Synthesis and In Vitro Antiprotozoan Evaluation of 4-/8-Aminoquinoline-Based Lactams and Tetrazoles

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TableS1: Yields and HPLC purity of the synthesised compounds

Compound	n	R'	R	Yield/[%]	HPLC Purity/[%][a]
4a	**1**	H	H	30	95.6
4b	**1**	H	OCH_3	9	95.6
4c	**1**	H	Me	6	94.6
4d	**1**	Cl	Cl	4	99.5
4e	**1**	H	Cl	14	99.2
4f*	**2**	H	H	5*	-*
4g	**3**	H	H	9	98
6a	**-**	H	H	21	99.3
6b	**-**	H	OCH_3	40	99.5
6c	**-**	H	CH_3	50	99.4
6d	**-**	Cl	Cl	17	99.5
6e	**-**	H	Cl	41	99.7

[a]HPLC Purity was determined as an area under a curve (λ = 220 and 254 nm);*This compound still contained traces of the Schiff bases even after extensive purification

Analytical and preparative HPLC experimental conditions:

HPLC mobile phase: All HPLC separations were performed using mobile phase A, an aqueous 10 mM ammonium bicarbonate solution at pH 11, mixed on-line with mobile phase B which consisted of 10 mM ammonium bicarbonate solution (pH 11) in 90% methanol (prepared from the same 100 mM ammonium bicarbonate pH 11 buffer stock solution; pH adjusted with 25 % ammonia solution).

Preparative HPLC conditions: Sample solutions for purification were prepared at *ca.* 50 mg/mL in methanol. Injection volumes ranged between 50 µL and 1 mL, depending on the sample, the mobile phase flow rate was 20 mL/min for all purifications and the column heater was set at 30°C. A linear mobile phase gradient was used, 60 % to 100 % mobile phase B over 9 min. (remain at 100 % B for 2 min.).

Analytical HPLC conditions: Solutions for analysis were prepared at *ca.* 1 mg/mL in methanol. Injection volume for all analyses was 20 µL, the mobile phase flow rate was 1.2 mL/min and the column temperature was maintained at 30 °C. A linear gradient was used, 20 % to 100 % mobile phase B over 9 min. (remain at 100 % B for 8 min.).

Instrumentation: Both analytical and preparative HPLC separations were performed on a modular Waters HPLC system (Microsep, Tygervalley, South Africa) consisting of a 2767 sample manager, 2545 quaternary gradient pump, 1500 series column heater and a 2998 photodiode array detector (PDA) with a Prep 2998 flowcell. MassLynx software (version 4.1) was used for instrument control and data acquisition, while FractionLynx software (version 4.1) was used to control the collection of HPLC fractions. A Waters Xbridge C_{18}, 4.6 x 150 mm column with 5 µm particles was used for the analytical scale HPLC analysis and a Waters Xbridge C_{18}, OBD 19 x 250 mm preparative HPLC column was used for the and purifications. Xbridge C_{18}, 5 µm, 4.6 x 20 mm and Xbridge C_{18}, 5 µm, 19 x 10 mm guard columns were connected to the inlets of the analytical and preparative HPLC columns respectively.

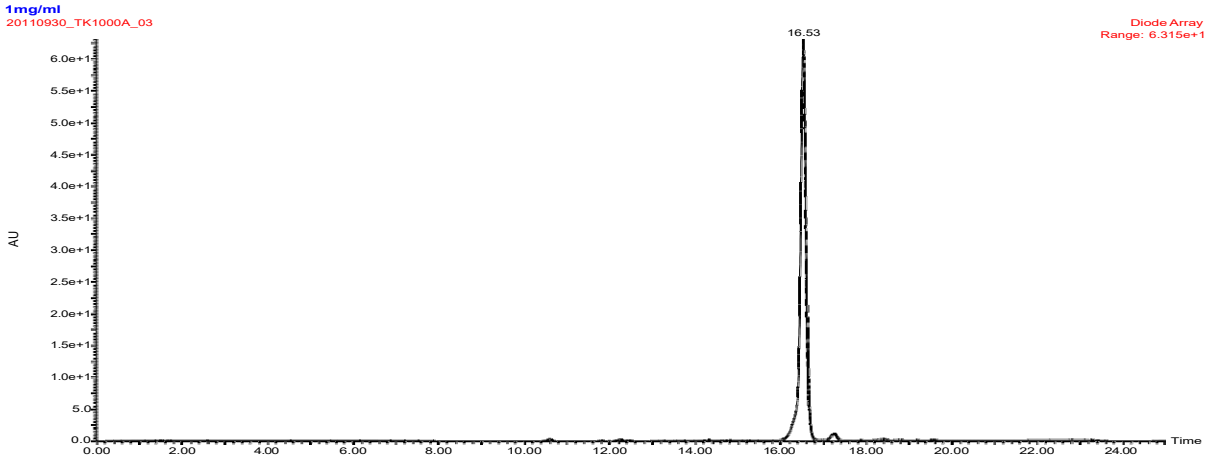


Figure S1: HPLC-PDA chromatogram of **6a**.

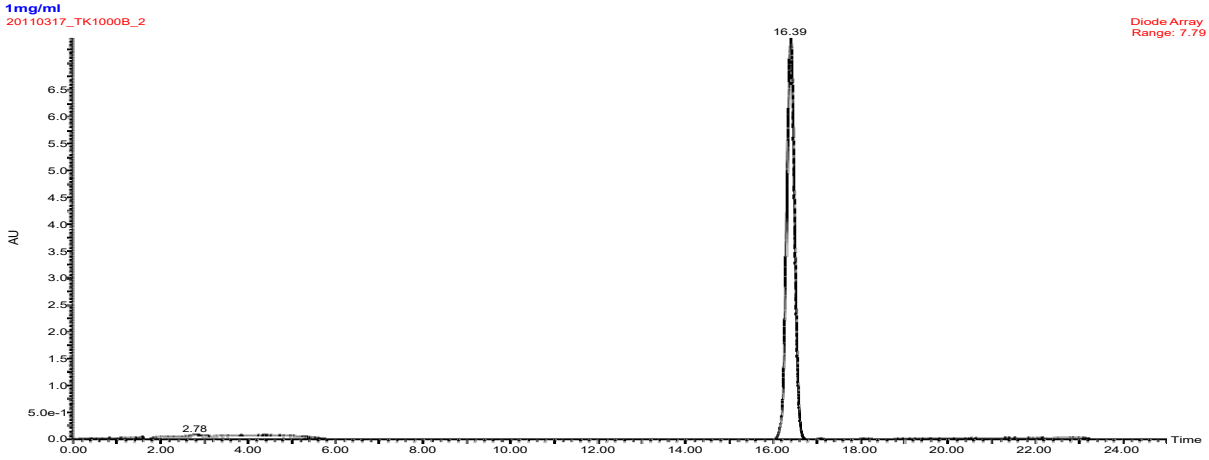


Figure S2: HPLC- PDA chromatogram of **6b**.

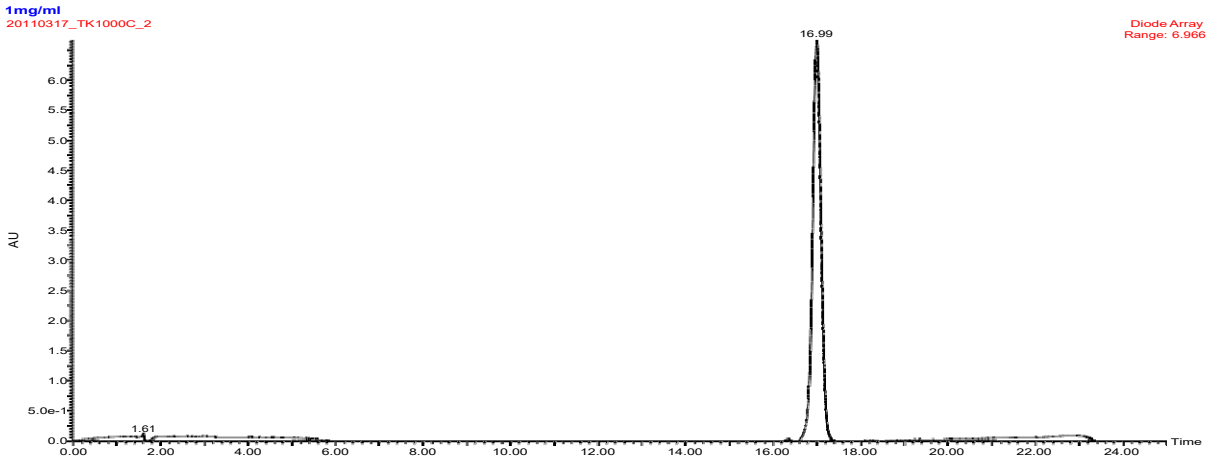


Figure S3: HPLC- PDA chromatogram of **6c**.

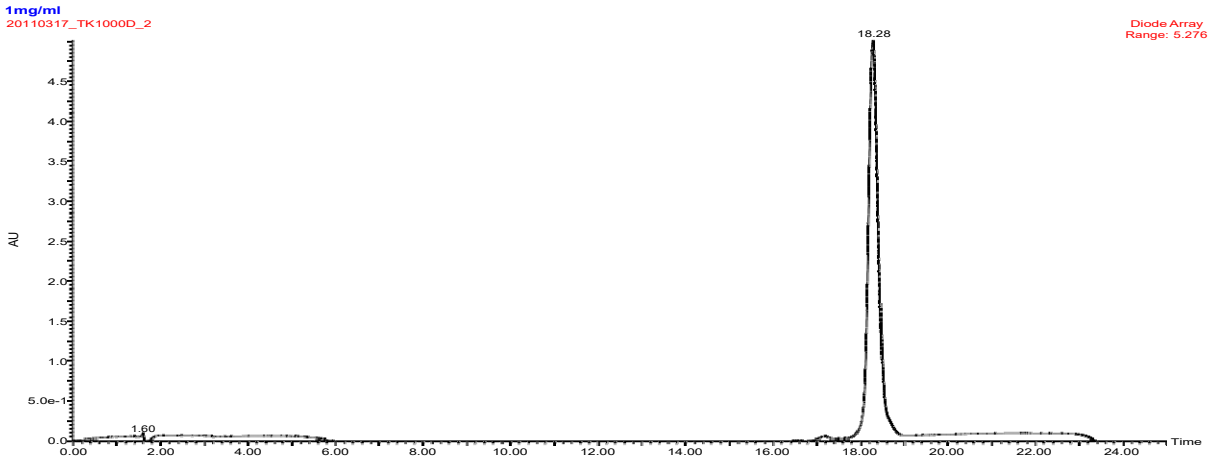


Figure S4: HPLC- PDA chromatogram of **6d**.

