Supporting Information

Harnessing fluorine-sulfur contacts and multipolar interactions for the design of p53 mutant Y220C rescue drugs

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Supporting Information:

Coordinates used for quantum chemical calculations

The XYZ atom coordinates for the optimized complex of the truncated p53-Y220C binding pocket and an *N*-ethyl-pyrrole ligand are provided here. Row 1 describes the atom type and rows 2, 3, and 4 states the respective X, Y, and Z coordinate. A “f” in position 5 labels the atom as being frozen for the DFT-D3 calculations.

Truncated model of the p53-Y220C binding pocket:

C	132.84599	101.56000	-39.92800 f
H	133.30679	102.33800	-40.51860
C	131.47000	101.38200	-39.95600 f
H	130.86230	102.02610	-40.57430
C	133.62700	100.72700	-39.13200 f
H	134.69839	100.86020	-39.10380
C	130.85300	100.37000	-39.18700 f
H	129.78081	100.24320	-39.21450
C	133.02400	99.70700	-38.36000 f
H	133.63300	99.06030	-37.74580
C	131.63600	99.53900	-38.39500 f
H	131.17200	98.76210	-37.80550
C	127.05600	102.00900	-37.06300 f
H	128.05380	101.84840	-36.65470
H	126.33750	101.94520	-36.24580
C	126.89400	103.38700	-37.69700 f
O	125.79600	103.74700	-38.12100 f
C	126.81200	100.94200	-38.12900 f
H	127.68330	100.91310	-38.78330
H	125.93440	101.23500	-38.70530
C	126.57600	99.53000	-37.59200 f
H	125.73880	99.53830	-36.89410
C	126.25000	98.59600	-38.76200 f
H	127.08540	98.58540	-39.46210
H	125.35380	98.95060	-39.27110
H	126.07890	97.58760	-38.38520
C	127.80500	99.04400	-36.85700 f
H	128.65440	99.02880	-37.53990
H	127.62670	98.03830	-36.47640
H	128.01970	99.71460	-36.02500

N	127.99300	104.13700	-37.73500 f
H	128.84830	103.75720	-37.35520
C	128.02000	105.48300	-38.30000 f
H	127.02170	105.70850	-38.67500
H	128.30670	106.20870	-37.53890
C	129.04700	105.56200	-39.42800 f
O	130.13300	104.99100	-39.31100 f
N	128.70500	106.27000	-40.51000 f
H	127.77170	106.65030	-40.57660
C	129.65800	106.50700	-41.60500 f
H	130.65131	106.31540	-41.19910
H	129.51640	107.52670	-41.96300
C	129.45100	105.56900	-42.83100 f
H	130.05650	105.93390	-43.66060
C	129.89799	104.14100	-42.48300 f
H	129.29900	103.76480	-41.65370
H	130.94980	104.14900	-42.19720
H	129.76230	103.49610	-43.35120
C	128.00999	105.57500	-43.24900 f
H	127.39200	105.21200	-42.42780
H	127.88030	104.92660	-44.11550
H	127.71080	106.59080	-43.50730
N	128.29601	103.52200	-48.04700 f
H	128.05330	104.37760	-48.52570
C	129.06200	102.42800	-48.65000 f
H	129.96590	102.72240	-49.18330
H	128.47250	101.94520	-49.42940
C	129.40700	101.54400	-47.45800 f
H	130.32950	101.87240	-46.97930
H	129.50481	100.50070	-47.75790
C	128.23700	101.73600	-46.55700 f
H	128.48990	101.46250	-45.53260
H	127.38890	101.13960	-46.89340
C	127.92500	103.21700	-46.65600 f
H	126.86720	103.41060	-46.47780
H	128.52370	103.79470	-45.95180
C	128.31799	95.11500	-40.22200 f
H	127.42910	94.56780	-39.90820
H	129.00250	94.47530	-40.77900
H	128.84351	95.47780	-39.33870
C	127.87400	96.26500	-41.10800 f
H	128.74710	96.82920	-41.43580
H	127.20790	96.92010	-40.54650

H 127.34820 95.87140 -41.97790

C 125.09800 96.70500 -43.76200 f

H 124.86020 96.65030 -42.69970

H 125.06260 95.70790 -44.20090

C 124.09200 97.55300 -44.51800 f

O 124.35100 97.96900 -45.65300 f

C 126.49400 97.31600 -43.87900 f

H 126.64610 97.65700 -44.90310

H 127.23490 96.55440 -43.63590

S 126.70500 98.72500 -42.75100

H 127.93640 99.22480 -42.88830

N 122.94100 97.78100 -43.89600 f

H 122.80800 97.42340 -42.96080

C 121.86600 98.53300 -44.52700 f

H 122.07370 98.50770 -45.59670

H 120.91310 98.08600 -44.24380

C 121.81100 99.98800 -44.09800 f

O 122.28100 100.36100 -43.02300 f

N 121.23000 100.83600 -44.95500 f

H 120.86850 100.48900 -45.83190

C 121.11200 102.25800 -44.63800 f

H 122.05360 102.72710 -44.35260

H 120.74590 102.72100 -45.55430

H 120.45430 102.38520 -43.77820

C 121.74700 104.32100 -38.14600 f

H 122.21350 105.29350 -38.09020

O 120.52500 104.25300 -38.03300 f

N 122.52200 103.26100 -38.33300 f

H 123.51800 103.39400 -38.43470

C 121.98000 101.91300 -38.39600 f

H 120.89930 101.94410 -38.53450

H 122.21450 101.40760 -37.45910

C 122.59400 101.16200 -39.55800 f

H 123.67740 101.13070 -39.44250

O 122.23200 101.84400 -40.76900 f

H 122.63650 101.37150 -41.50030

C 122.08500 99.72300 -39.60400 f

H 122.36220 99.21000 -38.68310

H 122.52970 99.20730 -40.45520

H 120.99980 99.72450 -39.70660

C 132.81000 98.36900 -42.31900 f

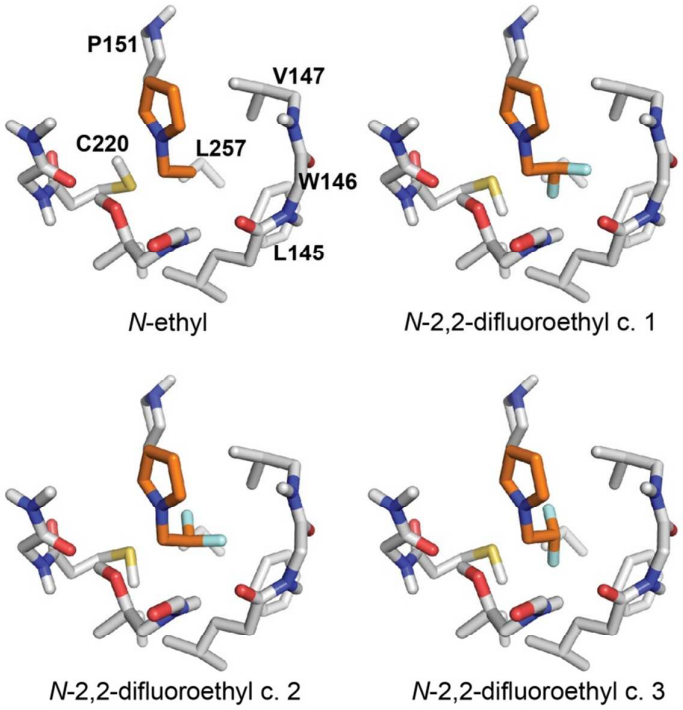
H 133.80569 98.72130 -42.58830

H 132.51469 98.80800 -41.36600

H	132.81090	97.28180	-42.24090
C	131.82100	98.84000	-43.39700 f
H	131.97321	98.24990	-44.30070
H	131.99480	99.89950	-43.58520
C	130.37000	98.63600	-42.93300 f
H	130.19270	99.21760	-42.02830
H	130.20020	97.57960	-42.72500
H	129.68810	98.96620	-43.71670

N-Ethyl-pyrrole ligand:

