Supplementary Information

Development and characterization of novel selective, non-basic dopamine D_2 receptor antagonists for the treatment of schizophrenia

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Content:

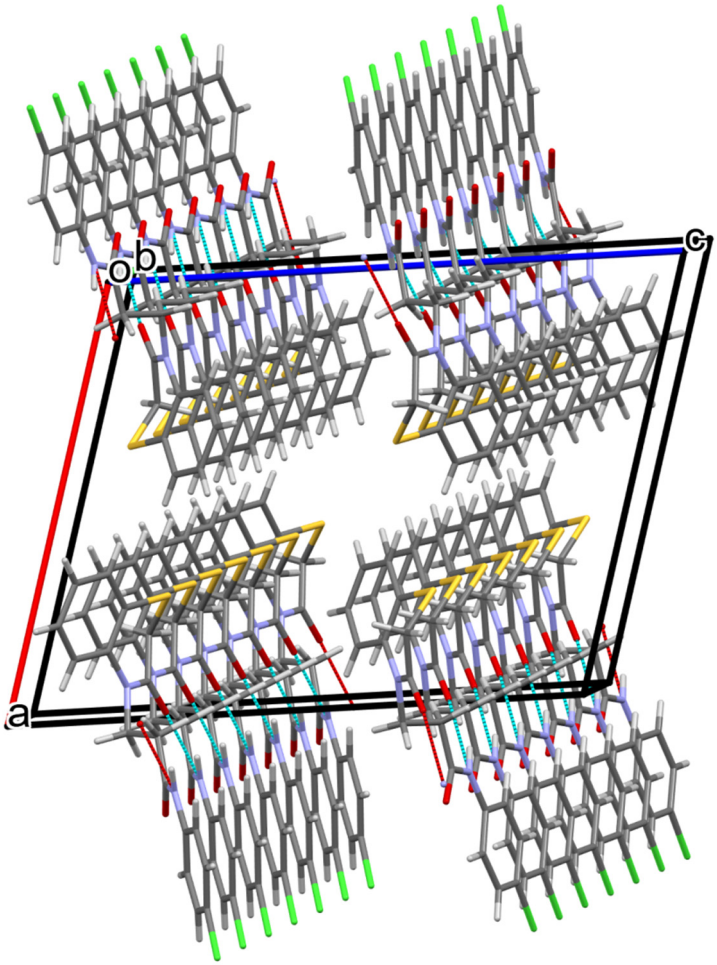


Figure S1. Packing diagrams of **17** viewed along the *b*-axis showing formation of the infinite chains along [010] generated by N2-H2N···O2 hydrogen bonds.

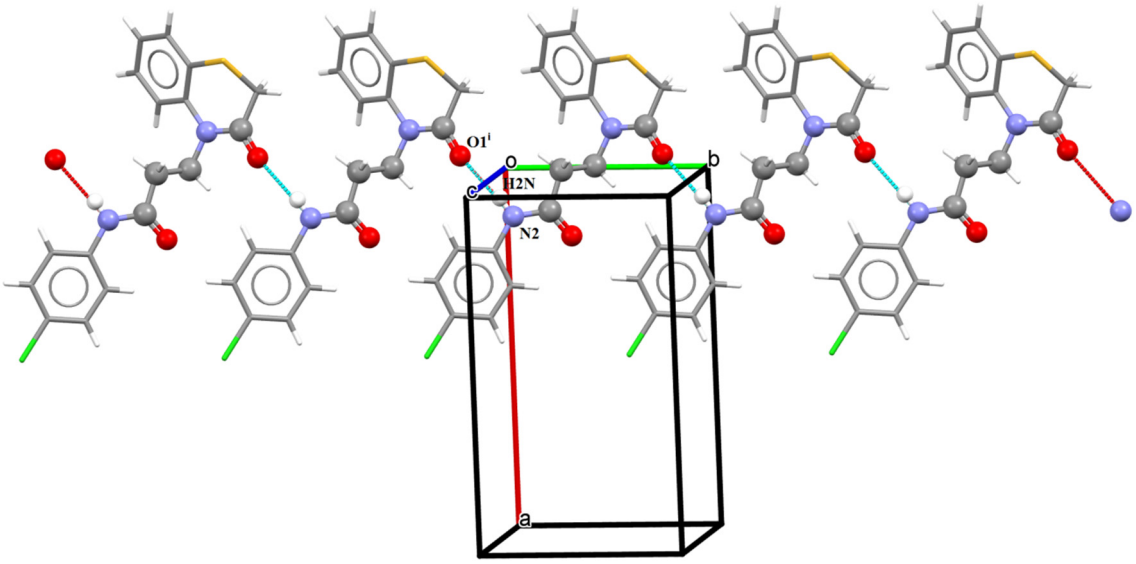


Figure S2. Part of the crystal structure of **17** showing C(8) infinite chain motif linked by N2-H2N···O2 hydrogen bonds propagating in the *b*-axis direction. Atoms involved in chain motif formation are shown in ball stick format. Symmetry code: (i) x, y-1, z.

Table S1. Interatomic distances and selected bond angles for compound **17**.

Bond lengths (Å)			
C1–O1	1.226(4)	C9–C10	1.507(5)
C1–N1	1.355(4)	C10–C11	1.509(5)
C1–C2	1.498(5)	O2–C11	1.204(4)
C2–S1	1.789(4)	C12–C17	1.384(4)
C3–C8	1.387(4)	C12–C13	1.385(4)
C3–C4	1.389(4)	C12–N2	1.414(4)
C3–S1	1.754(4)	C13–C14	1.376(4)
C4–C5	1.367(5)	C14–C15	1.375(5)
C5–C6	1.364(5)	C15–C16	1.365(5)
C6–C7	1.381(5)	C15–Cl1	1.740(4)
C7–C8	1.386(5)	C16–C17	1.381(5)
C8–N1	1.434(4)	N2–C11	1.341(5)
C9–N1	1.473(4)		
Bond angles (º)			
O1–C1–N1	122.2(3)	C14–C15–Cl1	119.4(3)
O1–C1–C2	121.1(4)	C11–N2–C12	128.8(3)
N1–C9–C10	111.3(3)	O2–C11–N2	122.7(4)
C16–C15–Cl1	120.2(3)	O2–C11–C10	122.1(4)
Torsion angles (º)			
C3–C8–N1–C1	-26.9(5)	C10–C9–N1–C8	-65.8(5)
C2–C1–N1–C8	-2.7(5)	C10–C9–N1–C1	109.7(4)
N1–C1–C2–S1	49.3(4)	C12–N2–C11–O2	3.3(8)
C1–C2–S1–C3	-59.2(3)	C9–C10–C11–O2	28.9(7)
C8–C3–S1–C2	35.1(3)	C17–C12–N2–C11	175.7(4)
S1–C3–C8–N1	3.2(5)	C13–C12–N2–C11	-5.3(7)

Table S2. Detailed experimental conditions employed in radioligand binding assays.

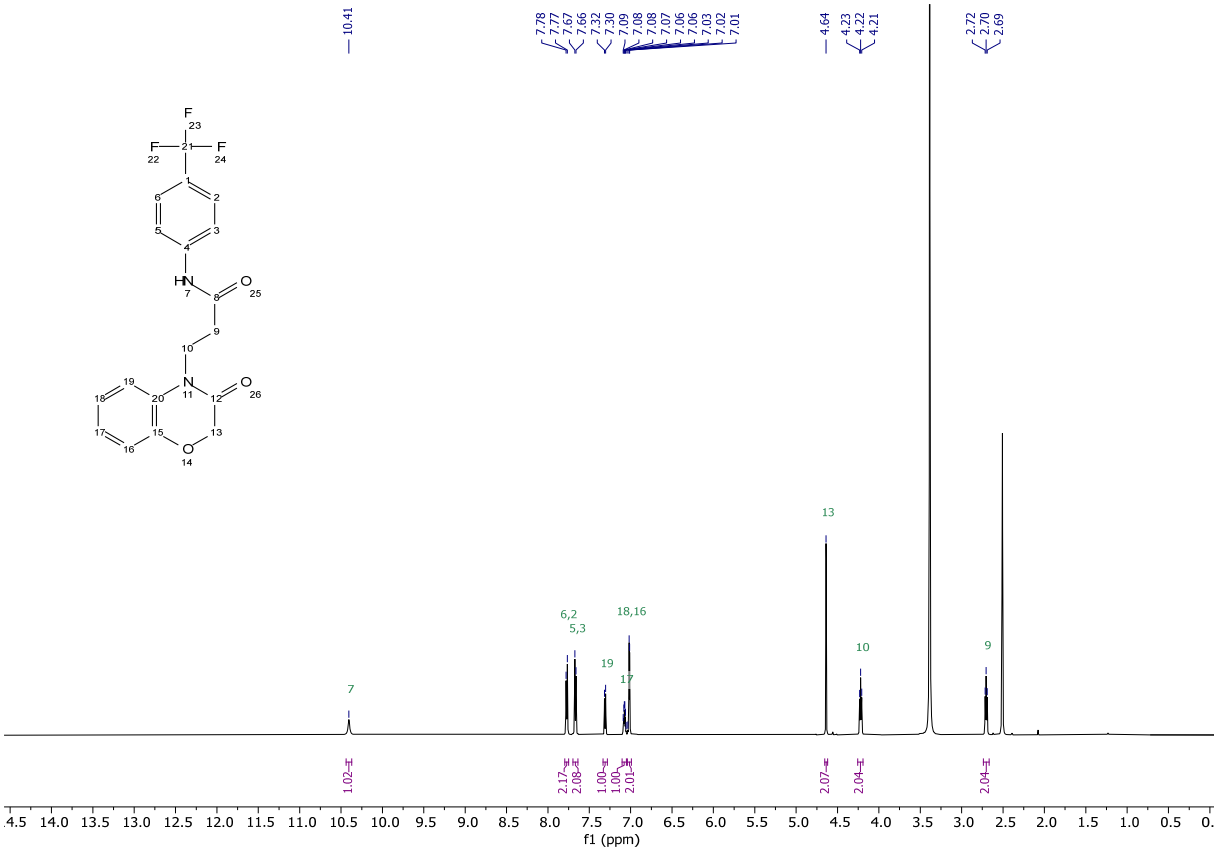
	*h*D$_1$	*h*D$_2$	*h*D$_3$	*h*5-HT$_{1A}$	*h*5-HT$_{2A}$	*h*5-HT$_7$
Protein per well	12 µg	35 µg	2 µg	10 µg	130 µg	2 µg
Assay buffer	50 mM Tris-HCl, 5 mM $MgCl_2$ (pH = 7.4)	50 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, 5 mM $MgCl_2$, 1 mM EDTA (pH = 7.4)	50 mM Tris-HCl, 5 mM $MgCl_2$ (pH = 7.4)	50 mM Tris-HCl, 5 mM $MgSO_4$ (pH = 7.4)	50 mM Tris-HCl (pH = 7.5)	50 mM Tris-HCl, 4 mM $CaCl_2$, 1 mM L-Ascorbic acid, 0.1 mM Pargyline hydrochloride (pH = 7.4)
Radioligand	0.7 nM [^{3}H]- SCH-23390[a]	0.6 nM [^{3}H]-Spiperone[b]	1 nM [^{3}H]- Spiperone[b]	1 nM [^{3}H]-8-OH-DPAT[c]	1.25 nM [^{3}H]-Ketanserin[d]	2 nM [^{3}H]-SB269970[e]
Nonspecific binding	1 µM (+)-Butaclamol	100 µM Sulpiride	1 µM Haloperidol	10 µM Serotonin	1 µM Methysergide	20 µM Clozapine
Incubation	27ºC/60 min	25ºC/120 min	25ºC/60 min	37ºC/120 min	37ºC/30 min	37ºC/60 min
Filter plate	GF/C[f]	GF/C[f]	GF/C[f]	GF/C[f]	GF/B[g]	GF/C[f]
Filter plate pre-treatment	presoaked with 0.5% PEI[h] for 1 h and washed with 250 µl incubation buffer	presoaked with 0.5% PEI[h] for 1 h and washed with 250 µl incubation buffer	presoaked with 0.5% PEI[h] for 1 h and washed with 250 µl incubation buffer	presoaked with 0.5% PEI[h] for 1 h and washed with 250 µl incubation buffer	presoaked with 0.5% PEI[h] for 1 h and washed with 250 µl incubation buffer	presoaked with 0.5% PEI[h] for 1 h and washed with 250 µl incubation buffer
Wash buffer	50 mM Tris-HCl (pH = 7.4)	50 mM Tris-HCl, 0.9% NaCl (pH = 7.4)	50 mM Tris-HCl (pH = 7.4)	50 mM Tris-HCl (pH = 7.4)	50 mM Tris-HCl (pH = 6.6)	50 mM Tris-HCl, 4 mM $CaCl_2$, 1 mM L-Ascorbic acid, 0.1 mM Pargyline hydrochloride (pH = 7.4)
Washing steps	4 x 250 µl wash buffer	4 x 250 µl wash buffer	4 x 250 µl wash buffer	4 x 250 µl wash buffer	6 x 250 µl wash buffer	4 x 250 µl wash buffer

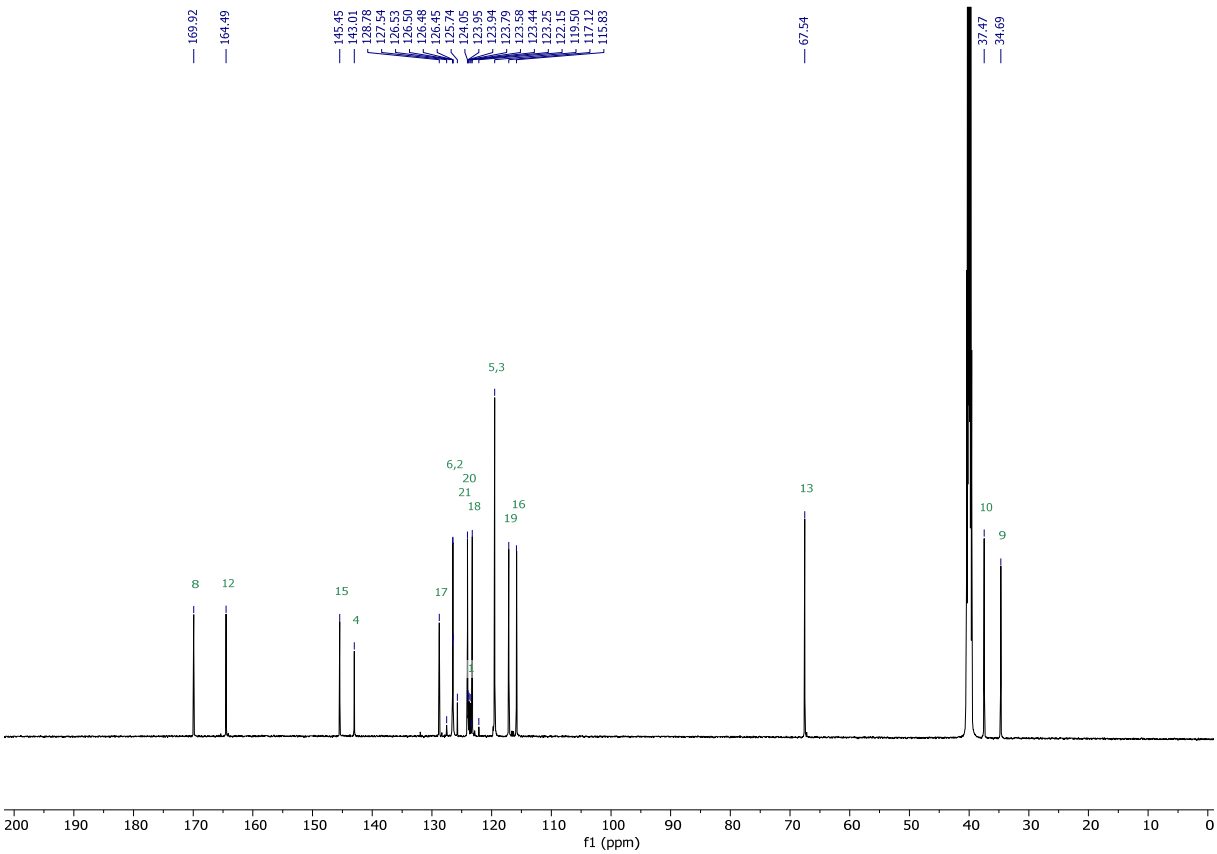
[a] 83.2 Ci/mmol, 1 mCi/ml, PerkinElmer NET930250UC. [b] 54.3 Ci/mmol, 1 mCi/ml, PerkinElmer NET1187250UC. [c] 200 Ci/mmol, 1 mCi/ml, PerkinElmer NET929250UC. [d] 47.3 Ci/mmol, 1 mCi/ml, PerkinElmer NET791250UC. [e] 32.7 Ci/mmol, 0.25 mCi/ml, PerkinElmer NET1198U250UC. [f] MultiScreen$_{HTS}$ FB Filter Plate, PerkinElmer MSFCN6. [g] MultiScreen$_{HTS}$ FB Filter Plate, PerkinElmer MSFBN6. [h] PEI, Polyethyleneimine.

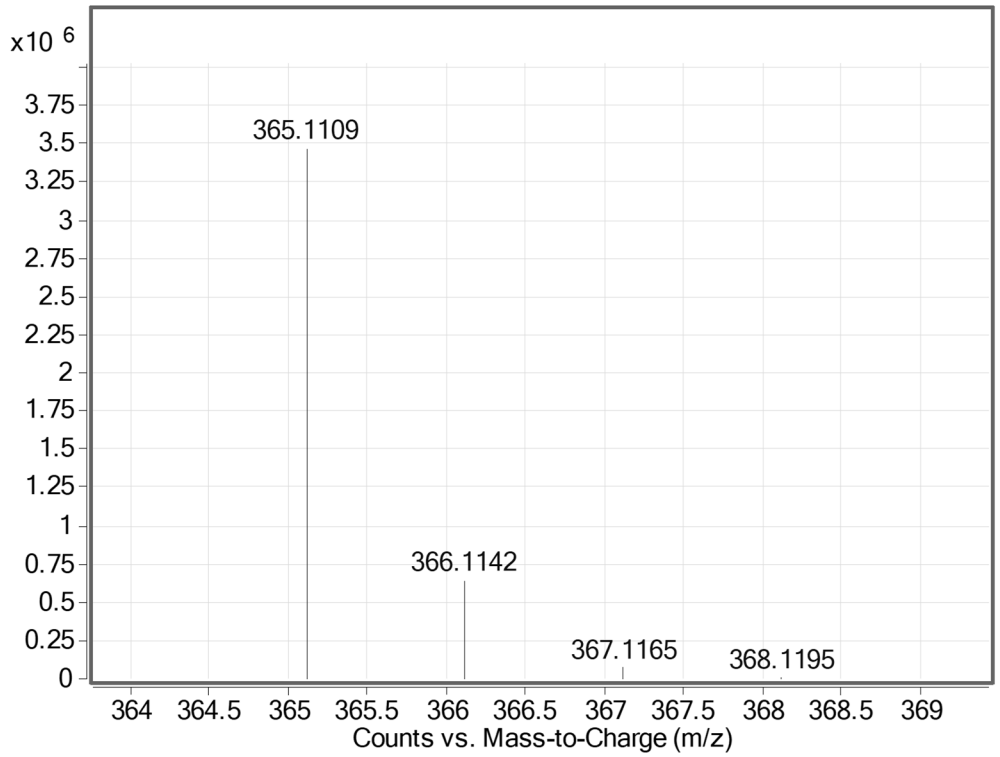
Table S3. Crystal data and structure refinement for compound **17**.

