A $POCl_3$-mediated synthesis of substituted fused azoacridones derivatives

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Synthesis of 2-(pyridin-2-ylamino)benzoic acid (1b)

2-chlorobenzoic acid (626 mg, 4.0 mmol) and 2-Aminopyrimidine (188 mg, 2.0 mmol) were dissolved in DMF (10 mL), and then K_2CO_3 (552 mg, 4.0 mmol) and Cu (64 mg, 1.0 mmol) were added. The mixture was stirred overnight at 130 °C, which was then cooled to room temperature. The mixture was pooled into ice water. Diluted hydrochloric acid was added and precipitate occurred, which was filtered, washed with water, and dried to give crude compound **1b**, which was used without further purifaction.

Synthesis of 2-((4-(phenylamino)pyrimidin-2-yl)amino)benzoic acid (1e)[1]

2,4-dichloropyrimidines (290 mg, 2.0 mmol) and aniline (465 mg, 5.0 mmol) were added into H_2O (10 mL), then 6N HCl (0.5 mL) was added. The mixture was refluxed for 2-3 h, which was then cooled to room temperature and filtered. The solid was directly added into EtOH (10 mL), then anthranilic acid (301 mg, 2.2 mmol) and 6N HCl (0.5 mL) was added. The mixture was refluxed for 2-3 h, which was then cooled to room temperature and filtered, washed the precipitate with EtOH and dried to give white powder **1e** (412 mg, 67%).

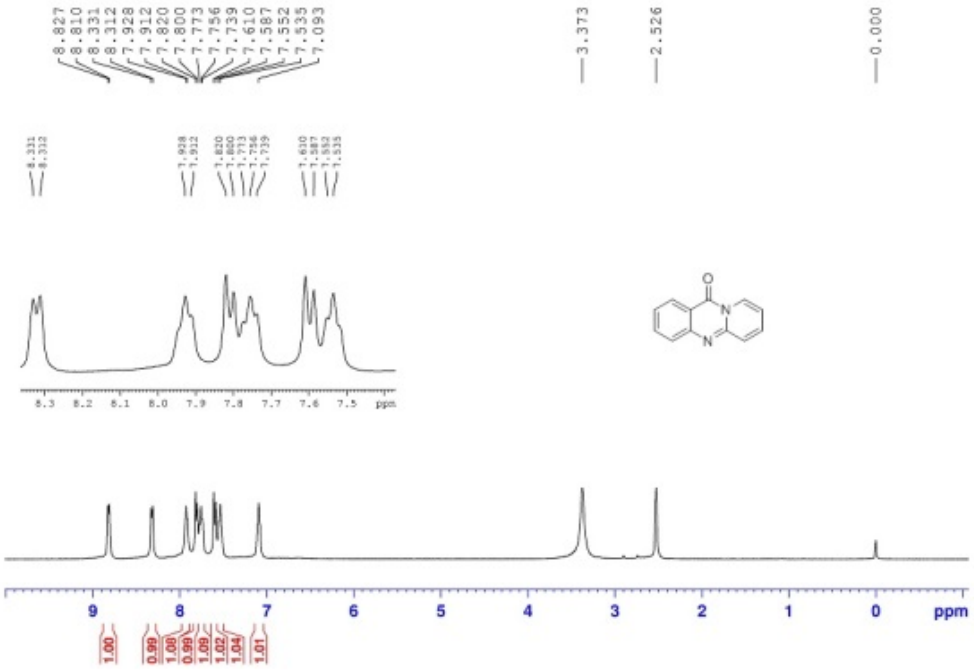
The synthesis method of **1e** was also used to synthesize compounds **1f-1h, 5q-5t.**

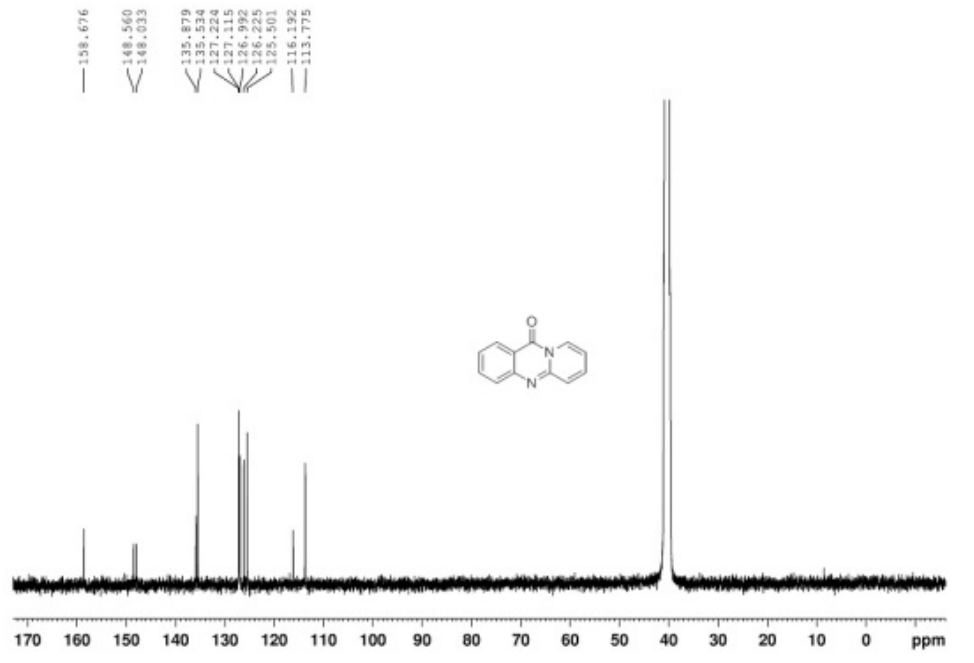
5a-5t:2,4-dichloropyrimidines (2.0 mmol) and anthranilic acids (5.0 mmol) were dissolved in EtOH (10 mL), then 6N HCl (0.5 mL) was added. The mixture was refluxed for **2-3 h,** which was the cooled to room temperature and filtered, washed the precipitate with EtOH and dried to give pure products **5a-5t**.

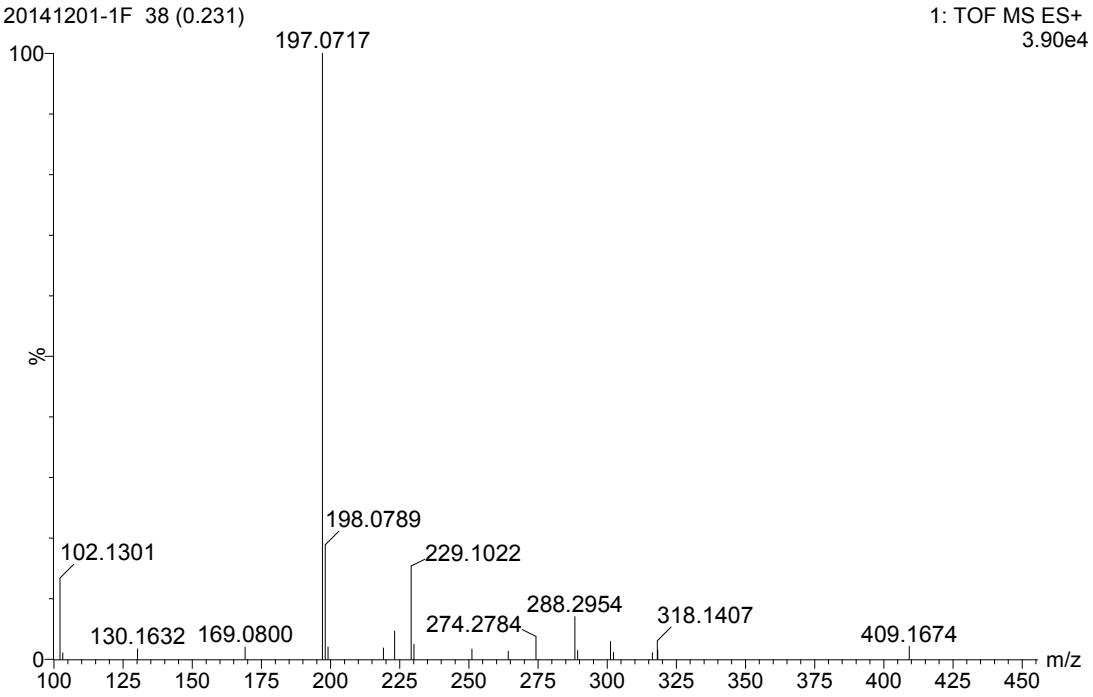
1. H. R. Lawrence et al. *J. Med. Chem.*, 2012, **55**, 7392-7416.

Charts of ^{1}H-NMR, ^{13}C-NMR and HRMS of products

2d



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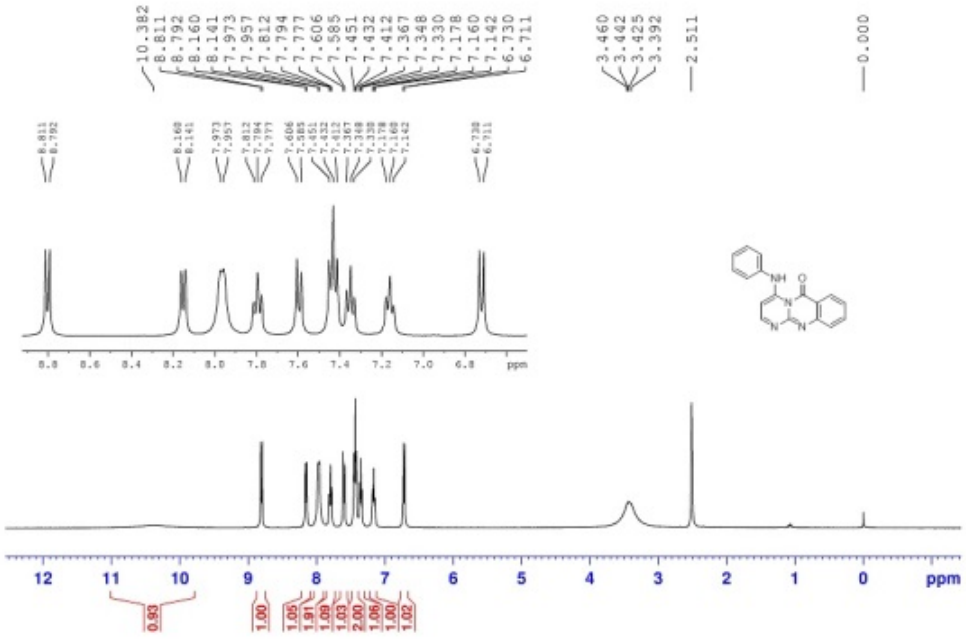
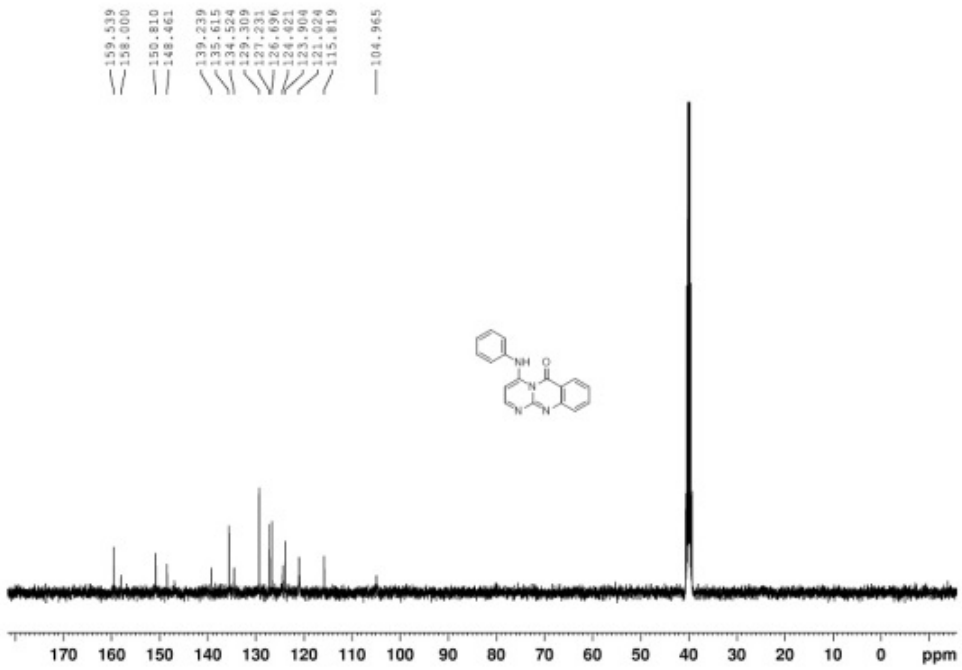
3.90e4
197.0717
198.0789
102.1301
229.1022
288.2954
318.1407
274.2784
130.1632
169.0800
409.1674
%
m/z

2ga


ppm


159.539
158.000
150.810
148.461
139.239
135.615
134.524
129.309
127.231
126.696
124.421
123.904
121.024
115.819
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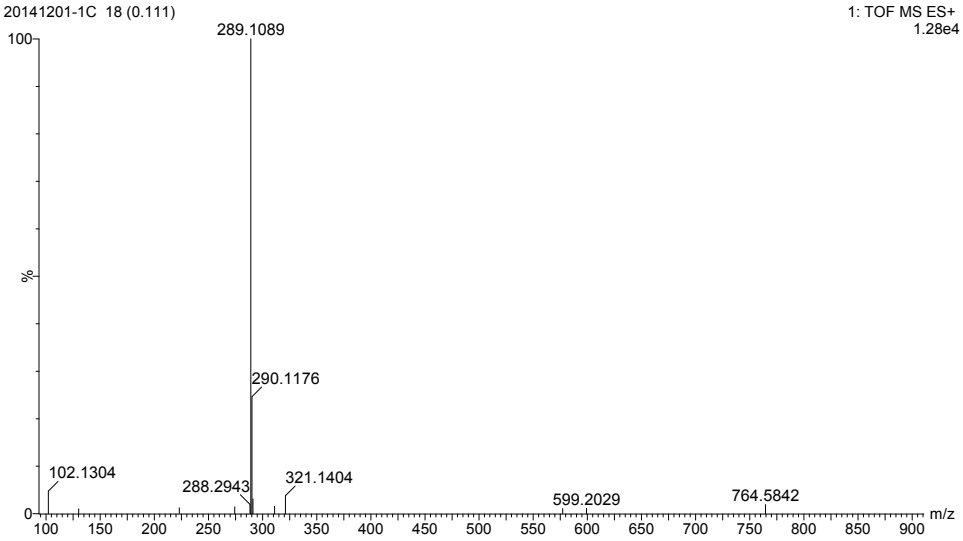
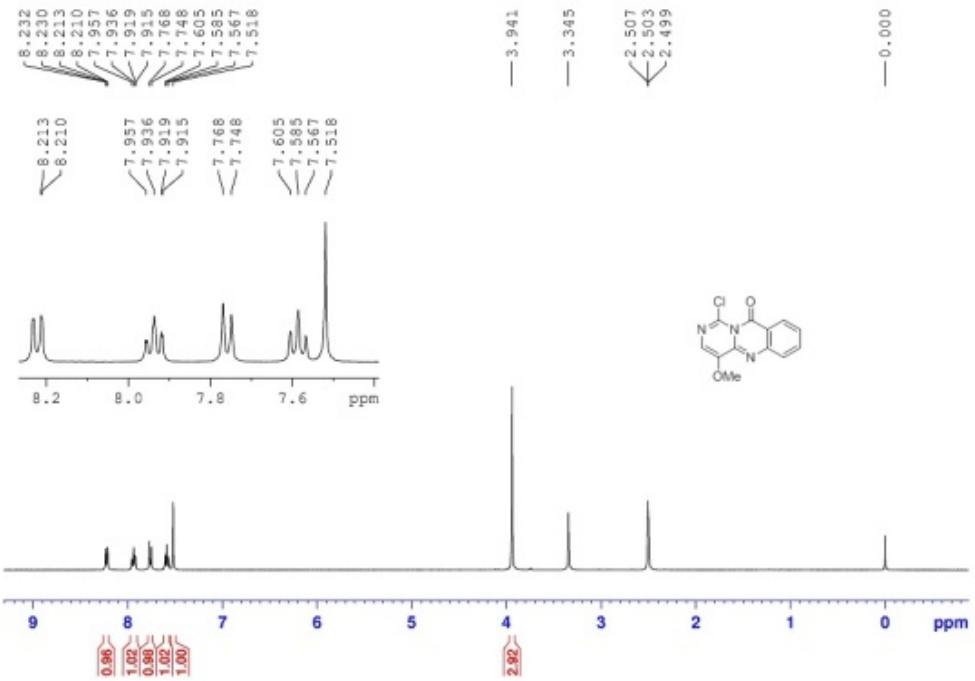
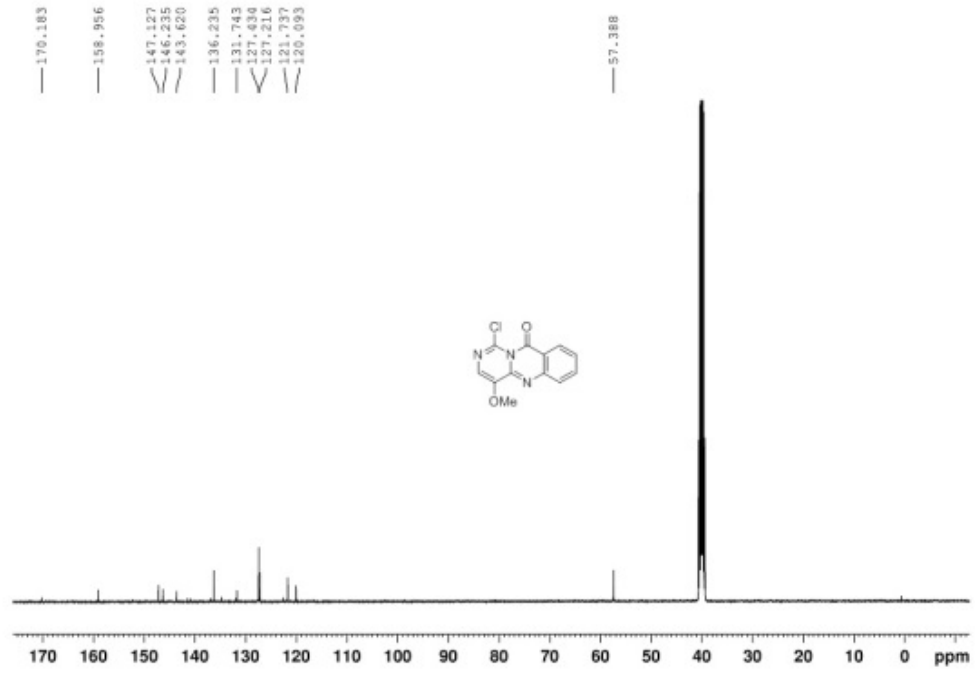
NH
O
N
N
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

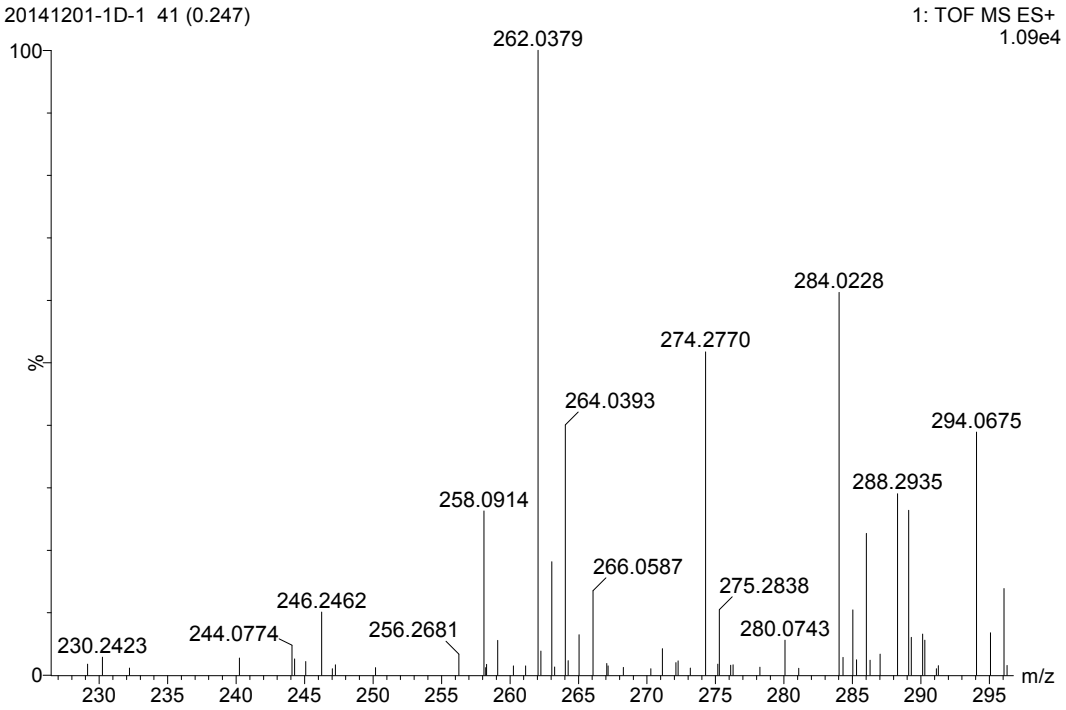

20141201-1C 18 (0.111)
1: TOF MS ES+
1.28e4
100
%
289.1089
290.1176
102.1304
288.2943
321.1404
599.2029
764.5842
0
100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900
m/z

