Supporting Information

Darzens reaction of thioisatins and sulfonium salts: approach to synthesis of thiochromenone derivatives with anticancer potency

Jinhui Shen,[‡a] Yang Yang,[‡b] Xiaoli Hou,[a] Wenlei Zeng,[a] Aimin Yu,[a] and Xiangtai Meng[a]*

[a]Tianjin Key Laboratory of Organic Solar Cells and Photochemical Conversion, School of Chemistry & Chemical Engineering, Tianjin University of Technology, Tianjin 300384, P. R. China
[b]Guilin Medical University, Guilin 541004, Guangxi, P. R. China
E-mail: mengxiangtai23@mail.nankai.edu.cn

Contents

1. Table S1. Crystal data and structure refinement for 3a.

Identification code	**3a**
Empirical formula	$C_{17}H_{12}O_3S$
Formula weight	296.33
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 8.2863(10)Å α = 87.057(10) deg. b = 8.9590(11) Å β = 70.068(11) deg. c = 10.6474(12) Å γ = 71.080(11) deg.
Volume	701.38(15) $Å^{-3}$
Z, Calculated density	2, 1.403 mg/m^{-3}
Absorption coefficient	0.237 mm^{-1}
F(000)	308
Crystal size	0.12 x 0.10 x 0.08 mm
Theta range for data collection	2.04 to 25.00 deg.
Limiting indices	-9<=h<=9, -10<=k<=6, -12<=l<=12
Reflections collected / unique	3368 / 2470 [R(int) =0.0226]
Completeness to theta = 25.00	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.84063
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2470 / 0 / 192
Goodness-of-fit on F^2	1.084
Final R indices [I>2sigma(I)]	R1 = 0.0450, wR2 = 0.1096
R indices (all data)	R1 = 0.0685, wR2 = 0.1364
Largest diff. peak and hole	0.249 and -0.236 e.A^-3

2. Cytotoxicity assay

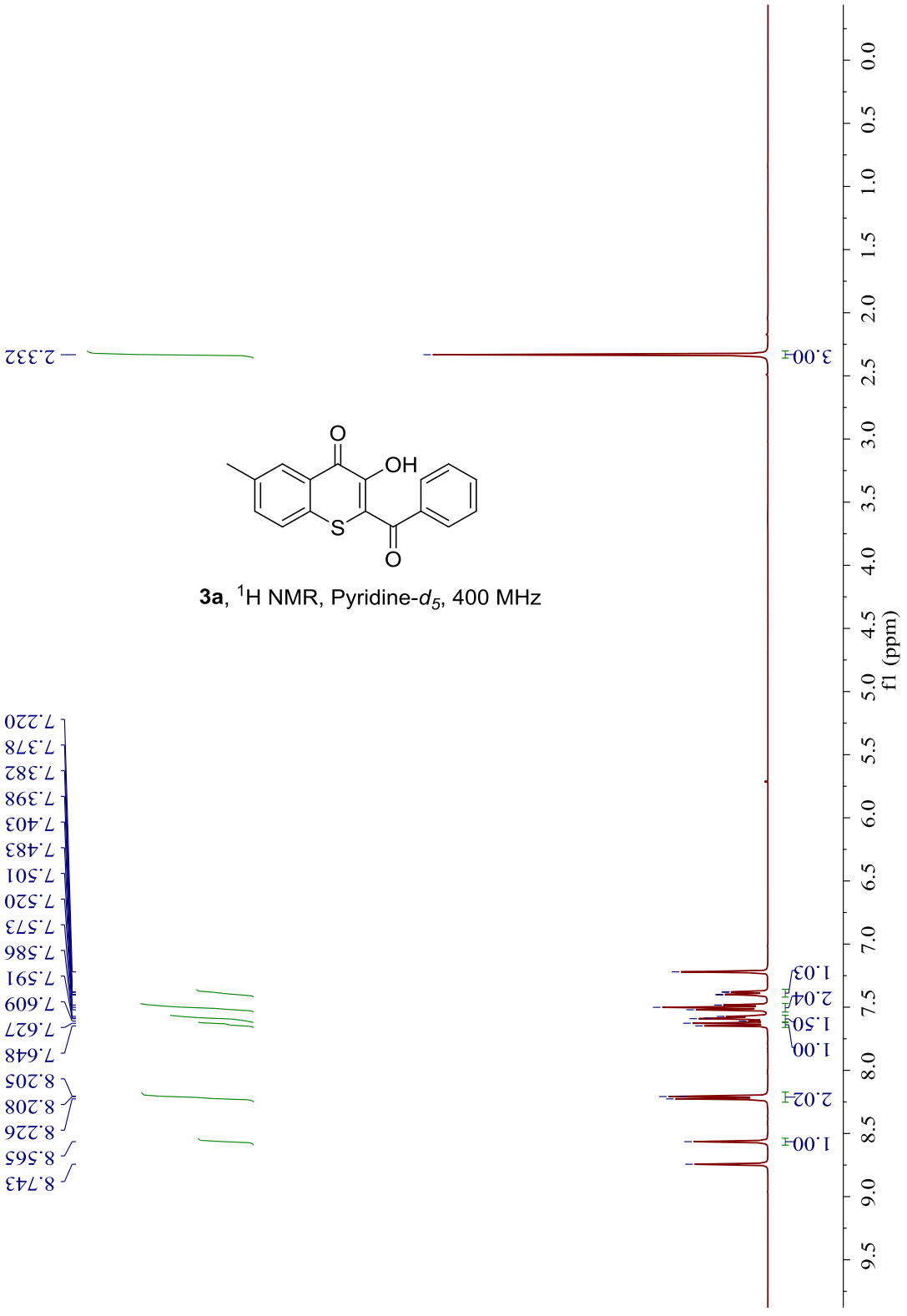
The cytotoxicities of all the compounds were evaluated by a modified MTT assay. MGC-803, T-24, NCI-H460, HepG2, Hep-3B and SMMC-7721 cell lines used in this study were all purchased from the Institute of Biochemistry and Cell Biology, China Academy of Sciences. All were supplemented with 10% heat-inactivated fetal bovine serum in a humidified atmosphere of 5% CO_2/95% air at 37°C. The cells were cultured in 96-well plates containing 100 μl of the growth medium per well at a concentration of 5000 cells/well. After 24 h, a series of concentrations of compounds in dimethylsulfoxide (DMSO, Sigma) was added to triplicate wells at doses of 2.5, 5, 10, 15, 20, 25, 30, 40, 50 μM. The final concentration of DMSO in the culture medium was maintained at 1.0% (v/v) to avoid toxicity of the solvent. After 48 h, cells were treated with 20 μl of 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide (MTT, 5 mg/ml, Sigma) and incubated for 4 h at 37°C. The medium was removed and 100 μl of DMSO was added to each well. After shaking for 10 min, the absorbance was measured at 490 nm. Cytotoxicity is expressed as the concentration of samples inhibiting cell growth by 50% (IC50), compared with the control (using cells treated with 1.0% DMSO). All tests and analyses were run in triplicate and averaged.

3. Table S2. IC50 values of thiochromenones towards six selected tumor cell lines.[a]

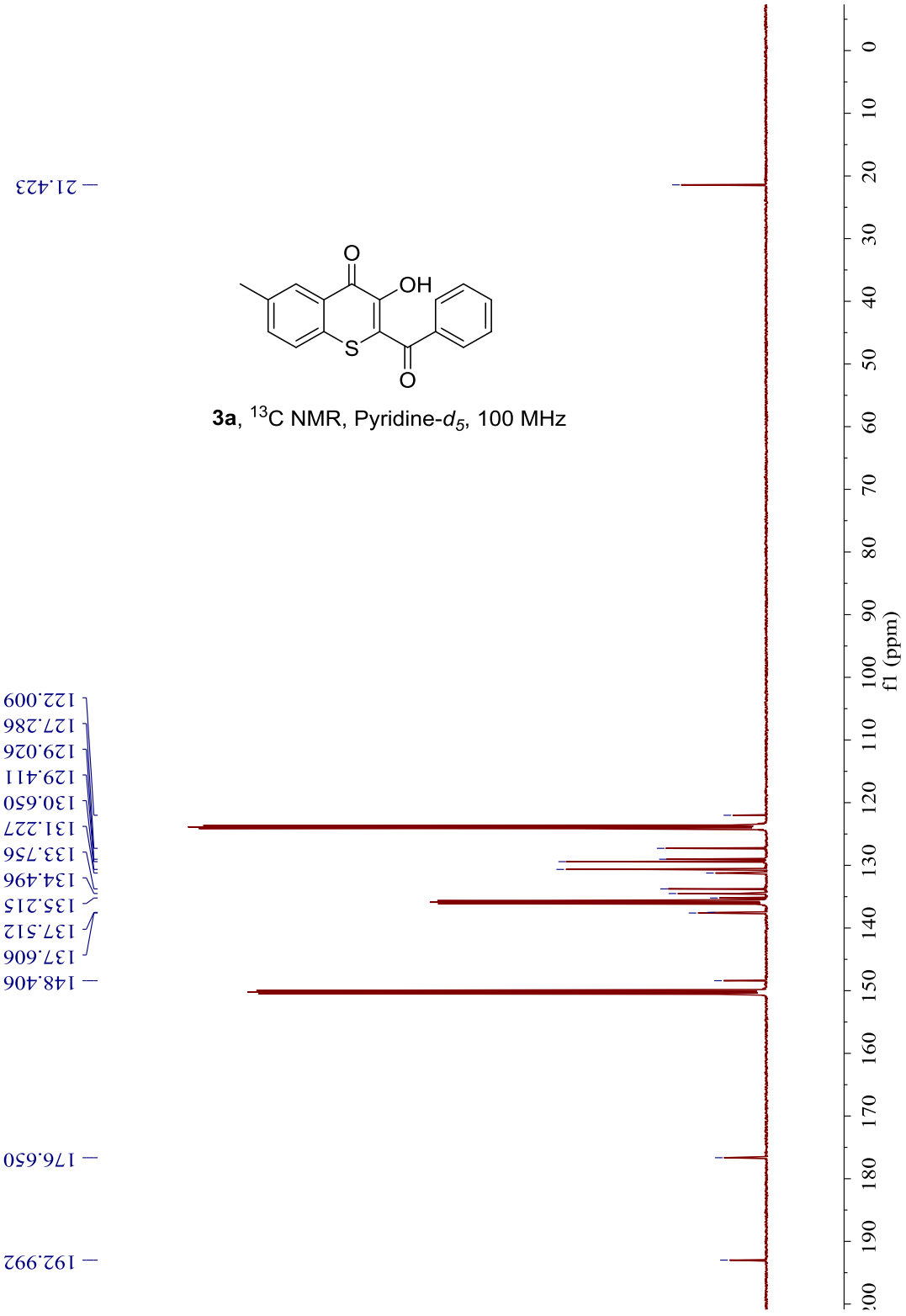
Compounds	IC_{50} (μM)					
	MGC-803	T-24	NCI-H460	HepG2	Hep-3B	SMMC-7721
3a	>50	15.81±1.65	>50	15.65±3.31	>50	18.23±2.54
3b	6.80±0.93	4.24±0.34	>50	>50	>50	16.48±0.63
3c	8.29±0.99	12.02±0.26	>30	14.53±2.59	>30	>30
3d	6.79±0.48	4.13±0.61	>20	>20	8.41±1.07	5.16±0.57
3e	7.94±2.14	7.94±1.64	>20	>20	>20	>20
3f	6.93±1.40	5.01±0.15	25.20±2.56	5.26±0.17	9.58±0.60	7.34±0.88
3g	>50	>50	>50	>50	>50	>50
3h	>50	>50	>50	46.57±2.95	47.27±1.58	>50
3i	>25	>25	>25	23.72±0.25	>25	>25
3j	>50	>50	>50	10.56±0.77	30.15±3.36	>50
3k	>50	>50	>50	>50	>50	>50
3l	>50	>50	>50	>50	>50	>50
3m	>50	35.69±3.75	>50	24.52±3.87	>50	11.38±1.07
3n	>50	>50	>50	>50	>50	15.99±1.53
3o	>50	>50	>50	34.62±3.59	>50	11.76±2.39
3p	>25	>25	>25	>25	>25	>25
3q	>50	44.95±2.09	47.93±0.17	38.02±2.02	>50	>50
3r	>50	24.91±2.75	42.62±1.66	25.79±1.41	>50	>50
3s	>50	>50	>50	>50	>50	>50
3t	>50	>50	>50	28.36±2.23	>50	>50

[a] IC_{50} values are presented as the mean ± SD (standard error of the mean) from three separated experiments.

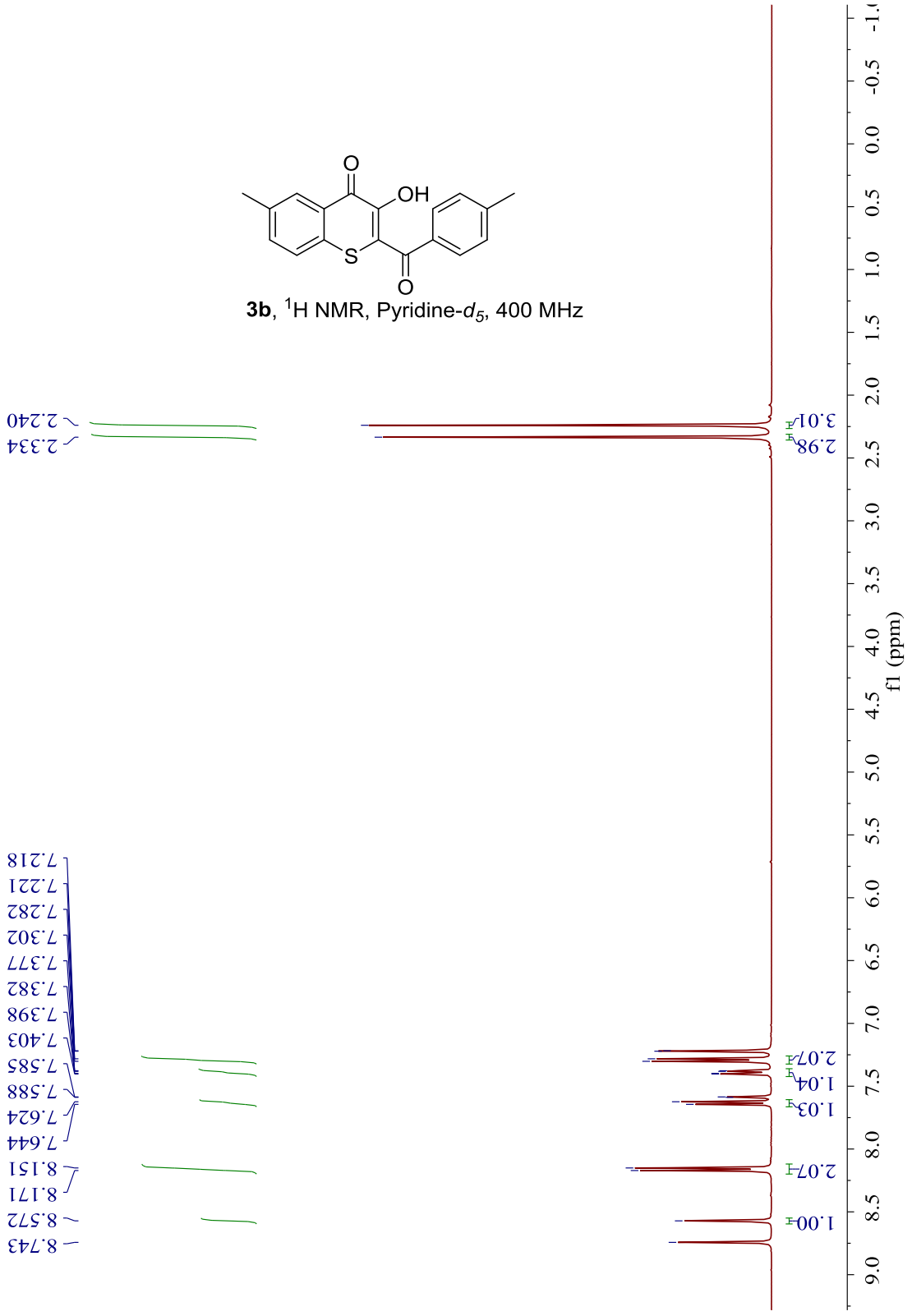
4. Copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds



