Supporting information

Macrocyclic peptidomimetics with antimicrobial activity: synthesis, bioassay, and molecular modeling studies

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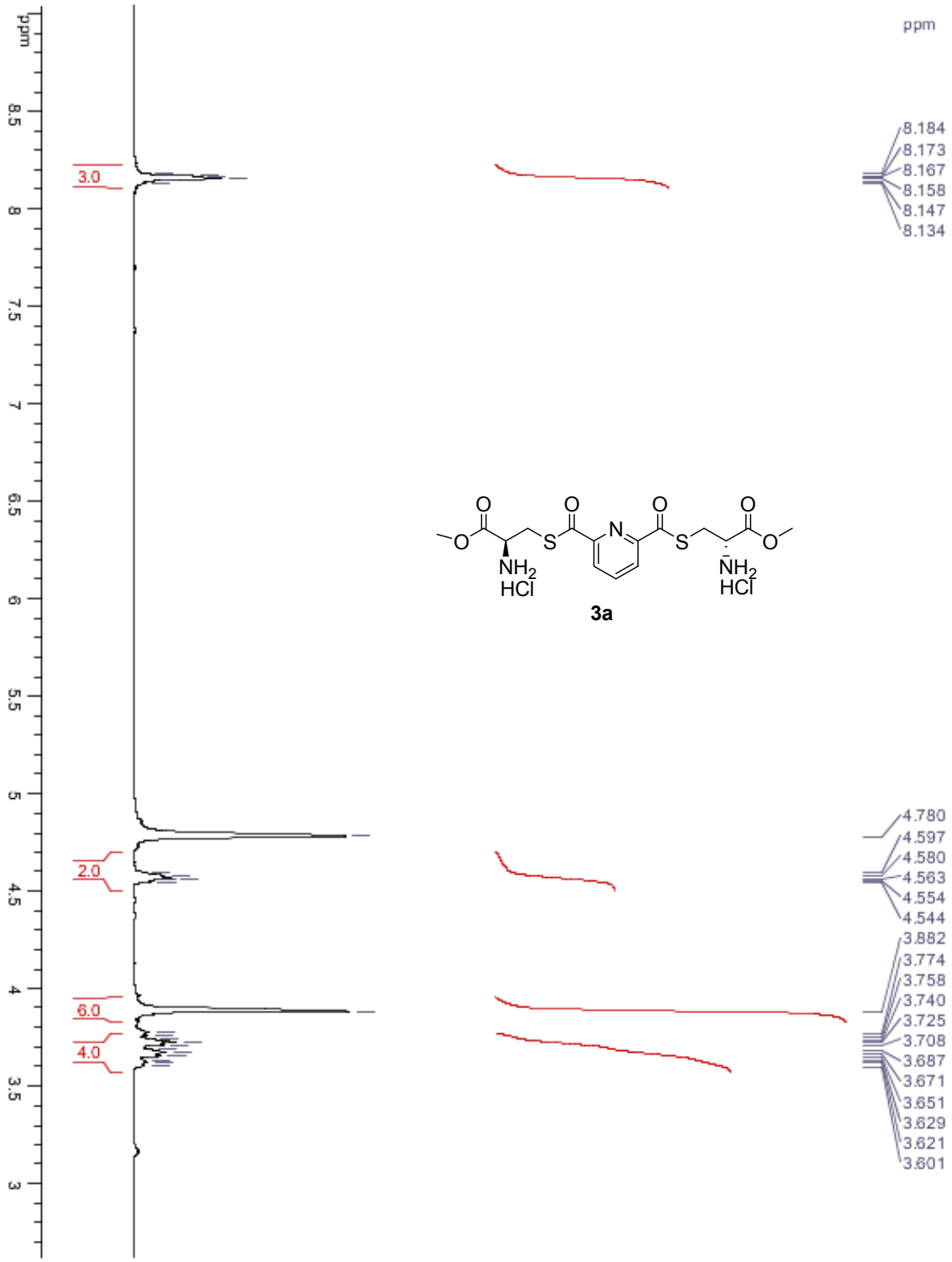
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NH2
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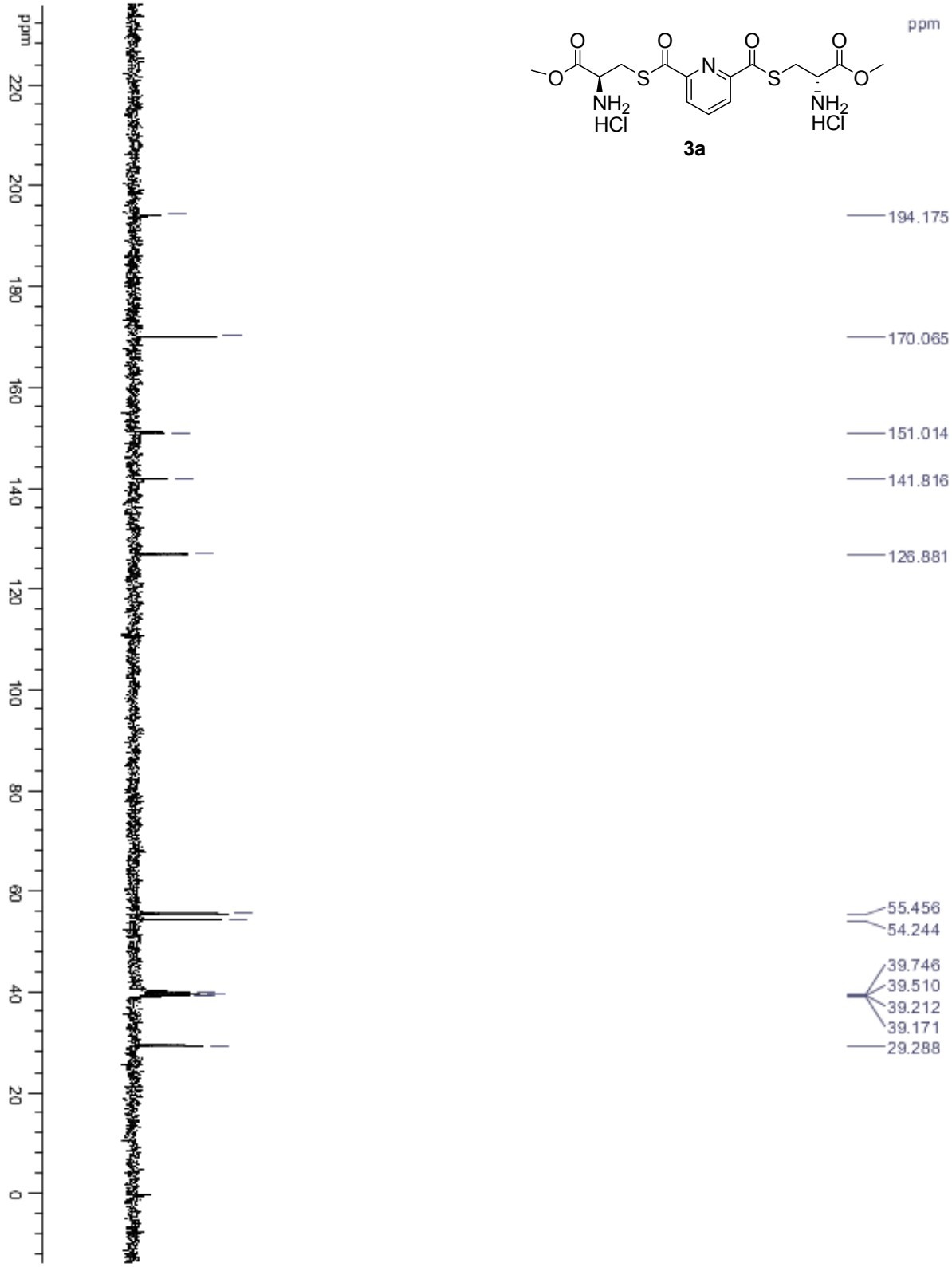
3a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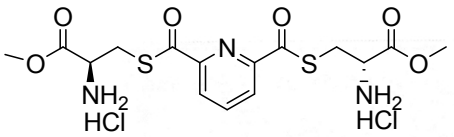
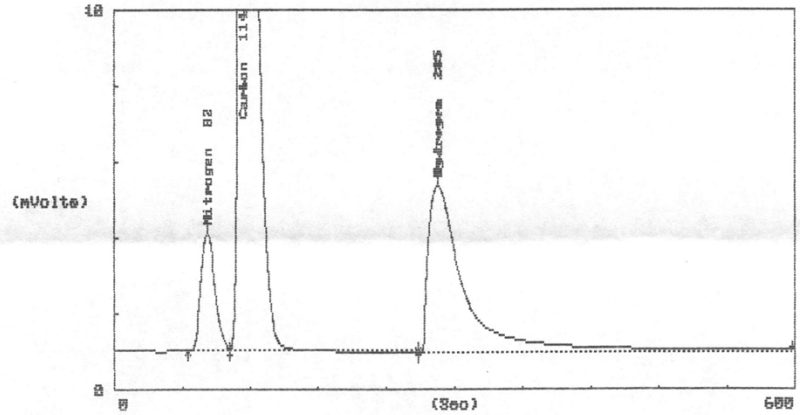


3a

EAGER 200 Stripchart

Sample Ident. : 20 Maaa6esterHCl Filename :266420
Analysed : 01-11-12 08:53:19 Printed :01-11-2012 09:03:20



EAGER 200 Peak Integration Report

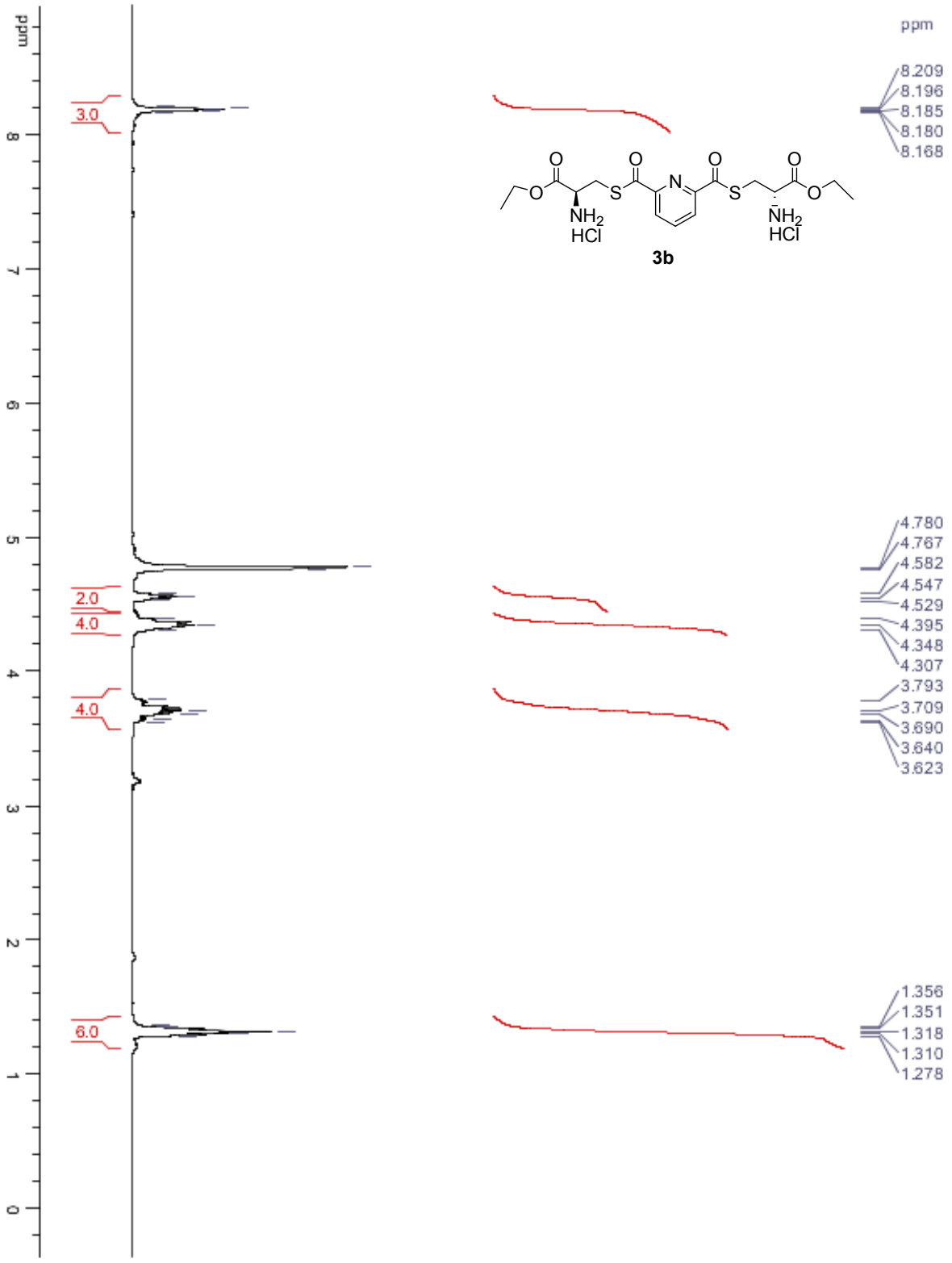
Instrument name : Instrument #1 Bline drift (fV):-4.7
Company Name : U of Florida Operator Ident. : KOU
Analysed : 01-11-12 08:53:19 Printed : 01-11-2012 09:03:21
Sample Ident. : 20 Maaa6esterHCl Filename : 266420
Sample Weight : 2.168 Calc.method: using 'K. Factors'

No. (#)	Type (#)	Start (Sec)	End (Sec)	Ret Time (Sec)	Height (fV)	Area (fV*Sec)	Area % (%)	Name
1	FU	65	102	82	3092.2	42236	6.08	Nitrogen
2	FU	102	268	114	33619.0	492721	70.94	Carbon
3	RS	268	598	285	4358.5	159626	22.98	Hydrogen
						694583	100.00	

EAGER 200 Unk Report

Instrument name : Instrument #1 Bline drift (fV):-4.7
Company Name : U of Florida Operator Ident. : KOU
Analysed : 01-11-12 08:53:19 Printed : 01-11-2012 09:03:21
Sample Ident. : 20 Maaa6esterHCl Filename : 266420
Sample Weight : 2.168 Calc.method: using 'K. Factors'

Pk. (#)	Ret Time (Sec)	Area (fV*Sec)	Element % (%)	Area Ratio	Name
1	82	42236	8.828	.116658E+02	Nitrogen
2	114	492721	37.745	.100000E+01	Carbon
3	285	159626	4.569	.308673E+01	Hydrogen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3.793
3.709
3.690
3.640
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6.0
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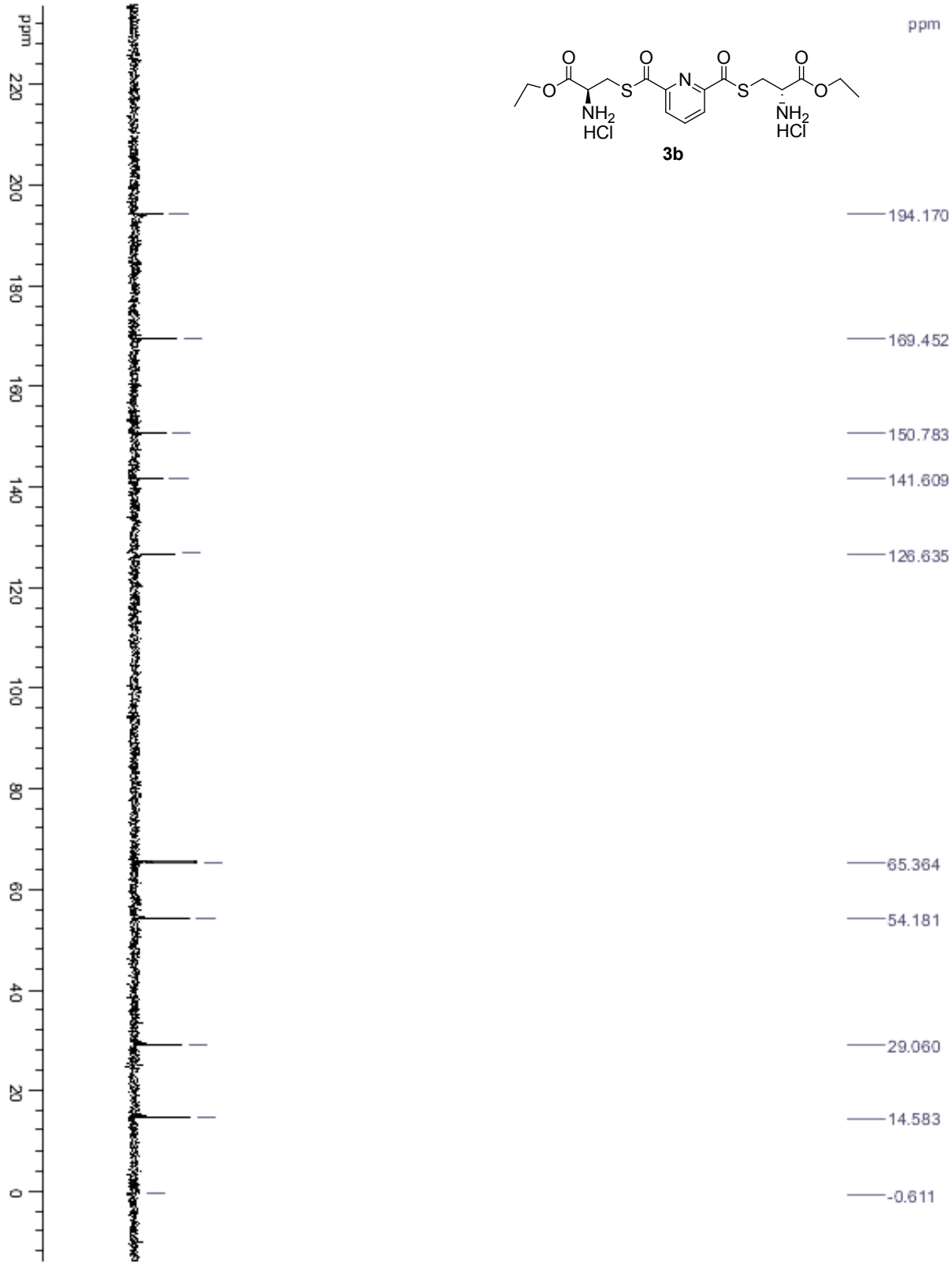
HCl
NH2
HCl
3b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141.609
126.635
65.364
54.181
29.060
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-0.611
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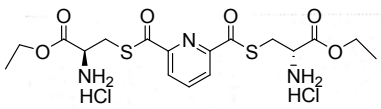
O
O
O
O
S
S
N
NH2
HCl
NH2
HCl

3b



3b

EAGER 200 Stripchart

Sample Ident. : 20 maaa6ethyl Filename :267120
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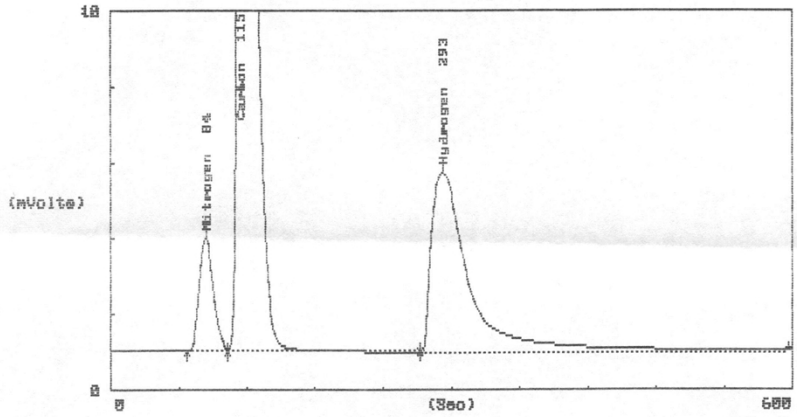


EAGER 200 Peak Integration Report

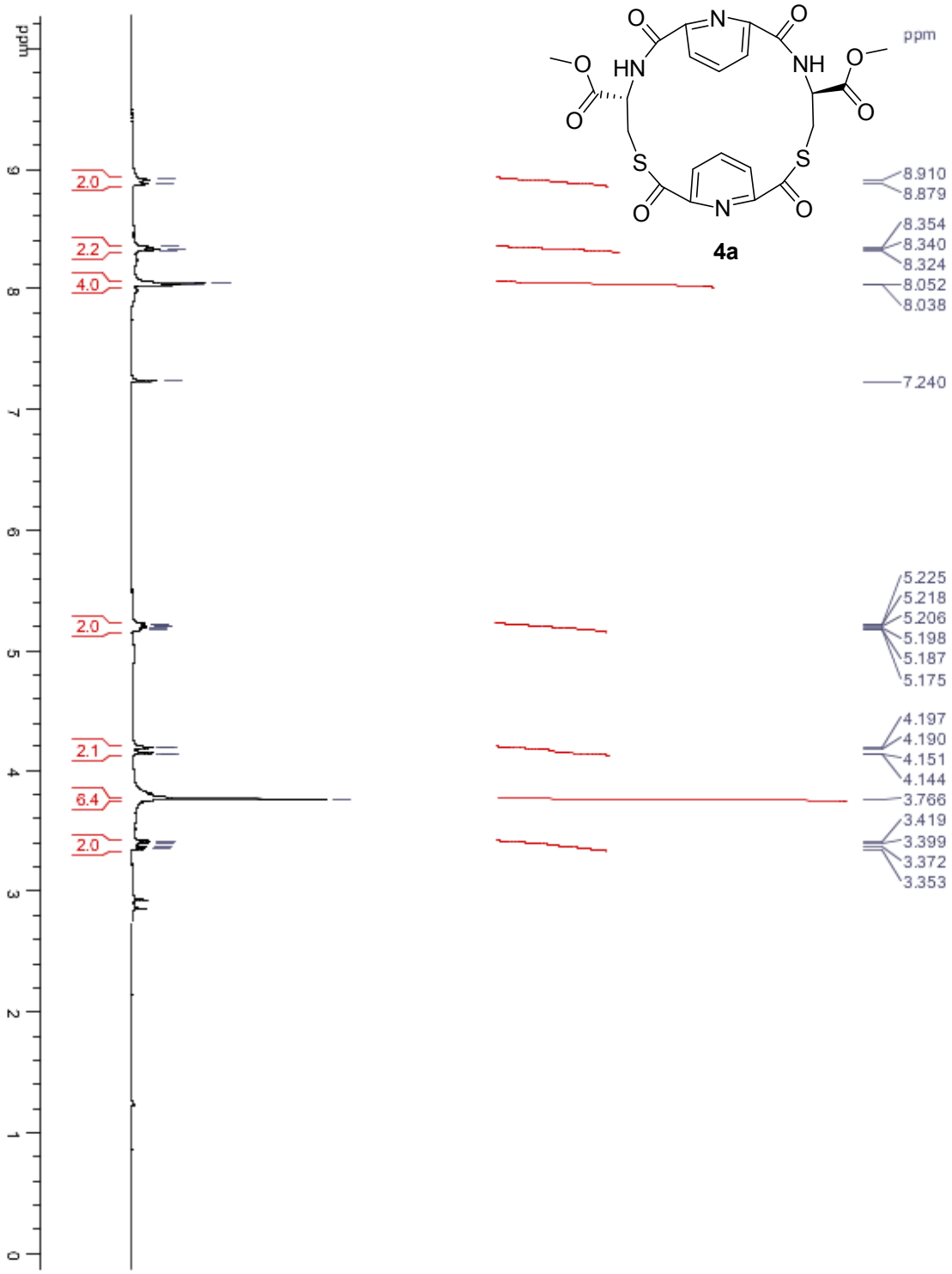
Instrument name : Instrument #1 Bline drift (fV): .9
Company Name : U of Florida Operator Ident. : KOU
Analysed : 02-14-12 08:47:21 Printed : 02-14-2012 08:57:24
Sample Ident. : 20 maaa6ethyl Filename : 267120
Sample Weight : 2.172 Calc.method: using 'K. Factors'

No. (#)	Type (#)	Start (Sec)	End (Sec)	Ret Time (Sec)	Height (fV)	Area (fV*Sec)	Area % (%)	Name
1	FU	67	103	84	2962.1	40633	5.34	Nitrogen
2	FU	103	272	115	36689.9	538909	70.78	Carbon
3	RS	272	597	293	4711.7	181833	23.88	Hydrogen
						761375	100.00	

EAGER 200 Unk Report

Instrument name : Instrument #1 Bline drift (fV): .9
Company Name : U of Florida Operator Ident. : KOU
Analysed : 02-14-12 08:47:21 Printed : 02-14-2012 08:57:24
Sample Ident. : 20 maaa6ethyl Filename : 267120
Sample Weight : 2.172 Calc.method: using 'K. Factors'

Pk. (#)	Ret Time (Sec)	Area (fV*Sec)	Element % (%)	Area Ratio	Name
1	84	40633	8.454	.132628E+02	Nitrogen
2	115	538909	40.999	.100000E+01	Carbon
3	293	181833	5.372	.296375E+01	Hydrogen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8.052
8.038
7.240
5.225
5.218
5.206
5.198
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4.190
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3.419
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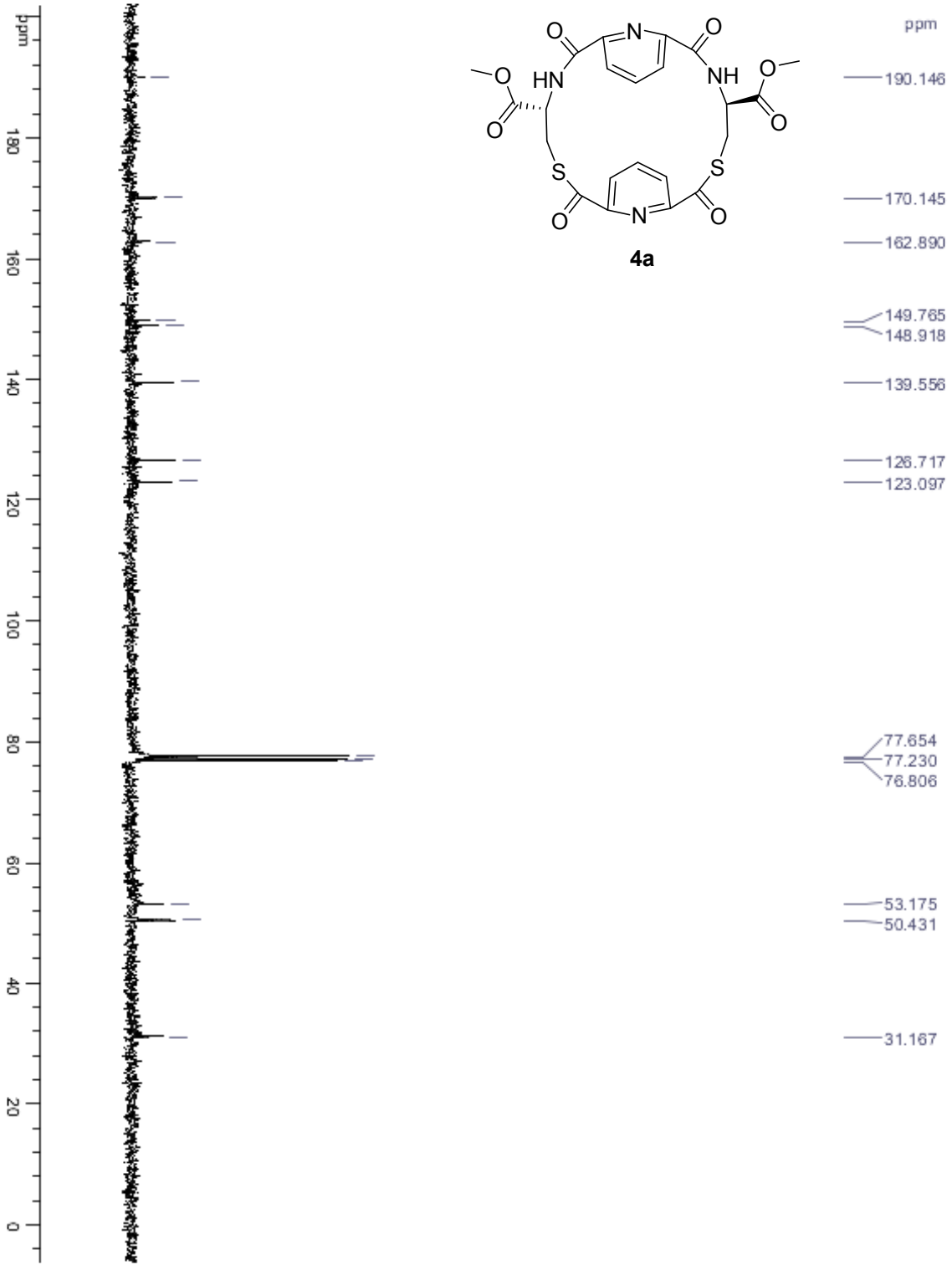
3.372
3.353
4a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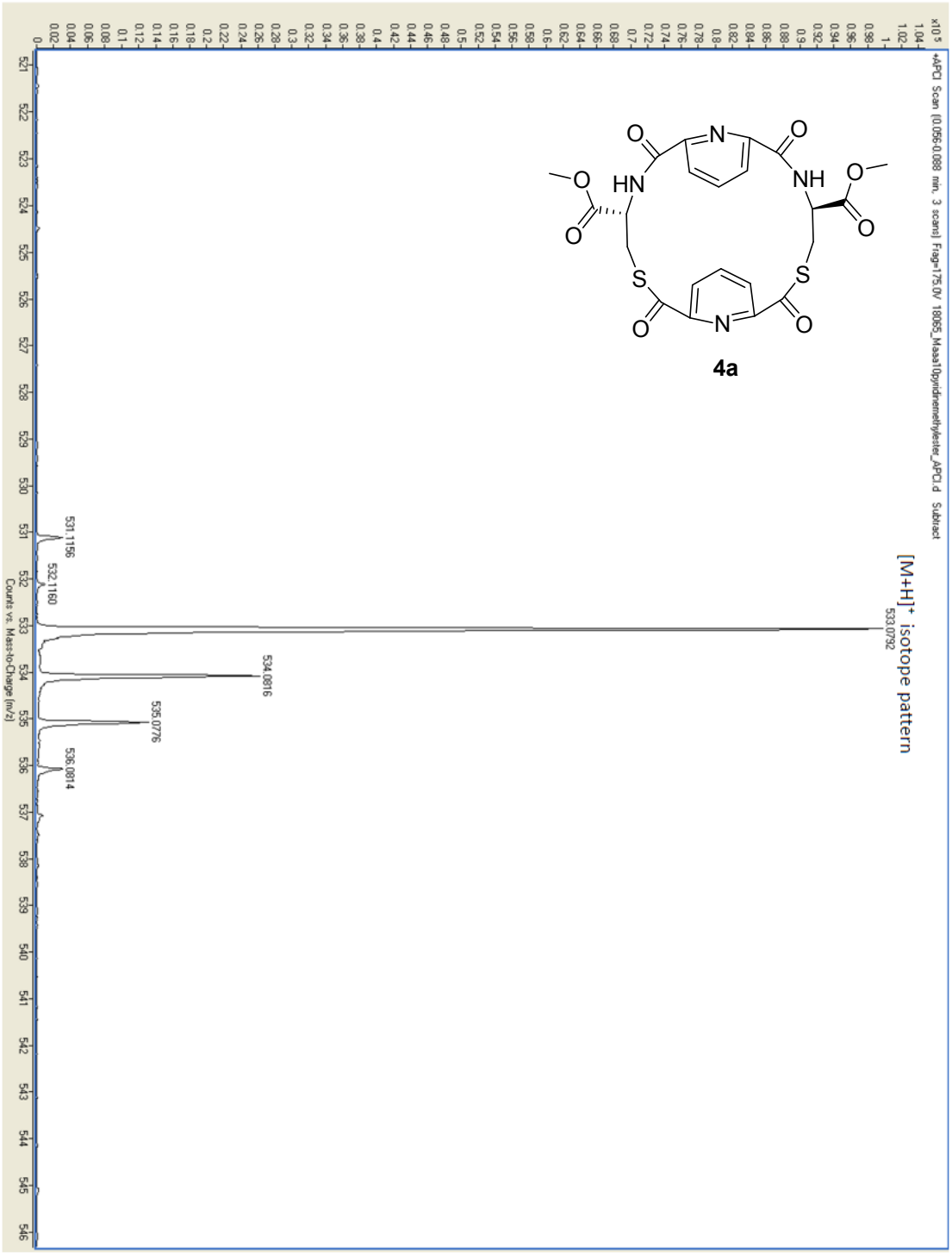
76.806
53.175
50.431
31.167

4a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[M+H]+ isotope pattern
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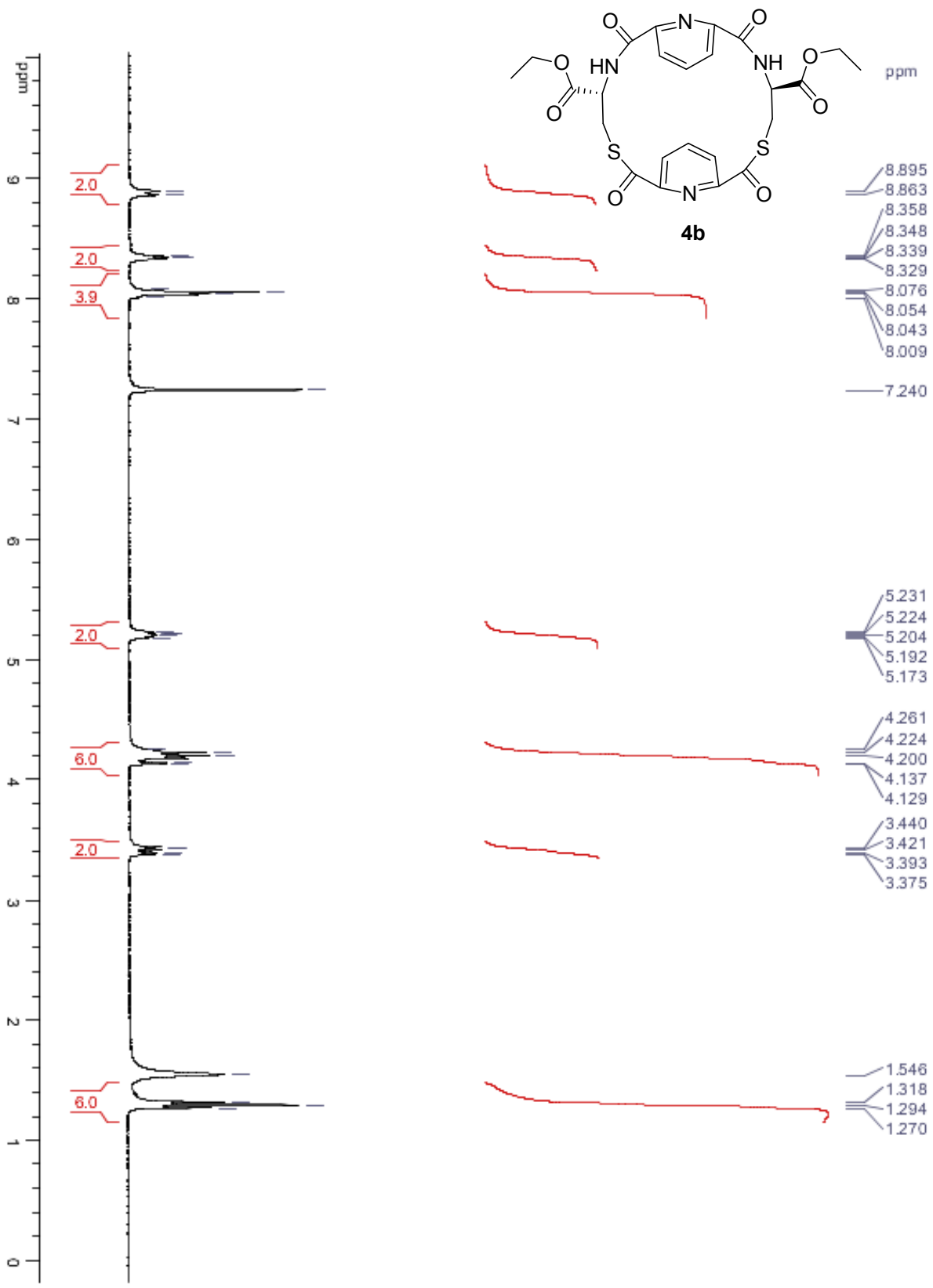
535.0776
536.0814
531.1156
532.1160
Counts vs. Mass-to-Charge (m/z)
4a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8.076
8.054
8.043
8.009
7.240
5.231
5.224
5.204
5.192
5.173
4.261
4.224
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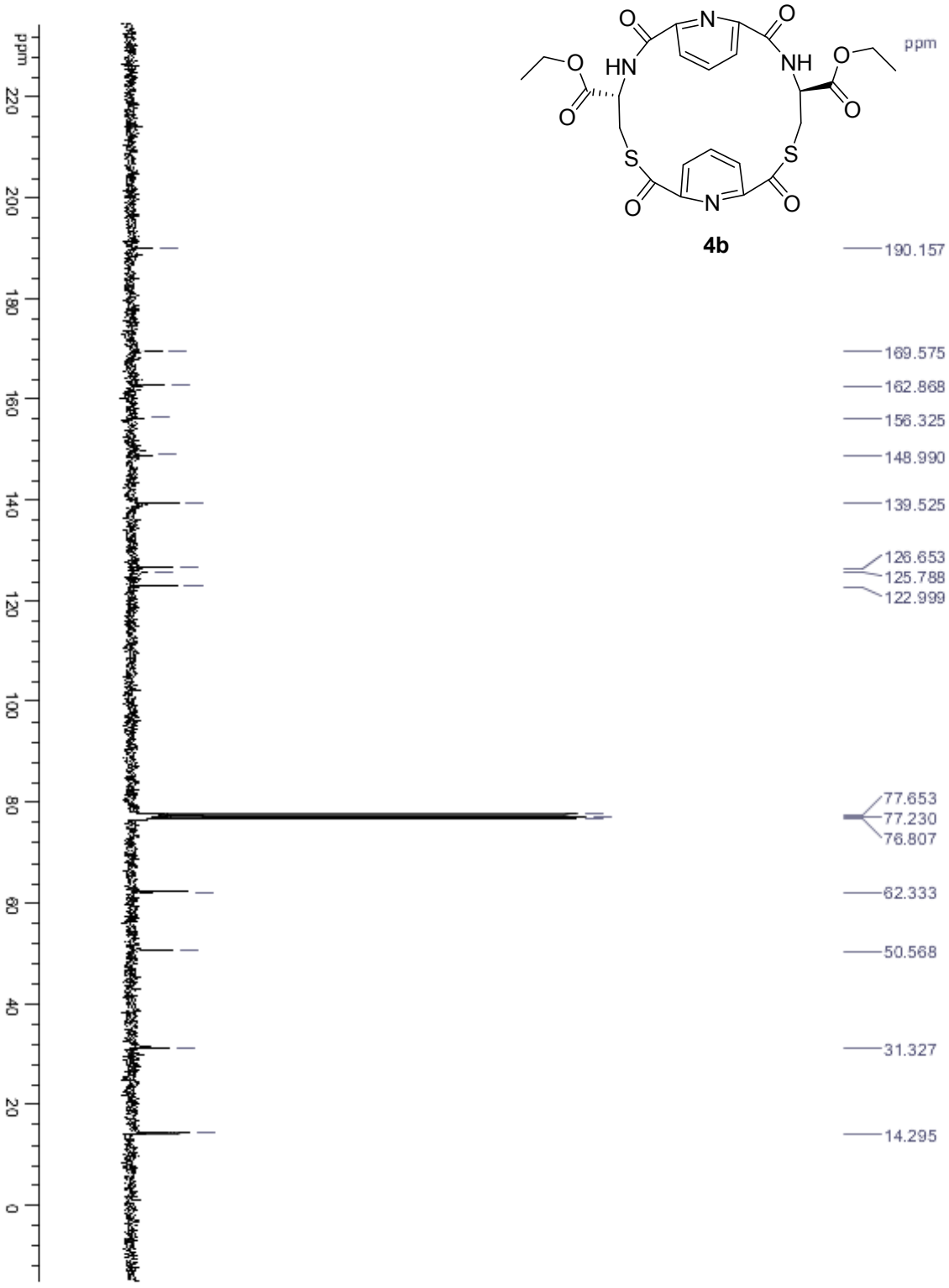
1.318
1.294
1.270
4b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HN
NH
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O
N
O
ppm
190.157
169.575
162.868
156.325
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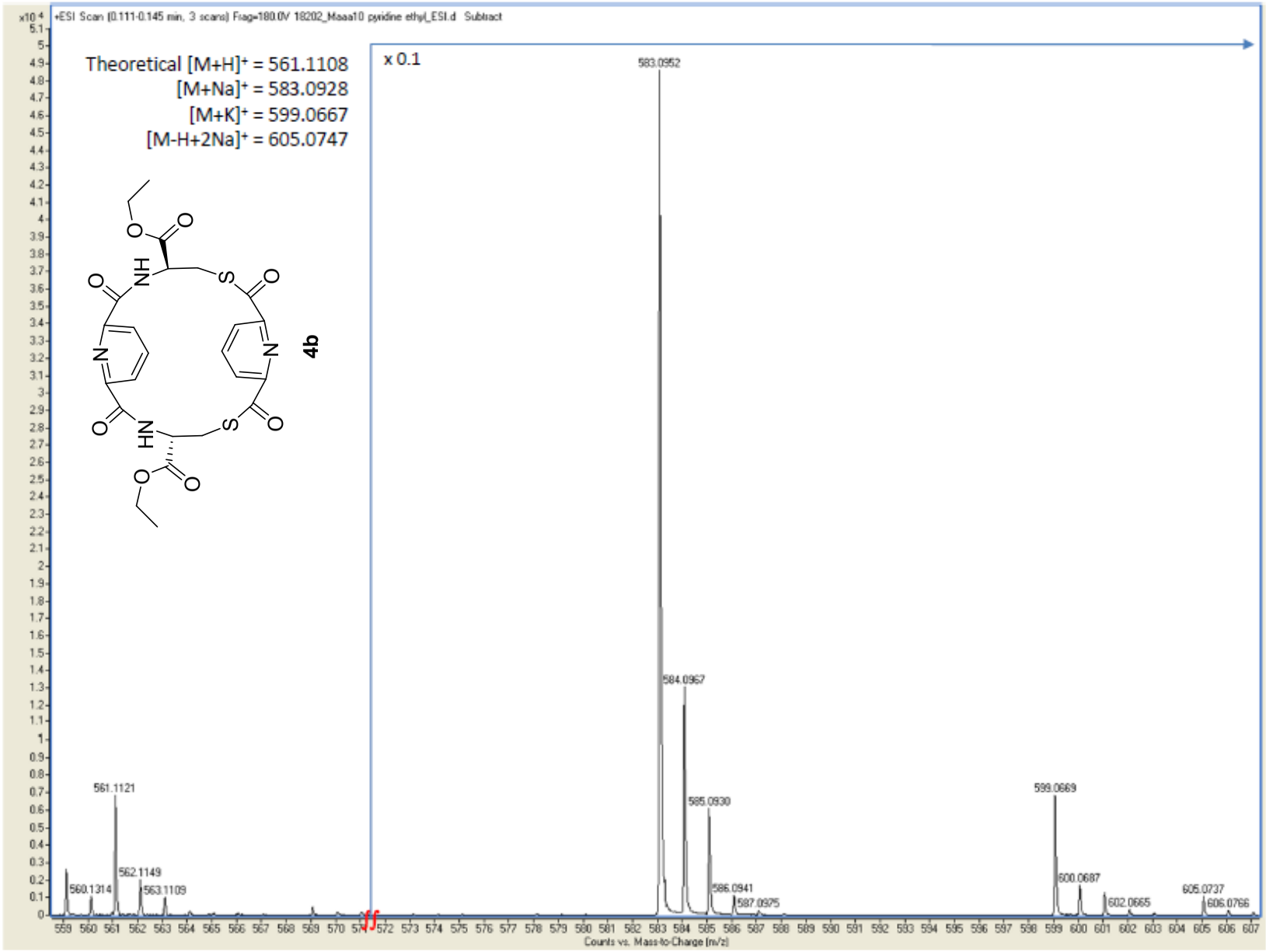
31.327
14.295

4b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Theoretical [M+H]+ = 561.1108
[M+Na]+ = 583.0928
[M+K]+ = 599.0667
[M-H+2Na]+ = 605.0747
x 0.1
4b
583.0952
584.0957
585.0930
586.0941
587.0975
561.1121
560.1314
562.1149
563.1109
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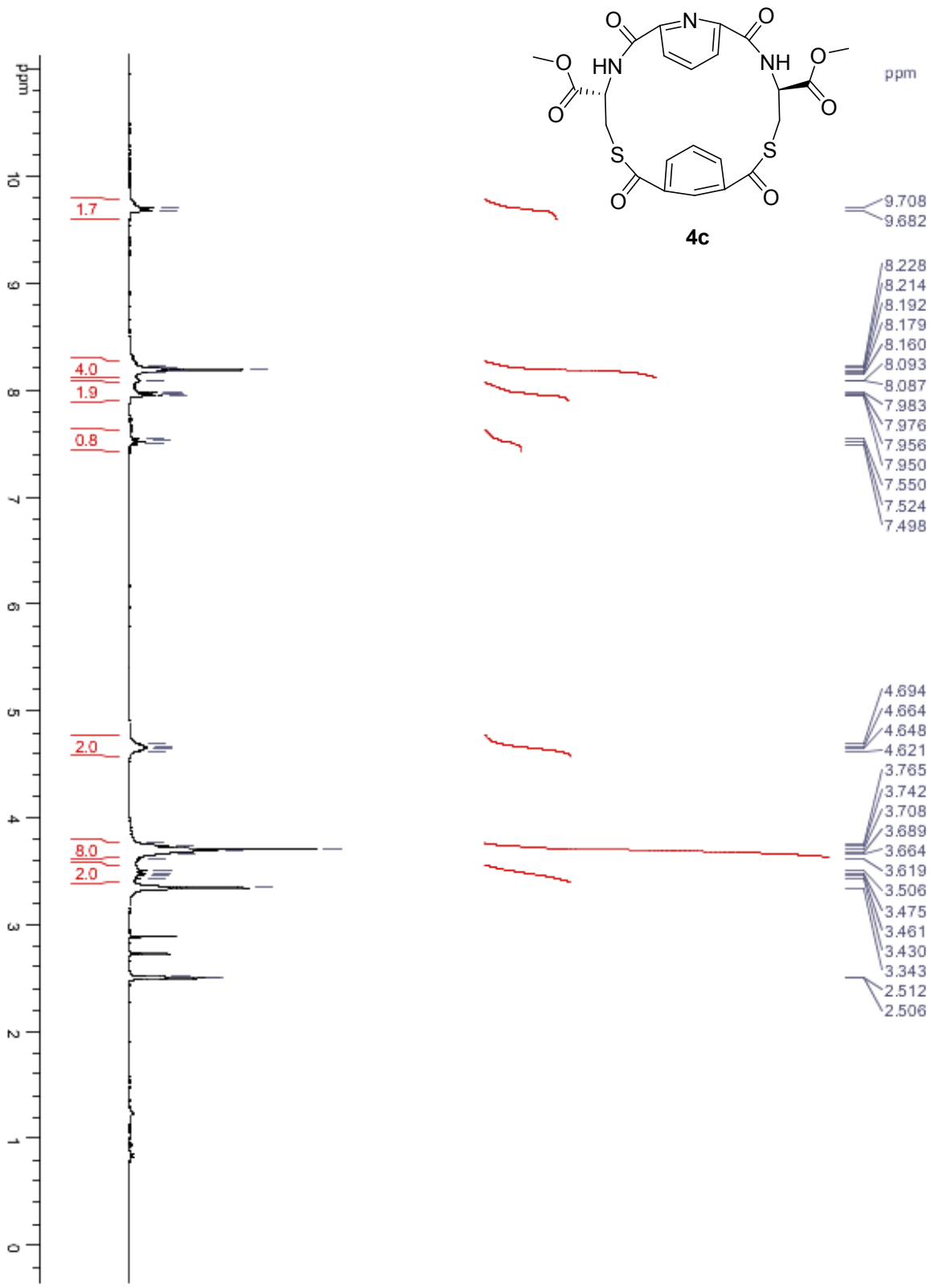
600.0687
602.0665
605.0737
606.0766
Counts vs. Mass-to-Charge (m/z)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HN
NH
O
N
S
4c
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9.682
8.228
8.214
8.192
8.179
8.160
8.093
8.087
7.983
7.976
7.956
7.950
7.550
7.524
7.498
4.694
4.664
4.648
4.621
3.765
3.742
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3.343
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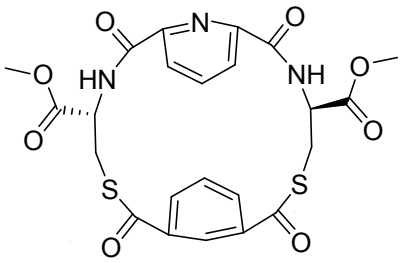
2.506