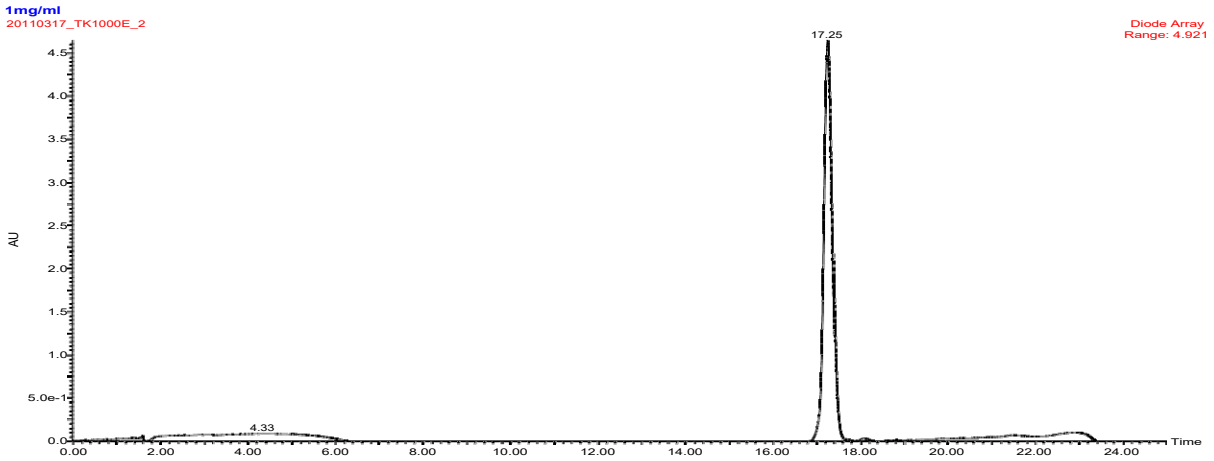
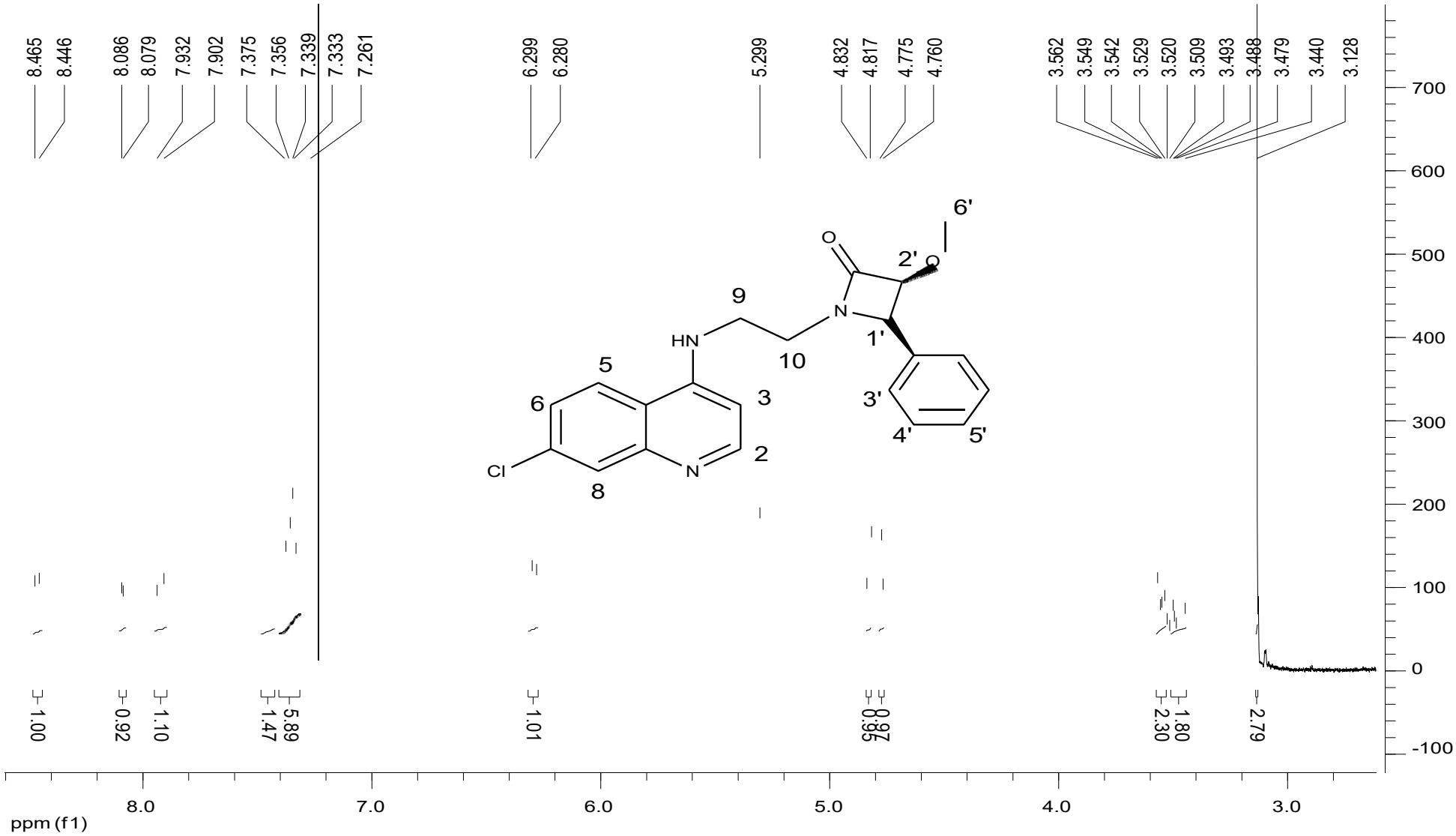
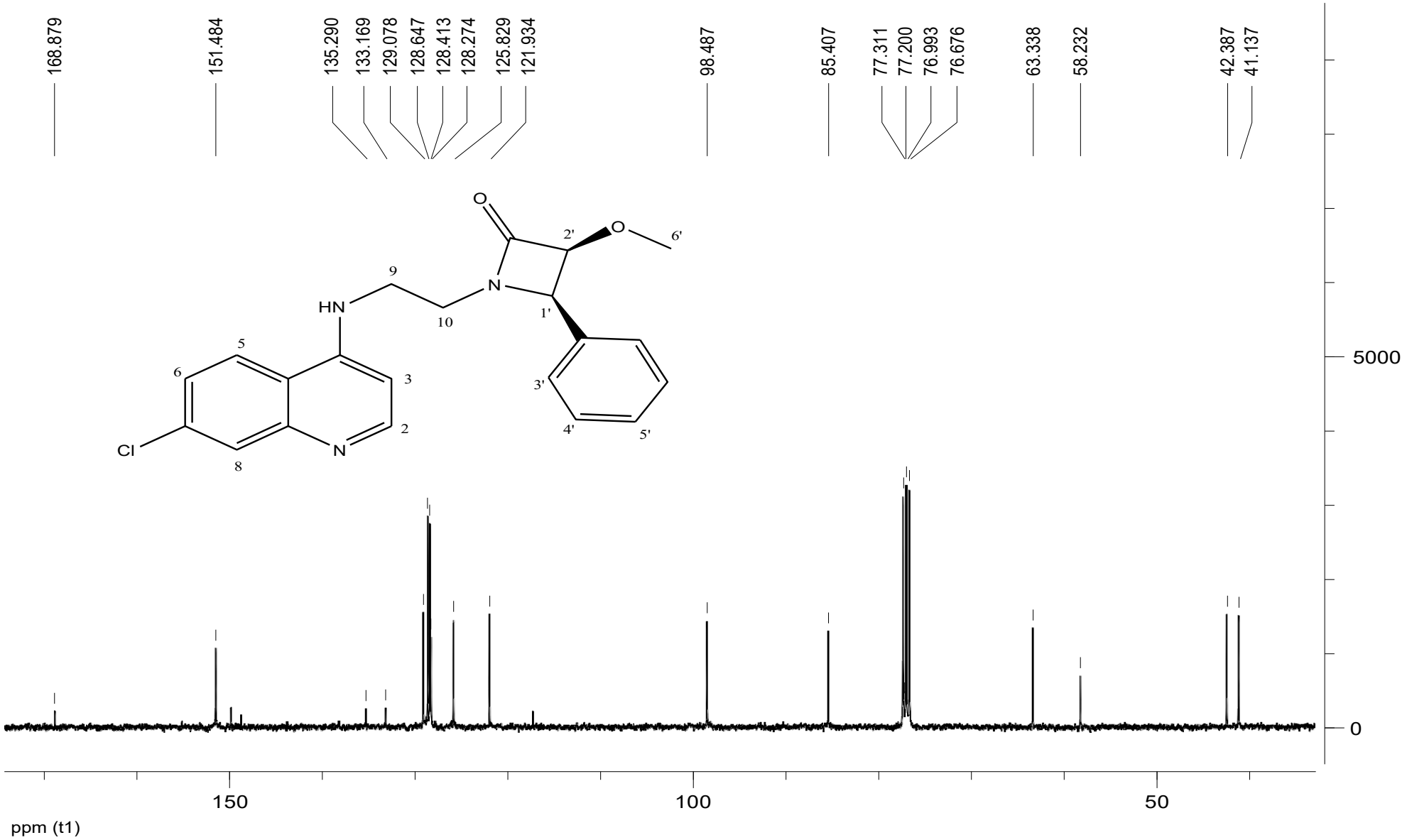


Figure S5: HPLC- PDA chromatogram of **6e**.

NMR Spectra of the target compounds:

