Rational design of CYP3A4 inhibitors: A one-atom linker elongation in ritonavir-like compounds leads to a marked improvement in the binding strength

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SUPPLEMENTAL MATERIALS

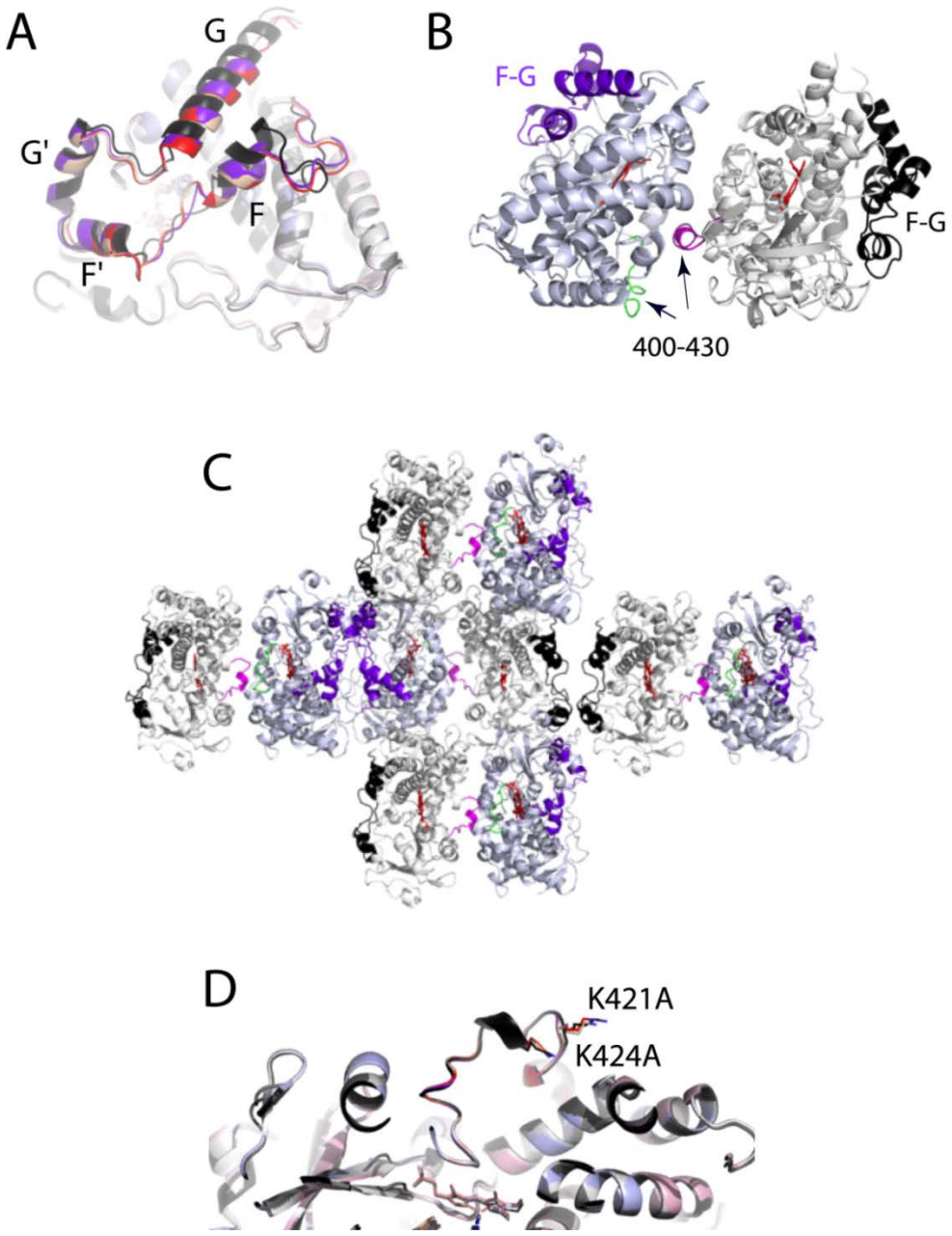

Figure S1. (**A**) Restructuring of the F-F' helix/loop region triggered by distinct crystal packing in the C2 space group. The F-F'-G'-G fragments of ligand-free (5VCE; I222) and **3a**-, **3e**- and **3**i-bound CYP3A4 (C2) are shown in black, red, beige and purple, respectively. (**B, C**) Crystallographic dimer of CYP3A4 and its spatial arrangement in C2 crystals, respectively. The 400-430 fragment (in green and magenta) is at the monomer-monomer interface, whereas the F-G fragment (in black and purple) mediates inter-dimer contacts. (**D**) A view at the proximal face of CYP3A4. The water-bound protein (5VCC structure) is in gray; **3a**- and **3e**-bound complexes of WT CYP3A4 are in pink and light blue, respectively; and **3**i-bound K421A/K424A CYP3A4 is in black. Structural superposition shows that substitution of surface K421 and K424 with alanine does not distort the proximal loop region. Non-mutated lysine side chains are displayed.

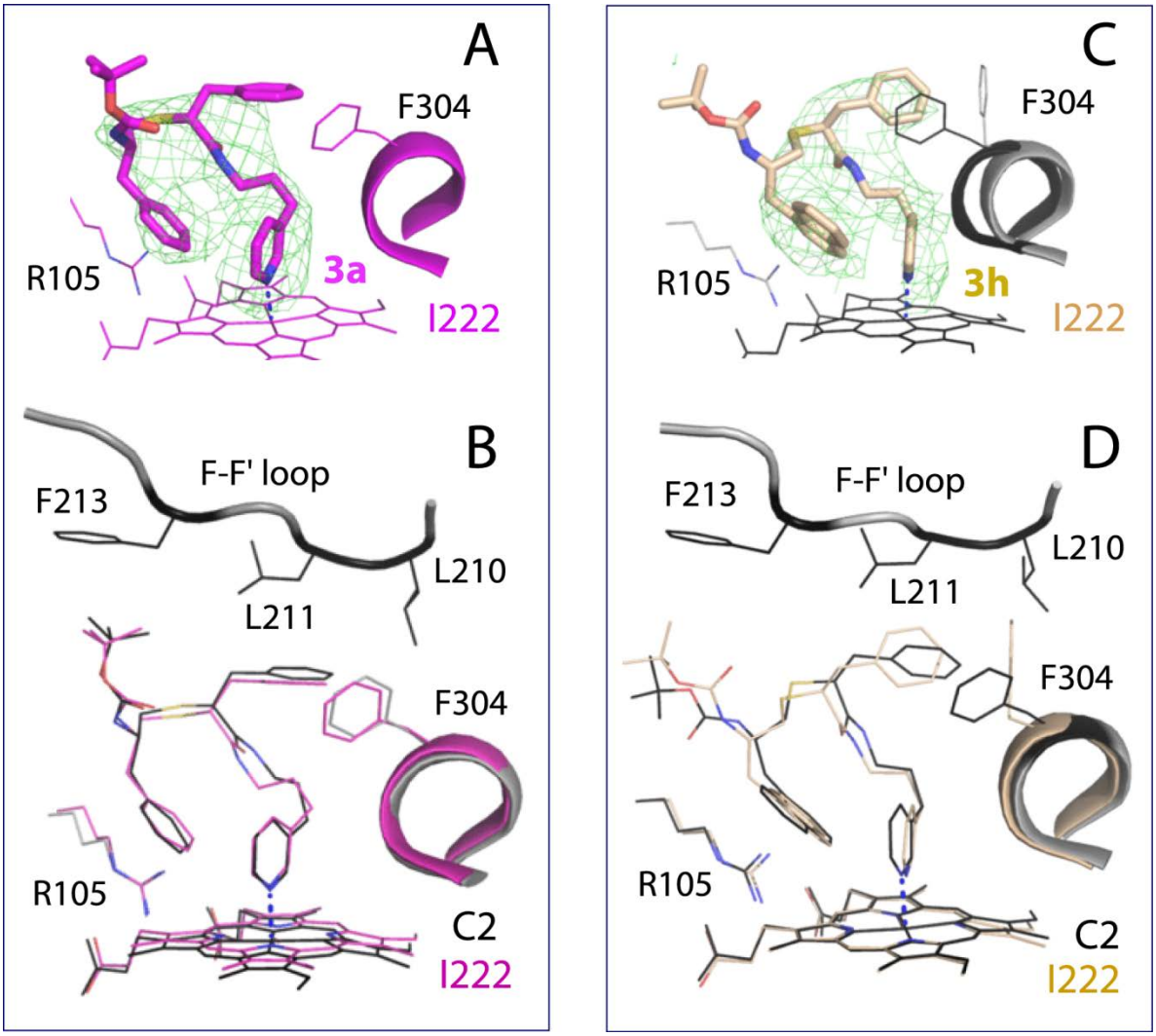

Figure S2. Binding of **3a** (**A**, **B**) and **3h** (**B**, **C**) to the active site of CYP3A4 crystallized in I222 and C2 space groups. For both **3a** and **3h**, electron density maps were not clearly defined in the I222 structures (green mesh in **A** and **C**, respectively). Therefore, **3a**- and **3h**-bound CYP3A4 was recrystallized in a more densely packed C2 space group. (**B**, **D**) Comparison of the ligand binding modes observed in the I222 and C2 structures shows that there are virtually no (for **3a**) or only minor distortions (for **3h**), primarily imposed by changes in the F-F' loop (residues 210-213).

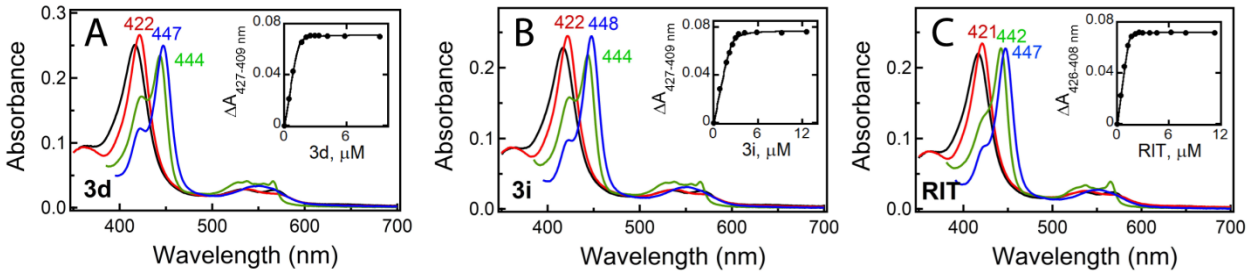

Figure S3. Spectral and ligand-binding properties of K421A/K424A CYP3A4. (**A**-**C**) Spectral changes induced in the mutant by **3d**, **3i** and ritonavir, respectively. Absorbance spectra of ferric ligand-free and inhibitor-bound CYP3A4 (2 μM) were recorded in 0.1 M phosphate buffer, pH 7.4, supplemented with 20% glycerol and 1 mM dithiothreitol, and displayed in black and red, respectively. Spectra of the ferrous form and its CO-adduct are in green and blue, respectively. The inhibitor concentration was 10 μM. Equilibrium titrations were conducted as described in the Materials and Methods section in the main text. Titration plots with quadratic fittings are shown in insets. The derived dissociation constants were 0,019 μM, 0.025 μM and 0.023 μM for **3d**, **3i** and ritonavir, respectively.

Table S1. Data collection and refinement statistics

Ligand	**3a**	**3b**	**3c**	**3d**	**8**
CYP3A4	WT	WT	WT	K421A/K424A	WT
PDB ID	7KNH	7KVI	7KVJ	7KVK	7KVM
Data statistics					
Space group	C2	I222	I222	C2	I222
Unit cell	*a, b, c* = 93 x 95 x 153 Å; α, β, γ = 90 x 90 x 124°	*a, b, c* = 77 x 103 x 126 Å; α, β, γ = 90°	*a, b, c* = 76 x 100 x 124 Å; α, β, γ = 90°	*a, b, c* = 76 x 101 x 125 Å; α, β, γ = 90°	*a, b, c* = 78 x 101 x 129 Å; α, β, γ = 90°
Resolution range (Å)	39.55-2.79 (2.79-2.94) [a]	79.64-2.55 (2.55-2.69)	78.17-2.65 (2.79-2.65)	77.80-2.55 (2.69-2.55)	79.64-2.70 (2.85-2.70)
Total reflections	167,933	81,756	51,716	159,292	56,723
Unique reflections	27,176	16,474	13,659	37,311	13,668
Redundancy	6.2 (6.0)	5.0 (4.8)	3.8 (4.0)	4.3 (4.4)	4.2 (4.3)
Completeness	98.3 (96.9)	99.2 (99.5)	97.1 (98.3)	99.8 (99.8)	95.9 (97.4)
Average $I/\sigma I$	5.8 (1.1)	8.3 (1.0)	7.4 (1.0)	8.4 (1.1)	8.5 (0.9)
R_{merge}	0.163 (2.561)	0.077 (1.163)	0.070 (2.029)	0.080 (1.443)	0.047 (2.926)
R_{pim}	0.107 (1.155)	0.038 (0.592)	0.042 (1.127)	0.043 (0.768)	0.038 (1.358)
CC ½	0.993 (0.489)	0.998 (0.532)	0.998 (0.320)	0.999 (0.398)	0.996 (0.313)
Refinement statistics					
R/R_{free} [b]	23.8/27.8	22.5/26.2	22.5/28.0	23.7/27.7	22.7/27.6
Number of atoms:					
Protein	3657/3555 [c]	3654	3341	3716/3581	3720
Solvent	24	21	4	14	0
R.m.s. deviations					
Bond lengths, Å	0.002	0.002	0.002	0.002	0.003
Bond angles, °	0.490	0.531	0.490	0.467	0.661
Wilson B-factor, $Å^2$	83	79	96	73	112
Average *B*-factor, $Å^2$:					
Protein	91/110 [c]	112	136	89/131	141
Ligand	85/104 [c]	140	162	102/126	149
Ramachandran plot [d] (residues; %)					
Preferred	816 (93.0%)	427 (96.0%)	388 (95.0%)	848 (94.9%)	435 (95.0%)
Allowed	60 (6.8%)	17 (3.8%)	20 (5.0%)	44 (4.9%)	25 (5.0%)
Outliers	2 (0.2%)	1 (0.2%)	none	2 (0.2%)	none

[a] Values in brackets are for the highest resolution shell.
[b] R_{free} was calculated from a subset of 5% of the data that were excluded during refinement.
[c] Values for two molecules in the asymmetric unit.
[d] Analyzed with PROCHECK.