Formula	$C_{17}H_{15}ClN_2O_2S$
Formula weight	346.82
Temperature K	298(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a (Å)	13.5626(11)
b (Å)	7.2478(5)
c (Å)	17.2446(17)
β (°)	106.262(9)
Volume (Å^3)	1627.3(2)
Z	4
Calculated density (g cm^{-3})	1.416
μ (mm^{-1})	0.373
Absorption correction	multi-scan
F(000)	720
Crystal size (mm)	0.15 x 0.45 x 0.50
θ range (º)	2.461to 26.733
Limiting indices	$-17\leq h\leq 17$, $-9\leq k\leq 8$, $-19\leq l\leq 21$
Reflections collected/unique	12931/3458
R_{int}	0.0860
Data/restraints/parameters	3458/0/213
GooF on F^2	1.029
Final R indices[I>2σ(I)]	$R_1 = 0.0684$, $wR_2 = 0.1165$
R indices(all data)	$R_1 = 0.1636$, $wR_2 = 0.1551$
Extinction coefficient	0.0031(7)
Largest diff. peak/hole, e Å^{-3}	0.406/-0.367
CCDC No.	2259221

3-(3-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)propanamide (1)



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0
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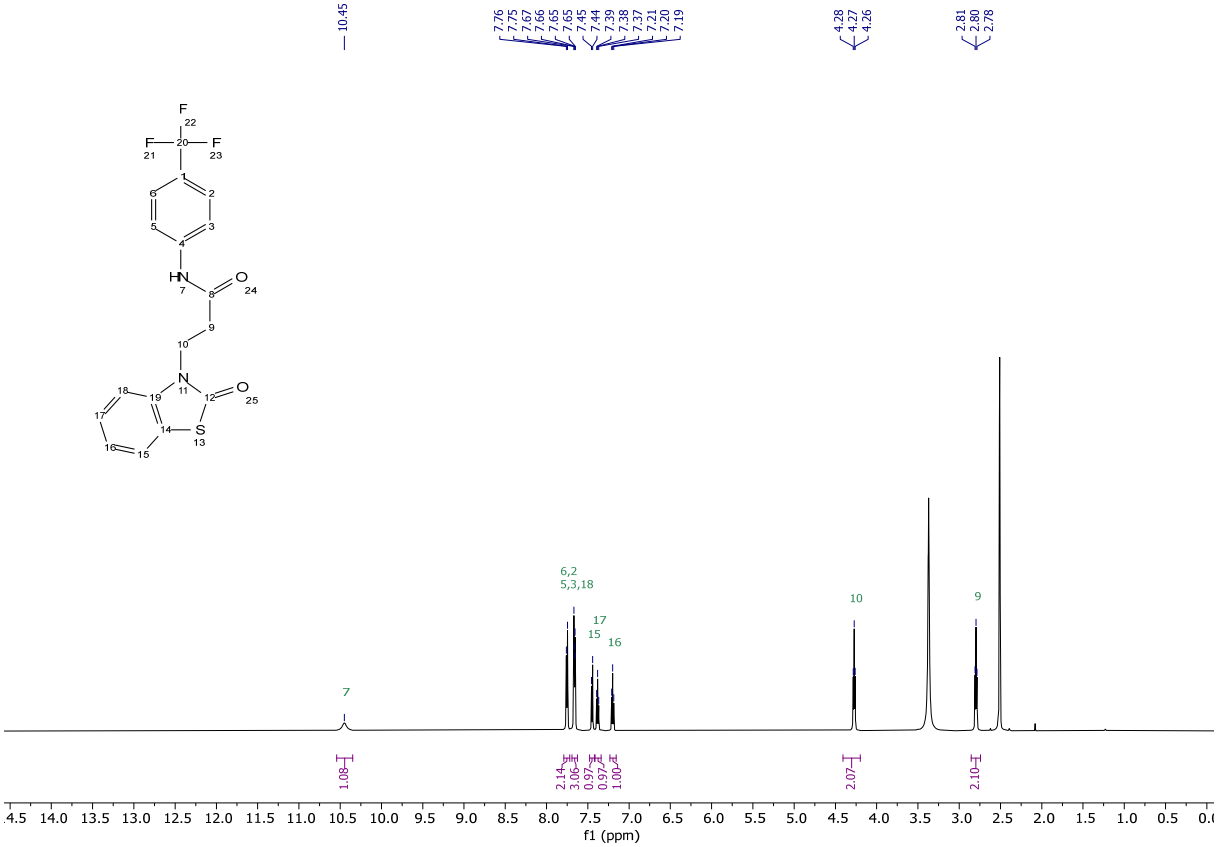
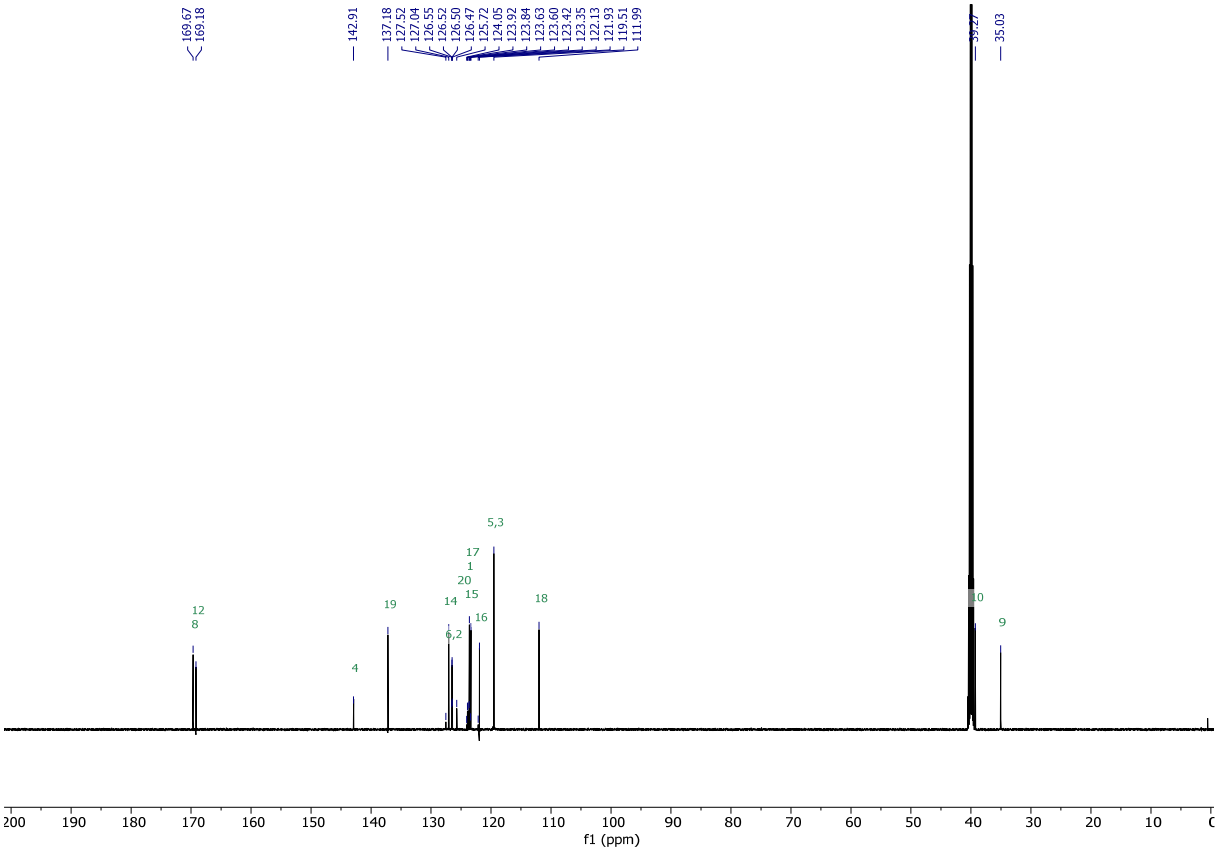
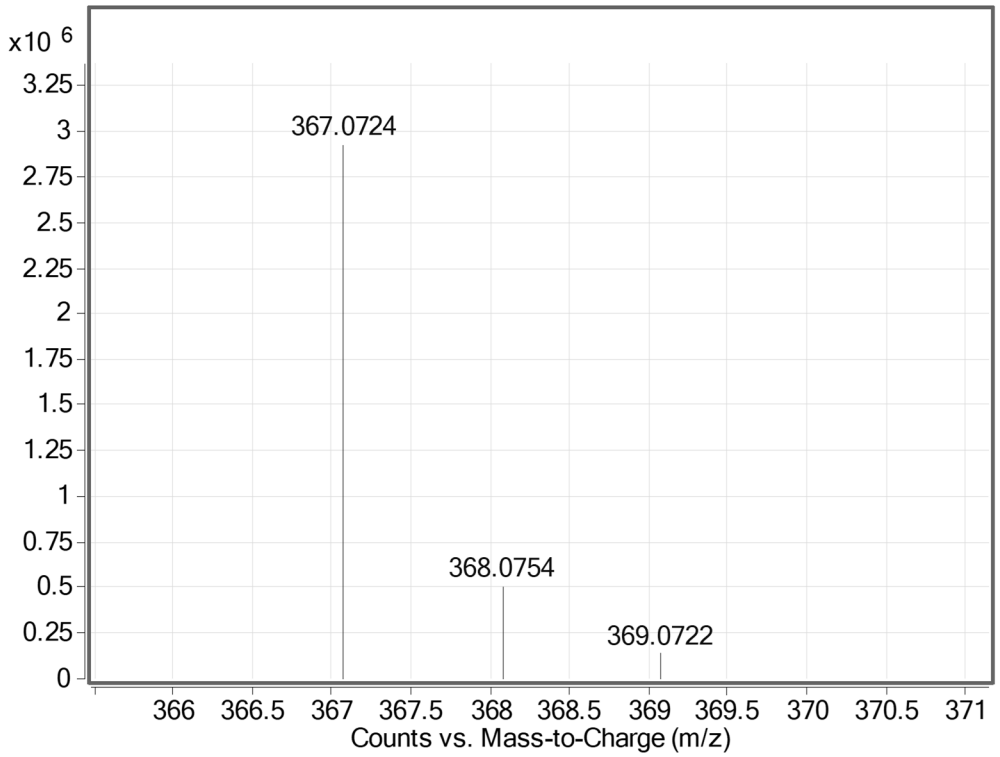
366.1142
367.1165
368.1195
364
364.5
365
365.5
366
366.5
367
367.5
368
368.5
369
Counts vs. Mass-to-Charge (m/z)

3-(2-oxobenzo[*d*]thiazol-3(2*H*)-yl)-*N*-(4-(trifluoromethyl)phenyl)propanamide (2)



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368.0754
369.0722
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366.5
367
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368
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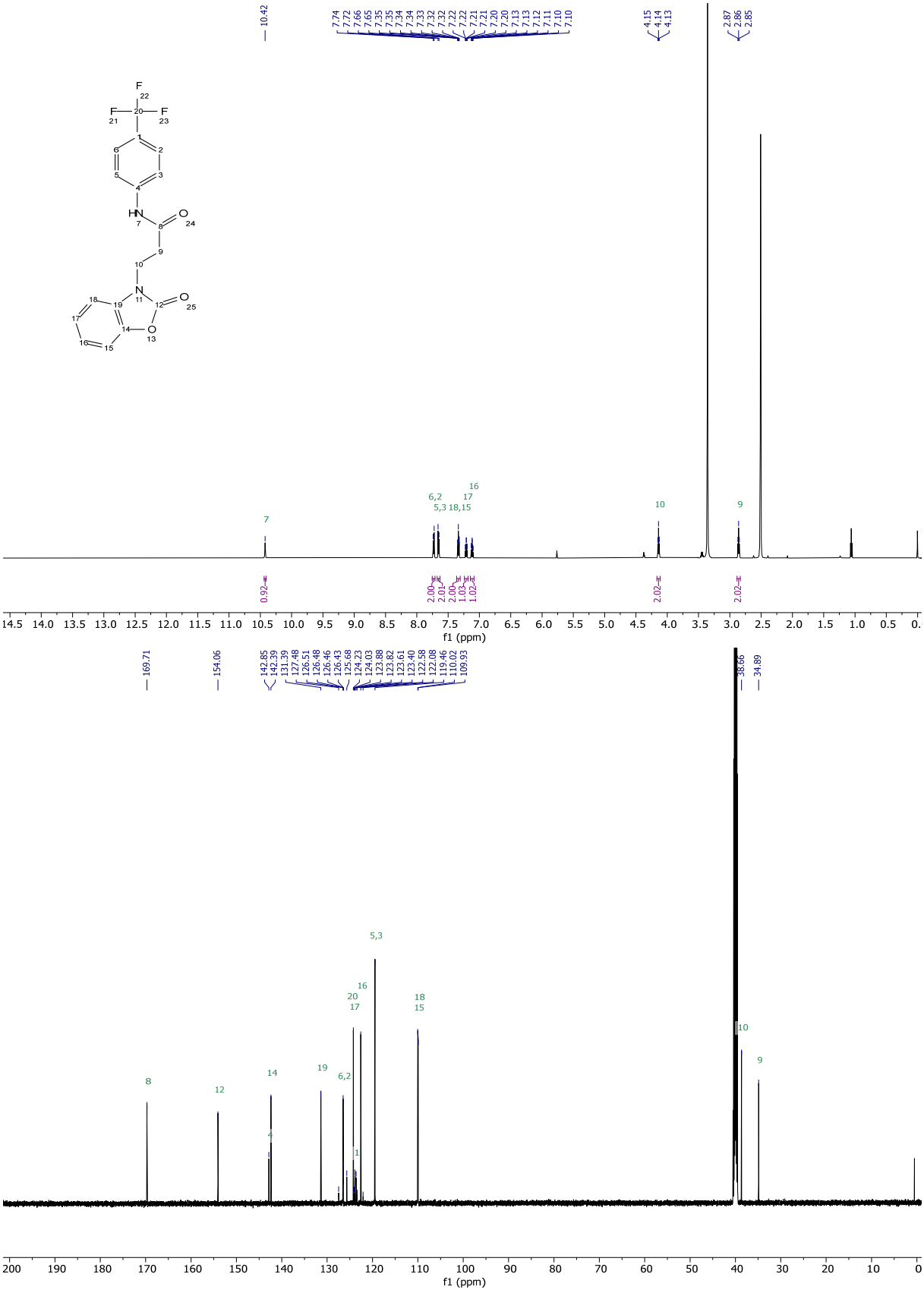
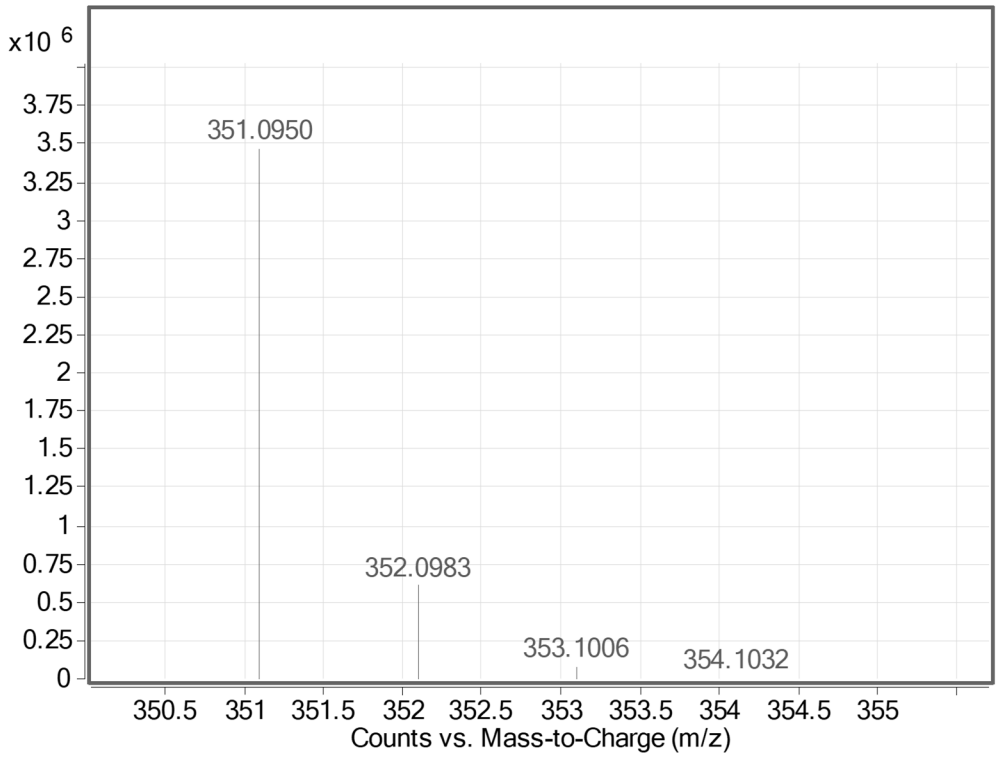
370
370.5
371
Counts vs. Mass-to-Charge (m/z)

3-(2-oxobenzo[*d*]oxazol-3(2*H*)-yl)-*N*-(4-(trifluoromethyl)phenyl)propanamide (3)

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354.1032
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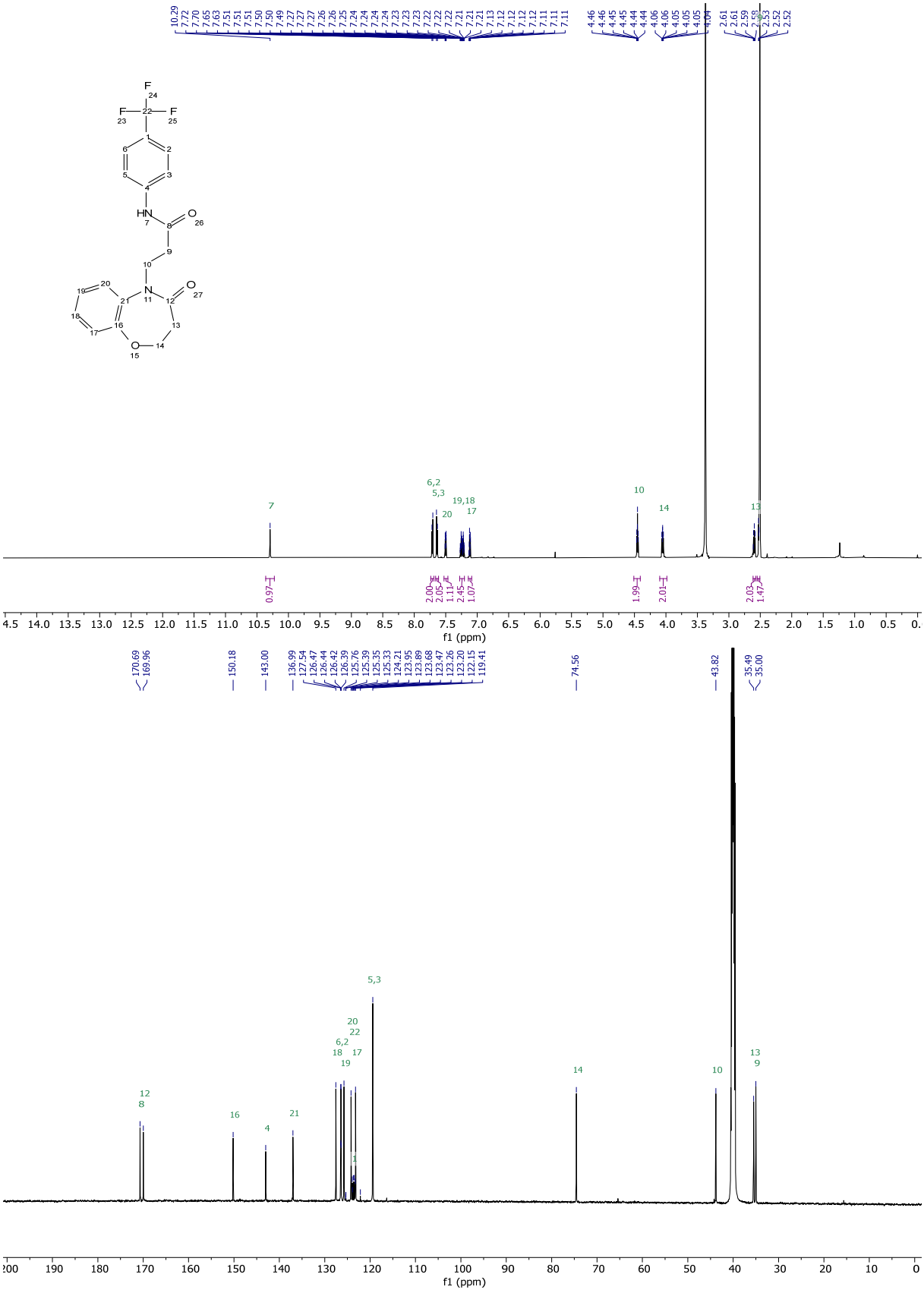
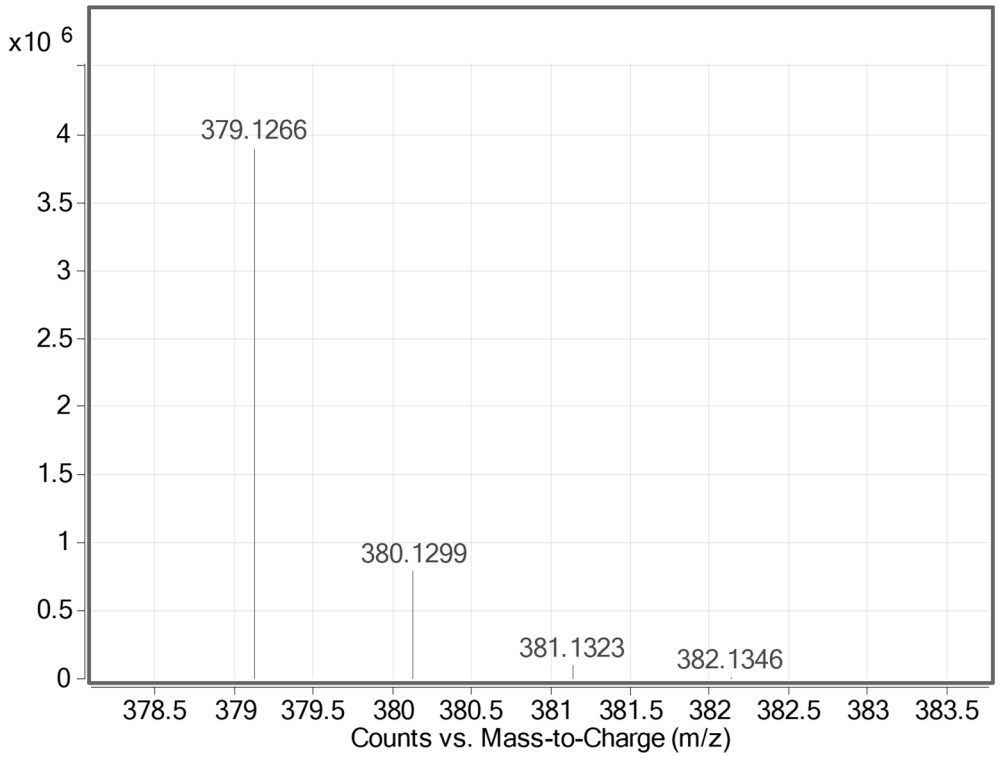
351
351.5
352
352.5
353
353.5
354
354.5
355
Counts vs. Mass-to-Charge (m/z)

