Electronic Supplementary Material (ESI) for RSC Advances.

Electronic Supplementary Material

Harnessing the pyrroloquinoxaline scaffold for FAAH and MAGL interaction: definition of the structural determinants for enzyme inhibition

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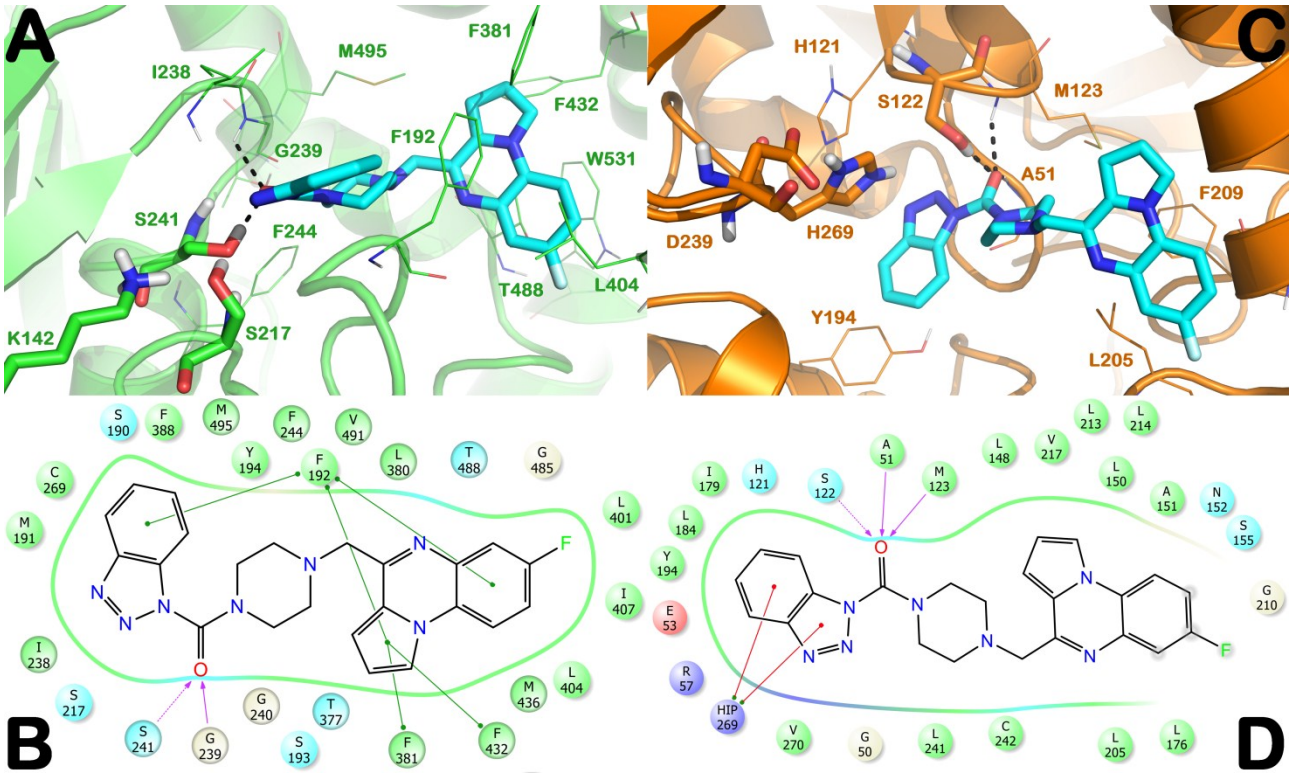
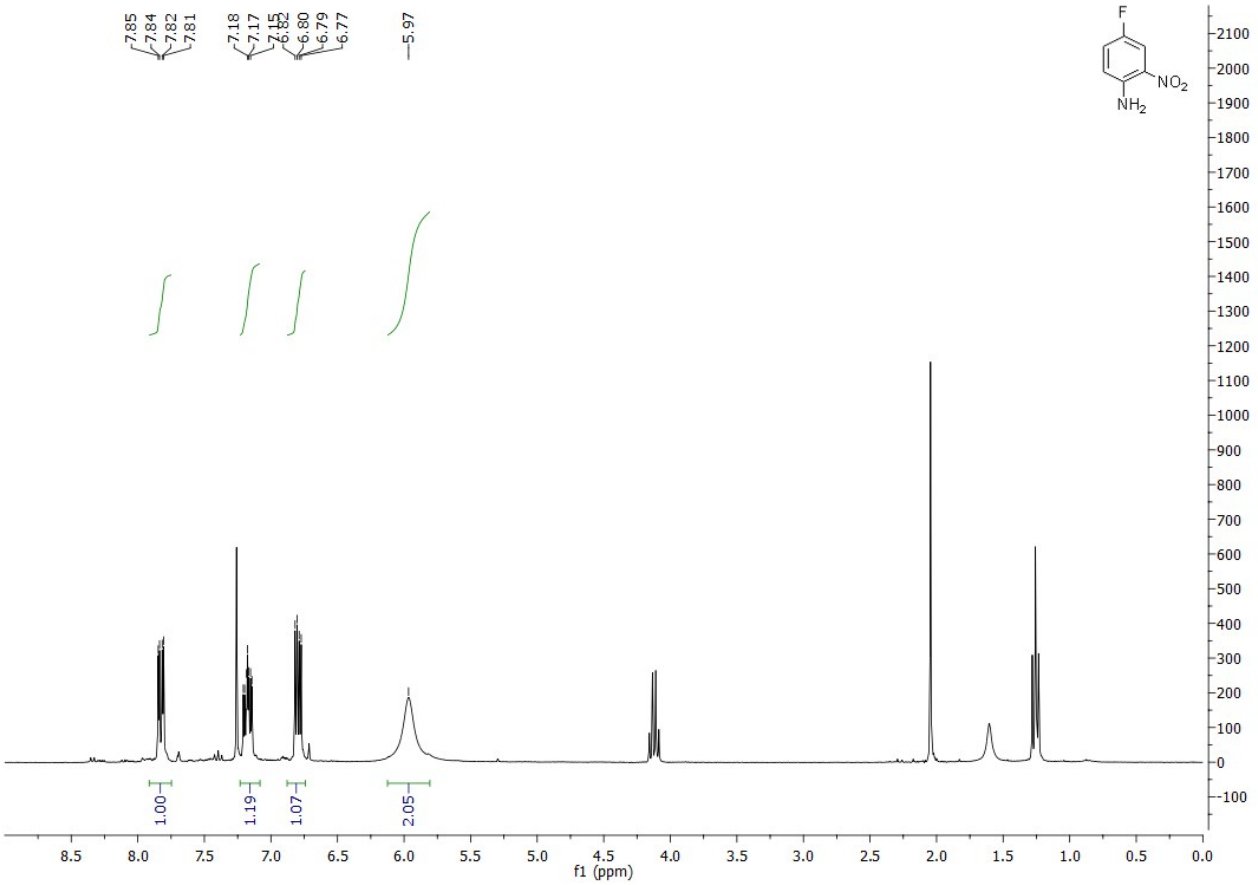


Fig. S1. (A,B) IFD pose and ligand interaction diagram of **5j** (cyan sticks) into FAAH enzyme (PDB ID: 3PPM in green cartoon). (C,D) IFD pose and ligand interaction diagram of **5j** (cyan sticks) into MAGL enzyme (PDB ID: 3HJU in orange cartoon). The catalytic triad of two enzymes is represented by sticks, while the interacting residues are represented by lines. The H-bonds are represented by black dotted lines. The pictures were generated by PyMOL and Maestro (Maestro, version 9.3, Schrödinger, LLC, New York, NY, 2012); HIP stands for protonated histidine.

Fig. S1A,B depicts the representative pose of **5j** into FAAH where the compound strongly interacts within its binding site through a network of π-π stackings established with F192, F381 and F432. The urea carbonyl group sits in close proximity of the catalytic triad and is involved in H-bonds with S241 (catalytic residue) and with the backbone of G239 (Fig. 3B).

Compound **5j** still maintains some of the hydrophobic contacts already described for **5e** (Fig. 2C,D). However, although **5j** H-binds the catalytic residue S122 through its carbonyl group (additional H-bonds with the backbones of A51 and M123 were also observed) and establishes a cation-π stacking with H269 by its benzotriazole ring, differently from **5e** it does not establish the key interactions with H121 and Y194 (Fig. S1C,D). This different pattern of interactions can be responsible for the slight decrease in MAGL inhibition observed for this compound (Table 1 Main Text).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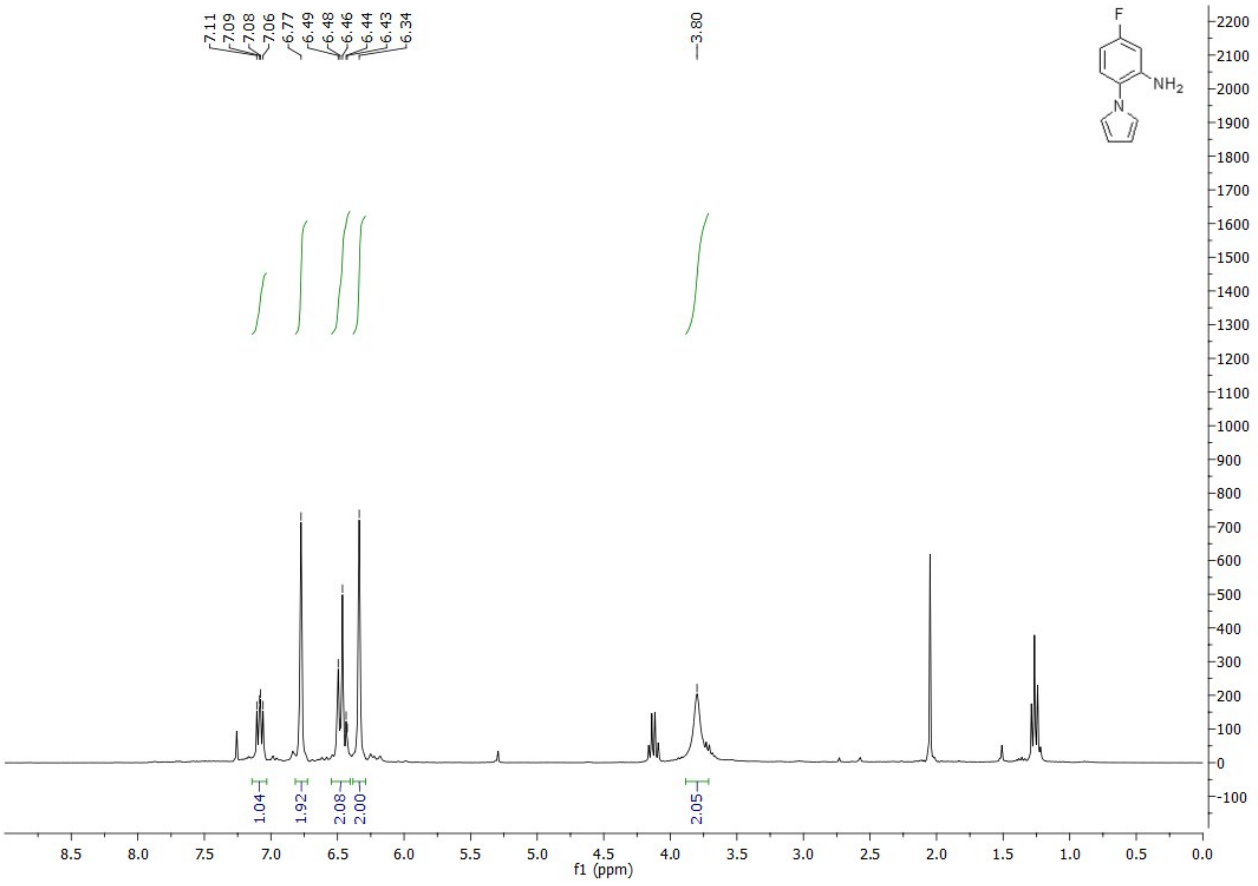
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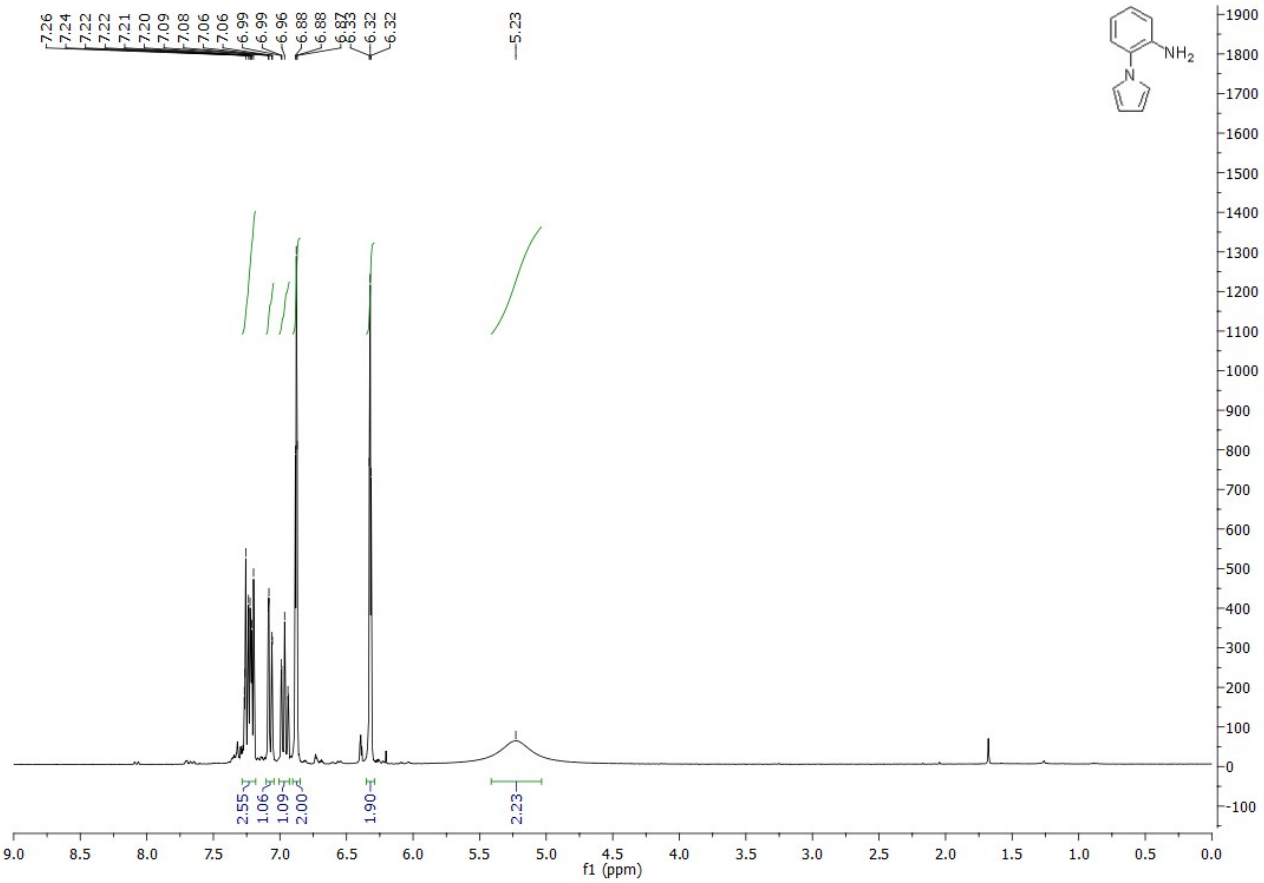
