Supplementary Material for

Synthesis and evaluation of hybrid molecules targeting the vinca domain of tubulin

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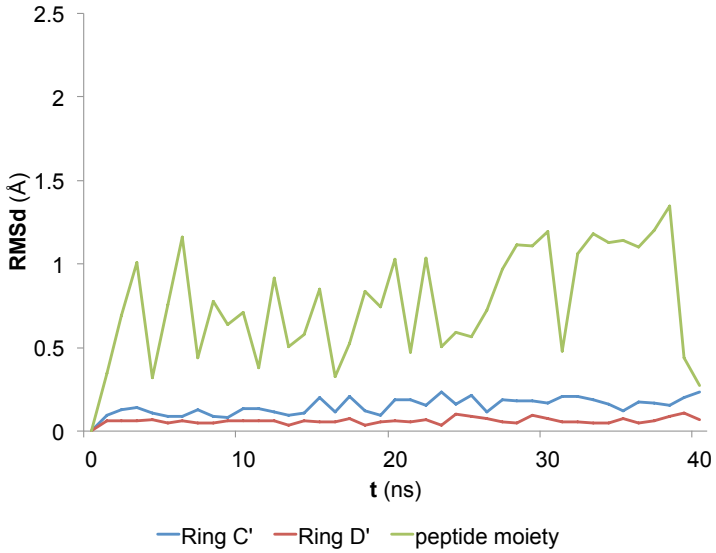
(a)



(b)

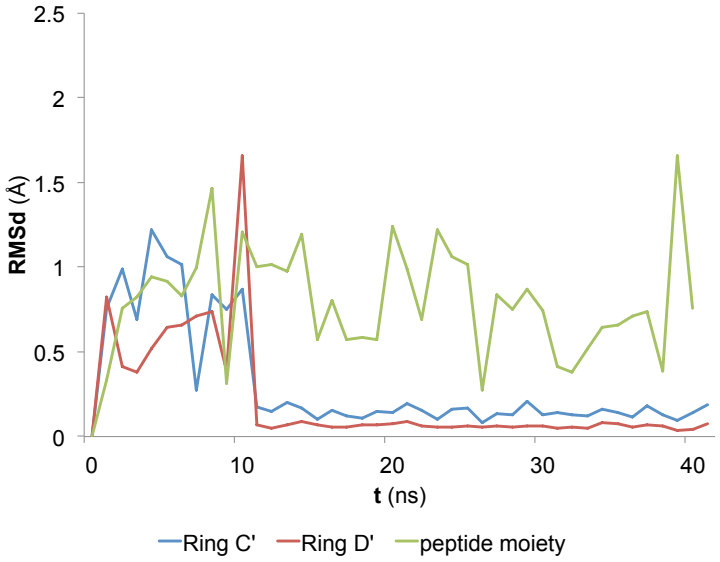


Figure S1. Time evolution of the root-mean-square deviation (RMSd, Å) of **25** (a) and **22** (b) along the unrestrained MD simulation in a box of explicit solvent at 300 K.

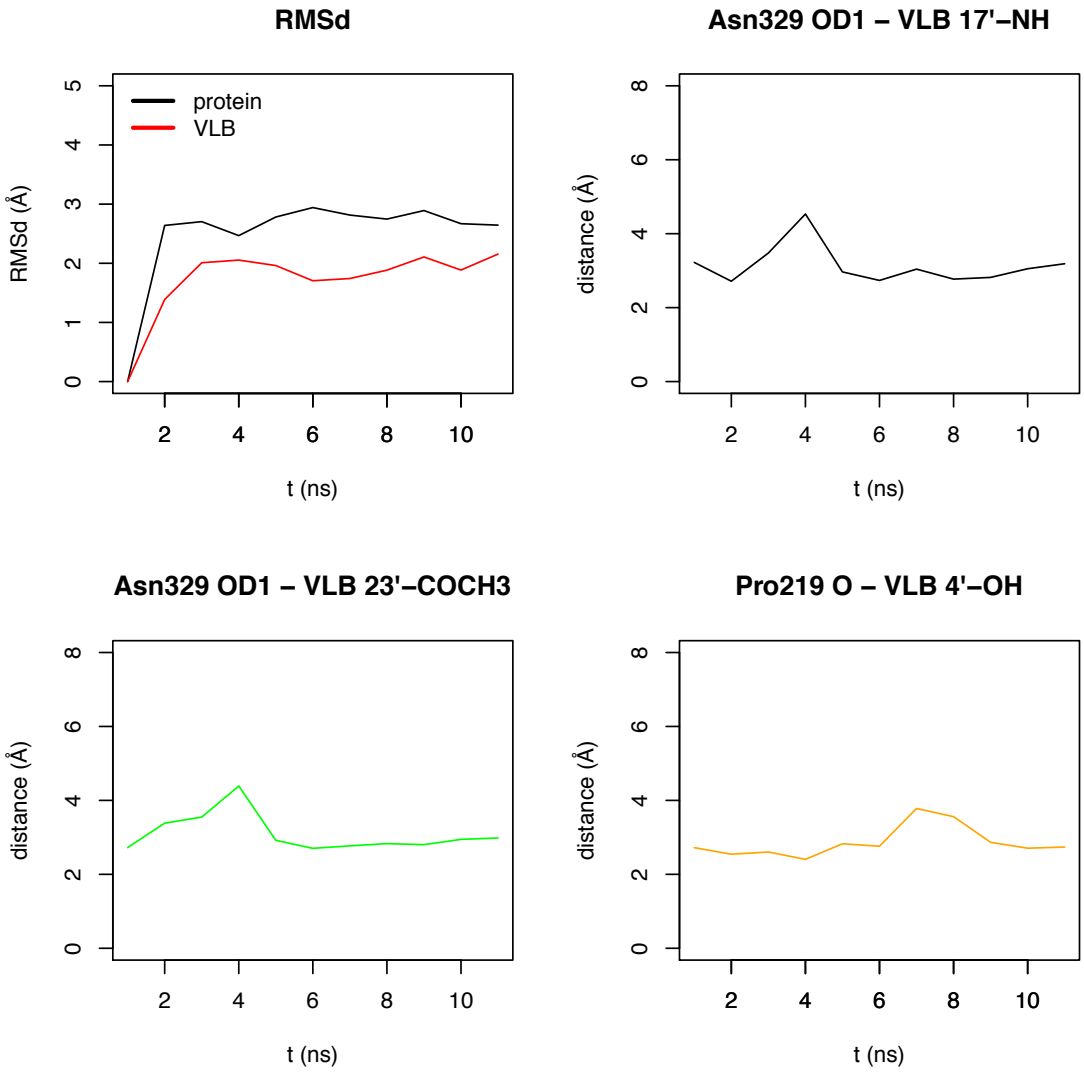


Figure S2. Time evolution of the root-mean-square deviation (RMSd, Å) and key distances (Å) corresponding to the main interactions observed for **1** within the vinca-binding domain along the unrestrained MD simulation in a box of explicit solvent at 300 K.

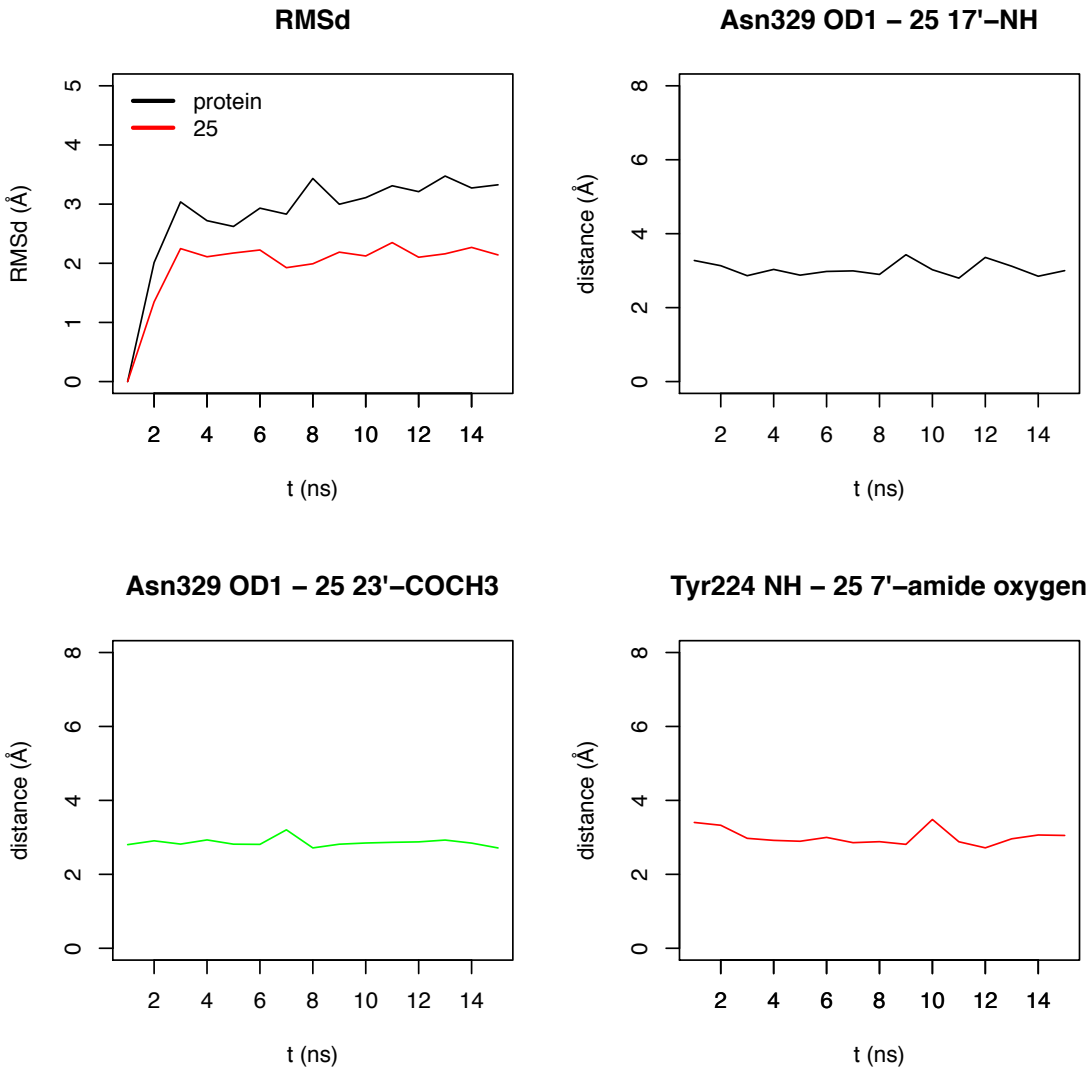


Figure S3. Time evolution of the root-mean-square deviation (RMSd, Å) and key distances (Å) corresponding to the main interactions observed for **25** within the vinca-binding domain along the unrestrained MD simulation in a box of explicit solvent at 300 K.