C	124.65300	105.29500	-43.42700 f
H	124.51890	106.36530	-43.47990
C	124.51500	104.37300	-44.51100
H	124.25360	104.62240	-45.52880
C	124.78300	103.07000	-44.01100
H	124.76580	102.14890	-44.57460
N	125.07300	103.20800	-42.65100 f
C	125.00000	104.54600	-42.26200
H	125.17260	104.93920	-41.27100
C	125.41800	102.08600	-41.76600
H	124.99680	101.16750	-42.17470
H	124.99760	102.27000	-40.77730
C	126.93500	101.92900	-41.64300
H	127.36230	101.74470	-42.62870
H	127.16130	101.08920	-40.98610
H	127.36210	102.84130	-41.22660



9H-carbazole substitution	*N*-ethyl	*N*-2,2-difluoroethyl conf. 1	*N*-2,2-difluoroethyl conf. 2	*N*-2,2-difluoroethyl conf. 3
DFT-D ΔΔE (kcal/mol)	0.0	-6.9	-6.3	-3.9

Figure S1. DFT-D3 optimized snapshots of the PhiKan083 *N*-ethyl group and its difluorinated analog in different conformations (orange sticks). Ineraction energies of each ligand model were compared to the *N*-ethyl reference interaction energy ΔE to calculate relative interaction energies ($\Delta\Delta E = \Delta E_{Ligand} - \Delta E_{N\text{-ethyl}}$). For the DFT-D optimizations truncated models of PhiKan083 (*N*-ethylpyrrole) and the p53-Y220C pocket (as depicted) were used (only non-hydrogen atoms and polar protons are shown). Pictures were rendered using pymol (www.pymol.org).

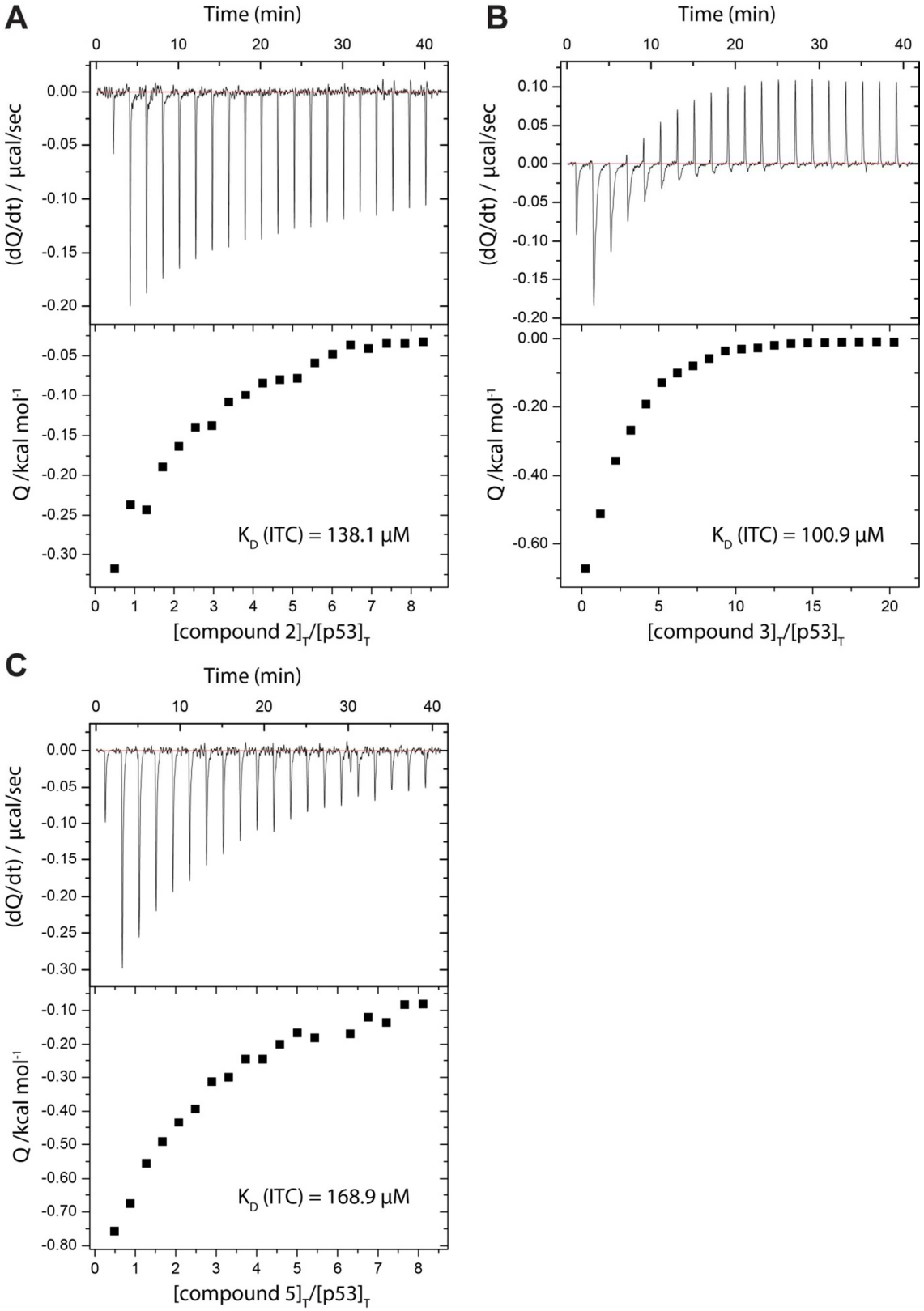
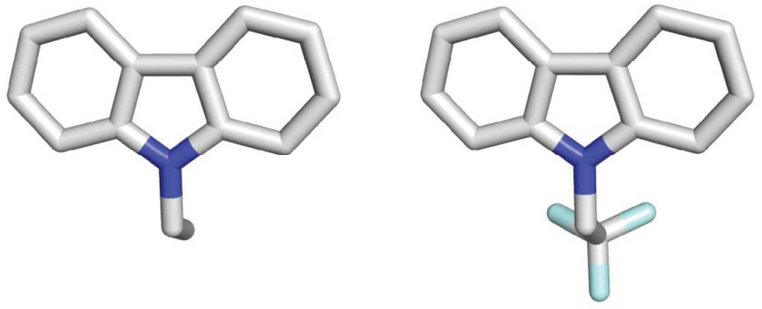
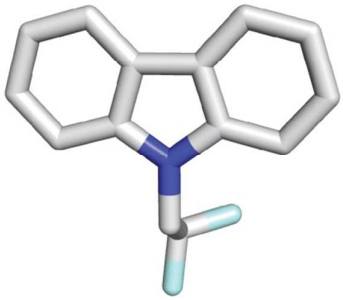


Figure S2. Binding of **2**, **3**, and **5** to p53-Y220C as characterized by isothermal titration calorimetry (ITC).