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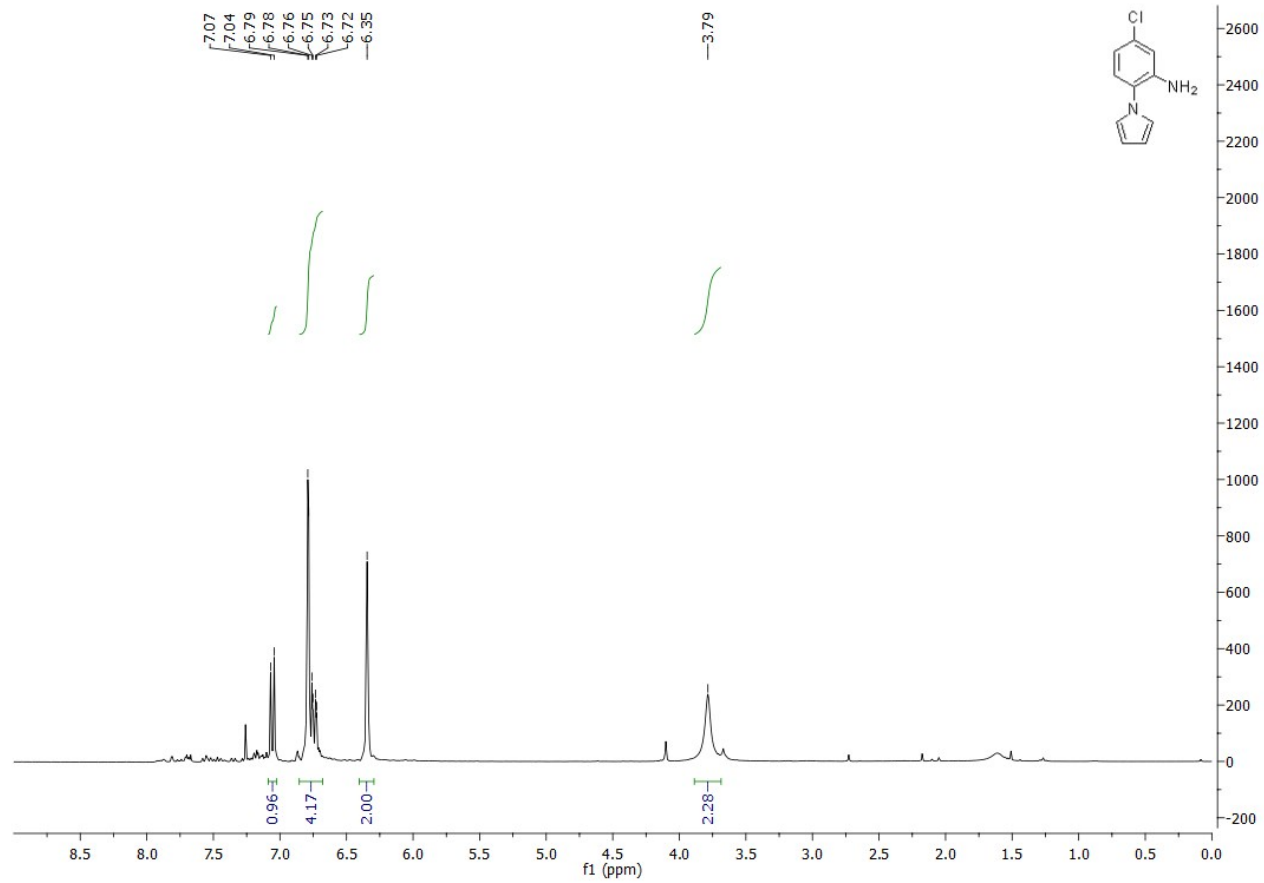
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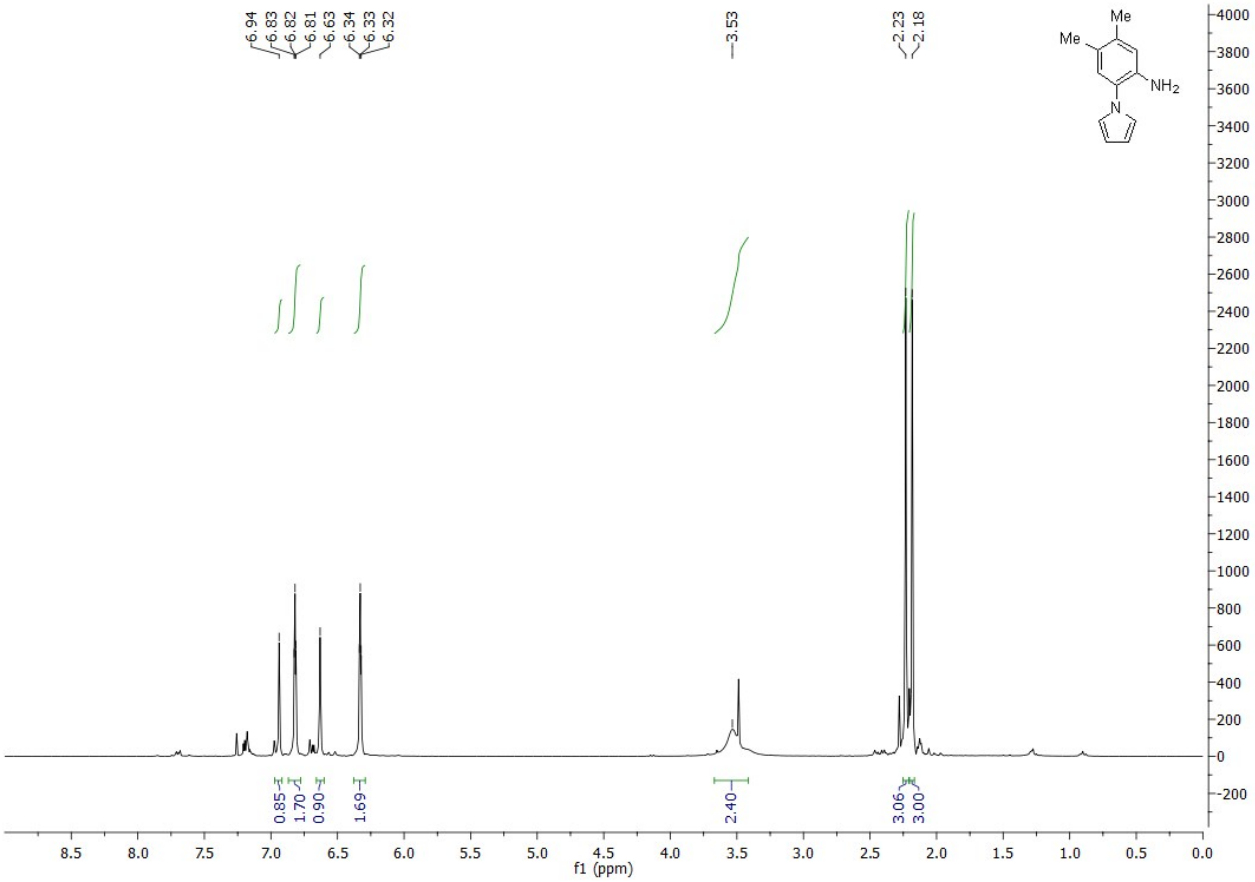
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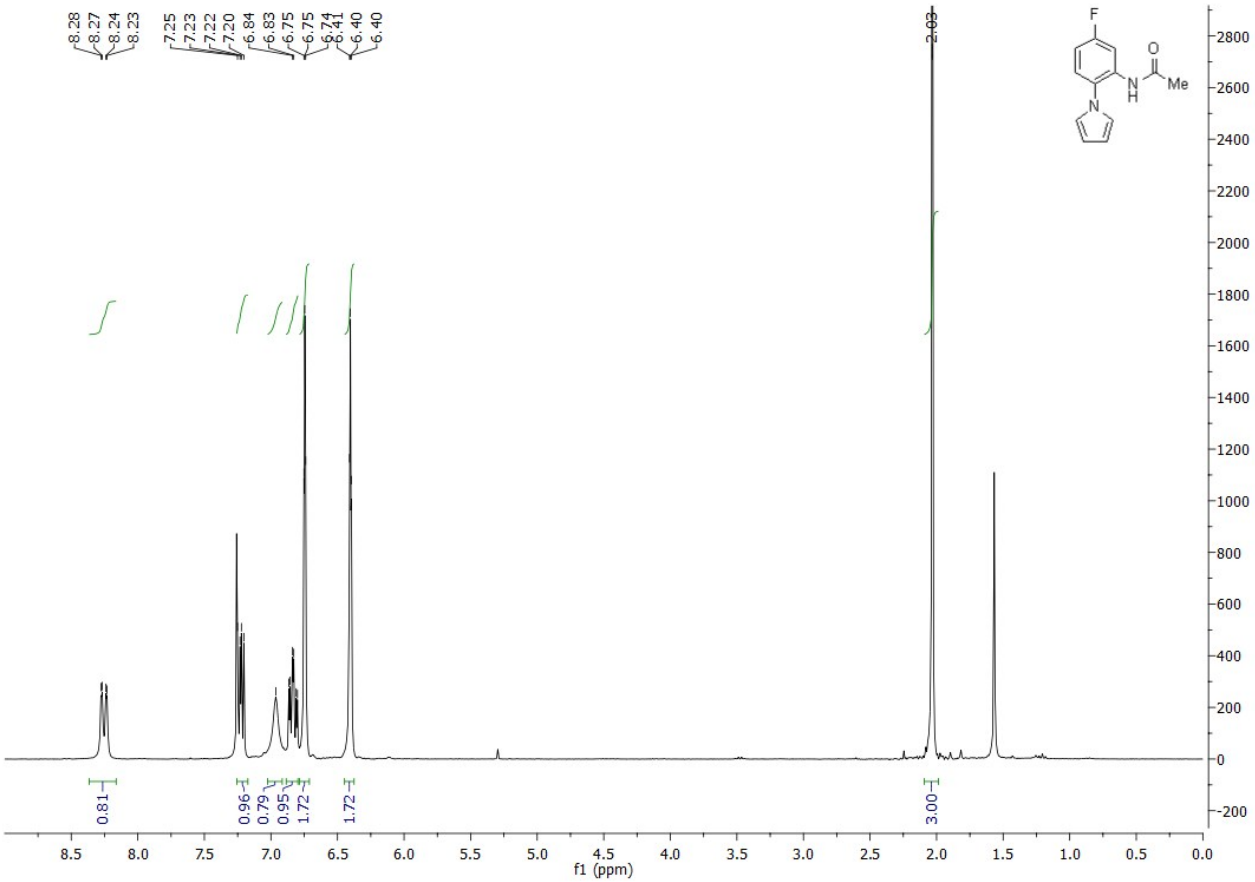
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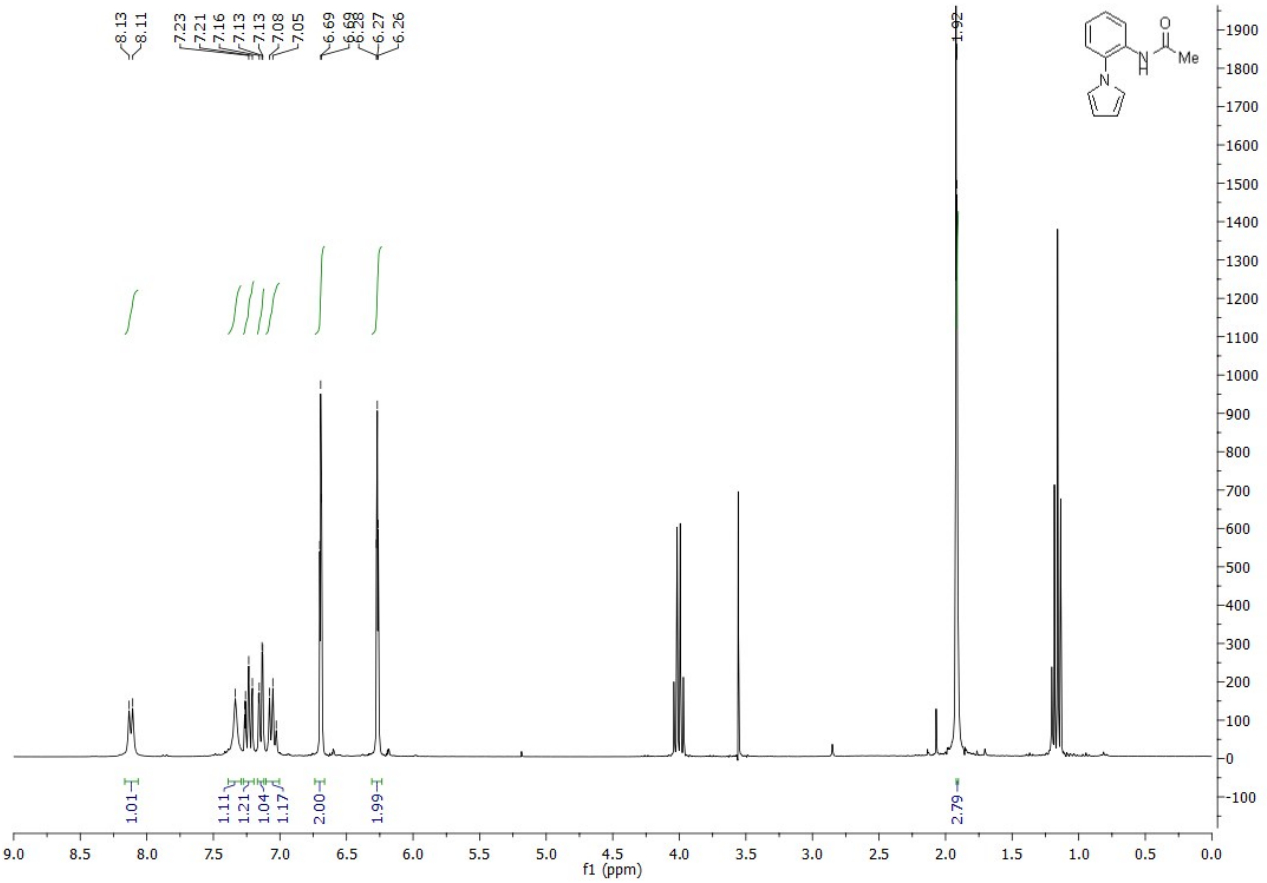
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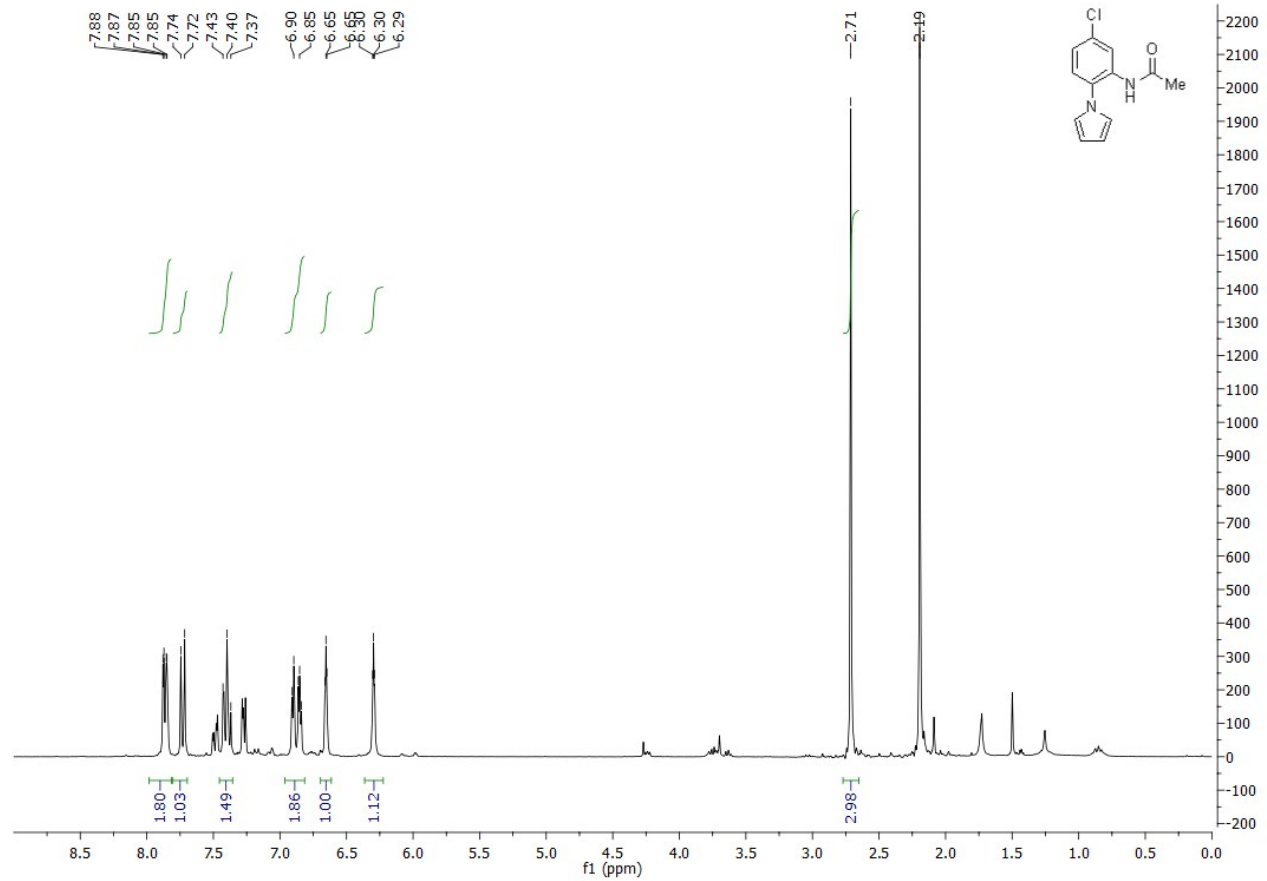
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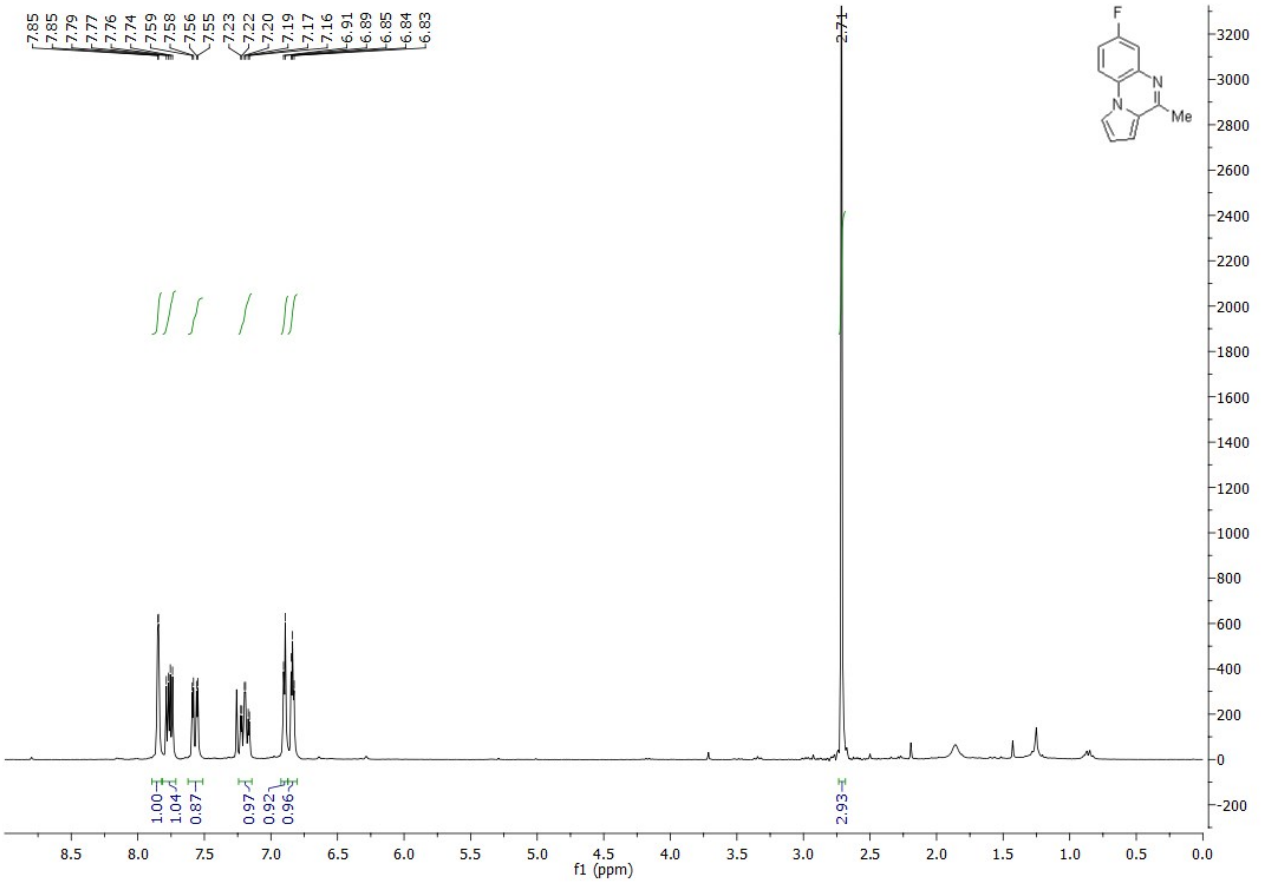
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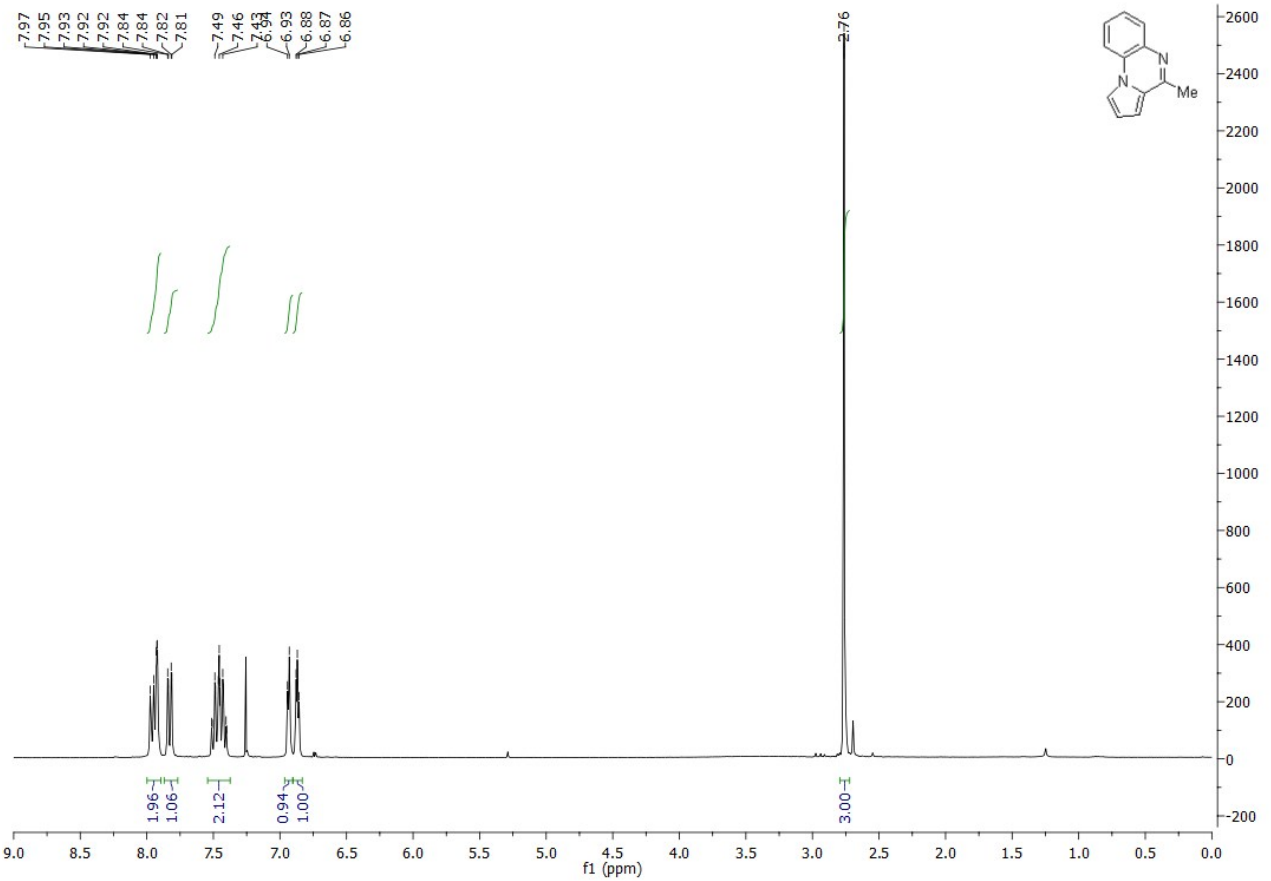
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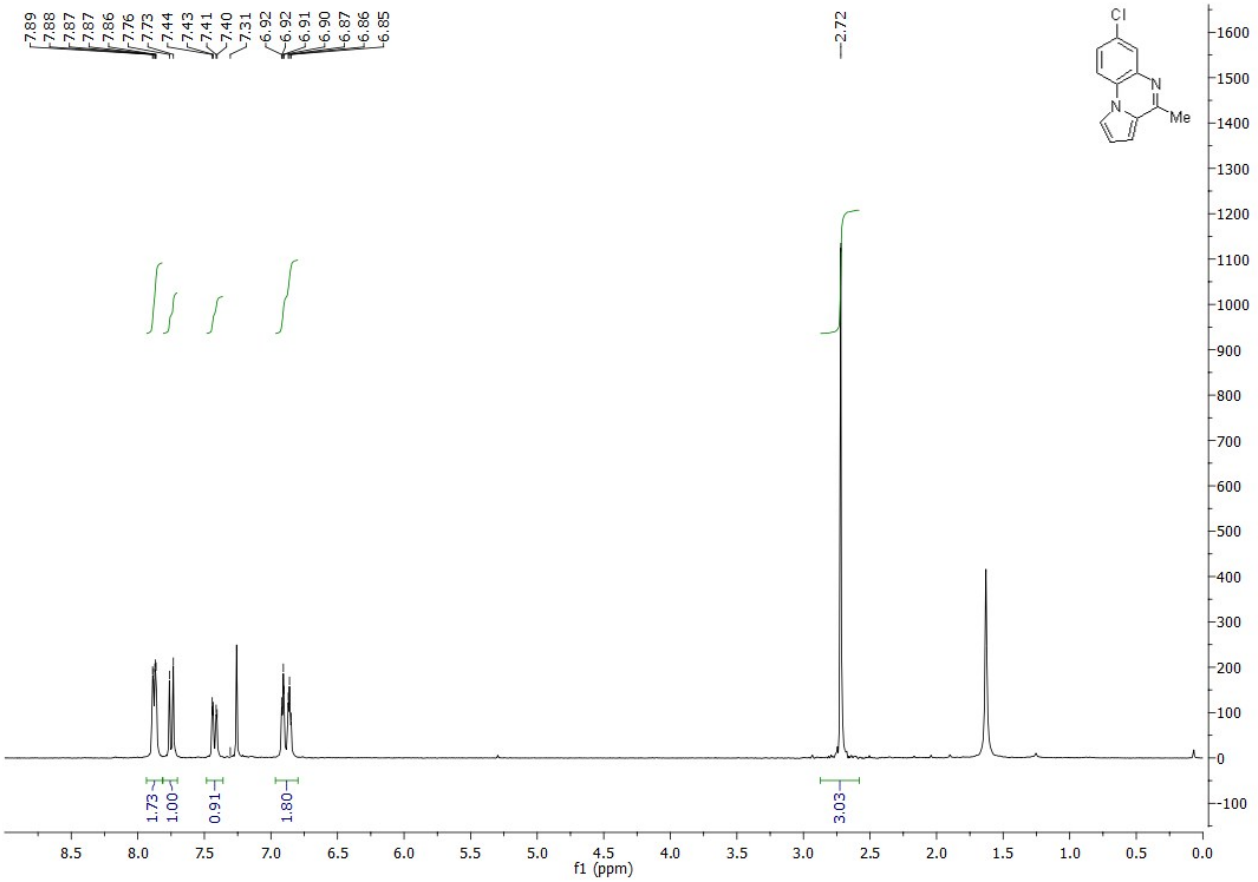
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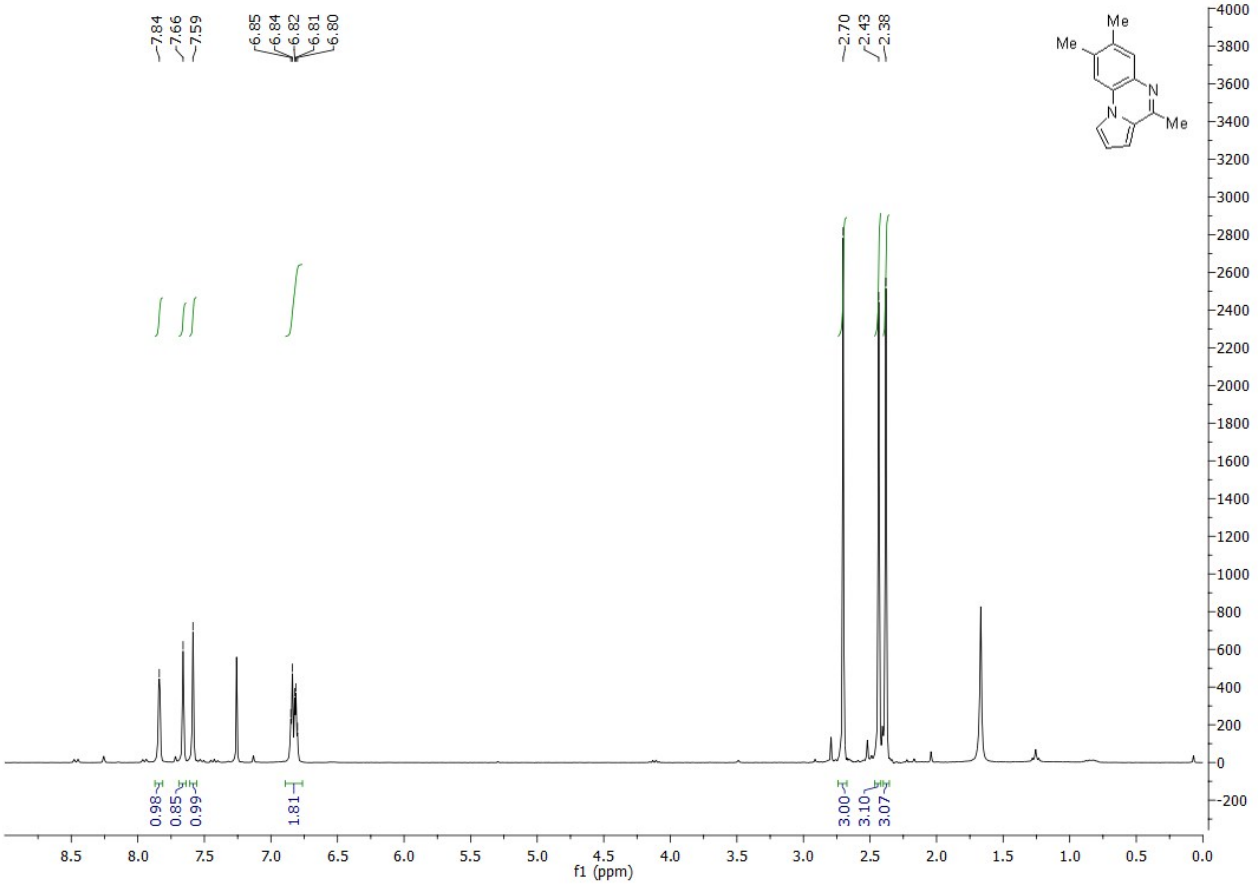
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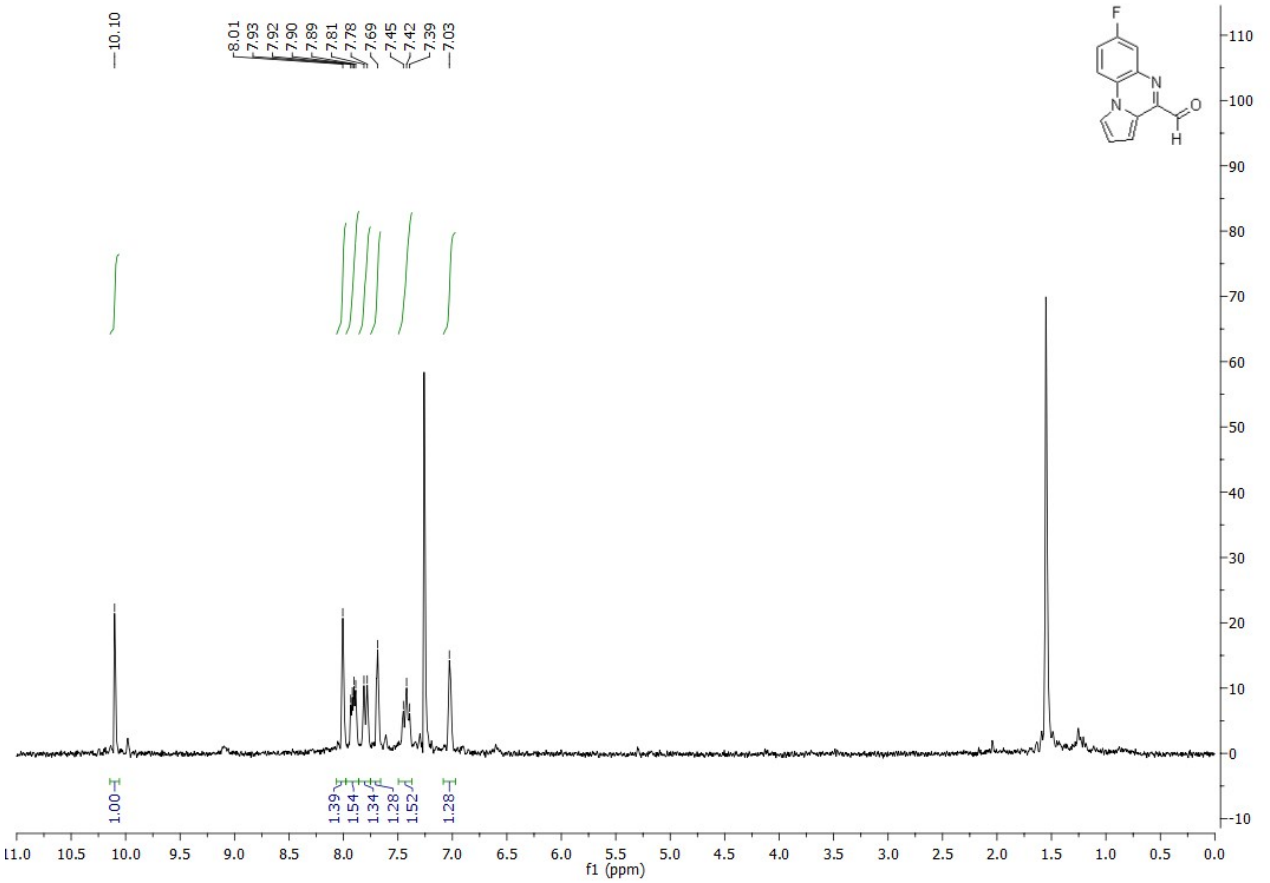
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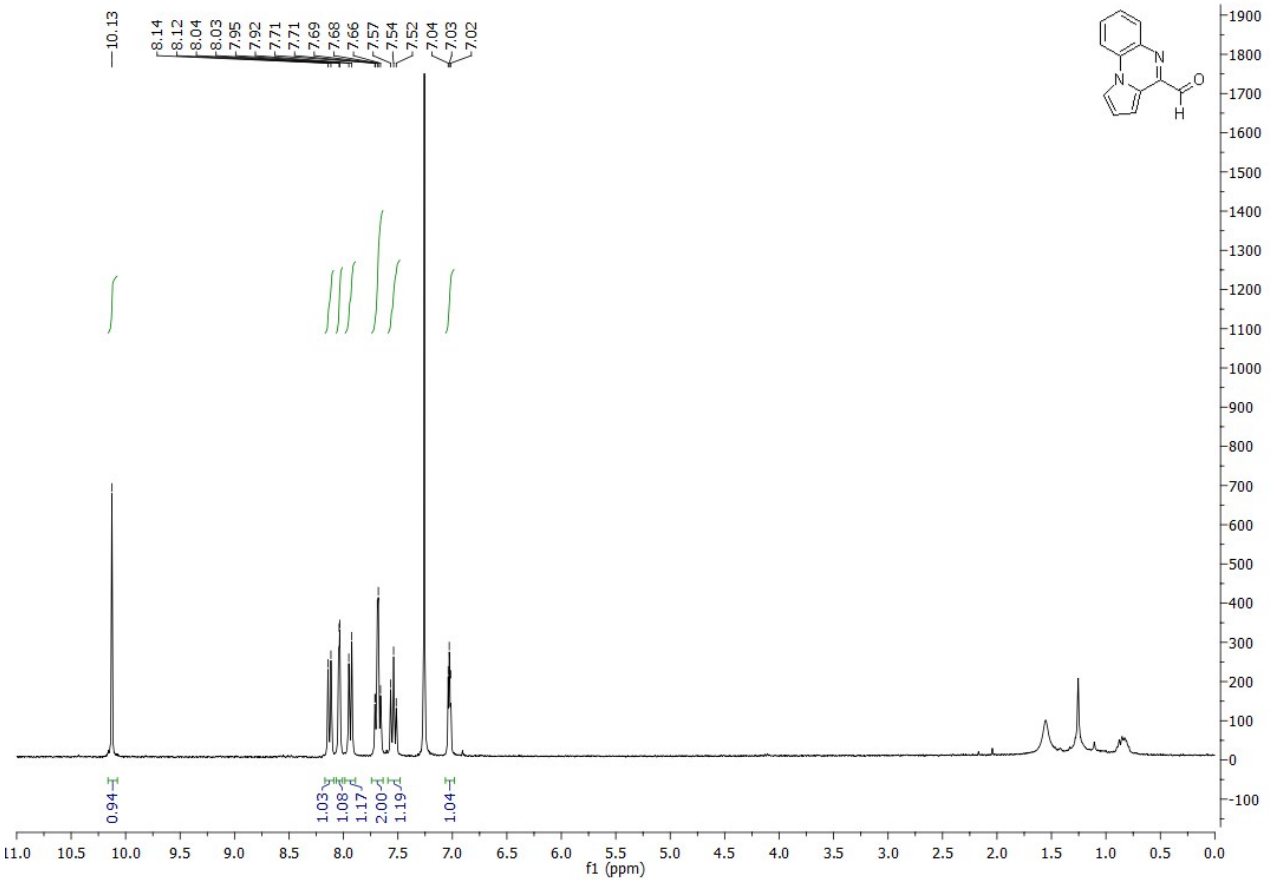
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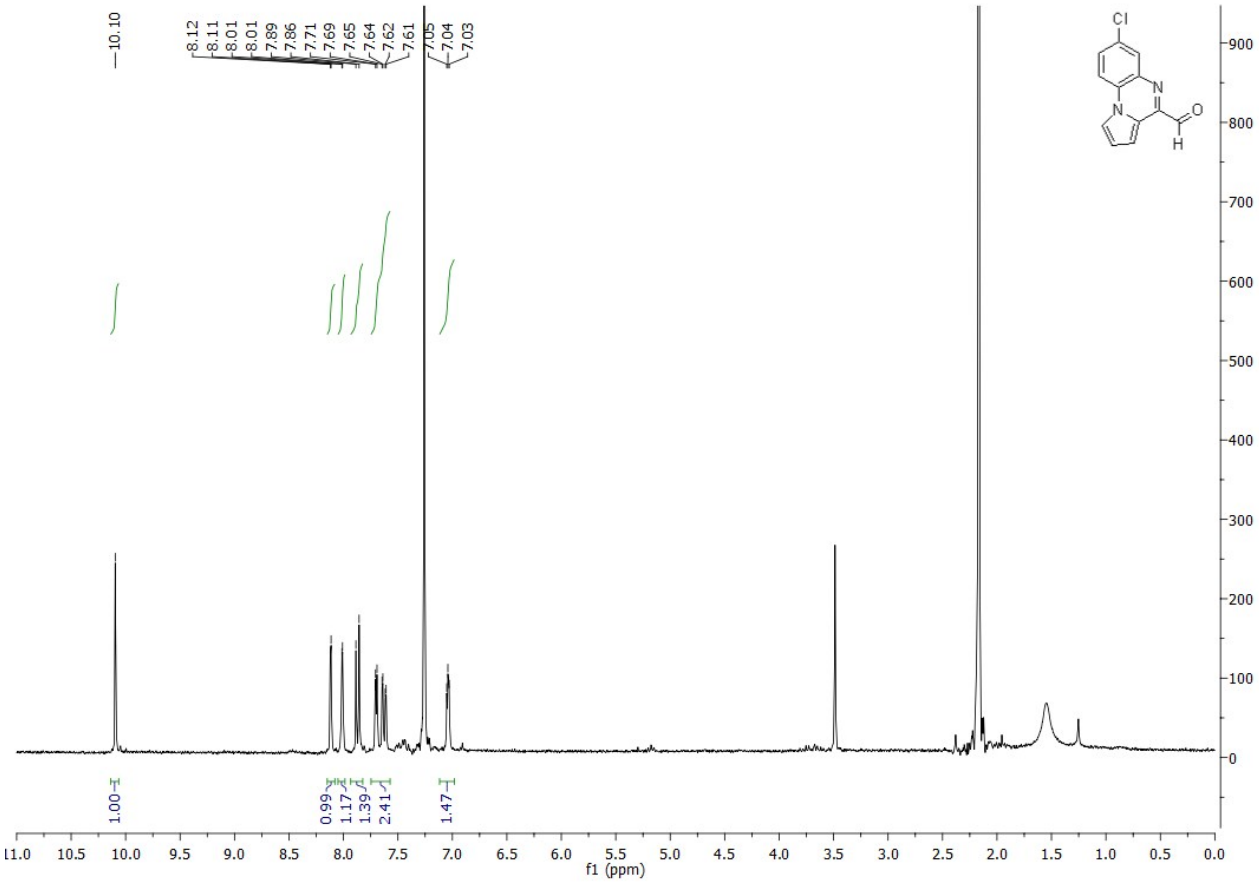
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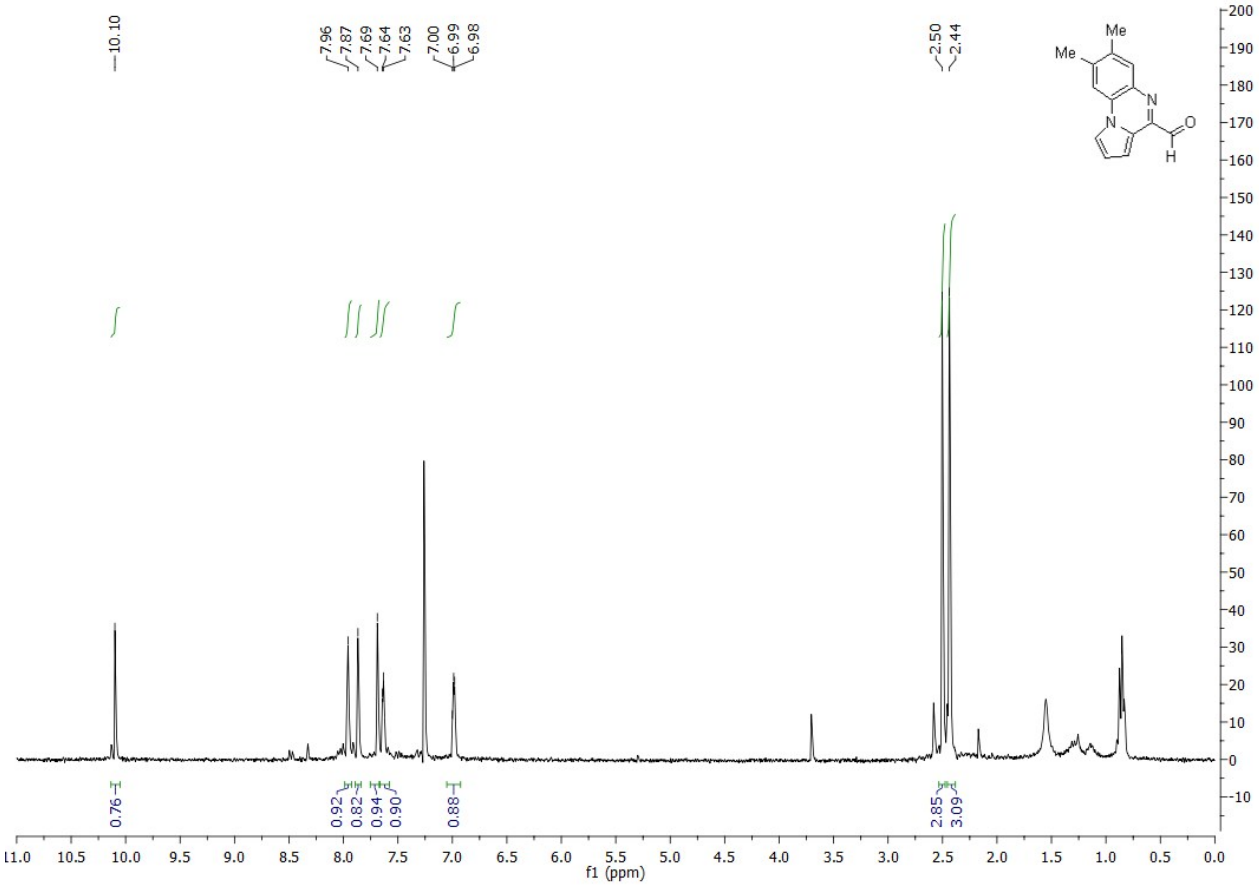
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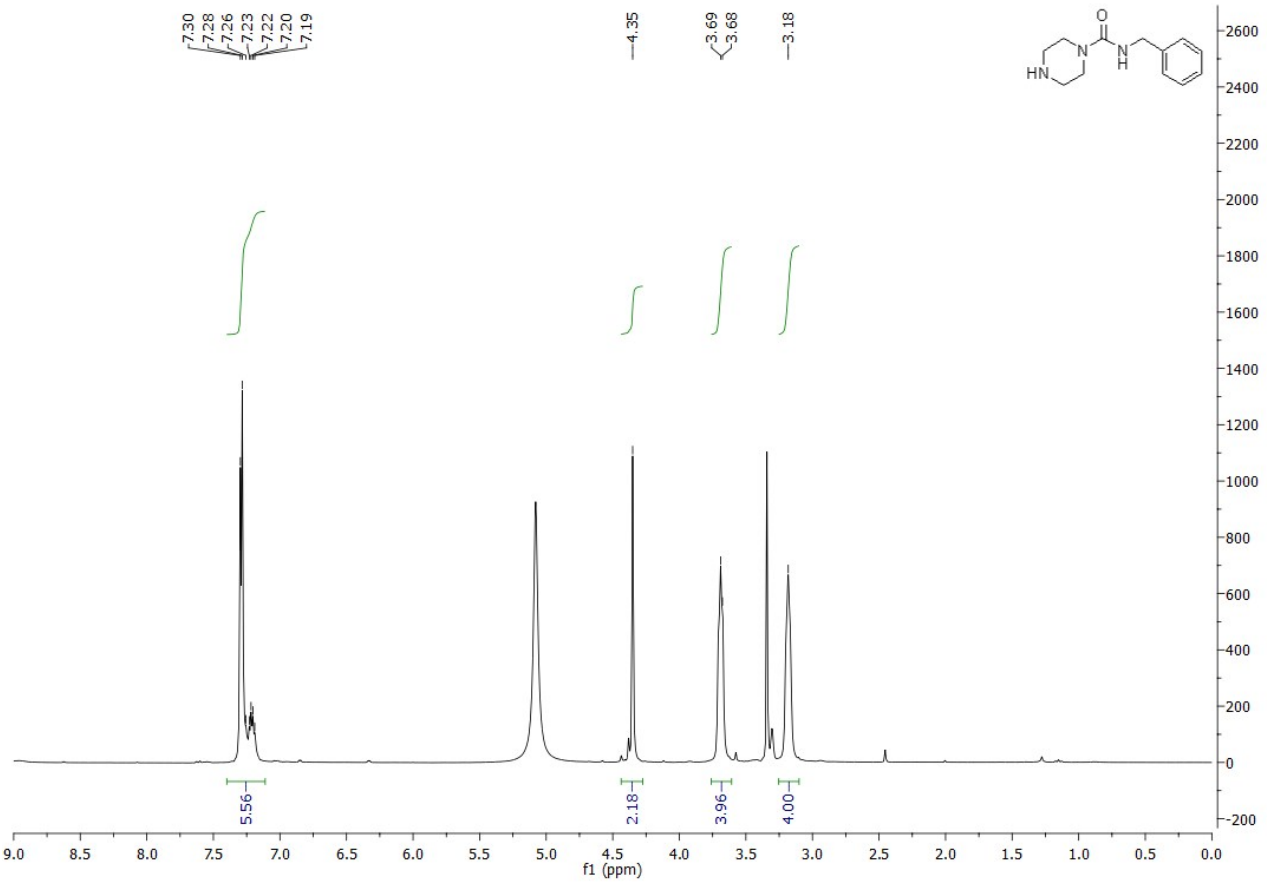
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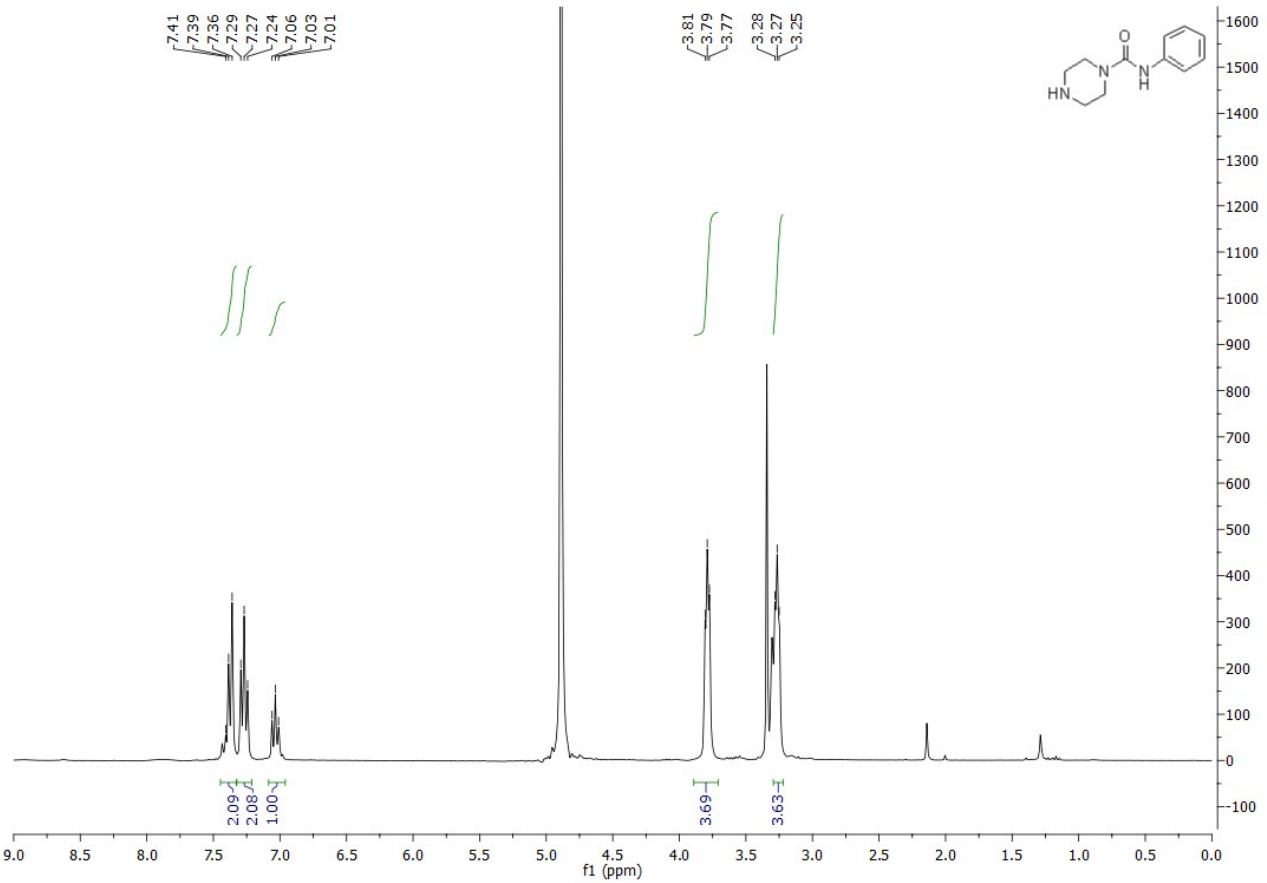
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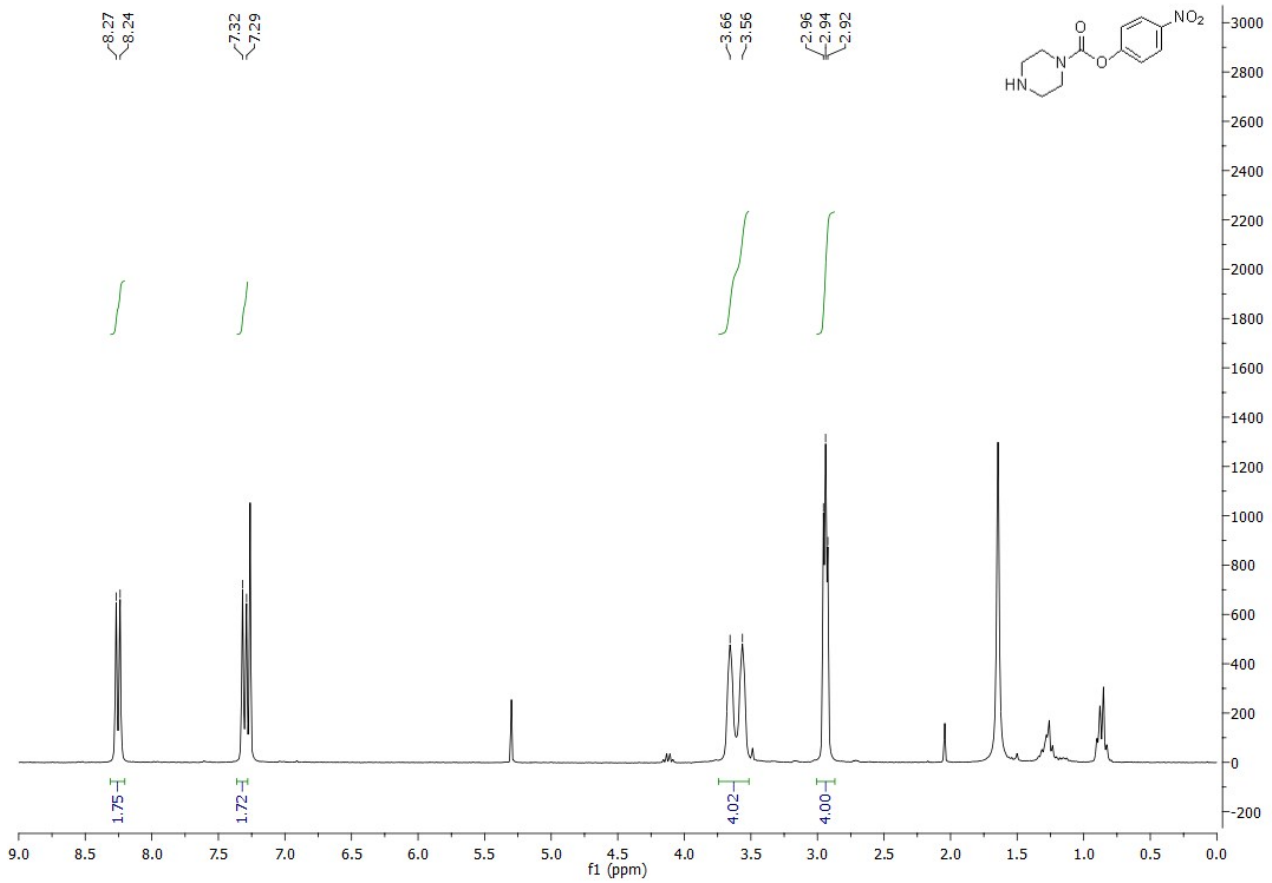
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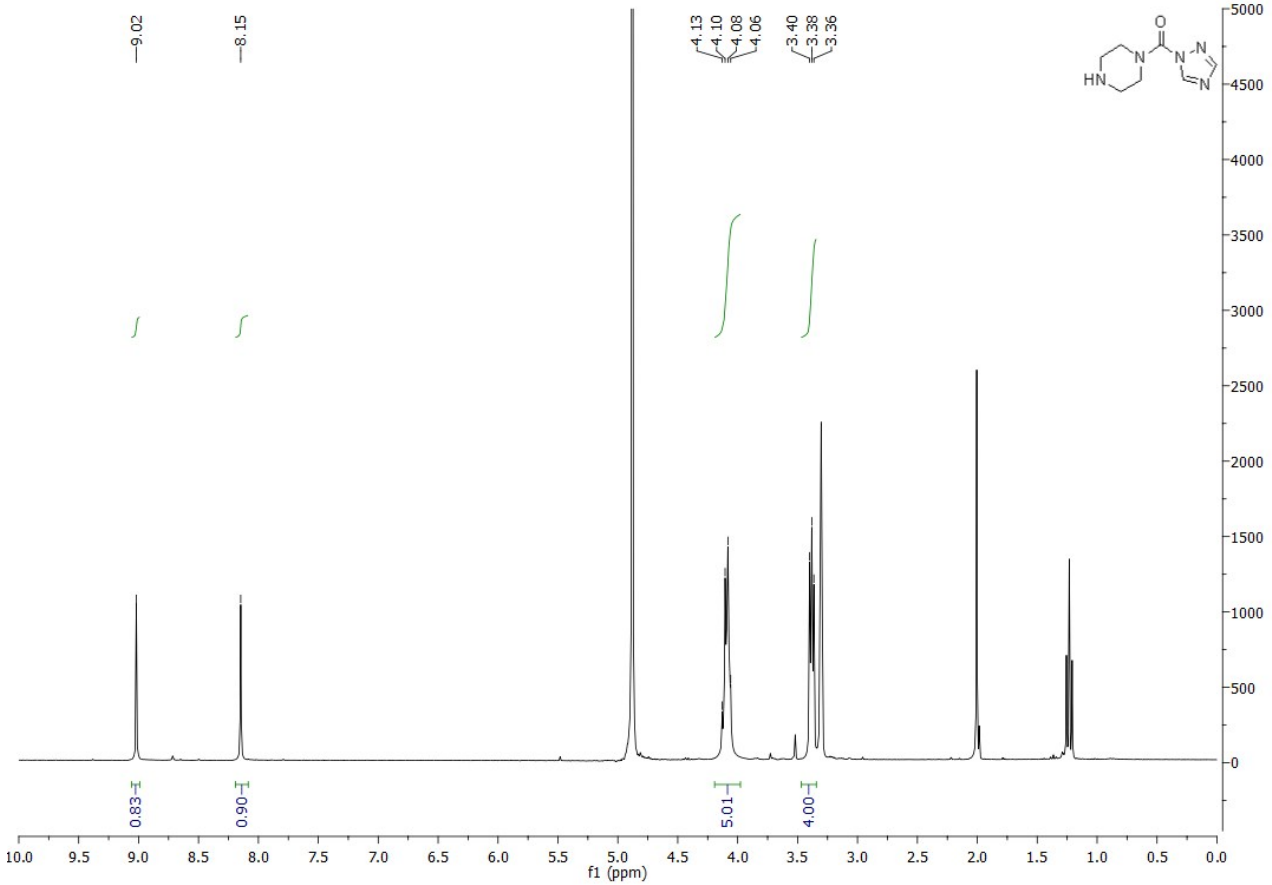
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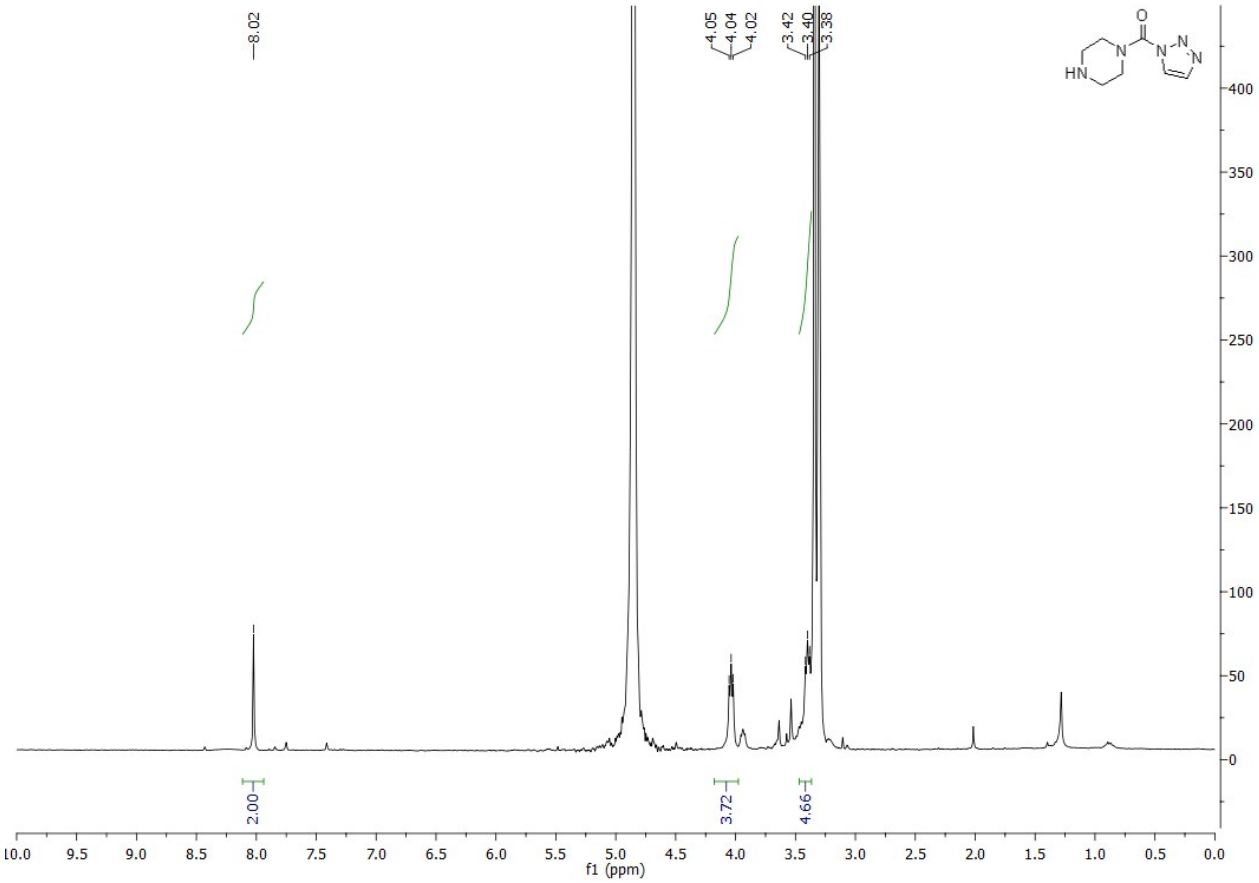
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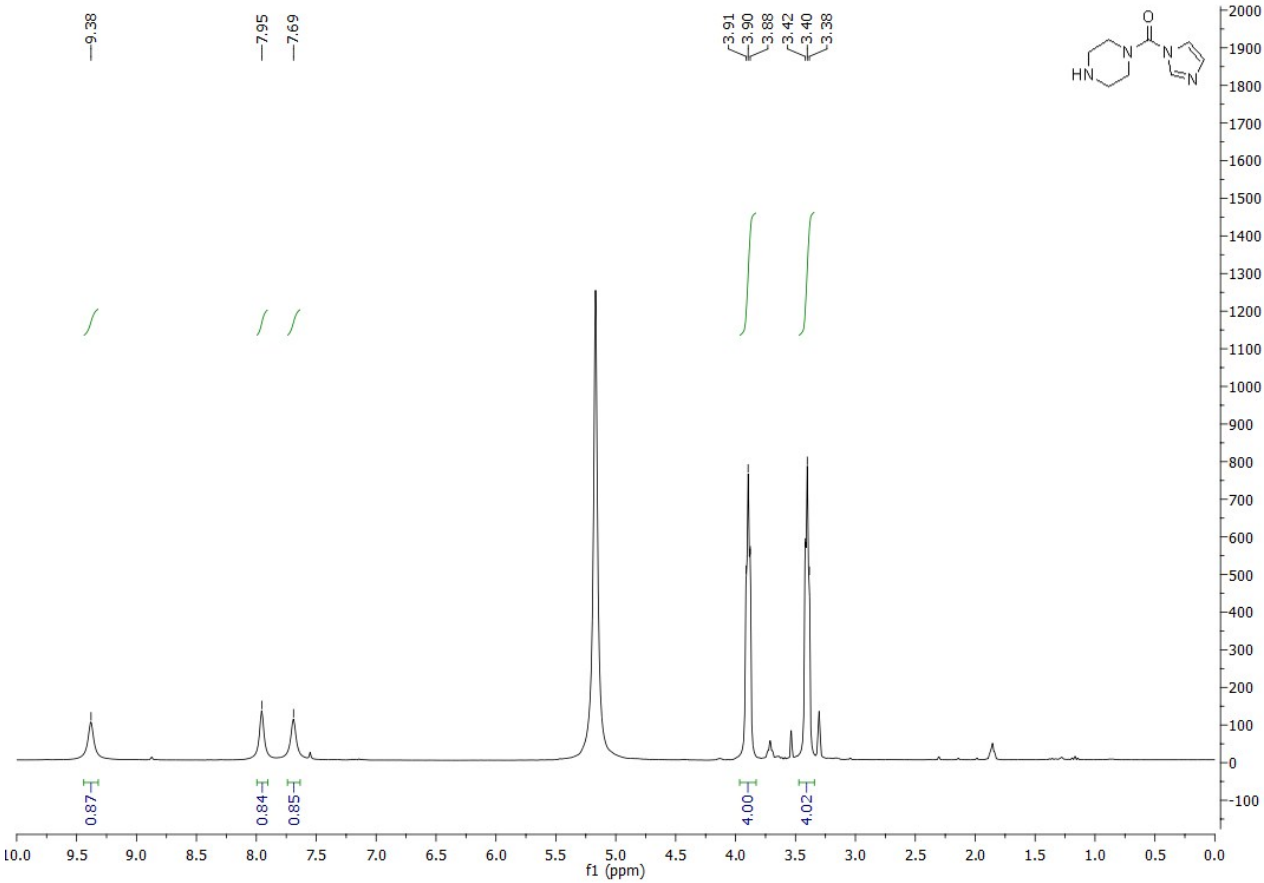
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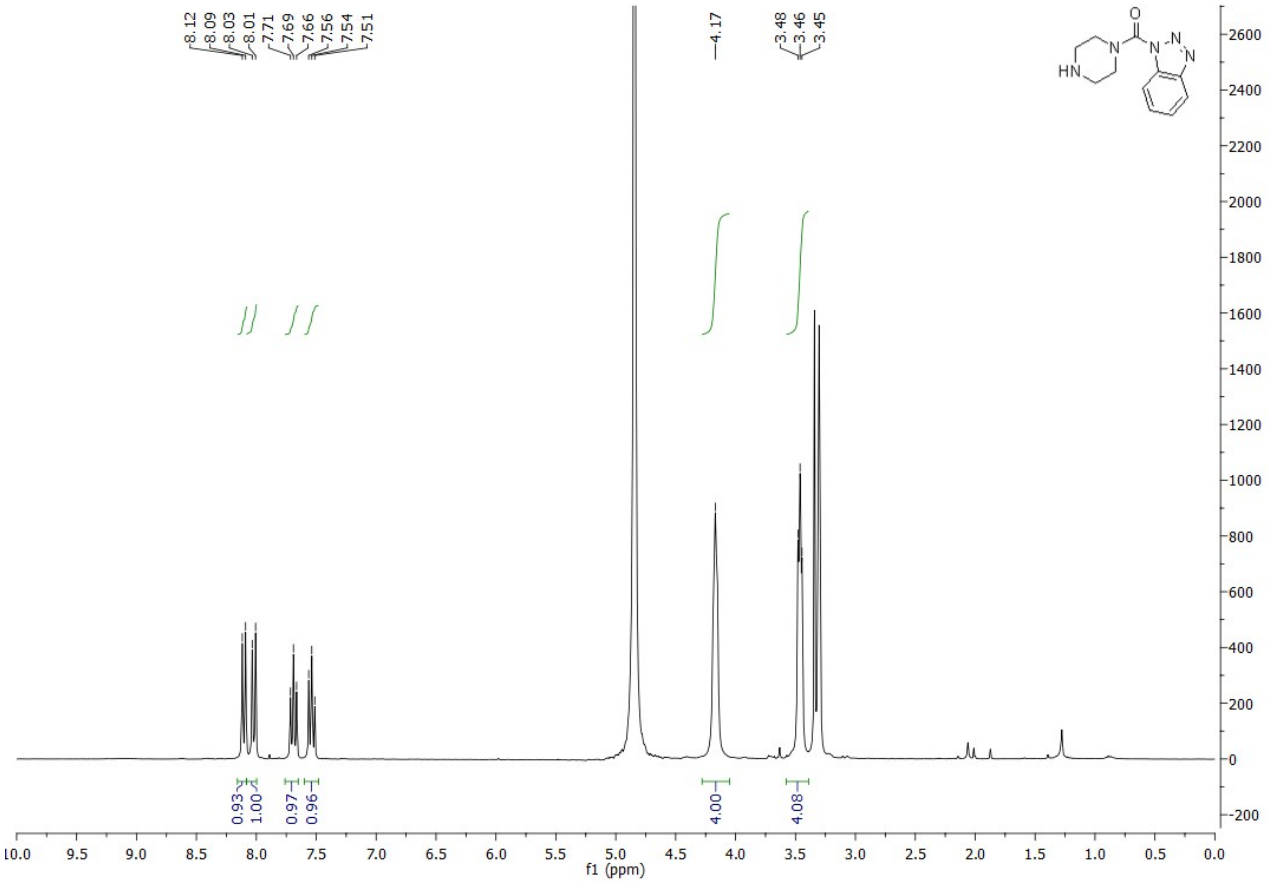
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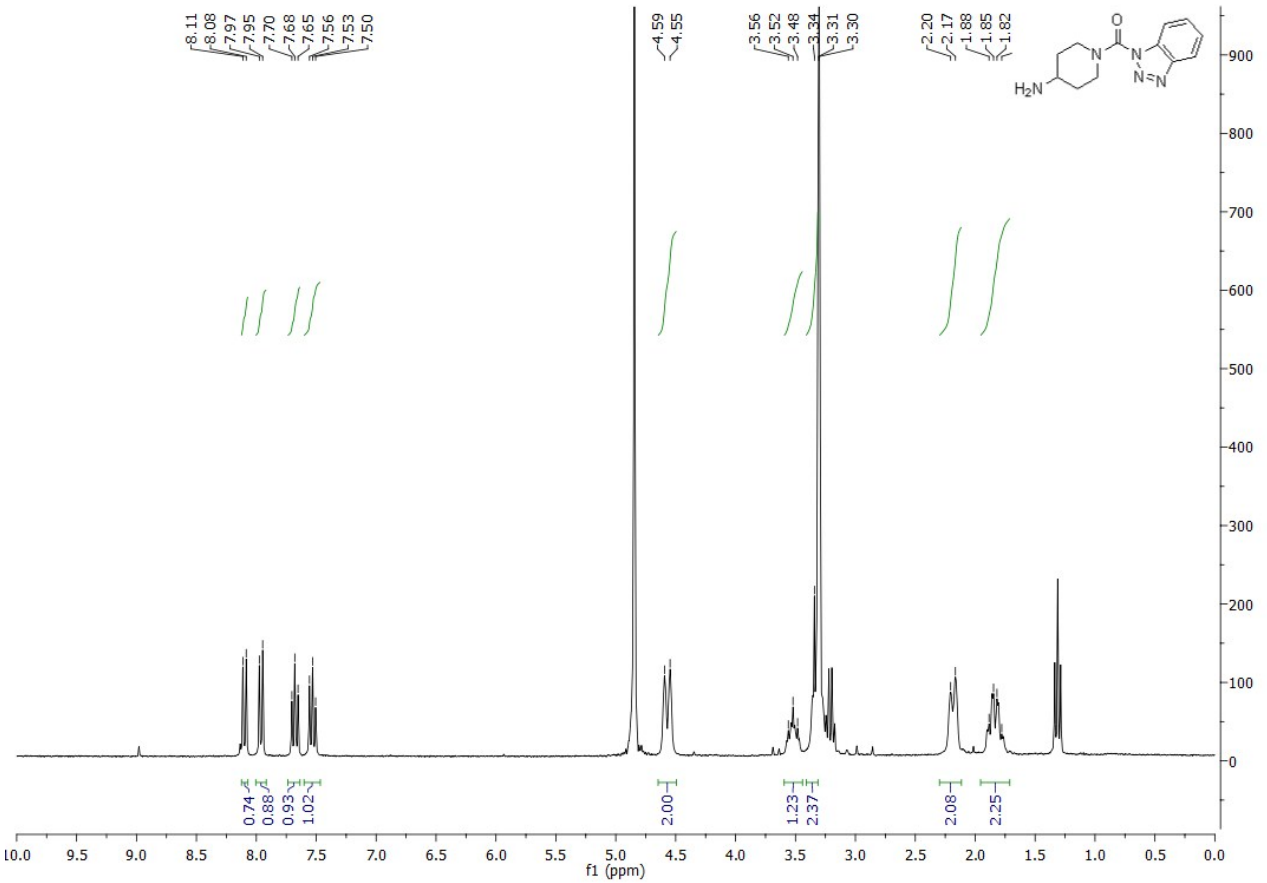
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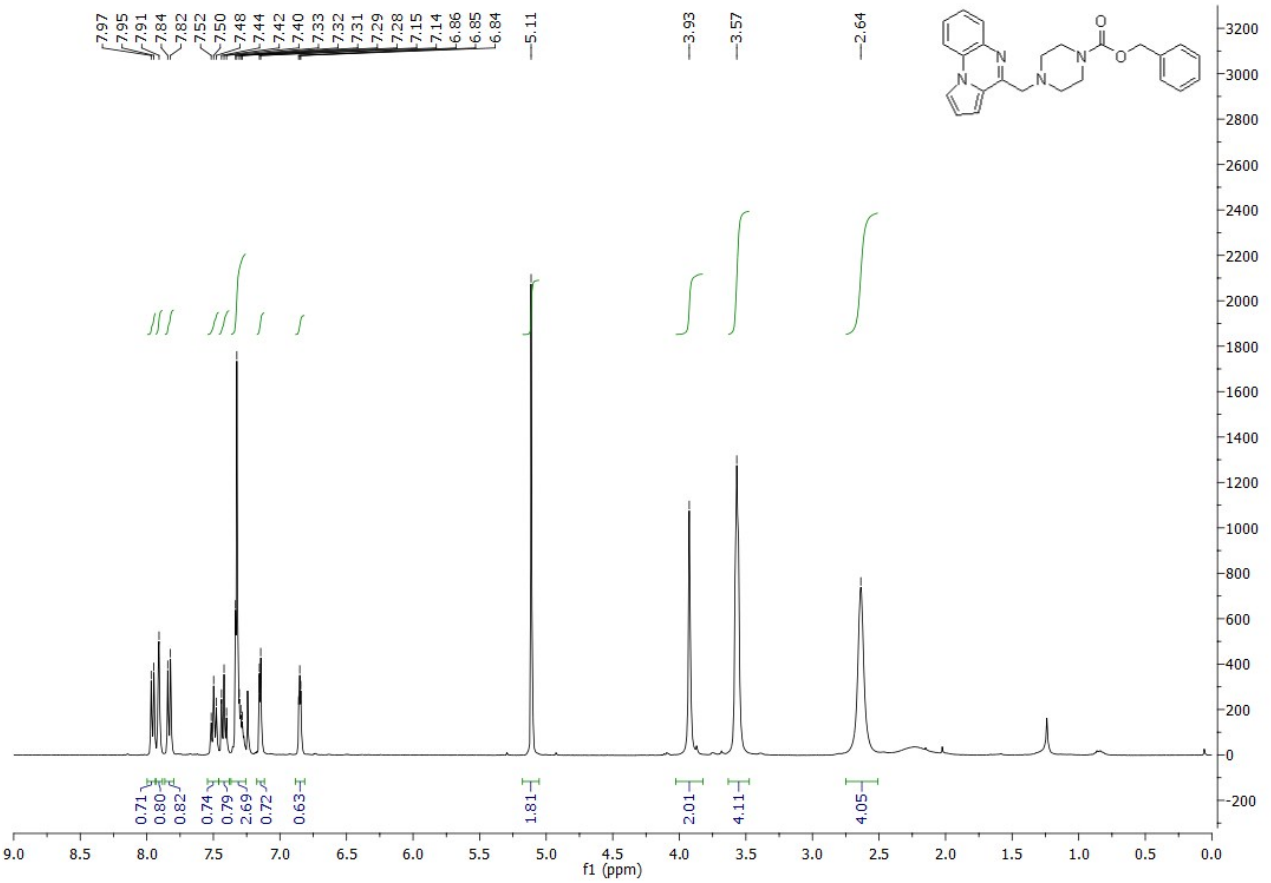
