
596.31
558.68
530.19
435.26
2

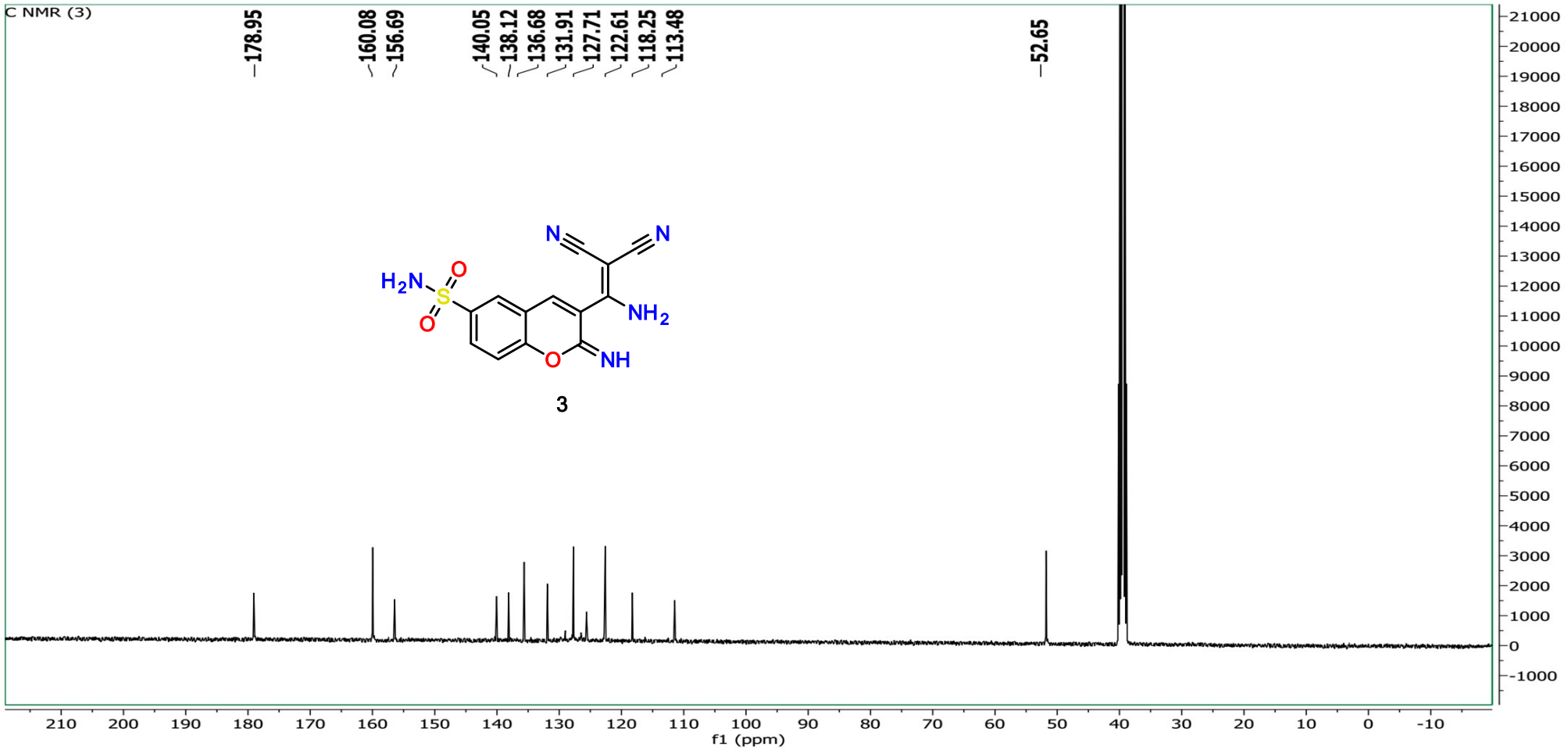

H NMR 2
9.393
8.764
8.399
8.102
7.867
7.846
7.805
7.795
7.325
7.303
3.339
2.500
1.01
1.17
1.08
1.94
1.17
1.15
f1 (ppm)
2

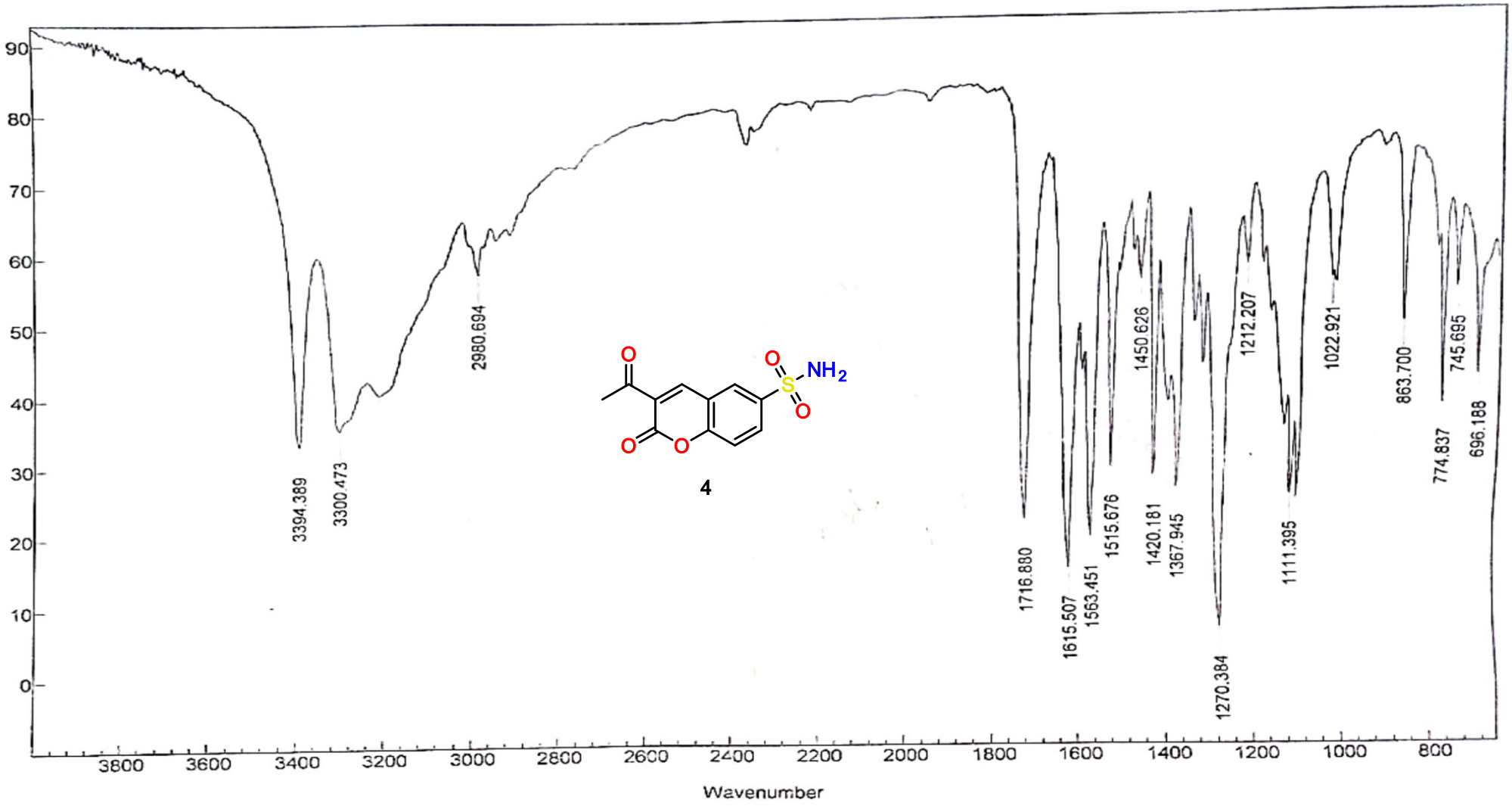

C NMR 2
160.53
157.90
138.12
131.91
127.71
122.61
118.25
116.21
111.45
96.01
H2N
O
S
O
N
O
NH
2
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

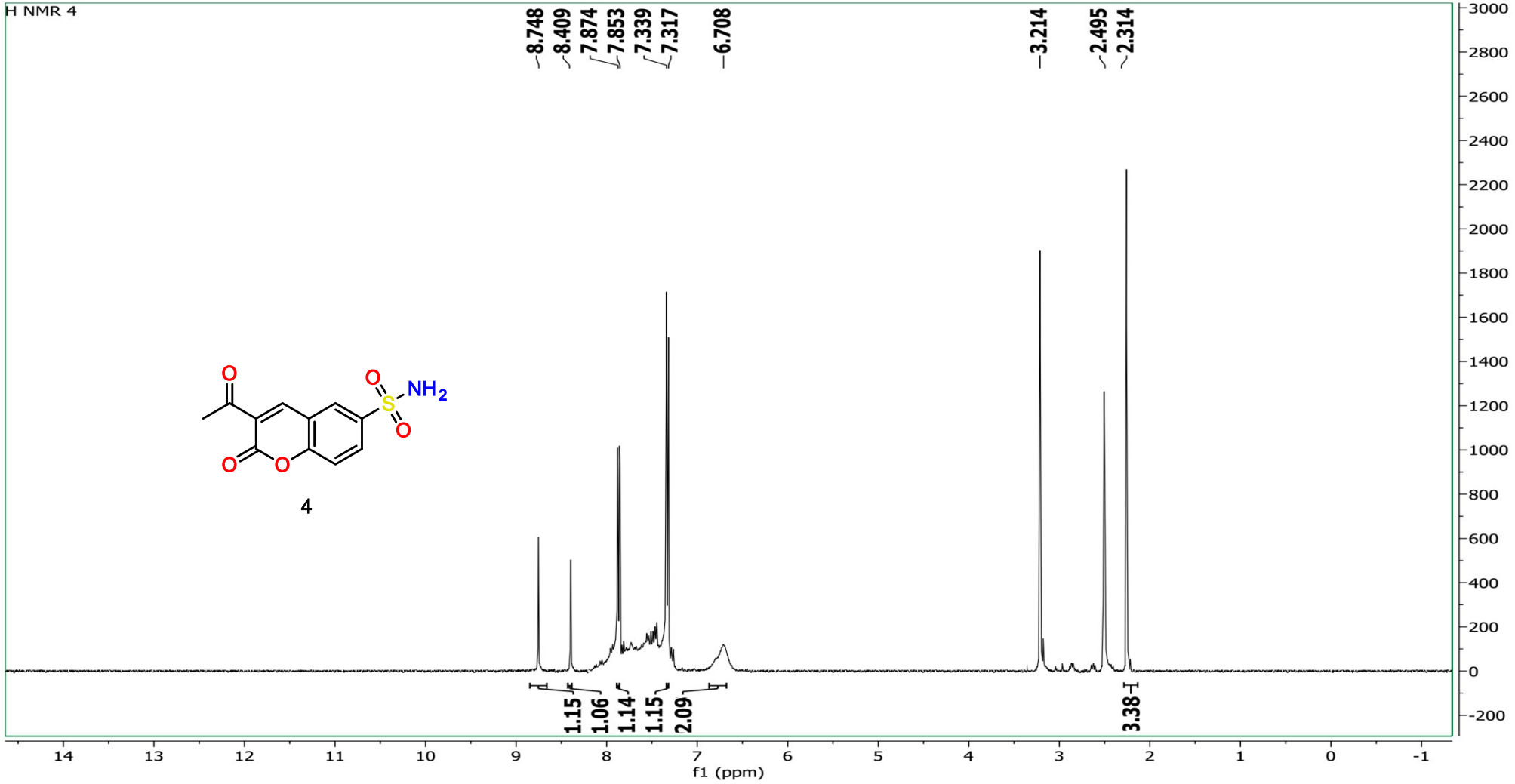

F18
% Transmittance
Wavenumbers (cm-1)
3418.98
3336.20
3227.60
2203.60
1621.94
1568.84
1482.75
1424.50
1400.91
1332.30
1263.72
1185.68
1124.39
1104.29
1032.81
891.62
831.90
767.28
707.56
650.85
597.87
438.31
N
N
H2N
O
S
O
NH2
O
NH

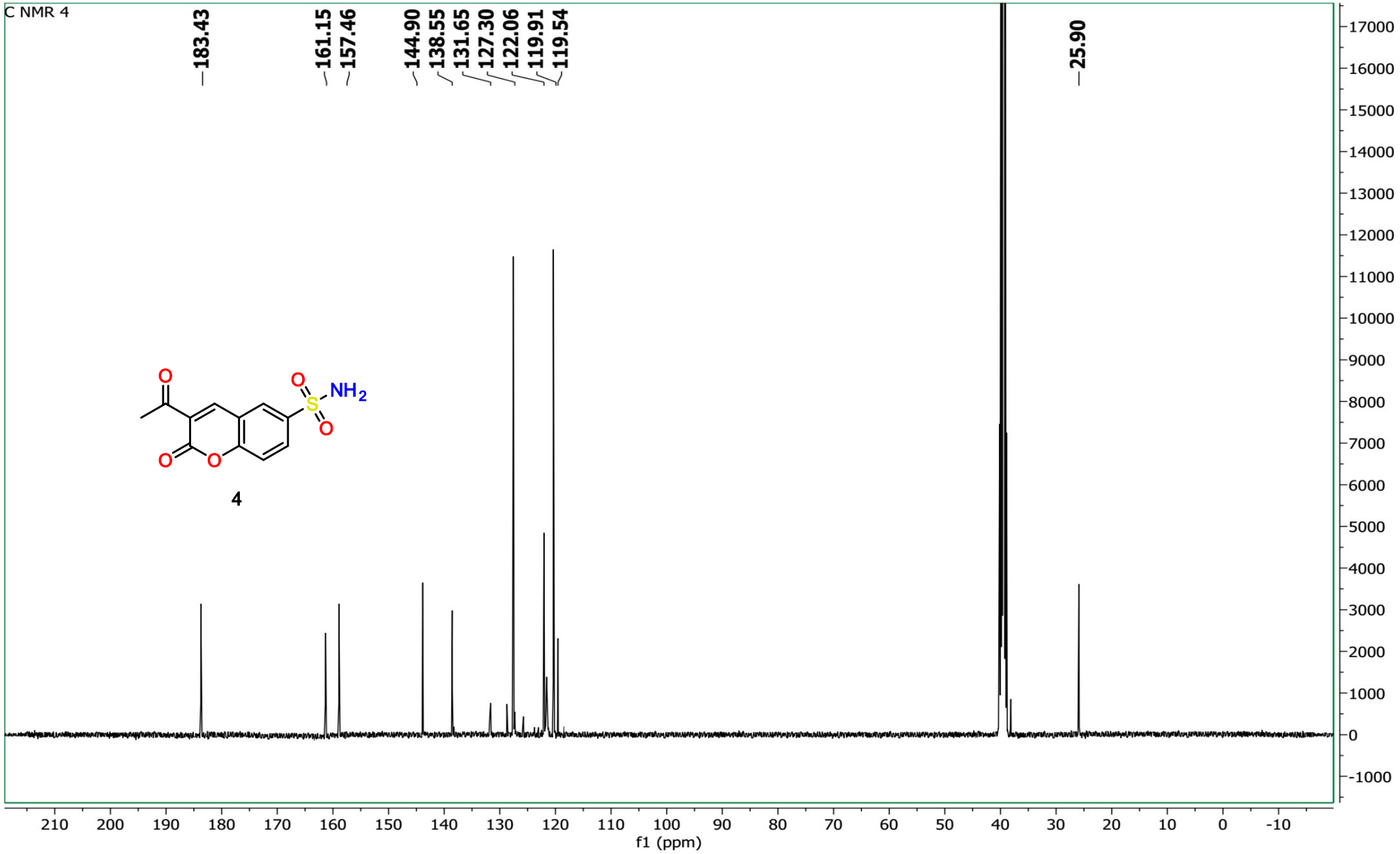
3

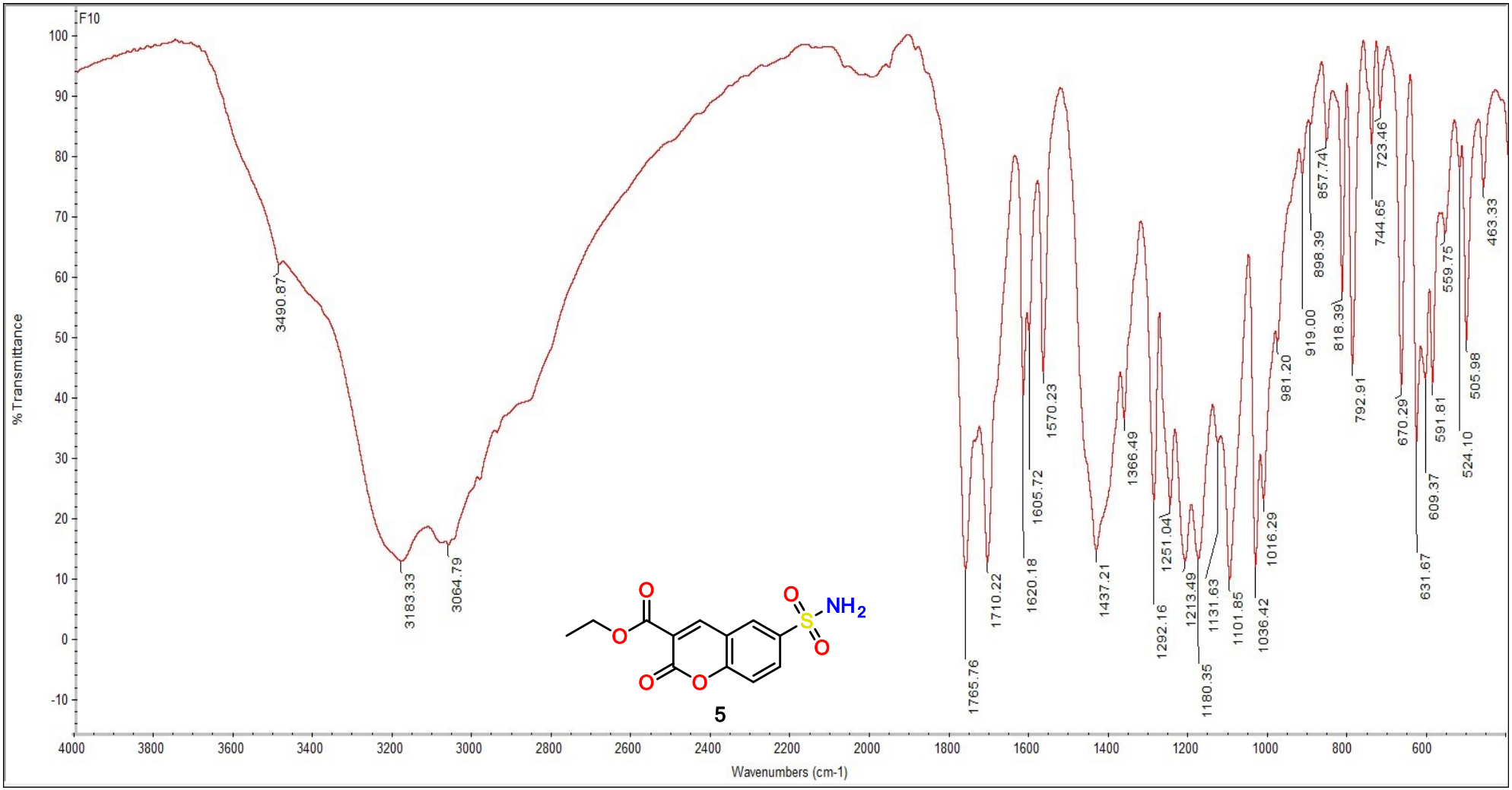

H NMR 3
8.079
7.957
7.663
7.537
7.408
7.387
6.941
6.921
4.997
3.361
2.491
1.14
0.91
1.32
1.74
1.26
1.02
2.09
f1 (ppm)
3