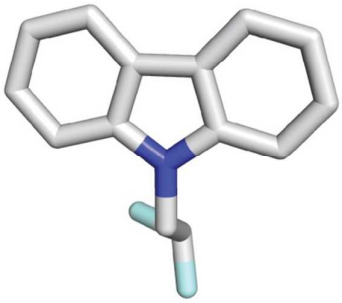


N-Ethyl

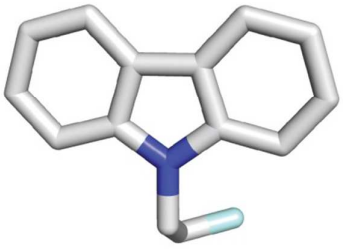
N-2.2.2-Trifluoroethyl



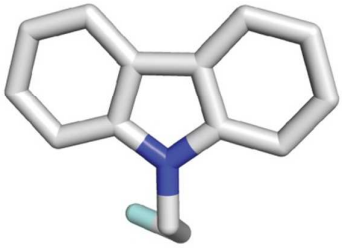
N-2,2-Difluoroethyl conf. 1



N-2,2-Difluoroethyl conf. 2



N-2-Fluoroethyl conf. 1



N-2-Fluoroethyl conf. 2

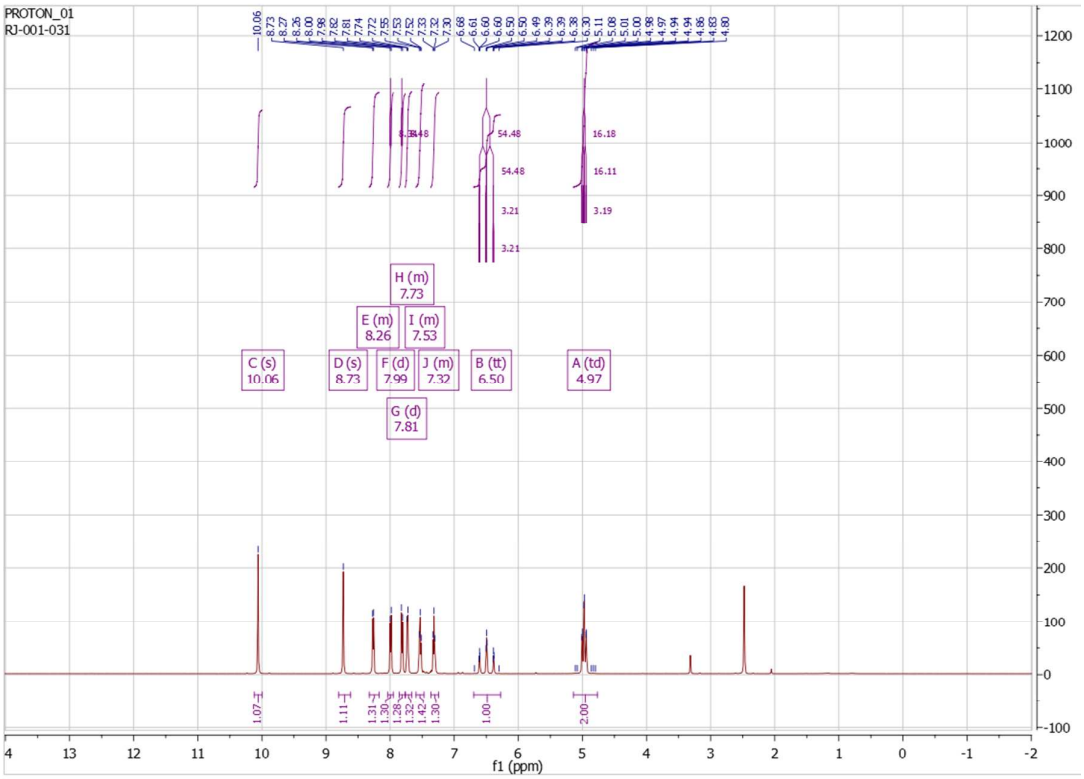
	N-Ethyl	*N*-2,2,2-Trifluoroethyl	*N*-2,2-Difluoroethyl conf. 1	*N*-2,2-Difluoroethyl conf. 2	*N*-2-Fluoroethyl conf. 1	*N*-2-Fluoroethyl conf. 2
solvation energy (kcal/mol)	-3.1	-3.1	-4.1	-4.1	-5.9	-5.9

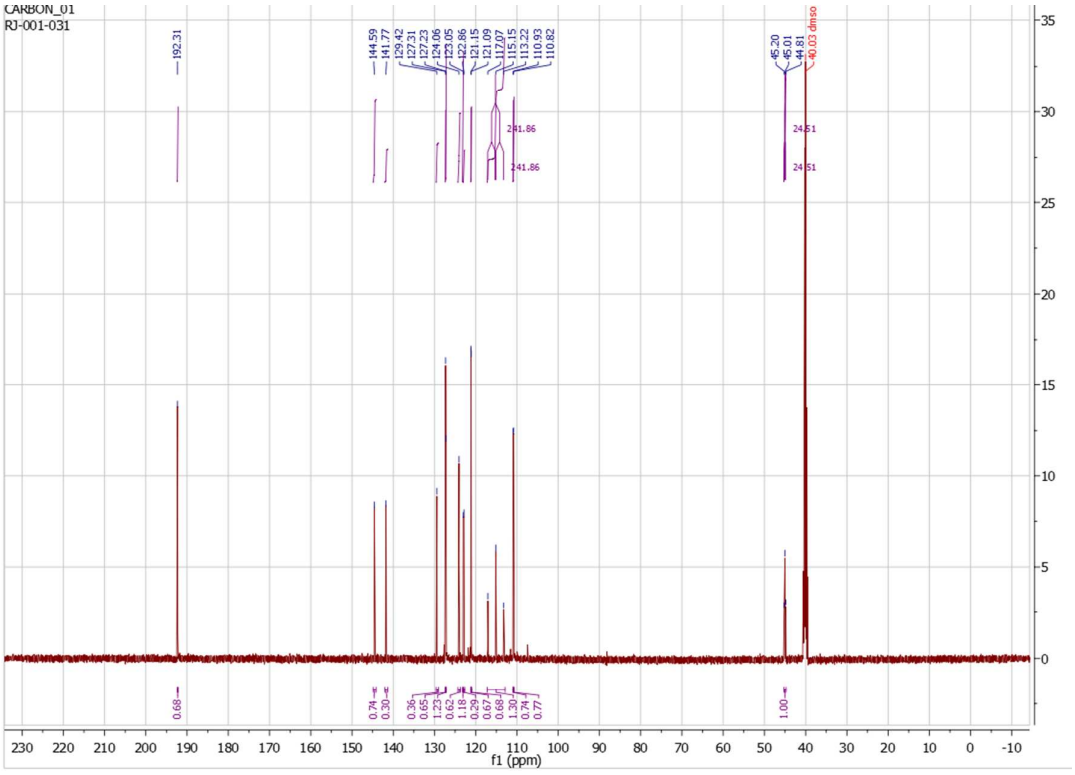
Figure S3. DFT-D3 optimized structures and calculated solvation energies of fluorinated and non-fluorinated *N*-ethylcarbazoles. The global minimum conformations (two equivalent conformers *N*-2-fluoroethyl and *N*-2,2-difluoroethyl carbazoles) were determined by DFT-D3 calculations with TURBOMOLE 6.4 and used as input structures for solvent energy calculations with Jaguar 8.9 using

the SM8 water model. *N*-Ethyl and *N*-2,2,2-trifluoroethyl substituted carbazoles showed significantly smaller solvation energies than the *N*-2-fluoroethyl and *N*-2,2-difluoroethyl analogs.

