

Efficient Synthesis of an Exo-enone Analogue of LL-Z1640-2 and Evaluation of its Protein Kinase Inhibitory Activities

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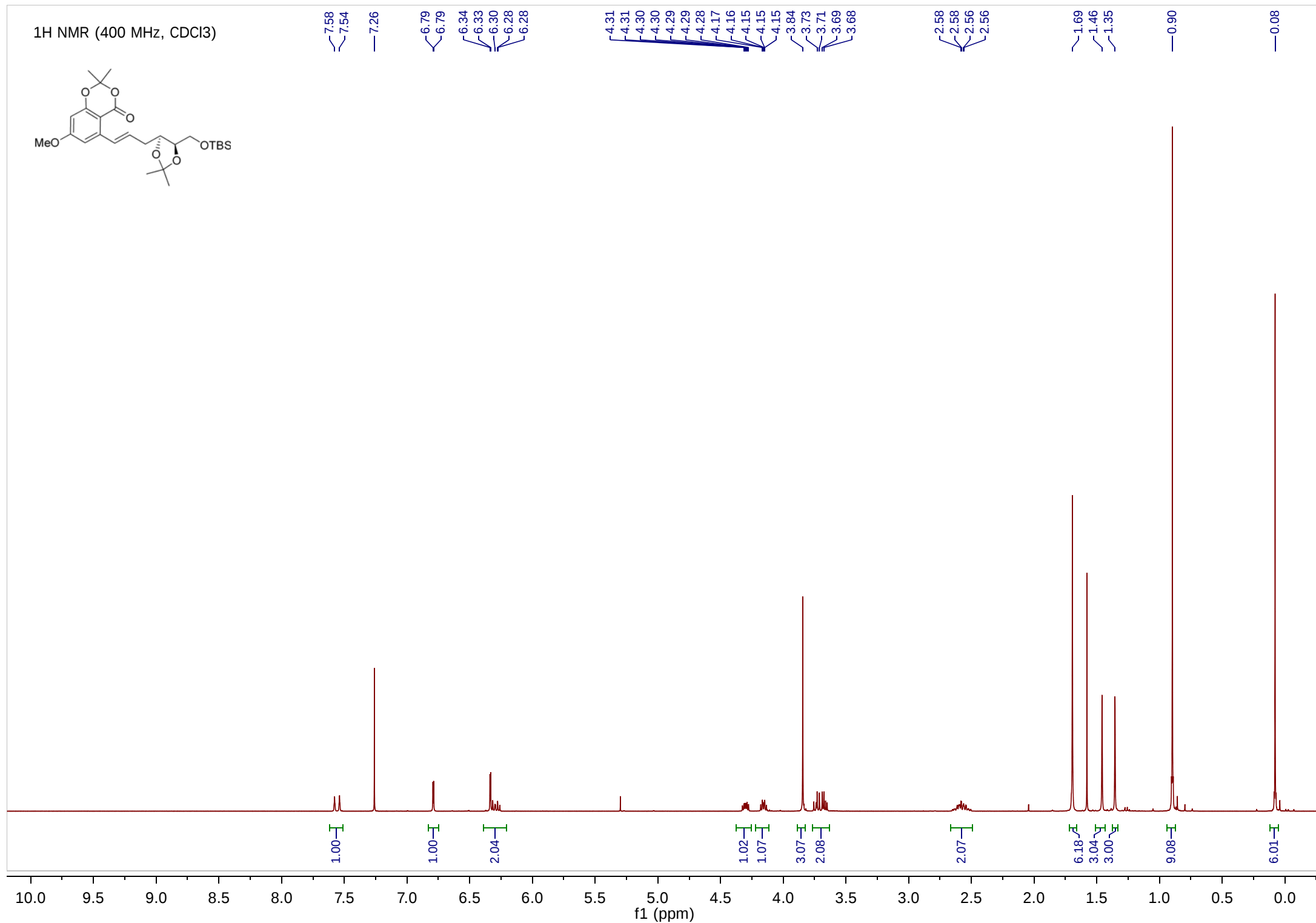
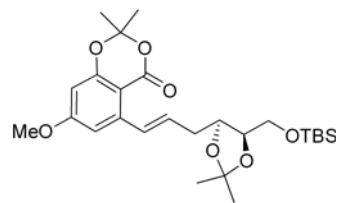
^b *Department of Pharmacy, National University of Singapore, 18 Science Drive 4, Singapore 117543E-mail: phacllc@nus.edu.sg (C. L. L. Chai)*

Supplementary Information

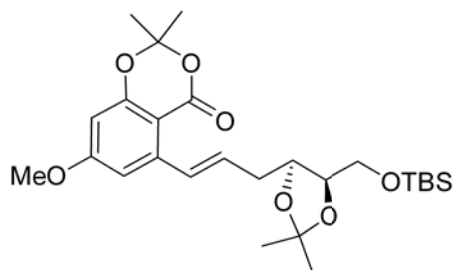
Copies of ¹H and ¹³C NMR spectra for new compounds 2-25

Kinase profiling data for 62 kinases 26-27

¹H NMR (400 MHz, CDCl₃)



¹³C (100 MHz, CDCl₃)



164.88
160.39
158.82

143.93

131.46
130.26

108.37
108.21
105.09
103.88
100.44

77.97
77.48
77.36
77.26
77.16
76.84

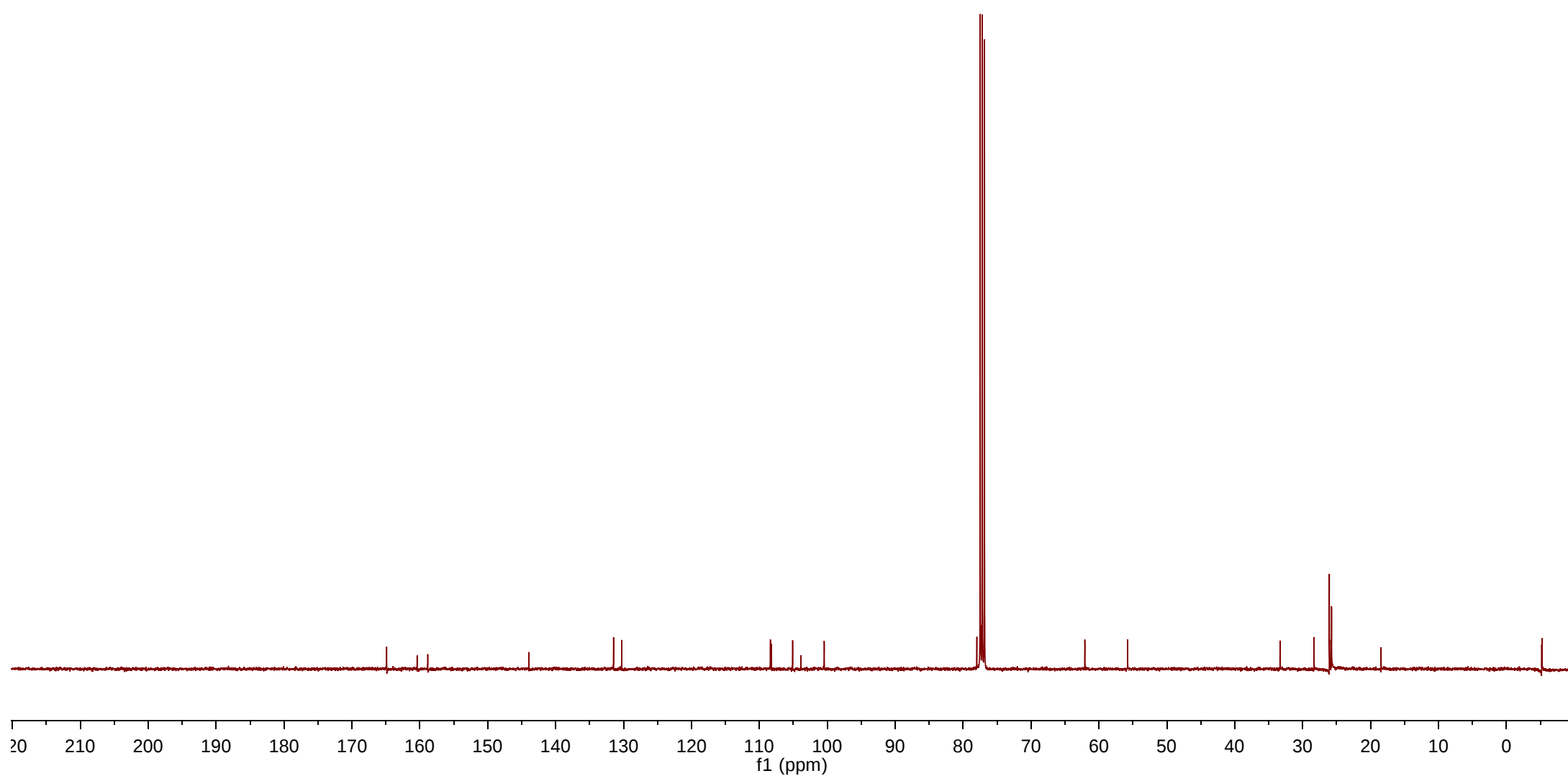
62.07

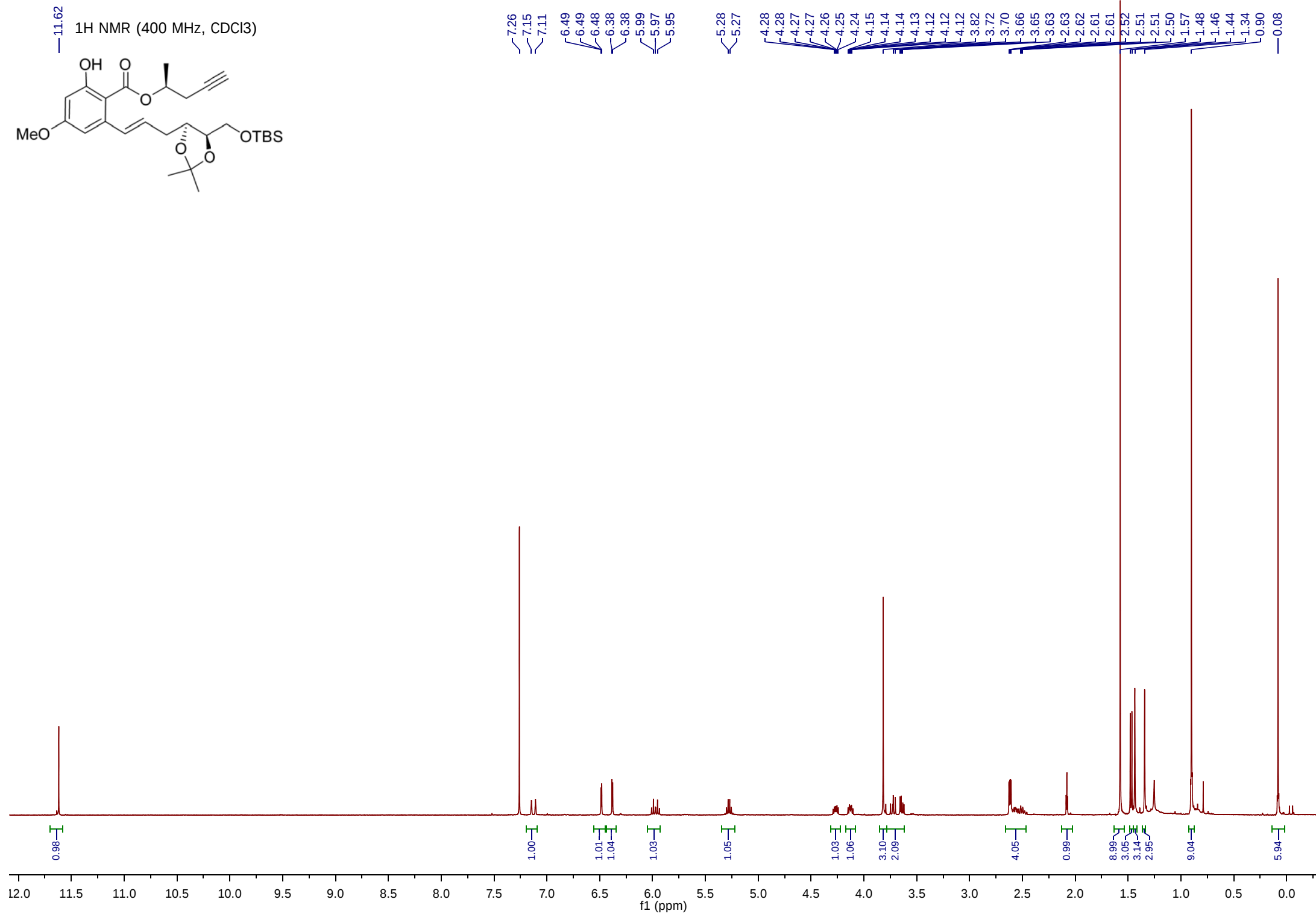
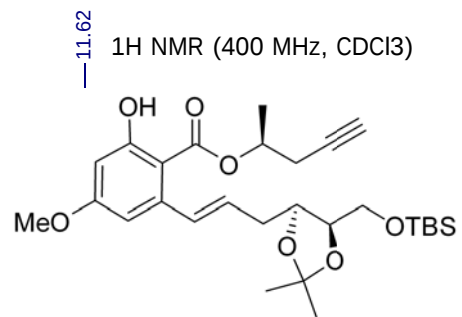
55.77