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77.311
77.200
76.993
76.676
63.338
58.232
42.387
41.137
O
O
6'
2'
9
N
HN
10
1'
5
6
3
3'
2
4'
5'
Cl
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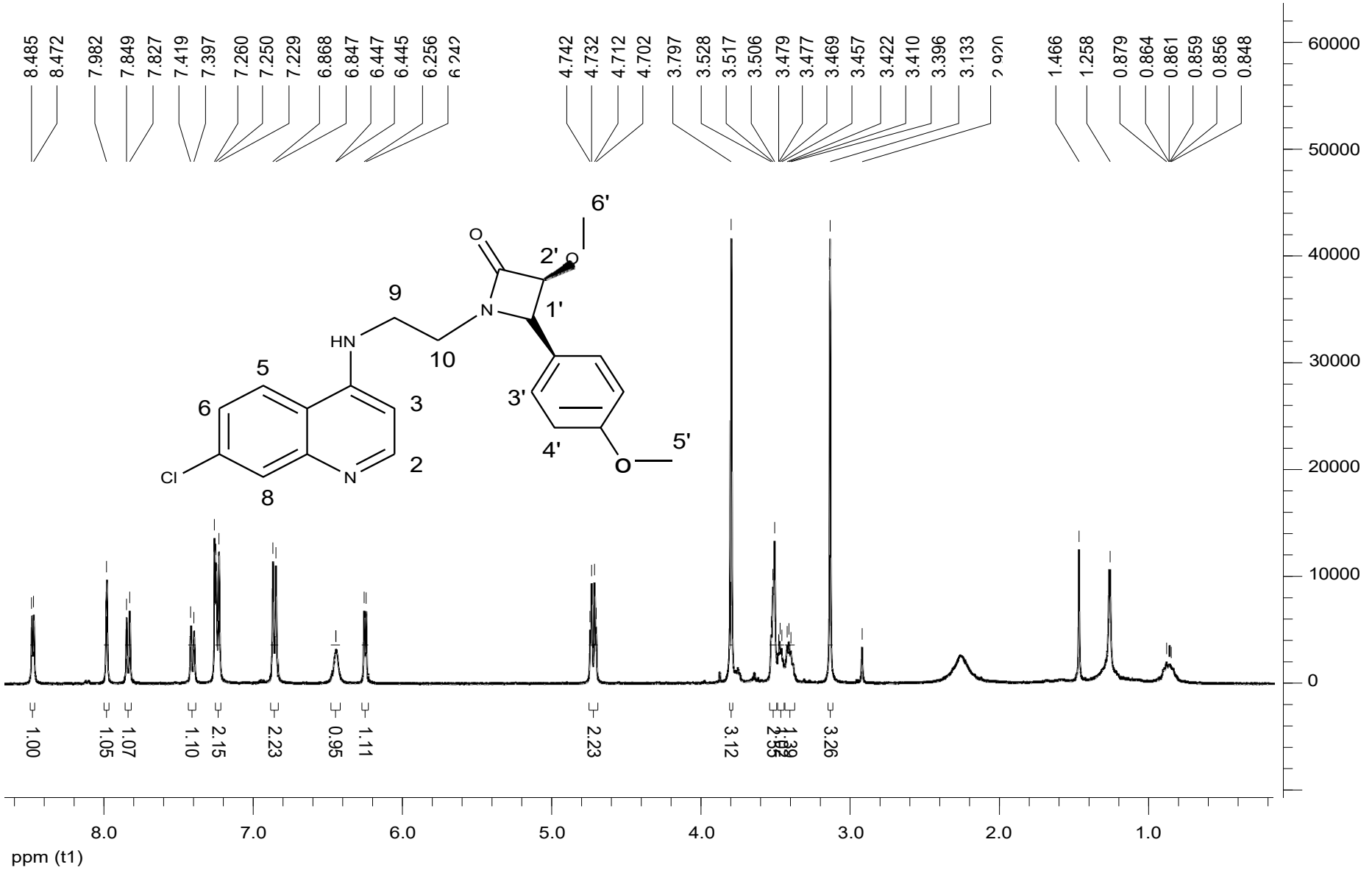
0
150
100
50
ppm (t1)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6.447
6.445
6.256
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4.732
4.712
4.702
3.797
3.528
3.517
3.506
3.479
3.477
3.469
3.457
3.422
3.410
3.396
3.133
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1.258
0.879
0.864
0.861
0.859
0.856
0.848
6'
O
2'
O
9
N
1'
HN
10
5
6
3
3'
4'
5'
O
Cl
N
2
8
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50000
40000
30000
20000
10000
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1.07
1.10
2.15
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0.95
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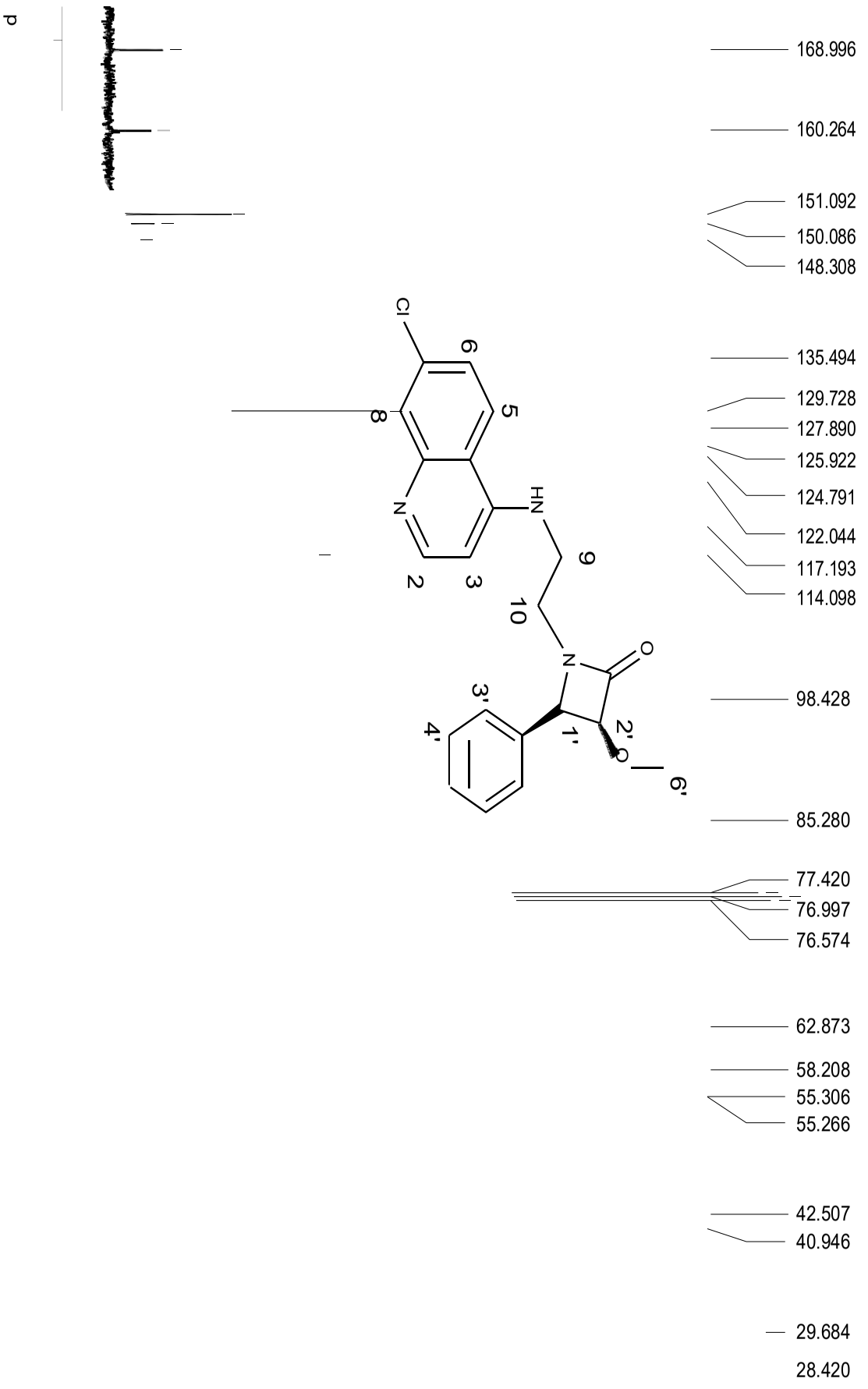
ppm (t1)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55.266
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3'
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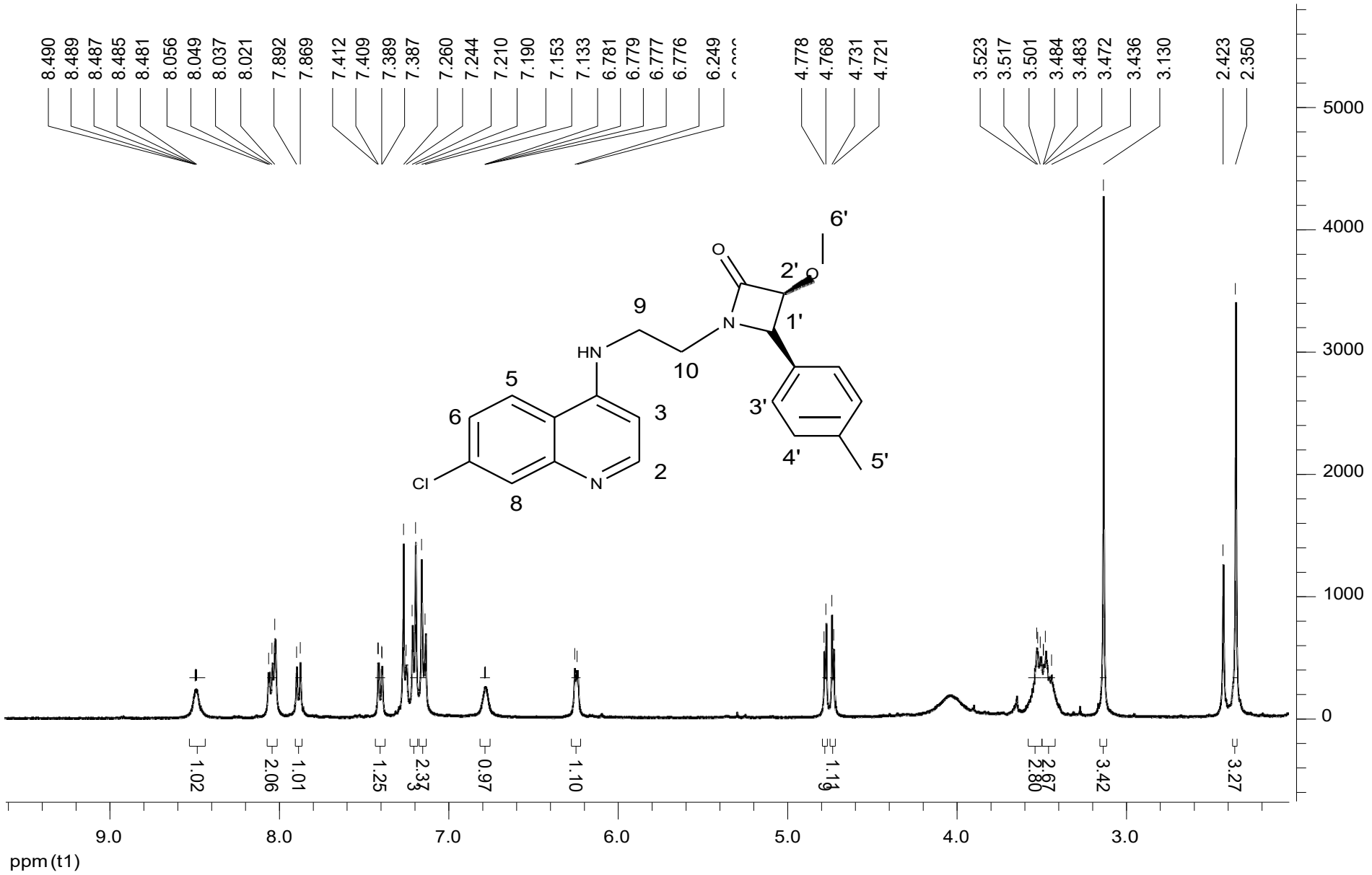
2'
O
6'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6.779
6.777
6.776
6.249
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4.768