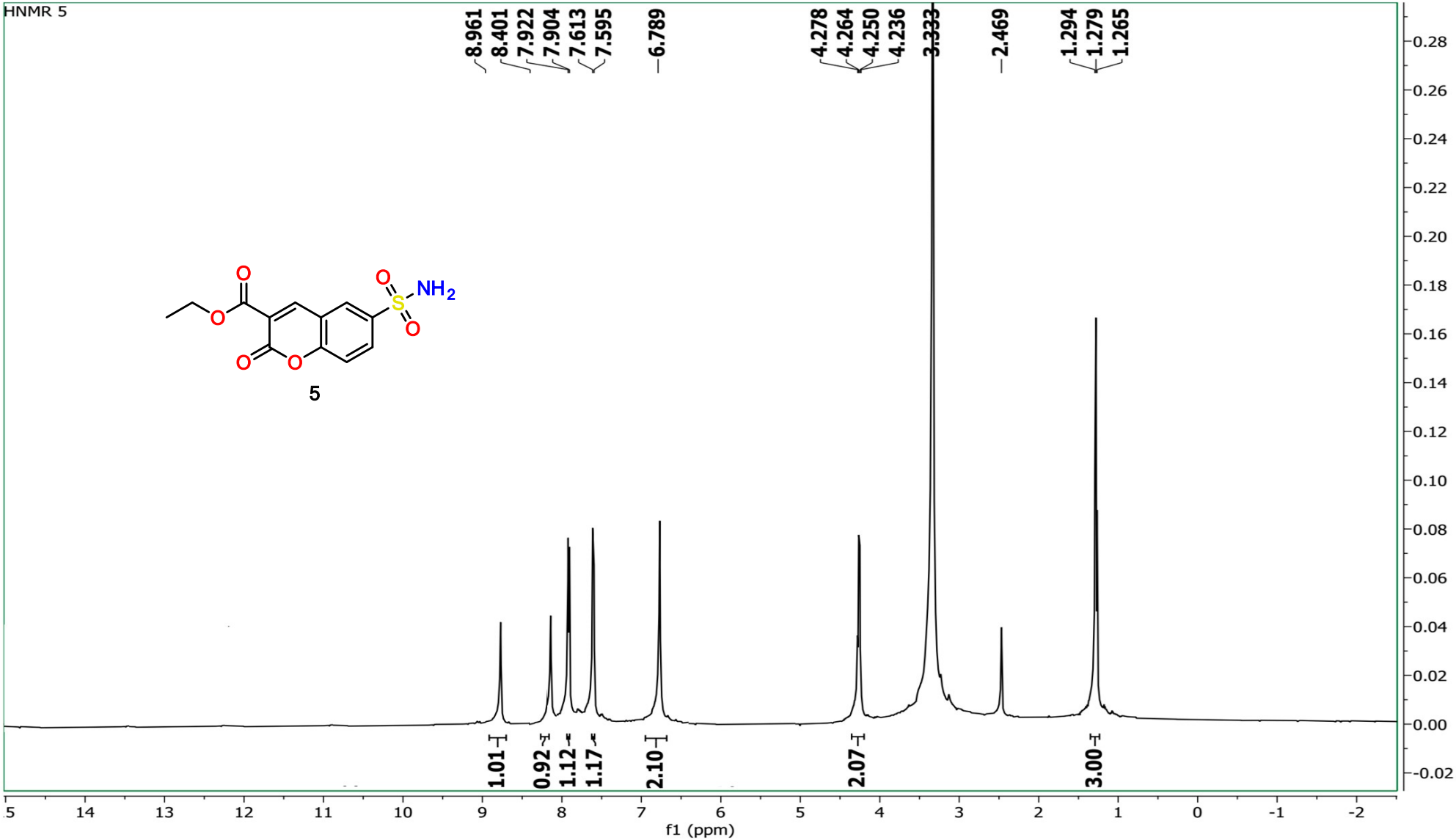

C NMR (3)
178.95
160.08
156.69
140.05
138.12
136.68
131.91
127.71
122.61
118.25
113.48
52.65
N
N
H_2N
O
S
O
NH_2
O
NH
3
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

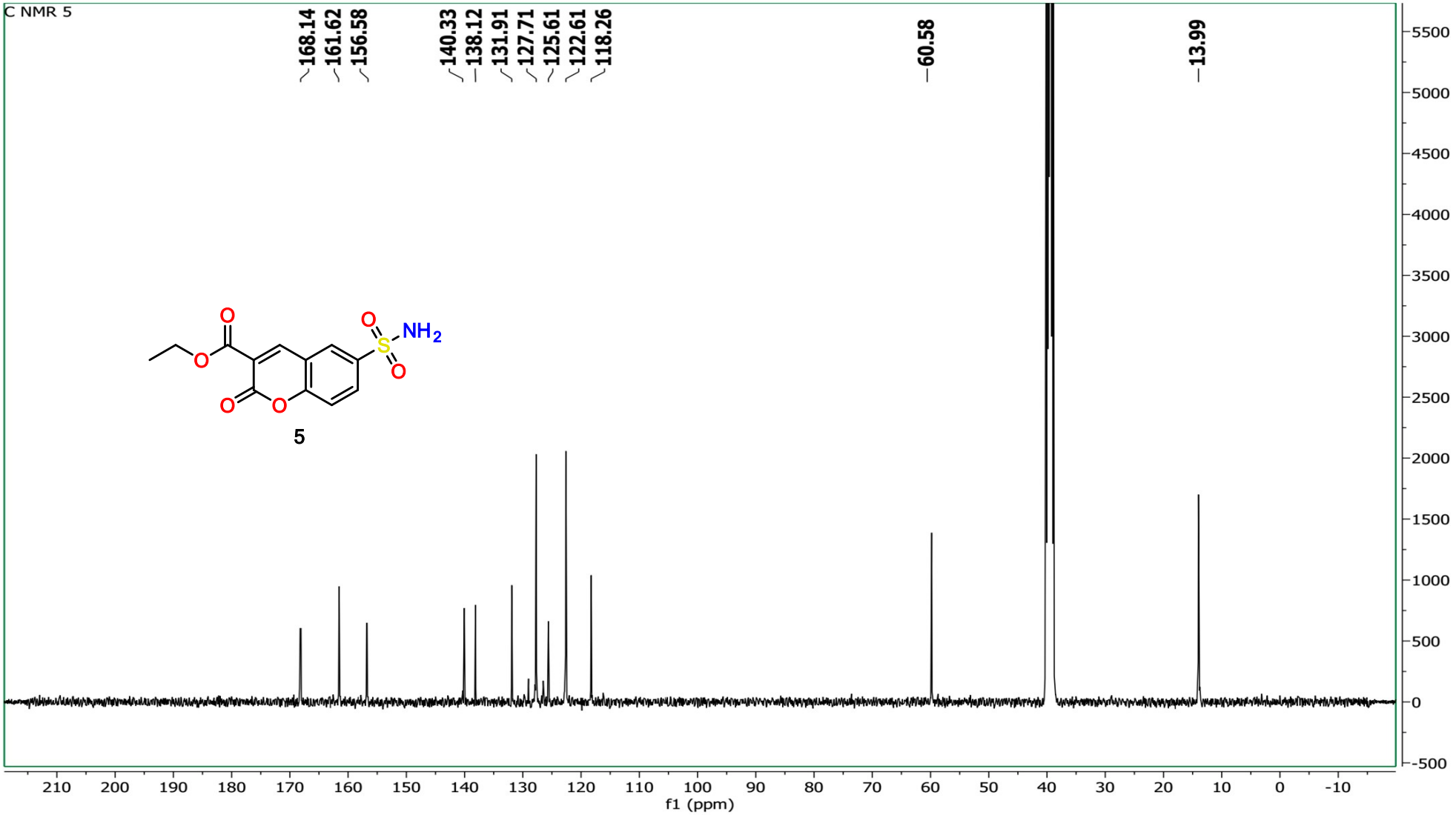

3394.389
3300.473
2980.694
1716.880
1615.507
1563.451
1515.676
1450.626
1420.181
1367.945
1270.384
1212.207
1111.395
1022.921
863.700
774.837
745.695
696.188
4
Wavenumber

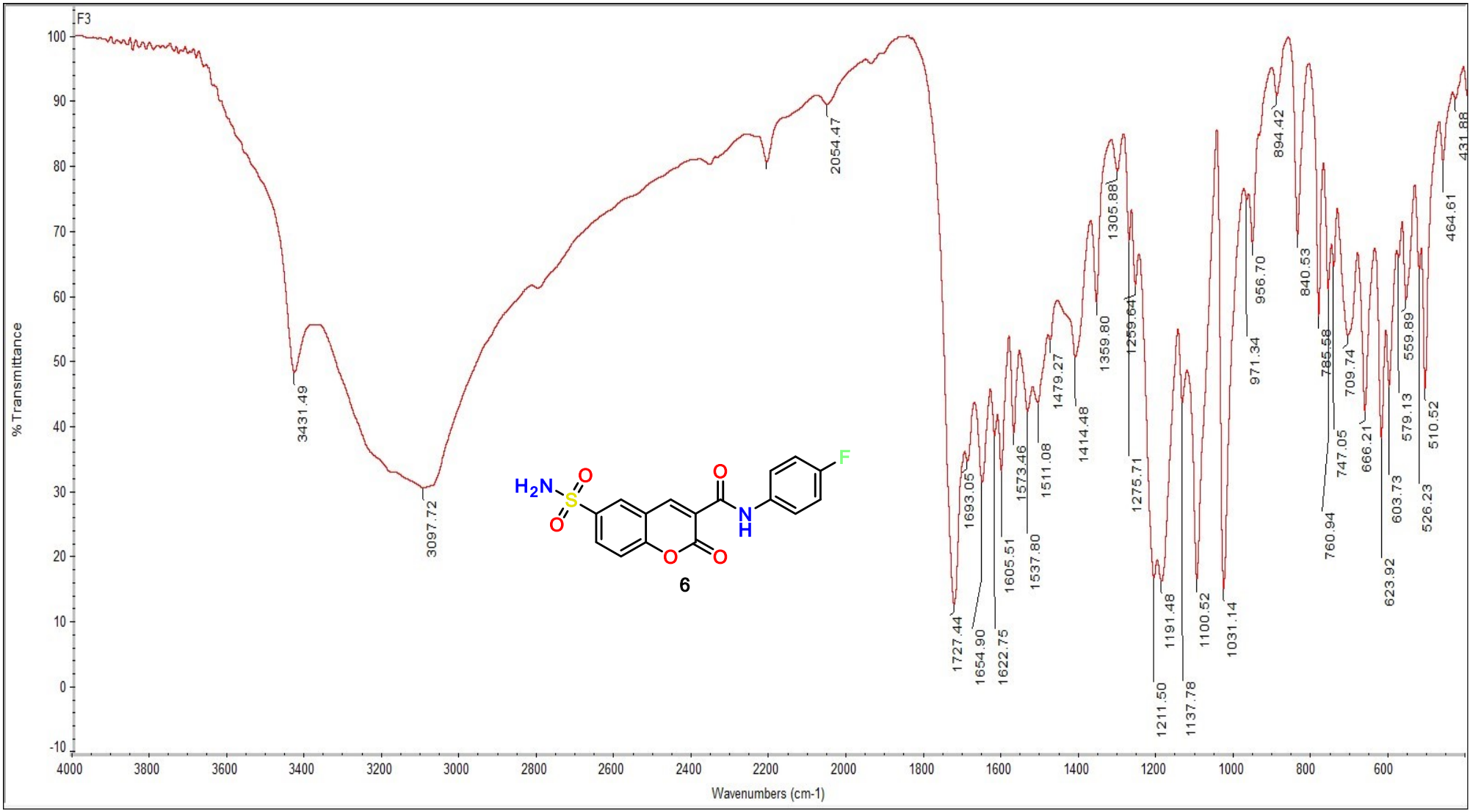

H NMR 4
8.748
8.409
7.874
7.853
7.339
7.317
6.708
3.214
2.495
2.314
1.15
1.06
1.14
1.15
2.09
3.38
O
O
O
O
S
O
NH2
4
f1 (ppm)

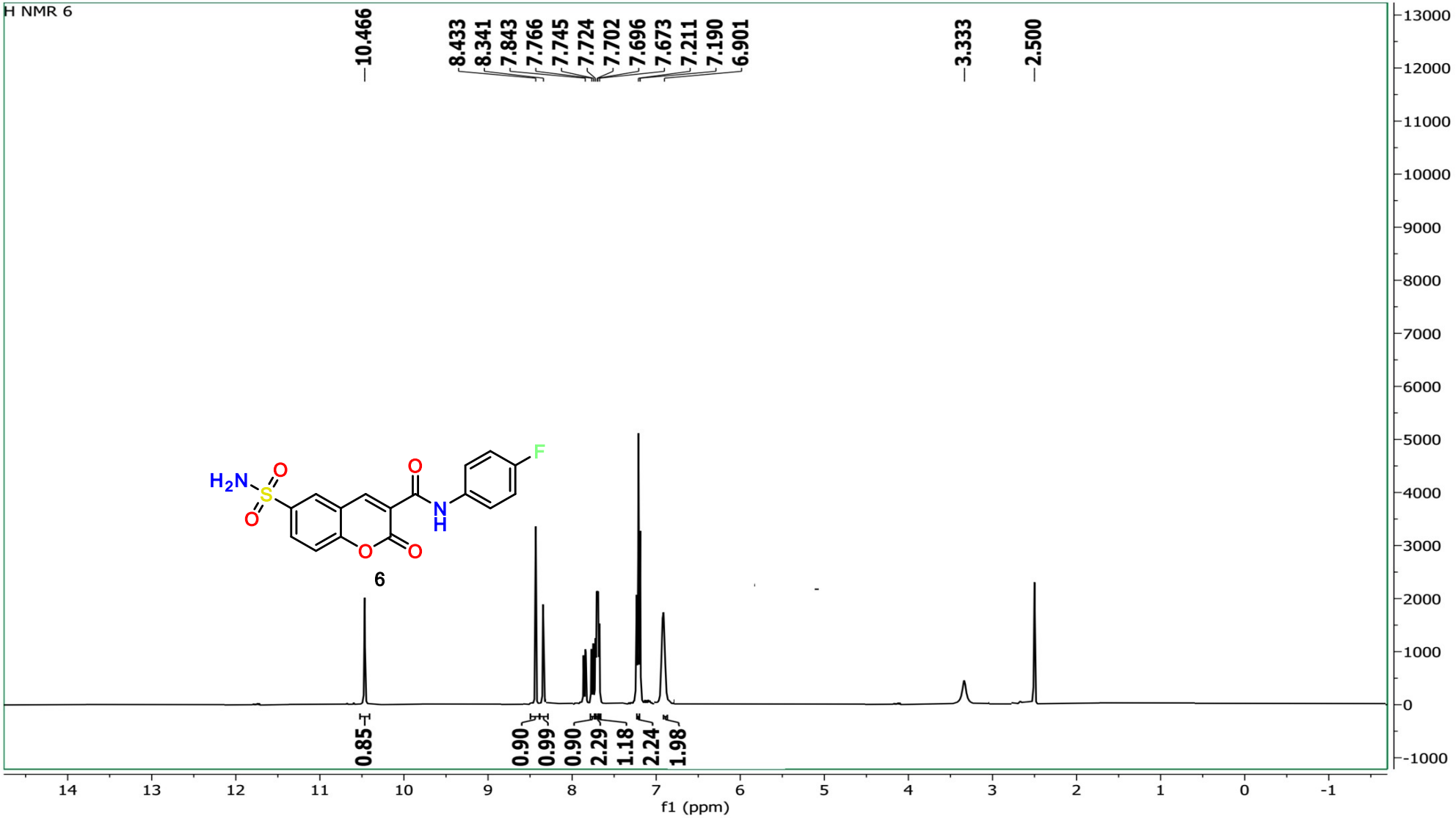

C NMR 4
183.43
161.15
157.46
144.90
138.55
131.65
127.30
122.06
119.91
119.54
25.90
O
O
O
O
S
O
NH2
4
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