33.32
28.33
26.07
25.82
25.74

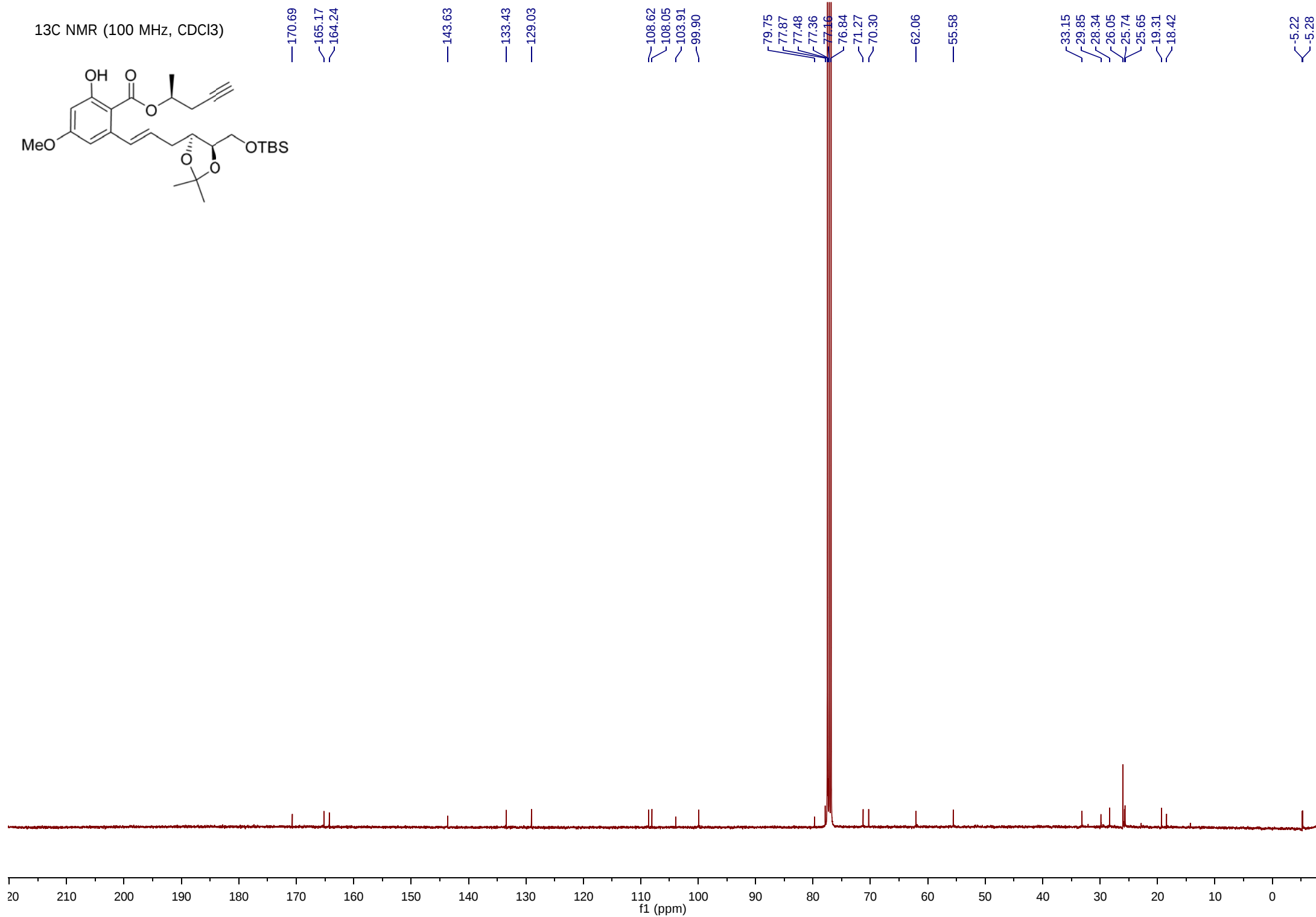
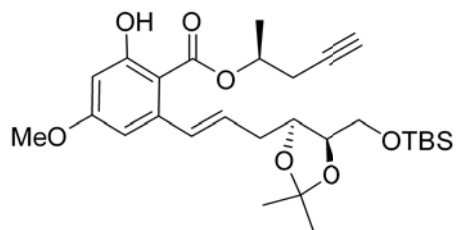
18.44

-5.21
-5.26

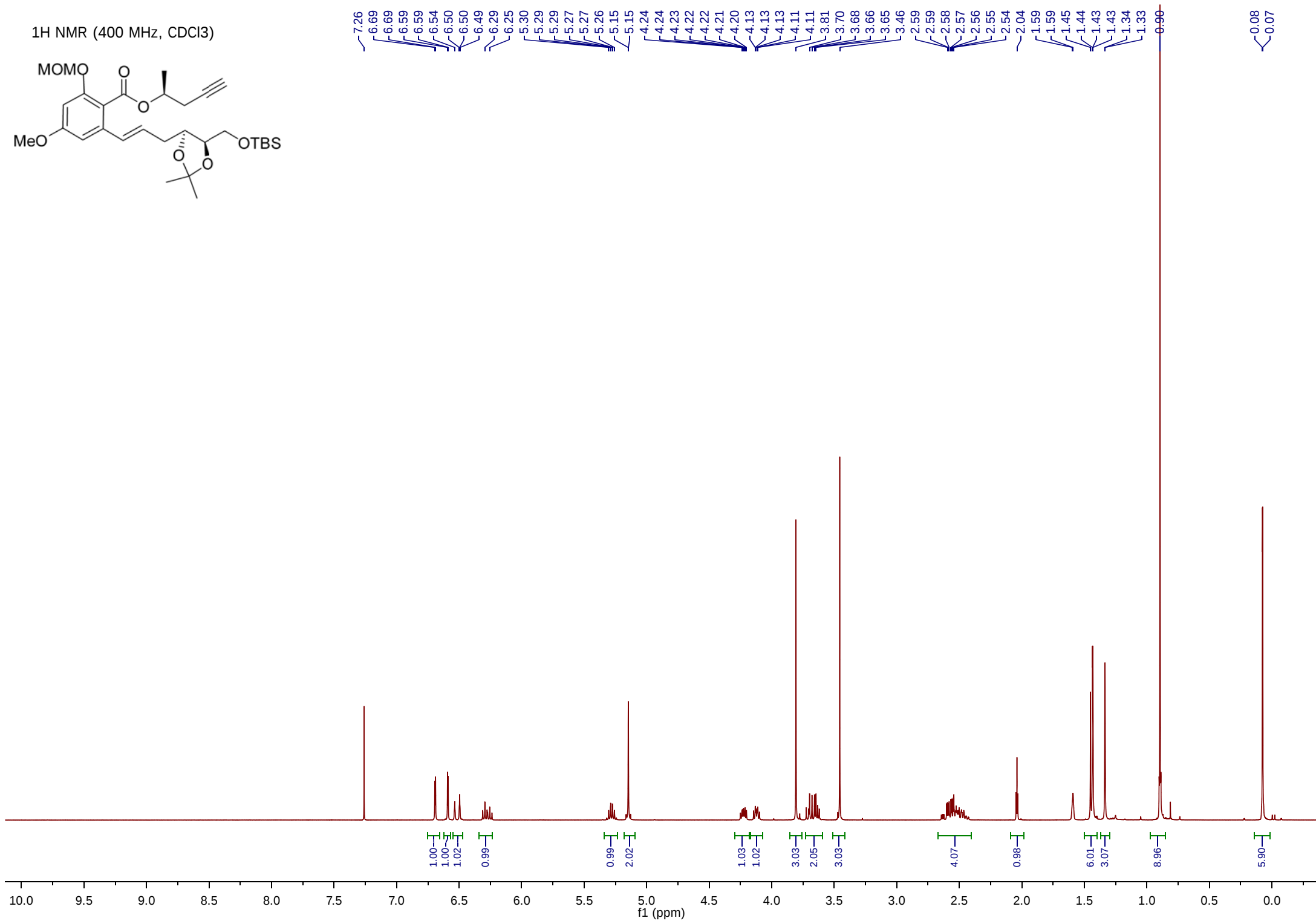
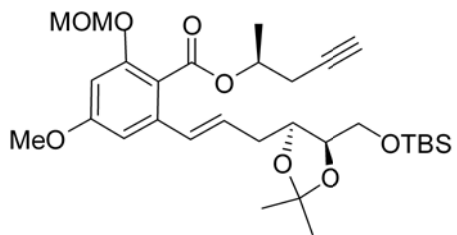




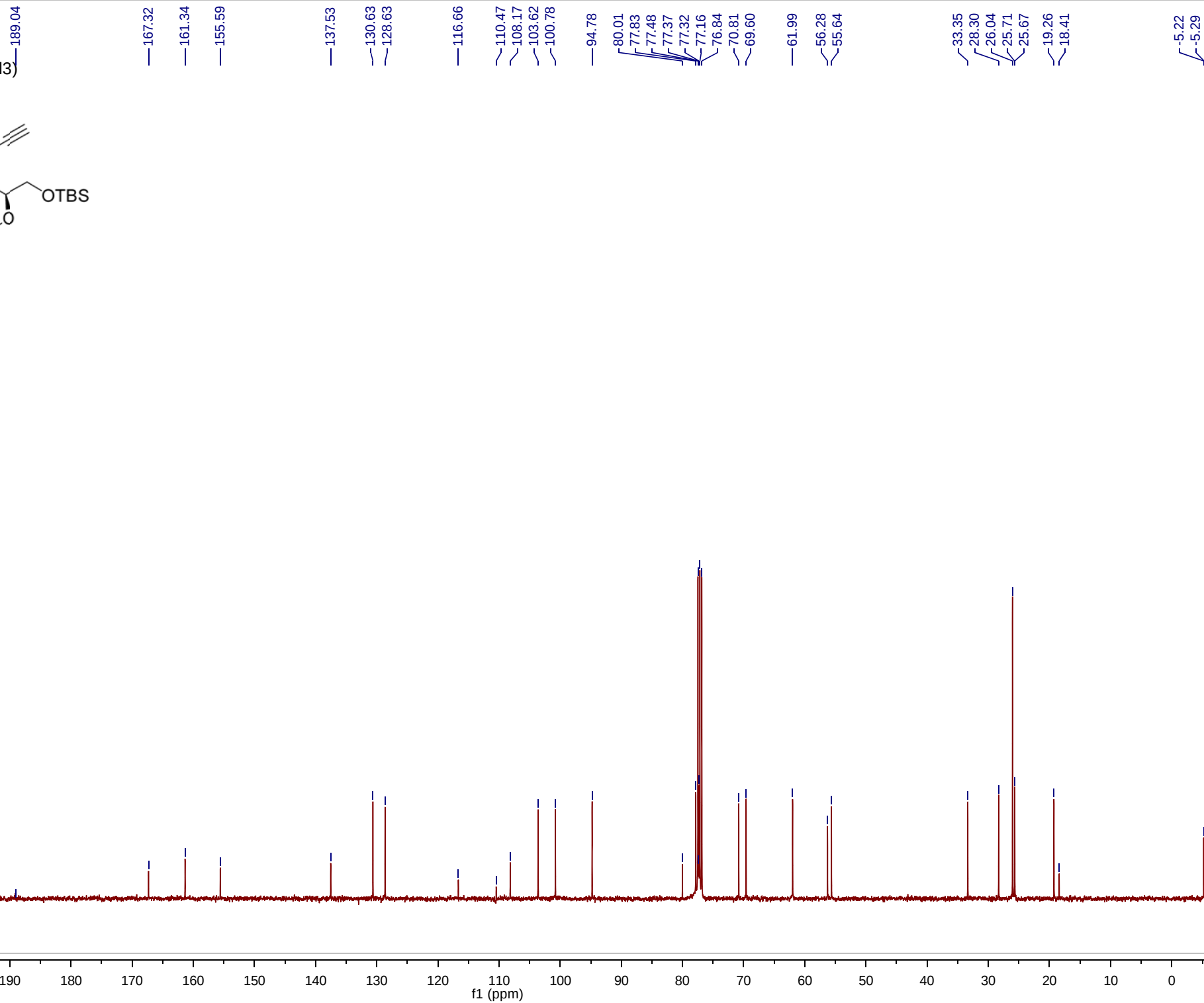
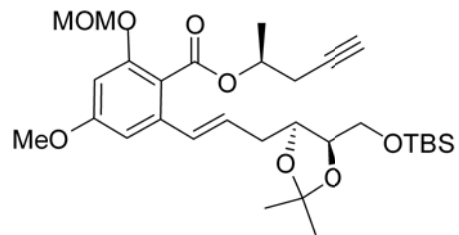
¹³C NMR (100 MHz, CDCl₃)