Table S2. Data collection and refinement statistics

Ligand	**3e**	**3f**	**3g**	**3h**	**3i**
CYP3A4	WT	WT	WT	WT	K421A/K424A
PDB ID	7KVN	7KVO	7KVP	7KVQ	7KVS
Data statistics					
Space group	C2	I2	I222	C2	C2
Unit cell	*a, b, c* = 93 x 96 x 153 Å; α, β, γ = 90 x 90 x 124°	*a, b, c* = 93 x 98 x 128 Å; α, β, γ = 90 x 90 x 93°	*a, b, c* = 78 x 102 x 128 Å; α, β, γ = 90°	*a, b, c* = 93 x 97 x 154 Å; α, β, γ = 90 x 90 x 124°	*a, b, c* = 93 x 98 x 155 Å; α, β, γ = 90 x 90 x 124°
Resolution range (Å)	76.93-2.70 (2.85-2.70) [a]	49.04-2.65 (2.79-2.65)	80.00-2.75 (2.907-2.75)	77.28-2.70 (2.85-2.70)	77.82-2.50 (2.64-2.50)
Total reflections	136,528	223,503	43,178	177,490	246,329
Unique reflections	28,152	33,059	13,250	30,116	38,953
Redundancy	4.8 (4.3)	6.8 (6.7)	3.3 (3.4)	5.9 (6.0)	6.3 (6.3)
Completeness	91.9 (84.0)	99.9 (99.9)	97.3 (98.6)	94.4 (97.2)	97.6 (97.4)
Average $I/\sigma I$	4.0 (1.0)	12.3 (1.1)	5.9 (0.7)	8.5 (1.1)	11.0 (1.0)
R_{merge}	0.233 (1.598)	0.070 (2.278)	0.072 (2.466)	0.093 (1.641)	0.075 (1.922)
R_{pim}	0.115 (0.841)	0.029 (0.944)	0.045 (1.566)	0.040 (0.723)	0.032 (0.830)
CC ½	0.970 (0.571)	0.999 (0.390)	0.998 (0.481)	0.999 (0.372)	0.999 (0.345)
Refinement statistics					
R/R_{free} [b]	24.8/29.0	24.1/29.3	22.7/27.3	25.0/28.0	23.5/27.5
Number of atoms:					
Protein	3653/3646 [c]	3721/3631	3653	3669/3605	3689/3538
Solvent	88	0	2	0	47
R.m.s. deviations					
Bond lengths, Å	0.003	0.003	0.004	0.002	0.002
Bond angles, °	0.563	0.570	0.731	0.497	0.500
Wilson B-factor, Å^2	69	91	113	89	80
Average *B*-factor, Å^2:					
Protein	75/93 [c]	107/160	96	100/167	99/151
Ligand	65/88 [c]	164/177	163	128/177	132/182
Ramachandran plot [d] (residues; %)					
Preferred	826 (92.9%)	842 (94.1%)	435 (97.0%)	837 (93.9%)	836 (94.1%)
Allowed	62 (9.0%)	52 (5.8%)	14 (3.0%)	53 (6.0%)	51 (5.8%)
Outliers	1 (0.1%)	1 (0.1%)	none	1 (0.1%)	1 (0.1%)

[a] Values in brackets are for the highest resolution shell.
[b] R_{free} was calculated from a subset of 5% of the data that were excluded during refinement.
[c] Values for two molecules in the asymmetric unit.
[d] Analyzed with PROCHECK

Table S3. Local correlation coefficients (CC) and CC_{peak} between three polder maps ($F_{obs} = |F_{model}|$)

Map 1 (m1), calculated F_{obs} assuming that the omitted ligand atoms are present. Map 2 (m2), calculated F_{obs} assuming that the omitted ligand atoms are not present. Map 3 (m3), polder map using experimental data.

		m1-m2		m1-m3		m2-m3	
Ligand/PDB ID		CC	CC_{peak}	CC	CC_{peak}	CC	CC_{peak}
3a	7KVH	0.4949	0.4797	0.8790	0.8579	0.4998	0.4709
3b	7KVI	0.6654	0.6106	0.8934	0.8439	0.6464	0.6431
3c	7KNJ	0.6304	0.6167	0.8333	0.7082	0.4517	0.3954
3d	7KVK	0.5390	0.4609	0.9078	0.8797	0.5149	0.4463
8	7KVM	0.6183	0.5721	0.8442	0.7824	0.6879	0.6878
3e	7KVN	0.5025	0.5048	0.8715	0.8431	0.4884	0.4780
3f	7KVO	0.7812	0.7598	0.8015	0.7899	0.6965	0.6741
3g	7KVP	0.6169	0.6394	0.8884	0.8461	0.5352	0.5618
3h	7KVQ	0.6701	0.6616	0.8005	0.7598	0.6414	0.6466
3i	7KVS	0.6324	0.6383	0.8551	0.8222	0.7047	0.6985

Correlation coefficients for polder maps were calculated using phenix.*polder* in the PHENIX software package.[1]

For all ligands, CC(1,3) was > 0.8 and higher than CC(1,2) and CC(2,3), meaning that the polder maps displayed in Figures 3 and 6 of the main text show the omitted ligand atoms.[2]

[1]Adams, P.D.; Afonine, P.V.; Bunkoczi, G.; Chen, V.B.; Davis, I.W.; Echols, N.; Headd, J.J.; Hung, L.W.; Kapral, G.J.; Grosse-Kunstleve, R.W., et al. PHENIX: a comprehensive Python-based system for macromolecular structure solution. *Acta Crystallogr. Section D* **2010**, *66*, 213-321

[2]Liebschner D., Afonine P.V.; Moriarty N.W.; Poon B.K.; Sobolev O.V.; Terwilliger T.C.; Adams P.D. Polder maps: improving OMIT maps by excluding bulk solvent. *Acta Crystallogr. Section D* **2016**, *73*, 148-157.

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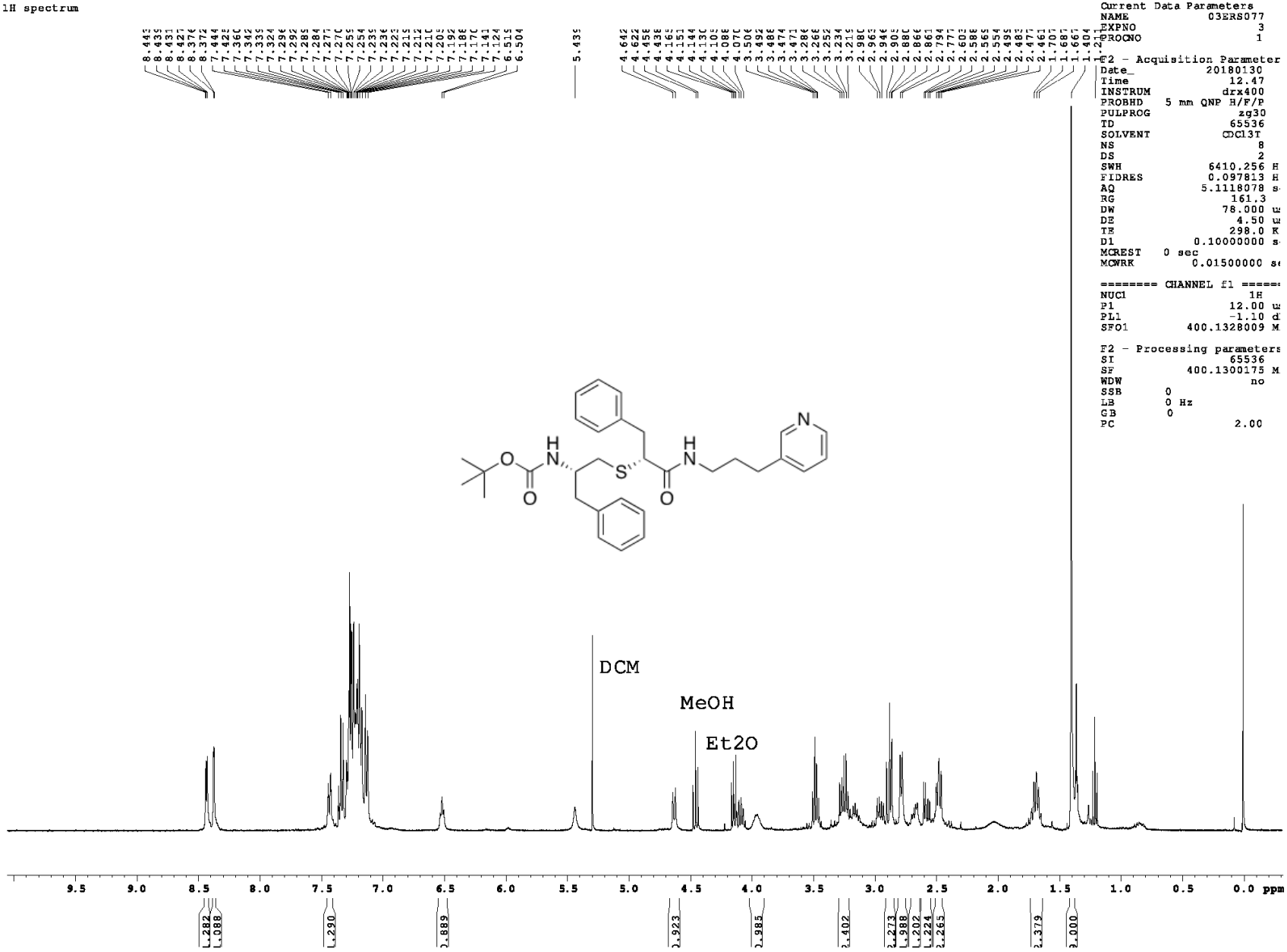

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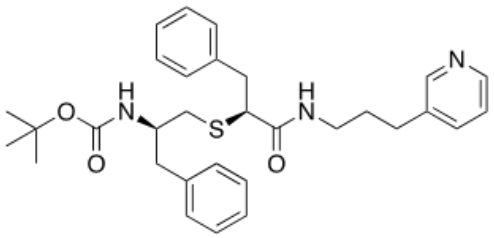

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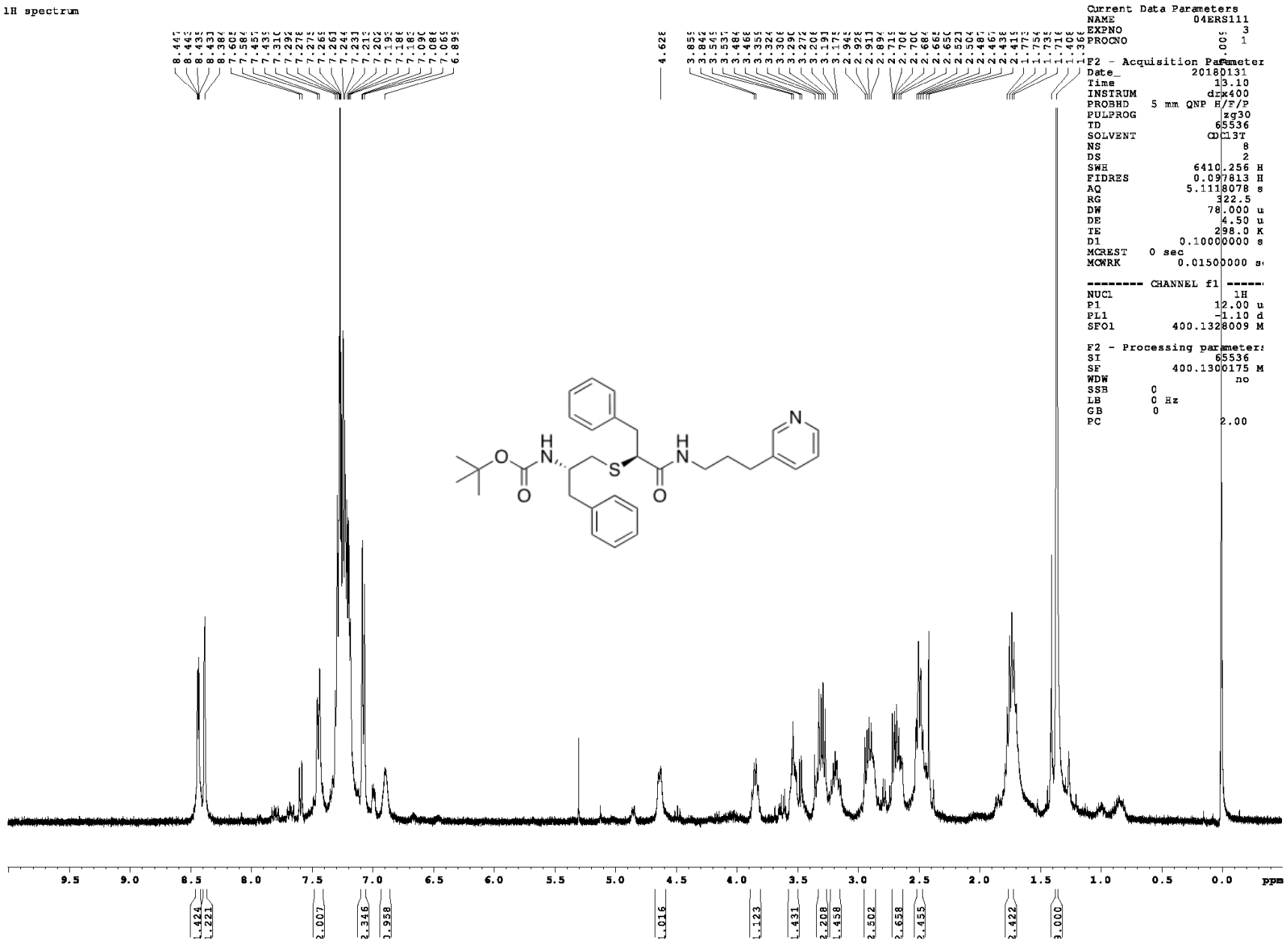
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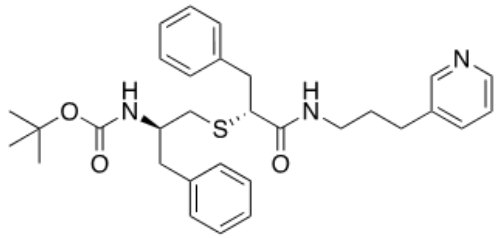

