Supplementary

Unlocking the Antidiabetic Potential of Novel Pyrazole–Triazole Hybrids Through Synthesis, Dual α-Amylase/α-Glucosidase Inhibition, Multiscale Biological Evaluation, and Molecular Dynamics Studies

Mariam M. Fakhry[1*], Mahmoud S. Elkotamy[2], Mohamed K. Elgohary[1], Mahmoud Abdelrahman Alkabbani[3], Mayada H. Mohamed[4], Abdulrahman A. Almehizia[5], Ahmed M. Naglah[5*], Morkoss M. Fakhry[6], Mohamed Fares [1,7], Hatem A Abdel-Aziz[8*], Jalloul Bouajila[9*]

[1] Pharmaceutical Chemistry Department, Faculty of Pharmacy, Egyptian Russian University, Badr, Egypt.

[2] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Alsalam University, Kafr Alzayat 31611, Algharbia, Egypt.

[3.] Pharmacology and Toxicology Department, Faculty of Pharmacy, Egyptian Russian University, Badr City, Cairo 11829, Egypt.

[4] University Family Medicine Center, Department of Family and Community Medicine, College of Medicine, King Saud University Medical City, P.O. Box 2925, Riyadh 11472, Saudi Arabia.

[5] Drug Exploration and Development Chair (DEDC), Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia.

[6] Biochemistry Department, Faculty of Pharmacy, Egyptian Russian University, Badr City, Cairo 11829, Egypt.

[7.] Sydney Pharmacy School, The University of Sydney, Sydney, New South Wales 2006, Australia

[8] Applied Organic Chemistry Department, National Research Center, Dokki, Cairo 12622, Egypt.

[9] Laboratoire de Génie Chimique, Université de Toulouse, Toulouse INP, CNRS, LGC, Toulouse, France.

***Corresponding Authors**

Mariam-medhat@eru.edu.eg, anaglah@ksu.edu.sa, Hatem_741@yahoo.com, jalloul.bouajila@univ-tlse3.fr

Supplementary content

Supplementary content..... 3

Results and discussion 7

Table S 1. The %inhibition of 8a-i and 12a-i against α-glucosidase at 25 µM. 14

Table S 2. Effect of compounds 8g, 12d, and 12e on postprandial blood glucose levels in alloxan-induced diabetic rats 15

Data are expressed as mean ± SD and were analyzed using two-way ANOVA followed by Tukey's post hoc test. The letters a, b, and c indicate statistically significant differences at $p < 0.05$, where [a] denotes comparison with the normal control group, [b] with the diabetic control group, and [c] with the vildagliptin-treated group..... 15

Figure S 1. Food intake in normoglycemic mice during the oral glucose tolerance test. Data are expressed as mean ± SD and were analyzed using one-way ANOVA, followed by Tukey's post hoc test. No statistically significant differences were observed among groups ($p > 0.05$), indicating that changes in blood glucose levels were not attributable to altered food intake..... 16

Figure S 2: *Effect of compounds 8g, 12d, and 12e on blood glucose levels in normoglycemic mice during the oral glucose tolerance test. Data are expressed as mean ± SD and were analyzed using two-way ANOVA followed by Tukey's post hoc test. The letters a, b, and c indicate statistically significant differences at $p < 0.05$, where a denotes comparison with the normal control group, b with the diabetic control group, and c with the vildagliptin-treated group.* 16

Molecular Docking..... 18

Figure S 3. Binding mode of co-crystalized ligand in the biding site of co-crystalized MALTOPENTAOSE in amylase active site (PDB:1BAG)..... 19

Figure S 4. Superimposition of co-crystalized MALTOPENTAOSE (purple) and redocked MALTOPENTAOSE (blue) for validation of docking protocol. 20

Figure S 5. Binding mode of co-crystalized ligand in the biding site of co-crystalized α-D-Glucopyranose in glycosidase active site (PDB:3A4A). 20

Figure S 6. Superimposition of co-crystalized α-D-Glucopyranose (purple) and redocked α-D-Glucopyranose (blue) for validation of docking protocol..... 21

Table S 3. Binding score, amino acid interaction and bond length of compounds 7g, 10d and 10e within the active site of alpha-amylase and alpha glycosidase active sites. 22

Virtual ADMET Studies..... 24

^{1}HNMR and ^{13}CNMR Spectra..... 26

Figure S 8. ^{1}H NMR of compound 8a..... 27

Figure S 9. ^{13}C NMR of compound 8a 28

Figure S 10. ^{1}H NMR of compound 8b 29

Figure S 11. ^{13}C NMR of compound 8b 30

Figure S 12. ^{1}H NMR of compound 8c..... 31

Figure S 13. ^{13}C NMR of compound 8c 32

Figure S 14. ^{1}H NMR of compound 8d 33

Figure S 15.. ^{13}C NMR of compound 8d 34

Figure S 16. ^{1}H NMR of compound 8e..... 35

Figure S 17..n^{13}C NMR of compound 8e 36

Figure S 18. ^{1}H NMR of compound 8f..... 37

Figure S 19.. ^{13}C NMR of compound 8f..... 38

Figure S 20. ^{1}H NMR of compound 8g 39

Figure S 21. ^{13}C NMR of compound 8g 40

Figure S 22. ^{1}H NMR of compound 8h 41

Figure S 23. ^{13}C NMR of compound 8h 42

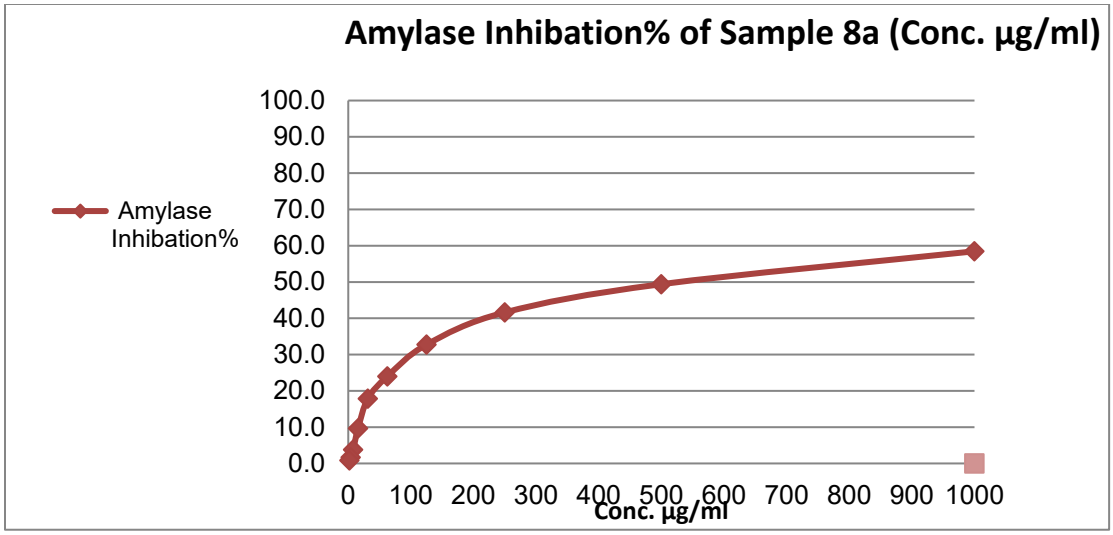
Figure S 24. ^{1}H NMR of compound 8i 43

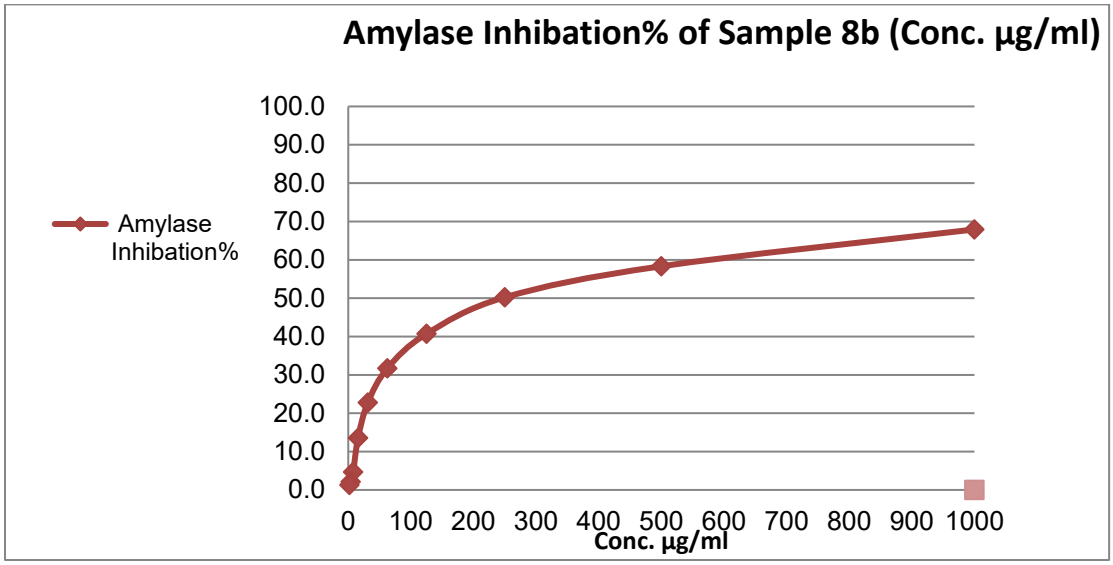
Figure S 25. ^{13}C NMR of compound 8i 44

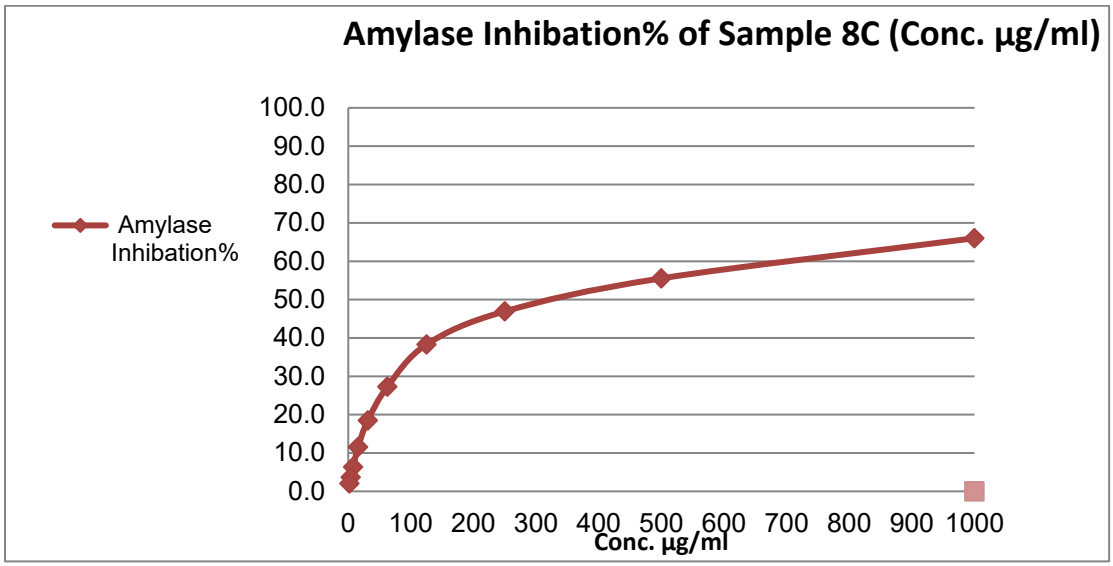
Figure S 26. ^{1}H NMR of compound 12a 45
Figure S 27. ^{13}C NMR of compound 12a 47
Figure S 28. ^{1}H NMR of compound 12b 49
Figure S 29. ^{13}C NMR of compound 12b 51
Figure S 30. ^{1}H NMR of compound 12c 53
Figure S 31. ^{13}C NMR of compound 12c 55
Figure S 32. ^{1}H NMR of compound 12d 57
Figure S 33 ^{13}C NMR of compound 12d 59
Figure S 34. ^{1}H NMR of compound 12e 61
Figure S 35. ^{13}C NMR of compound 12e 63
Figure S 36. ^{1}H NMR of compound 12f 65
Figure S 37. ^{13}C NMR of compound 12f 67
Figure S 38. ^{1}H NMR of compound 12g 69
Figure S 39. ^{13}C NMR of compound 12g 71
Figure S 40. ^{1}H NMR of compound 12h 73
Figure S 41. ^{13}C NMR of compound 12h 75
Figure S 42. ^{1}H NMR of compound 12i 77
Figure S43: ^{13}C NMR of compound 12i 79
High Resolution Mass Spectroscopy 80
Figure S 44: Mass of compound 8a 81
Figure S 45. Mass of compound 8b 82
Figure S 46. Mass of compound 8c 83
Figure S 47. Mass of compound 8d 84
Figure S 48. Mass of compound 8e 85

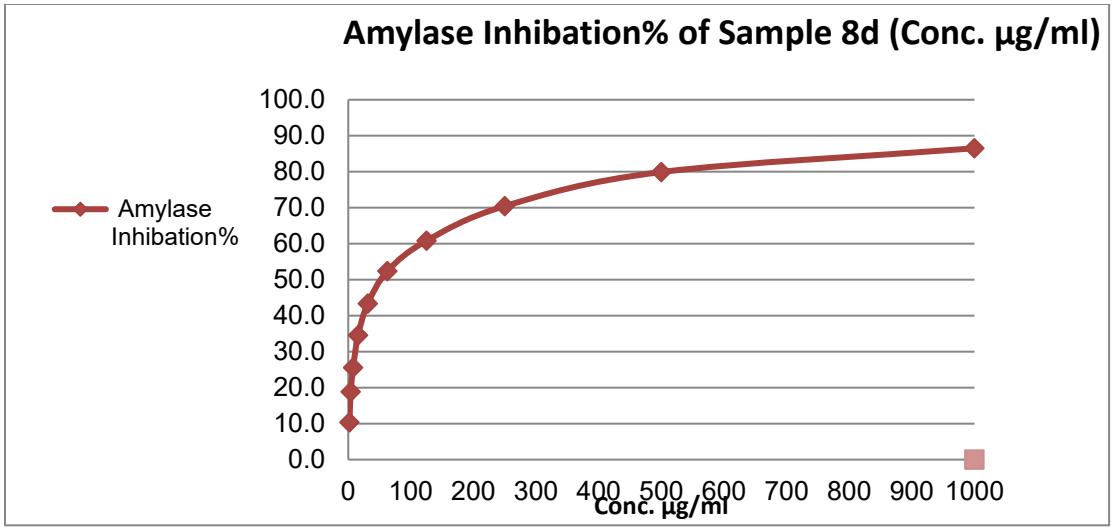
Figure S 49. Mass of compound 8f 86
Figure S 50. Mass of compound 8g 87
Figure S 51. Mass of compound 8h 88
Figure S 52. Mass of compound 8i 89
Figure S 53. Mass of compound 12a 90
Figure S 54. Mass of compound 12b 91
Figure S 55. Mass of compound 12c 92
Figure S 56. Mass of compound 12d 93
Figure S 57. Mass of compound 12e 94
Figure S 58. Mass of compound 12f 95
Figure S 59. Mass of compound 12g 96
Figure S 60. Mass of compound 12h 97
Figure S 61. Mass of compound 12i 98
Infera Red Charts 63
Figure S 62. IR of compound 8a 64
Figure S 63. IR of compound 8b 65
Figure S 64. IR of compound 8c 66
Figure S 65. IR of compound 8d 67
Figure S 66. IR of compound 8e 68
Figure S 67. IR of compound 8f 69
Figure S 68. IR of compound 8g 70
Figure S 69. IR of compound 8h 71
Figure S 70. IR of compound 8i 72
Figure S 71. IR of compound 12i 73

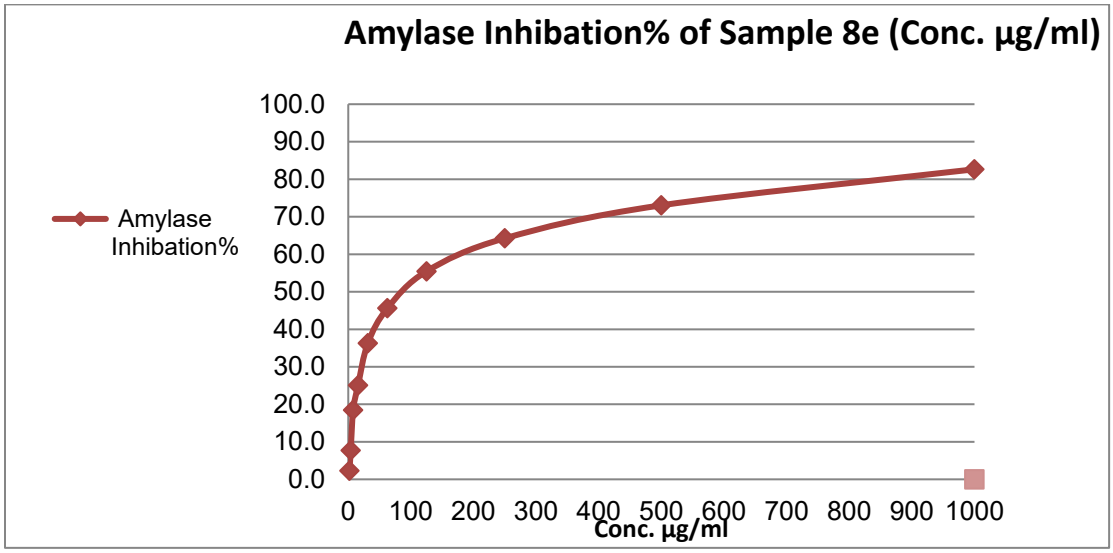
Results and discussion

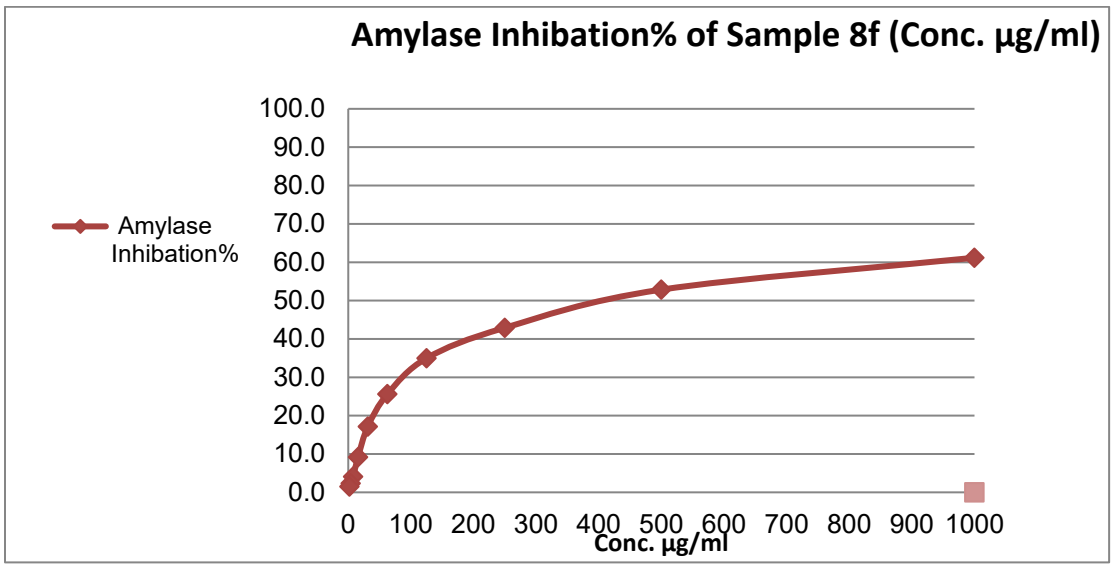

Amylase Inhibation% of Sample 8a (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 100 200 300 400 500 600 700 800 900 1000
Conc. µg/ml

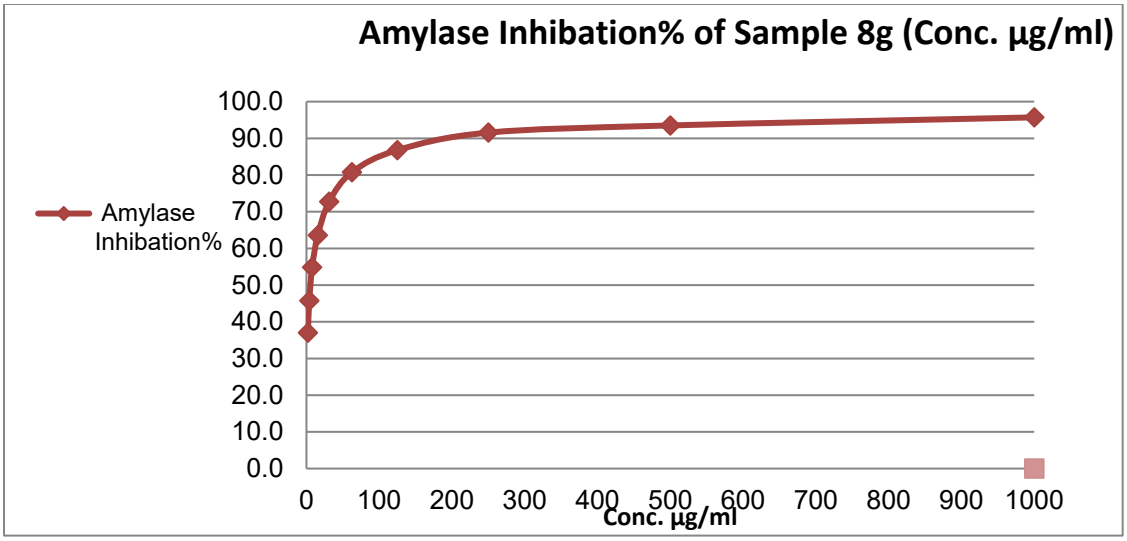

Amylase Inhibation% of Sample 8b (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 100 200 300 400 500 600 700 800 900 1000
Conc. µg/ml

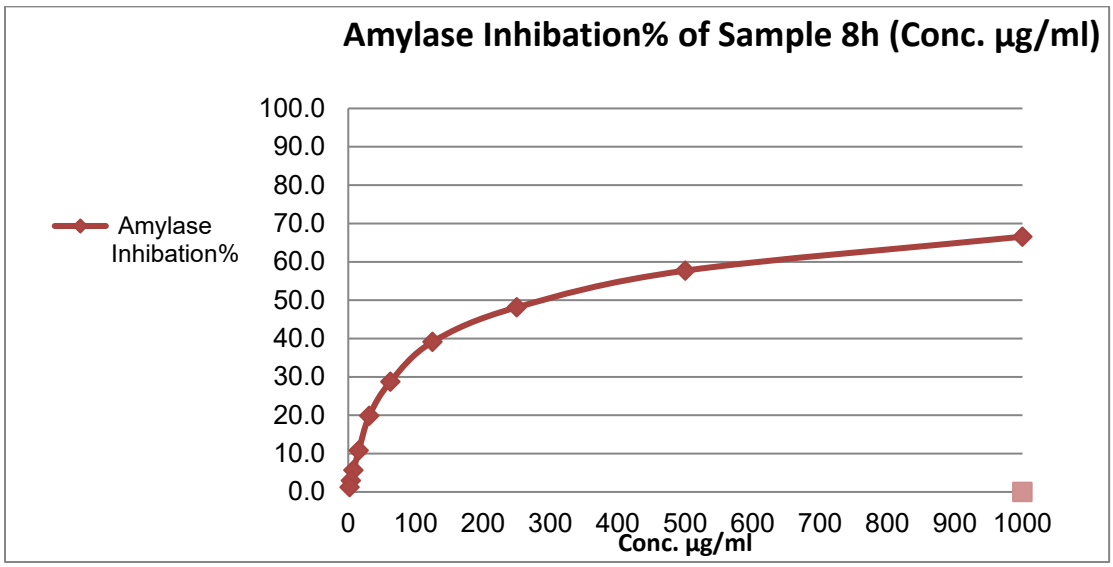

Amylase Inhibation% of Sample 8C (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 100 200 300 400 500 600 700 800 900 1000
Conc. µg/ml

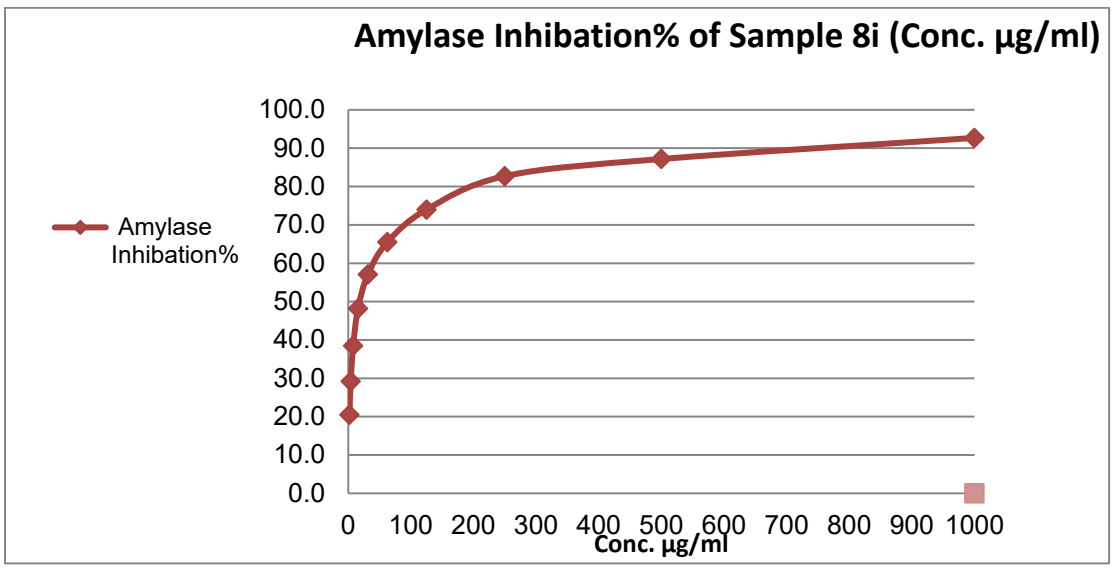

Amylase Inhibation% of Sample 8d (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 100 200 300 400 500 600 700 800 900 1000
Conc. µg/ml

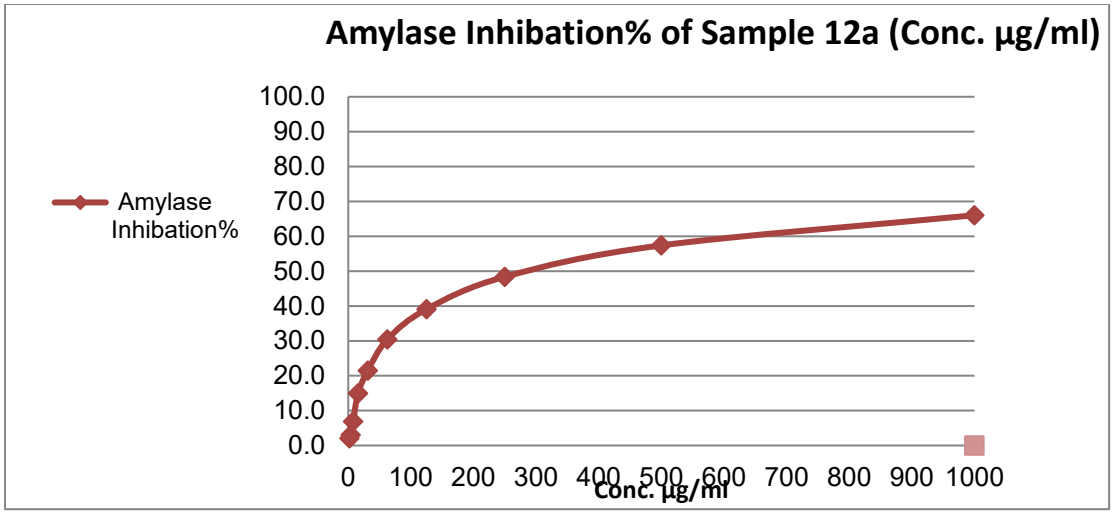

Amylase Inhibation% of Sample 8e (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 100 200 300 400 500 600 700 800 900 1000
Conc. µg/ml

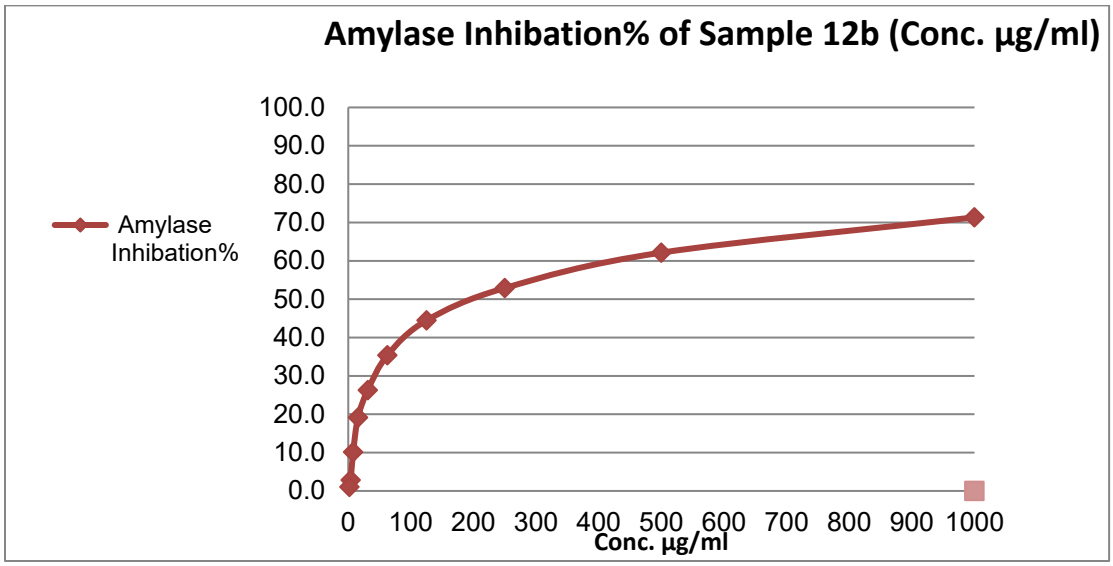

Amylase Inhibation% of Sample 8f (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 100 200 300 400 500 600 700 800 900 1000
Conc. µg/ml

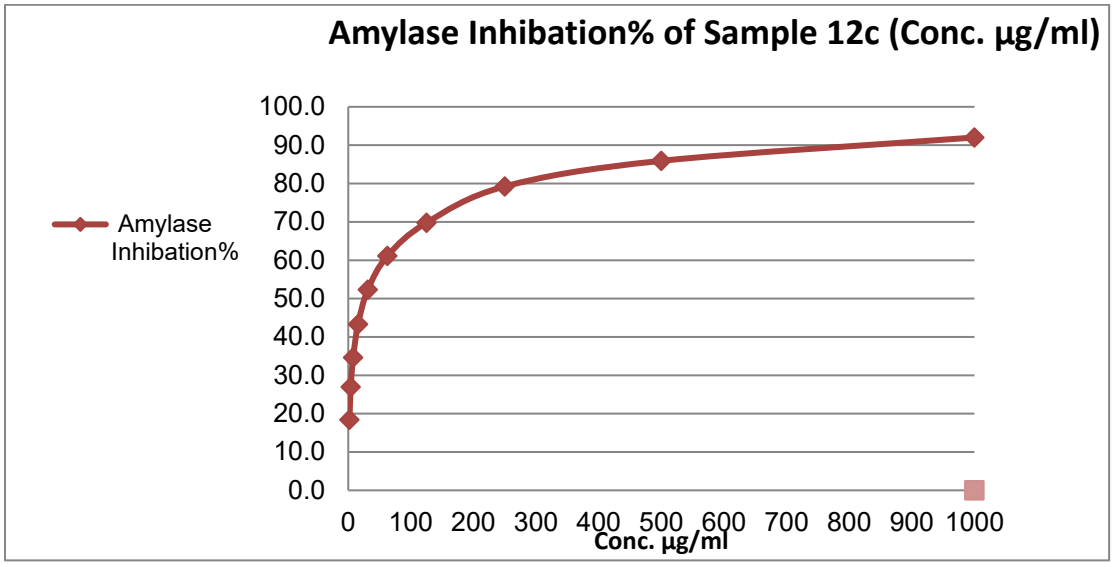

Amylase Inhibation% of Sample 8g (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
100
200
300
400
500
600
700
800
900
1000
Conc. µg/ml

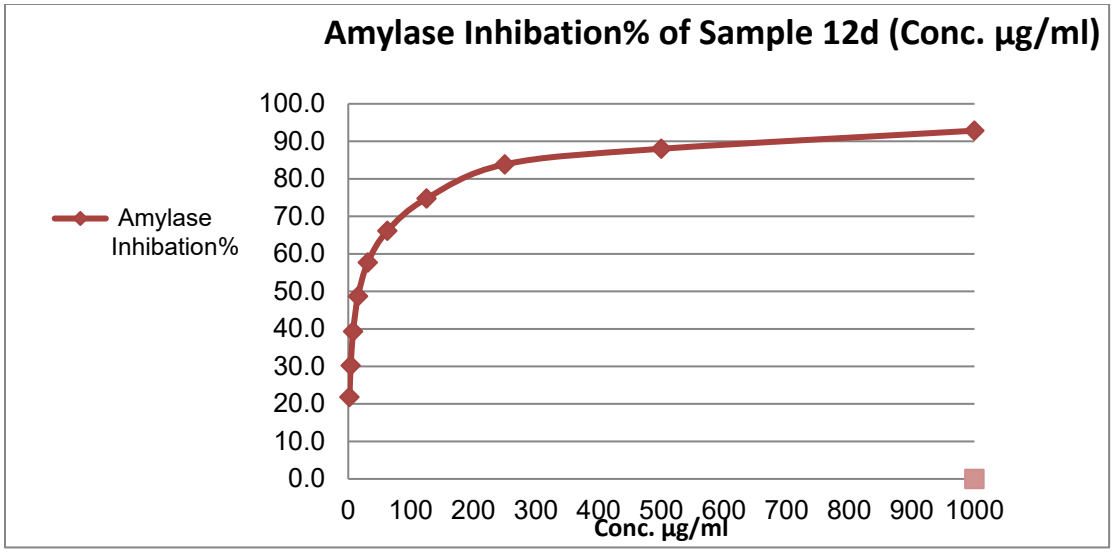

Amylase Inhibation% of Sample 8h (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
100
200
300
400
500
600
700
800
900
1000
Conc. µg/ml

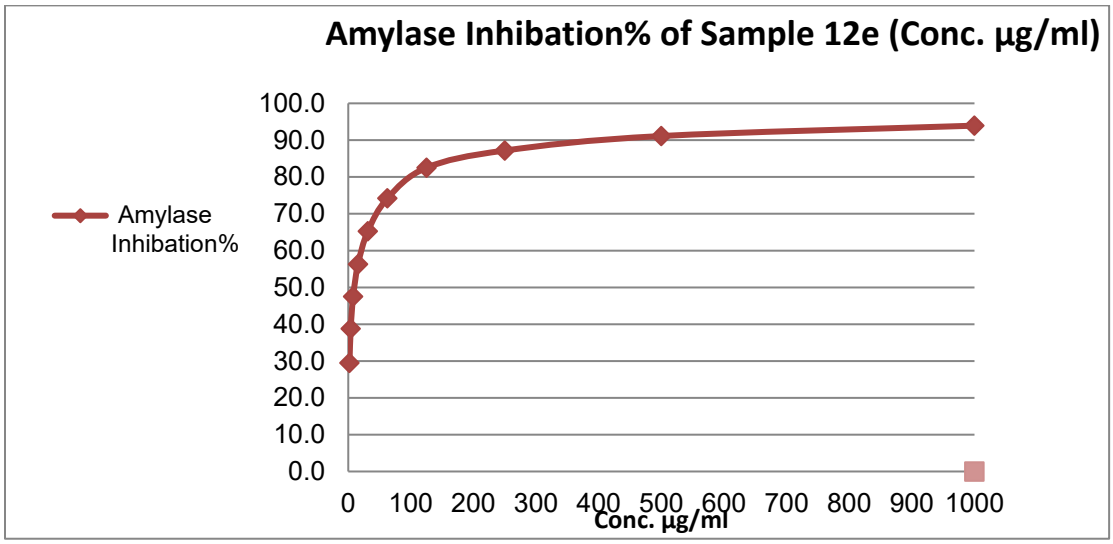

Amylase Inhibation% of Sample 8i (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
100
200
300
400
500
600
700
800
900
1000
Conc. µg/ml

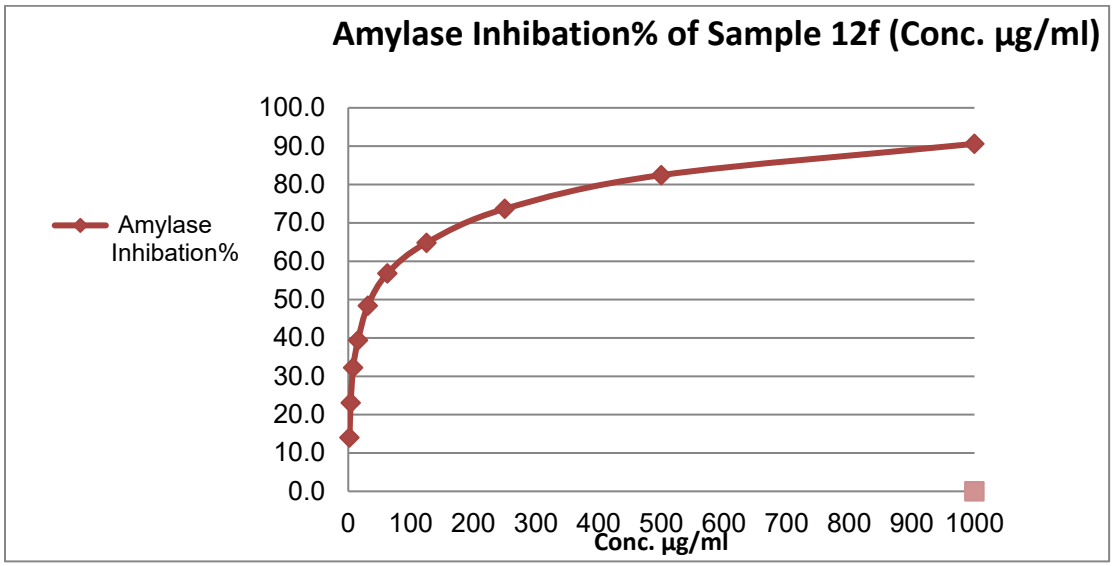

Amylase Inhibation% of Sample 12a (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 100 200 300 400 500 600 700 800 900 1000
Conc. µg/ml

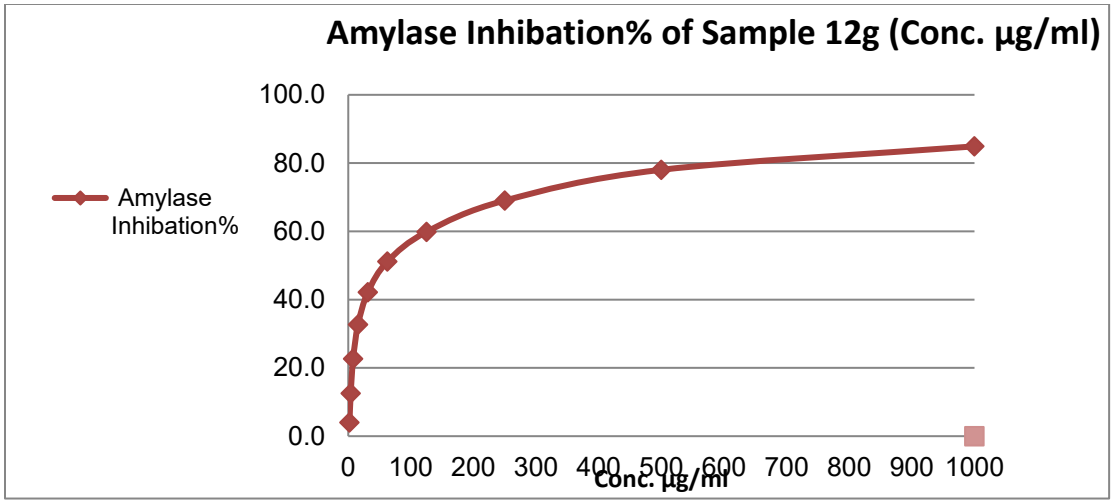

Amylase Inhibation% of Sample 12b (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 100 200 300 400 500 600 700 800 900 1000
Conc. µg/ml

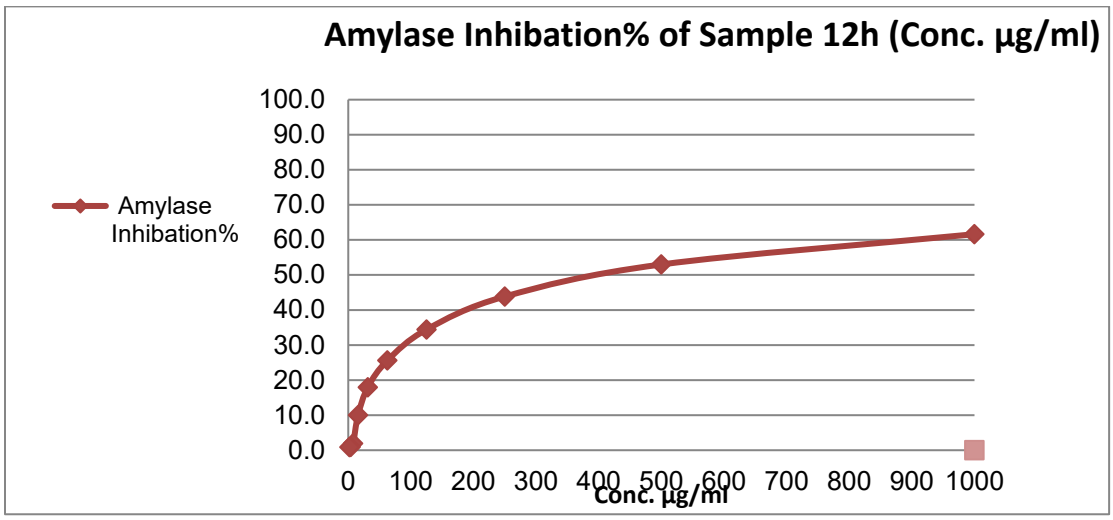

Amylase Inhibation% of Sample 12c (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 100 200 300 400 500 600 700 800 900 1000
Conc. µg/ml


Amylase Inhibation% of Sample 12d (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 100 200 300 400 500 600 700 800 900 1000
Conc. µg/ml


Amylase Inhibation% of Sample 12e (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 100 200 300 400 500 600 700 800 900 1000
Conc. µg/ml


Amylase Inhibation% of Sample 12f (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 100 200 300 400 500 600 700 800 900 1000
Conc. µg/ml


Amylase Inhibation% of Sample 12g (Conc. µg/ml)
Amylase Inhibation%
100.0
80.0
60.0
40.0
20.0
0.0
0
100
200
300
400
500
600
700
800
900
1000
Conc. µg/ml


Amylase Inhibation% of Sample 12h (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
100
200
300
400
500
600
700
800
900
1000
Conc. µg/ml

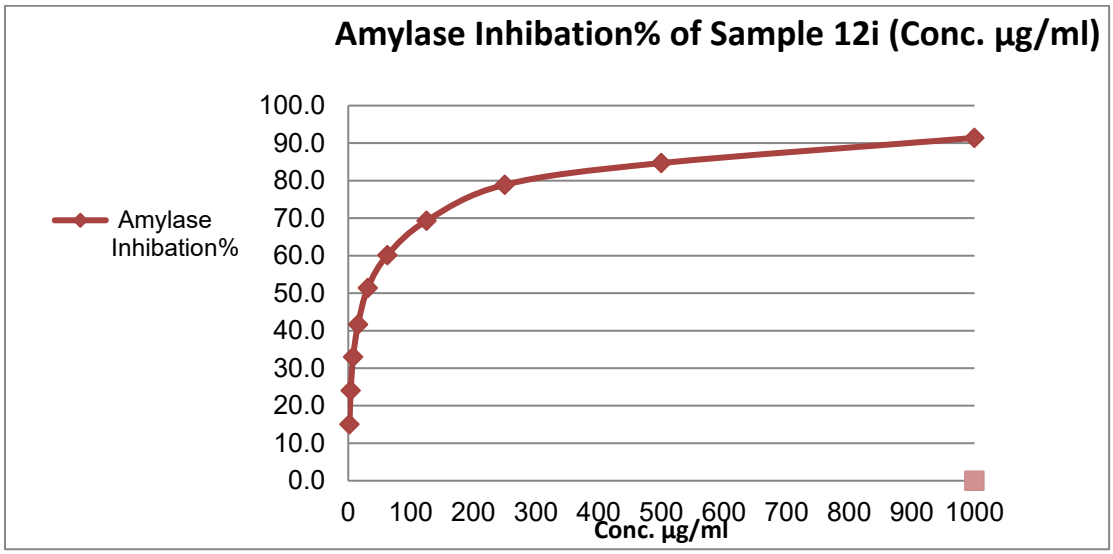

Amylase Inhibation% of Sample 12i (Conc. µg/ml)
Amylase Inhibation%
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
100
200
300
400
500
600
700
800
900
1000
Conc. µg/ml

Table S 1. The %inhibition of **8a-i** and **12a-i** against α-glucosidase at 25 μM.