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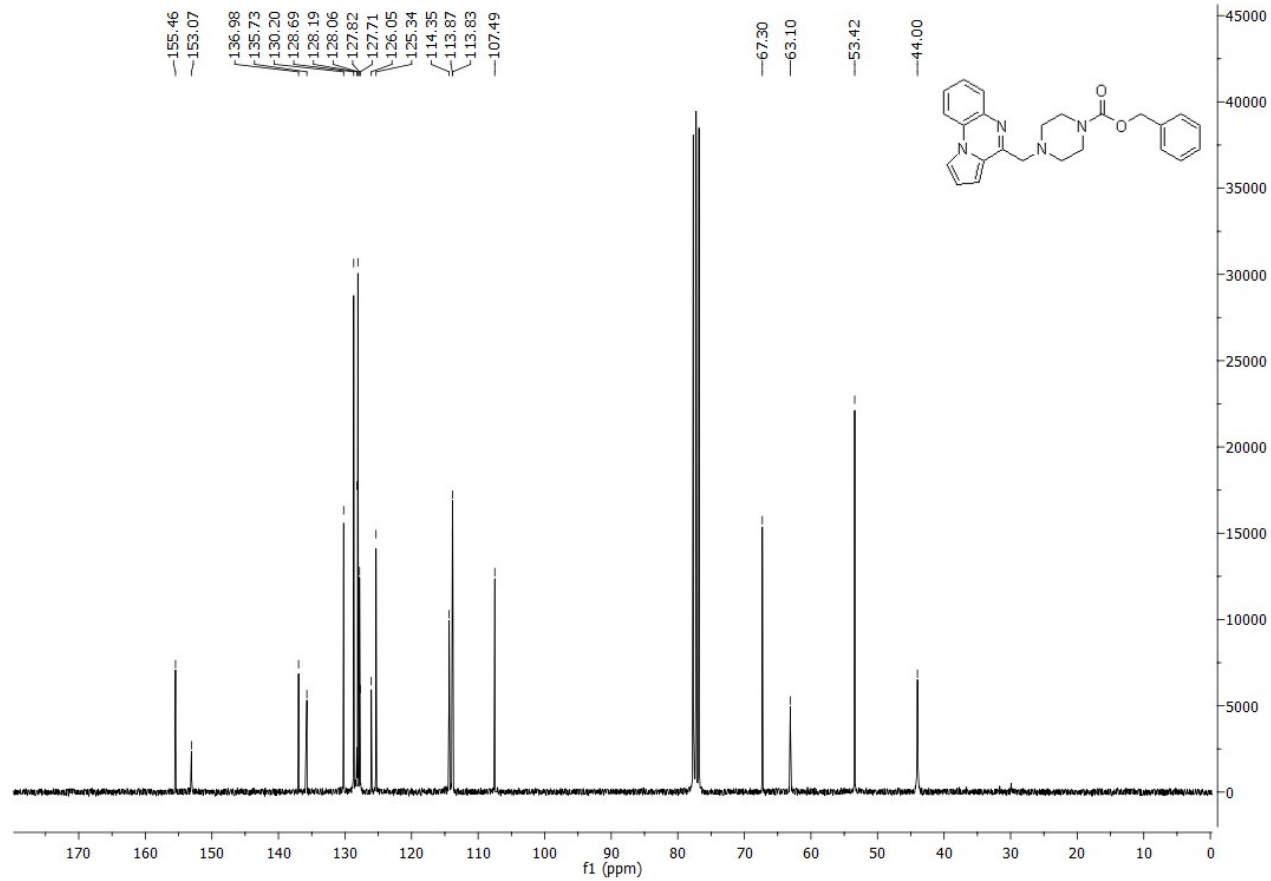
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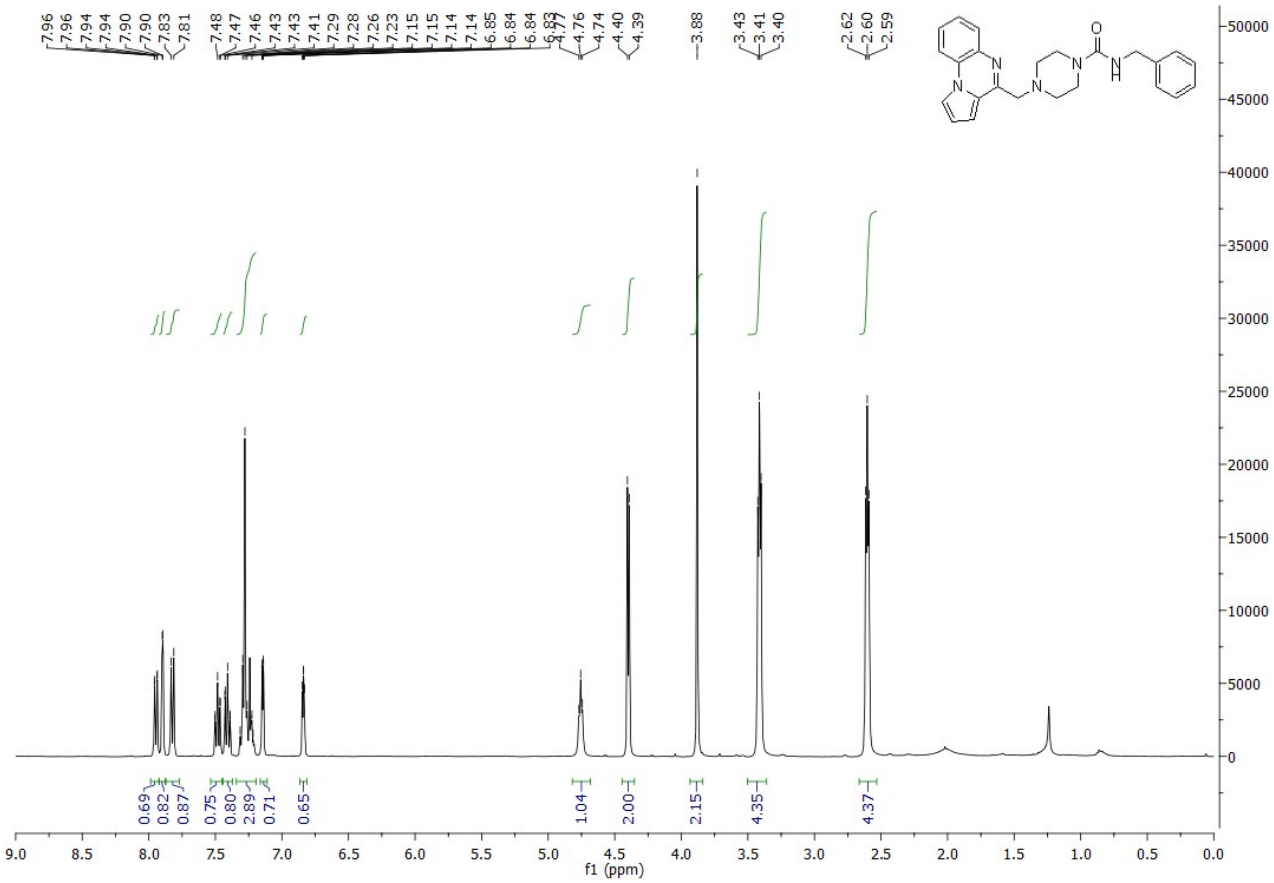
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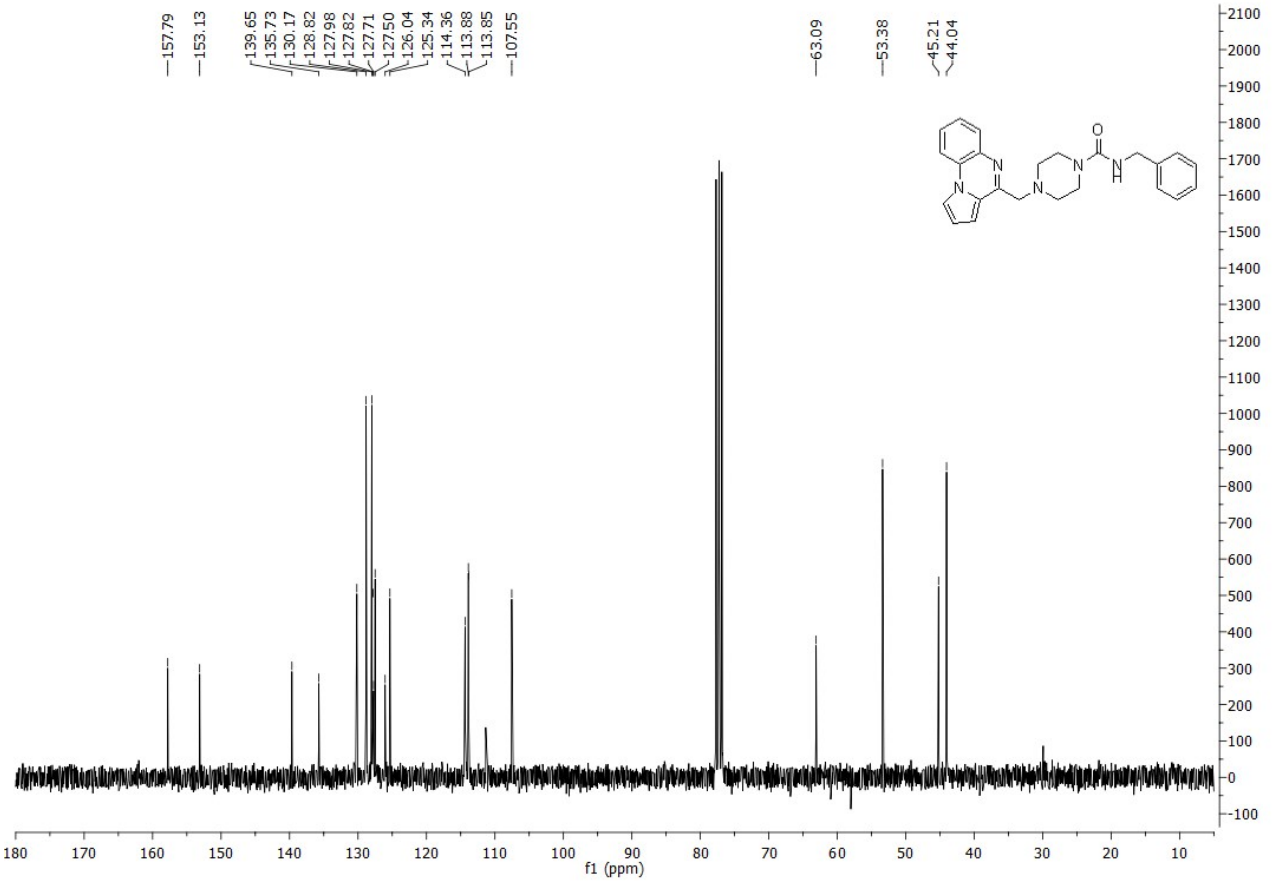
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127.98
127.82
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113.85
107.55
63.09
53.38
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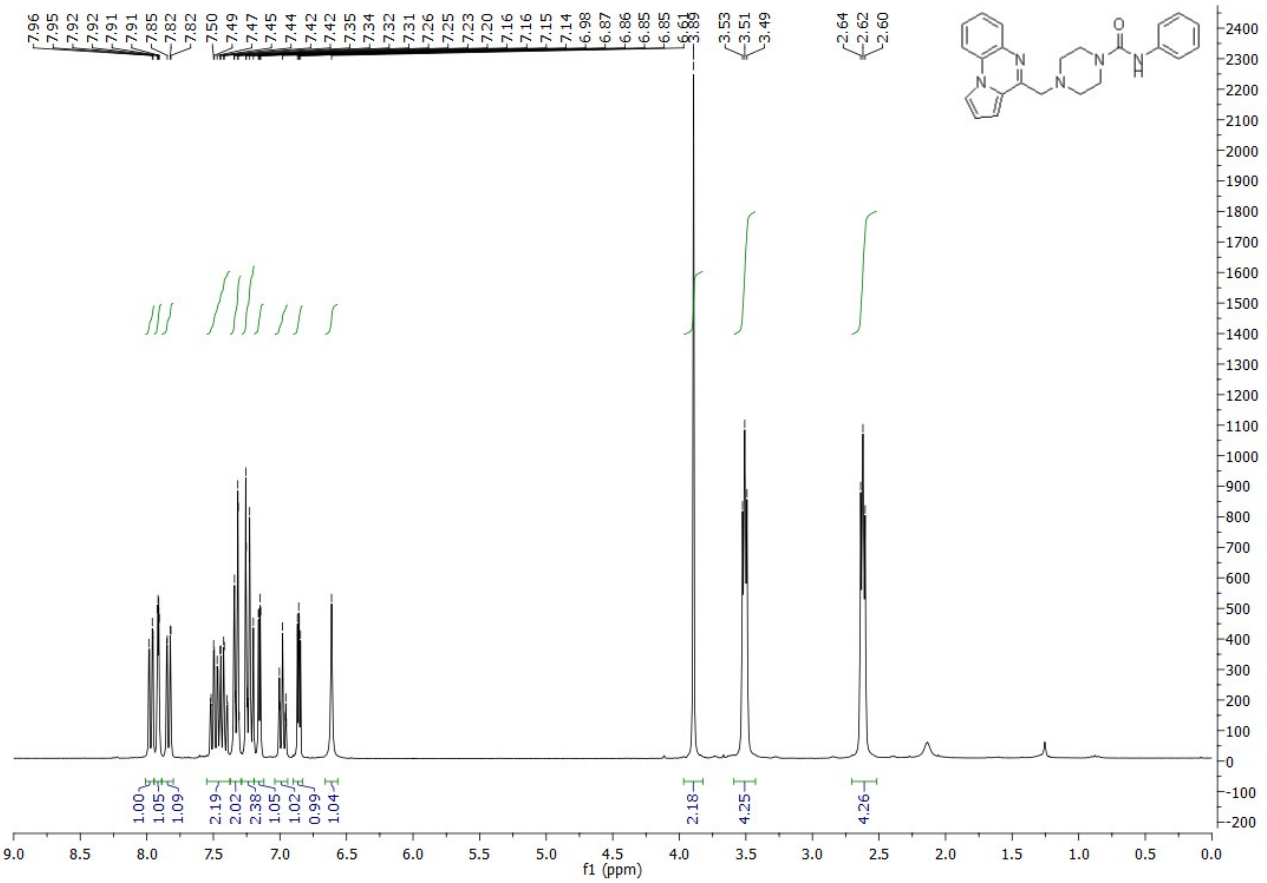
44.04
f1 (ppm)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7.50
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7.47
7.45
7.44
7.42
7.42
7.35
7.34
7.32
7.31
7.26
7.25
7.23
7.20
7.16
7.15
7.14
6.98
6.87
6.86
6.85
6.85
6.61
3.89
3.53
3.51
3.49
2.64
2.62
2.60
1.00
1.05
1.09
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2.38
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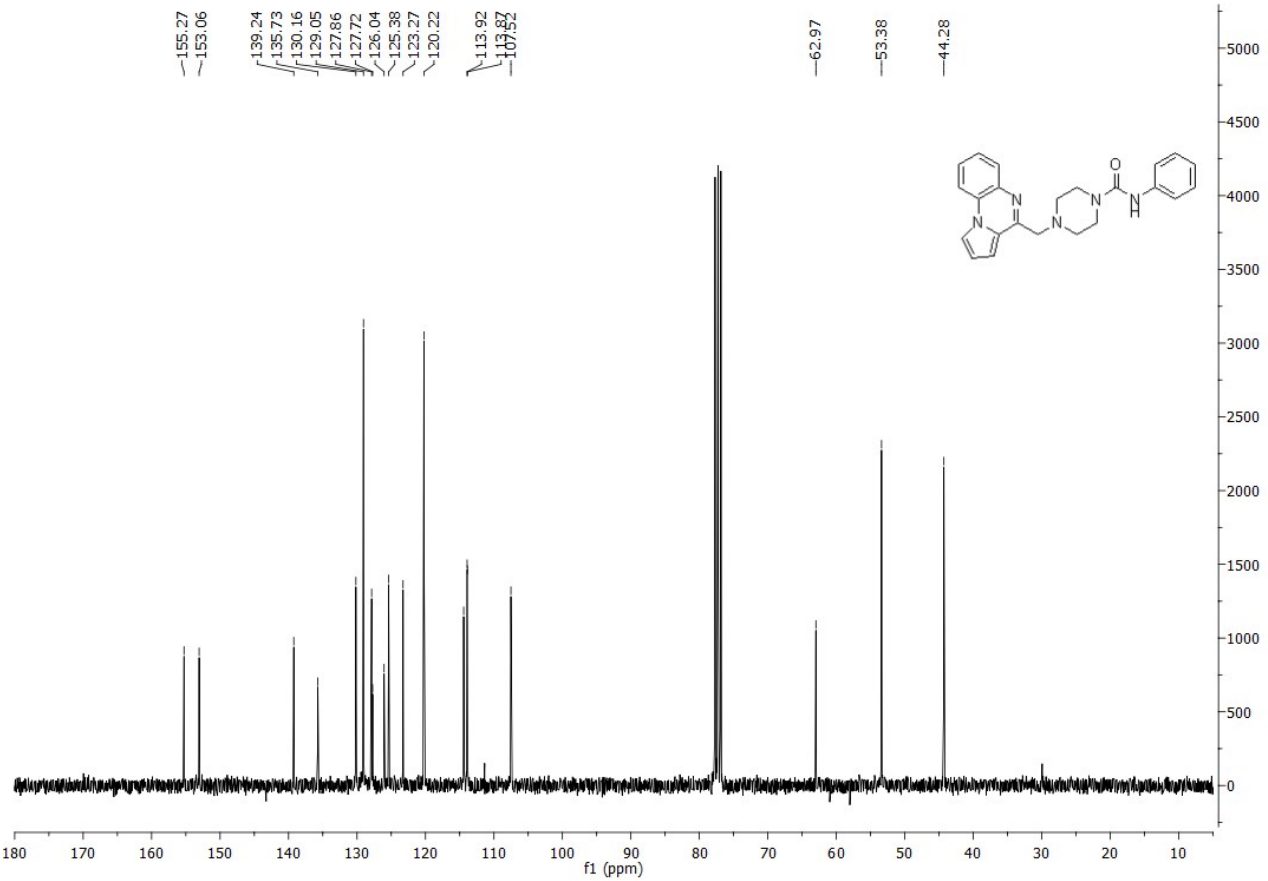
1.04
2.18
4.25
4.26
f1 (ppm)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129.05
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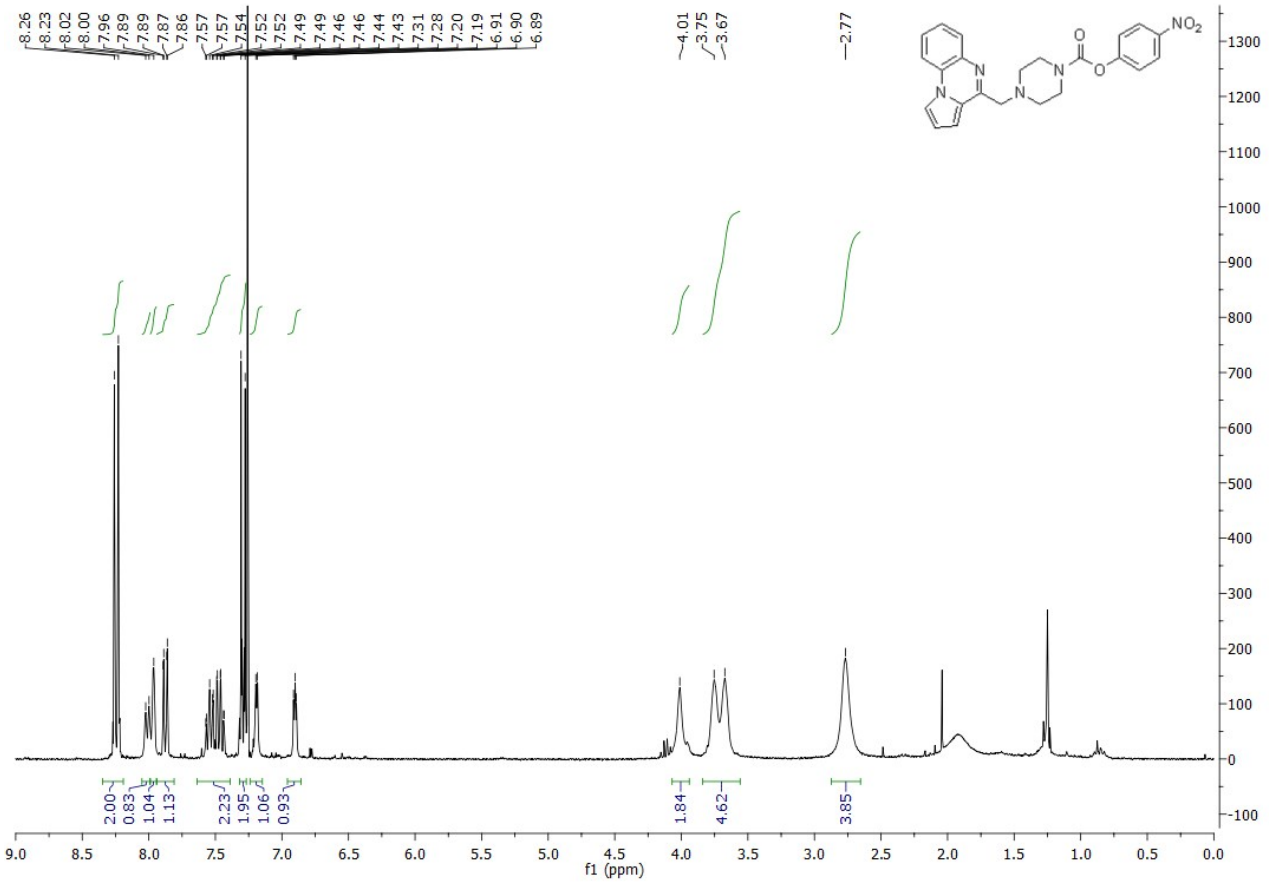
113.92
113.87
107.52
62.97
53.38
44.28
f1 (ppm)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7.87
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7.57
7.54
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7.52
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7.49
7.46
7.46
7.44
7.43
7.31
7.28
7.20
7.19
6.91
6.90
6.89
4.01
3.75
3.67
2.77
NO2
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1.95
1.06
0.93
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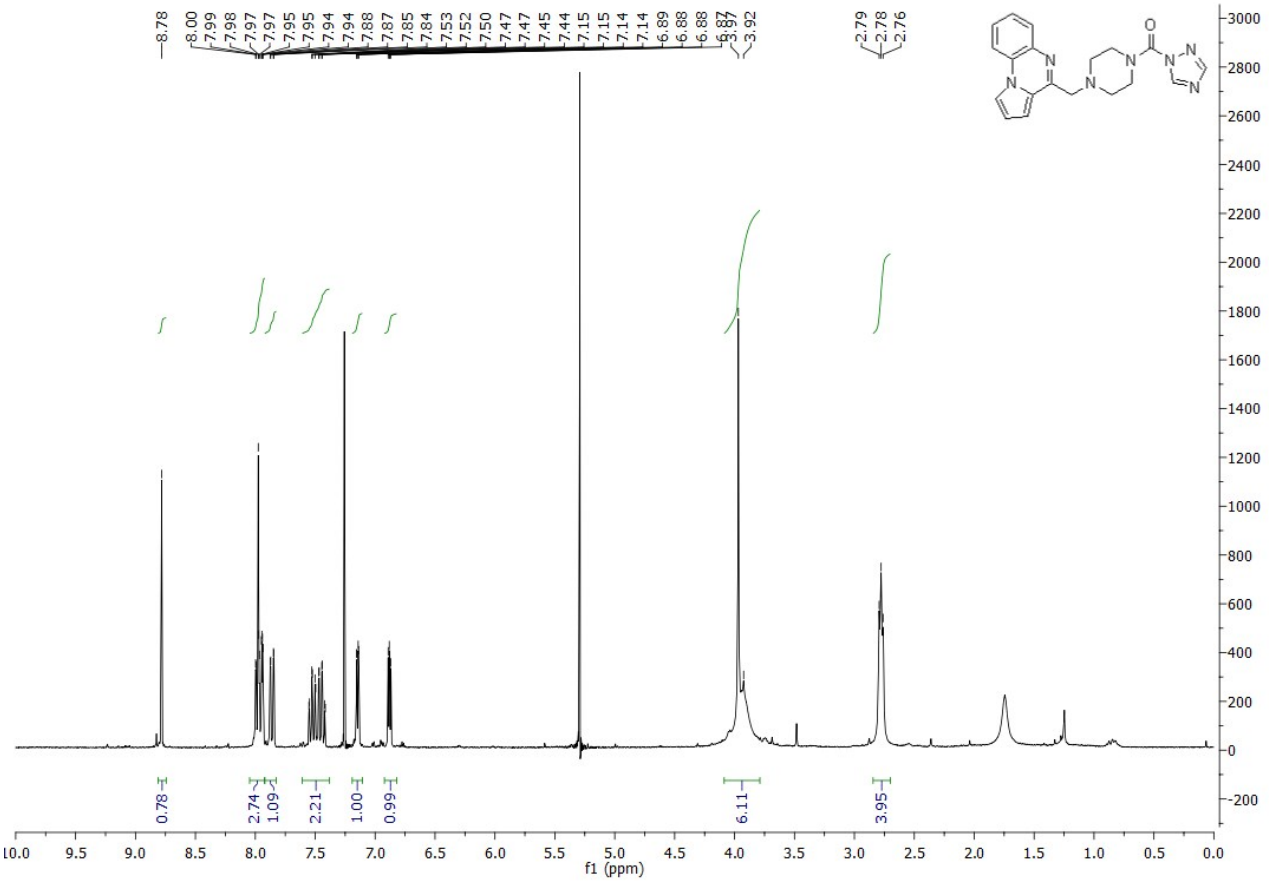
4.62
3.85
f1 (ppm)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7.94
7.88
7.87
7.85
7.84
7.53
7.52
7.50
7.47
7.47
7.45
7.44
7.15
7.15
7.14
7.14
6.89
6.88
6.88
3.92
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2.78
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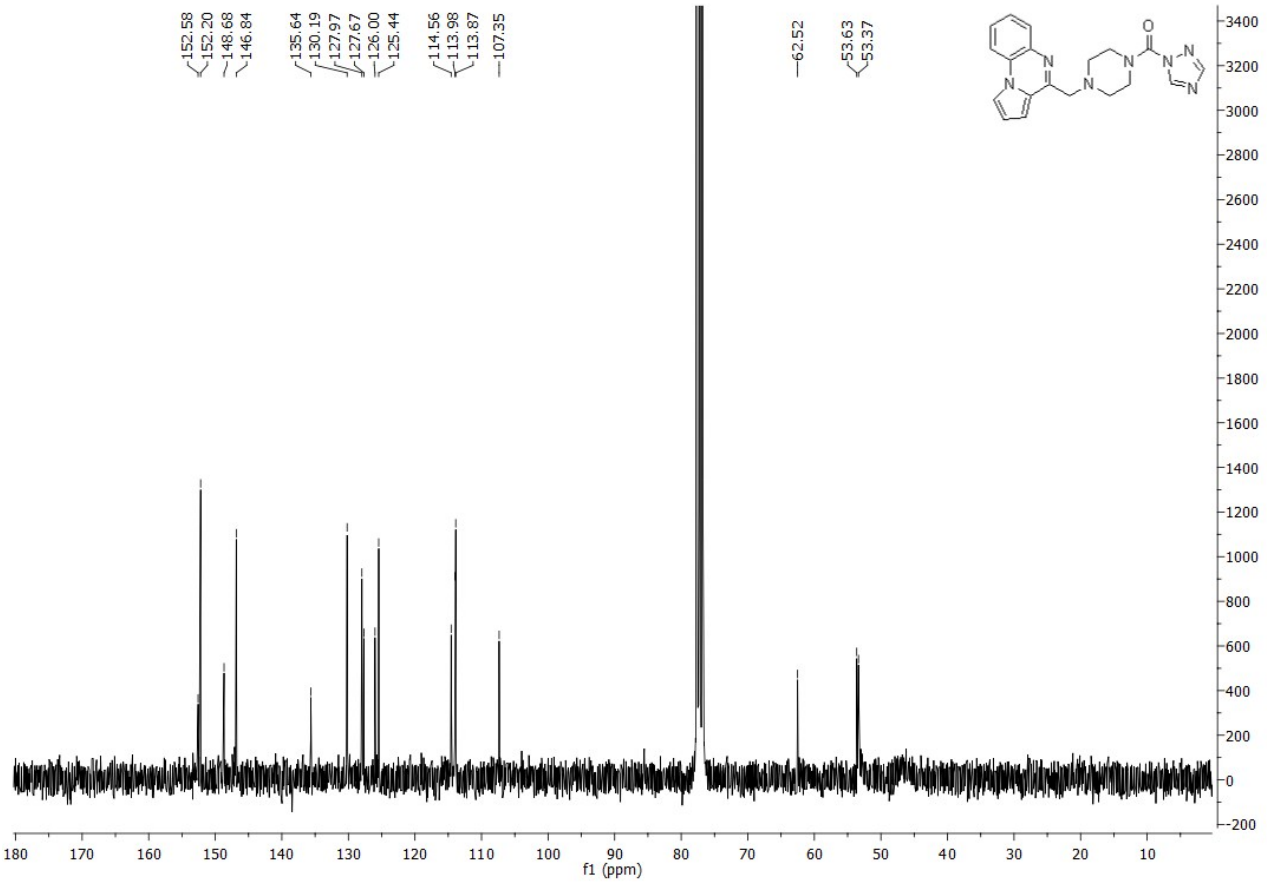
0.78
2.74
1.09
2.21
1.00
0.99
6.11
3.95
f1 (ppm)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130.19