3a, ^{1}H NMR, Pyridine-d_5, 400 MHz



3a, ^{13}C NMR, Pyridine-d_5, 100 MHz



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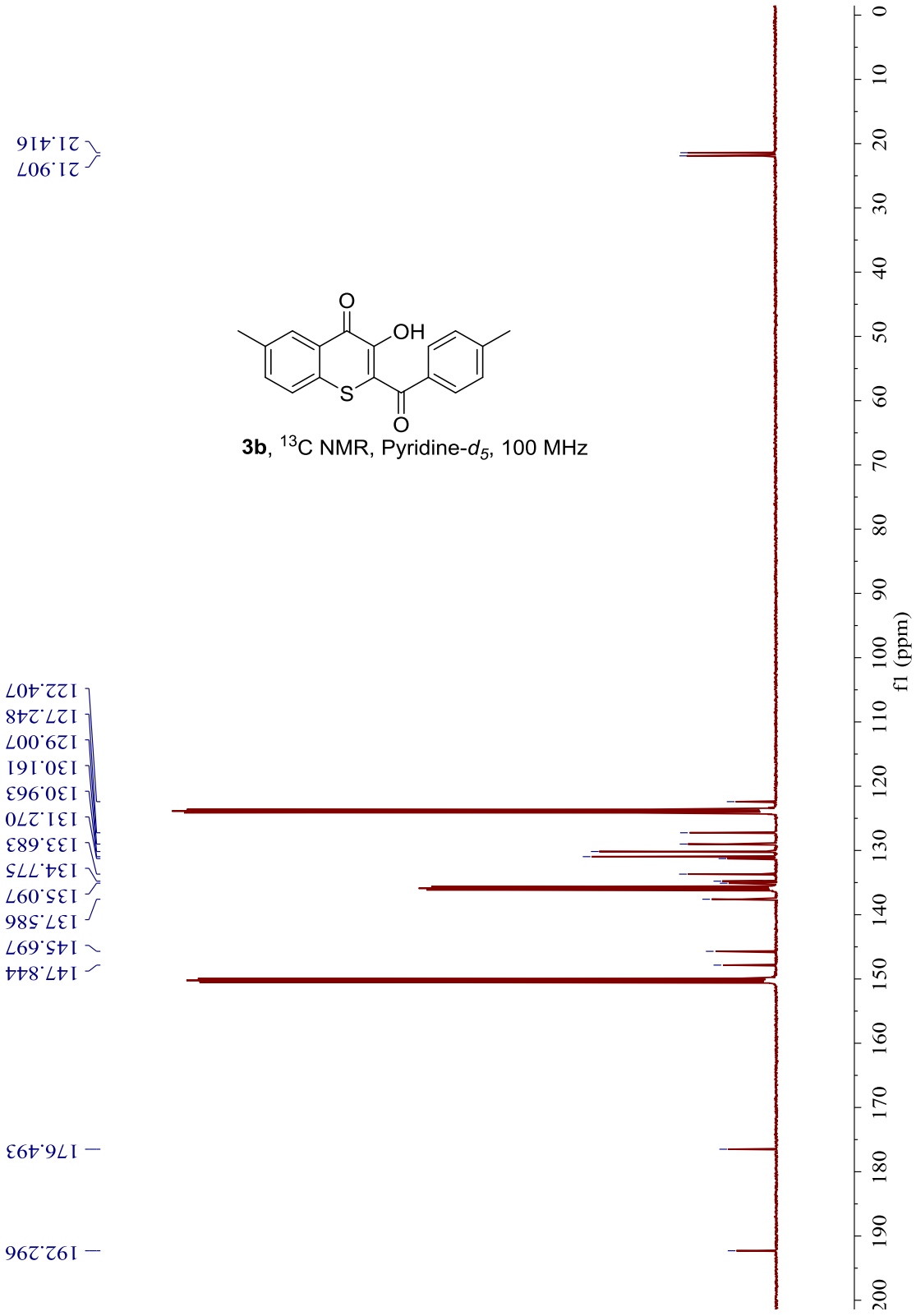
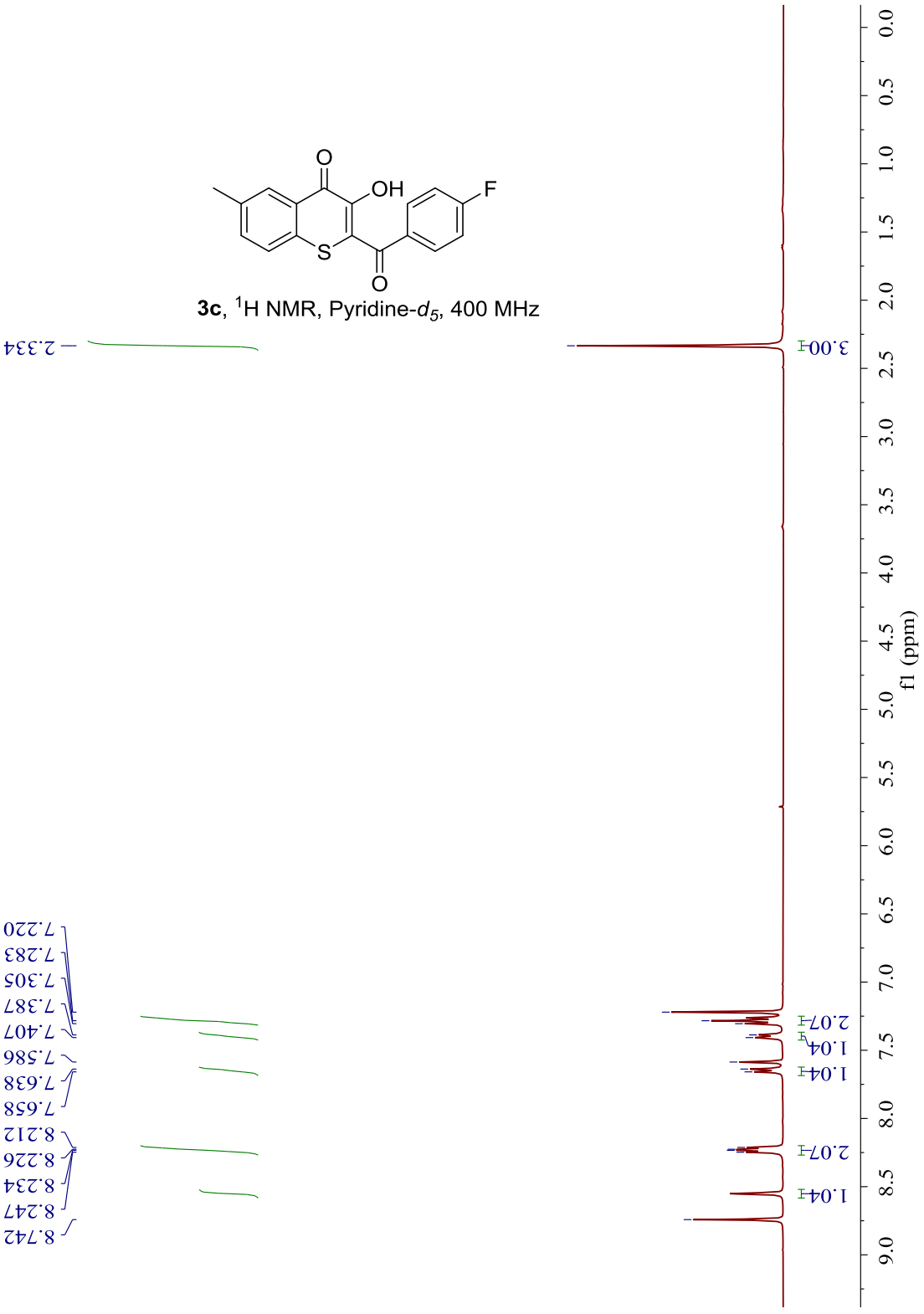
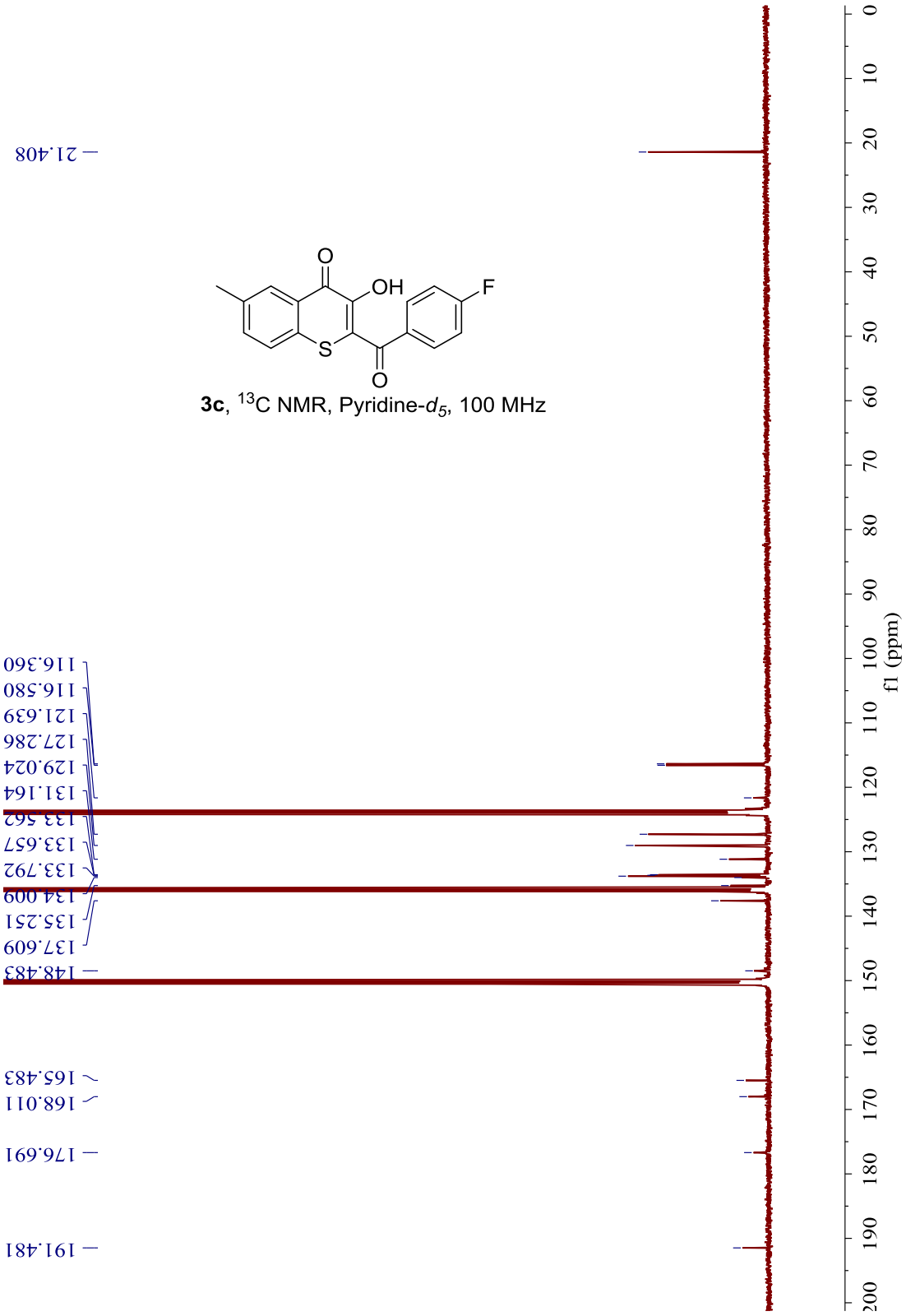
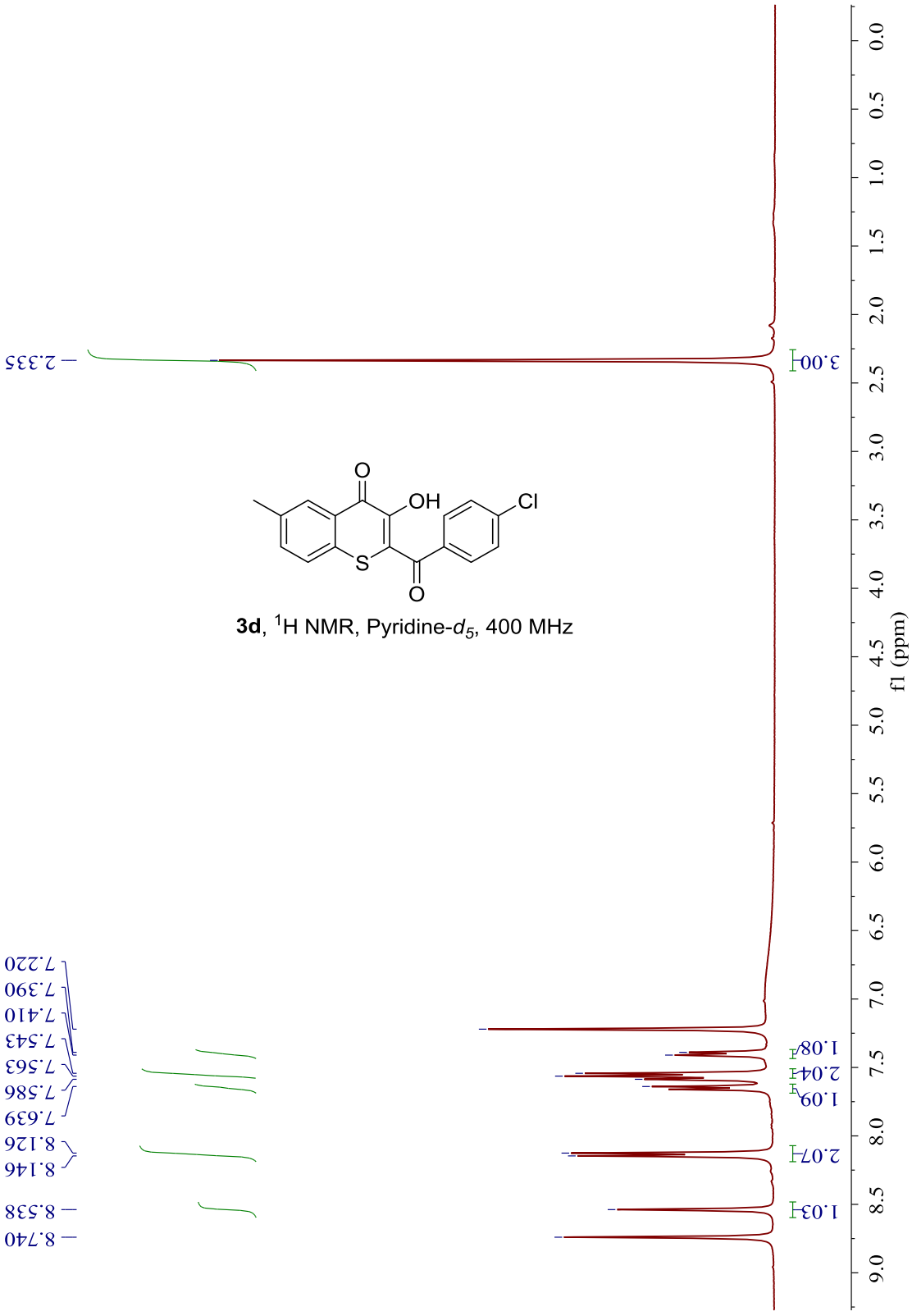


3b, ^{13}C NMR, Pyridine-d_5, 100 MHz

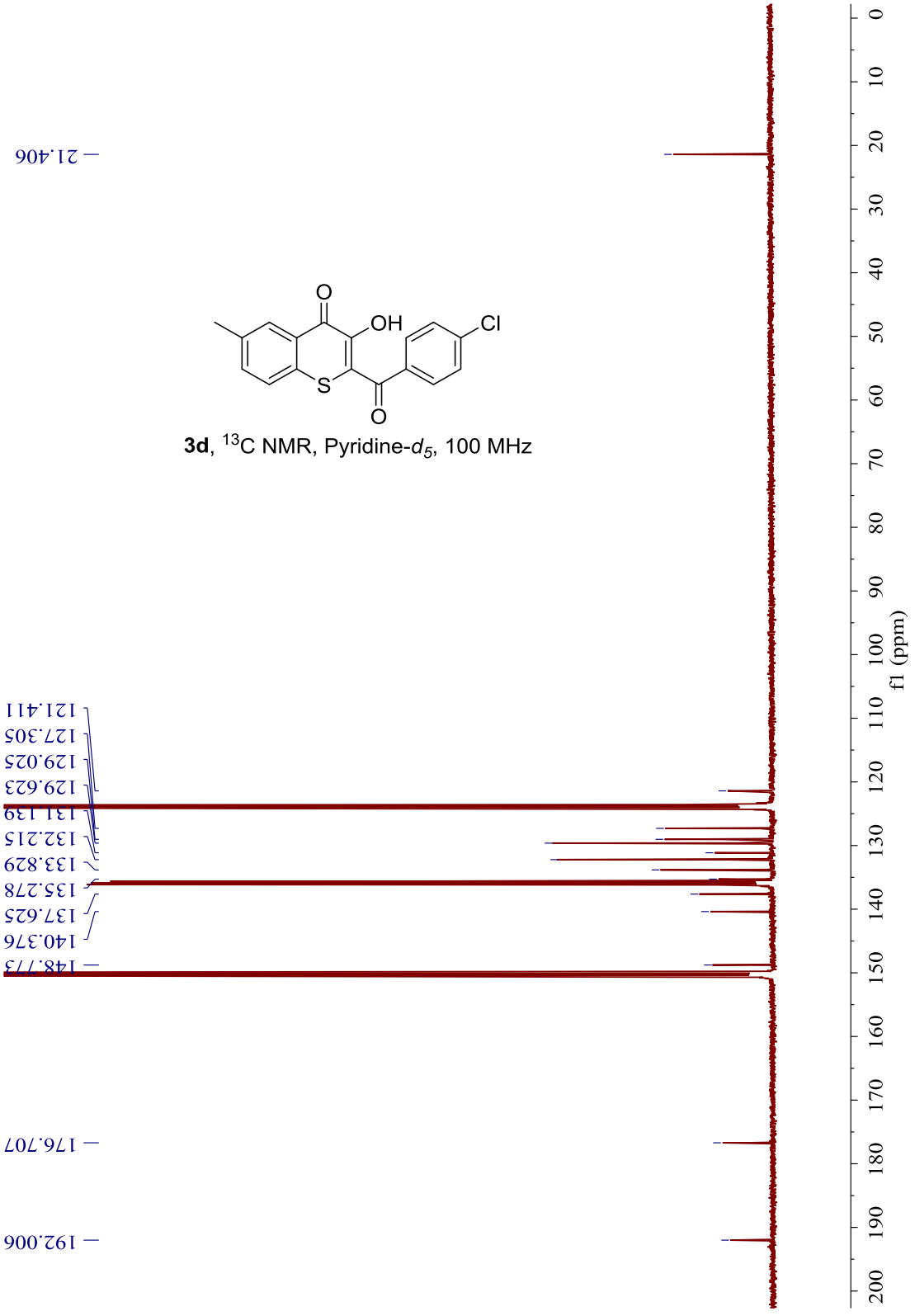

O
OH
F
S
O
3c, 1H NMR, Pyridine-d5, 400 MHz
2.334
3.00
2.07
1.04
1.04
2.07
1.04
2.07
8.742
8.247
8.234
8.226
8.212
7.658
7.638
7.586
7.407
7.387
7.305
7.283
7.220
f1 (ppm)



