1-Substituted β-carbolines by a Pictet-Spengler cyclization with thioorthoesters and carbon-carbon bond formation *via N*-sulfonyl iminium ions generated from *N,S*-sulfonyl acetals

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Supporting information

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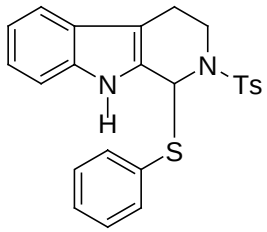
General considerations:

All reactions were carried out with anhydrous solvents in oven dried and nitrogen charged glassware. Anhydrous dichloromethane was distilled from P_2O_5. Solvents used for chromatography and extraction procedures were distilled prior to use. All other chemicals were commercially available and used without further purification.
^{1}H-NMR spectra were recorded at either 200, 400 or 500 MHz on Bruker ARX-200, ARX-400 and ARX-500 spectrometers, respectively. ^{13}C-NMR spectra were acquired at 50, 100 and 125 MHz, respectively, on the same instruments. Unless otherwise noted, NMR spectra were obtained in $CDCl_3$ with tetramethylsilane as internal standard and are recorded in ppm. Abbreviations for signal couplings are as follows: s, singlet; d, doublet; t, triplet; q, quartet; sx, sextuplet; m, multiplet and br for broad signals. Coupling constants are expressed in Hertz. High resolution mass spectra were provided by the Mass Spectrometry Center of the University of Pennsylvania and IR spectra were collected on a Perkin Elmer Spectrum BX spectrometer as neat films. Analytical thin layer chromatography was performed on silica gel 60 F_{254} plates. Flash column chromatography was carried out using silica gel 60 (230-400 mesh).

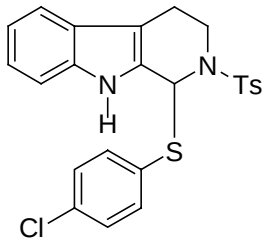
General procedure for the preparation of *N,S*-acetals 3

A solution of *N*-tosyl-tryptamine (1 mmol) and the corresponding thioorthoester [$HC(SR)_3$, 1.3 mmol] in anhydrous CH_2Cl_2 (8 mL) was cooled to -78 ºC and treated dropwise with $SnCl_4$

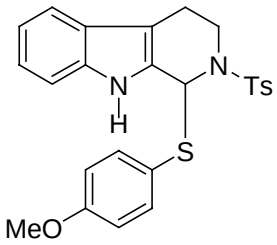
(0.29 mL, 2.5 mmol). The reaction system was allowed to reach room temperature and stirred for 5 h. Then, an aqueous solution of $NaHCO_3$ (10 mL) was added, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL); the combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was flash chromatographed, resulting in the *N,S*-sulfonylacetal **3**.



Compound 3a: mp: 156-158^{o}C; IR (KBr, *v*): 3449, 3018, 2971, 1300 and 1140 cm^{-1}; ^{1}H NMR (500 MHz, δ): 2.33 (s, 3H), 2.45-2.56 (m, 2H), 3.42-3.46 (m, 1H), 3.91 (ddd, 1H, *J*= 1.0, 4.0 and 13.0), 6.73 (s, 1H), 7.10-7.33 (m, 7H), 7.28 (d, 2H, *J*= 8.3), 7.41 (d, 2H, *J*= 8.0), 7.53 (d, 2H, *J*= 8.3) and 8.02 (s, 1H); ^{13}C NMR (125 MHz, δ): 20.33, 21.60, 39.56, 62.29, 110.97, 111.35, 118.74, 119.87, 123.10, 126.40, 127.32 (2C), 128.98, 129.20 (2C), 129.48 (2C), 129.63, 131.89, 134.97 (2C), 136.24, 137.60 and 143.63; HRMS calcd for $C_{24}H_{22}N_2O_2NaS_2$ $(M+Na)^+$ 457.1020; found 457.1023.

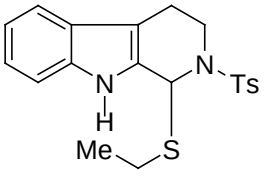


Compound 3b: IR (neat, *v*): 3400, 2980, 1475, 1304 and 1159 cm^{-1}; ^{1}H NMR (500 MHz, δ): 2.35 (s, 3H), 2.48-2.57 (m, 2H), 3.46 (ddd, 1H, *J*= 7.0, 7.5 and 12.0), 3.95 (dd, 1H, *J*= 5.0 and 13.5), 6.68 (s, 1H), 7.09 (t, 1H, *J*= 7.5), 7.13 (d, 2H, *J*= 8.0), 7.20-7.23 (m, 3H), 7.29 (d, 2H, *J*= 11.0), 7.36 (t, 2H, *J*= 8.5), 7.53 (d, 2H, *J*= 8.5) and 8.08 (s, 1H); ^{13}C NMR (125 MHz, δ): 20.17, 21.43, 39.44, 62.36, 111.05, 111.24, 118.60, 119.78, 123.07, 126.18, 127.05 (2C), 128.79, 129.14 (2C), 129.49 (2C), 130.19, 135.21, 136.00 (2C), 136.13, 137.45 and 143.62; HRMS calcd for $C_{24}H_{21}ClN_2O_2NaS_2$ $(M+Na)^+$ 493.0601; found 493.0594.

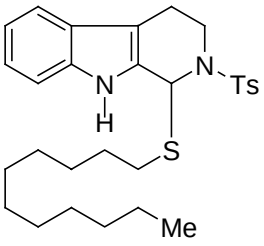


Compound 3c: mp: 180-182 ^{o}C; IR (KBr, *v*): 3446, 3019, 1593, 1340 and 1144 cm^{-1}; ^{1}H NMR (500 Mhz, δ): 2.33 (s, 3H), 2.46-2.53 (m, 2H), 3.38 (ddd, 1H, *J*= 7.1, 11.5 and 14.0), 3.76 (s, 3H), 3.91 (dd, 1H, *J*= 5.0 and 14.0), 6.59 (s, 1H), 6.75 (d, 2H, *J*= 8.5), 7.07 (dd, 1H, *J*= 7.5 and 8.0), 7.12 (d, 2H, *J*= 8.5), 7.18 (dd, 1H, *J*= 7.5 and 8.0), 7.23 (d, 2H, *J*= 8.5), 7.31 (d, 1H, *J*= 8.0), 7.34 (d, 1H, *J*= 8.0), 7.58 (d, 2H, *J*= 8.5) and 8.06 (s, 1H); ^{13}C NMR (125 MHz, δ): 20.23, 21.44, 39.50, 55.23, 62.31, 110.74, 111.18, 114.53 (2C), 118.53, 119.65, 122.07, 122.83 (2C), 126.29, 127.18 (2C), 129.46 (2C), 136.09, 136.96 (2C), 137.72, 143.41 and 160.48; HRMS calcd for $C_{25}H_{24}N_2O_3NaS_2$ $(M+Na)^+$ 487.1126; found 487.1129.

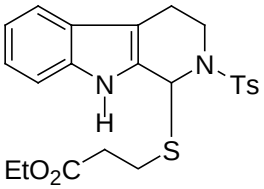
Compound 3d: mp: 73-75^{o}C; IR (KBr, ν): 3391, 3058, 1597, 1339 and 1160 cm^{-1}; ^{1}H NMR (400 MHz, δ): 1.34 (t, 3H, *J*= 7.4), 2.25-2.32 (m, 1H), 2.28 (s, 3H), 2.48 (dd, 1H, *J*= 4.5 and 15.0) and 2.73 (sx, 1H, *J*= 7.4), 2.95 (sx, 1H, *J*= 7.4), 3.74 (dt, 1H, *J*= 4.5 and 14.6), 4.03 (dd, 1H, *J*= 5.6 and 14.6), 6.55 (s, 1H), 7.04 (dt, 1H, *J*=



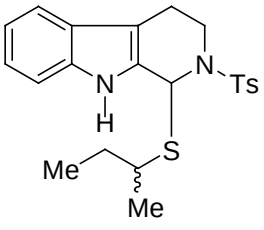
1.2 and 8.0), 7.09 (d, 2H, *J*= 8.2), 7.15 (dt, 1H, *J*= 1.2 and 8.0), 7.27 (d, 1H, *J*= 8.0), 7.28 (d, 1H, *J*= 8.0), 7.63 (d, 2H, *J*= 8.2) and 8.09 (s, 1H); ^{13}C NMR (100 MHz, δ): 14.90, 19.51, 21.36, 25.85, 38.76, 58.41, 109.98, 111.13, 118.38, 119.54, 122.68, 126.25, 126.75 (2C), 129.37, 129.56 (2C), 136.04, 137.76 and 143.55; HRMS calcd for $C_{20}H_{22}N_2O_2NaS_2$ $(M+Na)^+$ 386.1123; found 386.1136.



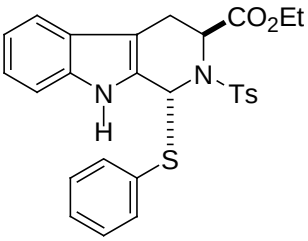
Compound 3e: mp: 70-71^{o}C; IR (KBr, *v*): 3384, 3057, 1597, 1337 and 1159 cm^{-1}; ^{1}H NMR (200 MHz, δ): 0.80-0.98 (m, 3H), 1.20-1.40 (m, 20H), 1.44-1.68 (m, 2H), 2.26 (s, 3H), 2.68 (m, 1H), 2.90 (m, 1H), 3.73 (dt, 1H, *J*= 4.4 and 12.0), 4.02 (dd, 1H, *J*= 5.4 and 14.6), 6.52 (s, 1H), 7.08 (m, 4H), 7.27 (d, 2H, *J*= 8.2), 7.64 (d, 2H, *J*= 8.2) and 8.02 (s, 1H); ^{13}C NMR (50 MHz, δ): 14.05, 19.58, 21.33, 22.63, 28.97, 29.23, 29.30, 29.51, 29.59, 29.63, 29.70, 29.81, 31.75, 31.86, 38.78, 58.71, 109.95, 111.12, 114.48, 118.36, 119.55, 122.66, 126.26, 126.77 (2C), 129.52 (2C), 136.06, 137.84 and 143.47; HRMS calcd for $C_{30}H_{42}N_2O_2NaS_2$ $(M+Na)^+$ 549.2585; found 549.2613.



Compound 3f: IR (neat, *v*): 3382, 3058, 2980, 1731, 1596, 1340 and 1161 cm^{-1}; ^{1}H NMR (500 MHz, δ): 1.31 (t, 3H, *J*= 7.0), 2.30 (s, 3H), 2.27-2.34 (m, 1H), 2.52 (dd, 1H, *J*= 5.0 and 16.0), 2.80-2.88 (m, 2H), 2.97-3.02 (m, 1H), 3.27-3.32 (m, 1H), 3.70 (ddd, 1H, J= 4.5, 12.5 and 15.0), 4.05 (dd, 1H, *J*= 6.0 and 15.0), 4.23 (q, 2H, *J*= 7.0), 6.56 (s, 1H), 7.05 (dt, 1H, *J*= 1.0 and 8.0), 7.15 (d, 2H, *J*= 7.4), 7.18 (dt, 1H, *J*= 1.0 and 8.0), 7.31 (dd, 1H, *J*= 1.0 and 8.0), 7.32 (dd, 1H, *J*= 1.0 and 8.0), 7.64 (d, 2H, *J*= 7.4) and 8.22 (s, 1H); ^{13}C NMR (125 MHz, δ): 14.46, 19.82, 21.67, 27.18, 35.33, 39.21, 58.95, 61.09, 110.15, 111.43, 118.65, 119.76, 122.98, 126.39, 127.00 (2C), 129.48, 129.89 (2C), 136.30, 137.85, 143.89 and 172.00; HRMS calcd for $C_{23}H_{26}N_2O_4NaS_2$ $(M+Na)^+$ 481.1232; found 481.1249.



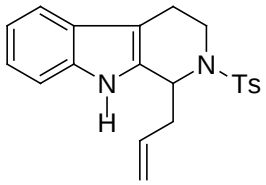
Compound 3g: IR (neat, *v*): 3381, 2962, 1304 and 1160 cm^{-1}; ^{1}H NMR (acetone-$_{d6}$, 200 MHz, major diastereomer, δ): 0.88 (t, 3H, *J*= 7.5), 1.35 (d, 3H, *J*= 7.0), 1.34-1.56 (m, 2H), 2.05-2.20 (m, 2H), 2.07 (s, 3H), 2.96-3.04 (m, 1H), 3.71 (dt, 1H, *J*= 5.0 and 15), 3.93 (dd, 1H, *J*= 5.9 and 15), 6.49 (s, 1H), 6.78 (t, 1H, *J*= 13.5), 6.70-7.25 (m, 3H), 7.19 (d, 2H, *J*= 8.0), 7.53 (d, 2H, *J*= 8.0) and 9.85 (s, 1H); ^{13}C NMR (acetone-$_{d6}$, 100 MHz, major diastereomer, δ): 11.55, 19.62, 20.69, 22.11, 30.45, 38.91, 42.22, 58.74, 109.24, 111.76, 118.50, 119.42, 122.59, 126.83, 127.27 (2C), 129.94 (2C), 130.48, 137.04, 138.96 and 143.98; HRMS calcd for $C_{22}H_{26}N_2O_2NaS_2$ $(M+Na)^+$ 437.1232; found 437.1221.



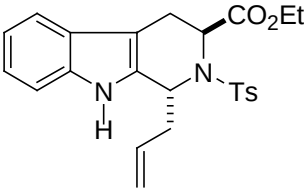
Compound 3i: mp: 154-156ºC; IR (KBr, *v*): 3370, 3058, 1732, 1480, 1337 and 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major diastereomer, δ): 1.35 (t, 3H, *J*= 7.1), 2.26 (s, 3H), 2.89 (dd, 1H, *J*= 16.2 and 4.5), 3.25 (dd, 1H, J= 16.2 and 10.4), 4.36-4.25 (m, 2H), 5.05-5.01 (m, 1H), 6.40 (s, 1H), 7.79-6.95 (m, 13H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz, major diastereomer, δ): 14.01, 21.50, 23.20, 55.10, 61.64, 64.73, 110.95, 111.19, 118.68, 119.84, 123.01, 126.19, 127.53 (2C), 128.67, 129.25 (2C), 129.46 (2C), 129.59, 133.11, 135.26 (2C), 136.32, 136.94, 143.51, 170.14; HRMS calcd for $C_{27}H_{26}N_2O_4NaS_2$ $(M+Na)^+$ 529.1232; found 529.1222. [α]= -3.90 (*c*= 0.1, $CHCl_3$).

General procedure for the synthesis of tetrahydro-β-carbolines 4a-g from *N,S*-acetals 3.

An aliquot of the *N,S*-sulfonyl acetal **3** (0.5 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and the resulting solution was cooled to –78 ºC. $SnCl_4$ or $ZnBr_2$ (0.5 mmol, 0.06 mL) were then added, followed by treatment with the desired nucleophile (0.7 mmol). After stirring 2-10 h, the reaction was quenched with water and extracted with CH_2Cl_2 (3 x 10 mL). Drying ($MgSO_4$), concentration and flash chromatography of the combined organic extracts furnished the corresponding tetrahydro-β-carboline **4**.

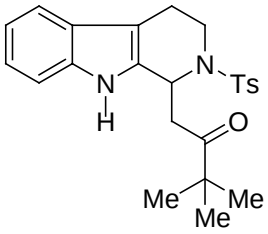


Compound 4a: IR (neat, *v*): 3380, 2924, 1597, 1328, 1091 and 923 cm^{-1}; ^1H NMR (500 MHz, δ): 2.29 (s, 3H), 2.46 (ddd, 1H, *J*= 5.5, 6.0 and 14.4), 2.55 (dd, 1H, *J*= 6.0 and 14.4), 2.65-2.75 (m, 2H), 3.43 (ddd, 1H, *J*= 5.5, 6.0 and 14.4), 4.15 (dd, 1H, *J*= 5.5 and 14.4), 5.18 (m, 3H), 5.96 (m, 1H), 7.06 (dd, 1H, *J*= 7.8 and 8.0), 7.13 (d, 2H, *J*= 8.5), 7.15 (dd, 1H, *J*= 7.8 and 8.0), 7.29 (dd, 1H, *J*= 0.5 and 8.0), 7.35 (d, 1H, *J*= 8.0), 7.65 (d, 2H, *J*= 8.5) and 7.88 (brs, 1H); ^{13}C NMR (125 MHz, δ): 20.09, 21.37, 40.01, 40.49, 52.65, 108.10, 110.90, 118.10, 118.95, 119.40, 122.00, 126.43, 126.71, 129.53 (2C), 132.46 (2C), 133.94, 135.75, 138.08 and 143.24; HRMS calcd for $C_{21}H_{22}N_2O_2NaS$ $(M+Na)^+$ 389.1300; found 389.1315.

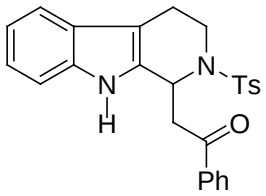


Compound 4b: IR (neat, *v*): 3388, 2925, 1732, 1598, 1336, 1092 and 922 cm^{-1}; ^1H NMR (400 MHz, δ): 1.19 (t, 3H, *J*= 9.0), 2.35 (s, 3H), 2.63 (ddd, 1H, *J*= 2.0, 6.5 and 16.0), 2.70 (dt, 1H, *J*= 11,0 and 16.0), 3.02-3.08 (m, 1H), 3.36 (dd, 1H, *J*= 2.0 and 16.0), 4.09 (q, 2H, *J*= 9.0), 5.10 (ddd, 2H, *J*= 2.0, 6.5 and 11.0), 5.26-5.36 (m, 2H), 6.14-6.25 (m, 1H), 7.06 (ddd, 1H, *J*= 0.8, 7.2 and 8.0), 7.14 (ddd, 1H, *J*= 0.8, 8.0 and 8.0), 7.23 (d, 2H, *J*= 8.4), 7.25 (d, 1H, *J*= 7.2), 7.41 (d, 1H, *J*= 8.0), 7.72 (d, 2H, *J*= 8.4) and 8.05 (brs, 1H); ^{13}C NMR (100 MHz, δ): 13.96, 21.46, 22.03, 42.33, 52.28, 53.66, 61.71, 105.59, 110.89, 118.26, 118.85, 119.59, 122.25, 126.07, 126.93 (2C), 129.83 (2C), 132.25, 135.85, 136.54, 137.40, 143.69 and 170.86; HRMS calcd for $C_{24}H_{26}N_2O_4NaS$ $(M+Na)^+$ 461.1511; found 461.1521. [α]= +34.7 (c= 0.2, $CHCl_3$).

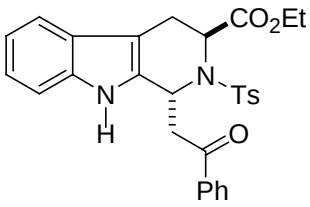
Compound 4c: IR (neat, ν): 3403, 3055, 2968, 2929, 1696, 1337, and 1159 cm^{-1}; ^1H NMR (400 MHz, δ): 1.16 (s, 9H), 2.28 (s, 3H),



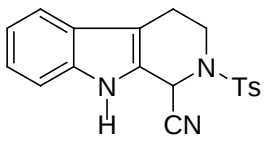
2.44-2.48 (m, 2H), 2.50 (ddd, 1H, *J*= 4.4, 5.6 and 14.4), 3.20 (dd, 1H, *J*= 10.4 and 14.4), 3.37 (dd, 1H, *J*= 4.4 and 10.4), 4.27 (dd, 1H, *J*= 5.6 and 14.4), 5.44 (d, 1H, *J*= 10.0), 7.03 (ddd, 1H, *J*= 0.5, 6.8, and 6.8), 7.11 (d, 2H, *J*= 8.4), 7.13 (dd, 1H, *J*= 6.8 and 6.8), 7.28 (d, 1H, *J*= 6.8), 7.31 (d, 1H, *J*= 6.8), 7.63 (d, 2H, *J*= 8.4) and 8.71 (brs, 1H); ^{13}C NMR (100 MHz, δ): 20.25, 21.34, 25.23, 26.37, 34.62, 40.57, 44.48, 45.01, 48.87, 107.21, 111.09, 117.99, 119.22, 121.98, 126.25, 126.56 (2C), 129.61 (2C), 132.65, 135.51, 137.86, 143.31 and 217.40; HRMS (electrospray ionization) calcd for $C_{24}H_{28}N_2O_3S$ $(M+H)^+$ 425.1899; found 425.1882.



Compound 4d: IR (neat, ν): 3410, 3.055, 2922, 1677, 1336 and 1157 cm^{-1}; ^{1}H NMR (500 MHz, δ): 2.29 (s, 3H), 2.62-2.52 (m, 2H), 3.50-3.44 (m, 1H), 3.89-3.71 (m, 2H), 4.32 (dd, 1H, *J*= 13 and 2), 5.72 (bd, 1H, *J*= 4), 7.01-7.61 (m, 9H), 7.12 (d, 2H, *J*= 7.2), 7.97 (d, 2H, *J*= 7.2) and 8.81 (brs, 1H); ^{13}C NMR (125 MHz, δ): 20.32, 21.39, 40.66, 46.66, 48.84, 111.13, 118.04, 119.29, 122.11, 126.67 (2C), 128.18 (2C), 128.78 (2C), 129.69 (2C), 133.97, 135.53, 143.40; Anal calcd: C, 70.16; H, 5.64; N, 5.88; found: C, 70.25, H, 5.44, N, 6.30.