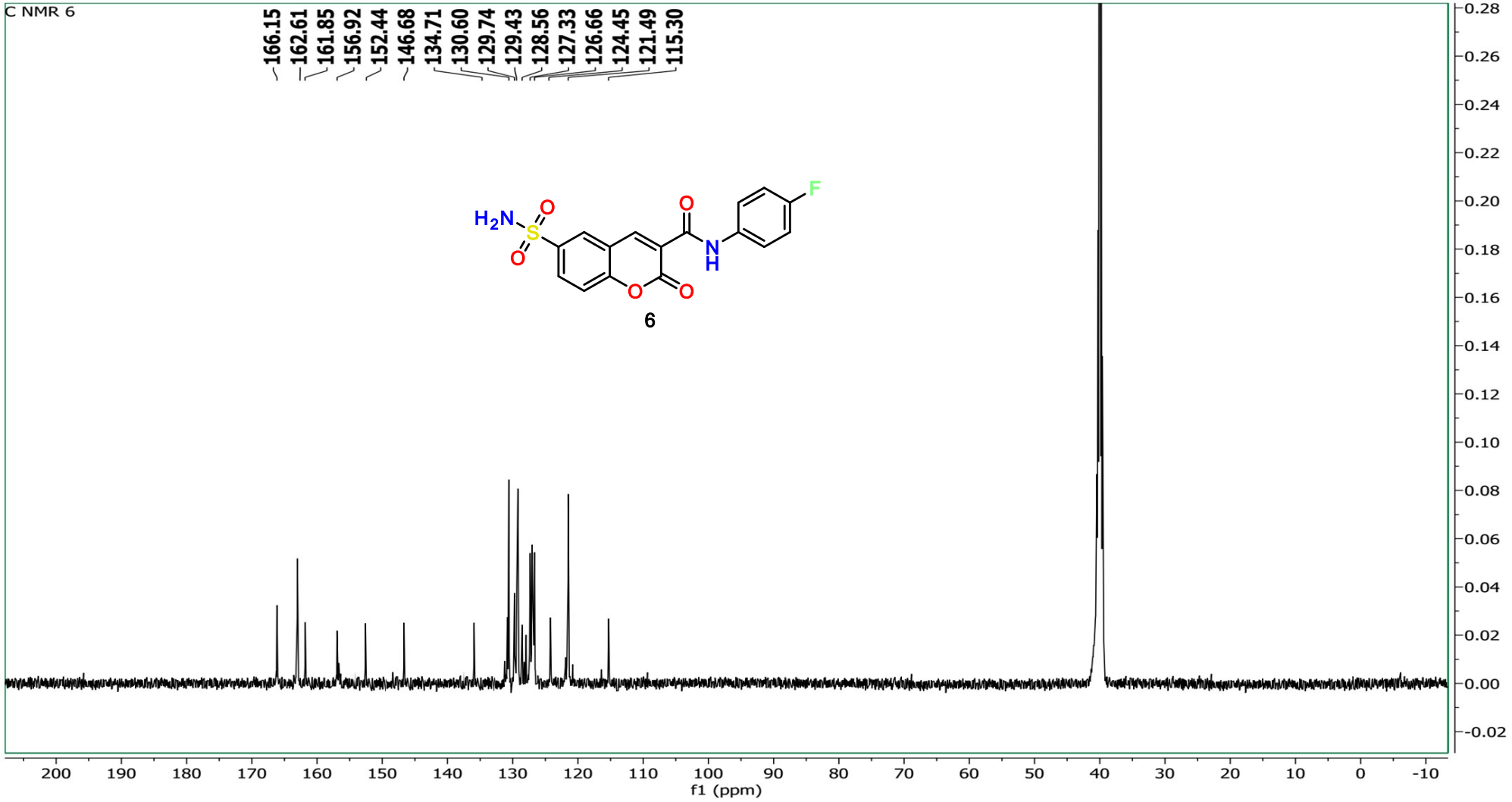

F10
% Transmittance
Wavenumbers (cm-1)
3490.87
3183.33
3064.79
1765.76
1710.22
1620.18
1605.72
1570.23
1437.21
1366.49
1292.16
1251.04
1213.49
1180.35
1131.63
1101.85
1036.42
1016.29
981.20
919.00
898.39
857.74
818.39
792.91
744.65
723.46
670.29
631.67
609.37
591.81
559.75
524.10
505.98
463.33
NH2
5

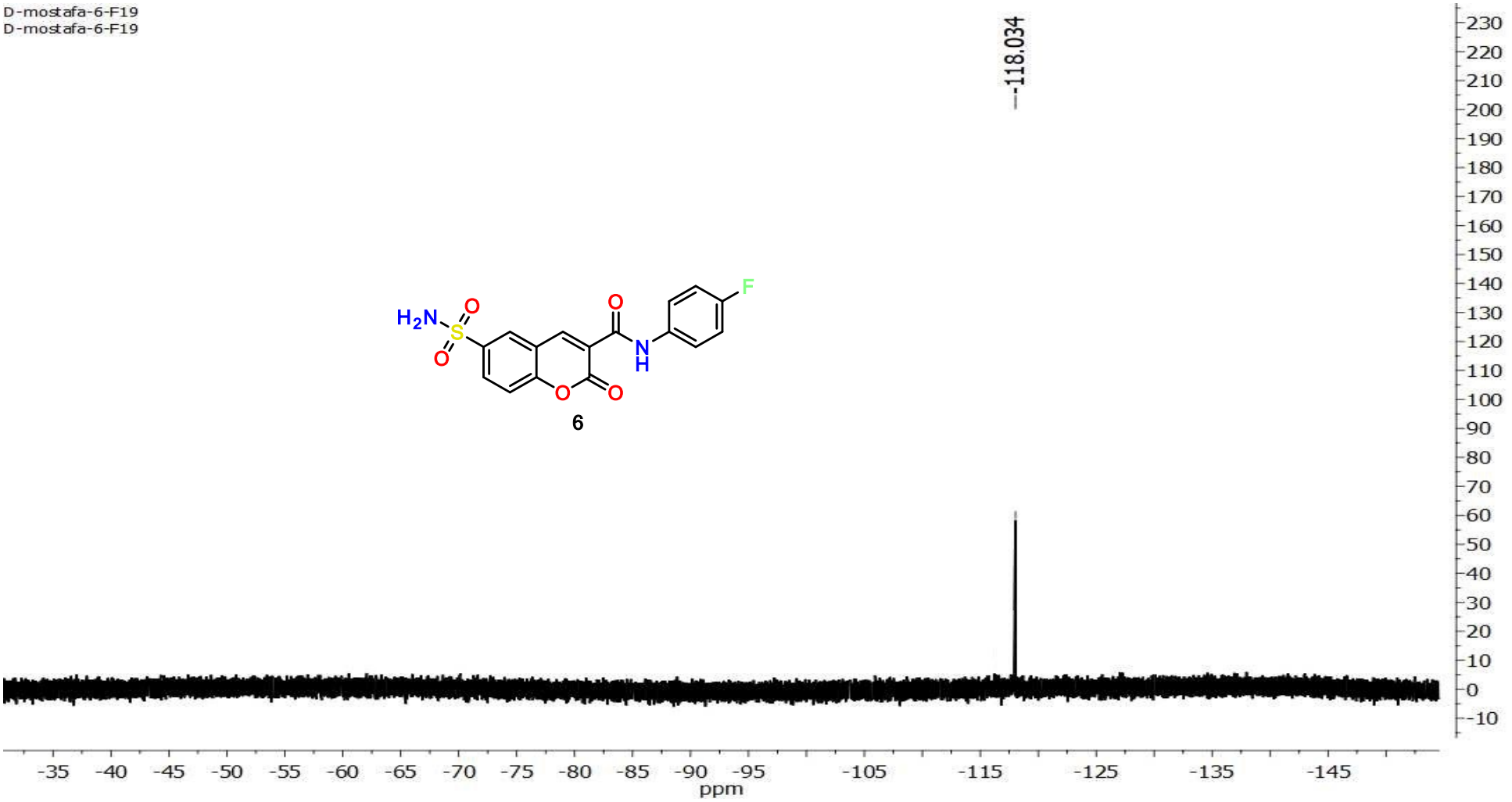

HNMR 5
8.961
8.401
7.922
7.904
7.613
7.595
6.789
4.278
4.264
4.250
4.236
3.333
2.469
1.294
1.279
1.265
1.01
0.92
1.12
1.17
2.10
2.07
3.00
O
O
O
O
O
S
NH2
5
f1 (ppm)


C NMR 5
168.14
161.62
156.58
140.33
138.12
131.91
127.71
125.61
122.61
118.26
60.58
13.99
O
O
O
O
O
S
O
NH2
5
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

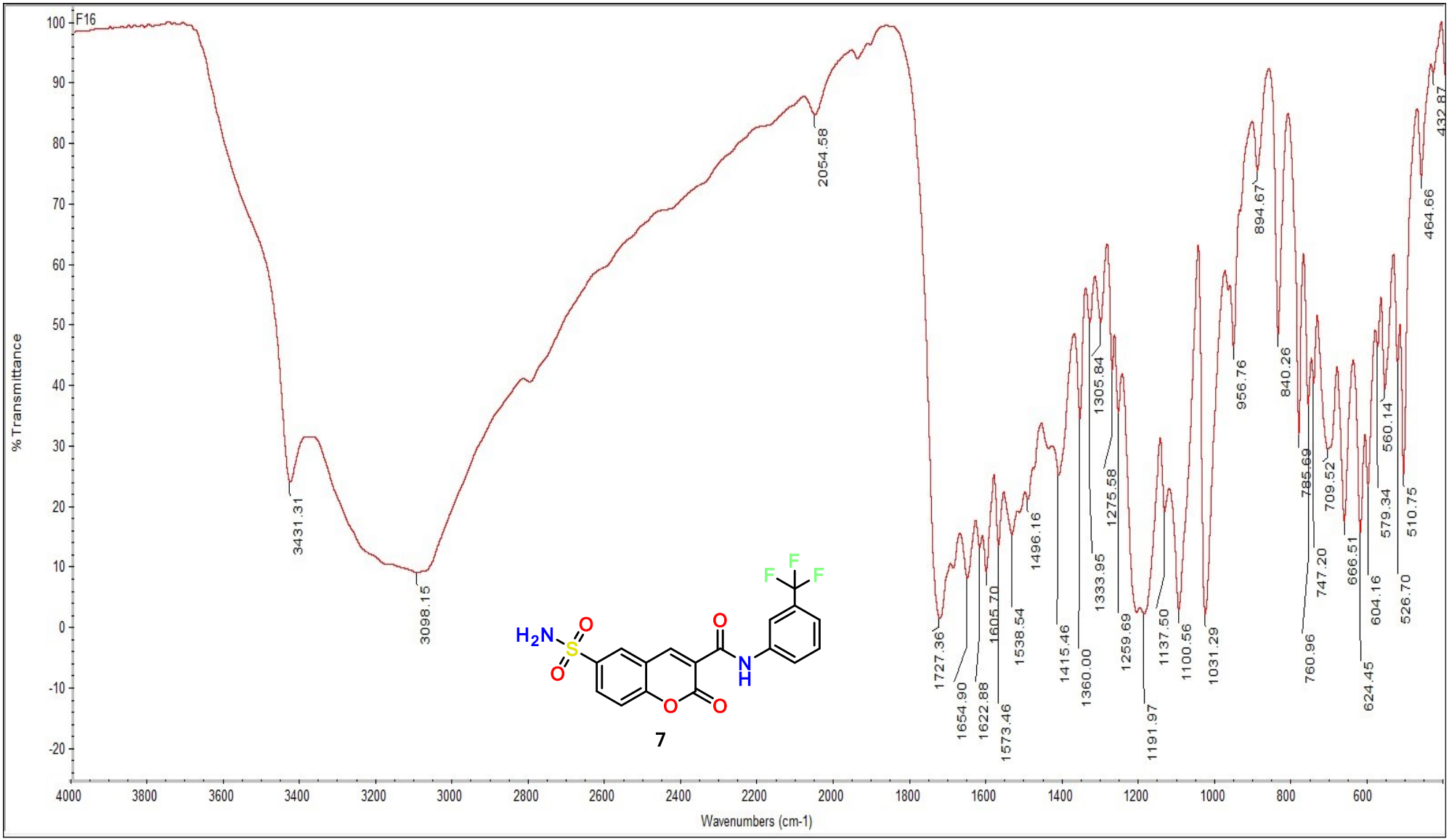

F3
% Transmittance
Wavenumbers (cm-1)
3431.49
3097.72
2054.47
1727.44
1693.05
1654.90
1622.75
1605.51
1573.46
1537.80
1511.08
1479.27
1414.48
1359.80
1305.88
1275.71
1259.64
1211.50
1191.48
1137.78
1100.52
1031.14
971.34
956.70
894.42
840.53
785.58
760.94
747.05
709.74
666.21
623.92
603.73
579.13
559.89
526.23
510.52
464.61
431.88
6

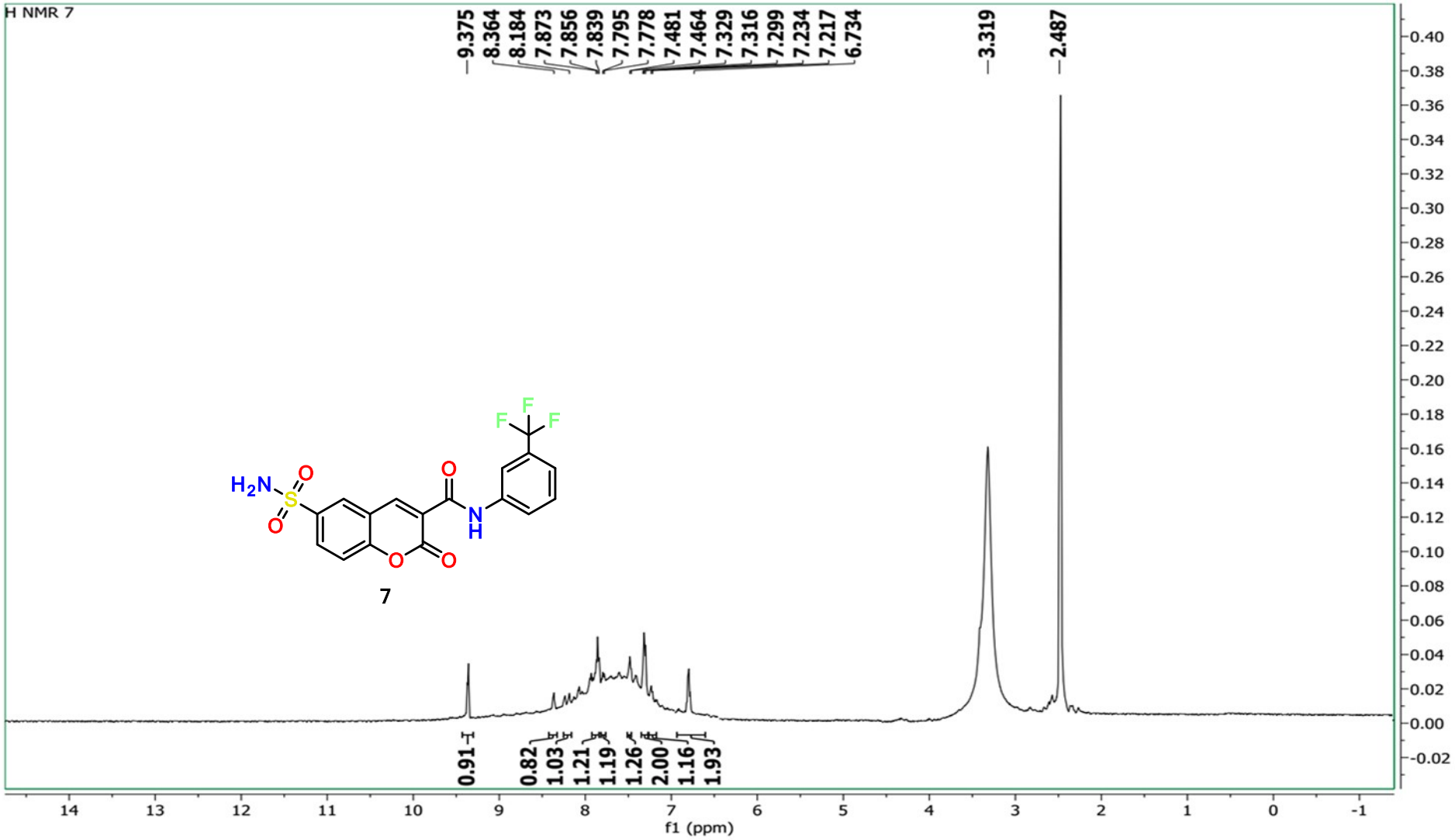

H NMR 6
10.466
8.433
8.341
7.843
7.766
7.745
7.724
7.702
7.696
7.673
7.211
7.190
6.901
3.333
2.500
0.85
0.90
0.99
0.90
2.29
1.18
2.24
1.98
6
f1 (ppm)