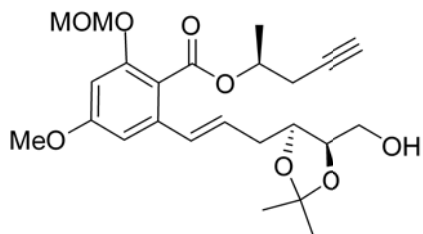
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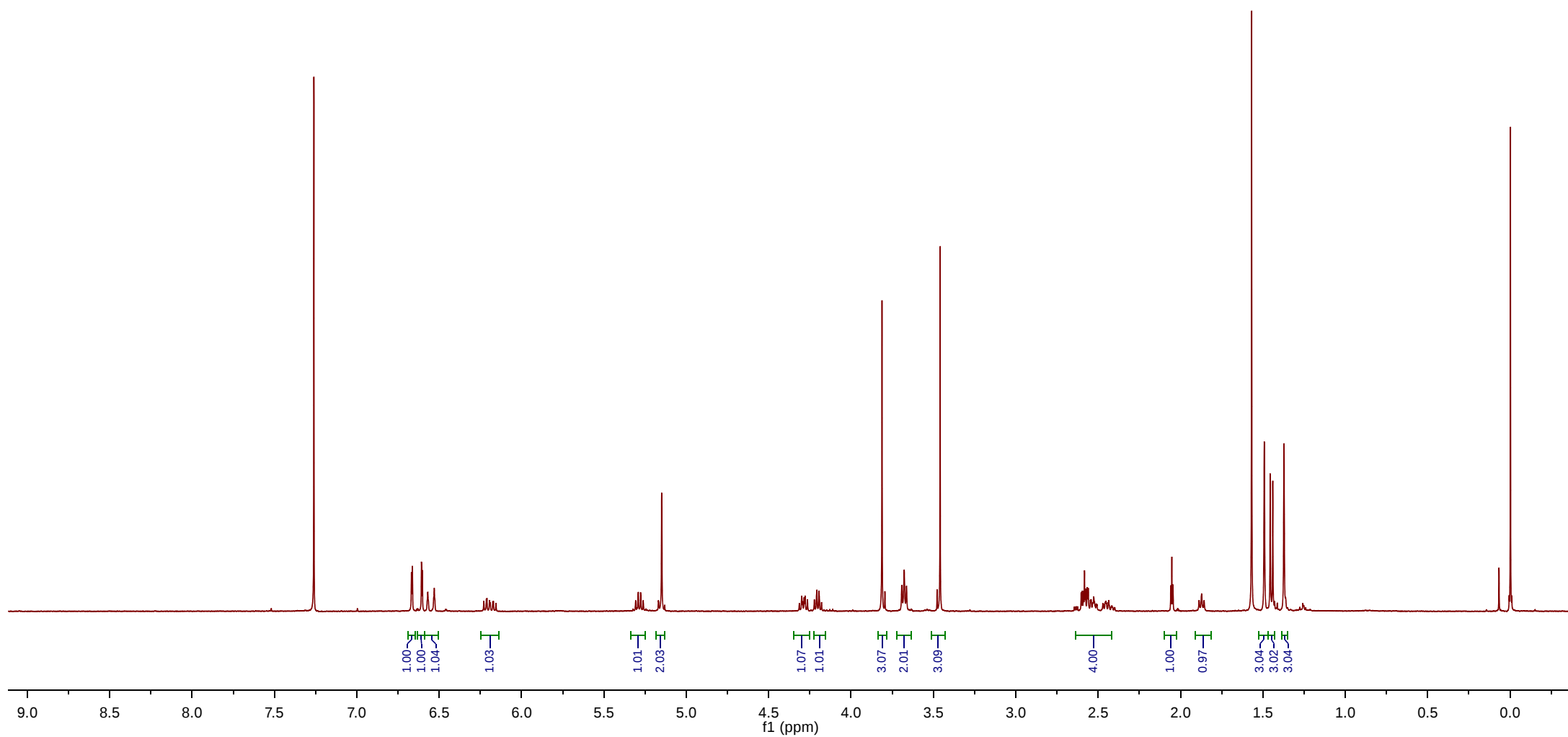
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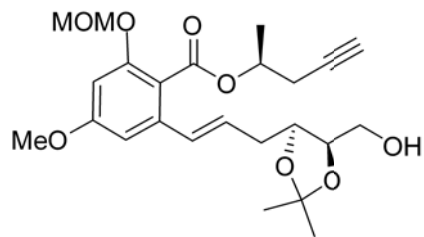
¹H NMR (400 MHz, CDCl₃)



7.26, 6.67, 6.66, 6.61, 6.60, 6.57, 6.57, 6.53, 6.53, 6.53, 6.21, 6.21, 6.19, 5.29, 5.29, 5.28, 5.28, 5.15, 5.15, 4.30, 4.28, 4.28, 4.26, 4.22, 4.21, 4.21, 4.19, 4.19, 3.81, 3.69, 3.68, 3.68, 3.66, 3.46, 2.60, 2.59, 2.58, 2.58, 2.57, 2.56, 2.46, 2.45, 2.45, 2.44, 2.44, 2.06, 2.05, 2.05, 1.89, 1.87, 1.86, 1.49, 1.46, 1.44, 1.37, 1.37, -0.00



¹³C NMR (100 MHz, CDCl₃)



— 167.37

— 161.46

— 155.77

— 137.46

129.56

129.26

— 116.63

108.50

103.89

100.86

— 94.83

80.10

77.92

77.52

77.41

77.20

76.89

76.57

70.87

69.72

— 61.78

56.35

55.70

— 33.33

28.27

25.75

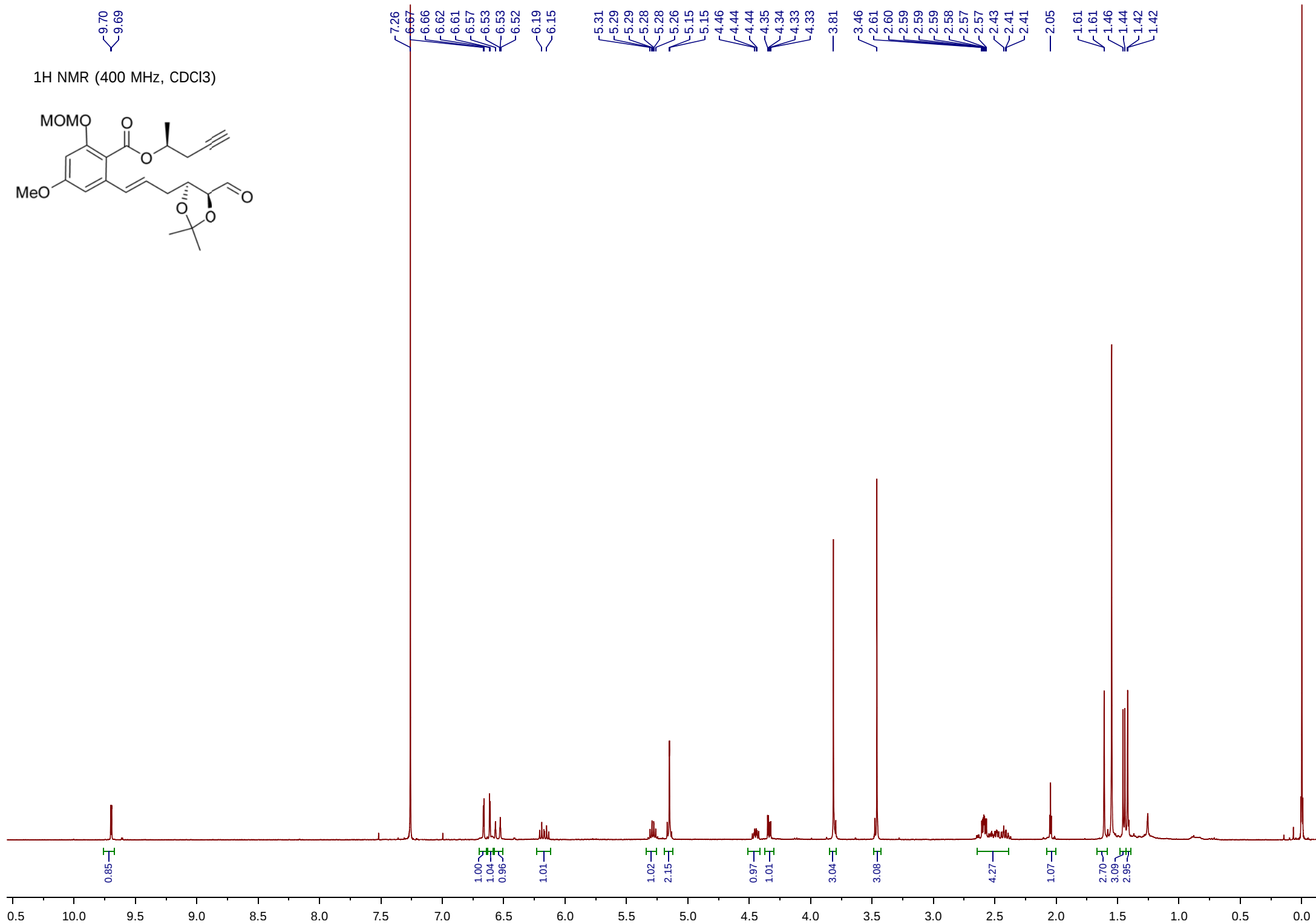
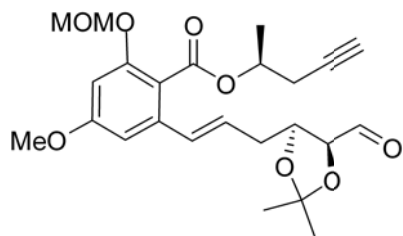
25.60