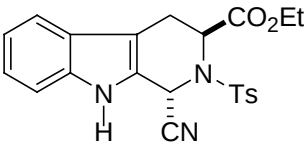


Compound 4e: mp: 151-153^{o}C; IR (KBr, ν): 3368, 3.058, 2980, 2925, 1739, 1676, 1329 and 1157 cm^{-1}; ^{1}H NMR (500 MHz, δ): 1.23 (t, 3H, *J*= 10), 2.29 (s, 3H), 3.07 (dd, 1H, *J*= 15.9 and 4.5), 3.29 (dd, 1H, J= 15.9 and 8.6), 3.54 (dd, 1H, 18.2 and 10.3), 4.02 (dd, 1H, J= 18.2 and 2.1), 4.21-4.10 (m, 2H), 4.56 (dd, 1H, J= 8.6 and 4.5), 5.69 (brd, 1H, J= 10.10), 7.02 (t, 1H, J= 7.6), 7.11 (t, 1H, J= 8.0), 7.17 (d, 2H, J= 8.0), 7.25 (d, 2H, J= 7.9), 7.37 (d, 1H, J= 7.8), 7.45 (t, 2H, J= 7.9), 7.58 (t, 1H, J= 7.3), 7.77 (d, 2H, J= 8.2). 7.90 (d, 2H, J= 8.3), 8.61 (brs, 1H); ^{13}C NMR (125 MHz, δ): 13.98, 21.42, 23.93, 46.36, 51.01, 57.19, 61.60, 106.64, 111.09, 118.02, 119.47, 122.12, 126.18, 127.54 (2C), 128.13 (2C), 128.75 (2C), 129.37 (2C), 133.34, 133.97, 135.64, 136.00, 137.00, 143.86, 169.90, 199.40; HRMS calcd for $C_{29}H_{28}N_2O_5NaS$ $(M+Na)^+$ 539.1638; found 539.1617. [α]= -3.3 (*c*= 0.25, $CHCl_3$).



Compound 4f: IR (neat, *v*): 3405, 2939, 2254, 1355 and 908 cm^{-1}; ^{1}H NMR (500 MHz, δ): 2.42 (s, 3H), 2.79 (ddd, 1H, *J*= 1.0, 4.5 and 14), 2.88 (ddd, 1H, *J*= 1.0, 6.0 and 12), 3.23 (ddd, 1H, *J*= 4.5, 12 and 14), 4.20 (dd, 1H, *J*= 6.0 and 14), 6.05 (s, 1H), 7.12 (dt, 1H, *J*= 1.0 and 8.0), 7.24 (dt, 1H, *J*= 1.0 and 8.0), 7.34 (dd, 2H, *J*= 2.0 and 7.0), 7.35 (d, 1H, *J*= 8.0), 7.46 (d, 1H, *J*= 8.0), 7.80 (dd, 2H, *J*= 2.0 and 7.0) and 8.08 (brs, 1H); ^{13}C NMR (125 MHz, δ): 21.11, 21.62, 41.57, 43.80, 110.93, 111.58, 114.96, 118.87, 120.39, 122.99, 123.76, 126.05, 127.57 (2C), 130.02 (2C), 135.05, 136.60 and 144.72; HRMS calcd for $C_{19}H_{17}N_3O_2S$ 351.1041; found 351.1036.

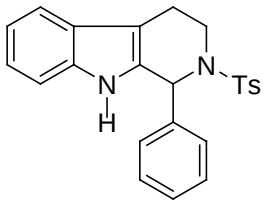
Compound 4g: IR (neat, *v*): 3405, 2939, 2254, 1739, 1355 and 908 cm^{-1}; ^{1}H NMR (200 MHz, δ): 0.98 (s, 3H, *J*= 7.2), 2.43 (s, 3H), 3.03 (dd, 1H, *J*= 5.6 and 16.0), 3.46 (d, 1H, *J*= 16.0), 3.93 (q, 2H, *J*=



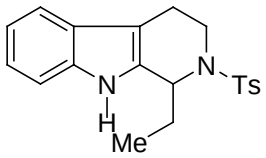
7.2), 5.14 (d, 1H, *J*= 5.6), 6.26 (s, 1H), 7.05-7.55 (m, 4H), 7.17 (d, 2H, *J*= 8.2), 7.86 (d, 2H, *J*= 8.2) and 8.30 (brs, 1H); ^{13}C NMR (50 MHz, δ): 13.67, 21.59, 23.91, 41.97, 53.63, 62.06, 108.33, 111.51, 115.58, 118.89, 120.46, 121.69, 123.78, 125.93 (2C), 127.67, 129.94 (2C), 135.67, 136.77, 144.78 and 169.34; HRMS calcd for $C_{22}H_{21}N_3O_4S$ 423.1253; found 423.1254. [α]= -17.4 ($CHCl_3$).

General procedure for the synthesis of tetrahydro-β-carbolines 4h-j from *N,S*-acetal 3a.

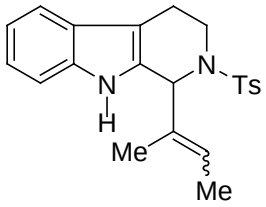
An aliquot of the *N,S*-sulfonyl acetal **3a** (0.5 mmol) was dissolved in dry THF (5 mL), followed by addition of the desired Grignard reagent (0.7 mmol). After stirring 0.2-0.5 h, the reaction was quenched with water and extracted with CH_2Cl_2 (3 x 10 mL). Drying ($MgSO_4$), concentration and flash chromatography of the combined organic extracts furnished the corresponding tetrahydro-β-carboline **4**.



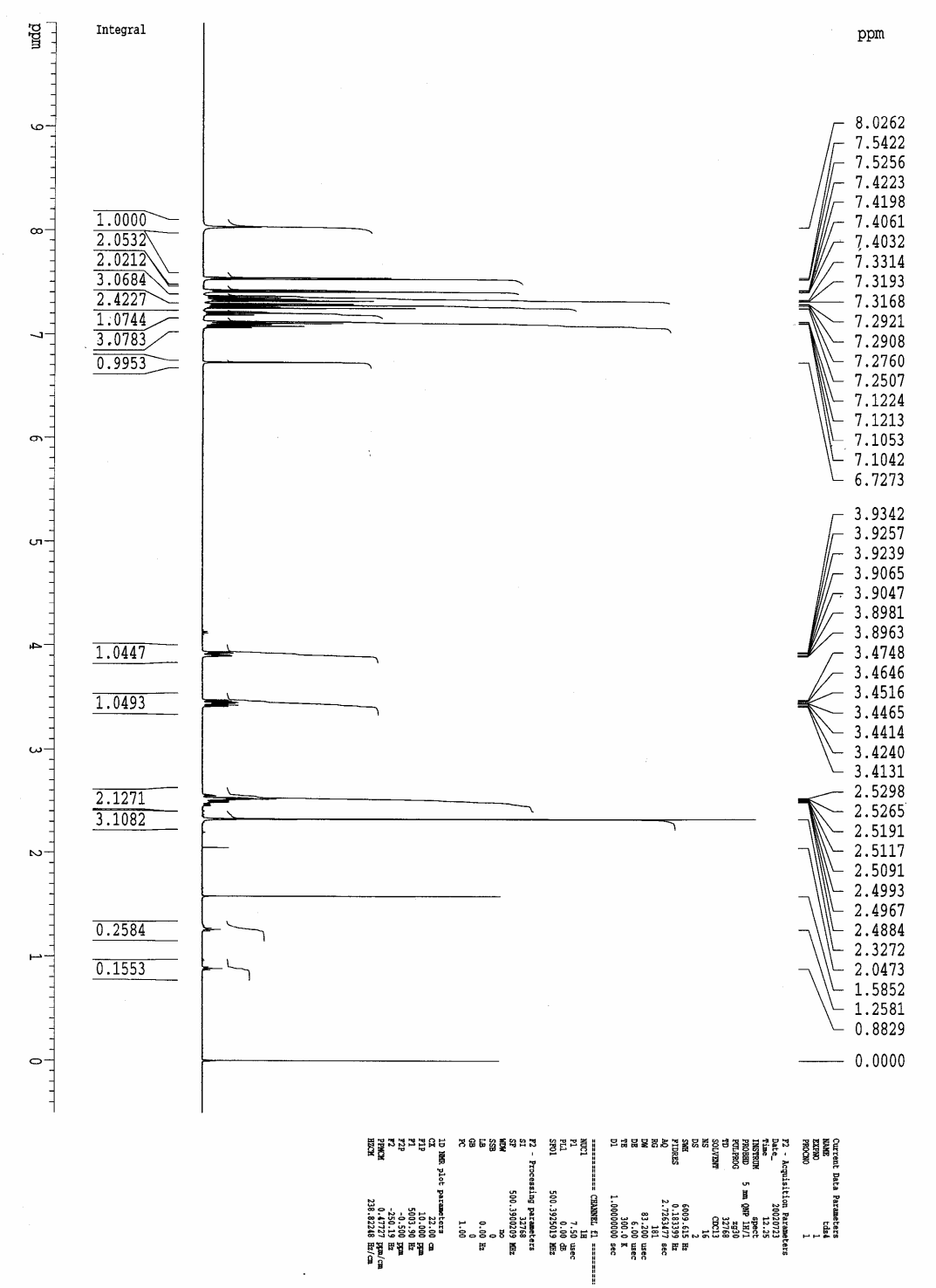
Compound 4h: mp: 176-178°C; IR (KBr, *v*): 3392, 3055, 2923, 1332 and 1158 cm^{-1}; ^{1}H NMR (500 MHz, δ): 2.27 (s, 3H), 2.66-2.54 (m, 2H), 3.29 (ddd, 1H, *J*= 4.8, 11.7 and 14.5), 3.99 (dd, 1H, *J*= 5.4 and 14.5), 6.31 (s, 1H), 7.03 (d, 2H, *J*= 8.2), 7.05-7.40 (m, 4H), 7.27 (s, 5H), 7.55 (d, 2H, *J*= 8.2) and 7.80 (brs, 1H); ^{13}C NMR (125 MHz, δ): 20.15, 21.36, 39.46, 55.81, 109.97, 110.95, 118.32, 119.62, 122.33, 126.82 (2C), 128.41, 128.61 (4C), 129.39 (2C), 130.34, 136.13, 137.93, 139.19, 139.24, 143.17; HRMS calcd for $C_{24}H_{23}N_2O_2S$ $(M+H)^+$ 403.1480; found 425.1463.



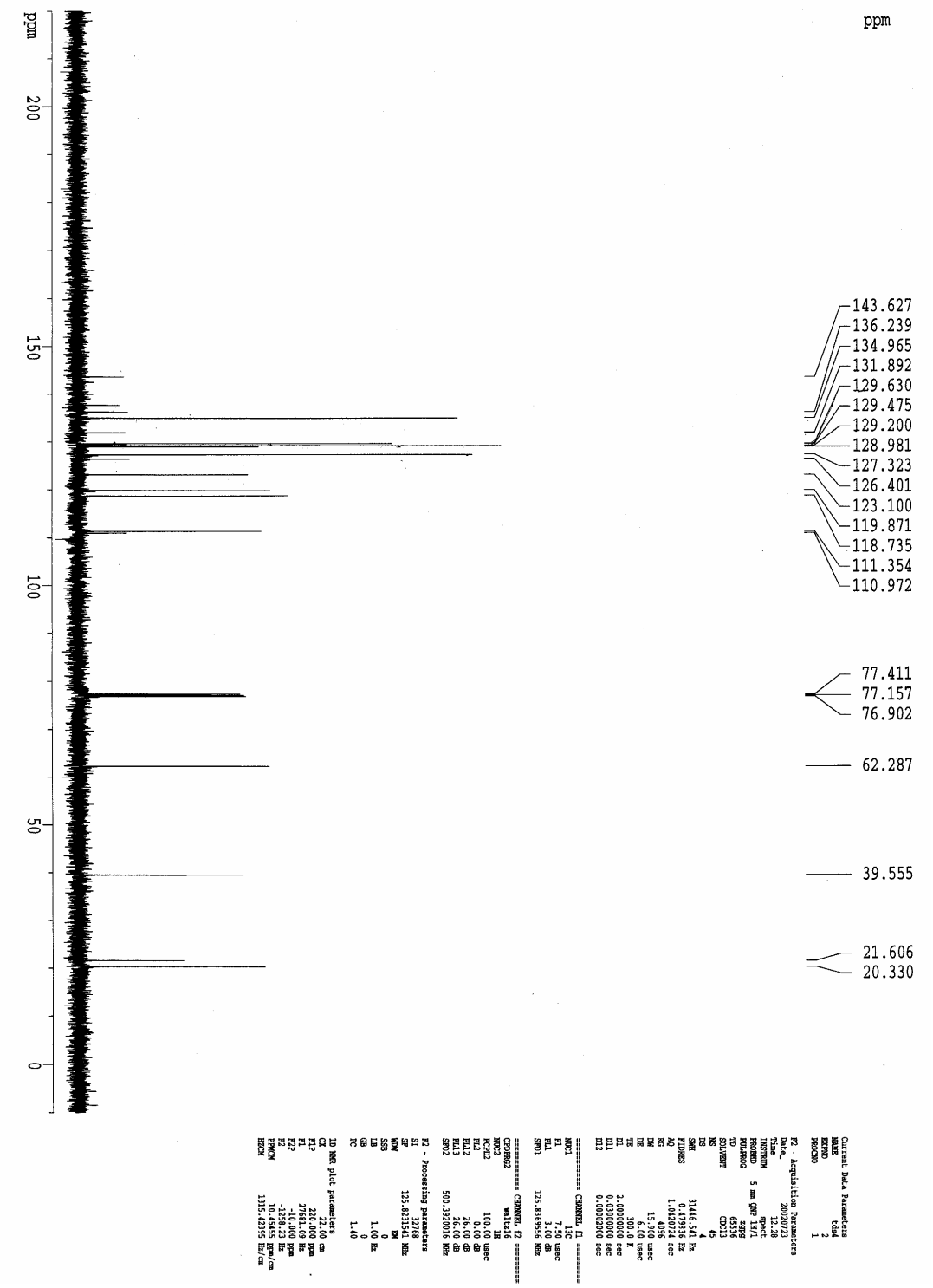
Compound 4i: mp: 71-73°C; IR (KBr, *v*): 3387, 3055, 2968, 2932, 1334 and 1159 cm^{-1}; ^{1}H NMR (500 MHz, δ): 1.11 (t, 3H, *J*= 7.4), 1.98-1.81 (m, 2H), 2.27 (s, 3H), 2.40-2.31 (m, 1H), 2.48 (dd, 1H, J= 15.6 and 4.5), 3.39 (ddd, 1H, *J*= 4.5, 12.0 and 14.6), 4.12 (dd, 1H, *J*= 5.7 and 14.6), 5.06 (dd, 1H, *J*= 5.1 and 8.2), 7.04 (t, 1H, J= 7.7), 7.09 (d, 2H, J= 8.2), 7.14 (t, 1H, J= 8.2), 7.30 (t, 2H, J= 7.5), 7.63 (d, 2H, J= 8.2), 7.80 (brs, 1H); ^{13}C NMR (100 MHz, δ): 10.86, 19.78, 21.37, 28.98, 39.70, 54.46, 107.85, 110.79, 118.12, 119.47, 121.98, 126.67, 126.76 (2C), 129.46 (2C), 133.06, 135.80, 138.21, 143.15; HRMS calcd for $C_{20}H_{23}N_2O_2S$ $(M+H)^+$ 355.1480; found 355.1470.



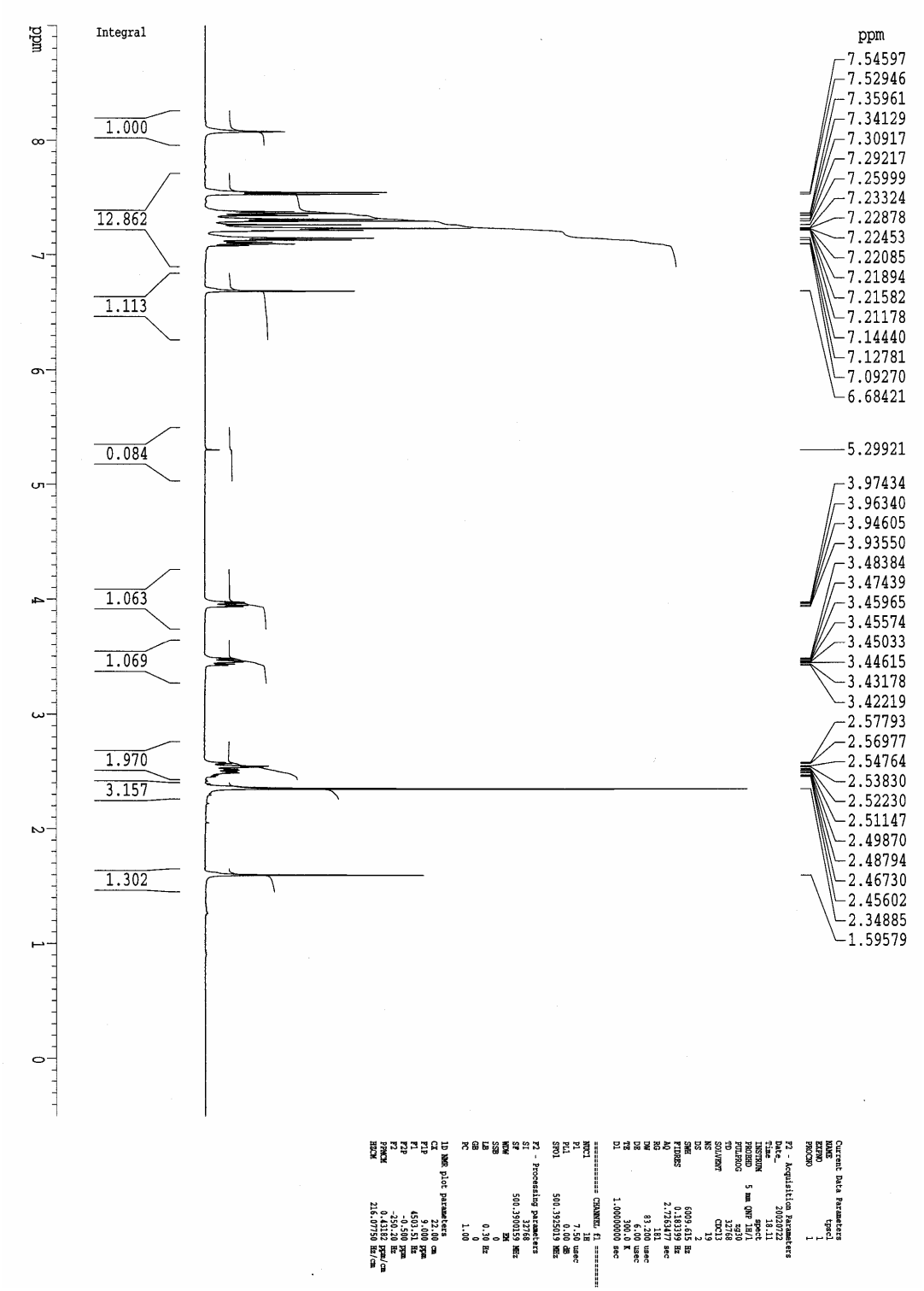
Compound 4j: IR (neat, *v*): 3390, 2972, 2934, 1335 and 1159 cm^{-1}; ^{1}H NMR (500 MHz, major diastereomer, δ): 1.36 (s, 3H), 1.97 (d, 3H, J= 6.8), 2.37 (s, 3H), 2.75-2.62 (m, 2H), 3.35-3.41 (ddd, 1H, *J*= 4.6, 10.4 and 14.0), 4.16 (dd, 1H, *J*= 4.6 and 14.0), 5.51-5.47 (m, 1H), 6.01 (s, 1H), 7.00-7.75 (m, 9H); ^{13}C NMR (125 MHz, major diastereomer, δ): 13.45, 19.27, 21.19, 21.47, 43.01, 51.85, 109.53, 110.85, 118.16, 119.64, 122.10, 124.39, 127.01 (2C), 129.22, 129.48 (2C), 130.81, 135.03, 136.10, 137.74, 143.13; HRMS calcd for $C_{22}H_{25}N_2O_2S$ $(M+H)^+$ 381.1637; found 381.1634.