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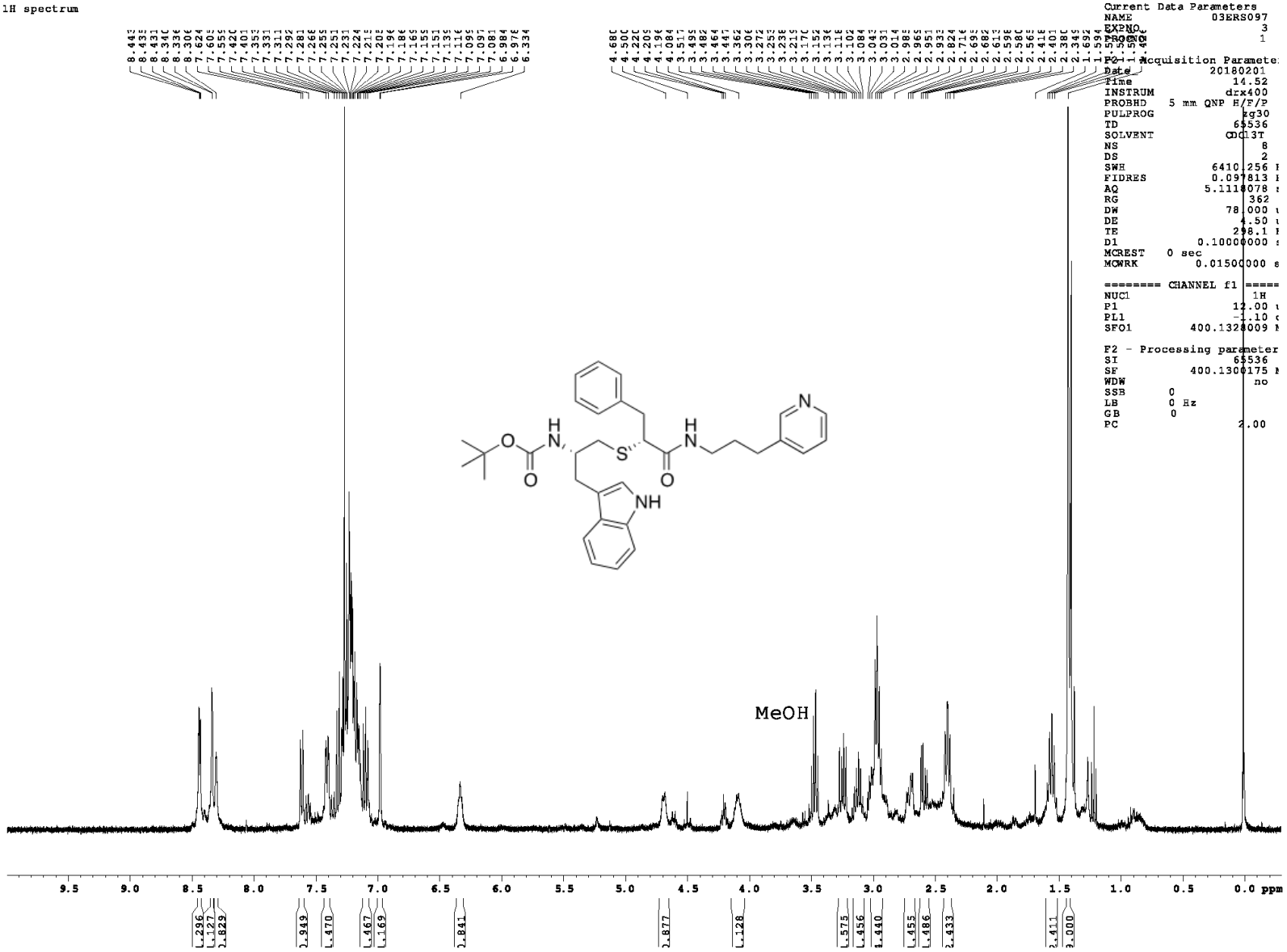
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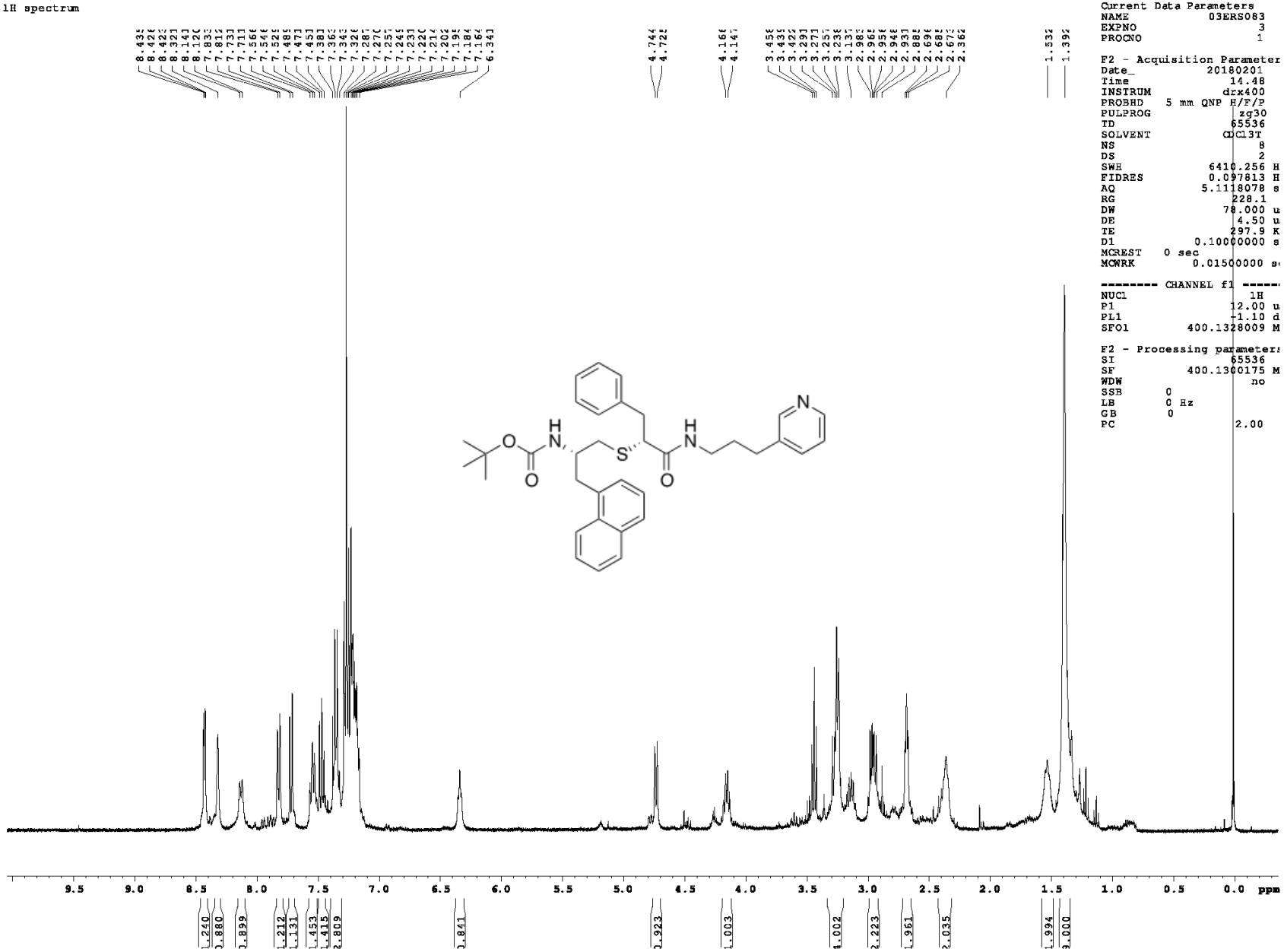
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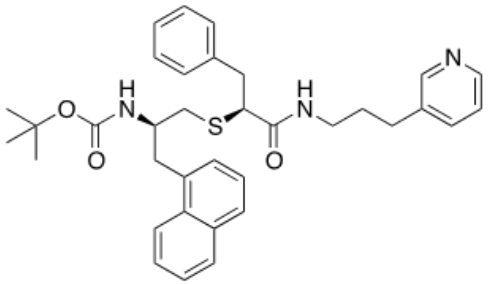