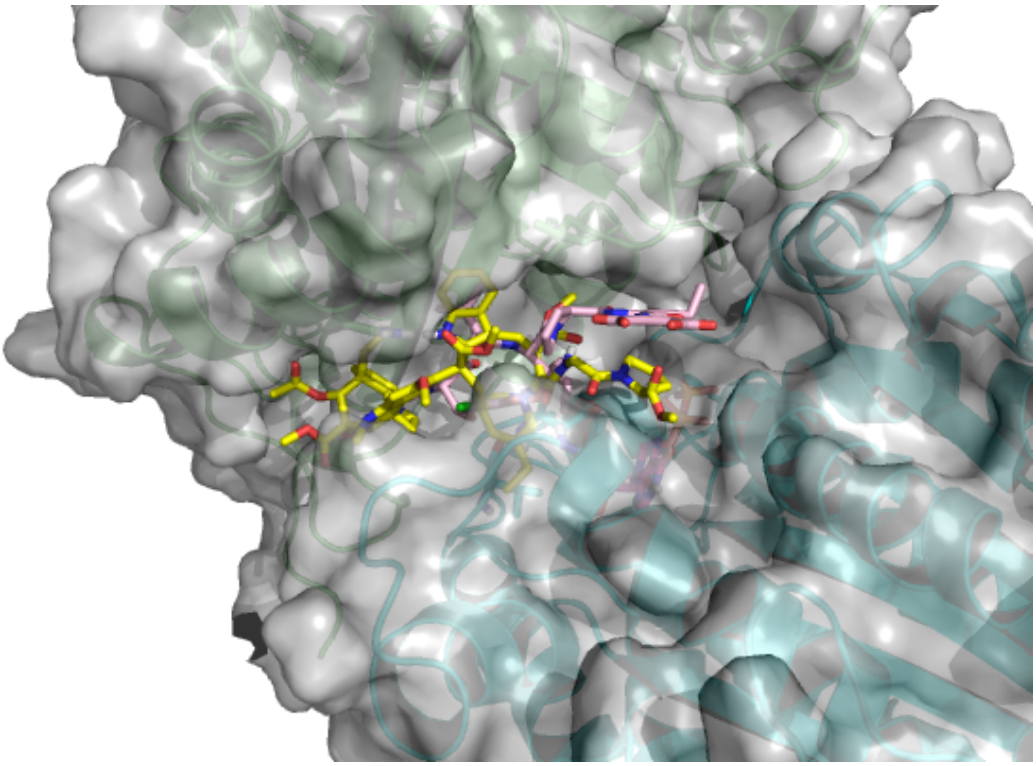
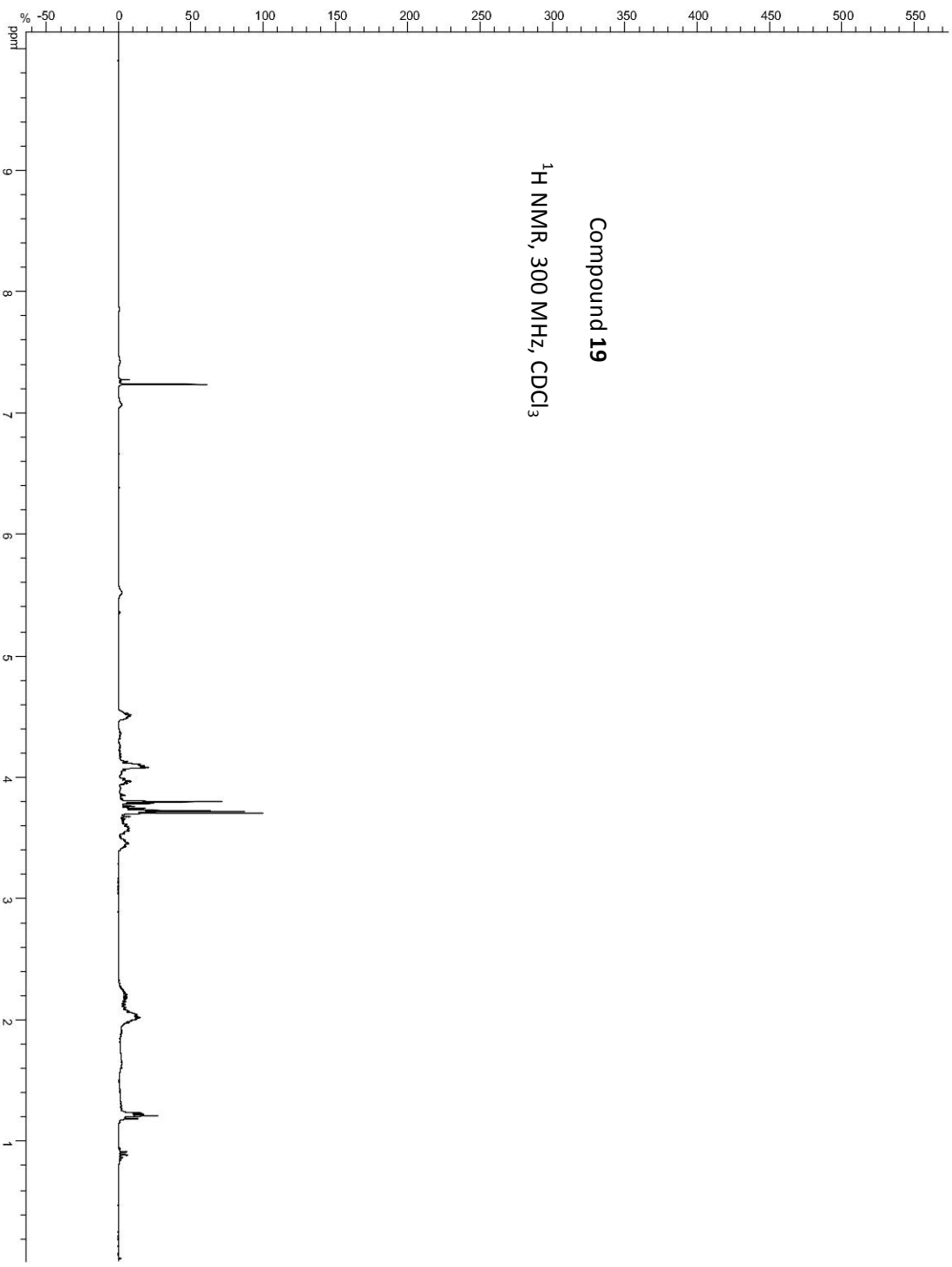
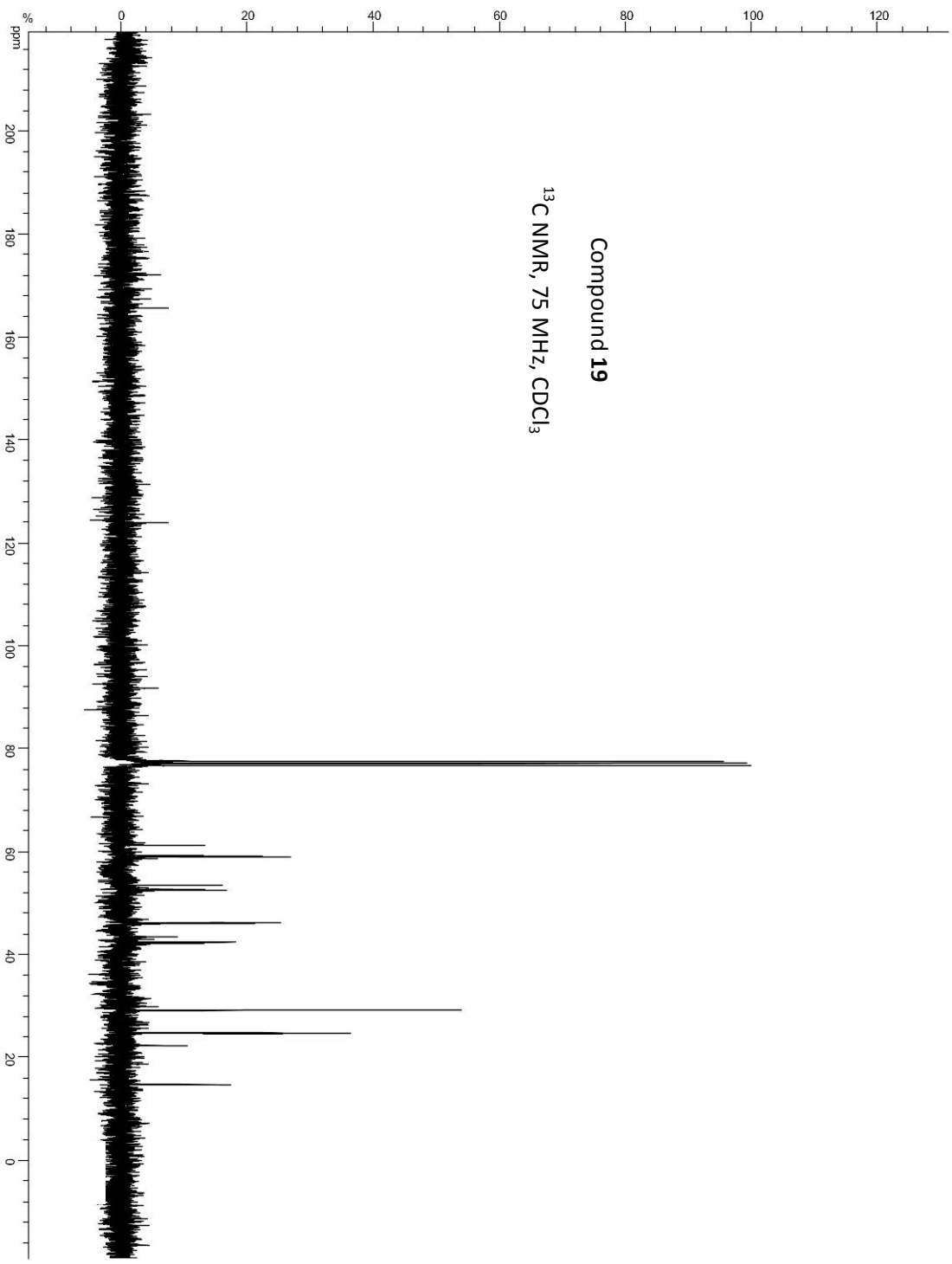


Figure S4. View of the inter-dimer interface showing bound **25** (sticks, C atoms in yellow) in a representative conformation and overlaid **4** (sticks, C atoms in pink) for reference after a best-fit superposition of the protein, which appears enveloped within a semitransparent surface. Cartoon representations of β_1- and α_2-tubulin are coloured cyan and green, respectively.