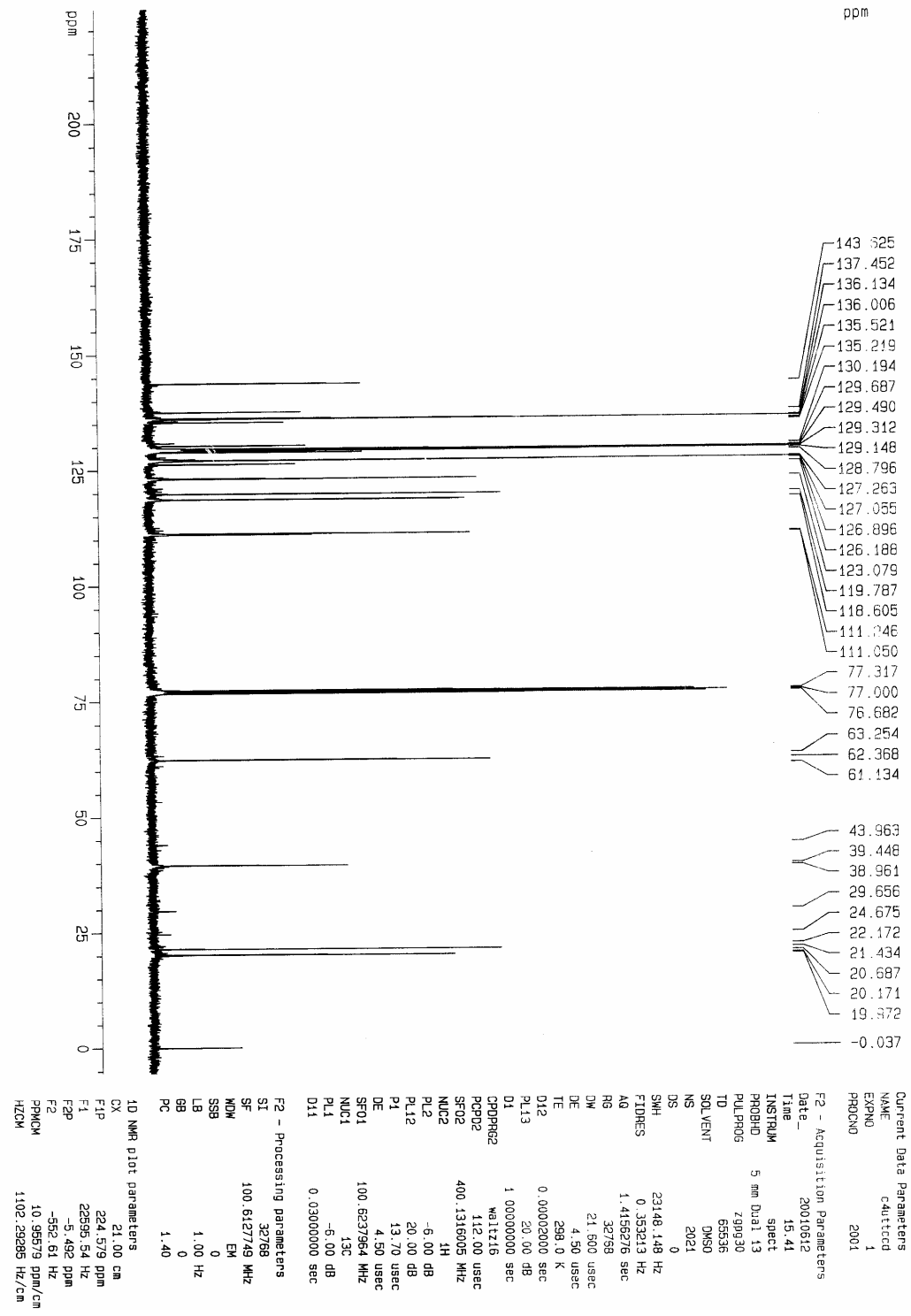
^{1}H NMR spectrum of Compound **3a**.



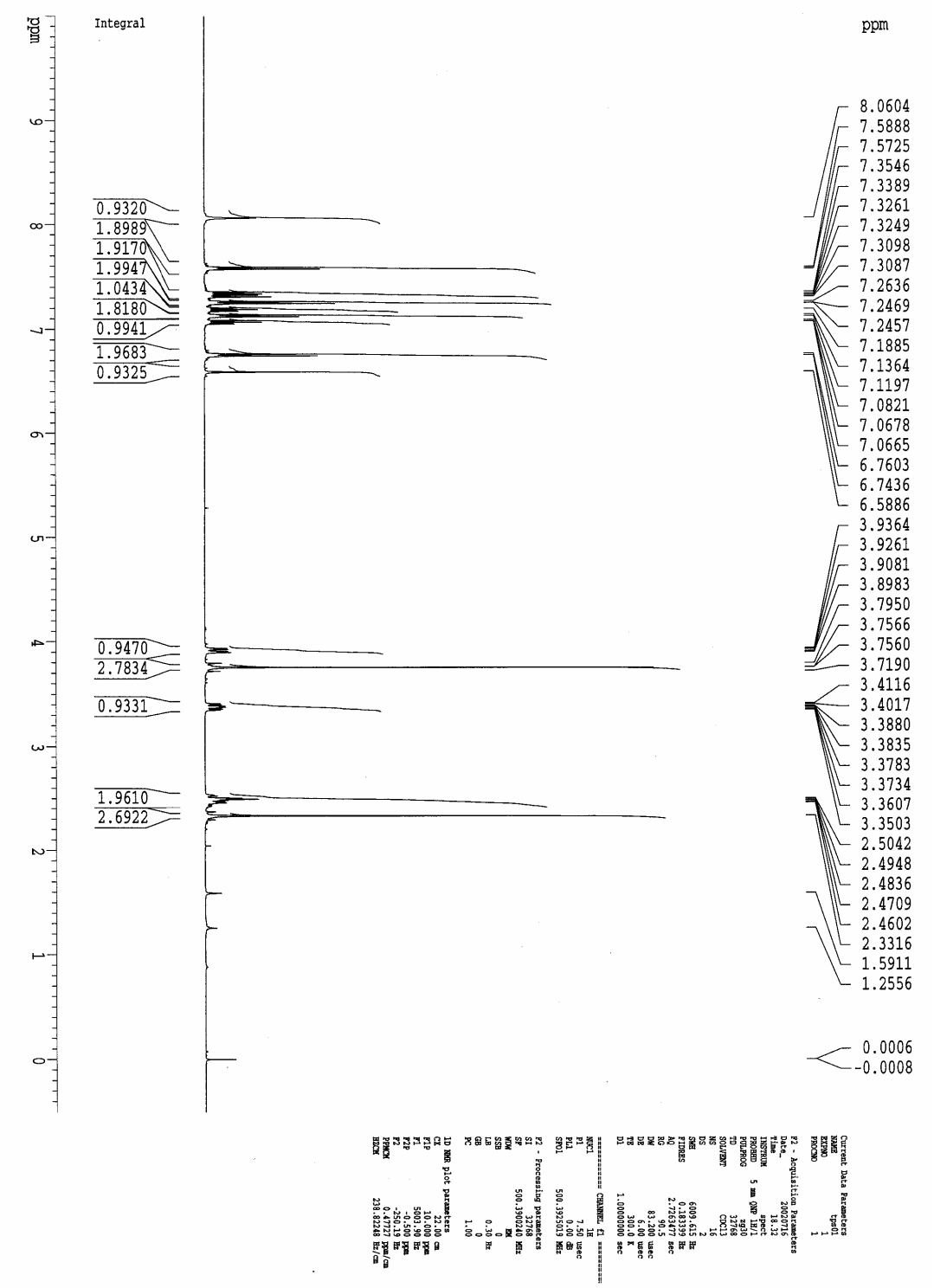
^{13}C NMR spectrum of Compound **3a**.



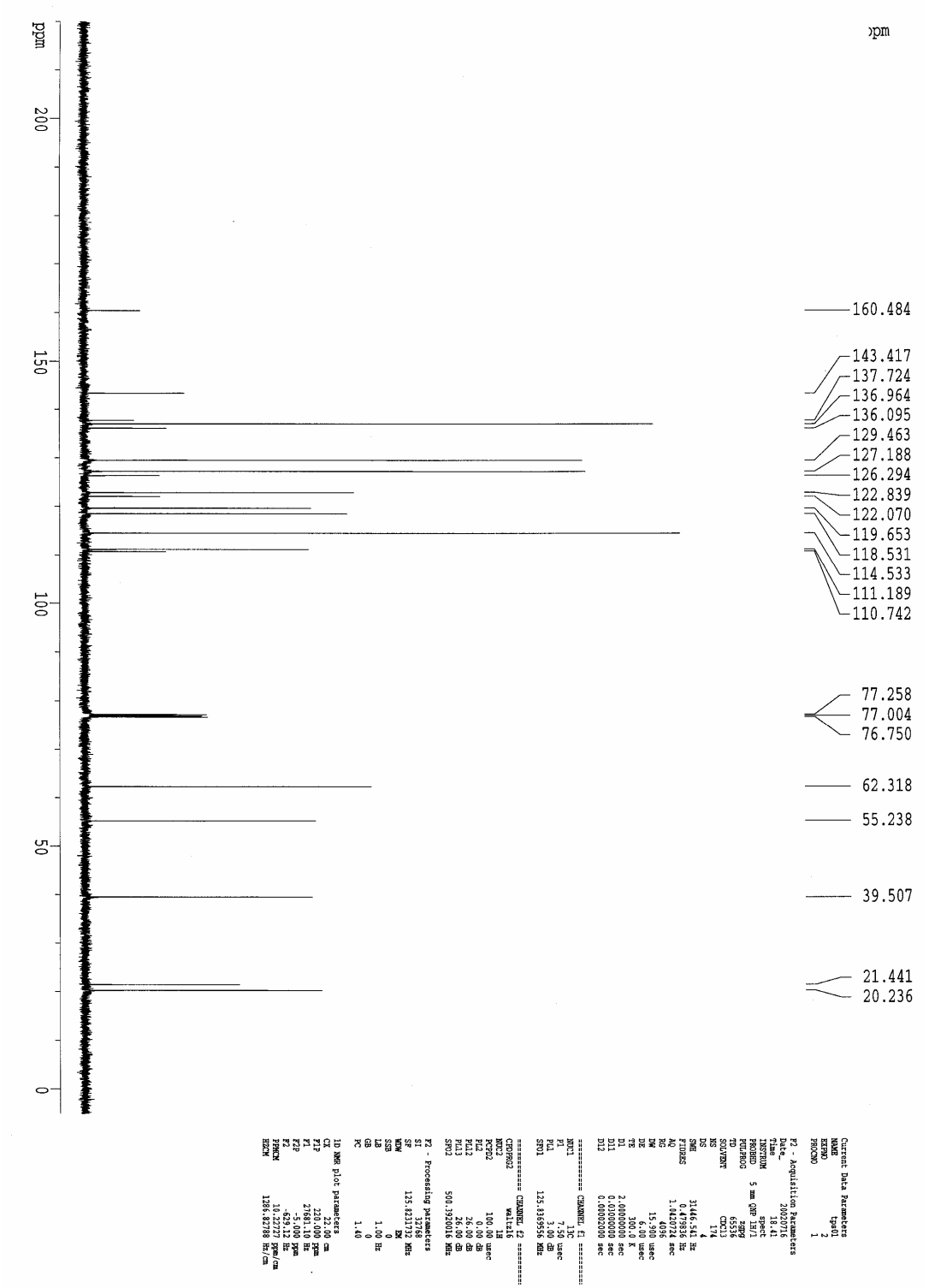
^{1}H NMR spectrum of compound **3b**.



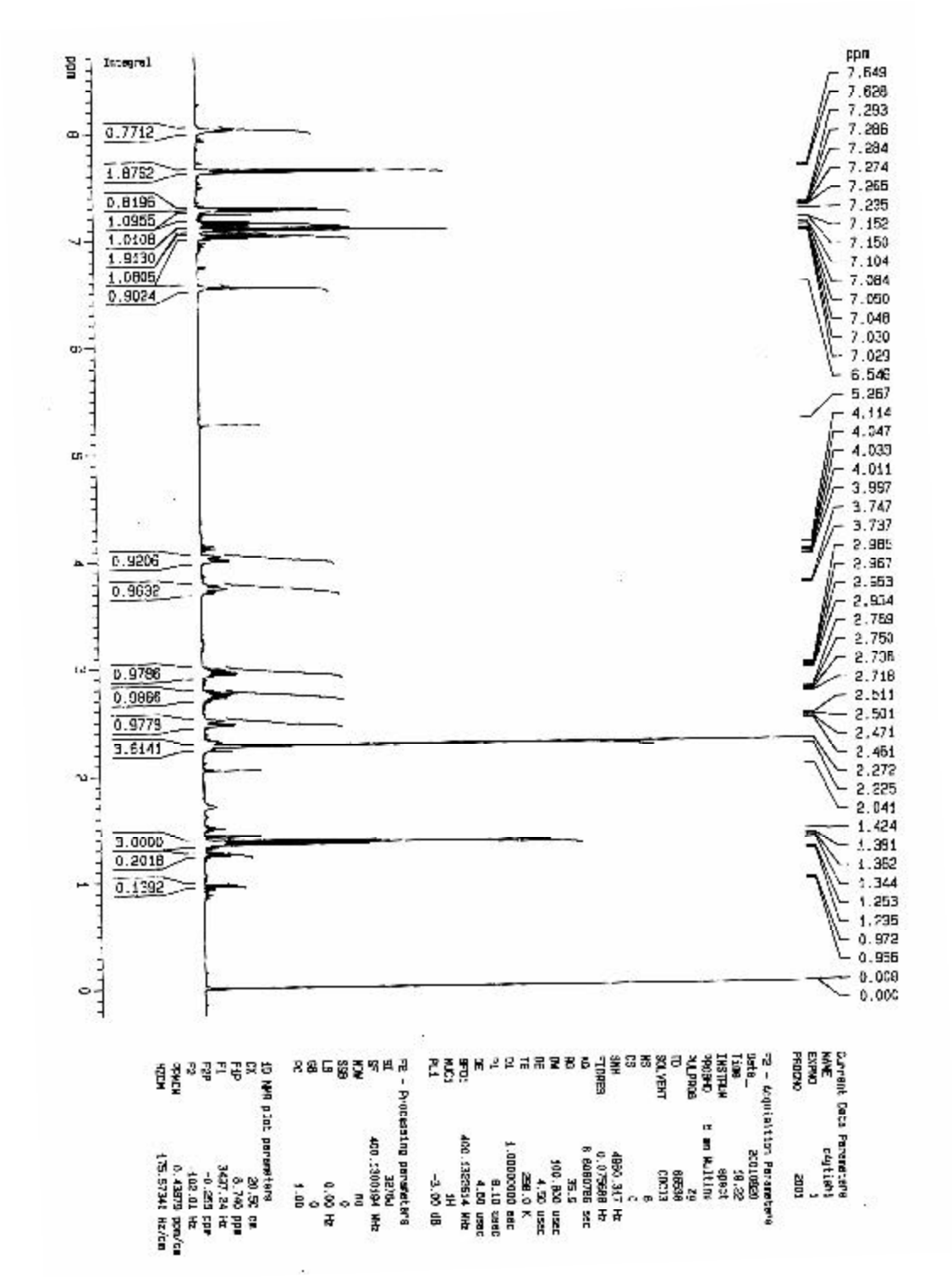
^{13}C NMR spectrum of Compound **3b**.



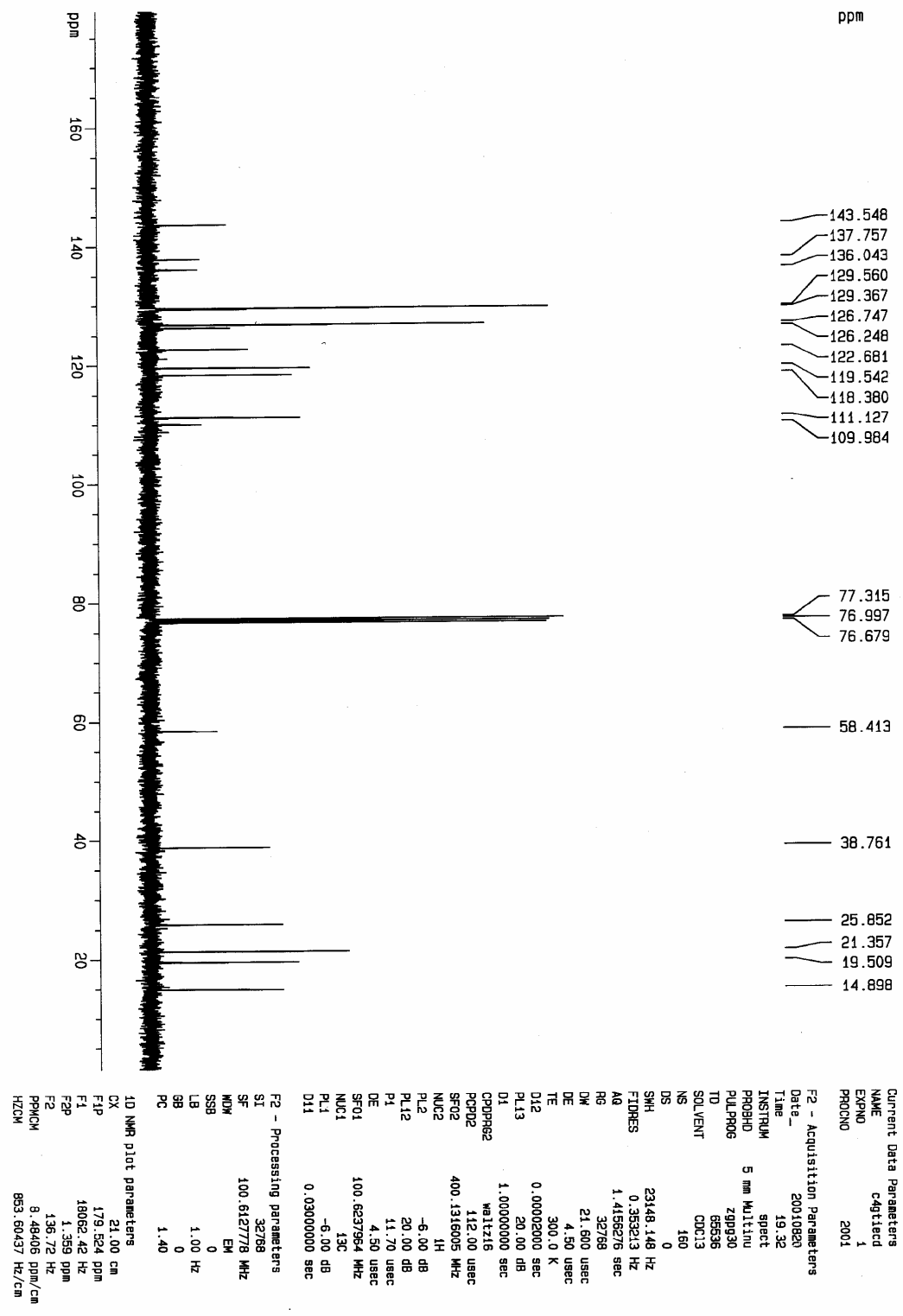
^{1}H NMR spectrum of compound **3c**.



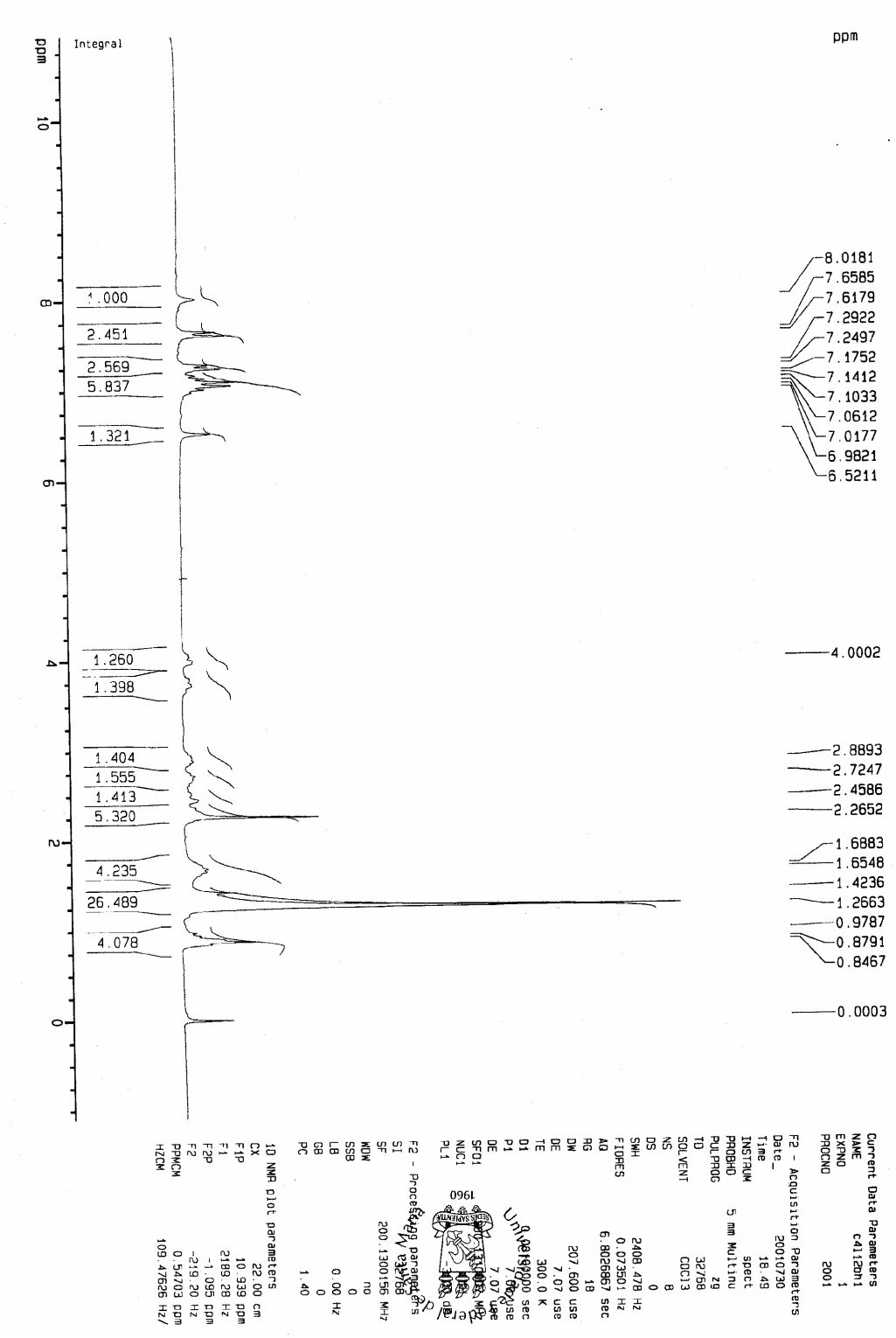
^{13}C NMR spectrum of Compound **3c**.