O
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O
HN
NH
O
O
O
O
S
S
O
O

4c

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139.871
136.473
131.714
130.051
124.913
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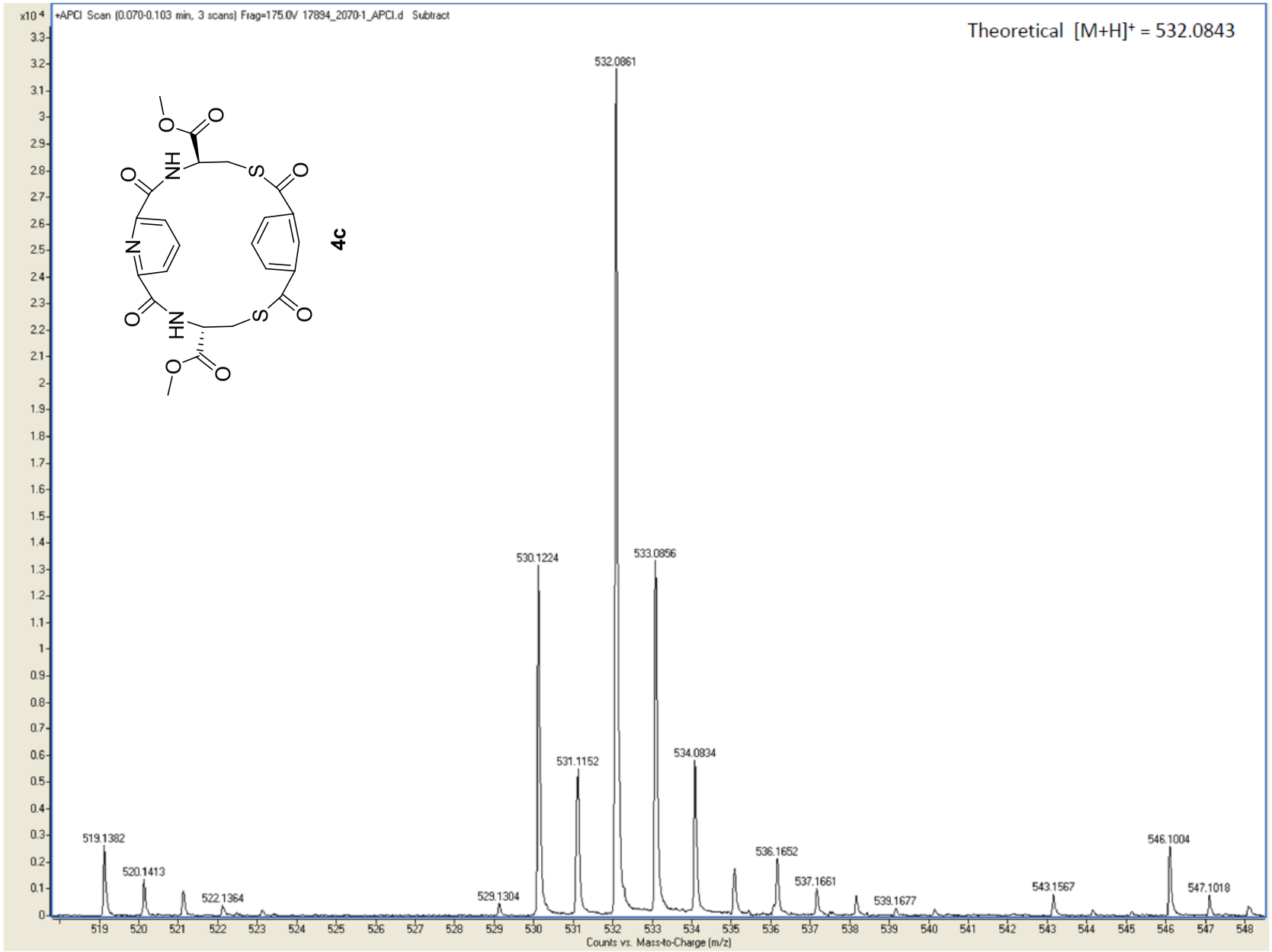
ppm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Theoretical [M+H]+ = 532.0843
4c
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533.0856
531.1152
534.0834
519.1382
520.1413
522.1364
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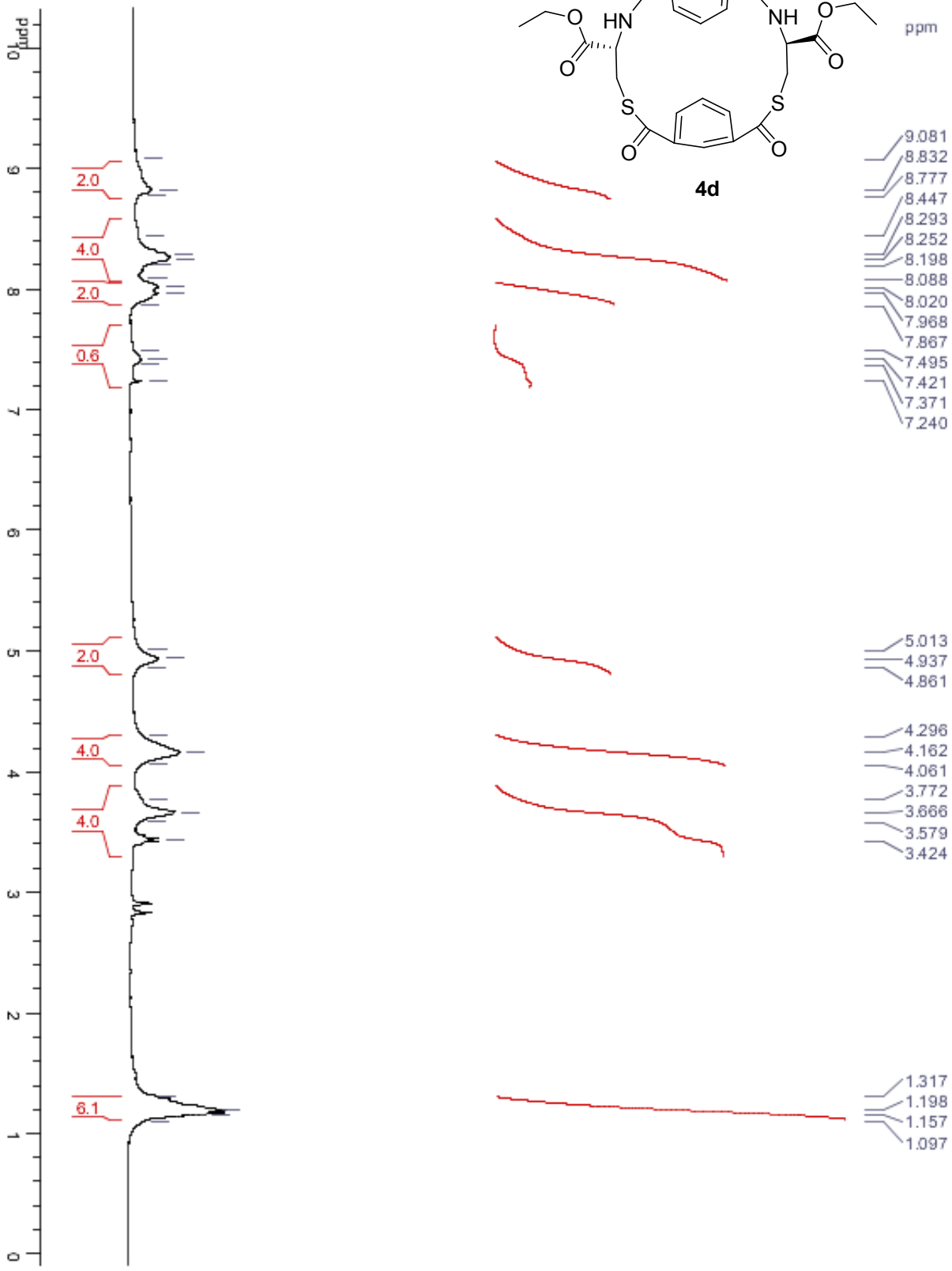
547.1018
Counts vs. Mass-to-Charge (m/z)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4.0
4.0
6.1
O
N
O
HN
NH
O
O
O
S
S
O
O
4d
ppm
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8.447
8.293
8.252
8.198
8.088
8.020
7.968
7.867
7.495
7.421
7.371
7.240
5.013
4.937
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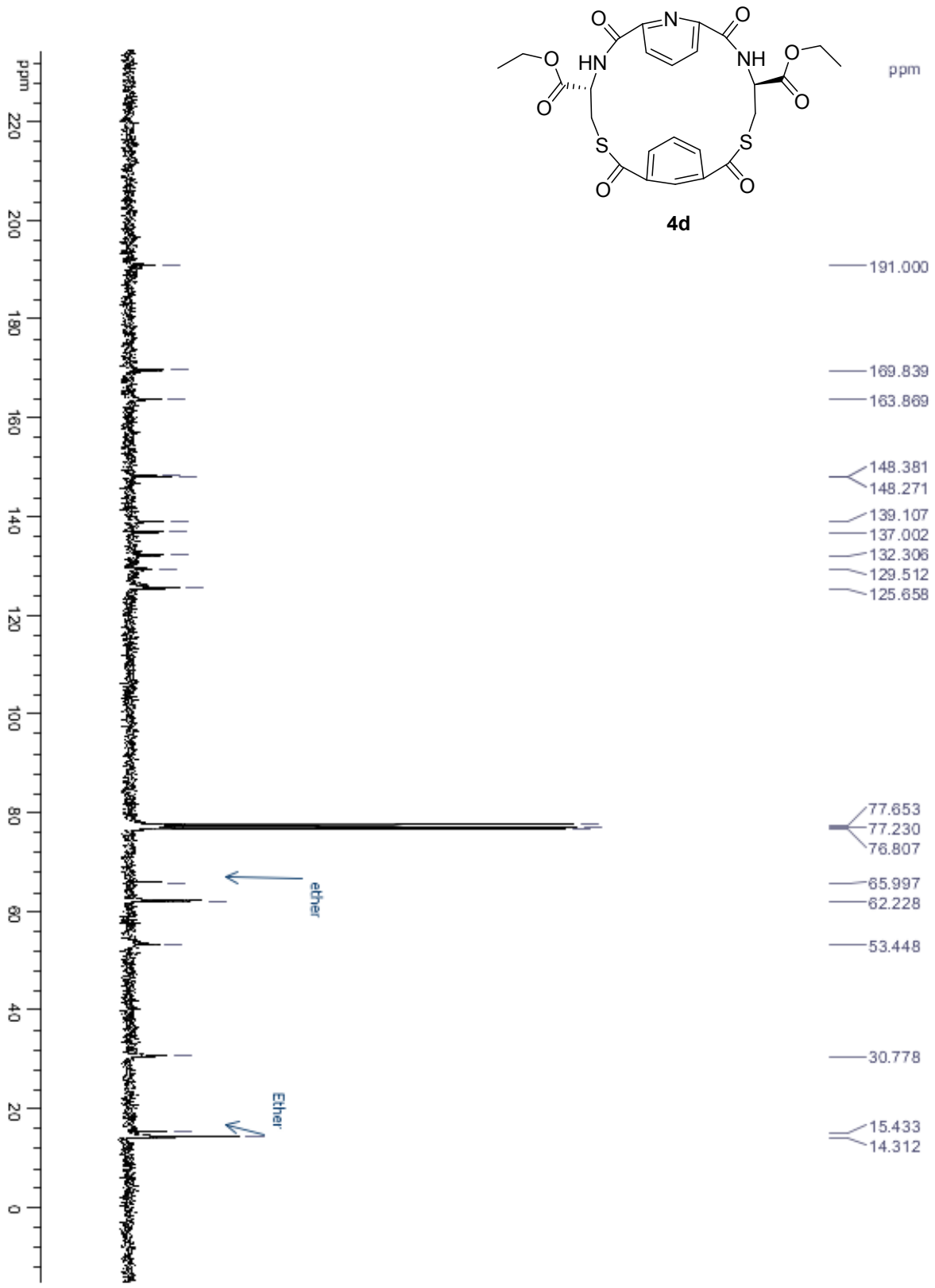
1.157
1.097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139.107
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132.306
129.512
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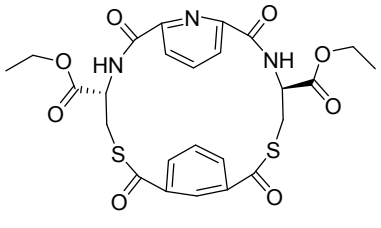
77.230
76.807
65.997
62.228
53.448
30.778
15.433
14.312

4d

EAGER 200 Stripchart

Sample Ident. : 23 macrocyclic Phthalic ethyl ester Filename :269423
Analysed : 04-25-12 08:12:19 Printed :04-25-2012 08:22:21



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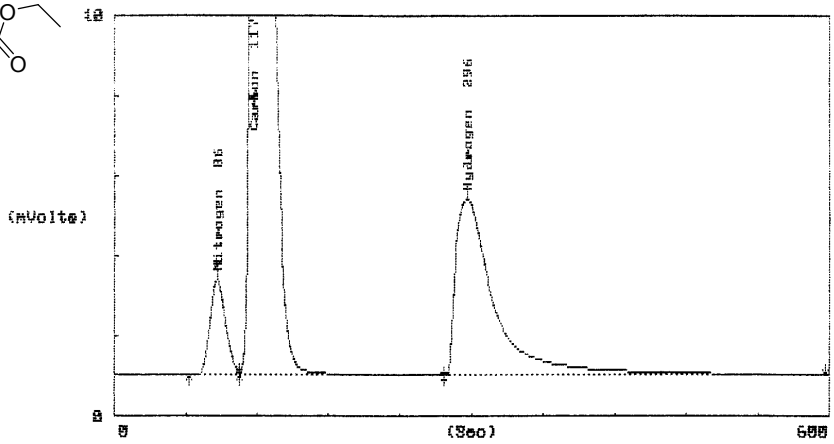


EAGER 200 Peak Integration Report

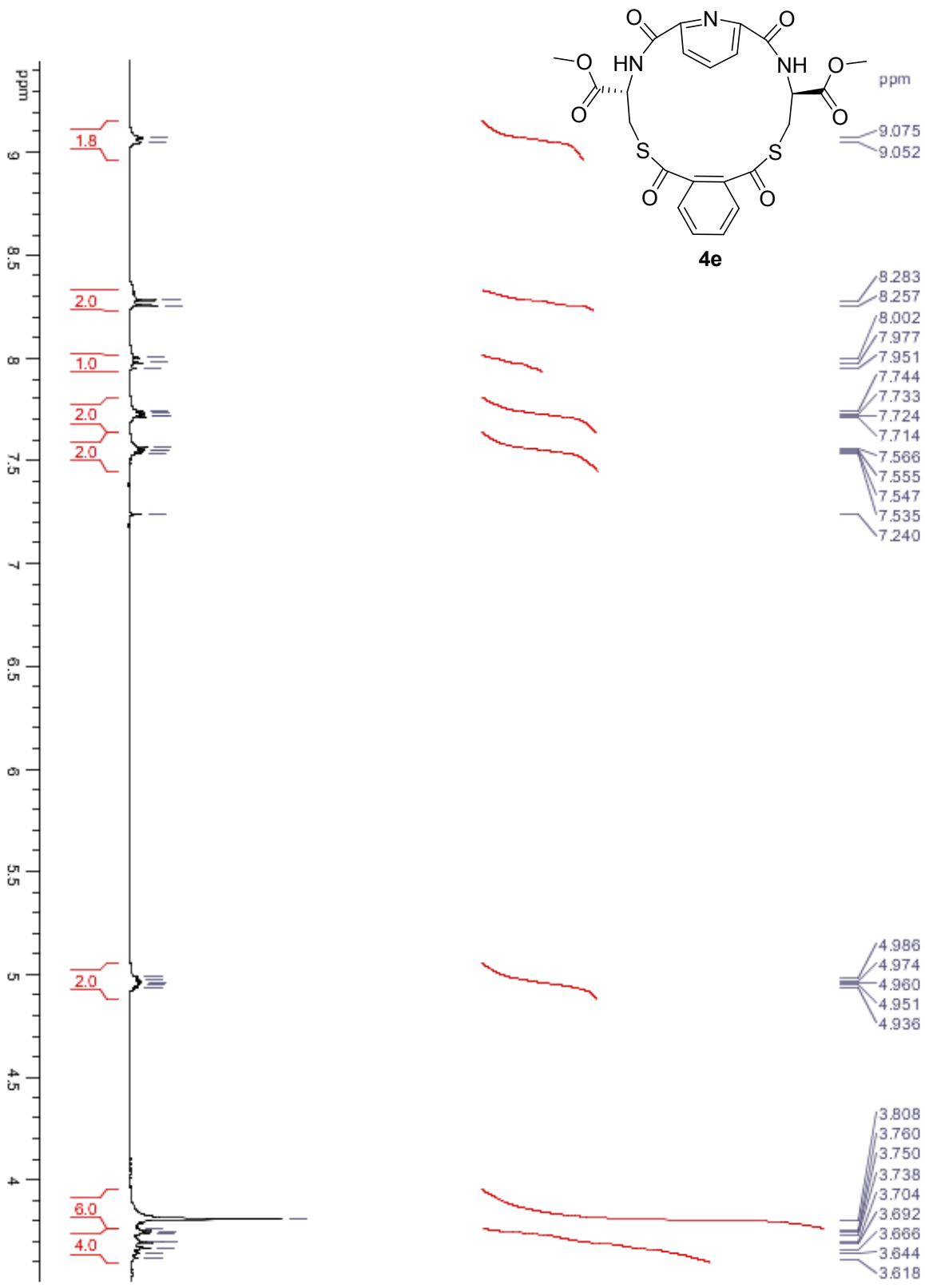
Instrument name : Instrument #1 Bline drift (fV): 6.8
Company Name : U of Florida Operator Ident. : KOU
Analysed : 04-25-12 08:12:19 Printed : 04-25-2012 08:22:22
Sample Ident. : 23 1985-01 Filename : 269423
Sample Weight : 2.111 Calc.method: using 'K. Factors'

No. (#)	Type (#)	Start (Sec)	End (Sec)	Ret Time (Sec)	Height (fV)	Area (fV*Sec)	Area % (%)	Name
1	FU	63	105	86	2391.2	34425	3.82	Nitrogen
2	FU	105	277	117	44233.0	696815	77.23	Carbon
3	RS	277	597	296	4385.9	171012	18.95	Hydrogen
						902252	100.00	

EAGER 200 Unk Report

Instrument name : Instrument #1 Bline drift (fV): 6.8
Company Name : U of Florida Operator Ident. : KOU
Analysed : 04-25-12 08:12:19 Printed : 04-25-2012 08:22:22
Sample Ident. : 23 1985-01 Filename : 269423
Sample Weight : 2.111 Calc.method: using 'K. Factors'

Pk. (#)	Ret Time (Sec)	Area (fV*Sec)	Element % (%)	Area Ratio	Name
1	86	34425	7.248	.202415E+02	Nitrogen
2	117	696815	53.546	.100000E+01	Carbon
3	296	171012	4.749	.407465E+01	Hydrogen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6.0
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S
O
O
4e
ppm
9.075
9.052
8.283
8.257
8.002
7.977
7.951
7.744
7.733
7.724
7.714
7.566
7.555
7.547
7.535
7.240
4.986
4.974
4.960
4.951
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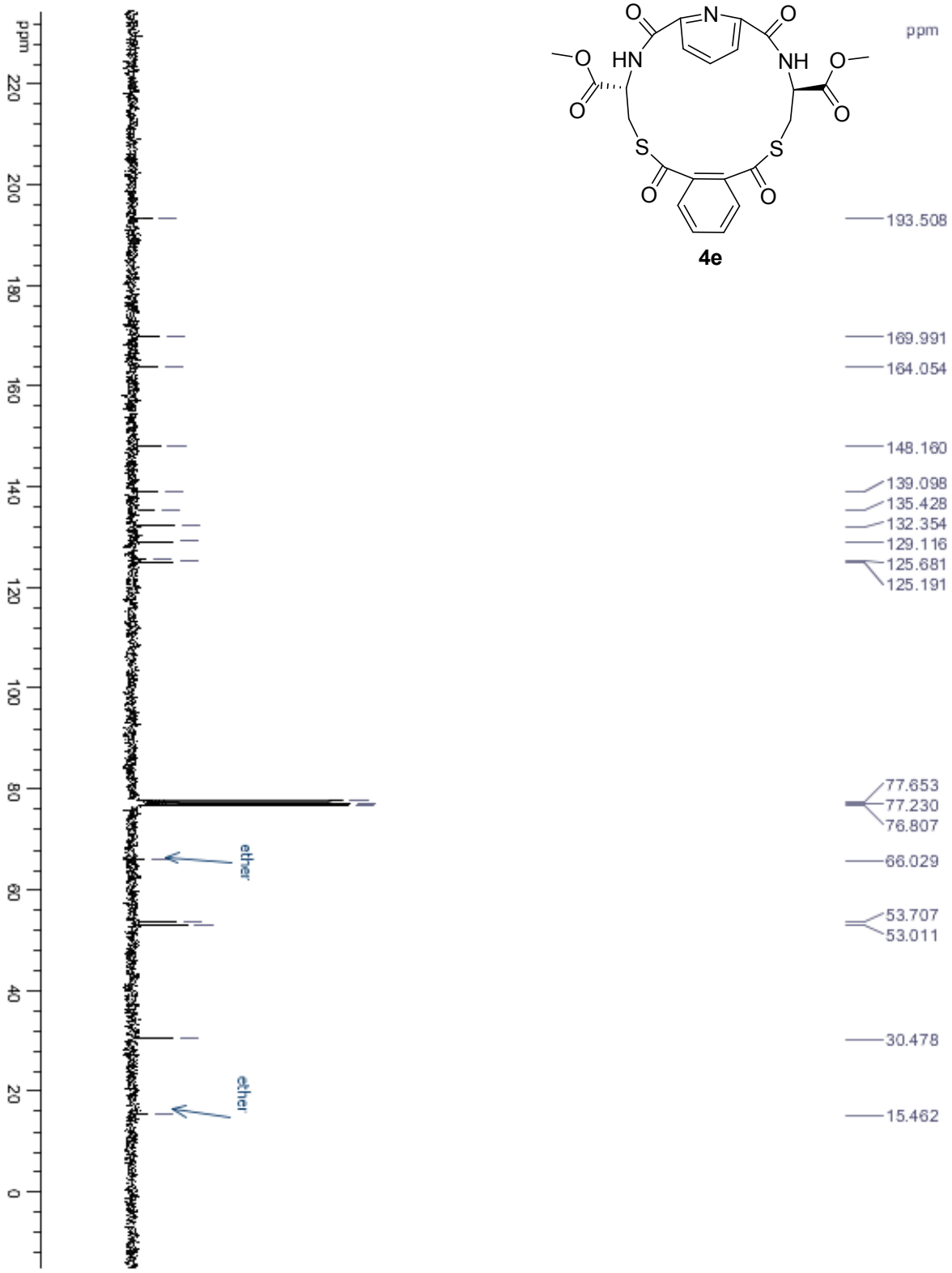
3.750
3.738
3.704
3.692
3.666
3.644
3.618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140
120
100
80
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HN
NH
O
O
O
O
S
S
O
O
4e
ppm
193.508
169.991
164.054
148.160
139.098
135.428
132.354
129.116
125.681
125.191
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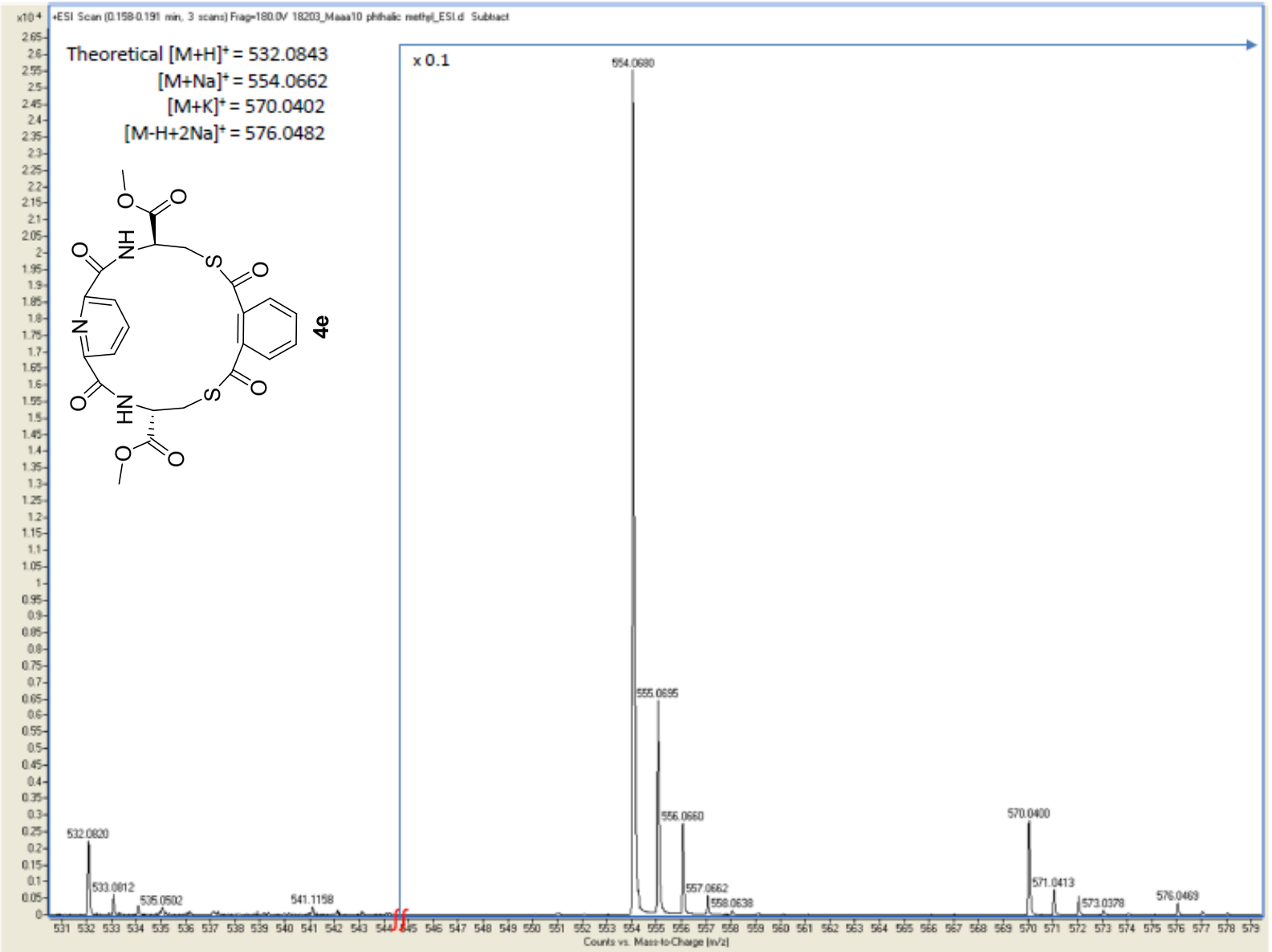
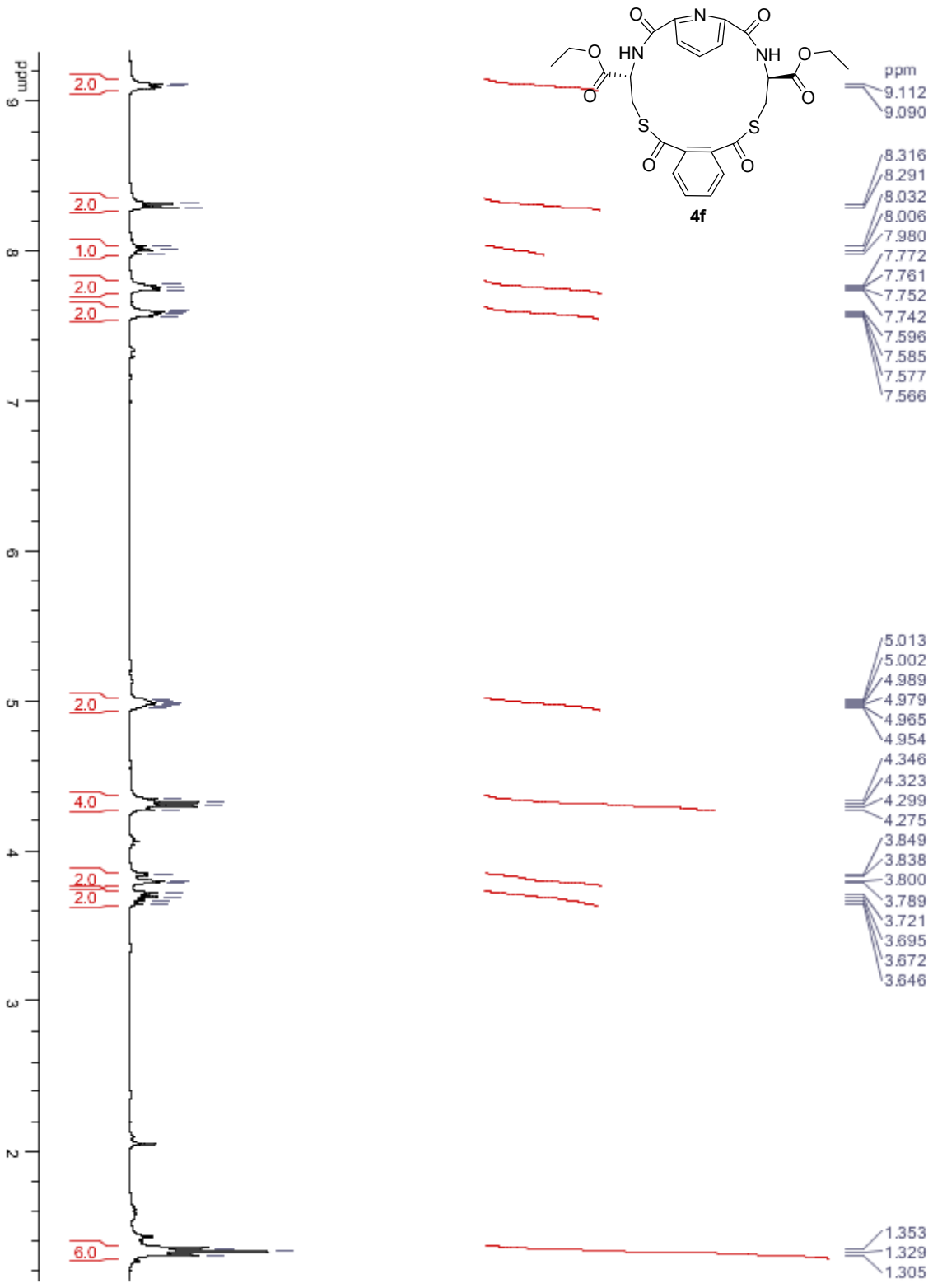
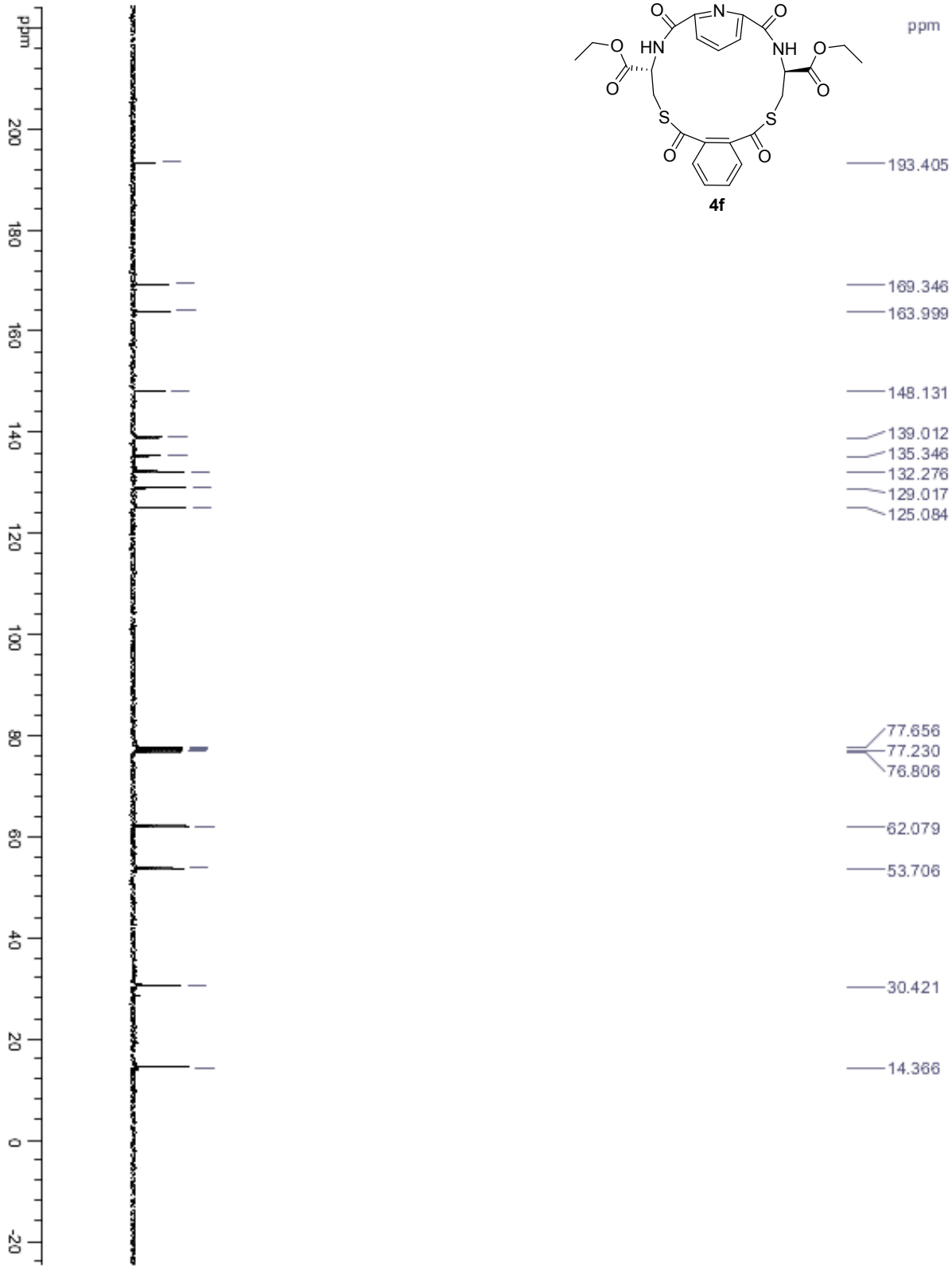
53.011
30.478
15.462


+ESI Scan (0.158-0.191 min, 3 scans) Frag=180.0V 18203_Maaa10 phthalic methyl_ESI.d Subtract
Theoretical [M+H]+ = 532.0843
[M+Na]+ = 554.0662
[M+K]+ = 570.0402
[M-H+2Na]+ = 576.0482
4e
x 0.1
554.0680
555.0695
556.0660
557.0662
558.0638
532.0820
533.0812
535.0502
541.1158
570.0400
571.0413
573.0378
576.0469
Counts vs. Mass-to-Charge (m/z)


4f
ppm
9.112
9.090
8.316
8.291
8.032
8.006
7.980
7.772
7.761
7.752
7.742
7.596
7.585
7.577
7.566
5.013
5.002
4.989
4.979
4.965
4.954
4.346
4.323
4.299
4.275
3.849
3.838
3.800
3.789
3.721
3.695
3.672
3.646
1.353
1.329
1.305
2.0
2.0
1.0
2.0
2.0
2.0
4.0
2.0
2.0
6.0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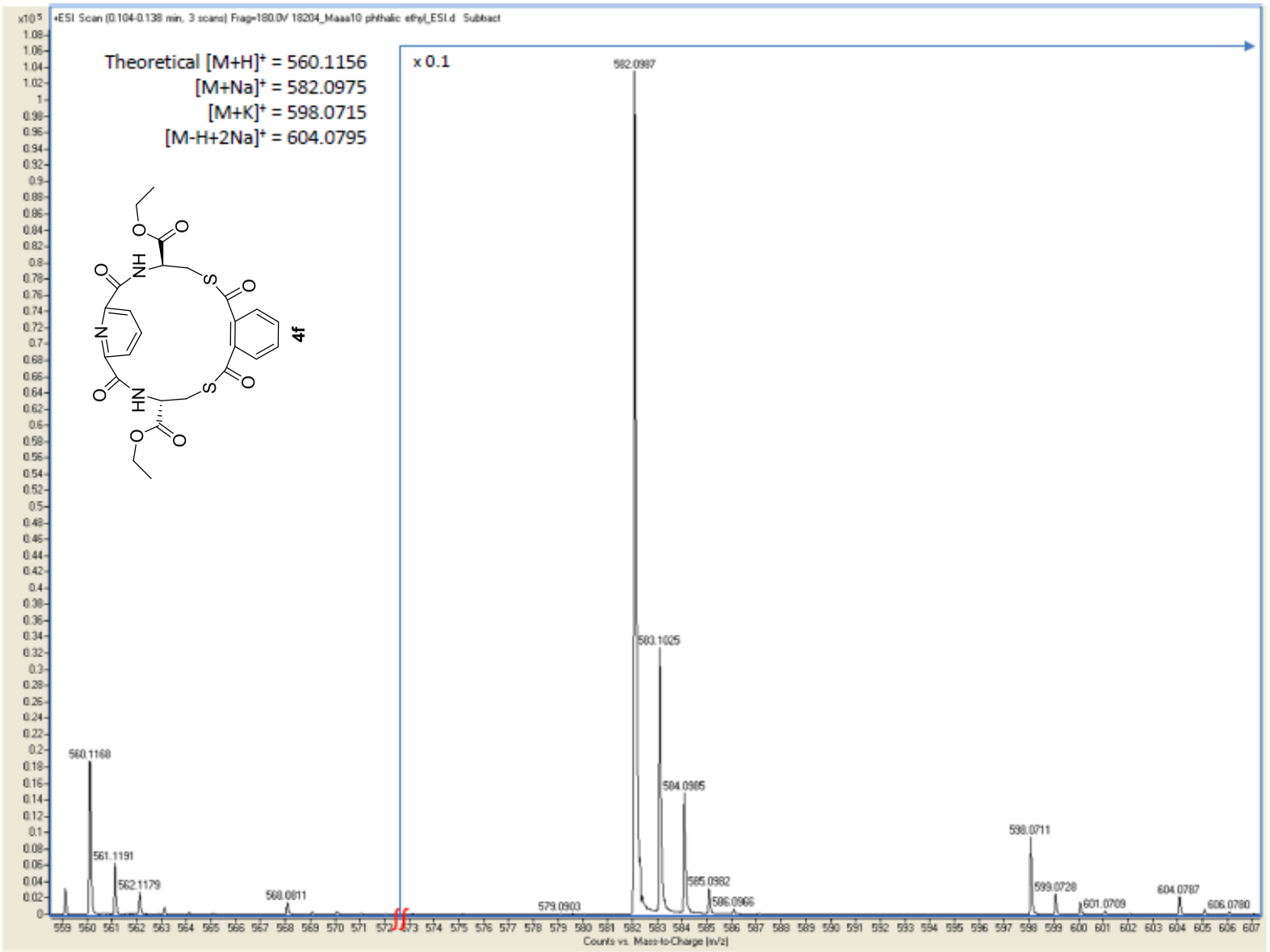
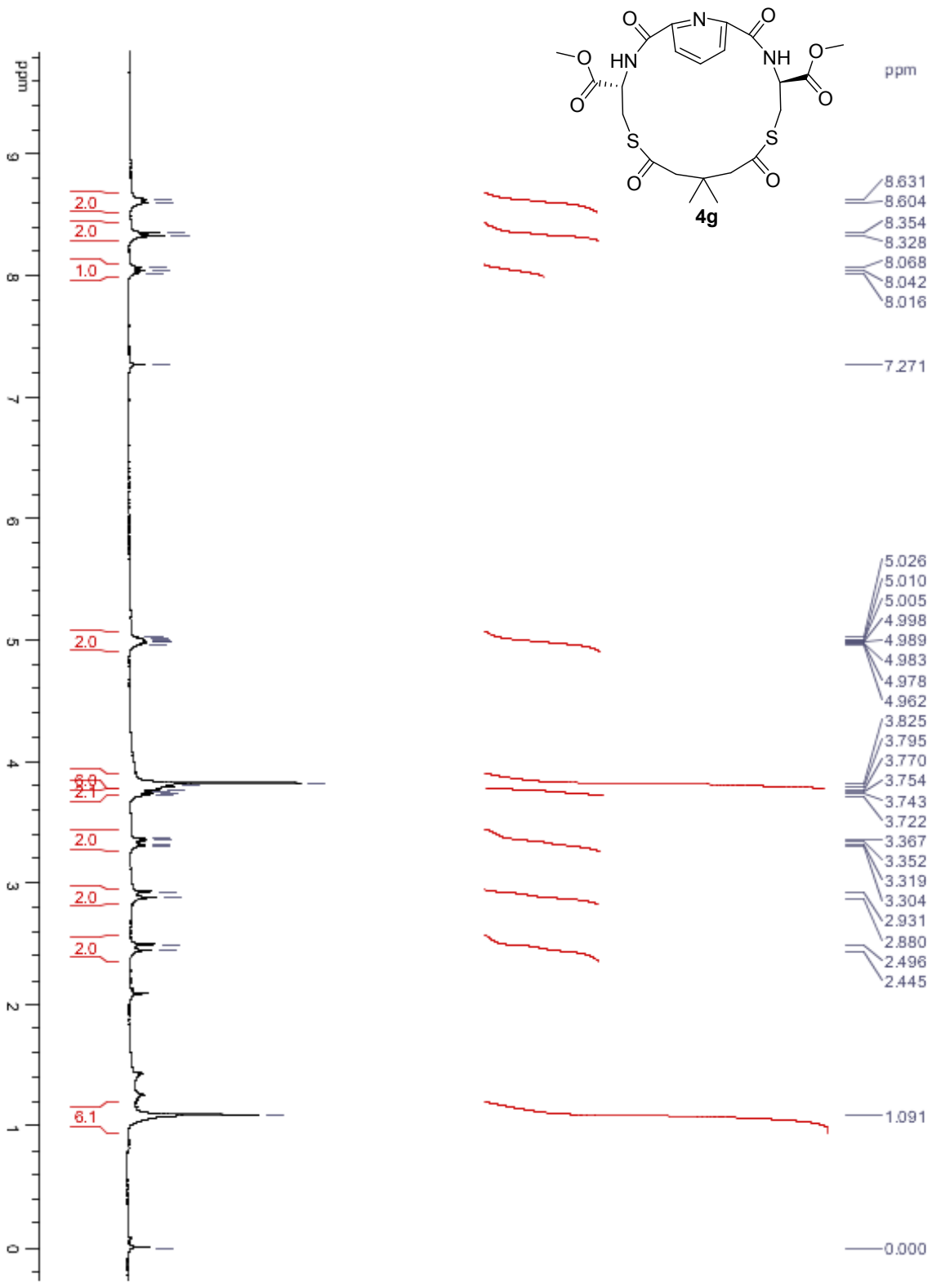
160
140
120
100
80
60
40
20
0
-20
ppm
193.405
169.346
163.999
148.131
139.012
135.346
132.276
129.017
125.084
77.656
77.230
76.806
62.079
53.706
30.421
14.366
4f