— 19.32

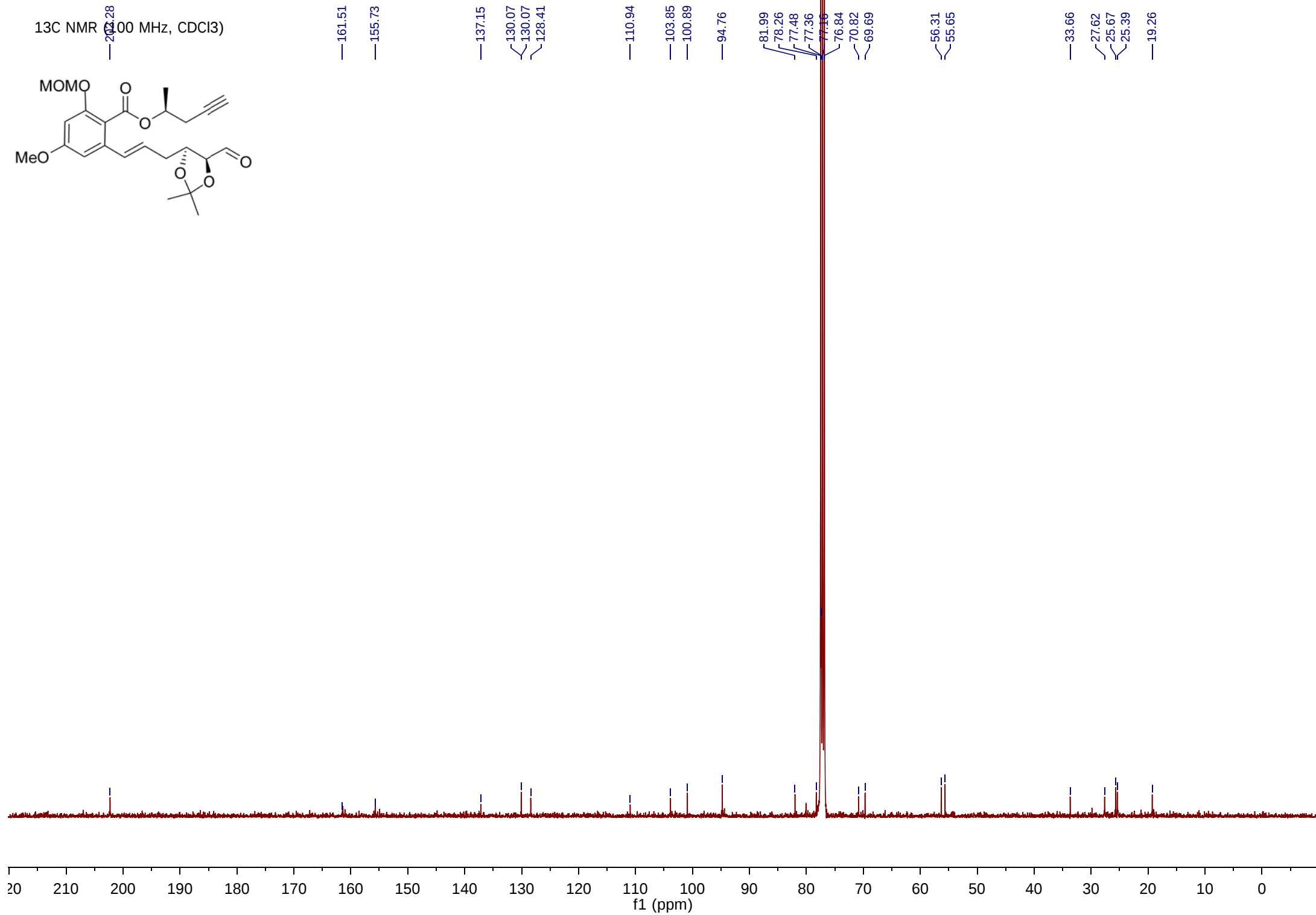
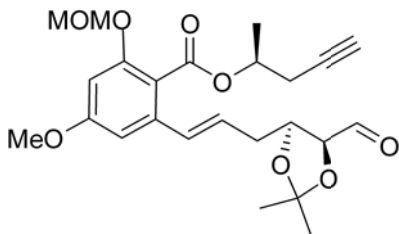
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

¹H NMR (400 MHz, CDCl₃)



¹³C NMR (100 MHz, CDCl₃)



¹H NMR (400 MHz, CDCl₃)

7.26

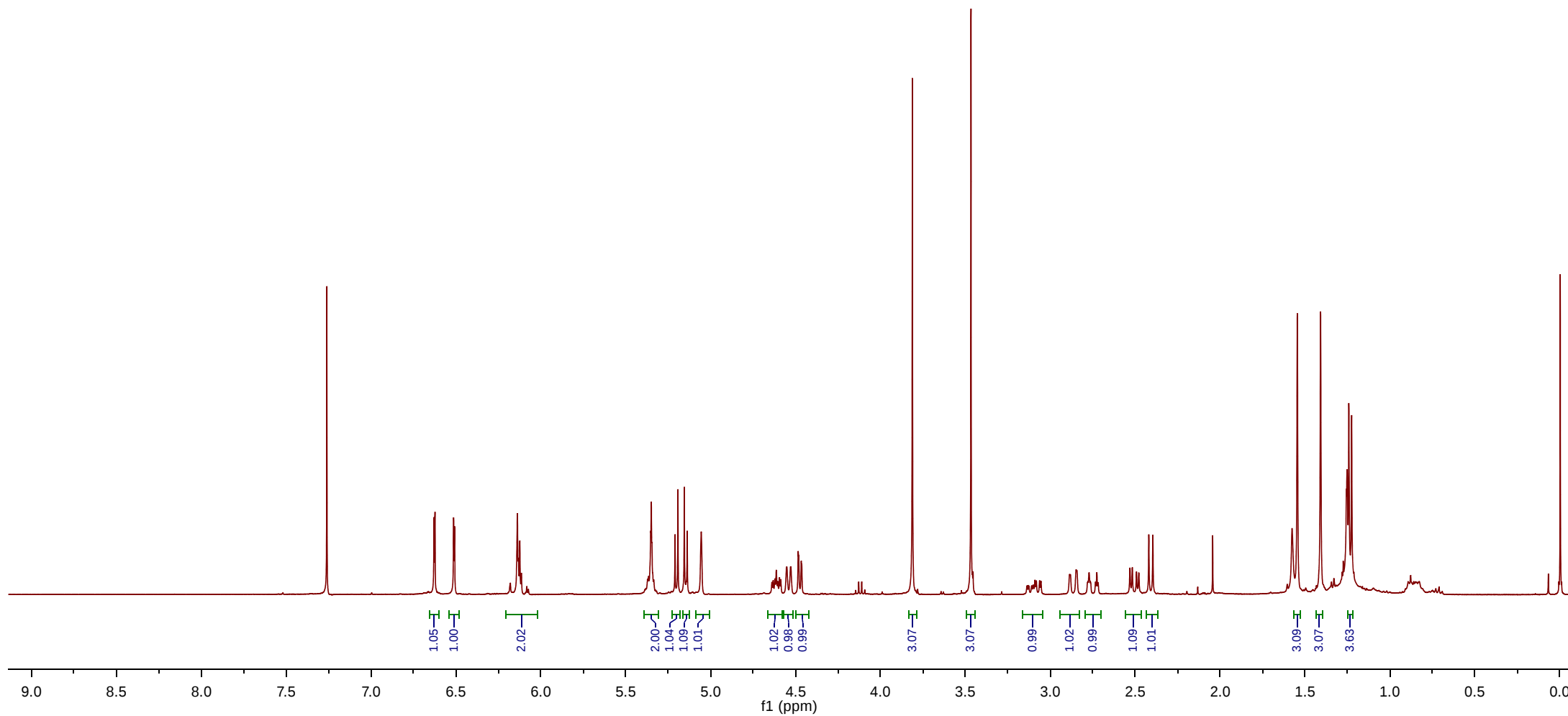
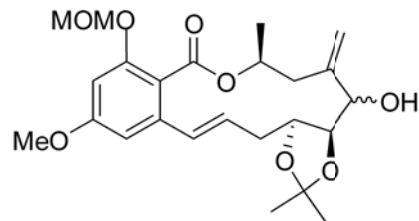
6.63
6.62
6.51
6.51
6.14
6.13
6.12
6.11

5.35
5.35
5.35
5.21
5.19
5.15
5.14
5.06

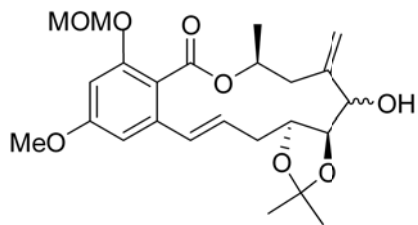
4.62
4.61
4.59
4.55
4.55
4.53
4.53
4.48
4.48
4.47
4.46
3.81

3.47
3.13
3.09
3.08
3.06
3.05
2.89
2.89
2.88
2.88
2.85
2.84
2.77
2.76
2.73
2.53
2.52
2.49
2.42
2.40
1.55
1.41
1.24
1.23

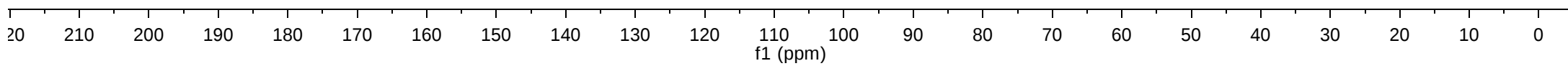
-0.00



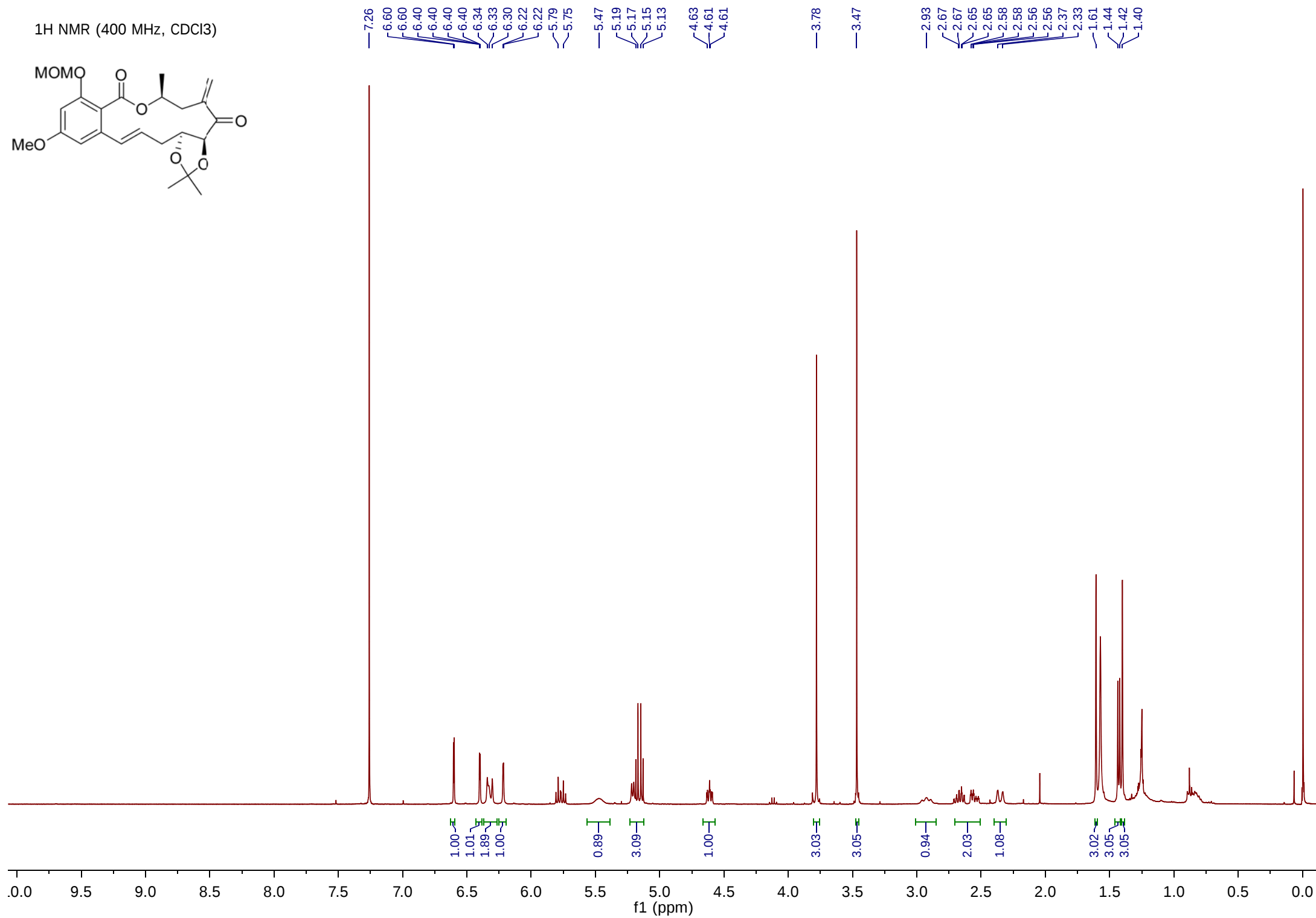
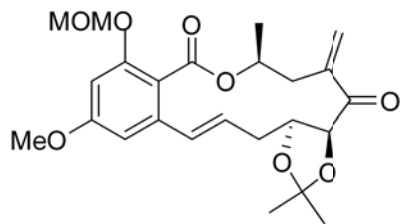
¹³C NMR (100 MHz, CDCl₃)