Compounds	Inhibition%
8a	33.88 ± 3.28
8b	30.74 ± 0.61
8c	59.05 ± 2.74
8d	50.34 ± 2.68
8e	20.42 ± 3.523
8f	35.12 ± 3.96
8g	62.46 ± 3.40
8h	7.89 ± 2.49
8i	9.36 ± 1.37
12a	65.18 ± 5.01
12b	54.99 ± 0.76
12c	51.73 ± 5.34
12d	21.08 ± 2.35
12e	10.38 ± 0.83
12f	5.07 ± 1.21
12g	14.00 ± 1.15
12h	12.59 ± 1.09
12i	3.97 ± 0.64
Acarbose	63.42 ± 1.24

Table S 2. Effect of compounds **8g**, **12d**, and **12e** on postprandial blood glucose levels in alloxan-induced diabetic rats

	Glucose (mg/dL)				
	0 Mins	**30 Mins**	**60 Mins**	**90 Mins**	**120 Mins**
Normal Control	82.17 ± 6.52	167.17 ± 3.76	160.5 ± 7.45	146.17 ± 4.54	137.33 ± 6.92
Diabetic Control	286.17 ± 8.35[a]	399.33 ± 14.18[a]	373 ± 5.29[a]	358.5 ± 4.97[a]	342.67 ± 9.81[a]
Vildagliptin	280.5 ± 5.86[a]	324.83 ± 5.12[ab]	289.67 ± 10.89[ab]	278.83 ± 5.34[ab]	285.5 ± 6.98[ab]
8g	290.17 ± 7.05[a]	301.5 ± 6.22[abc]	268.83 ± 5.12[abc]	228.83 ± 5.04[abc]	209.83 ± 4.96[abc]
12d	288.17 ± 13.51[a]	322.83 ± 9.33[ab]	295.83 ± 5.52[ab]	283 ± 2.19[ab]	280.33 ± 4.08[ab]
12e	286.17 ± 4.26[a]	310.33 ± 2.88[abc]	291.17 ± 3.6[ab]	240.17 ± 2.93[abc]	242.17 ± 4.17[abc]

Data are expressed as mean ± SD and were analyzed using two-way ANOVA followed by Tukey's post hoc test. The letters a, b, and c indicate statistically significant differences at $p < 0.05$, where [a] denotes comparison with the normal control group, [b] with the diabetic control group, and [c] with the vildagliptin-treated group.

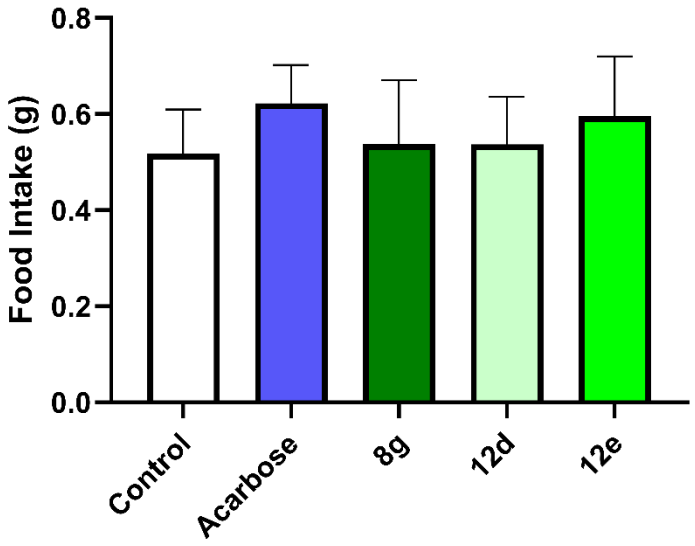


Figure S 1. Food intake in normoglycemic mice during the oral glucose tolerance test. Data are expressed as mean ± SD and were analyzed using one-way ANOVA, followed by Tukey's post hoc test. No statistically significant differences were observed among groups ($p > 0.05$), indicating that changes in blood glucose levels were not attributable to altered food intake.

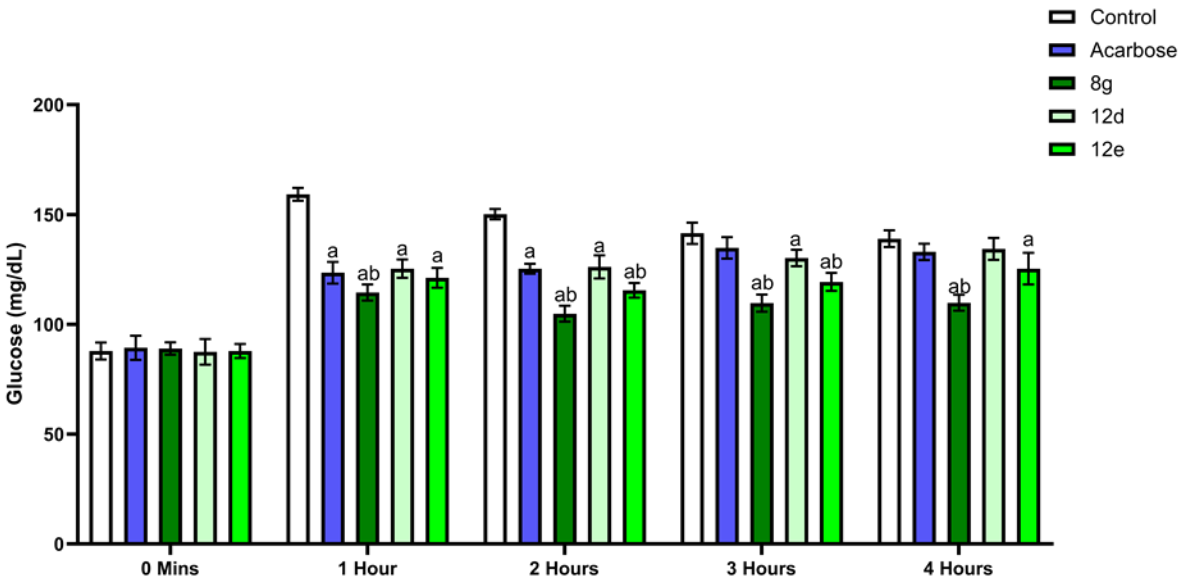


Figure S 2: *Effect of compounds **8g, 12d,** and **12e** on blood glucose levels in normoglycemic mice during the oral glucose tolerance test. Data are expressed as mean ± SD and were analyzed using two-way ANOVA followed by Tukey's post hoc test. The letters a, b, and c indicate statistically significant differences at*

$p < 0.05$, where a denotes comparison with the normal control group, b with the diabetic control group, and c with the vildagliptin-treated group.

Molecular Docking

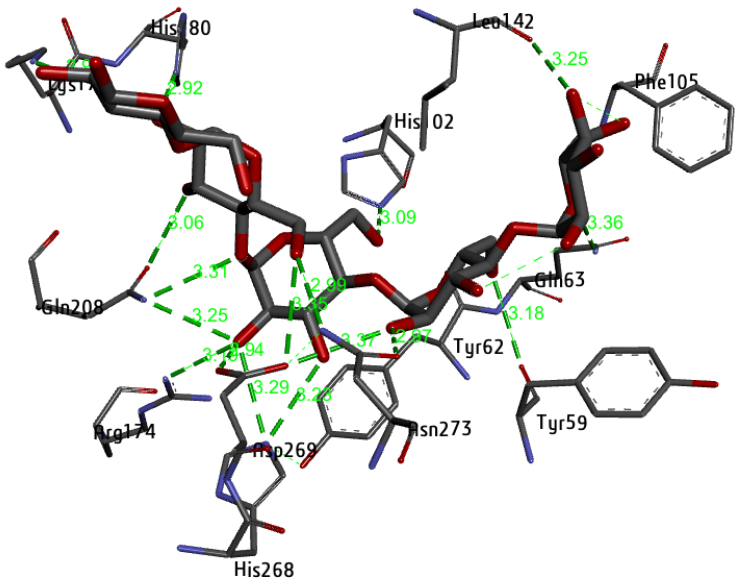


Figure S 3. Binding mode of co-crystalized ligand in the biding site of co-crystalized MALTOPENTAOSE in amylase active site **(PDB:1BAG).**

Validation of docking protocol was done by redocking of the bound conformer of co-crystalized Maltopentaose in amylase active site (PDB:1BAG). MALTOPENTAOSE redocked almost at the same position as the co-crystalized (docking score = -9.4 kcal/mol) employing that the docking protocol adopted in the current study is reliable to predict the binding mode of the compound under investigation

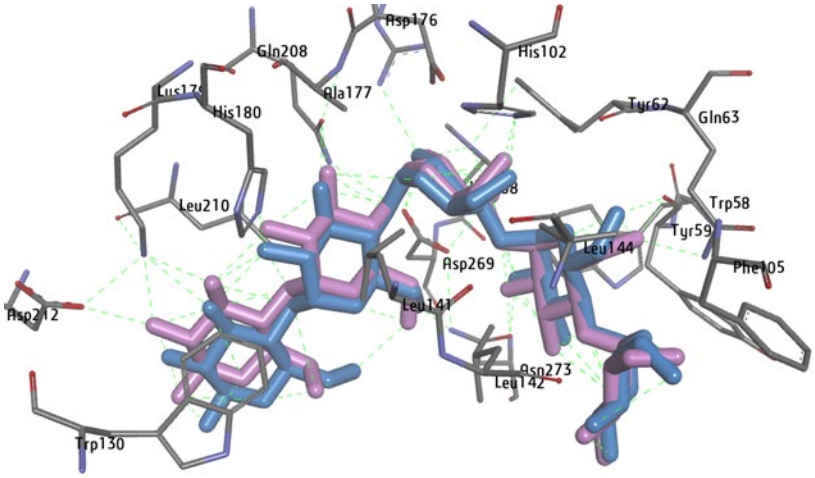


Figure S 4. Superimposition of co-crystalized MALTOPENTAOSE (purple) and redocked MALTOPENTAOSE (blue) for validation of docking protocol.

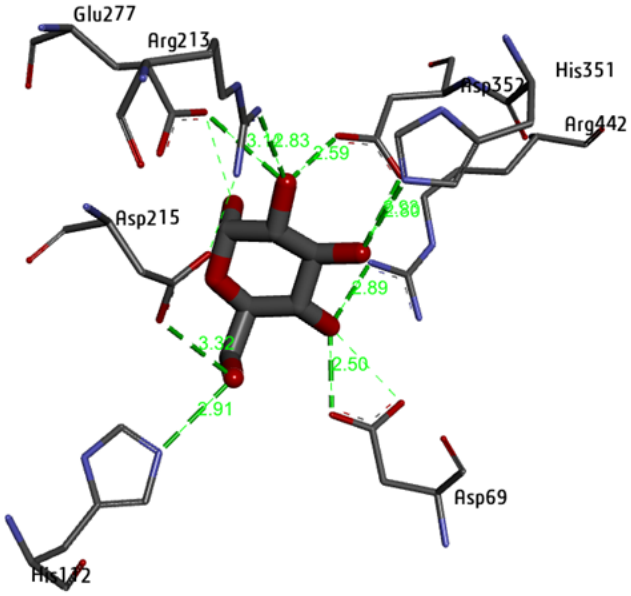


Figure S 5. Binding mode of co-crystalized ligand in the biding site of co-crystalized α-D-Glucopyranose in glycosidase active site **(PDB:3A4A).**

Validation of docking protocol was done by redocking of the bound conformer of co-crystalized **α**-D-Glucopyranose in glycosidase active site (PDB:3A4A). **α**-D-Glucopyranose redocked almost at the same position as the co-crystalized (docking score = -5.1 kcal/mol) employing that the

docking protocol adopted in the current study is reliable to predict the binding mode of the compound under investigation.

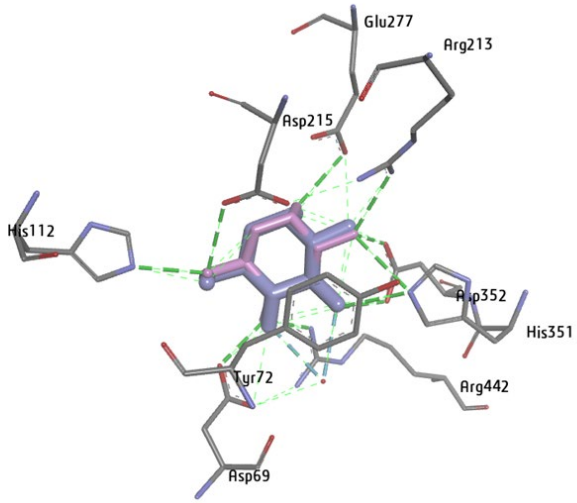
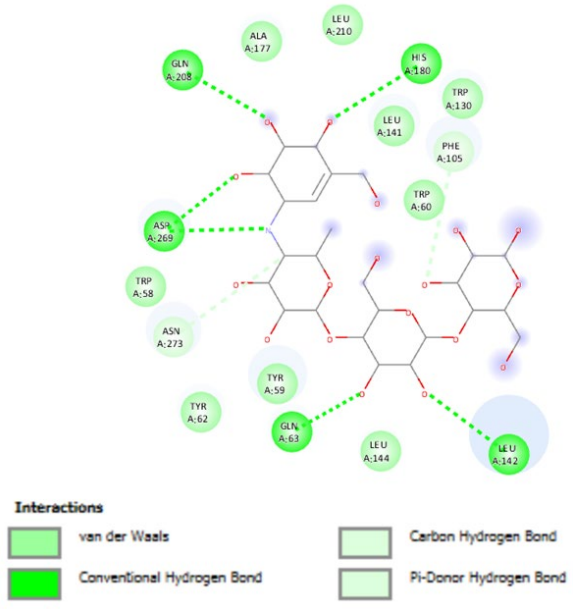
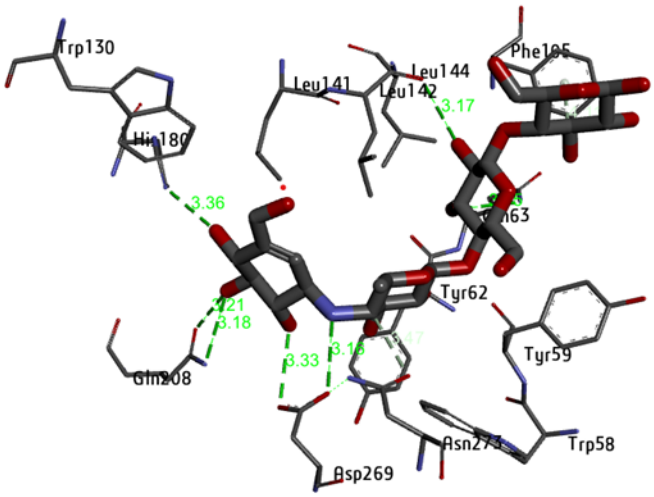


Figure S 6. Superimposition of co-crystalized α-D-Glucopyranose **(purple) and redocked** α-D-Glucopyranose **(blue)** for validation of docking protocol.

A]  	
B]	

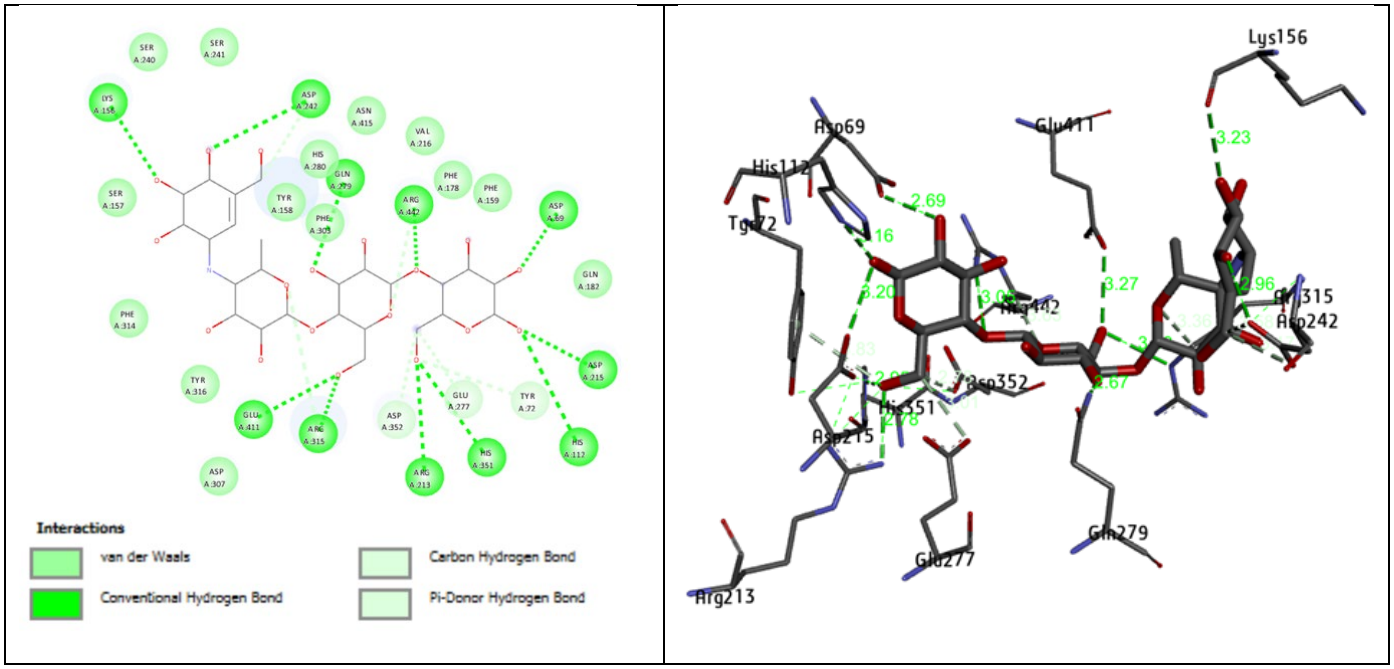


Figure S 7. A. *The docking pose of Acarbose, the standard drµg, against the Alpha-Amylase enzyme (PDB code 1BAG). B. The docking pose of Acarbose, the standard drµg, against the Glycosidase enzyme (PDB code 3A4A).*

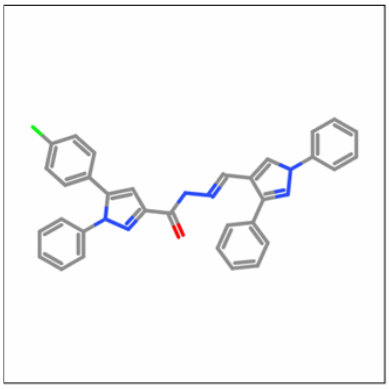
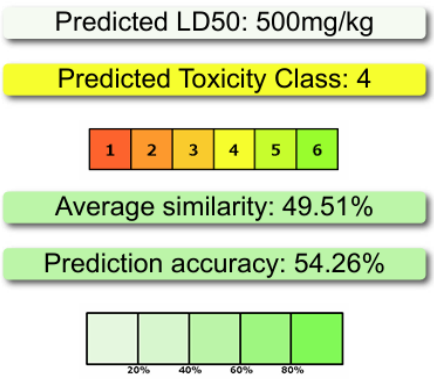
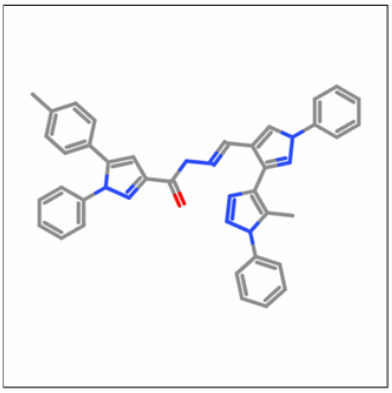
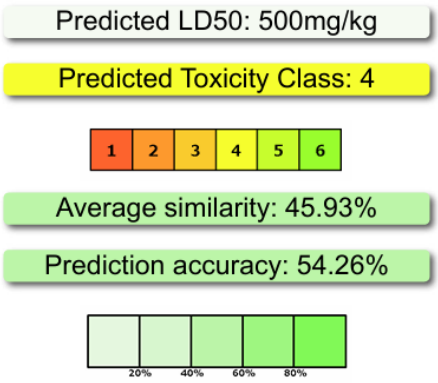
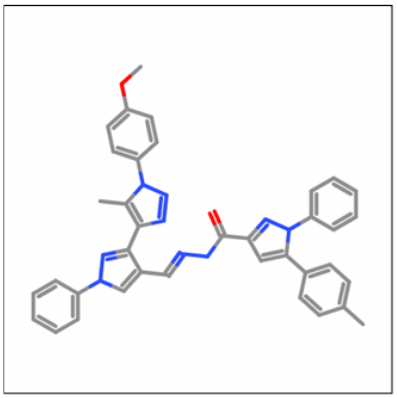
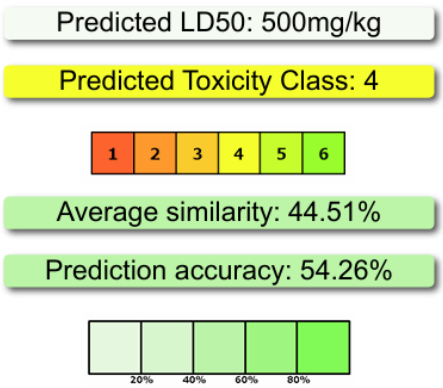
Table S 3. Binding score, amino acid interaction and bond length of compounds **7g, 10d** and **10e** within the active site of alpha-amylase and alpha glycosidase active sites.

Compounds	Binding Score (kcal/mol)	Interaction	Amino acid	Enzyme	Code
Acarbose	-8.6	H bond H bond H bond H bond H bond	Gln208 Asp269 Gln63 His180 Leu142	Amylase	1BAG
7g	-9.9	H. bond π -anion π - π stack π - π stack	Gln63 Asp269 Tyr59 Phe105	Amylase	1BAG
10d	-9.2	H. bond H. bond π -anion π - π stack π - π stack π - π stack π -anion	Gln63 Asn273 Asp269 Phe105 Trp58 Tyr62 Asp274	Amylase	1BAG

10d	-10.2	H. bond	Gln63	Amylase	1BAG
		π - π stack	Phe105		
		π - π stack	Trp58		
		π -sigma	Leu142		
		π - π stack	Tyr59		
		H. bond	Asp274		
		H. bond	His268		
Acarbose	-8.0	H. bond	Asp242	glycosidase	3A4A
		H. bond	Arg442		
		H. bond	Gln279		
		H. bond	His351		
		H. bond	Arg315		
		H. bond	Arg213		
		H. bond	Asp69		
		H. bond	Asp215		
10d	-9.4	π - π stack	Tyr158	glycosidase	3A4A
		H. bond	Gln279		
		H. bond	Asp352		
		π - π stack	Phe178		
		π - π stack	Tyr72		
		π -anion	Asp69		
		π -anion	Asp215		

Virtual ADMET Studies

Table S 4: ProTox-III properties of the newly synthesized derivatives **8g, 12d**, and **12e**.