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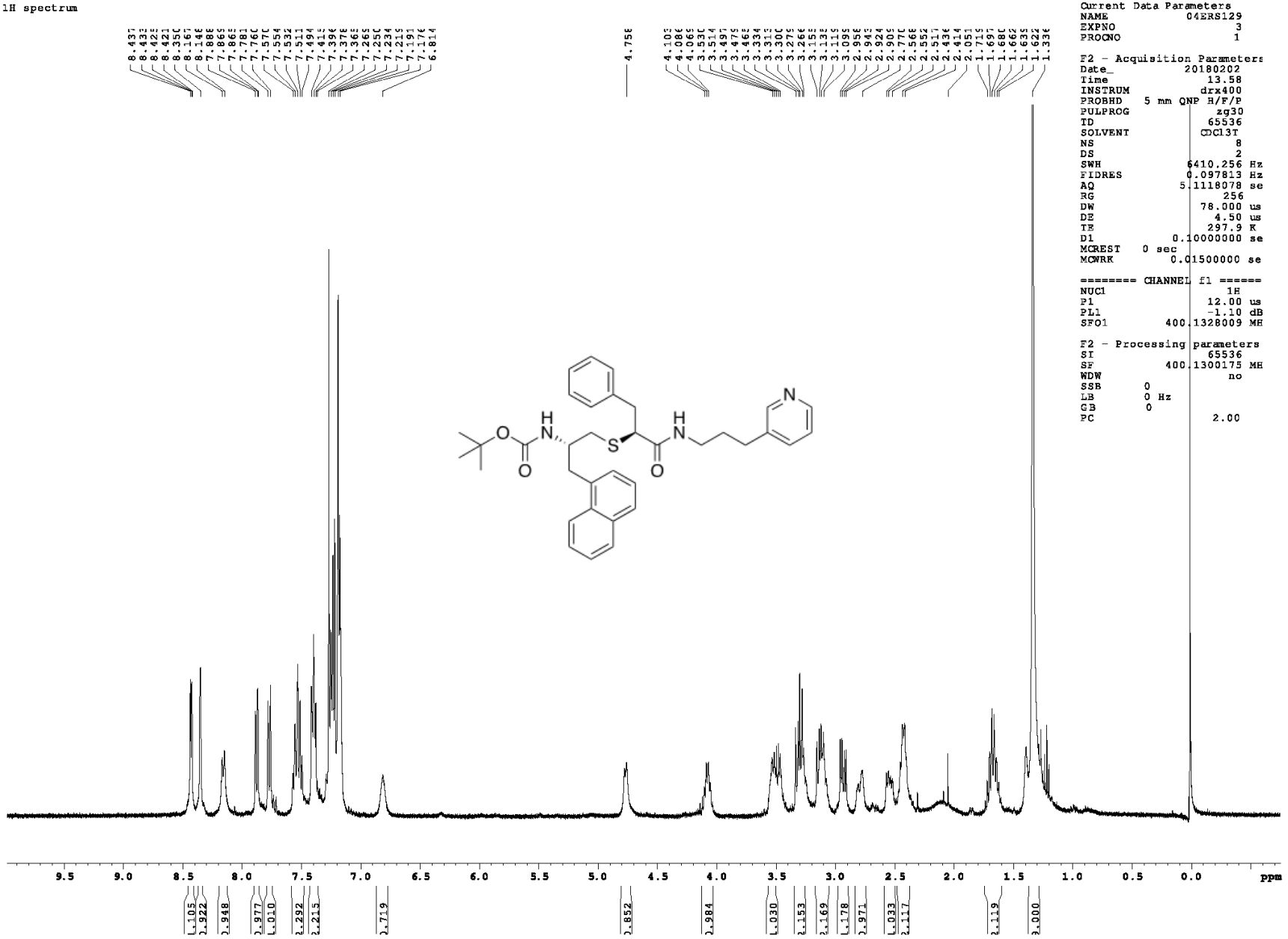
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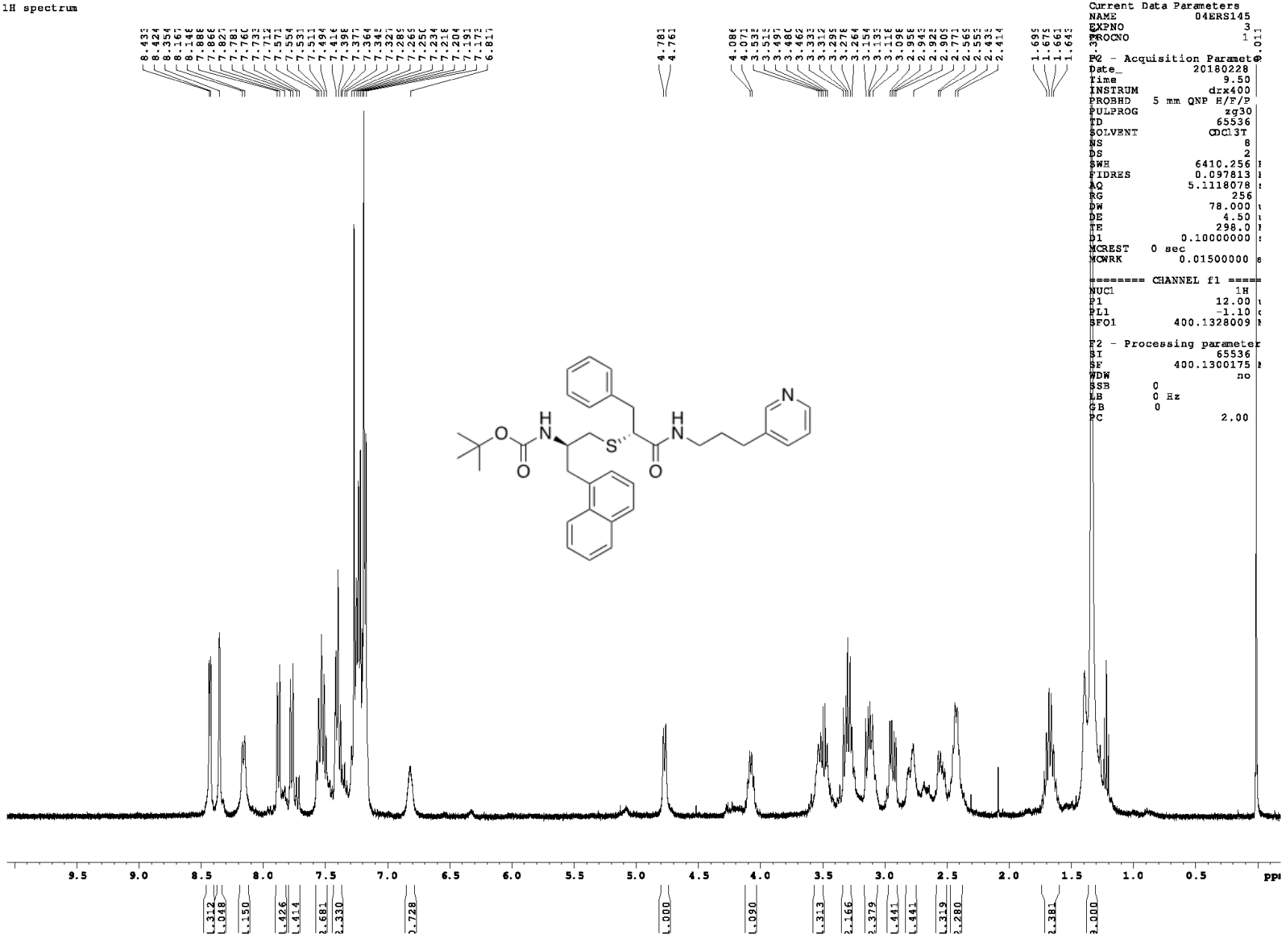
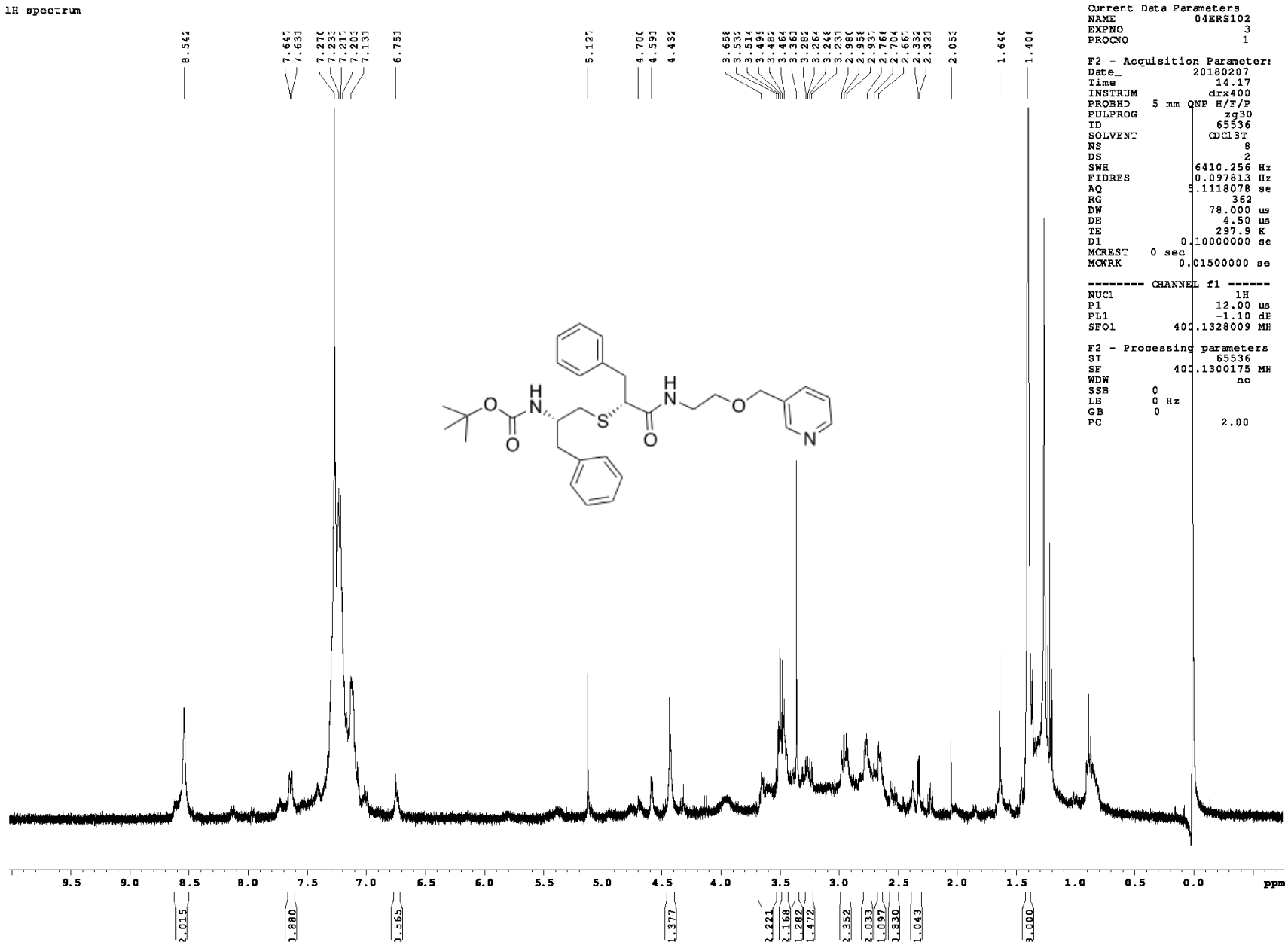
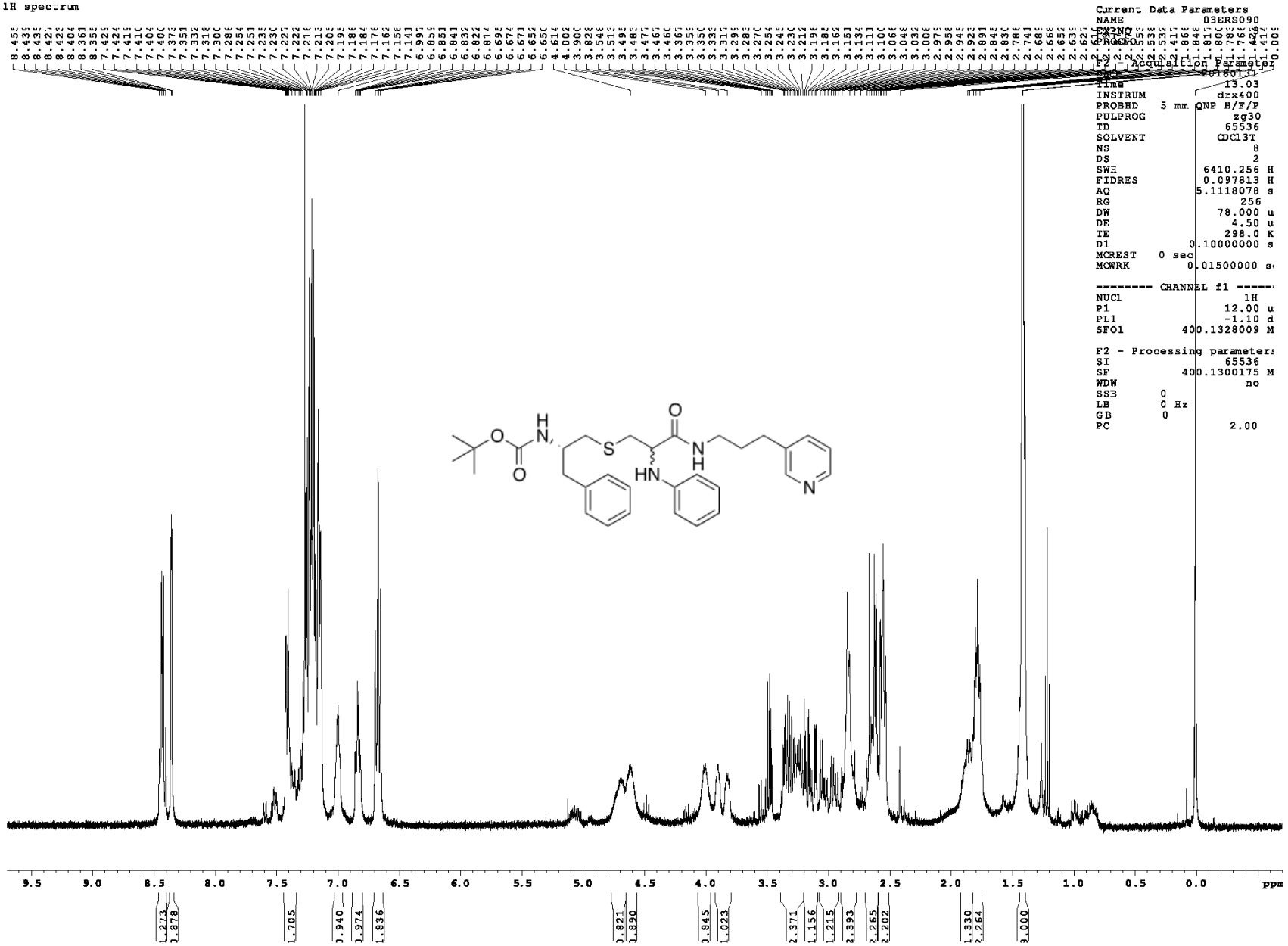
ppm