Compound **19**

^{1}H NMR, 300 MHz, $CDCl_3$



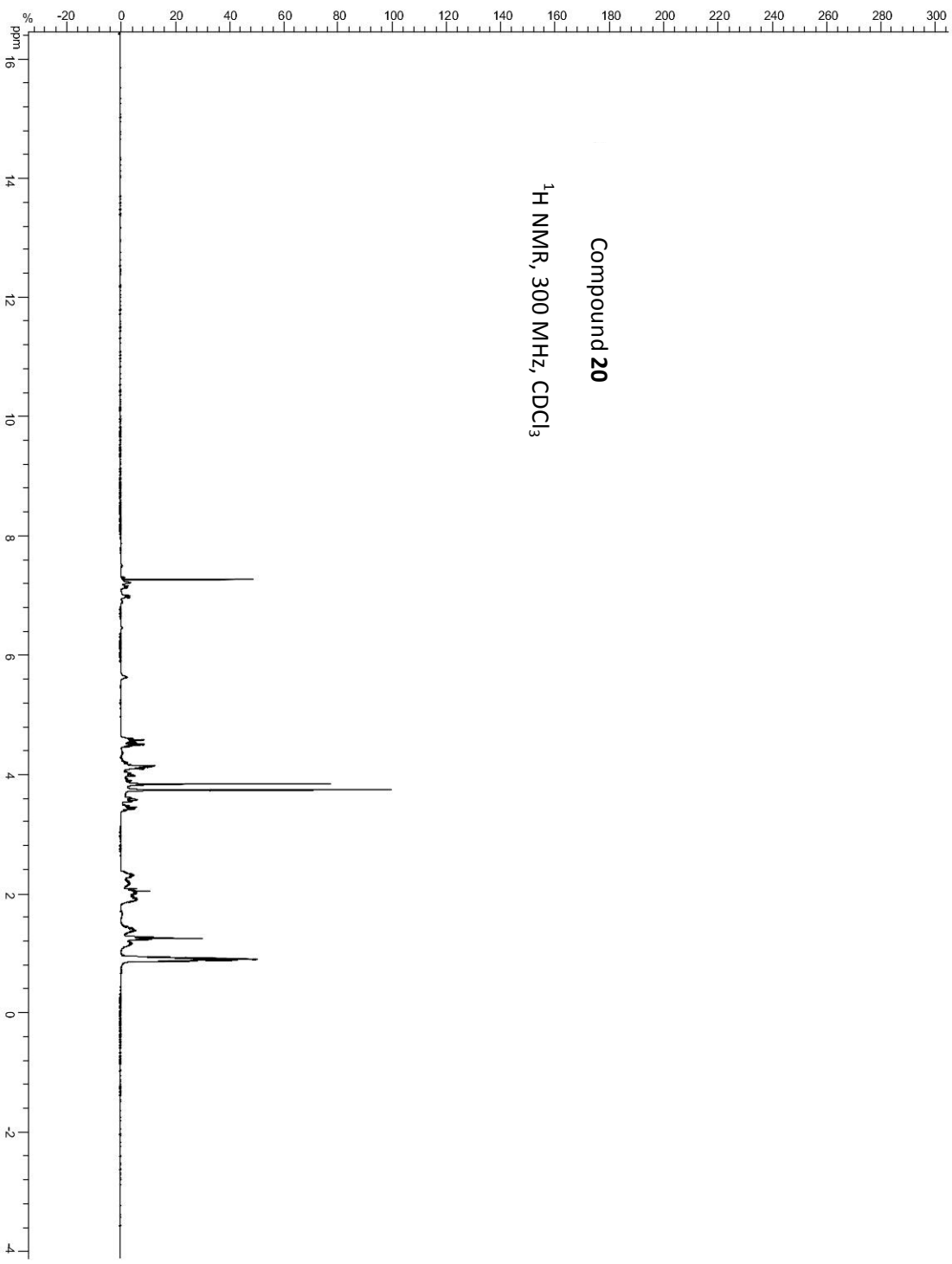


Compound **19**

^{13}C NMR, 75 MHz, $CDCl_3$

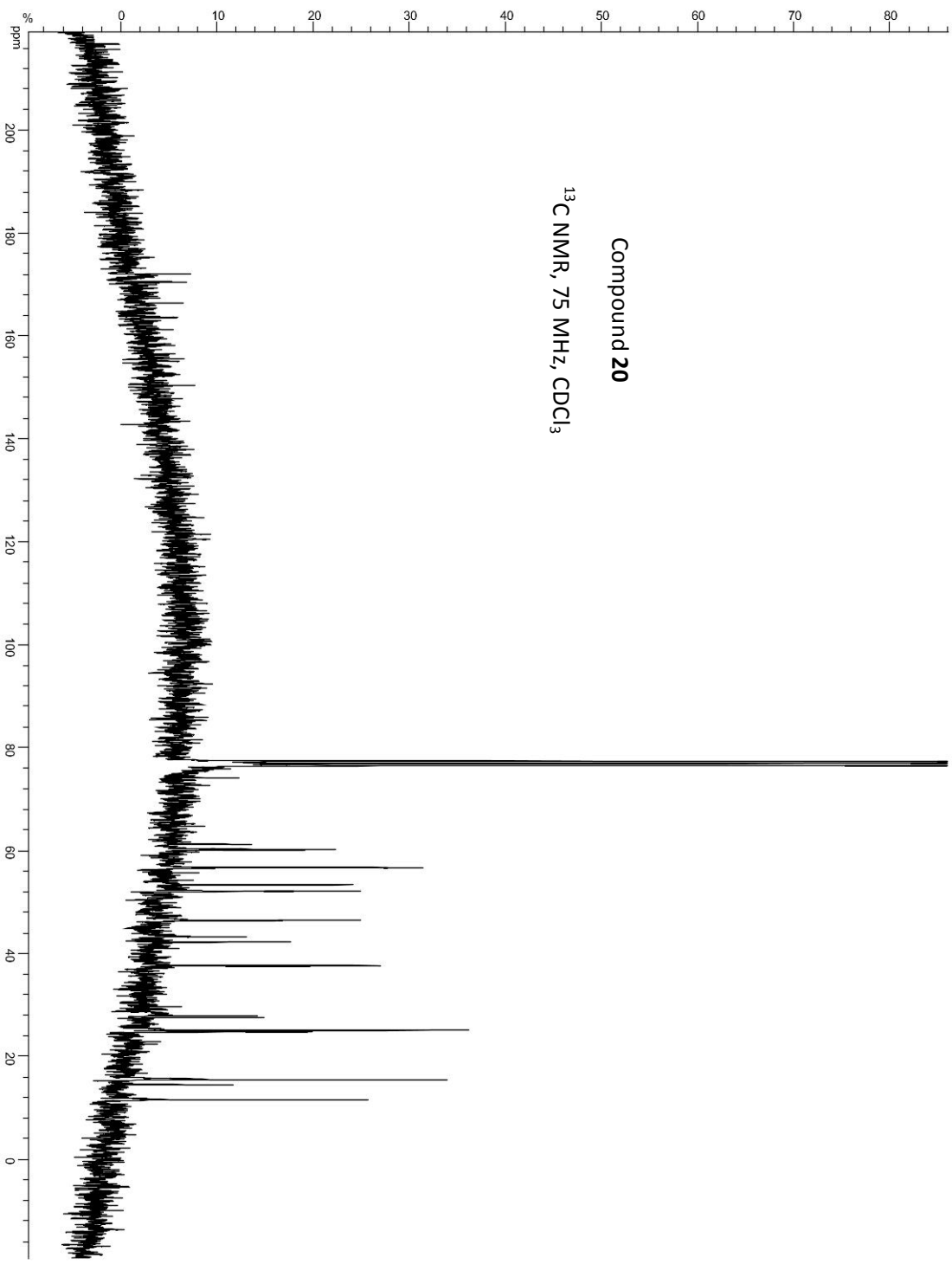
Compound **20**

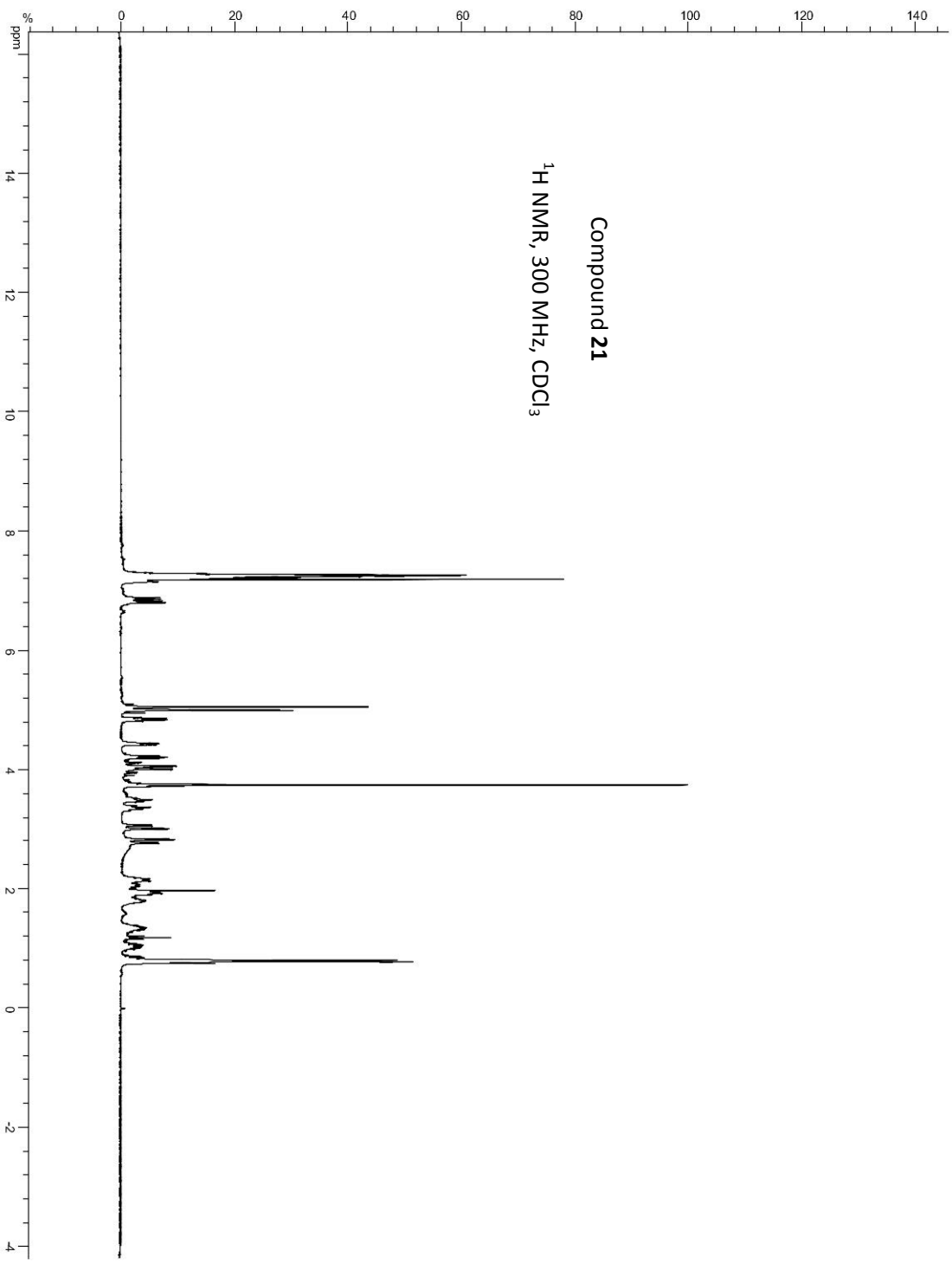
^{1}H NMR, 300 MHz, $CDCl_3$