4.731
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3.517
3.501
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3.483
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2'
O
9
N
1'
HN
10
5
3'
6
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4'
5'
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Cl
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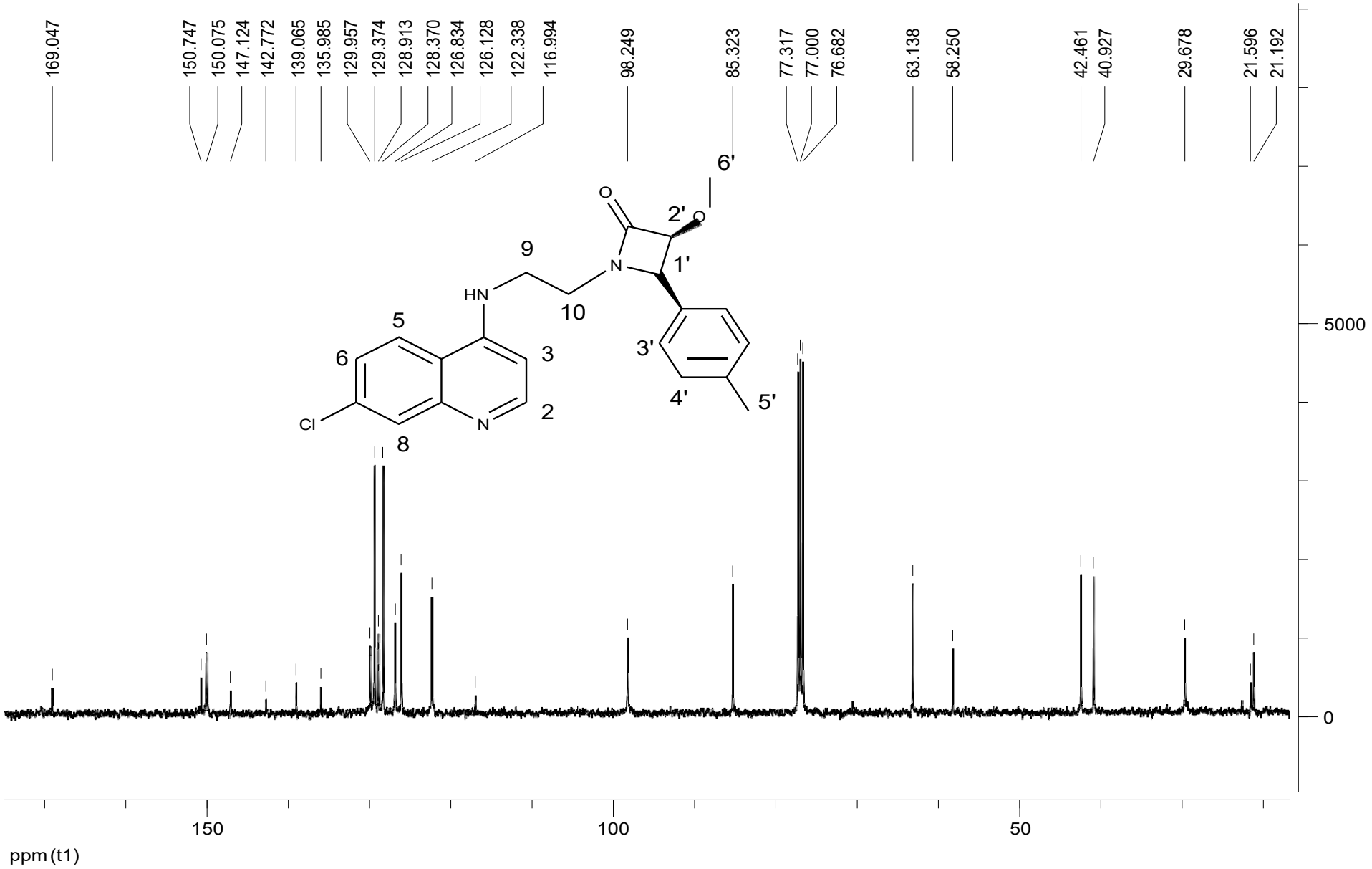
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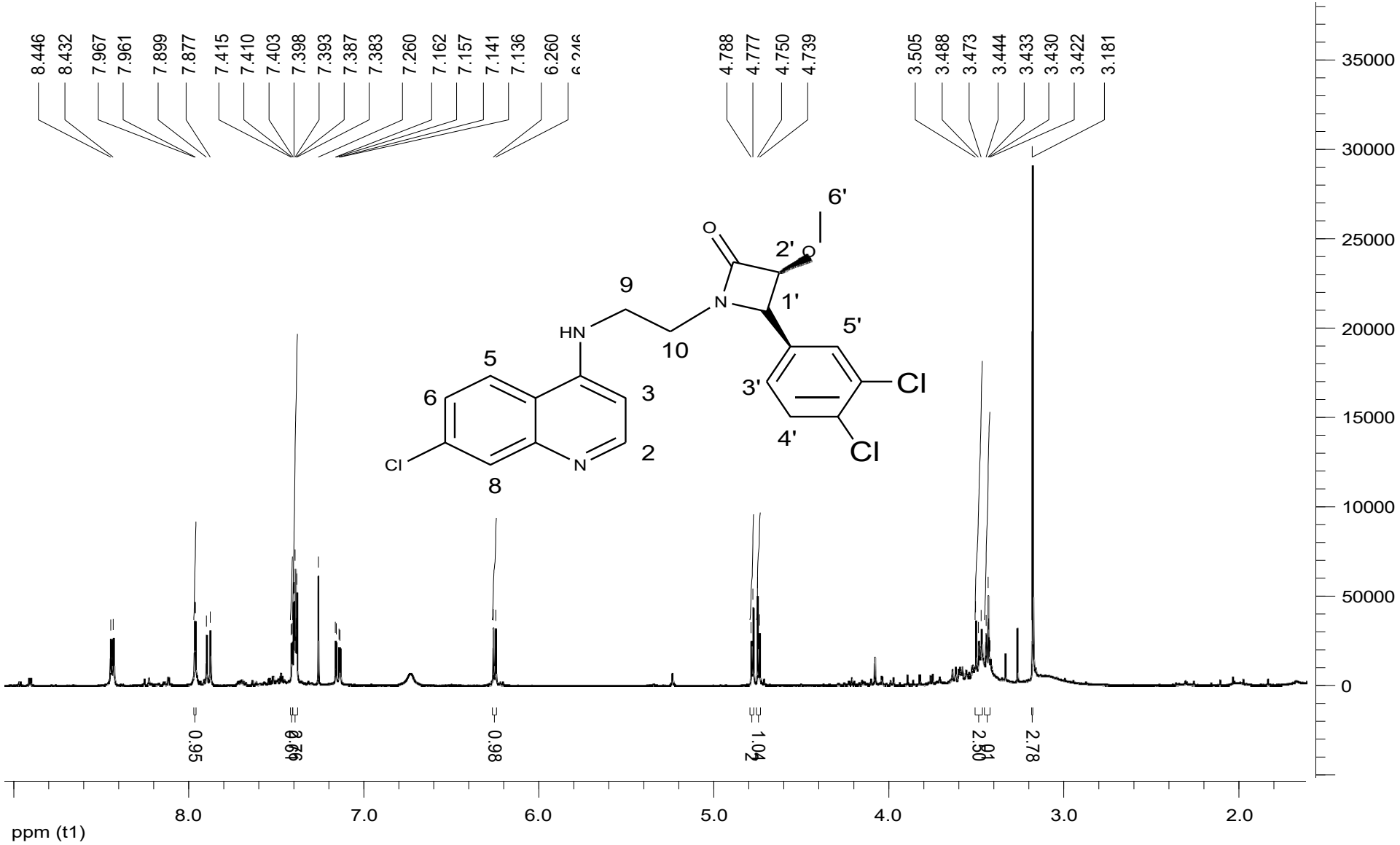
ppm (t1)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2'
O
9
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1'
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5'
5
6
3
3'
Cl
2
4'
Cl
Cl
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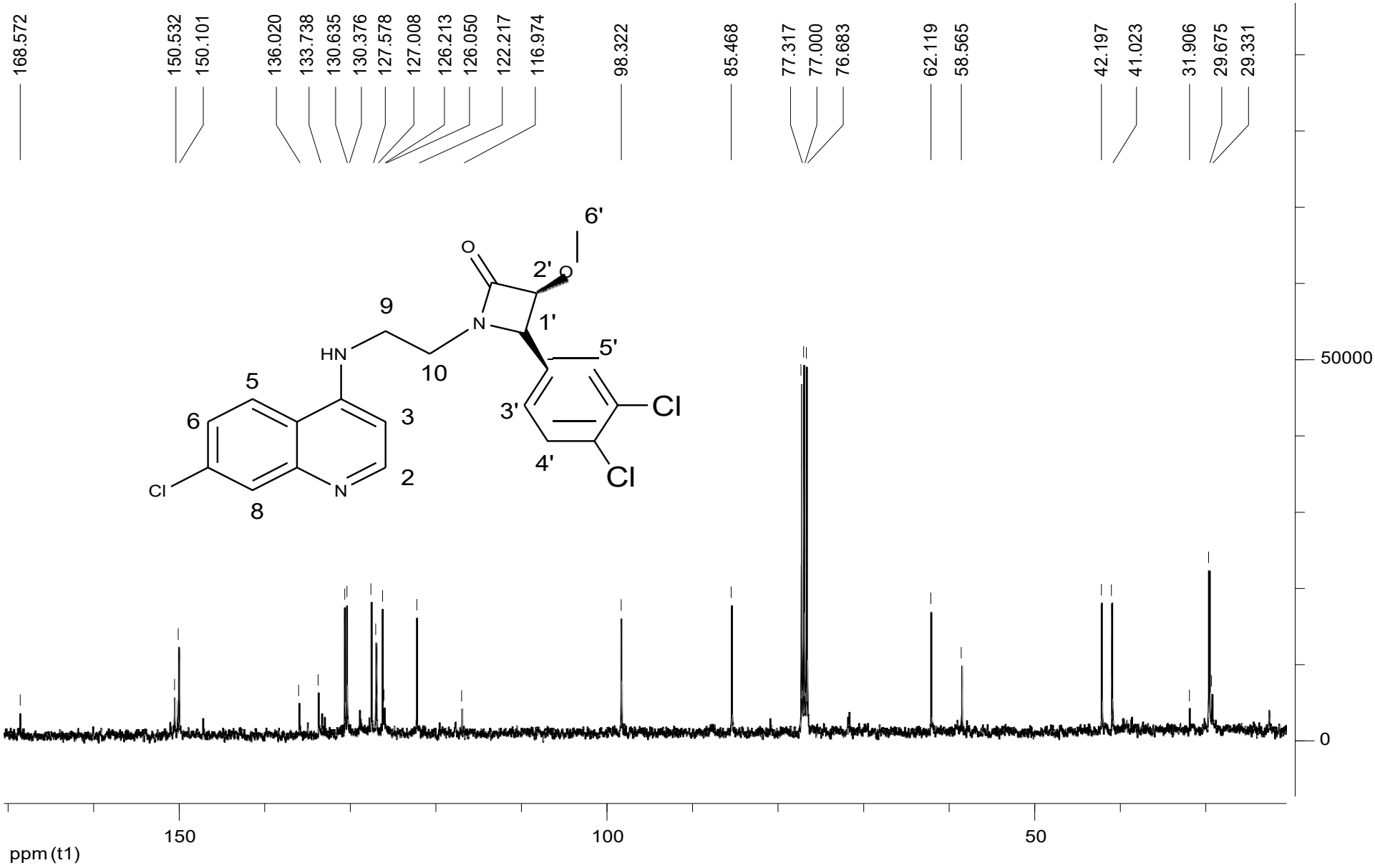
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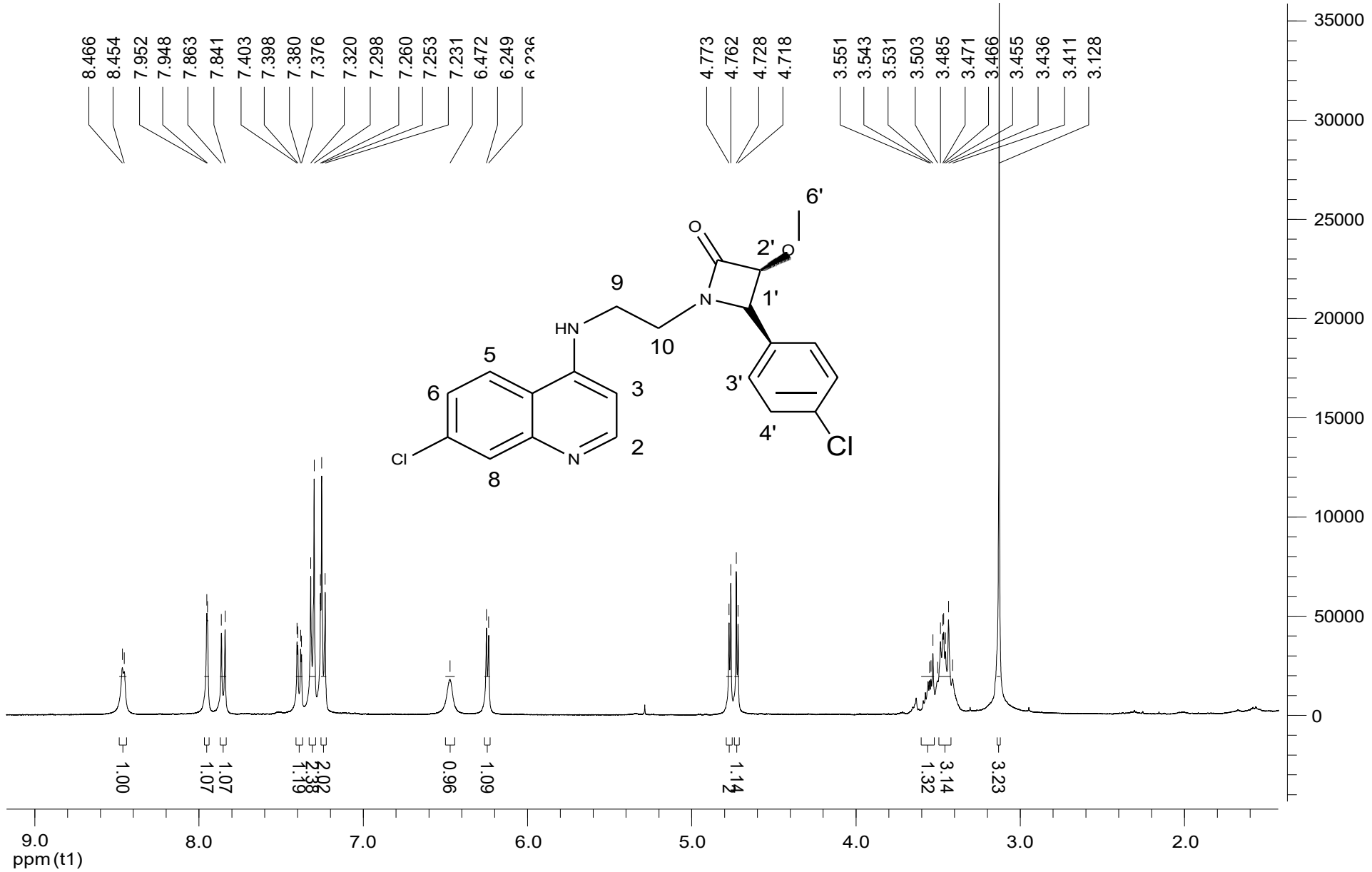
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4.718
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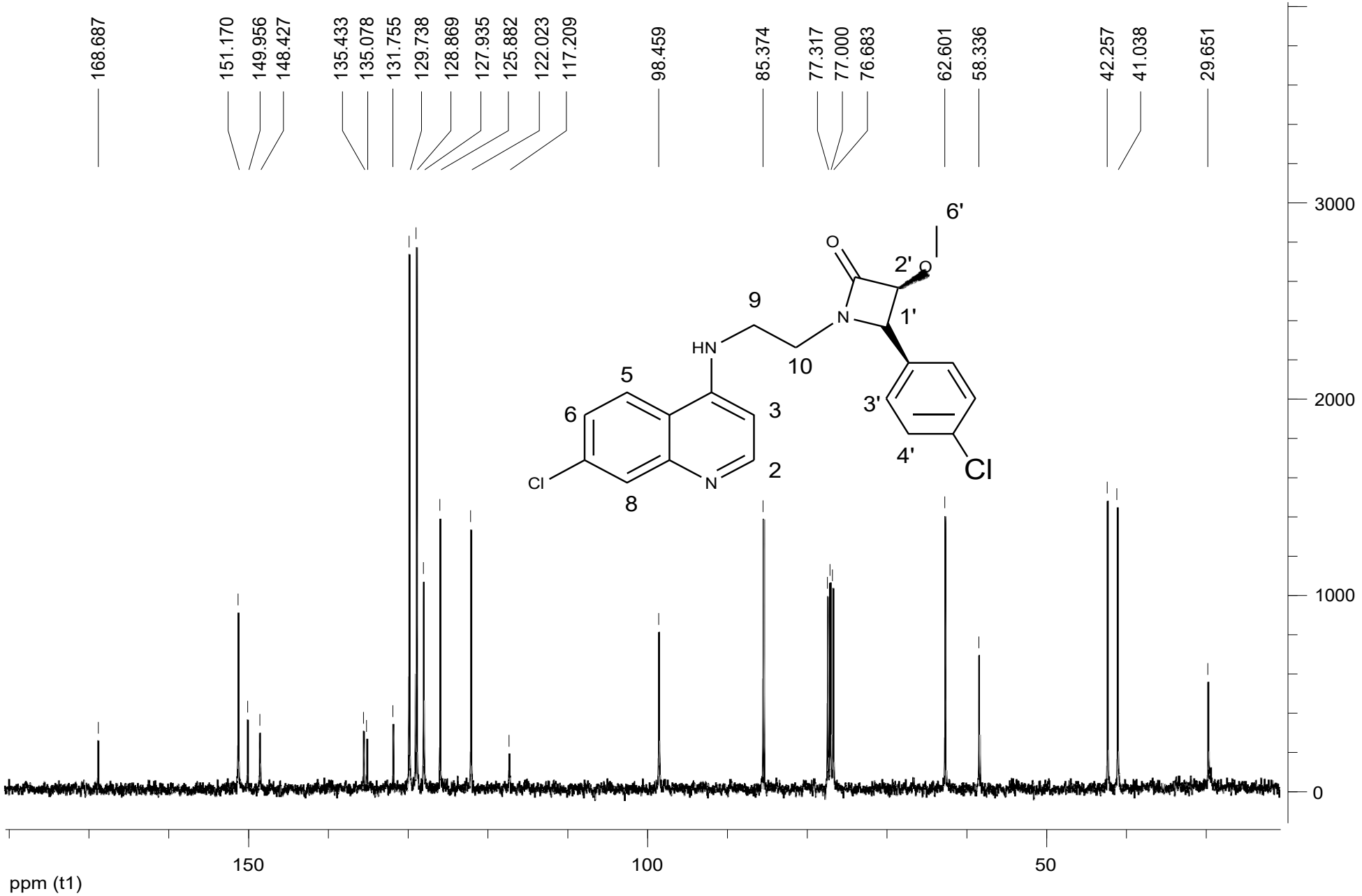
ppm (t1)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O
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HN
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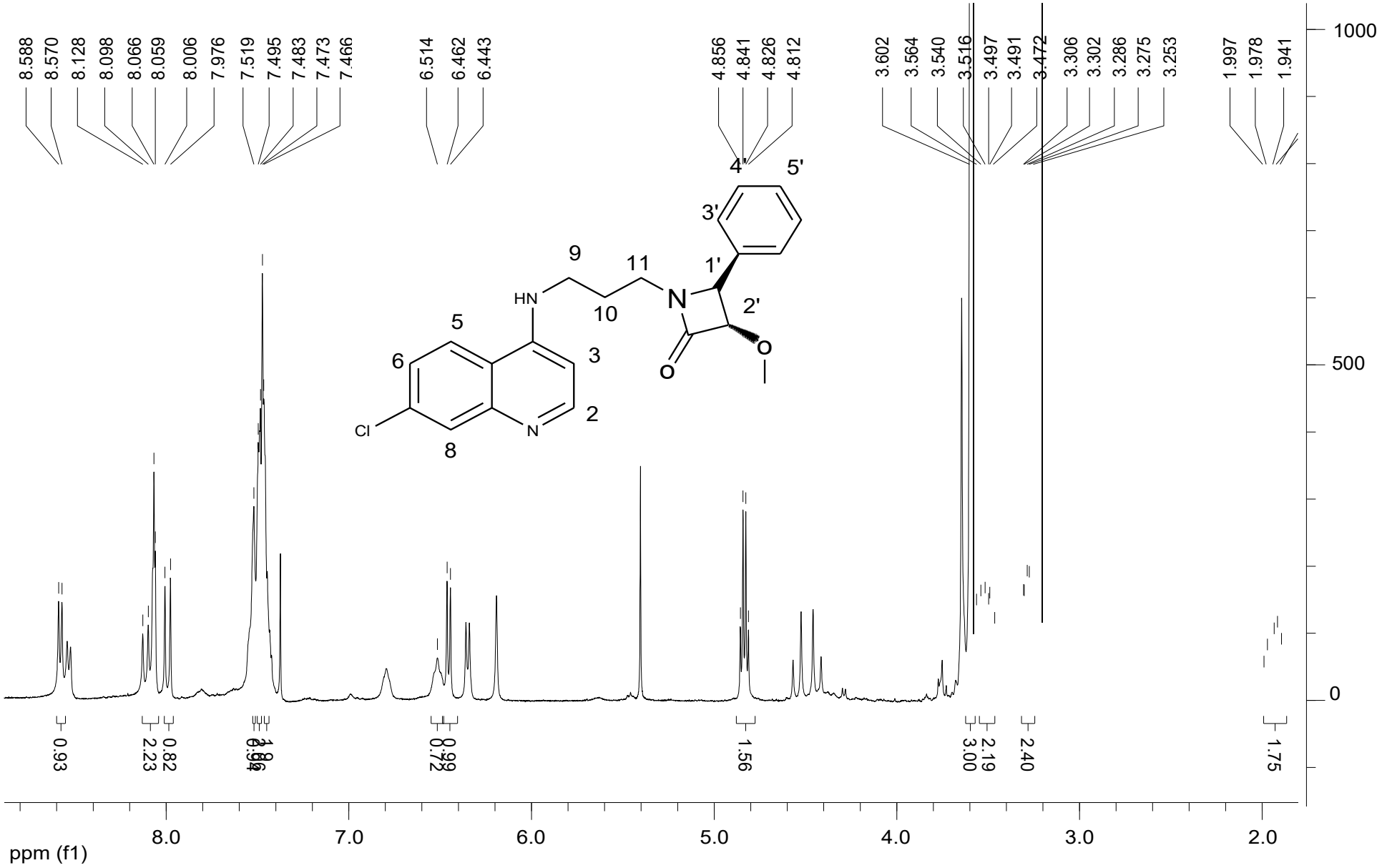