+ESI Scan (0.104-0.138 min, 3 scans) Frag=180.0V 18204_Maaa10 phthalic ethyl_ESI.d Subtract
Theoretical [M+H]+ = 560.1156
[M+Na]+ = 582.0975
[M+K]+ = 598.0715
[M-H+2Na]+ = 604.0795
x 0.1
4f
582.0987
583.1025
560.1168
561.1191
562.1179
568.0811
579.0903
584.0985
585.0982
586.0966
598.0711
599.0728
601.0709
604.0787
606.0780
Counts vs. Mass-to-Charge (m/z)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7
6
5
4
3
2
1
0
2.0
2.0
1.0
2.0
6.0
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2.0
2.0
2.0
6.1
O
N
O
HN
NH
O
O
O
S
S
O
O
O
O
4g
ppm
8.631
8.604
8.354
8.328
8.068
8.042
8.016
7.271
5.026
5.010
5.005
4.998
4.989
4.983
4.978
4.962
3.825
3.795
3.770
3.754
3.743
3.722
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3.352
3.319
3.304
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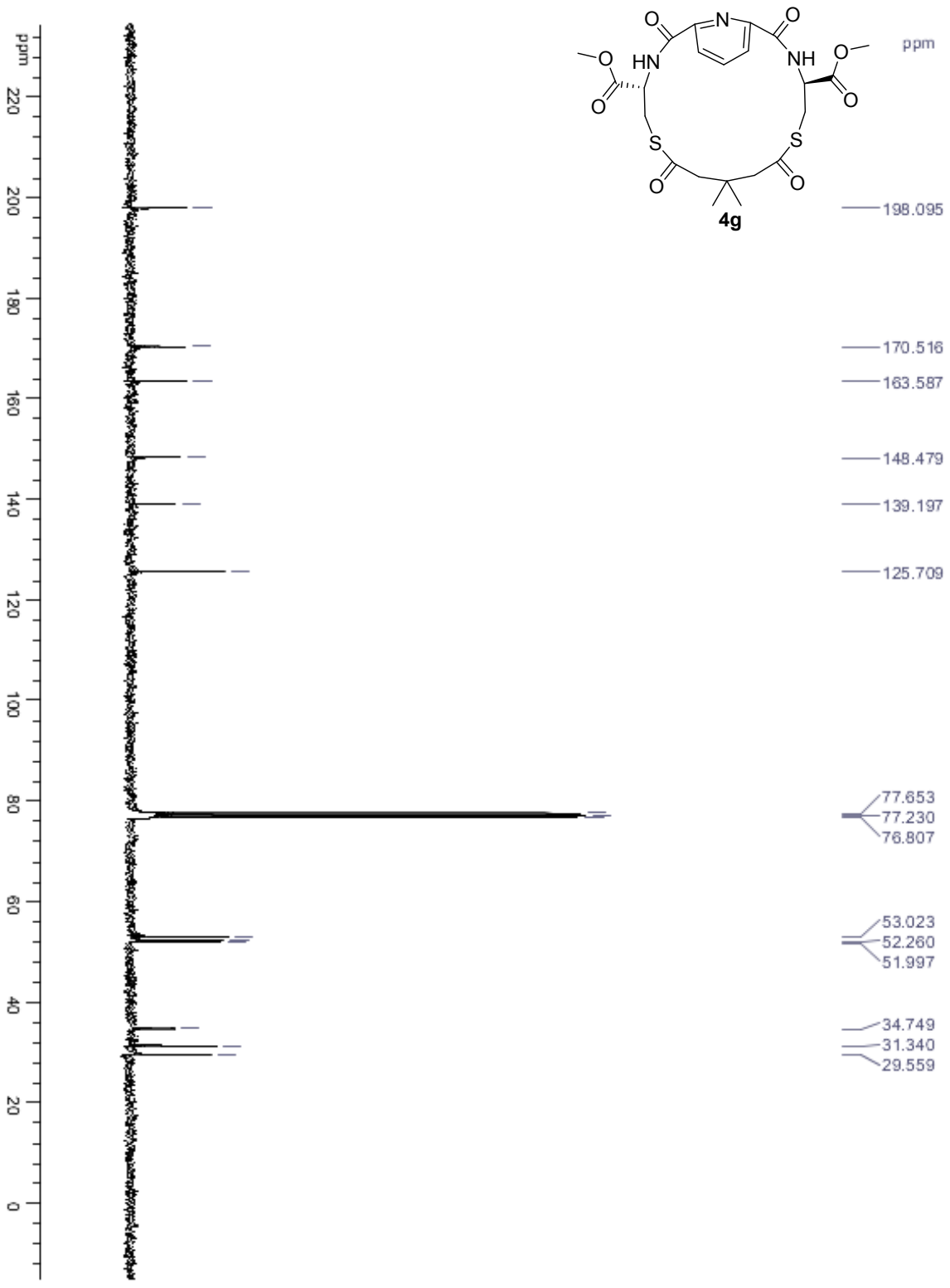
1.091
0.000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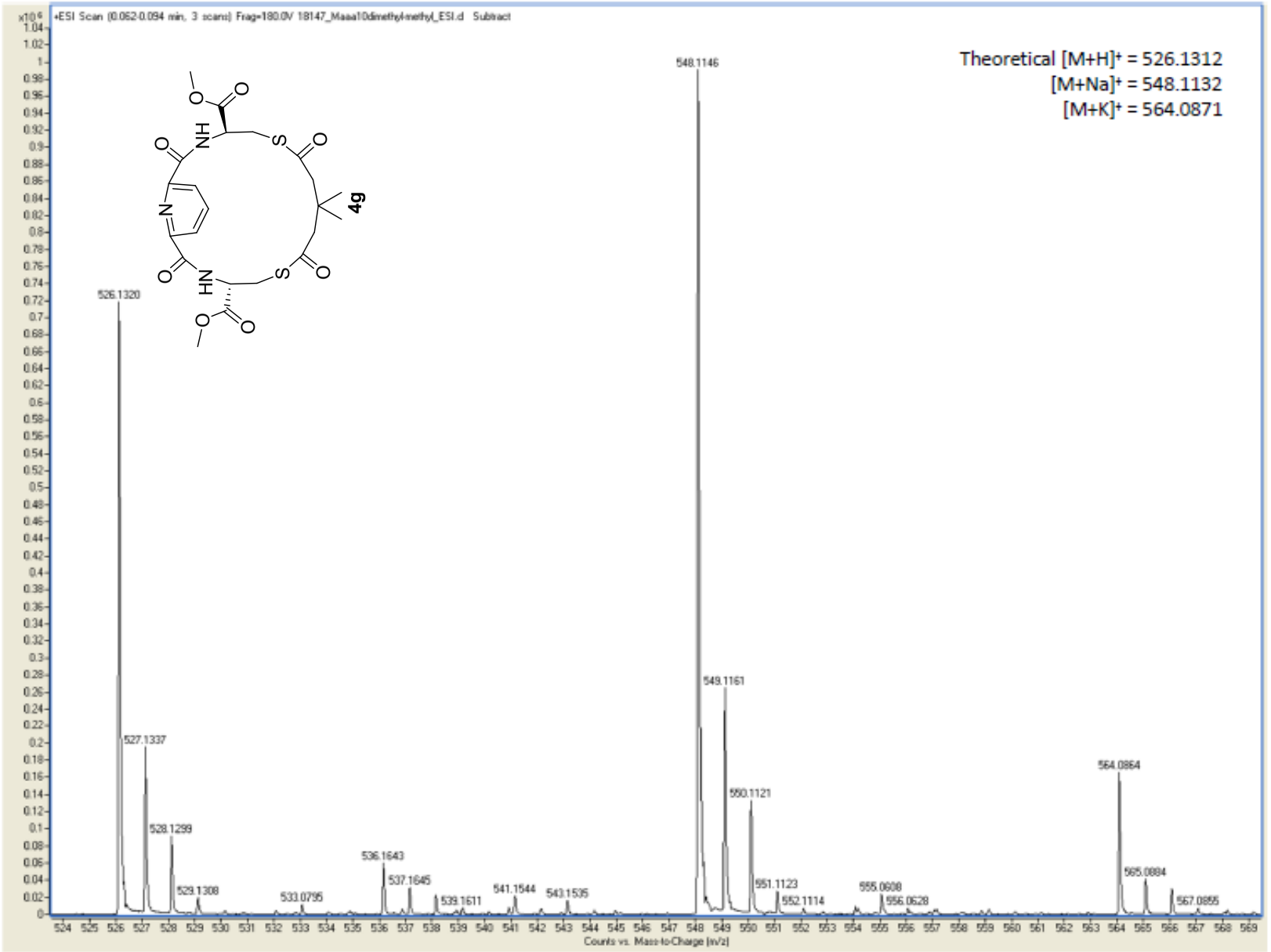
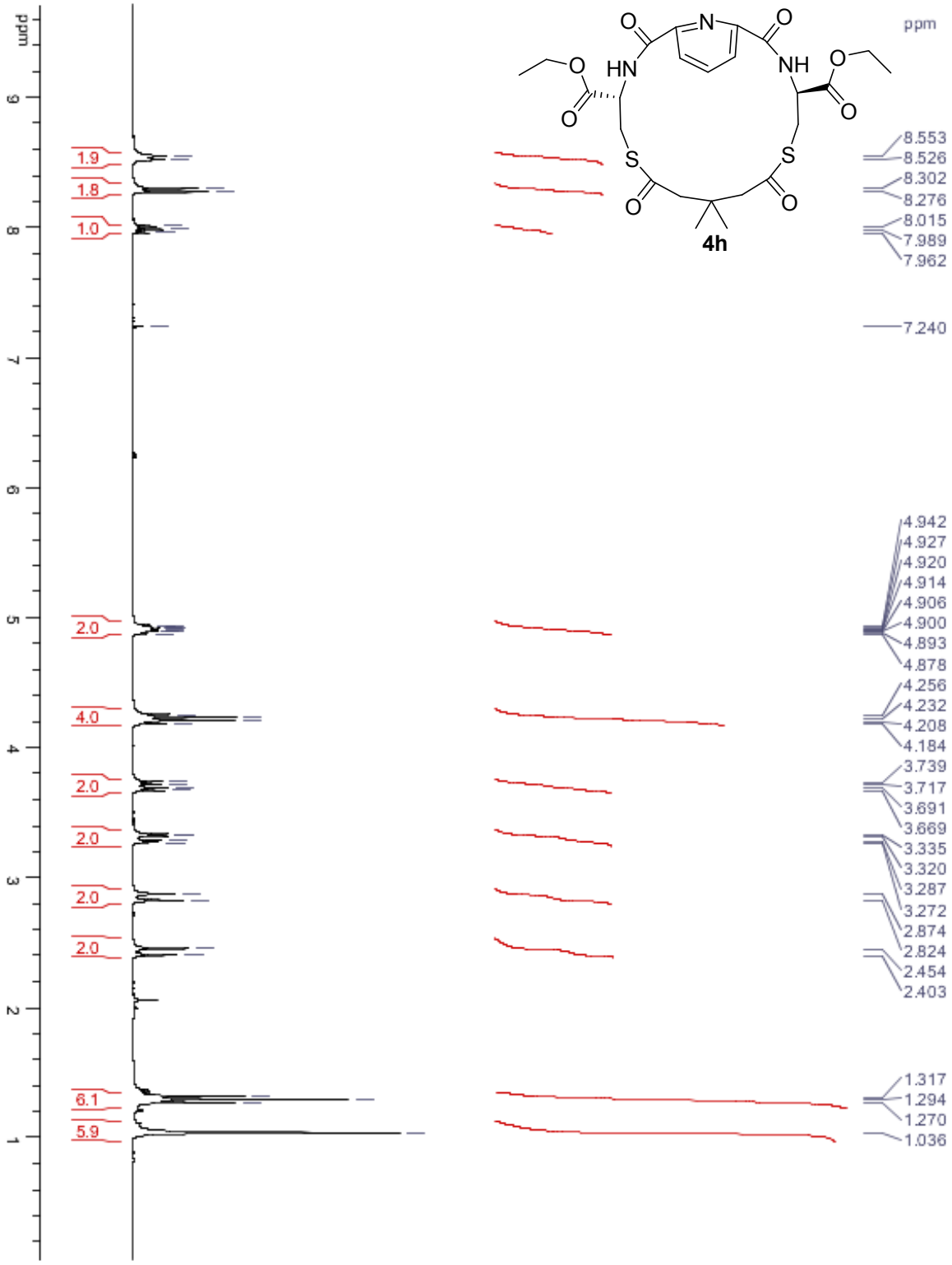
200
180
160
140
120
100
80
60
40
20
0
O
N
O
HN
NH
O
O
O
O
S
S
O
O
4g
ppm
198.095
170.516
163.587
148.479
139.197
125.709
77.653
77.230
76.807
53.023
52.260
51.997
34.749
31.340
29.559


+ESI Scan (0.062-0.094 min, 3 scans) Frag=180.0V 18147_Maaa10dimethyl-methyl_ESI.d Subtract
Theoretical [M+H]+ = 526.1312
[M+Na]+ = 548.1132
[M+K]+ = 564.0871
4g
526.1320
527.1337
528.1299
529.1308
533.0795
536.1643
537.1645
539.1611
541.1544
543.1535
548.1146
549.1161
550.1121
551.1123
552.1114
555.0608
556.0628
564.0864
565.0884
567.0855
Counts vs. Mass-to-Charge (m/z)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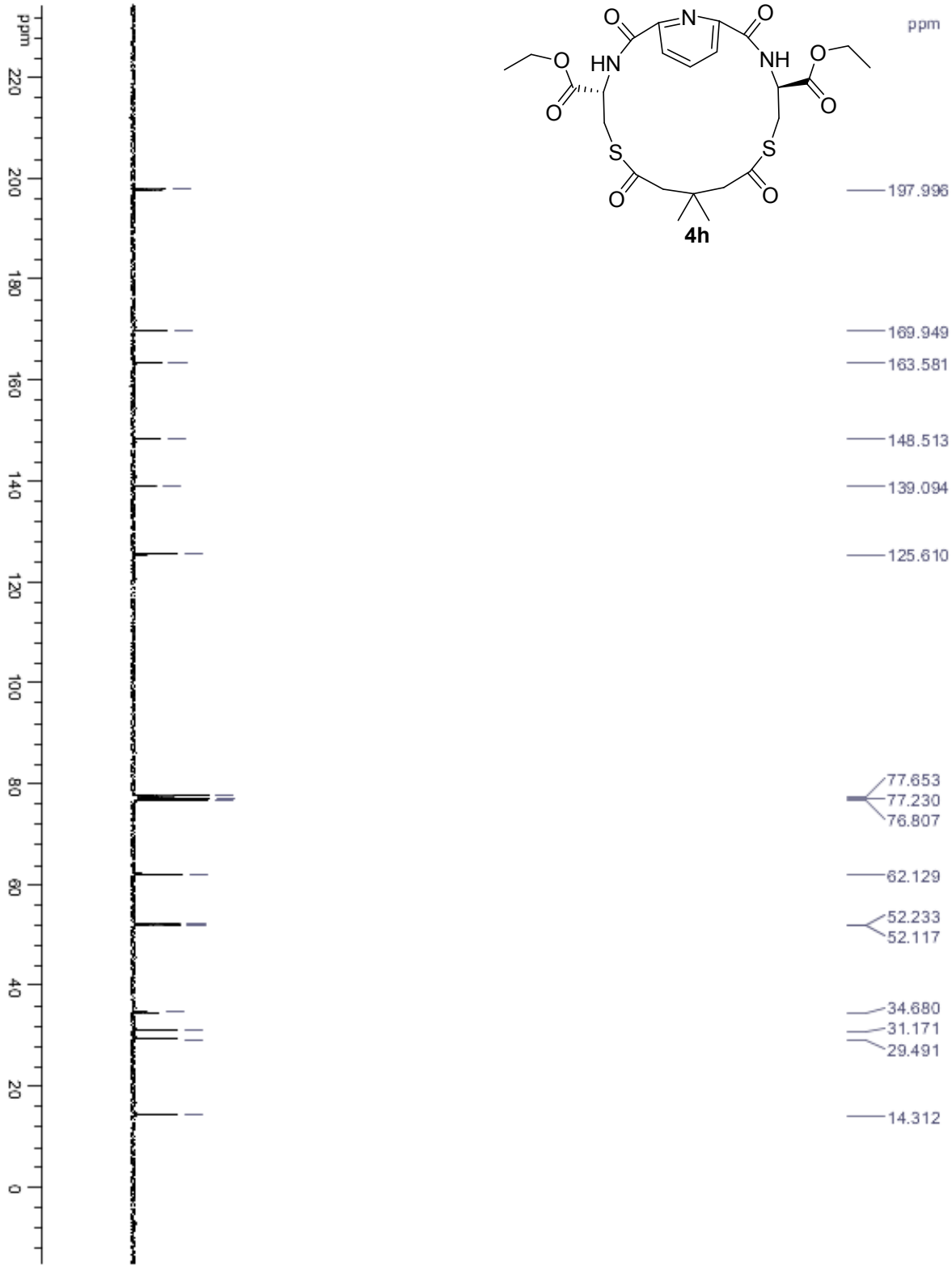
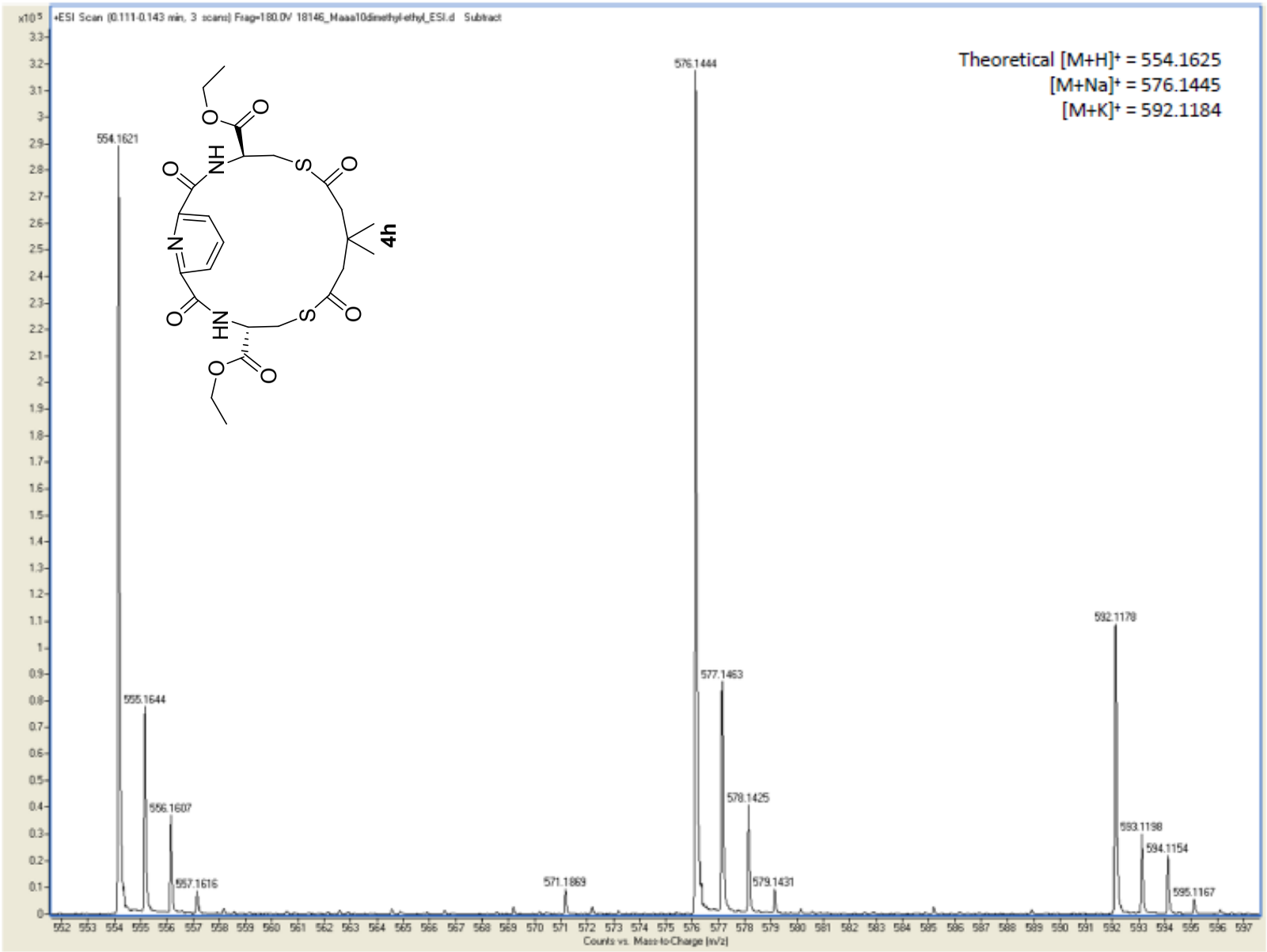
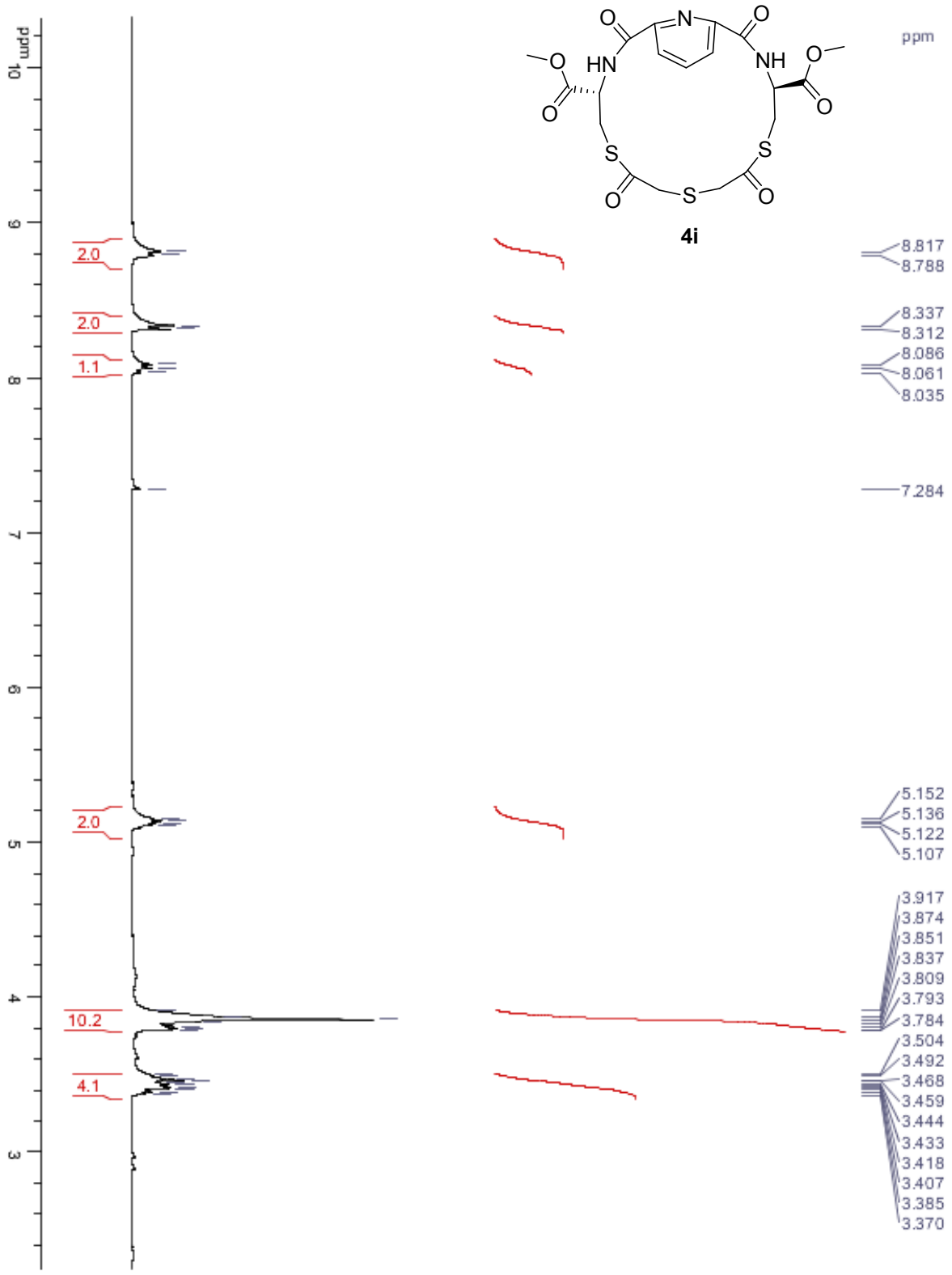
7
6
5
4
3
2
1
1.9
1.8
1.0
2.0
4.0
2.0
2.0
2.0
2.0
6.1
5.9
O
N
O
HN
NH
O
O
O
S
S
O
O
4h
ppm
8.553
8.526
8.302
8.276
8.015
7.989
7.962
7.240
4.942
4.927
4.920
4.914
4.906
4.900
4.893
4.878
4.256
4.232
4.208
4.184
3.739
3.717
3.691
3.669
3.335
3.320
3.287
3.272
2.874
2.824
2.454
2.403
1.317
1.294
1.270
1.036


ppm
220
200
180
160
140
120
100
80
60
40
20
0
O
N
O
HN
NH
O
O
O
O
S
S
O
O
4h
ppm
197.996
169.949
163.581
148.513
139.094
125.610
77.653
77.230
76.807
62.129
52.233
52.117
34.680
31.171
29.491
14.312


+ESI Scan (0.111-0.143 min, 3 scans) Frag=180.0V 18146_Maaa10dimethyl-ethyl_ESI.d Subtract
Theoretical [M+H]+ = 554.1625
[M+Na]+ = 576.1445
[M+K]+ = 592.1184
4h
554.1621
555.1644
556.1607
557.1616
571.1869
576.1444
577.1463
578.1425
579.1431
592.1178
593.1198
594.1154
595.1167
Counts vs. Mass-to-Charge (m/z)


ppm
10
9
8
7
6
5
4
3
2.0
2.0
1.1
2.0
10.2
4.1
O
N
O
HN
NH
O
O
O
O
S
S
S
O
O
O
4i
ppm
8.817
8.788
8.337
8.312
8.086
8.061
8.035
7.284
5.152
5.136
5.122
5.107
3.917
3.874
3.851
3.837
3.809
3.793
3.784
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3.492
3.468
3.459
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3.433
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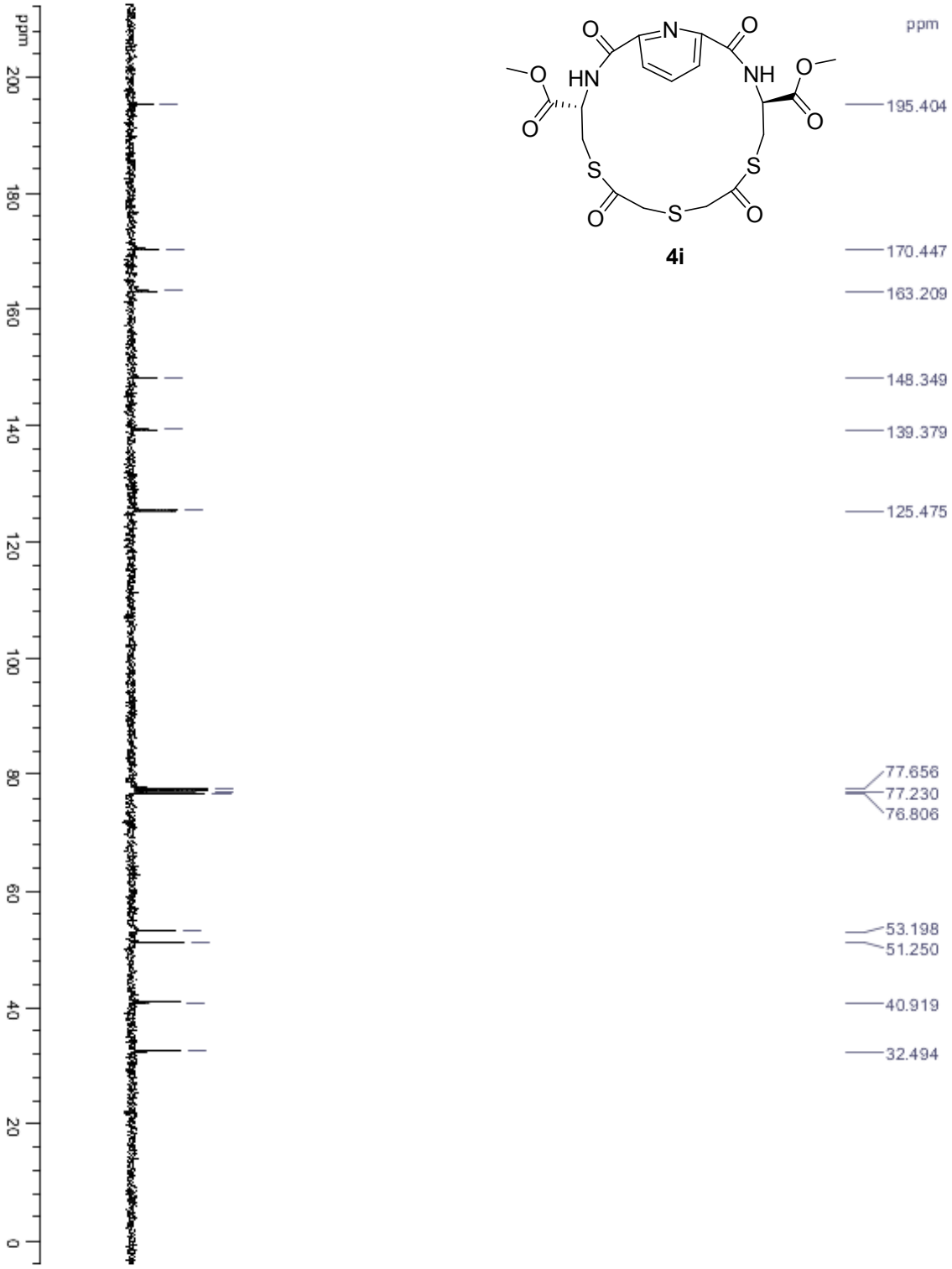
3.407
3.385
3.370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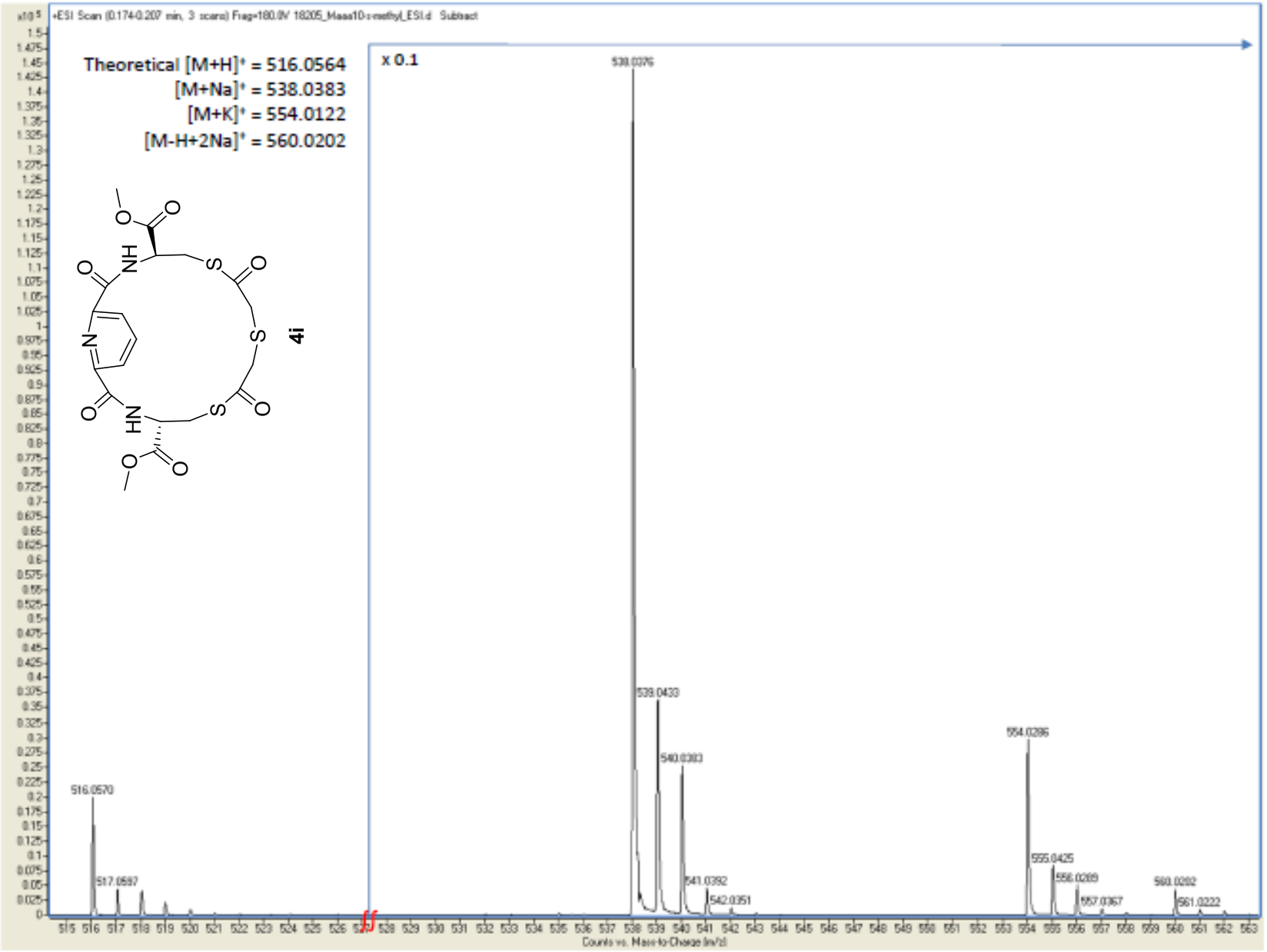
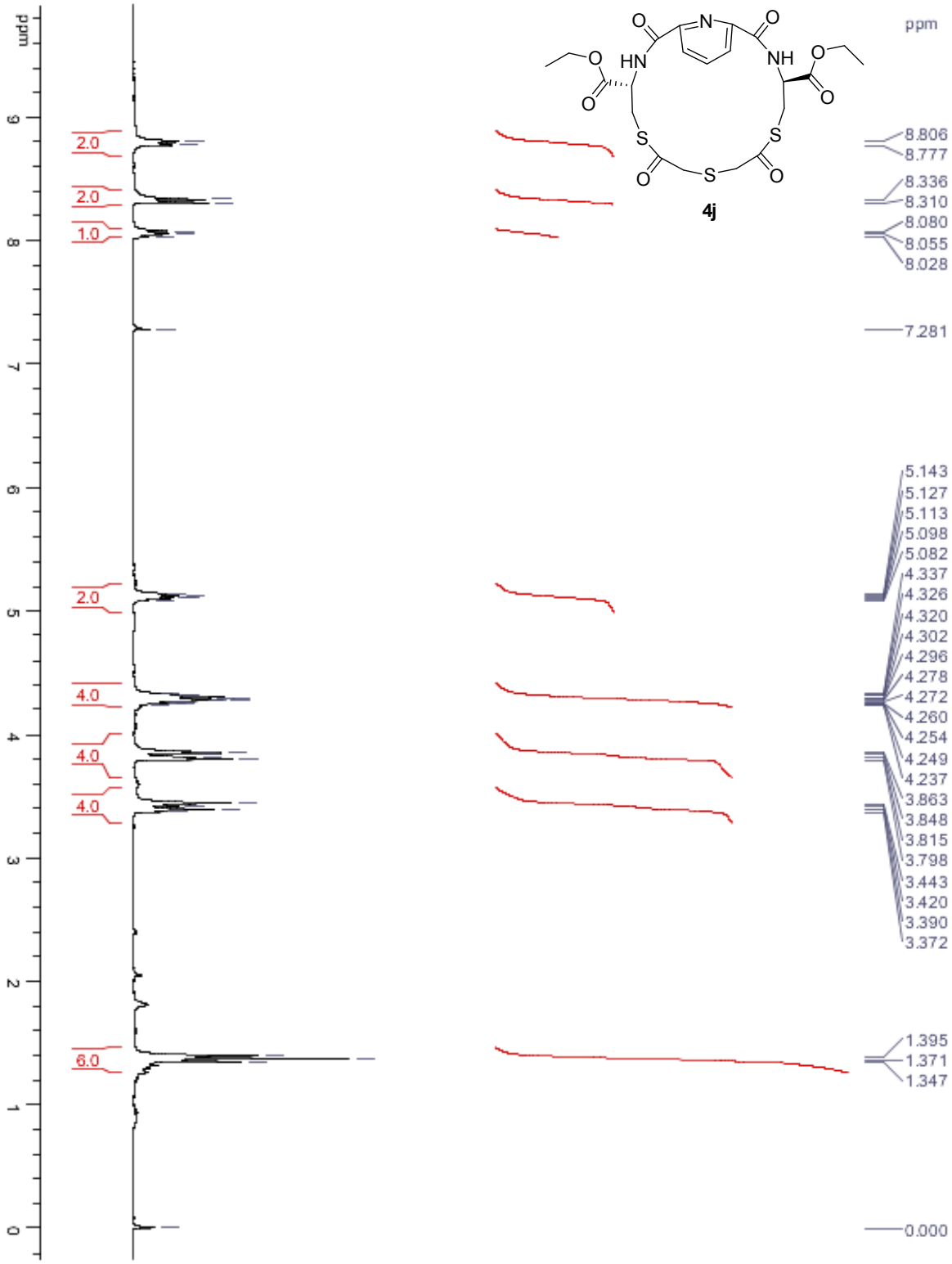
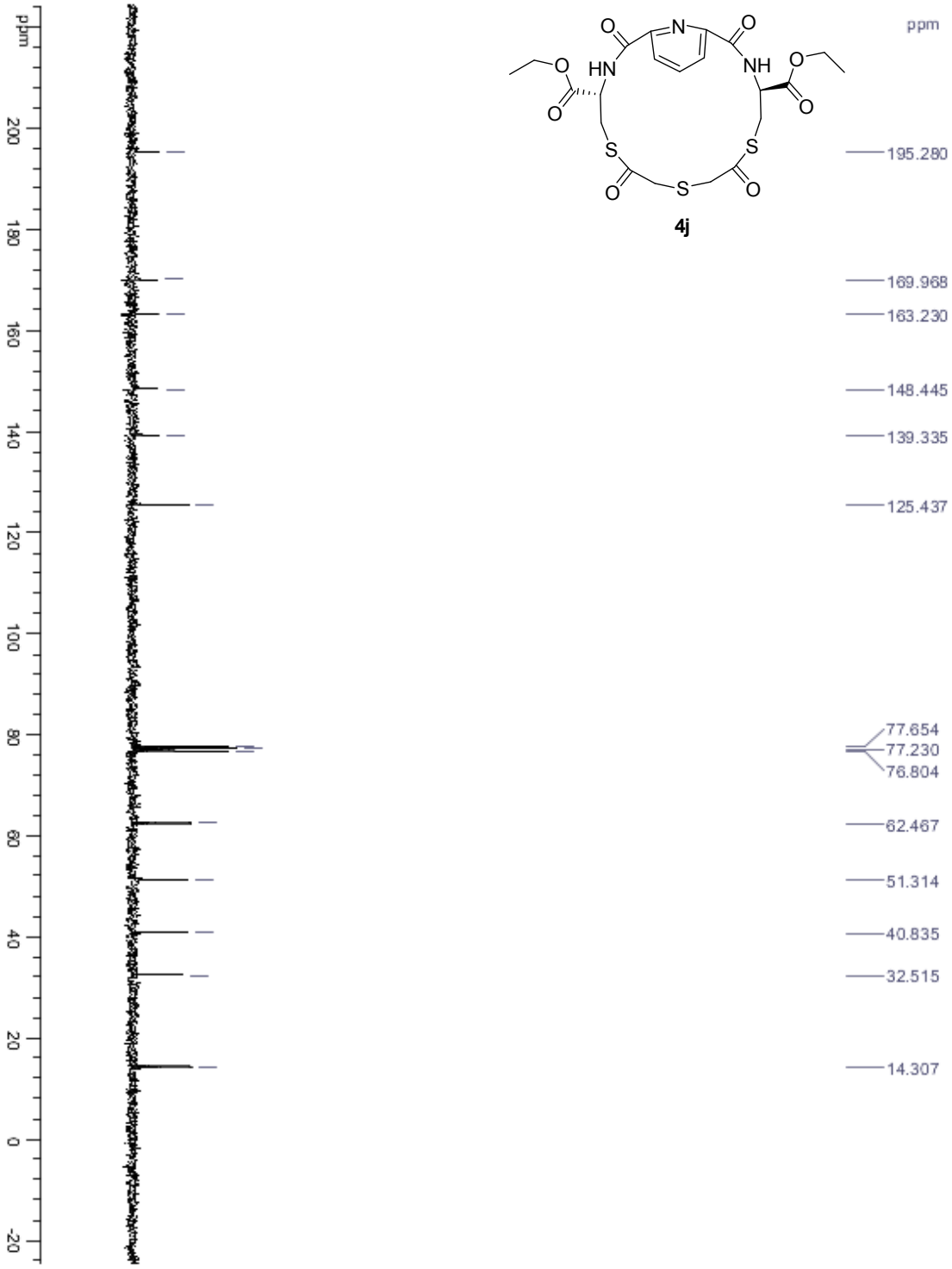
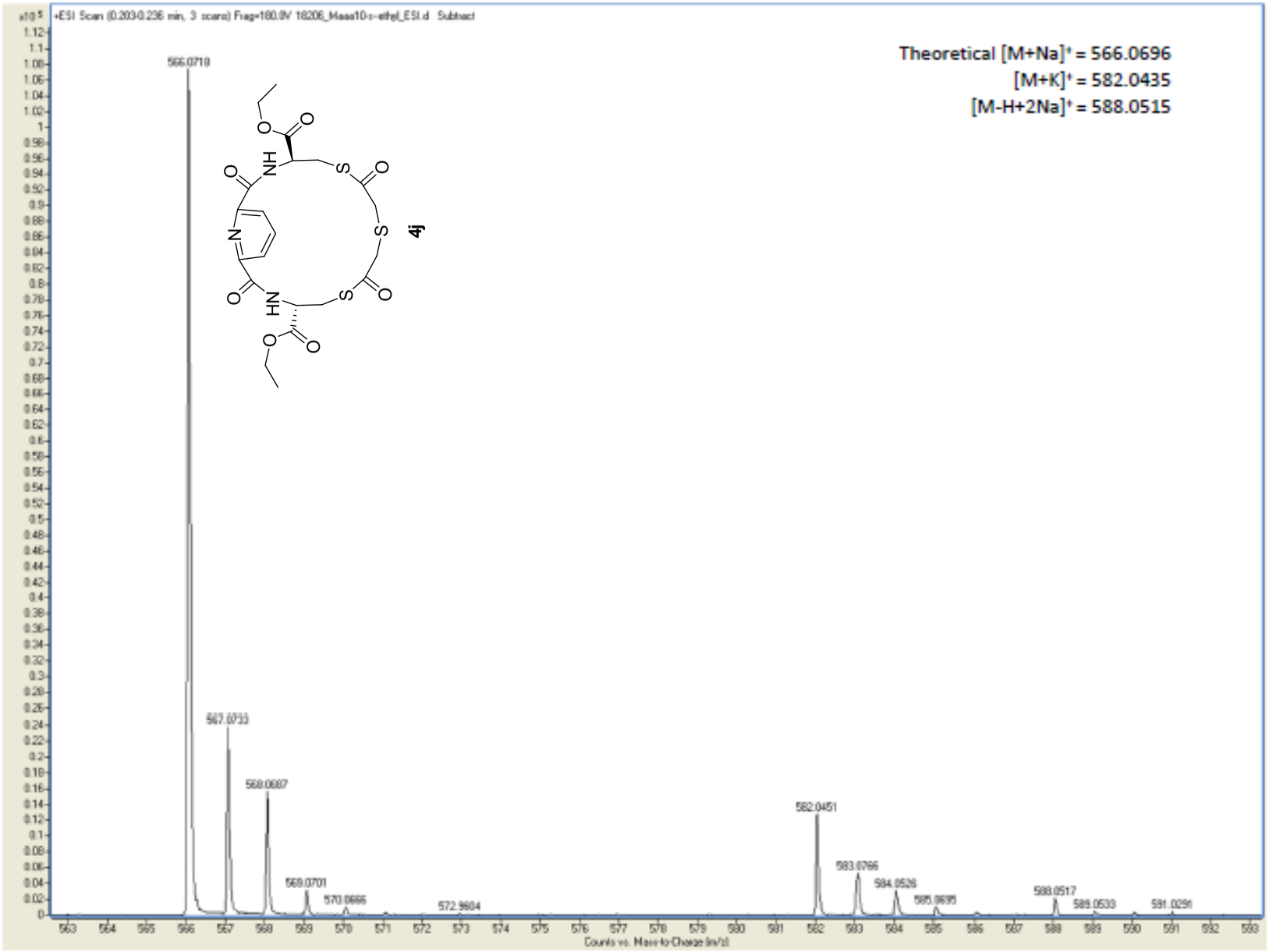
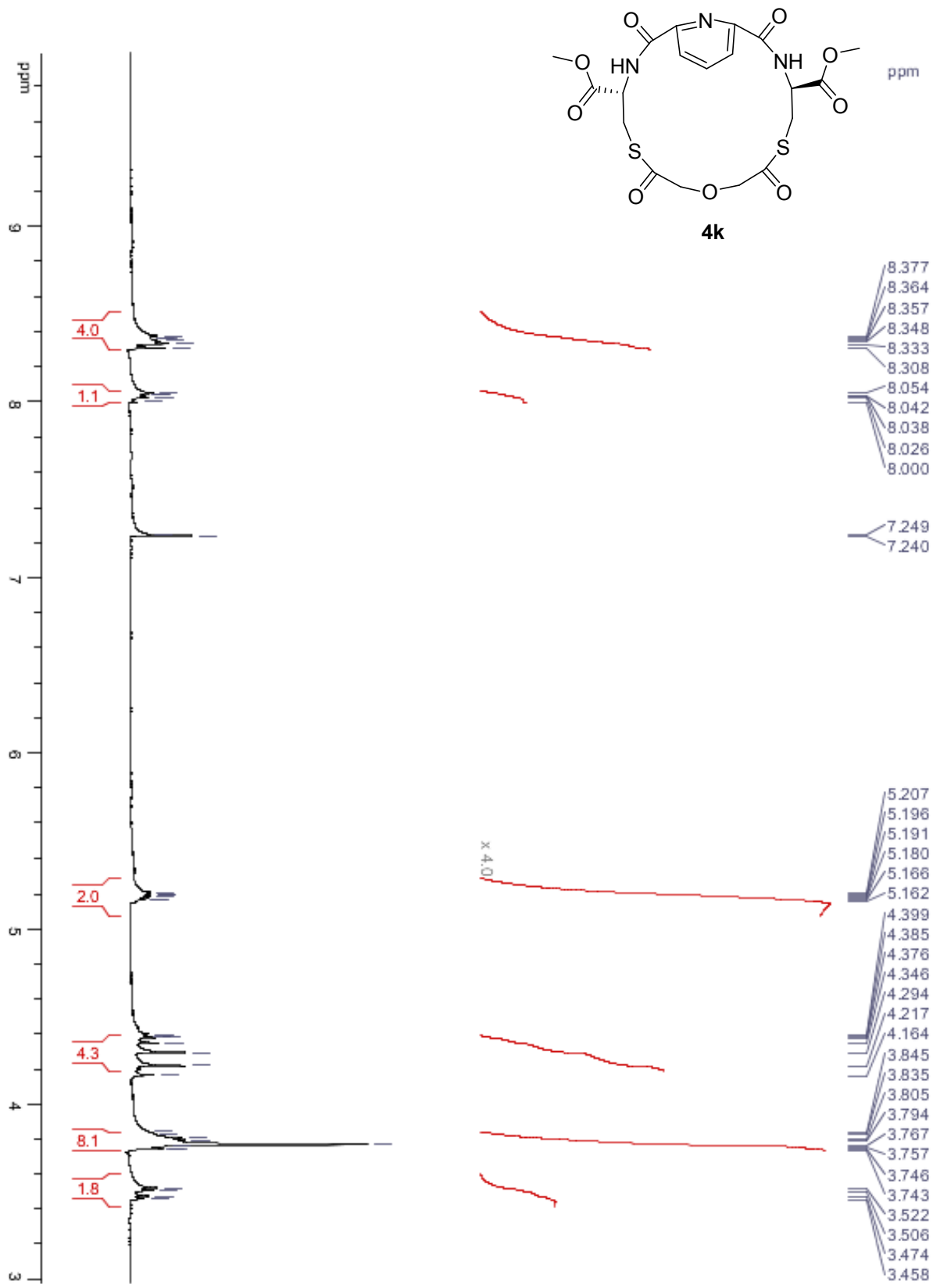
140
120
100
80
60
40
20
0
O
N
O
HN
NH
O
O
O
O
S
S
S
O
O
O
4i
ppm
195.404
170.447
163.209
148.349
139.379
125.475
77.656
77.230
76.806
53.198
51.250
40.919
32.494