2i

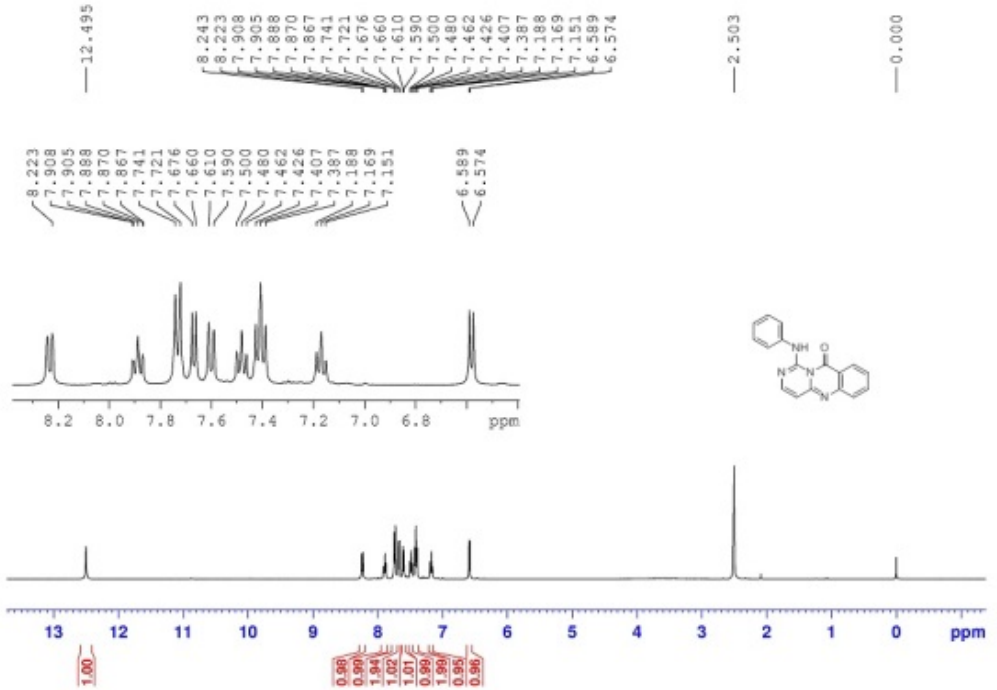


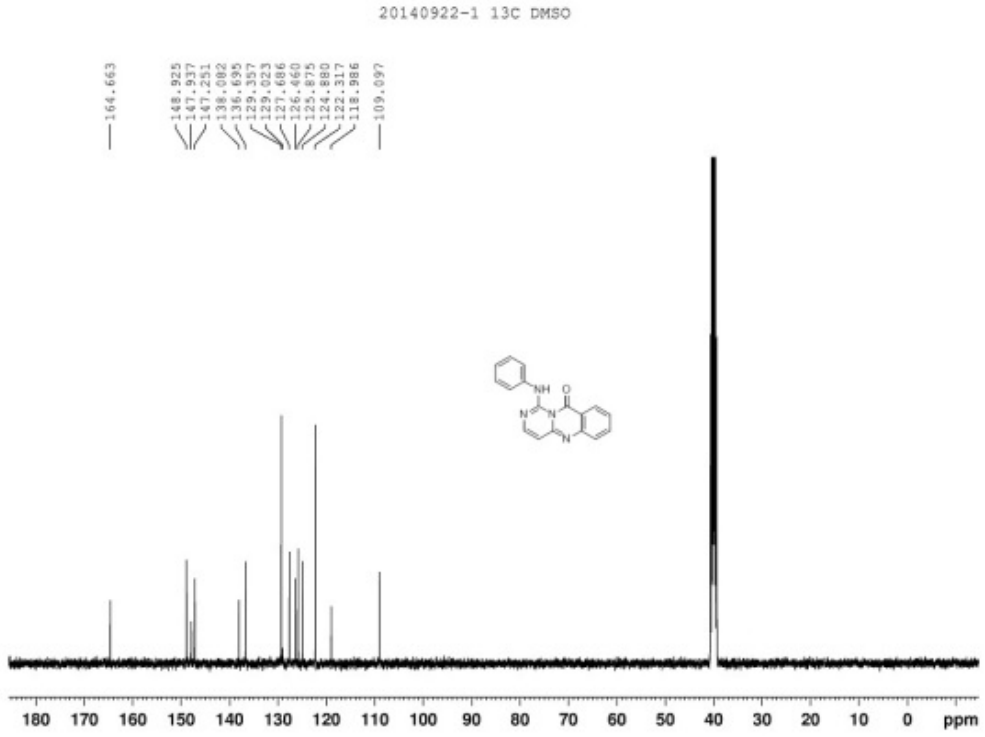
20141103-4 13C DMSO

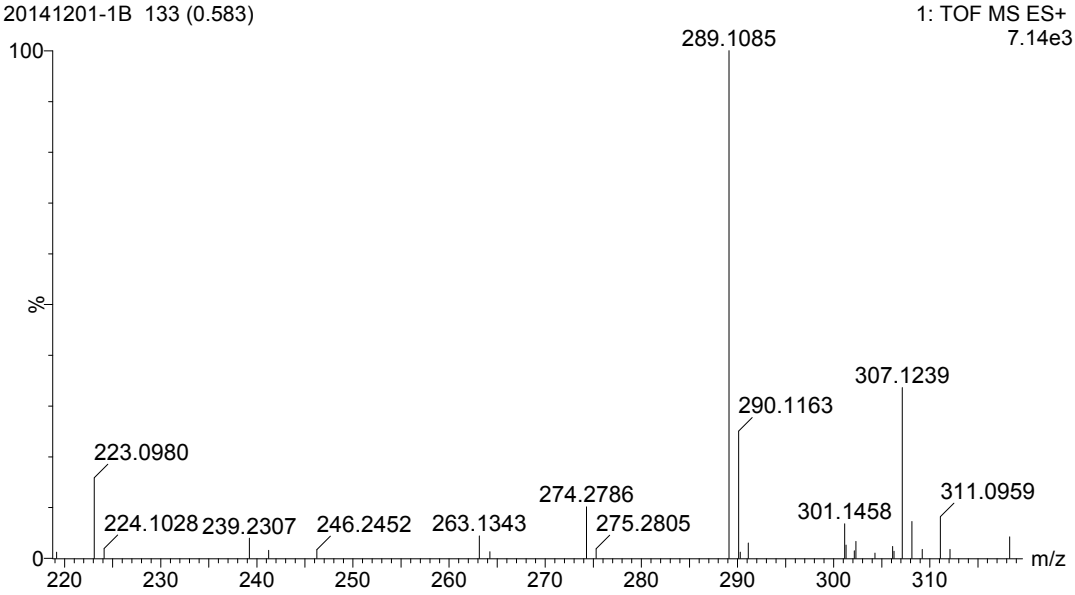



20141201-1D-1 41 (0.247)
1: TOF MS ES+
1.09e4
100
%
0
262.0379
284.0228
274.2770
264.0393
294.0675
288.2935
258.0914
266.0587
275.2838
246.2462
244.0774
256.2681
280.0743
230.2423
m/z
230 235 240 245 250 255 260 265 270 275 280 285 290 295

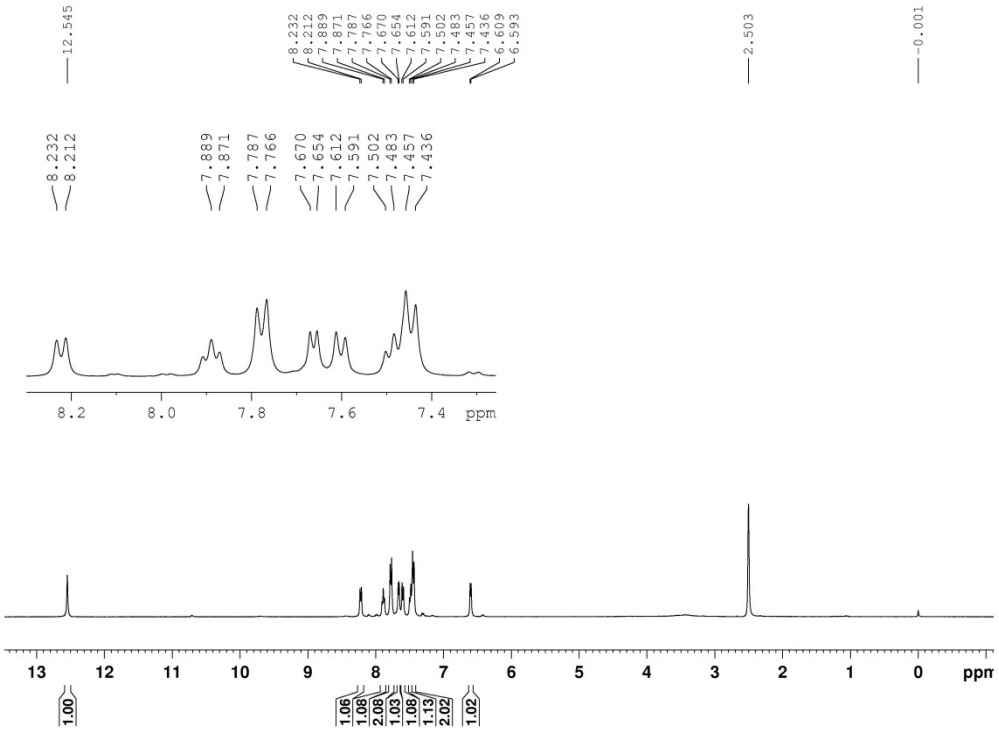
2j


12.495
8.243
8.223
7.908
7.905
7.888
7.870
7.867
7.741
7.721
7.676
7.660
7.610
7.590
7.500
7.480
7.462
7.426
7.407
7.387
7.188
7.169
7.151
6.589
6.574
2.503
0.000
8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
0.98
0.99
1.94
1.02
1.01
0.99
1.99
0.95
0.96

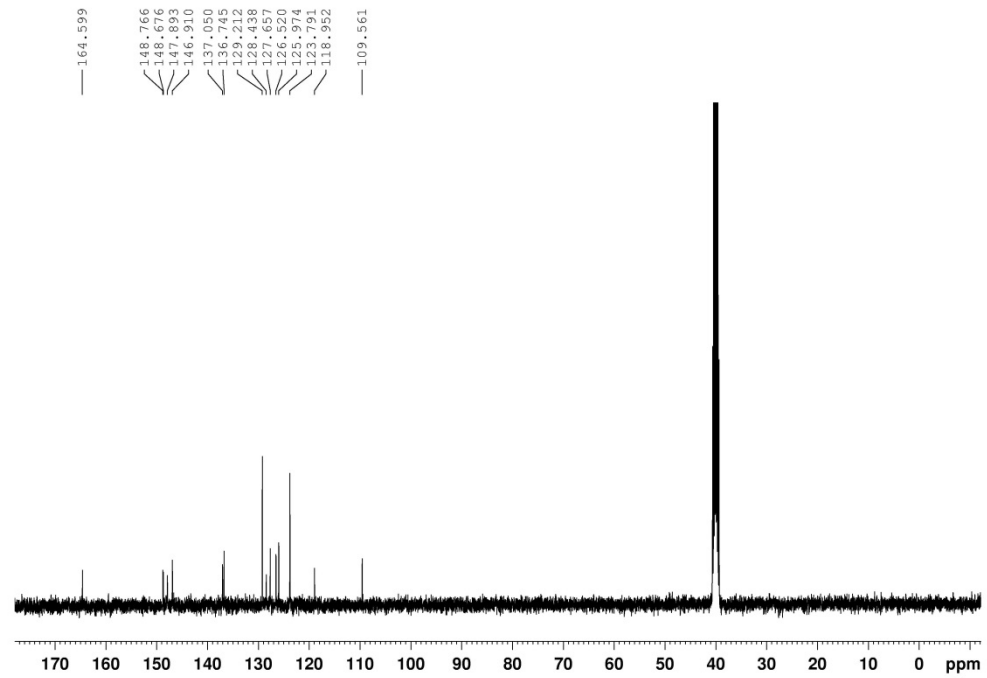

20140922-1 13C DMSO
164.663
148.925
147.337
147.251
138.082
136.695
129.357
129.023
127.686
126.460
125.875
124.880
122.317
118.986
109.097
NH
O
N
N
N
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

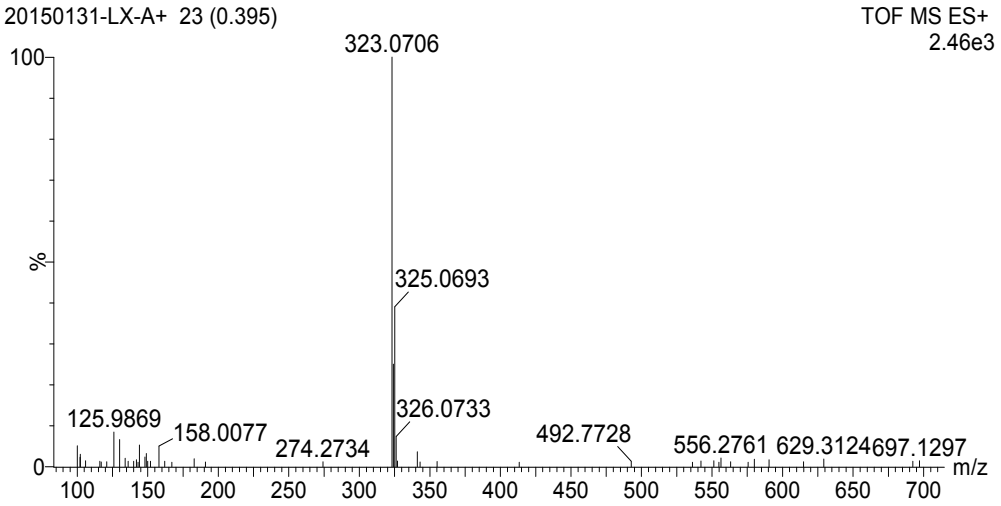

20141201-1B 133 (0.583)
1: TOF MS ES+
7.14e3
100
%
0
289.1085
307.1239
290.1163
223.0980
311.0959
274.2786
301.1458
224.1028
239.2307
246.2452
263.1343
275.2805
m/z
220 230 240 250 260 270 280 290 300 310

2k

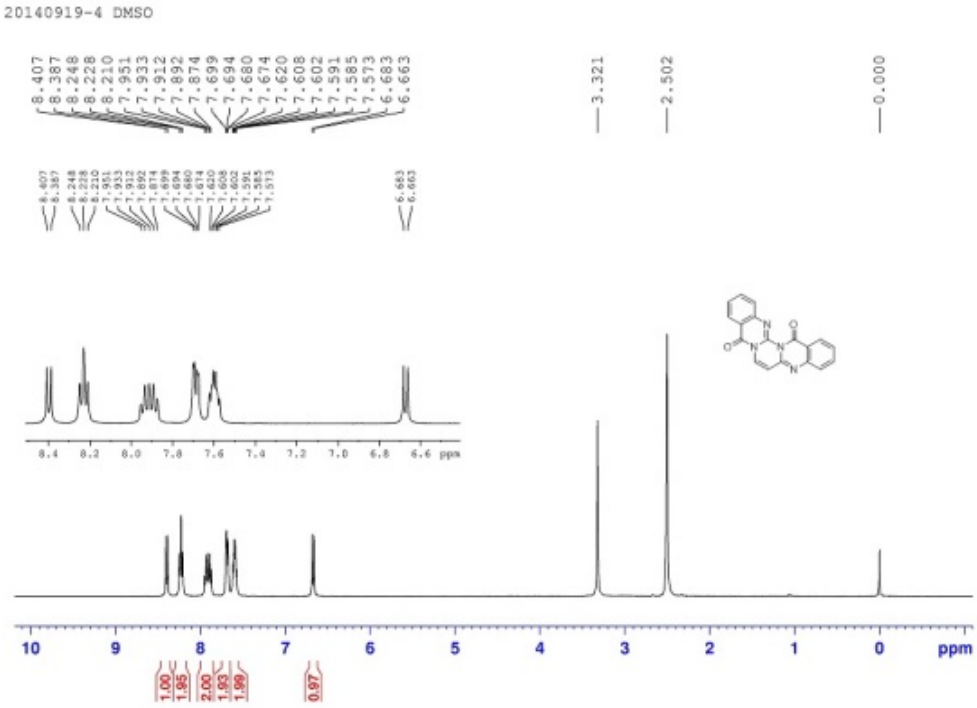


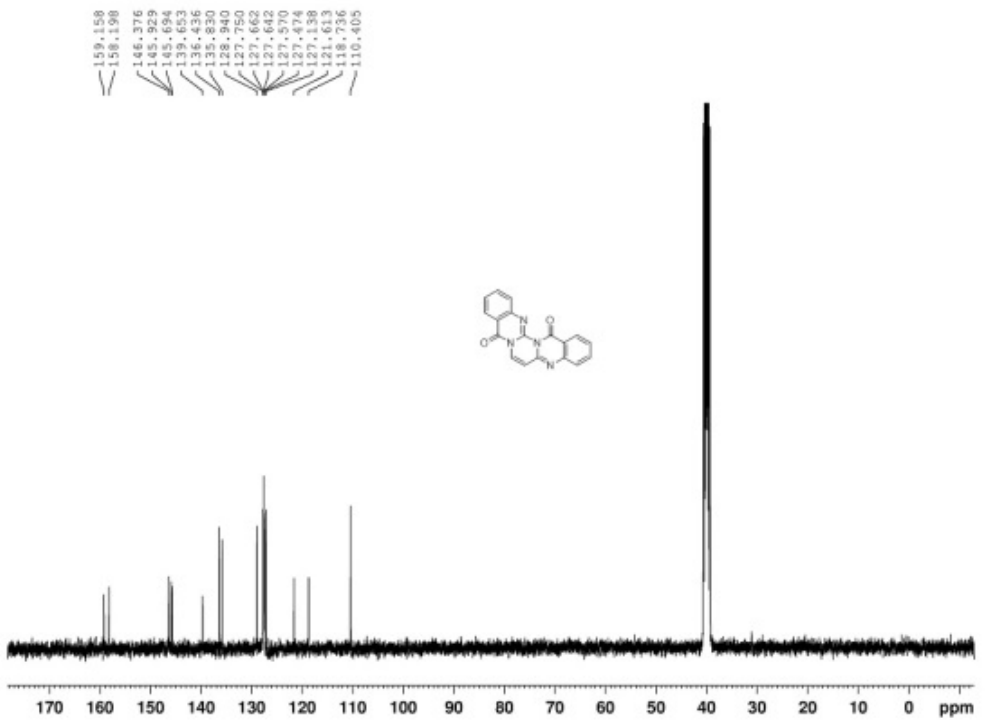
20150129 13C DMSO

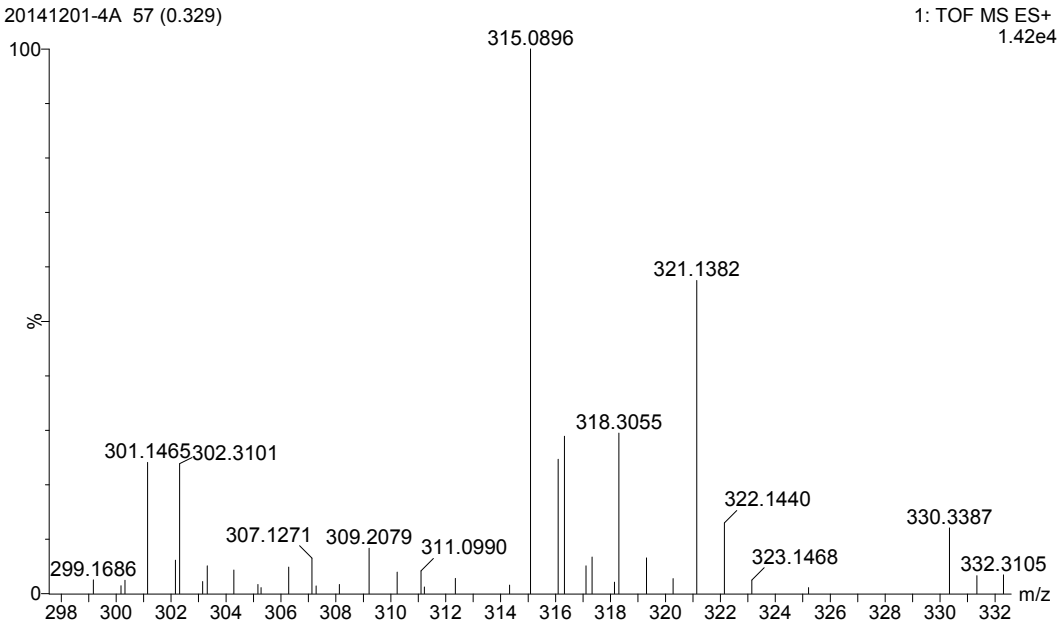



20150131-LX-A+ 23 (0.395)
TOF MS ES+
2.46e3
100
%
0
323.0706
325.0693
326.0733
125.9869
158.0077
274.2734
492.7728
556.2761
629.3124
697.1297
m/z
100 150 200 250 300 350 400 450 500 550 600 650 700