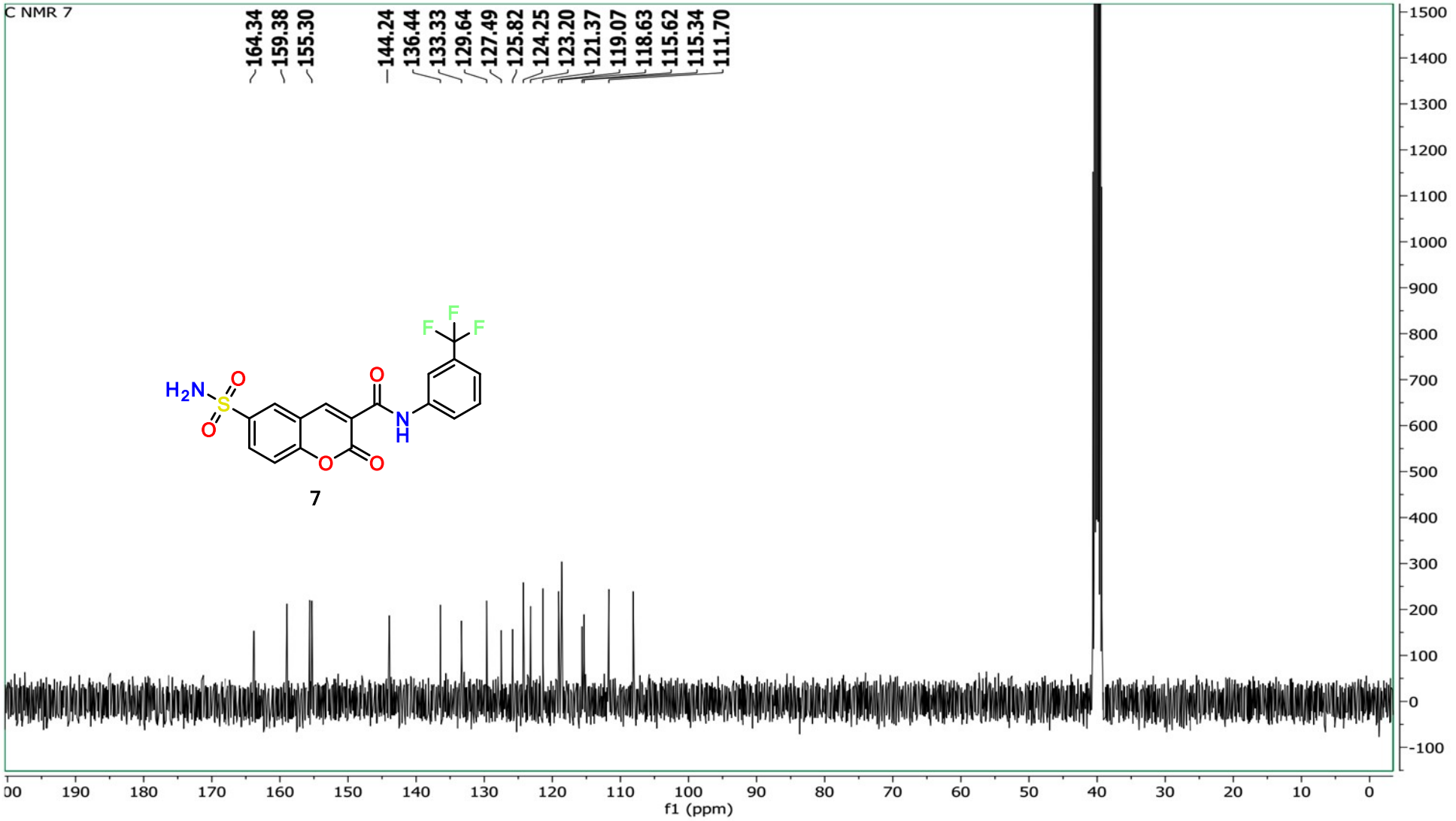

C NMR 6
166.15
162.61
161.85
156.92
152.44
146.68
134.71
130.60
129.74
129.43
128.56
127.33
126.66
124.45
121.49
115.30
H2N
S
O
O
O
N
H
O
O
F
6
0.28
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

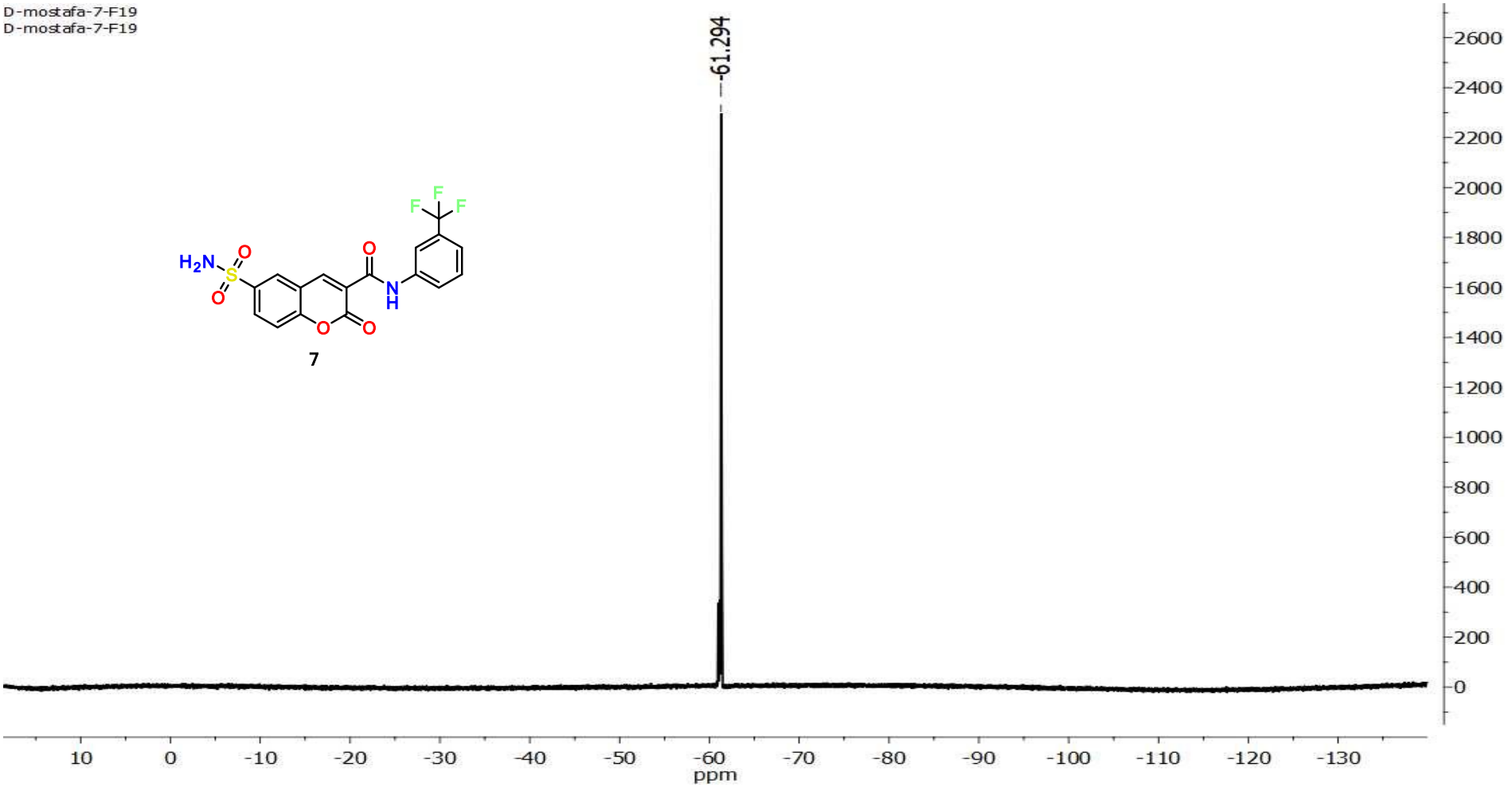


^{19}F NMR of compound 6 in (376 MHz, DMSO-d_6)

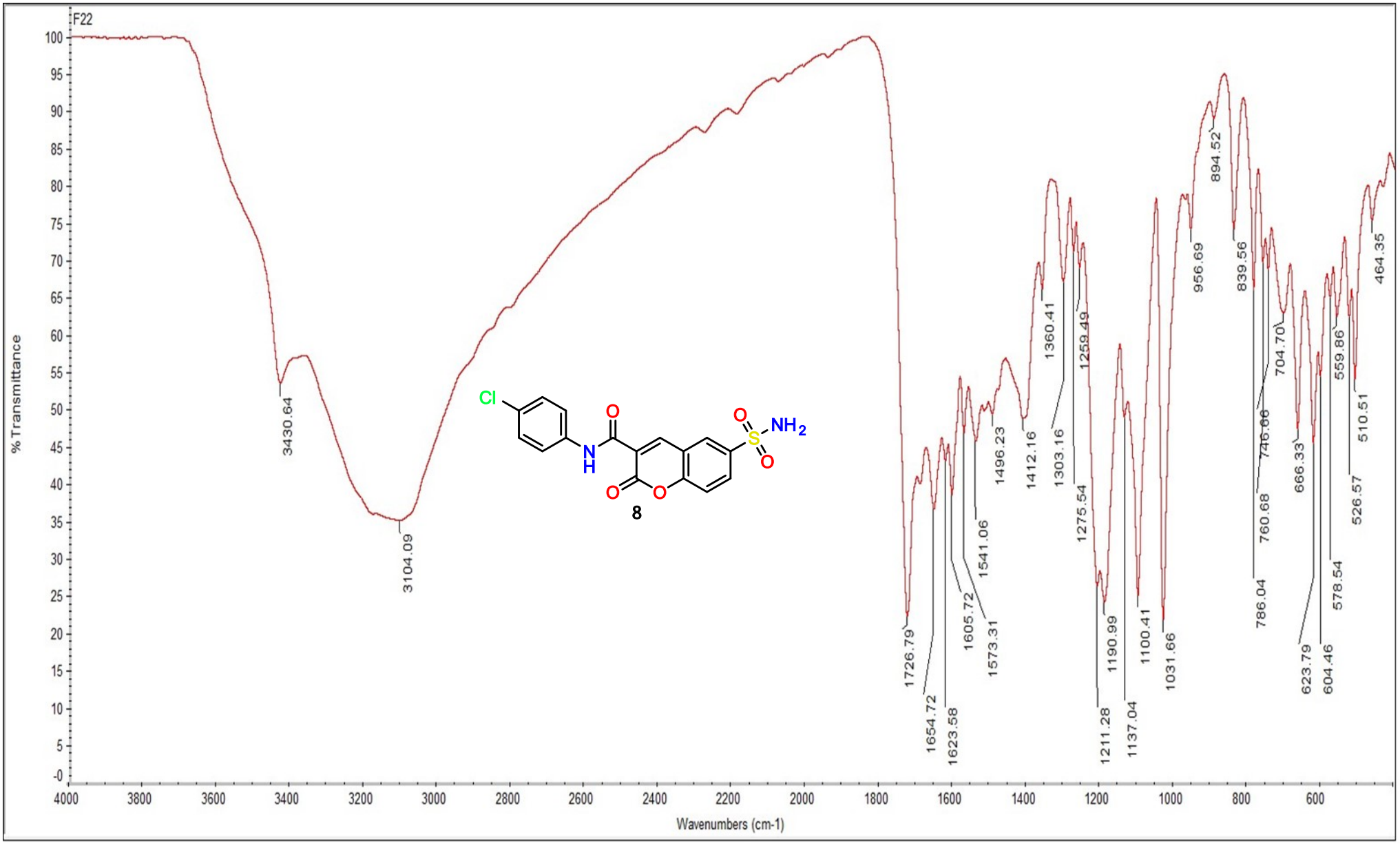

F16
% Transmittance
Wavenumbers (cm-1)
3431.31
3098.15
2054.58
1727.36
1654.90
1622.88
1605.70
1573.46
1538.54
1496.16
1415.46
1360.00
1333.95
1305.84
1275.58
1259.69
1191.97
1137.50
1100.56
1031.29
956.76
894.67
840.26
785.69
760.96
747.20
709.52
666.51
624.45
604.16
579.34
560.14
526.70
510.75
464.66
432.87
7

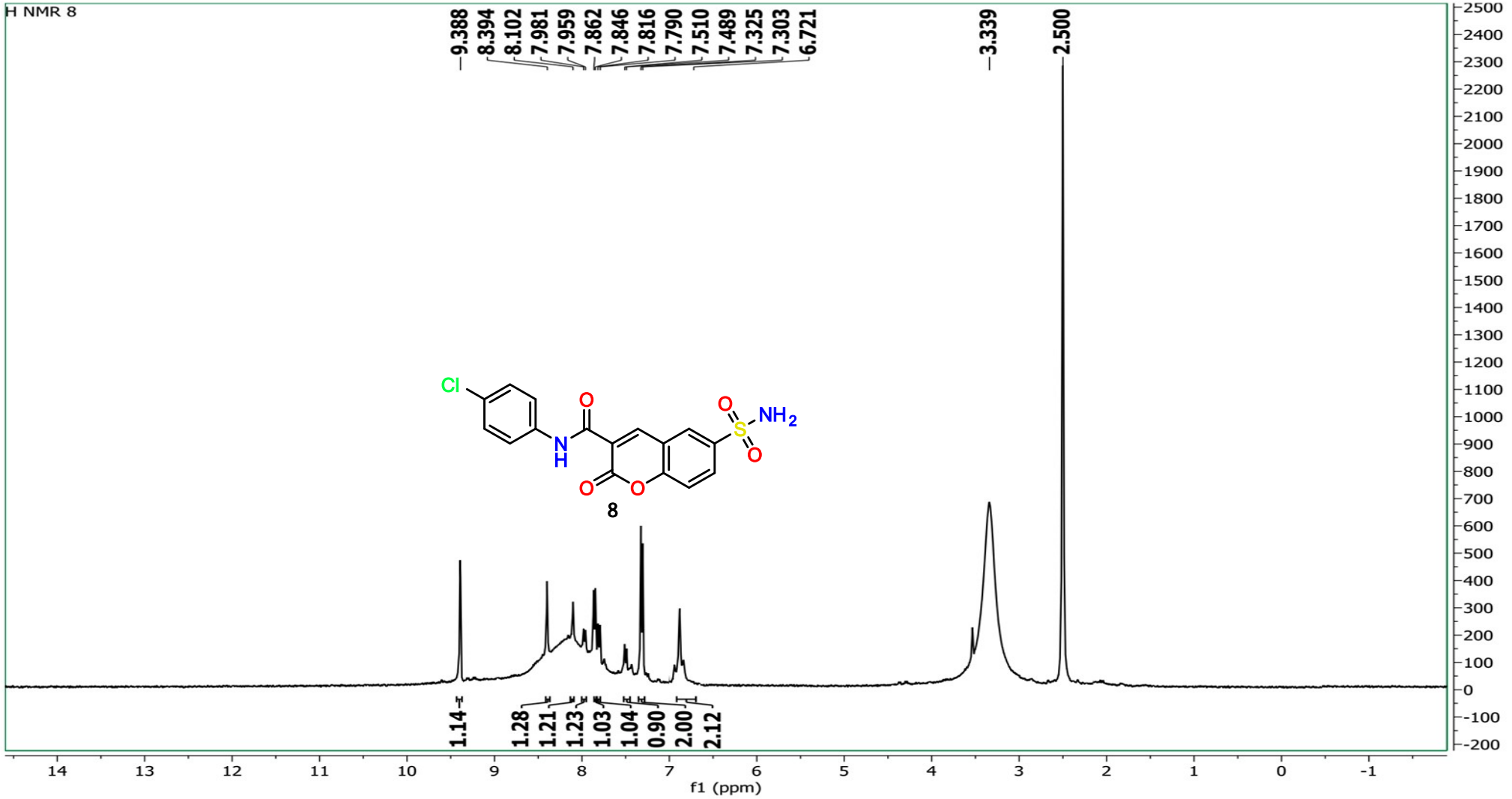

H NMR 7
9.375
8.364
8.184
7.873
7.856
7.839
7.795
7.778
7.481
7.464
7.329
7.316
7.299
7.234
7.217
6.734
3.319
2.487
0.91
0.82
1.03
1.21
1.19
1.26
2.00
1.16
1.93
f1 (ppm)
7

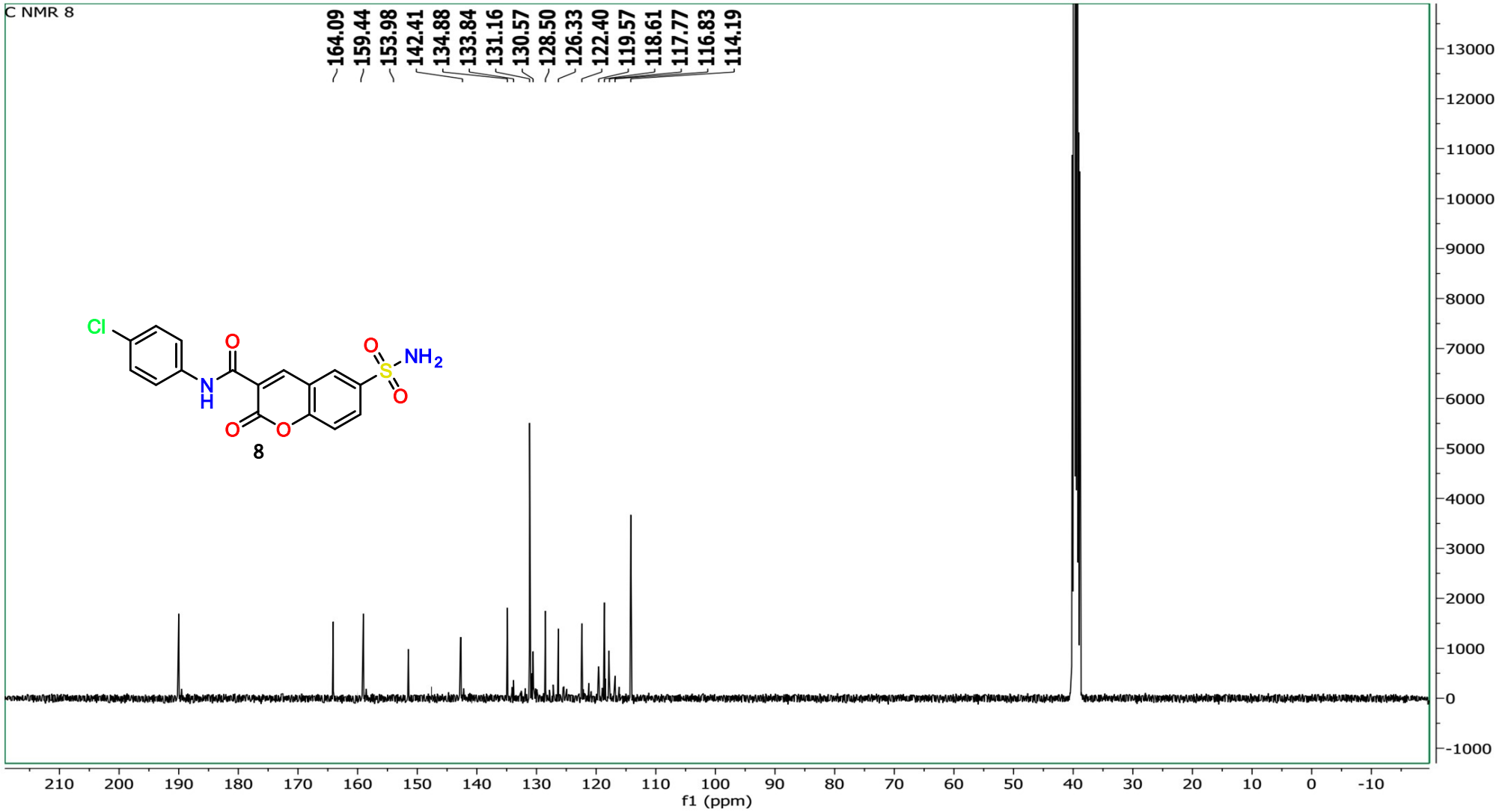

C NMR 7
164.34
159.38
155.30
144.24
136.44
133.33
129.64
127.49
125.82
124.25
123.20
121.37
119.07
118.63
115.62
115.34
111.70
F
F
F
O
N
H
O
O
O
H_2N
S
O
O
7
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