3-(4-oxo-3,4-dihydrobenzo[b][1,4]oxazepin-5(2*H*)-yl)-*N*-(4-(trifluoromethyl)phenyl)propanamide (4)

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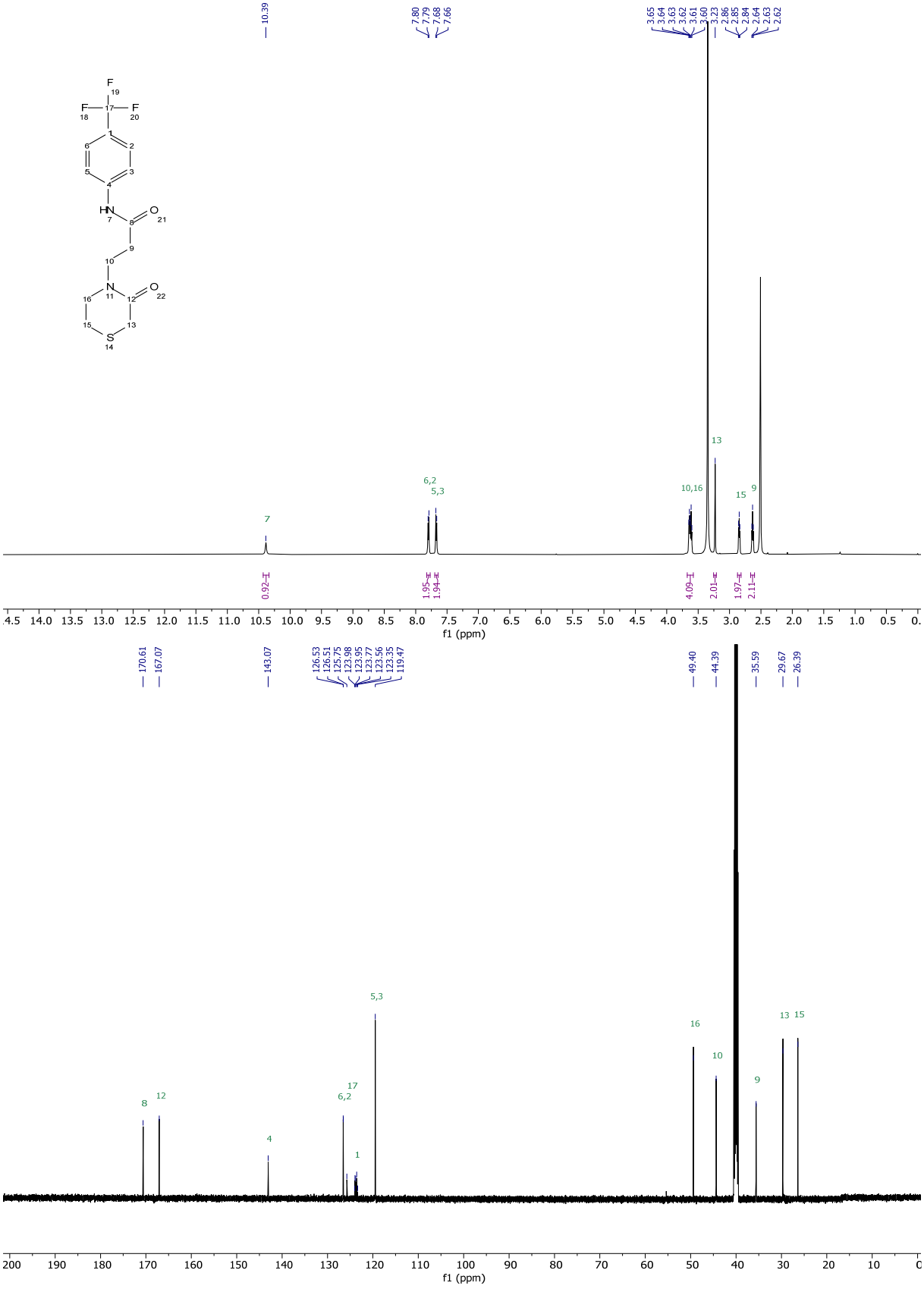
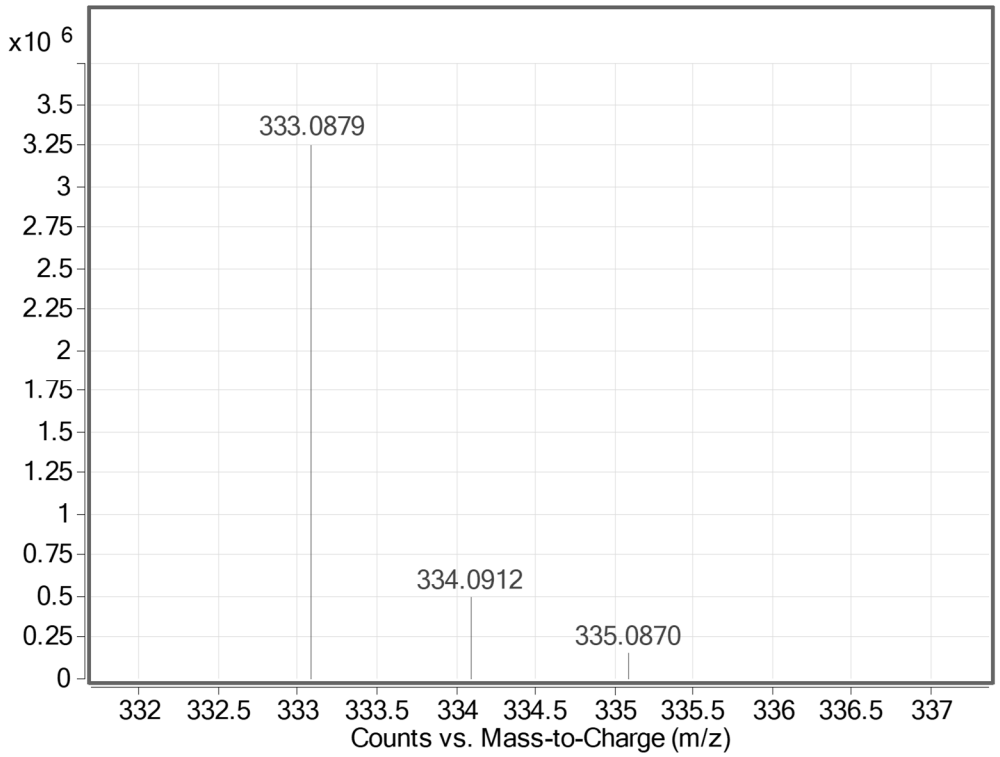
378.5
379
379.5
380
380.5
381
381.5
382
382.5
383
383.5
Counts vs. Mass-to-Charge (m/z)

3-(3-oxothiomorpholino)-*N*-(4-(trifluoromethyl)phenyl)propanamide (5)

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334.0912
335.0870
332
332.5
333
333.5
334
334.5
335
335.5
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336.5
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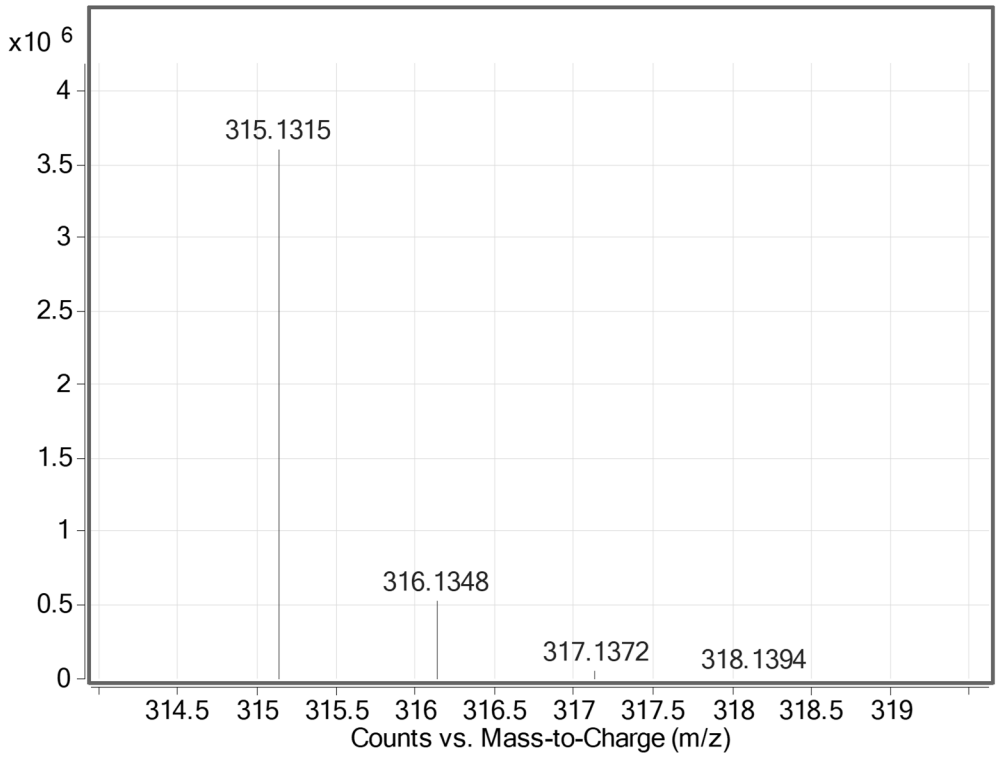
Counts vs. Mass-to-Charge (m/z)

3-(2-oxopiperidin-1-yl)-*N*-(4-(trifluoromethyl)phenyl)propanamide (6)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315.5
316
316.5
317
317.5
318
318.5
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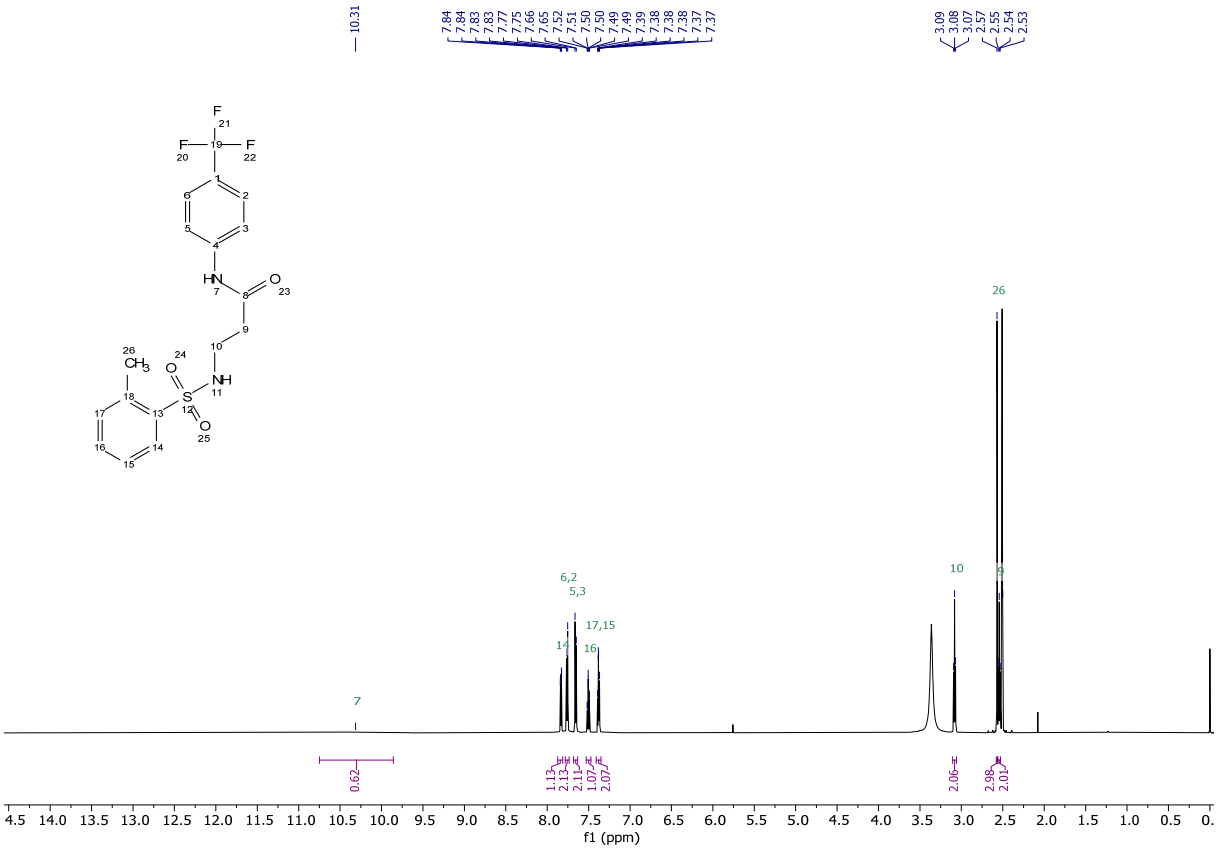
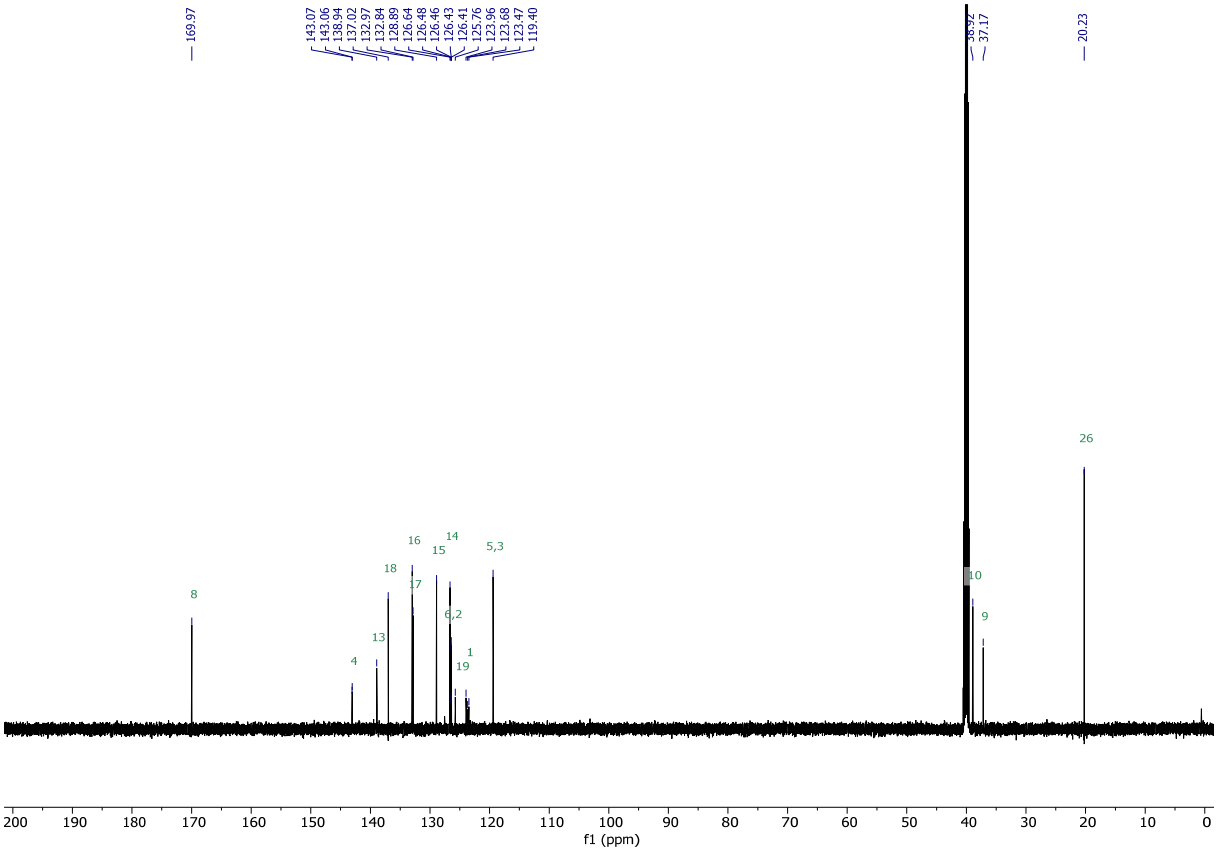
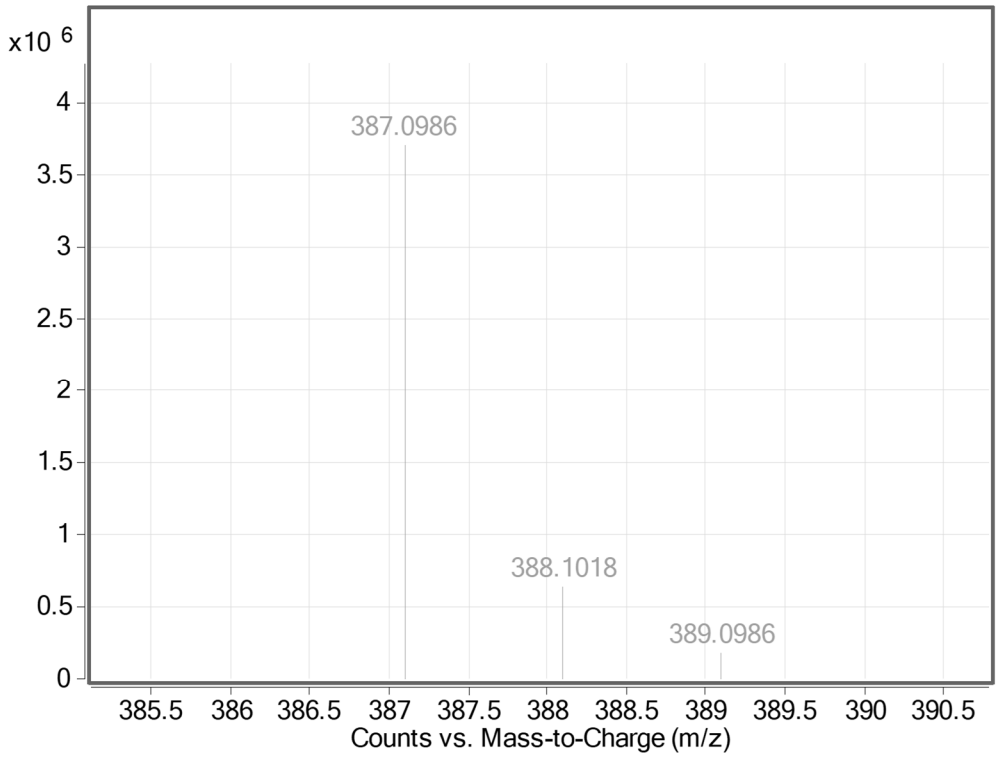
Counts vs. Mass-to-Charge (m/z)

3-((2-methylphenyl)sulfonamido)-*N*-(4-(trifluoromethyl)phenyl)propanamide (7)