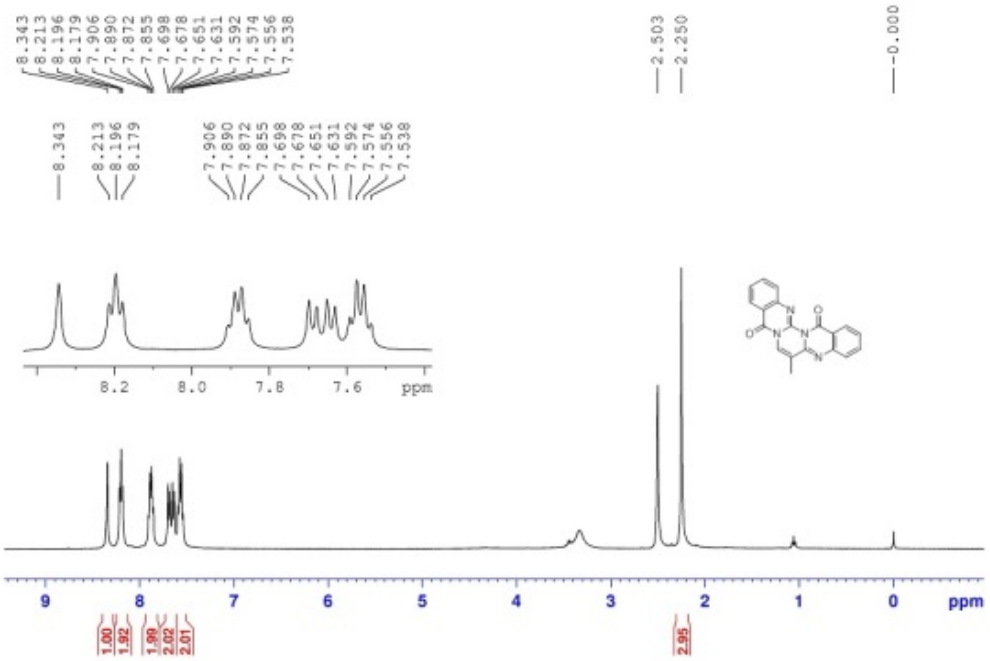
6a

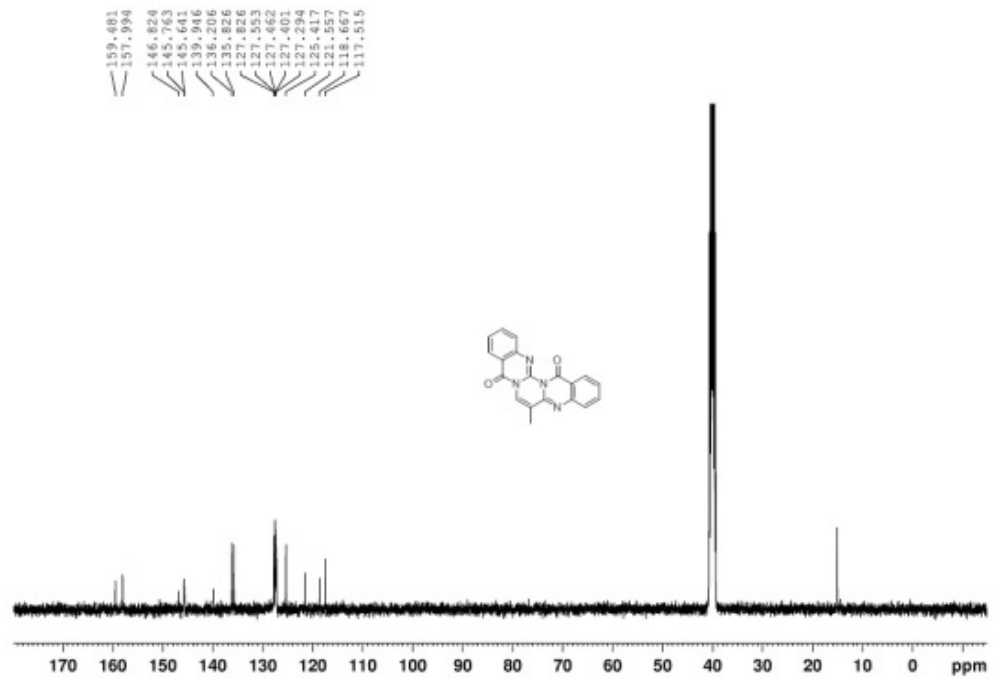

20140919-4 DMSO
8.407
8.387
8.248
8.228
8.210
7.951
7.933
7.912
7.892
7.874
7.699
7.694
7.680
7.674
7.620
7.608
7.602
7.591
7.585
7.573
6.683
6.663
3.321
2.502
0.000
10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
1.95
2.00
1.83
1.98
0.97

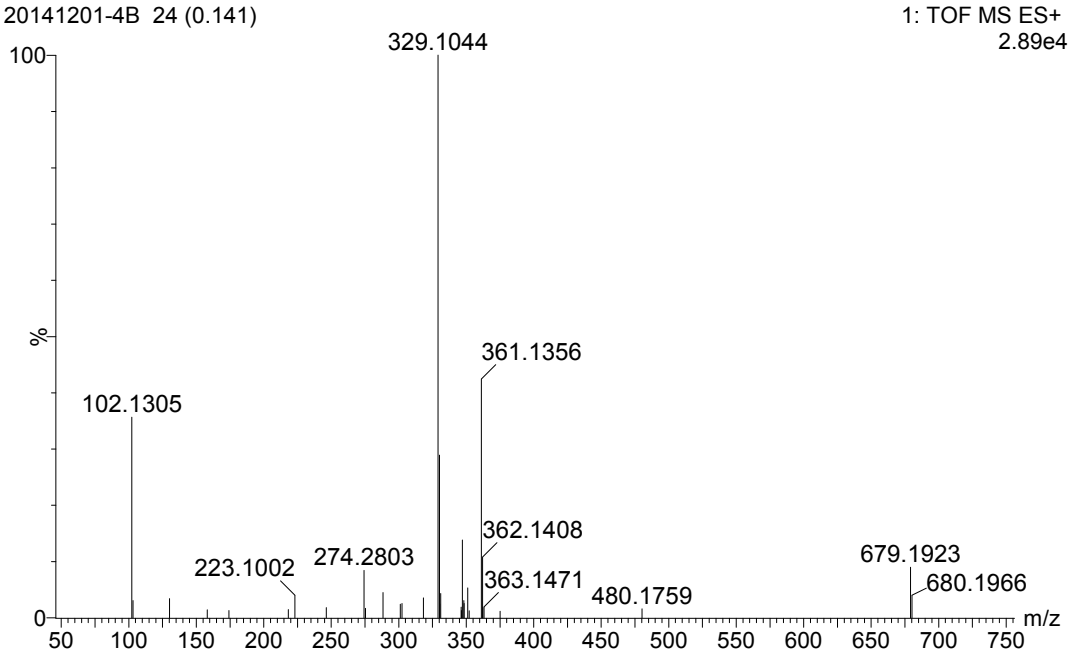

159.158
158.198
146.376
145.929
145.694
139.653
136.436
135.830
128.940
127.750
127.662
127.642
127.570
127.474
127.138
121.613
118.736
110.405
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


20141201-4A 57 (0.329)
1: TOF MS ES+
1.42e4
100
%
0
315.0896
321.1382
318.3055
301.1465
302.3101
322.1440
330.3387
307.1271
309.2079
311.0990
323.1468
332.3105
299.1686
298 300 302 304 306 308 310 312 314 316 318 320 322 324 326 328 330 332
m/z

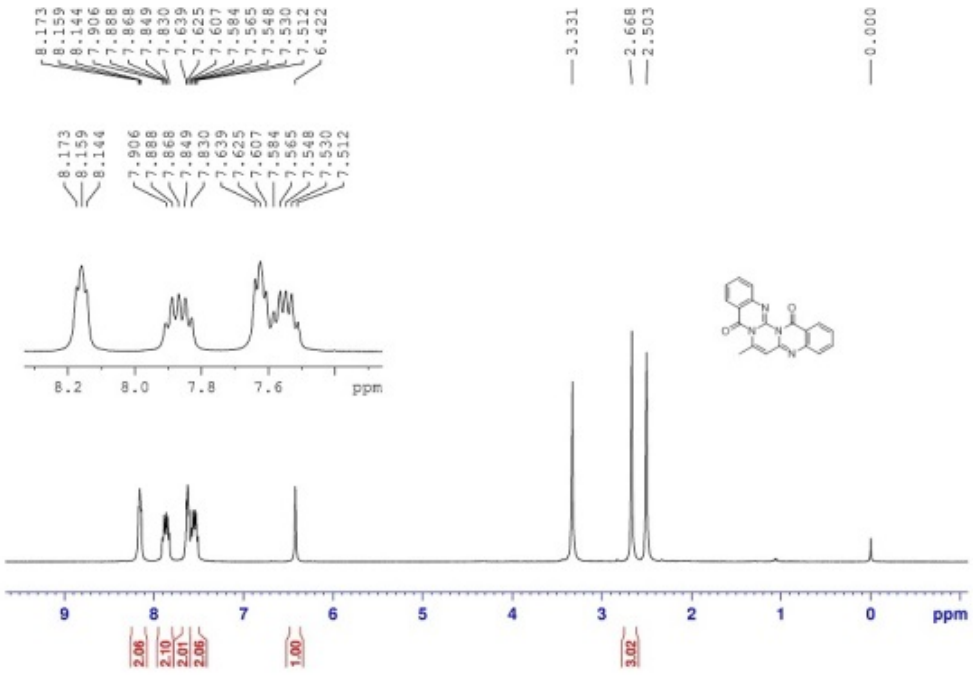
6b

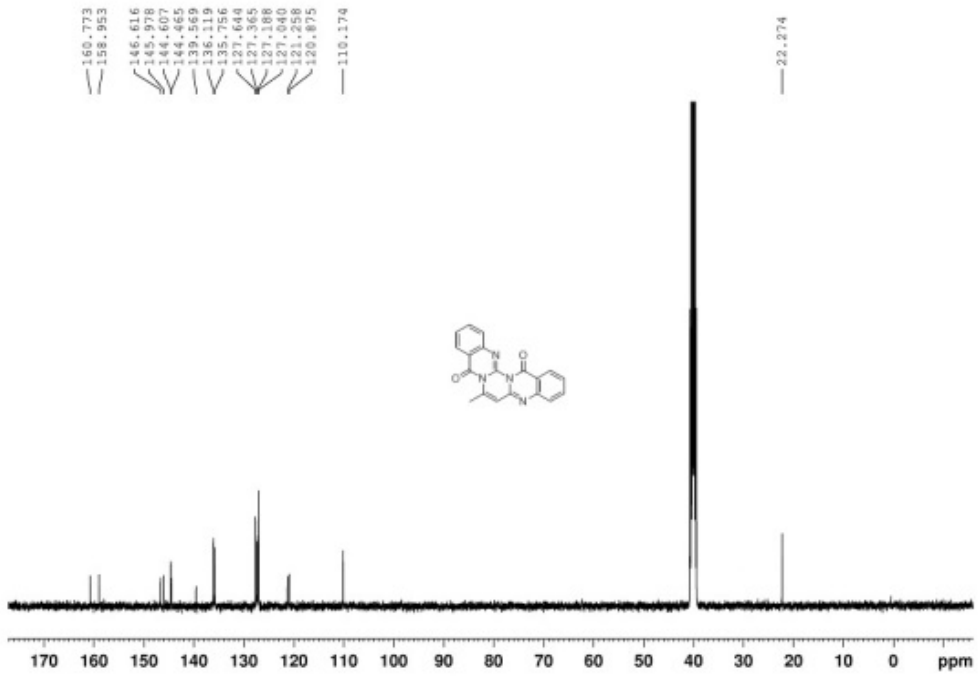

8.343
8.213
8.196
8.179
7.906
7.890
7.872
7.855
7.698
7.678
7.651
7.631
7.592
7.574
7.556
7.538
2.503
2.250
0.000
8.2
8.0
7.8
7.6
ppm
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.92
1.90
2.02
2.01
2.95

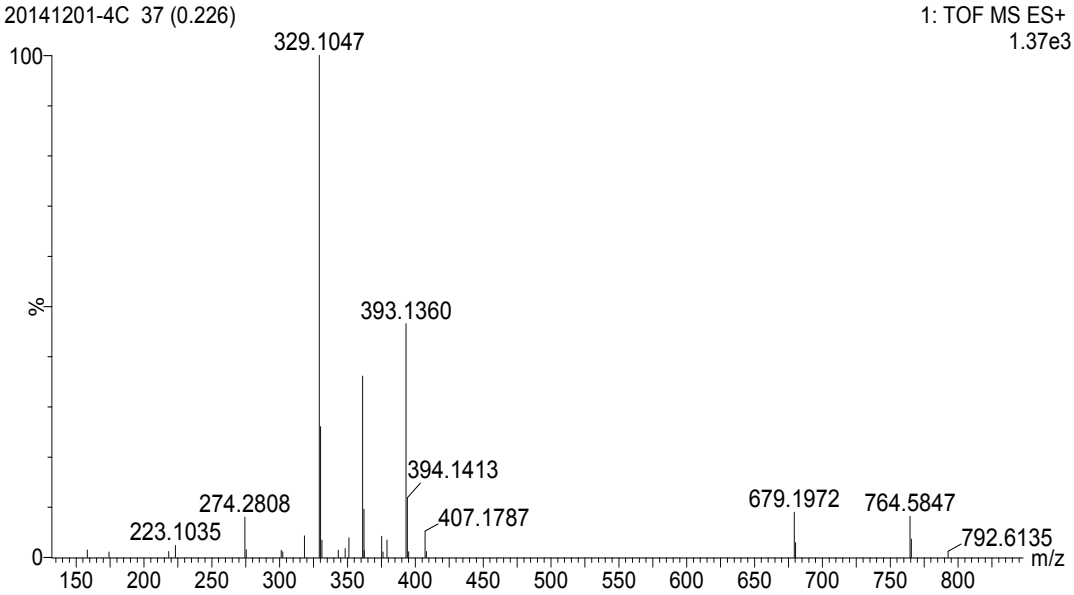

159.481
157.994
146.824
145.763
145.641
139.946
136.206
135.826
127.826
127.553
127.462
127.401
127.294
125.417
121.557
118.667
117.515
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


20141201-4B 24 (0.141)
1: TOF MS ES+
2.89e4
100
%
0
329.1044
361.1356
102.1305
362.1408
223.1002
274.2803
679.1923
363.1471
680.1966
480.1759
m/z
50 100 150 200 250 300 350 400 450 500 550 600 650 700 750

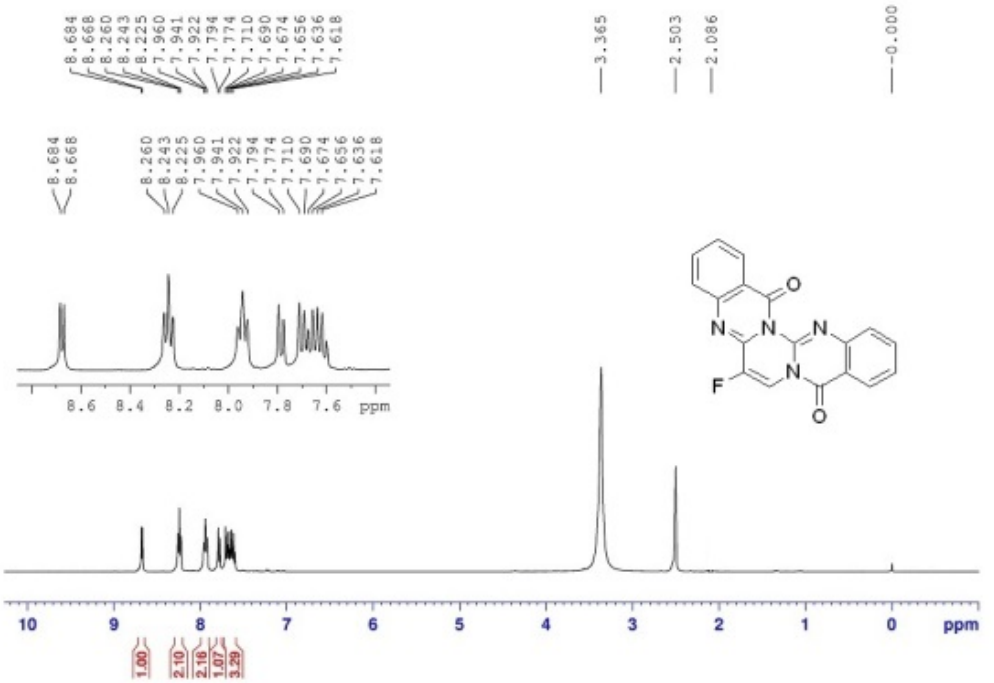
6c


8.173
8.159
8.144
7.906
7.888
7.868
7.849
7.830
7.639
7.625
7.607
7.584
7.565
7.548
7.530
7.512
6.422
3.331
2.668
2.503
0.000
8.2
8.0
7.8
7.6
ppm
9 8 7 6 5 4 3 2 1 0 ppm
2.06
2.10
2.01
2.06
1.00
3.02

