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Subtilisin integrated artificial plant cell walls as heterogeneous catalysts for asymmetric synthesis of (*S*)-amides

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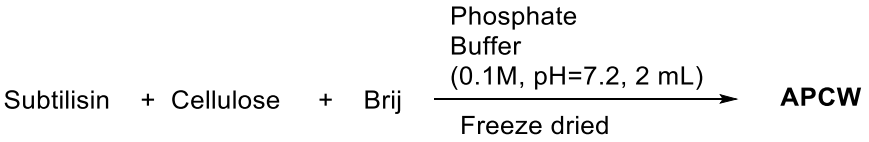
General methods:

Chemicals and solvents were purchased from commercial suppliers and used as received or purified by standards techniques. Avicel® PH-101 (~50 µm particle size), Proteinase bacterial (Type XXIV, 7.0-14.0 units/mg solid, lyophilized powder), Brij® C10 (average Mn ~683) were purchased from Aldrich and used as received. Dry toluene was column-dried directly before use by a VAC: Solvent Purifier system. ^{1}H NMR spectra were recorded on a Bruker Avance 500 (500 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuterium incorporation as the internal standard (CDCl3: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz), integration. ^{13}C NMR spectra were recorded on a Bruker Avance 500 (125.8 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl3: δ 77.26 ppm). High-resolution mass spectrometry was performed on an Agilent Technologies 6520- Q-TOF ESI-MS (positive mode) at the Mid-Sweden University Mass Spectrometry Facility. Enantiomeric ratios were determined by HPLC (Chiral Agilent Technologies Chiralpak OD-H, OJ-H, AS-H, AM-H column (4.6 mm x 250 mm)) in comparison with authentic racemic materials. Optical rotations were measured on a Perkin-Elmer 341 Polarimeter. Unless otherwise noted, all reactions were performed with distilled solvents in oven- dried (160^{o}C) glassware. X-ray photoelectron spectroscopy was used to determine the structure and oxidation states of the Pd nanoparticles. Elemental analyses on the Pd content were carried out by Medac LTD Analytical and chemical consultancy services (United Kingdom) by ICP-OES. Infrared spectra were recorded by Thermo Scientific NICOLET 6700 FT-IR, Smart orbit, Diamond 30000-200 cm^{-1}.

Self-assembly of APCW catalyst.

In a plastic beaker was added cellulose, sodium phosphate buffer (0.1 M, pH 7.2) and Brij C10. The suspension was stirred with a spatula until completely solubilization of brij. Next subtilisin (20 mg) was added, the mixture was stirred with a spatula until completely solubilization of the enzyme and rapidly frozen in liquid nitrogen. The catalyst was lyophilized for 70 hours to give a solid white foam. Cellulose/subtilisin was stored at -20°C.

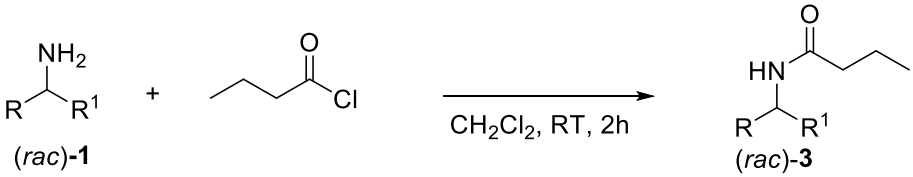
Table S1. Reagents for the assembling of APCW catalyst.



Entry	Catalyst	Subtilisin [mg]	Cellulose [mg]	Brij [mg]
1[a]	Sub/Brij (1:1)	20	-	20
2[a]	**APCW1** CNC/Sub/Brij (1:1:0)	20	CNC (20)	-
3[a]	**APCW2** CNC/Sub/Brij (1:1:1)	20	CNC (20)	20
4[a]	**APCW3** MCC/Sub/Brij (1:1:1)	20	Avicel (20)	20
5[b]	**APCW4** MCC/Sub/Brij (3:1:1)	20	Avicel (60)	20
6[b]	**APCW5** FNC/Sub/Brij (3:1:1)	20	FNC (60)	20
7[b]	**APCW6** MCC/Sub/Brij (3:1:3)	20	Avicel (60)	60

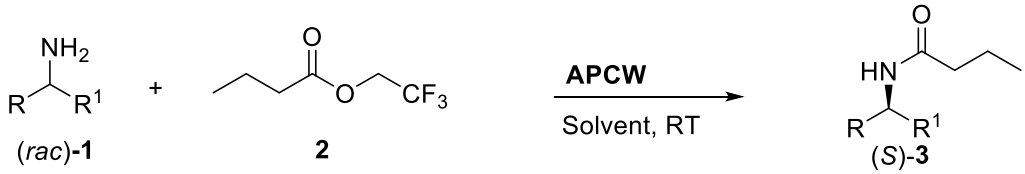
[a] Phosphate buffer 2 mL used. [b] Phosphate buffer 6 mL used.

General procedure for the synthesis of the racemic compounds.

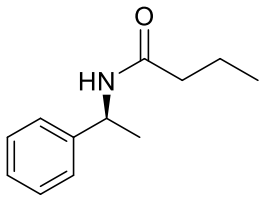


In a microwave vial was added amine (*rac*)-**1** (0.5 mmol, 2 equiv), CH_2Cl_2 (2 mL) and butyryl chloride (26 mg, 0.25 mmol, 1 equiv). The vial was sealed and flushed with nitrogen. The reaction was stirred at room temperature for 2 hours. Next 2mL of HCl (1.0 M) were added and the reaction was stirred for 5 minutes. The reaction was transferred to a separatory funnel, dilute with CH_2Cl_2 (50 mL), washed 3 times with HCl (1.0 M, 20 mL), H_2O, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the pure racemic product (*rac*)-**3** without further purification.

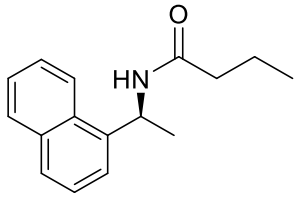
General procedure for the kinetic resolution of rac-1a catalyzed by APCW.



In a microwave vial was added **APCW**, solvent (1 mL), amine (*rac*)-**1** (0.25 mmol, 1 equiv) and 2,2,2-trifluoroethyl butyrate **2** (85 mg, 0.5 mmol, 2 equiv). The vial was sealed and flushed with nitrogen. The reaction was stirred at room temperature for the time reported in the table. The reaction mixture was directly purified by column chromatography (hexane: ethylacetate) to afford the desired product (*S*)-**3** in the reported yield and ee.

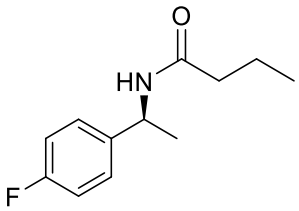


(*S*)-N-(1-phenylethyl)butyramide 3a: 23 mg, 48% yield; white solid**; ^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.36 – 7.29 (m, 4H), 7.28 – 7.24 (m, 1H), 5.69 (s, 1H), 5.26 – 5.04 (m, 1H), 2.21 – 2.10 (m, 2H), 1.66 (dt, *J* = 14.8, 7.4 Hz, 2H), 1.49 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.1, 143.4, 128.8, 127.5, 126.3, 48.7, 38.9, 21.8, 19.3, 13.9 (s)ppm; $[\alpha]_D^{25}$=-88.9 (c=1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH-column, n-hexane/i-PrOH = 97/3, λ = 210 nm, 1,0 ml/min) tr (major enantiomer) = 33.8 min, tr (minor enantiomer) = 28.7 min. **HRMS (ESI):** calculated for $C_{12}H_{18}NO$ $[M+H]^+$ 192.1383; found 192.1373.

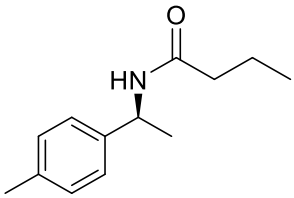


(*S*)-N-(1-(naphthalen-1-yl)ethyl)butyramide 3b: 29 mg, 48% yield; white solid; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.10 (d, *J* = 8.5 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.48 (m, 3H), 7.49 – 7.44 (m, 1H), 6.06 – 5.85 (m, 1H), 5.63 (s, 1H), 2.20 – 2.05 (m, 2H), 1.73 – 1.61 (m, 5H), 0.92 (t, *J* = 7.4 Hz, 3H). ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.9, 138.4, 133.9, 131.2, 128.8, 128.4, 126.5, 125.9, 125.2, 123.6, 122.6, 44.5, 38.7, 20.7, 19.2, 13.78 ppm; $[\alpha]_D^{25}$=-96.5 (c=1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (AMH-column,

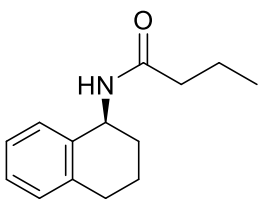
n-hexane/i-PrOH = 98/2, λ = 210 nm, 1,0 ml/min) tr (major enantiomer) = 39.6 min, tr (minor enantiomer) = 36.7 min. **HRMS (ESI):** calculated for $C_{16}H_{20}NO$ $[M+H]^+$ 242.1539; found 242.1532.



(*S*)-N-(1-(4-fluorophenyl)ethyl)butyramide 3c: 22mg, 42% yield; white solid; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.30 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.03 (t, *J* = 8.6 Hz, 2H), 5.68 (s, 1H), 5.15 (p, *J* = 7.1 Hz, 1H), 2.17 (t, *J* = 7.5 Hz, 2H), 1.72 – 1.64 (m, 2H), 1.49 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H). ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.1, 163.1, 161.2, 139.4, 127.93 (d, *J* = 8.0 Hz), 115.6, 115.46, 48.1, 38.9, 21.9, 19.3, 13.83ppm; $[\alpha]_D^{25}$=-90.2 (c=1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ADH-column, n-hexane/i-PrOH = 95/5, λ = 210 nm, 1,0 ml/min) tr (major enantiomer) = 14.8 min, tr (minor enantiomer) = 11.8 min. **HRMS (ESI):** calculated for $C_{12}H_{17}FNO$ $[M+H]^+$ 210.1289; found 210.1285.

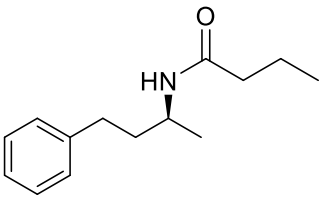


(*S*)-N-(1-(p-tolyl)ethyl)butyramide 3d: 25 mg, 48% yield; white solid; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.20 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 5.61 (s, 1H), 5.11 (p, *J* = 7.0 Hz, 1H), 2.33 (s, 3H), 2.14 (t, *J* = 7.5 Hz, 2H), 1.65 (dt, *J* = 11.1, 5.5 Hz, 2H), 1.47 (d, *J* = 6.9 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.0, 140.6, 137.1, 129.5, 126.3, 48.5, 39.0, 21.8, 21.1, 19.3, 13.8 ppm; $[\alpha]_D^{25}$=-115.3 (c=1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH-column, n-hexane/i-PrOH = 95/5, λ = 210 nm, 1,0 ml/min) tr (major enantiomer) = 13.6 min, tr (minor enantiomer) = 11.0 min. **HRMS (ESI):** calculated for $C_{13}H_{20}FNO$ $[M+H]^+$ 206.1539; found 206.1536.

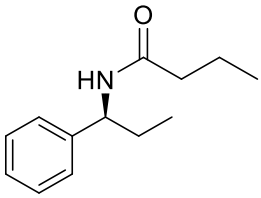


(*S*)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)butyramide 3e: 20 mg, 37% yield; white solid; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.29 (t, *J* = 4.5 Hz, 1H), 7.23 – 7.15 (m, 2H), 7.15 – 7.09 (m, 1H), 5.66 (s, 1H), 5.32 – 5.12

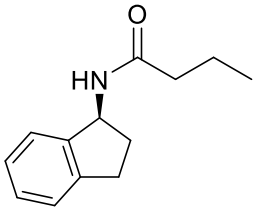
(m, 1H), 2.88 – 2.73 (m, 2H), 2.21 (t, *J* = 7.4 Hz, 2H), 2.07 (dt, *J* = 7.8, 3.6 Hz, 1H), 1.89 – 1.80 (m, 3H), 1.78 – 1.68 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.1, 143.4, 128.8, 127.5, 126.3, 48.7, 38.9, 21.8, 19.3, 13.9 ppm; $[\alpha]_D^{25}$=-78.3 (c=1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH-column, n-hexane/i-PrOH = 95/5, λ = 210 nm, 1,0 ml/min) tr (major enantiomer) = 22.6 min, tr (minor enantiomer) = 13.2 min. **HRMS (ESI):** calculated for $C_{14}H_{20}NO$ $[M+H]^+$ 218.1539; found 218.1537.



(*S*)-N-(4-phenylbutan-2-yl)butyramide 3f: 22 mg, 48% yield; white solid; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.17 (d, *J* = 6.8 Hz, 1H), 4.17 – 3.95 (m, 1H), 2.66 (d, *J* = 7.9 Hz, 2H), 2.10 (t, *J* = 7.4 Hz, 2H), 1.76 (dt, *J* = 9.9, 6.7 Hz, 2H), 1.71 – 1.60 (m, 2H), 1.17 (d, *J* = 6.3 Hz, 3H), 0.95 (dd, *J* = 7.4, 6.9 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.3, 141.9, 128.6, 128.5, 126.0, 45.1, 39.1, 38.9, 32.7, 21.3, 19.4, 13.9. ppm; $[\alpha]_D^{25}$=-42.2 (c=1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH-column, n-hexane/i-PrOH = 94/6, λ = 210 nm, 1,0 ml/min) tr (major enantiomer) = 22.7 min, tr (minor enantiomer) = 16.0 min. **HRMS (ESI):** calculated for $C_{14}H_{21}NO$ $[M+H]^+$ 220.1696; found 220.1691.

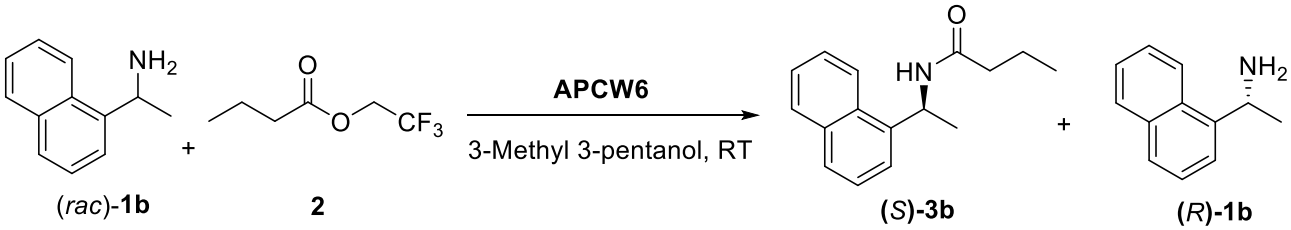


(S)-N-(1-phenylpropyl)butyramide 3g: 26 mg, 50% yield; transparent oil; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.41 – 7.33 (m, 2H), 7.33 – 7.23 (m, 3H), 5.77 (d, *J* = 6.4 Hz, 1H), 4.92 (q, *J* = 7.6 Hz, 1H), 2.18 (t, *J* = 7.4 Hz, 2H), 1.92 – 1.76 (m, 2H), 1.68 (ddd, *J* = 8.8, 7.1, 3.8 Hz, 2H), 0.93 (dt, *J* = 17.7, 7.4 Hz, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.3, 142.4, 128.7, 127.4, 126.7, 54.8, 38.9, 29.2, 19.3, 13.9, 10.8 ppm; $[\alpha]_D^{25}$=-84.5 (c=1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH-column, n-hexane/i-PrOH = 95/5, λ = 210 nm, 1,0 ml/min) tr (major enantiomer) = 19.5 min., tr (minor enantiomer) = 13.7 min. **HRMS (ESI):** calculated for $C_{13}H_{20}NO$ $[M+H]^+$ 206.1539; found 206.1549.



(S)-N-(2,3-dihydro-1H-inden-1-yl)butyramide 3h: 25 mg, 49% yield; yellow solid; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.25 (ddd, *J* = 9.8, 6.5, 4.0 Hz, 4H), 5.84 (d, *J* = 6.8 Hz, 1H), 5.50 (q, *J* = 7.8 Hz, 1H), 2.98 (ddd, *J* = 15.9, 8.8, 3.8 Hz, 1H), 2.87 (dt, *J* = 16.1, 8.2 Hz, 1H), 2.60 (dtd, *J* = 11.7, 7.9, 3.8 Hz, 1H), 2.25 – 2.14 (m, 2H), 1.80 (ddd, *J* = 16.1, 12.9, 8.4 Hz, 1H), 1.76 – 1.65 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.8, 143.3, 143.3, 127.9, 126.7, 124.8, 123.9, 54.5, 38.8, 34.1, 30.2, 19.3, 13.8 ppm; $[\alpha]_D^{25}$=-49.7 (c=1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH-column, n-hexane/i-PrOH = 95/5, λ = 210 nm, 1,0 ml/min) tr (major enantiomer) = 25.7 min., tr (minor enantiomer) = 19.5 min. **HRMS (ESI):** calculated for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1383; found 204.1387.

Recycling of APCW6 catalyst (Table S2).



(*rac*)-**1b** **2** (*S*)-**3b** (*R*)-**1b**

In a microwave vial was added **APCW6** (54 mg), 3-methyl 3-pentanol (2 mL), 1-(naphthalen-1-yl)ethan-1-amine (85 mg, 0.5 mmol, 1 equiv) and 2,2,2-trifluoroethyl butyrate (170 mg, 1.0 mmol, 2 equiv). The vial was sealed and flushed with nitrogen. The reaction was stirred at room temperature for the time reported in the table. Next, dry diethylether was added to the vial and the reaction mixture was centrifuged 3 times collecting the supernatant after each cycle. The recycled catalyst was dried flushing nitrogen through the septum and used directly for the next reaction. The collected supernatant was concentrated under reduced pressure and the crude mixture was purified by column chromatography (hexane/ ethyl acetate 1:1, ethyl acetate: methanol 6:1) to afford (*S*)-**3b** and (*R*)-**1b** in the reported yield and ee.

Table S2. Recycling of the **APCW6** catalyst for the KRs of racemic **1b**.[a]

Cycle	Time (h)	Yield **3b** [%][b]	Yield 1**b** [%][b]	Ee **3b**[%][c]	Ee **1b**[%][c]	E[d]
0	22	39	56	96	99	259
1	22	41	49	95	99	206
2	22	51	49	94	99	170
3	22	42	49	97	94	235
4	22	46	49	96	96	194
5	23	45	49	96	94	175
6	22	42	51	96	85	133
7	22	38	54	98	70	208
8	27	38	54	98	68	203
9	43	40	58	97	76	151

[a] Reaction conditions: **1b** (0.5 mmol, 1equiv), **2** (1.0 mmol, 2 equiv), 3-methyl 3-pentanol (2 mL), **APCW6** MCC/Sub/Brij (3:1:3) (54 mg), room temperature. [b] Isolated yield. [c] Determined by chiral HPLC. [d] E = Enantiomeric ratio, selectivity factor as determined by Chen et al.

