(IPr)CuF-Catalyzed *α*-Site Regiocontrolled *trans*-Hydrofluorination of Ynamides

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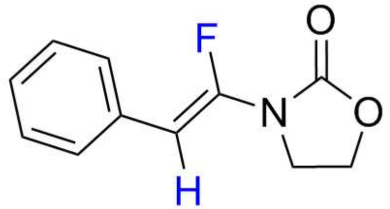
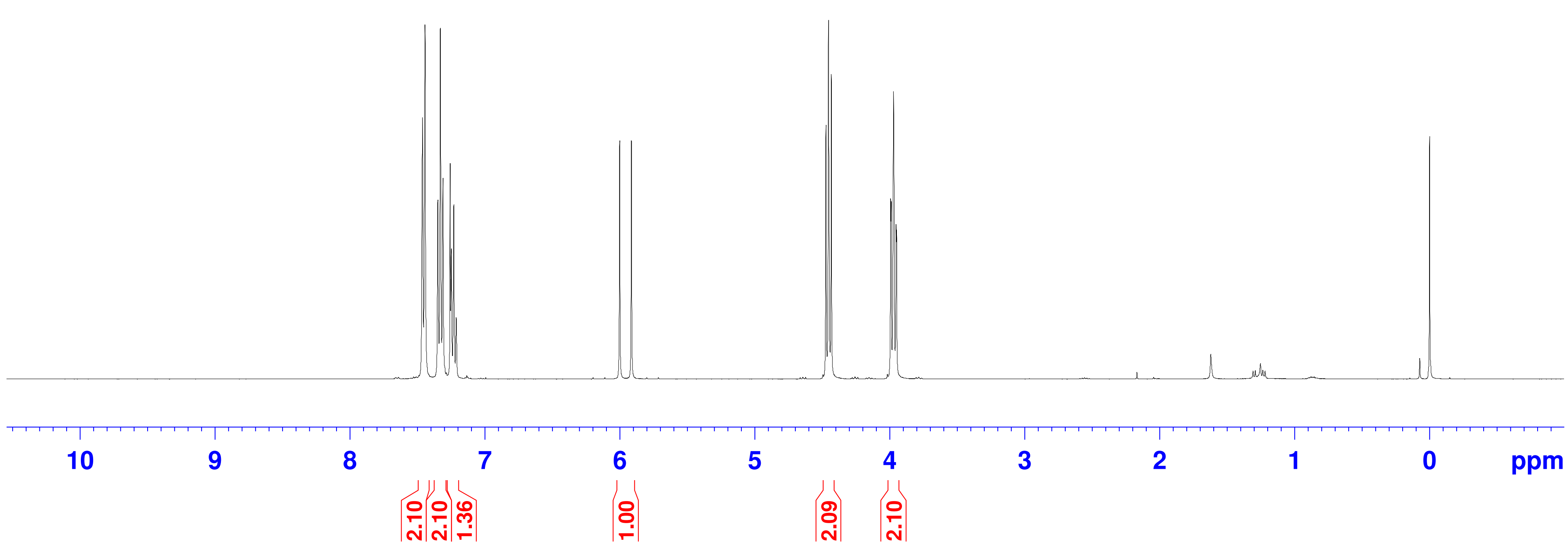
*E-mails: hegk@njtech.edu.cn; zhuhj@njtech.edu.cn.

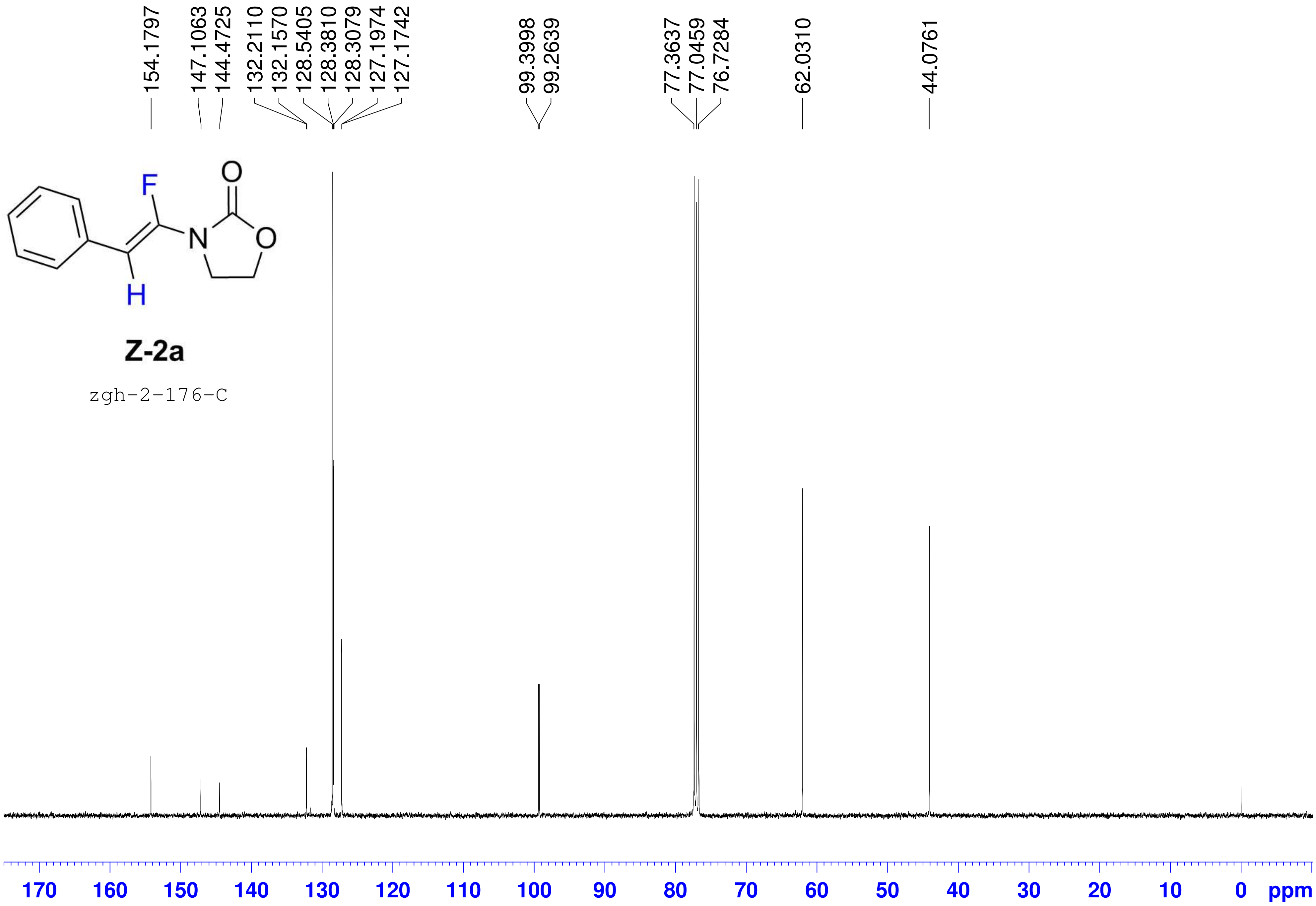
Spectra of compounds *Z*-2a-4o

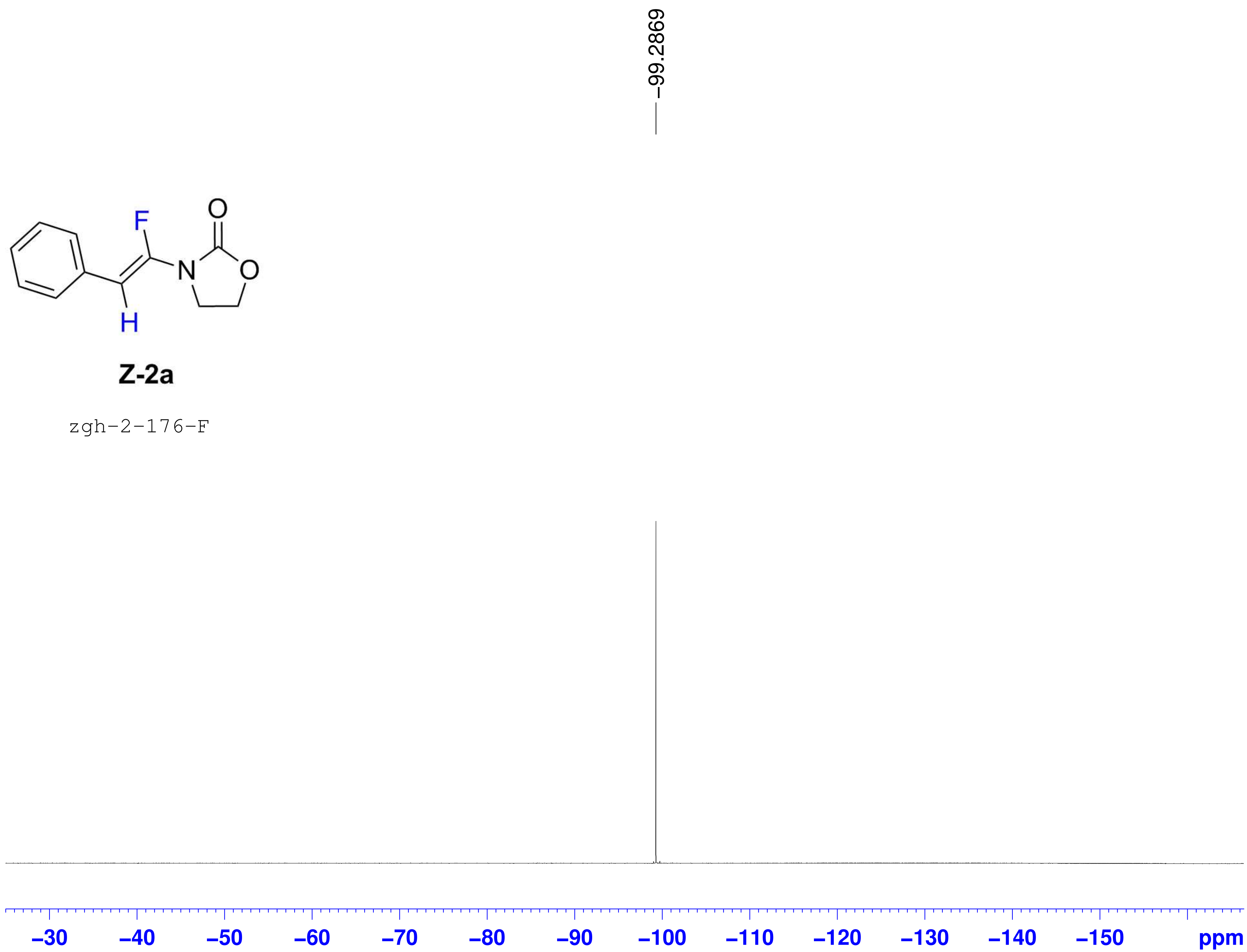


Z-2a

zgh-2-176-H




154.1797
147.1063
144.4725
132.2110
132.1570
128.5405
128.3810
128.3079
127.1974
127.1742
99.3998
99.2639
77.3637
77.0459
76.7284
62.0310
44.0761
F
O
N
O
H
Z-2a
zgh-2-176-C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



F
H
O
N
O
Z-2a
zgh-2-176-F
-99.2869
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-50
-60
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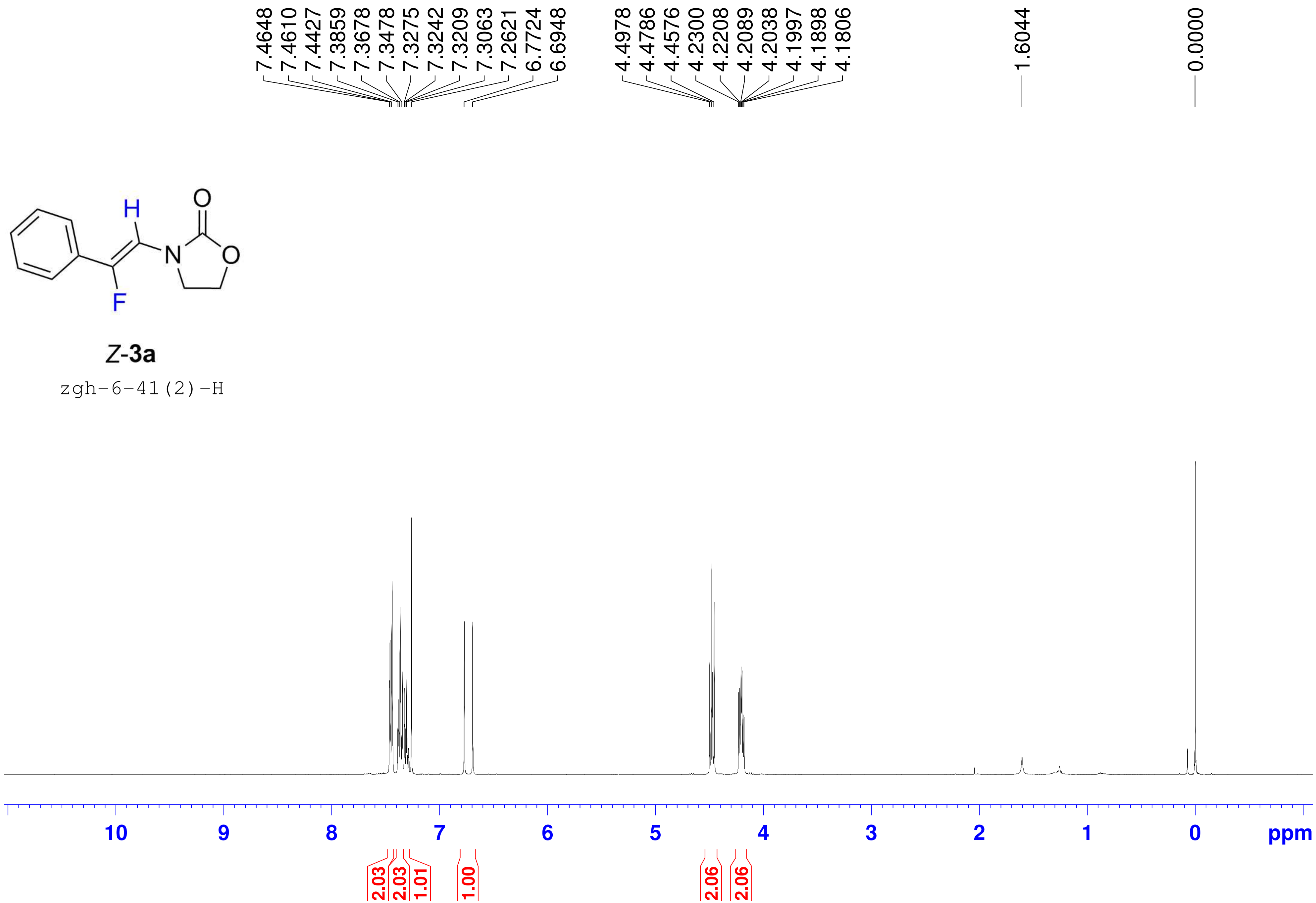
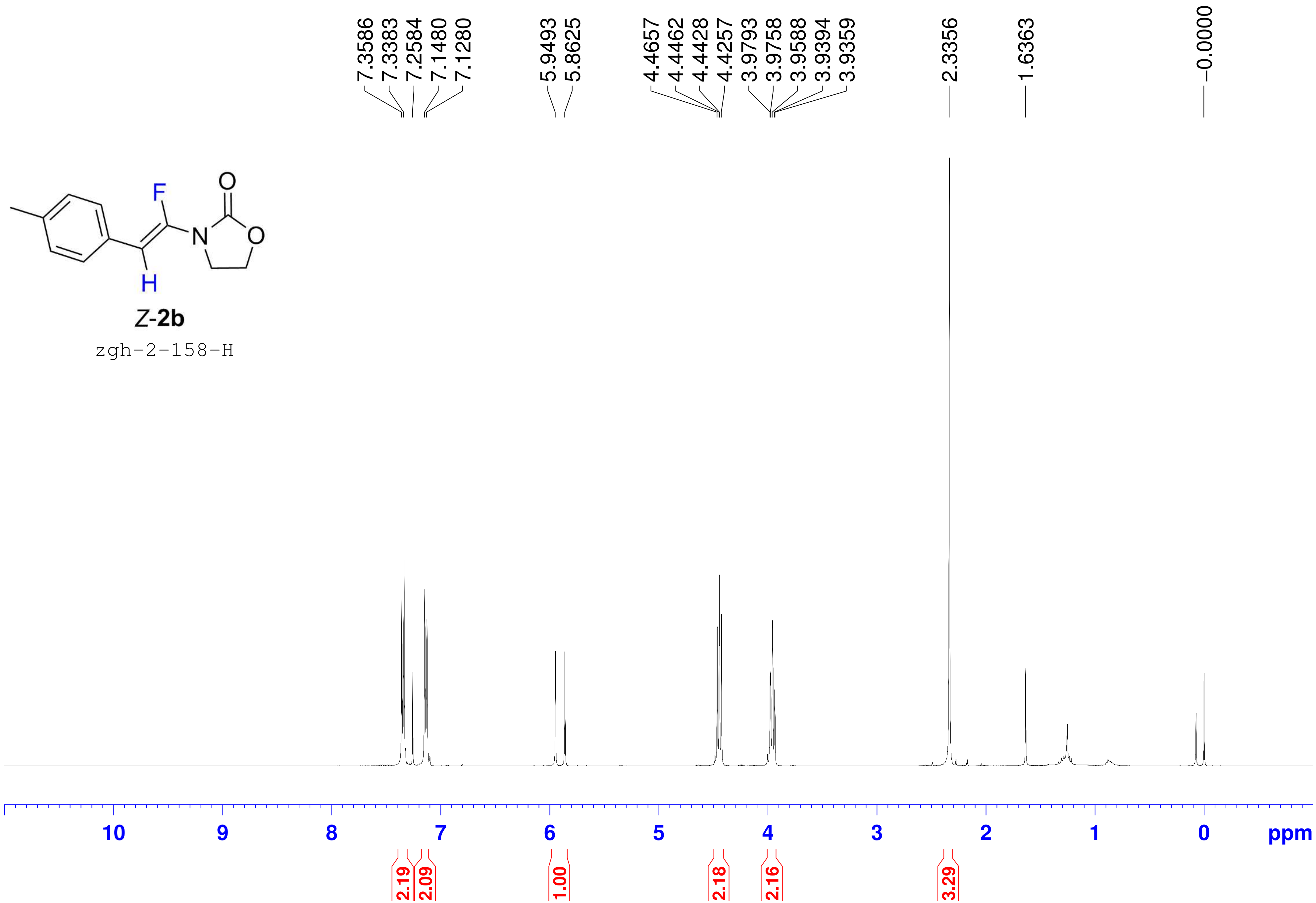
-130
-140
-150
ppm



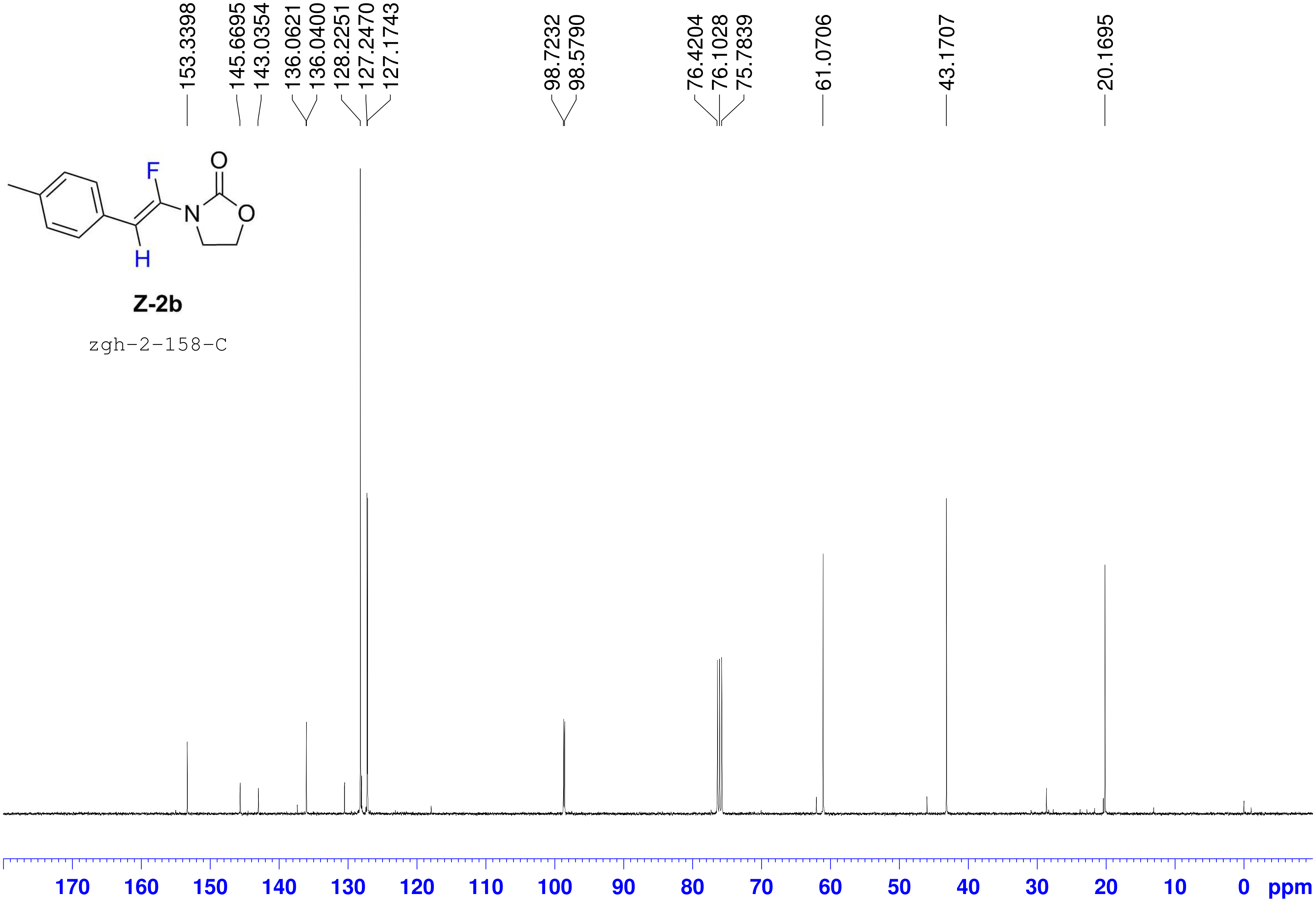
Z-**3a**

zgh-6-41(2)-H



Z-**2b**

zgh-2-158-H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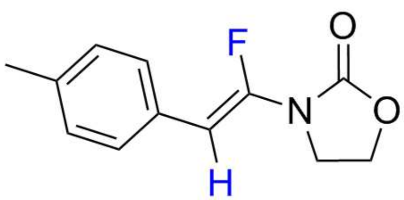
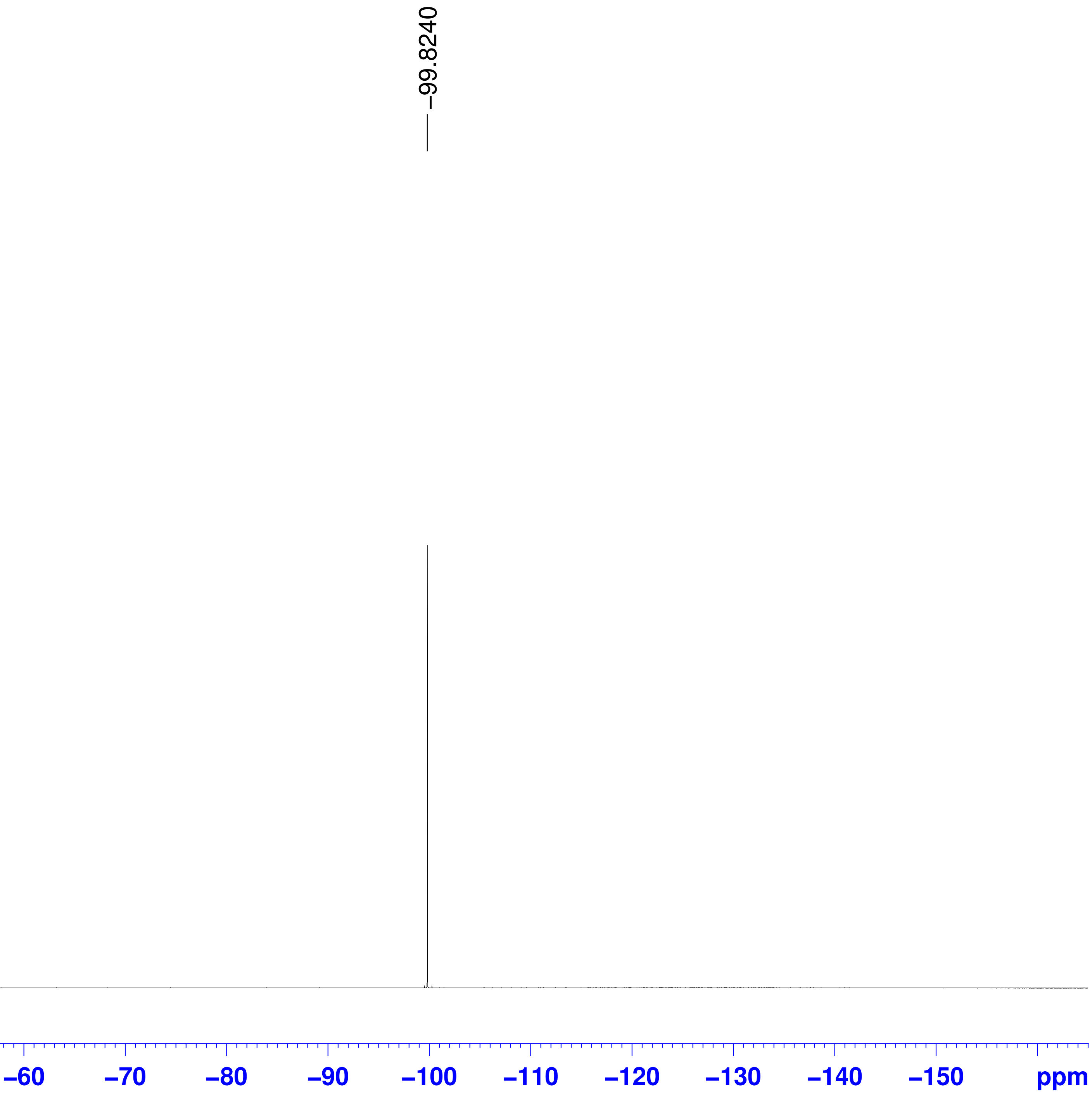
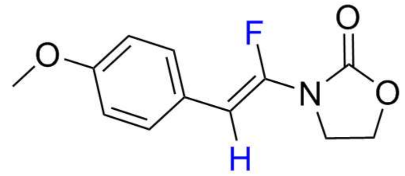
143.0354
136.0621
136.0400
128.2251
127.2470
127.1743
98.7232
98.5790
76.4204
76.1028
75.7839
61.0706
43.1707
20.1695
F
O
N
O
H
Z-2b
zgh-2-158-C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



