Supporting Information

Exploiting a water network to achieve enthalpy-driven, bromodomain-selective BET inhibitors

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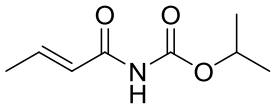
Synthetic Chemistry

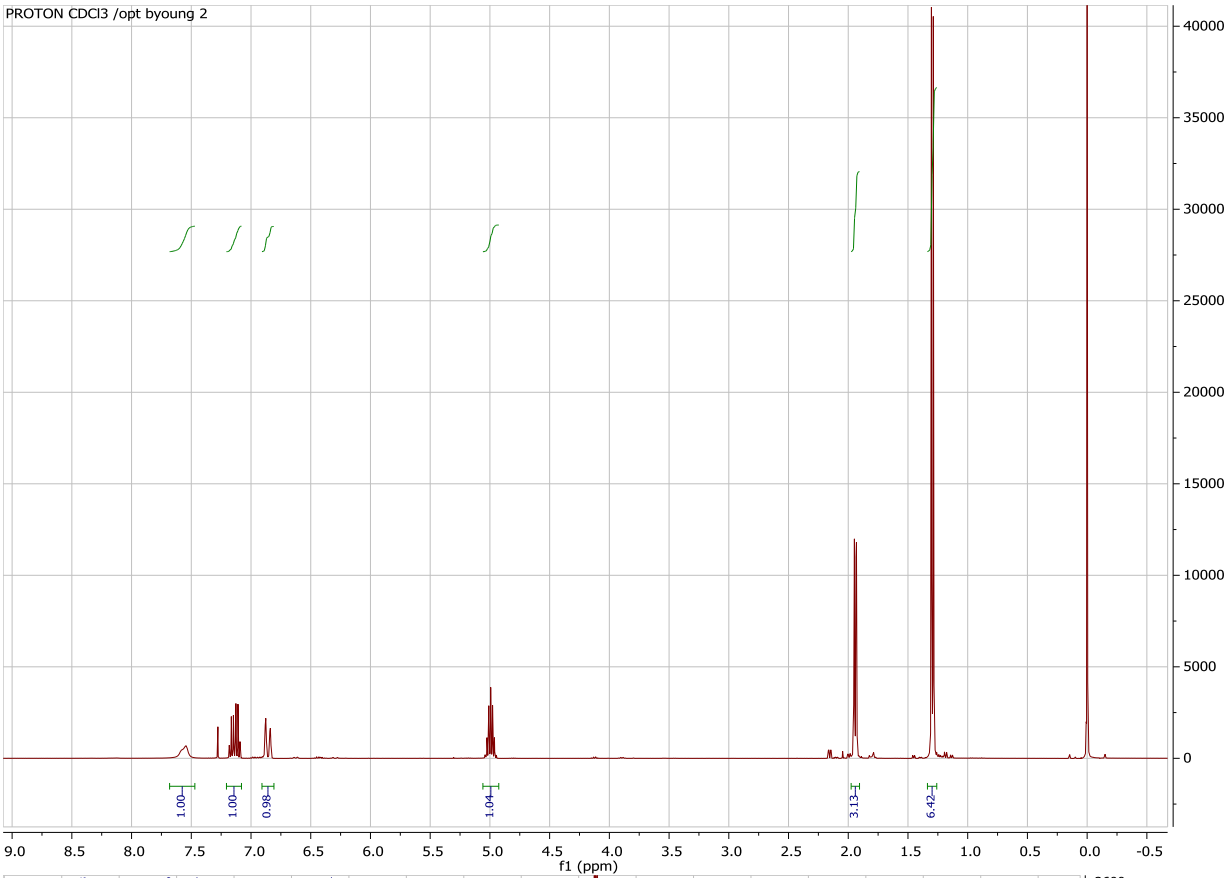
*General procedure for parallel Suzuki couplings (**9**-**14**).* To a microwave reaction* vessel flame-dried and purged with nitrogen was added bromide **8** (35 mgs, 0.10 mmol), boronic acid (20-40 mgs, 0.15 mmol), K_3PO_4 (70 mgs, 0.50 mmol), BrettPhos** (5 mgs, 0.01 mmol) and BrettPhos Palladacycle Gen. 3*** (10 mgs, 0.01 mmol). The vessel(s) were treated with anhydrous 2-methyl-2-butanol (0.5 mL), sealed under nitrogen and heated to 100 ºC for 17 h. Reaction were quenched via addition of EtOAc (2 mL) and water (2 mL). Organic solution was collected and concentrated. Crude products were purified via automated normal phase chromatography (EtOAc: hexane). Reactions can also be purified in an automated reverse phase (acetonitrile: 0.1% formic acid) manner as well (singular or parallel format). The yields of the reported compounds vary from 31-89%. See below for individual reaction yields, % purity and characterization, respectively.

*microwave vessels purchased from Biotage.
**BrettPhos was purchased from Strem Chemicals [15-1152]
***BrettPhos Palladacycle G3 was purchased from Strem Chemicals [46-0322]

Characterization



Isopropyl (E)-but-2-enoylcarbamate (**5**). To a solution of isopropyl carbamate (15.85 g, 154 mmol) in anhydrous THF (150 mL) in a flame-dried flask at -78 ºC was added crotonoyl chloride (14.16 mL, 146 mmol), followed by LiHMDS (300 mL, 1.0 M in THF). Reaction was permitted to slowly warm to rt and stir at rt overnight. Reaction was quenched via addition of chilled (~0 ºC) saturated aq ammonium chloride (175 mL). Upon warming, solution was extracted with EtOAc (3 x 75 mL). Combined organics were washed with sat NaCl and dried with $MgSO_4$, filtered and concentrated under reduced pressure. Crude product was purified via automated normal phase chromatography (EtOAc: hexanes, 20:80) to provide the desired imide as a white solid (12.3 g, 64% yield, m.pt.: 91 ºC). LCMS/UPLC (method: formate) retention time 0.82 min, $[M + H]^+$ = 172.27. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (s, 1H), 7.14 (dq, *J* = 15.3, 6.9 Hz, 1H), 6.86 (dq, *J* = 15.2, 1.7 Hz, 1H), 4.99 (p, *J* = 6.3 Hz, 1H), 1.94 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.30 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.03, 151.36, 146.34, 122.94, 70.23, 21.78, 18.40.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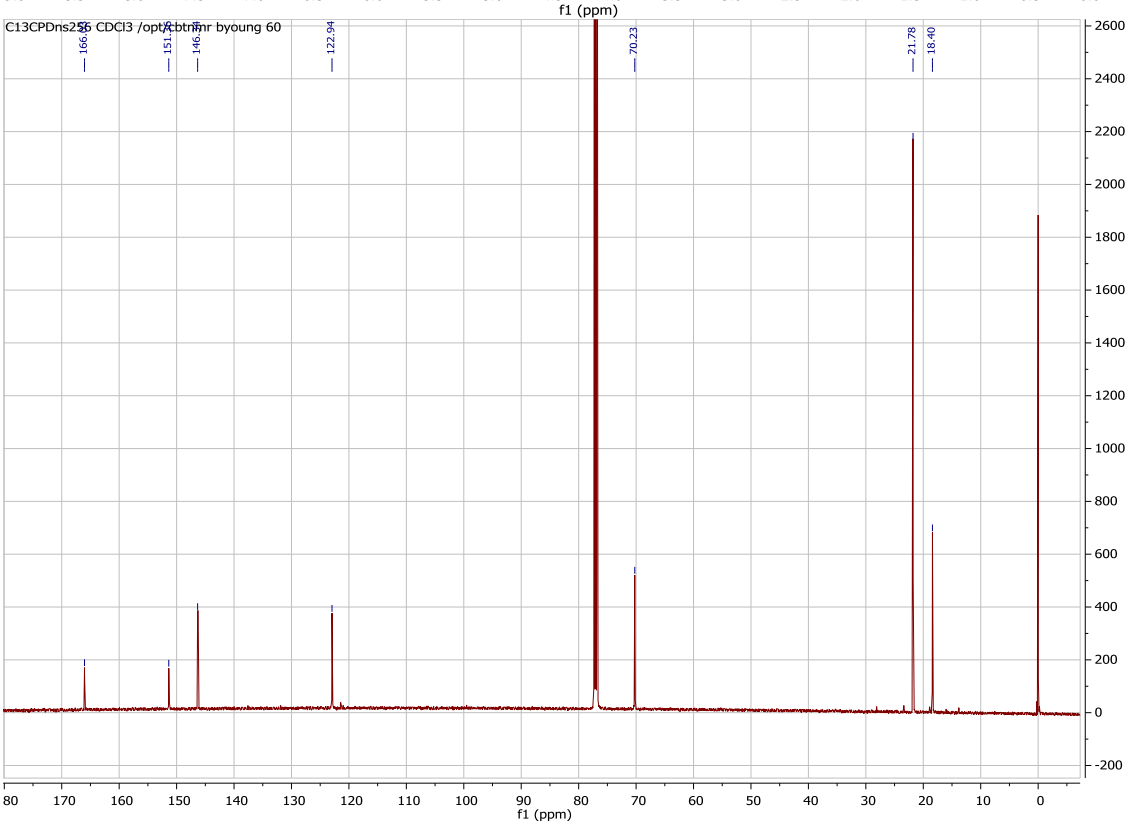
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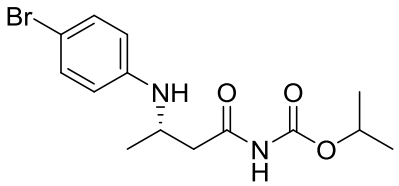
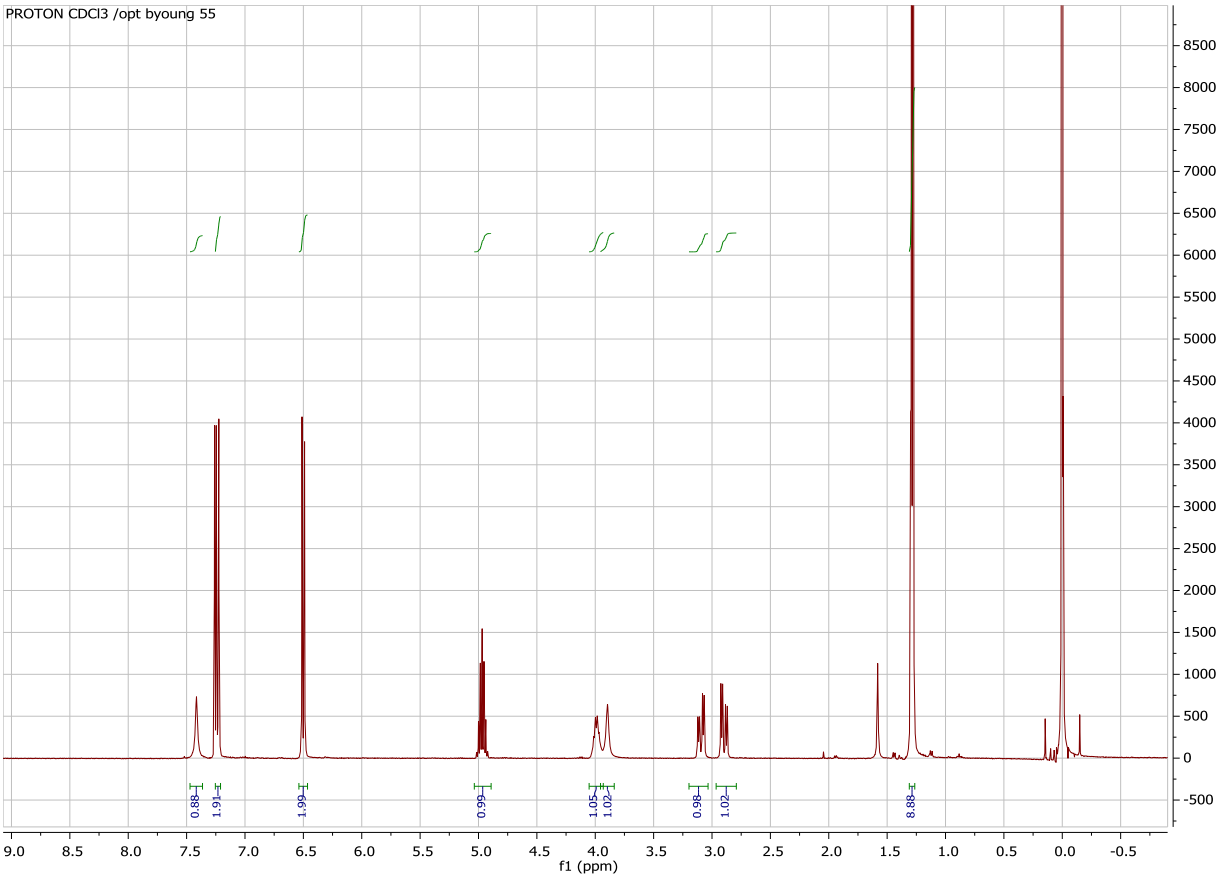
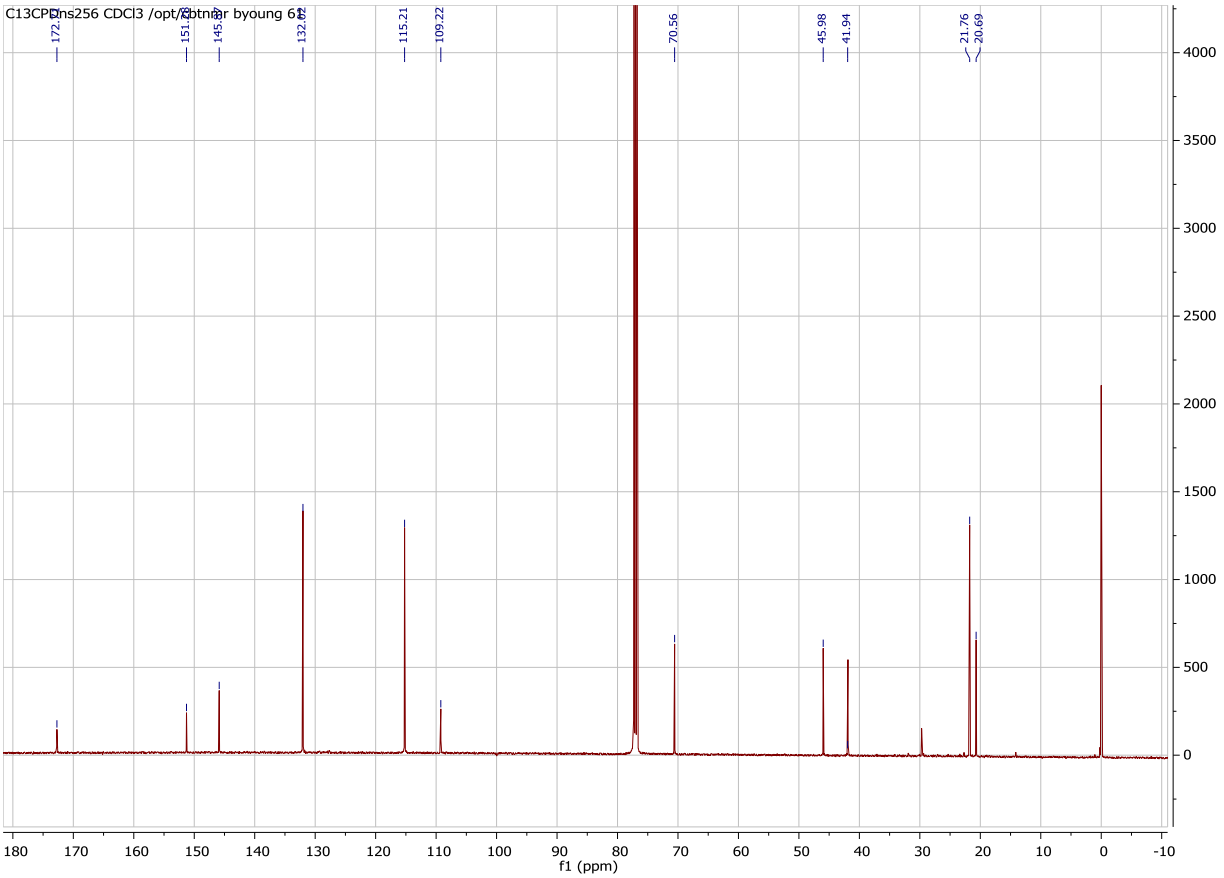


Isopropyl (S)-(3-((4-bromophenyl)amino)butanoyl)carbamate (**6**). To a suspension of imide **5** (5.0 g, 29.2 mmol) and (R)-(+)-BINAP-Pd(OH)$_2$(OTf)$_2$ (1.45 g, 1.36 mmol) in anhydrous toluene (80 mL) at rt was added 4-bromoaniline (3.35 g, 19.47 mmol) slowly over 1 h (alternatively aniline can be dissolved in toluene and added dropwise). Resulting reaction was permitted to stir at rt for 17-72 h. Catalyst can become gummy during the course of the reaction (see Gosmini et al., *J Med Chem*, 2014, *57* (19), 8111-8131). Loading catalyst and aniline in portions can help avoid gumminess. Heating the reaction gently (temperature = 45 ºC) can help as well without negatively influencing the ee of the reaction. Once reaction was deemed complete, the reaction was concentrated under vacuum. Residual was purified via automated normal phase chromatography (EtOAc: hexanes, 20:80) to provide the desired Michael adduct as an off-white solid (6.12 g, 92% yield, m.pt.: 131 ºC). Chiral SFC (method: methanol: liquid CO_2) retention time 7.40 min (major enantiomer, 92.2% UV), 10.58 min (minor enantiomer, 7.8% UV); 85% ee. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (s, 1H), 7.25 – 7.21 (m, 2H), 6.54 – 6.46 (m, 2H), 4.97 (hept, *J* = 6.3 Hz, 1H), 3.99 (q, *J* = 6.3 Hz, 1H), 3.90 (s, 1H), 3.09 (dd, *J* = 16.0, 5.7 Hz, 1H), 2.90 (dd, *J* = 16.0, 6.0 Hz, 1H), 1.29 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.71, 151.28, 145.87, 132.02, 115.21, 109.22, 70.56, 45.98, 41.94, 21.76, 20.69.