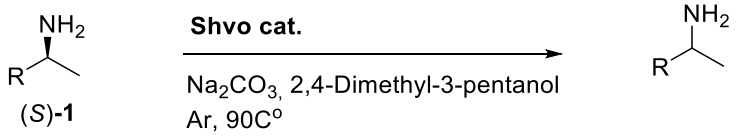
Procedure for monitoring the formation of amide (*R*)-3a as a function of time for the amidation of (*rac*)-2a using CALB and modified CALB with different structural components in toluene.

In a microwave vial were added the catalyst (0.996 mg of lyophilized subtilisin content), 2,4-Dimethyl-3-pentanol (1 mL), amine (*rac*)-**1a** (0.25 mmol, 1 equiv) and 2,2,2-trifluoroethyl butyrate **2** (85 mg, 0.5 mmol, 2 equiv). The vial was capped, flushed with nitrogen and the reaction was stirred at room temperature. At short intervals a small aliquot was taken from the crude mixture and analyzed by ^{1}H-NMR to determine the degree of conversion for amide (*S*)-**3a** as function of time (see figure 3 in the manuscript).

General procedure for the racemization of (*S*)-1 catalyzed by Shvo catalyst.

In a microwave vial was added Shvo catalyst, Na_2CO_3 (29 mg, 0.275mmol, 1.1 equiv) 2,4-Dimethyl-3-pentanol (1 mL), amine (S)-**1** (0.25 mmol, 1 equiv). The vial was sealed and an argon balloon was connected. The reaction was stirred at 90^{o}C for the time reported in the Table S3. Next, butyryl chloride was added to the reaction mixture and the solution was stirred for additional 3 hours. The solution was diluted with ethyl acetate, washed with sodium bicarbonate, water, brine and the organic phase was dried over sodium sulfate. The crude mixture was concentrated under vacuum and directly analyzed by HPLC.

Table S3. Screening for the racemization catalyzed by SHVO catalyst.

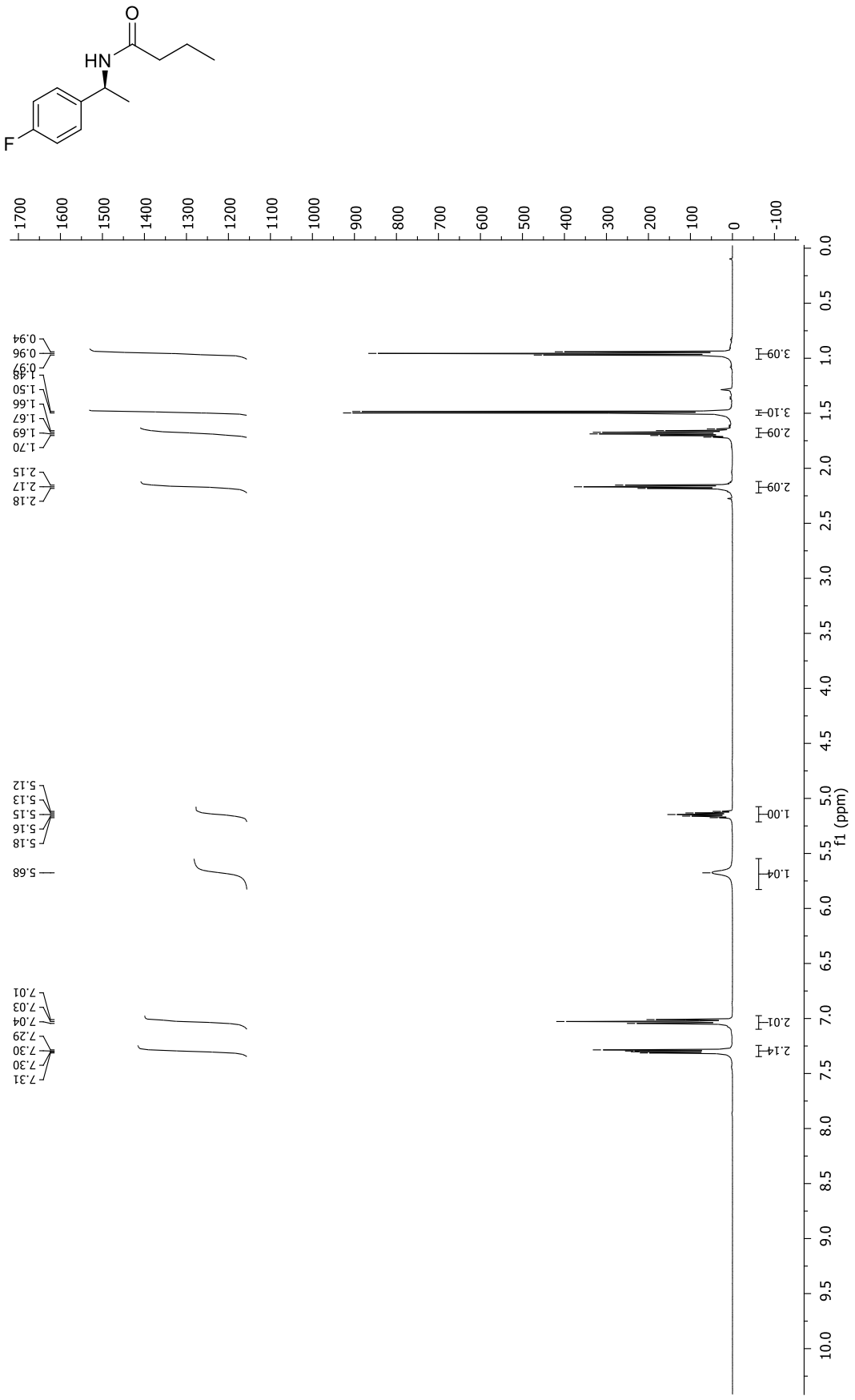


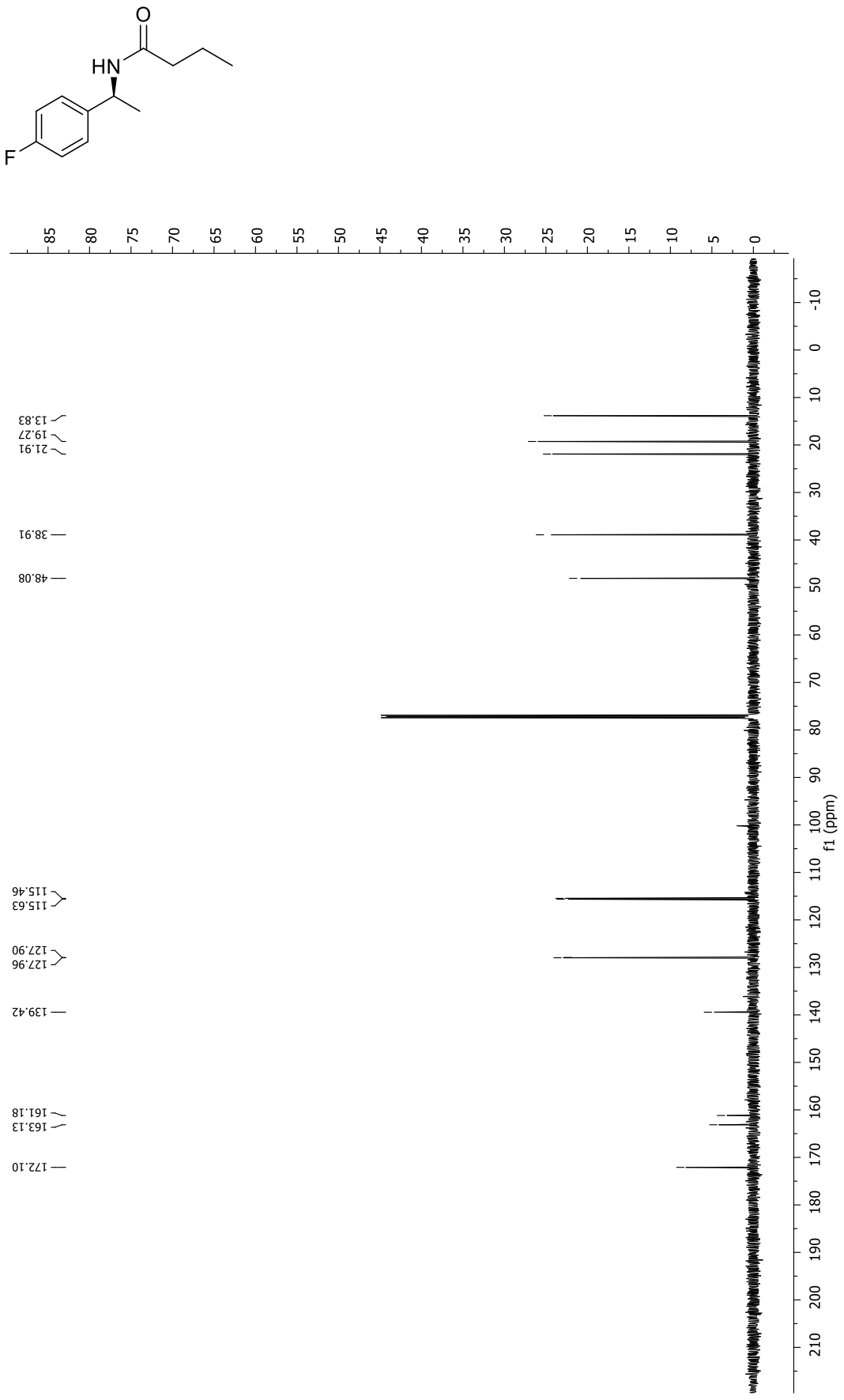
Entry	R	Catalyst [mol%]	Time [h]	Ee **1** [%][b]
1	1-Naft	4.4	22	94
2	1-Naft	18.4	23	74
3	Ph	4.4	24	67

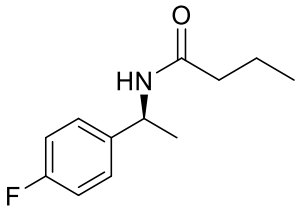
[a] Reaction conditions: **1** (0.25 mmol, 1equiv), 2,4-Dimethyl-3-pentanol (1 mL), Shvo catalyst, Na_2CO_3 (0.275 mmol, 1.1 equiv), 90°C, Ar. [b] Determined by chiral HPLC.

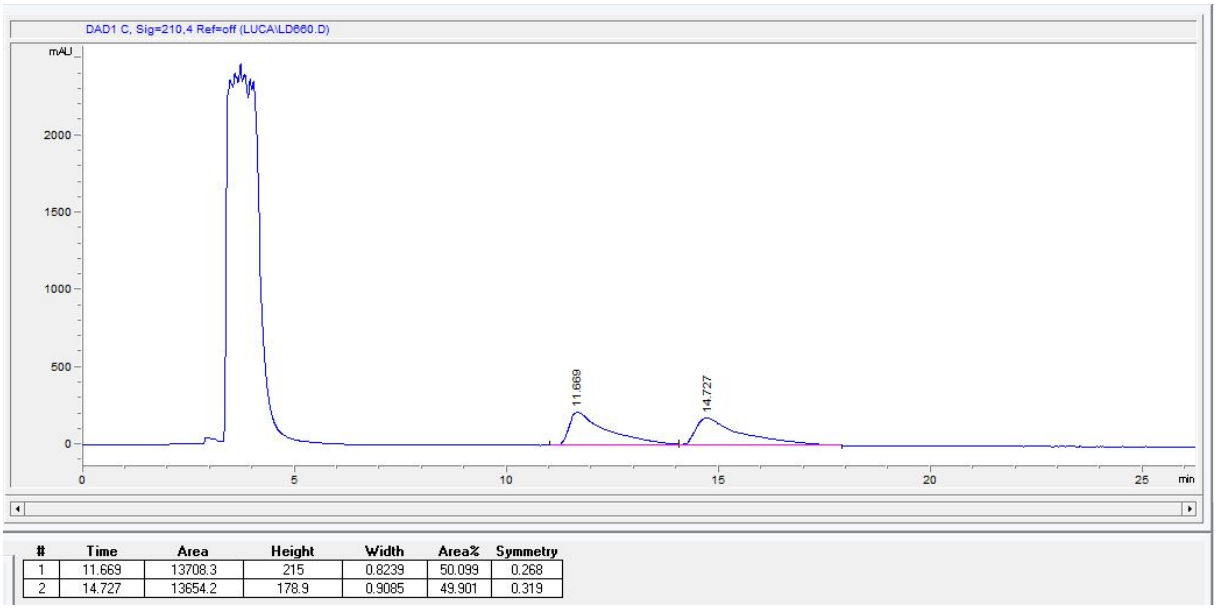
General procedure for the DKR of (*rac*)-catalyzed by APCW4 and Shvo catalyst.

In a microwave vial was added the **APCW4**, Shvo catalyst, 2,4-Dimethyl-3-pentanol (1 mL), amine rac-**1** (0.25 mmol, 1 equiv), 2,2,2-trifluoroethyl butyrate **2** (85 mg, 0.5 mmol, 2 equiv). and Na_2CO_3 The vial was sealed and an argon balloon was connected. The reaction was stirred at 90°C for the time reported in Table 4 of the manuscript. The reaction mixture was directly purified by column chromatography (hexane/ ethyl acetate 1:1) to afford the corresponding amide **3** in the reported yield and ee.


O
HN
F
f1 (ppm)

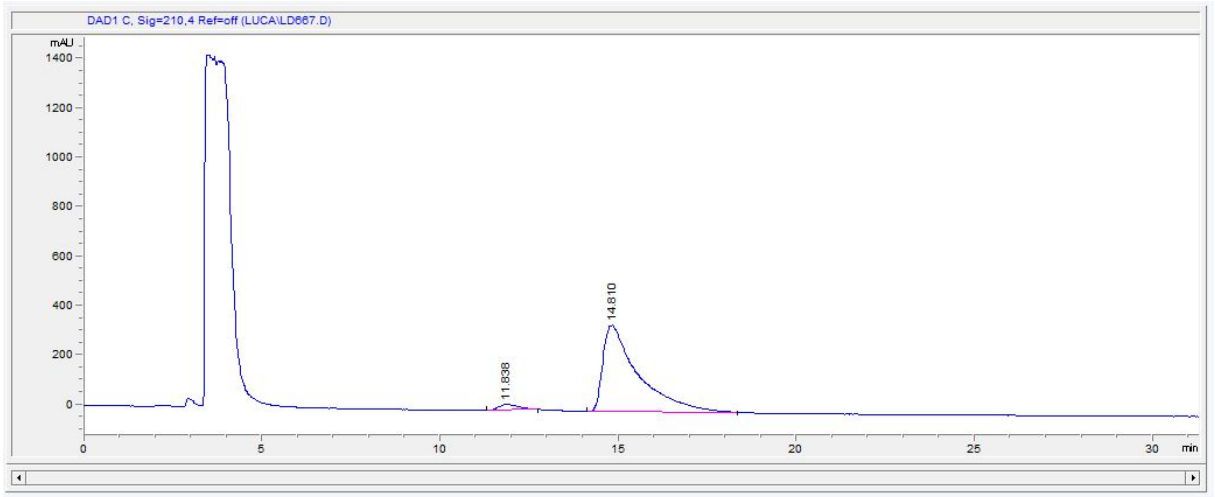

O
HN
F
13.83
19.27
21.91
38.91
48.08
115.63
115.46
127.96
127.90
139.42
161.18
163.13
172.10
f1 (ppm)





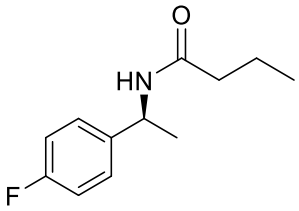
#	Time	Area	Height	Width	Area%	Symmetry
1	11.669	13708.3	215	0.8239	50.099	0.268
2	14.727	13654.2	178.9	0.9085	49.901	0.319

Figure S1. Racemic amide **3c**.



#	Time	Area	Height	Width	Area%	Symmetry
1	11.838	962.1	23.8	0.4856	3.823	0.572
2	14.81	24205.9	349.2	0.8587	96.177	0.317

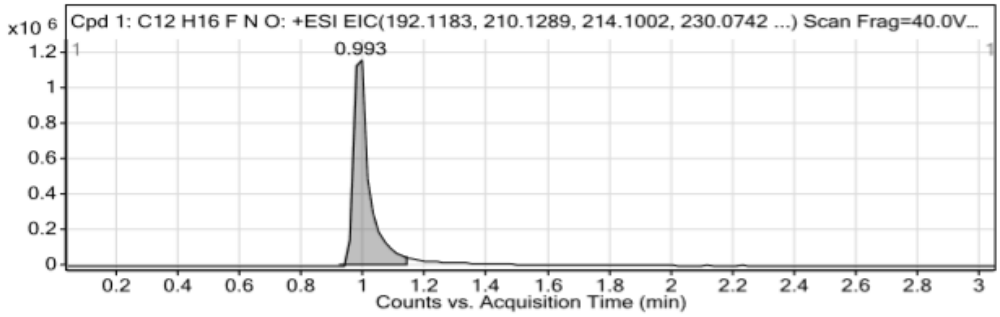
Figure S2. HPLC of amide (*S*)-**3c**.

