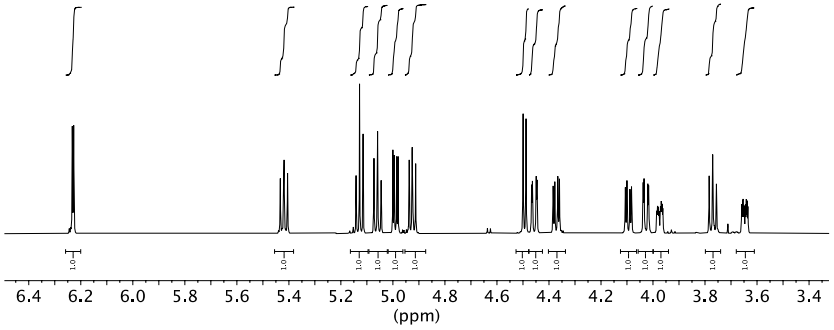
NMR Data Analysis By and For Synthetic Chemists: Is there a better way?

Eric Hughes and Alan Kenwright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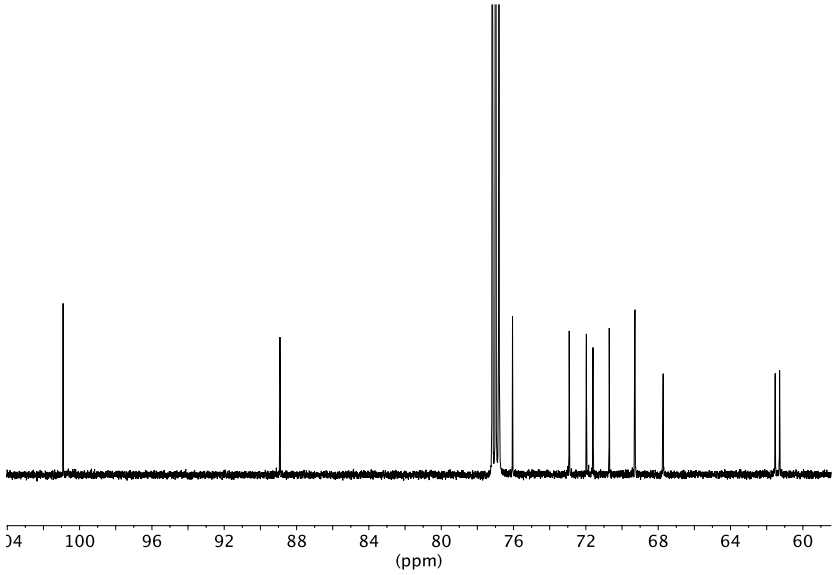
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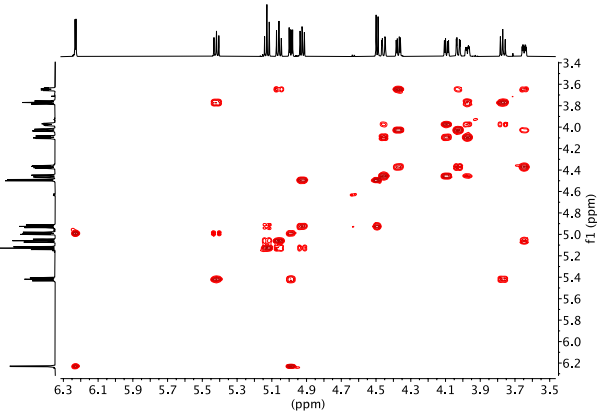
(ppm)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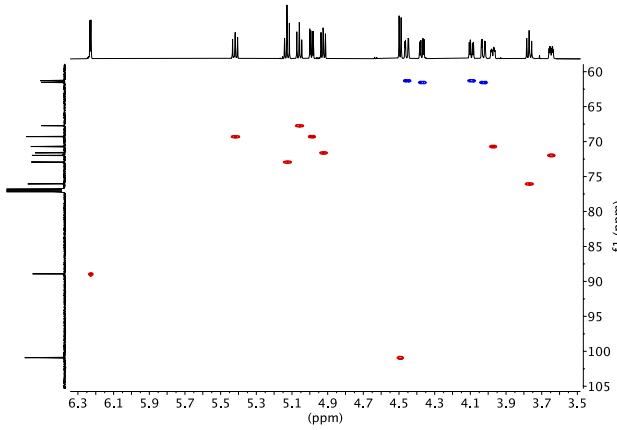
(ppm)
f1 (ppm)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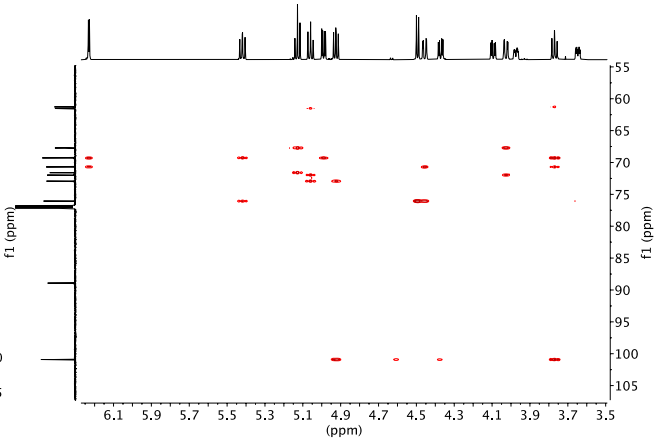
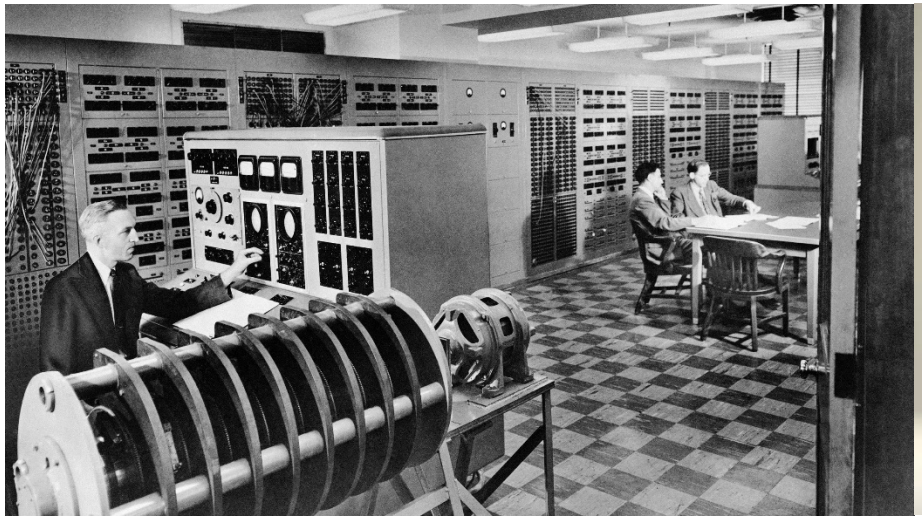
(ppm)
f1 (ppm)


6.1 5.9 5.7 5.5 5.3 5.1 4.9 4.7 4.5 4.3 4.1 3.9 3.7 3.5
(ppm)
f1 (ppm)

A Mismatch?

