Enzymatic Resolution of Bicyclic 1-Heteroaryl Amines Using Candida Antarctica Lipase B

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Supporting Information

Table of Contents:

5,6,7,8-Tetrahydroquinoxalin-5-ylamine (**1e**). To a solution of 5,6,7,8-tetrahydroquinoxaline **5** (3.08 g, 23.0 mmol) in CCl_4 (200 mL) was added *N*-bromosuccinamide (4.09 g, 23.0 mmol) and a catalytic amount (56 mg) of benzoyl peroxide. The reaction mixture was heated at reflux for 17 hours. Saturated sodium bicarbonate solution was added (100 mL), the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 200 mL). The organic extracts were dried and concentrated. The crude material contained 1:3:1 ratio (GC) of starting material, mono- and dibromo products which were separated by column chromatography on silica gel using a mixture of 1:1 EtOAc:hexanes to give 5-bromo-5,6,7,8-tetrahydroquinoxaline (3.03 g, 54%) as a brown liquid: ^{1}H NMR δ 1.99-2.03 (m, 1H), 2.20-2.49 (m, 3H), 2.97-3.10 (m, 1H), 3.11-3.20 (m, 1H), 5.48 (t, 1H, *J* = 1.5 Hz), 8.40 (s, 2H). It should be noted that this material is unstable when exposed to air over 2-3 days and was used immediately in the next reaction.

5-bromo-5,6,7,8-tetrahydroquinoxaline (2.75 g, 12.9 mmol) and sodium azide (1.68 g, 25.8 mmol) were dissolved in DMF (50 mL) under nitrogen atmosphere and the reaction mixture was warmed to 60 °C for 2 days. The mixture was cooled to room temperature and poured over water (500 mL), and was extracted with CH_2Cl_2 (3 x 300 mL). The organic extracts were washed with brine (2 x 200 mL), dried and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel using 1:1 EtOAc/hexanes to afford 2.19 g (97%) of 5-azido-5,6,7,8-tetrahydroquinoxaline as a yellow liquid which displayed: ^{1}H NMR δ 1.80-1.96 (m, 1H), 2.00-2.10 (m, 3H), 2.75-3.06 (m, 2H), 4.74 (t, 1H, *J* = 6.5 Hz), 8.44 (d, 1H, *J* = 3 Hz), 8.45 (d, 1H, *J* = 3 Hz); ^{13}C NMR δ 18.6, 28.9, 31.7, 60.2, 142.6, 144.3, 150.3, 153.6. A Parr shaker flask was charged with 5-azido-5,6,7,8-tetrahydroquinoxaline (1.81 g, 10.33 mmol) and 10% palladium on carbon (10 wt% of Pd/C; 0.18 g). The reaction vessel was evacuated and filled with nitrogen. Methanol (30 mL) was added and the reaction was hydrogenated at 30 psi for 40 minutes. The reaction mixture was flushed with nitrogen and filtered through a plug of Celite® to provide 5,6,7,8-tetrahydroquinoxalin-5-ylamine (**1e**) as a orange liquid (1.54 g, 99%), which would rapidly turn dark brown. It was stored under an argon atmosphere at –20 °C. ^{1}H NMR δ 1.62-1.79 (m, 1H), 1.80-2.18 (m, 4H), 2.18-

2.30 (m, 1H), 2.91-3.01 (m, 2H), 4.07 (dd, 1H, *J* = 8.4, 5.4 Hz), 8.32-8.38 (m, 2H); ^{13}C NMR δ 19.7, 31.7, 32.2, 51.5, 142.0, 142.5, 152.6, 155.4; MS *m/z*: 150 ($M+H^+$), 133.

3,4-Dihydro-2*H*-pyrano[3,2-b]pyridin-4-ylamine (**1f**). To a solution of 2,3,-dihydropyrano[3,2-b]pyridin-4-one[1] (841 mg, 5.64 mmol) in MeOH (15 mL) was added hydroxylamine hydrochloride (470 mg, 6.77 mmol) and the reaction mixture was stirred at room temperature overnight. Aqueous saturated $NaHCO_3$ solution was added until the pH of the mixture was ~7 and it was extracted with CH_2Cl_2 (5 x 50 mL). The organic extracts were washed with brine (2 x 200 mL), were dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 924 mg of the oxime. To a cool (0 °C) suspension of the oxime in a mixture of ethanol (5 mL), ammonium hydroxide solution (26 mL) and ammonium acetate (488 mg, 6.32 mmol) was added zinc powder portion-wise. The reaction mixture was warmed to room temperature and stirred for 17 hours. The mixture was filtered through a plug of glass wool and washed with H_2O (30 mL), extracted with CH_2Cl_2 (3 x 50 mL), washed with brine, dried ($MgSO_4$), filtered and concentrated to yield 3,4-dihydro-2*H*-pyrano[3,2-b]pyridin-4-ylamine (**1f**) as a pink liquid (743 mg, 86%) which displayed: ^{1}H NMR δ 1.84 (br s, 2H), 1.90-2.01 (m, 1H), 2.24-2.34 (m, 1H), 4.12 (dd, 1H, *J* = 5.7, 6.9 Hz), 4.18-4.26 (m, 1H), 4.28-4.36 (m, 1H), 7.06-7.13 (m, 2H), 8.15 (dd, 1H, *J* = 1.8, 3.6 Hz); ^{13}C NMR δ 31.5, 47.8, 64.2, 123.8, 124.5, 142.1, 147.0, 151.1; MS *m/z*: 151.0 ($M+H^+$), 134.0 ($M-NH_2$); Anal. Calc. for $C_8H_{10}N_2O \cdot 0.1H_2O$: C, 63.22; H, 6.76; N, 18.43. Found: C, 62.99; H, 6.81; N, 18.22.

4,5,6,7-tetrahydrobenzofuran-7-ylamine (**1k**). To a 0 °C solution of 4,5,6,7-tetrahydrobenzofuran-7-ol[2] (1.20 g, 8.69 mmol) in toluene (50 mL) was added DBU (3.89 mL, 26.1 mmol) and diphenyl phosphorazidate (5.60 mL, 26.1 mmol).[3] The reaction mixture was warmed to room temperature and was stirred for 1 hour. The resulting two-phase mixture was washed with $NaHCO_3$ (50 mL) and was extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel

[1] Bridger, G.; Skerlj, R.; Kaller, A.; Harwig, C.; Bogucki, D.; Wilson, T. R.; Crawford, J.; McEachern, E. J., Astma, B.; Nan, S.; Zhou, Y.; Schols, D.; Smith, C. D.; DiFluri, R. PCT Int.Appl. **2002**, WO 0222600.
[2] Seki, M.; Sakamoto, T.; Suemune, H.; Kanematsu, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1707-1714.
[3] Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886-5888.

using a 1:4 EtOAc/hexanes mixture and upon removal of traces of solvent on high vacuum 7-azido-4,5,6,7-tetrahydrobenzofuran was obtained as a clear liquid (0.89 g, 63%). This compound was found to be volatile when subjected to reduced pressure. ^{1}H NMR δ 1.71-1.91 (m, 2H), 1.92-2.08 (m, 2H), 2.31-2.46 (m, 1H), 2.55 (dt, 1H, *J* = 16.2, 5.0 Hz), 4.59 (t, 1H, *J* = 4.5 Hz), 6.24 (d, 1H, *J* = 1.8 Hz), 7.35 (d, 1H, *J* = 1.8 Hz); ^{13}C NMR δ 19.9, 22.3, 30.4, 54.3, 110.7, 121.8, 143.1, 147.8; MS *m/z*: 121 (M-N_3). To a flask charged with 7-azido-4,5,6,7-tetrahydrobenzofuran (405 mg, 2.48 mmol) and Pd/C (10 wt% Pd/C; 44 mg) was added MeOH. The reaction mixture was flushed with hydrogen and was hydrogenated for 1 hour at room temperature. The mixture was purged with nitrogen gas and was filtered through a plug of Celite®, concentrated in vacuo and purified by chromatography on silica gel to yield 4,5,6,7-tetrahydrobenzofuran-7-ylamine (**1k**) (205 mg, 60%) as a clear liquid which was volatile when subjected to high vacuum. ^{1}H NMR δ 1.50-1.75 (m, 4H), 1.76-1.90 (m, 1H), 2.01-2.20 (m, 1H), 2.30-2.50 (m, 2H), 3.94 (t, 1H, *J* = 5.7 Hz), 6.17 (d, 1H, *J* = 1.5 Hz), 7.26 (d, 1H, *J* = 1.5 Hz); ^{13}C NMR δ 21.1, 22.6, 34.0, 45.5, 110.5, 117.9, 141.3, 153.6; MS *m/z*: 160 (M+Na^{+}).

Preparation of 9. (*S*)-8-amino-5,6,7,8-tetrahydroquinoline ((*S*)-**1b**) (66 mg, 0.44 mmol) dissolved in acetonitrile (2 mL) was added via syringe to a purple solution of chlorooxo[[2,2'-(thio-•S)bis[ethanethiolato-•S]](2-)]-rhenium (117 mg, 0.30 mmol) in acetonitrile (20 mL) at room temperature under argon. Upon addition of the amine the reaction mixture immediately turned dark green. The mixture was stirred at room temperature for 1 hour to yield a green precipitate, which was isolated via suction filtration, washed with acetonitrile (2 x 5 mL) and dried *in vacuo* (84 mg, 55 %). X-ray quality crystals were grown under argon using a two-chamber slow diffusion apparatus. Slow diffusion of diethyl ether into a chloroform solution of **9** yielded green/brown crystals. Of note, **9** appears to be relatively stable in the solid state; however, if it is dissolved in the presence of air it will rapidly decompose. ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 1.90-2.30 (m, 6H), 2.42 (m, 1H), 2.65 (m, 1H), 2.88 (m, 2H), 2.99 (m, 1H), 3.72 (br t, 2H), 3.84 (dm, 1H), 4.68 (m, 1H), 7.32 (dd, 1H, *J* = 5.7, 2.6 Hz), 7.67 (d, 1H, *J* = 8.1 Hz), 8.94 (d, 1H, *J* = 6.0 Hz), 9.15 (br s, 1H); MS *m/z*: 503 $(M+H)^{+}$. IR (KBr) ν (cm^{-1})

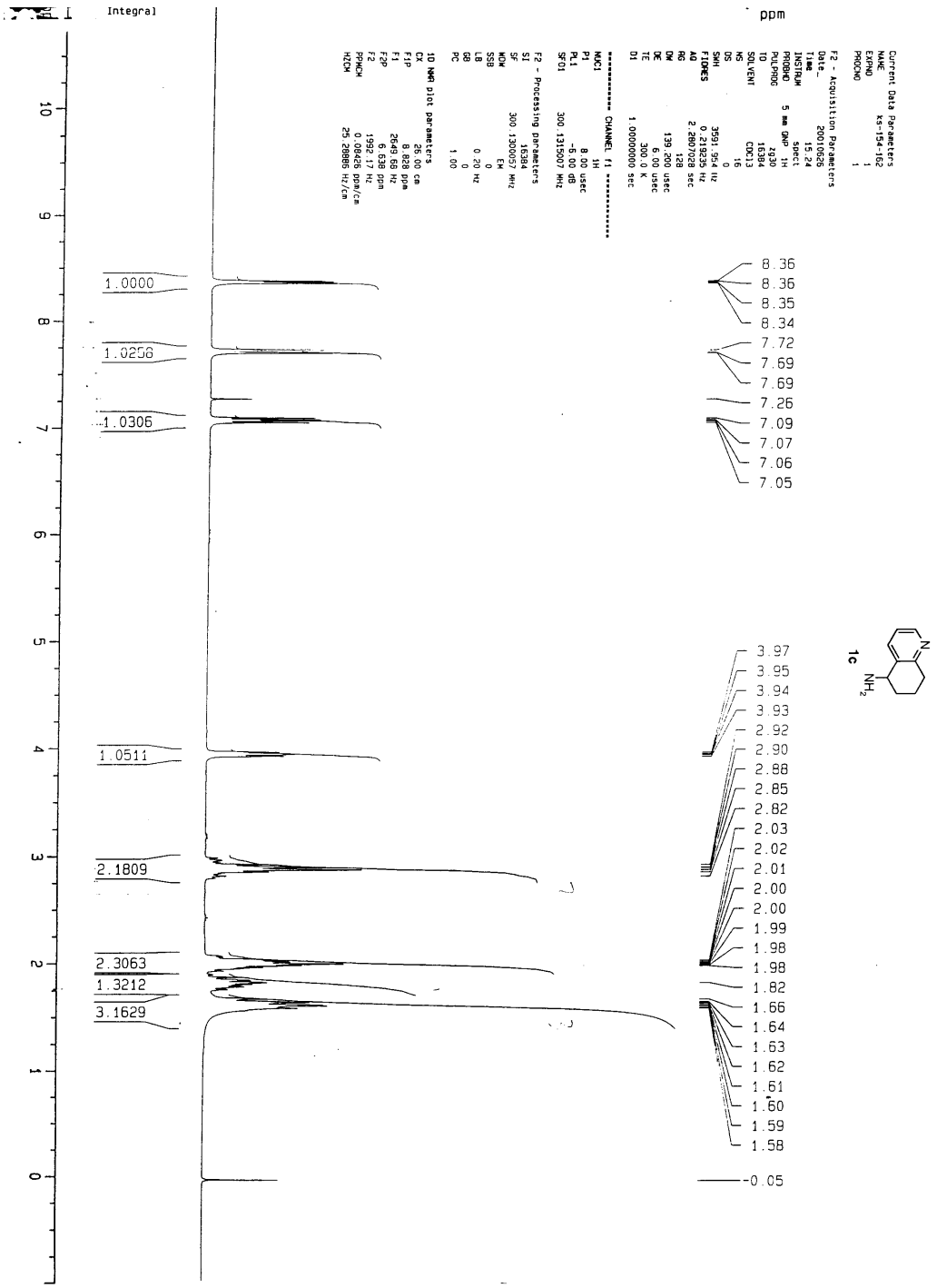
886 (Re=O). Anal. Calcd. for $C_{13}H_{19}N_2OS_3Re \cdot 0.1C_2H_3N \cdot 0.5H_2O$: C, 30.80, H, 3.97; N, 5.71; S, 18.68. Found: C, 30.67; H, 3.84; N, 5.96; S, 18.75.