^{1}H and ^{13}C NMR Spectra

7





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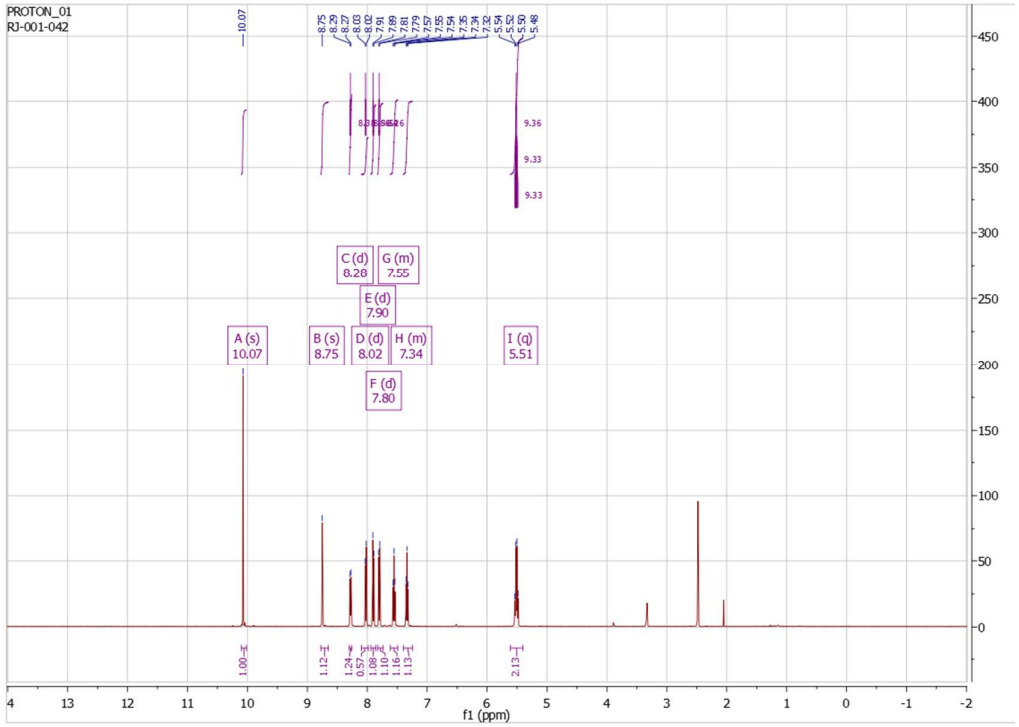
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A (s)
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B (s)
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C (d)
8.28
D (d)
8.02
E (d)
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F (d)
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G (m)
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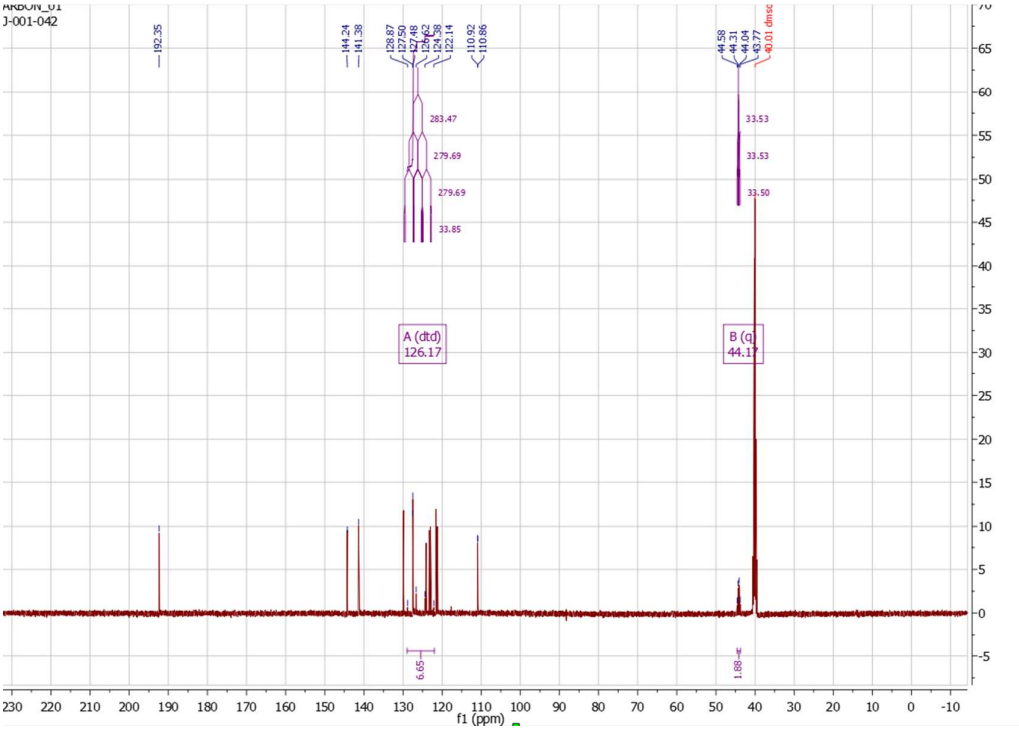
H (m)
7.34
I (q)
5.51
f1 (ppm)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B (q)
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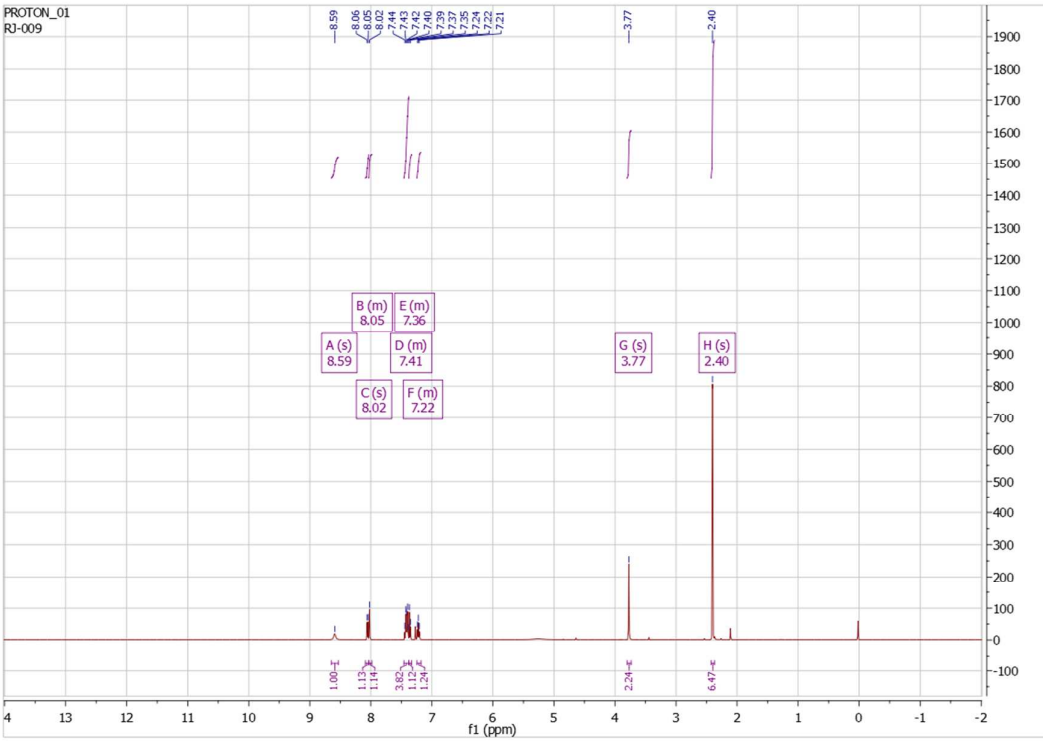
f1 (ppm)

9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7.37
7.35
7.24
7.22
7.21
3.77
2.40
B (m) 8.05
E (m) 7.36
A (s) 8.59
D (m) 7.41
G (s) 3.77
H (s) 2.40
C (s) 8.02
F (m) 7.22
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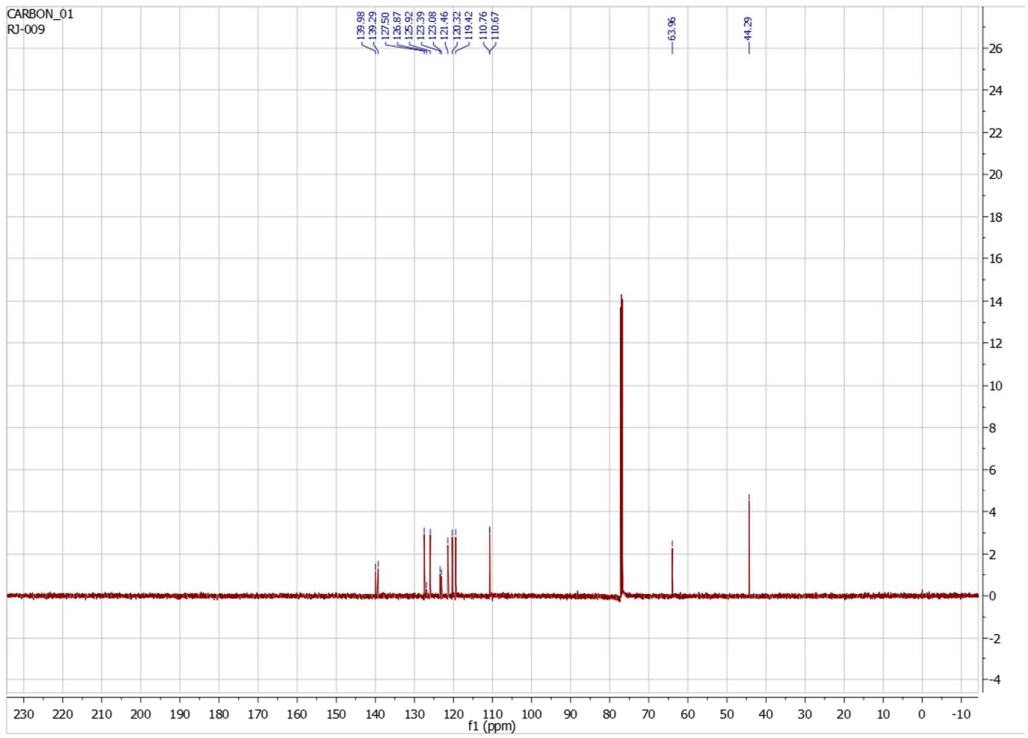
f1 (ppm)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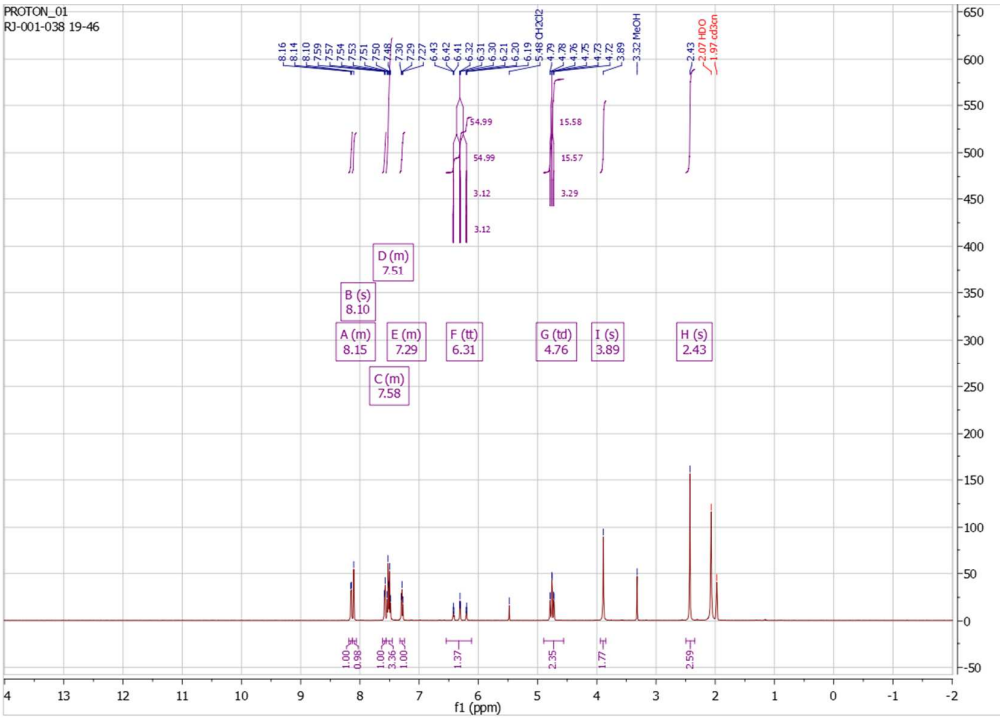
f1 (ppm)