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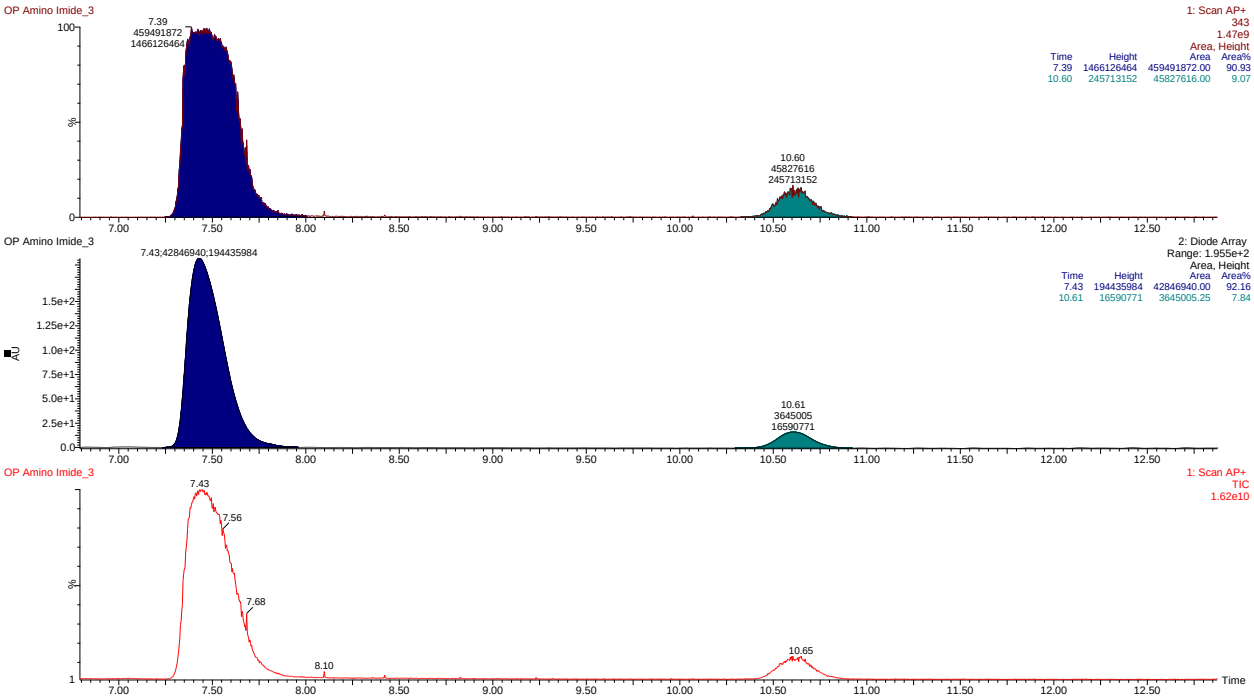

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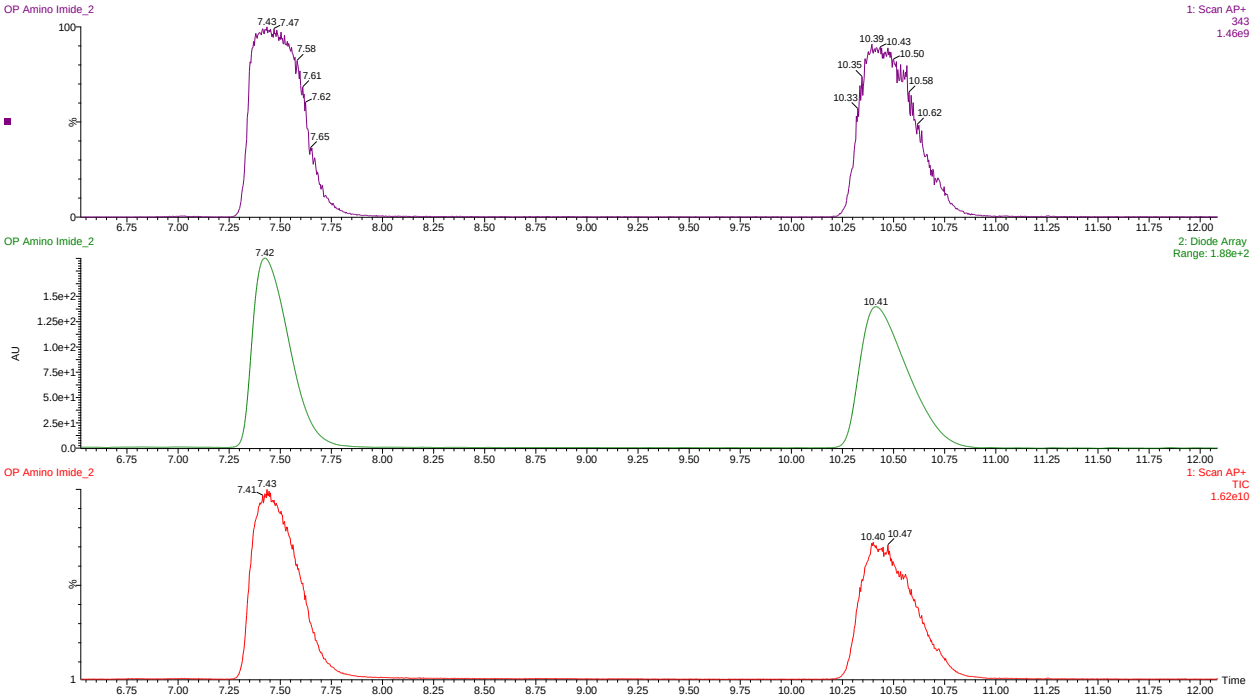
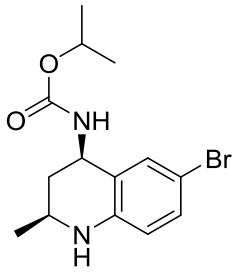
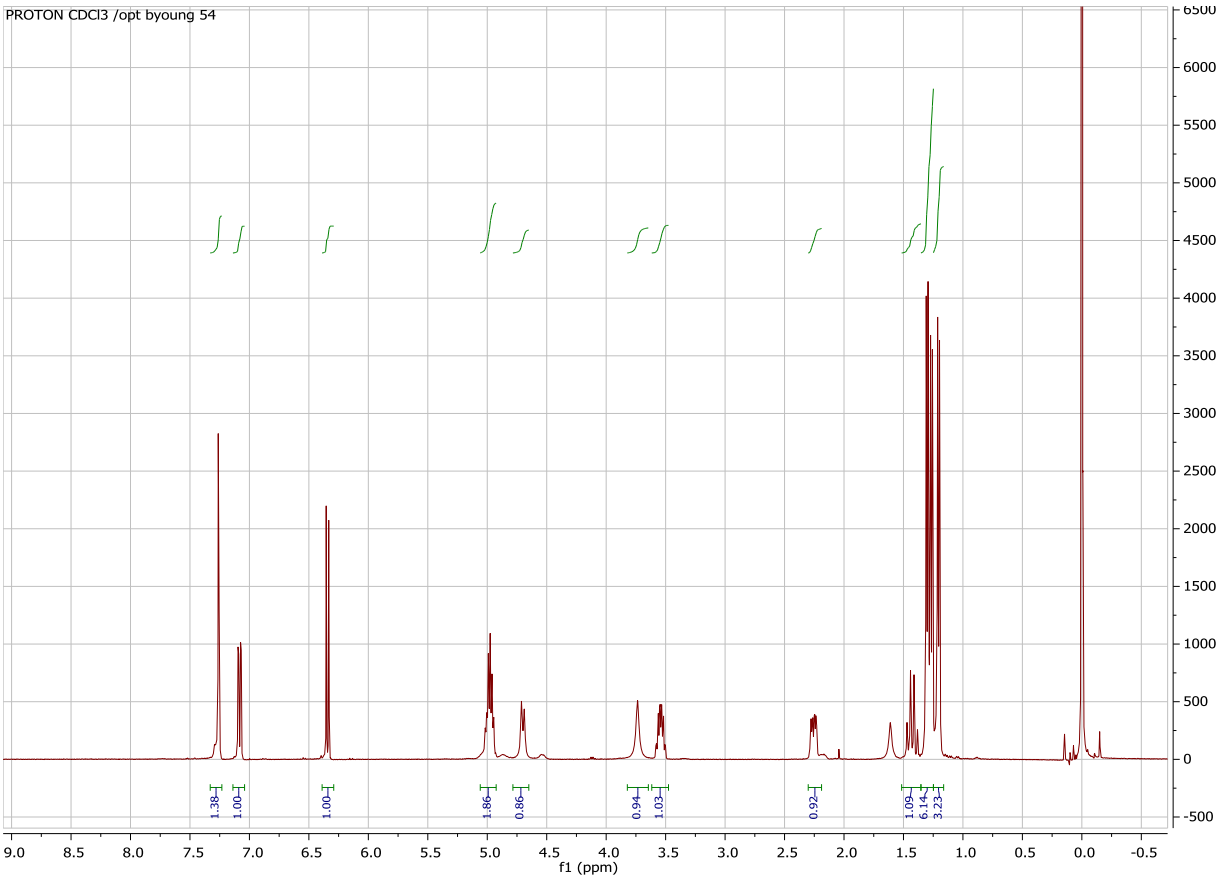
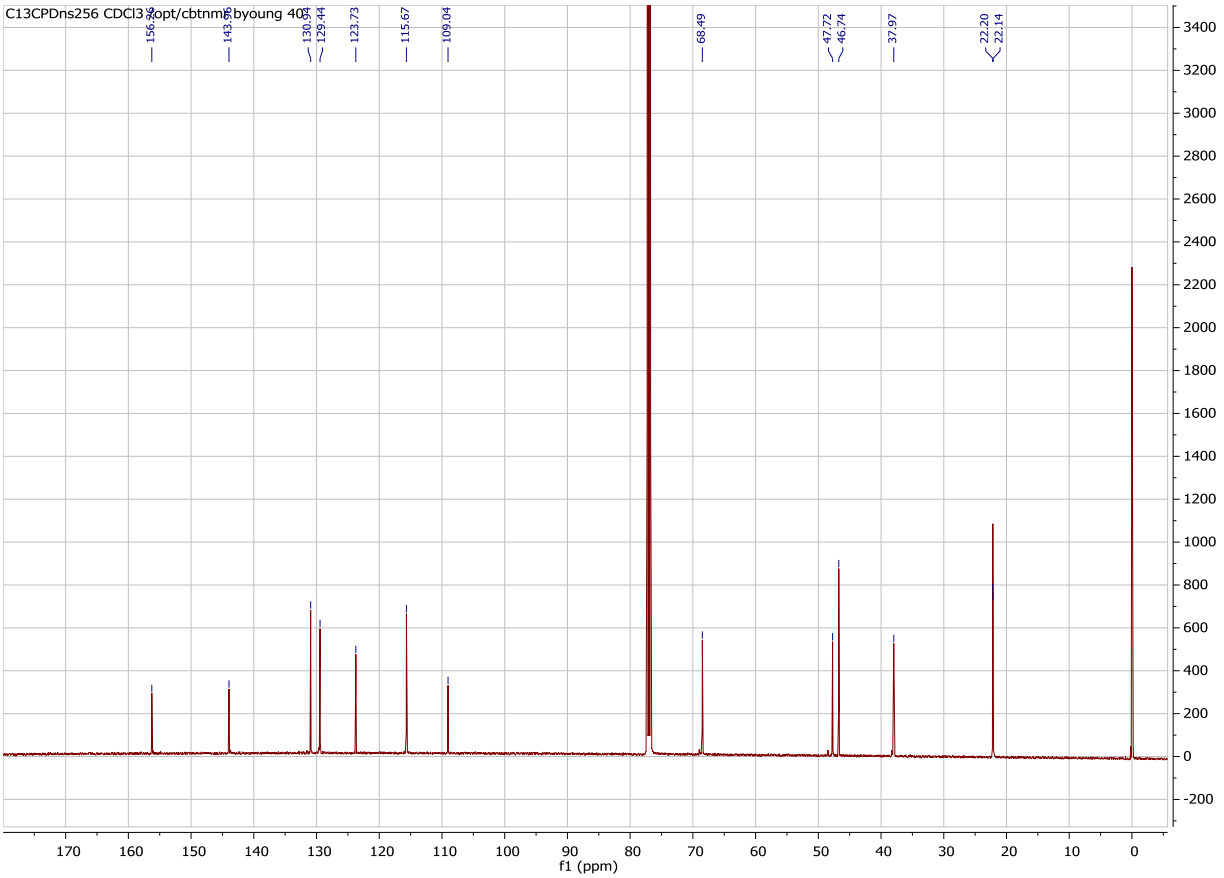




isopropyl ((2S,4R)-6-bromo-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (**7**). To a solution of amino imide **6** (6.12 g, 17.83 mmol) in EtOH (90 mL) at -10 ºC was added $NaBH_4$ (0.51 g, 13.37 mmol) in one portion, followed by an aqueous solution of $MgCl_2.6H_2O$ (3.99 g, 19.61 mmol, dissolved in 12 mL water) dropwise such that the internal temperature did not exceed -10 ºC. The resulting solution was permitted to stir at 0 ºC for 1 h, followed by rt for 1 h. The reaction was quenched via addition of citric acid (6.5 g, 2.5 eq) dissolved in aq 1M HCl (54 mL), followed by treatment of CH_2Cl_2 (50 mL). After 1 h of heterogeneous stirring, organic solution was collected, followed by aqueous extractions with CH_2Cl_2 (2 x 30 mL). Combined organics were washed with sat aq NaCl, dried over $MgSO_4$, filtered and concentrated. Crude product was purified via automated normal phase chromatography (EtOAc: hexanes) to provide cyclized amine as a white solid (2.1 g, 91% yield, m.pt.: 167 ºC). LCMS/UPLC (method: formate) retention time 1.19 min, $[M + H]^+$ = 327.01. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 (d, *J* = 1.1 Hz, 1H), 7.08 (dd, *J* = 8.5, 0.9 Hz, 1H), 6.34 (dd, *J* = 8.5, 0.9 Hz, 1H), 4.98 (m, *J* = 5.4 Hz, 2H), 4.70 (d, *J* = 9.5 Hz, 1H), 3.74 (s, 1H), 3.62 – 3.48 (m, 1H), 2.26 (ddd, *J* = 12.6, 6.0, 2.3 Hz, 1H), 1.43 (q, *J* = 11.7 Hz, 1H), 1.28 (dd, *J* = 14.6, 6.3 Hz, 6H), 1.20 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.26, 143.96, 130.94, 129.44, 123.73, 115.67, 109.04, 68.49, 47.72, 46.74, 37.97, 22.20, 22.14.

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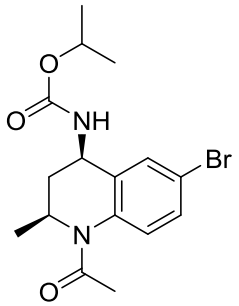
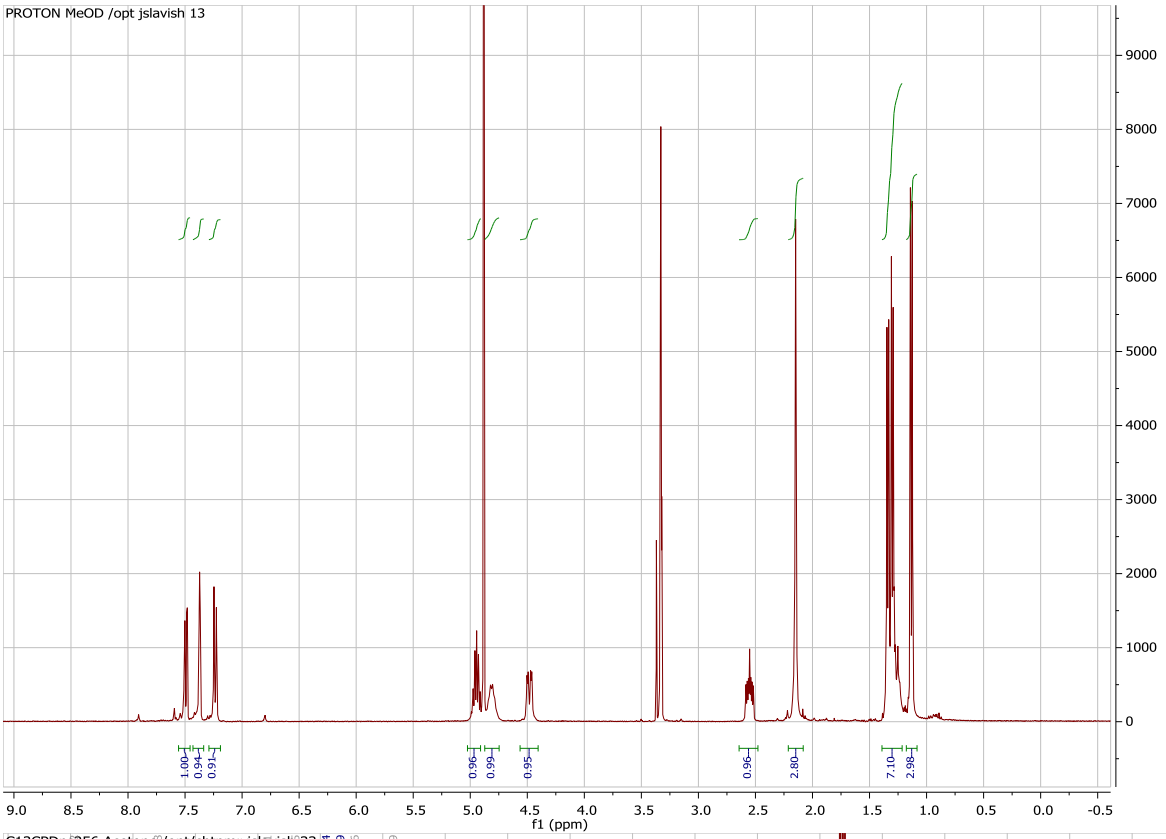