+ESI Scan (0.174-0.207 min, 3 scans) Frag=180.0V 18205_Maaa10-t-methyl_ESI.d Subtract
Theoretical [M+H]⁺ = 516.0564
[M+Na]⁺ = 538.0383
[M+K]⁺ = 554.0122
[M-H+2Na]⁺ = 560.0202
x 0.1
4i
516.0570
517.0597
538.0376
539.0433
540.0383
541.0392
542.0351
554.0286
555.0425
556.0289
557.0367
560.0202
561.0222
Counts vs. Mass-to-Charge (m/z)


ppm
9
8
7
6
5
4
3
2
1
0
2.0
2.0
1.0
2.0
4.0
4.0
4.0
6.0
O
N
O
HN
NH
O
O
O
S
S
O
S
O
4j
ppm
8.806
8.777
8.336
8.310
8.080
8.055
8.028
7.281
5.143
5.127
5.113
5.098
5.082
4.337
4.326
4.320
4.302
4.296
4.278
4.272
4.260
4.254
4.249
4.237
3.863
3.848
3.815
3.798
3.443
3.420
3.390
3.372
1.395
1.371
1.347
0.000


ppm
200
180
160
140
120
100
80
60
40
20
0
-20
O
N
O
HN
NH
O
O
O
O
S
S
S
O
O
O
4j
ppm
195.280
169.968
163.230
148.445
139.335
125.437
77.654
77.230
76.804
62.467
51.314
40.835
32.515
14.307


+ESI Scan (0.203-0.236 min, 3 scans) Frag=180.0V 18206_Maaa10-r--ethyl_ESI.d Subtract
Theoretical [M+Na]⁺ = 566.0696
[M+K]⁺ = 582.0435
[M-H+2Na]⁺ = 588.0515
4j
566.0719
567.0733
568.0687
569.0701
570.0666
572.9604
582.0451
583.0766
584.0526
585.0695
588.0517
589.0533
591.0291
Counts vs. Mass-to-Charge (m/z)


ppm
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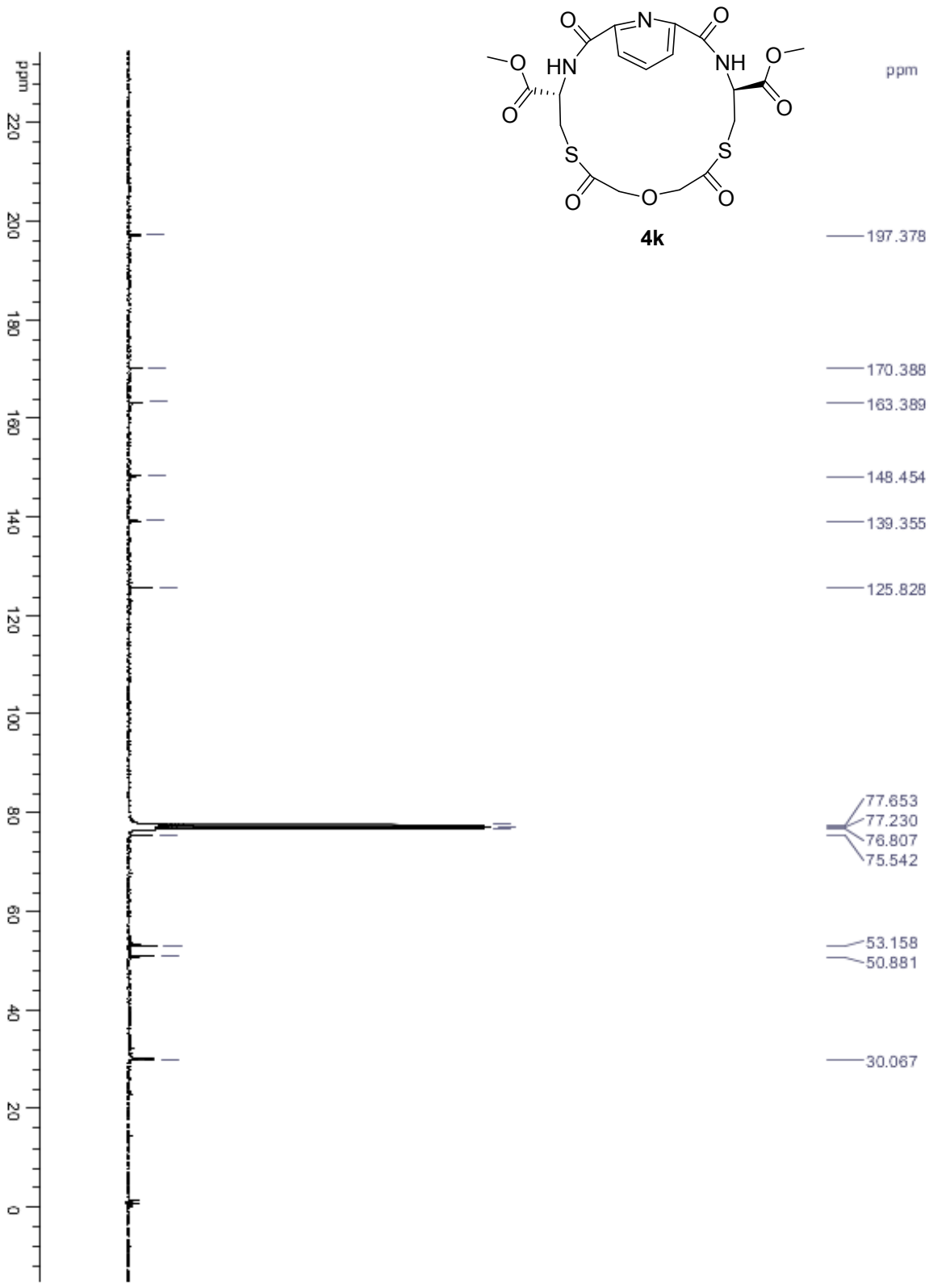
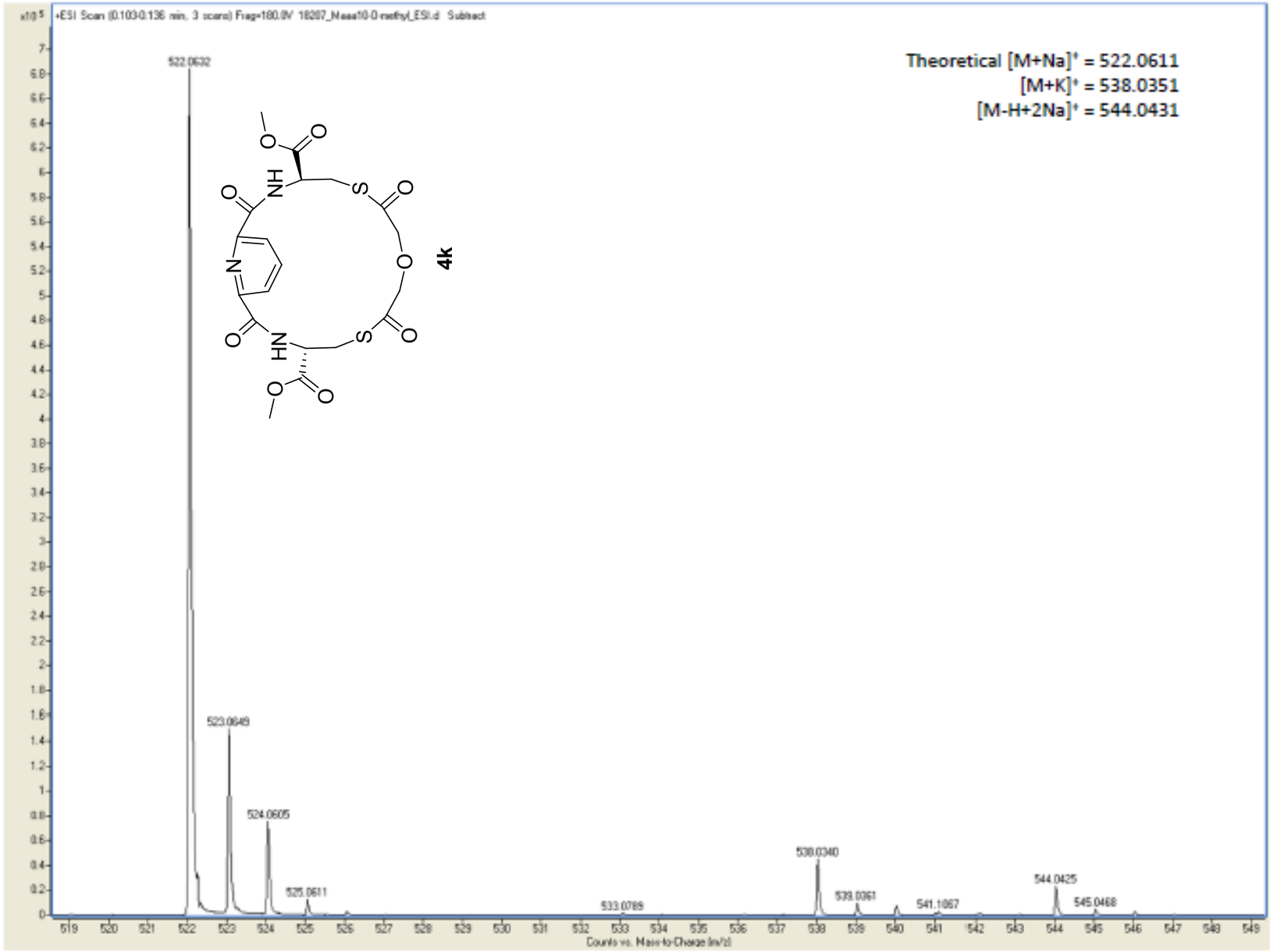
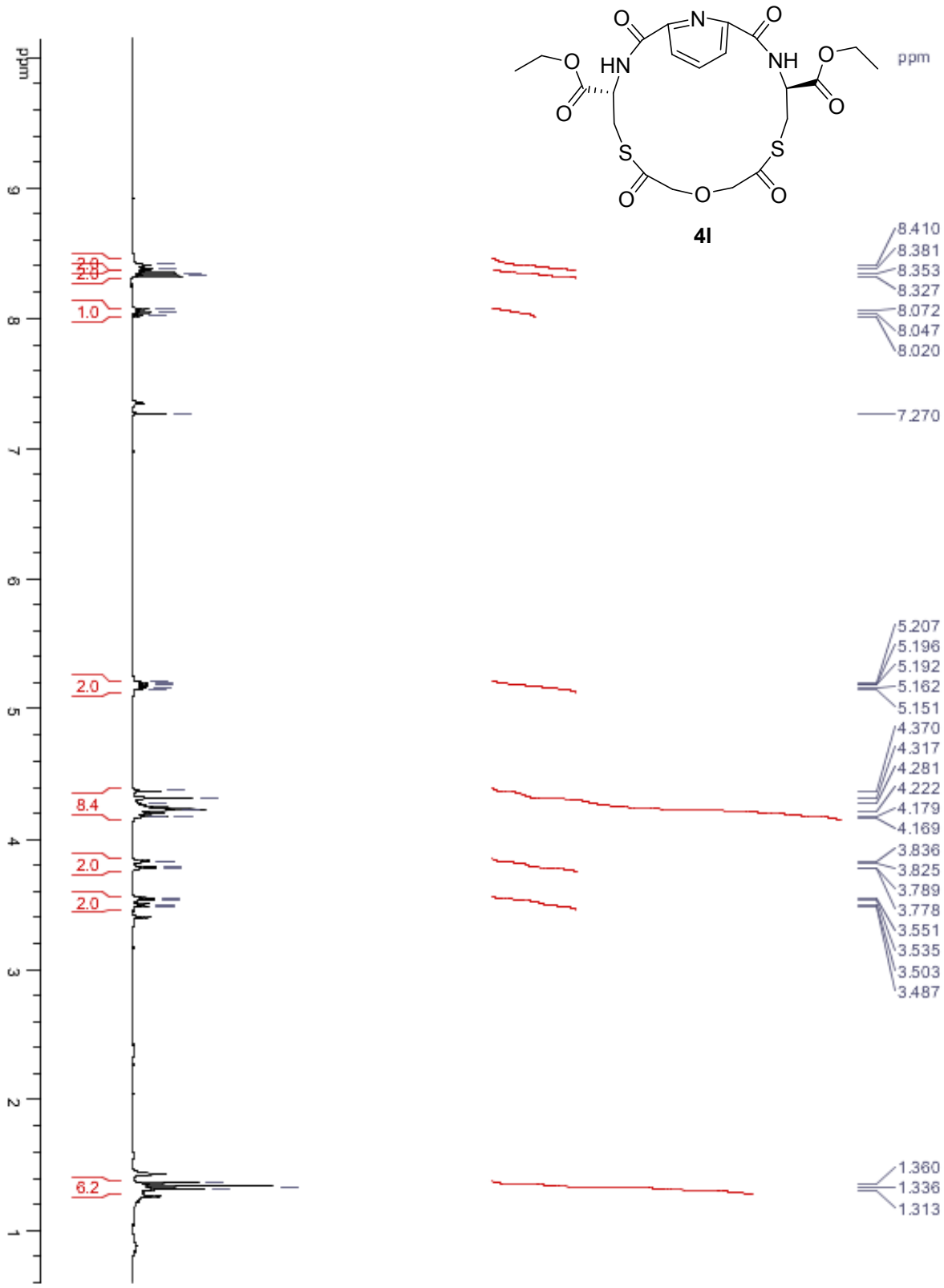
8
7
6
5
4
3
4.0
1.1
2.0
4.3
8.1
1.8
x 4.0
8.377
8.364
8.357
8.348
8.333
8.308
8.054
8.042
8.038
8.026
8.000
7.249
7.240
5.207
5.196
5.191
5.180
5.166
5.162
4.399
4.385
4.376
4.346
4.294
4.217
4.164
3.845
3.835
3.805
3.794
3.767
3.757
3.746
3.743
3.522
3.506
3.474
3.458

O
N
O
HN
NH
O
O
O
O
S
S
O
O
O
ppm

4k


ppm
220
200
180
160
140
120
100
80
60
40
20
0
O
N
O
HN
NH
O
O
O
O
S
S
O
O
O
O
4k
ppm
197.378
170.388
163.389
148.454
139.355
125.828
77.653
77.230
76.807
75.542
53.158
50.881
30.067


Theoretical [M+Na]⁺ = 522.0611
[M+K]⁺ = 538.0351
[M-H+2Na]⁺ = 544.0431
4k
522.0632
523.0649
524.0605
525.0611
533.0789
538.0340
539.0361
541.1067
544.0425
545.0468
Counts vs. Mass-to-Charge (m/z)


ppm
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7
6
5
4
3
2
1
2.0
2.0
2.0
1.0
2.0
8.4
2.0
2.0
6.2
O
N
O
HN
NH
O
O
O
O
S
S
O
O
O
4l
ppm
8.410
8.381
8.353
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8.072
8.047
8.020
7.270
5.207
5.196
5.192
5.162
5.151
4.370
4.317
4.281
4.222
4.179
4.169
3.836
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3.789
3.778
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3.503
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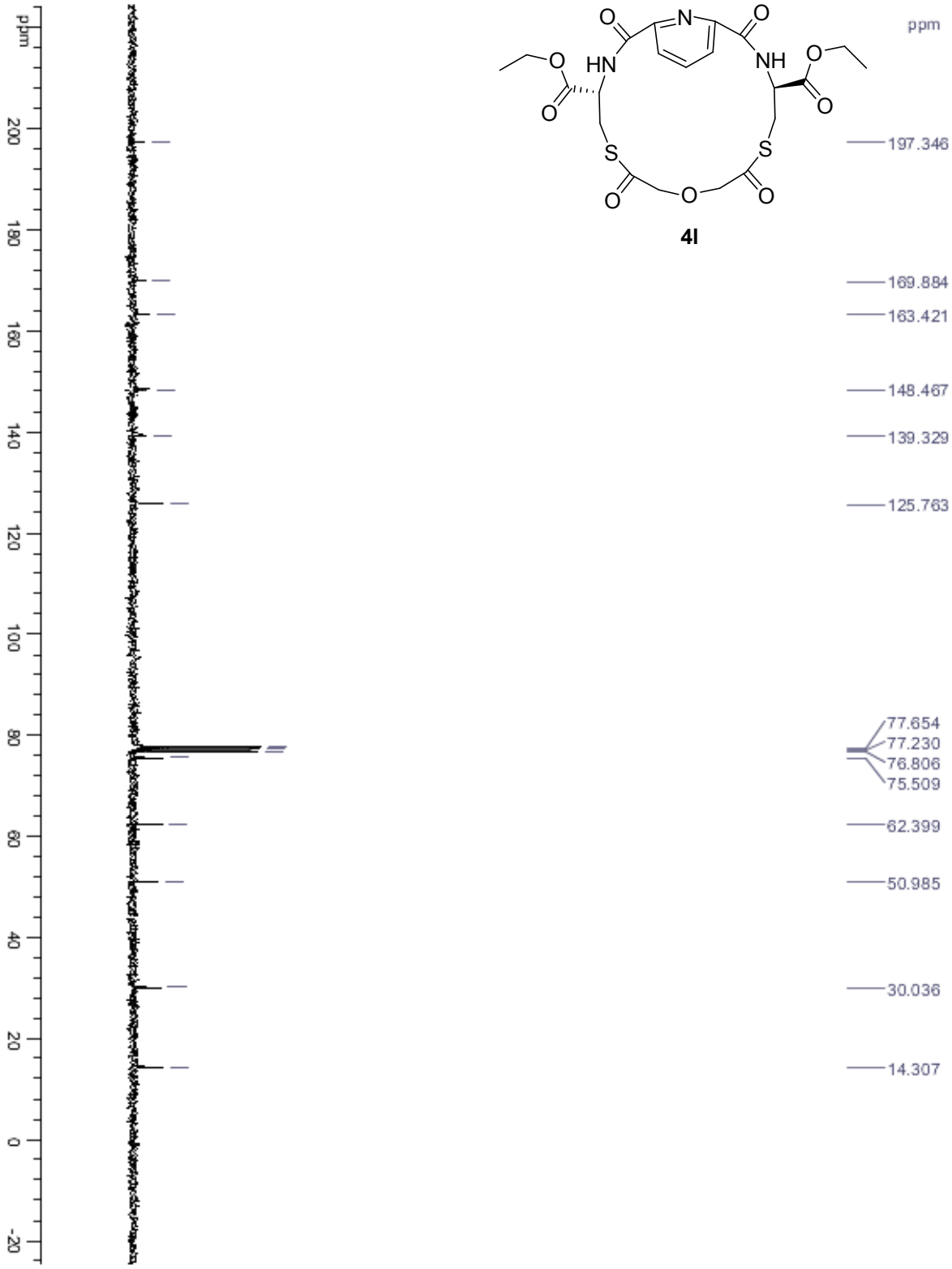
1.360
1.336
1.313


ppm
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140
120
100
80
60
40
20
0
-20
O
N
O
HN
NH
O
O
O
O
S
S
O
O
O
4l
ppm
197.346
169.884
163.421
148.467
139.329
125.763
77.654
77.230
76.806
75.509
62.399
50.985
30.036
14.307

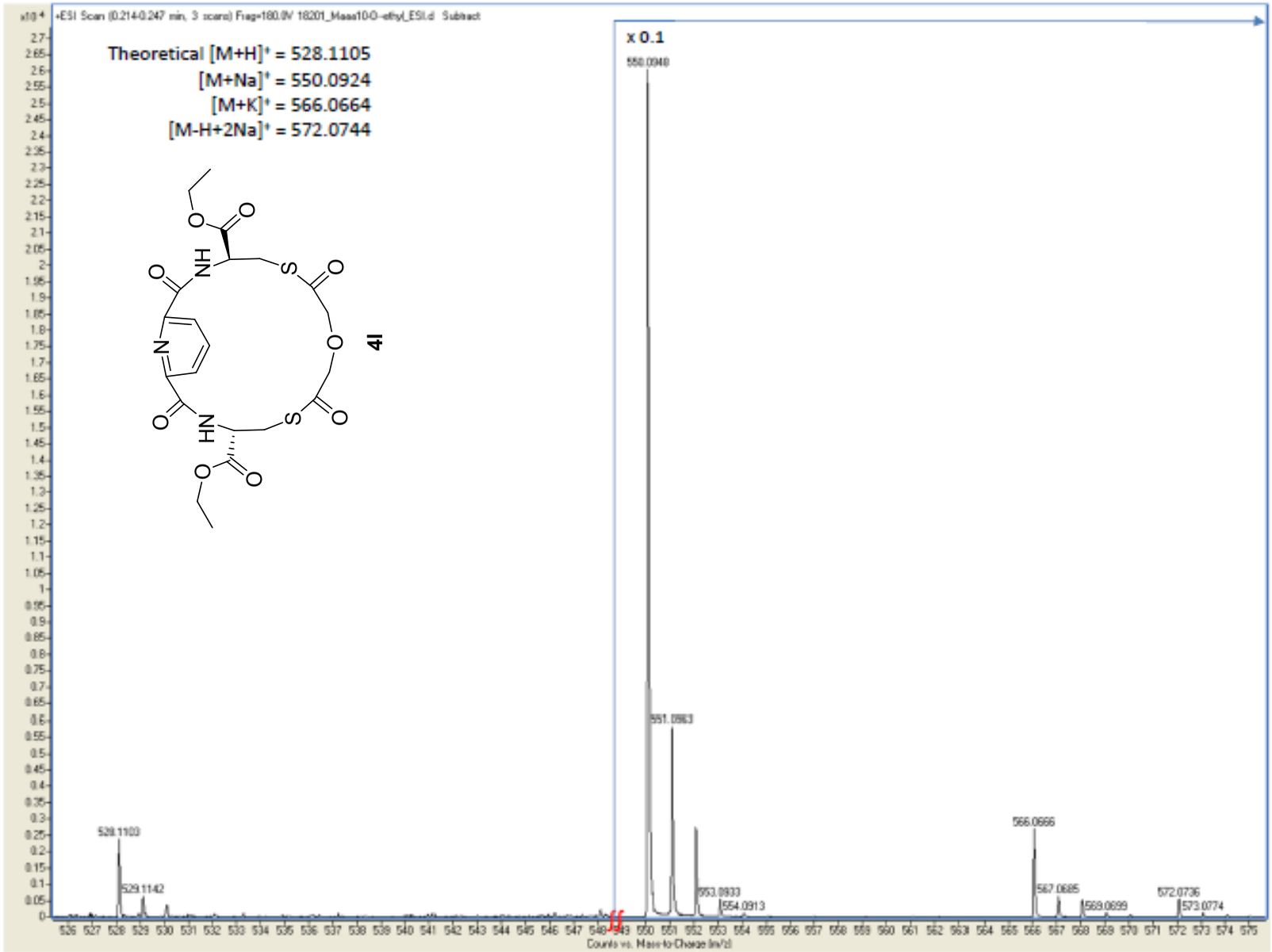

+ESI Scan (0.214-0.247 min, 3 scans) Frag=180.0V 18201_Maaa10-O-ethyl_ESI.d Subtract
Theoretical [M+H]+ = 528.1105
[M+Na]+ = 550.0924
[M+K]+ = 566.0664
[M-H+2Na]+ = 572.0744
4l
x 0.1
550.0948
551.0963
528.1103
529.1142
553.0933
554.0913
566.0666
567.0685
569.0699
572.0736
573.0774
Counts vs. Mass-to-Charge (m/z)

Table S1. Molecular descriptor values of the BMLR-QSAR model for the antifungal active macrocyclic peptidomimetics.

Entry	Compd.	Descriptors*		
		D_1	D_2	D_3
1	**4a**	0.0043	-1153.12	19.5355
2	**4b**	0.0046	-1209.1	19.4839
3	**4c**	0.00623	-1264.3	19.5096
4	**4d**	0.00455	-1460.3	19.5223
5	**4e**	0.00944	-1268.36	19.5329
6	**4f**	0.0091	-1300.97	19.4882
7	**4g**	0.00238	-1221.38	19.468
8	**4h**	0.00213	-1061.68	19.4667
9	**4i**	0.00559	-1047.9	19.4659
10	**4j**	0.00159	-1017.77	19.4645
11	**4k**	0.00755	-934.668	19.5165
12	**4l**	0.00235	-1179.24	19.4717
13	**5**	0.01884	-1221.8	19.5034
14	**6**	0.02522	-1232.66	19.5044
15	**7**	0.01537	-900.929	19.472

*D_1 = FHDCA Fractional HDCA (HDCA/TMSA) (MOPAC PC), D_2 = WNSA-2 Weighted PNSA (PNSA2*TMSA/1000) (MOPAC PC), D_3 = Max. total interaction for bond C-C.

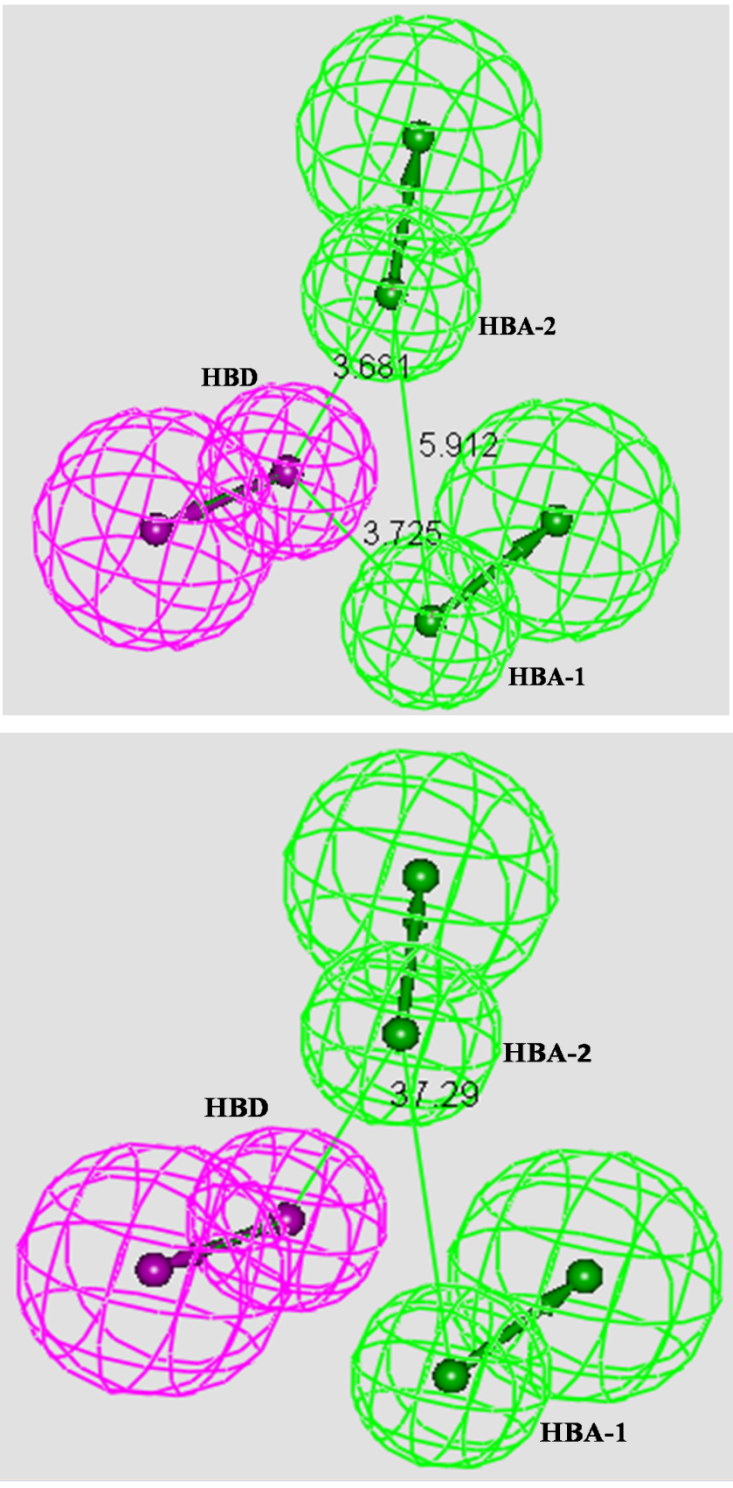
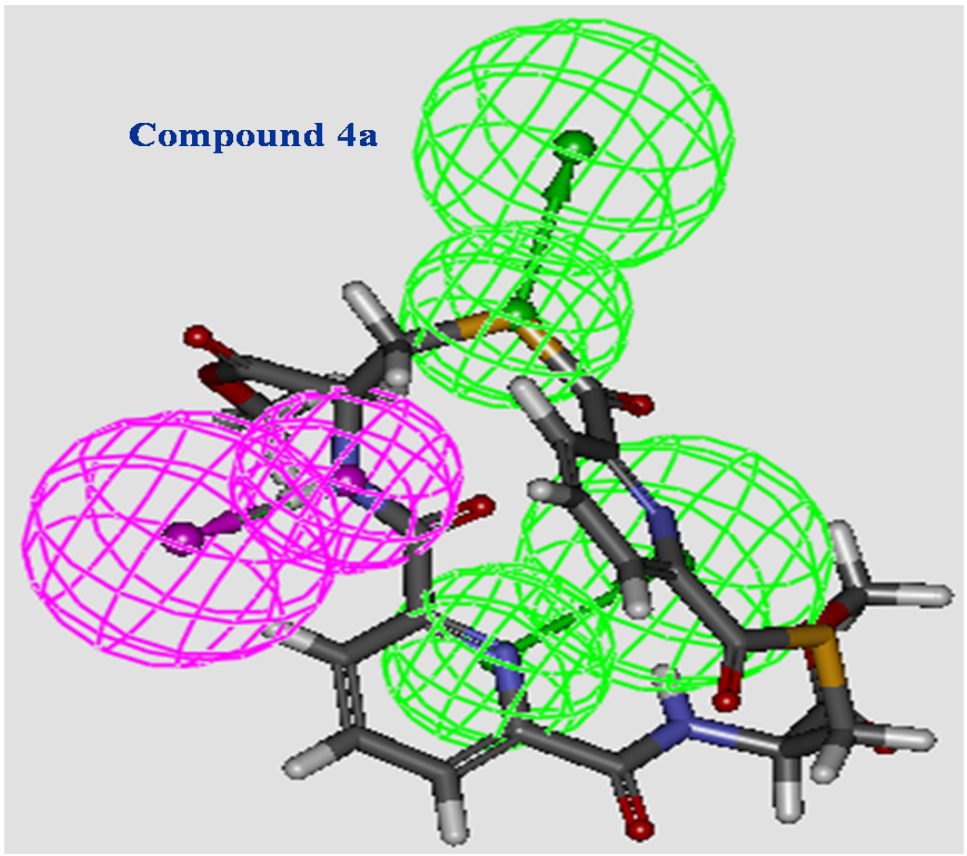
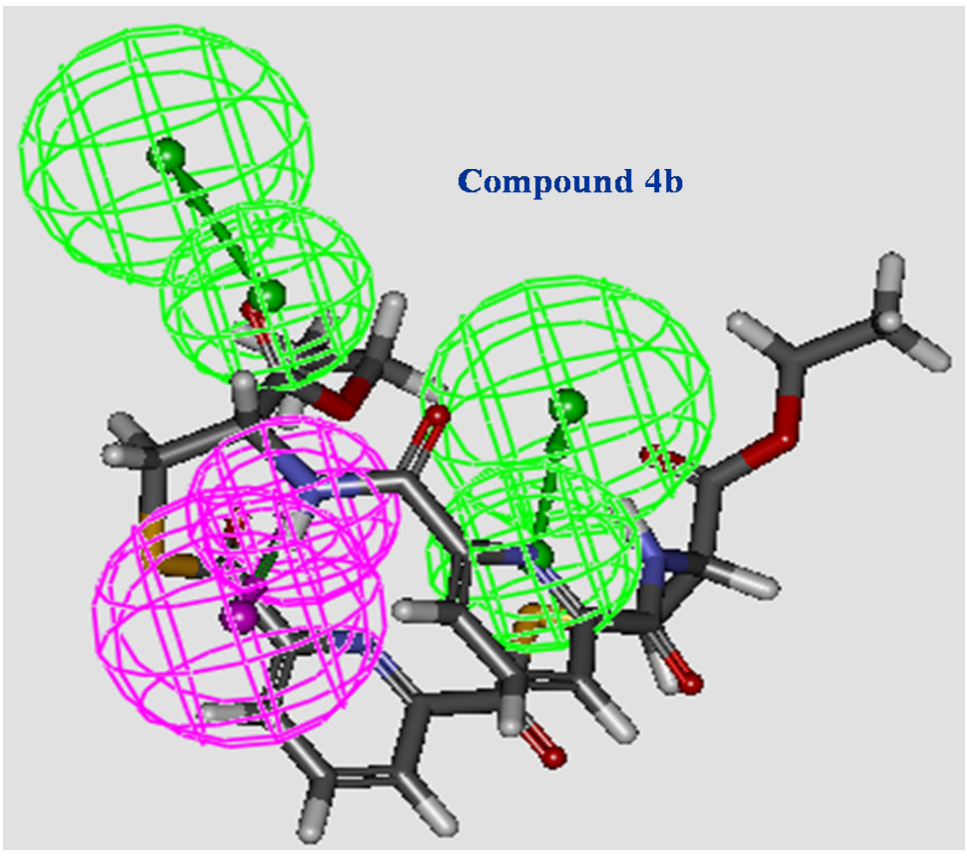
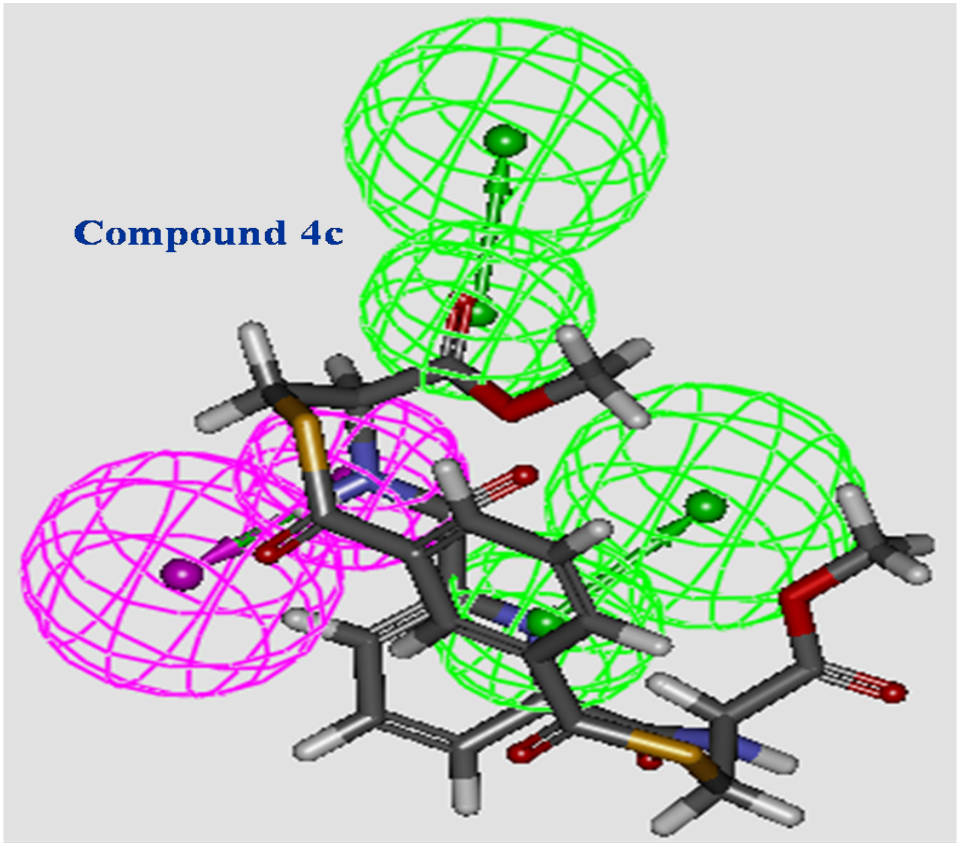
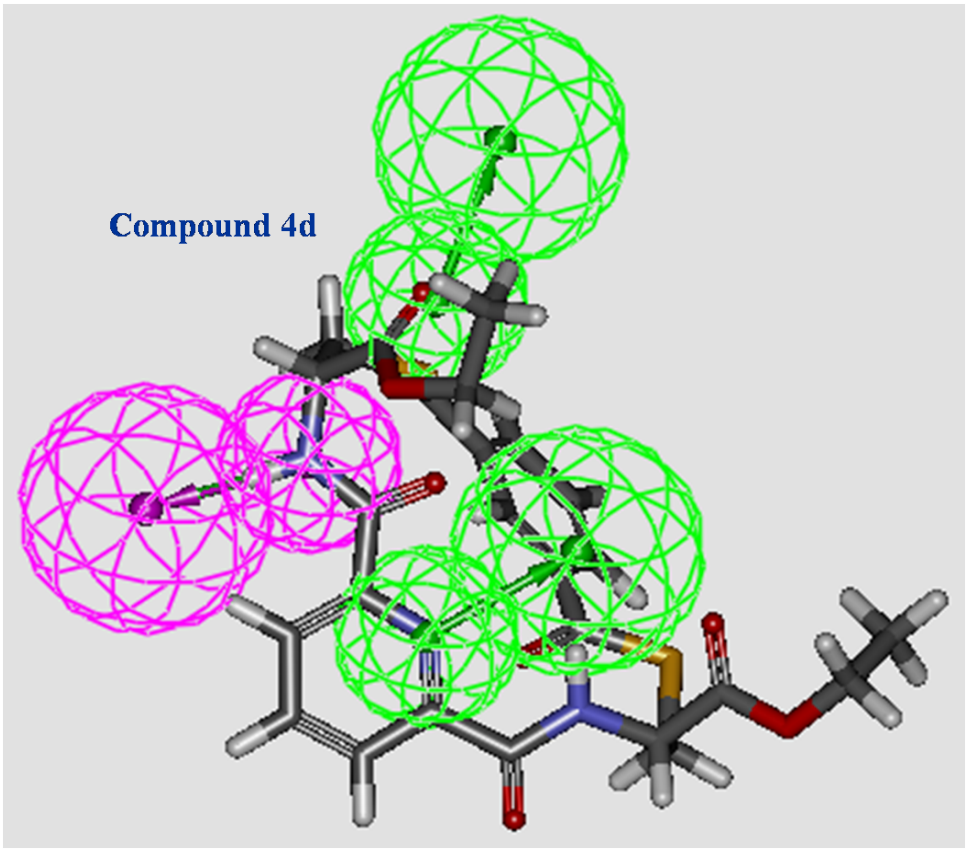


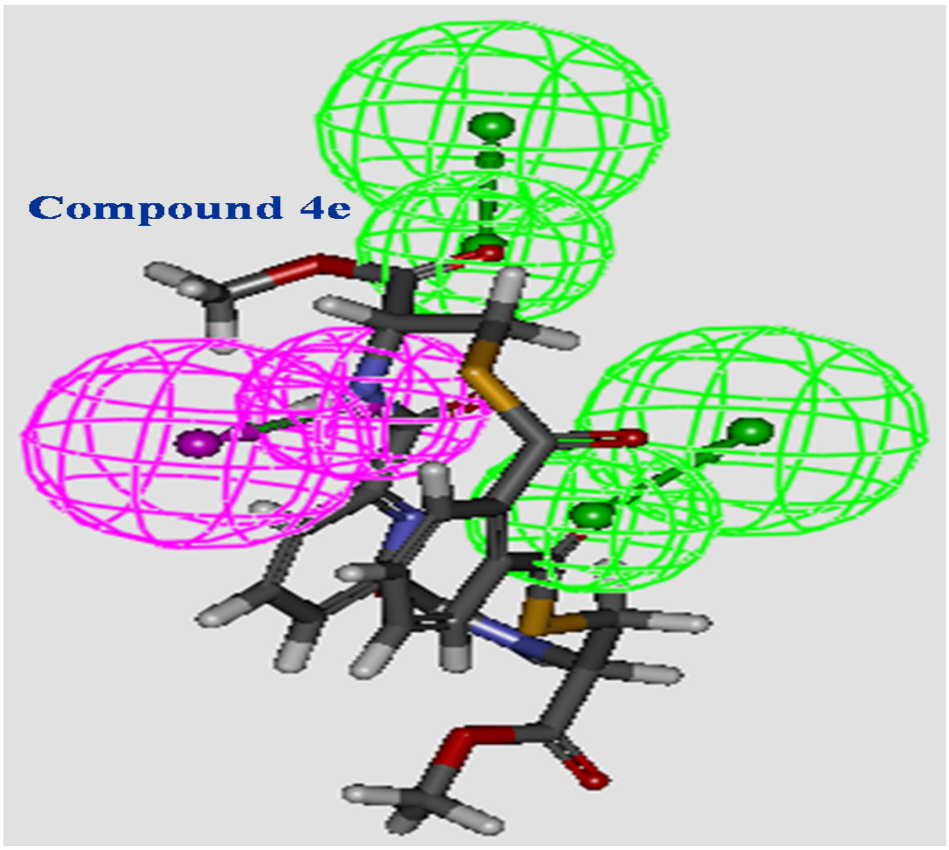
Figure S1. (**A**) Constraint distances, and (**B**) constraint angle of the generated 3D-pharmacophore for the antifungal bio-active compounds **4a-4l,** and **5-7** against *C. albicans* which contains two hydrogen bonding acceptor (HBA-1, HBA-2, green), and one hydrogen bonding donor (HBD, purple).