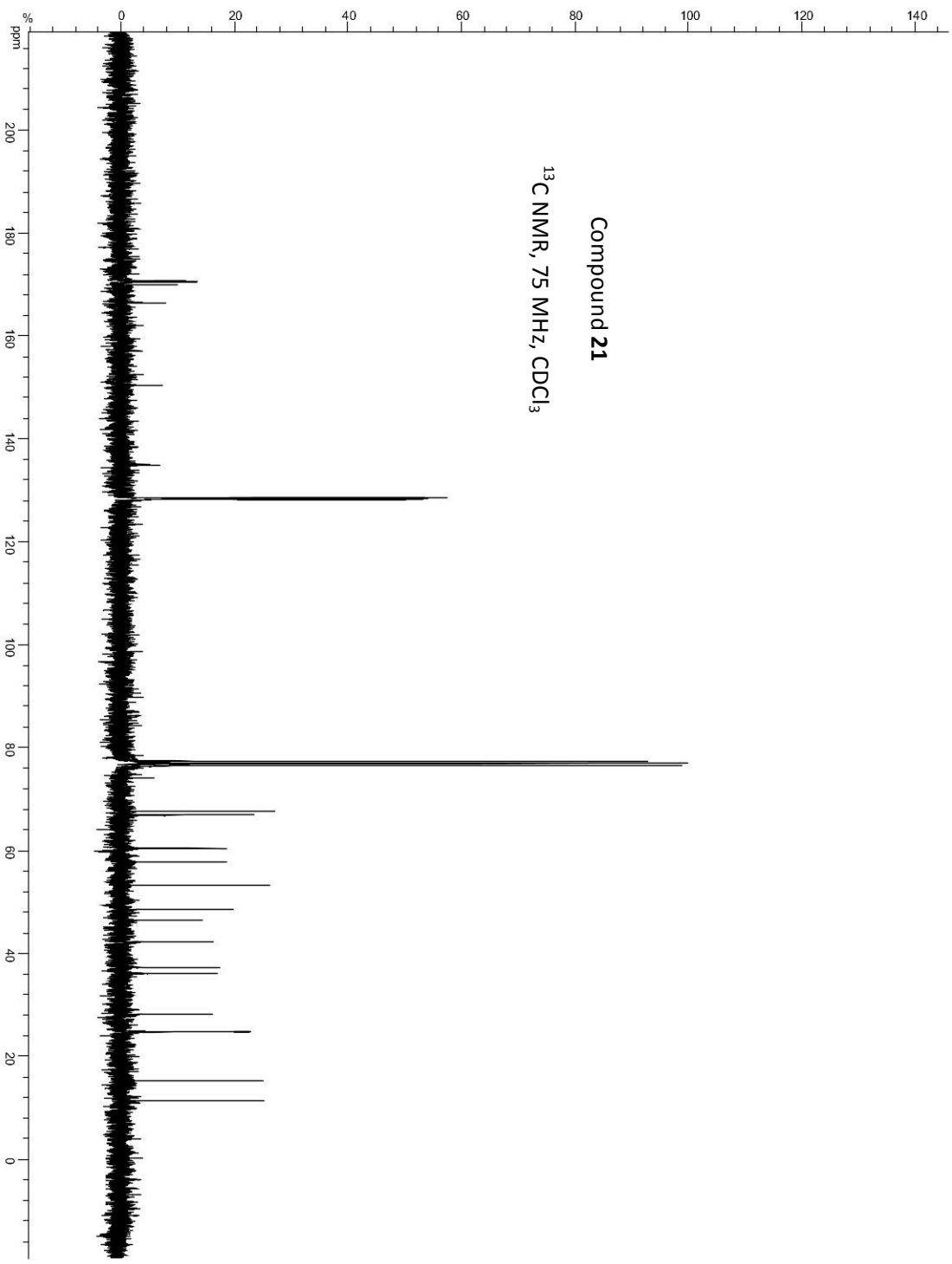


Compound **20**

^{13}C NMR, 75 MHz, $CDCl_3$

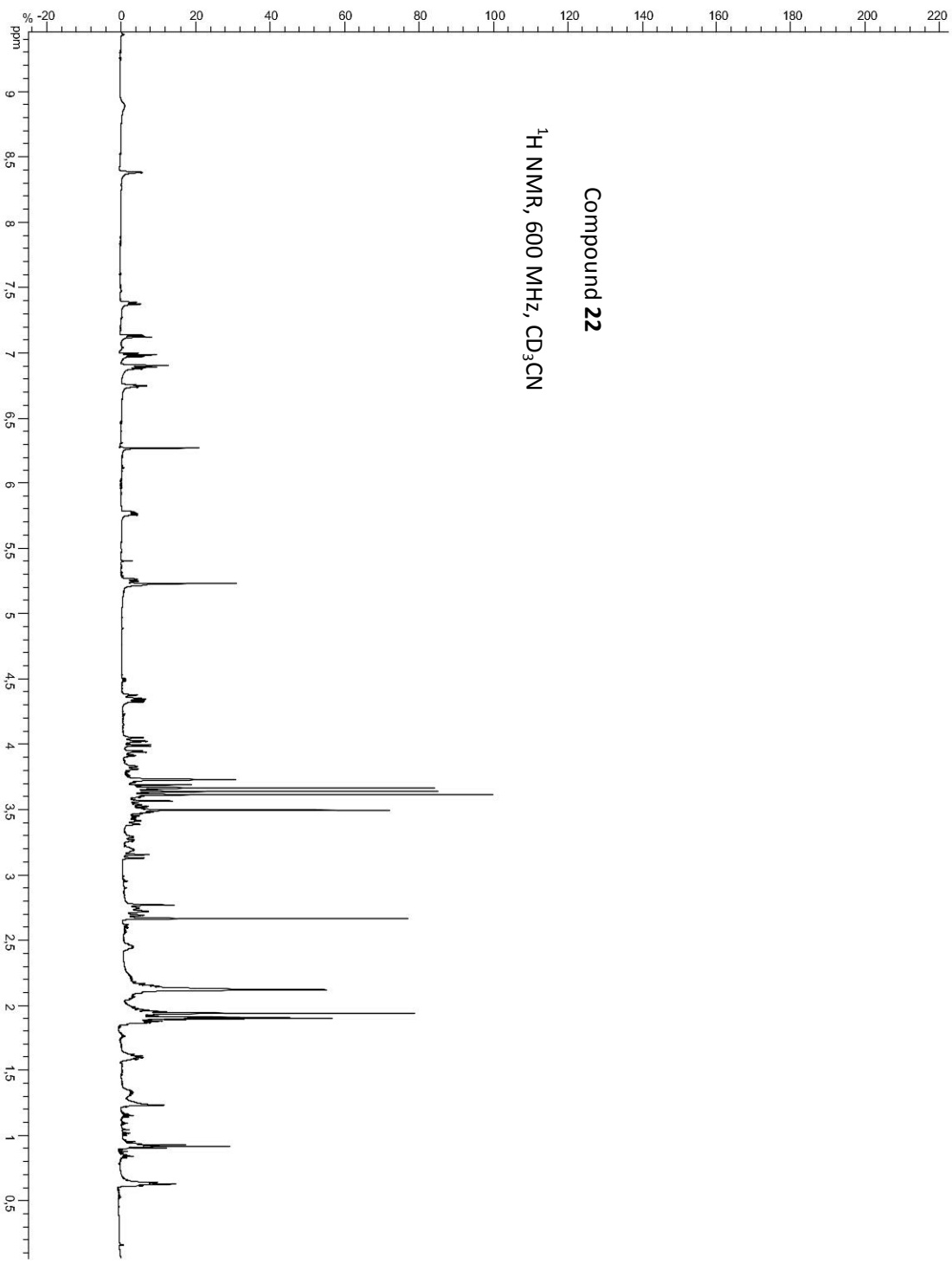


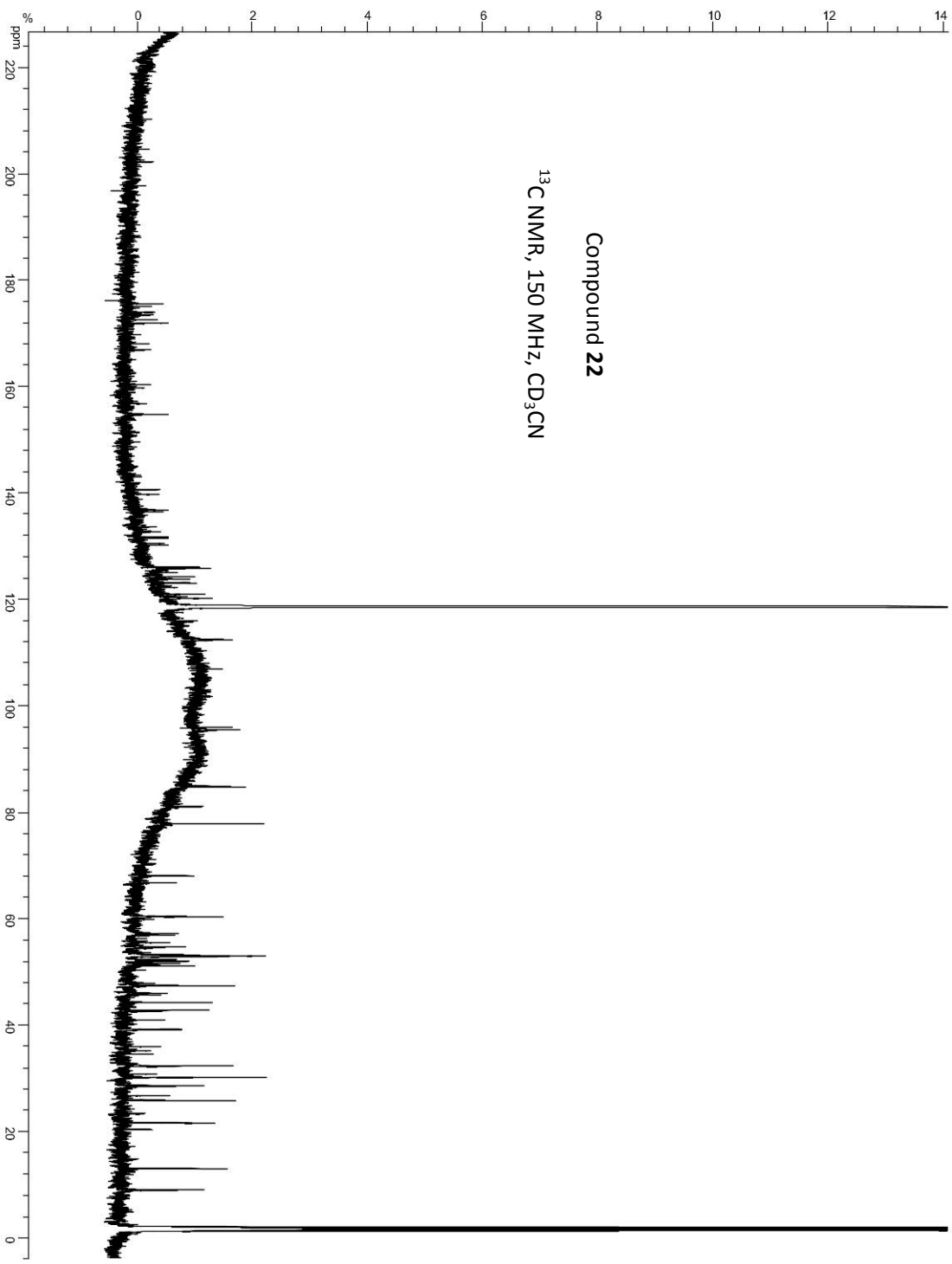

Compound 21
^{1}H NMR, 300 MHz, $CDCl_3$
%
ppm
0
20
40
60
80
100
120
140
14
12
10
8
6
4
2
0
-2
-4