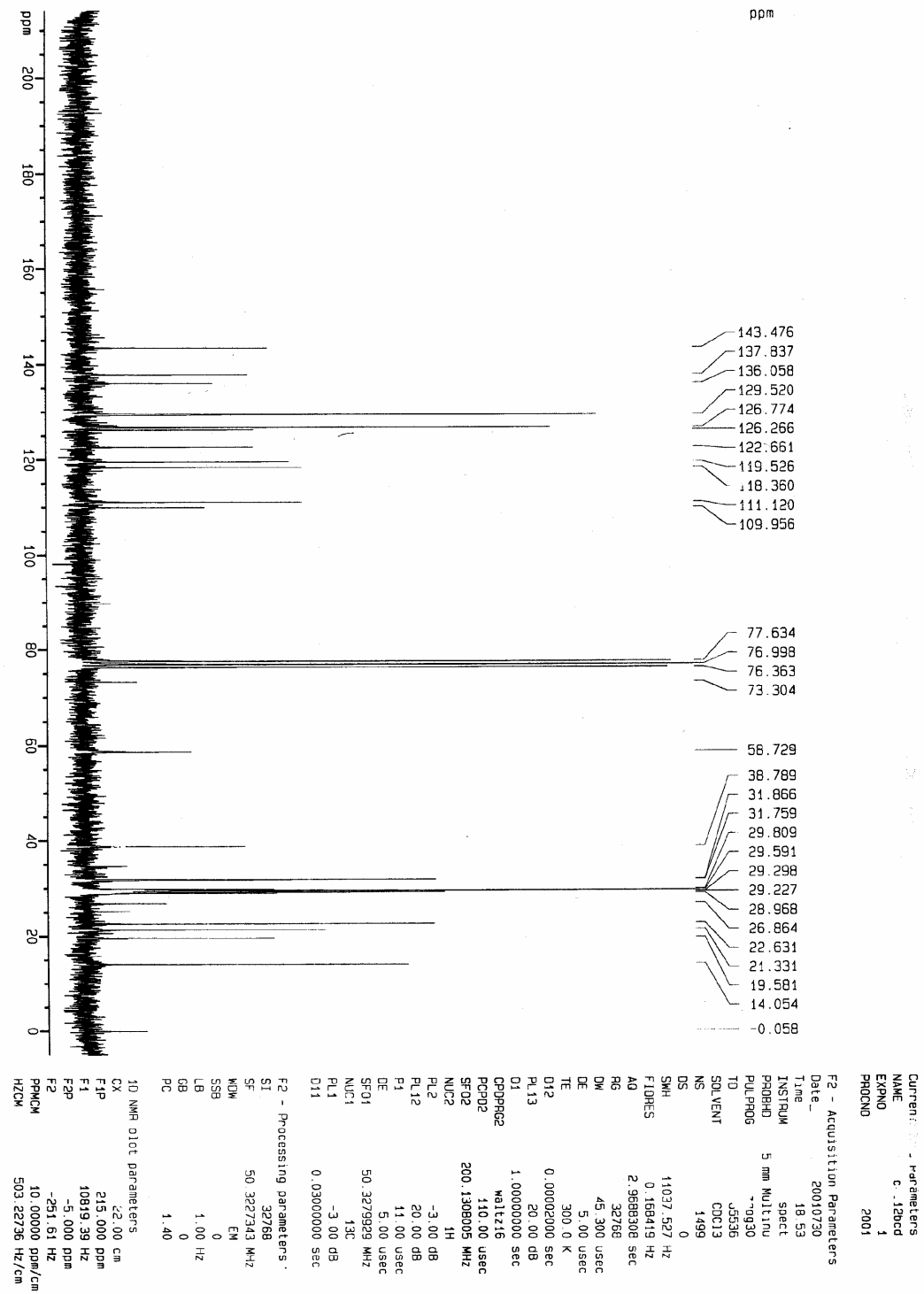
^{1}H NMR spectrum of Compound **3d**.



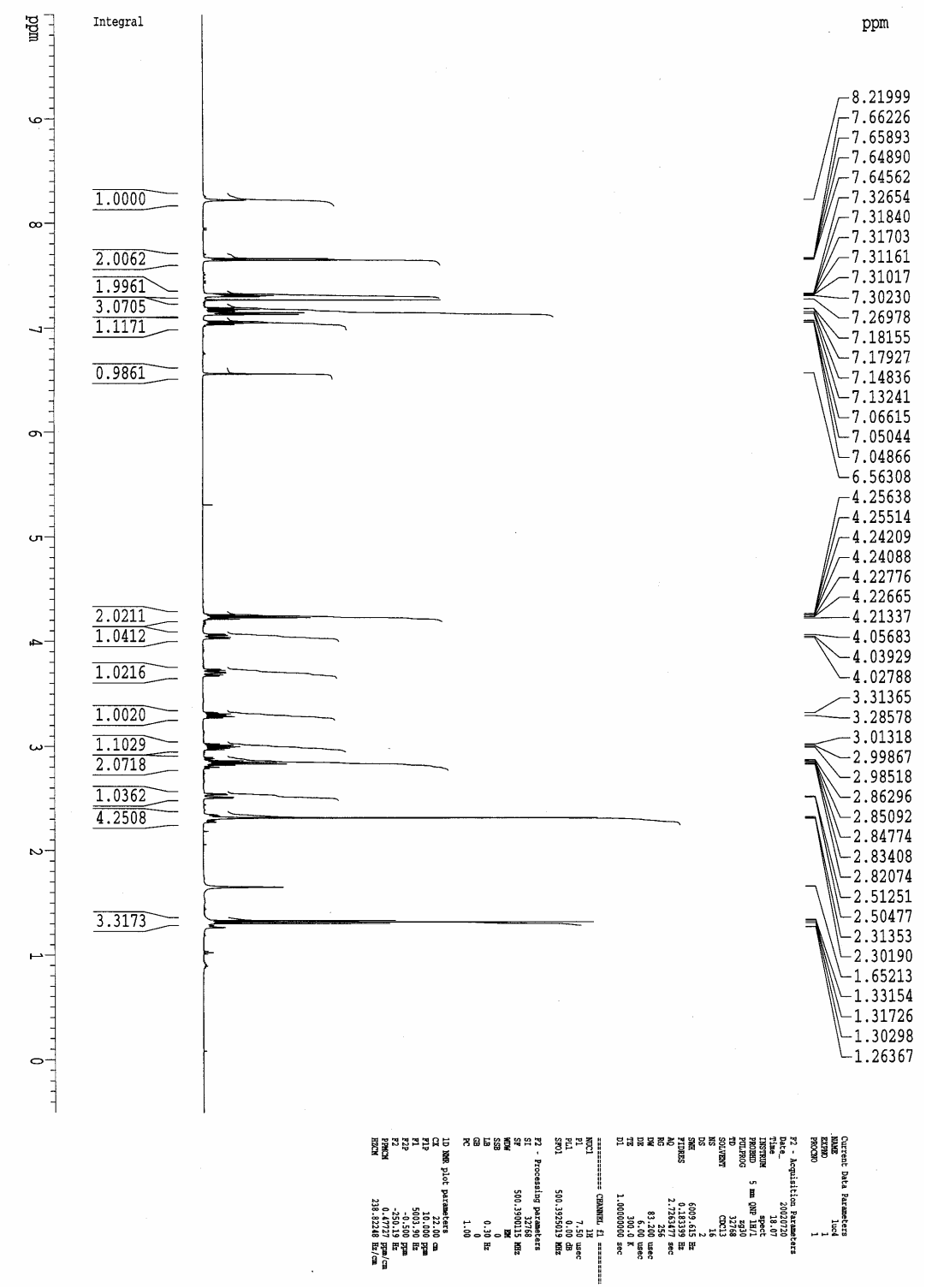
^{13}C NMR spectrum of Compound **3d**.



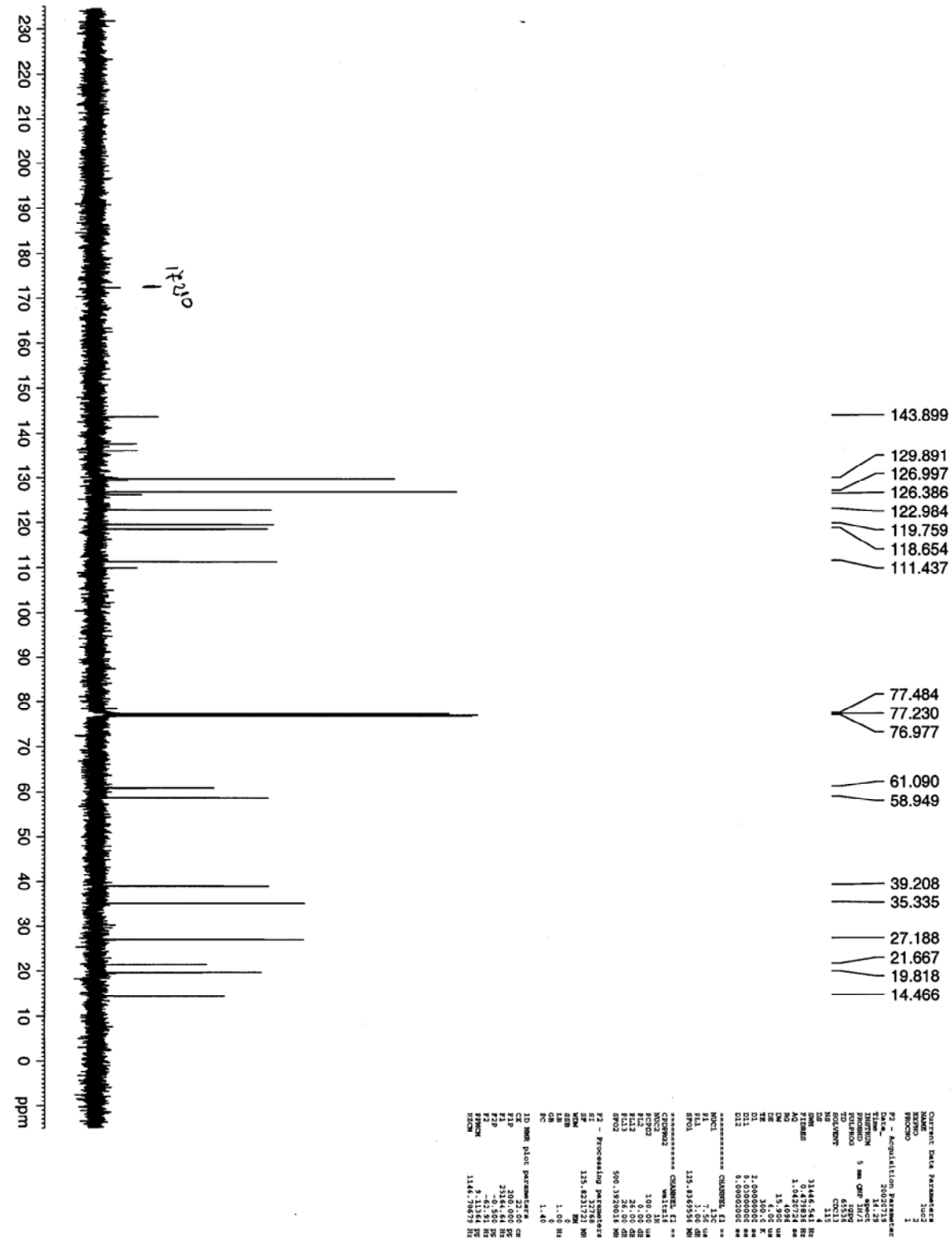
^{1}H NMR spectrum of Compound **3e**.



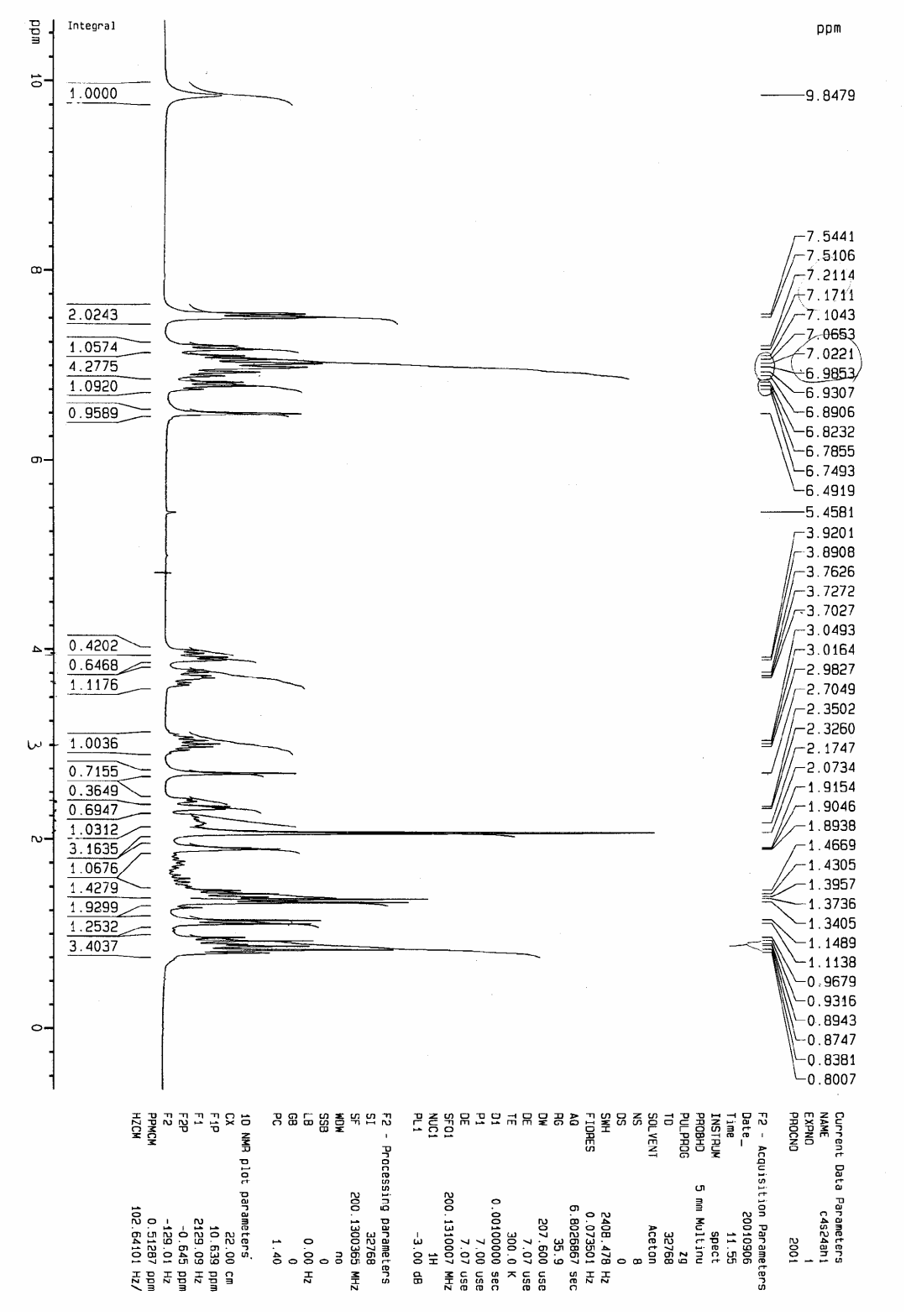
^{13}C NMR spectrum of Compound **3e** .



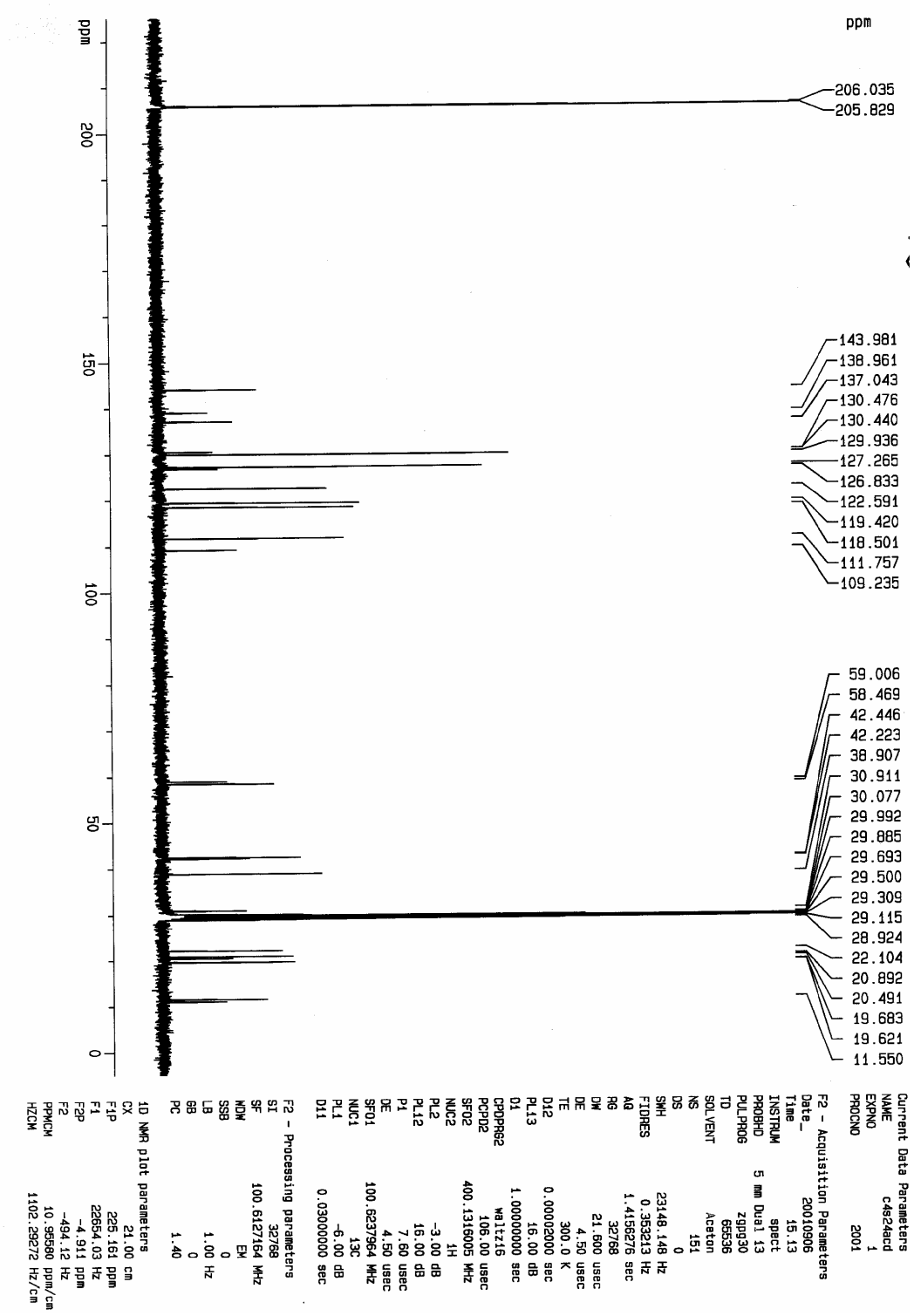
^{1}H NMR spectrum of Compound **3f**.