1H spectrum

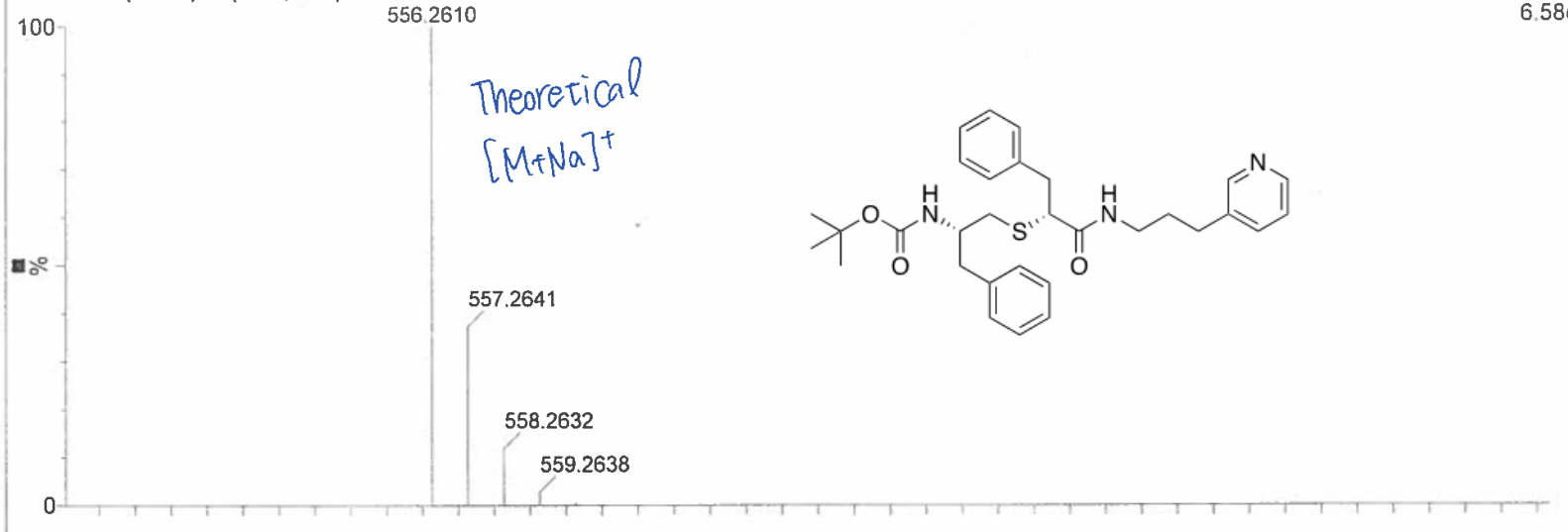

Current Data Parameters
NAME 04ERS145
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180228
Time 9.50
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3T
NS 8
DS 2
SWH 6410.256
FIDRES 0.097813
AQ 5.1118078
RG 256
DW 78.000
DE 4.50
TE 298.0
D1 0.10000000
MCREST 0 sec
MCWRK 0.01500000
======== CHANNEL f1 ======
NUC1 1H
P1 12.00
PL1 -1.10
SFO1 400.1328009
F2 - Processing parameters
SI 65536
SF 400.1300175
WDW no
SSB 0
LB 0 Hz
GB 0
PC 2.00
8.433
8.424
8.354
8.167
8.146
7.888
7.868
7.827
7.781
7.760
7.733
7.712
7.571
7.554
7.531
7.511
7.494
7.416
7.398
7.377
7.364
7.342
7.327
7.285
7.265
7.250
7.234
7.218
7.204
7.191
7.173
6.817
4.781
4.761
4.086
4.071
3.532
3.515
3.497
3.480
3.462
3.333
3.312
3.295
3.278
3.264
3.154
3.133
3.118
3.098
2.956
2.943
2.922
2.905
2.771
2.565
2.555
2.435
2.414
1.695
1.675
1.661
1.643
O
N
H
O
O
N
H
S
N
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.312
1.048
1.150
1.426
1.414
2.681
2.330
2.728
1.000
1.090
3.313
2.166
2.379
1.441
1.441
1.319
2.280
2.381
3.000


1H spectrum
Current Data Parameters
NAME 04ERS102
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180207
Time 14.17
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3T
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118078 se
RG 362
DW 78.000 us
DE 4.50 us
TE 297.9 K
D1 0.10000000 se
MCREST 0 sec
MCWRK 0.01500000 se
-------- CHANNEL f1 ------
NUC1 1H
P1 12.00 us
PL1 -1.10 dB
SFO1 400.1328009 MH
F2 - Processing parameters
SI 65536
SF 400.1300175 MH
WDW no
SSB 0
LB 0 Hz
GB 0
PC 2.00
8.542
7.643
7.631
7.270
7.235
7.217
7.203
7.133
6.751
5.127
4.700
4.591
4.432
3.658
3.532
3.514
3.495
3.482
3.464
3.363
3.282
3.264
3.248
3.233
2.980
2.958
2.937
2.768
2.704
2.667
2.332
2.321
2.053
1.640
1.408
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.015
1.880
1.565
1.377
2.221
2.168
1.282
1.472
2.352
2.033
1.097
1.830
1.043
9.000


1H spectrum
Current Data Parameters
NAME 03ERS090
F2 - Acquisition Parameter
Time 13.03
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3T
NS 8
DS 2
SWH 6410.256 H
FIDRES 0.097813 H
AQ 5.1118078 s
RG 256
DW 78.000 u
DE 4.50 u
TE 298.0 K
D1 0.10000000 s
MCREST 0 sec
MCWRK 0.01500000 s
-------- CHANNEL f1 ------
NUC1 1H
P1 12.00 u
PL1 -1.10 d
SFO1 400.1328009 M
F2 - Processing parameters
SI 65536
SF 400.1300175 M
WDW no
SSB 0
LB 0 Hz
GB 0
PC 2.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.273 1.878 1.705 1.940 1.974 1.836 1.821 1.890 1.845 1.023 2.371 1.156 1.215 2.393 2.265 2.202 1.330 2.264 3.000

ES-377-a (0.019) Is (1.00,0.01) C31H39N3O3SNa

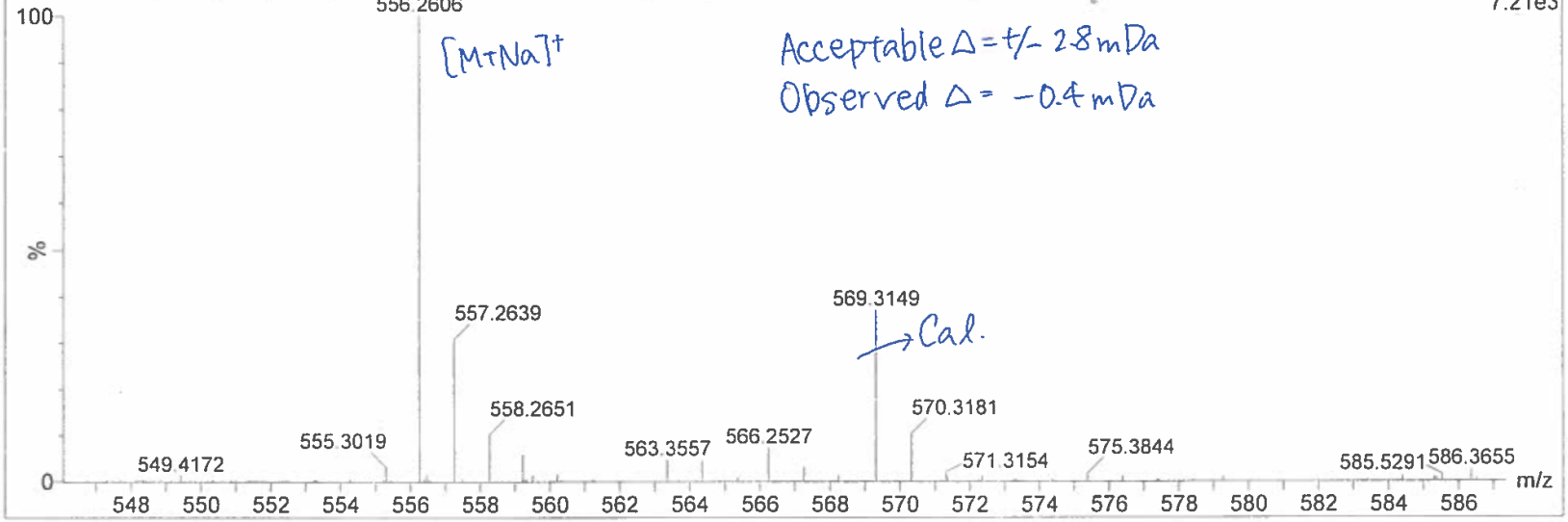
TOF MS ES+
6.58e12



Theoretical
$[M+Na]^+$

ES-377-a 18 (0.330) AM (Cen,5, 80.00, Ar,8000.0,569.31,0.70); Sm (SG, 2x3.00); Sb (1,40.00)