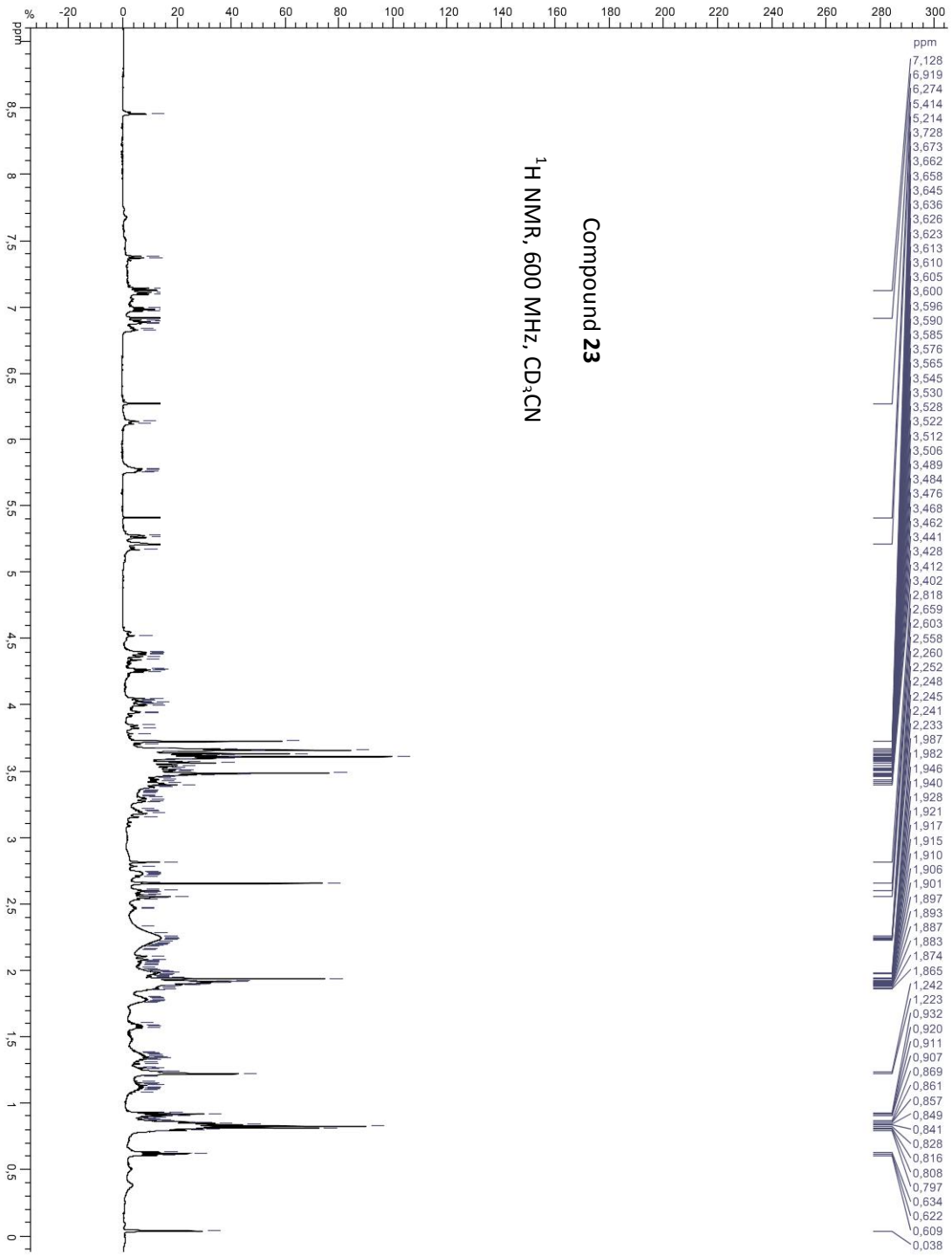

Compound 21
^{13}C NMR, 75 MHz, $CDCl_3$
%
ppm
0
20
40
60
80
100
120
140
200
180
160
140
120
100
80
60
40
20
0

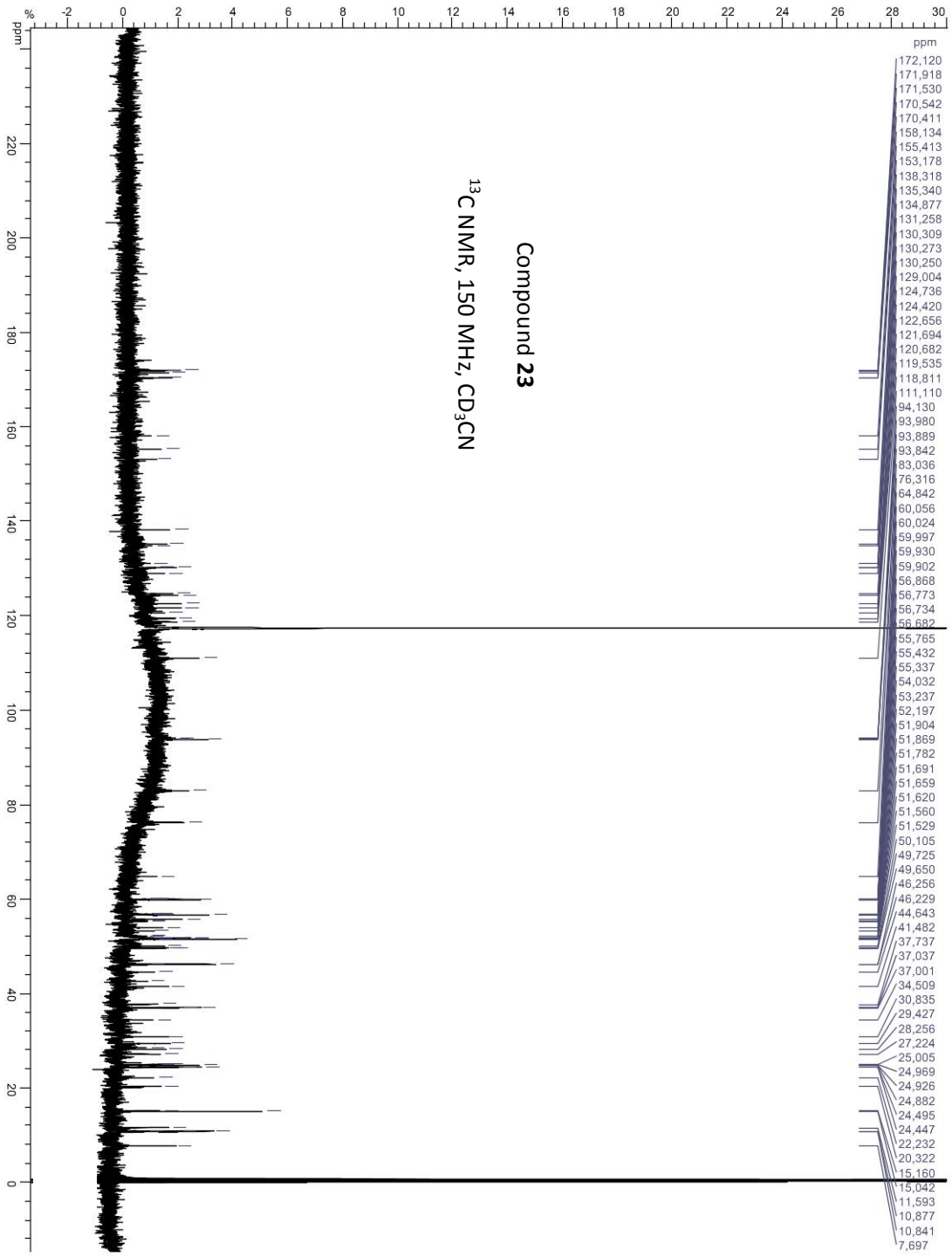
Compound **22**

^{1}H NMR, 600 MHz, CD_3CN



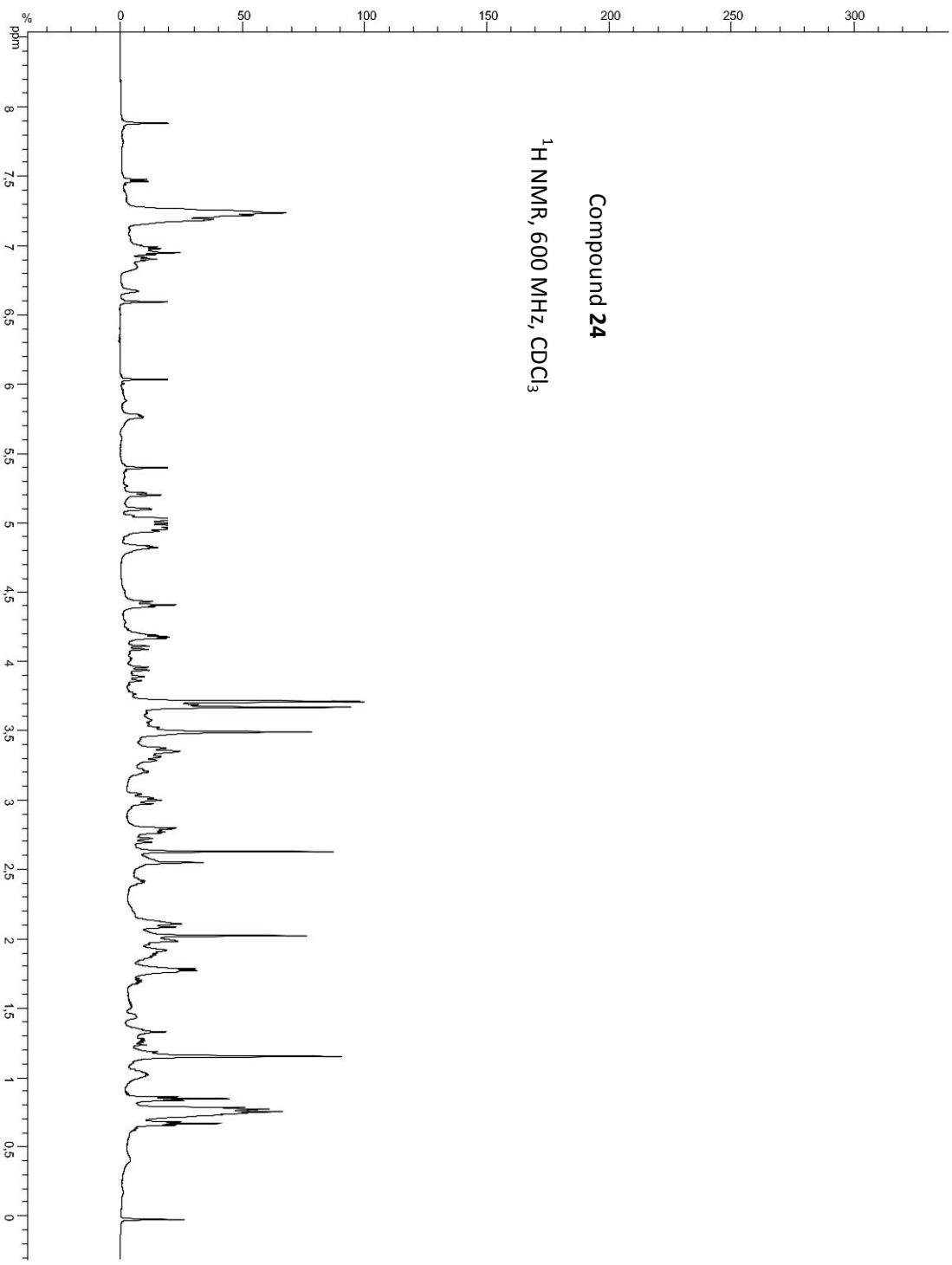

Compound **22**
^{13}C NMR, 150 MHz, CD_3CN
%
ppm
0
2
4
6
8
10
12
14
220
200
180
160
140
120
100
80
60
40
20
0