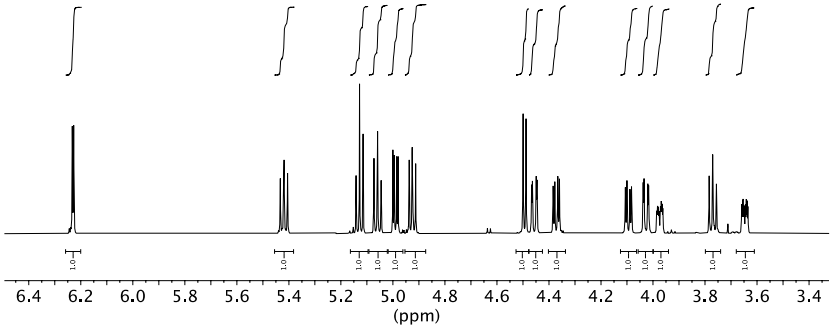
People in NMR Labs



Know a lot about NMR theory so should be well placed to interpret spectra (in theory). Think in terms of spectral features.

Synthetic Chemists

Do a lot of spectral assignment
Don't necessarily know a lot about NMR theory. Think in terms of structural fragments.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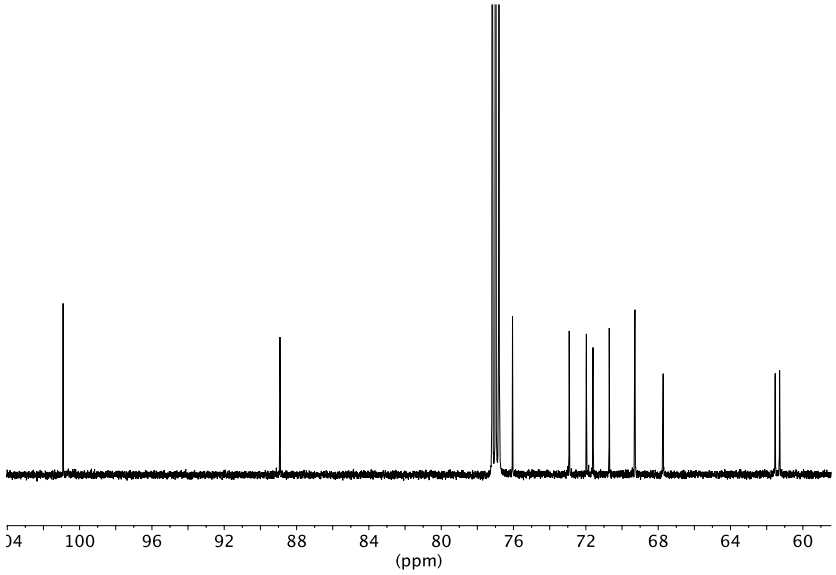
(ppm)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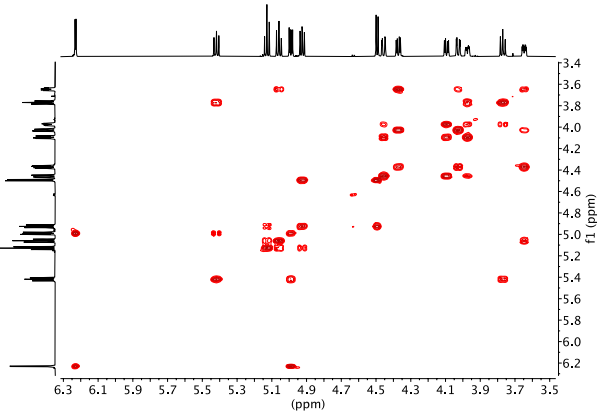
(ppm)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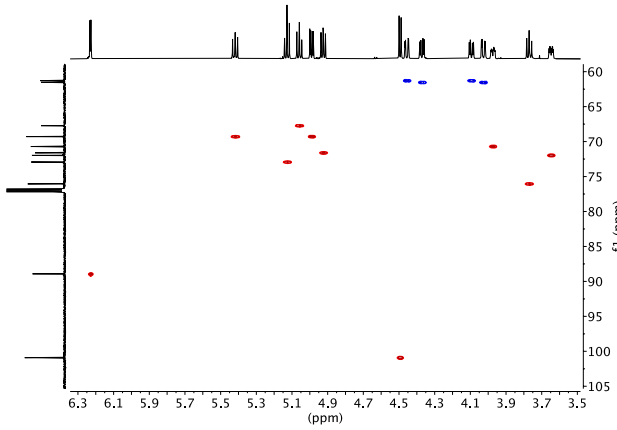
(ppm)
f1 (ppm)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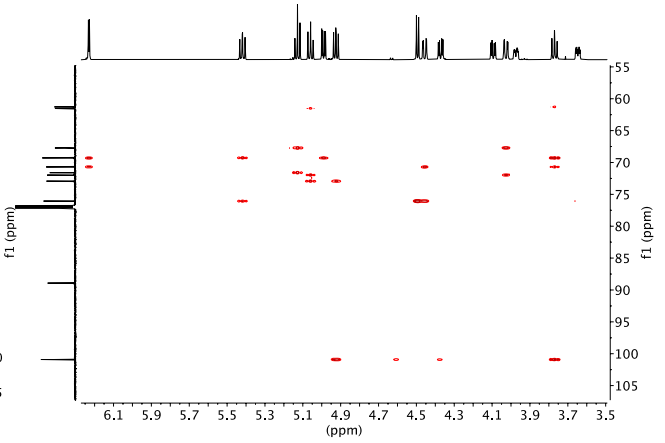
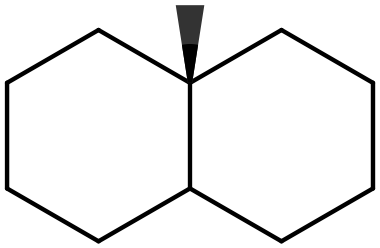
(ppm)
f1 (ppm)

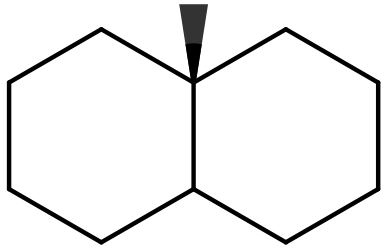

6.1 5.9 5.7 5.5 5.3 5.1 4.9 4.7 4.5 4.3 4.1 3.9 3.7 3.5
(ppm)
f1 (ppm)

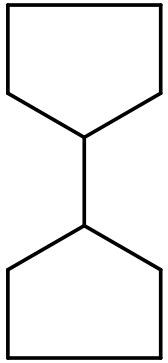
Constitution Verification

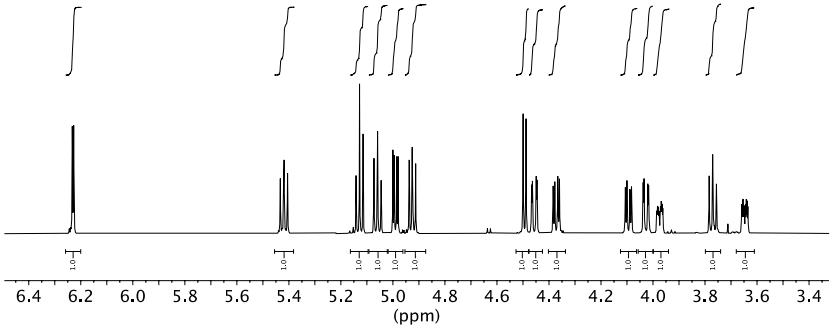
"Constitution" – pure connectivity of atoms within a molecule – no information on spatial arrangement e.g. cis/trans, E/Z, chirality, etc. The "flat" molecule.