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127.67
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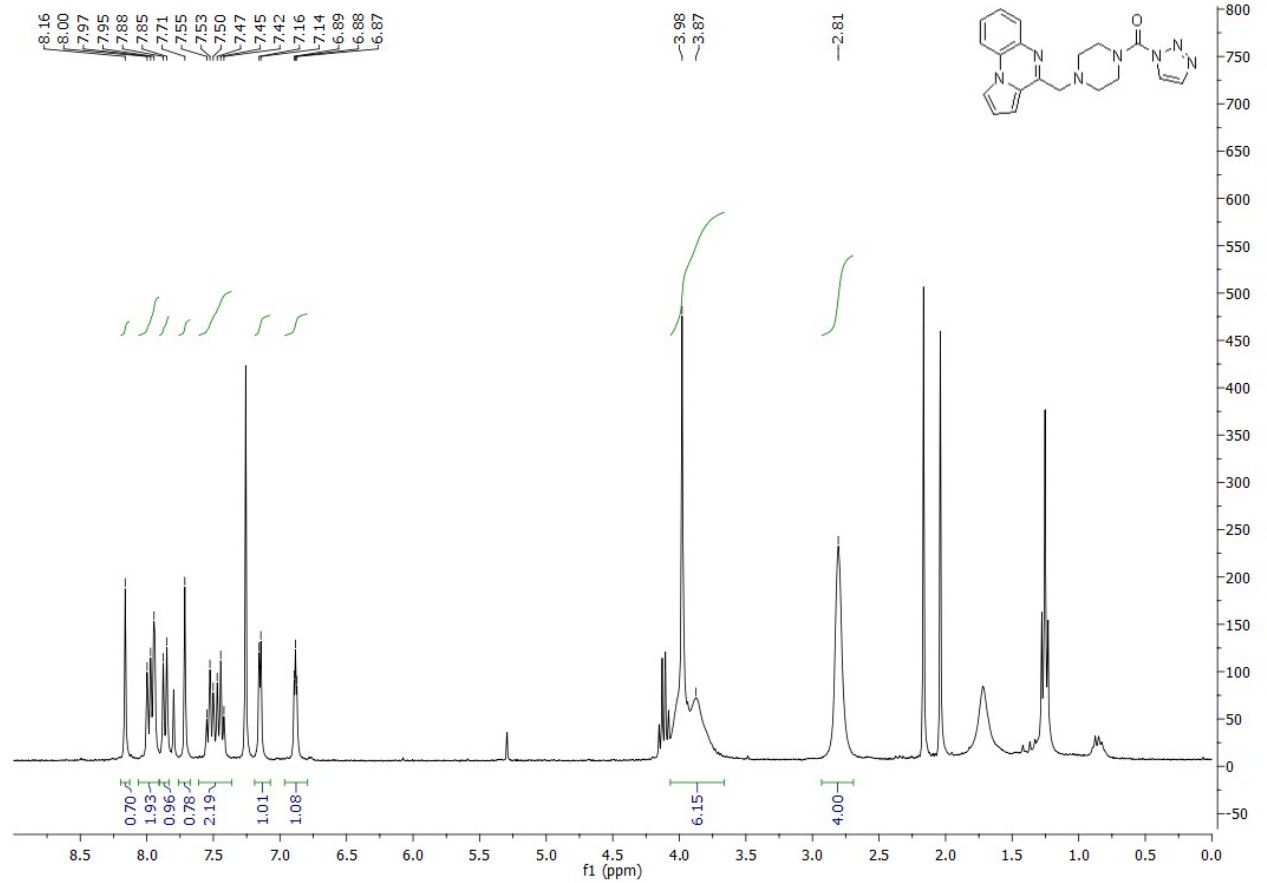
125.44
114.56
113.98
113.87
107.35
62.52
53.63
53.37
f1 (ppm)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7.71
7.55
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7.50
7.47
7.45
7.42
7.16
7.14
6.89
6.88
6.87
3.98
3.87
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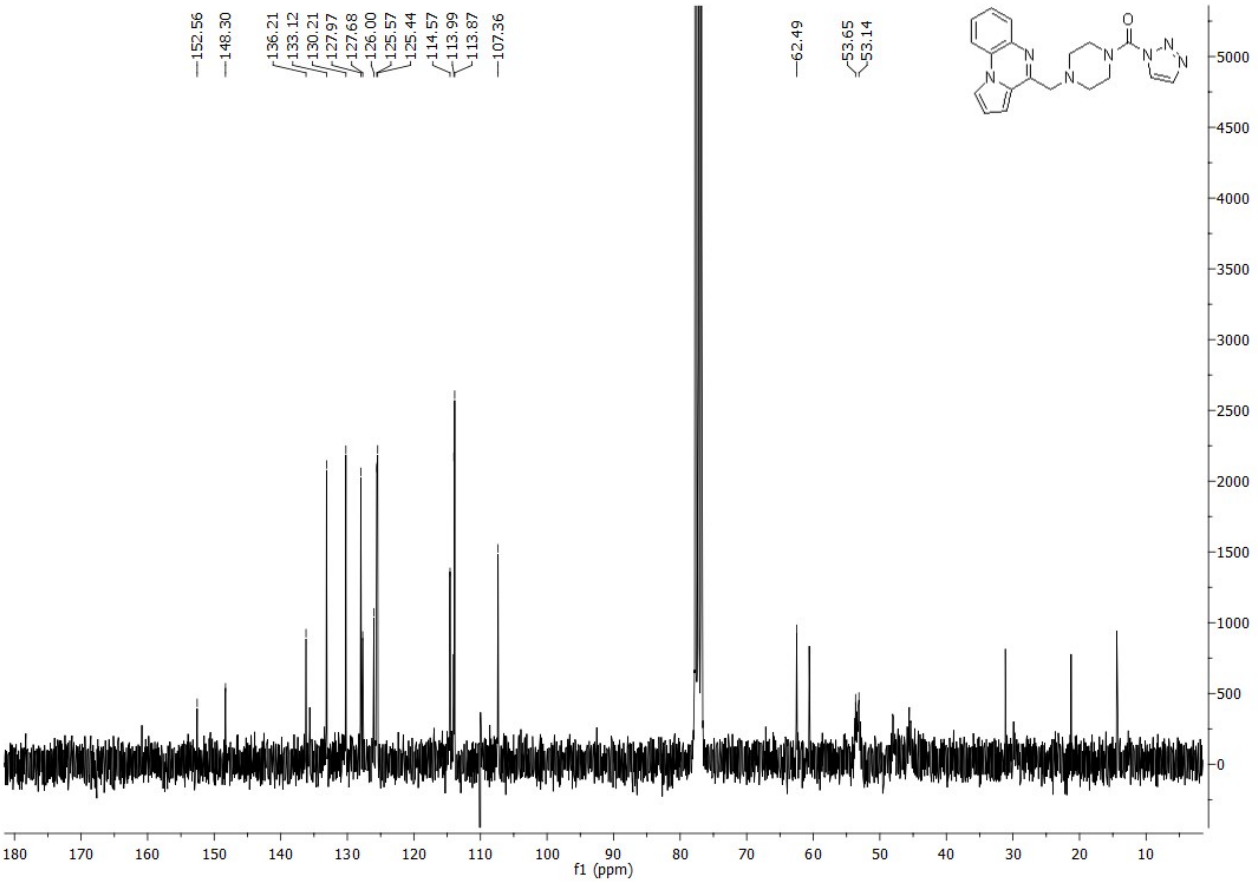
1.93
0.96
0.78
2.19
1.01
1.08
6.15
4.00
f1 (ppm)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136.21
133.12
130.21
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125.44
114.57
113.99
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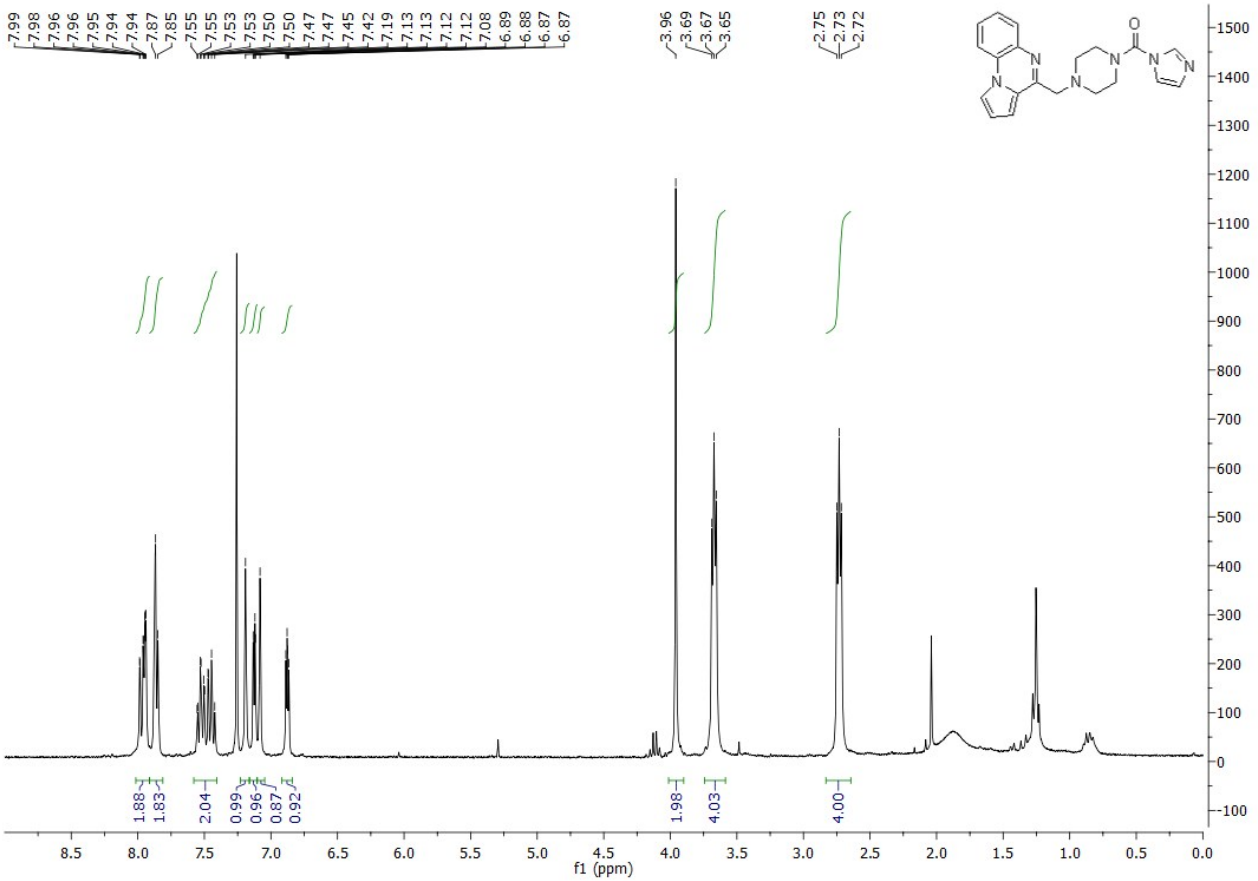
107.36
62.49
53.65
53.14
f1 (ppm)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7.98
7.96
7.96
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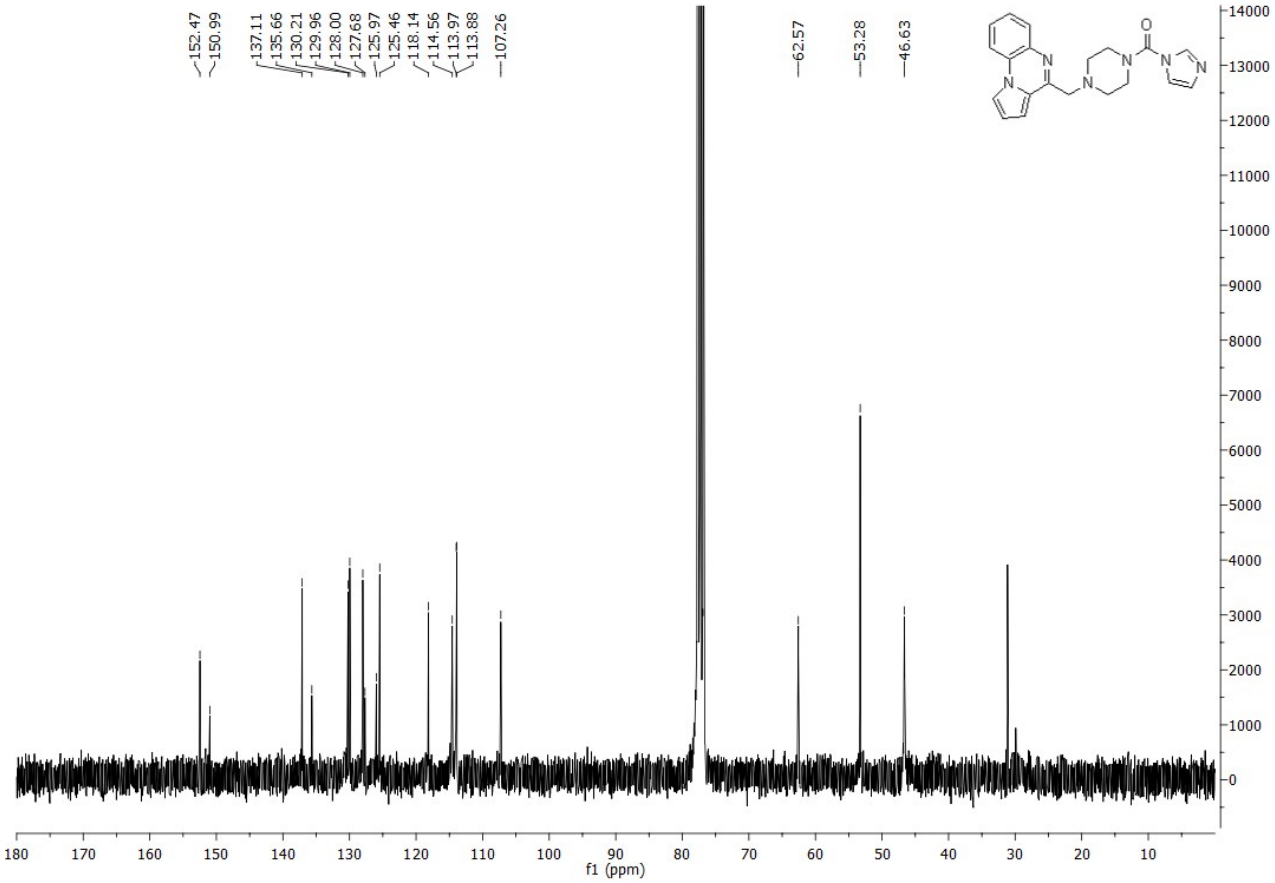
7.94
7.94
7.87
7.85
7.55
7.55
7.53
7.53
7.50
7.50
7.47
7.47
7.45
7.42
7.19
7.13
7.12
7.12
7.08
6.89
6.88
6.87
6.87
3.96
3.69
3.67
3.65
2.75
2.73
2.72
1.88
1.83
2.04
0.99
0.96
0.87
0.92
1.98
4.03
4.00
f1 (ppm)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129.96
128.00
127.68
125.97
125.46
118.14
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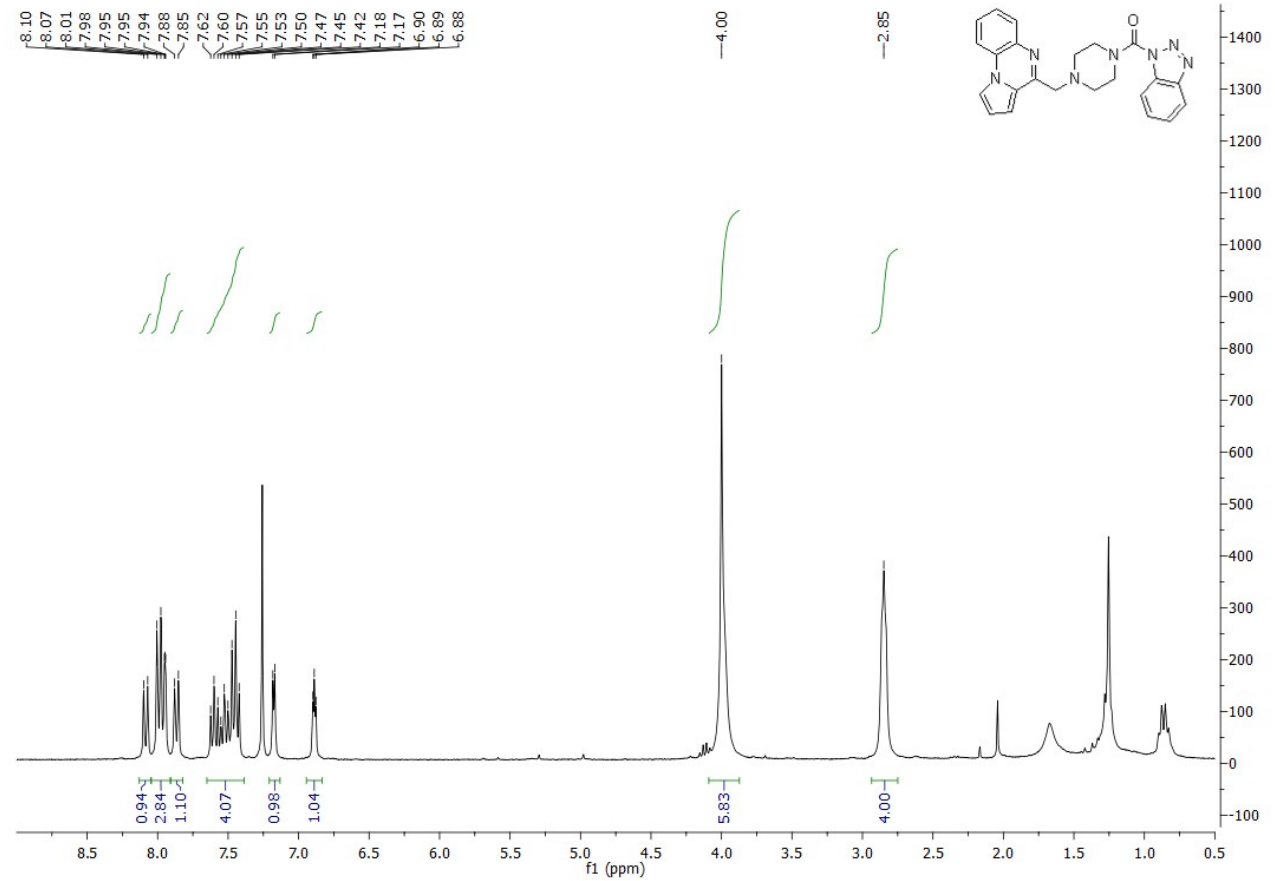
113.97
113.88
107.26
62.57
53.28
46.63
f1 (ppm)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8.07
8.01
7.98
7.95
7.95
7.94
7.88
7.85
7.62
7.60
7.57
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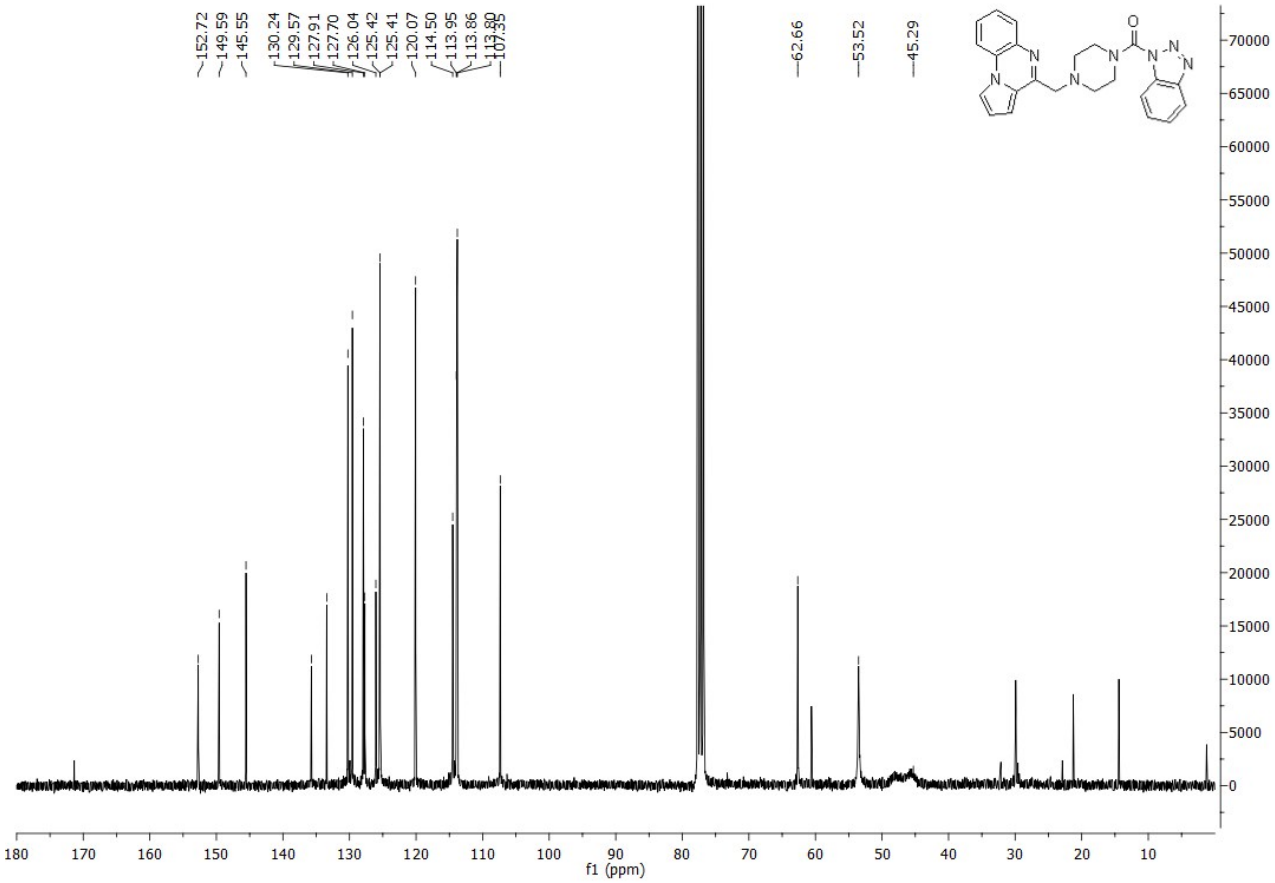
7.53
7.50
7.47
7.45
7.42
7.18
7.17
6.90
6.89
6.88
4.00
2.85
0.94
2.84
1.10
4.07
0.98
1.04
5.83
4.00
f1 (ppm)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125.41
120.07
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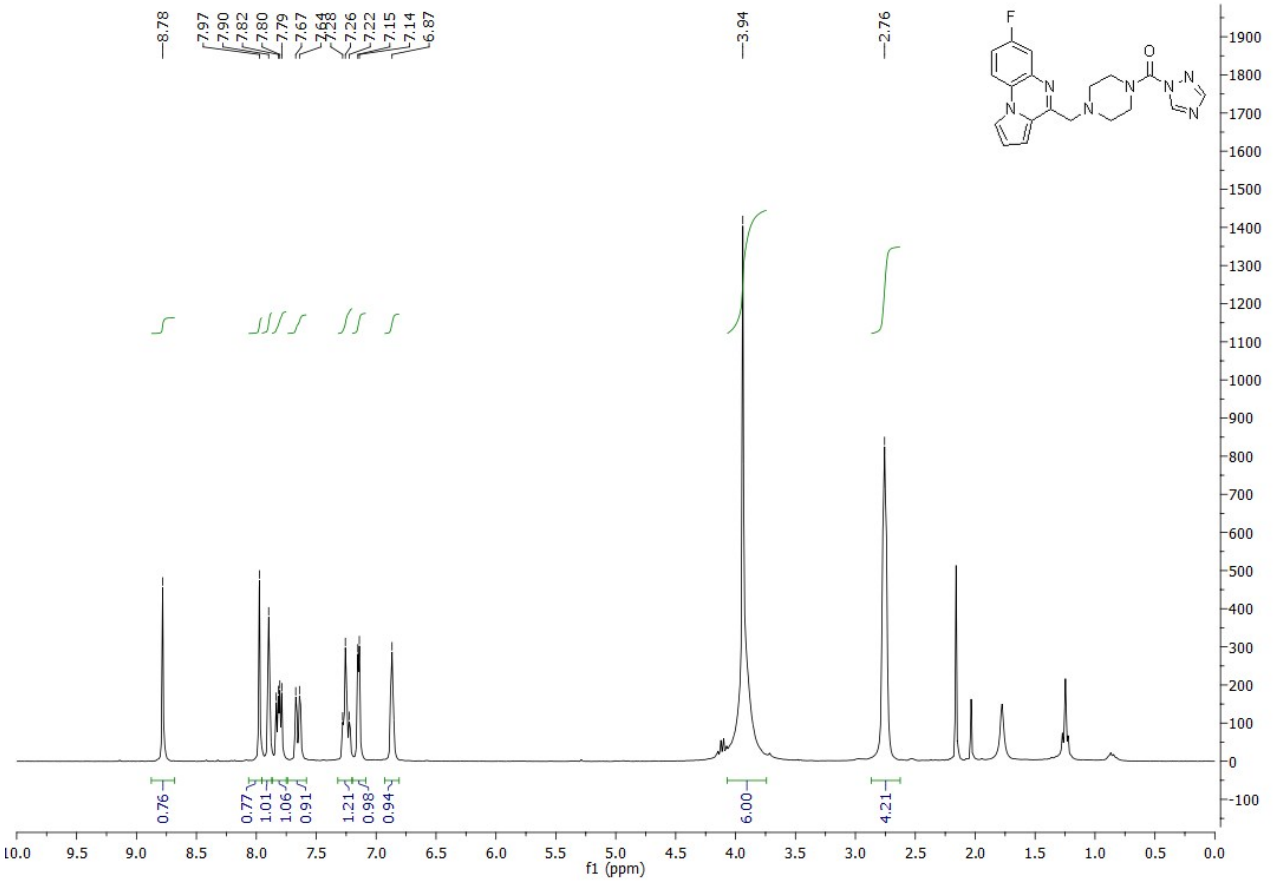
113.95
113.86
62.66
53.52
45.29
f1 (ppm)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7.79
7.67
7.64
7.28
7.26
7.22
7.15
7.14
6.87
3.94