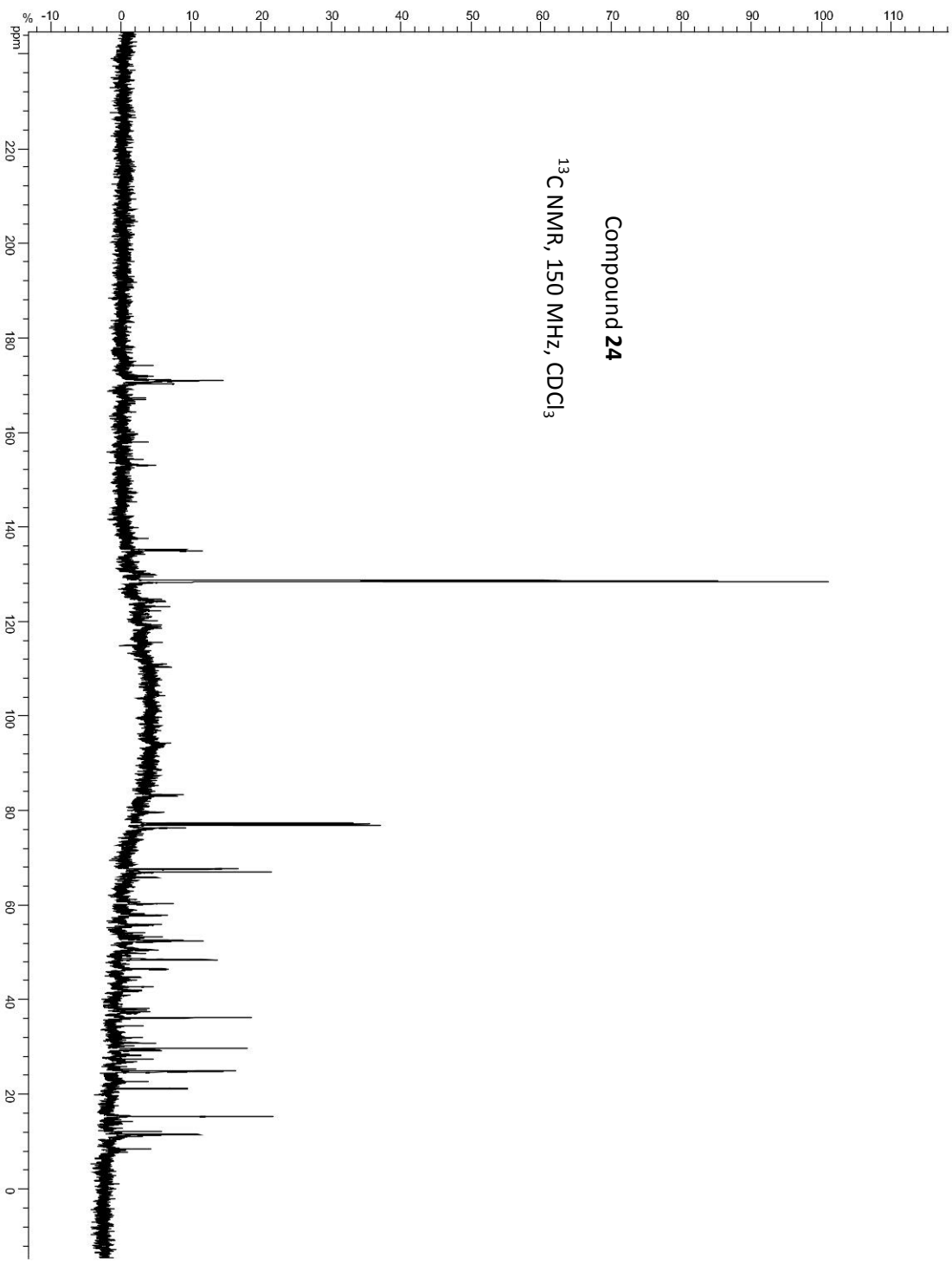

Compound 23
^{1}H NMR, 600 MHz, CD_3CN
ppm
7,128
6,919
6,274
5,414
5,214
3,728
3,673
3,662
3,658
3,645
3,636
3,626
3,623
3,613
3,610
3,605
3,600
3,596
3,590
3,585
3,576
3,565
3,545
3,530
3,528
3,522
3,512
3,506
3,489
3,484
3,476
3,468
3,462
3,441
3,428
3,412
3,402
2,818
2,659
2,603
2,558
2,260
2,252
2,248
2,245
2,241
2,233
1,987
1,982
1,946
1,940
1,928
1,921
1,917
1,915
1,910
1,906
1,901
1,897
1,893
1,887
1,883
1,874
1,865
1,242
1,223
0,932
0,920
0,911
0,907
0,869
0,861
0,857
0,849
0,841
0,828
0,816
0,808
0,797
0,634
0,622
0,609
0,038

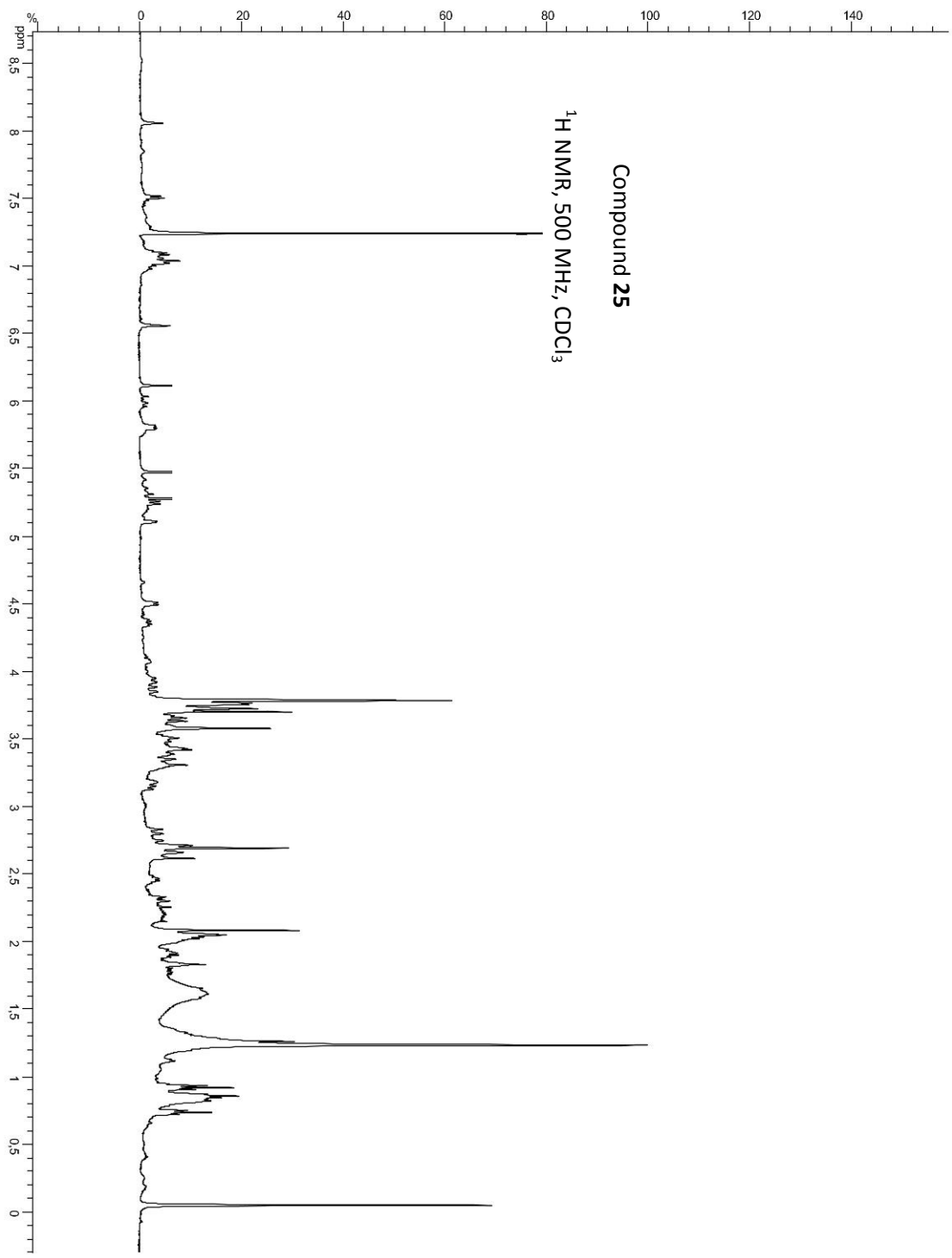

Compound 23
^{13}C NMR, 150 MHz, CD_3CN
ppm
172,120
171,918
171,530
170,542
170,411
158,134
155,413
153,178
138,318
135,340
134,877
131,258
130,309
130,273
130,250
129,004
124,736
124,420
122,656
121,694
120,682
119,535
118,811
111,110
94,130
93,980
93,889
93,842
83,036
76,316
64,842
60,056
60,024
59,997
59,930
59,902
56,868
56,773
56,734
56,682
55,765
55,432
55,337
54,032
53,237
52,197
51,904
51,869
51,782
51,691
51,659
51,620
51,560
51,529
50,105
49,725
49,650
46,256
46,229
44,643
41,482
37,737
37,037
37,001
34,509
30,835
29,427
28,256
27,224
25,005
24,969
24,926
24,882
24,495
24,447
22,232
20,322
15,160
15,042
11,593
10,877
10,841
7,697