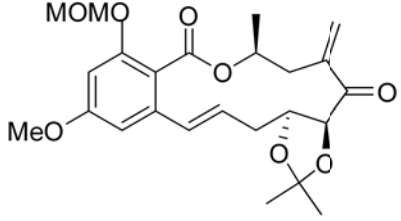


— 167.41 — 161.62 — 155.75 — 144.68 — 138.47 — 130.82 — 129.02 — 116.02 — 107.56 — 104.99 — 101.17 — 95.09 — 77.48 — 77.16 — 77.16 — 76.84 — 76.14 — 75.51 — 72.08 — 69.66 — 56.34 — 55.64 — 39.37 — 32.85 — 29.84 — 26.69 — 23.92 — 19.02

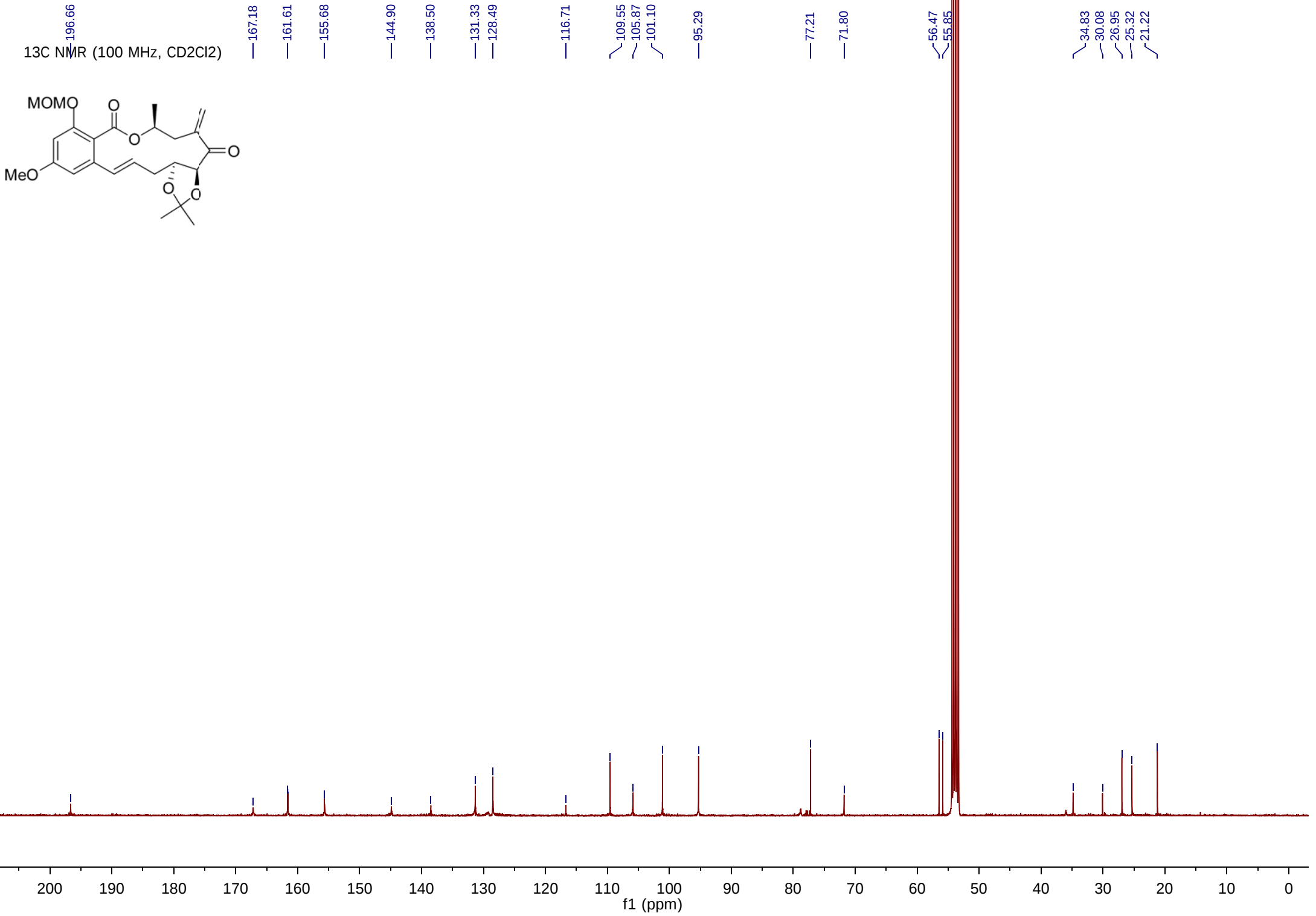


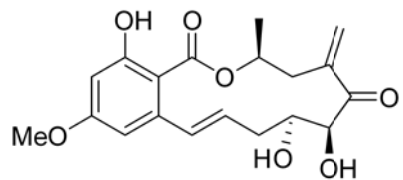
¹H NMR (400 MHz, CDCl₃)