3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B (s) 8.10
A (m) 8.15
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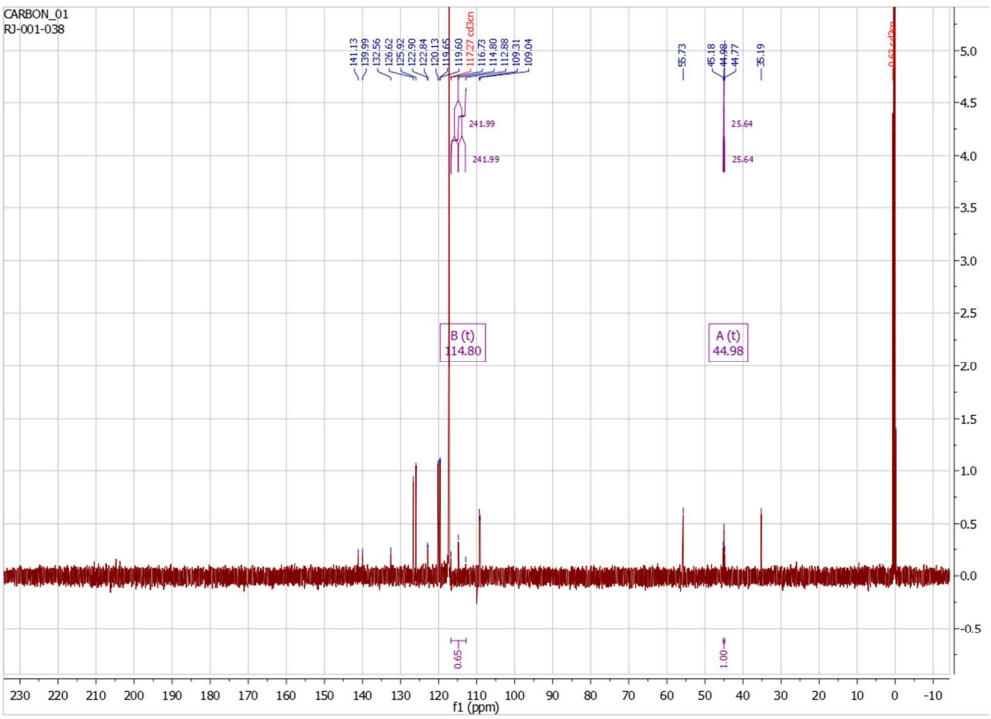
I (s) 3.89
H (s) 2.43
C (m) 7.58
f1 (ppm)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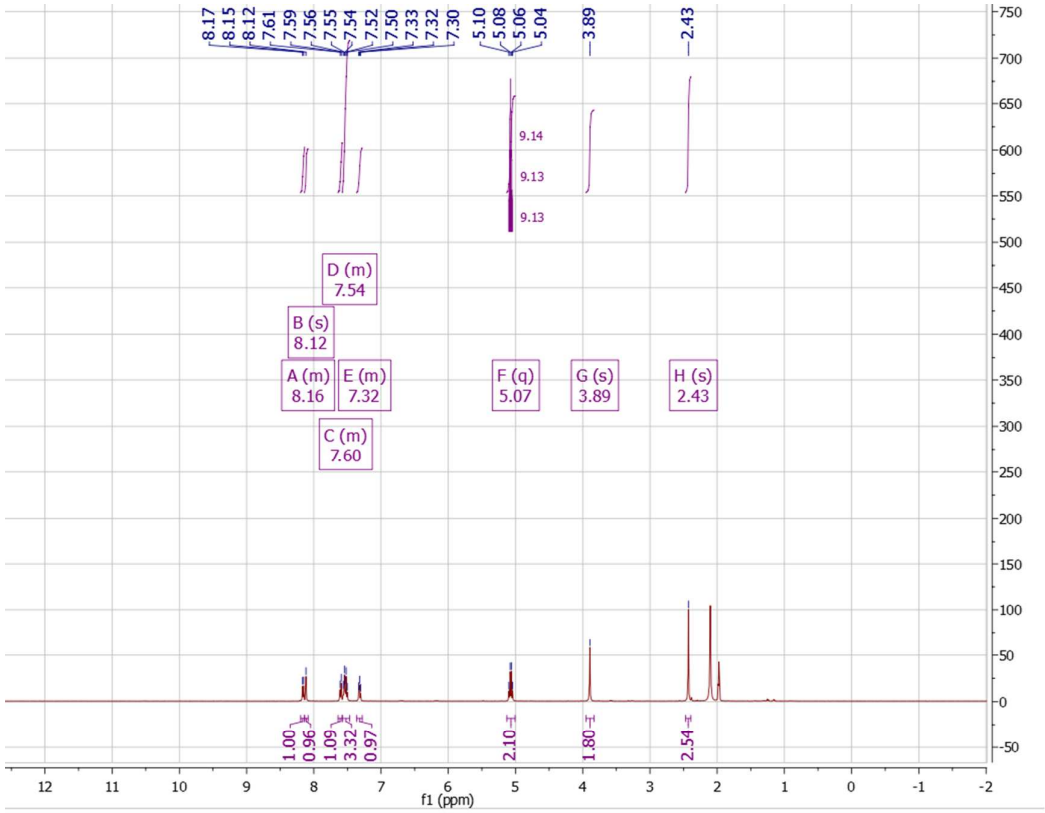
4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7.33
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7.30
5.10
5.08
5.06
5.04
3.89
2.43
9.14
9.13
9.13
D (m)
7.54
B (s)
8.12
A (m)
8.16
E (m)
7.32
C (m)
7.60
F (q)
5.07
G (s)
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H (s)
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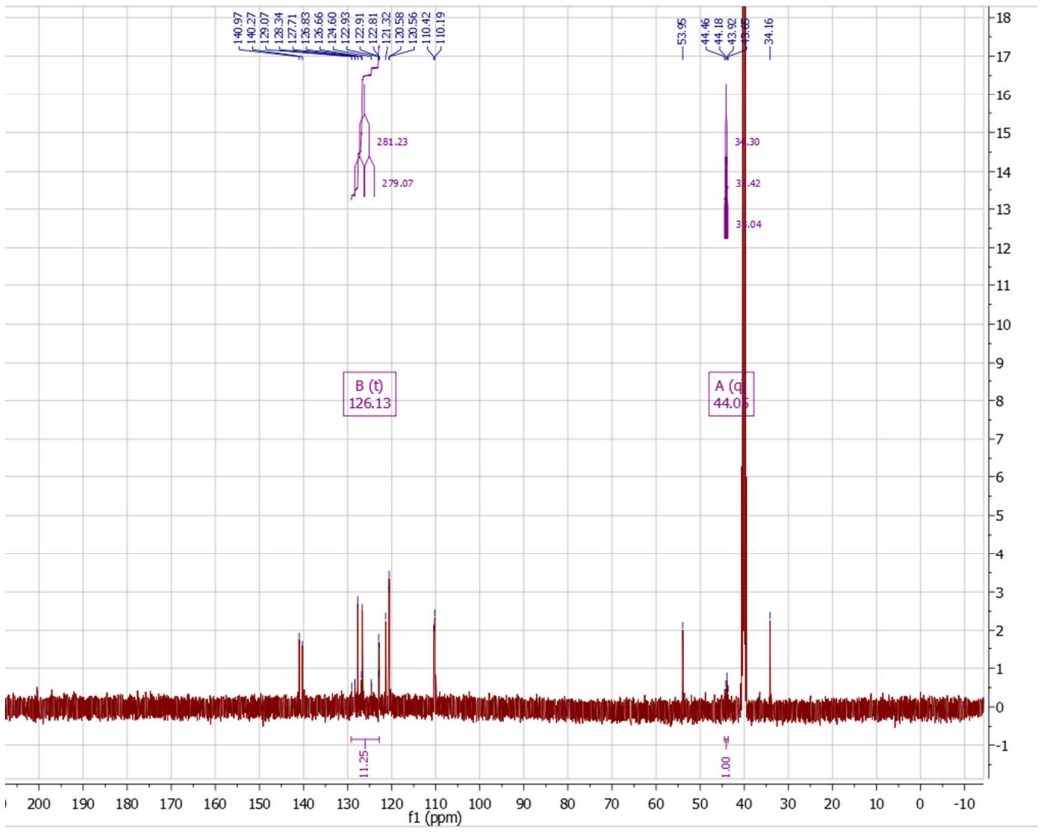
f1 (ppm)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121.58
120.95
110.42
110.19
281.23
279.07
53.95
44.46
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34.16
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A (q)
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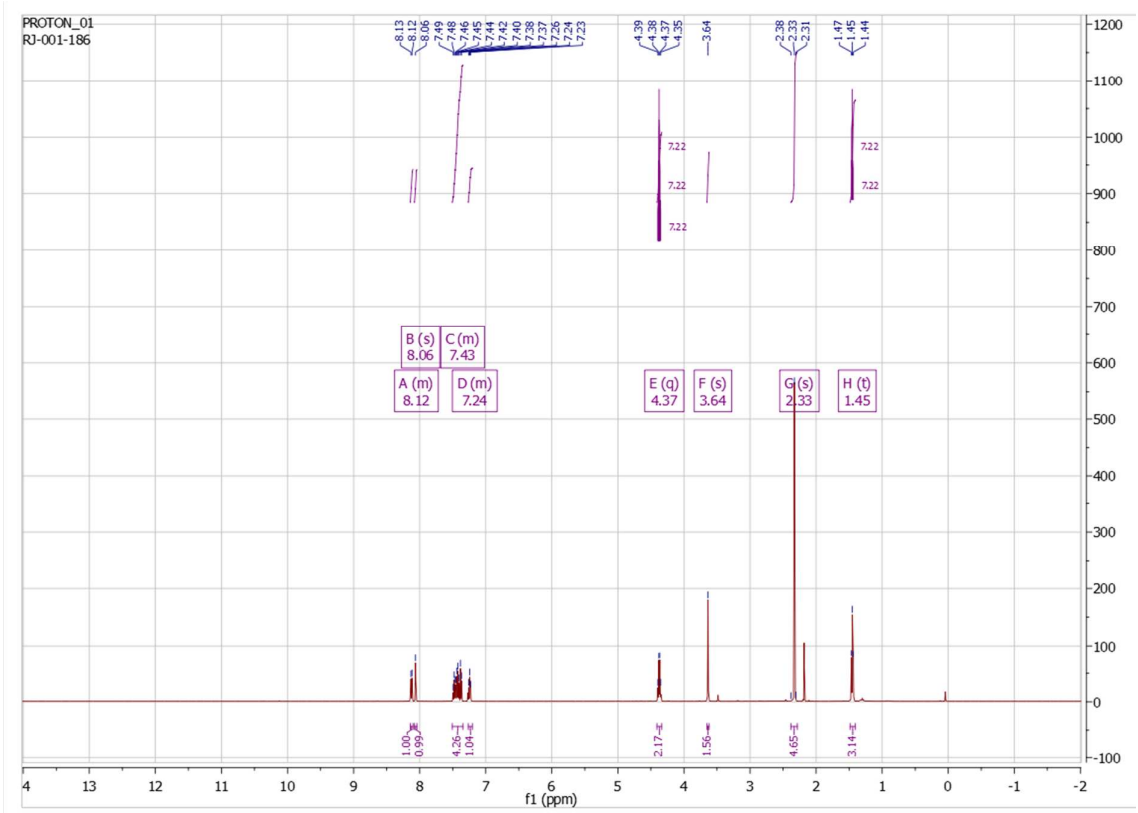
1.00
f1 (ppm)