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387.5
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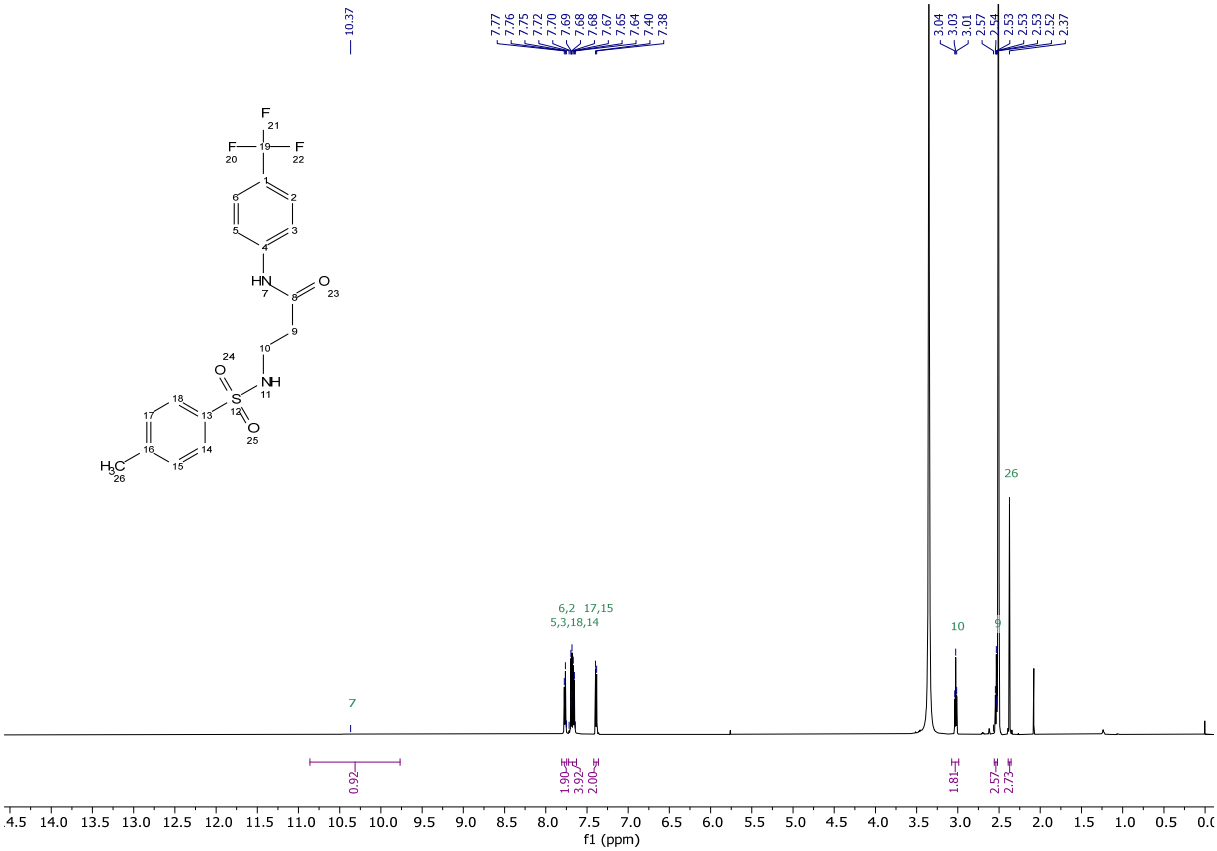
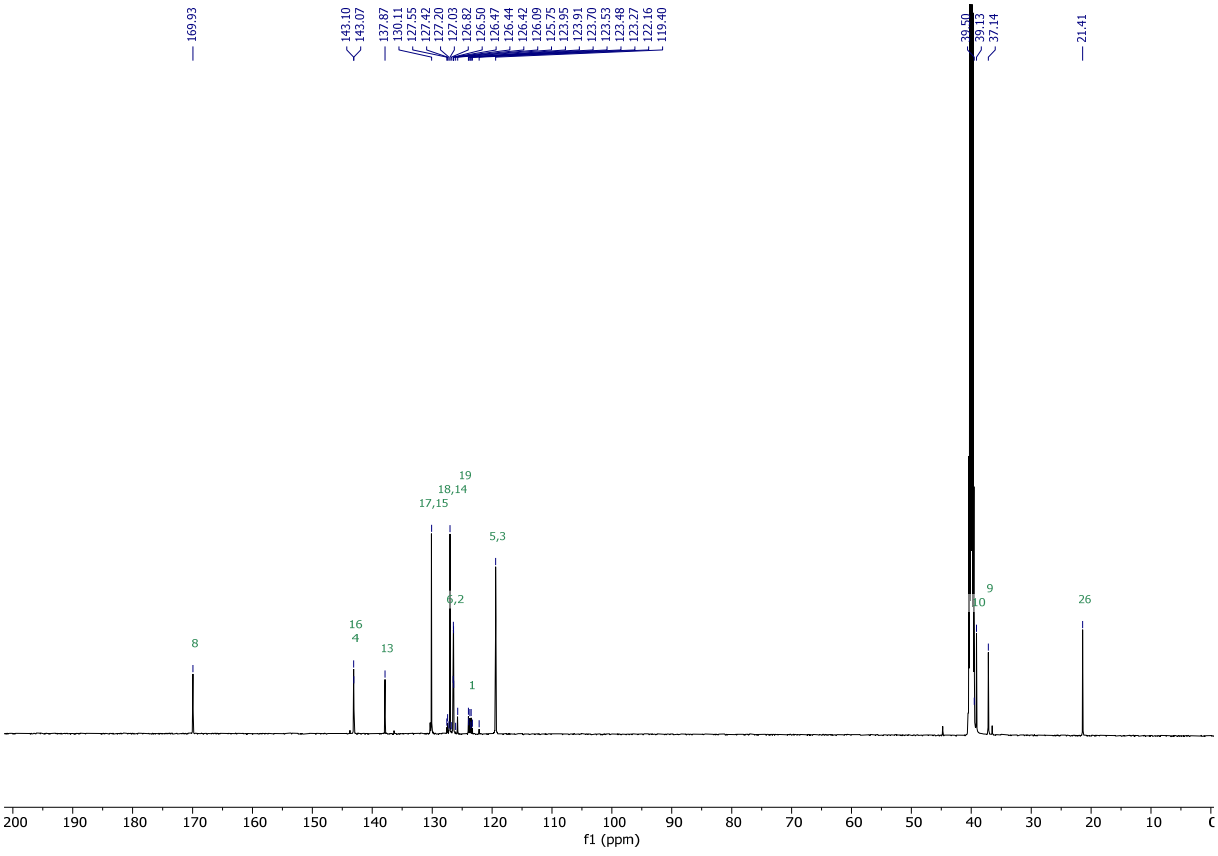
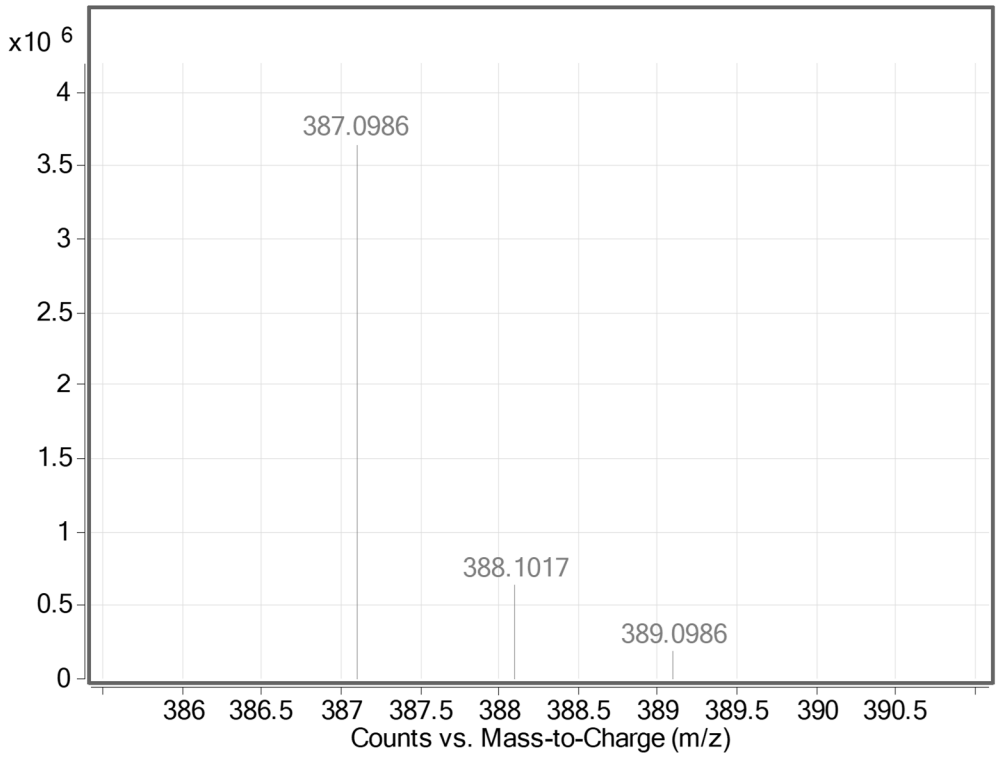
Counts vs. Mass-to-Charge (m/z)

3-((4-methylphenyl)sulfonamido)-*N*-(4-(trifluoromethyl)phenyl)propanamide (8)



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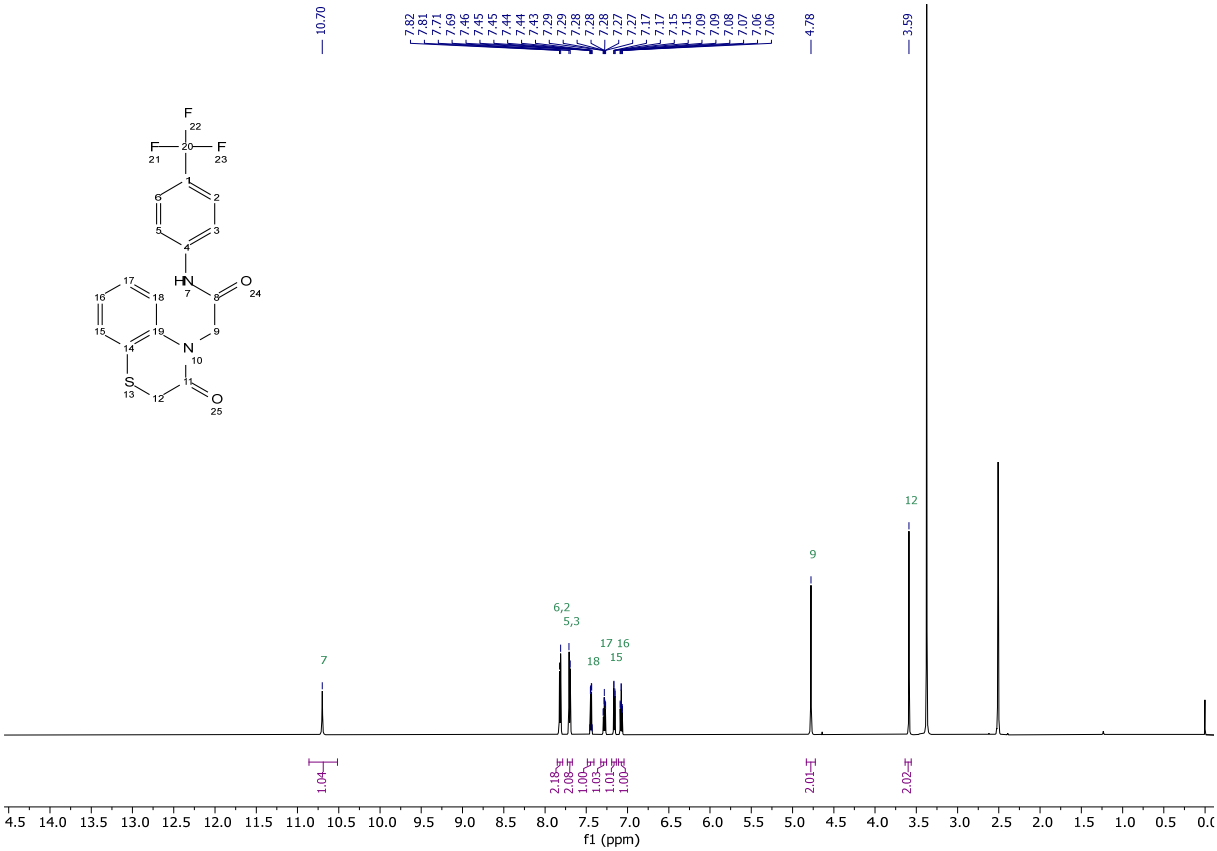
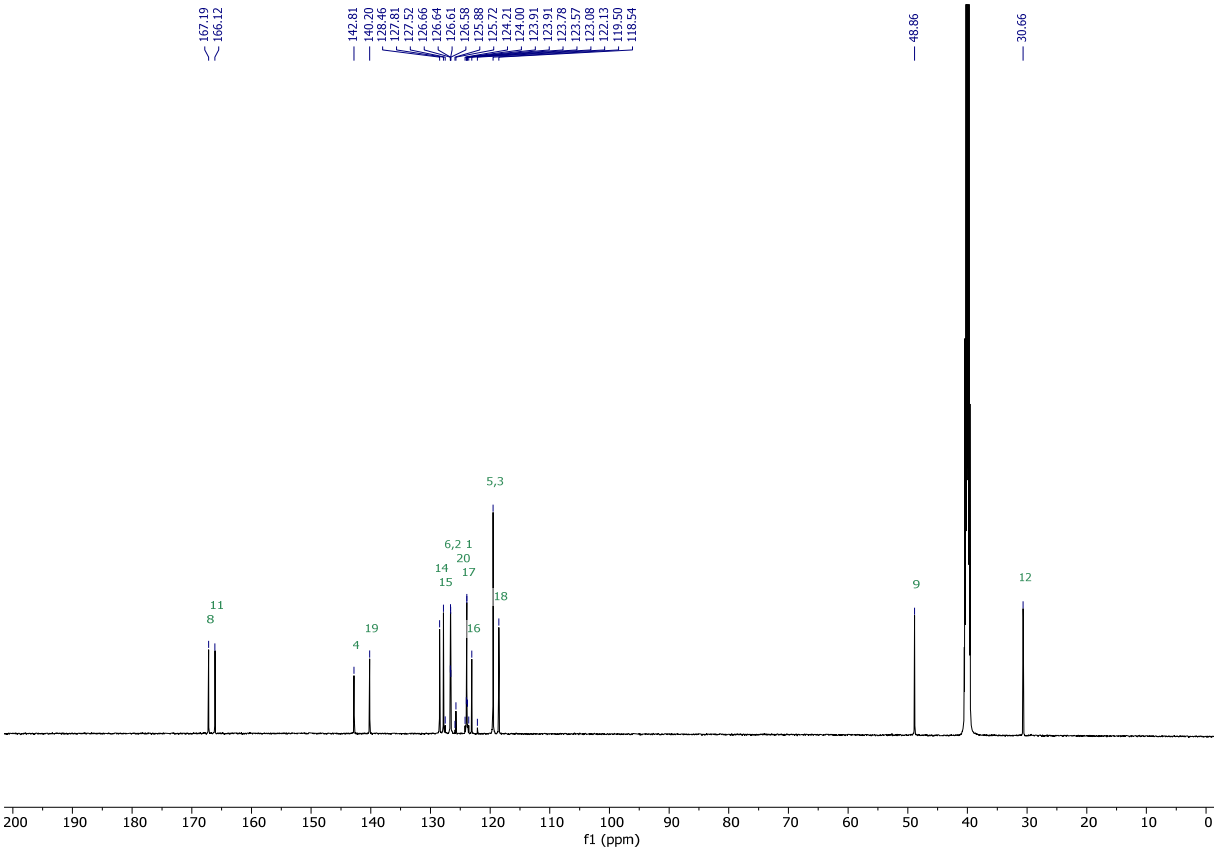
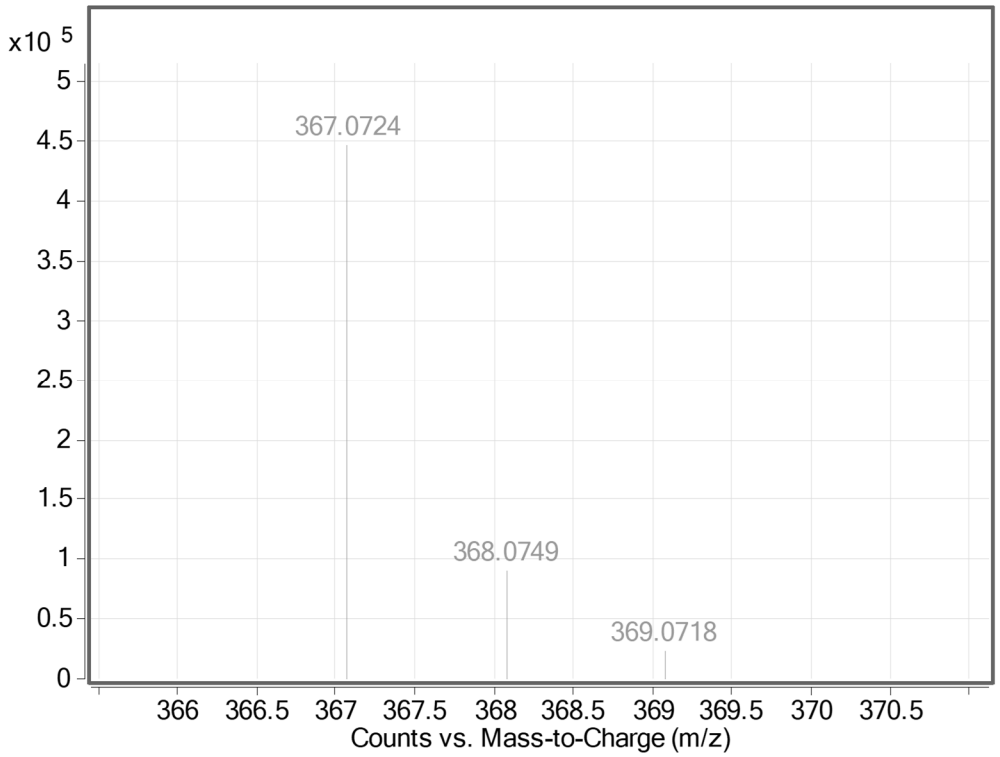
387
387.5
388
388.5
389
389.5
390
390.5
Counts vs. Mass-to-Charge (m/z)

2-(3-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4]thiazin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)acetamide (9)



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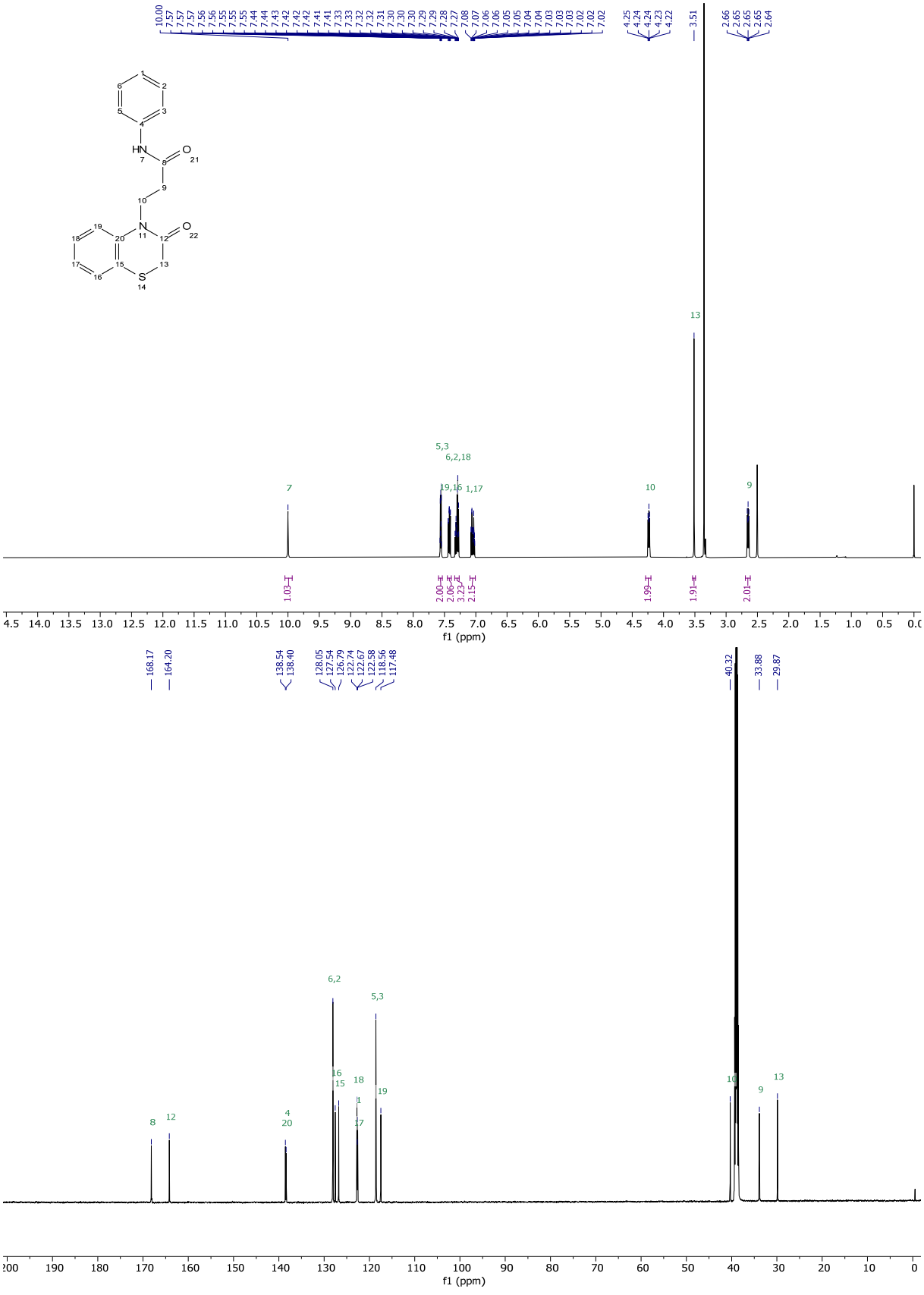
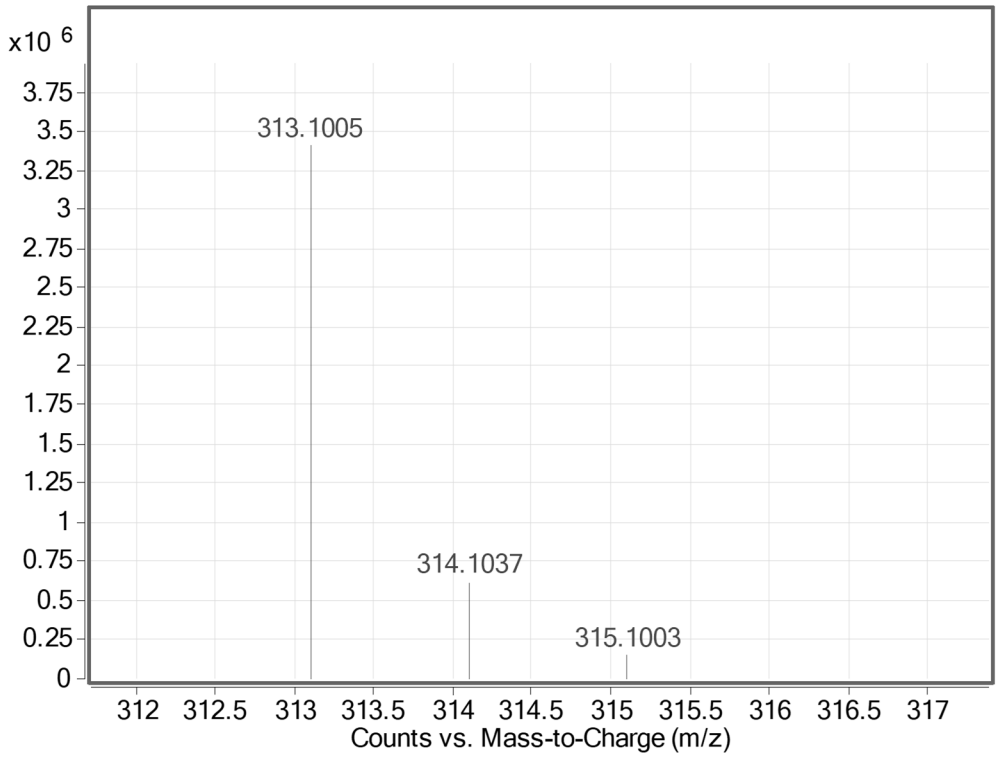
366
366.5
367
367.5
368
368.5
369
369.5
370
370.5
Counts vs. Mass-to-Charge (m/z)