Isopropyl ((2S,4R)-1-acetyl-6-bromo-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (**8**). To a solution of amine **7** (5.32 g, 16.26 mmol) in CH_2Cl_2 (35 mL) and pyridine (3.94 mL) under nitrogen at rt was added dropwise acetyl chloride (1.89 mL, 24.39 mmol). Reaction was permitted to stir at rt for 3-17 h. Reaction was then treated with CH_2Cl_2 (50 mL) and sat aq. $NaHCO_3$ (50 mL). The phases were separated; aqueous solution was extracted with CH_2Cl_2 (2 x 20 mL). Combined organics were washed with sat. NaCl, dried over $MgSO_4$, filtered and concentrated. Residual was purified via automated normal phase chromatography (EtOAc:hexanes, 25:75) to provide amide product as a white solid (1.8 g, 95% yield, m.pt.: 163 ºC). Chiral SFC (method: methanol: liquid CO_2) retention time 5.66 min (major enantiomer, 95.2% UV), 6.06 min (minor enantiomer, 4.8% UV); 90.2% ee. Further purification of the desired enantiomer was possible but was not performed for these studies in the interest of expediency. Optical rotation. $[\alpha]_D$ = 251.1º (c = 6.1 mg/1 mL EtOH, temperature = 23.1 ºC, l = 0.5 dm). Literature: $[\alpha]_D$ = 281.1º (c = 0.508 g/100 mL, EtOH temperature = 20 ºC, l = 0.1 dm) (source: Gosmini et al., *J Med Chem*, 2014, *57* (19), 8111-8131). Optical purity (according to optical rotation) = 89.3% ee. LCMS/UPLC (method: formate) retention time 1.11 min, $[M + H]^+$ = 368.88.^{1}H NMR (400 MHz, Methanol-d_4) δ 7.49 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.37 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 4.95 (dq, *J* = 12.5, 6.1 Hz, 1H), 4.81 (d, *J* = 7.2 Hz, 1H), 4.48 (dd, *J* = 12.5, 4.1 Hz, 1H), 2.55 (ddd, *J* = 12.8, 8.7, 4.4 Hz, 1H), 2.15 (s, 3H), 1.39 – 1.21 (m, 7H), 1.13 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, Acetone) δ 169.22, 155.78, 138.21, 133.75, 128.64, 126.59, 124.46, 118.09, 67.08, 46.79, 46.62, 38.39, 20.07, 19.74, 18.76.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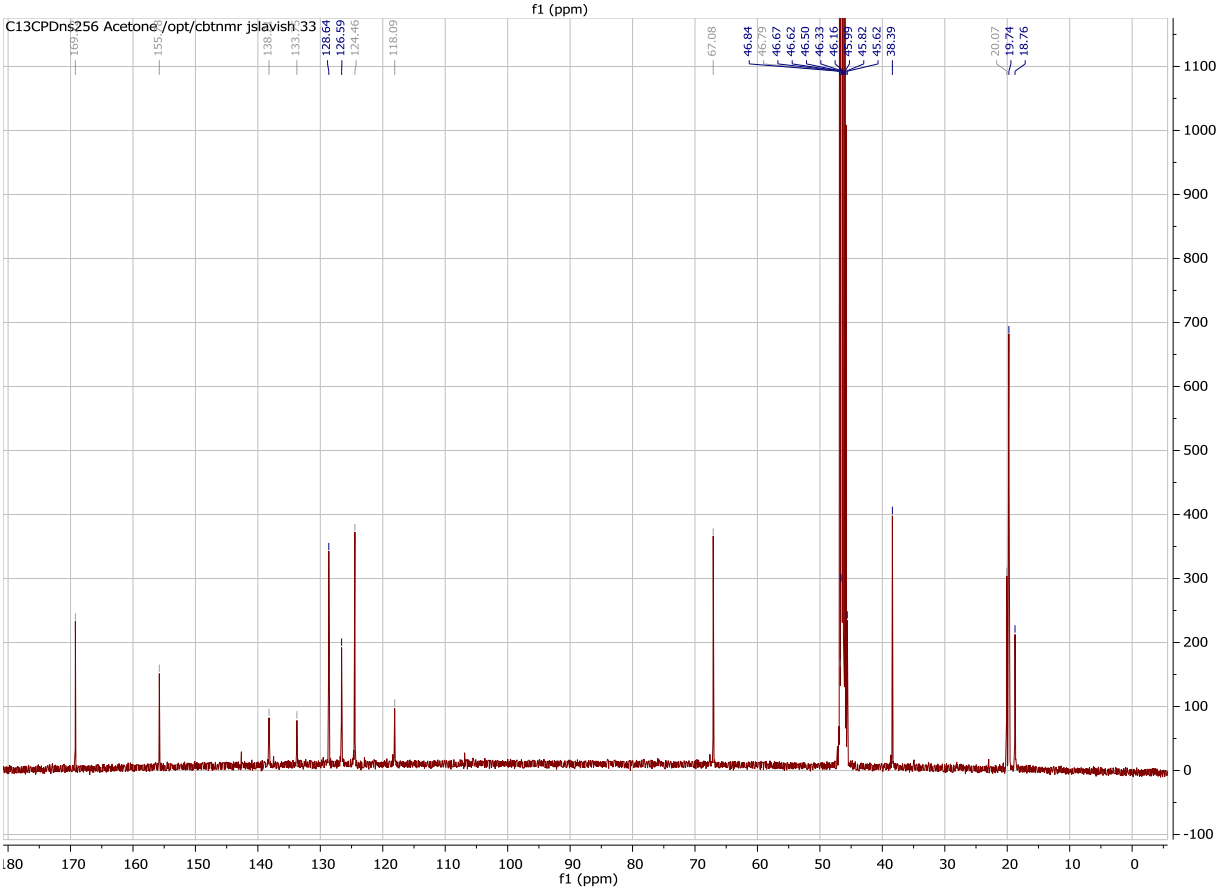
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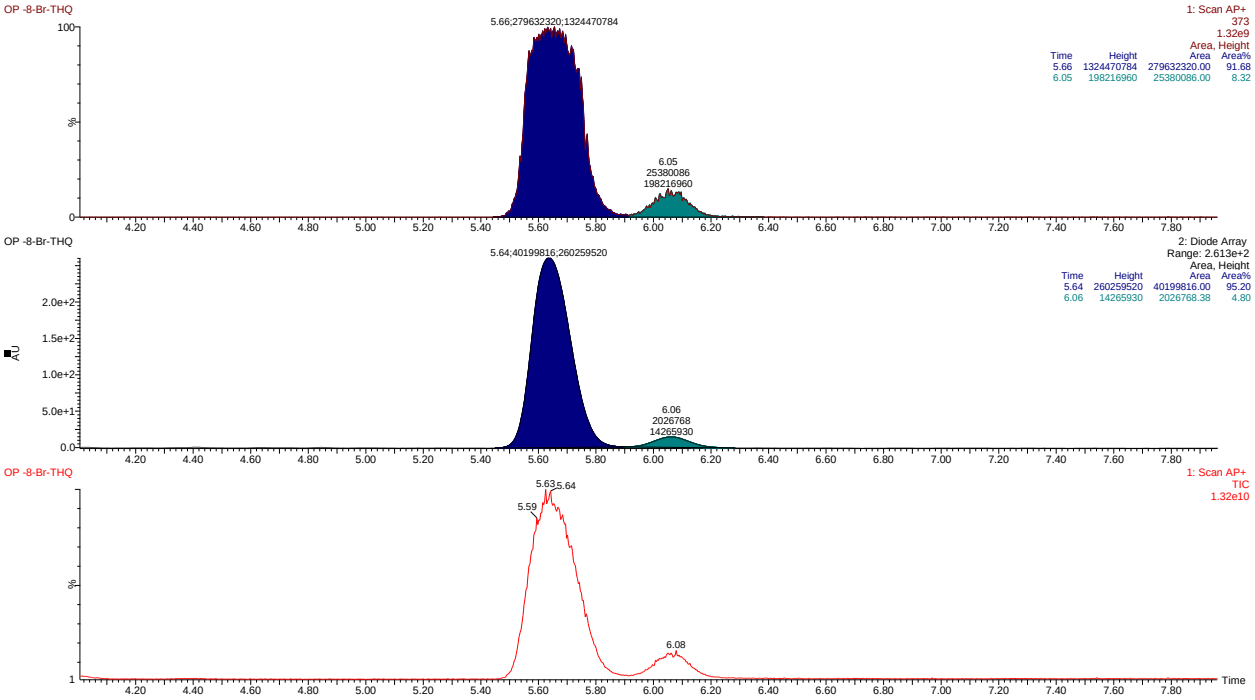
Optically Active **8**



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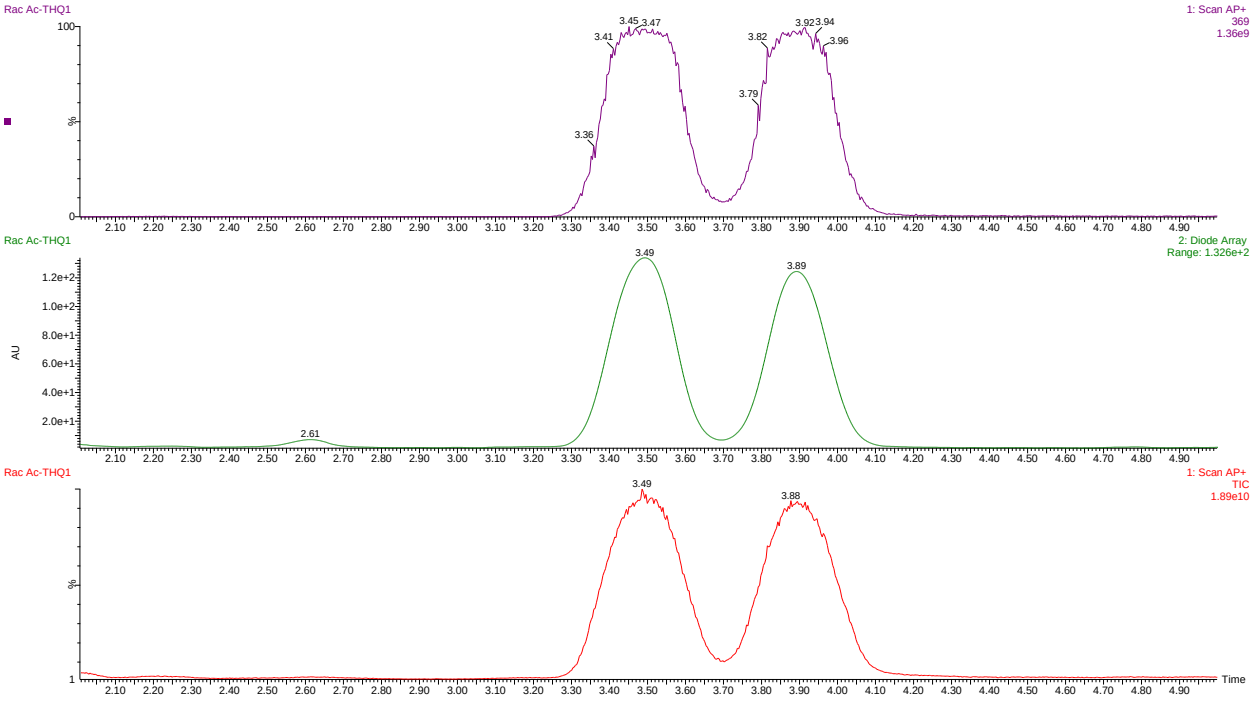
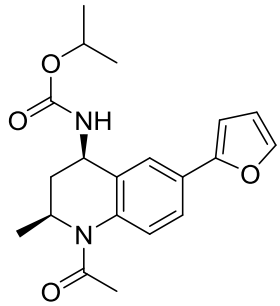
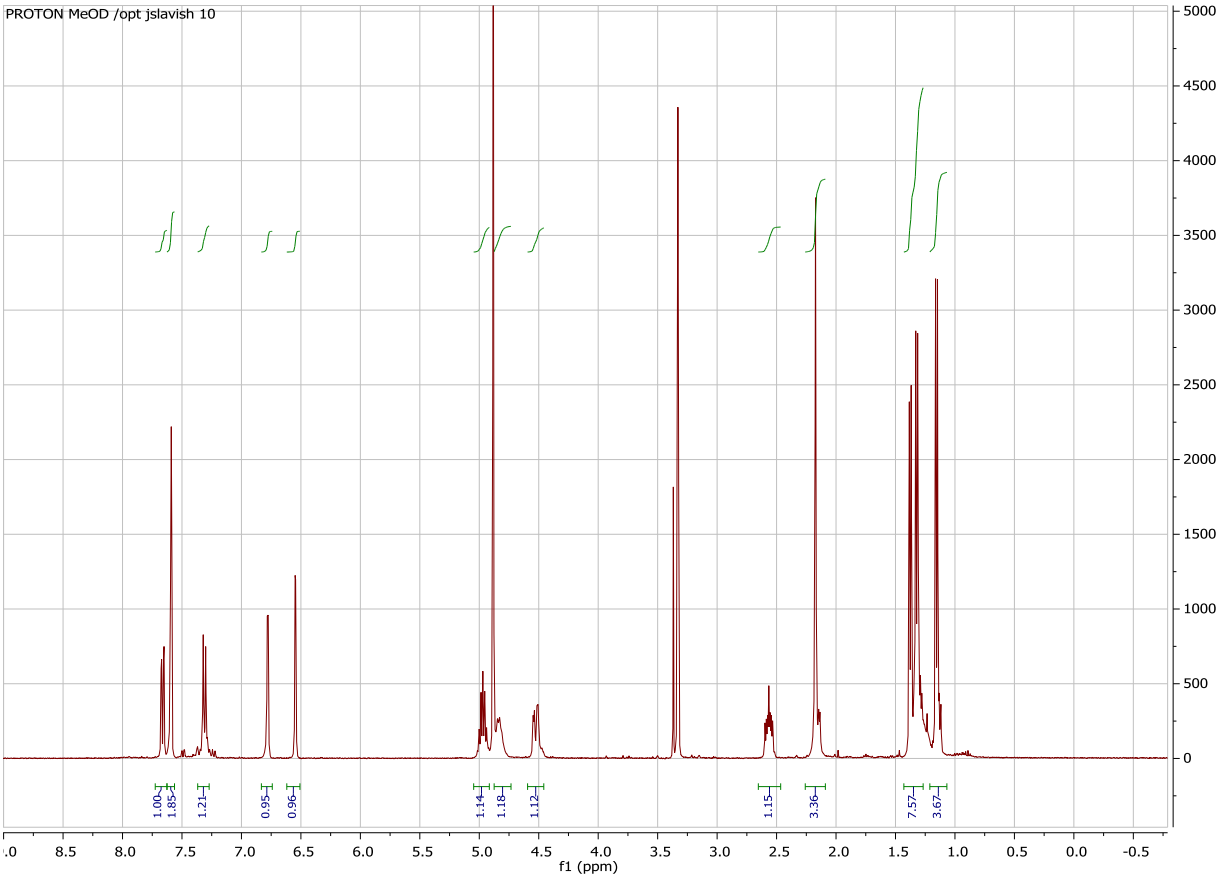
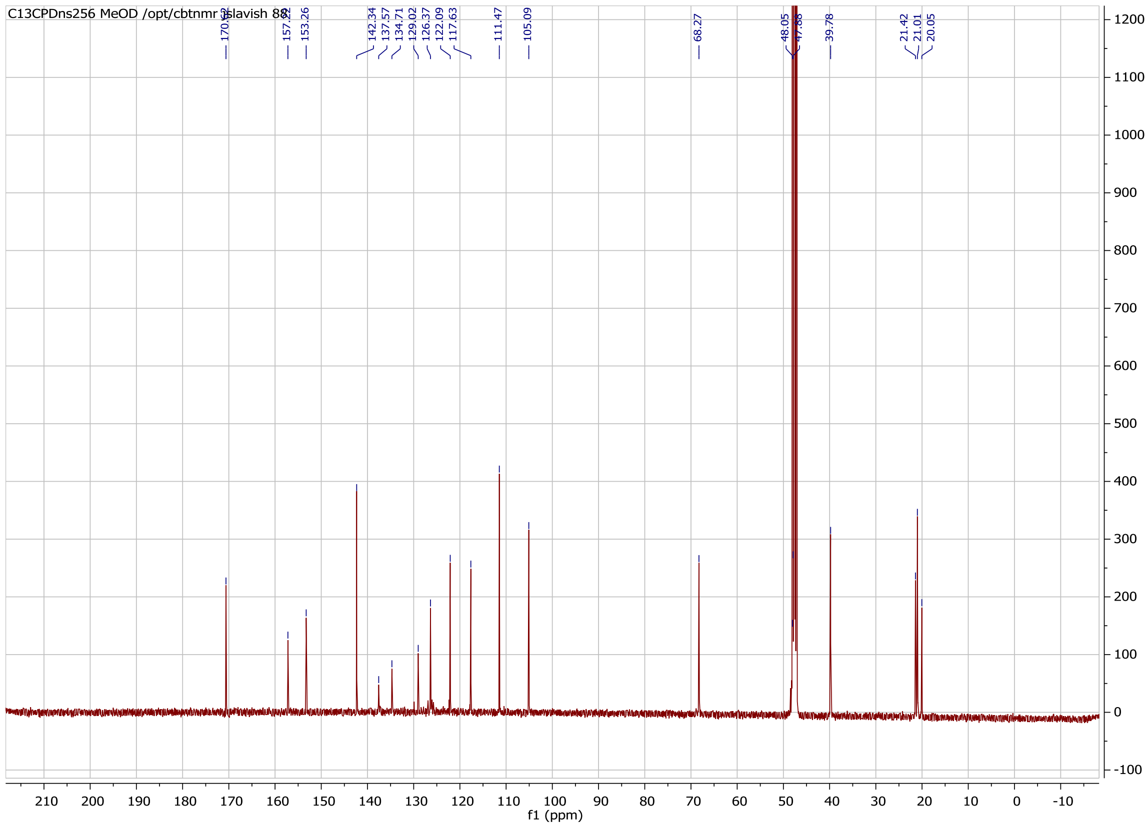




Isopropyl ((2S,4R)-1-acetyl-6-(furan-2-yl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (**9**). Yield: 31%.^{1}H NMR (400 MHz, Methanol-d_4) δ 7.66 (dd, J = 8.2, 1.8 Hz, 1H), 7.62 – 7.57 (m, 2H), 7.31 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 3.3 Hz, 1H), 6.55 (dd, J = 3.4, 1.8 Hz, 1H), 4.97 (p, J = 6.3 Hz, 1H), 4.84 (d, J = 6.7 Hz, 1H), 4.53 (dd, J = 12.5, 4.0 Hz, 1H), 2.57 (ddd, J = 12.7, 8.7, 4.4 Hz, 1H), 2.17 (s, 3H), 1.46 – 1.20 (m, 7H), 1.15 (t, J = 5.7 Hz, 3H).^{13}C NMR (126 MHz, MeOD) δ 170.62, 157.22, 153.26, 142.34, 137.57, 134.71, 129.02, 126.37, 122.09, 117.63, 111.47, 105.09, 68.27, 48.05, 47.88, 39.78, 21.42, 21.01, 20.05. HRMS: calculated: 357.1814 m/z found: 357.1814 m/z.

