Supporting Information

Acoustic Droplet Ejection Enabled Automated Reaction Scouting

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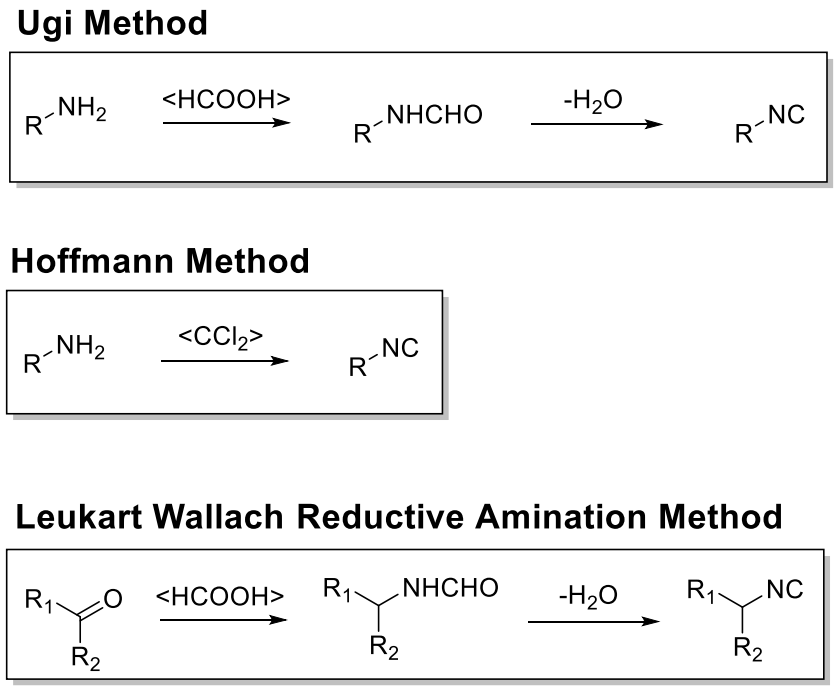
1. General information

1.1. Materials and methods

All reagents and solvents were purchased from commercial suppliers and used without any purification unless otherwise noted. All isocyanides were prepared in house by either performing the Ugi,[1-4] Hoffman[5,6] or our recently described Leukart-Wallach reductive amination procedure[7] (Scheme S1).



Scheme S1. Isocyanide Syntheses.

Other reagents were purchased from Sigma Aldrich, ABCR, Acros and AK Scientific and were used without further purification. Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker Avance 500 spectrometer (^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz)). Chemical shifts for ^{1}H NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Chemical shifts for ^{13}C NMR reported in ppm relative to the solvent peak. Flash chromatography was performed using RediSep R_f Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230-400 mesh). Electrospray ionization mass spectra (ESI-MS) were recorded on a Waters Investigator Semi-prep 15 SFC-MS instrument. High resolution mass spectra were recorded using an LTQ-Orbitrap-XL (Thermo Fisher Scientific; ESI^+ mode) at a resolution of 60000@m/z400.

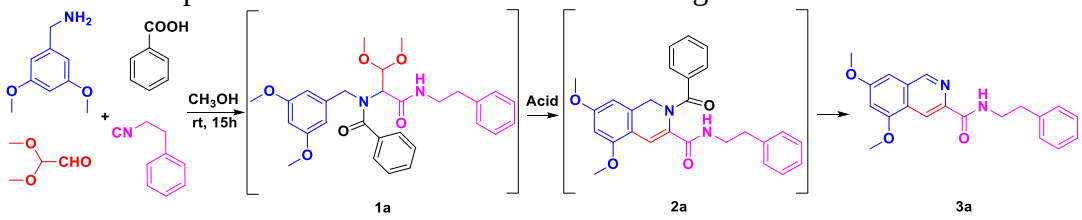
Analytical chemicals and reagents: MeOH (technical grade), CH_3CN (HPLC gradient grade), dioxane (99+% extra pure, stabilized), ethylene glycol (99+% extra pure) and fuming HCl (37%, for analysis). Formic acid (≥98.0%), acetic acid (≥99.8%), trifluoroacetic acid (≥99.0%), methanesulfonic acid (≥99.0%), benzoic acid (≥99.5%), 2,2-dimethoxyacetaldehyde (60 wt. % in H_2O), 3,4,5-trimethoxybenzylamine (98%), 3,4-dimethoxybenzylamine (97%), piperonylamine (97%), 2,3-dimethoxybenzylamine (99%), 2,5-dimethoxybenzylamine (97%).

2. Optimization of the novel isoquinoline reaction

In a model reaction, (3,5-dimethoxyphenyl)methane amine (1 mmol), 2,2-dimethoxy acetaldehyde (1 mmol), benzoic acid (1 mmol) and phenylethyl isocyanide (1 mmol) were stirred at room temperature in MeOH (1 M) for 15 h. Upon completion (TLC control), solvent was removed under vacuum. The Ugi adduct **1a** was directly used without any purification in the acid-catalyzed cyclisation/oxidation reaction.

In order to optimize the cyclisation/oxidation reaction, various acidic conditions (1 mL) were screened (Table S1). The desired product **3a** was formed in 68% yield in the presence of 37% $HCl_{(aq)}$ solution in dioxane (1 mL, 1:1, v/v) as solvent at room temperature (Table S1, entry 10).

Table S1. Optimization of reaction conditions for Ugi/Schlittler-Müller reaction.



Entry	Solvent	Isolated yield (%)
1	HCOOH	0
2	CH_3COOH	0
3	CF_3COOH	0
4	CH_3SO_3H (10 eq)/ CH_3CN	0
5	CH_3SO_3H	0
6	CH_3COOH/conc. H_2SO_4 (2:1, v/v)	33
7	CH_3COOH/ conc. H_2SO_4 (1:1, v/v)	26
8	$HCl_{(aq)}$/ dioxane (1:4, v/v)	34
9	$HCl_{(aq)}$/ dioxane (1:2, v/v)	43
10	**$HCl_{(aq)}$/ dioxane (1:1, v/v)**	**68**
11	$HCl_{(aq)}$	52

3. General workflow for nanoscale synthesis

The general method typically follows the steps summarized in Table S2, with the implicit details for each step provided in the following text.

Table S2. General workflow.

No.	Step	Short Description
1	Stock solution preparation	Stock solutions were prepared at 0.5 M in ethylene glycol or 2-methoxy ethanol and sealed and kept at -20 °C.
2	Source plate preparation	The stock solutions were pipetted into the 384 well source plates.
3	Nanoscale synthesis	Sequence tables and methods were loaded into Echo 555 software and automatic transfer of the reagents started.
4	QC by SFC	384 Well synthesis plate was diluted with methanol and SFC-MS analytic performed with autosampler.

5	QC by TLC	384 Well synthesis plate was diluted with methanol and spotted onto silica TLC plates and eluted. The UV active spots were eluted and transferred into the Advion desktop MS.

4. Nanomole-scale chemical reactions

4.1. General materials

Stock solutions were prepared in glass flat bottom vials (Screening devices, Catalog#: 9920-812FBT, 2.0 mL (Topas) Plate) and they were kept at -20 °C.

Nanomole-scale chemistry was performed using Echo qualified 384-well polypropylene microplate (Labcyte, Catalog#: PP-0200, clear, flat bottom) according to the producers' manual.

384-Well source and destination plates were sealed by a sealing tape (Thermo Scientific, Catalog#: 232701, polyolefin acrylate) and were kept at -20 °C.

4.2. Instrumentation

The Echo 555 liquid handler (Labcyte) was used in order to transfer nL droplets of starting materials from the 384-well source plate to the 384-well destination plate.

4.3. Nanomole-scale automated chemistry

Stock solutions of aldehyde, acid, amines (A1-A7) and isocyanides (I1-I3, I6-I8, I10-16, I18, I19, I21, I28, I29, I31, I34, I35, I42-I44, I48, I50-I62) were prepared as 0.5 M ethylene glycole. Due to the insolubility of some isocyanides (I4, I5, I9, I17, I20, I22-I27, I30, I32, I33, I36-I41, I45-I47, I49) in ethylene glycole, their stock solutions were instead prepared as 0.5 M in 2-methoxyethanol.

The stock solutions were dispensed to a 384-well source plate using Eppendorf multi-channel pipettes. The Echo 555 was used to transfer 750 nL (375 nmol) of each starting material into the corresponding well in the destination plate. Labcyte Echo plate reformat software using custom mapping mode with the run protocol as defined by a pick list was used (Fig. S1B).

In order to generate a random library of products (N=384), a modified version of our previously reported program RandReactor was used.[8] The smiles files of the starting materials with the corresponding location in the source plate and mrv file of reaction were the input of the RandReactor program. The smiles file of the randomly generated products with their corresponding locations in the source and destination plate were the output of the RandReactor program. The smiles file was converted to a csv file which was the required format for Labcyte Echo plate reformat software (Fig. S1A).

Once the starting materials transfer was completed (~150 min), the destination plate was covered with the sealing film and was then placed for 15 h at 23 °C on an orbital shacker. Then, 10 μL of 37% $HCl_{(aq)}$/dioxane solution (1:1, v/v) was added to each well using a multichannel

pipettor and the plate was sealed and kept at 23 °C for another 12 h. Then the plate was dried from the solvent by applying a mild stream of nitrogen. The plates were sealed and stored at -20 °C for further processing. The structures of the products are shown in Fig. S2.

A

	Source Plate Name	Source Well	Destination Plate Name	Destination well	Transfer Volume
2	Sample Plate 1	H20	Destination 1	A1	750
3	Sample Plate 1	A1	Destination 1	A1	750
4	Sample Plate 1	A2	Destination 1	A1	750
5	Sample Plate 1	B14	Destination 1	A1	750
6	Sample Plate 1	F20	Destination 1	A2	750
7	Sample Plate 1	A1	Destination 1	A2	750
8	Sample Plate 1	A2	Destination 1	A2	750
9	Sample Plate 1	A17	Destination 1	A2	750
10	Sample Plate 1	H20	Destination 1	A3	750
11	Sample Plate 1	A1	Destination 1	A3	750
12	Sample Plate 1	A2	Destination 1	A3	750
13	Sample Plate 1	A17	Destination 1	A3	750
14	Sample Plate 1	G19	Destination 1	A4	750
15	Sample Plate 1	A1	Destination 1	A4	750
16	Sample Plate 1	A2	Destination 1	A4	750
17	Sample Plate 1	D16	Destination 1	A4	750
18	Sample Plate 1	F20	Destination 1	A5	750
19	Sample Plate 1	A1	Destination 1	A5	750
20	Sample Plate 1	A2	Destination 1	A5	750
21	Sample Plate 1	B14	Destination 1	A5	750
22	Sample Plate 1	G19	Destination 1	A6	750
23	Sample Plate 1	A1	Destination 1	A6	750

B

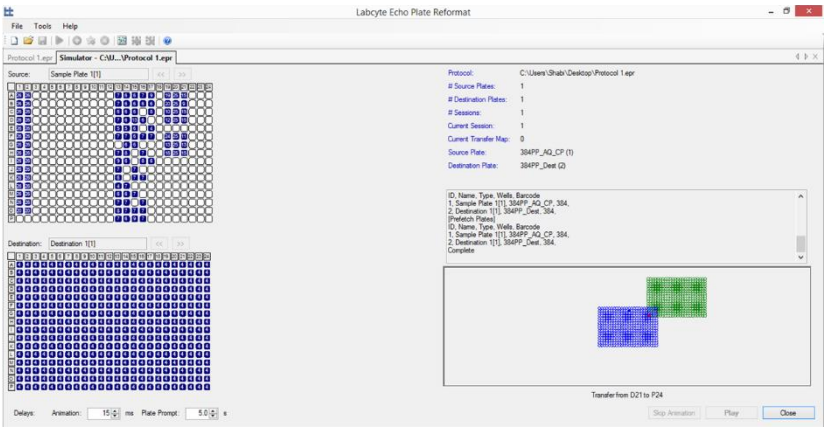


Fig. S1. A: Pick list in csv format required for Labcyte Echo plate reformat software; **B:** Labcyte Echo plate reformat software, showing on top the source plate and below the destination plate.

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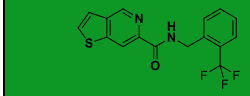
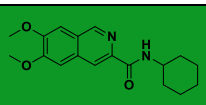
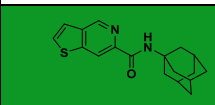
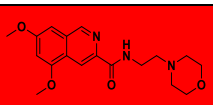
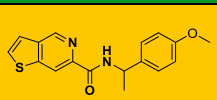
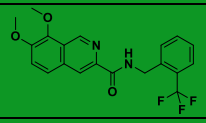
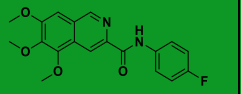
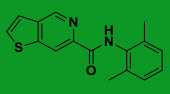
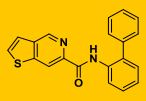
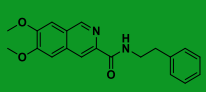
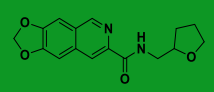
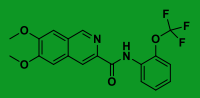
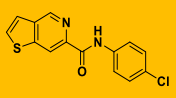
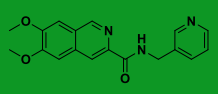
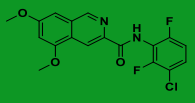
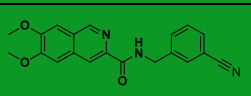
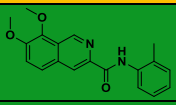
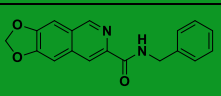
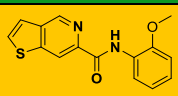
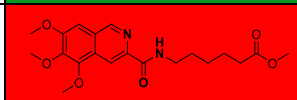
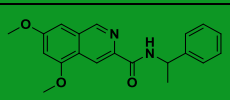
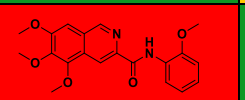
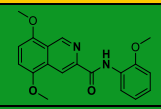
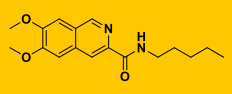
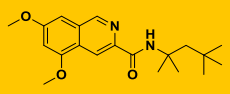
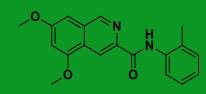
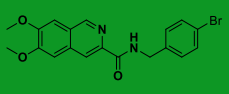
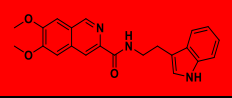
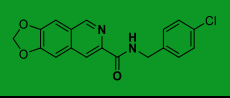
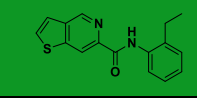
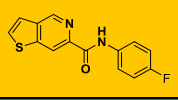
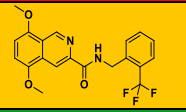
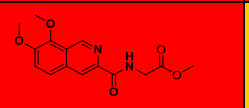
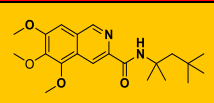
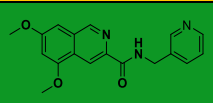
A				
B				
C				
D				
E				
F				
G				
H				
I				
J				
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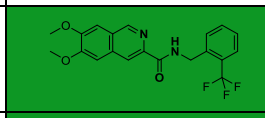
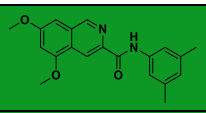
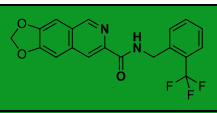
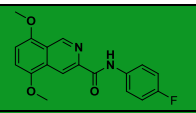
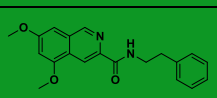
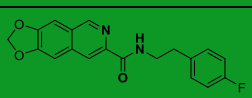
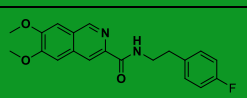
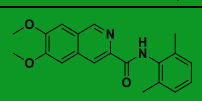
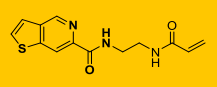
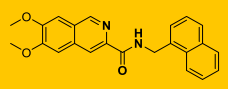
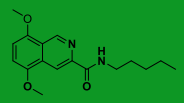
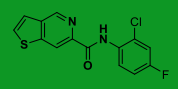
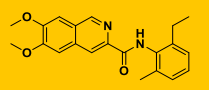
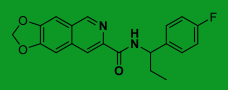
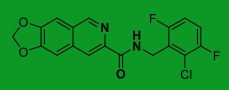
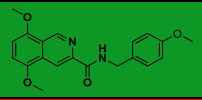
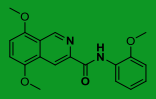
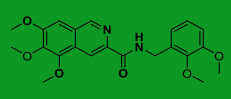
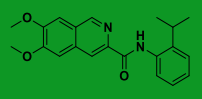
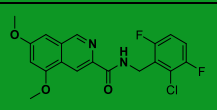
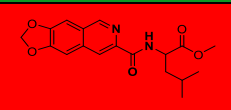
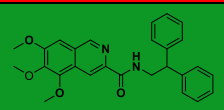
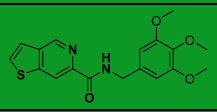
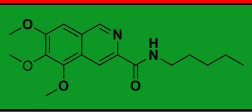
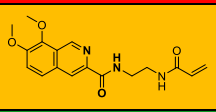
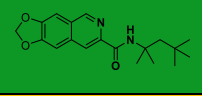
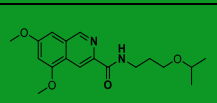
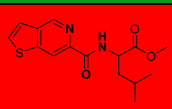
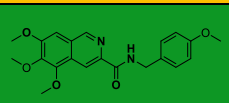
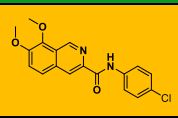
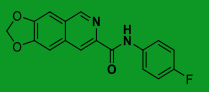
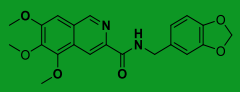
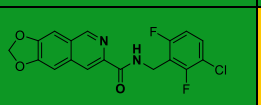
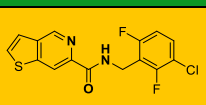
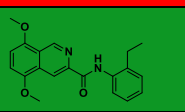
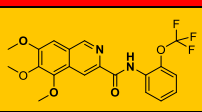
A				
B				
C				
D				
E				
F				
G				
H				
I				
J				
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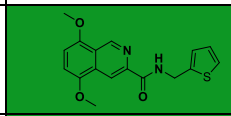
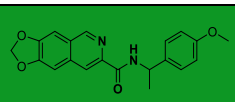
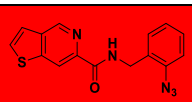
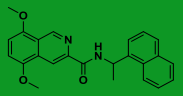
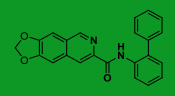
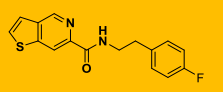
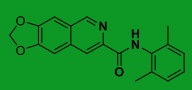
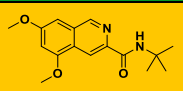
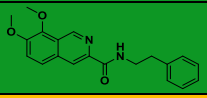
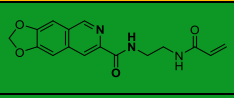
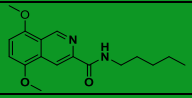
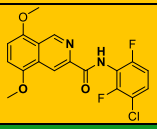
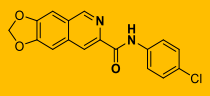
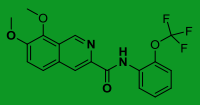
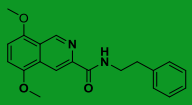
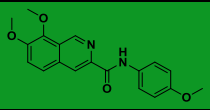
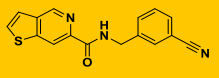
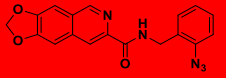
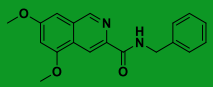
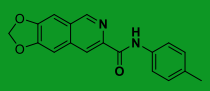
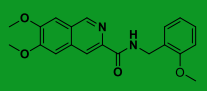
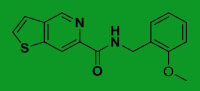
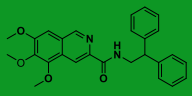
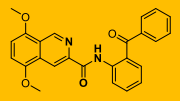
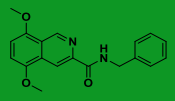
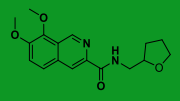
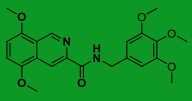
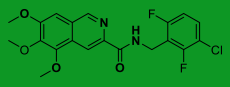
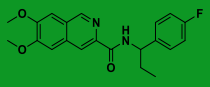
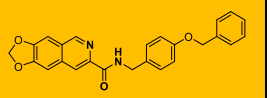
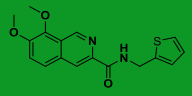
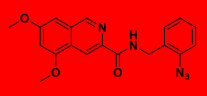
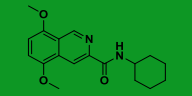
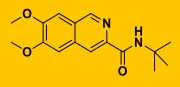
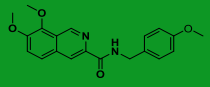
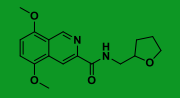
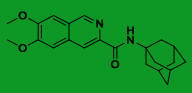
A				
B				
C				
D				
E				
F				
G				
H				
I				
J				
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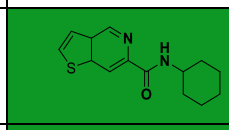
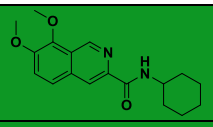
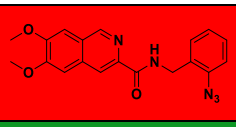
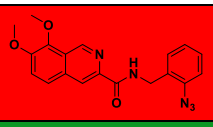
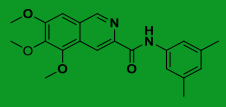
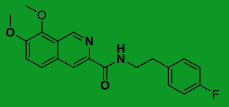
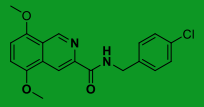
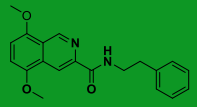
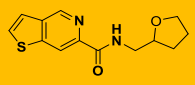
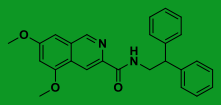
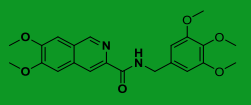
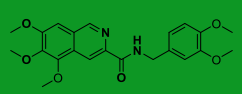
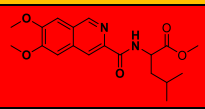
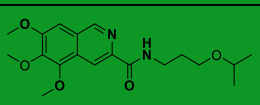
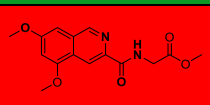
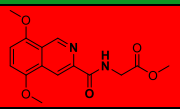
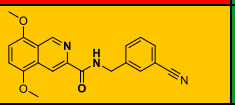
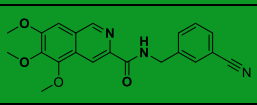
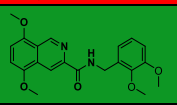
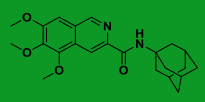
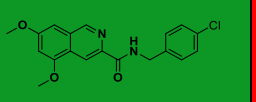
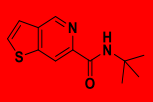
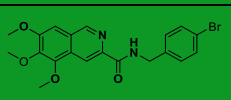
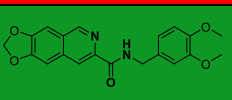
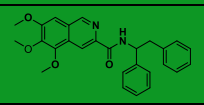
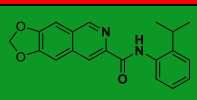
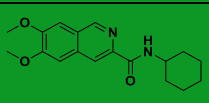
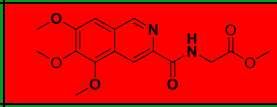
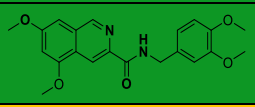
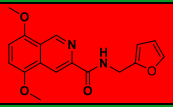
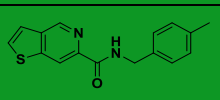
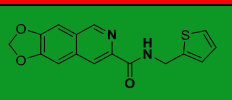
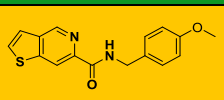
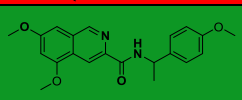
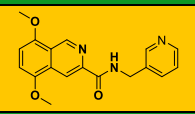
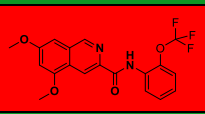
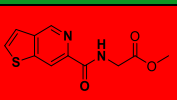
A				
B				
C				
D				
E				
F				
G				
H				
I				
J				
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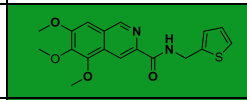
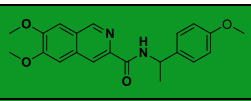
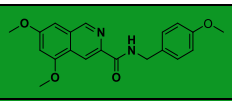
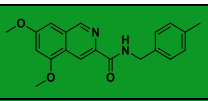
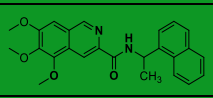
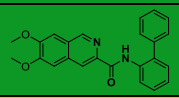
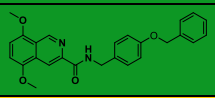
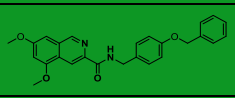
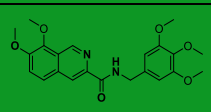
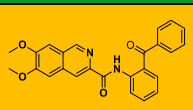
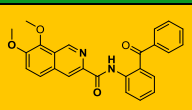
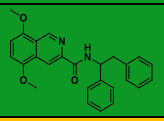
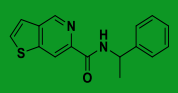
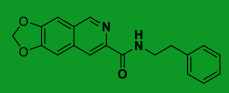
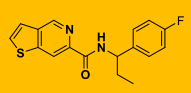
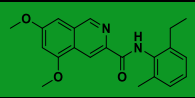
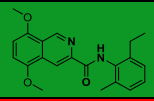
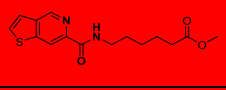
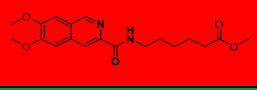
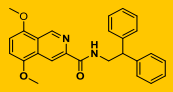
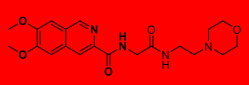
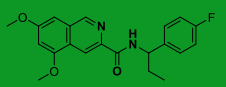
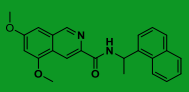
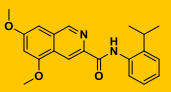
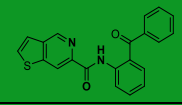
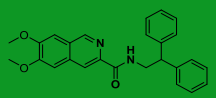
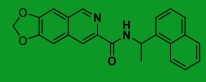
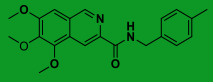
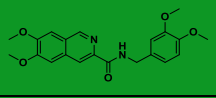
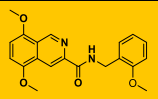
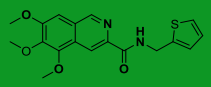
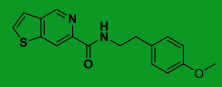
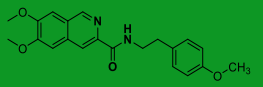
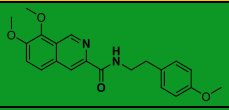
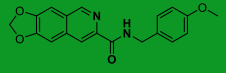
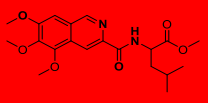
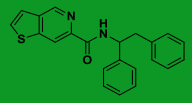
A				
B				
C				
D				
E				
F				
G				
H				
I				
J				
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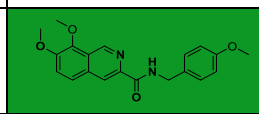
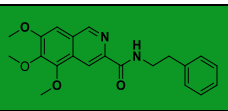
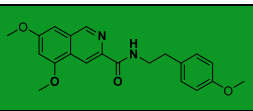
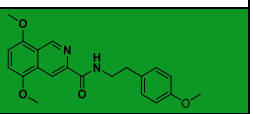
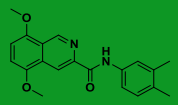
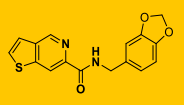
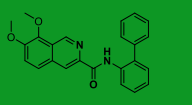
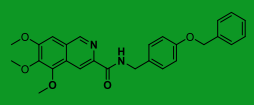
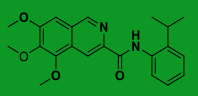
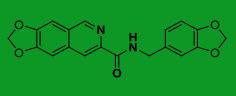
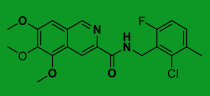
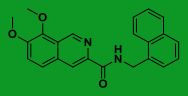
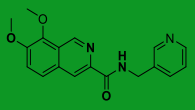
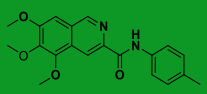
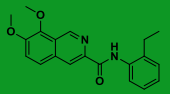
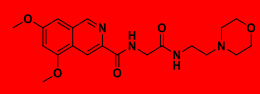
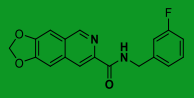
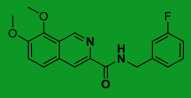
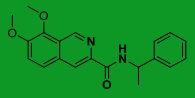
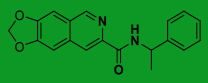
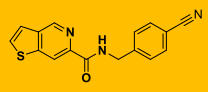
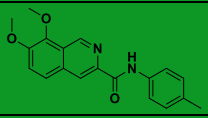
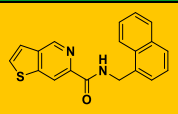
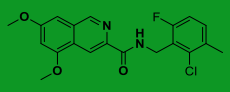
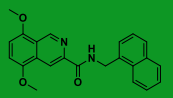
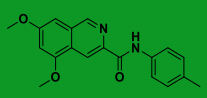
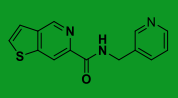
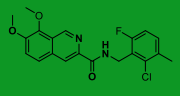
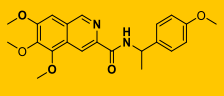
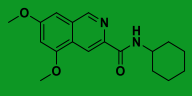
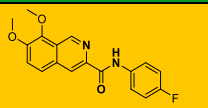
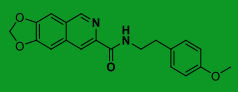
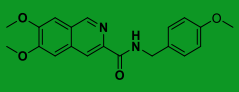
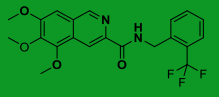
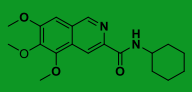
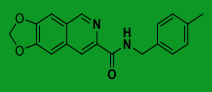
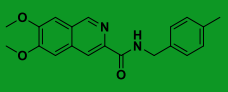
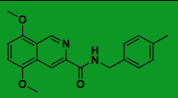
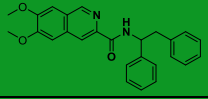
A				
B				
C				
D				
E				
F				
G				
H				
I				
J				
K				
L				
M				
N				
O				
P				

Fig. S2. Heat maps with product structures.

4.4. Quality control (QC)

The analytics of all wells was performed by two complementary methods, SFC-UV-MS and TLC-UV-MS.

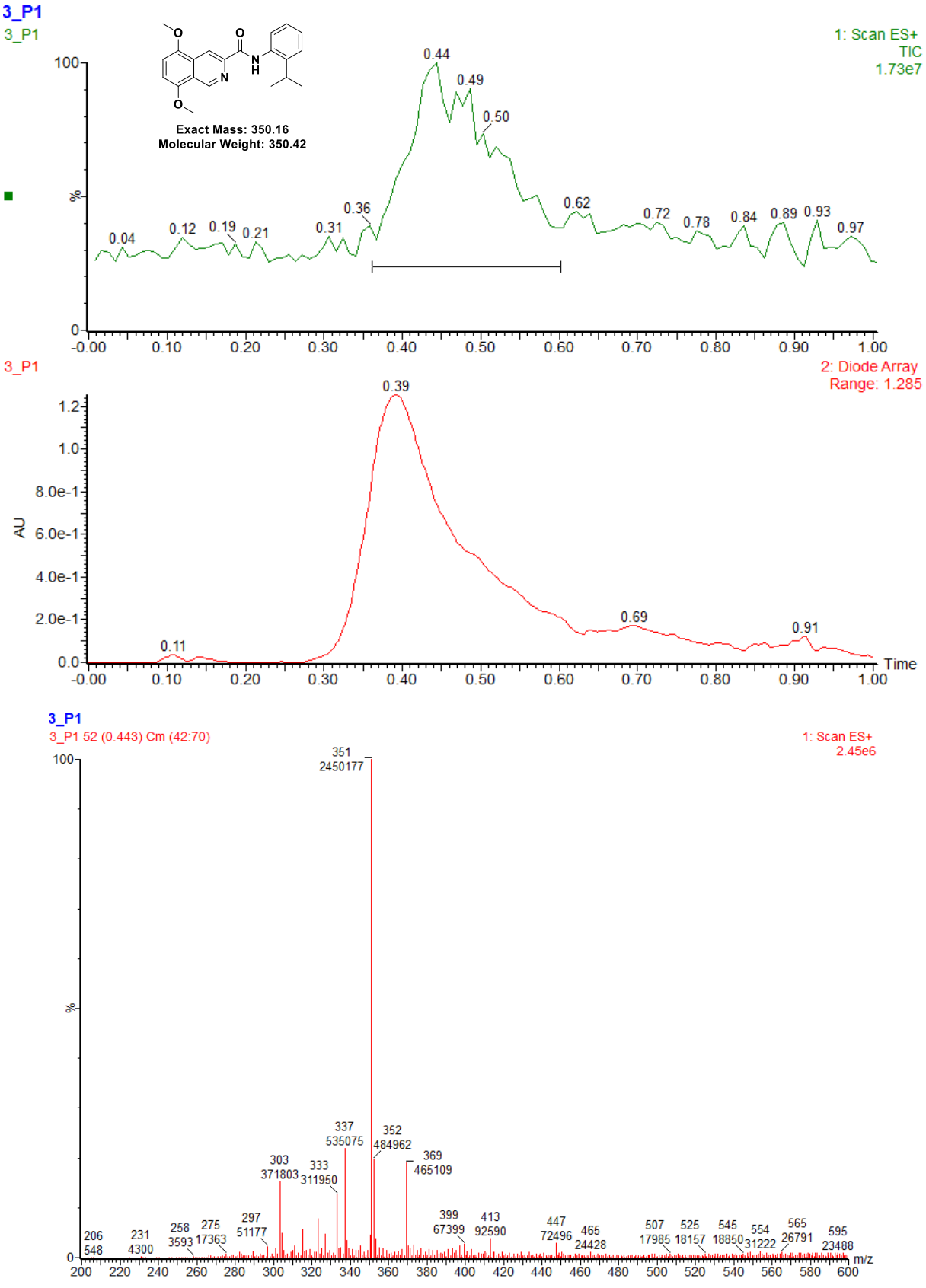
4.4.1. SFC-UV-MS analysis

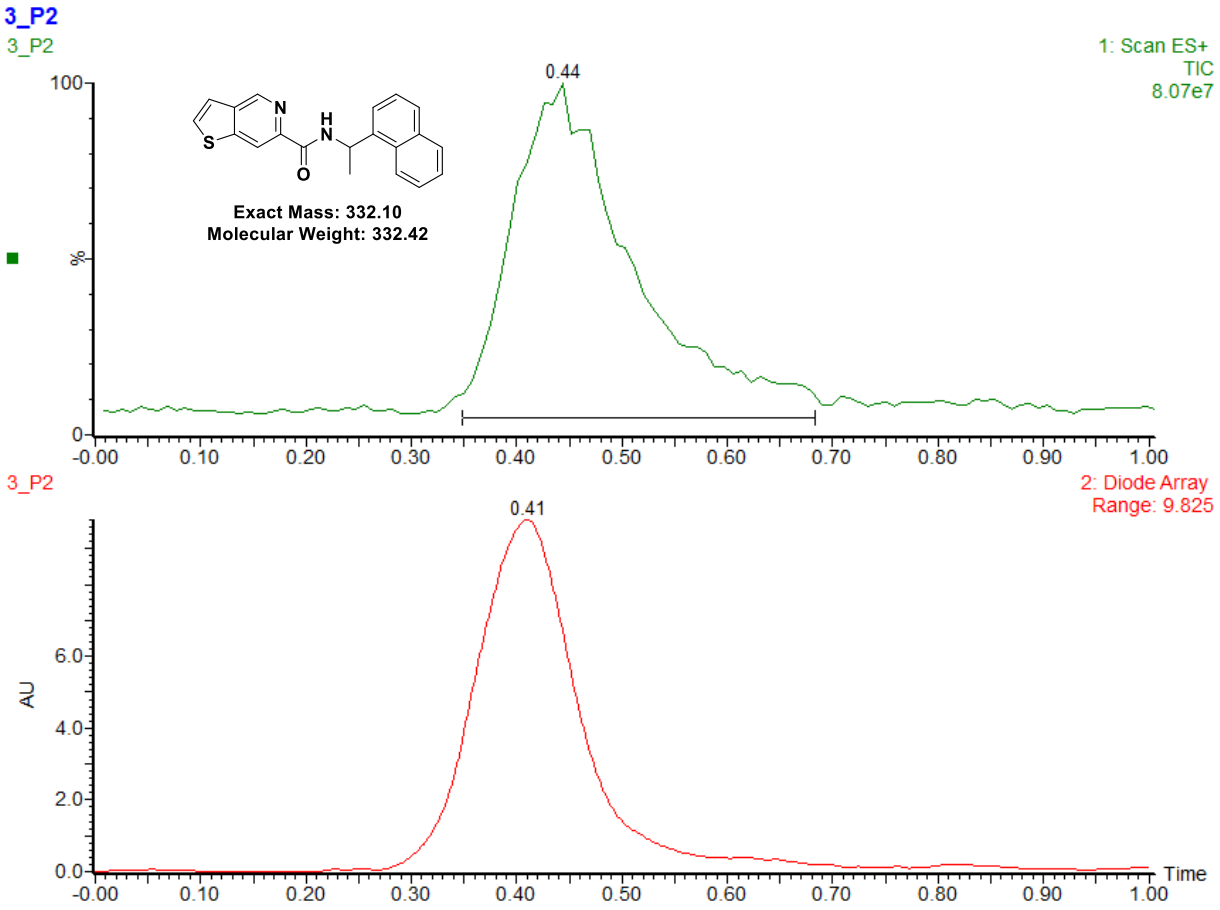
Mass spectra were measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI^+) on a Kromasil SFC-2.5-2EP (3.0 × 50 mm) column and MassLynx software.
Conditions; mobile phase: CO_2 with 35% MeOH (isocratic), run time: 1 min, flow rate: 4 mL/min, temperature: 40 °C, pressure: 120 bar.

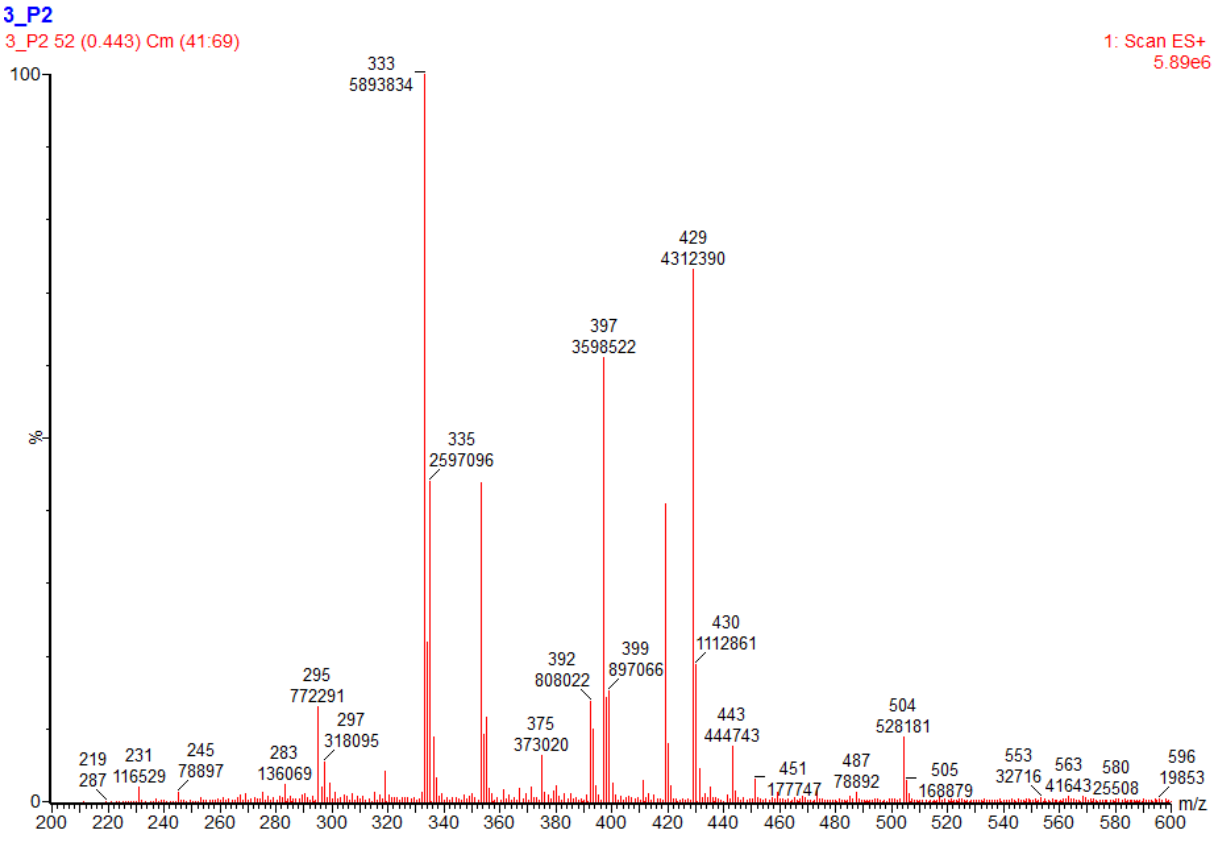
Each well of the destination plate was diluted with 100 µL MeOH and then the chromatographic analysis was done by SFC-UV-MS using an autosampler. A right-click and drag operation of the total ion current (TIC) spectrum generated a mass chromatogram for the selected range. If the peak corresponding to M+1 was the major peak, the well got a green designation and otherwise yellow. If the peak of M+1 was absent, the well got a red designation.

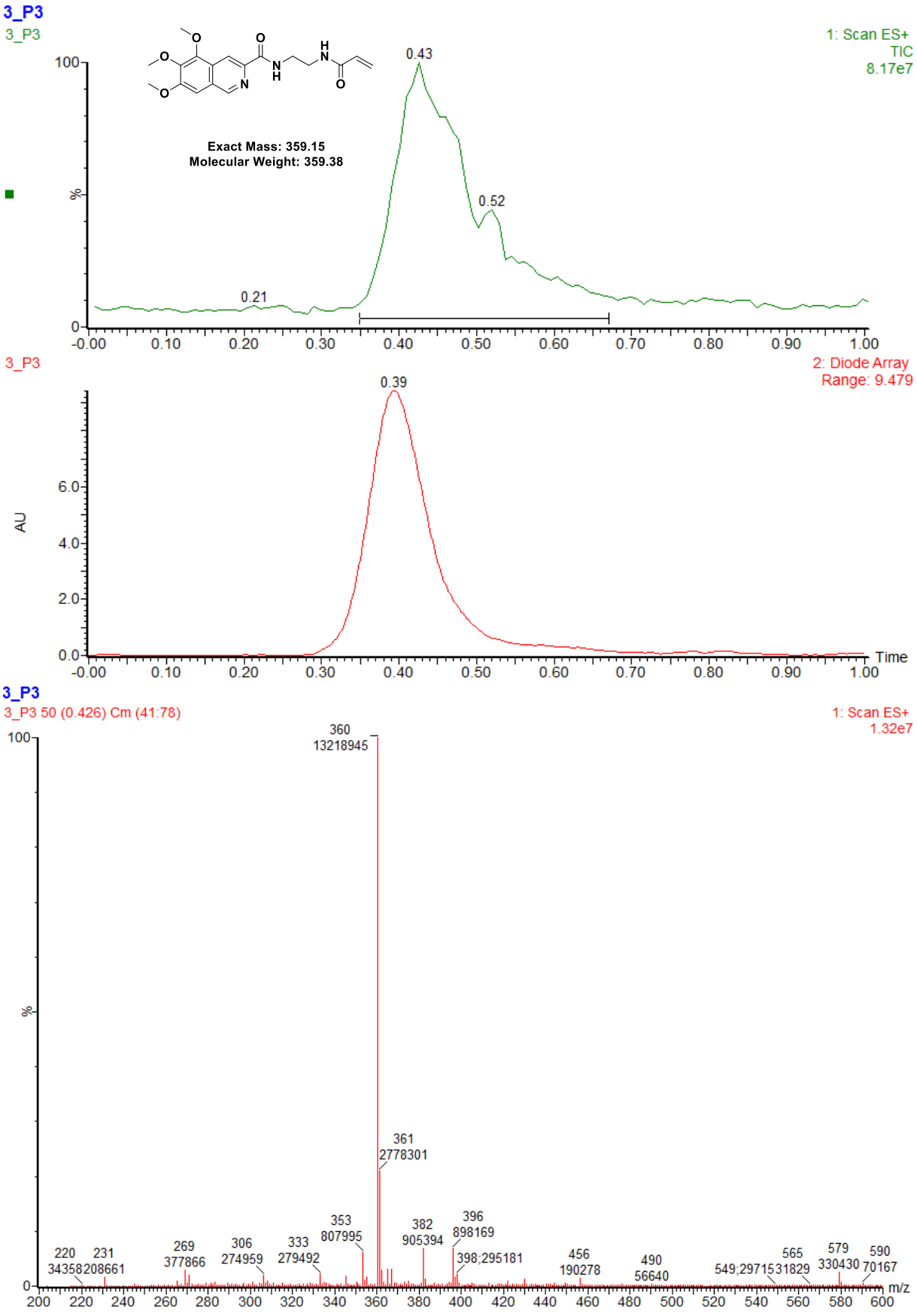
The SFC analytic of one well took ~1 min, resulting in an overall measuring time for the 384 well plate of less than one night.

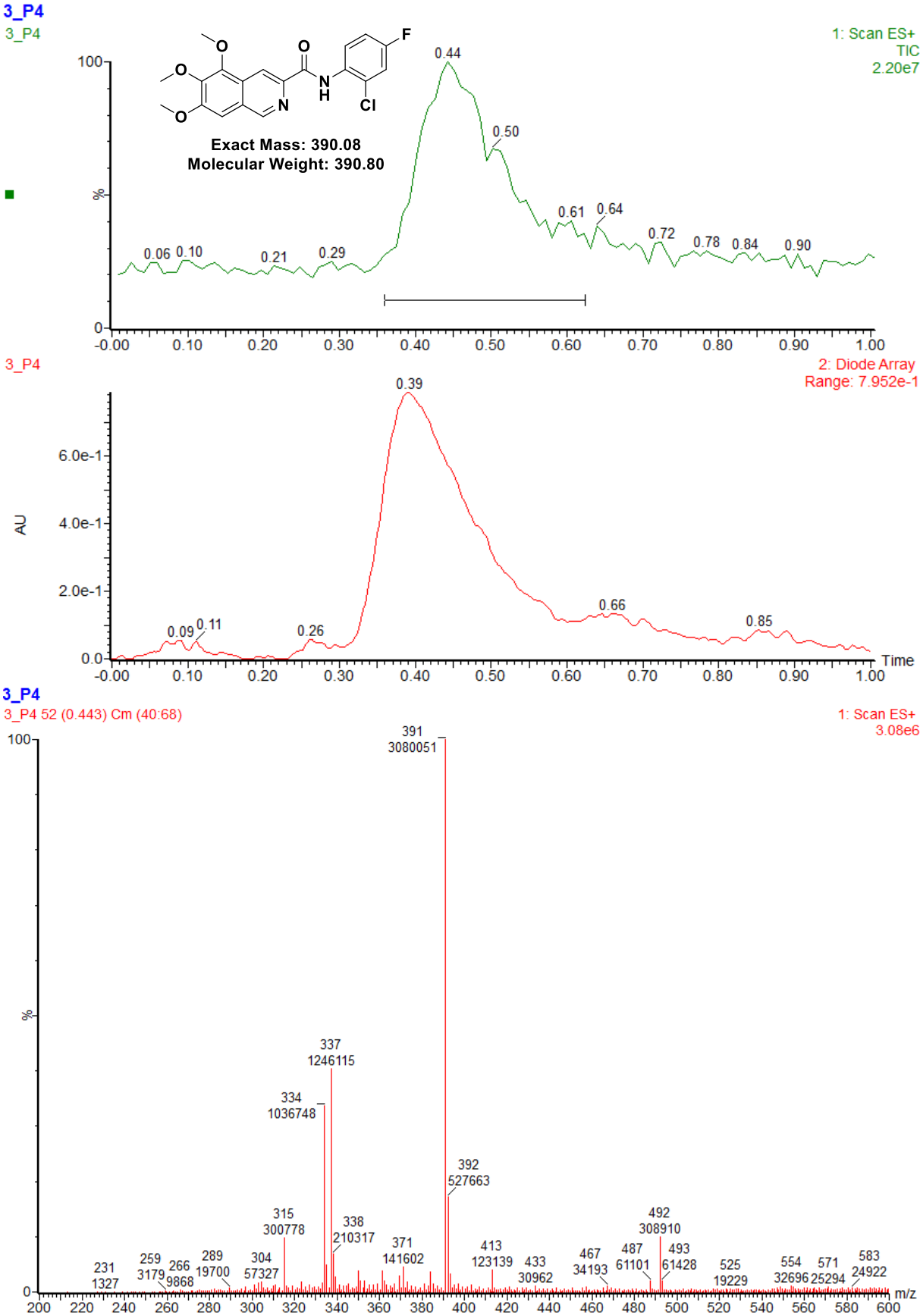
Examples of SFC-UV-MS analytics of the row P1-P24

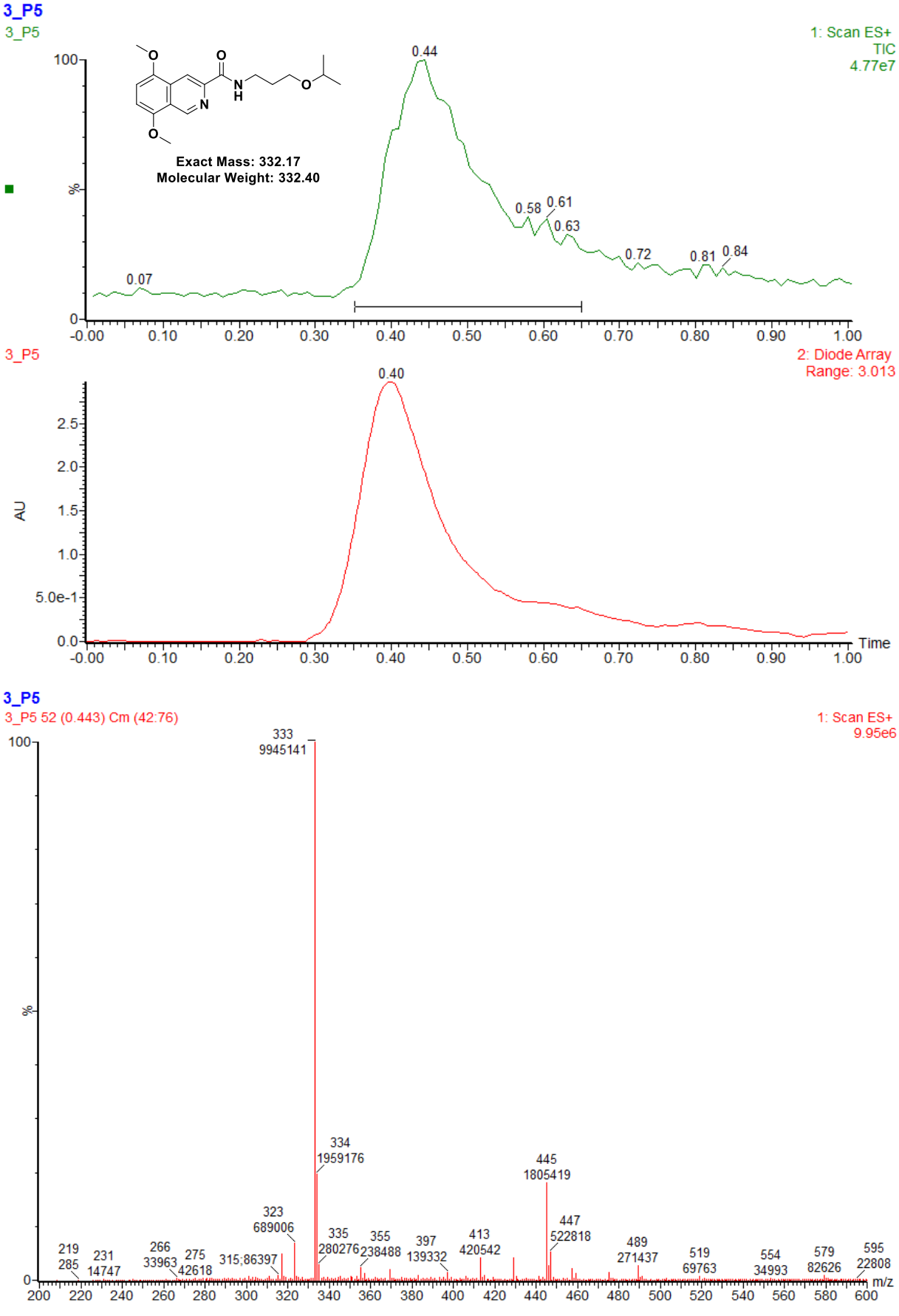


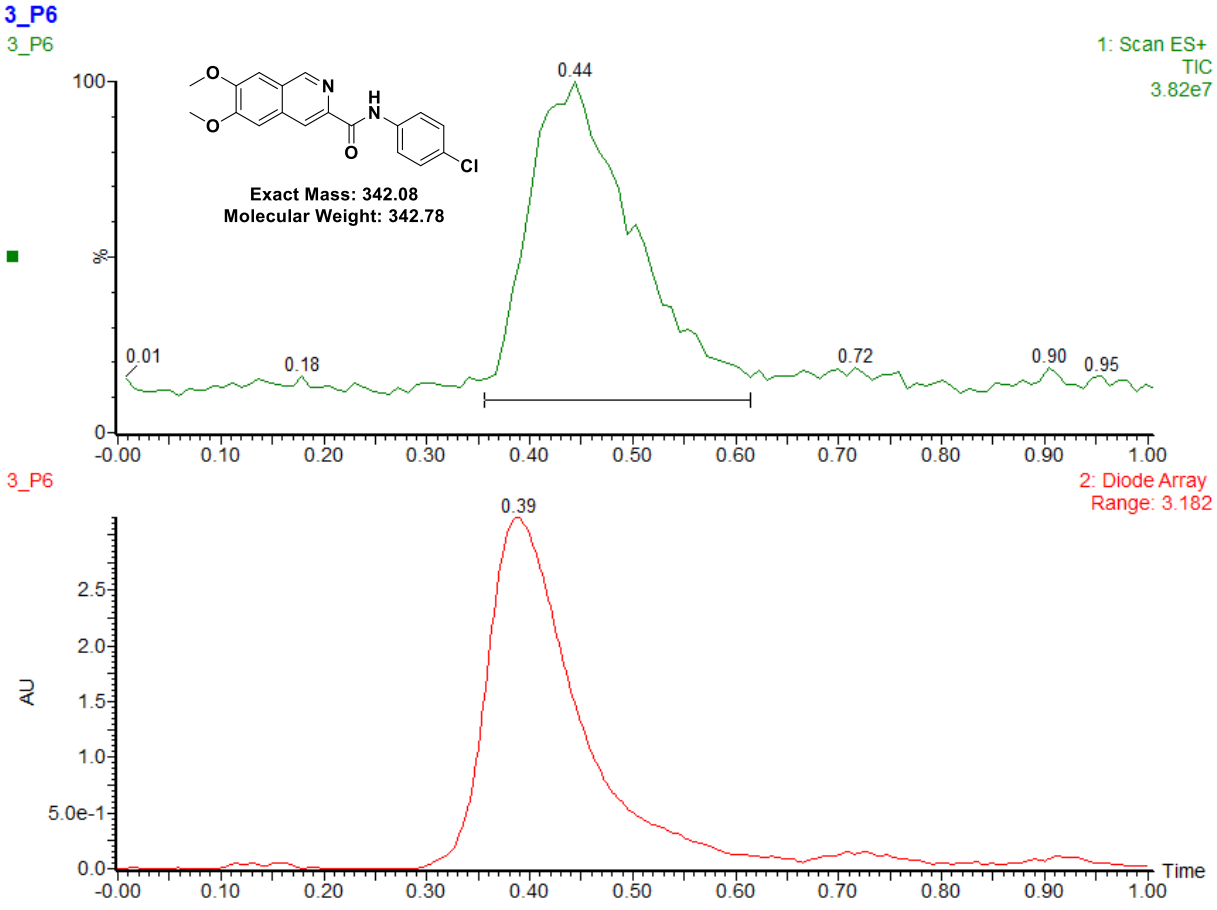

3_P2
3_P2
1: Scan ES+
TIC
8.07e7
0.44
Exact Mass: 332.10
Molecular Weight: 332.42
%
3_P2
2: Diode Array
Range: 9.825
0.41
AU
Time

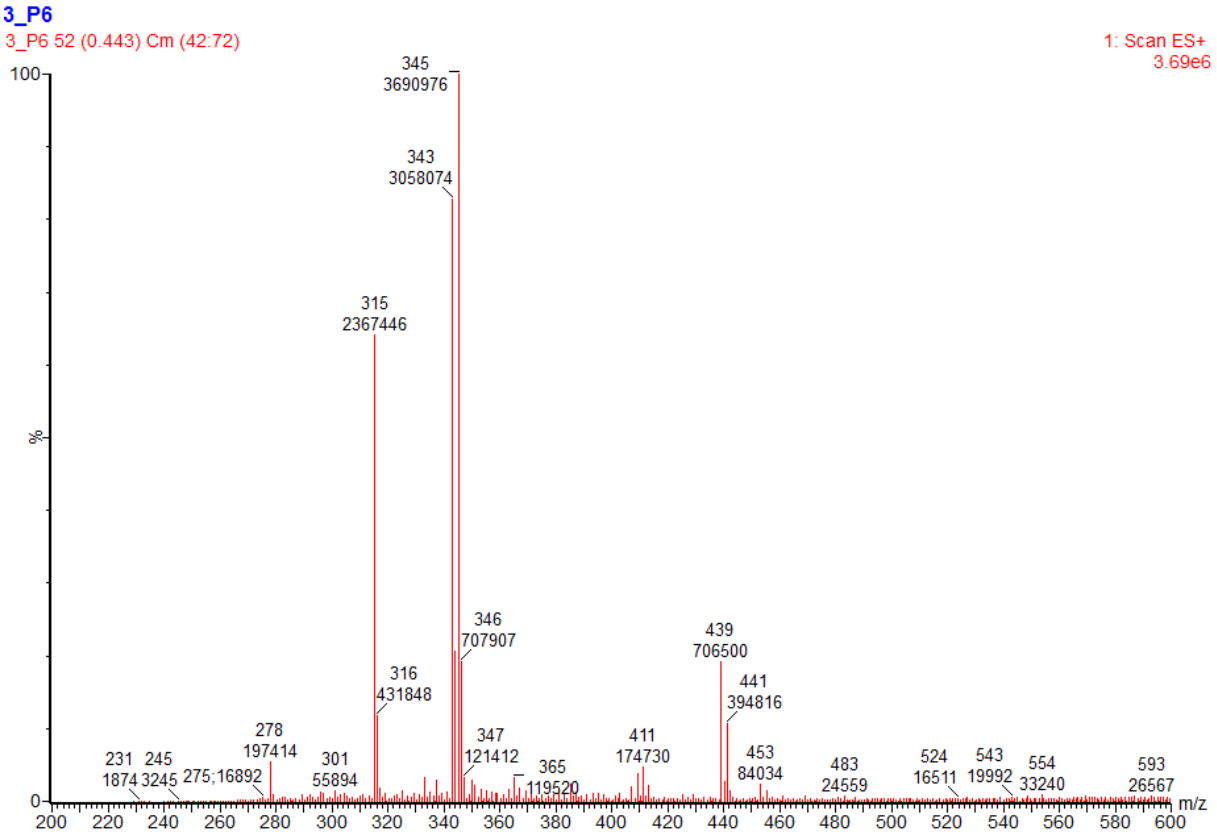

3_P2
3_P2 52 (0.443) Cm (41:69)
1: Scan ES+
5.89e6
333 5893834
429 4312390
397 3598522
335 2597096
430 1112861
399 897066
392 808022
443 444743
295 772291
297 318095
375 373020
504 528181
219 287
231 116529
245 78897
283 136069
451 177747
487 78892
505 168879
553 32716
563 41643
580 25508
596 19853
%
m/z

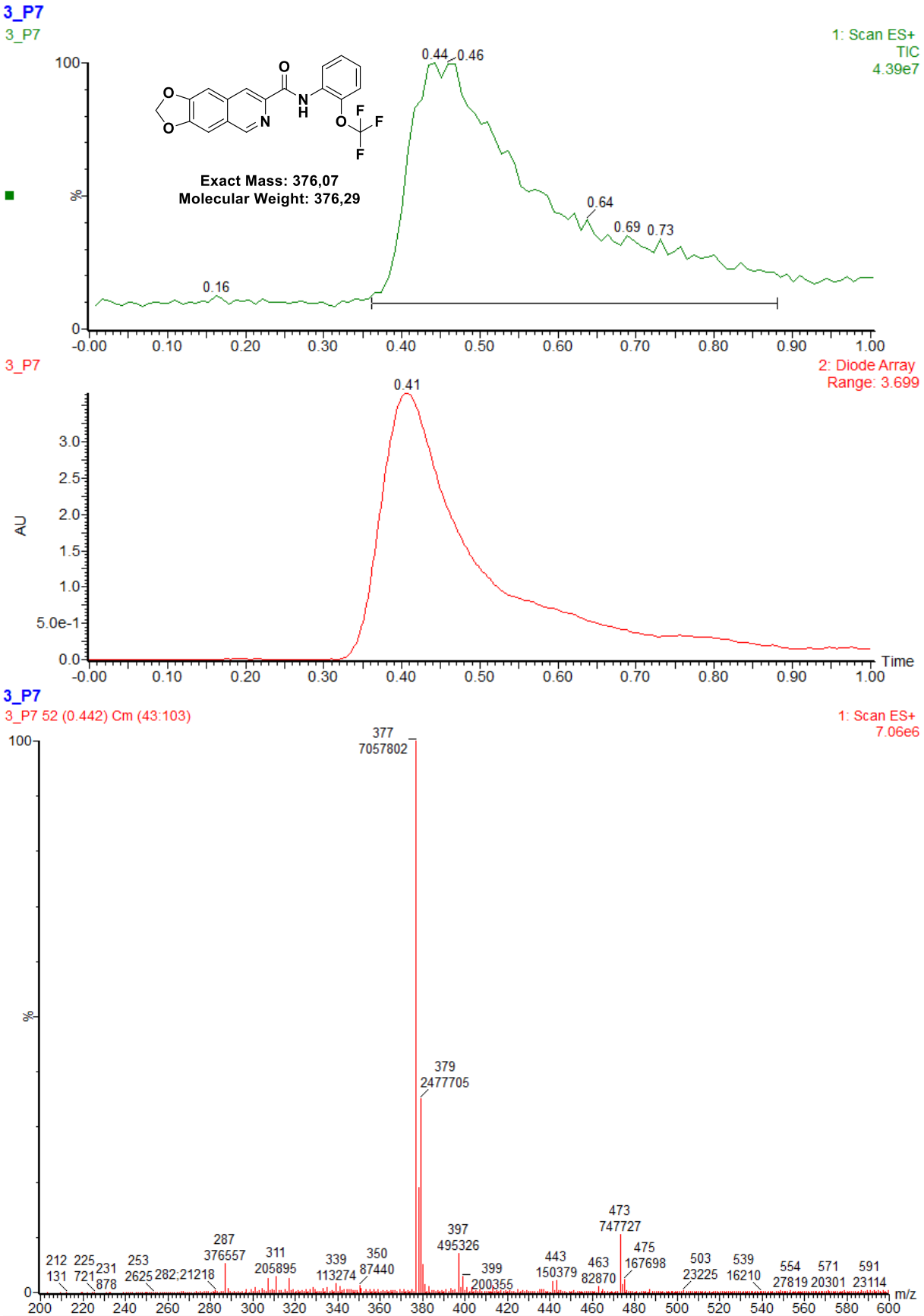

3_P3
3_P3
1: Scan ES+
TIC
8.17e7
Exact Mass: 359.15
Molecular Weight: 359.38
0.43
0.52
0.21
%
100
0
-0.00
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.90
1.00
3_P3
2: Diode Array
Range: 9.479
0.39
AU
6.0
4.0
2.0
0.0
Time
3_P3
3_P3 50 (0.426) Cm (41:78)
1: Scan ES+
1.32e7
360
13218945
361
2778301
353
807995
382
905394
396
898169
398;295181
269
377866
306
274959
333
279492
220
34358
231
208661
456
190278
490
56640
565
549;297
531829
579
330430
590
70167
m/z
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500
520
540
560
580
600

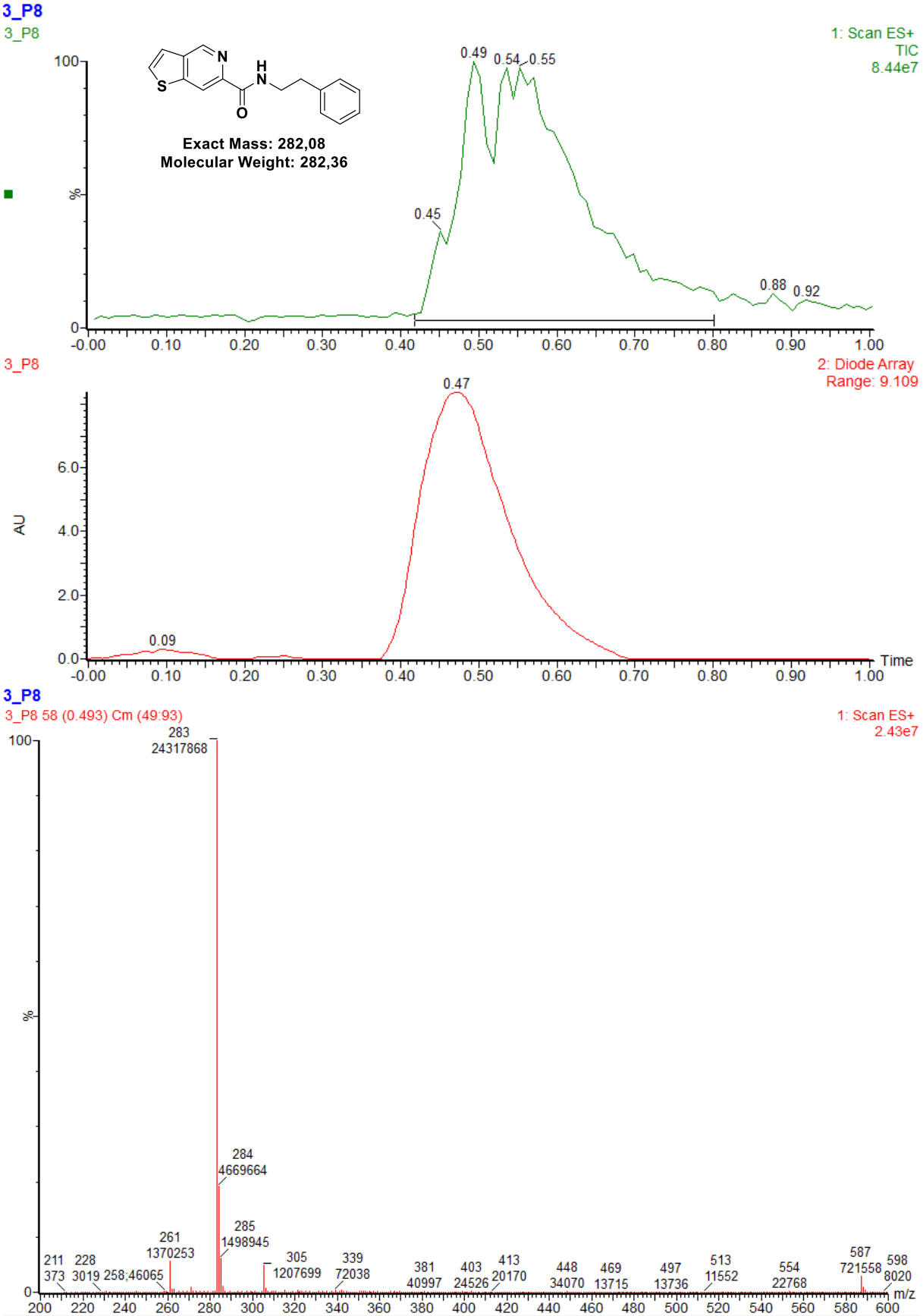

3_P4
3_P4
1: Scan ES+
TIC
2.20e7
Exact Mass: 390.08
Molecular Weight: 390.80
0.44
0.50
0.61
0.64
0.72
0.78
0.84
0.90
0.06
0.10
0.21
0.29
%
3_P4
2: Diode Array
Range: 7.952e-1
0.39
0.66
0.85
0.09
0.11
0.26
AU
Time
3_P4
3_P4 52 (0.443) Cm (40:68)
1: Scan ES+
3.08e6
391
3080051
337
1246115
334
1036748
392
527663
315
300778
338
210317
371
141602
492
308910
231
1327
259
3179
266
9868
289
19700
304
57327
413
123139
433
30962
467
34193
487
61101
493
61428
525
19229
554
32696
571
25294
583
24922
%
m/z

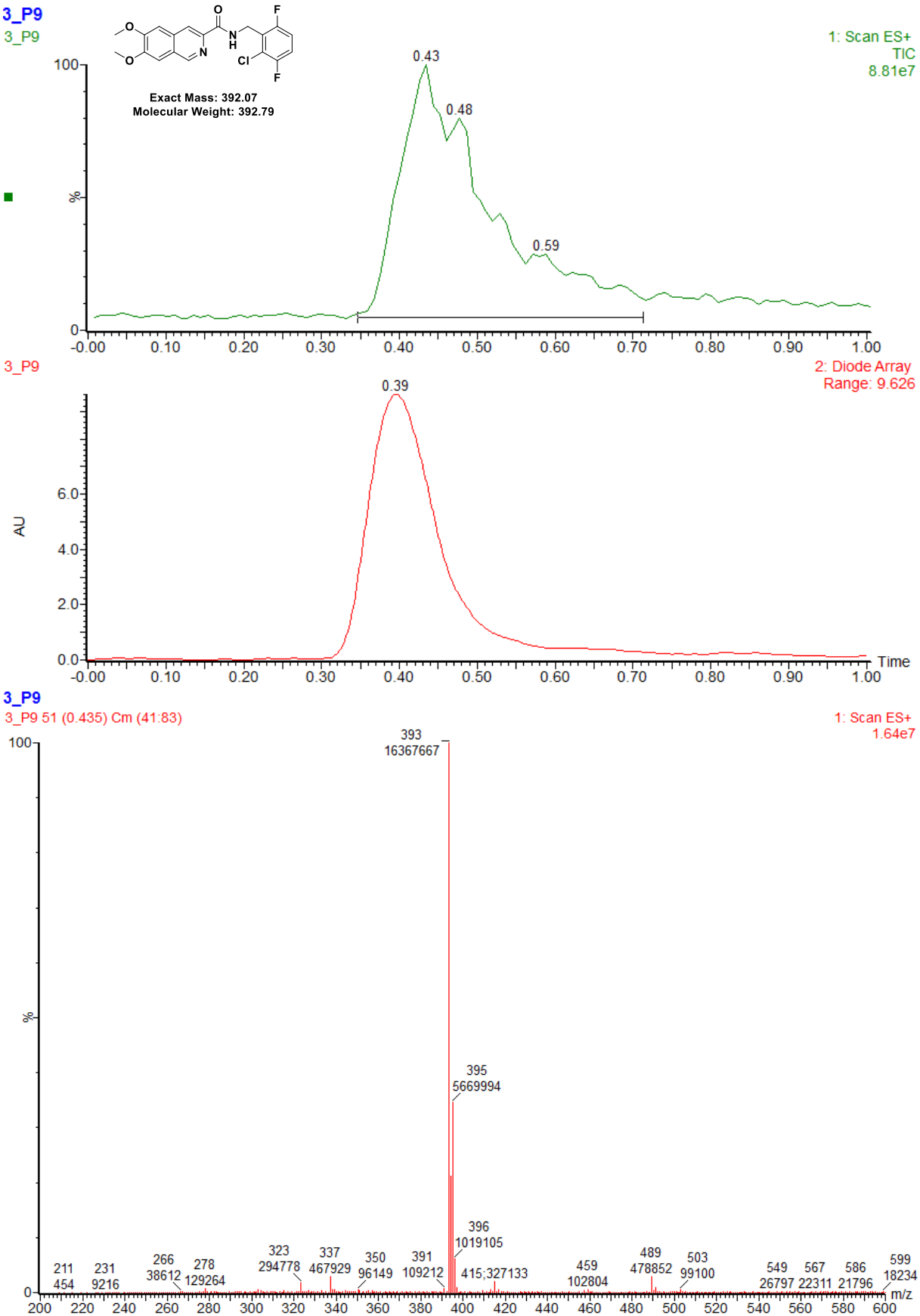

3_P5
3_P5
1: Scan ES+
TIC
4.77e7
Exact Mass: 332.17
Molecular Weight: 332.40
0.44
0.58
0.61
0.63
0.72
0.81
0.84
0.07
3_P5
2: Diode Array
Range: 3.013
0.40
AU
Time
3_P5
3_P5 52 (0.443) Cm (42:76)
1: Scan ES+
9.95e6
333
9945141
334
1959176
445
1805419
323
689006
447
522818
335
280276
355
238488
397
139332
413
420542
489
271437
519
69763
554
34993
579
82626
595
22808
219
285
231
14747
266
33963
275
42618
315;86397
m/z