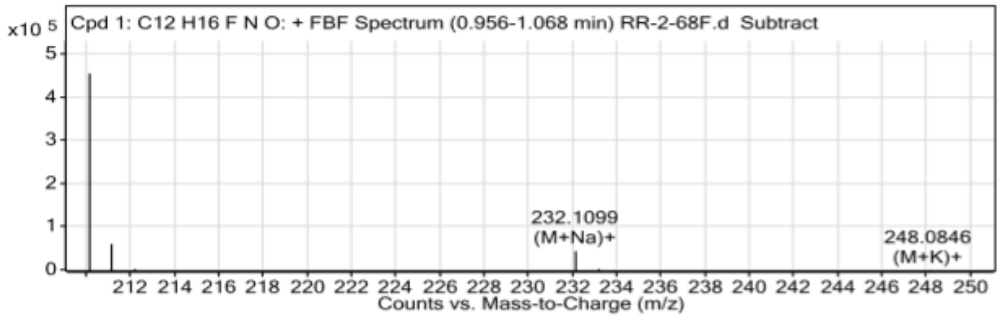


Qualitative Analysis Report

Data Filename	RR-2-68F.d	**Sample Name**	Unavailable
Sample Type	Unavailable	**Position**	Unavailable
Instrument Name	Unavailable	**User Name**	Unavailable
Acq Method		**Acquired Time**	Unavailable
IRM Calibration Status	Success	**DA Method**	Default.m
Comment	Sample information is unavailable		

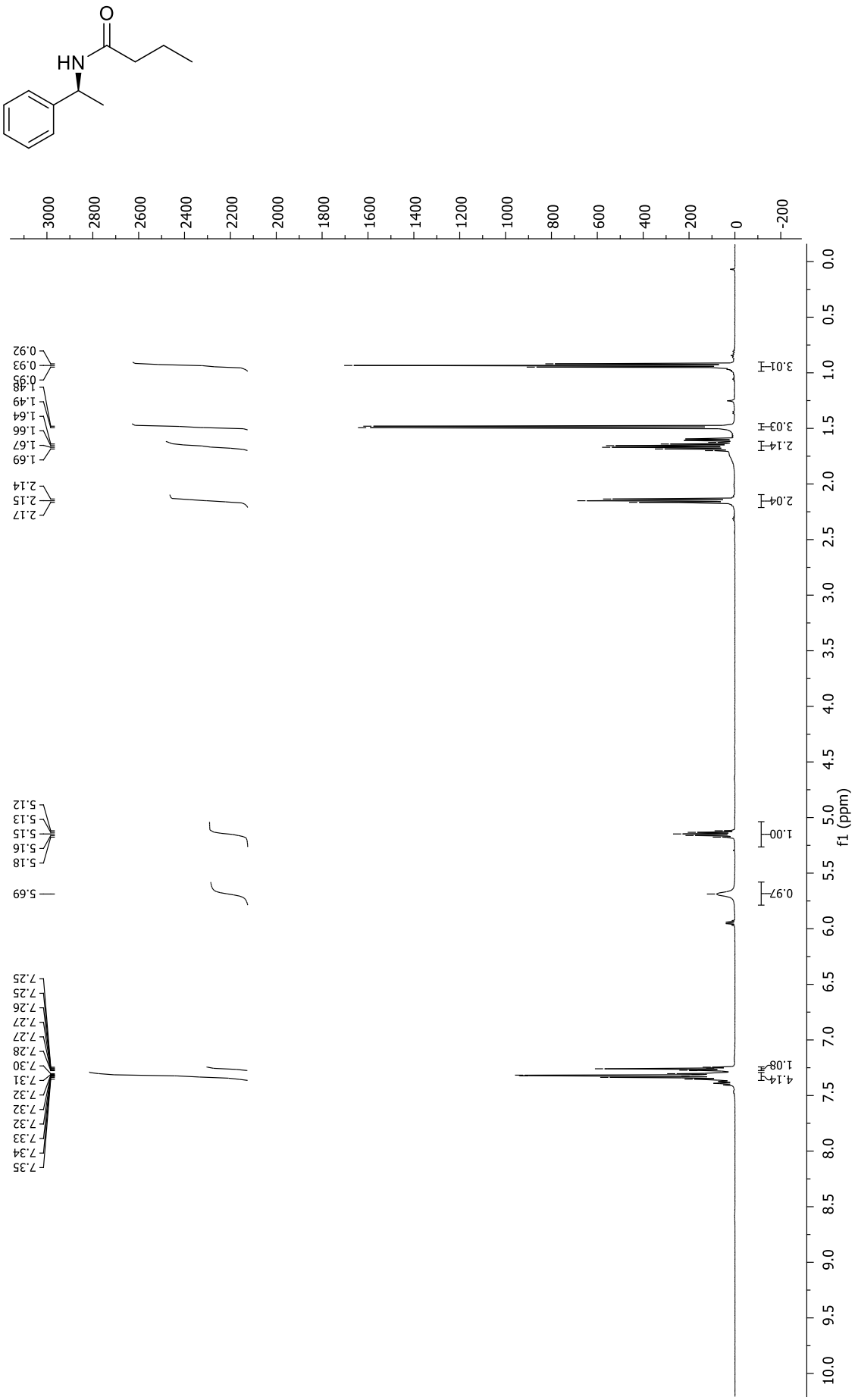
Compounds

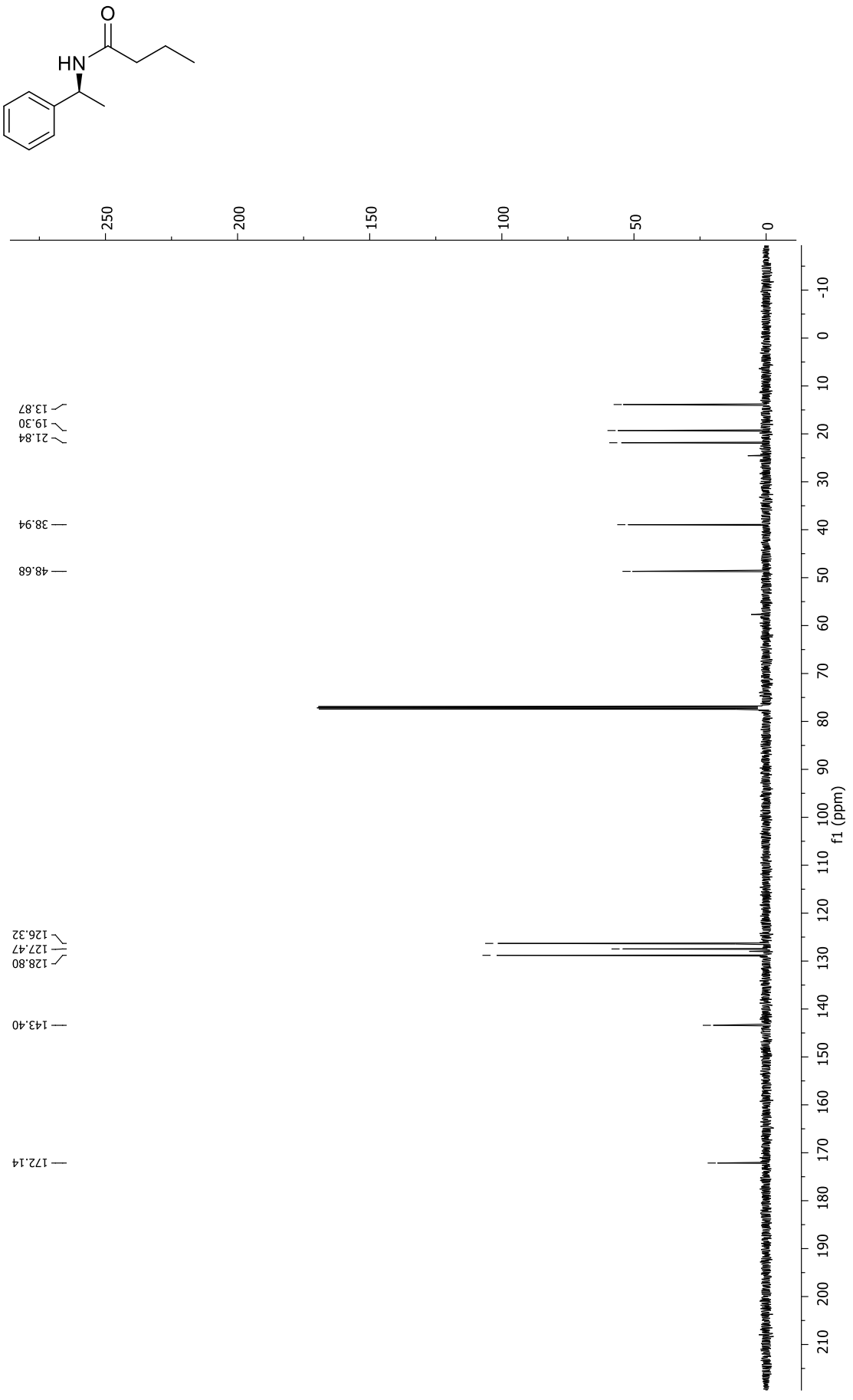


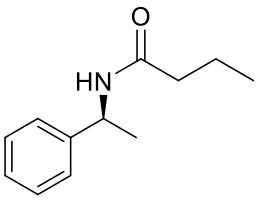


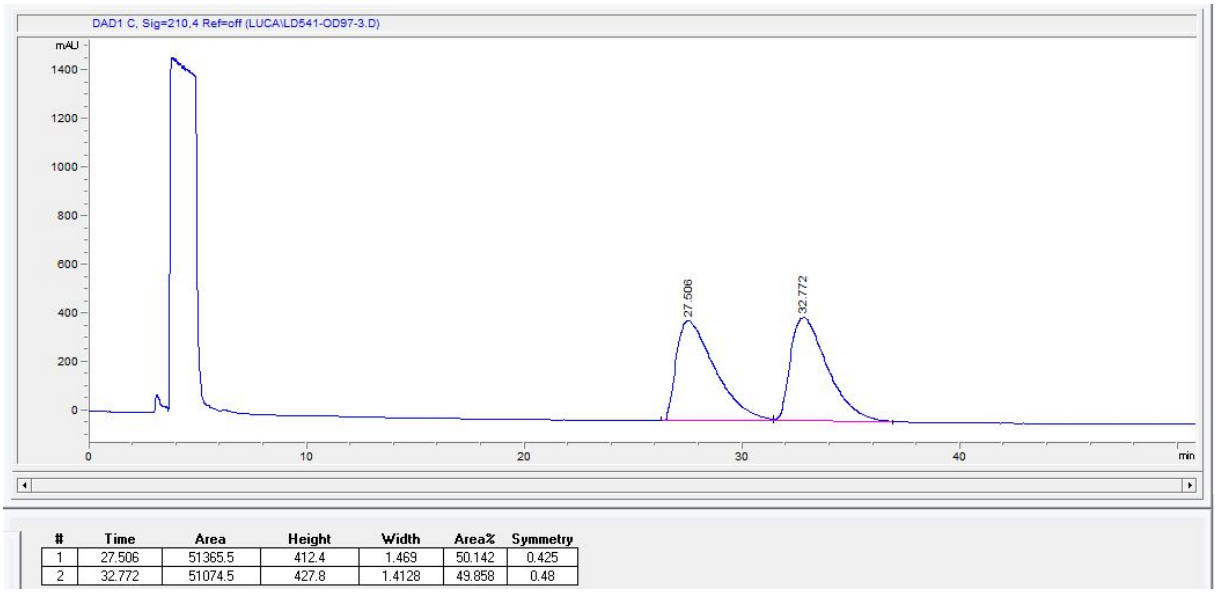
Peak List

m/z	z	Abund	Formula	Ion
210.1285	1	457623.56	C12H17FNO	(M+H)+
211.1316	1	62820.43	C12H17FNO	(M+H)+
212.1344	1	4787.97	C12H17FNO	(M+H)+
213.1356	1	247.56	C12H17FNO	(M+H)+
232.1099	1	47485.97	C12H16FNNaO	(M+Na)+
233.1136	1	6217.46	C12H16FNNaO	(M+Na)+
234.118	1	629.28	C12H16FNNaO	(M+Na)+
248.0846	1	1995.39	C12H16FKNO	(M+K)+
249.0893	1	238.35	C12H16FKNO	(M+K)+
250.0826	1	141.64	C12H16FKNO	(M+K)+


O
HN
f1 (ppm)
0.92
0.93
0.95
1.48
1.49
1.64
1.66
1.67
1.69
2.14
2.15
2.17
5.12
5.13
5.15
5.16
5.18
5.69
7.25
7.25
7.26
7.27
7.27
7.28
7.30
7.31
7.32
7.32
7.32
7.33
7.34
7.35
3.01
3.03
2.14
2.04
1.00
0.97
4.14
1.08

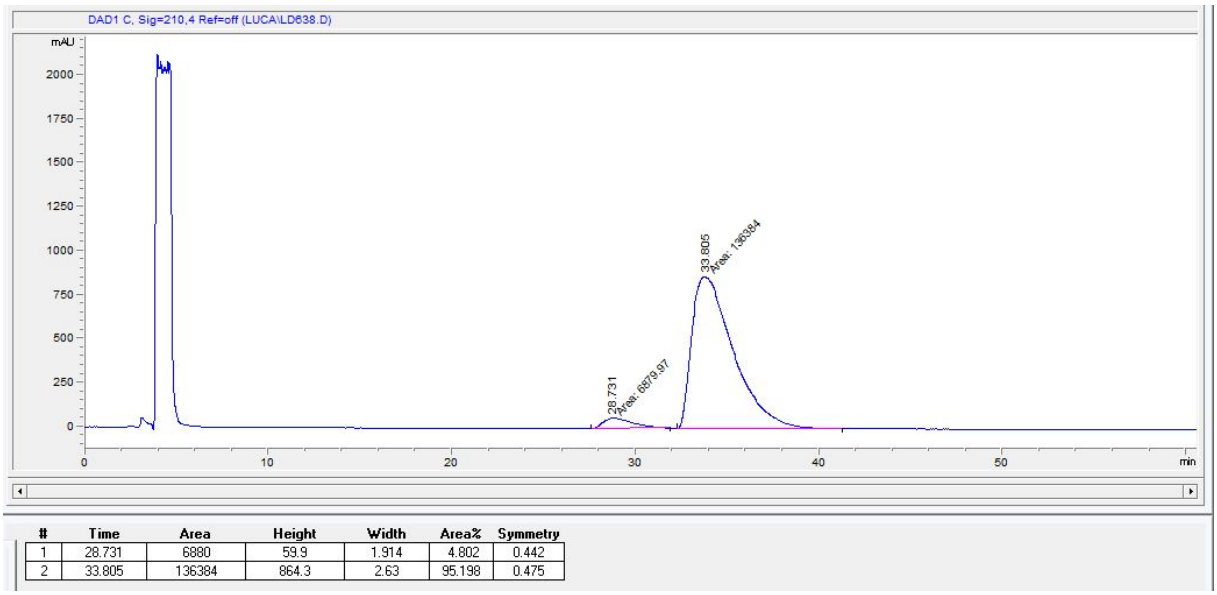

O
HN
250
200
150
100
50
0
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)
13.87
19.30
21.84
38.94
48.68
126.32
127.47
128.80
143.40
172.14





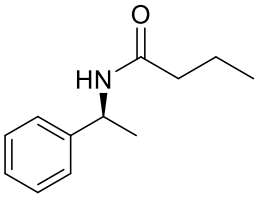
#	Time	Area	Height	Width	Area%	Symmetry
1	27.506	51365.5	412.4	1.469	50.142	0.425
2	32.772	51074.5	427.8	1.4128	49.858	0.48

Figure S3. Racemic amide **3a**.



#	Time	Area	Height	Width	Area%	Symmetry
1	28.731	6880	59.9	1.914	4.802	0.442
2	33.805	136384	864.3	2.63	95.198	0.475

Figure S4. HPLC of amide (*S*)-**3a**.

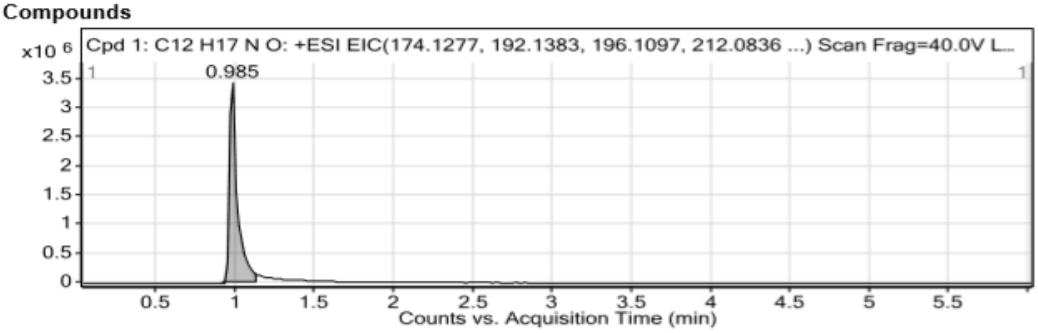


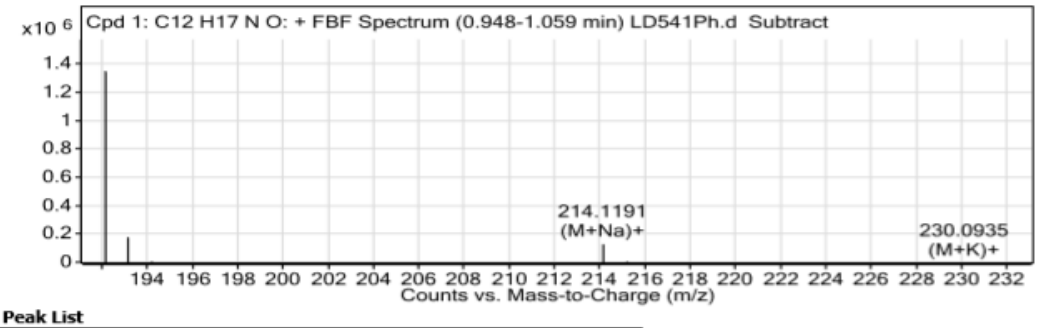
Qualitative Analysis Report

Data Filename	LD541Ph.d	**Sample Name**	LD541Ph
Sample Type	Sample	**Position**	Vial 1
Instrument Name	QTOF	**User Name**	QTOF-PC\admin
Acq Method	ACgroup_new.m	**Acquired Time**	2020-07-28 12:52:18
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.00 (B5042.2)