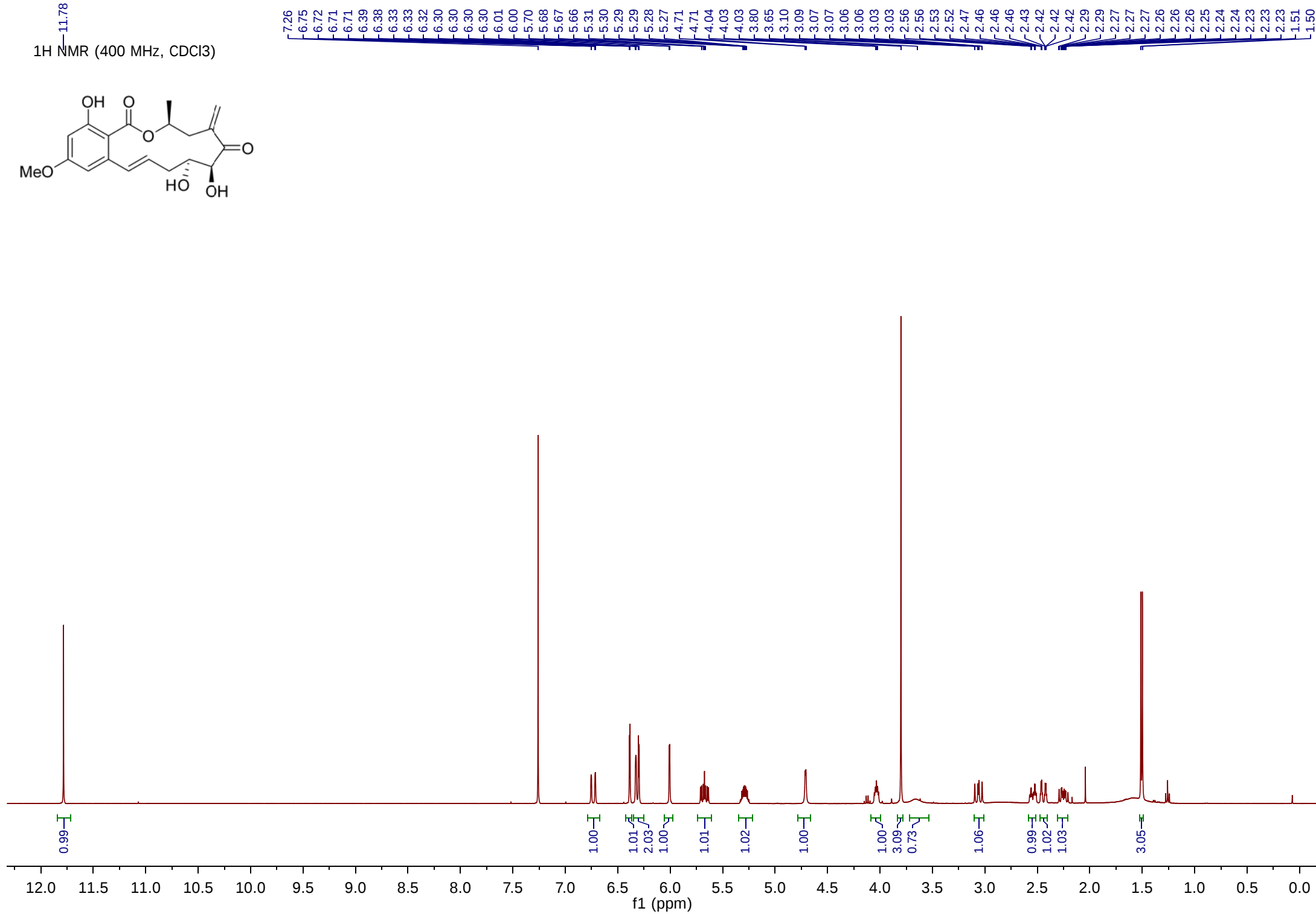


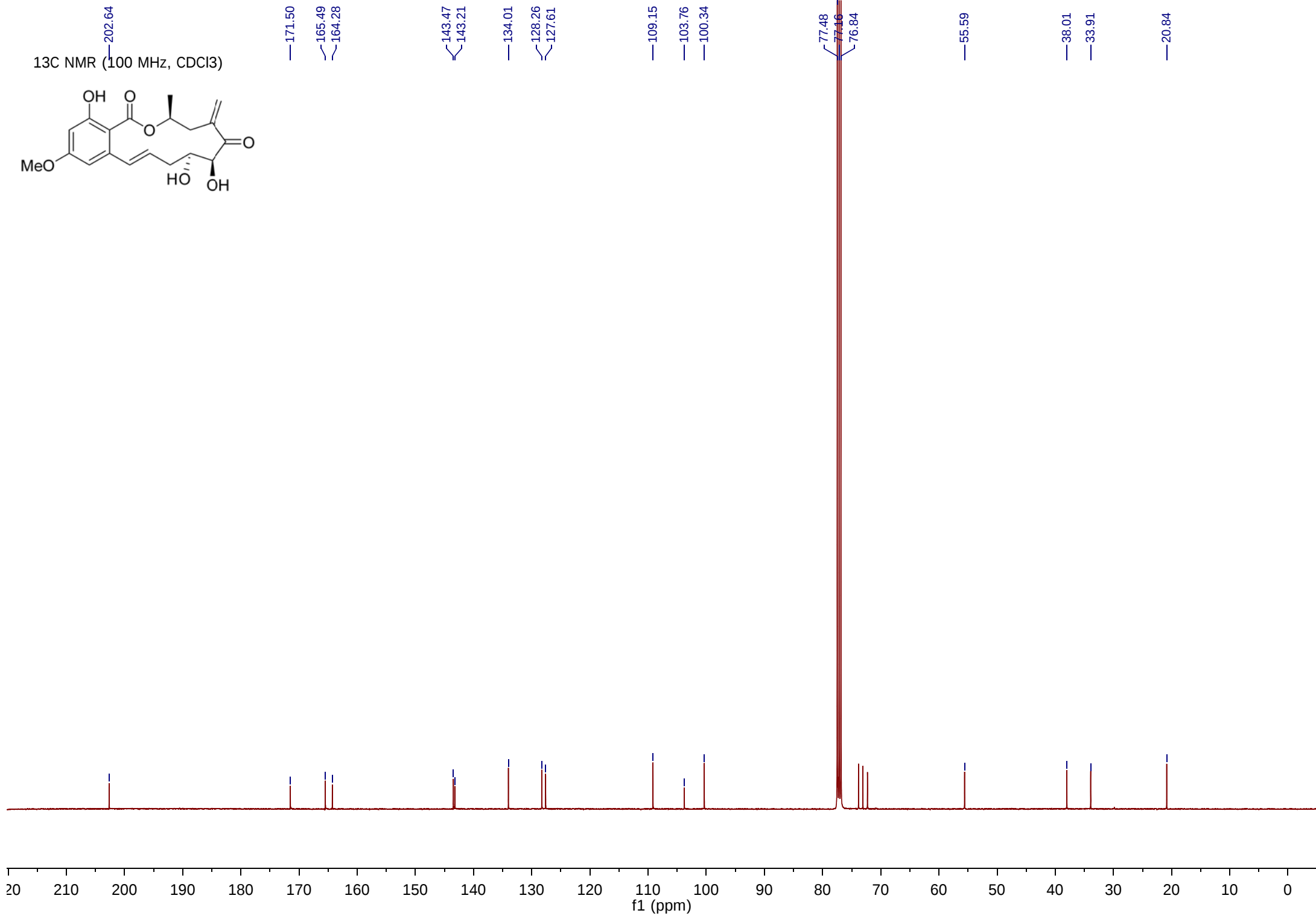
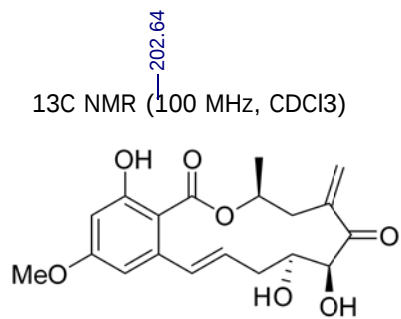
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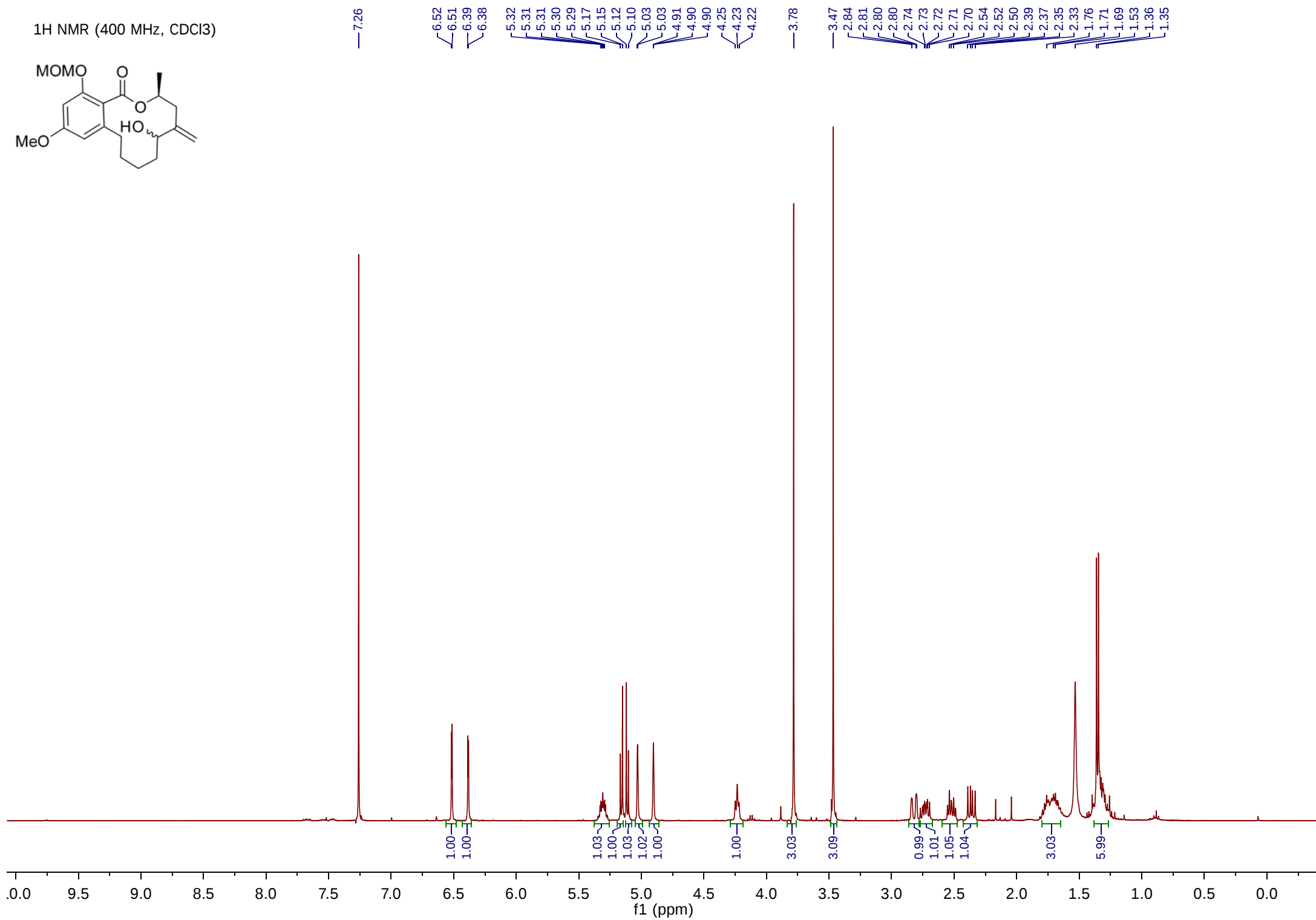
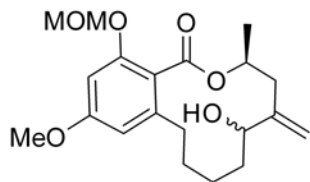


¹H NMR (400 MHz, CDCl₃)

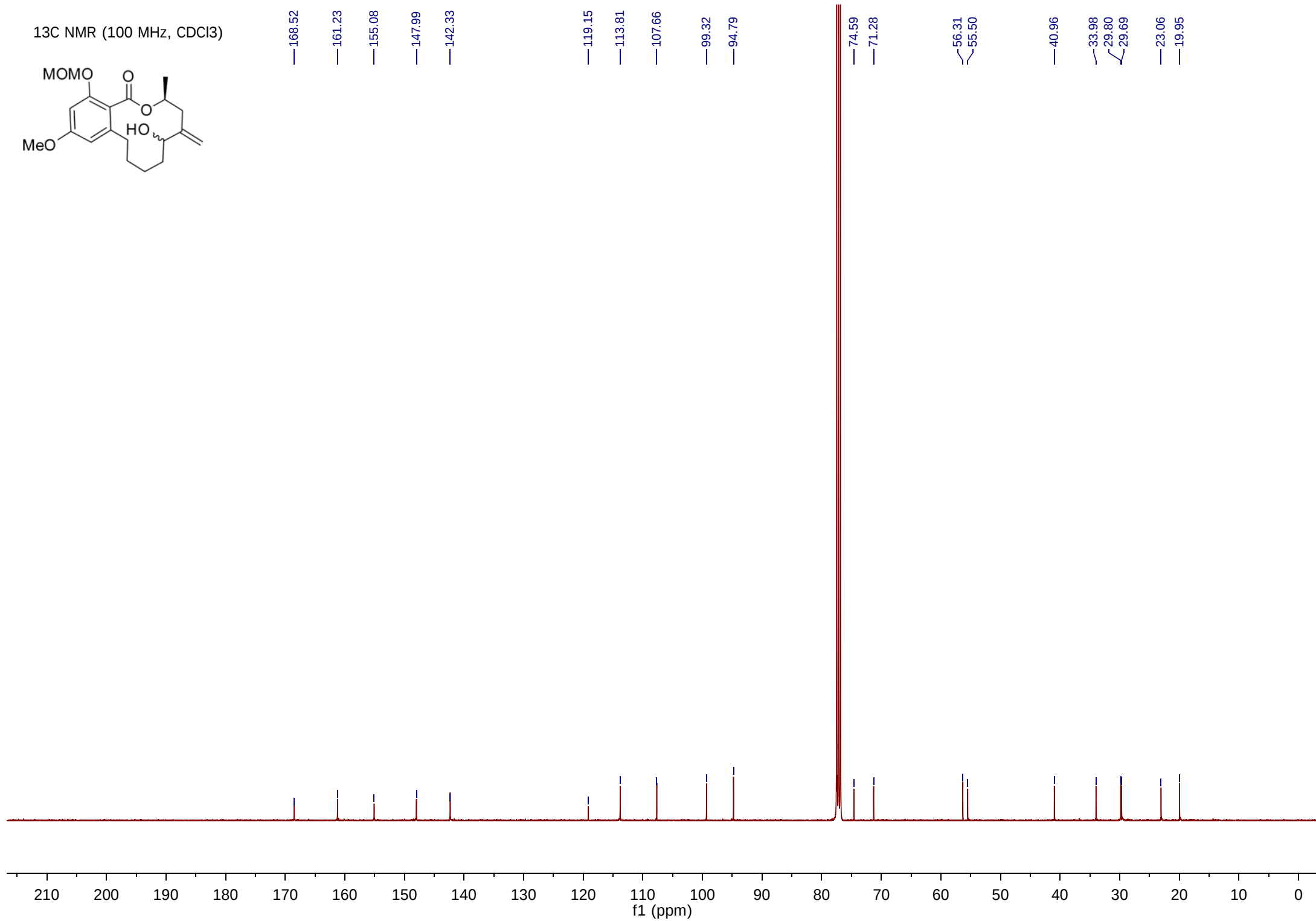
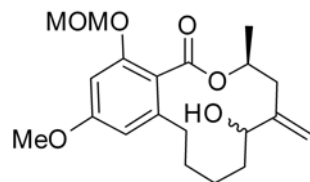




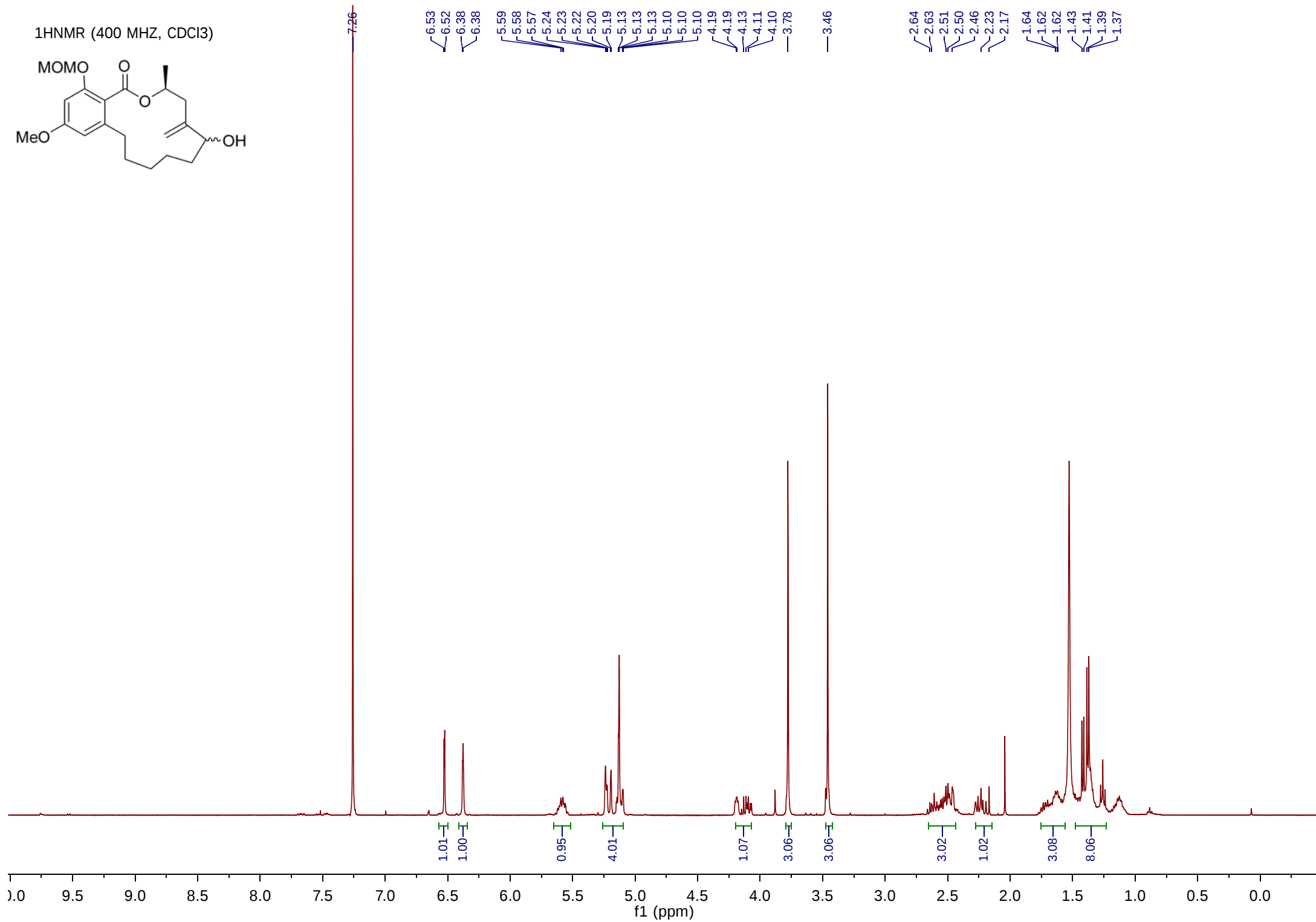
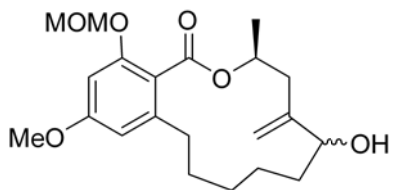
¹H NMR (400 MHz, CDCl₃)