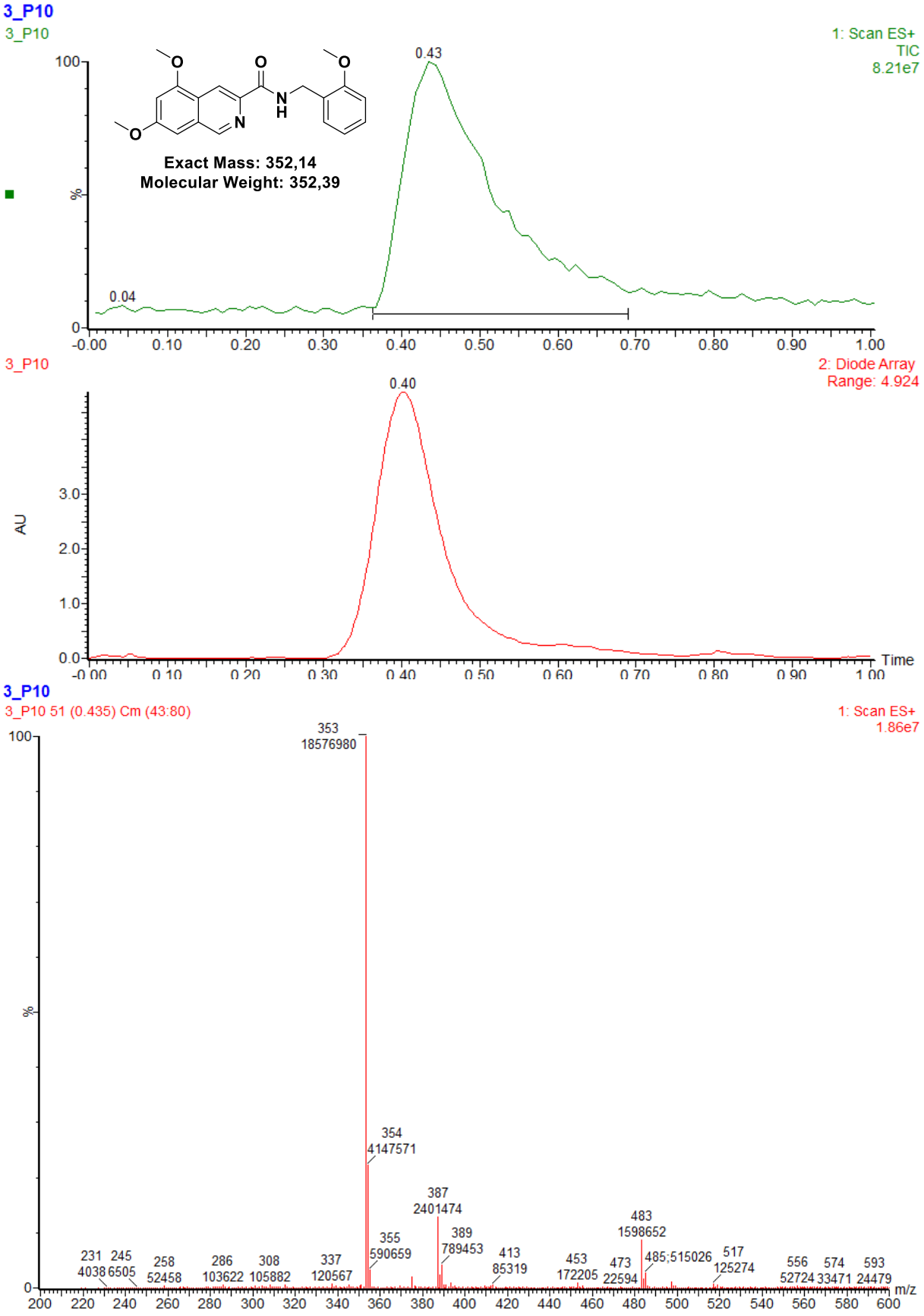

3_P6
3_P6
1: Scan ES+
TIC
3.82e7
Exact Mass: 342.08
Molecular Weight: 342.78
0.44
0.01
0.18
0.72
0.90
0.95
%
3_P6
2: Diode Array
Range: 3.182
0.39
AU
Time

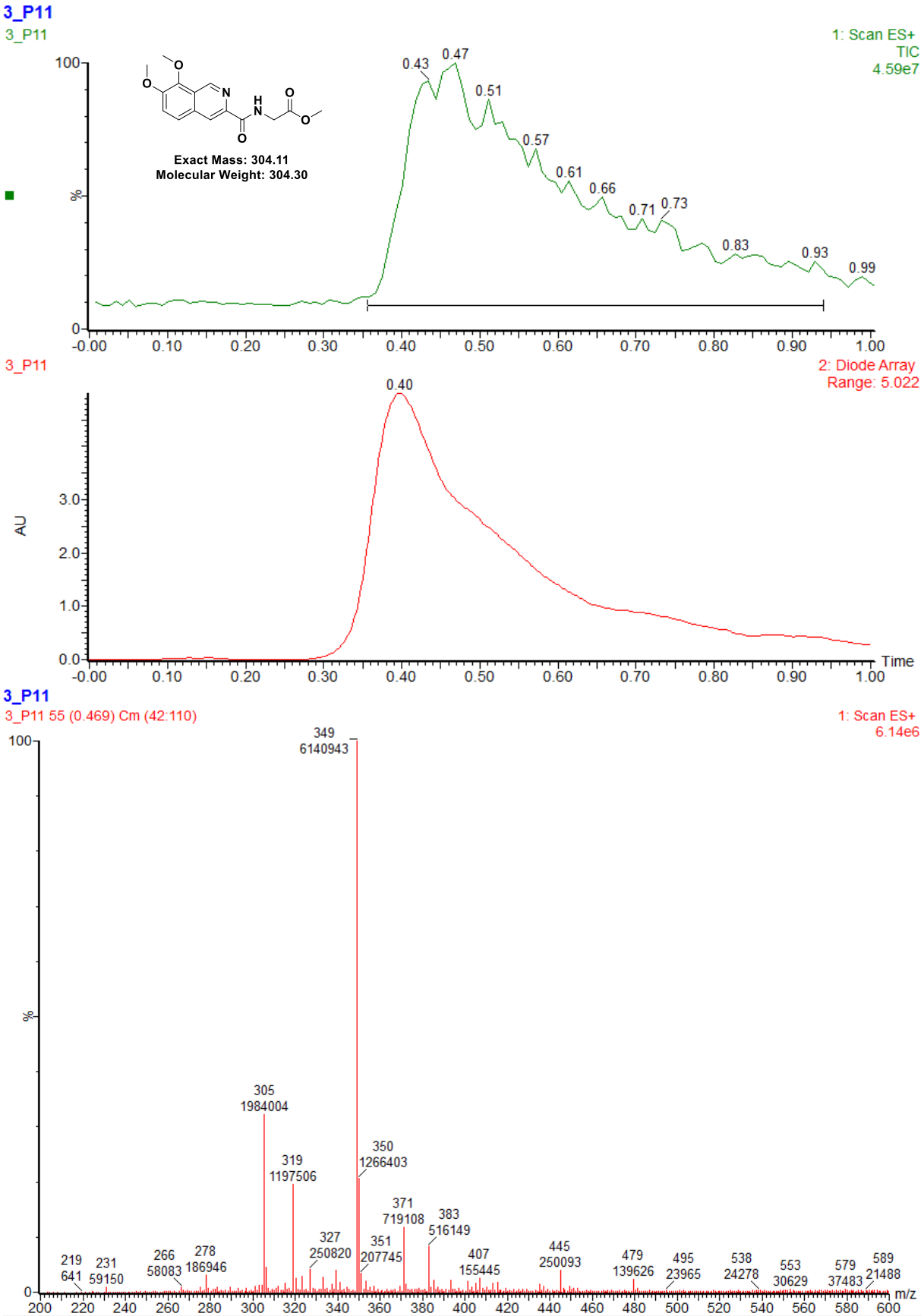

3_P6
3_P6 52 (0.443) Cm (42:72)
1: Scan ES+
3.69e6
345
3690976
343
3058074
315
2367446
346
707907
316
431848
439
706500
441
394816
278
197414
347
121412
411
174730
453
84034
231
1874
245
3245
275;16892
301
55894
365
119520
483
24559
524
16511
543
19992
554
33240
593
26567
%
m/z

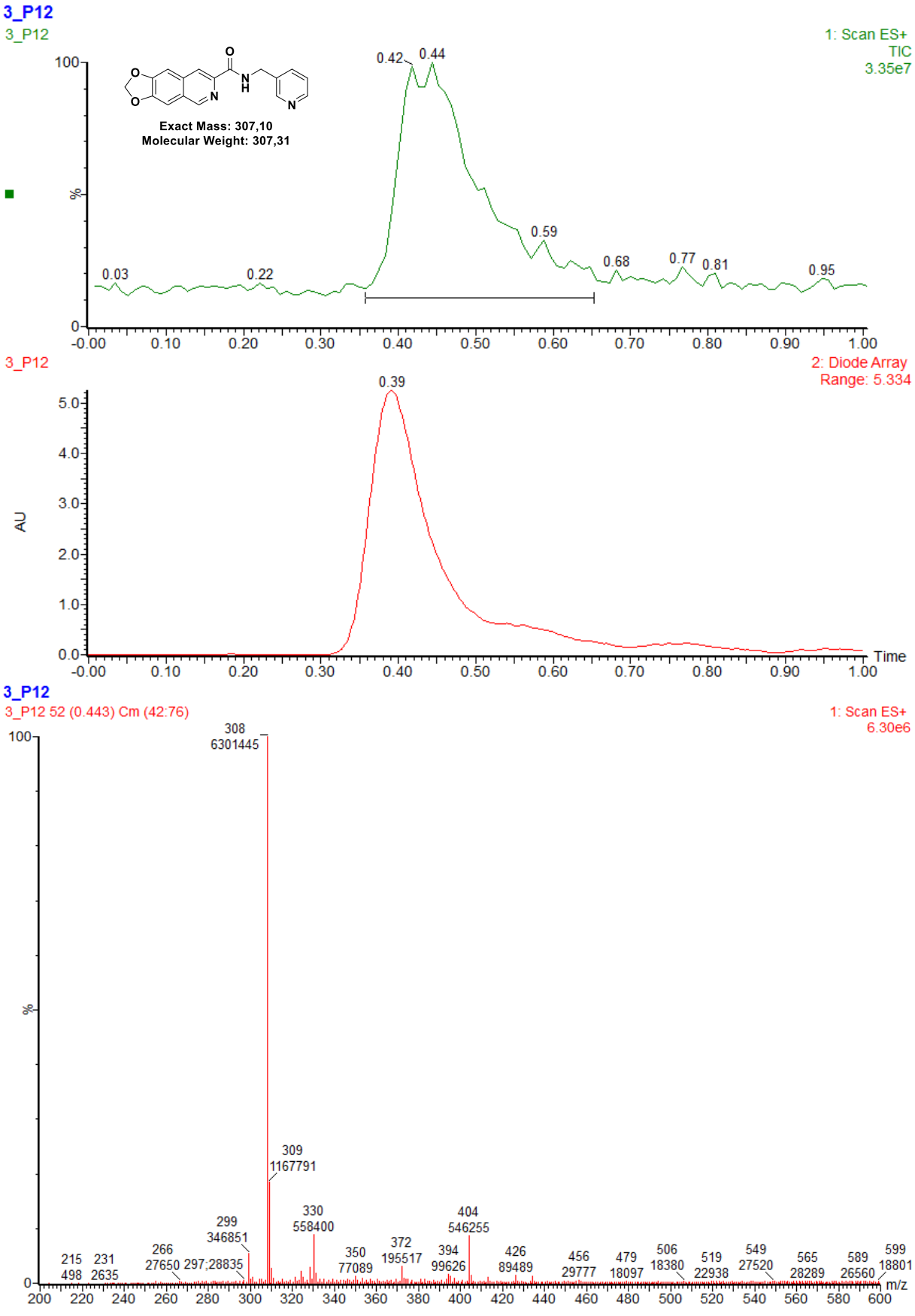

3_P7
3_P7
1: Scan ES+
TIC
4.39e7
Exact Mass: 376,07
Molecular Weight: 376,29
0.44
0.46
0.64
0.69
0.73
0.16
3_P7
2: Diode Array
Range: 3.699
0.41
AU
Time
3_P7
3_P7 52 (0.442) Cm (43:103)
1: Scan ES+
7.06e6
377
7057802
379
2477705
397
495326
473
747727
475
167698
287
376557
311
205895
339
113274
350
87440
399
200355
443
150379
463
82870
503
23225
539
16210
554
27819
571
20301
591
23114
212
131
225
721
231
878
253
2625
282;21218
m/z

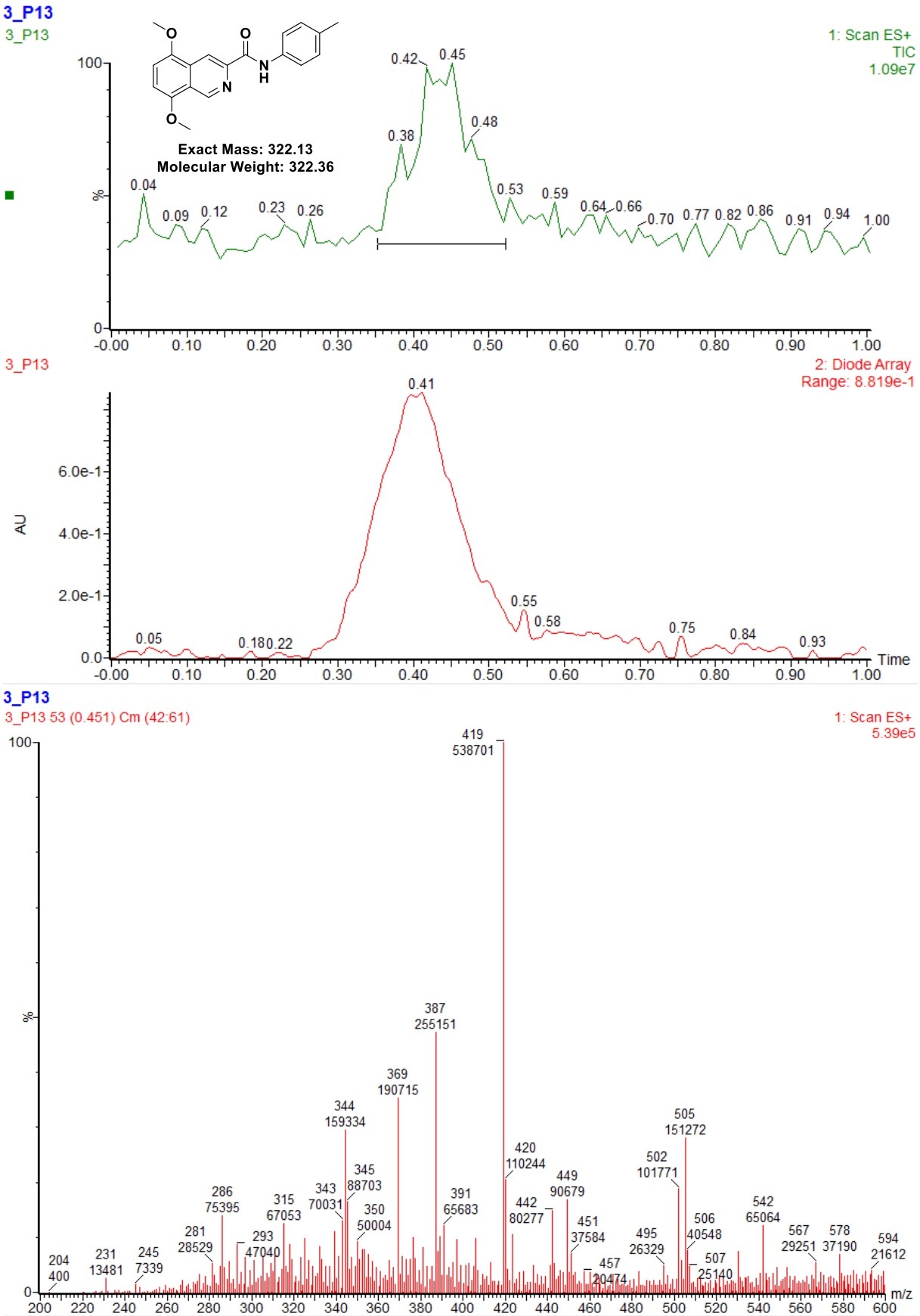

3_P8
3_P8
1: Scan ES+
TIC
8.44e7
Exact Mass: 282,08
Molecular Weight: 282,36
0.49
0.54
0.55
0.45
0.88
0.92
%
3_P8
2: Diode Array
Range: 9.109
0.47
0.09
AU
Time
3_P8
3_P8 58 (0.493) Cm (49:93)
1: Scan ES+
2.43e7
283
24317868
284
4669664
285
1498945
261
1370253
211
373
228
3019
258;46065
305
1207699
339
72038
381
40997
403
24526
413
20170
448
34070
469
13715
497
13736
513
11552
554
22768
587
721558
598
8020
%
m/z

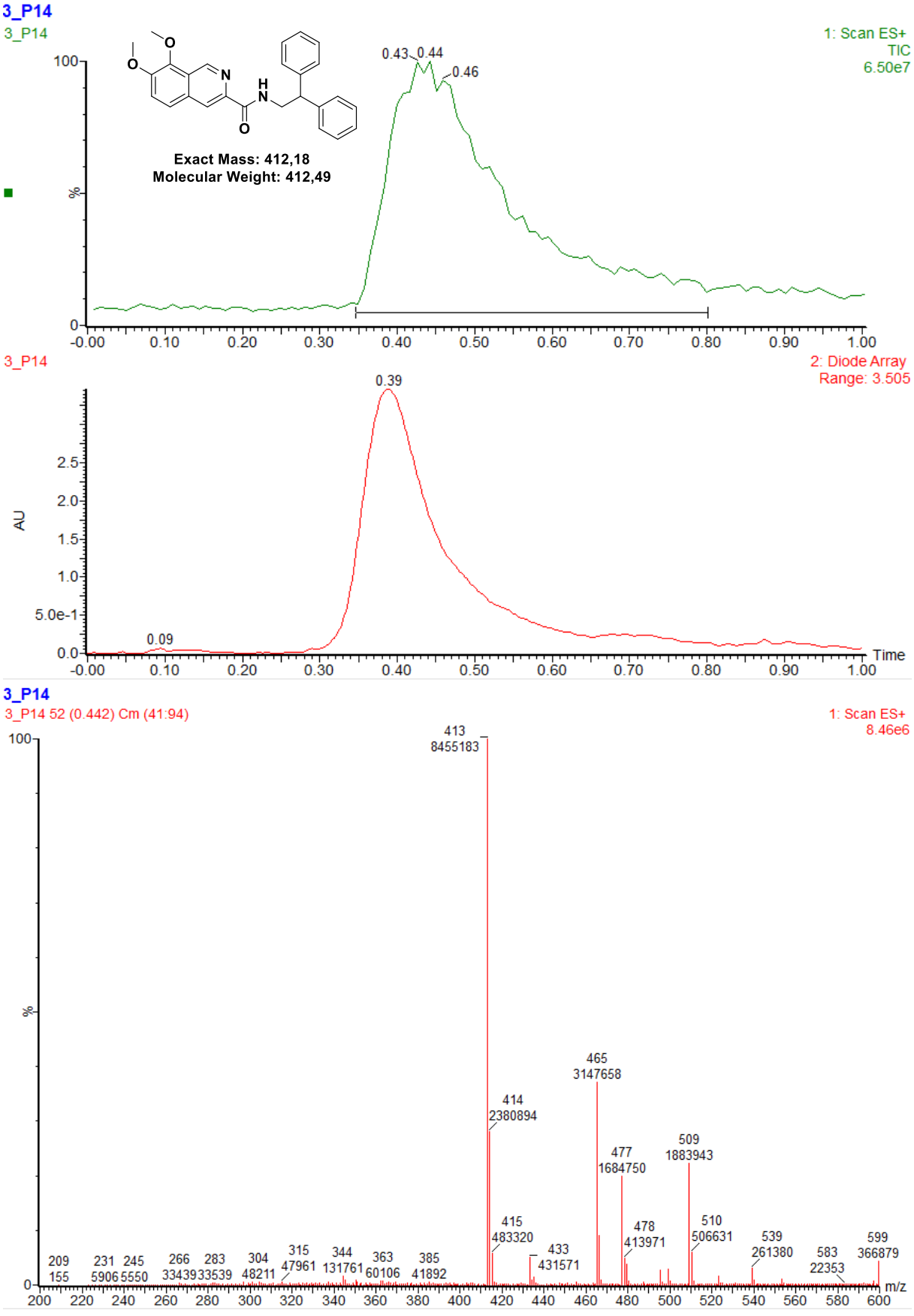

3_P9
3_P9
Exact Mass: 392.07
Molecular Weight: 392.79
1: Scan ES+
TIC
8.81e7
0.43
0.48
0.59
%
3_P9
2: Diode Array
Range: 9.626
0.39
AU
Time
3_P9
3_P9 51 (0.435) Cm (41:83)
1: Scan ES+
1.64e7
393
16367667
395
5669994
396
1019105
211 454
231 9216
266 38612
278 129264
323 294778
337 467929
350 96149
391 109212
415;327133
459 102804
489 478852
503 99100
549 26797
567 22311
586 21796
599 18234
m/z

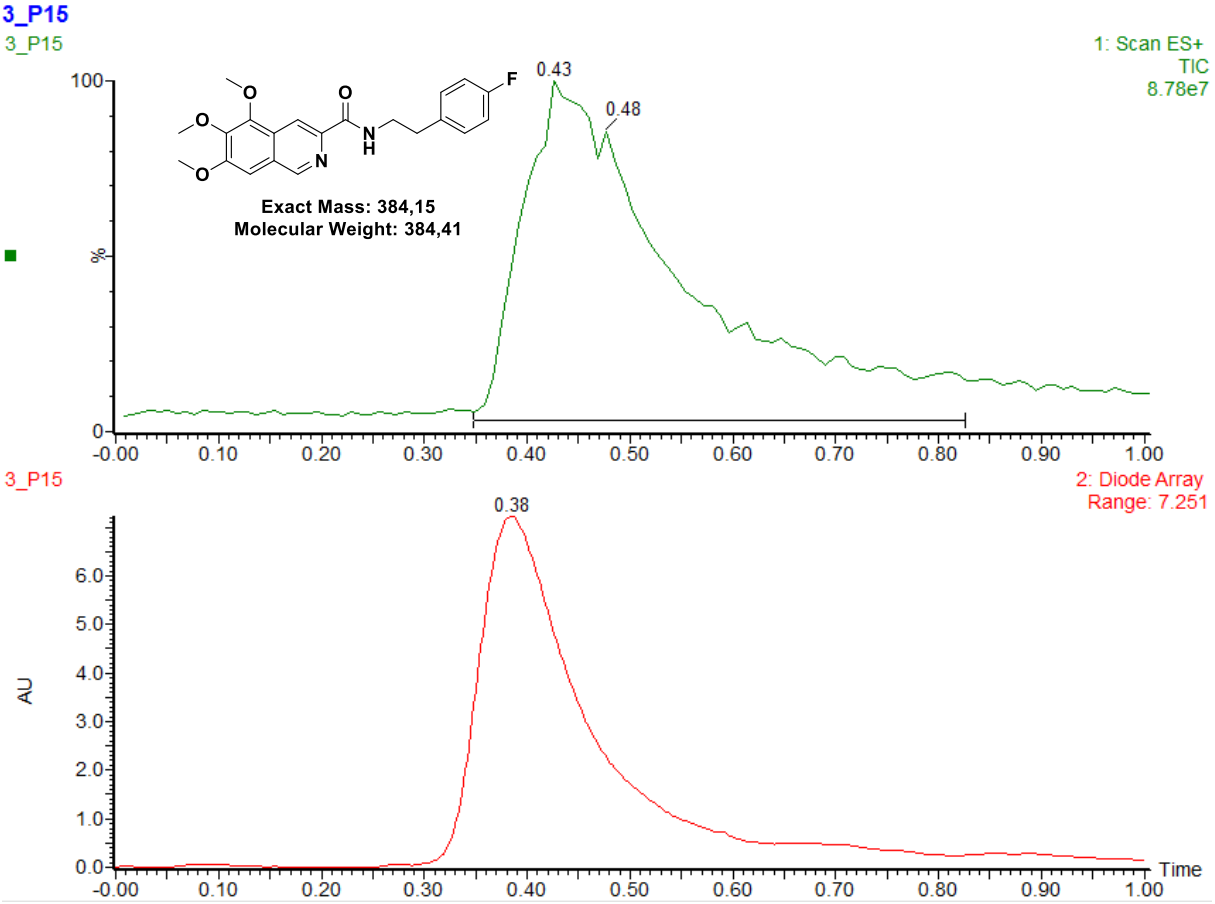

3_P10
3_P10
1: Scan ES+
TIC
8.21e7
Exact Mass: 352,14
Molecular Weight: 352,39
0.43
0.04
%
3_P10
2: Diode Array
Range: 4.924
0.40
AU
Time
3_P10
3_P10 51 (0.435) Cm (43:80)
1: Scan ES+
1.86e7
353
18576980
354
4147571
387
2401474
389
789453
355
590659
483
1598652
485;515026
231 245
4038 6505
258
52458
286
103622
308
105882
337
120567
413
85319
453
172205
473
22594
517
125274
556
52724
574
33471
593
24479
%
m/z

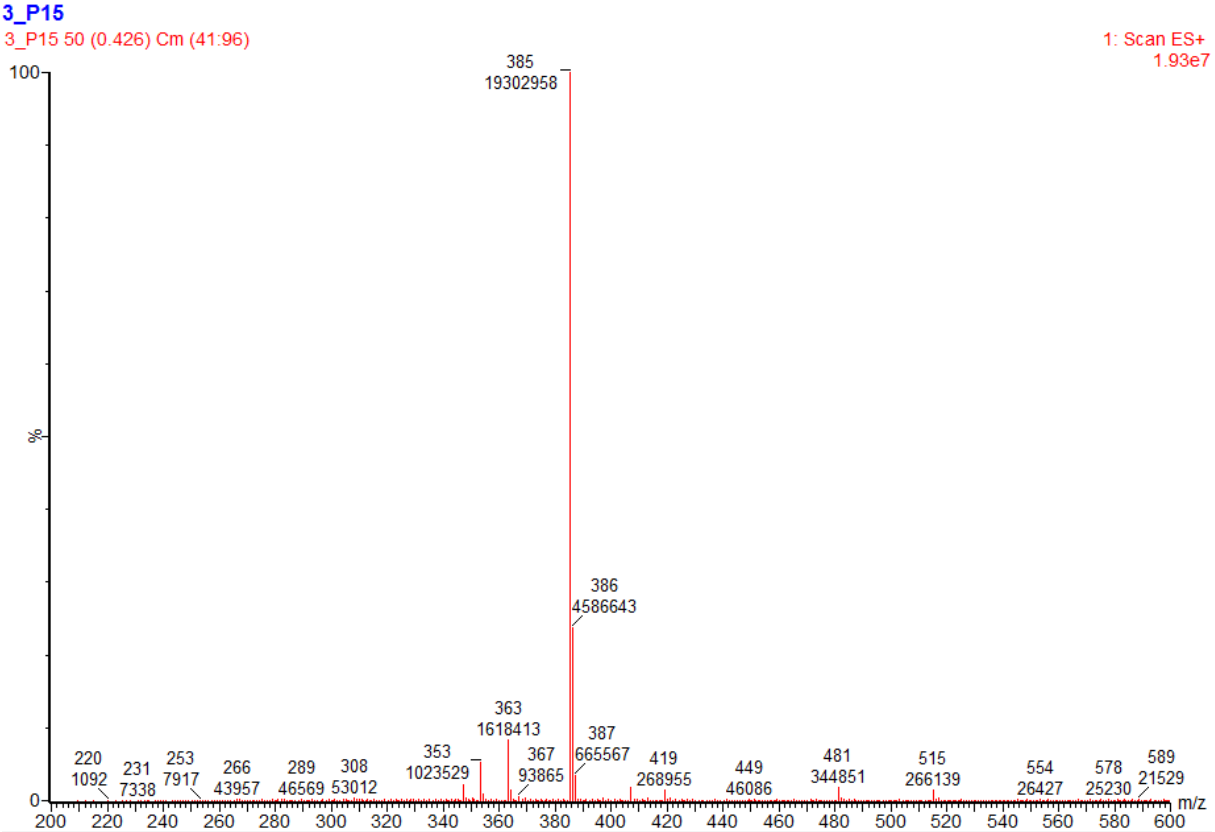

3_P11
3_P11
1: Scan ES+
TIC
4.59e7
Exact Mass: 304.11
Molecular Weight: 304.30
0.43
0.47
0.51
0.57
0.61
0.66
0.71
0.73
0.83
0.93
0.99
3_P11
2: Diode Array
Range: 5.022
0.40
AU
Time
3_P11
3_P11 55 (0.469) Cm (42:110)
1: Scan ES+
6.14e6
349
6140943
305
1984004
319
1197506
350
1266403
371
719108
383
516149
327
250820
351
207745
407
155445
445
250093
479
139626
495
23965
538
24278
553
30629
579
37483
589
21488
219
641
231
59150
266
58083
278
186946
m/z

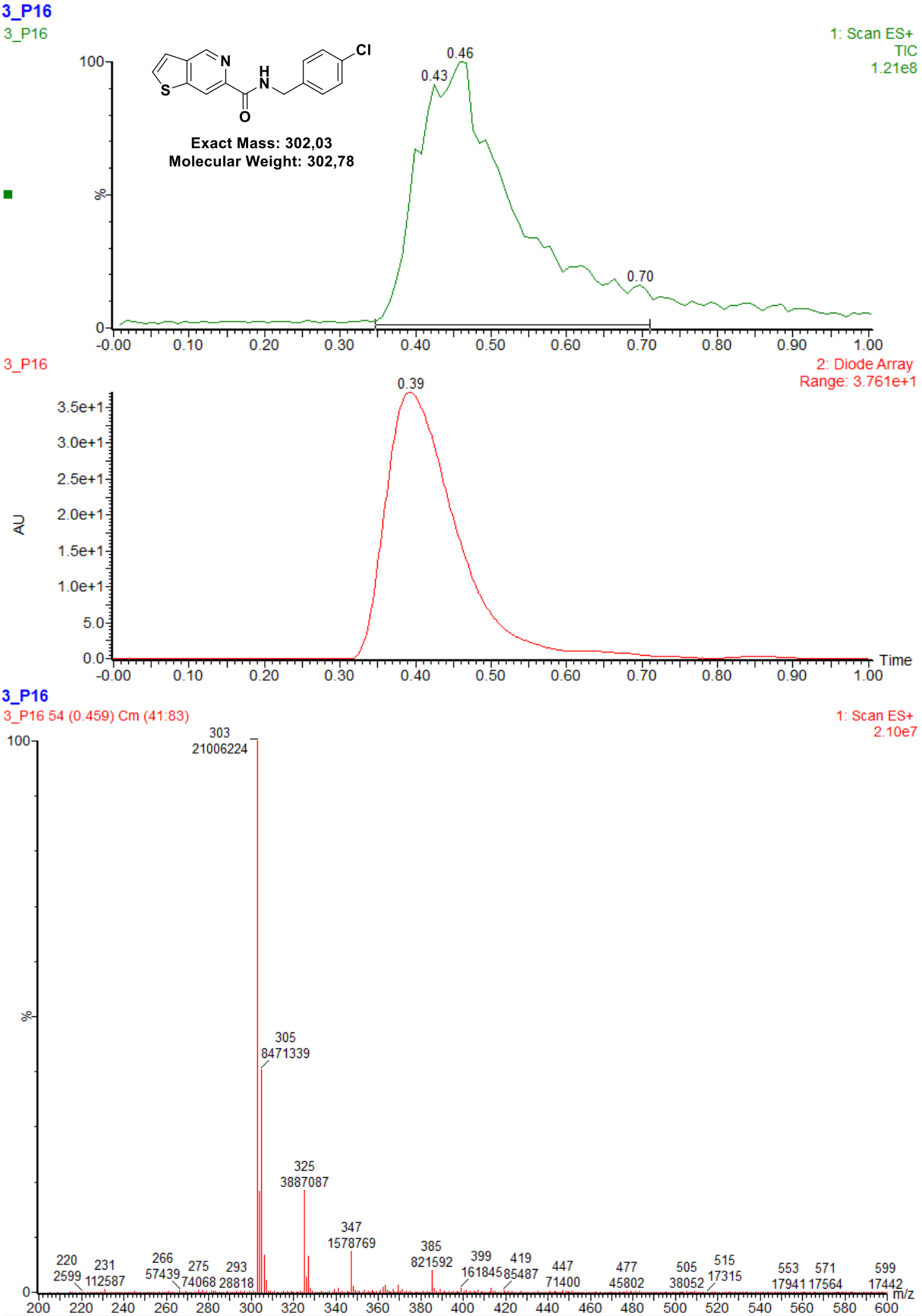

3_P12
3_P12
1: Scan ES+
TIC
3.35e7
Exact Mass: 307,10
Molecular Weight: 307,31
0.42
0.44
0.59
0.68
0.77
0.81
0.95
0.03
0.22
%
3_P12
2: Diode Array
Range: 5.334
0.39
AU
Time
3_P12
3_P12 52 (0.443) Cm (42:76)
1: Scan ES+
6.30e6
308
6301445
309
1167791
330
558400
299
346851
404
546255
372
195517
394
99626
350
77089
426
89489
456
29777
479
18097
506
18380
519
22938
549
27520
565
28289
589
26560
599
18801
215
498
231
2635
266
27650
297;28835
%
m/z

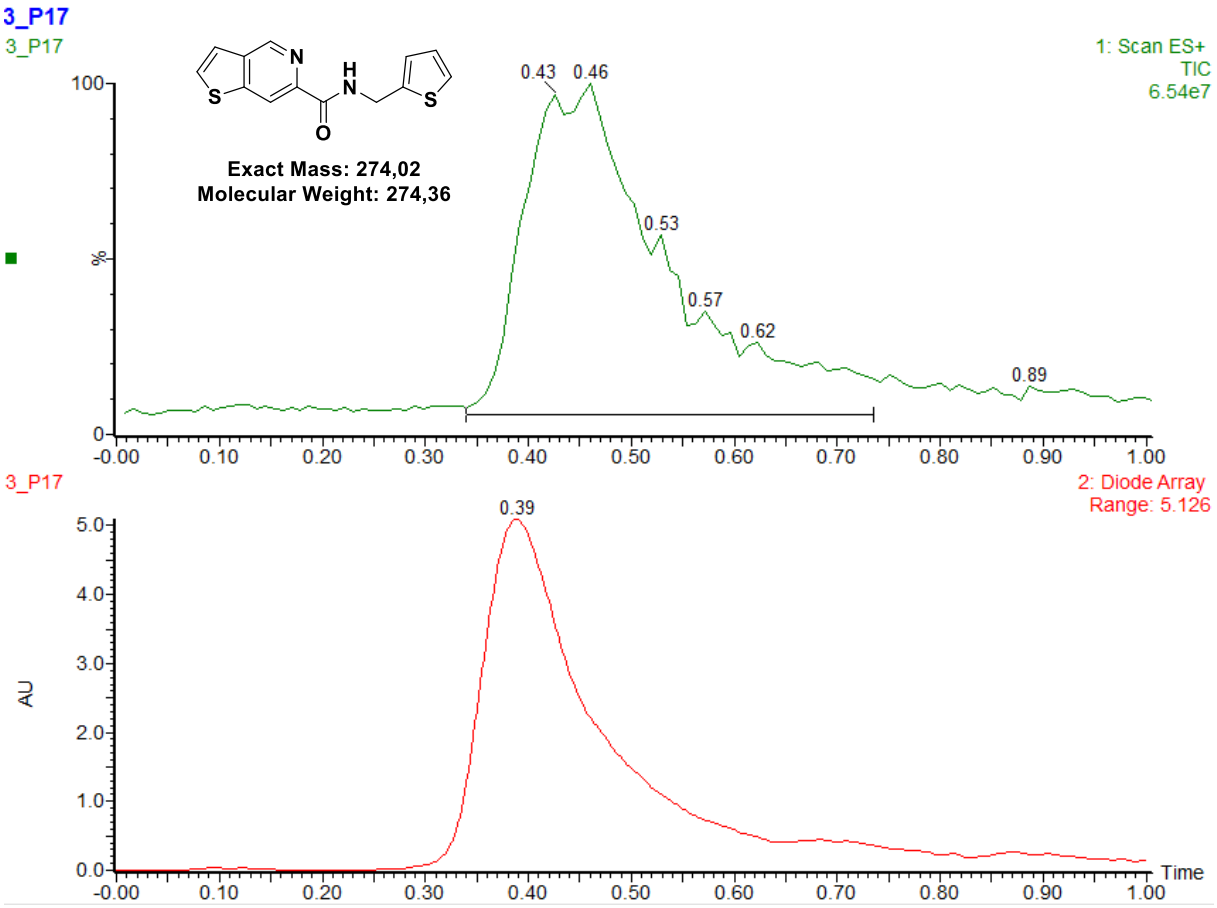

3_P13
3_P13
1: Scan ES+
TIC
1.09e7
Exact Mass: 322.13
Molecular Weight: 322.36
3_P13
2: Diode Array
Range: 8.819e-1
AU
Time
3_P13
3_P13 53 (0.451) Cm (42:61)
1: Scan ES+
5.39e5
m/z

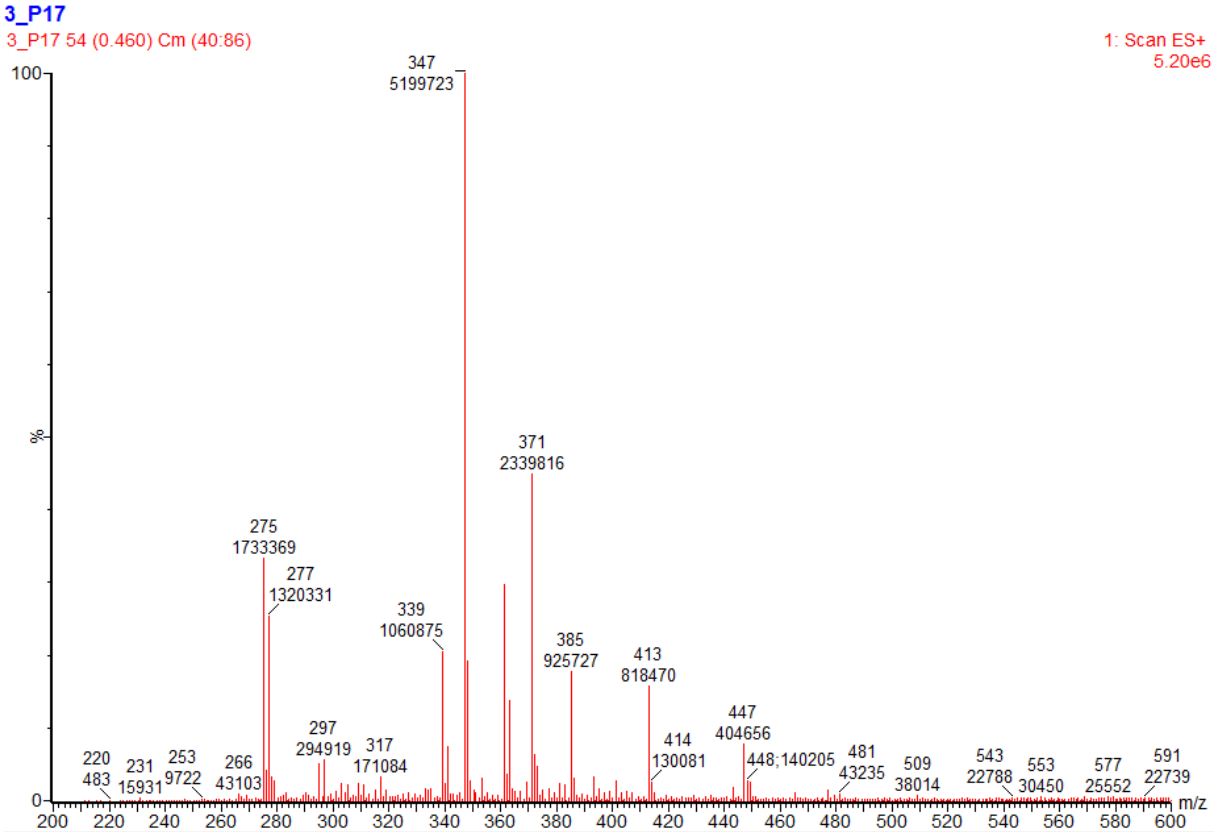

3_P14
3_P14
1: Scan ES+
TIC
6.50e7
Exact Mass: 412,18
Molecular Weight: 412,49
0.43
0.44
0.46
%
3_P14
2: Diode Array
Range: 3.505
0.39
0.09
AU
Time
3_P14
3_P14 52 (0.442) Cm (41:94)
1: Scan ES+
8.46e6
413
8455183
465
3147658
414
2380894
509
1883943
477
1684750
415
483320
478
413971
510
506631
433
431571
539
261380
599
366879
583
22353
209
155
231
5906
245
5550
266
33439
283
33539
304
48211
315
47961
344
131761
363
60106
385
41892
%
m/z

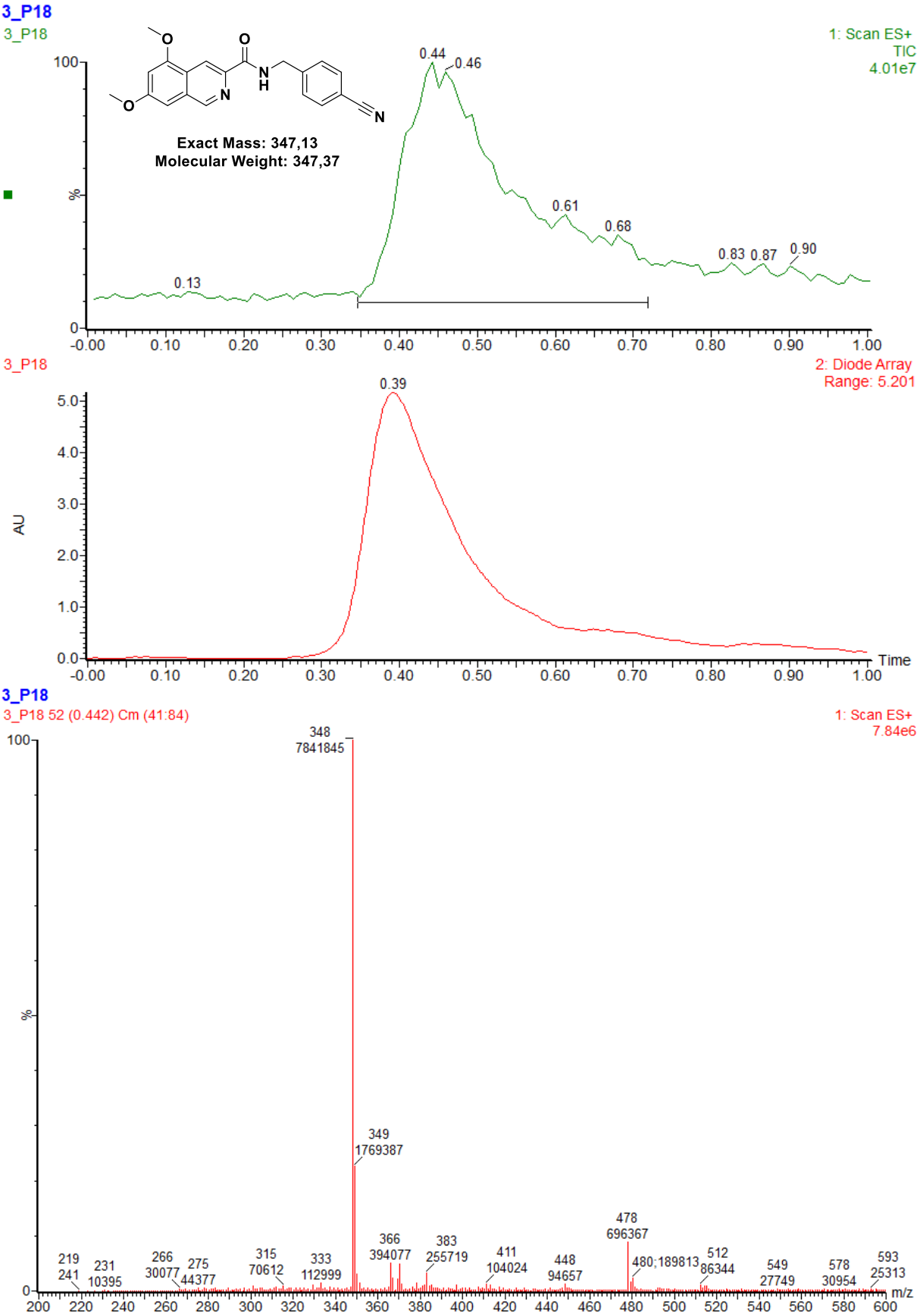

3_P15
3_P15
1: Scan ES+
TIC
8.78e7
0.43
0.48
Exact Mass: 384,15
Molecular Weight: 384,41
%
-0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
3_P15
2: Diode Array
Range: 7.251
0.38
AU
Time

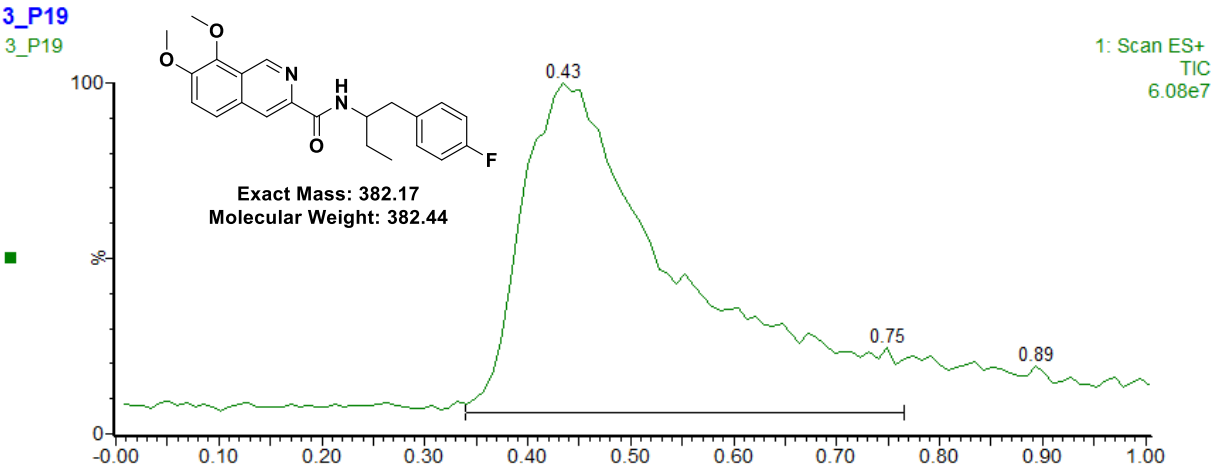

3_P15
3_P15 50 (0.426) Cm (41:96)
1: Scan ES+
1.93e7
385
19302958
386
4586643
363
1618413
387
665567
220 1092
231 7338
253 7917
266 43957
289 46569
308 53012
353 1023529
367 93865
419 268955
449 46086
481 344851
515 266139
554 26427
578 25230
589 21529
%
m/z

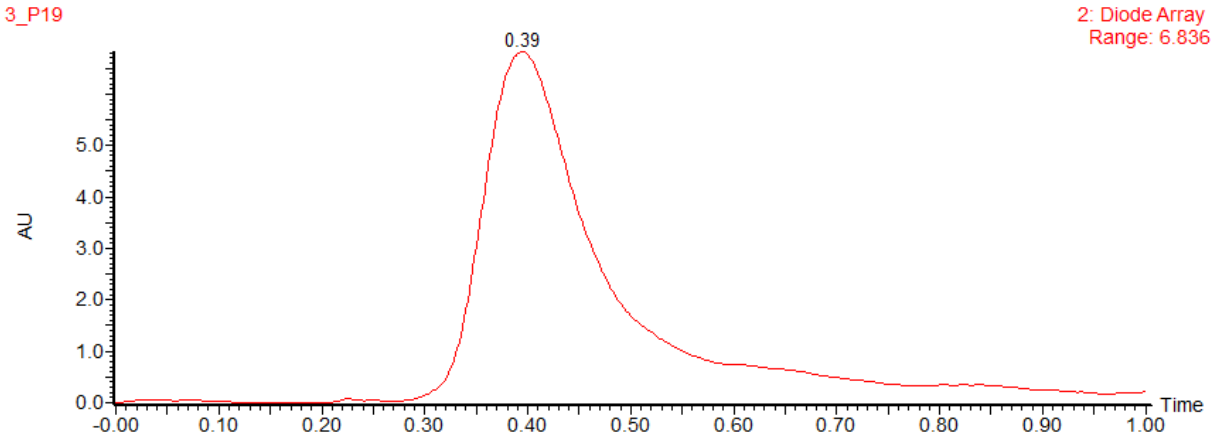

3_P16
3_P16
1: Scan ES+
TIC
1.21e8
Exact Mass: 302,03
Molecular Weight: 302,78
0.46
0.43
0.70
%
3_P16
2: Diode Array
Range: 3.761e+1
0.39
AU
Time
3_P16
3_P16 54 (0.459) Cm (41:83)
1: Scan ES+
2.10e7
303
21006224
305
8471339
325
3887087
347
1578769
385
821592
m/z

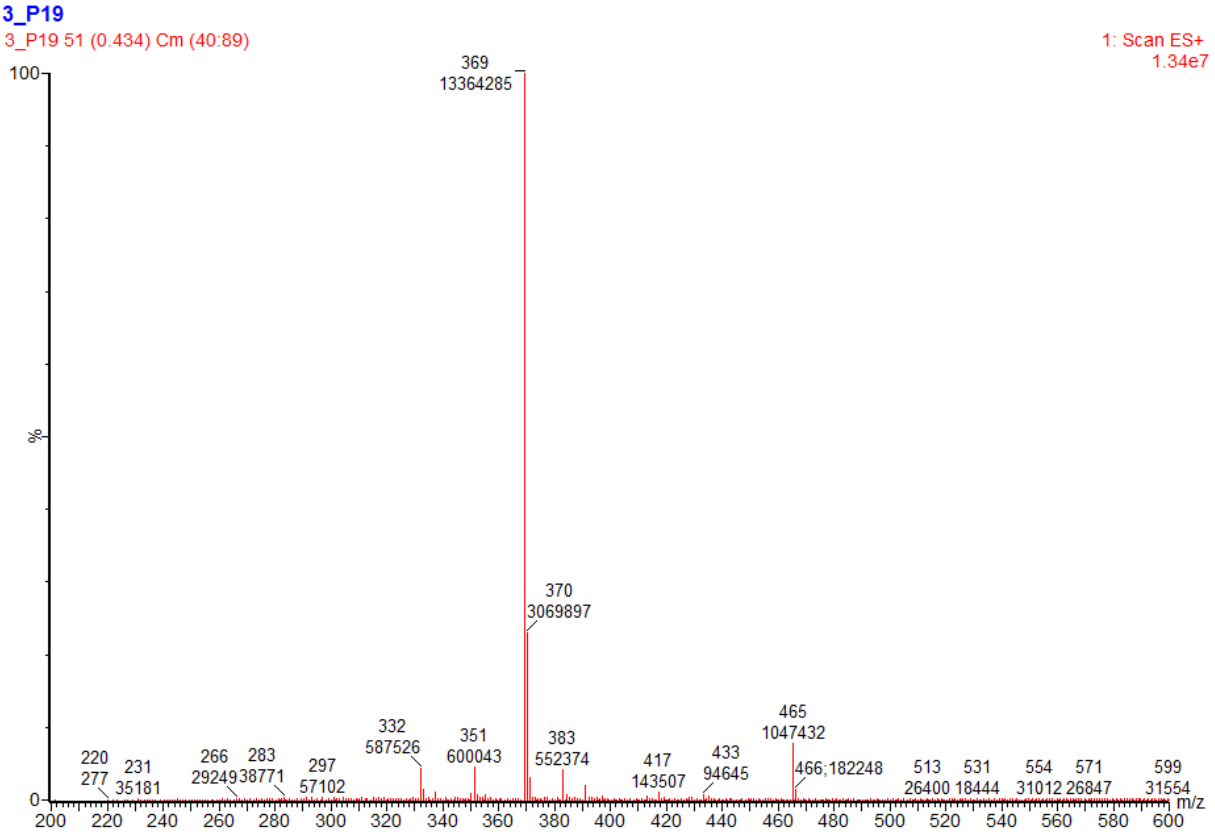

3_P17
3_P17
1: Scan ES+
TIC
6.54e7
Exact Mass: 274,02
Molecular Weight: 274,36
0.43
0.46
0.53
0.57
0.62
0.89
%
Time
3_P17
2: Diode Array
Range: 5.126
0.39
AU

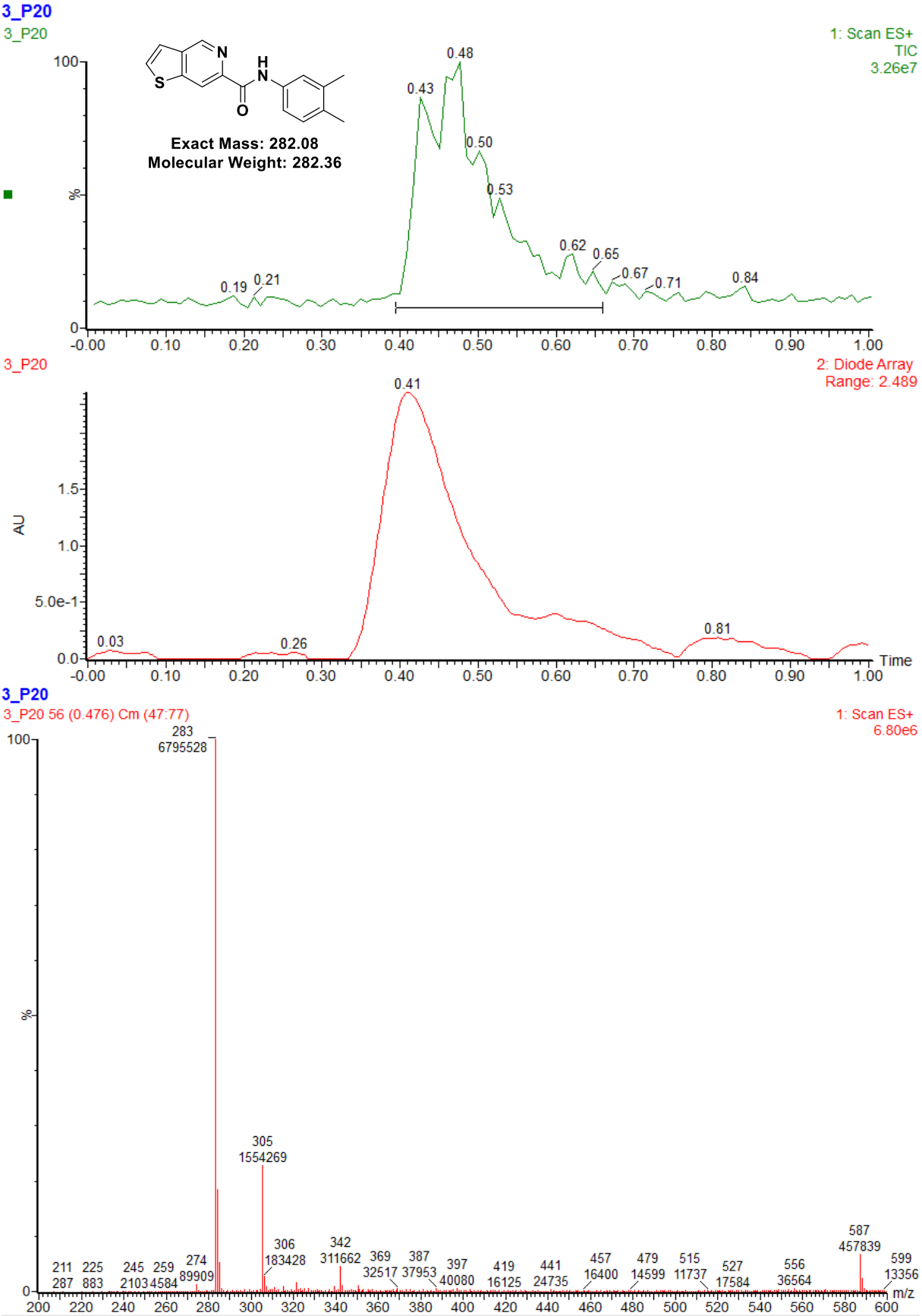

3_P17
3_P17 54 (0.460) Cm (40:86)
1: Scan ES+
5.20e6
347
5199723
371
2339816
275
1733369
277
1320331
339
1060875
385
925727
413
818470
447
404656
297
294919
317
171084
414
130081
448;140205
481
43235
509
38014
543
22788
553
30450
577
25552
591
22739
220
483
231
15931
253
9722
266
43103
%
m/z

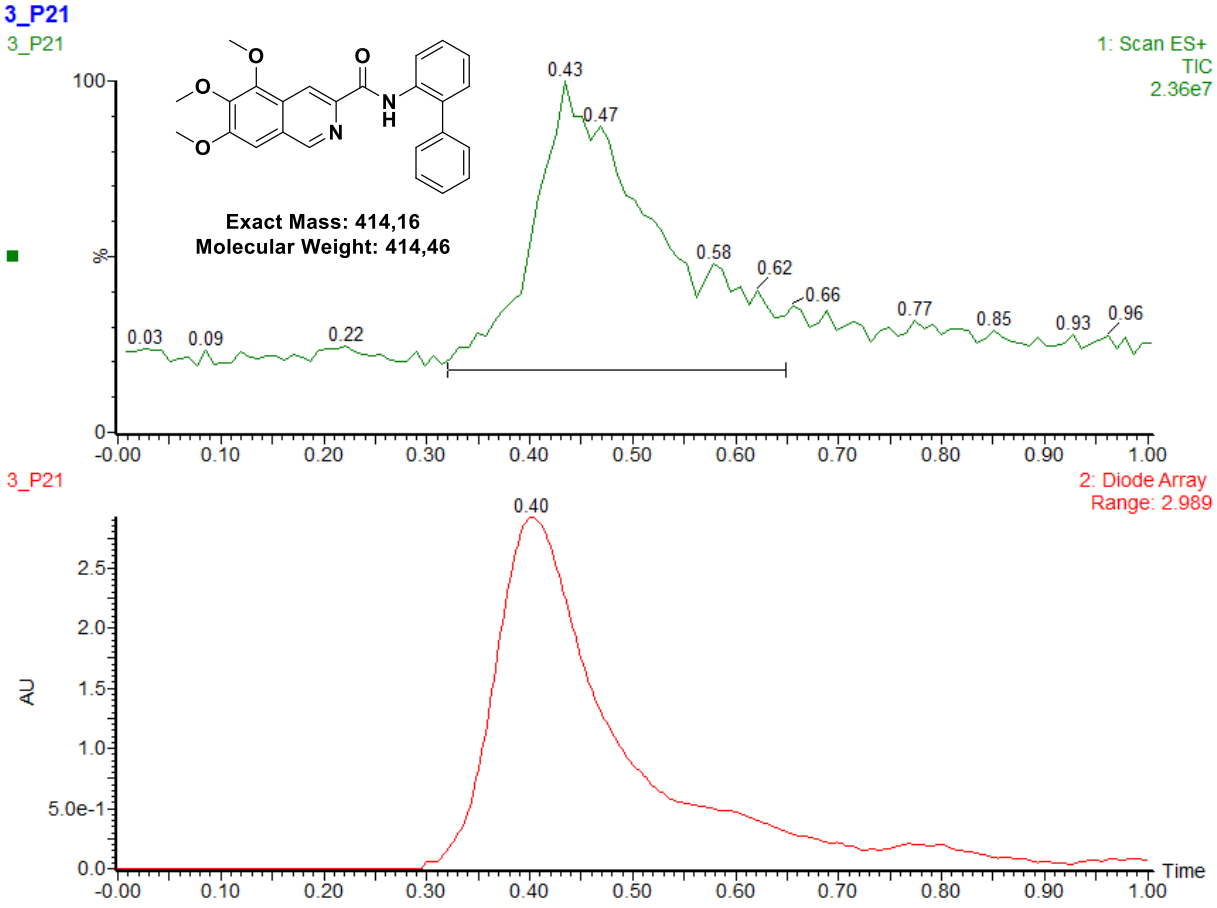

3_P18
3_P18
1: Scan ES+
TIC
4.01e7
Exact Mass: 347,13
Molecular Weight: 347,37
0.44
0.46
0.61
0.68
0.83
0.87
0.90
0.13
%
3_P18
2: Diode Array
Range: 5.201
0.39
AU
Time
3_P18
3_P18 52 (0.442) Cm (41:84)
1: Scan ES+
7.84e6
348
7841845
349
1769387
366
394077
383
255719
411
104024
448
94657
478
696367
480;189813
512
86344
549
27749
578
30954
593
25313
315
70612
333
112999
266
30077
275
44377
219
241
231
10395
%
m/z


3_P19
3_P19
1: Scan ES+
TIC
6.08e7
Exact Mass: 382.17
Molecular Weight: 382.44
0.43
0.75
0.89
%

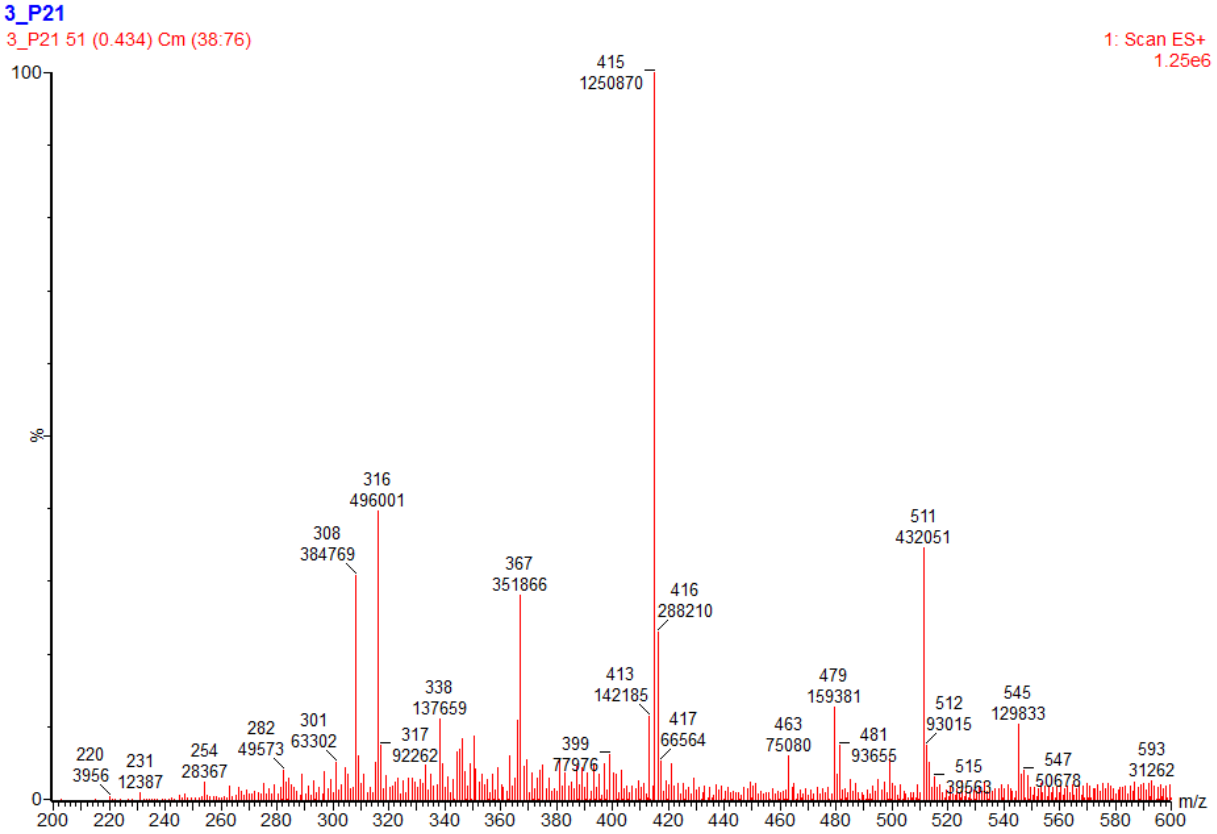

3_P19
2: Diode Array
Range: 6.836
0.39
AU
Time

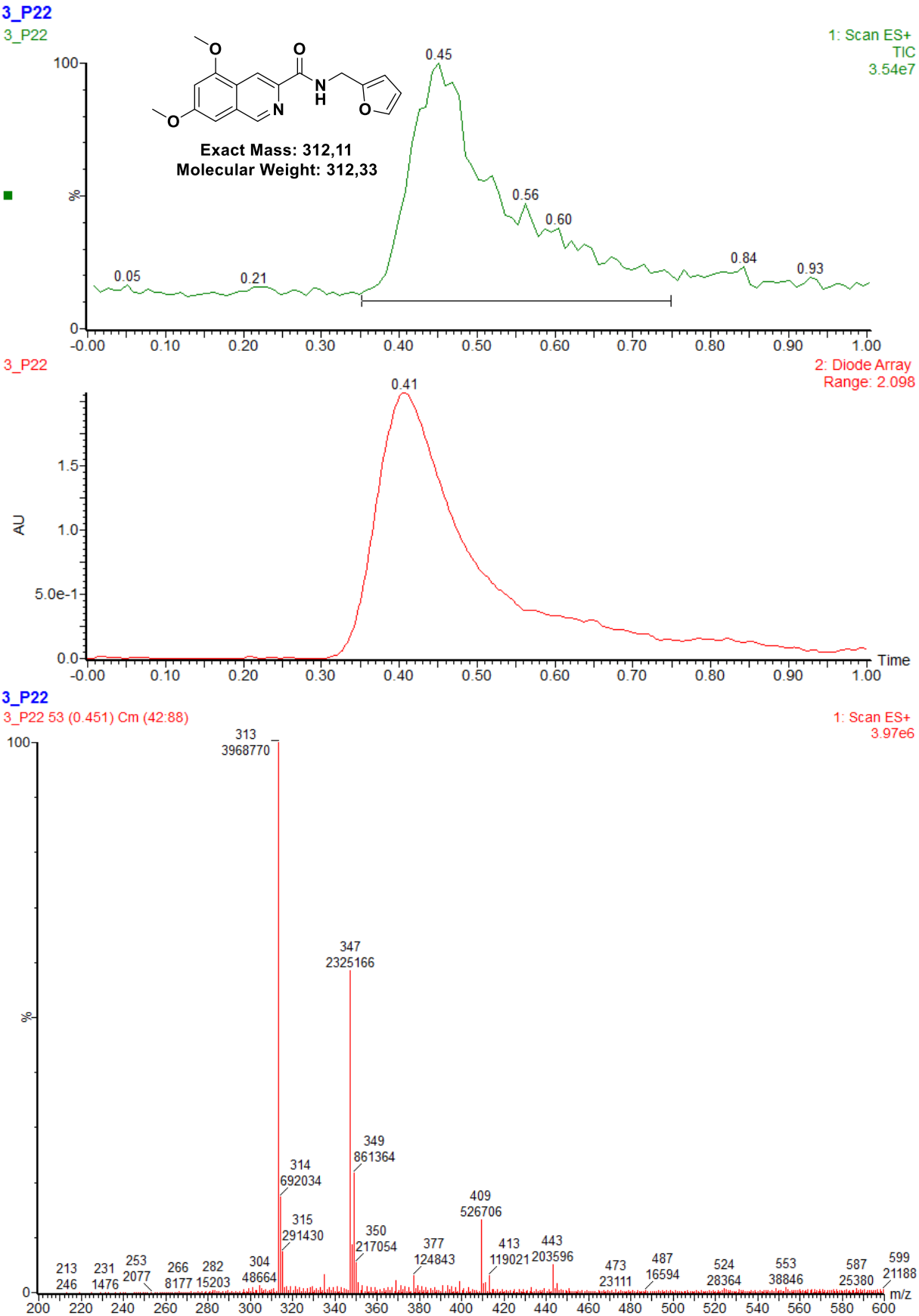

3_P19
3_P19 51 (0.434) Cm (40:89)
1: Scan ES+
1.34e7
369
13364285
370
3069897
465
1047432
332
587526
351
600043
383
552374
417
143507
433
94645
466;182248
%
m/z

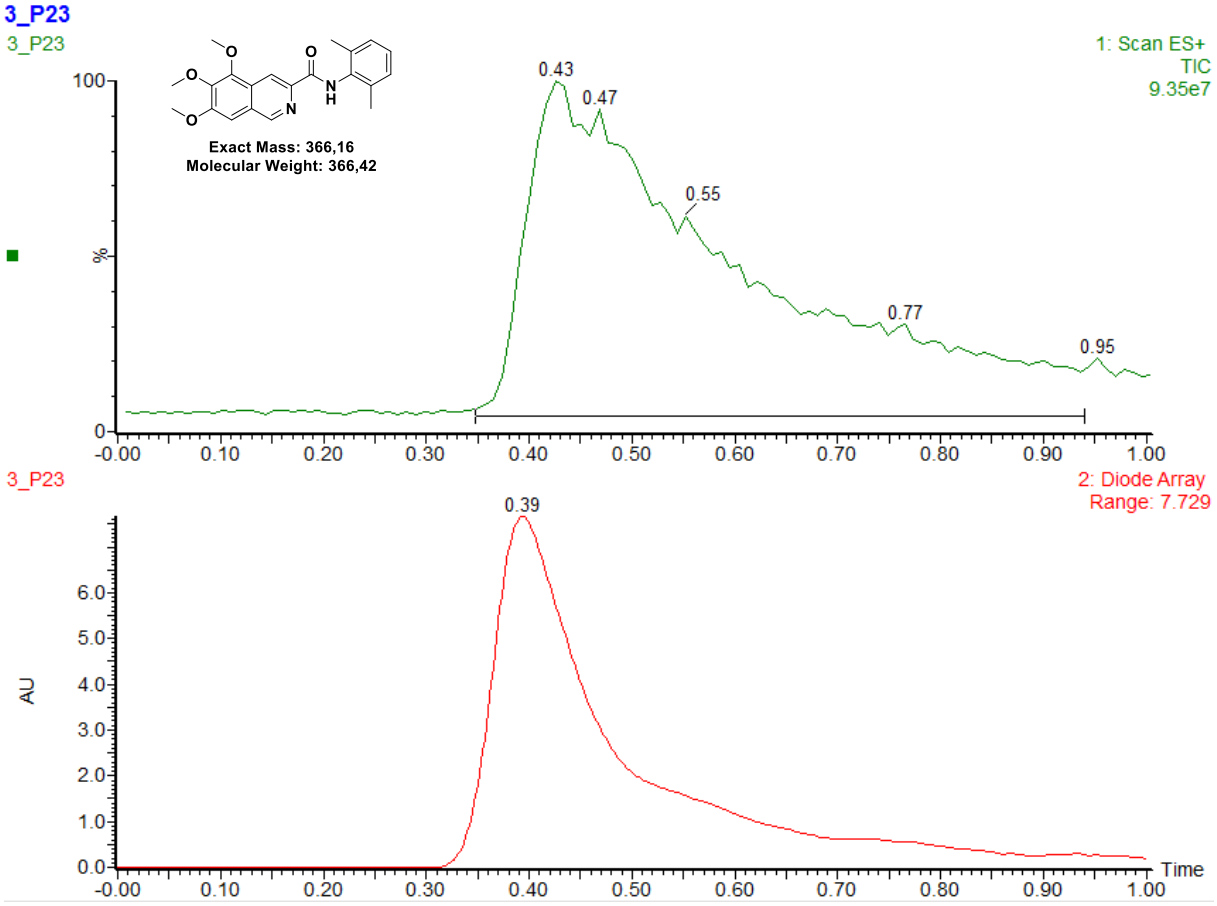

3_P20
3_P20
1: Scan ES+
TIC
3.26e7
Exact Mass: 282.08
Molecular Weight: 282.36
0.48
0.43
0.50
0.53
0.62
0.65
0.67
0.71
0.84
0.19
0.21
3_P20
2: Diode Array
Range: 2.489
0.41
0.03
0.26
0.81
AU
Time
3_P20
3_P20 56 (0.476) Cm (47:77)
1: Scan ES+
6.80e6
283
6795528
305
1554269
306
183428
342
311662
369
32517
387
37953
397
40080
419
16125
441
24735
457
16400
479
14599
515
11737
527
17584
556
36564
587
457839
599
13356
211
287
225
883
245
2103
259
4584
274
89909
m/z