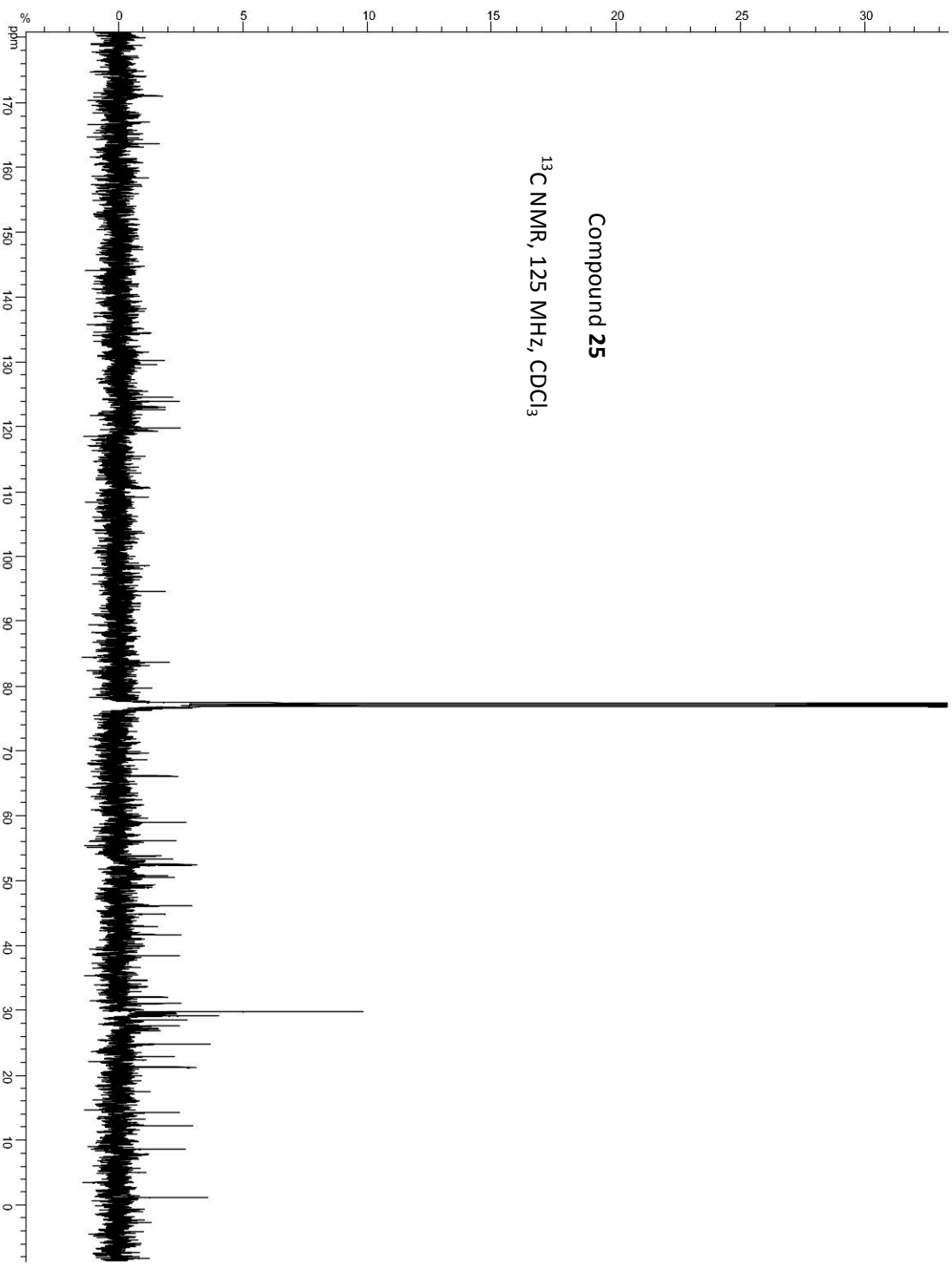
Compound **24**

^{1}H NMR, 600 MHz, $CDCl_3$



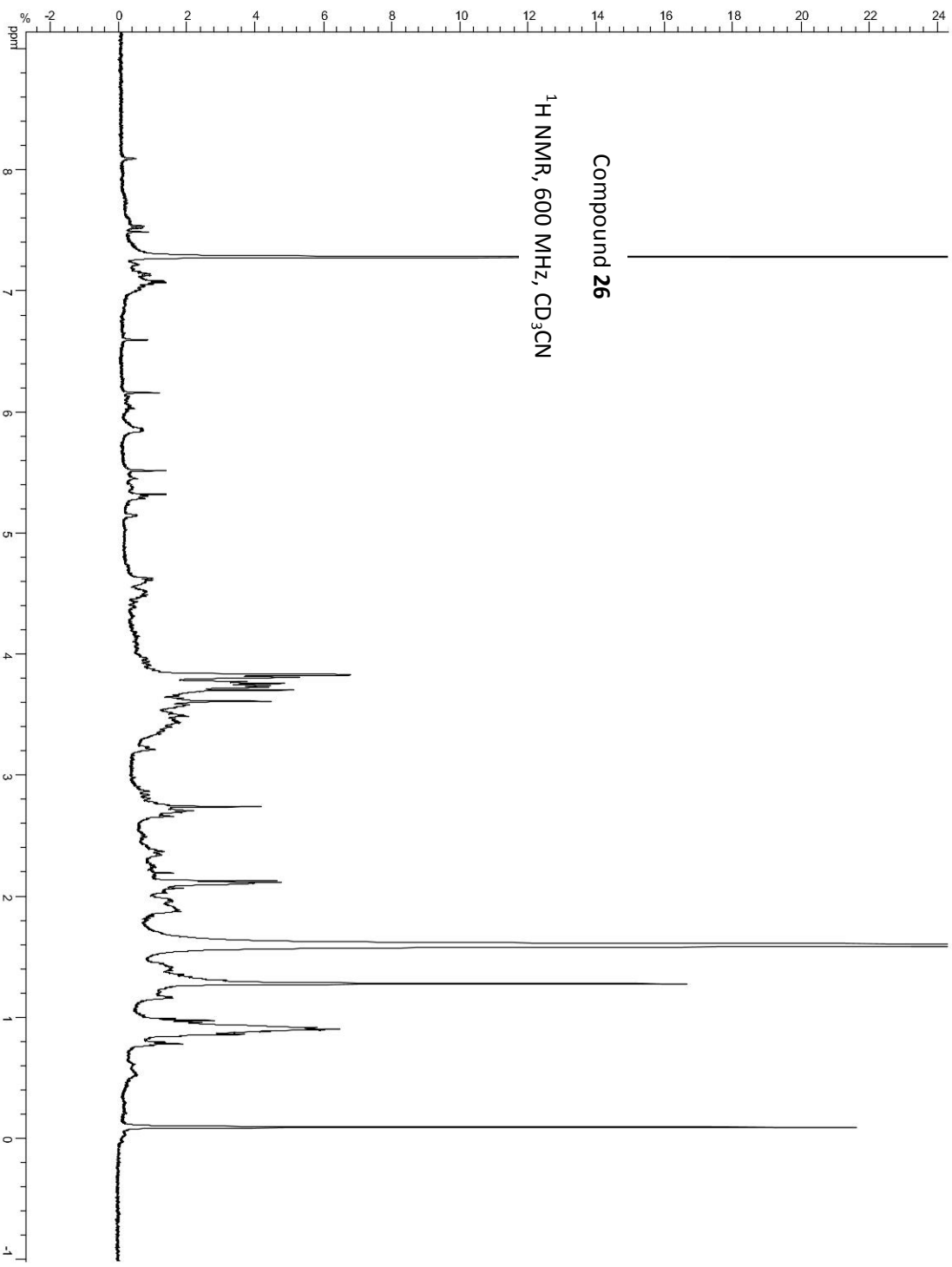

Compound 24
^{13}C NMR, 150 MHz, $CDCl_3$
% -10 0 10 20 30 40 50 60 70 80 90 100 110
ppm
220 200 180 160 140 120 100 80 60 40 20 0