3-(3-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4]thiazin-4-yl)-*N*-phenylpropanamide (10)

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312.5
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313.5
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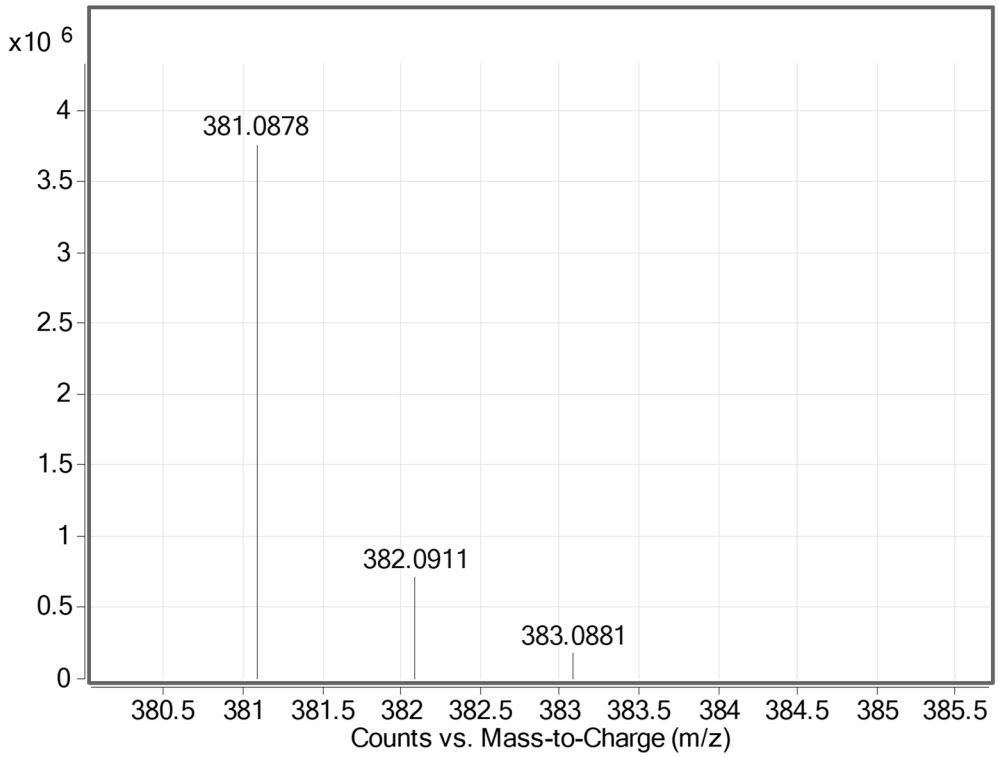
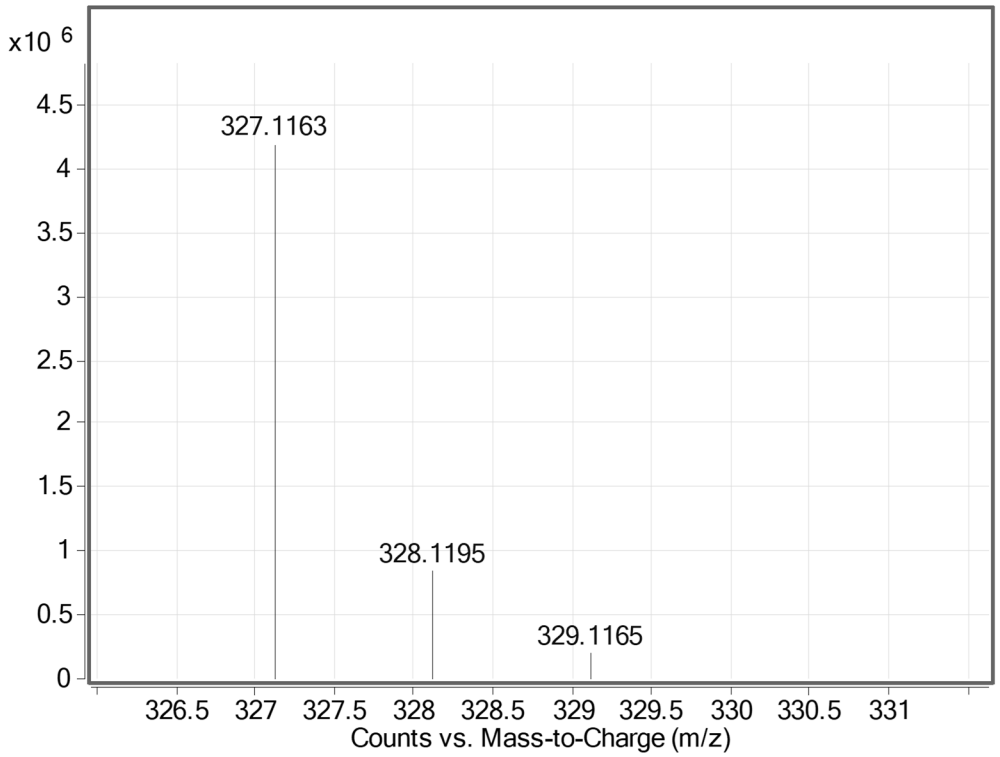
314.5
315
315.5
316
316.5
317
Counts vs. Mass-to-Charge (m/z)

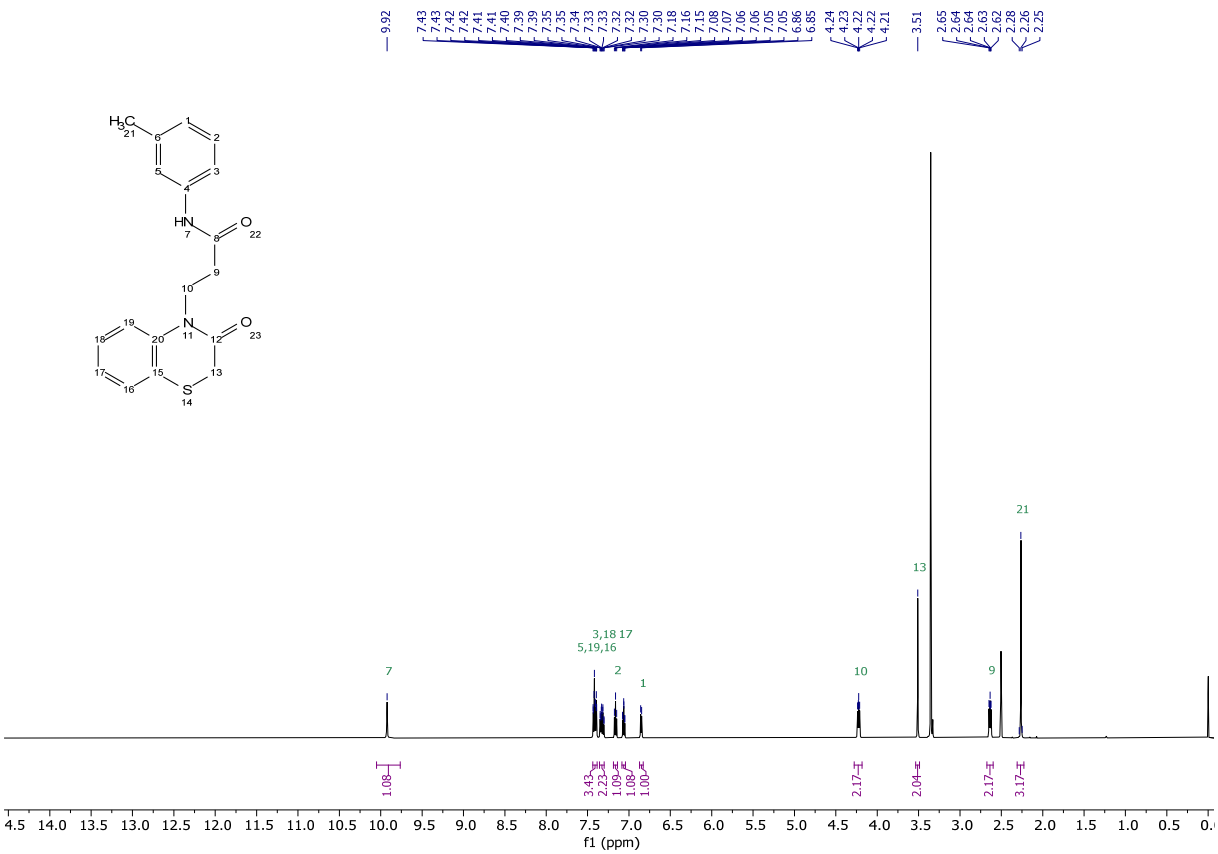
3-(3-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4]thiazin-4-yl)-*N*-(2-(trifluoromethyl)phenyl)propanamide (11)

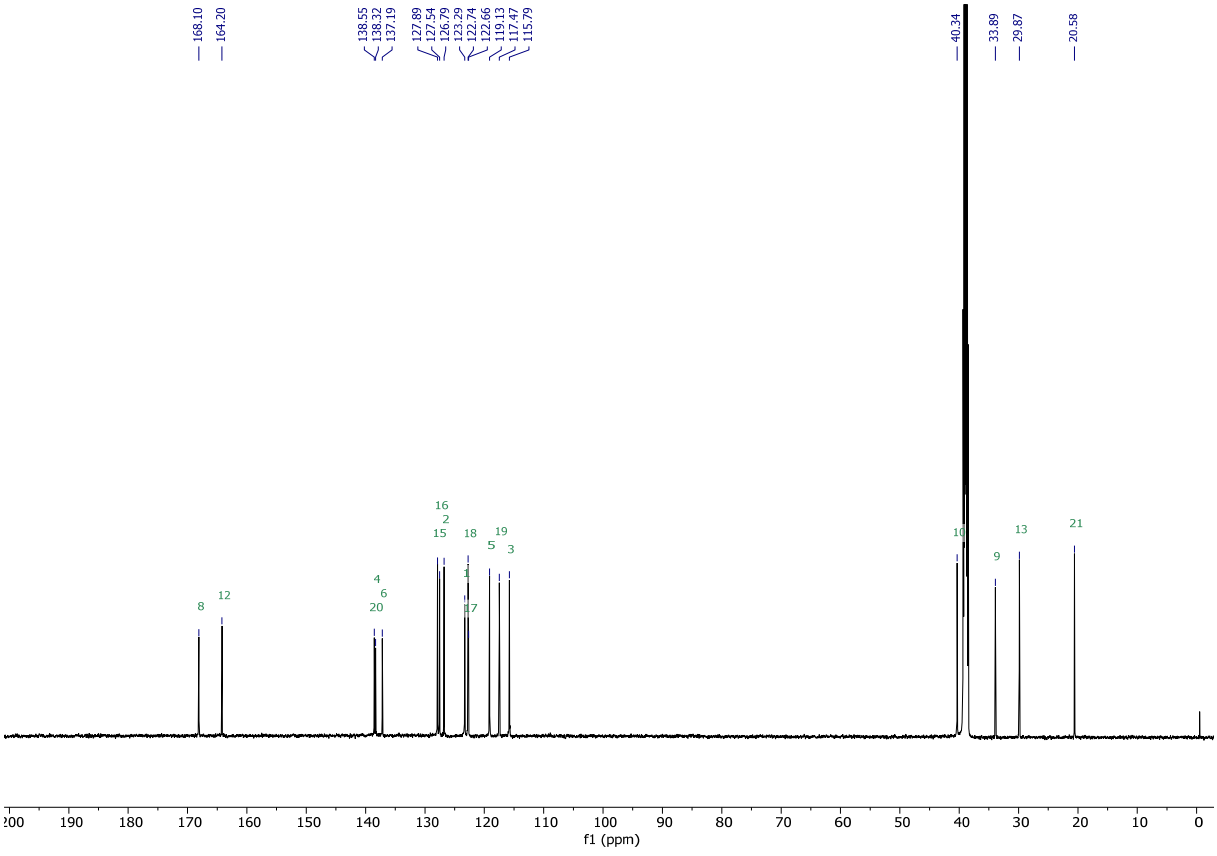

x10 6
4
3.5
3
2.5
2
1.5
1
0.5
0
381.0878
382.0911
383.0881
380.5
381
381.5
382
382.5
383
383.5
384
384.5
385
385.5
Counts vs. Mass-to-Charge (m/z)

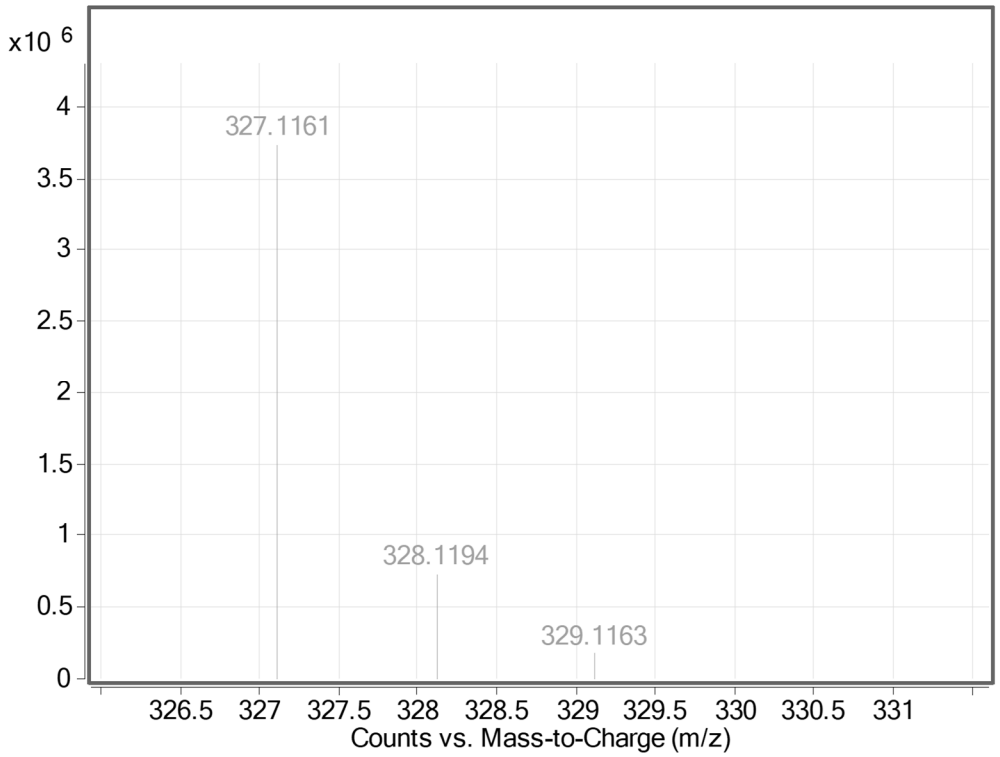
3-(3-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4]thiazin-4-yl)-*N*-(*o*-tolyl)propanamide (12)


x10 6
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
327.1163
328.1195
329.1165
326.5
327
327.5
328
328.5
329
329.5
330
330.5
331
Counts vs. Mass-to-Charge (m/z)

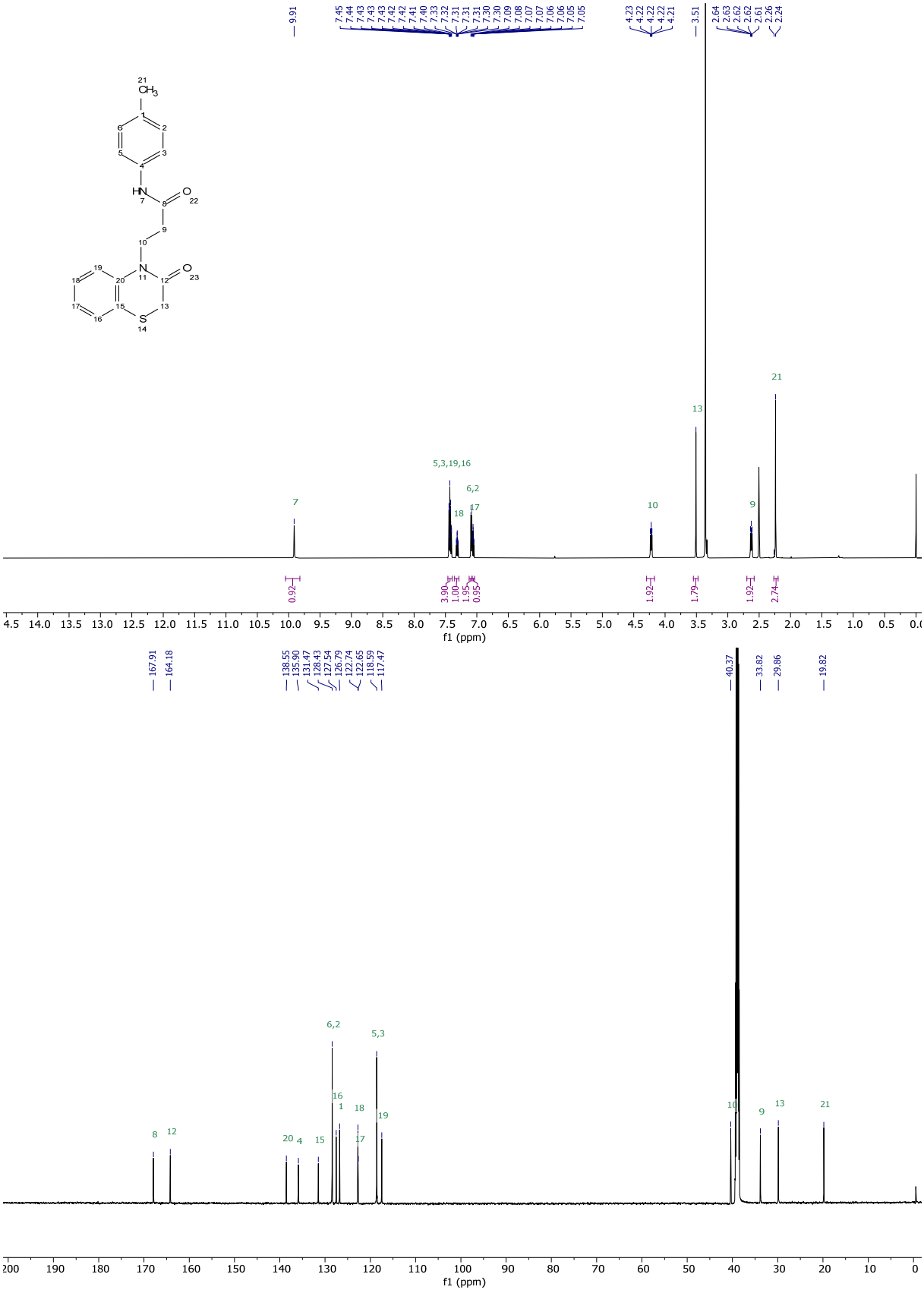
3-(3-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4]thiazin-4-yl)-*N*-(*m*-tolyl)propanamide (13)