Compound	ProTox-III
8g	 
12d	 
12e	 

^{1}HNMR and ^{13}CNMR Spectra

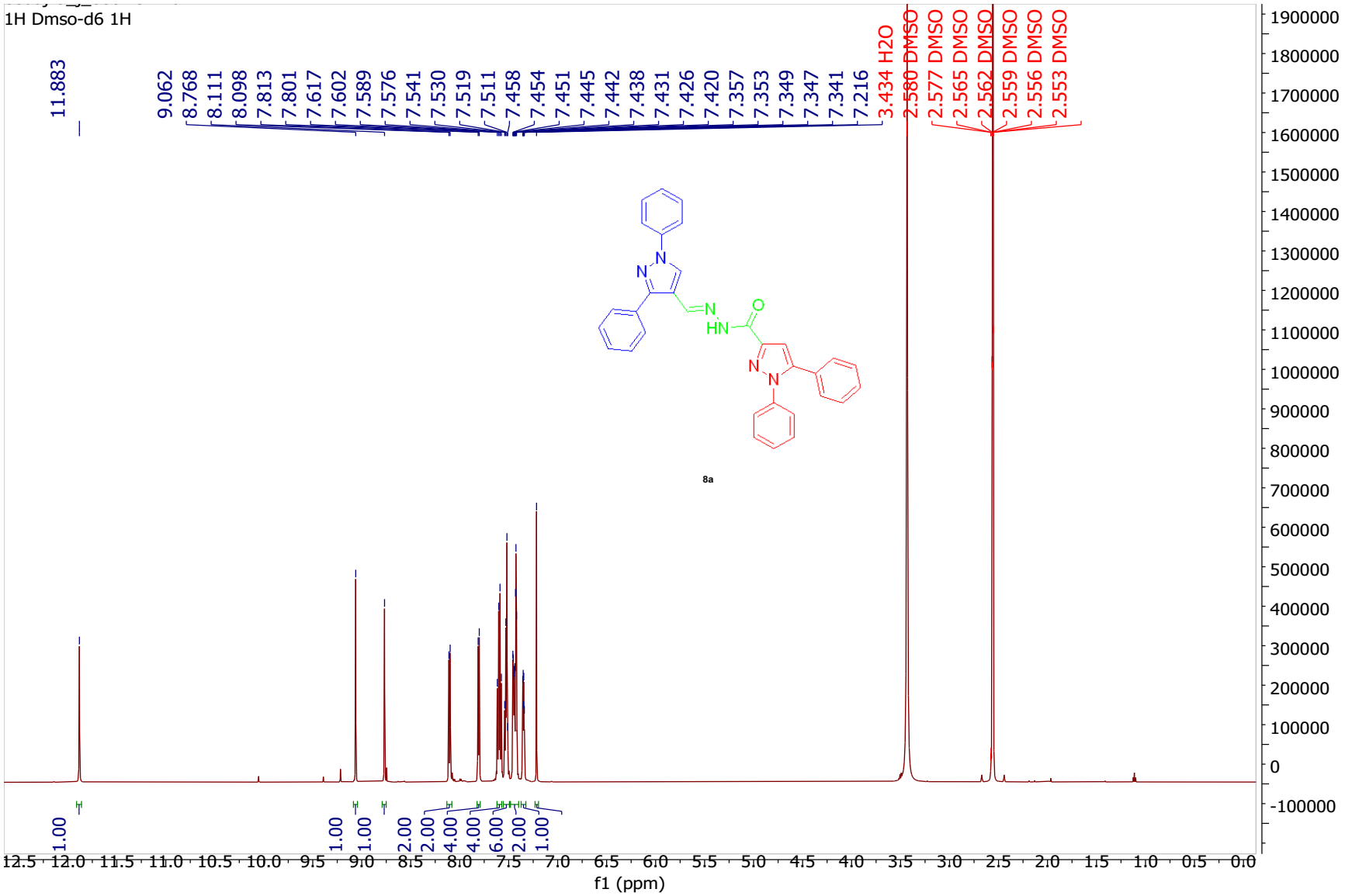


Figure S 8. [1]H NMR of compound **8a**

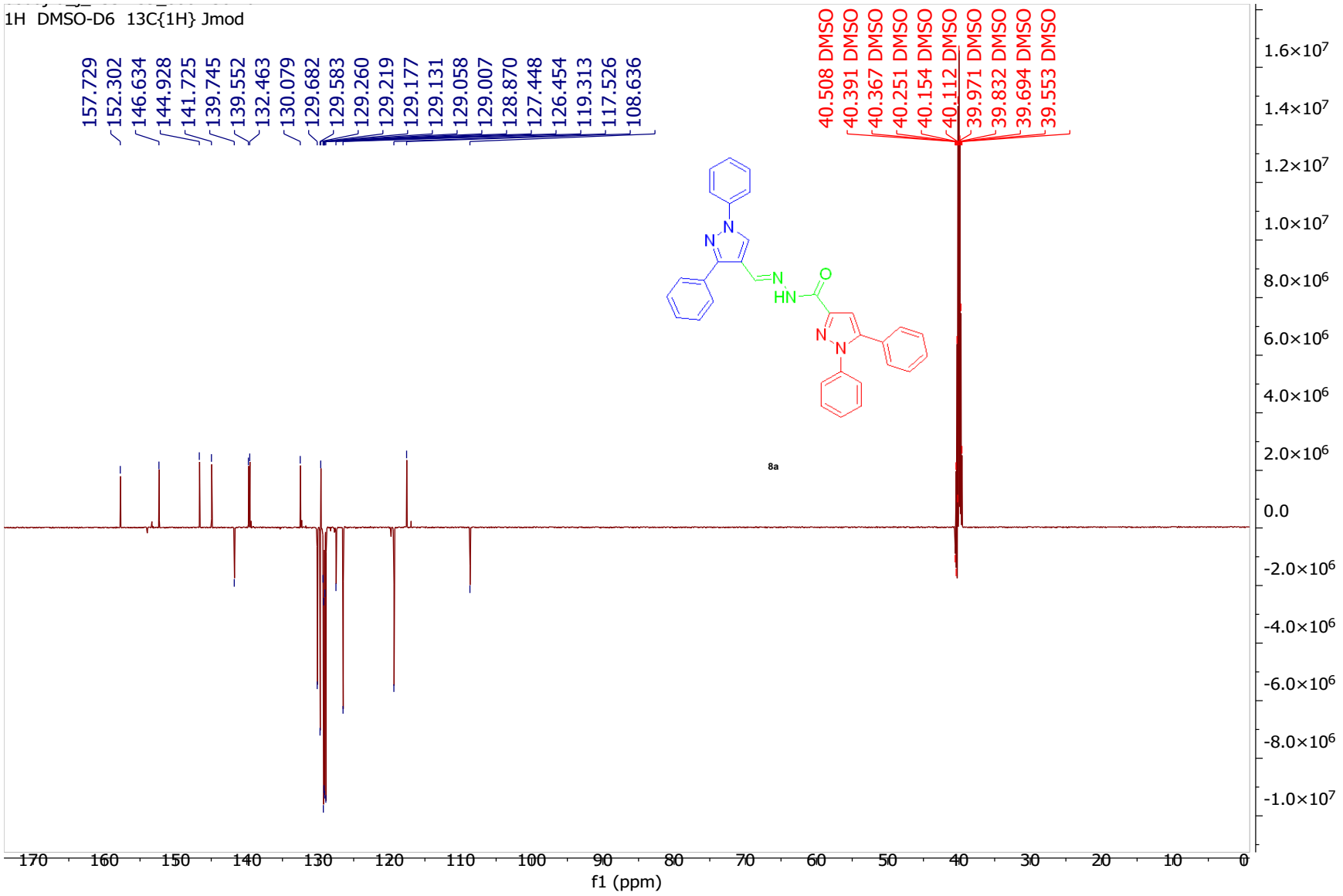


Figure S 9. ^{13}C NMR of compound **8a**

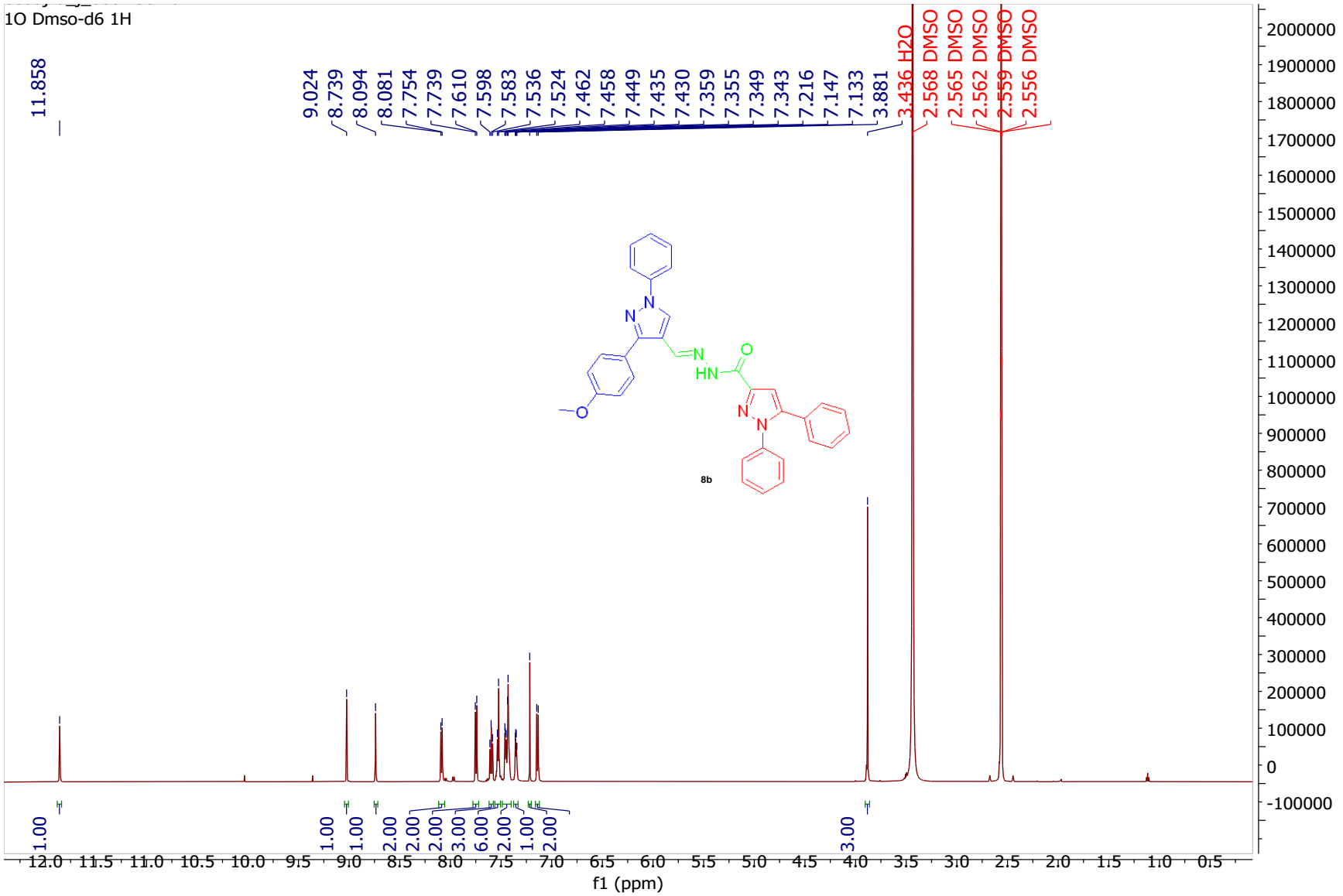


Figure S 10. ^{1}H NMR of compound **8b**

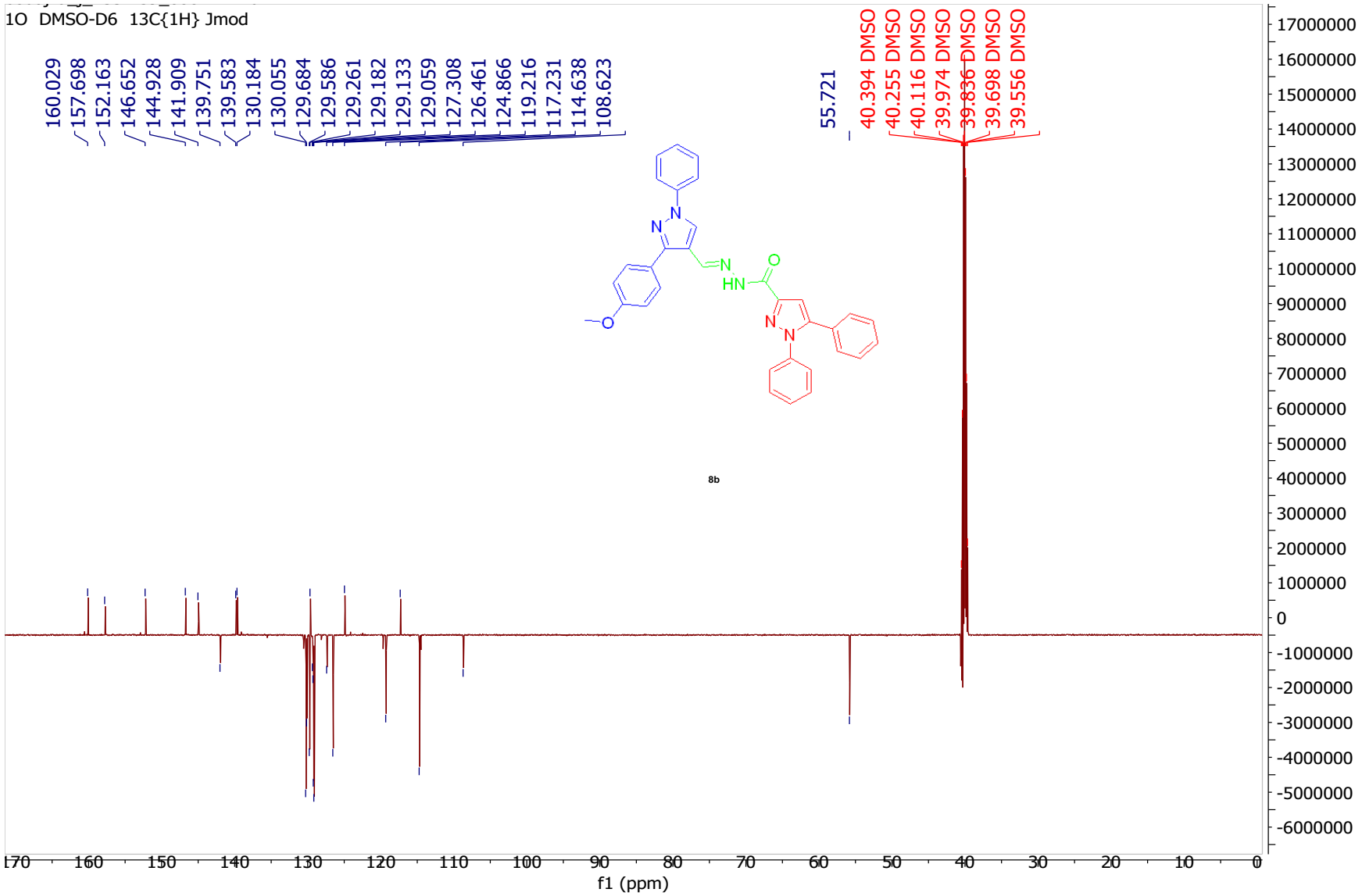


Figure S 11. ^{13}C NMR of compound **8b**

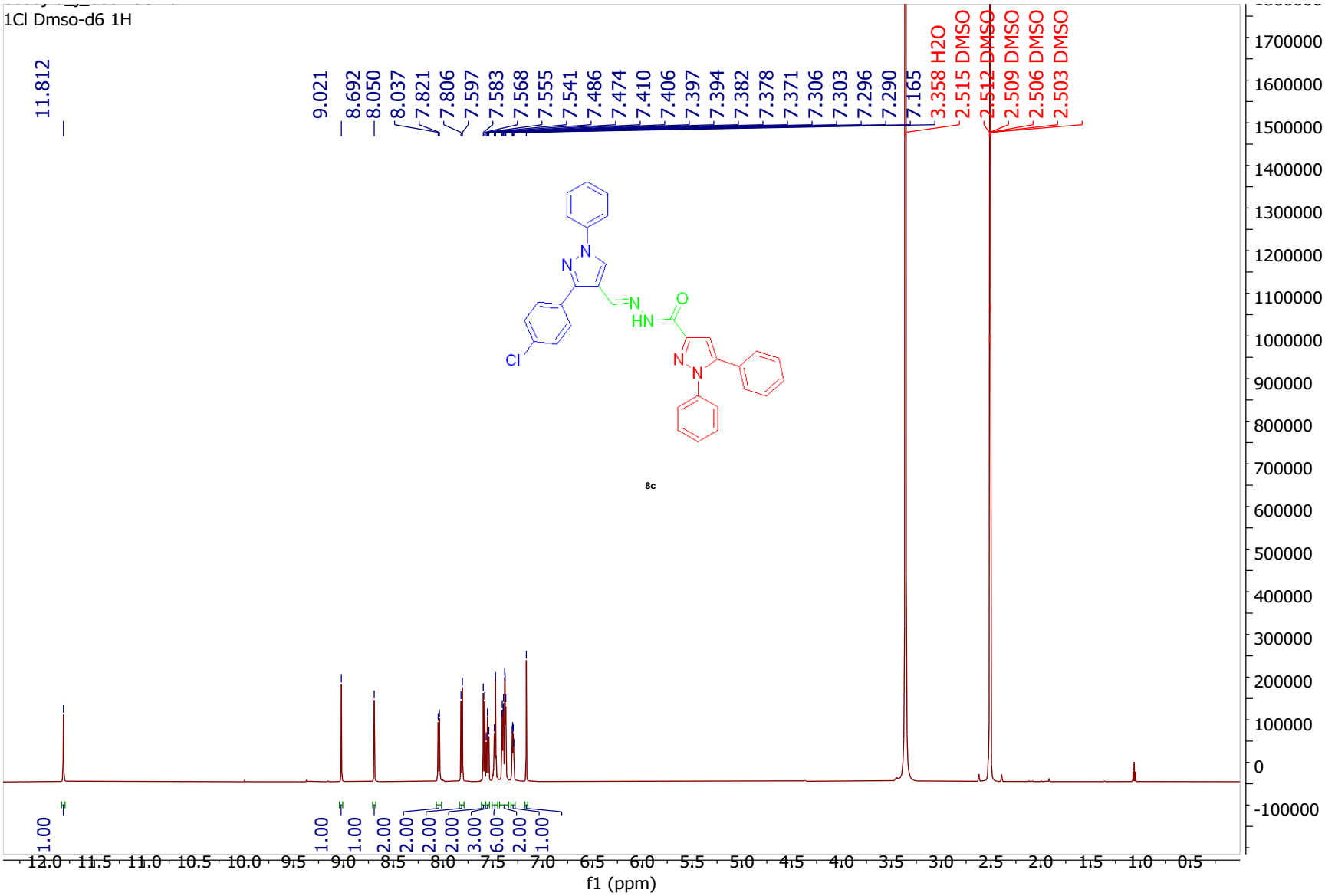


Figure S 12. ^{1}H NMR of compound **8c**

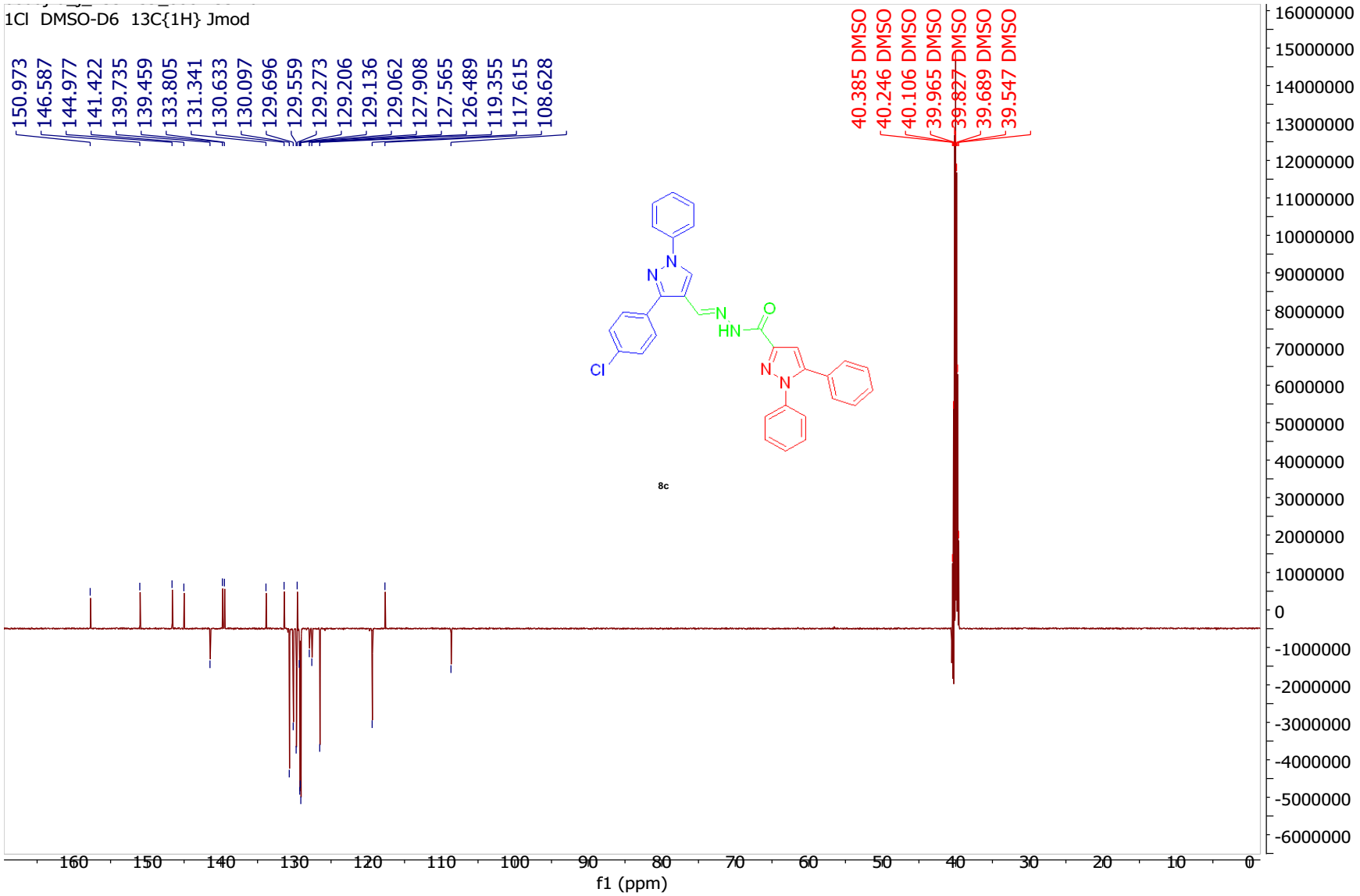


Figure S 13. ^{13}C NMR of compound **8c**

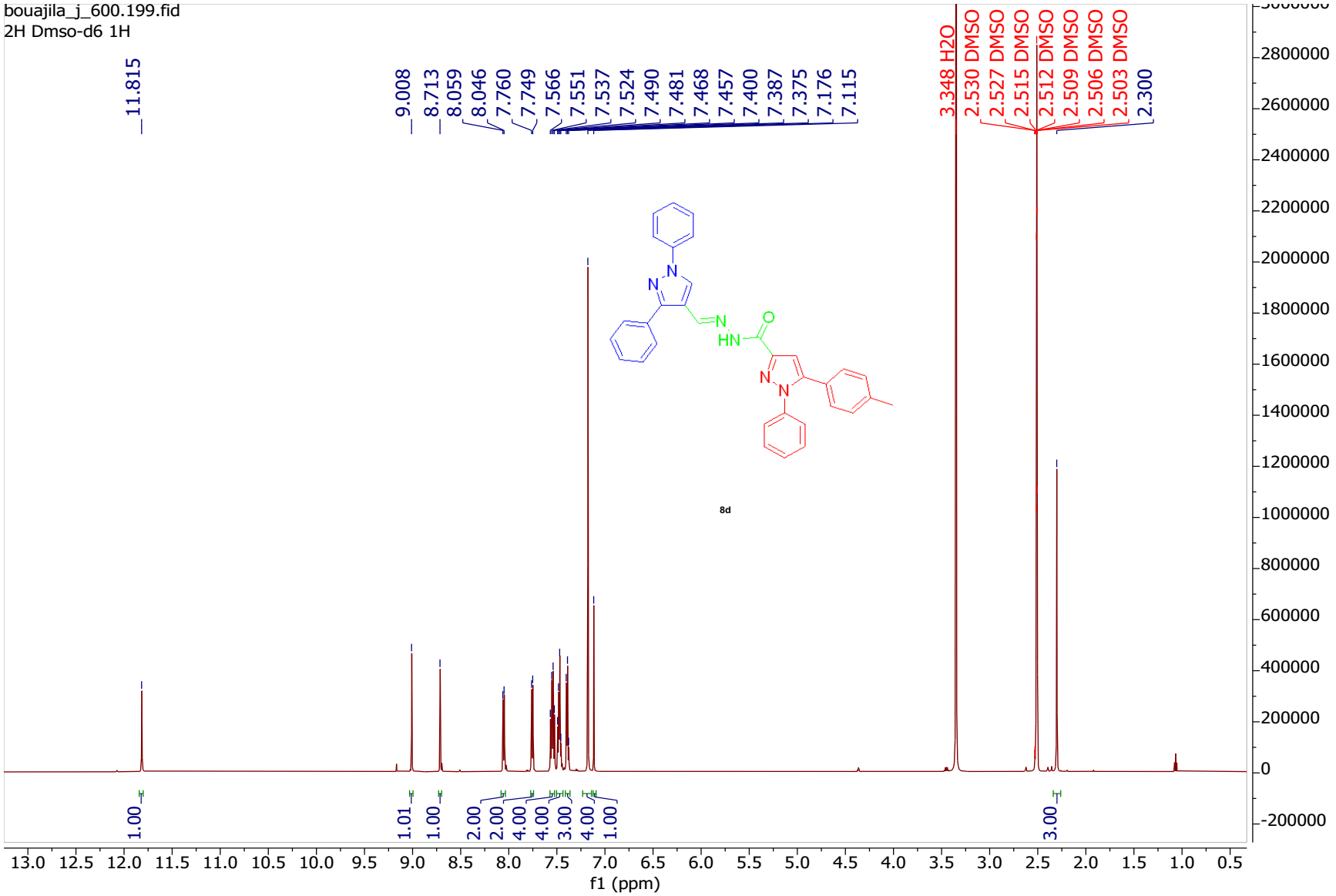


Figure S 14. ^{1}H NMR of compound **8d**

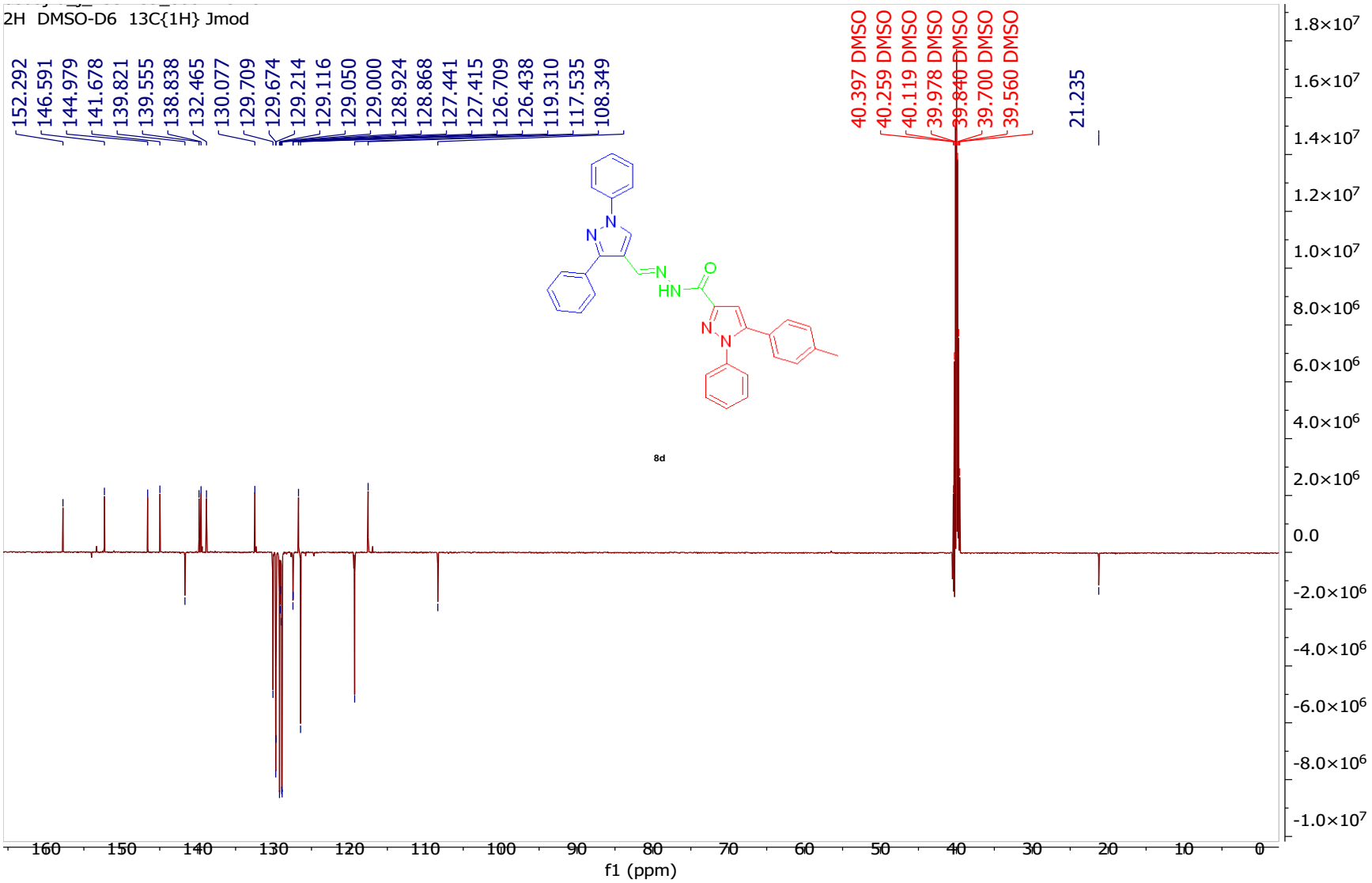


Figure S 15.. ^{13}C NMR of compound **8d**

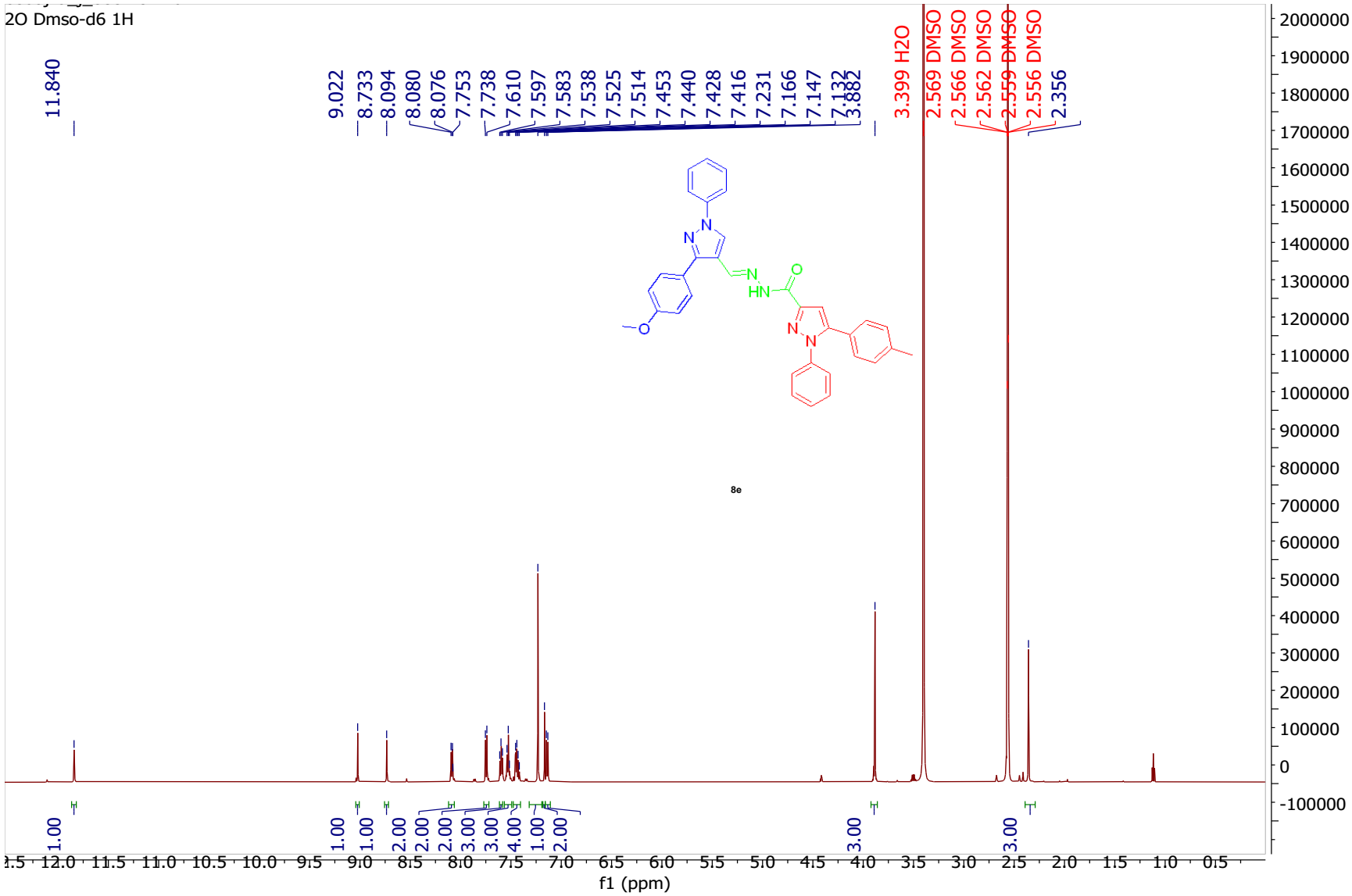


Figure S 16. ^{1}H NMR of compound **8e**

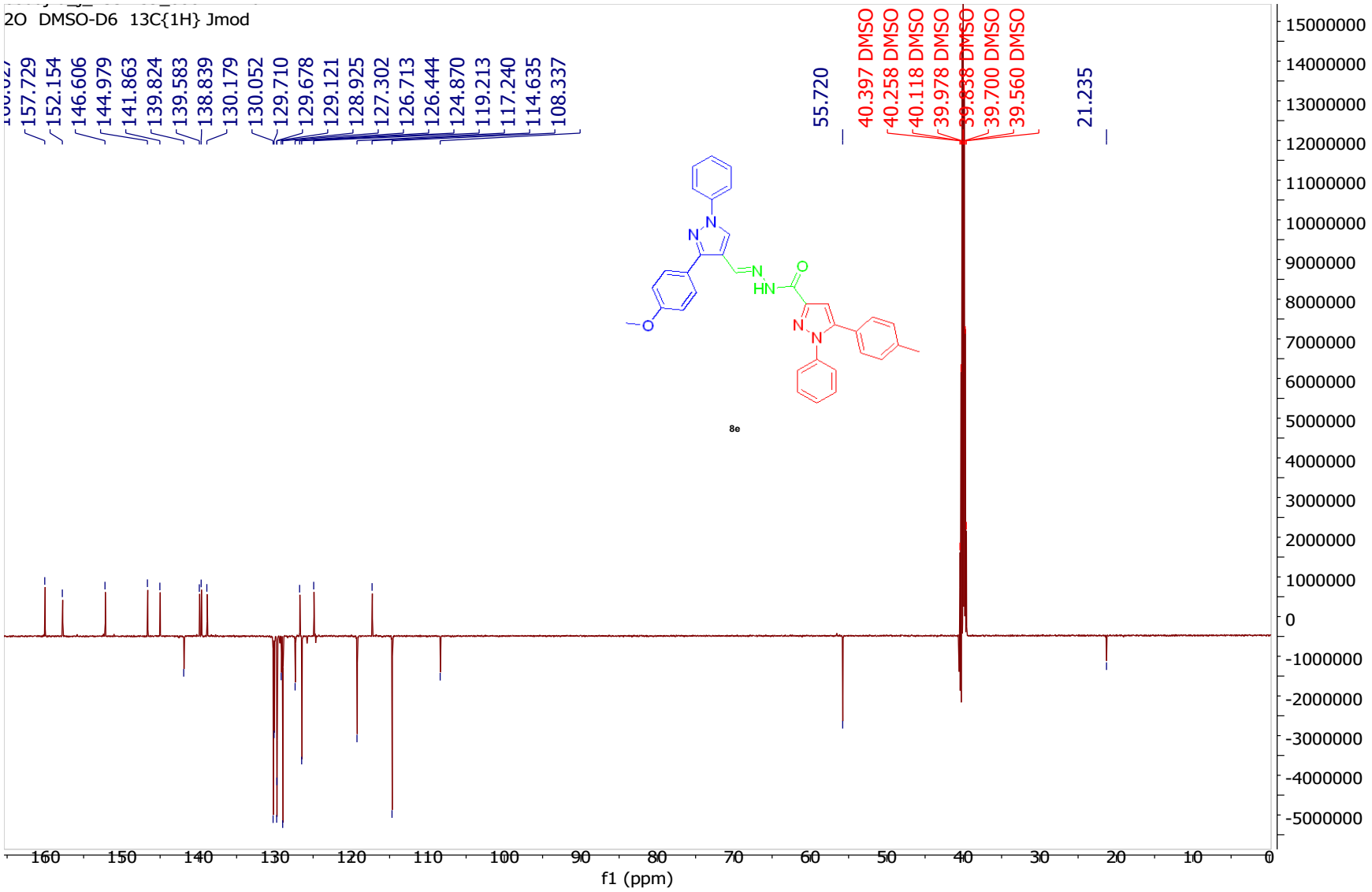


Figure S 17..n^{13}C NMR of compound **8e**

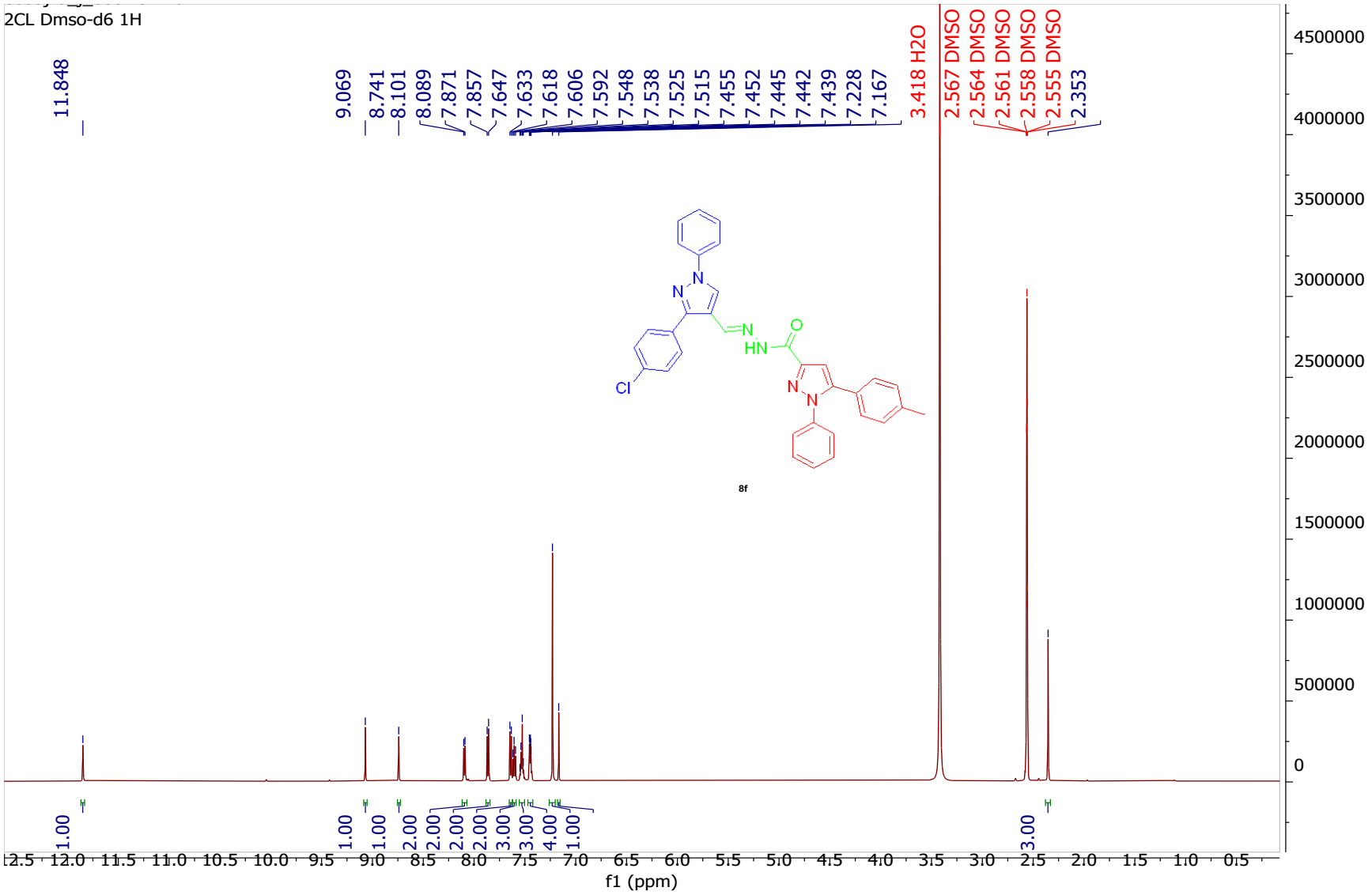


Figure S 18. ^{1}H NMR of compound **8f**

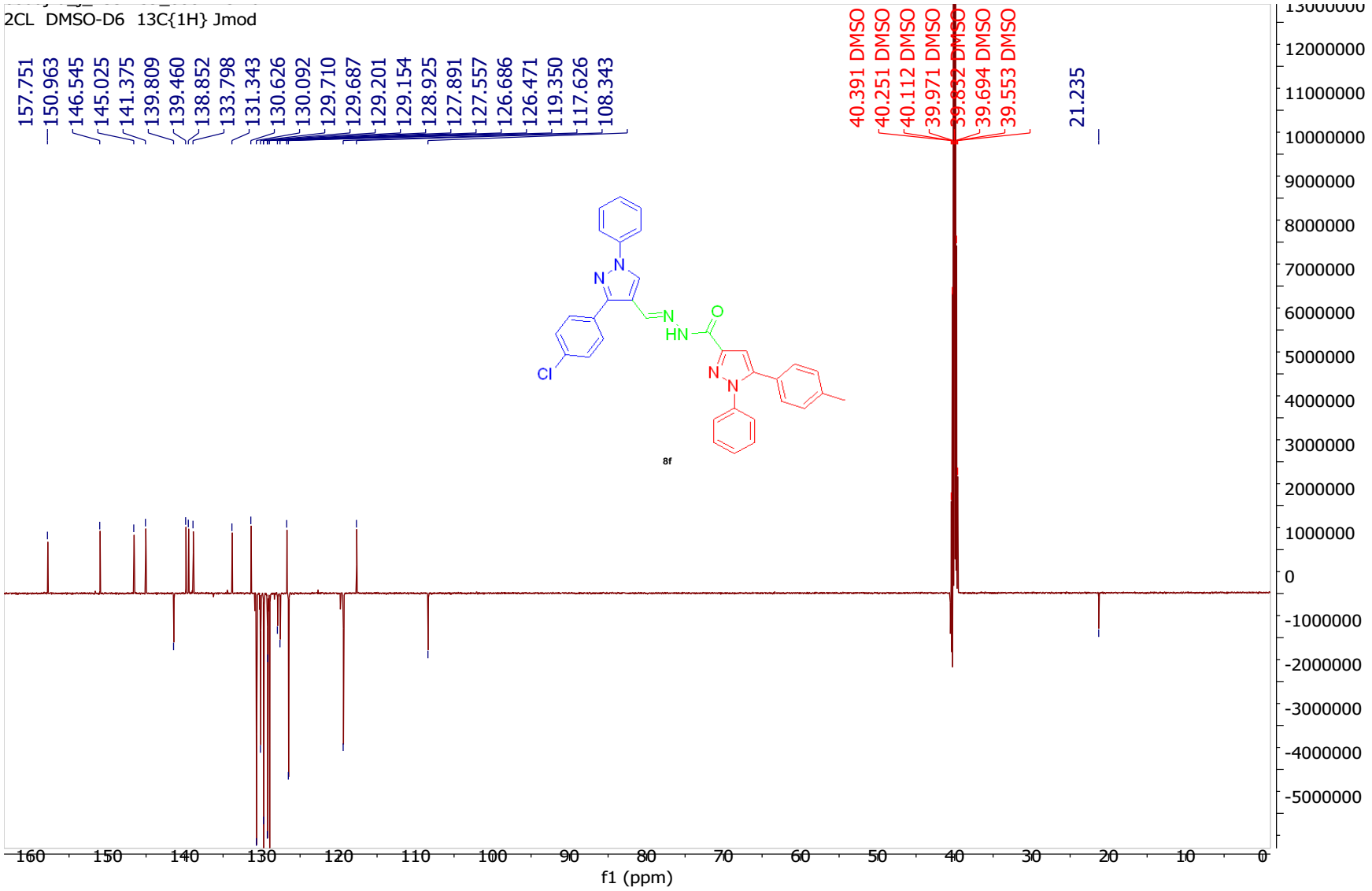


Figure S 19.. ^{13}C NMR of compound **8f**

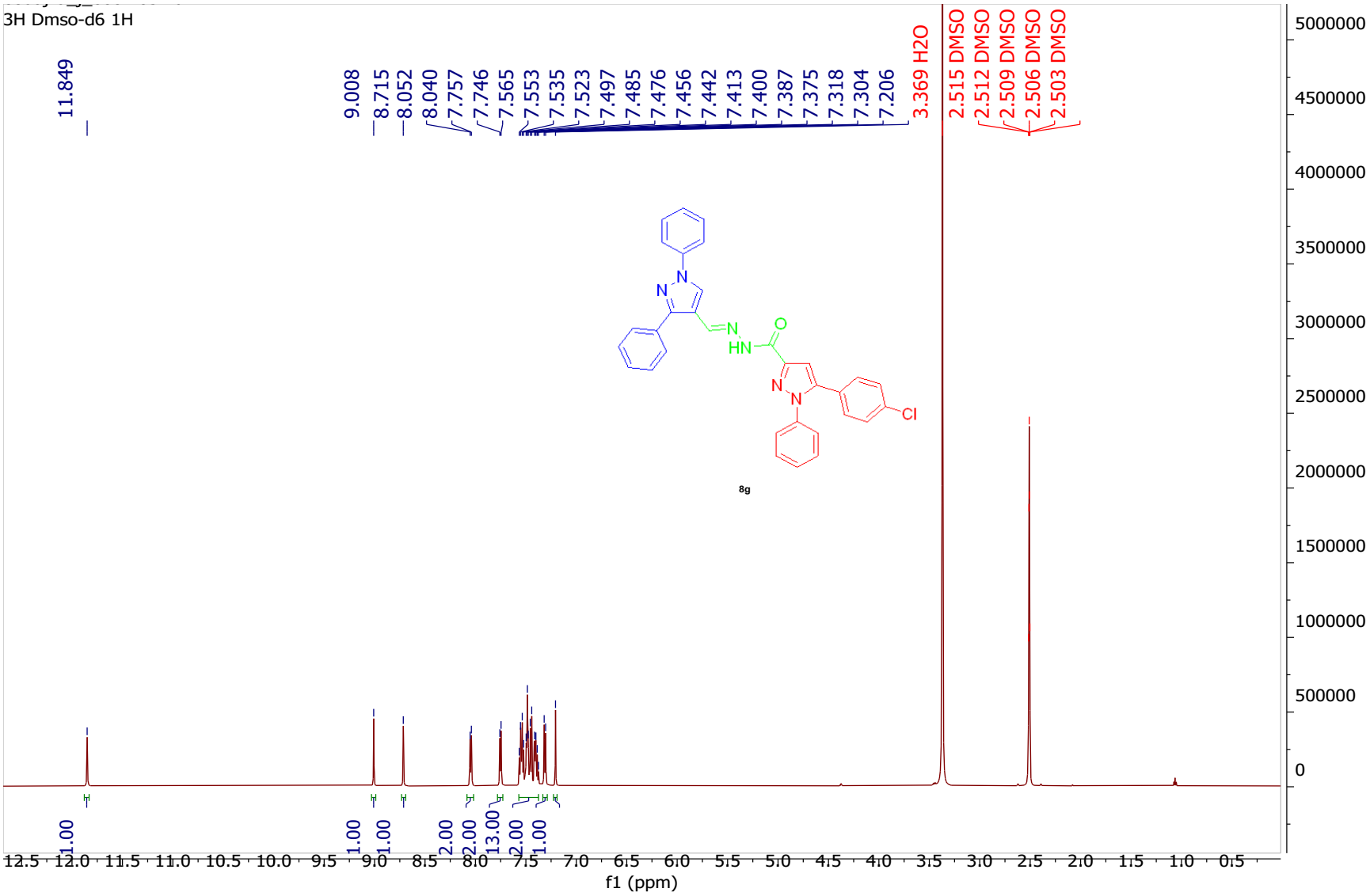


Figure S 20. ^{1}H NMR of compound **8g**

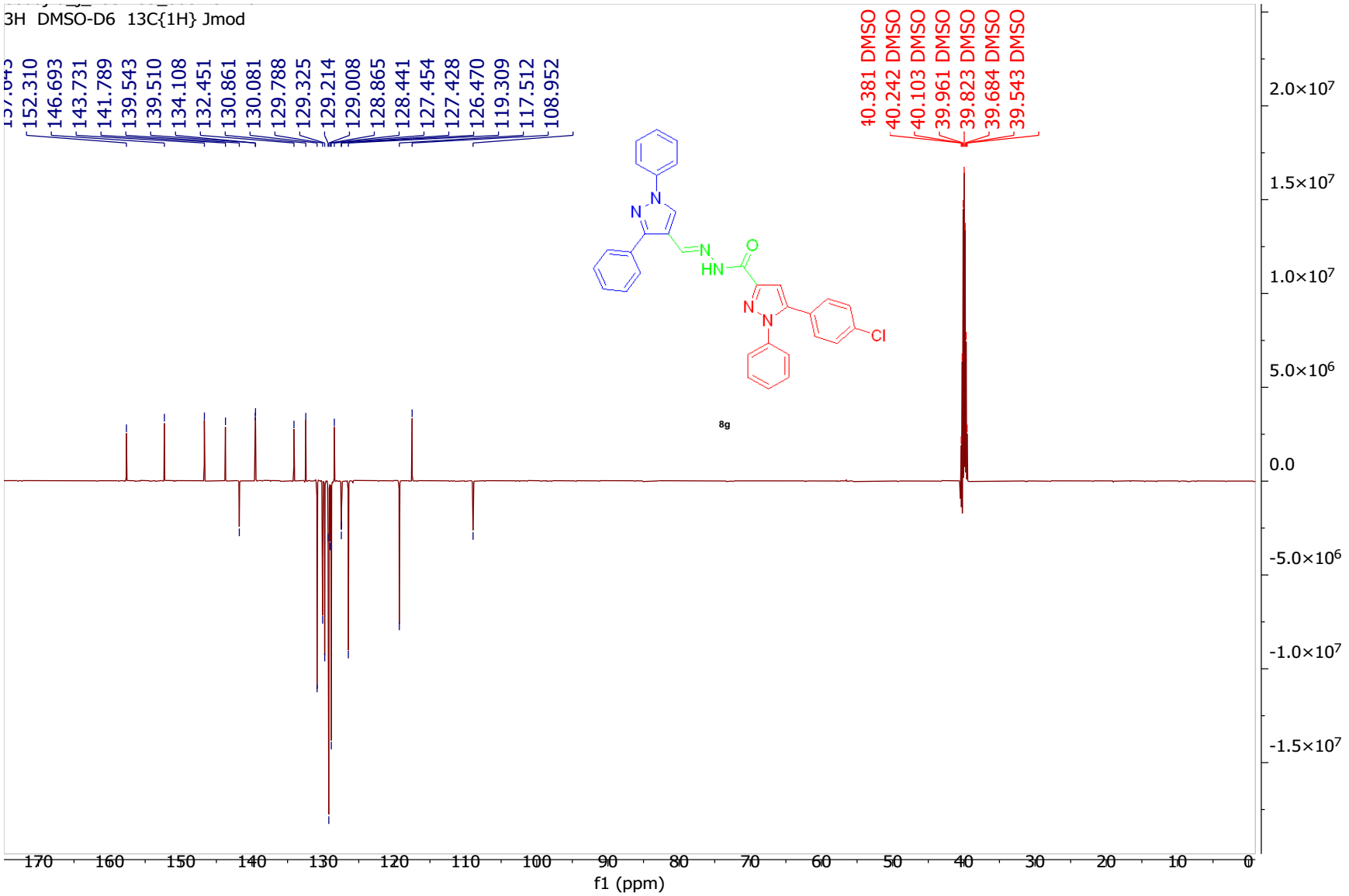


Figure S 21. ^{13}C NMR of compound **8g**

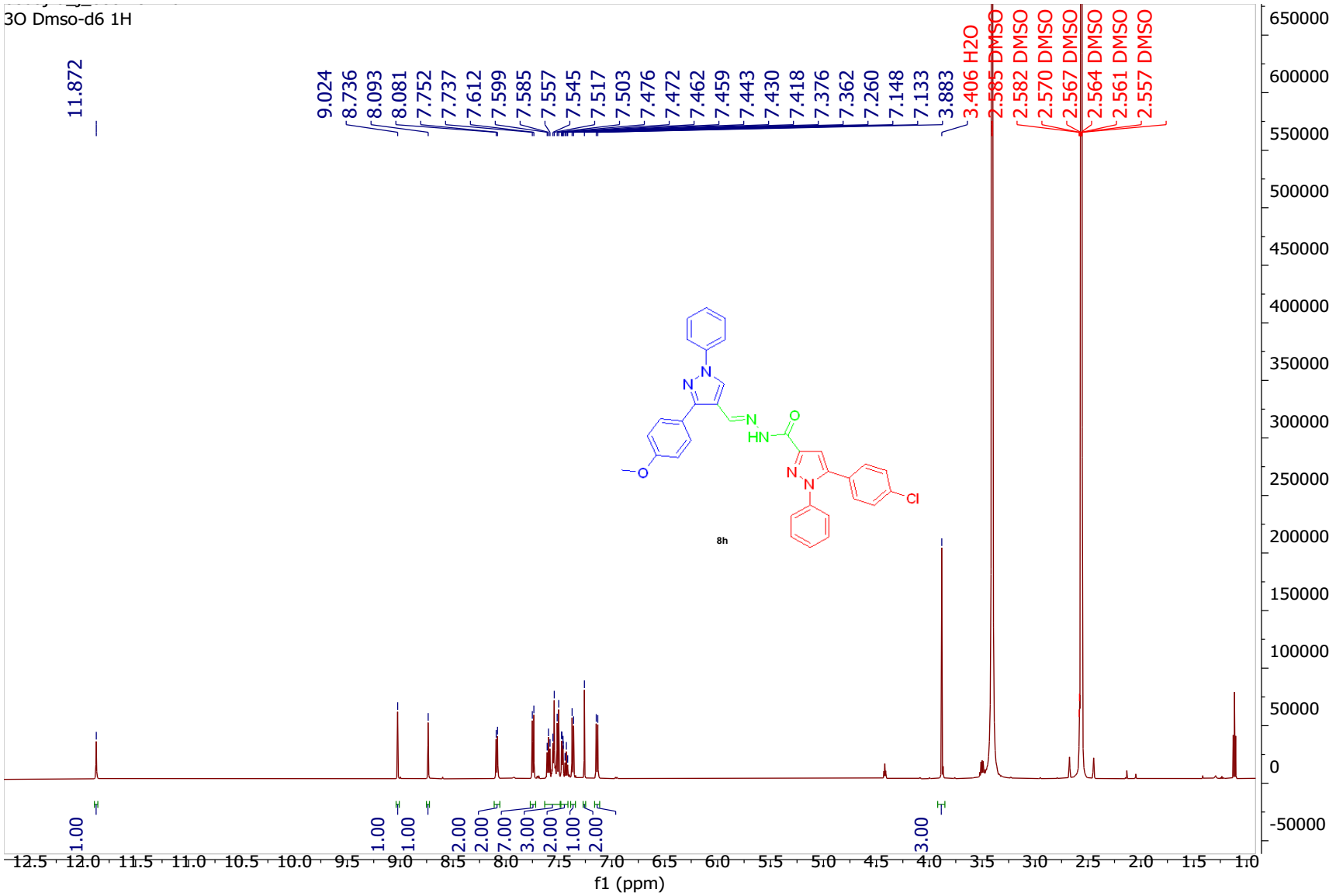


Figure S 22. ^{1}H NMR of compound **8h**

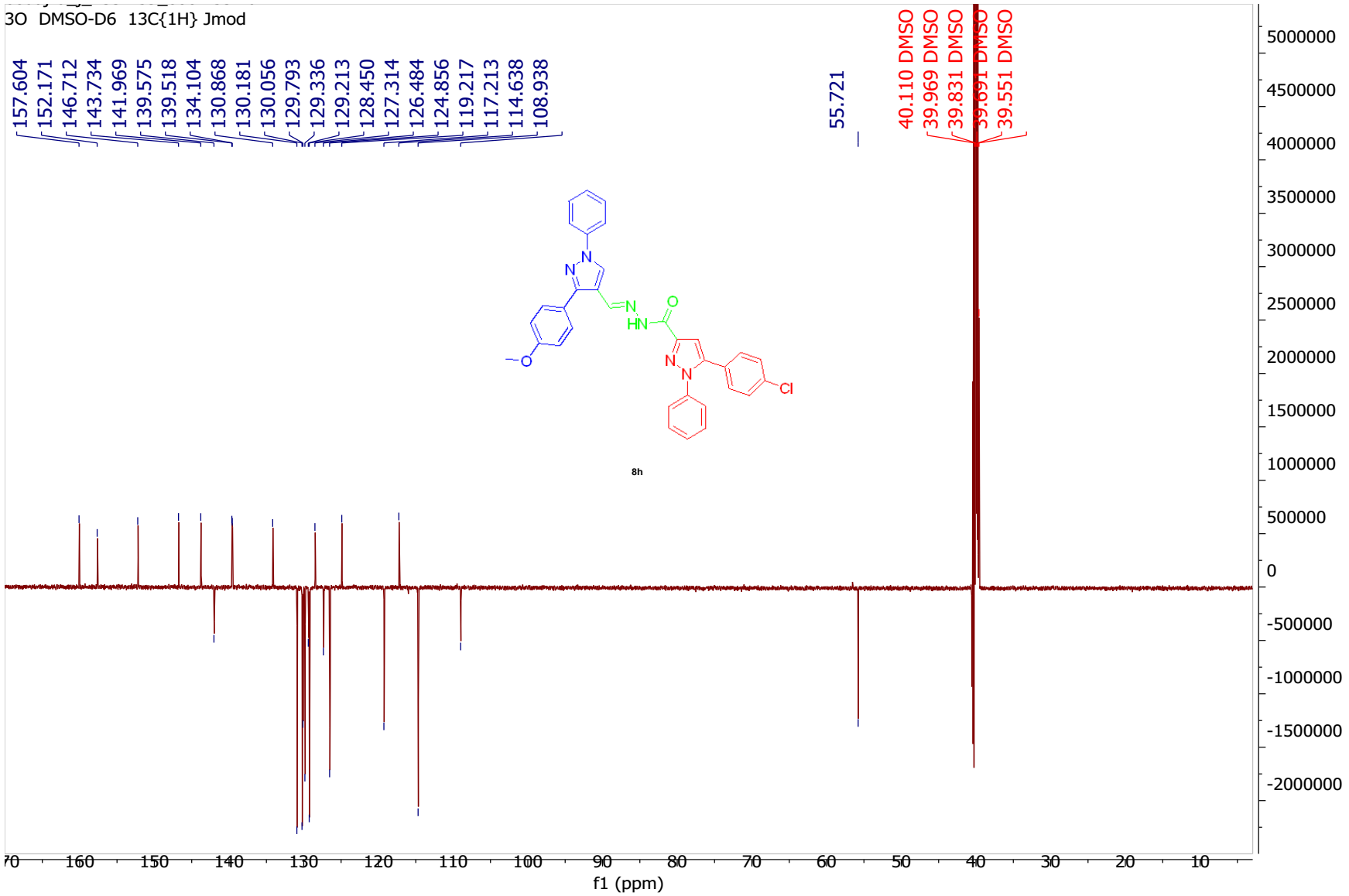


Figure S 23. ^{13}C NMR of compound **8h**

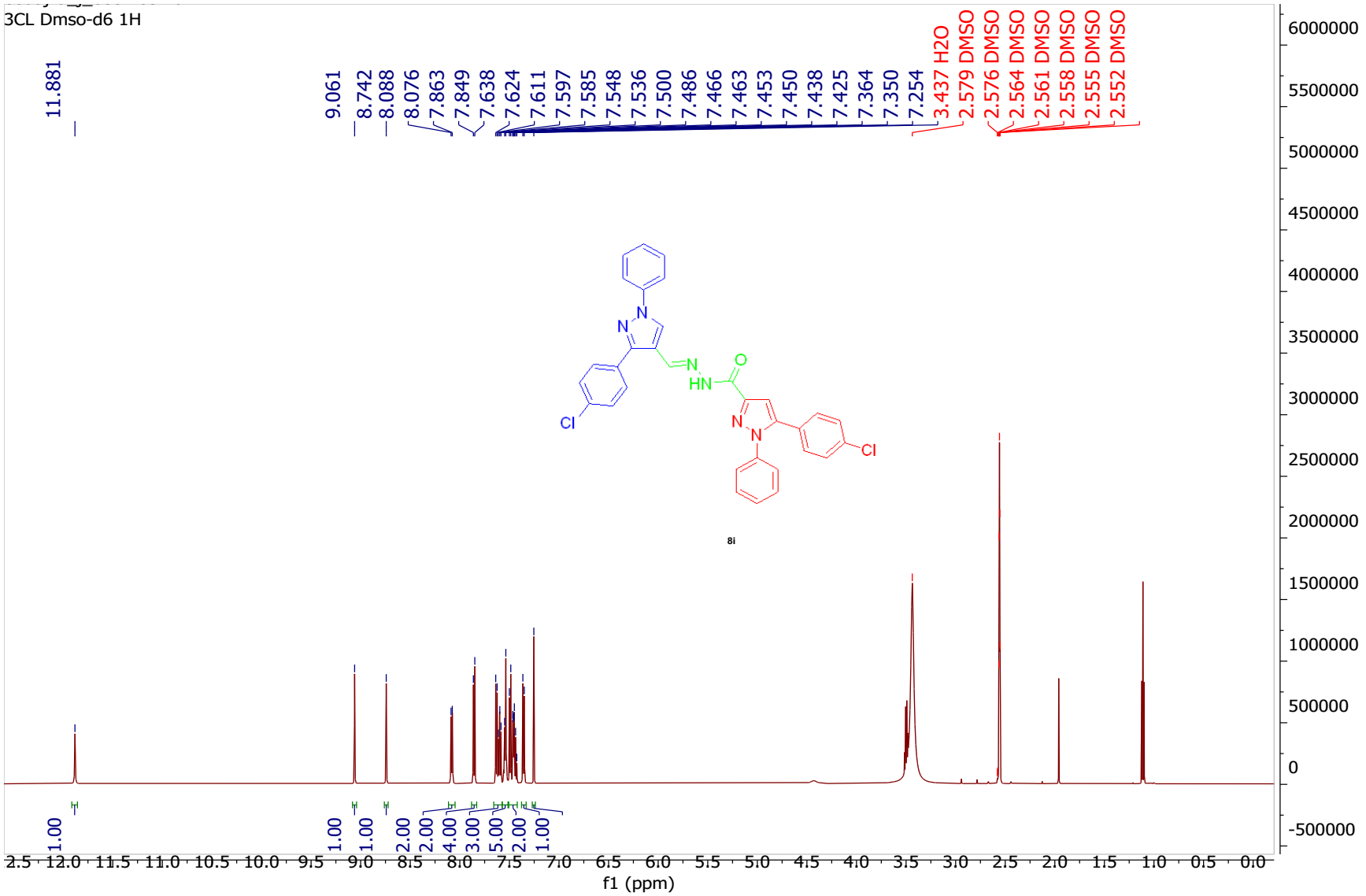


Figure S 24. ^{1}H NMR of compound **8i**

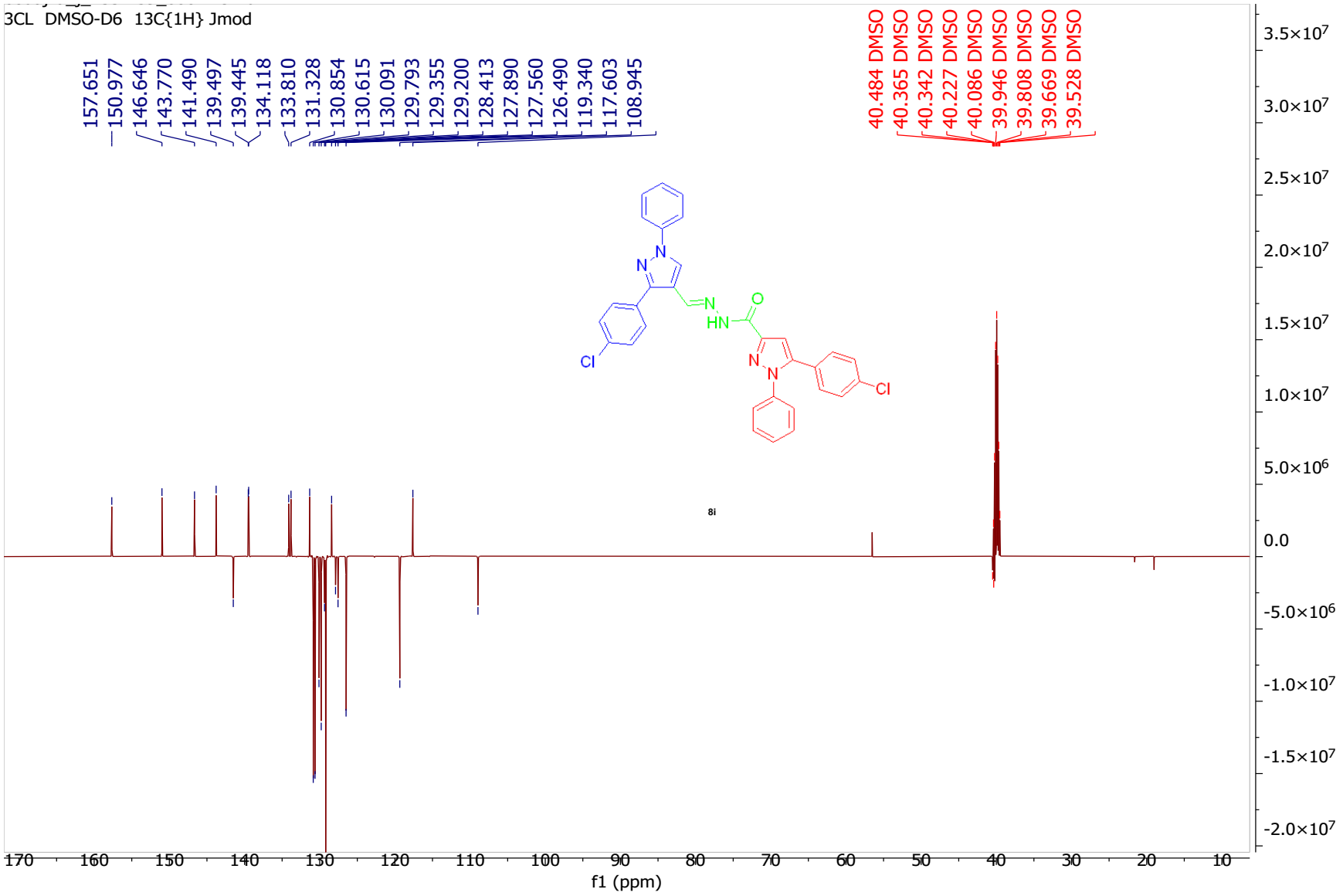


Figure S 25. ^{13}C NMR of compound **8i**

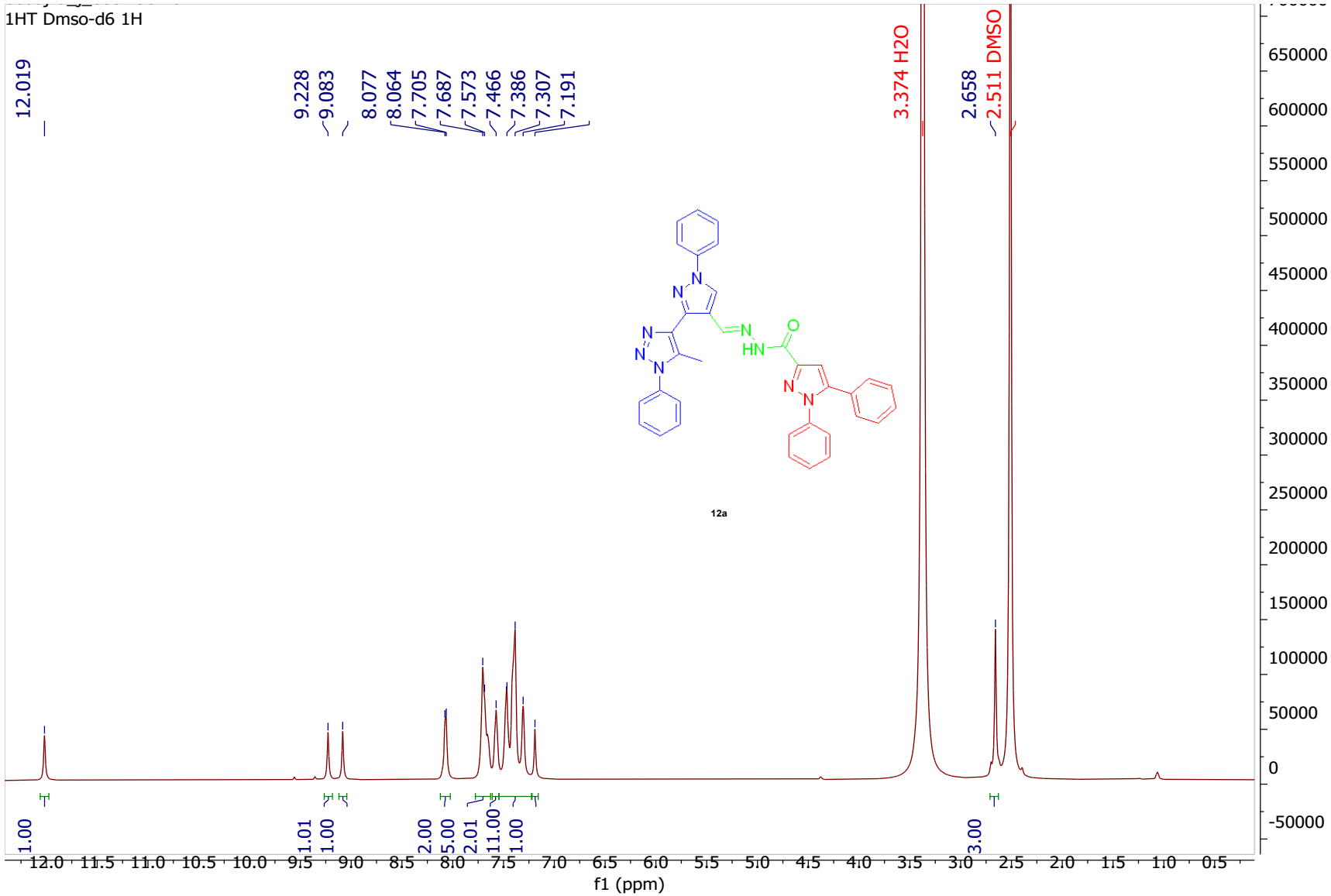


Figure S 26. ^{1}H NMR of compound **12a**

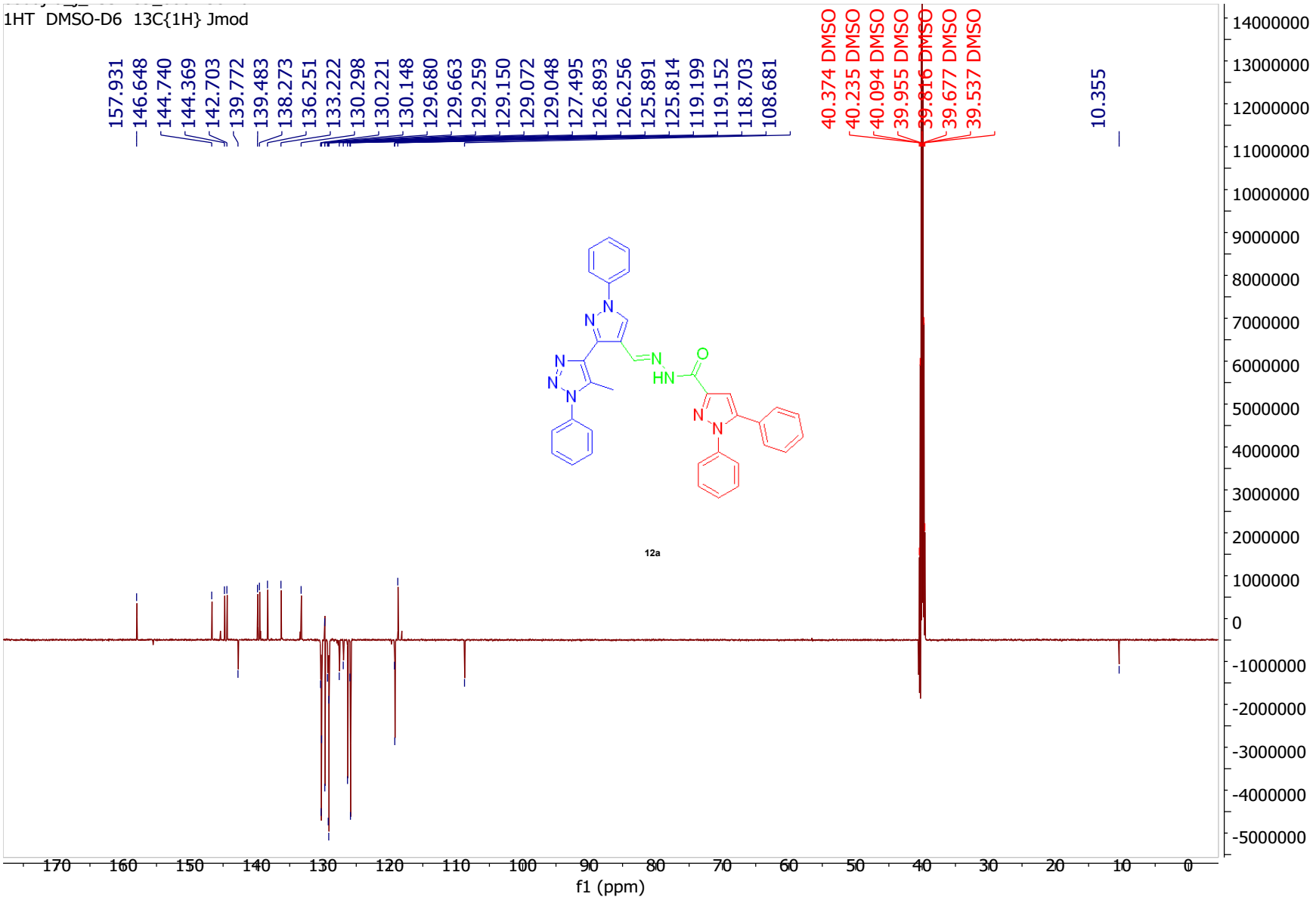

1HT DMSO-D6 13C{1H} Jmod
157.931
146.648
144.740
144.369
142.703
139.772
139.483
138.273
136.251
133.222
130.298
130.221
130.148
129.680
129.663
129.259
129.150
129.072
129.048
127.495
126.893
126.256
125.891
125.814
119.199
119.152
118.703
108.681
40.374 DMSO
40.235 DMSO
40.094 DMSO
39.955 DMSO
39.816 DMSO
39.677 DMSO
39.537 DMSO
10.355
12a
f1 (ppm)

Figure S 27. ^{13}C NMR of compound **12a**

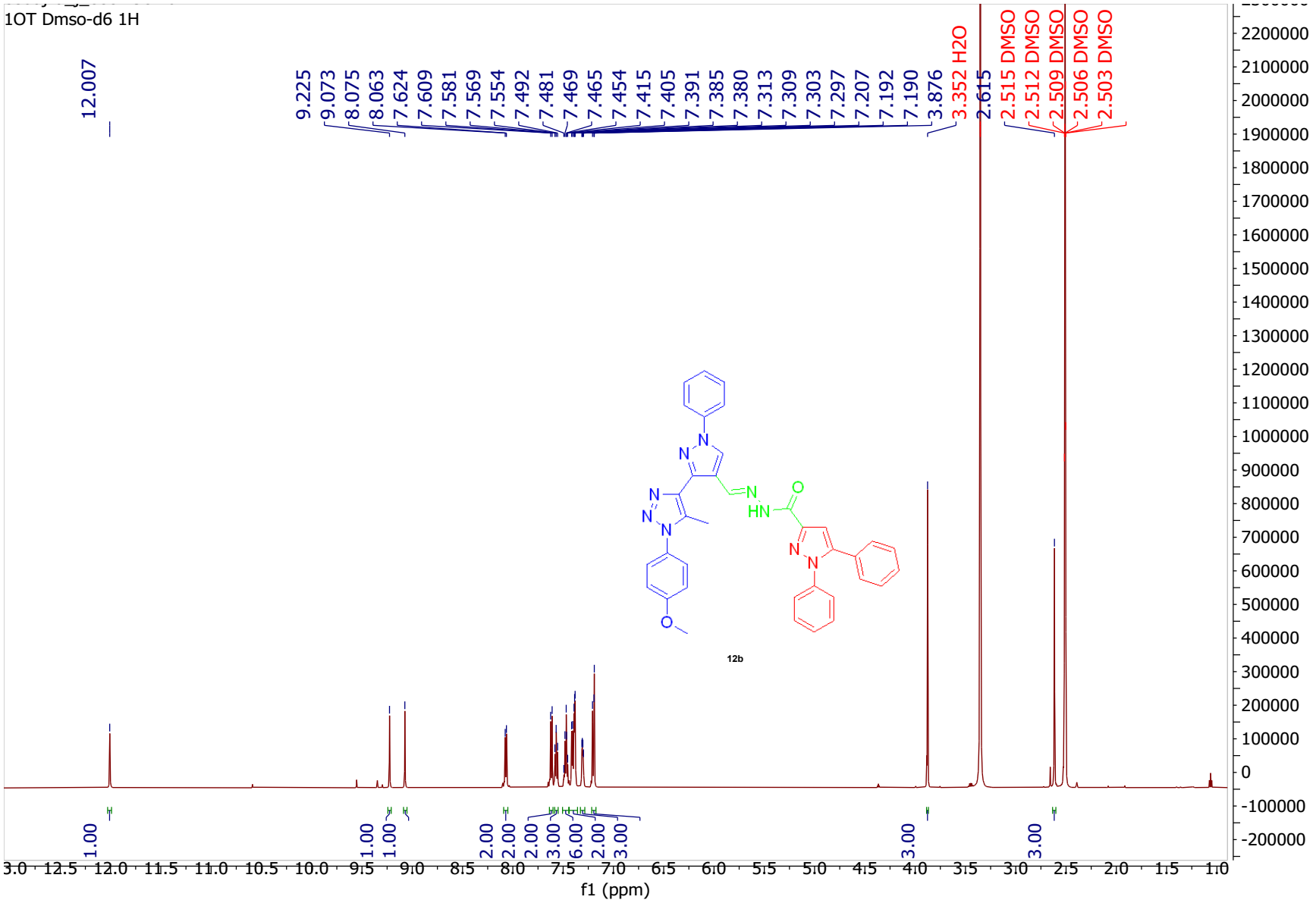

1OT Dmso-d6 1H
12.007
9.225
9.073
8.075
8.063
7.624
7.609
7.581
7.569
7.554
7.492
7.481
7.469
7.465