ppm (t1)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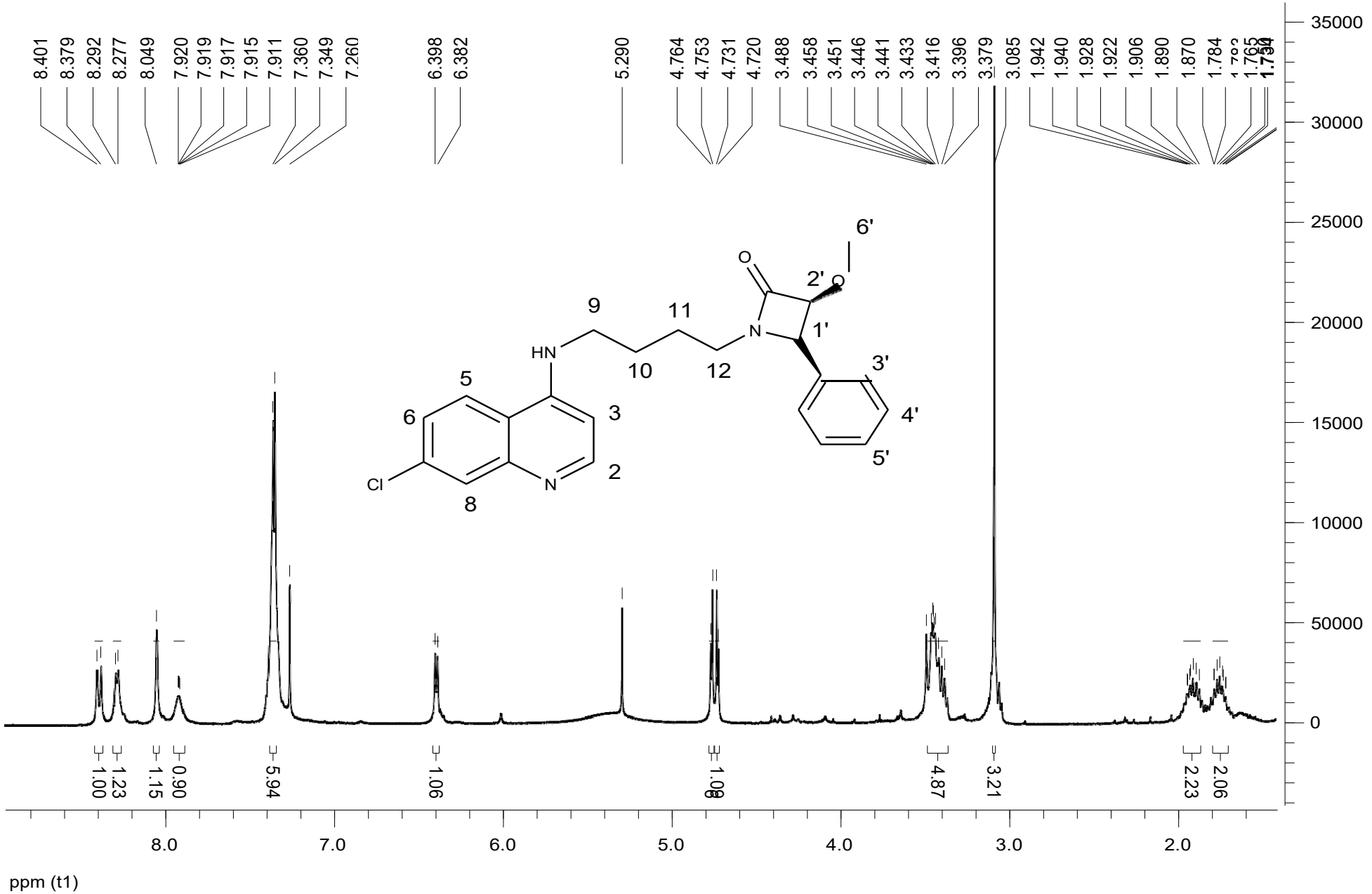
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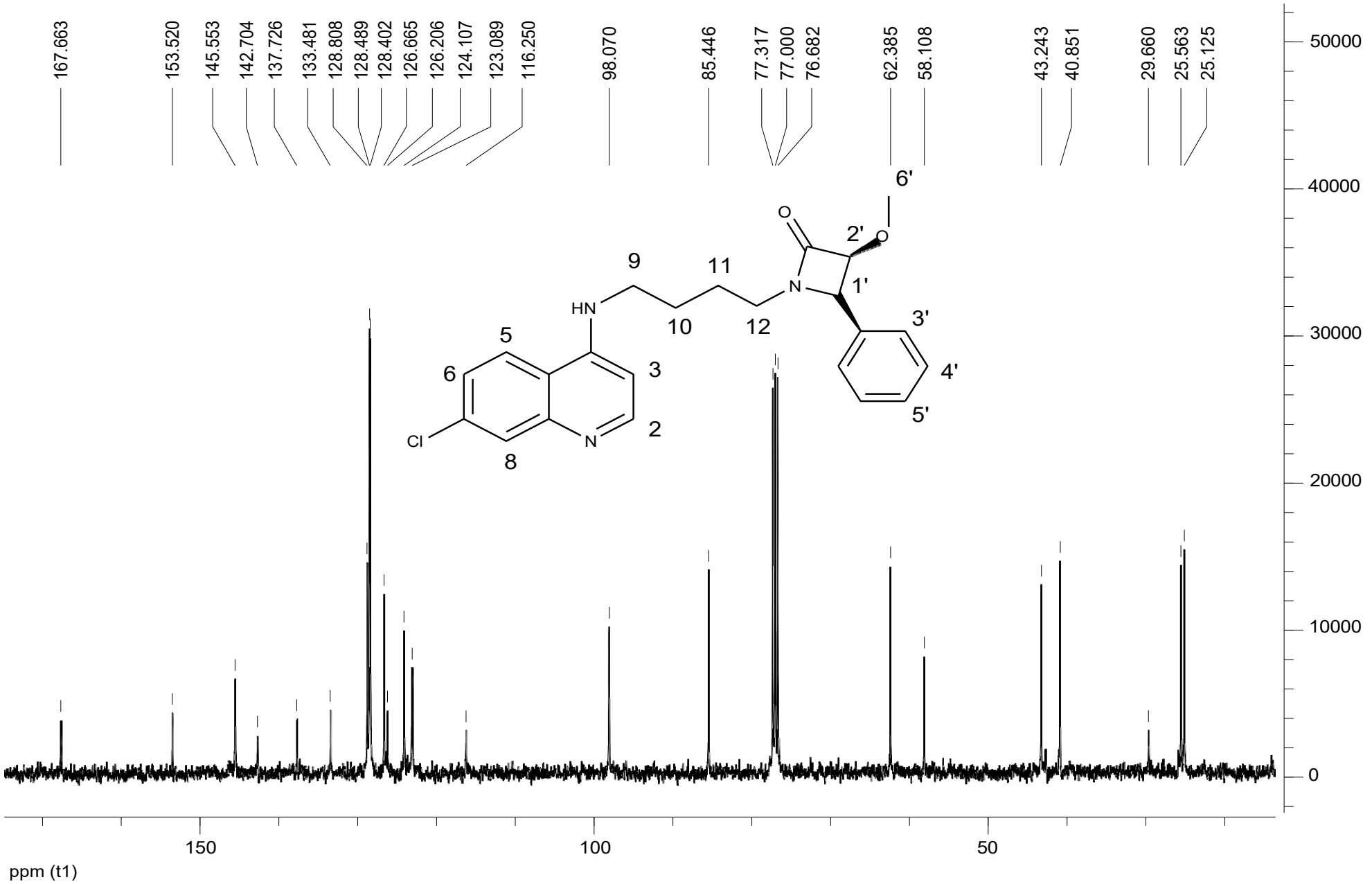
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62.385
58.108
43.243
40.851
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25.125
50000
40000
30000
20000
10000
0
150
100
50
ppm (t1)
6'
O
2'
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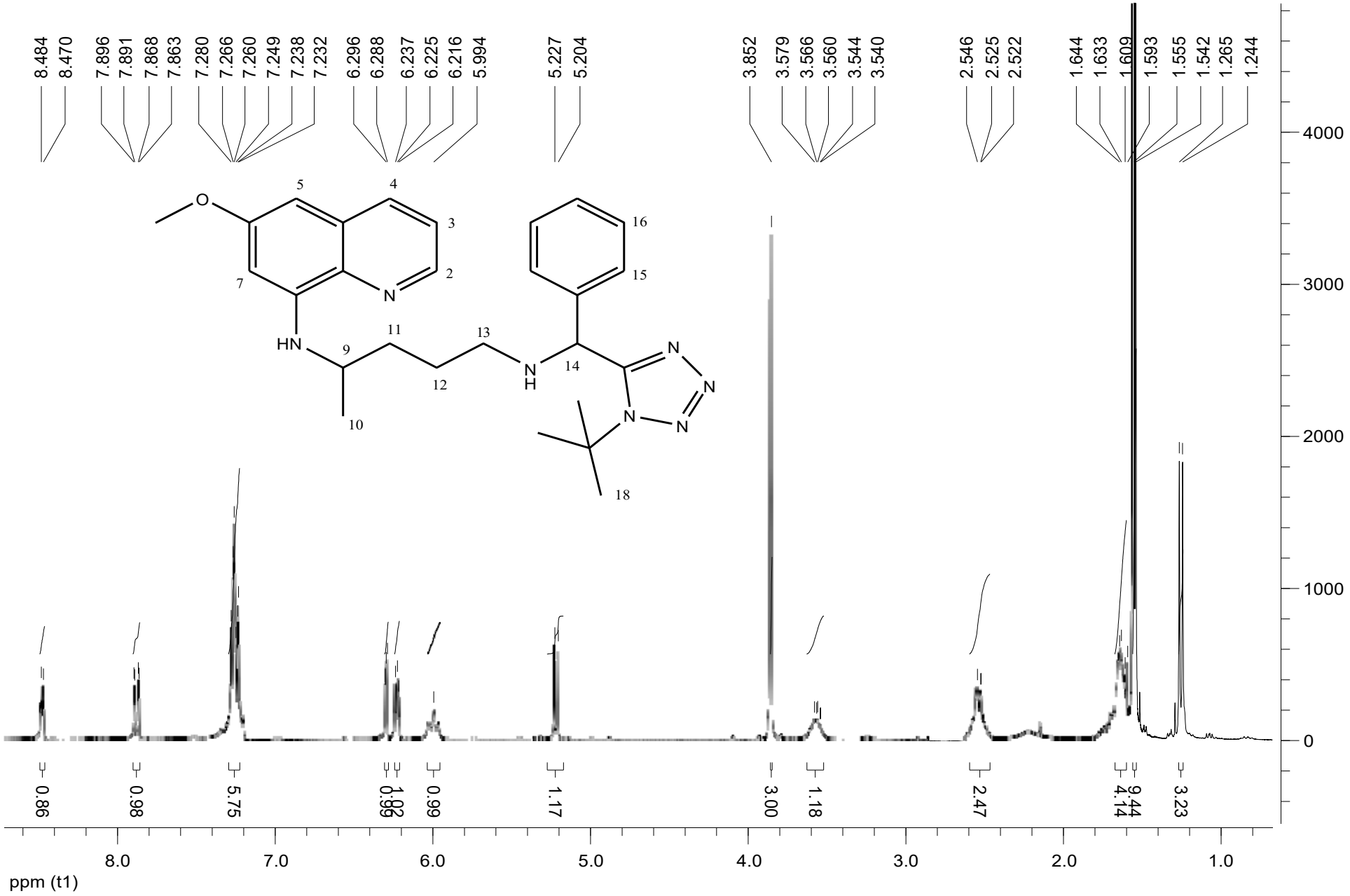
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6.216
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2000
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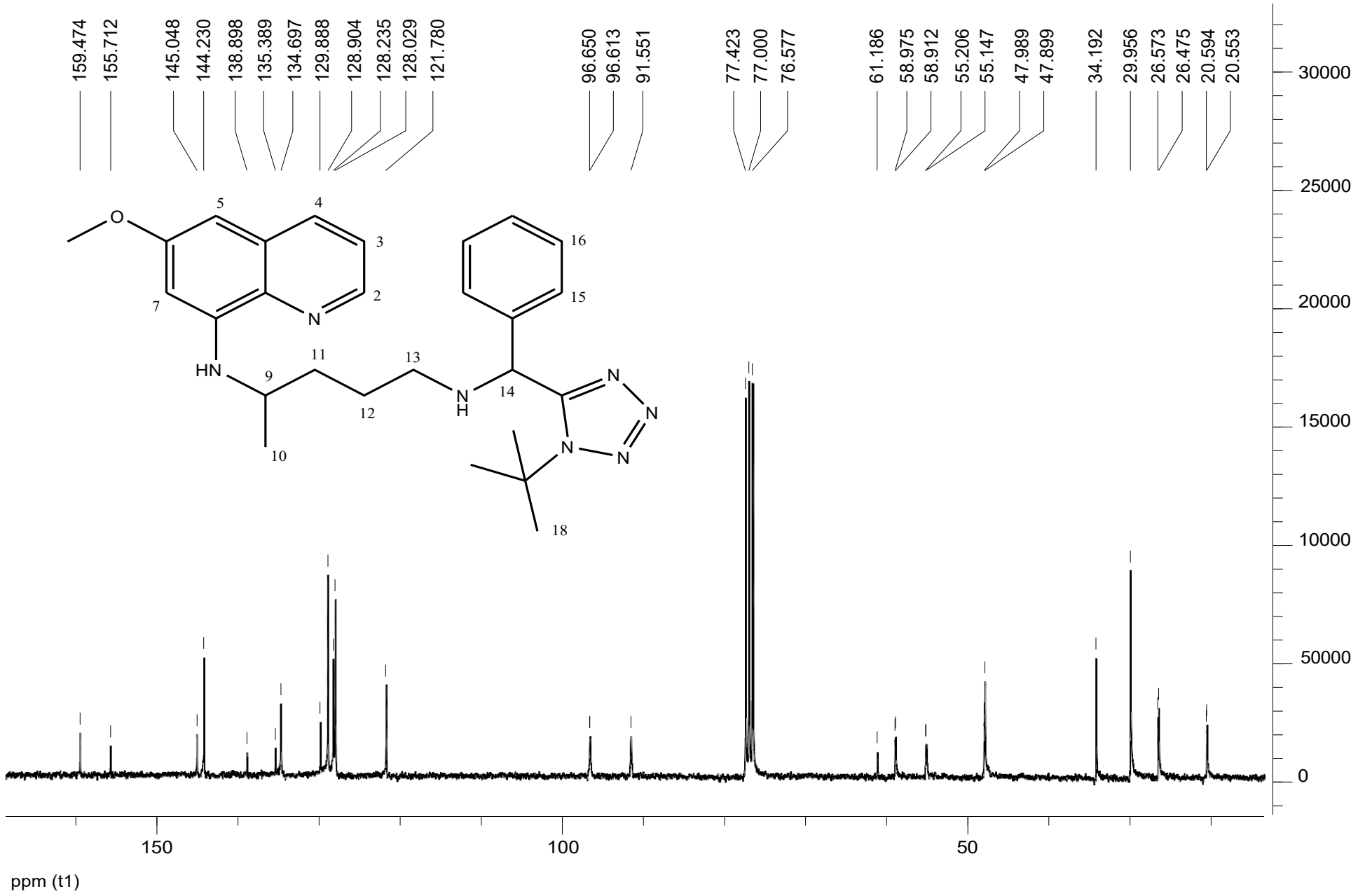
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96.613
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77.000
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47.899
34.192
29.956
26.573
26.475
20.594
20.553
30000
25000
20000
15000
10000
50000
0
150
100
50
ppm (t1)
O
N
HN
NH
N
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7
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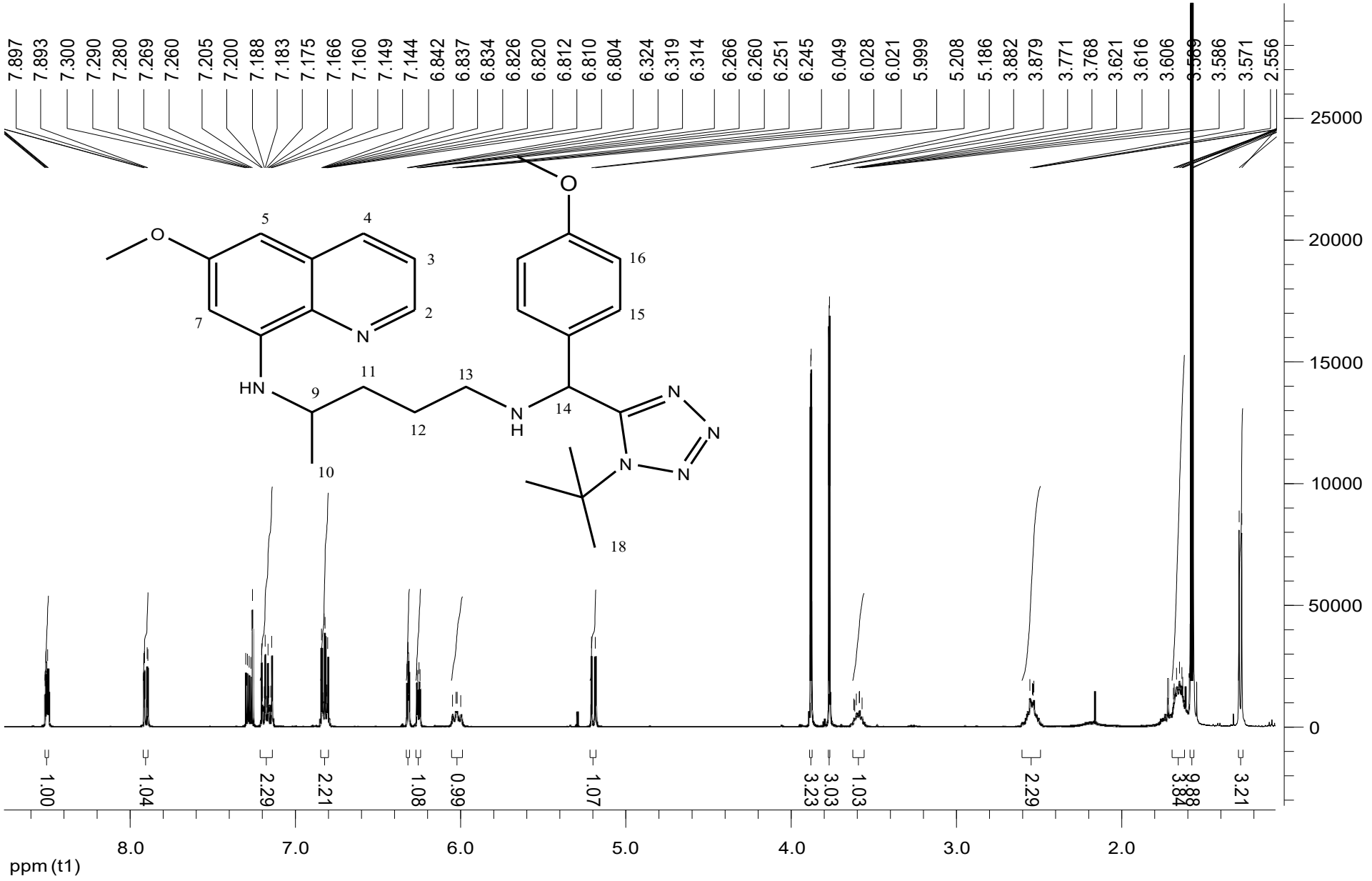
10
11
12
13
14
15
16
18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3.606