Thermal Racemization of (*R*)-2d and (*R*)-2a

(*R*)-5,6,7,8-*N*-(Tetrahydroisoquinolin-5-yl)acetamide ((*R*)-**2d**) (60 mg ; 94% ee determined by chiral GC) was placed in a sealed pressure tube flushed with argon. The reaction tube was placed in a hot (150 ºC) oil bath until the starting material melted and heating was continued for 2 hours. The material at this point (60 mg recovery, quant. yield) had an enantiomeric excess of 0% and its ^{1}H NMR was unchanged in comparison with the starting material.

Racemization of (*R*)-1-pyridin-2-ylethylamine ((*R*)-**2a**) (242 mg, 79%ee) provided after 5 days of heating at 150 ºC, **2a** (242 mg) in 9%ee.

Figure 1.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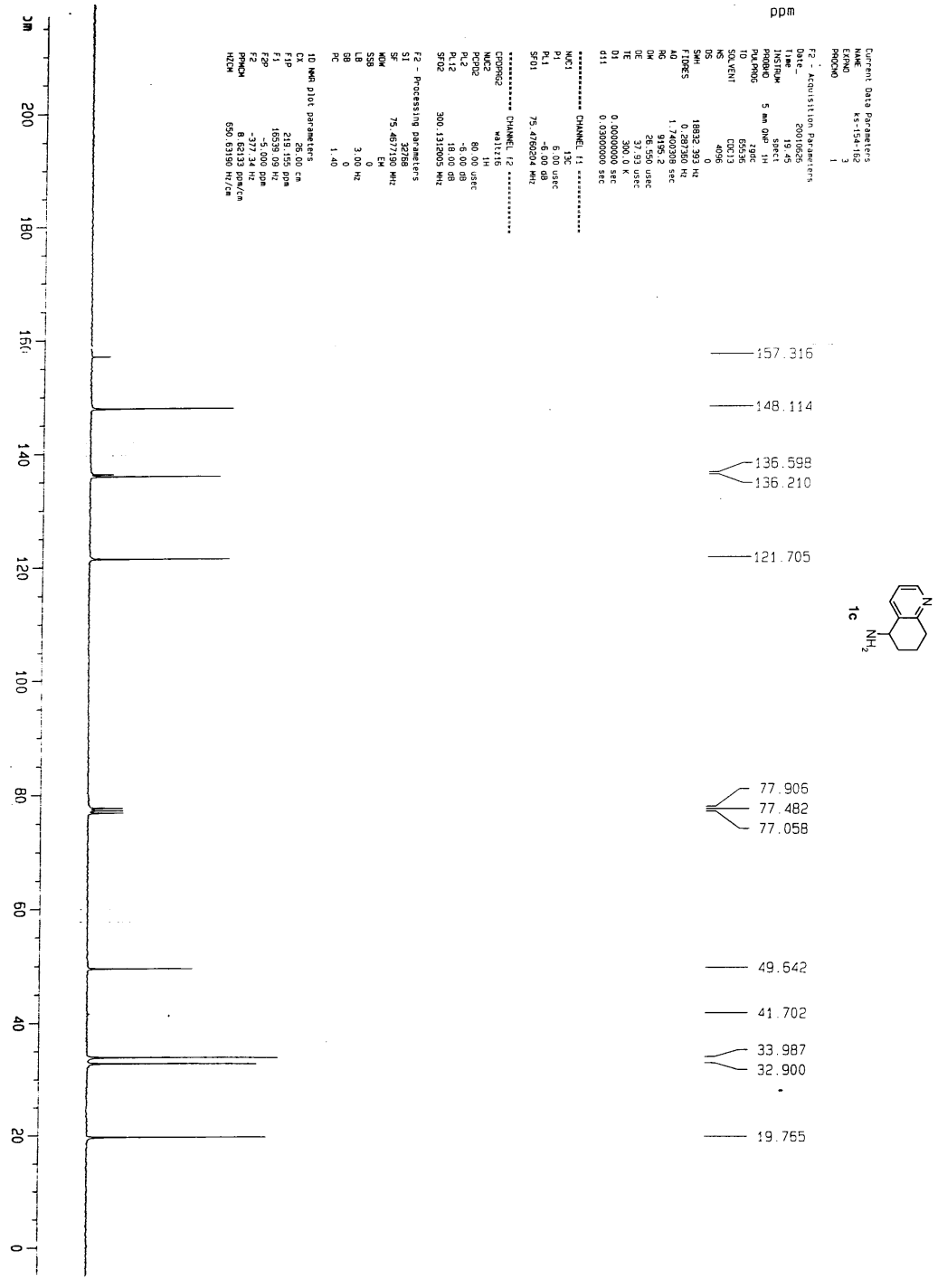
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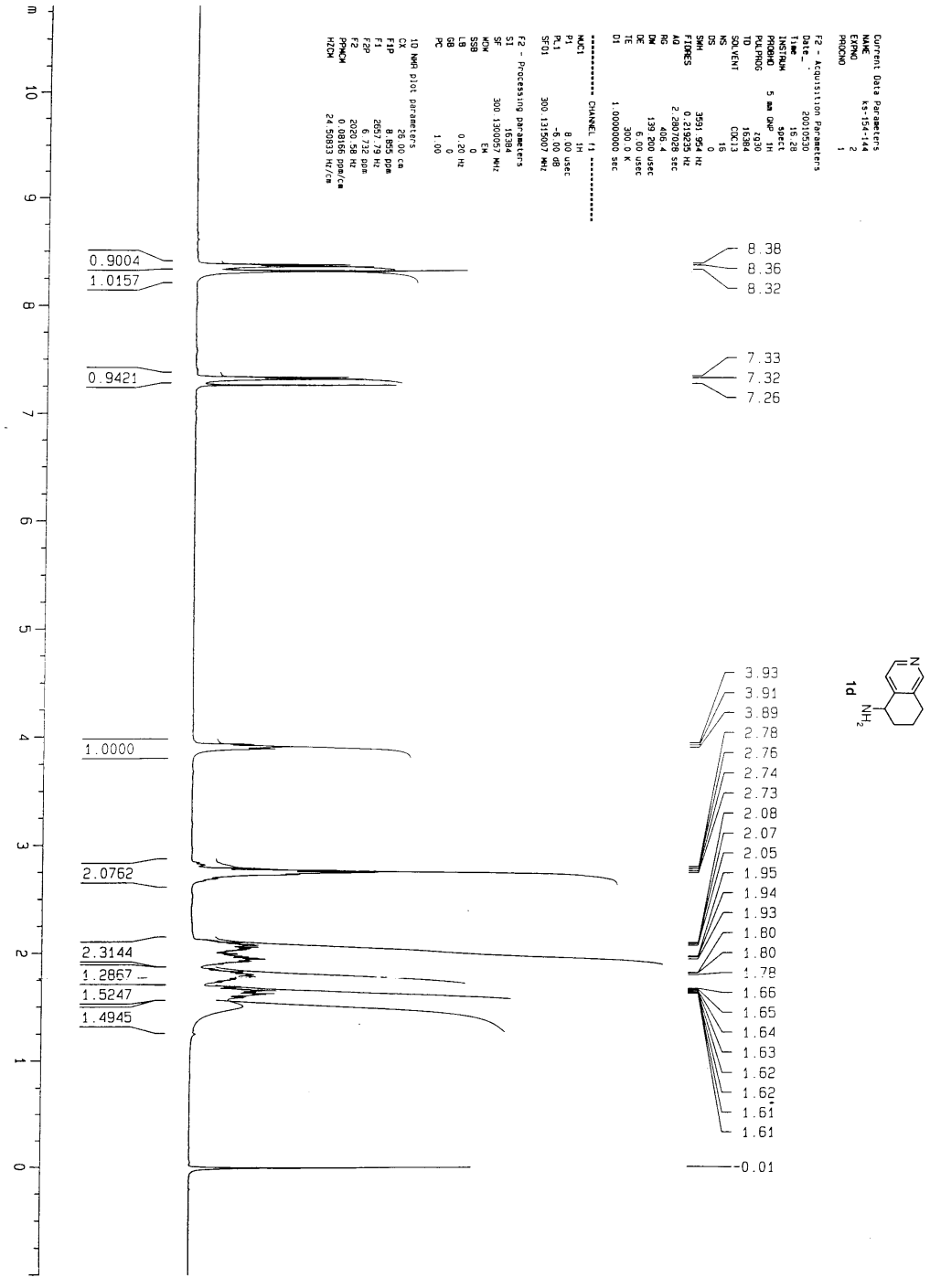
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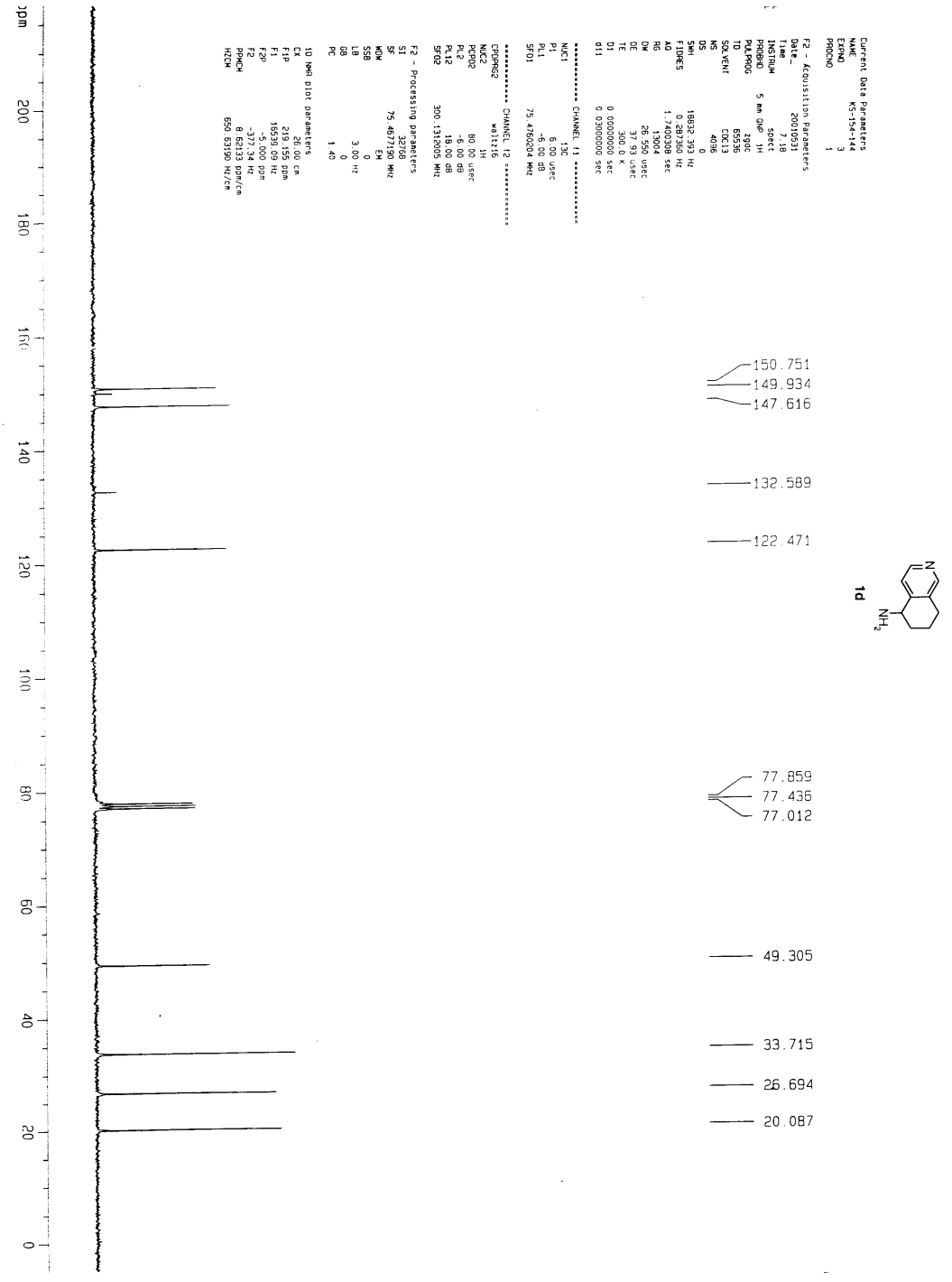
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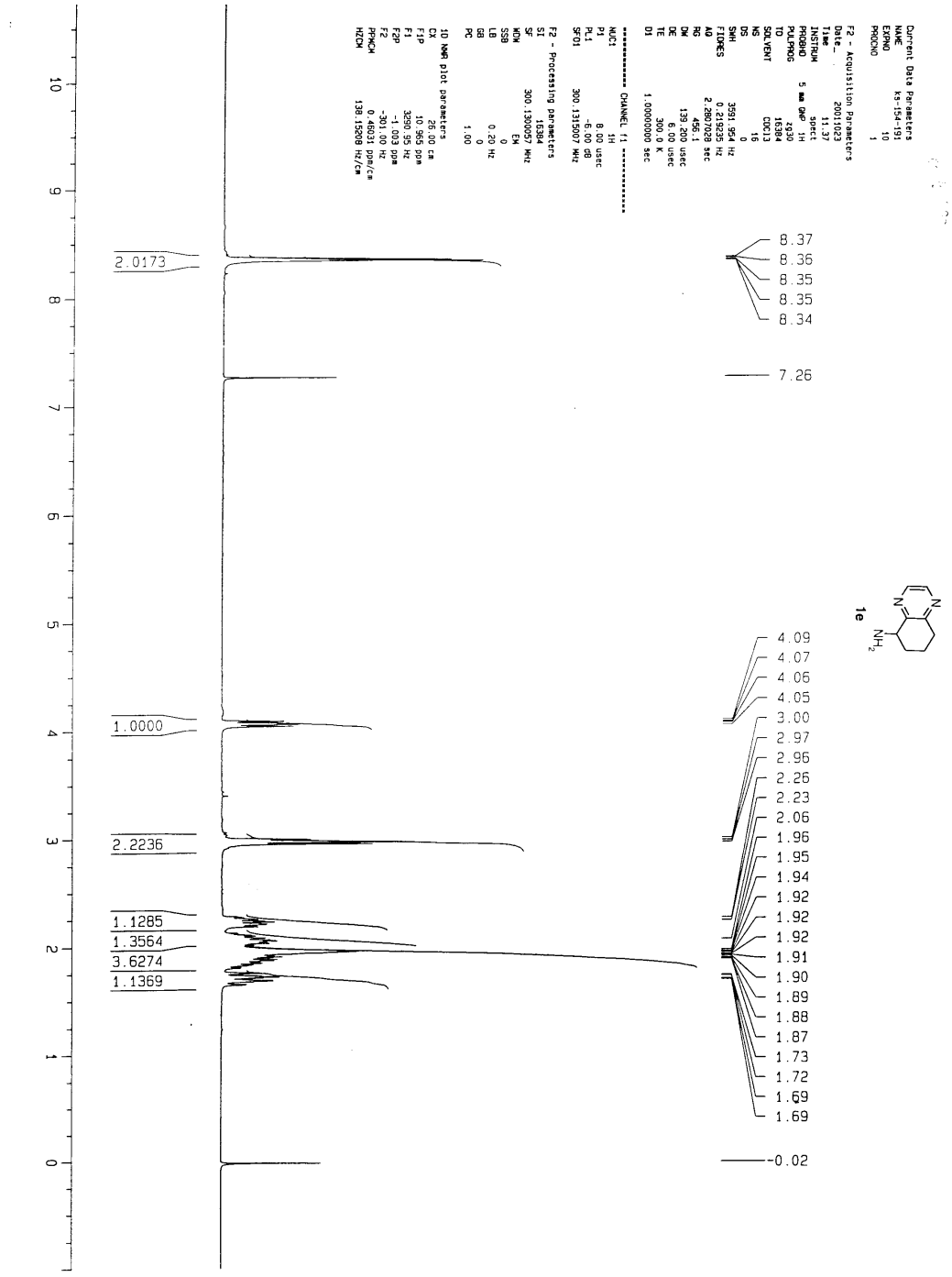
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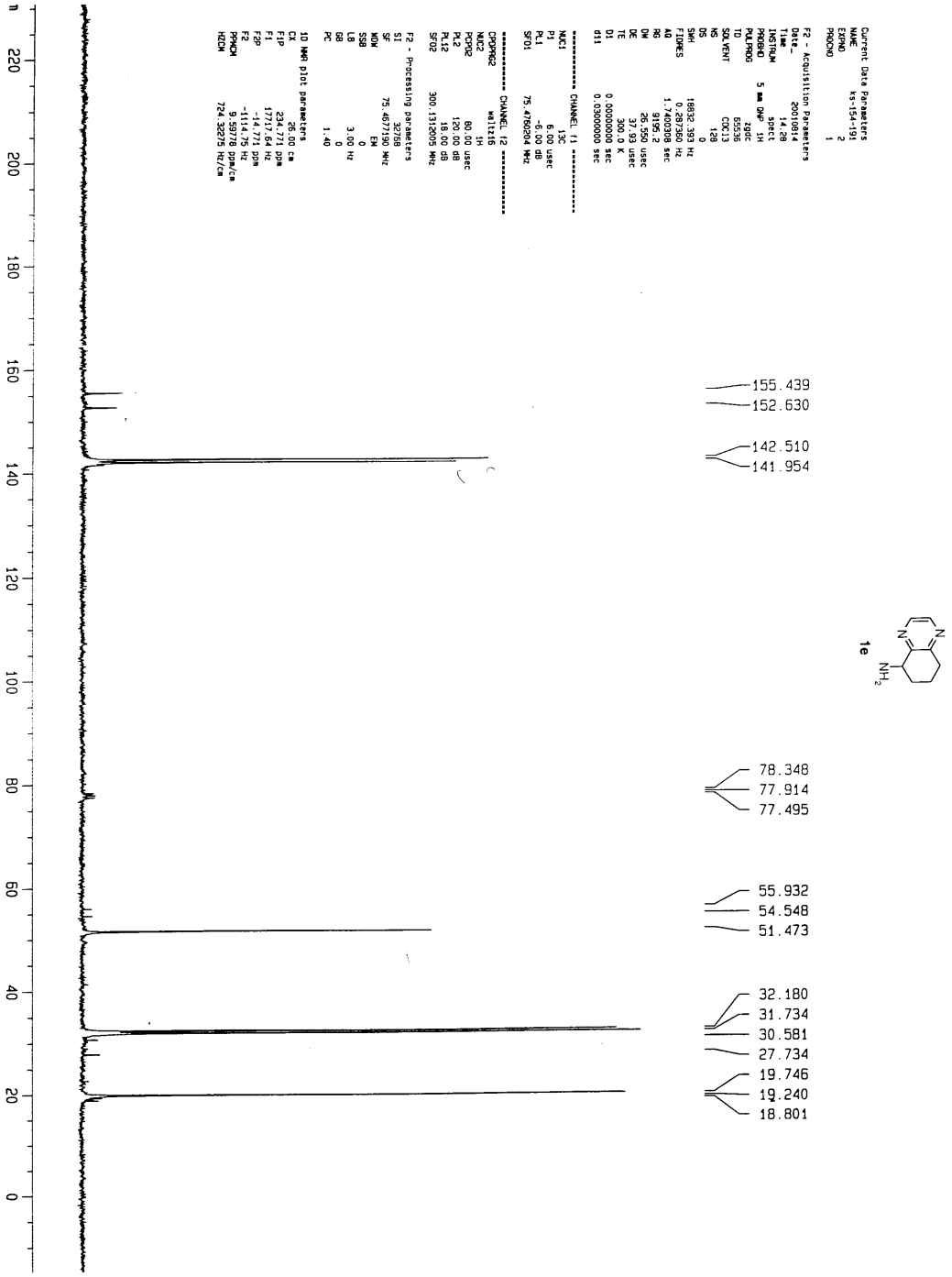