Z-2b

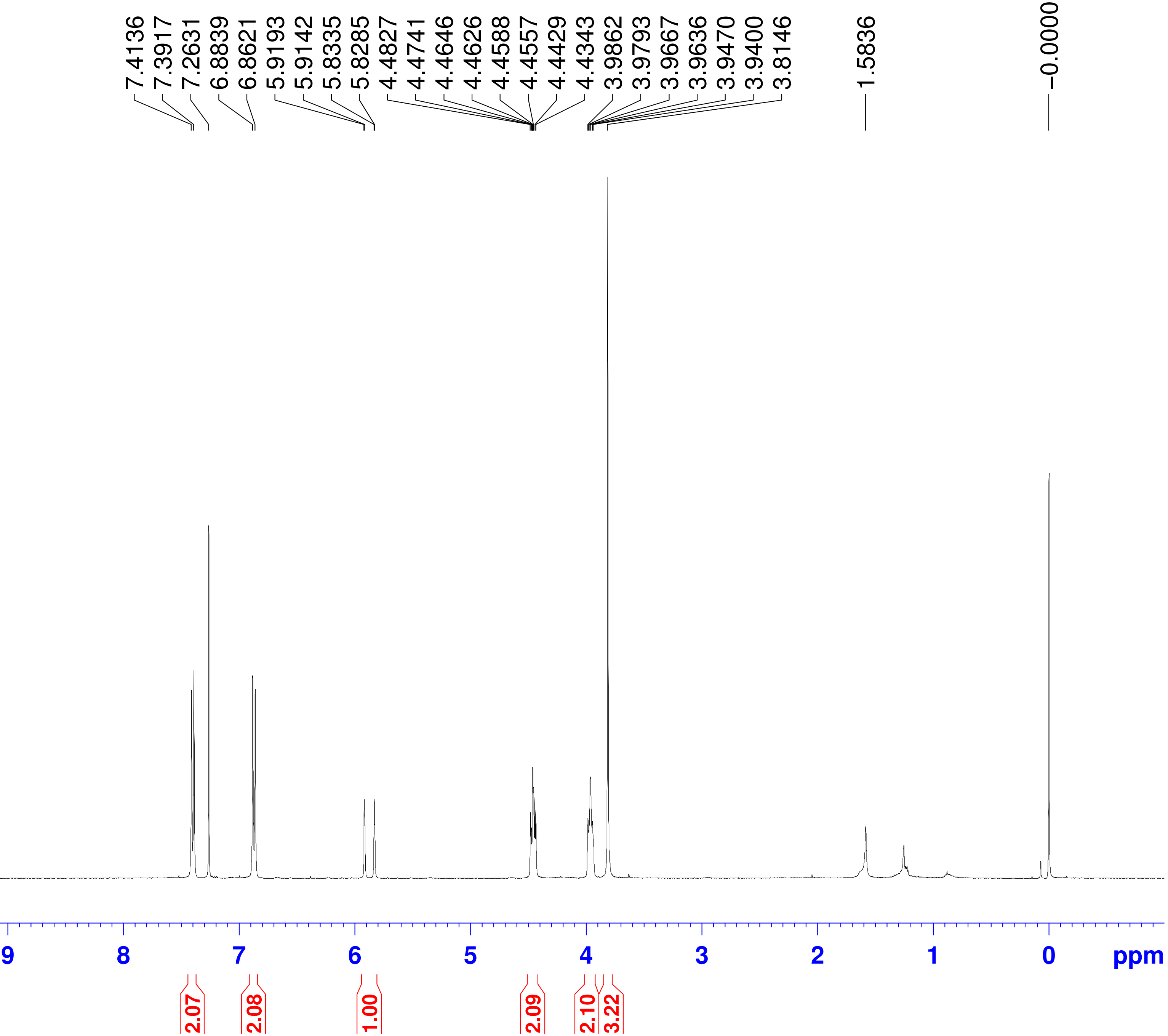
zgh-2-158-F

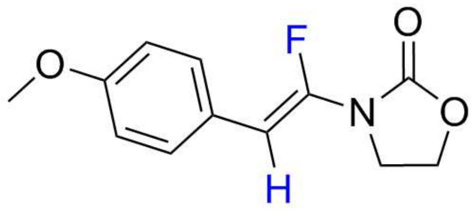




Z-**2c**

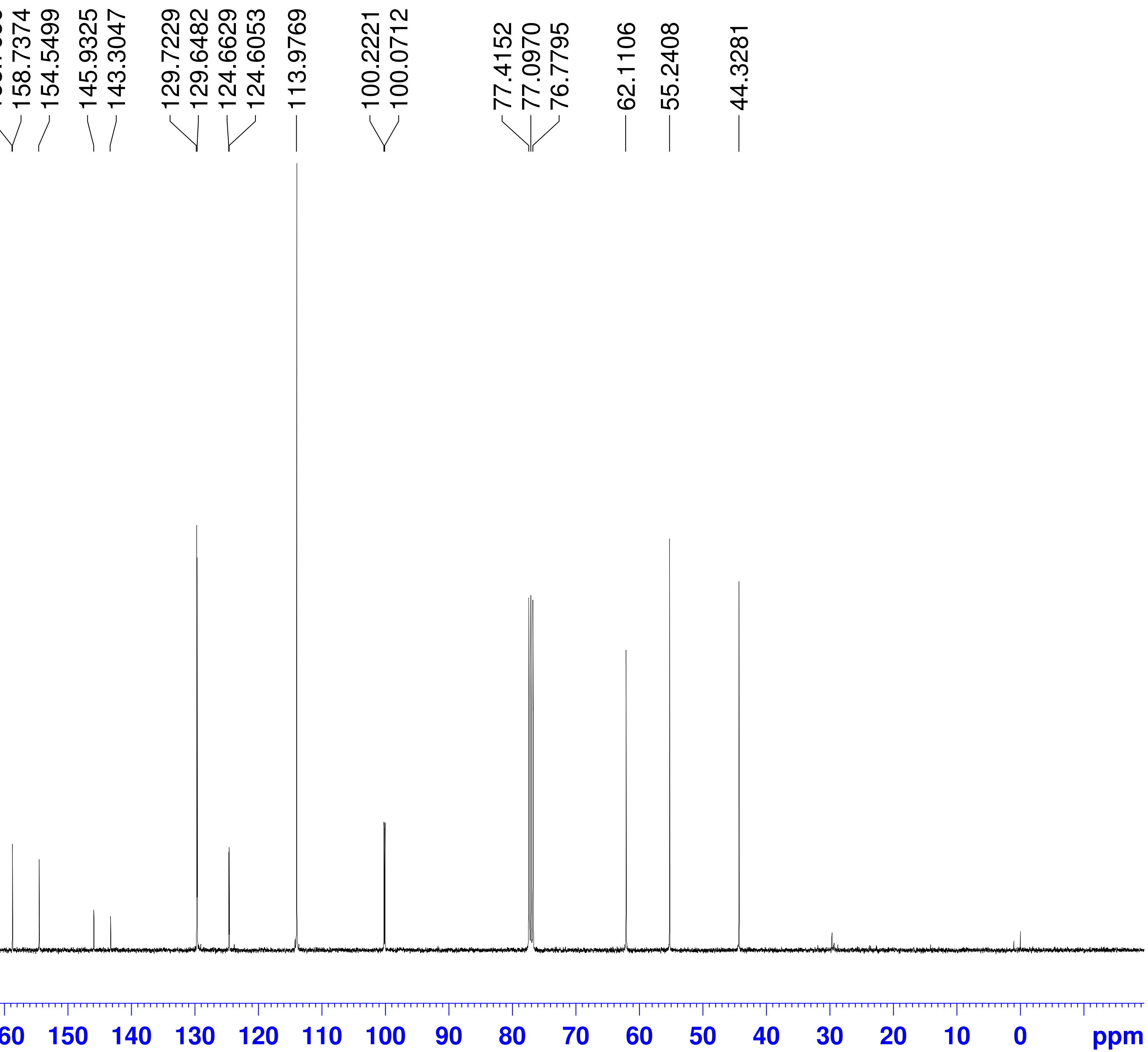
zgh-2-178-H

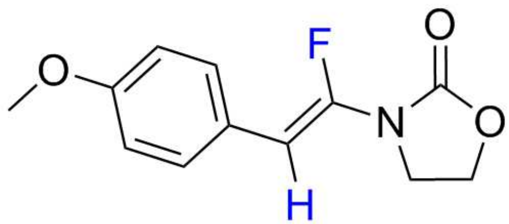




Z-2c

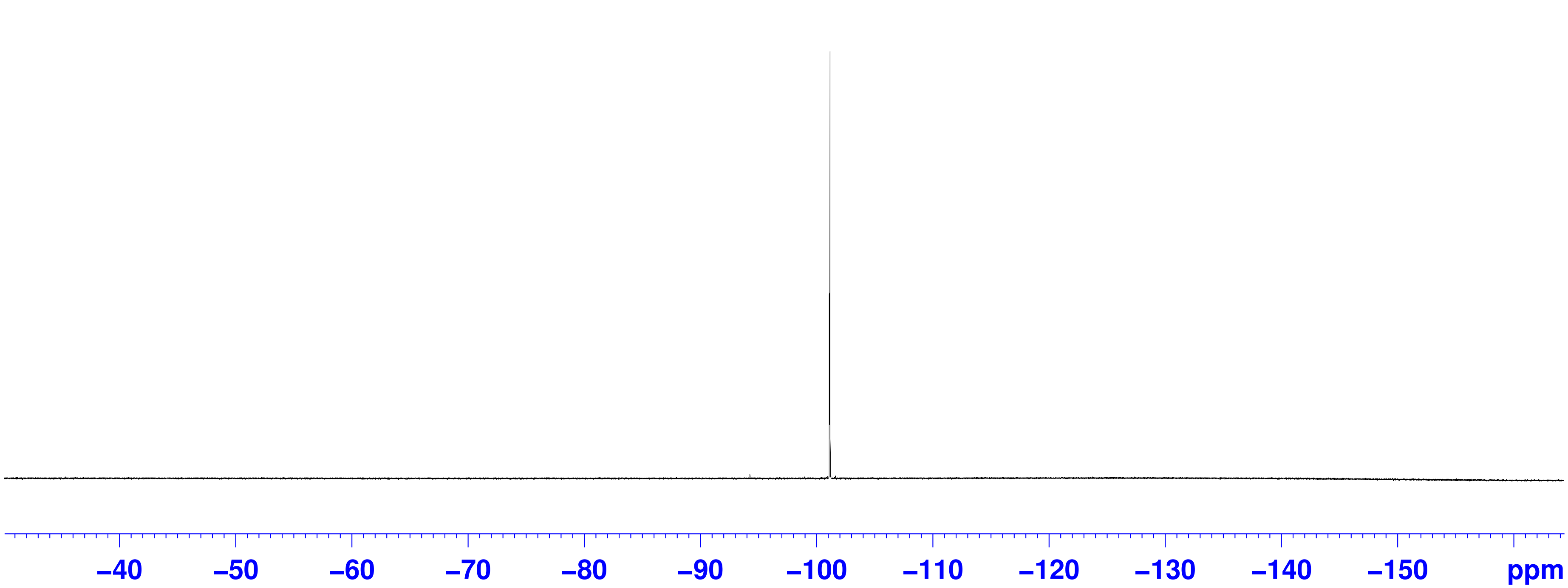
zgh-2-178-C

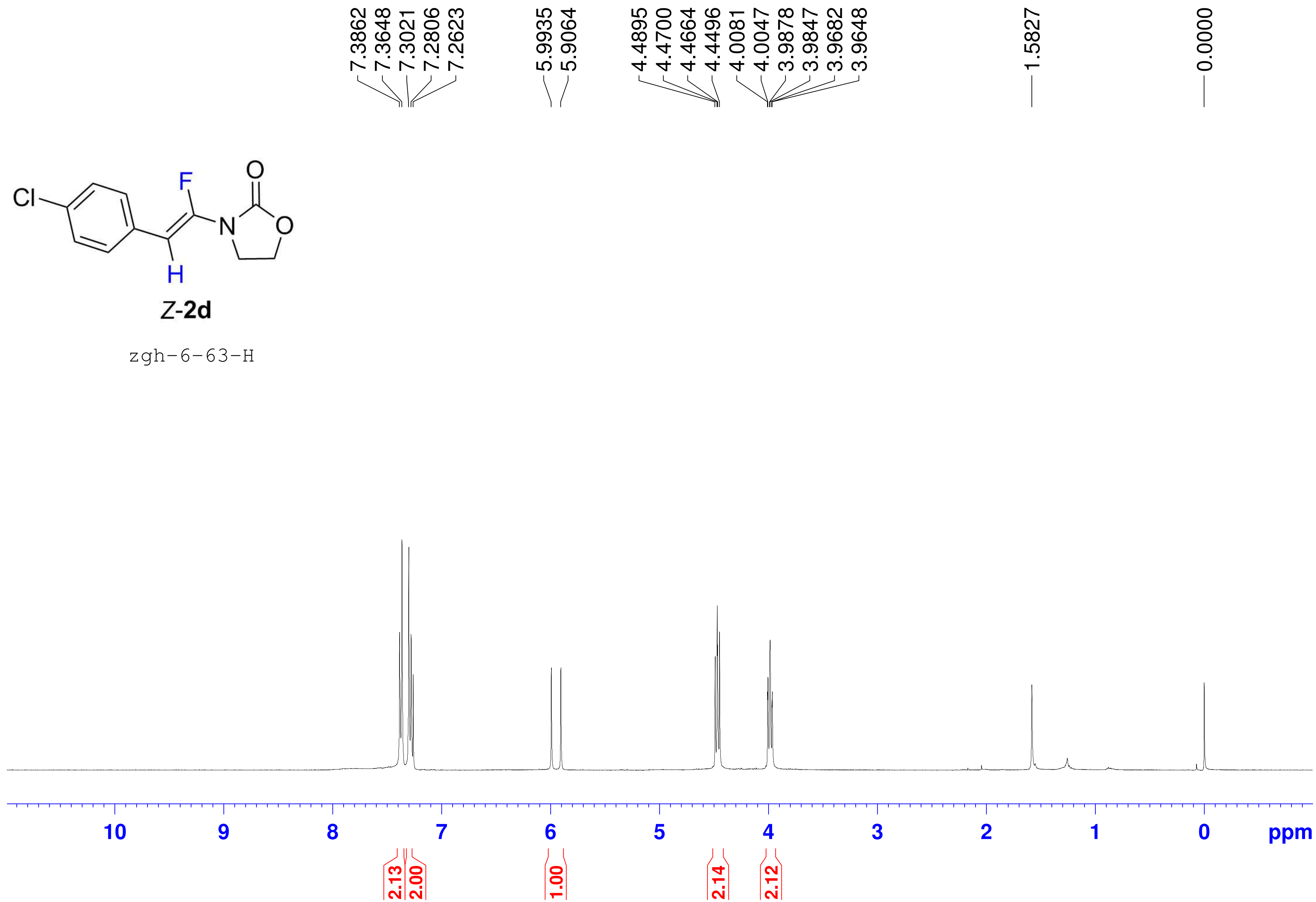




Z-2c

zgh-2-178-F





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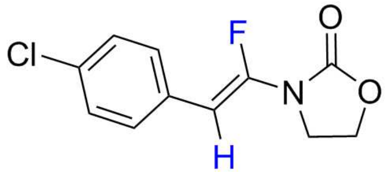
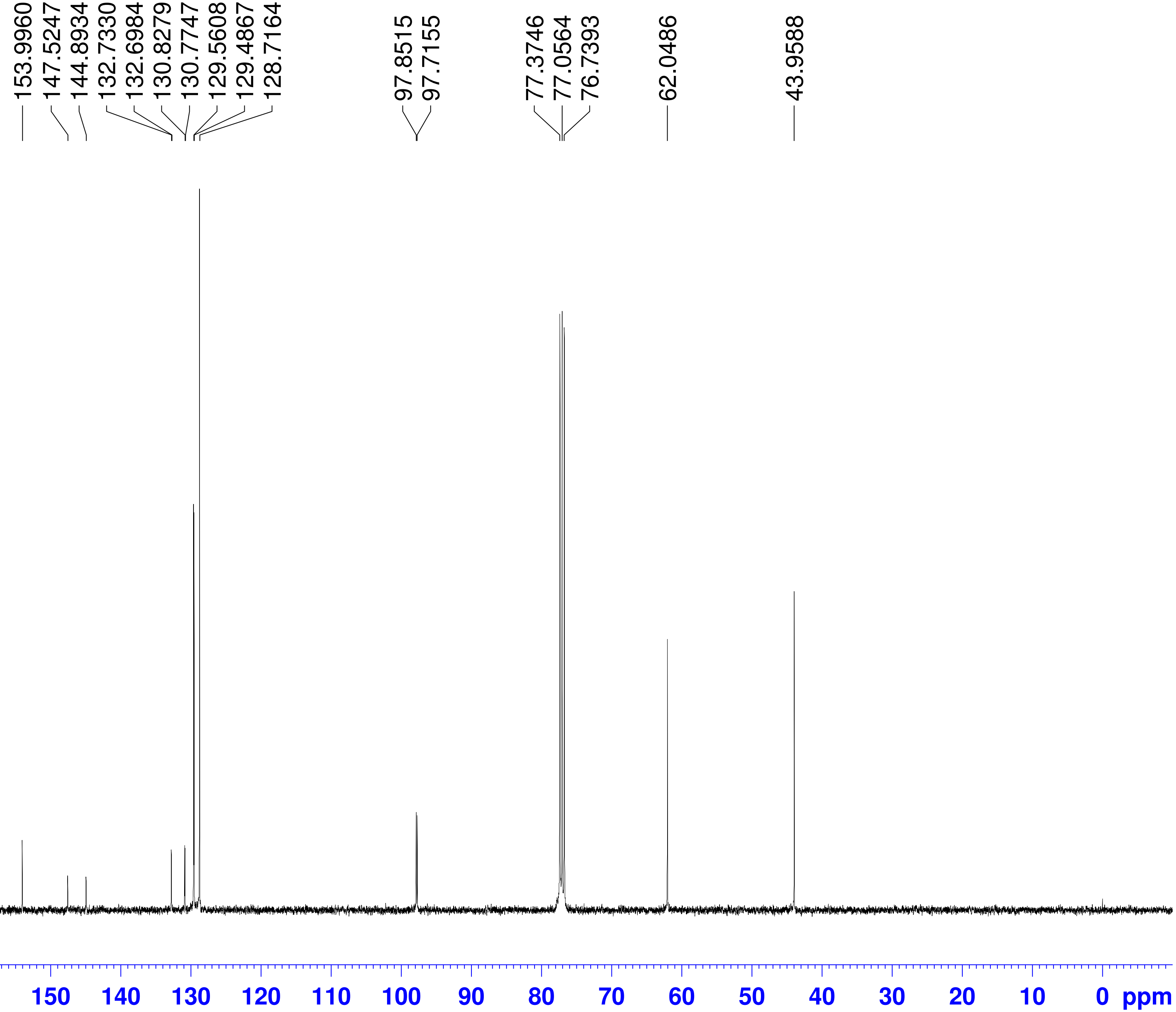
7.3648
7.3021
7.2806
7.2623
5.9935
5.9064
4.4895
4.4700
4.4664
4.4496
4.0081
4.0047
3.9878
3.9847
3.9682
3.9648
1.5827
0.0000
Cl
F
O
N
O
H
Z-2d
zgh-6-63-H
10
9
8
7
6
5
4
3
2
1
0
ppm
2.13
2.00
1.00
2.14
2.12



Z-**2d**

zgh-6-63-C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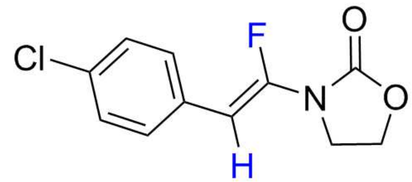
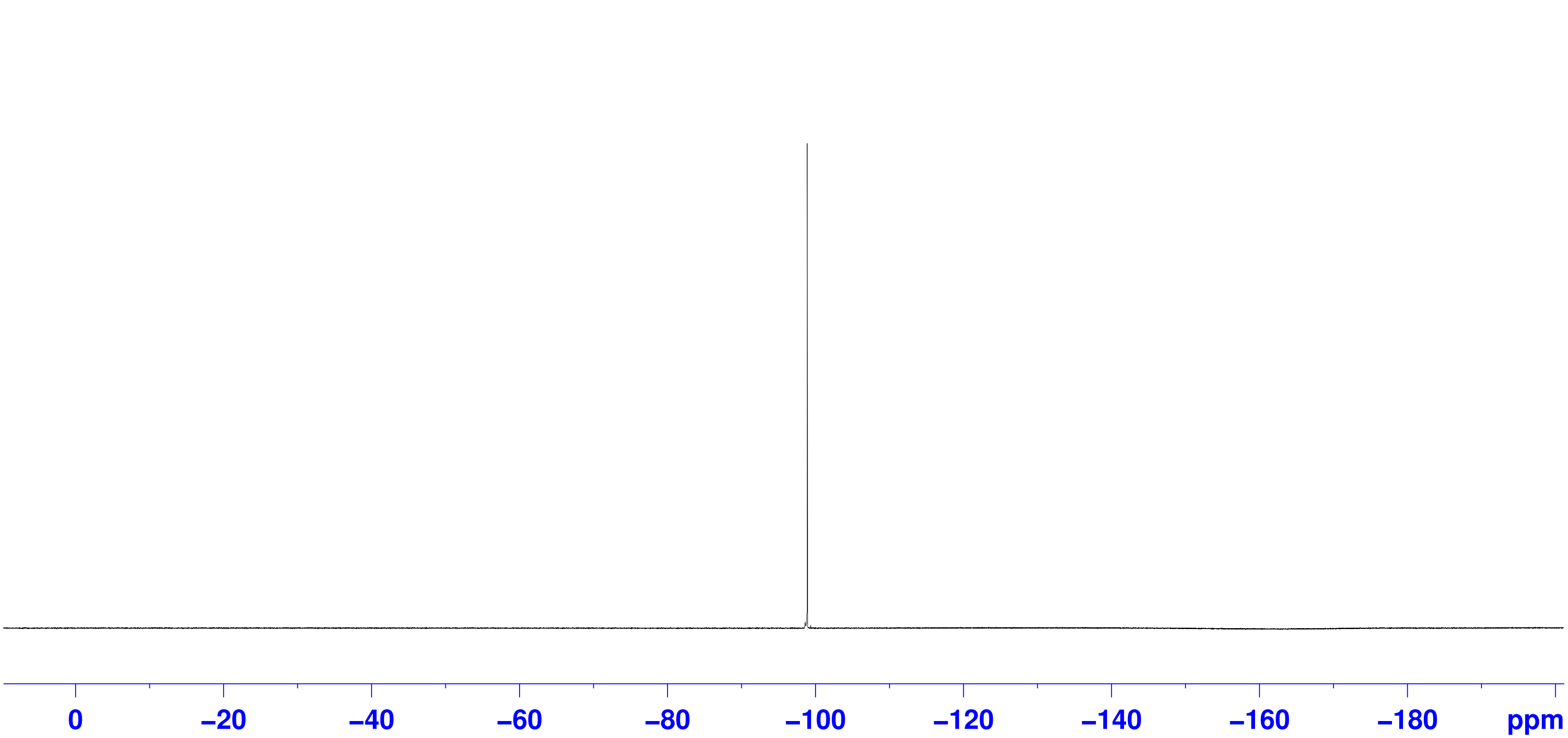
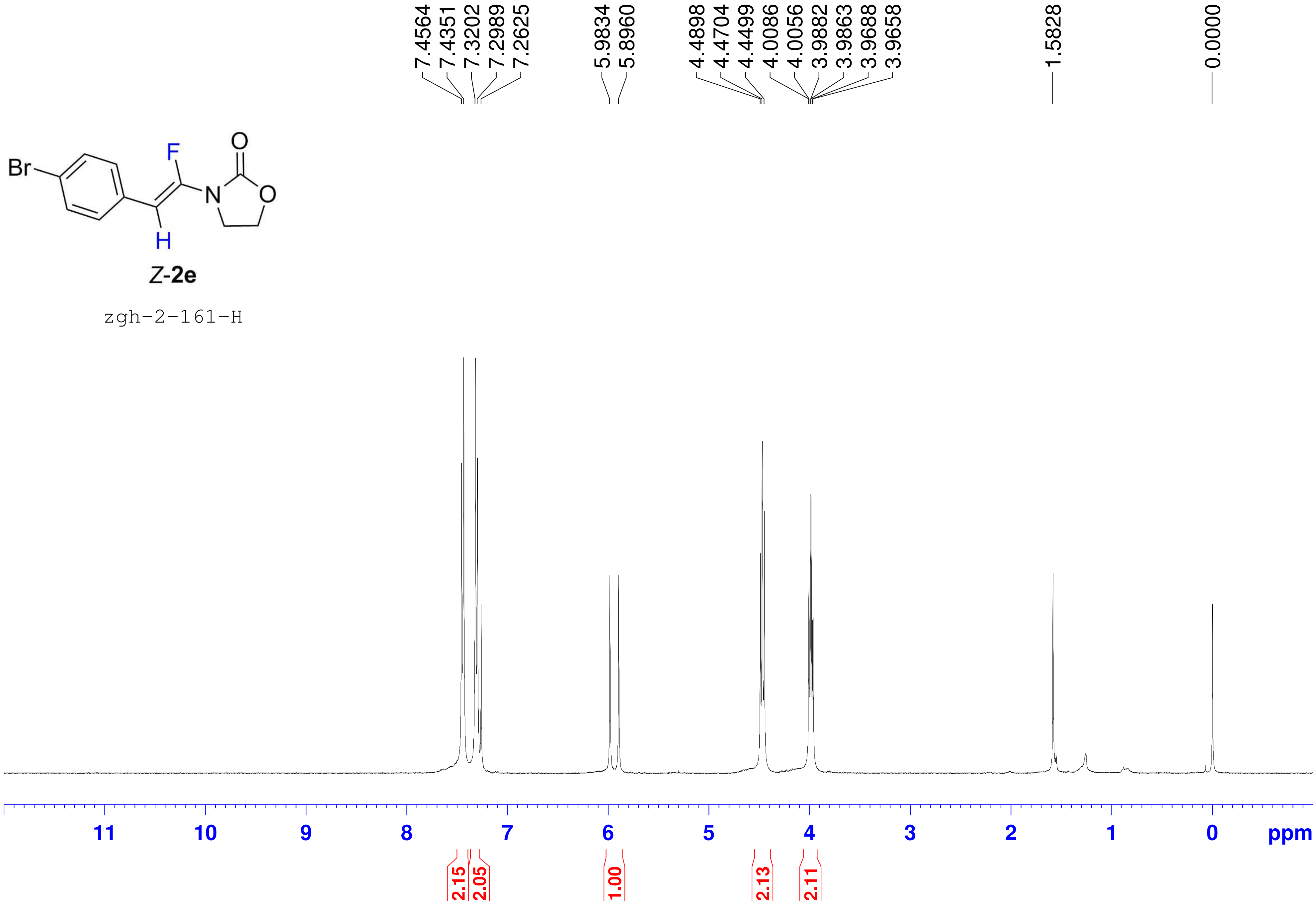
147.5247
144.8934
132.7330
132.6984
130.8279
130.7747
129.5608
129.4867
128.7164
97.8515
97.7155
77.3746
77.0564
76.7393
62.0486
43.9588
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