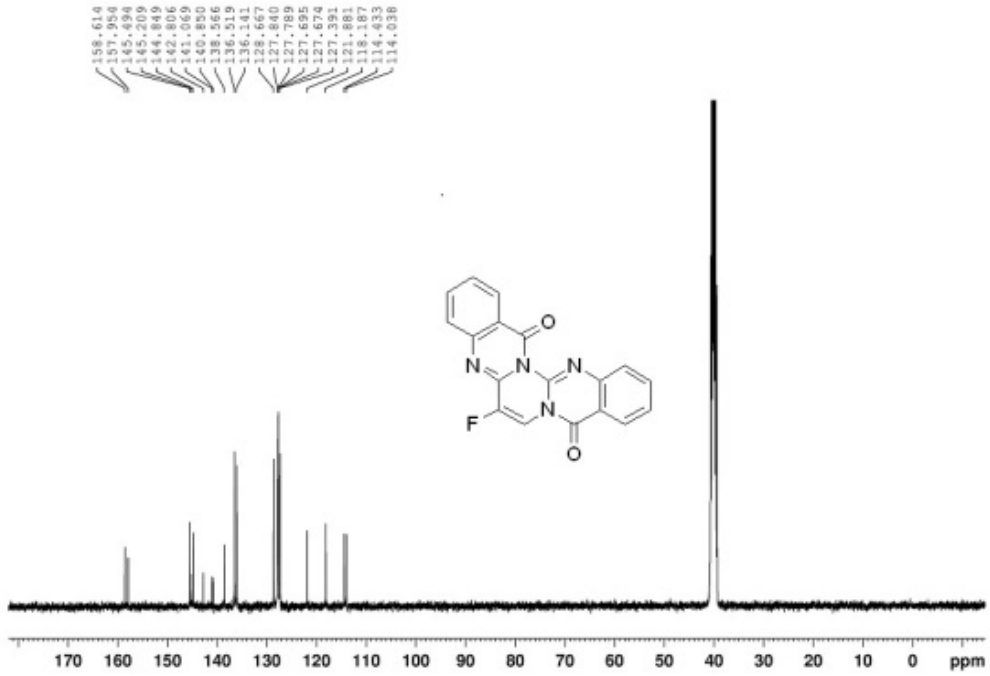

160.773
158.953
146.616
145.978
144.607
144.465
139.569
136.119
135.756
127.644
127.365
127.188
127.040
121.258
120.875
110.174
22.274
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

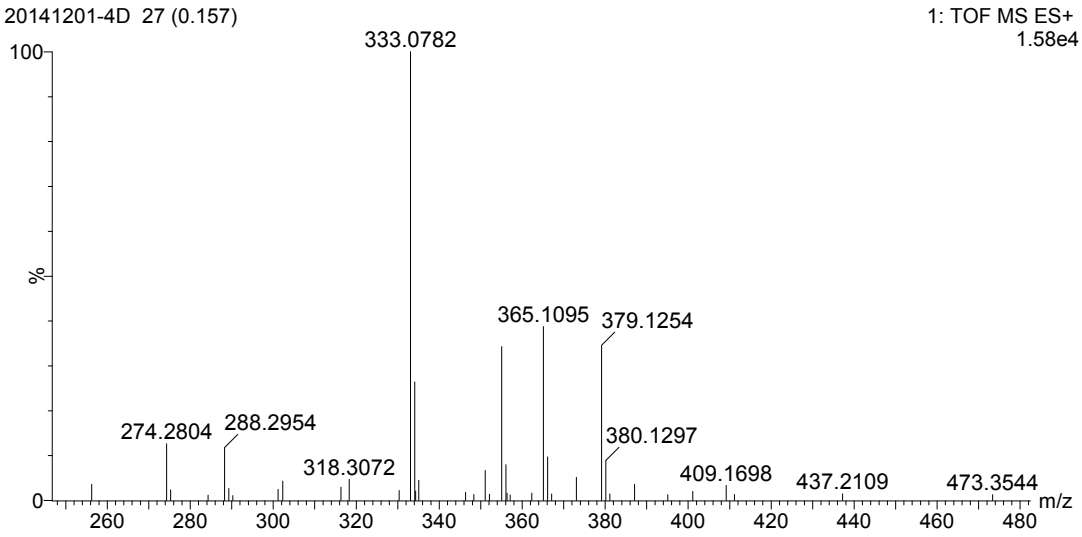

20141201-4C 37 (0.226)
1: TOF MS ES+
1.37e3
100
%
0
329.1047
393.1360
394.1413
274.2808
223.1035
407.1787
679.1972
764.5847
792.6135
150 200 250 300 350 400 450 500 550 600 650 700 750 800
m/z

6d

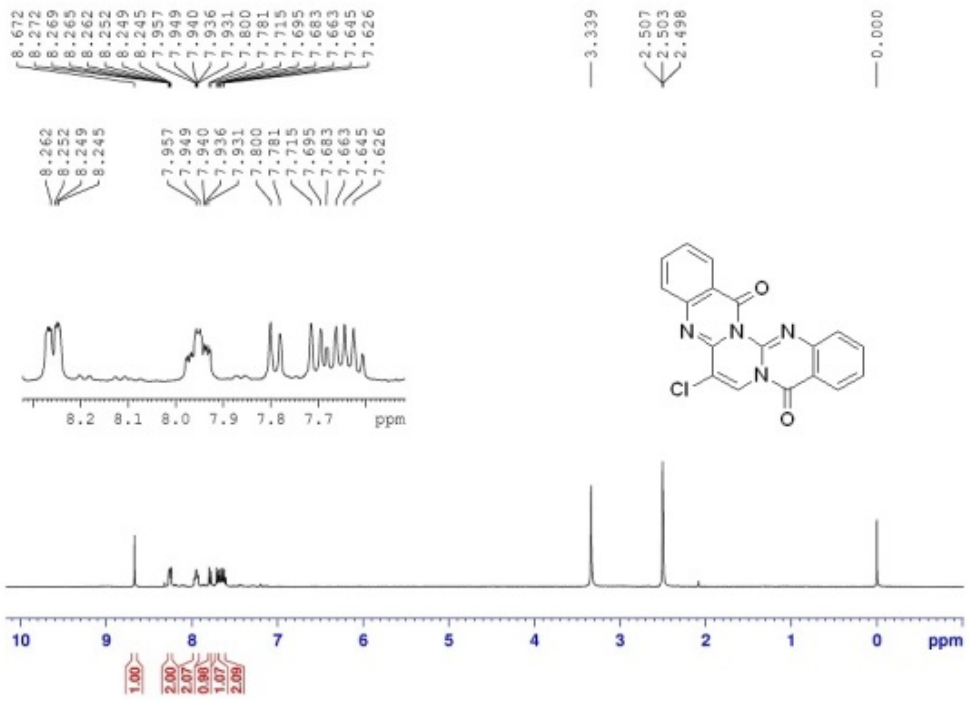


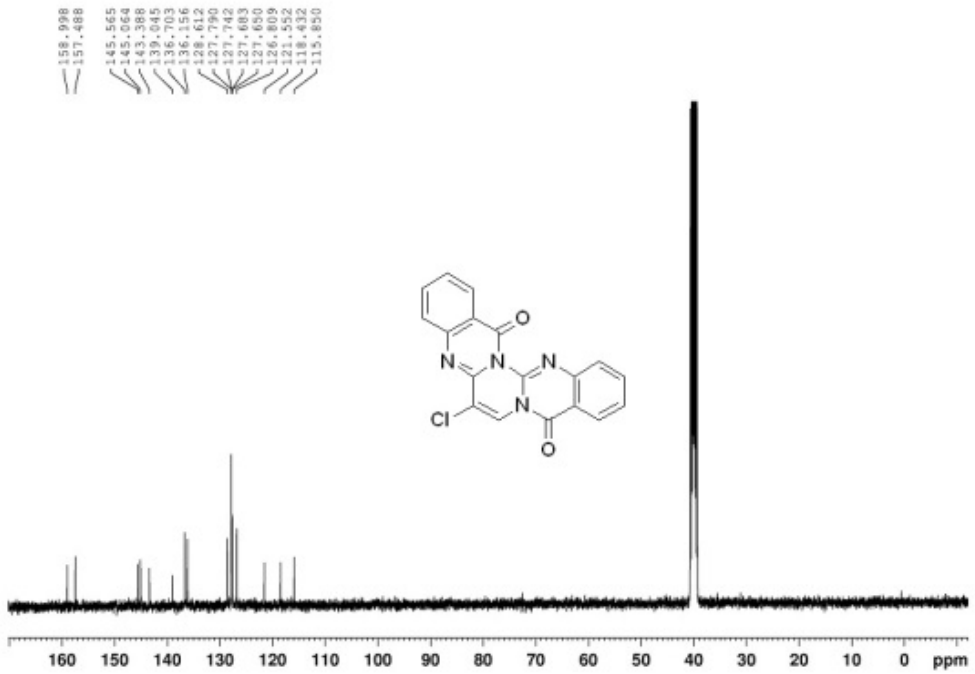
20141011-2 13C DMSO

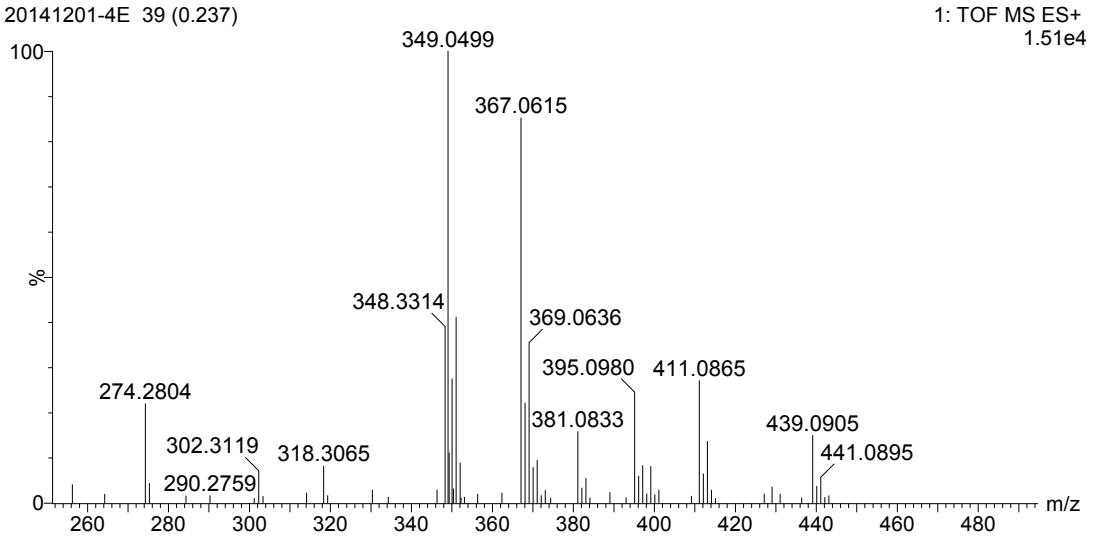



20141201-4D 27 (0.157)
1: TOF MS ES+
1.58e4
333.0782
365.1095
379.1254
274.2804
288.2954
380.1297
318.3072
409.1698
437.2109
473.3544
%
m/z

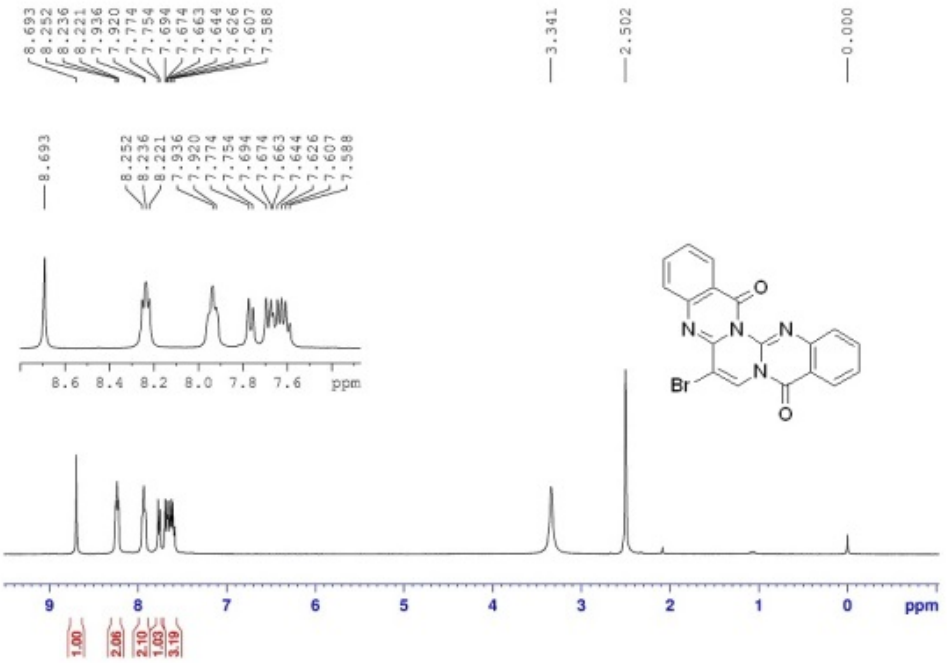
6e

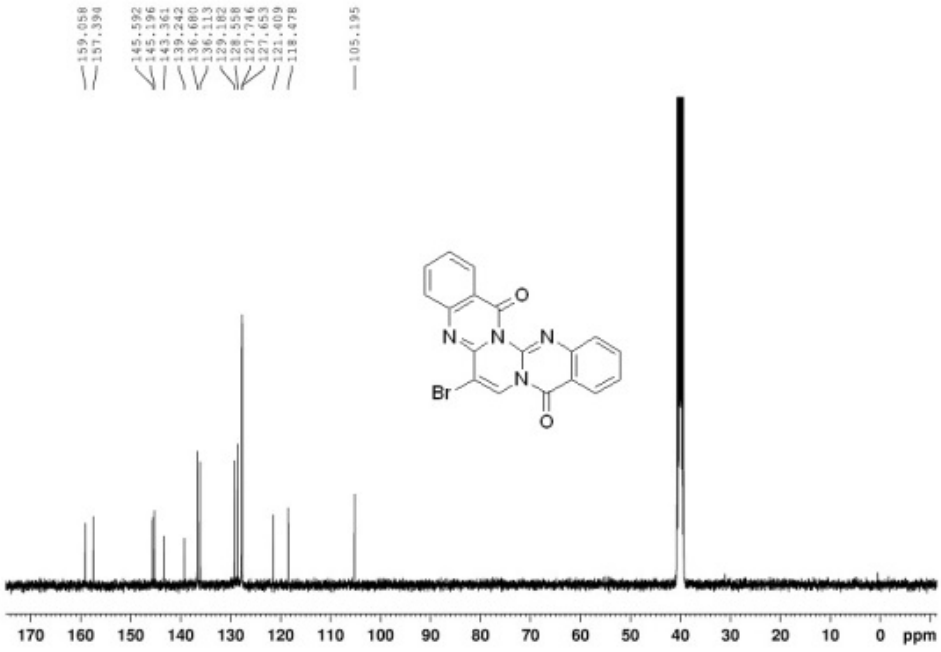

8.672
8.272
8.269
8.265
8.262
8.252
8.249
8.245
7.957
7.949
7.940
7.936
7.931
7.800
7.781
7.715
7.695
7.683
7.663
7.645
7.626
3.339
2.507
2.503
2.498
0.000
ppm
Cl
O
N

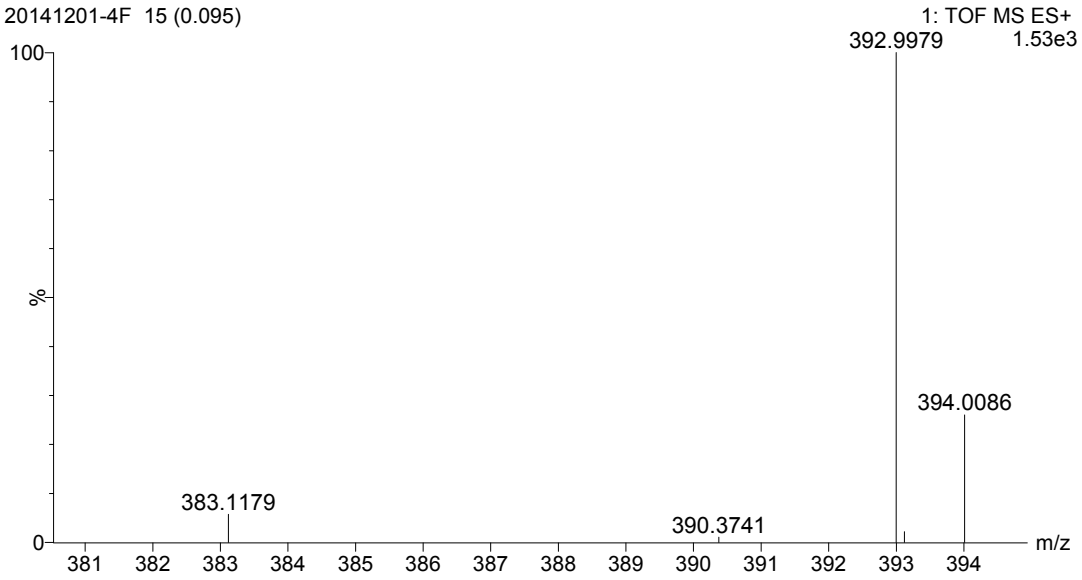

158.998
157.488
145.565
145.064
143.388
139.645
136.703
136.156
128.612
127.790
127.742
127.683
127.650
126.809
121.552
118.432
115.850
O
N
N
N
N
Cl
O
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


20141201-4E 39 (0.237)
1: TOF MS ES+
1.51e4
100
%
0
349.0499
367.0615
348.3314
369.0636
395.0980
411.0865
274.2804
381.0833
439.0905
302.3119
318.3065
441.0895
290.2759
260 280 300 320 340 360 380 400 420 440 460 480
m/z

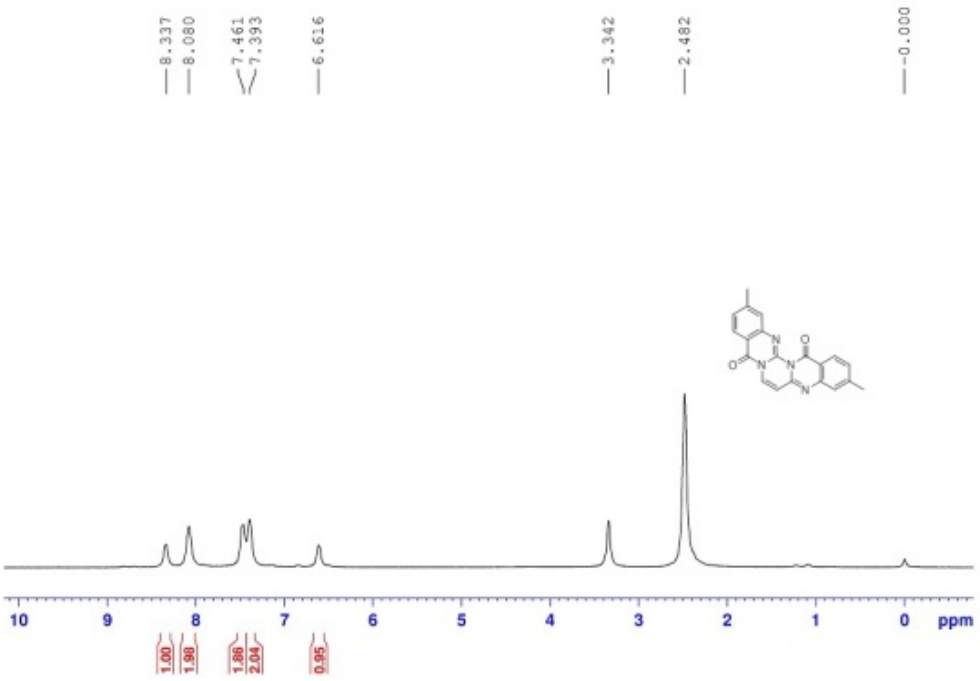
6f

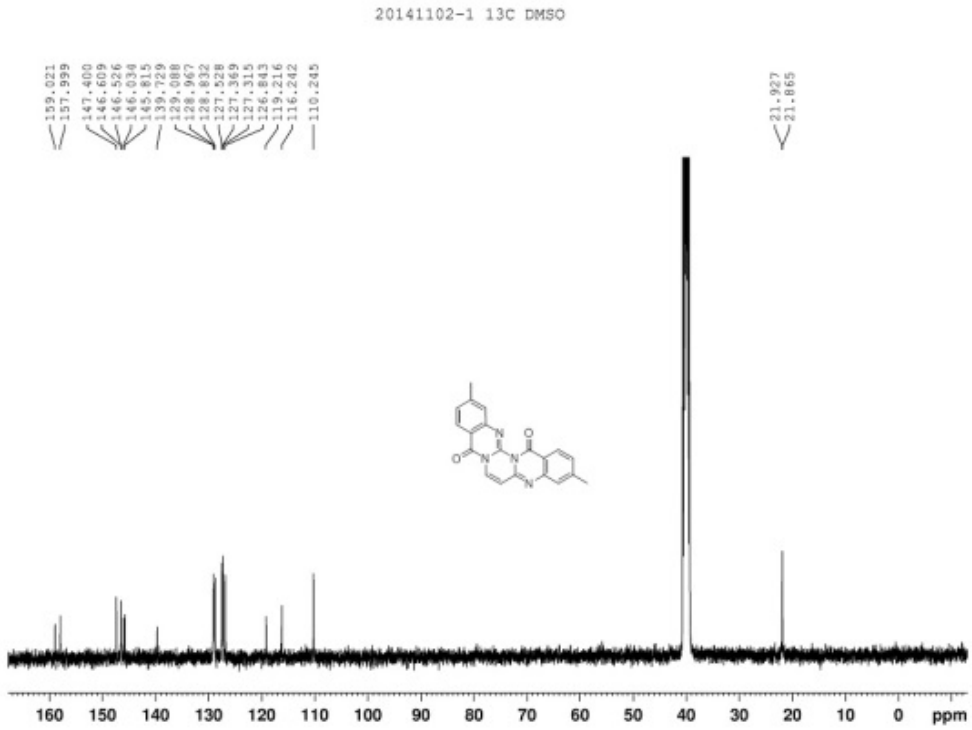

8.693
8.252
8.236
8.221
7.936
7.920
7.774
7.754
7.694
7.674
7.663
7.644
7.626
7.607
7.588
3.341
2.502
0.000
8.6 8.4 8.2 8.0 7.8 7.6 ppm
O
N
N
N
N
Br
O
9 8 7 6 5 4 3 2 1 0 ppm
1.00
2.06
2.10
1.03
3.19