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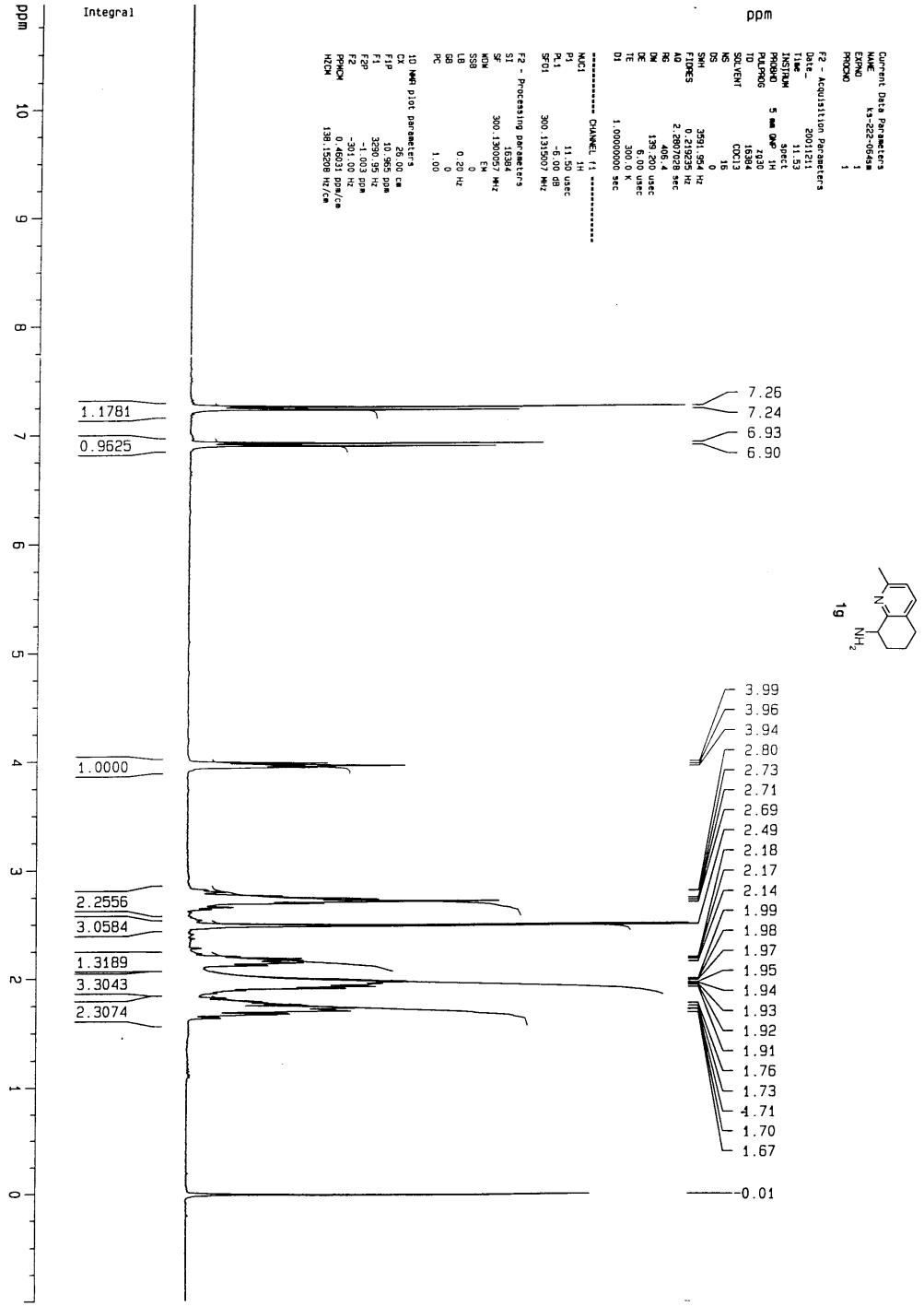
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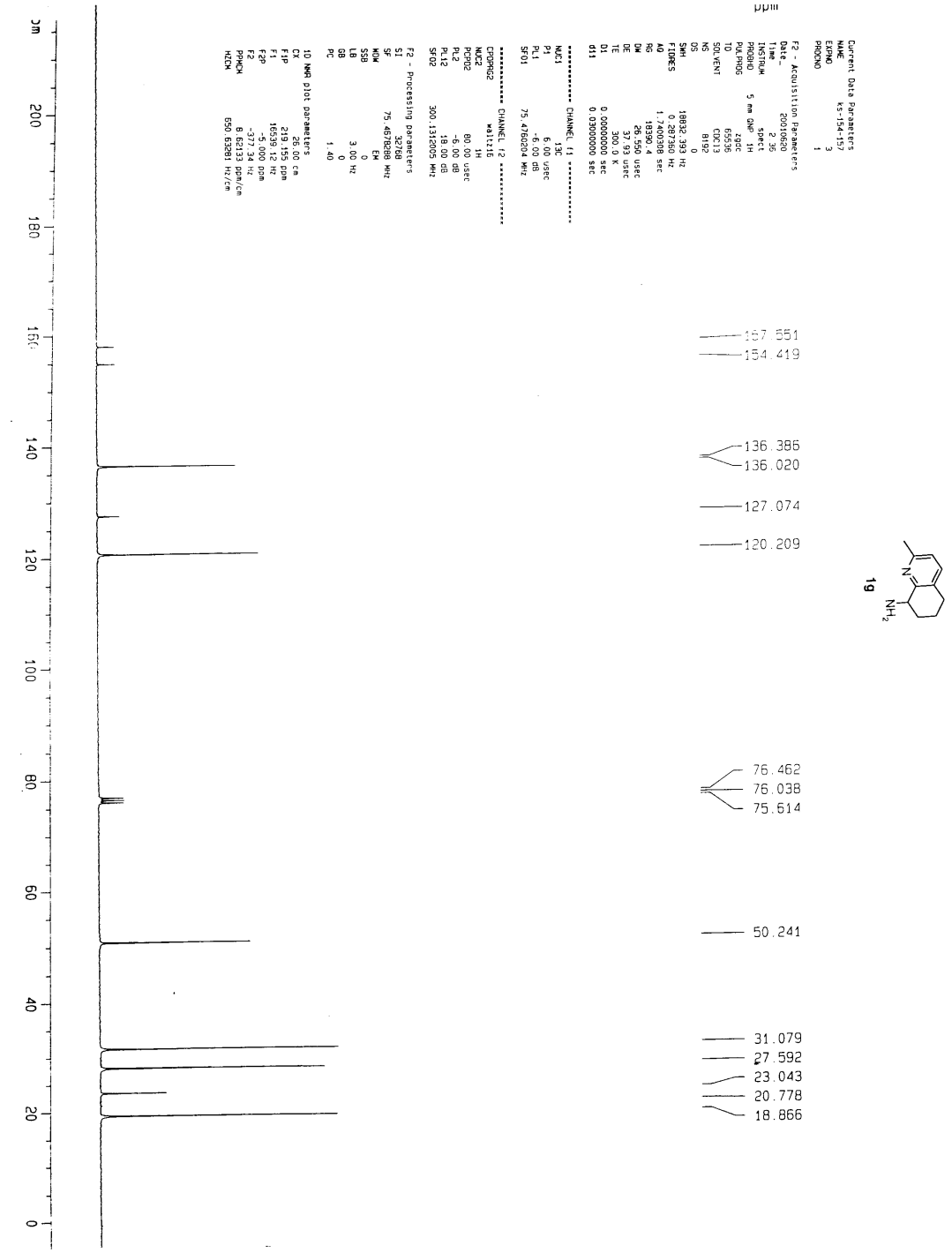
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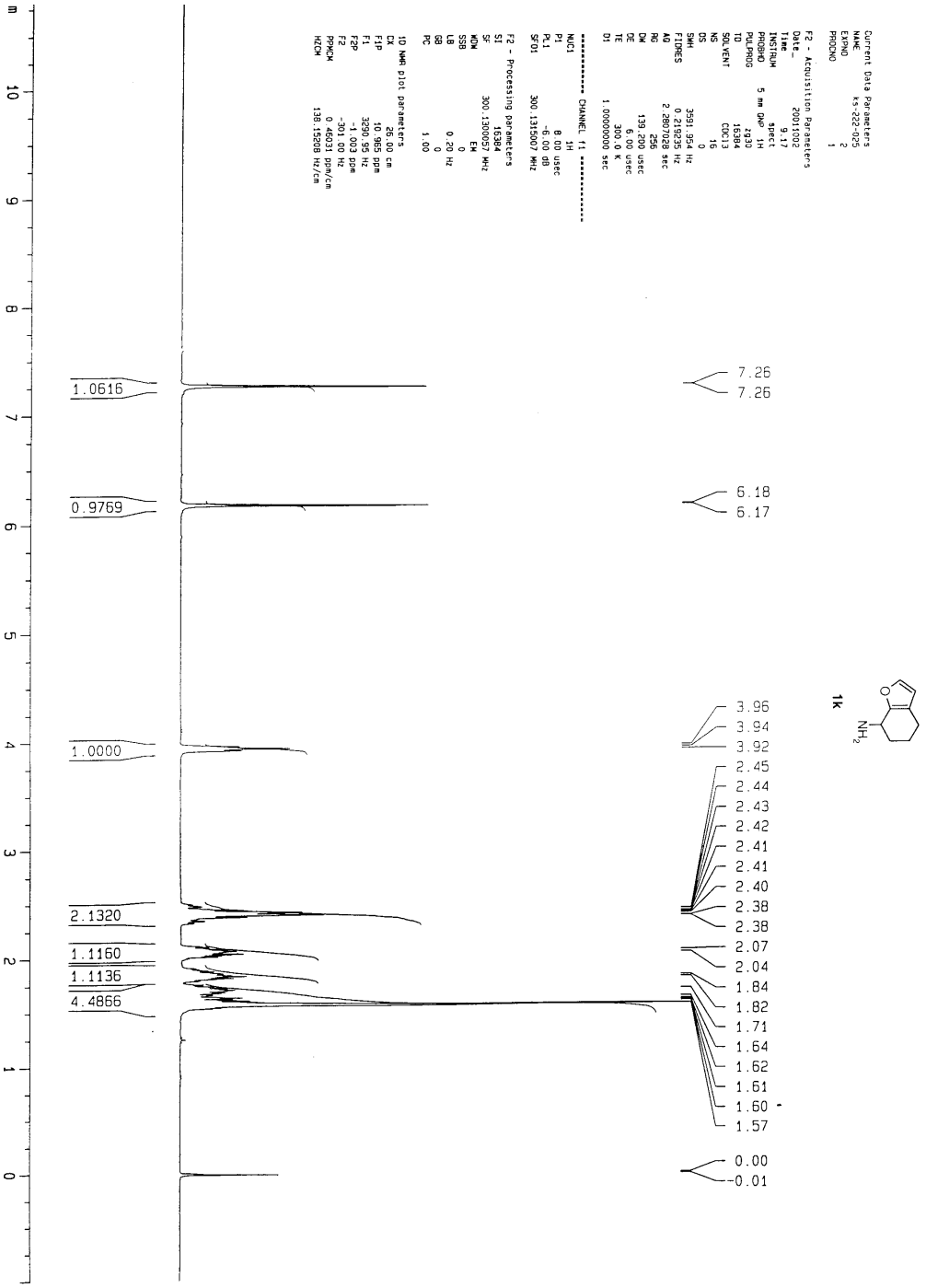
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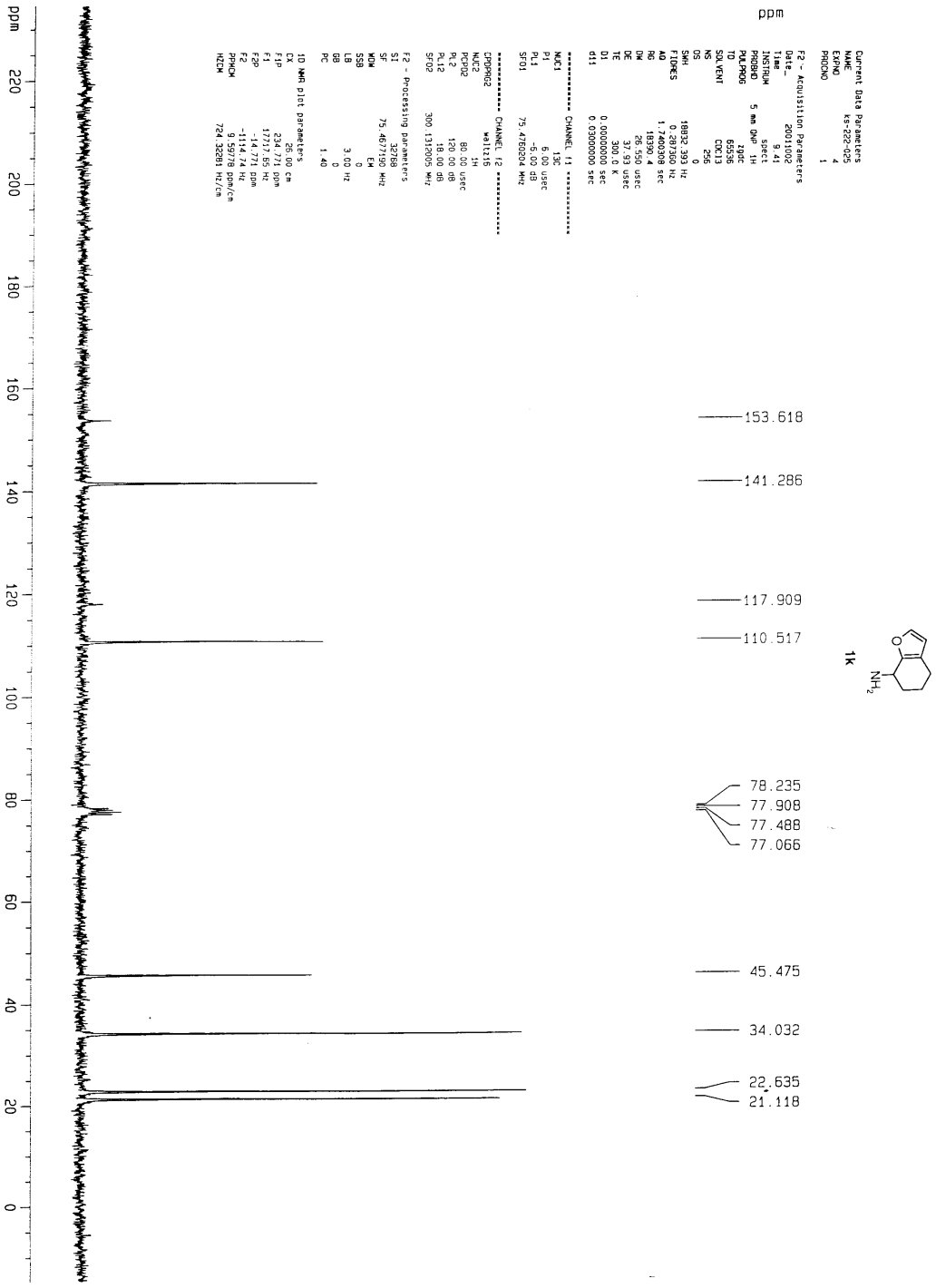
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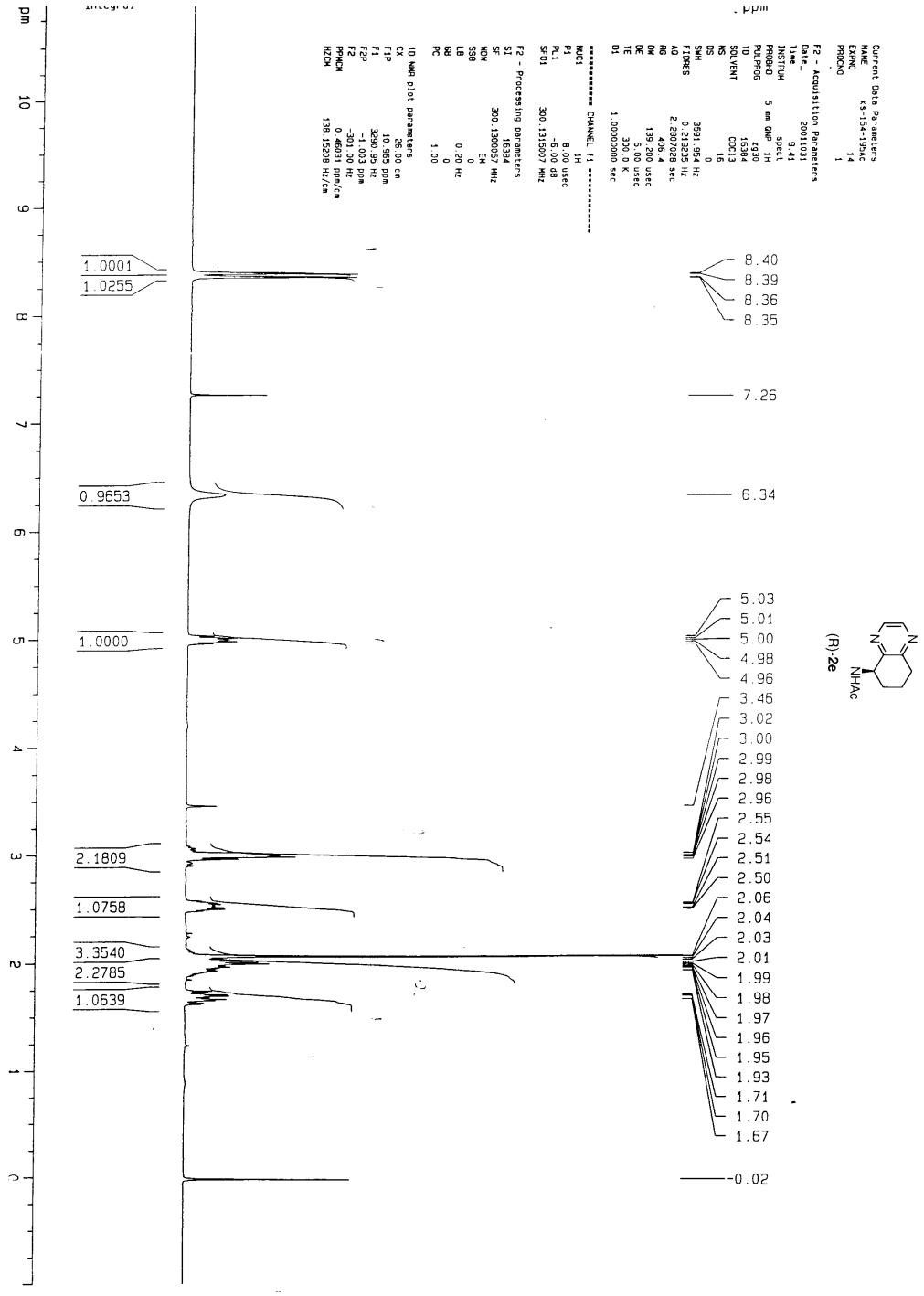
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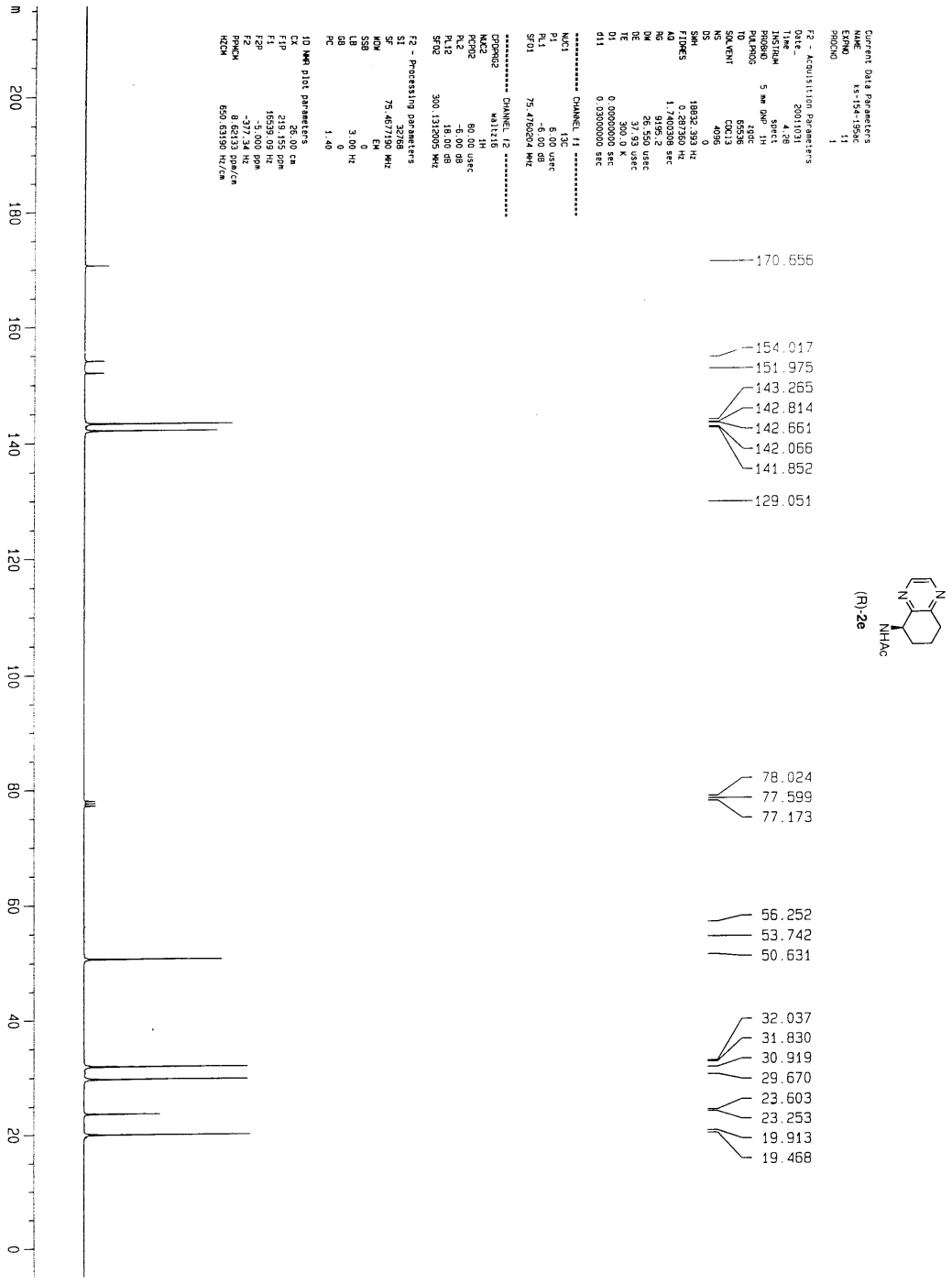