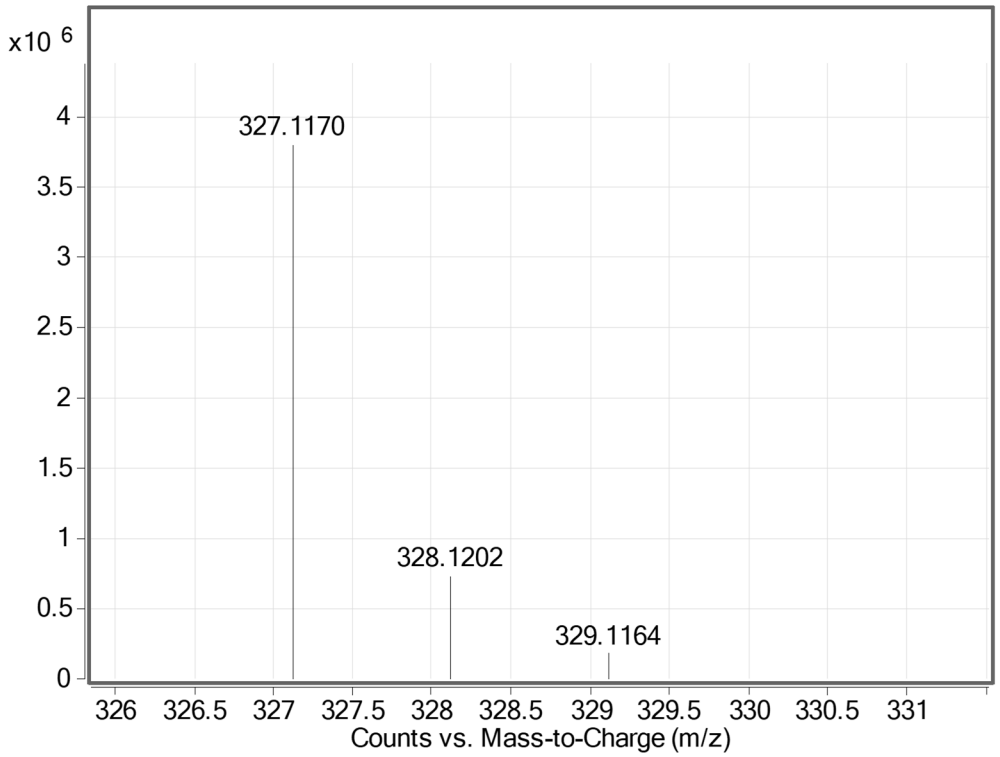




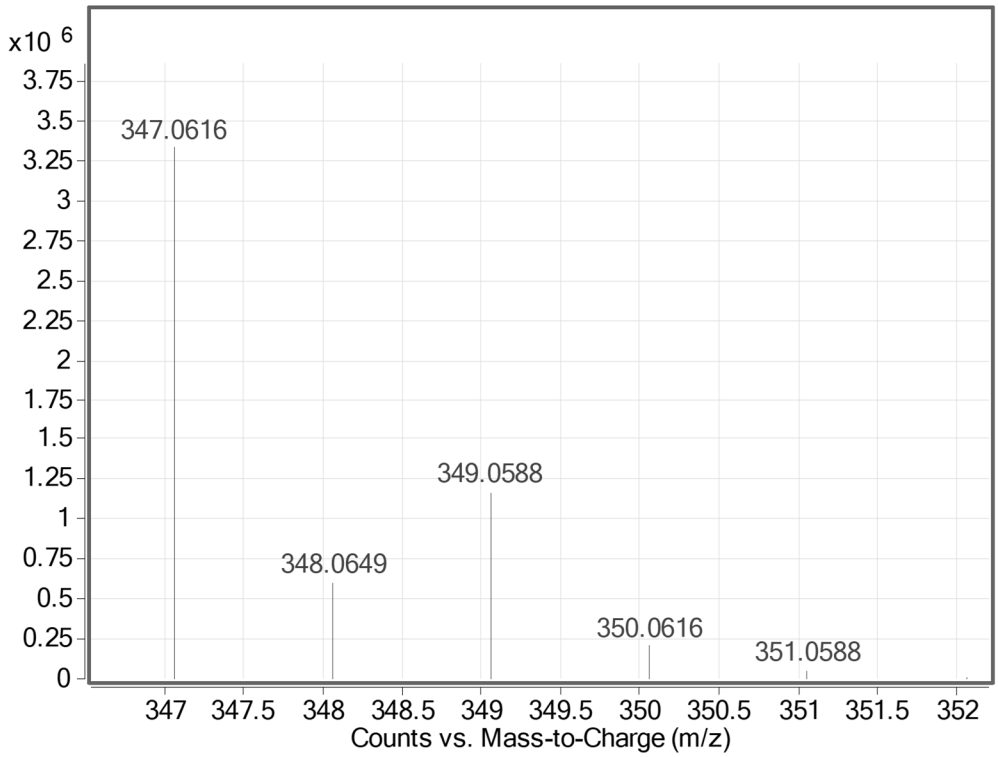

x10 6
4
3.5
3
2.5
2
1.5
1
0.5
0
327.1161
328.1194
329.1163
326.5
327
327.5
328
328.5
329
329.5
330
330.5
331
Counts vs. Mass-to-Charge (m/z)

3-(3-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4]thiazin-4-yl)-*N*-(*p*-tolyl)propanamide (14)

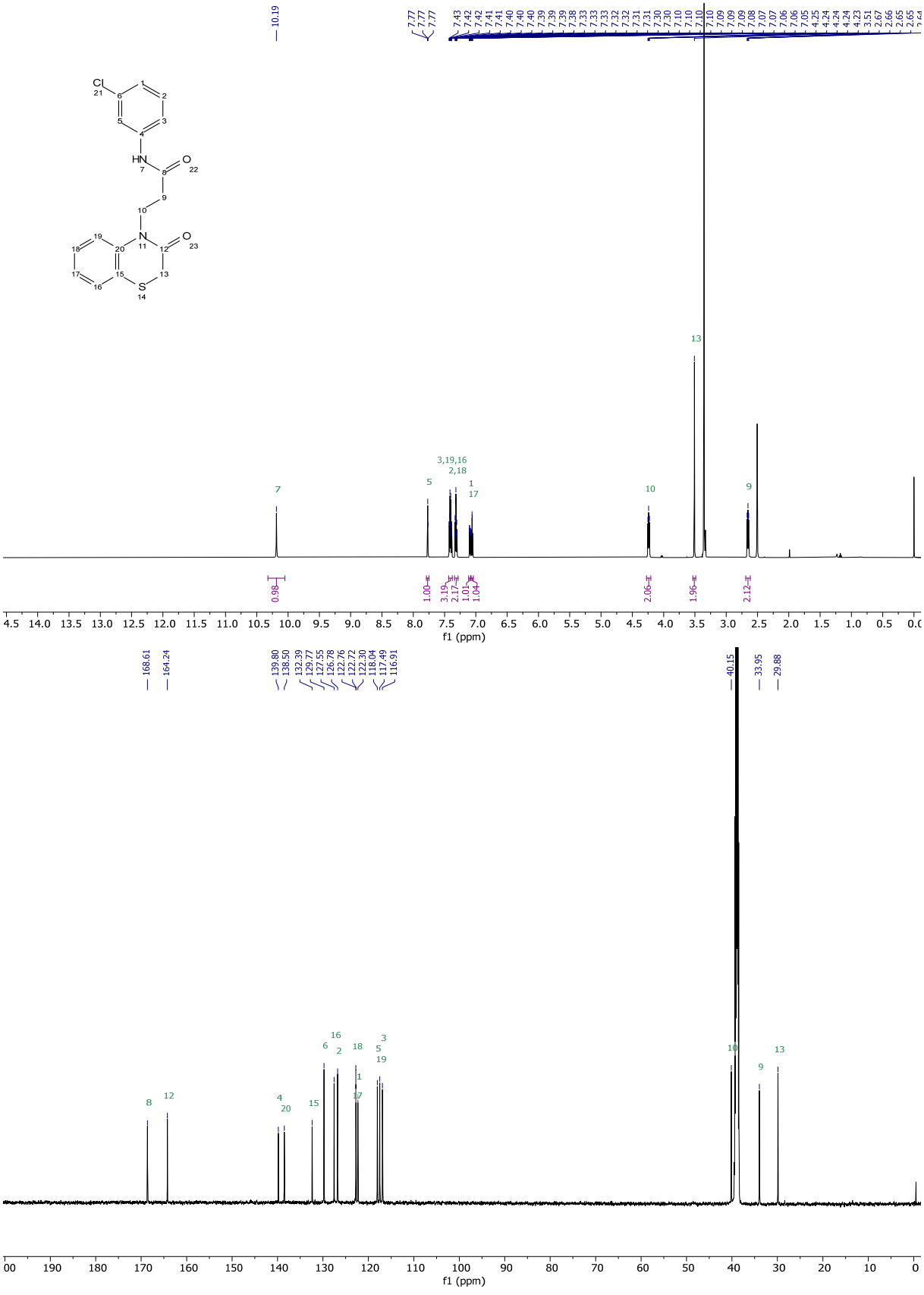


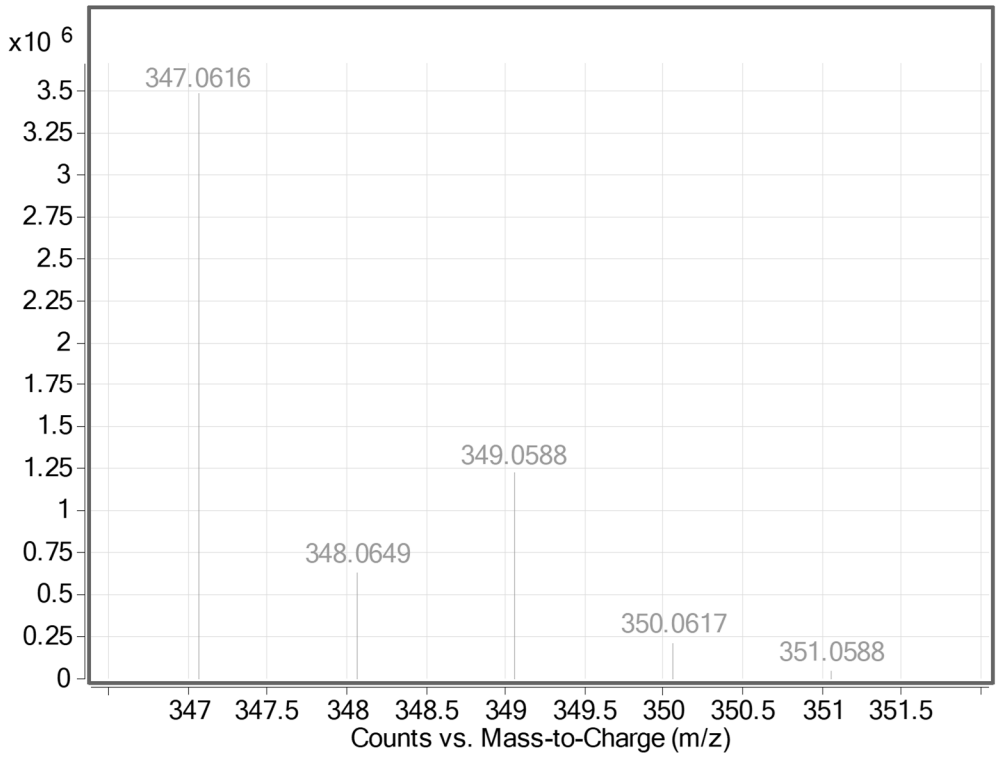

x10 6
4
3.5
3
2.5
2
1.5
1
0.5
0
327.1170
328.1202
329.1164
326
326.5
327
327.5
328
328.5
329
329.5
330
330.5
331
Counts vs. Mass-to-Charge (m/z)

_N_-(2-chlorophenyl)-3-(3-oxo-2,3-dihydro-4_H_-benzo[_b_][1,4]thiazin-4-yl)propanamide (15)

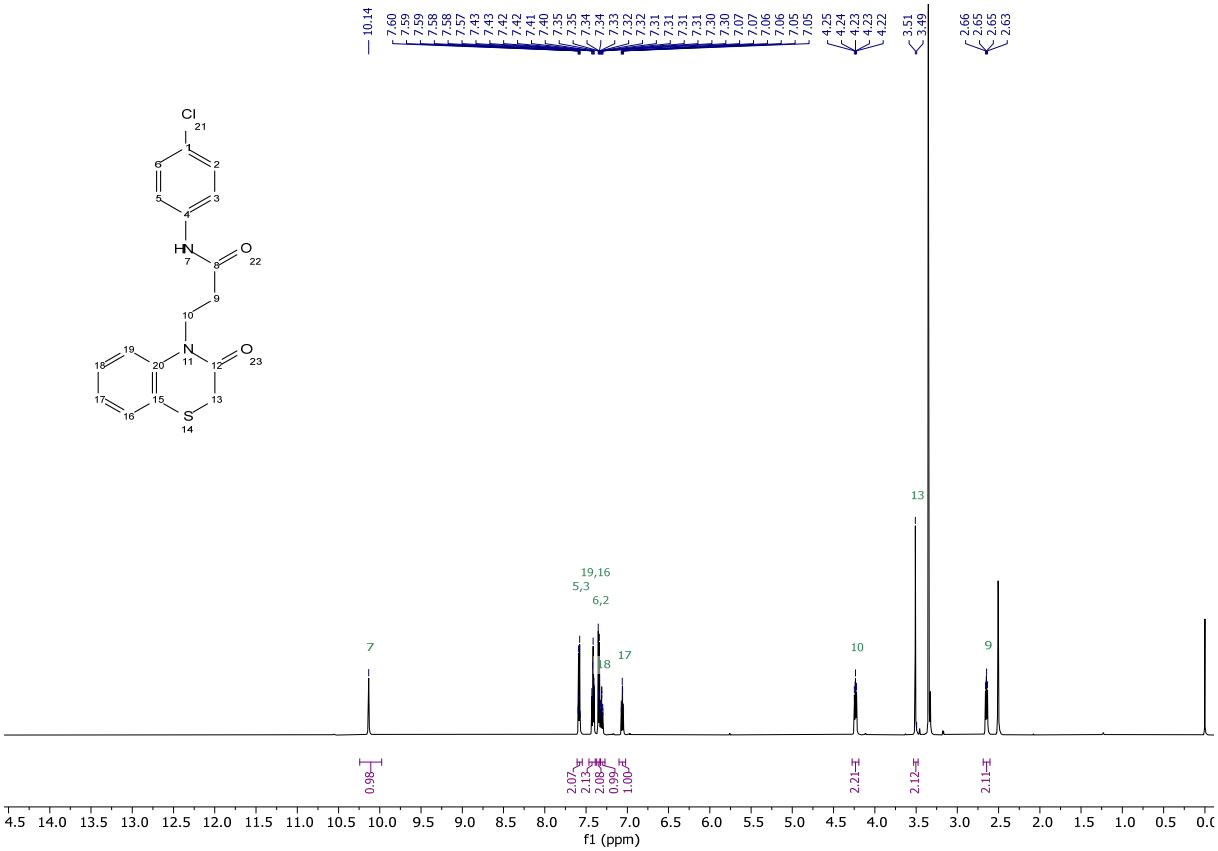

x10 6
3.75
3.5
3.25
3
2.75
2.5
2.25
2
1.75
1.5
1.25
1
0.75
0.5
0.25
0
347.0616
348.0649
349.0588
350.0616
351.0588
347
347.5
348
348.5
349
349.5
350
350.5
351
351.5
352
Counts vs. Mass-to-Charge (m/z)

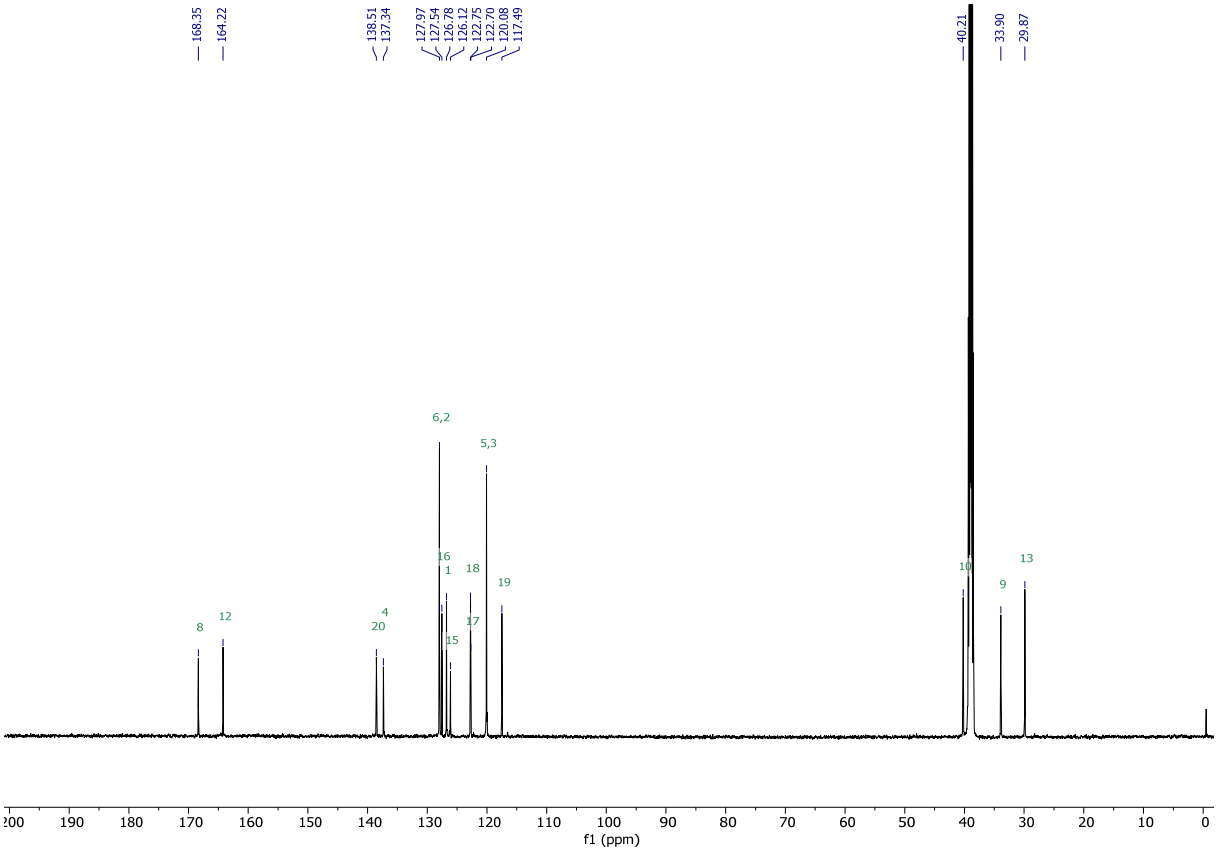
_N_-(3-chlorophenyl)-3-(3-oxo-2,3-dihydro-4_H_-benzo[_b_][1,4]thiazin-4-yl)propanamide (16)

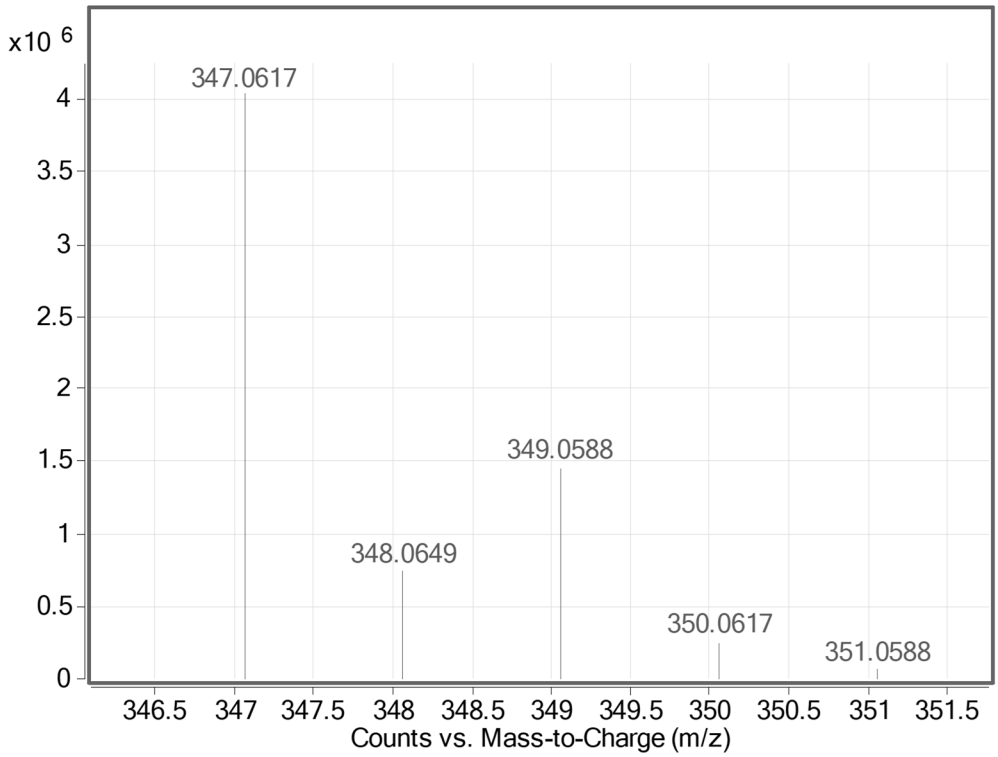



x10 6
3.5
3.25
3
2.75
2.5
2.25
2
1.75
1.5
1.25
1
0.75
0.5
0.25
0
347.0616
349.0588
348.0649
350.0617
351.0588
347
347.5
348
348.5
349
349.5
350
350.5
351
351.5
Counts vs. Mass-to-Charge (m/z)

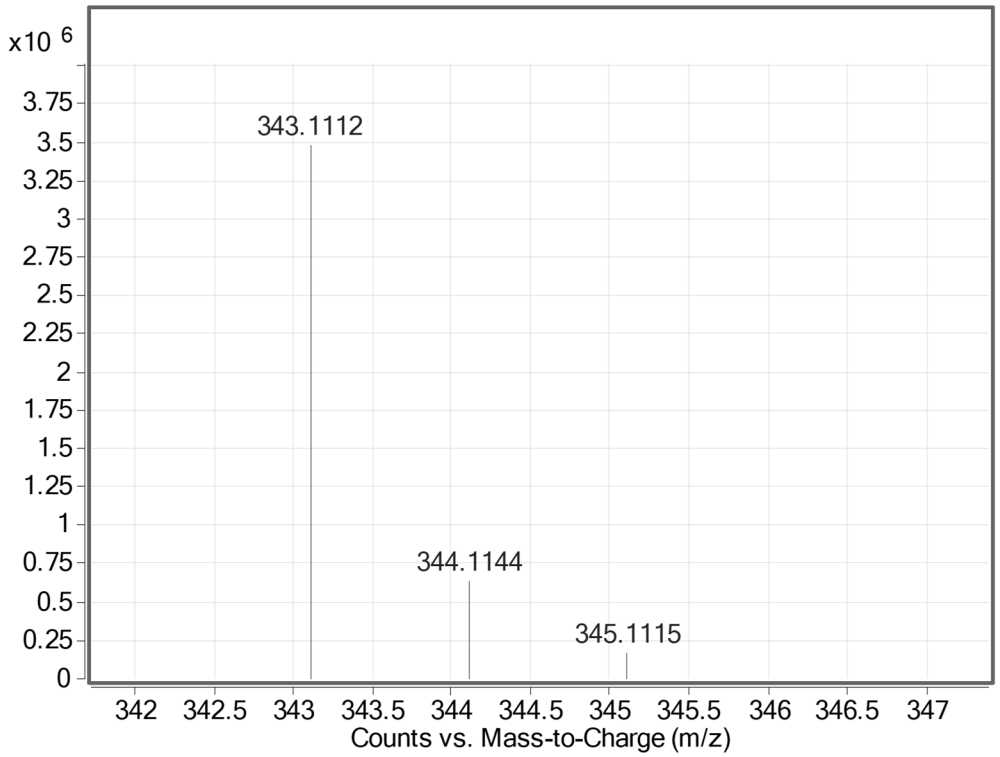
***N*-(4-chlorophenyl)-3-(3-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4]thiazin-4-yl)propanamide (17)**