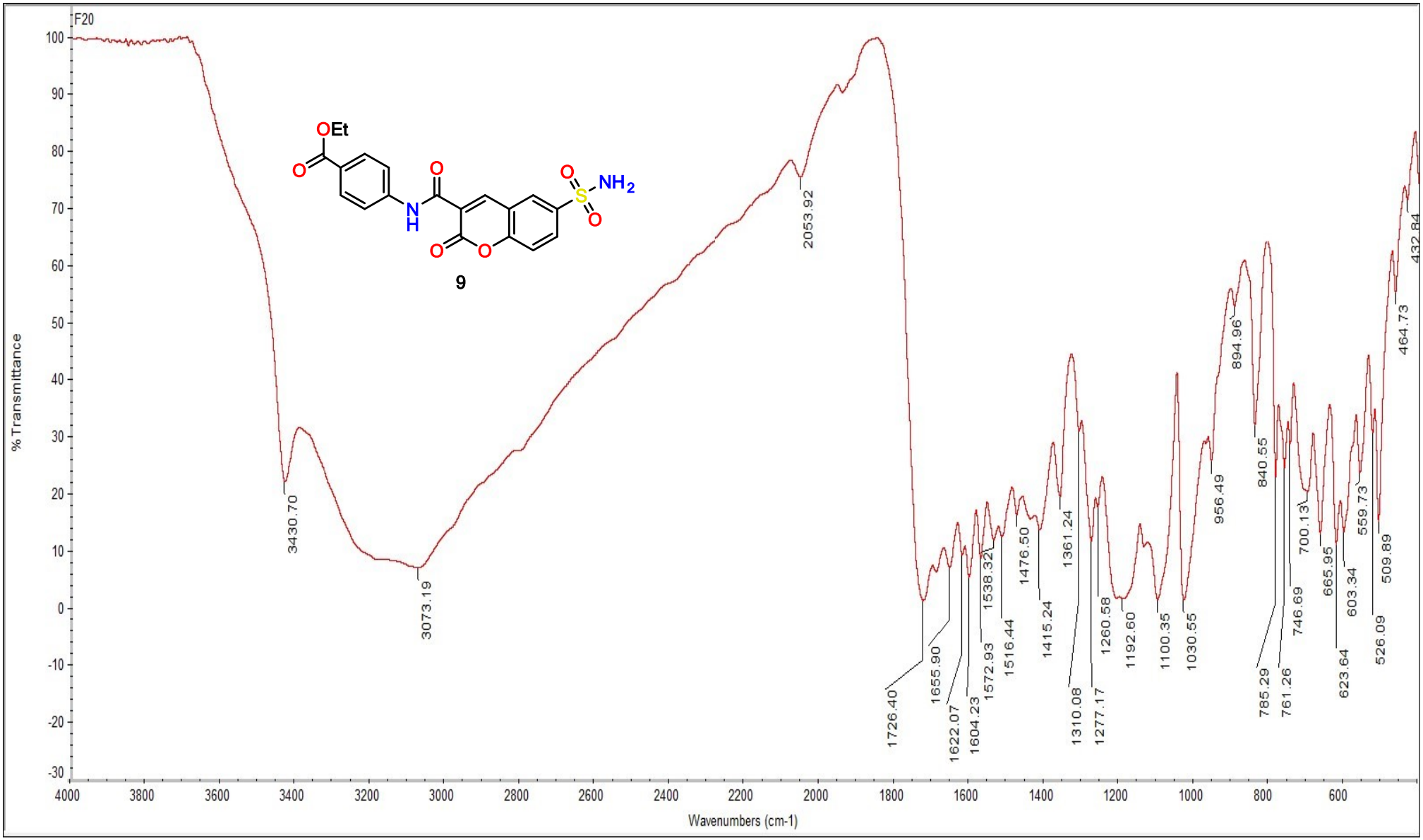


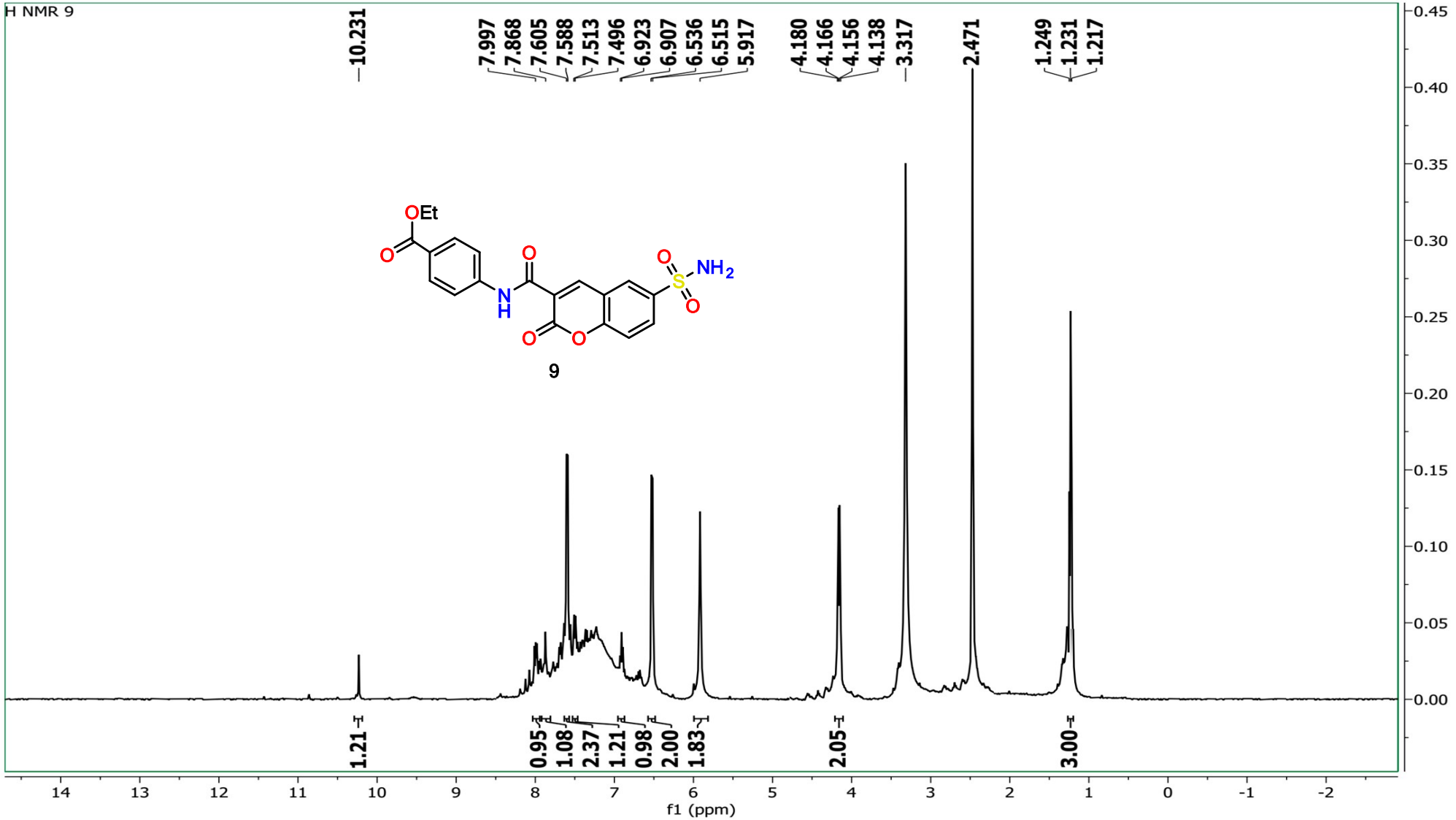
^{19}F NMR of compound 7 in (376 MHz, DMSO-d_6)

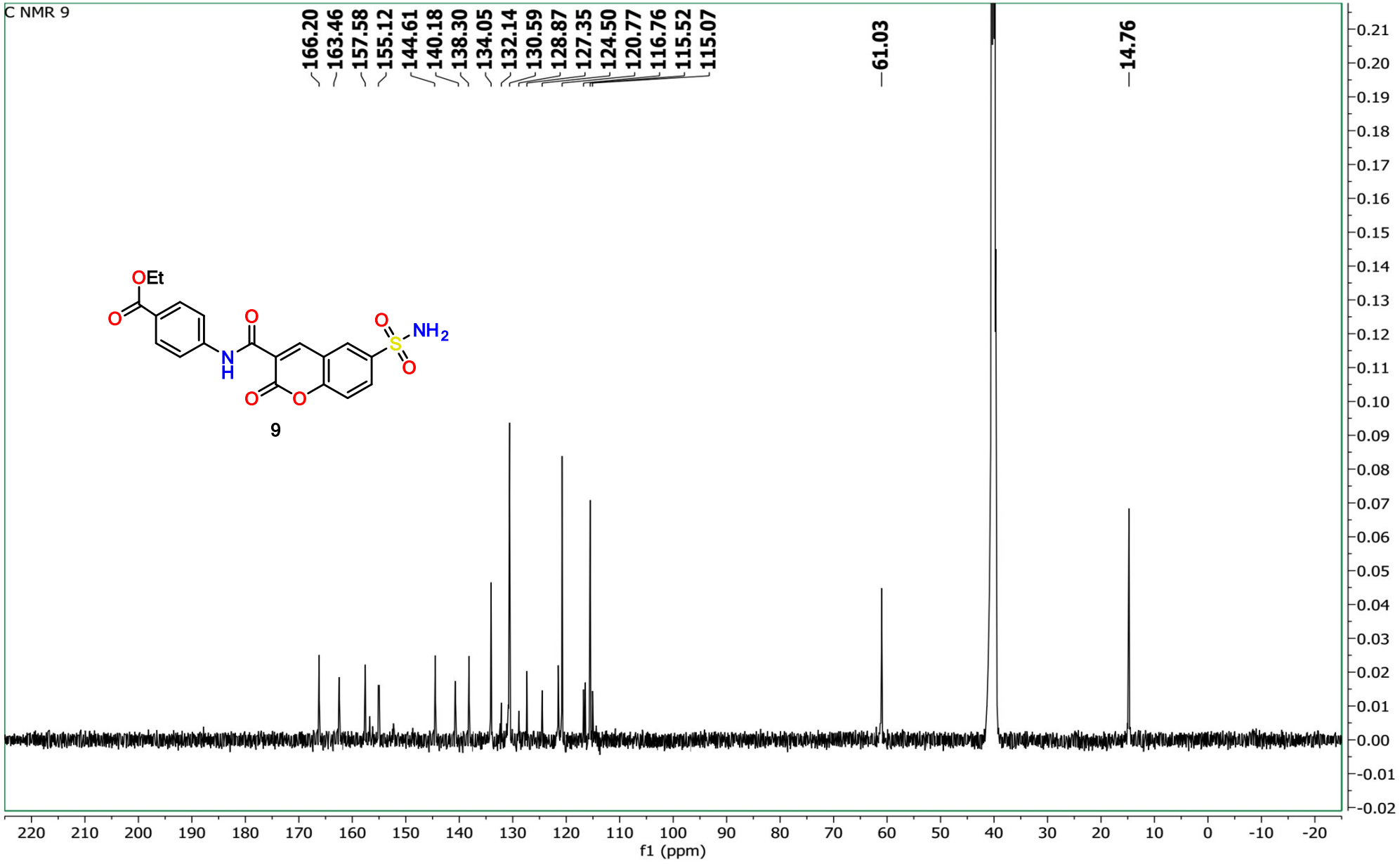

F22
% Transmittance
Wavenumbers (cm-1)
3430.64
3104.09
1726.79
1654.72
1623.58
1605.72
1573.31
1541.06
1496.23
1412.16
1360.41
1303.16
1275.54
1259.49
1211.28
1190.99
1137.04
1100.41
1031.66
956.69
894.52
839.56
786.04
760.68
746.66
704.70
666.33
623.79
604.46
578.54
559.86
526.57
510.51
464.35
Cl
NH2
8


H NMR 8
9.388
8.394
8.102
7.981
7.959
7.862
7.846
7.816
7.790
7.510
7.489
7.325
7.303
6.721
3.339
2.500
Cl
O
N
H
O
O
O
S
O
NH2
8
1.14
1.28
1.21
1.23
1.03
1.04
0.90
2.00
2.12
f1 (ppm)


C NMR 8
164.09
159.44
153.98
142.41
134.88
133.84
131.16
130.57
128.50
126.33
122.40
119.57
118.61
117.77
116.83
114.19
Cl
O
N
H
O
O
O
S
O
NH2
8
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


F20
% Transmittance
Wavenumbers (cm-1)
OEt
NH2
9
3430.70
3073.19
2053.92
1726.40
1655.90
1622.07
1604.23
1572.93
1538.32
1516.44
1476.50
1415.24
1361.24
1310.08
1277.17
1260.58
1192.60
1100.35
1030.55
956.49
894.96
840.55
785.29
761.26
746.69
700.13
665.95
623.64
603.34
559.73
526.09
509.89
464.73
432.84


H NMR 9
10.231
7.997
7.868
7.605
7.588
7.513
7.496
6.923
6.907
6.536
6.515
5.917
4.180
4.166
4.156
4.138
3.317
2.471
1.249
1.231
1.217
OEt
O
O
N
H
O
O
O
S
NH2
O
9
1.21
0.95
1.08
2.37
1.21
0.98
2.00
1.83
2.05
3.00
f1 (ppm)


C NMR 9
166.20
163.46
157.58
155.12
144.61
140.18
138.30
134.05
132.14
130.59
128.87
127.35
124.50
120.77
116.76
115.52
115.07
61.03
14.76
OEt
O
O
N
H
O
O
O
S
O
NH2
9
f1 (ppm)

Biological evaluation

Researcher	: Dr.Yosri ammar	email:	**mob.**
Date	: 30-11-2023		
Assay	: α-Amylase assay		
Samples	: 08 samples .		

Lab Report II

ser	compound			α- Amylase	DF=100
	Original code	Manuscript No.	conc mg/ml	IC_{50}	SD ±
1	**F3**	**6**	361.35	2.11	0.03
2	**F4**	**2**	249.24	1.75	0.01
3	**F10**	**5**	297.28	32.53	0.33
4	**F16**	**7**	411.36	4.39	0.06
5	**F18**	**3**	316.29	14.62	0.16
6	**F20**	**9**	415.42	1.08	0.02
7	**F22**	**8**	401.48	4.23	0.06
8	**F6**	**4**	267.26	**8.551**	0.312
***	**Acarbose**		361.35	**0.43**	0.01

Detailed results.

α- Amylase

Code	IC50	conc	log	%inh	T2	T1	ΔT	RFU2	RFU1	ΔRFU	slope	K.Activity
f3		100	2	95.4	30	0	30	4.62	0	4.62	3.333	5.544
		10	1	88.6	30	0	30	11.41	0	11.41	3.333	13.692
		1	0	81.2	30	0	30	18.77	0	18.77	3.333	22.524
		0.1	-1	70.1	30	0	30	29.91	0	29.91	3.333	35.892
		0.01	-2	43.7	30	0	30	56.29	0	56.29	3.333	67.548
EC				0	30	0	30	100	0	100	3.333	120

code	IC50	conc	log	%inh	T2	T1	ΔT	RFU2	RFU1	ΔRFU	slope	K.Activity
f4		100	2	96.1	30	0	30	3.88	0	3.88	3.333	4.656
		10	1	91.2	30	0	30	8.79	0	8.79	3.333	10.548
		1	0	77.8	30	0	30	22.15	0	22.15	3.333	26.58
		0.1	-1	68.9	30	0	30	31.14	0	31.14	3.333	37.368
		0.01	-2	50.3	30	0	30	49.67	0	49.67	3.333	59.604
EC				0	30	0	30	100	0	100	3.333	120

code	IC50	conc	log	%inh	T2	T1	ΔT	RFU2	RFU1	ΔRFU	slope	K.Activity
f10		100	2	93.4	30	0	30	6.59	0	6.59	3.333	7.908

		10	1	85.6	30	0	30	14.38	0	14.38	3.333	17.256
		1	0	72	30	0	30	28.02	0	28.02	3.333	33.624
		0.1	-1	48.8	30	0	30	51.18	0	51.18	3.333	61.416
		0.01	-2	31.6	30	0	30	68.43	0	68.43	3.333	82.116
EC				0	30	0	30	100	0	100	3.333	120
code	IC50	conc	log	%inh	T2	T1	ΔT	RFU2	RFU1	ΔRFU	slope	K.Activity
f16		100	2	96.2	30	0	30	3.76	0	3.76	3.333	4.512
		10	1	89.6	30	0	30	10.42	0	10.42	3.333	12.504
		1	0	80.8	30	0	30	19.15	0	19.15	3.333	22.98
		0.1	-1	54.9	30	0	30	45.13	0	45.13	3.333	54.156
		0.01	-2	46.1	30	0	30	53.89	0	53.89	3.333	64.668
EC				0	30	0	30	100	0	100	3.333	120
code	IC50	conc	log	%inh	T2	T1	ΔT	RFU2	RFU1	ΔRFU	slope	K.Activity
f18		100	2	96	30	0	30	3.99	0	3.99	3.333	4.788
		10	1	88	30	0	30	12.03	0	12.03	3.333	14.436
		1	0	73.5	30	0	30	26.51	0	26.51	3.333	31.812
		0.1	-1	60.2	30	0	30	39.77	0	39.77	3.333	47.724
		0.01	-2	33.8	30	0	30	66.18	0	66.18	3.333	79.416
EC				0	30	0	30	100	0	100	3.333	120

code	IC50	conc	log	%inh	T2	T1	ΔT	RFU2	RFU1	ΔRFU	slope	K.Activity
f20		100	2	96.6	30	0	30	3.39	0	3.39	3.333	4.068
		10	1	90	30	0	30	9.95	0	9.95	3.333	11.94
		1	0	82.6	30	0	30	17.41	0	17.41	3.333	20.892
		0.1	-1	73.5	30	0	30	26.54	0	26.54	3.333	31.848
		0.01	-2	45.8	30	0	30	54.15	0	54.15	3.333	64.98
EC				0	30	0	30	100	0	100	3.333	120
code	IC50	conc	log	%inh	T2	T1	ΔT	RFU2	RFU1	ΔRFU	slope	K.Activity
f22		100	2	95.4	30	0	30	4.61	0	4.61	3.333	5.532
		10	1	88.6	30	0	30	11.39	0	11.39	3.333	13.668
		1	0	75.8	30	0	30	24.16	0	24.16	3.333	28.992
		0.1	-1	60.5	30	0	30	39.51	0	39.51	3.333	47.412
		0.01	-2	44.5	30	0	30	55.47	0	55.47	3.333	66.564
EC				0	30	0	30	100	0	100	3.333	120
F6	IC50	conc	log	%inh	T2	T1	ΔT	RFU2	RFU1	ΔRFU	slope	K.Activity
		100	2	94.2	30	0	30	5.75	0	5.75	3.333	6.9
		10	1	84.7	30	0	30	15.29	0	15.29	3.333	18.348
		1	0	70.5	30	0	30	29.46	0	29.46	3.333	35.352
		0.1	-1	52.6	30	0	30	47.41	0	47.41	3.333	56.892
		0.01	-2	31.8	30	0	30	68.22	0	68.22	3.333	81.864

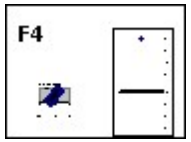
				0	30	0	30	100	0	100	3.333	120
code	IC50	conc	log	%inh	T2	T1	ΔT	RFU2	RFU1	ΔRFU	slope	K.Activity
Acarbose		100	2	96.5	30	0	30	3.45	0	3.45	3.333	4.14
		10	1	90.2	30	0	30	9.81	0	9.81	3.333	11.772
		1	0	84.3	30	0	30	15.73	0	15.73	3.333	18.876
		0.1	-1	75.4	30	0	30	24.63	0	24.63	3.333	29.556
		0.01	-2	47.5	30	0	30	52.46	0	52.46	3.333	62.952
EC				0	30	0	30	100	0	100	3.333	120

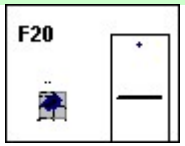
Lab Report I

ser	compound			α-glucosidase IC50	DF=100 SD ±
	code		M.W	mg/ml	
1	F4	2	---	0.548	0.02
2	F20	9	---	2.435	0.09
***	Acarbose		---	0.604	0.02

Detailed results.