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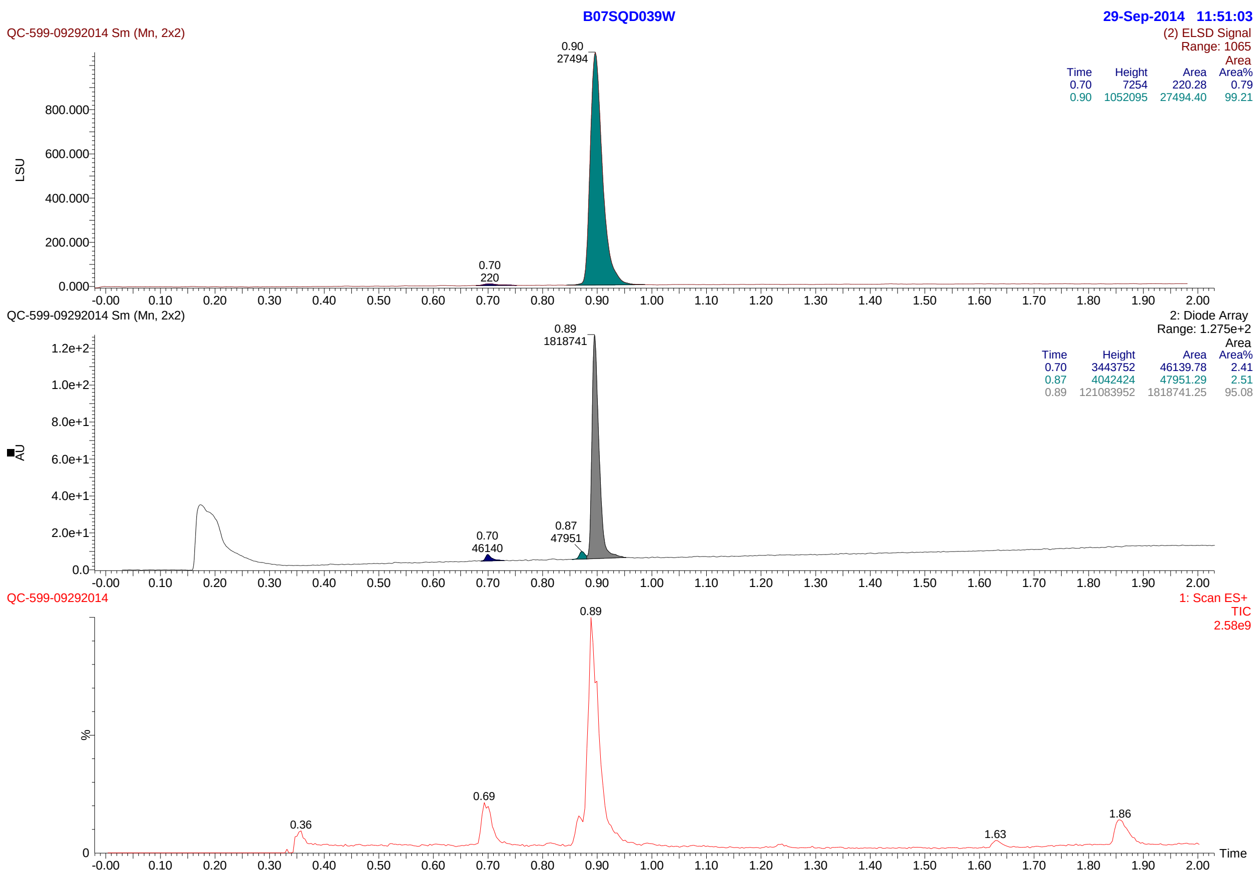
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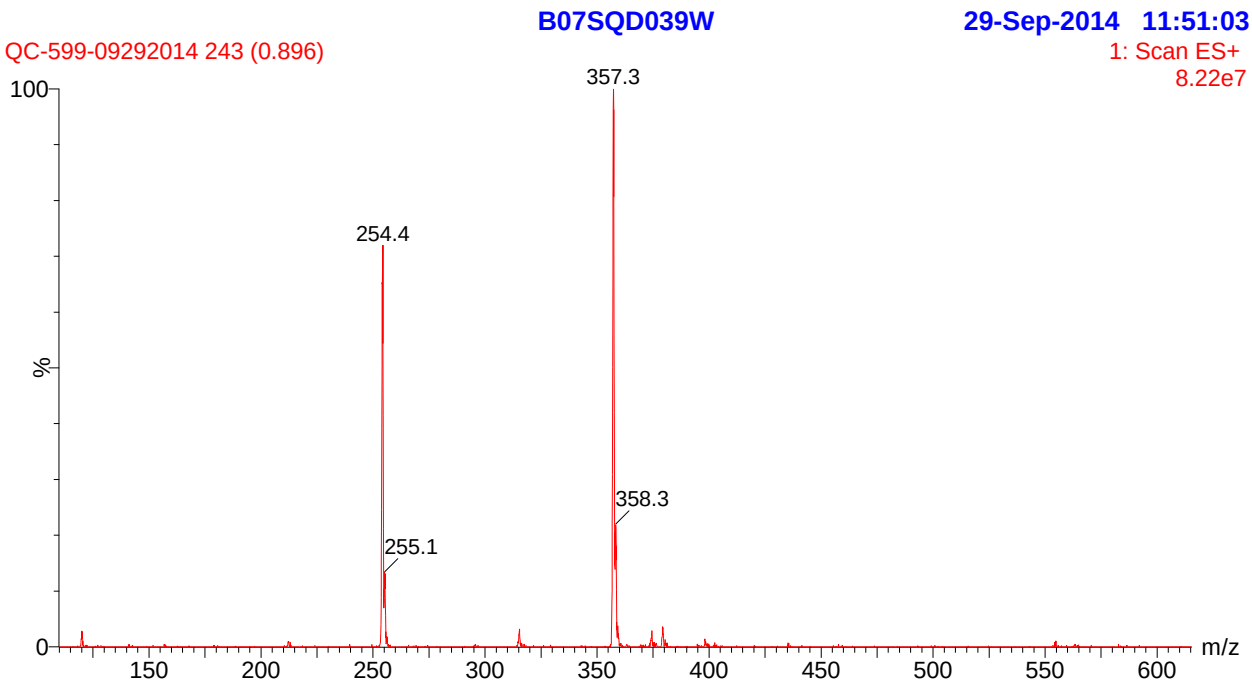
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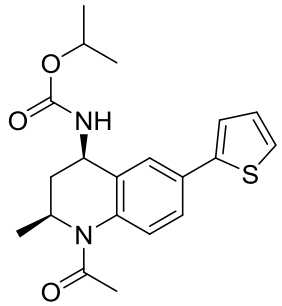
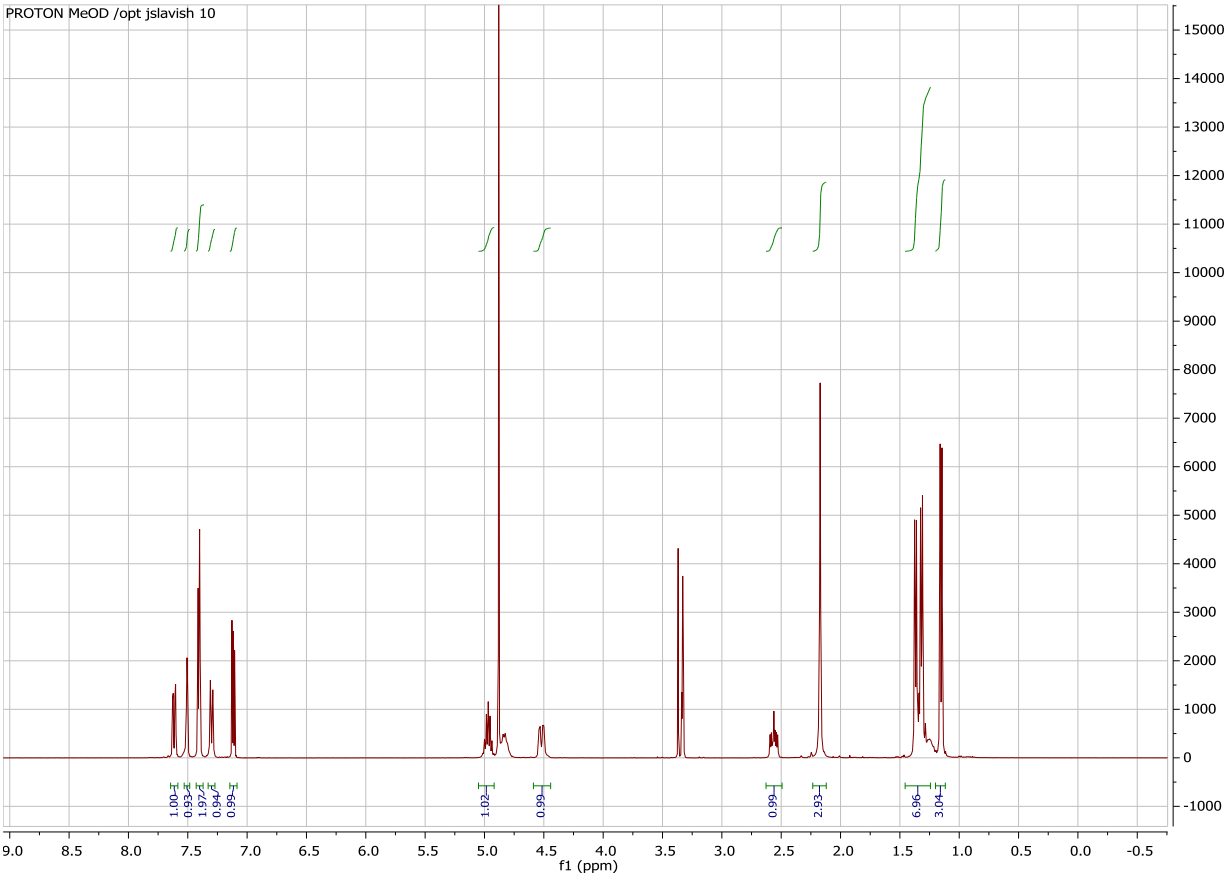
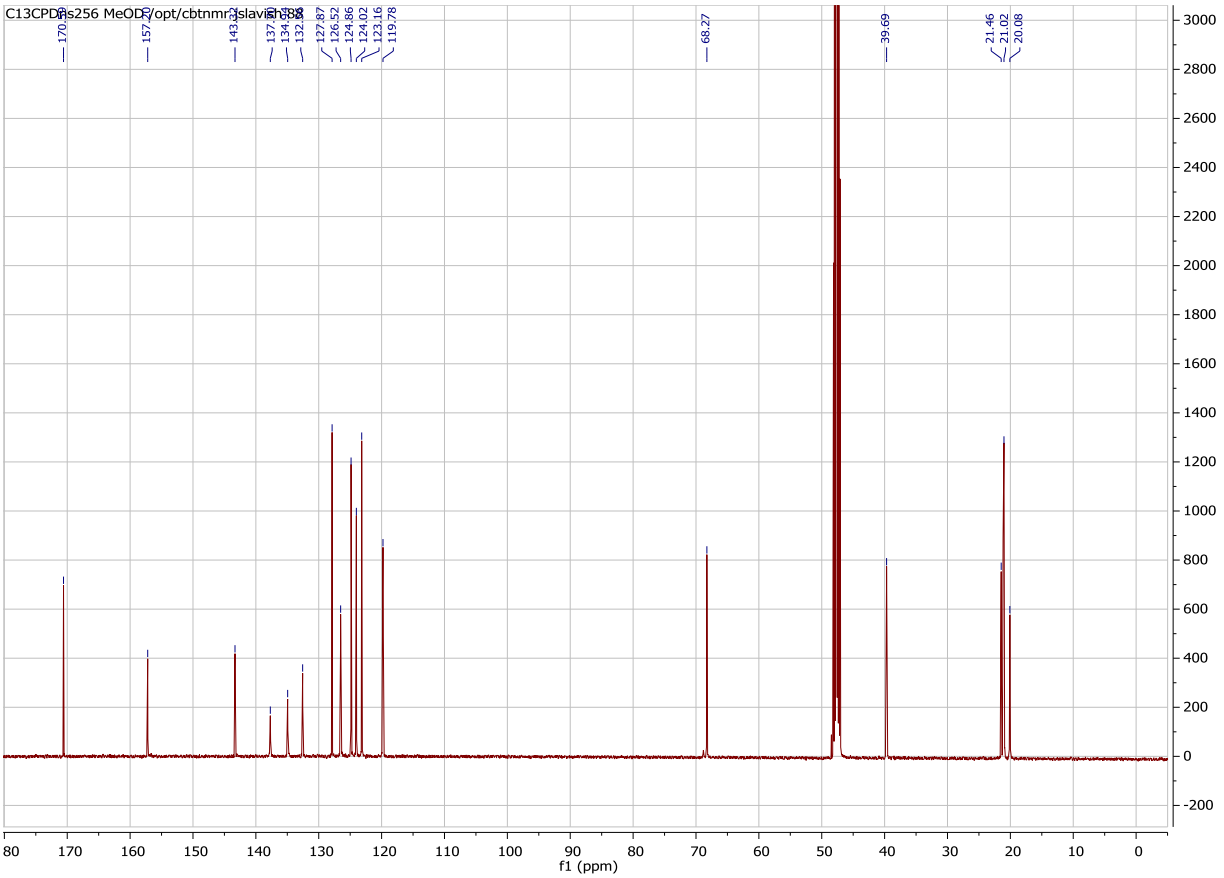


Isopropyl ((2S,4R)-1-acetyl-2-methyl-6-(thiophen-2-yl)-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (**10**). Yield: 83%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.61 (dd, J = 8.2, 1.7 Hz, 1H), 7.51 (s, 1H), 7.46 – 7.36 (m, 2H), 7.30 (d, J = 8.2 Hz, 1H), 7.12 (dd, J = 5.0, 3.7 Hz, 1H), 4.97 (p, J = 6.2 Hz, 1H), 4.52 (dd, J = 12.5, 4.0 Hz, 1H), 2.56 (ddd, J = 12.8, 8.7, 4.4 Hz, 1H), 2.17 (s, 3H), 1.43 – 1.22 (m, 7H), 1.15 (d, J = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 170.59, 157.20, 143.32, 137.70, 134.94, 132.56, 127.87, 126.52, 124.86, 124.02, 123.16, 119.78, 68.27, 39.69, 21.46, 21.02, 20.08. HRMS: calculated: 373.1586, found: 373.1580 m/z.

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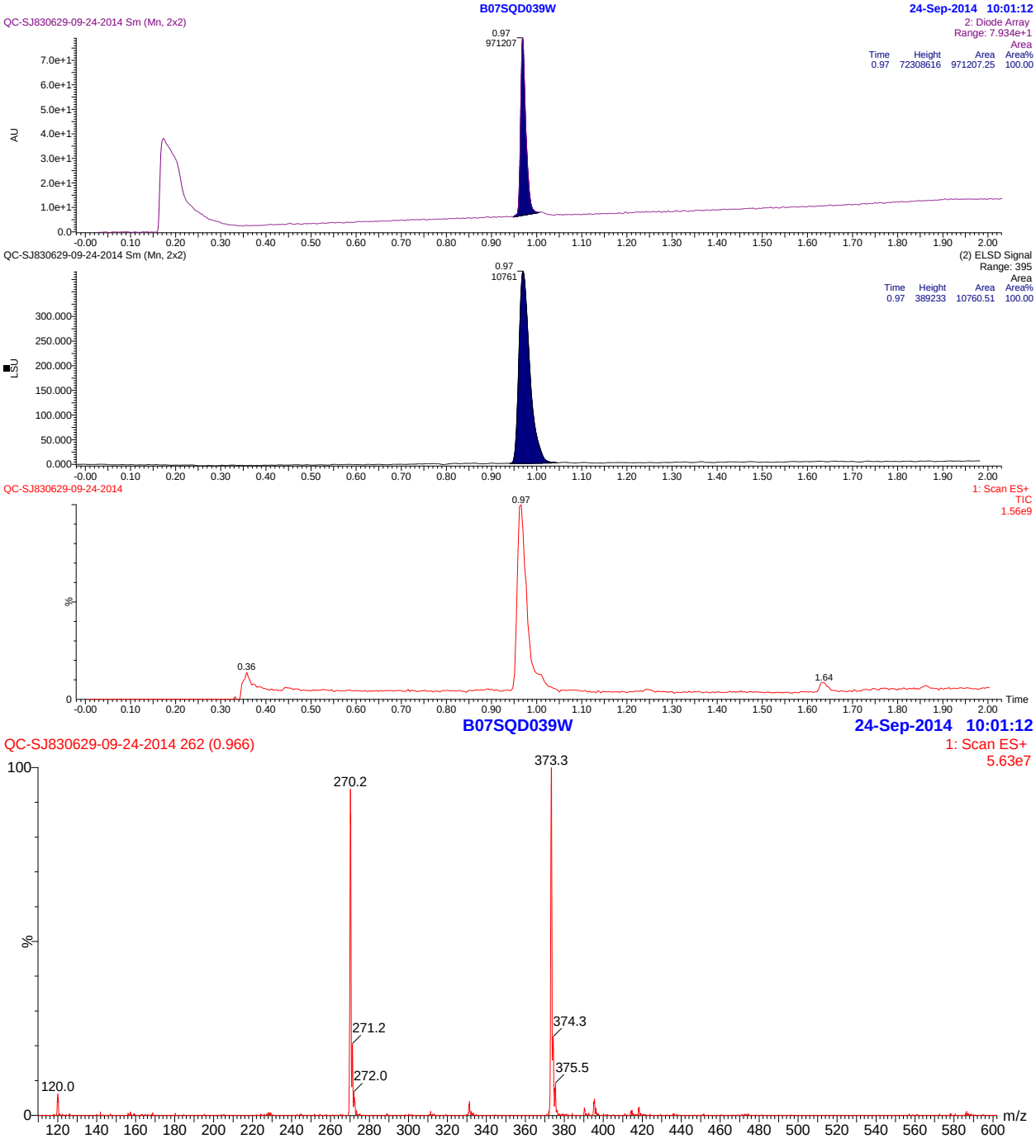
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10761
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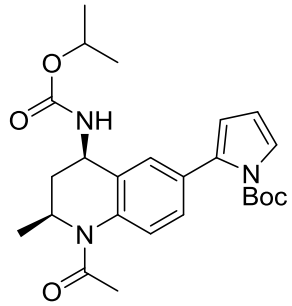
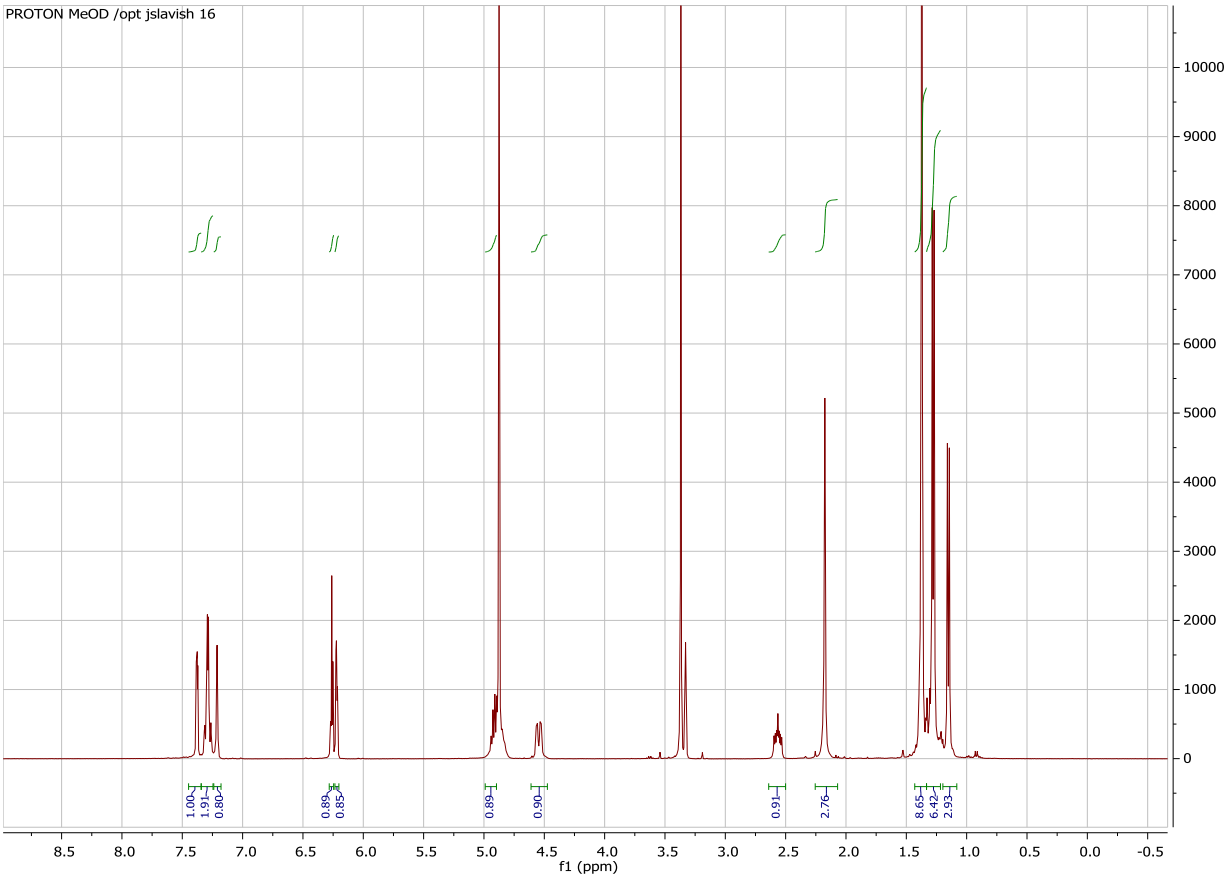
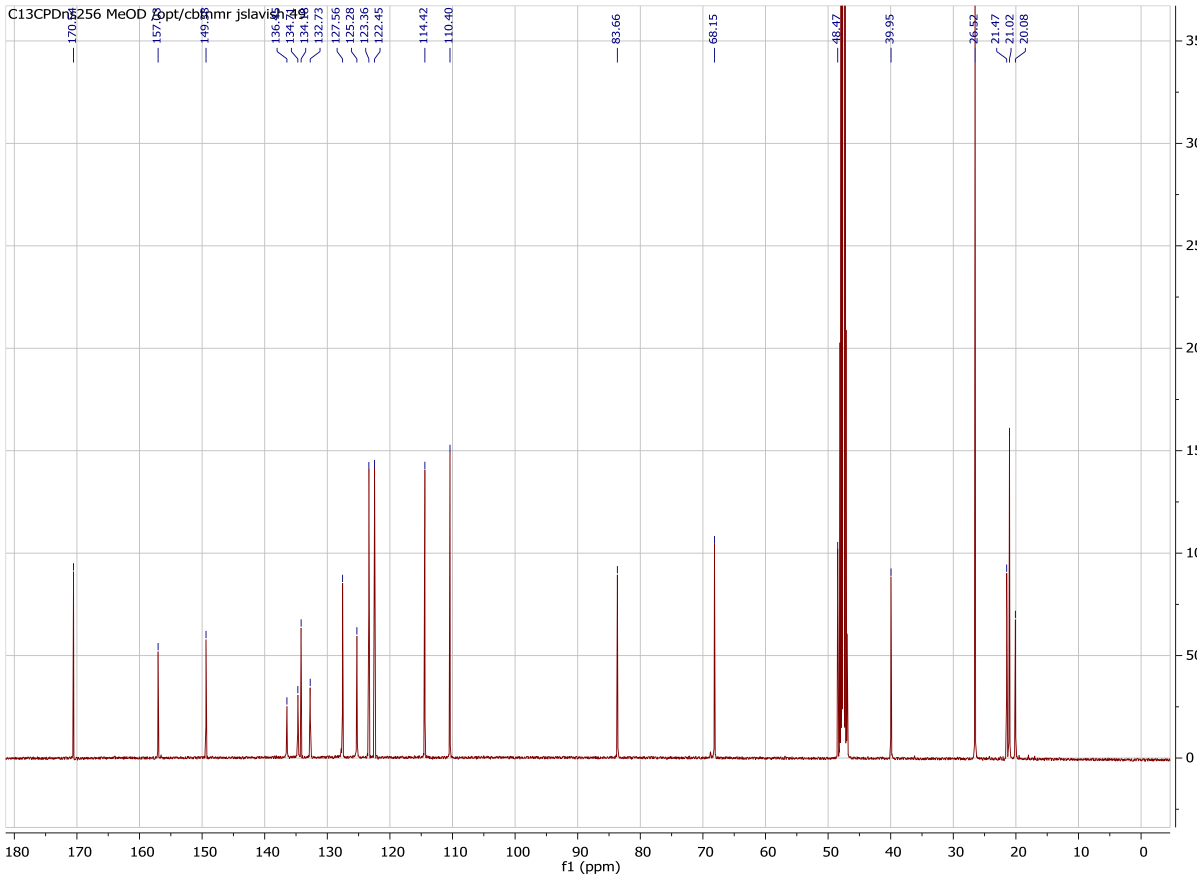
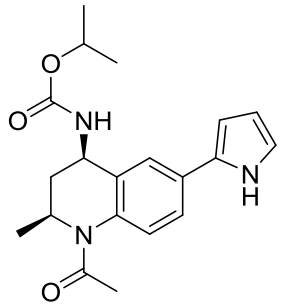
QC-SJ830629-09-24-2014
1: Scan ES+
TIC
1.56e9
0.97
0.36
1.64
%
Time
B07SQD039W
24-Sep-2014 10:01:12
QC-SJ830629-09-24-2014 262 (0.966)
1: Scan ES+
5.63e7
373.3
270.2
271.2
374.3
375.5
272.0
120.0
%
m/z