TOF MS ES+
7.21e3

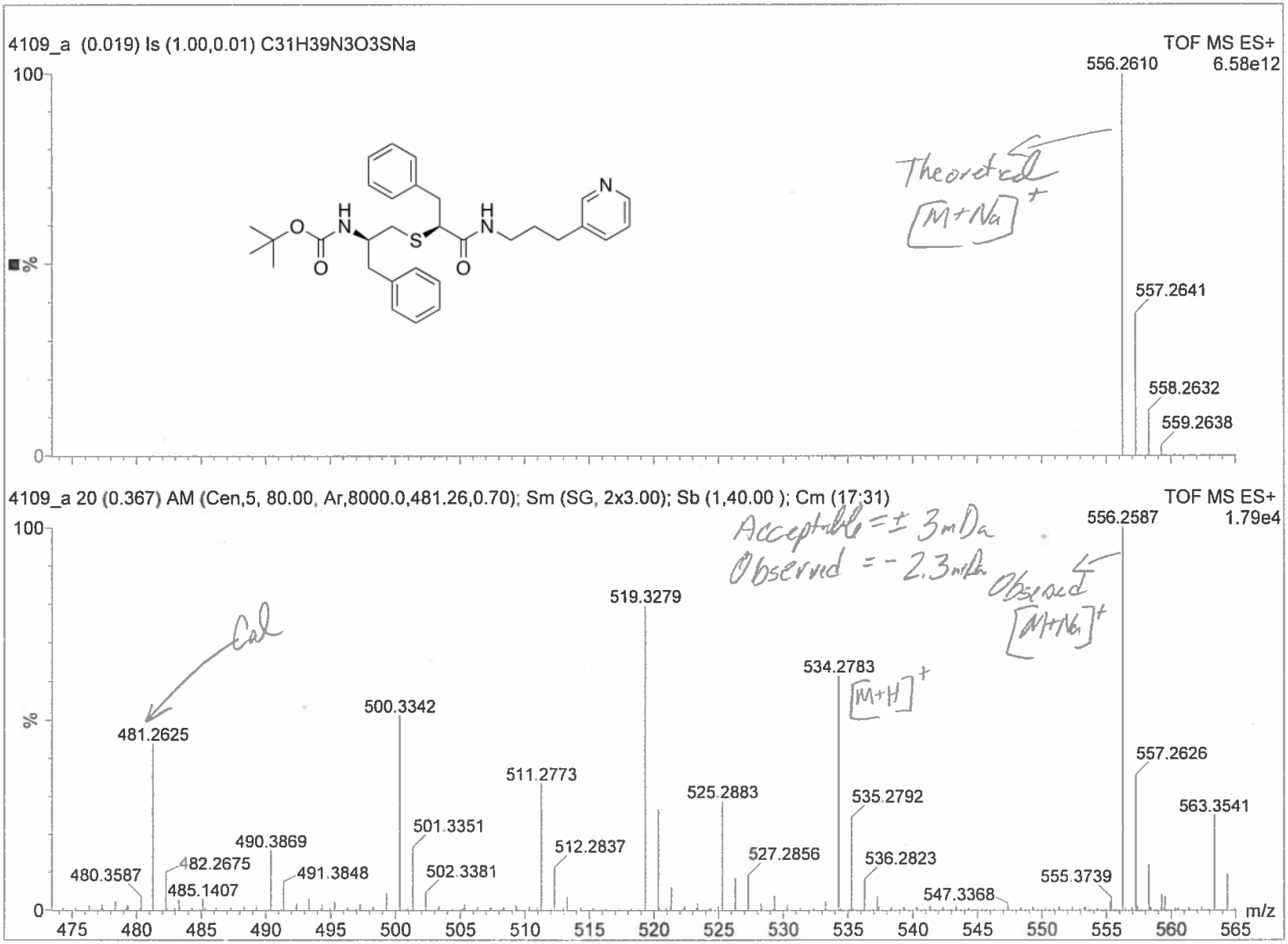


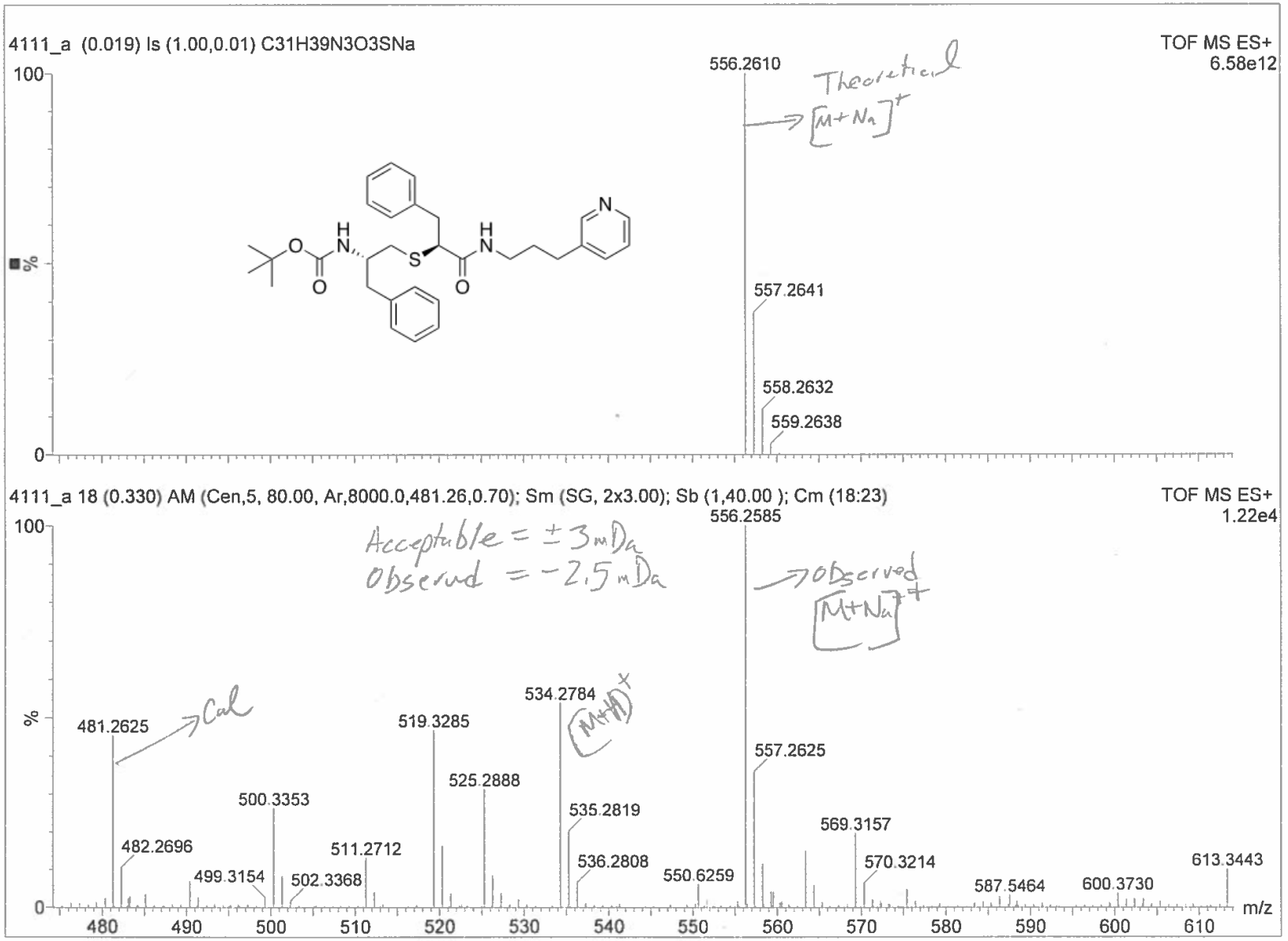
$[M+Na]^+$

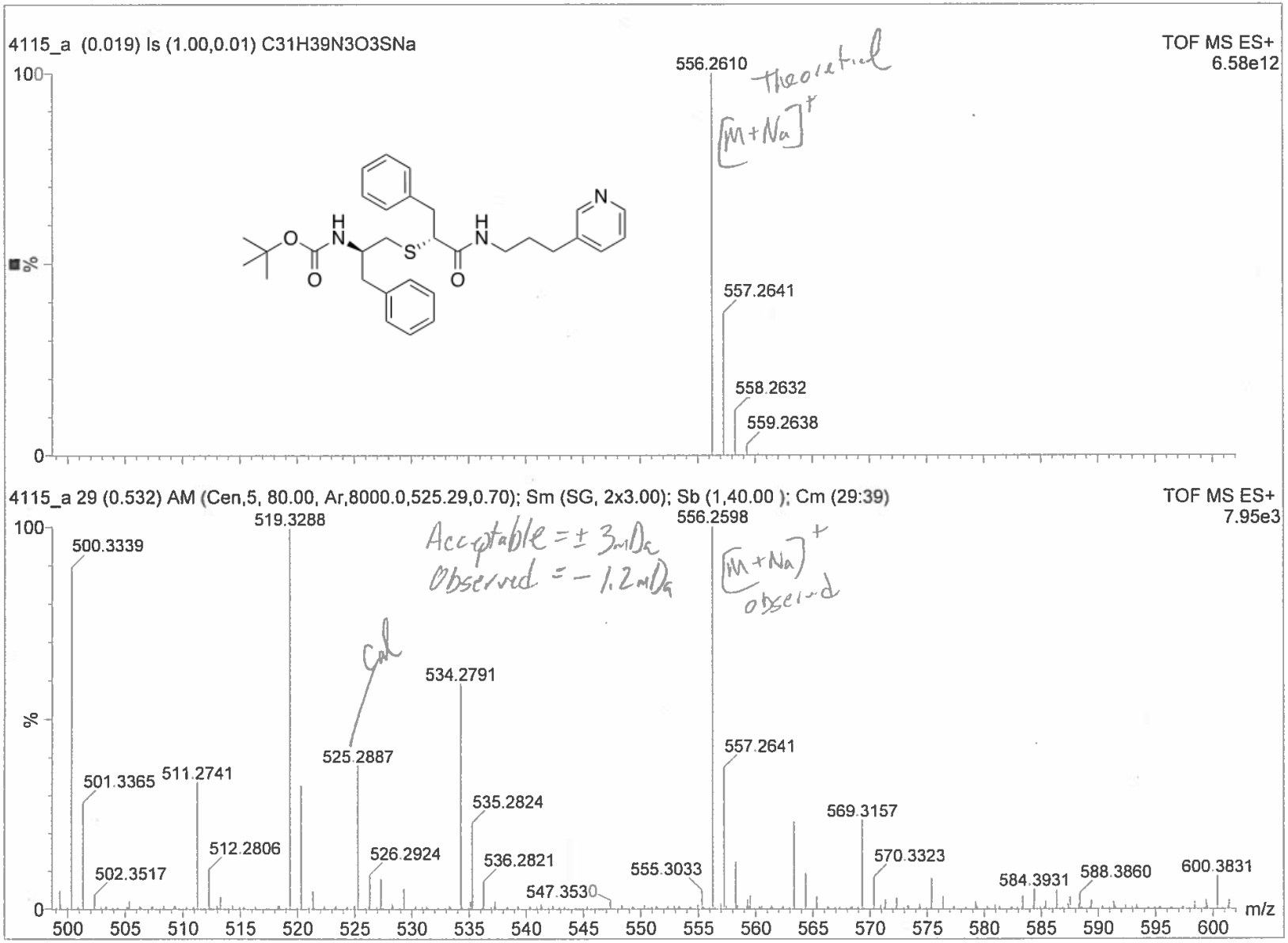
Acceptable $\Delta = +/- 2.8$ mDa

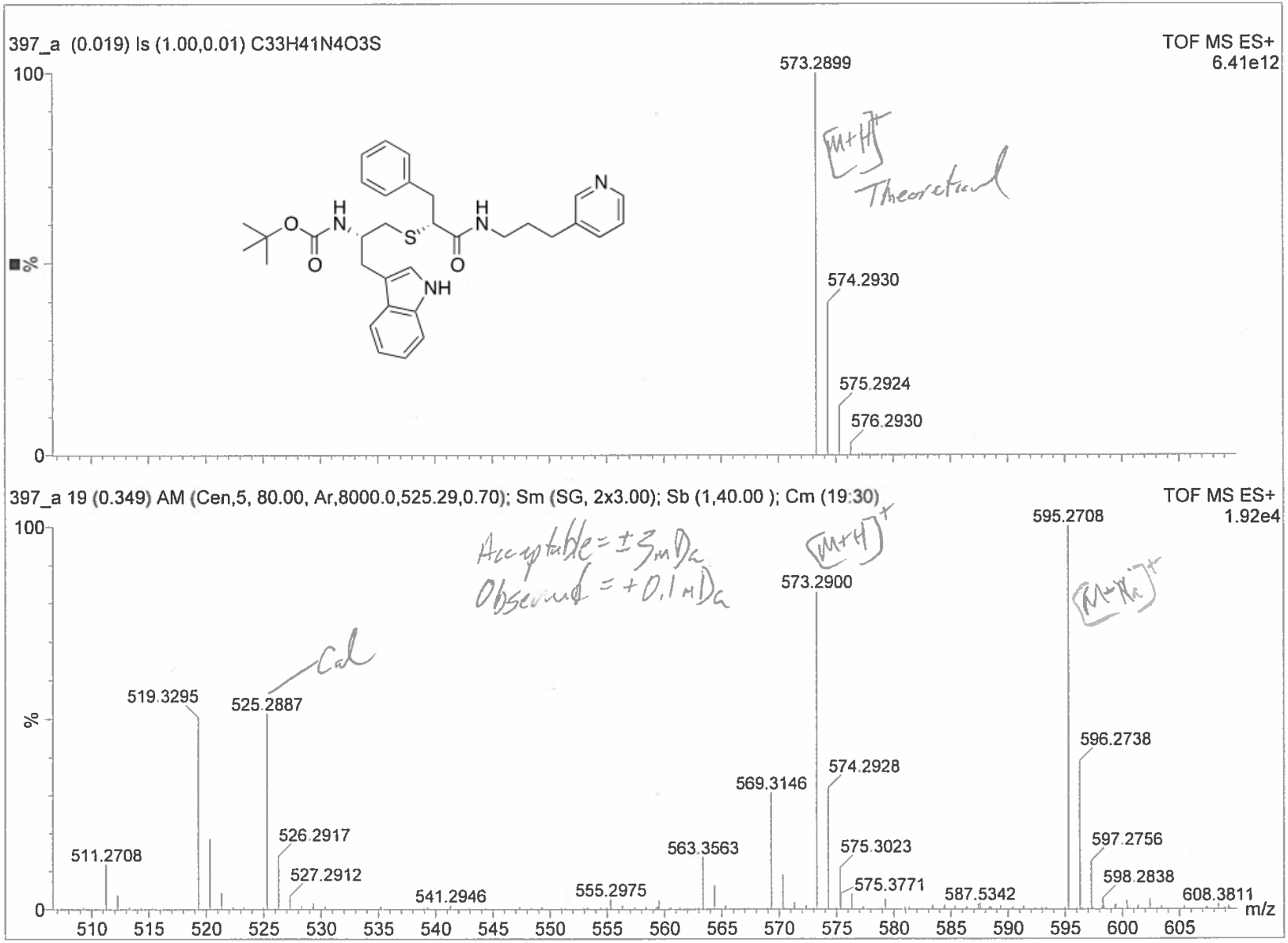
Observed $\Delta = -0.4$ mDa

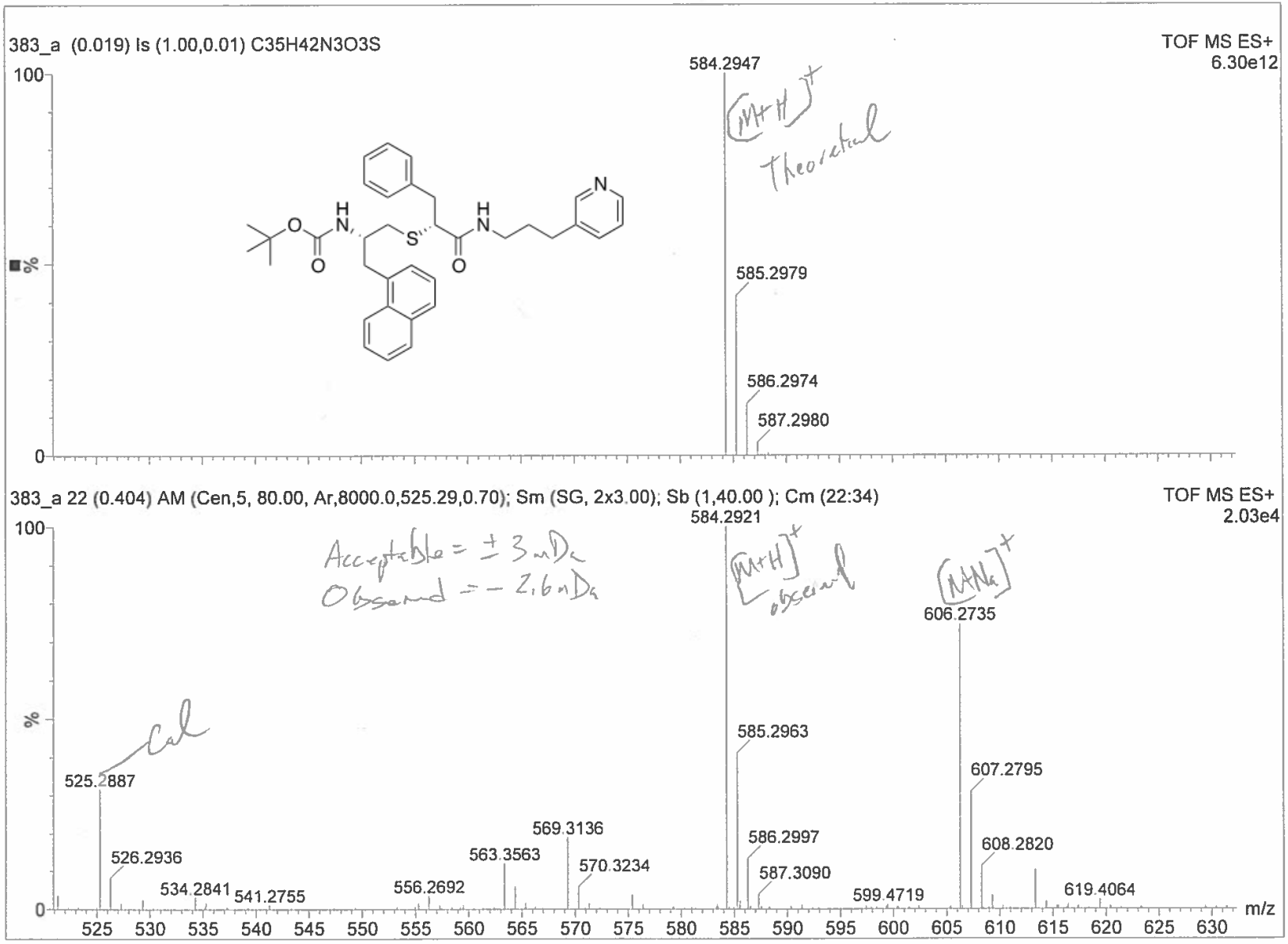
Cal.