Z-**2d**

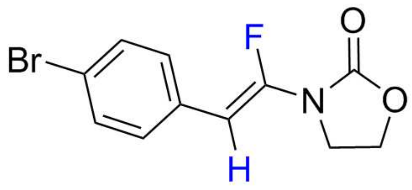
zgh-6-63-F





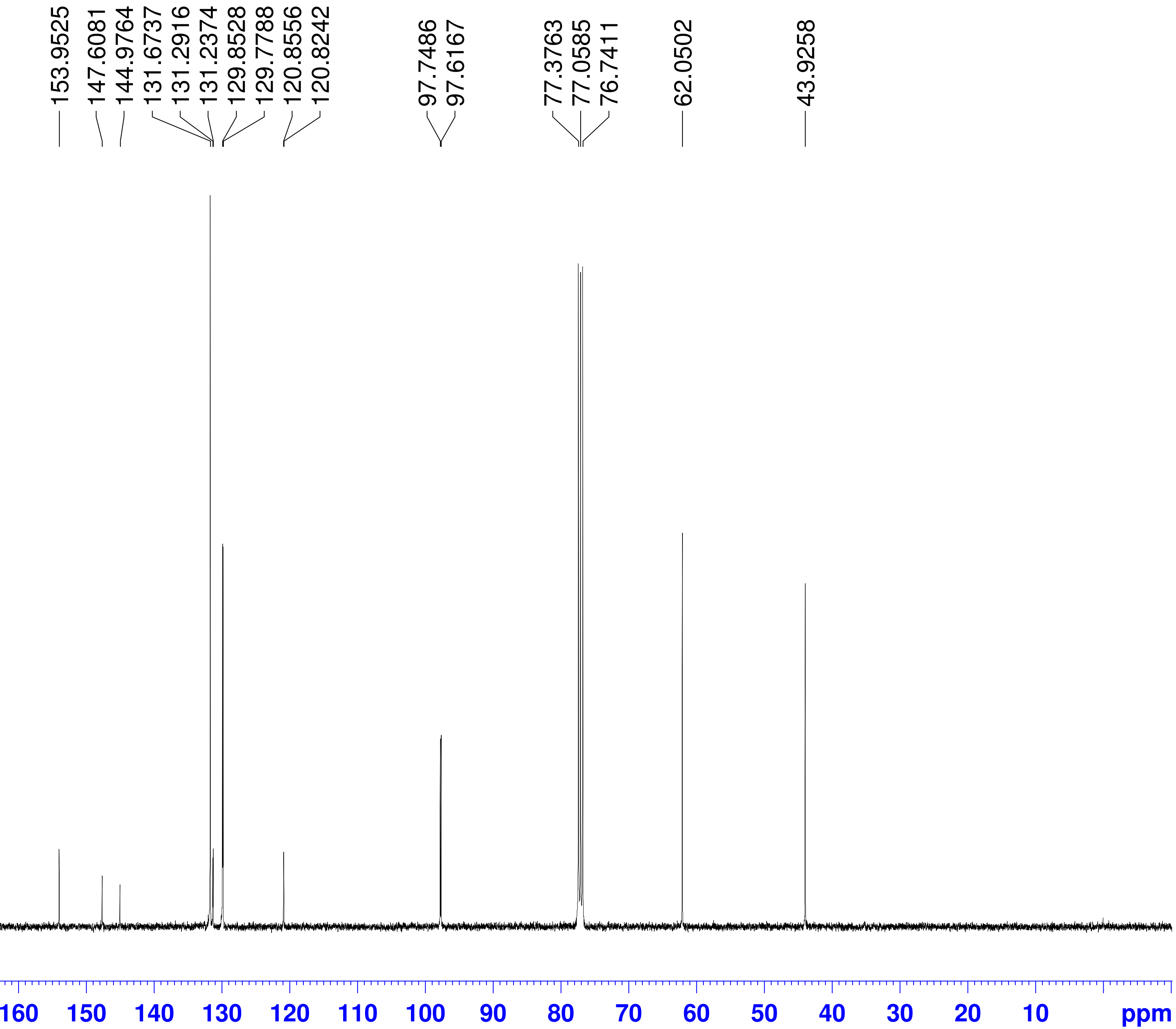
Z-**2e**

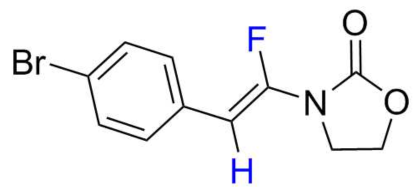
zgh-2-161-H



Z-**2e**

zgh-2-161-C





Z-**2e**

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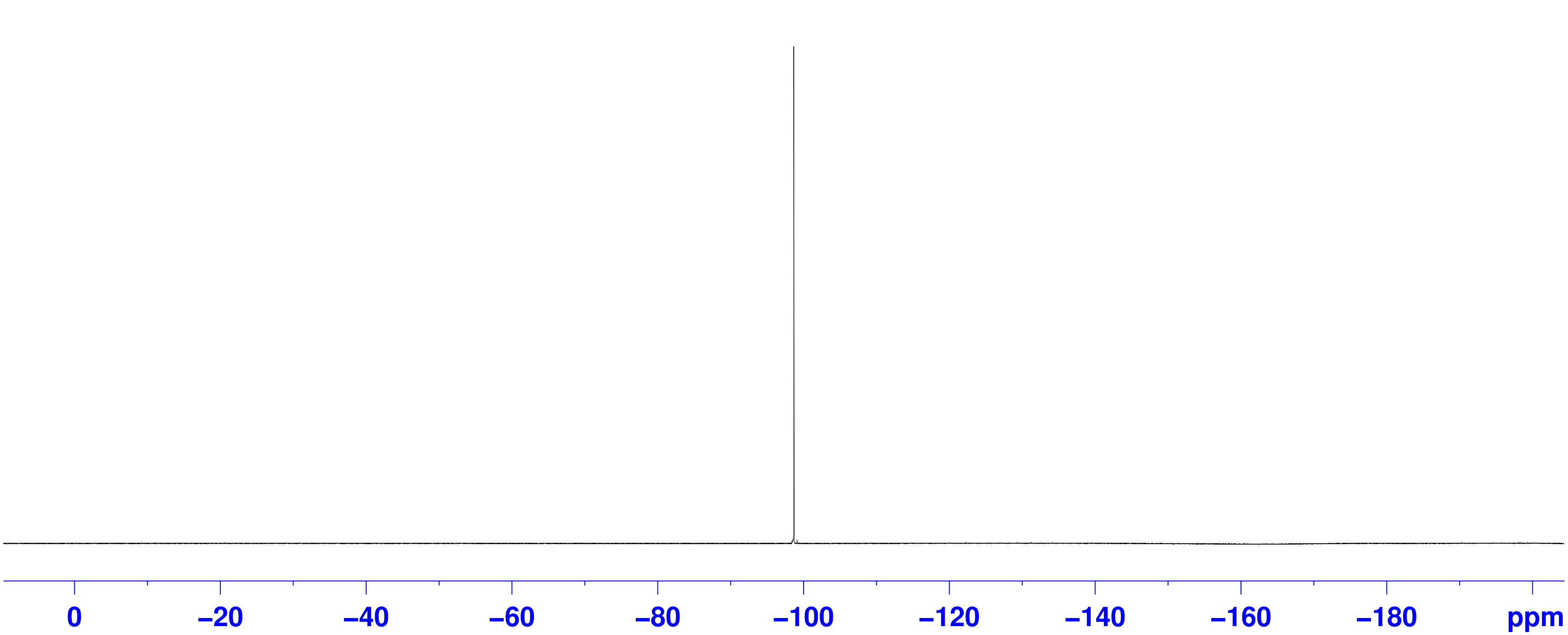
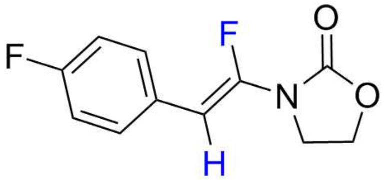
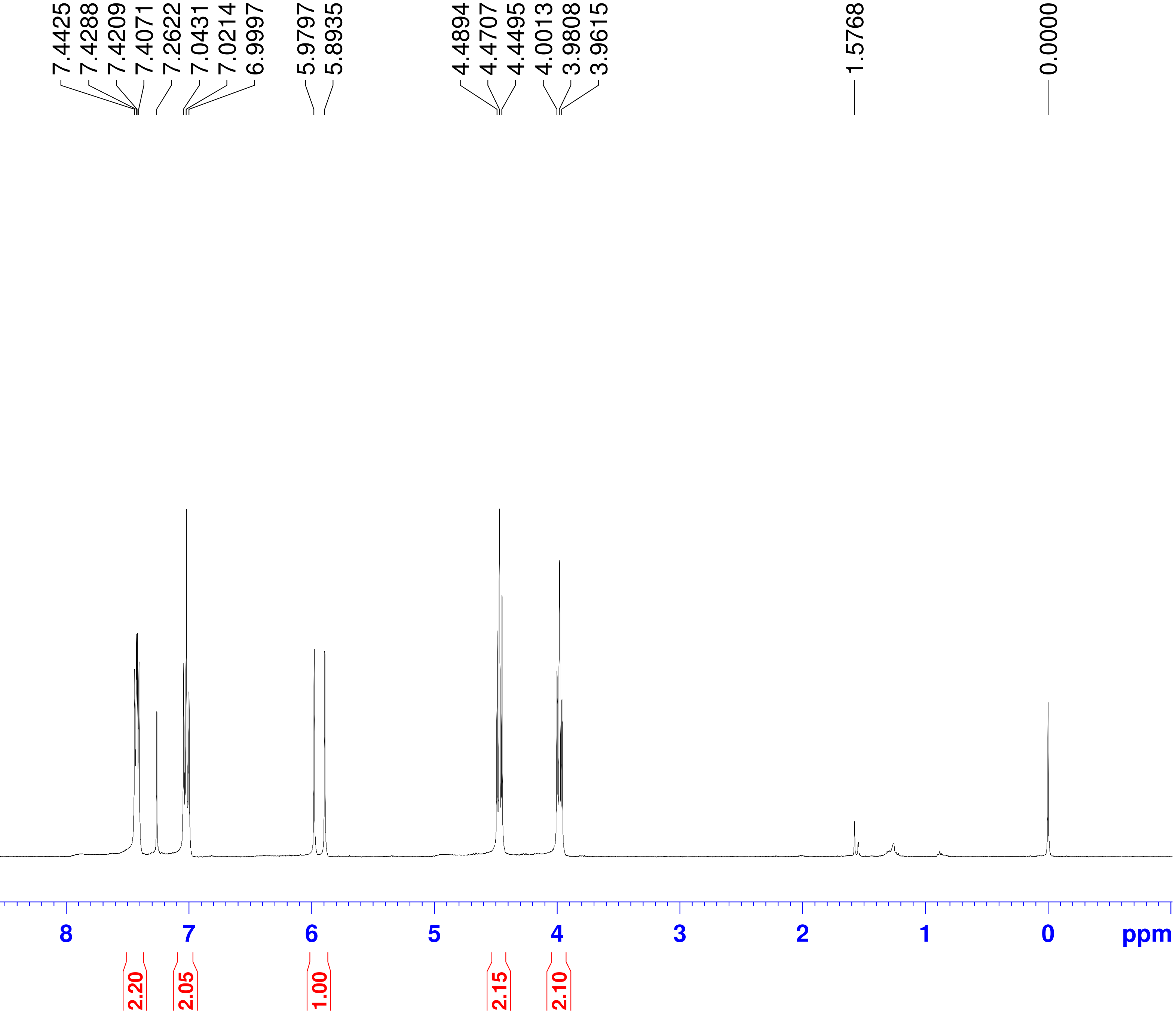




Z-**2f**

zgh-6-64-H



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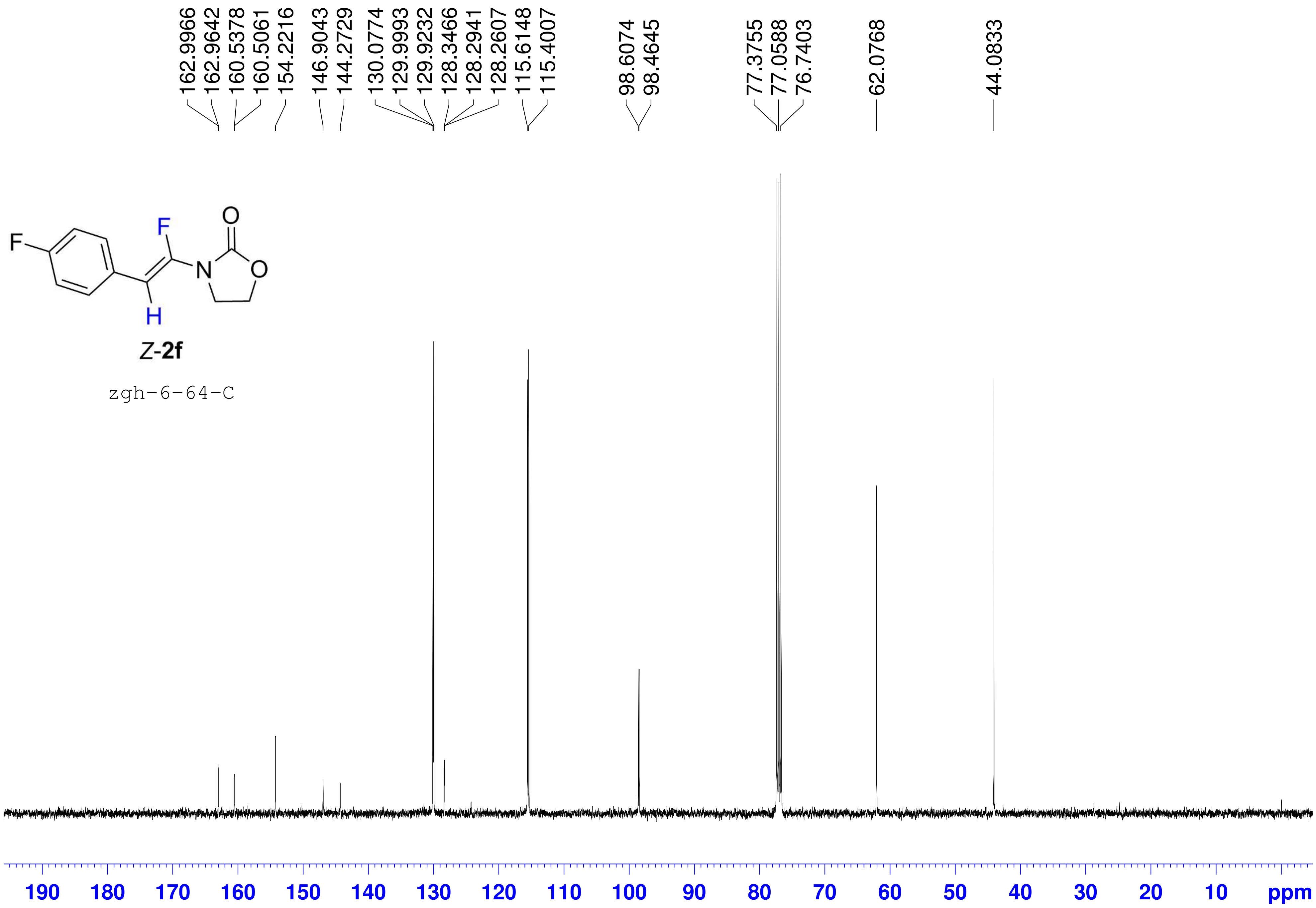
7.4209
7.4071
7.2622
7.0431
7.0214
6.9997
5.9797
5.8935
4.4894
4.4707
4.4495
4.0013
3.9808
3.9615
1.5768
0.0000
10
9
8
7
6
5
4
3
2
1
0
ppm
2.20
2.05
1.00
2.15
2.10



Z-**2f**

zgh-6-64-C

162.9966
162.9642
160.5378
160.5061
154.2216
146.9043
144.2729
130.0774
129.9993
129.9232
128.3466
128.2941
128.2607
115.6148
115.4007
98.6074
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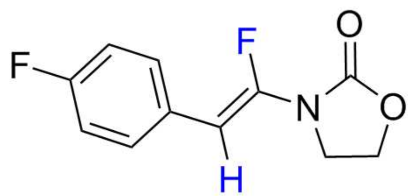
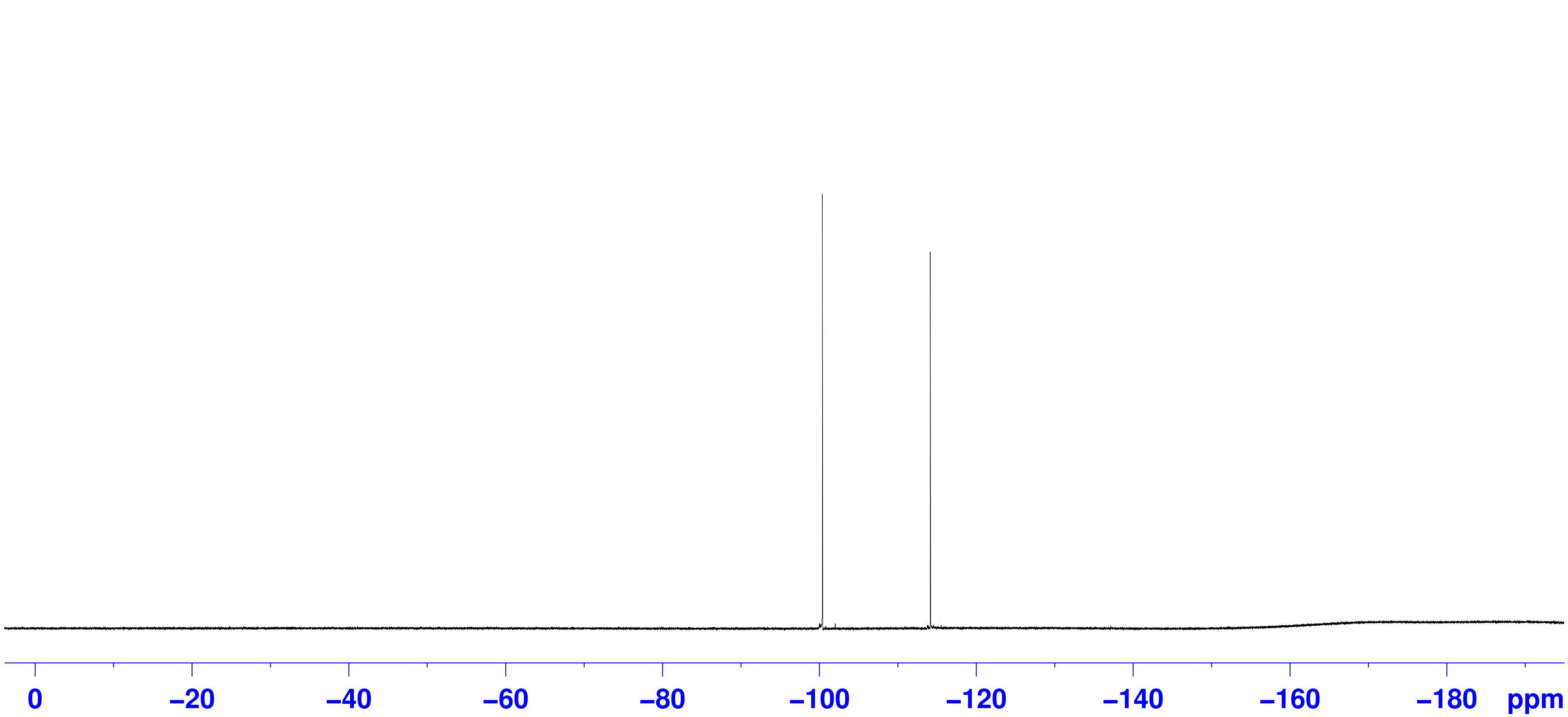
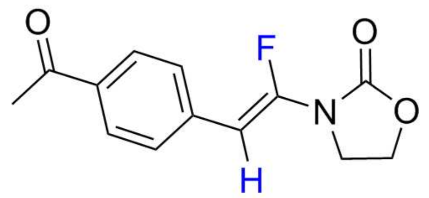
77.0588
76.7403
62.0768
44.0833
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