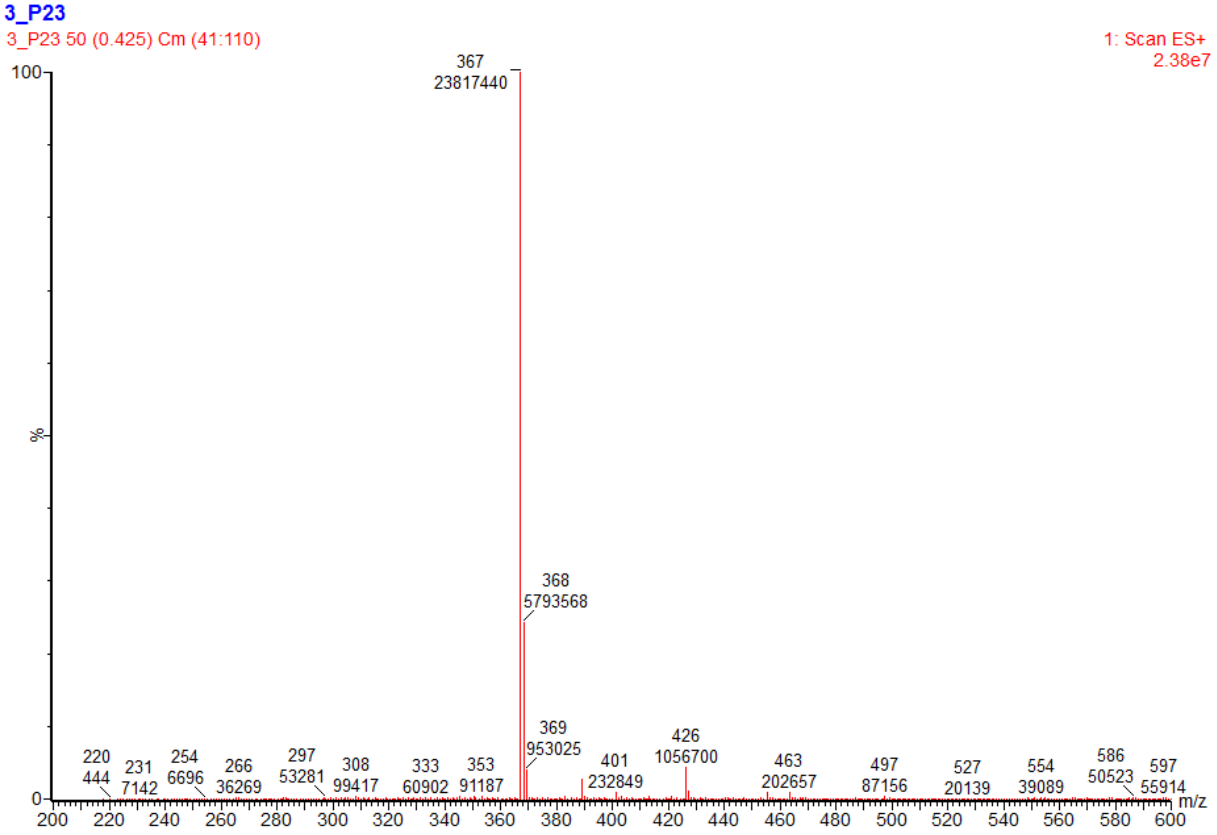

3_P21
3_P21
1: Scan ES+
TIC
2.36e7
Exact Mass: 414,16
Molecular Weight: 414,46
0.43
0.47
0.58
0.62
0.66
0.77
0.85
0.93
0.96
0.03
0.09
0.22
%
Time

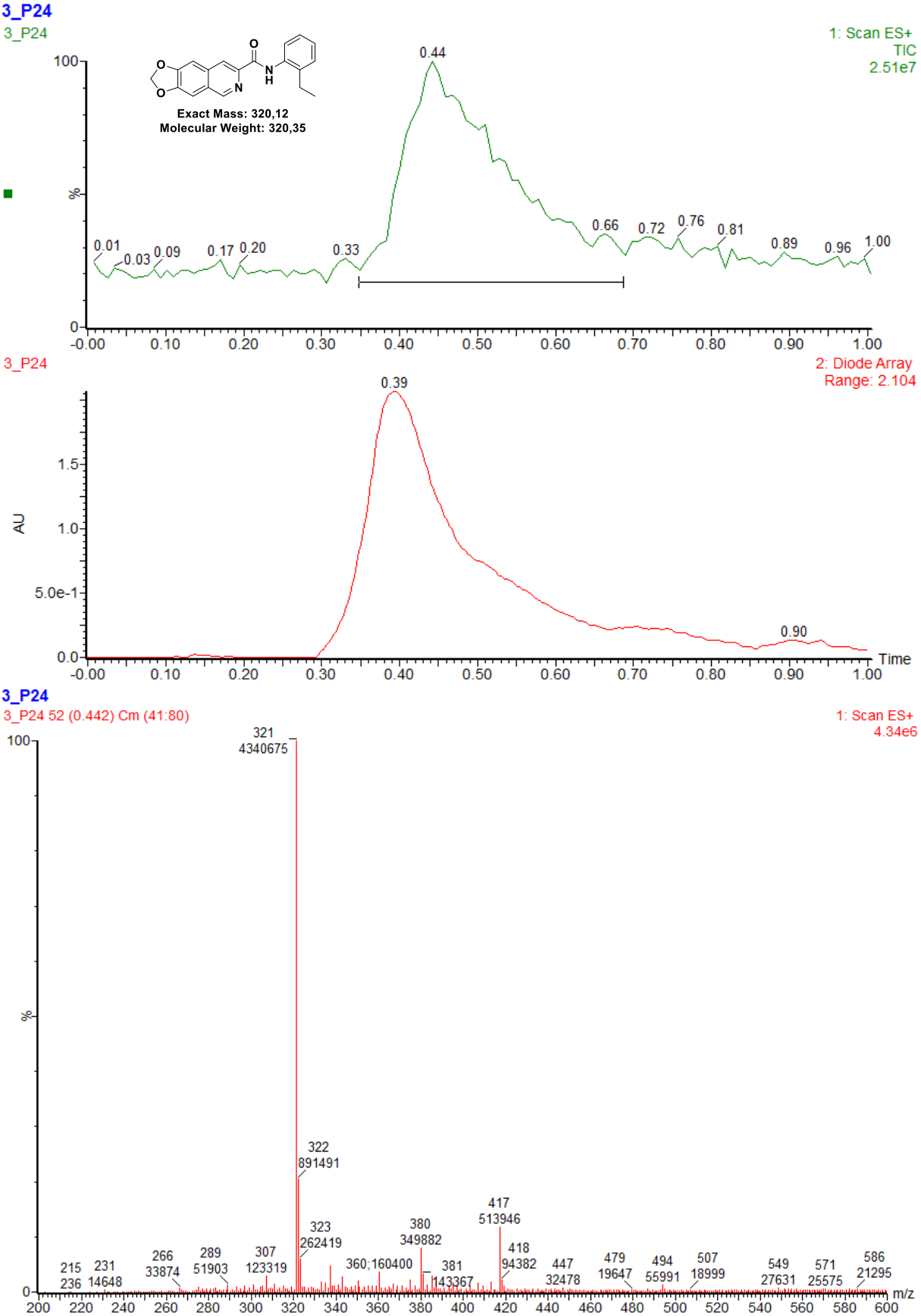
3_P21
2: Diode Array
Range: 2.989
0.40
AU
Time

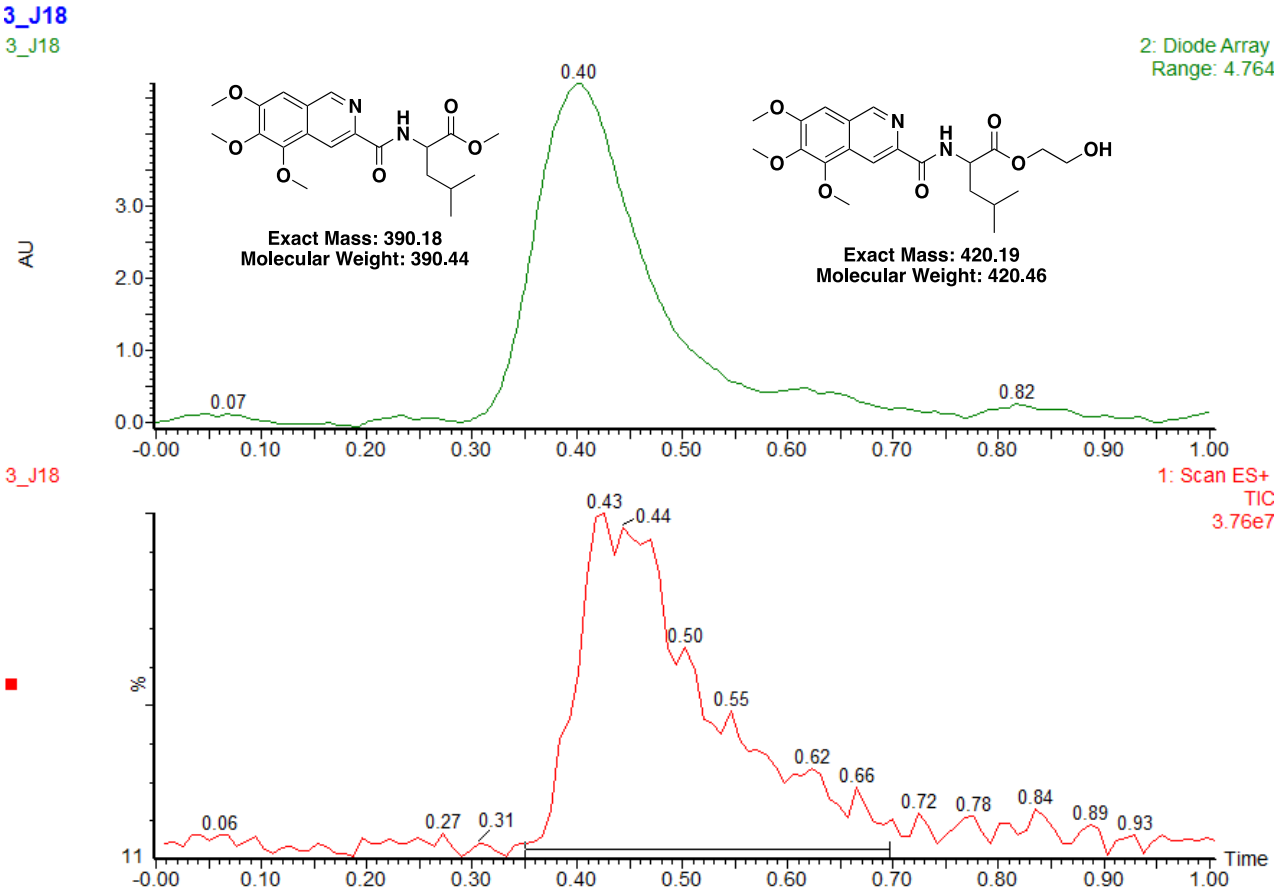

3_P21
3_P21 51 (0.434) Cm (38:76)
1: Scan ES+
1.25e6
415
1250870
316
496001
308
384769
367
351866
416
288210
511
432051
338
137659
413
142185
479
159381
512
93015
545
129833
317
92262
417
66564
463
75080
481
93655
593
31262
282
49573
301
63302
254
28367
399
77976
220
3956
231
12387
515
39568
547
50678
%
m/z

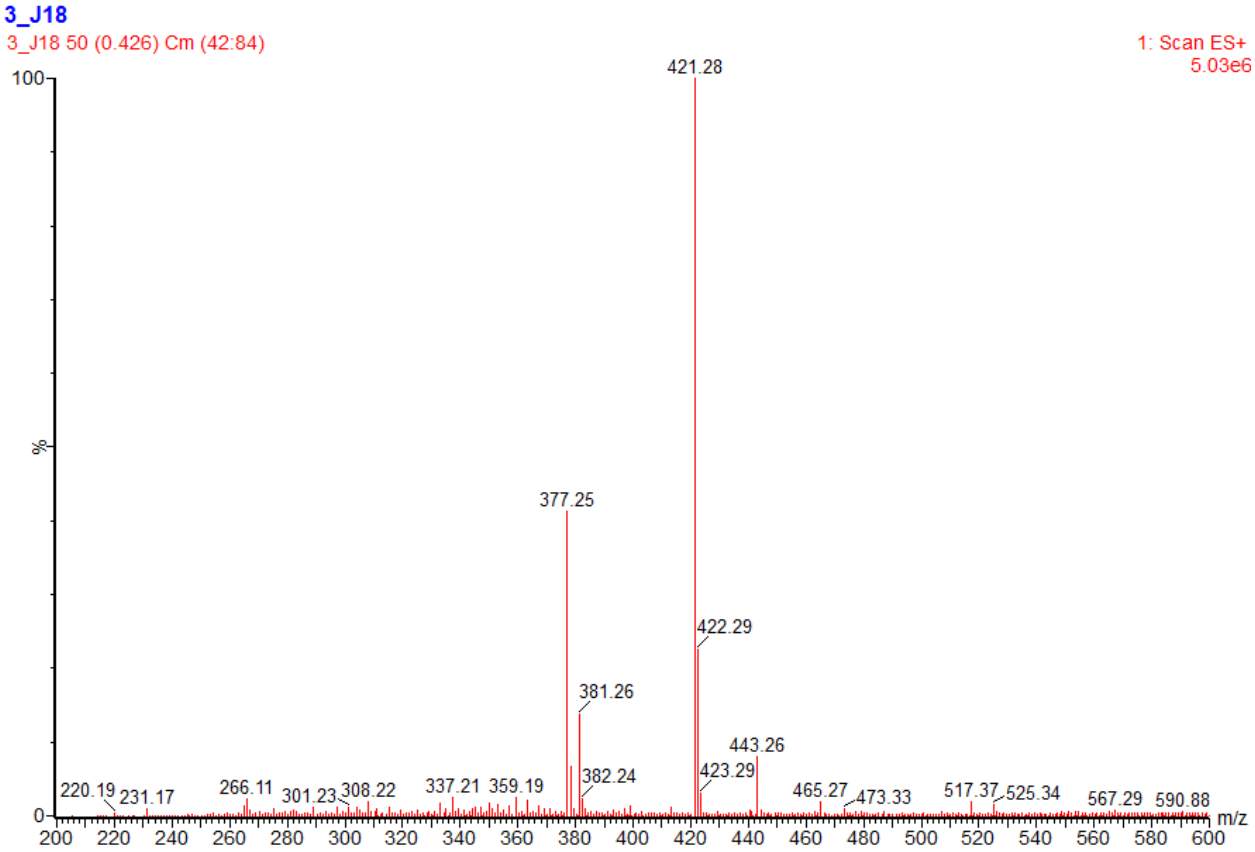

3_P22
3_P22
1: Scan ES+
TIC
3.54e7
Exact Mass: 312,11
Molecular Weight: 312,33
0.45
0.56
0.60
0.84
0.93
0.05
0.21
%
3_P22
2: Diode Array
Range: 2.098
0.41
AU
Time
3_P22
3_P22 53 (0.451) Cm (42:88)
1: Scan ES+
3.97e6
313
3968770
347
2325166
349
861364
314
692034
315
291430
350
217054
409
526706
377
124843
413
119021
443
203596
213
246
231
1476
253
2077
266
8177
282
15203
304
48664
473
23111
487
16594
524
28364
553
38846
587
25380
599
21188
m/z

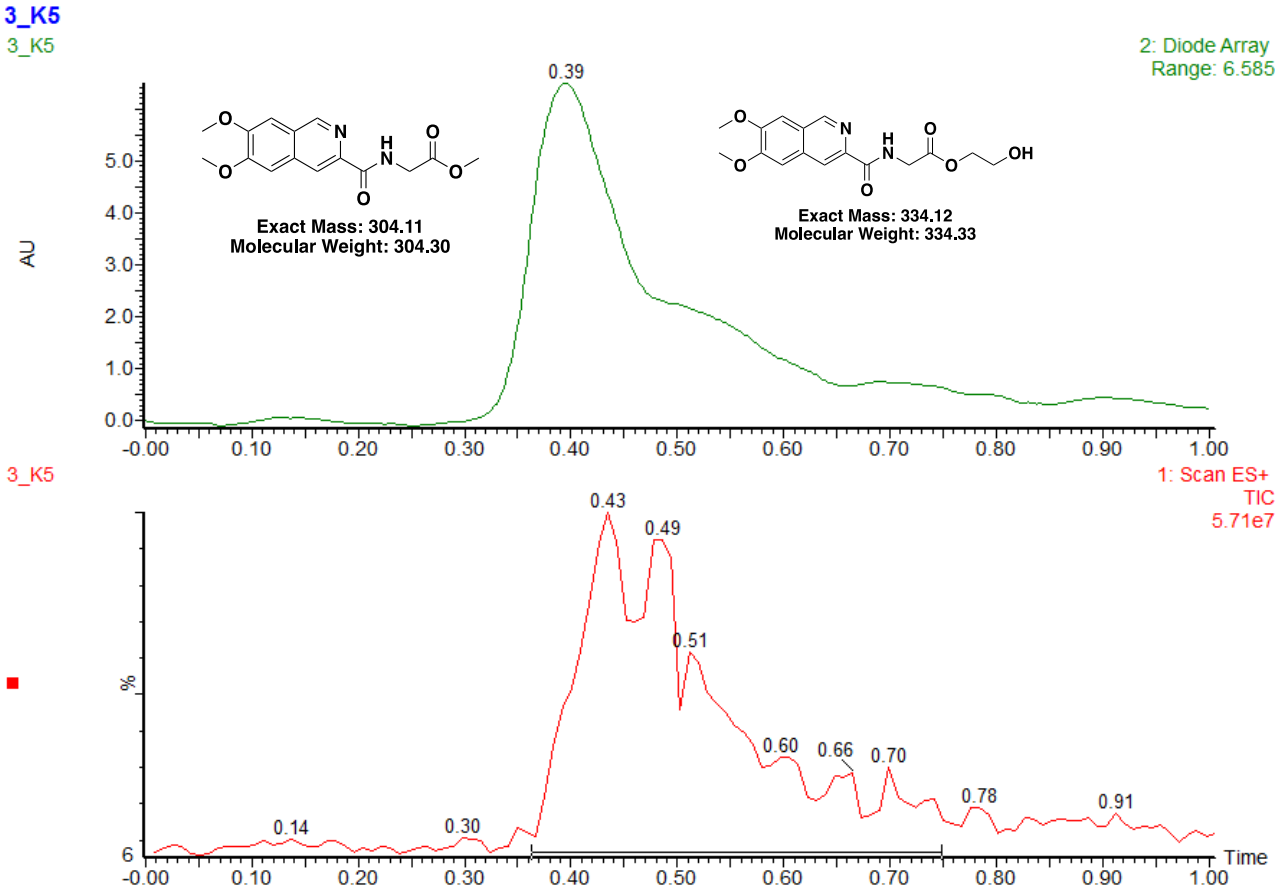

3_P23
3_P23
1: Scan ES+
TIC
9.35e7
Exact Mass: 366,16
Molecular Weight: 366,42
0.43
0.47
0.55
0.77
0.95
%
3_P23
2: Diode Array
Range: 7.729
0.39
AU
Time

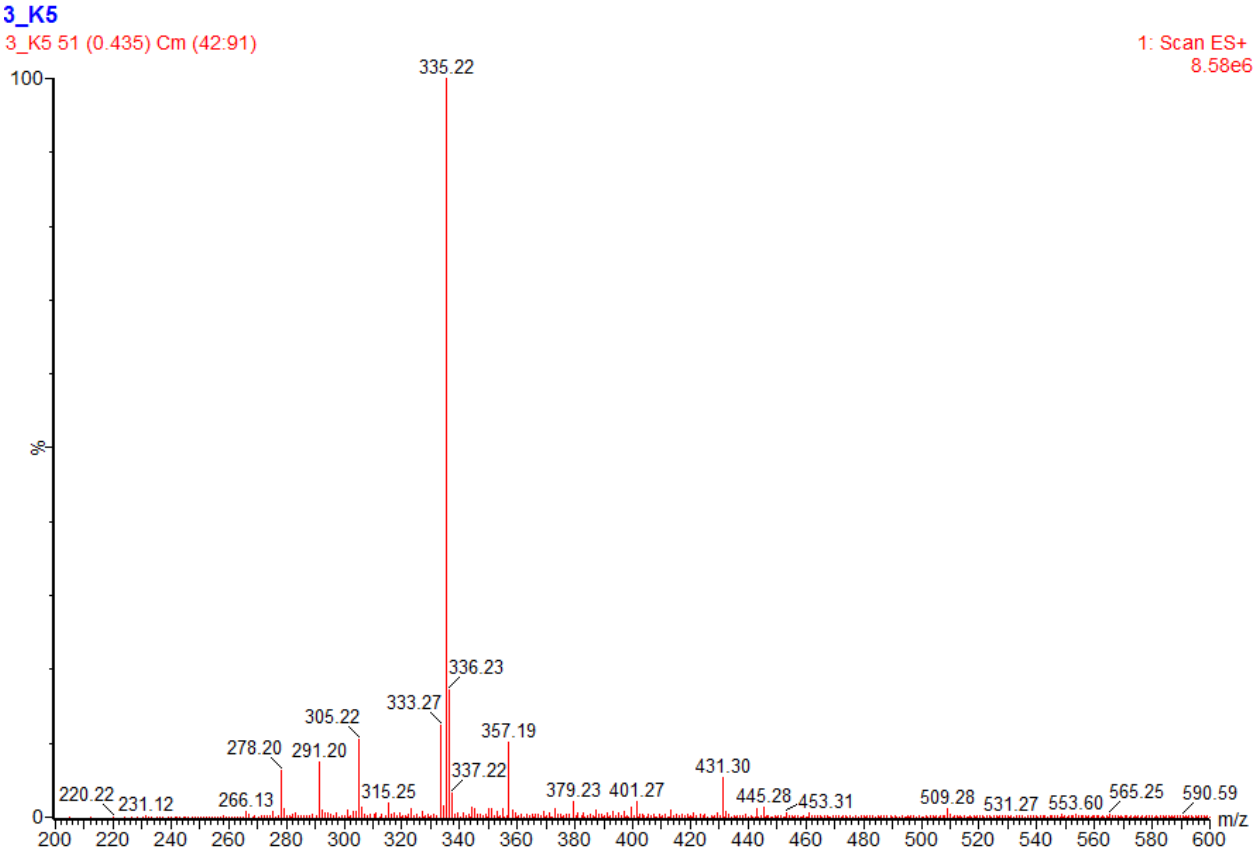

3_P23
3_P23 50 (0.425) Cm (41:110)
1: Scan ES+
2.38e7
367
23817440
368
5793568
369
953025
426
1056700
%
m/z


3_P24
3_P24
1: Scan ES+
TIC
2.51e7
Exact Mass: 320,12
Molecular Weight: 320,35
100
%
0
0.01
0.03
0.09
0.17
0.20
0.33
0.44
0.66
0.72
0.76
0.81
0.89
0.96
1.00
-0.00
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.90
1.00
3_P24
2: Diode Array
Range: 2.104
AU
1.5
1.0
5.0e-1
0.0
0.39
0.90
Time
3_P24
3_P24 52 (0.442) Cm (41:80)
1: Scan ES+
4.34e6
100
%
0
321
4340675
322
891491
323
262419
215
236
231
14648
266
33874
289
51903
307
123319
360;160400
380
349882
381
143367
417
513946
418
94382
447
32478
479
19647
494
55991
507
18999
549
27631
571
25575
586
21295
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500
520
540
560
580
600
m/z


3_J18
3_J18
2: Diode Array
Range: 4.764
Exact Mass: 390.18
Molecular Weight: 390.44
Exact Mass: 420.19
Molecular Weight: 420.46
AU
0.40
0.07
0.82
3_J18
1: Scan ES+
TIC
3.76e7
%
0.43
0.44
0.50
0.55
0.62
0.66
0.72
0.78
0.84
0.89
0.93
0.06
0.27
0.31
Time


3_J18
3_J18 50 (0.426) Cm (42:84)
1: Scan ES+
5.03e6
%
421.28
377.25
422.29
381.26
443.26
423.29
382.24
220.19
231.17
266.11
301.23
308.22
337.21
359.19
465.27
473.33
517.37
525.34
567.29
590.88
m/z


3_K5
3_K5
2: Diode Array
Range: 6.585
0.39
Exact Mass: 304.11
Molecular Weight: 304.30
Exact Mass: 334.12
Molecular Weight: 334.33
AU
3_K5
1: Scan ES+
TIC
5.71e7
0.43
0.49
0.51
0.60
0.66
0.70
0.78
0.91
0.14
0.30
%
Time

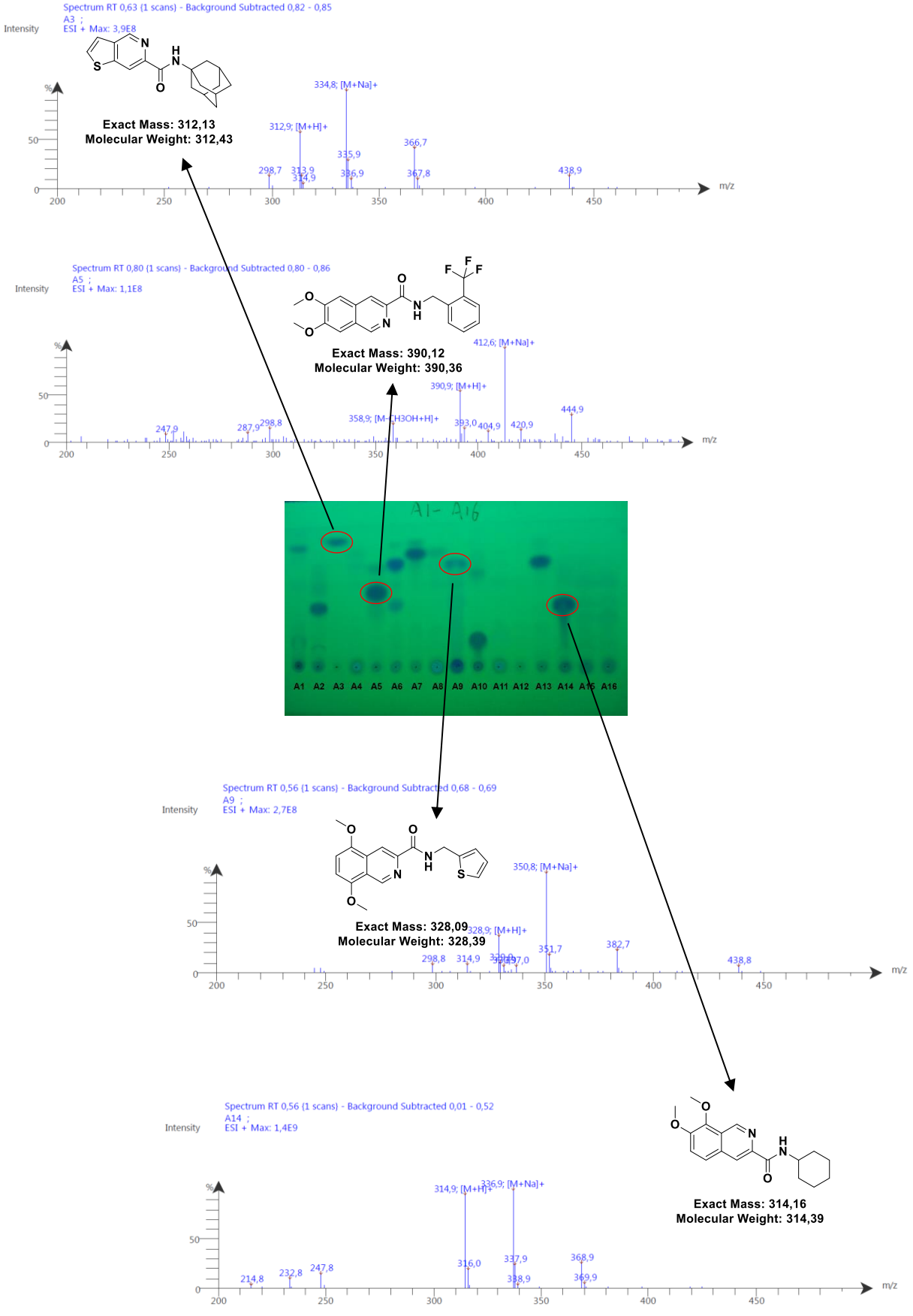

3_K5
3_K5 51 (0.435) Cm (42:91)
1: Scan ES+
8.58e6
335.22
336.23
333.27
305.22
357.19
278.20
291.20
337.22
431.30
220.22
231.12
266.13
315.25
379.23
401.27
445.28
453.31
509.28
531.27
553.60
565.25
590.59
%
m/z

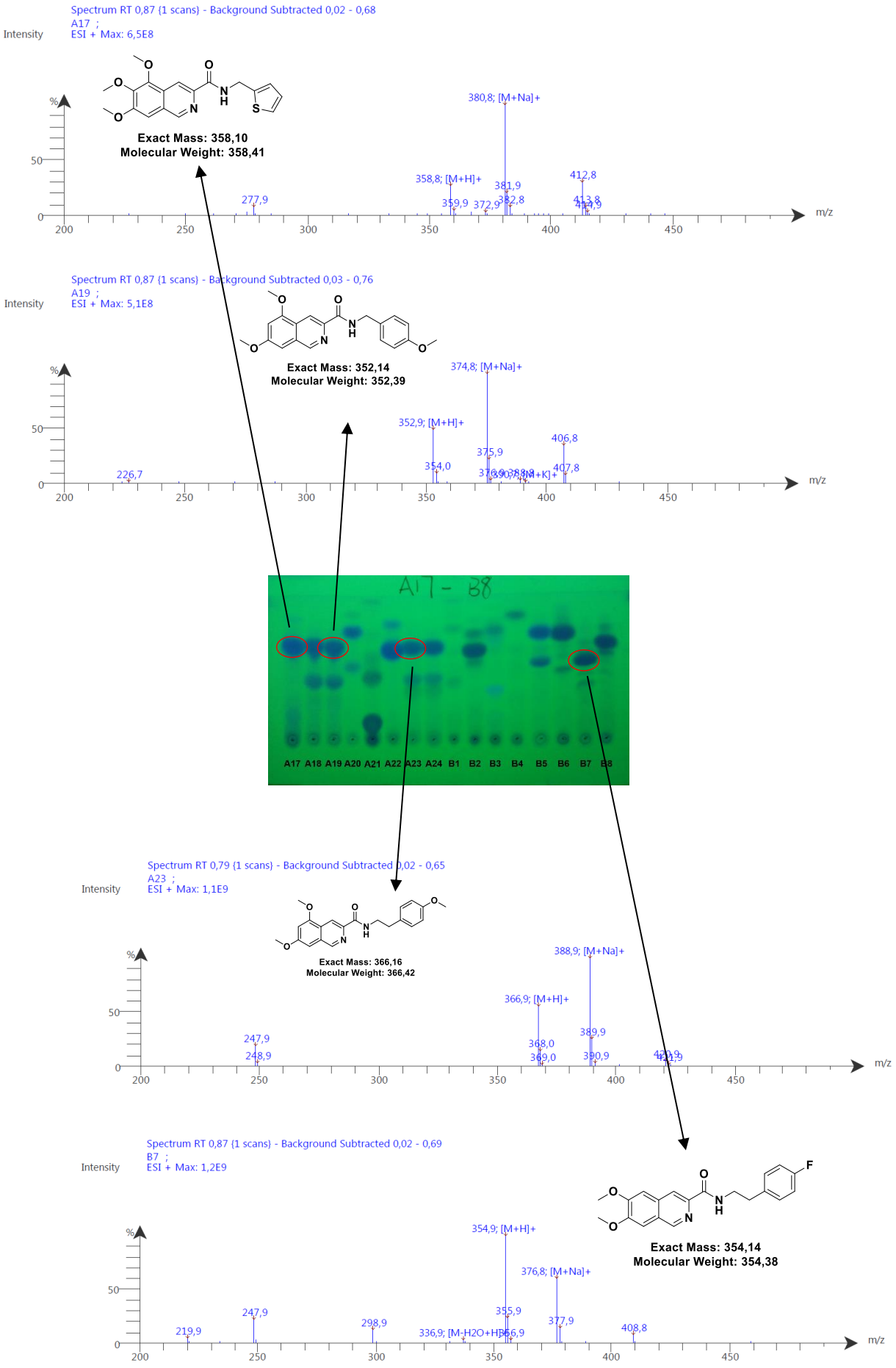
4.4.2. TLC-UV-MS analysis

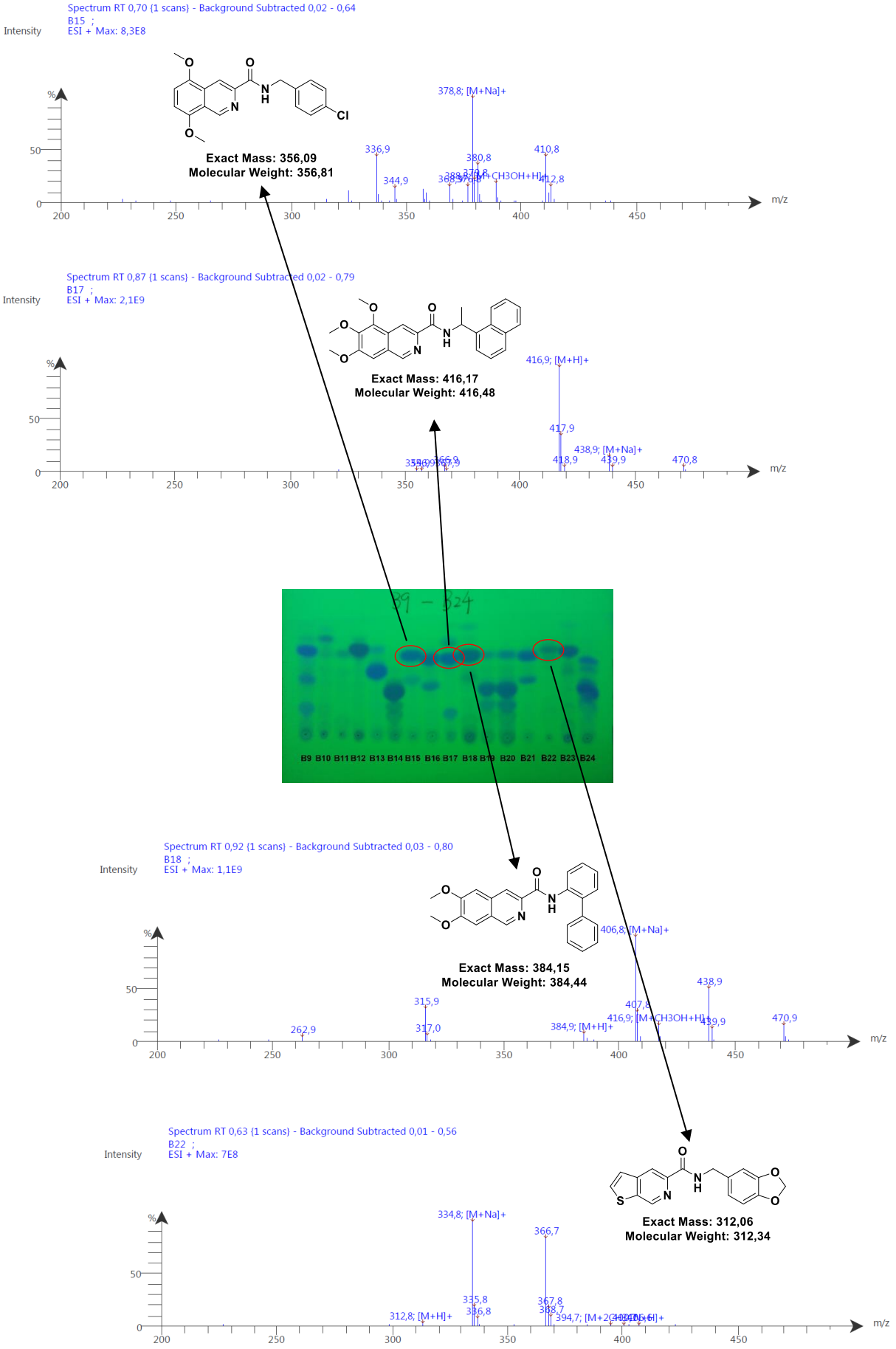
Thin layer chromatography was performed on silica gel plates (0.20 mm thick, particle size 25 µm, Merck). Mass analysis of TLC plates was performed on an Advion Plate Express connected to an Advion compact mass spectrometer (CMS) fitted with an electrospray ionization (ESI^+) and using Mass Express software.
The isocratic elution was performed with MeOH, 5% H_2O, 0.1% formic acid, at a flow rate of 0.2 mL/min. Full scan mass spectra were recorded in the positive ionization mode (ESI^+) using a capillary temperature of 250 °C, voltage of 150 V, source voltage offset of 20 V, source voltage span of 30, source gas temperature of 200 °C, and an ESI voltage of 3.5 kV.

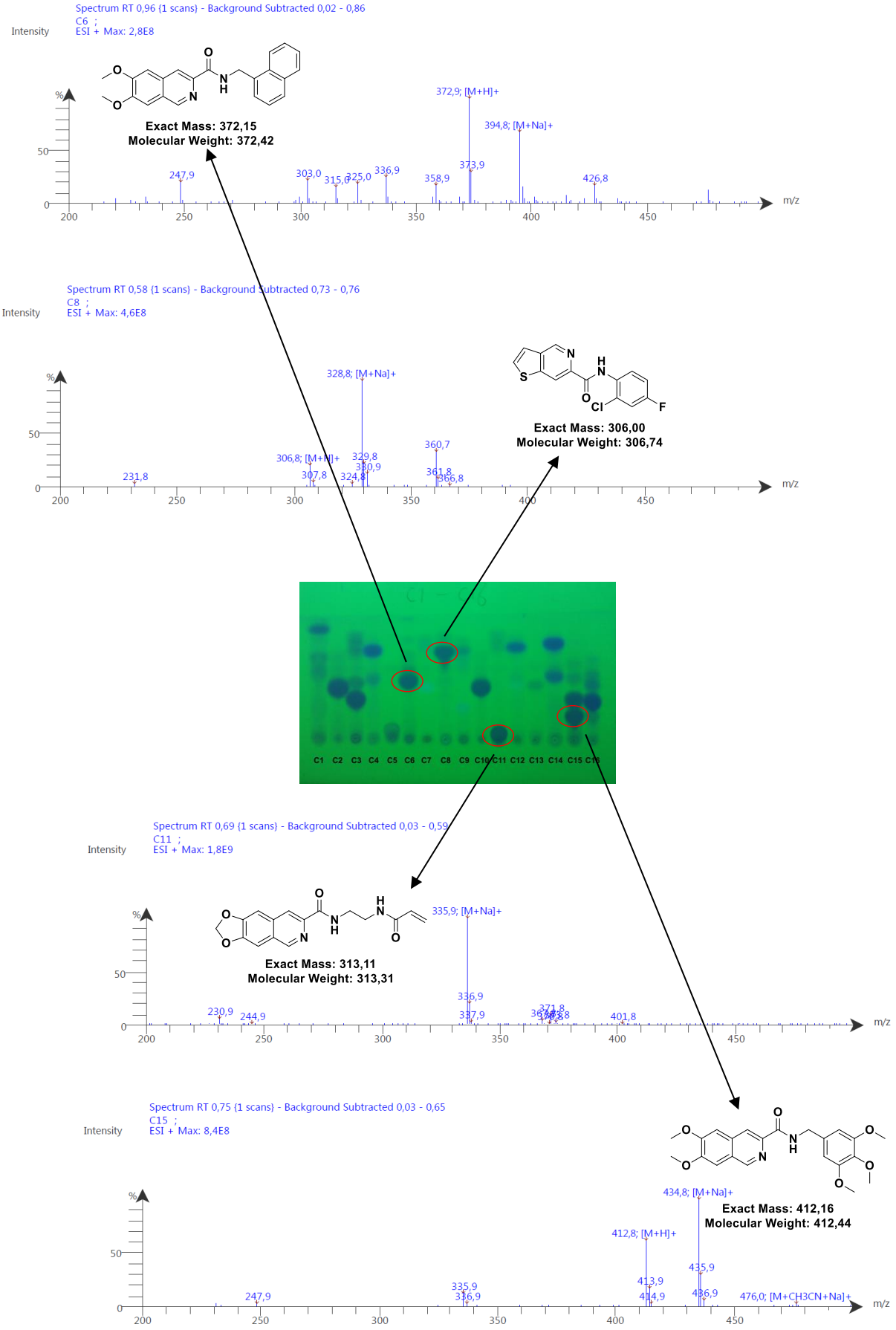
Each well of the 384 well destination plate was diluted with 20 µL MeOH. In order to analyze the 384 well destination plate, 24 TLC plates with each 16 spots (one row of the 384 well plate) were developed with petroleum ether - ethyl acetate (1:1, v/v). The developed TLC plates were placed into the plate express. Major spots of interest detected by UV were marked with a soft pencil on the plate and then directly transferred to the CMS. Advion Mass Express and Data Express software was used for mass measurements and data processing.

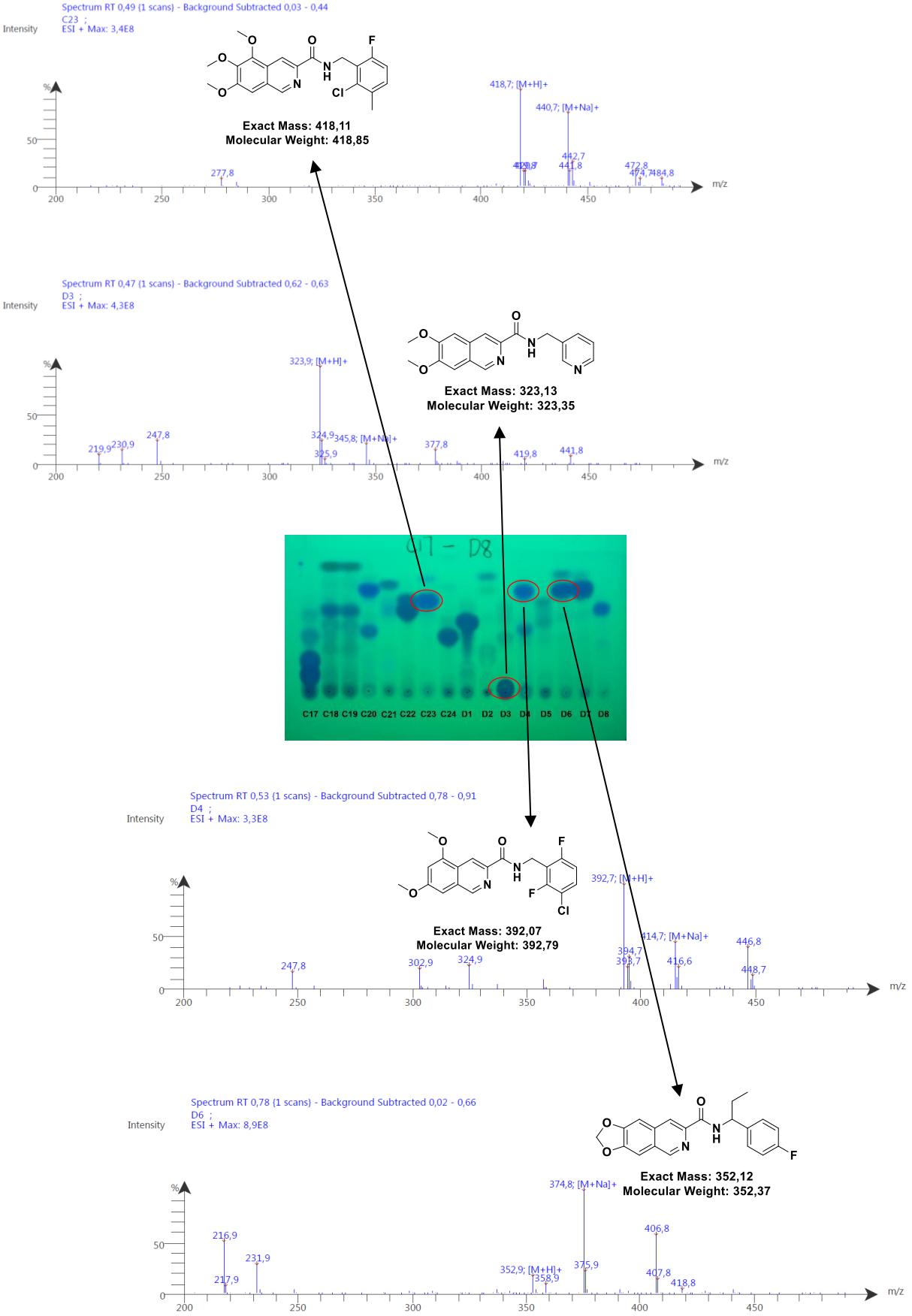
Examples of TLC-UV-MS analytics

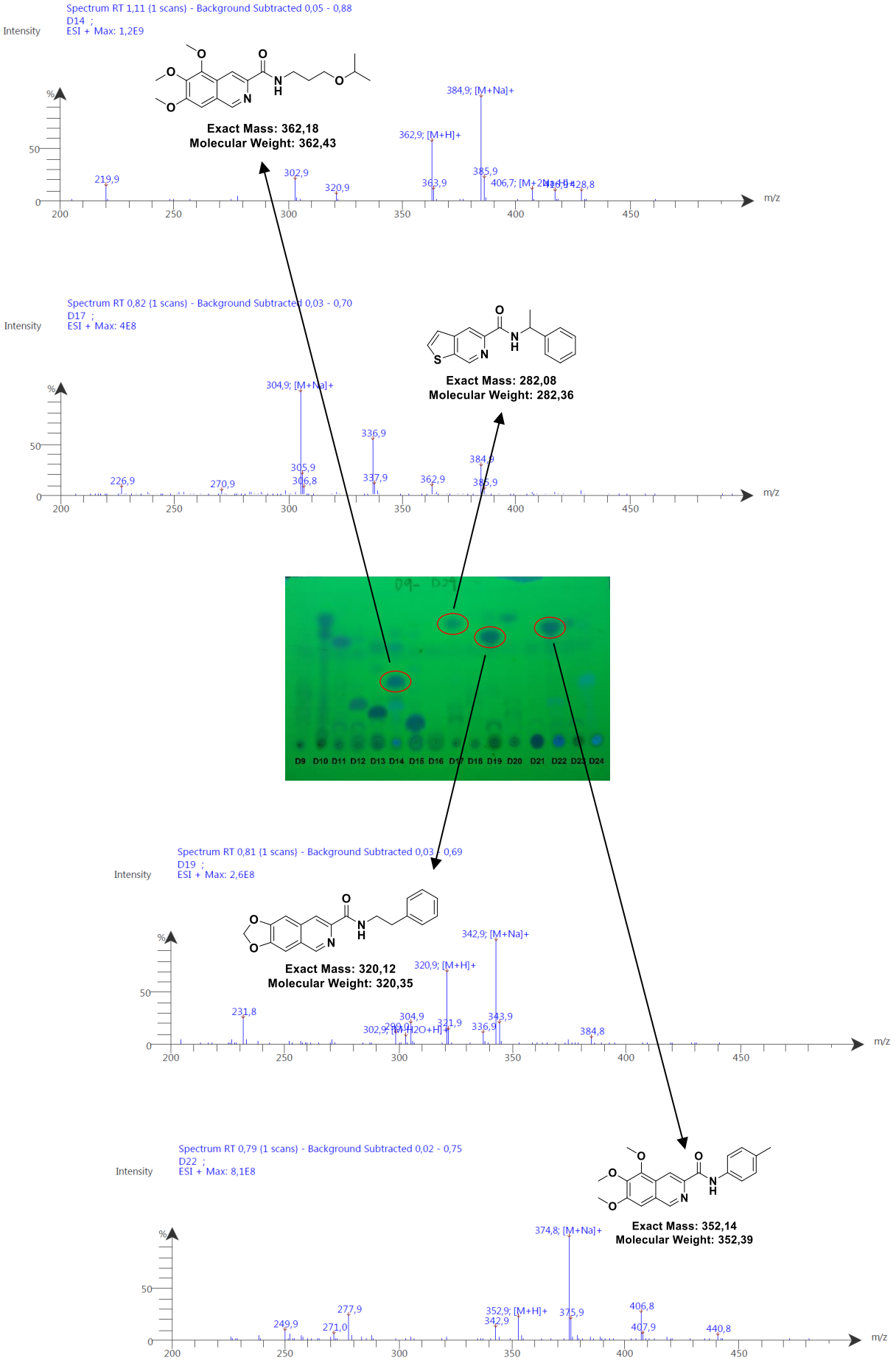


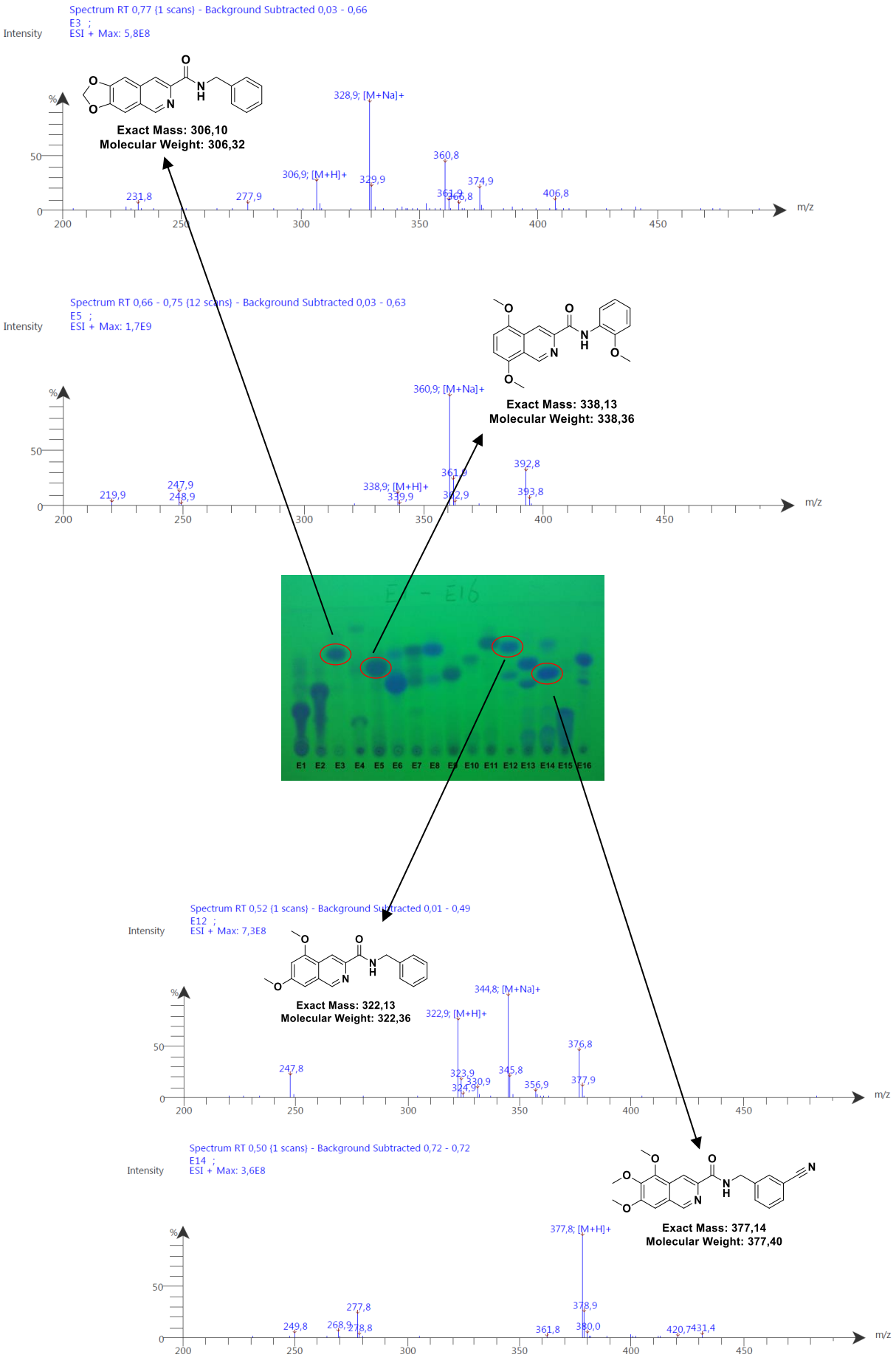

Spectrum RT 0,87 {1 scans} - Background Subtracted 0,02 - 0,68
A17 ;
Intensity
ESI + Max: 6,5E8
Exact Mass: 358,10
Molecular Weight: 358,41
380,8; [M+Na]+
358,8; [M+H]+
412,8
277,9
Spectrum RT 0,87 {1 scans} - Background Subtracted 0,03 - 0,76
A19 ;
Intensity
ESI + Max: 5,1E8
Exact Mass: 352,14
Molecular Weight: 352,39
374,8; [M+Na]+
352,9; [M+H]+
406,8
375,9
354,0
226,7
407,8
A17 - B8
A17 A18 A19 A20 A21 A22 A23 A24 B1 B2 B3 B4 B5 B6 B7 B8
Spectrum RT 0,79 {1 scans} - Background Subtracted 0,02 - 0,65
A23 ;
Intensity
ESI + Max: 1,1E9
Exact Mass: 366,16
Molecular Weight: 366,42
388,9; [M+Na]+
366,9; [M+H]+
247,9
248,9
368,0
369,0
389,9
390,9
Spectrum RT 0,87 {1 scans} - Background Subtracted 0,02 - 0,69
B7 ;
Intensity
ESI + Max: 1,2E9
Exact Mass: 354,14
Molecular Weight: 354,38
354,9; [M+H]+
376,8; [M+Na]+
247,9
219,9
298,9
355,9
377,9
408,8
m/z

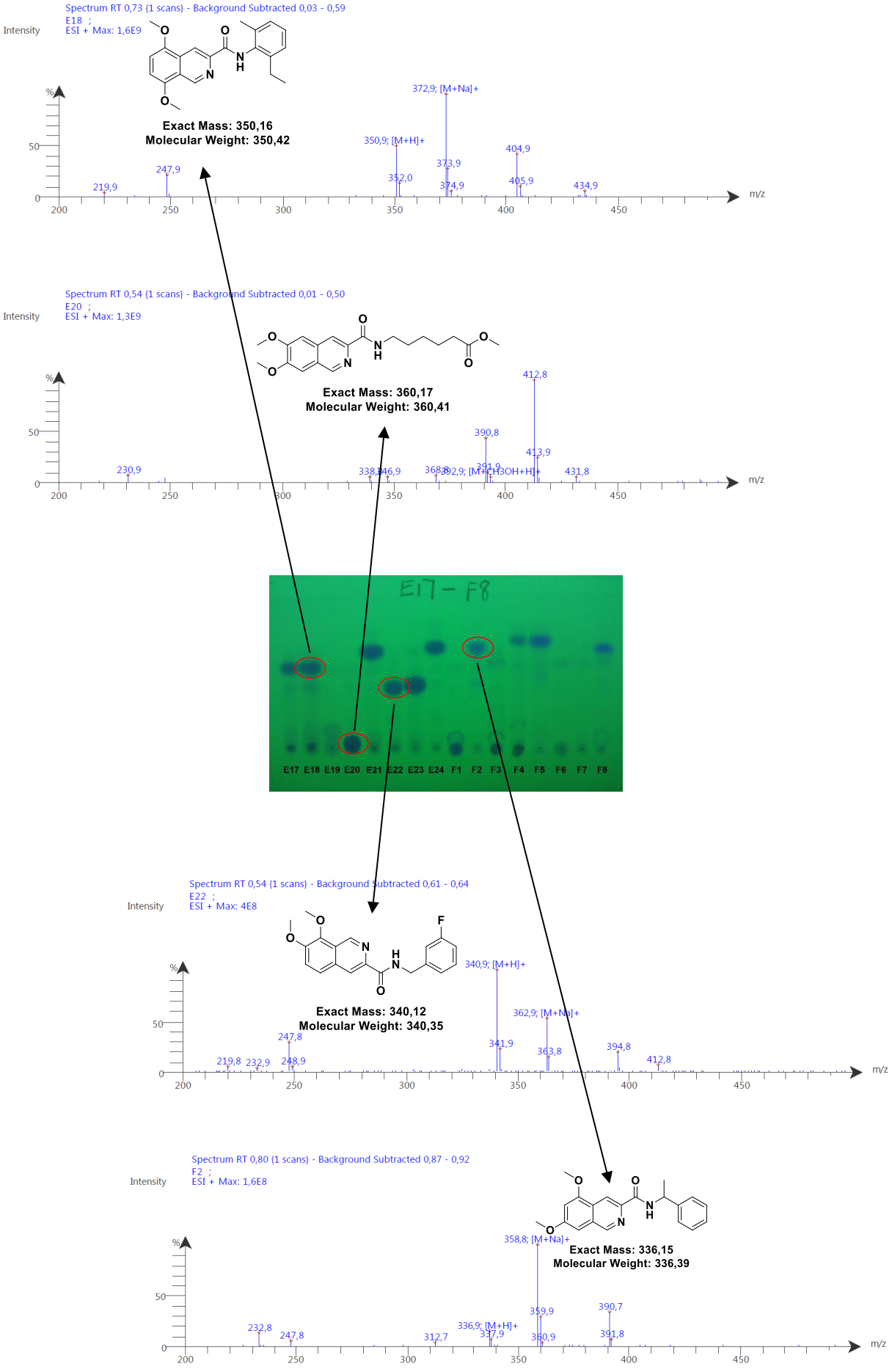

Spectrum RT 0,70 (1 scans) - Background Subtracted 0,02 - 0,64
B15 ;
Intensity
ESI + Max: 8,3E8
Exact Mass: 356,09
Molecular Weight: 356,81
378,8; [M+Na]+
336,9
410,8
380,8
344,9
412,8
Spectrum RT 0,87 (1 scans) - Background Subtracted 0,02 - 0,79
B17 ;
Intensity
ESI + Max: 2,1E9
Exact Mass: 416,17
Molecular Weight: 416,48
416,9; [M+H]+
417,9
438,9; [M+Na]+
470,8
B9 B10 B11 B12 B13 B14 B15 B16 B17 B18 B19 B20 B21 B22 B23 B24
Spectrum RT 0,92 (1 scans) - Background Subtracted 0,03 - 0,80
B18 ;
Intensity
ESI + Max: 1,1E9
Exact Mass: 384,15
Molecular Weight: 384,44
406,8; [M+Na]+
438,9
315,9
407,8
262,9
317,0
384,9; [M+H]+
416,9; [M+CH3OH+H]+
439,9
470,9
Spectrum RT 0,63 (1 scans) - Background Subtracted 0,01 - 0,56
B22 ;
Intensity
ESI + Max: 7E8
Exact Mass: 312,06
Molecular Weight: 312,34
334,8; [M+Na]+
366,7
335,8
367,8
312,8; [M+H]+
336,8
368,7
m/z

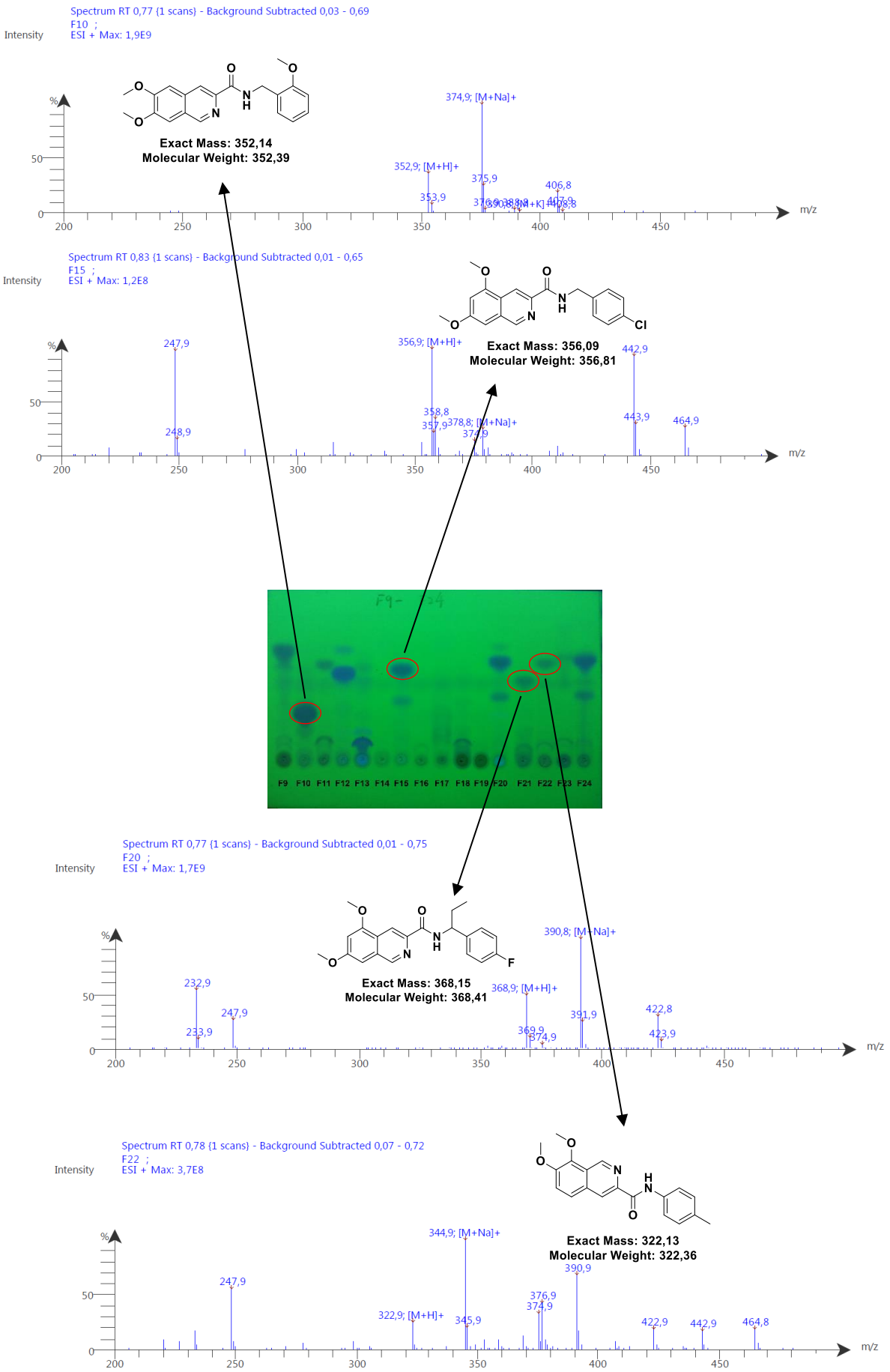

Spectrum RT 0,96 (1 scans) - Background Subtracted 0,02 - 0,86
C6 ;
ESI + Max: 2,8E8
Intensity
Exact Mass: 372,15
Molecular Weight: 372,42
372,9; [M+H]+
394,8; [M+Na]+
247,9
303,0
315,0
325,0
336,9
358,9
373,9
426,8
m/z
Spectrum RT 0,58 (1 scans) - Background Subtracted 0,73 - 0,76
C8 ;
ESI + Max: 4,6E8
Intensity
328,8; [M+Na]+
Exact Mass: 306,00
Molecular Weight: 306,74
231,8
306,8; [M+H]+
307,8
324,8
329,8
330,9
360,7
361,8
366,8
m/z
C1 C2 C3 C4 C5 C6 C7 C8 C9 C10 C11 C12 C13 C14 C15 C16
Spectrum RT 0,69 (1 scans) - Background Subtracted 0,03 - 0,59
C11 ;
ESI + Max: 1,8E9
Intensity
335,9; [M+Na]+
Exact Mass: 313,11
Molecular Weight: 313,31
230,9
244,9
336,9
337,9
371,8
401,8
m/z
Spectrum RT 0,75 (1 scans) - Background Subtracted 0,03 - 0,65
C15 ;
ESI + Max: 8,4E8
Intensity
434,8; [M+Na]+
Exact Mass: 412,16
Molecular Weight: 412,44
412,8; [M+H]+
435,9
413,9
414,9
436,9
247,9
335,9
336,9
476,0; [M+CH3CN+Na]+
m/z

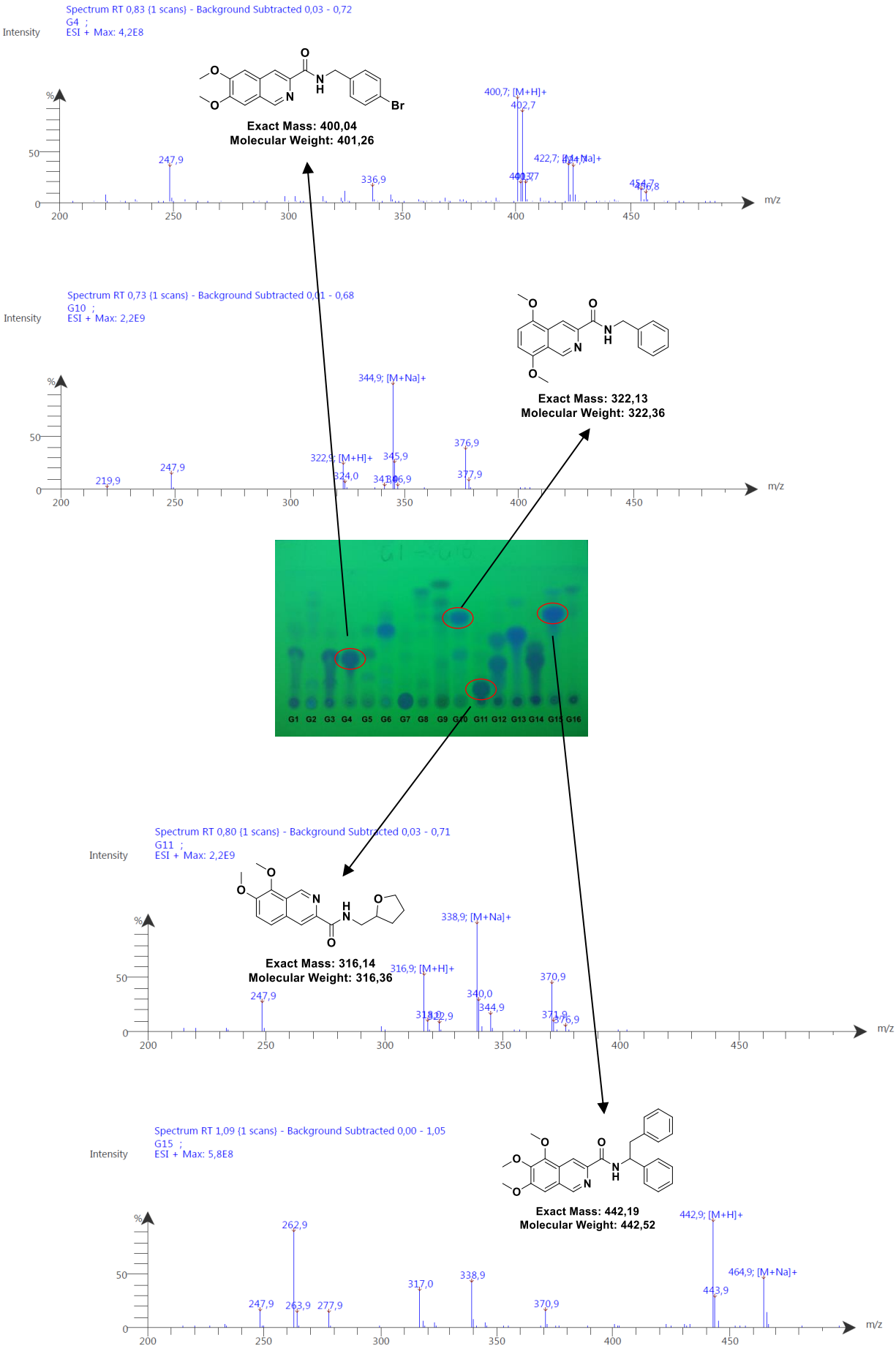

Spectrum RT 0,49 (1 scans) - Background Subtracted 0,03 - 0,44
C23 ;
Intensity
ESI + Max: 3,4E8
Exact Mass: 418,11
Molecular Weight: 418,85
418,7; [M+H]+
440,7; [M+Na]+
277,8
442,7
441,8
472,8
474,7
484,8
m/z
Spectrum RT 0,47 (1 scans) - Background Subtracted 0,62 - 0,63
D3 ;
Intensity
ESI + Max: 4,3E8
Exact Mass: 323,13
Molecular Weight: 323,35
323,9; [M+H]+
219,9
230,9
247,8
324,9
345,8; [M+Na]+
325,9
377,8
419,8
441,8
m/z
C17 C18 C19 C20 C21 C22 C23 C24 D1 D2 D3 D4 D5 D6 D7 D8
Spectrum RT 0,53 (1 scans) - Background Subtracted 0,78 - 0,91
D4 ;
Intensity
ESI + Max: 3,3E8
Exact Mass: 392,07
Molecular Weight: 392,79
392,7; [M+H]+
414,7; [M+Na]+
247,8
302,9
324,9
394,7
393,7
416,6
446,8
448,7
m/z
Spectrum RT 0,78 (1 scans) - Background Subtracted 0,02 - 0,66
D6 ;
Intensity
ESI + Max: 8,9E8
Exact Mass: 352,12
Molecular Weight: 352,37
374,8; [M+Na]+
216,9
231,9
217,9
352,9; [M+H]+
358,9
375,9
406,8
407,8
418,8
m/z