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3.571
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15000
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1.08
0.99
1.07
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3.03
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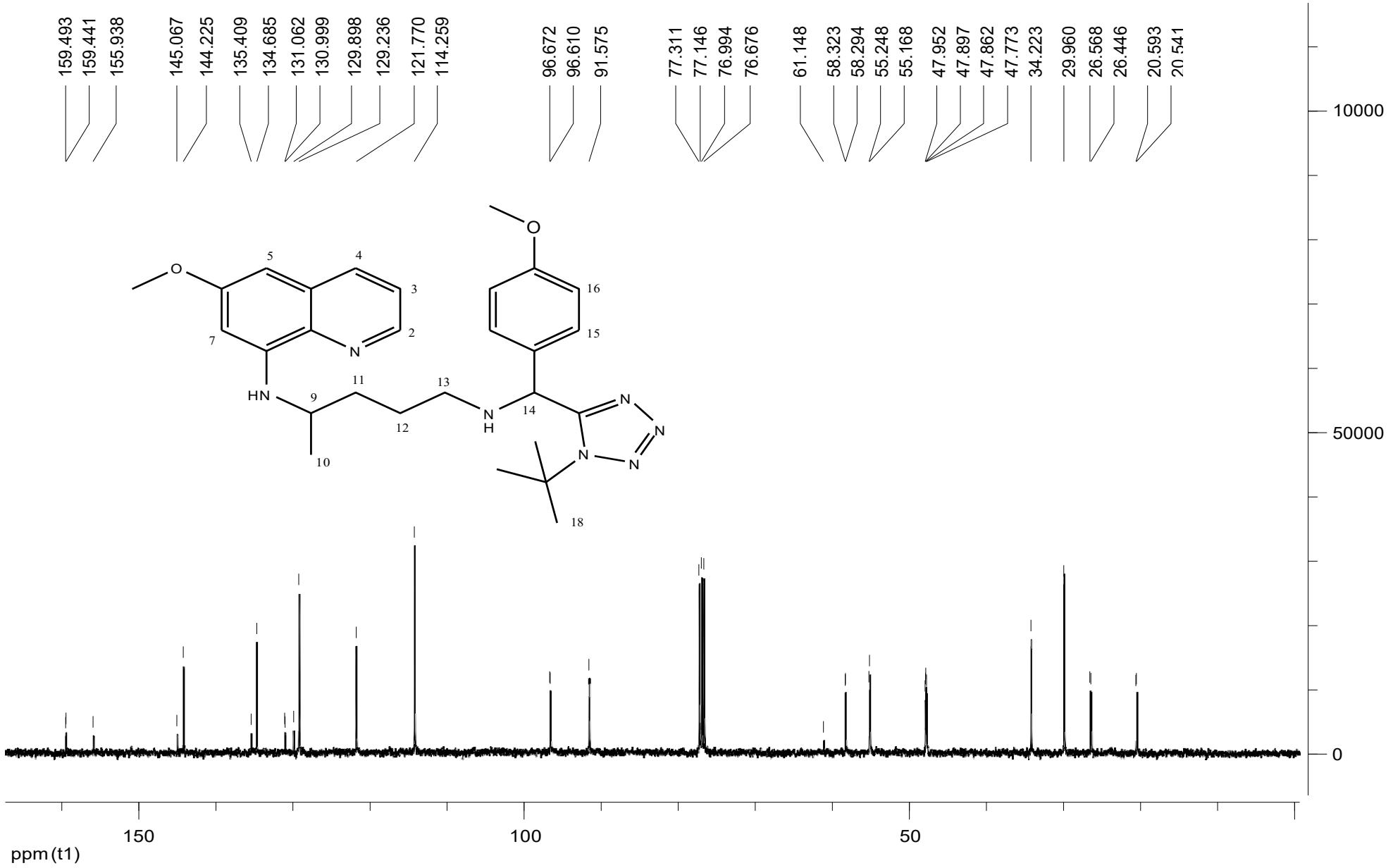
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96.672
96.610
91.575
77.311
77.146
76.994
76.676
61.148
58.323
58.294
55.248
55.168
47.952
47.897
47.862
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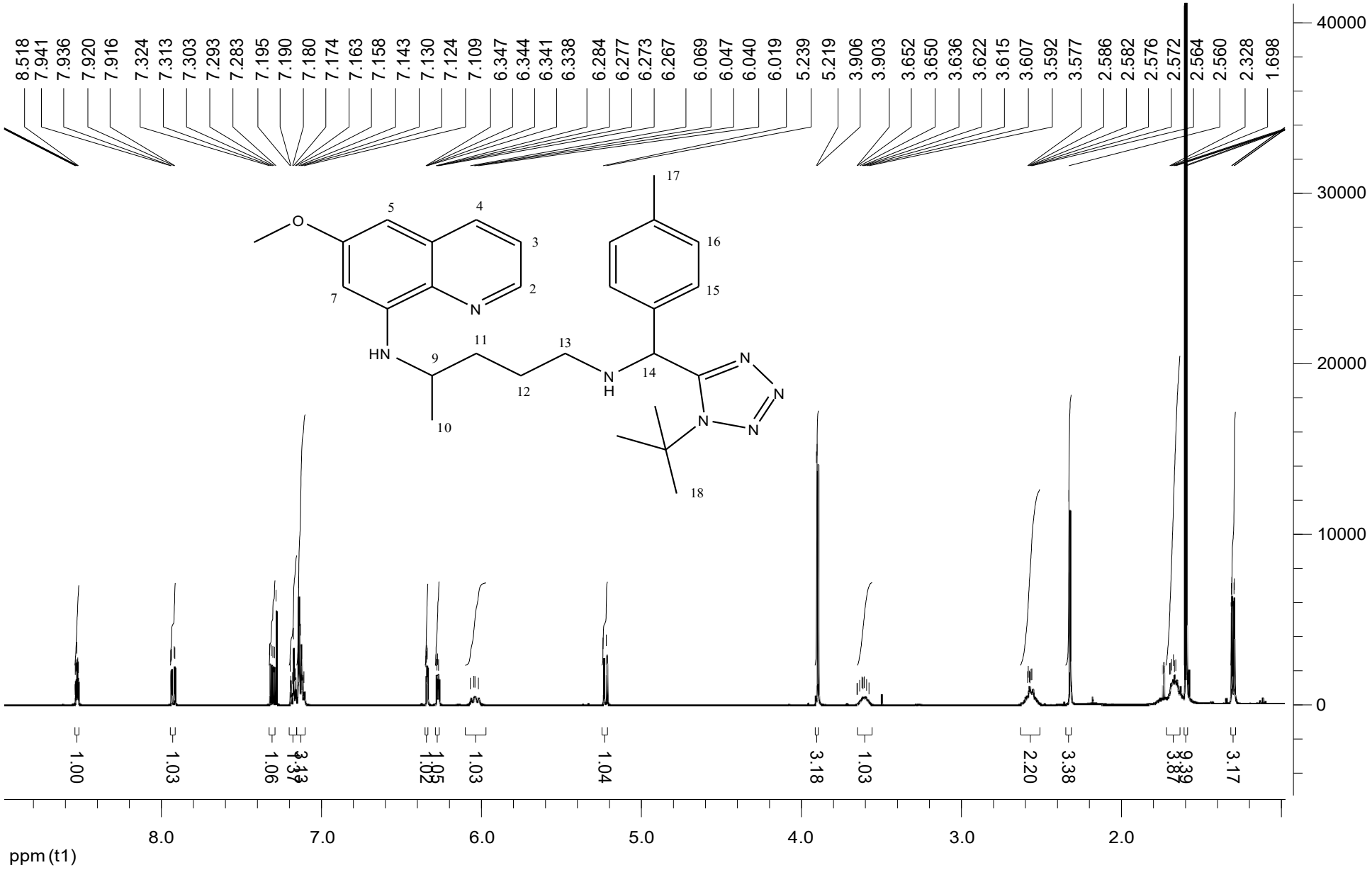
ppm (t1)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7.190
7.180
7.174
7.163
7.158
7.143
7.130
7.124
7.109
6.347
6.344
6.341
6.338
6.284
6.277
6.273
6.267
6.069
6.047
6.040
6.019
5.239
5.219
3.906
3.903
3.652
3.650
3.636
3.622
3.615
3.607
3.592
3.577
2.586
2.582
2.576
2.572
2.564
2.560
2.328
1.698
O
N
HN
NH
N
N
N
N
1
2
3
4
5
7
9
10
11
12
13
14
15
16
17
18
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30000
20000
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1.03
1.06
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1.03
1.04
3.18
1.03
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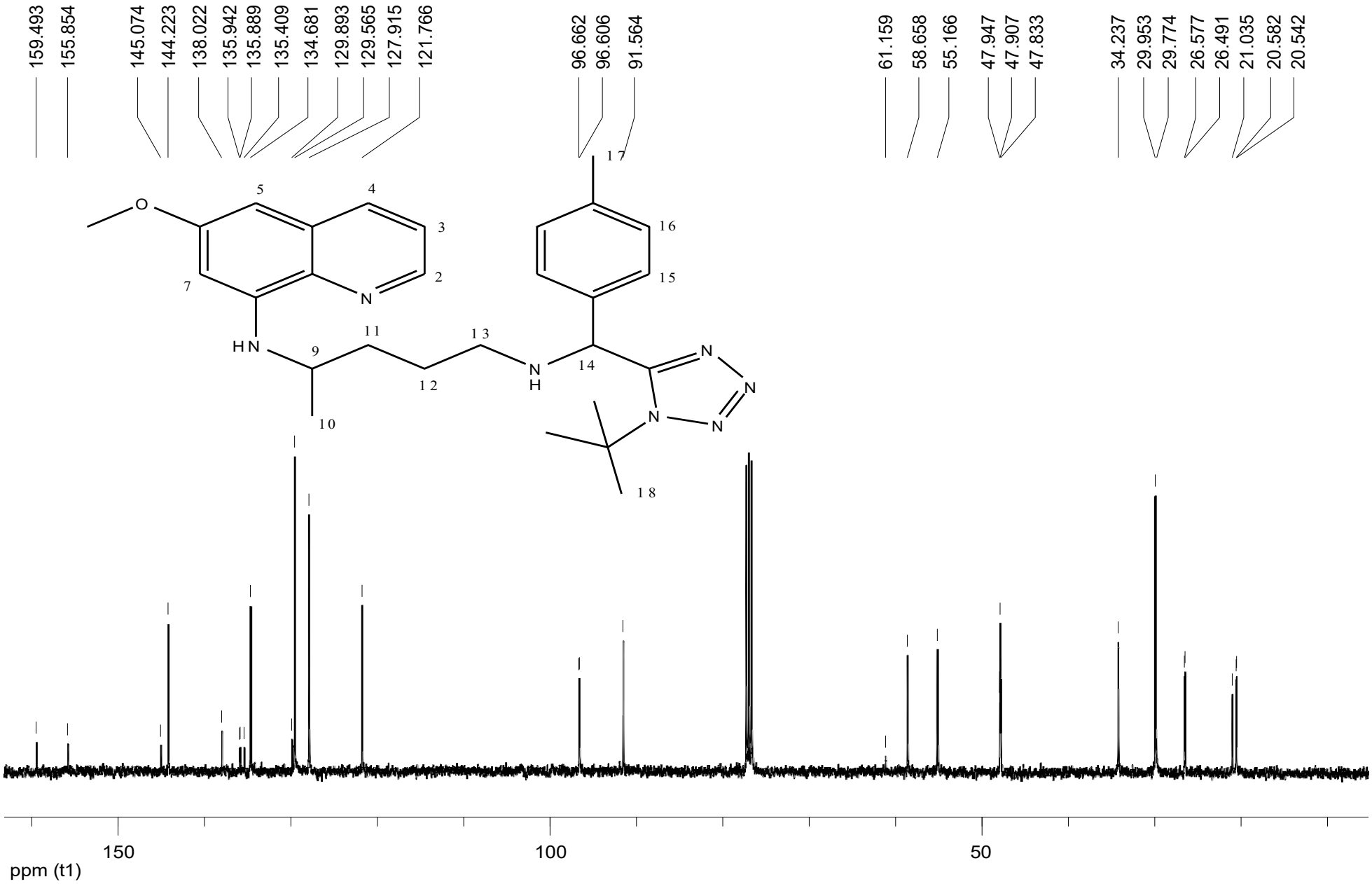