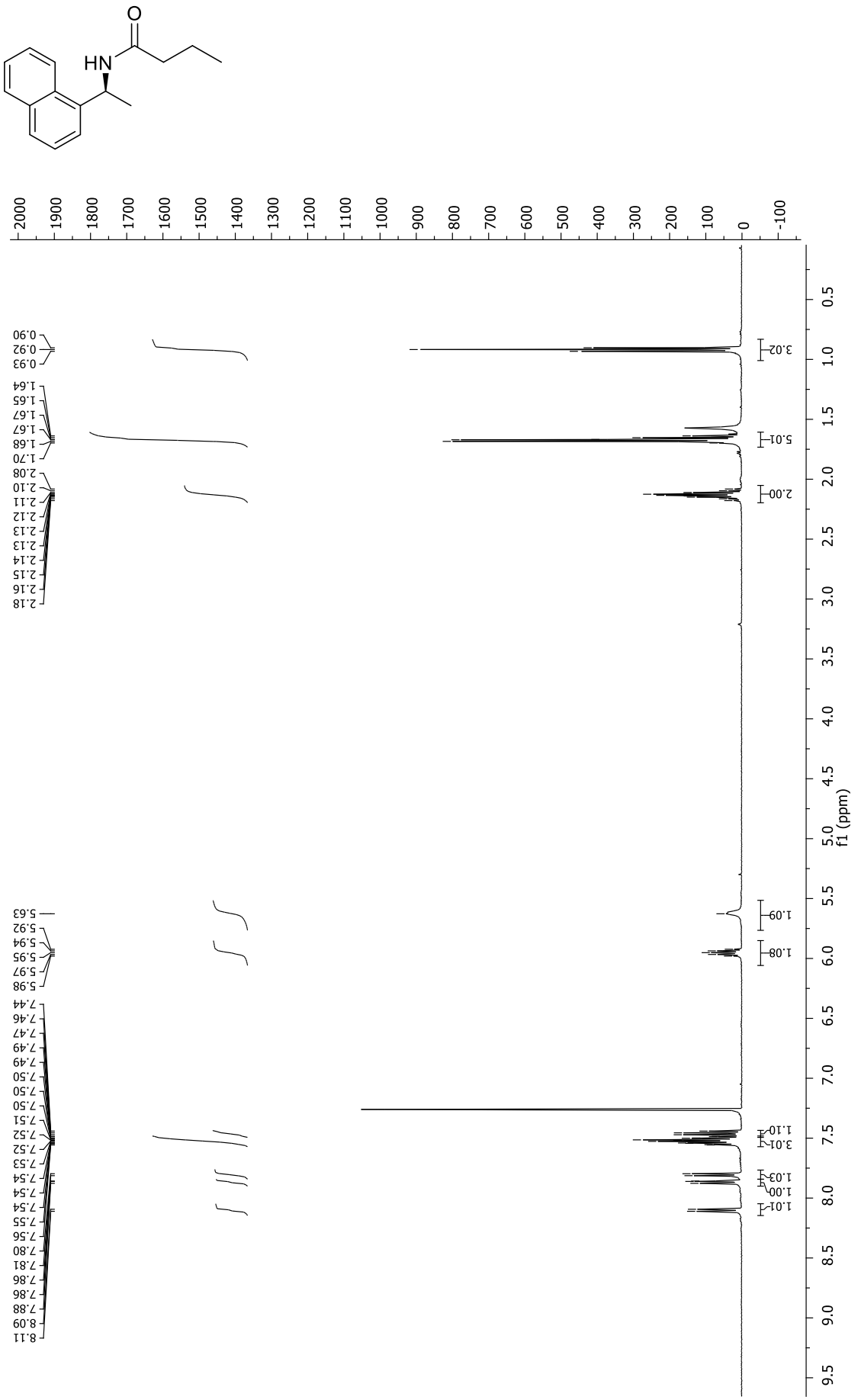
Compounds

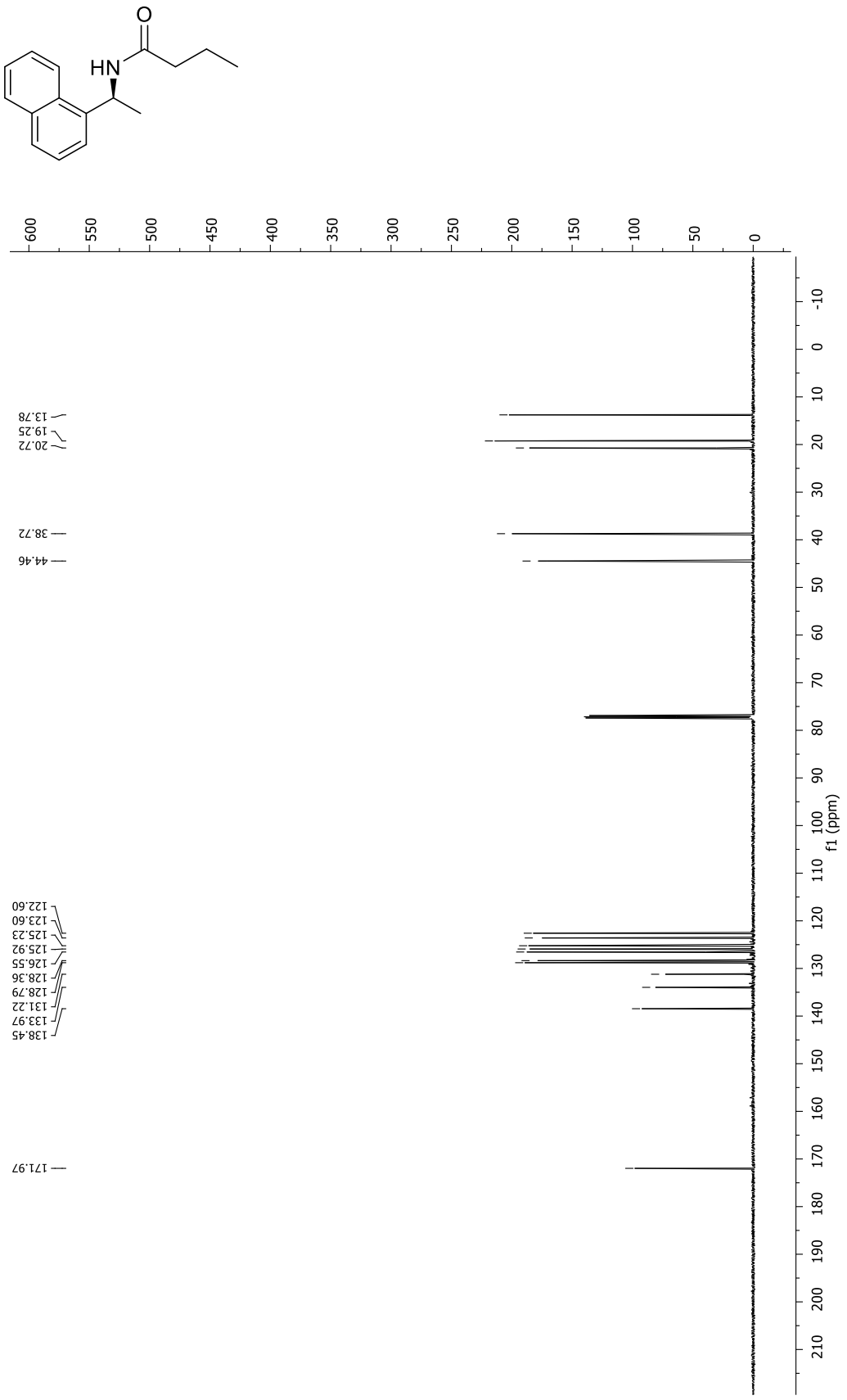


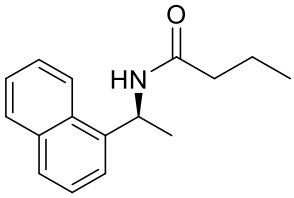


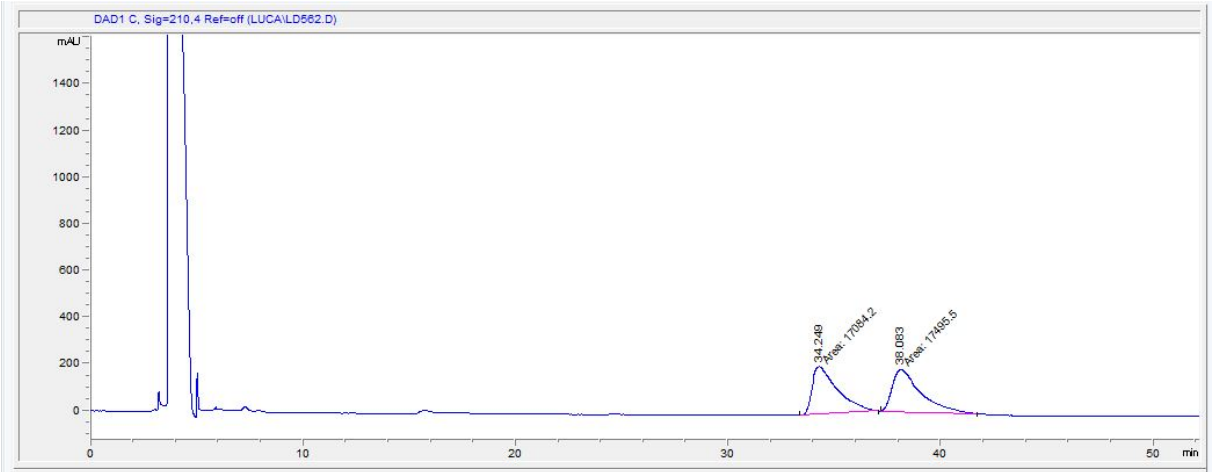
Peak List

m/z	z	Abund	Formula	Ion
192.1373	1	1354116.75	C12H18NO	(M+H)+
193.1409	1	182544.25	C12H18NO	(M+H)+
194.1435	1	14083.26	C12H18NO	(M+H)+
195.1452	1	836.11	C12H18NO	(M+H)+
214.1191	1	141593.45	C12H17NNaO	(M+Na)+
215.1225	1	19619.62	C12H17NNaO	(M+Na)+
216.1256	1	1480.87	C12H17NNaO	(M+Na)+
230.0935	1	6744.09	C12H17KNO	(M+K)+
231.0975	1	967.75	C12H17KNO	(M+K)+
232.0924	1	595.24	C12H17KNO	(M+K)+


O
HN
f1 (ppm)

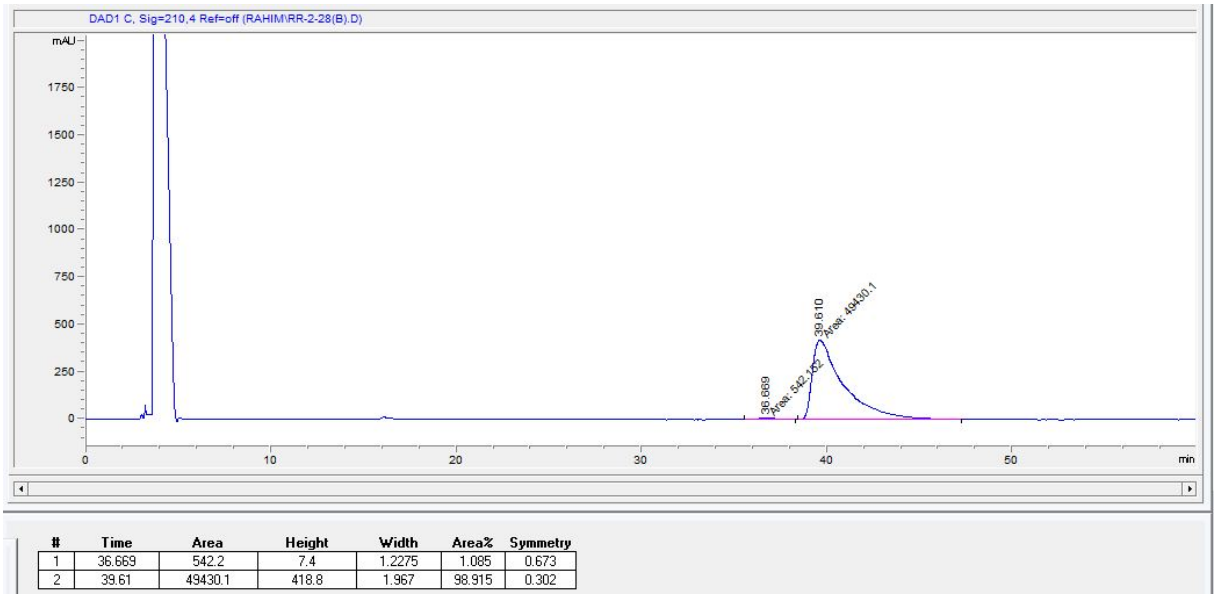

O
HN
600
550
500
450
400
350
300
250
200
150
100
50
0
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)
13.78
19.25
20.72
38.72
44.46
122.60
123.60
125.23
125.92
126.55
128.36
128.79
131.22
133.97
138.45
171.97





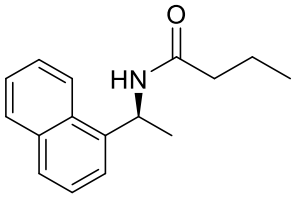
#	Time	Area	Height	Width	Area%	Symmetry
1	34.249	17084.2	204	1.3955	49.405	0.358
2	38.083	17495.5	182.6	1.5969	50.595	0.383

Figure S5. Racemic amide **3b**.



#	Time	Area	Height	Width	Area%	Symmetry
1	36.669	542.2	7.4	1.2275	1.085	0.673
2	39.61	49430.1	418.8	1.967	98.915	0.302

Figure S6. HPLC of amide (*S*)-**3b**.

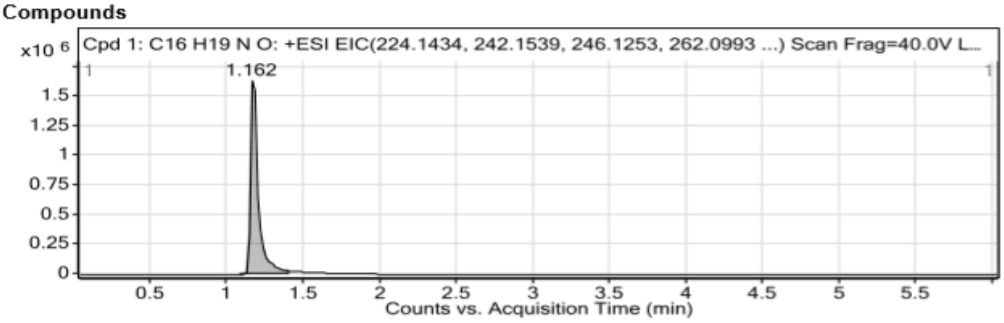


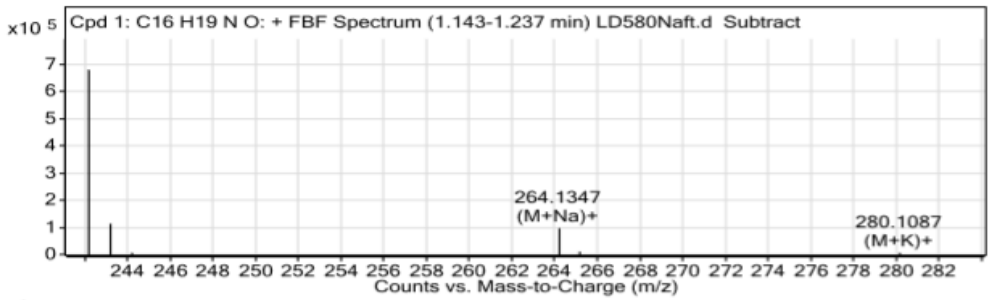
Qualitative Analysis Report

Data Filename	LD580Naft.d	**Sample Name**	LD580Naft
Sample Type	Sample	**Position**	Vial 1
Instrument Name	QTOF	**User Name**	QTOF-PC\admin
Acq Method	ACgroup_new.m	**Acquired Time**	2020-07-21 11:30:38
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.00 (B5042.2)

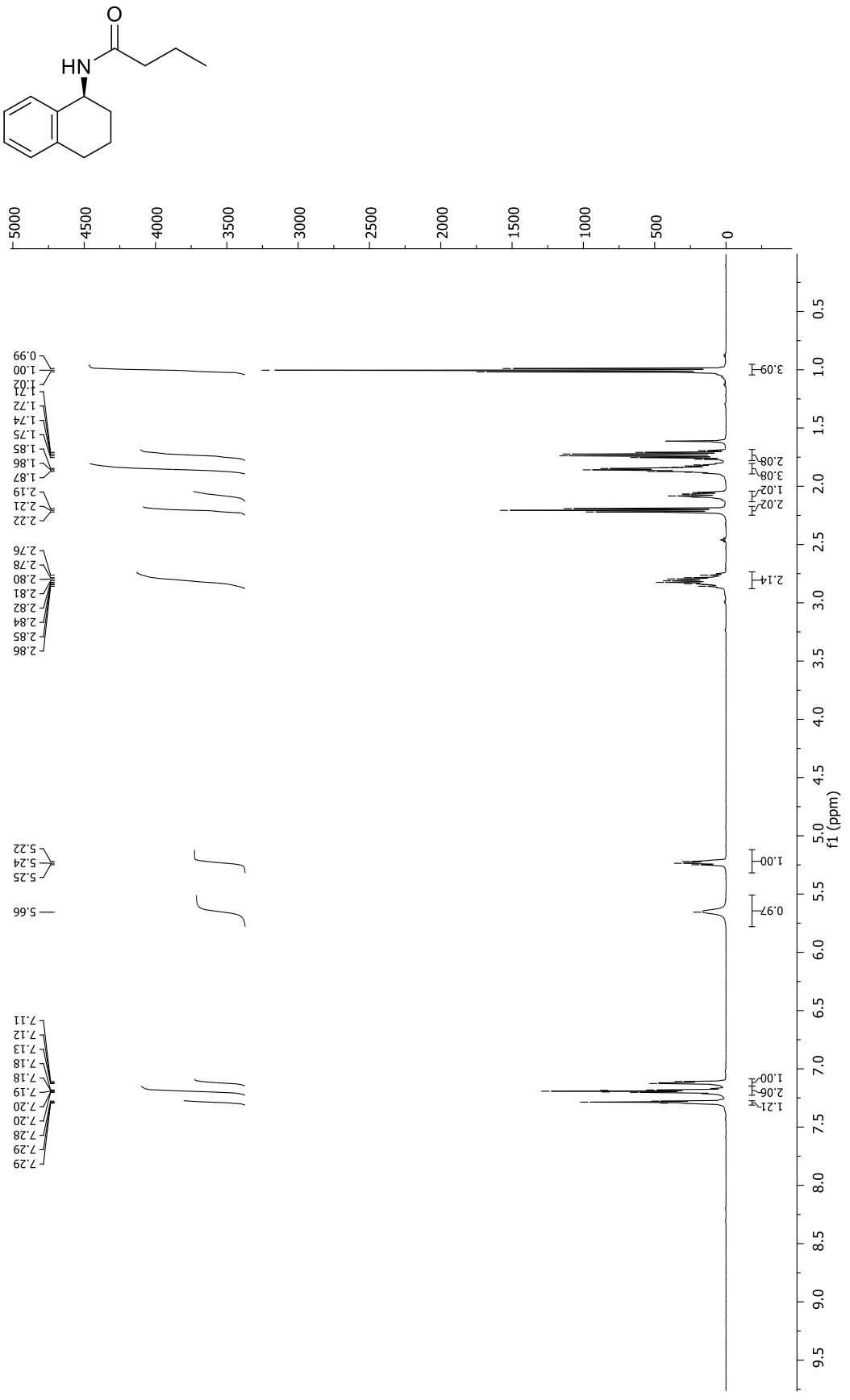
Compounds





Peak List

m/z	z	Abund	Formula	Ion
242.1532	1	684500.31	C16H20NO	(M+H)+
243.1565	1	119363.06	C16H20NO	(M+H)+
244.1592	1	11337.36	C16H20NO	(M+H)+
245.1626	1	1027.8	C16H20NO	(M+H)+
264.1347	1	101224.6	C16H19NNaO	(M+Na)+
265.1378	1	17841.88	C16H19NNaO	(M+Na)+
266.1407	1	1832.74	C16H19NNaO	(M+Na)+
280.1087	1	10313.37	C16H19KNO	(M+K)+
281.1124	1	1824.41	C16H19KNO	(M+K)+
282.109	1	951.53	C16H19KNO	(M+K)+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HN
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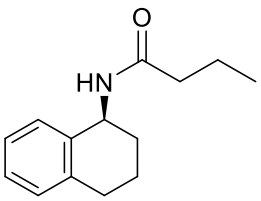
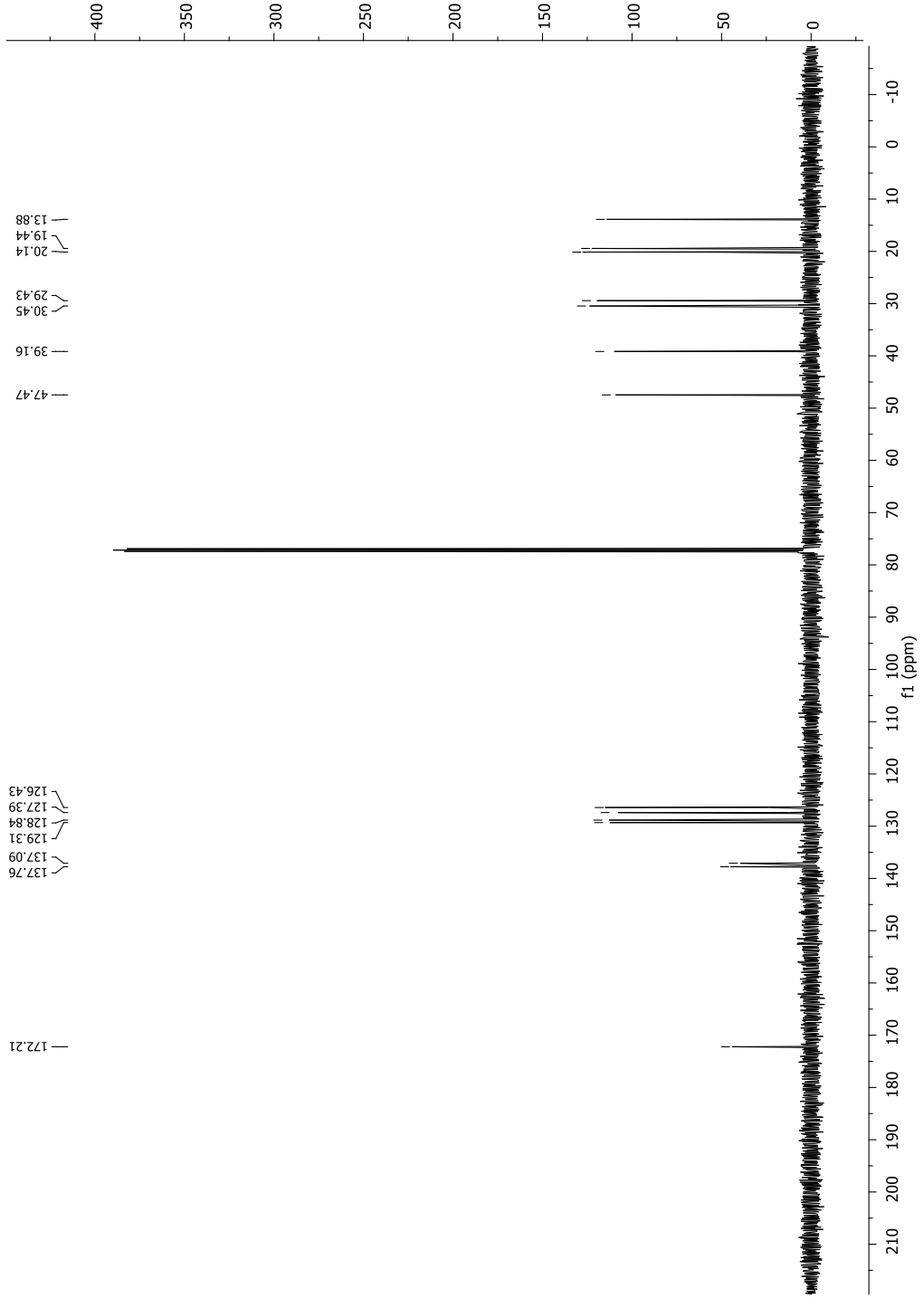
4500
4000
3500
3000
2500
2000
1500
1000
500
0
f1 (ppm)