5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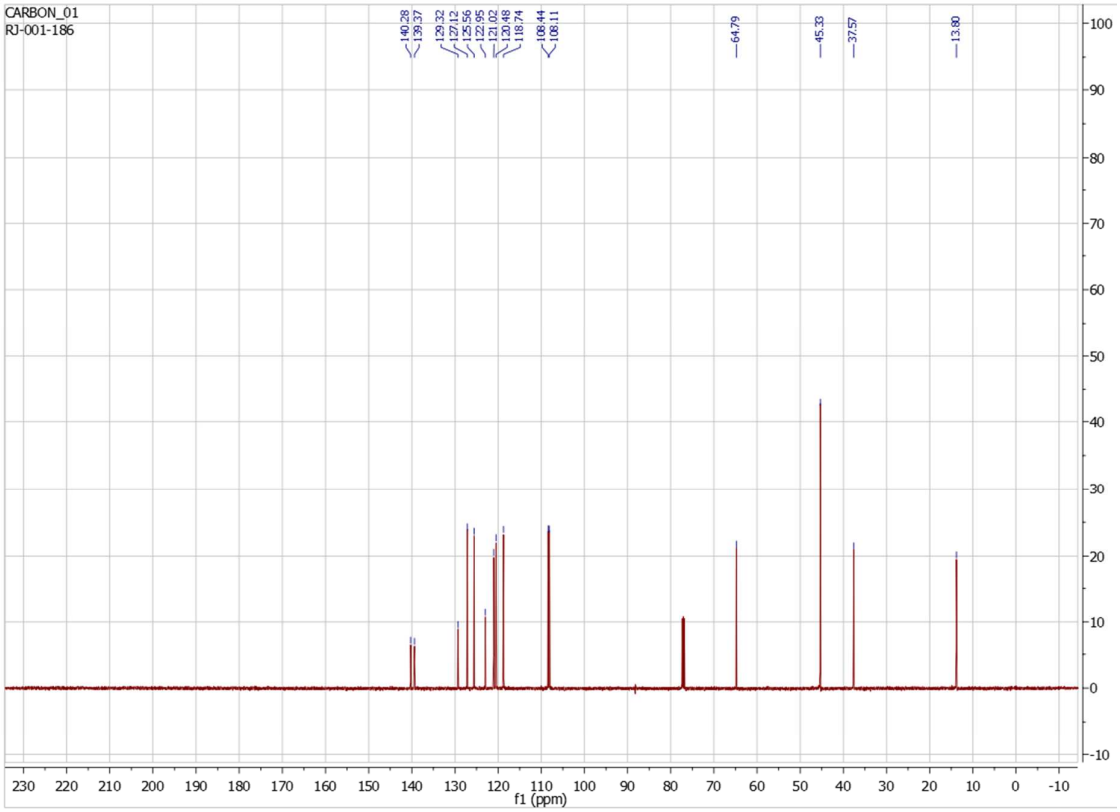
f1 (ppm)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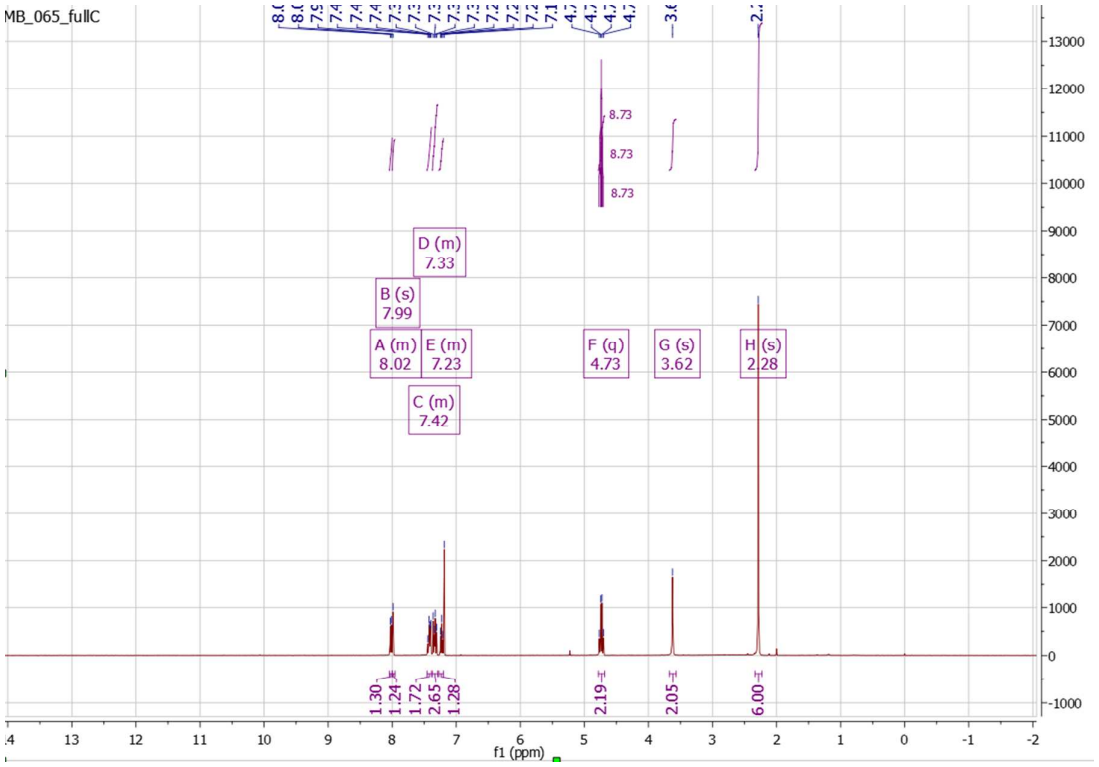
f1 (ppm)