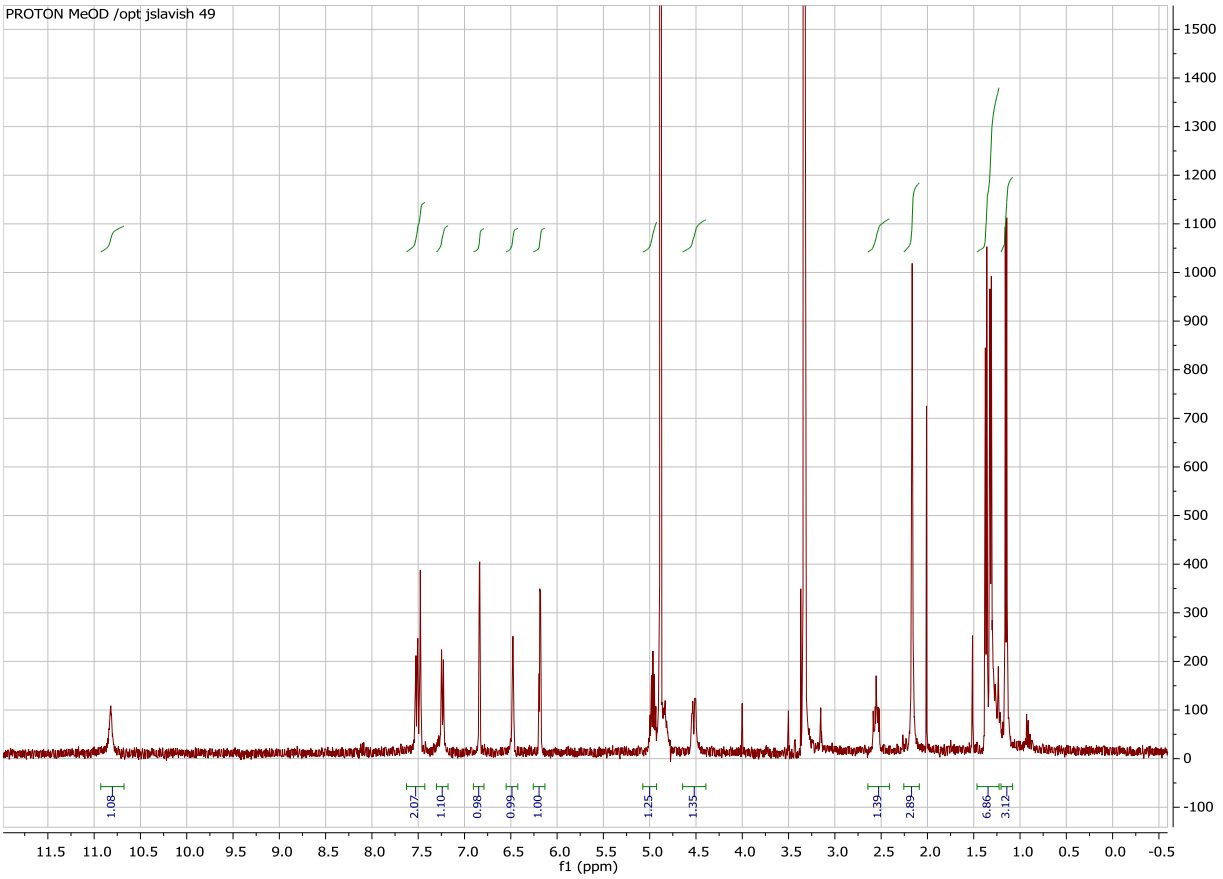
tert-butyl 2-((2S,4R)-1-acetyl-4-((isopropoxycarbonyl)amino)-2-methyl-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrrole-1-carboxylate ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.38 (dd, J = 3.3, 1.8 Hz, 1H), 7.34 – 7.25 (m, 2H), 7.21 (s, 1H), 6.26 (t, J = 3.3 Hz, 1H), 6.22 (dd, J = 3.2, 1.8 Hz, 1H), 4.99 – 4.90 (m, 1H), 4.55 (dd, J = 12.6, 4.0 Hz, 1H), 2.56 (ddd, J = 12.7, 8.7, 4.3 Hz, 1H), 2.18 (s, 3H), 1.37 (s, 9H), 1.29 (t, J = 7.2 Hz, 6H), 1.15 (d, J = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 170.54, 157.03, 149.38, 136.45, 134.71, 134.18, 132.73, 127.56, 125.28, 123.36, 122.45, 114.42, 110.40, 83.66, 68.15, 48.47, 39.95, 26.52, 21.47, 21.02, 20.08.

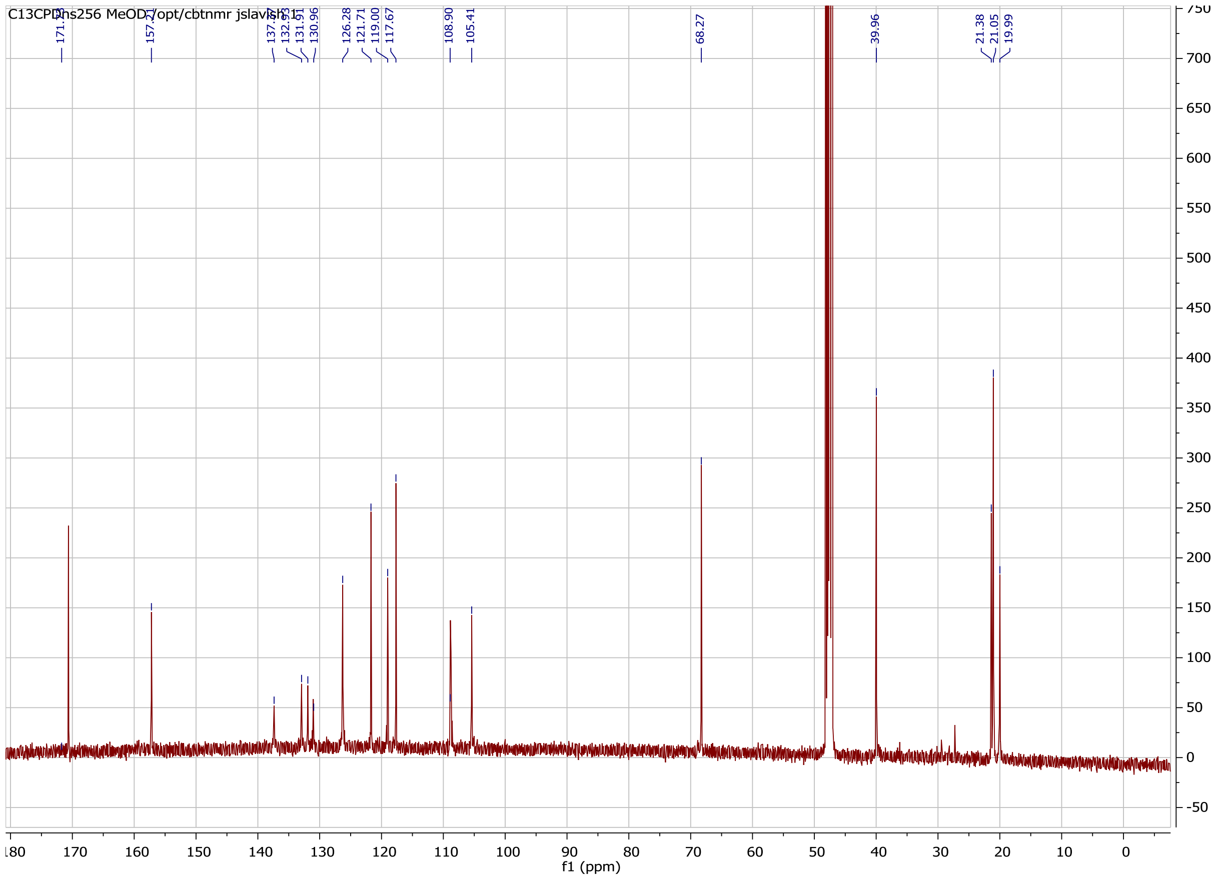


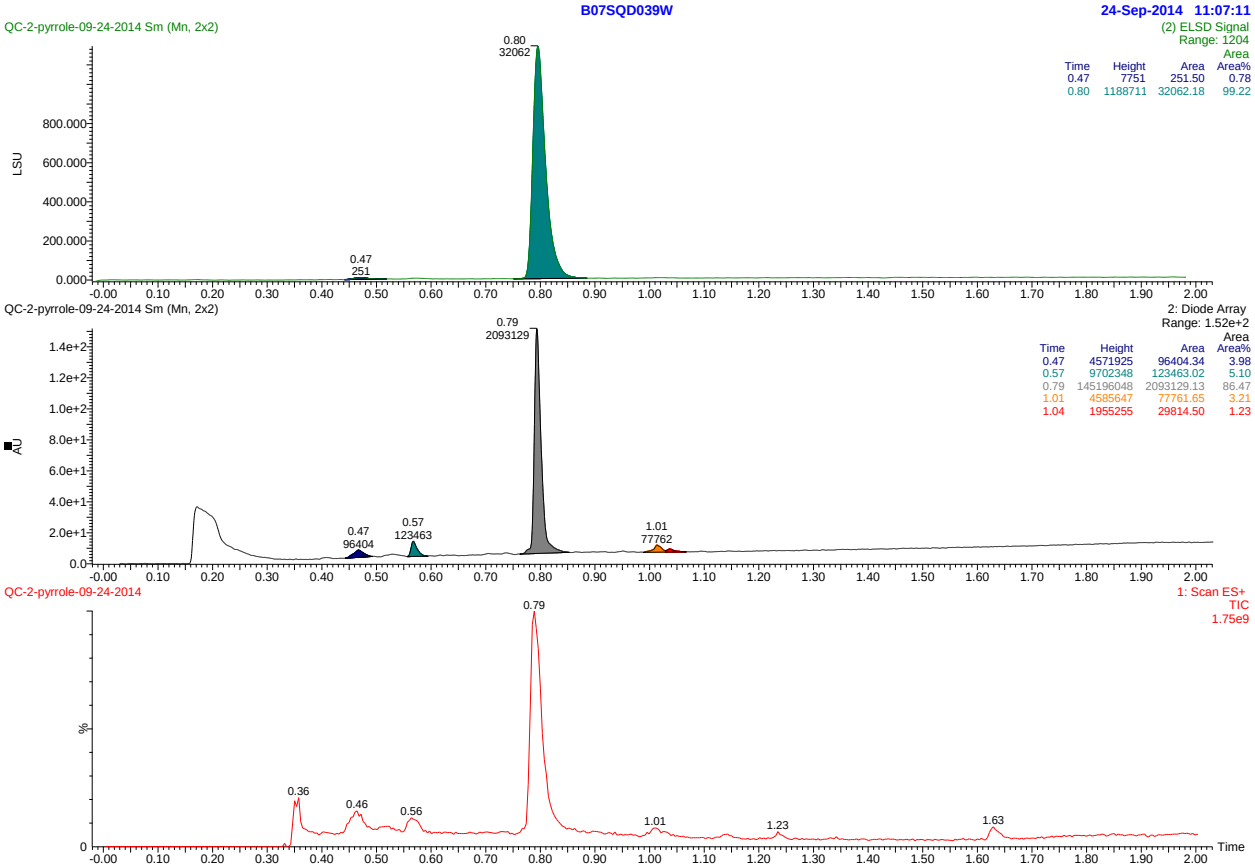

C13CPDns256 MeOD /opt/cbfnmr jslavish 49
170.54
157.03
149.38
136.45
134.71
134.18
132.73
127.56
125.28
123.36
122.45
114.42
110.40
83.66
68.15
48.47
39.95
26.52
21.47
21.02
20.08
3500
3000
2500
2000
1500
1000
500
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

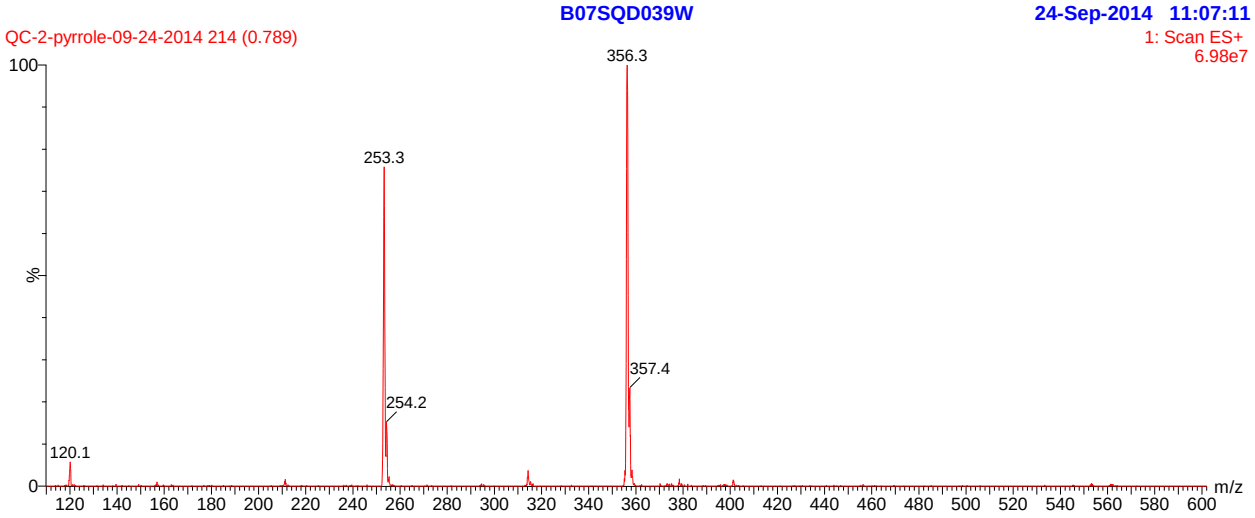


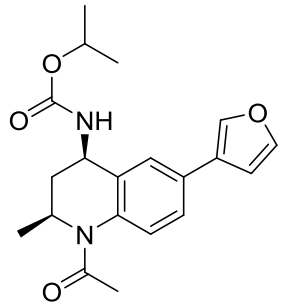
isopropyl ((2S,4R)-1-acetyl-2-methyl-6-(1H-pyrrol-2-yl)-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (**11**). To freshly purified N-BOC pyrrole was added TFA (0.2 mL) and CH_2Cl_2 (0.2 mL). Reaction was permitted to stir for 1 h, then concentrated and product was purified via automated normal phase chromatography to provide desired product (17 mgs, 48% yield over two steps). ^{1}H NMR (400 MHz, Methanol-d_4) δ 10.82 (s, 1H), 7.63 – 7.43 (m, 2H), 7.24 (d, *J* = 8.2 Hz, 1H), 6.90 – 6.79 (m, 1H), 6.48 (s, 1H), 6.26 – 6.13 (m, 1H), 4.96 (dt, *J* = 12.8, 6.4 Hz, 1H), 4.52 (d, *J* = 8.0 Hz, 1H), 2.64 – 2.41 (m, 1H), 2.16 (s, 3H), 1.34 (dd, *J* = 19.6, 6.3 Hz, 7H), 1.15 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 171.73, 157.21, 137.37, 132.93, 131.91, 130.96, 126.28, 121.71, 119.00, 117.67, 108.90, 105.41, 68.27, 39.96, 21.38, 21.05, 19.99.