7.454
7.415
7.405
7.391
7.385
7.380
7.313
7.309
7.303
7.297
7.207
7.192
7.190
3.876
3.352 H2O
2.615
2.515 DMSO
2.512 DMSO
2.509 DMSO
2.506 DMSO
2.503 DMSO
12b
1.00
1.00
1.00
2.00
2.00
2.00
3.00
6.00
2.00
3.00
3.00
3.00
f1 (ppm)

Figure S 28. ^{1}H NMR of compound **12b**

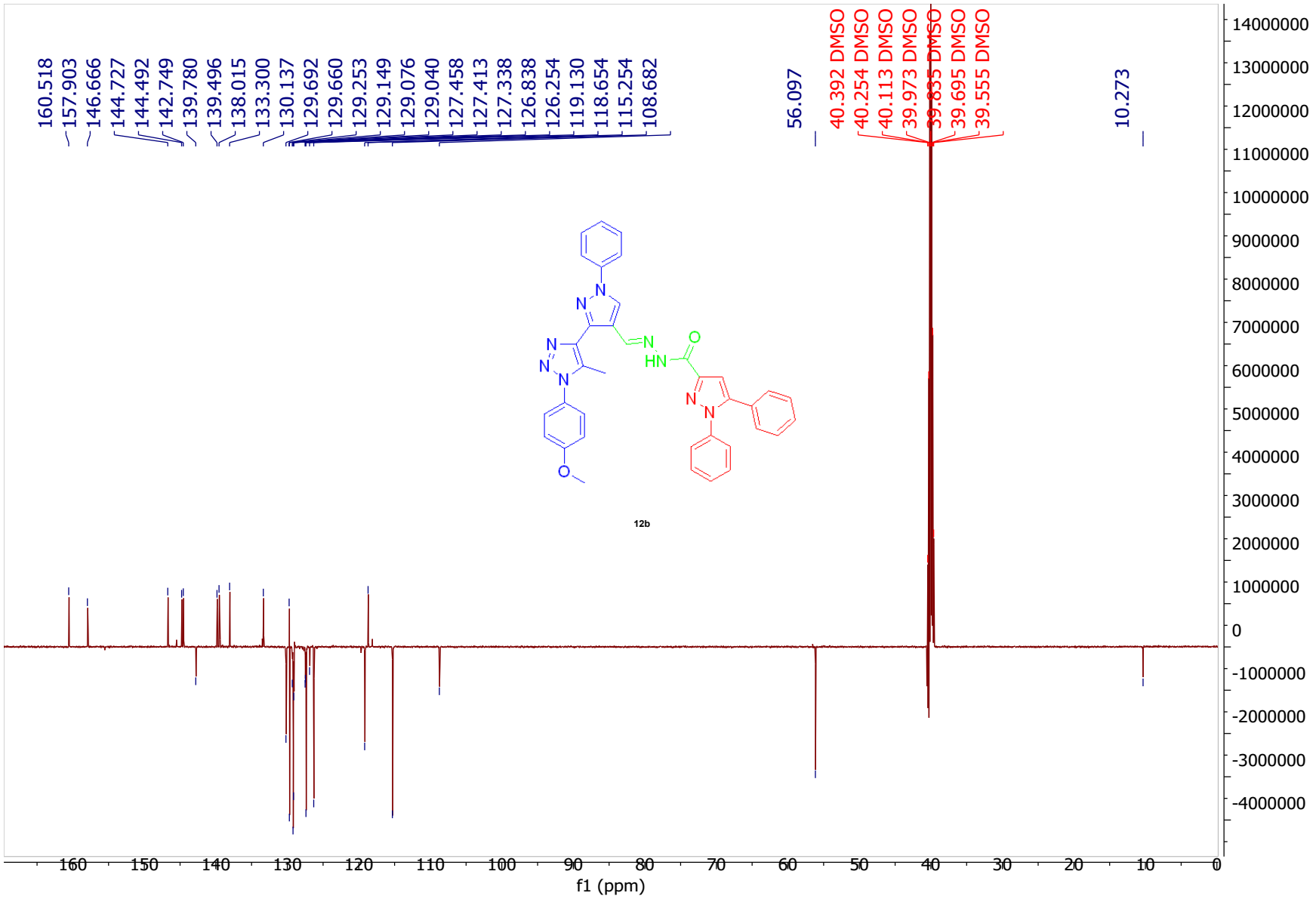

160.518
157.903
146.666
144.727
144.492
142.749
139.780
139.496
138.015
133.300
130.137
129.692
129.660
129.253
129.149
129.076
129.040
127.458
127.413
127.338
126.838
126.254
119.130
118.654
115.254
108.682
56.097
40.392 DMSO
40.254 DMSO
40.113 DMSO
39.973 DMSO
39.835 DMSO
39.695 DMSO
39.555 DMSO
10.273
12b
f1 (ppm)

Figure S 29. ^{13}C NMR of compound **12b**

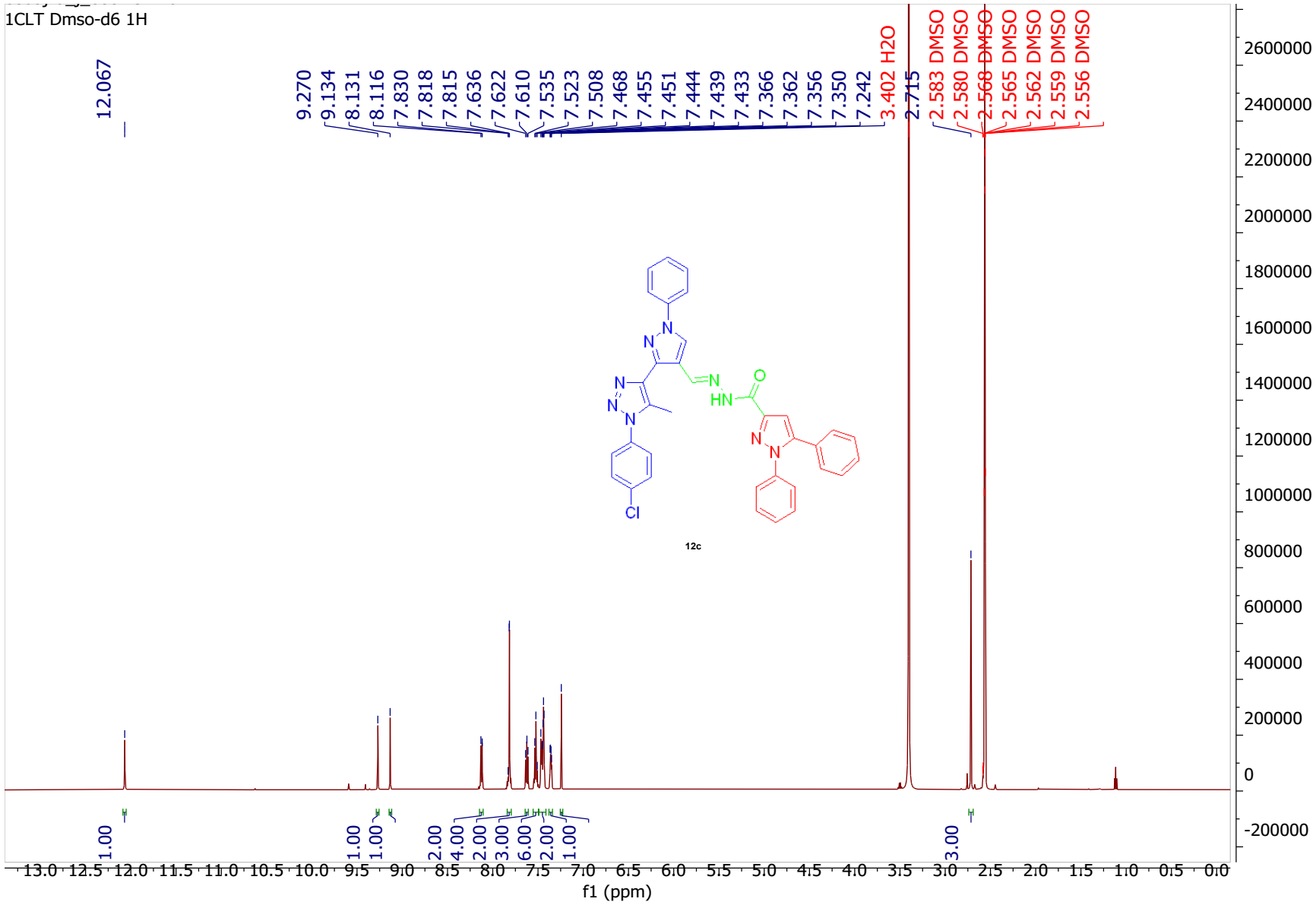

1CLT Dmso-d6 1H
12.067
9.270
9.134
8.131
8.116
7.830
7.818
7.815
7.636
7.622
7.610
7.535
7.523
7.508
7.468
7.455
7.451
7.444
7.439
7.433
7.366
7.362
7.356
7.350
7.242
3.402 H2O
2.715
2.583 DMSO
2.580 DMSO
2.568 DMSO
2.565 DMSO
2.562 DMSO
2.559 DMSO
2.556 DMSO
12c
1.00
1.00
1.00
2.00
4.00
2.00
3.00
6.00
2.00
1.00
3.00
f1 (ppm)

Figure S 30. ^{1}H NMR of compound **12c**

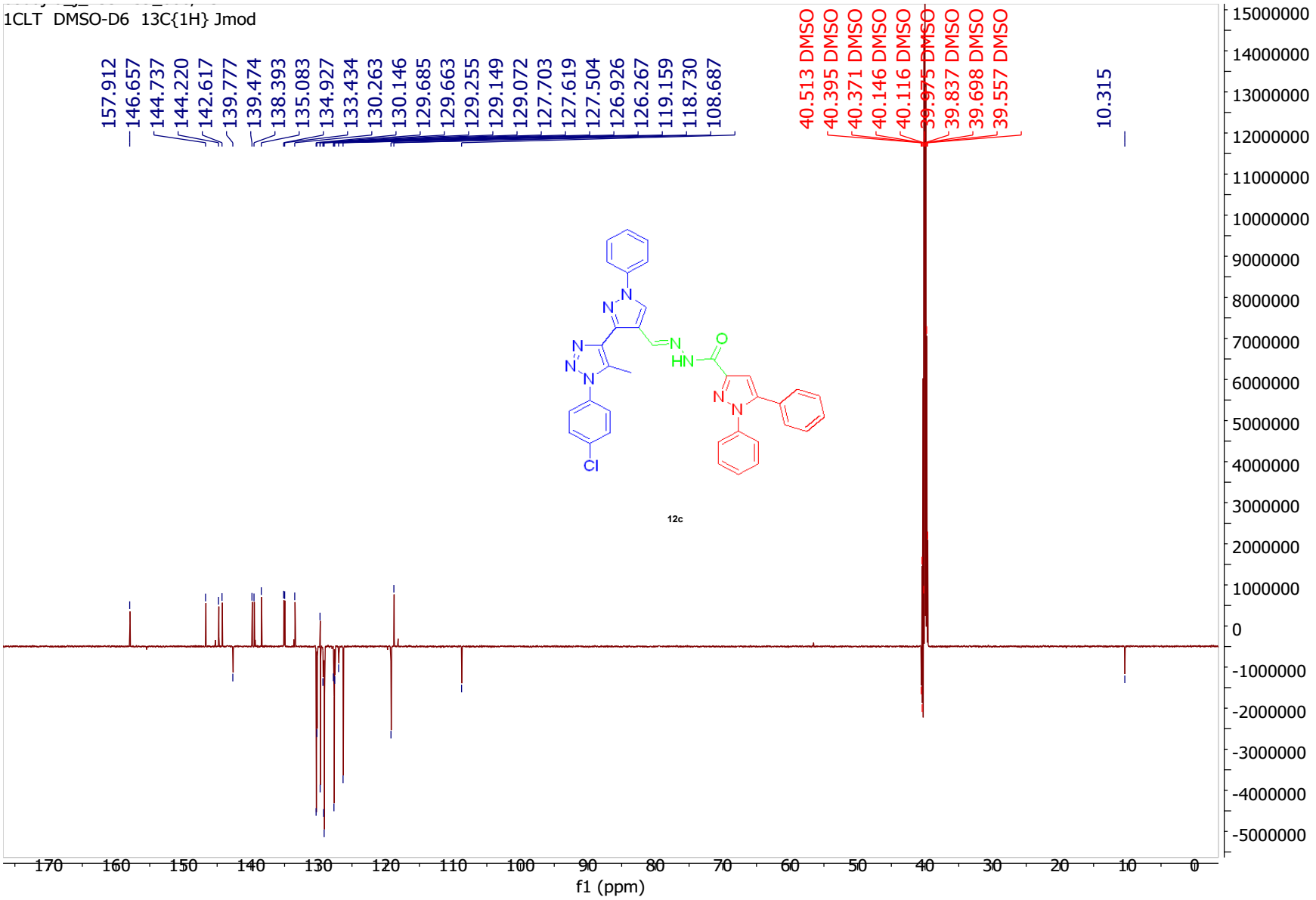

1CLT DMSO-D6 13C{1H} Jmod
157.912
146.657
144.737
144.220
142.617
139.777
139.474
138.393
135.083
134.927
133.434
130.263
130.146
129.685
129.663
129.255
129.149
129.072
127.703
127.619
127.504
126.926
126.267
119.159
118.730
108.687
40.513 DMSO
40.395 DMSO
40.371 DMSO
40.146 DMSO
40.116 DMSO
39.975 DMSO
39.837 DMSO
39.698 DMSO
39.557 DMSO
10.315
12c
f1 (ppm)

Figure S 31. ^{13}C NMR of compound **12c**

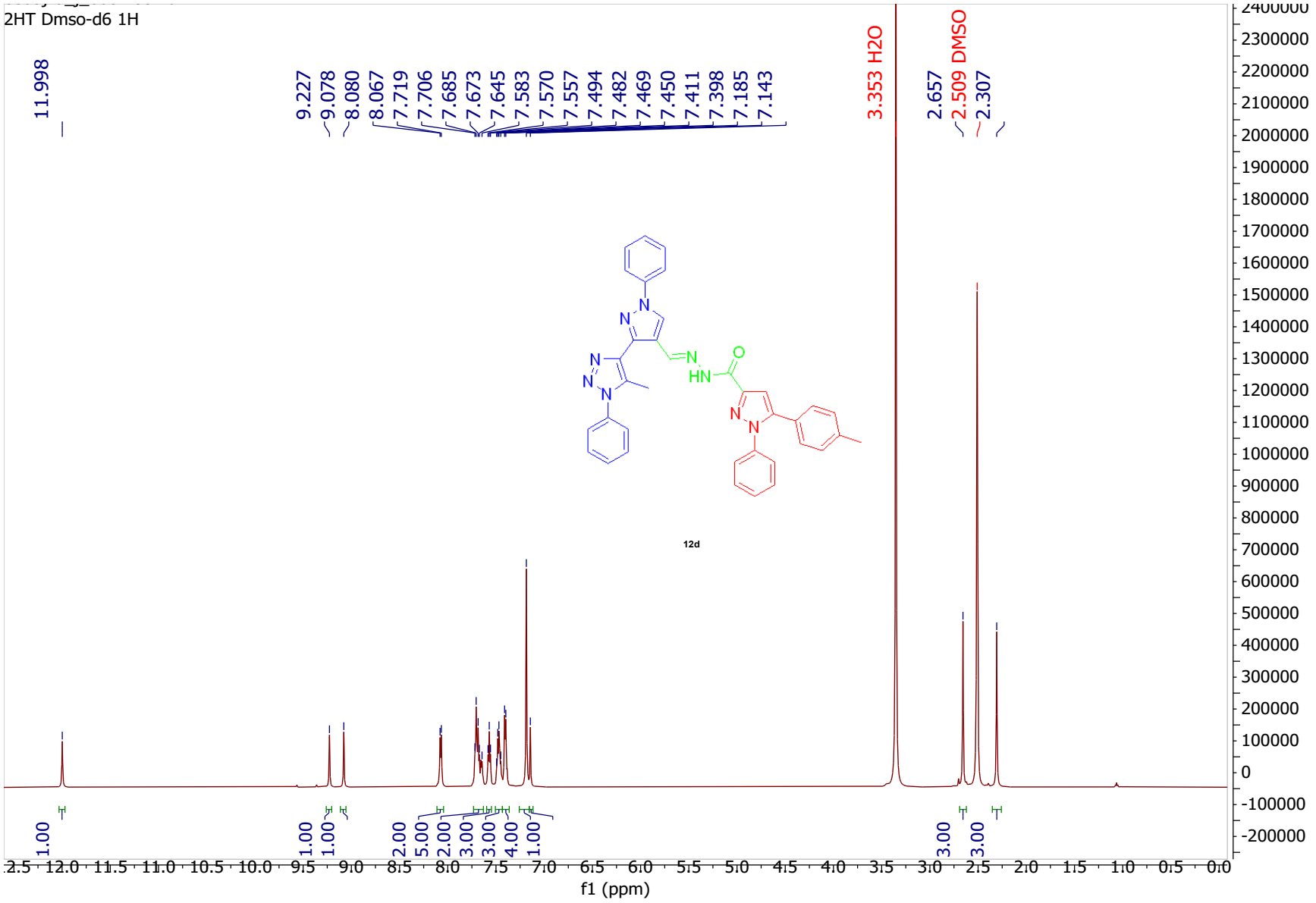

2HT Dmso-d6 1H
11.998
9.227
9.078
8.080
8.067
7.719
7.706
7.685
7.673
7.645
7.583
7.570
7.557
7.494
7.482
7.469
7.450
7.411
7.398
7.185
7.143
3.353 H2O
2.657
2.509 DMSO
2.307
12d
1.00
1.00
1.00
2.00
5.00
2.00
3.00
3.00
4.00
1.00
3.00
3.00
f1 (ppm)

Figure S 32. ^{1}H NMR of compound **12d**

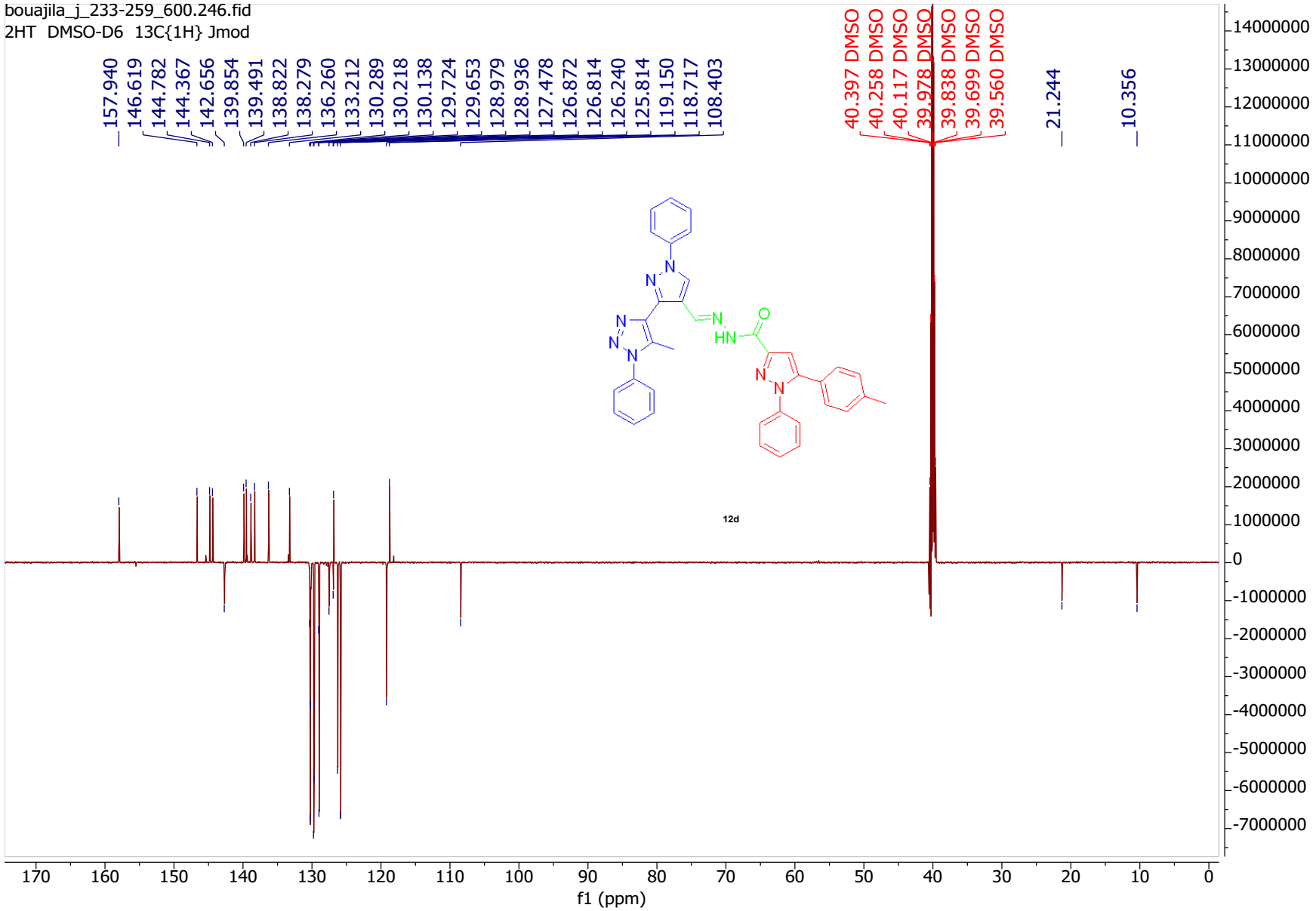

bouajila_j_233-259_600.246.fid
2HT DMSO-D6 13C{1H} Jmod
157.940
146.619
144.782
144.367
142.656
139.854
139.491
138.822
138.279
136.260
133.212
130.289
130.218
130.138
129.724
129.653
128.979
128.936
127.478
126.872
126.814
126.240
125.814
119.150
118.717
108.403
40.397 DMSO
40.258 DMSO
40.117 DMSO
39.978 DMSO
39.838 DMSO
39.699 DMSO
39.560 DMSO
21.244
10.356
12d
f1 (ppm)