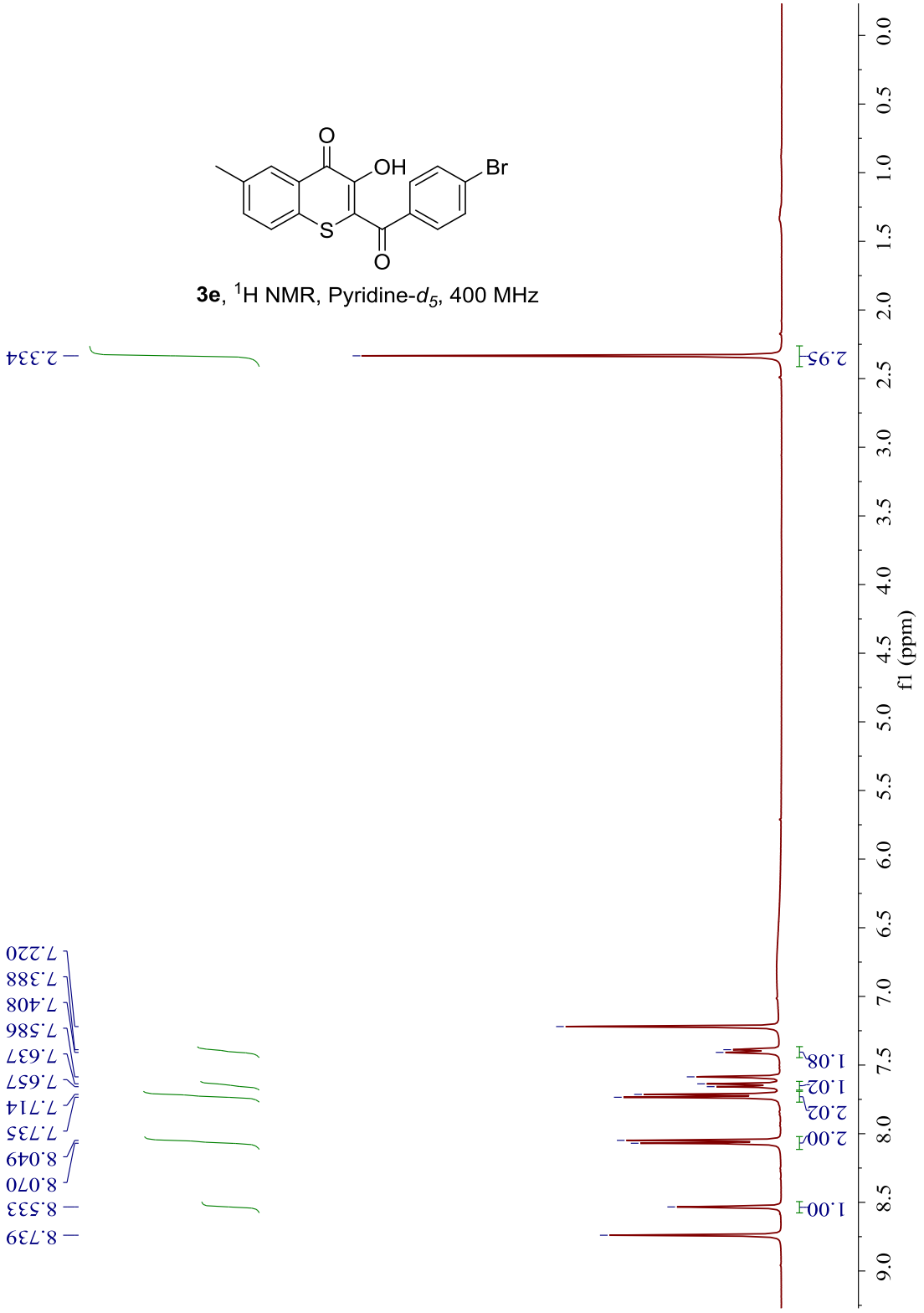
3c, ^{13}C NMR, Pyridine-d_5, 100 MHz



3d, ^{1}H NMR, Pyridine-d_5, 400 MHz



3d, ^{13}C NMR, Pyridine-d_5, 100 MHz


O
OH
Br
S
O
3e, 1H NMR, Pyridine-d5, 400 MHz
2.334
8.739
8.533
8.070
8.049
7.735
7.714
7.657
7.637
7.586
7.408
7.388
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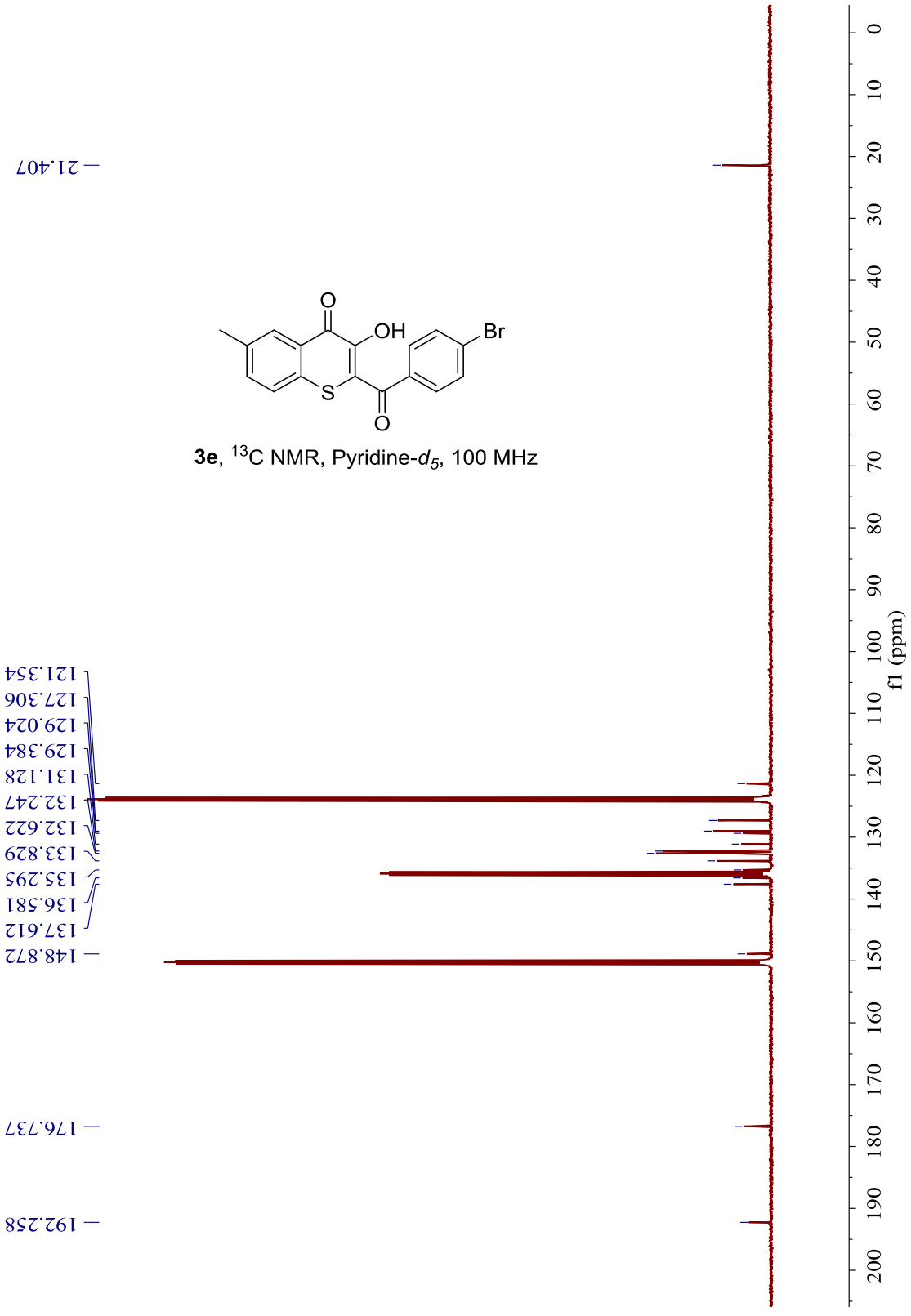
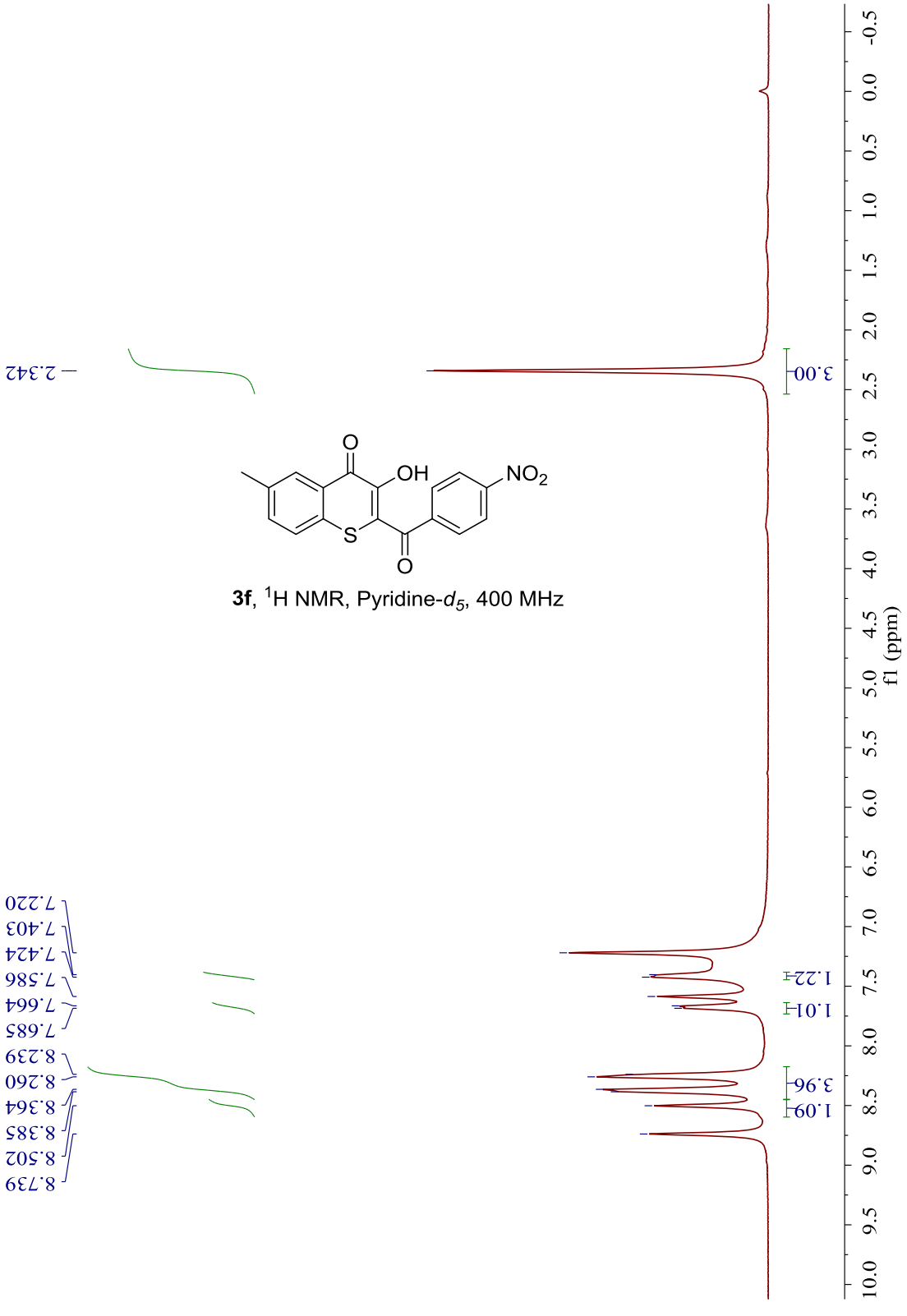
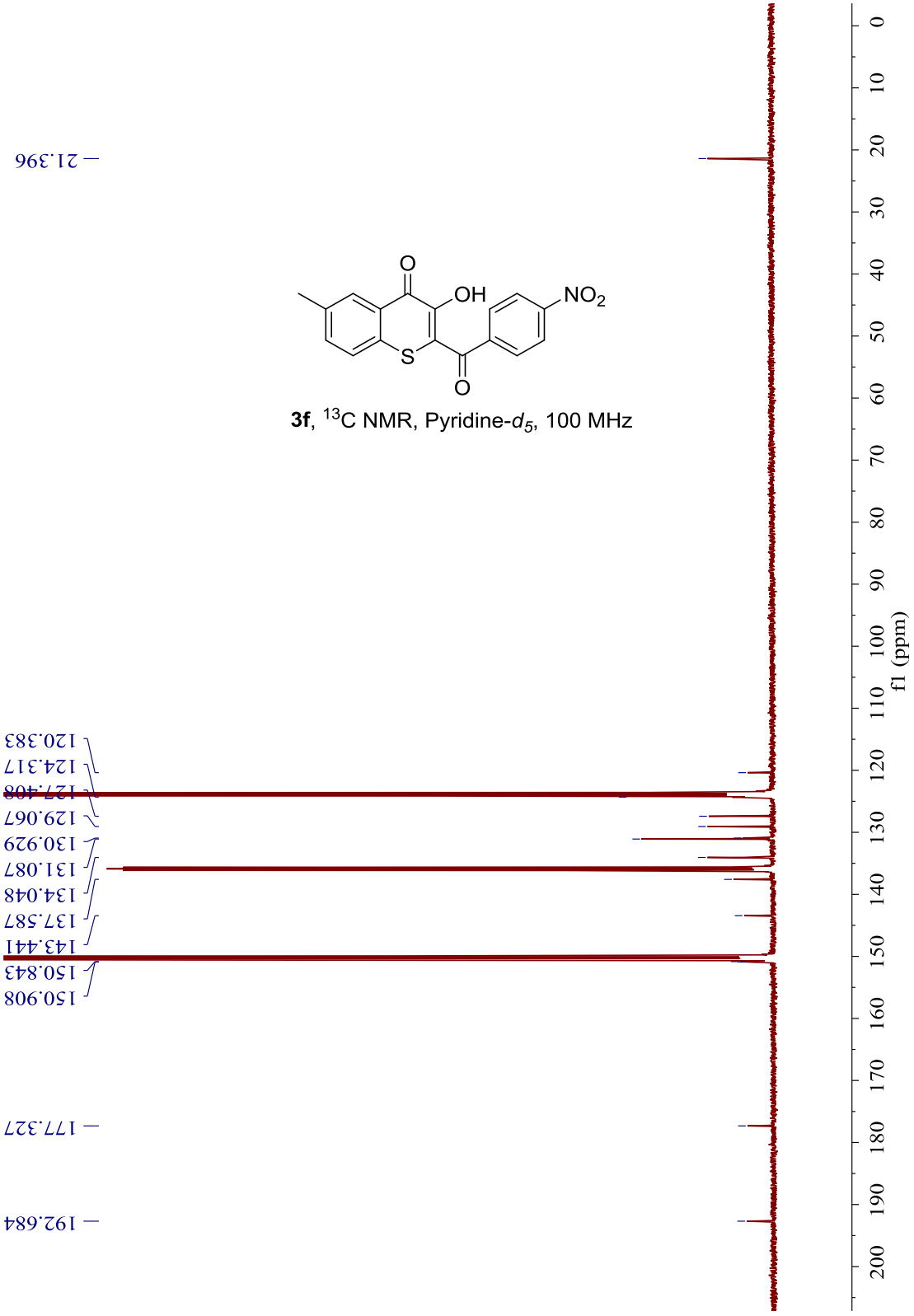
1.00
2.00
2.02
1.02
1.08
2.95
f1 (ppm)