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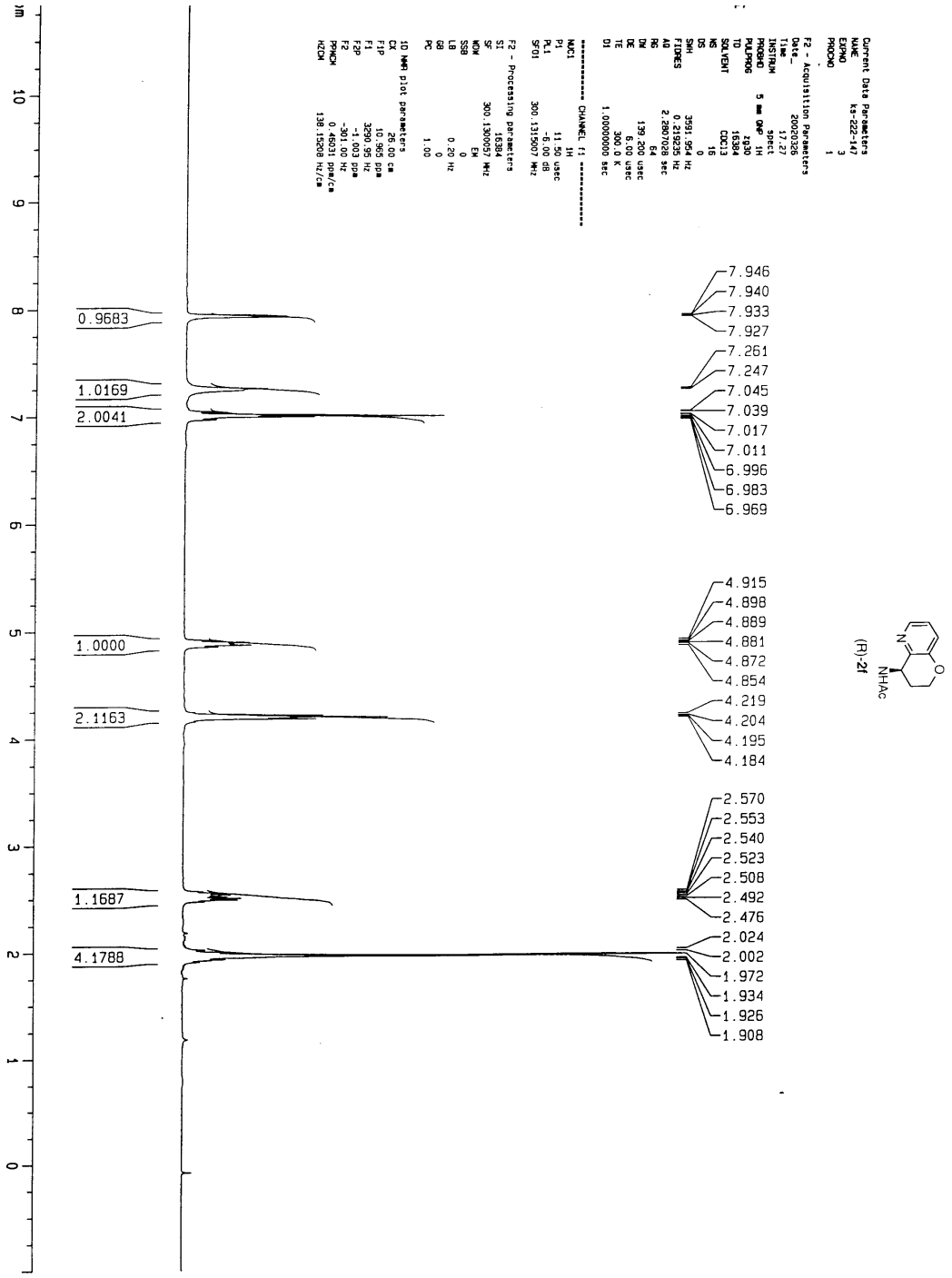
Figure 13.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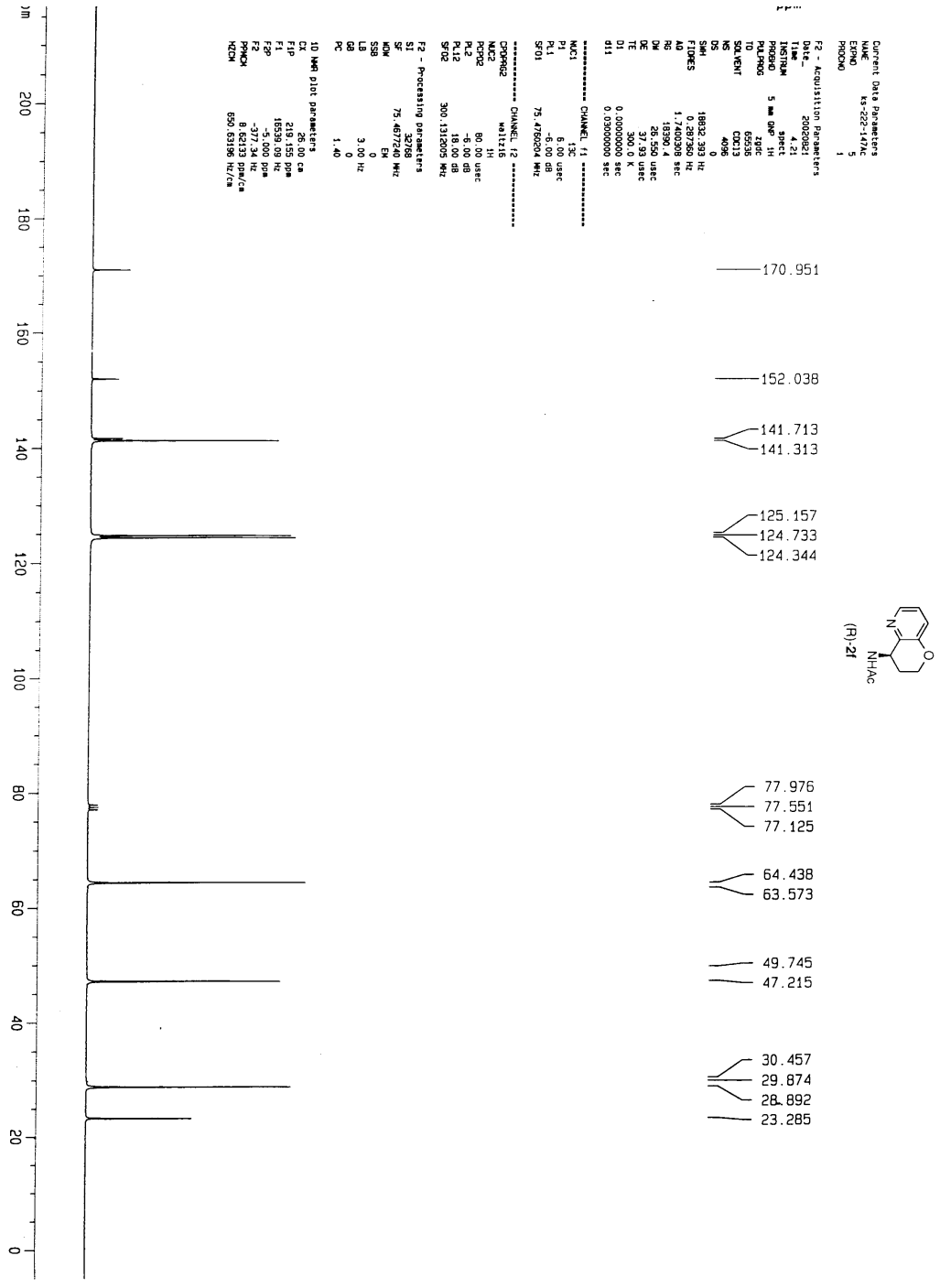
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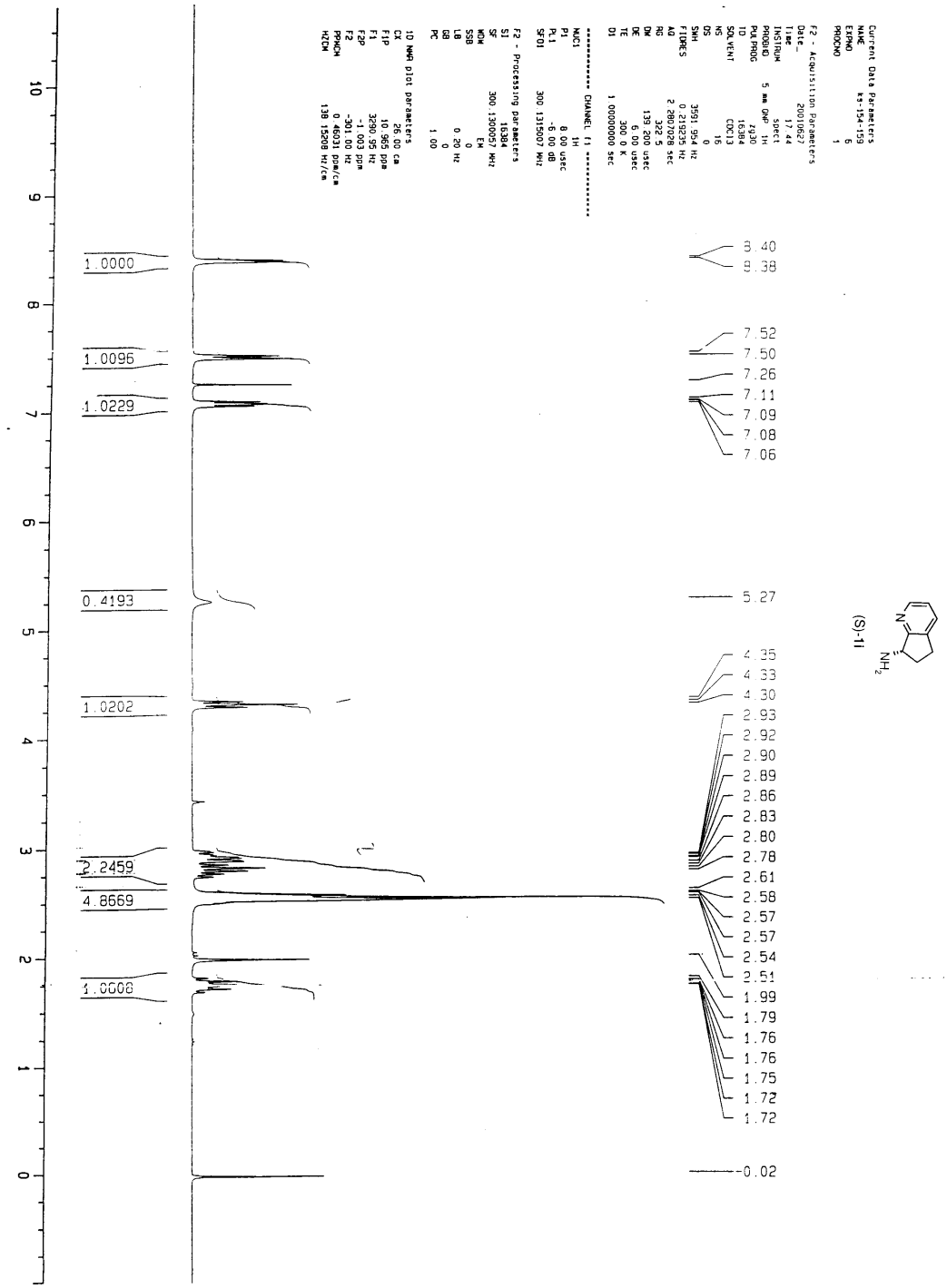
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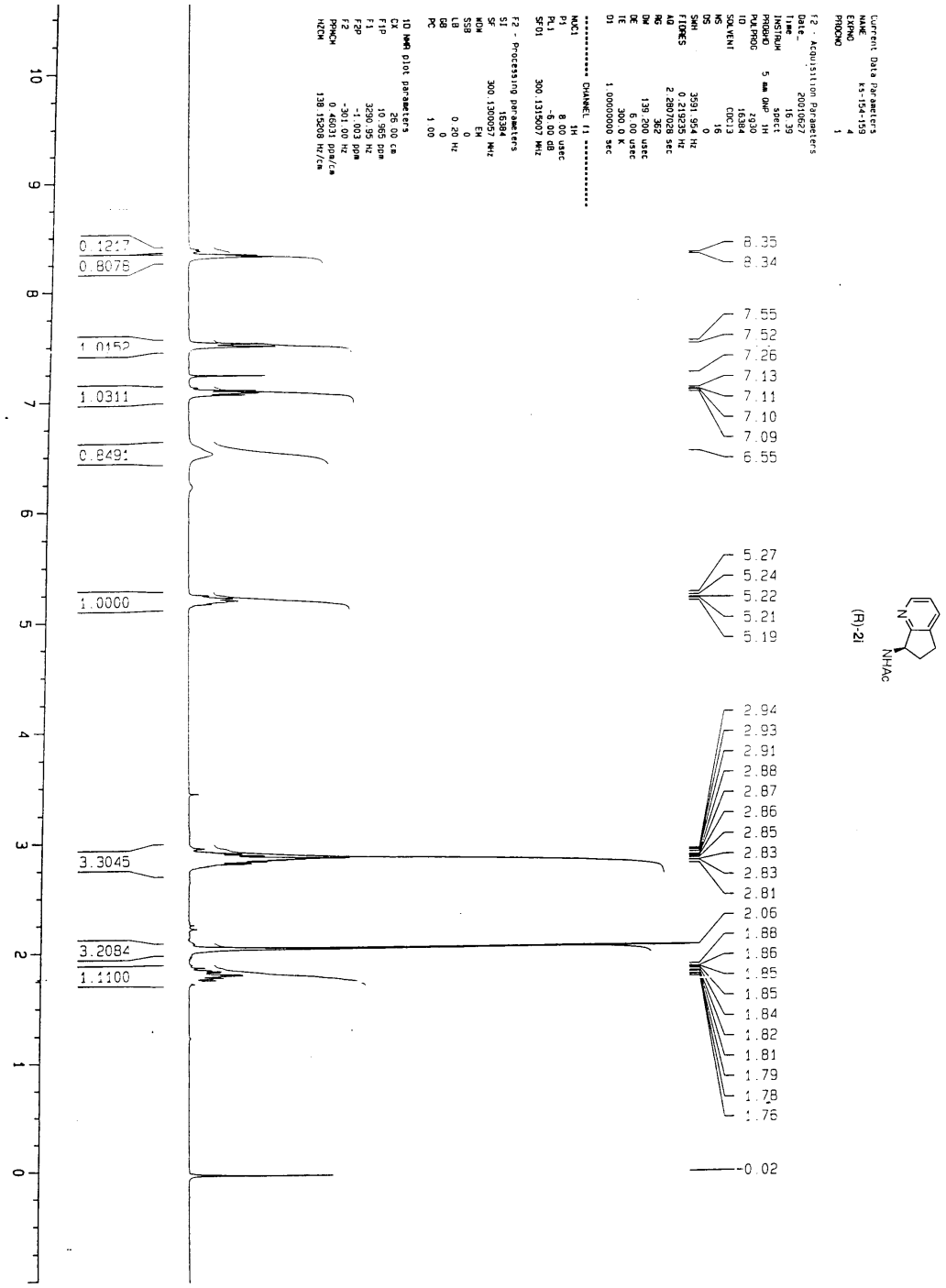
Figure 16.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1.85
1.84
1.82
1.81
1.79
1.78
1.76
0.02
0.1217
0.8078
1.0152
1.0311
0.8491
1.0000
3.3045
3.2084
1.1100
(R)-2i
NHAc