Figure S 33 ^{13}C NMR of compound **12d**

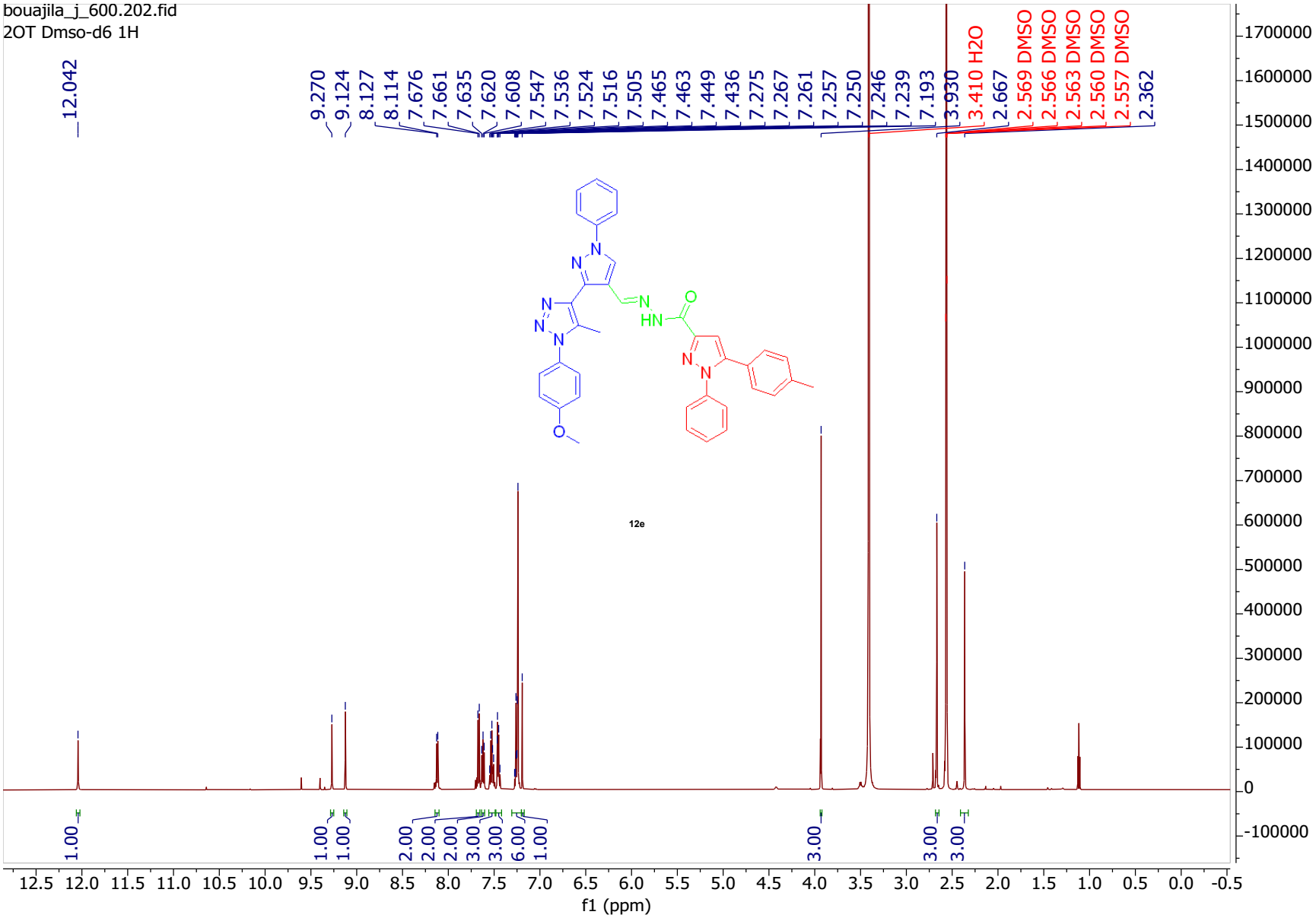

bouajila_j_600.202.fid
2OT Dmso-d6 1H
12.042
9.270
9.124
8.127
8.114
7.676
7.661
7.635
7.620
7.608
7.547
7.536
7.524
7.516
7.505
7.465
7.463
7.449
7.436
7.275
7.267
7.261
7.257
7.250
7.246
7.239
7.193
3.930
3.410 H2O
2.667
2.569 DMSO
2.566 DMSO
2.563 DMSO
2.560 DMSO
2.557 DMSO
2.362
12e
1.00
1.00
1.00
2.00
2.00
2.00
3.00
3.00
6.00
1.00
3.00
3.00
3.00
f1 (ppm)

Figure S 34. ^{1}H NMR of compound **12e**

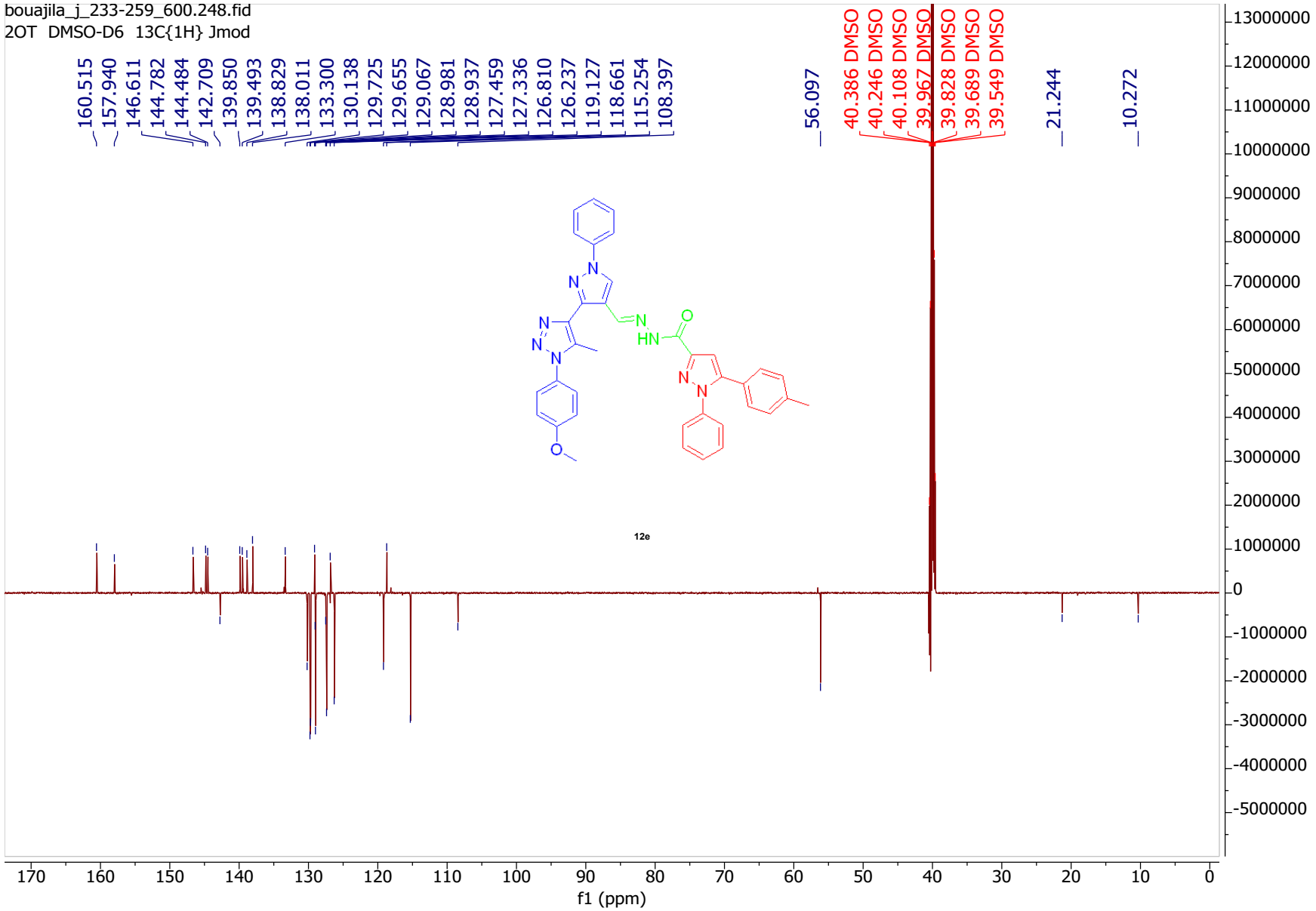

bouajila_j_233-259_600.248.fid
2OT DMSO-D6 13C{1H} Jmod
160.515
157.940
146.611
144.782
144.484
142.709
139.850
139.493
138.829
138.011
133.300
130.138
129.725
129.655
129.067
128.981
128.937
127.459
127.336
126.810
126.237
119.127
118.661
115.254
108.397
56.097
40.386 DMSO
40.246 DMSO
40.108 DMSO
39.967 DMSO
39.828 DMSO
39.689 DMSO
39.549 DMSO
21.244
10.272
12e
f1 (ppm)

Figure S 35. ^{13}C NMR of compound **12e**

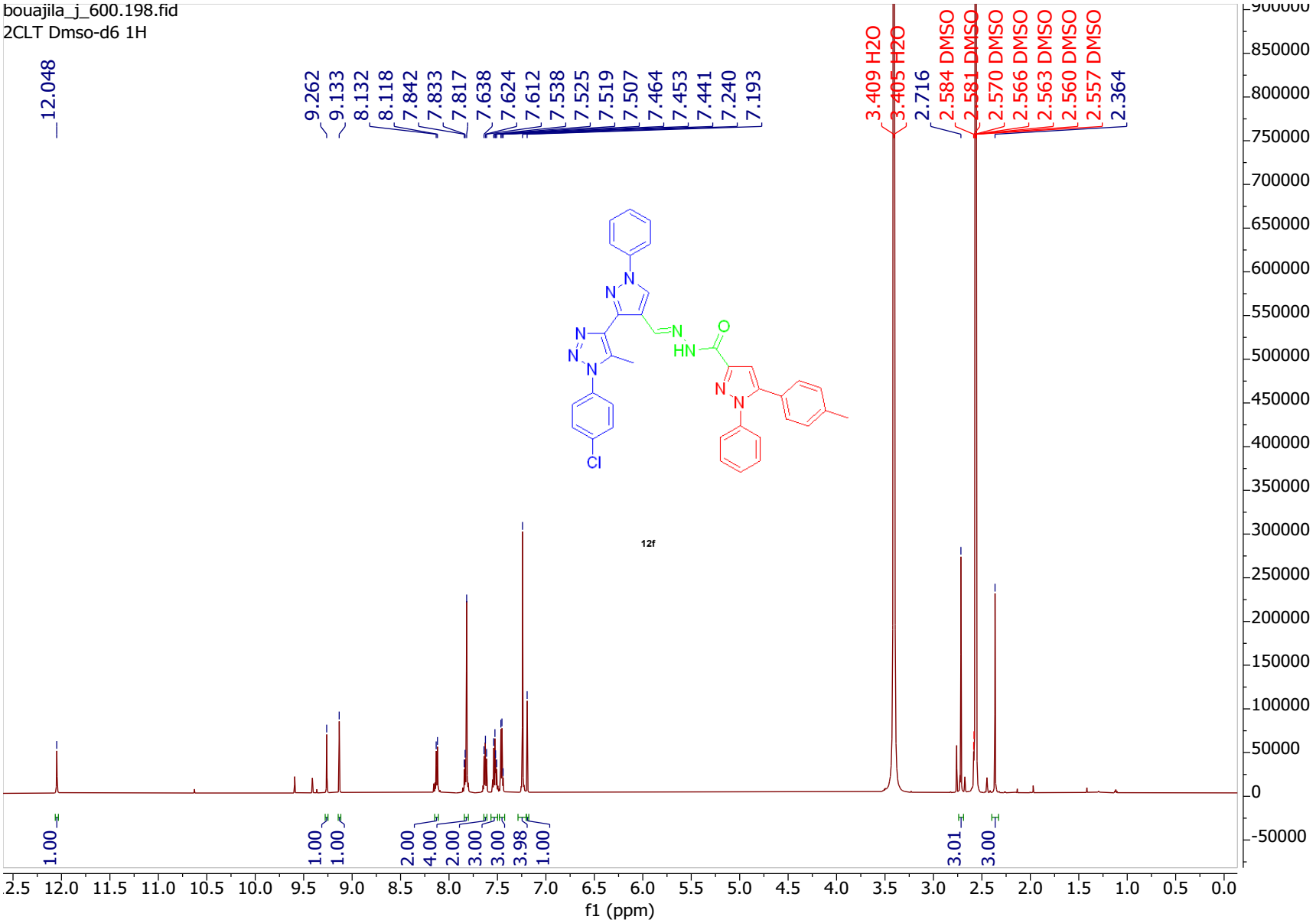

bouajila_j_600.198.fid
2CLT Dmso-d6 1H
12.048
9.262
9.133
8.132
8.118
7.842
7.833
7.817
7.638
7.624
7.612
7.538
7.525
7.519
7.507
7.464
7.453
7.441
7.240
7.193
3.409 H2O
3.405 H2O
2.716
2.584 DMSO
2.581 DMSO
2.570 DMSO
2.566 DMSO
2.563 DMSO
2.560 DMSO
2.557 DMSO
2.364
12f
1.00
1.00
1.00
2.00
4.00
2.00
3.00
3.00
3.98
1.00
3.01
3.00
f1 (ppm)

Figure S 36. ^{1}H NMR of compound **12f**

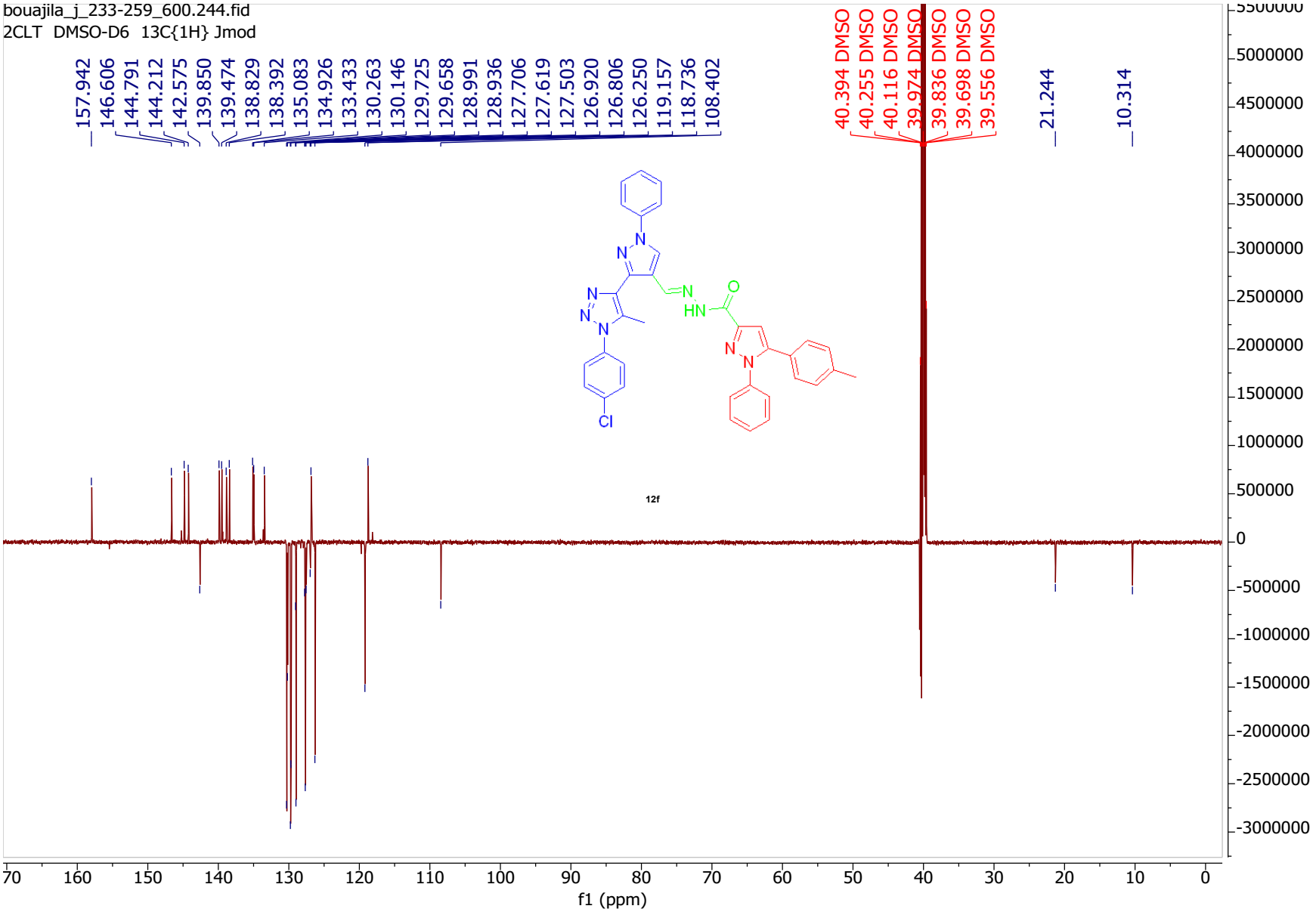

bouajila_j_233-259_600.244.fid
2CLT DMSO-D6 13C{1H} Jmod
157.942
146.606
144.791
144.212
142.575
139.850
139.474
138.829
138.392
135.083
134.926
133.433
130.263
130.146
129.725
129.658
128.991
128.936
127.706
127.619
127.503
126.920
126.806
126.250
119.157
118.736
108.402
40.394 DMSO
40.255 DMSO
40.116 DMSO
39.974 DMSO
39.836 DMSO
39.698 DMSO
39.556 DMSO
21.244
10.314
12f
f1 (ppm)

Figure S 37. ^{13}C NMR of compound **12f**

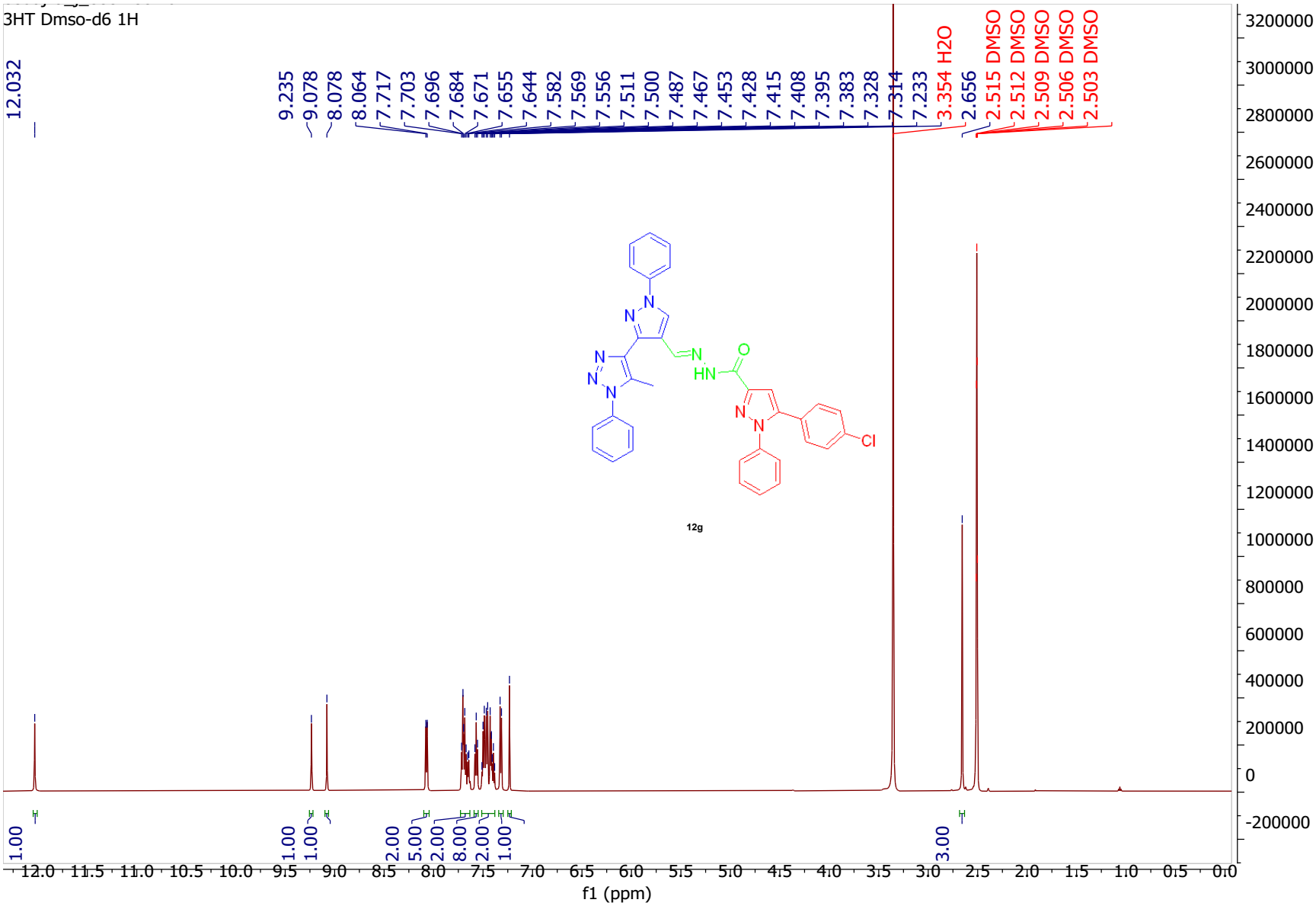

3HT Dmso-d6 1H
12.032
9.235
9.078
8.078
8.064
7.717
7.703
7.696
7.684
7.671
7.655
7.644
7.582
7.569
7.556
7.511
7.500
7.487
7.467
7.453
7.428
7.415
7.408
7.395
7.383
7.328
7.314
7.233
3.354 H2O
2.656
2.515 DMSO
2.512 DMSO
2.509 DMSO
2.506 DMSO
2.503 DMSO
12g
1.00
1.00
1.00
2.00
5.00
2.00
8.00
2.00
1.00
3.00
f1 (ppm)

Figure S 38. ^{1}H NMR of compound **12g**

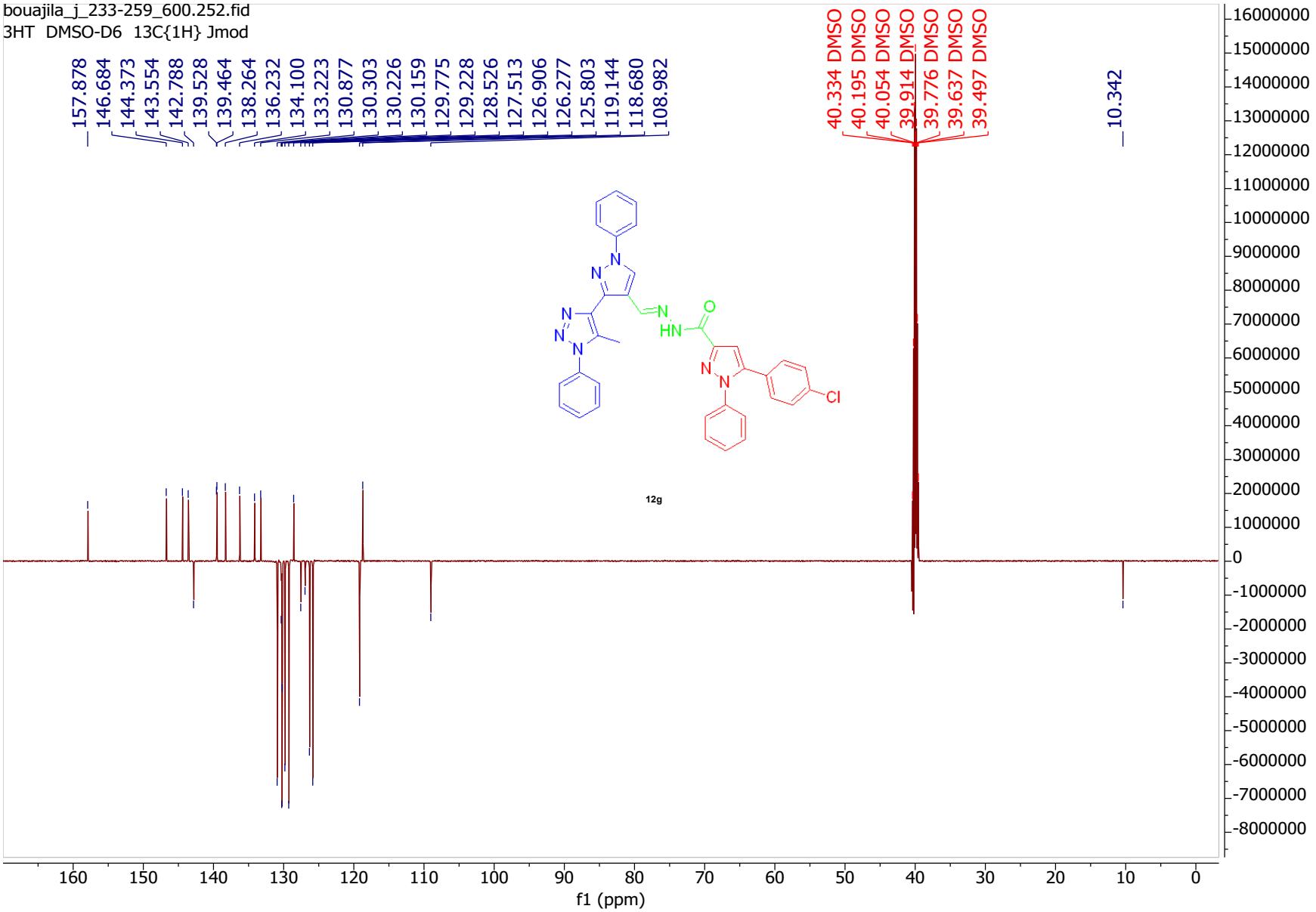

bouajila_j_233-259_600.252.fid
3HT DMSO-D6 13C{1H} Jmod
157.878
146.684
144.373
143.554
142.788
139.528
139.464
138.264
136.232
134.100
133.223
130.877
130.303
130.226
130.159
129.775
129.228
128.526
127.513
126.906
126.277
125.803
119.144
118.680
108.982
40.334 DMSO
40.195 DMSO
40.054 DMSO
39.914 DMSO
39.776 DMSO
39.637 DMSO
39.497 DMSO
10.342
12g
f1 (ppm)

Figure S 39. ^{13}C NMR of compound **12g**

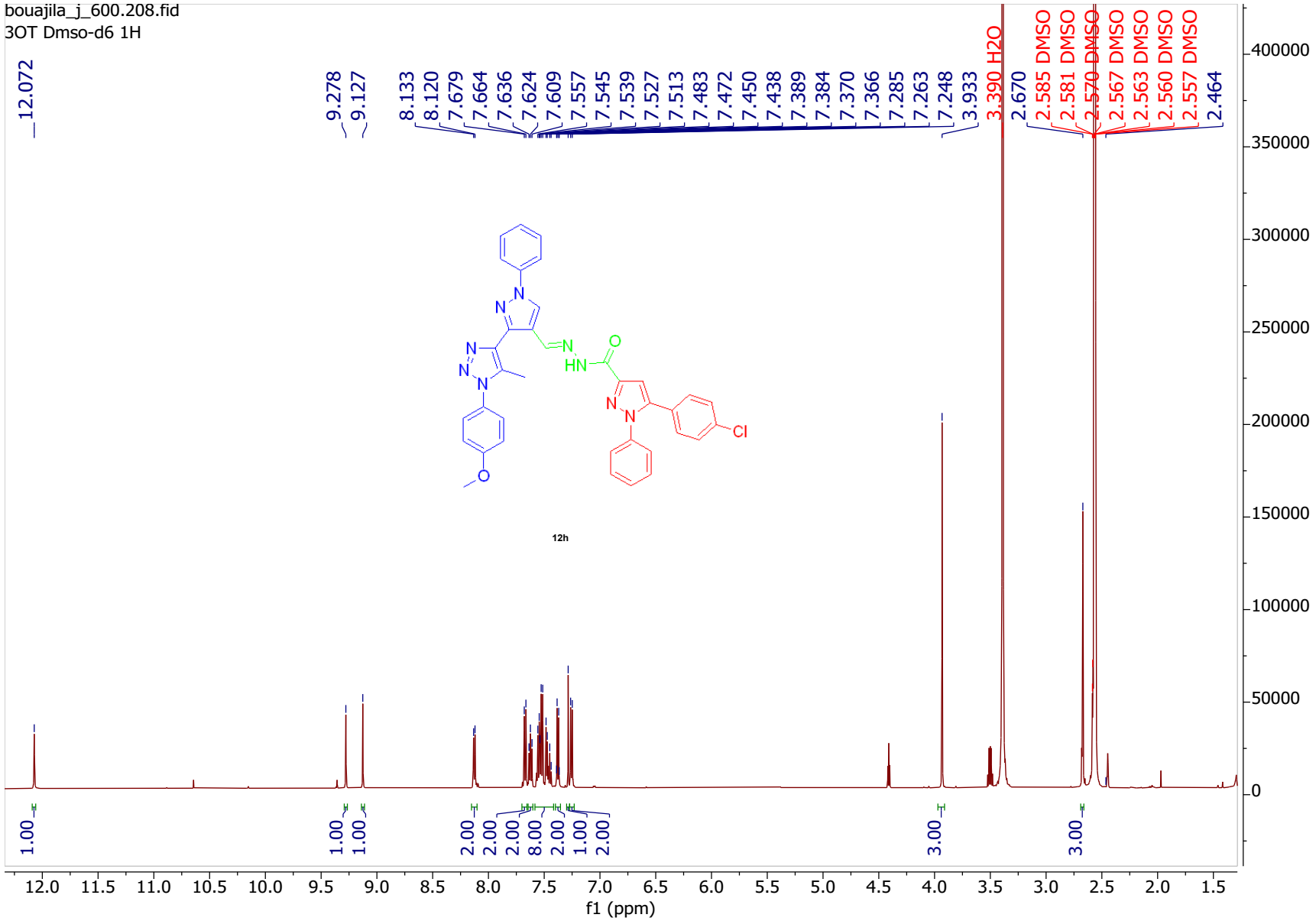

bouajila_j_600.208.fid
3OT Dmso-d6 1H
12.072
9.278
9.127
8.133
8.120
7.679
7.664
7.636
7.624
7.609
7.557
7.545
7.539
7.527
7.513
7.483
7.472
7.450
7.438
7.389
7.384
7.370
7.366
7.285
7.263
7.248
3.933
3.390 H2O
2.670
2.585 DMSO
2.581 DMSO
2.570 DMSO
2.567 DMSO
2.563 DMSO
2.560 DMSO
2.557 DMSO
2.464
12h
1.00
1.00
1.00
2.00
2.00
2.00
8.00
2.00
1.00
2.00
3.00
3.00
f1 (ppm)

Figure S 40. ^{1}H NMR of compound **12h**

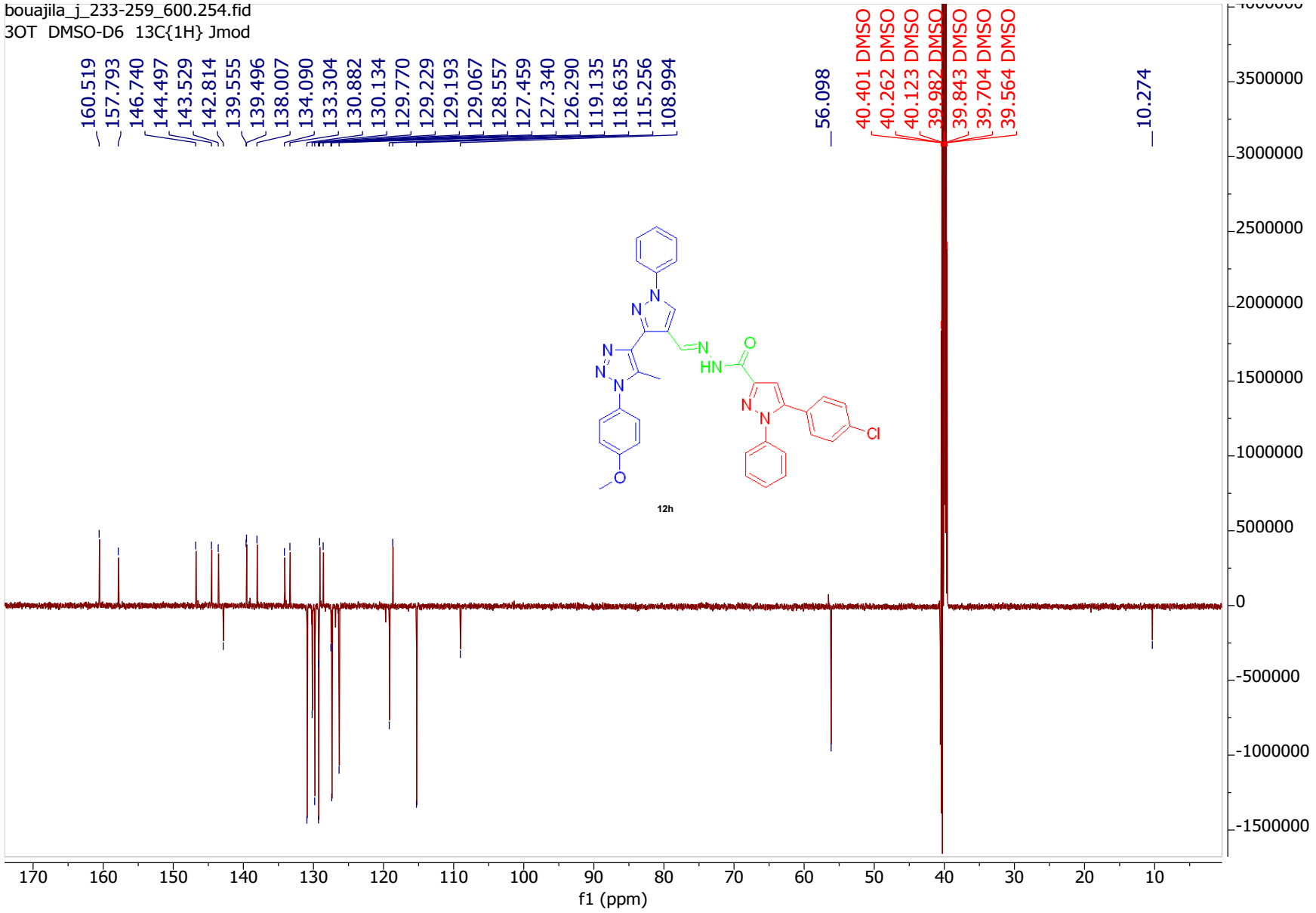

bouajila_j_233-259_600.254.fid
3OT DMSO-D6 13C{1H} Jmod
160.519
157.793
146.740
144.497
143.529
142.814
139.555
139.496
138.007
134.090
133.304
130.882
130.134
129.770
129.229
129.193
129.067
128.557
127.459
127.340
126.290
119.135
118.635
115.256
108.994
56.098
40.401 DMSO
40.262 DMSO
40.123 DMSO
39.982 DMSO
39.843 DMSO
39.704 DMSO
39.564 DMSO
10.274
12h
f1 (ppm)

Figure S 41. ^{13}C NMR of compound **12h**

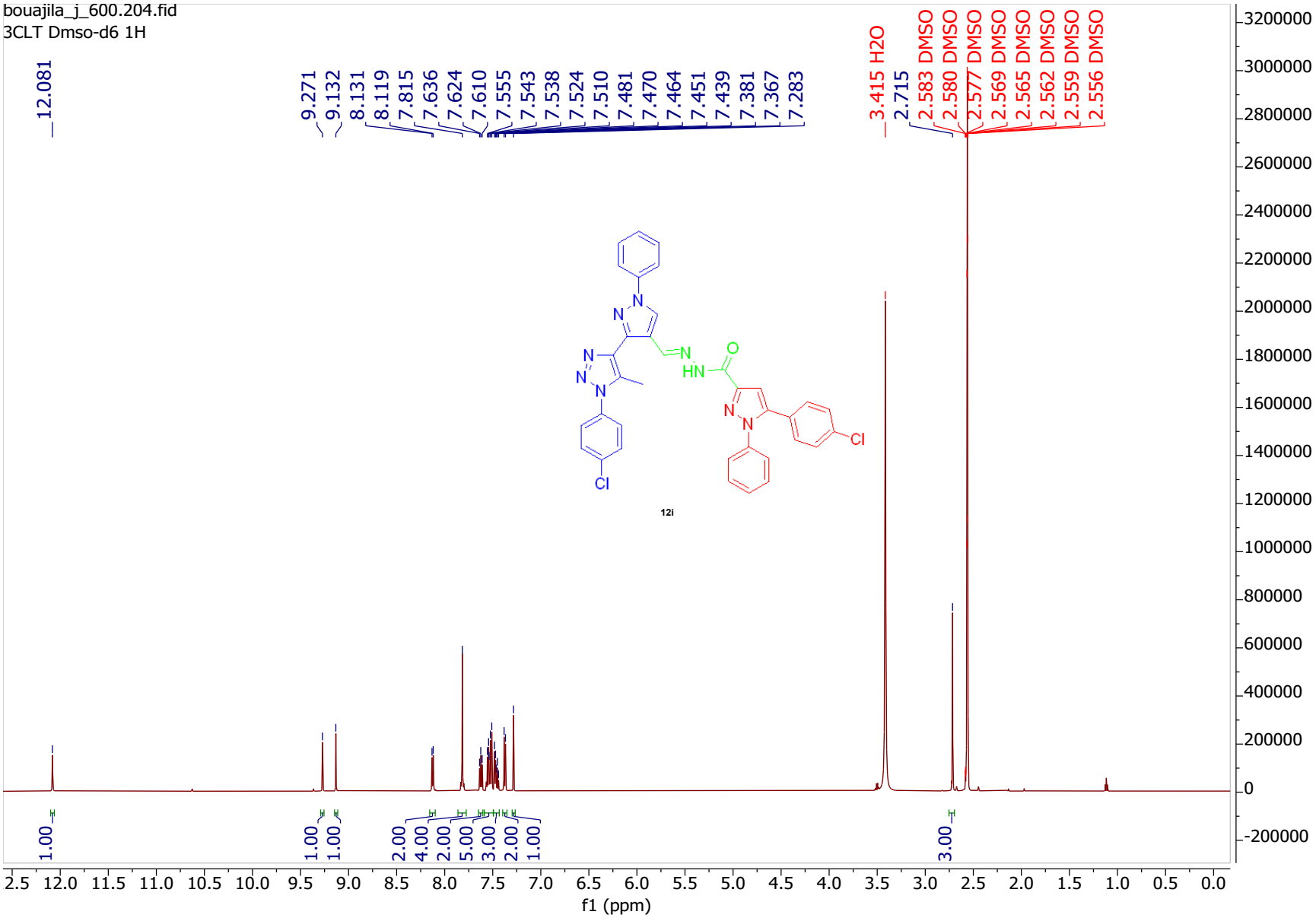

bouajila_j_600.204.fid
3CLT Dmso-d6 1H
12.081
9.271
9.132
8.131
8.119
7.815
7.636
7.624
7.610
7.555
7.543
7.538
7.524
7.510
7.481
7.470
7.464
7.451
7.439
7.381
7.367
7.283
3.415 H2O
2.715
2.583 DMSO
2.580 DMSO
2.577 DMSO
2.569 DMSO
2.565 DMSO
2.562 DMSO
2.559 DMSO
2.556 DMSO
12i
1.00
1.00
1.00
2.00
4.00
2.00
5.00
3.00
2.00
1.00
3.00
f1 (ppm)