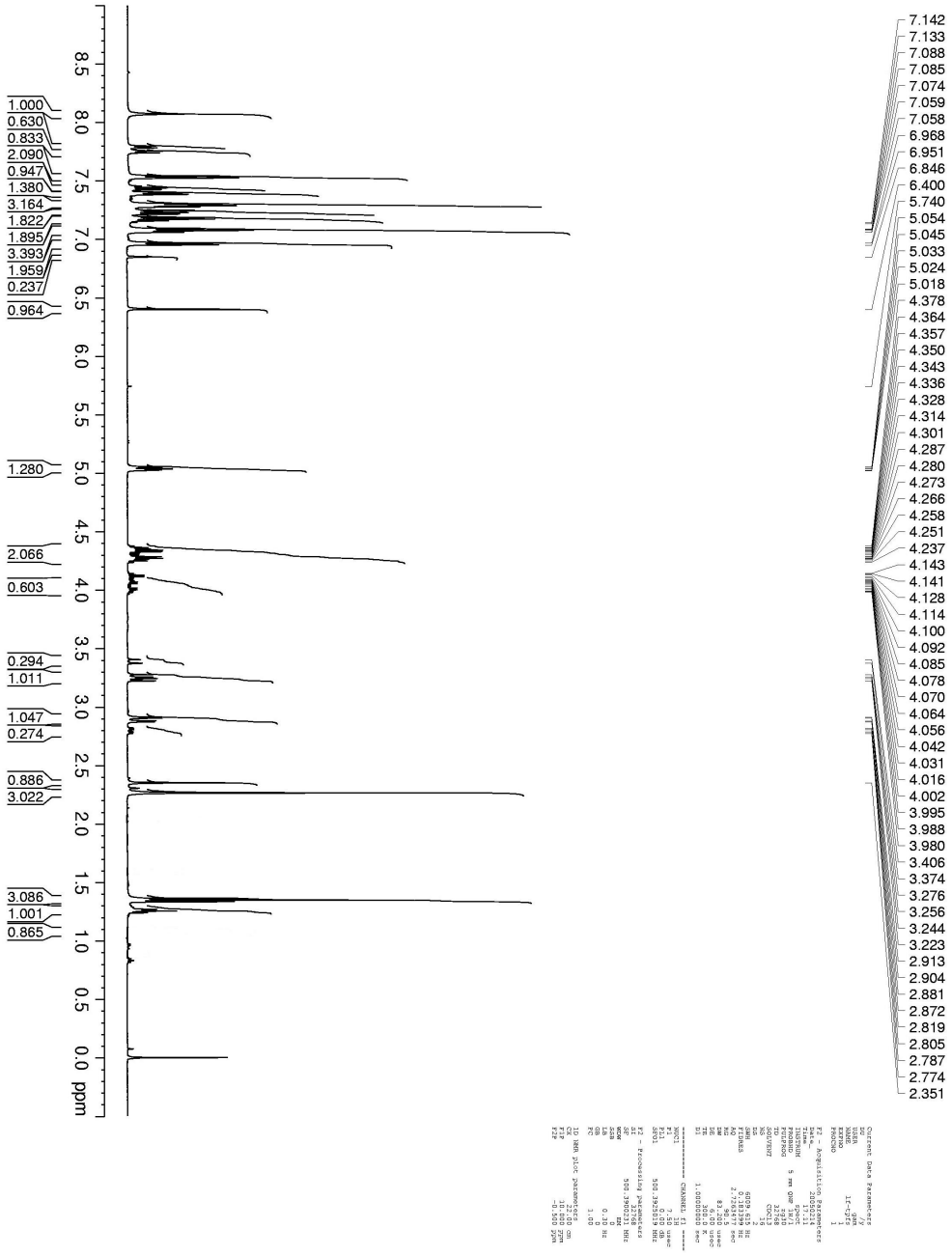
^{13}C NMR spectrum of Compound 3**f.**



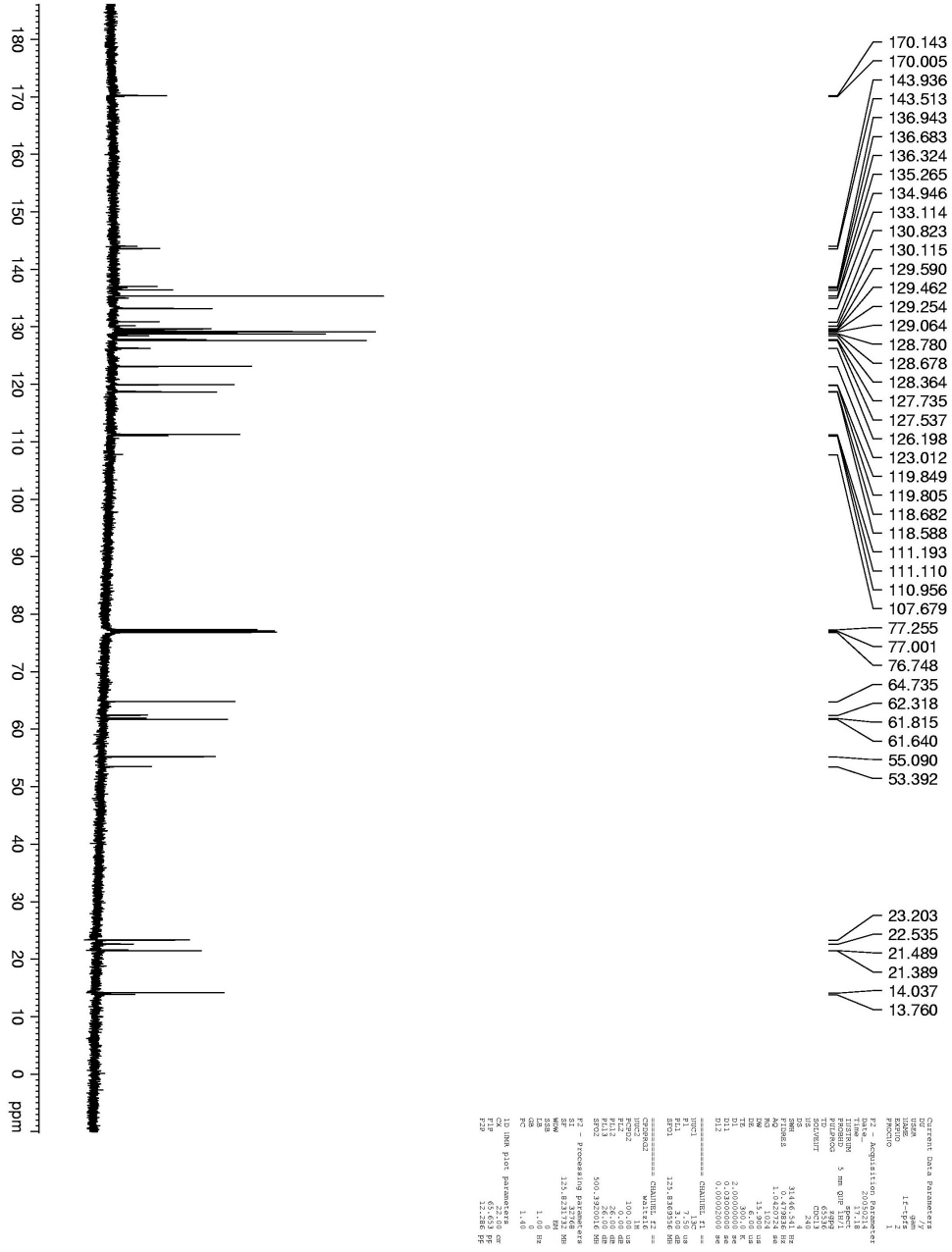
^{1}H NMR spectrum of Compound **3g**.



^{13}C NMR spectrum of Compound **3g**.



^{1}H NMR Spectrum of Compound **3i.**



^{13}C NMR Spectrum of Compound **3 i**

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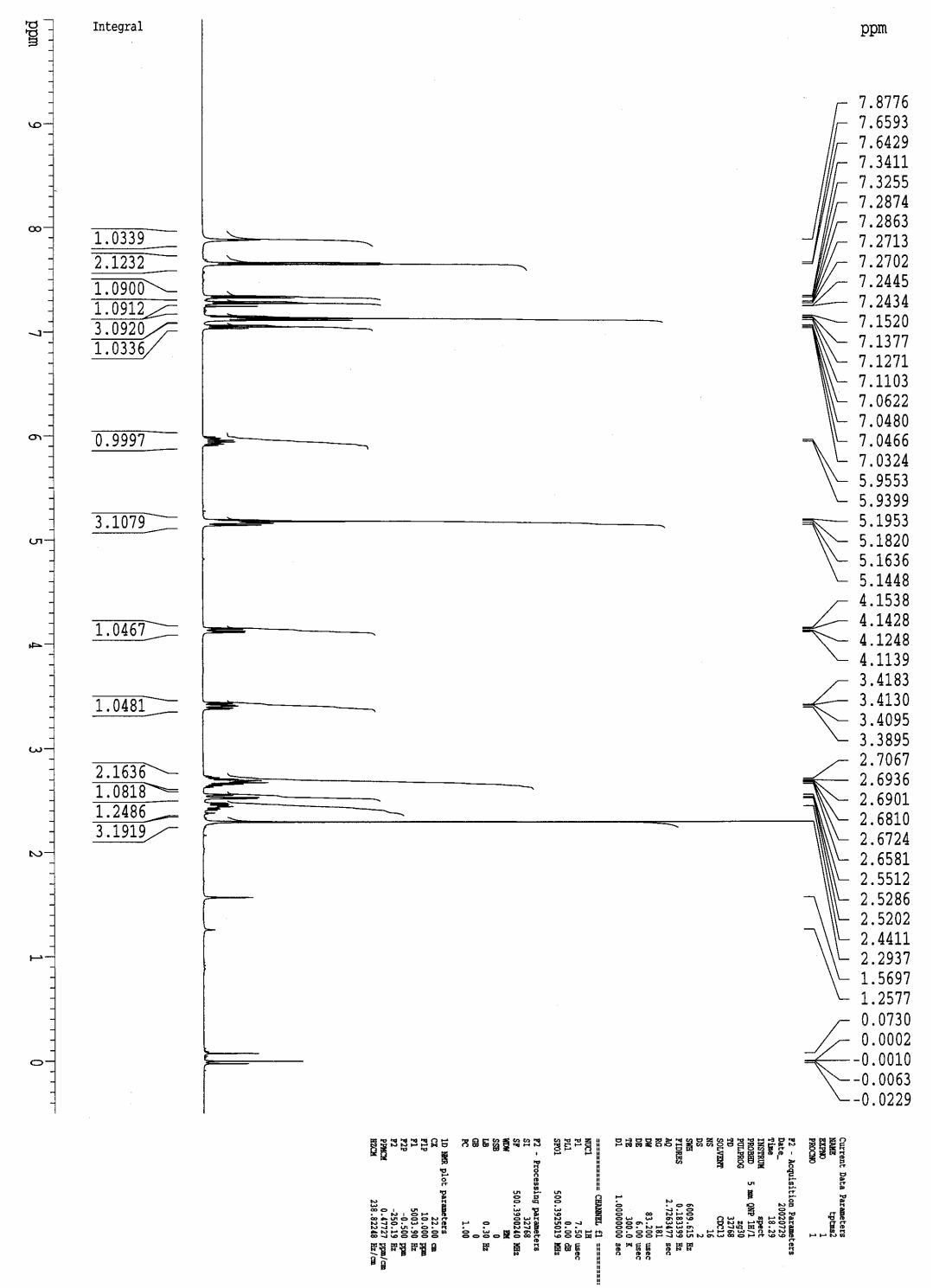
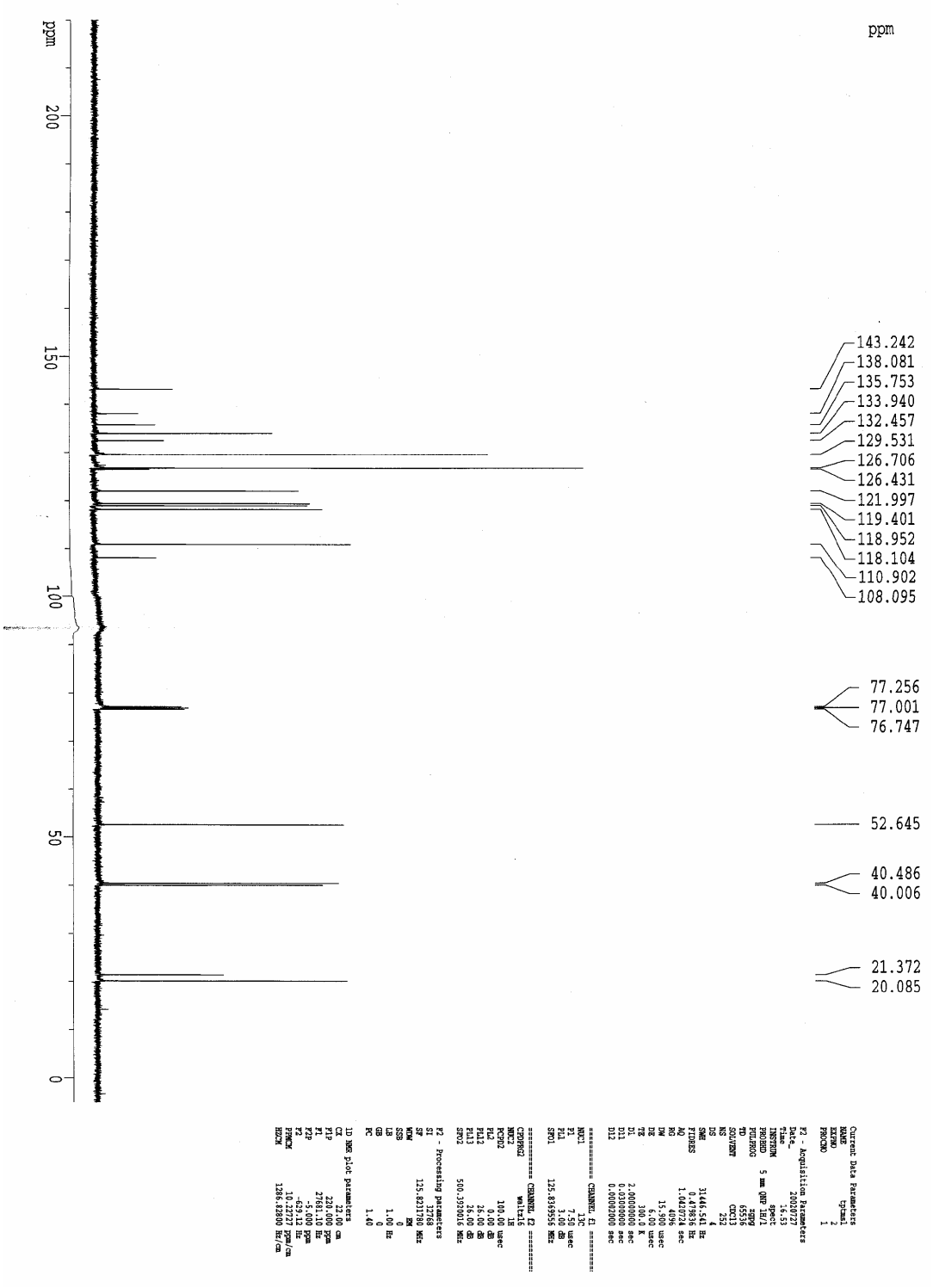
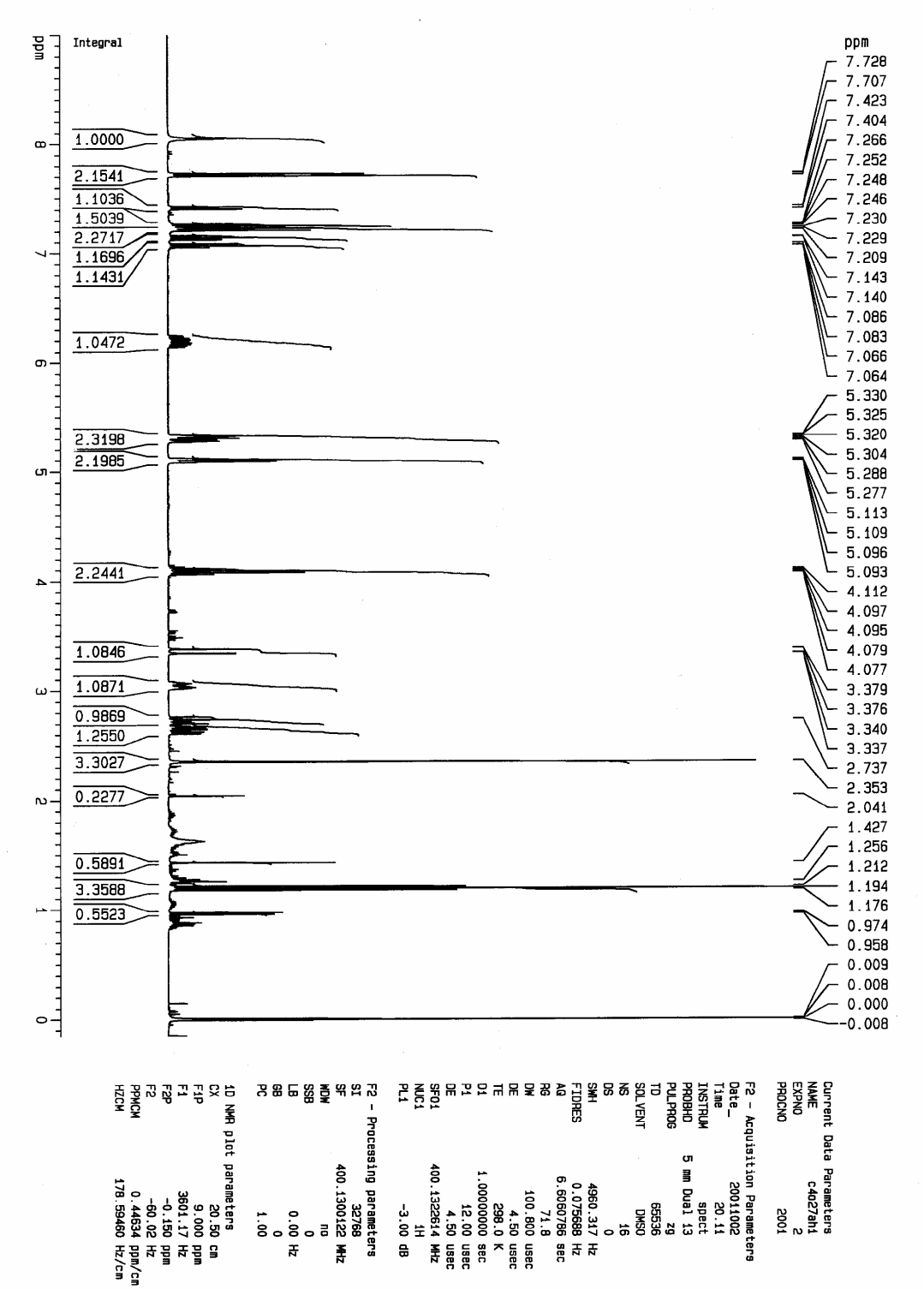


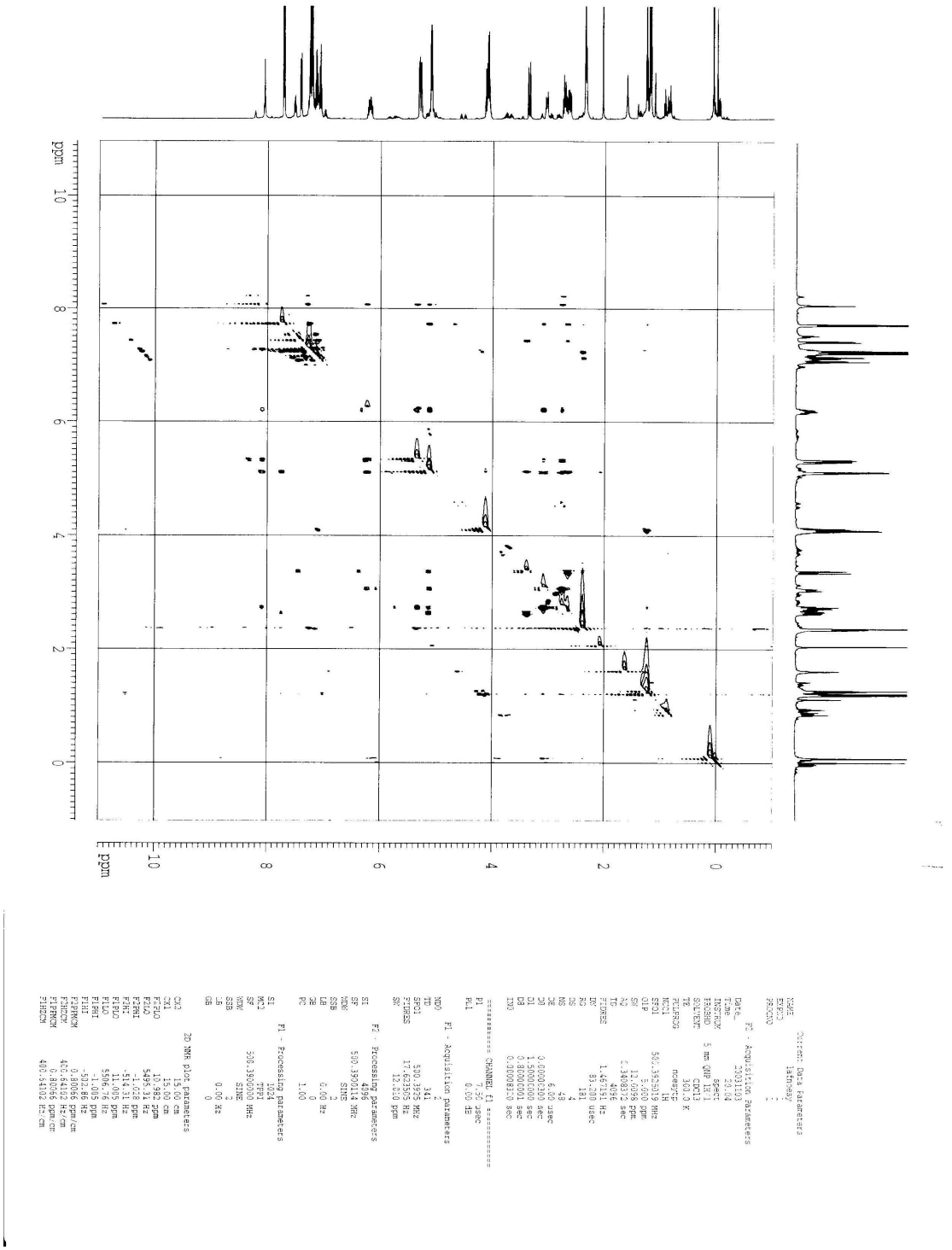
^{1}H NMR spectrum of Compound **4a**.