Figure 17.

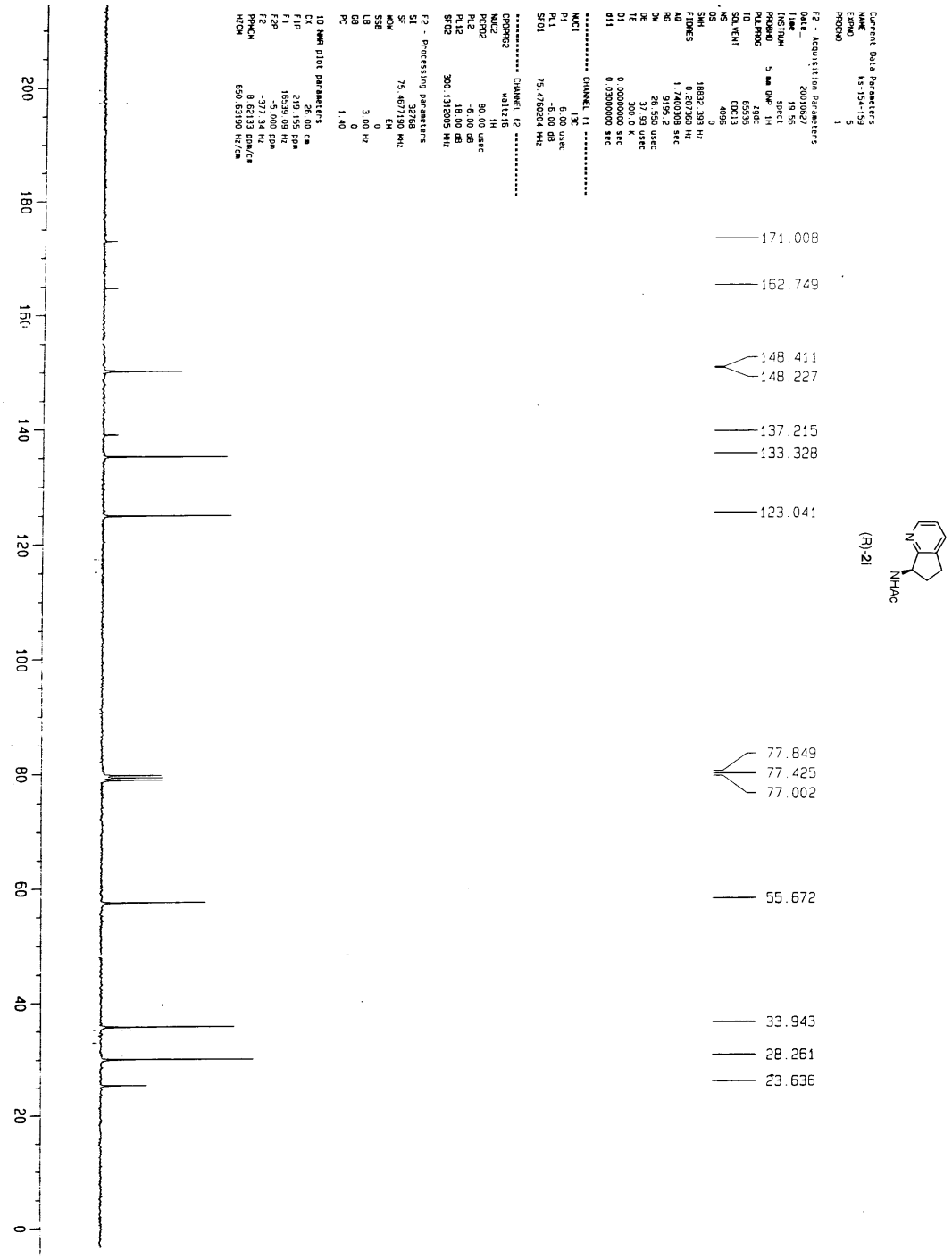

171.008
162.749
148.411
148.227
137.215
133.328
123.041
77.849
77.425
77.002
55.672
33.943
28.261
23.636
(R)-21
NHAc
N

Figure 18.

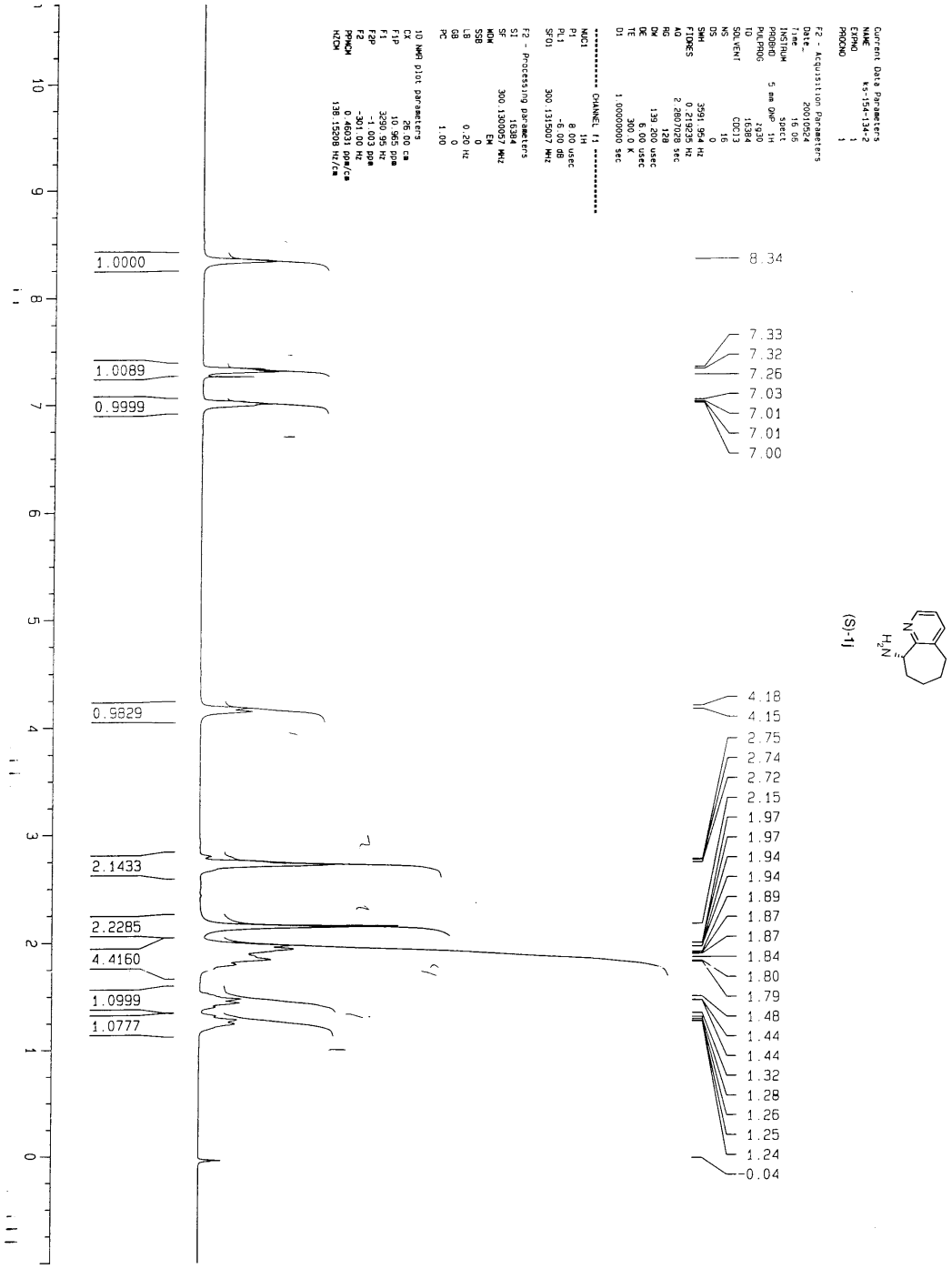

1.0000
1.0089
0.9999
0.9829
2.1433
2.2285
4.4160
1.0999
1.0777
8.34
7.33
7.32
7.26
7.03
7.01
7.01
7.00
4.18
4.15
2.75
2.74
2.72
2.15
1.97
1.97
1.94
1.94
1.89
1.87
1.87
1.84
1.80
1.79
1.48
1.44
1.44
1.32
1.28
1.26
1.25
1.24
-0.04
(S)-1j

Figure 19.