O
HN


400
350
300
250
200
150
100
50
0
-10
0
10
20
30
40
50
60
70
80
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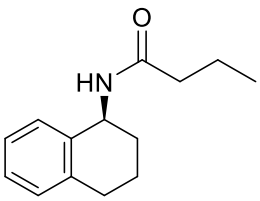
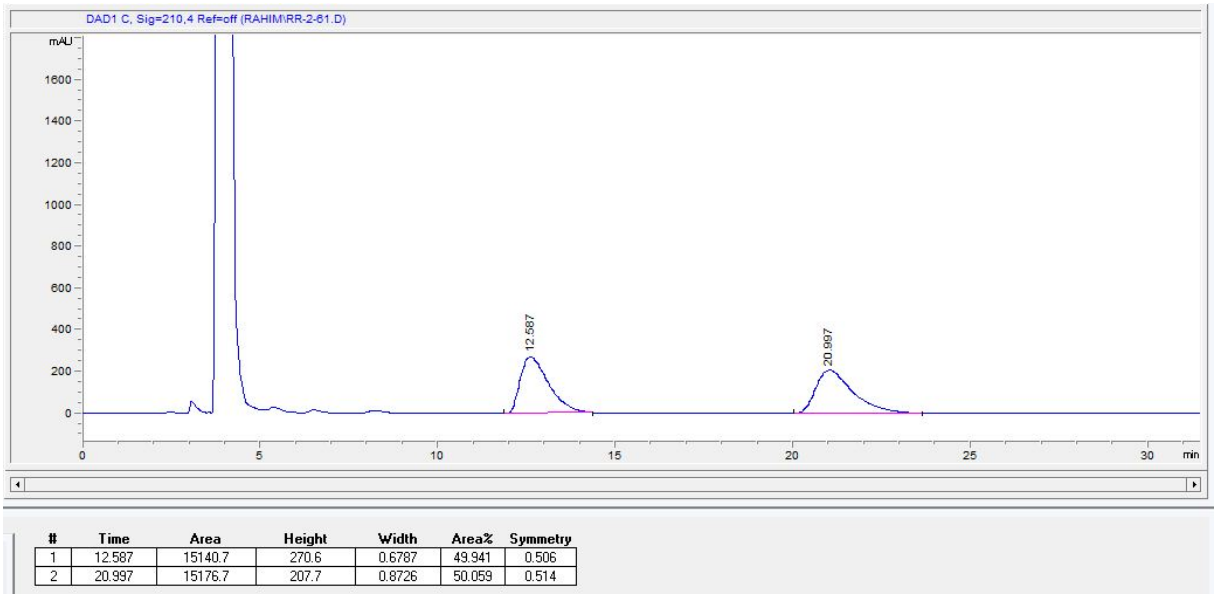
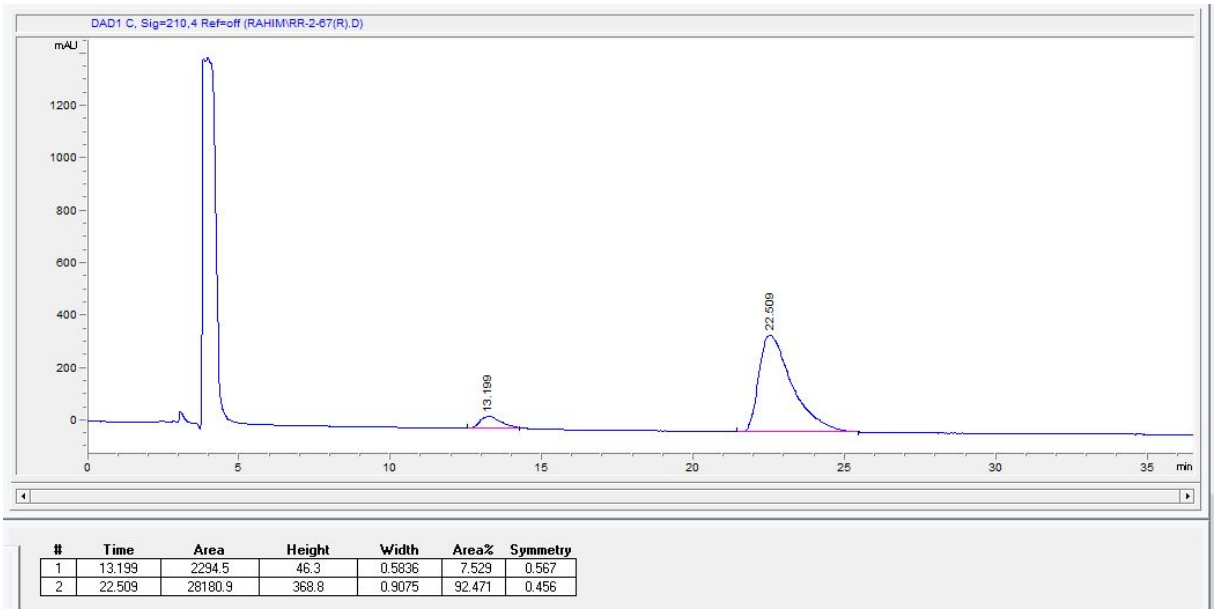
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)
13.88
19.44
20.14
29.43
30.45
39.16
47.47
126.43
127.39
128.84
129.31
137.09
137.76
172.21





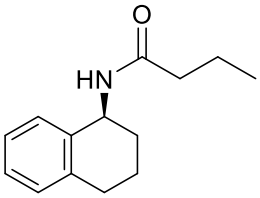
#	Time	Area	Height	Width	Area%	Symmetry
1	12.587	15140.7	270.6	0.6787	49.941	0.506
2	20.997	15176.7	207.7	0.8726	50.059	0.514

Figure S7. Racemic amide **3e**.



#	Time	Area	Height	Width	Area%	Symmetry
1	13.199	2294.5	46.3	0.5836	7.529	0.567
2	22.509	28180.9	368.8	0.9075	92.471	0.456

Figure S8. HPLC of amide (*S*)-**3e**.

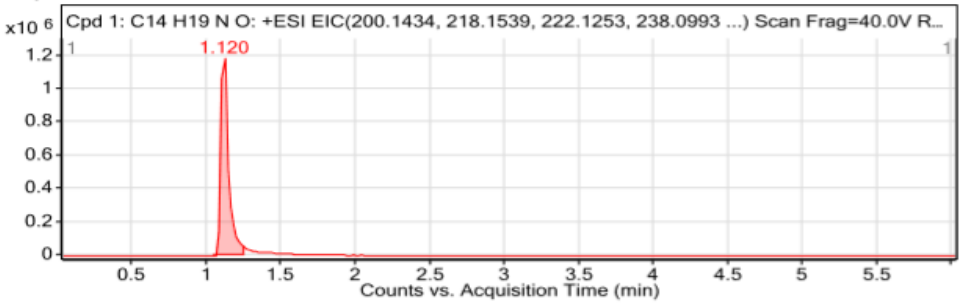


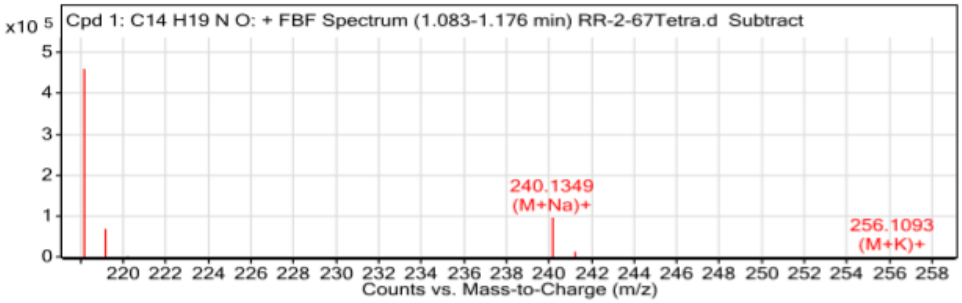
Qualitative Analysis Report

Data Filename	RR-2-67Tetra.d	**Sample Name**	RR-2-67Tetra
Sample Type	Sample	**Position**	Vial 1
Instrument Name	QTOF	**User Name**	QTOF-PC\admin
Acq Method	ACgroup_new.m	**Acquired Time**	2020-07-21 11:23:42
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.00 (B5042.2)

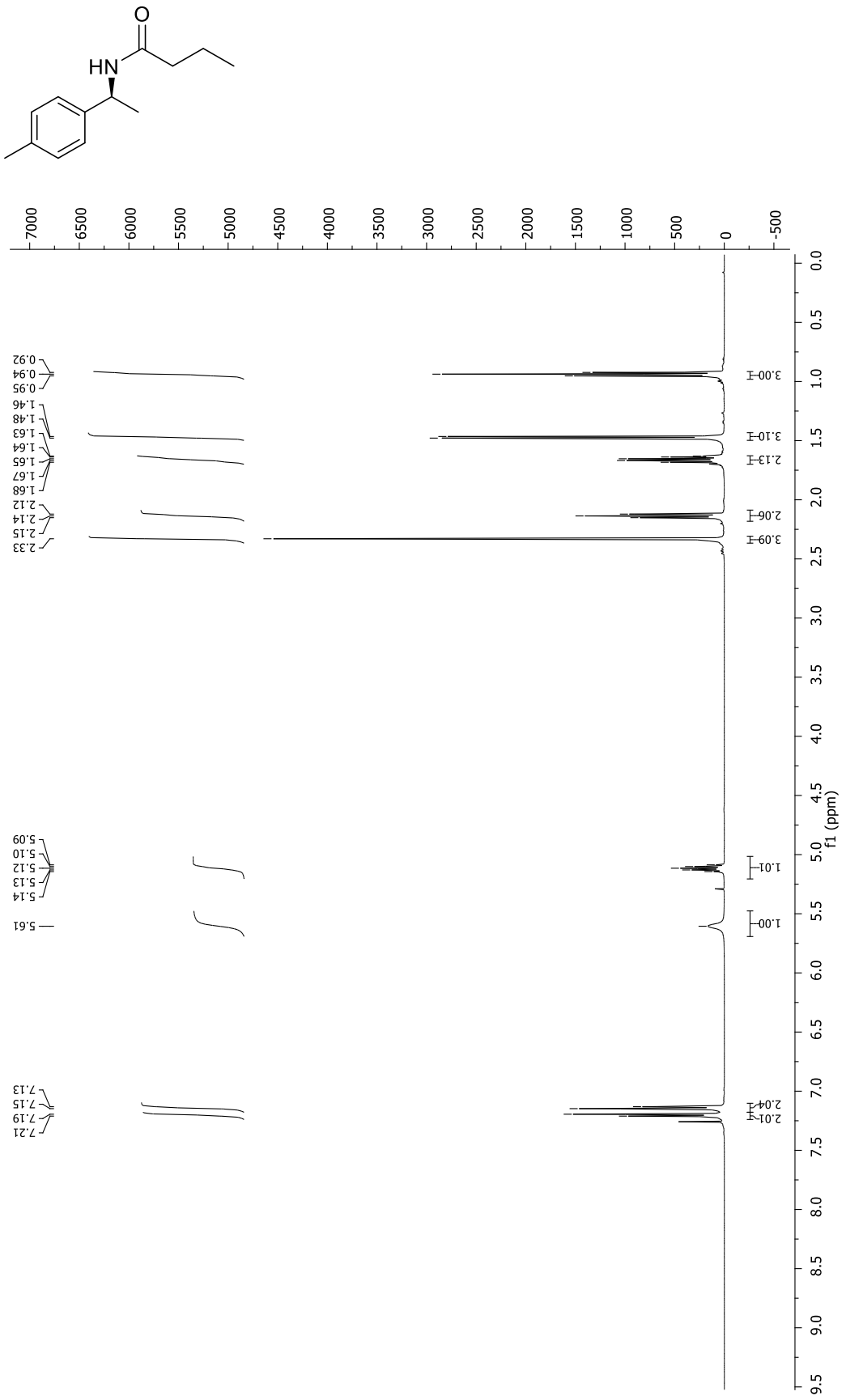
Compounds

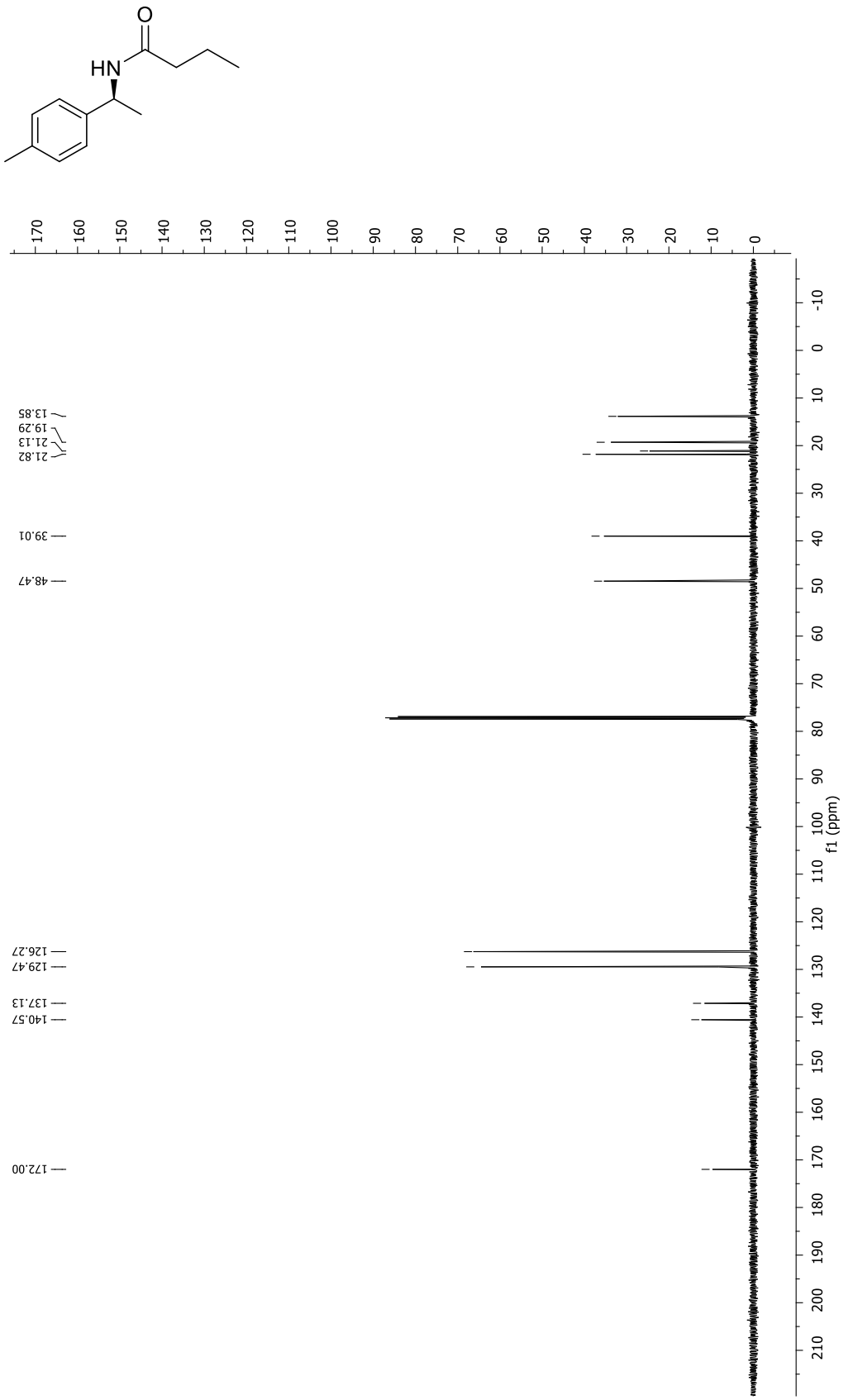


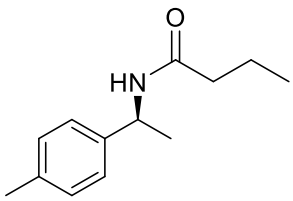


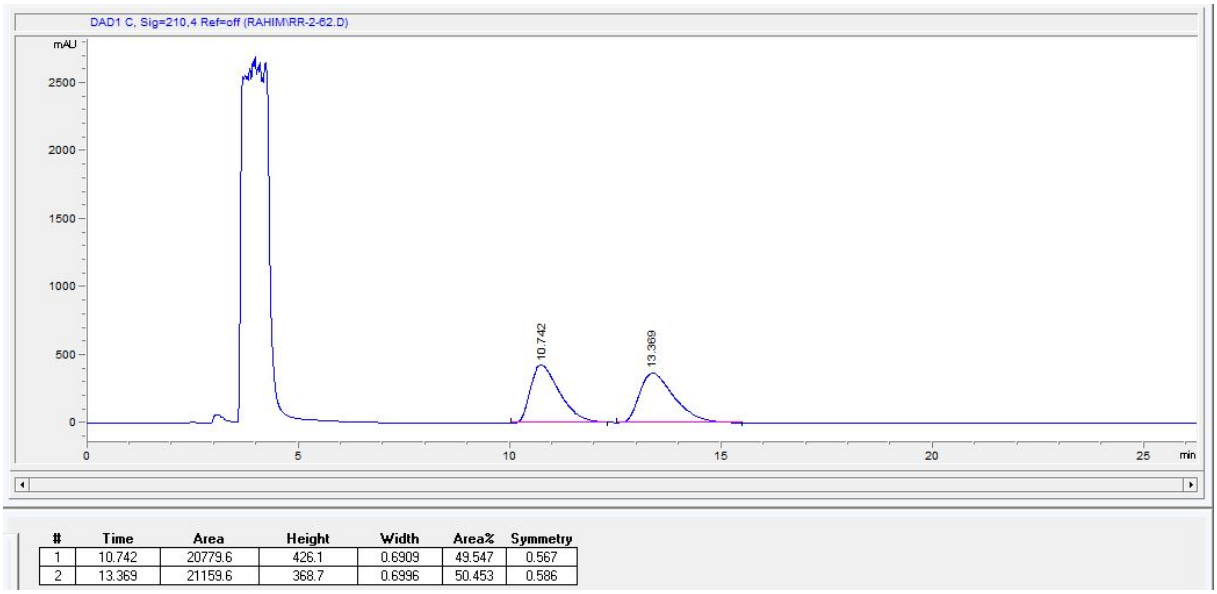
Peak List

m/z	z	Abund	Formula	Ion
218.1537	1	462253.09	C14H20NO	(M+H)+
219.1568	1	71438.23	C14H20NO	(M+H)+
220.1597	1	6684.34	C14H20NO	(M+H)+
221.164	1	420.41	C14H20NO	(M+H)+
240.1349	1	99093.78	C14H19NNaO	(M+Na)+
241.138	1	15785.82	C14H19NNaO	(M+Na)+
242.142	1	1467.16	C14H19NNaO	(M+Na)+
256.1093	1	3041.77	C14H19KNO	(M+K)+
257.1158	1	513.73	C14H19KNO	(M+K)+
258.1095	1	209.25	C14H19KNO	(M+K)+