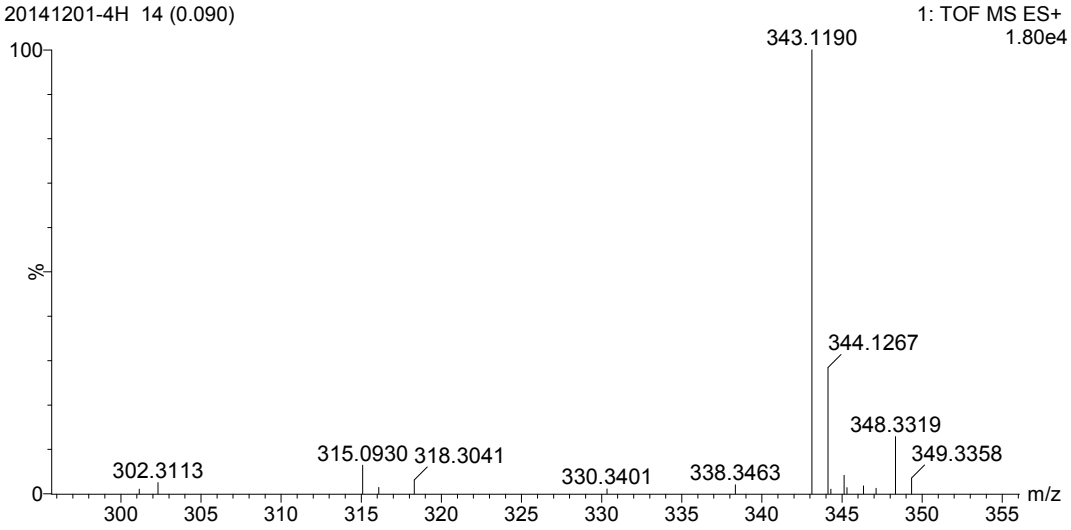

159.058
157.390
145.592
145.196
143.361
139.242
136.680
136.113
129.182
128.558
127.746
127.653
121.409
118.478
105.195
O
N
N
N
N
Br
O
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


20141201-4F 15 (0.095)
1: TOF MS ES+
1.53e3
392.9979
100
%
394.0086
383.1179
390.3741
0
m/z
381 382 383 384 385 386 387 388 389 390 391 392 393 394

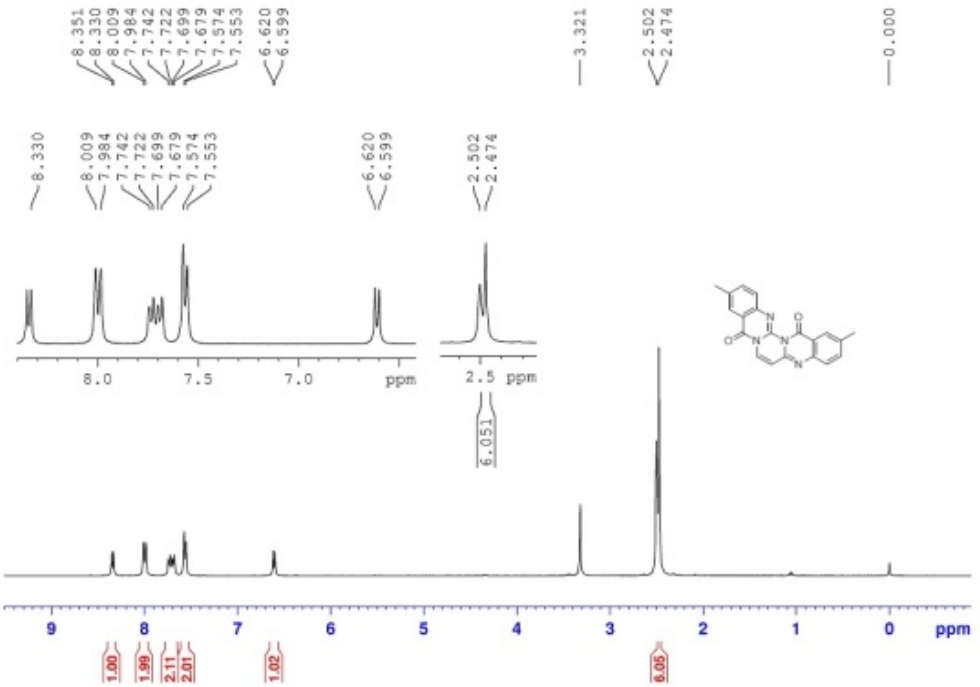
6h

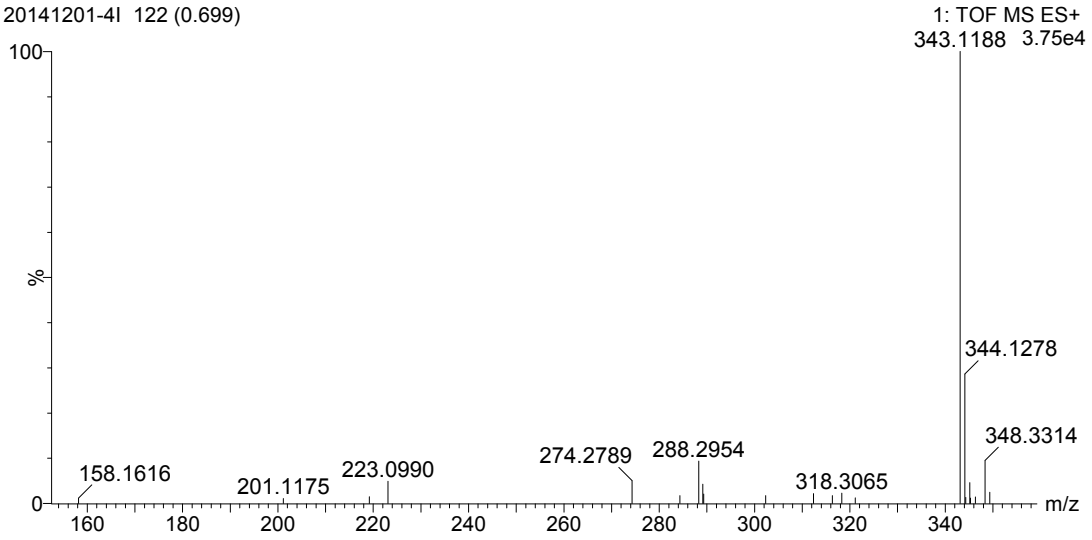

8.337
8.080
7.461
7.393
6.616
3.342
2.482
0.000
10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
1.90
1.86
2.04
0.95


20141102-1 13C DMSO
159.021
157.999
147.400
146.609
146.526
146.034
145.815
139.729
129.088
128.967
128.832
127.328
127.369
127.315
126.843
119.216
116.242
110.245
21.927
21.865
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

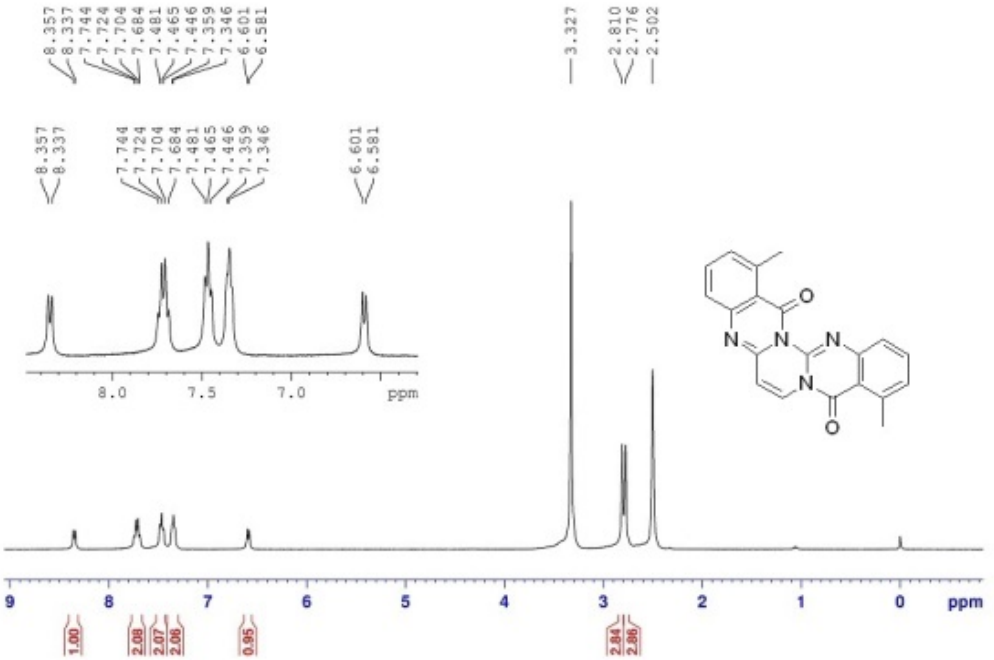

20141201-4H 14 (0.090)
1: TOF MS ES+
1.80e4
100
%
0
343.1190
344.1267
348.3319
349.3358
302.3113
315.0930
318.3041
330.3401
338.3463
300 305 310 315 320 325 330 335 340 345 350 355
m/z

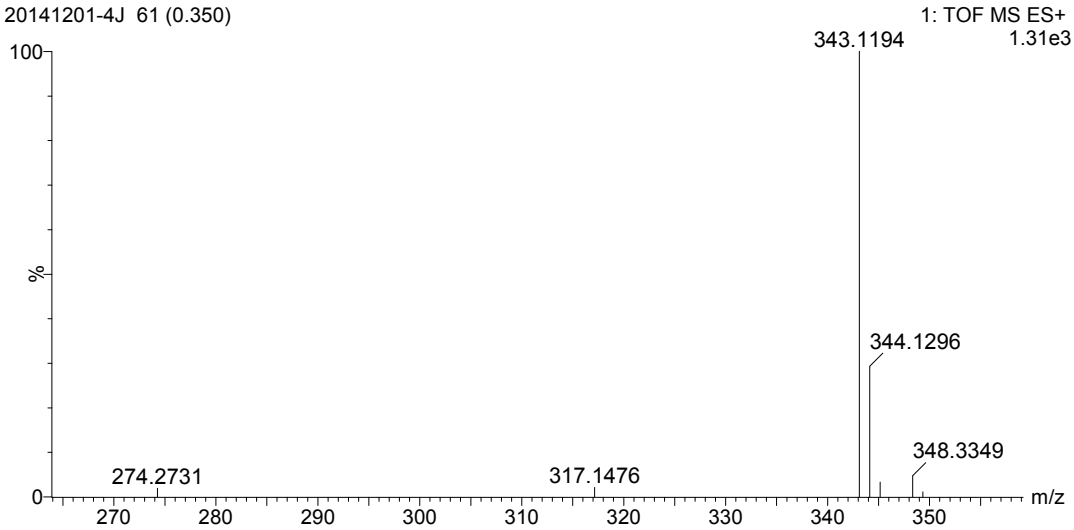
6i


8.351
8.330
8.009
7.984
7.742
7.722
7.699
7.679
7.574
7.553
6.620
6.599
3.321
2.502
2.474
0.000
8.0
7.5
7.0
ppm
2.5 ppm
6.051
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.99
2.11
2.01
1.02
6.05

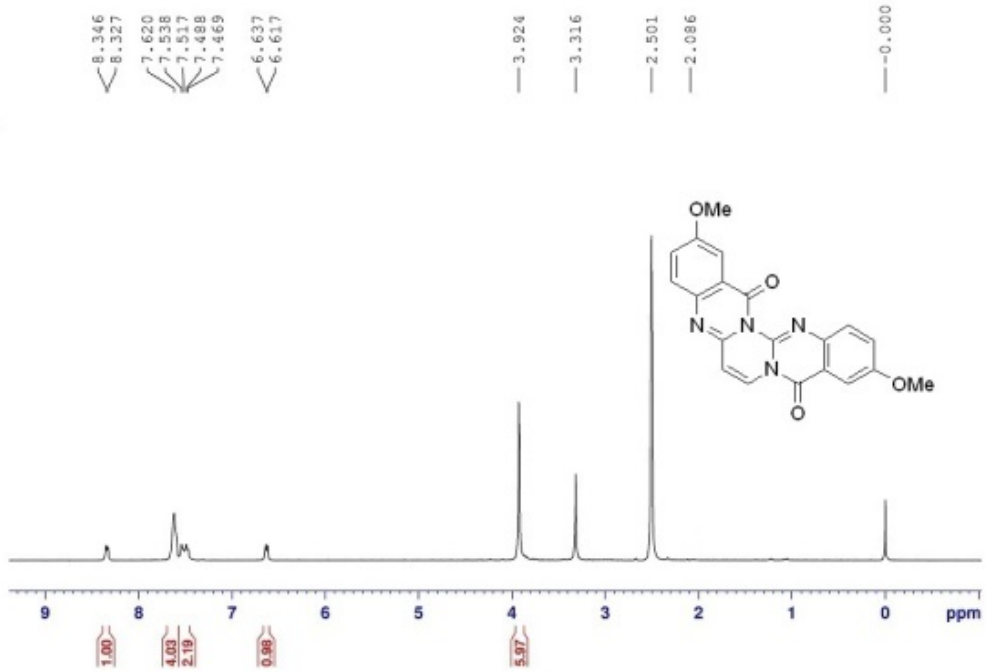

20141201-4I 122 (0.699)
1: TOF MS ES+
343.1188 3.75e4
100
%
0
344.1278
348.3314
158.1616
201.1175
223.0990
274.2789
288.2954
318.3065
m/z
160
180
200
220
240
260
280
300
320
340

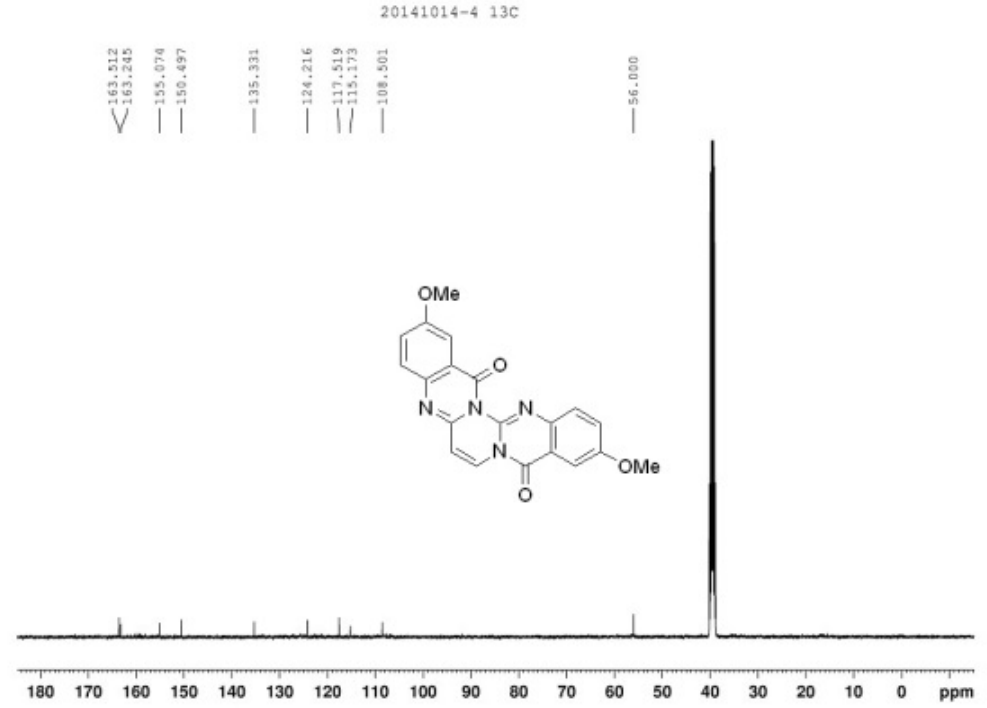
6j

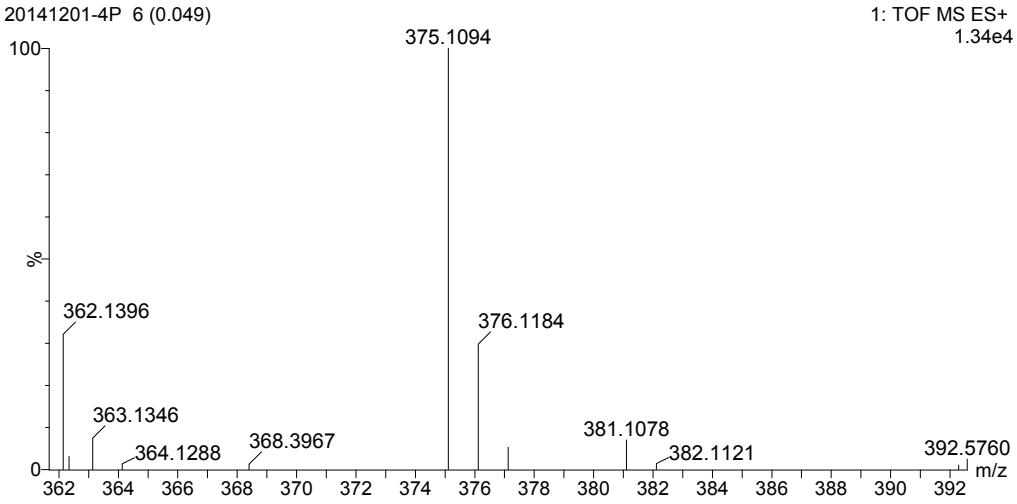

8.357
8.337
7.744
7.724
7.704
7.684
7.481
7.465
7.446
7.359
7.346
6.601
6.581
3.327
2.810
2.776
2.502
8.0
7.5
7.0
ppm
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.08
2.07
2.06
0.95
2.84
2.86
O
N
N
N
N
O


20141201-4J 61 (0.350)
1: TOF MS ES+
1.31e3
343.1194
344.1296
348.3349
274.2731
317.1476
100
%
0
270
280
290
300
310
320
330
340
350
m/z