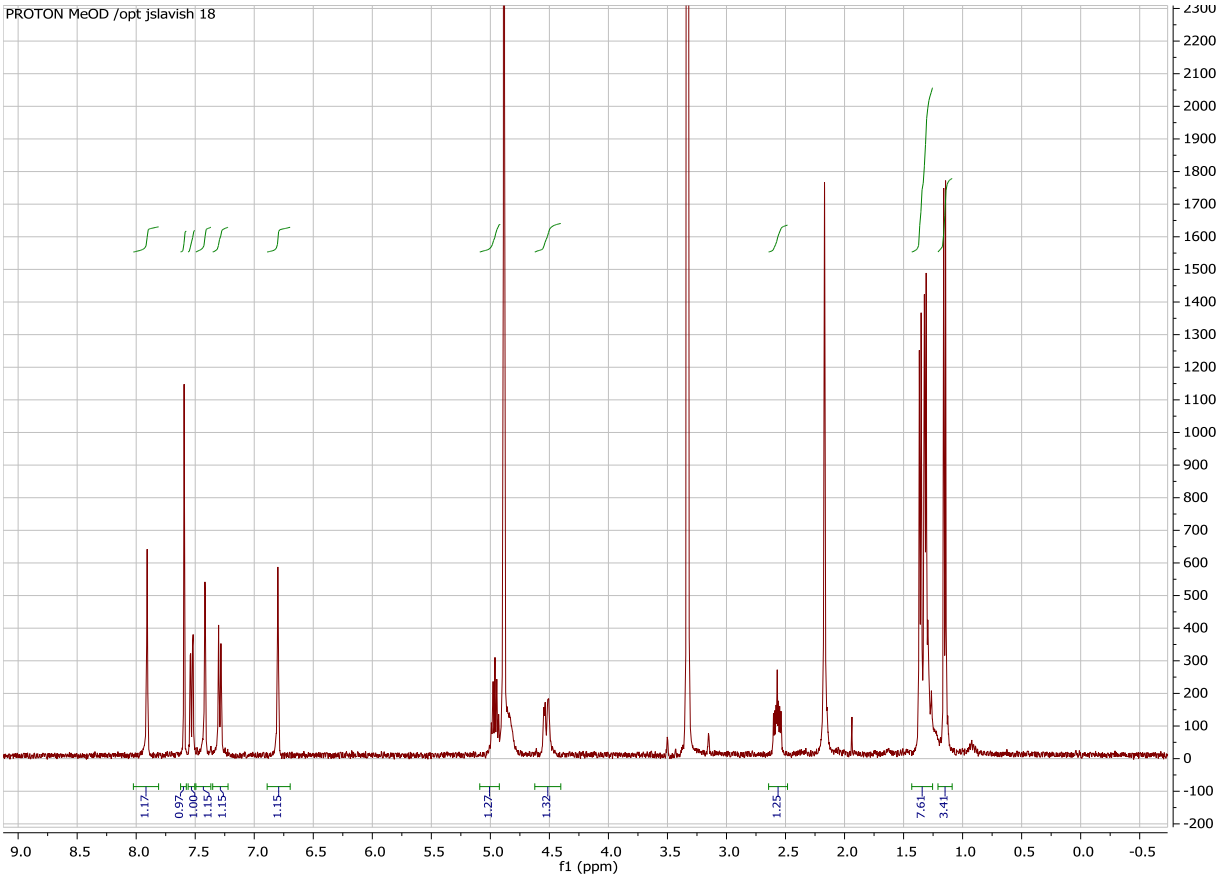

C13CPDns256 MeOD /opt/cbtnmr jslavish 1
171.1
157.2
137.7
132.9
131.9
130.96
126.28
121.71
119.00
117.67
108.90
105.41
68.27
39.96
21.38
21.05
19.99
f1 (ppm)

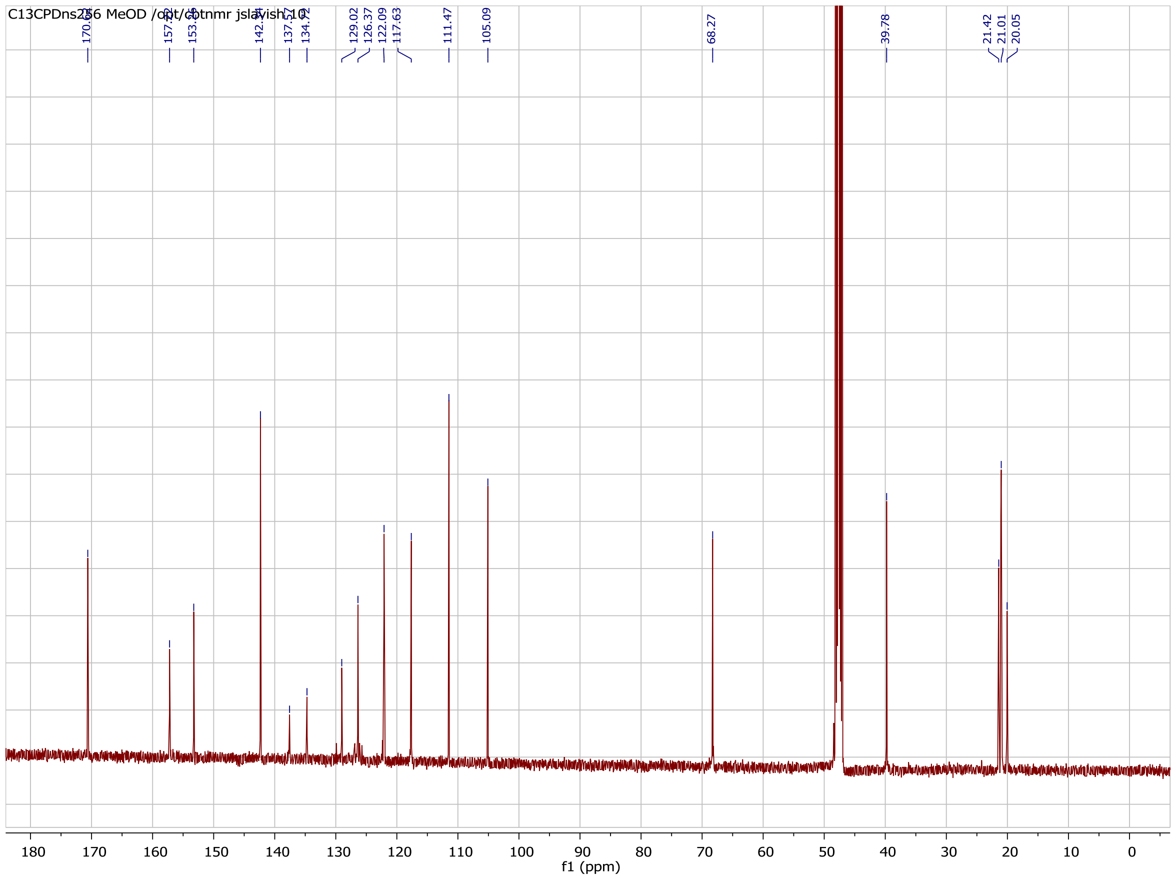

B07SQD039W
24-Sep-2014 11:07:11
QC-2-pyrrole-09-24-2014 Sm (Mn, 2x2)
(2) ELSD Signal
Range: 1204
Area
Time Height Area Area%
0.47 7751 251.50 0.78
0.80 1188711 32062.18 99.22
LSU
0.80
32062
0.47
251
QC-2-pyrrole-09-24-2014 Sm (Mn, 2x2)
2: Diode Array
Range: 1.52e+2
Area
Time Height Area Area%
0.47 4571925 96404.34 3.98
0.57 9702348 123463.02 5.10
0.79 145196048 2093129.13 86.47
1.01 4585647 77761.65 3.21
1.04 1955255 29814.50 1.23
AU
0.79
2093129
0.47
96404
0.57
123463
1.01
77762
QC-2-pyrrole-09-24-2014
1: Scan ES+
TIC
1.75e9
%
0.79
0.36
0.46
0.56
1.01
1.23
1.63
Time

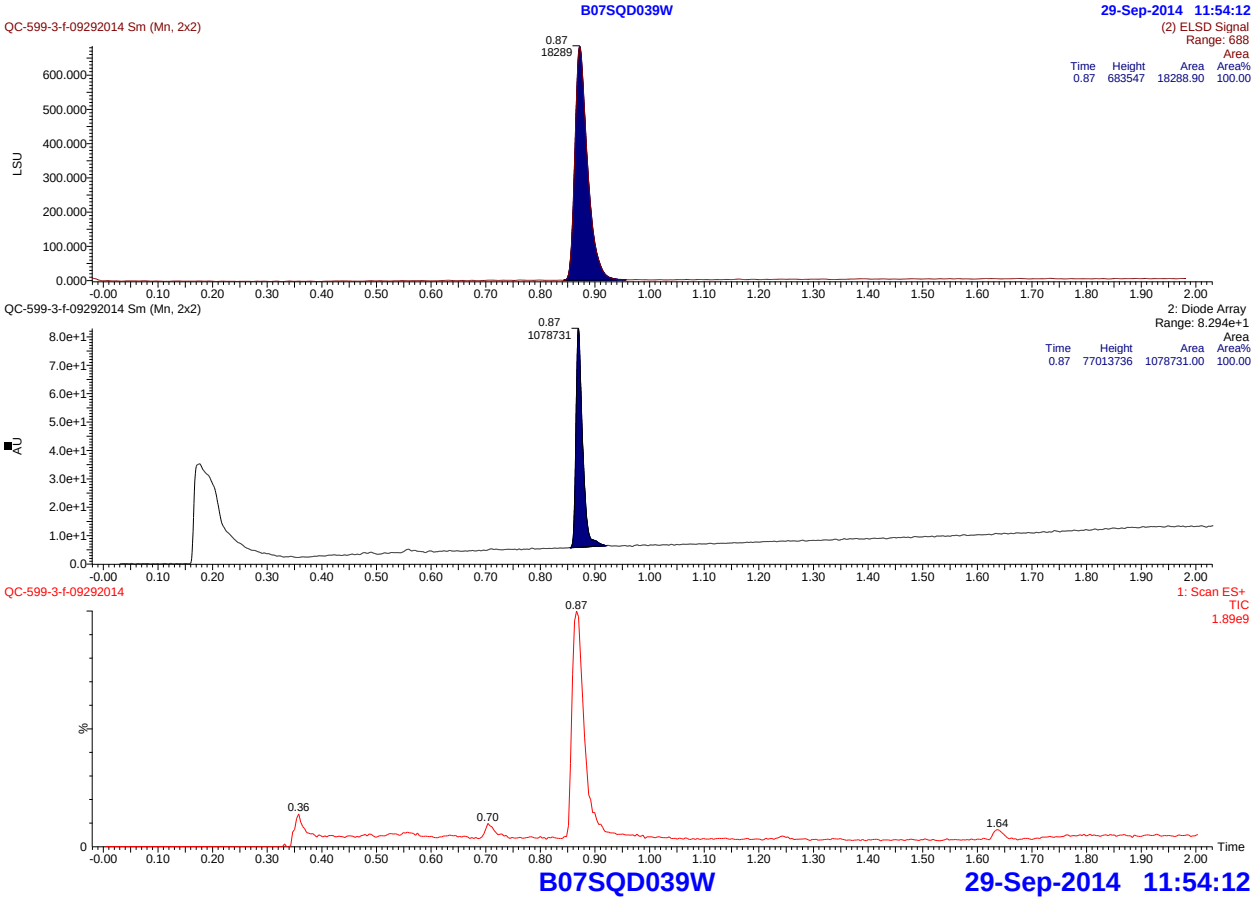

B07SQD039W
24-Sep-2014 11:07:11
QC-2-pyrrole-09-24-2014 214 (0.789)
1: Scan ES+
6.98e7
356.3
253.3
357.4
254.2
120.1
%
m/z

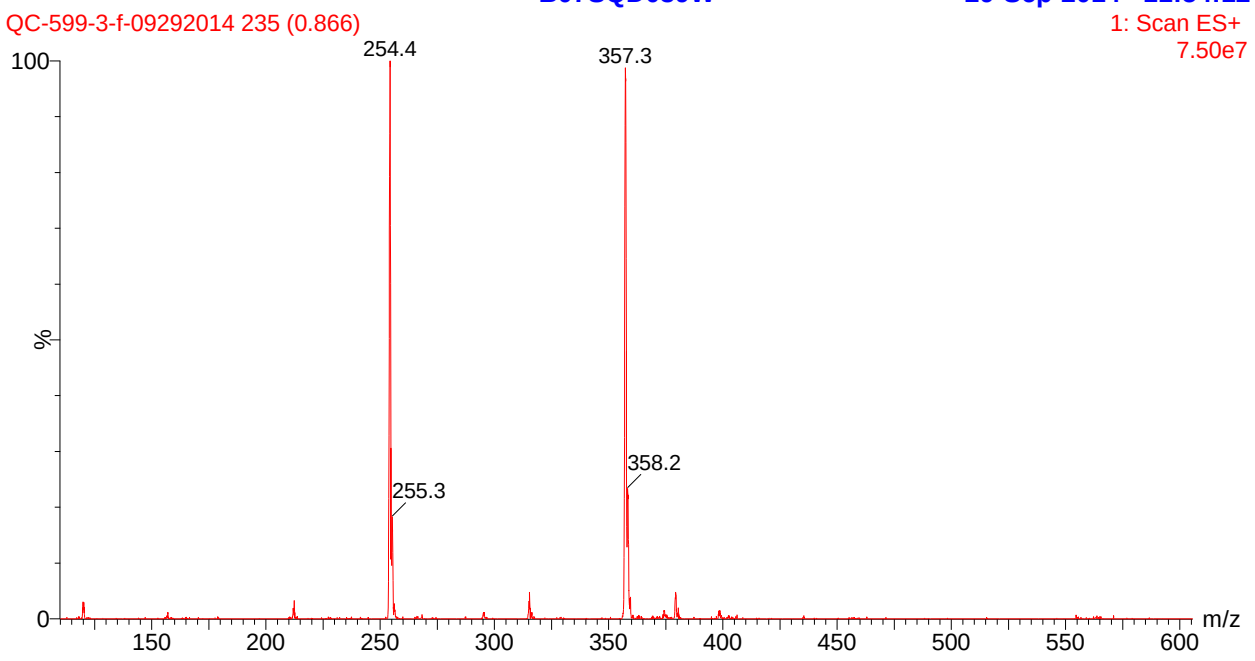


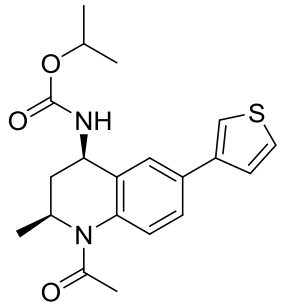
Isopropyl ((2S,4R)-1-acetyl-6-(furan-3-yl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (**12**). Yield: 37% yield. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.91 (s, 1H), 7.59 (t, *J* = 1.7 Hz, 1H), 7.53 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.42 (s, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 6.80 (s, 1H), 4.96 (dt, *J* = 12.5, 6.2 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 2.57 (ddd, *J* = 12.6, 8.6, 4.2 Hz, 1H), 1.43 – 1.25 (m, 7H), 1.15 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 170.62, 157.22, 153.26, 142.34, 137.57, 134.72, 129.02, 126.37, 122.09, 117.63, 111.47, 105.09, 68.27, 39.78, 21.42, 21.01, 20.05. HRMS: calculated:357.1814 m/z, found: 357.1813 m/z.



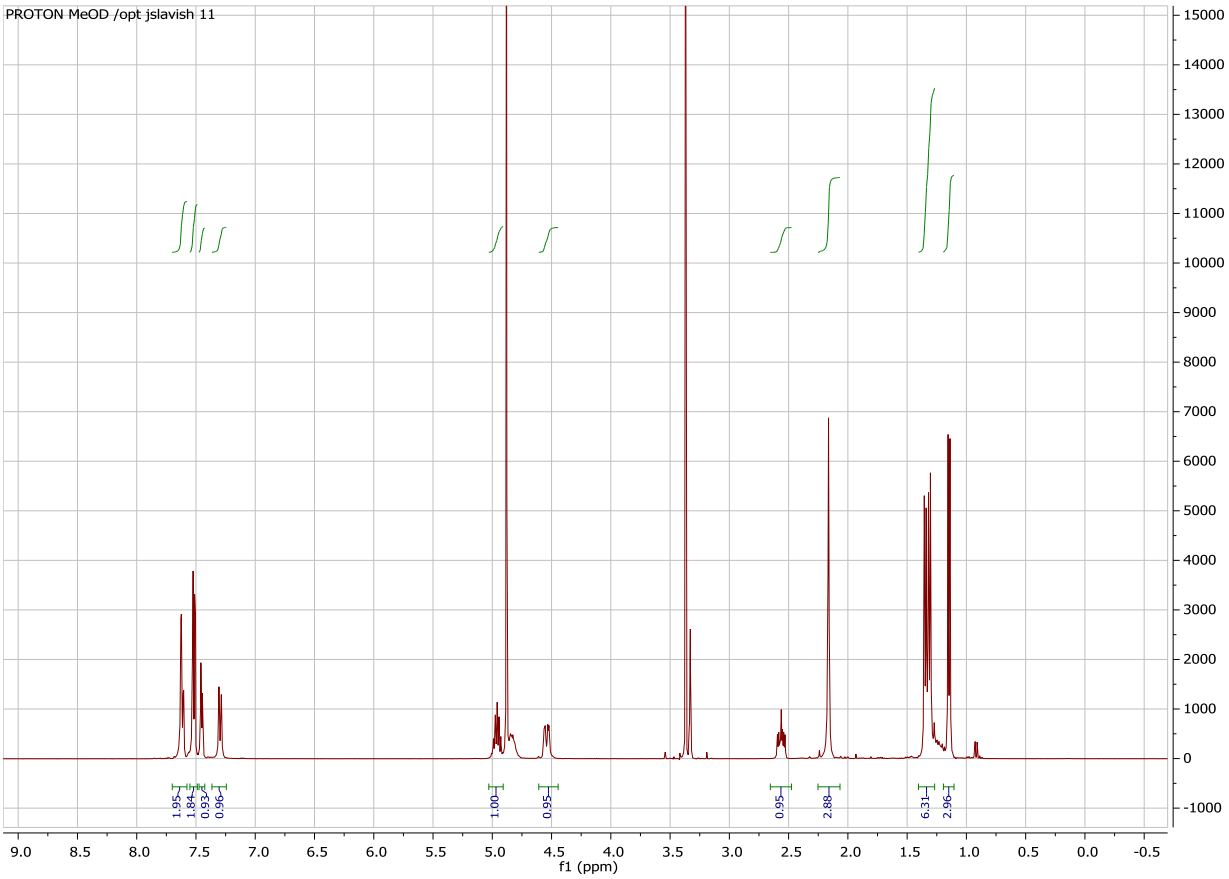

C13CPDns256 MeOD /opt/cotnmr jslavish 10
170.
157.
153.
142.
137.
134.
129.02
126.37
122.09
117.63
111.47
105.09
68.27
39.78
21.42
21.01
20.05
f1 (ppm)

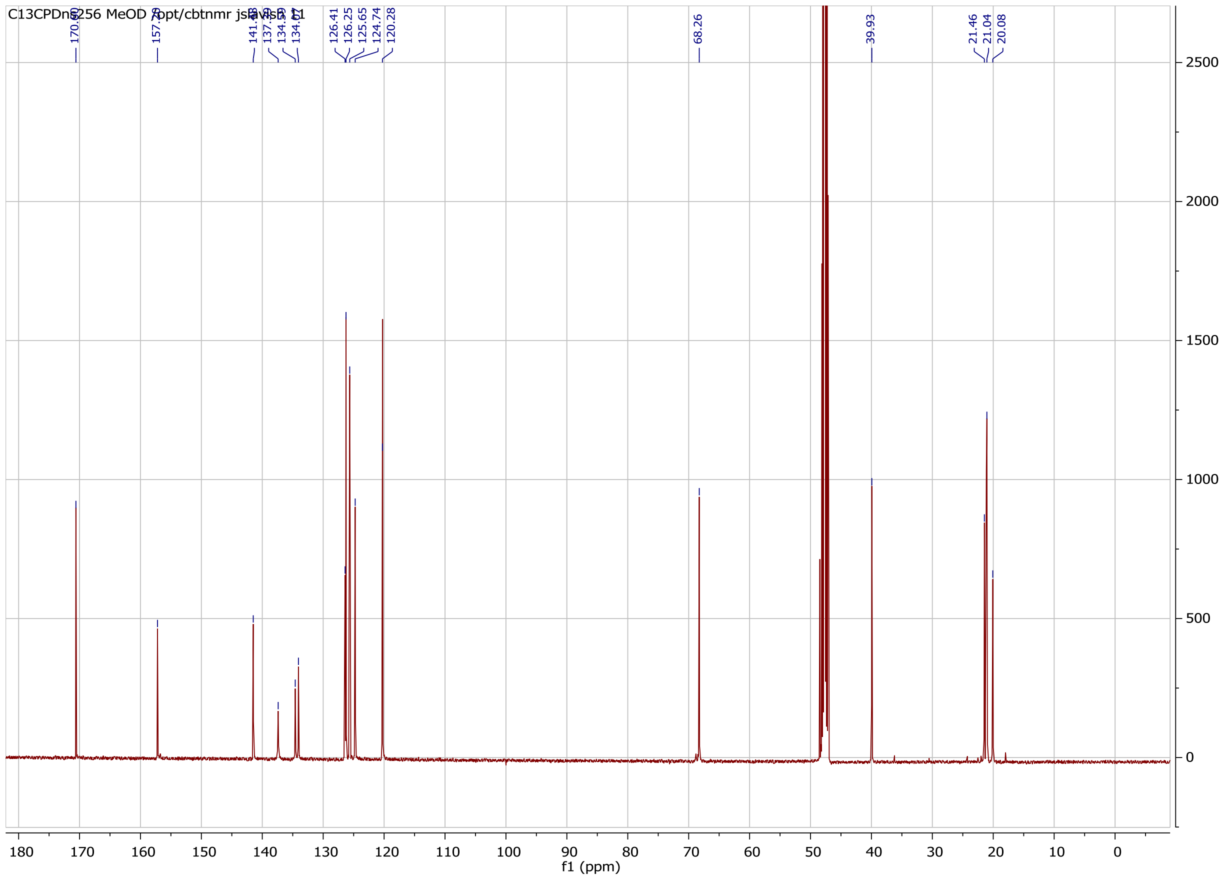

B07SQD039W
29-Sep-2014 11:54:12
QC-599-3-f-09292014 Sm (Mn, 2x2)
(2) ELSD Signal
Range: 688
Area
Time Height Area Area%
0.87 683547 18288.90 100.00
0.87
18289
LSU
600.000
500.000
400.000
300.000
200.000
100.000
0.000
-0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00 1.10 1.20 1.30 1.40 1.50 1.60 1.70 1.80 1.90 2.00
QC-599-3-f-09292014 Sm (Mn, 2x2)
2: Diode Array
Range: 8.294e+1
Area
Time Height Area Area%
0.87 77013736 1078731.00 100.00
0.87
1078731
AU
8.0e+1
7.0e+1
6.0e+1
5.0e+1
4.0e+1
3.0e+1
2.0e+1
1.0e+1
0.0
-0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00 1.10 1.20 1.30 1.40 1.50 1.60 1.70 1.80 1.90 2.00
QC-599-3-f-09292014
1: Scan ES+
TIC
1.89e9
0.87
%
0.36
0.70
1.64
0
Time
-0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00 1.10 1.20 1.30 1.40 1.50 1.60 1.70 1.80 1.90 2.00