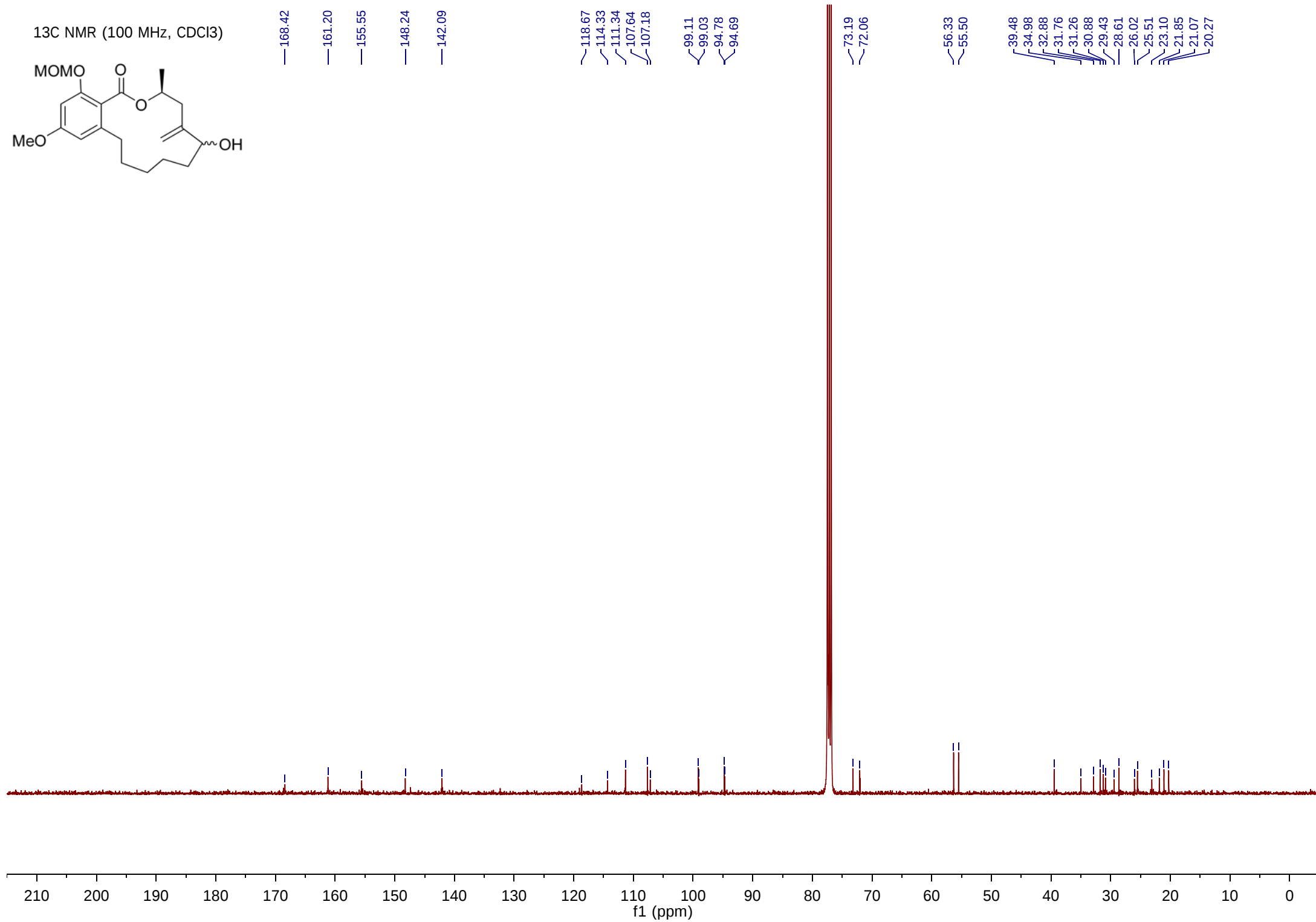


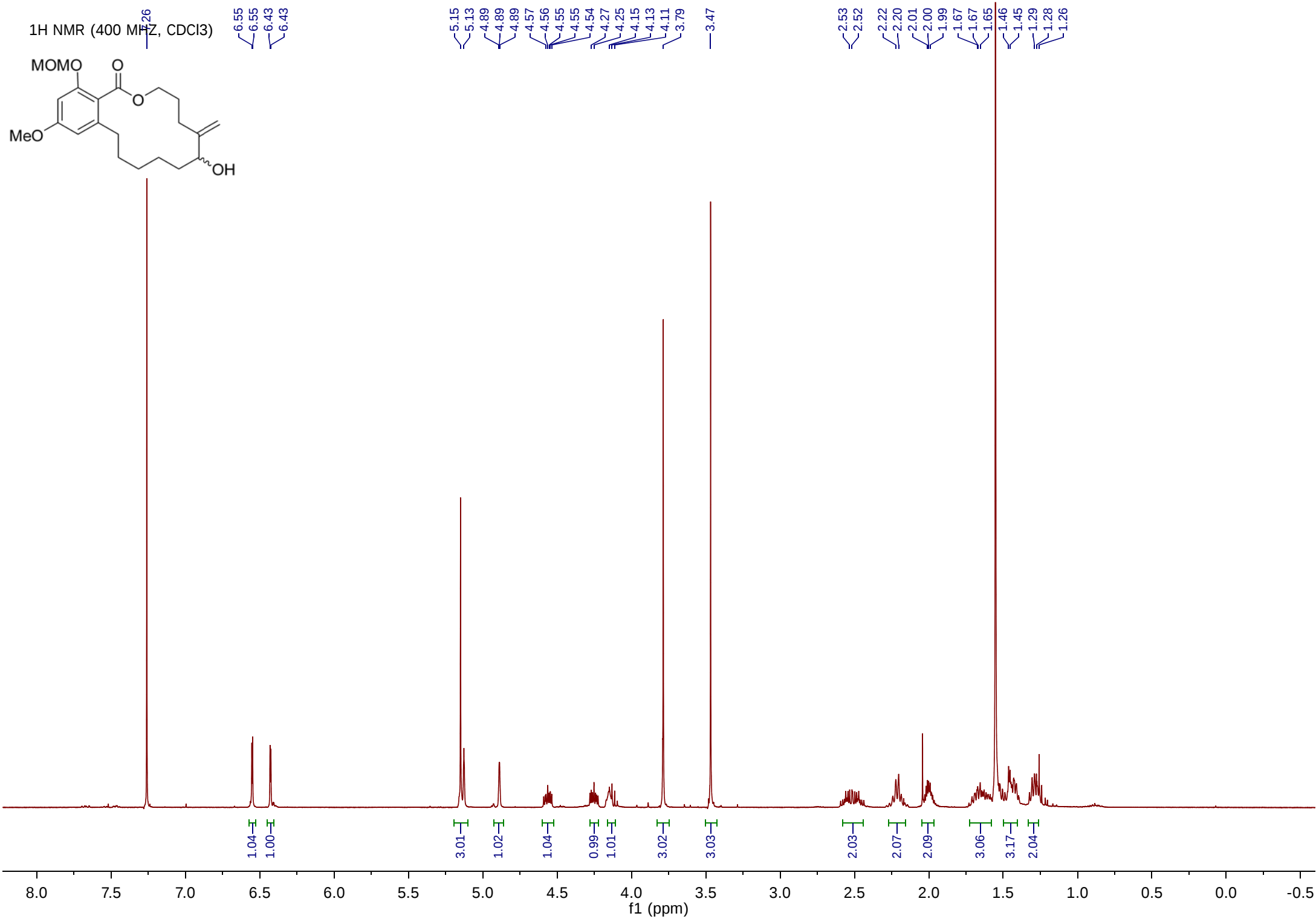
¹³C NMR (100 MHz, CDCl₃)



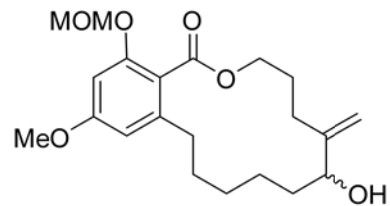
1HNMR (400 MHz, CDCl₃)







¹³C NMR (100 MHz, CDCl₃)