Z-**2f**

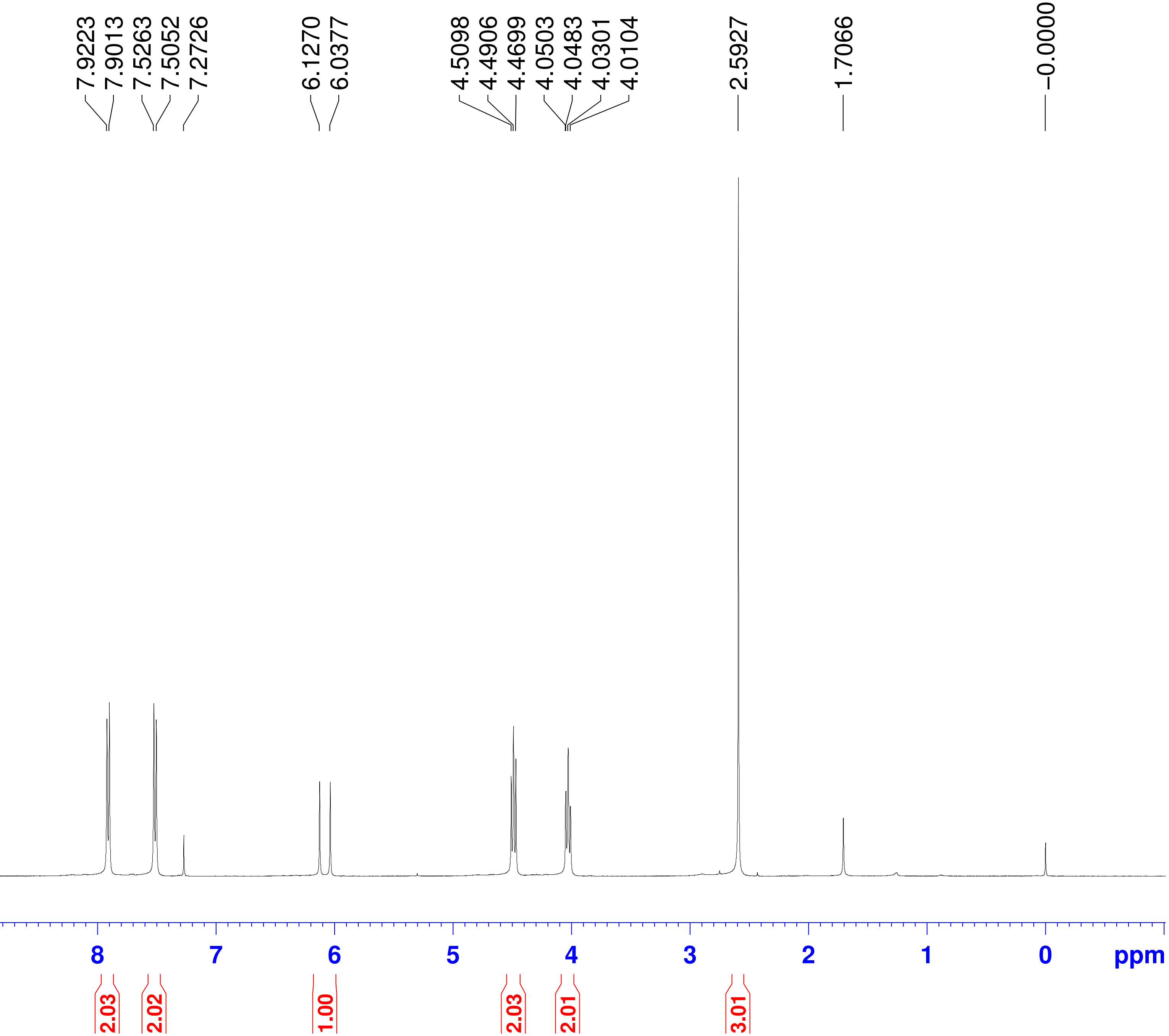
zgh-6-64-F

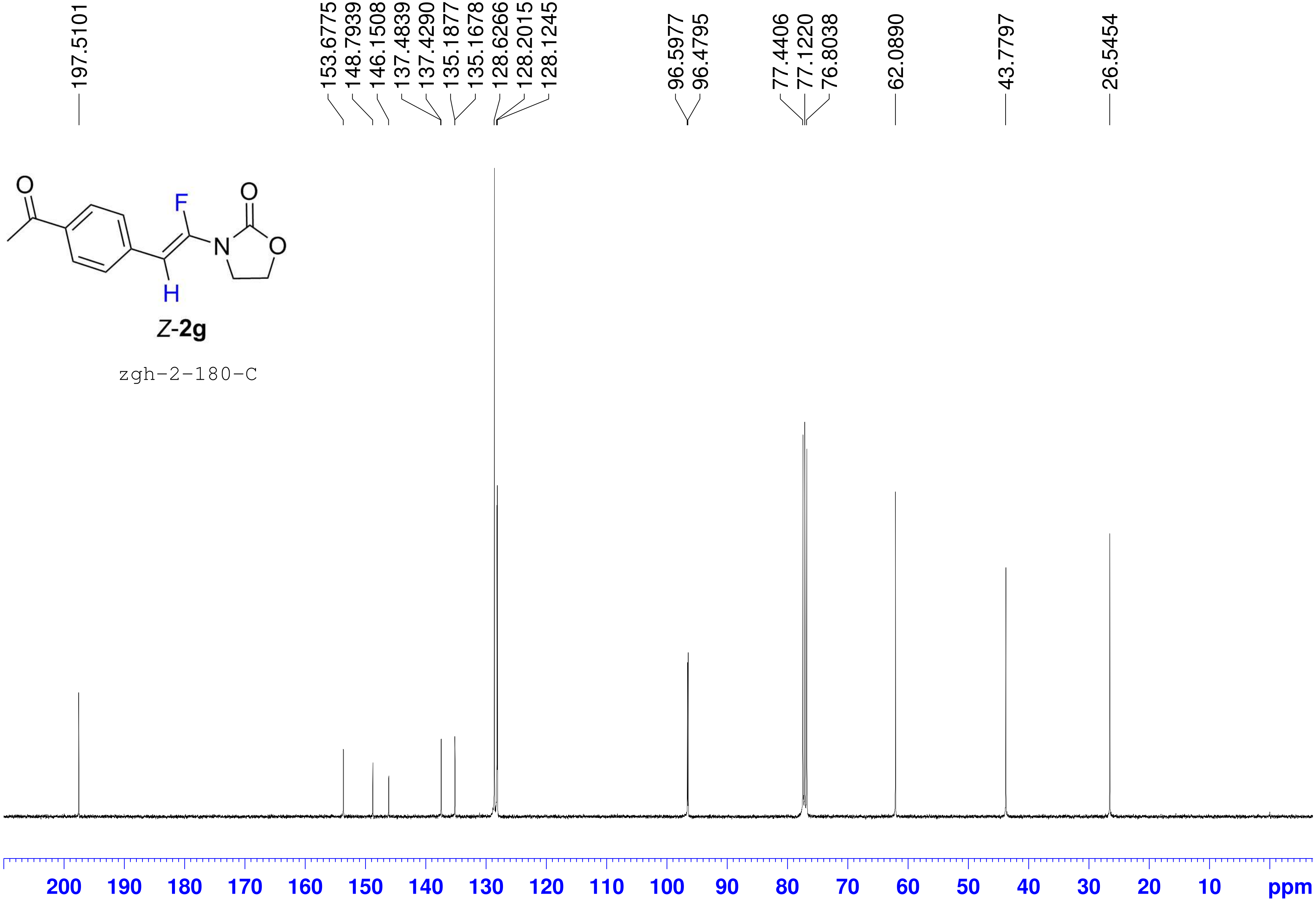




Z-**2g**

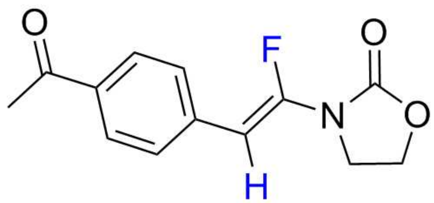
zgh-2-180-H





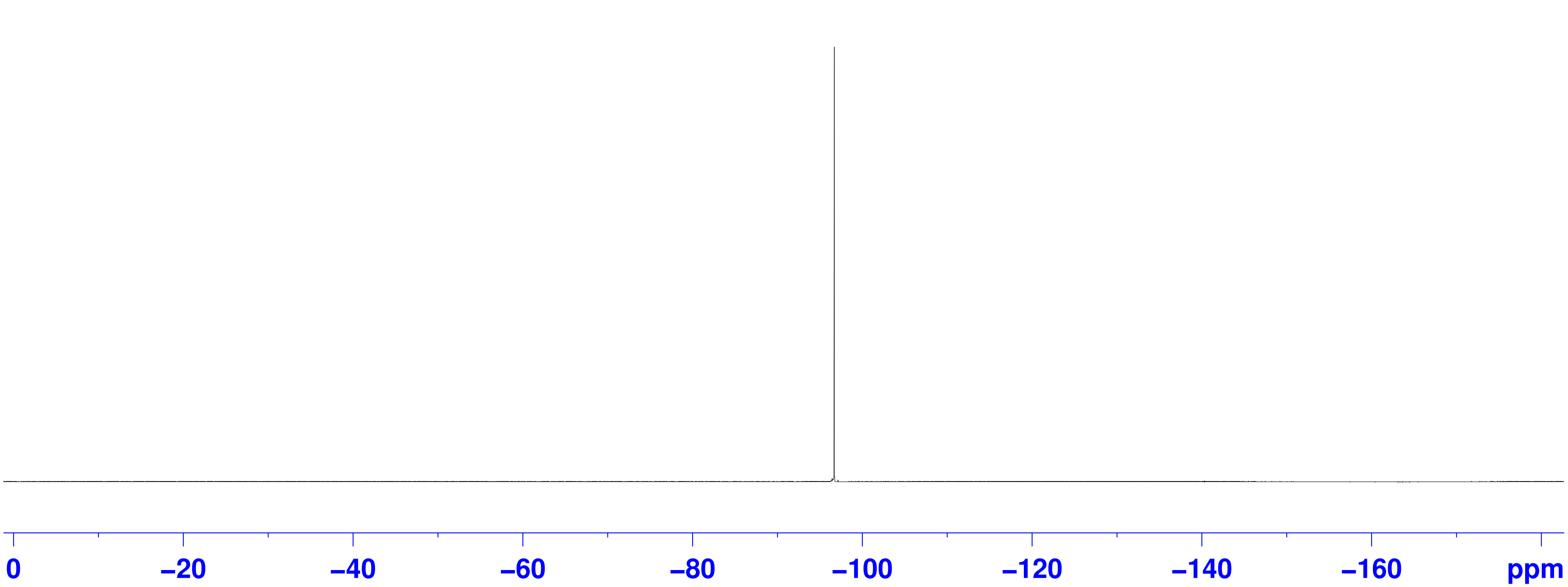
Z-**2g**

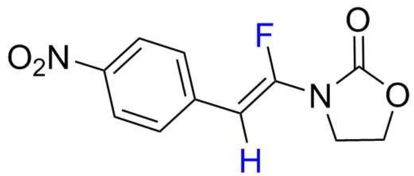
zgh-2-180-C



Z-**2g**

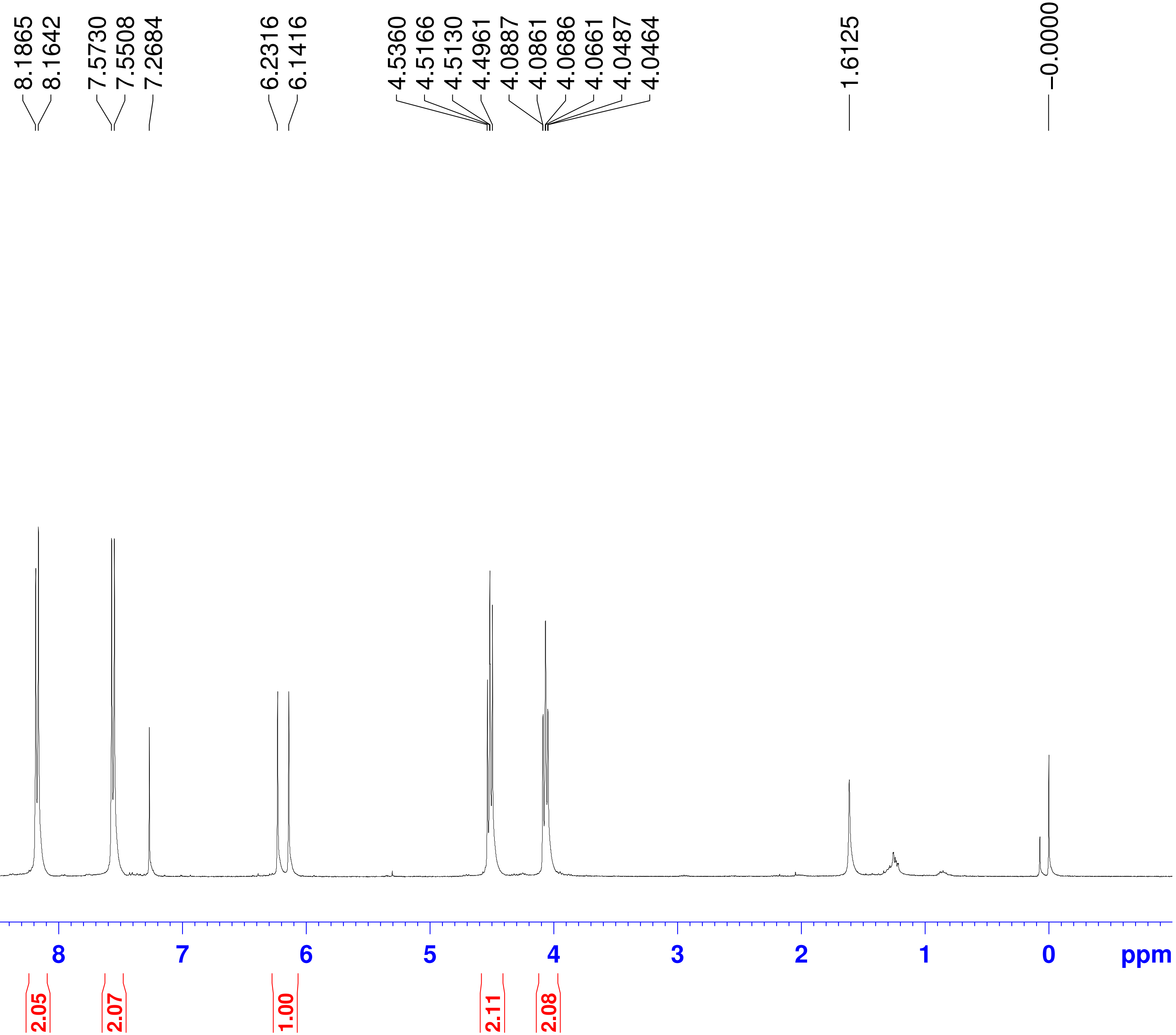
zgh-2-180-F

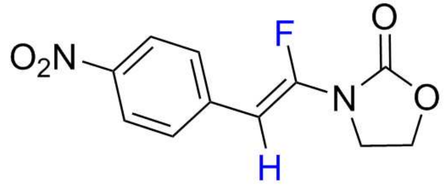




Z-**2h**

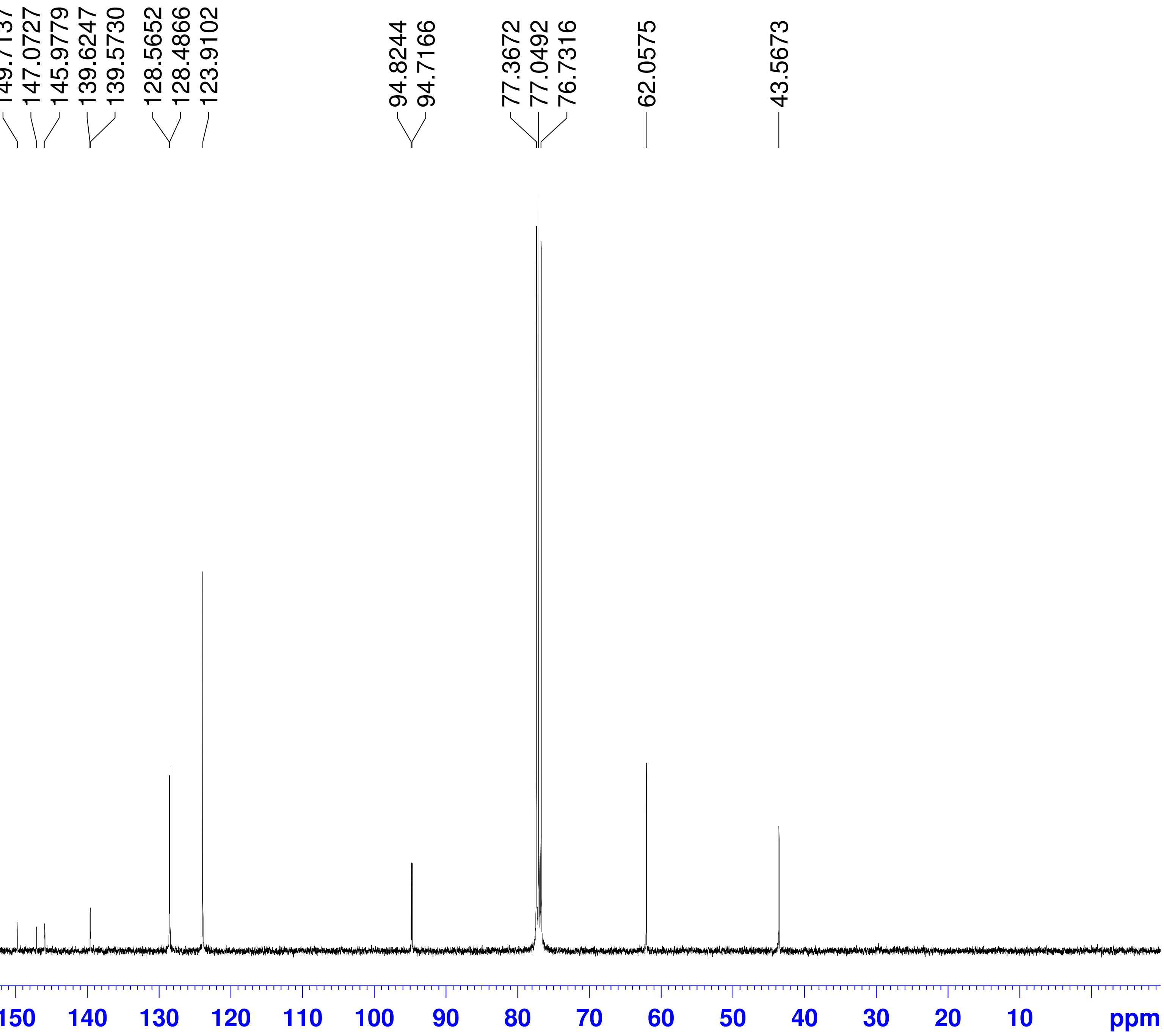
zgh-2-164-H

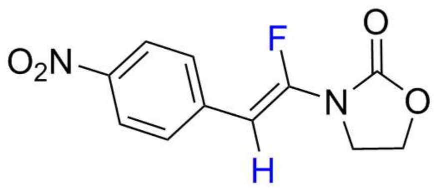




Z-**2h**

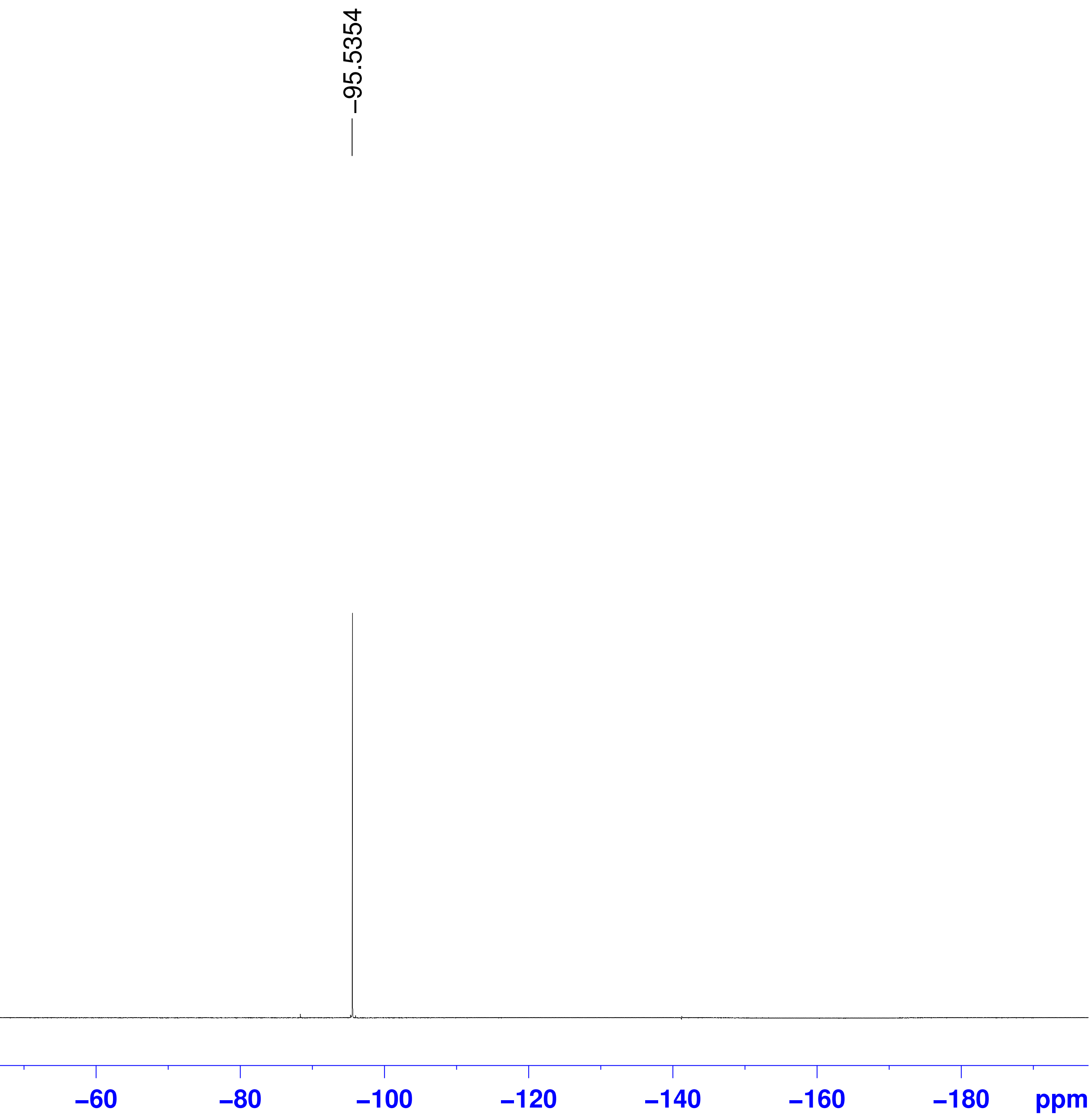
zgh-2-164-C

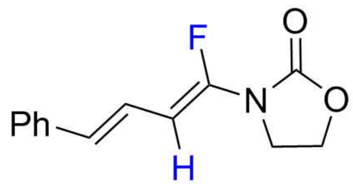




Z-**2h**

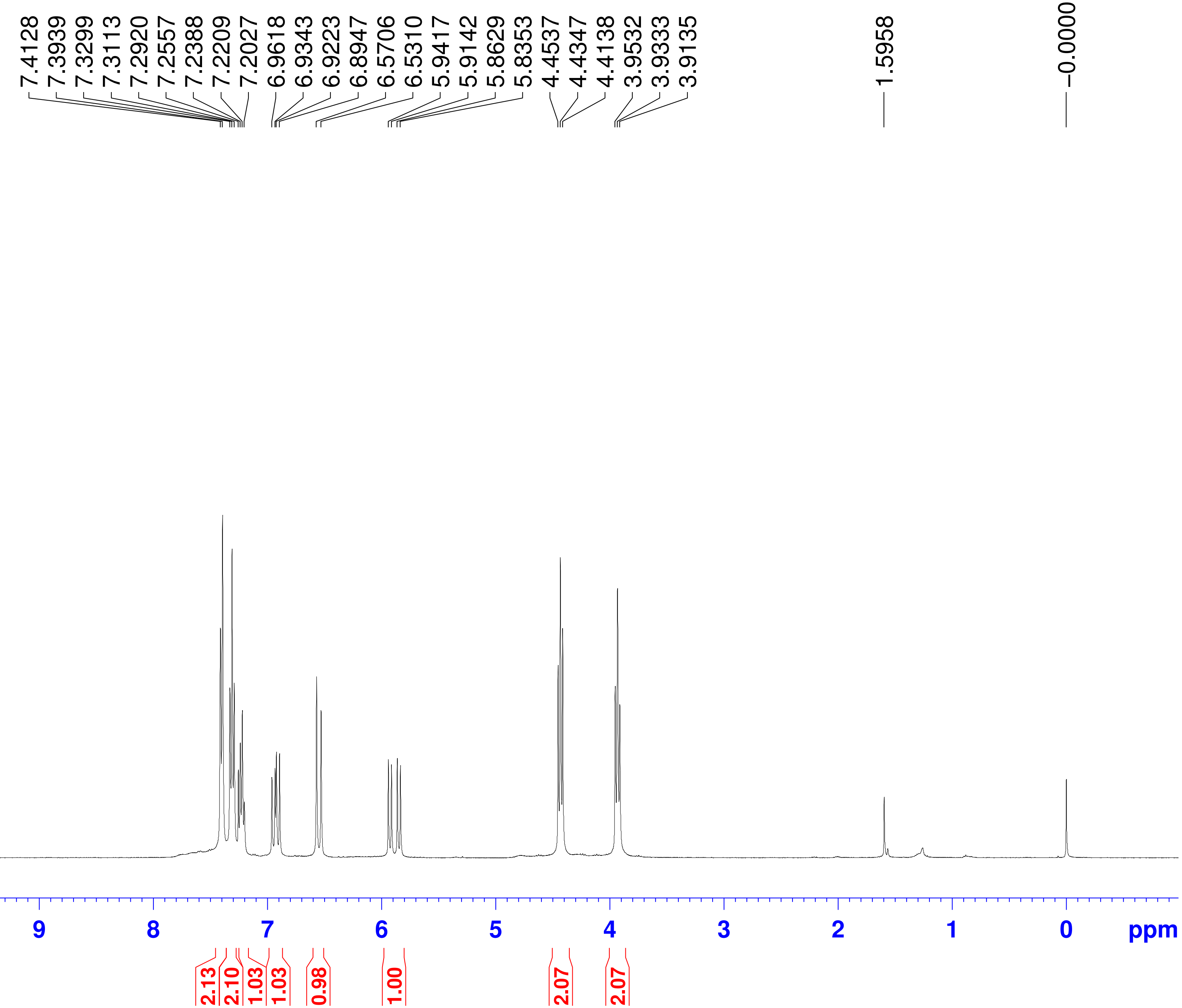
zgh-2-164-F

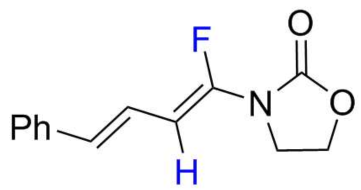




Z-**2i**

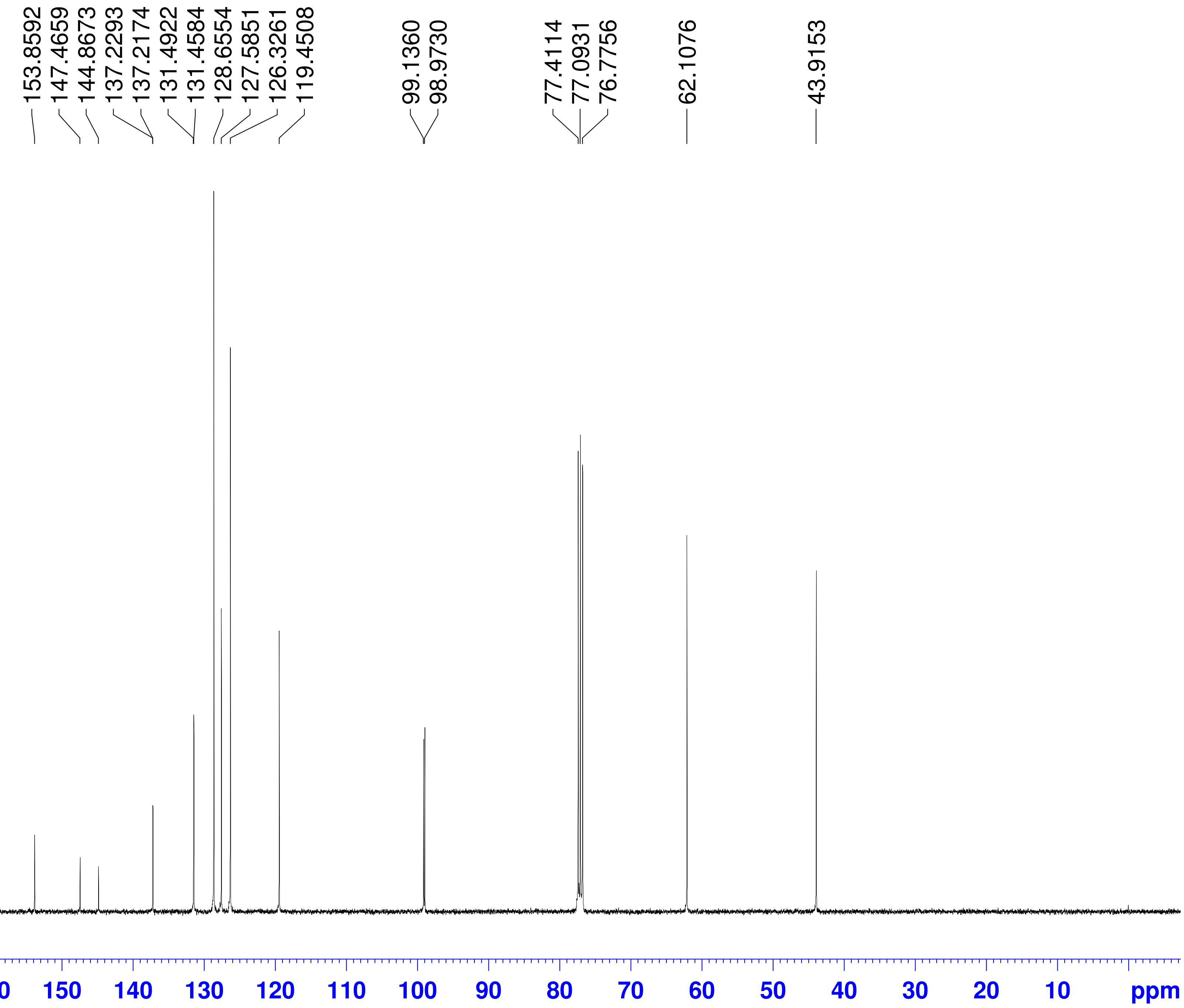
zgh-5-174-H

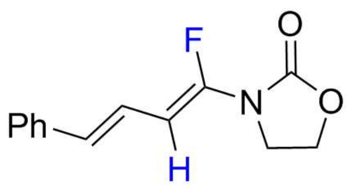




Z-**2i**

zgh-5-174-C





Z-**2i**

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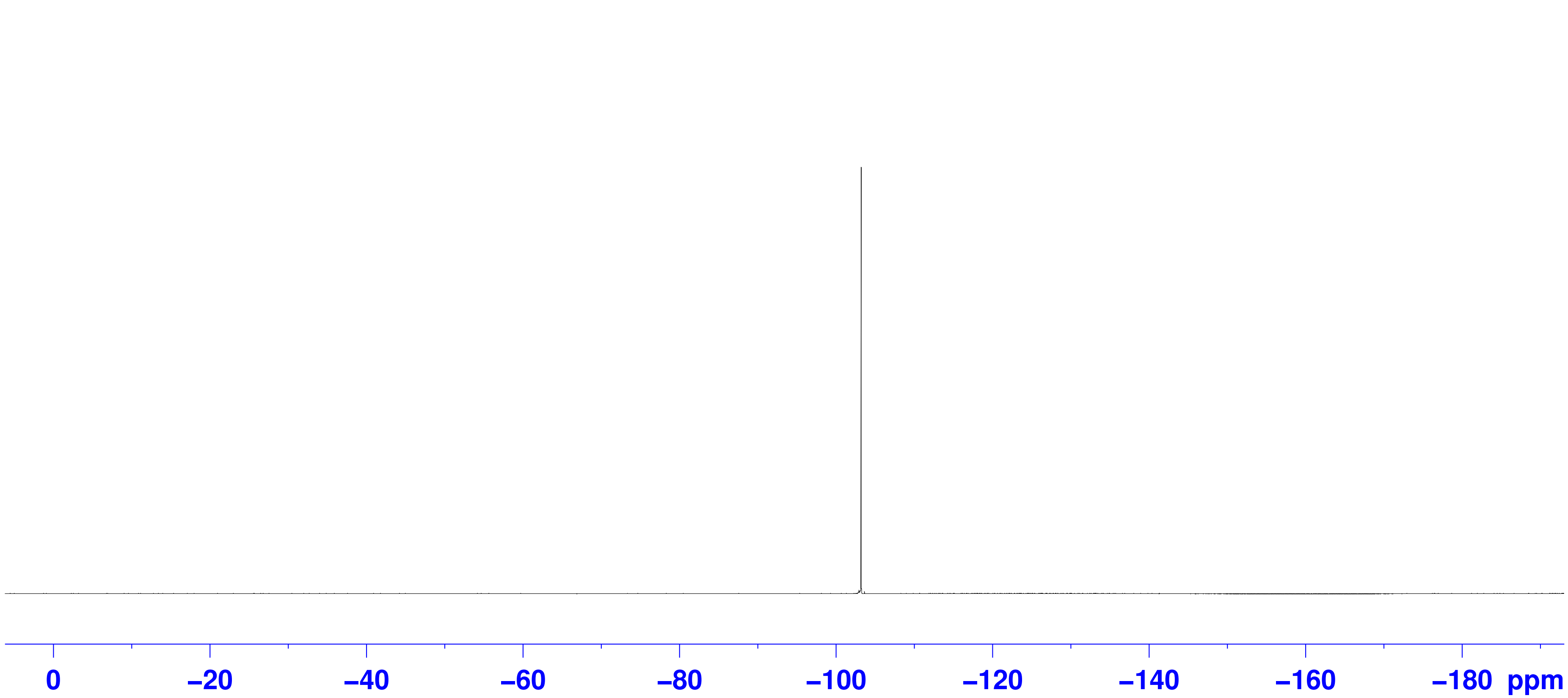
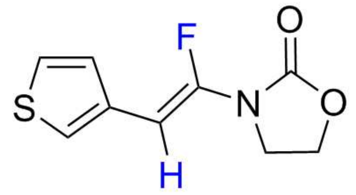
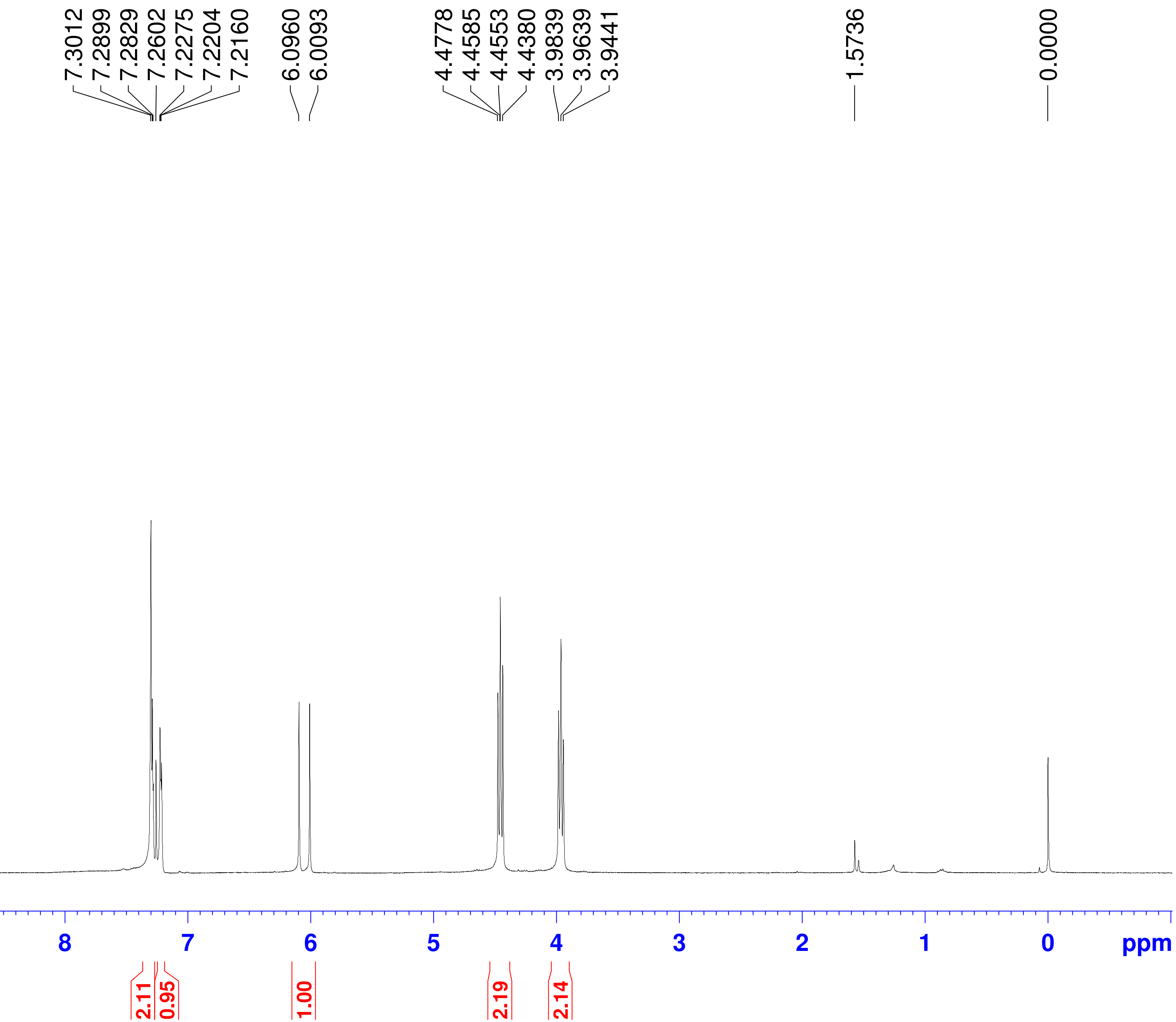