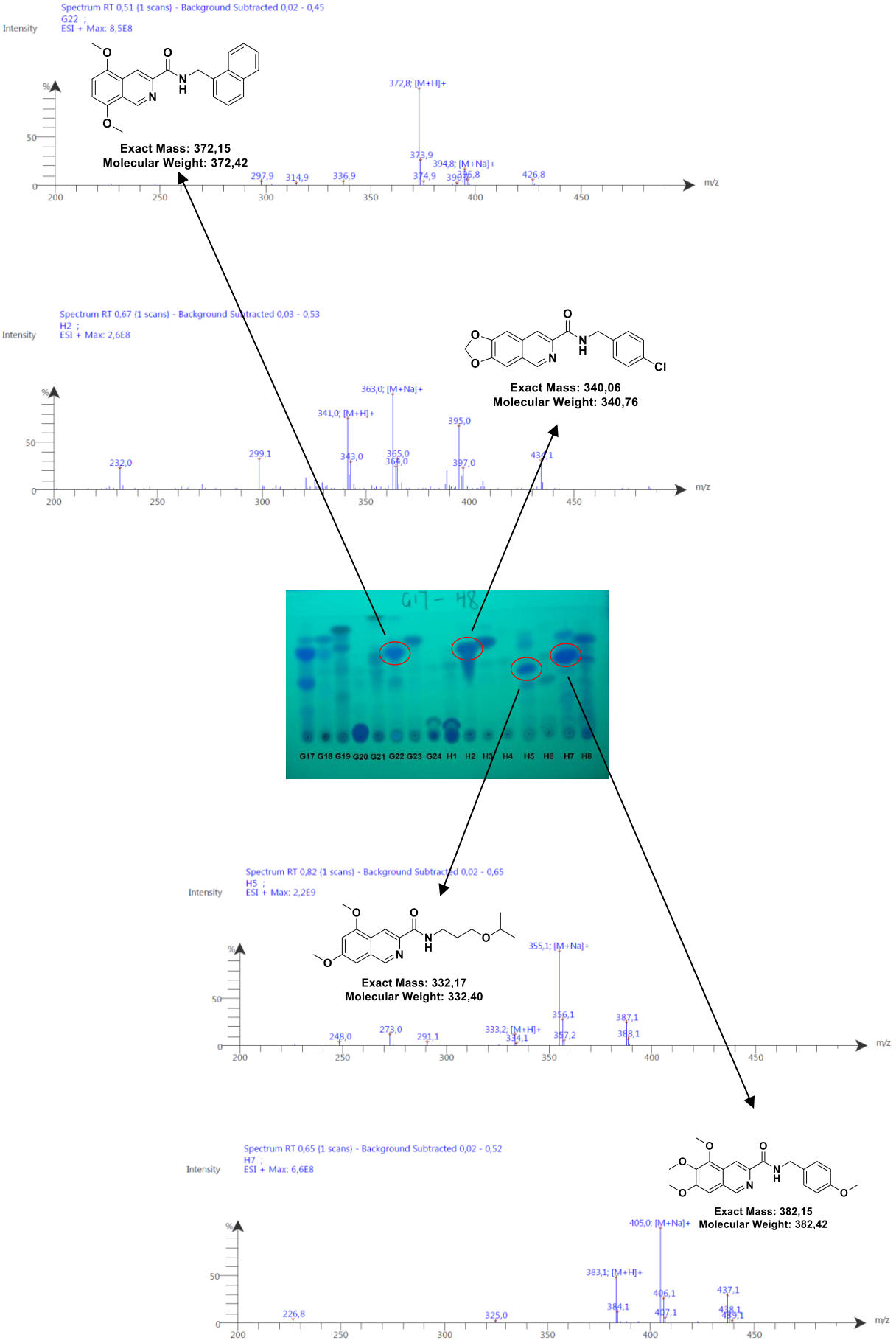

Spectrum RT 1,11 {1 scans} - Background Subtracted 0,05 - 0,88
D14 ;
Intensity
ESI + Max: 1,2E9
Exact Mass: 362,18
Molecular Weight: 362,43
384,9; [M+Na]+
362,9; [M+H]+
302,9
219,9
320,9
363,9
385,9
406,7; [M+2Na-H]+
428,8
m/z
Spectrum RT 0,82 {1 scans} - Background Subtracted 0,03 - 0,70
D17 ;
Intensity
ESI + Max: 4E8
Exact Mass: 282,08
Molecular Weight: 282,36
304,9; [M+Na]+
336,9
305,9
306,8
384,9
226,9
270,9
337,9
362,9
385,9
m/z
D9 D10 D11 D12 D13 D14 D15 D16 D17 D18 D19 D20 D21 D22 D23 D24
Spectrum RT 0,81 {1 scans} - Background Subtracted 0,03 - 0,69
D19 ;
Intensity
ESI + Max: 2,6E8
Exact Mass: 320,12
Molecular Weight: 320,35
342,9; [M+Na]+
320,9; [M+H]+
231,8
304,9
343,9
321,9
336,9
384,8
m/z
Spectrum RT 0,79 {1 scans} - Background Subtracted 0,02 - 0,75
D22 ;
Intensity
ESI + Max: 8,1E8
Exact Mass: 352,14
Molecular Weight: 352,39
374,8; [M+Na]+
277,9
249,9
271,0
352,9; [M+H]+
342,9
375,9
406,8
407,9
440,8
m/z

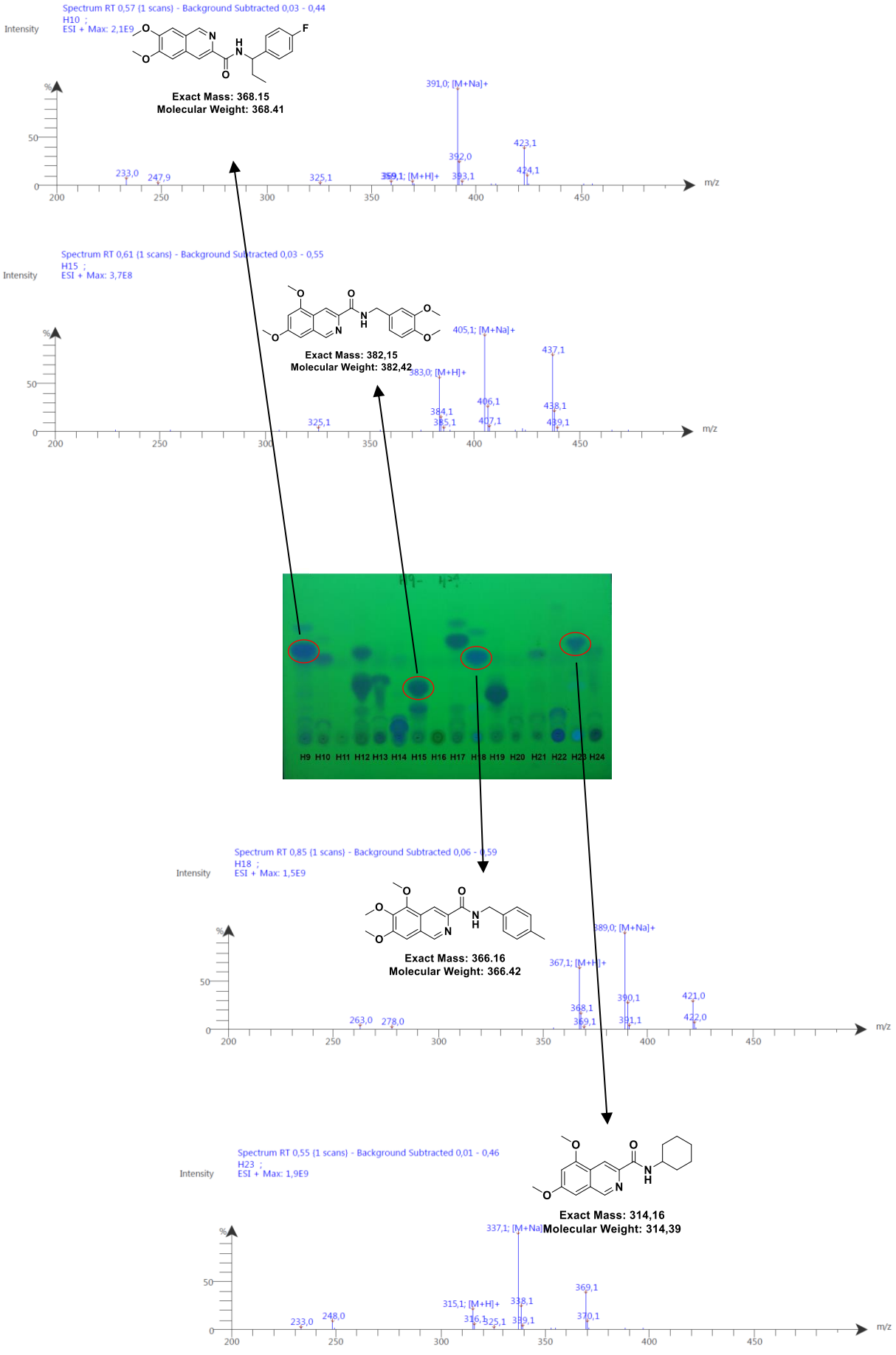

Spectrum RT 0,77 {1 scans} - Background Subtracted 0,03 - 0,66
E3 ;
Intensity
ESI + Max: 5,8E8
Exact Mass: 306,10
Molecular Weight: 306,32
328,9; [M+Na]+
306,9; [M+H]+
360,8
329,9
374,9
231,8
277,9
406,8
m/z
Spectrum RT 0,66 - 0,75 {12 scans} - Background Subtracted 0,03 - 0,63
E5 ;
Intensity
ESI + Max: 1,7E9
Exact Mass: 338,13
Molecular Weight: 338,36
360,9; [M+Na]+
392,8
361,9
247,9
219,9
248,9
338,9; [M+H]+
339,9
362,9
393,8
m/z
E1 E2 E3 E4 E5 E6 E7 E8 E9 E10 E11 E12 E13 E14 E15 E16
Spectrum RT 0,52 {1 scans} - Background Subtracted 0,01 - 0,49
E12 ;
Intensity
ESI + Max: 7,3E8
Exact Mass: 322,13
Molecular Weight: 322,36
344,8; [M+Na]+
322,9; [M+H]+
376,8
247,8
323,9
345,8
330,9
356,9
377,9
m/z
Spectrum RT 0,50 {1 scans} - Background Subtracted 0,72 - 0,72
E14 ;
Intensity
ESI + Max: 3,6E8
Exact Mass: 377,14
Molecular Weight: 377,40
377,8; [M+H]+
378,9
277,8
249,8
268,9
278,8
361,8
380,0
420,7431,4
m/z

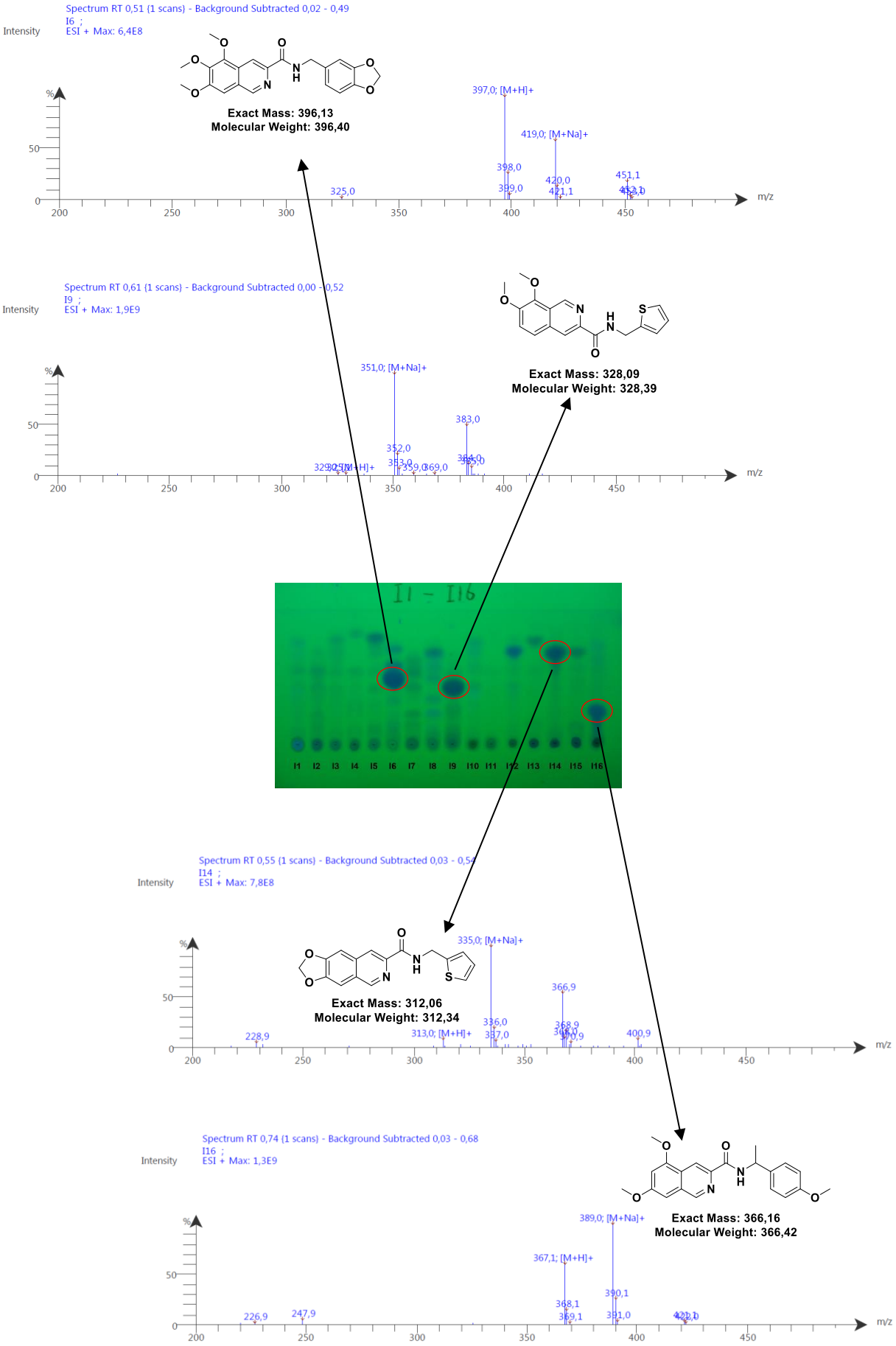

Spectrum RT 0,73 {1 scans} - Background Subtracted 0,03 - 0,59
E18 ;
ESI + Max: 1,6E9
Intensity
Exact Mass: 350,16
Molecular Weight: 350,42
372,9; [M+Na]+
350,9; [M+H]+
404,9
373,9
247,9
219,9
352,0
374,9
405,9
434,9
m/z
Spectrum RT 0,54 {1 scans} - Background Subtracted 0,01 - 0,50
E20 ;
ESI + Max: 1,3E9
Intensity
Exact Mass: 360,17
Molecular Weight: 360,41
412,8
390,8
413,9
230,9
431,8
m/z
E17 - F8
E17 E18 E19 E20 E21 E22 E23 E24 F1 F2 F3 F4 F5 F6 F7 F8
Spectrum RT 0,54 {1 scans} - Background Subtracted 0,61 - 0,64
E22 ;
ESI + Max: 4E8
Intensity
Exact Mass: 340,12
Molecular Weight: 340,35
340,9; [M+H]+
362,9; [M+Na]+
247,8
341,9
363,8
394,8
219,8
232,9
248,9
412,8
m/z
Spectrum RT 0,80 {1 scans} - Background Subtracted 0,87 - 0,92
F2 ;
ESI + Max: 1,6E8
Intensity
Exact Mass: 336,15
Molecular Weight: 336,39
358,8; [M+Na]+
359,9
390,7
232,8
247,8
336,9; [M+H]+
312,7
337,9
360,9
391,8
m/z

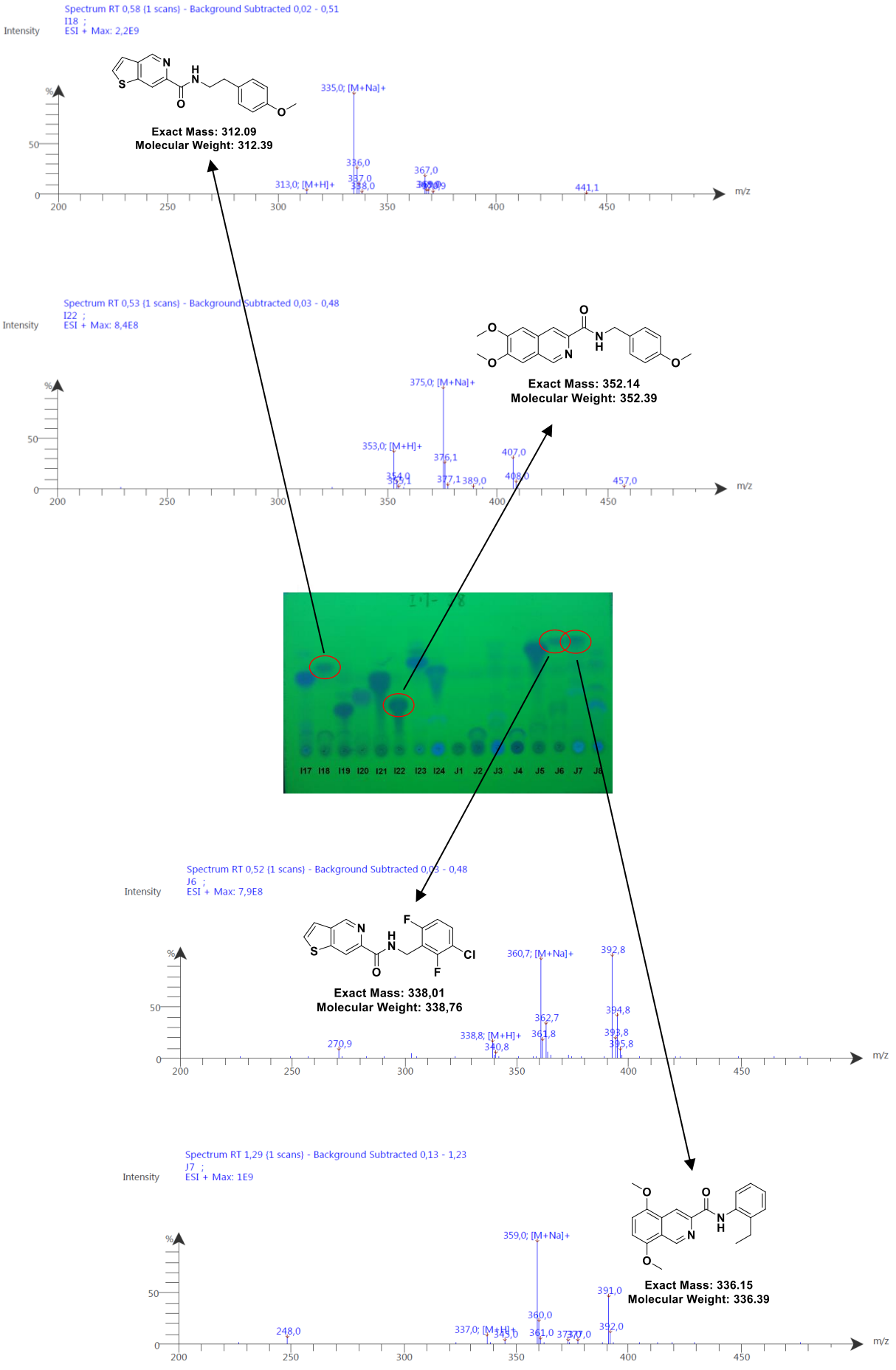

Spectrum RT 0,77 {1 scans} - Background Subtracted 0,03 - 0,69
F10 ;
Intensity
ESI + Max: 1,9E9
Exact Mass: 352,14
Molecular Weight: 352,39
374,9; [M+Na]+
352,9; [M+H]+
375,9
406,8
353,9
m/z
Spectrum RT 0,83 {1 scans} - Background Subtracted 0,01 - 0,65
F15 ;
Intensity
ESI + Max: 1,2E8
Exact Mass: 356,09
Molecular Weight: 356,81
247,9
356,9; [M+H]+
442,9
358,8
357,9
378,8; [M+Na]+
443,9
464,9
248,9
m/z
F9 F10 F11 F12 F13 F14 F15 F16 F17 F18 F19 F20 F21 F22 F23 F24
Spectrum RT 0,77 {1 scans} - Background Subtracted 0,01 - 0,75
F20 ;
Intensity
ESI + Max: 1,7E9
Exact Mass: 368,15
Molecular Weight: 368,41
390,8; [M+Na]+
232,9
368,9; [M+H]+
247,9
391,9
422,8
233,9
369,9
374,9
423,9
m/z
Spectrum RT 0,78 {1 scans} - Background Subtracted 0,07 - 0,72
F22 ;
Intensity
ESI + Max: 3,7E8
Exact Mass: 322,13
Molecular Weight: 322,36
344,9; [M+Na]+
247,9
390,9
376,9
374,9
322,9; [M+H]+
345,9
422,9
442,9
464,8
m/z

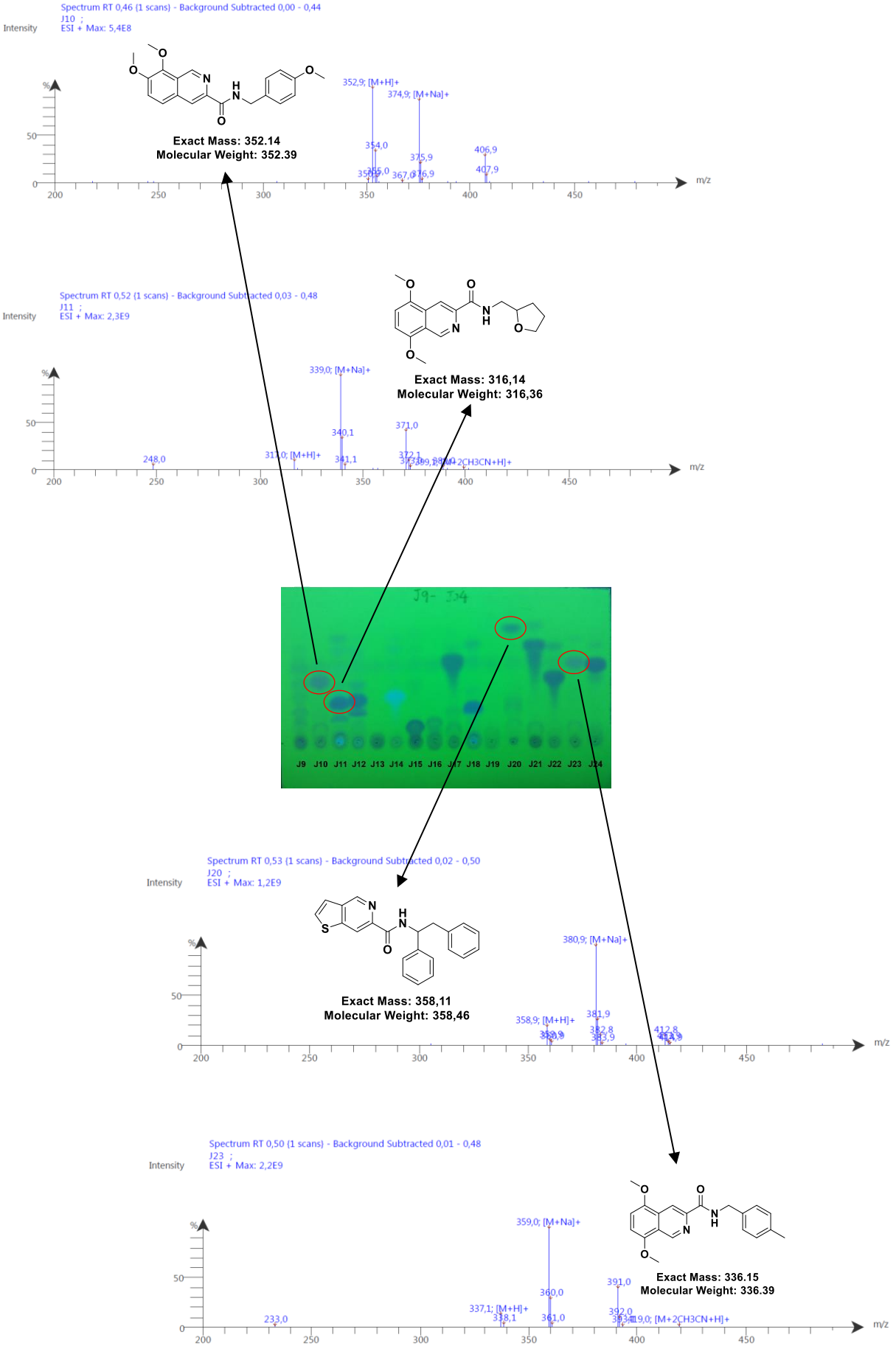

Spectrum RT 0,83 (1 scans) - Background Subtracted 0,03 - 0,72
G4 ;
Intensity
ESI + Max: 4,2E8
Exact Mass: 400,04
Molecular Weight: 401,26
400,7; [M+H]+
402,7
422,7; [M+Na]+
247,9
336,9
454,7
m/z
Spectrum RT 0,73 (1 scans) - Background Subtracted 0,01 - 0,68
G10 ;
Intensity
ESI + Max: 2,2E9
Exact Mass: 322,13
Molecular Weight: 322,36
344,9; [M+Na]+
376,9
322,9; [M+H]+
345,9
247,9
219,9
377,9
m/z
G1 G2 G3 G4 G5 G6 G7 G8 G9 G10 G11 G12 G13 G14 G15 G16
Spectrum RT 0,80 (1 scans) - Background Subtracted 0,03 - 0,71
G11 ;
Intensity
ESI + Max: 2,2E9
Exact Mass: 316,14
Molecular Weight: 316,36
338,9; [M+Na]+
316,9; [M+H]+
370,9
247,9
340,0
344,9
m/z
Spectrum RT 1,09 (1 scans) - Background Subtracted 0,00 - 1,05
G15 ;
Intensity
ESI + Max: 5,8E8
Exact Mass: 442,19
Molecular Weight: 442,52
442,9; [M+H]+
262,9
464,9; [M+Na]+
338,9
317,0
443,9
247,9
263,9
277,9
370,9
m/z

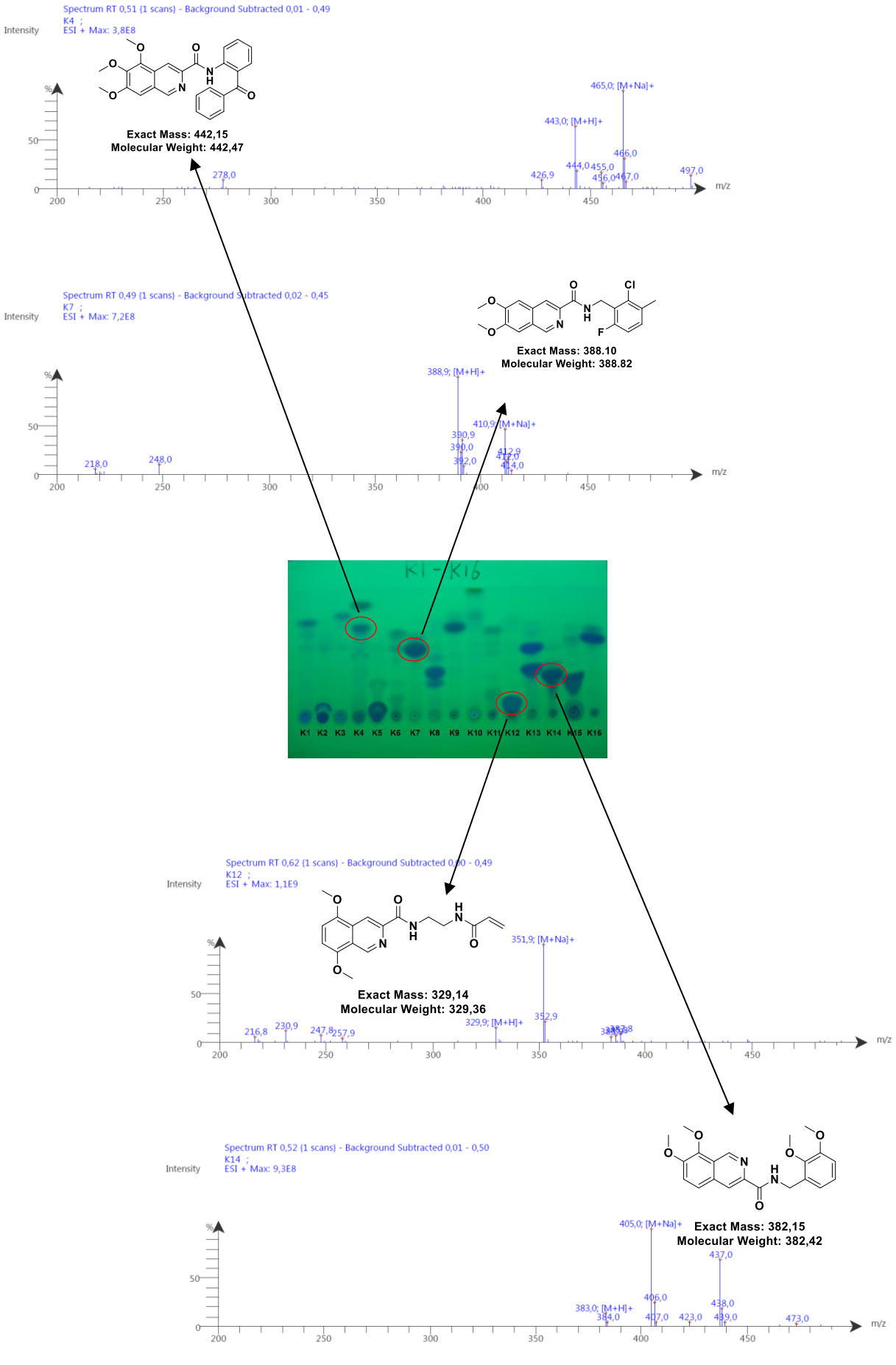

Spectrum RT 0,51 (1 scans) - Background Subtracted 0,02 - 0,45
G22 ;
ESI + Max: 8,5E8
Intensity
Exact Mass: 372,15
Molecular Weight: 372,42
372,8; [M+H]+
394,8; [M+Na]+
m/z
Spectrum RT 0,67 (1 scans) - Background Subtracted 0,03 - 0,53
H2 ;
ESI + Max: 2,6E8
Intensity
Exact Mass: 340,06
Molecular Weight: 340,76
363,0; [M+Na]+
341,0; [M+H]+
395,0
m/z
G17 G18 G19 G20 G21 G22 G23 G24 H1 H2 H3 H4 H5 H6 H7 H8
Spectrum RT 0,82 (1 scans) - Background Subtracted 0,02 - 0,65
H5 ;
ESI + Max: 2,2E9
Intensity
Exact Mass: 332,17
Molecular Weight: 332,40
355,1; [M+Na]+
m/z
Spectrum RT 0,65 (1 scans) - Background Subtracted 0,02 - 0,52
H7 ;
ESI + Max: 6,6E8
Intensity
Exact Mass: 382,15
Molecular Weight: 382,42
405,0; [M+Na]+
383,1; [M+H]+
m/z

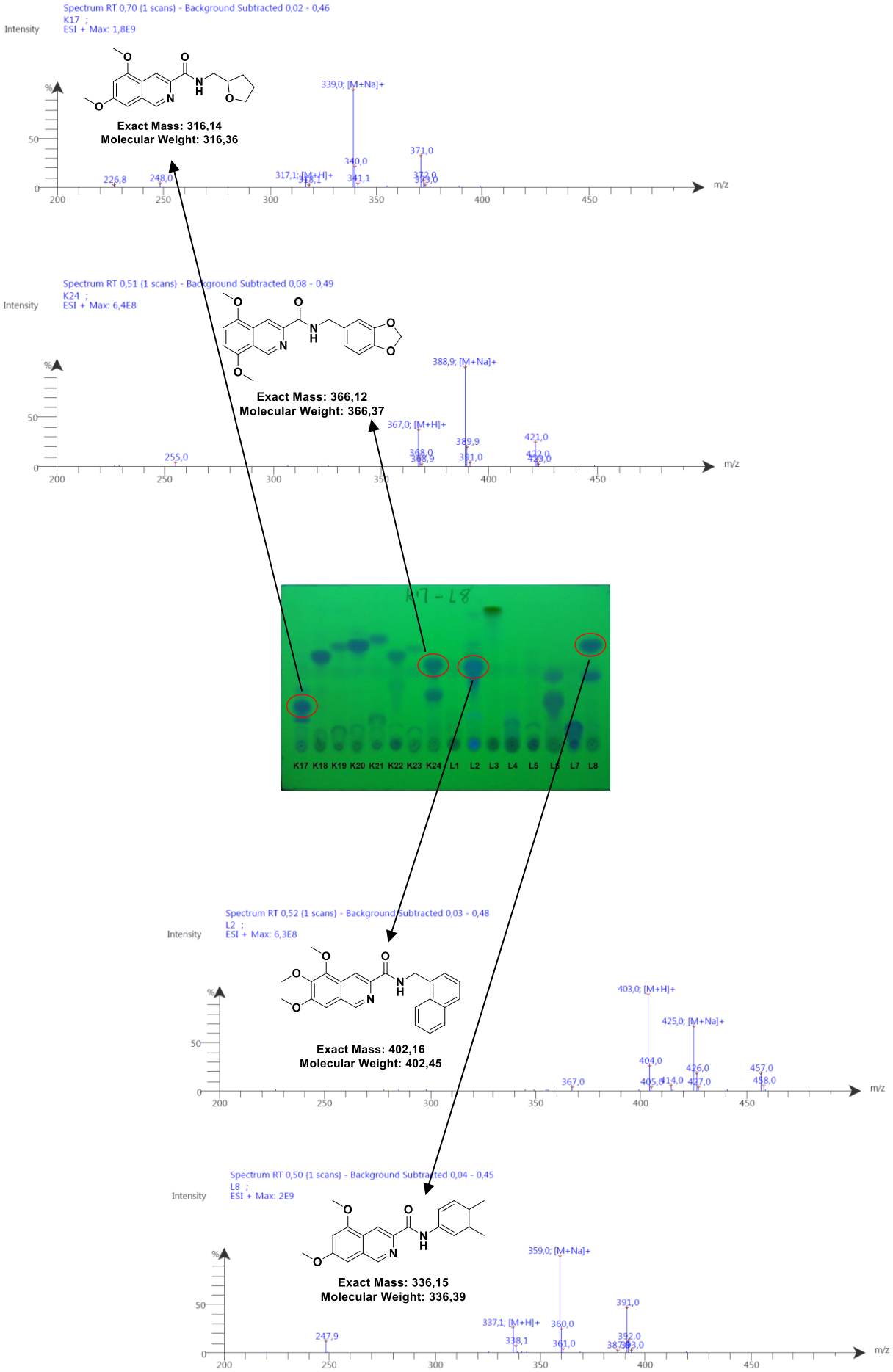

Spectrum RT 0,57 (1 scans) - Background Subtracted 0,03 - 0,44
H10 ;
ESI + Max: 2,1E9
Intensity
Exact Mass: 368.15
Molecular Weight: 368.41
391,0; [M+Na]+
423,1
392,0
424,1
233,0
247,9
325,1
359,1; [M+H]+
393,1
m/z
Spectrum RT 0,61 (1 scans) - Background Subtracted 0,03 - 0,55
H15 ;
ESI + Max: 3,7E8
Intensity
Exact Mass: 382,15
Molecular Weight: 382,42
405,1; [M+Na]+
437,1
383,0; [M+H]+
406,1
438,1
384,1
385,1
407,1
439,1
325,1
m/z
H9 H10 H11 H12 H13 H14 H15 H16 H17 H18 H19 H20 H21 H22 H23 H24
Spectrum RT 0,85 (1 scans) - Background Subtracted 0,06 - 0,59
H18 ;
ESI + Max: 1,5E9
Intensity
Exact Mass: 366.16
Molecular Weight: 366.42
389,0; [M+Na]+
367,1; [M+H]+
390,1
421,0
368,1
422,0
263,0
278,0
369,1
391,1
m/z
Spectrum RT 0,55 (1 scans) - Background Subtracted 0,01 - 0,46
H23 ;
ESI + Max: 1,9E9
Intensity
Exact Mass: 314,16
Molecular Weight: 314,39
337,1; [M+Na]+
369,1
315,1; [M+H]+
338,1
233,0
248,0
316,1
325,1
339,1
370,1
m/z

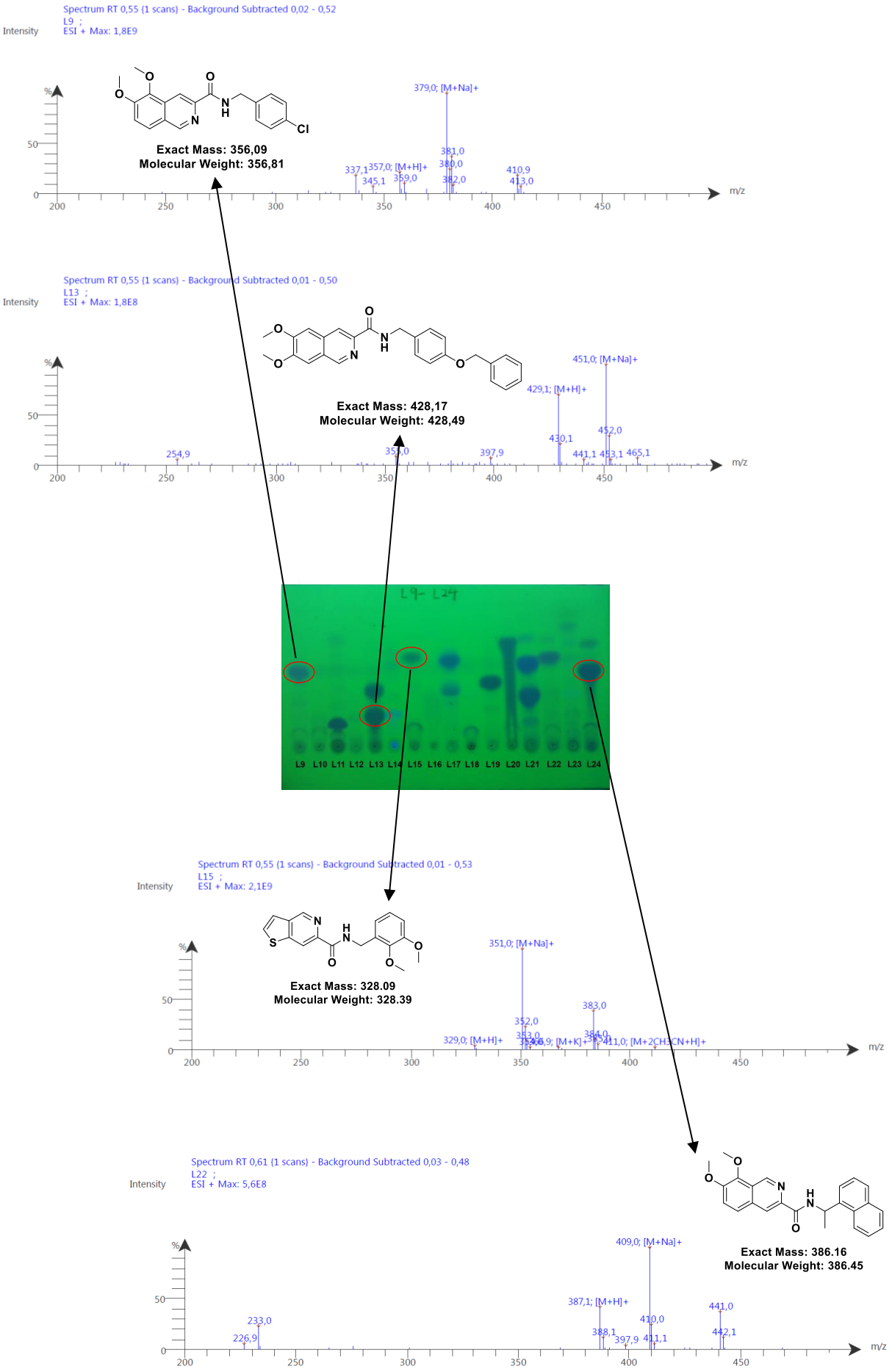

Spectrum RT 0,51 (1 scans) - Background Subtracted 0,02 - 0,49
I6 ;
Intensity
ESI + Max: 6,4E8
Exact Mass: 396,13
Molecular Weight: 396,40
397,0; [M+H]+
419,0; [M+Na]+
325,0
398,0
399,0
420,0
421,1
451,1
Spectrum RT 0,61 (1 scans) - Background Subtracted 0,00 - 0,52
I9 ;
Intensity
ESI + Max: 1,9E9
Exact Mass: 328,09
Molecular Weight: 328,39
351,0; [M+Na]+
383,0
352,0
I1 - I16
I1 I2 I3 I4 I5 I6 I7 I8 I9 I10 I11 I12 I13 I14 I15 I16
Spectrum RT 0,55 (1 scans) - Background Subtracted 0,03 - 0,54
I14 ;
Intensity
ESI + Max: 7,8E8
Exact Mass: 312,06
Molecular Weight: 312,34
335,0; [M+Na]+
366,9
228,9
313,0; [M+H]+
336,0
337,0
400,9
Spectrum RT 0,74 (1 scans) - Background Subtracted 0,03 - 0,68
I16 ;
Intensity
ESI + Max: 1,3E9
Exact Mass: 366,16
Molecular Weight: 366,42
389,0; [M+Na]+
367,1; [M+H]+
390,1
368,1
369,1
391,0
226,9
247,9
m/z

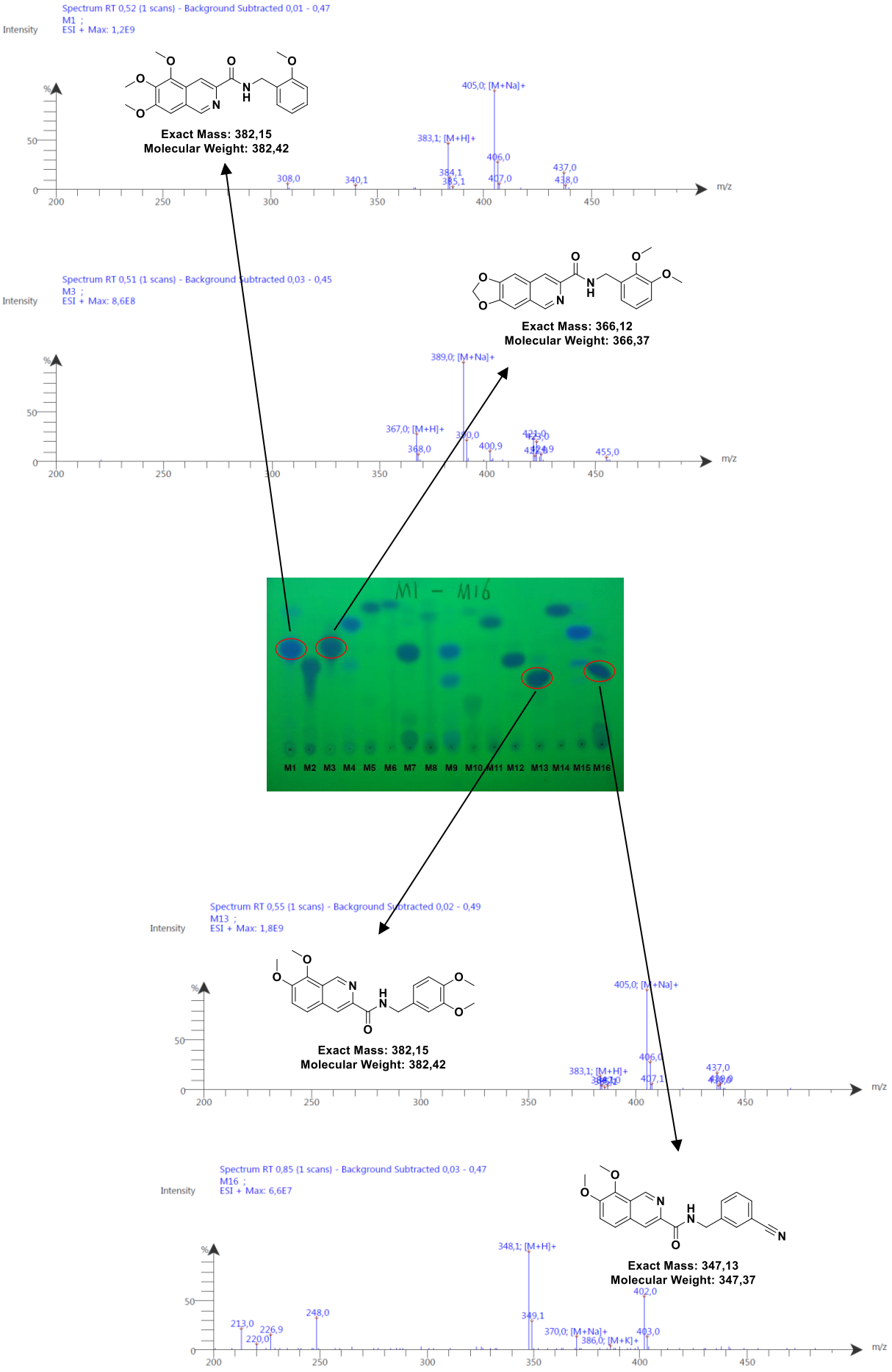

Spectrum RT 0,58 (1 scans) - Background Subtracted 0,02 - 0,51
I18 ;
ESI + Max: 2,2E9
Intensity
Exact Mass: 312.09
Molecular Weight: 312.39
335,0; [M+Na]+
336,0
337,0
367,0
313,0; [M+H]+
441,1
Spectrum RT 0,53 (1 scans) - Background Subtracted 0,03 - 0,48
I22 ;
ESI + Max: 8,4E8
Intensity
Exact Mass: 352.14
Molecular Weight: 352.39
375,0; [M+Na]+
353,0; [M+H]+
376,1
407,0
377,1
389,0
408,0
457,0
I17 I18 I19 I20 I21 I22 I23 I24 J1 J2 J3 J4 J5 J6 J7 J8
Spectrum RT 0,52 (1 scans) - Background Subtracted 0,03 - 0,48
J6 ;
ESI + Max: 7,9E8
Intensity
Exact Mass: 338,01
Molecular Weight: 338,76
360,7; [M+Na]+
392,8
362,7
394,8
338,8; [M+H]+
361,8
393,8
340,8
395,8
270,9
Spectrum RT 1,29 (1 scans) - Background Subtracted 0,13 - 1,23
J7 ;
ESI + Max: 1E9
Intensity
Exact Mass: 336.15
Molecular Weight: 336.39
359,0; [M+Na]+
391,0
360,0
248,0
337,0; [M+H]+
392,0
361,0
m/z

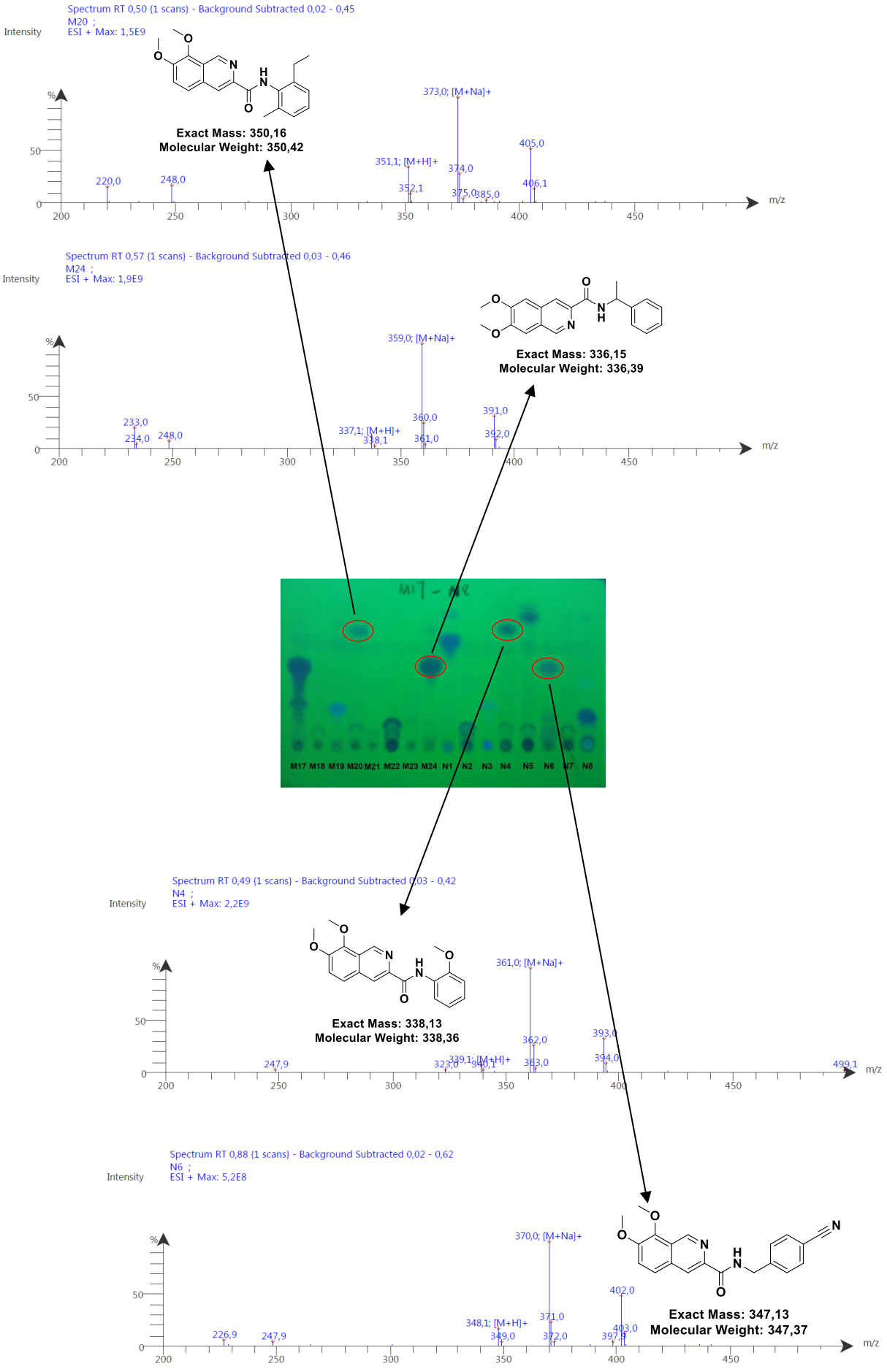

Spectrum RT 0,46 (1 scans) - Background Subtracted 0,00 - 0,44
J10 ;
Intensity
ESI + Max: 5,4E8
Exact Mass: 352.14
Molecular Weight: 352.39
352,9; [M+H]+
374,9; [M+Na]+
Spectrum RT 0,52 (1 scans) - Background Subtracted 0,03 - 0,48
J11 ;
Intensity
ESI + Max: 2,3E9
Exact Mass: 316,14
Molecular Weight: 316,36
339,0; [M+Na]+
Spectrum RT 0,53 (1 scans) - Background Subtracted 0,02 - 0,50
J20 ;
Intensity
ESI + Max: 1,2E9
Exact Mass: 358,11
Molecular Weight: 358,46
380,9; [M+Na]+
358,9; [M+H]+
Spectrum RT 0,50 (1 scans) - Background Subtracted 0,01 - 0,48
J23 ;
Intensity
ESI + Max: 2,2E9
Exact Mass: 336.15
Molecular Weight: 336.39
359,0; [M+Na]+
337,1; [M+H]+
m/z

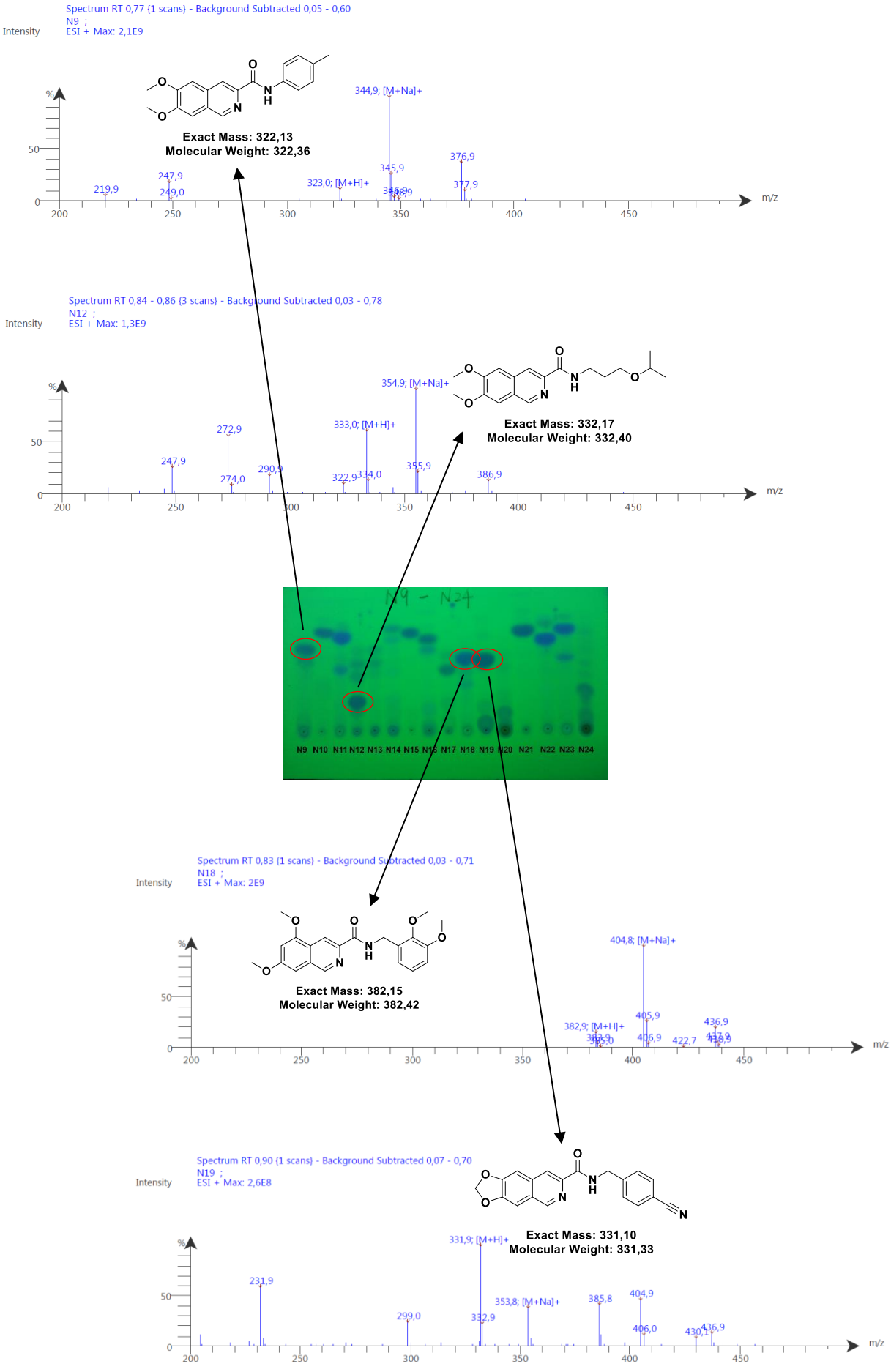

Spectrum RT 0,51 (1 scans) - Background Subtracted 0,01 - 0,49
K4 ;
ESI + Max: 3,8E8
Intensity
Exact Mass: 442,15
Molecular Weight: 442,47
465,0; [M+Na]+
443,0; [M+H]+
466,0
444,0
455,0
456,0
467,0
426,9
278,0
497,0
m/z
Spectrum RT 0,49 (1 scans) - Background Subtracted 0,02 - 0,45
K7 ;
ESI + Max: 7,2E8
Intensity
Exact Mass: 388.10
Molecular Weight: 388.82
388,9; [M+H]+
410,9; [M+Na]+
390,9
390,0
412,9
412,0
392,0
414,0
218,0
248,0
m/z
K1 - K16
K1 K2 K3 K4 K5 K6 K7 K8 K9 K10 K11 K12 K13 K14 K15 K16
Spectrum RT 0,62 (1 scans) - Background Subtracted 0,00 - 0,49
K12 ;
ESI + Max: 1,1E9
Intensity
Exact Mass: 329,14
Molecular Weight: 329,36
351,9; [M+Na]+
329,9; [M+H]+
352,9
216,8
230,9
247,8
257,9
m/z
Spectrum RT 0,52 (1 scans) - Background Subtracted 0,01 - 0,50
K14 ;
ESI + Max: 9,3E8
Intensity
Exact Mass: 382,15
Molecular Weight: 382,42
405,0; [M+Na]+
437,0
406,0
383,0; [M+H]+
438,0
384,0
407,0
423,0
439,0
473,0
m/z

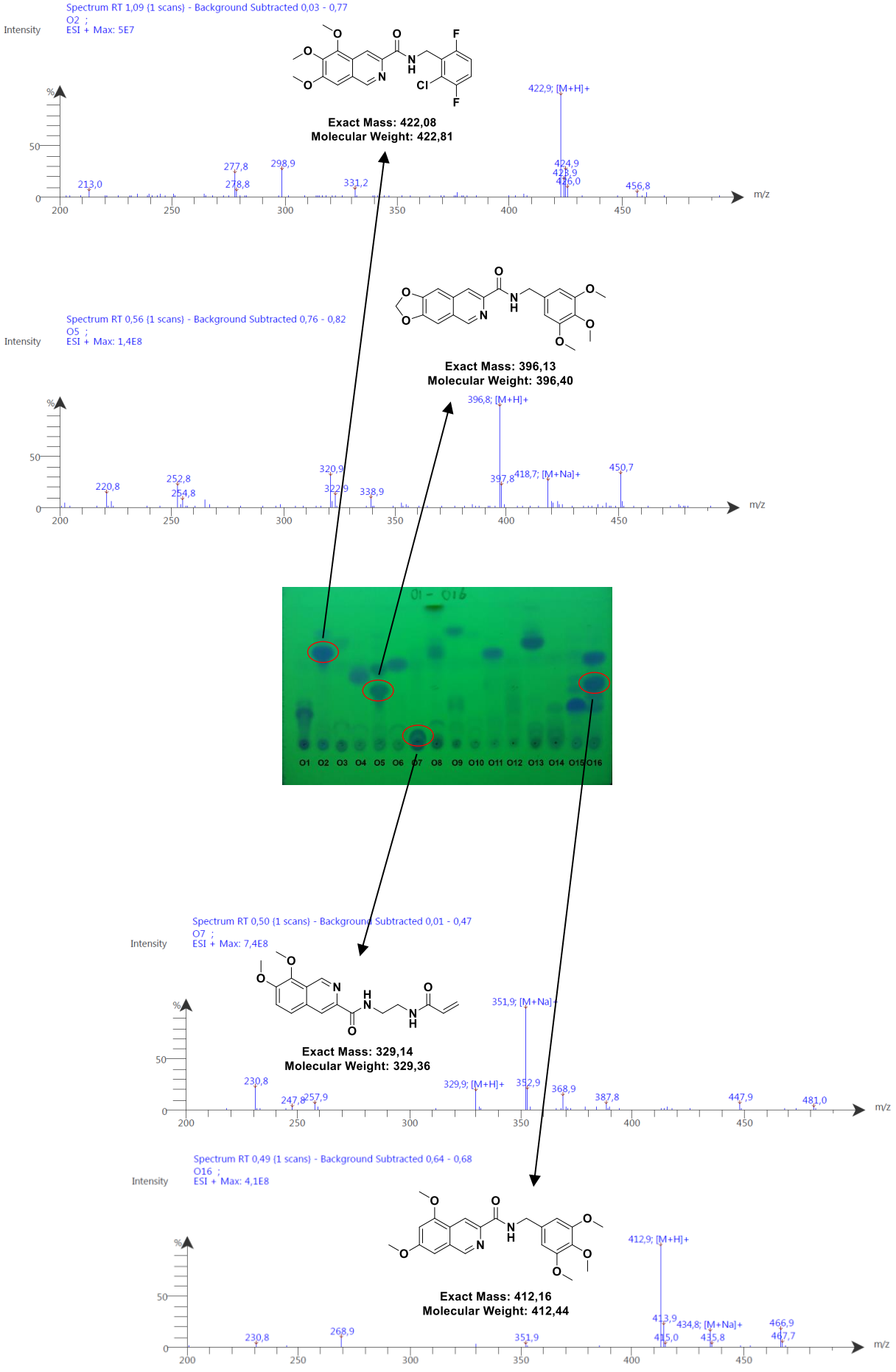

Spectrum RT 0,70 (1 scans) - Background Subtracted 0,02 - 0,46
K17 ;
ESI + Max: 1,8E9
Intensity
Exact Mass: 316,14
Molecular Weight: 316,36
339,0; [M+Na]+
371,0
340,0
317,1; [M+H]+
Spectrum RT 0,51 (1 scans) - Background Subtracted 0,08 - 0,49
K24 ;
ESI + Max: 6,4E8
Exact Mass: 366,12
Molecular Weight: 366,37
388,9; [M+Na]+
367,0; [M+H]+
421,0
255,0
K17 K18 K19 K20 K21 K22 K23 K24 L1 L2 L3 L4 L5 L6 L7 L8
Spectrum RT 0,52 (1 scans) - Background Subtracted 0,03 - 0,48
L2 ;
ESI + Max: 6,3E8
Exact Mass: 402,16
Molecular Weight: 402,45
403,0; [M+H]+
425,0; [M+Na]+
404,0
426,0
457,0
367,0
Spectrum RT 0,50 (1 scans) - Background Subtracted 0,04 - 0,45
L8 ;
ESI + Max: 2E9
Exact Mass: 336,15
Molecular Weight: 336,39
359,0; [M+Na]+
391,0
337,1; [M+H]+
360,0
247,9
338,1
361,0
m/z

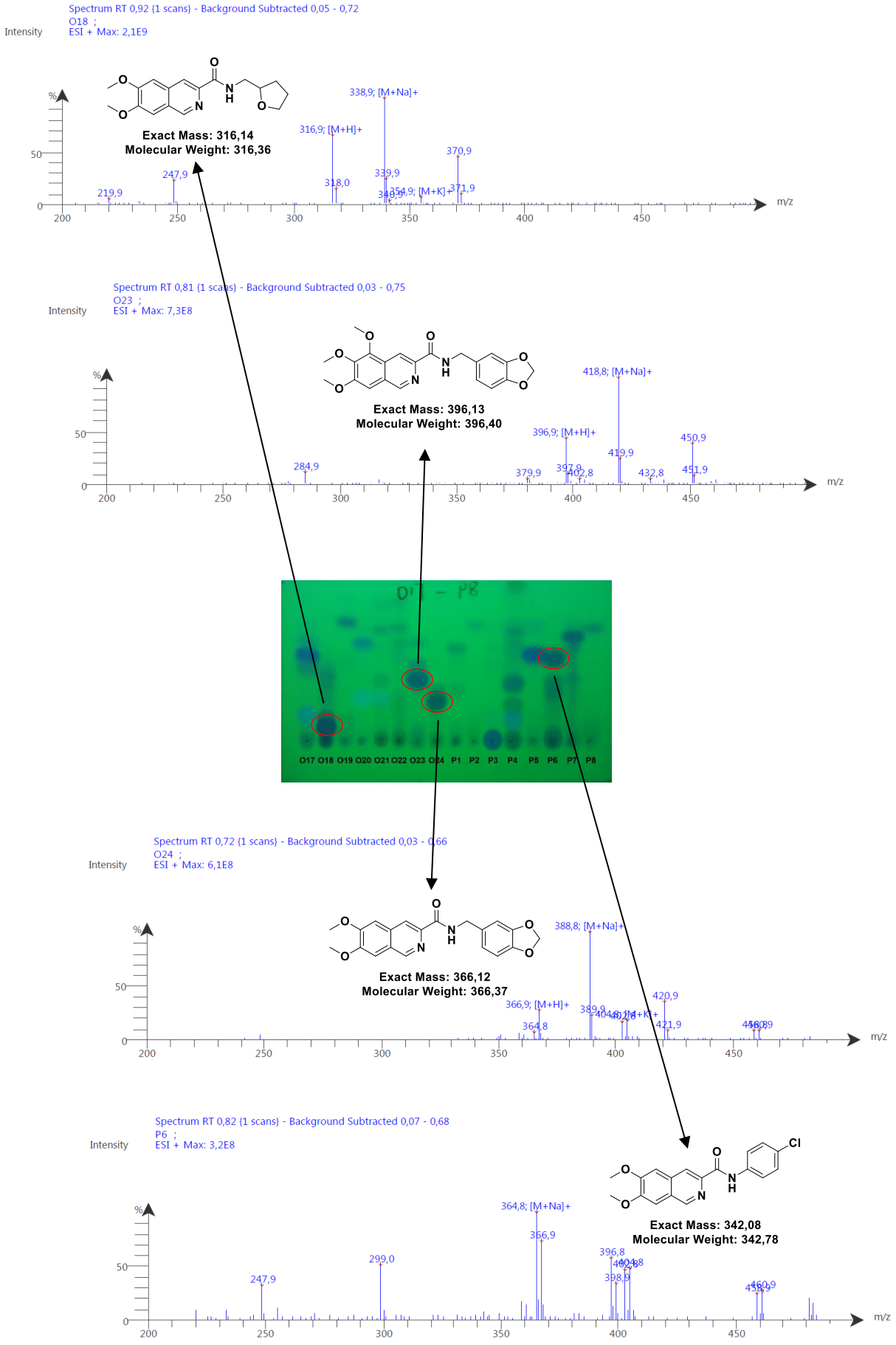

Spectrum RT 0,55 (1 scans) - Background Subtracted 0,02 - 0,52
L9 ;
Intensity
ESI + Max: 1,8E9
Exact Mass: 356,09
Molecular Weight: 356,81
379,0; [M+Na]+
357,0; [M+H]+
Spectrum RT 0,55 (1 scans) - Background Subtracted 0,01 - 0,50
L13 ;
Intensity
ESI + Max: 1,8E8
Exact Mass: 428,17
Molecular Weight: 428,49
451,0; [M+Na]+
429,1; [M+H]+
L9 L10 L11 L12 L13 L14 L15 L16 L17 L18 L19 L20 L21 L22 L23 L24
Spectrum RT 0,55 (1 scans) - Background Subtracted 0,01 - 0,53
L15 ;
Intensity
ESI + Max: 2,1E9
Exact Mass: 328.09
Molecular Weight: 328.39
351,0; [M+Na]+
329,0; [M+H]+
Spectrum RT 0,61 (1 scans) - Background Subtracted 0,03 - 0,48
L22 ;
Intensity
ESI + Max: 5,6E8
Exact Mass: 386.16
Molecular Weight: 386.45
409,0; [M+Na]+
387,1; [M+H]+
m/z

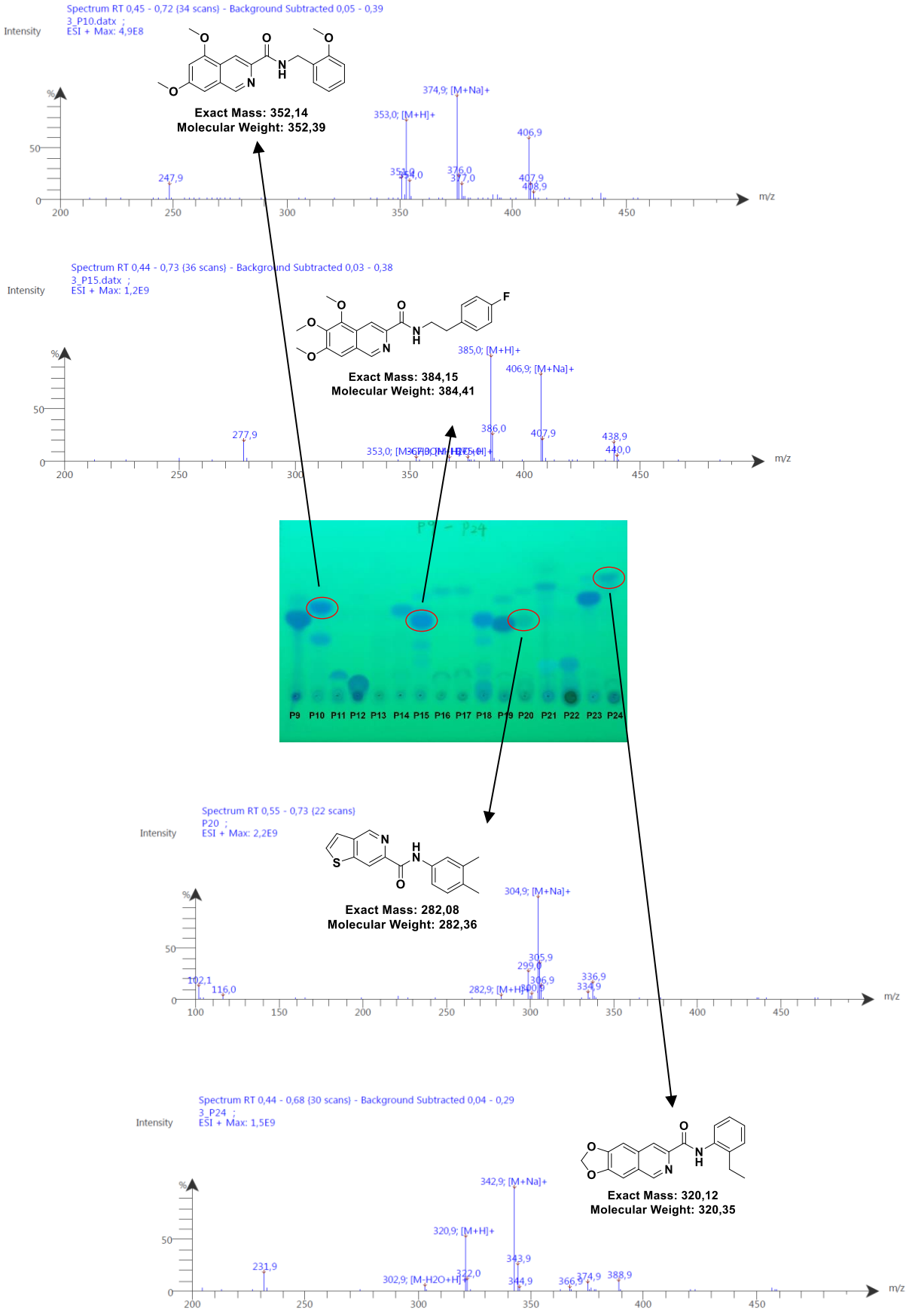

Spectrum RT 0,52 (1 scans) - Background Subtracted 0,01 - 0,47
M1 ;
ESI + Max: 1,2E9
Intensity
Exact Mass: 382,15
Molecular Weight: 382,42
405,0; [M+Na]+
383,1; [M+H]+
406,0
437,0
308,0
340,1
m/z
Spectrum RT 0,51 (1 scans) - Background Subtracted 0,03 - 0,45
M3 ;
ESI + Max: 8,6E8
Intensity
Exact Mass: 366,12
Molecular Weight: 366,37
389,0; [M+Na]+
367,0; [M+H]+
368,0
400,9
455,0
M1 – M16
M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 M12 M13 M14 M15 M16
Spectrum RT 0,55 (1 scans) - Background Subtracted 0,02 - 0,49
M13 ;
ESI + Max: 1,8E9
Intensity
Exact Mass: 382,15
Molecular Weight: 382,42
405,0; [M+Na]+
383,1; [M+H]+
406,0
437,0
Spectrum RT 0,85 (1 scans) - Background Subtracted 0,03 - 0,47
M16 ;
ESI + Max: 6,6E7
Intensity
Exact Mass: 347,13
Molecular Weight: 347,37
348,1; [M+H]+
402,0
349,1
248,0
213,0
226,9
220,0
370,0; [M+Na]+
386,0; [M+K]+
403,0
m/z


Spectrum RT 0,50 (1 scans) - Background Subtracted 0,02 - 0,45
M20 ;
Intensity
ESI + Max: 1,5E9
Exact Mass: 350,16
Molecular Weight: 350,42
373,0; [M+Na]+
405,0
351,1; [M+H]+
374,0
352,1
406,1
220,0
248,0
375,0
385,0
m/z
Spectrum RT 0,57 (1 scans) - Background Subtracted 0,03 - 0,46
M24 ;
Intensity
ESI + Max: 1,9E9
Exact Mass: 336,15
Molecular Weight: 336,39
359,0; [M+Na]+
391,0
360,0
233,0
337,1; [M+H]+
234,0
248,0
338,1
361,0
392,0
m/z
M17 M18 M19 M20 M21 M22 M23 M24 N1 N2 N3 N4 N5 N6 N7 N8
Spectrum RT 0,49 (1 scans) - Background Subtracted 0,03 - 0,42
N4 ;
Intensity
ESI + Max: 2,2E9
Exact Mass: 338,13
Molecular Weight: 338,36
361,0; [M+Na]+
362,0
393,0
247,9
339,1; [M+H]+
323,0
340,1
363,0
394,0
499,1
m/z
Spectrum RT 0,88 (1 scans) - Background Subtracted 0,02 - 0,62
N6 ;
Intensity
ESI + Max: 5,2E8
Exact Mass: 347,13
Molecular Weight: 347,37
370,0; [M+Na]+
402,0
371,0
348,1; [M+H]+
226,9
247,9
349,0
372,0
403,0
m/z