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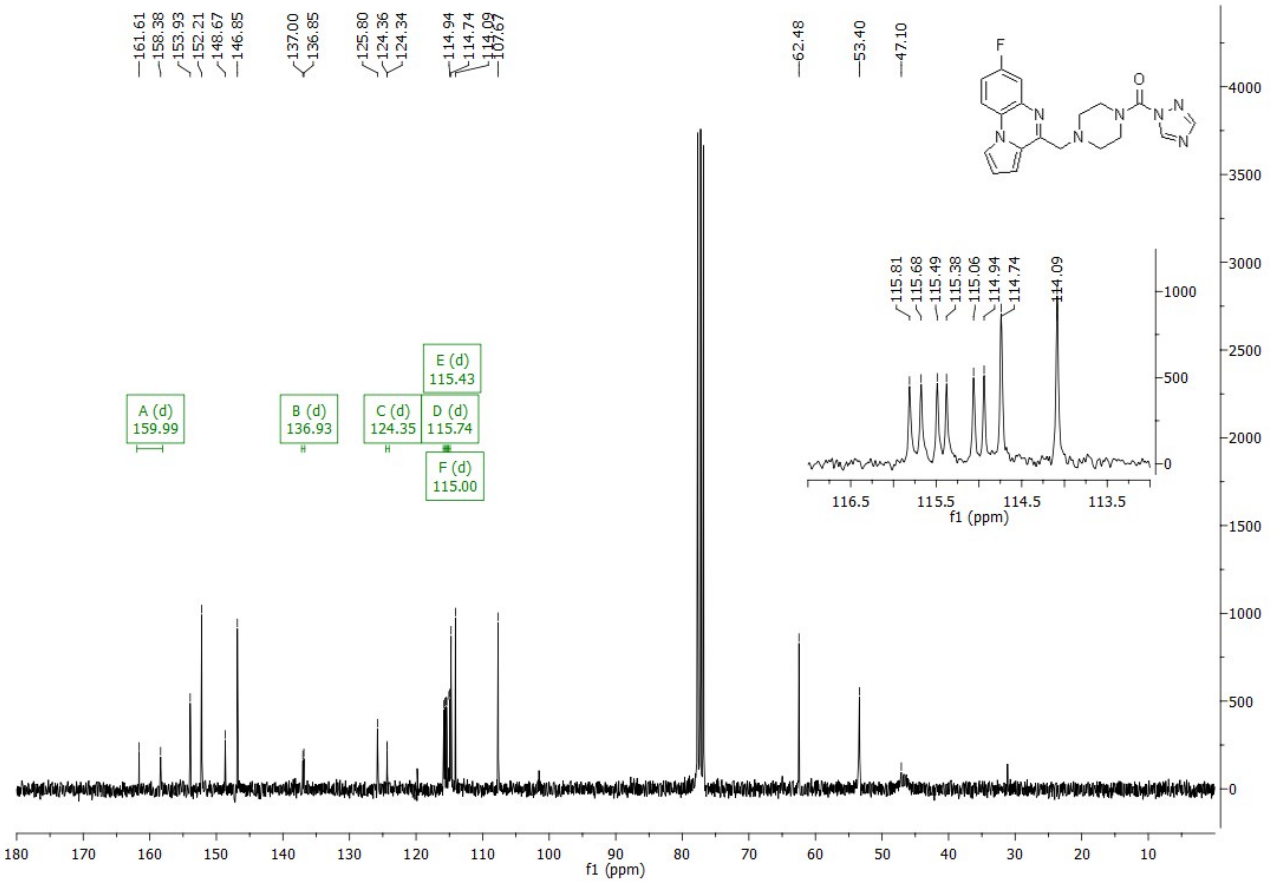
0.76
0.77
1.01
1.06
0.91
1.21
0.98
0.94
6.00
4.21
f1 (ppm)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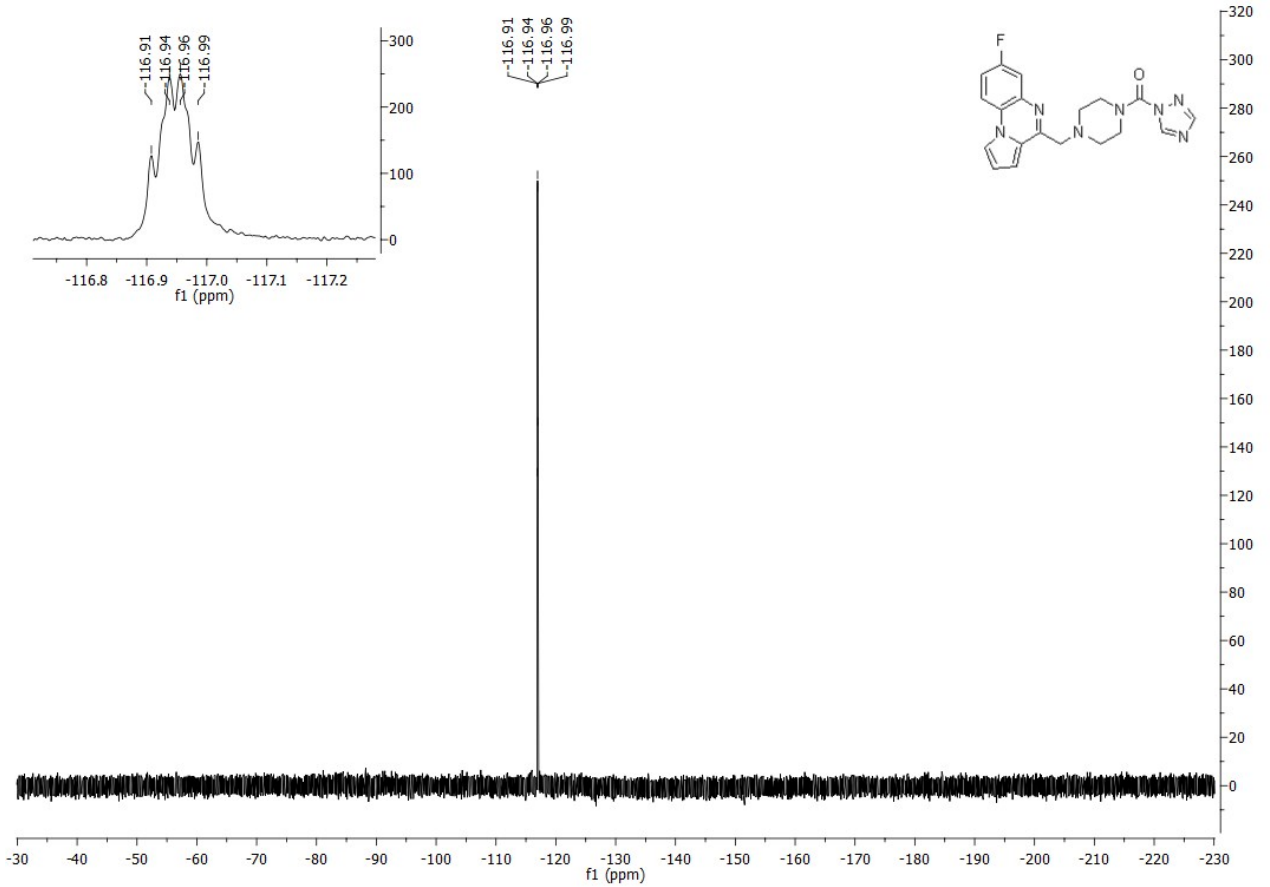
136.85
125.80
124.36
124.34
114.94
114.74
114.09
107.67
62.48
53.40
47.10
A (d) 159.99
B (d) 136.93
C (d) 124.35
D (d) 115.74
E (d) 115.43
F (d) 115.00
115.81
115.68
115.49
115.38
115.06
114.94
114.74
114.09
f1 (ppm)
f1 (ppm)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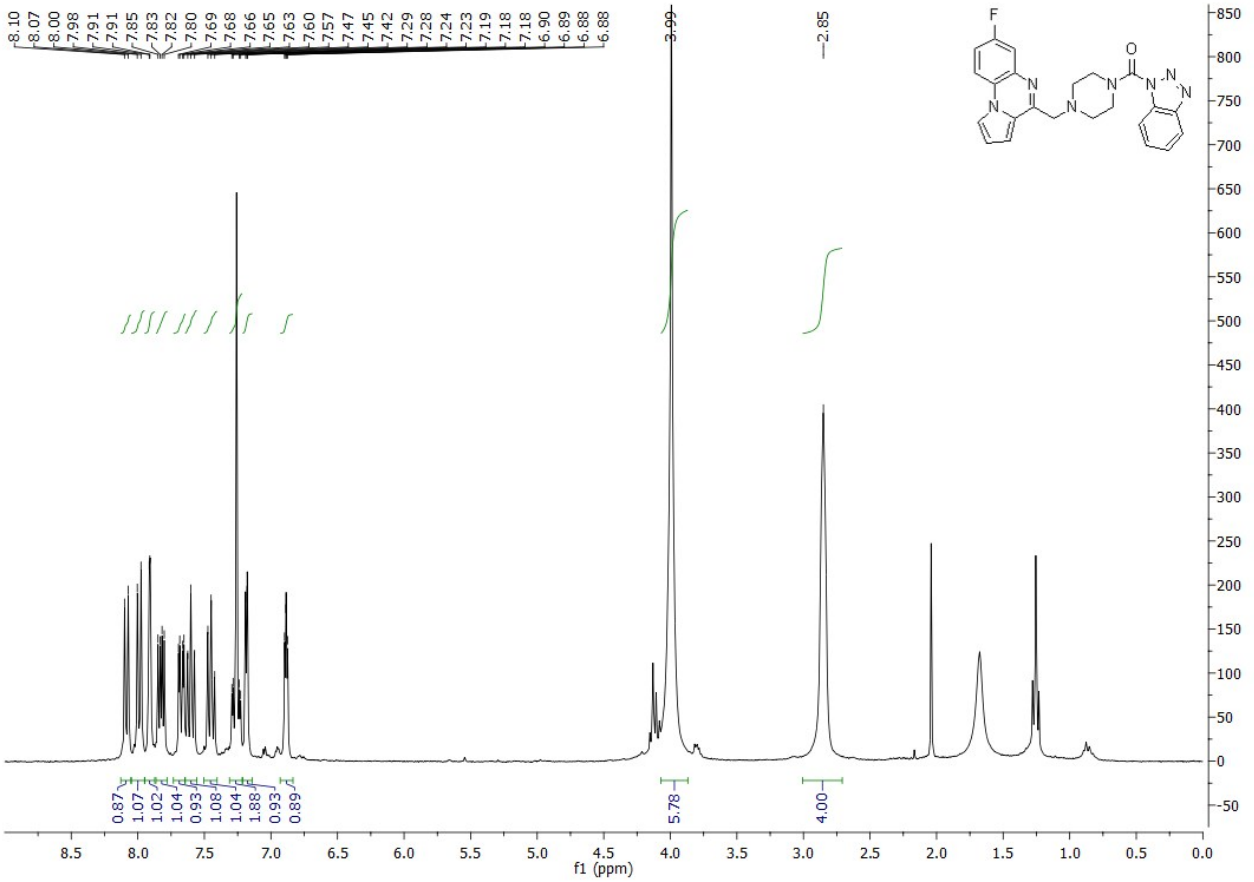
116.94
116.96
116.99
f1 (ppm)
f1 (ppm)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8.00
7.98
7.91
7.91
7.85
7.83
7.82
7.80
7.69
7.68
7.66
7.65
7.63
7.60
7.57
7.47
7.45
7.42
7.29
7.28
7.24
7.23
7.19
7.18
7.18
6.90
6.89
6.88
6.88
3.99
2.85
0.87
1.07
1.02
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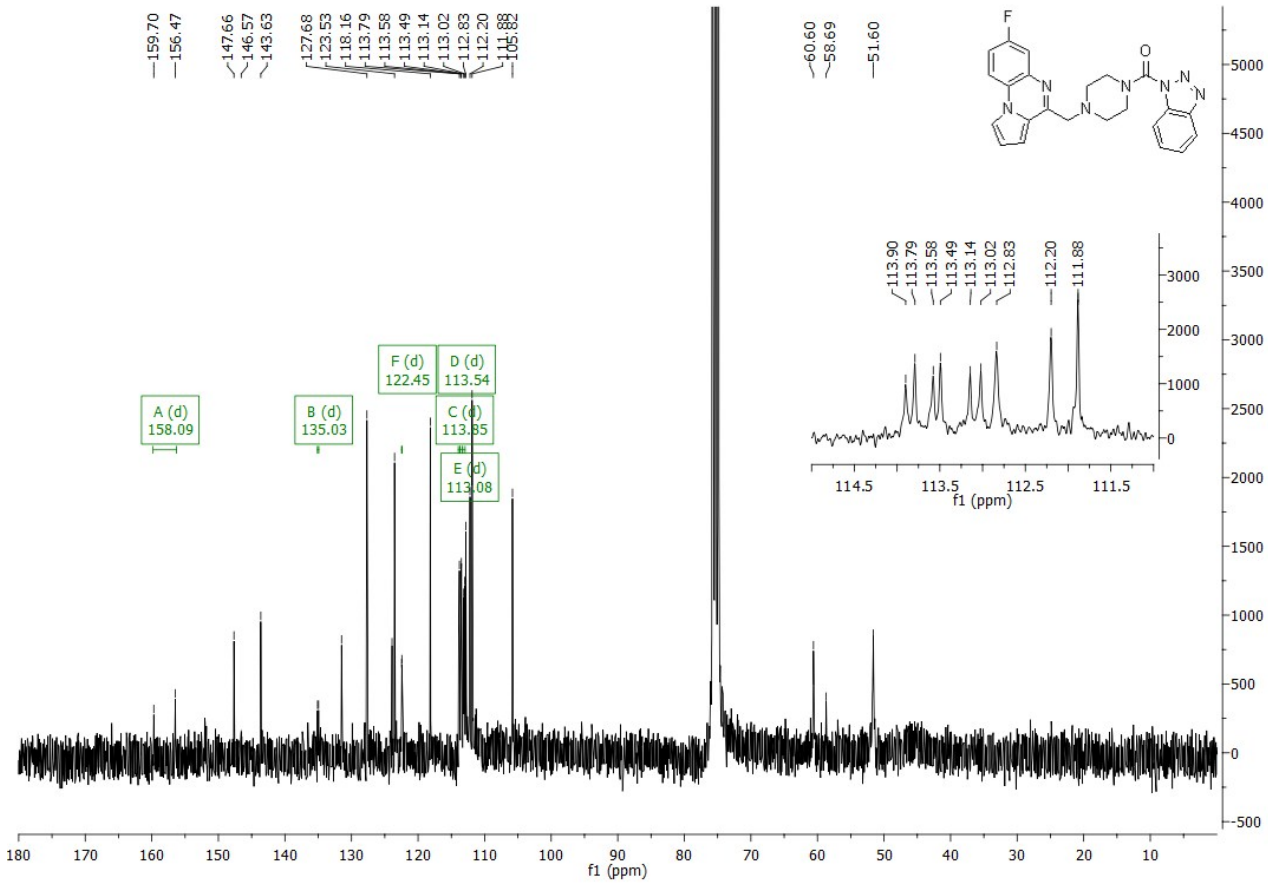
0.93
1.08
1.04
1.88
0.93
0.89
5.78
4.00
f1 (ppm)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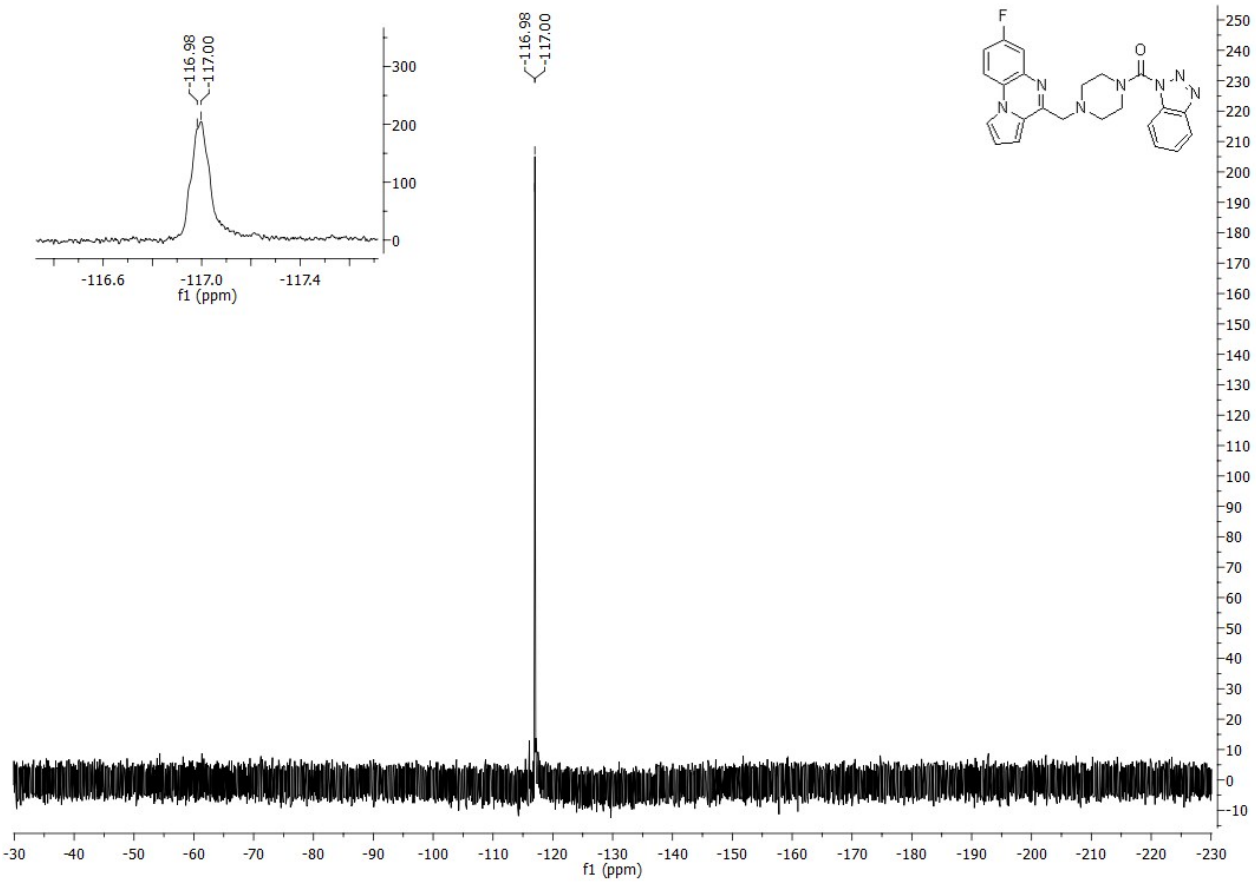
127.68
123.53
118.16
113.79
113.58
113.49
113.14
113.02
112.83
112.20
111.88
105.82
60.60
58.69
51.60
A (d)
158.09
B (d)
135.03
F (d)
122.45
D (d)
113.54
C (d)
113.35
E (d)
113.08
f1 (ppm)


-116.98
-117.00
-116.6
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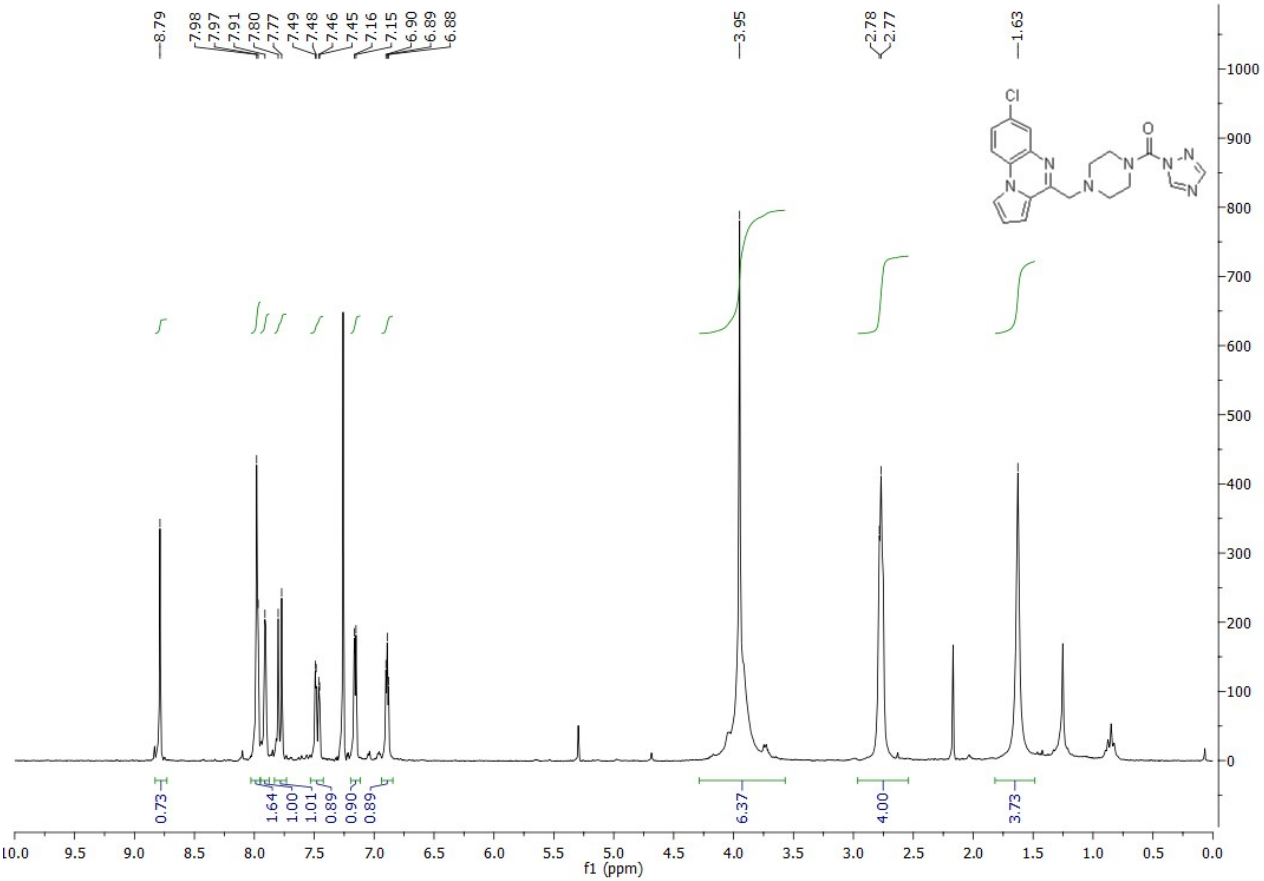
-117.4
f1 (ppm)
F
O
N
N
N
N
N
N
N
f1 (ppm)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7.80
7.77
7.49
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7.46
7.45
7.16
7.15
6.90
6.89
6.88
3.95
2.78
2.77
1.63
Cl
O
N
N
N
N
N
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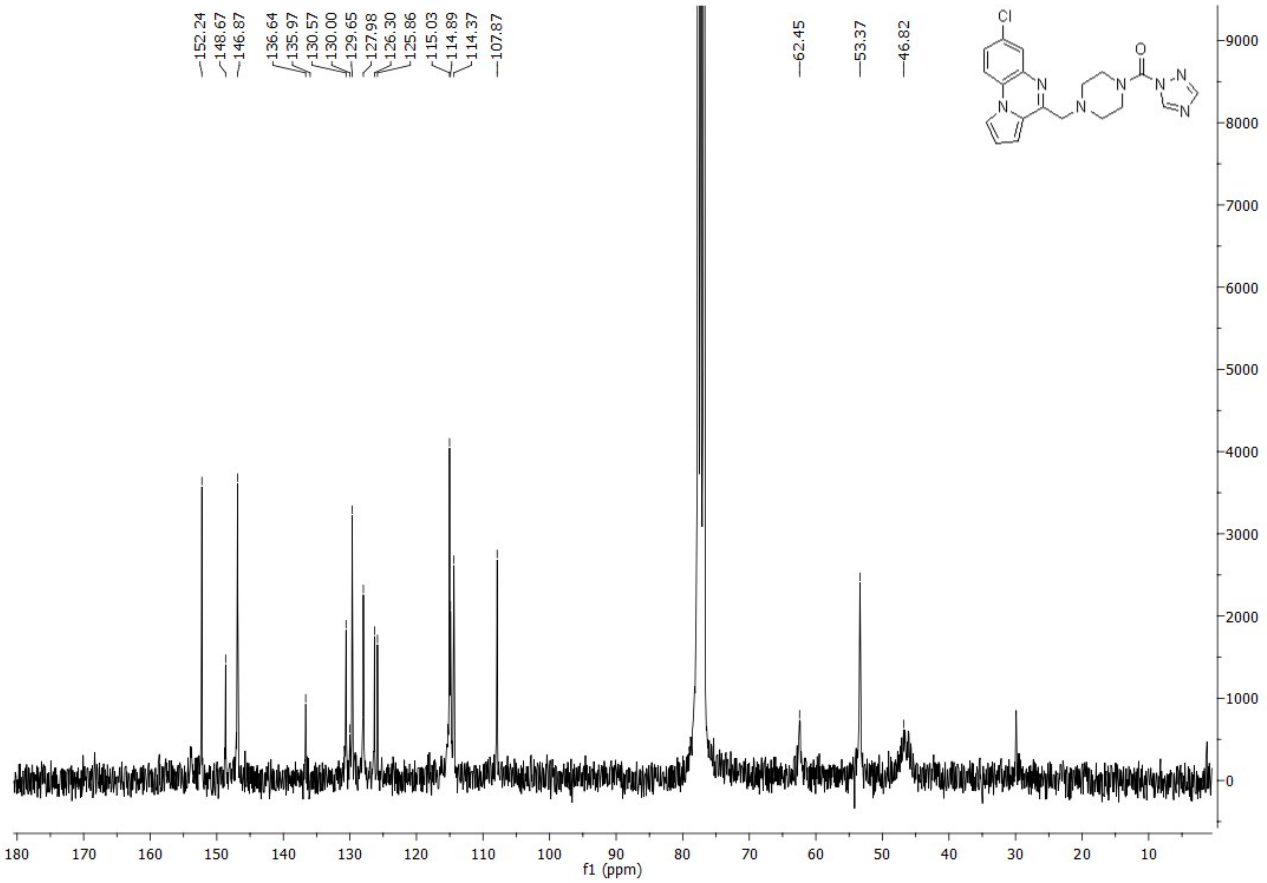
1.00
1.01
0.89
0.90
0.89
6.37
4.00
3.73
f1 (ppm)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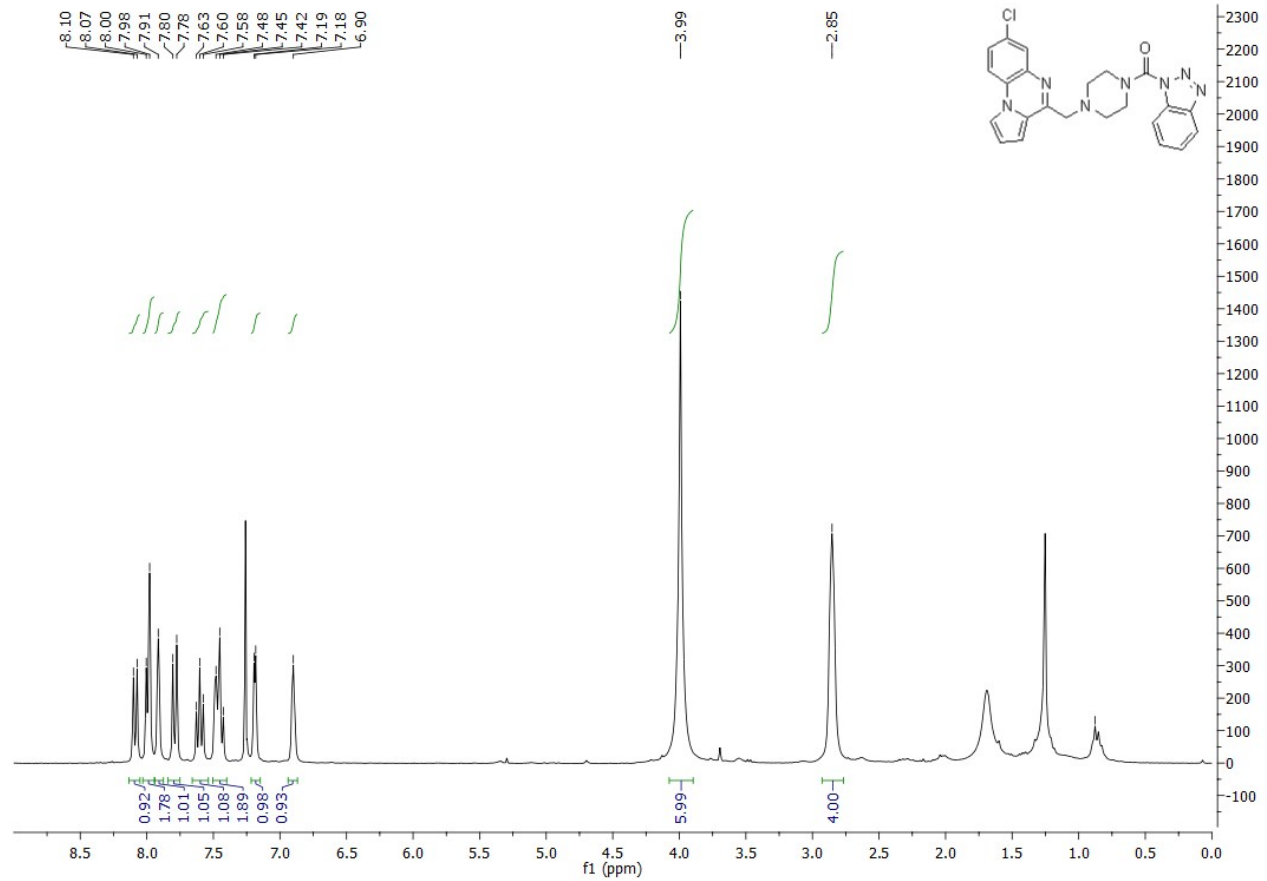
107.87
62.45
53.37
46.82
Cl
O
N
f1 (ppm)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7.91
7.80
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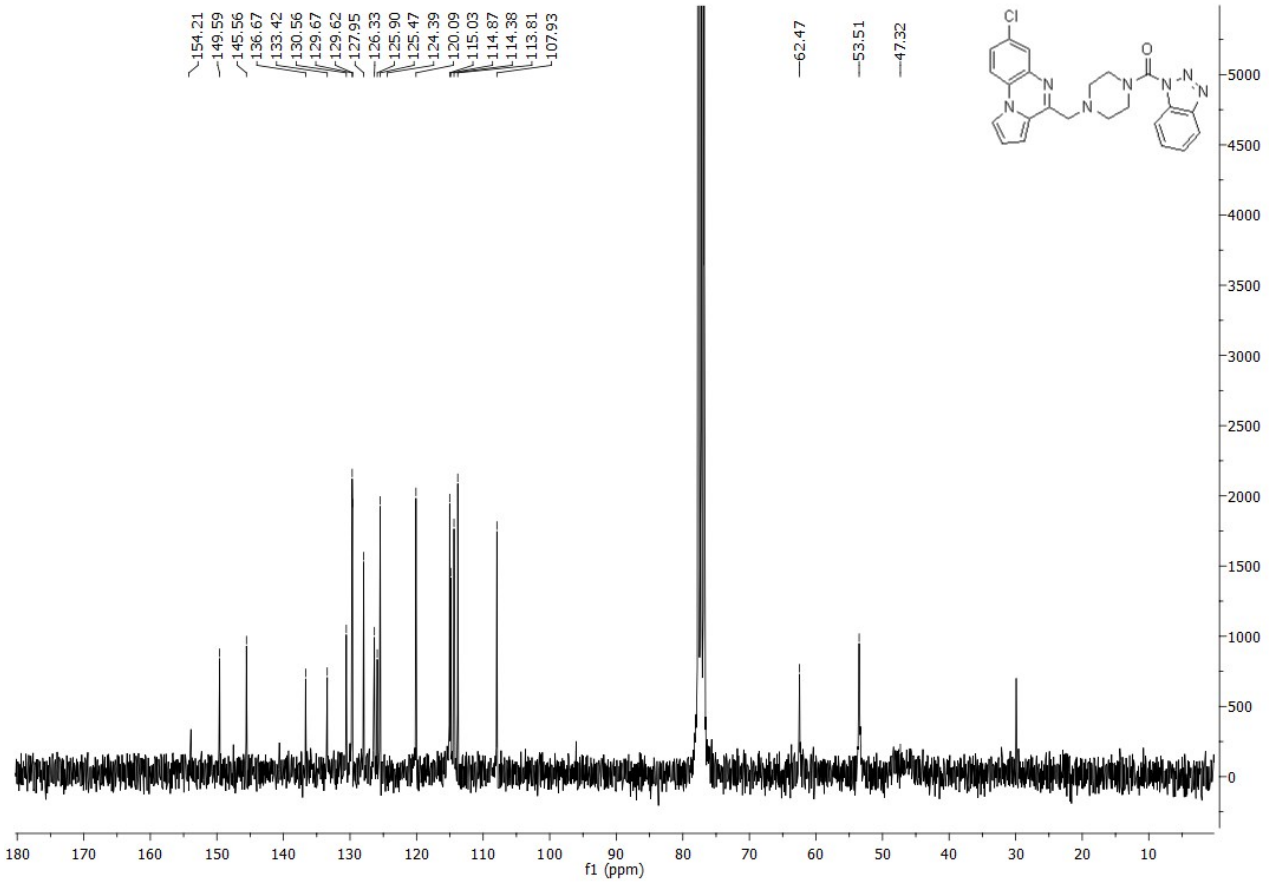
7.63
7.60
7.58
7.48
7.45
7.42
7.19
7.18
6.90
3.99
2.85
Cl
O
N
0.92