F
O
S
N
O
H

Z-**2j**

zgh-6-8-H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4.4585
4.4553
4.4380
3.9839
3.9639
3.9441
1.5736
0.0000
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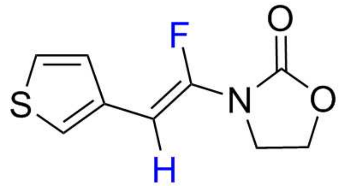
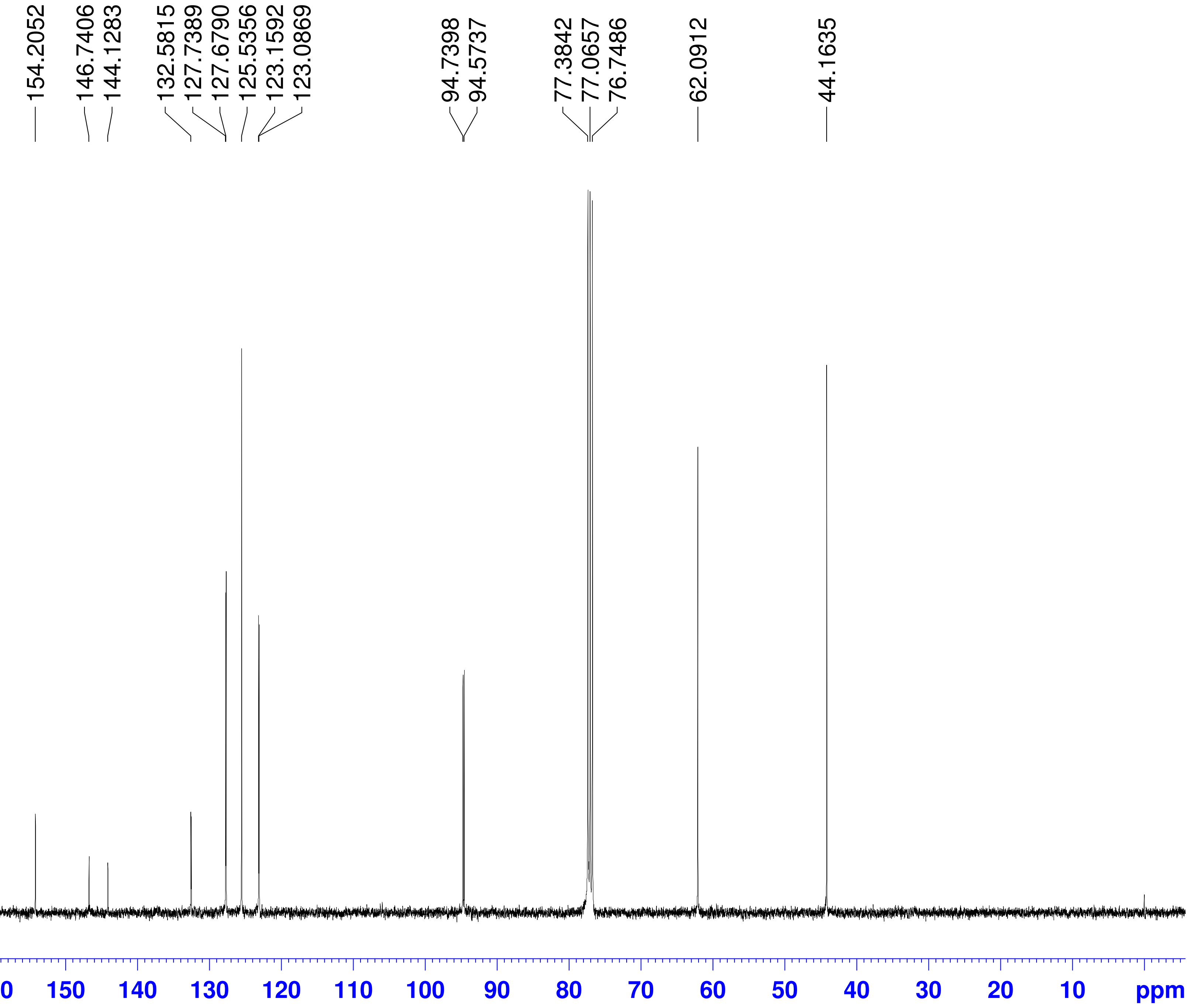


Z-**2j**

zgh-6-8-C



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132.5815
127.7389
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125.5356
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123.0869
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94.5737
77.3842
77.0657
76.7486
62.0912
44.1635
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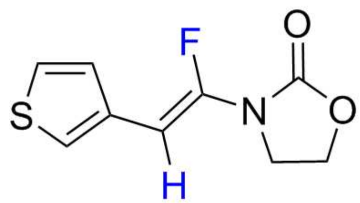
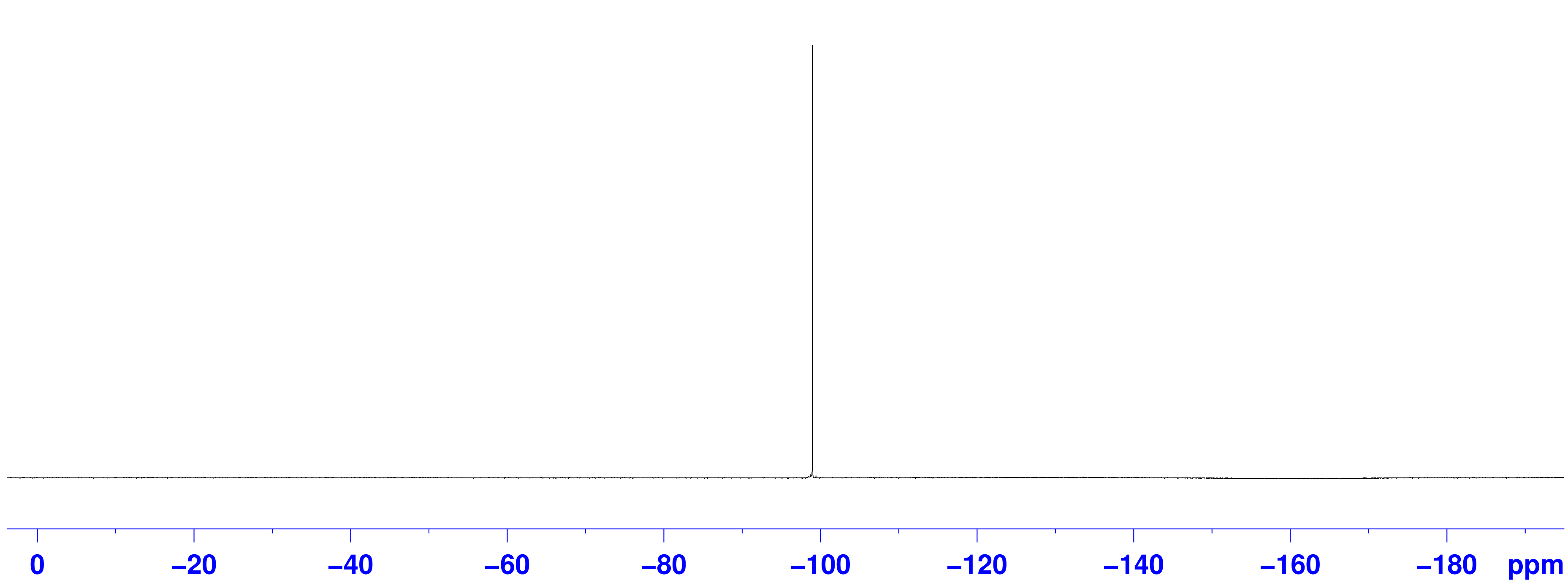
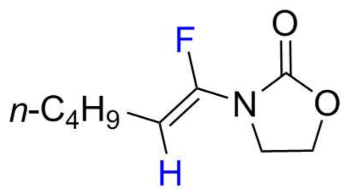
10
ppm



Z-**2j**

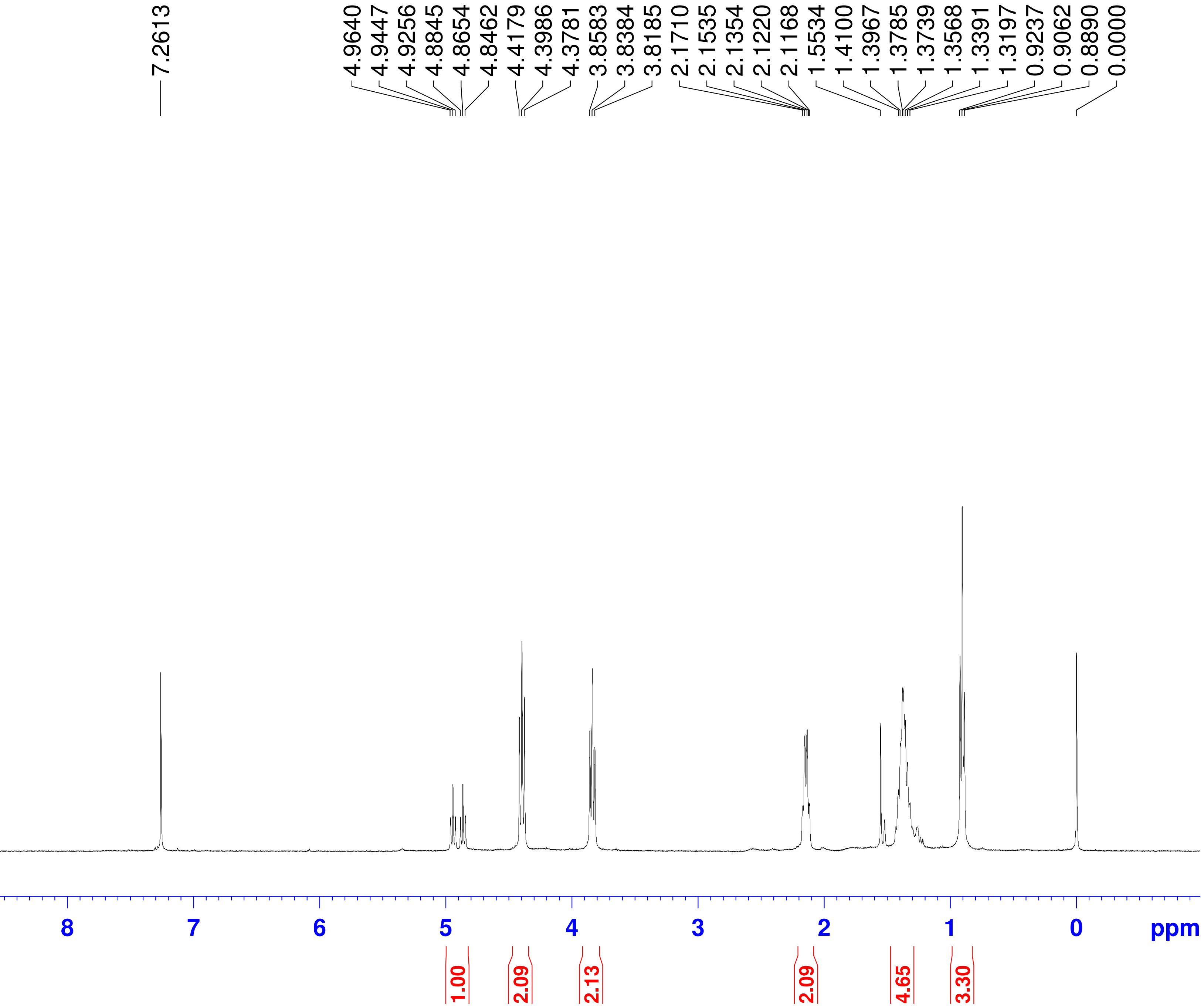
zgh-6-8-F





Z-**2k**

zgh-6-2-H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4.9256
4.8845
4.8654
4.8462
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4.3986
4.3781
3.8583
3.8384
3.8185
2.1710
2.1535
2.1354
2.1220
2.1168
1.5534
1.4100
1.3967
1.3785
1.3739
1.3568
1.3391
1.3197
0.9237
0.9062
0.8890
0.0000
10
9
8
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4
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ppm
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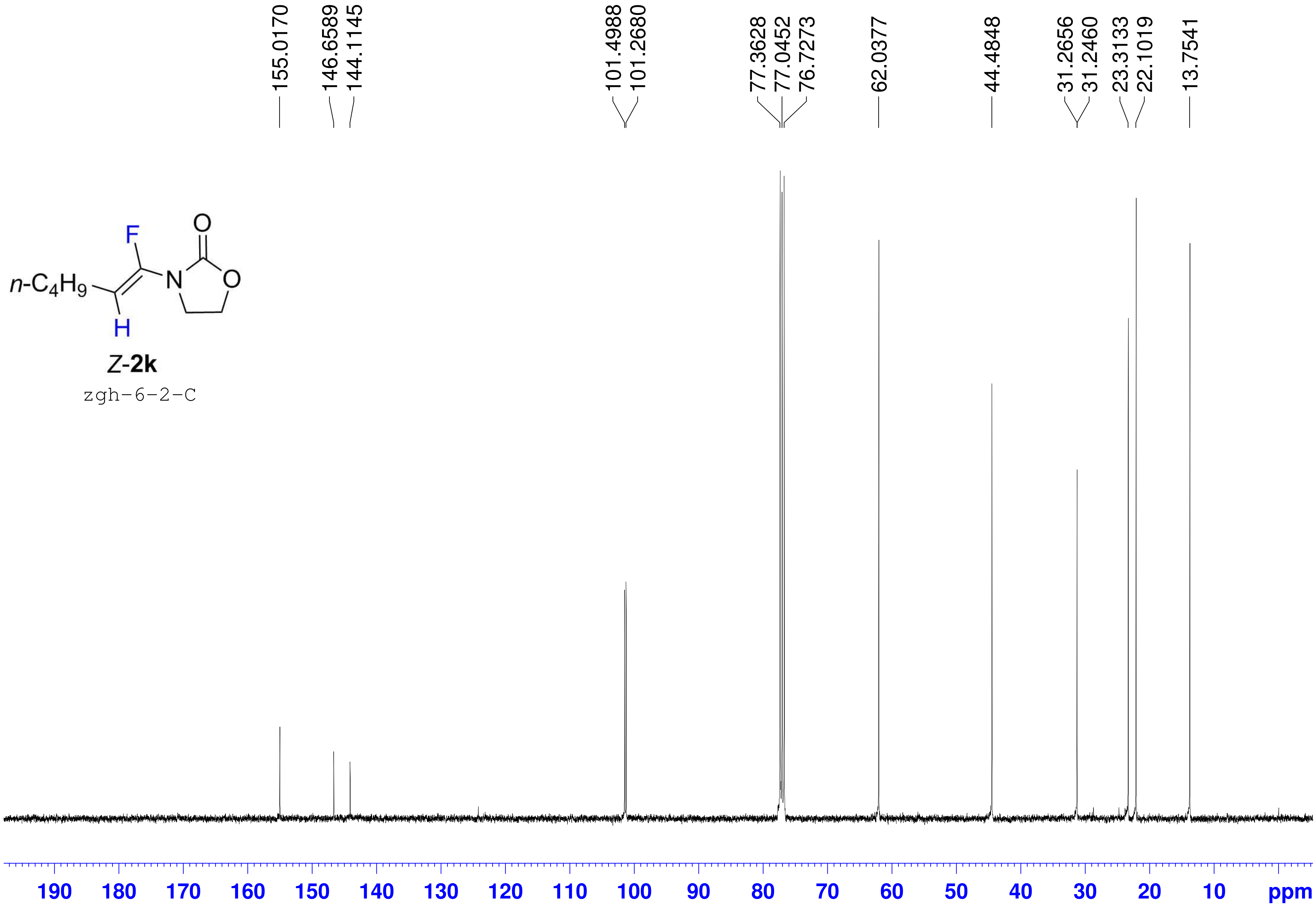
2.09
2.13
2.09
4.65
3.30



155.0170
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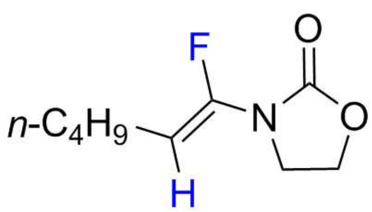
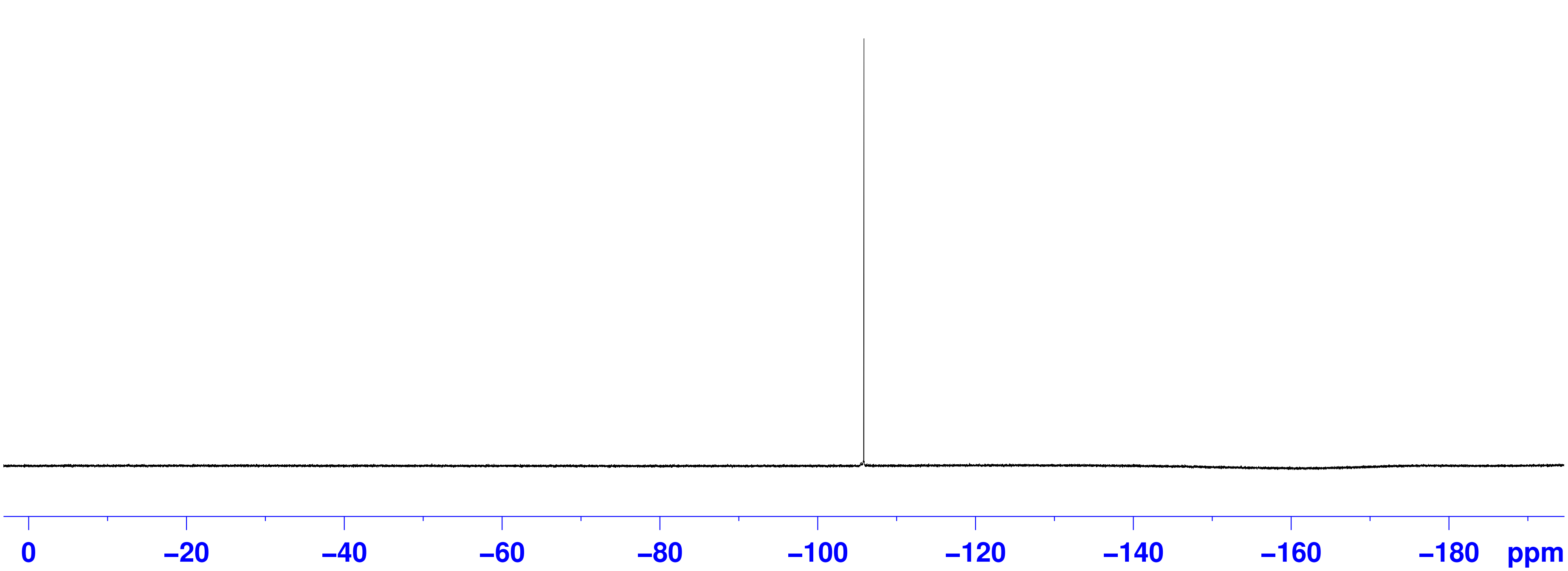
144.1145
101.4988
101.2680
77.3628
77.0452
76.7273
62.0377
44.4848
31.2656
31.2460
23.3133
22.1019
13.7541
F
N
O
O
n-C_4H_9
H
Z-**2k**
zgh-6-2-C
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

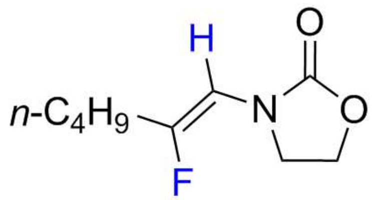


Z-**2k**

zgh-6-2-F

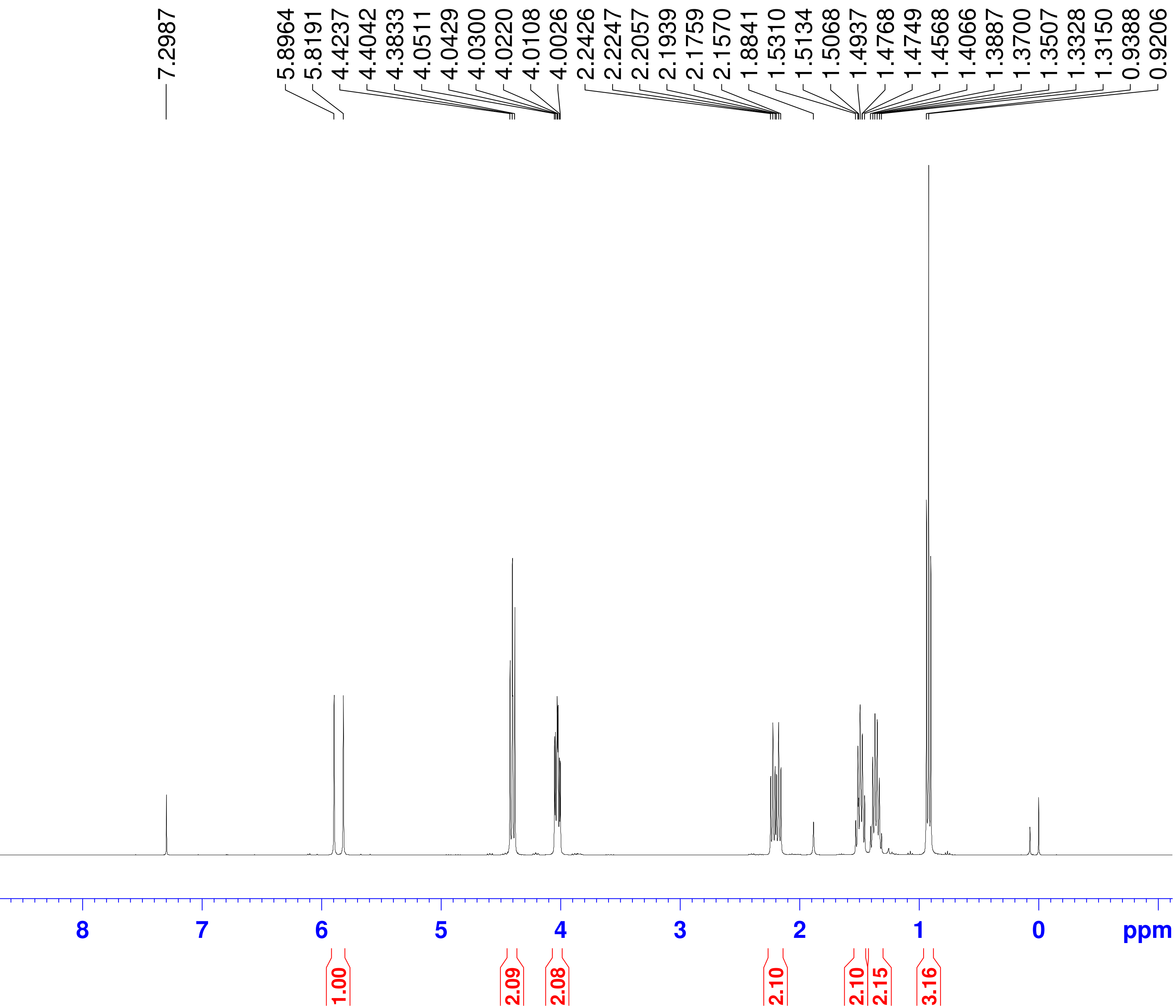
-105.8722

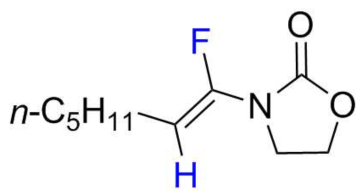




Z-**3k**

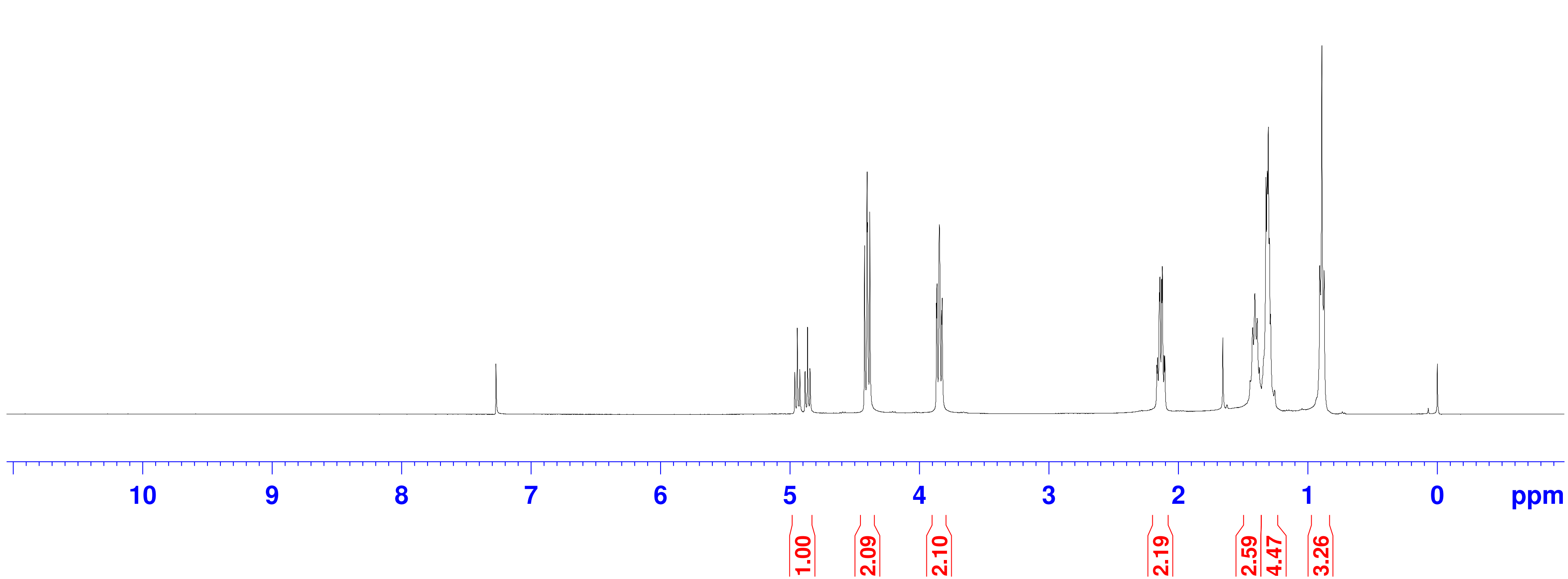
zgh-6-2(2)-H

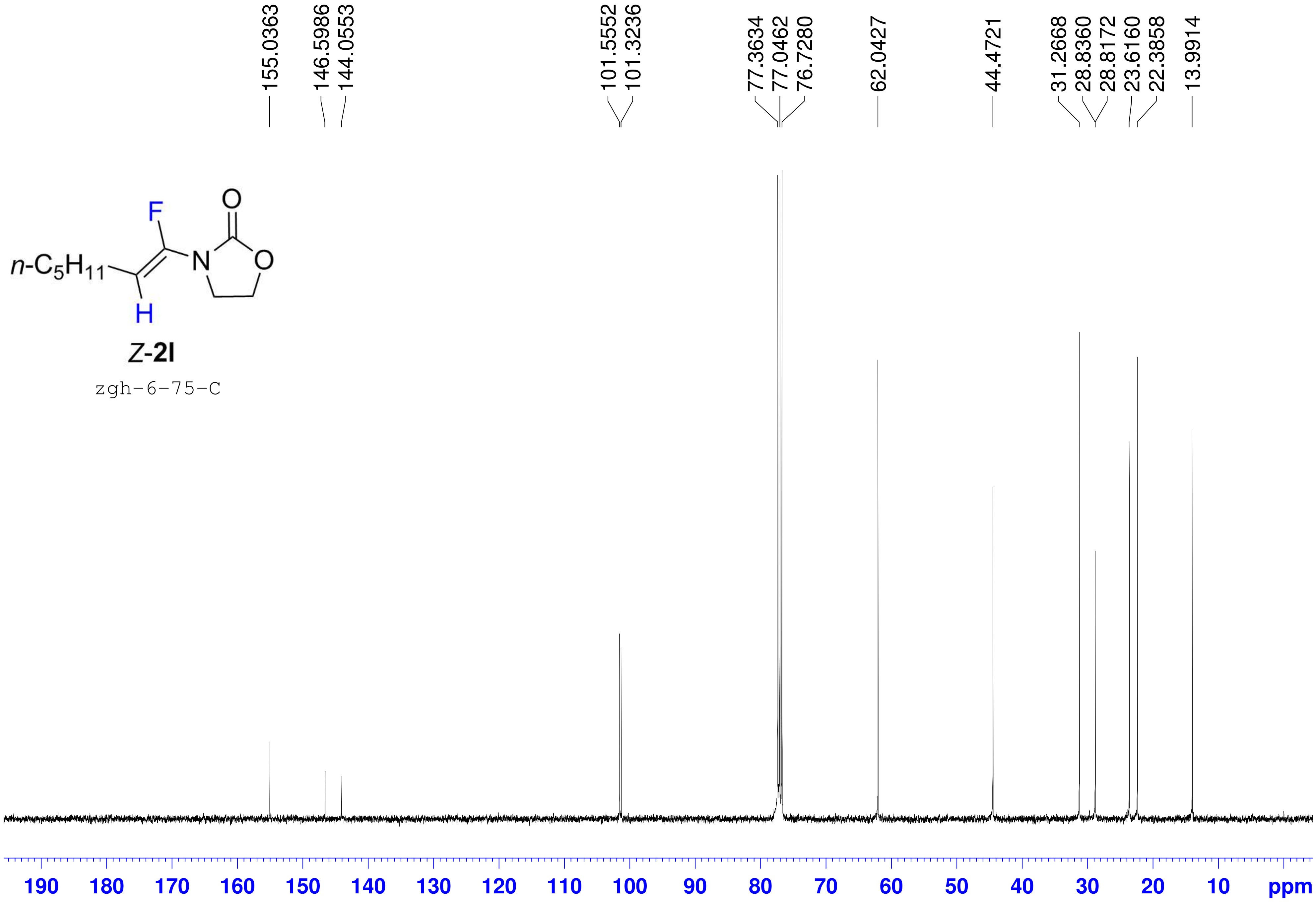

7.2987
5.8964
5.8191
4.4237
4.4042
4.3833
4.0511
4.0429
4.0300
4.0220
4.0108
4.0026
2.2426
2.2247
2.2057
2.1939
2.1759
2.1570
1.8841
1.5310
1.5134
1.5068
1.4937
1.4768
1.4749
1.4568
1.4066
1.3887
1.3700
1.3507
1.3328
1.3150
0.9388
0.9206
1.00
2.09
2.08
2.10
2.10
2.15
3.16
10
9
8
7
6
5
4
3
2
1
0
ppm