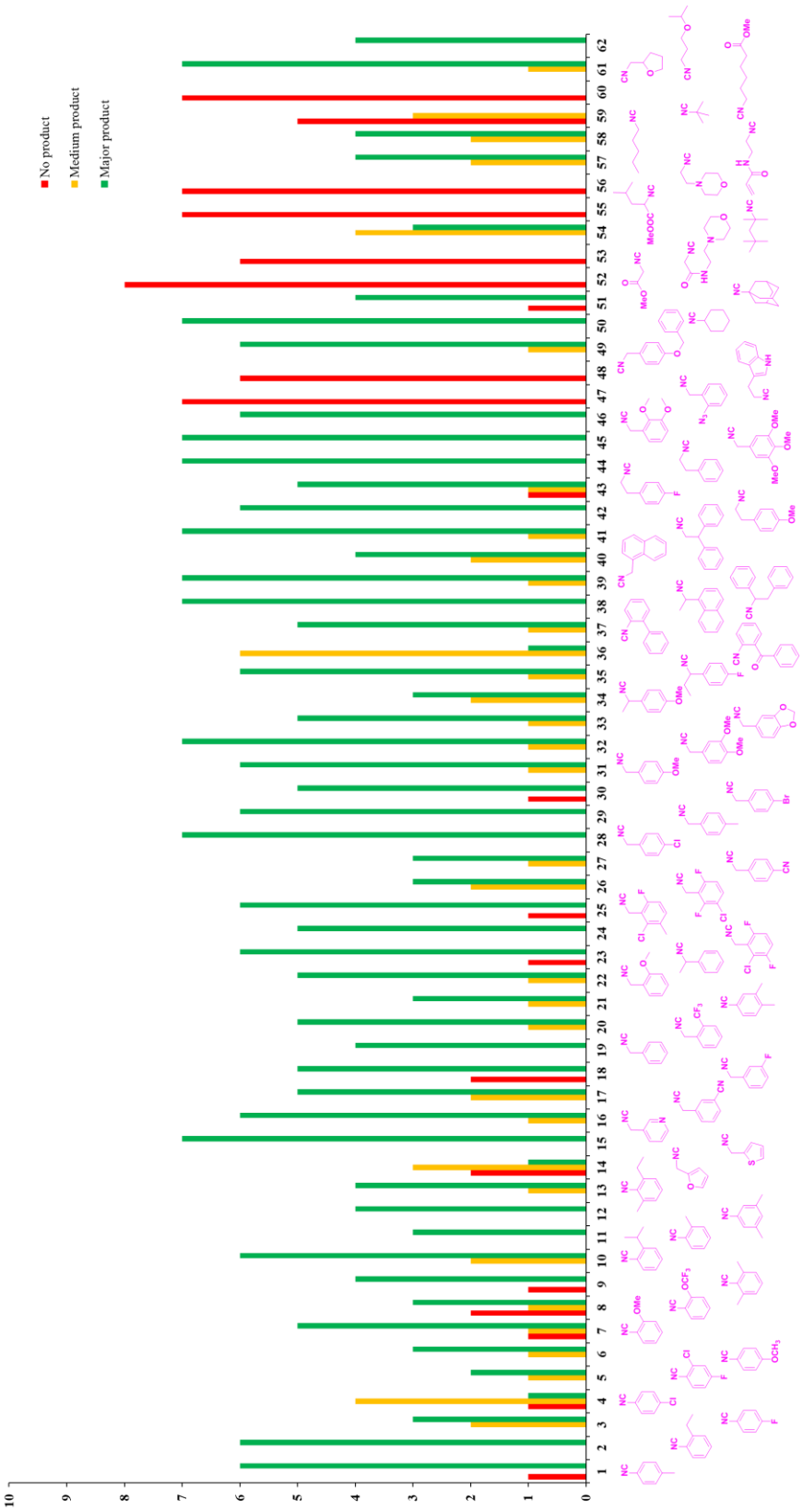

Spectrum RT 0,77 (1 scans) - Background Subtracted 0,05 - 0,60
N9 ;
Intensity
ESI + Max: 2,1E9
Exact Mass: 322,13
Molecular Weight: 322,36
344,9; [M+Na]+
376,9
345,9
247,9
219,9
249,0
323,0; [M+H]+
377,9
m/z
Spectrum RT 0,84 - 0,86 (3 scans) - Background Subtracted 0,03 - 0,78
N12 ;
Intensity
ESI + Max: 1,3E9
354,9; [M+Na]+
Exact Mass: 332,17
Molecular Weight: 332,40
272,9
333,0; [M+H]+
247,9
290,9
274,0
322,9
334,0
355,9
386,9
m/z
N9 - N24
N9 N10 N11 N12 N13 N14 N15 N16 N17 N18 N19 N20 N21 N22 N23 N24
Spectrum RT 0,83 (1 scans) - Background Subtracted 0,03 - 0,71
N18 ;
Intensity
ESI + Max: 2E9
Exact Mass: 382,15
Molecular Weight: 382,42
404,8; [M+Na]+
405,9
382,9; [M+H]+
436,9
422,7
m/z
Spectrum RT 0,90 (1 scans) - Background Subtracted 0,07 - 0,70
N19 ;
Intensity
ESI + Max: 2,6E8
Exact Mass: 331,10
Molecular Weight: 331,33
331,9; [M+H]+
231,9
353,8; [M+Na]+
385,8
404,9
299,0
332,9
406,0
436,9
m/z


Spectrum RT 1,09 (1 scans) - Background Subtracted 0,03 - 0,77
O2 ;
Intensity
ESI + Max: 5E7
Exact Mass: 422,08
Molecular Weight: 422,81
422,9; [M+H]+
Spectrum RT 0,56 (1 scans) - Background Subtracted 0,76 - 0,82
O5 ;
Intensity
ESI + Max: 1,4E8
Exact Mass: 396,13
Molecular Weight: 396,40
396,8; [M+H]+
418,7; [M+Na]+
O1 O2 O3 O4 O5 O6 O7 O8 O9 O10 O11 O12 O13 O14 O15 O16
Spectrum RT 0,50 (1 scans) - Background Subtracted 0,01 - 0,47
O7 ;
Intensity
ESI + Max: 7,4E8
Exact Mass: 329,14
Molecular Weight: 329,36
351,9; [M+Na]+
329,9; [M+H]+
Spectrum RT 0,49 (1 scans) - Background Subtracted 0,64 - 0,68
O16 ;
Intensity
ESI + Max: 4,1E8
Exact Mass: 412,16
Molecular Weight: 412,44
412,9; [M+H]+
434,8; [M+Na]+
m/z

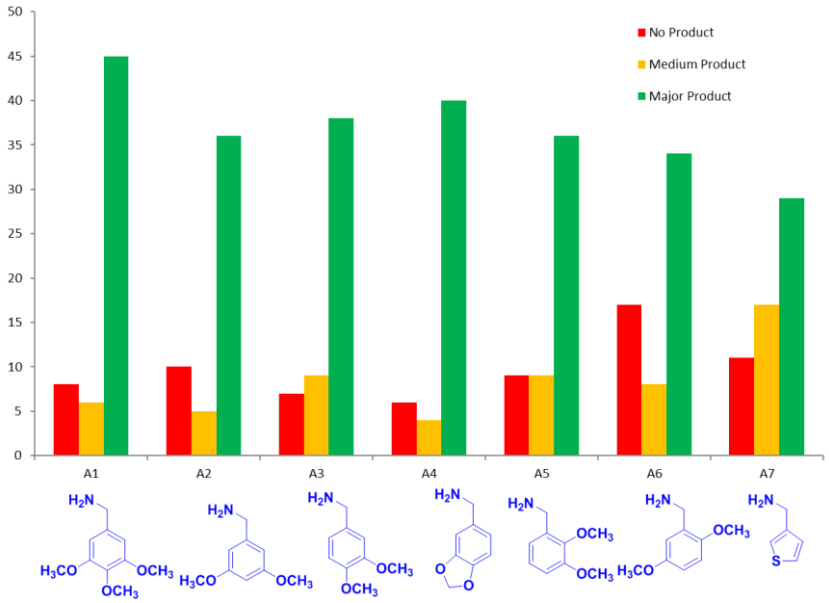

Spectrum RT 0,92 {1 scans} - Background Subtracted 0,05 - 0,72
O18 ;
Intensity
ESI + Max: 2,1E9
Exact Mass: 316,14
Molecular Weight: 316,36
338,9; [M+Na]+
316,9; [M+H]+
370,9
247,9
339,9
318,0
219,9
354,9; [M+K]+
371,9
m/z
Spectrum RT 0,81 {1 scans} - Background Subtracted 0,03 - 0,75
O23 ;
Intensity
ESI + Max: 7,3E8
Exact Mass: 396,13
Molecular Weight: 396,40
418,8; [M+Na]+
396,9; [M+H]+
450,9
419,9
284,9
379,9
397,9
402,8
432,8
451,9
m/z
O17 O18 O19 O20 O21 O22 O23 O24 P1 P2 P3 P4 P5 P6 P7 P8
Spectrum RT 0,72 {1 scans} - Background Subtracted 0,03 - 0,66
O24 ;
Intensity
ESI + Max: 6,1E8
Exact Mass: 366,12
Molecular Weight: 366,37
388,8; [M+Na]+
366,9; [M+H]+
420,9
389,9
364,8
421,9
m/z
Spectrum RT 0,82 {1 scans} - Background Subtracted 0,07 - 0,68
P6 ;
Intensity
ESI + Max: 3,2E8
Exact Mass: 342,08
Molecular Weight: 342,78
364,8; [M+Na]+
366,9
396,8
299,0
247,9
398,9
460,9
m/z


Spectrum RT 0,45 - 0,72 (34 scans) - Background Subtracted 0,05 - 0,39
3_P10.datx ;
ESI + Max: 4,9E8
Intensity
Exact Mass: 352,14
Molecular Weight: 352,39
374,9; [M+Na]+
353,0; [M+H]+
406,9
247,9
m/z
Spectrum RT 0,44 - 0,73 (36 scans) - Background Subtracted 0,03 - 0,38
3_P15.datx ;
ESI + Max: 1,2E9
Intensity
Exact Mass: 384,15
Molecular Weight: 384,41
385,0; [M+H]+
406,9; [M+Na]+
277,9
386,0
407,9
438,9
440,0
m/z
P9 P10 P11 P12 P13 P14 P15 P16 P17 P18 P19 P20 P21 P22 P23 P24
Spectrum RT 0,55 - 0,73 (22 scans)
P20 ;
ESI + Max: 2,2E9
Intensity
Exact Mass: 282,08
Molecular Weight: 282,36
304,9; [M+Na]+
305,9
299,0
306,9
336,9
102,1
116,0
282,9; [M+H]+
m/z
Spectrum RT 0,44 - 0,68 (30 scans) - Background Subtracted 0,04 - 0,29
3_P24 ;
ESI + Max: 1,5E9
Intensity
Exact Mass: 320,12
Molecular Weight: 320,35
342,9; [M+Na]+
320,9; [M+H]+
343,9
231,9
322,0
344,9
374,9
388,9
m/z

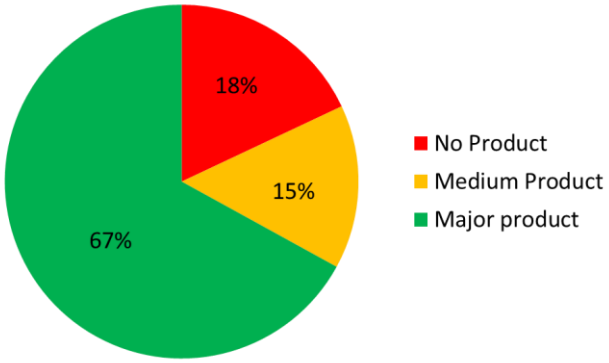
5. Statistical reaction analysis



Scheme S2. Frequency of the isocyanides in the plate along with the QC results.



Scheme S3. Frequency of the benzyl amines in the plate along with the QC results.



Scheme S4. QC results for the 384-destination plate.

6. Mg scale reactions

6.1. General procedure

To a stirred solution of 2,2-dimethoxyacetaldehyde (1 mmol) in MeOH (1M) at room temperature, amine (1 mmol), benzoic acid (1 mmol) and isocyanide (1 mmol) were added. The resulting mixture was stirred at room temperature for 15 h. Upon completion, the solvent was evaporated under vacuum. Then, the crude Ugi-adduct was dissolved in 37% $HCl_{(aq)}$ solution in dioxane (1 mL, 1:1, v/v) and was stirred at room temperature for 12 h. The reaction was diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate solution (3 x 10 mL). Finally, the solvent was evaporated under vacuum and the crude product was purified by flash column chromatography using petroleum ether/ethyl acetate (Fig. S3).

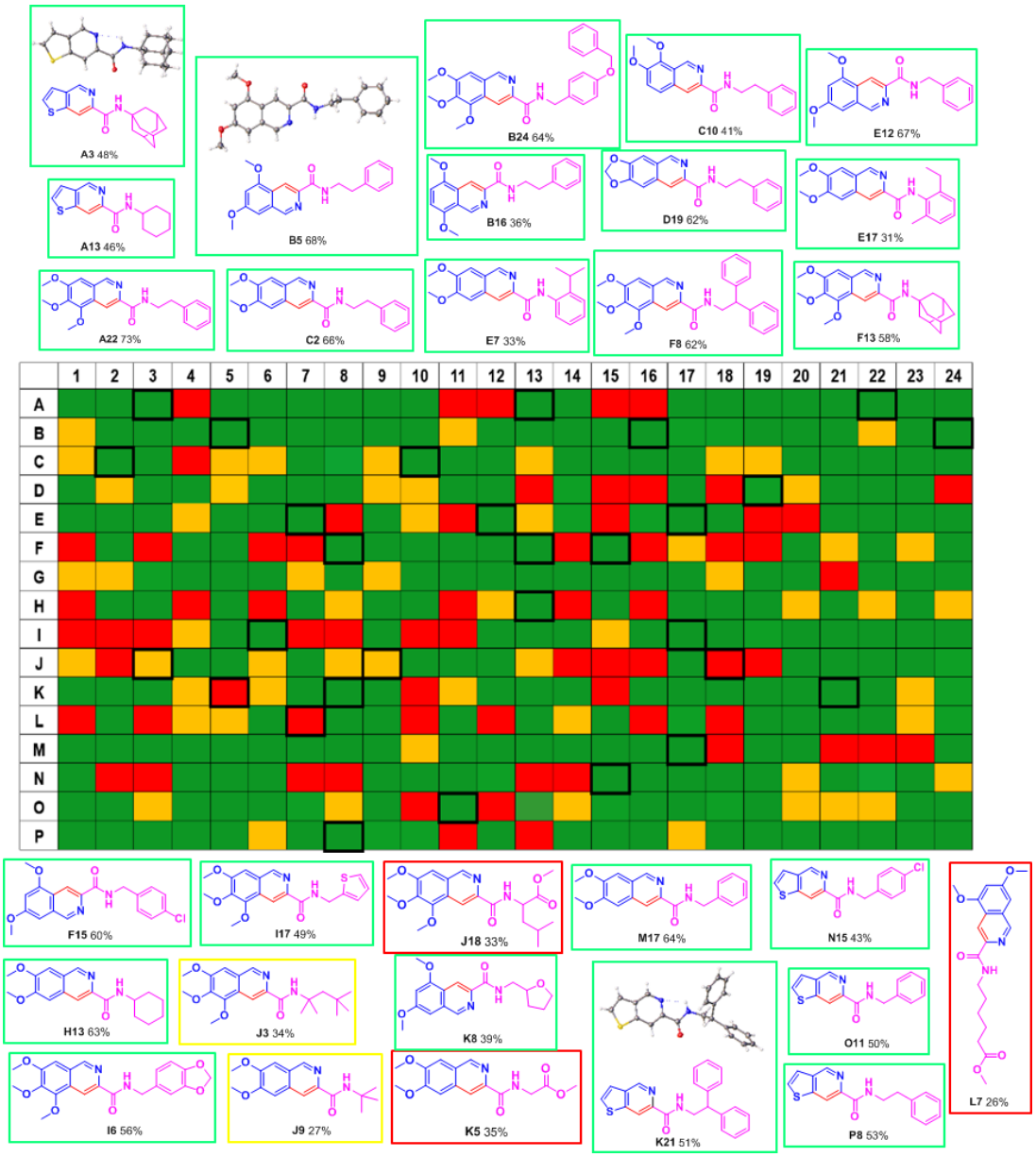
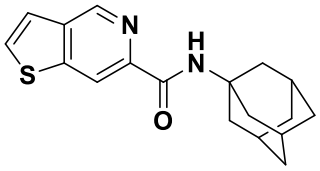


Fig. S3. Structures of the randomly resynthesized isoquinolines on mg scale and selected X-ray structures.

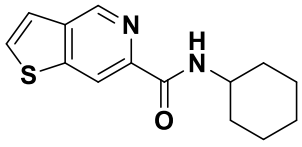
6.2. Characterization of the products

_N_-((1S,3s)-adamantan-1-yl)thieno[3,2-c]pyridine-6-carboxamide (A3)



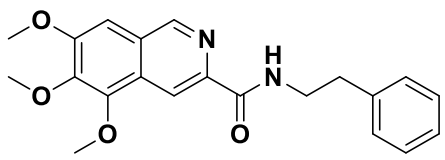
White solid (149 mg, 48% yield), M.P.= 221 – 223 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (d, *J* = 0.9 Hz, 1H), 8.68 (d, *J* = 1.0 Hz, 1H), 8.03 (s, 1H), 7.62 (d, *J* = 5.5 Hz, 1H), 7.50 – 7.47 (m, 1H), 2.19 (d, *J* = 2.8 Hz, 6H), 2.16 – 2.11 (m, 3H), 1.79 – 1.67 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 148.2, 144.5, 143.5, 137.2, 130.1, 122.4, 116.1, 51.7, 41.6, 36.4, 29.5; HRMS (ESI) m/z calculated for $C_{18}H_{21}N_2OS$ $[M+H]^+$: 313.1369; found $[M+H]^+$: 313.1367.

_N_-cyclohexylthieno[3,2-c]pyridine-6-carboxamide (A13)



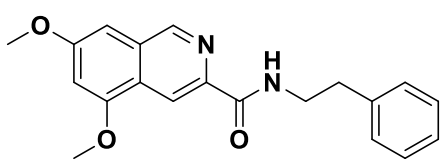
White solid (119 mg, 46% yield), M.P.= 109 – 111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.0 (d, *J* = 0.9 Hz, 1H), 8.7 (s, 1H), 8.1 (d, *J* = 8.6 Hz, 1H), 7.6 (d, *J* = 5.5 Hz, 1H), 7.5 – 7.5 (m, 1H), 4.1 – 3.9 (m, 1H), 2.1 – 2.0 (m, 2H), 1.9 – 1.7 (m, 2H), 1.7 (m, 1H), 1.5 – 1.4 (m, 2H), 1.4 – 1.3 (m, 2H), 1.3 – 1.2 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.7, 148.2, 143.9, 137.5, 130.4, 130.2, 122.4, 116.7, 48.4, 33.3, 25.7, 25.7; HRMS (ESI) m/z calculated for $C_{14}H_{17}N_2OS$ $[M+H]^+$: 261.1056; found $[M+H]^+$: 261.1058.

5,6,7-Trimethoxy-_N_-phenethylisoquinoline-3-carboxamide (A22)



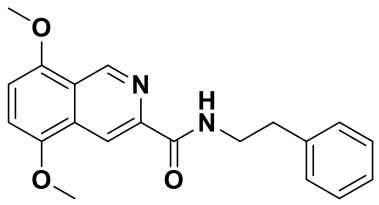
White solid (267 mg, 73% yield), M.P.= 121 – 123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.76 (s, 1H), 8.28 (t, *J* = 6.2 Hz, 1H), 7.33 – 7.20 (m, 5H), 7.05 (s, 1H), 4.06 (s, 3H), 4.01 (s, 3H), 4.00 (s, 3H), 3.81 – 3.74 (m, 2H), 2.97 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 155.3, 148.8, 148.1, 144.6, 142.2, 139.2, 128.9, 128.6, 127.9, 127.1, 126.5, 114.7, 101.6, 61.8, 61.3, 56.2, 40.9, 36.1; HRMS (ESI) m/z calculated for $C_{21}H_{23}N_2O_4$ $[M+H]^+$: 367.1652; found $[M+H]^+$: 367.1652.

5,7-Dimethoxy-_N_-phenethylisoquinoline-3-carboxamide (B5)



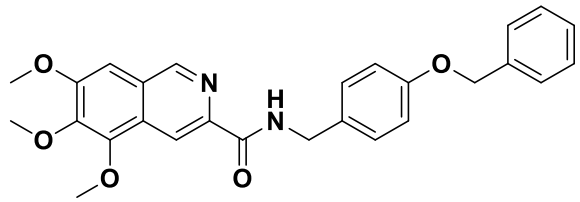
Grey solid (229 mg, 68% yield), M.P.= 159 – 161 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.83 (s, 1H), 8.24 (t, *J* = 6.2 Hz, 1H), 7.35 – 7.20 (m, 5H), 6.79 (d, *J* = 2.2 Hz, 1H), 6.65 (d, *J* = 2.1 Hz, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.81 – 3.74 (m, 2H), 2.98 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 160.7, 157.0, 148.9, 141.8, 139.3, 131.6, 128.9, 128.7, 126.5, 125.0, 115.3, 101.9, 96.8, 55.9, 55.7, 40.9, 36.2; HRMS (ESI) m/z calculated for $C_{20}H_{21}N_2O_3$ $[M+H]^+$: 337.1547; found $[M+H]^+$: 337.1545.

5,8-Dimethoxy-_N_-phenethylisoquinoline-3-carboxamide (B16)



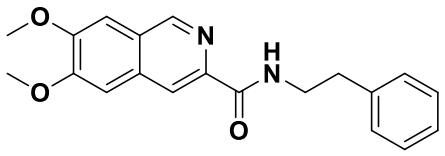
Yellow solid (121 mg, 36% yield), M.P.= 120 – 122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.89 (s, 1H), 8.36 (t, *J* = 6.2 Hz, 1H), 7.34 – 7.20 (m, 5H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.83 – 3.75 (m, 2H), 2.99 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 150.1, 149.5, 146.0, 144.0, 139.3, 129.5, 129.0, 128.7, 126.5, 122.0, 114.8, 108.5, 106.5, 56.0, 55.9, 41.0, 36.2; HRMS (ESI) m/z calculated for $C_{20}H_{21}N_2O_3$ $[M+H]^+$: 337.1547; found $[M+H]^+$: 337.1546.

***N*-(4-(benzyloxy)benzyl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (B24)**



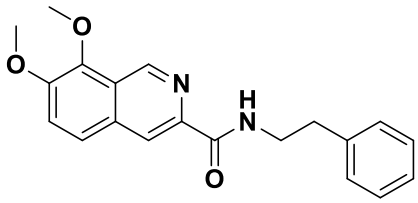
Grey solid (293 mg, 64% yield), M.P.= 110 – 112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.80 (s, 1H), 8.45 (t, *J* = 5.9 Hz, 1H), 7.45 – 7.29 (m, 7H), 7.06 (s, 1H), 6.95 (d, *J* = 8.2 Hz, 2H), 5.05 (s, 2H), 4.65 (d, *J* = 5.9 Hz, 2H), 4.07 (s, 3H), 4.02 (s, 3H), 4.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 158.2, 155.4, 148.8, 148.1, 144.7, 142.2, 137.1, 131.1, 129.4, 128.7, 128.0, 128.0, 127.5, 127.2, 115.1, 115.0, 101.6, 70.1, 61.9, 61.4, 56.3, 43.1; HRMS (ESI) m/z calculated for $C_{27}H_{27}N_2O_5$ $[M+H]^+$: 459.1915; found $[M+H]^+$: 459.1914.

6,7-Dimethoxy-*N*-phenethylisoquinoline-3-carboxamide (C2)



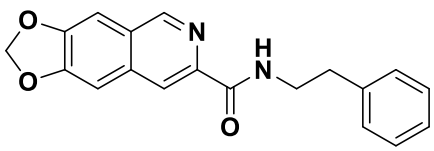
White solid (220 mg, 66% yield), M.P.= 158 – 160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.9 (s, 1H), 8.8 (s, 1H), 8.2 (t, *J* = 6.2 Hz, 1H), 7.3 – 7.2 (m, 5H), 6.8 (s, 1H), 6.6 (s, 1H), 4.0 (s, 3H), 3.9 (s, 3H), 3.8 – 3.7 (m, 2H), 3.0 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 153.5, 151.7, 148.5, 142.9, 139.3, 132.9, 129.0, 128.7, 126.5, 126.1, 119.1, 106.1, 105.4, 56.4, 56.3, 40.9, 36.2; HRMS (ESI) m/z calculated for $C_{20}H_{21}N_2O_3$ $[M+H]^+$: 337.1547; found $[M+H]^+$: 337.1545.

7,8-Dimethoxy-*N*-phenethylisoquinoline-3-carboxamide (C10)



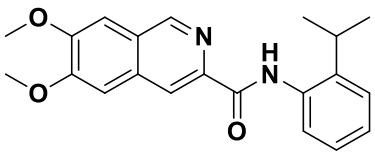
Color-less semi-solid (138 mg, 41% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.52 (s, 1H), 8.33 (t, *J* = 6.3 Hz, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.54 (d, *J* = 8.9 Hz, 1H), 7.36 – 7.22 (m, 5H), 4.07 (s, 3H), 4.03 (s, 3H), 3.79 (q, *J* = 7.0 Hz, 2H), 2.98 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 150.4, 146.1, 144.0, 142.2, 139.2, 131.5, 129.0, 128.7, 126.6, 125.2, 124.6, 120.1, 119.9, 61.8, 56.9, 40.9, 36.2; HRMS (ESI) m/z calculated for $C_{20}H_{21}N_2O_3$ $[M+H]^+$: 337.1547; found $[M+H]^+$: 337.1546.

***N*-phenethyl-[1,3]dioxolo[4,5-f]isoquinoline-8-carboxamide (D19)**



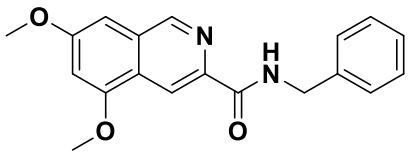
White solid (198 mg, 62% yield), M.P.= 138 – 140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.40 (s, 1H), 8.27 (t, *J* = 6.3 Hz, 1H), 7.33 – 7.21 (m, 5H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.10 (s, 2H), 3.82 – 3.70 (m, 2H), 2.97 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 151.5, 149.7, 148.7, 143.1, 139.2, 134.5, 128.9, 128.7, 127.4, 126.5, 119.6, 103.9, 103.3, 102.1, 40.9, 36.1; HRMS (ESI) m/z calculated for $C_{19}H_{17}N_2O_3$ $[M+H]^+$: 321.1234; found $[M+H]^+$: 321.1234.

***N*-(2-isopropylphenyl)-6,7-dimethoxyisoquinoline-3-carboxamide (E7)**



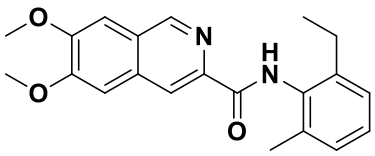
White solid (115 mg, 33% yield), M.P.= 180 – 182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.99 (s, 1H), 8.56 (s, 1H), 8.27 – 8.22 (m, 1H), 7.35 – 7.31 (m, 1H), 7.30 – 7.26 (m, 2H), 7.22 (s, 1H), 7.20 – 7.15 (m, 1H), 4.05 (s, 3H), 4.05 (s, 3H), 3.32 – 3.24 (m, 1H), 1.36 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 153.7, 151.9, 148.6, 143.1, 139.1, 134.9, 133.0, 126.7, 126.3, 125.7, 125.2, 122.8, 119.5, 106.2, 105.6, 56.5, 56.4, 28.4, 23.1; HRMS (ESI) m/z calculated for $C_{21}H_{23}N_2O_3$ $[M+H]^+$: 351.1703; found $[M+H]^+$: 351.1701.

***N*-benzyl-5,7-dimethoxyisoquinoline-3-carboxamide (E12)**



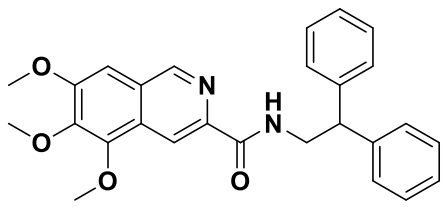
White solid (215 mg, 67% yield), M.P.= 146 – 148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 8.90 (s, 1H), 8.87 (s, 1H), 7.45 – 7.23 (m, 5H), 6.79 (s, 1H), 6.69 – 6.56 (m, 1H), 4.72 (d, *J* = 6.0 Hz, 2H), 3.97 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 160.8, 157.0, 148.9, 141.6, 138.7, 131.6, 128.7, 128.0, 127.4, 124.9, 115.5, 101.9, 96.8, 55.9, 55.7, 43.6; HRMS (ESI) m/z calculated for $C_{19}H_{19}N_2O_3$ $[M+H]^+$: 323.1390; found $[M+H]^+$: 323.1390.

***N*-(2-ethyl-6-methylphenyl)-6,7-dimethoxyisoquinoline-3-carboxamide (E17)**



White solid (109 mg, 31% yield), M.P.= 225 – 227 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ δ 9.64 (s, 1H), 9.01 (s, 1H), 8.57 (s, 1H), 7.29 (s, 1H), 7.22 (s, 1H), 7.21 – 7.17 (m, 1H), 7.17 – 7.13 (m, 2H), 4.07 (s, 3H), 4.04 (s, 3H), 2.69 (q, *J* = 7.6 Hz, 2H), 2.32 (s, 3H), 1.21 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8, 153.6, 151.8, 148.6, 142.7, 141.3, 136.1, 133.7, 132.9, 128.3, 127.5, 126.4, 126.3, 119.5, 106.1, 105.5, 56.4, 56.3, 25.2, 18.8, 14.6; HRMS (ESI) m/z calculated for $C_{21}H_{23}N_2O_3$ $[M+H]^+$: 351.1703; found $[M+H]^+$: 351.1702.

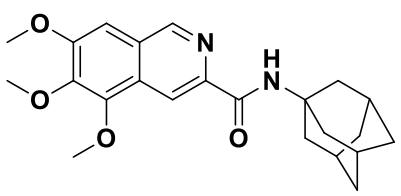
***N*-(2,2-diphenylethyl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (F8)**



White solid (274 mg, 62% yield), M.P.= 171 – 172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.75 (s, 1H), 8.21 (t, *J* = 6.1 Hz, 1H), 7.35 – 7.30 (m, 8H), 7.25 – 7.20 (m, 2H), 7.03 (s, 1H), 4.38 (t, *J* = 7.8 Hz, 1H), 4.19 – 4.14 (m, 2H), 4.06 (s, 3H), 4.01 (s, 3H), 4.01 (s, 3H); ^{13}C NMR

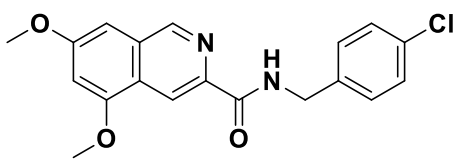
(126 MHz, $CDCl_3$) 165.3, 155.4, 148.8, 148.1, 144.7, 142.4, 142.2, 128.8, 128.3, 128.0, 127.2, 126.8, 114.8, 101.6, 61.9, 61.4, 56.3, 51.0, 44.1; HRMS (ESI) m/z calculated for $C_{27}H_{27}N_2O_4$ $[M+H]^+$: 443.1965; found $[M+H]^+$: 443.1957.

***N*-((1s,3s)-adamantan-1-yl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (F13)**



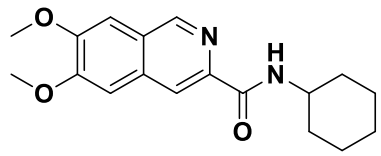
White solid (229 mg, 58% yield), M.P.= 167 – 169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.73 (s, 1H), 8.01 (s, 1H), 7.07 (s, 1H), 4.04 (s, 3H), 4.02 (s, 6H), 2.21 (d, *J* = 2.8 Hz, 6H), 2.17 – 2.12 (m, 3H), 1.84 – 1.66 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1, 155.2, 148.5, 148.1, 144.8, 143.3, 128.2, 127.0, 114.3, 101.6, 61.9, 61.4, 56.3, 51.7, 41.8, 36.6, 29.7; HRMS (ESI) m/z calculated for $C_{23}H_{29}N_2O_4$ $[M+H]^+$: 397.2122; found $[M+H]^+$: 397.2117.

***N*-(4-chlorobenzyl)-5,7-dimethoxyisoquinoline-3-carboxamide (F15)**



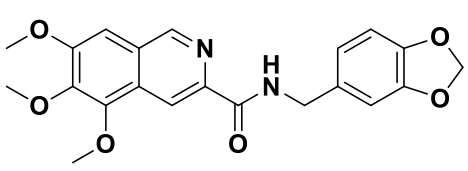
Color-less semi-solid (213 mg, 60% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.86 (s, 1H), 8.49 (t, *J* = 6.2 Hz, 1H), 7.34 – 7.27 (m, 4H), 6.81 (d, *J* = 2.1 Hz, 1H), 6.66 (d, *J* = 2.1 Hz, 1H), 4.67 (d, *J* = 6.2 Hz, 2H), 3.97 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 160.9, 157.1, 149.0, 141.5, 137.3, 133.2, 131.7, 129.3, 128.8, 125.0, 115.7, 102.1, 102.0, 96.9, 96.8, 55.9, 55.8, 42.9; HRMS (ESI) m/z calculated for $C_{19}H_{18}ClN_2O_3$ $[M+H]^+$: 357.1001; found $[M+H]^+$: 357.1001.

***N*-cyclohexyl-6,7-dimethoxyisoquinoline-3-carboxamide (H13)**



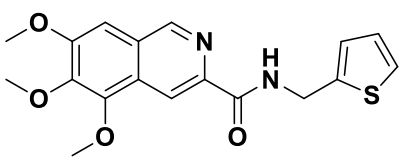
White solid (198 mg, 63% yield), M.P.= 179 – 180 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.43 (s, 1H), 8.08 (d, *J* = 8.6 Hz, 1H), 7.21 (s, 1H), 7.16 (s, 1H), 4.01 (s, 3H), 4.01 (s, 3H), 4.00 – 3.96 (m, 1H), 2.07 – 1.97 (m, 2H), 1.80 – 1.73 (m, 2H), 1.67 – 1.60 (m, 1H), 1.47 – 1.37 (m, 2H), 1.37 – 1.28 (m, 2H), 1.26 – 1.18 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.2, 153.4, 151.5, 148.3, 143.1, 132.8, 126.0, 119.0, 106.0, 105.4, 57.3, 56.2, 48.2, 33.3, 25.7, 25.0; HRMS (ESI) m/z calculated for $C_{18}H_{23}N_2O_3$ $[M+H]^+$: 315.1703; found $[M+H]^+$: 315.1702.

***N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (I6)**



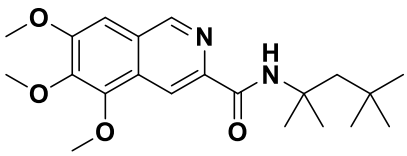
Light yellow solid (221 mg, 56% yield), M.P.= 123 – 125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.79 (s, 1H), 8.44 (t, *J* = 6.2 Hz, 1H), 7.07 (s, 1H), 6.90 (d, *J* = 1.7 Hz, 1H), 6.87 – 6.84 (m, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 5.93 (s, 2H), 4.62 (d, *J* = 6.0 Hz, 2H), 4.07 (s, 3H), 4.02 (d, *J* = 2.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 155.5, 148.8, 148.1, 148.0, 147.0, 144.8, 142.1, 132.6, 128.0, 127.2, 121.3, 115.1, 108.7, 108.4, 101.6, 101.1, 61.9, 61.4, 56.3, 43.5; HRMS (ESI) m/z calculated for $C_{21}H_{21}N_2O_6$ $[M+H]^+$: 397.1394; found $[M+H]^+$: 397.1390.

5,6,7-Trimethoxy-*N*-(thiophen-2-ylmethyl)isoquinoline-3-carboxamide (I17)



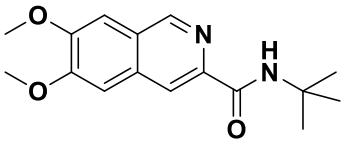
White solid (175 mg, 49% yield), M.P.= 115 – 117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (d, *J* = 0.9 Hz, 1H), 8.80 (s, 1H), 8.51 (t, *J* = 6.1 Hz, 1H), 7.24 – 7.22 (m, 1H), 7.08 – 7.05 (m, 2H), 6.98 – 6.95 (m, 1H), 4.90 – 4.86 (m, 2H), 4.07 (s, 3H), 4.02 (d, *J* = 1.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 155.5, 148.9, 148.1, 144.7, 142.0, 141.3, 128.0, 127.3, 127.0, 126.2, 125.2, 115.2, 101.6, 61.9, 61.4, 56.3, 38.4; HRMS (ESI) m/z calculated for $C_{18}H_{19}N_2O_4S$ $[M+H]^+$: 359.1060; found $[M+H]^+$: 359.1057.

5,6,7-Trimethoxy-*N*-(2,4,4-trimethylpentan-2-yl)isoquinoline-3-carboxamide (J3)



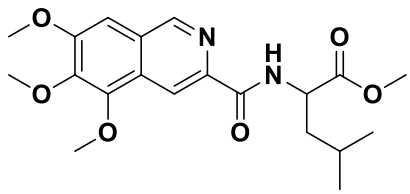
Color-less semi-solid (127 mg, 34% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.74 (s, 1H), 8.22 (s, 1H), 7.05 (s, 1H), 4.03 (s, 3H), 4.01 (d, *J* = 1.2 Hz, 6H), 1.91 (s, 2H), 1.58 (s, 6H), 1.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.08, 155.20, 148.58, 148.10, 144.70, 143.33, 128.18, 126.97, 114.16, 101.57, 77.36, 61.85, 61.36, 56.27, 54.79, 51.98, 31.85, 31.62, 29.42; HRMS (ESI) m/z calculated for $C_{21}H_{31}N_2O_4$ $[M+H]^+$: 375.2278; found $[M+H]^+$: 375.2279.

***N*-(tert-butyl)-6,7-dimethoxyisoquinoline-3-carboxamide (J9)**



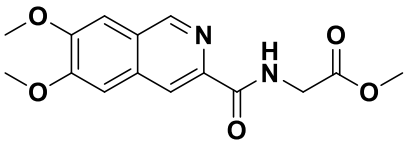
White solid (78 mg, 27% yield), M.P.= 188 – 190 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.41 (s, 1H), 8.14 (s, 1H), 7.22 (s, 1H), 7.16 (s, 1H), 4.03 (s, 6H), 1.52 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 153.4, 151.5, 148.1, 143.7, 132.9, 125.9, 118.4, 106.0, 105.4, 56.3, 56.2, 50.9, 29.0; HRMS (ESI) m/z calculated for $C_{16}H_{21}N_2O_3$ $[M+H]^+$: 289.1547; found $[M+H]^+$: 289.1547.

Methyl (5,6,7-trimethoxyisoquinoline-3-carbonyl)leucinate (J18)



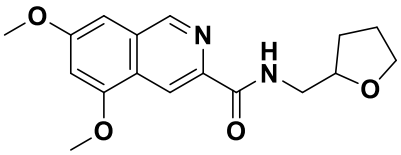
Color-less semi-solid (129 mg, 33% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.75 (s, 1H), 8.48 (d, *J* = 8.7 Hz, 1H), 7.08 (s, 1H), 4.96 – 4.84 (m, 1H), 4.04 (s, 3H), 4.02 (s, 3H), 4.01 (s, 3H), 3.76 (s, 3H), 1.87 – 1.69 (m, 3H), 1.00 (d, *J* = 6.0 Hz, 3H), 0.98 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 164.9, 155.4, 148.8, 148.0, 144.6, 141.6, 127.8, 127.2, 115.1, 101.6, 61.8, 61.3, 56.2, 52.3, 50.8, 41.8, 25.0, 23.0, 21.9; HRMS (ESI) m/z calculated for $C_{20}H_{27}N_2O_6$ $[M+H]^+$: 391.1864; found $[M+H]^+$: 391.1867.

Methyl (6,7-dimethoxyisoquinoline-3-carbonyl) glycinate (K5)



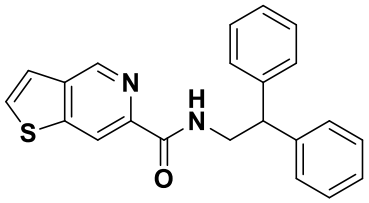
Yellow solid (106 mg, 35% yield), M.P.= 197 – 198 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.61 (t, *J* = 5.7 Hz, 1H), 8.44 (s, 1H), 7.25 (s, 1H), 7.19 (s, 1H), 4.32 (d, *J* = 5.7 Hz, 2H), 4.05 (s, 3H), 4.04 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 165.6, 153.6, 151.8, 148.7, 142.2, 132.7, 126.3, 119.3, 106.1, 105.5, 56.4, 56.3, 52.5, 41.5; HRMS (ESI) m/z calculated for $C_{15}H_{17}N_2O_5$ $[M+H]^+$: 305.1132; found $[M+H]^+$: 305.1132.

5,7-Dimethoxy-*N*-((tetrahydrofuran-2-yl)methyl)isoquinoline-3-carboxamide (K8)



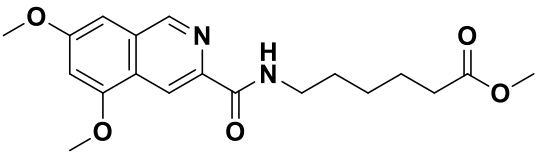
White solid (123 mg, 39% yield), M.P.= 119 – 121 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.81 (s, 1H), 8.44 (t, *J* = 6.1 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 6.64 (d, *J* = 2.1 Hz, 1H), 4.17 – 4.05 (m, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.84 – 3.71 (m, 2H), 3.51 – 3.40 (m, 1H), 2.11 – 1.98 (m, 1H), 1.98 – 1.85 (m, 2H), 1.75 – 1.58 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 160.7, 157.0, 149.0, 141.8, 131.6, 125.0, 115.4, 102.0, 96.9, 78.0, 68.3, 55.9, 55.7, 43.3, 28.9, 26.0; HRMS (ESI) m/z calculated for $C_{17}H_{21}N_2O_4$ $[M+H]^+$: 317.1496; found $[M+H]^+$: 317.1497.

***N*-(2,2-diphenylethyl)thieno[3,2-c]pyridine-6-carboxamide (K21)**



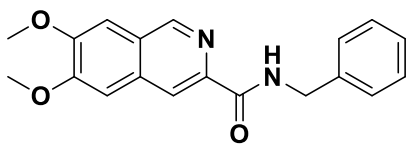
Yellow solid (182 mg, 51% yield), M.P.= 175 – 177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.72 (s, 1H), 8.23 (t, *J* = 6.2 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.45 (d, *J* = 5.4 Hz, 1H), 7.35 – 7.29 (m, 8H), 7.27 – 7.19 (m, 2H), 4.38 (t, *J* = 7.8 Hz, 1H), 4.21 – 4.13 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 148.0, 144.0, 143.4, 142.2, 137.5, 130.5, 128.8, 128.2, 126.8, 122.5, 122.4, 116.7, 50.9, 44.1; HRMS (ESI) m/z calculated for $C_{22}H_{19}N_2OS$ $[M+H]^+$: 359.1213; found $[M+H]^+$: 359.1212.

Methyl 6-(5,7-dimethoxyisoquinoline-3-carboxamido)hexanoate (L7)



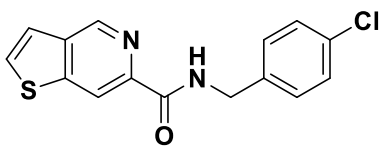
Color-less semi-solid (94 mg, 26% yield); ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.94 (s, 1H), 8.83 (s, 1H), 8.15 (s, 1H), 6.83 (s, 1H), 6.67 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.66 (s, 3H), 3.55 – 3.49 (m, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.74 – 1.64 (m, 4H), 1.49 – 1.41 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 165.2, 160.8, 157.1, 148.9, 141.9, 131.6, 125.1, 115.4, 102.1, 96.9, 55.9, 51.7, 39.3, 34.1, 29.7, 26.7, 24.8; HRMS (ESI) m/z calculated for $C_{19}H_{25}N_2O_5$ $[M+H]^+$: 361.1758; found $[M+H]^+$: 361.1756.

***N*-benzyl-6,7-dimethoxyisoquinoline-3-carboxamide (M17)**



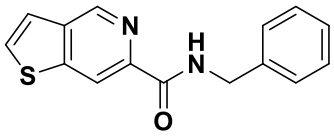
Grey solid (206 mg, 64% yield), M.P.= 160 – 162 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.58 – 8.46 (m, 2H), 7.43 – 7.27 (m, 5H), 7.23 (s, 1H), 7.20 (s, 1H), 4.72 (d, *J* = 6.0 Hz, 2H), 4.04 (s, 3H), 4.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 153.5, 151.7, 148. 5, 142.7, 138.6, 132.8, 128.8, 128.0, 127.5, 126.2, 119.3, 106.1, 105. 5, 56.4, 56.3, 43.7; HRMS (ESI) m/z calculated for $C_{19}H_{19}N_2O_3$ $[M+H]^+$: 323.1390; found $[M+H]^+$: 323.1390.

***N*-(4-chlorobenzyl)thieno[3,2-c]pyridine-6-carboxamide (N15)**



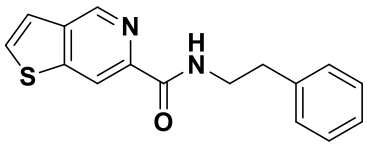
White solid (129 mg, 43% yield), M.P.= 129 – 131 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (d, *J* = 1.0 Hz, 1H), 8.77 (s, 1H), 8.53 (s, 1H), 7.66 (d, *J* = 5.4 Hz, 1H), 7.56 – 7.46 (m, 1H), 7.32 – 7.30 (m, 4H), 4.67 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 148.2, 144.0, 143.2, 137.7, 137.1, 133.3, 130.7, 130.5, 129.3, 128.9, 122.6, 122.5, 117.0, 43.0; HRMS (ESI) m/z calculated for $C_{15}H_{12}ClN_2OS$ $[M+H]^+$: 303.0353; found $[M+H]^+$: 303.0354.

_N_-benzylthieno[3,2-c]pyridine-6-carboxamide (O11)



White solid (134 mg, 50% yield), M.P.= 100 – 102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.0 (d, *J* = 0.9 Hz, 1H), 8.8 (s, 1H), 8.5 (s, 1H), 7.7 (d, *J* = 5.4 Hz, 1H), 7.5 – 7.5 (m, 1H), 7.4 – 7.4 (m, 2H), 7.4 – 7.3 (m, 2H), 7.3 – 7.3 (m, 1H), 4.7 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 148.2, 144.0, 143.5, 138.5, 137.6, 130.6, 130.4, 128.9, 128.1, 127.6, 122.6, 122.4, 117.0, 43.8; HRMS (ESI) m/z calculated for $C_{15}H_{13}N_2OS$ $[M+H]^+$: 269.0743; found $[M+H]^+$: 269.0743.

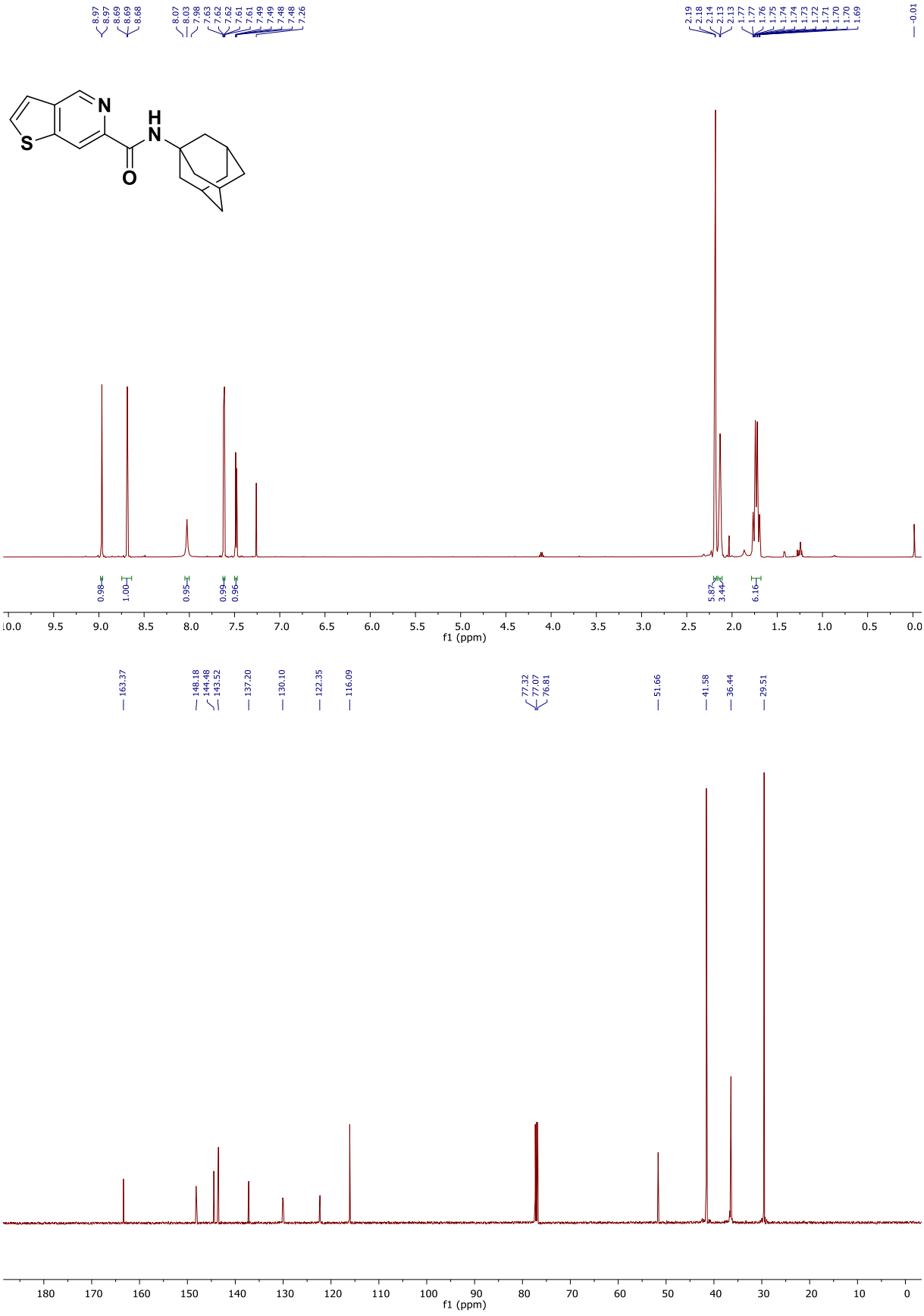
_N_-phenethylthieno[3,2-c]pyridine-6-carboxamide (P8)

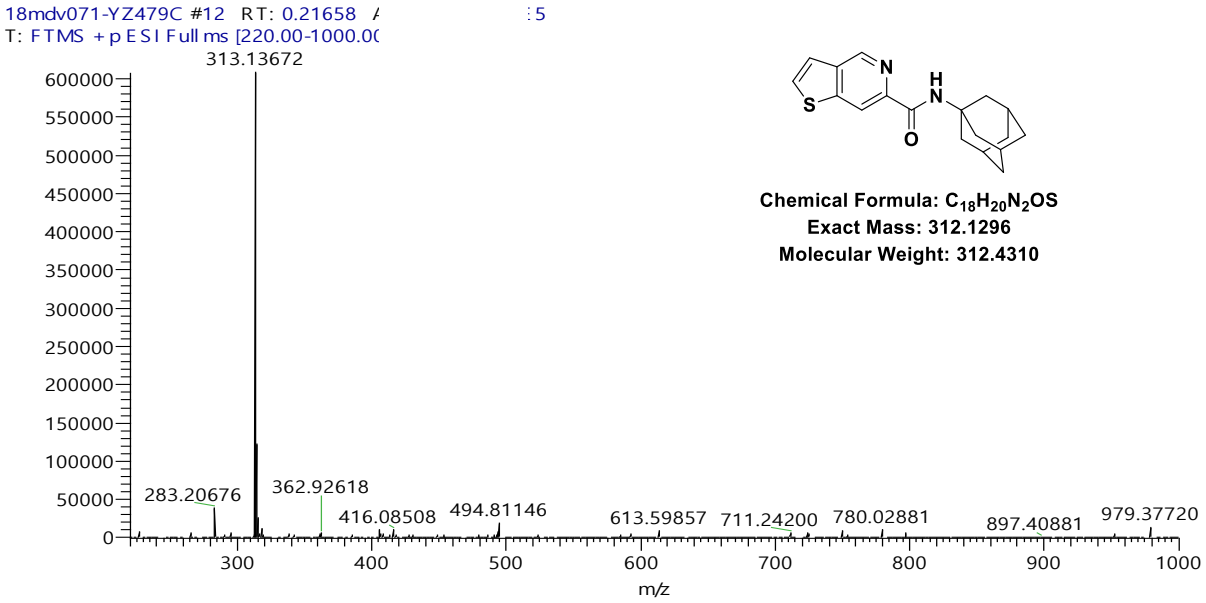


White solid (149 mg, 53% yield), M.P.= 108 – 109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (d, *J* = 0.9 Hz, 1H), 8.75 (d, *J* = 1.0 Hz, 1H), 8.28 (s, 1H), 7.65 (d, *J* = 5.5 Hz, 1H), 7.51 – 7.49 (m, 1H), 7.35 – 7.22 (m, 5H), 3.82 – 3.73 (m, 2H), 2.98 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 148.1, 144.0, 143.6, 139.2, 137.6, 130.5, 128.9, 128.7, 126.6, 122.5, 116.7, 41.0, 36.1; HRMS (ESI) m/z calculated for $C_{16}H_{15}N_2OS$ $[M+H]^+$: 283.0900; found $[M+H]^+$: 283.0899.

6.3. ^{1}H and ^{13}C NMR spectra, HRMS

N-((1S,3s)-adamantan-1-yl)thieno[3,2-c]pyridine-6-carboxamide (A3)

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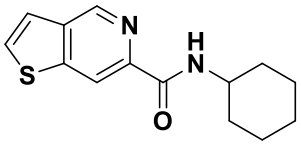
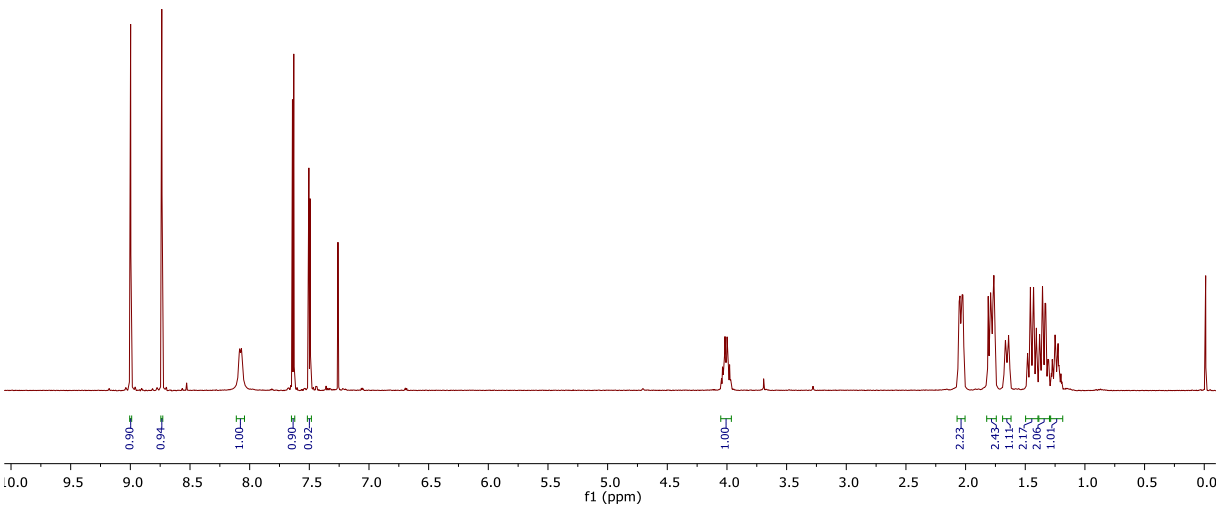
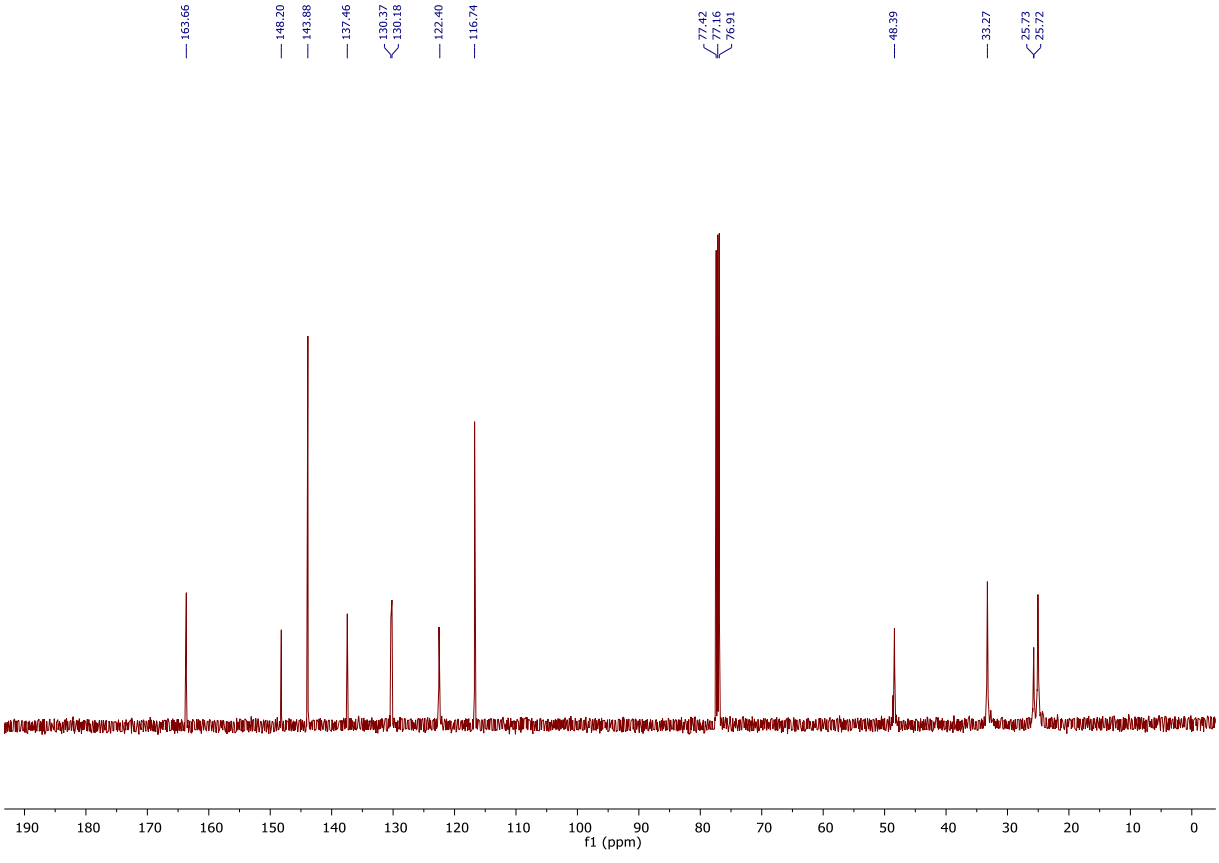
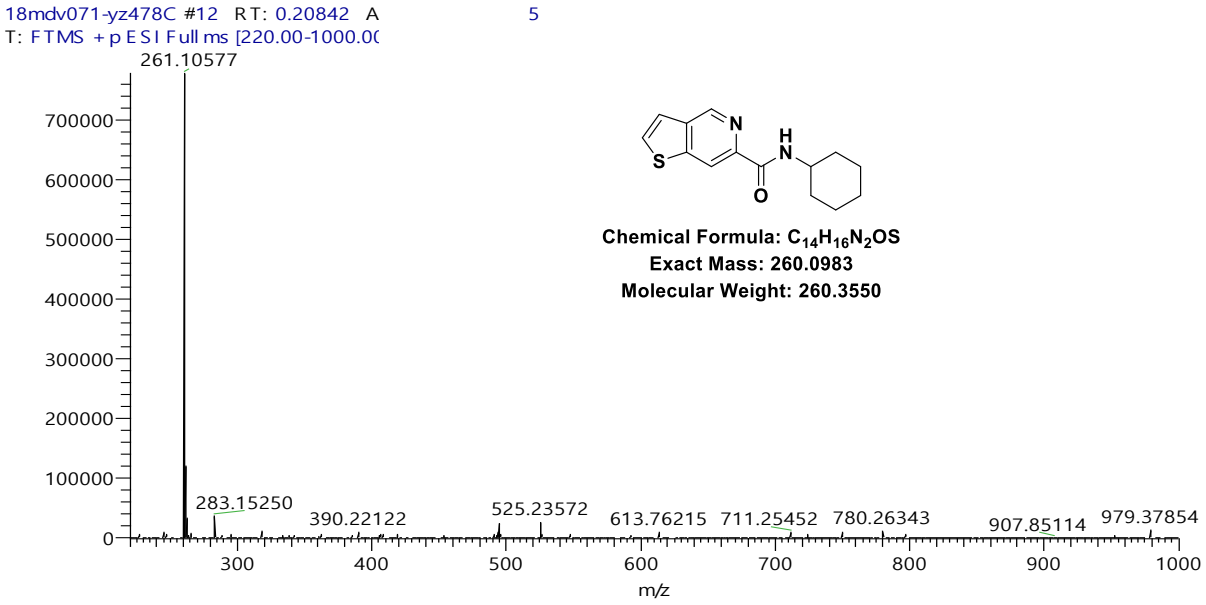
T: FTMS + p ESI Full ms [220.00-1000.0
313.13672
283.20676
362.92618
416.08508
494.81146
613.59857
711.24200
780.02881
897.40881
979.37720
m/z
Chemical Formula: C18H20N2OS
Exact Mass: 312.1296
Molecular Weight: 312.4310

N-cyclohexylthieno[3,2-*c*]pyridine-6-carboxamide (A13)

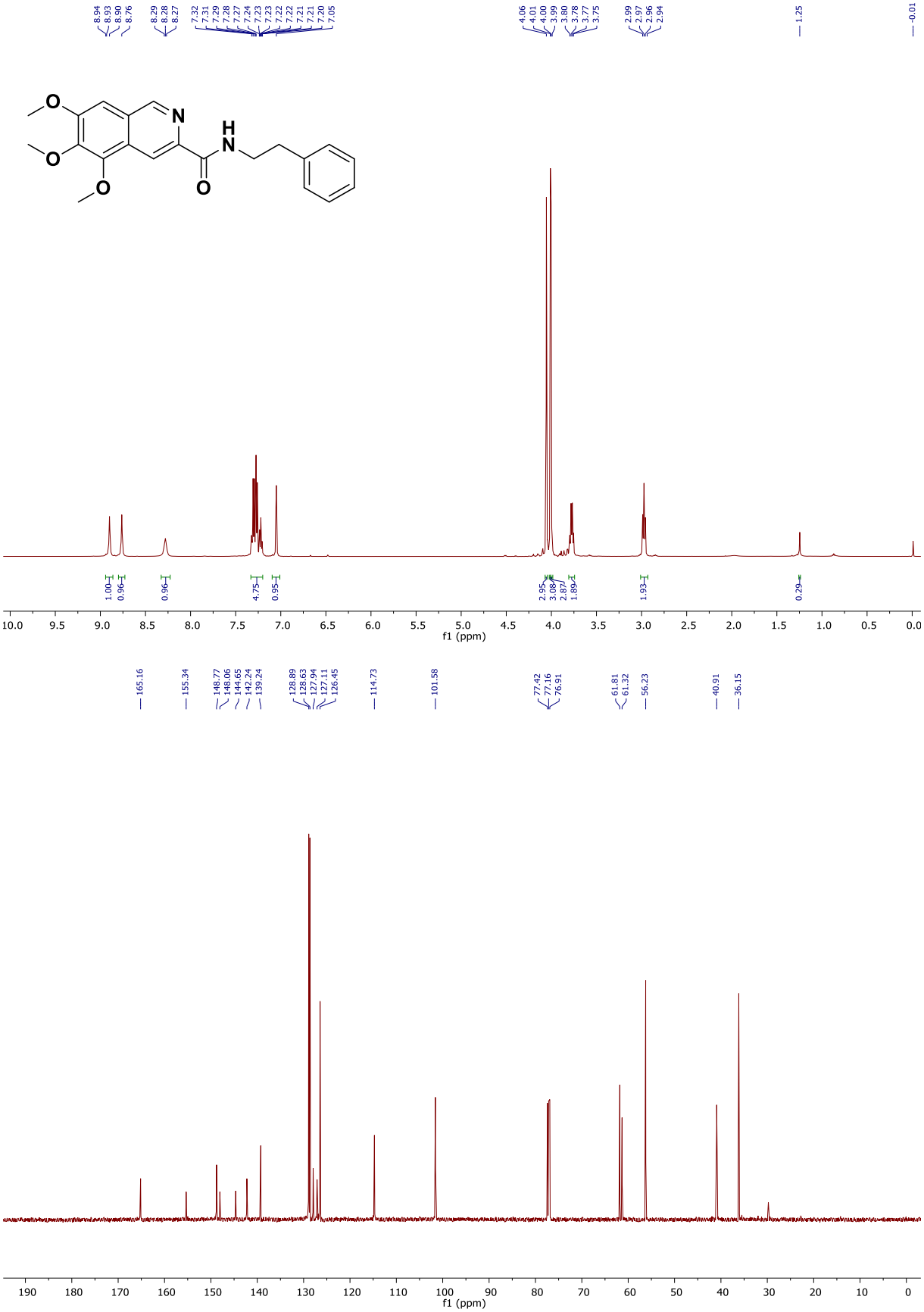


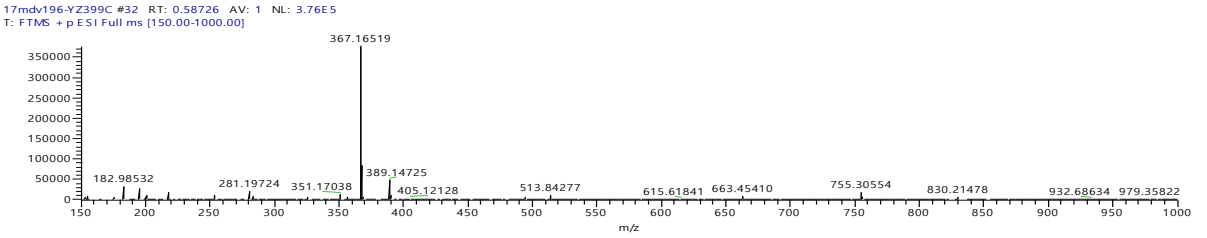


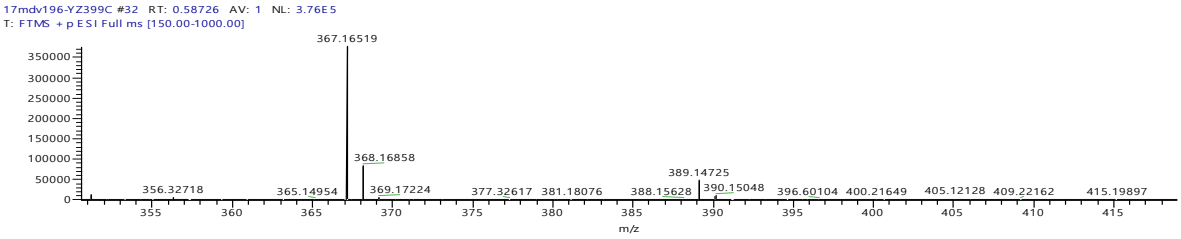


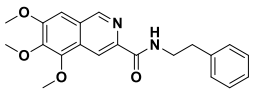

18mdv071-yz478C #12 RT: 0.20842 A 5
T: FTMS + p ESI Full ms [220.00-1000.0(
261.10577
283.15250
390.22122
525.23572
613.76215
711.25452
780.26343
907.85114
979.37854
700000
600000
500000
400000
300000
200000
100000
0
300
400
500
600
700
800
900
1000
m/z
N
H
N
S
O
Chemical Formula: C14H16N2OS
Exact Mass: 260.0983
Molecular Weight: 260.3550

5,6,7-Trimethoxy-*N*-phenethylisoquinoline-3-carboxamide (A22)



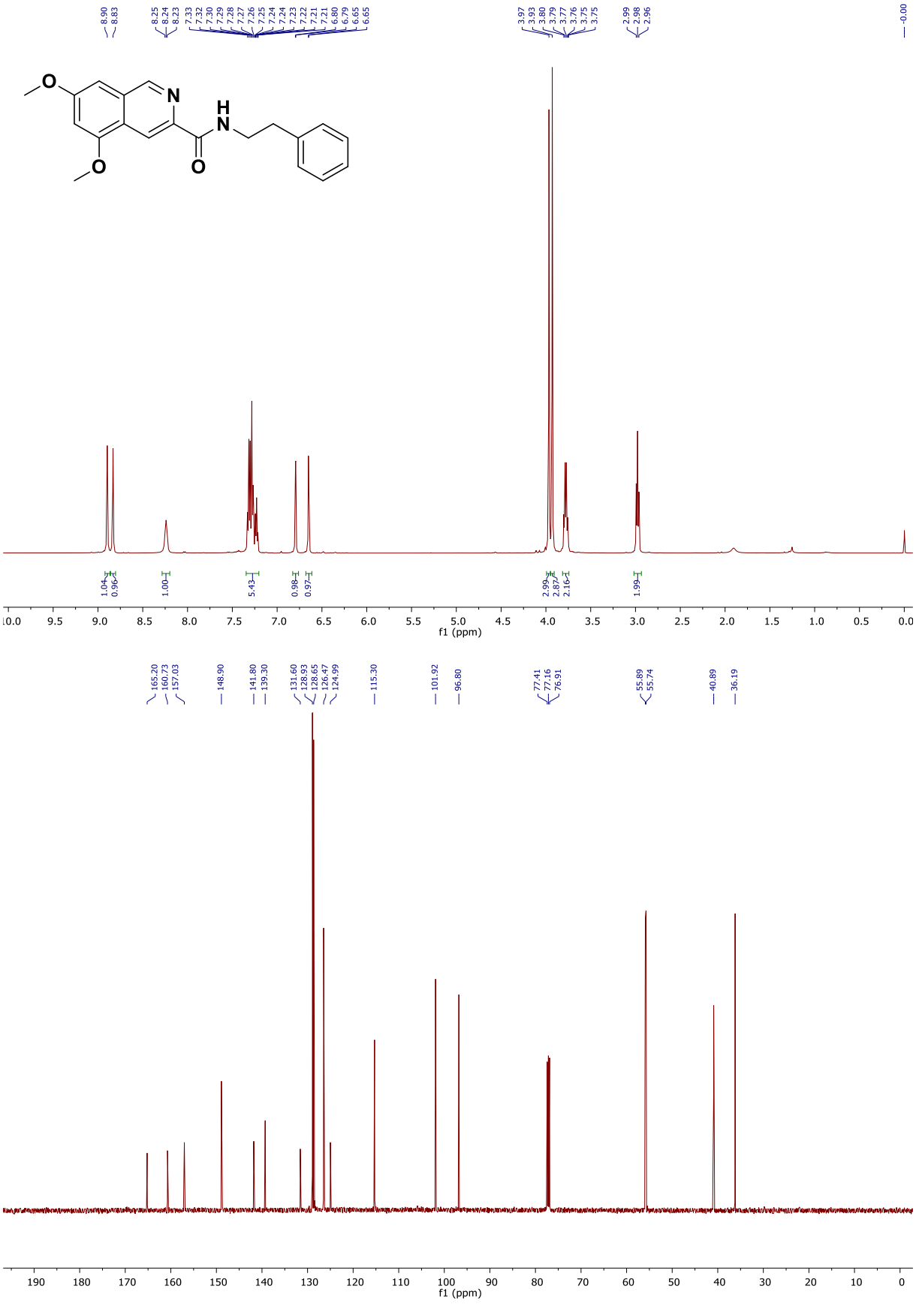




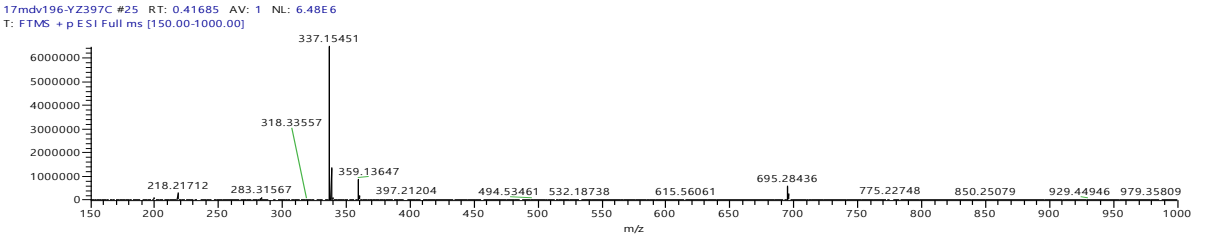


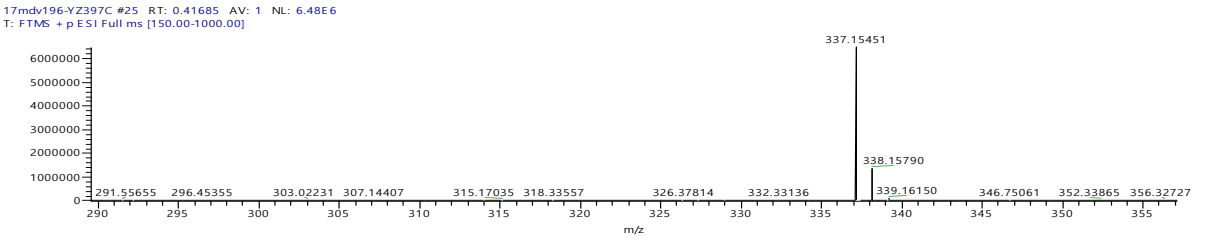
Chemical Formula: $C_{21}H_{22}N_2O_4$
Exact Mass: 366.1580
Molecular Weight: 366.4170