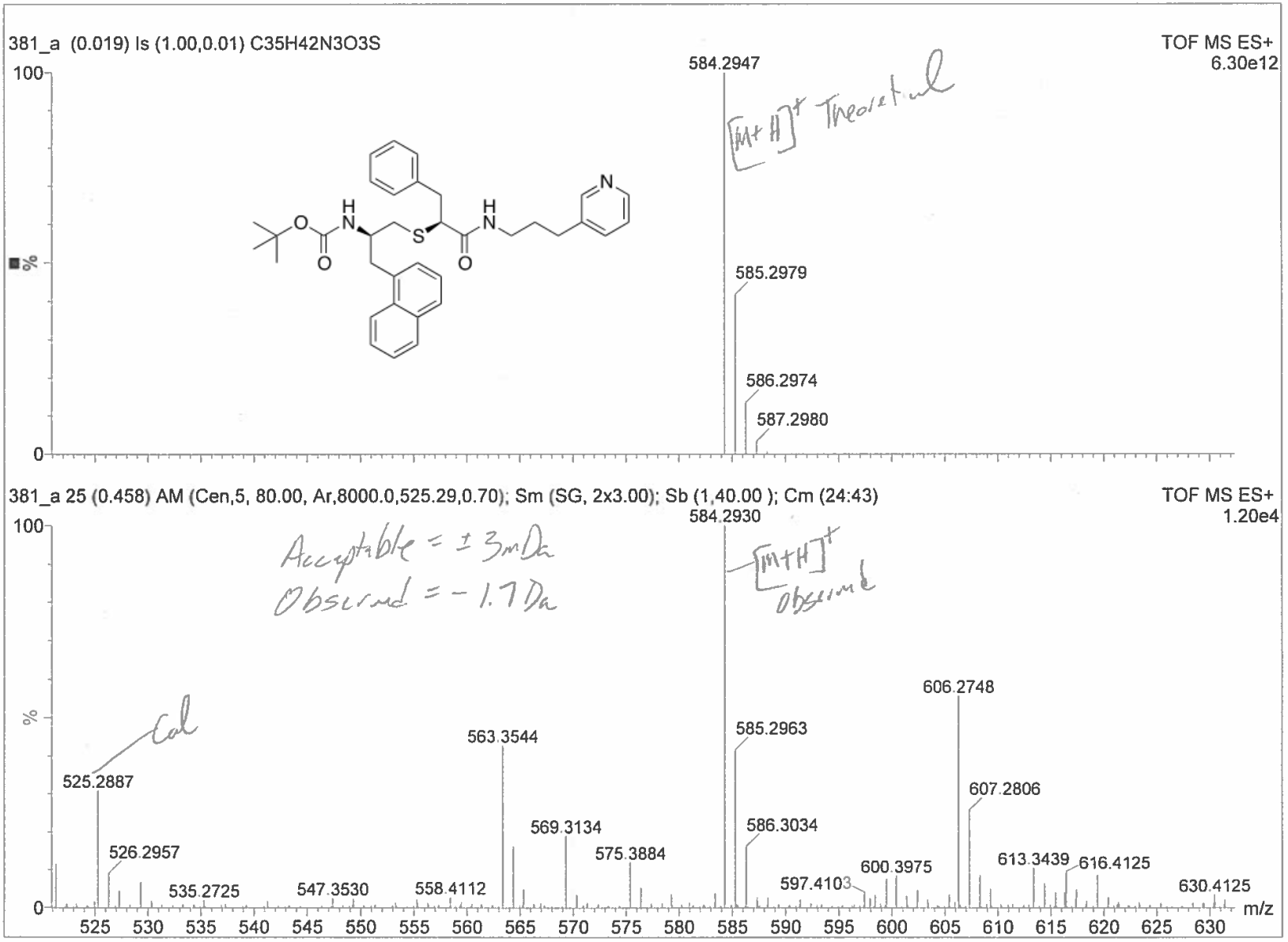

4109_a (0.019) Is (1.00,0.01) C31H39N3O3SNa
TOF MS ES+
6.58e12
556.2610
557.2641
558.2632
559.2638
Theoretical
[M+Na]+
4109_a 20 (0.367) AM (Cen,5, 80.00, Ar,8000.0,481.26,0.70); Sm (SG, 2x3.00); Sb (1,40.00); Cm (17:31)
TOF MS ES+
1.79e4
556.2587
Acceptable = ± 3mDa
Observed = -2.3mDa
Observed
[M+Na]+
519.3279
534.2783
[M+H]+
481.2625
500.3342
511.2773
525.2883
535.2792
557.2626
563.3541
501.3351
512.2837
490.3869
482.2675
527.2856
536.2823
480.3587
485.1407
491.3848
502.3381
555.3739
547.3368
Cal
m/z

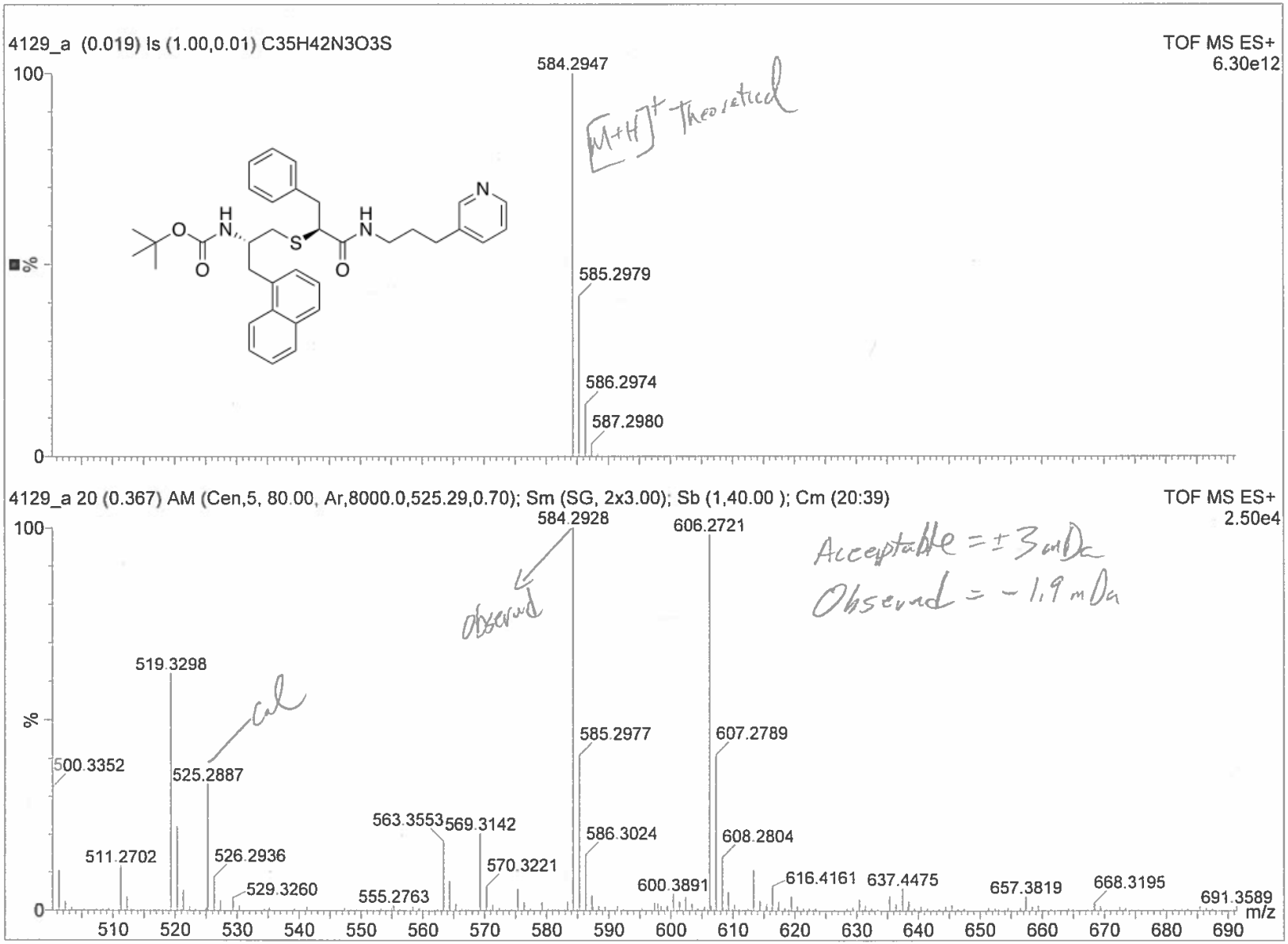

4111_a (0.019) Is (1.00,0.01) C31H39N3O3SNa
TOF MS ES+
6.58e12
556.2610
Theoretical
[M+Na]+
557.2641
558.2632
559.2638
4111_a 18 (0.330) AM (Cen,5, 80.00, Ar,8000.0,481.26,0.70); Sm (SG, 2x3.00); Sb (1,40.00); Cm (18:23)
TOF MS ES+
1.22e4
556.2585
Acceptable = ±3mDa
Observed = -2.5mDa
Observed
[M+Na]+
534.2784
[M+H]+
481.2625
Cal
519.3285
525.2888
500.3353
535.2819
557.2625
569.3157
482.2696
511.2712
536.2808
570.3214
613.3443
499.3154
502.3368
550.6259
587.5464
600.3730
m/z

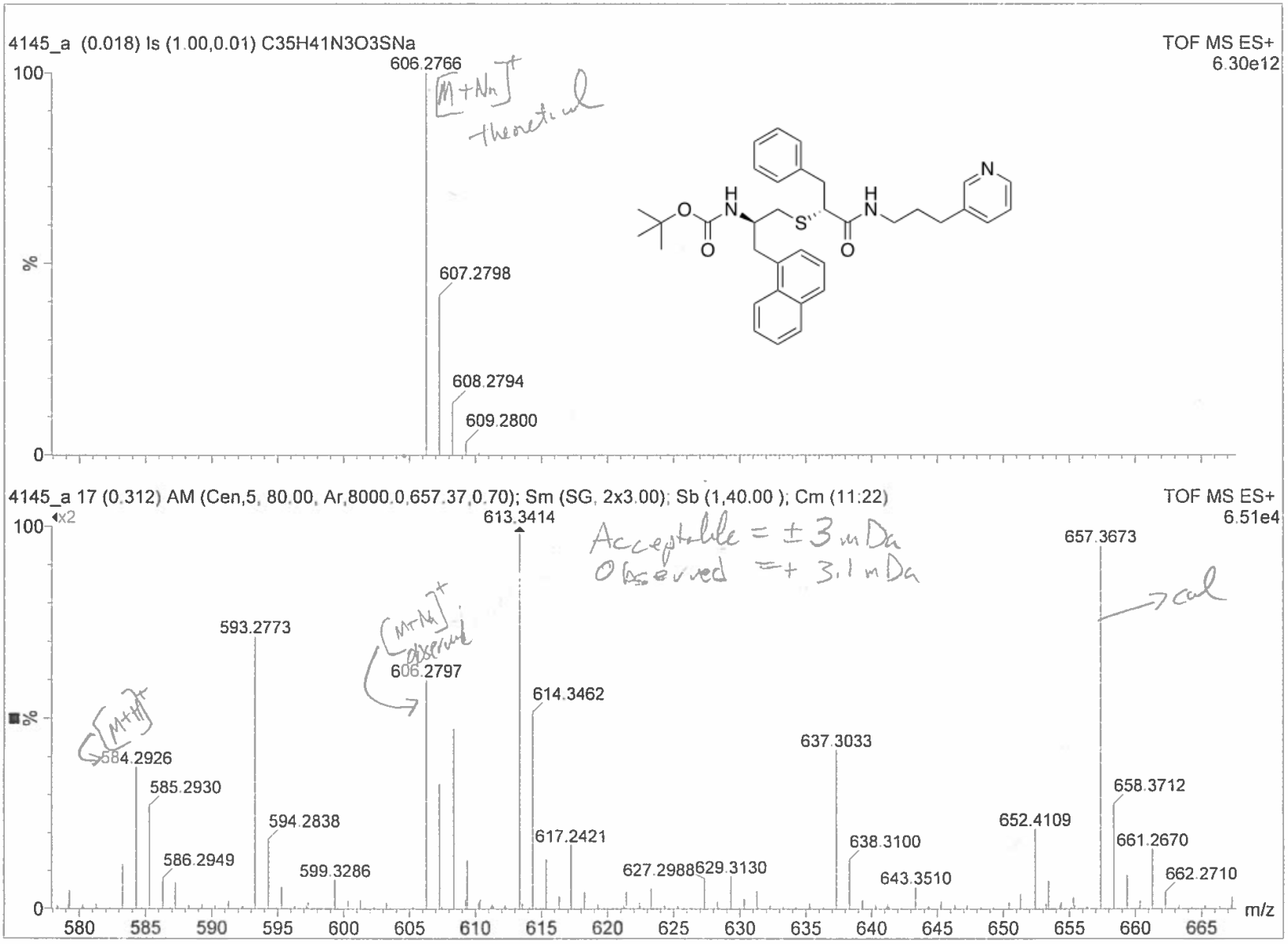

4115_a (0.019) Is (1.00,0.01) C31H39N3O3SNa
TOF MS ES+
6.58e12
556.2610
Theoretical
[M+Na]+
557.2641
558.2632
559.2638
4115_a 29 (0.532) AM (Cen,5, 80.00, Ar,8000.0,525.29,0.70); Sm (SG, 2x3.00); Sb (1,40.00); Cm (29:39)
TOF MS ES+
7.95e3
519.3288
556.2598
Acceptable = ± 3mDa
Observed = −1.2mDa
[M+Na]+ observed
500.3339
Cal
534.2791
525.2887
501.3365
511.2741
557.2641
535.2824
569.3157
512.2806
526.2924
536.2821
570.3323
502.3517
555.3033
584.3931
588.3860
600.3831
547.3530
m/z