Z-**2l**

zgh-6-75-H

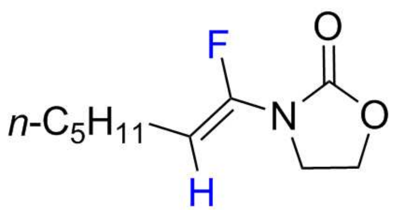

7.2723
4.9639
4.9447
4.9254
4.8846
4.8653
4.8461
4.4247
4.4052
4.4018
4.3848
3.8692
3.8652
3.8484
3.8469
3.8451
3.8293
3.8253
2.1668
2.1612
2.1481
2.1431
2.1299
2.1244
2.1110
2.1053
1.6570
1.4457
1.4264
1.4098
1.3922
1.3755
1.3618
1.3418
1.3237
1.3142
1.3058
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.09
2.10
2.19
2.59
4.47
3.26



n-C_5H_{11}
F
H
N
O
O
155.0363
146.5986
144.0553
101.5552
101.3236
77.3634
77.0462
76.7280
62.0427
44.4721
31.2668
28.8360
28.8172
23.6160
22.3858
13.9914
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

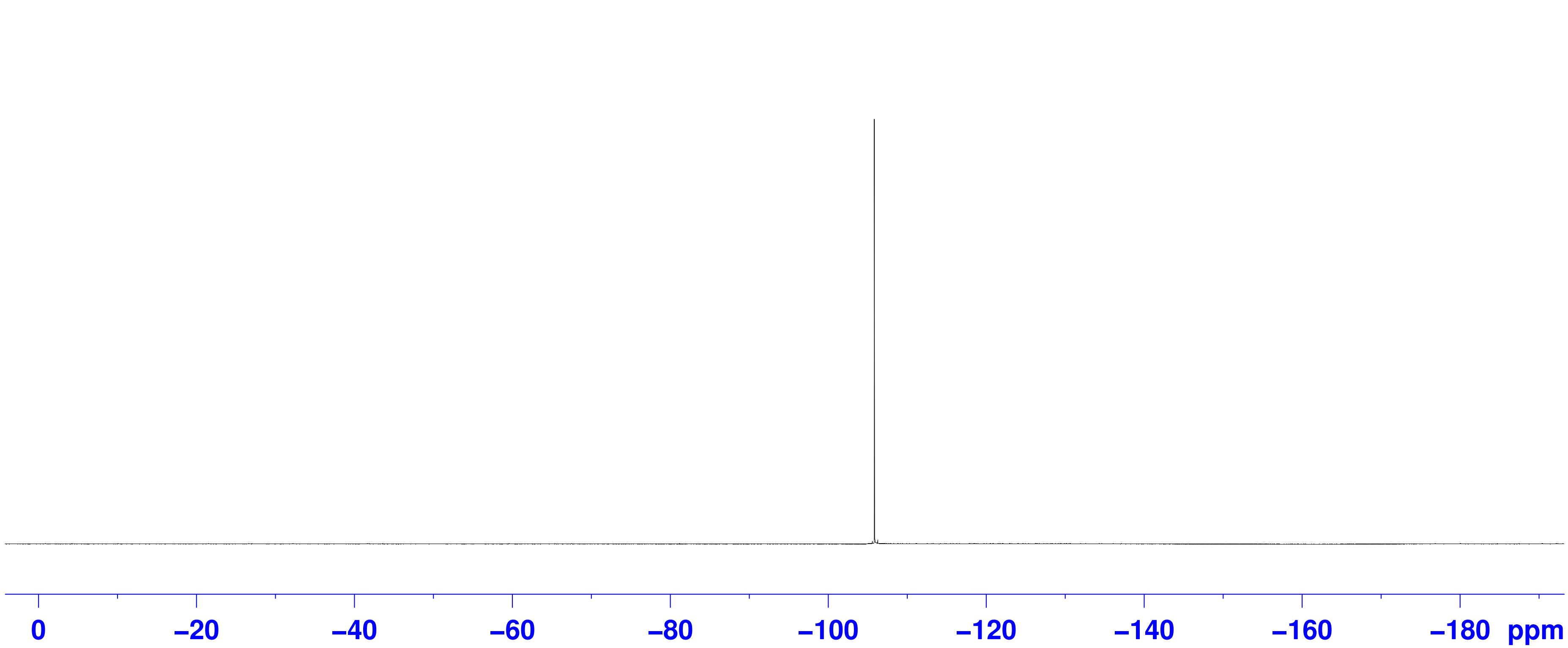
Z-**2l**

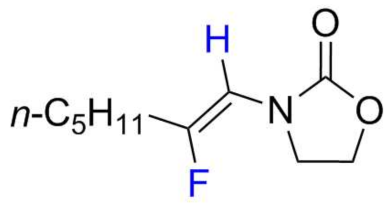
zgh-6-75-C



Z-**2l**

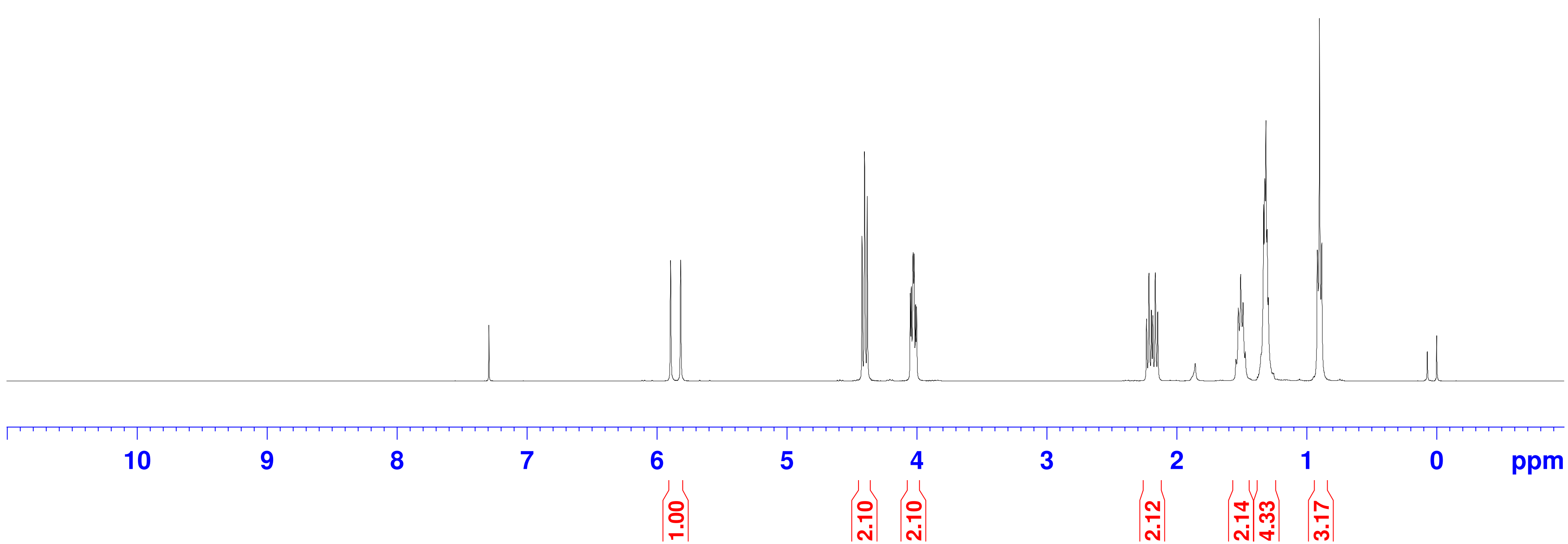
zgh-6-75-F

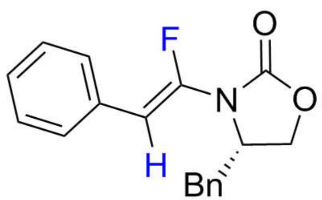




Z-**3l**

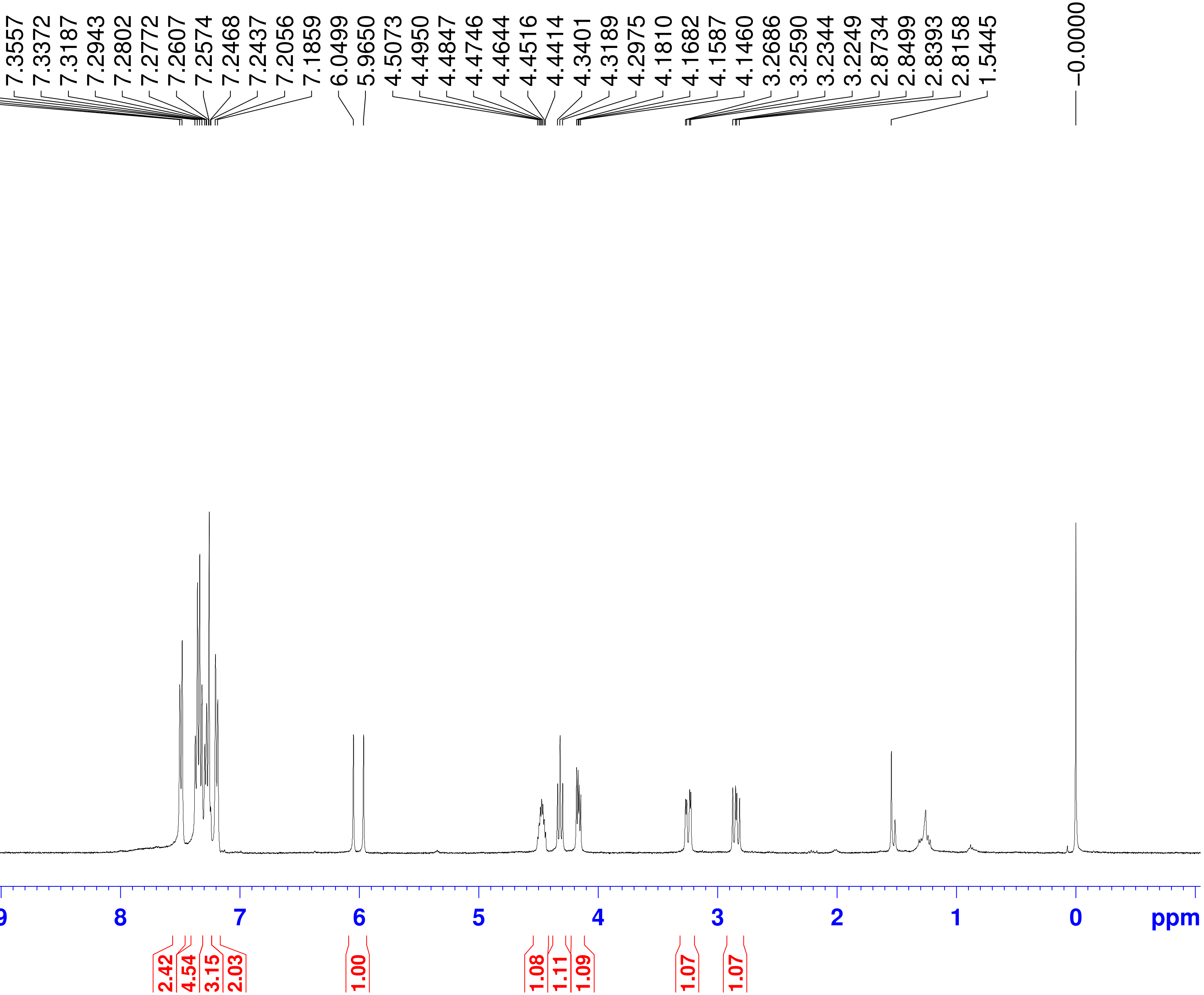
zgh-6-75(2)-H

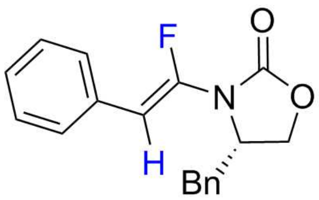




Z-**2m**

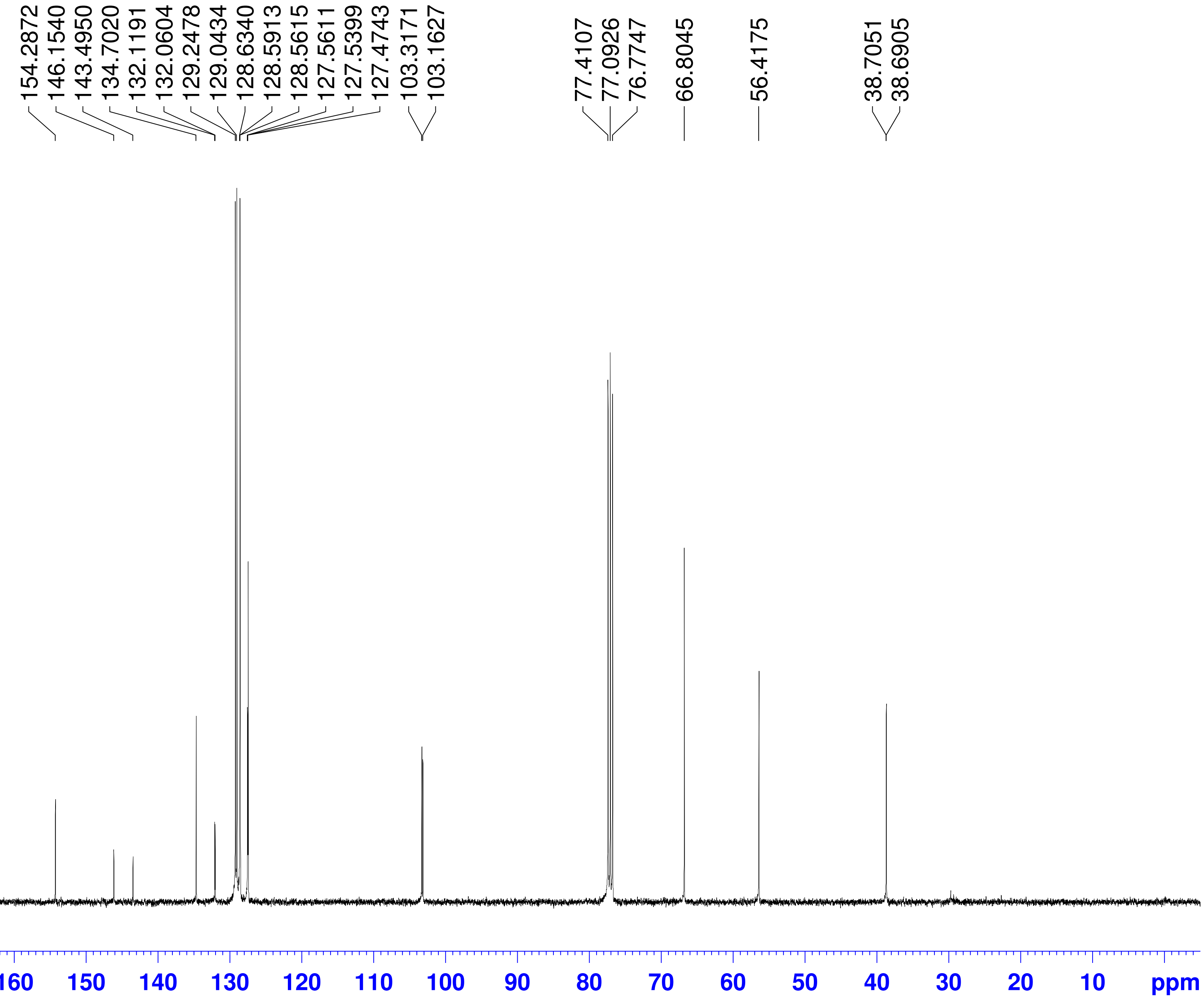
zgh-5-177-H

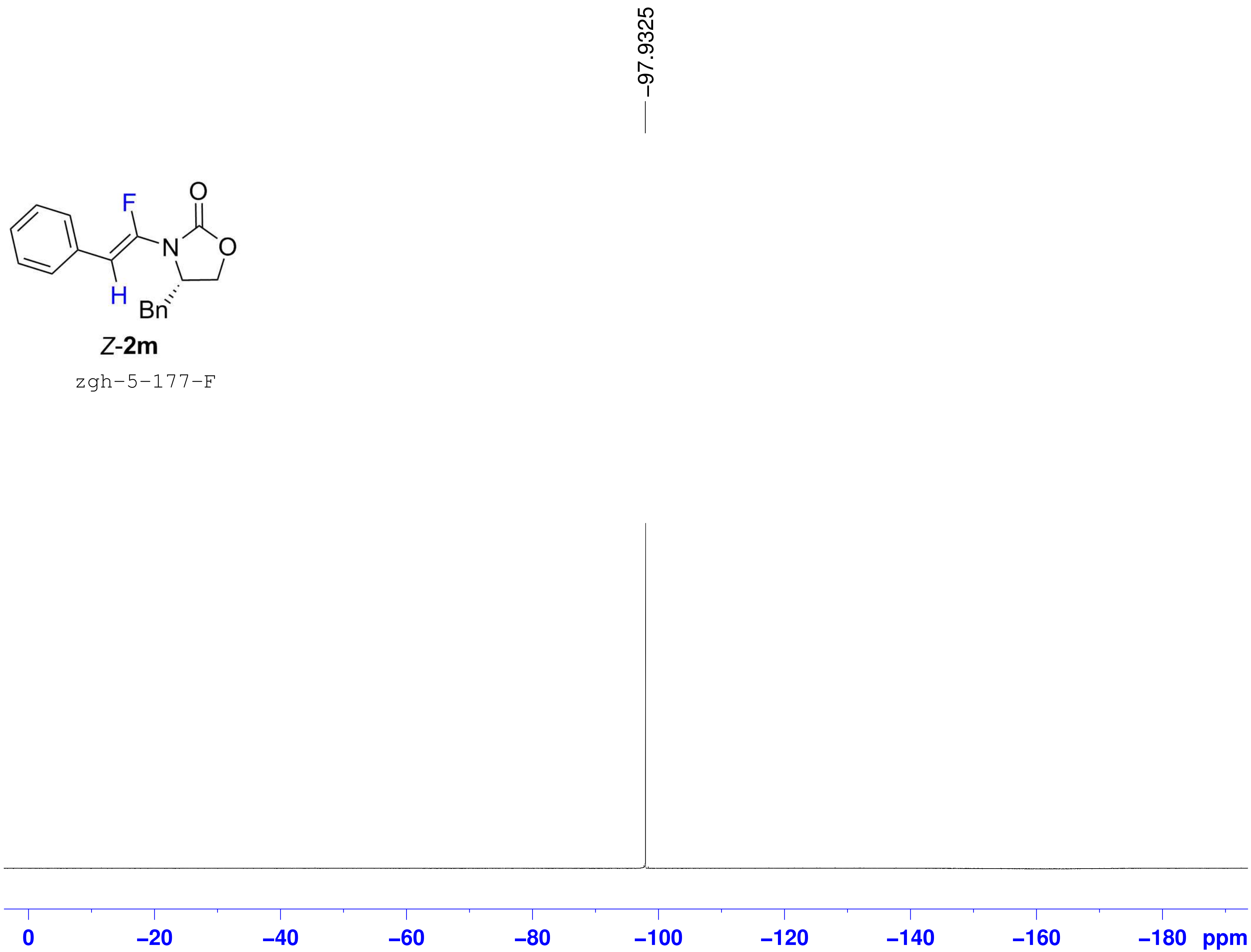




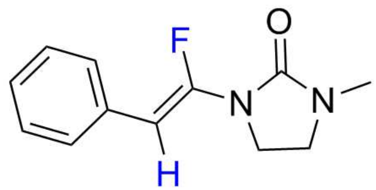
Z-**2m**

zgh-5-177-C





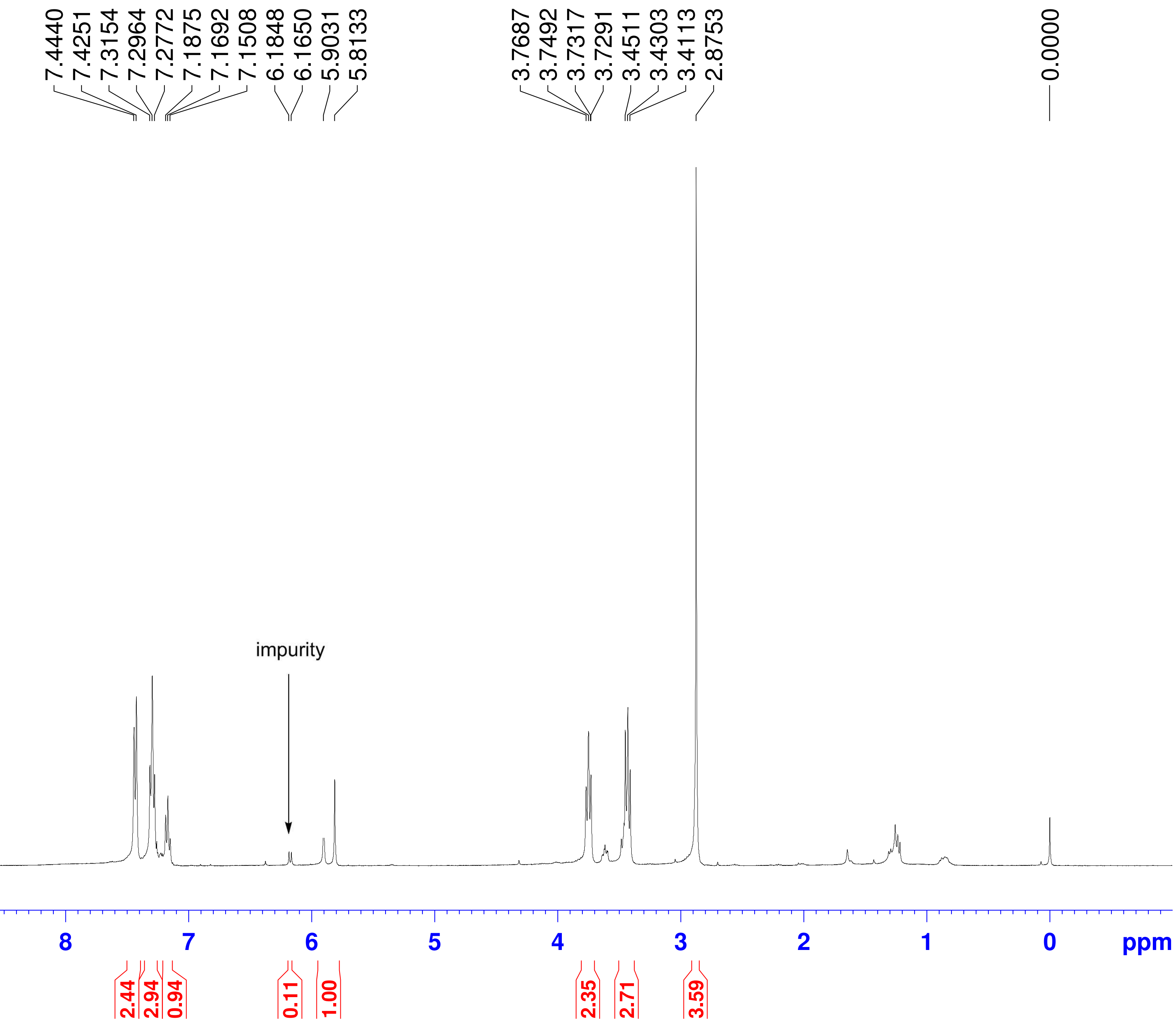
−97.9325
F
O
N
O
H
Bn
Z-2m
zgh-5-177-F
0
−20
−40
−60
−80
−100
−120
−140
−160
−180
ppm