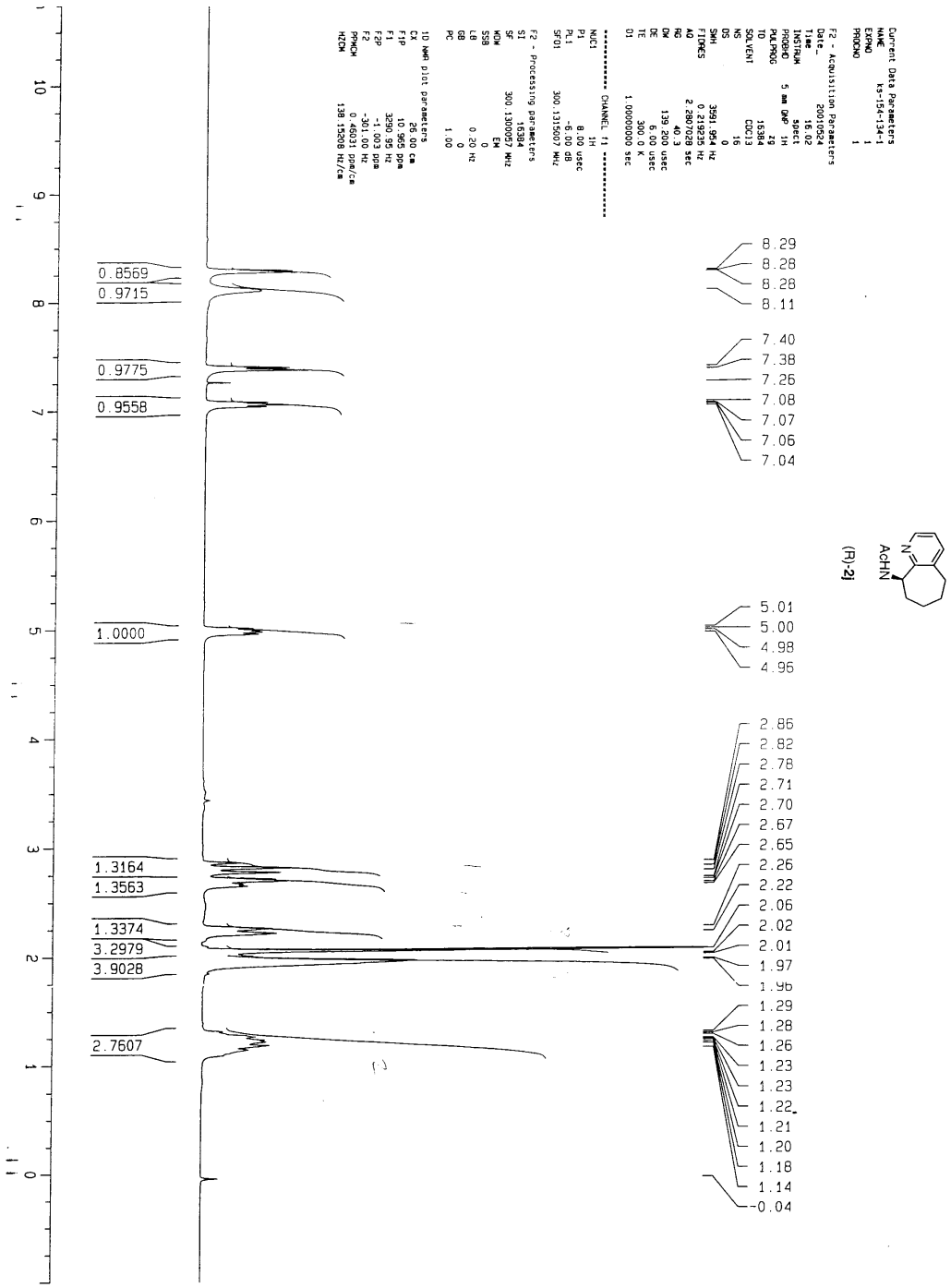

0.8569
0.9715
0.9775
0.9558
1.0000
1.3164
1.3563
1.3374
3.2979
3.9028
2.7607
8.29
8.28
8.28
8.11
7.40
7.38
7.26
7.08
7.07
7.06
7.04
5.01
5.00
4.98
4.96
2.86
2.82
2.78
2.71
2.70
2.67
2.65
2.26
2.22
2.06
2.02
2.01
1.97
1.96
1.29
1.28
1.26
1.23
1.23
1.22
1.21
1.20
1.18
1.14
-0.04
AcHN
(R)-2j

Figure 20.

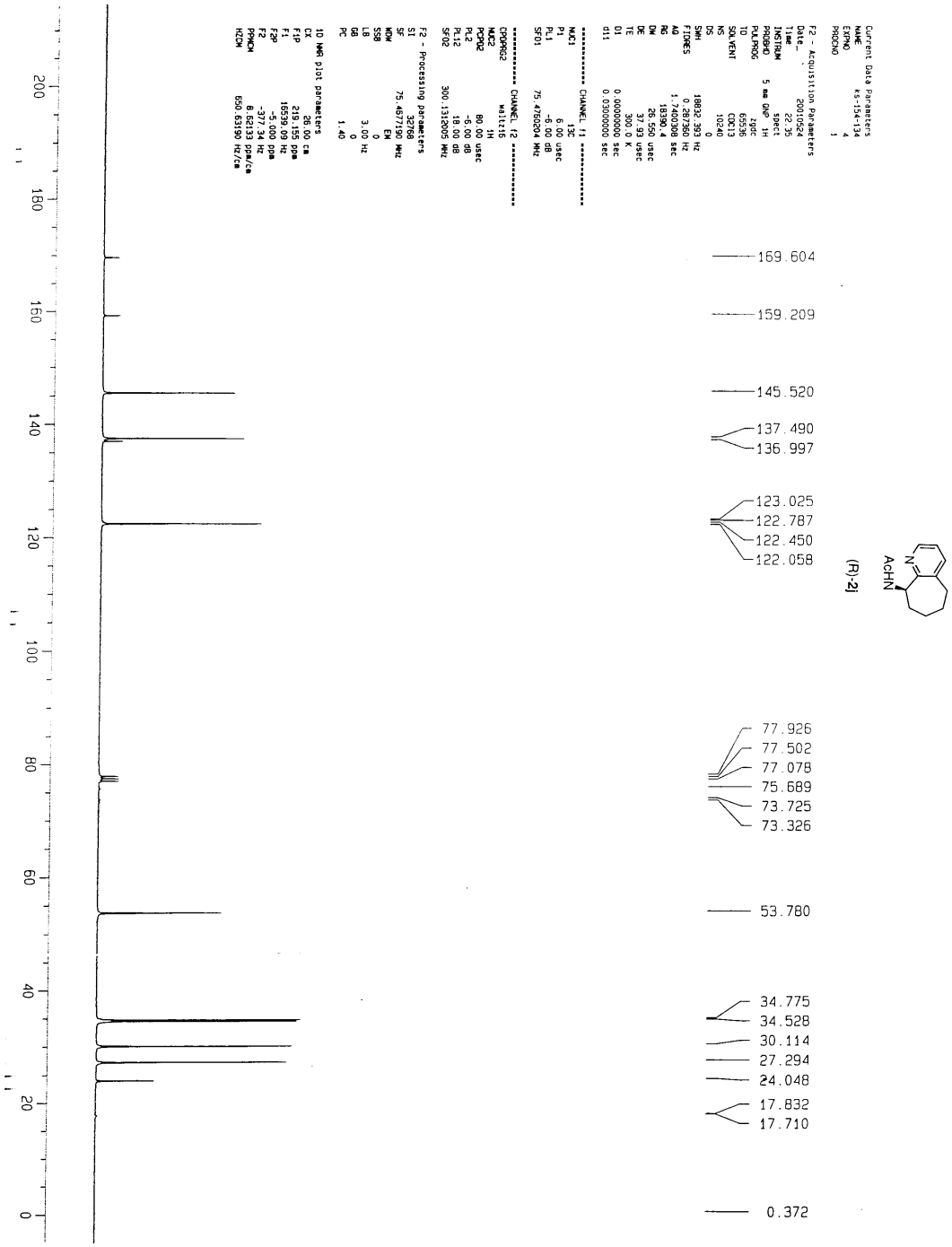

169.604
159.209
145.520
137.490
136.997
123.025
122.787
122.450
122.058
77.926
77.502
77.078
75.689
73.725
73.326
53.780
34.775
34.528
30.114
27.294
24.048
17.832
17.710
0.372
AcHN
(R)-2j

Figure 21.

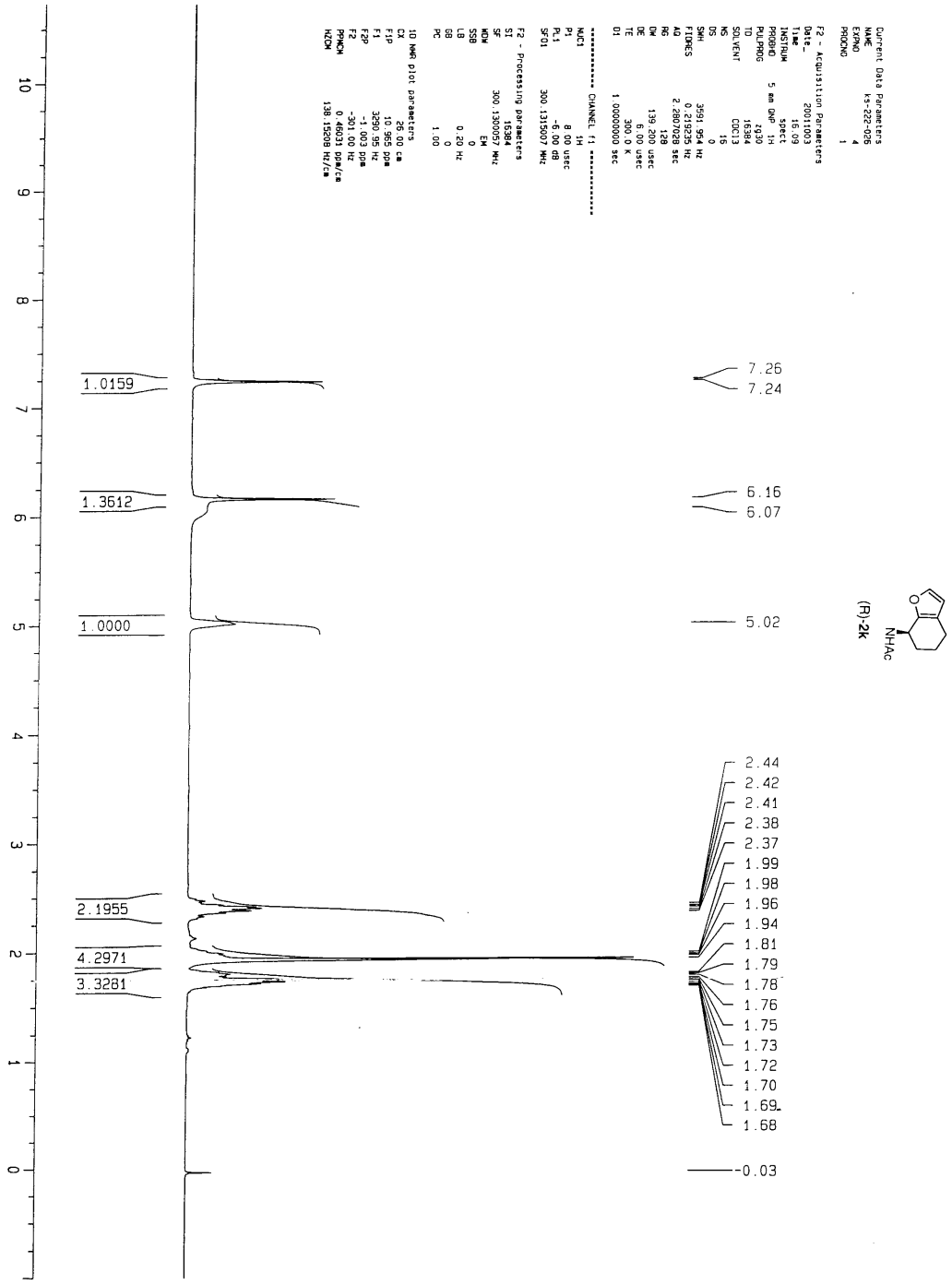

1.0159
1.3612
1.0000
2.1955
4.2971
3.3281
7.26
7.24
6.16
6.07
5.02
2.44
2.42
2.41
2.38
2.37
1.99
1.98
1.96
1.94
1.81
1.79
1.78
1.76
1.75
1.73
1.72
1.70
1.69
1.68
-0.03
NHAc
(R)-2k

Figure 22.

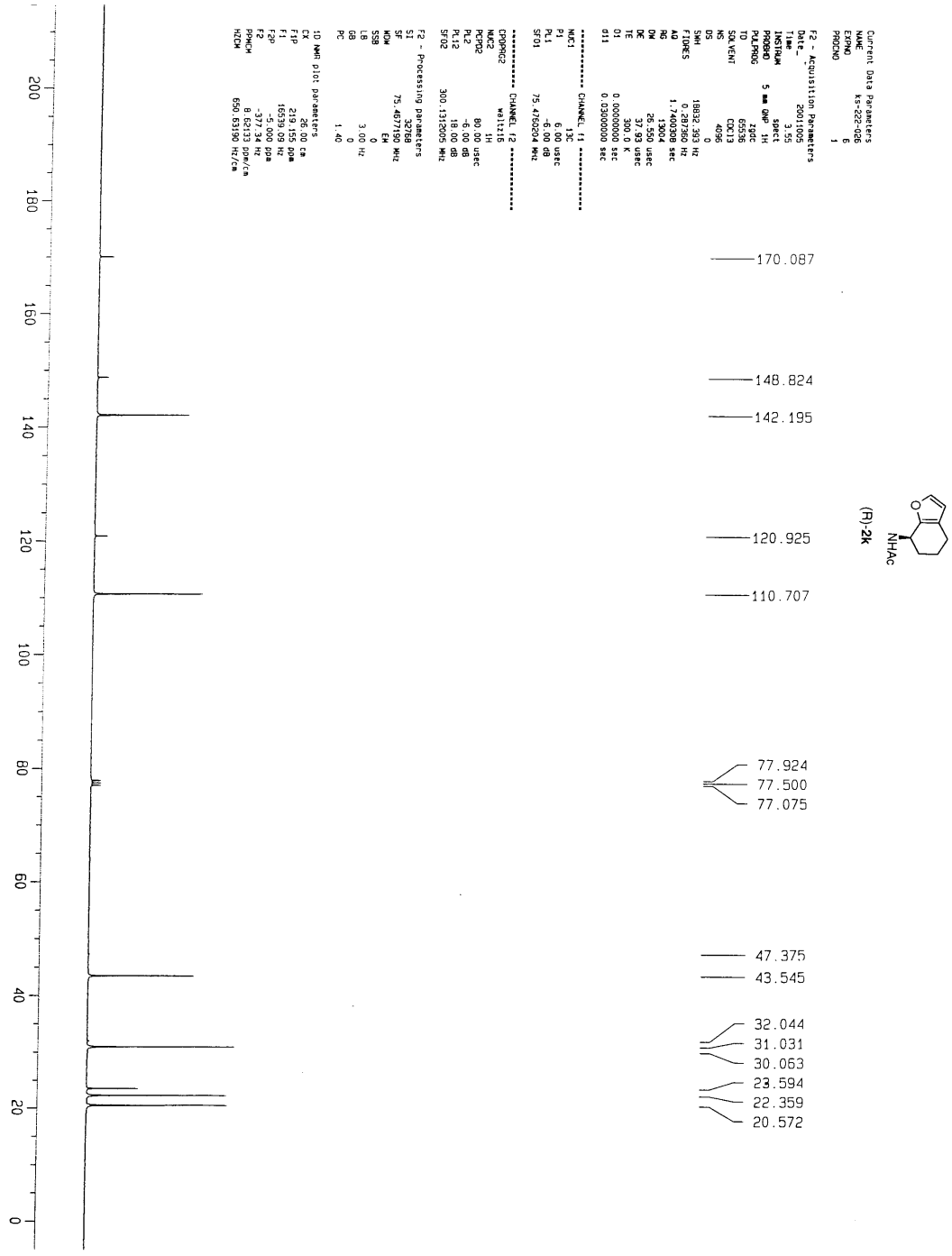

170.087
148.824
142.195
120.925
110.707
77.924
77.500
77.075
47.375
43.545
32.044
31.031
30.063
23.594
22.359
20.572
(R)-2k
NHAc

Figure 23.