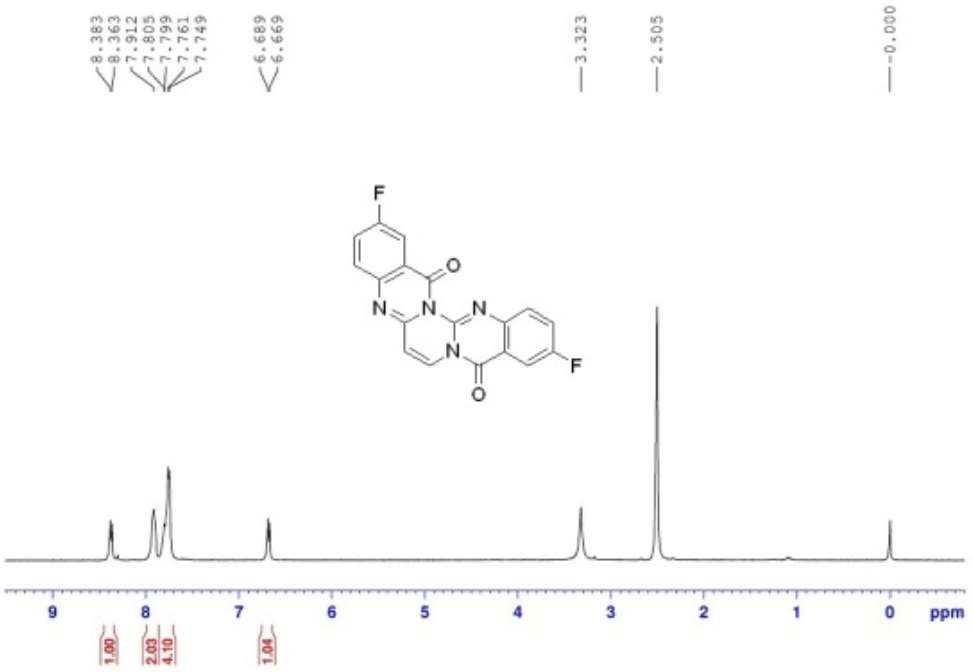
6k


8.346
8.327
7.620
7.538
7.517
7.488
7.469
6.637
6.617
3.924
3.316
2.501
2.086
0.000
OMe
O
N
N
N
N
OMe
O
9
8
7
6
5
4
3
2
1
0
ppm
1.00
4.03
2.19
0.98
5.97

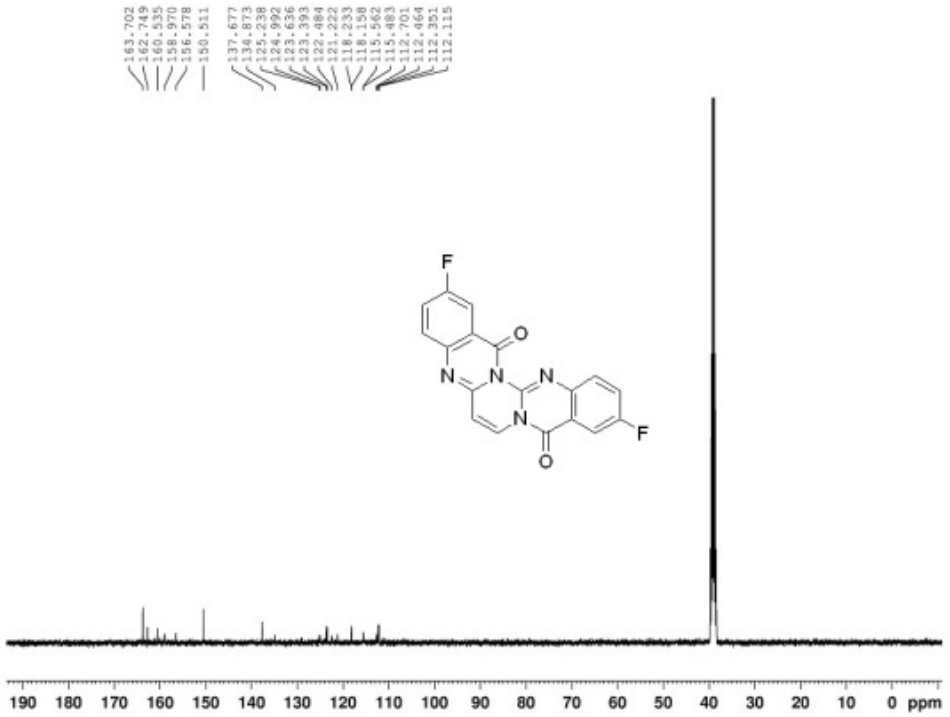

20141014-4 13C
163.512
163.245
155.074
150.497
135.331
124.216
117.519
115.173
108.501
56.000
OMe
O
N
N
N
N
OMe
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

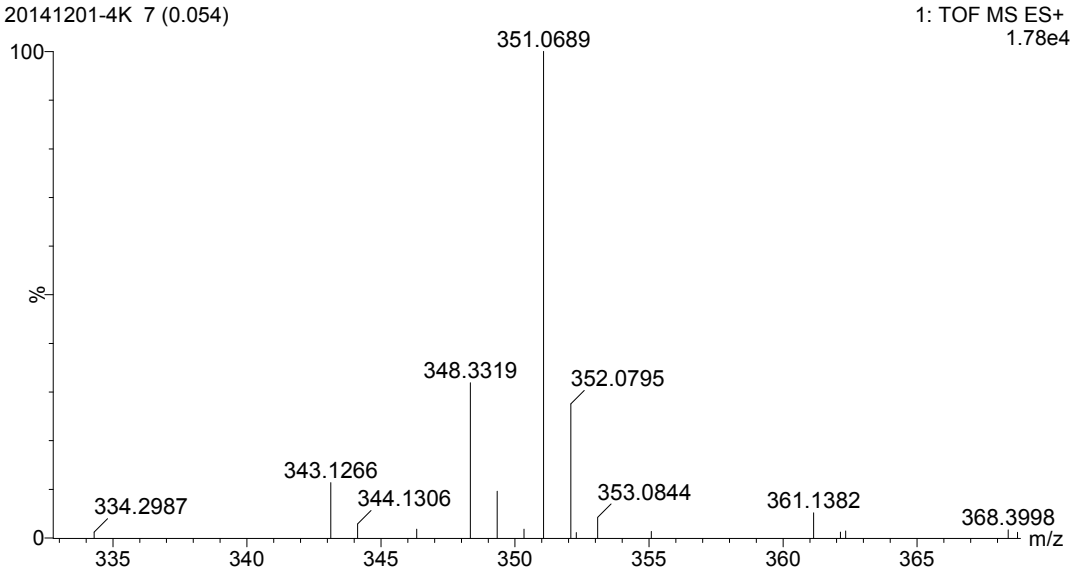

20141201-4P 6 (0.049)
1: TOF MS ES+
1.34e4
100
%
0
375.1094
362.1396
376.1184
363.1346
364.1288
368.3967
381.1078
382.1121
392.5760
m/z
362 364 366 368 370 372 374 376 378 380 382 384 386 388 390 392

6l

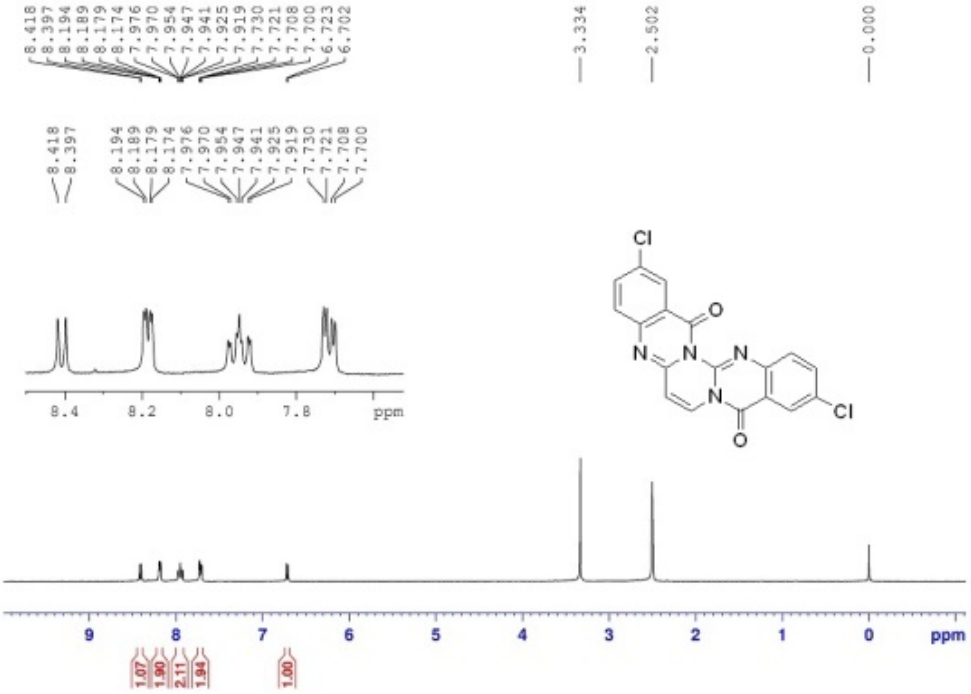

8.383
8.363
7.912
7.805
7.799
7.761
7.749
6.689
6.669
3.323
2.505
0.000
F
O
N
N
N
N
F
O
9 8 7 6 5 4 3 2 1 0 ppm
1.00
2.03
4.10
1.04

`

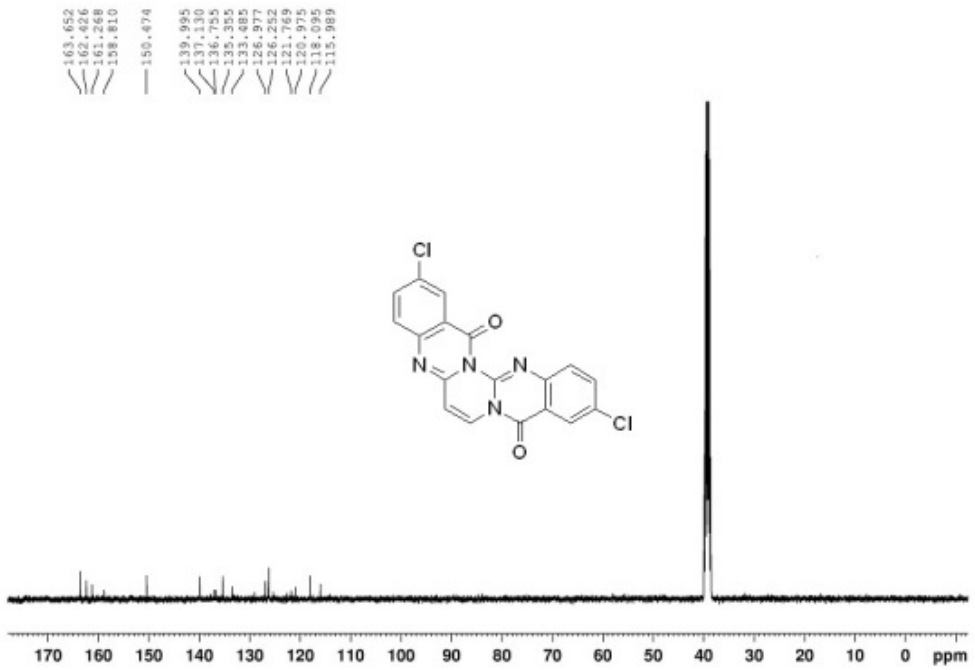

163.702
162.749
160.535
158.970
156.578
150.511
137.677
134.873
125.238
124.992
123.636
123.393
122.484
121.222
118.233
118.158
115.562
115.483
112.701
112.464
112.351
112.115
F
O
N
N
N
N
F
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

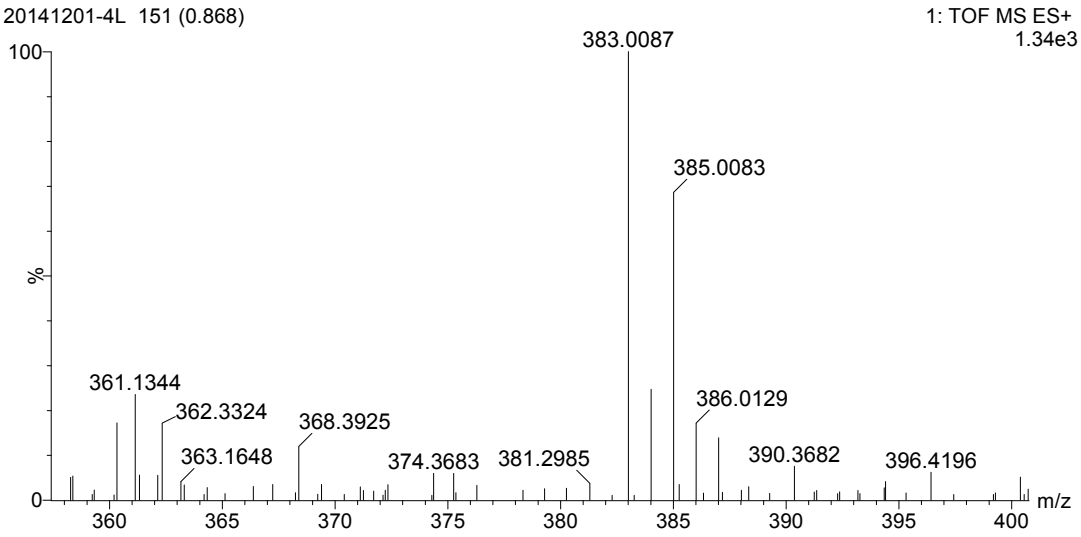

20141201-4K 7 (0.054)
1: TOF MS ES+
1.78e4
100
%
0
351.0689
348.3319
352.0795
343.1266
344.1306
353.0844
361.1382
368.3998
334.2987
335
340
345
350
355
360
365
m/z

6m

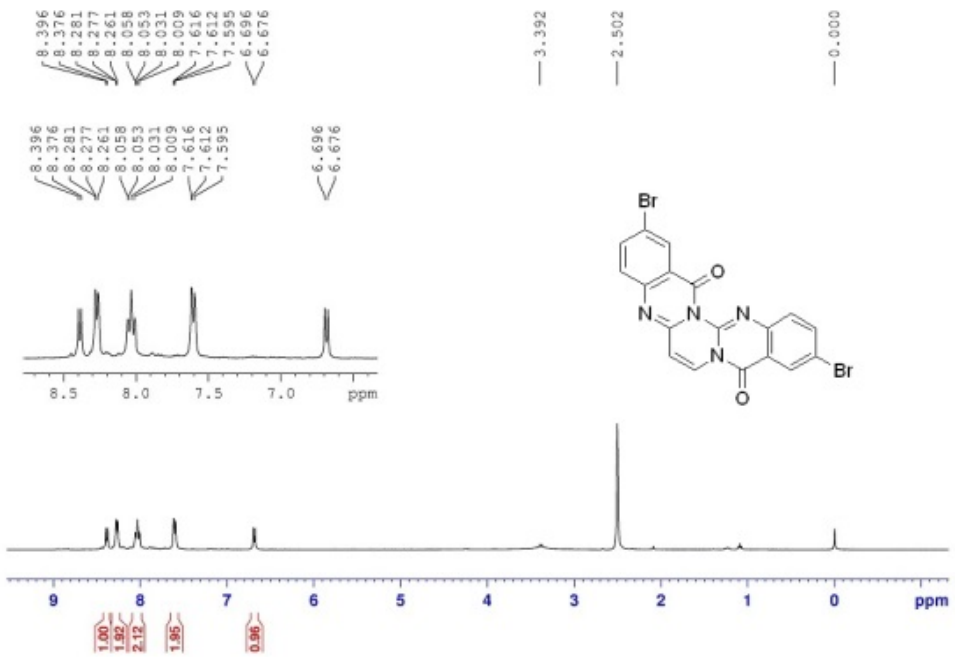


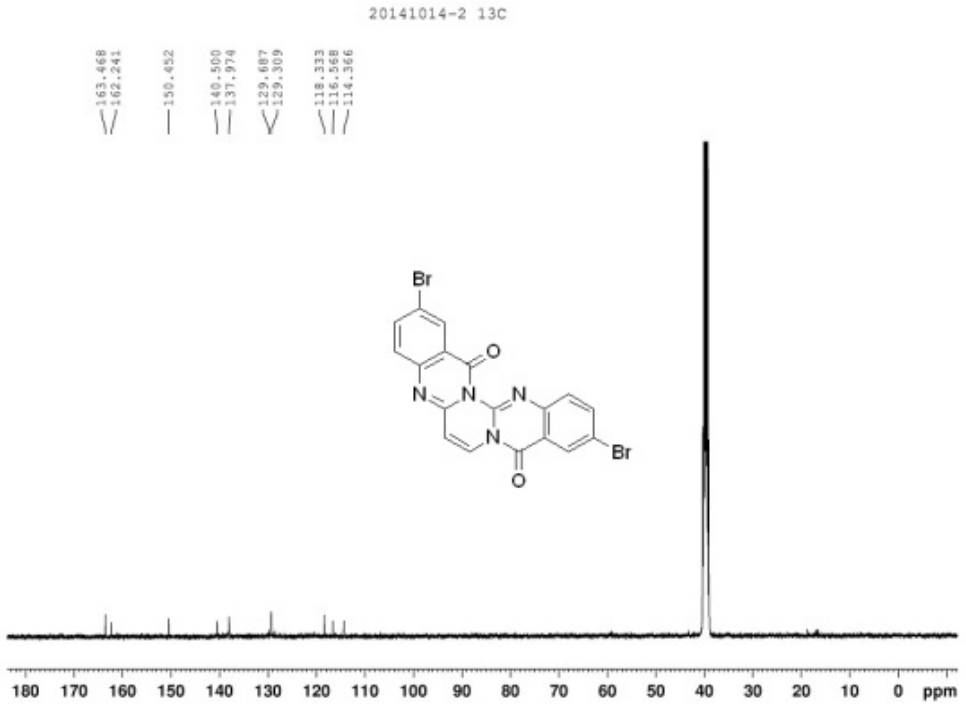
20141014-1 13C DMSO

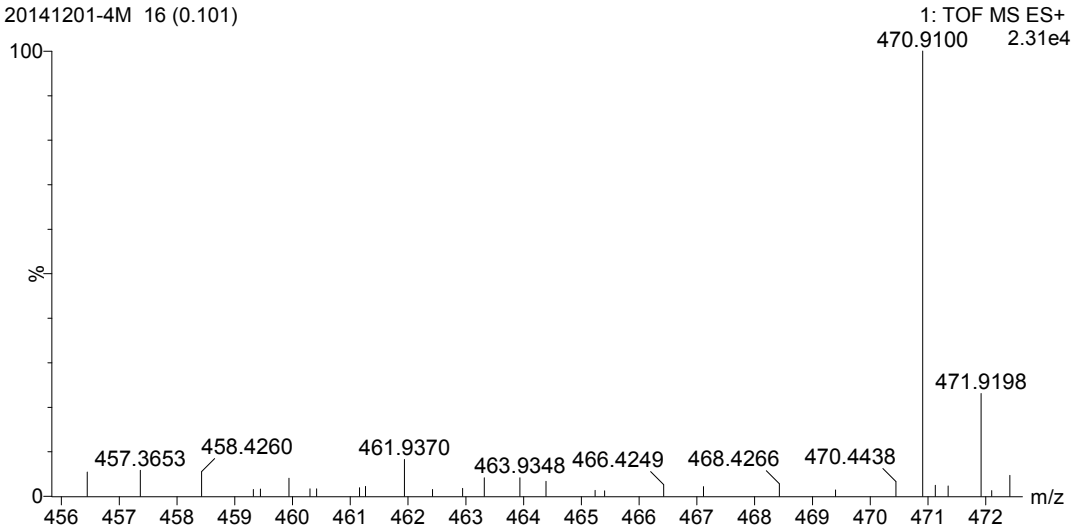



20141201-4L 151 (0.868)
1: TOF MS ES+
1.34e3
100
%
0
383.0087
385.0083
361.1344
362.3324
368.3925
363.1648
374.3683
381.2985
386.0129
390.3682
396.4196
360
365
370
375
380
385
390
395
400
m/z