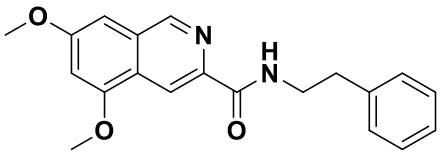
5,7-Dimethoxy-*N*-phenethylisoquinoline-3-carboxamide (B5)



17mdv196-YZ397C 10/06/17 12:16:22

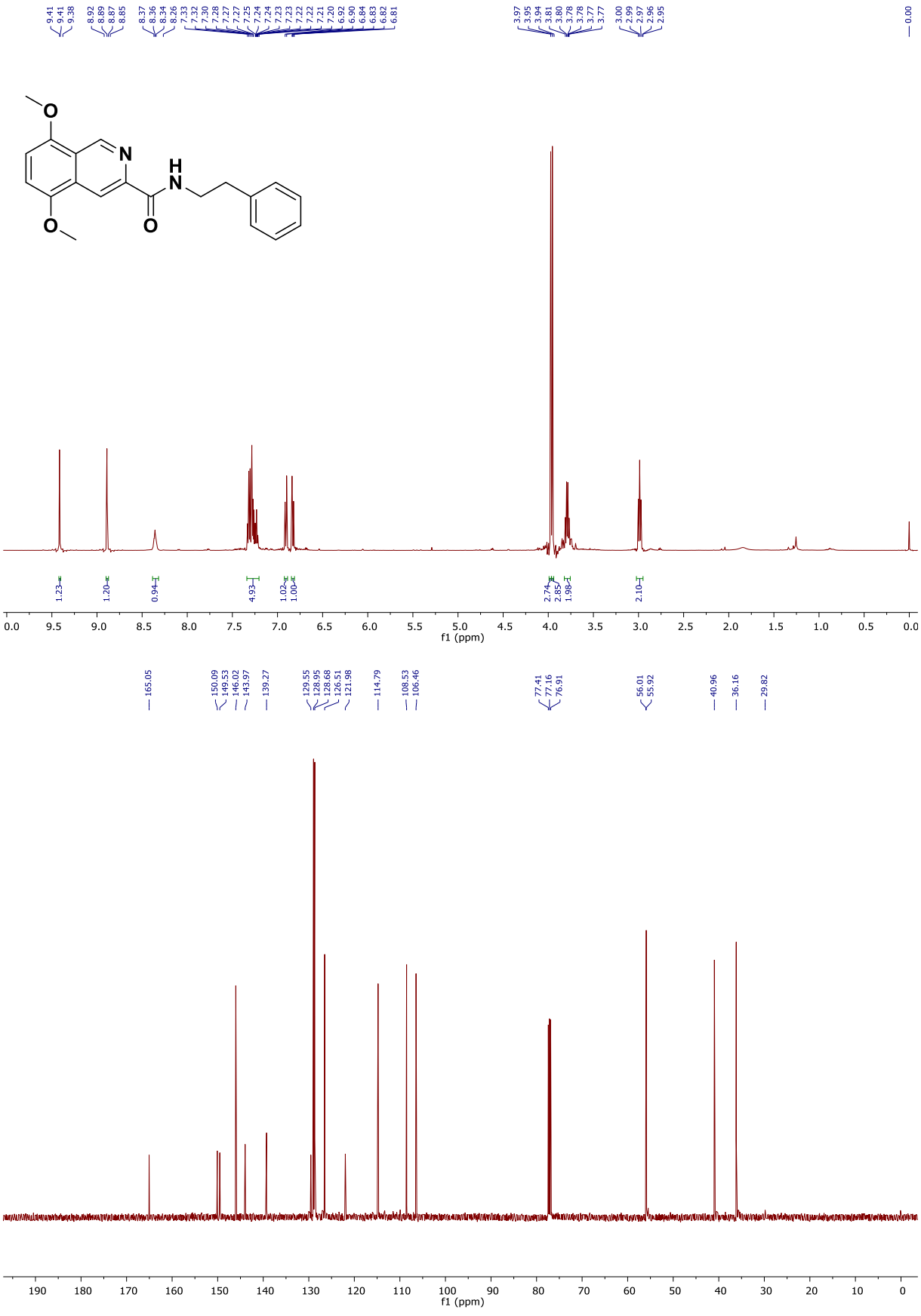


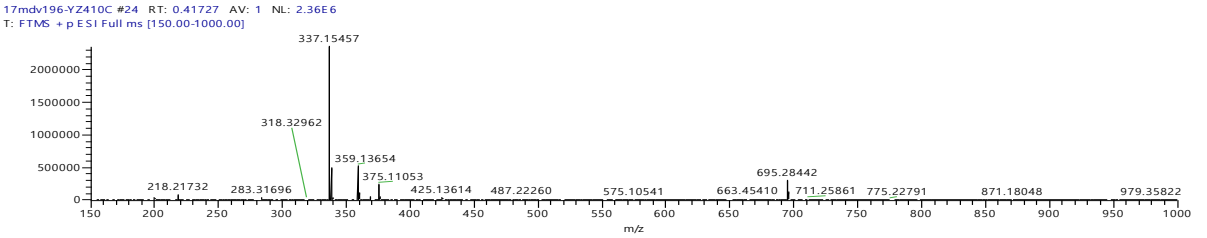


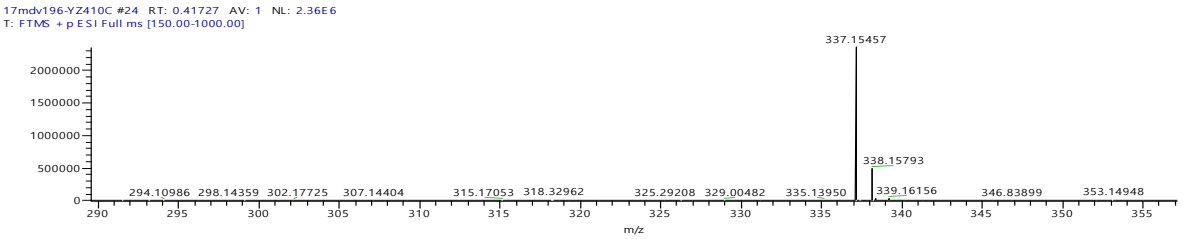


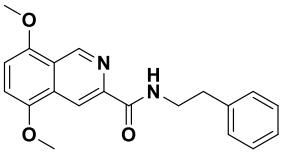
Chemical Formula: $C_{20}H_{20}N_2O_3$
Exact Mass: 336,15
Molecular Weight: 336,39

5,8-Dimethoxy-*N*-phenethylisoquinoline-3-carboxamide (B16)



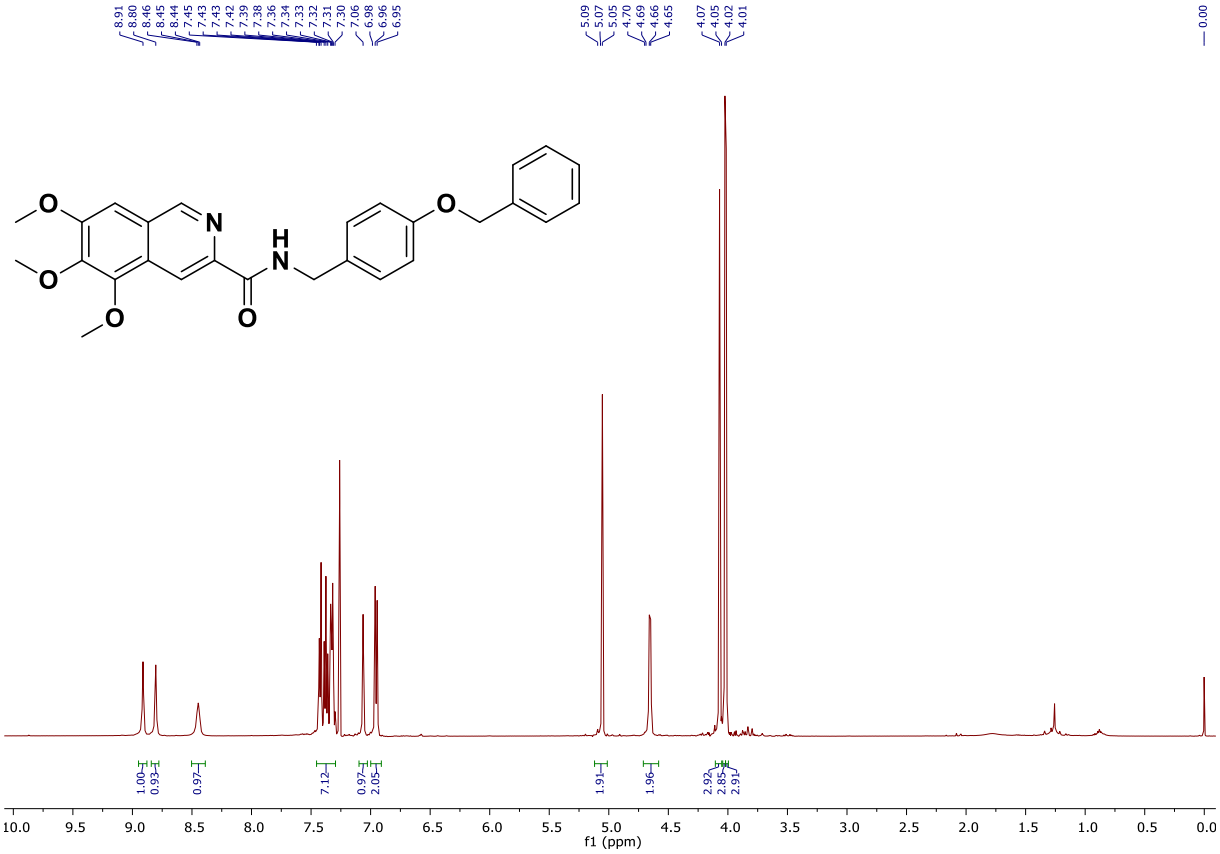


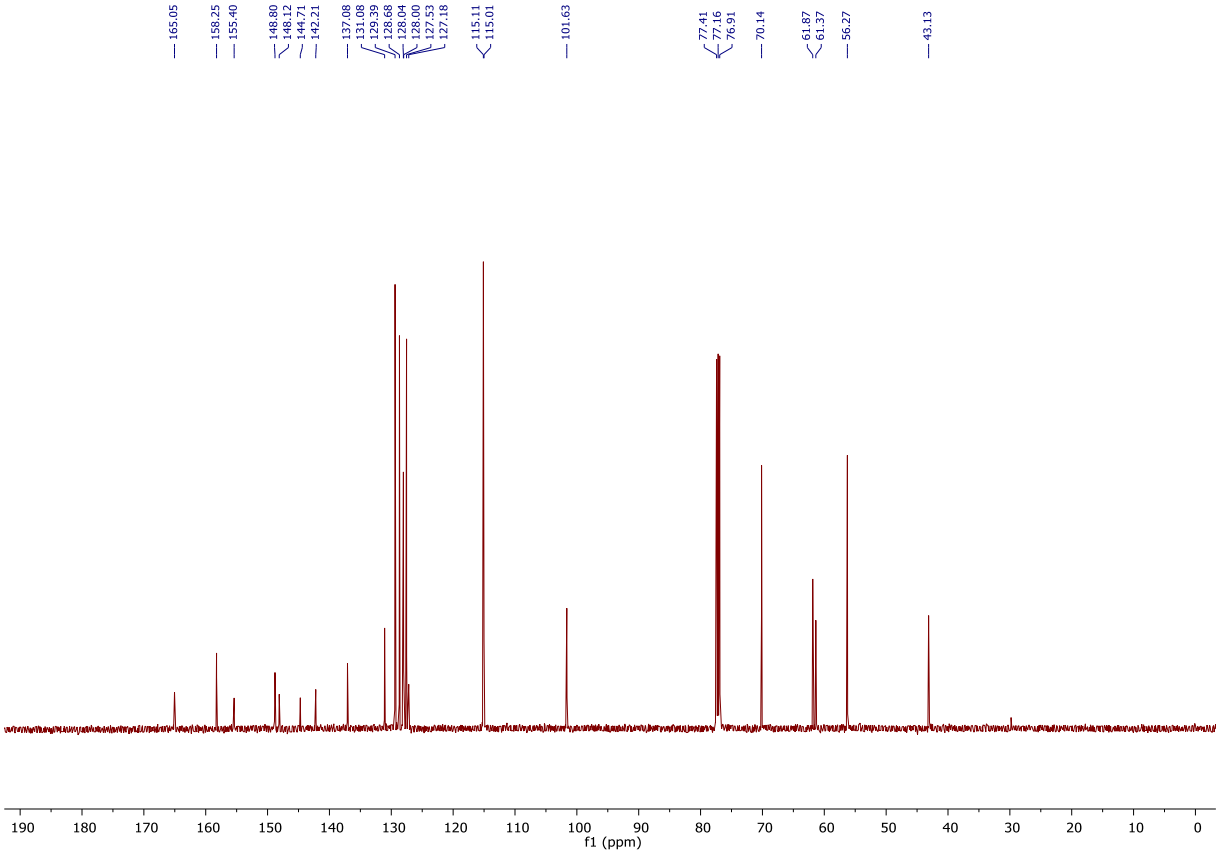


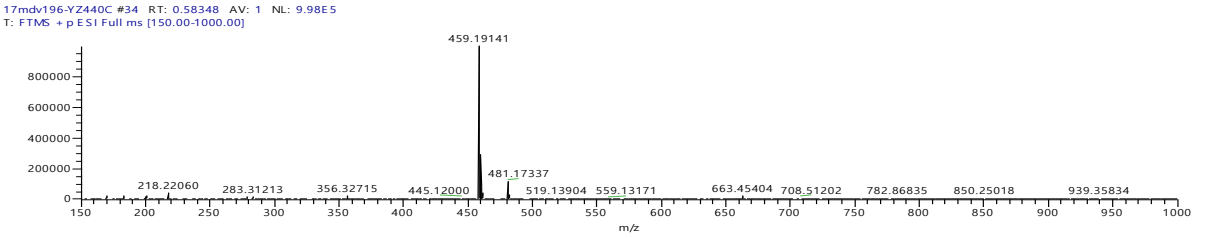


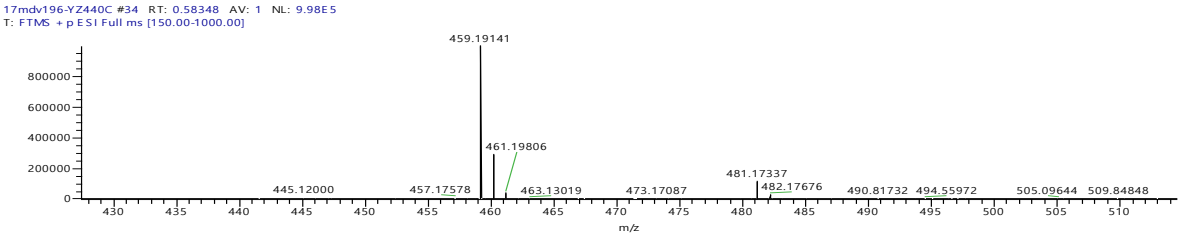
Chemical Formula: $C_{20}H_{20}N_2O_3$
Exact Mass: 336.1474
Molecular Weight: 336.3910

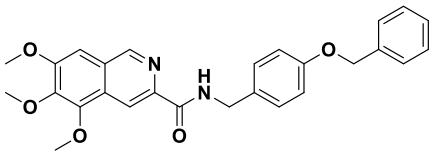
N-(4-(benzyloxy)benzyl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (B24)





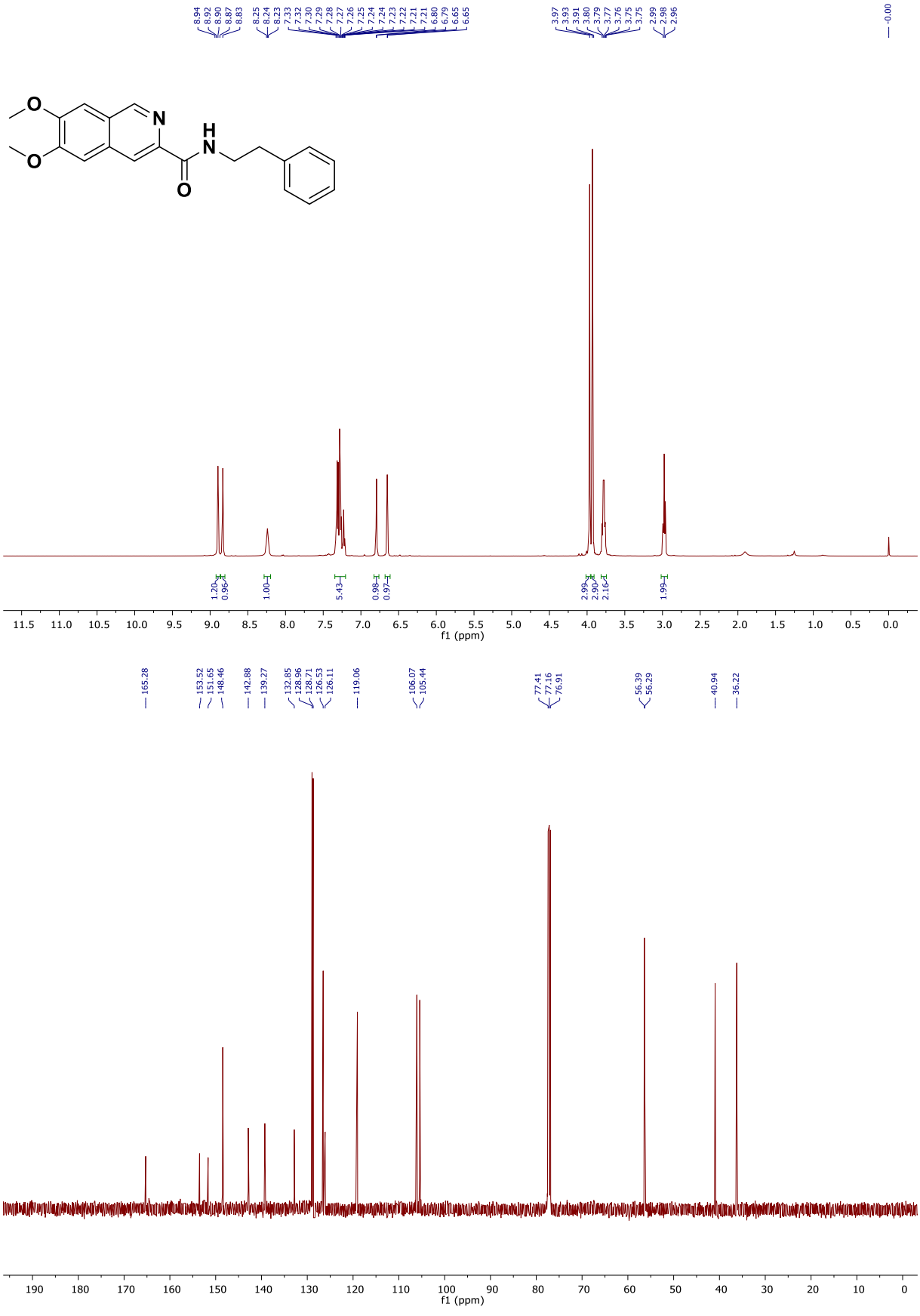


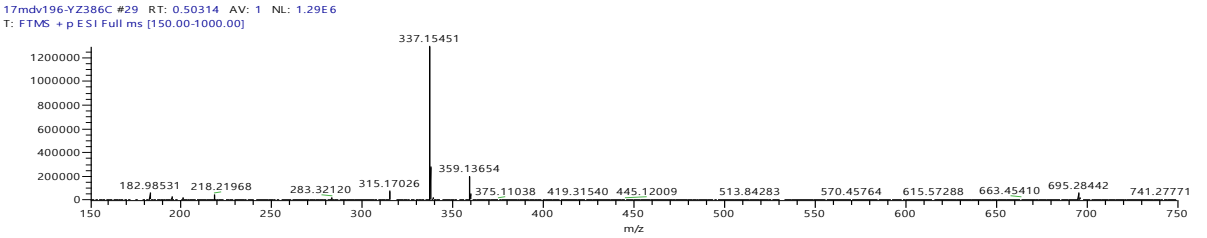


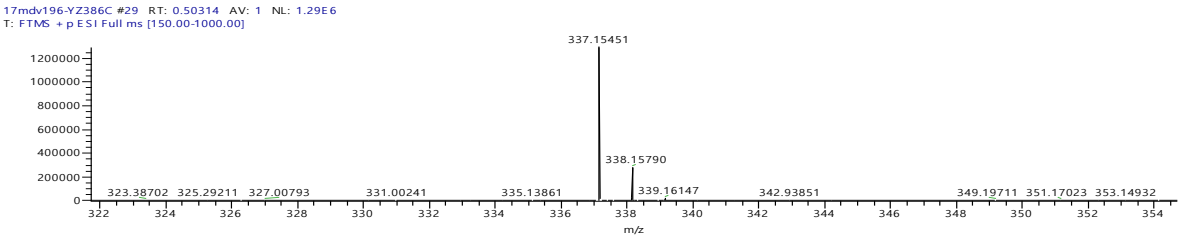


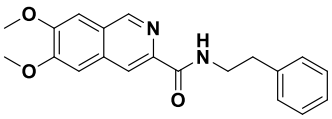
Chemical Formula: $C_{27}H_{26}N_2O_5$
Exact Mass: 458.1842
Molecular Weight: 458.5140

6,7-Dimethoxy-*N*-phenethylisoquinoline-3-carboxamide (C2)



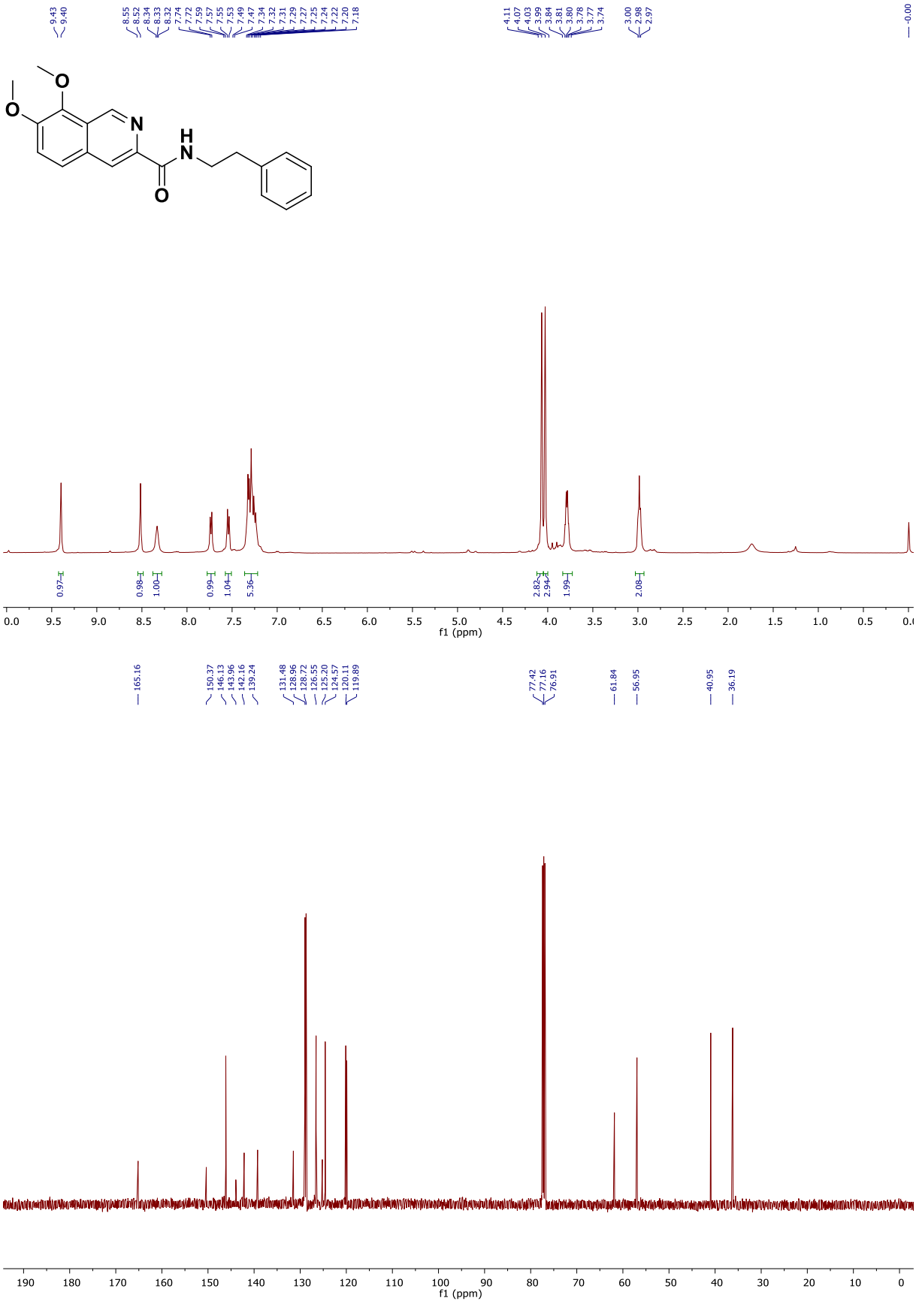


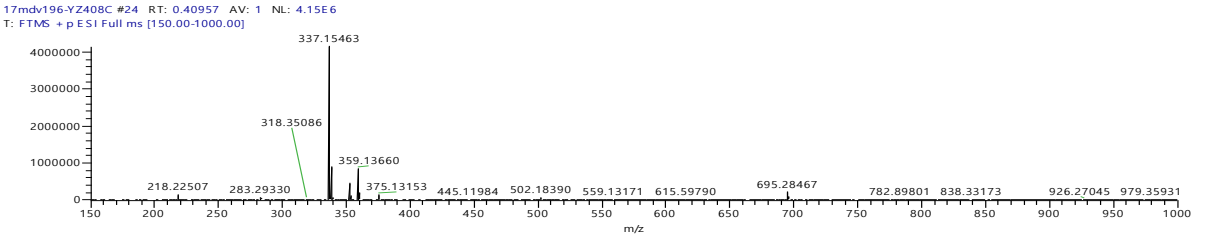


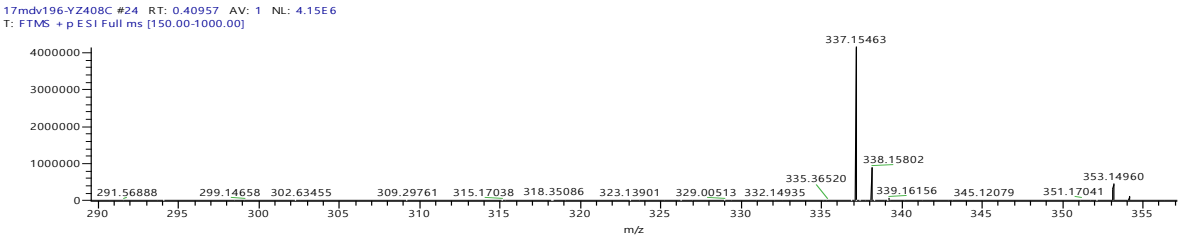


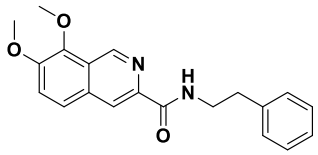
Chemical Formula: $C_{20}H_{20}N_2O_3$
Exact Mass: 336.1474
Molecular Weight: 336.3910

7,8-Dimethoxy-*N*-phenethylisoquinoline-3-carboxamide (C10)



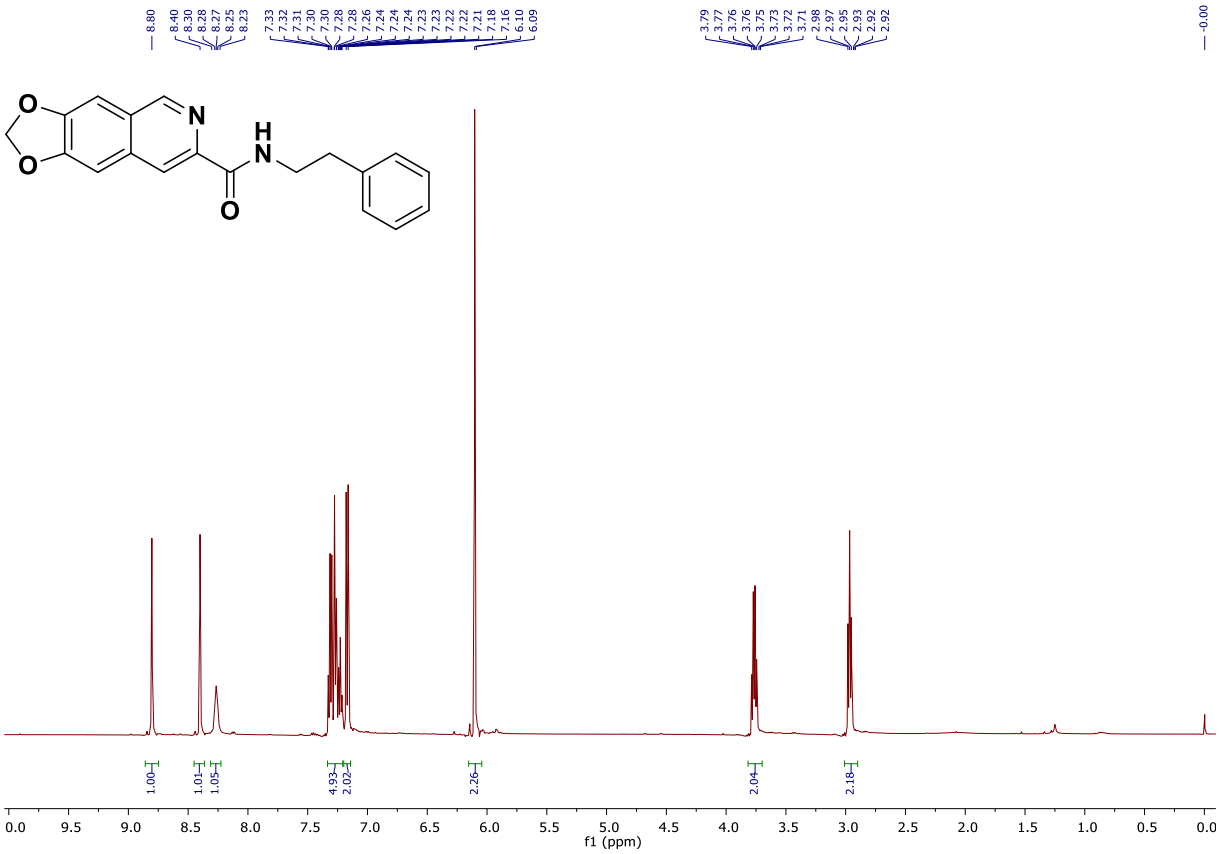


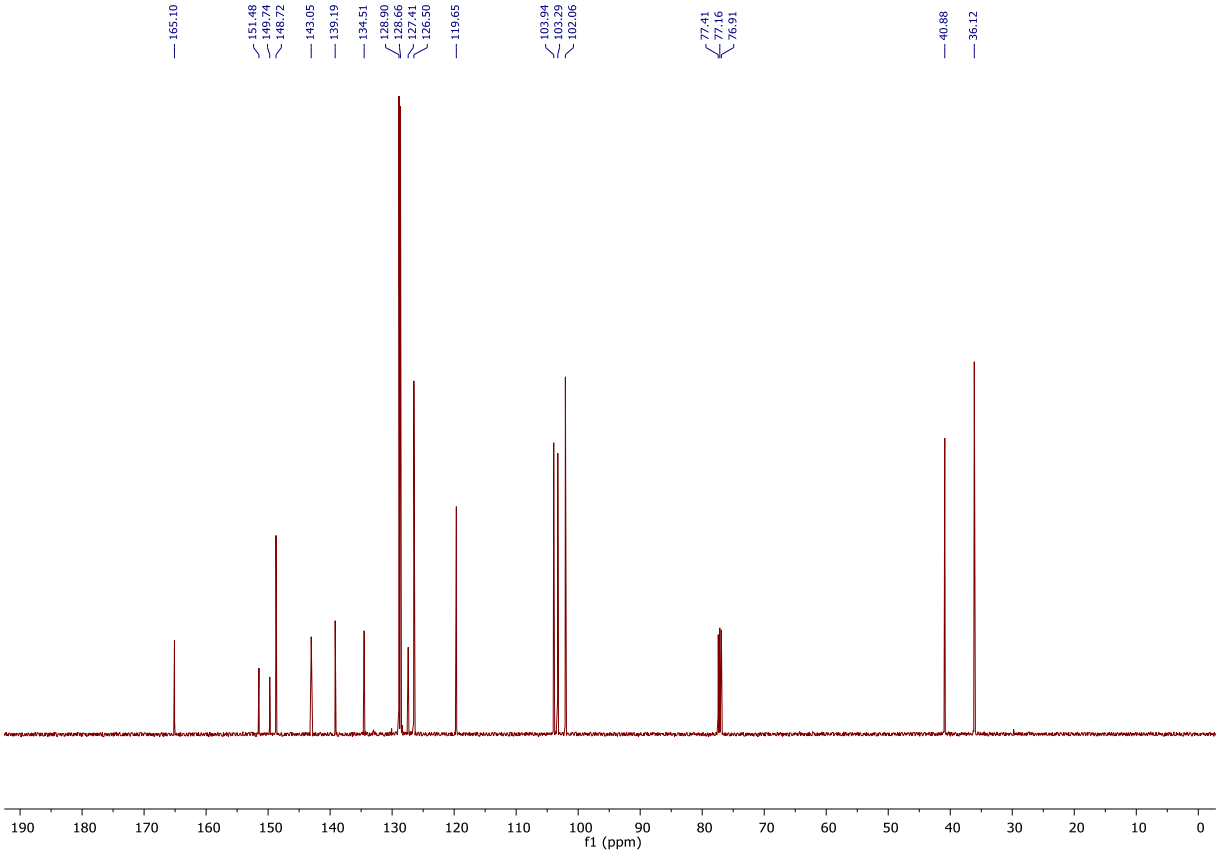


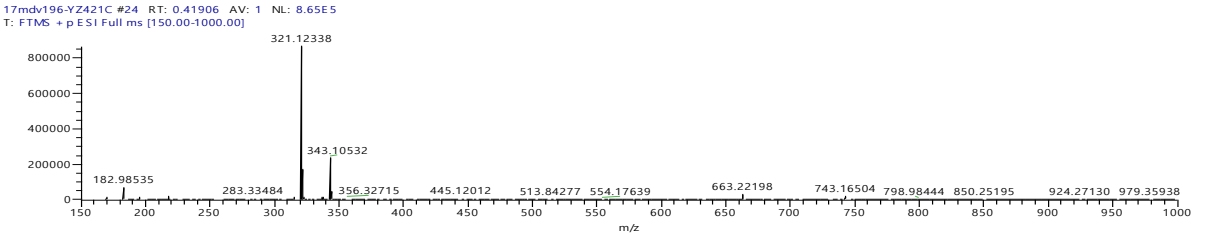


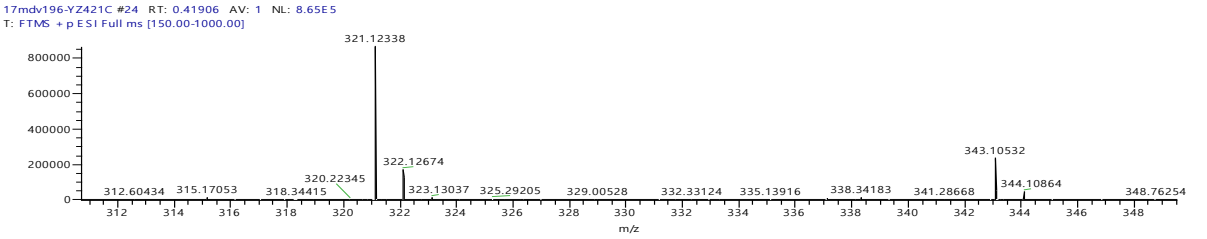
Chemical Formula: $C_{20}H_{20}N_2O_3$
Exact Mass: 336.1474
Molecular Weight: 336.3910

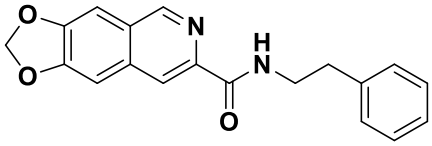
N-phenethyl-[1,3]dioxolo[4,5-*f*]isoquinoline-8-carboxamide (D19)





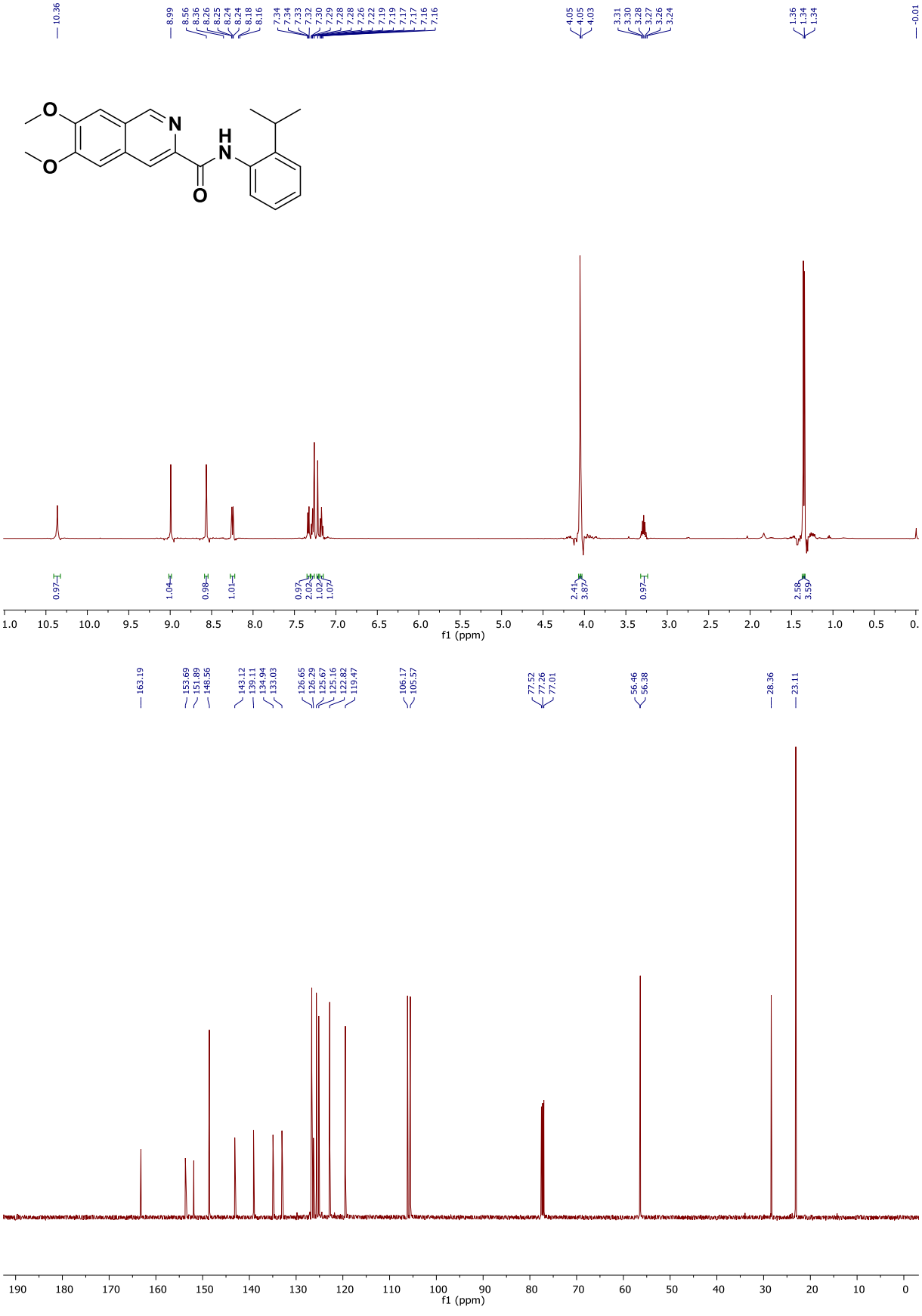


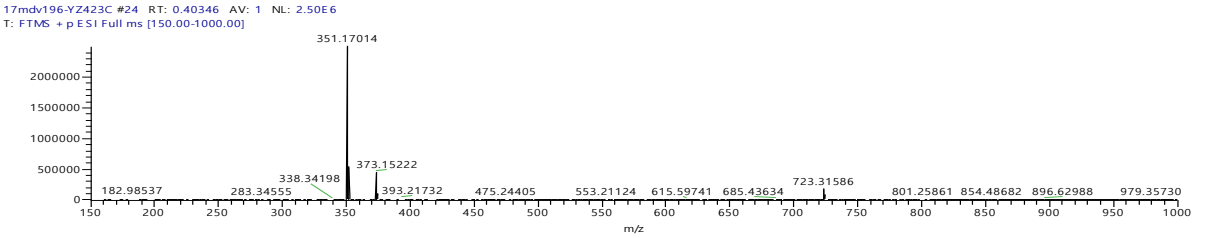


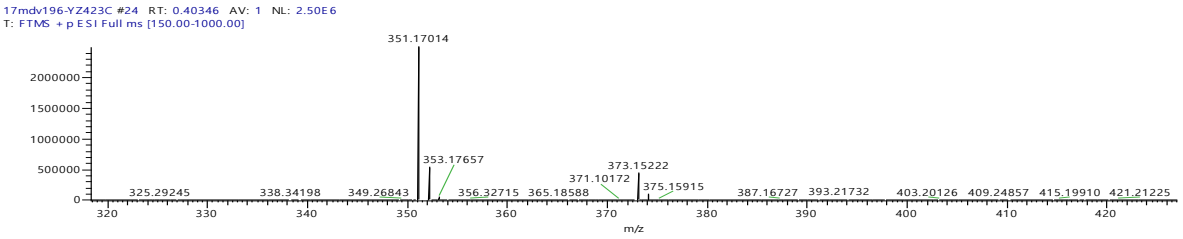


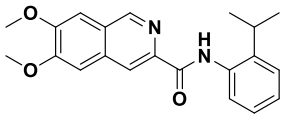
Chemical Formula: $C_{19}H_{16}N_2O_3$
Exact Mass: 320,1161
Molecular Weight: 320,3480

N-(2-isopropylphenyl)-6,7-dimethoxyisoquinoline-3-carboxamide (E7)



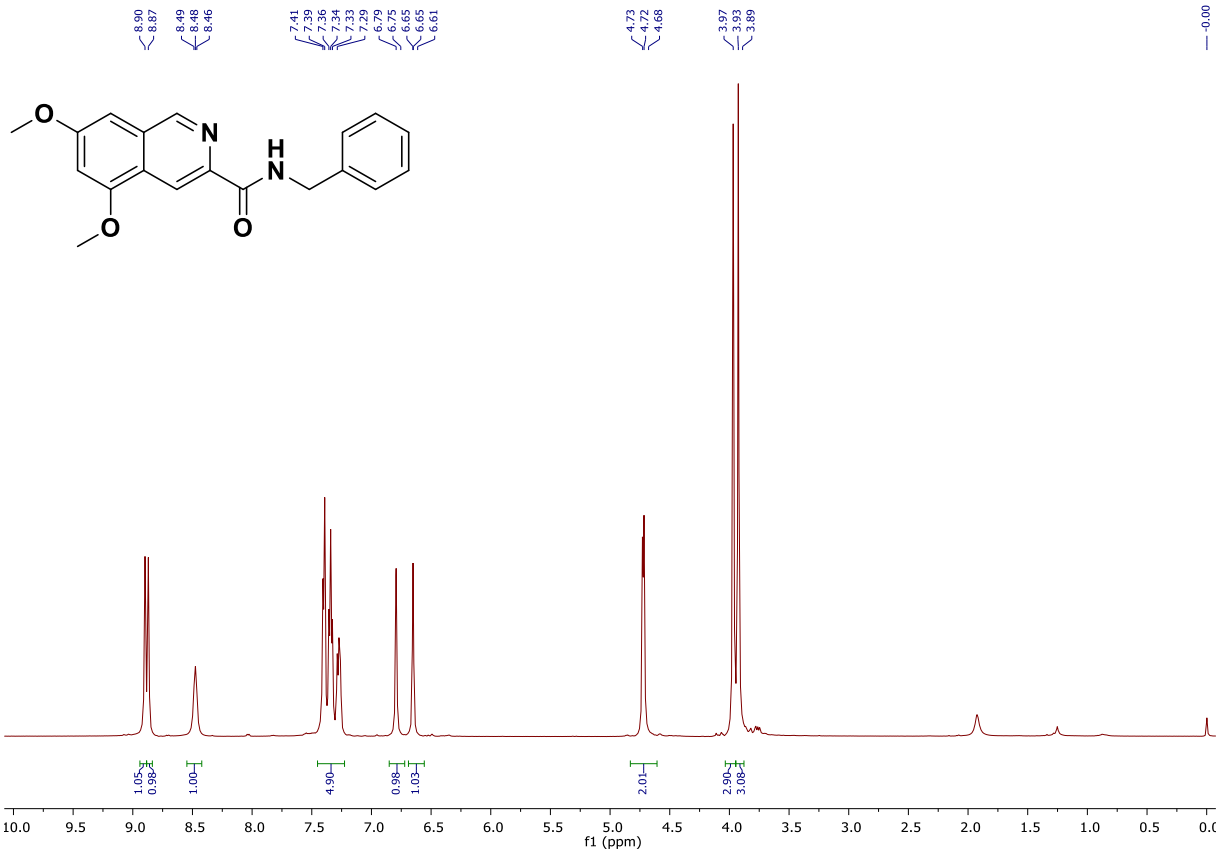


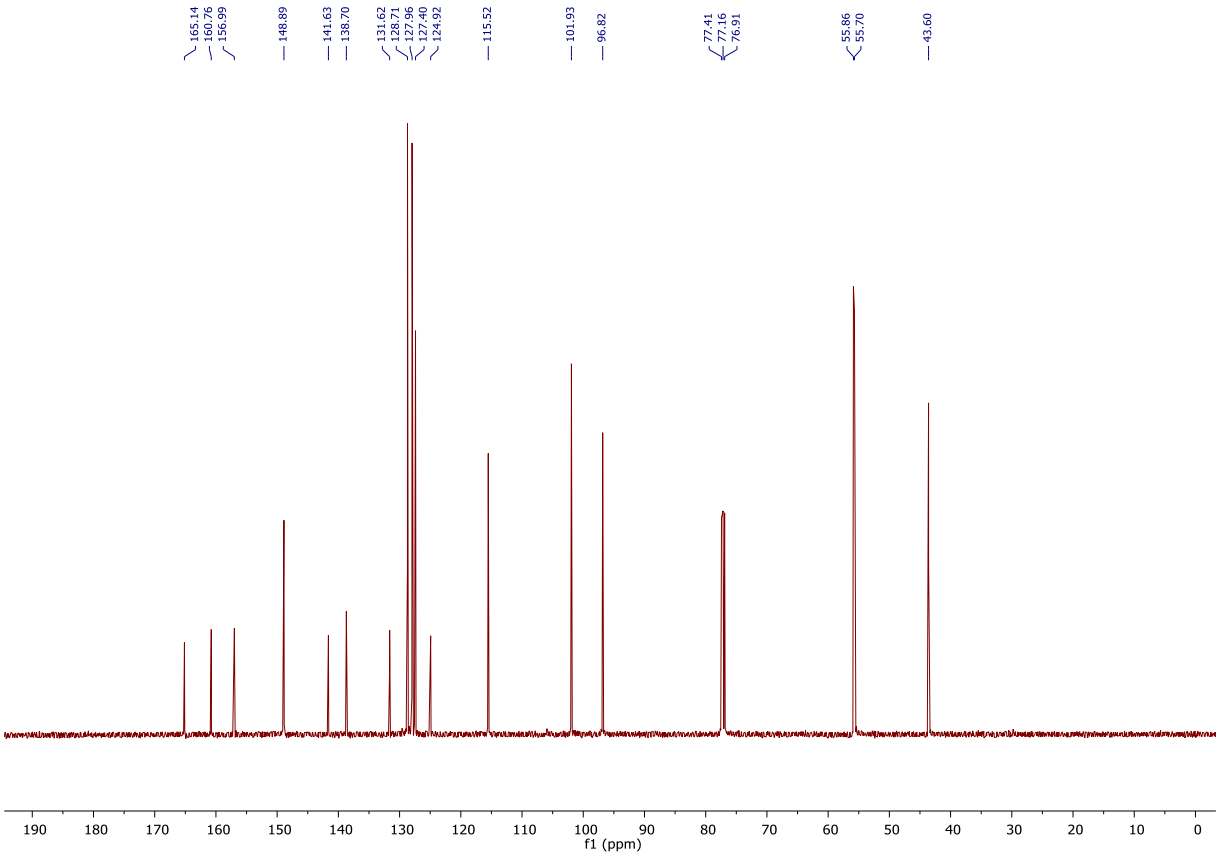


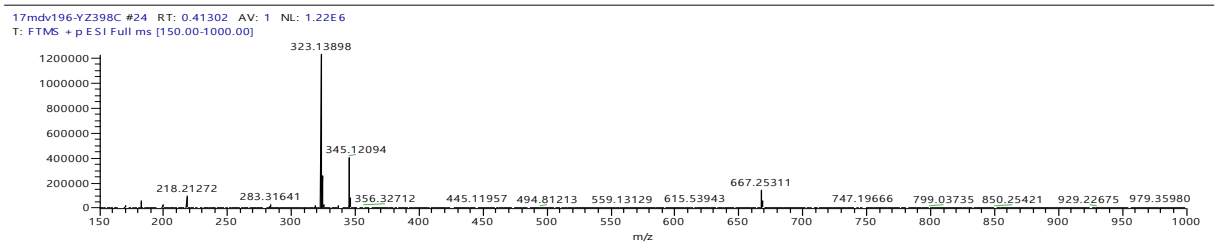


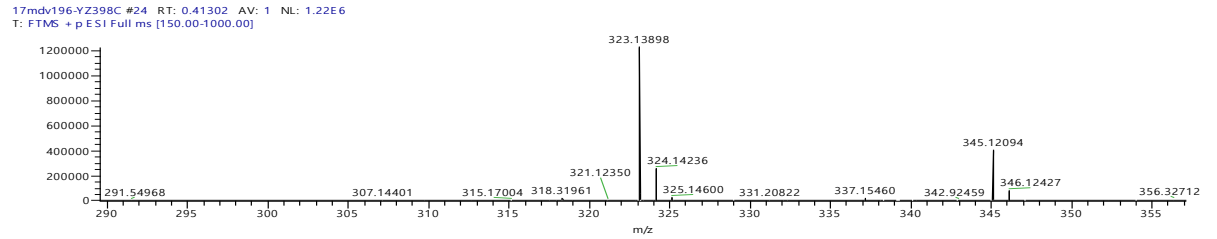
Chemical Formula: $C_{21}H_{22}N_2O_3$
Exact Mass: 350.1630
Molecular Weight: 350.4180

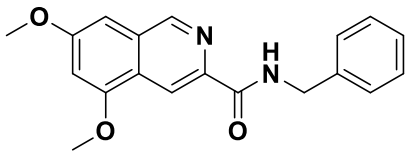
N-benzyl-5,7-dimethoxyisoquinoline-3-carboxamide (E12)





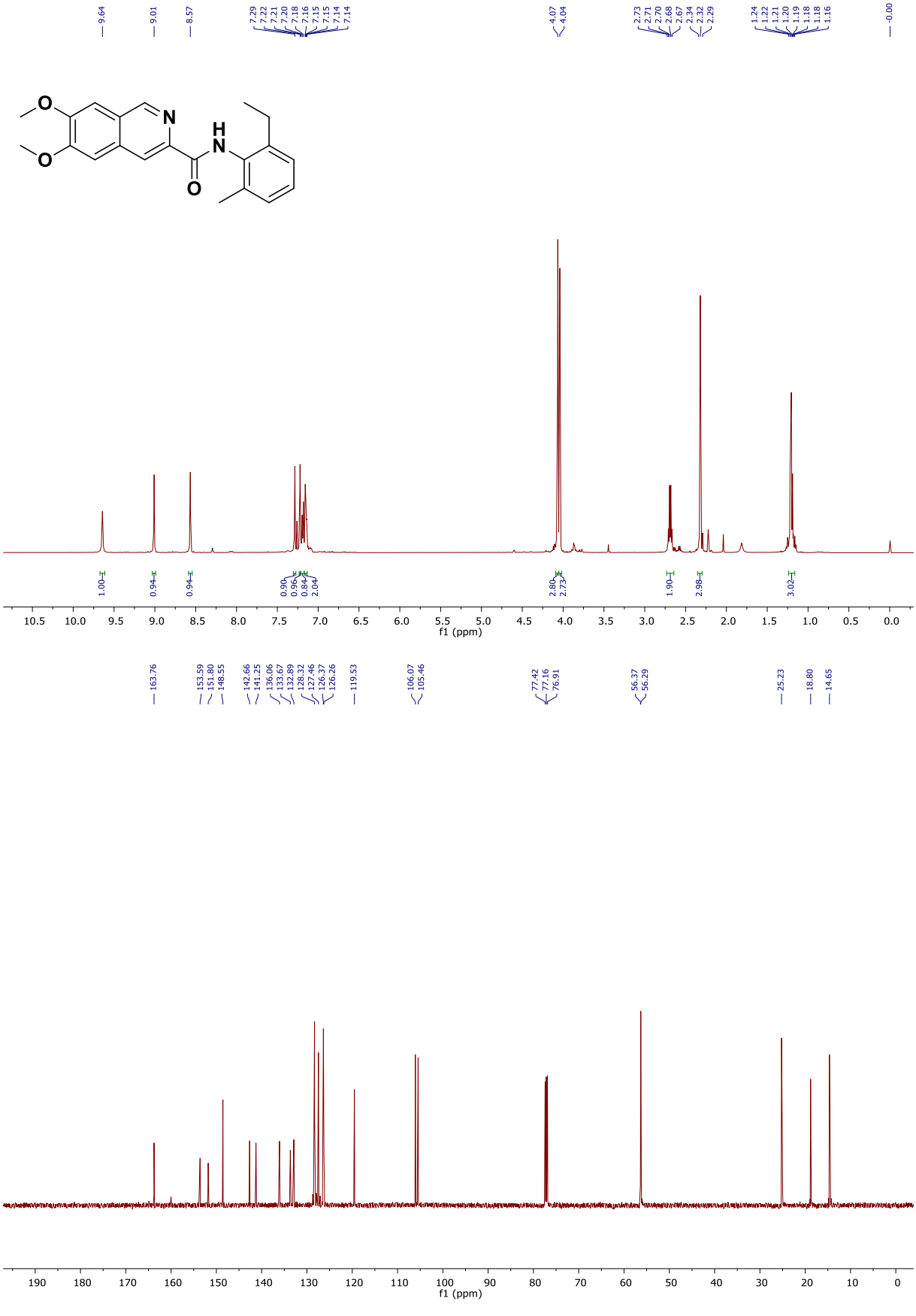


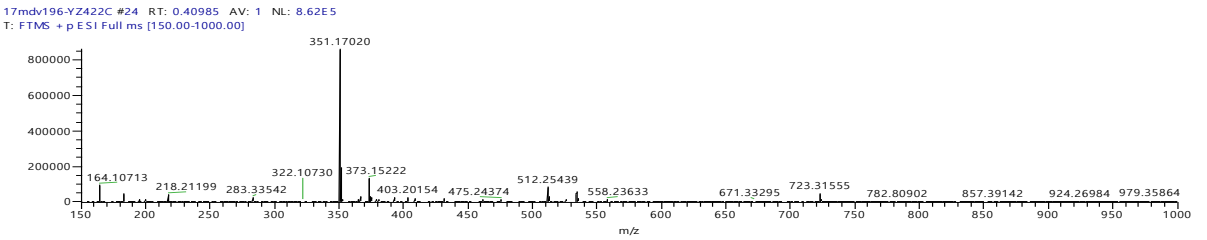


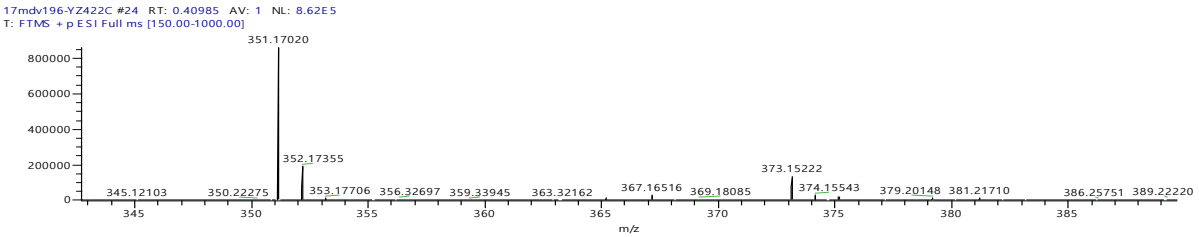


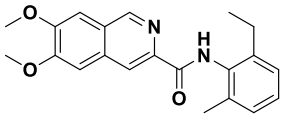
Chemical Formula: $C_{19}H_{18}N_2O_3$
Exact Mass: 322,13
Molecular Weight: 322,36

N-(2-ethyl-6-methylphenyl)-6,7-dimethoxyisoquinoline-3-carboxamide (E17)



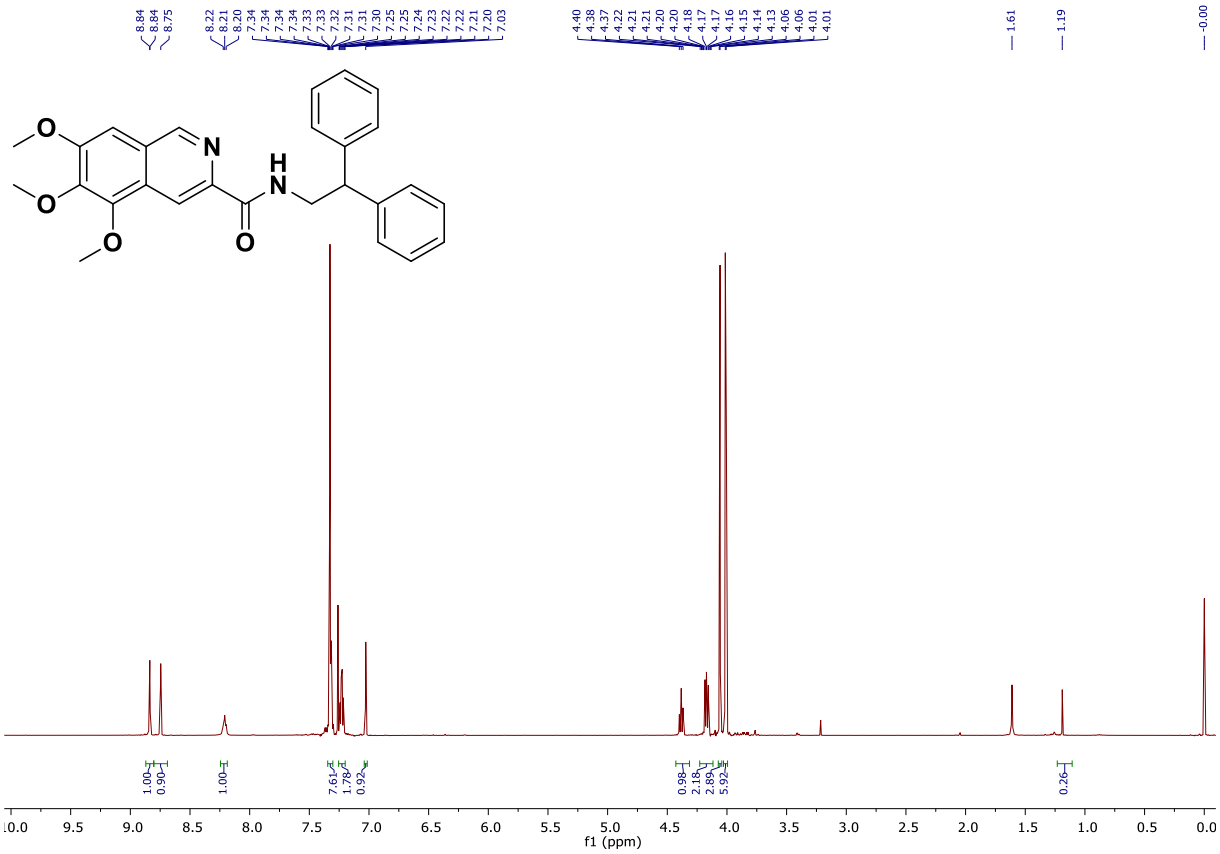


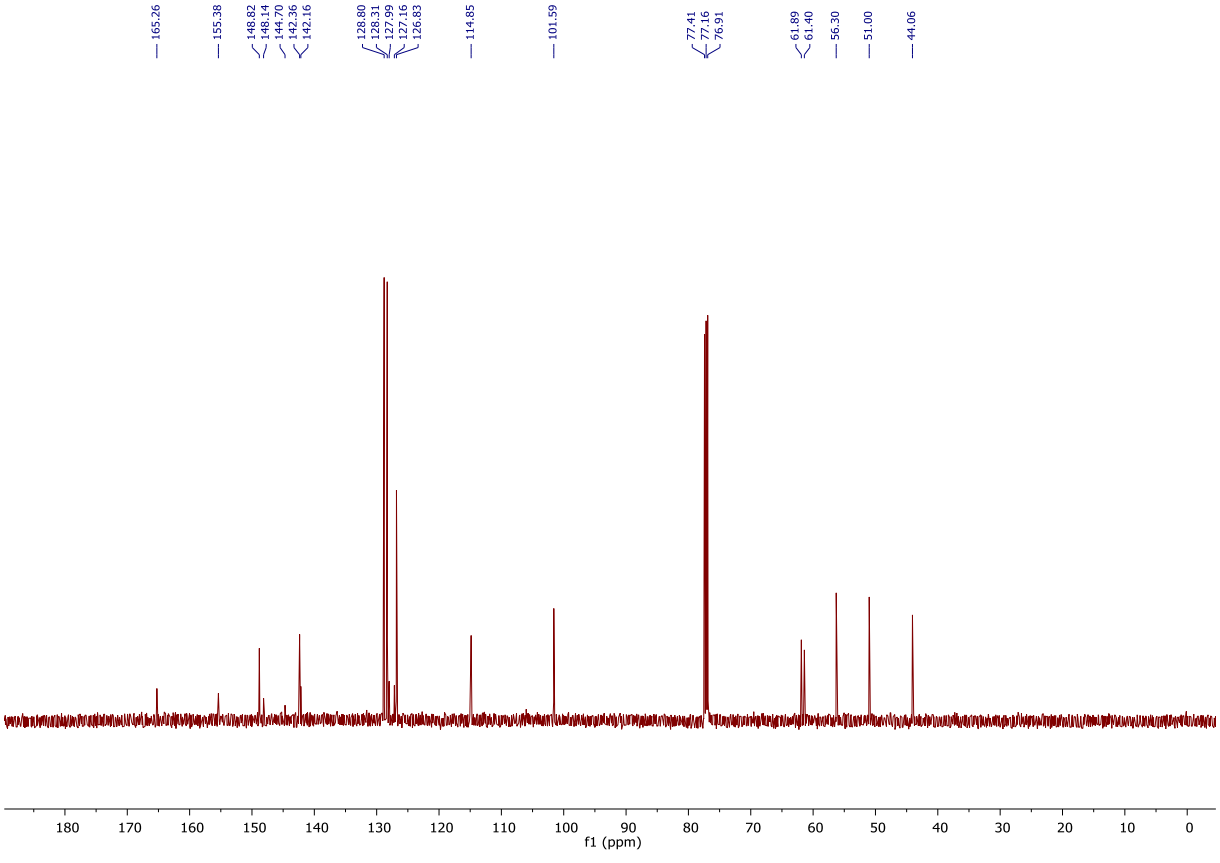




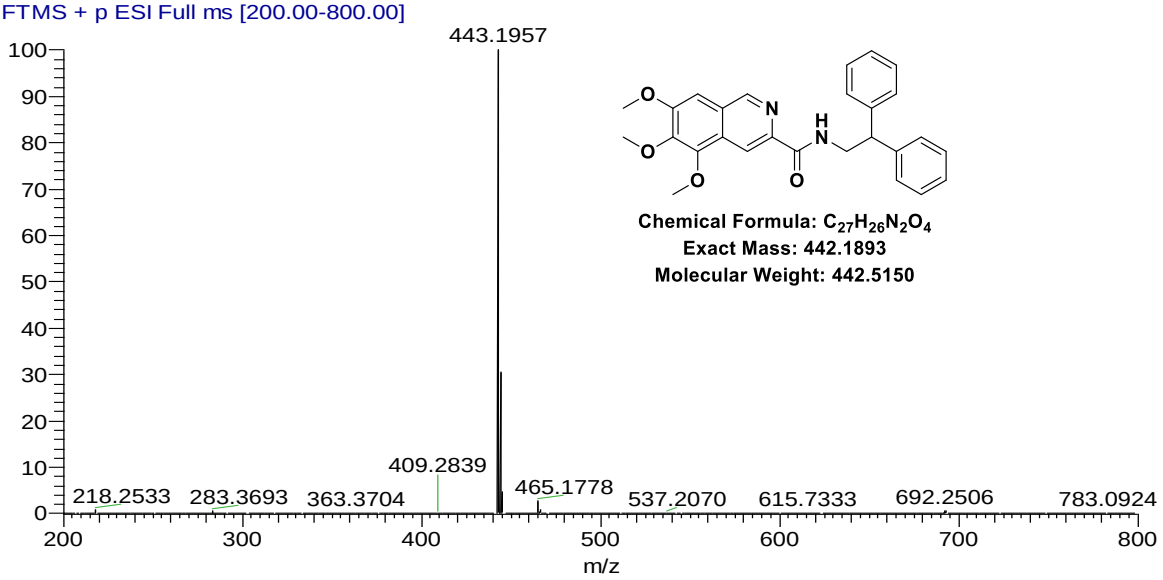
Chemical Formula: $C_{21}H_{22}N_2O_3$
Exact Mass: 350.1630
Molecular Weight: 350.4180

N-(2,2-diphenylethyl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (F8)



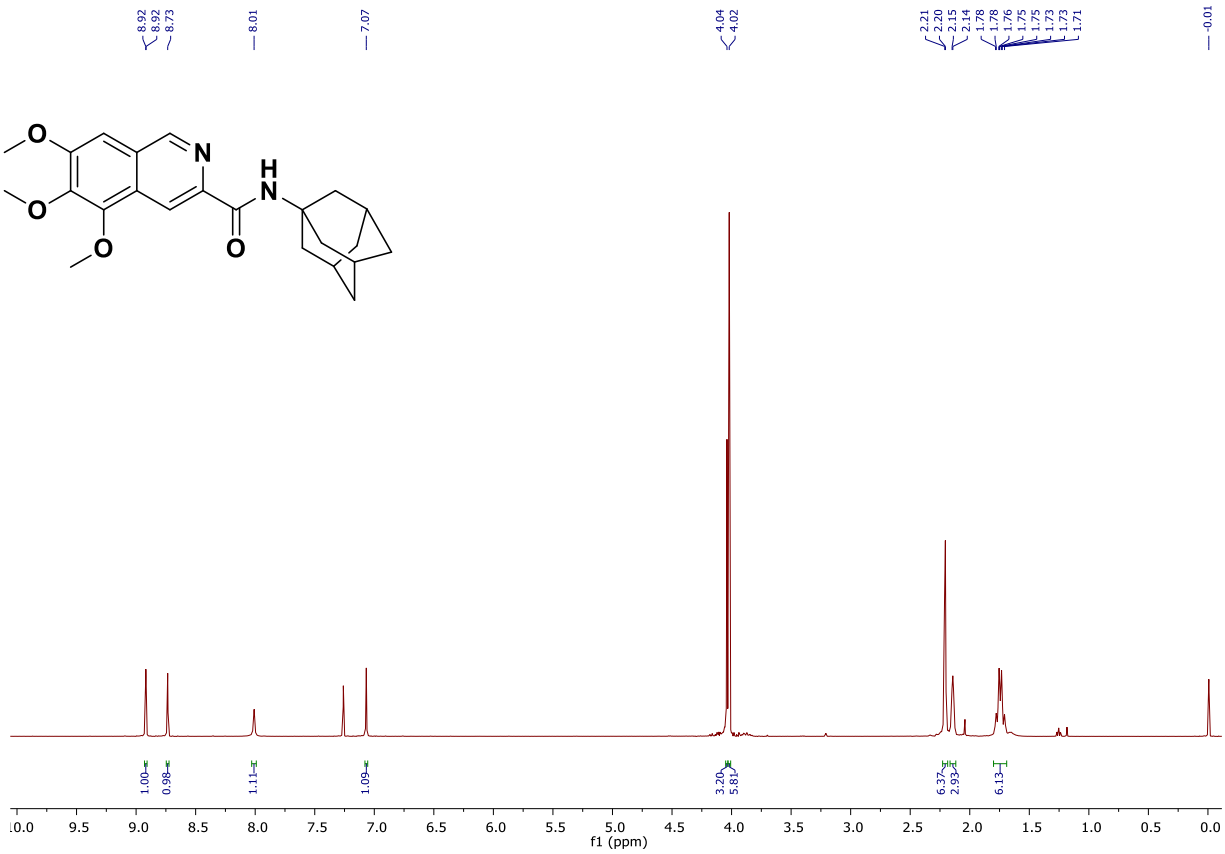


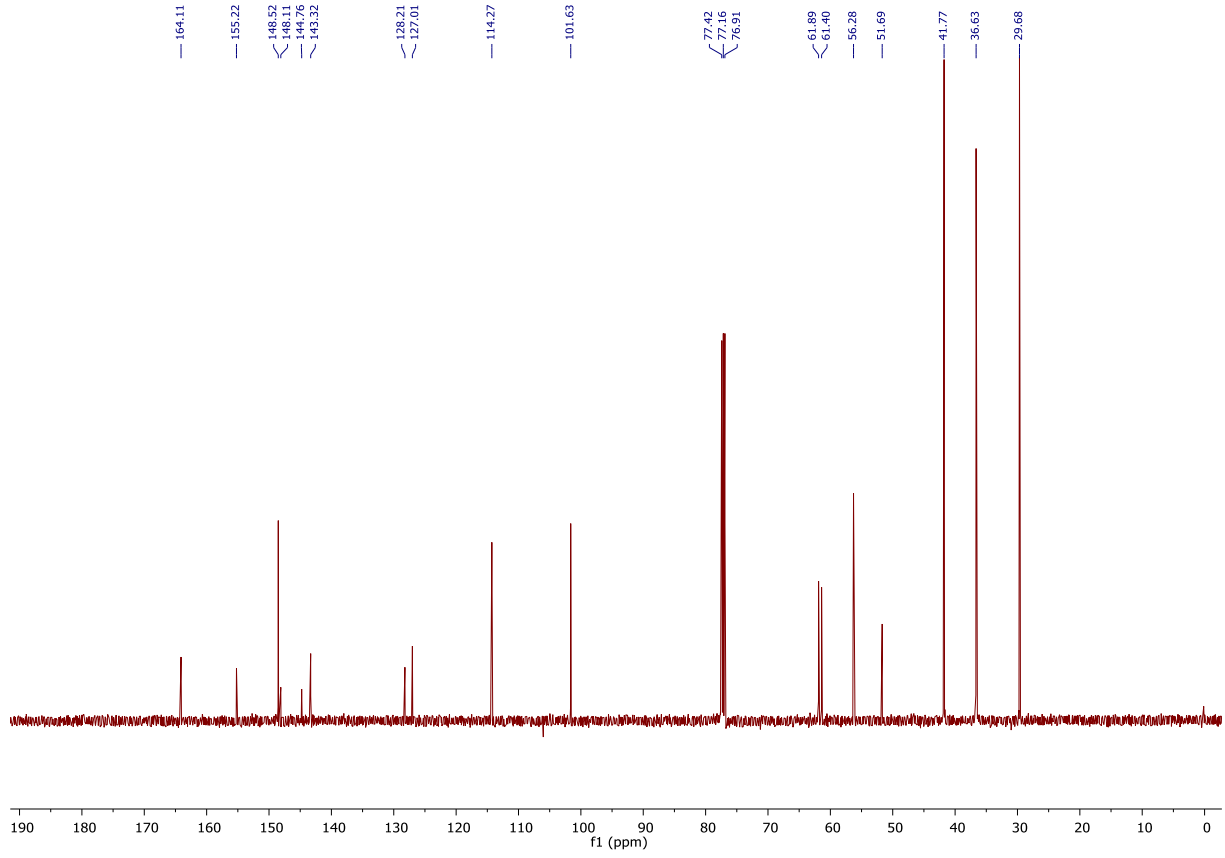
17mdv207-yz444c #280 RT: 5.25 AV: 1 NL: 2.69E8
T: FTMS + p ESI Full ms [200.00-800.00]