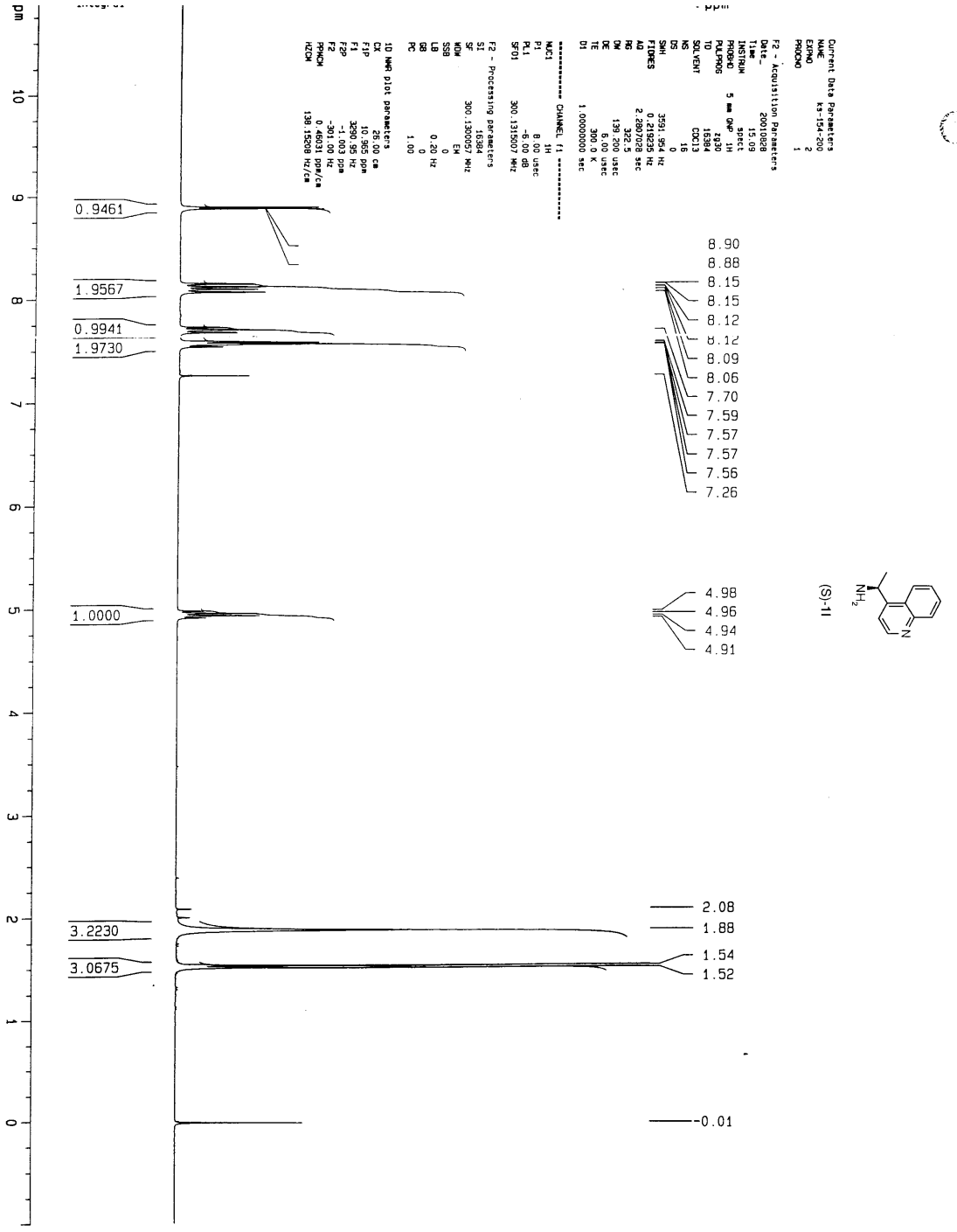

0.9461
1.9567
0.9941
1.9730
1.0000
3.2230
3.0675
8.90
8.88
8.15
8.15
8.12
8.12
8.09
8.06
7.70
7.59
7.57
7.57
7.56
7.26
4.98
4.96
4.94
4.91
2.08
1.88
1.54
1.52
-0.01
(S)-11

Figure 24.

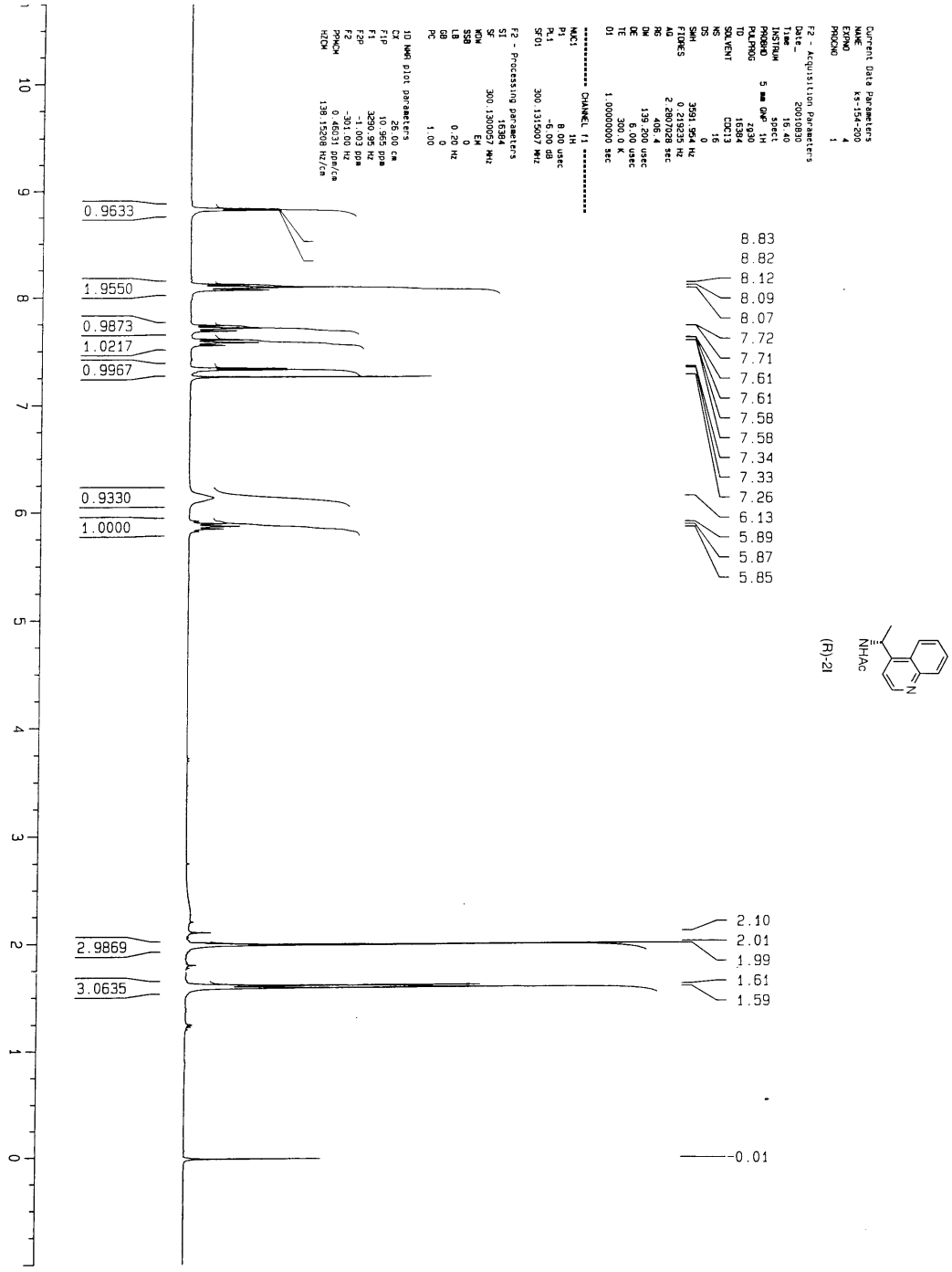
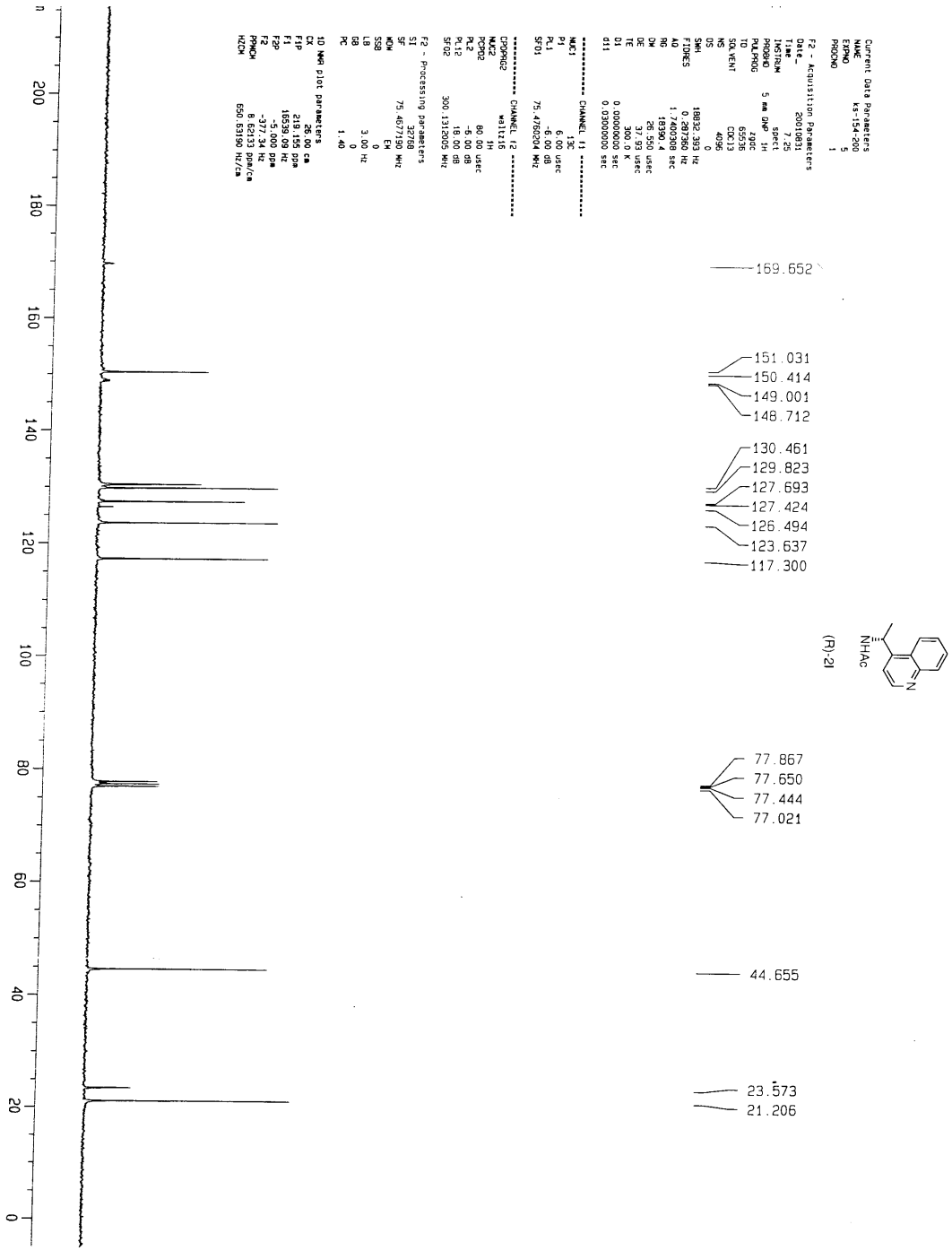

0.9633
1.9550
0.9873
1.0217
0.9967
0.9330
1.0000
2.9869
3.0635
8.83
8.82
8.12
8.09
8.07
7.72
7.71
7.61
7.61
7.58
7.58
7.34
7.33
7.26
6.13
5.89
5.87
5.85
2.10
2.01
1.99
1.61
1.59
-0.01
NHAc
N
(R)-21

Figure 25.


169.652
151.031
150.414
149.001
148.712
130.461
129.823
127.693
127.424
126.494
123.637
117.300
77.867
77.650
77.444
77.021
44.655
23.573
21.206
NHAc
N
(R)-21