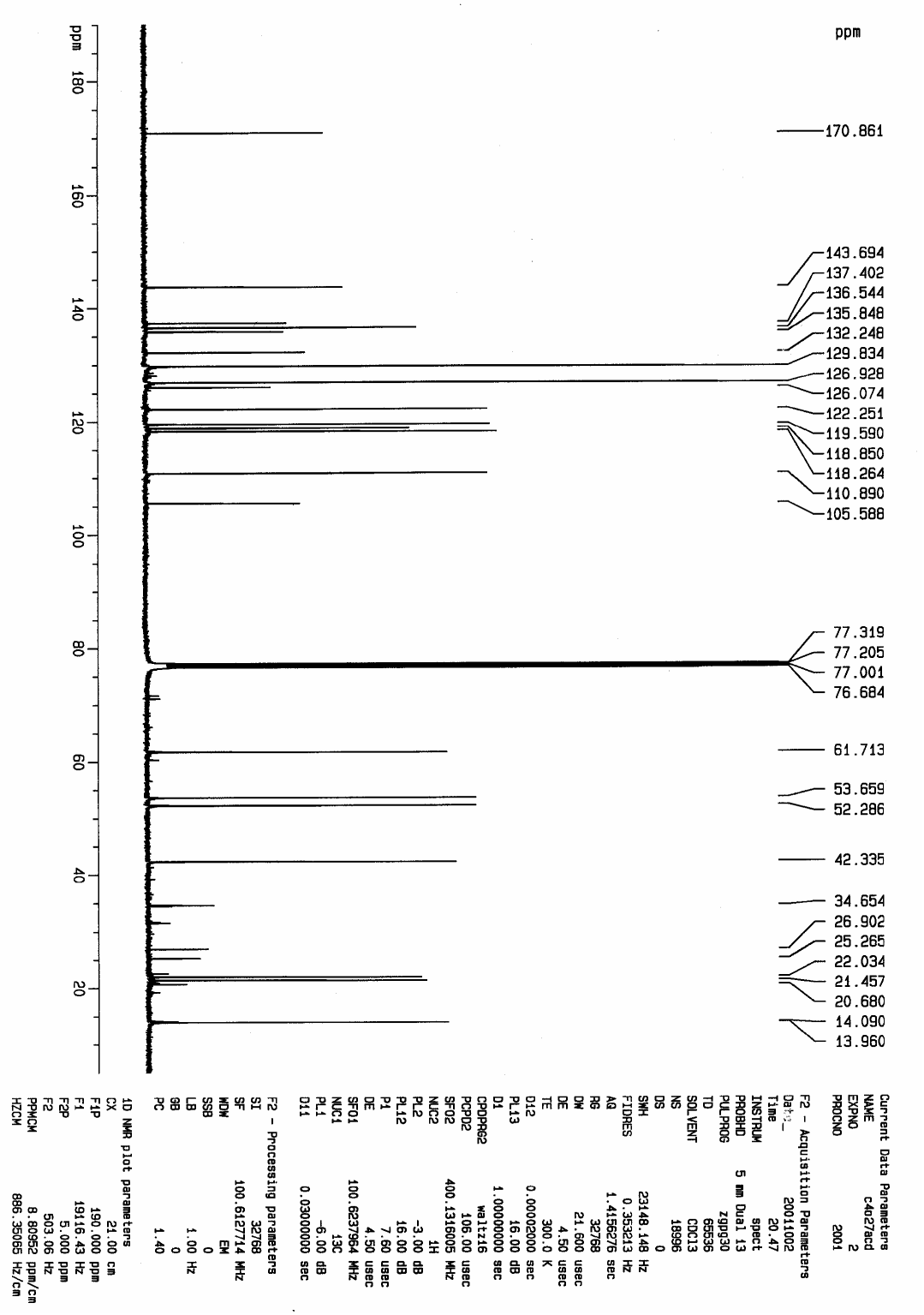
^{13}C NMR spectrum of Compound **4a**.



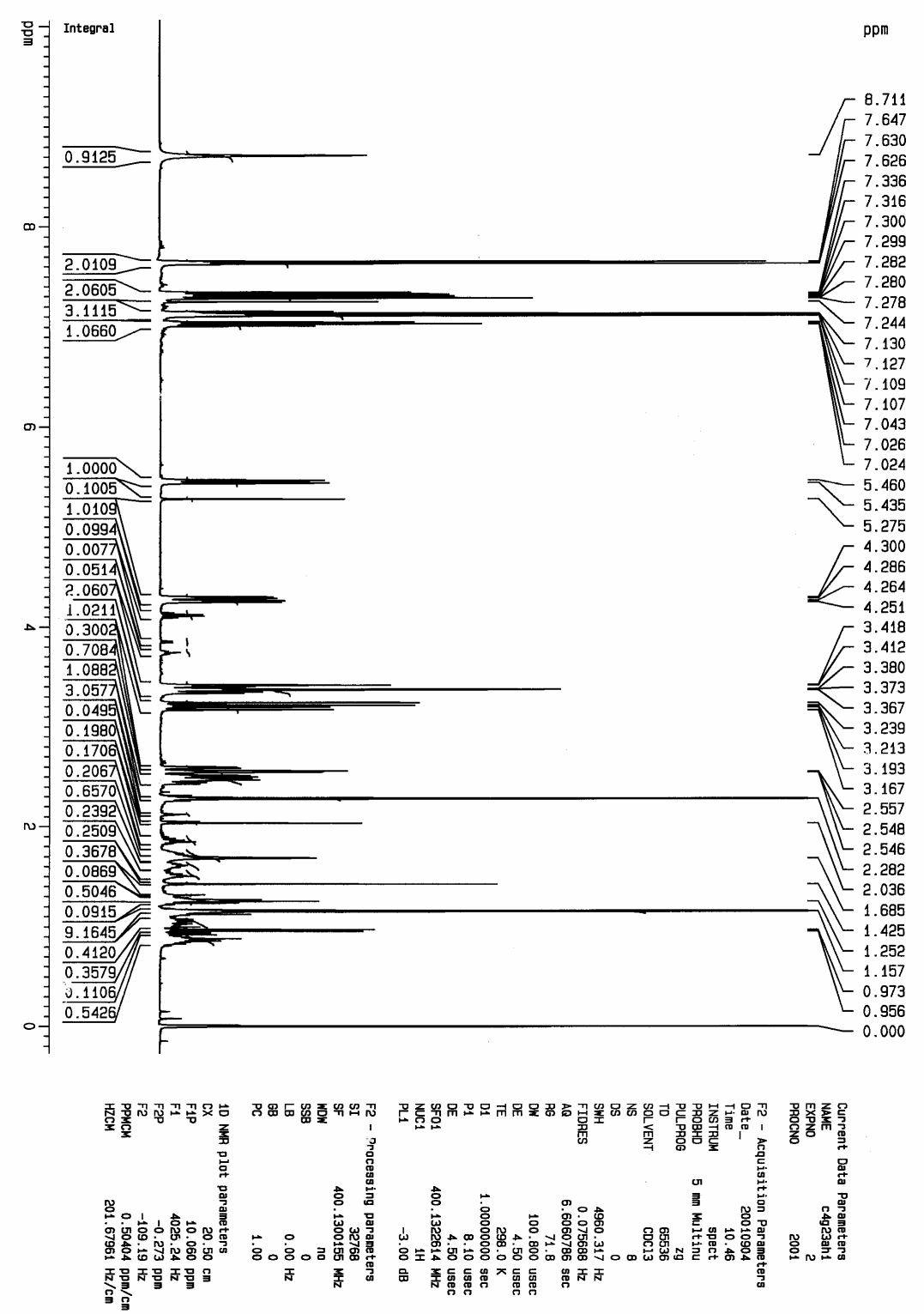
^{1}H NMR spectrum of Compound **4b**.



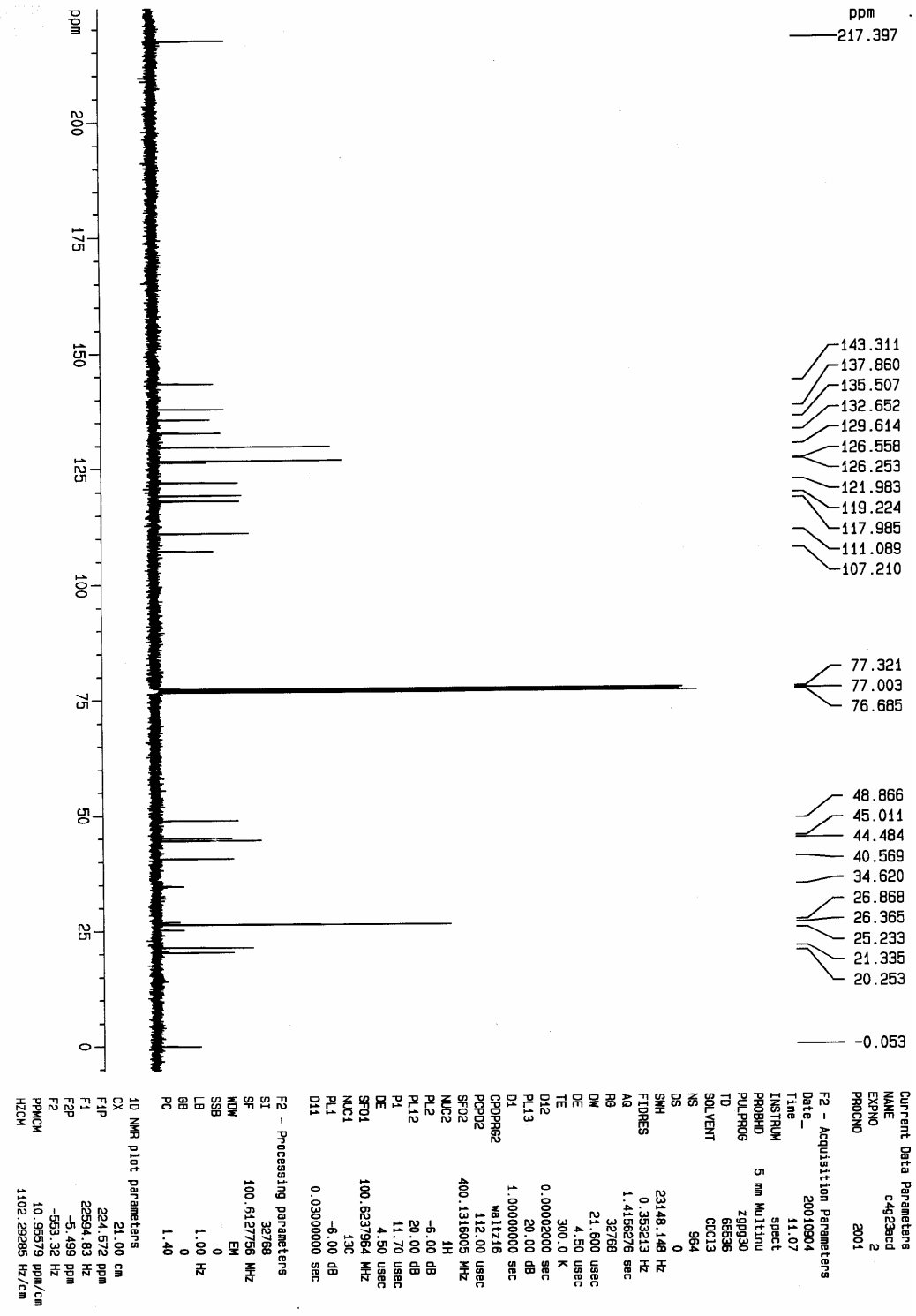
NOESY of Compound **4b.**



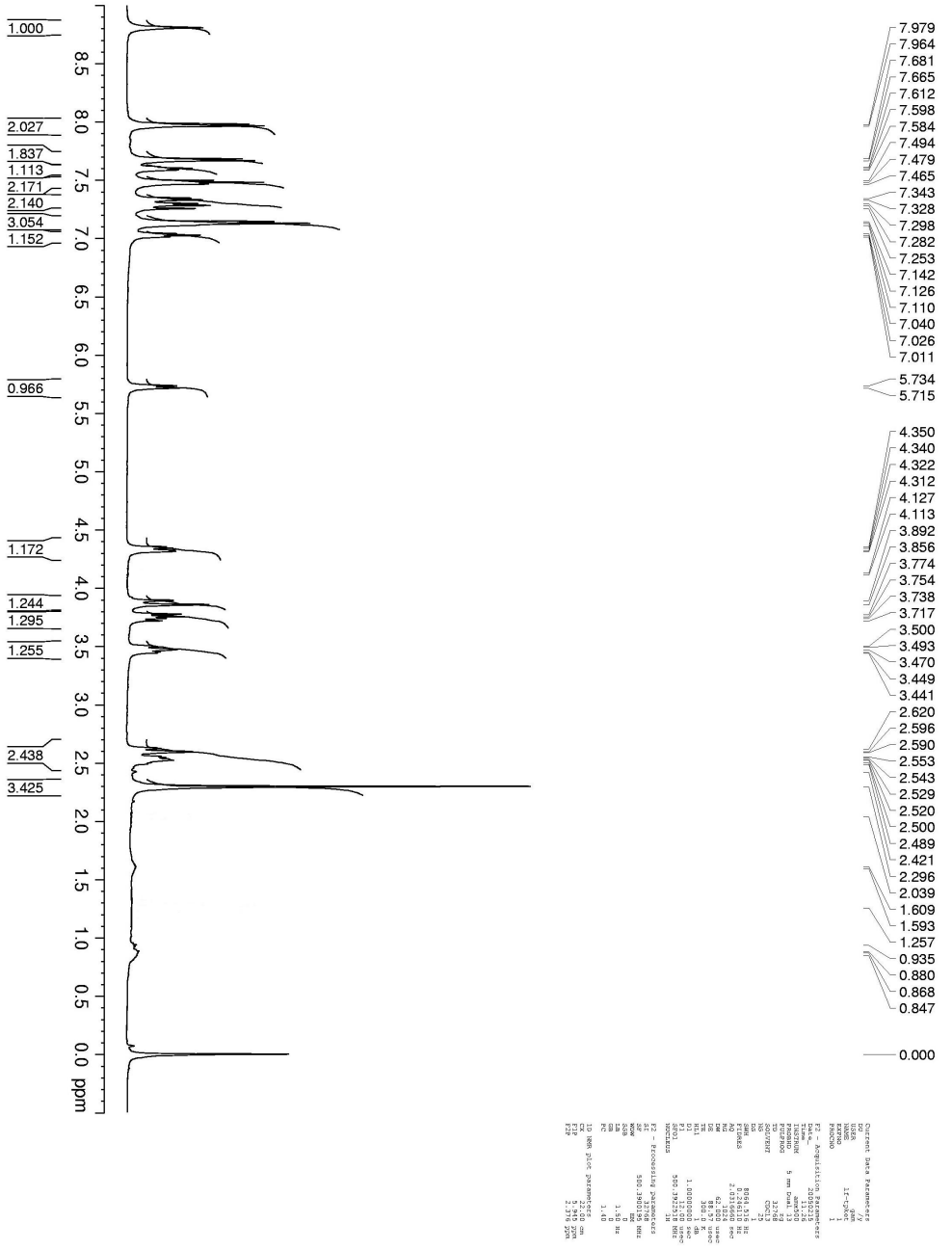
^{13}C NMR spectrum of Compound **4b**.



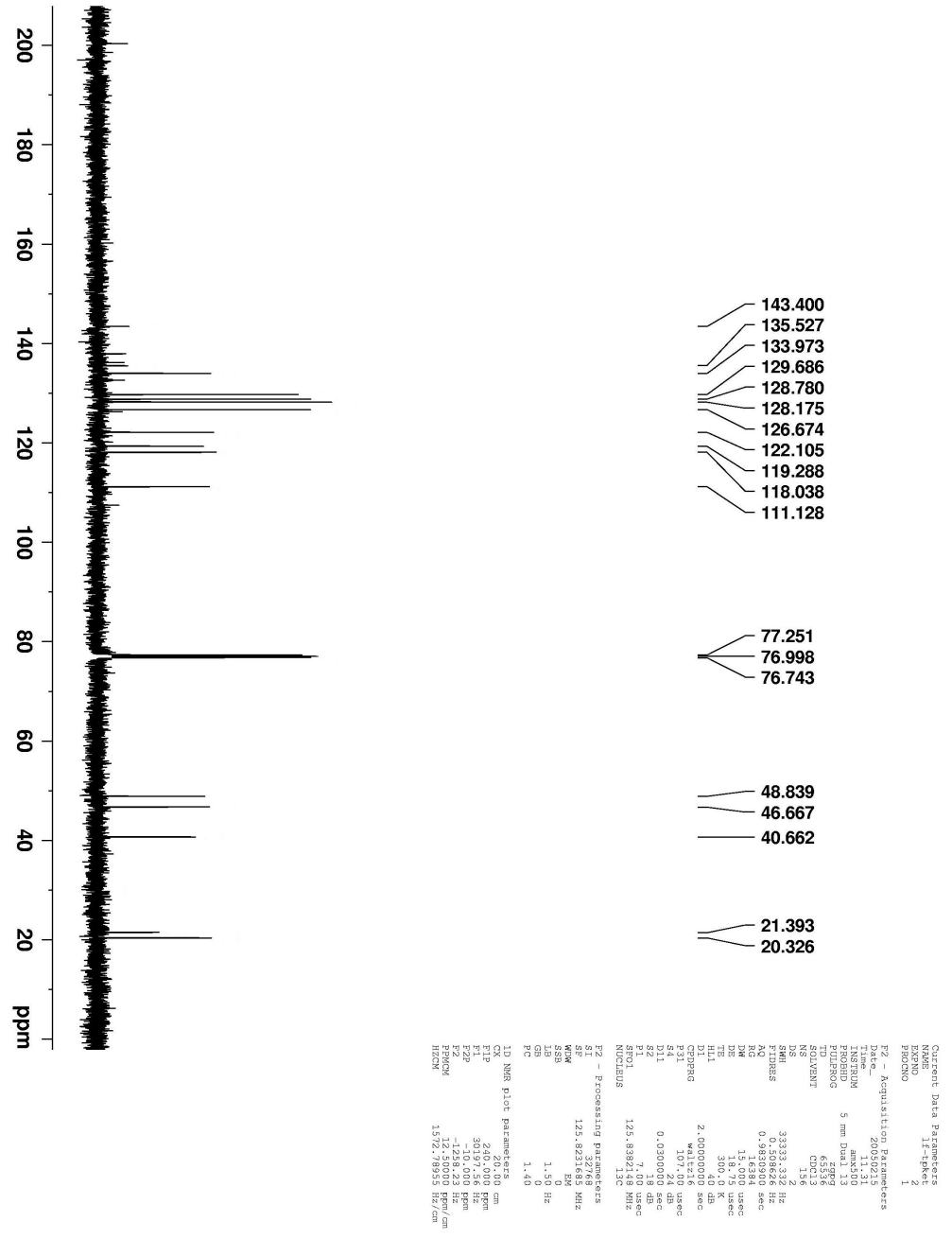
^{1}H NMR spectrum of Compound **4c**.