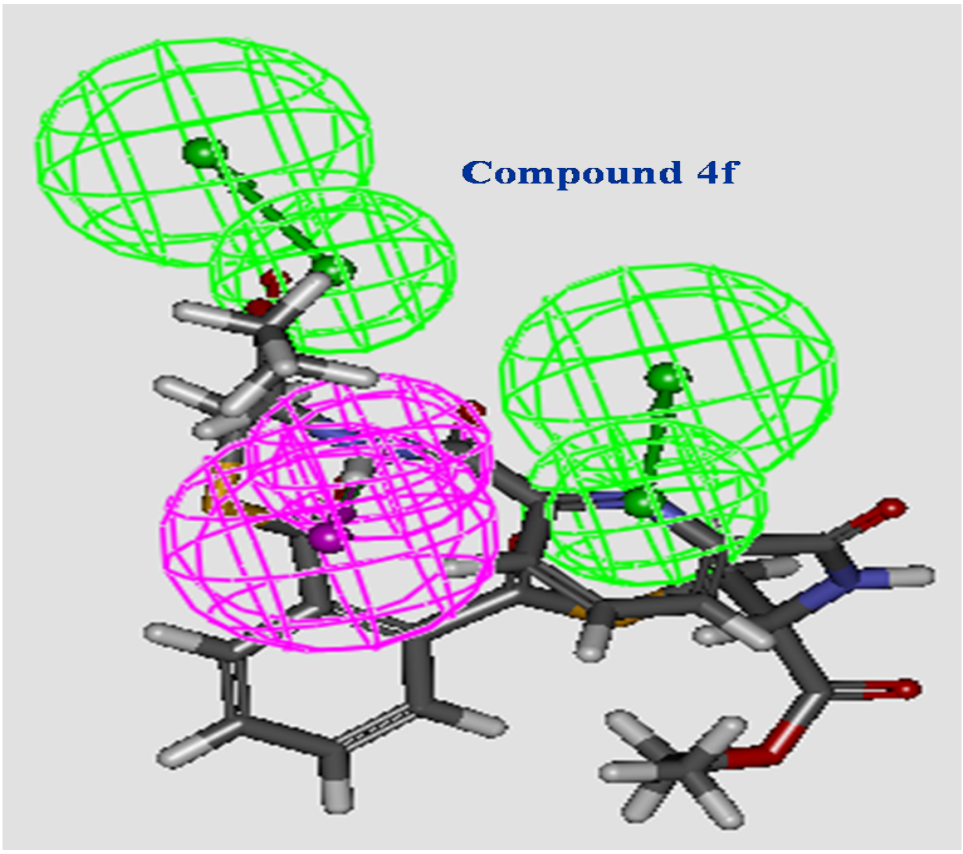

Compound 4a

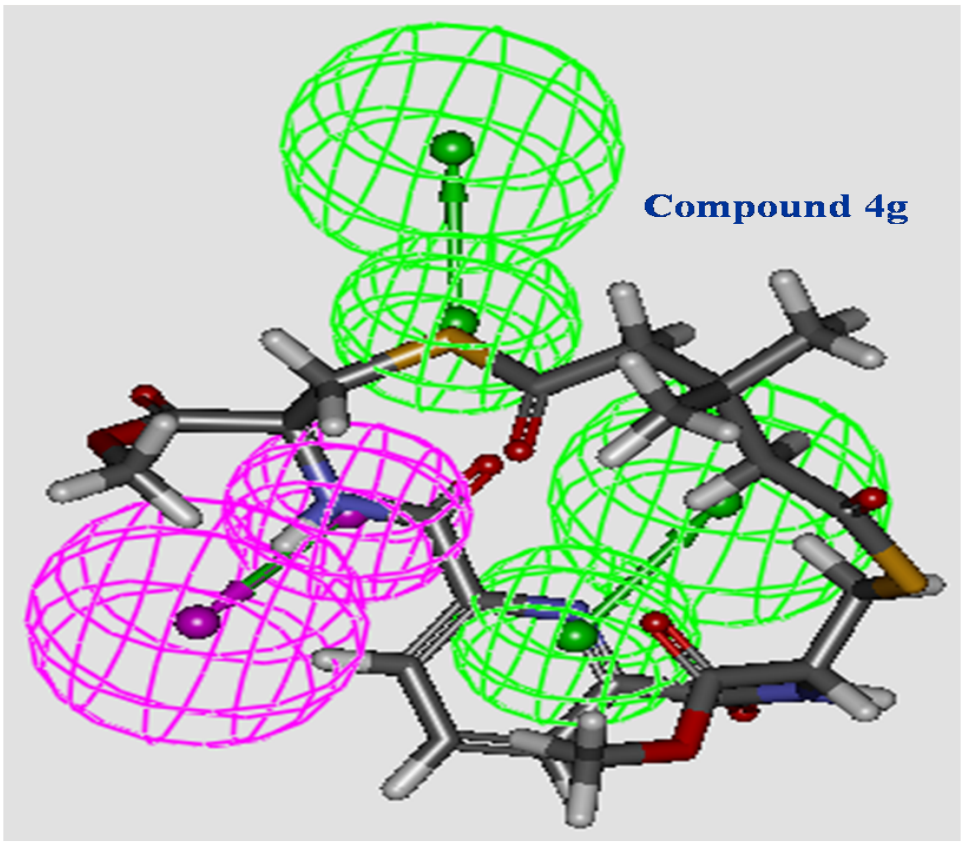

Compound 4b

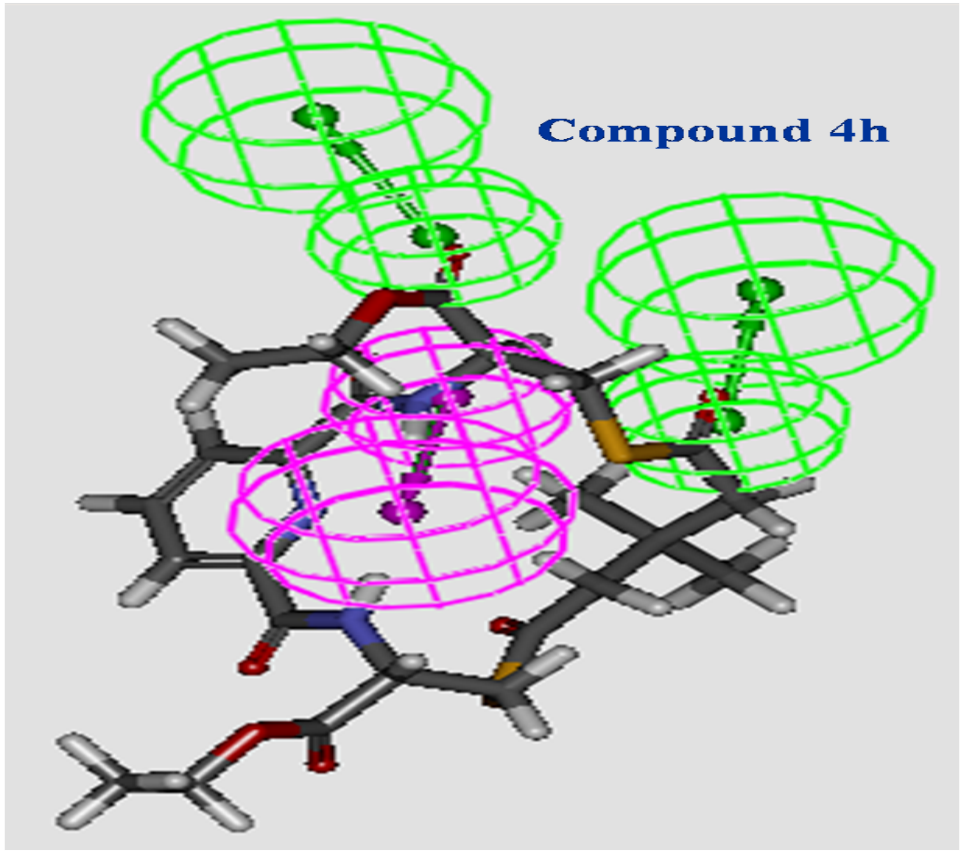

Compound 4c

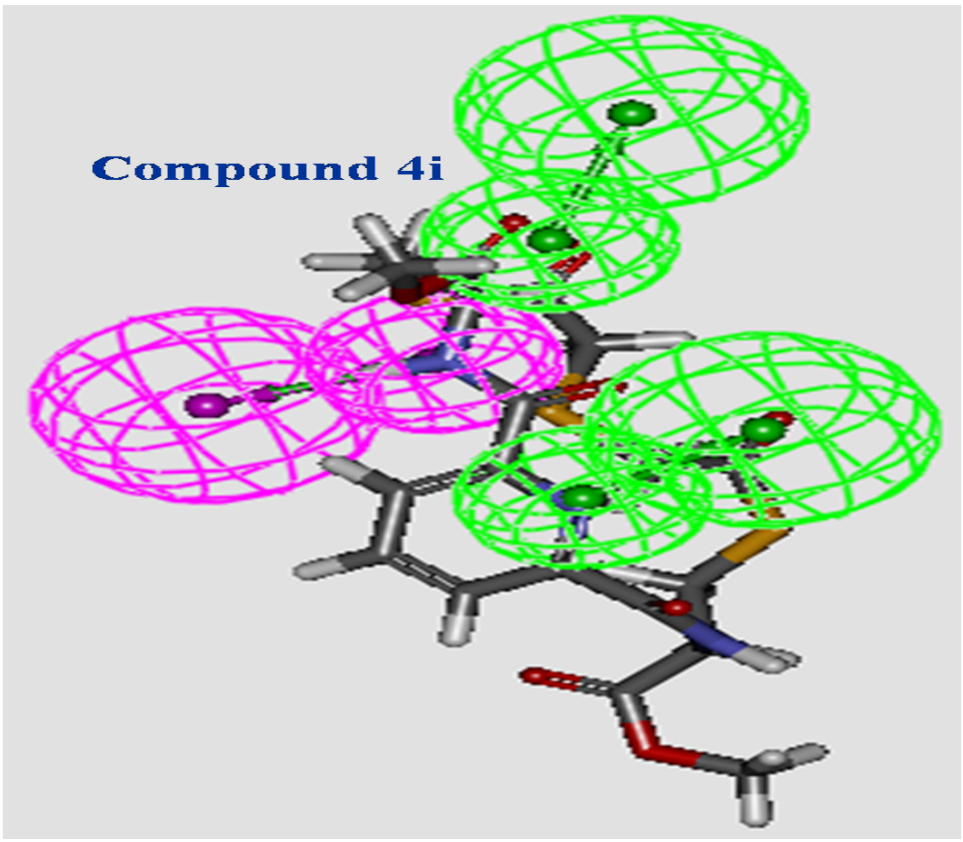

Compound 4d

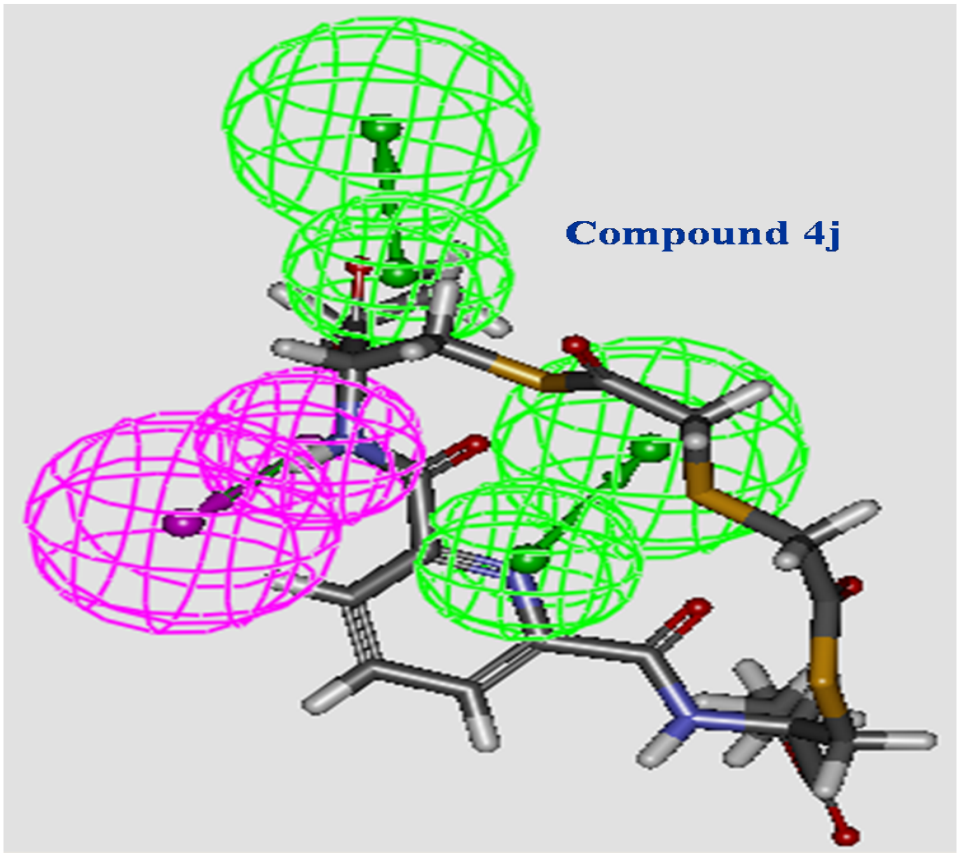

Compound 4e

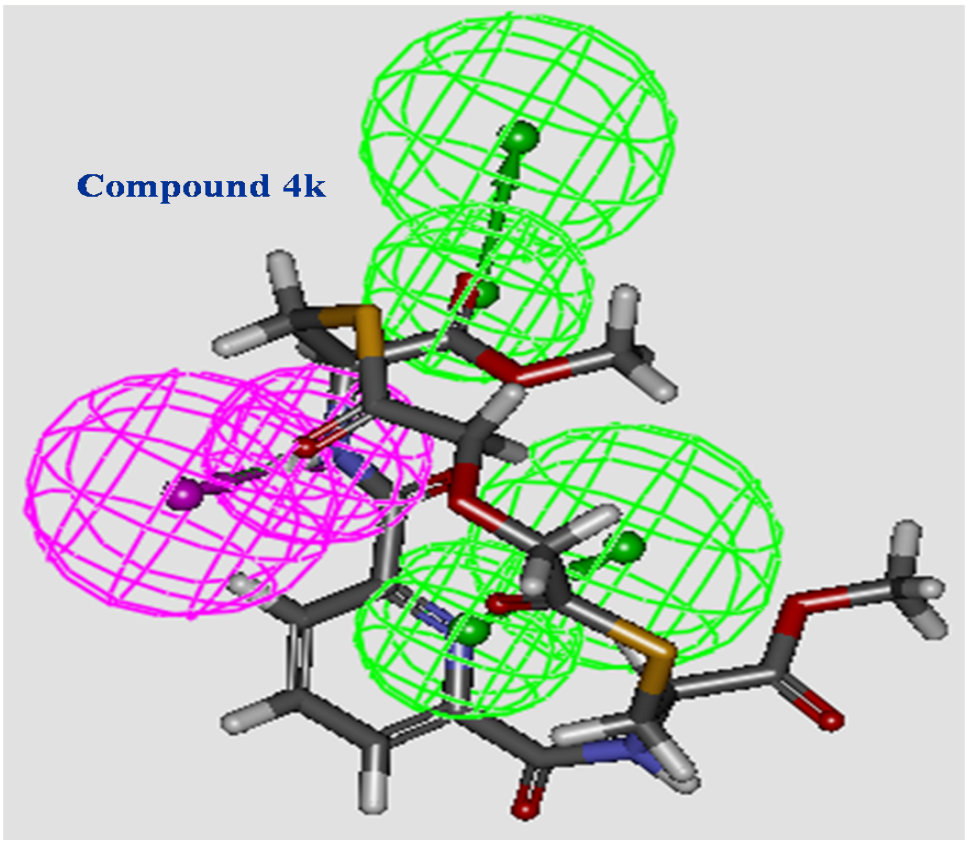

Compound 4f

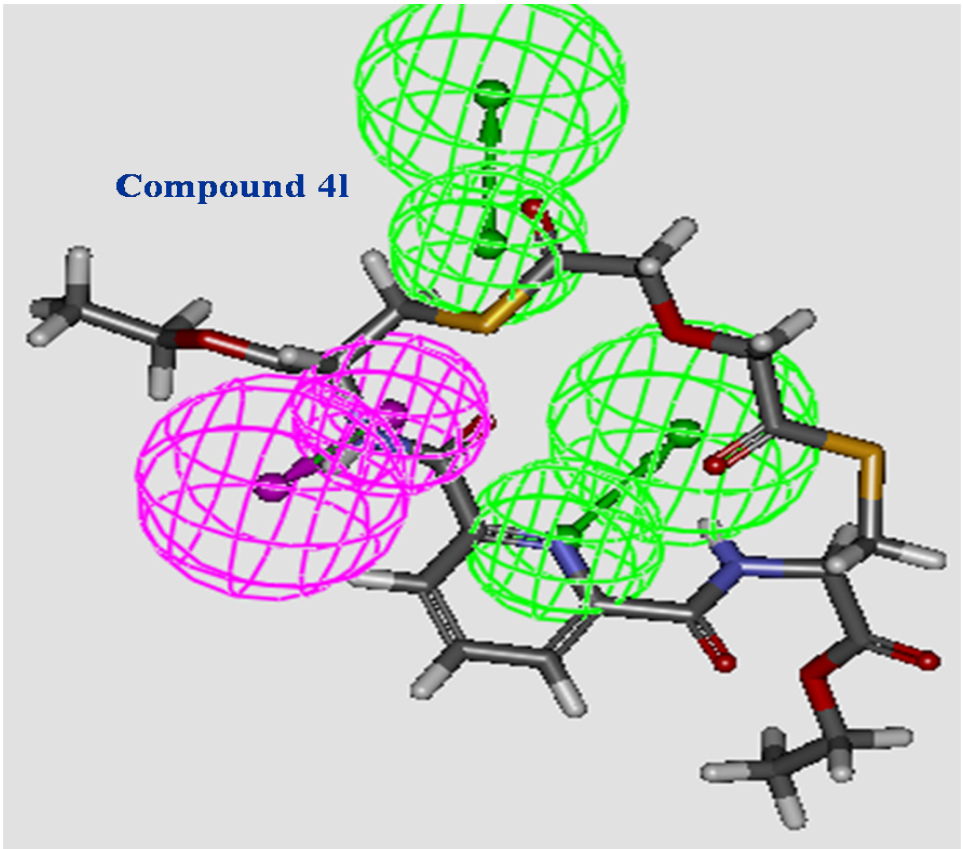

Compound 4g

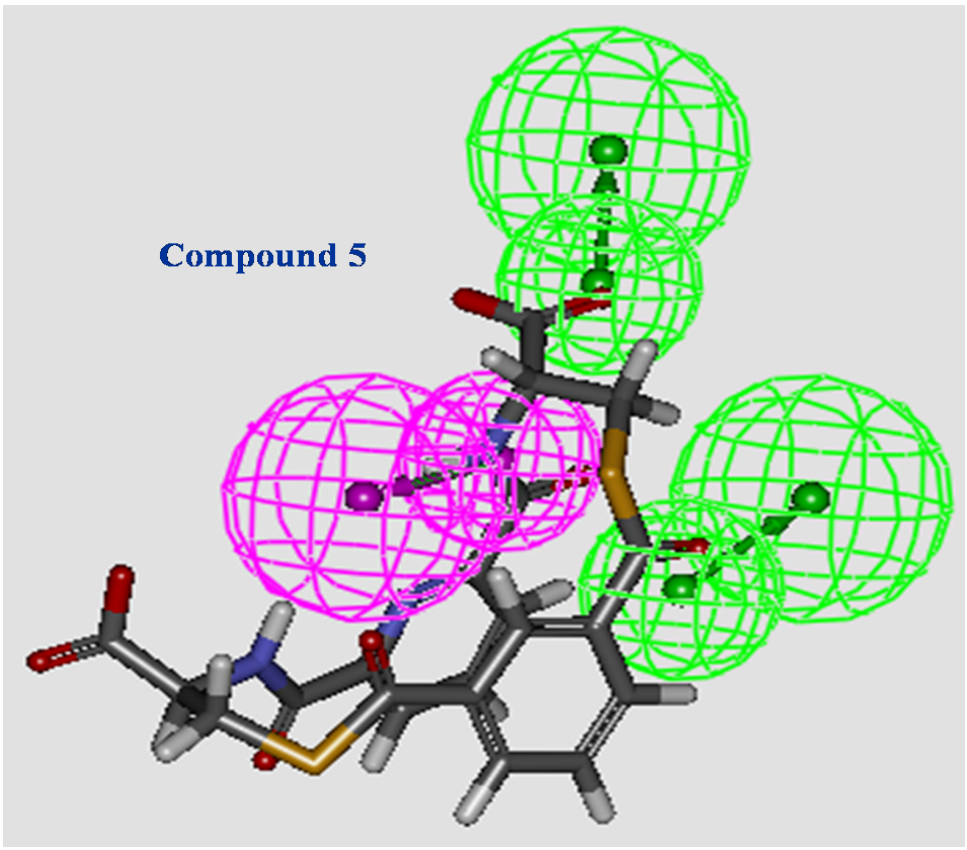

Compound 4h

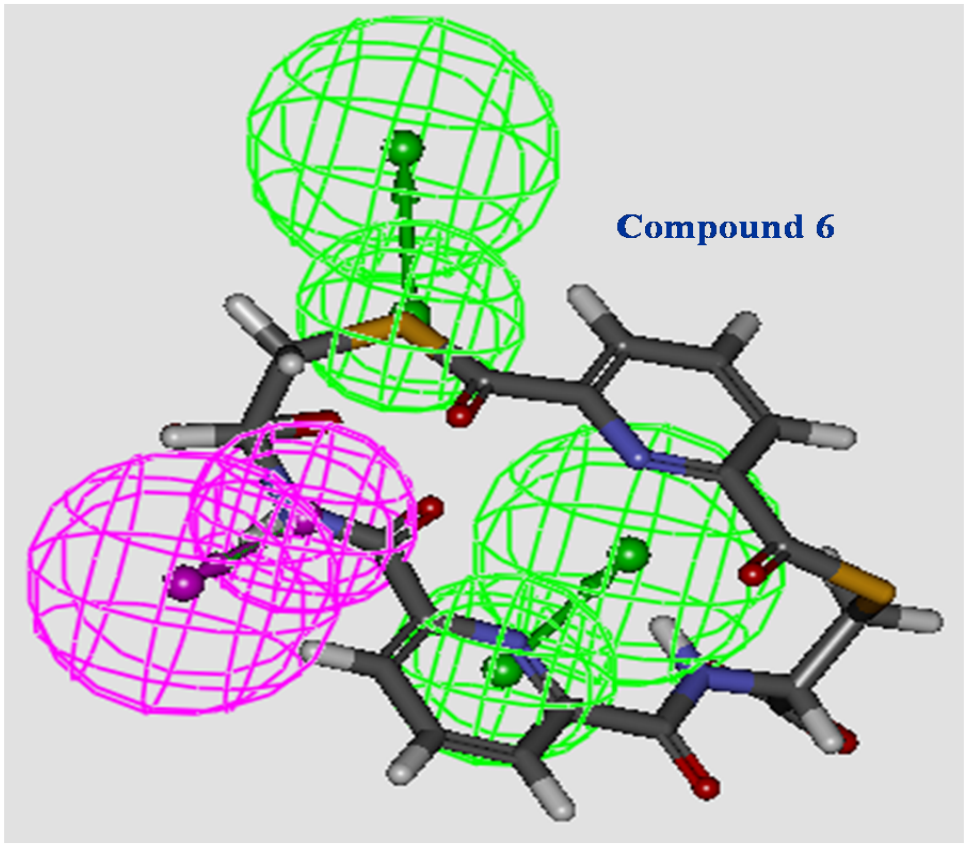

Compound 4i


Compound 4j


Compound 4k


Compound 4l


Compound 5


Compound 6

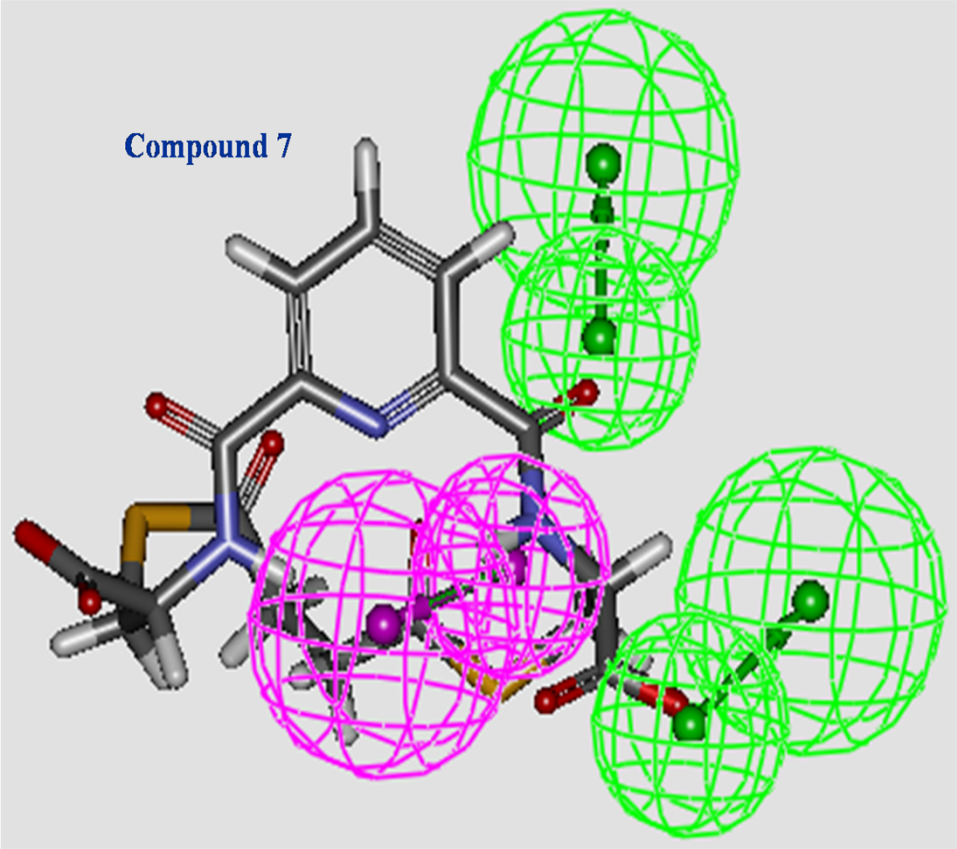
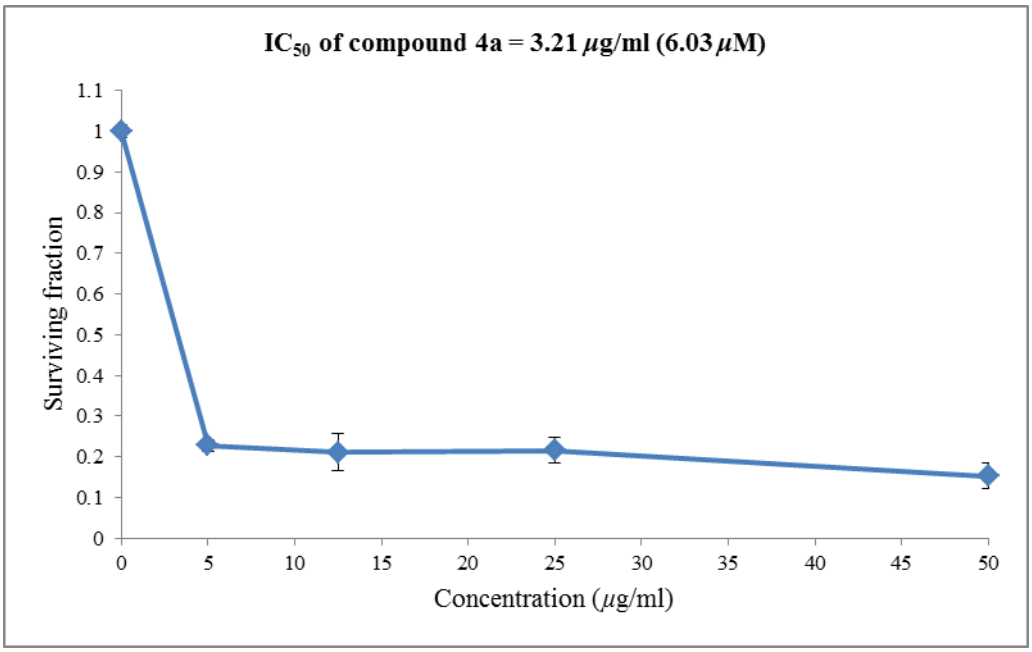
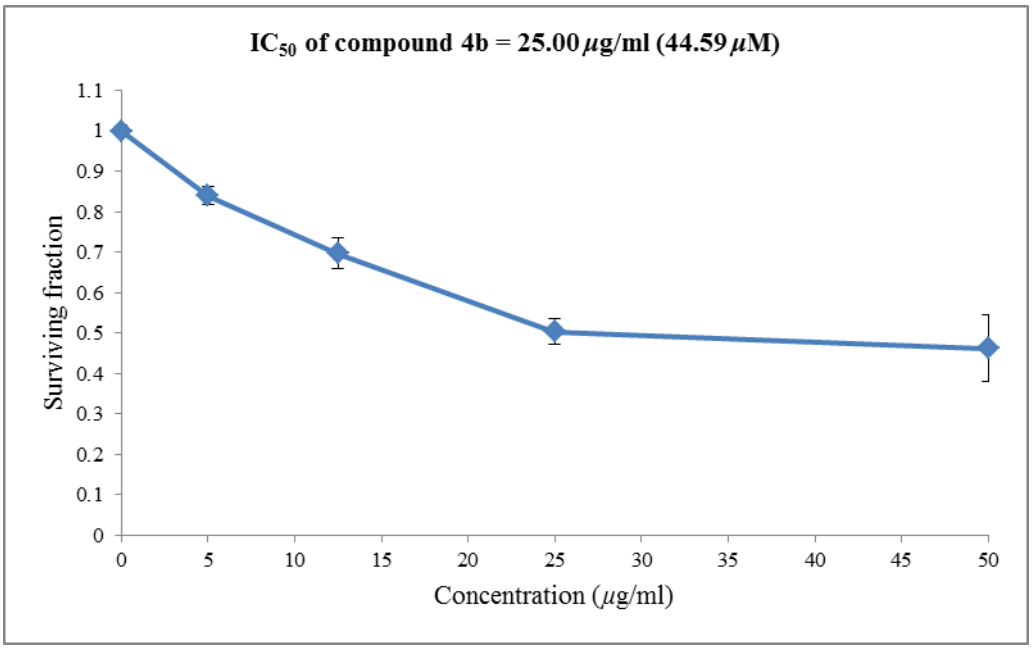
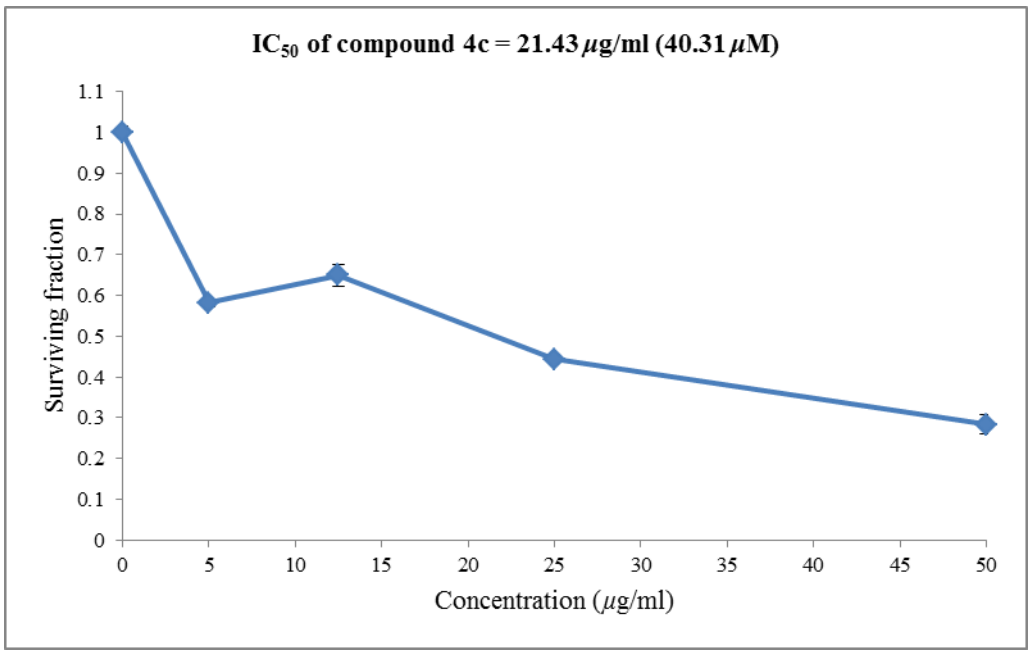
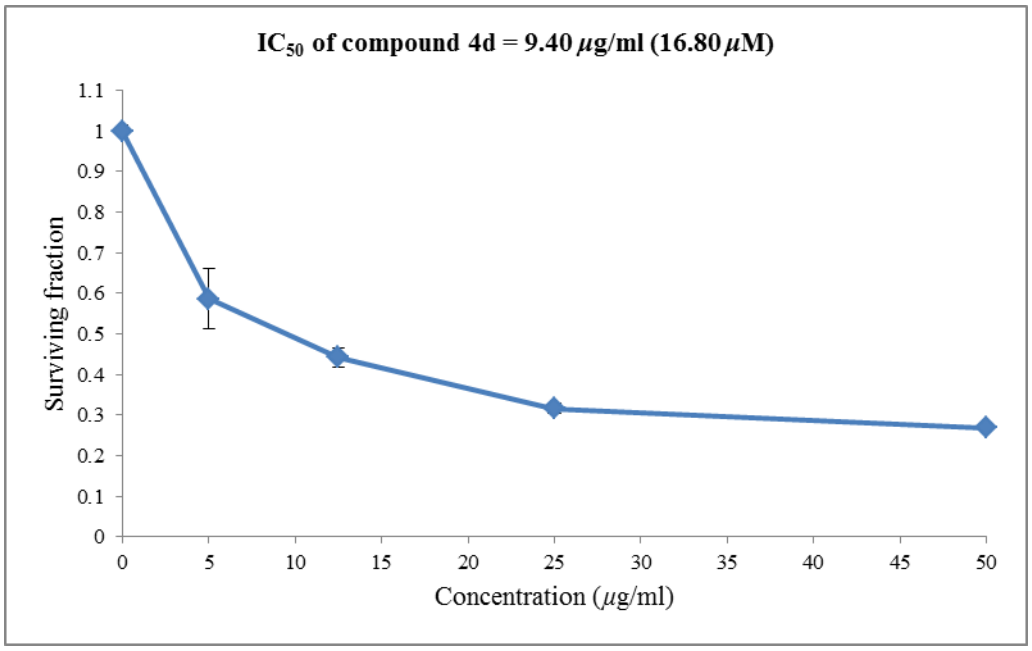


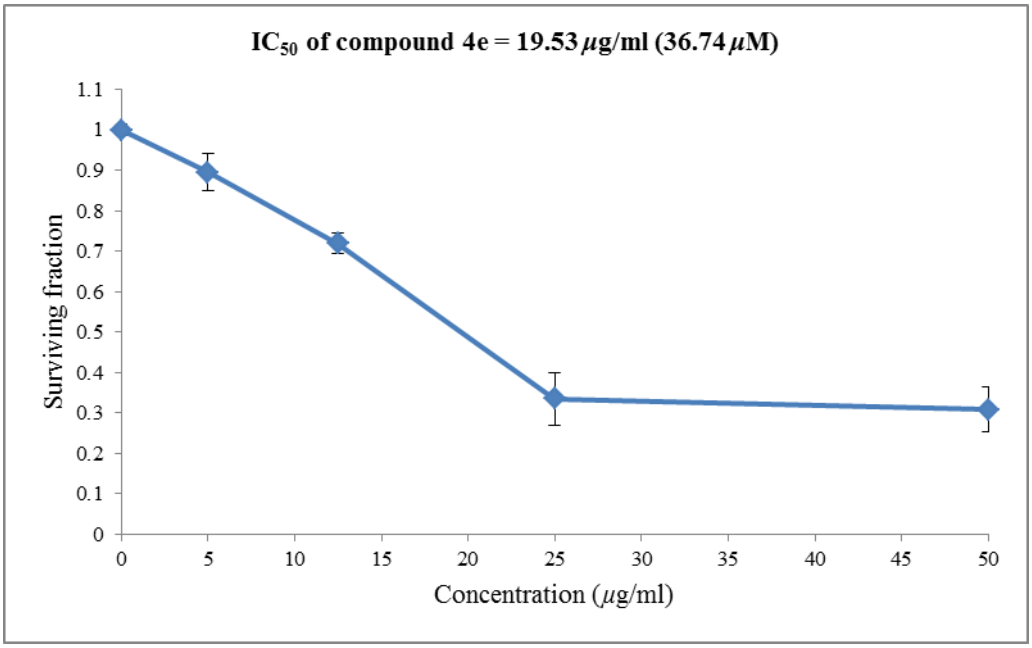
Figure S2. 3D-pharmacophore mapped on the antifungal macrocyclic peptidomimetics **4a-4l,** and **5-7**.

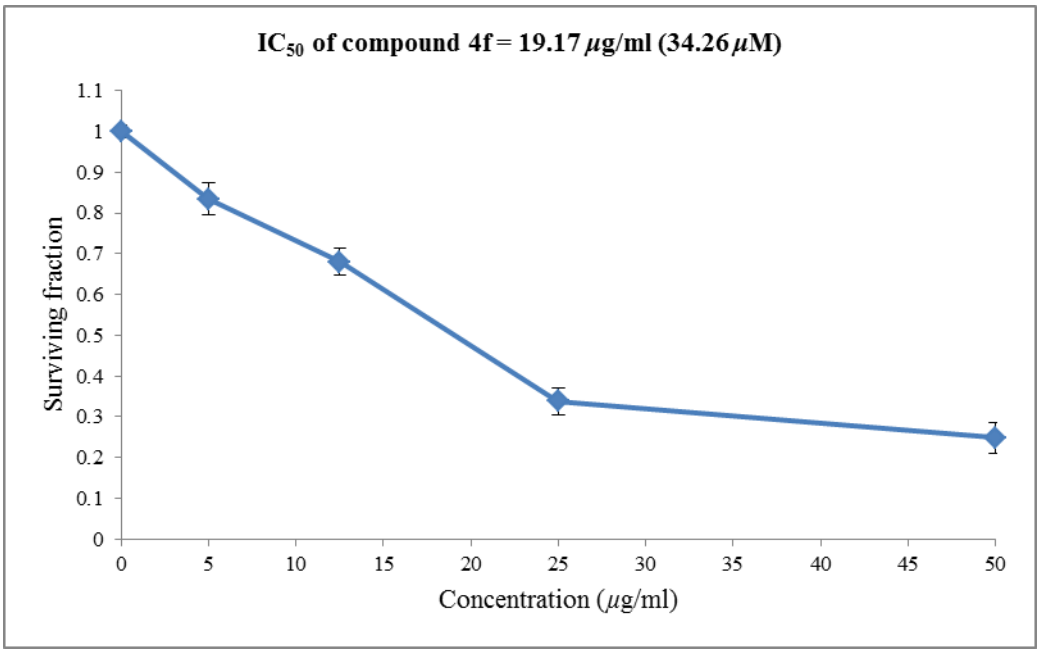

IC50 of compound 4a = 3.21 μg/ml (6.03 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

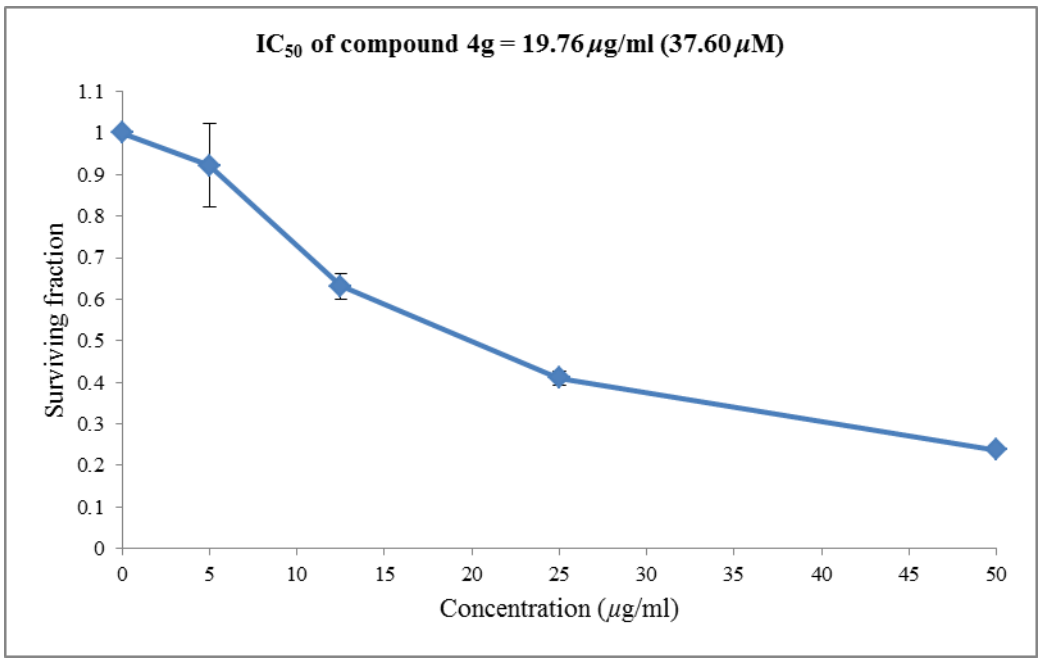

IC50 of compound 4b = 25.00 μg/ml (44.59 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

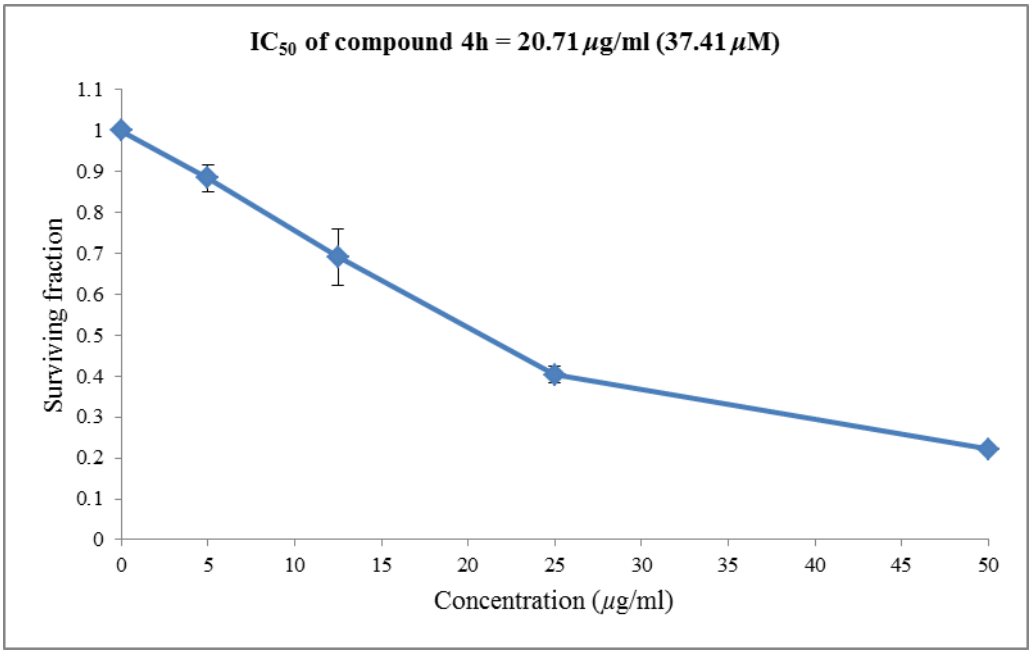

IC50 of compound 4c = 21.43 μg/ml (40.31 μM)
Surviving fraction
Concentration (μg/ml)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
0
5
10
15
20
25
30
35
40
45
50

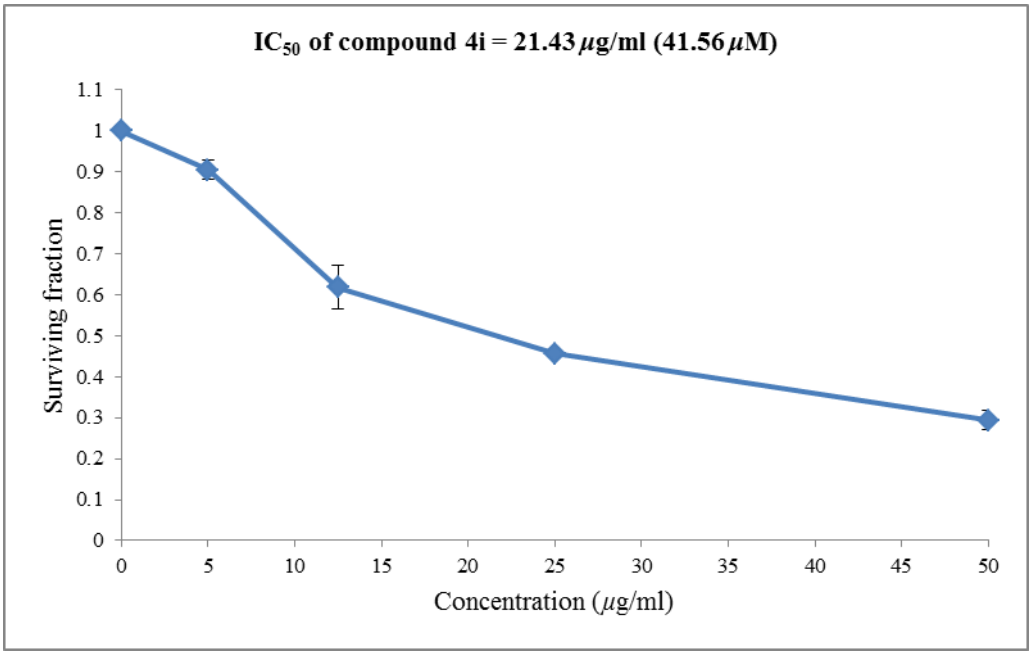

IC50 of compound 4d = 9.40 μg/ml (16.80 μM)
Surviving fraction
Concentration (μg/ml)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
0
5
10
15
20
25
30
35
40
45
50

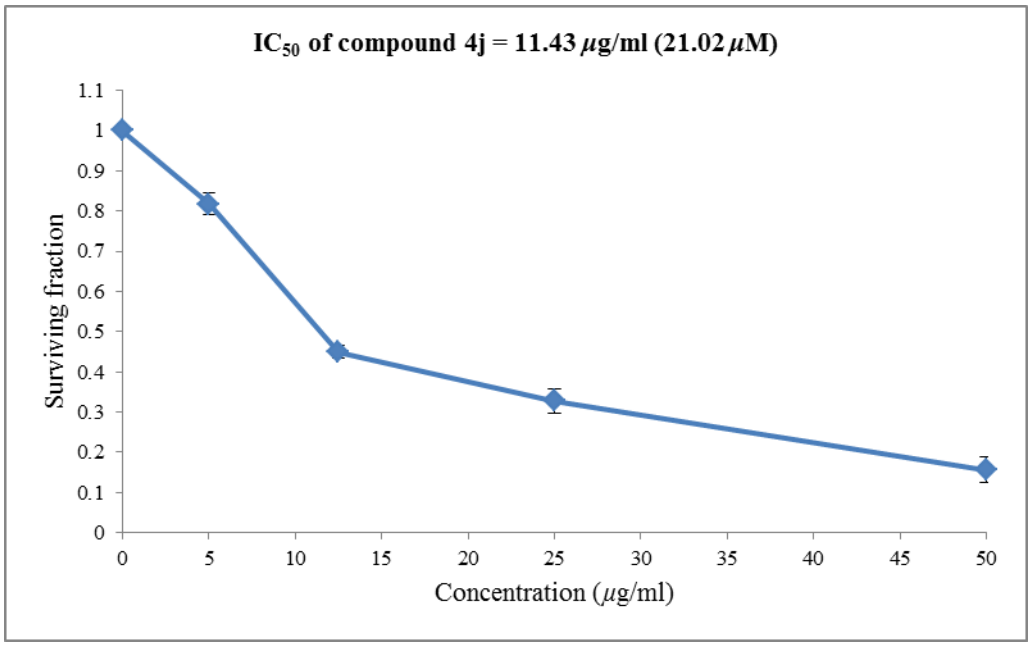

IC50 of compound 4e = 19.53 μg/ml (36.74 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

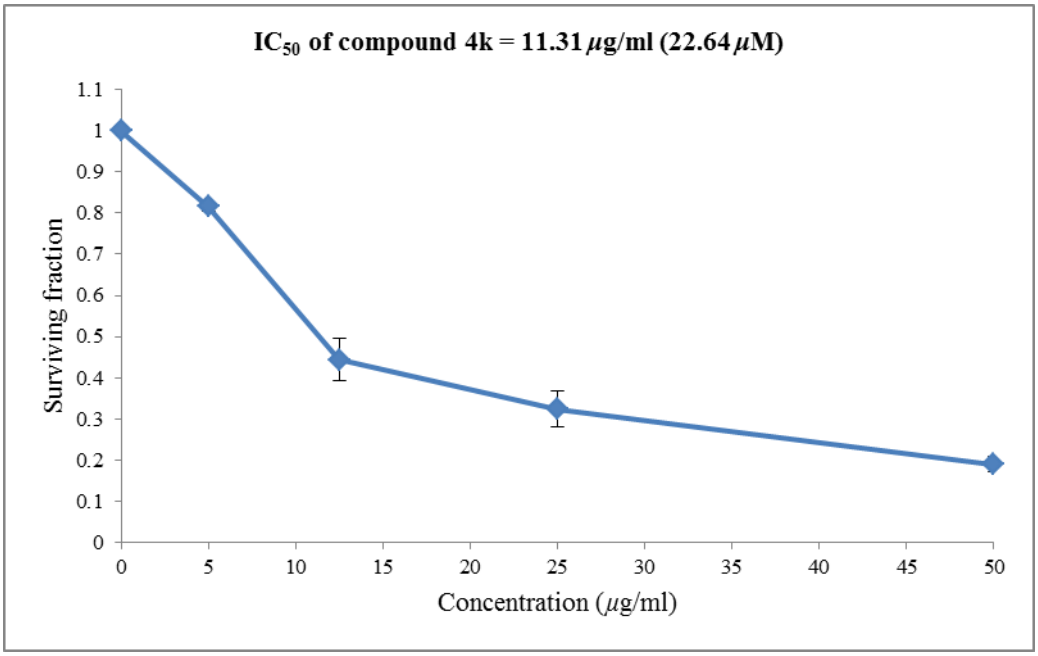

IC50 of compound 4f = 19.17 μg/ml (34.26 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

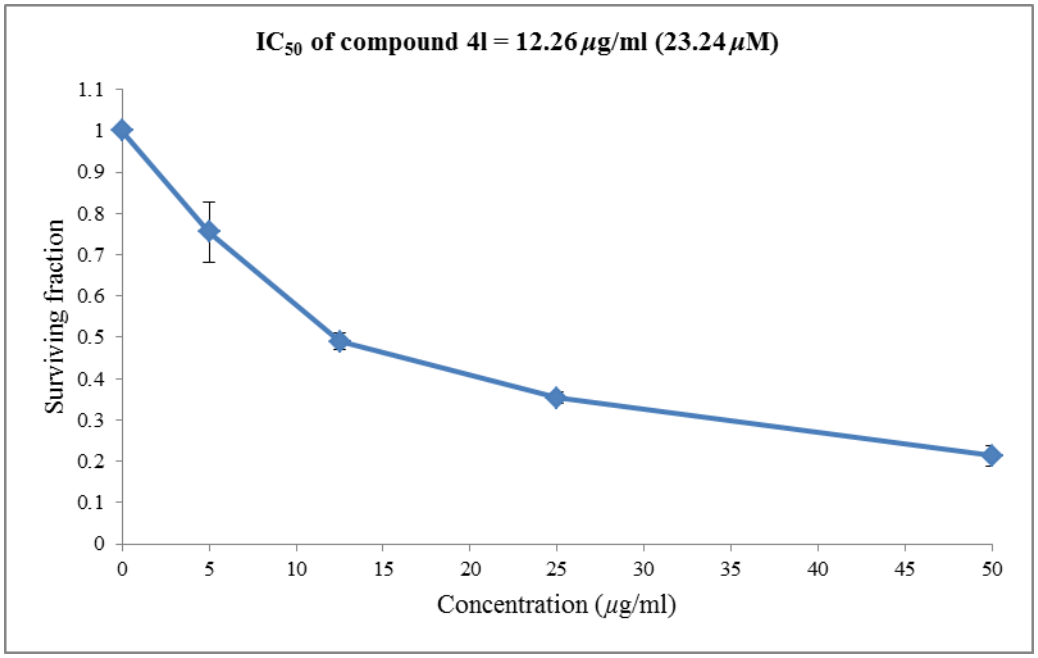

IC50 of compound 4g = 19.76 μg/ml (37.60 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