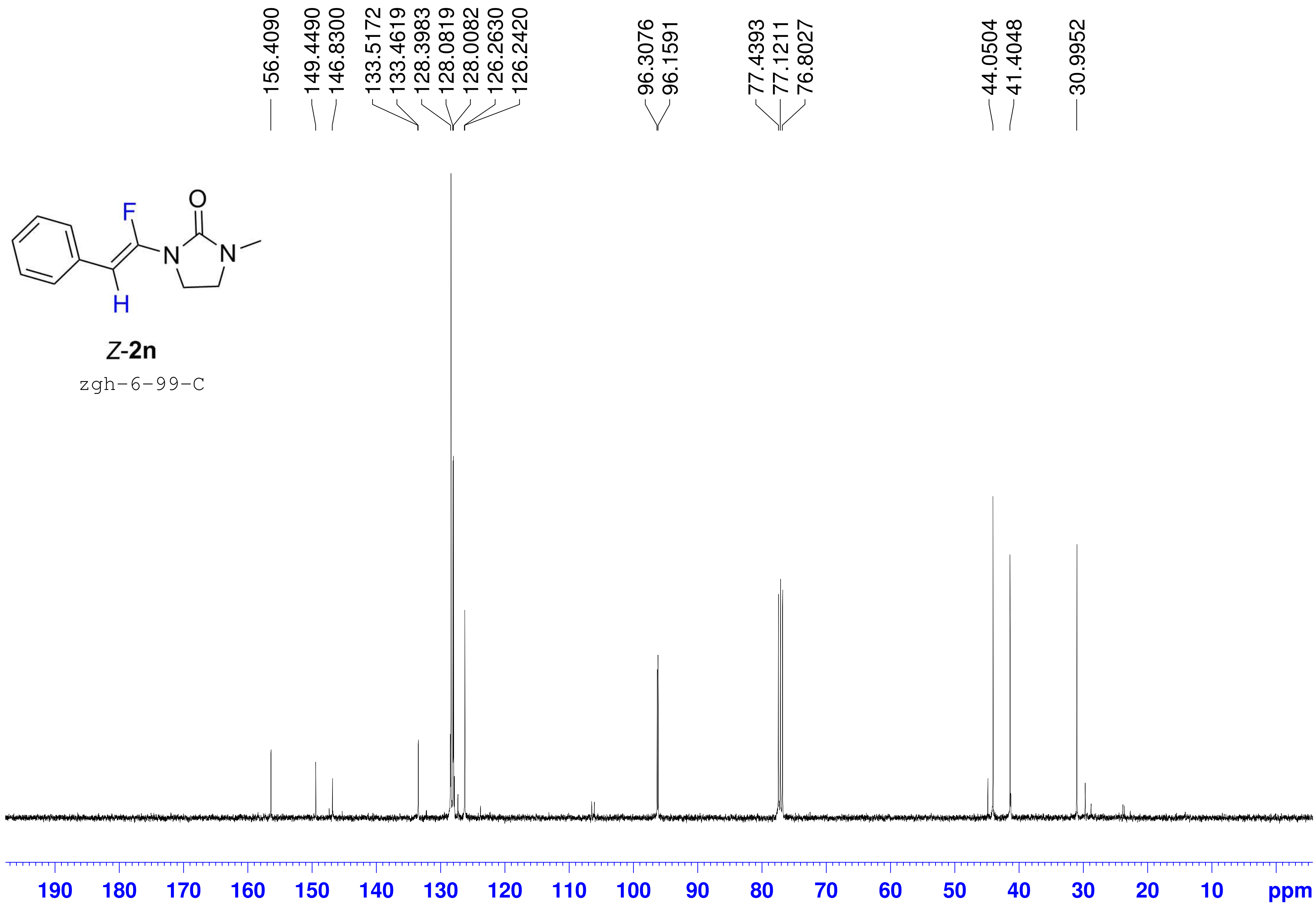
F
O
N
N
H

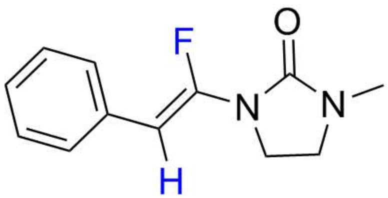
Z-**2n**

zgh-6-99-H



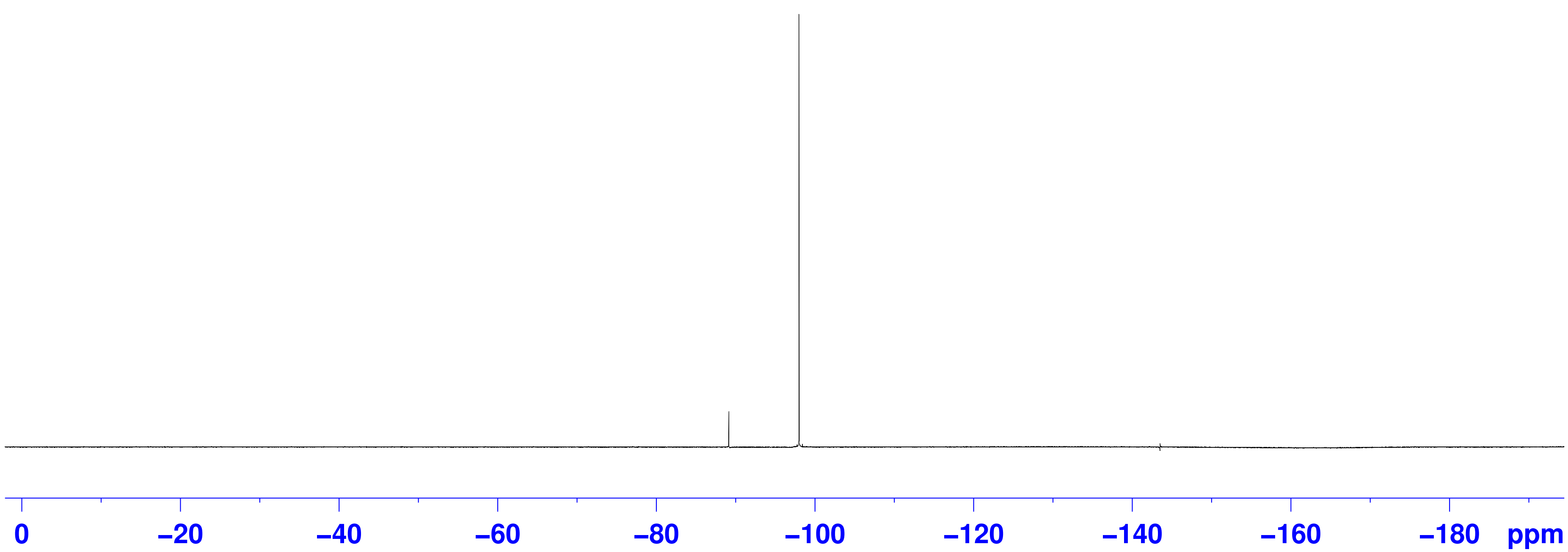
7.4440
7.4251
7.3154
7.2964
7.2772
7.1875
7.1692
7.1508
6.1848
6.1650
5.9031
5.8133
3.7687
3.7492
3.7317
3.7291
3.4511
3.4303
3.4113
2.8753
0.0000
impurity
10
9
8
7
6
5
4
3
2
1
0
ppm
2.44
2.94
0.94
0.11
1.00
2.35
2.71
3.59

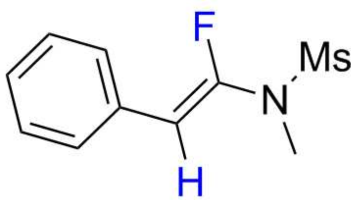

156.4090
149.4490
146.8300
133.5172
133.4619
128.3983
128.0819
128.0082
126.2630
126.2420
96.3076
96.1591
77.4393
77.1211
76.8027
44.0504
41.4048
30.9952
F
O
N
N
H
Z-2n
zgh-6-99-C
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



Z-**2n**

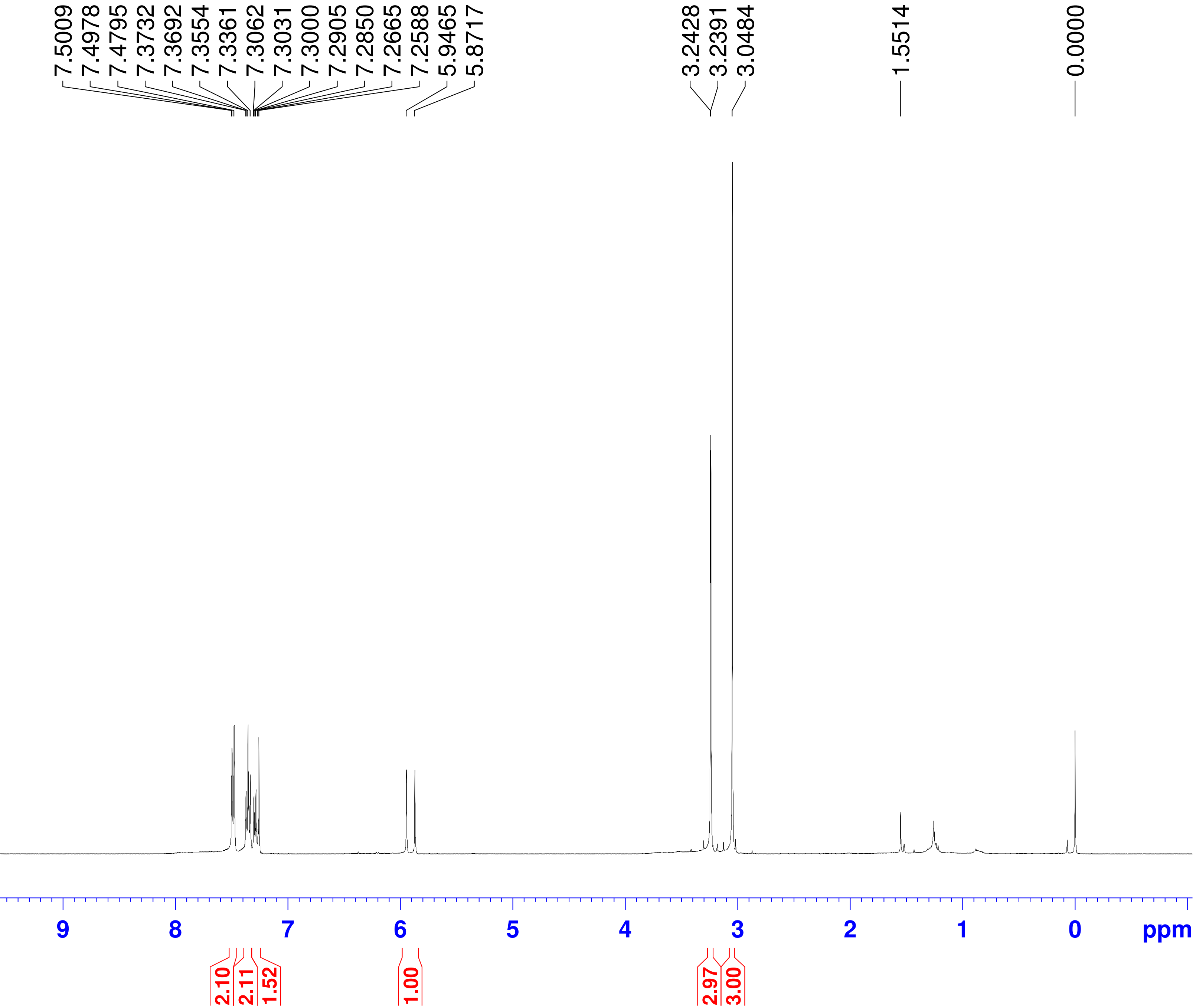
zgh-6-99-F

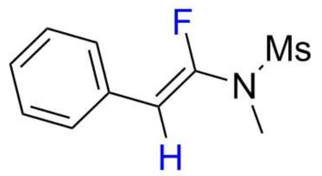



F
Ms
N
H

Z-**2o**

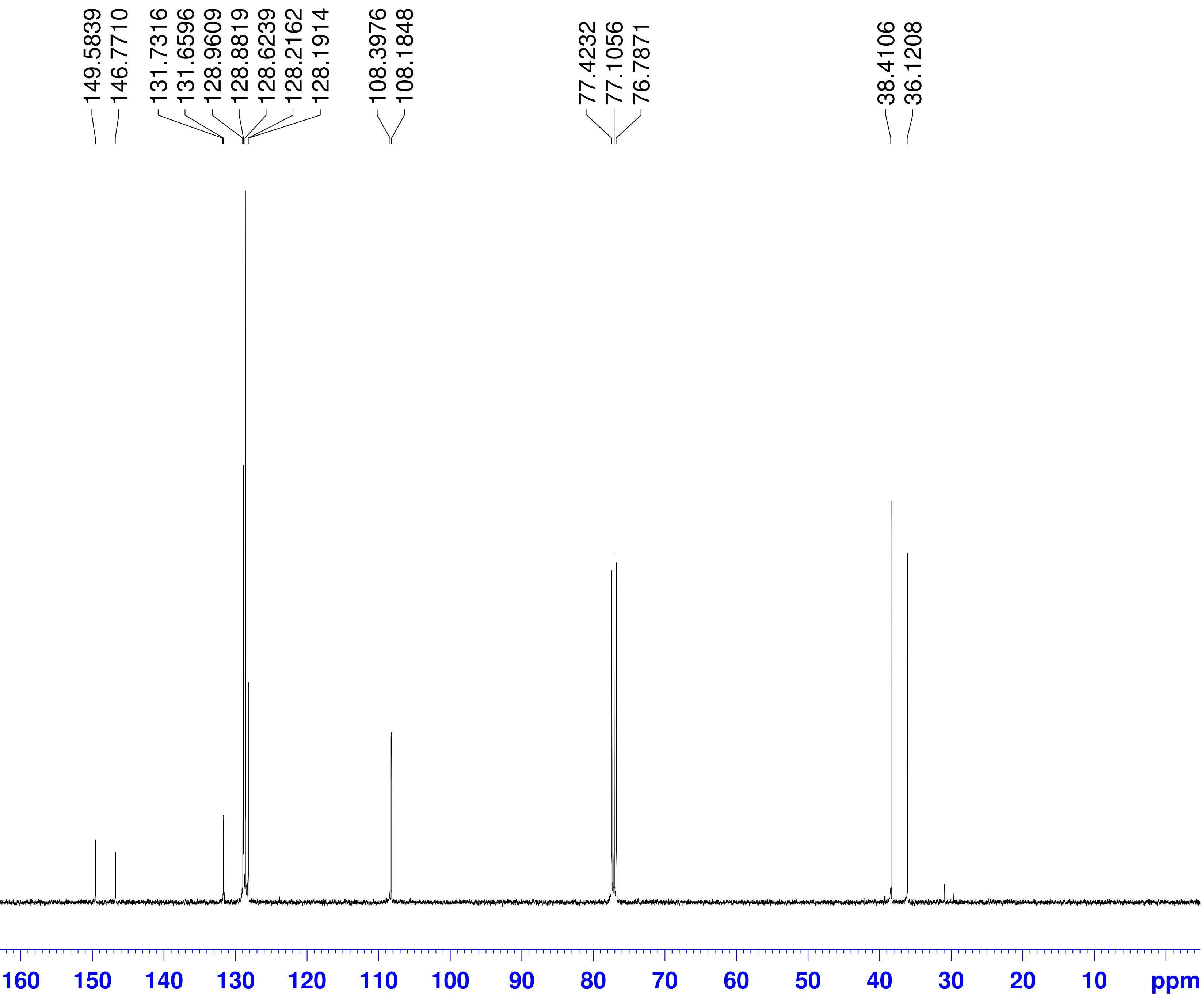
zgh-6-51-H

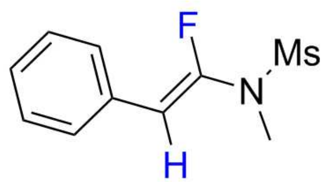

7.5009
7.4978
7.4795
7.3732
7.3692
7.3554
7.3361
7.3062
7.3031
7.3000
7.2905
7.2850
7.2665
7.2588
5.9465
5.8717
3.2428
3.2391
3.0484
1.5514
0.0000
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.10
2.11
1.52
1.00
2.97
3.00


F
Ms
N
H

Z-**2o**

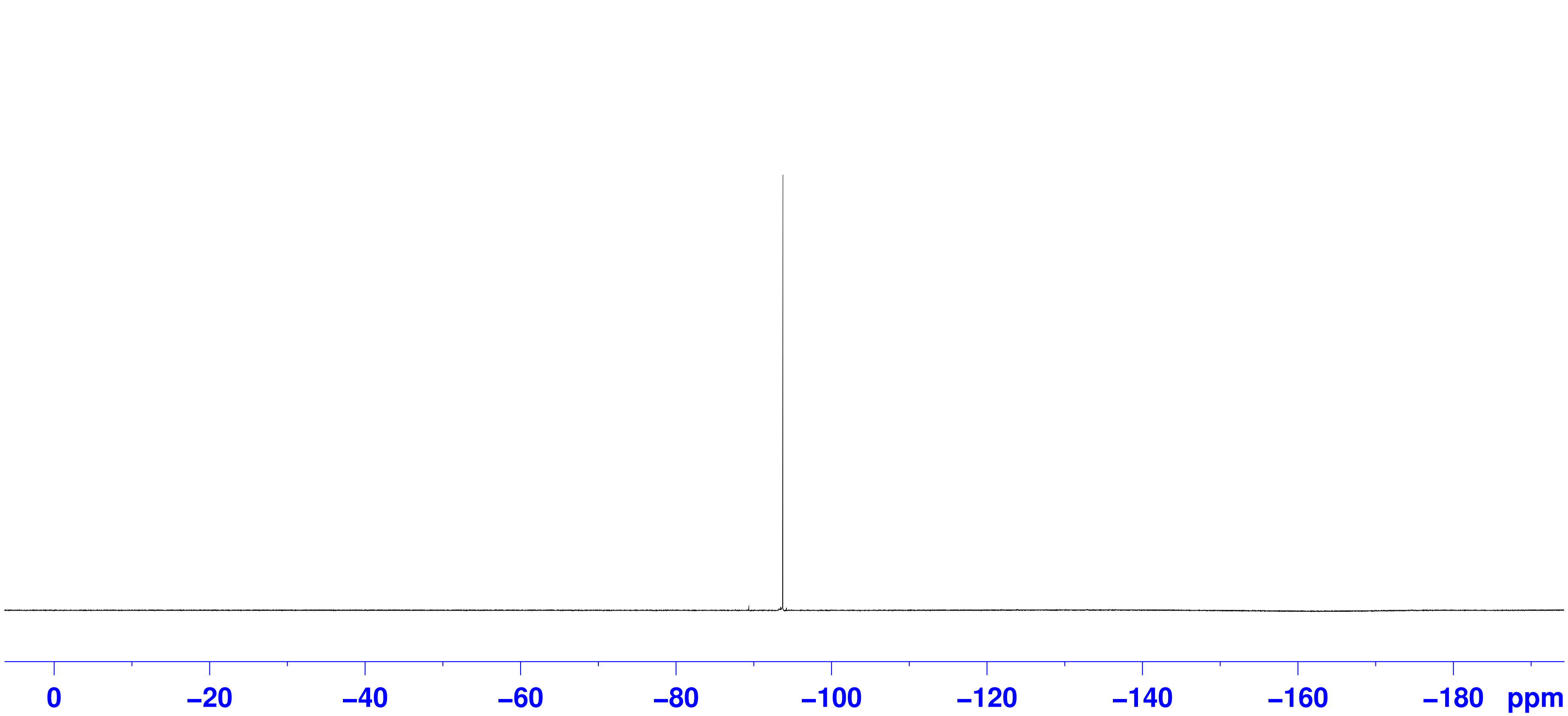
zgh-6-51-C

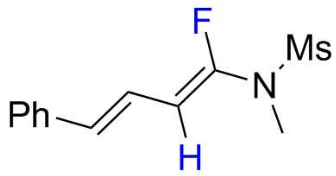

149.5839
146.7710
131.7316
131.6596
128.9609
128.8819
128.6239
128.2162
128.1914
108.3976
108.1848
77.4232
77.1056
76.7871
38.4106
36.1208
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



Z-**2o**

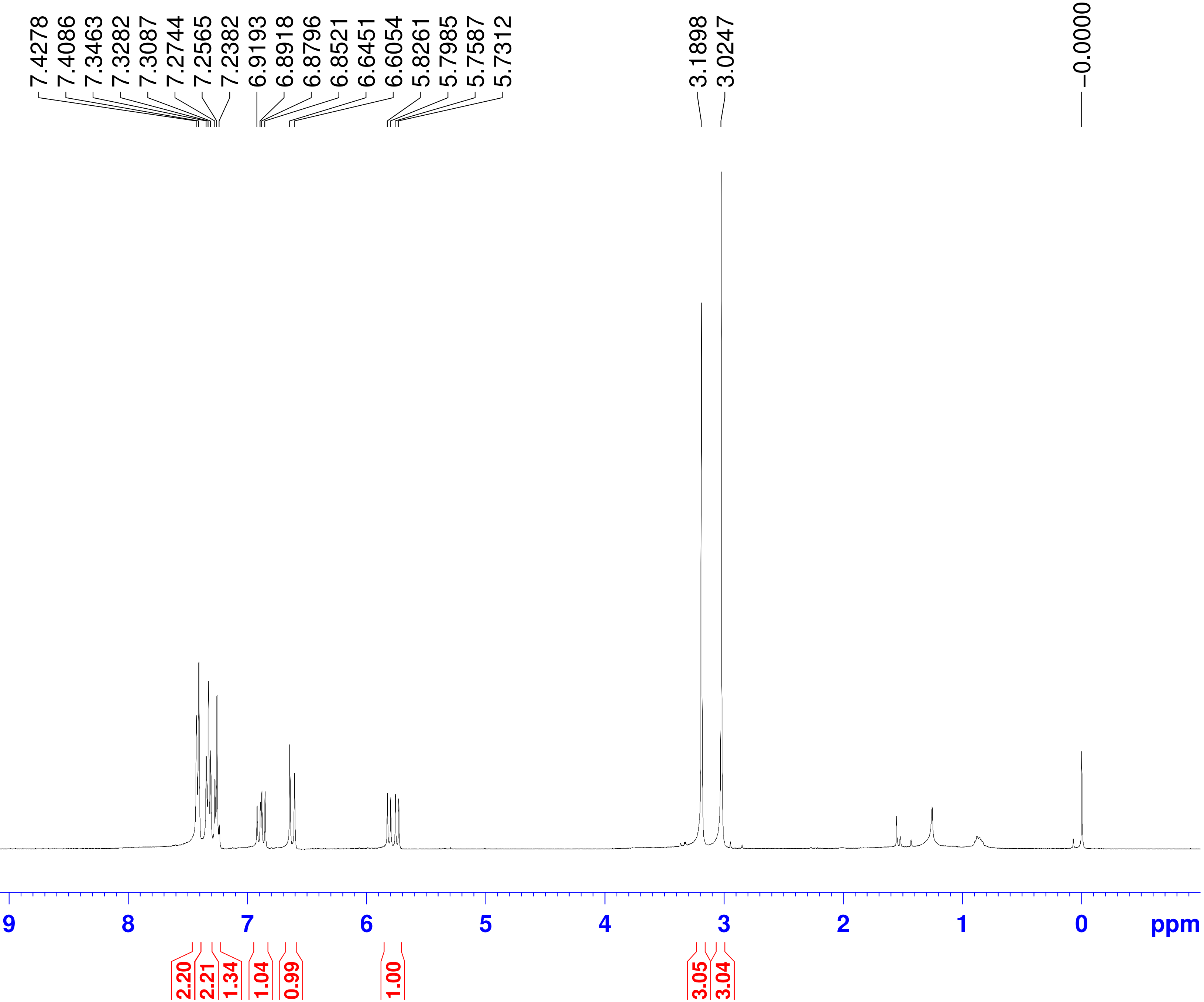
zgh-6-51-F

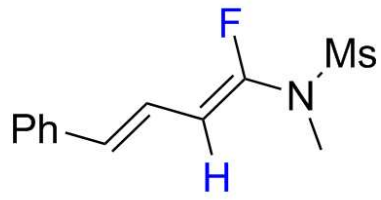



F
Ms
N
Ph
H

Z-**2p**

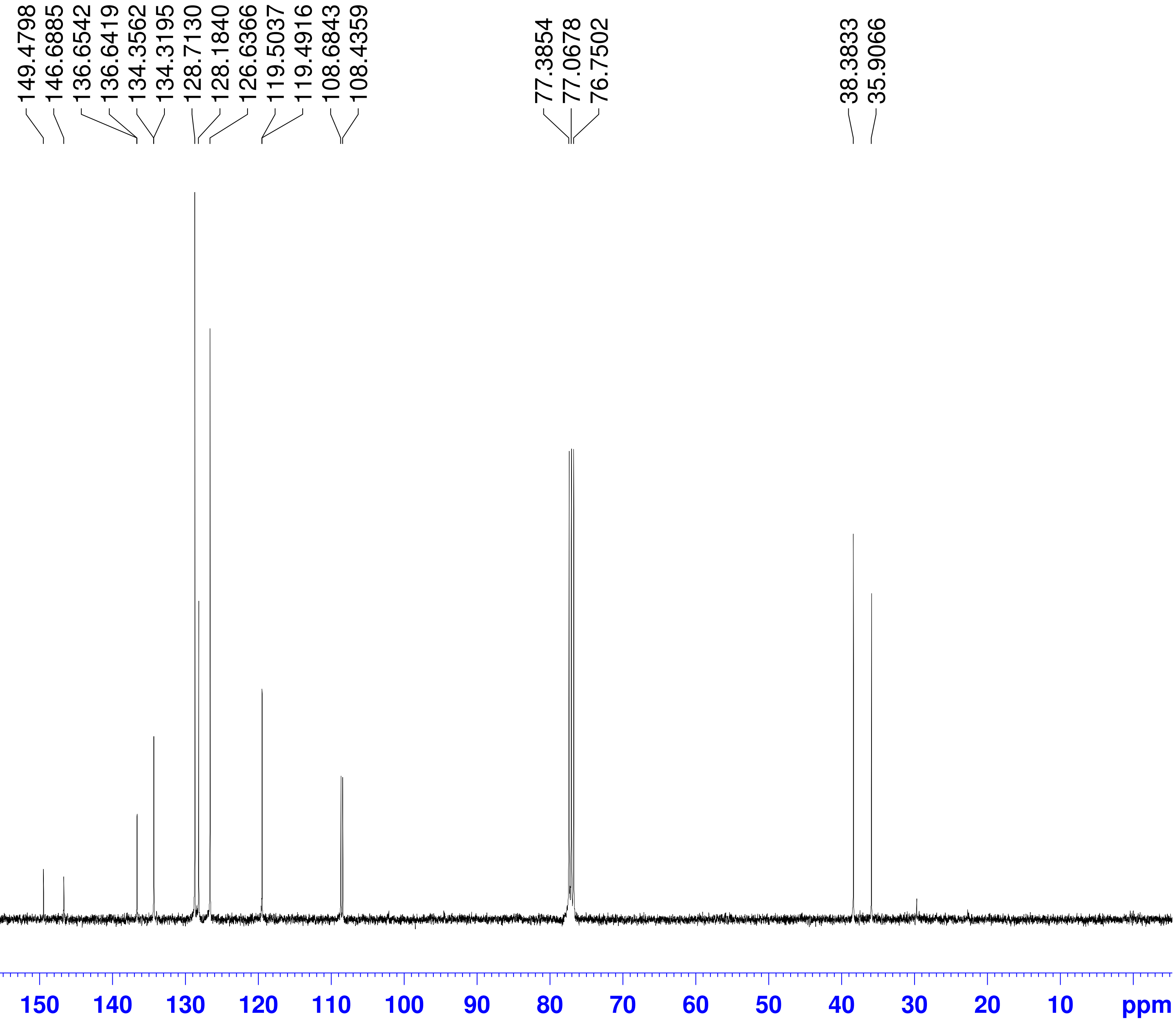
zgh-6-84-H

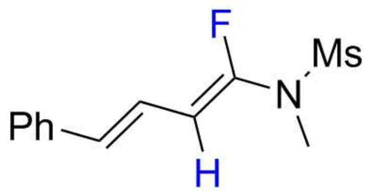

7.4278
7.4086
7.3463
7.3282
7.3087
7.2744
7.2565
7.2382
6.9193
6.8918
6.8796
6.8521
6.6451
6.6054
5.8261
5.7985
5.7587
5.7312
3.1898
3.0247
-0.0000
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.20
2.21
1.34
1.04
0.99
1.00
3.05
3.04