What are we verifying? That the spectral dataset is consistent with the postulated structure and that an assignment of the spectra can be made on that basis





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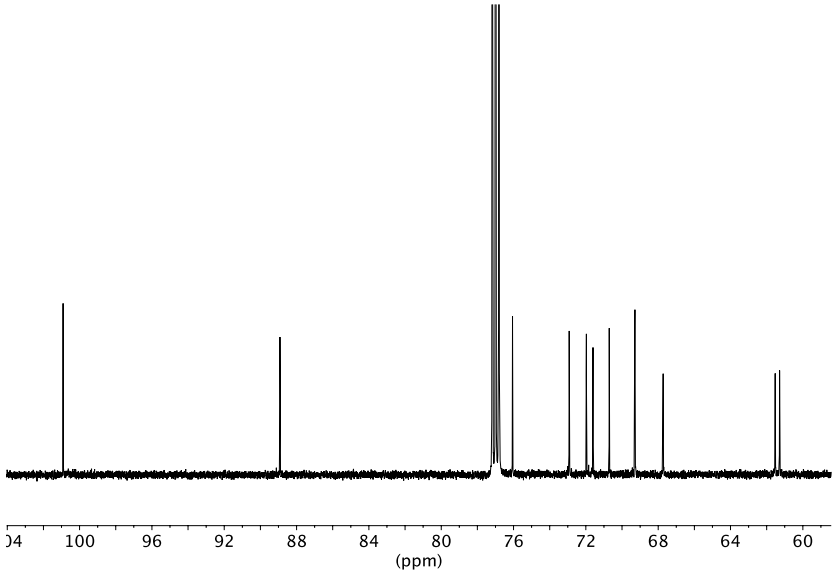
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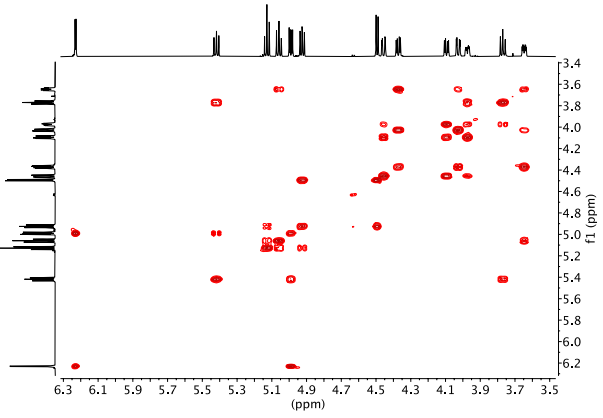
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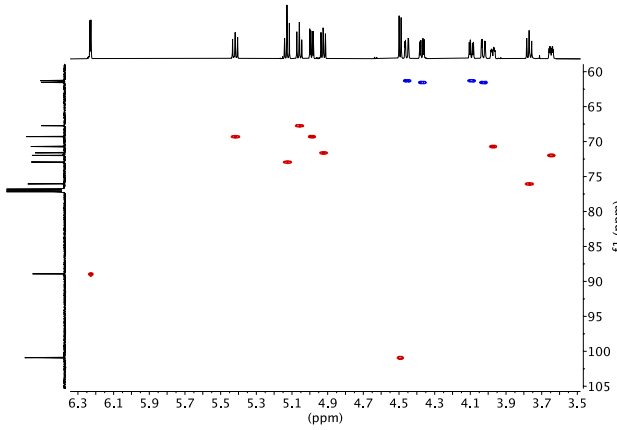
(ppm)
f1 (ppm)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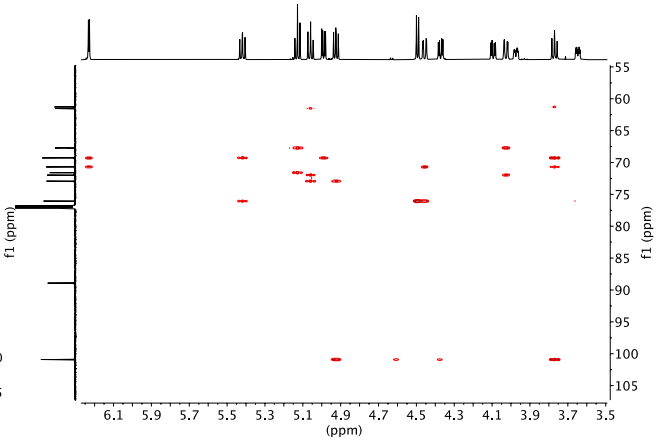
(ppm)
f1 (ppm)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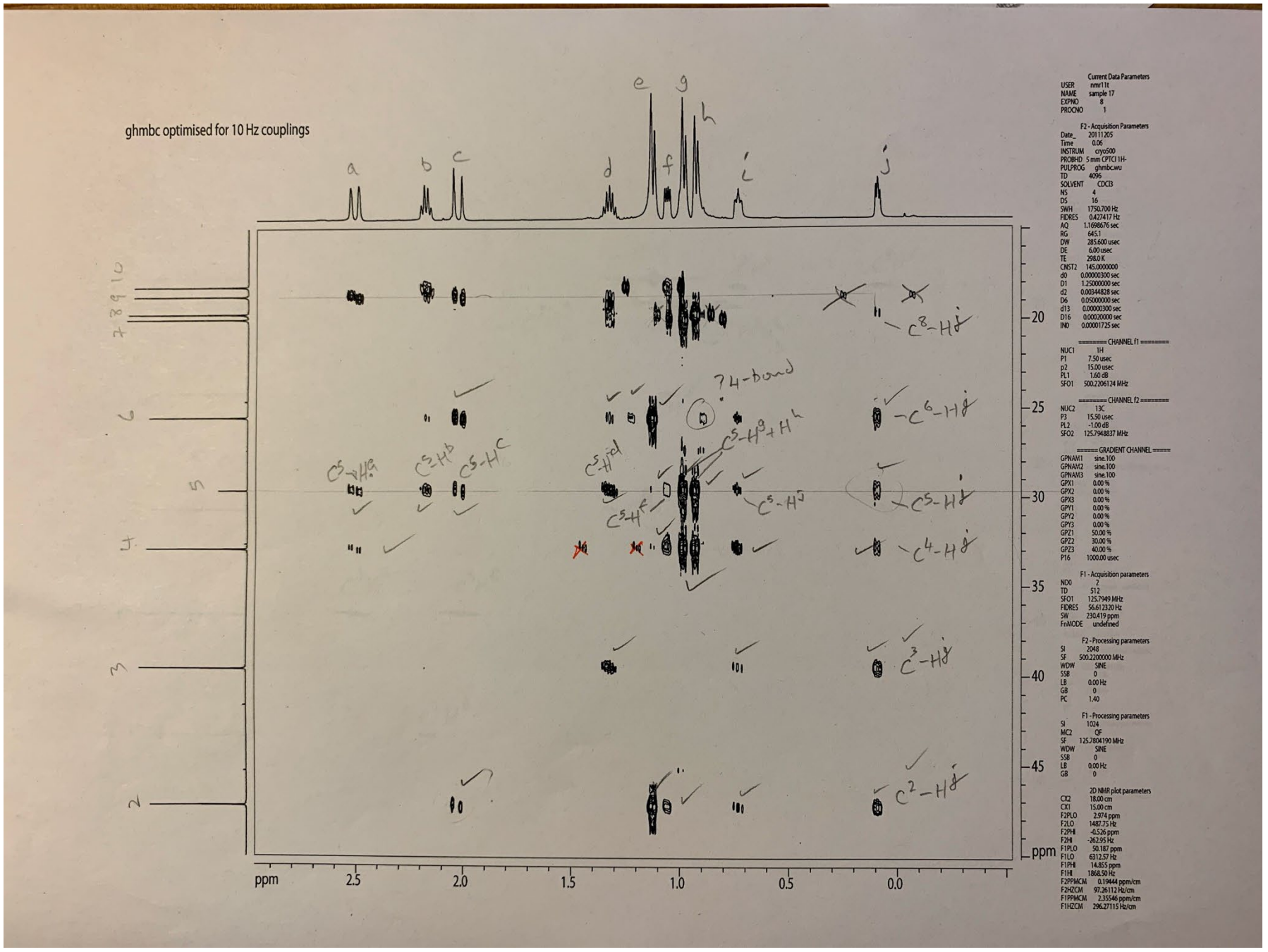
(ppm)
f1 (ppm)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a
b
c
d
e
f
g
h
i
j
ppm
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2.0
1.5
1.0
0.5
0.0
20
25
30
35
40
45
ppm
74-bond
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EXPNO 8
PROCNO 1
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Time 0.06
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SOLVENT CDCl3
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FIDRES 0.427417 Hz
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TE 298.0 K