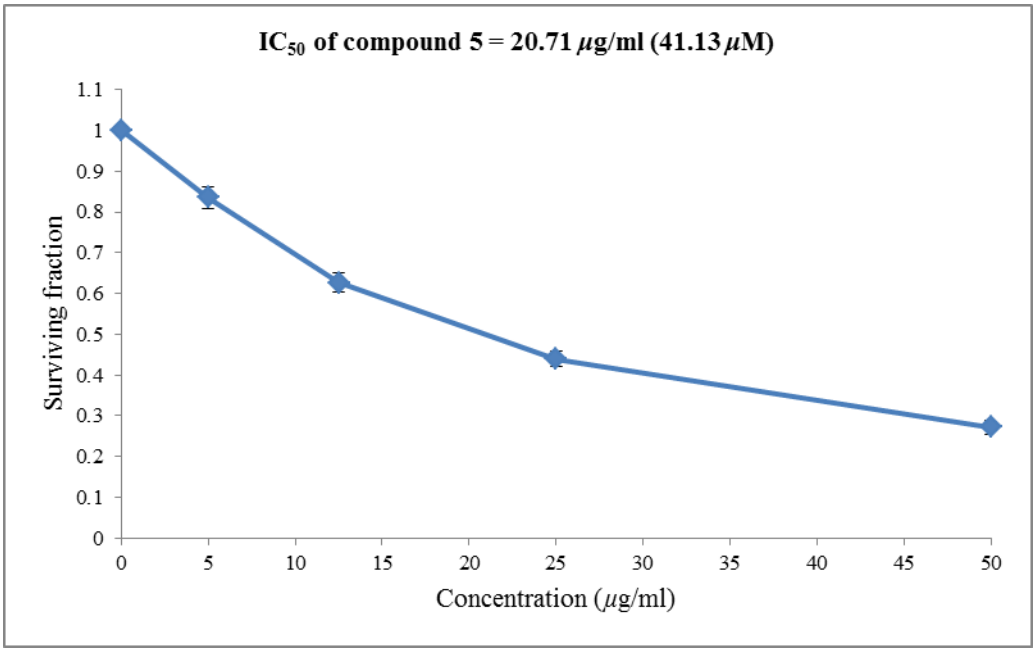

IC50 of compound 4h = 20.71 μg/ml (37.41 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

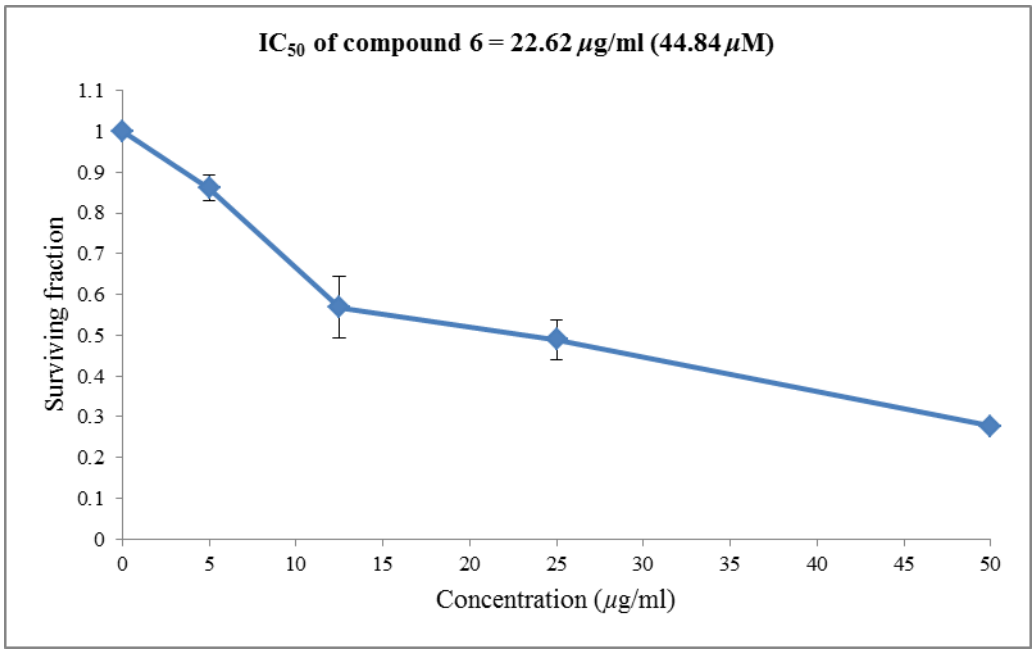

IC50 of compound 4i = 21.43 μg/ml (41.56 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4j = 11.43 μg/ml (21.02 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4k = 11.31 μg/ml (22.64 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4l = 12.26 μg/ml (23.24 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 5 = 20.71 μg/ml (41.13 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 6 = 22.62 μg/ml (44.84 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

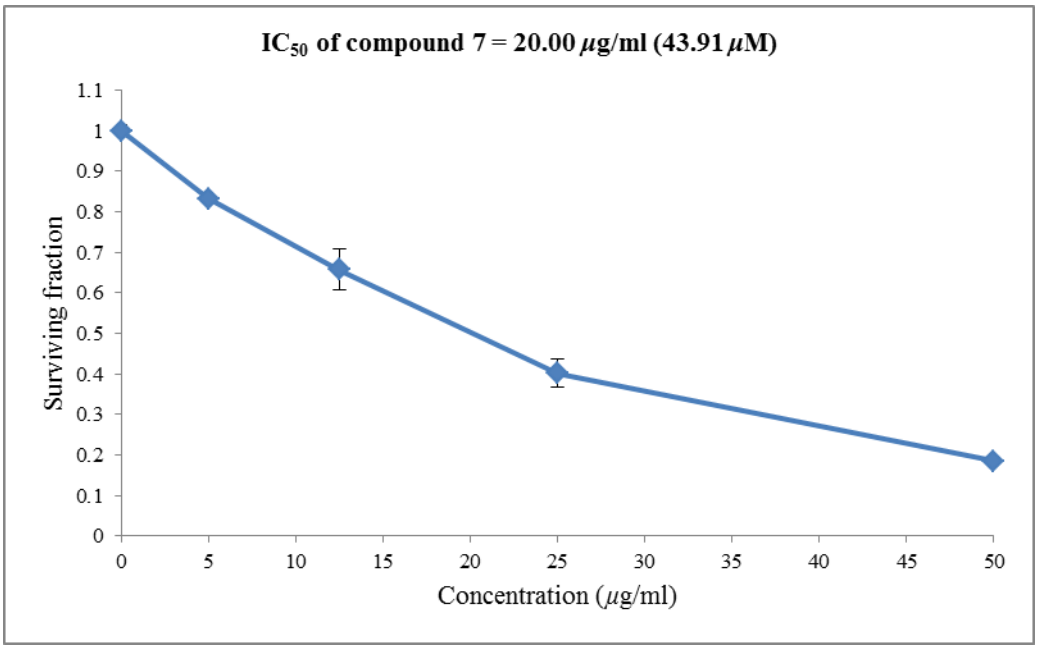
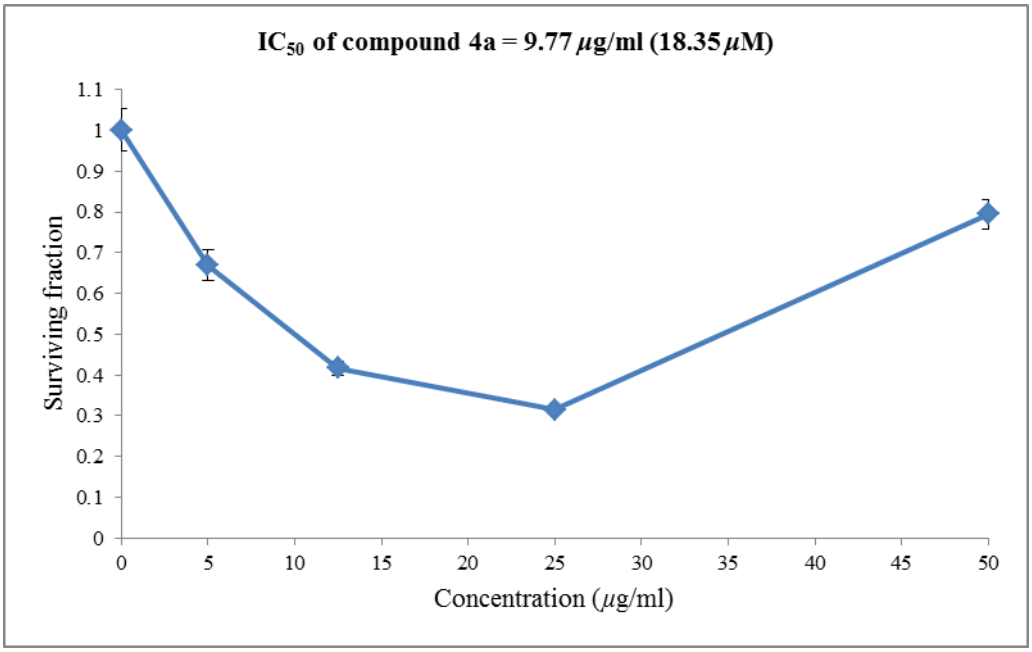
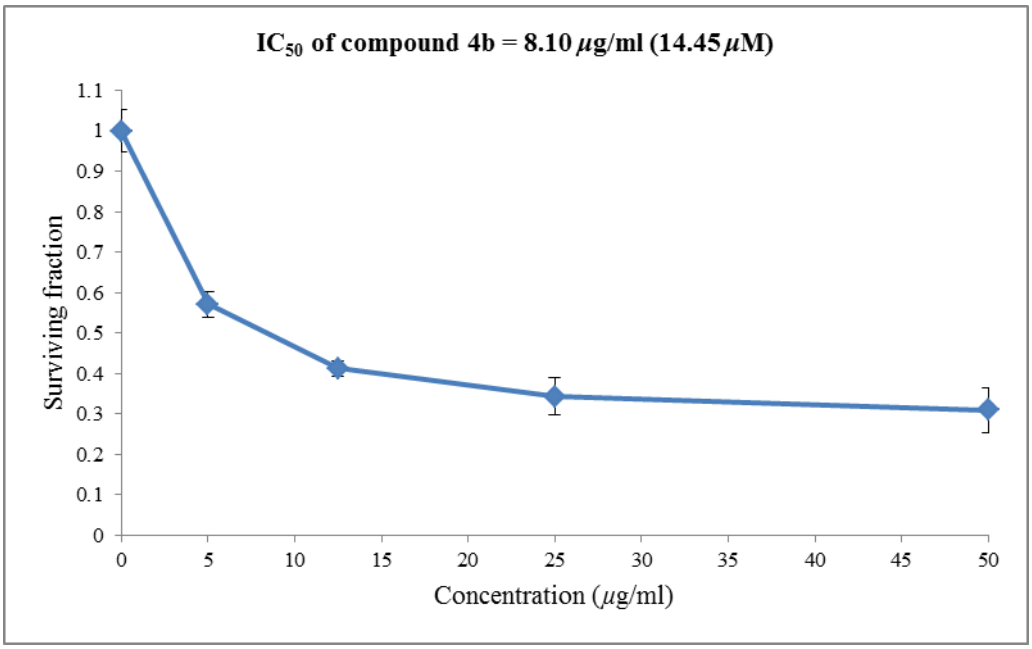
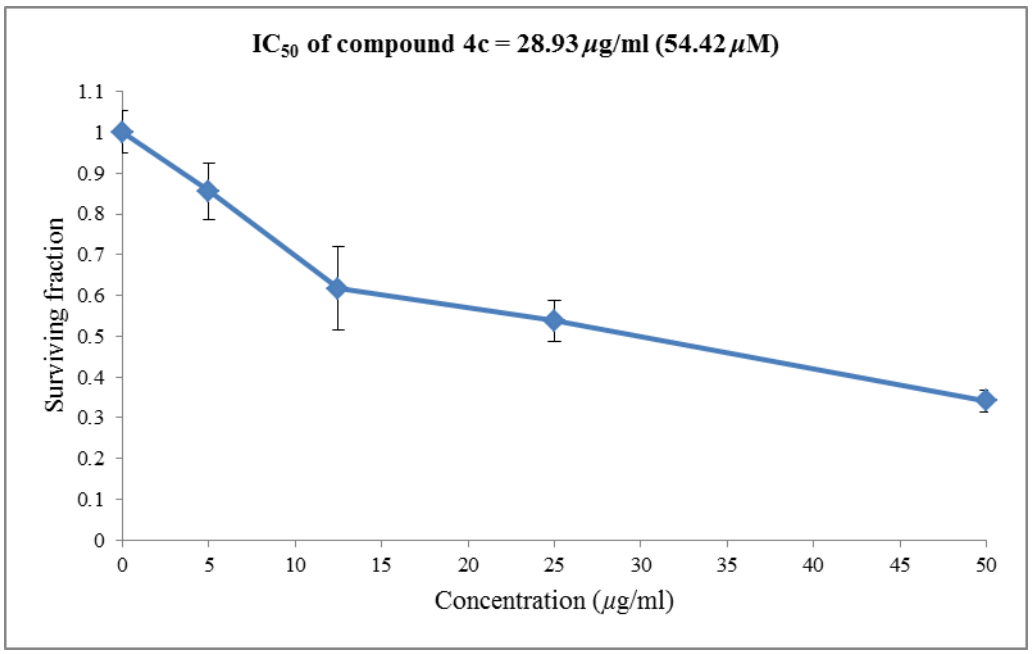
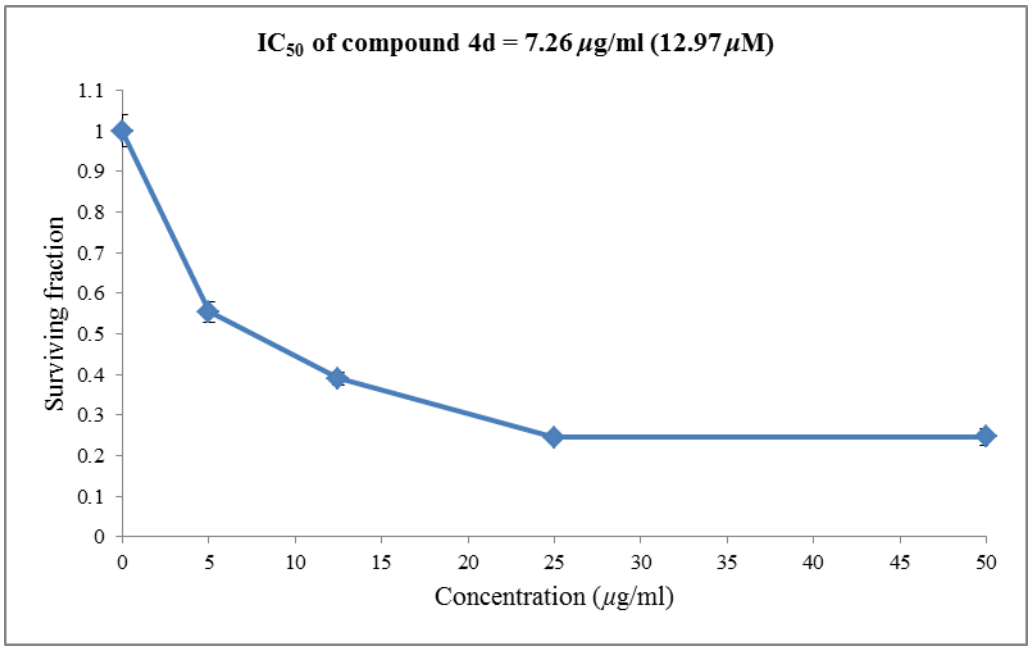


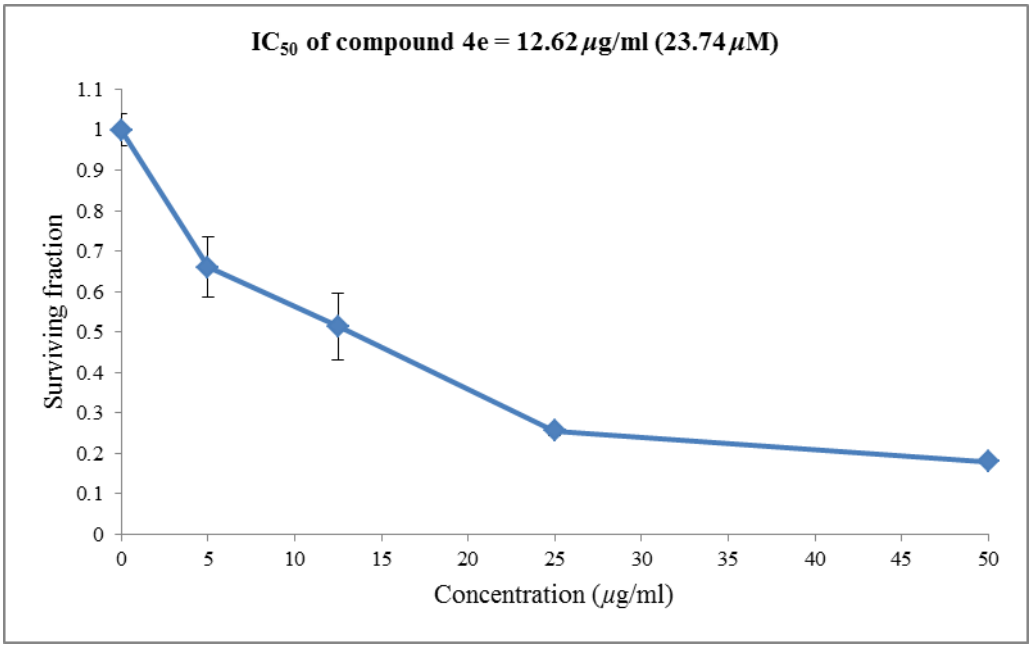
Figure S3. Dose-response curves of the macrocyclic peptidomimetics **4a-l,** and **5-7** against HepG2 (liver) human tumor cell line.

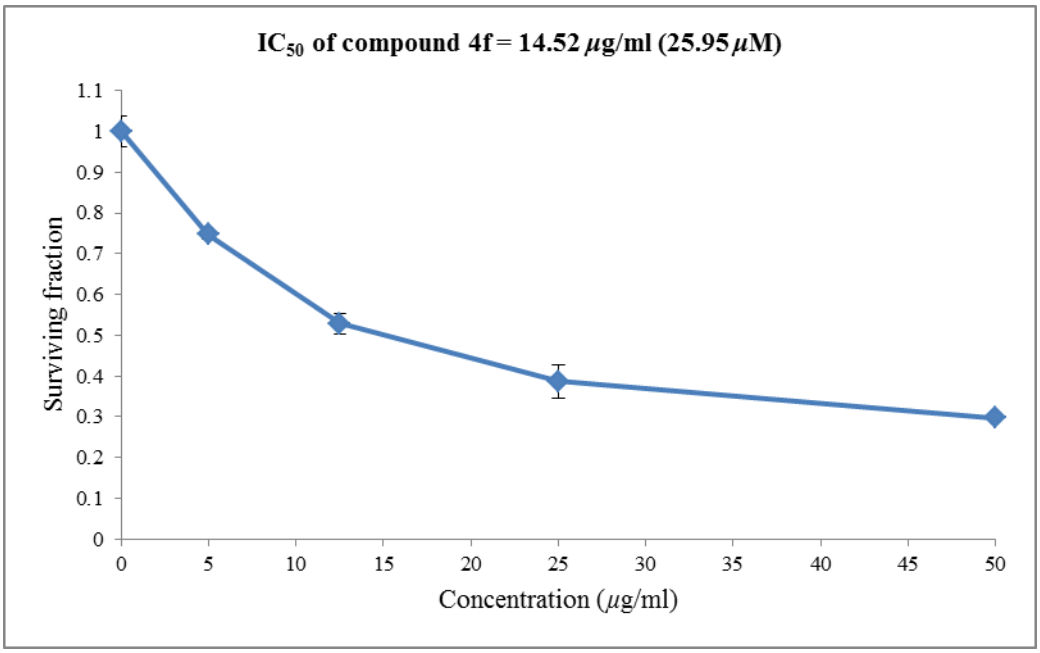

IC50 of compound 4a = 9.77 μg/ml (18.35 μM)
Surviving fraction
Concentration (μg/ml)

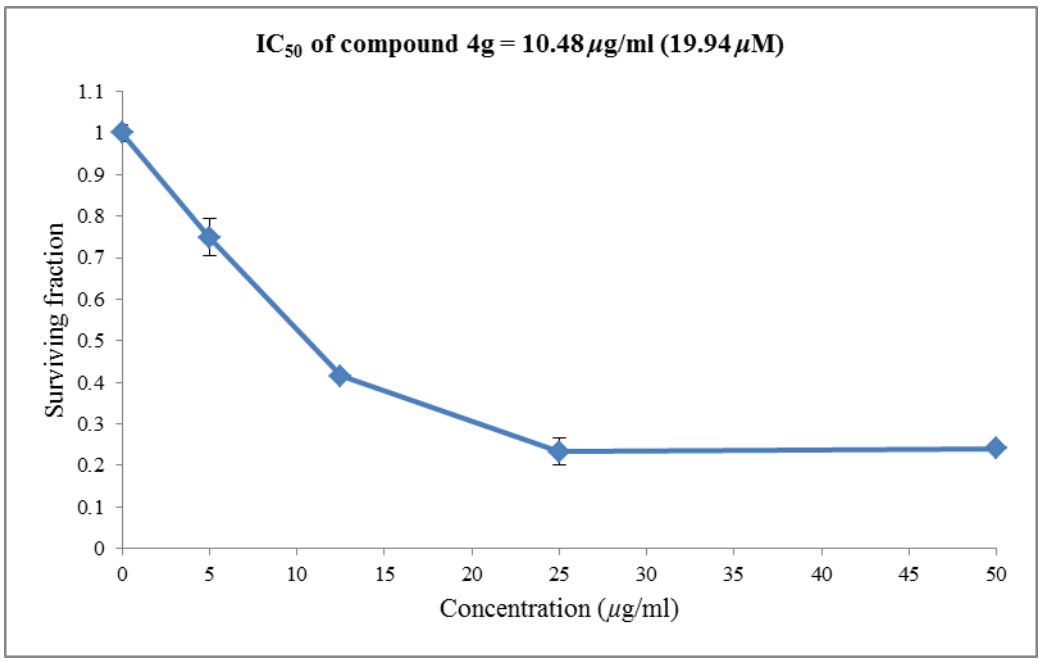

IC50 of compound 4b = 8.10 μg/ml (14.45 μM)
Surviving fraction
Concentration (μg/ml)

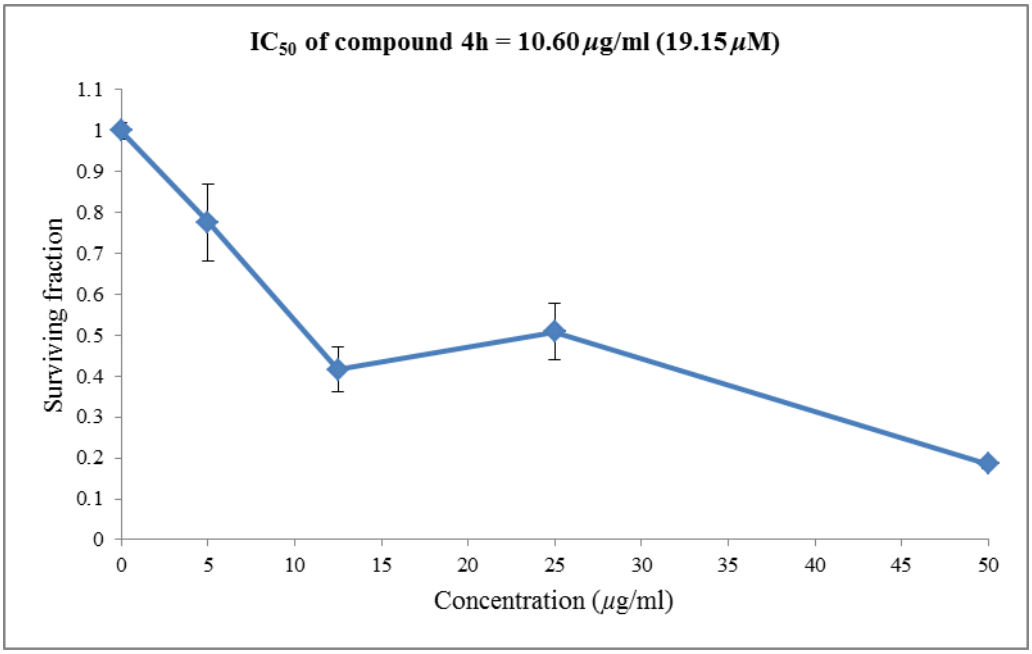

IC50 of compound 4c = 28.93 μg/ml (54.42 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

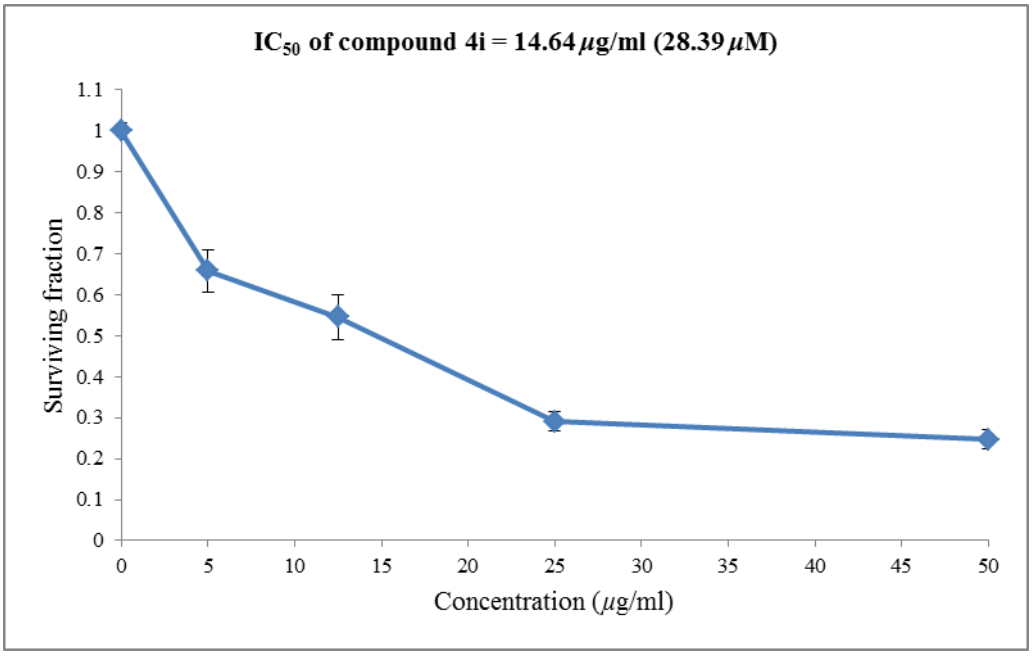

IC50 of compound 4d = 7.26 μg/ml (12.97 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

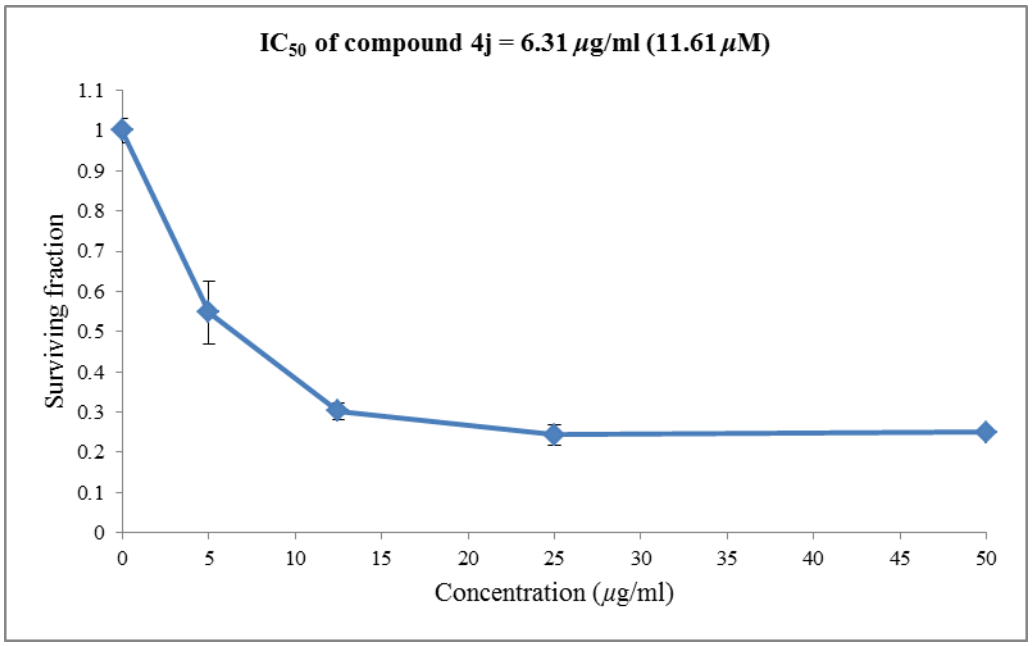

IC50 of compound 4e = 12.62 μg/ml (23.74 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

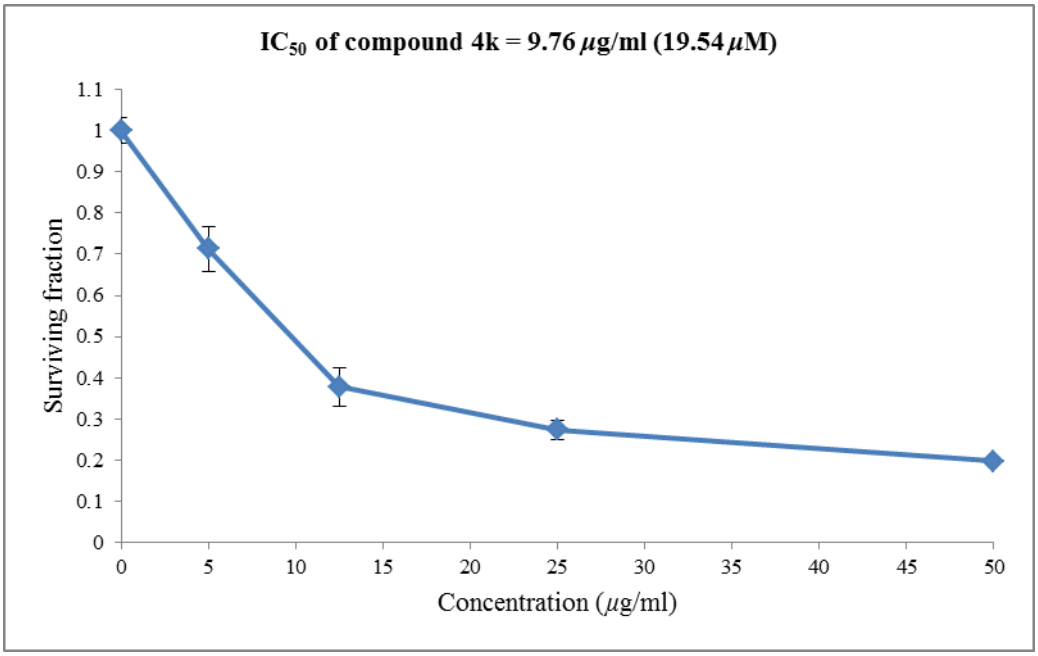

IC50 of compound 4f = 14.52 μg/ml (25.95 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

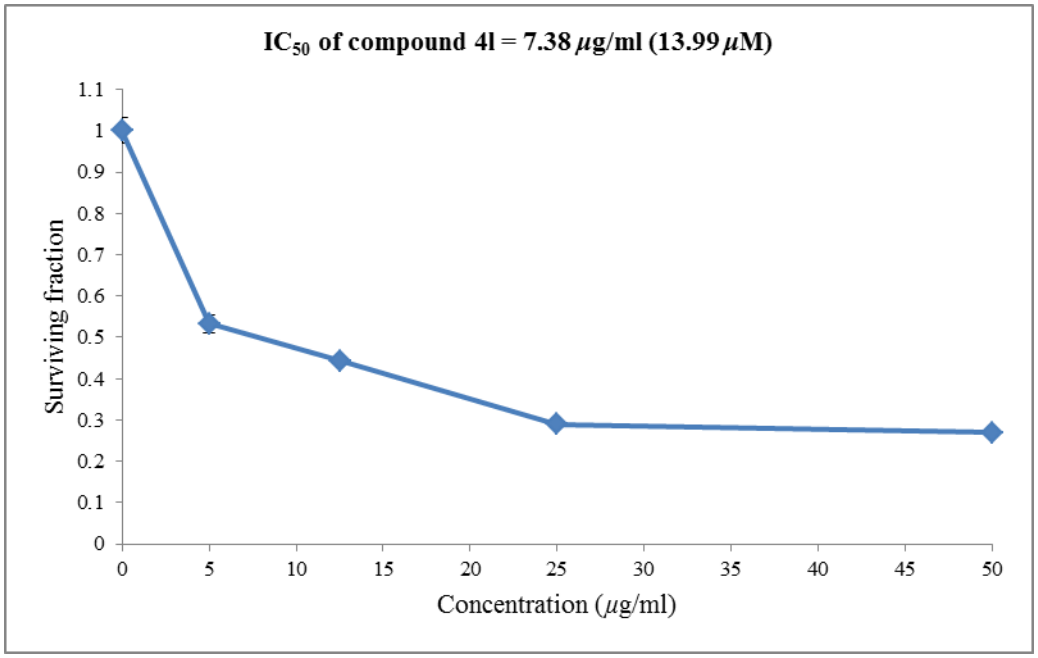

IC50 of compound 4g = 10.48 μg/ml (19.94 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

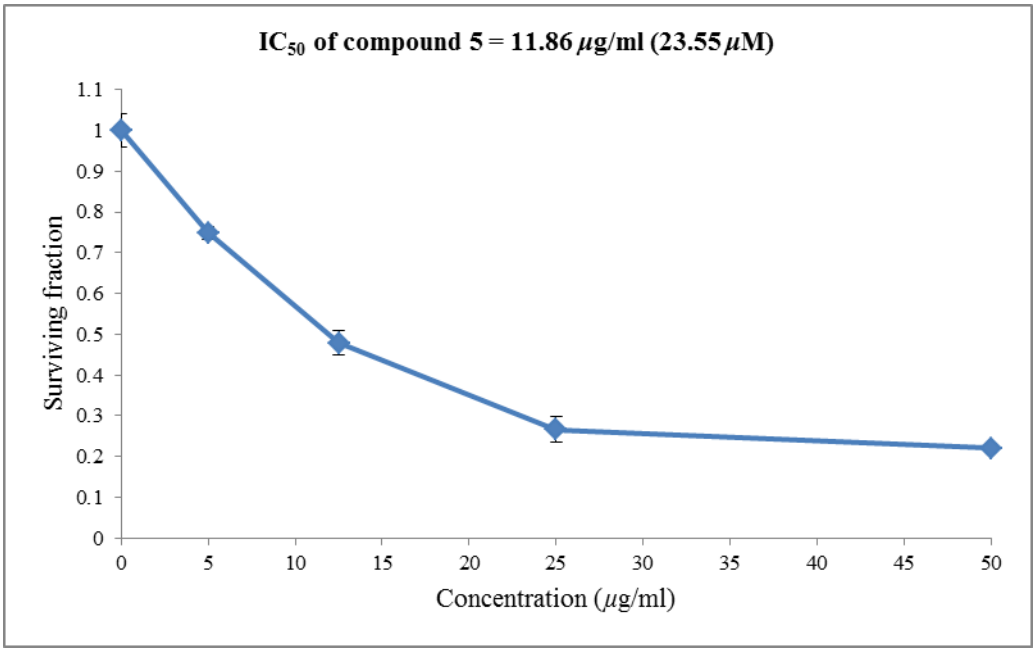

IC50 of compound 4h = 10.60 μg/ml (19.15 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

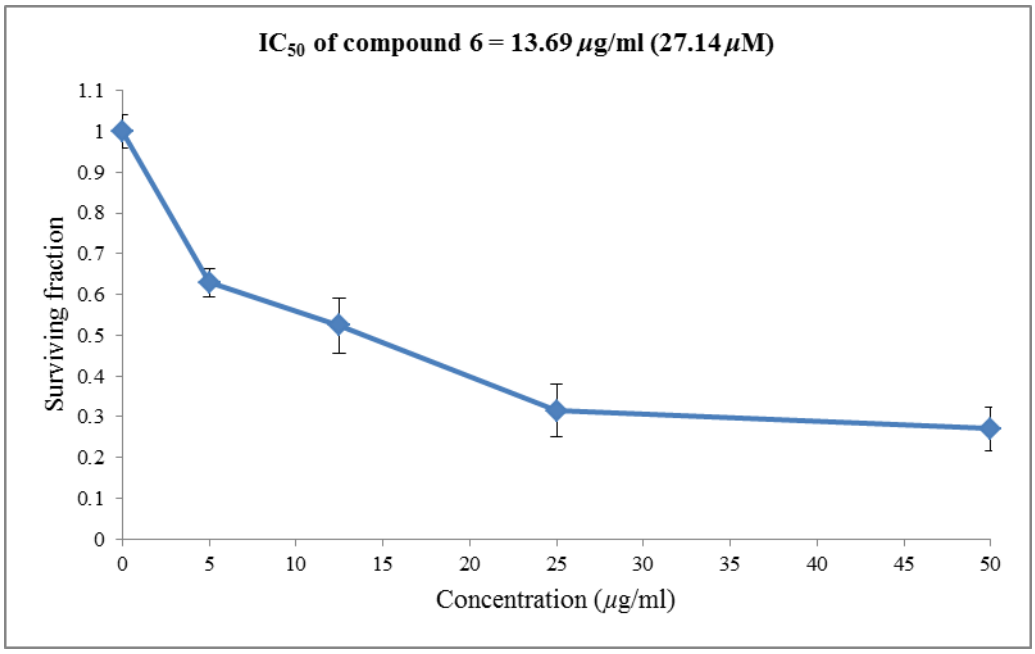

IC50 of compound 4i = 14.64 μg/ml (28.39 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4j = 6.31 μg/ml (11.61 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4k = 9.76 μg/ml (19.54 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4l = 7.38 μg/ml (13.99 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 5 = 11.86 μg/ml (23.55 μM)
Surviving fraction
Concentration (μg/ml)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
0
5
10
15
20
25
30
35
40
45
50


IC50 of compound 6 = 13.69 μg/ml (27.14 μM)
Surviving fraction
Concentration (μg/ml)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
0
5
10
15
20
25
30
35
40
45
50

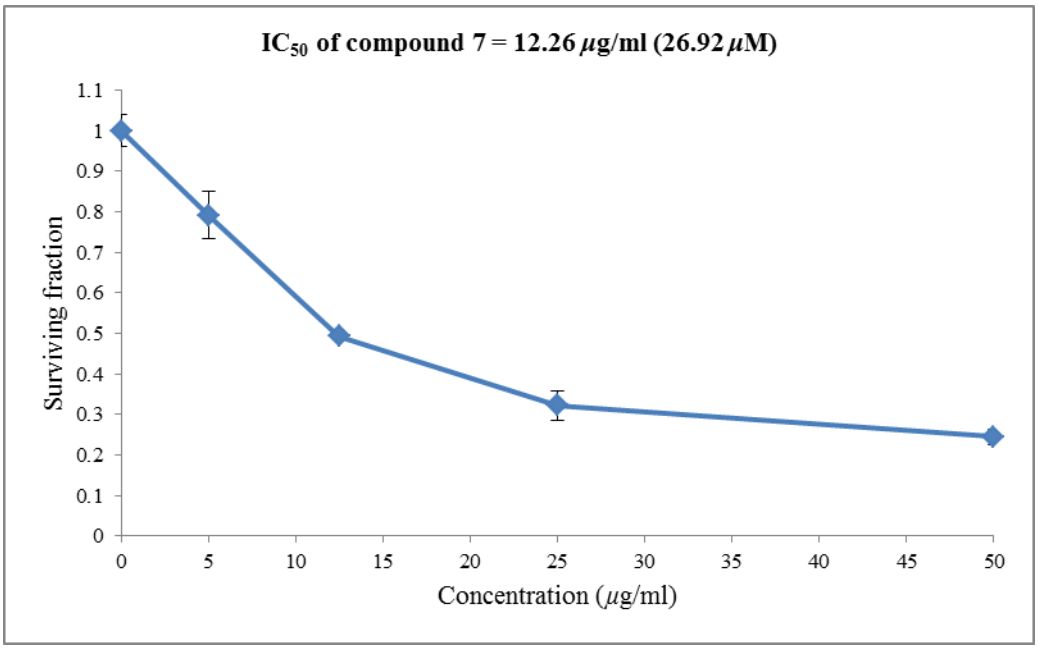
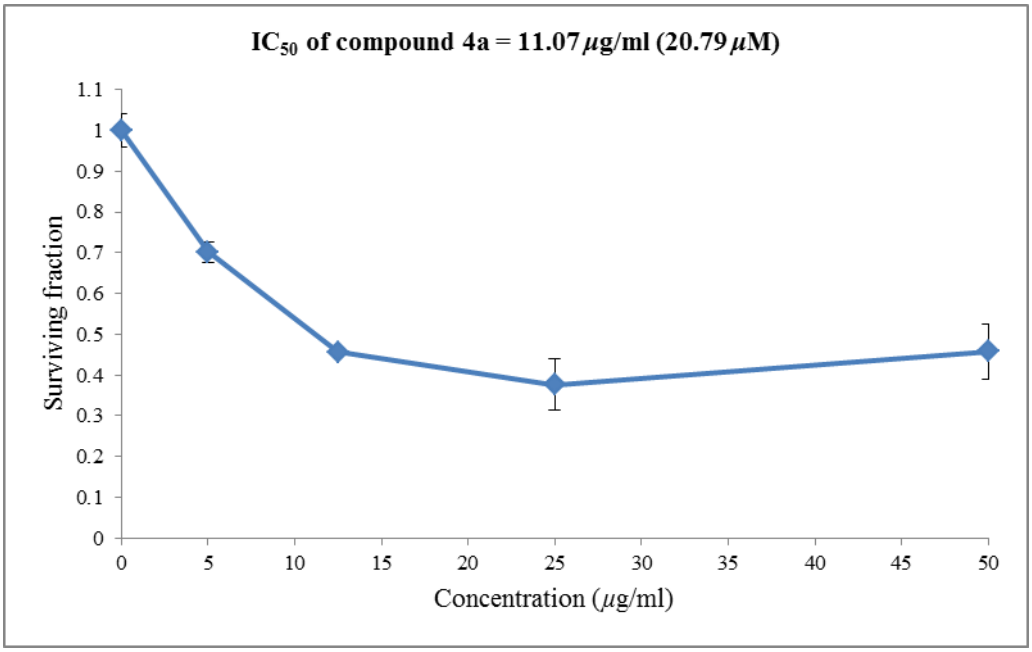
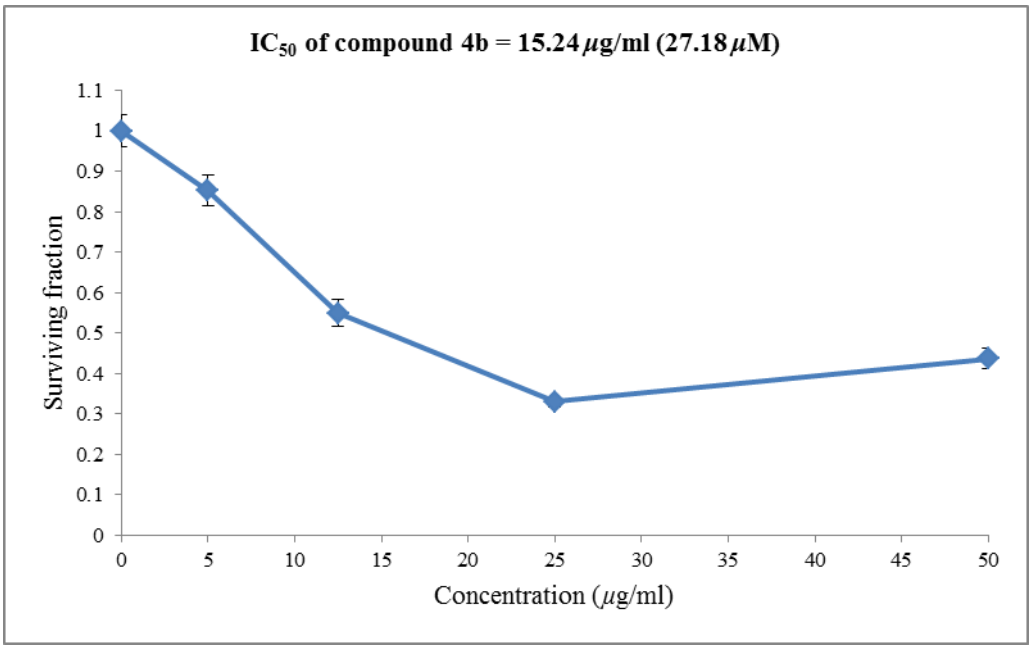
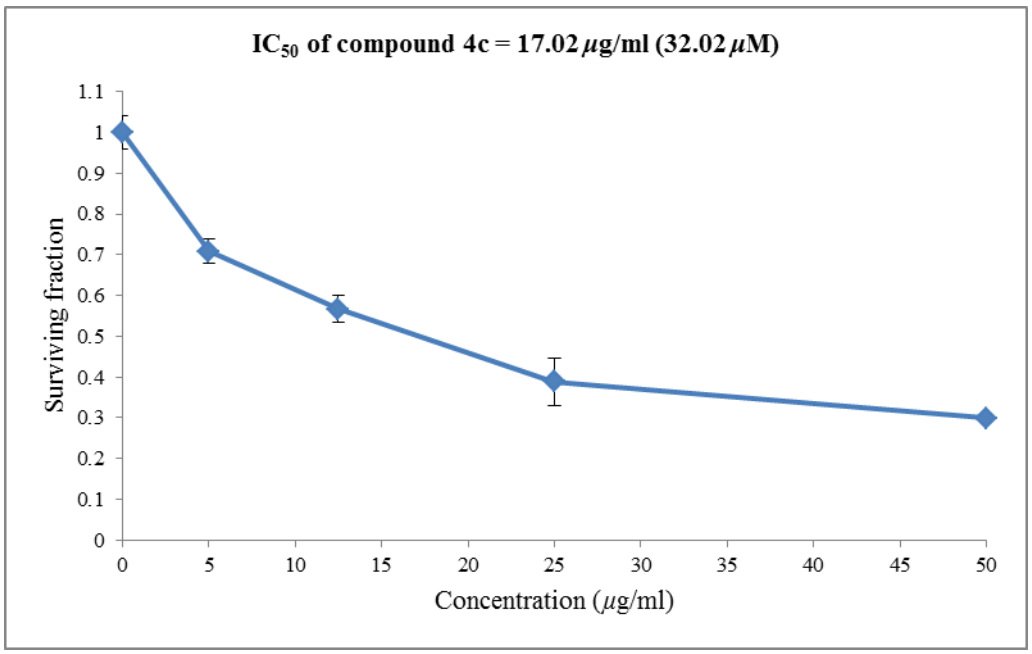
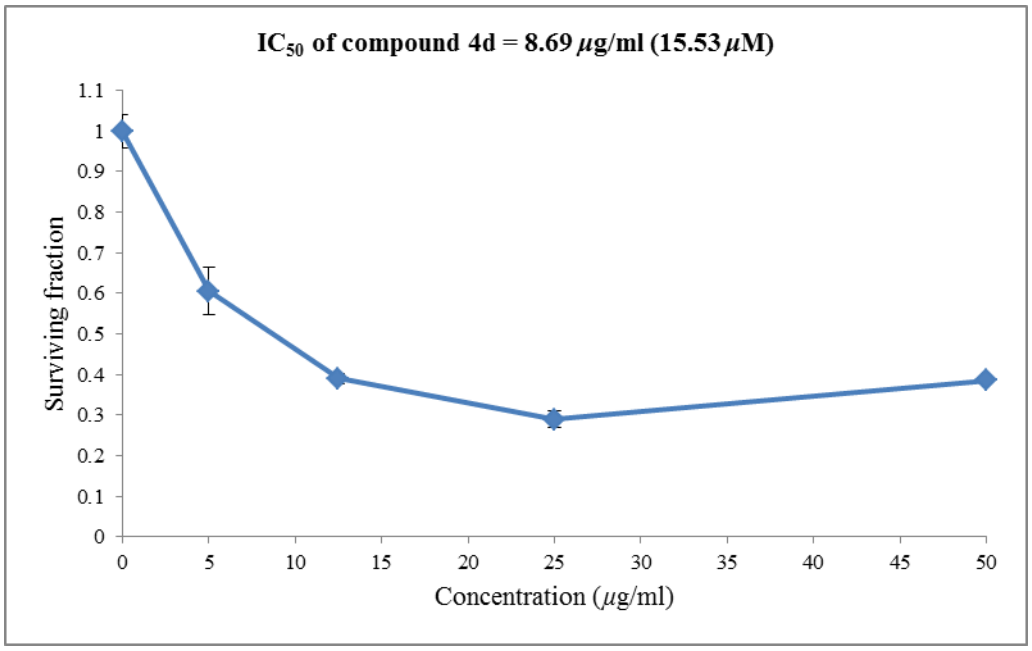


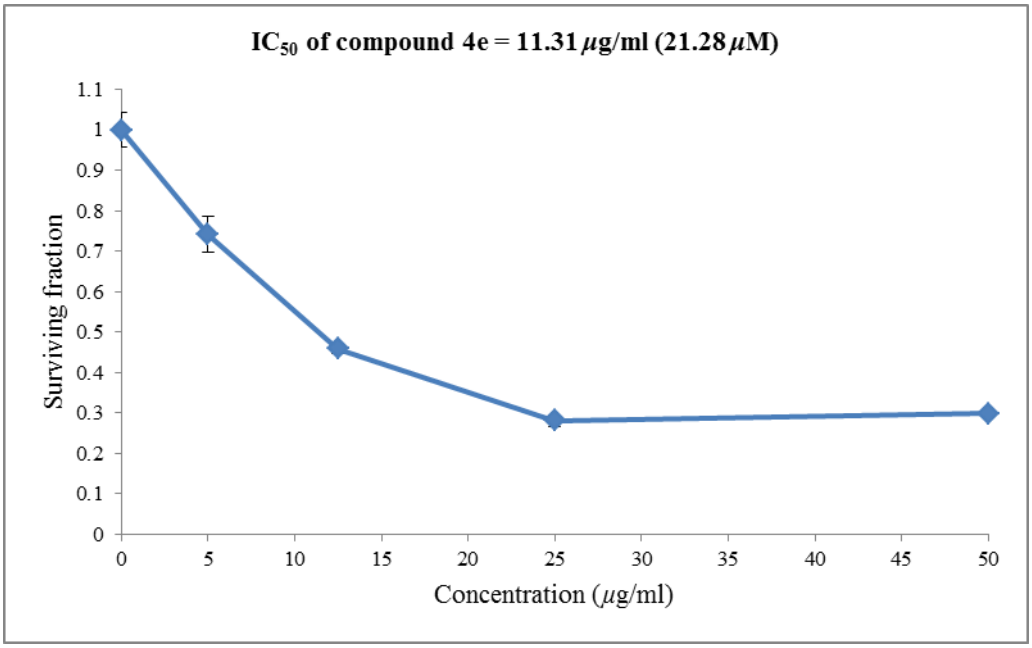
Figure S4. Dose-response curves of the macrocyclic peptidomimetics **4a-l,** and **5-7** against HeLa (cervical) human tumor cell line.