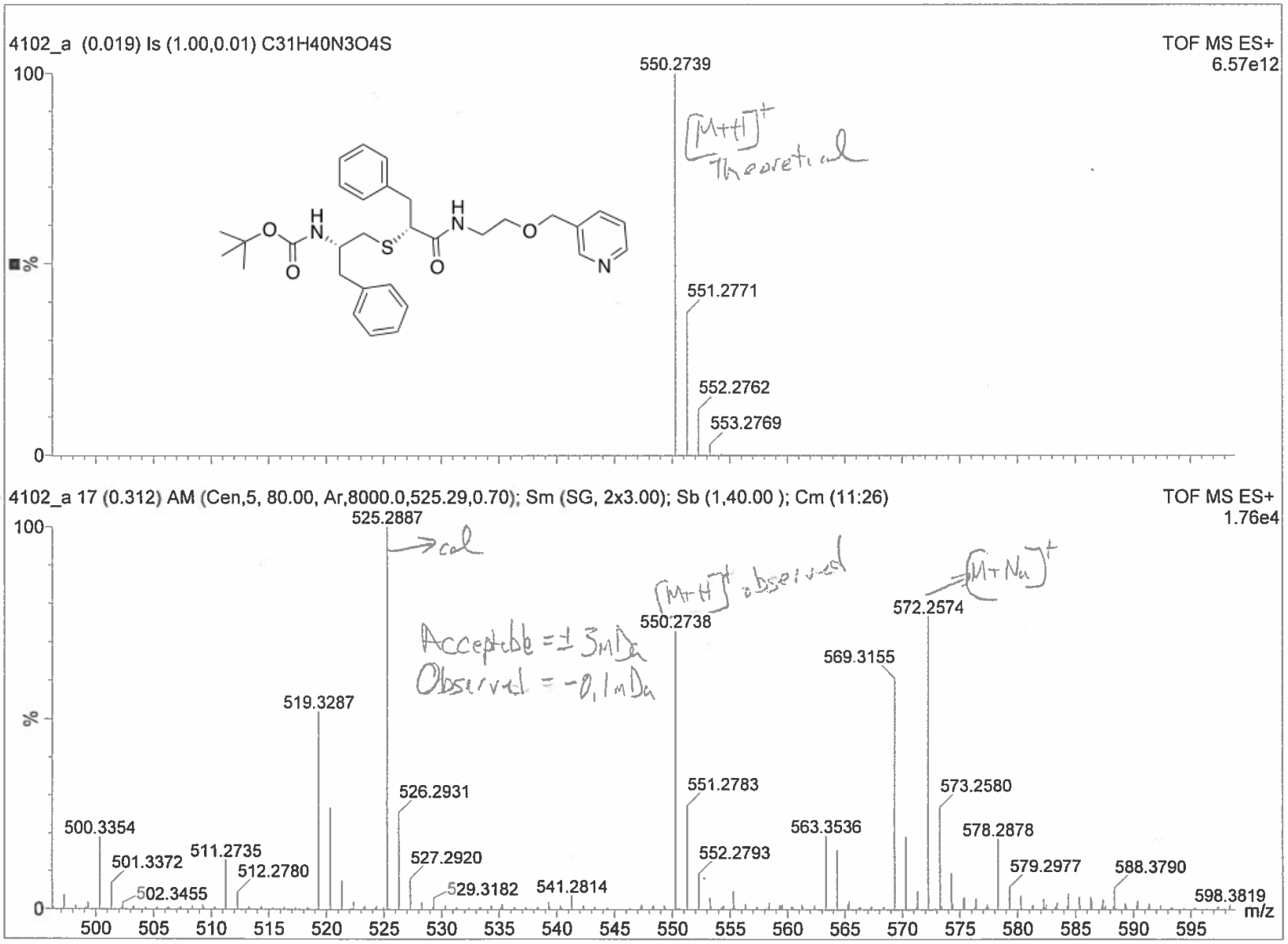

397_a (0.019) Is (1.00,0.01) C33H41N4O3S
TOF MS ES+
6.41e12
100
%
0
573.2899
574.2930
575.2924
576.2930
[M+H]+
Theoretical
397_a 19 (0.349) AM (Cen,5, 80.00, Ar,8000.0,525.29,0.70); Sm (SG, 2x3.00); Sb (1,40.00); Cm (19:30)
TOF MS ES+
1.92e4
Acceptable = ± 5mDa
Observed = +0.1 mDa
573.2900
595.2708
[M+Na]+
519.3295
525.2887
Cal
596.2738
574.2928
569.3146
526.2917
511.2708
563.3563
575.3023
597.2756
527.2912
575.3771
598.2838
541.2946
555.2975
587.5342
608.3811
m/z
510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605

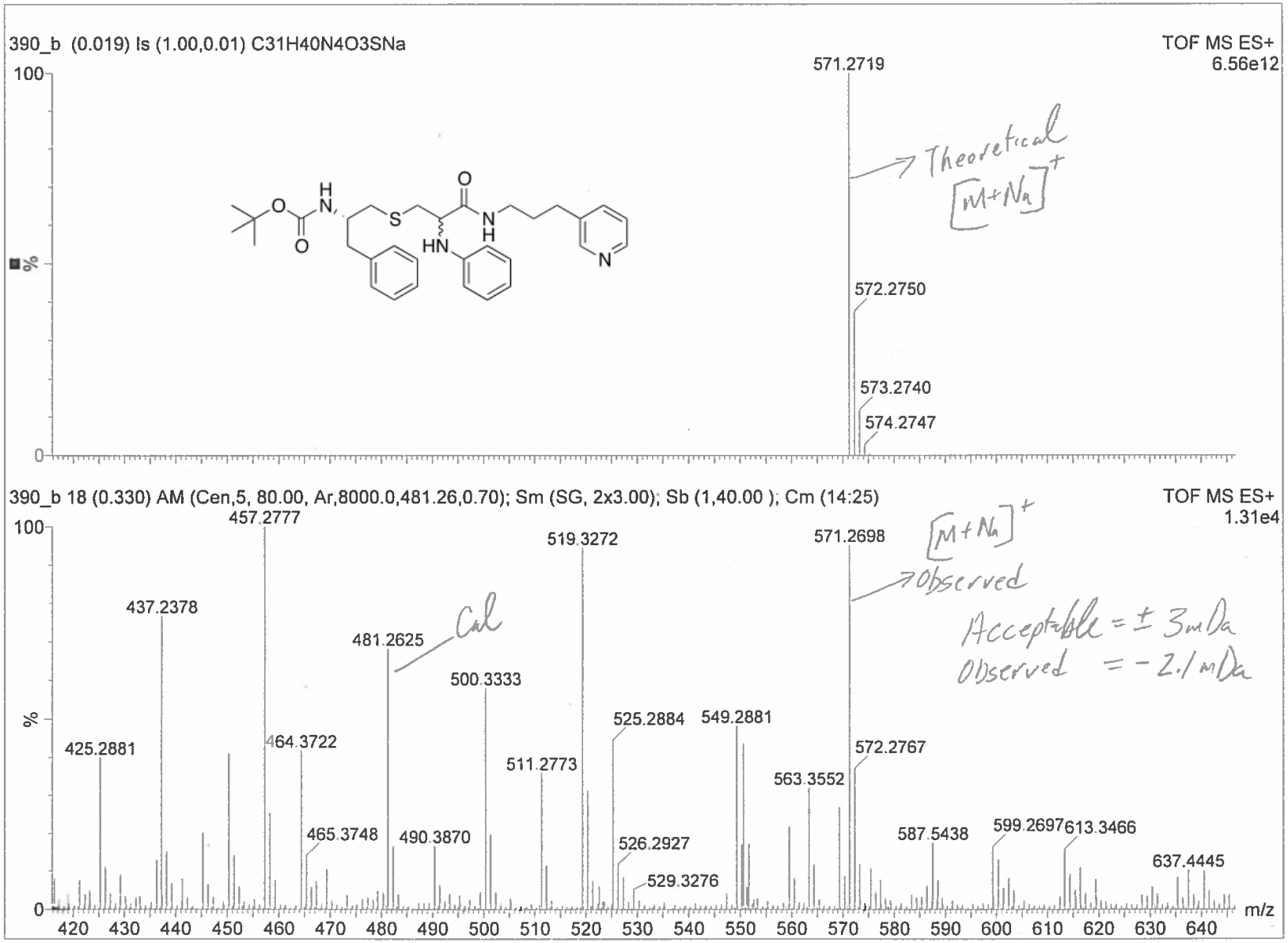

383_a (0.019) Is (1.00,0.01) C35H42N3O3S
TOF MS ES+
6.30e12
100
%
0
584.2947
585.2979
586.2974
587.2980
[MH]+
Theoretical
383_a 22 (0.404) AM (Cen,5, 80.00, Ar,8000.0,525.29,0.70); Sm (SG, 2x3.00); Sb (1,40.00); Cm (22:34)
TOF MS ES+
2.03e4
Acceptable = ± 3 mDa
Observed = − 2.6 mDa
584.2921
[MH]+
observed
606.2735
[MNa]+
585.2963
607.2795
586.2997
608.2820
587.3090
619.4064
599.4719
525.2887
Cal
526.2936
534.2841
541.2755
556.2692
563.3563
569.3136
570.3234
m/z
525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630


381_a (0.019) Is (1.00,0.01) C35H42N3O3S
TOF MS ES+
6.30e12
100
%
0
584.2947
585.2979
586.2974
587.2980
[M+H]+ Theoretical
381_a 25 (0.458) AM (Cen,5, 80.00, Ar,8000.0,525.29,0.70); Sm (SG, 2x3.00); Sb (1,40.00); Cm (24:43)
TOF MS ES+
1.20e4
584.2930
[M+H]+ Observed
Acceptable = ± 3mDa
Observed = -1.7Da
Cal
525.2887
526.2957
535.2725
547.3530
558.4112
563.3544
569.3134
575.3884
585.2963
586.3034
597.4103
600.3975
606.2748
607.2806
613.3439
616.4125
630.4125
m/z
525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630


4129_a (0.019) Is (1.00,0.01) C35H42N3O3S
TOF MS ES+
6.30e12
100
%
0
584.2947
585.2979
586.2974
587.2980
[M+H]+ Theoretical
4129_a 20 (0.367) AM (Cen,5, 80.00, Ar,8000.0,525.29,0.70); Sm (SG, 2x3.00); Sb (1,40.00); Cm (20:39)
TOF MS ES+
2.50e4
584.2928
606.2721
Observed
Acceptable = ± 3 mDa
Observed = -1.9 mDa
519.3298
cal
500.3352
525.2887
585.2977
607.2789
563.3553
569.3142
586.3024
608.2804
511.2702
526.2936
570.3221
529.3260
555.2763
600.3891
616.4161
637.4475
657.3819
668.3195
691.3589
m/z
510
520
530
540
550
560
570
580
590
600
610
620
630
640
650
660
670
680
690


4145_a (0.018) Is (1.00,0.01) C35H41N3O3SNa
TOF MS ES+
6.30e12
606.2766
[M+Na]+
theoretical
607.2798
608.2794
609.2800
4145_a 17 (0.312) AM (Cen,5, 80.00, Ar,8000.0,657.37,0.70); Sm (SG, 2x3.00); Sb (1,40.00); Cm (11:22)
TOF MS ES+
6.51e4
613.3414
Acceptable = ± 3 mDa
Observed = + 3.1 mDa
657.3673
calc
593.2773
[M+Na]+
observed
606.2797
[M+H]+
614.3462
584.2926
585.2930
637.3033
658.3712
594.2838
617.2421
652.4109
638.3100
661.2670
586.2949
599.3286
627.2988
629.3130
643.3510
662.2710
m/z


4102_a (0.019) Is (1.00,0.01) C31H40N3O4S
TOF MS ES+
6.57e12
100
%
0
550.2739
[M+H]+
Theoretical
551.2771
552.2762
553.2769
4102_a 17 (0.312) AM (Cen,5, 80.00, Ar,8000.0,525.29,0.70); Sm (SG, 2x3.00); Sb (1,40.00); Cm (11:26)
TOF MS ES+
1.76e4
525.2887
→ cal
[M+H]+ observed
550.2738
[M+Na]+
572.2574
Acceptable = ± 5mDa
Observed = -0.1mDa
519.3287
569.3155
526.2931
551.2783
573.2580
500.3354
563.3536
578.2878
511.2735
501.3372
512.2780
527.2920
552.2793
579.2977
588.3790
502.3455
529.3182
541.2814
598.3819
m/z
500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595


390_b (0.019) Is (1.00,0.01) C31H40N4O3SNa
TOF MS ES+
6.56e12
100
%
0
571.2719
572.2750
573.2740
574.2747
Theoretical
[M+Na]+
390_b 18 (0.330) AM (Cen,5, 80.00, Ar,8000.0,481.26,0.70); Sm (SG, 2x3.00); Sb (1,40.00); Cm (14:25)
TOF MS ES+
1.31e4
457.2777
519.3272
571.2698
[M+Na]+
Observed
437.2378
481.2625
Cal
Acceptable = ± 3mDa
Observed = -2.1mDa
500.3333
525.2884
549.2881
425.2881
464.3722
572.2767
511.2773
563.3552
465.3748
490.3870
526.2927
587.5438
599.2697
613.3466
637.4445
529.3276
m/z
420 430 440 450 460 470 480 490 500 510 520 530 540 550 560 570 580 590 600 610 620 630 640