O
HN
f1 (ppm)

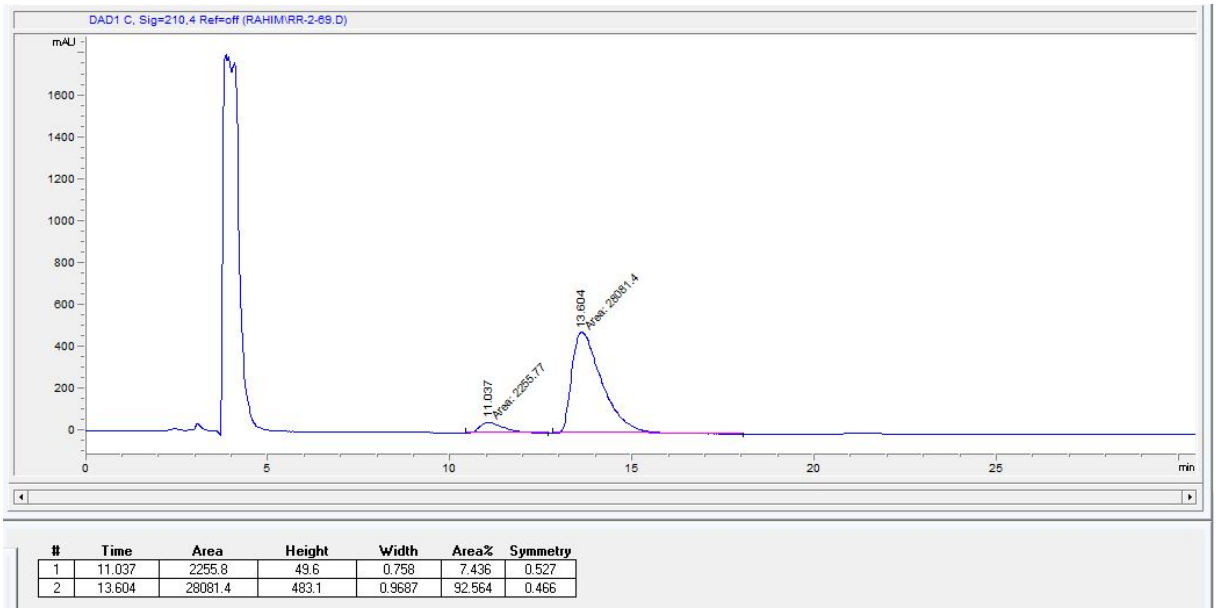

O
HN
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)
13.85
19.29
21.13
21.82
39.01
48.47
126.27
129.47
137.13
140.57
172.00





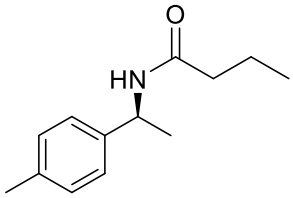
#	Time	Area	Height	Width	Area%	Symmetry
1	10.742	20779.6	426.1	0.6909	49.547	0.567
2	13.369	21159.6	368.7	0.6996	50.453	0.586

Figure S9. Racemic amide **3d**.



#	Time	Area	Height	Width	Area%	Symmetry
1	11.037	2255.8	49.6	0.758	7.436	0.527
2	13.604	28081.4	483.1	0.9687	92.564	0.466

Figure S10. HPLC of amide (*S*)-**3d**.

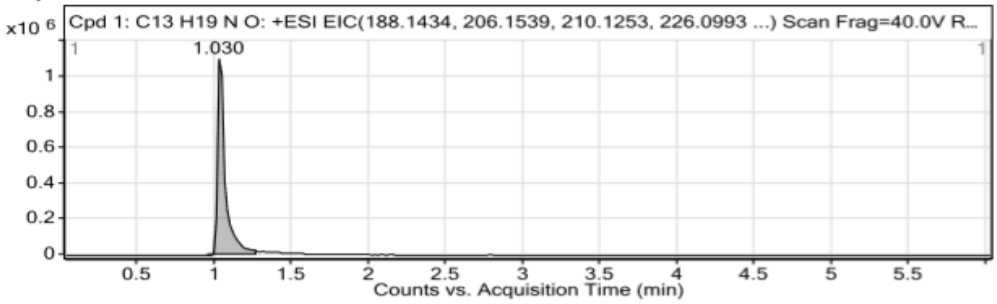


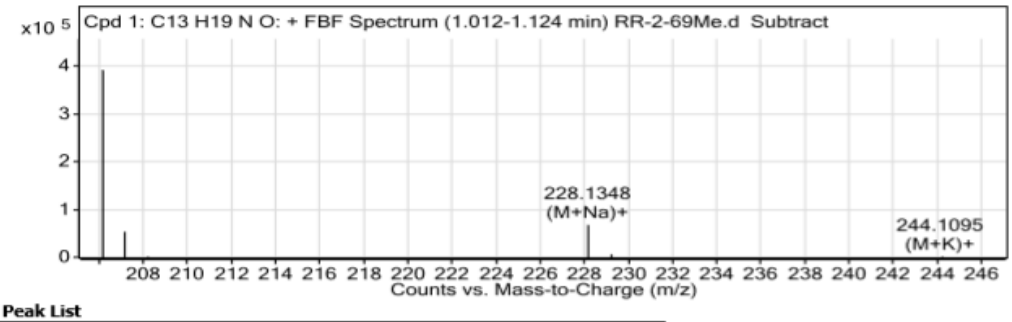
Qualitative Analysis Report

Data Filename	RR-2-69Me.d	**Sample Name**	RR-2-69Me
Sample Type	Sample	**Position**	Vial 1
Instrument Name	QTOF	**User Name**	QTOF-PC\admin
Acq Method	ACgroup_new.m	**Acquired Time**	2020-07-21 11:38:40
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.00 (B5042.2)

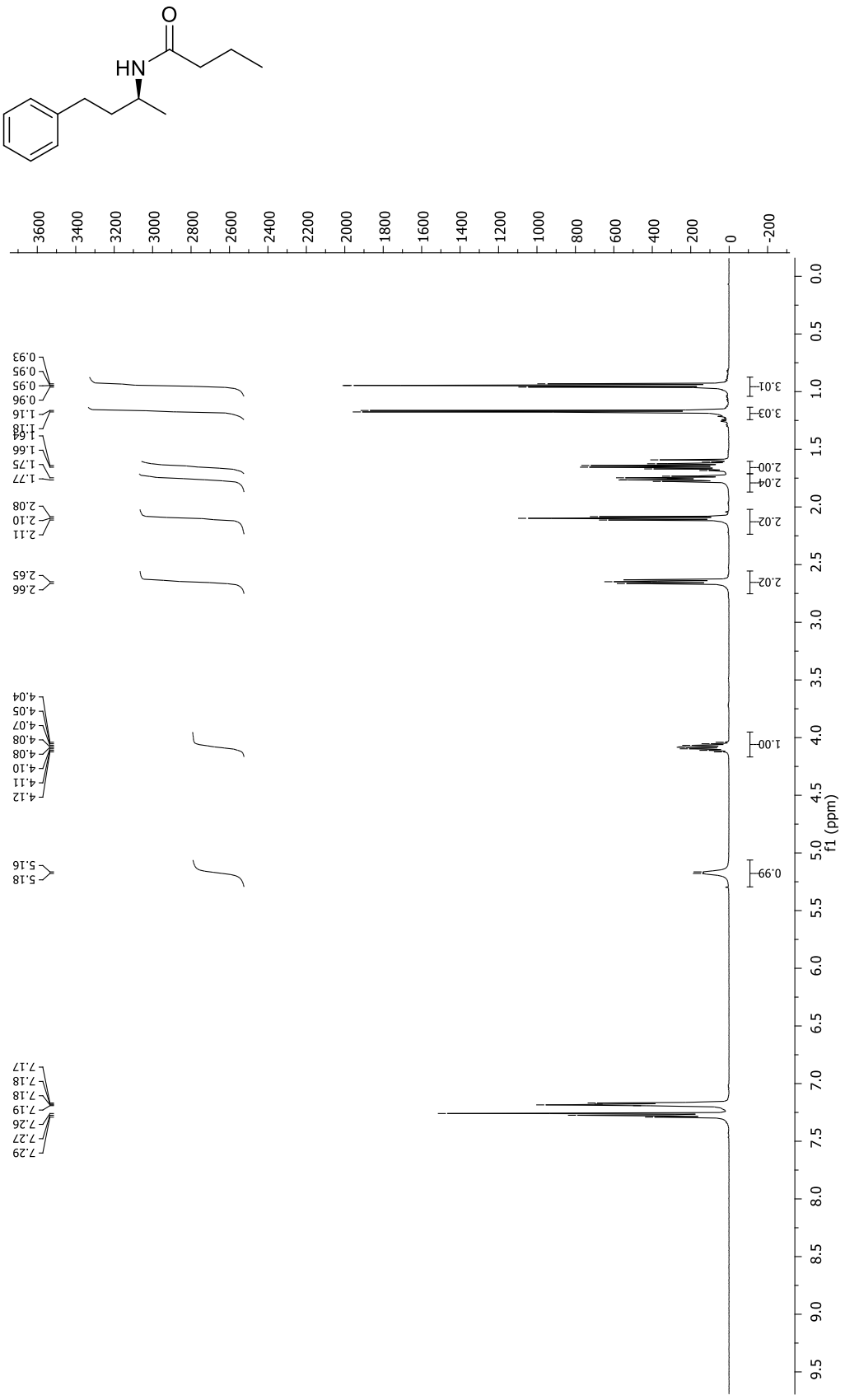
Compounds

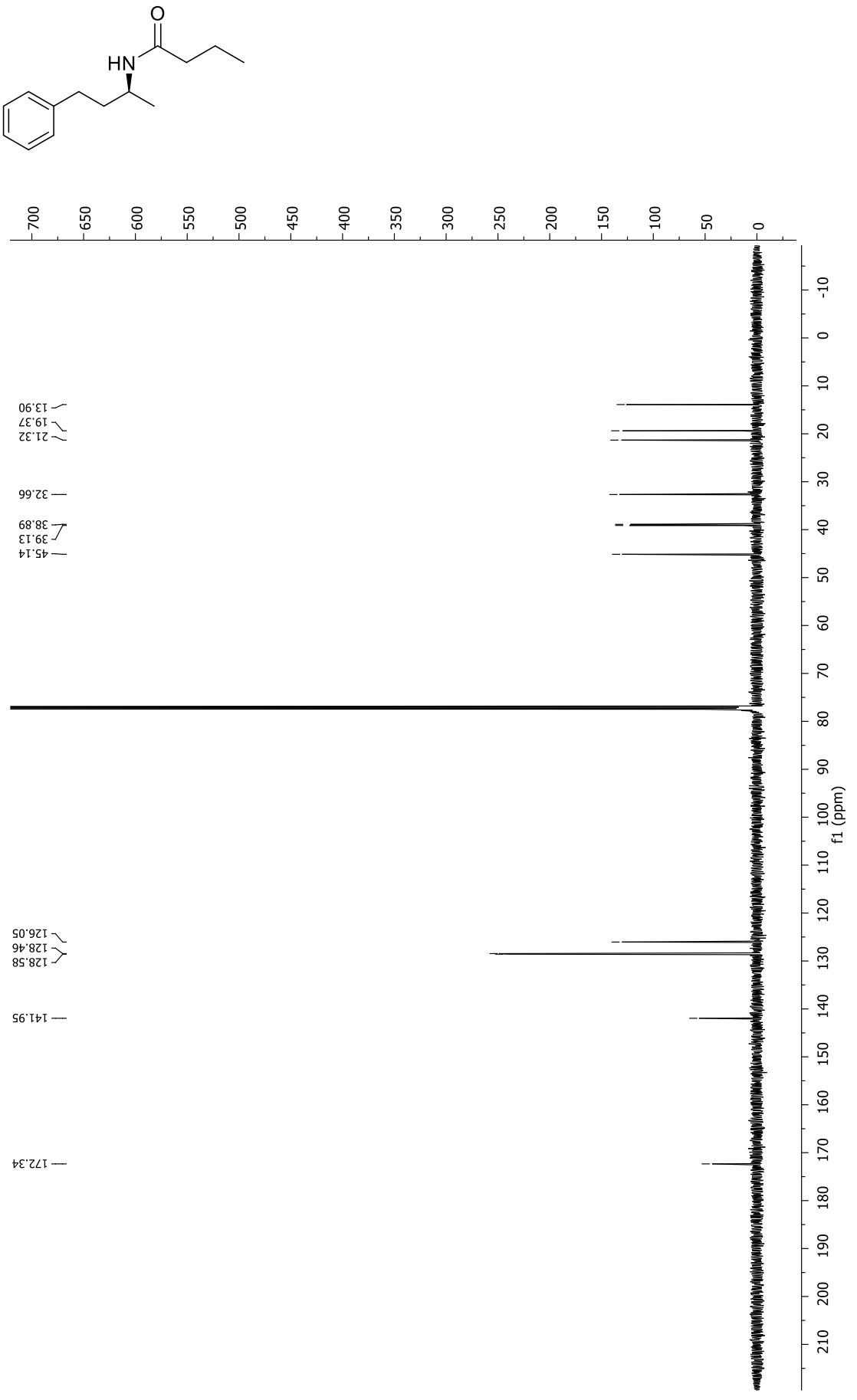


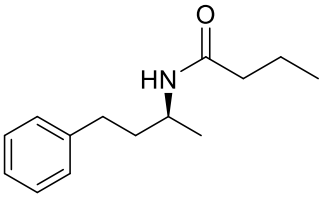


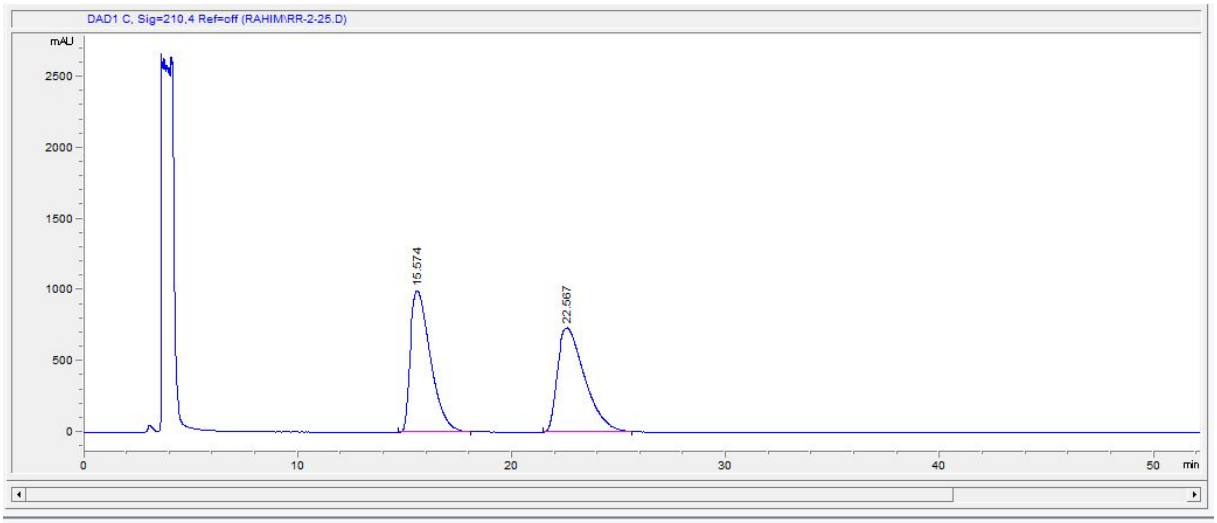
Peak List

m/z	z	Abund	Formula	Ion
206.1536	1	393800.66	C13H20NO	(M+H)+
207.1567	1	56523.54	C13H20NO	(M+H)+
208.1595	1	4853.72	C13H20NO	(M+H)+
210.1218	1	537.06	C13H17NNa	(M+Na)+[-H2O]
228.1348	1	70438.8	C13H19NNaO	(M+Na)+
229.138	1	10452.28	C13H19NNaO	(M+Na)+
230.1401	1	903.93	C13H19NNaO	(M+Na)+
244.1095	1	3997.9	C13H19KNO	(M+K)+
245.1137	1	696.93	C13H19KNO	(M+K)+
246.1085	1	292.46	C13H19KNO	(M+K)+


O
HN
f1 (ppm)

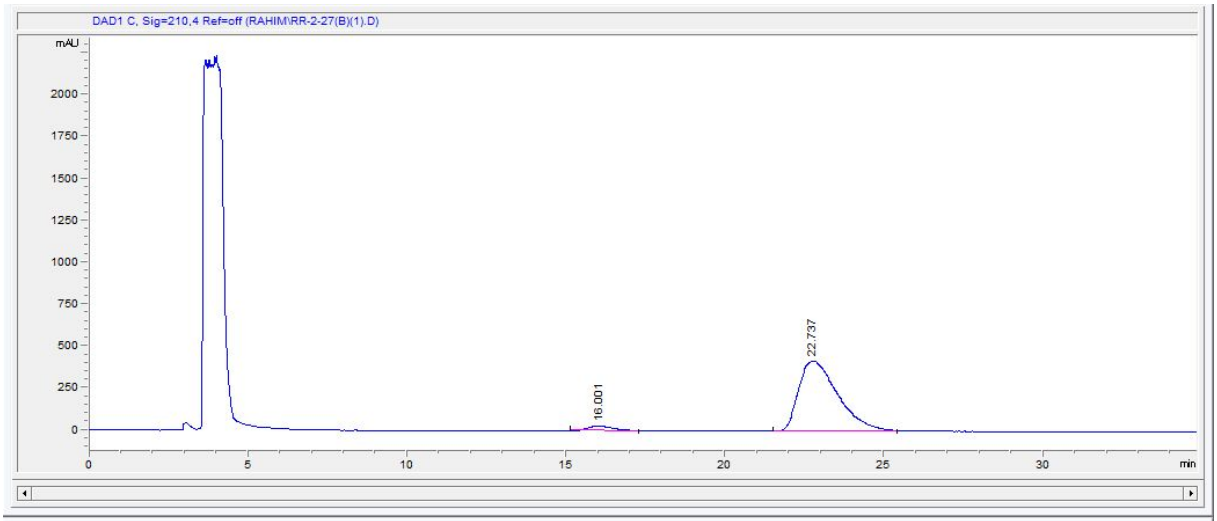

O
HN
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)
13.90
19.37
21.32
32.66
38.89
39.13
45.14
126.05
128.46
128.58
141.95
172.34





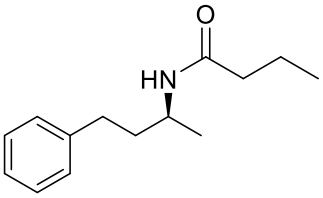
#	Time	Area	Height	Width	Area%	Symmetry
1	15.574	65178.2	993.9	0.7731	49.841	0.532
2	22.567	65593.1	736.7	1.0507	50.159	0.532

Figure S11. Racemic amide **3f**.