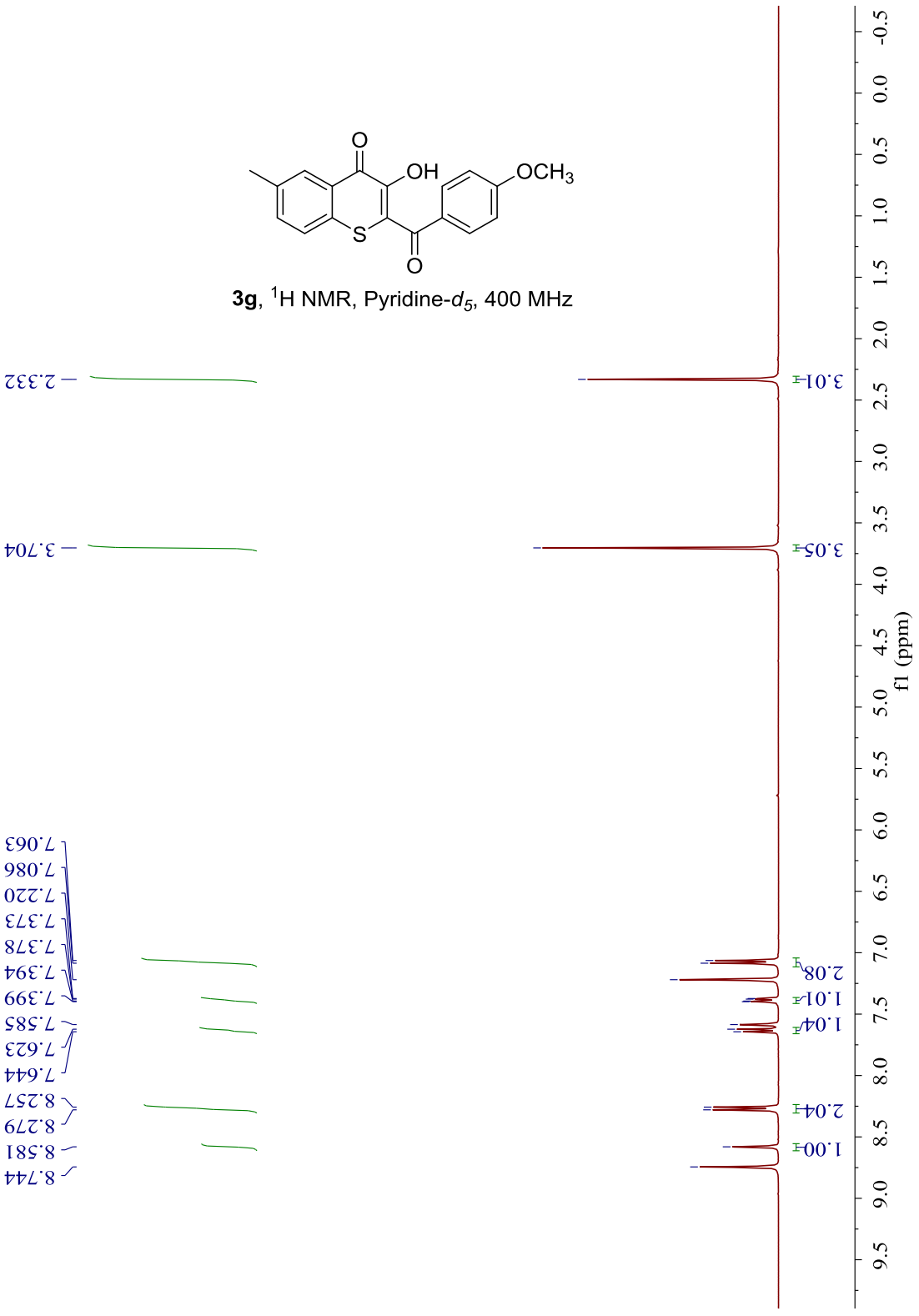
3e, ^{13}C NMR, Pyridine-d_5, 100 MHz

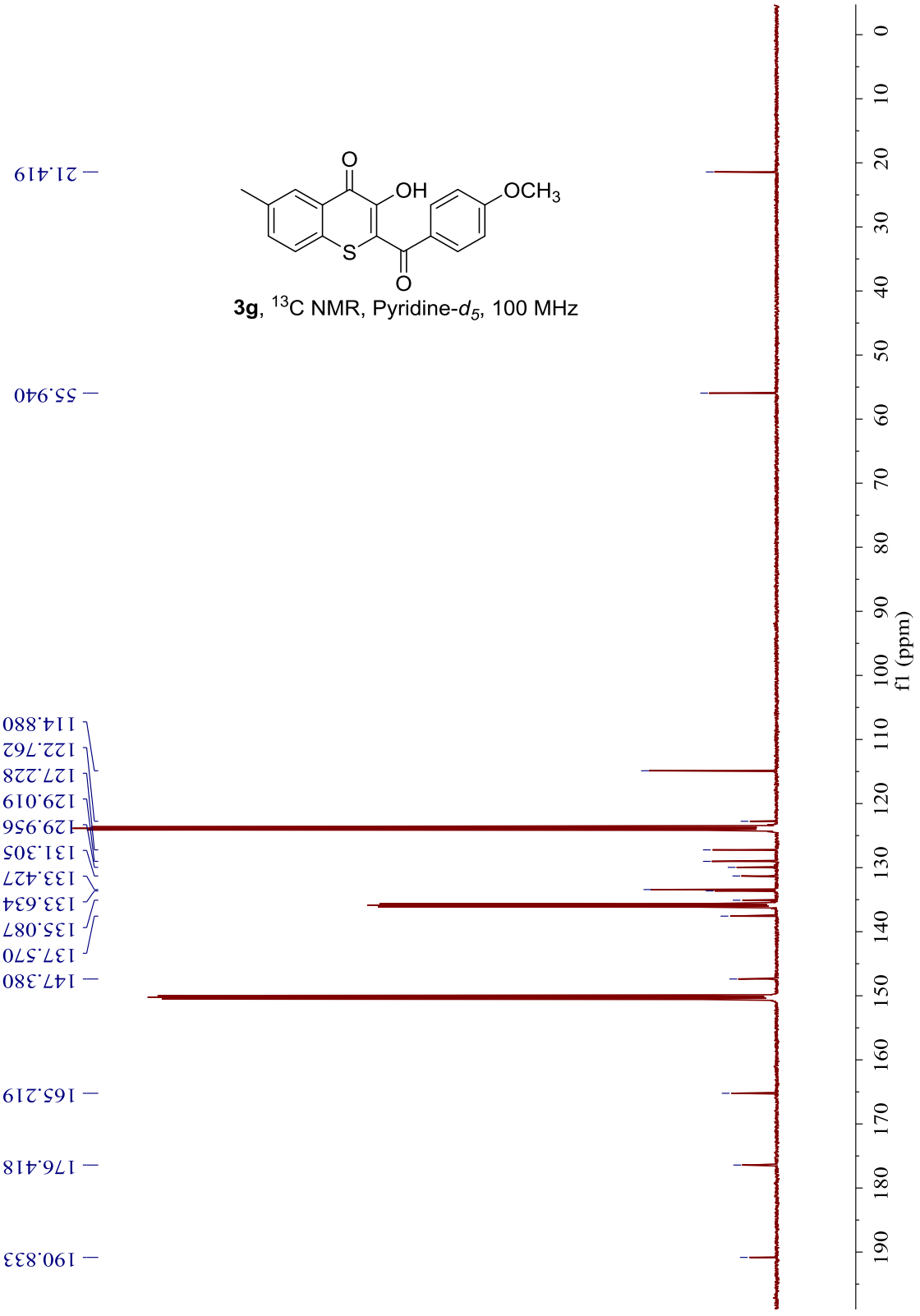


3f, ^{1}H NMR, Pyridine-d_5, 400 MHz

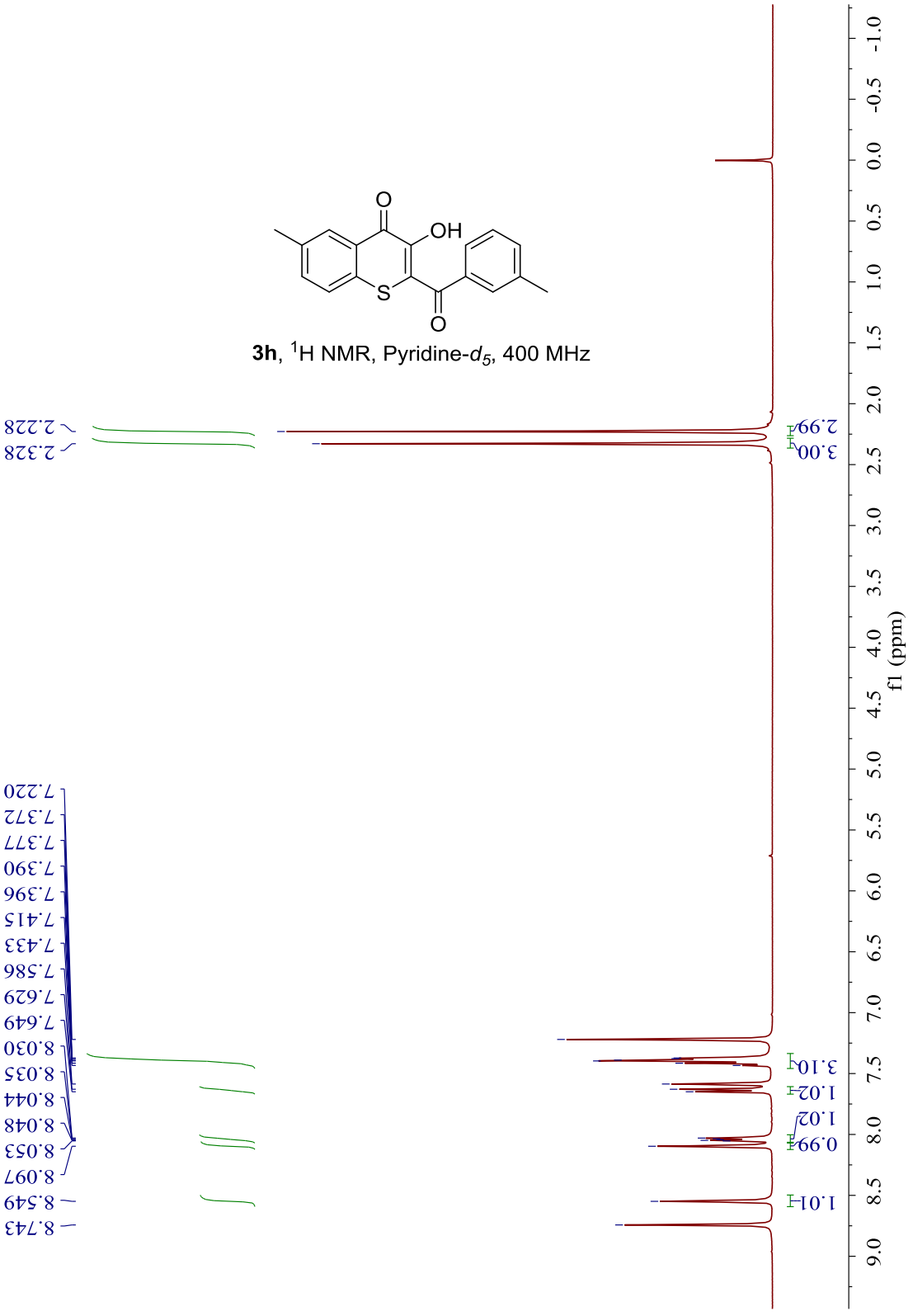


3f, ^{13}C NMR, Pyridine-d_5, 100 MHz

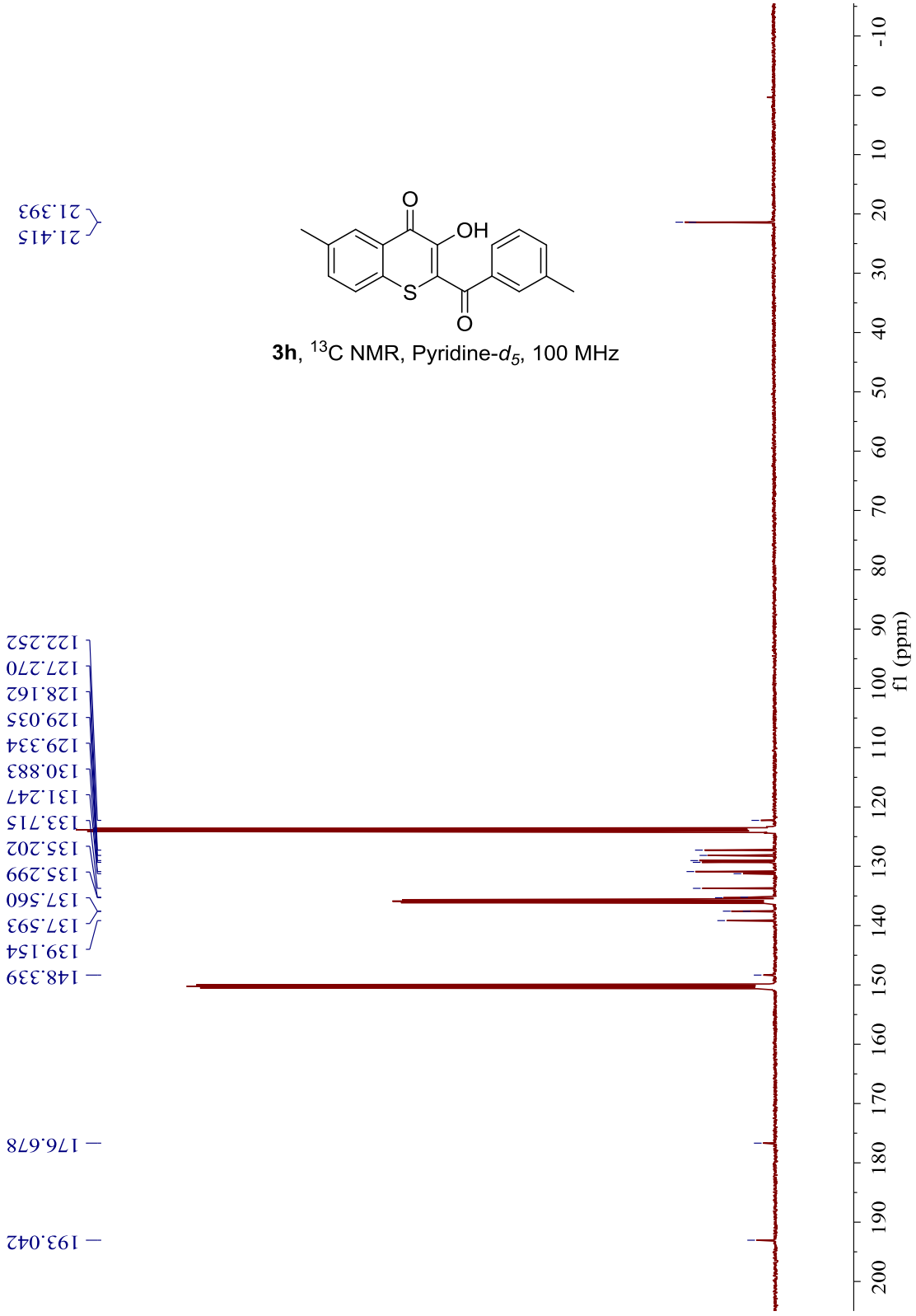

O
OH
OCH3
S
O
3g, 1H NMR, Pyridine-d5, 400 MHz
2.332
3.704
7.063
7.086
7.220
7.373
7.378
7.394
7.399
7.585
7.623
7.644
8.257
8.279
8.581
8.744
3.01
3.05
2.08
1.01
1.04
2.04
1.00
f1 (ppm)