— 168.38

— 161.37

— 155.78

— 142.86

— 117.43

— 107.97

— 99.21

— 95.01

— 83.21

77.16

76.84

— 69.18

63.56

63.08

56.32

55.53

33.86

32.81

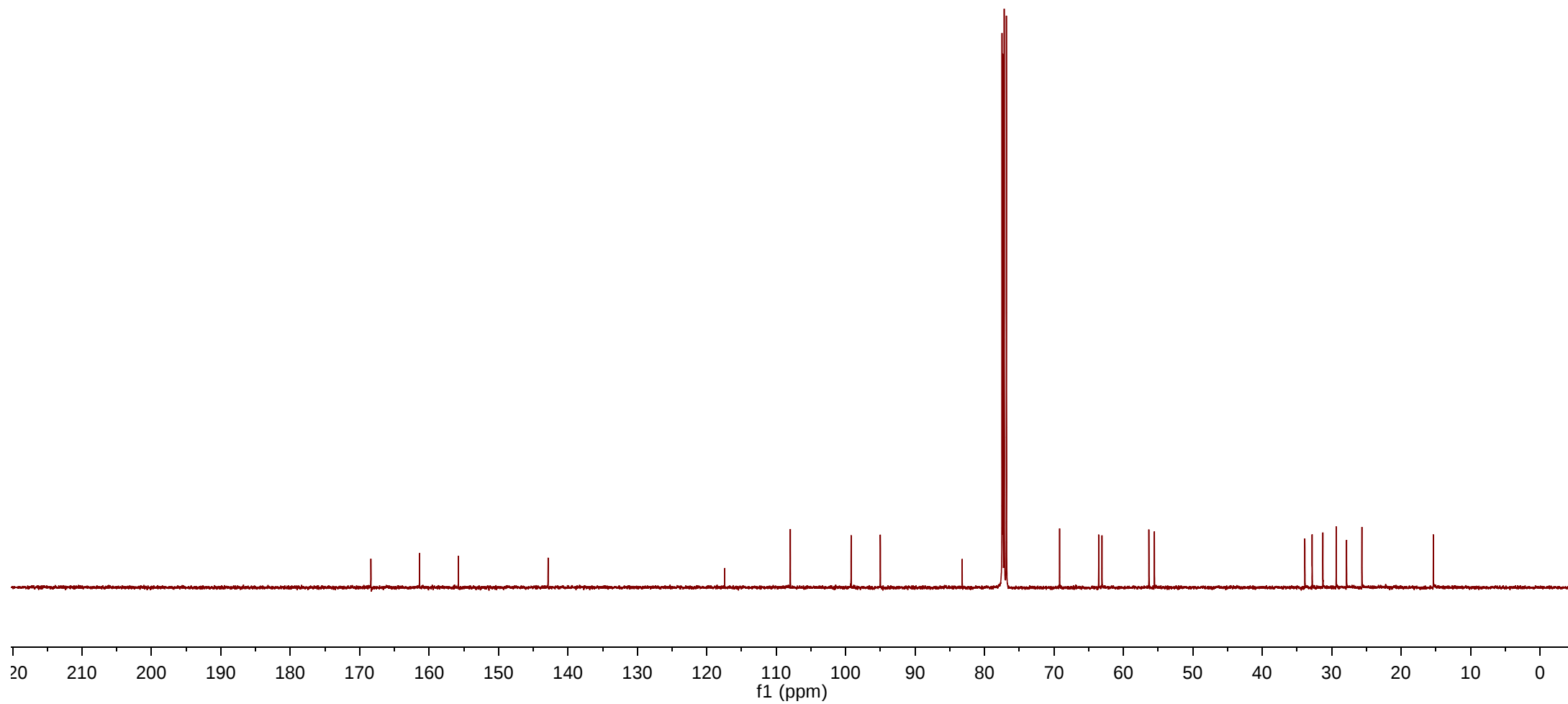
31.26

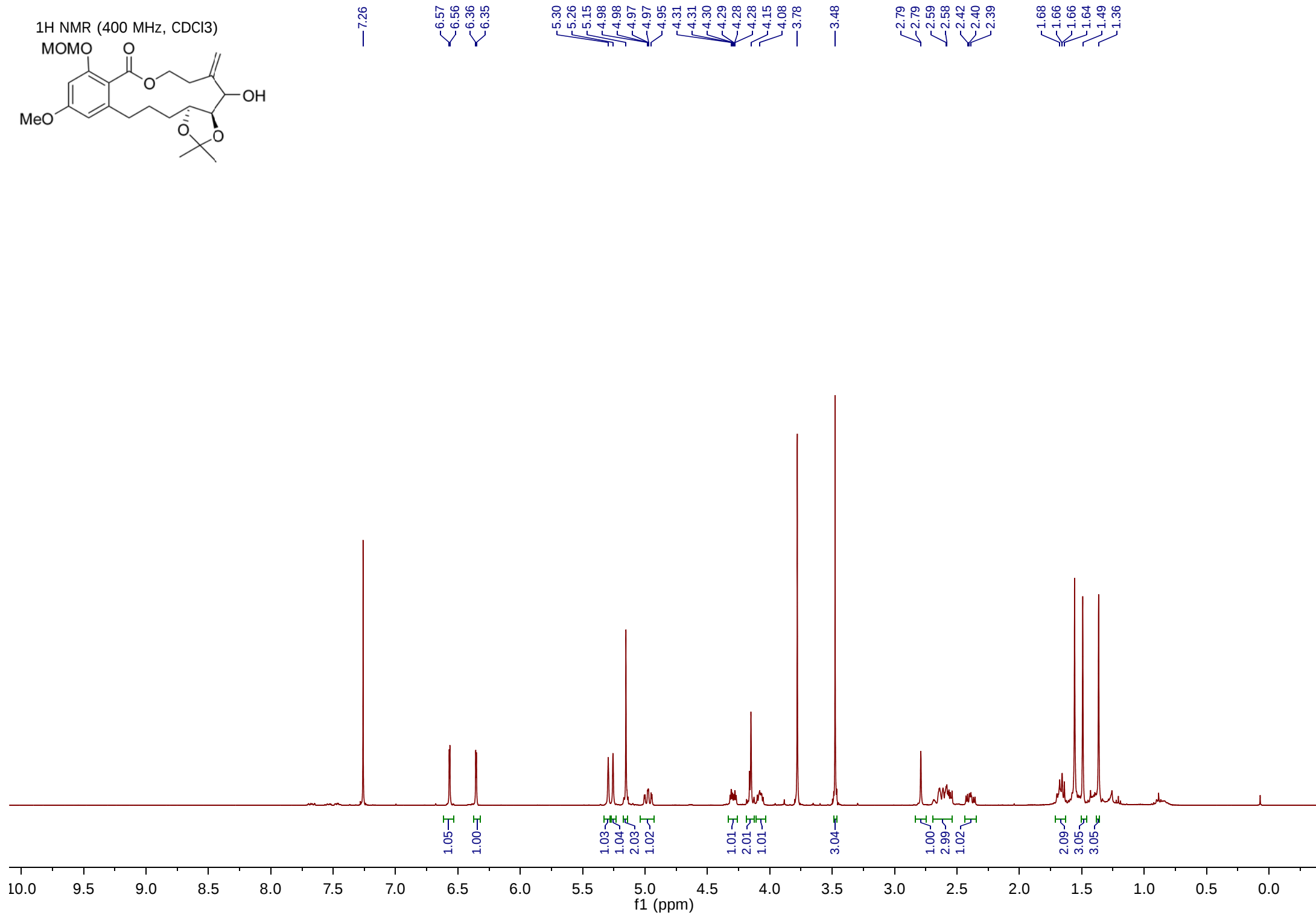
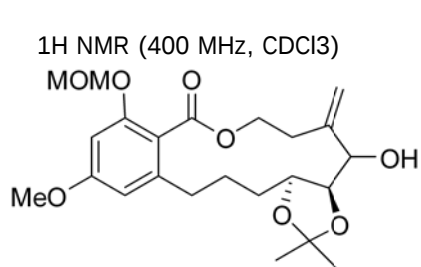
29.34

27.85

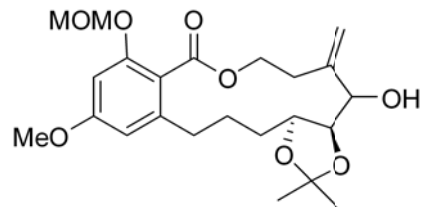
25.64

— 15.35





¹³C NMR (100 MHz, CDCl₃)



—168.00

—161.42

—155.78

~143.48

~142.11

—117.83

—115.59

~108.50

~107.97

—99.74

—95.04

~77.97

~77.35

—72.66

~61.52

~56.33

~55.51

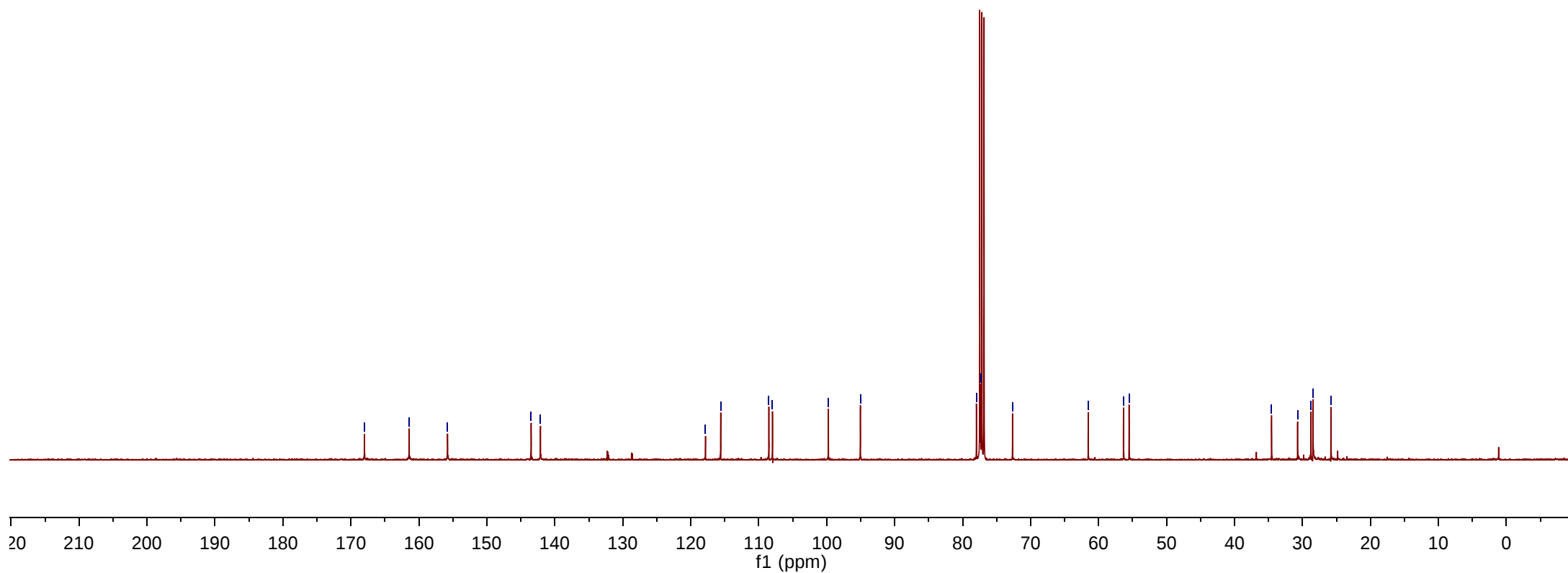
~34.55

~30.72

~28.78

~28.44

~25.82



Kinase profiling of exo-enone 5

S/N	Ambit Gene Symbol	Entrez Gene Symbol	% Control* at 10 μ M
1	AAK1	AAK1	99
2	ALK	ALK	100
3	AXL	AXL	68
4	BIKE	BMP2K	58
5	BMPR2	BMPR2	65
6	CDK11	CDC2L6	100
7	CDK2	CDK2	91
8	CDK3	CDK3	100
9	CDK4-cyclinD1	CDK4	100
10	CDK5	CDK5	100
11	CDK7	CDK7	66
12	CDK8	CDK8	100
13	CDK9	CDK9	100
14	CDKL1	CDKL1	84
15	CDKL2	CDKL2	17
16	CDKL3	CDKL3	61
17	CDKL5	CDKL5	100
18	DYRK1B	DYRK1B	74
19	EGFR(L858R)	EGFR	91
20	ERK1	MAPK3	90
21	ERK2	MAPK1	91
22	FGFR2	FGFR2	100
23	FGFR3	FGFR3	100
24	FLT1	FLT1	1.8
25	FLT3	FLT3	1.6
26	FLT4	FLT4	0.5
27	GAK	GAK	2.6
28	GSK3A	GSK3A	100
29	GSK3B	GSK3B	76
30	KIT	KIT	0.4
31	KIT(D816V)	KIT	9.2
32	MAPKAPK2	MAPKAPK2	95
33	MAPKAPK5	MAPKAPK5	43
34	MEK1	MAP2K1	0.65
35	MEK2	MAP2K2	1.3
36	MEK3	MAP2K3	22
37	MEK4	MAP2K4	28
38	MEK5	MAP2K5	0.8
39	MEK6	MAP2K6	37
40	MET	MET	100
41	MKNK1	MKNK1	79
42	MKNK2	MKNK2	1
43	NLK	NLK	62
44	PDGFRA	PDGFRA	0.45
45	PDGFRB	PDGFRB	0
46	PLK1	PLK1	97
47	PLK3	PLK3	80

48	PLK4	PLK4	54
49	PRKCE	PRKCE	68
50	PRKD1	PRKD1	50
51	PRKD2	PRKD2	60
52	PRKD3	PRKD3	64
53	PRP4	PRPF4B	100
54	RSK1(Kin.Dom.2-C-terminal)	RPS6KA1	91
55	RSK3(Kin.Dom.2-C-terminal)	RPS6KA2	78
56	RSK4(Kin.Dom.2-C-terminal)	RPS6KA6	62
57	STK36	STK36	10
58	TAK1	MAP3K7	13
59	TGFBR1	TGFBR1	100
60	TGFBR2	TGFBR2	3.6
61	VEGFR2	KDR	4.6
62	ZAK	ZAK	39

*DMSO used as a negative control (100%).