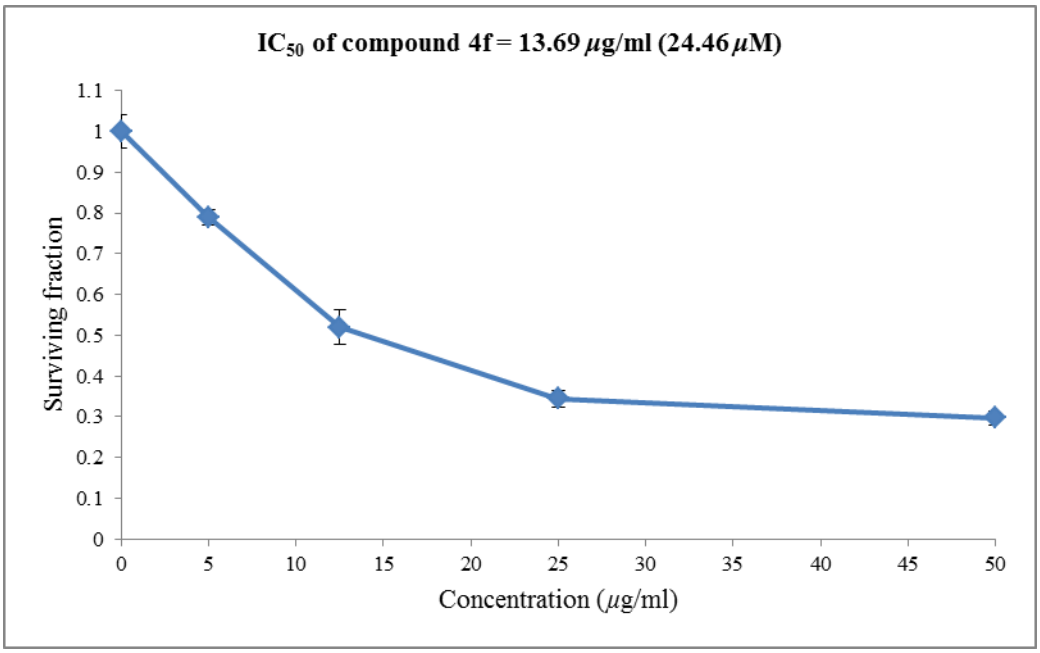

IC50 of compound 4a = 11.07 μg/ml (20.79 μM)
Surviving fraction
Concentration (μg/ml)

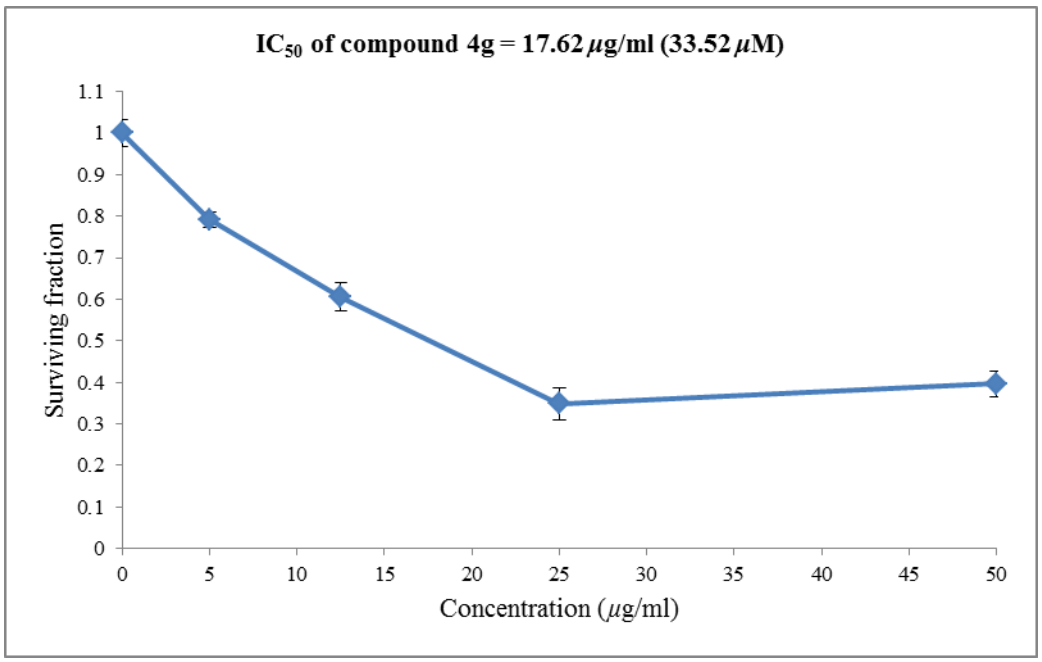

IC50 of compound 4b = 15.24 μg/ml (27.18 μM)
Surviving fraction
Concentration (μg/ml)

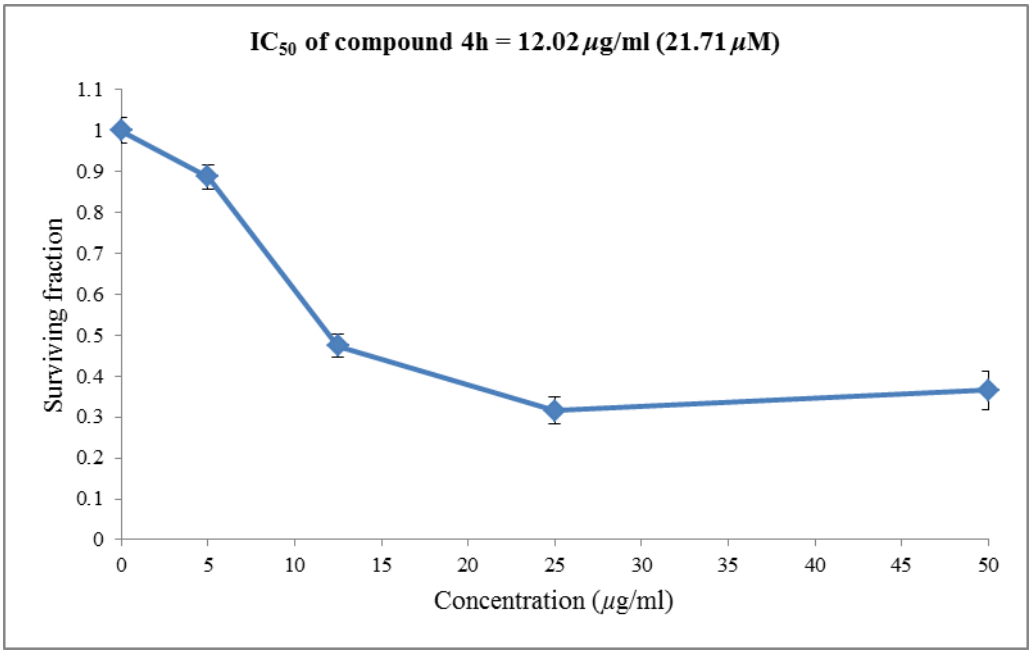

IC50 of compound 4c = 17.02 μg/ml (32.02 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

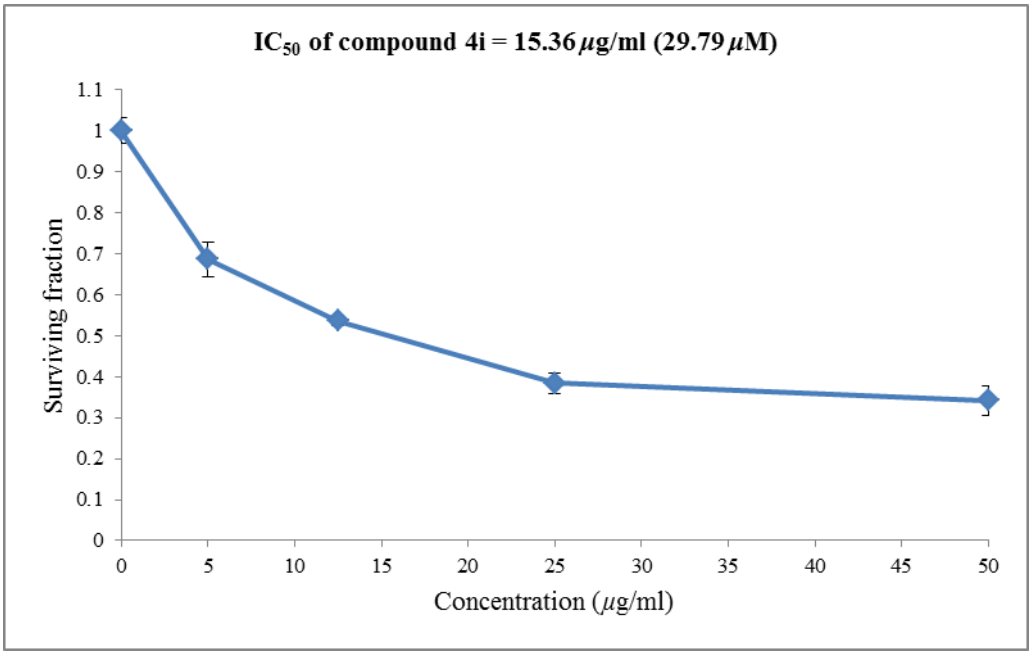

IC50 of compound 4d = 8.69 μg/ml (15.53 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

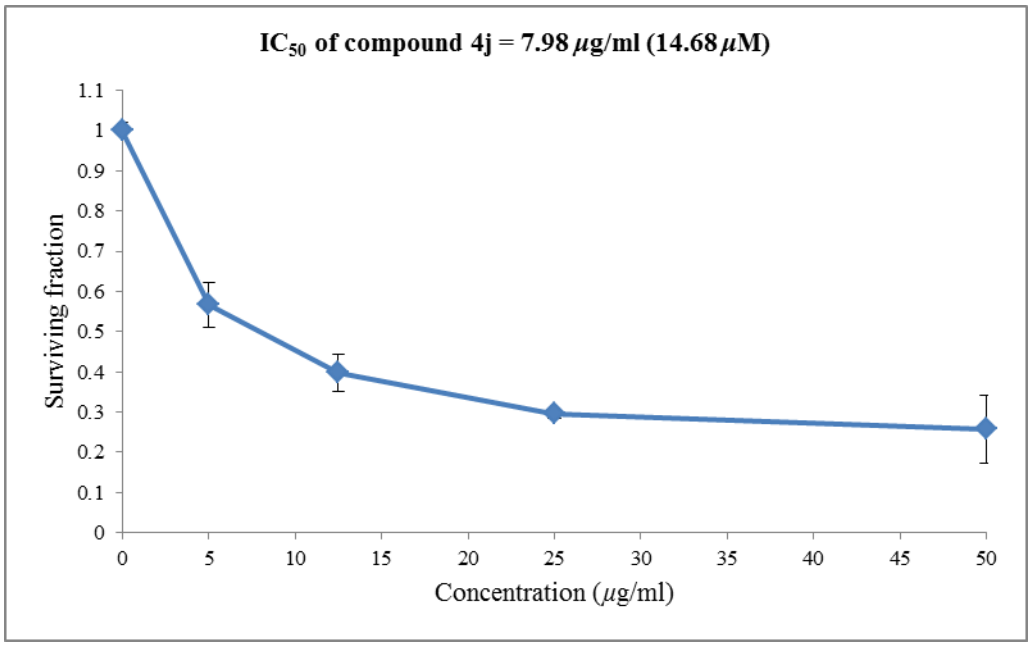

IC50 of compound 4e = 11.31 μg/ml (21.28 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

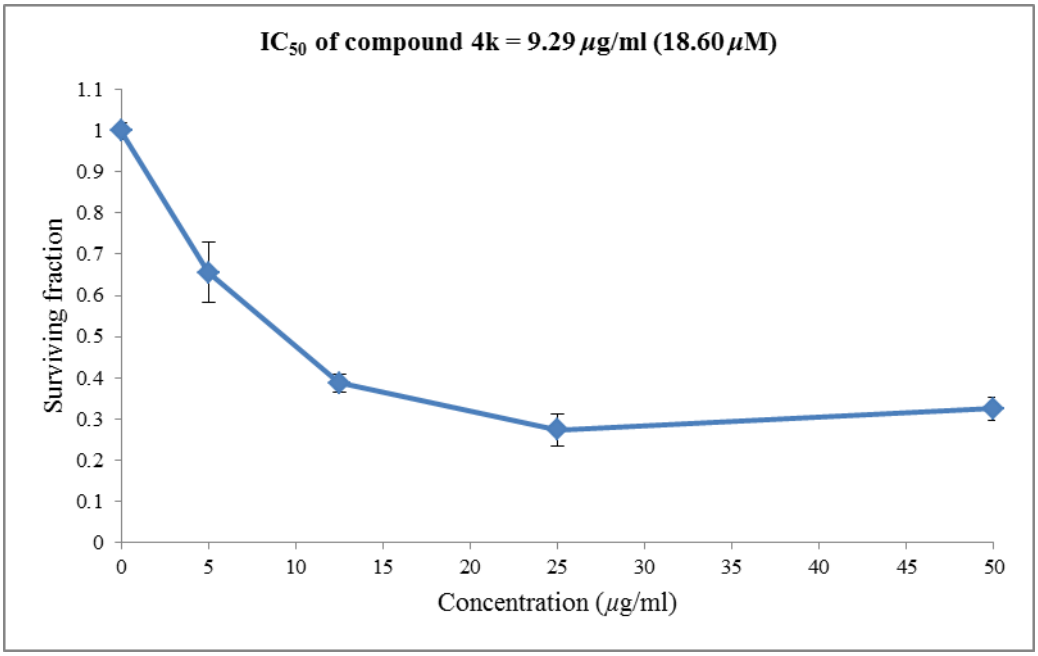

IC50 of compound 4f = 13.69 μg/ml (24.46 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

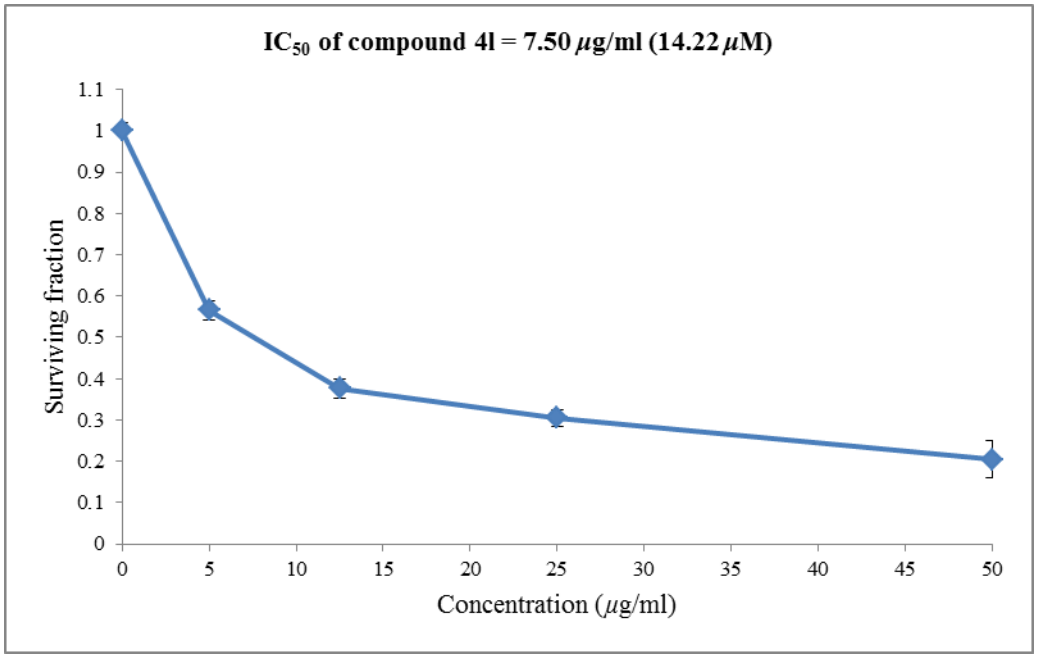

IC50 of compound 4g = 17.62 μg/ml (33.52 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

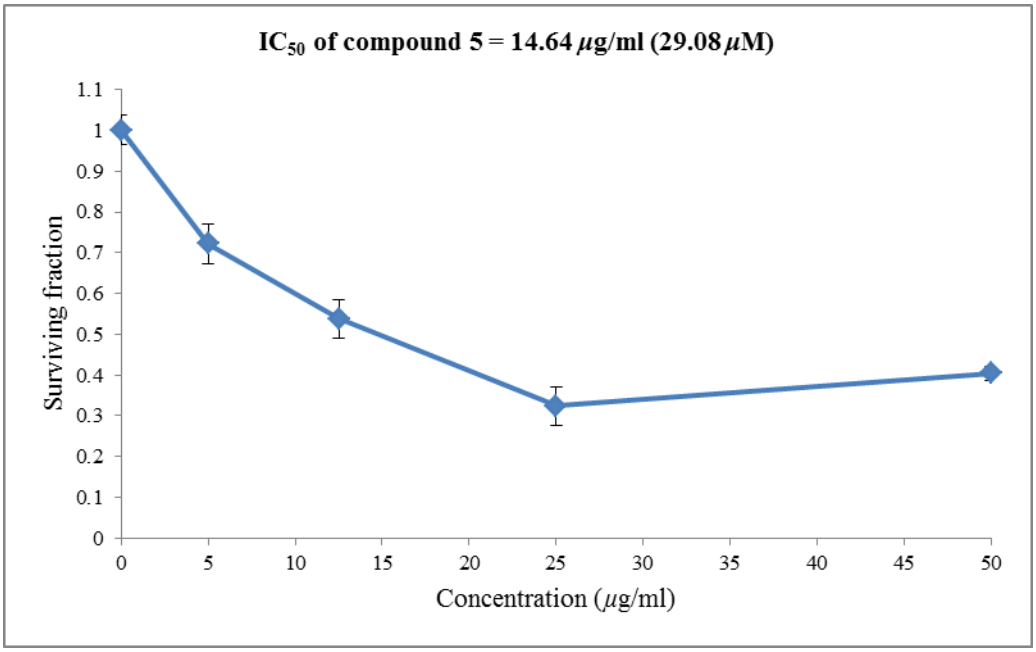

IC50 of compound 4h = 12.02 μg/ml (21.71 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

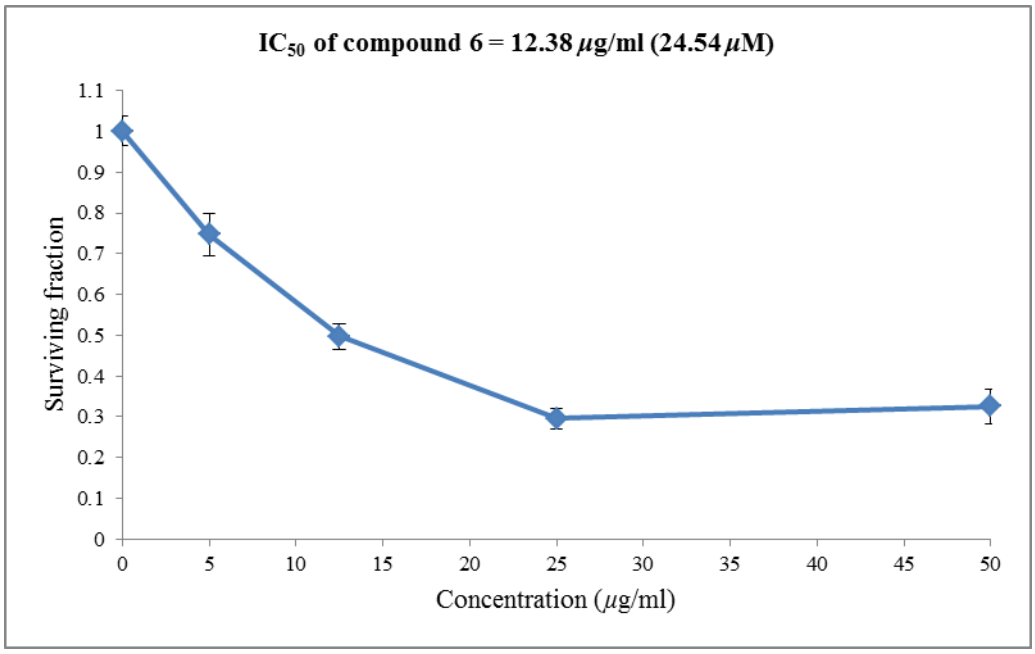

IC50 of compound 4i = 15.36 μg/ml (29.79 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4j = 7.98 μg/ml (14.68 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4k = 9.29 μg/ml (18.60 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4l = 7.50 μg/ml (14.22 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 5 = 14.64 μg/ml (29.08 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 6 = 12.38 μg/ml (24.54 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

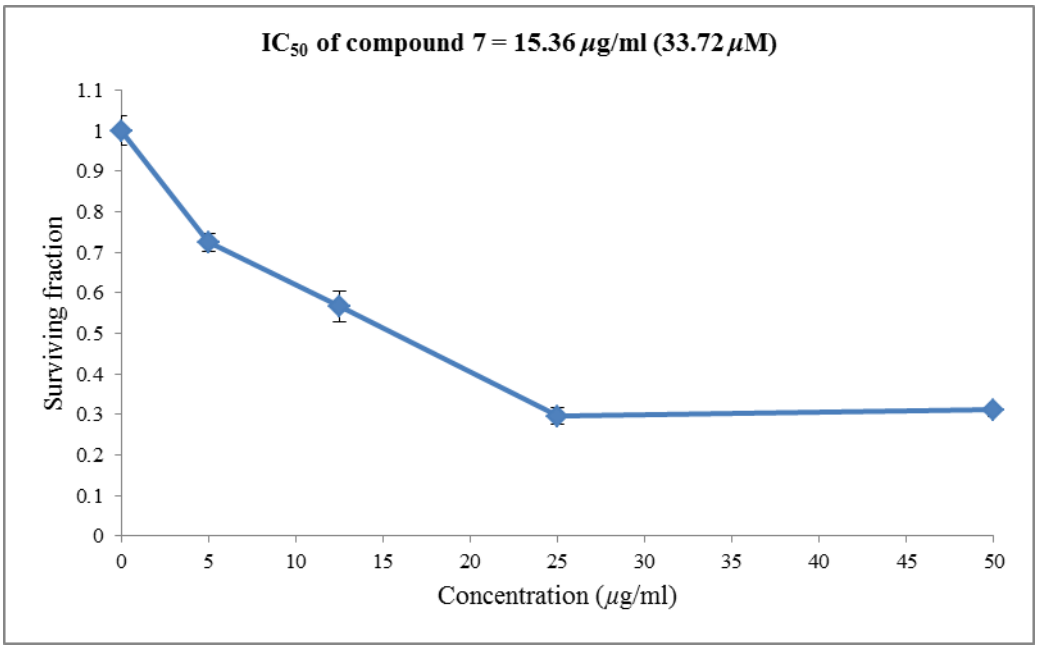
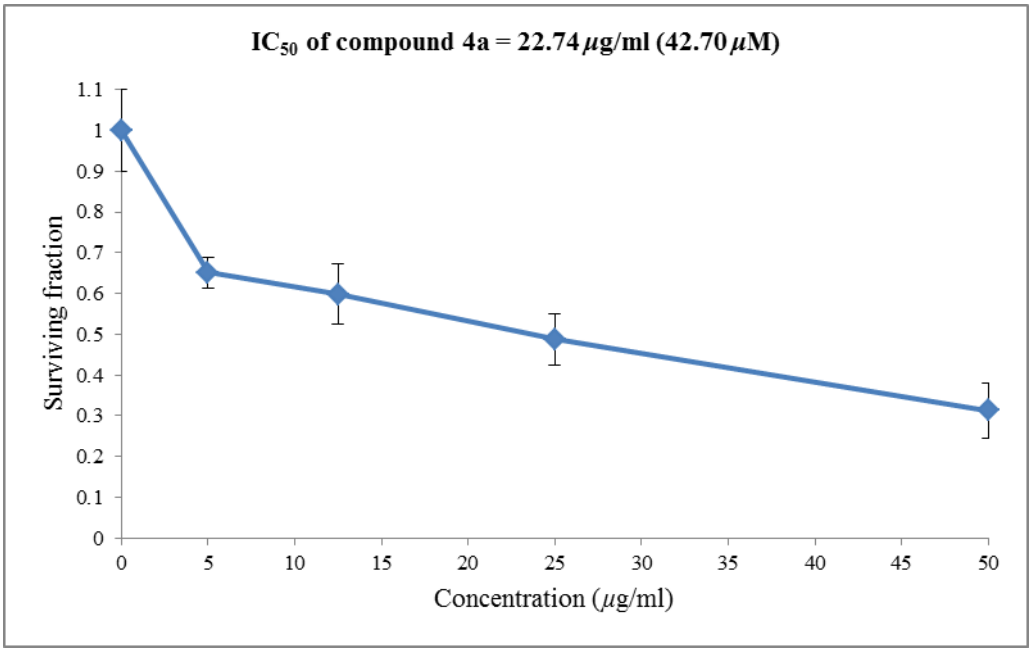
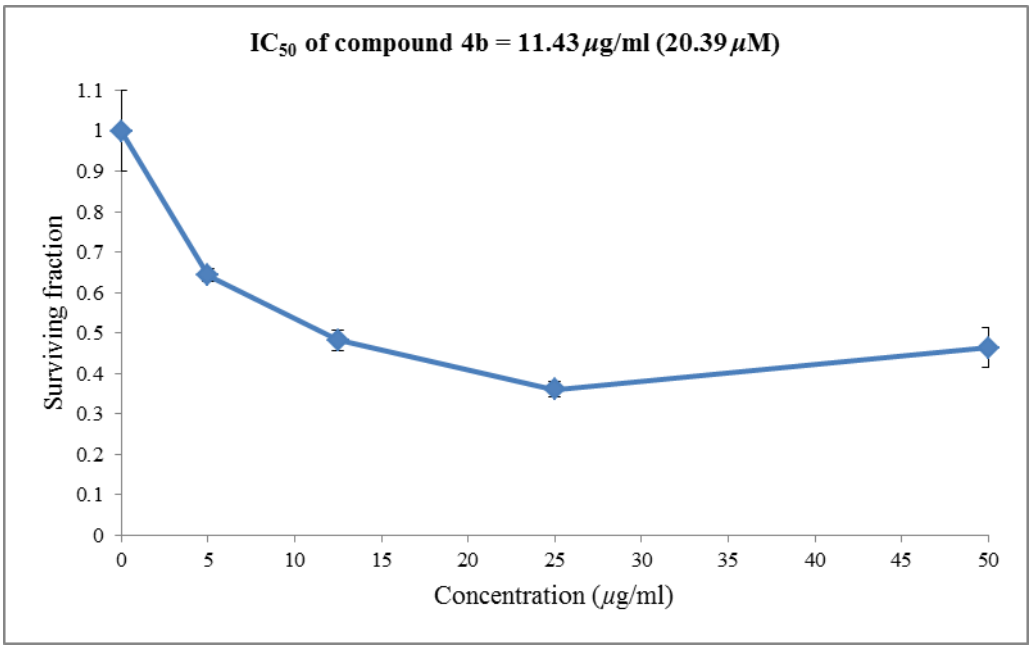
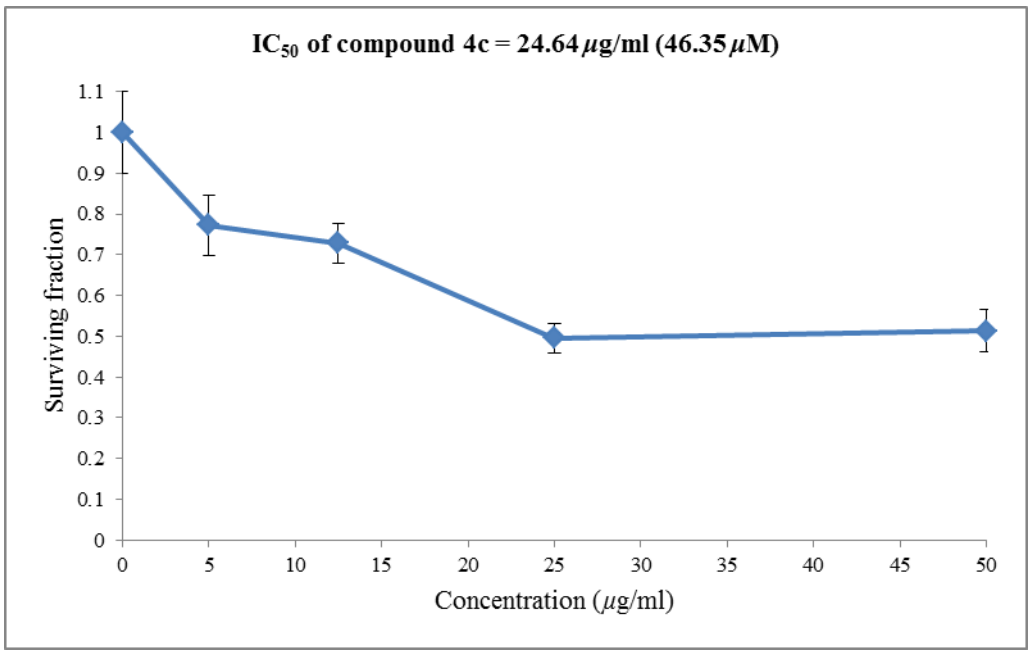
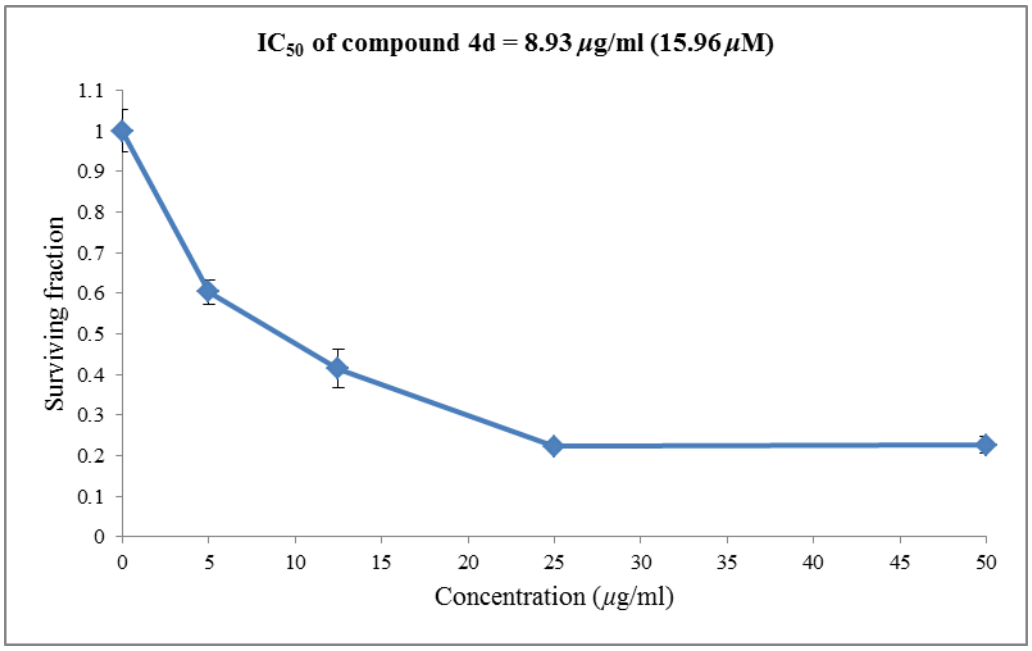


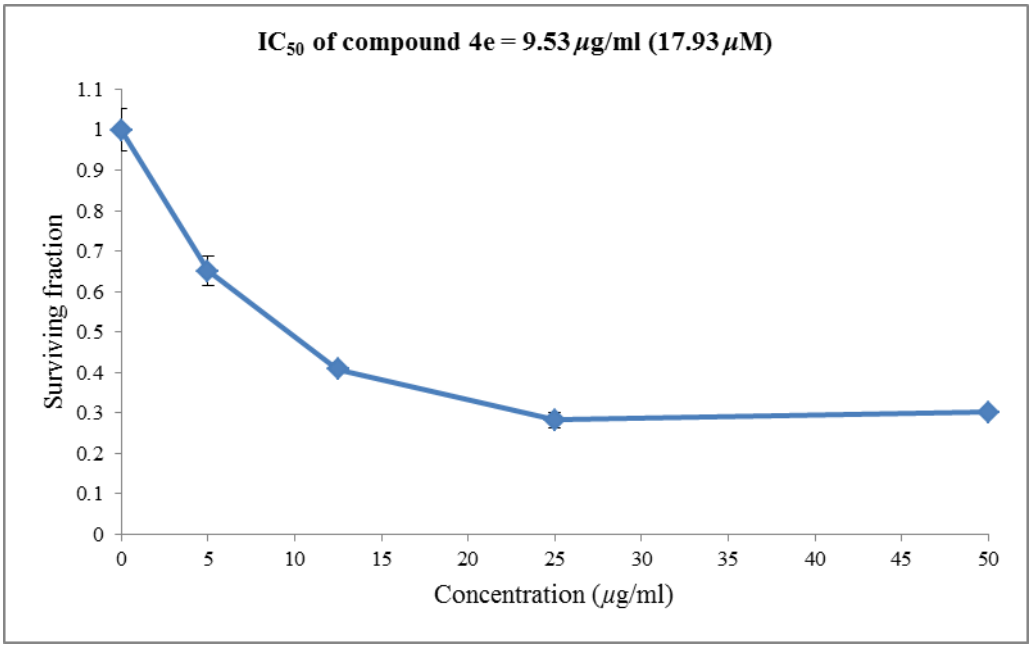
Figure S5. Dose-response curves of the macrocyclic peptidomimetics **4a-l,** and **5-7** against HCT116 (colon) human tumor cell line.

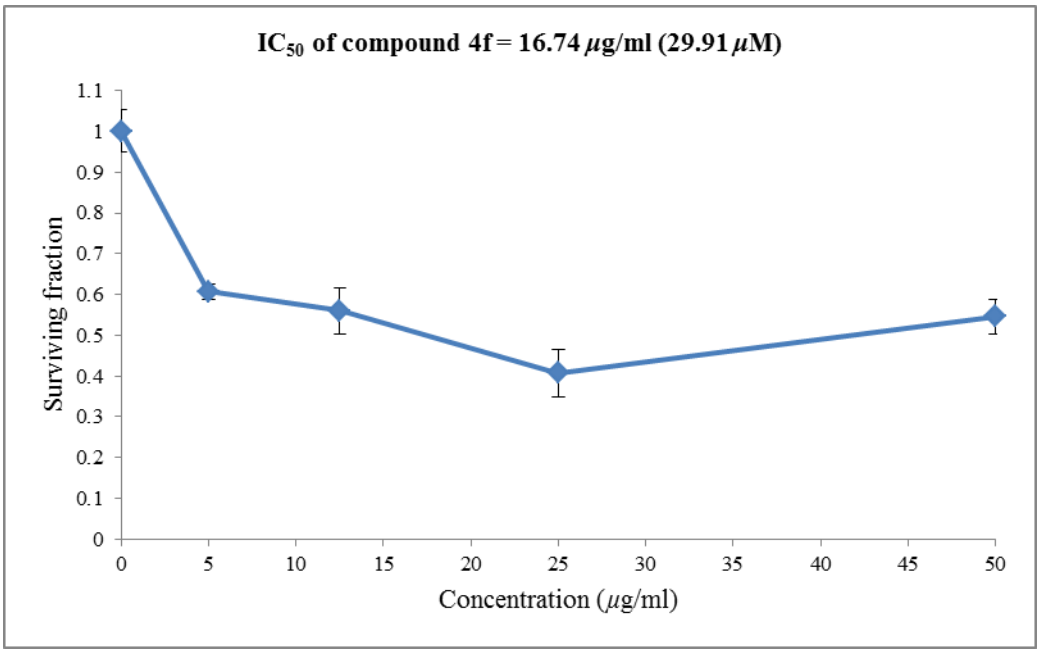

IC50 of compound 4a = 22.74 μg/ml (42.70 μM)
Surviving fraction
Concentration (μg/ml)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
0
5
10
15
20
25
30
35
40
45
50

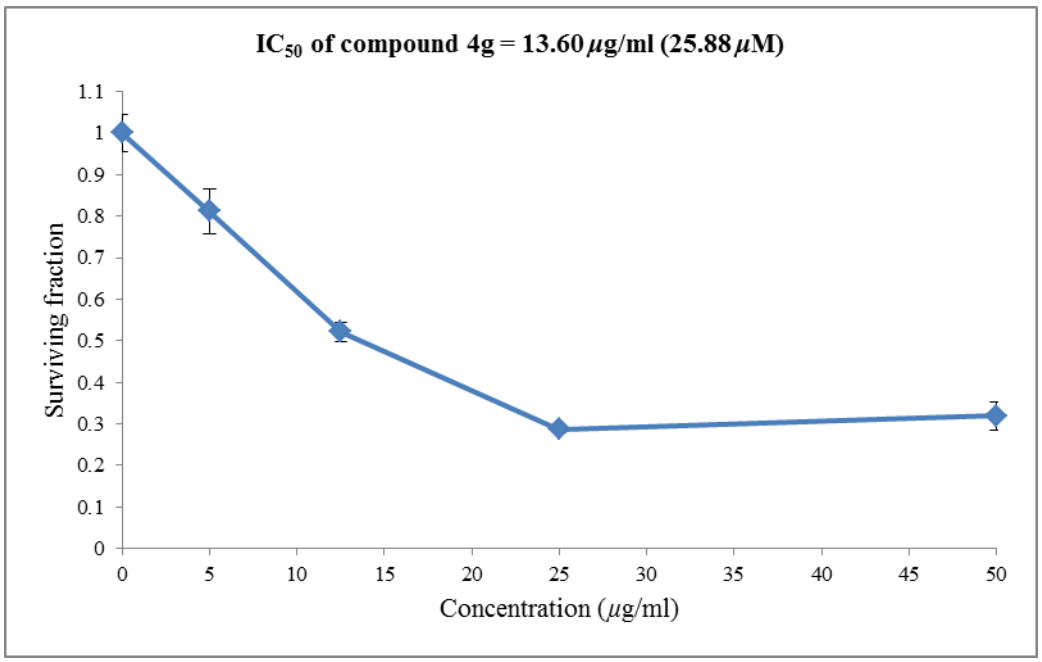

IC50 of compound 4b = 11.43 μg/ml (20.39 μM)
Surviving fraction
Concentration (μg/ml)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
0
5
10
15
20
25
30
35
40
45
50

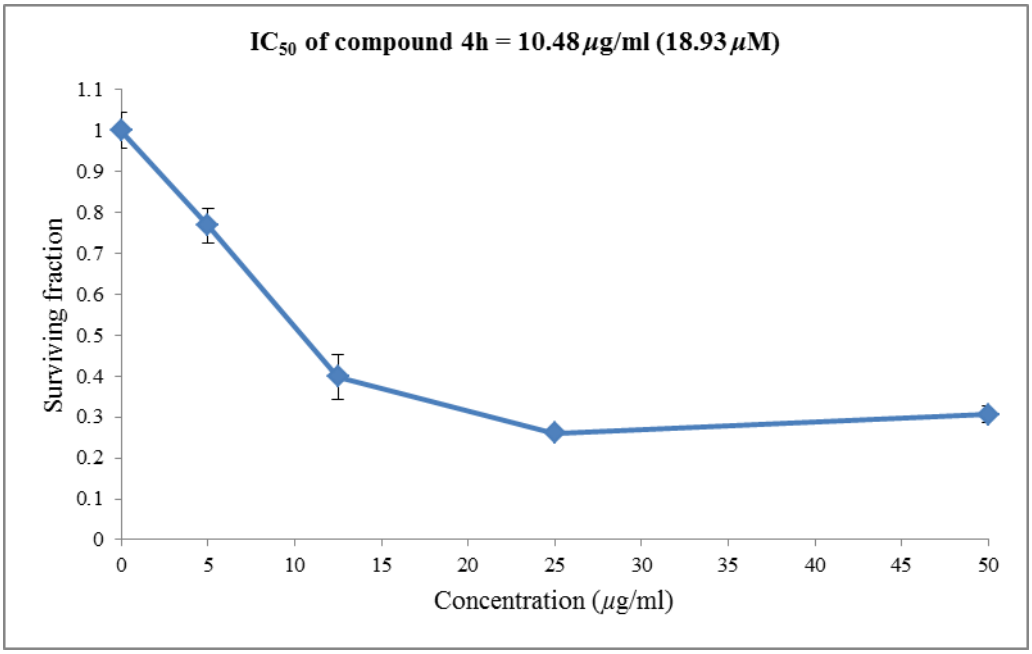

IC50 of compound 4c = 24.64 μg/ml (46.35 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

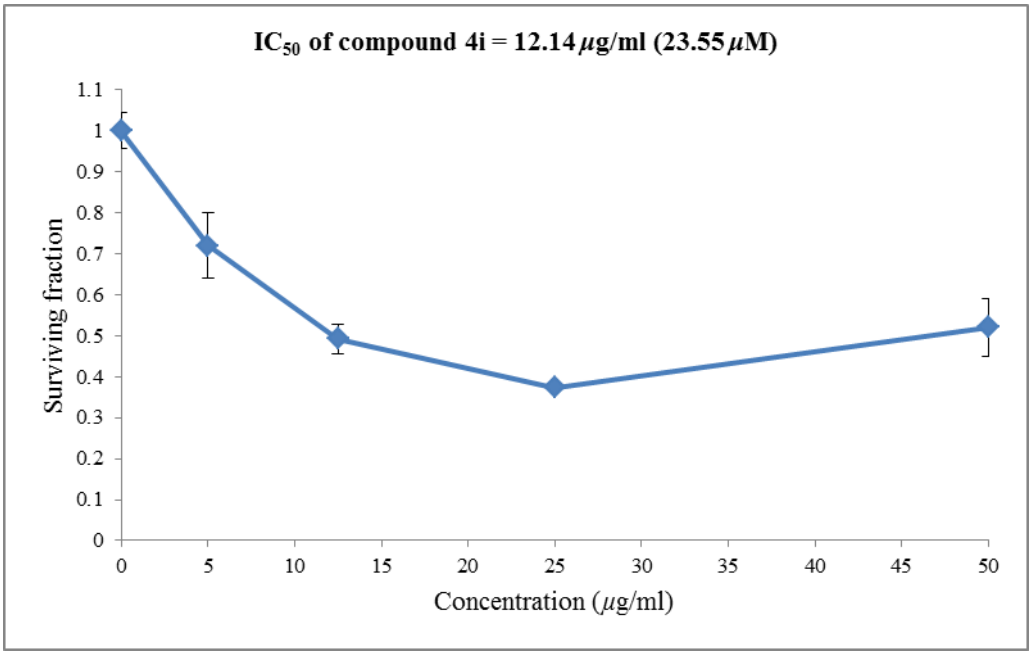

IC50 of compound 4d = 8.93 μg/ml (15.96 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