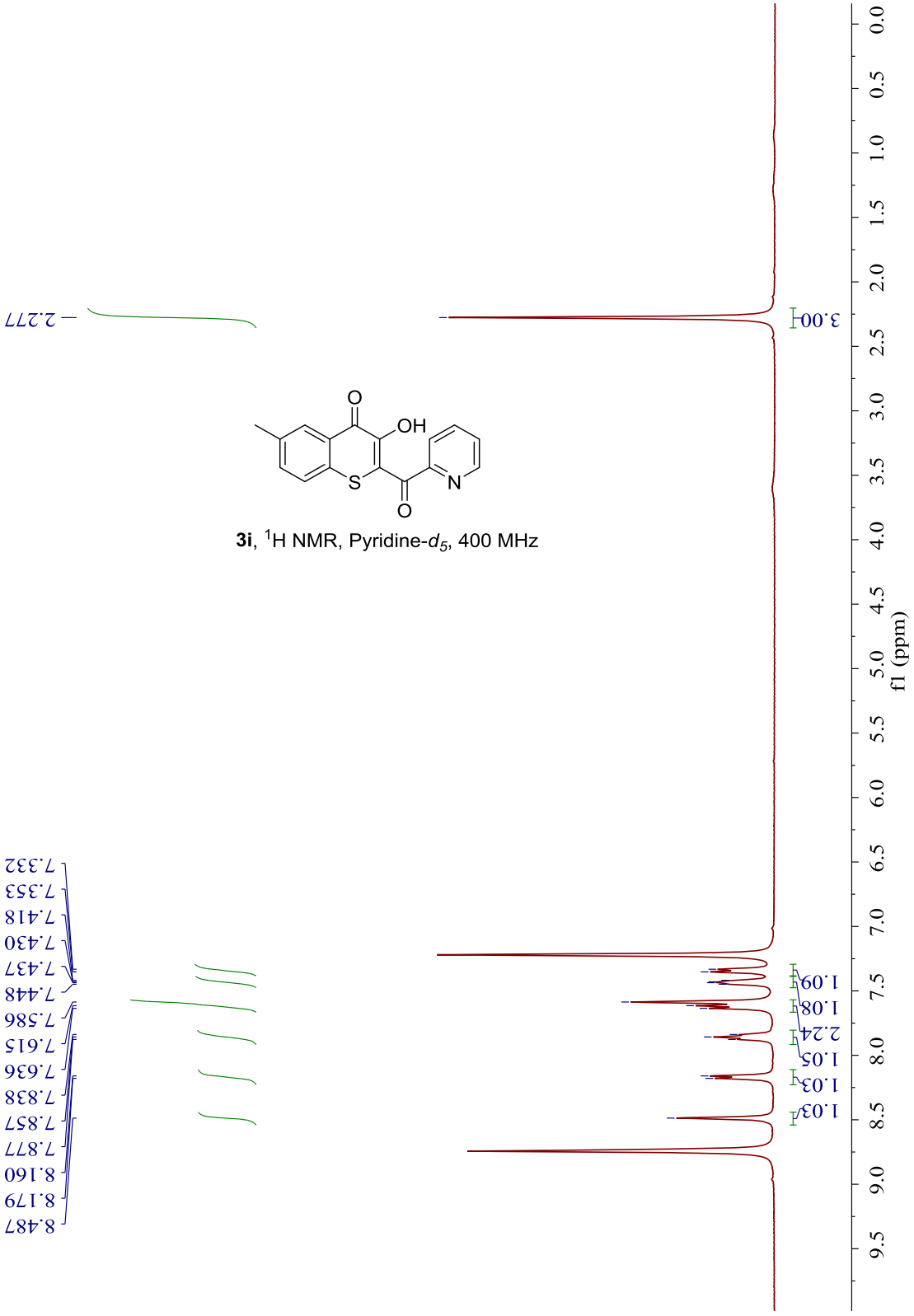
3g, ^{13}C NMR, Pyridine-d_5, 100 MHz



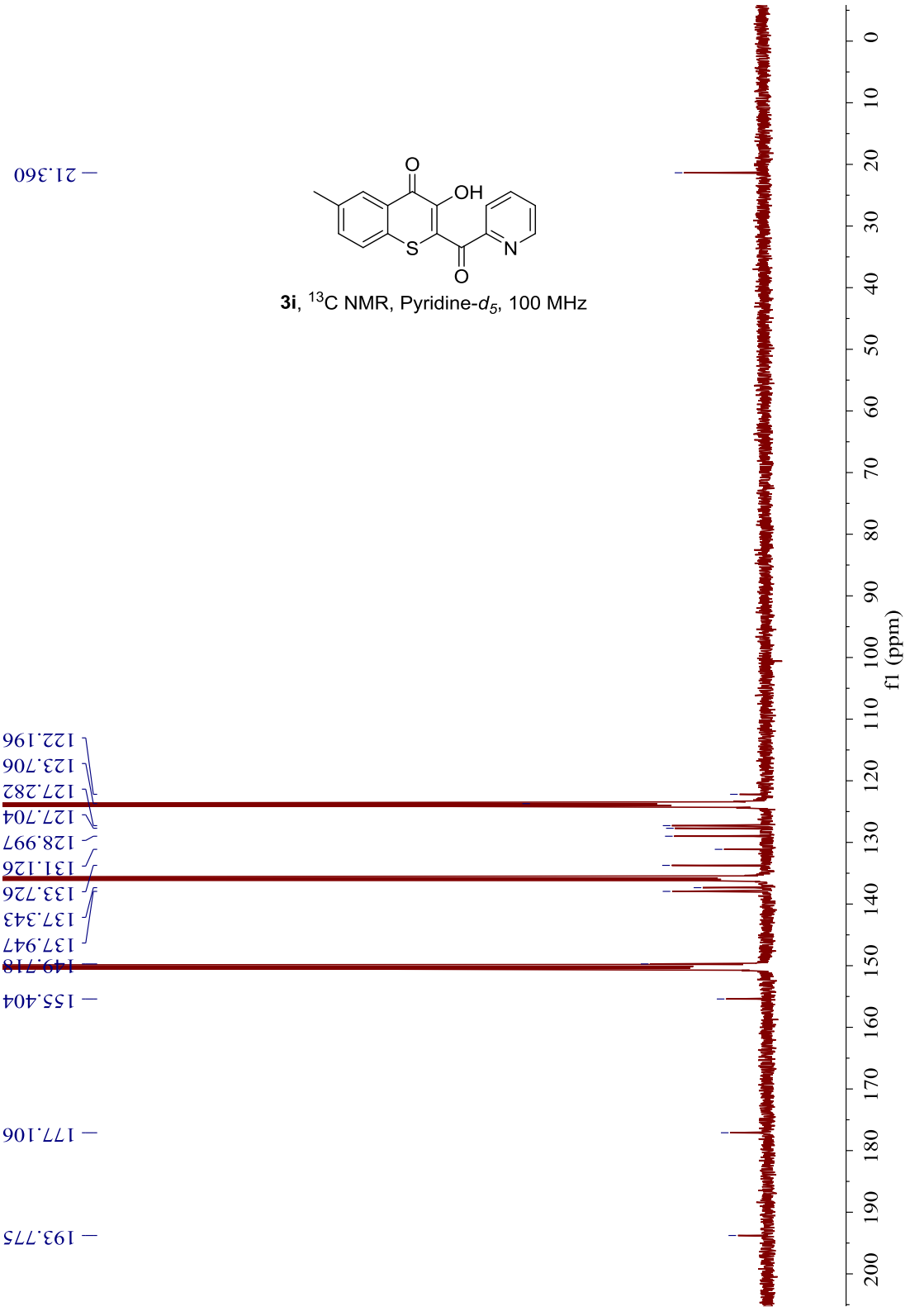
3h, ^{1}H NMR, Pyridine-d_5, 400 MHz



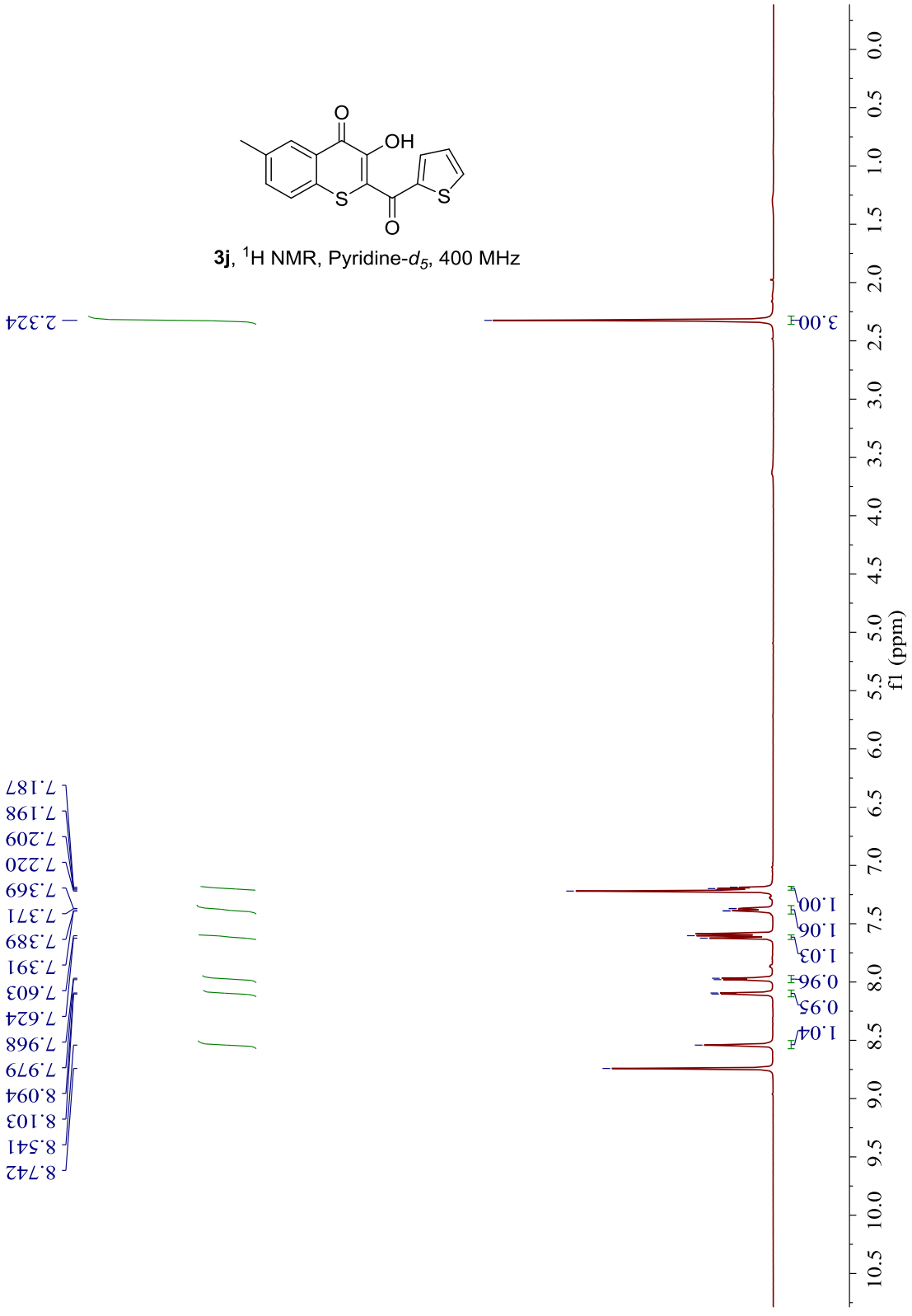
3h, ^{13}C NMR, Pyridine-d_5, 100 MHz

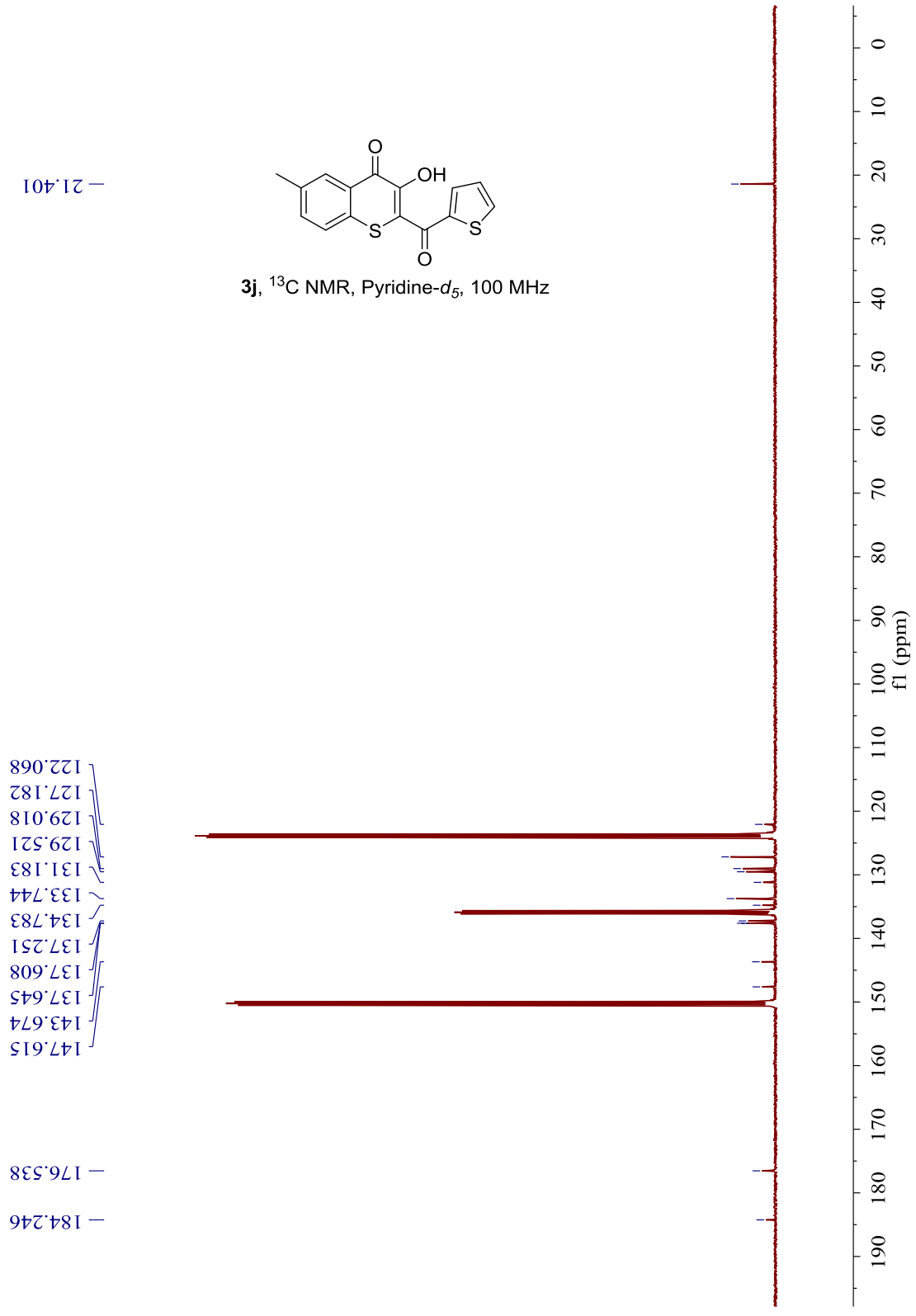


3i, ^{1}H NMR, Pyridine-d_5, 400 MHz

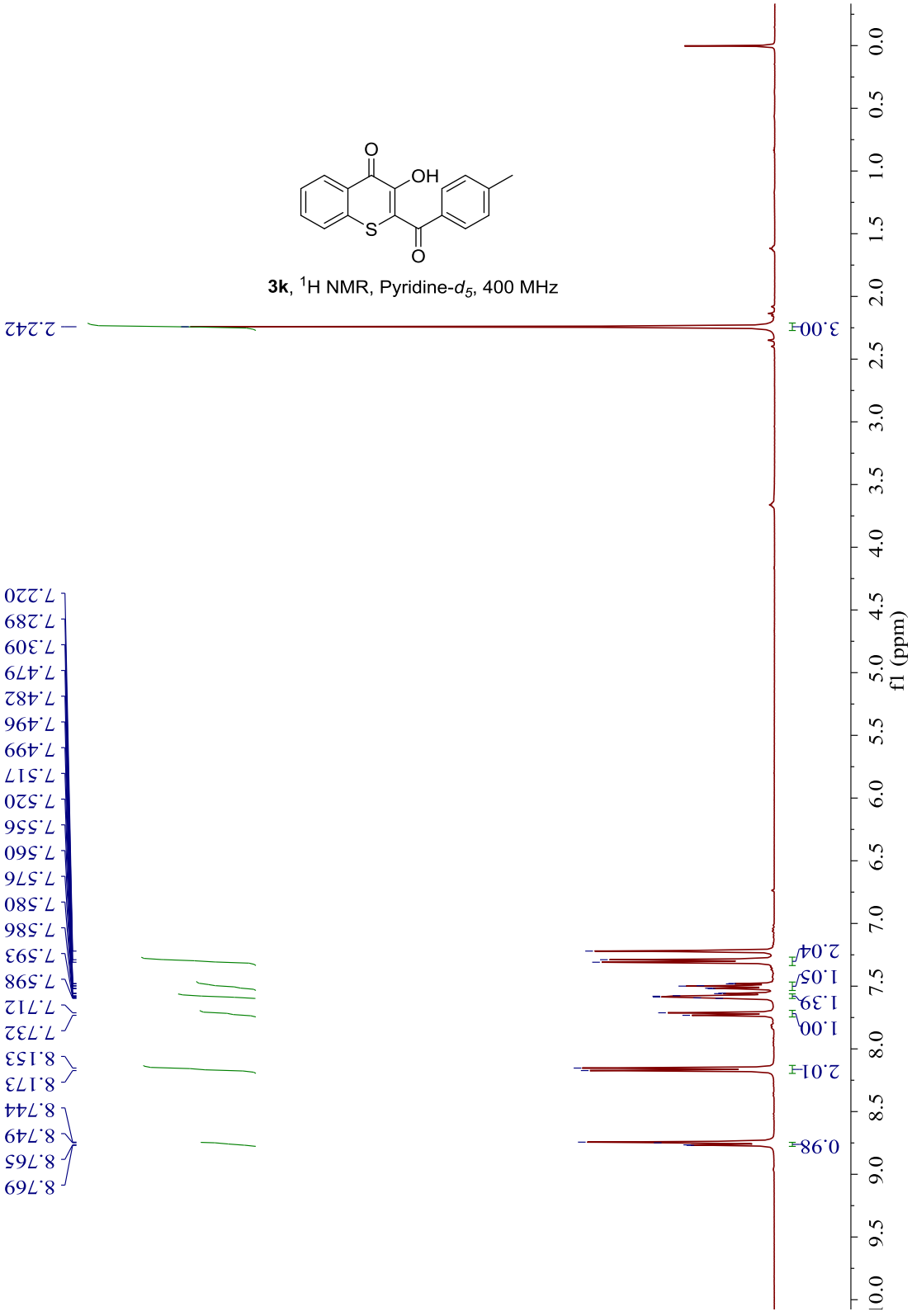


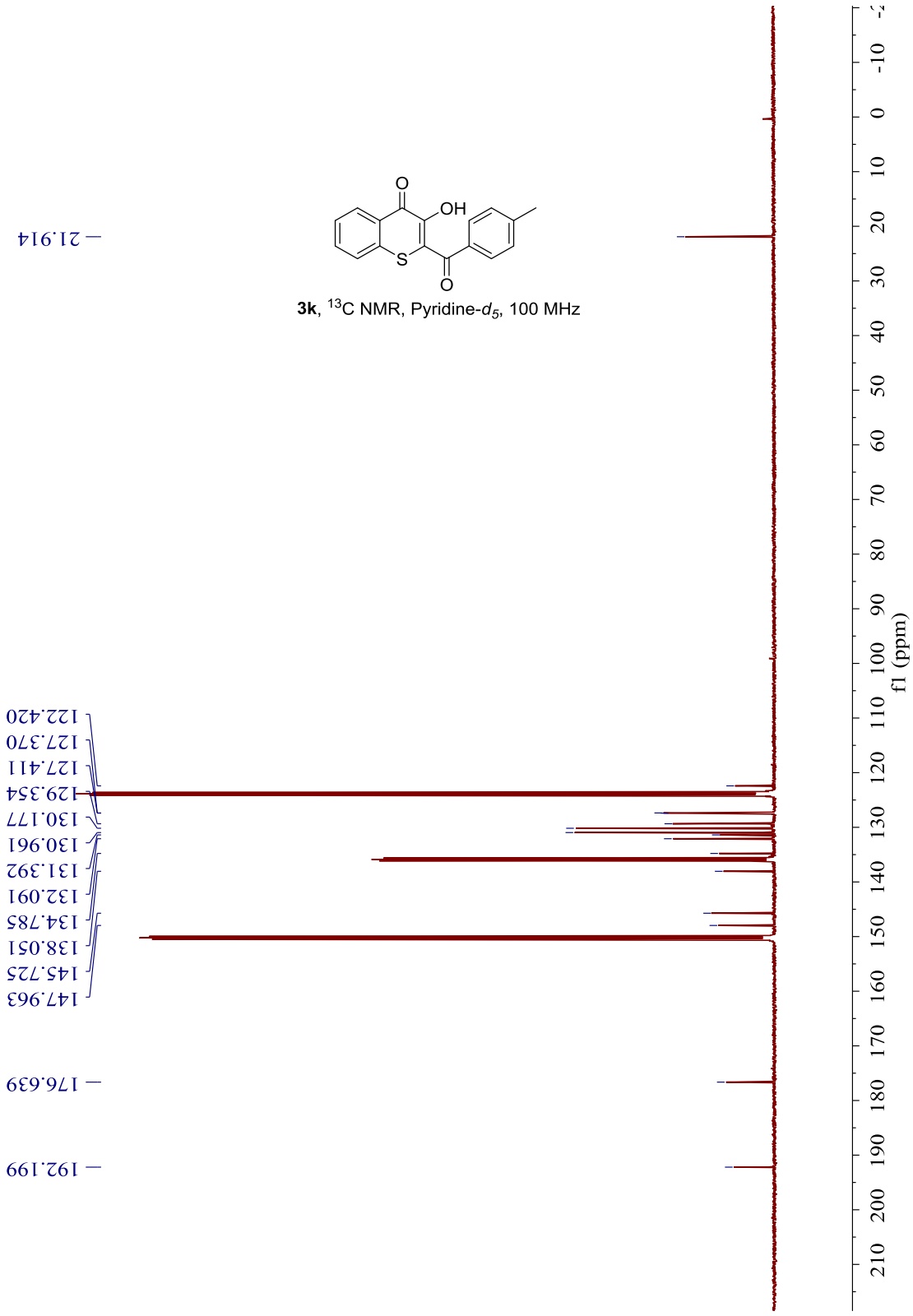
3i, ^{13}C NMR, Pyridine-d_5, 100 MHz


O
OH
S
S
O
3j, 1H NMR, Pyridine-d5, 400 MHz
2.324
3.00
1.00
1.06
1.03
0.96
0.95
1.04
7.187
7.198
7.209
7.220
7.369
7.371
7.389
7.391
7.603
7.624
7.968
7.979
8.094
8.103
8.541
8.742
f1 (ppm)

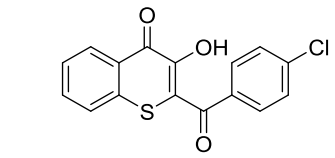


3j, ^{13}C NMR, Pyridine-d_5, 100 MHz

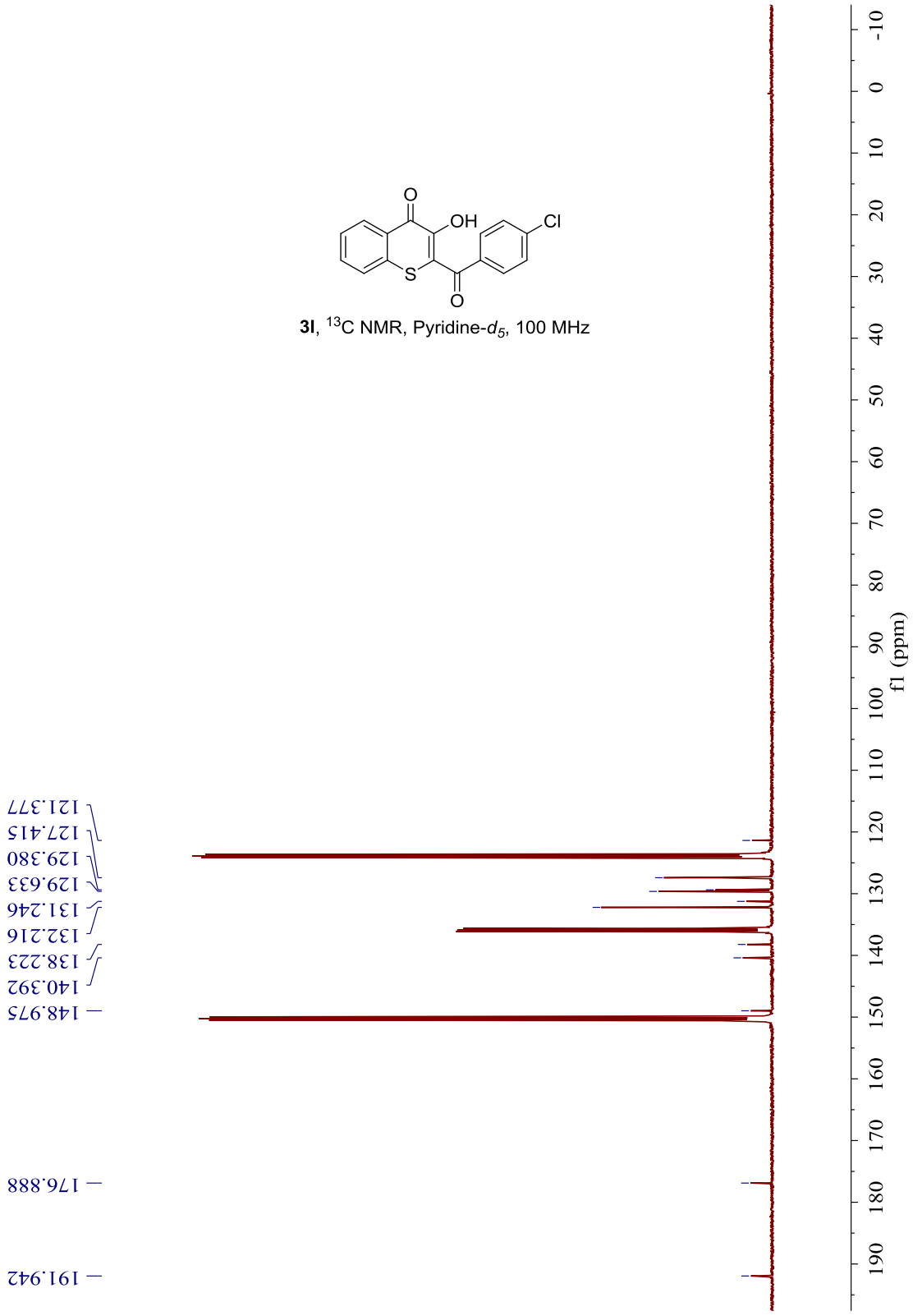

O
OH
S
O
3k, 1H NMR, Pyridine-d5, 400 MHz
2.242
7.220
7.289
7.309
7.479
7.482
7.496
7.499
7.517
7.520
7.556
7.560
7.576
7.580
7.586
7.593
7.598
7.712
7.732
8.153
8.173
8.744
8.749
8.765
8.769
3.00
2.04
1.05
1.39
1.00
2.01
0.98
f1 (ppm)