CNST2 145.0000000
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D16 0.00020000 sec
IN0 0.00001725 sec
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p2 15.00 usec
PL1 1.60 dB
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P3 15.50 usec
PL2 -1.00 dB
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GPY3 0.00 %
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GPZ2 30.00 %
GPZ3 40.00 %
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SF 500.2200000 MHz
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SSB 0
LB 0.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 1024
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LB 0.00 Hz
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2D NMR plot parameters
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CX1 15.00 cm
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F2LO 1487.75 Hz
F2PHI -0.526 ppm
F2HI -262.95 Hz
F1PLO 50.187 ppm
F1LO 6312.57 Hz
F1PHI 14.855 ppm
F1HI 1868.50 Hz
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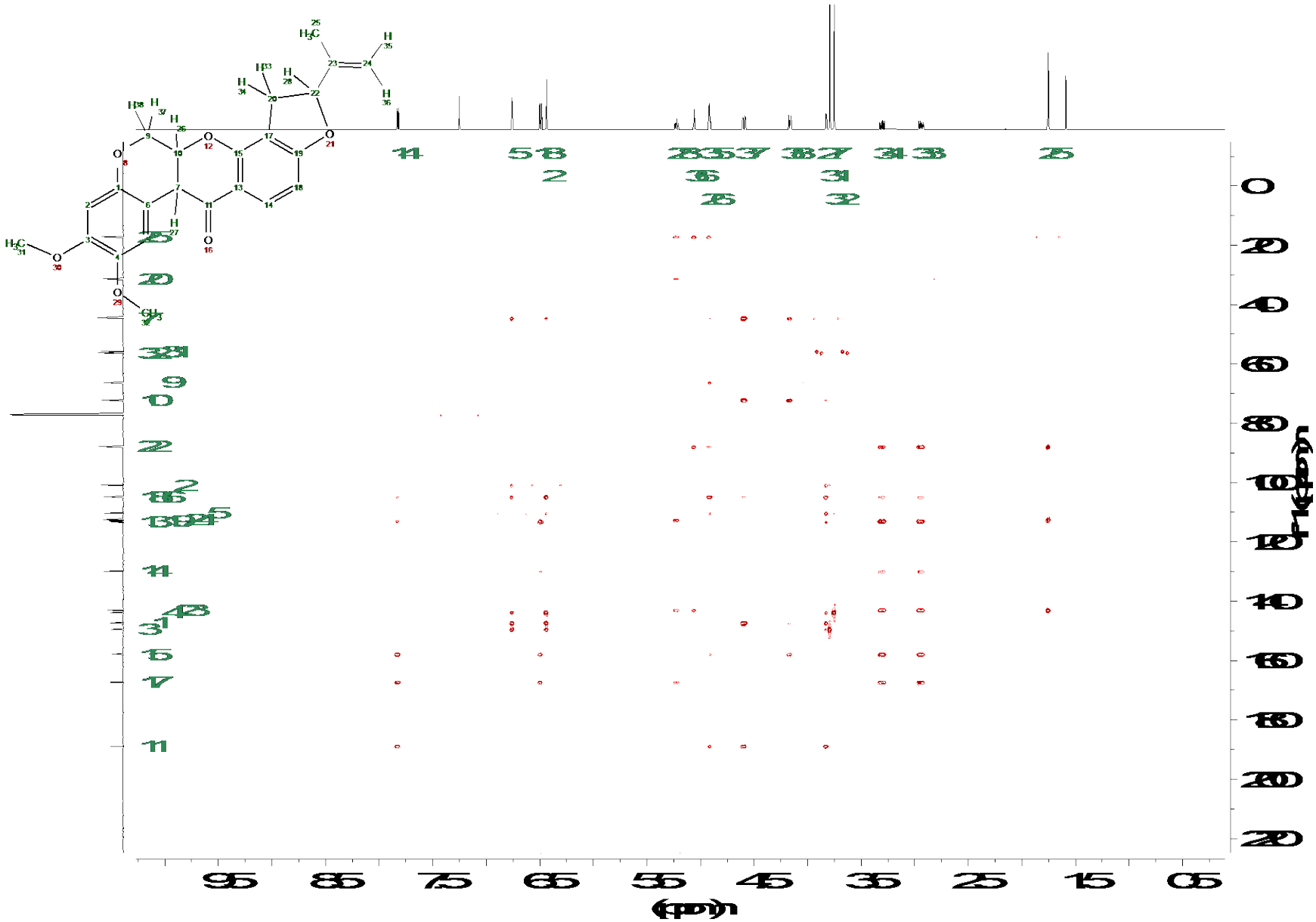
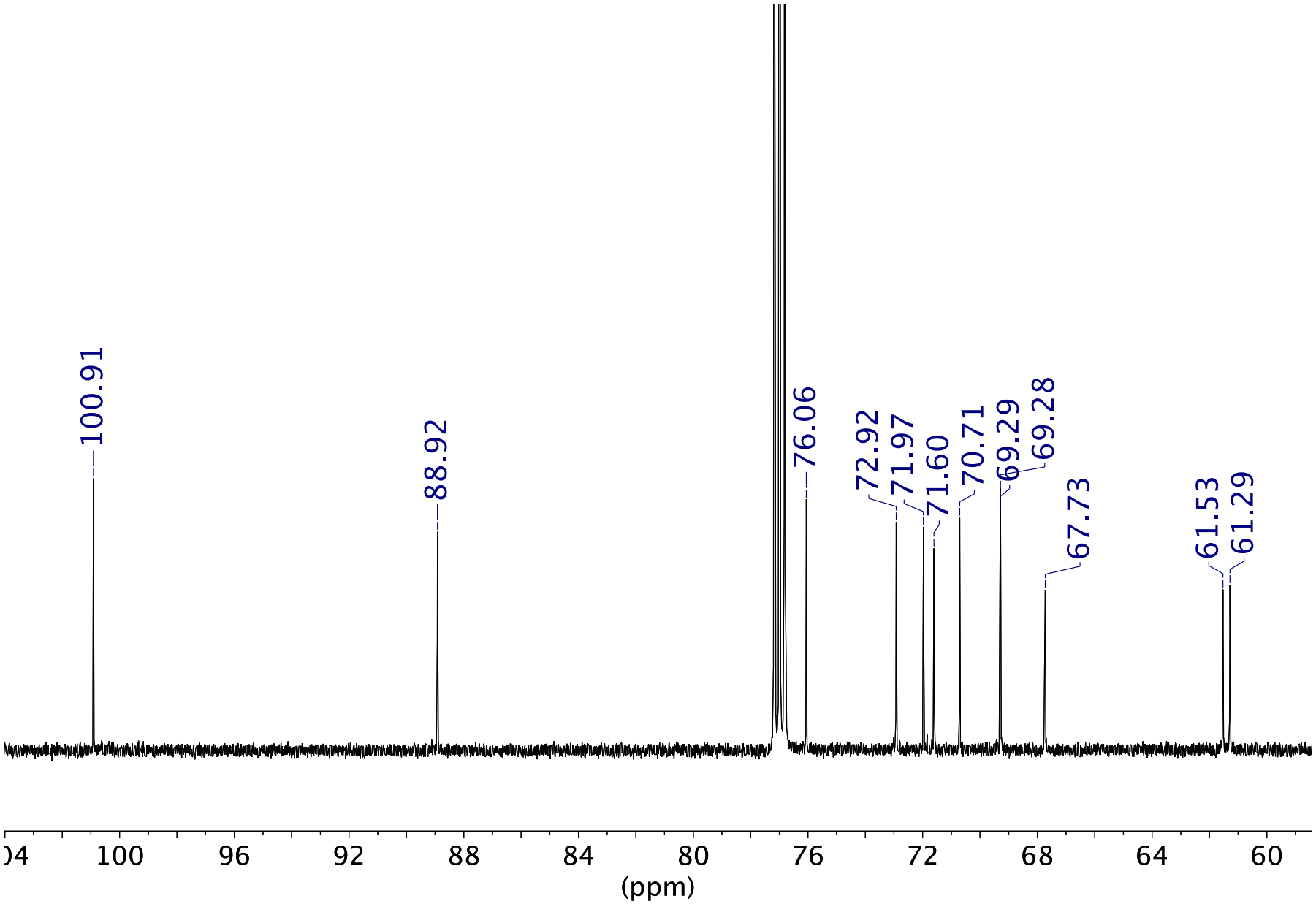
F1PPMCM 2.35546 ppm/cm
F1HZCM 296.27115 Hz/cm