6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B (s)
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A (m)
8.02
E (m)
7.23
C (m)
7.42
F (q)
4.73
G (s)
3.62
H (s)
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1.30
1.24
1.72
2.65
1.28
2.19
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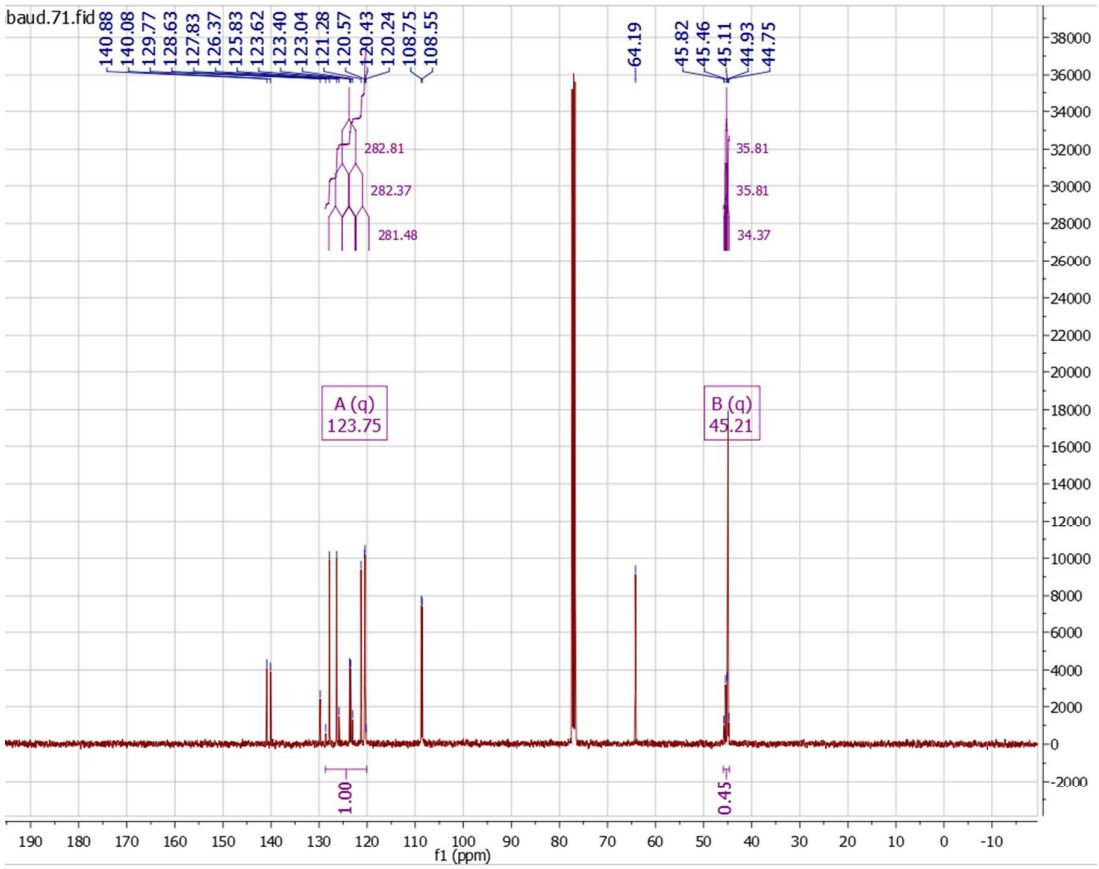
6.00
f1 (ppm)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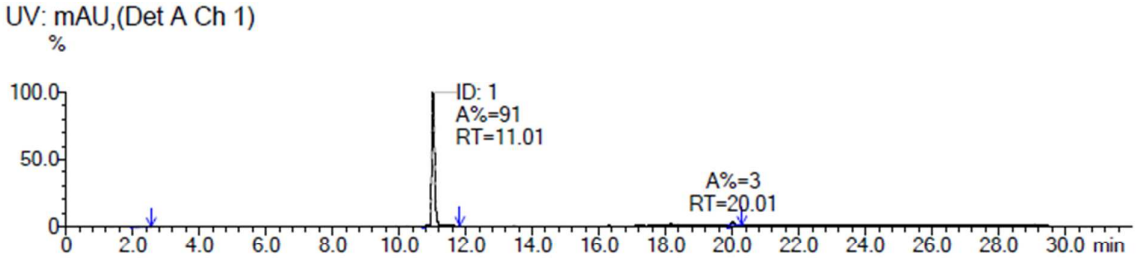
120.57
120.43
120.24
108.75
108.55
64.19
45.82
45.46
45.11
44.93
44.75
282.81
282.37
281.48
35.81
35.81
34.37
A (q)
123.75
B (q)
45.21
1.00
0.45
f1 (ppm)