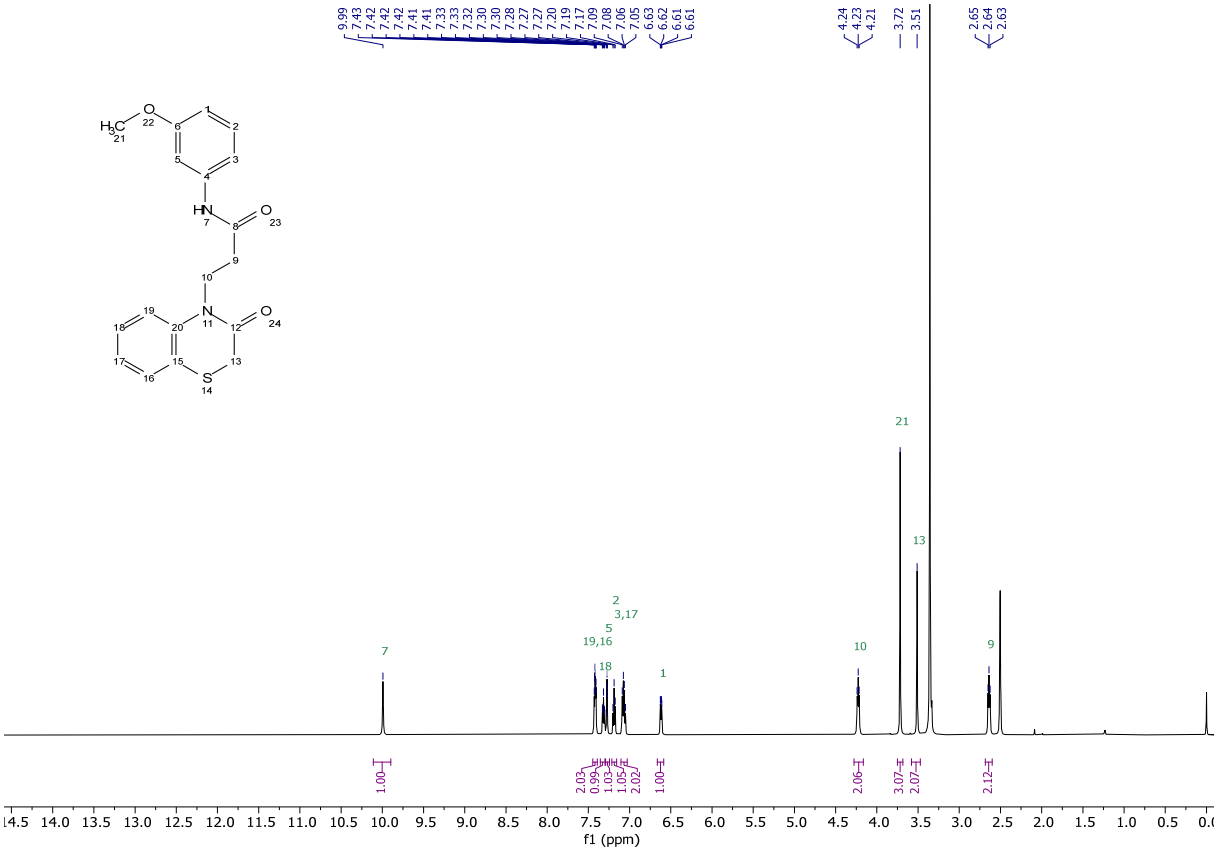


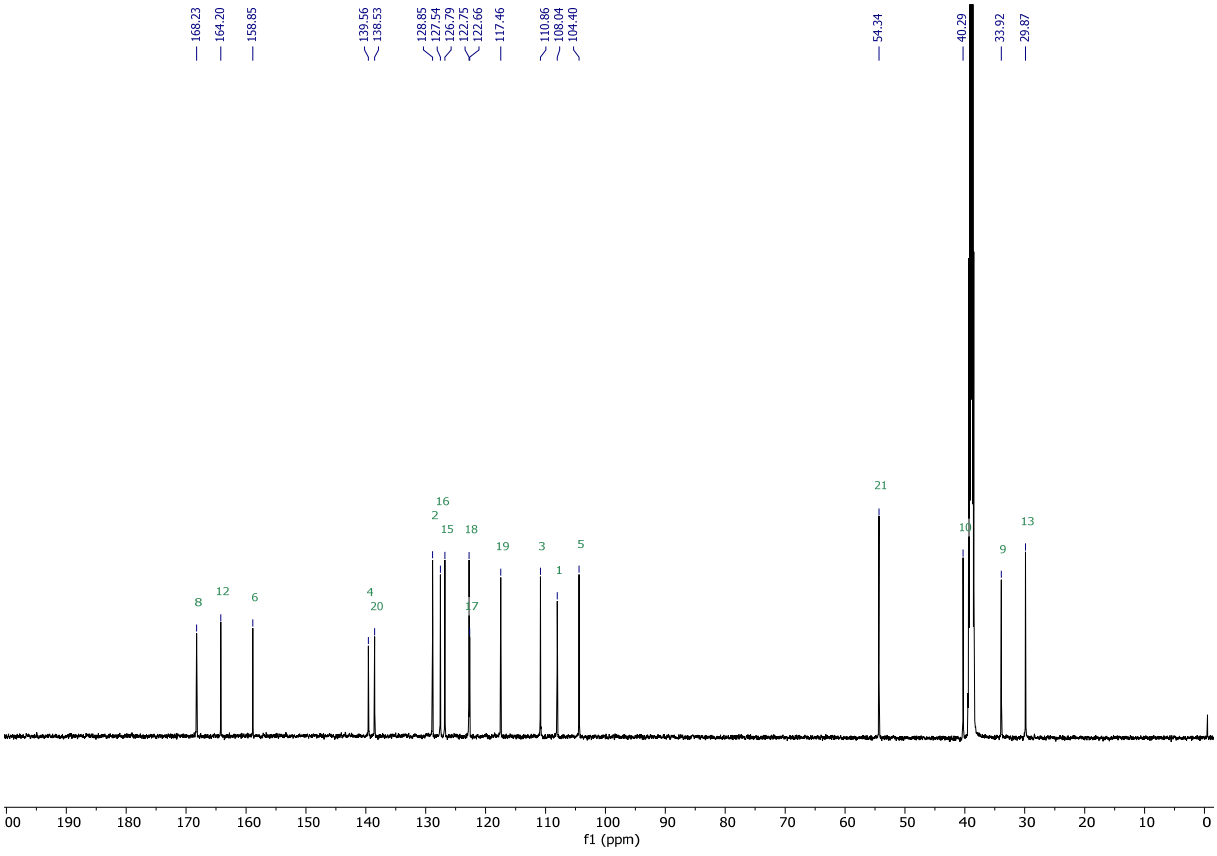

x10 6
4
3.5
3
2.5
2
1.5
1
0.5
0
347.0617
349.0588
348.0649
350.0617
351.0588
346.5
347
347.5
348
348.5
349
349.5
350
350.5
351
351.5
Counts vs. Mass-to-Charge (m/z)

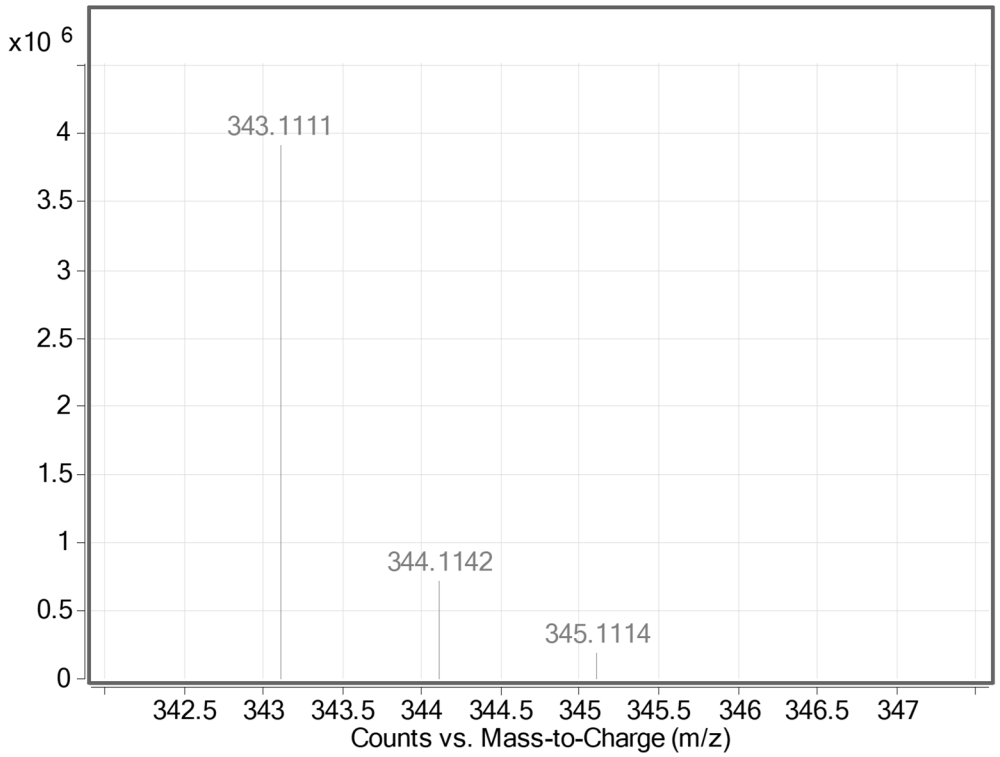
_N_-(2-methoxyphenyl)-3-(3-oxo-2,3-dihydro-4_H_-benzo[_b_][1,4]thiazin-4-yl)propanamide (18)


x10 6
3.75
3.5
3.25
3
2.75
2.5
2.25
2
1.75
1.5
1.25
1
0.75
0.5
0.25
0
343.1112
344.1144
345.1115
342
342.5
343
343.5
344
344.5
345
345.5
346
346.5
347
Counts vs. Mass-to-Charge (m/z)

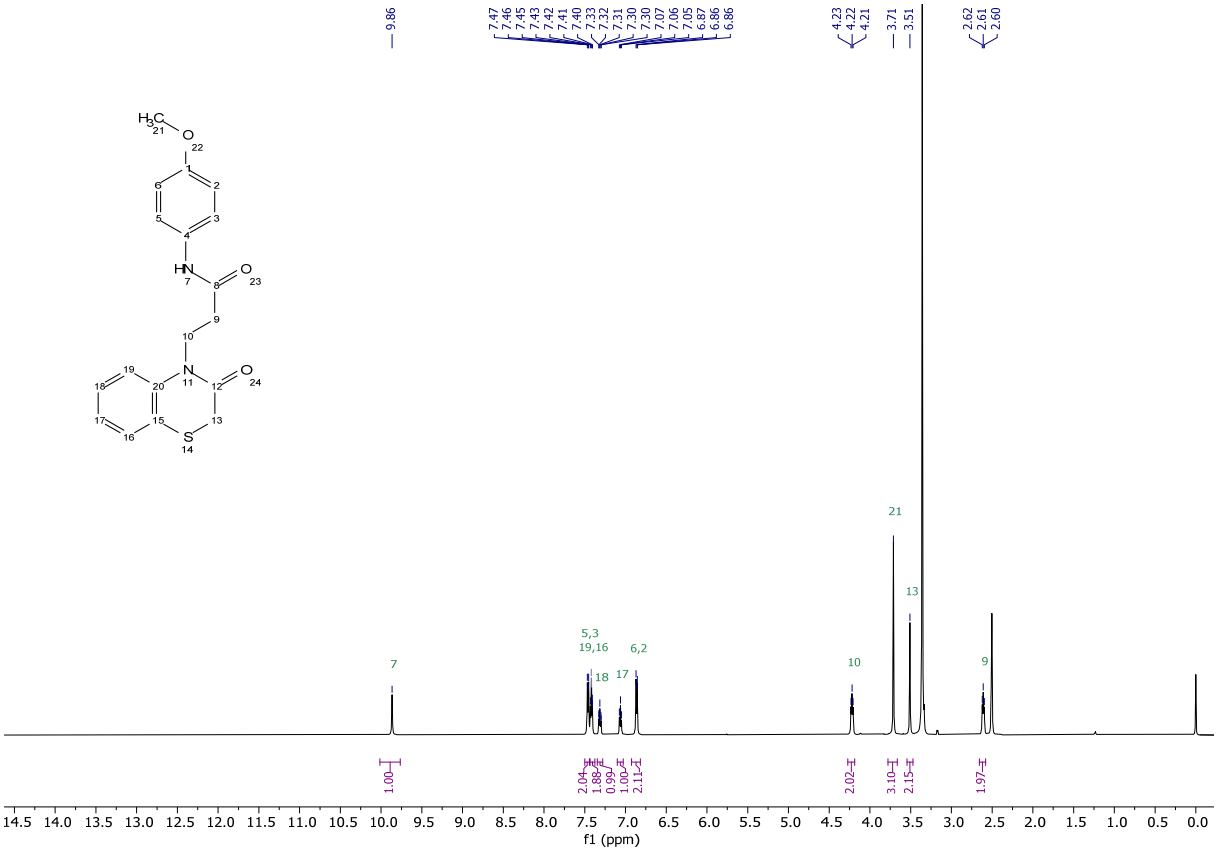
_N_-(3-methoxyphenyl)-3-(3-oxo-2,3-dihydro-4_H_-benzo[_b_][1,4]thiazin-4-yl)propanamide (19)

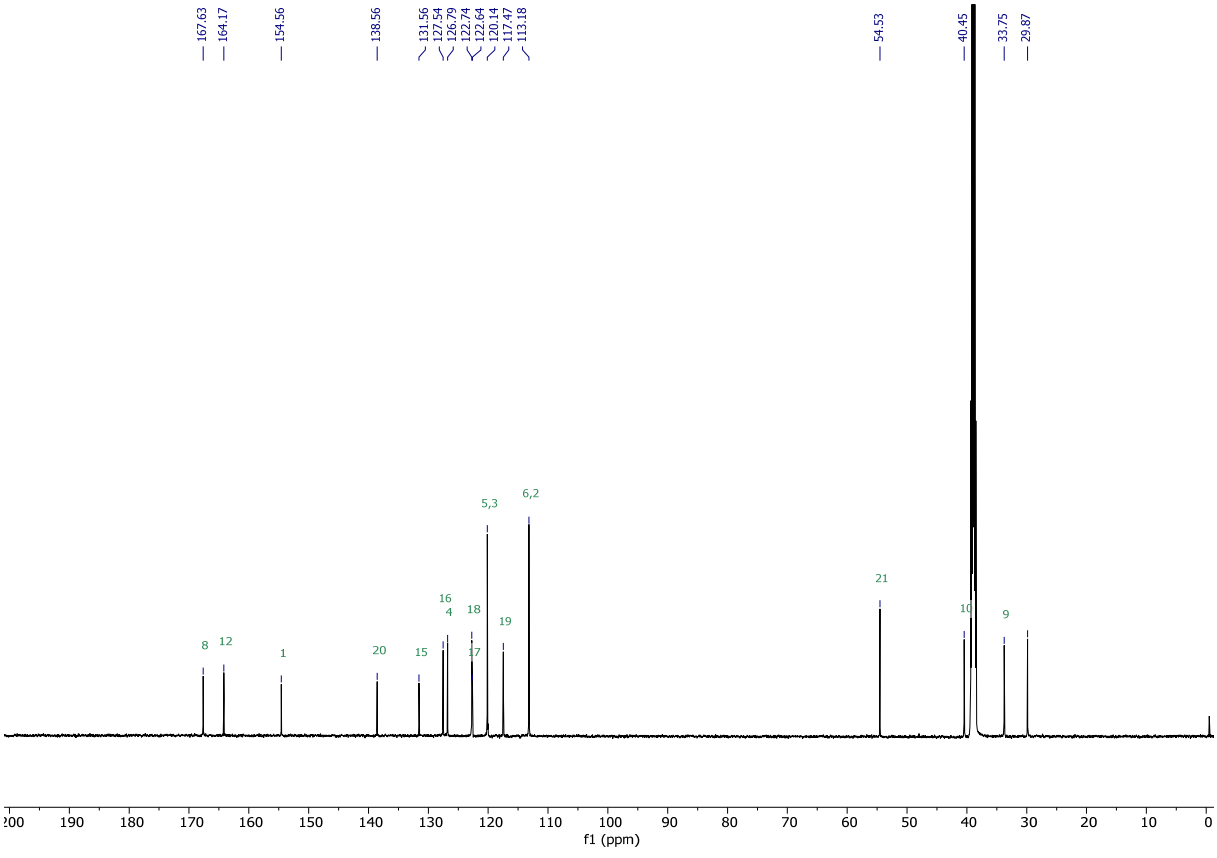


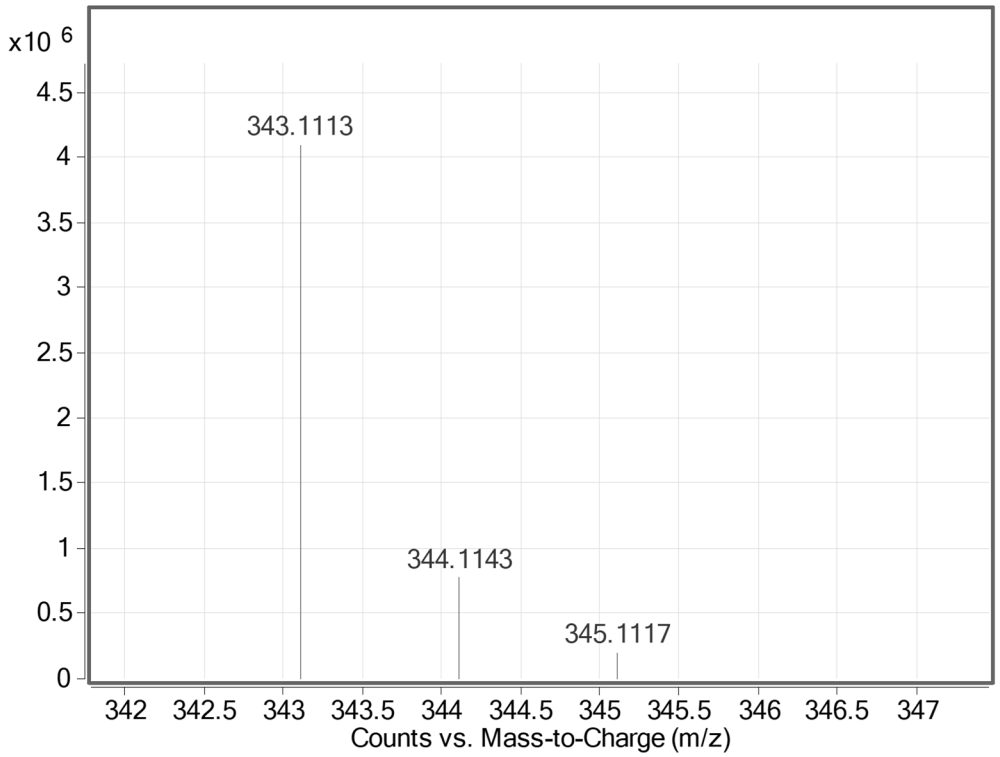



x10 6
4
3.5
3
2.5
2
1.5
1
0.5
0
343.1111
344.1142
345.1114
342.5
343
343.5
344
344.5
345
345.5
346
346.5
347
Counts vs. Mass-to-Charge (m/z)