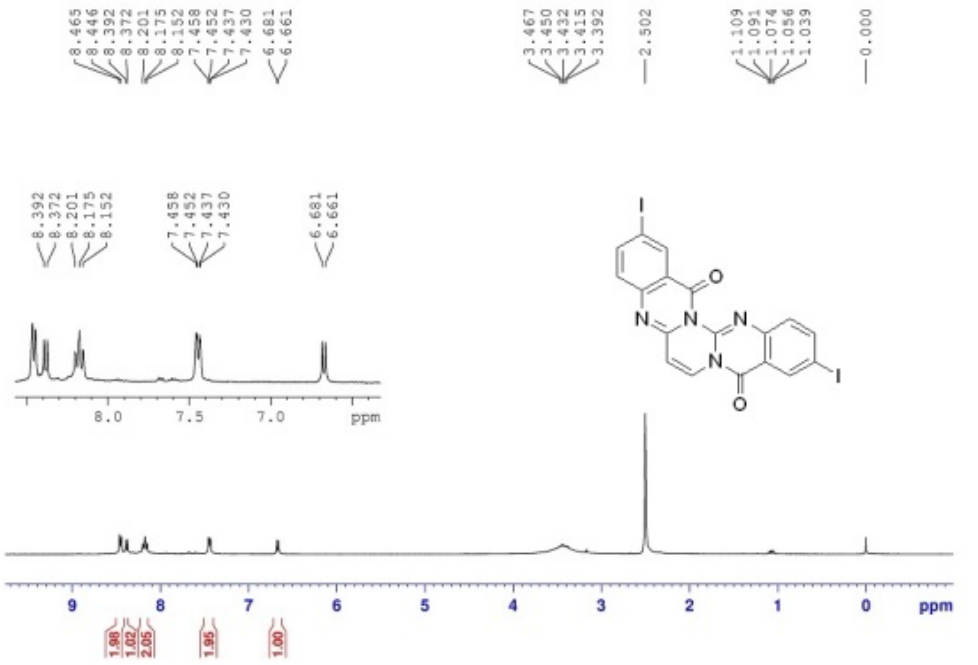
6n


8.396
8.376
8.281
8.277
8.261
8.058
8.053
8.031
8.009
7.616
7.612
7.595
6.696
6.676
3.392
2.502
0.000
Br
O
N
N
N
N
Br
O
8.5
8.0
7.5
7.0
ppm
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.92
2.12
1.95
0.96

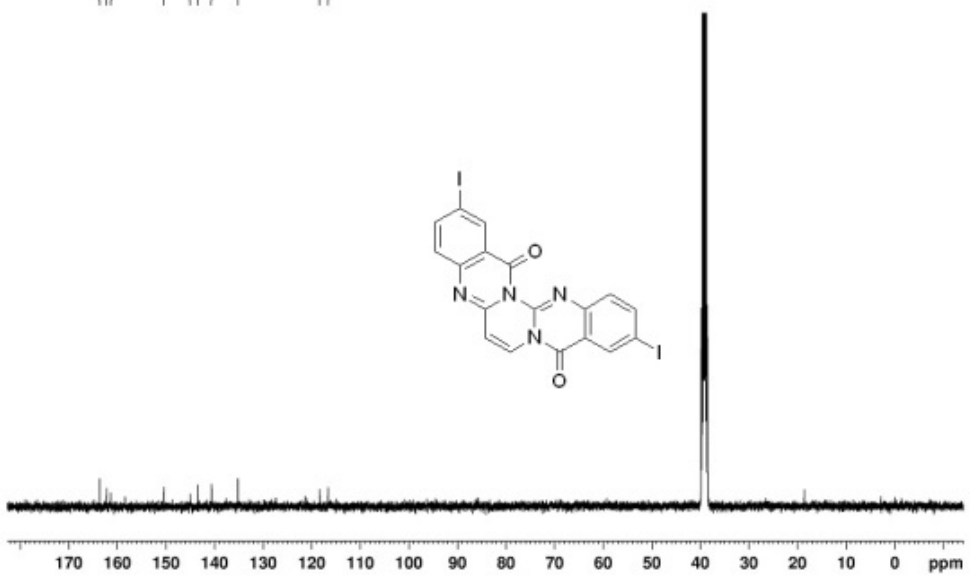

20141014-2 13C
163.468
162.241
150.452
140.500
137.974
129.687
129.309
118.333
116.568
114.366
Br
O
N
N
N
N
Br
O
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

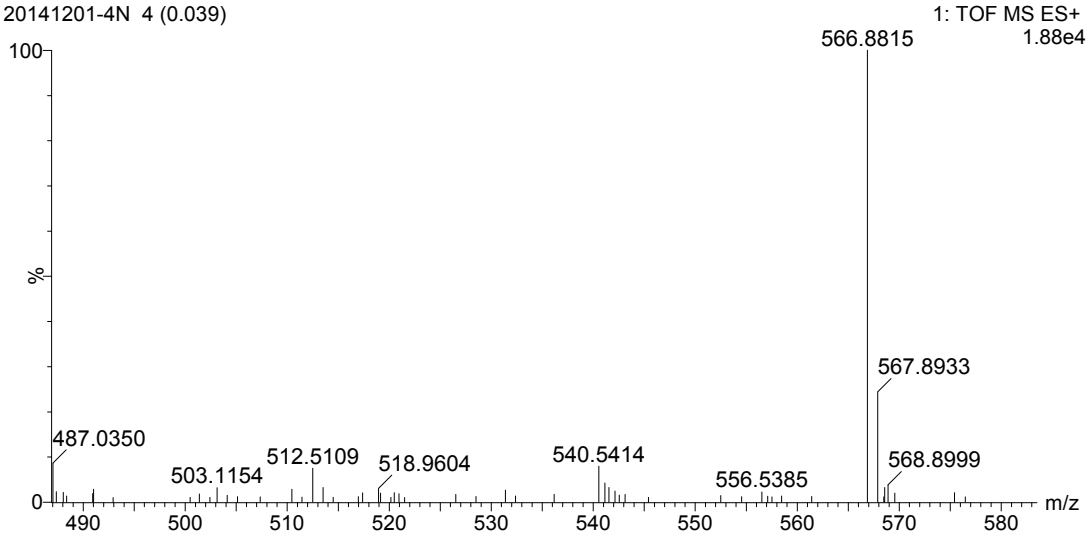

20141201-4M 16 (0.101)
1: TOF MS ES+
470.9100 2.31e4
100
%
0
471.9198
457.3653
458.4260
461.9370
463.9348
466.4249
468.4266
470.4438
m/z
456 457 458 459 460 461 462 463 464 465 466 467 468 469 470 471 472

6o

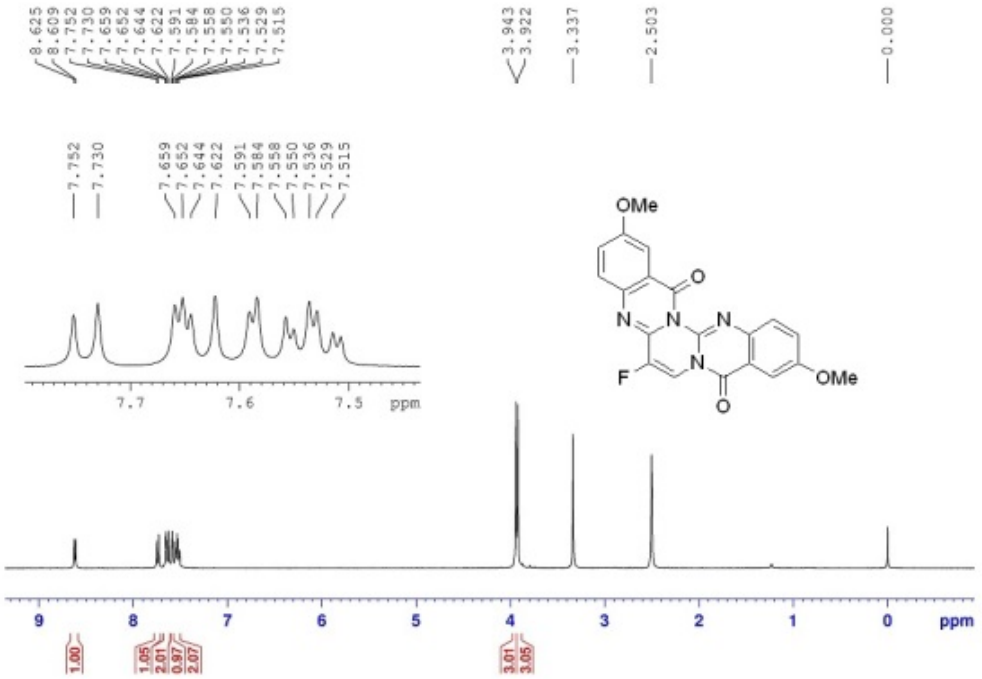


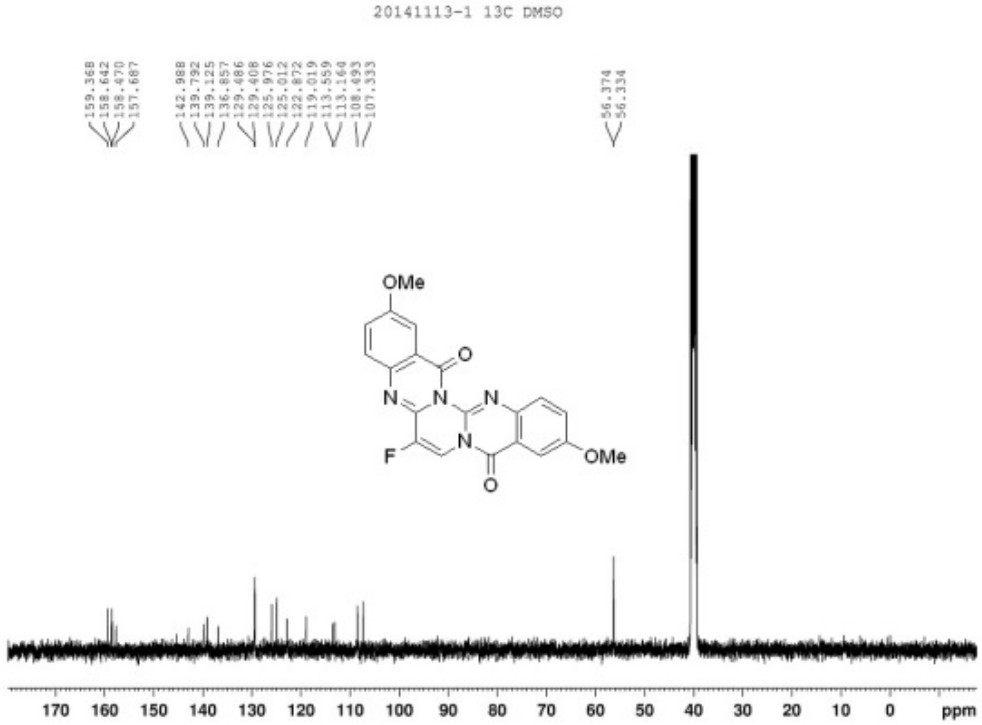
20141014-3 13C



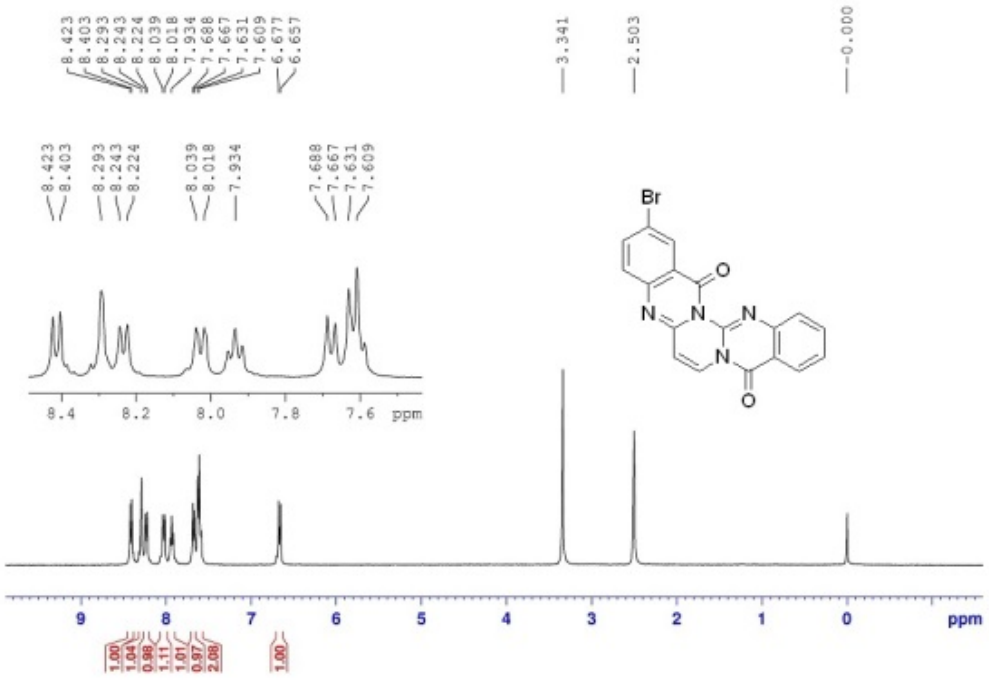

20141201-4N 4 (0.039)
1: TOF MS ES+
1.88e4
566.8815
567.8933
568.8999
487.0350
503.1154
512.5109
518.9604
540.5414
556.5385
100
%
0
m/z
490
500
510
520
530
540
550
560
570
580

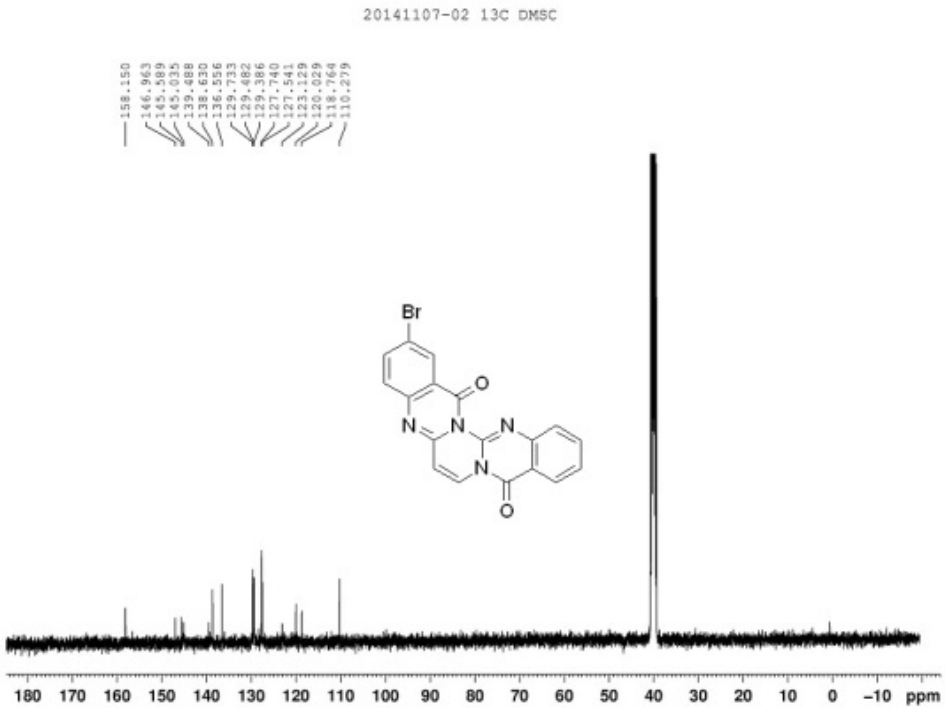
6p

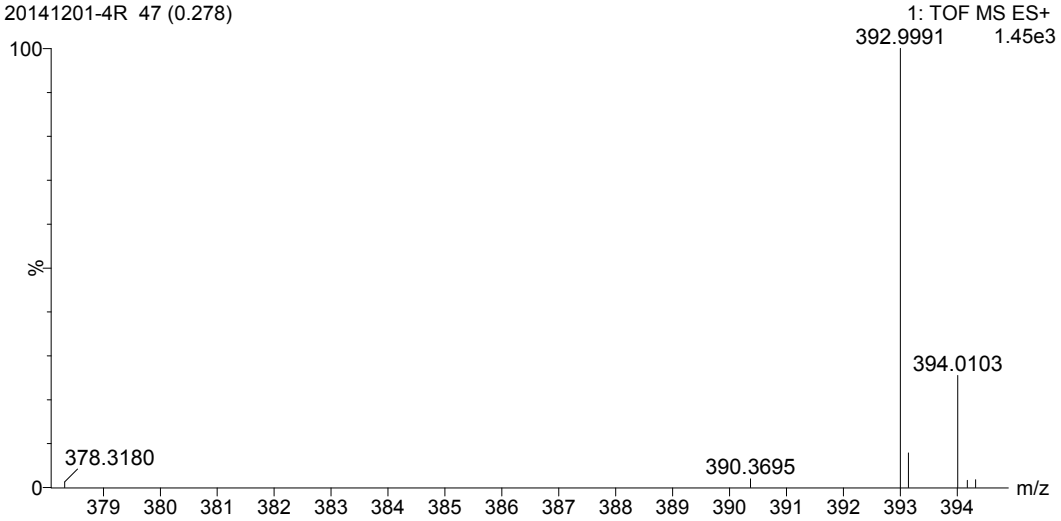

8.625
8.609
7.752
7.730
7.659
7.652
7.644
7.622
7.591
7.584
7.558
7.550
7.536
7.529
7.515
3.943
3.922
3.337
2.503
0.000
OMe
OMe
F
7.7
7.6
7.5
ppm
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.05
2.01
0.97
2.07
3.01
3.05


20141113-1 13C DMSO
159.368
158.642
158.470
157.687
142.988
139.792
139.125
136.857
129.486
129.408
125.976
125.012
122.872
119.019
113.559
113.160
108.493
107.333
56.374
56.334
OMe
O
N
N
N
N
F
O
OMe
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

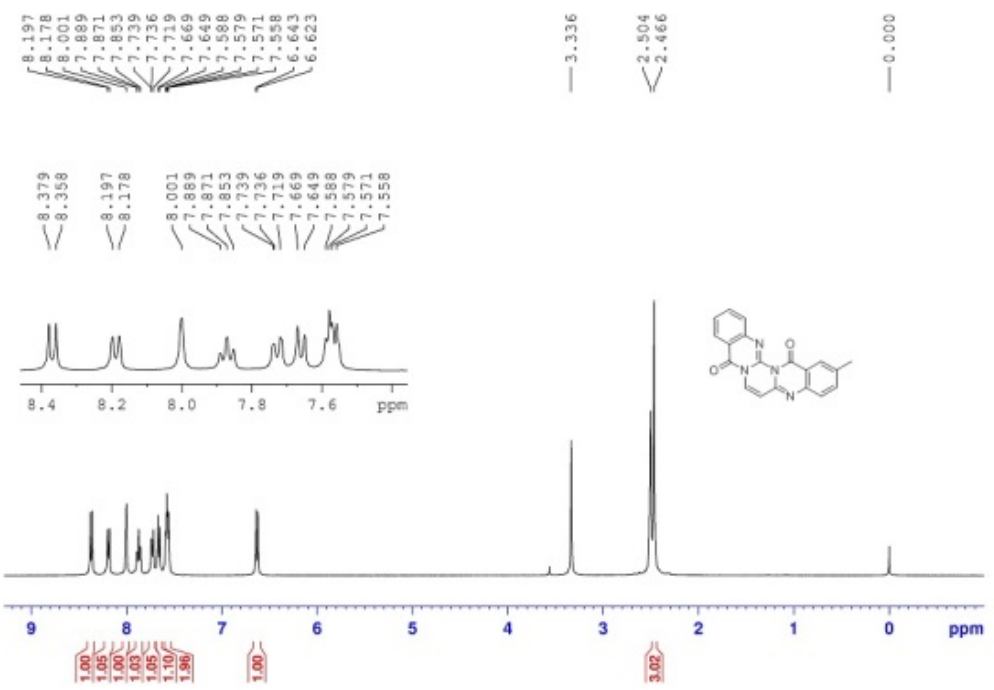
6qa

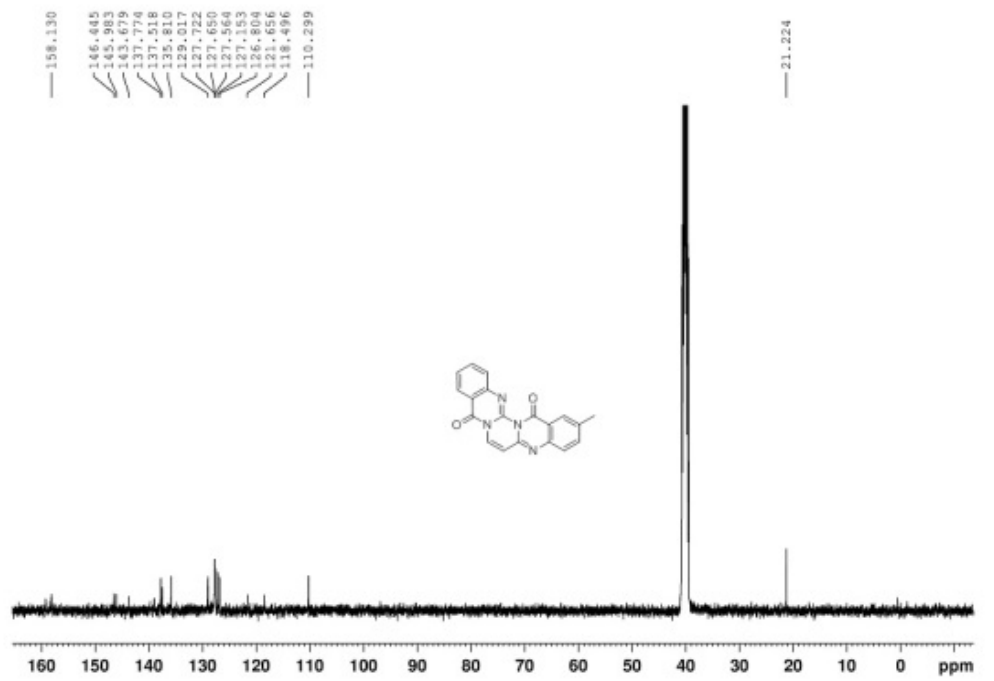

8.423
8.403
8.293
8.243
8.224
8.039
8.018
7.934
7.688
7.667
7.631
7.609
6.677
6.657
3.341
2.503
0.000
Br
O
N
N
N
N
O
8.4 8.2 8.0 7.8 7.6 ppm
9 8 7 6 5 4 3 2 1 0 ppm
1.00
1.04
0.98
1.11
1.01
0.97
2.08
1.00