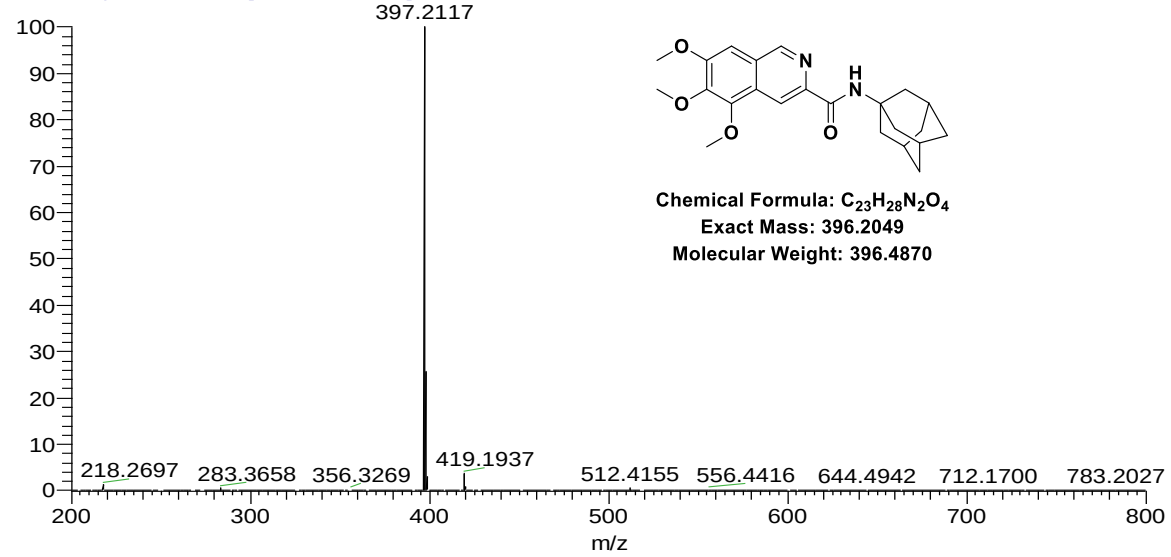
Chemical Formula: $C_{27}H_{26}N_2O_4$
Exact Mass: 442.1893
Molecular Weight: 442.5150

_N_-((1s,3s)-adamantan-1-yl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (F13)



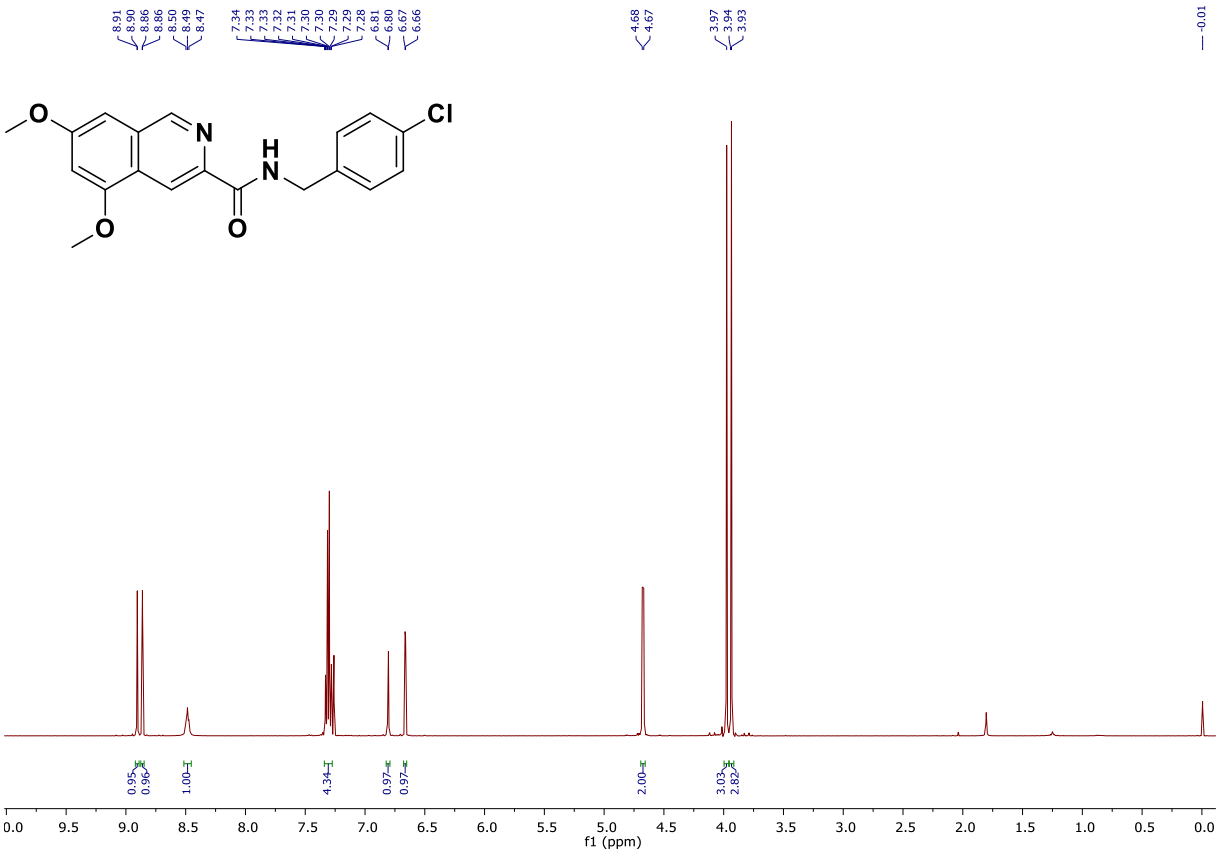


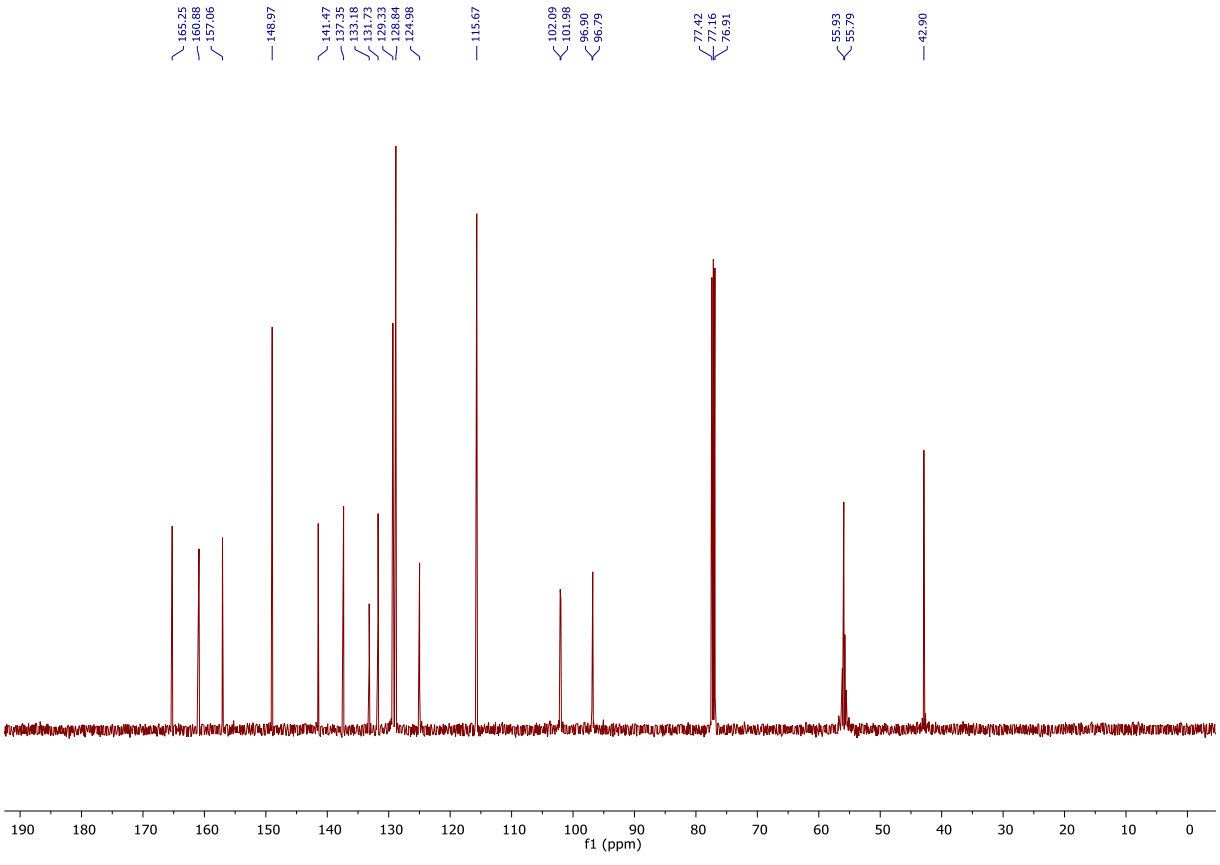
17mdv207-yz450c #283 RT: 5.69 AV: 1 NL: 1.25E7
T: FTMS + p ESI Full ms [200.00-800.00]

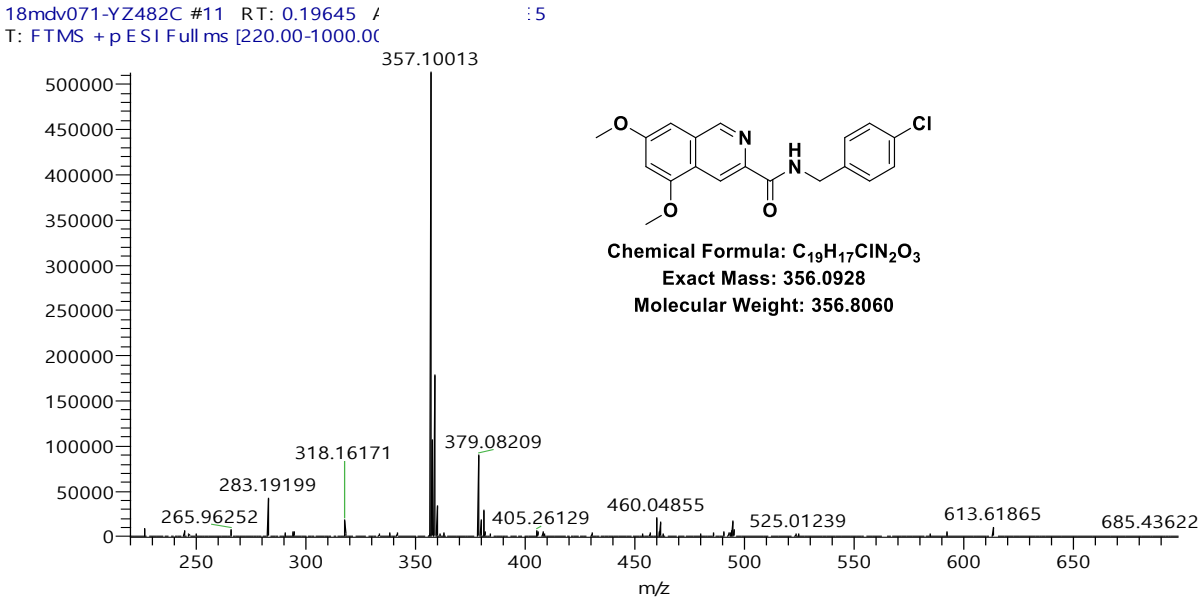


Chemical Formula: $C_{23}H_{28}N_2O_4$
Exact Mass: 396.2049
Molecular Weight: 396.4870

N-(4-chlorobenzyl)-5,7-dimethoxyisoquinoline-3-carboxamide (F15)






18mdv071-YZ482C #11 RT: 0.19645
T: FTMS + p ESI Full ms [220.00-1000.0
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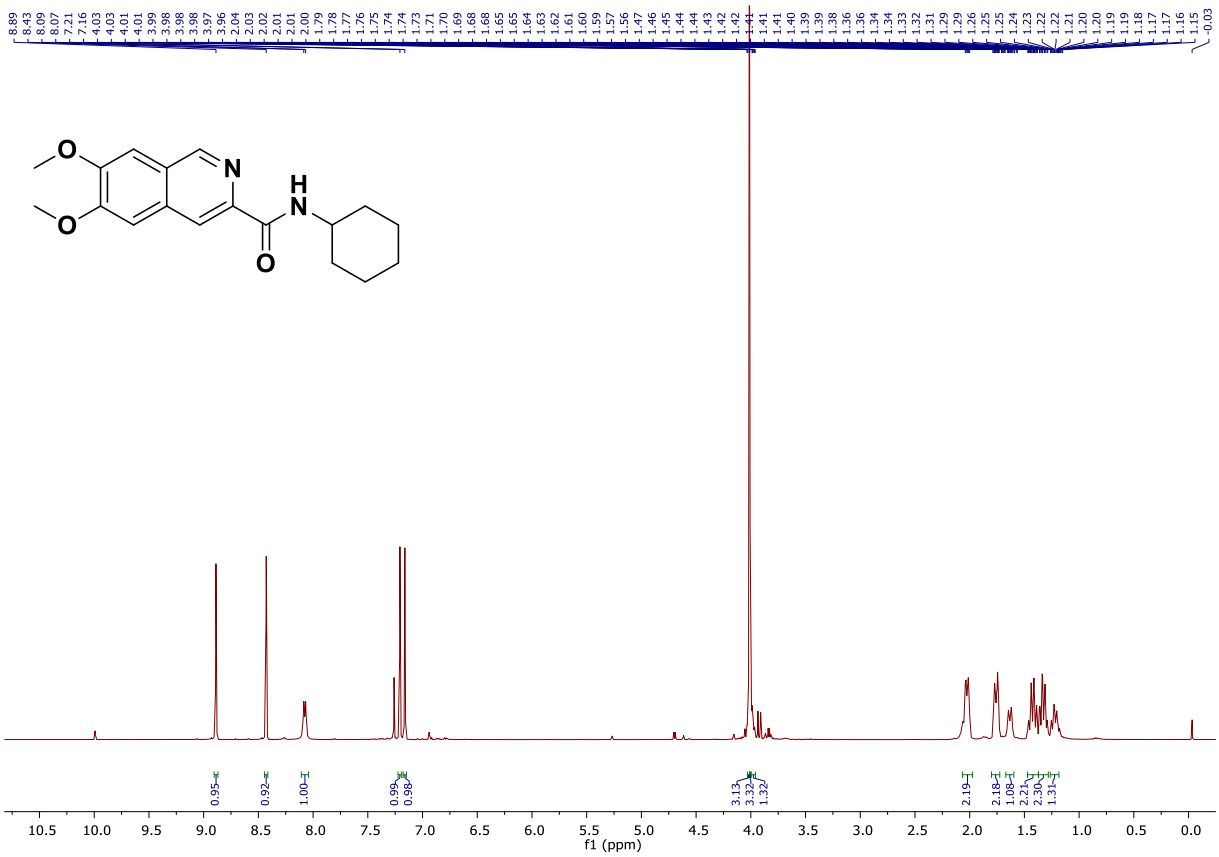
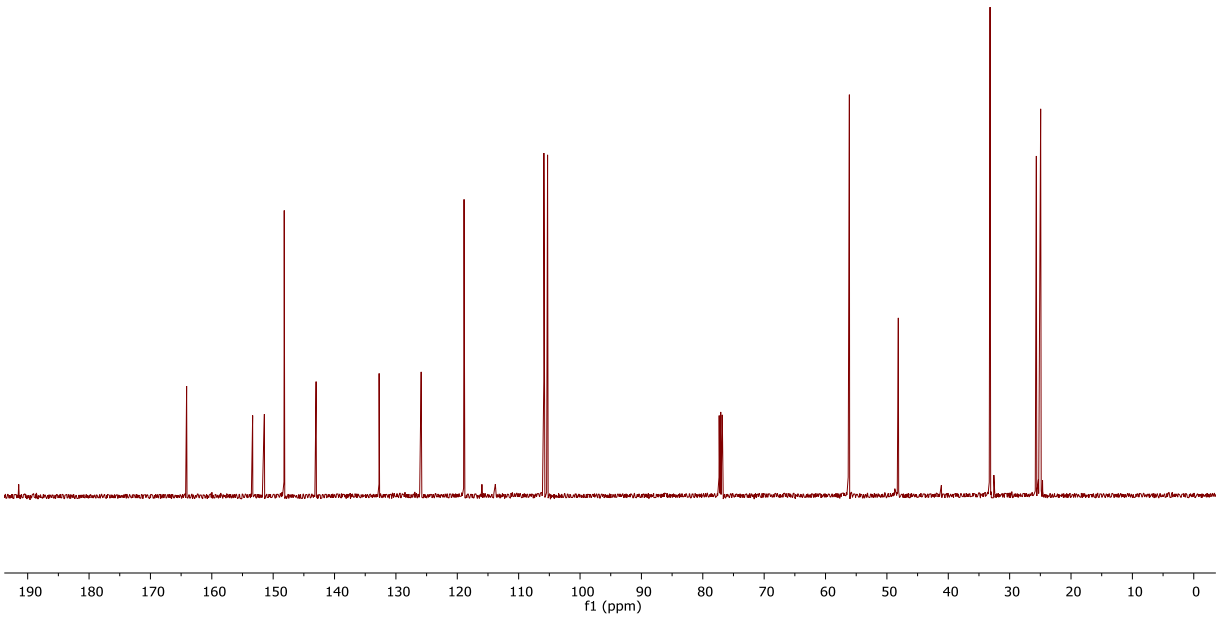
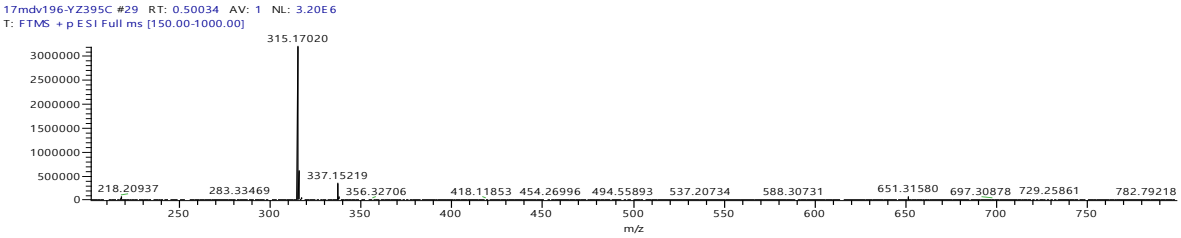
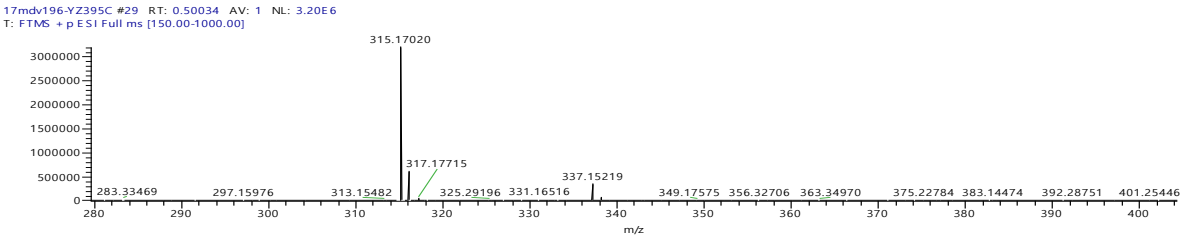
379.08209
318.16171
283.19199
265.96252
405.26129
460.04855
525.01239
613.61865
685.43622
m/z
Chemical Formula: C19H17ClN2O3
Exact Mass: 356.0928
Molecular Weight: 356.8060

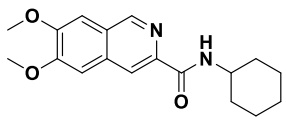
N-cyclohexyl-6,7-dimethoxyisoquinoline-3-carboxamide (H13)





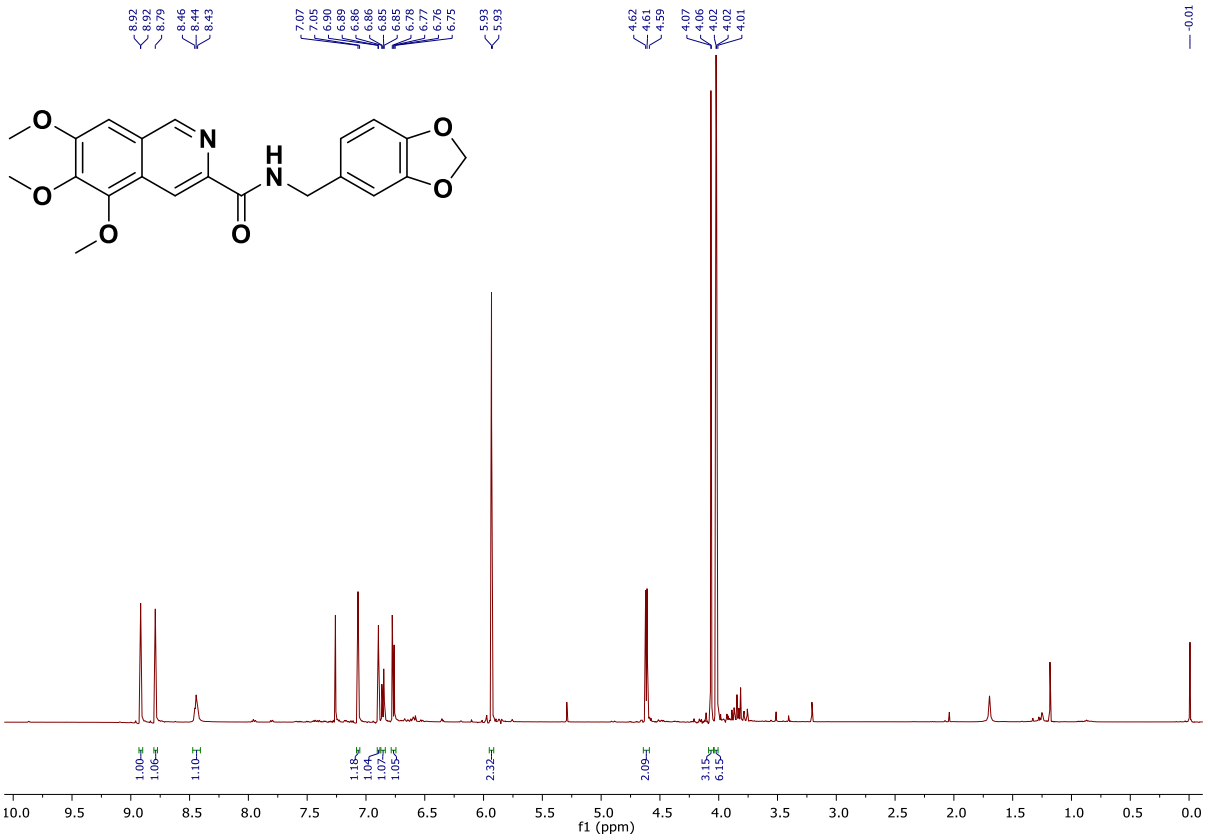


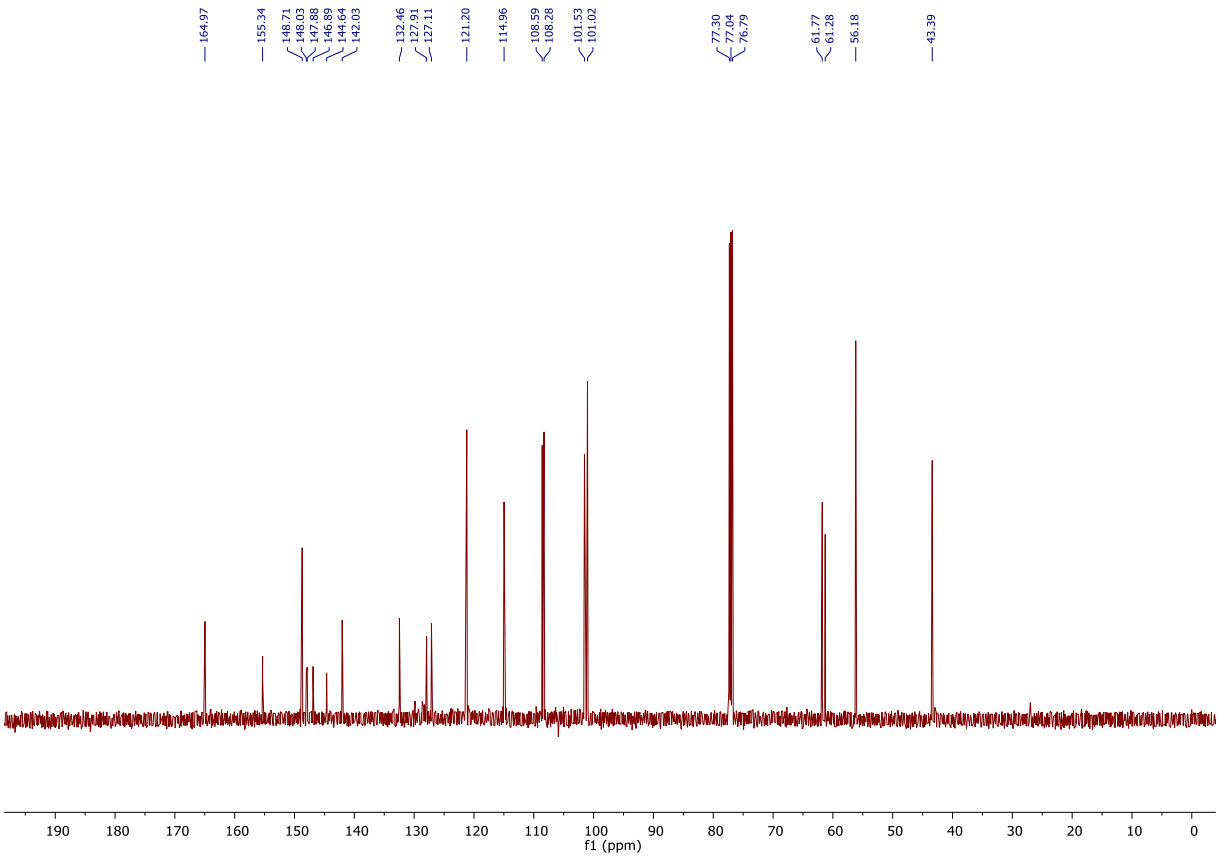




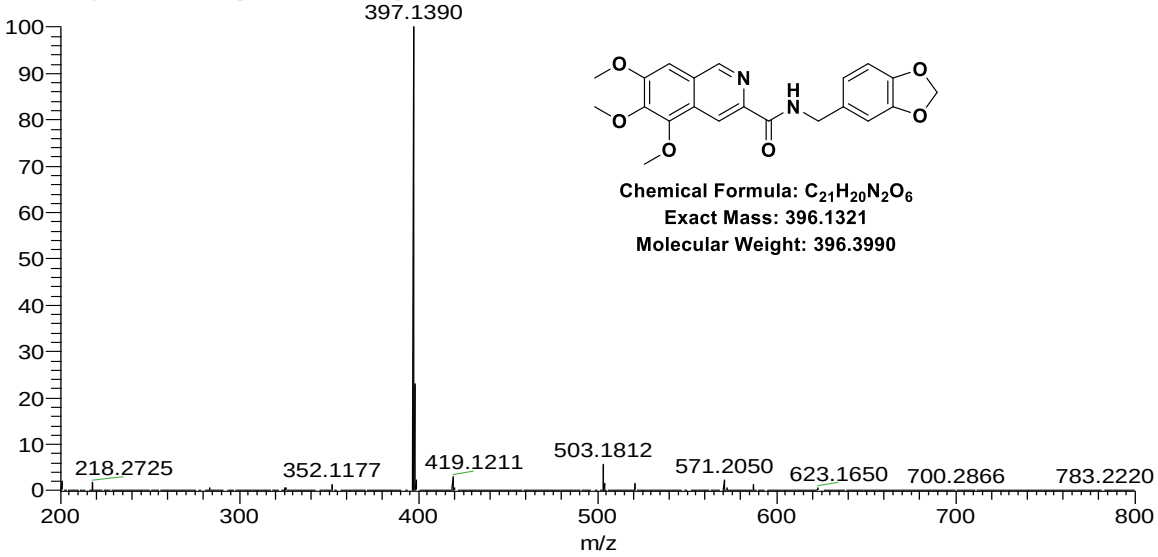
Chemical Formula: $C_{18}H_{22}N_2O_3$
Exact Mass: 314.1630
Molecular Weight: 314.3850

_N_-(benzo[_d_][1,3]dioxol-5-ylmethyl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (I6)



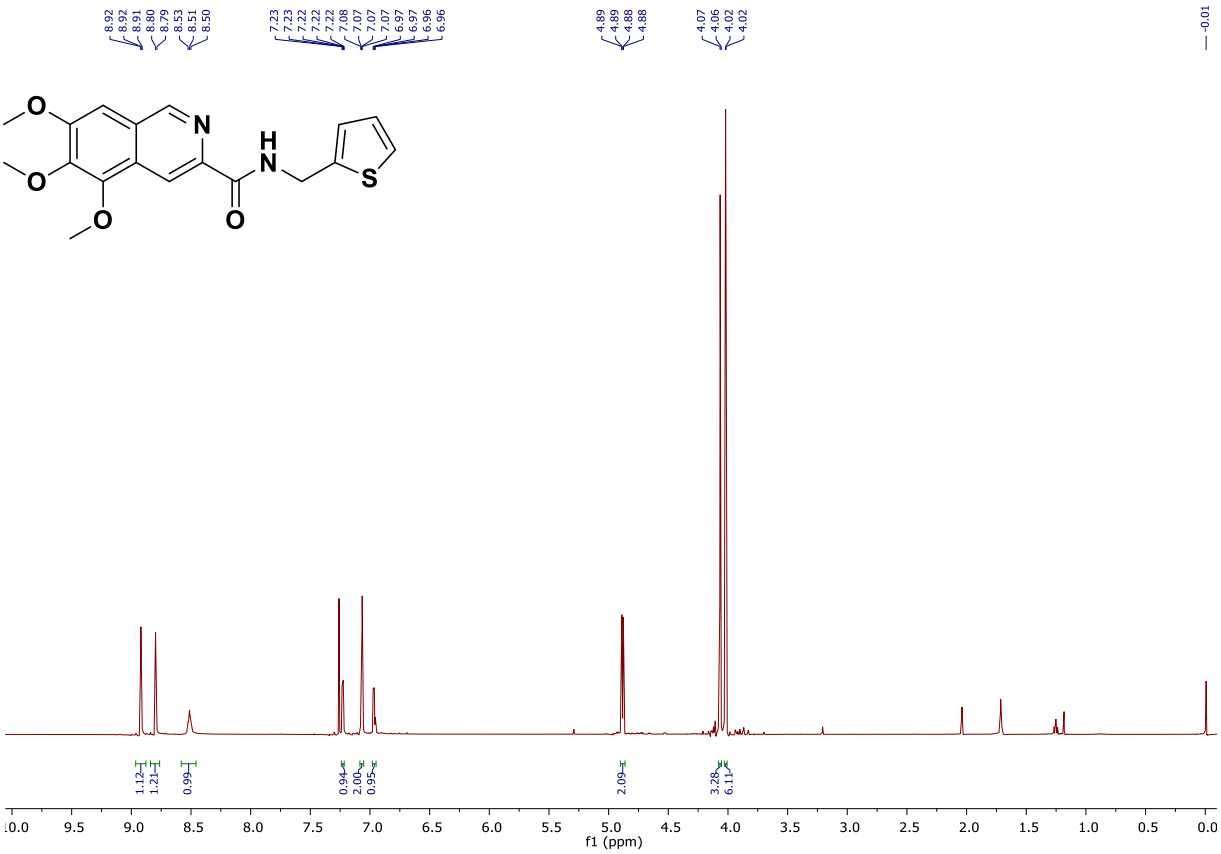


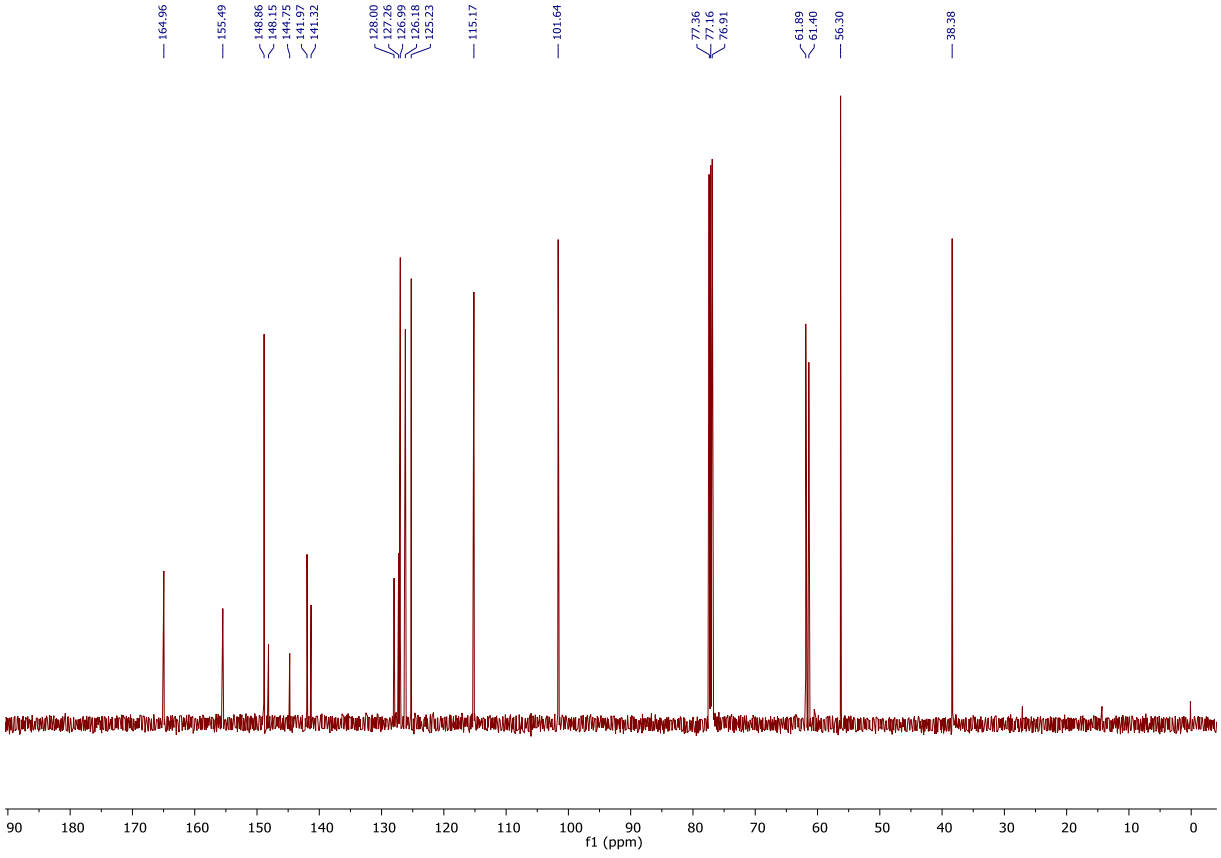
17mdv207-yz447 #226 RT: 4.62 AV: 1 NL: 6.02E6
T: FTMS + p ESI Full ms [200.00-800.00]



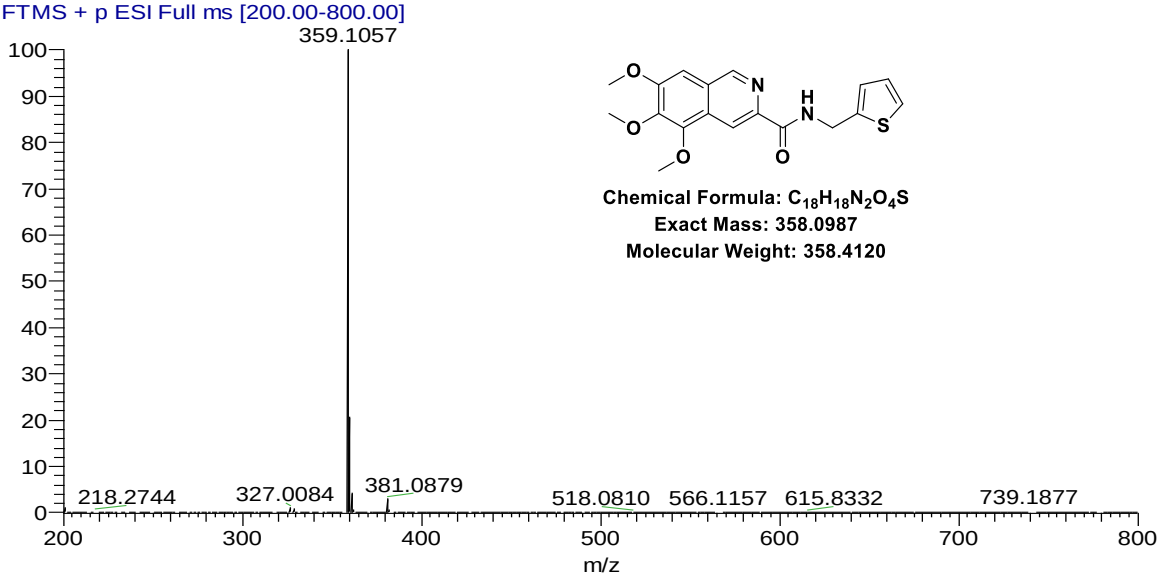
Chemical Formula: $C_{21}H_{20}N_2O_6$
Exact Mass: 396.1321
Molecular Weight: 396.3990

5,6,7-Trimethoxy-*N*-(thiophen-2-ylmethyl)isoquinoline-3-carboxamide (I17)



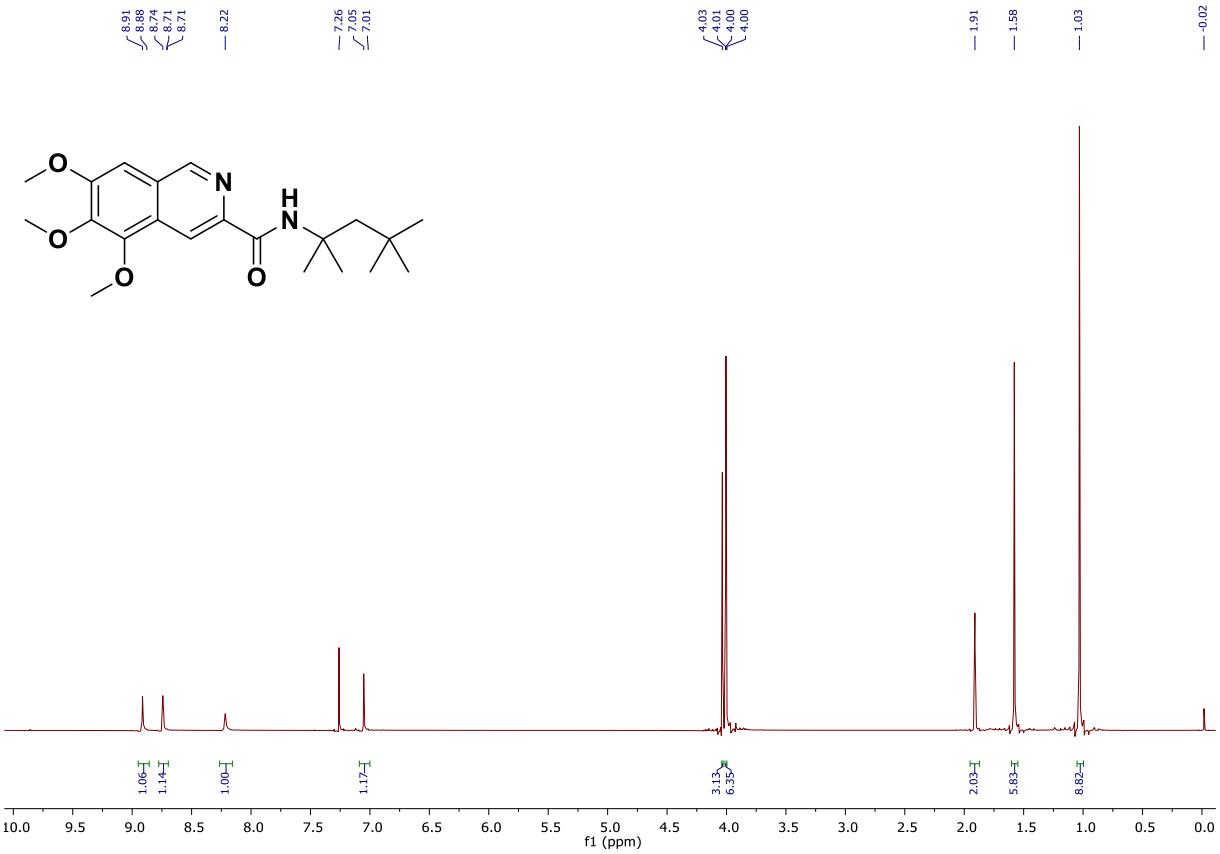


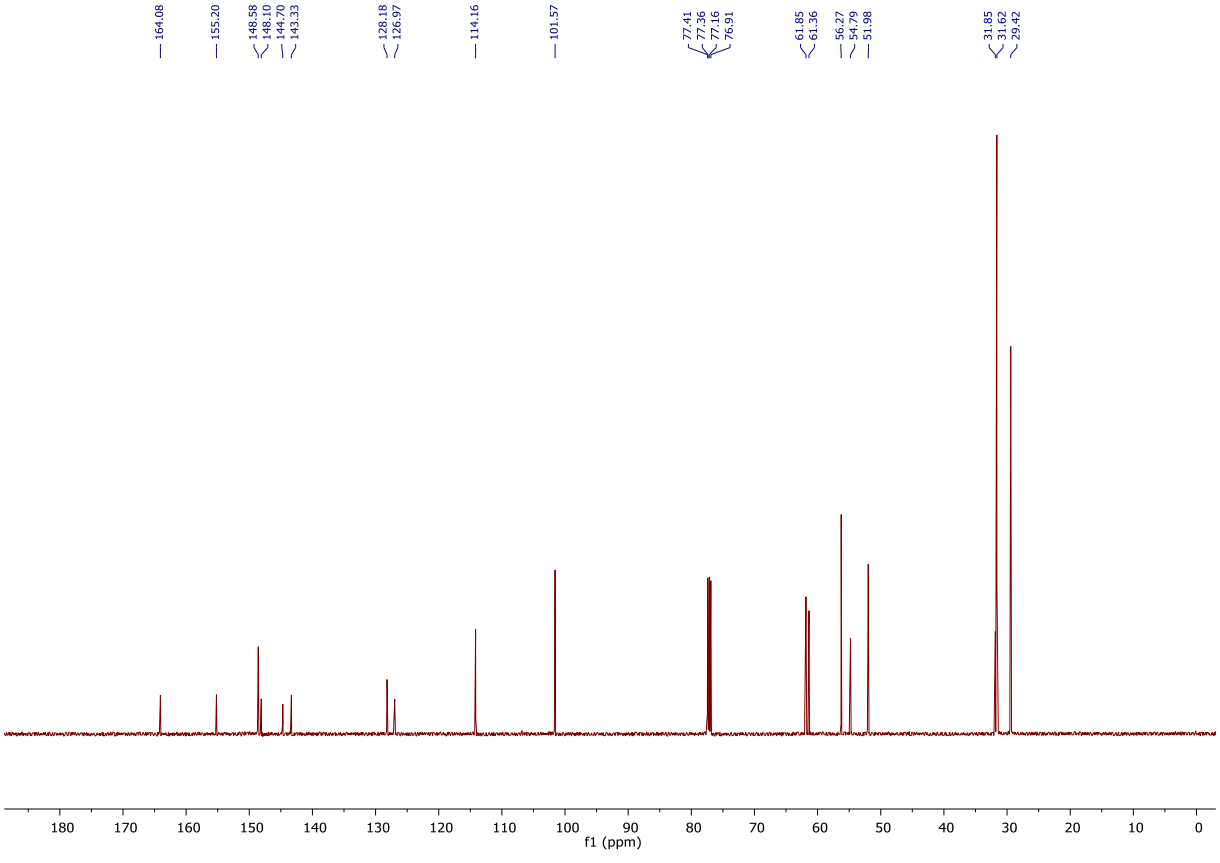
17mdv207-yz443c #217 RT: 4.55 AV: 1 NL: 8.98E6
T: FTMS + p ESI Full ms [200.00-800.00]

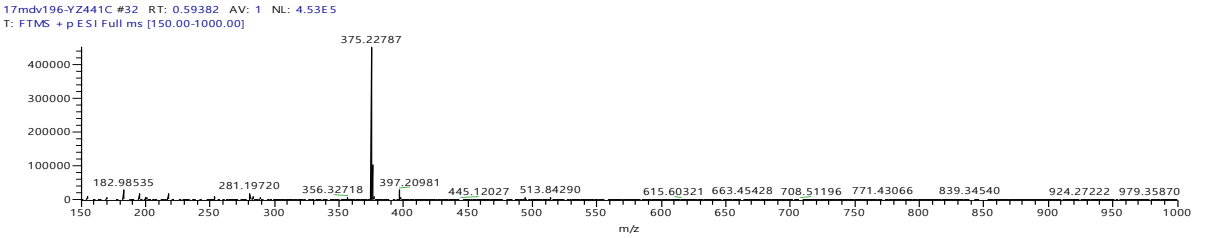


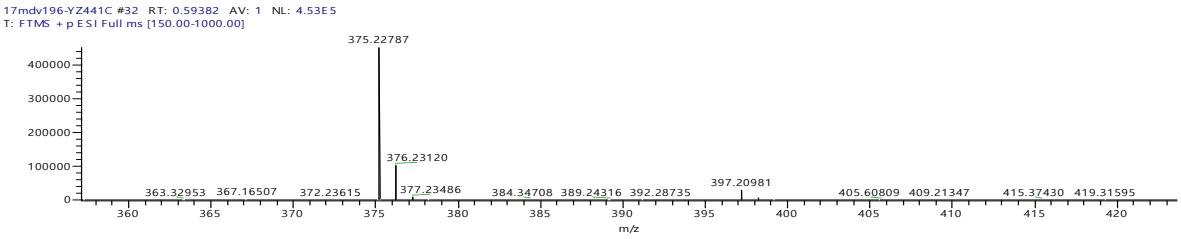
Chemical Formula: $C_{18}H_{18}N_2O_4S$
Exact Mass: 358.0987
Molecular Weight: 358.4120

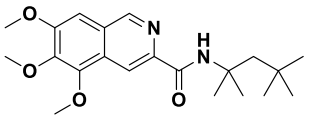
5,6,7-Trimethoxy-*N*-(2,4,4-trimethylpentan-2-yl)isoquinoline-3-carboxamide (J3)





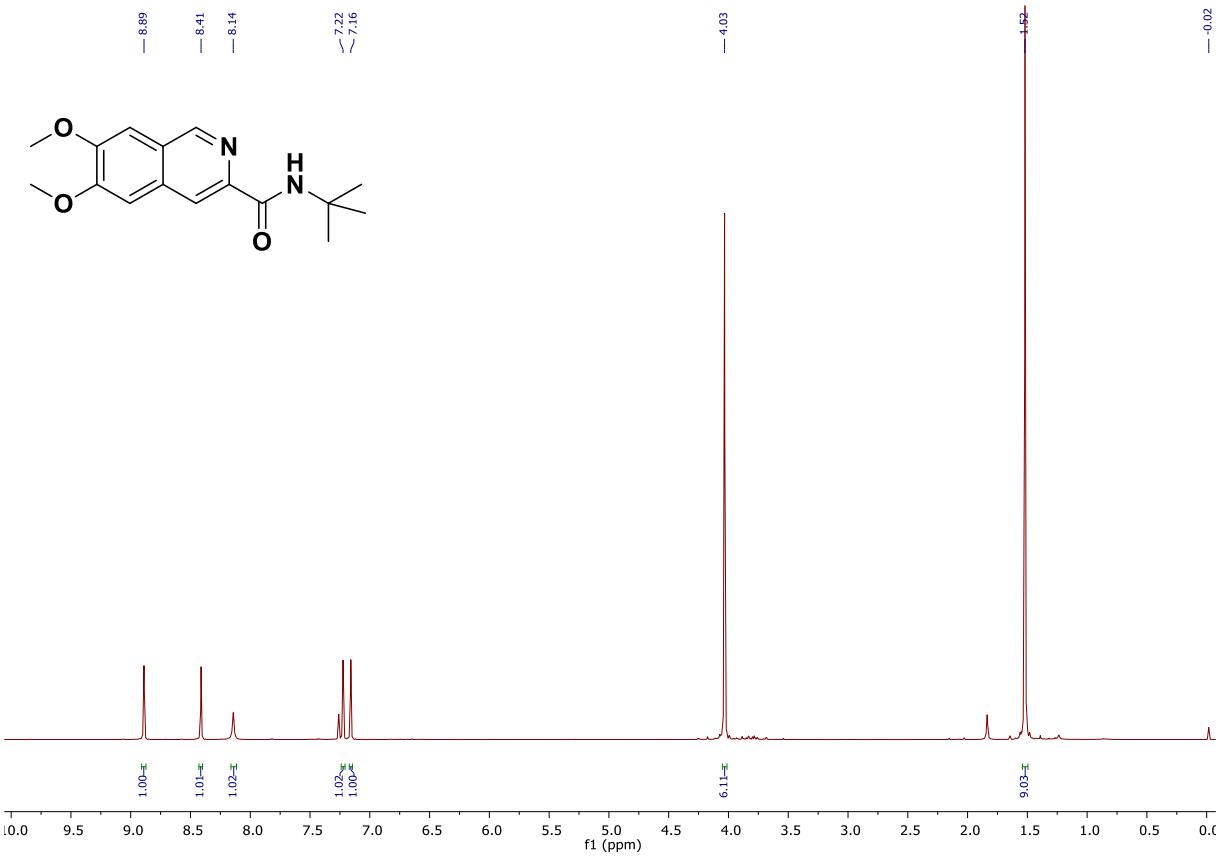


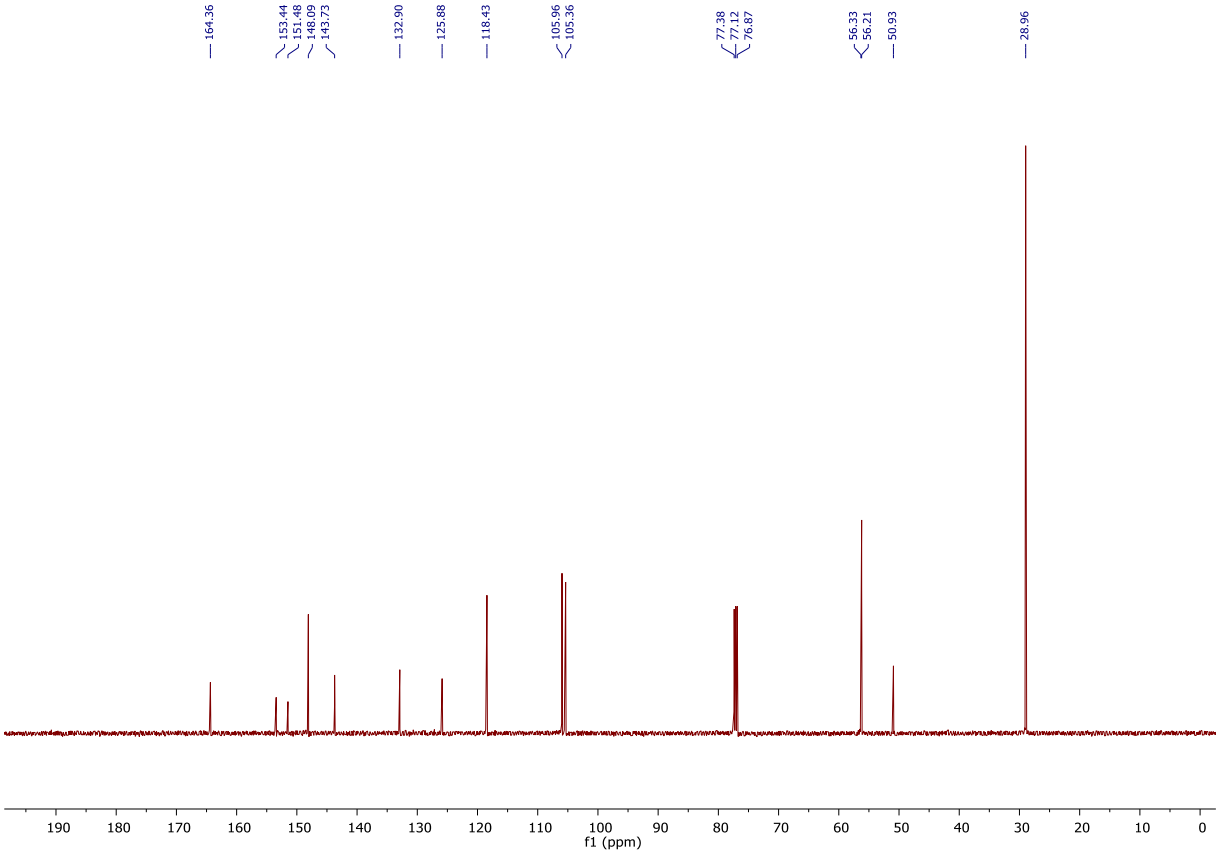


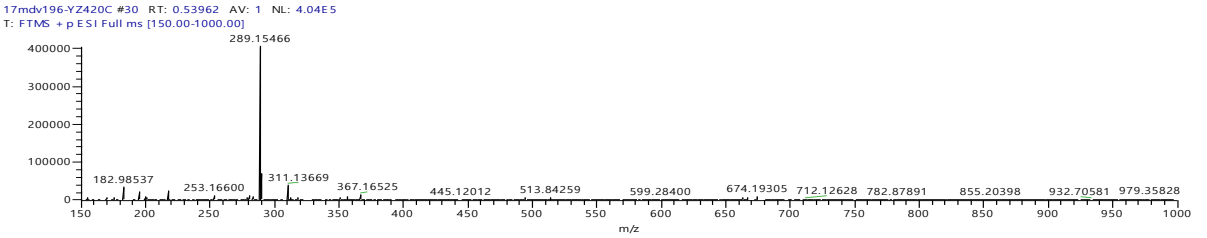


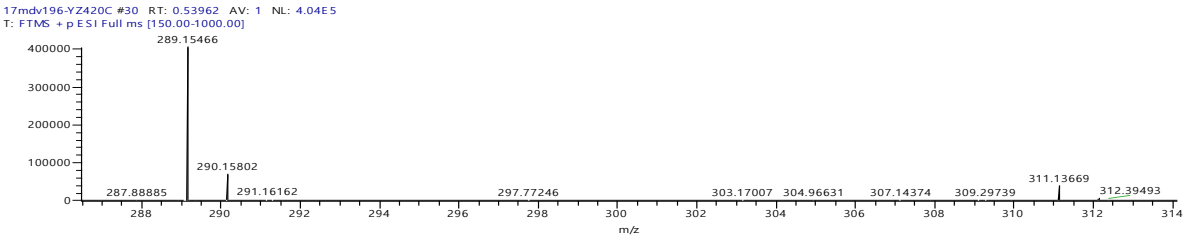
Chemical Formula: $C_{21}H_{30}N_2O_4$
Exact Mass: 374.2206
Molecular Weight: 374.4810

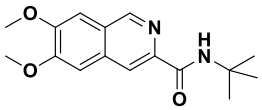
N-(tert-butyl)-6,7-dimethoxyisoquinoline-3-carboxamide (J9)





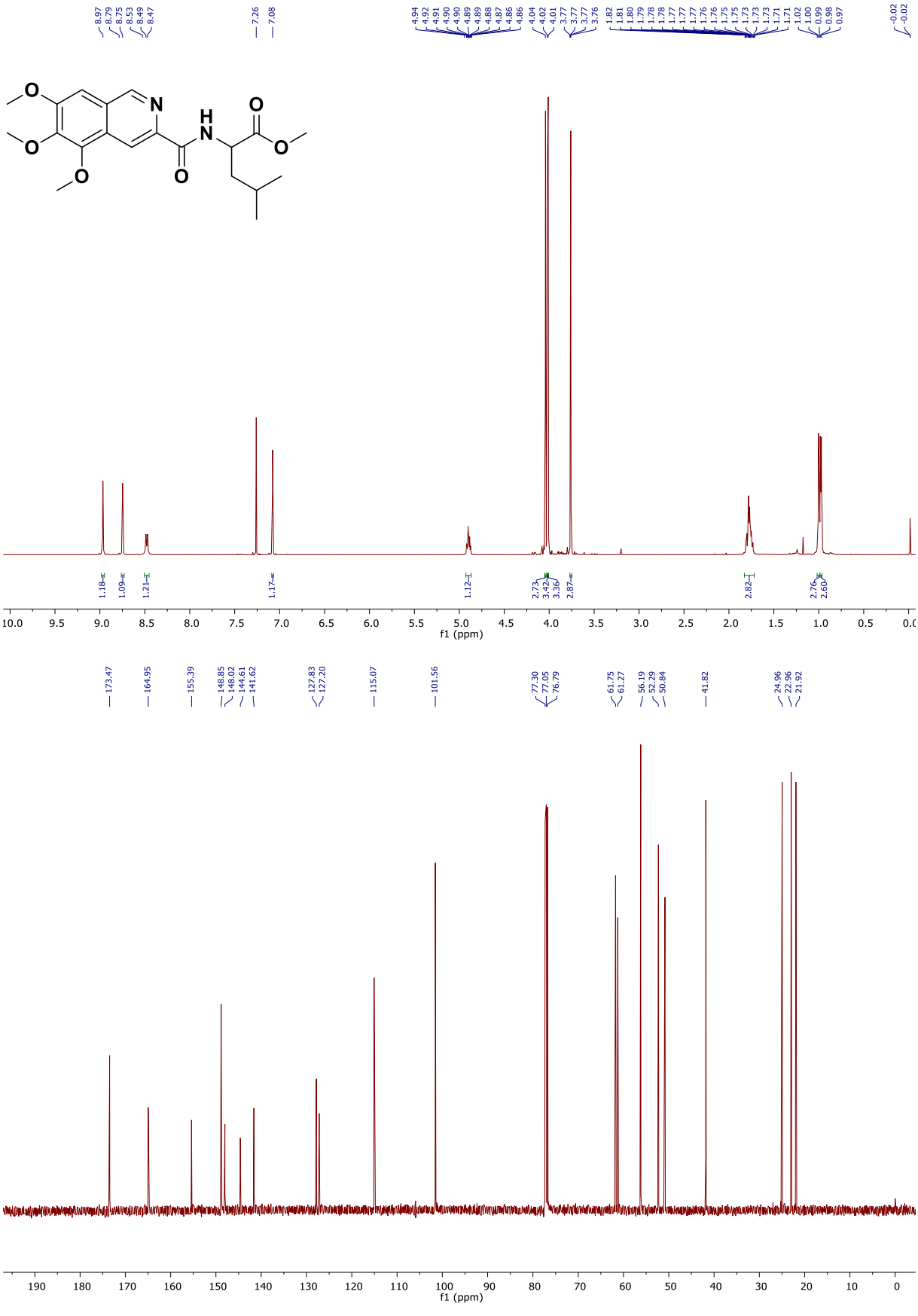






Chemical Formula: $C_{16}H_{20}N_2O_3$
Exact Mass: 288.1474
Molecular Weight: 288.3470

Methyl (5,6,7-trimethoxyisoquinoline-3-carbonyl)leucinate (J18)



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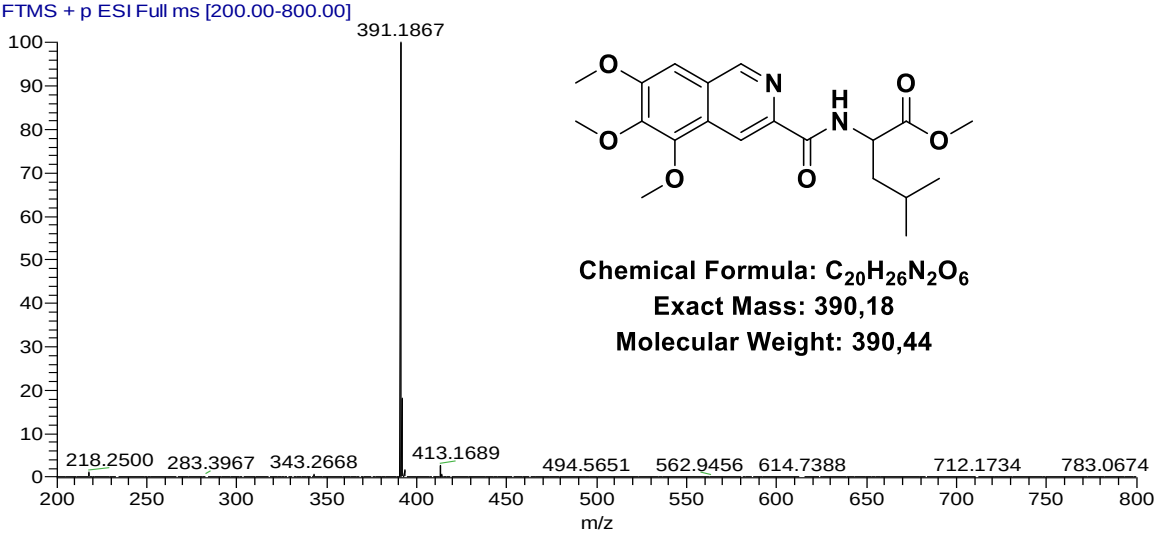
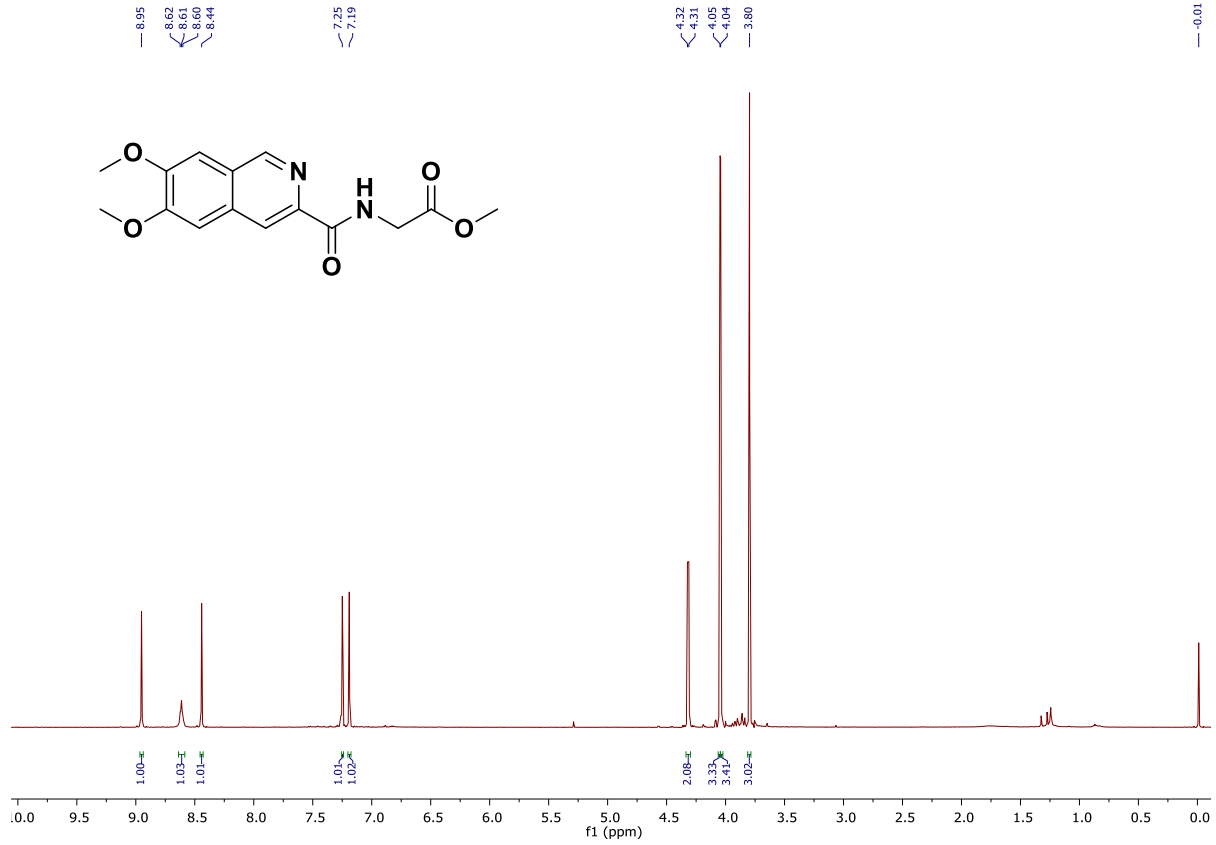
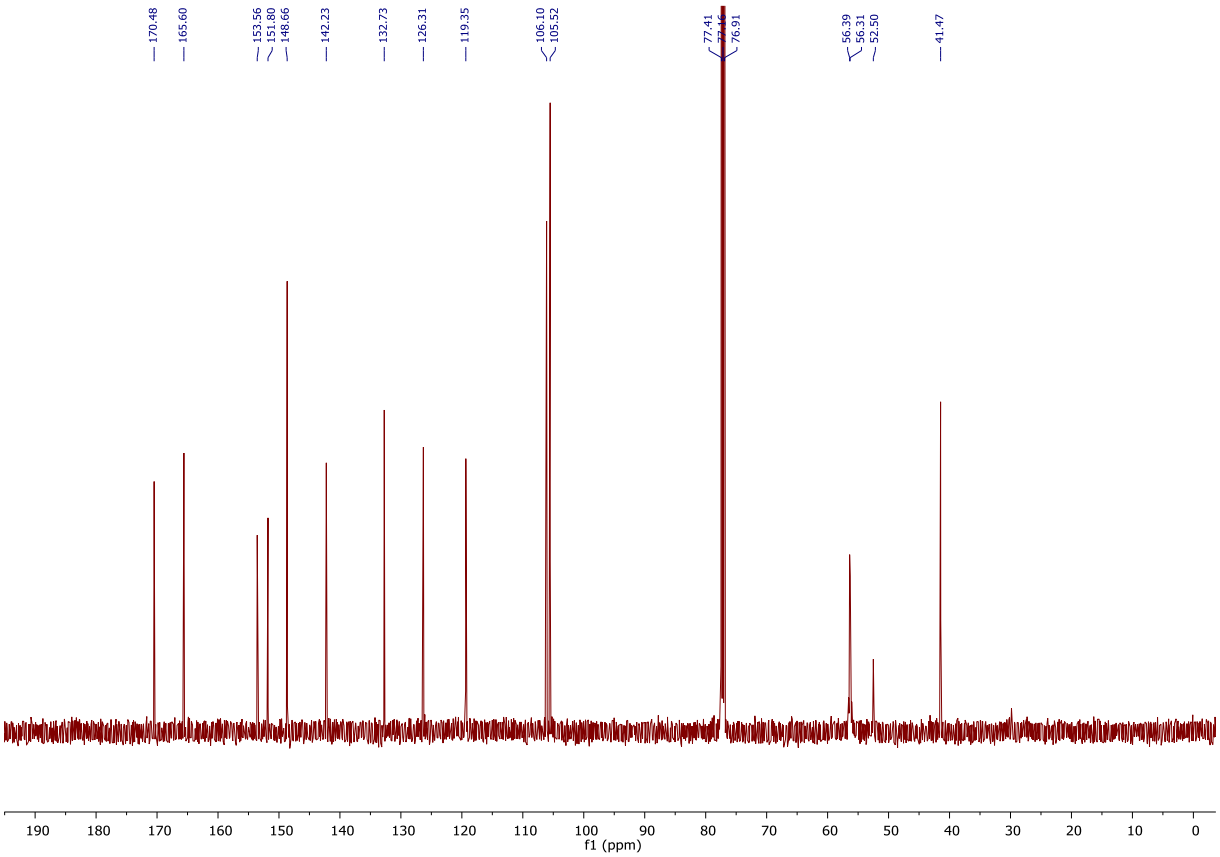
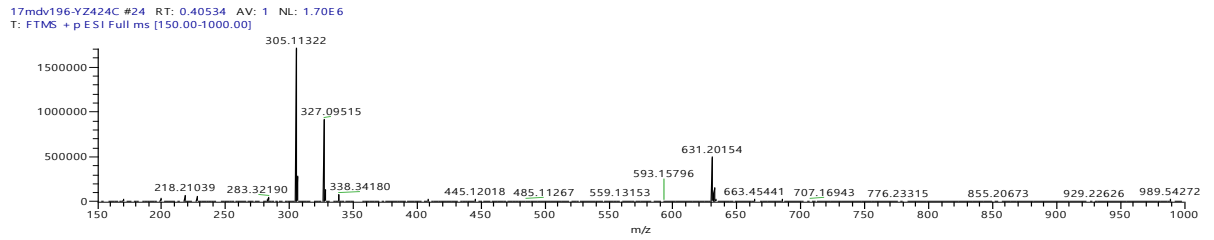


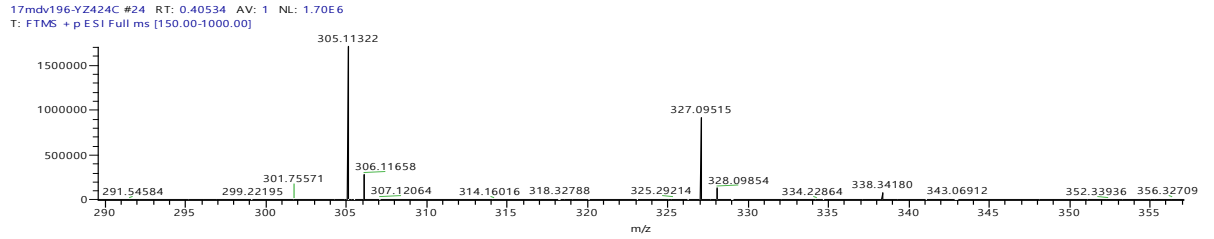
Chemical Formula: $C_{20}H_{26}N_2O_6$
Exact Mass: 390,18
Molecular Weight: 390,44