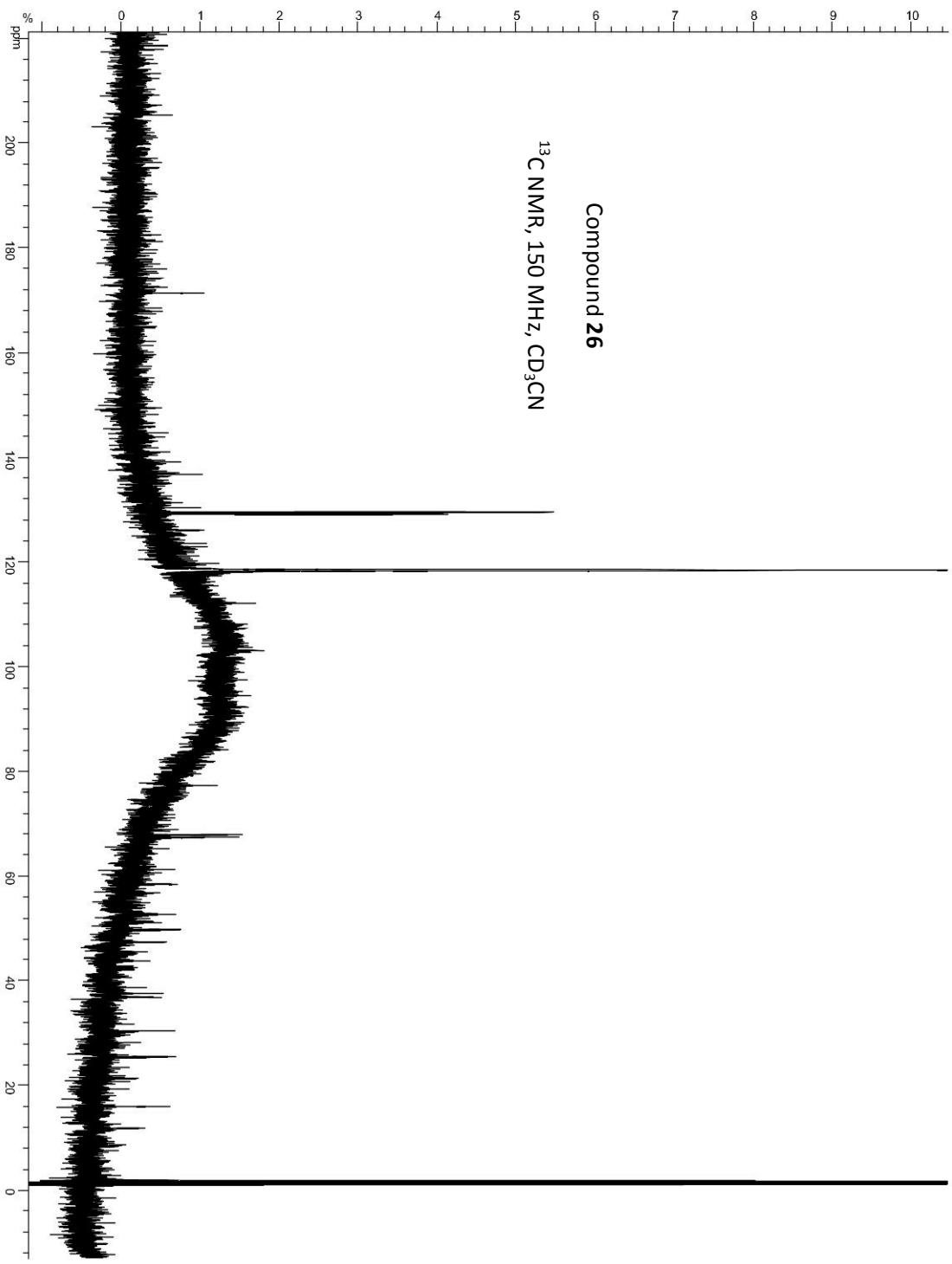

Compound 25
^{1}H NMR, 500 MHz, $CDCl_3$
%
ppm



Compound **25**

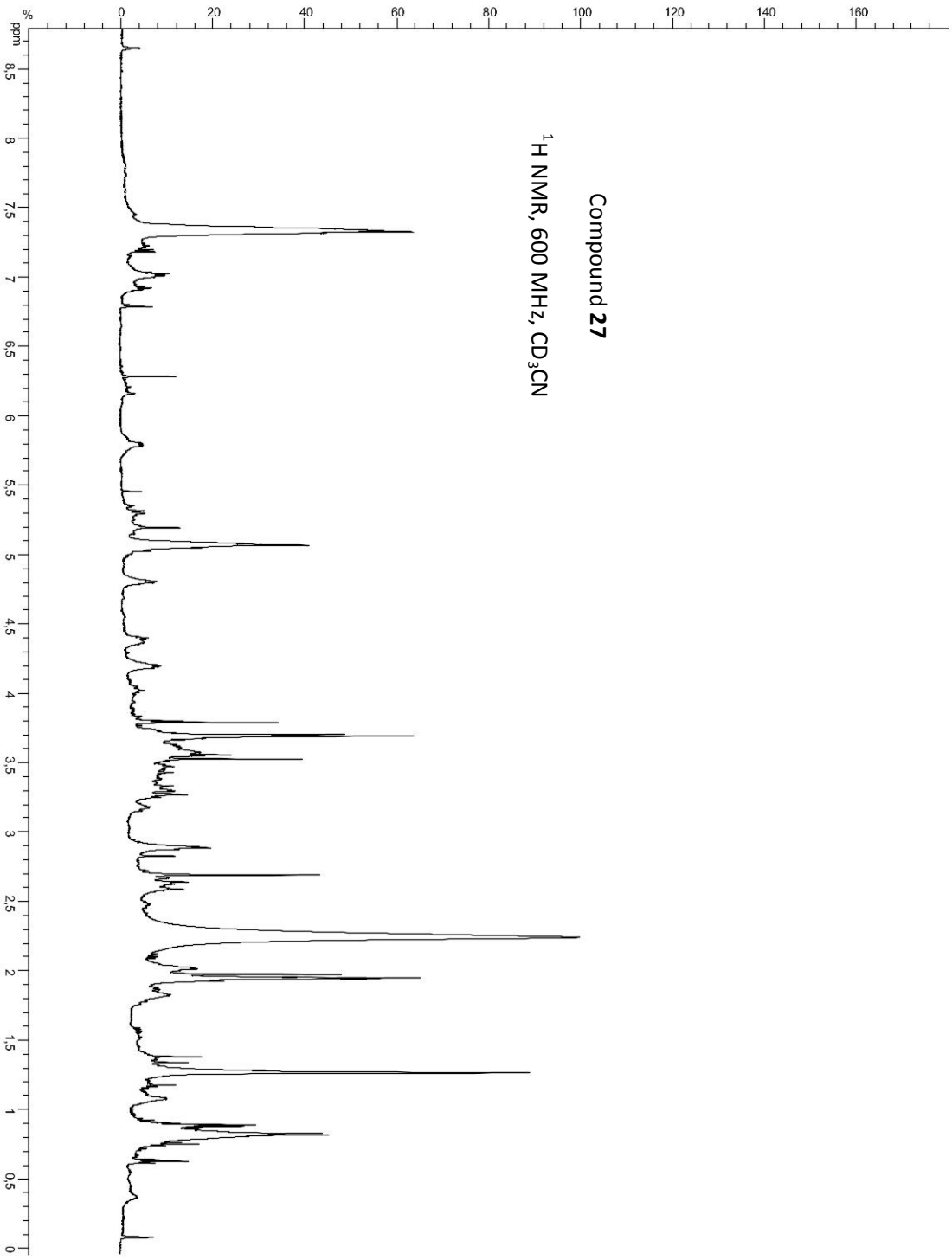
^{13}C NMR, 125 MHz, $CDCl_3$

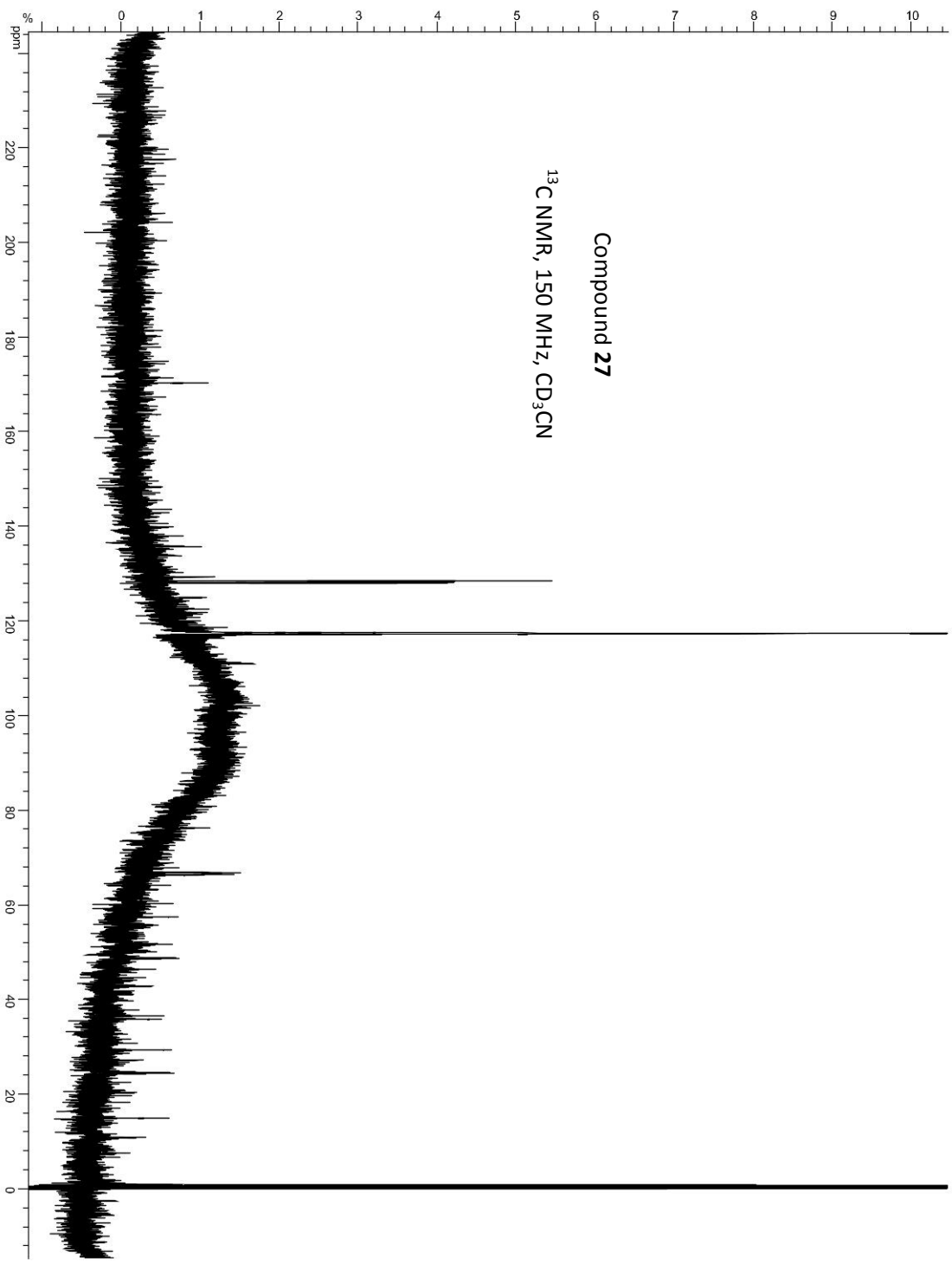

Compound 26
^{1}H NMR, 600 MHz, CD_3CN
ppm
%


Compound 26
^{13}C NMR, 150 MHz, CD_3CN
%
ppm
0
1
2
3
4
5
6
7
8
9
10
200
180
160
140
120
100
80
60
40
20
0

Compound **27**

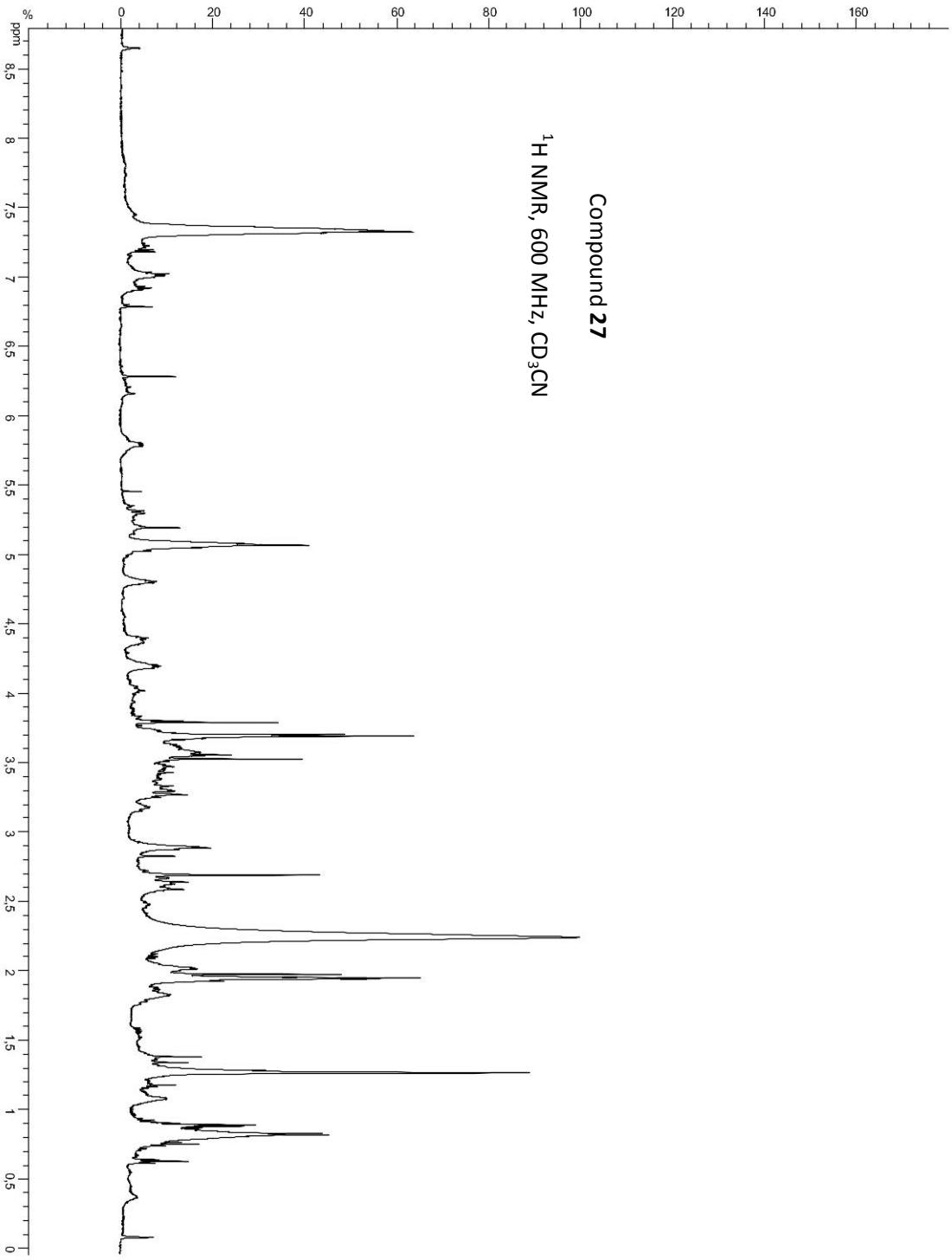
^{1}H NMR, 600 MHz, CD_3CN

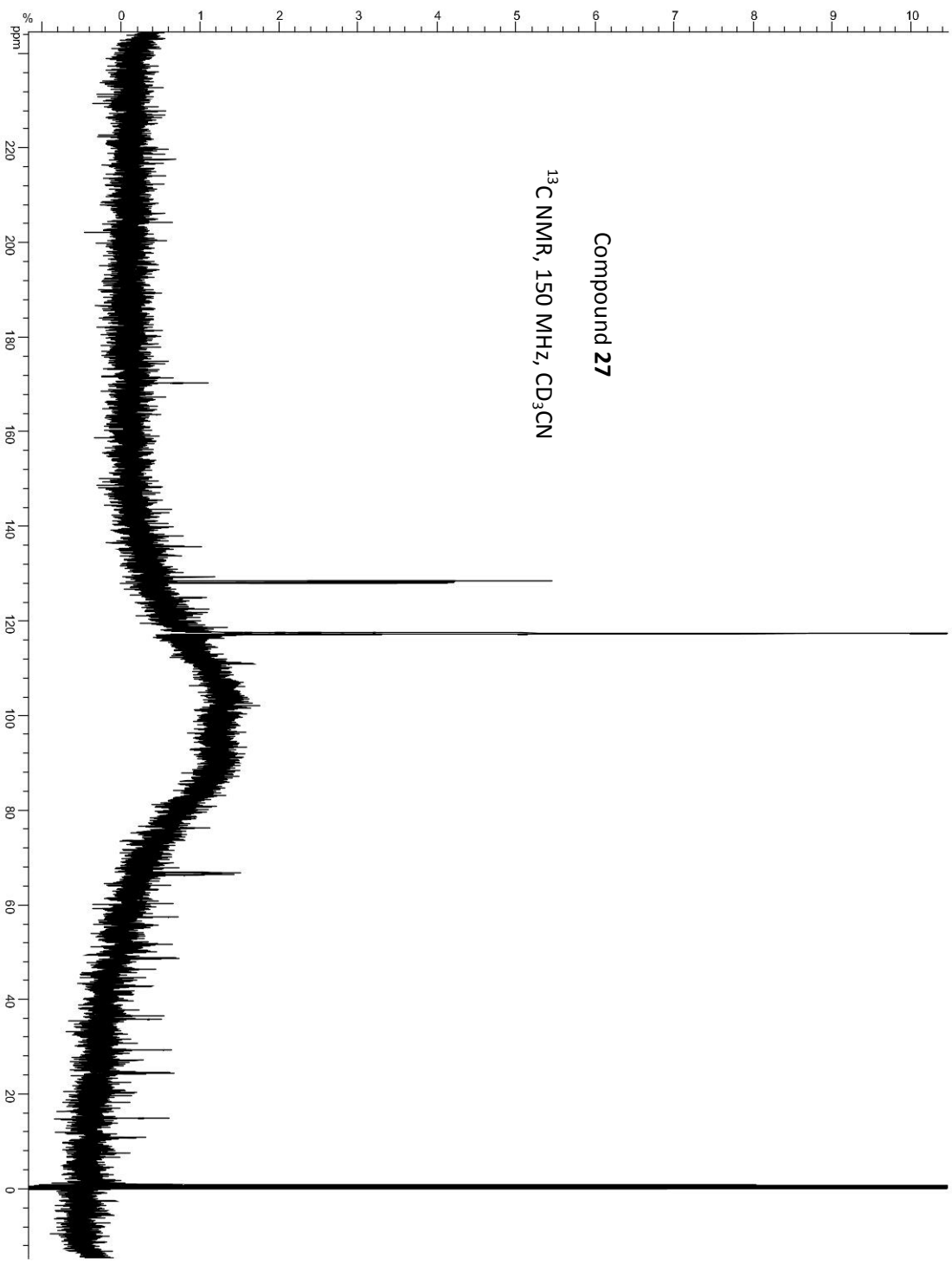



Compound 27
^{13}C NMR, 150 MHz, CD_3CN
%
ppm
0
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0

Compound **27**

^{1}H NMR, 600 MHz, CD_3CN




Compound 27
^{13}C NMR, 150 MHz, CD_3CN
%
ppm