Figure S 42. ^{1}H NMR of compound **12i**

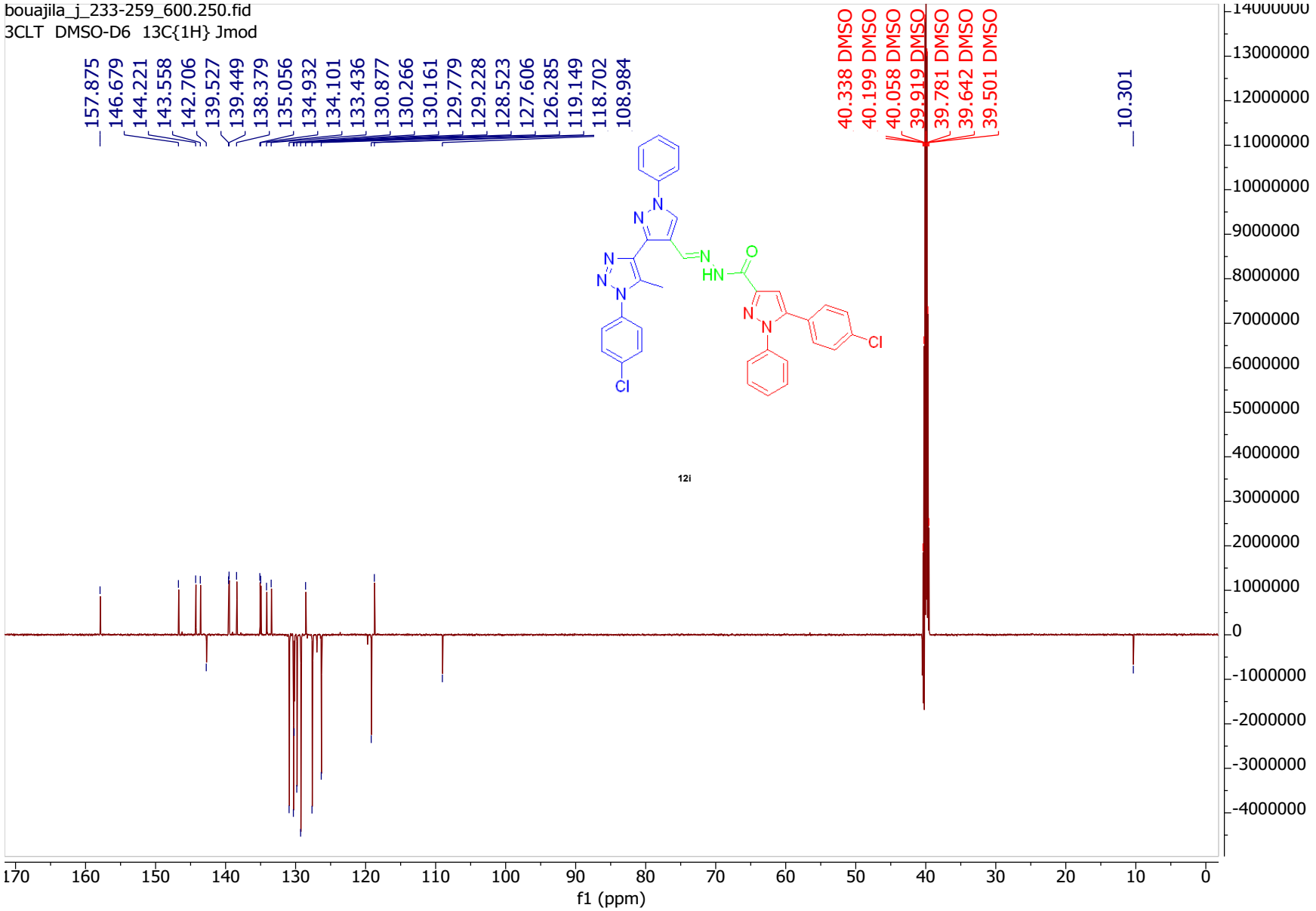

bouajila_j_233-259_600.250.fid
3CLT DMSO-D6 13C{1H} Jmod
157.875
146.679
144.221
143.558
142.706
139.527
139.449
138.379
135.056
134.932
134.101
133.436
130.877
130.266
130.161
129.779
129.228
128.523
127.606
126.285
119.149
118.702
108.984
40.338 DMSO
40.199 DMSO
40.058 DMSO
39.919 DMSO
39.781 DMSO
39.642 DMSO
39.501 DMSO
10.301
12i
f1 (ppm)

Figure S43: ^{13}C NMR of compound **12i**

High Resolution Mass Spectroscopy

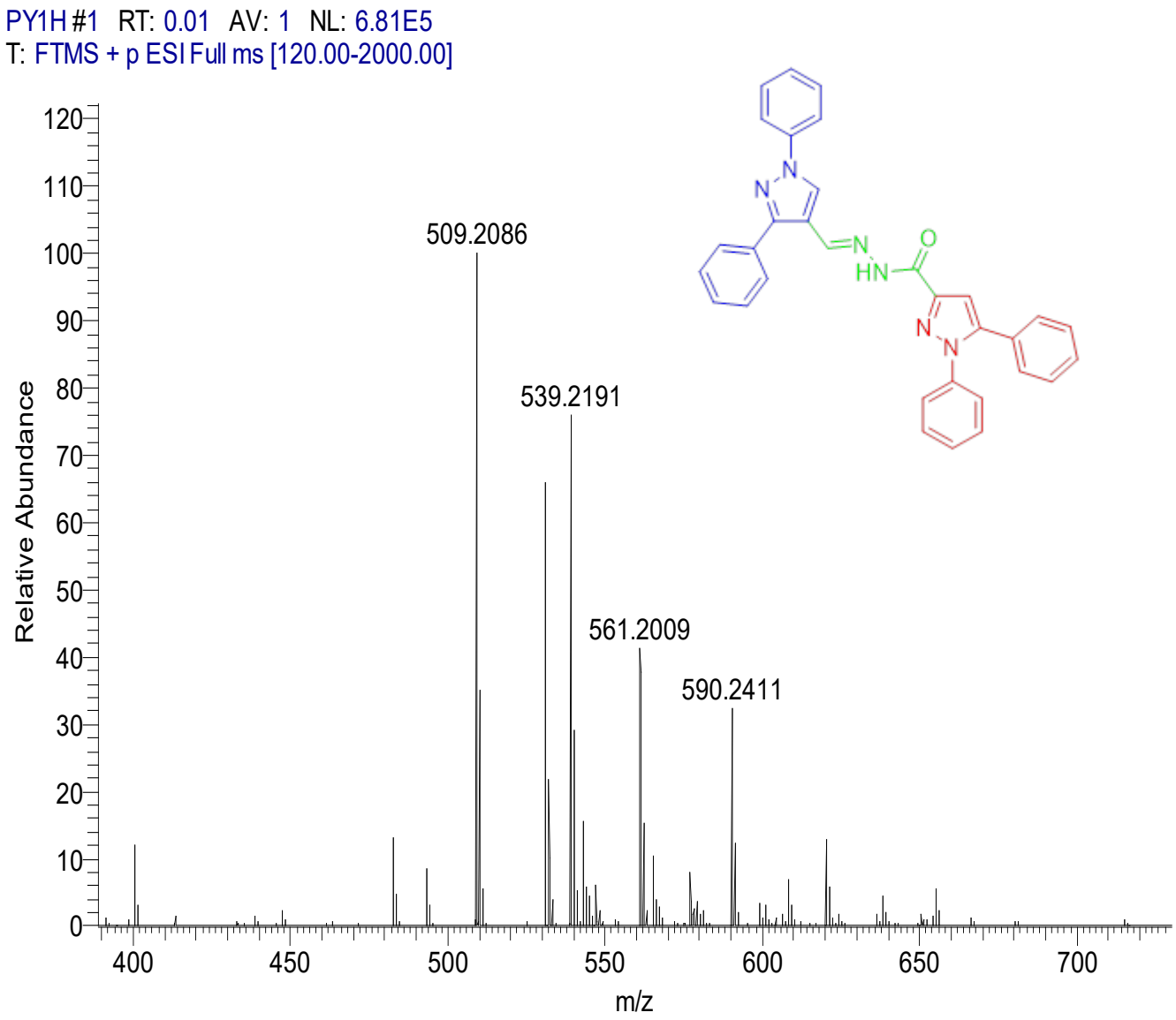


Figure S 44: Mass of compound **8a**

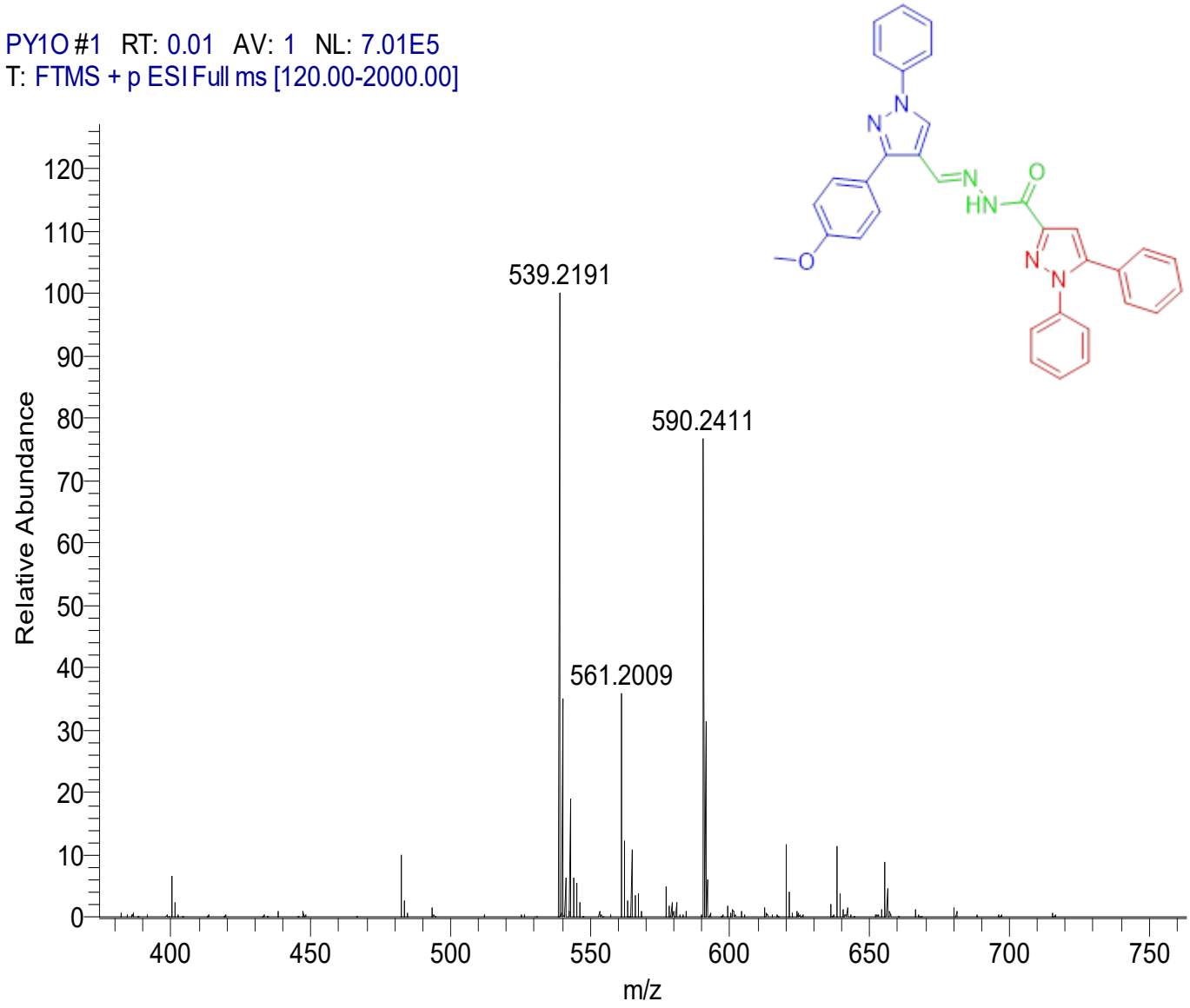


Figure S 45. Mass of compound **8b**

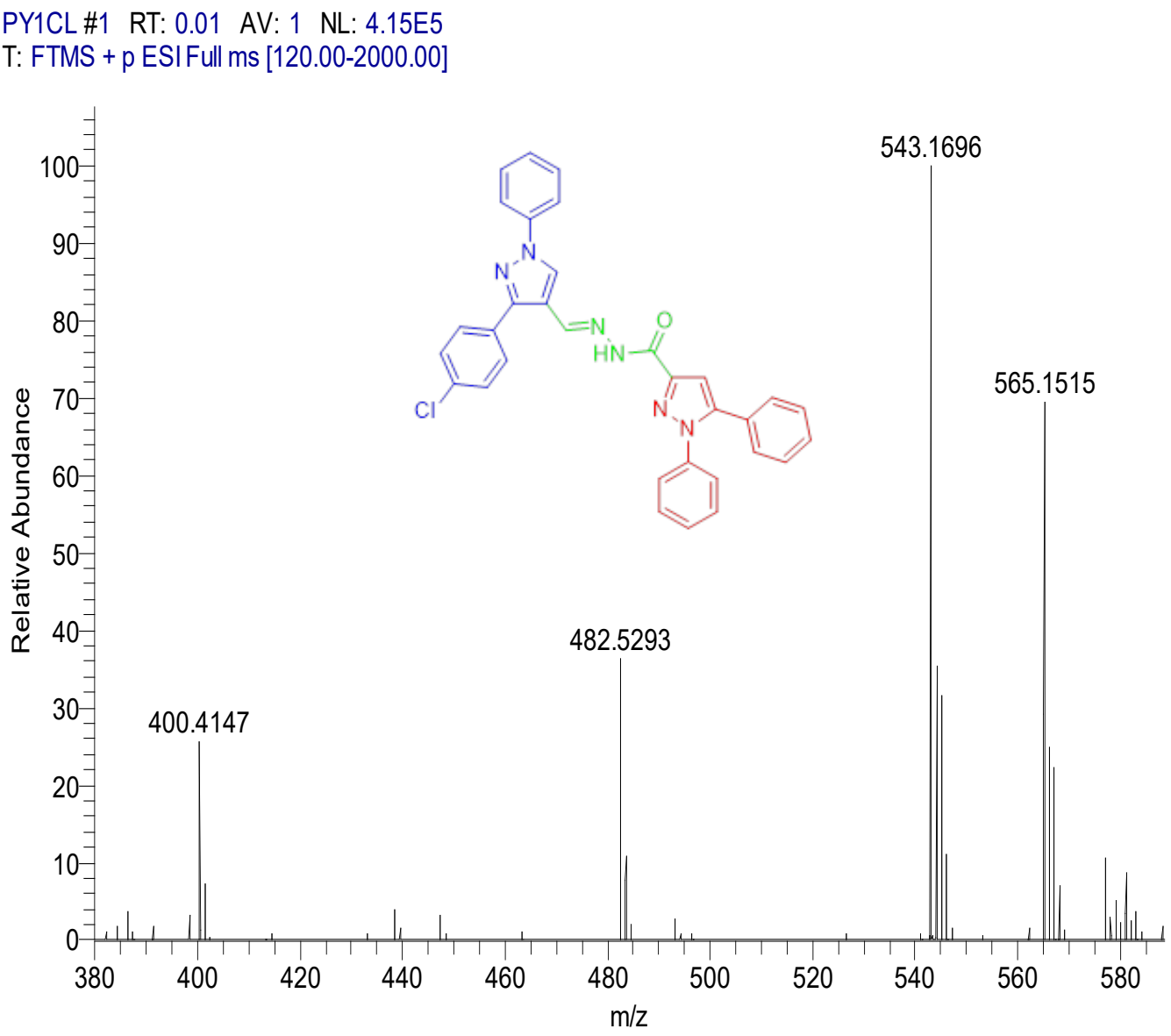


Figure S 46. Mass of compound **8c**

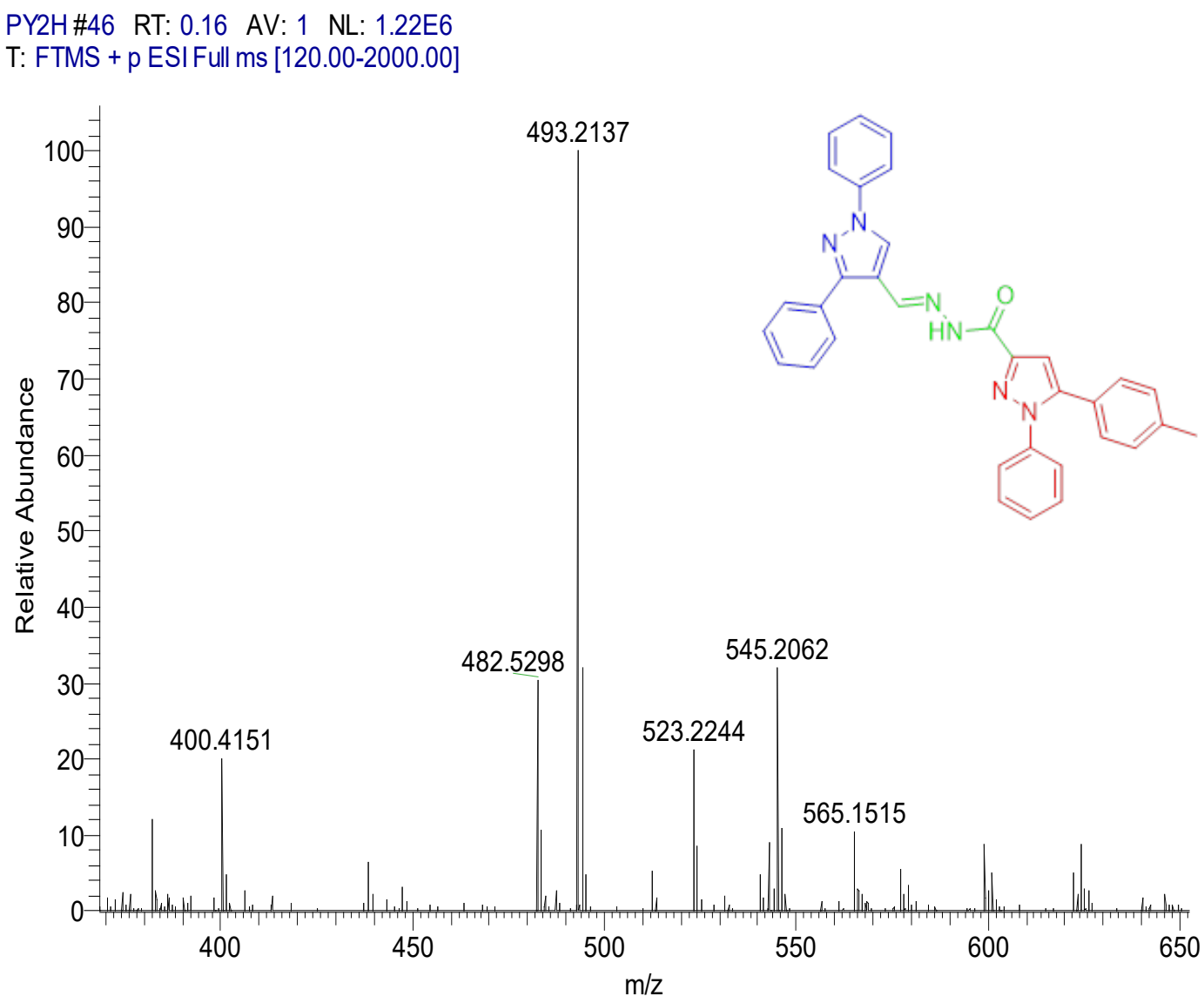


Figure S 47. Mass of compound **8d**

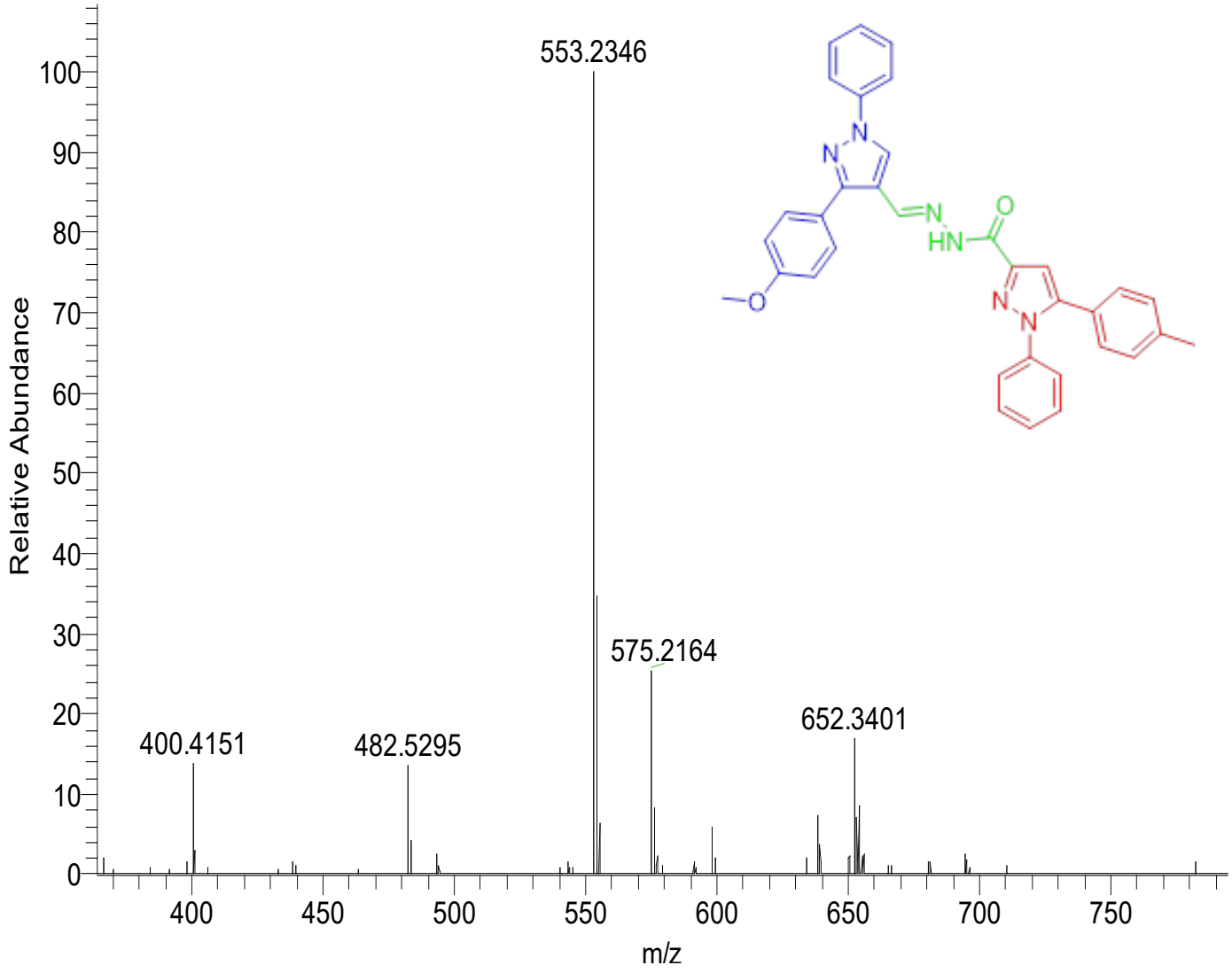


Figure S 48. Mass of compound **8e**

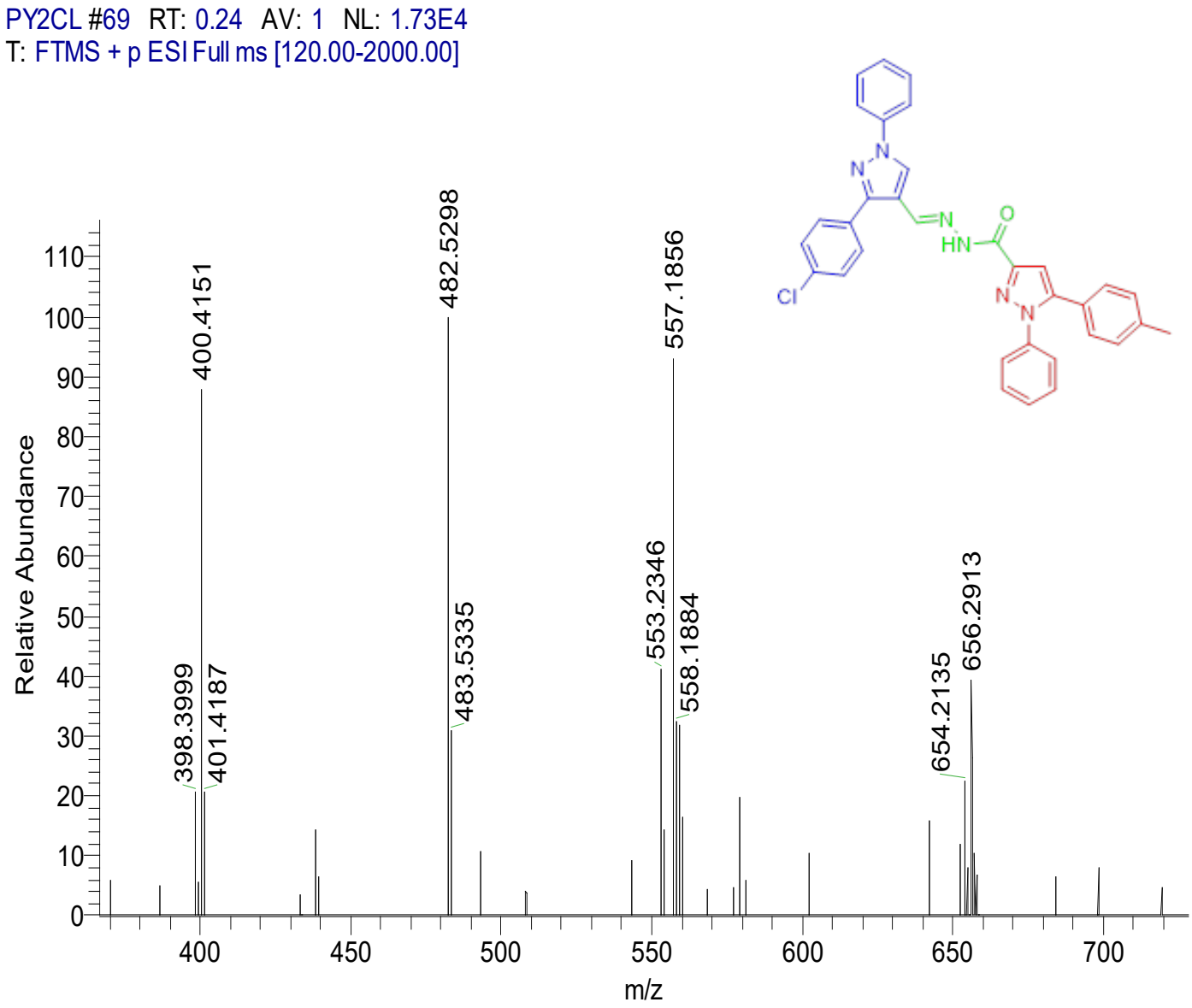


Figure S 49. Mass of compound **8f**

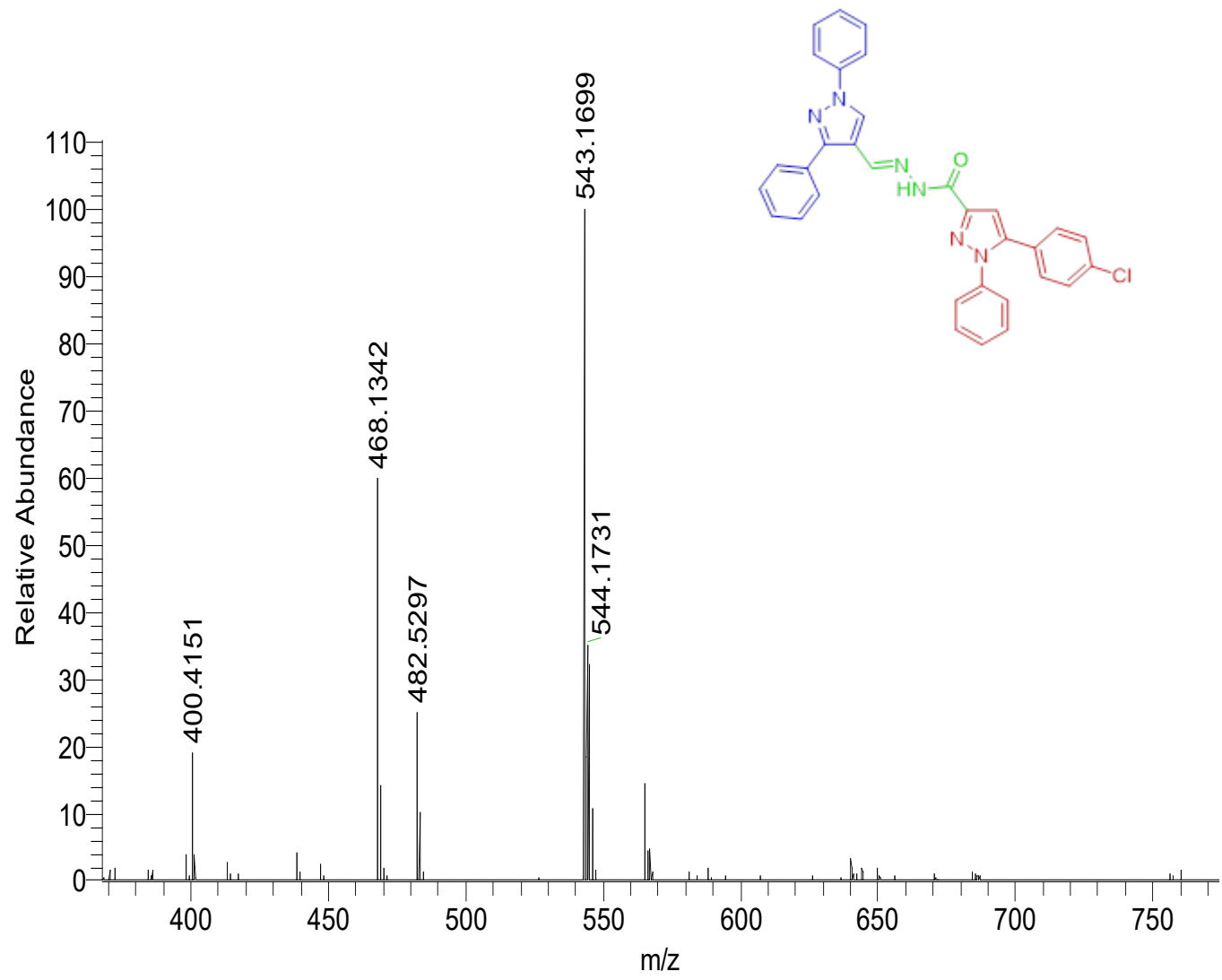


Figure S 50. Mass of compound **8g**

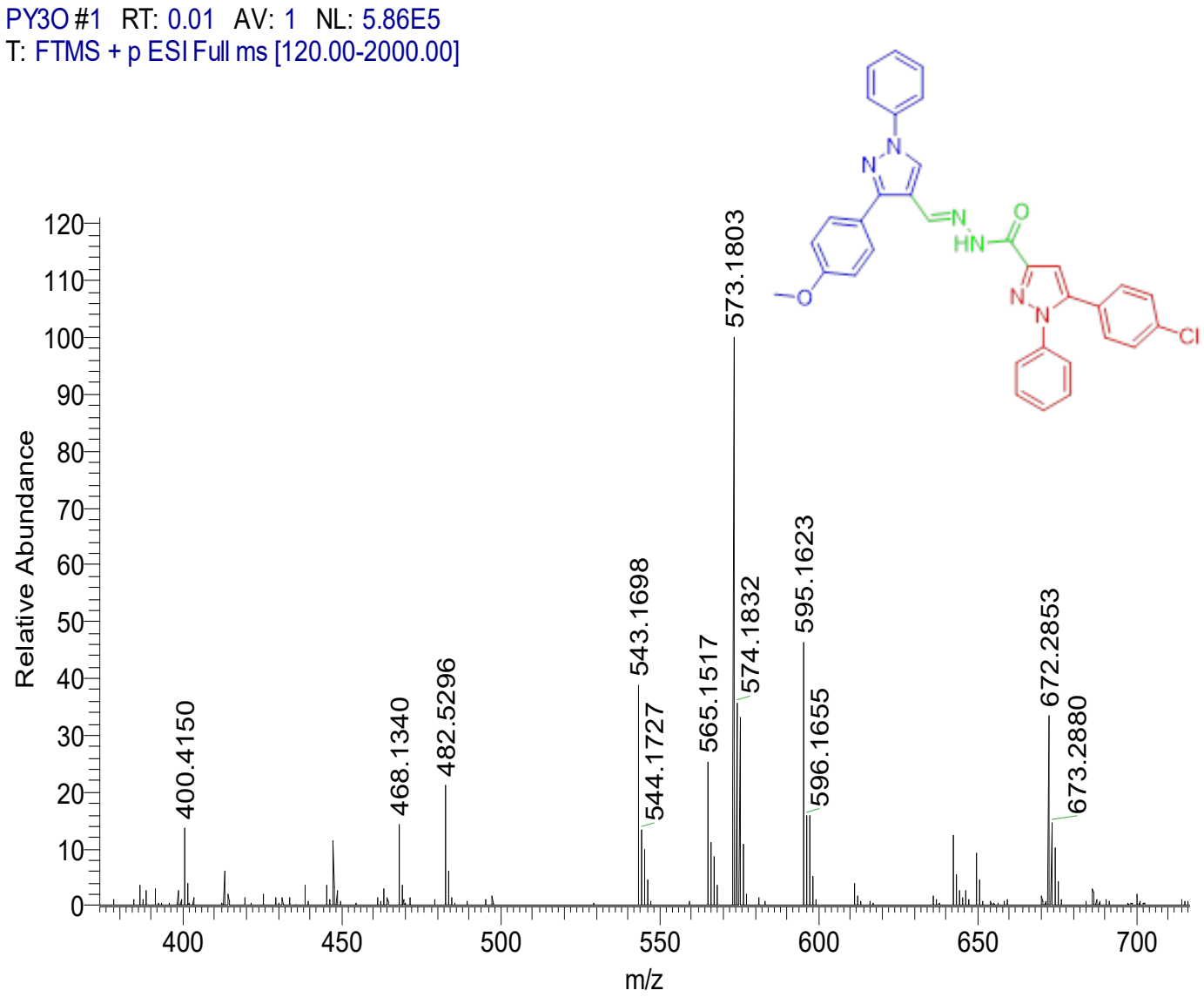
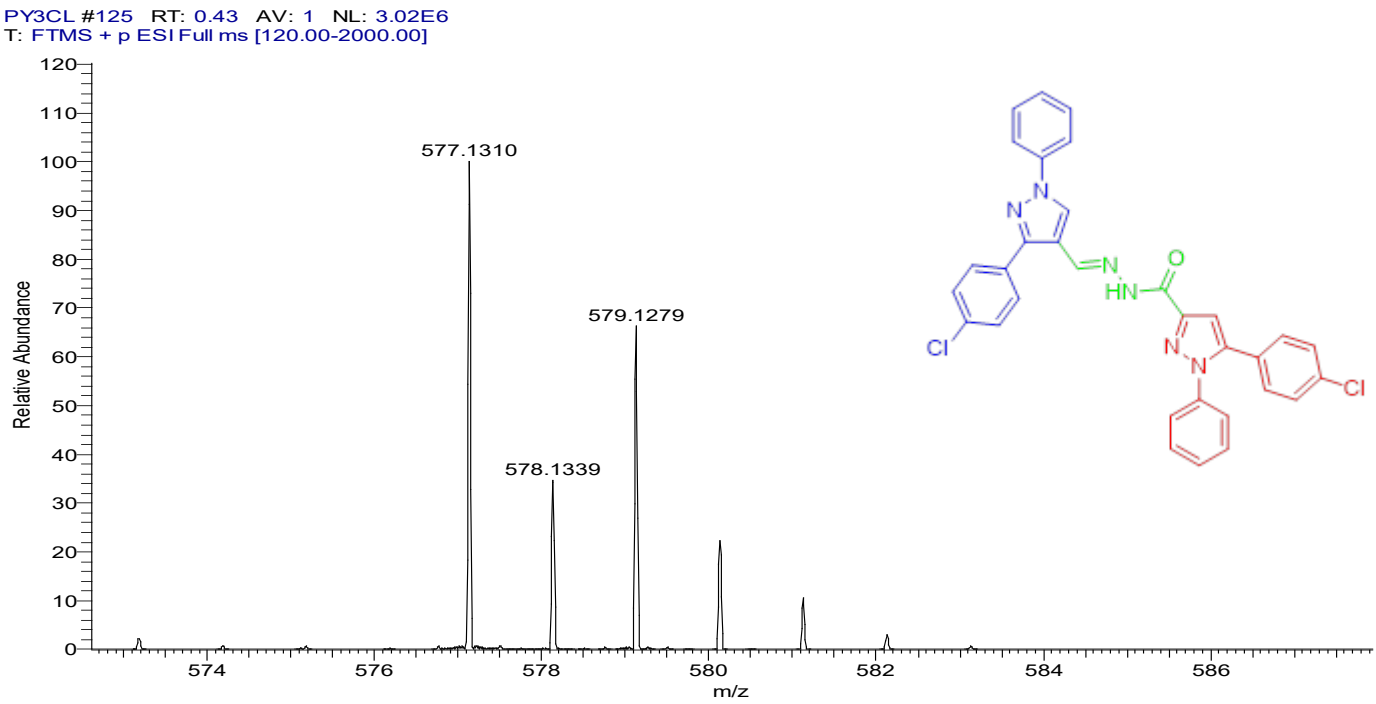