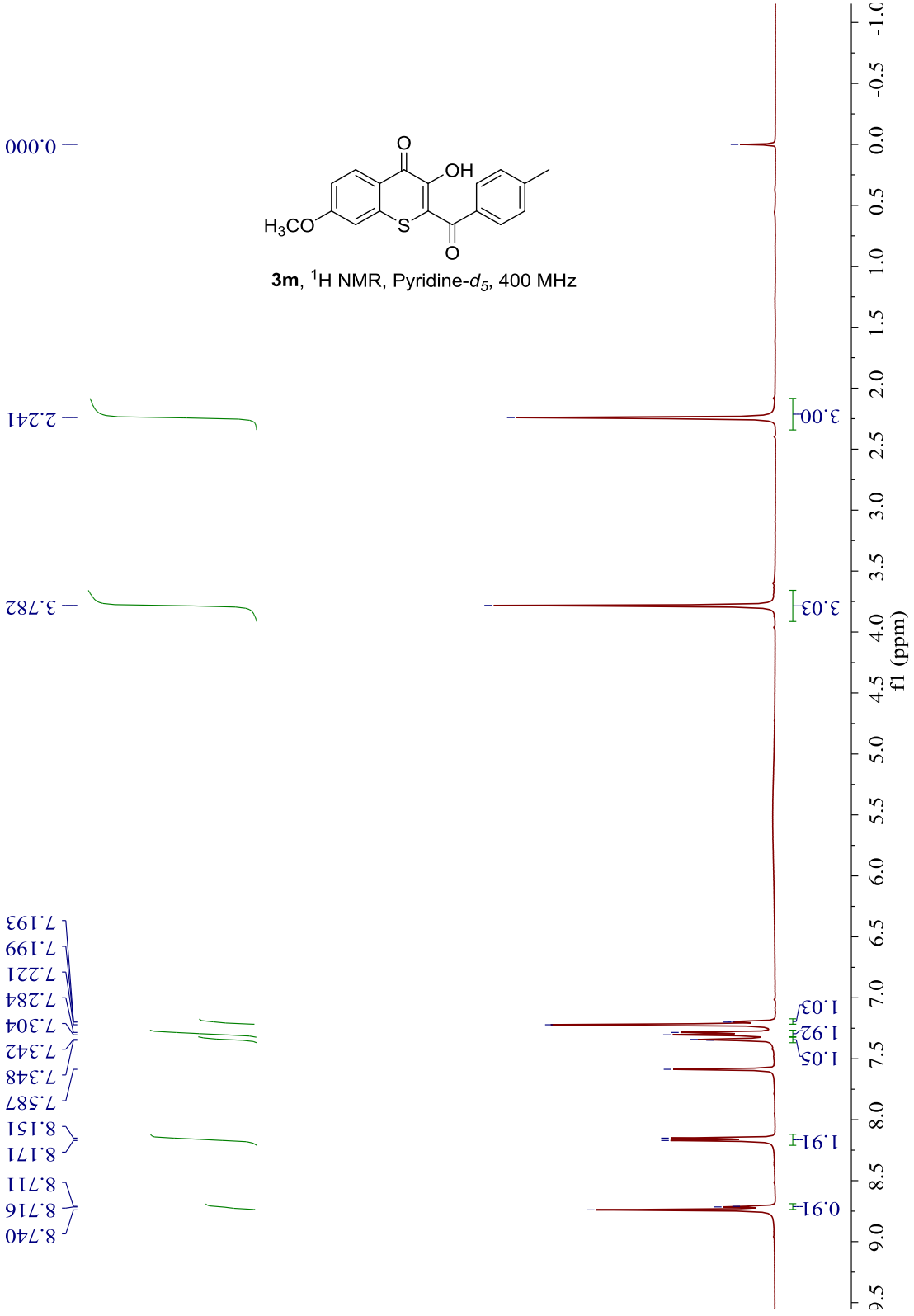


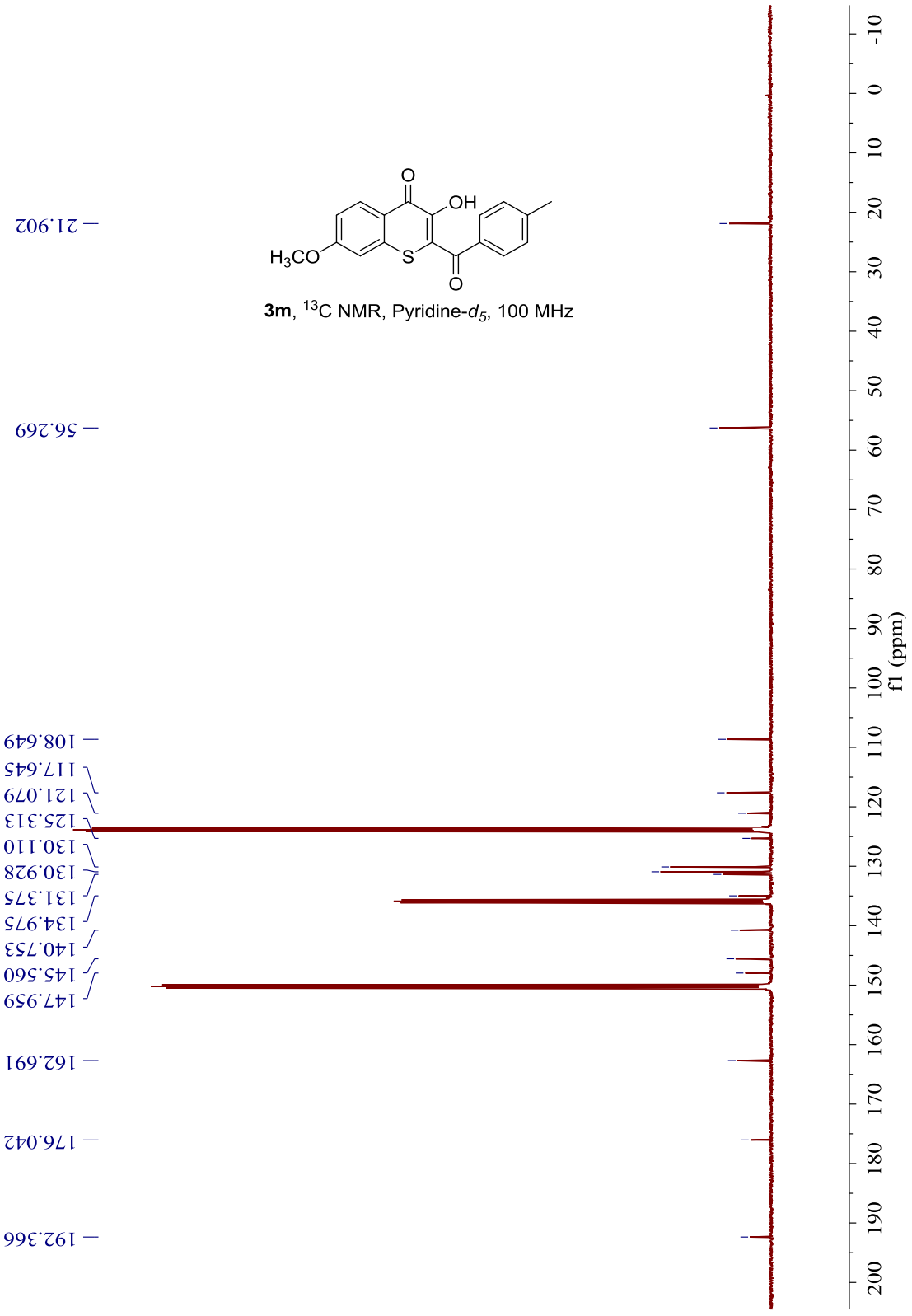
3k, ^{13}C NMR, Pyridine-d_5, 100 MHz



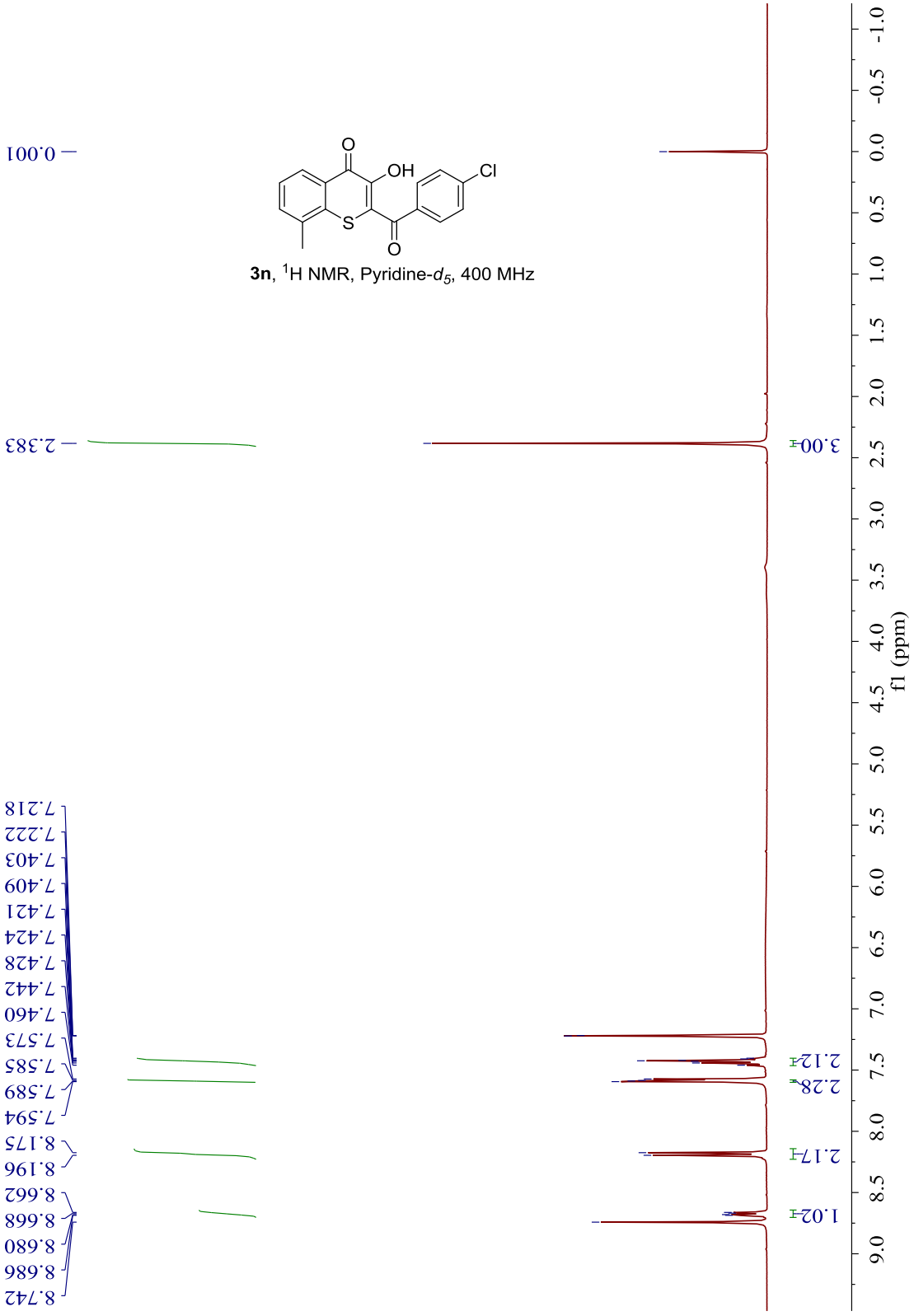
3l, ^{1}H NMR, Pyridine-d_5, 400 MHz

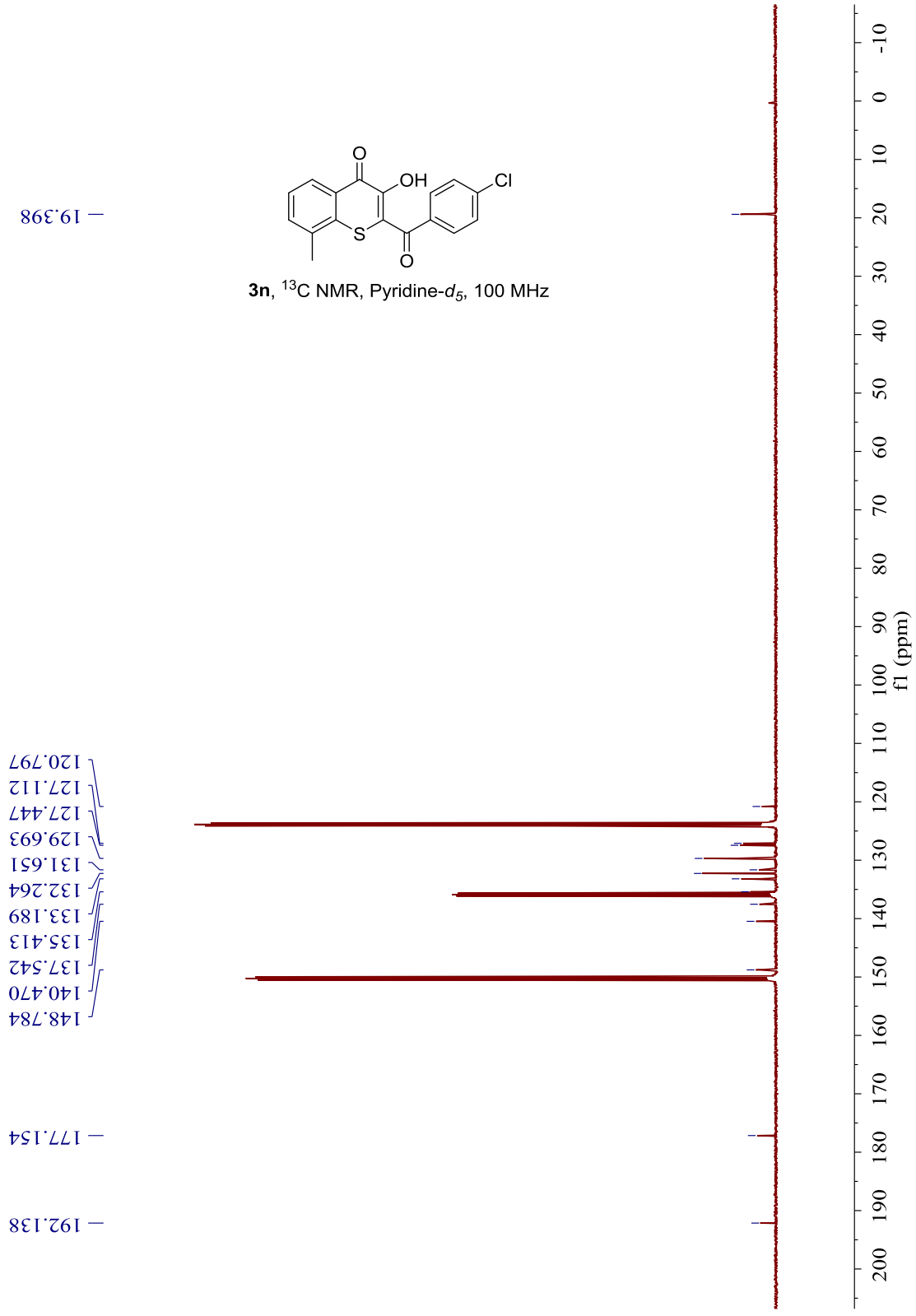

O
OH
Cl
S
O
3l, 13C NMR, Pyridine-d5, 100 MHz
191.942
176.888
148.975
140.392
138.223
132.216
131.246
129.633
129.380
127.415
121.377
f1 (ppm)


O
OH
H3CO
S
O
3m, 1H NMR, Pyridine-d5, 400 MHz
0.000
2.241
3.782
7.193
7.199
7.221
7.284
7.304
7.342
7.348
7.587
8.151
8.171
8.711
8.716
8.740
3.00
3.03
1.03
1.92
1.05
1.91
0.91
f1 (ppm)

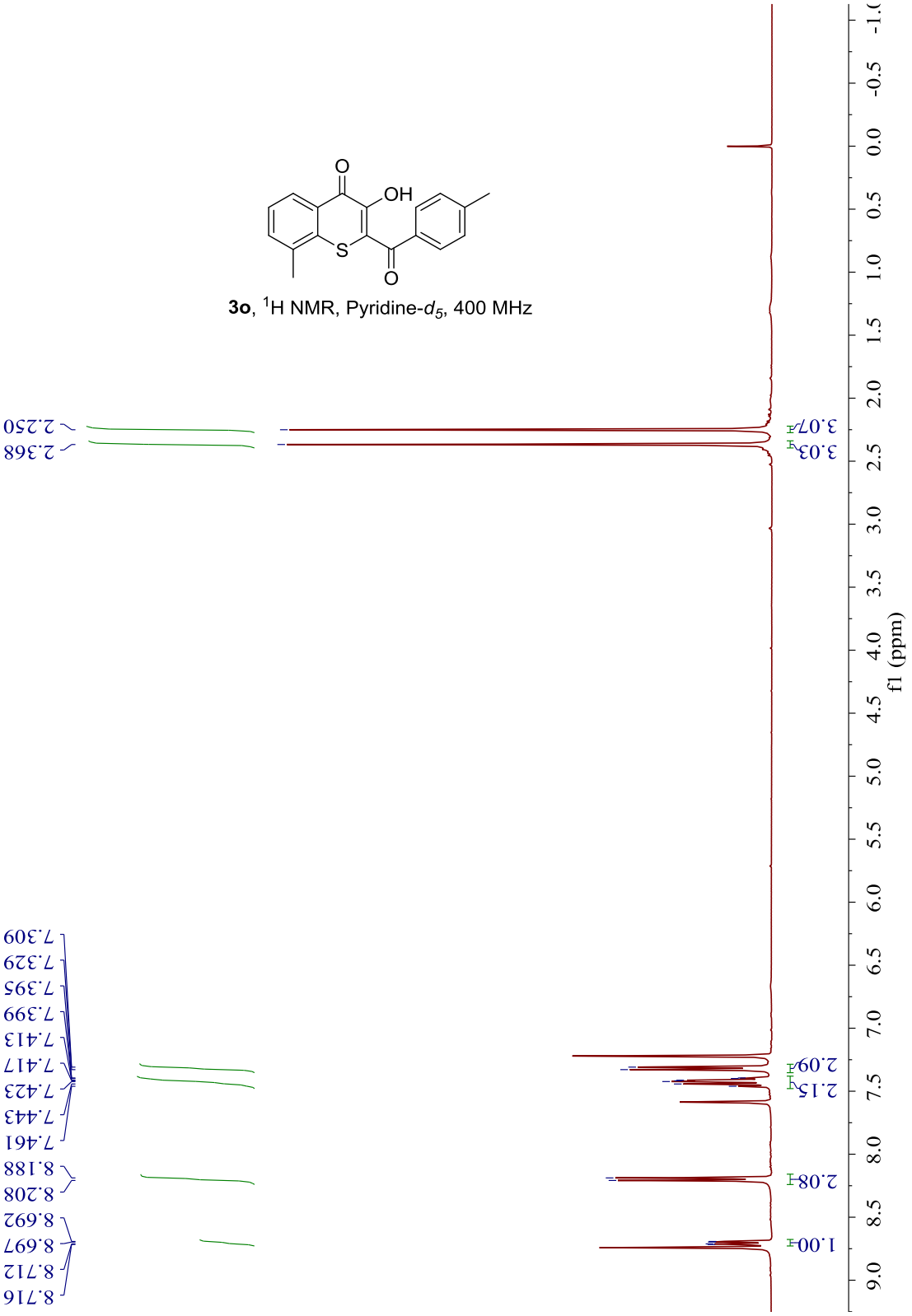


3m, ^{13}C NMR, Pyridine-d_5, 100 MHz

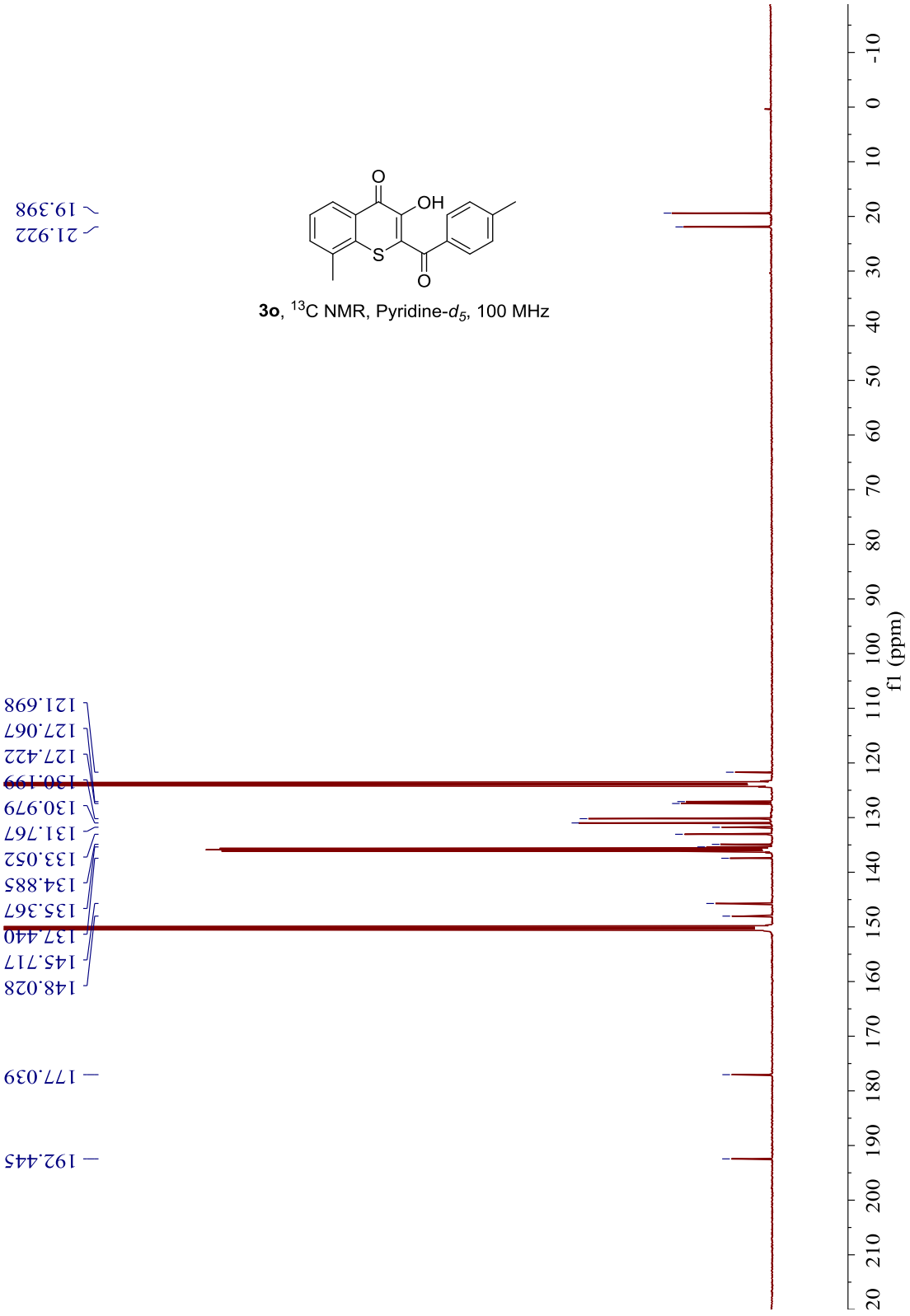

O
OH
Cl
S
O
3n, 1H NMR, Pyridine-d5, 400 MHz
0.001
2.383
7.218
7.222
7.403
7.409
7.421
7.424
7.428
7.442
7.460
7.573
7.585
7.589
7.594
8.175
8.196
8.662
8.668
8.680
8.686
8.742
3.00
2.12
2.28
2.17
1.02
f1 (ppm)