In order to simplify/speed the process, what information should we make use of?

Information that can be measured directly from the spectra without the need for interpretation / analysis at this point.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72.92
71.97
71.60
70.71
69.29
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67.73
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61.29
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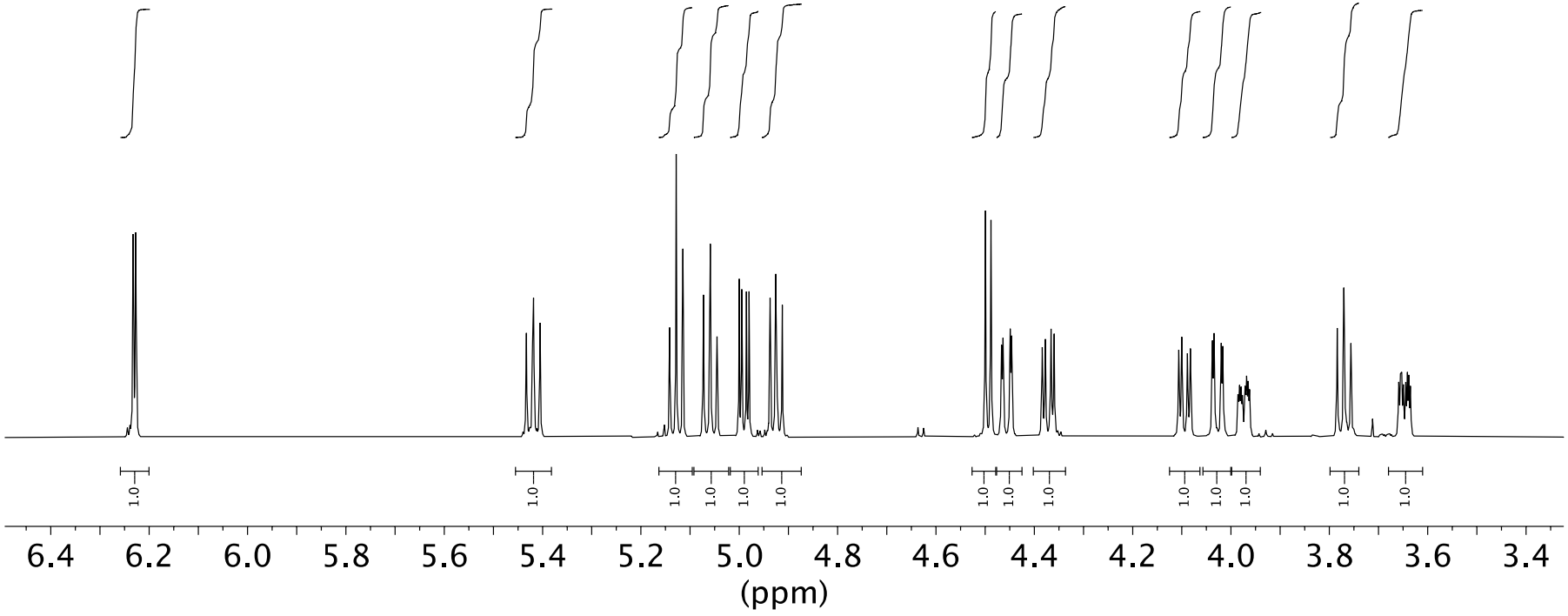
88
84
80
76
72
68
64
60
(ppm)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6.4
6.2
6.0
5.8
5.6
5.4
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5.0