F
Ms
N
Ph
H

Z-**2p**

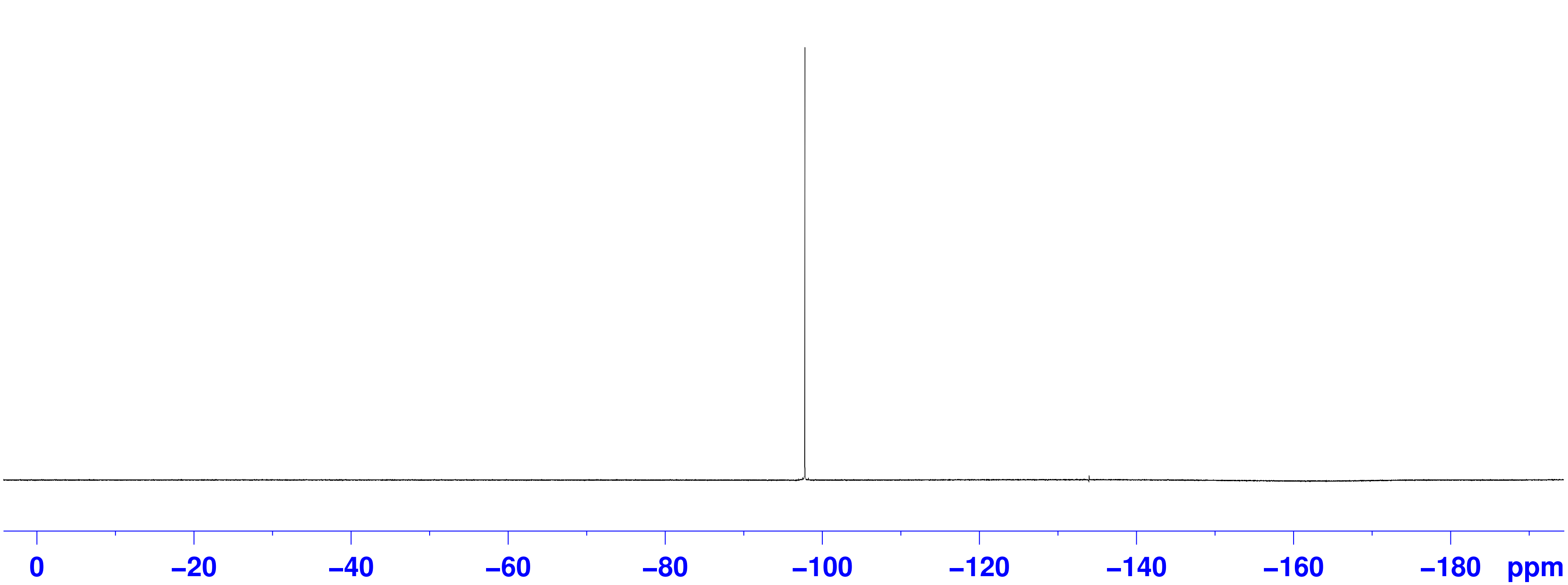
zgh-6-84-C

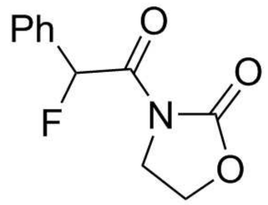

149.4798
146.6885
136.6542
136.6419
134.3562
134.3195
128.7130
128.1840
126.6366
119.5037
119.4916
108.6843
108.4359
77.3854
77.0678
76.7502
38.3833
35.9066
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



Z-**2p**

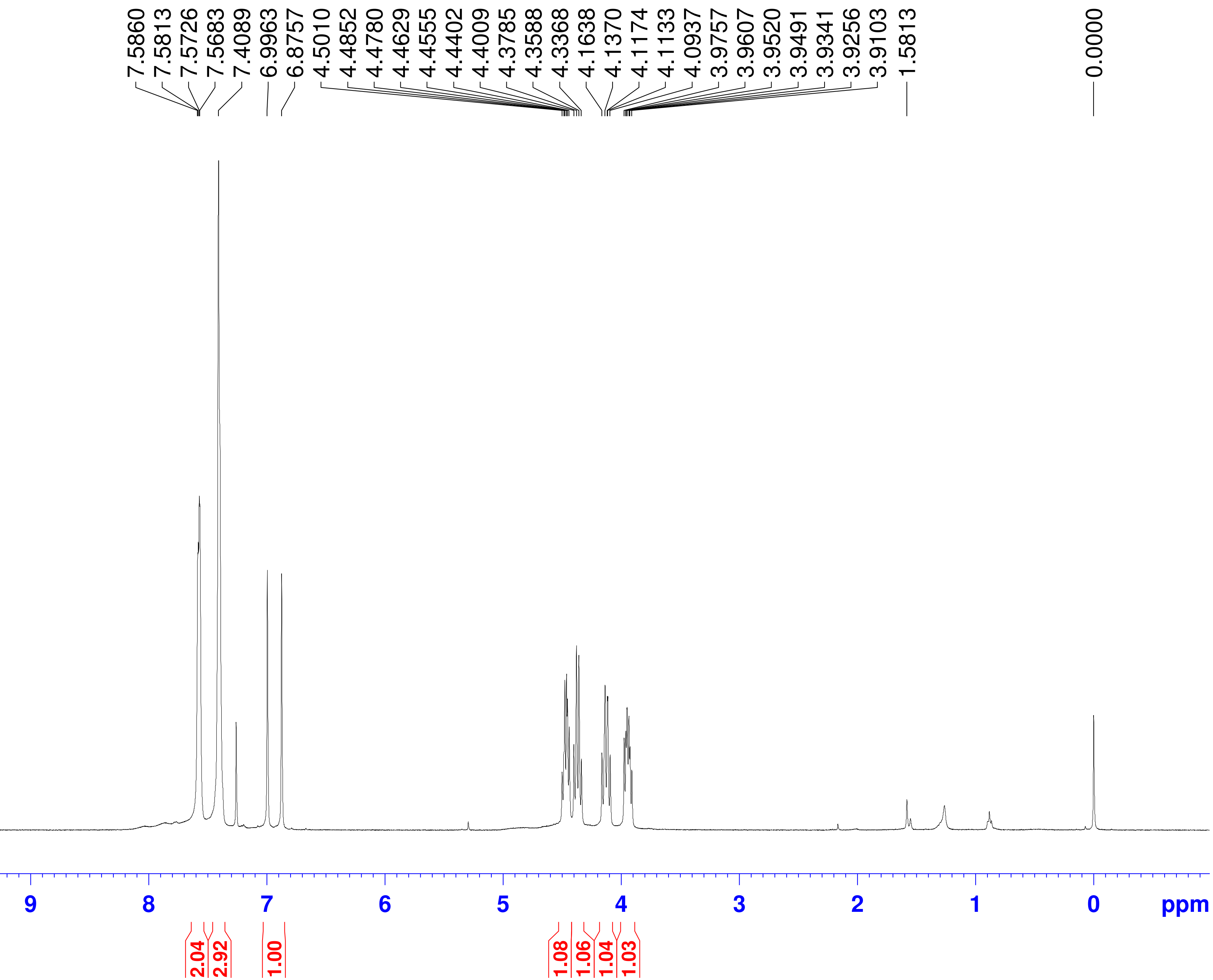
zgh-6-84-F

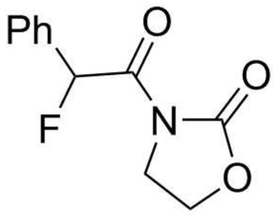




4a

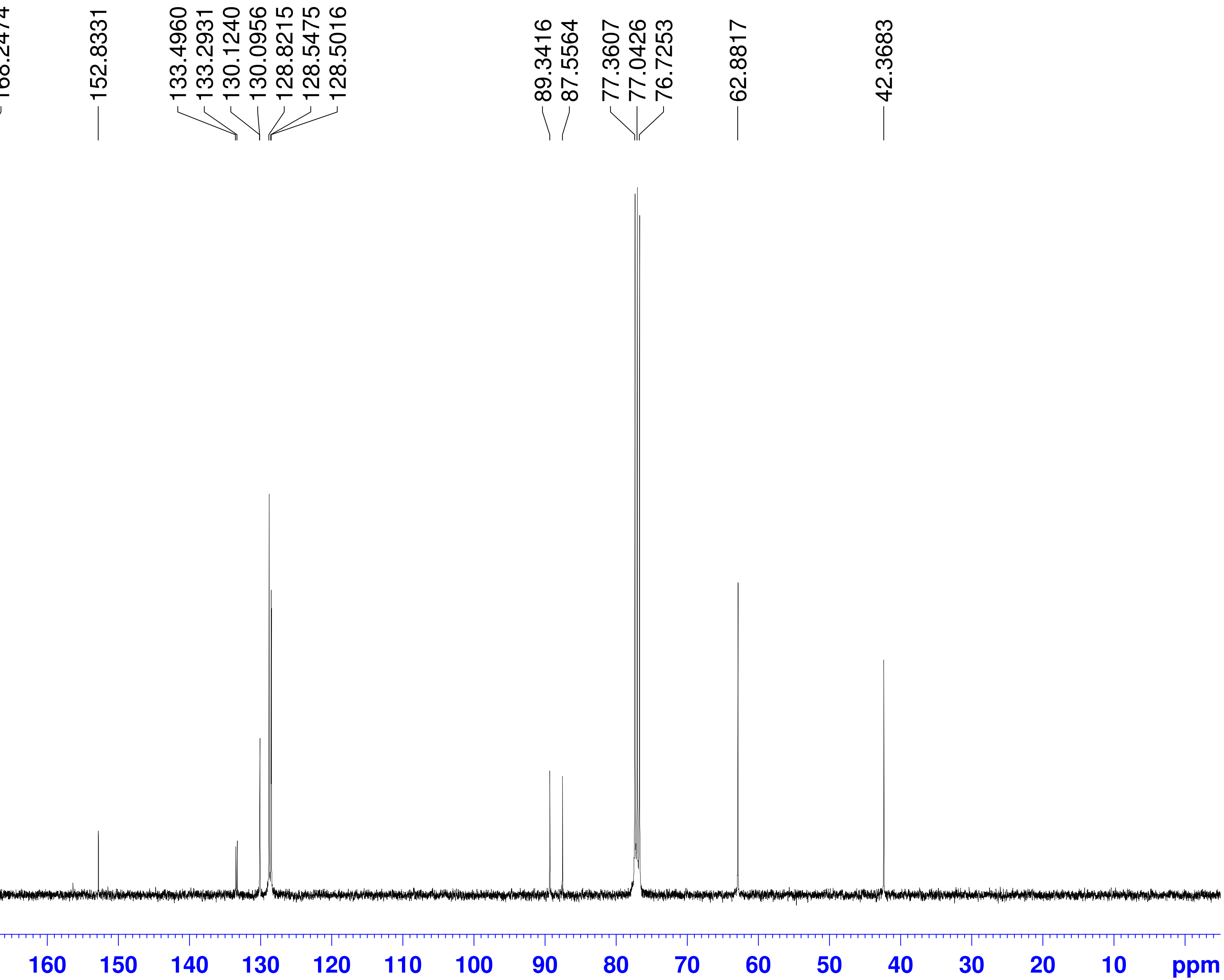
zgh-6-68-H


7.5860
7.5813
7.5726
7.5683
7.4089
6.9963
6.8757
4.5010
4.4852
4.4780
4.4629
4.4555
4.4402
4.4009
4.3785
4.3588
4.3368
4.1638
4.1370
4.1174
4.1133
4.0937
3.9757
3.9607
3.9520
3.9491
3.9341
3.9256
3.9103
1.5813
0.0000
10
9
8
7
6
5
4
3
2
1
0
ppm
2.04
2.92
1.00
1.08
1.06
1.04
1.03

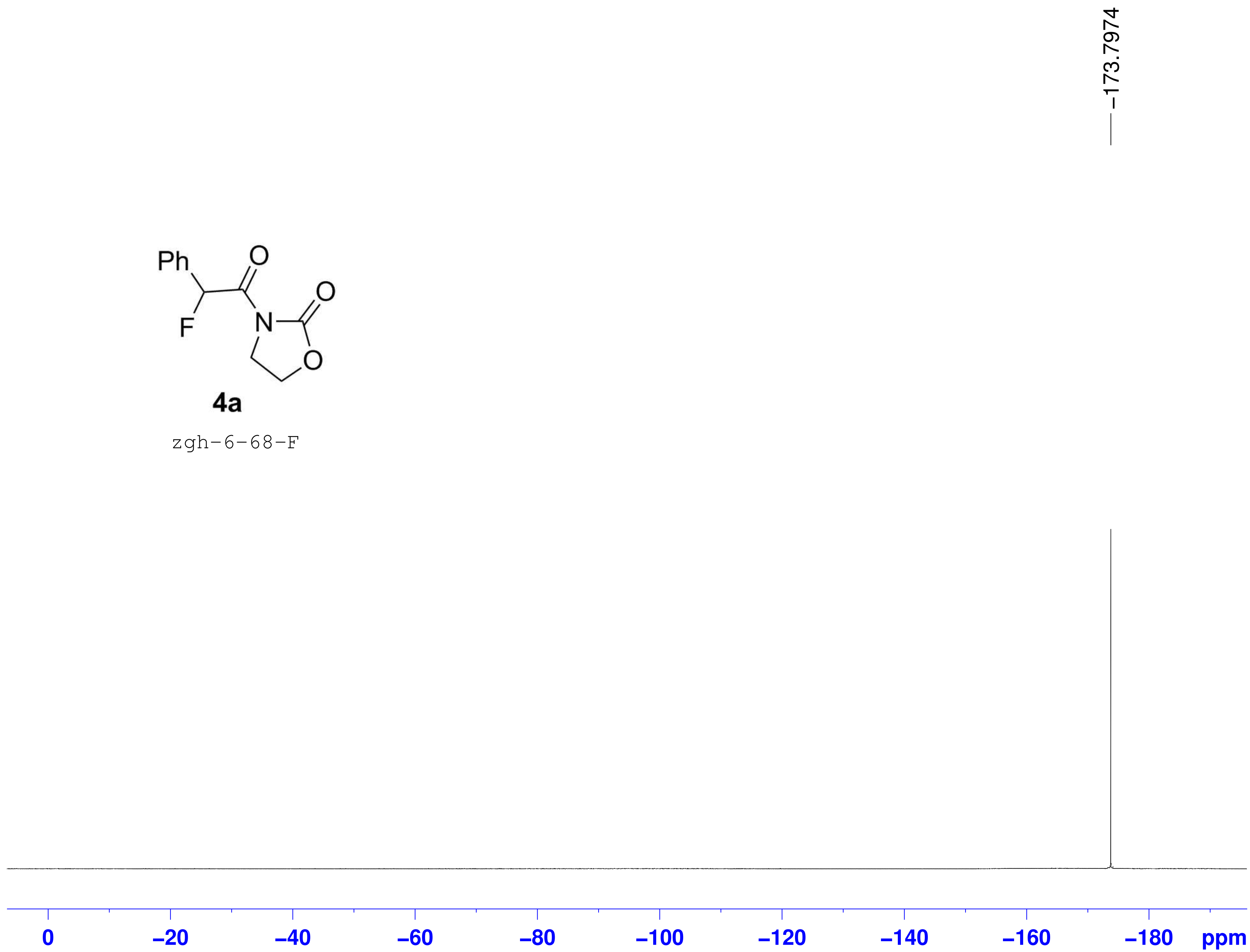


4a

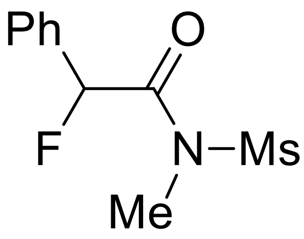
zgh-6-68-C



168.5193
168.2474
152.8331
133.4960
133.2931
130.1240
130.0956
128.8215
128.5475
128.5016
89.3416
87.5564
77.3607
77.0426
76.7253
62.8817
42.3683
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



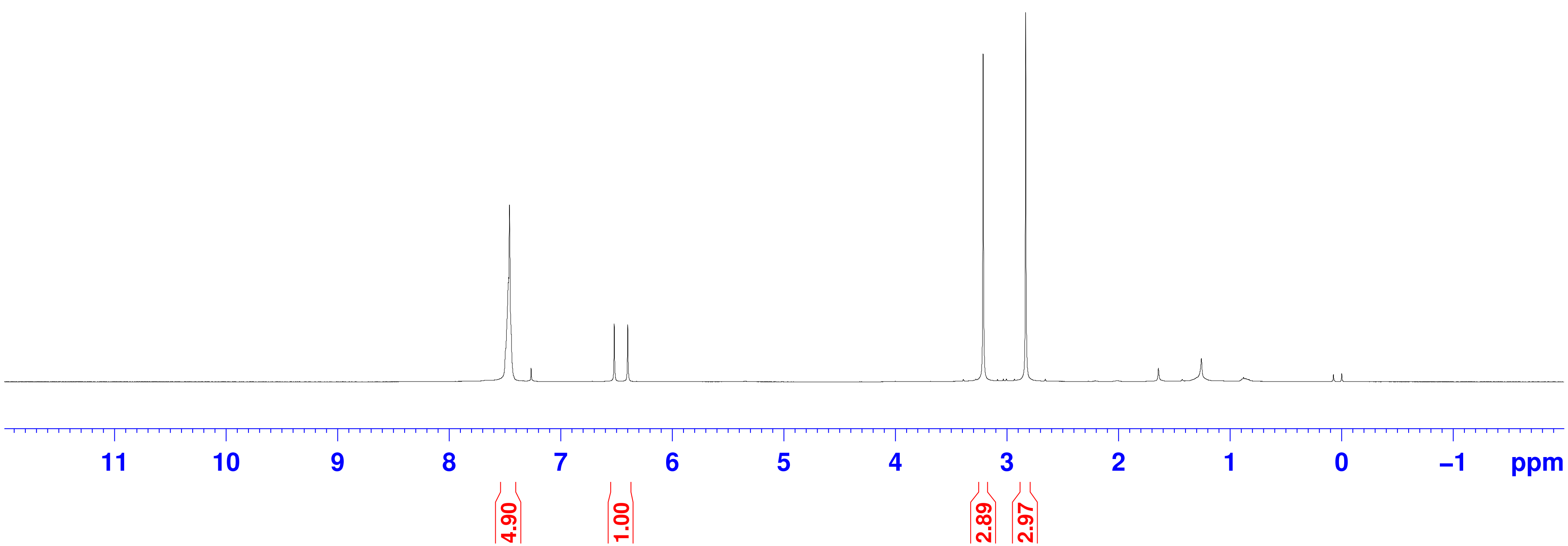
−173.7974
Ph
O
O
N
O
F
4a
zgh-6-68-F
0
−20
−40
−60
−80
−100
−120
−140
−160
−180
ppm



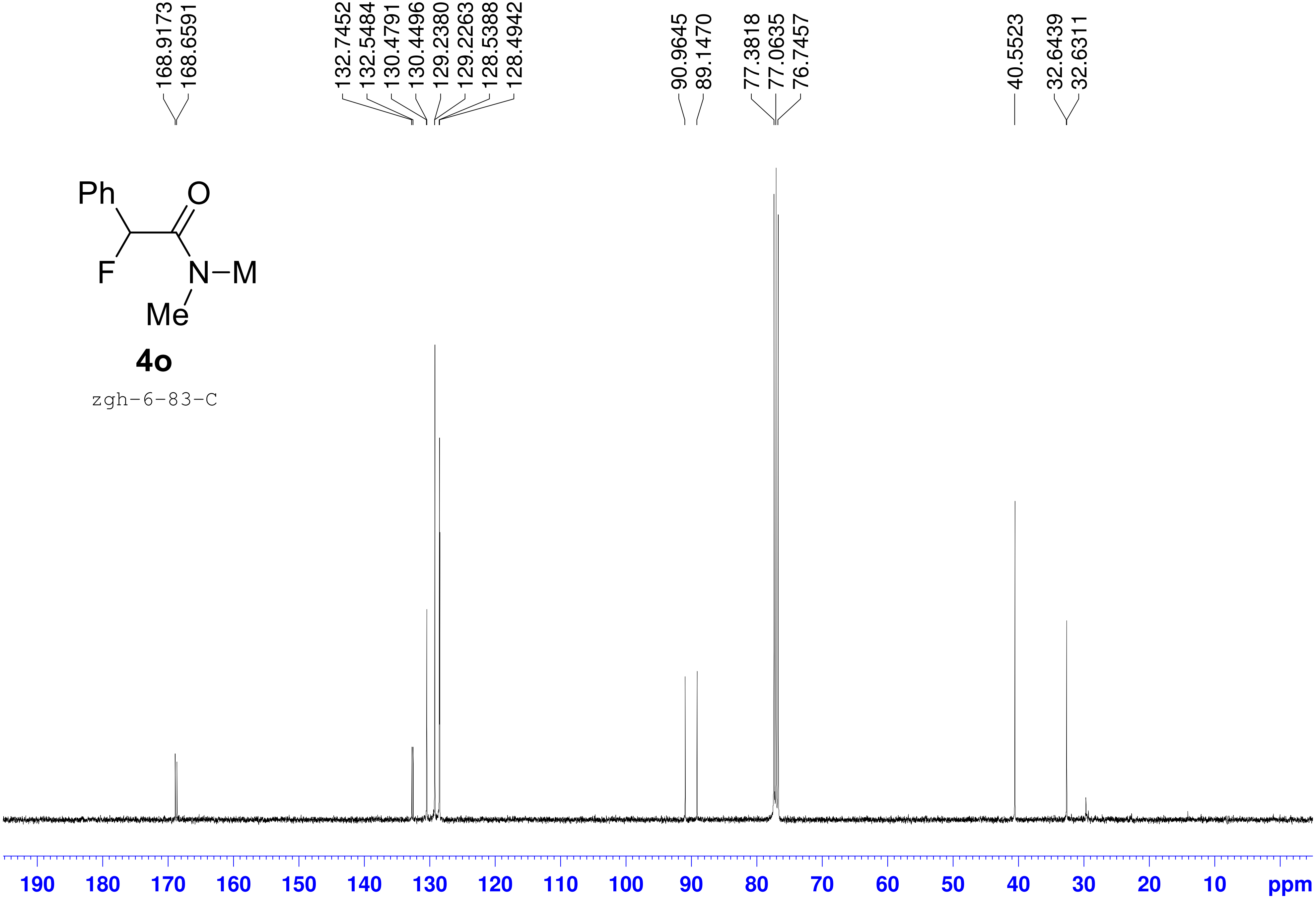
Ph
F
O
N–Ms
Me

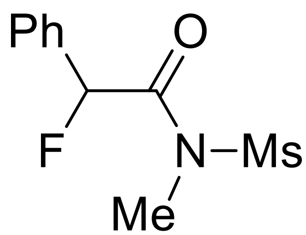
4o

zgh-6-83-H



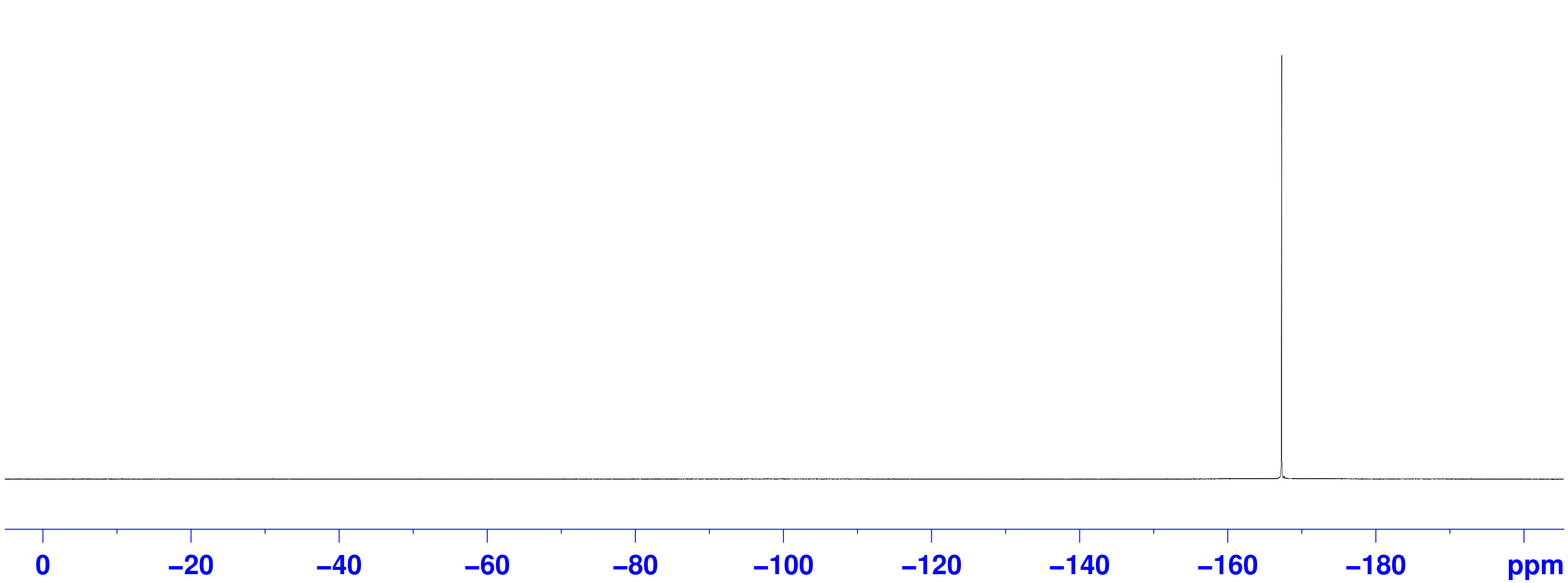
0.0000
2.8334
3.2143
6.4006
6.5214
7.2669
7.4486
7.4611
7.4670
7.4716
7.4958
2.97
2.89
1.00
4.90
ppm


168.9173
168.6591
132.7452
132.5484
130.4791
130.4496
129.2380
129.2263
128.5388
128.4942
90.9645
89.1470
77.3818
77.0635
76.7457
40.5523
32.6439
32.6311
Ph
O
F
N−M
Me
4o
zgh-6-83-C
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

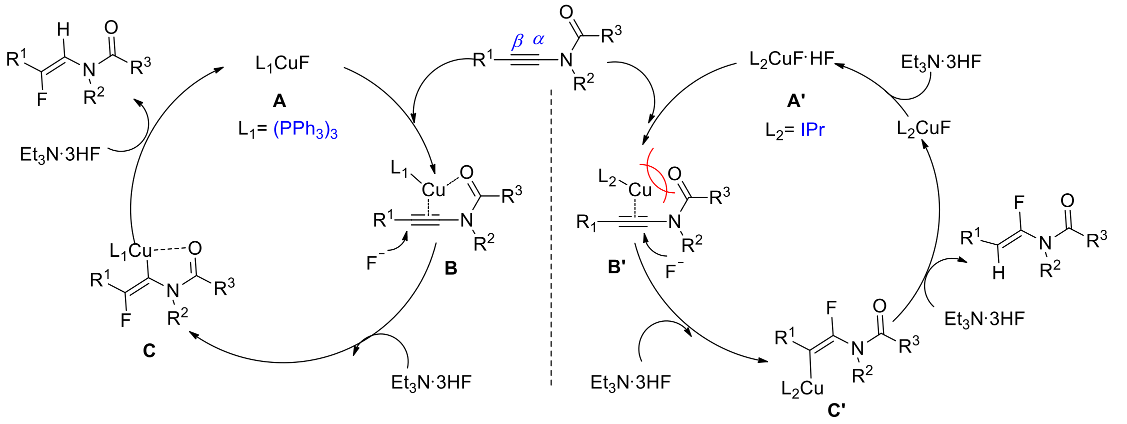


4o

zgh-6-83-F



Detailed discussions on the (IPr)CuF-catalyzed reaction mechanism:



(PPh$_3$)$_3$ as ligand	*IPr as ligand*
Shape of phosphine ligand: cone-shaped	NHCs are in general more electron-donating than phosphines
	Shape of NHCs ligand: fan-shaped

The regioselectivity of the hydrofluorination was controlled by the ligand[1] of the copper-catalyst. We think that the overall regioselectivity may be controlled in the coordination process (A→B or A'→B'), though we cannot provide any more direct evidence. For the cone-shaped ($Ph_3P)_3$ ligand, the chelation of Cu(I) cation to the ynamido carbonyl oxygen contributes to the regioselective attack of fluoride nucleophile at β-carbon of ynamides.[2] In contrast, the larger steric hindrance of IPr ligand suppresses the chelation process, thus fluoride nucleophile tends to attack α-carbon of ynamides.

References:

1. Differences between *N*-heterocyclic carbene and phosphine ligands: (*a*) R. H. Crabtree, *J. Organomet. Chem.*, 2005, **690**, 5451-5457; (*b*) H. Clavier and S. P. Nolan, *Chem. Commun.*, 2010, **46**, 841-861; (*c*) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature*, 2014, **510**, 485-496.
2. For the chelation of the organometal reagent to the carbamoyl moiety of ynamides: (*a*) Y. Fukudome, H. Naito, T. Hata and H. Urabe, *J. Am. Chem. Soc.*, 2008, **130**, 1820-1821; (*b*) H. Yasui, H. Yorimitsu and K. Oshima, *Bull. Chem. Soc. Jpn.*,

2008, **81**, 373-379; (*c*) B. Gourdet and H. W. Lam, *J. Am. Chem. Soc.*, 2009, **131**, 3802-3803; (*d*) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2010, **110**, 5064-5106; (*e*) Y. Minko, M. Pasco, L. Lercher, M. Botoshansky and I. Marek, *Nature*, 2012, **490**, 522-526.