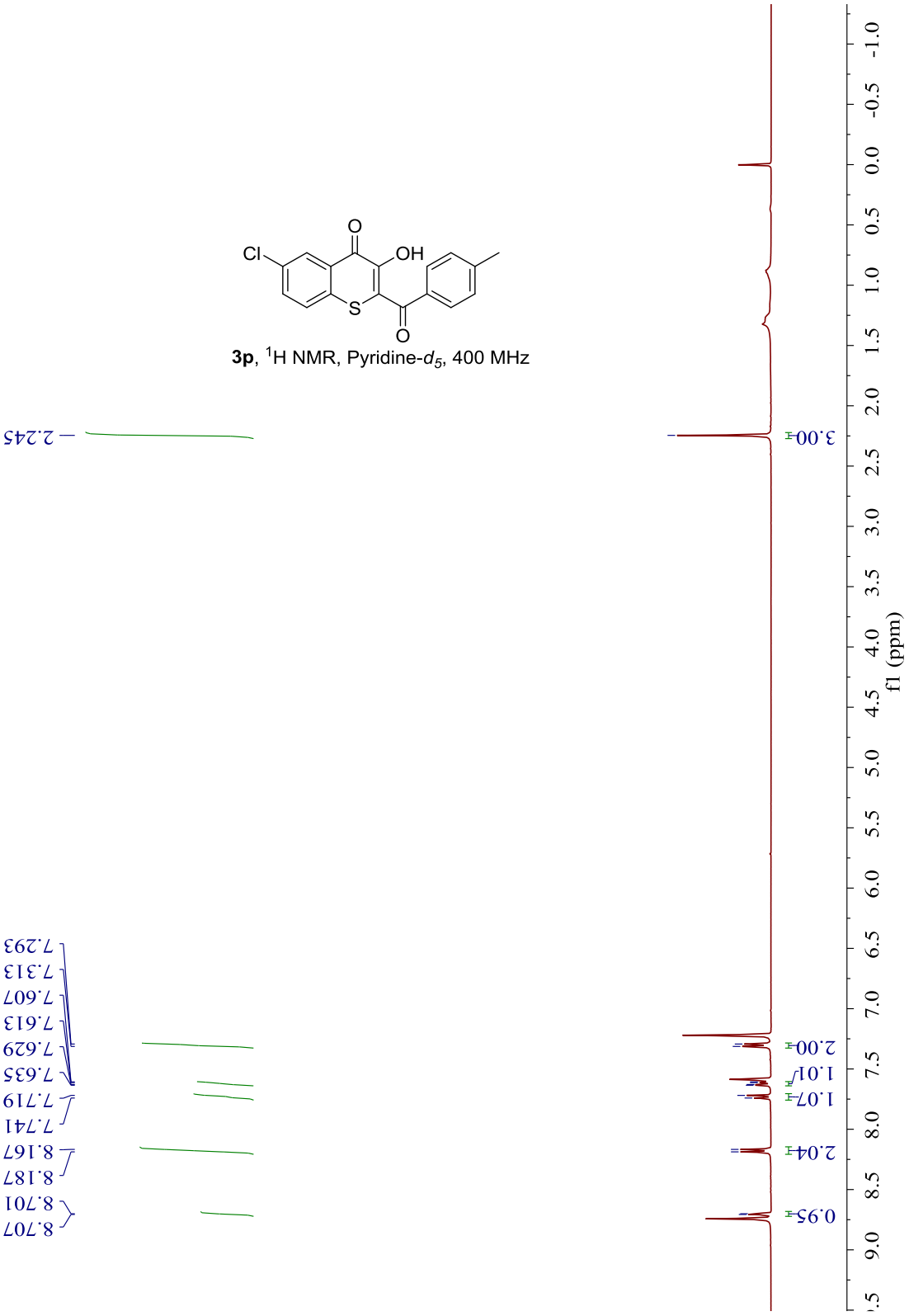
3n, ^{13}C NMR, Pyridine-d_5, 100 MHz

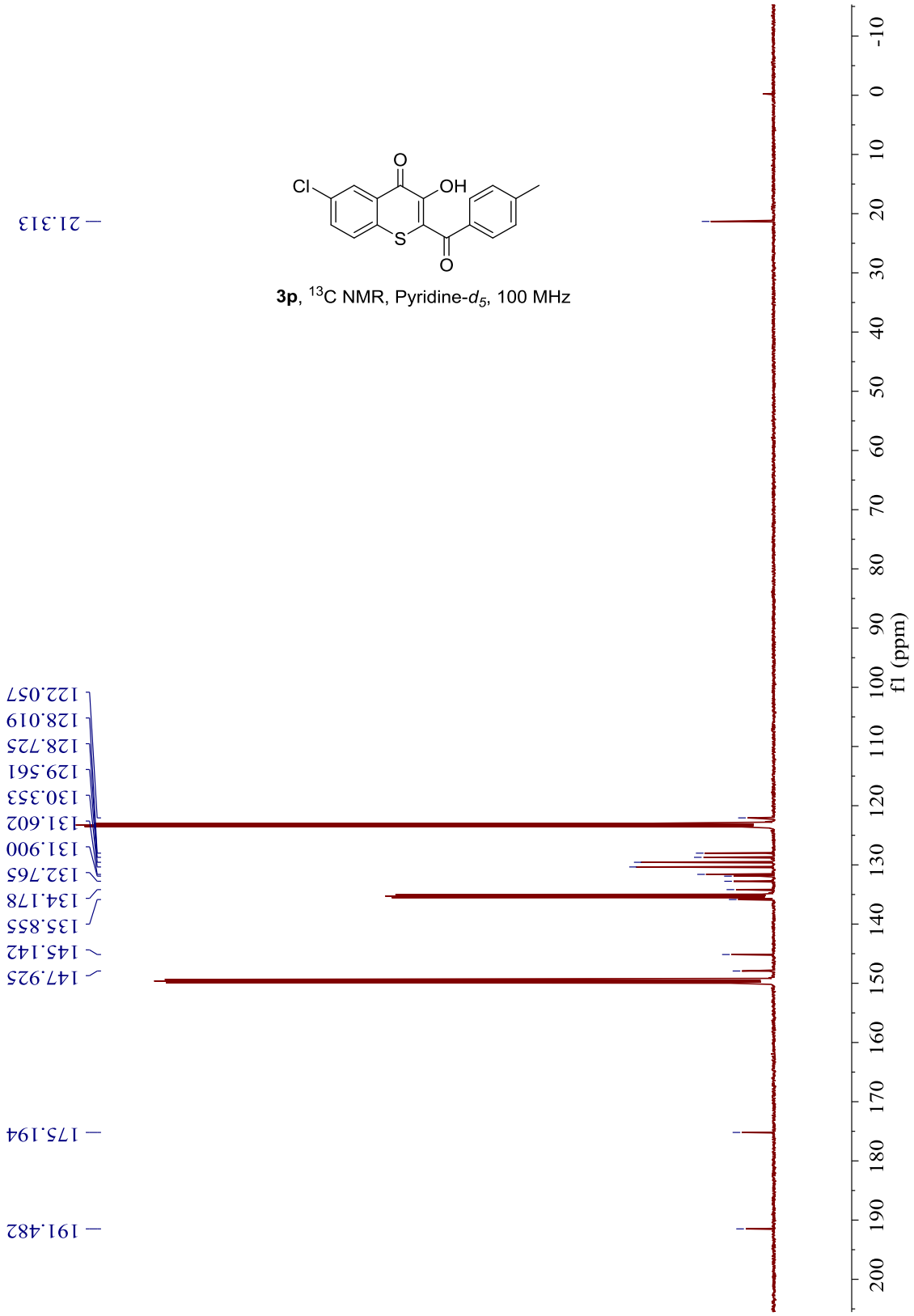


3o, ^{1}H NMR, Pyridine-d_5, 400 MHz

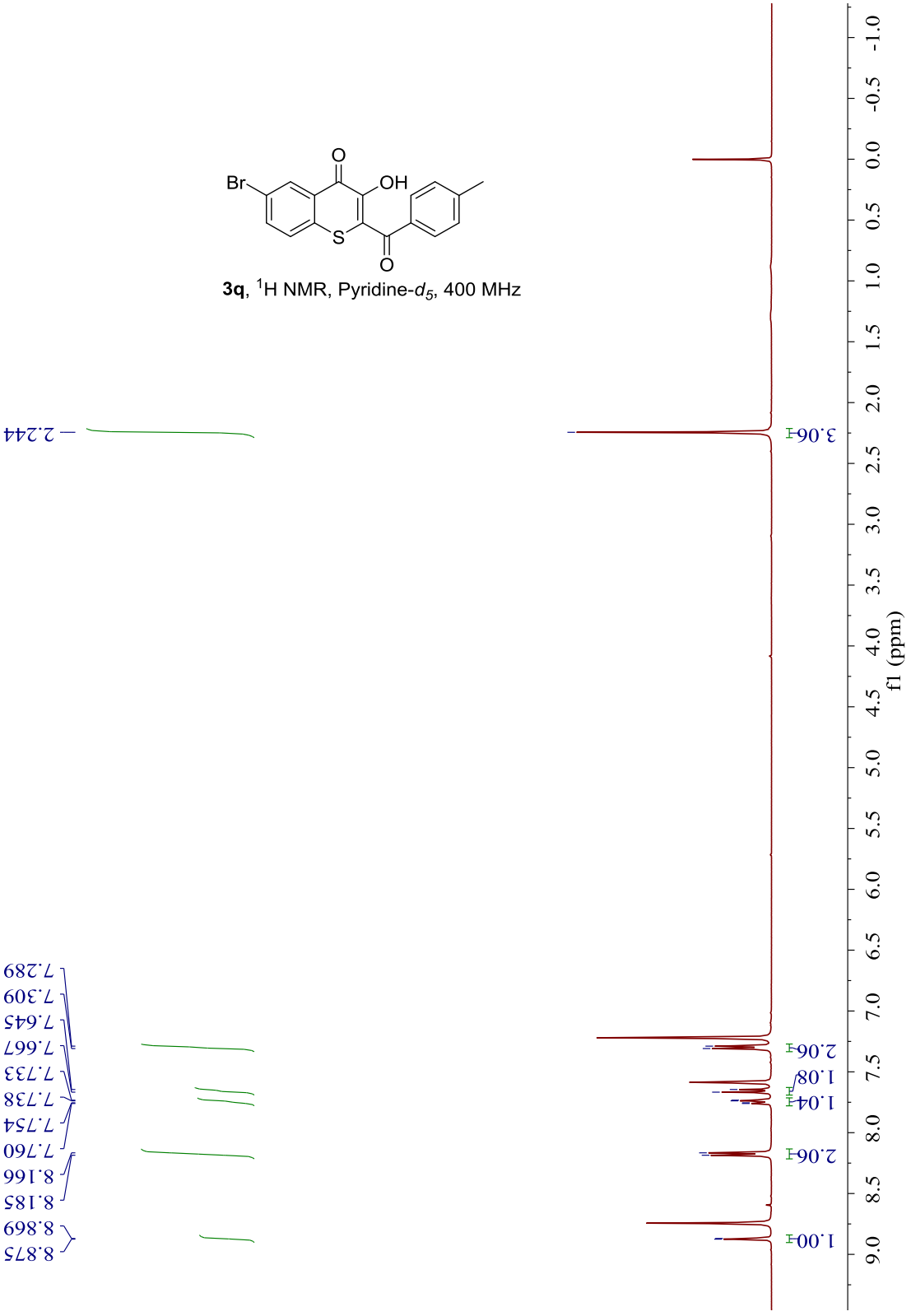


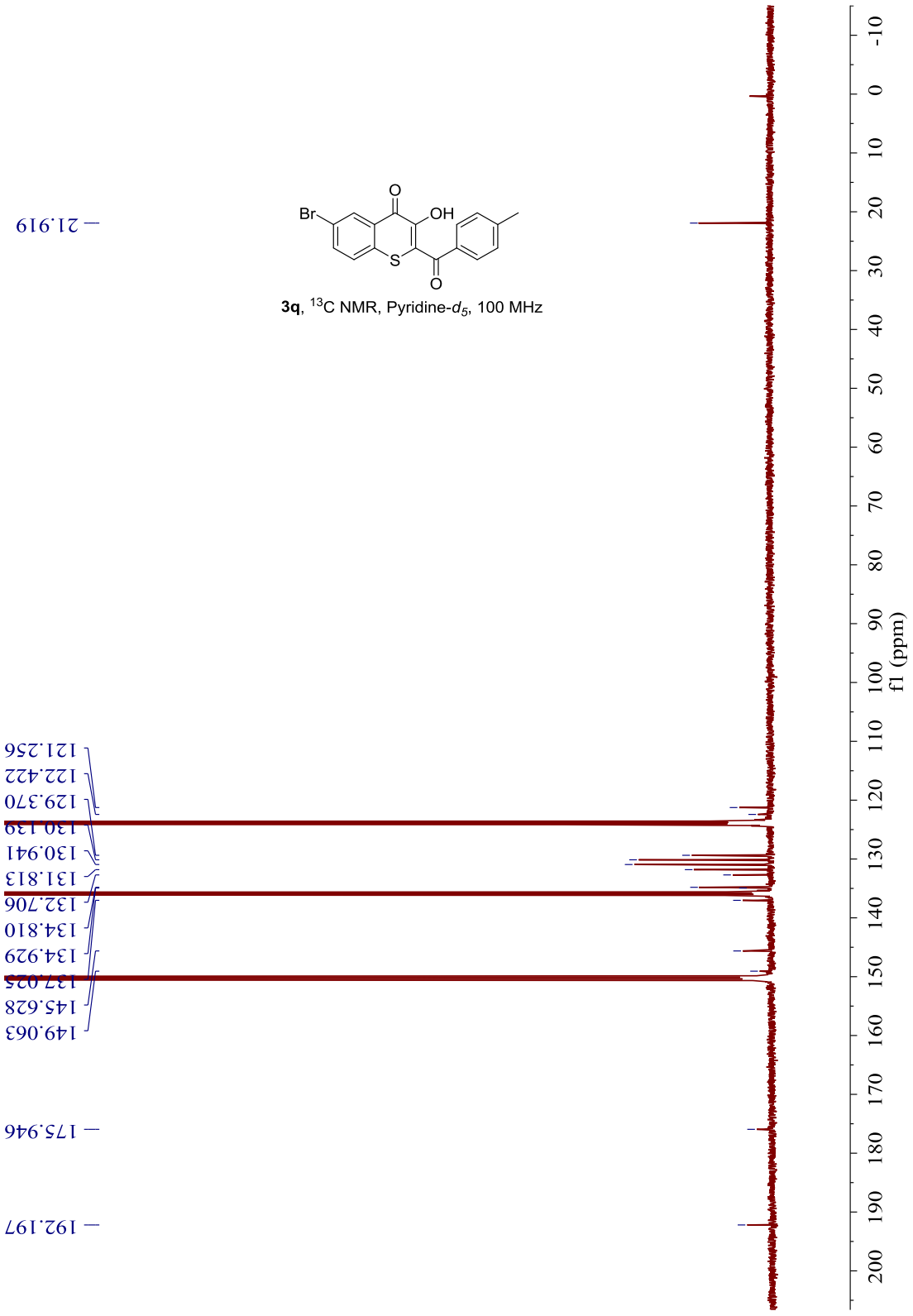
3o, ^{13}C NMR, Pyridine-d_5, 100 MHz


Cl
O
OH
S
O
3p, 1H NMR, Pyridine-d5, 400 MHz
2.245
8.707
8.701
8.187
8.167
7.741
7.719
7.635
7.629
7.613
7.607
7.313
7.293
3.00
2.00
1.01
1.07
2.04
0.95
f1 (ppm)

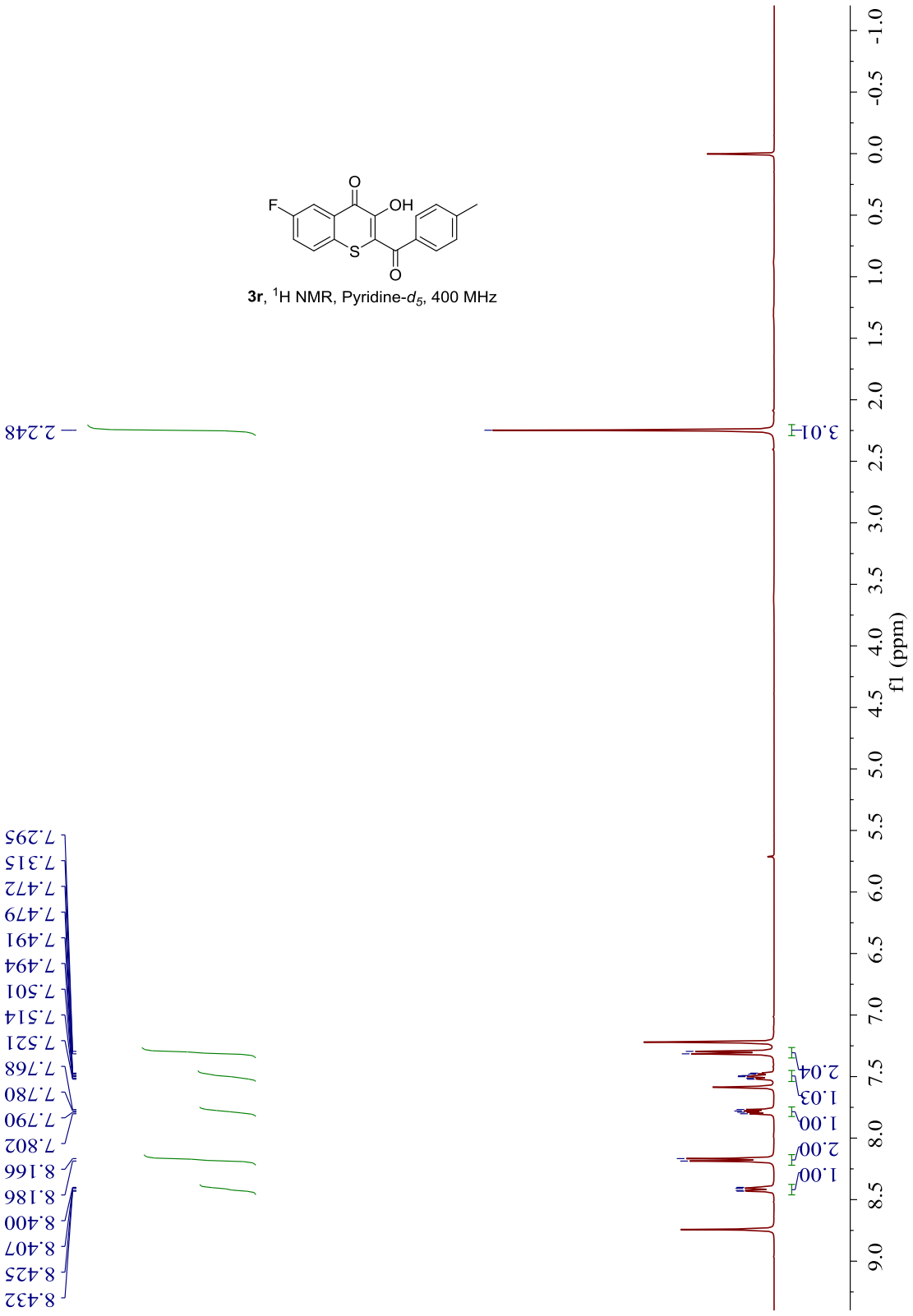


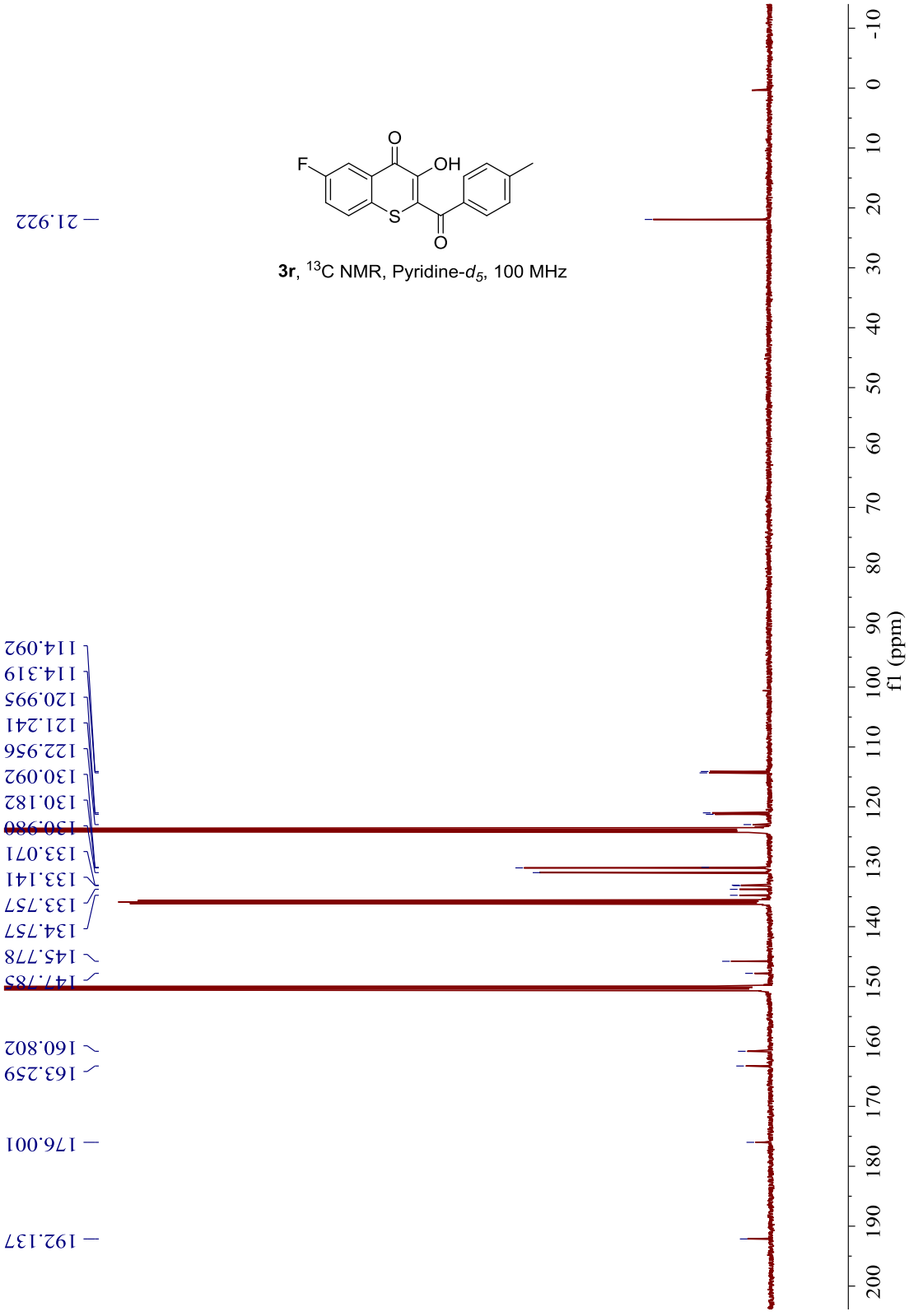
3p, ^{13}C NMR, Pyridine-d_5, 100 MHz


Br
OH
O
S
O
3q, 1H NMR, Pyridine-d5, 400 MHz
2.244
3.06
2.06
1.08
1.04
2.06
1.00
8.875
8.869
8.185
8.166
7.760
7.754
7.738
7.733
7.667
7.645
7.309
7.289
f1 (ppm)