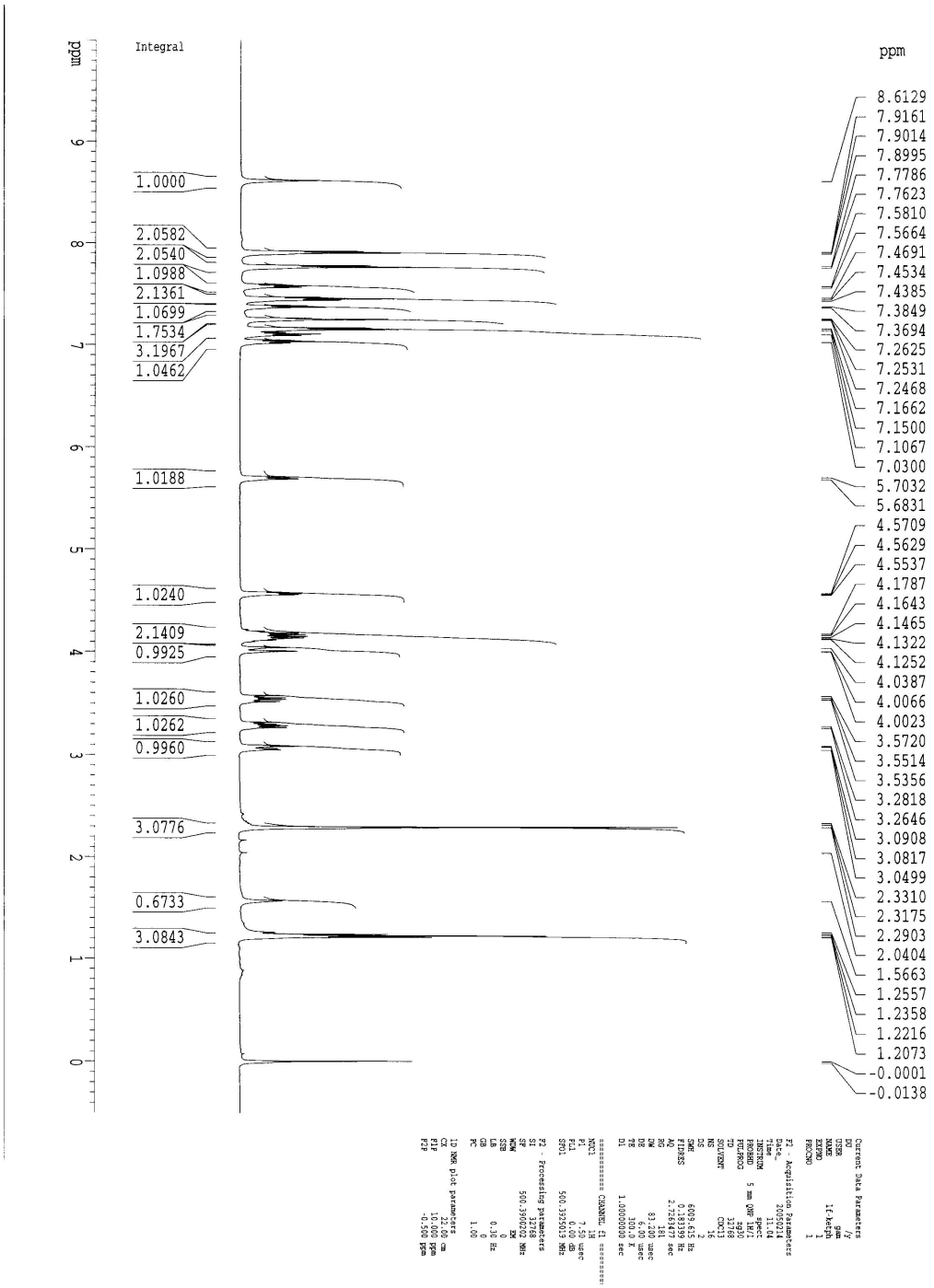
^{13}C NMR spectrum of Compound **4c**.



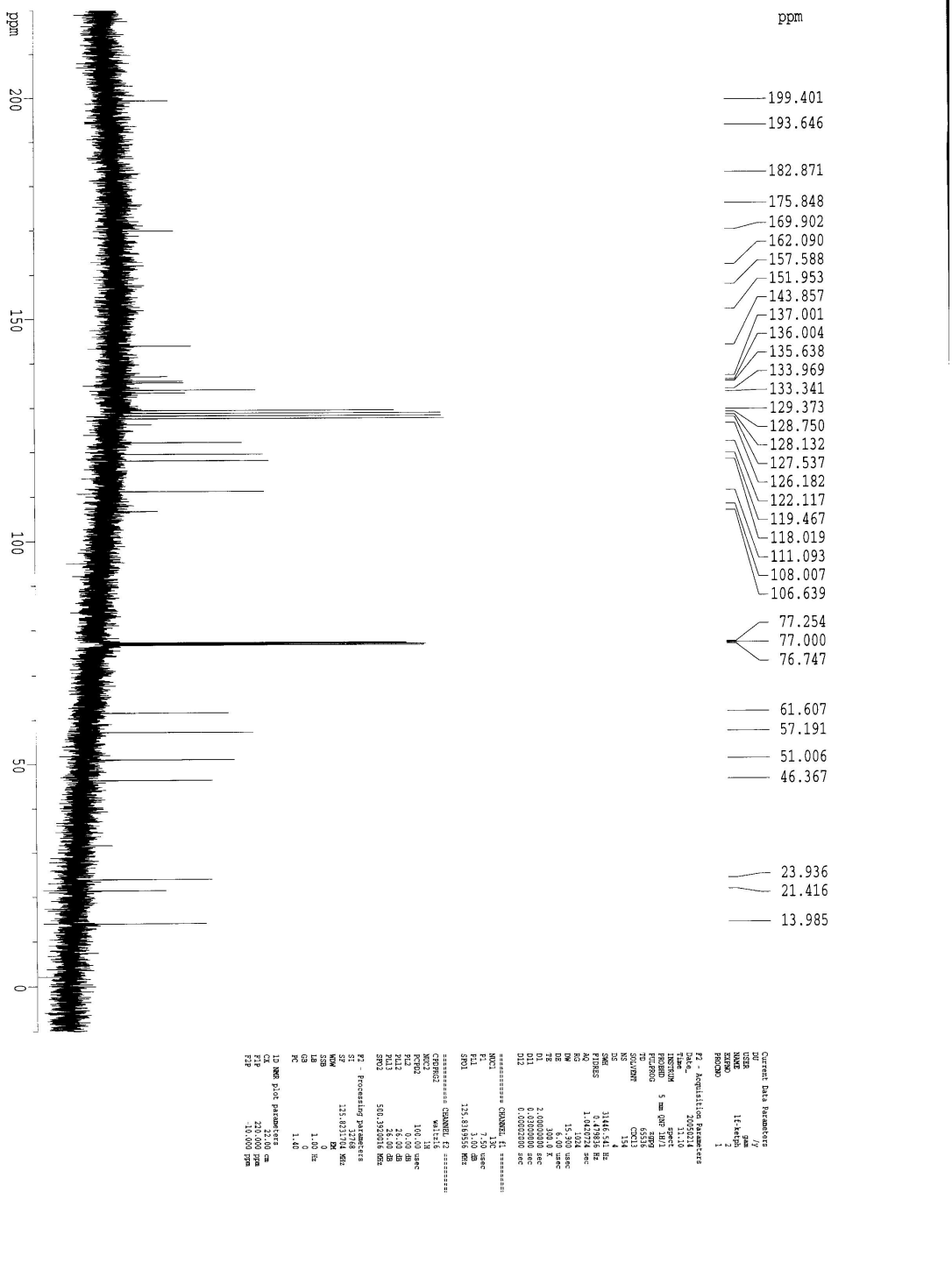
^{1}H NMR spectrum of Compound **4d**.



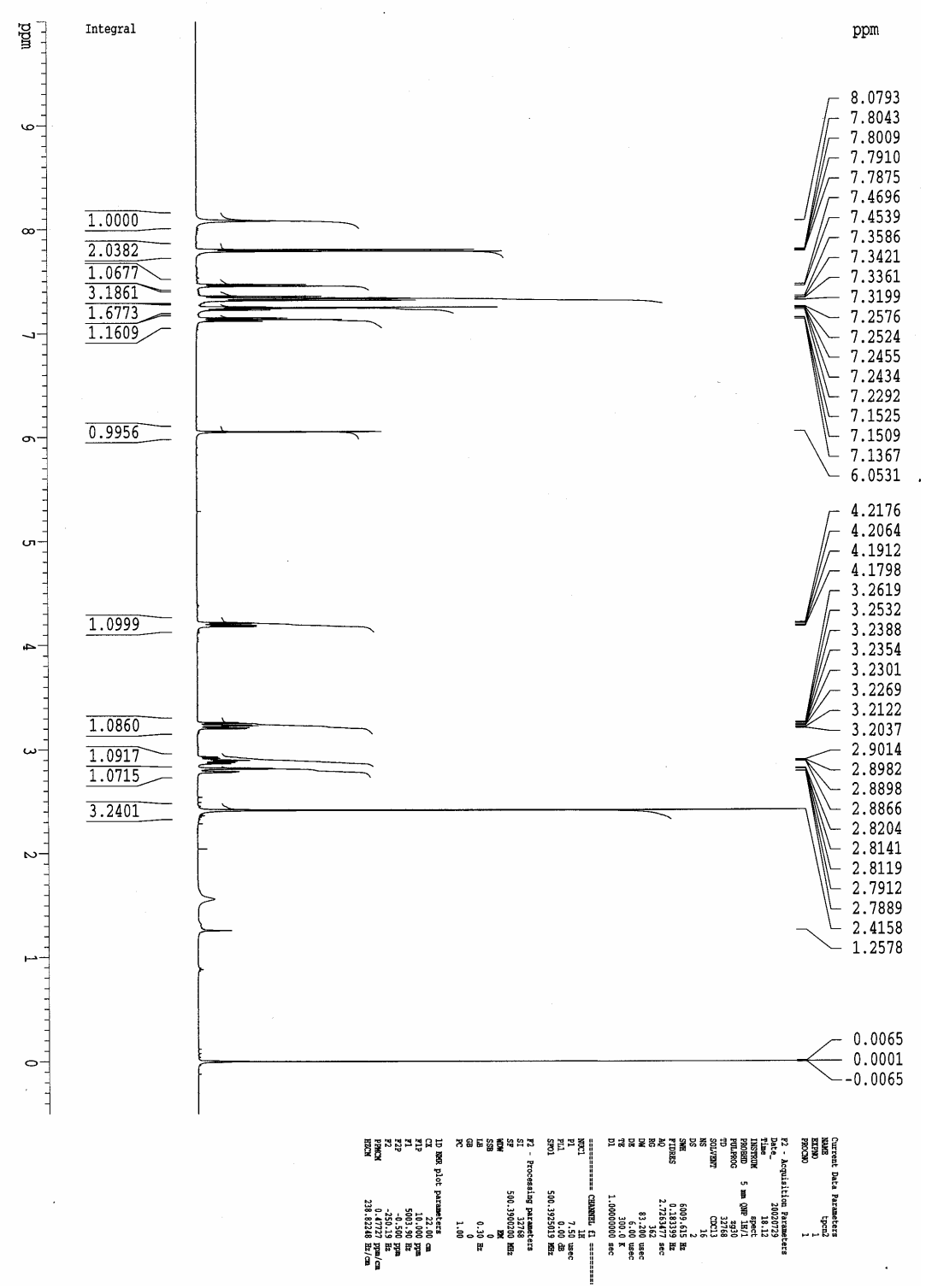
^{13}C NMR Spectrum of Compound **4d**.



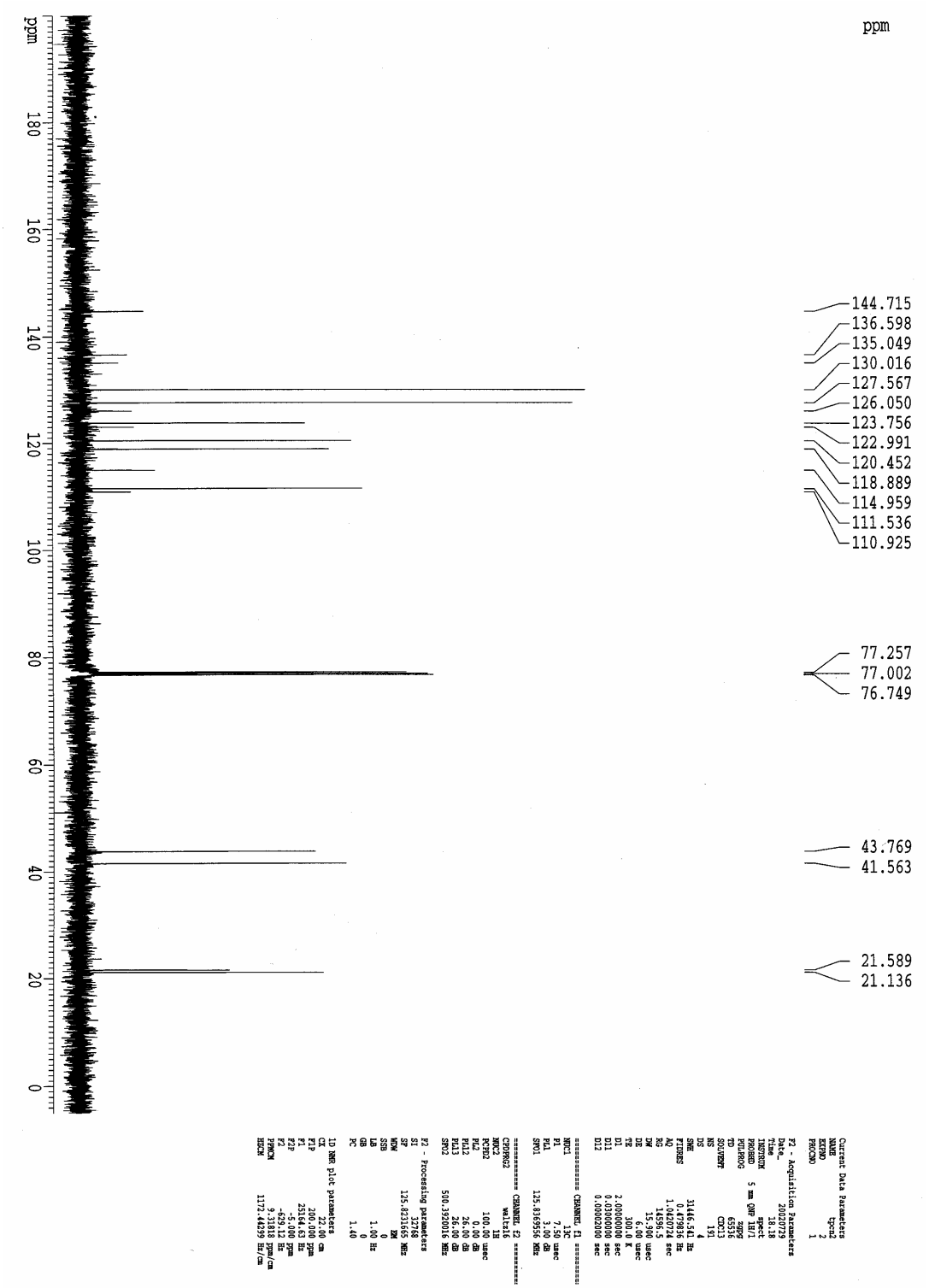
^{1}H NMR Spectrum of Compound **4e**.



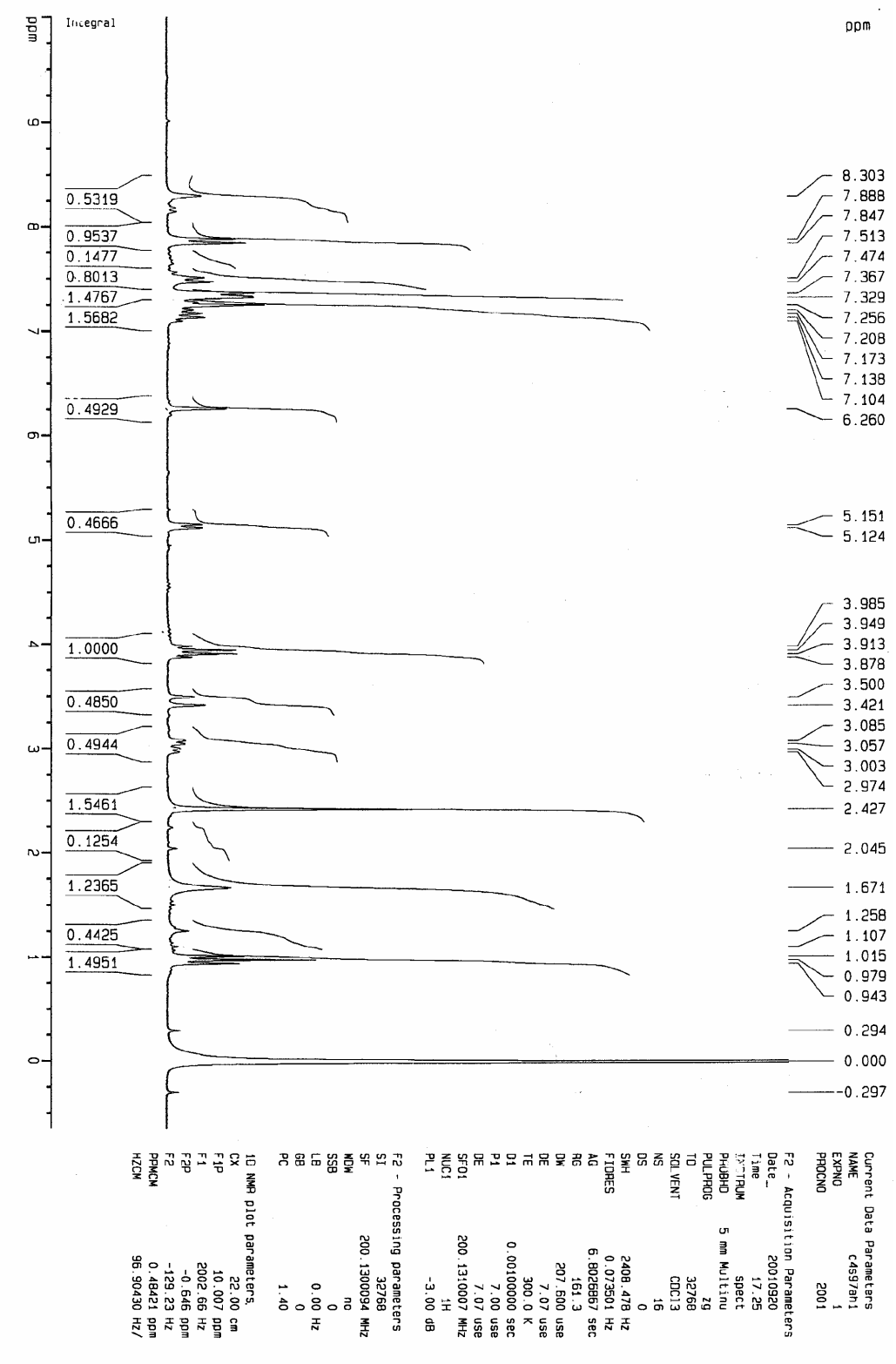
^{13}C NMR Spectrum of Compound **4e.**



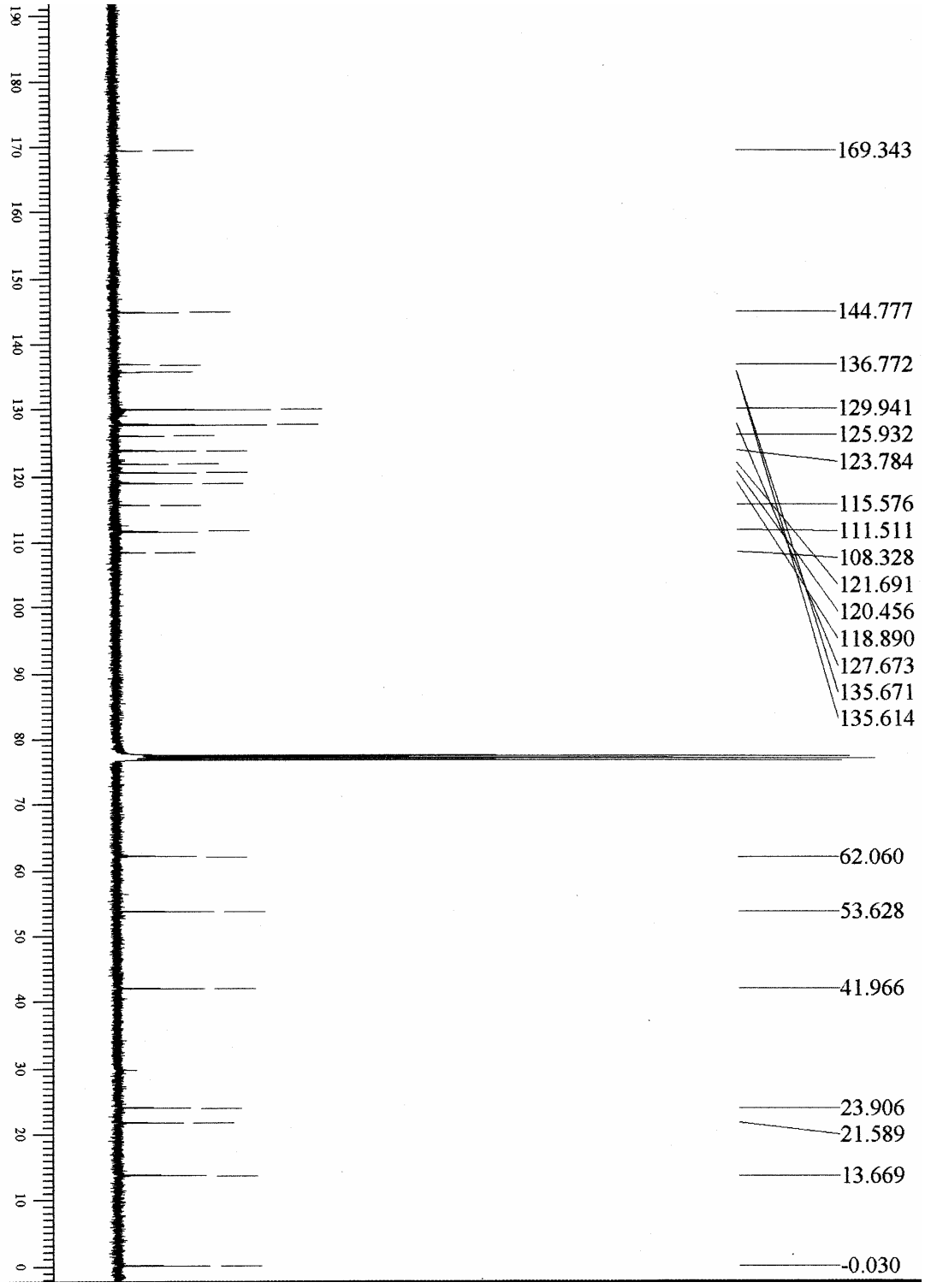
^{1}H NMR spectrum of Compound **4f**.