1.78
1.01
1.05
1.08
1.89
0.98
0.93
5.99
4.00
f1 (ppm)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125.47
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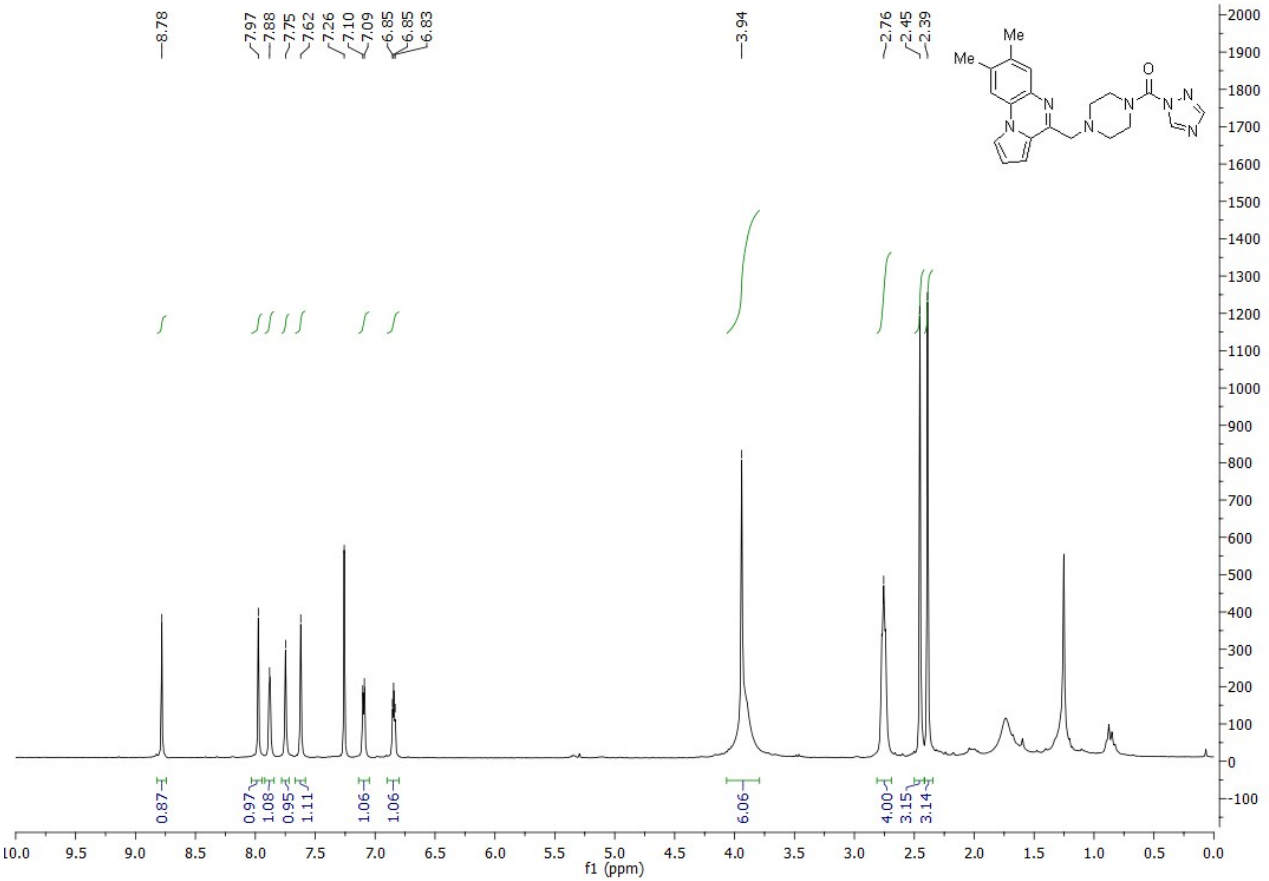
113.81
107.93
62.47
53.51
47.32
Cl
f1 (ppm)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7.26
7.10
7.09
6.85
6.85
6.83
3.94
2.76
2.45
2.39
Me
Me
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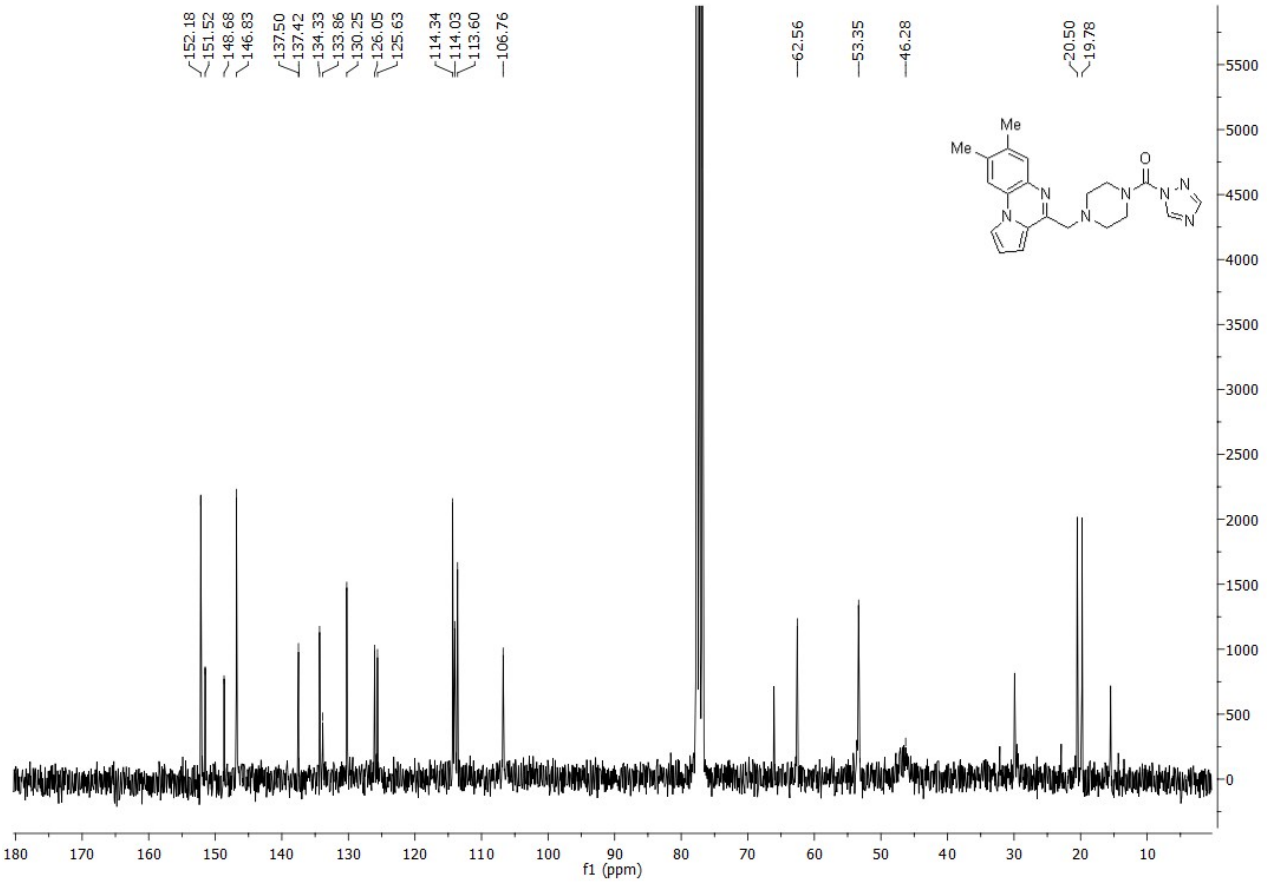
0.97
1.08
0.95
1.11
1.06
1.06
6.06
4.00
3.15
3.14
f1 (ppm)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133.86
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126.05
125.63
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106.76
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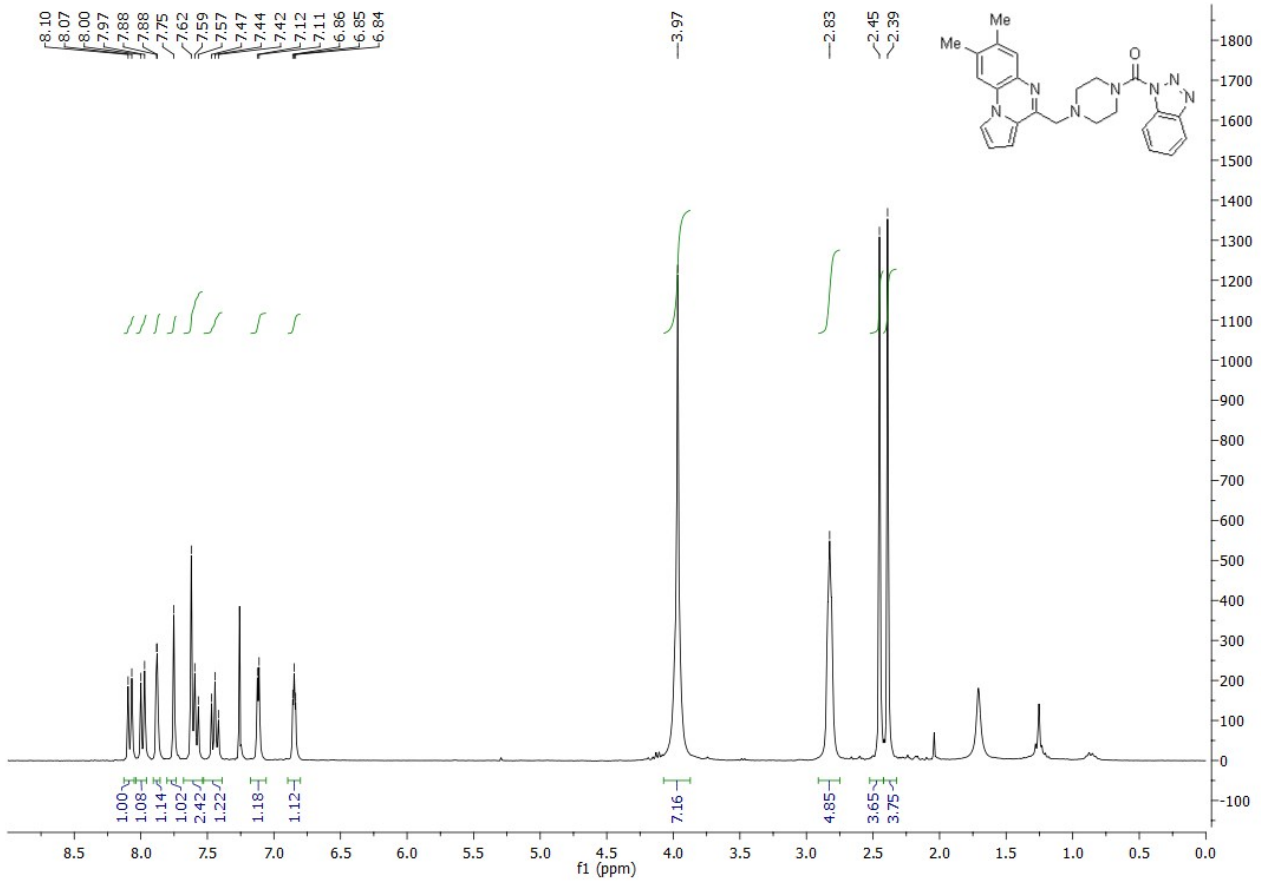
53.35
46.28
20.50
19.78
Me
Me
O
f1 (ppm)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7.59
7.57
7.47
7.44
7.42
7.12
7.11
6.86
6.85
6.84
3.97
2.83
2.45
2.39
Me
Me
O
1.00
1.08
1.14
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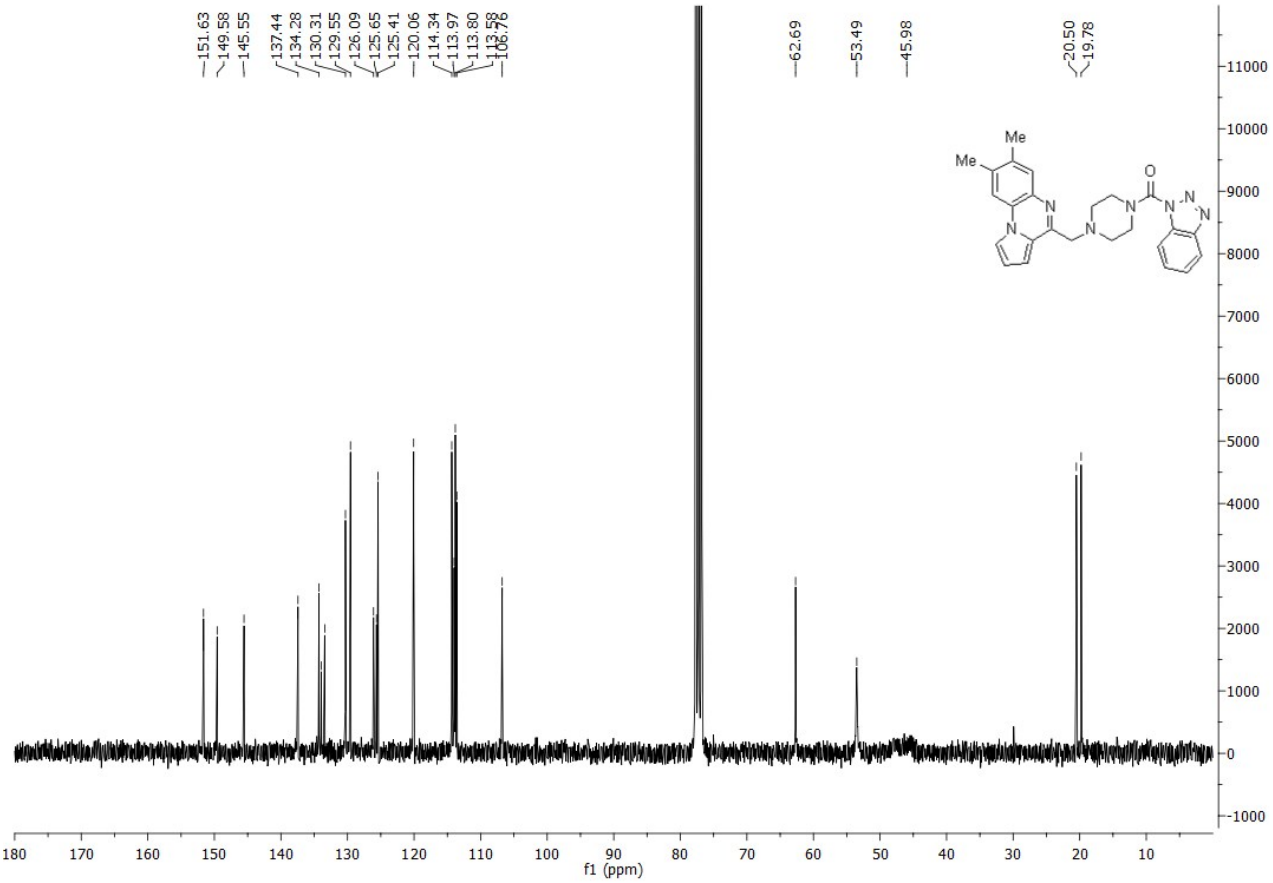
2.42
1.22
1.18
1.12
7.16
4.85
3.65
3.75
f1 (ppm)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125.41
120.06
114.34
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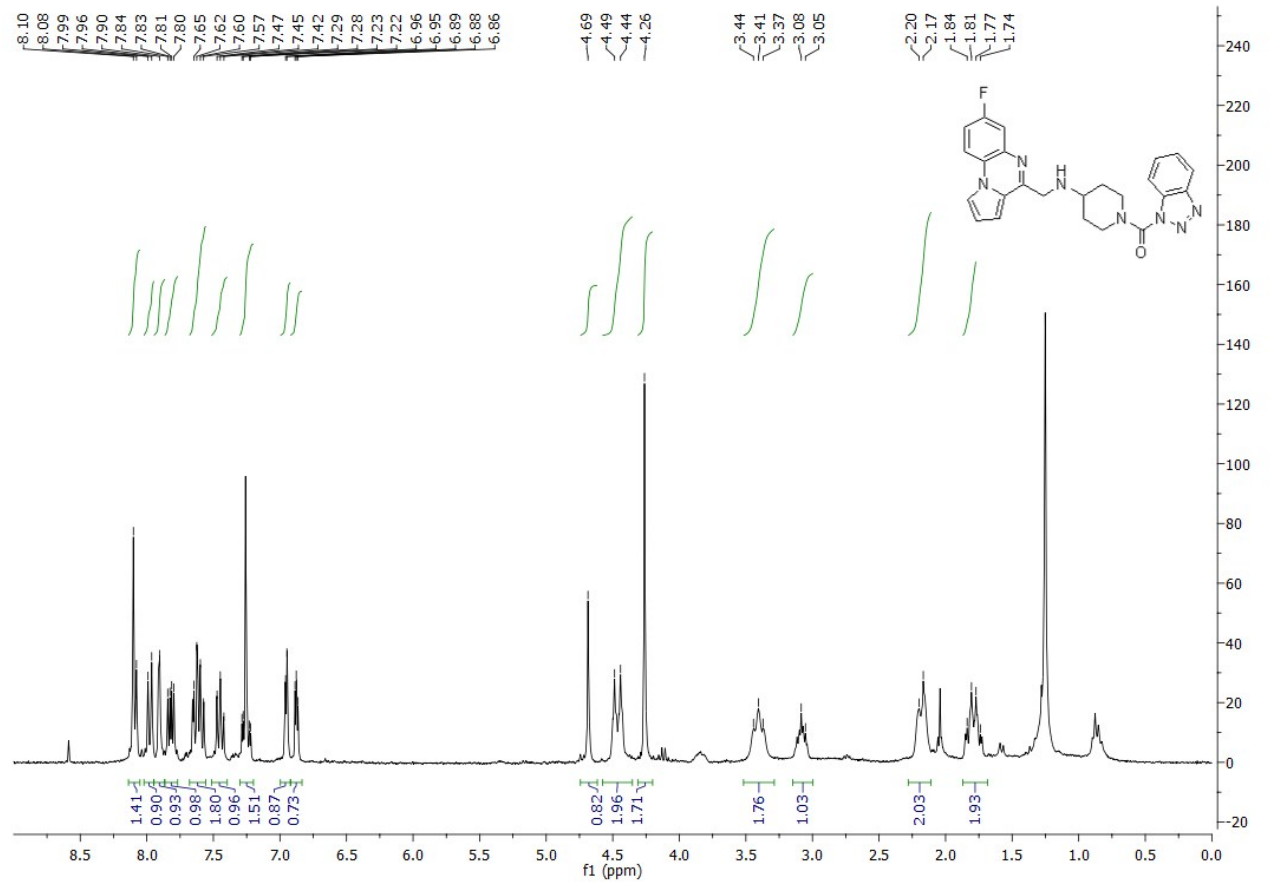
108.76
62.69
53.49
45.98
20.50
19.78
Me
Me
O
f1 (ppm)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8.08
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7.81
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7.57
7.47
7.45
7.42
7.29
7.28
7.23
7.22
6.96
6.95
6.89
6.88
6.86
4.69
4.49
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4.26
3.44
3.41
3.37
3.08
3.05
2.20
2.17
1.84
1.81
1.77
1.74
F
H
O
1.41
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0.93
0.98
1.80
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1.96
1.71
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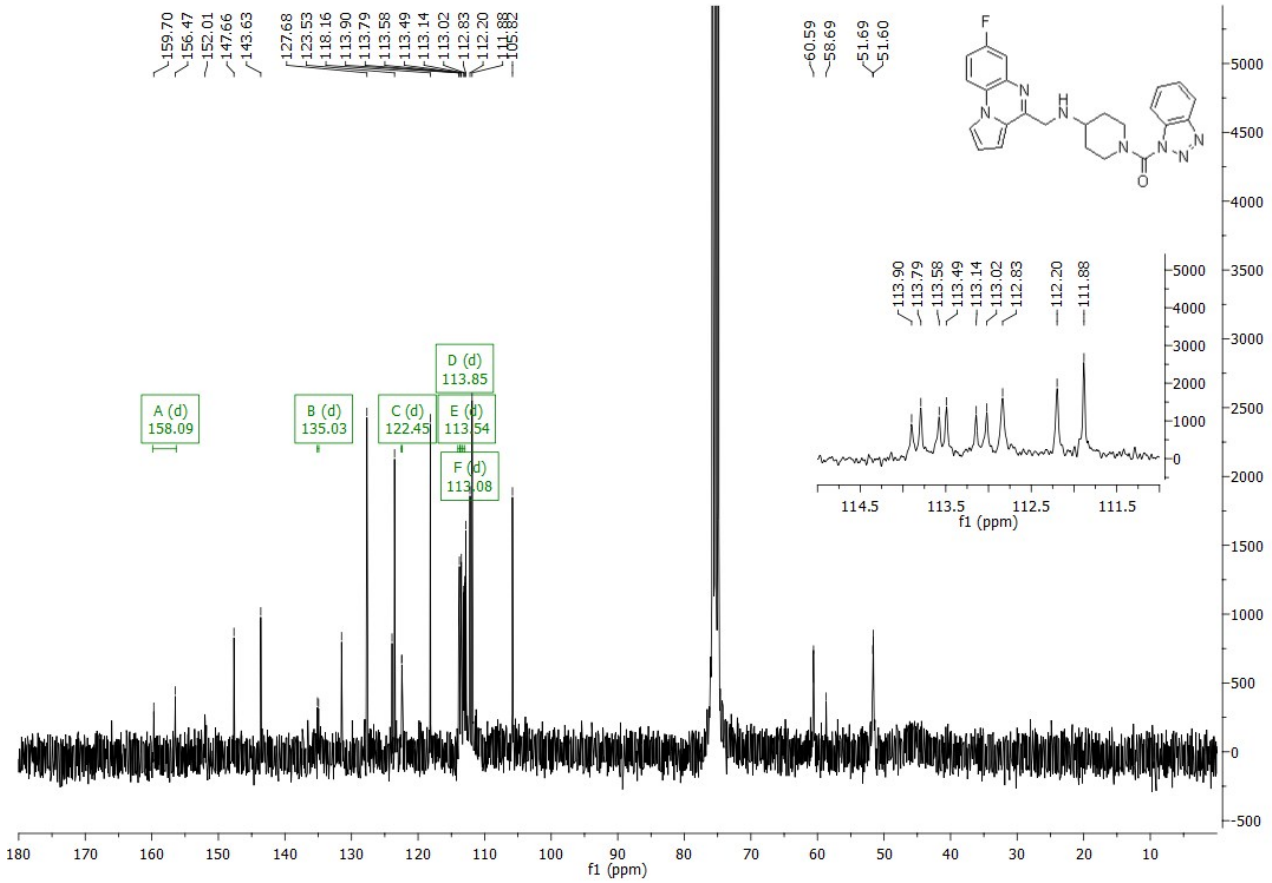
1.03
2.03
1.93
f1 (ppm)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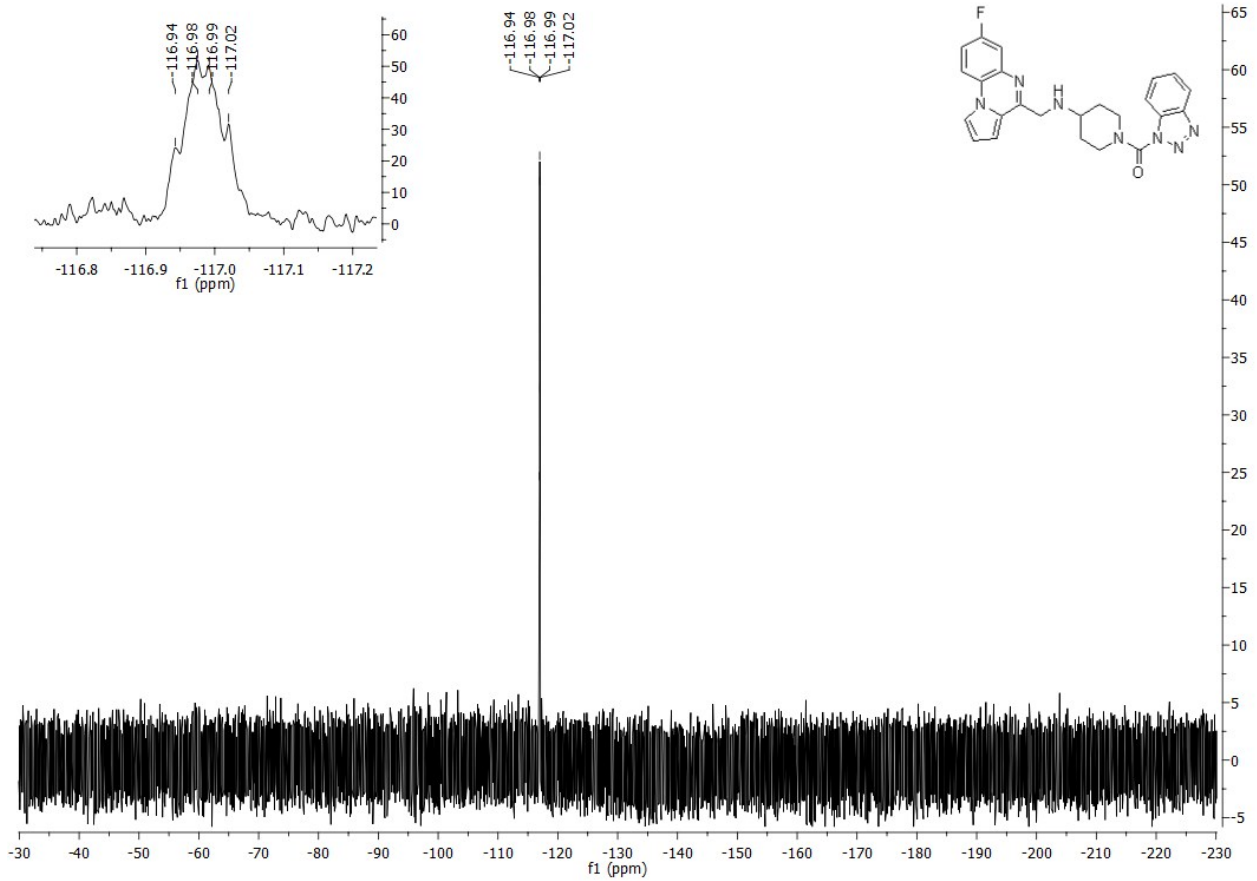
112.83
112.20
111.88
105.82