α- Glucosidase

code	IC50	conc	log	%inh	T2	T1	ΔT	RFU2	RFU1	ΔRFU	slope	K.Activity
F4		10	1	90.7	30	0	30	9.33	0	9.33	3.333	11.196
		5	0.7	76.4	30	0	30	23.62	0	23.62	3.333	28.344
		1	0	53.4	30	0	30	46.55	0	46.55	3.333	55.86
		0.1	-1	20.6	30	0	30	79.35	0	79.35	3.333	95.22
		0.01	-2	8.98	30	0	30	91.02	0	91.02	3.333	109.22
EC				0	30	0	30	100	0	100	3.333	120

code	IC50	conc	log	%inh	T2	T1	ΔT	RFU2	RFU1	ΔRFU	slope	K.Activity
F20		10	1	83.8	30	0	30	16.23	0	16.23	3.333	19.476
		5	0.7	54.2	30	0	30	45.77	0	45.77	3.333	54.924
		1	0	20.6	30	0	30	79.38	0	79.38	3.333	95.256
		0.1	-1	8.85	30	0	30	91.15	0	91.15	3.333	109.38
		0.01	-2	3.45	30	0	30	96.55	0	96.55	3.333	115.86
EC				0	30	0	30	100	0	100	3.333	120

code	IC50	conc	log	%inh	T2	T1	ΔT	RFU2	RFU1	ΔRFU	slope	K.Activity
Acarbose		10	1	90.1	30	0	30	9.86	0	9.86	3.333	11.832
		5	0.7	82.6	30	0	30	17.44	0	17.44	3.333	20.928
		1	0	51.4	30	0	30	48.63	0	48.63	3.333	58.356
		0.1	-1	13.8	30	0	30	86.22	0	86.22	3.333	103.46
		0.01	-2	5.95	30	0	30	94.05	0	94.05	3.333	112.86
EC				0	30	0	30	100	0	100	3.333	120

Lab Report

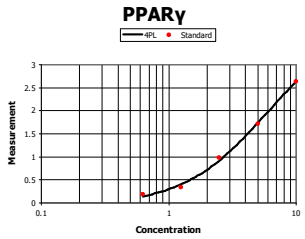
ser	sample			PPARγ	FLD
	Original code number	Manuscript number	Type	ug/ml	
1	**F4**	2		**3.152±0.03**	**1.365**
2	**F20**	--9-		**3.706±0.32**	**1.605**
3	**pioglitazone**	---		**4.884±0.29**	**2.115**
4	**control**	---		**2.309±0.02**	**1**

Detailed Results:

Standard conc.

ST	Conc.
St.1	10
St.2	5
St.3	2.5
St.4	1.25
St.5	0.625

Plate map



	1	2	3	4	5	6	7	8	9	10	11	12
A	St.1	**s9**	**pio**	--	--	--	--	--	--	--	--	--
B	St.2	**s9**	**pio**	--	--	--	--	--	--	--	--	--
C	St.3	**s21**	**cont**	--	--	--	--	--	--	--	--	--
D	St.4	**s21**	**cont**	--	--	--	--	--	--	--	--	--
E	St.5	**s4**	--	--	--	--	--	--	--	--	--	--
F	B	**s4**	--	--	--	--	--	--	--	--	--	--
G	B	**s20**	--	--	--	--	--	--	--	--	--	--
H	B	**s20**	--	--	--	--	--	--	--	--	--	--

Samples OD results

	1	2	3	4	5	6	7	8	9	10	11	12
A	2.649	1.313	1.771	0	0	0	0	0	0	0	0	0
B	1.717	1.246	1.658	0	0	0	0	0	0	0	0	0
C	0.993	1.661	0.862	0	0	0	0	0	0	0	0	0
D	0.339	1.643	0.847	0	0	0	0	0	0	0	0	0
E	0.186	1.166	0	0	0	0	0	0	0	0	0	0
F	0.015	1.183	0	0	0	0	0	0	0	0	0	0
G	0.004	1.439	0	0	0	0	0	0	0	0	0	0
H	0.007	1.287	0	0	0	0	0	0	0	0	0	0

Calibrator	Wells	Conc.	Raw (Corrected)	Backfit	Recovery %
Standard1	A1	10	2.64	10.06	100.6
Standard2	B1	5	1.71	4.89	97.8
Standard3	C1	2.5	0.984	2.662	106.5
Standard4	D1	1.25	0.33	1.079	86.29
Standard5	E1	0.625	0.177	0.7074	113.2

Sample	Wells	Raw	Background Corrected	Conc.	Conc. (Average)	%CV	SD	SEM
F4	E2	1.17	1.17	3.128	3.152	1.07	0.0336	0.0238
	F2	1.18		3.176				
F20	G2	1.44	1.35	3.937	3.706	8.84	0.328	0.232
	H2	1.29		3.474				
pioglitazone	A3	1.77	1.71	5.094	4.884	6.08	0.297	0.21
	B3	1.66		4.674				
control	C3	0.862	0.846	2.328	2.309	1.15	0.0265	0.0187
	D3	0.847		2.291				
Blank	F1	0.015	0	0.2304	0.2087	9.36	0.0195	0.0113
	G1	0.004		0.1926				
	H1	0.007		0.2031				

Docking simulation figures

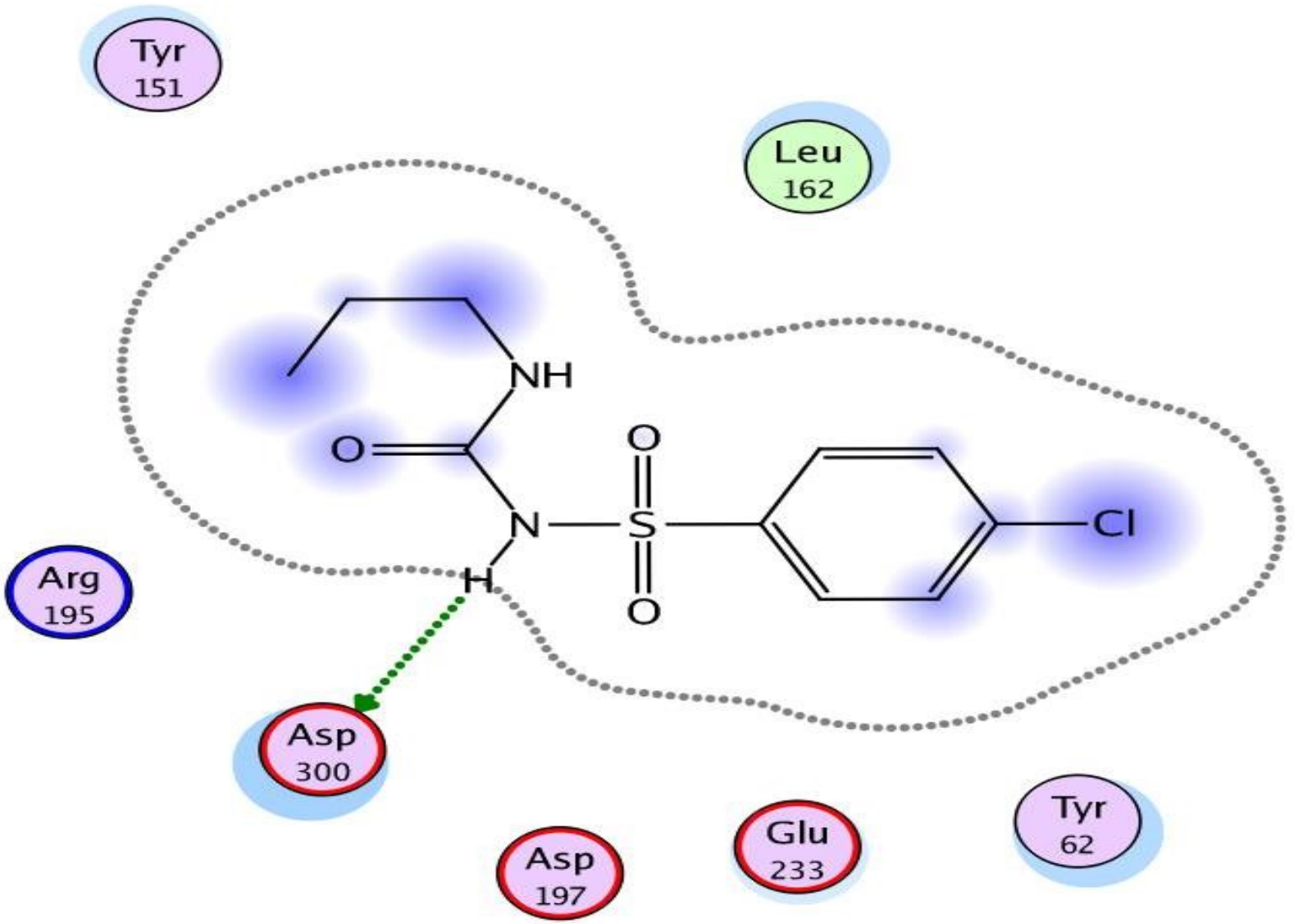


Figure S1: 2D interaction of **Chlorpropamide** inside the active site of α-amylase (PDB: 2QV4)

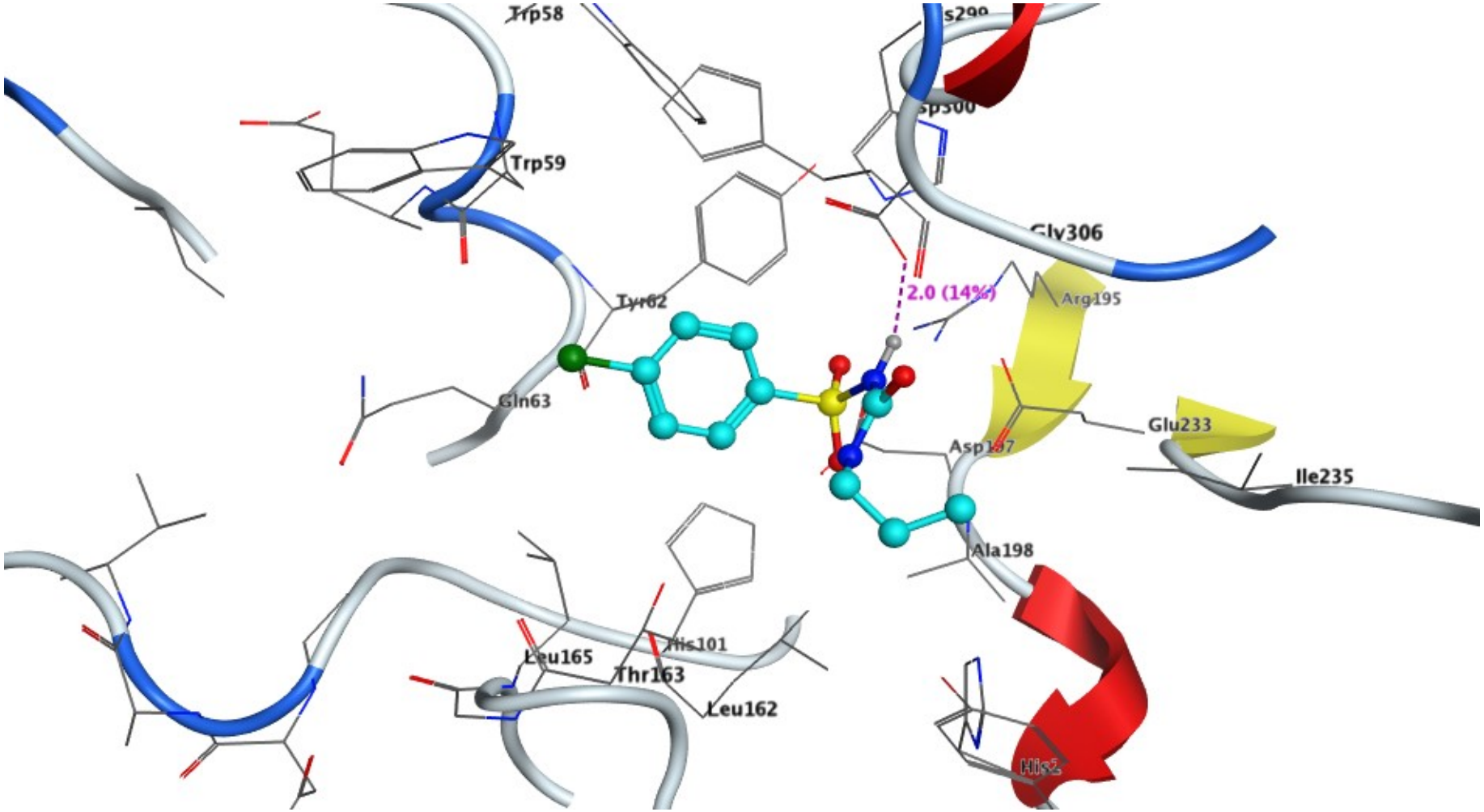


Figure S2: 3D interaction of **Chlorpropamide** inside the active site of α-amylase (PDB: 2QV4)

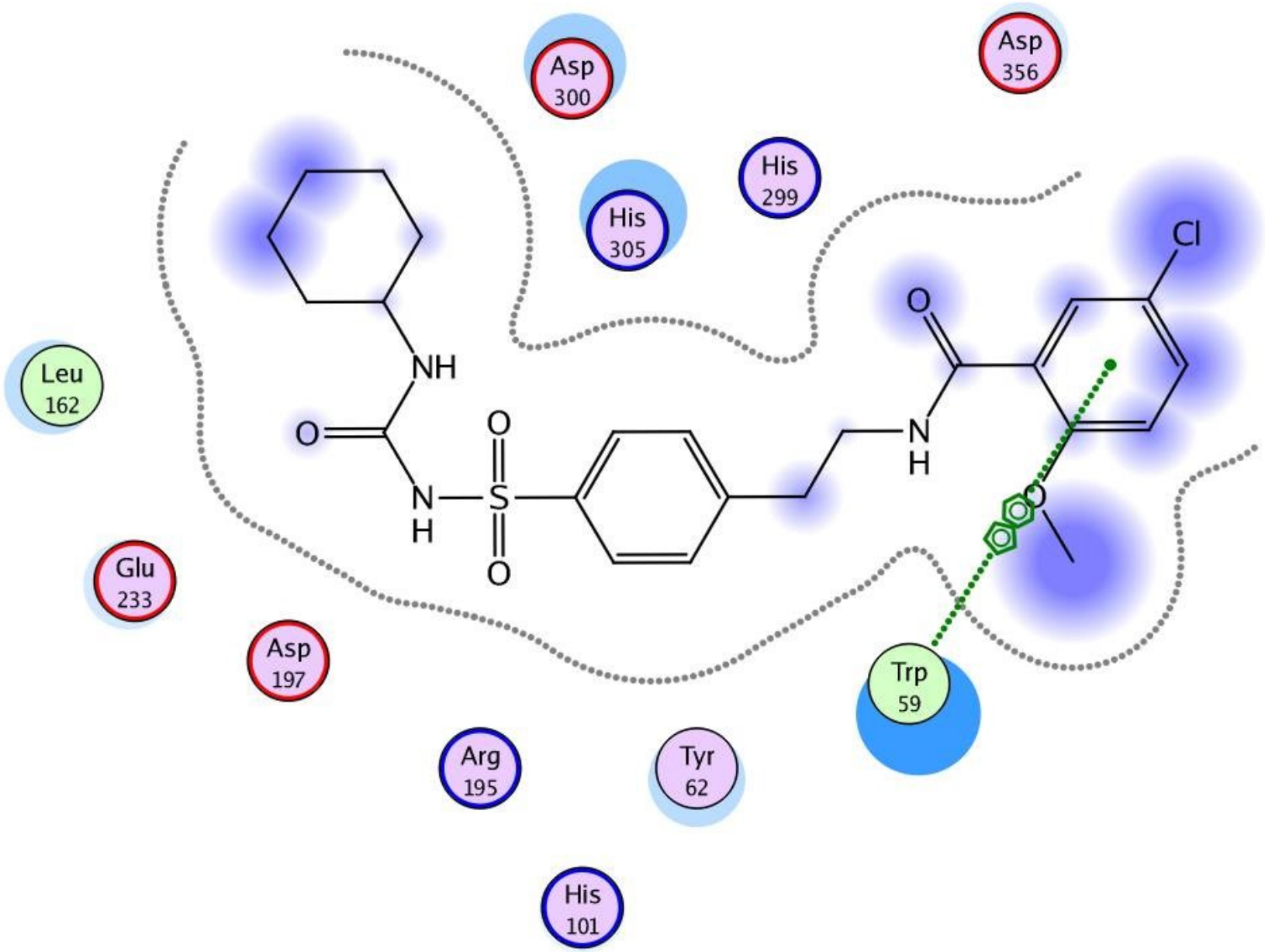


Figure S3: 2D interaction of **Glibenclamide** inside the active site of α-amylase (PDB: 2QV4)