Figure S 51. Mass of compound **8h**



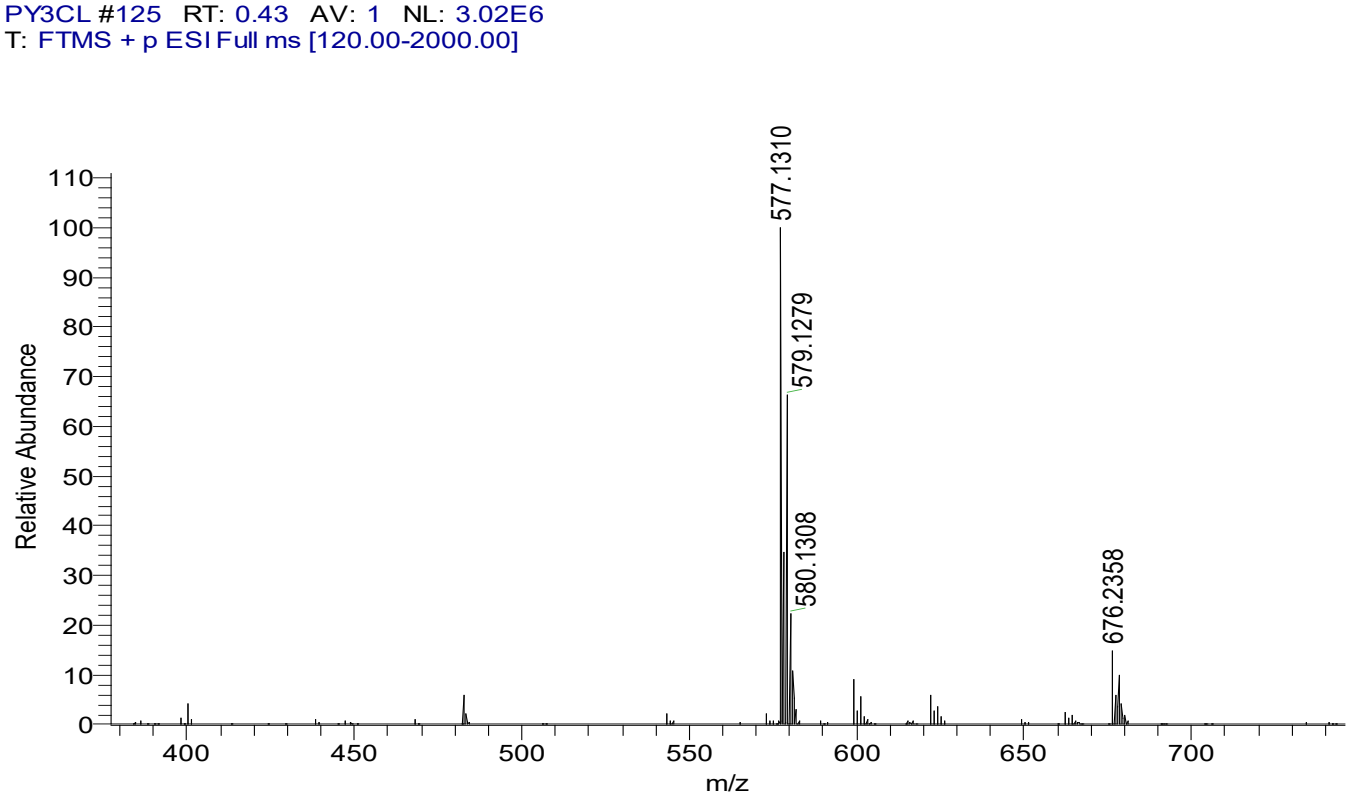


Figure S 52. Mass of compound **8i**

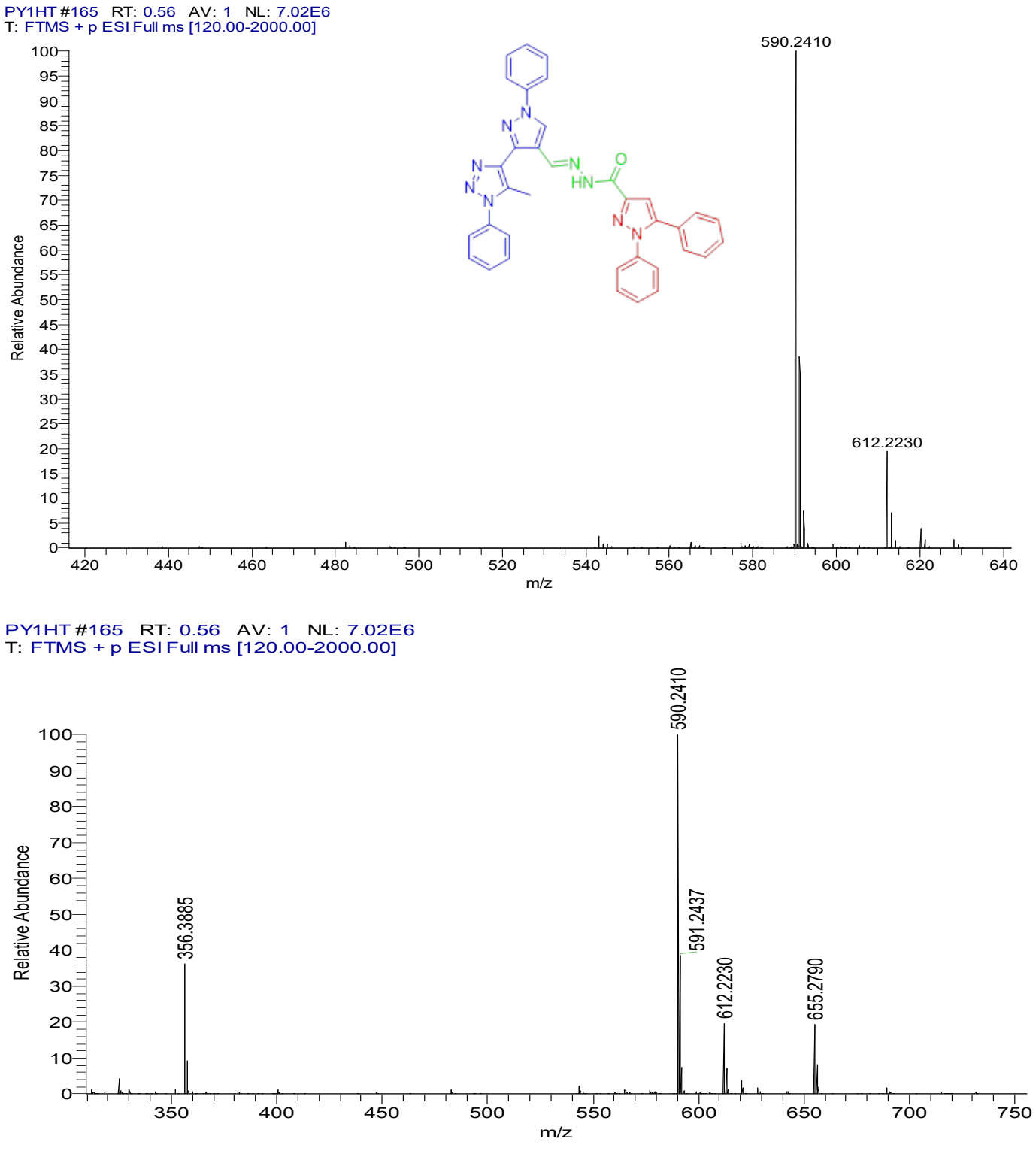


Figure S 53. Mass of compound **12a**

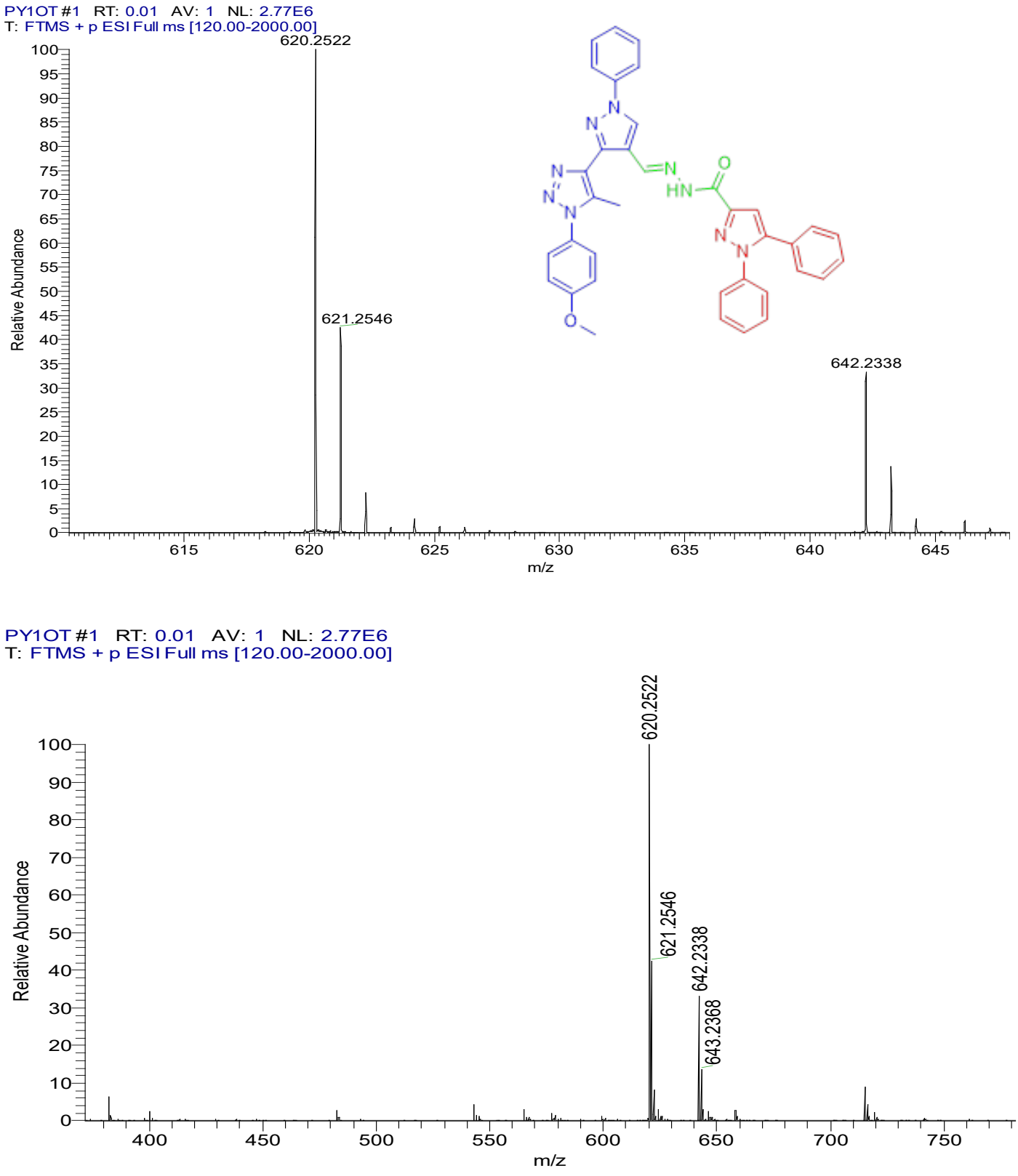


Figure S 54. Mass of compound **12b**

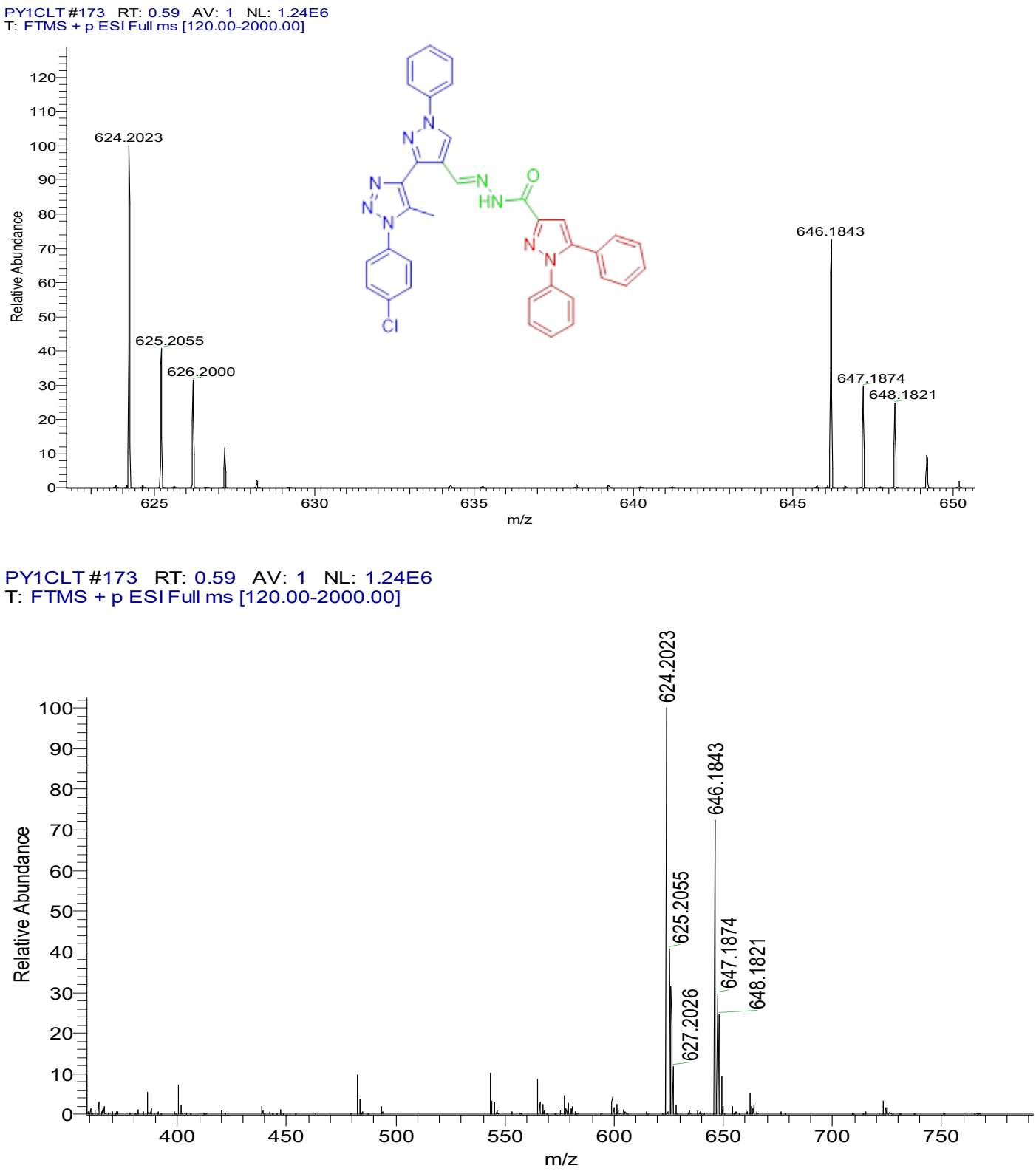
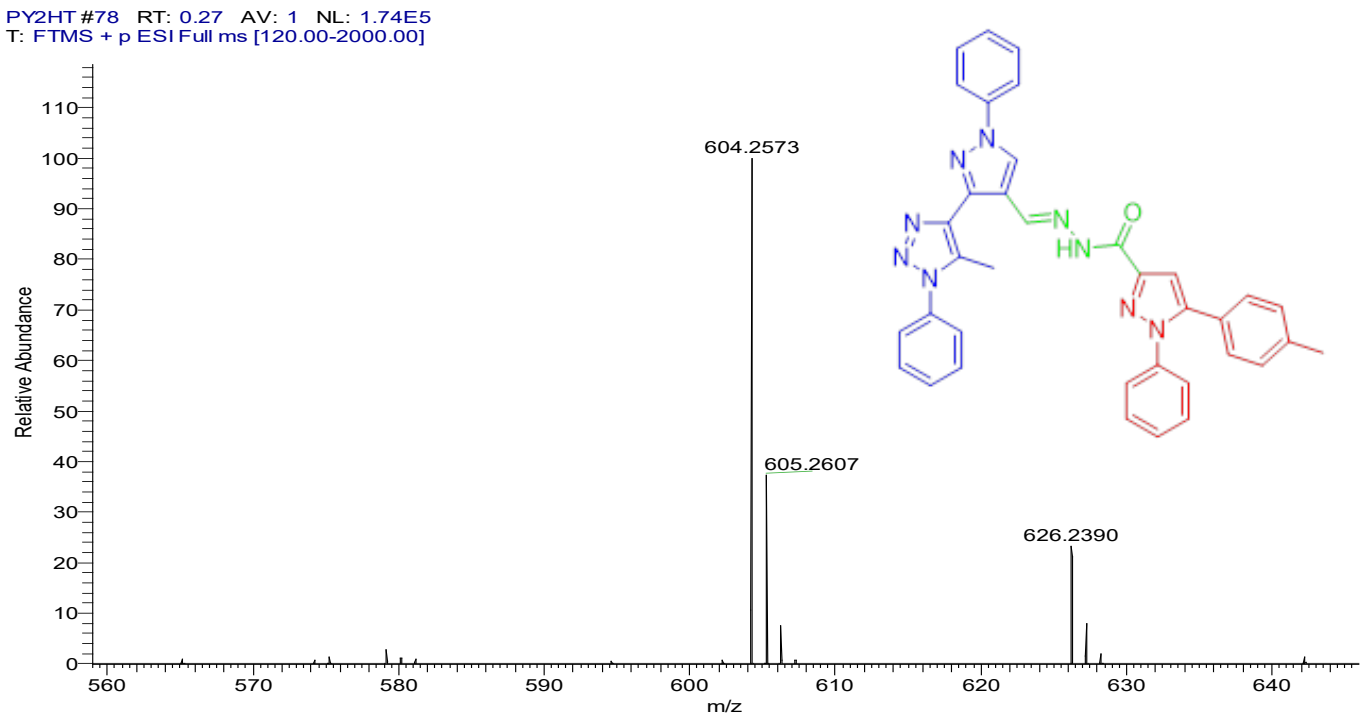


Figure S 55. Mass of compound **12c**



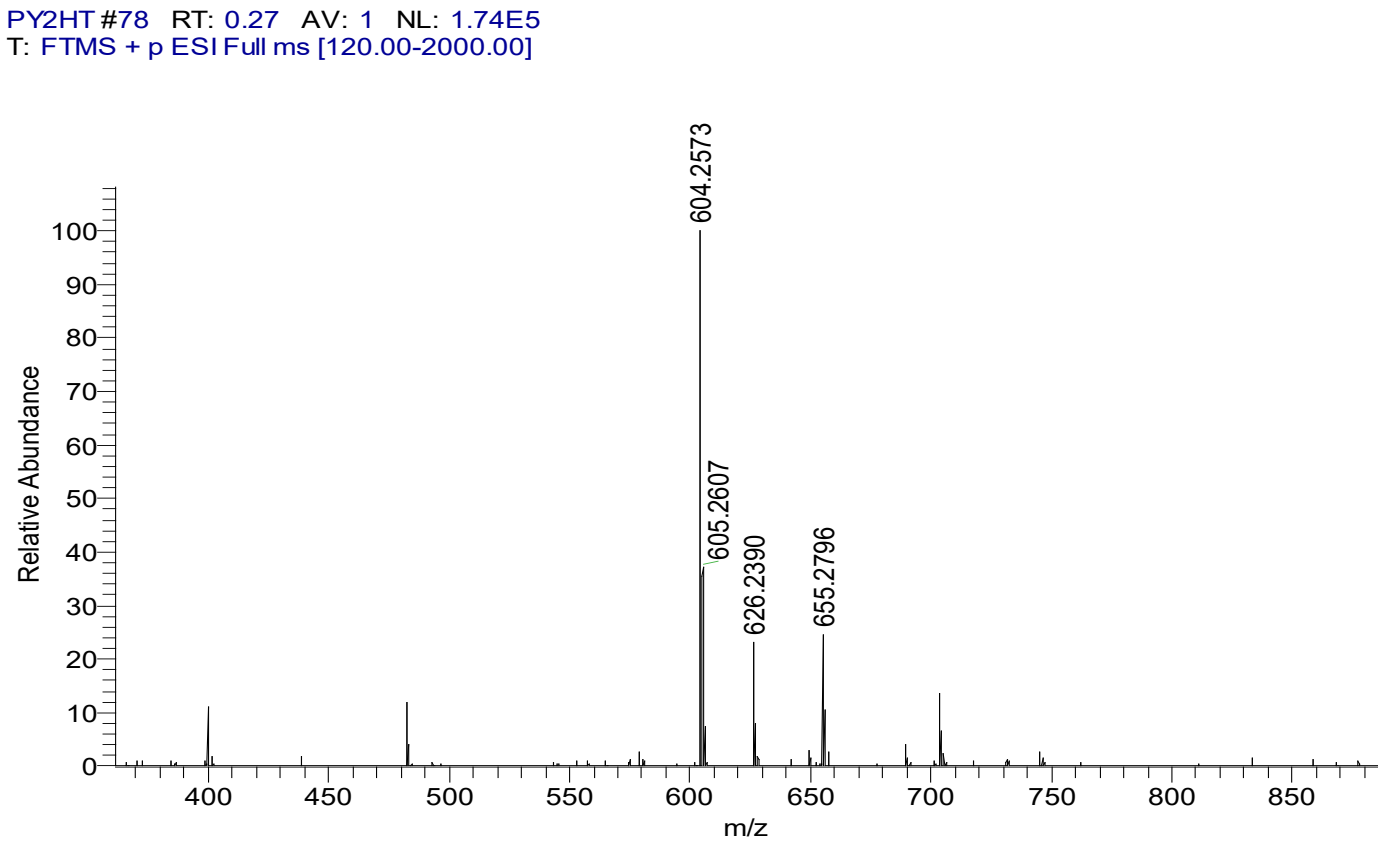


Figure S 56. Mass of compound **12d**

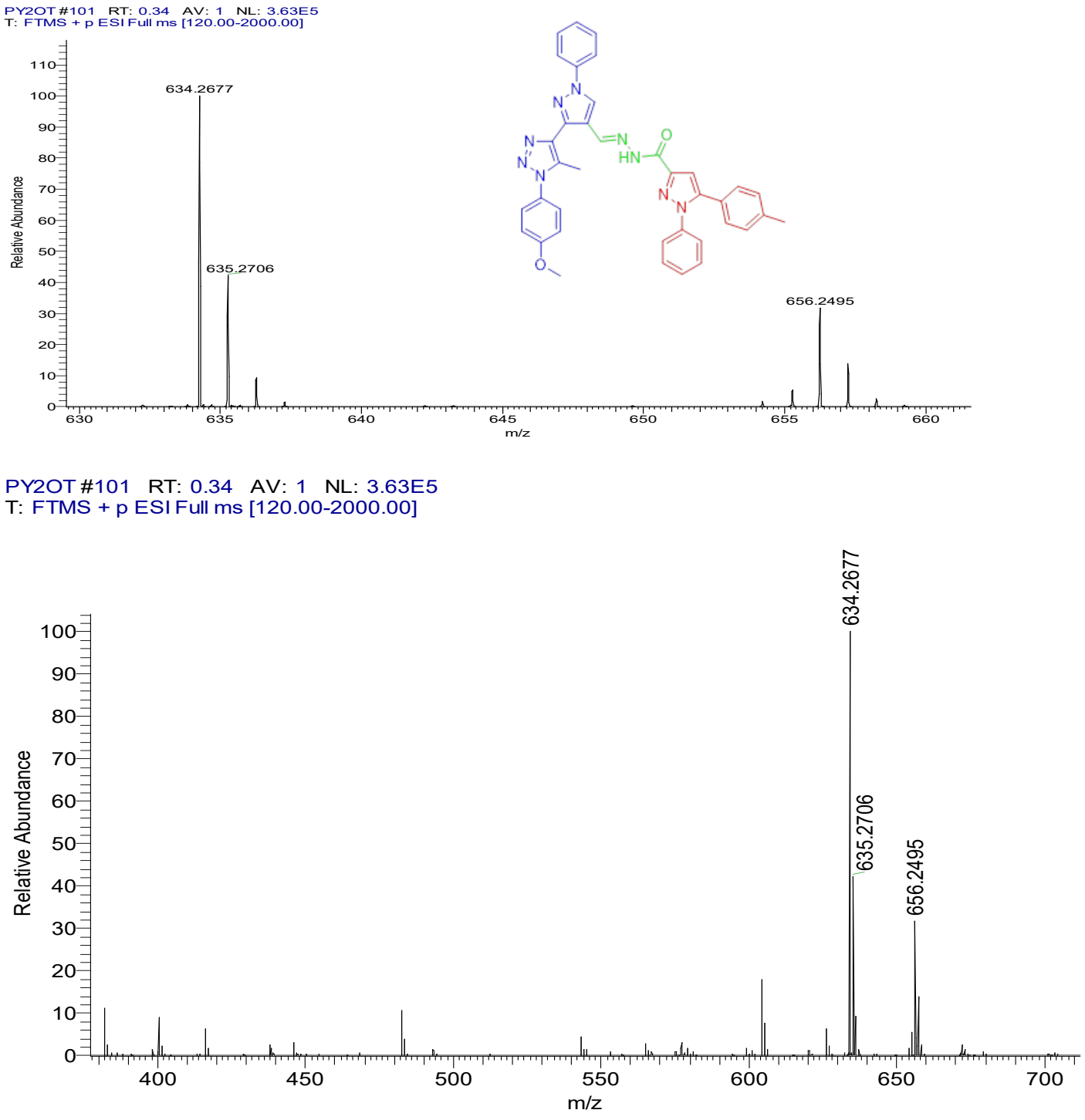
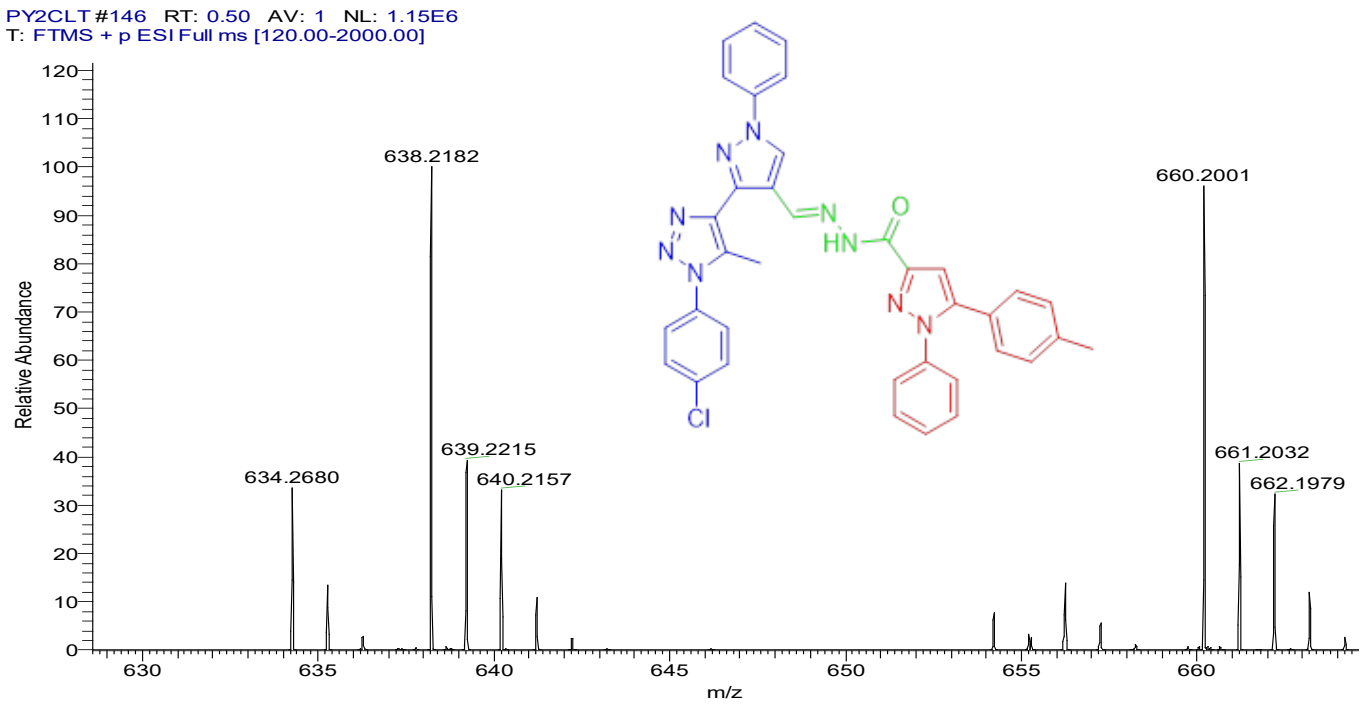


Figure S 57. Mass of compound **12e**



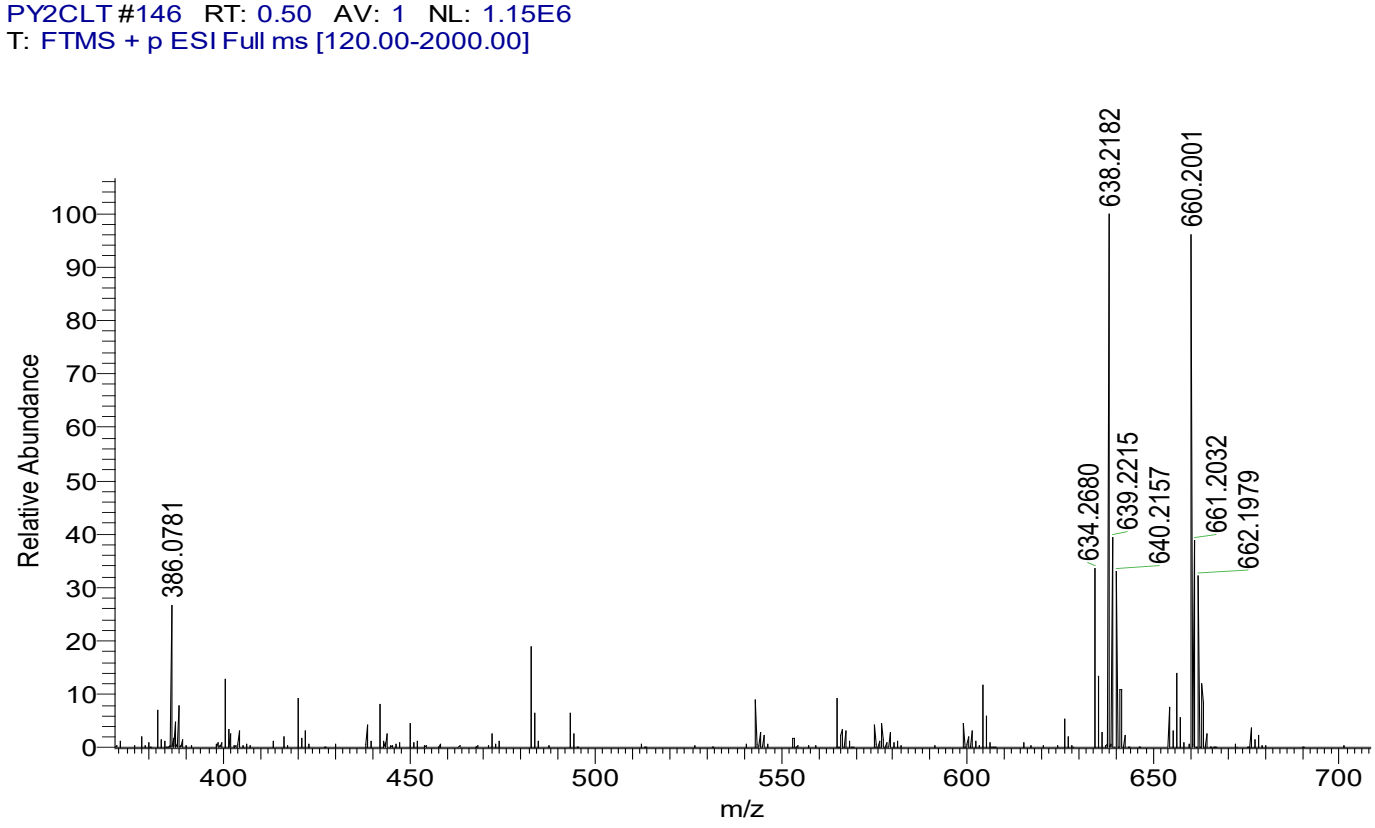
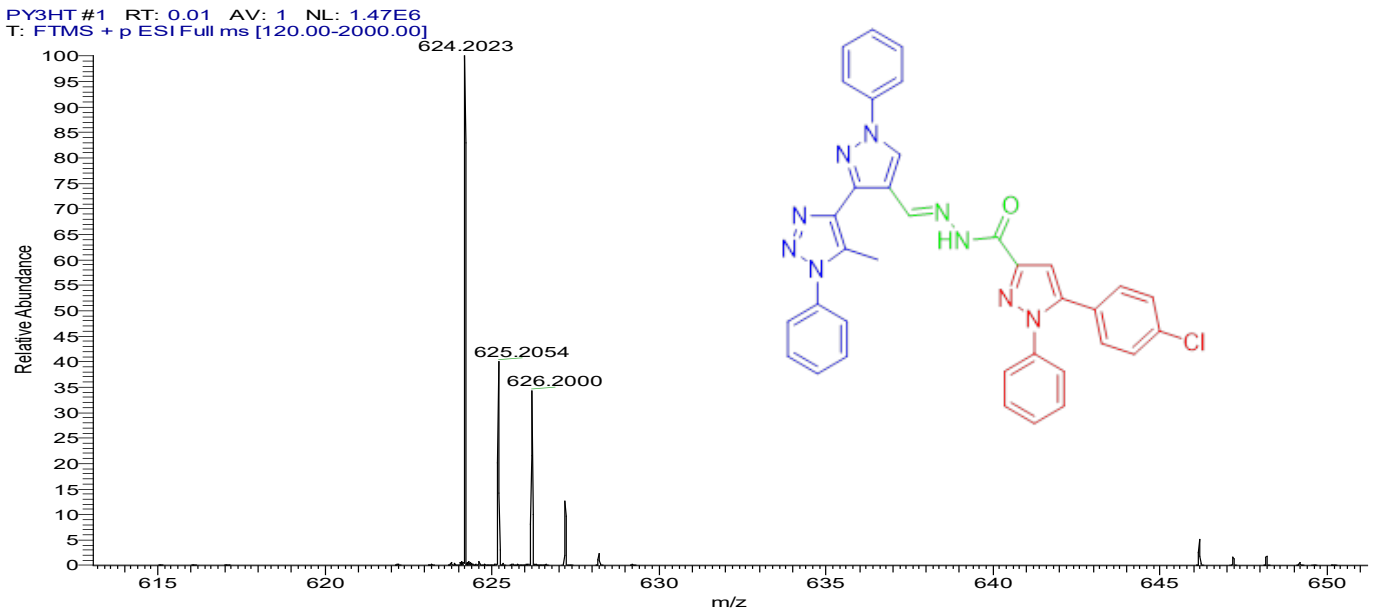


Figure S 58. Mass of compound **12f**



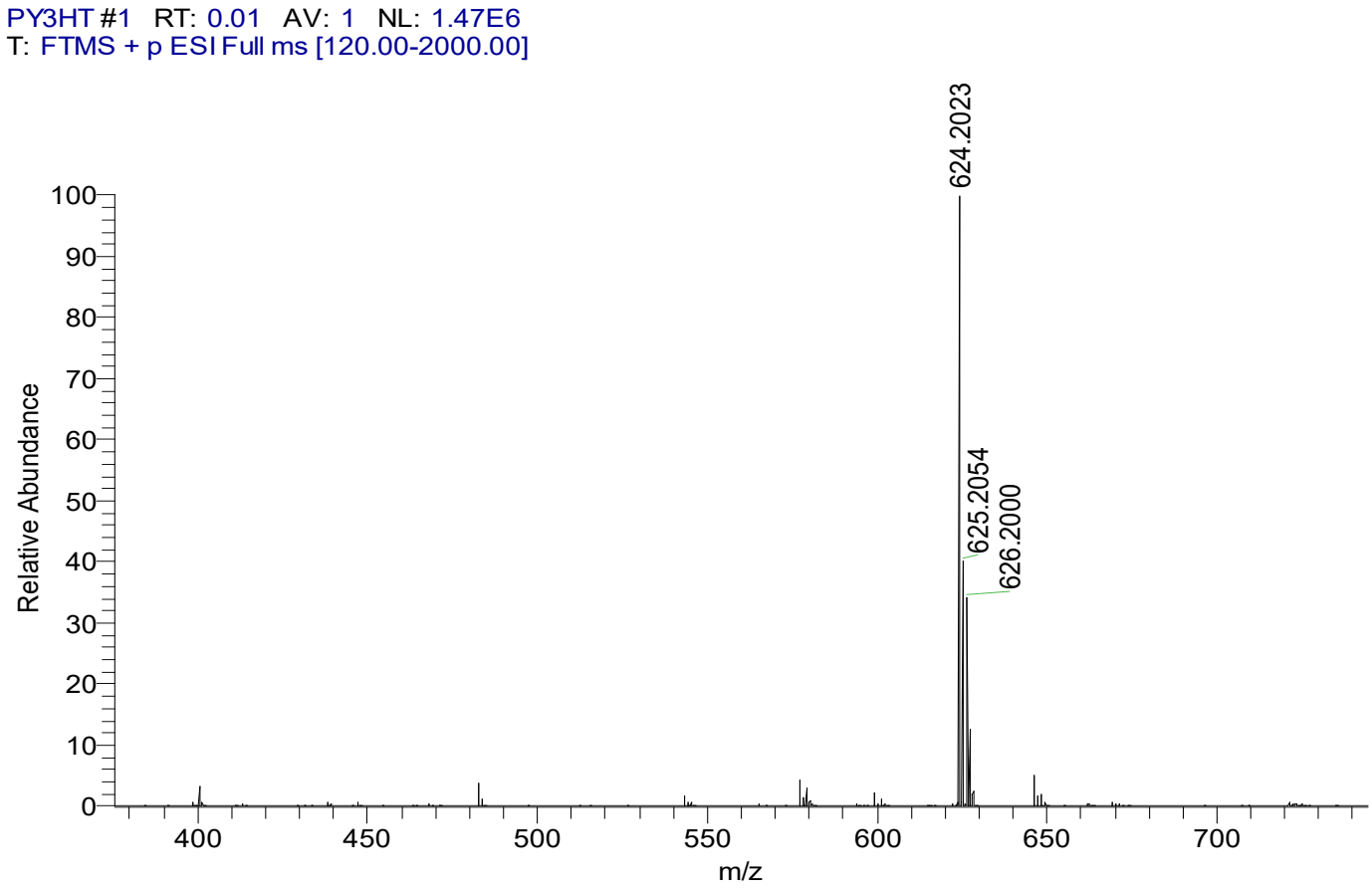
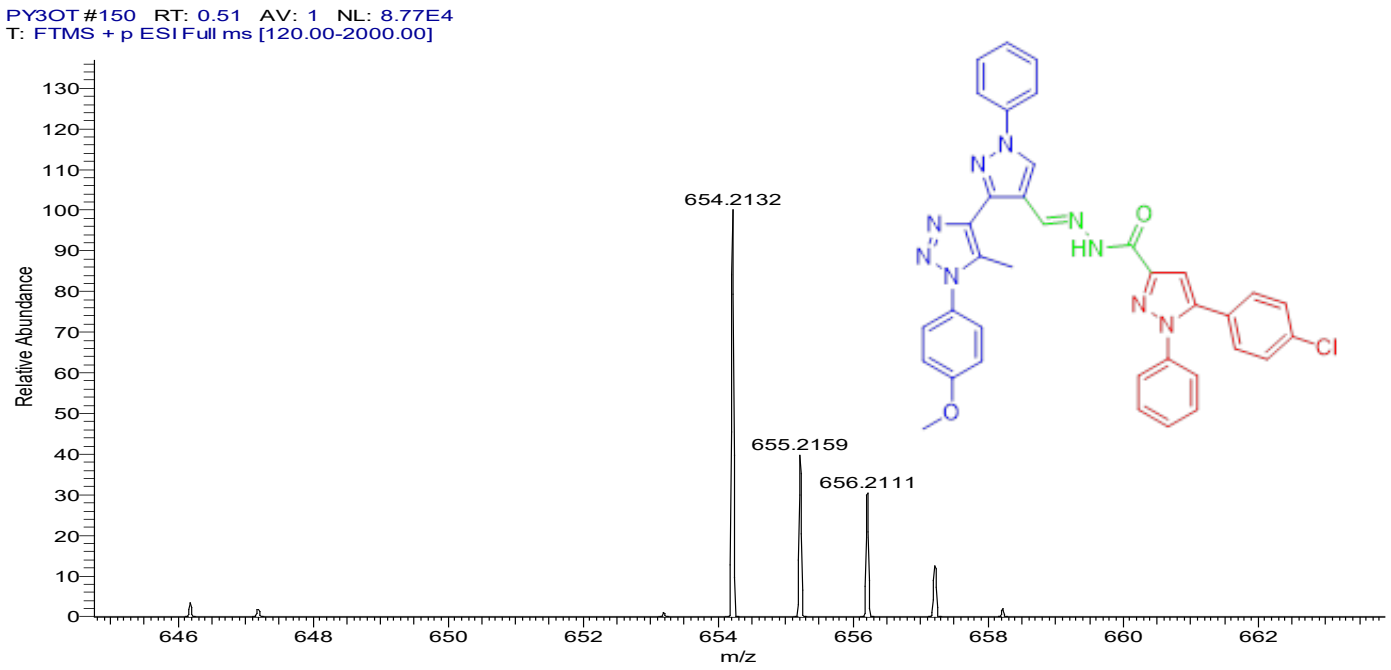


Figure S 59. Mass of compound **12g**



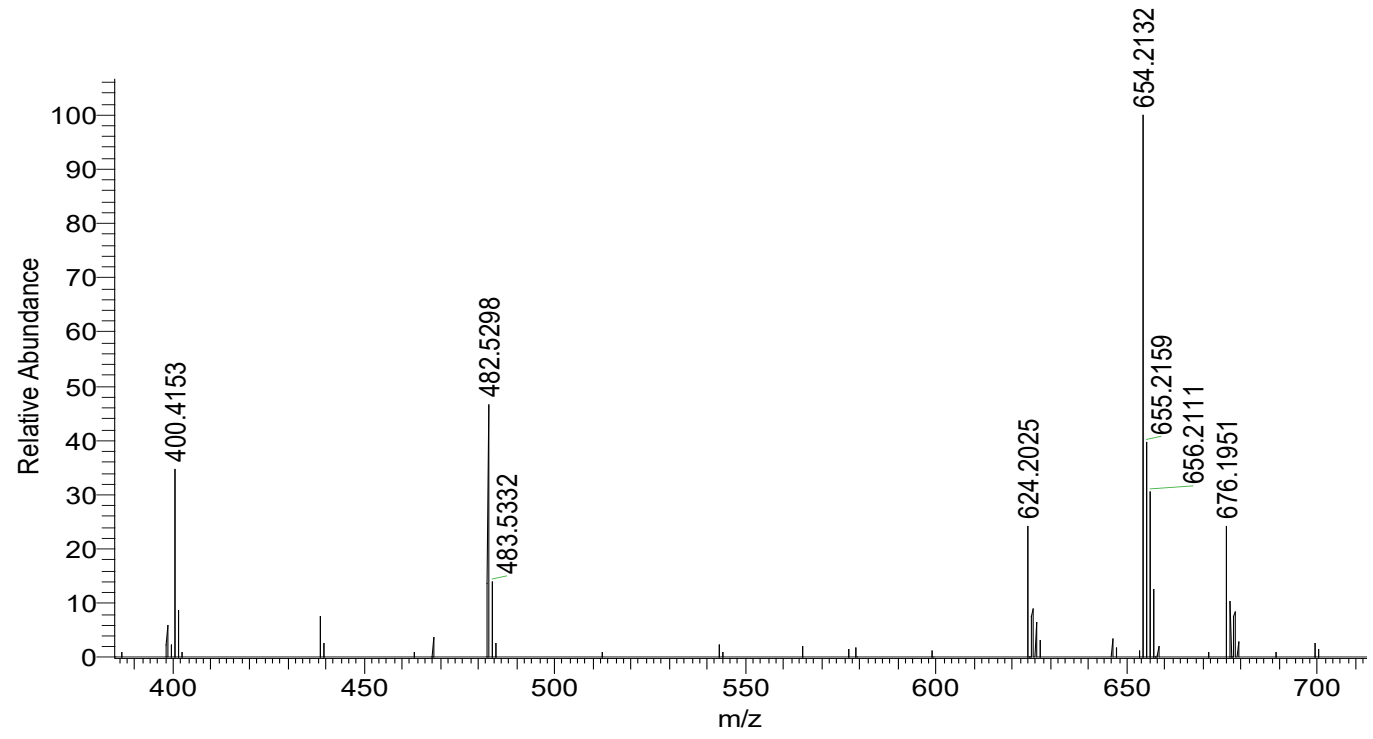
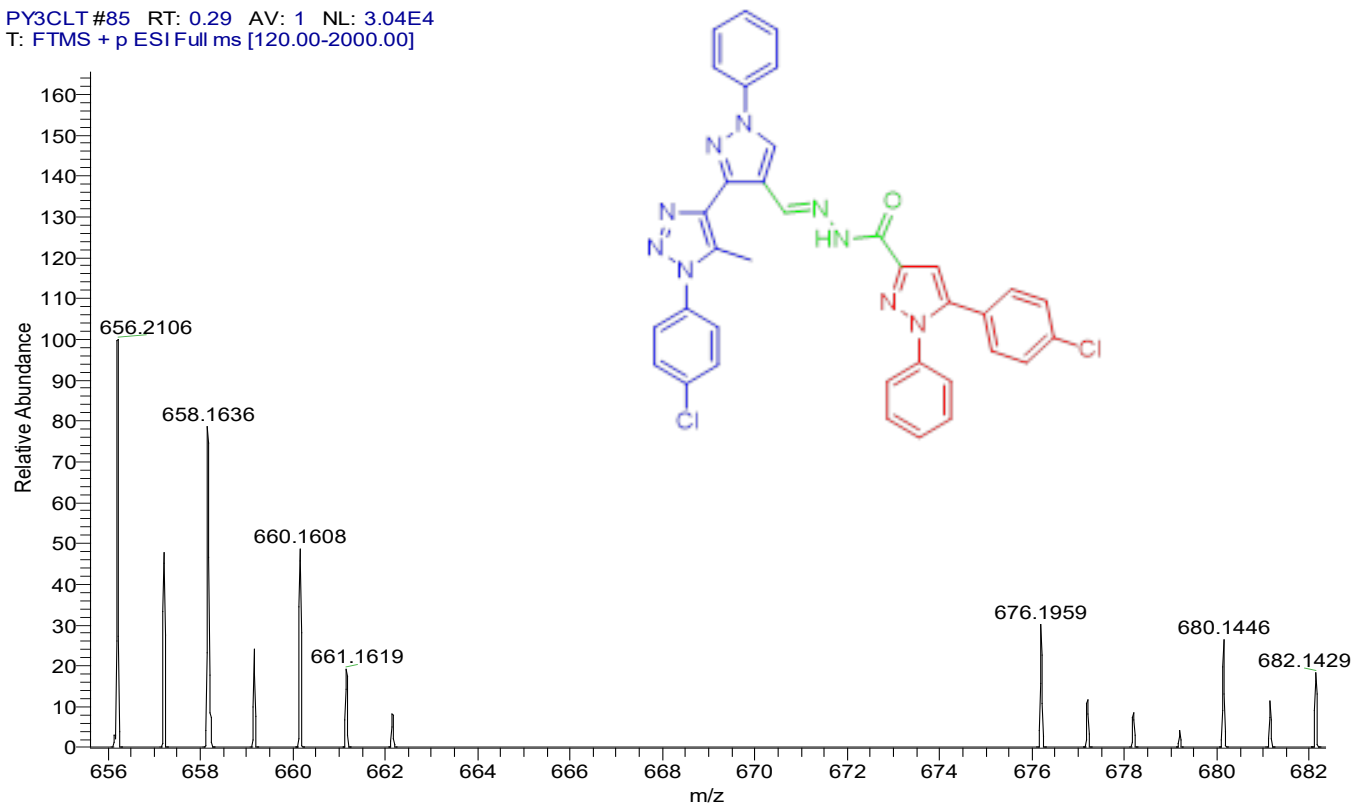