ppm (t1)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HN
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N
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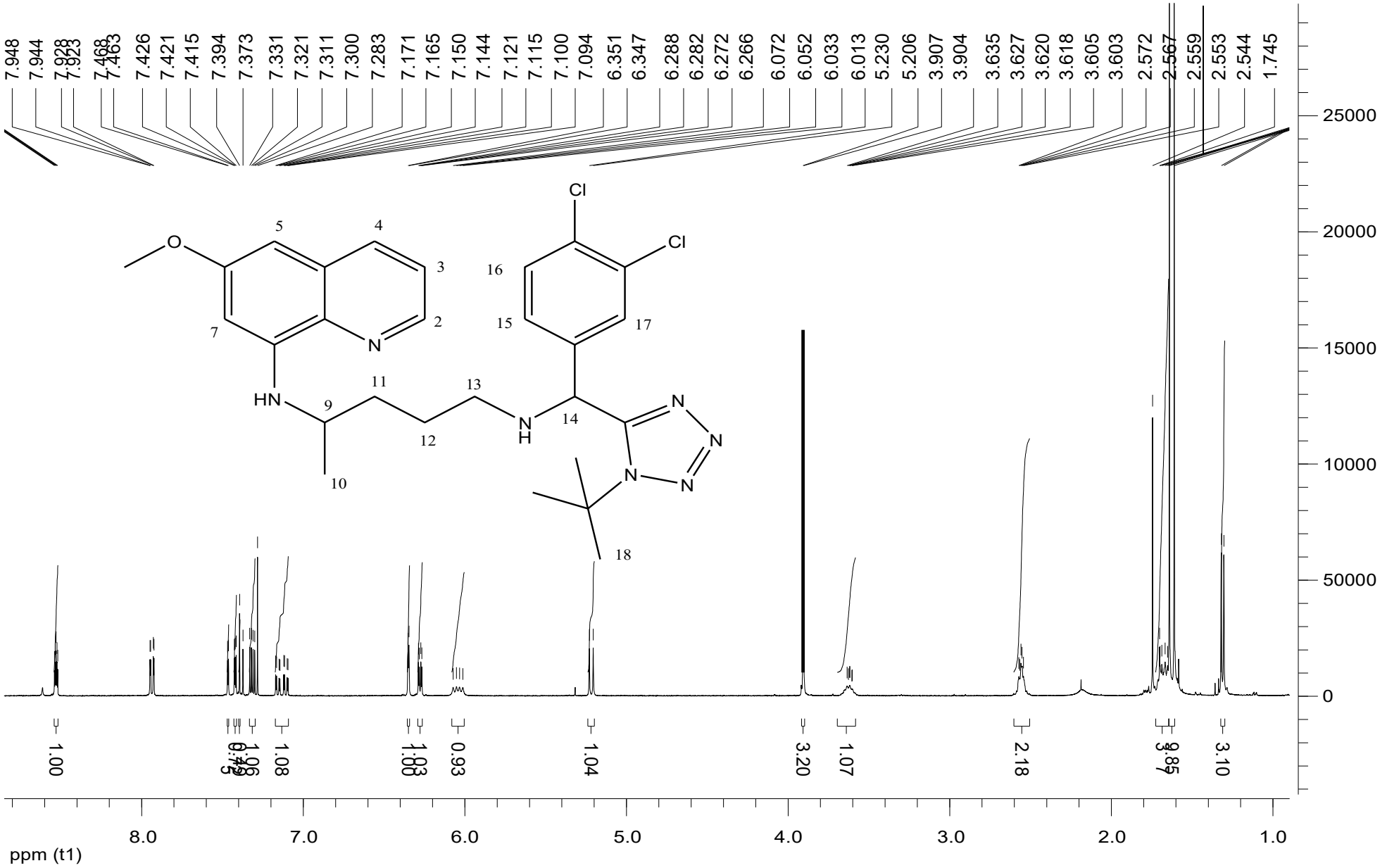
ppm (t1)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7.300
7.283
7.171
7.165
7.150
7.144
7.121
7.115
7.100
7.094
6.351
6.347
6.288
6.282
6.272
6.266
6.072
6.052
6.033
6.013
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5.206
3.907
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3.635
3.627
3.620
3.618
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2.567
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2.544
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Cl
Cl
O
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N
N
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N
H
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1.08
1.03
0.93
1.04
3.20
1.07
2.18
3.10
8.0
7.0
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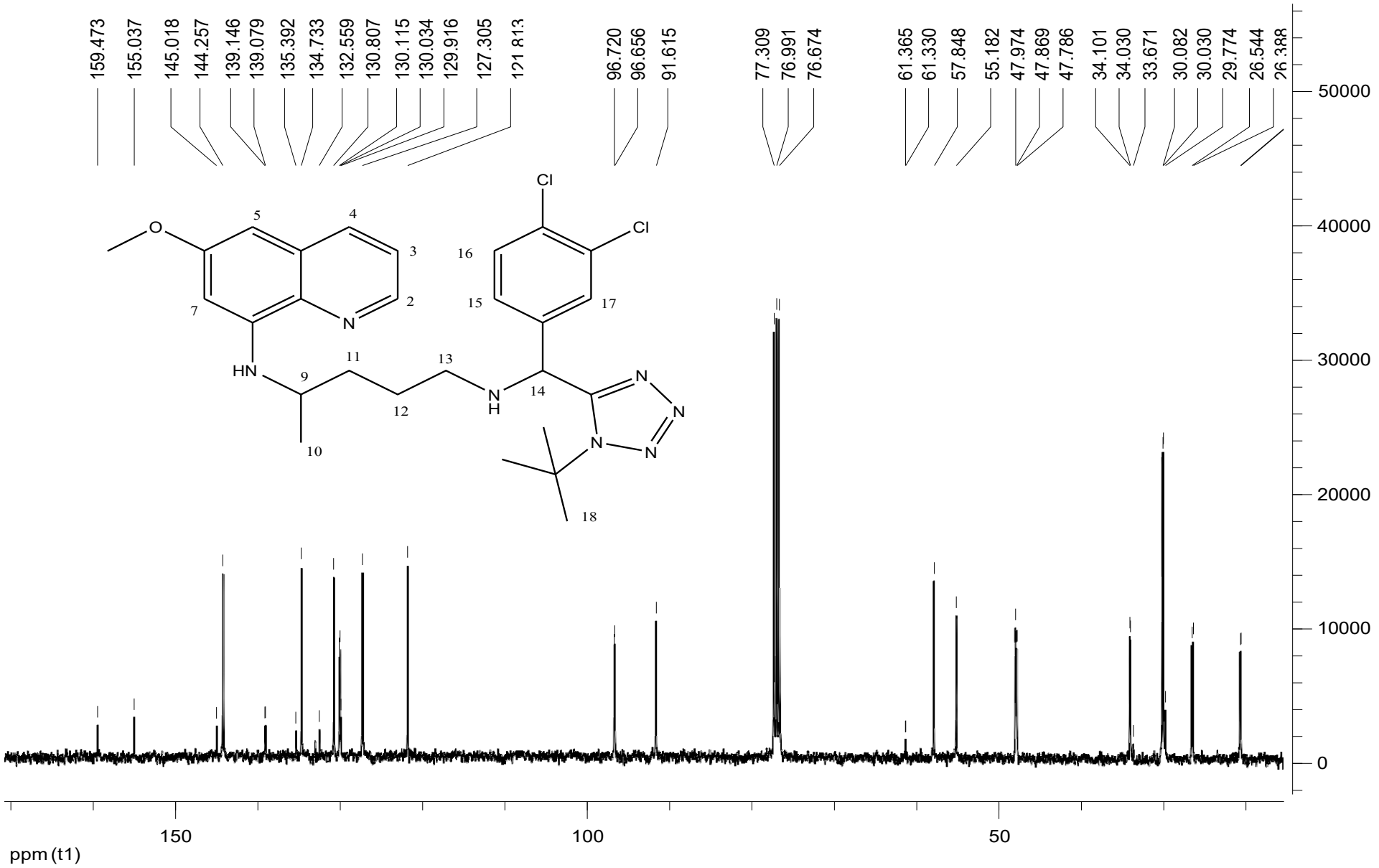
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127.305
121.813
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96.656
91.615
77.309
76.991
76.674
61.365
61.330
57.848
55.182
47.974
47.869
47.786
34.101
34.030
33.671
30.082
30.030
29.774
26.544
26.388