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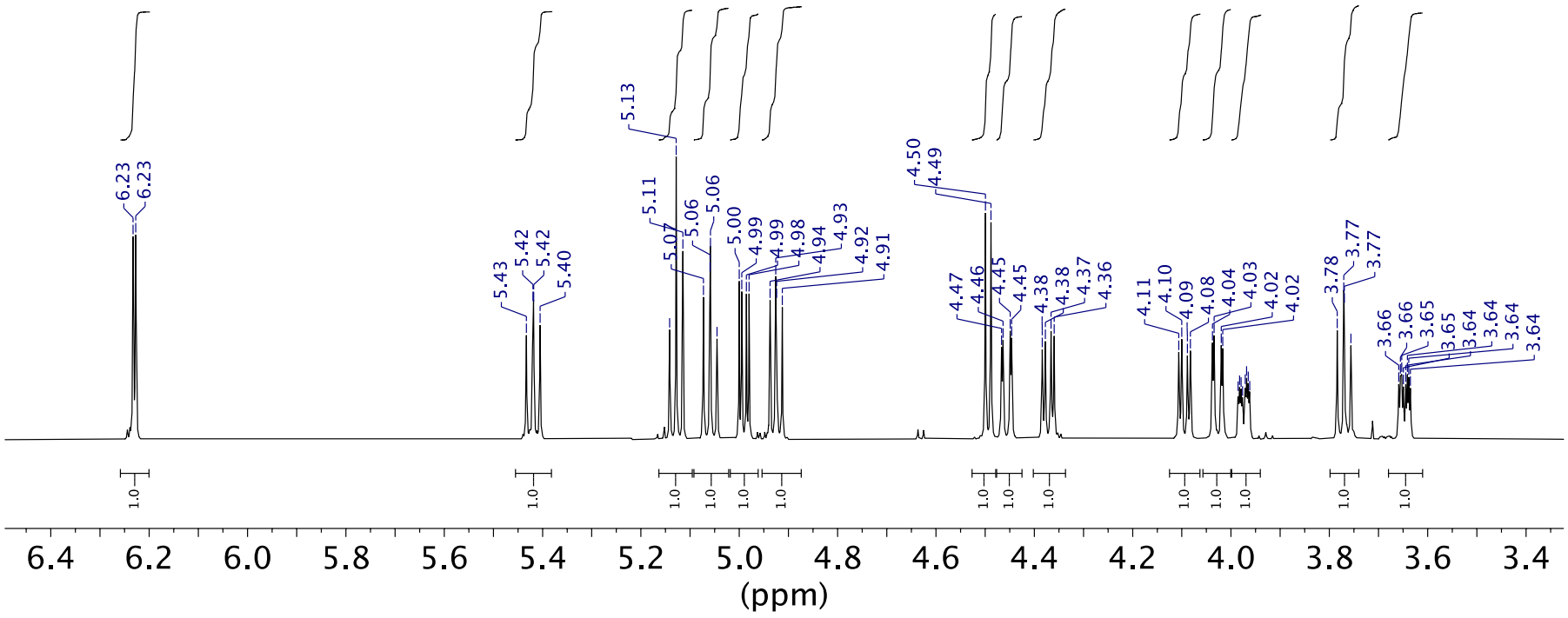
4.4
4.2
4.0
3.8
3.6
3.4
(ppm)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5.13
5.11
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5.06
5.06
5.00
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4.98
4.94
4.93
4.92
4.91
4.50
4.49
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4.46
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4.36
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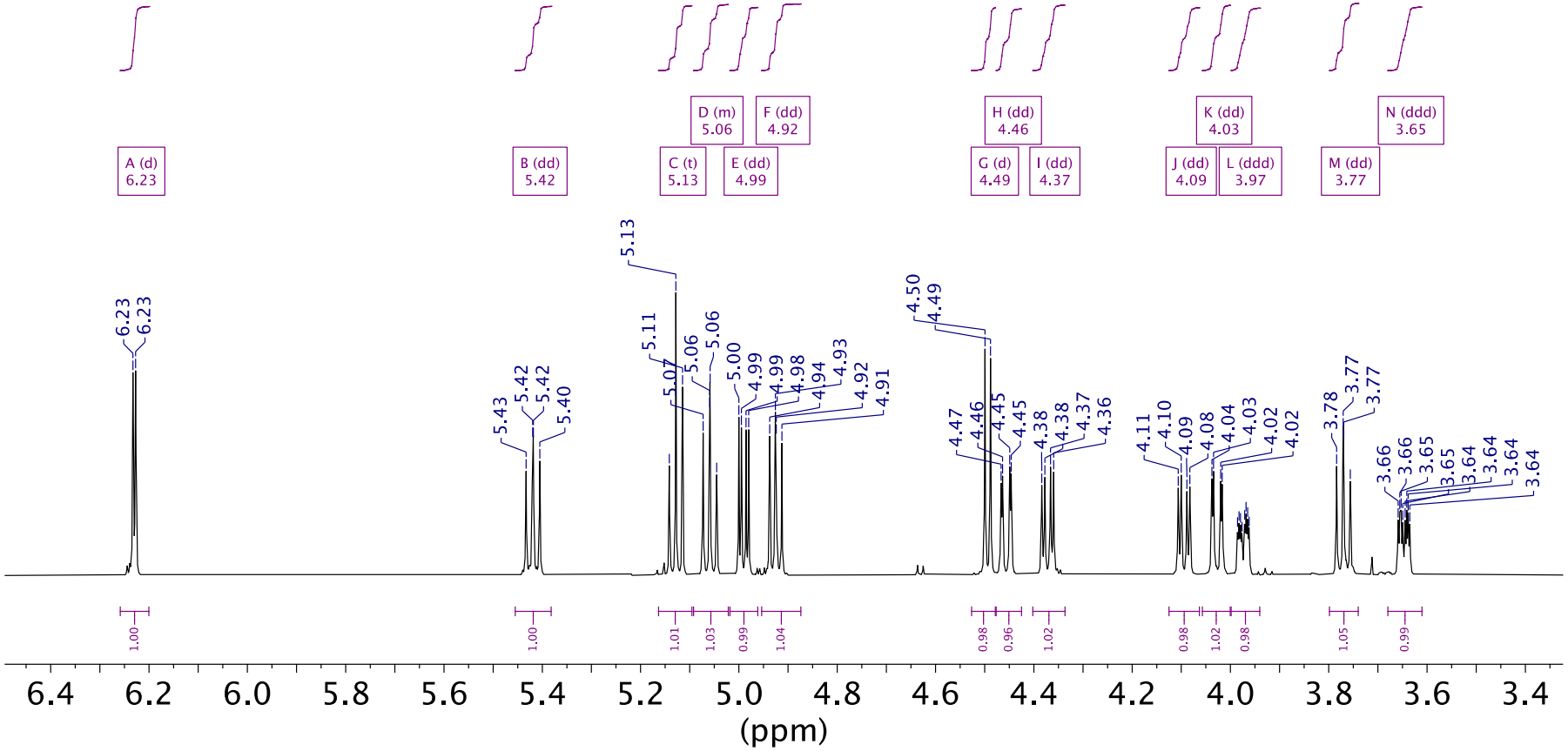
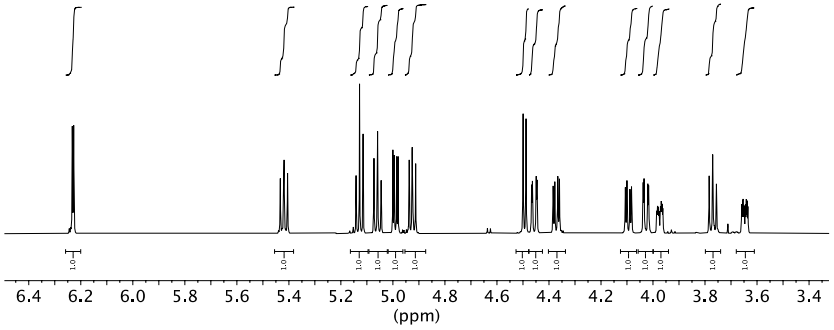
3.77
3.66
3.66
3.65
3.65
3.64
3.64
3.64
3.64
1.0
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
(ppm)