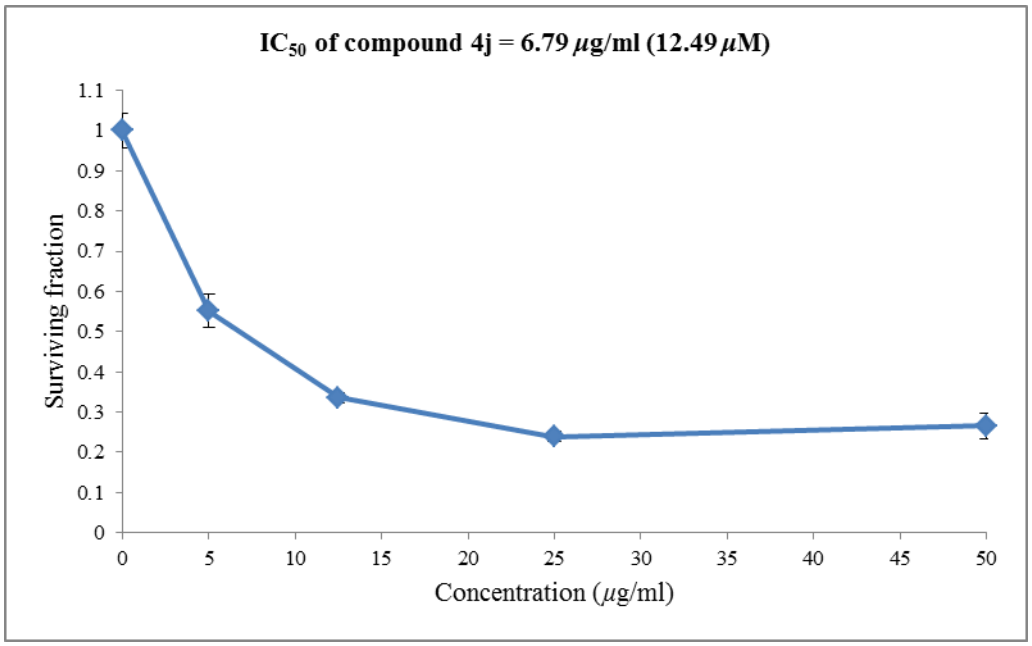

IC50 of compound 4e = 9.53 μg/ml (17.93 μM)
Surviving fraction
Concentration (μg/ml)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
0
5
10
15
20
25
30
35
40
45
50

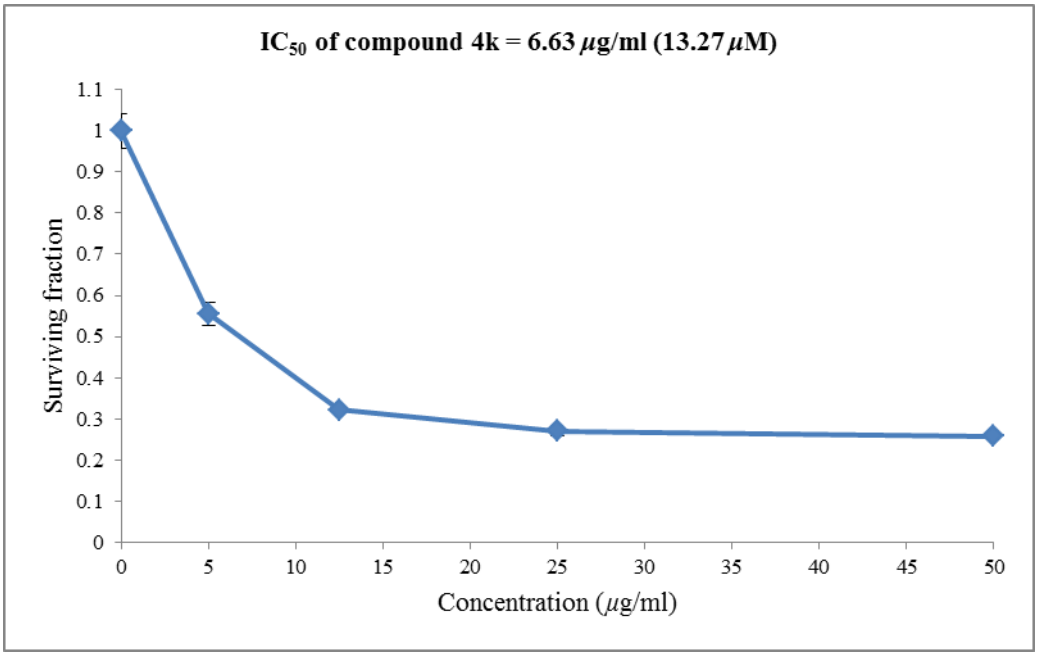

IC50 of compound 4f = 16.74 μg/ml (29.91 μM)
Surviving fraction
Concentration (μg/ml)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
0
5
10
15
20
25
30
35
40
45
50

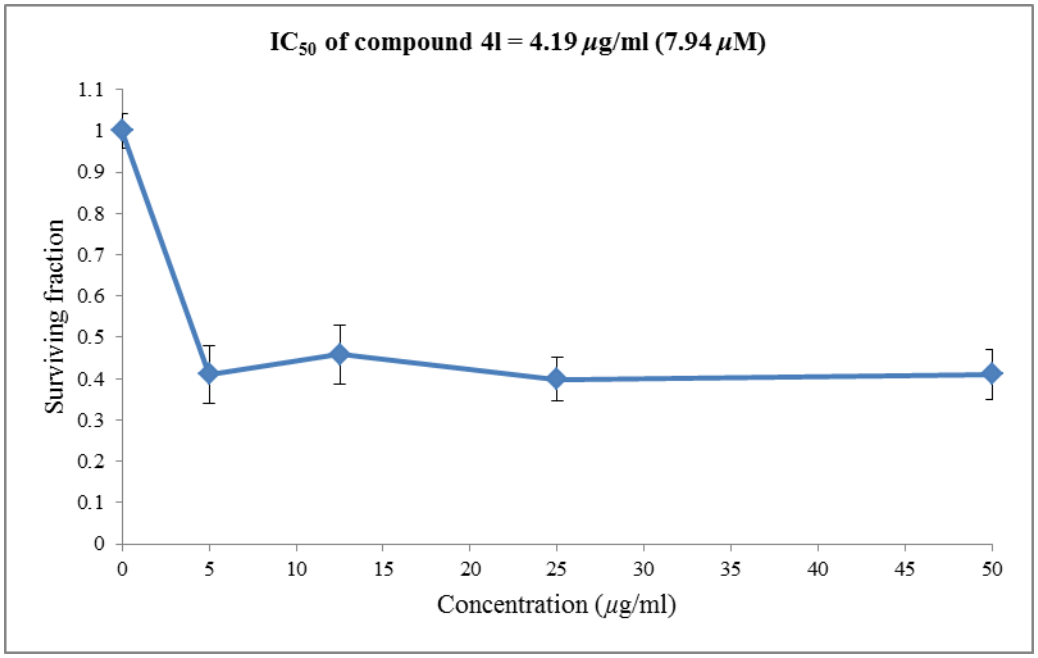

IC50 of compound 4g = 13.60 μg/ml (25.88 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

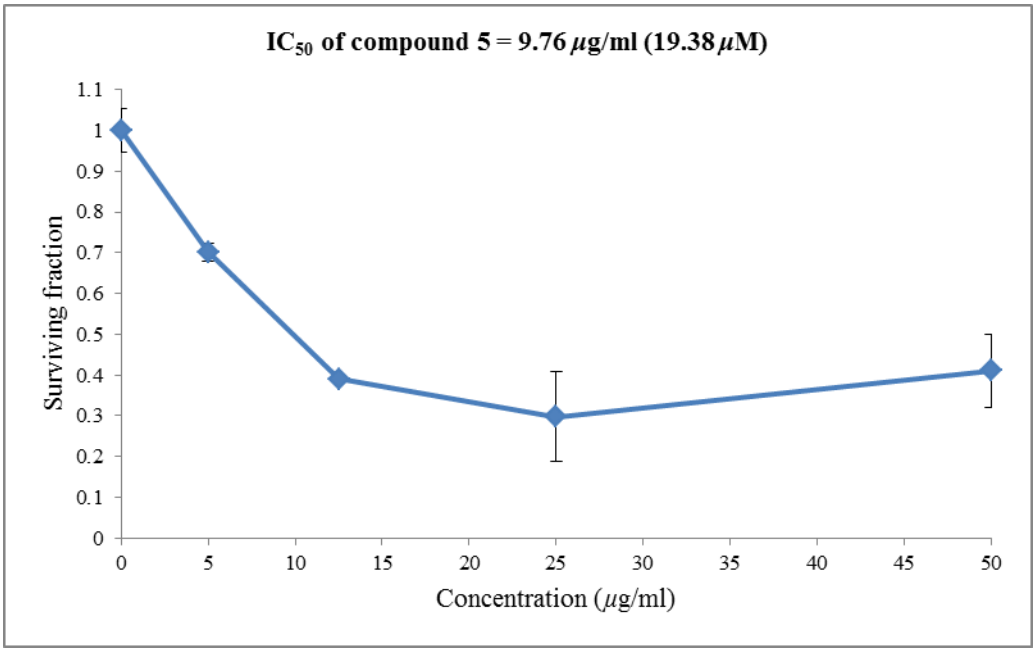

IC50 of compound 4h = 10.48 μg/ml (18.93 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

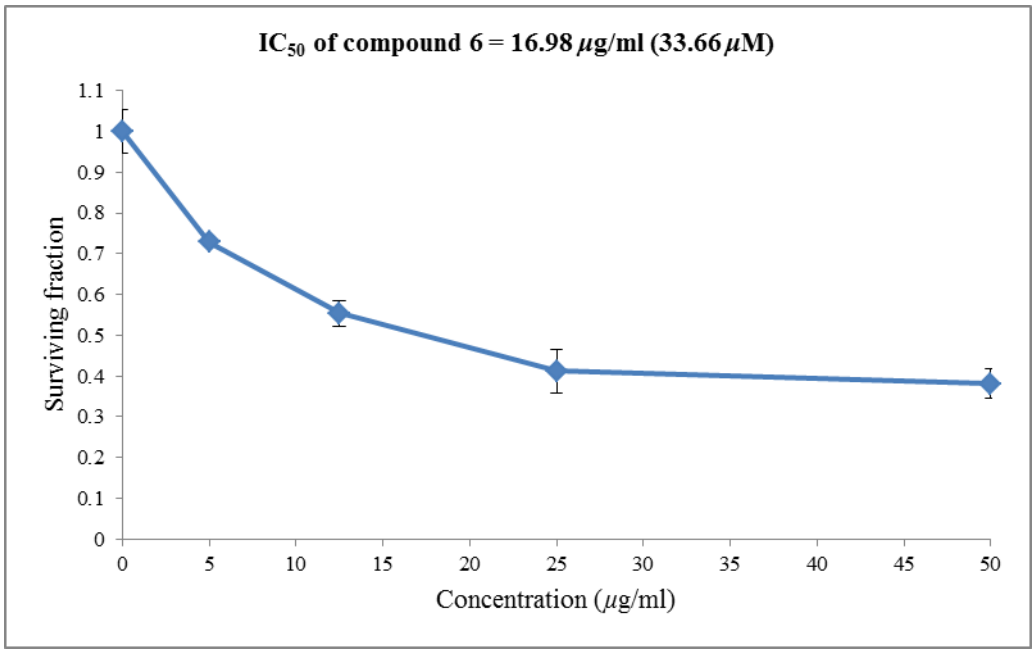

IC50 of compound 4i = 12.14 μg/ml (23.55 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4j = 6.79 μg/ml (12.49 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4k = 6.63 μg/ml (13.27 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4l = 4.19 μg/ml (7.94 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 5 = 9.76 μg/ml (19.38 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 6 = 16.98 μg/ml (33.66 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

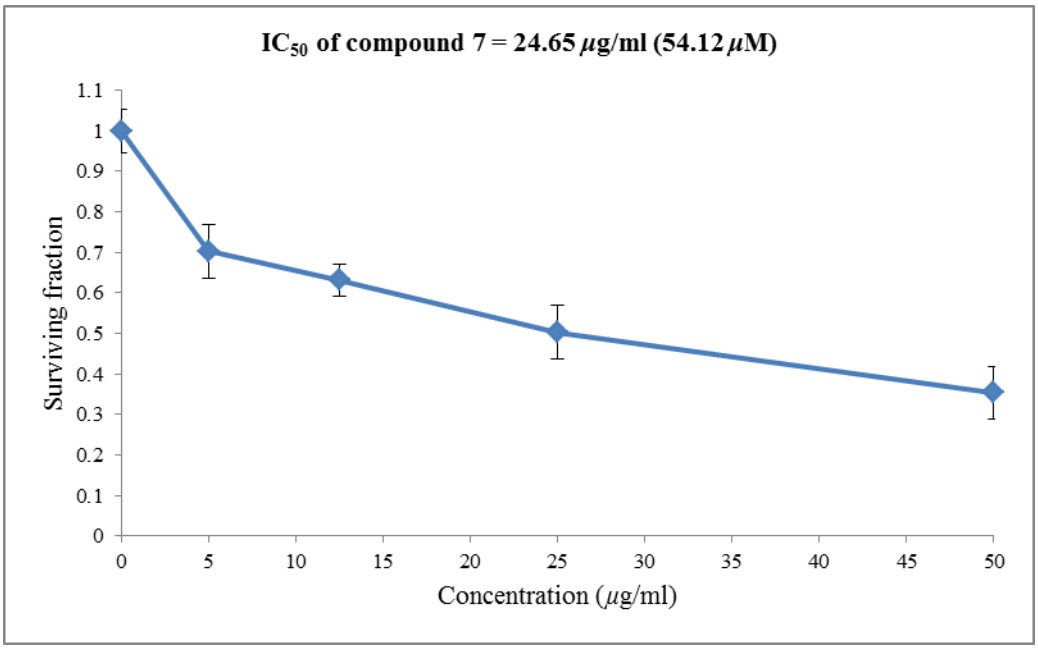
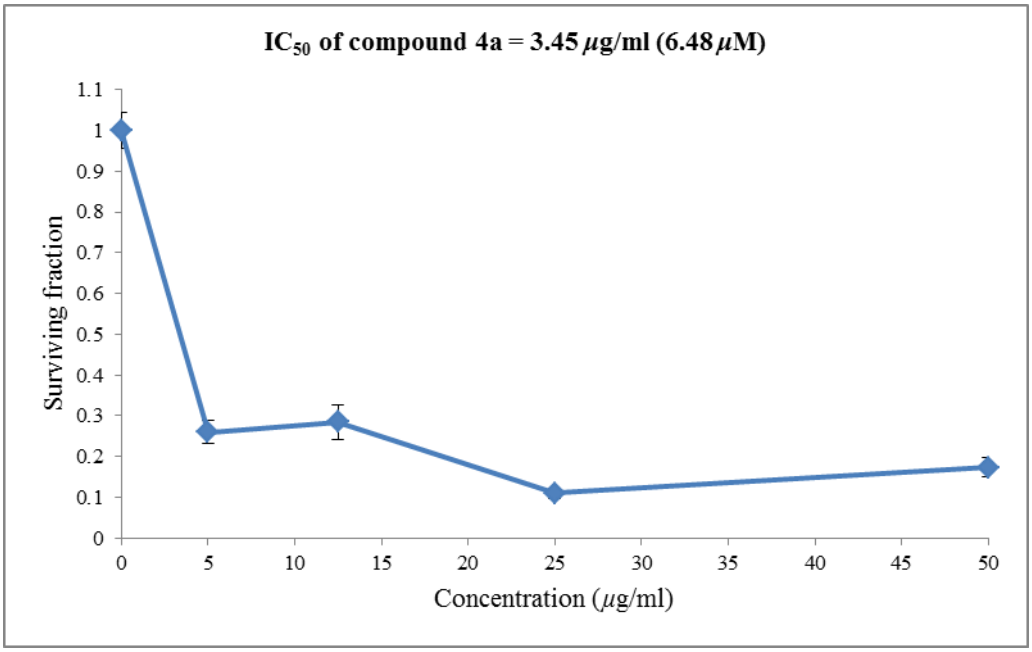
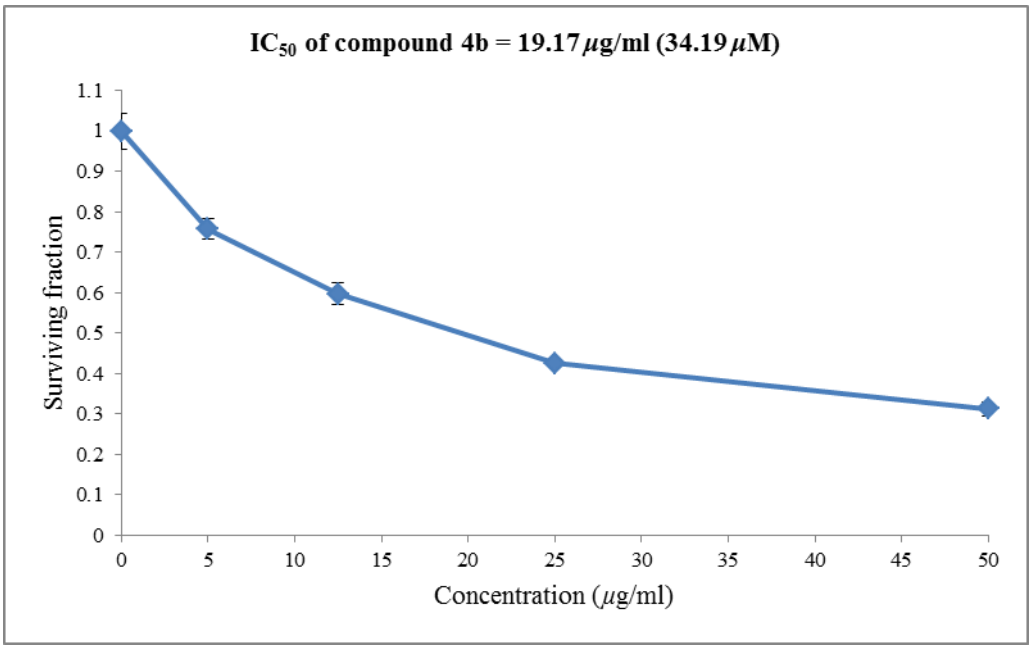
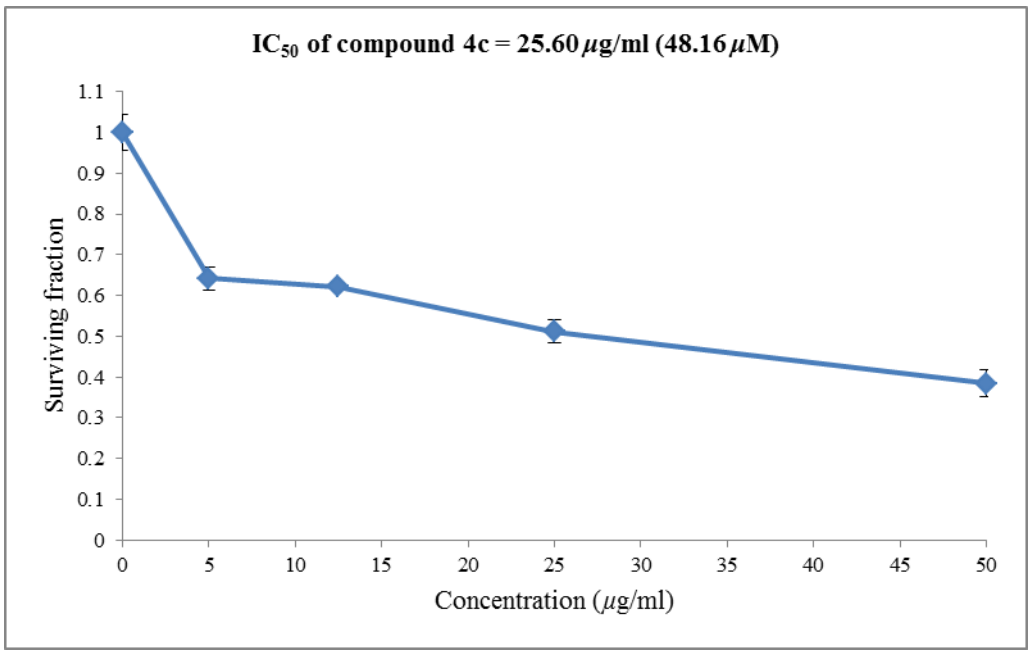
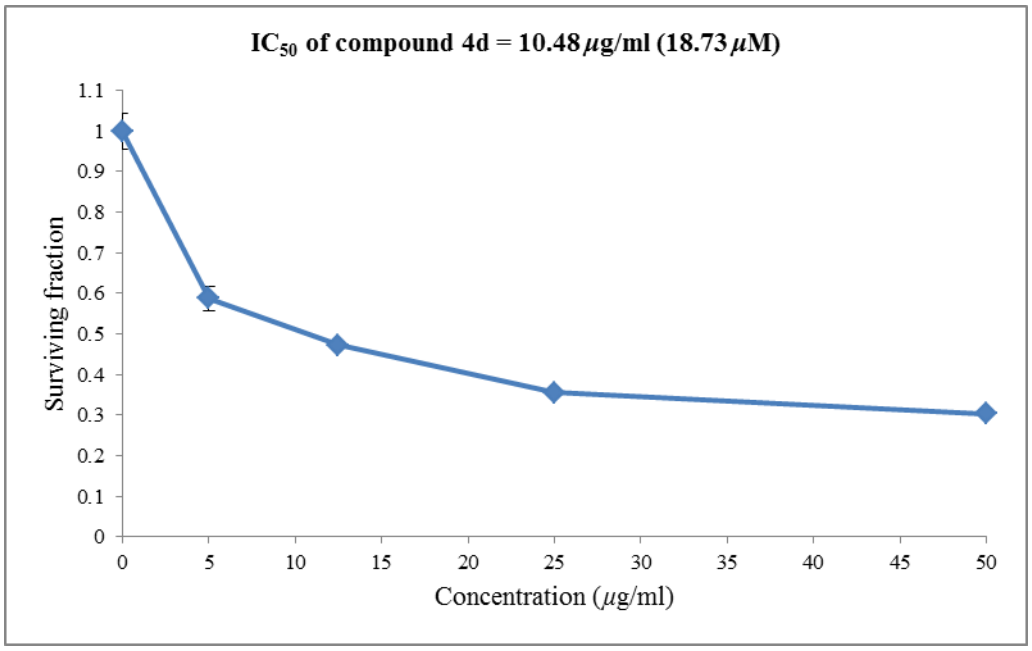


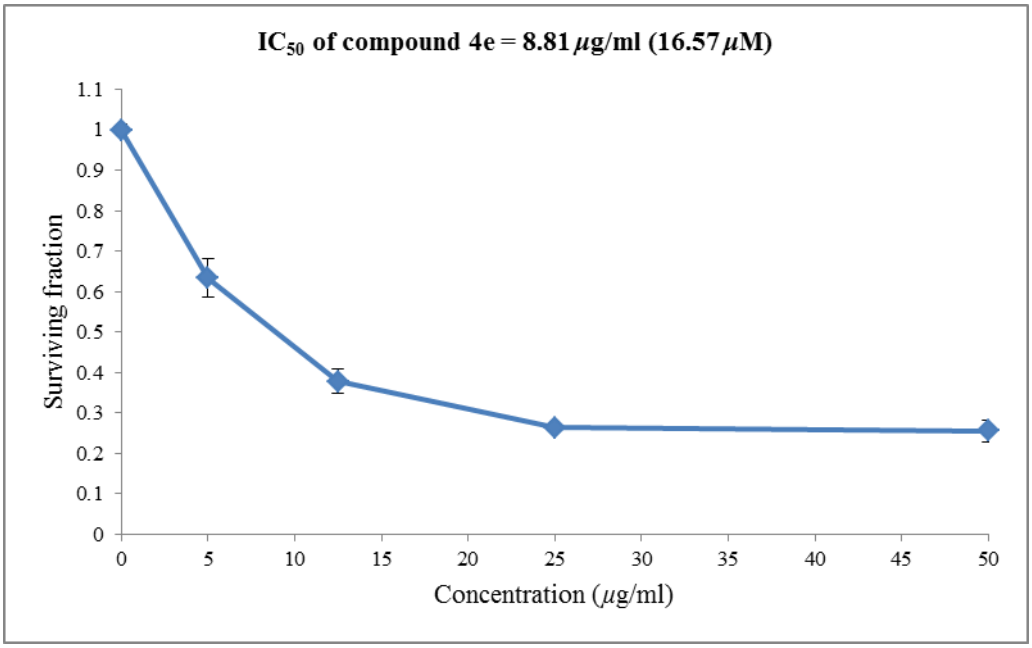
Figure S6. Dose-response curves of the macrocyclic peptidomimetics **4a-l,** and **5-7** against PC3 (prostate) human tumor cell line.

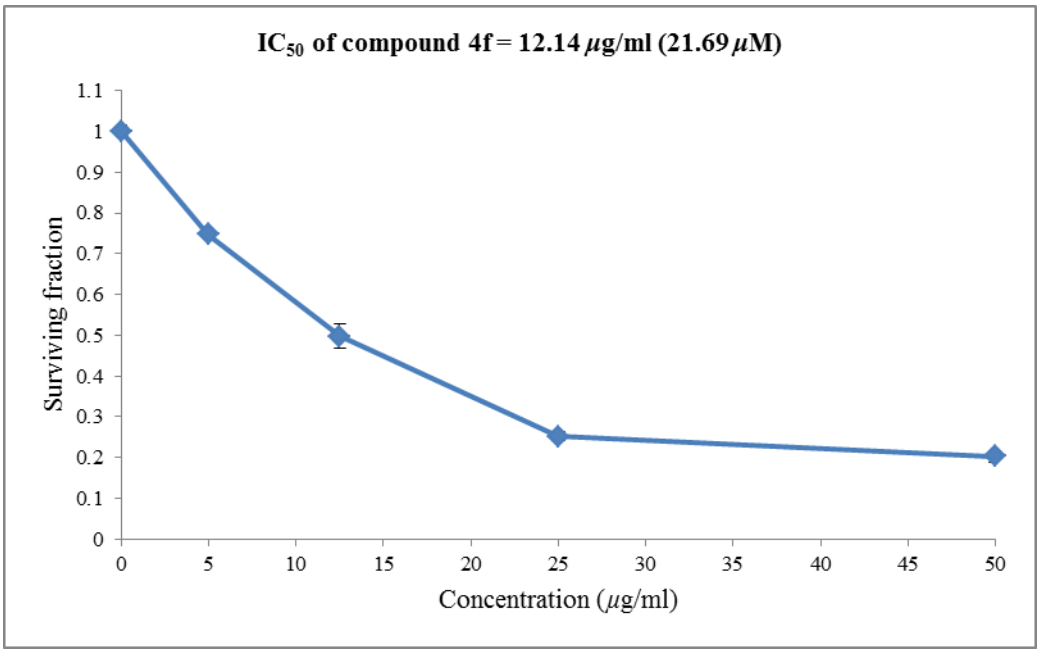

IC50 of compound 4a = 3.45 μg/ml (6.48 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

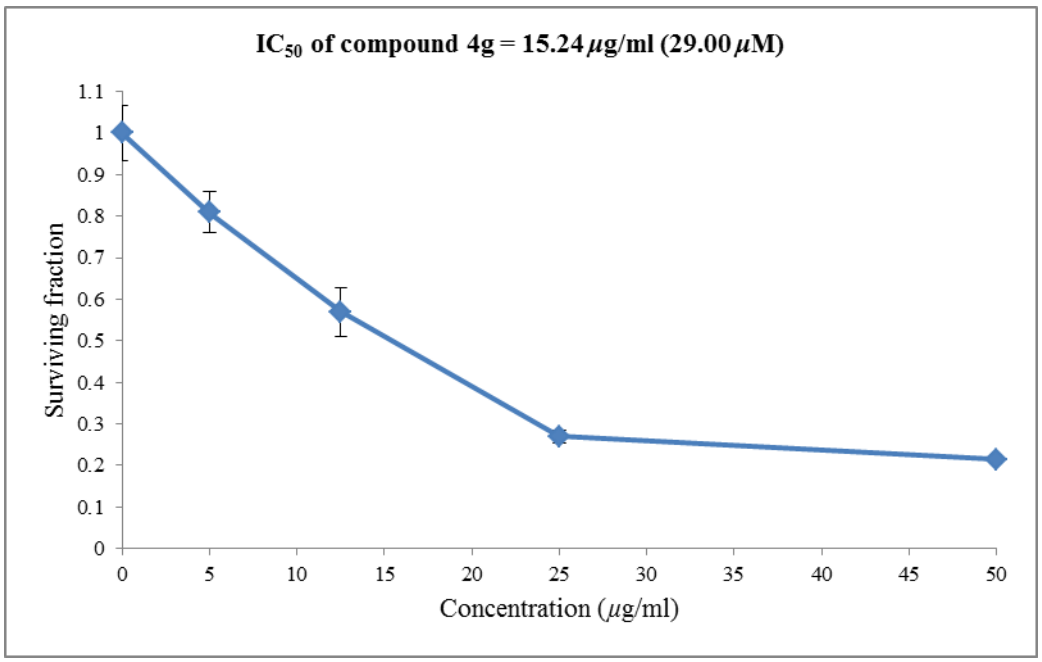

IC50 of compound 4b = 19.17 μg/ml (34.19 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

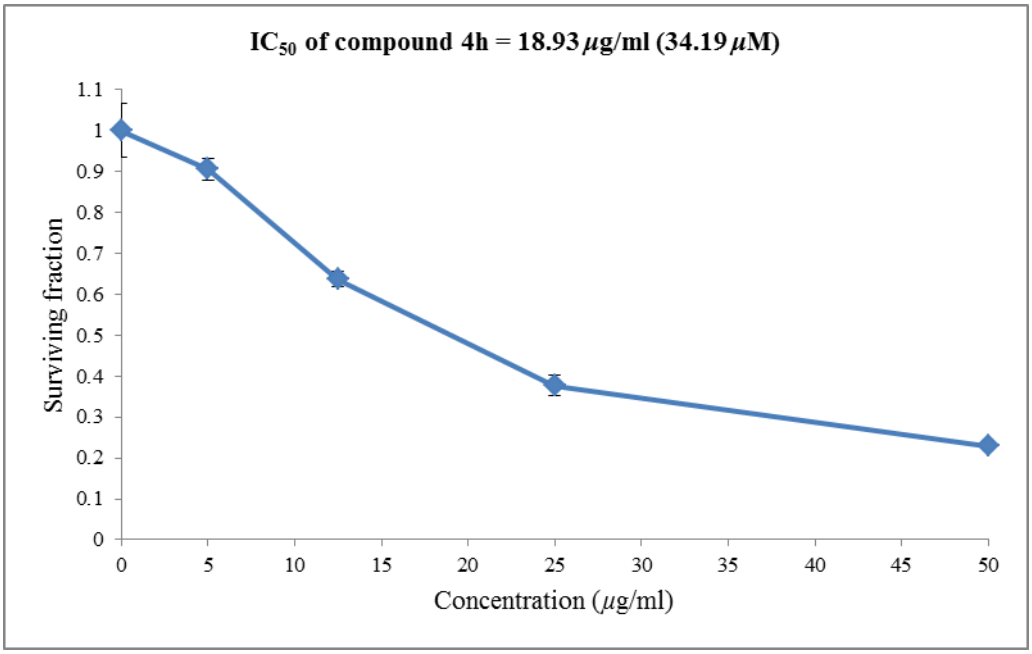

IC50 of compound 4c = 25.60 μg/ml (48.16 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

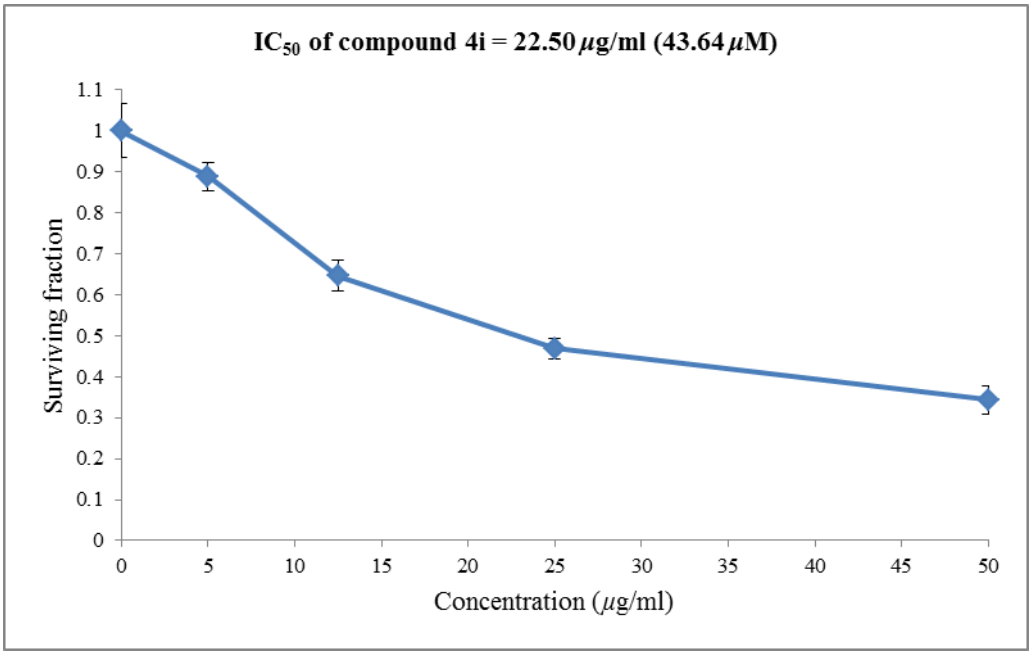

IC50 of compound 4d = 10.48 μg/ml (18.73 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

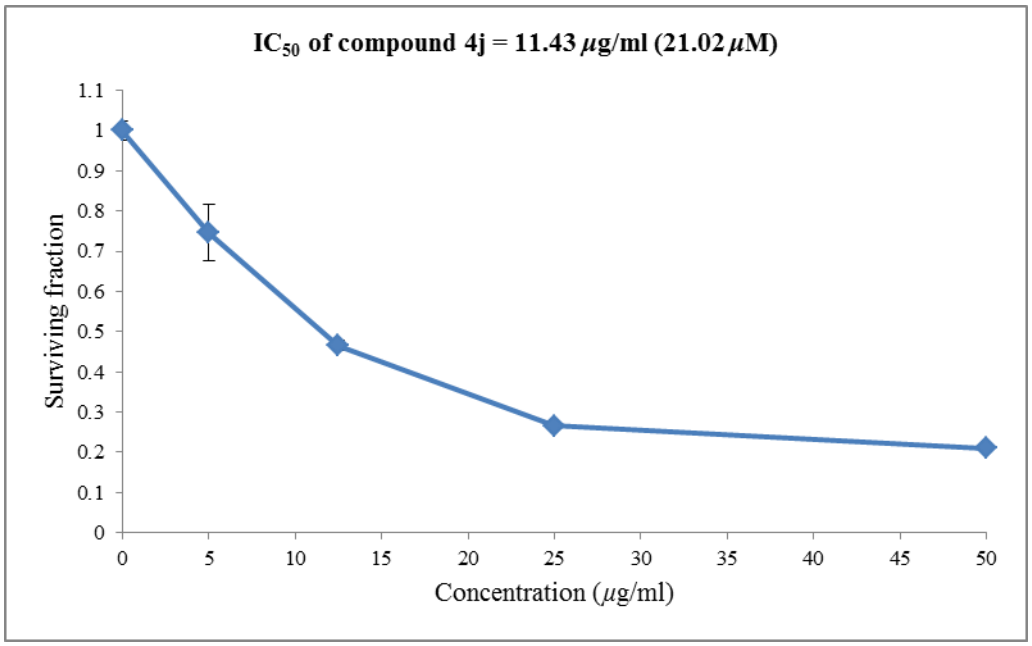

IC50 of compound 4e = 8.81 μg/ml (16.57 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

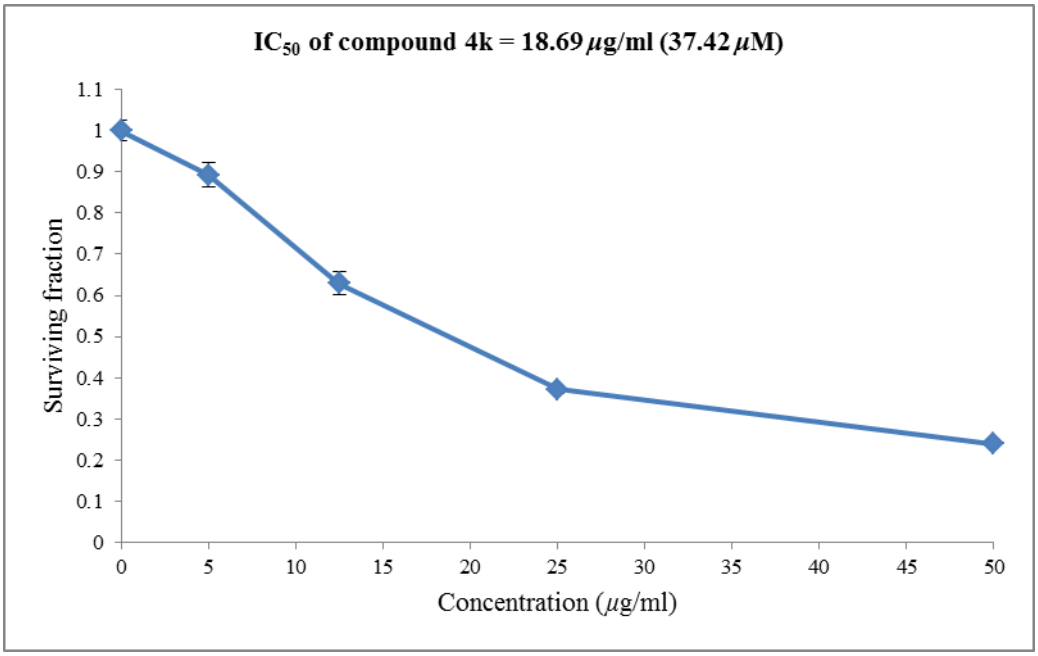

IC50 of compound 4f = 12.14 μg/ml (21.69 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

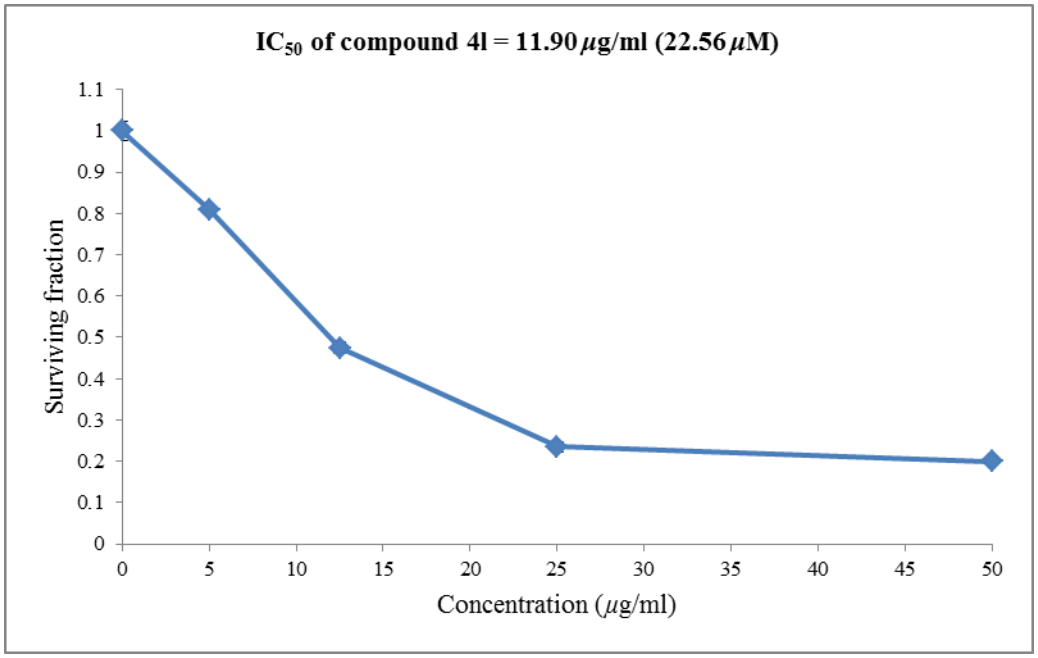

IC50 of compound 4g = 15.24 μg/ml (29.00 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

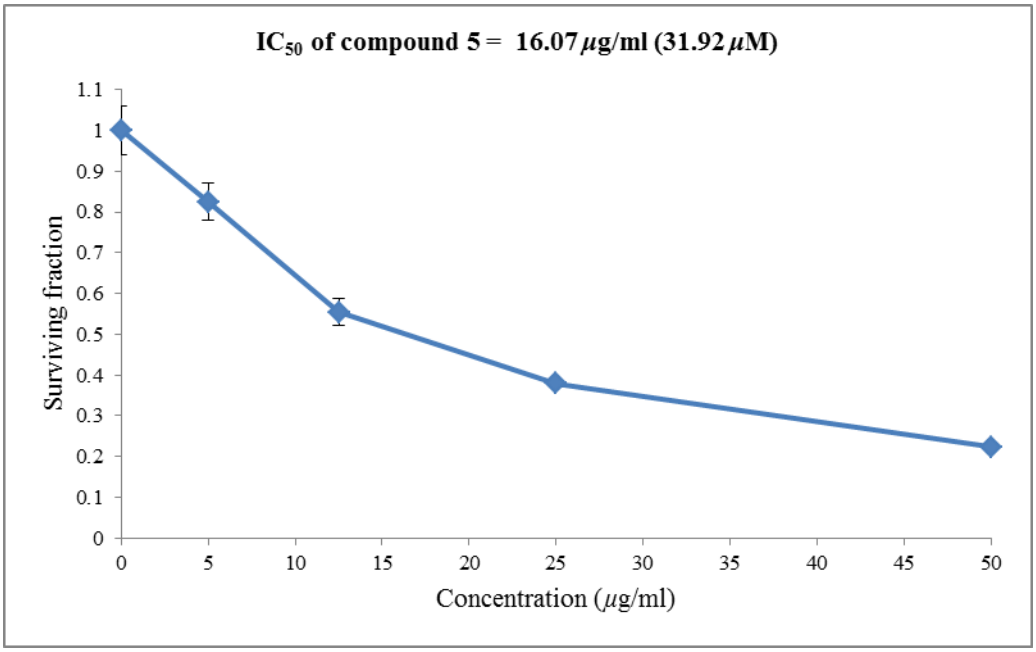

IC50 of compound 4h = 18.93 μg/ml (34.19 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

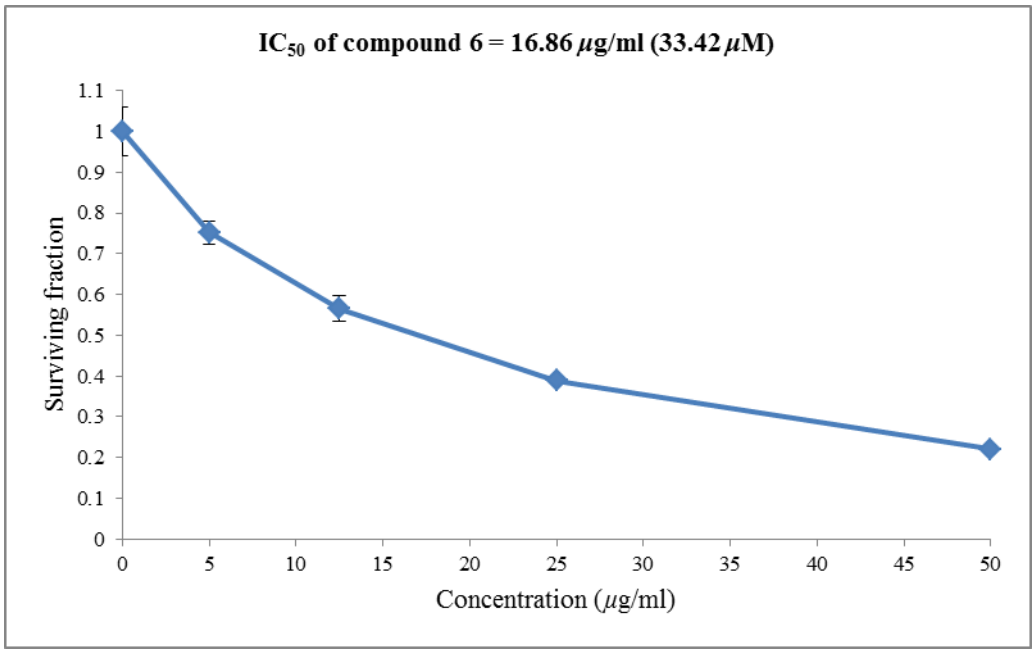

IC50 of compound 4i = 22.50 μg/ml (43.64 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4j = 11.43 μg/ml (21.02 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4k = 18.69 μg/ml (37.42 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 4l = 11.90 μg/ml (22.56 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 5 = 16.07 μg/ml (31.92 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 6 = 16.86 μg/ml (33.42 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

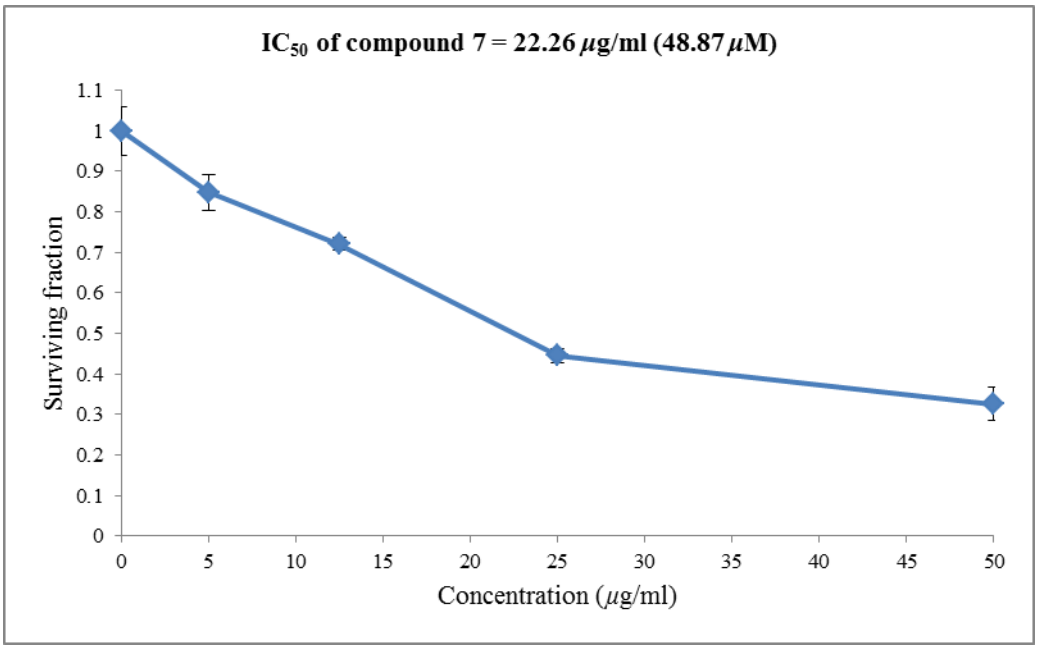


Figure S7. Dose-response curves of the macrocyclic peptidomimetics **4a-l,** and **5-7** against MCF7 (breast) human tumor cell line.