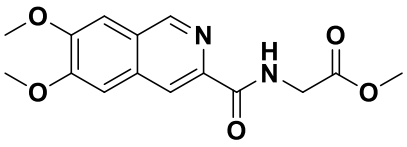
Methyl (6,7-dimethoxyisoquinoline-3-carbonyl) glycinate (K5)





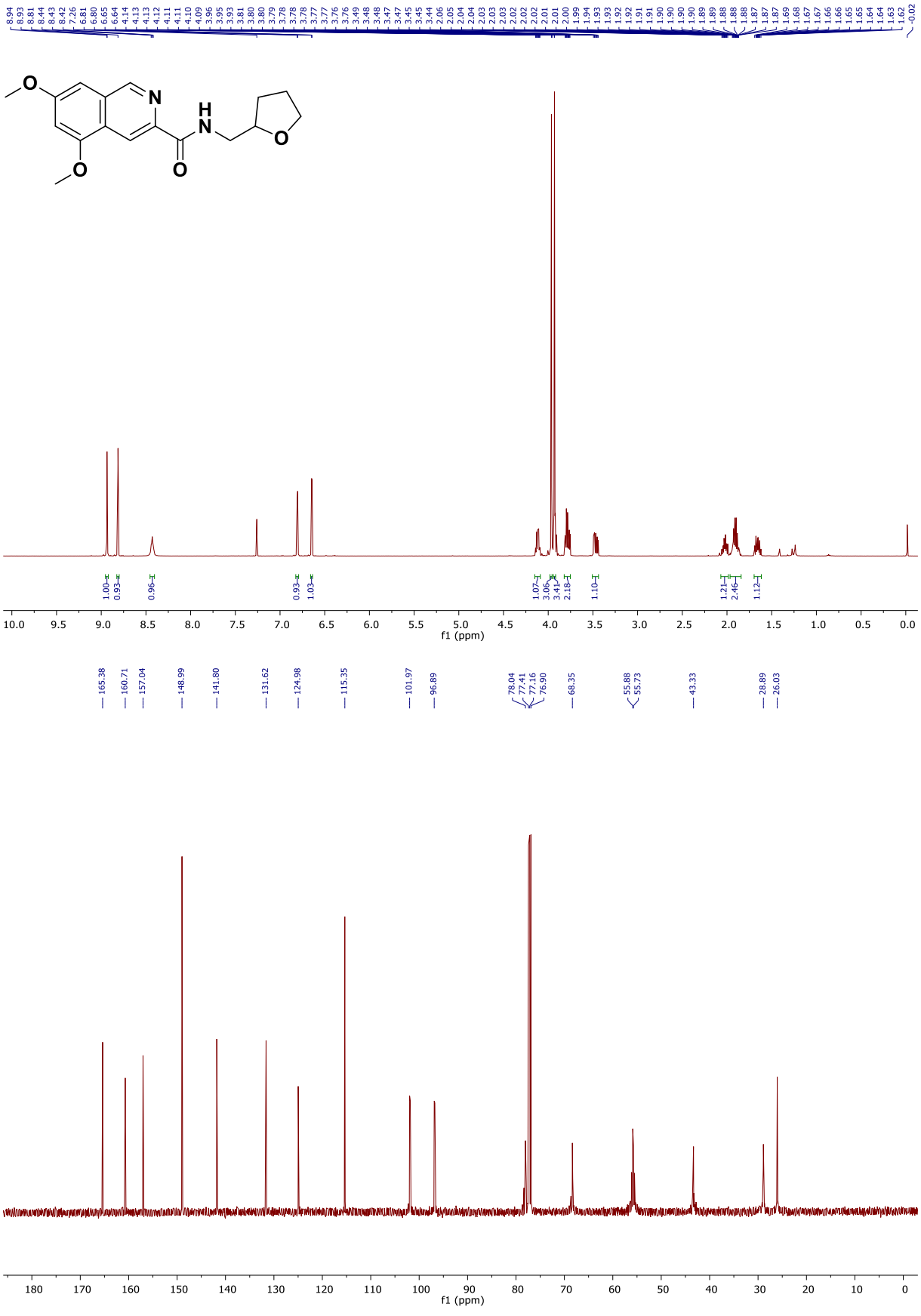


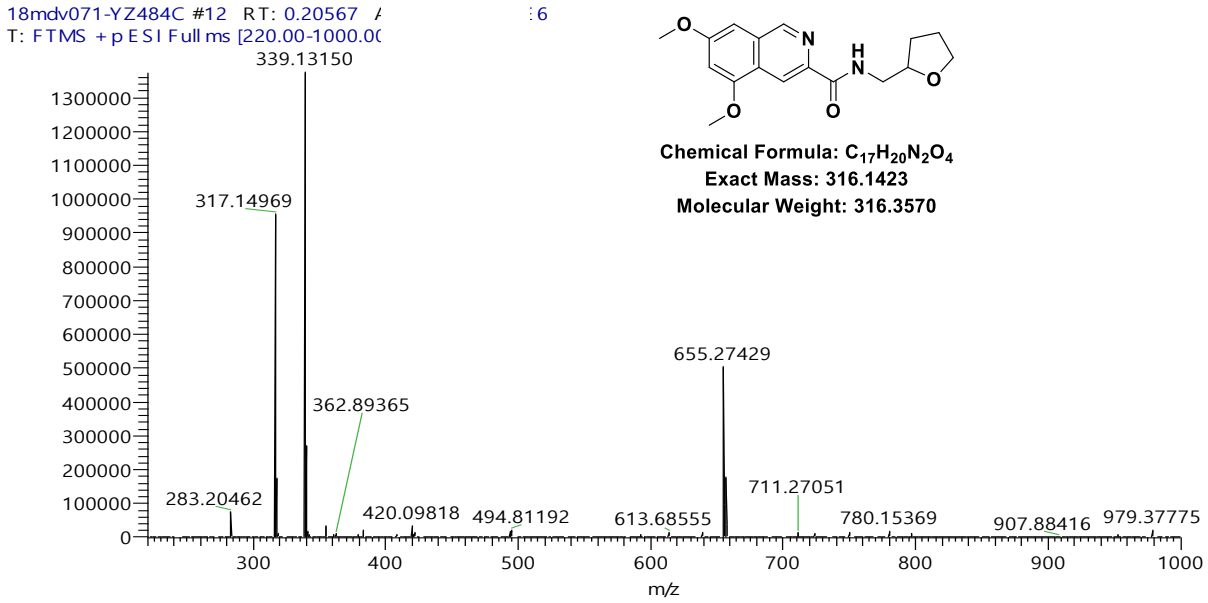




Chemical Formula: $C_{15}H_{16}N_2O_5$
Exact Mass: 304,11
Molecular Weight: 304,30

5,7-Dimethoxy-*N*-((tetrahydrofuran-2-yl)methyl)isoquinoline-3-carboxamide (K8)

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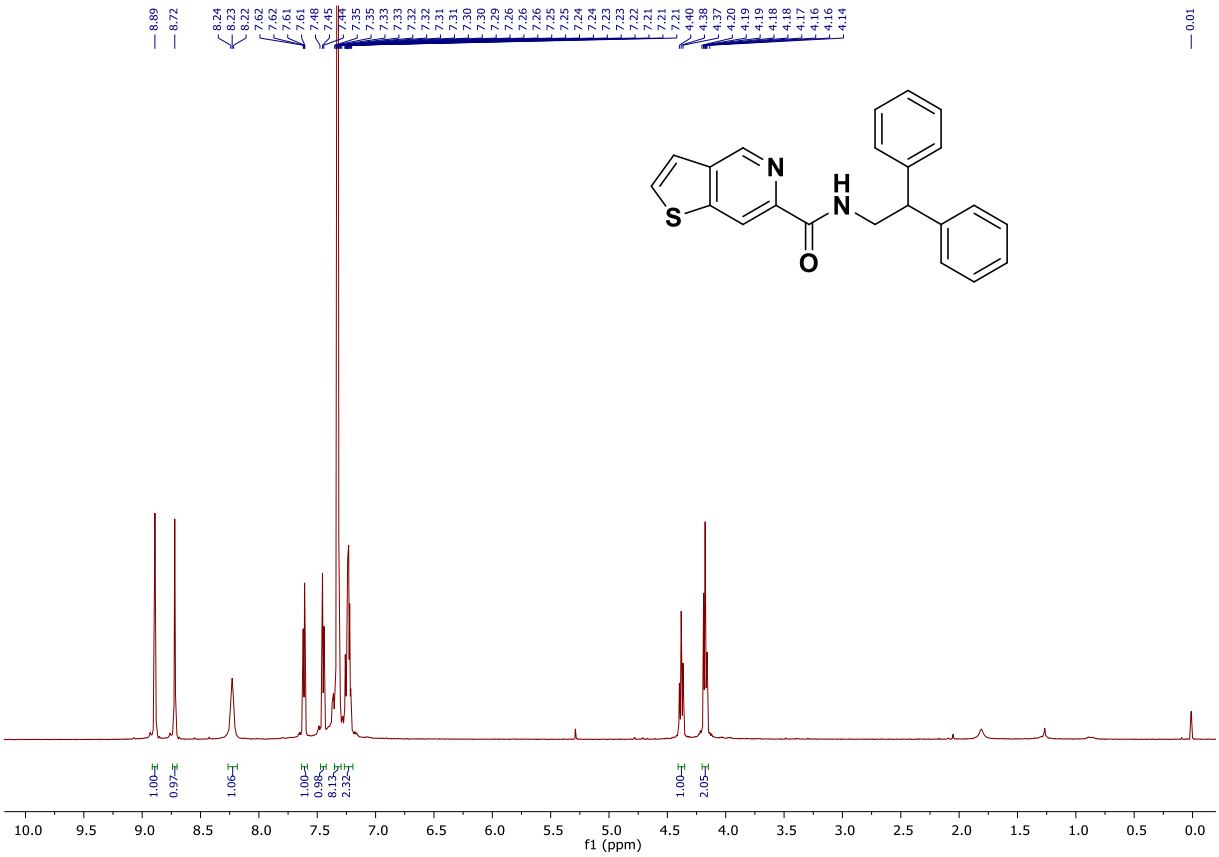
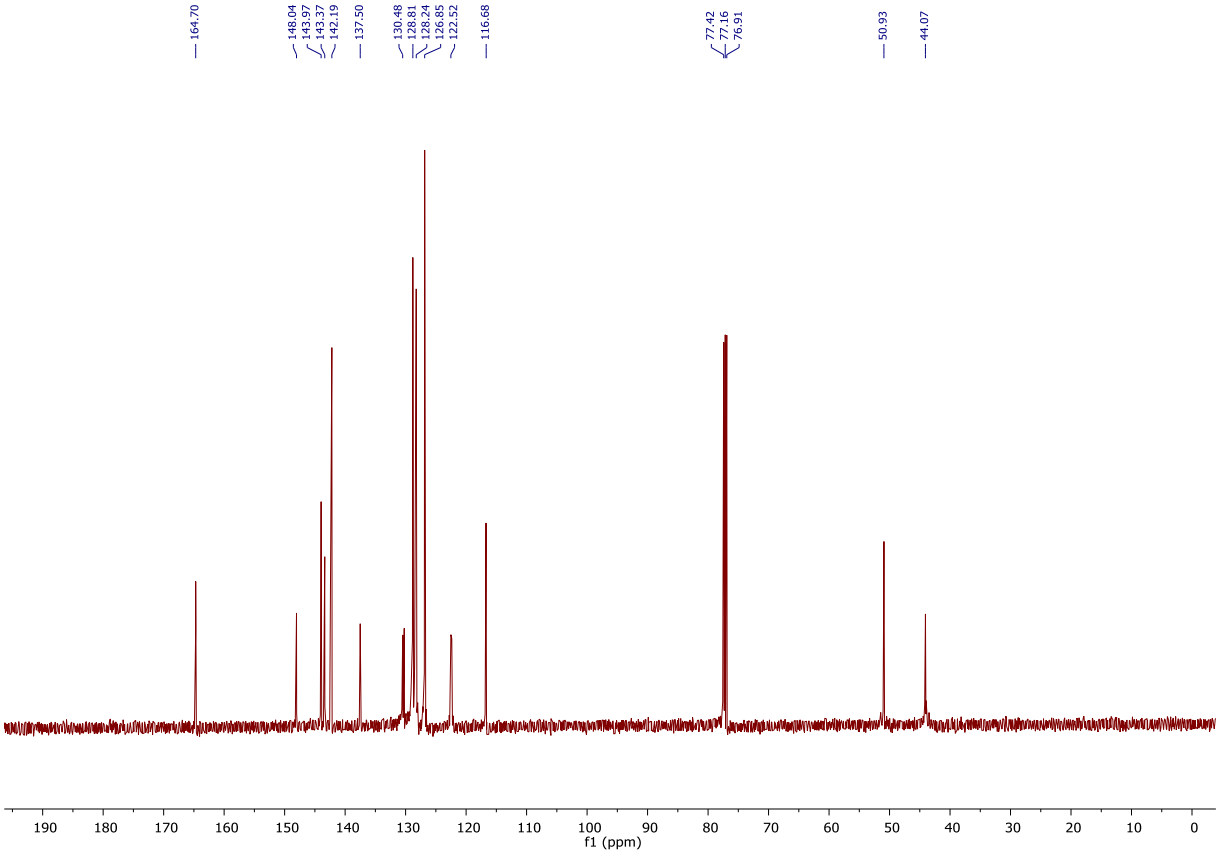
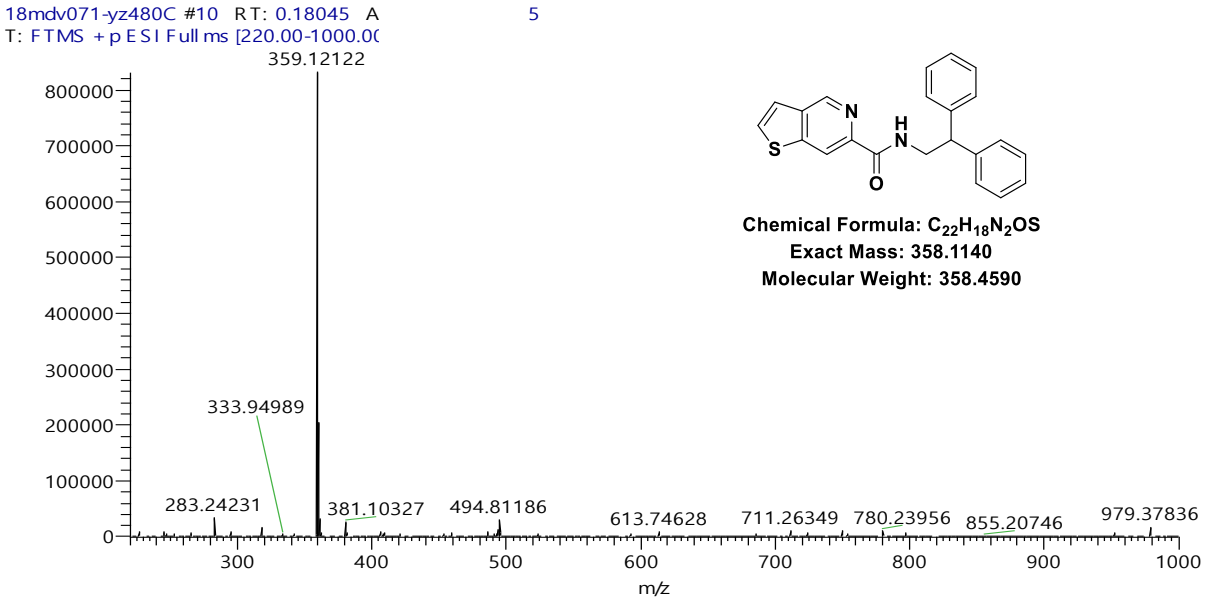
780.15369
907.88416
979.37775
m/z
Chemical Formula: C17H20N2O4
Exact Mass: 316.1423
Molecular Weight: 316.3570

N-(2,2-diphenylethyl)thieno[3,2-*c*]pyridine-6-carboxamide (K21)



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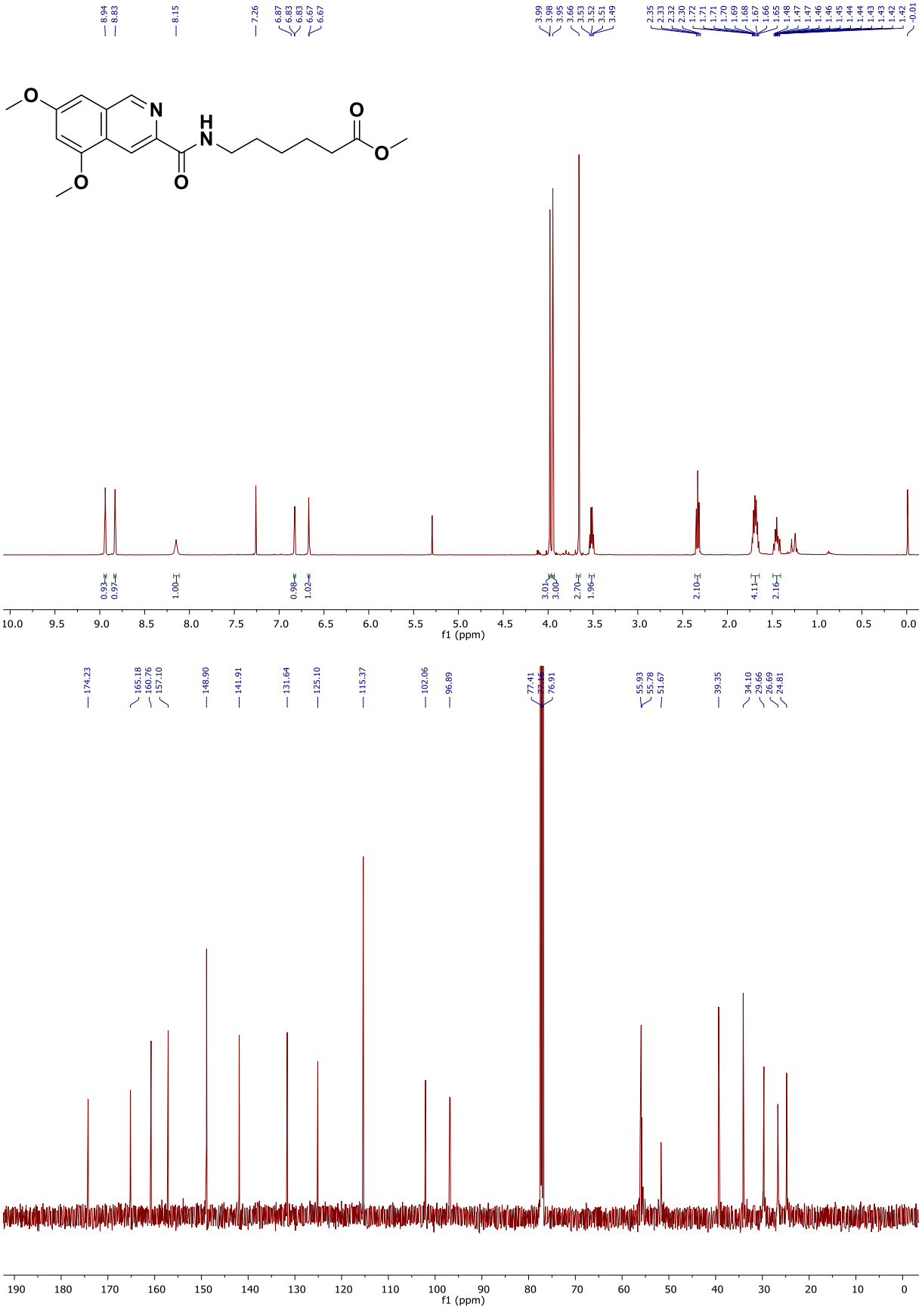
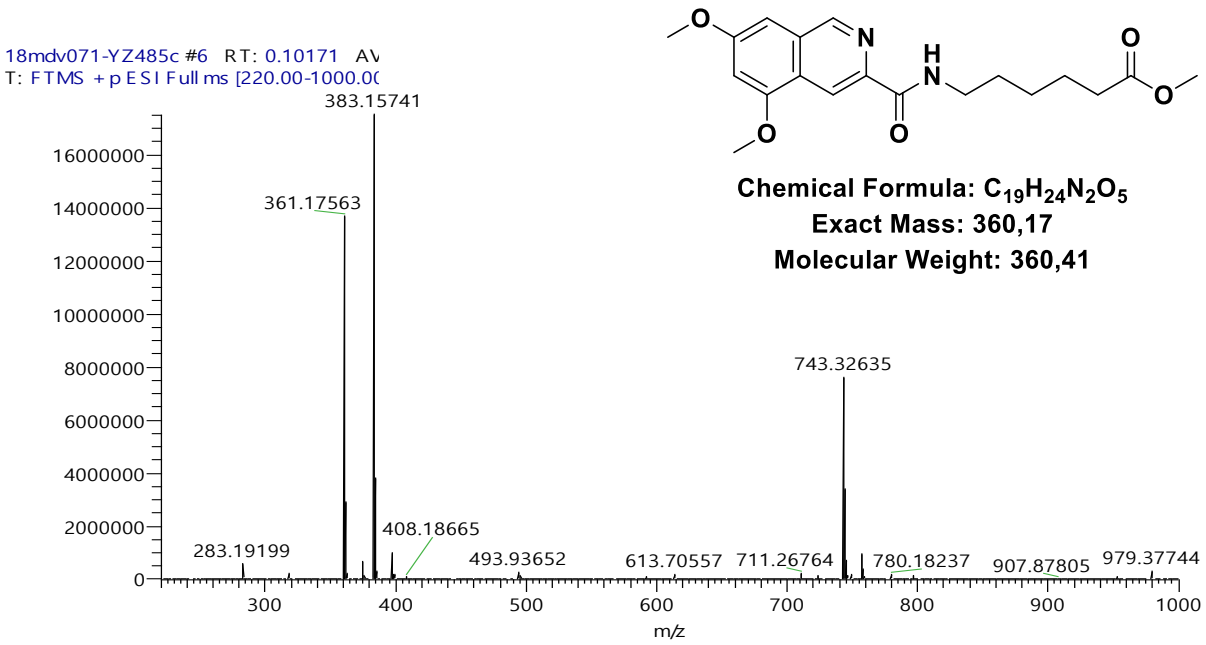
m/z
Chemical Formula: C22H18N2OS
Exact Mass: 358.1140
Molecular Weight: 358.4590

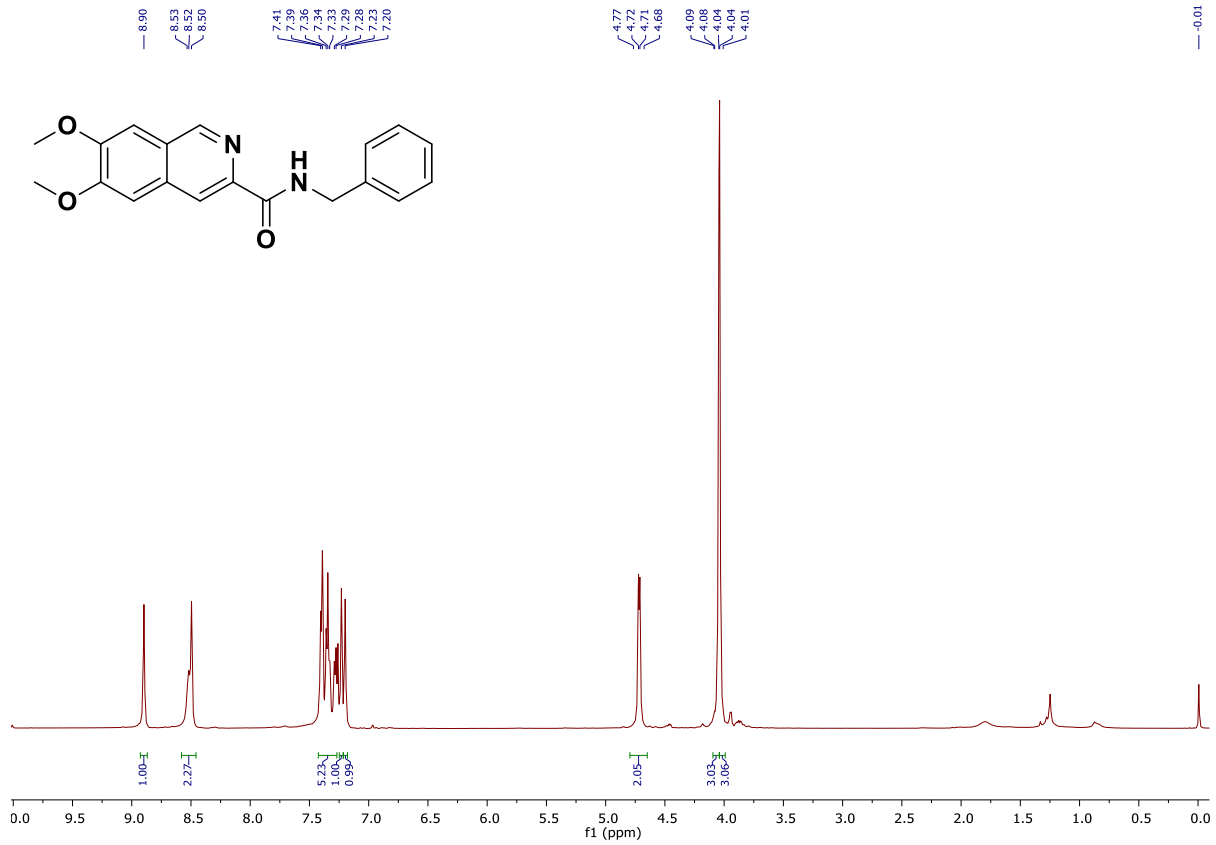
Methyl 6-(5,7-dimethoxyisoquinoline-3-carboxamido)hexanoate (L7)

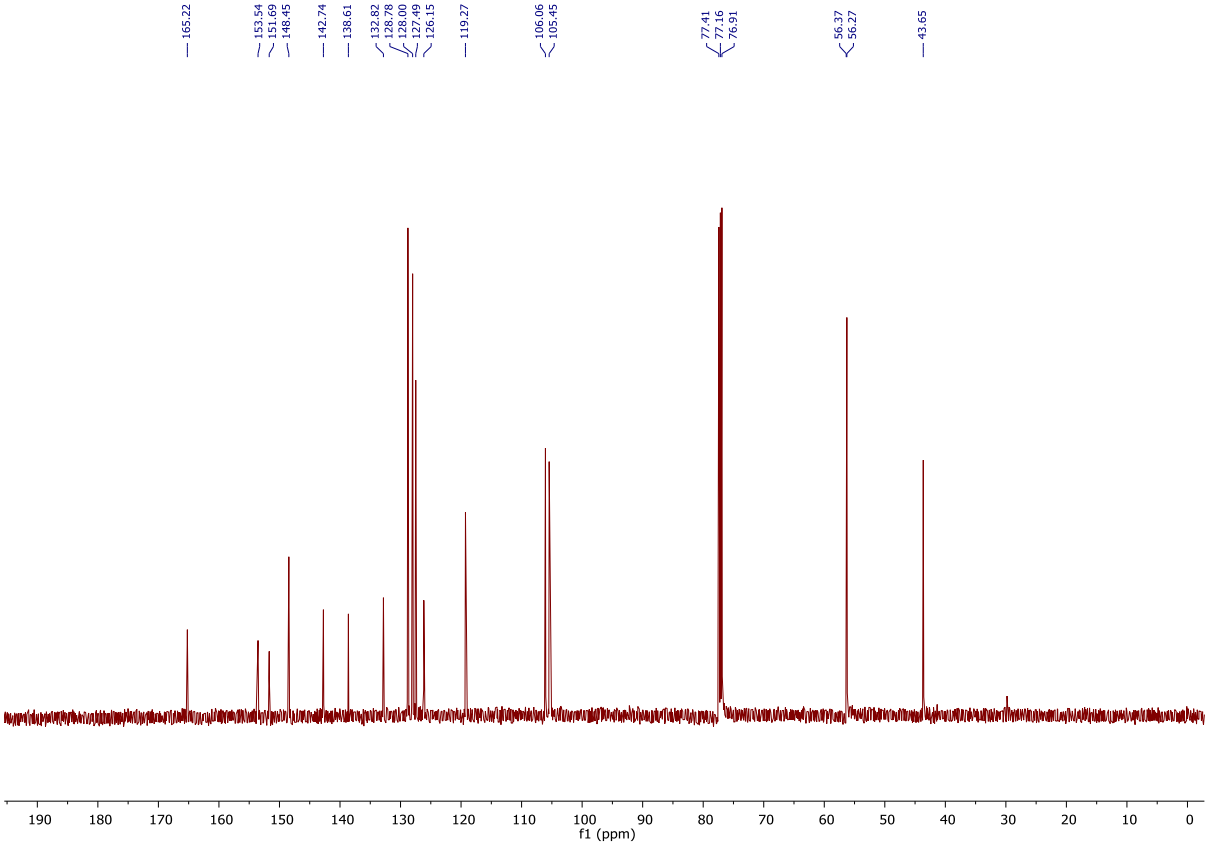


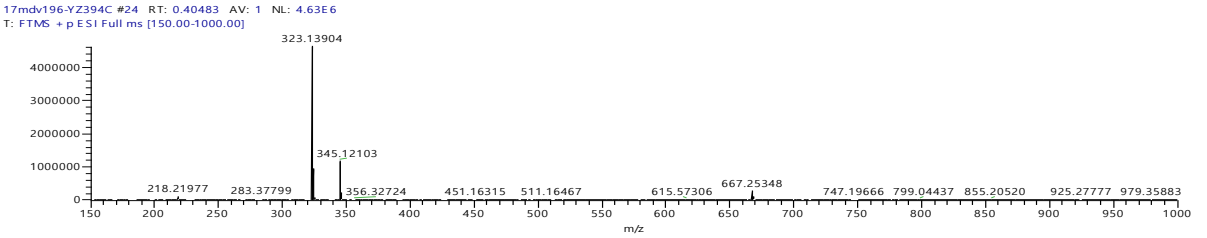


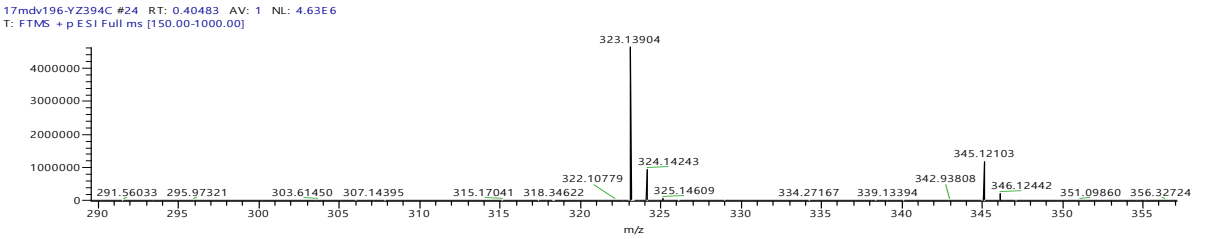
Chemical Formula: $C_{19}H_{24}N_2O_5$
Exact Mass: 360,17
Molecular Weight: 360,41

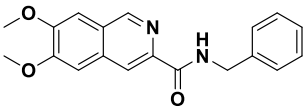
N-benzyl-6,7-dimethoxyisoquinoline-3-carboxamide (M17)





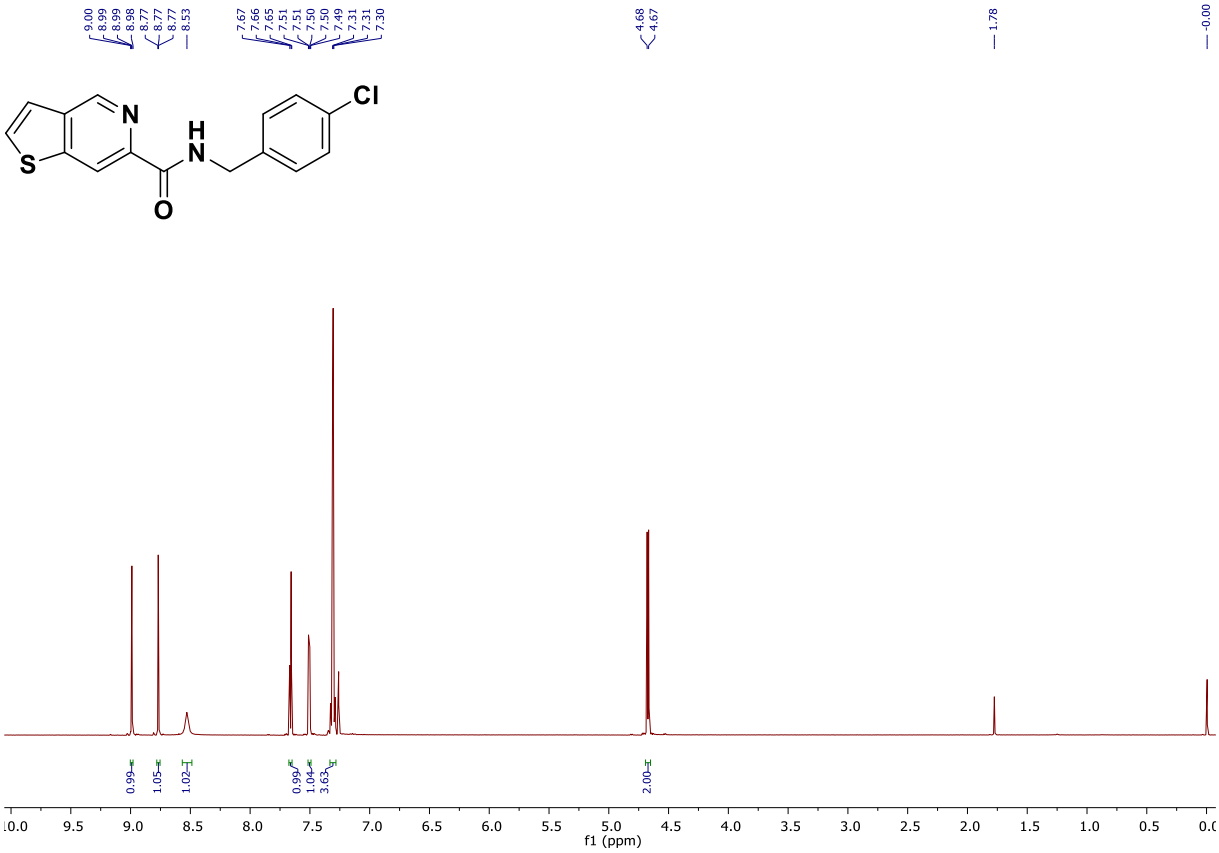


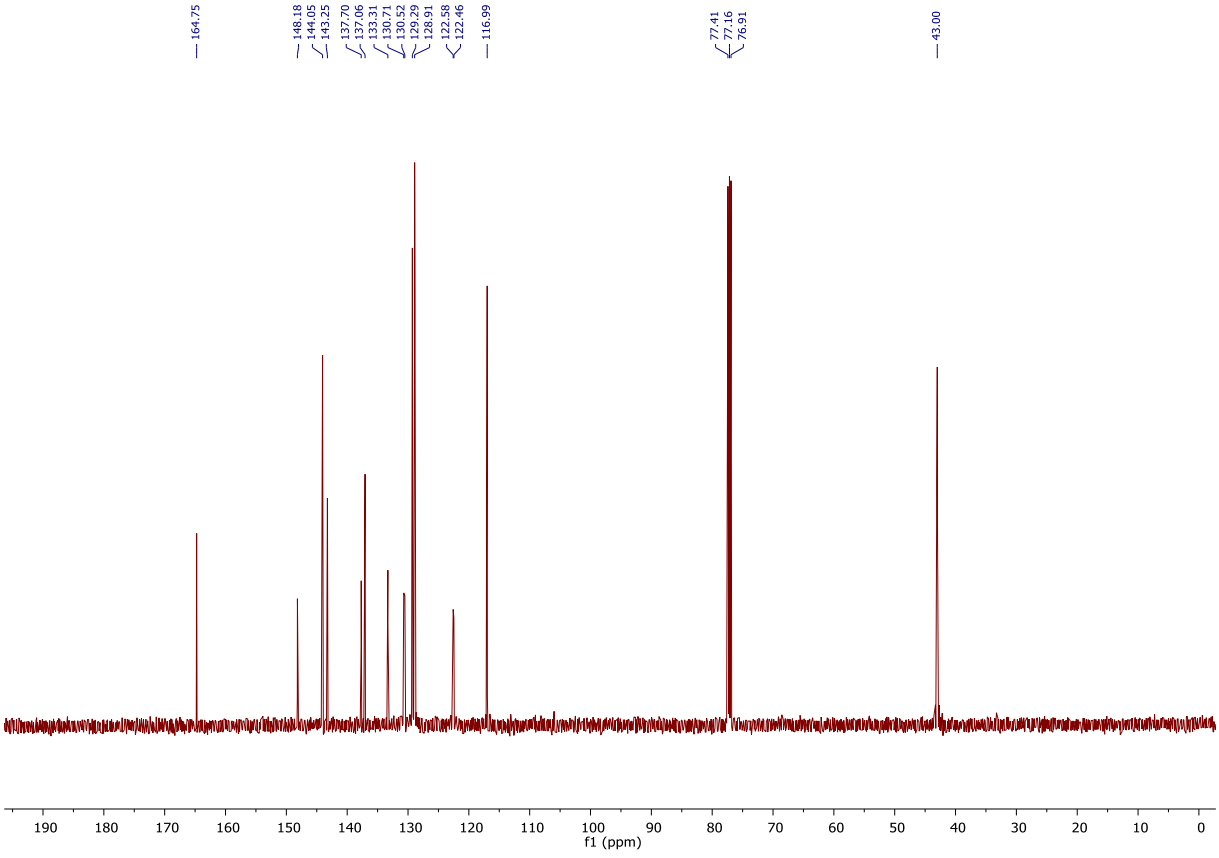


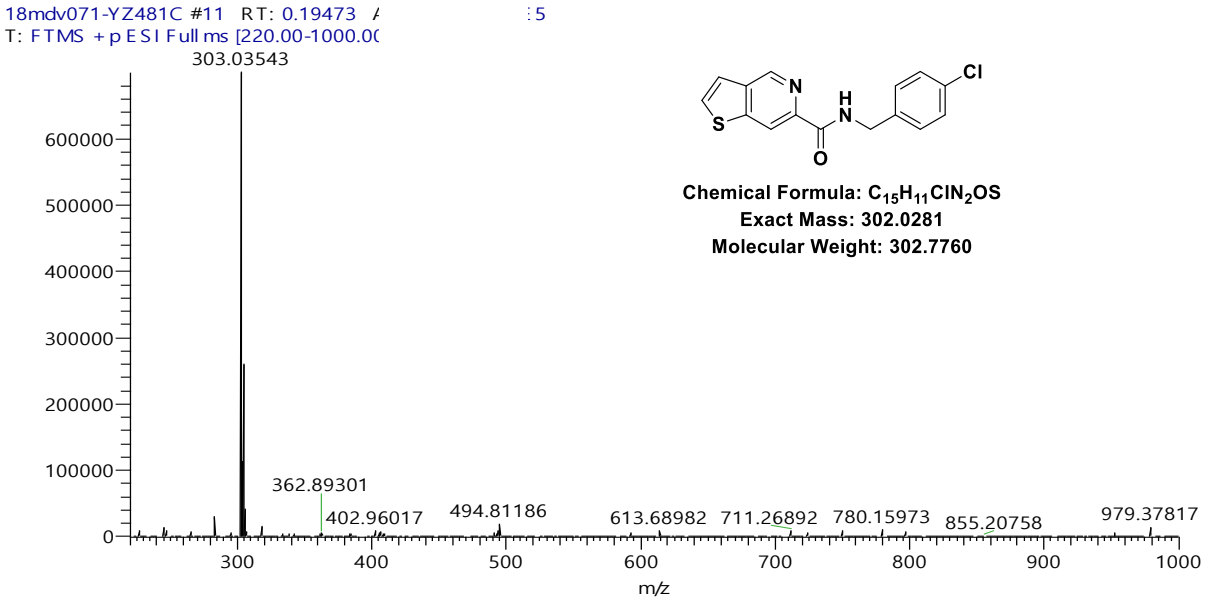


Chemical Formula: $C_{19}H_{18}N_2O_3$
Exact Mass: 322.1317
Molecular Weight: 322.3640

N-(4-chlorobenzyl)thieno[3,2-*c*]pyridine-6-carboxamide (N15)



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780.15973
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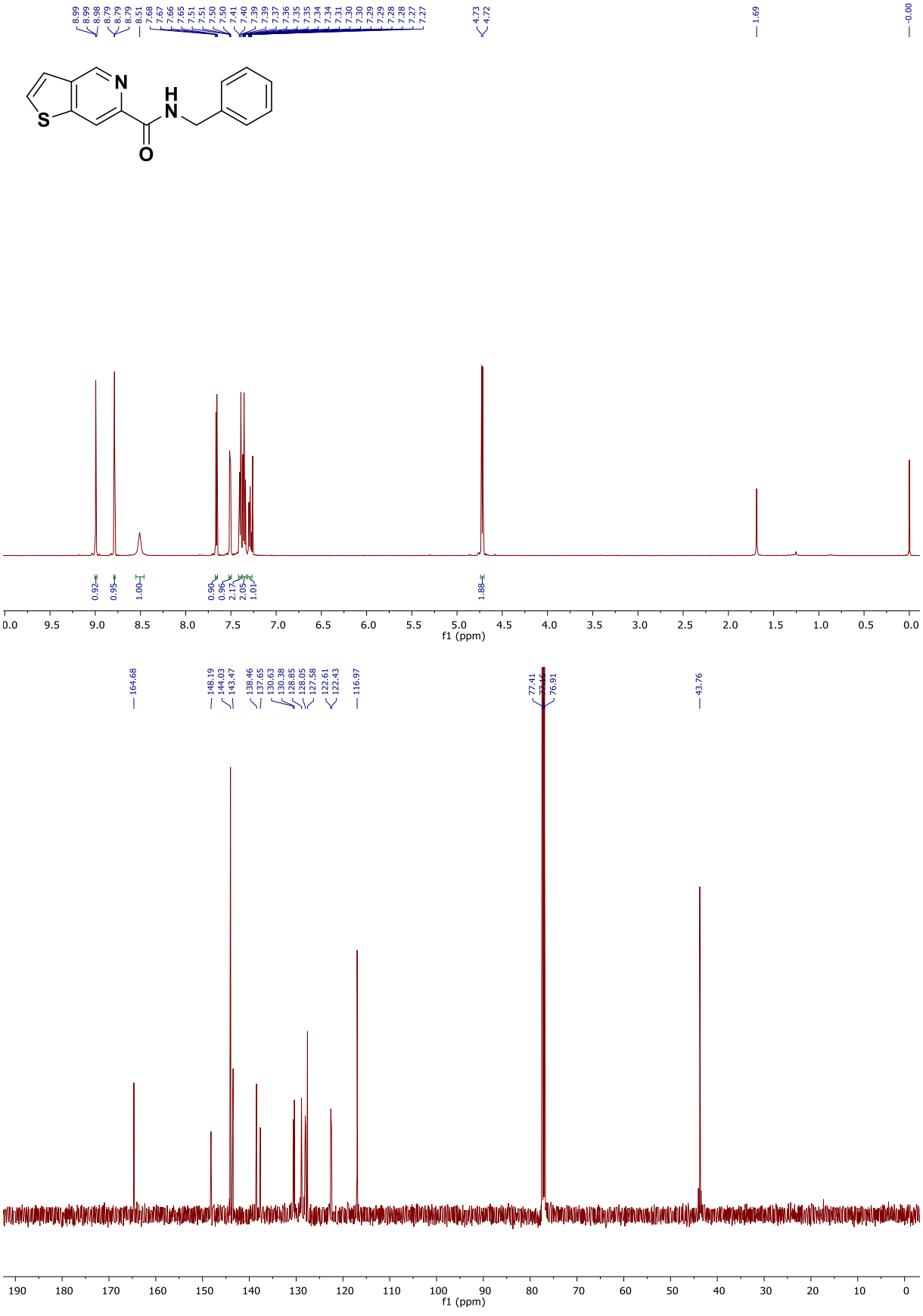
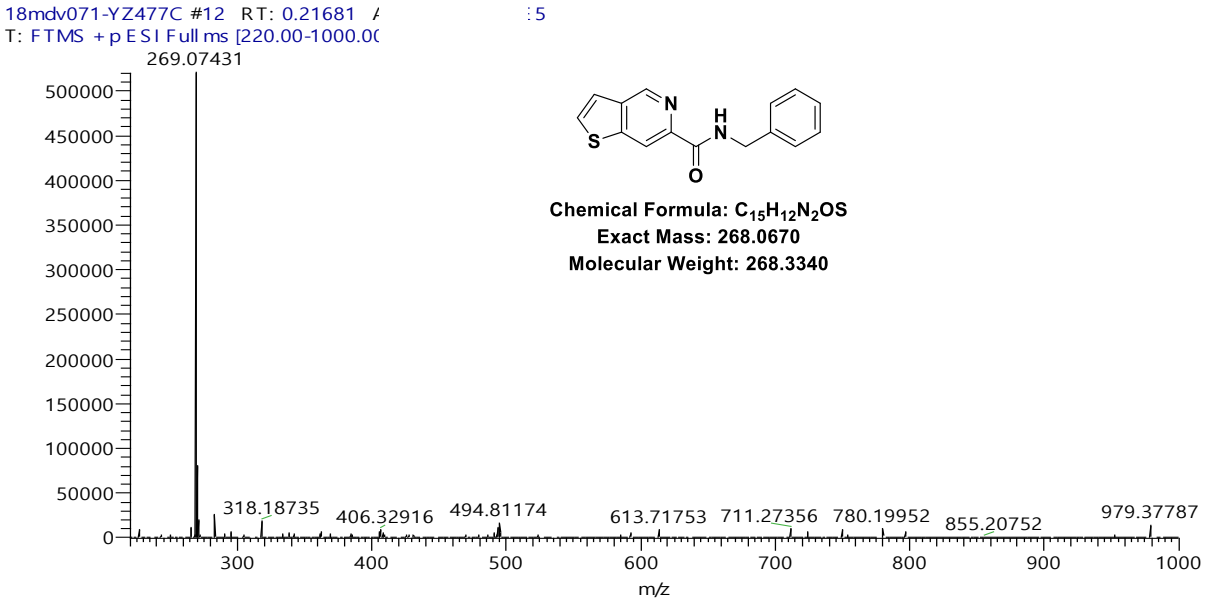
979.37817
300
400
500
600
700
800
900
1000
m/z
N
H
N
S
O
Cl
Chemical Formula: C15H11ClN2OS
Exact Mass: 302.0281
Molecular Weight: 302.7760

N-benzylthieno[3,2-*c*]pyridine-6-carboxamide (O11)

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780.19952
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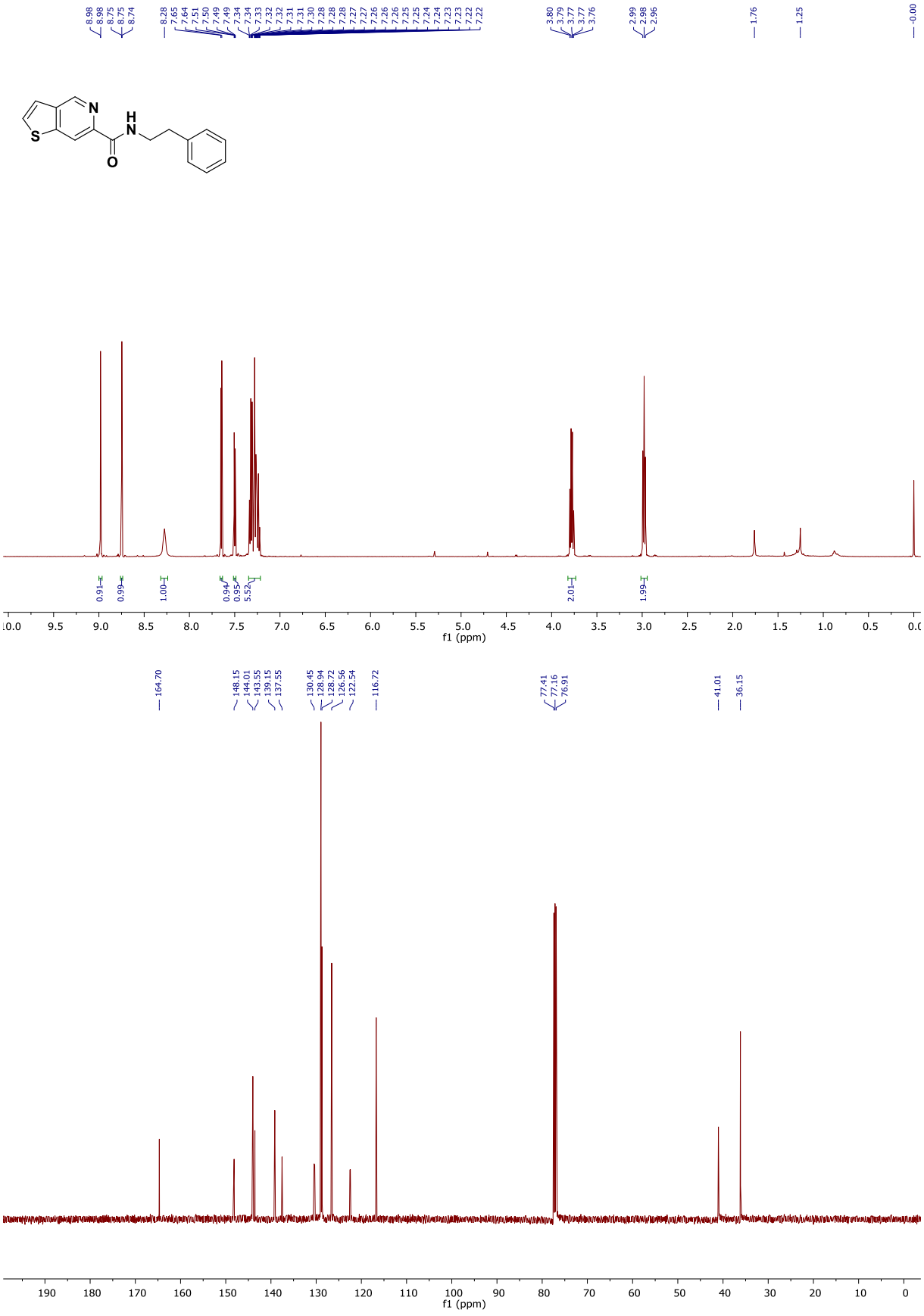
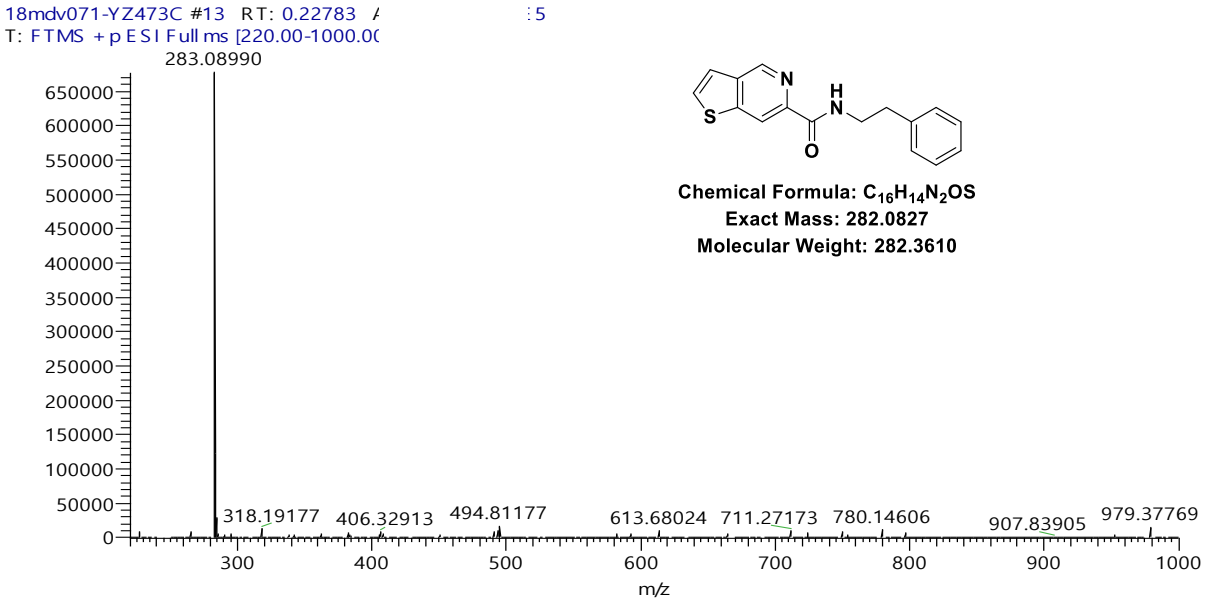
979.37787
m/z
Chemical Formula: C15H12N2OS
Exact Mass: 268.0670
Molecular Weight: 268.3340

N-phenethylthieno[3,2-*c*]pyridine-6-carboxamide (P8)

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150000
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50000
0
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406.32913
494.81177
613.68024
711.27173
780.14606
907.83905
979.37769
300
400
500
600
700
800
900
1000
m/z
N
H
N
S
O
Chemical Formula: C16H14N2OS
Exact Mass: 282.0827
Molecular Weight: 282.3610

7. Gram scale reaction procedure for the synthesis of 6,7-dimethoxy-*N*-phenethylisoquinoline-3-carboxamide

A round-bottomed flask (100 mL) equipped with a Teflon-coated magnetic stir bar was charged with 2,2-dimethoxyacetaldehyde (4.52 mL, 30 mmol) and 3,4-dimethoxybenzylamine (5.01 g, 30 mmol) in MeOH (20 mL). The reaction mixture was stirred at room temperature for 20 min, then, benzoic acid (3.66 g, 30 mmol) and phenylethylisocyanide (3.93g, 30 mmol) were added. The reaction mixture was stirred at room temperature for 15 h. Upon completion, the solvent was removed under vacuum. Then, the reaction mixture was dissolved in dioxane (15 mL) and 37% $HCl_{(aq)}$ (15 mL) was added dropwise via a pressure equalizing dropping funnel (60 mL). The reaction mixture was stirred at room temperature for 12 h. The precipitated product was dried under vacuum. Then, it was dissolved in dichloromethane (100 mL), transferred to a separatory funnel (250 mL), washed with saturated $NaHCO_3$ solution (3 x 50 mL), water (1 x 50 mL), brine (1 x 50 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the crude product was washed with cold tert-butyl methyl ether (7.26 g, yield: 72%, Fig. S4). The purity of the obtained product was determined by qHNMR using benzyl benzoate as internal standard.

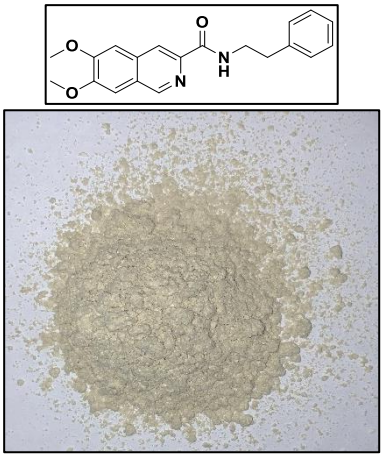


Fig. S4. Multi-gram synthesis.

7.1. qHNMR

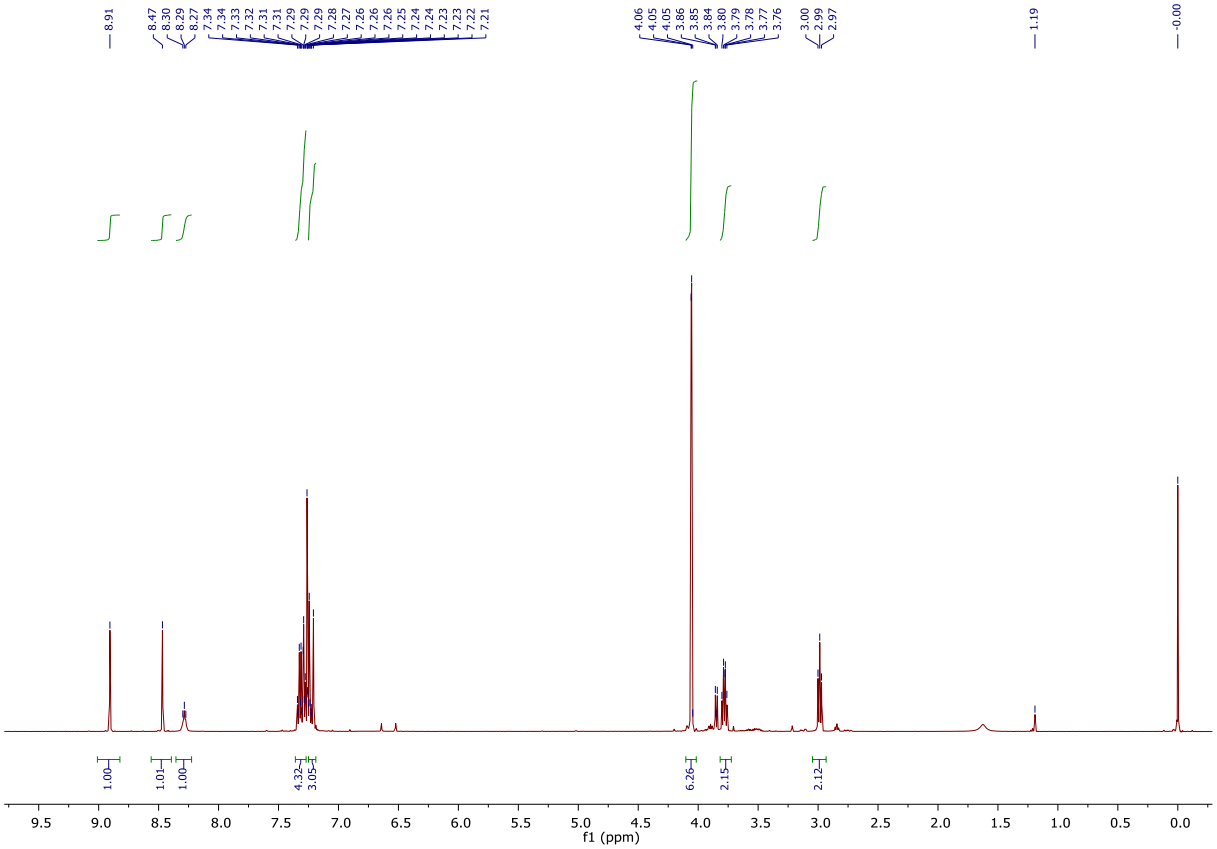
For the ^{1}H NMR experiment, 42.10 mg (~1/8 mmol) of the gram scale reaction sample and 28.67 mg (~1/8 mmol) of the internal standard were dissolved in $CDCl_3$.

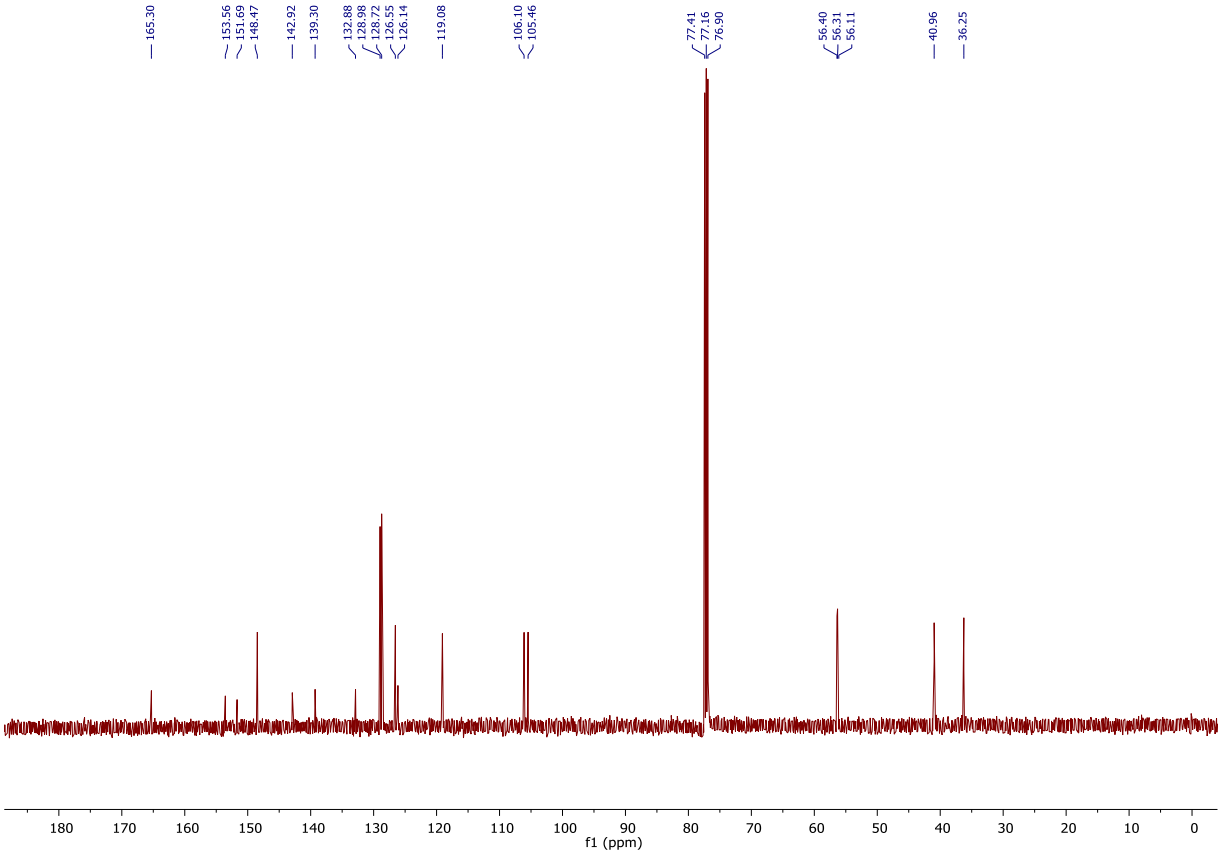
The following equation was used for quantification:[9]

$$P_x = \frac{I_x}{I_{std}} \frac{N_{std}}{N_x} \frac{M_x}{M_{std}} \frac{m_{std}}{m_x} P_{std} = \frac{3.18}{3.85} \frac{4}{4} \frac{336.39}{212.25} \frac{28.67}{42.10} 100 = 89\%$$

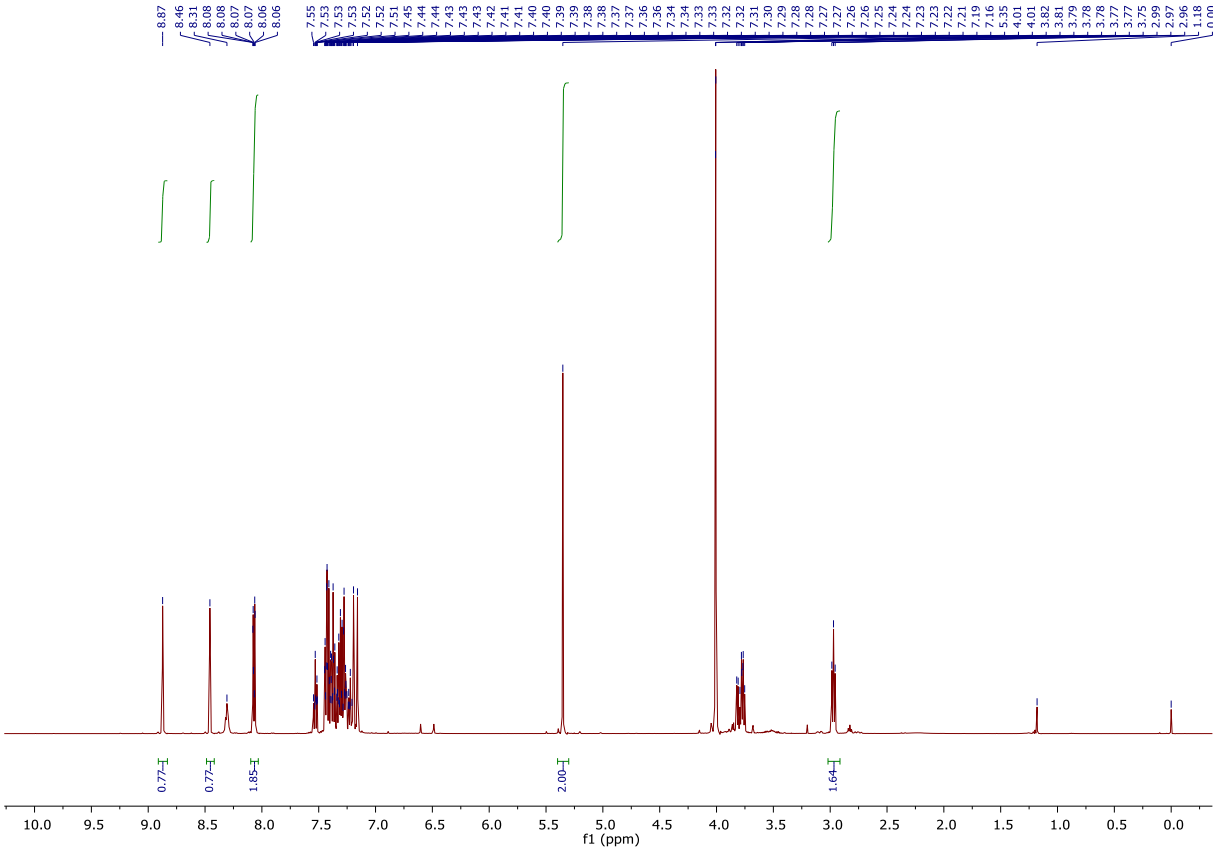
where I_x and I_{std} correspond to the integrated signal area of the NMR line of the sample and standard, respectively. N, M, m and P are number of spins (protons), molecular mass, weighed mass and the purity, respectively.

7.2. ^{1}H and ^{13}C NMR spectra of gram scale reaction





7.3. qHNMR spectrum of gram scale reaction



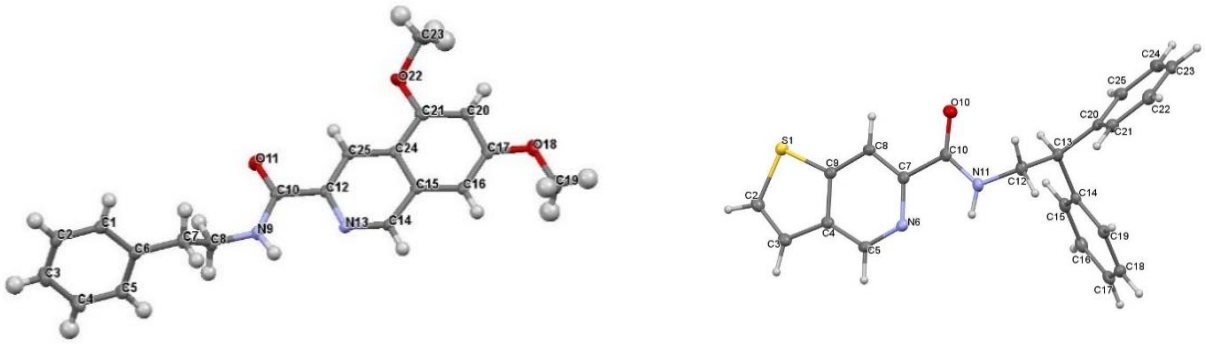
8. Crystal structure determination

X-ray diffraction data for single crystals of compounds **A3**, **B5** and **K21** were collected using SuperNova (Rigaku - Oxford Diffraction) four circle diffractometer with a mirror monochromator and a microfocus MoKα radiation source (λ = 0.71073 Å) which was used for monocrystals of **A3** and **K21**. Additionally, the diffractometer was equipped with a CryoJet HT cryostat system (Oxford Instruments) allowing low temperature experiments, performed at 130(2) K. The obtained data sets were processed with CrysAlisPro software.[10] The phase problem was solved with direct methods using SIR2004[11] or SUPERFLIP.[12] Parameters of obtained models were refined by full-matrix least-squares on F^2 using SHELXL-2014/6.[13] Calculations were performed using WinGX integrated system (ver. 2014.1).[14] Figure was prepared with Mercury 3.7 software.[15]

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms attached to carbon atoms were positioned with the idealised geometry and refined using the riding model with the isotropic displacement parameter $U_{iso}[H] = 1.2\ U_{eq}[C]$. The difference Fourier map was inspected in order to find position of hydrogens linked to nitrogen atoms. These hydrogen atoms were refined with no restrains on the isotropic displacement parameters. Crystal data and structure refinement results for presented crystal structures are shown in Table S3. The molecular geometry (asymmetric units) observed in presented crystal structures are shown in Fig. S5.

Crystals of compound **A3** exhibited the twinning phenomena. Obtained data show the two-component twin with approximately 52% and 48% of component 1 and component 2, respectively. Data was processed with twin option of the CrysAlisPro software[9]. The obtained model was refined against HKLF4.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos.: CCDC1828773 (**B5**), CCDC 1827864 (**K21**) and CCDC 1827863 (**A3**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).



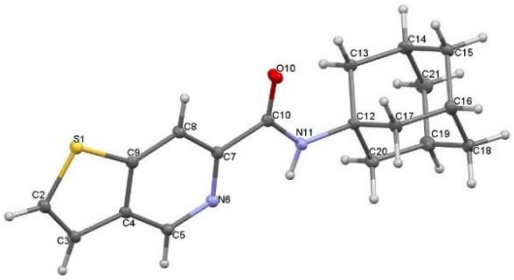


Fig. S5. Molecular geometry observed in crystal structures of compounds **B5**, **K21** and **A3**, showing the atom labelling scheme (here asymmetric units are presented except for **B5**, for which three independent molecules are observed in the asymmetric unit). Displacement ellipsoids of non-hydrogen atoms are drawn at the 30% probability level. H atoms are presented as small spheres with an arbitrary radius.

Table S3. Crystal data and structure refinement results for compounds **B5**, **K21** and **A3**.

	B5	**K21**	**A3**
Empirical moiety formula	3x (C_{20} H_{20} N_2 O_3)	C_{22} H_{18} N_2 O S	C_{18} H_{20} N_2 O S
Formula weight [g/mol]	336.38	358.44	312.42
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/a$	$P2_1/n$	$P2_1/c$
Unite cell dimensions	a = 9.3950(4)Å b = 43.7250(14)Å c = 12.6567(4)Å β=96.256(3)°	a = 8.9525(2) Å b = 19.7350(4) Å c = 10.1928(3) Å β=100.181(2)°	a = 11.8199(10) Å b = 11.5116(6) Å c = 11.5293(9) Å β=101.081(9)°
Volume [$Å^3$]	5168.4(3)	1772.48(8)	1539.5(2)
Z	12	4	4
D_{calc} [Mg/m^3]	1.297	1.343	1.348
μ [mm^{-1}]	0.088	0.196	0.214
F(000)	2136	752	664
Crystal size [mm^3]	0.4 x 0.3 x 0.1	0.5 x 0.3 x 0.1	0.5 x 0.5 x 0.1
Θ range	2.83° to 28.57°	2.90° to 28.60°	3.27° to 28.67°
Index ranges	$-12 \le h \le 7$, $-57 \le k \le 54$, $-16 \le l \le 15$	$-11 \le h \le 12$, $-25 \le k \le 25$, $-11 \le l \le 13$	$-13 \le h \le 14$, $-15 \le k \le 9$, $-14 \le l \le 14$
Refl. collected	33394	14761	8756
Independent reflections	12007 [R(int) = 0.0298]	4168 [R(int) = 0.0370]	2885 [R(int) = 0.1021]
Completeness [%] to Θ	99.7 (Θ 26.3°)	99.9 (Θ 25.2°)	98.7 (Θ 25.0°)
Absorption correction	Multi-scan	Multi-scan	Multi-scan
Tmin. and Tmax.	0.872 and 1.000	0.757 and 1.000	0.784 and 1.000
Data/ restraints/parameters	12007 / 0 / 683	4168 / 6 / 239	2885 / 0 / 203
GooF on F2	1.062	1.040	1.049
Final R indices [I>2sigma(I)]	R1= 0.0534, wR2= 0.1157	R1= 0.0405, wR2= 0.0860	R1= 0.0548, wR2= 0.1388
R indices (all data)	R1= 0.0777, wR2= 0.1296	R1= 0.0667, wR2= 0.0995	R1= 0.0629, wR2= 0.1464
$\Delta\rho_{max}$, $\Delta\rho_{min}$ [$e \cdot Å^{-3}$]	0.25 and -0.20	0.29 and -0.30	0.38 and -0.45

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