60.59
58.69
51.69
51.60
A (d)
158.09
B (d)
135.03
C (d)
122.45
D (d)
113.85
E (d)
113.54
F (d)
113.08
f1 (ppm)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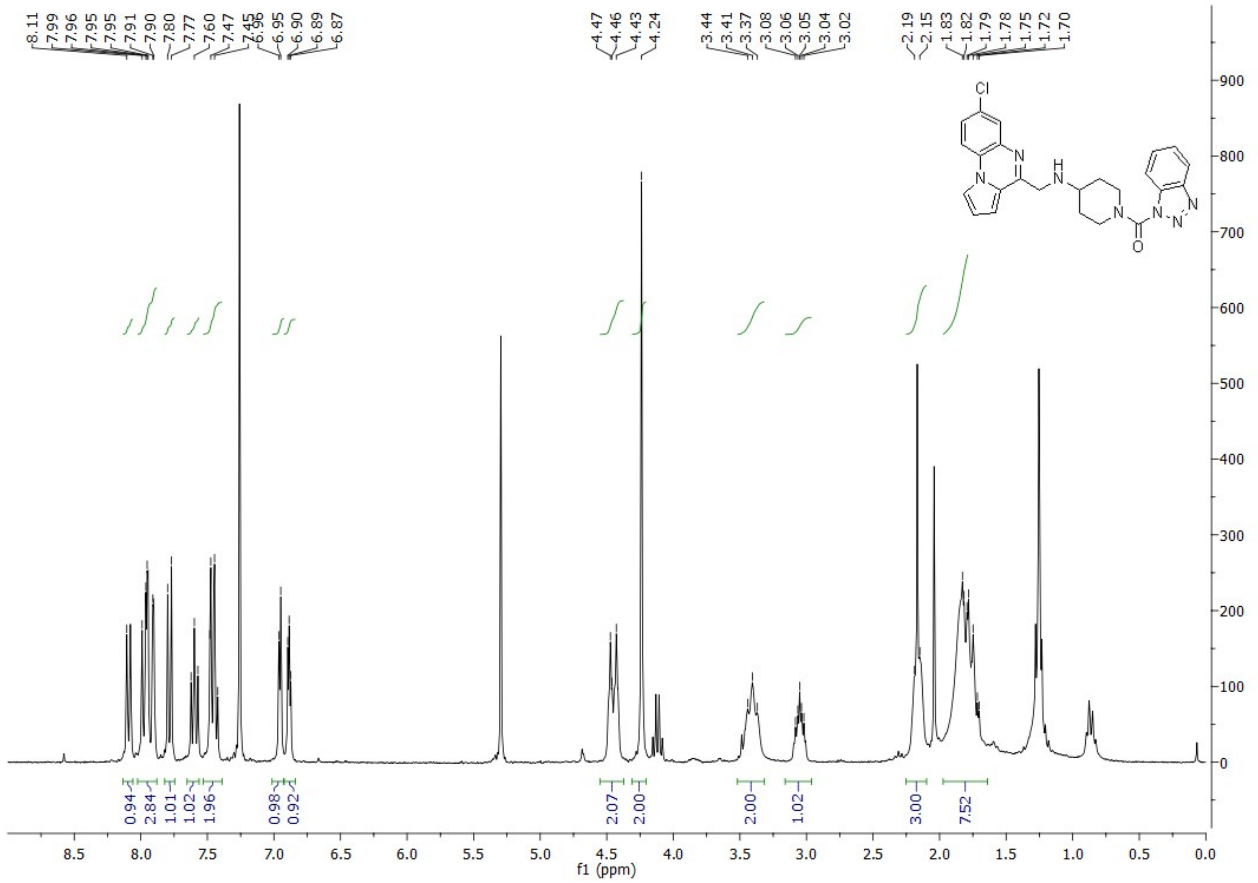
-116.98
-116.99
-117.02
f1 (ppm)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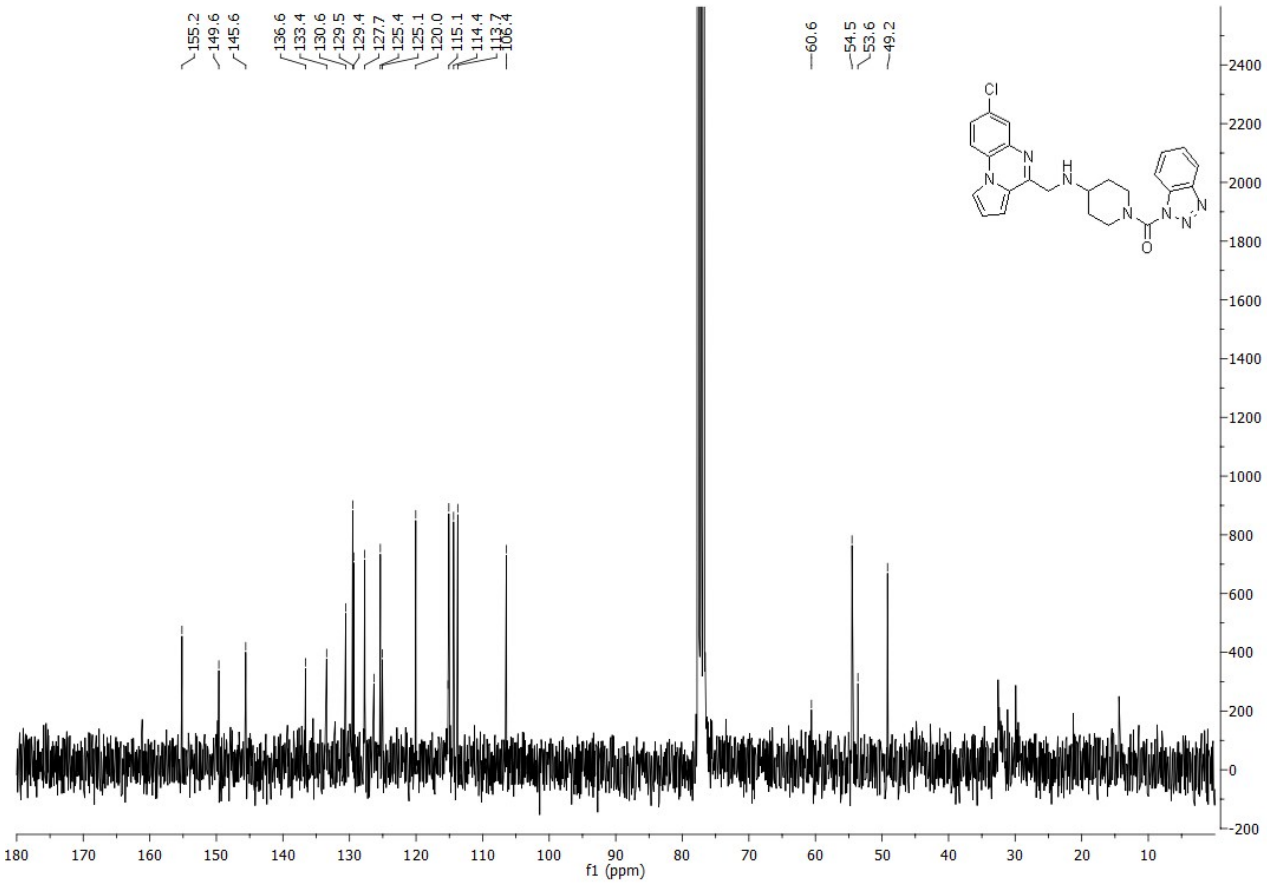
7.99
7.96
7.95
7.95
7.91
7.90
7.80
7.77
7.60
7.47
7.45
6.96
6.95
6.90
6.89
6.87
4.47
4.46
4.43
4.24
3.44
3.41
3.37
3.08
3.06
3.05
3.04
3.02
2.19
2.15
1.83
1.82
1.79
1.78
1.75
1.72
1.70
Cl
N
H
O
0.94
2.84
1.01
1.02
1.96
0.98
0.92
2.07
2.00
2.00
1.02
3.00
7.52
f1 (ppm)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149.6
145.6
136.6
133.4
130.6
129.5
129.4
127.7
125.4
125.1
120.0
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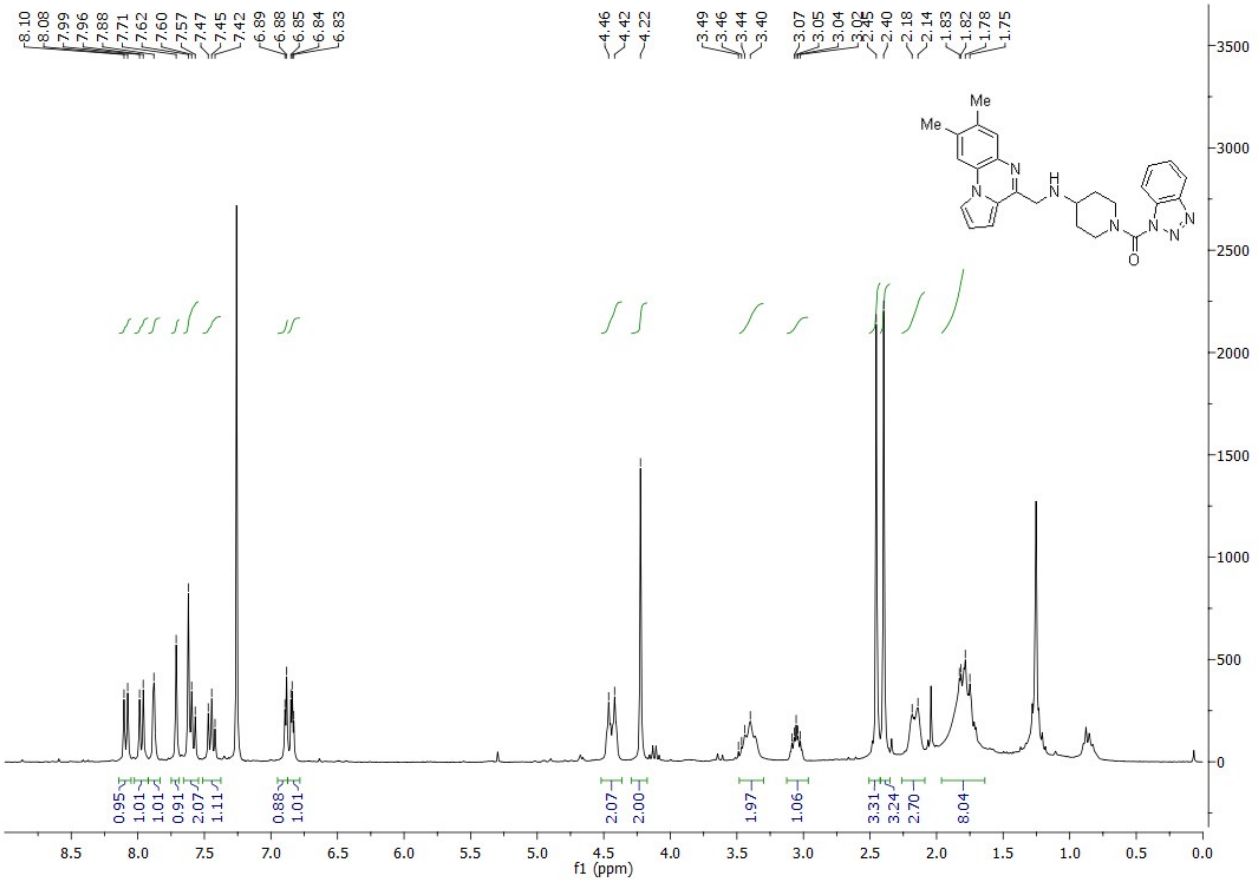
114.4
113.7
106.4
60.6
54.5
53.6
49.2
Cl
N
H
O
f1 (ppm)


8.10
8.08
7.99
7.96
7.88
7.71
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7.57
7.47
7.45
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6.85
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6.83
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4.42
4.22
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3.46
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3.40
3.07
3.05
3.04
3.02
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2.40
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1.78
1.75
Me
Me
N
H
N
N
N
N
O
3500
3000
2500
2000
1500
1000
500
0
0.95
1.01
1.01
0.91
2.07
1.11
0.88
1.01
2.07
2.00
1.97
1.06
3.31
3.24
2.70
8.04
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

Table S1. Physico-chemical properties for **5d, 5e, 5i, 5j, 5m** and the reference compounds **1** and **2** as calculated by using QikProp and cytotoxicity/genotoxicity prediction by using Toxicity Estimation Software Tool (TEST) distributed by US Environmental Protection Agency (EPA) (https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test)

Cmpd	QPlogP[a]	QPlogS[b]	QPPCaco[c]	QPlogBB[d]	QPPMDCK[e]	HOA[f]	Oral rat LD_{50} (mg/kg)[g]	Mutagenicity (AMES test)[g]