^{1}H NMR (700 MHz, cdcl$_3$) δ 6.23 (d, *J* = 3.7 Hz, 1H), 5.42 (dd, *J* = 10.3, 9.3 Hz, 1H), 5.13 (t, *J* = 9.4 Hz, 1H), 5.09 – 5.02 (m, 1H), 4.99 (dd, *J* = 10.3, 3.8 Hz, 1H), 4.92 (dd, *J* = 9.4, 7.9 Hz, 1H), 4.49 (d, *J* = 8.0 Hz, 1H), 4.46 (dd, *J* = 12.3, 2.1 Hz, 1H), 4.37 (dd, *J* = 12.5, 4.3 Hz, 1H), 4.09 (dd, *J* = 12.3, 4.3 Hz, 1H), 4.03 (dd, *J* = 12.5, 2.3 Hz, 1H), 3.97 (ddd, *J* = 10.1, 4.3, 2.1 Hz, 1H), 3.77 (dd, *J* = 10.1, 9.3 Hz, 1H), 3.65 (ddd, *J* = 10.0, 4.3, 2.3 Hz, 1H), 2.16 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H).

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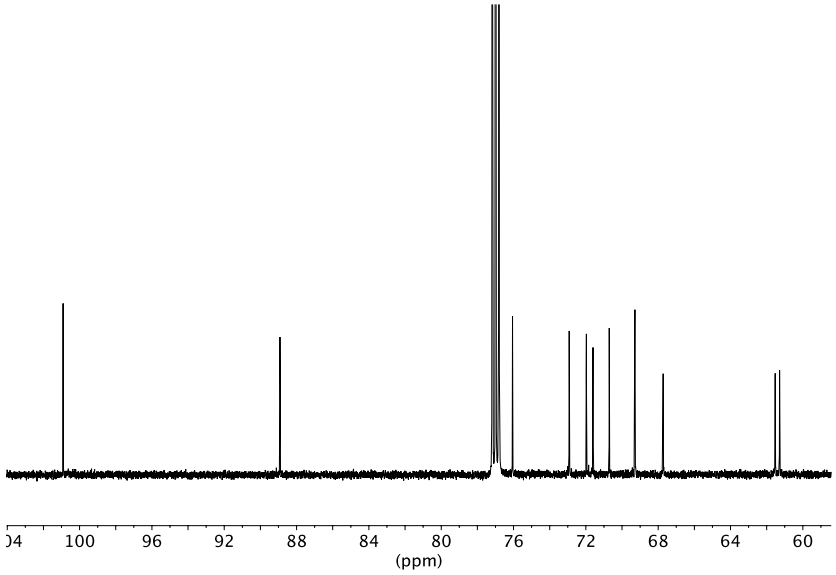
(ppm)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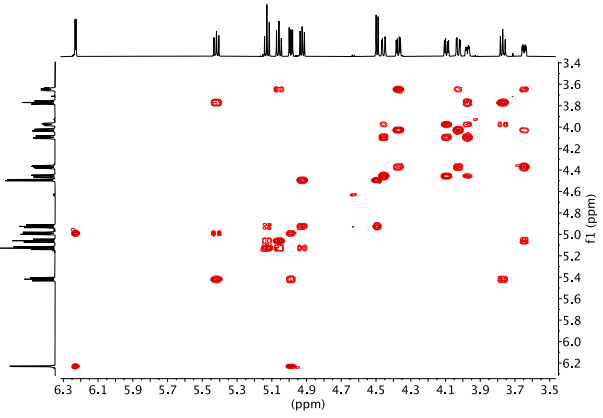
(ppm)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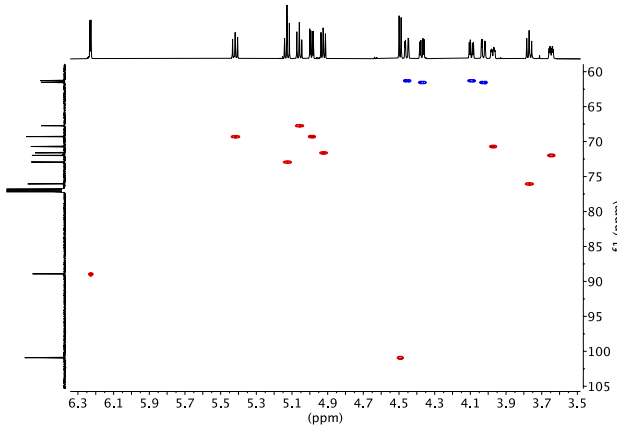
(ppm)
f1 (ppm)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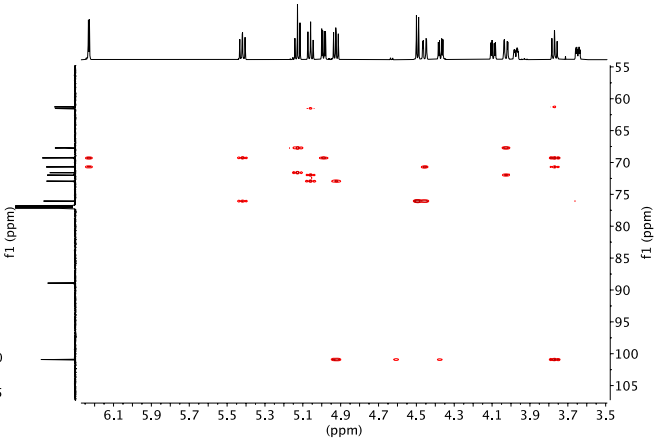
(ppm)
f1 (ppm)


6.1 5.9 5.7 5.5 5.3 5.1 4.9 4.7 4.5 4.3 4.1 3.9 3.7 3.5
(ppm)
f1 (ppm)

How do we extract data from the spectra?