#	Time	Area	Height	Width	Area%	Symmetry
1	16.001	1653.2	28.6	0.6819	4.434	0.739
2	22.737	35628.3	419.1	0.9997	95.566	0.536

Figure S12. HPLC of amide (*S*)-**3f**.

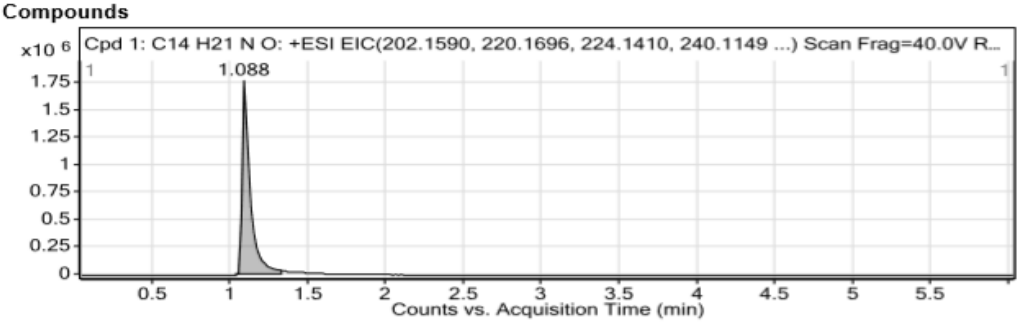


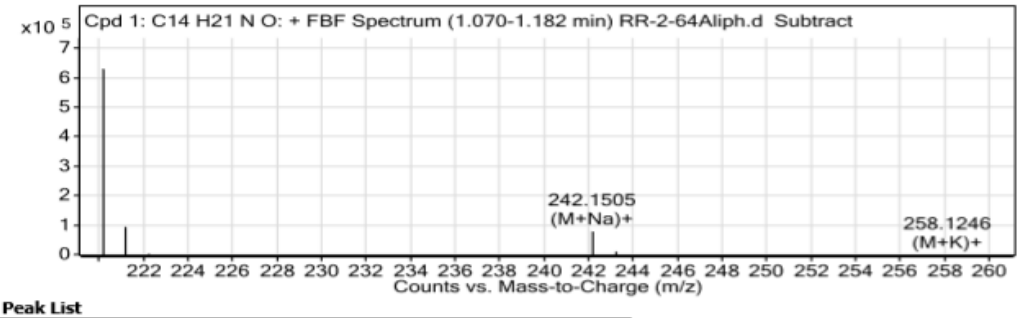
Qualitative Analysis Report

Data Filename	RR-2-64Aliph.d	**Sample Name**	RR-2-64Aliph
Sample Type	Sample	**Position**	Vial 1
Instrument Name	QTOF	**User Name**	QTOF-PC\admin
Acq Method	ACgroup_new.m	**Acquired Time**	2020-07-21 11:01:36
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.00 (B5042.2)

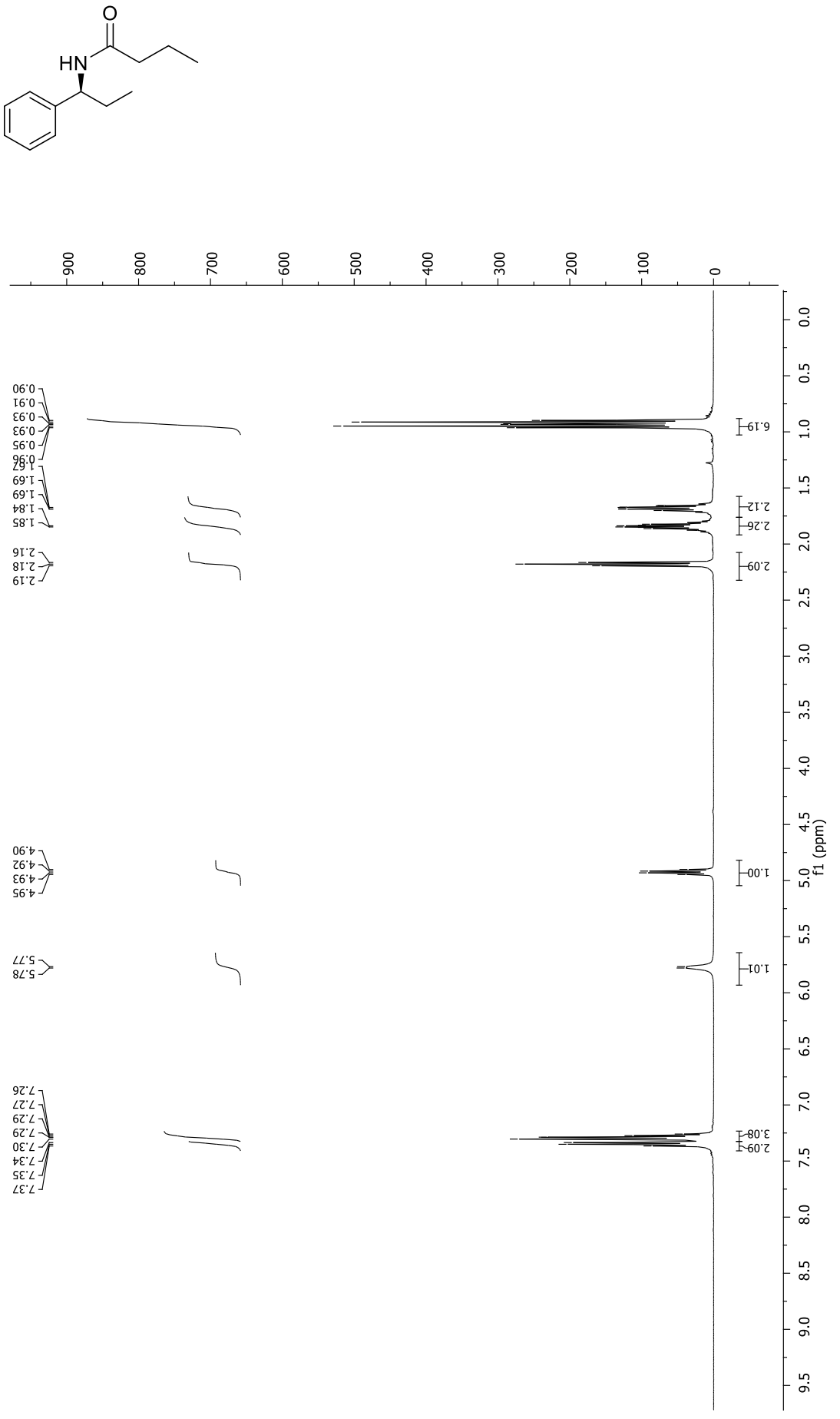
Compounds

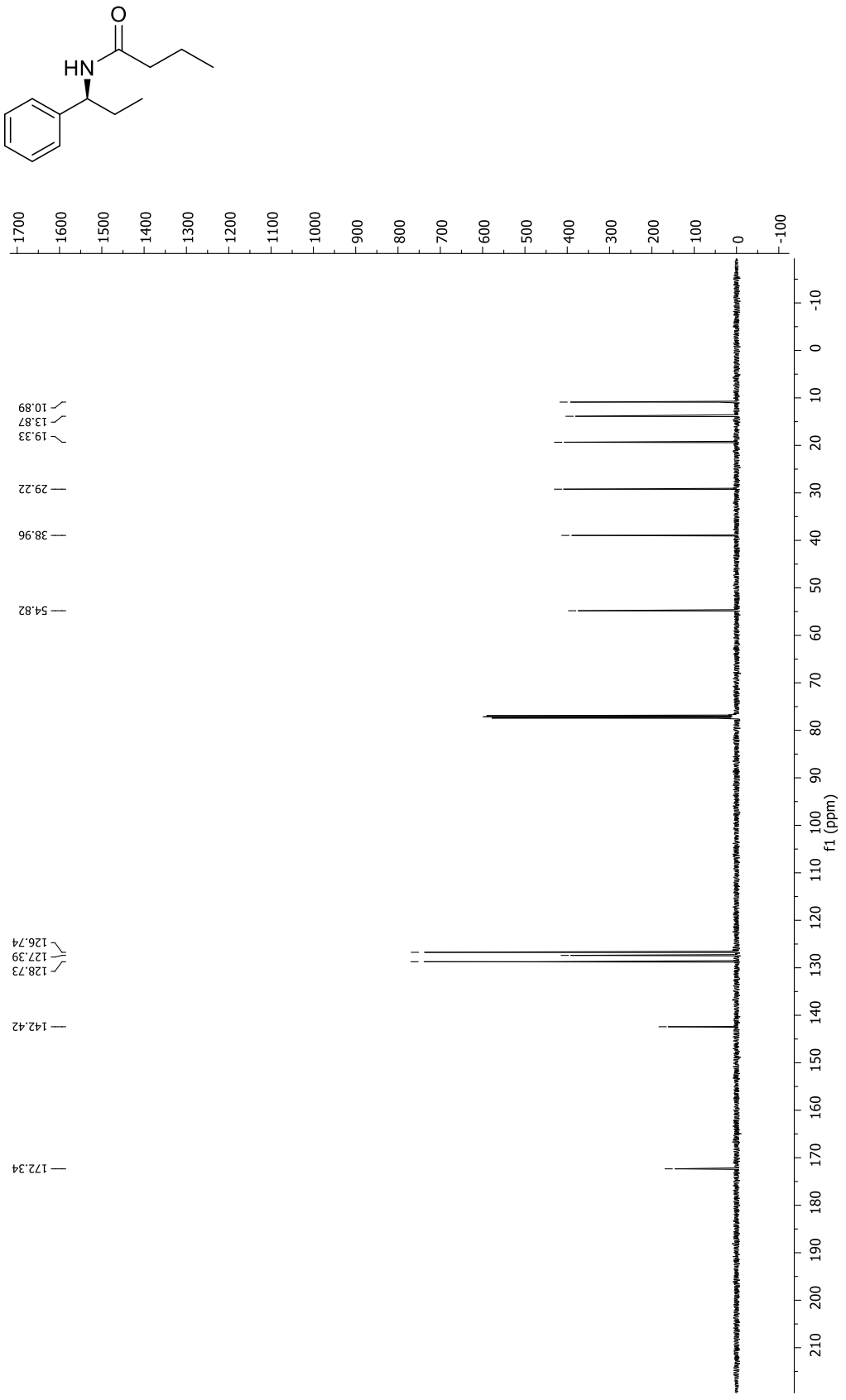


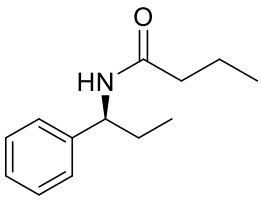


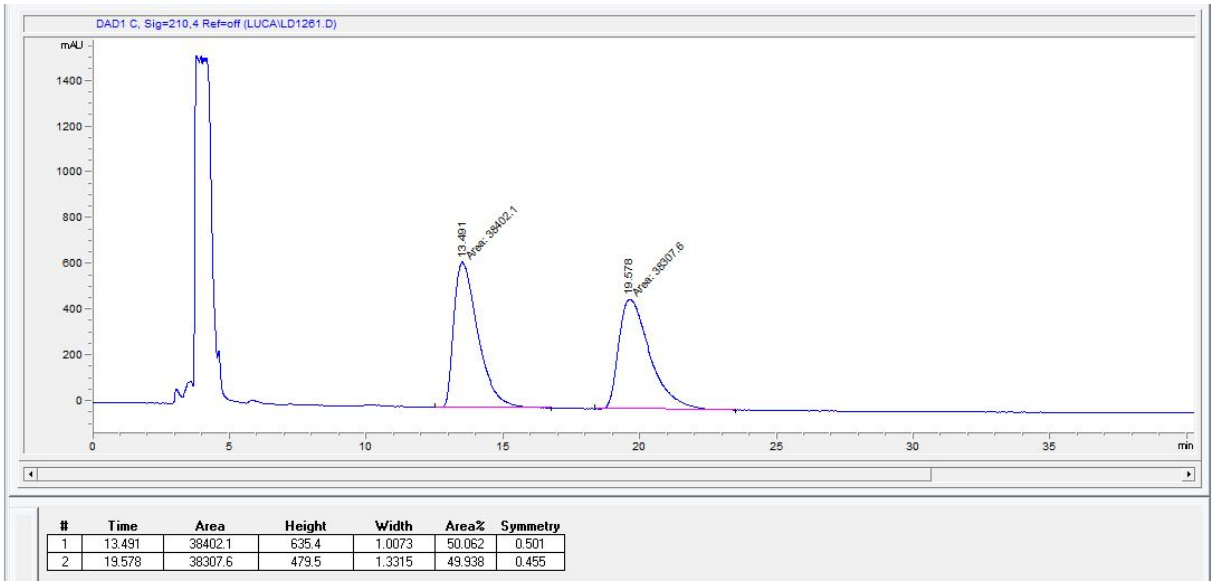
Peak List

m/z	z	Abund	Formula	Ion
220.1691	1	633188.69	C14H22NO	(M+H)+
221.1725	1	98736.27	C14H22NO	(M+H)+
222.1754	1	8725.76	C14H22NO	(M+H)+
223.1771	1	692.21	C14H22NO	(M+H)+
242.1505	1	83385.63	C14H21NNaO	(M+Na)+
243.1535	1	13361.52	C14H21NNaO	(M+Na)+
244.1565	1	1259.79	C14H21NNaO	(M+Na)+
258.1246	1	3294.03	C14H21KNO	(M+K)+
259.1305	1	679.18	C14H21KNO	(M+K)+
260.124	1	273.89	C14H21KNO	(M+K)+


O
HN
f1 (ppm)

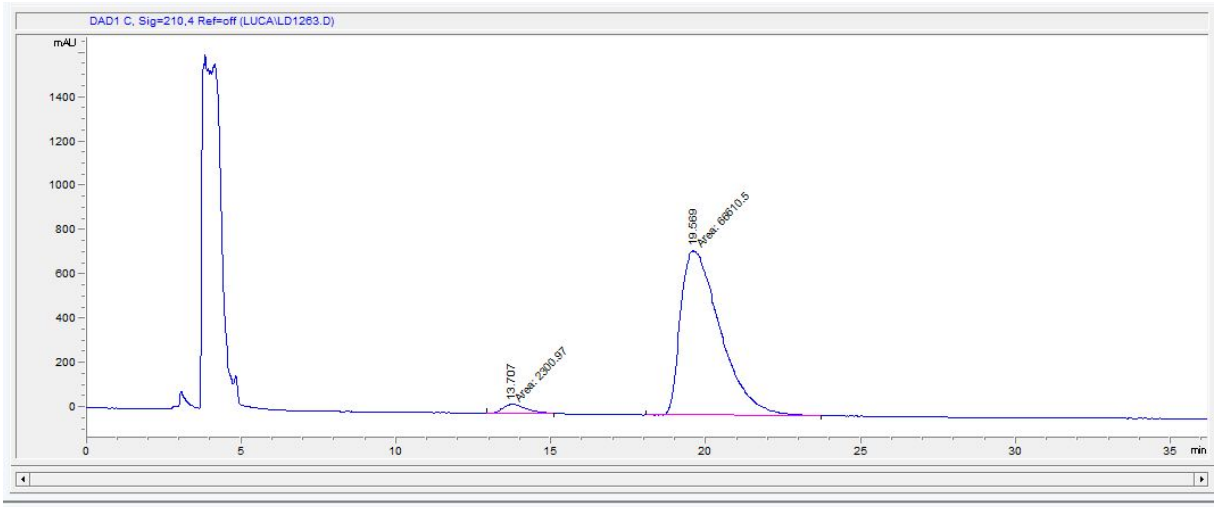

O
HN
10.89
13.87
19.33
29.22
38.96
54.82
126.74
127.39
128.73
142.42
172.34
f1 (ppm)





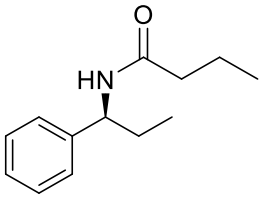
#	Time	Area	Height	Width	Area%	Symmetry
1	13.491	38402.1	635.4	1.0073	50.062	0.501
2	19.578	38307.6	479.5	1.3315	49.938	0.455

Figure S13. Racemic amide **3g**.