5d	3.45	-4.83	104.60	-0.86	47.69	3	1775.3	Negative
5e	1.52	-1.84	122.07	-0.27	144.16	3	1051.4	Negative
5i	1.76	-2.18	121.60	-0.16	187.31	3	2036.4	Negative
5j	3.22	-4.14	247.43	0.04	332.91	3	2745.0	Negative
5m	2.14	-2.94	119.02	-0.33	101.87	3	1142.9	Negative
1	4.84	-6.14	1700.33	-0.25	1373.98	3	710.7	Negative
2	4.12	-5.18	128.31	-0.90	59.48	3	617.93	Positive

[a]QPlogP predicted octanol/water partition coefficient (range or recommended value for 95%of known drugs -2 - 6.5); [b]QPlogS predicted aqueous solubility in mol/dm^3(range -6.5 - 0.5); [c]QPPCaco predicted apparent Caco-2 cell permeability in nm/sec (range < 25 poor > 500 great); [d]QPlogBB predicted brain/blood partition coefficient (range -3 - 1.2); [e]QPPMDCK predicted apparent MDCK cell permeability in nm/sec (range < 25 poor > 500 great); [f]HOA predicted qualitatively human oral absorption: 1, 2, and 3 for low, medium or high respectively. Range or recommended values are reported in QikProp user manual; [g]Calculations were performed adopting consensus method.

Table S2. Elemental Analysis

Compound	Formula	Calcd			Found		
		C	H	N	C	H	N
5a	$C_{24}H_{24}N_4O_2$	71.98	6.04	13.99	71.91	6.15	13.87
5b	$C_{24}H_{25}N_5O$	72.16	6.31	17.53	72.19	6.24	17.40
5c	$C_{23}H_{23}N_5O$	71.67	6.01	18.17	71.52	6.11	18.15
5d	$C_{23}H_{21}N_5O_4$	64.03	4.91	16.23	64.09	4.99	16.27
5e	$C_{19}H_{19}N_7O$	63.14	5.30	27.13	63.11	5.27	27.27
5f	$C_{19}H_{19}N_4O$	63.14	5.30	27.13	63.08	5.21	27.26
5g	$C_{20}H_{20}N_6O$	66.65	5.59	23.32	66.65	5.62	23.33
5h	$C_{23}H_{21}N_7O$	67.14	5.14	23.83	67.08	5.16	23.94
5i	$C_{19}H_{18}FN_7O$	60.15	4.78	25.84	60.25	4.75	25.77
5j	$C_{23}H_{20}FN_7O$	64.33	4.69	22.83	64.38	4.69	22.80
5k	$C_{19}H_{18}ClN_7O$	57.65	4.58	24.77	57.60	4.55	24.70
5l	$C_{23}H_{20}ClN_7O$	61.95	4.52	21.99	61.99	4.48	21.93
5m	$C_{21}H_{23}N_7O$	64.76	5.95	25.18	64.75	5.90	25.21
5n	$C_{25}H_{25}N_7O$	68.32	5.73	22.31	68.39	5.75	22.36
6a	$C_{24}H_{22}FN_7O$	65.00	5.00	22.11	65.11	4.98	22.24
6b	$C_{24}H_{22}ClN_7O$	62.67	4.82	21.32	62.55	4.74	21.30
6c	$C_{26}H_{27}N_7O$	68.85	6.00	21.62	68.91	6.05	21.53