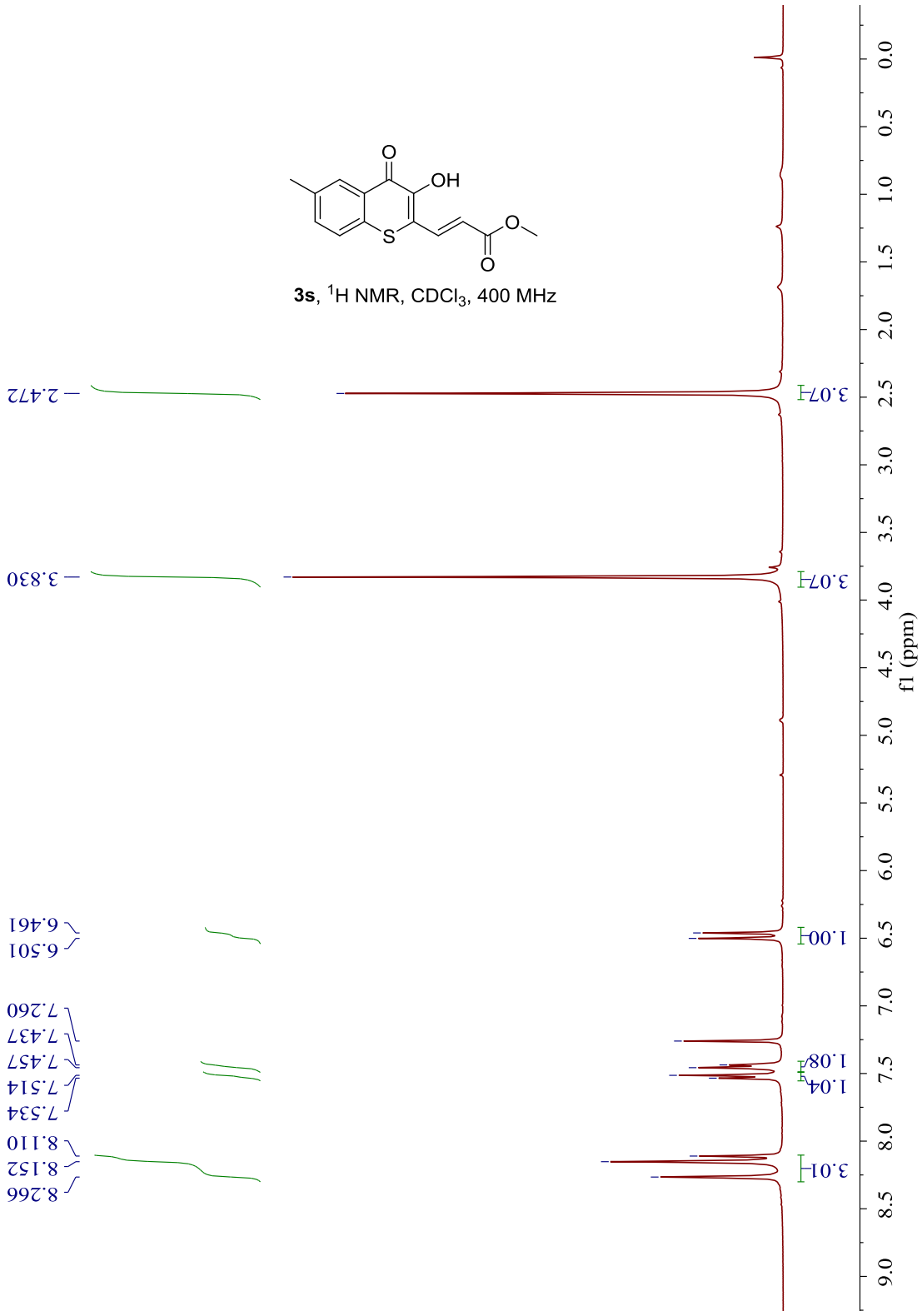


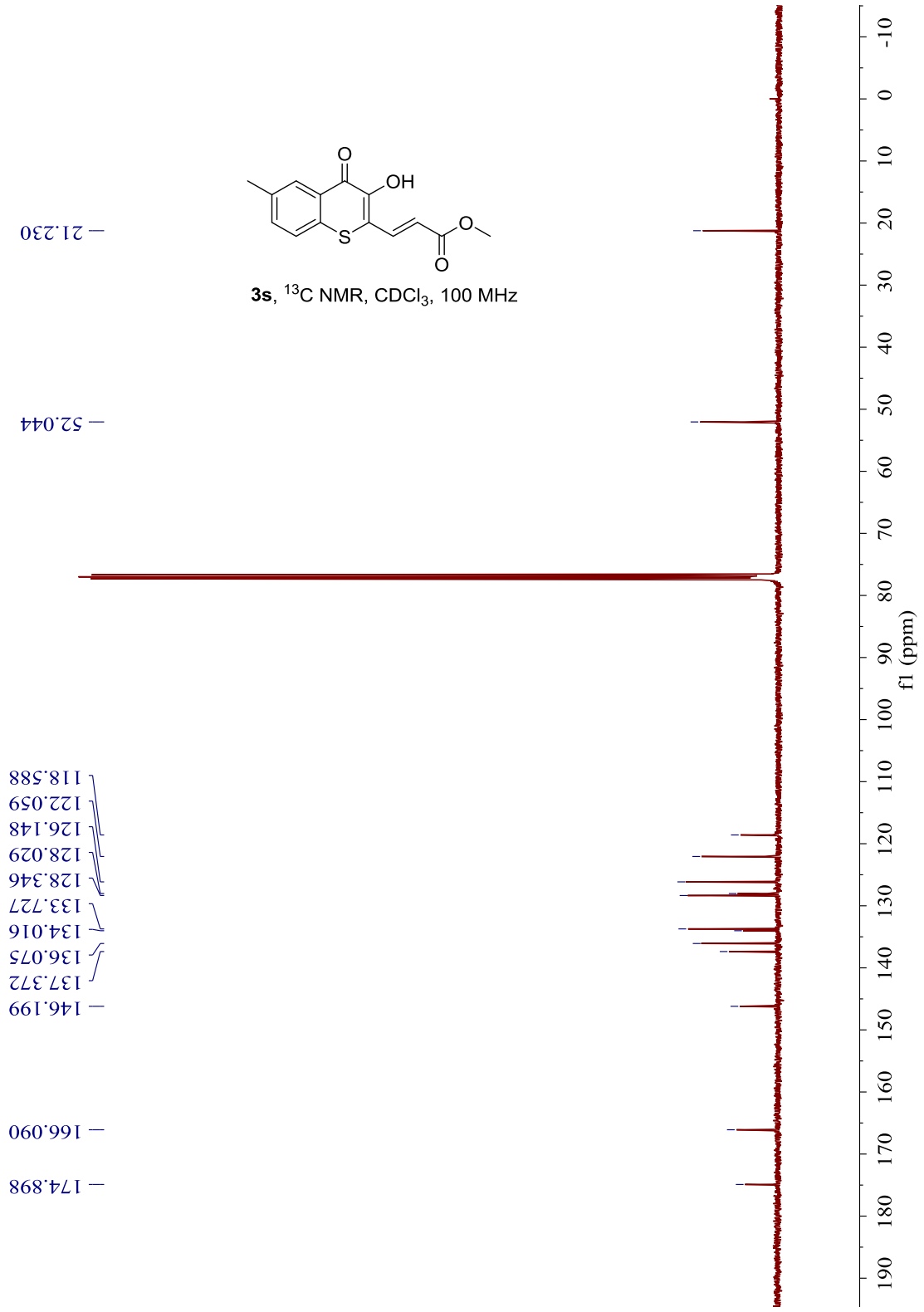
3q, ^{13}C NMR, Pyridine-d_5, 100 MHz


F
O
OH
S
O
3r, 1H NMR, Pyridine-d5, 400 MHz
2.248
3.01
1.00
2.00
1.00
1.03
2.04
8.432
8.425
8.407
8.400
8.186
8.166
7.802
7.790
7.780
7.768
7.521
7.514
7.501
7.494
7.491
7.479
7.472
7.315
7.295
f1 (ppm)

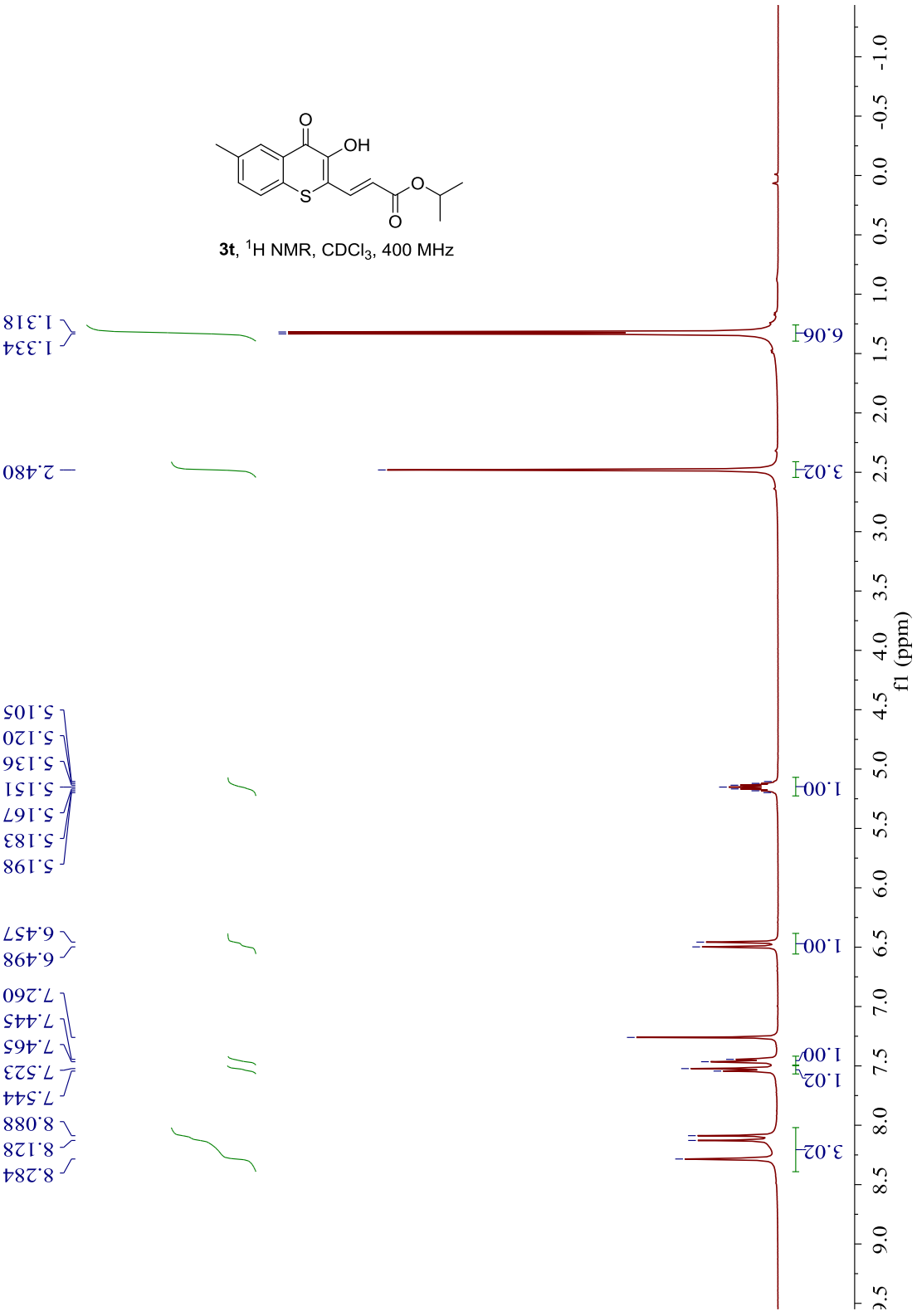


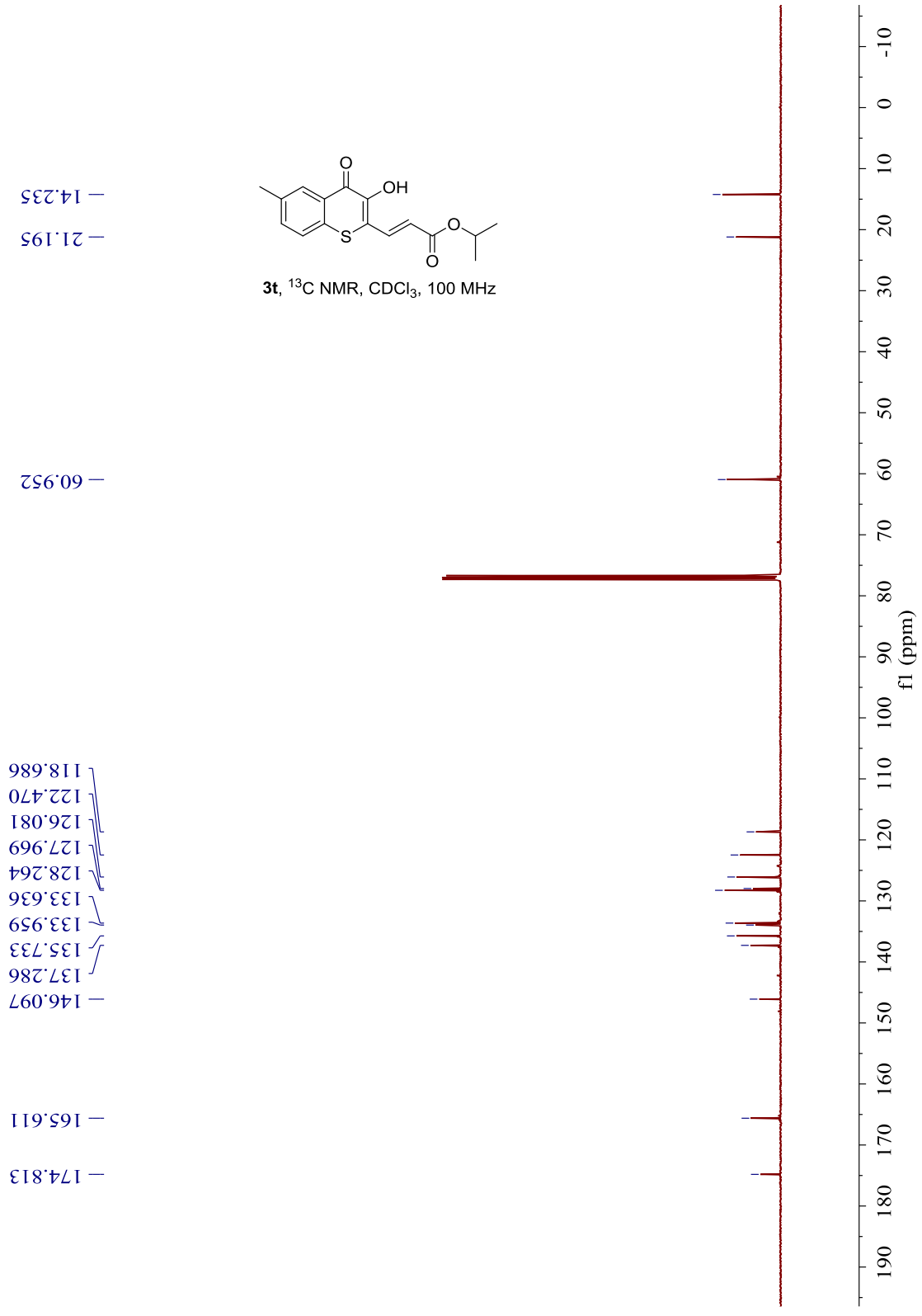
3r, ^{13}C NMR, Pyridine-d_5, 100 MHz


O
OH
S
O
O
3s, 1H NMR, CDCl3, 400 MHz
2.472
3.830
6.461
6.501
7.260
7.437
7.457
7.514
7.534
8.110
8.152
8.266
3.07
3.07
1.00
1.08
1.04
3.01
f1 (ppm)

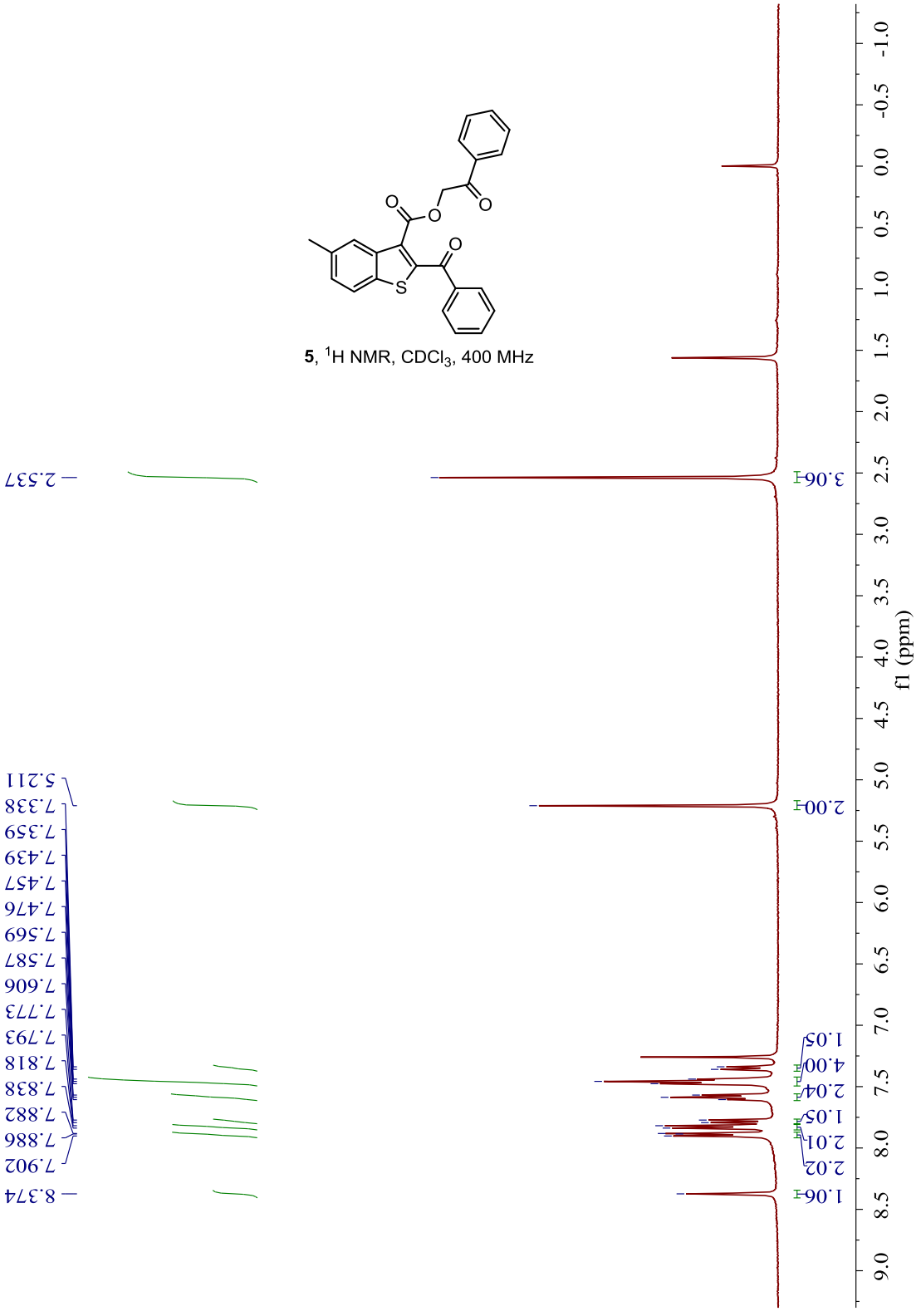


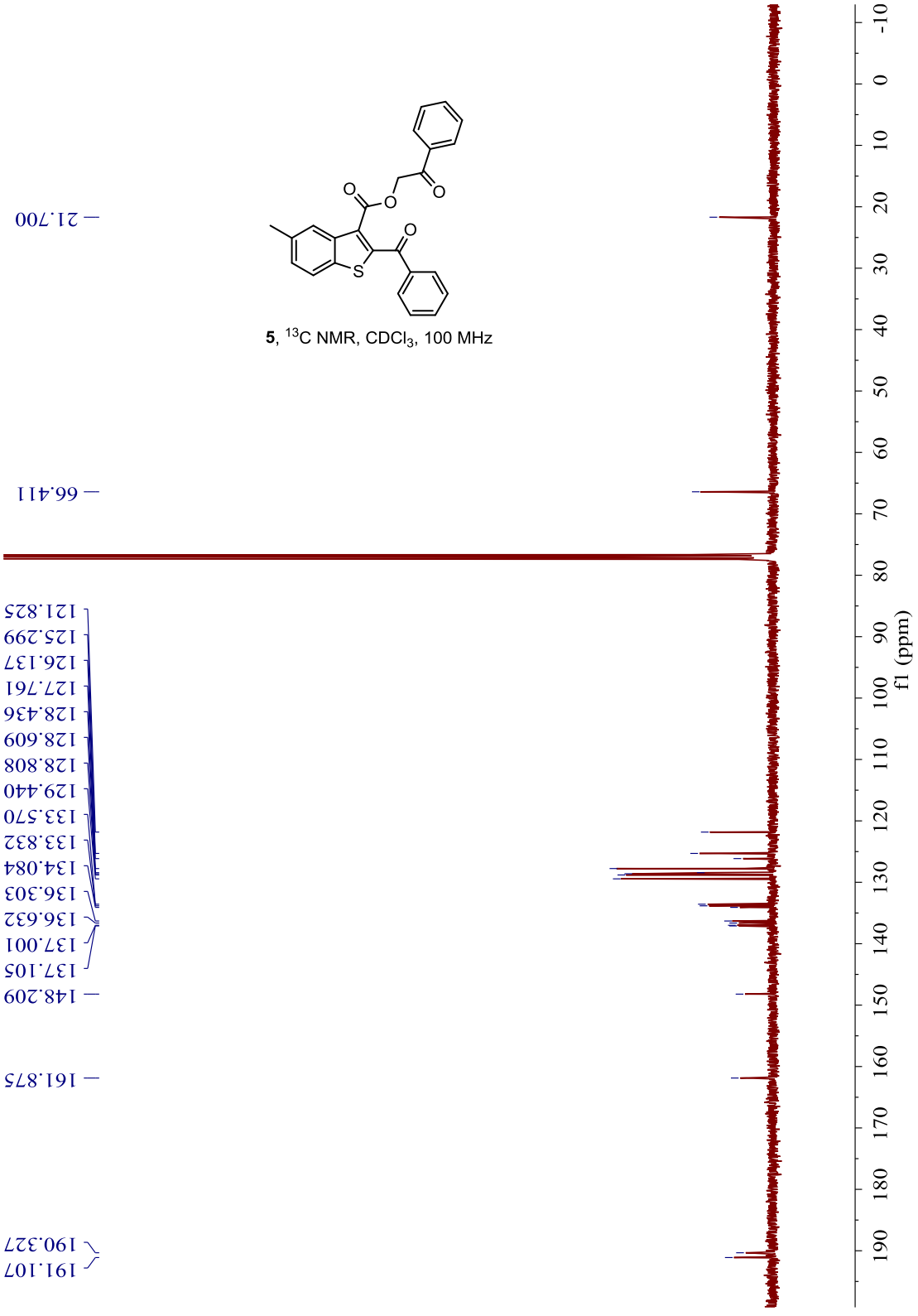
3s, ^{13}C NMR, $CDCl_3$, 100 MHz


O
OH
S
O
O
3t, 1H NMR, CDCl3, 400 MHz
1.318
1.334
2.480
5.105
5.120
5.136
5.151
5.167
5.183
5.198
6.457
6.498
7.260
7.445
7.465
7.523
7.544
8.088
8.128
8.284
6.06
3.02
1.00
1.00
1.02
1.00
3.02
f1 (ppm)



3t, ^{13}C NMR, $CDCl_3$, 100 MHz


O
O
O
O
S
O
5, 1H NMR, CDCl3, 400 MHz
2.537
8.374
7.902
7.886
7.882
7.838
7.818
7.793
7.773
7.606
7.587
7.569
7.476
7.457
7.439
7.359
7.338
5.211
3.06
2.00
1.06
2.02
2.01
1.05
2.04
4.00
1.05
f1 (ppm)



5, ^{13}C NMR, $CDCl_3$, 100 MHz