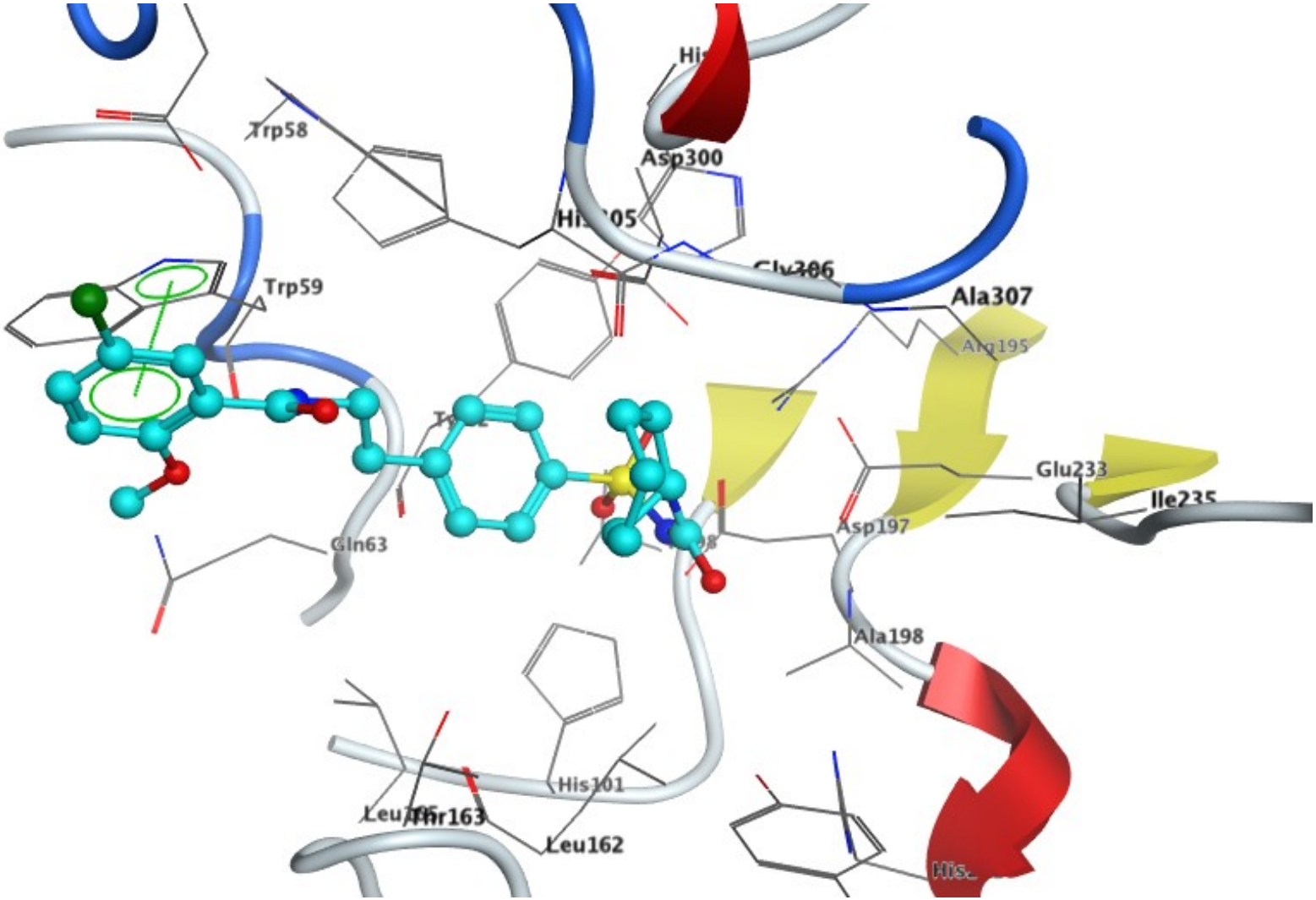


Figure S4: 3D interaction of **Glibenclamide** inside the active site of α-amylase (PDB: 2QV4)

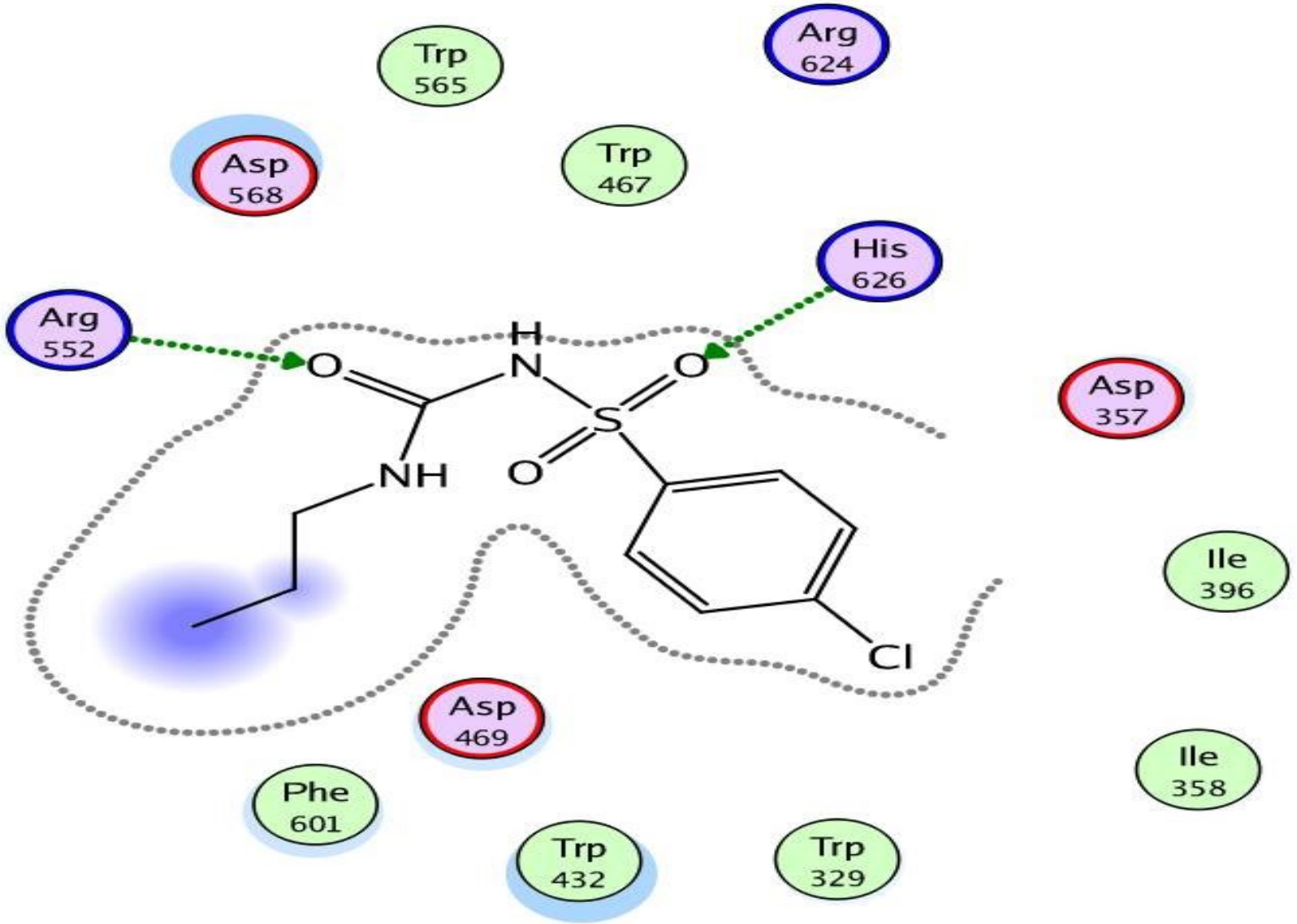


Figure S5: 2D interaction of **Chlorpropamide** inside the active site of α-glucosidase (PDB: 3w37)

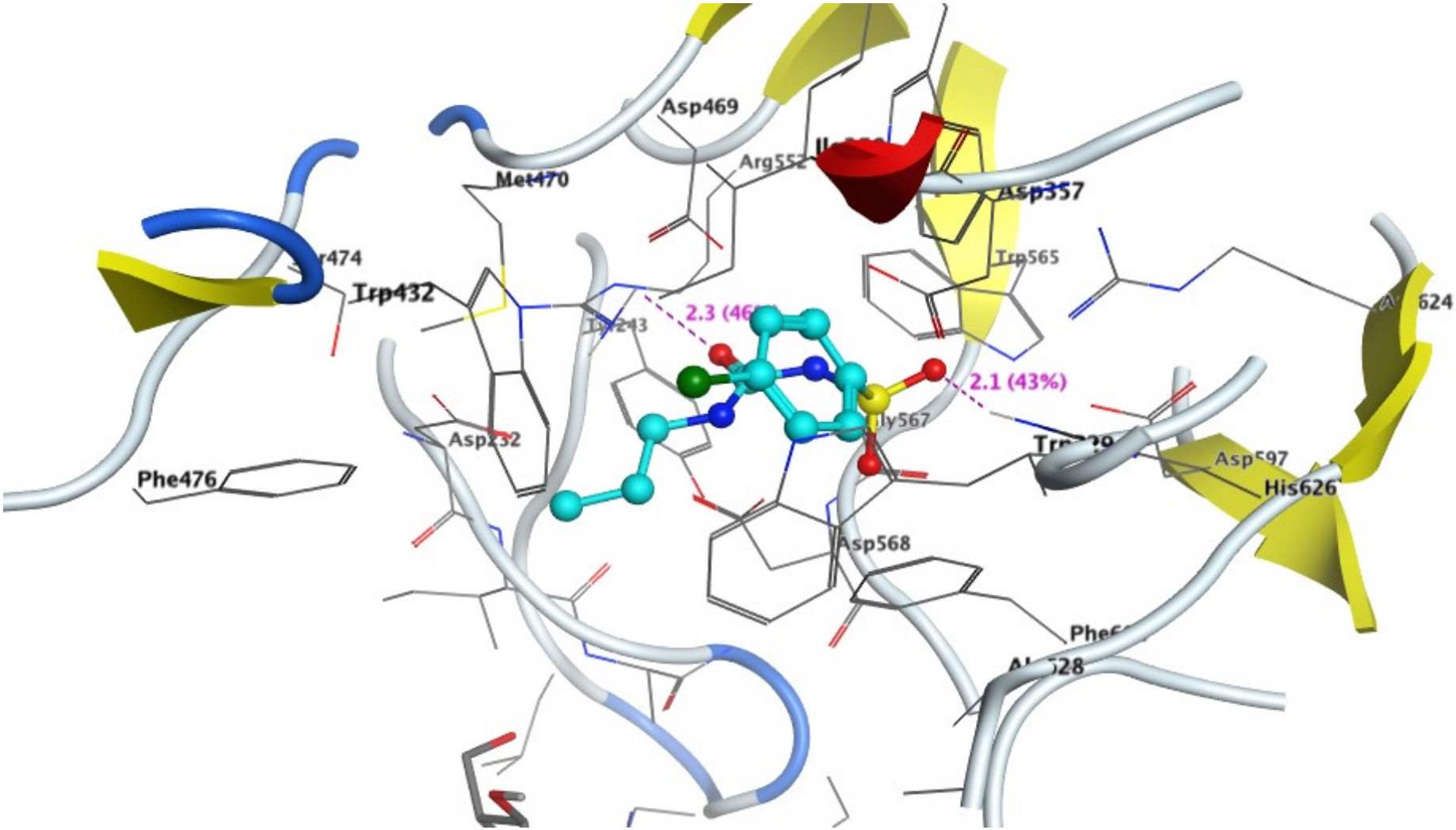


Figure S6: 3D interaction of **Chlorpropamide** inside the active site of α-glucosidase (PDB: 3w37)

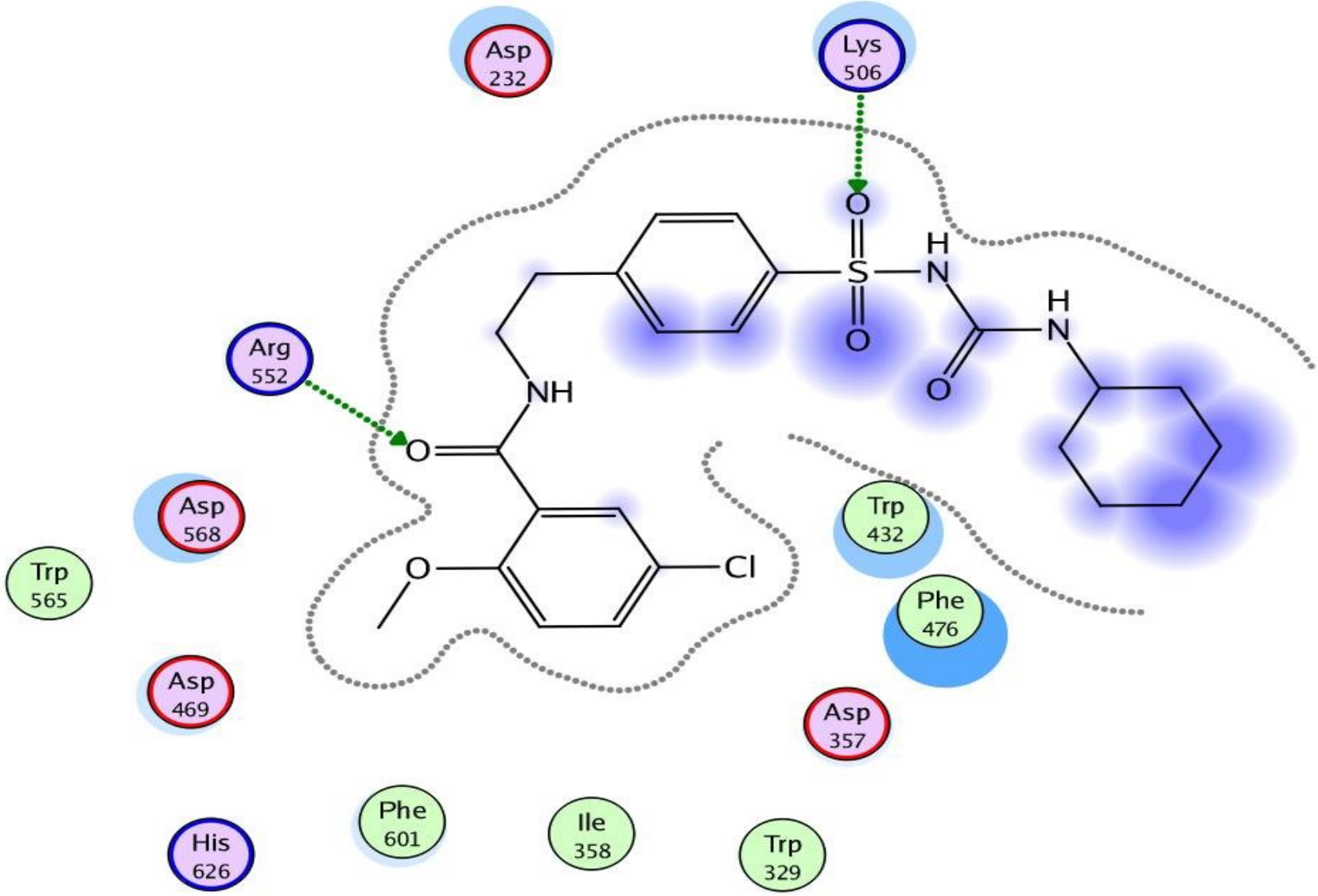


Figure S7: 2D interaction of **Glibenclamide** inside the active site of α-glucosidase (PDB: 3w37)