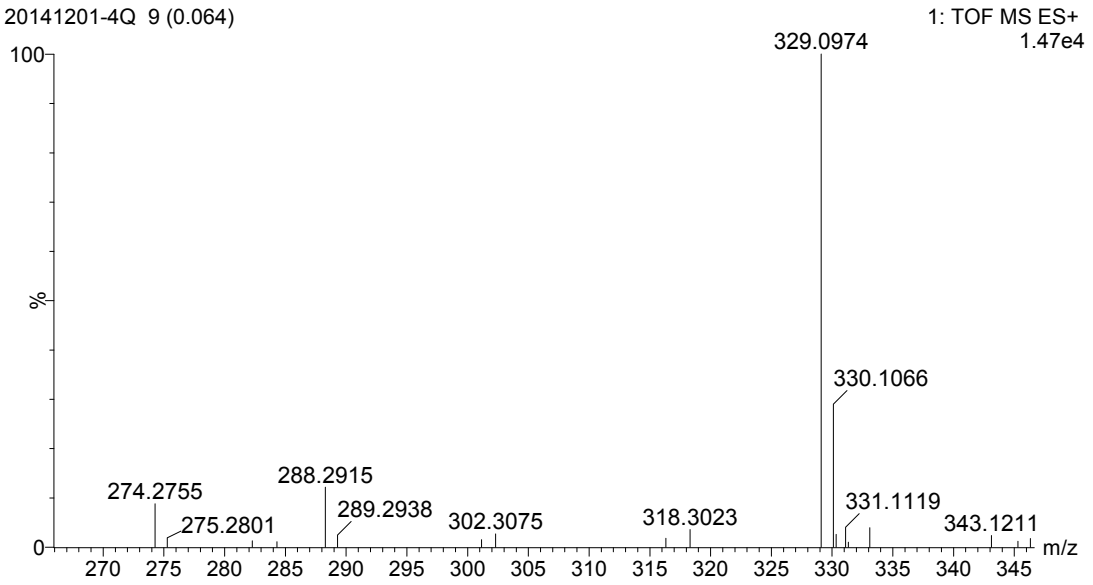

20141107-02 13C DMSC
158.150
146.963
145.589
145.035
139.488
138.630
136.556
129.733
129.482
129.386
127.740
121.541
123.129
120.029
118.764
110.279
Br
O
N
N
N
N
O
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 ppm

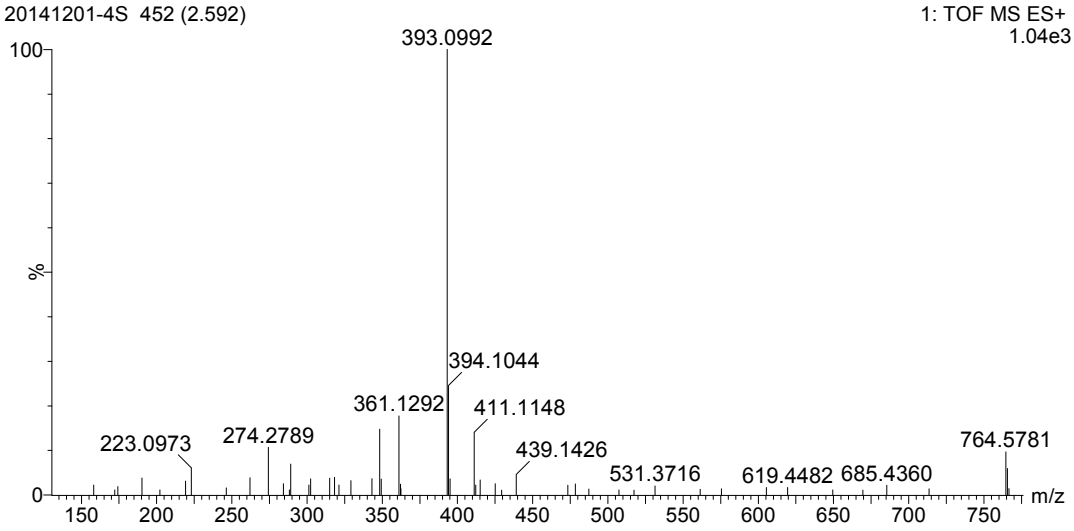

20141201-4R 47 (0.278)
1: TOF MS ES+
392.9991 1.45e3
100
%
0
394.0103
378.3180
390.3695
379 380 381 382 383 384 385 386 387 388 389 390 391 392 393 394
m/z

6r

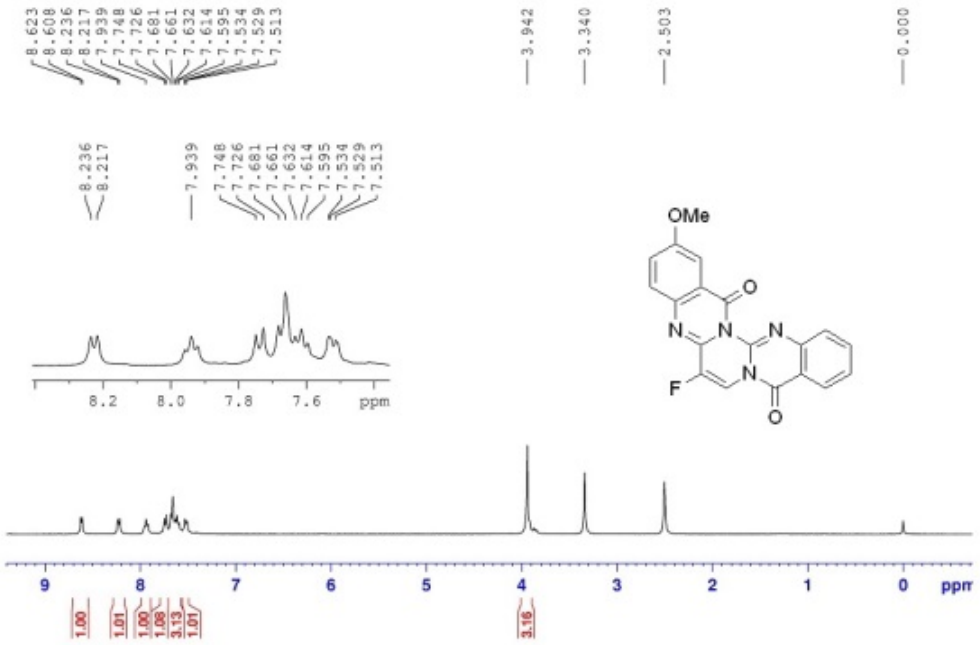

8.197
8.178
8.001
7.889
7.871
7.853
7.739
7.736
7.719
7.669
7.649
7.588
7.579
7.571
7.558
6.643
6.623
3.336
2.504
2.466
0.000
8.379
8.358
8.197
8.178
8.001
7.889
7.871
7.853
7.739
7.736
7.719
7.669
7.649
7.588
7.579
7.571
7.558
8.4
8.2
8.0
7.8
7.6
ppm
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.05
1.00
1.03
1.05
1.10
1.96
1.00
3.02


158.130
146.445
145.983
143.679
137.774
137.518
135.810
129.017
127.722
127.650
127.564
127.153
126.804
121.656
118.496
110.299
21.224
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

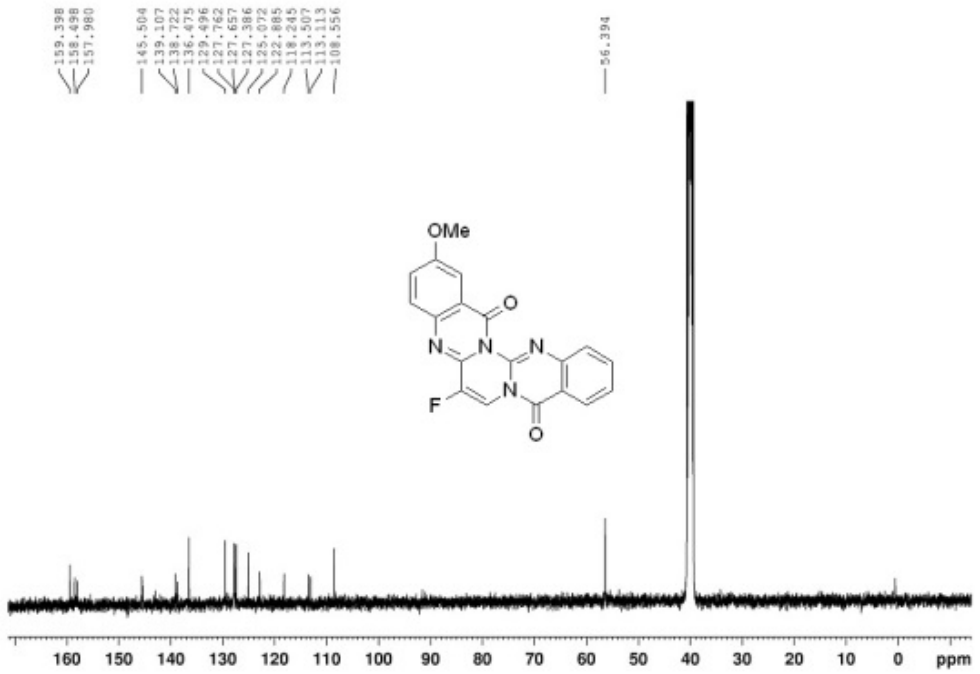

20141201-4Q 9 (0.064)
1: TOF MS ES+
1.47e4
329.0974
100
%
330.1066
274.2755
288.2915
289.2938
275.2801
302.3075
318.3023
331.1119
343.1211
0
m/z
270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345

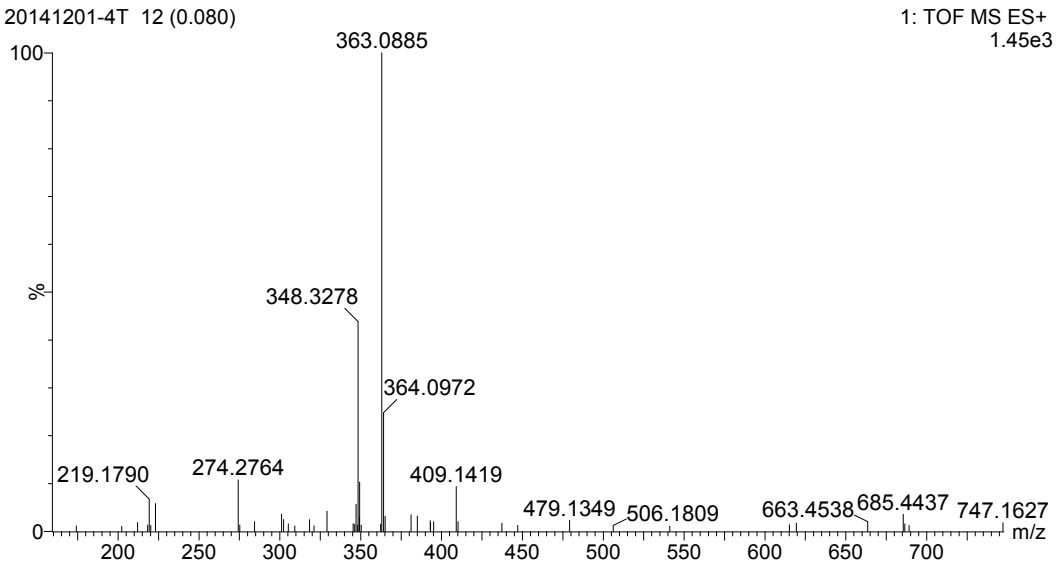

20141201-4S 452 (2.592)
1: TOF MS ES+
1.04e3
393.0992
100
%
394.1044
361.1292
411.1148
223.0973
274.2789
439.1426
764.5781
531.3716
619.4482
685.4360
0
m/z
150 200 250 300 350 400 450 500 550 600 650 700 750

6s

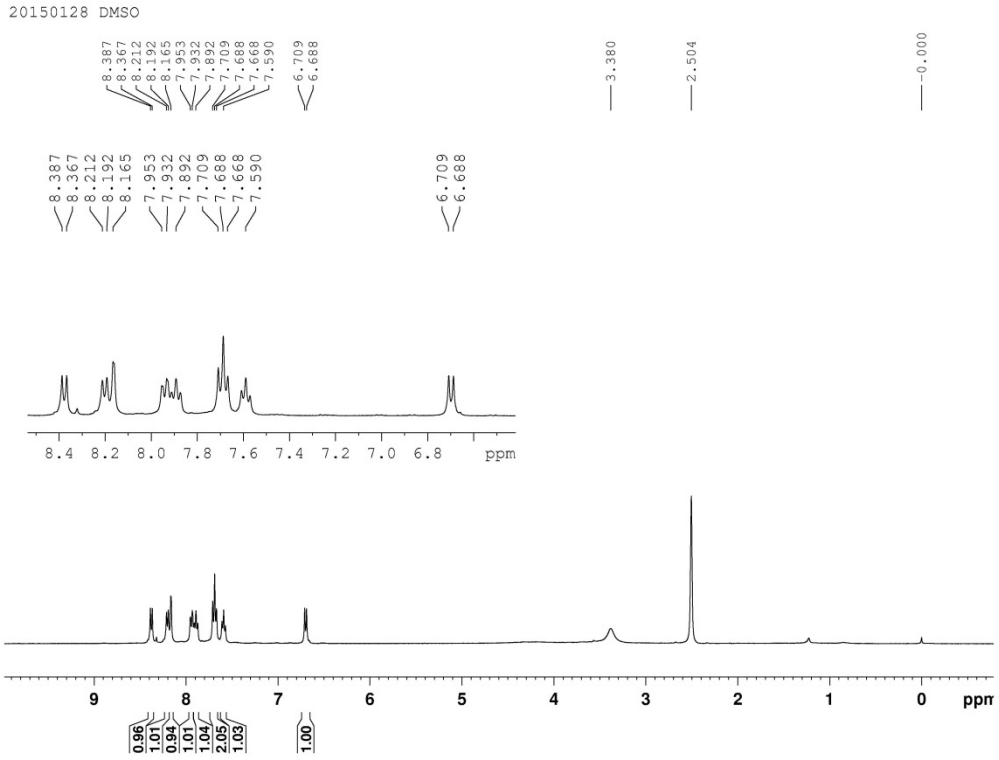


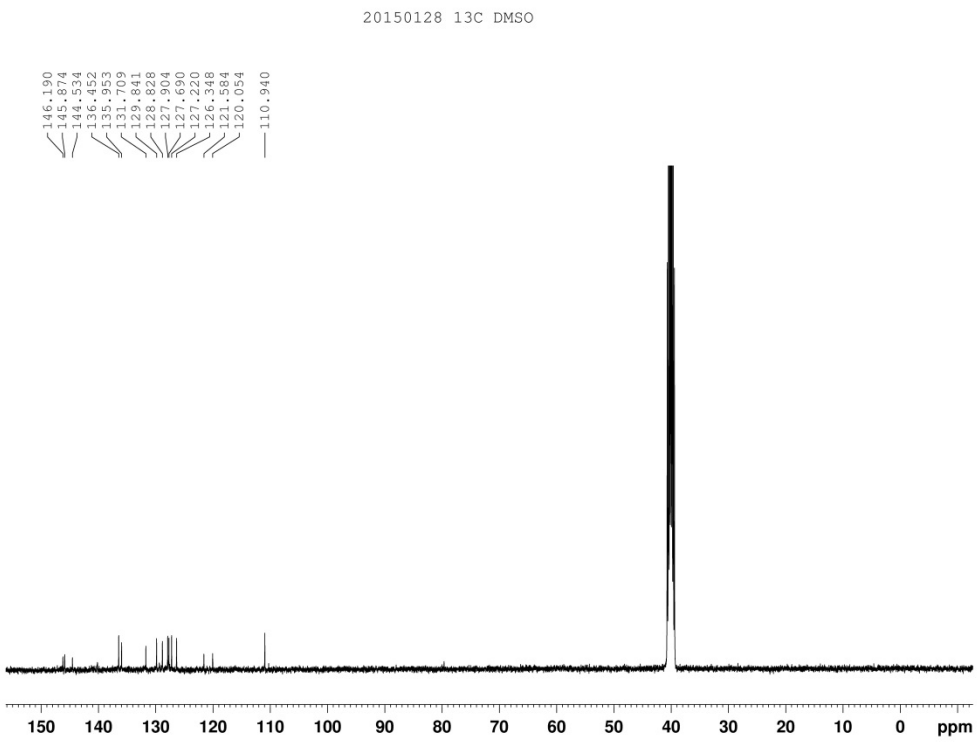
20141114 13C DMSO

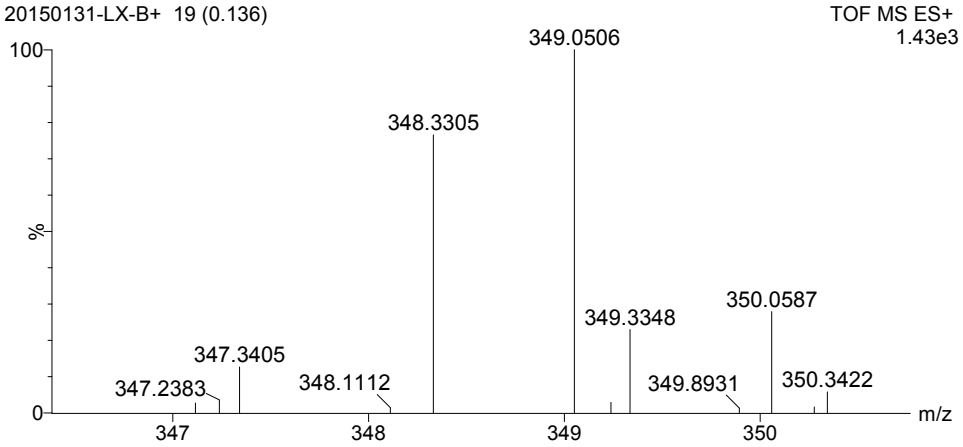



20141201-4T 12 (0.080)
1: TOF MS ES+
1.45e3
363.0885
348.3278
364.0972
219.1790
274.2764
409.1419
479.1349
506.1809
663.4538
685.4437
747.1627
m/z

6t


20150128 DMSO
8.387
8.367
8.212
8.192
8.165
7.953
7.932
7.892
7.709
7.688
7.668
7.590
6.709
6.688
3.380
2.504
0.000
ppm
0.96
1.01
0.94
1.01
1.04
2.05
1.03
1.00


20150128 13C DMSO
146.190
145.874
144.534
136.452
135.953
131.709
129.841
128.828
127.904
127.690
127.220
126.348
121.584
120.054
110.940
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


20150131-LX-B+ 19 (0.136)
TOF MS ES+
1.43e3
100
%
0
349.0506
348.3305
350.0587
349.3348
347.3405
347.2383
348.1112
349.8931
350.3422
m/z
347
348
349
350