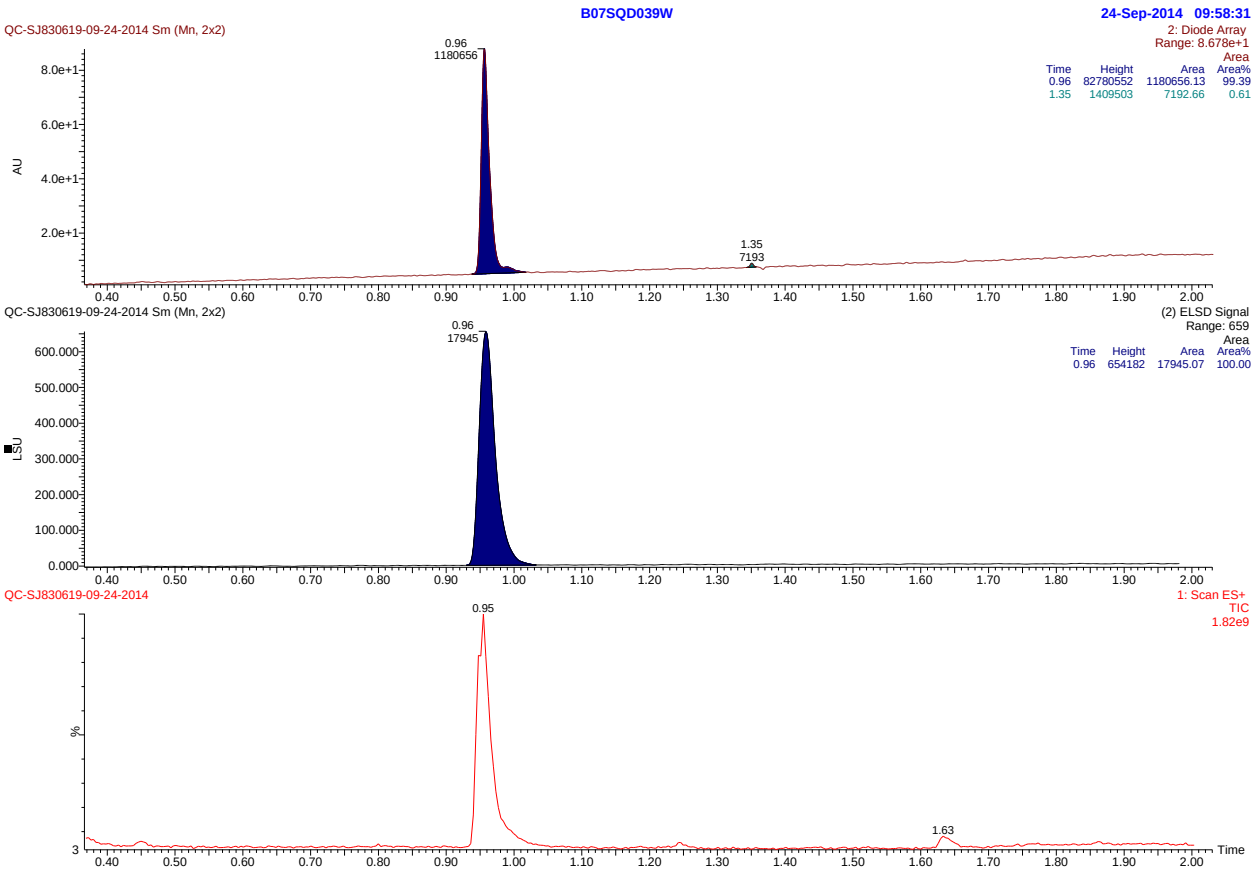

B07SQD039W
29-Sep-2014 11:54:12
QC-599-3-f-09292014 235 (0.866)
1: Scan ES+
7.50e7
100
%
0
254.4
357.3
255.3
358.2
150 200 250 300 350 400 450 500 550 600
m/z

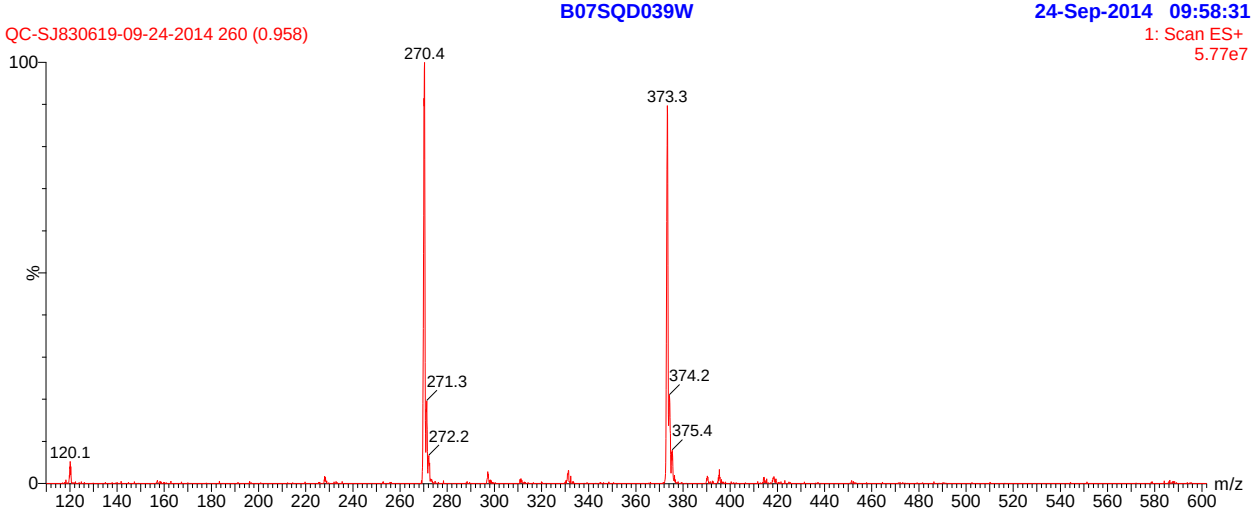


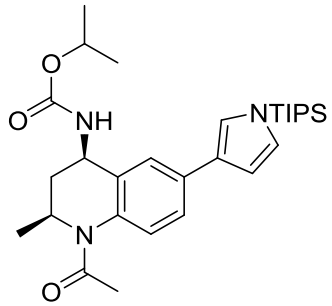
Isopropyl ((2S,4R)-1-acetyl-2-methyl-6-(thiophen-3-yl)-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (**13**). Yield: 89%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.70 – 7.58 (m, 2H), 7.51 (dd, *J* = 5.1, 3.0 Hz, 2H), 7.47 – 7.43 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 4.96 (hept, *J* = 6.3 Hz, 1H), 4.54 (dd, *J* = 12.4, 3.9 Hz, 1H), 2.56 (ddd, *J* = 12.7, 8.7, 4.4 Hz, 1H), 2.16 (s, 3H), 1.33 (dd, *J* = 14.4, 6.3 Hz, 6H), 1.15 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 170.60, 157.20, 141.48, 137.39, 134.59, 134.07, 126.41, 126.25, 125.65, 124.74, 120.28, 68.26, 39.93, 21.46, 21.04, 20.08. HRMS: calculated: 373.1586 m/z, found: 373.1581 m/z



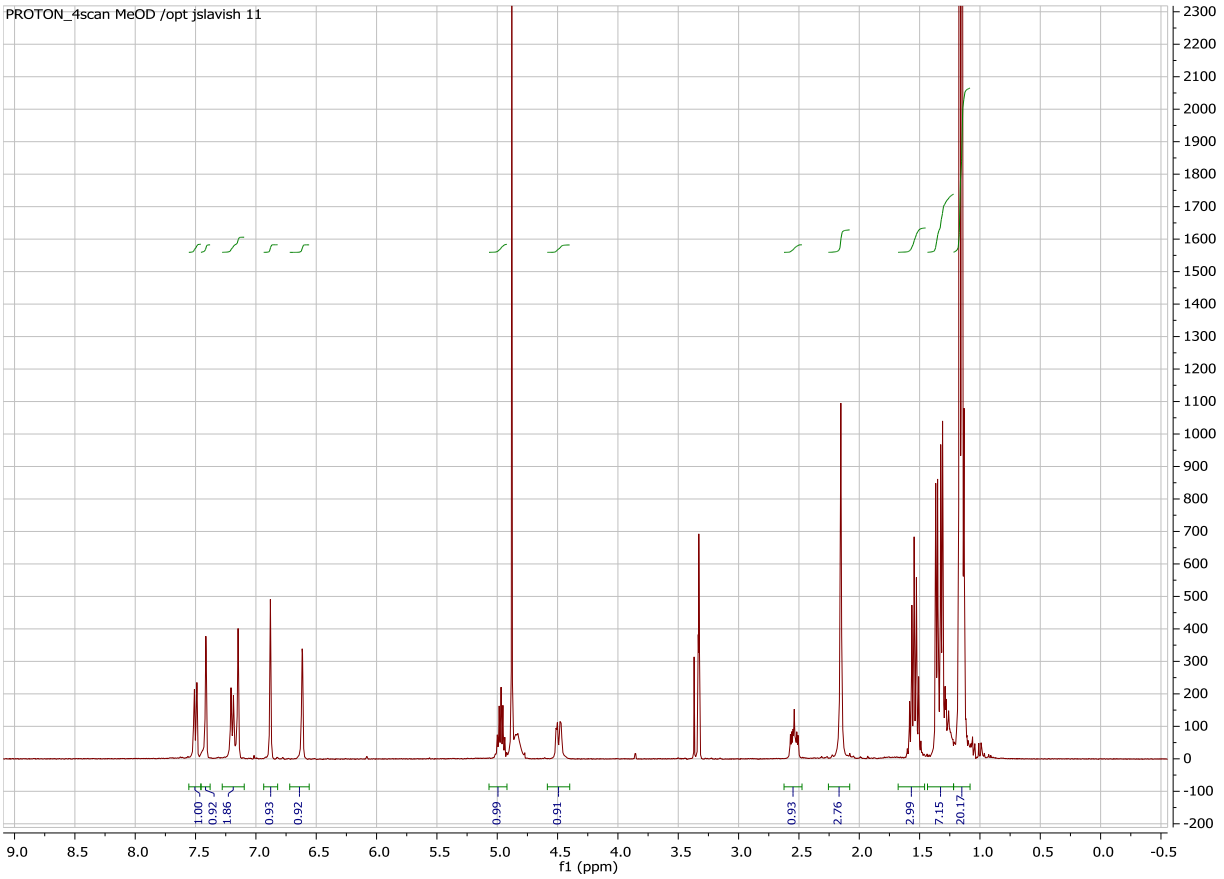

C13CPDns256 MeOD /opt/cbtnmr jslavish 11
126.41
126.25
125.65
124.74
120.28
68.26
39.93
21.46
21.04
20.08
2500
2000
1500
1000
500
0
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

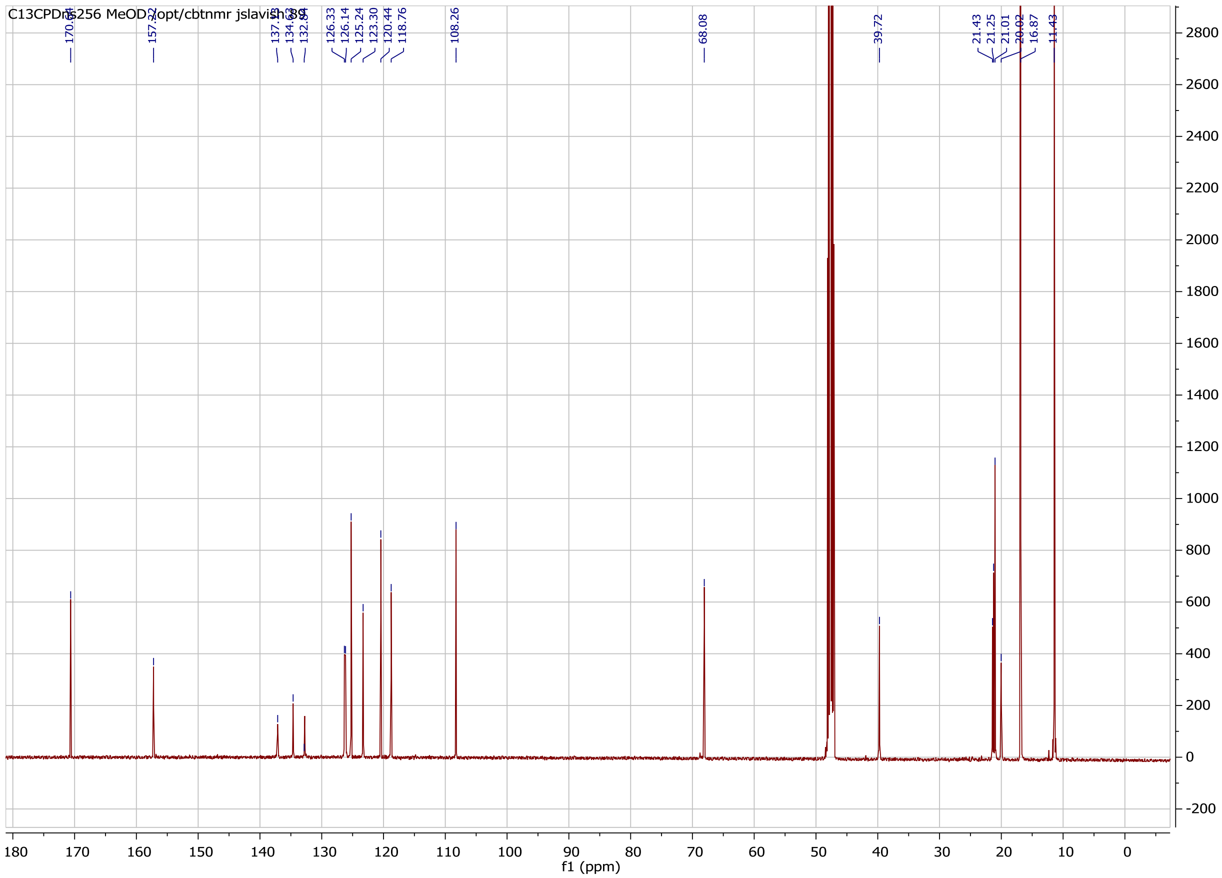

B07SQD039W
24-Sep-2014 09:58:31
QC-SJ830619-09-24-2014 Sm (Mn, 2x2)
2: Diode Array
Range: 8.678e+1
Area
Time Height Area Area%
0.96 82780552 1180656.13 99.39
1.35 1409503 7192.66 0.61
0.96
1180656
1.35
7193
AU
QC-SJ830619-09-24-2014 Sm (Mn, 2x2)
(2) ELSD Signal
Range: 659
Area
Time Height Area Area%
0.96 654182 17945.07 100.00
0.96
17945
LSU
QC-SJ830619-09-24-2014
1: Scan ES+
TIC
1.82e9
0.95
1.63
%
Time

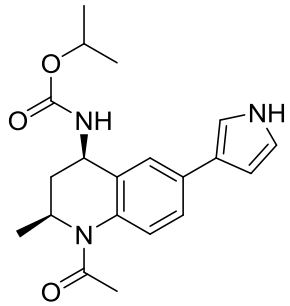

B07SQD039W
24-Sep-2014 09:58:31
QC-SJ830619-09-24-2014 260 (0.958)
1: Scan ES+
5.77e7
270.4
373.3
271.3
374.2
272.2
375.4
120.1
%
m/z



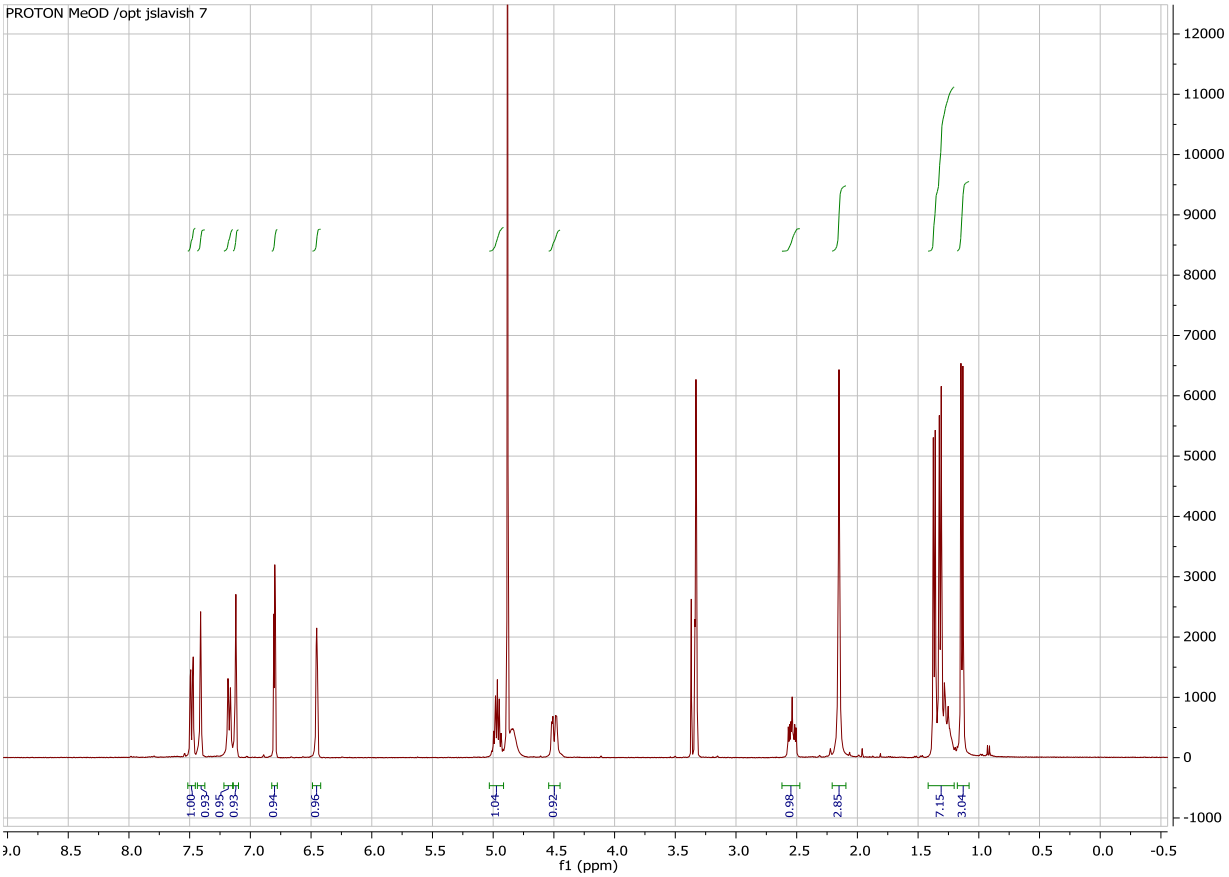
Isopropyl ((2S,4R)-1-acetyl-2-methyl-6-(1-(triisopropylsilyl)-1H-pyrrol-3-yl)-1,2,3,4-tetrahydroquinolin-4-yl)carbamate ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.50 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.41 (s, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.15 (s, 1H), 6.91 – 6.85 (m, 1H), 6.65 – 6.57 (m, 1H), 4.97 (p, *J* = 6.2 Hz, 1H), 4.49 (dd, *J* = 12.4, 3.8 Hz, 1H), 2.54 (ddd, *J* = 12.7, 8.7, 4.3 Hz, 1H), 2.15 (s, 3H), 1.55 (p, *J* = 7.5 Hz, 3H), 1.34 (dd, *J* = 16.4, 6.2 Hz, 6H), 1.16 (d, *J* = 7.5 Hz, 18H). ^{13}C NMR (126 MHz, MeOD) δ 170.64, 157.22, 137.13, 134.63, 132.84, 126.33, 126.14, 125.24, 123.30, 120.44, 118.76, 108.26, 68.08, 39.72, 21.43, 21.25, 21.01, 20.02, 16.87, 11.43.