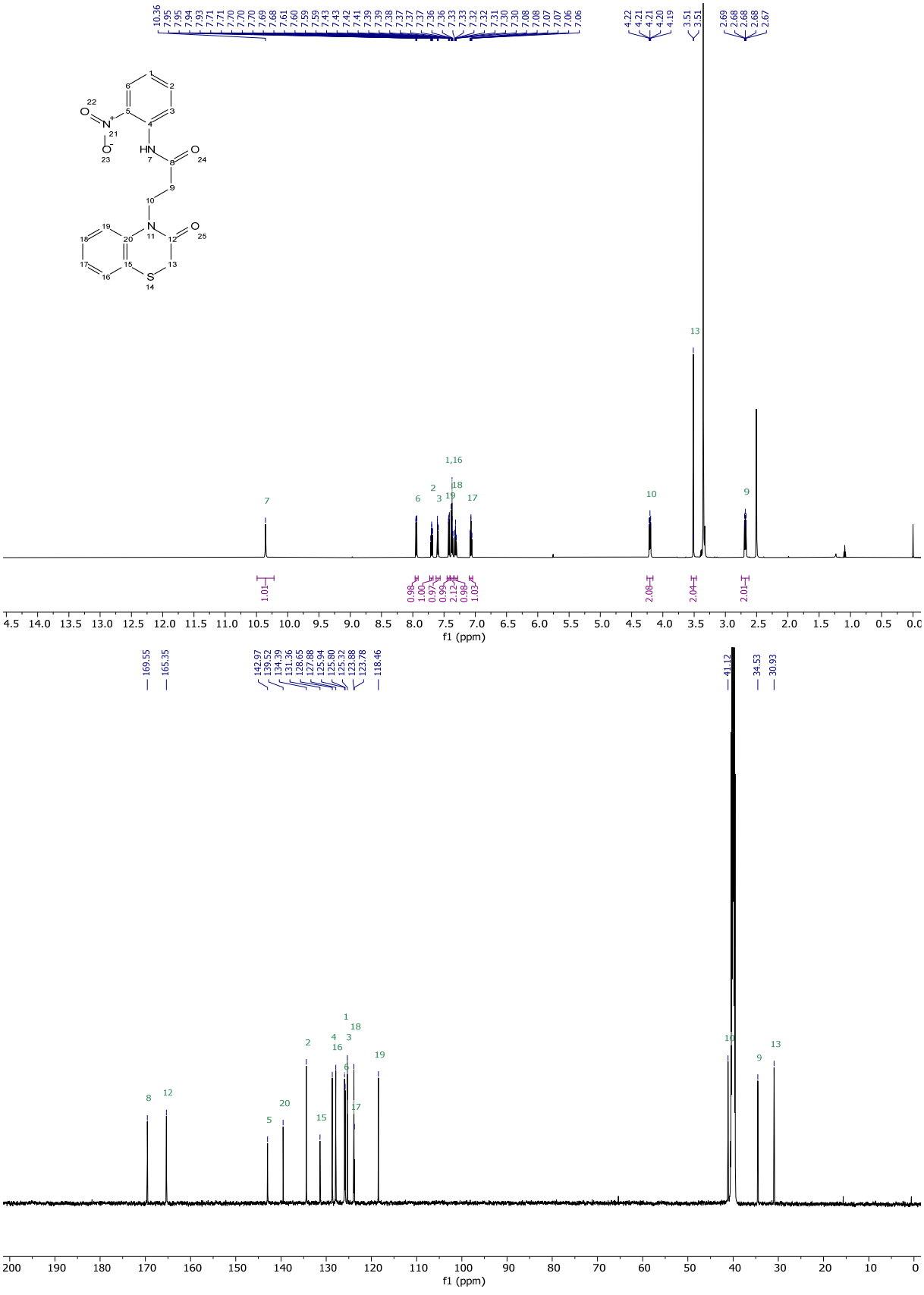
_N_-(4-methoxyphenyl)-3-(3-oxo-2,3-dihydro-4_H_-benzo[_b_][1,4]thiazin-4-yl)propanamide (20)

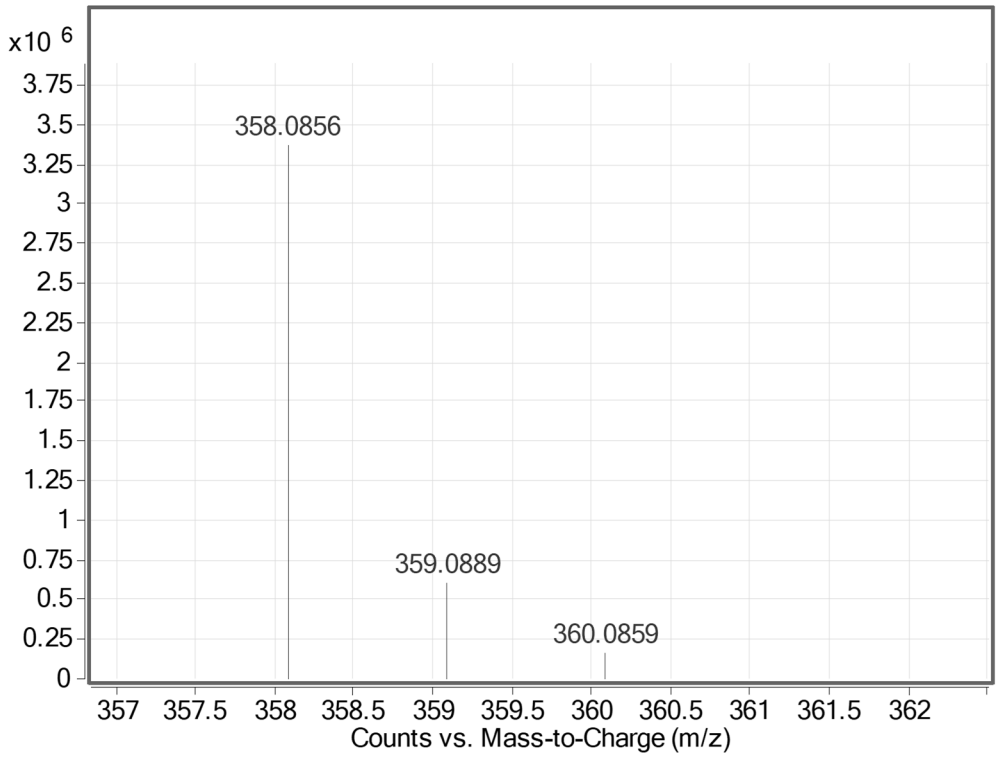




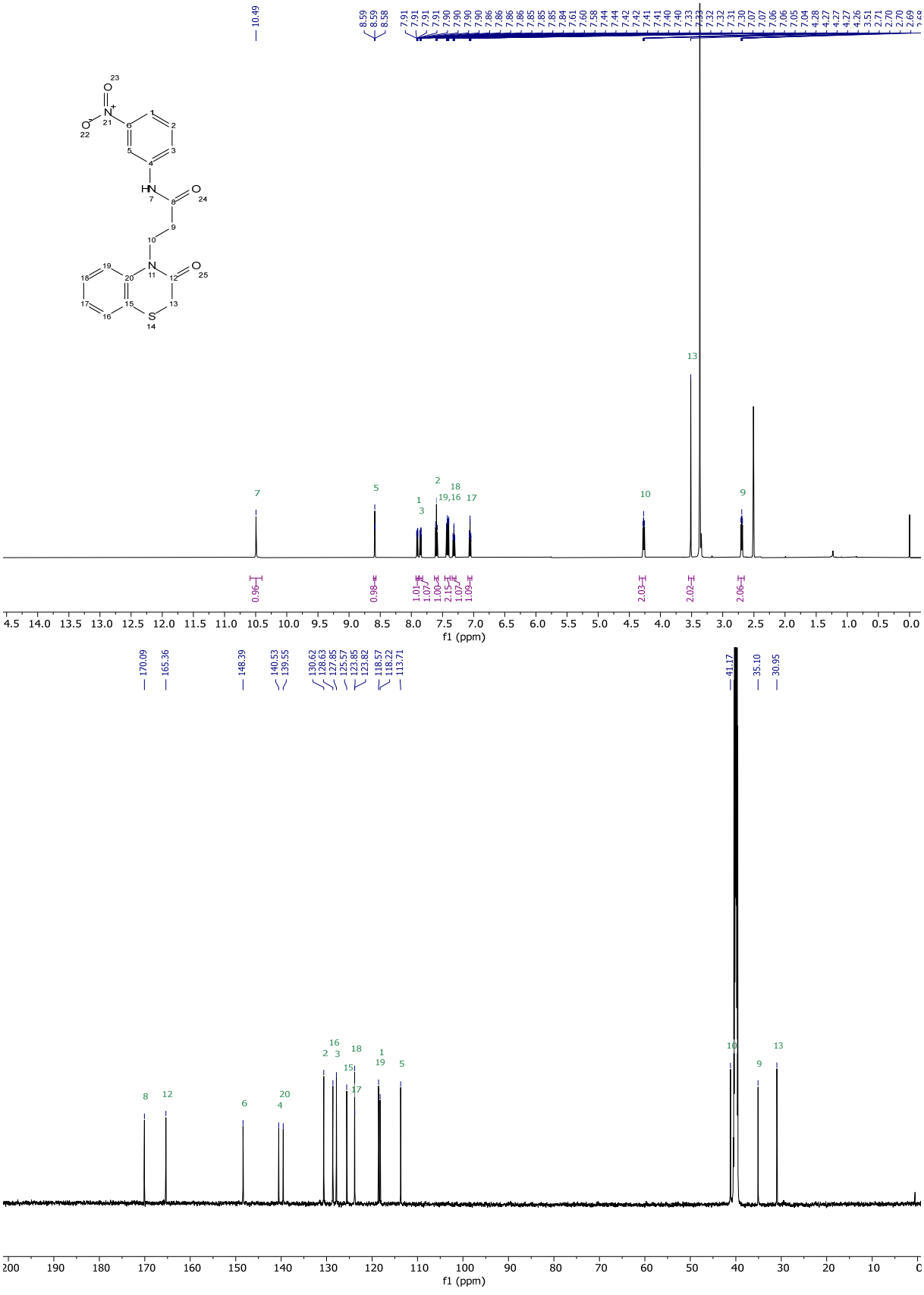

x10 6
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
343.1113
344.1143
345.1117
342
342.5
343
343.5
344
344.5
345
345.5
346
346.5
347
Counts vs. Mass-to-Charge (m/z)

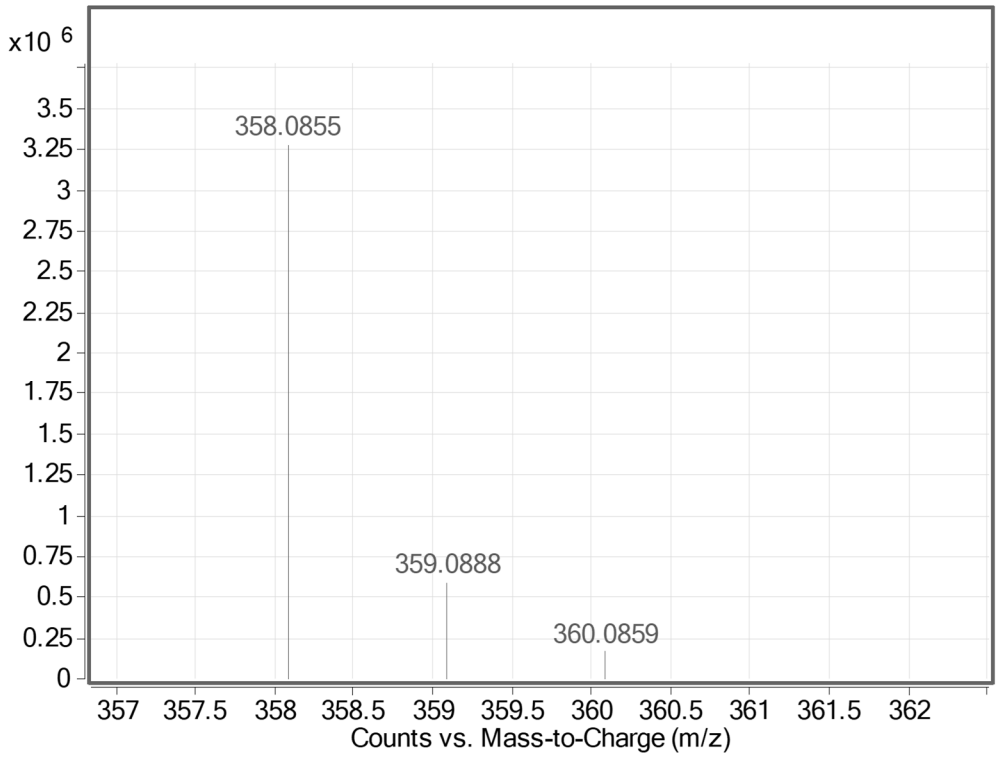
_N_-(2-nitrophenyl)-3-(3-oxo-2,3-dihydro-4_H_-benzo[_b_][1,4]thiazin-4-yl)propanamide (21)



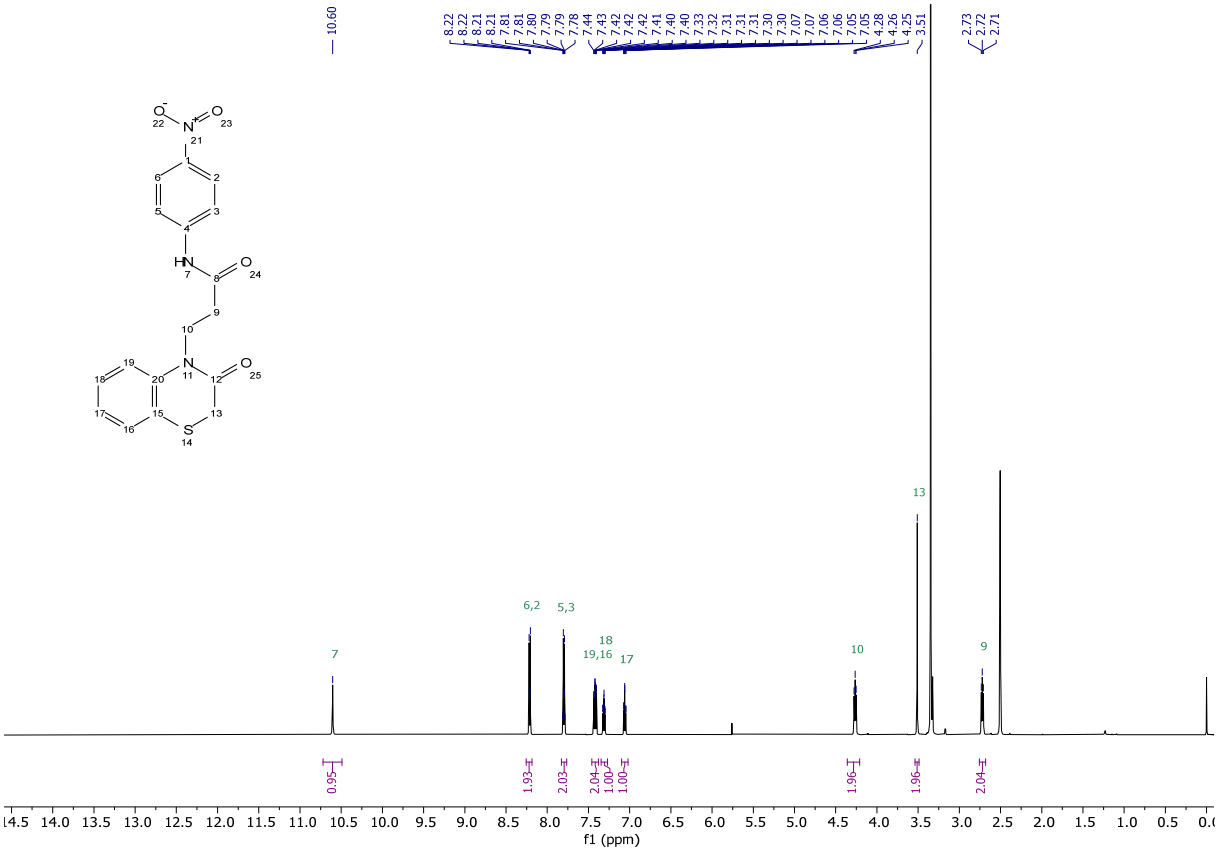

x10 6
3.75
3.5
3.25
3
2.75
2.5
2.25
2
1.75
1.5
1.25
1
0.75
0.5
0.25
0
358.0856
359.0889
360.0859
357
357.5
358
358.5
359
359.5
360
360.5
361
361.5
362
Counts vs. Mass-to-Charge (m/z)

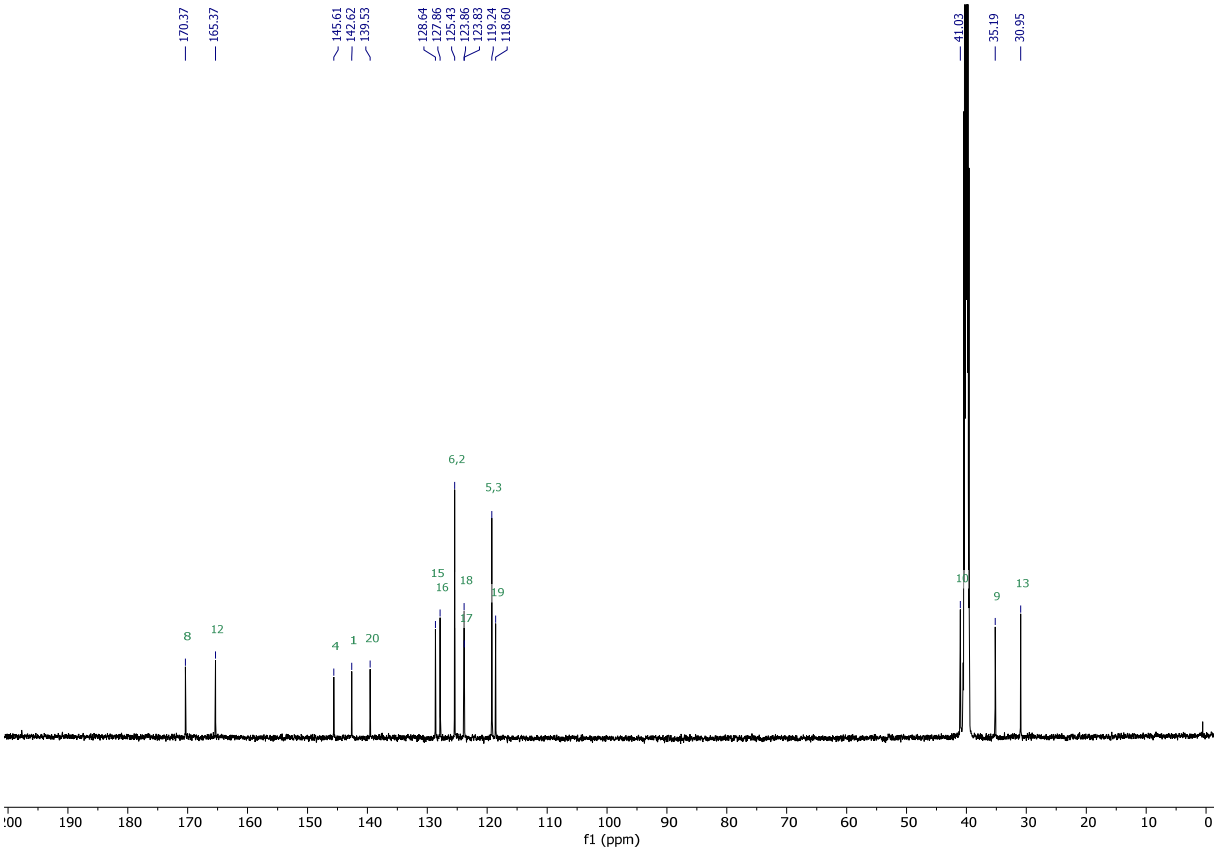
_N_-(3-nitrophenyl)-3-(3-oxo-2,3-dihydro-4_H_-benzo[_b_][1,4]thiazin-4-yl)propanamide (22)

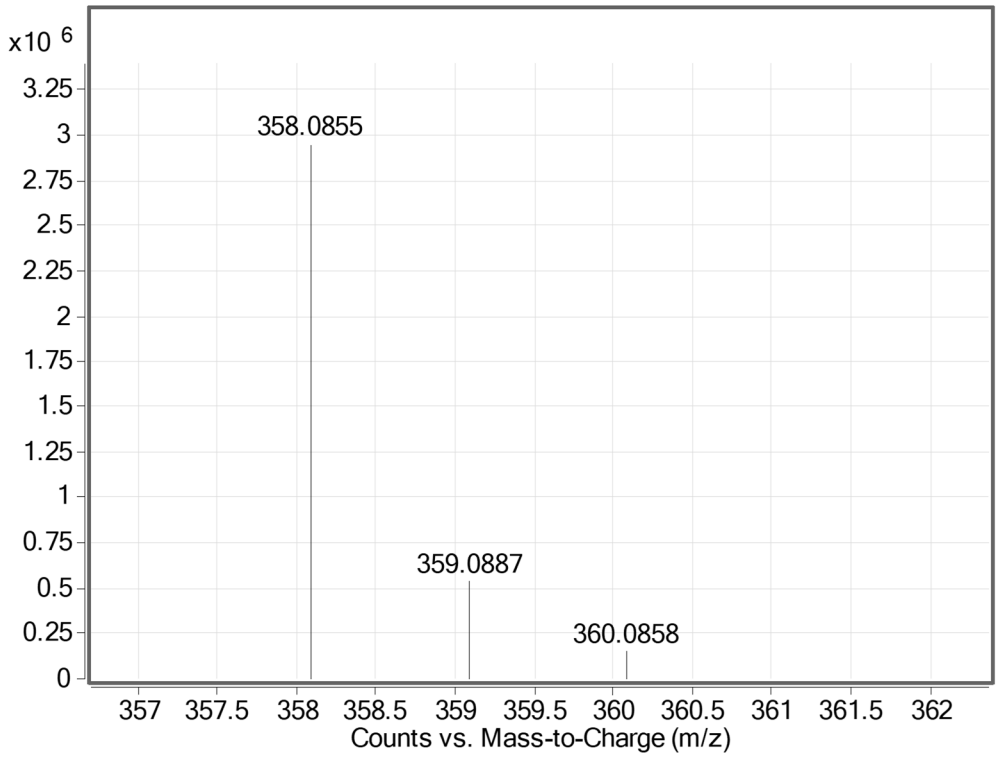



x10 6
3.5
3.25
3
2.75
2.5
2.25
2
1.75
1.5
1.25
1
0.75
0.5
0.25
0
358.0855
359.0888
360.0859
357
357.5
358
358.5
359
359.5
360
360.5
361
361.5
362
Counts vs. Mass-to-Charge (m/z)

***N*-(4-nitrophenyl)-3-(3-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4]thiazin-4-yl)propanamide (23)**






x10 6
3.25
3
2.75
2.5
2.25
2
1.75
1.5
1.25
1
0.75
0.5
0.25
0
358.0855
359.0887
360.0858
357
357.5
358
358.5
359
359.5
360
360.5
361
361.5
362
Counts vs. Mass-to-Charge (m/z)