#	Time	Area	Height	Width	Area%	Symmetry
1	13.707	2301	42.2	0.9091	3.339	0.582
2	19.569	66610.5	744.6	1.4909	96.661	0.446

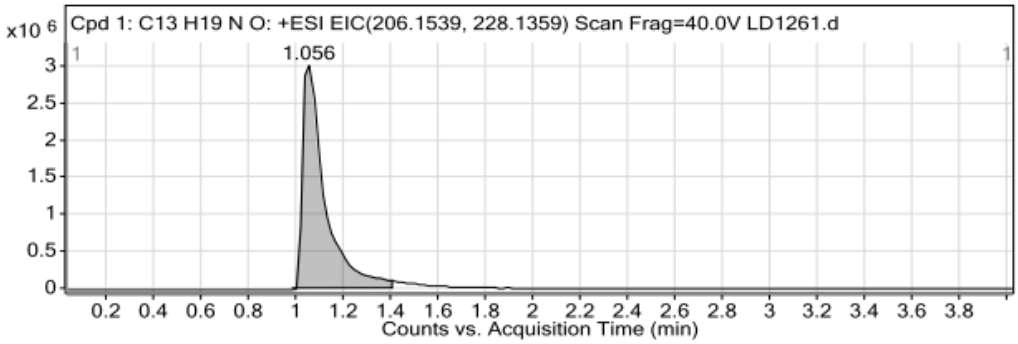
Figure S14. HPLC of amide (*S*)-**3g**.

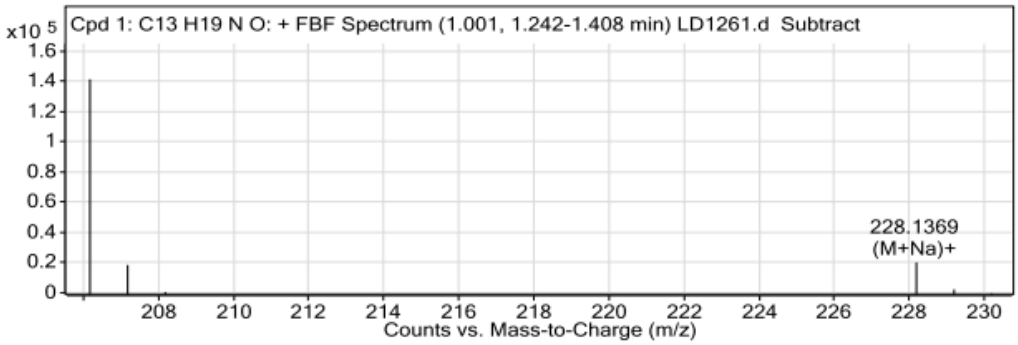


Qualitative Analysis Report

Data Filename	LD1261.d	**Sample Name**	Unavailable
Sample Type	Unavailable	**Position**	Unavailable
Instrument Name	Unavailable	**User Name**	Unavailable
Acq Method		**Acquired Time**	Unavailable
IRM Calibration Status	Success	**DA Method**	Default.m
Comment	Sample information is unavailable		

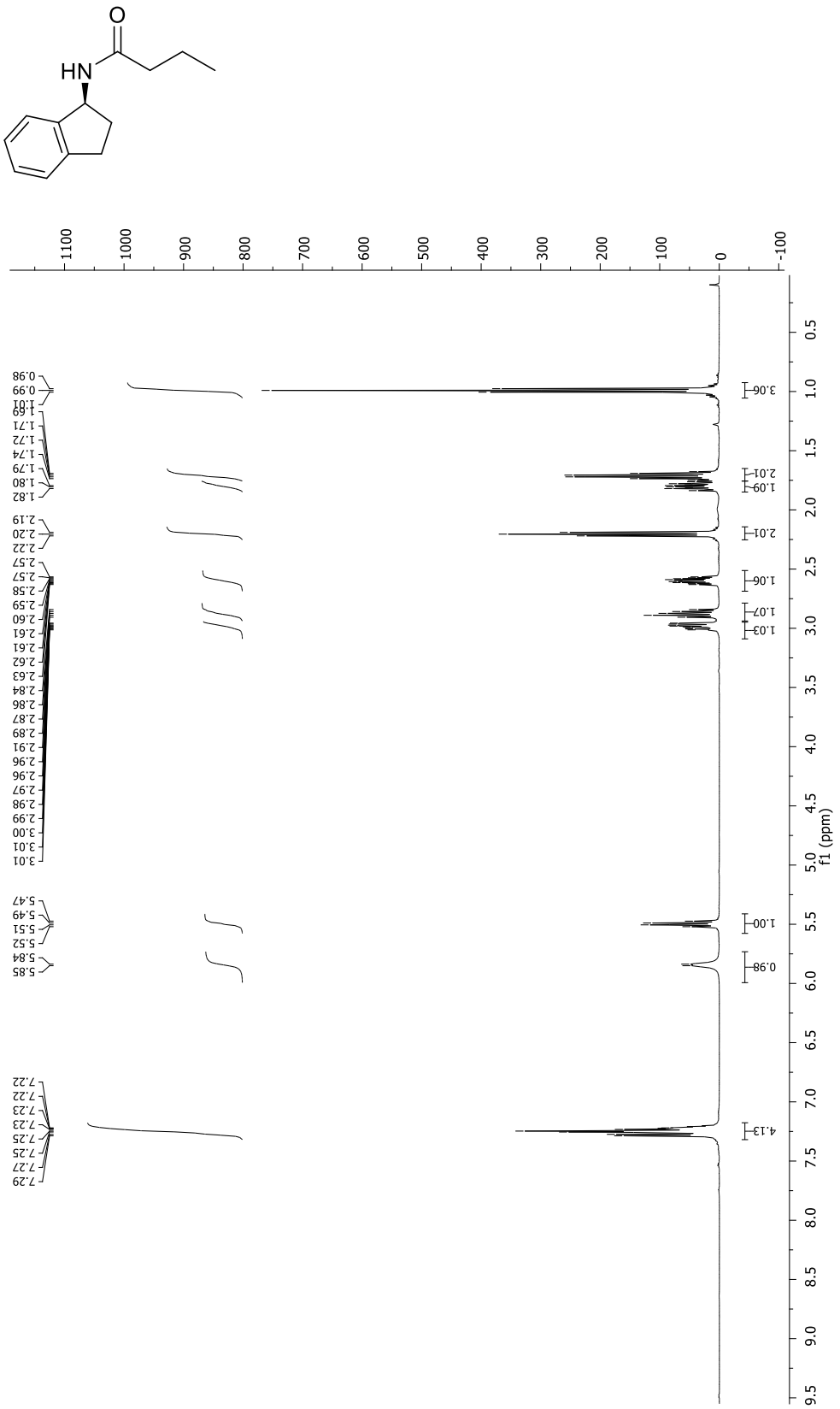
Compounds

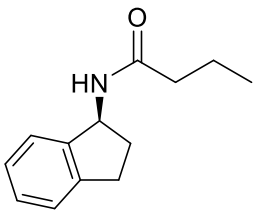


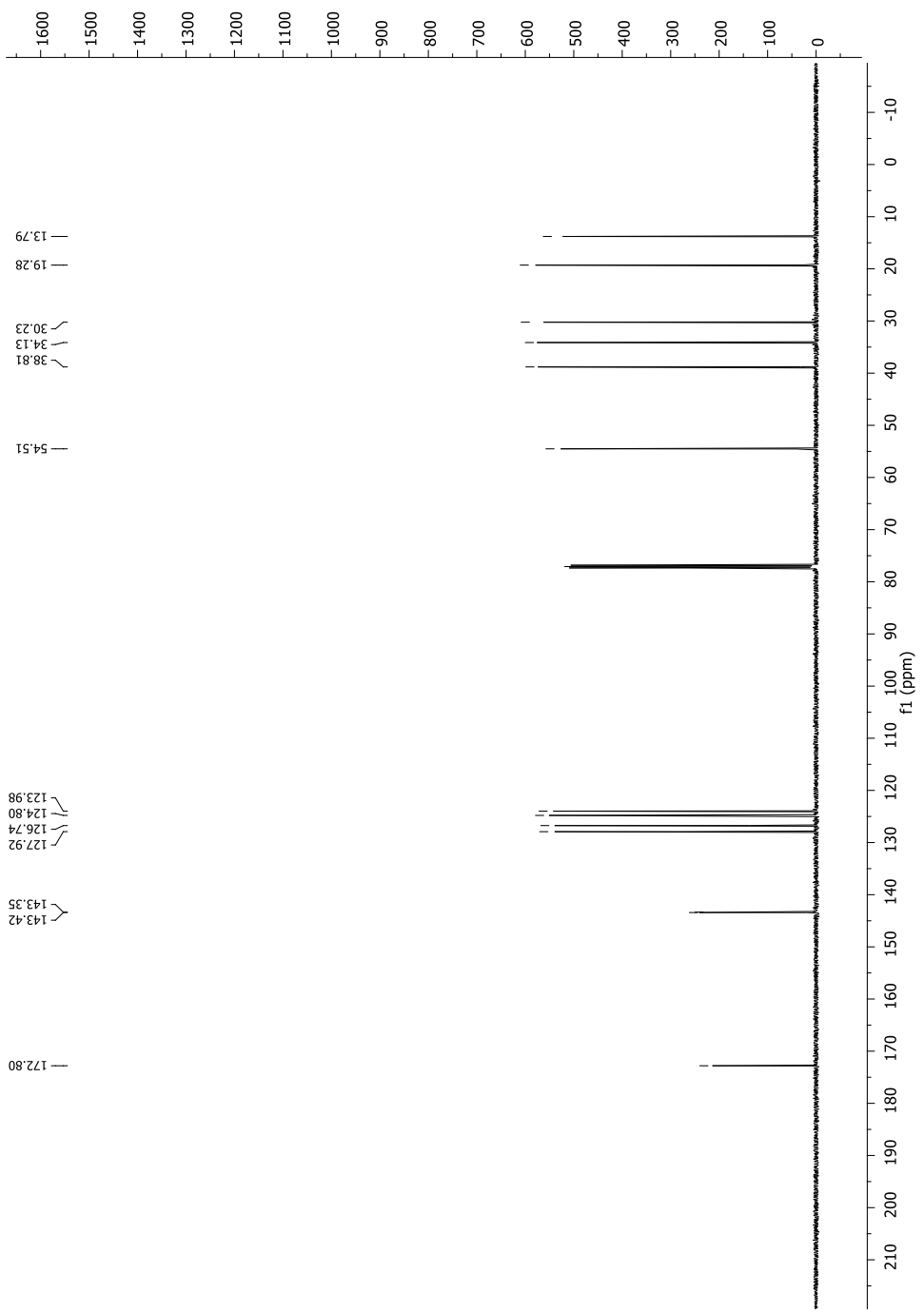


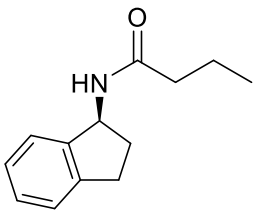
Peak List

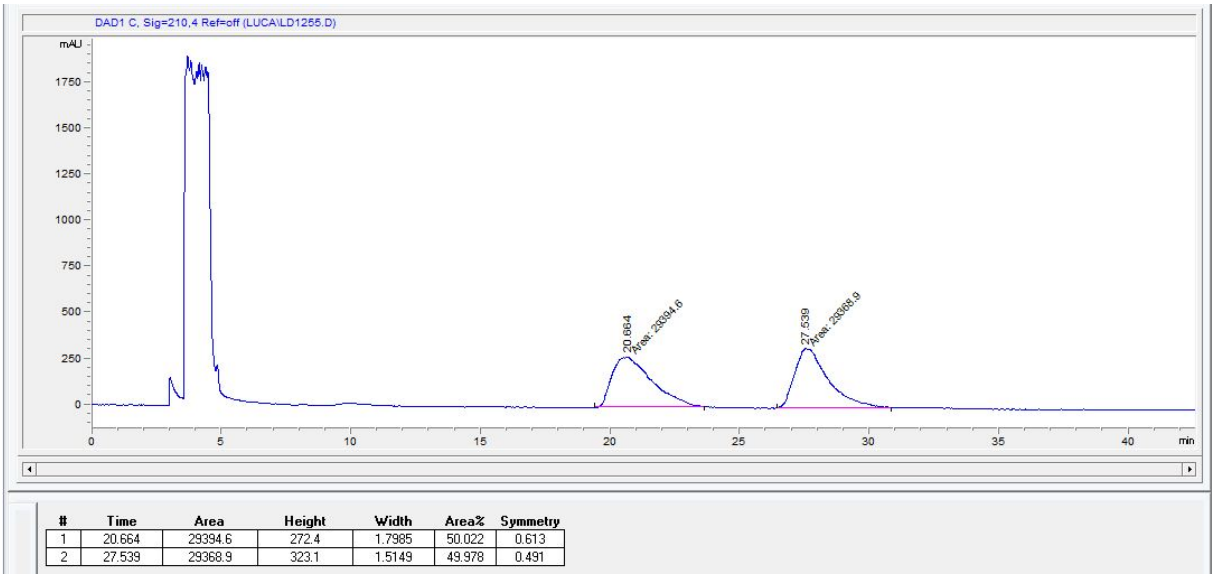
m/z	z	Abund	Formula	Ion
206.1549	1	142302.25	C13H20NO	(M+H)+
207.158	1	19824.5	C13H20NO	(M+H)+
208.1613	1	1641.99	C13H20NO	(M+H)+
228.1369	1	20929.16	C13H19NNaO	(M+Na)+
229.1409	1	3730.46	C13H19NNaO	(M+Na)+
230.1418	1	705.25	C13H19NNaO	(M+Na)+


O
HN
f1 (ppm)


O
HN

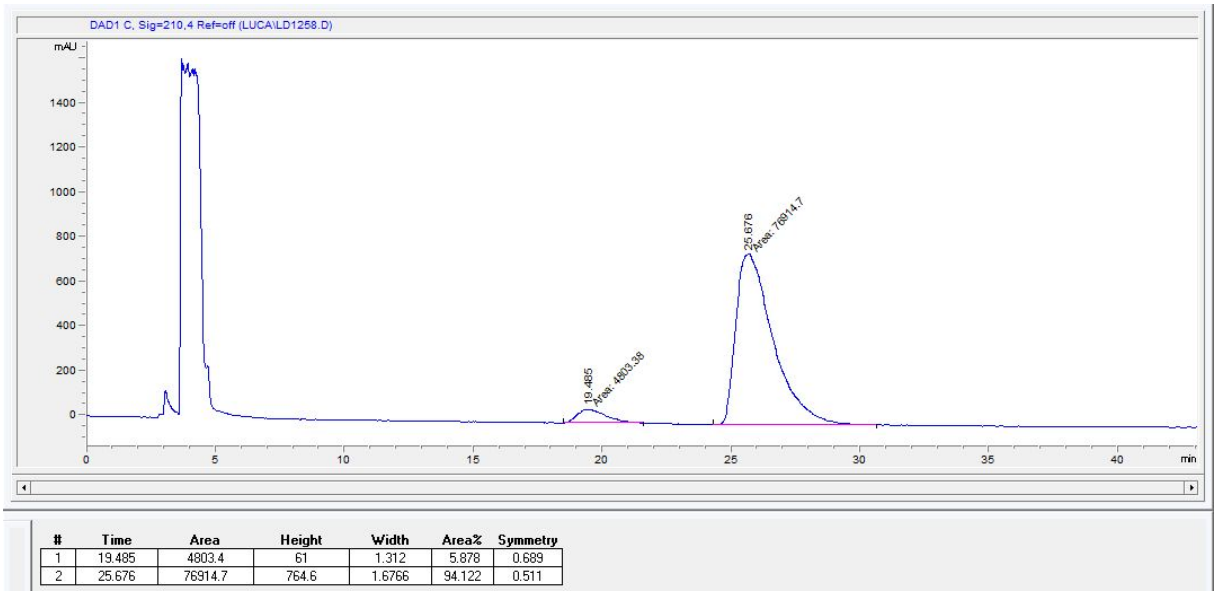

1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)
13.79
19.28
30.23
34.13
38.81
54.51
123.98
124.80
126.74
127.92
143.35
143.42
172.80





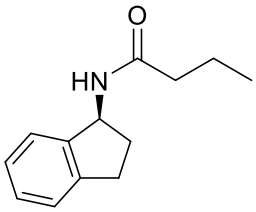
#	Time	Area	Height	Width	Area%	Symmetry
1	20.664	29394.6	272.4	1.7985	50.022	0.613
2	27.539	29368.9	323.1	1.5149	49.978	0.491

Figure S15. Racemic amide **3h**.



#	Time	Area	Height	Width	Area%	Symmetry
1	19.485	4803.4	61	1.312	5.878	0.689
2	25.676	76914.7	764.6	1.6766	94.122	0.511

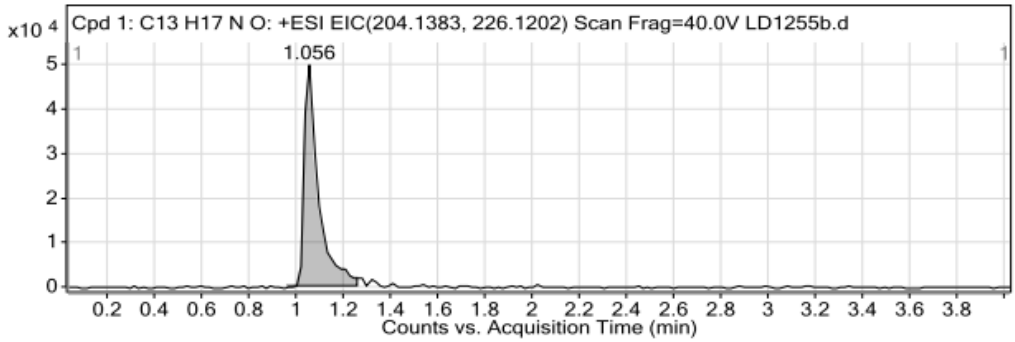
Figure S16. HPLC of amide (*S*)-**3h**.

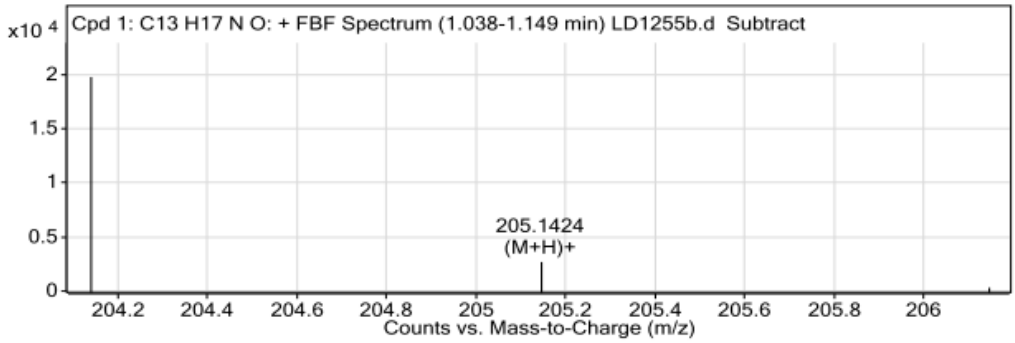


Qualitative Analysis Report

Data Filename	LD1255b.d	**Sample Name**	Unavailable
Sample Type	Unavailable	**Position**	Unavailable
Instrument Name	Unavailable	**User Name**	Unavailable
Acq Method		**Acquired Time**	Unavailable
IRM Calibration Status	Success	**DA Method**	Default.m
Comment	Sample information is unavailable		

Compounds





Peak List

m/z	z	Abund	Formula	Ion
204.1387	1	19804.53	C13H18NO	(M+H)+
205.1424	1	2873.13	C13H18NO	(M+H)+
206.1407	1	516.38	C13H18NO	(M+H)+