Figure S 60. Mass of compound **12h**



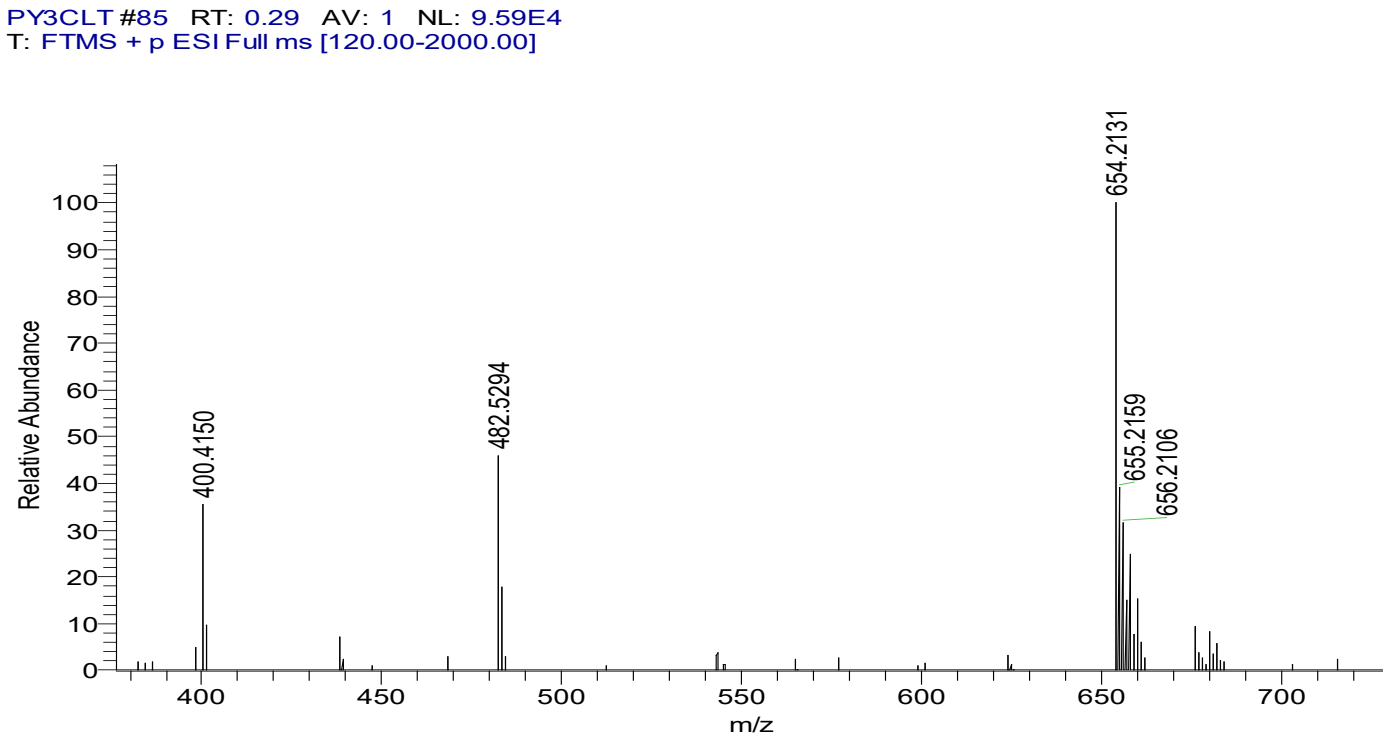


Figure S 61. Mass of compound **12i**

Infera Red Charts

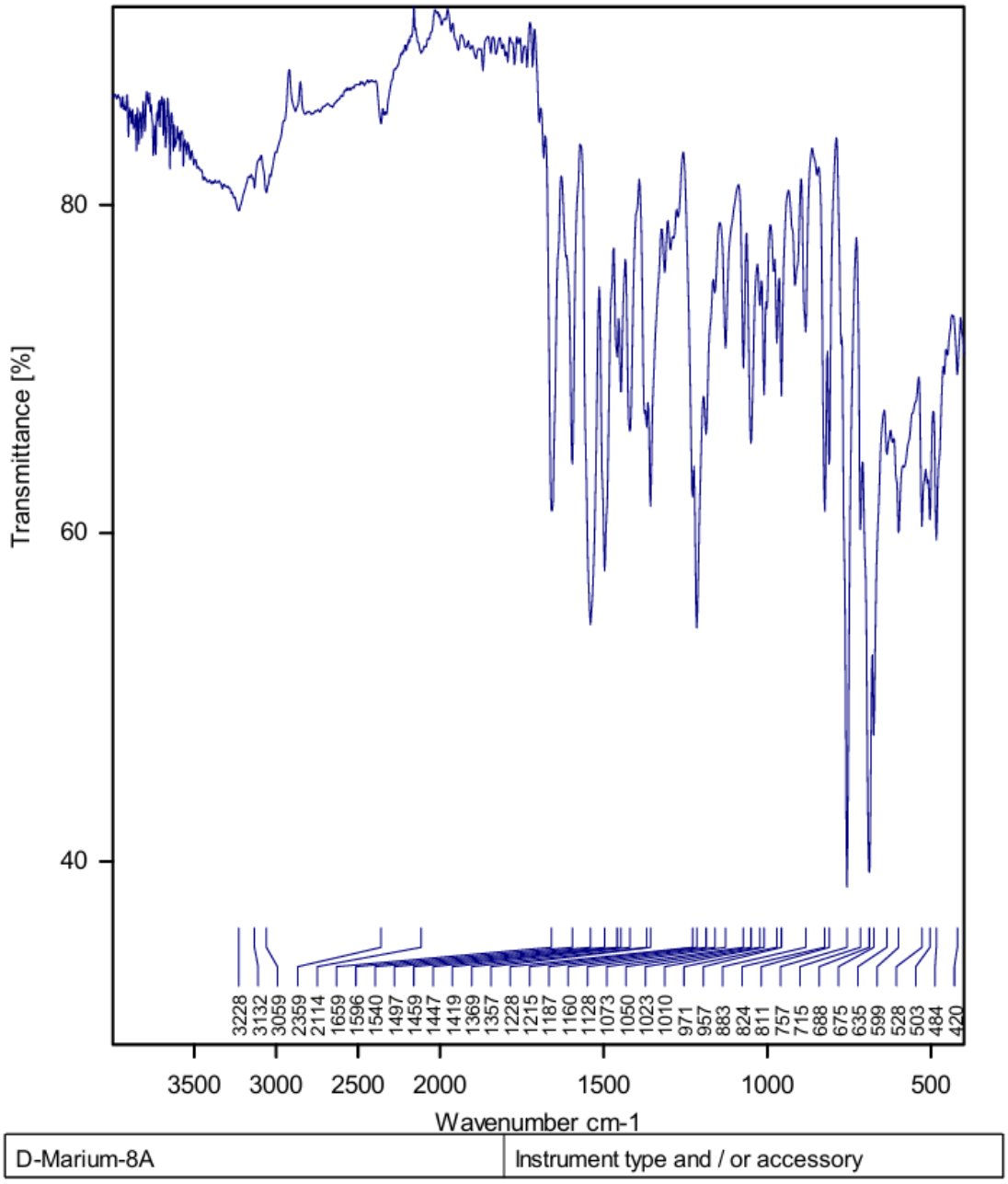


Figure S 62. IR of compound 8a

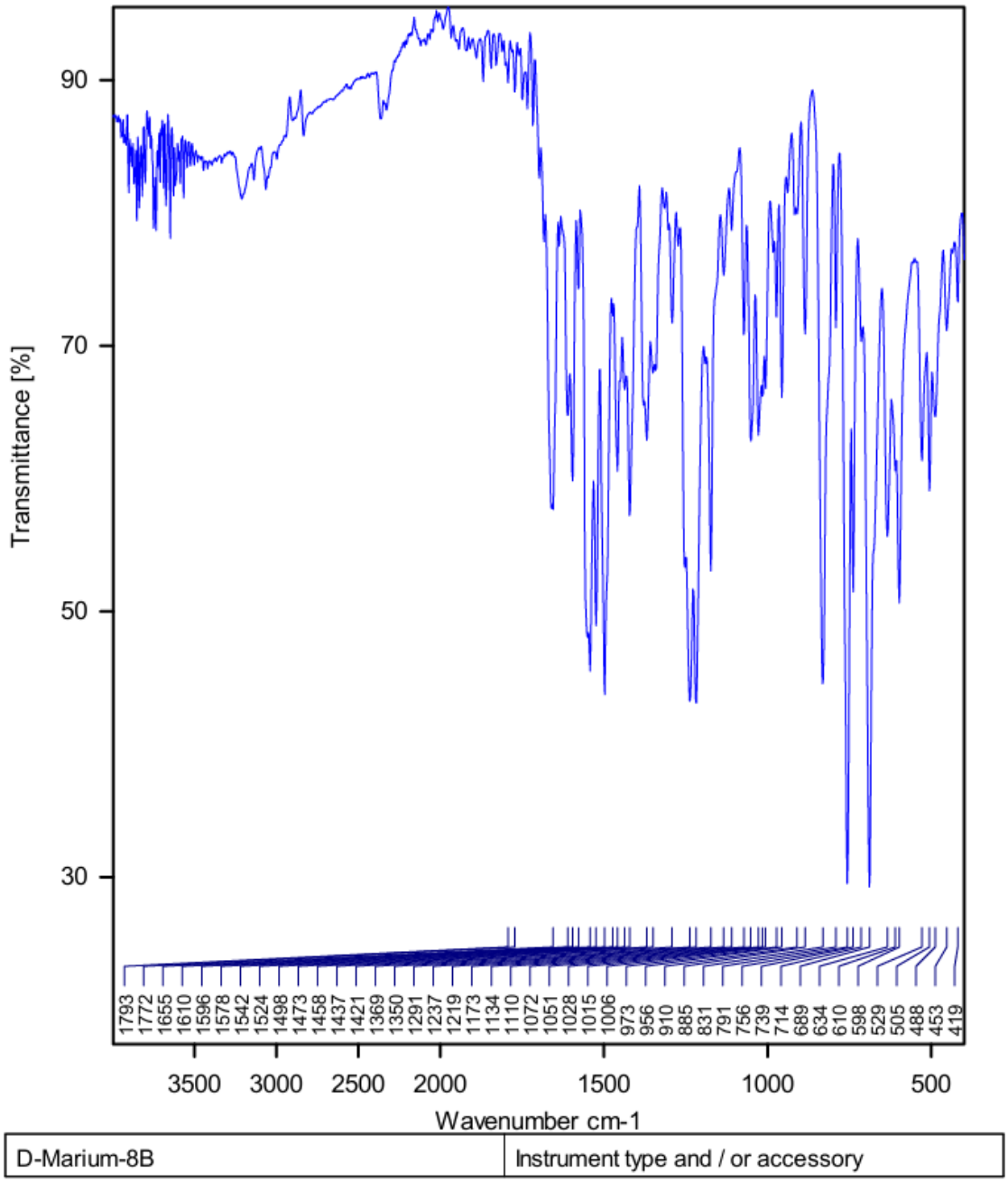


Figure S 63. IR of compound 8b

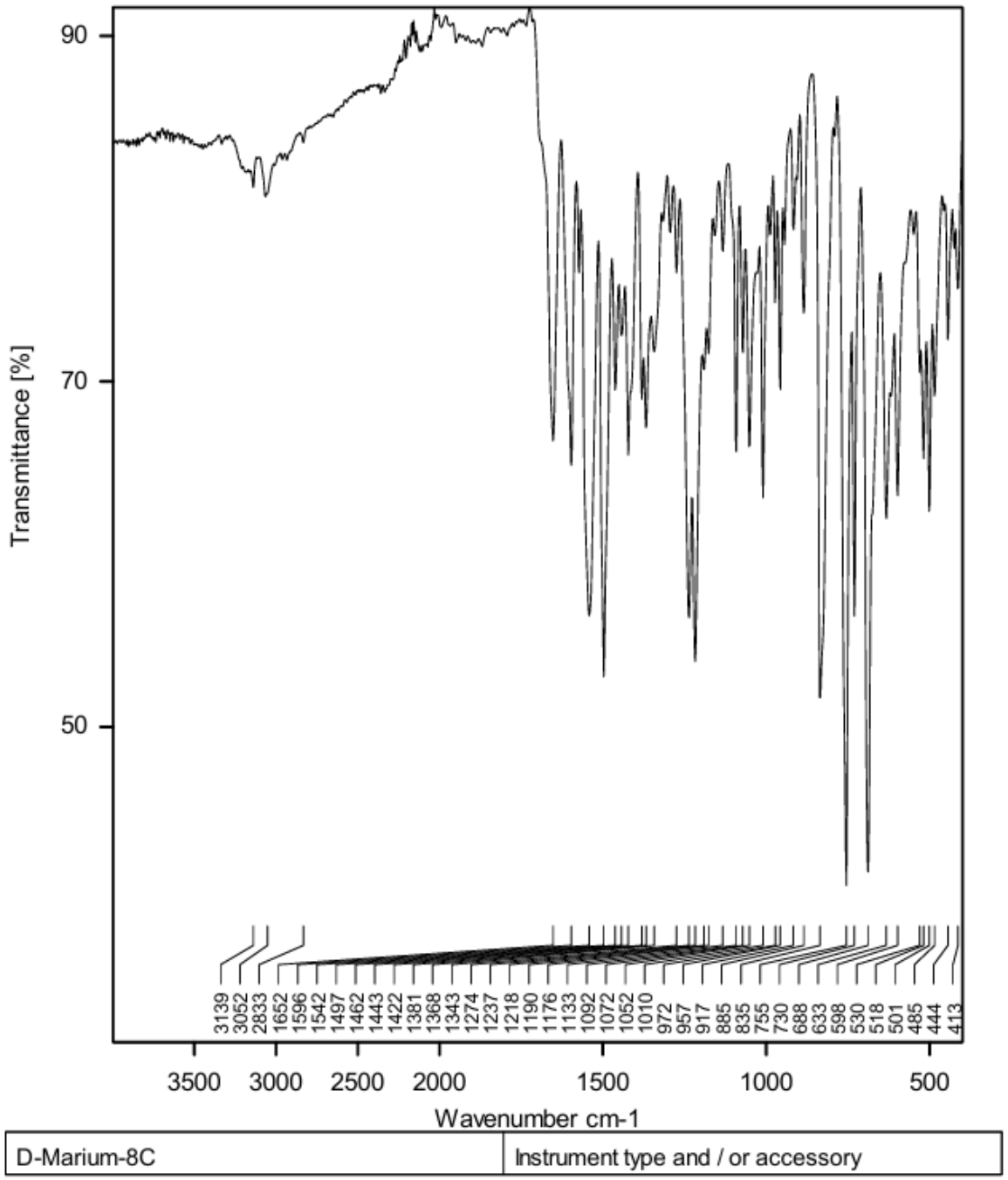


Figure S 64. IR of compound 8c

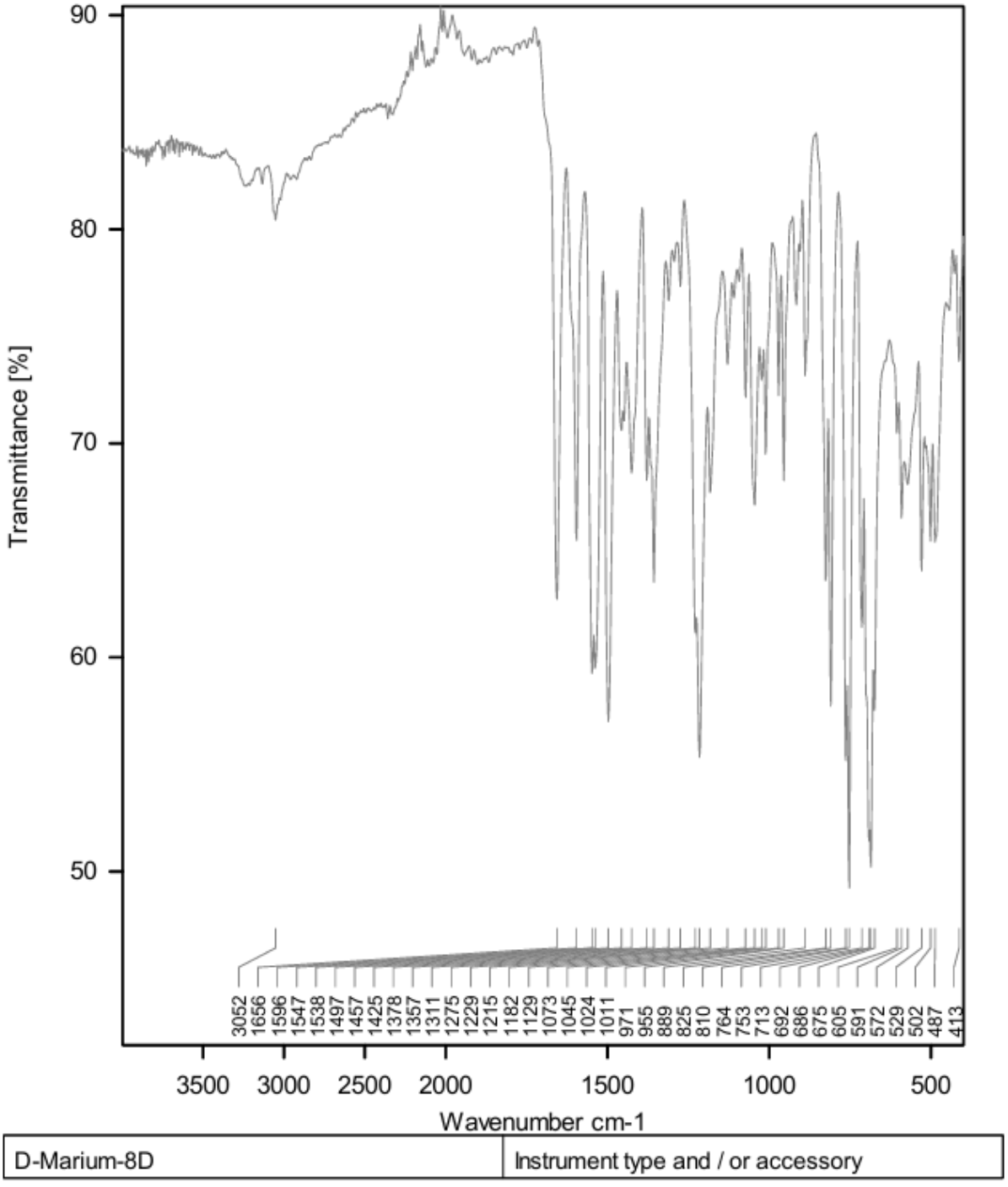


Figure S 65. IR of compound 8d

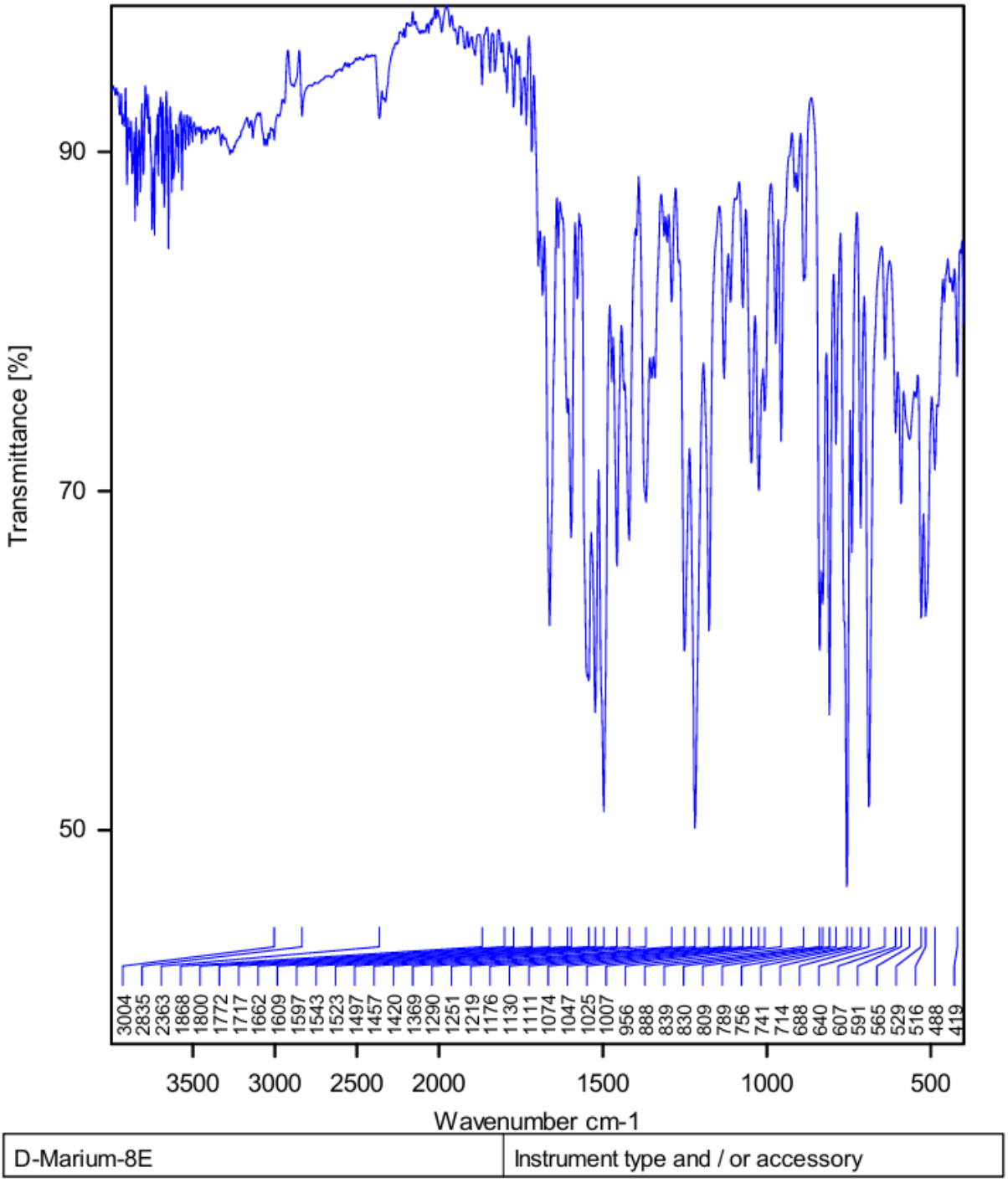


Figure S 66. IR of compound 8e

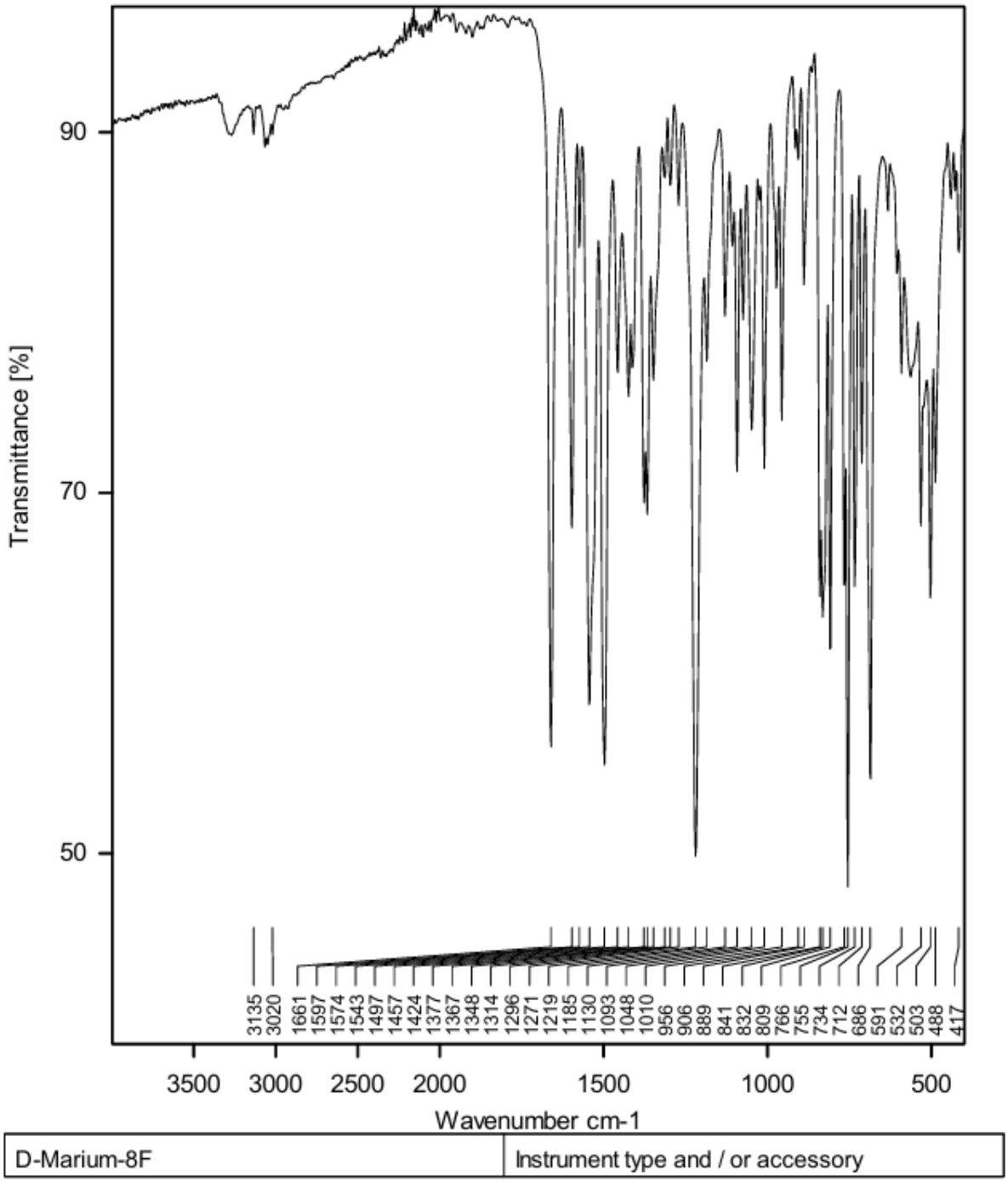


Figure S 67. IR of compound 8f

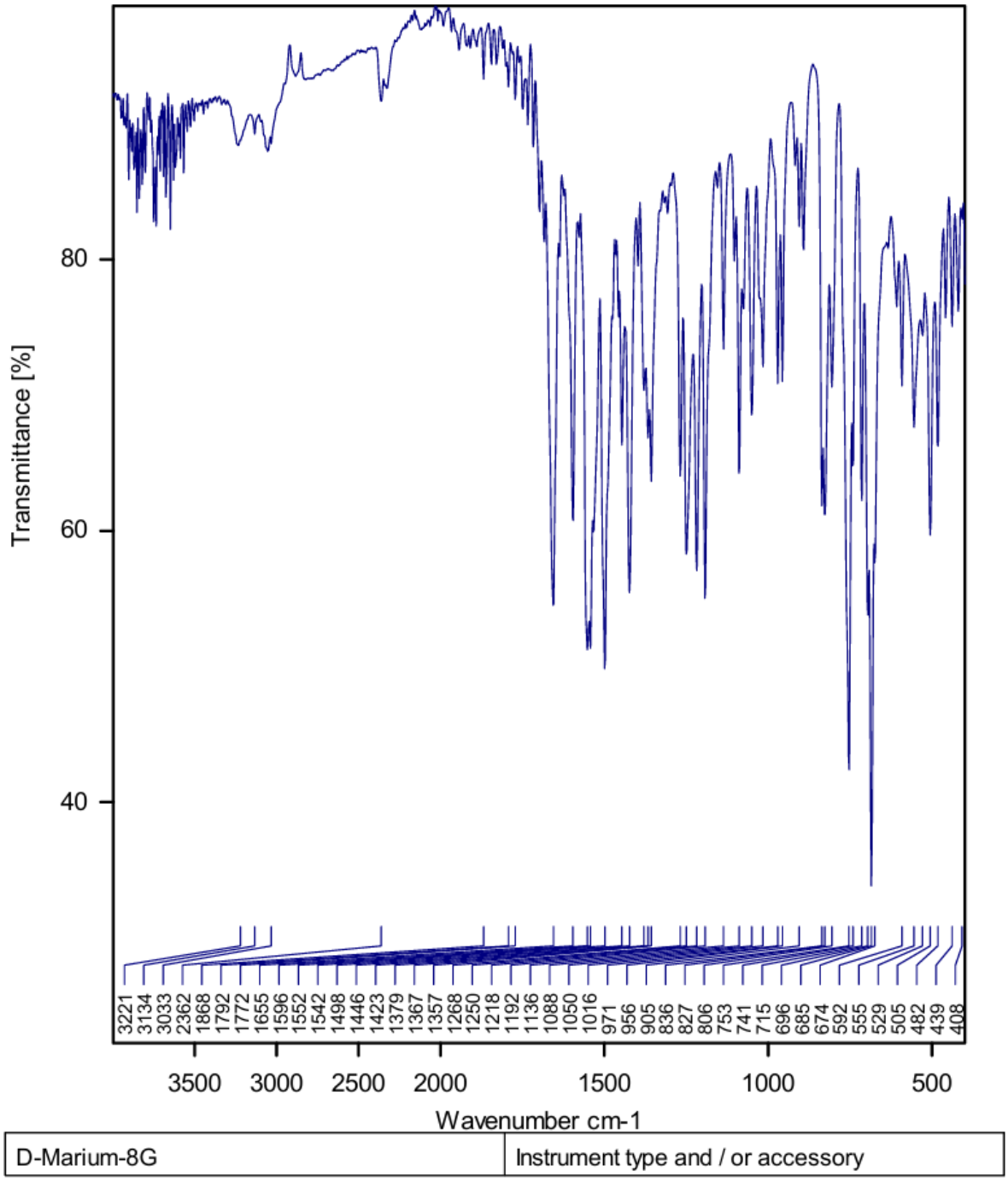


Figure S 68. IR of compound 8g

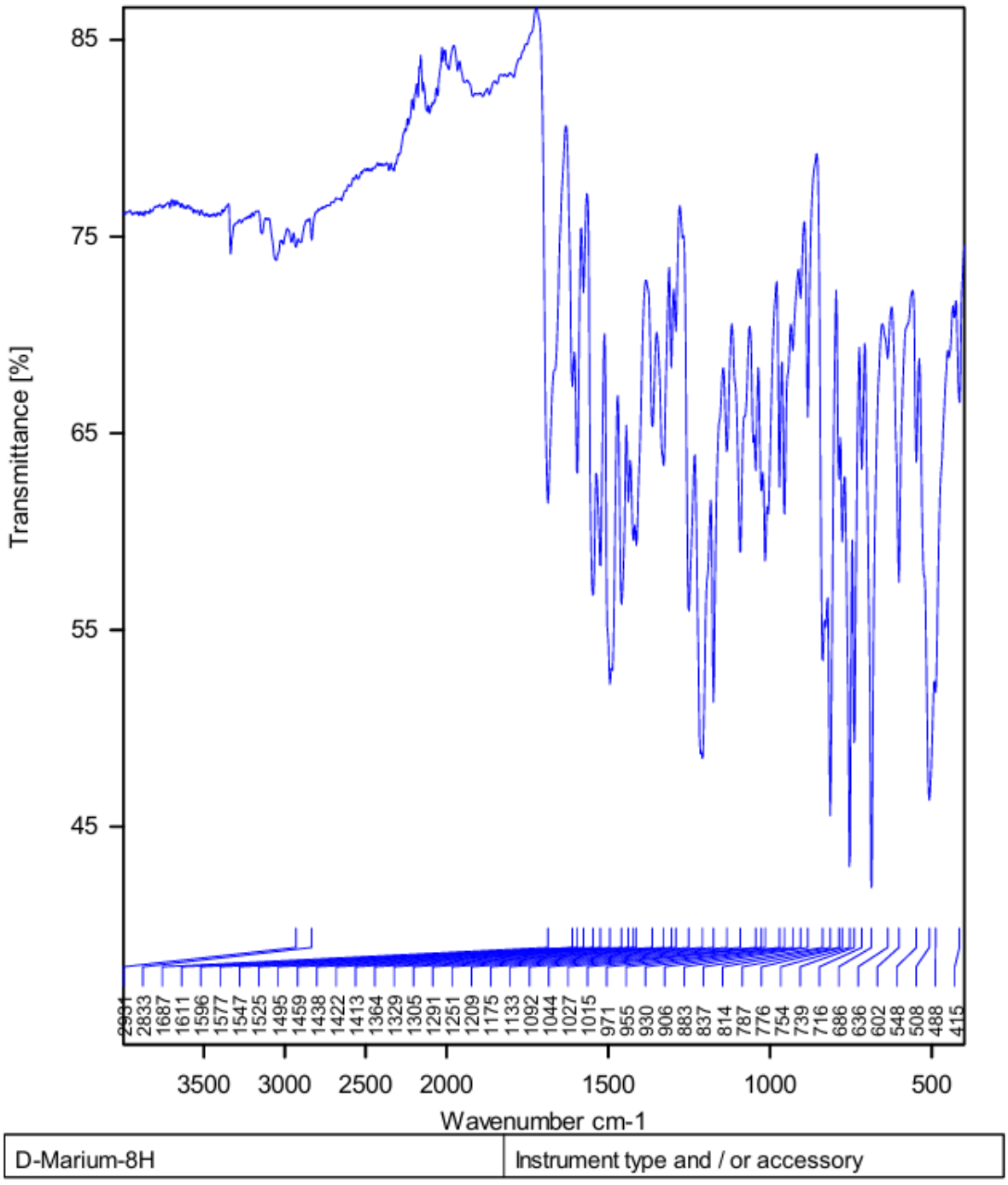


Figure S 69. IR of compound 8h

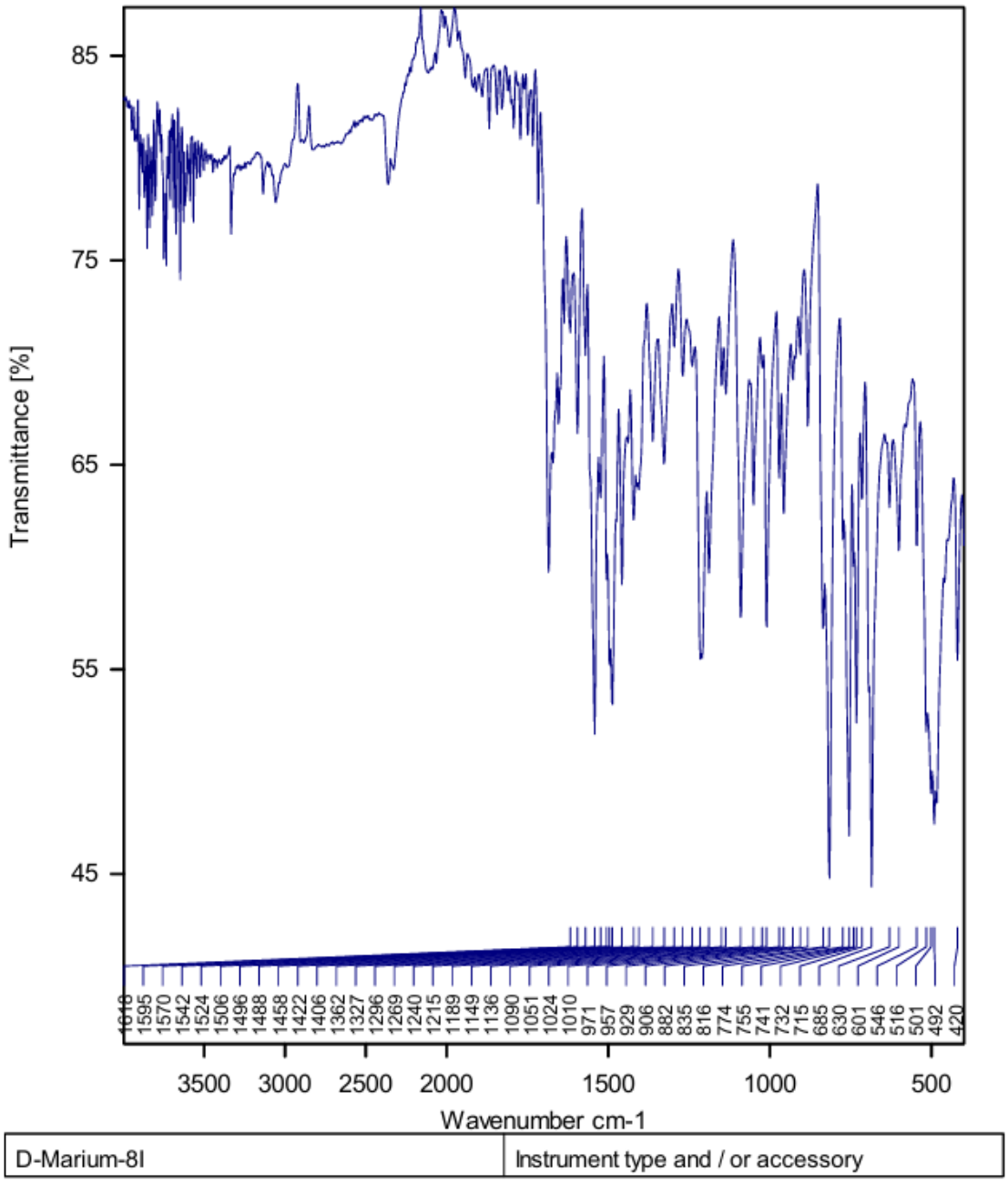


Figure S 70. IR of compound 8i

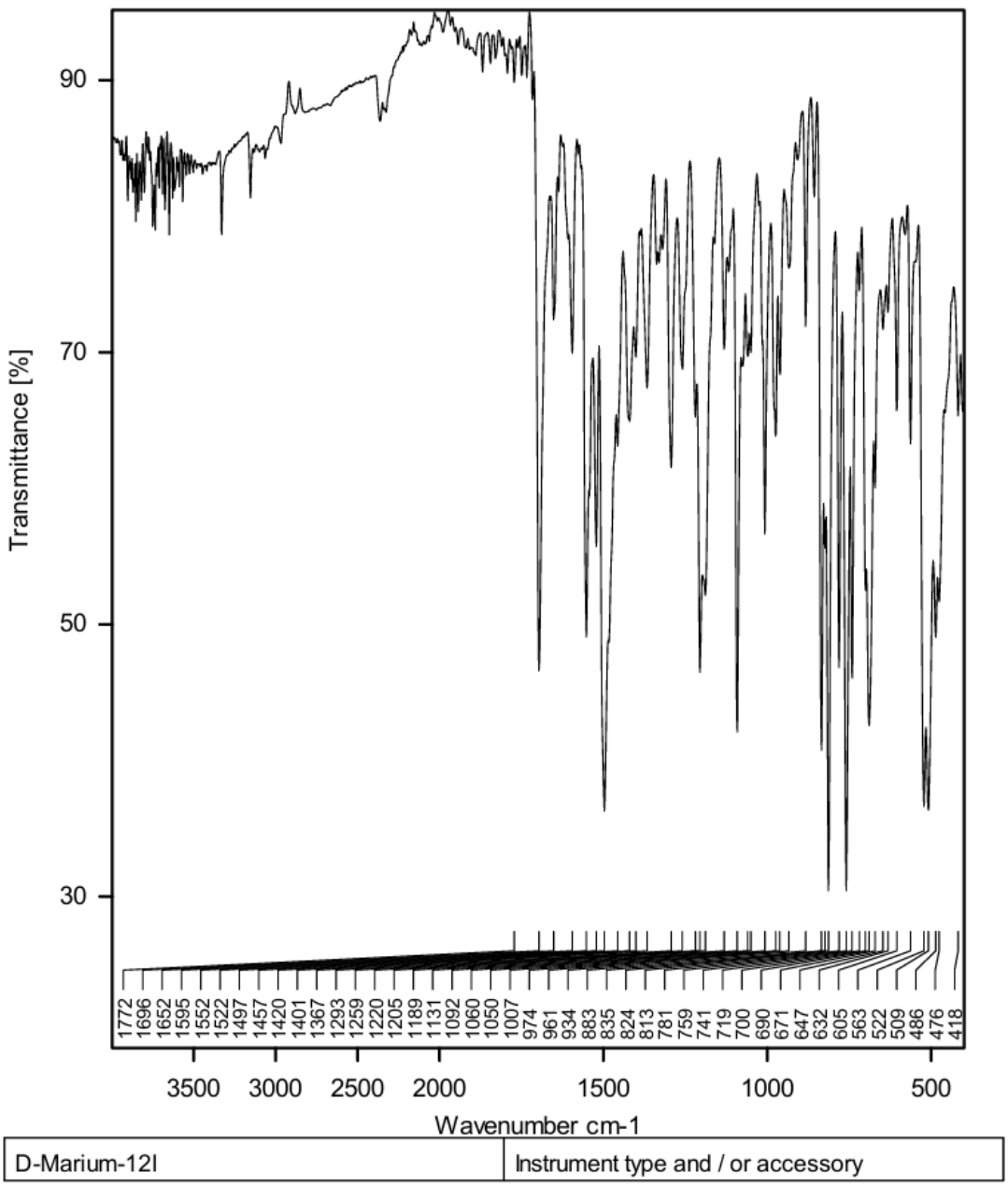


Figure S 71. IR of compound 12i