LC-MS

3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%
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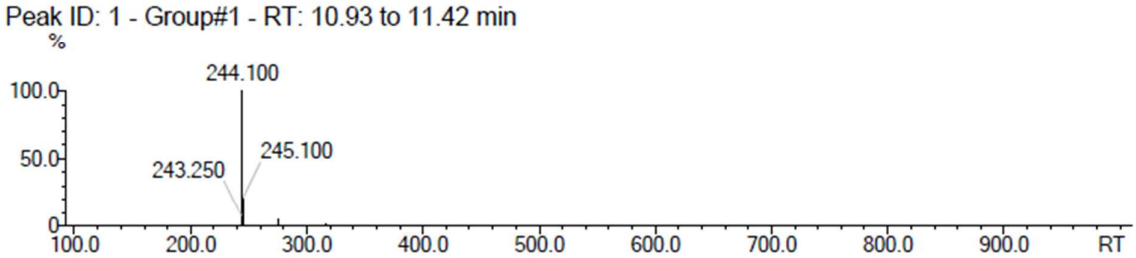
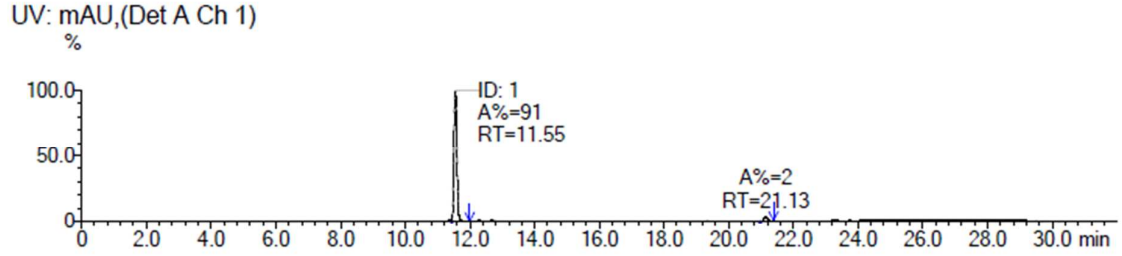
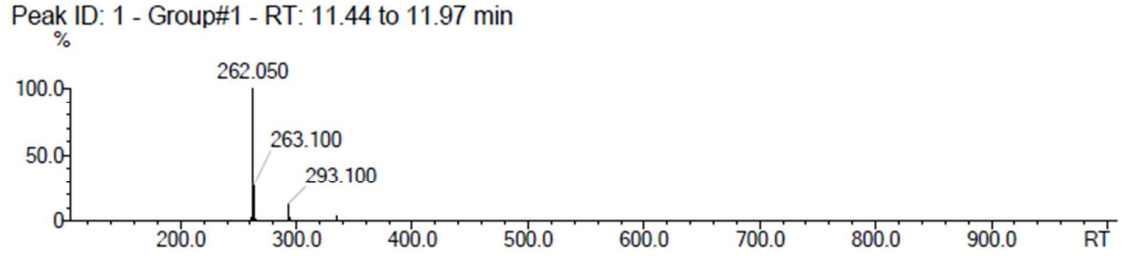
50.0
0
ID: 1
A%=91
RT=11.01
A%=3
RT=20.01
0 2.0 4.0 6.0 8.0 10.0 12.0 14.0 16.0 18.0 20.0 22.0 24.0 26.0 28.0 30.0 min

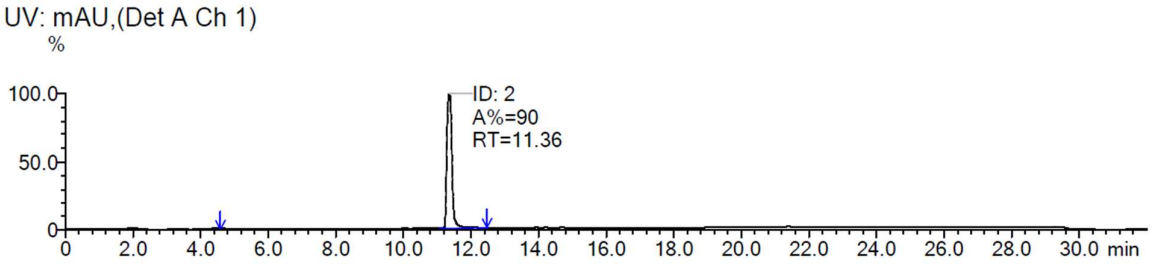

Peak ID: 1 - Group#1 - RT: 10.93 to 11.42 min
%
100.0
50.0
0
244.100
245.100
243.250
100.0 200.0 300.0 400.0 500.0 600.0 700.0 800.0 900.0 RT

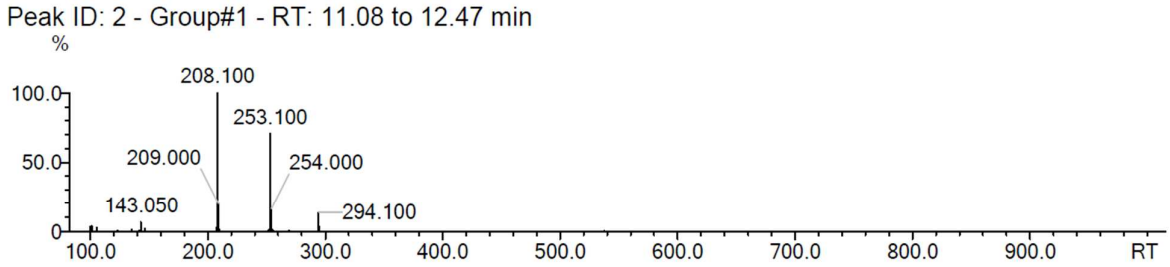
4


UV: mAU,(Det A Ch 1)
%
100.0
50.0
0
ID: 1
A%=91
RT=11.55
A%=2
RT=21.13
0 2.0 4.0 6.0 8.0 10.0 12.0 14.0 16.0 18.0 20.0 22.0 24.0 26.0 28.0 30.0 min

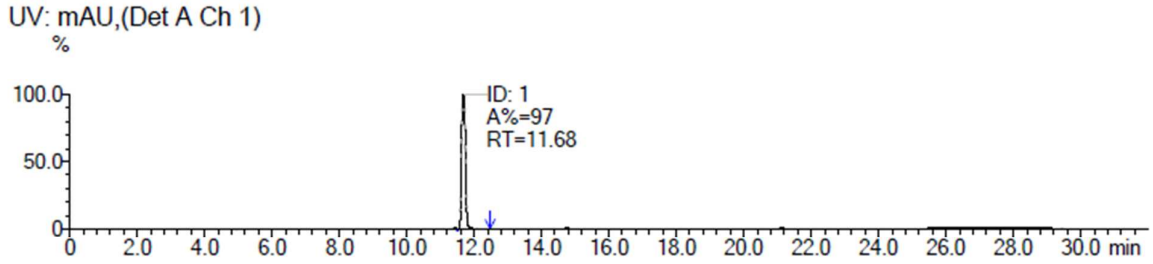

Peak ID: 1 - Group#1 - RT: 11.44 to 11.97 min
%
100.0
50.0
0
262.050
263.100
293.100
200.0 300.0 400.0 500.0 600.0 700.0 800.0 900.0 RT

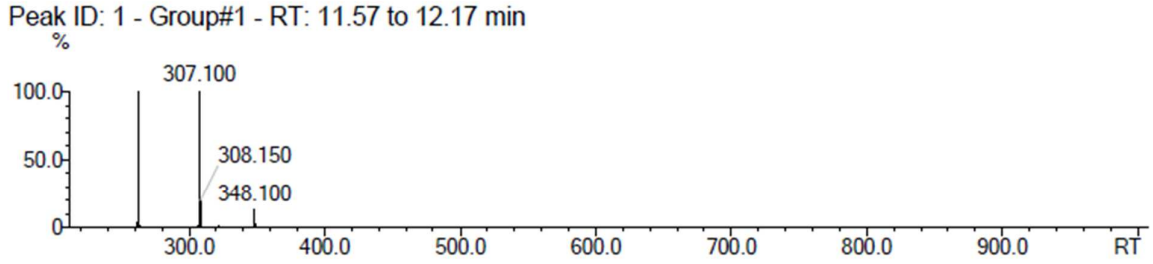
5


UV: mAU,(Det A Ch 1)
%
100.0
50.0
0
ID: 2
A%=90
RT=11.36
0 2.0 4.0 6.0 8.0 10.0 12.0 14.0 16.0 18.0 20.0 22.0 24.0 26.0 28.0 30.0 min


Peak ID: 2 - Group#1 - RT: 11.08 to 12.47 min
%
100.0
50.0
0
208.100
253.100
209.000
254.000
143.050
294.100
100.0 200.0 300.0 400.0 500.0 600.0 700.0 800.0 900.0 RT

6


UV: mAU,(Det A Ch 1)
%
100.0
50.0
0
ID: 1
A%=97
RT=11.68
0 2.0 4.0 6.0 8.0 10.0 12.0 14.0 16.0 18.0 20.0 22.0 24.0 26.0 28.0 30.0 min


Peak ID: 1 - Group#1 - RT: 11.57 to 12.17 min
%
100.0
50.0
0
307.100
308.150
348.100
300.0 400.0 500.0 600.0 700.0 800.0 900.0 RT