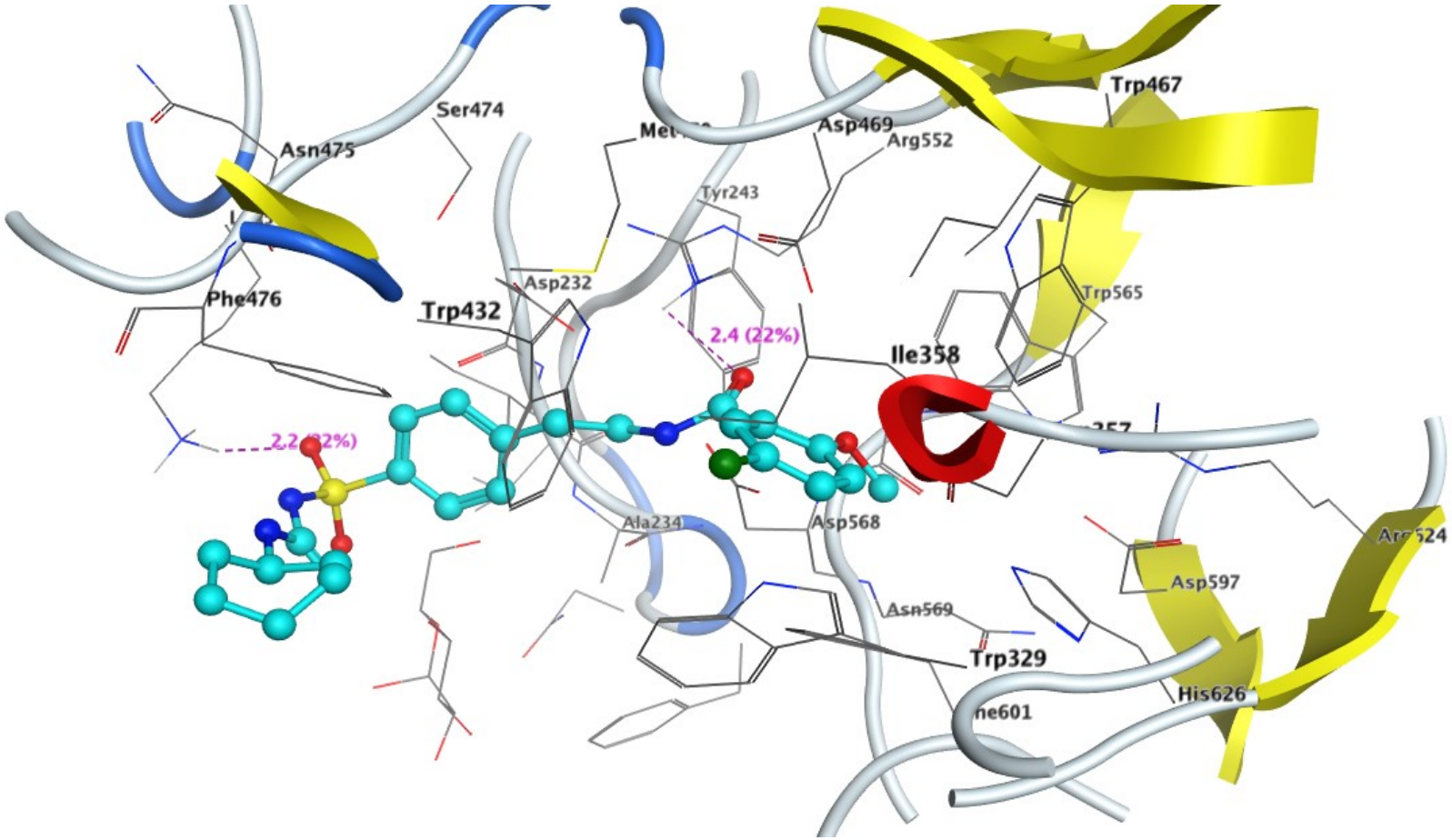


Figure S8: 3D interaction of **Glibenclamide** inside the active site of α-glucosidase (PDB: 3w37)

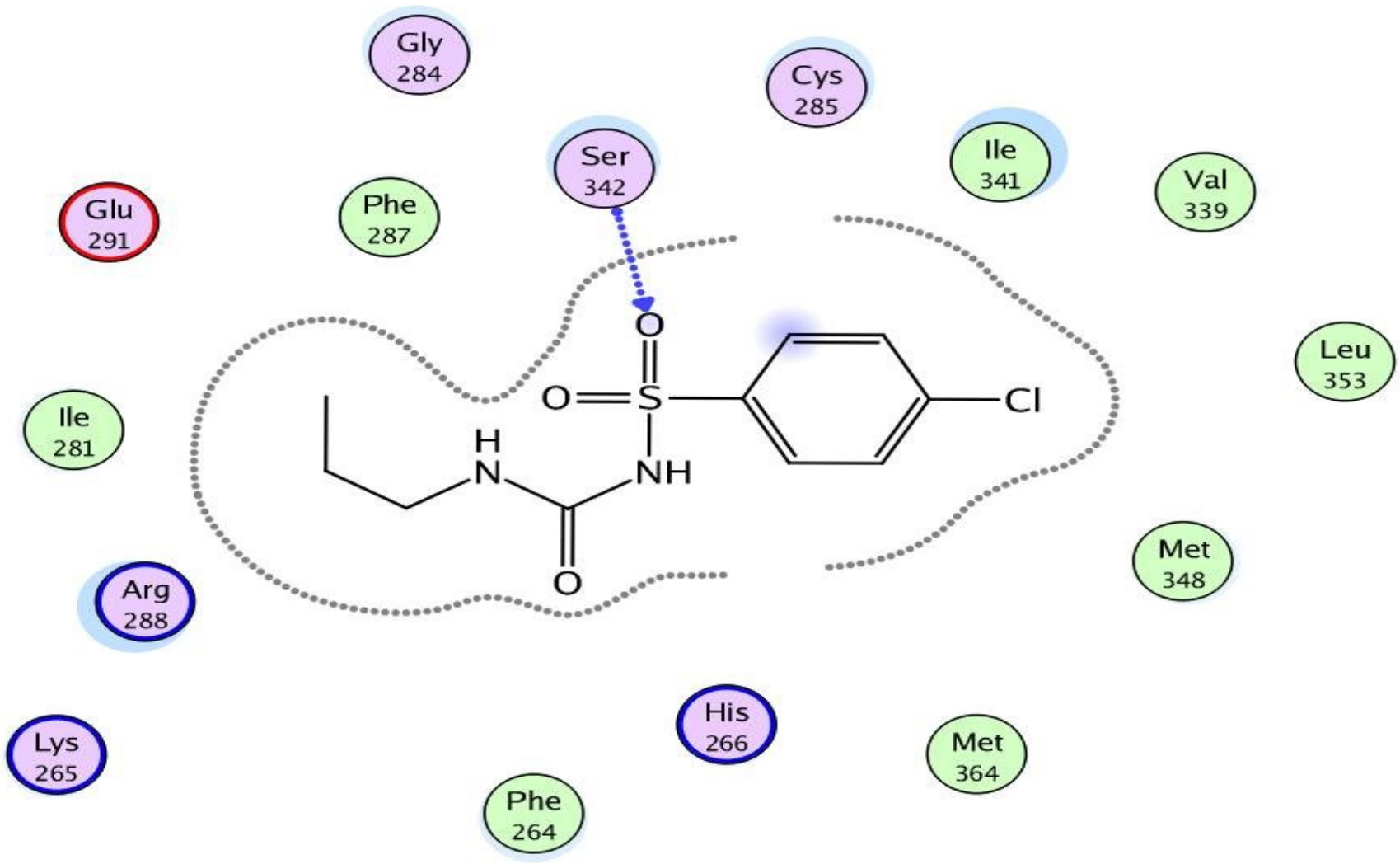


Figure S9: 2D interaction of **Chlorpropamide** inside the active site of PPAR-γ (PDB: 3SZ1)

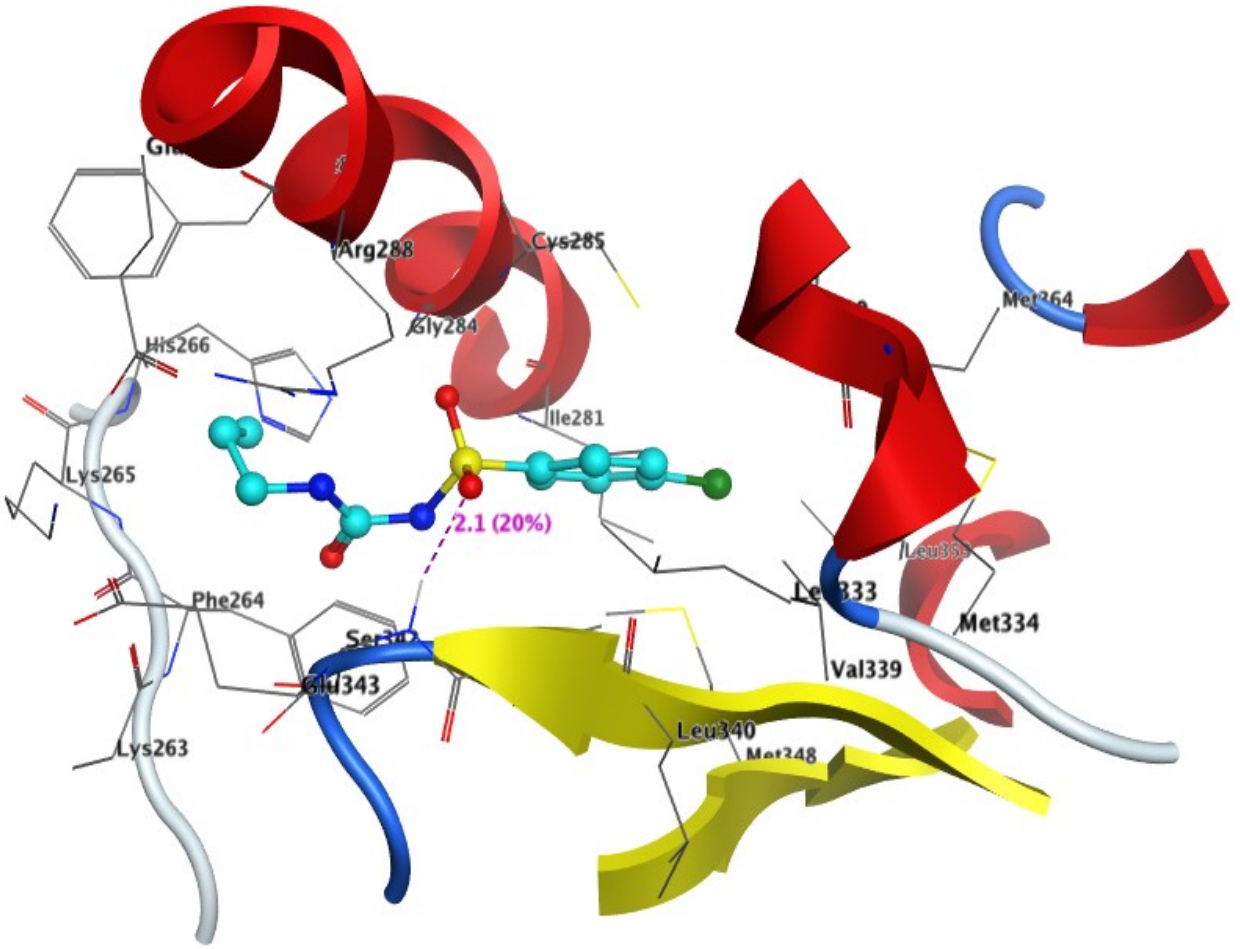


Figure S10: 3D interaction of **Chlorpropamide** inside the active site of PPAR-γ (PDB: 3SZ1)

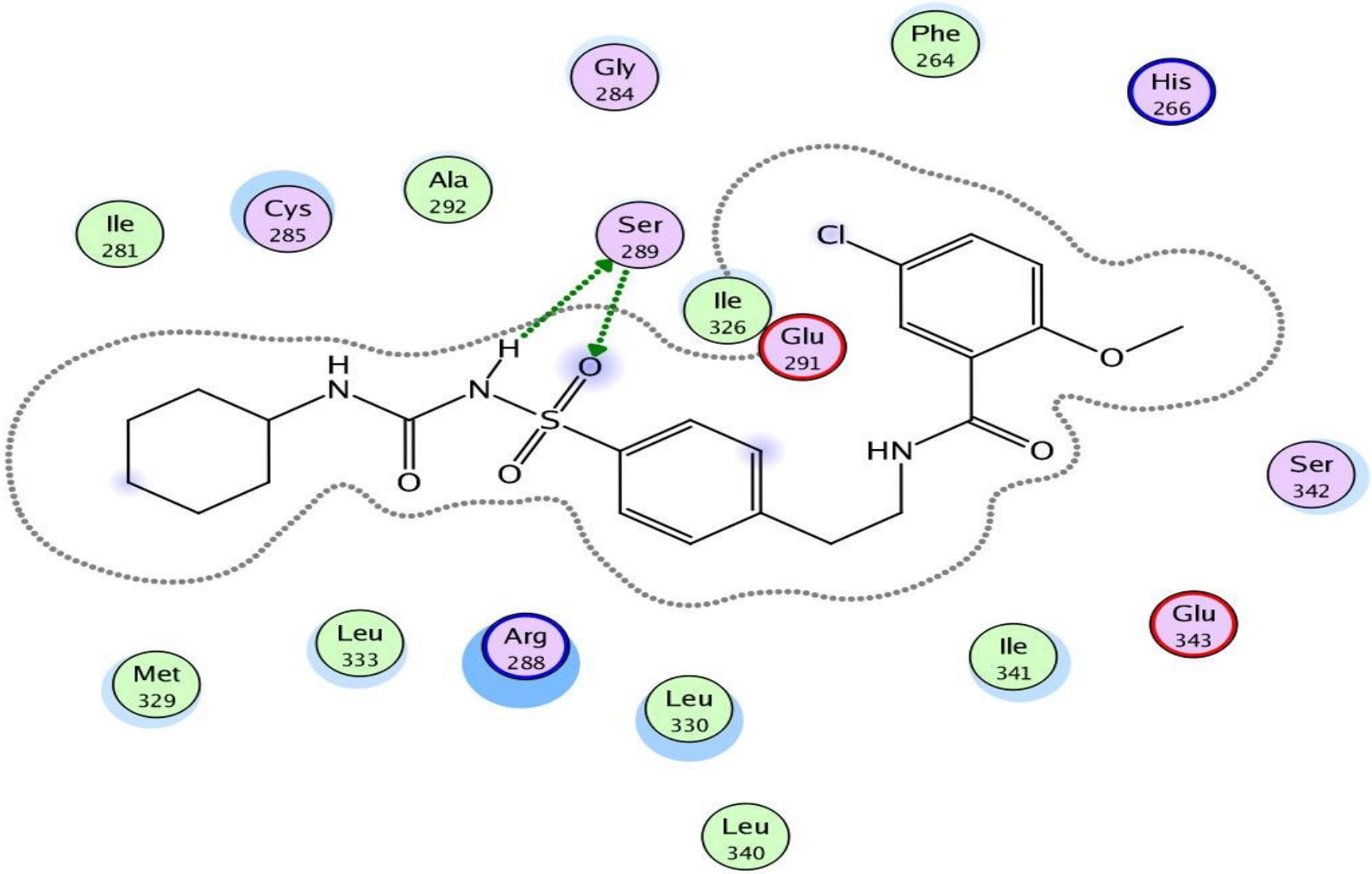


Figure S11: 2D interaction of **Glibenclamide** inside the active site of PPAR-γ (PDB: 3SZ1)

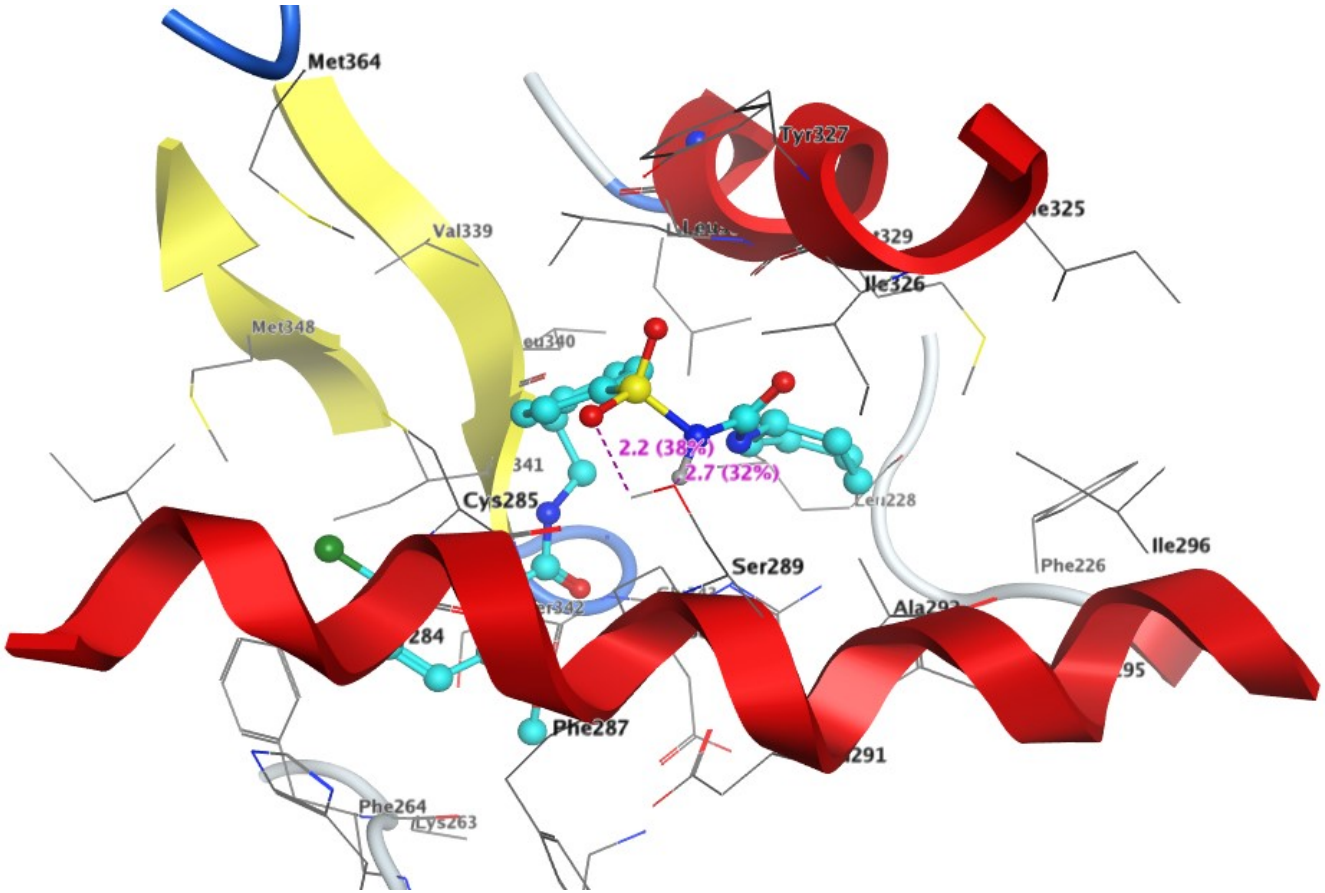


Figure S12: 3D interaction of **Glibenclamide** inside the active site of PPAR-γ (PDB: 3SZ1)