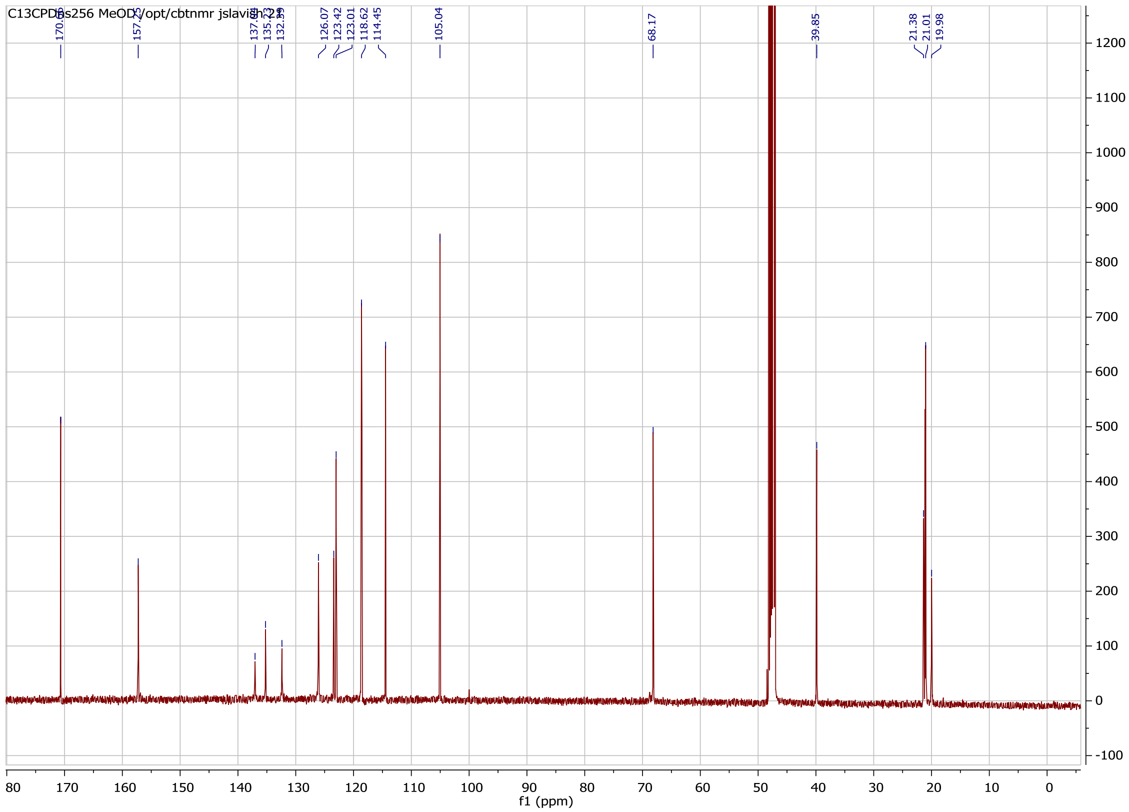


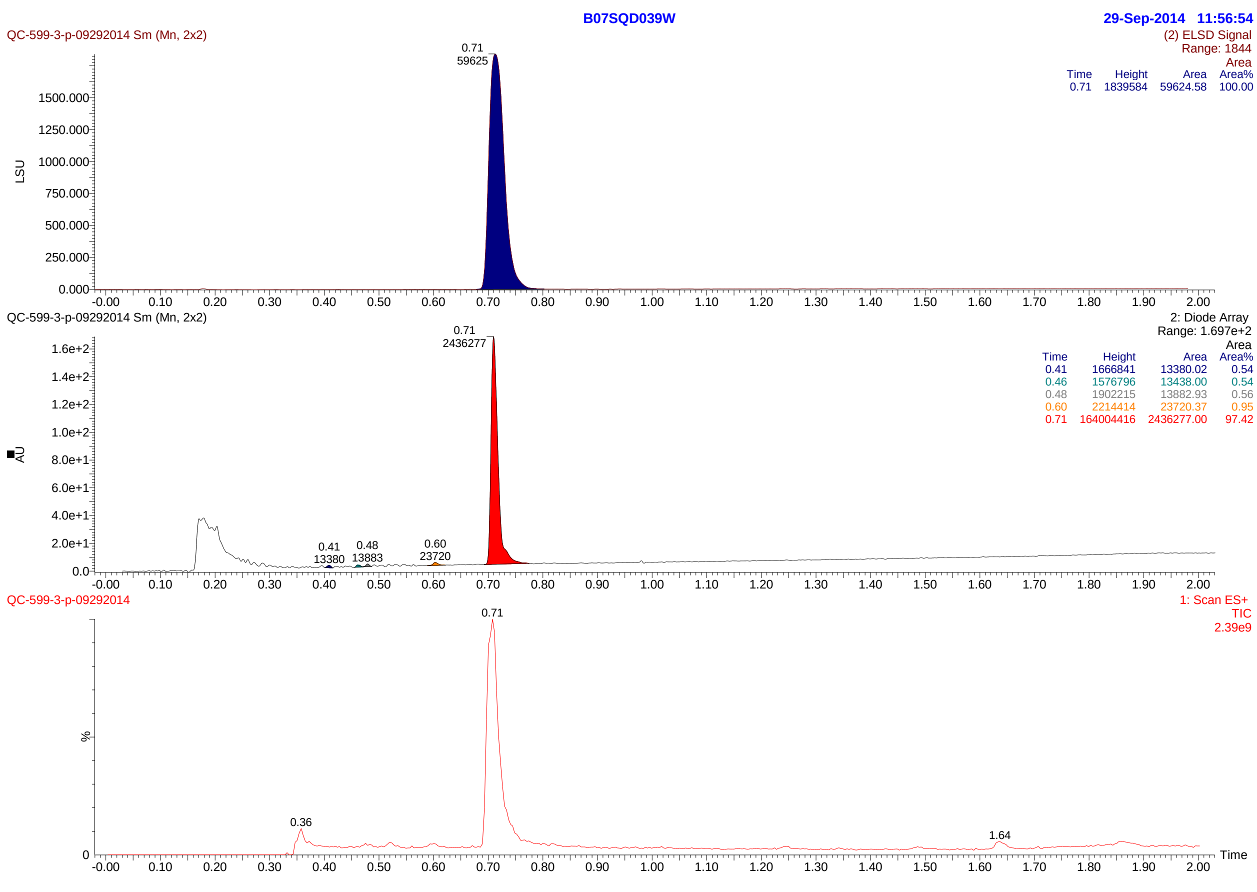

C13CPD ms256 MeOD /opt/cbtnmr jslavish 39
170.68
157.32
137.29
134.63
132.84
126.33
126.14
125.24
123.30
120.44
118.76
108.26
68.08
39.72
21.43
21.25
21.01
20.02
16.87
11.43
f1 (ppm)

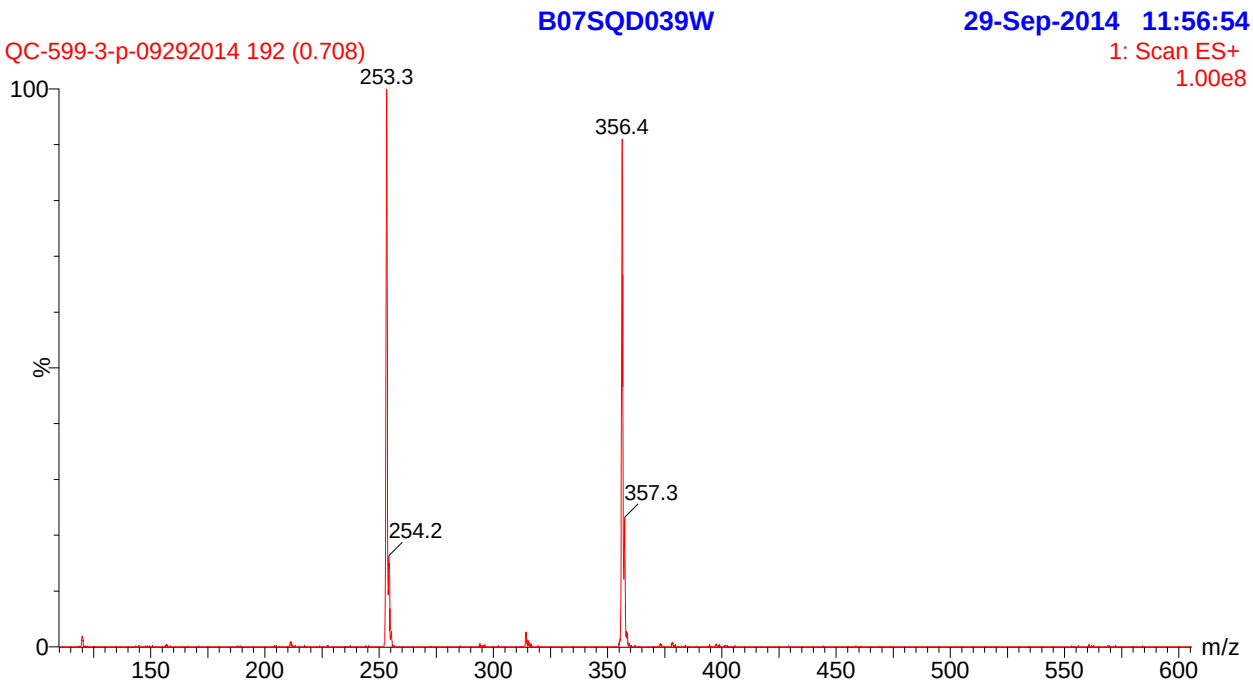


Isopropyl ((2S,4R)-1-acetyl-2-methyl-6-(1H-pyrrol-3-yl)-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (**14**). To freshly purified silyl pyrrole was added a solution of TBAF (0.1 mL, 1.0 M in THF). Reaction was permitted to stir for 1 h, then concentrated and product was purified via automated normal phase chromatography to provide desired product (54 % yield over two steps). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.48 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.41 (s, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 7.12 (s, 1H), 6.80 (dd, *J* = 2.7, 2.0 Hz, 1H), 6.49 – 6.41 (m, 1H), 4.96 (dq, *J* = 12.6, 6.3 Hz, 1H), 4.50 (dd, *J* = 12.5, 3.9 Hz, 1H), 2.54 (ddd, *J* = 12.7, 8.7, 4.3 Hz, 1H), 2.15 (s, 2H), 1.31 (ddd, *J* = 22.9, 16.1, 7.5 Hz, 7H), 1.14 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 170.66, 157.25, 137.04, 135.23, 132.39, 126.07, 123.42, 123.01, 118.62, 114.45, 105.04, 68.17, 39.85, 21.38, 21.01, 19.98. HRMS: calculated: 356.1974 m/z, found: 356.1971 m/z

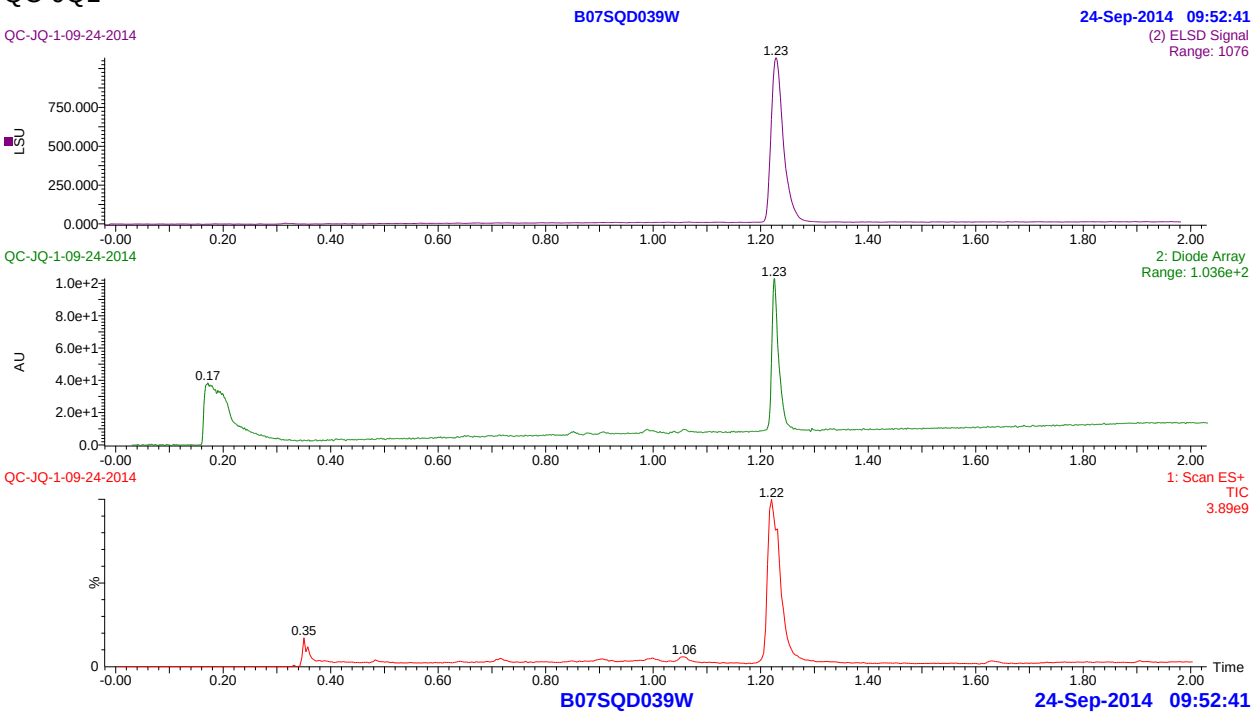


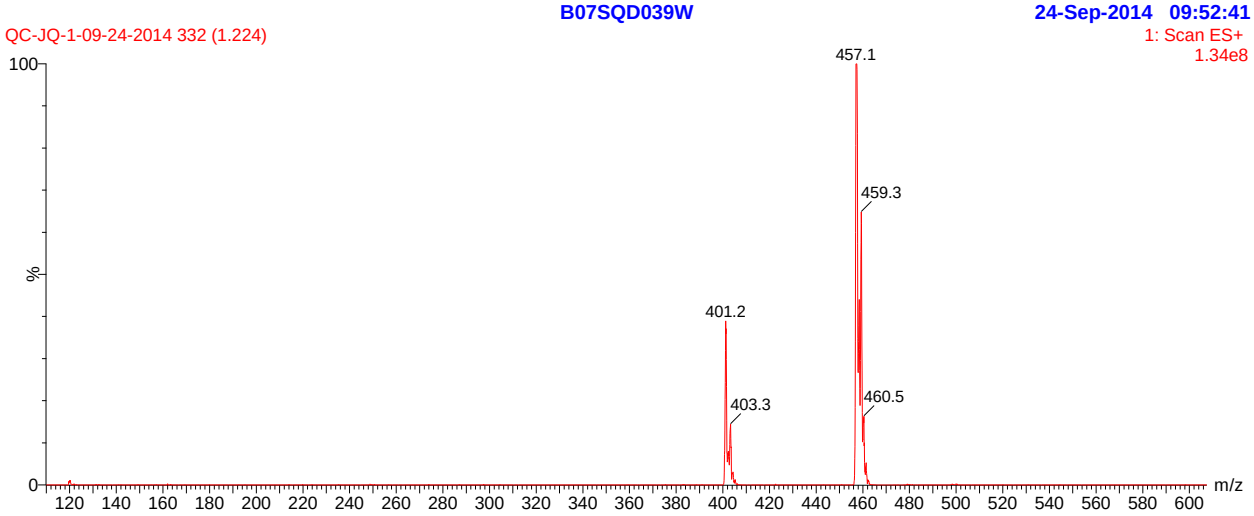

C13CPDs256 MeOD /opt/cbtnmr jslavish
126.07
123.42
123.01
118.62
114.45
105.04
68.17
39.85
21.38
21.01
19.98
f1 (ppm)


B07SQD039W
29-Sep-2014 11:56:54
QC-599-3-p-09292014 Sm (Mn, 2x2)
(2) ELSD Signal
Range: 1844
0.71
59625
Time Height Area Area%
0.71 1839584 59624.58 100.00
LSU
QC-599-3-p-09292014 Sm (Mn, 2x2)
2: Diode Array
Range: 1.697e+2
0.71
2436277
Time Height Area Area%
0.41 1666841 13380.02 0.54
0.46 1576796 13438.00 0.54
0.48 1902215 13882.93 0.56
0.60 2214414 23720.37 0.95
0.71 164004416 2436277.00 97.42
AU
0.41
13380
0.48
13883
0.60
23720
QC-599-3-p-09292014
1: Scan ES+
TIC
2.39e9
0.71
0.36
1.64
%
Time


B07SQD039W
29-Sep-2014 11:56:54
QC-599-3-p-09292014 192 (0.708)
1: Scan ES+
1.00e8
100
%
0
253.3
356.4
357.3
254.2
150
200
250
300
350
400
450
500
550
600
m/z

QC-JQ1





UV > 95%, ELSD >95%

Crystallization

Data collection and refinement statistics

PDB ID	5EK9
Protein	BRD2-BD2
Compound	Cmpd **9** (SJ830599)
Space group	C 2 2 2_1
Cell dimensions:	
a, b, c (Å)	59.70 69.75 141.21
α, β, γ (deg)	90.00 90.00 90.00
Resolution* (Å)	29.21 (2.08)
Unique observations*	17910 (1257)
Completeness* (%)	99.4 (92.8)
Redundancy*	12.6 (11.6)
Rmerge*	0.159 (0.986)
I/σI*	13.1 (3.1)
Refinement	
Resolution (Å)	2.08
R_{work} / R_{free} (%)	18.18 / 22.31
Number of atoms	
(protein/other/water)	1776 / 52 / 101
B-factors (A^2)	
(protein/other/water)	30.05 / 30.14 / 30.59
r.m.s.d bonds (Å)	0.012
r.m.s.d angles ($^{o)}$	1.483
Ramachandran	
Favoured (%)	100.00
Allowed (%)	0.00
Disallowed (%)	0.00

* Values in parentheses correspond to the highest resolution shell