50000
40000
30000
20000
10000
0
150
100
50
ppm (t1)
O
HN
N
NH
Cl
Cl
N
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11
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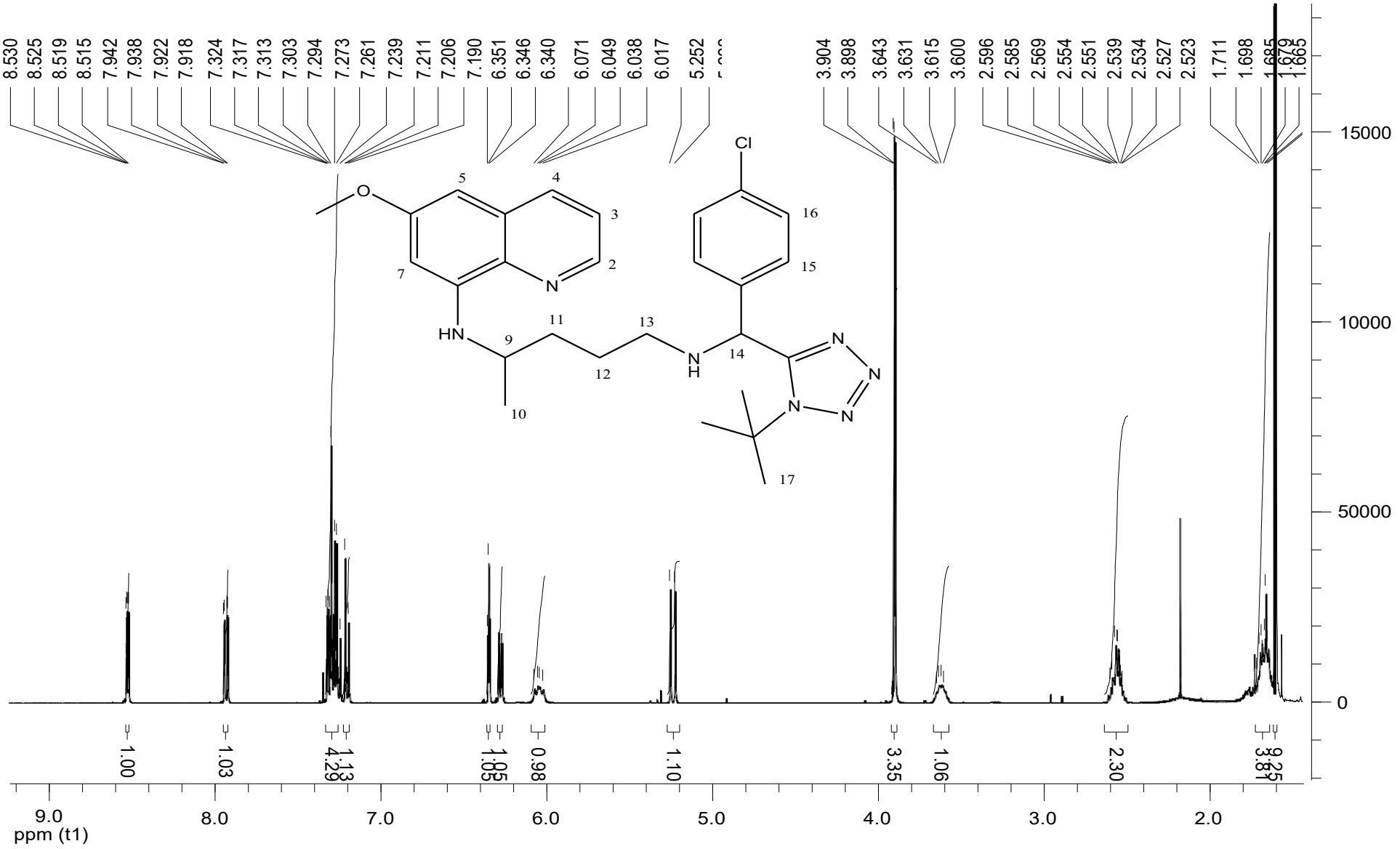
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6.340
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3.898
3.643
3.631
3.615
3.600
2.596
2.585
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2.554
2.551
2.539
2.534
2.527
2.523
1.711
1.698
1.685
1.679
1.665
Cl
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7
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14
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16
17
15000
10000
50000
0
1.00
1.03
4.29
1.13
1.05
0.98
1.10
3.35
1.06
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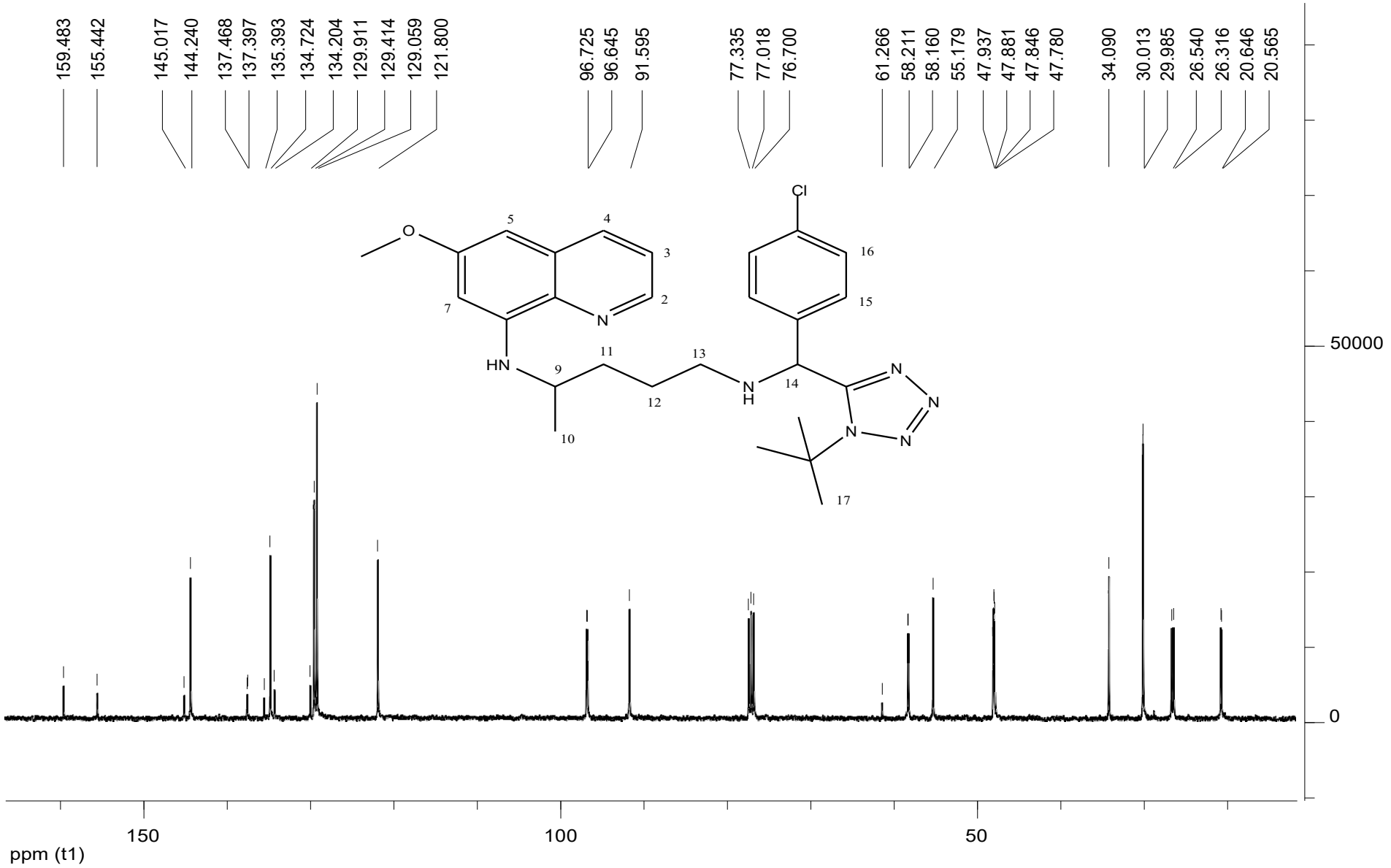
ppm (t1)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96.725
96.645
91.595
77.335
77.018
76.700
61.266
58.211
58.160
55.179
47.937
47.881
47.846
47.780
34.090
30.013
29.985
26.540
26.316
20.646
20.565
Cl
O
N
HN
H
N
N
N
N
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3
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7
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12
13
14
15
16
17
50000
0
150
100
50
ppm (t1)