Check consistent referencing

“Peak Picking”

Identify chemical shift correlations

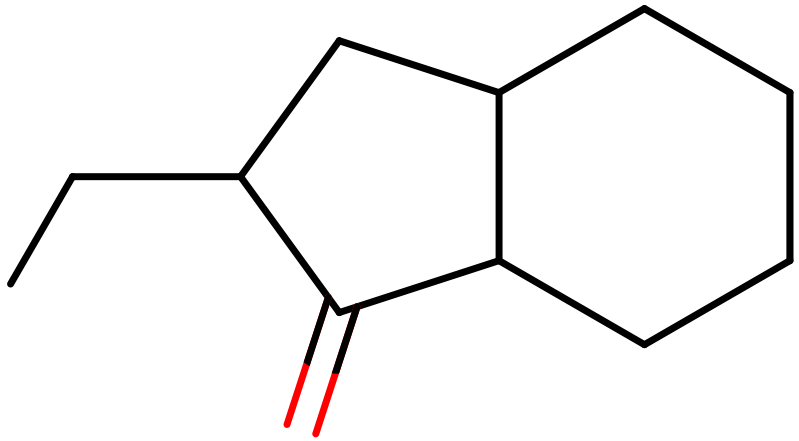
The Concept

Use extracted data to identify CH_x fragments, where x = 0, 1, 2, or 3 (ie quaternary, methine, methylene, methyl)

Position fragments over atoms in the structure (from smiles string)

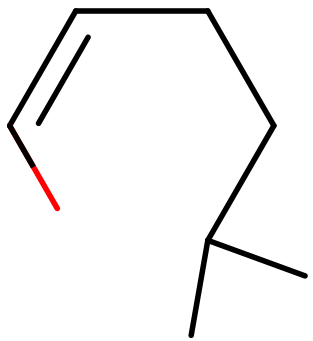
Display connectivity between fragments (COSY, HMBC) as well as displaying 1D ”spectra”

2-ethylindanone



The problem with predictions

beta-lapachone



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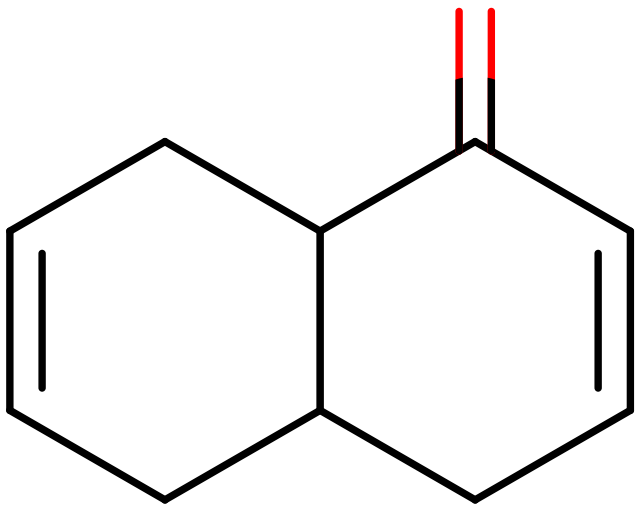
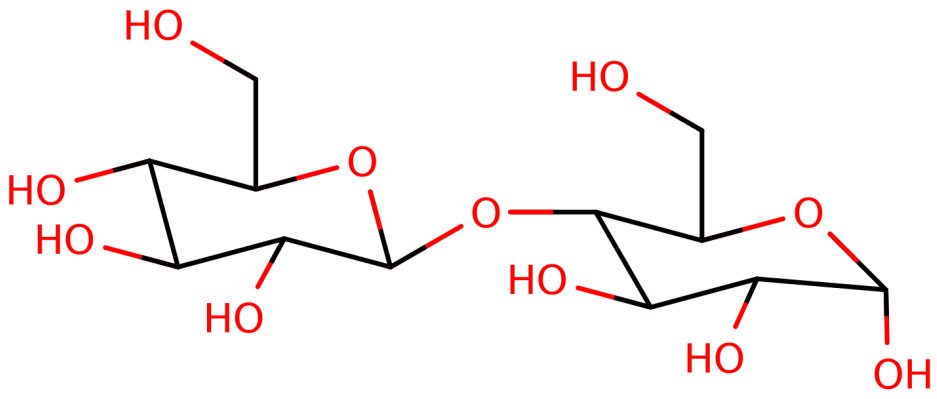


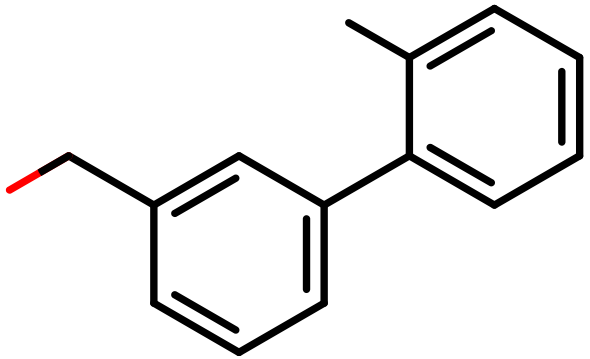
Cellobiose

Not really, I lied!



If you want to fully confirm the structure, rather than just the constitution, you need additional information from ^{1}H-^{1}H coupling constants and / or NOE's. But that task is made much easier by knowing where in the molecule each proton signal belongs.

Fasiglifam*



* Thanks to Christopher Sleigh of Sygnature Discovery

Advantages:

Relatively simple extraction of data – little or no interpretation required at the point of data extraction

Assignment involves positioning CH_x fragments on structure – concepts that chemists like

Possible to use 13C NMR prediction software to make initial placements

Can save assignment (and supporting evidence!)

Easy to check assignments and spot inconsistencies

Easy to change assignments and try an alternative

Areas most needing improvement:

Resolution in 2D spectra – particularly COSY (A)

Improved methods for identifying “x” in CH_x (A)

Improvements to “peak picking” to reliably identify chemical shift correlations (B)

A = NMR people problem! (a lot already underway)

B = Software problem (some work already in the literature)

SimpleNMR

Get simpleNMR from github.com:

https://github.com/EricHughesABC?tab=repositories

simpleNMR

Read the README file (bottom of page)

Releases v0.0.8

Select the appropriate executable