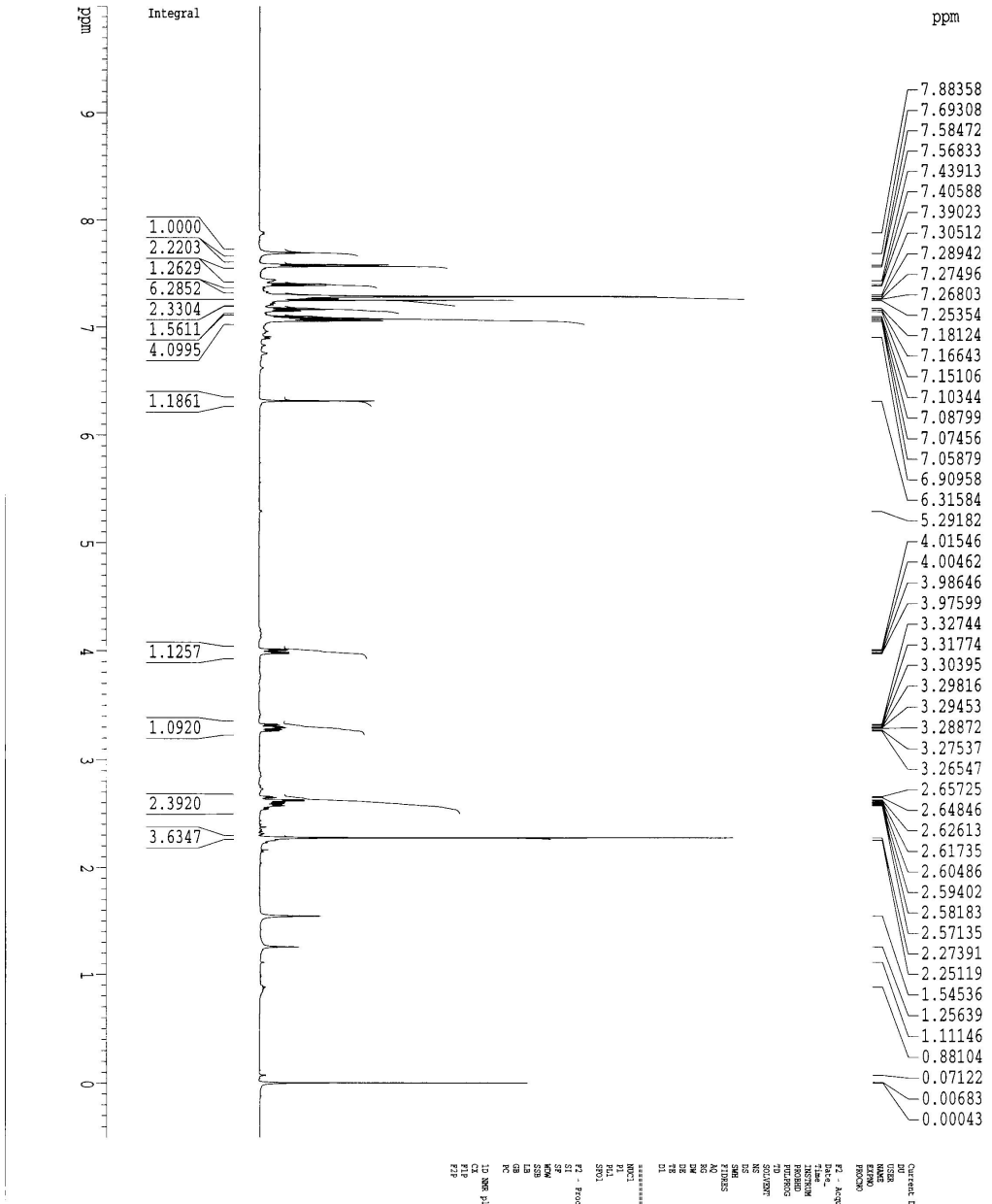
^{13}C NMR spectrum of Compound **4f**.



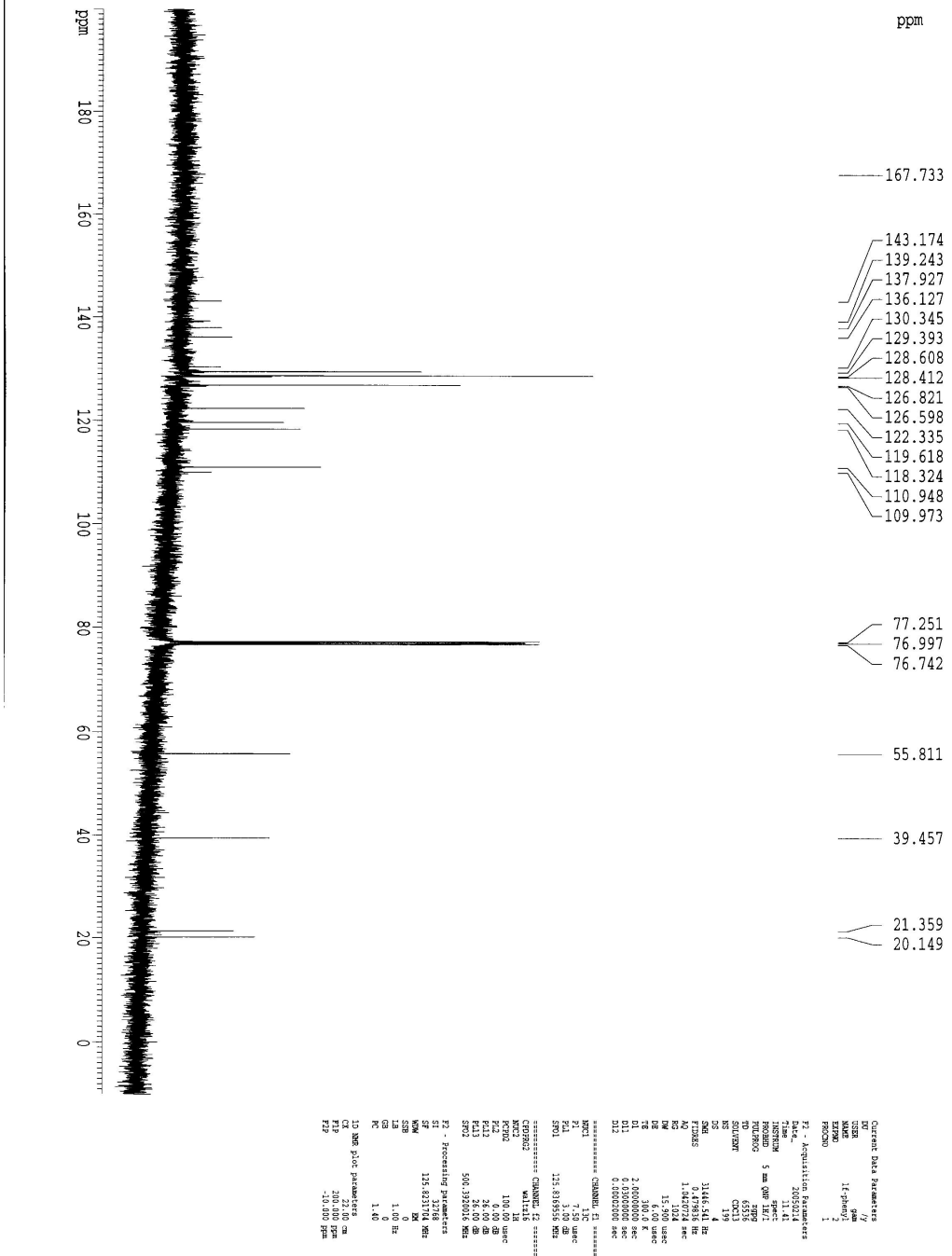
^{1}H NMR spectrum of Compound **4g**.



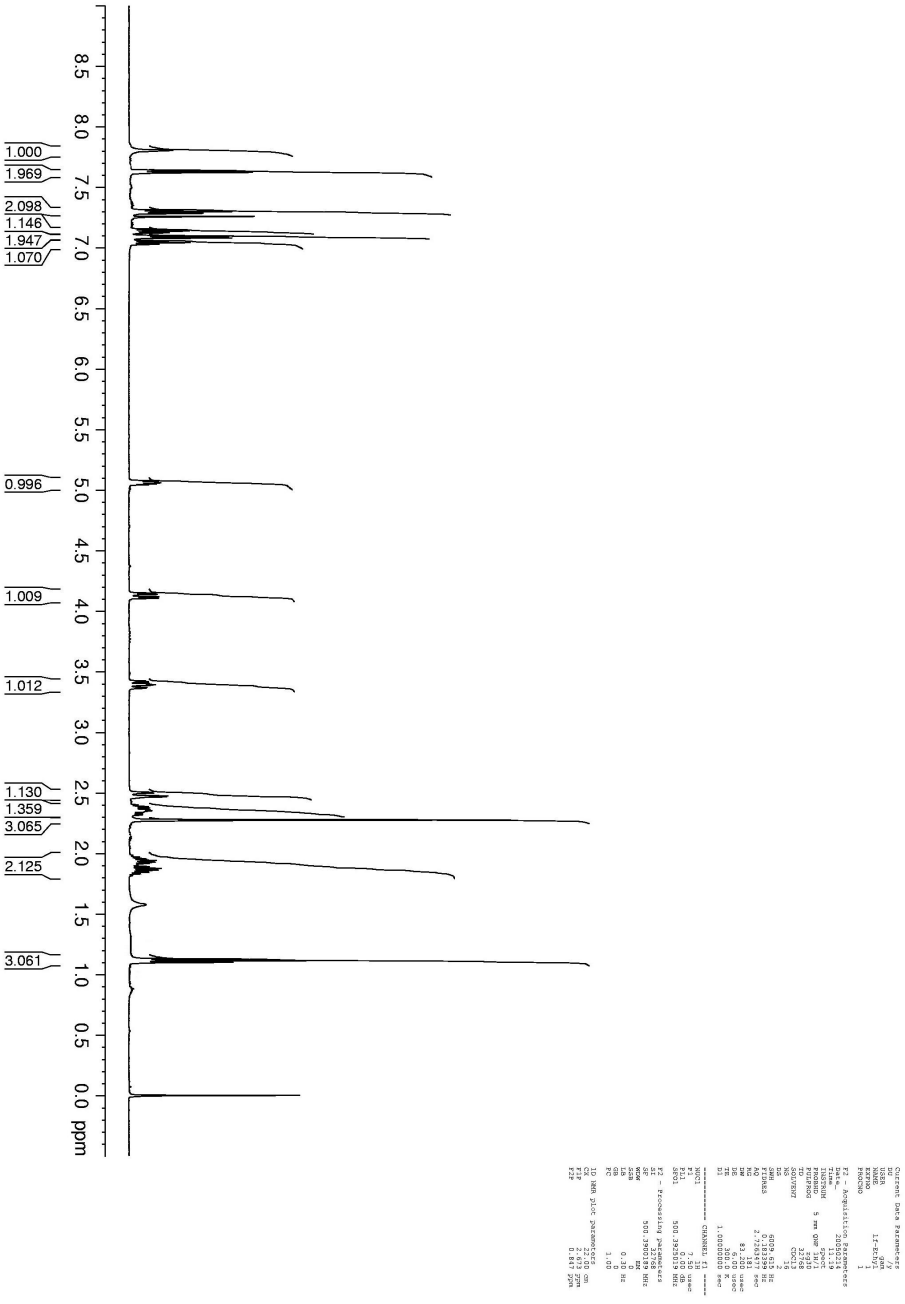
^{13}C NMR spectrum of Compound **4g**.



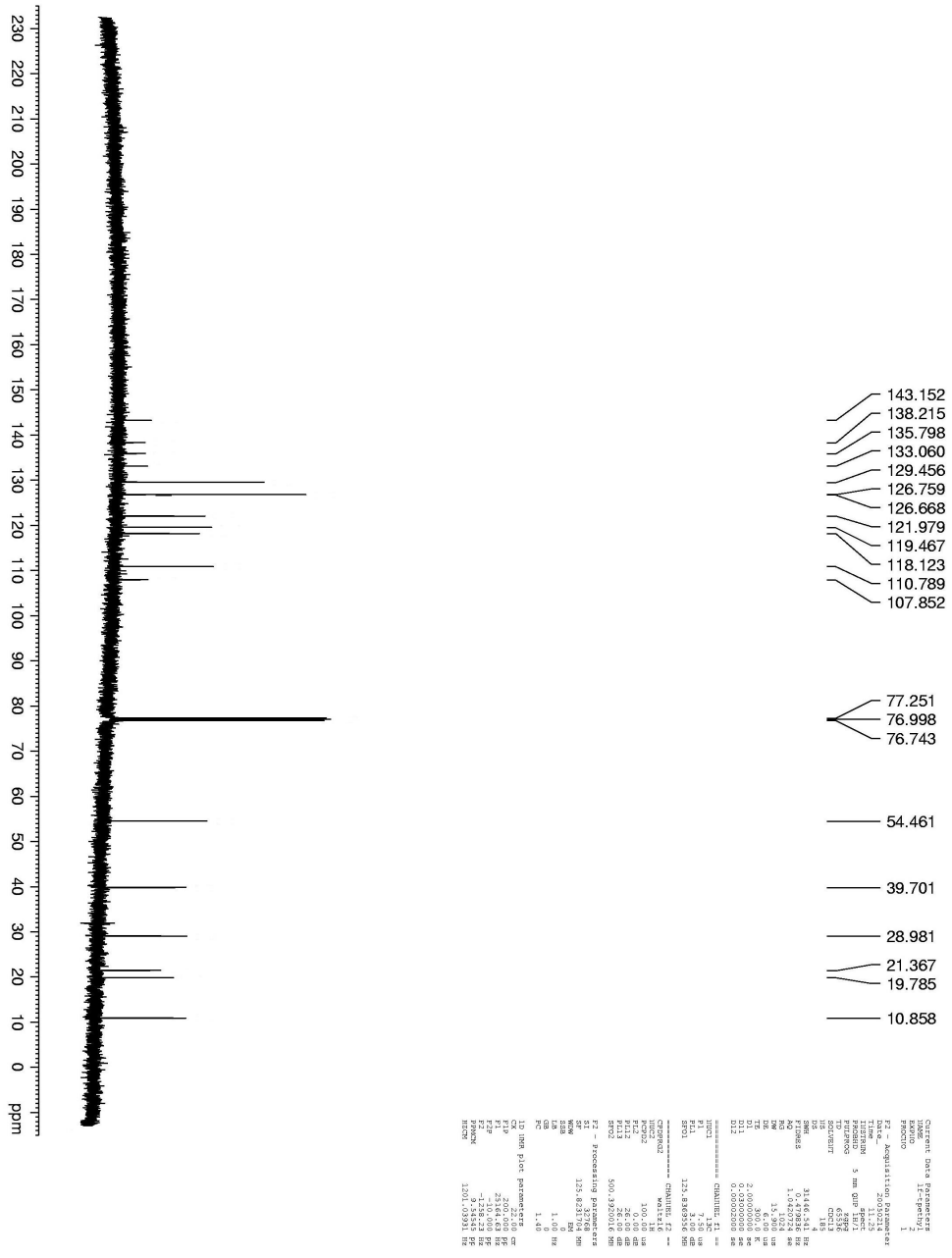
^{1}H NMR spectrum of Compound **4h**.



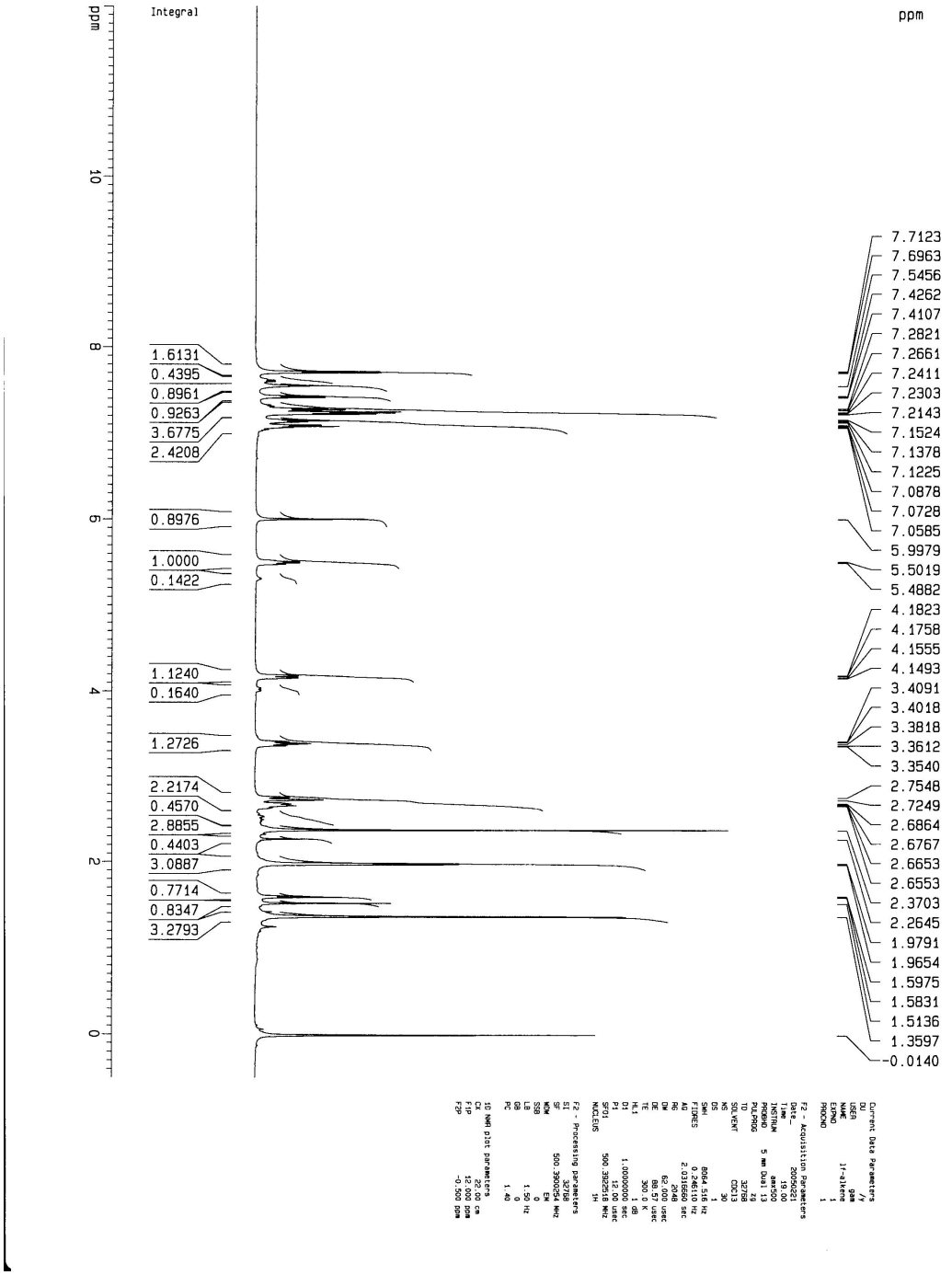
^{13}C NMR Spectrum of Compound **4 h**.



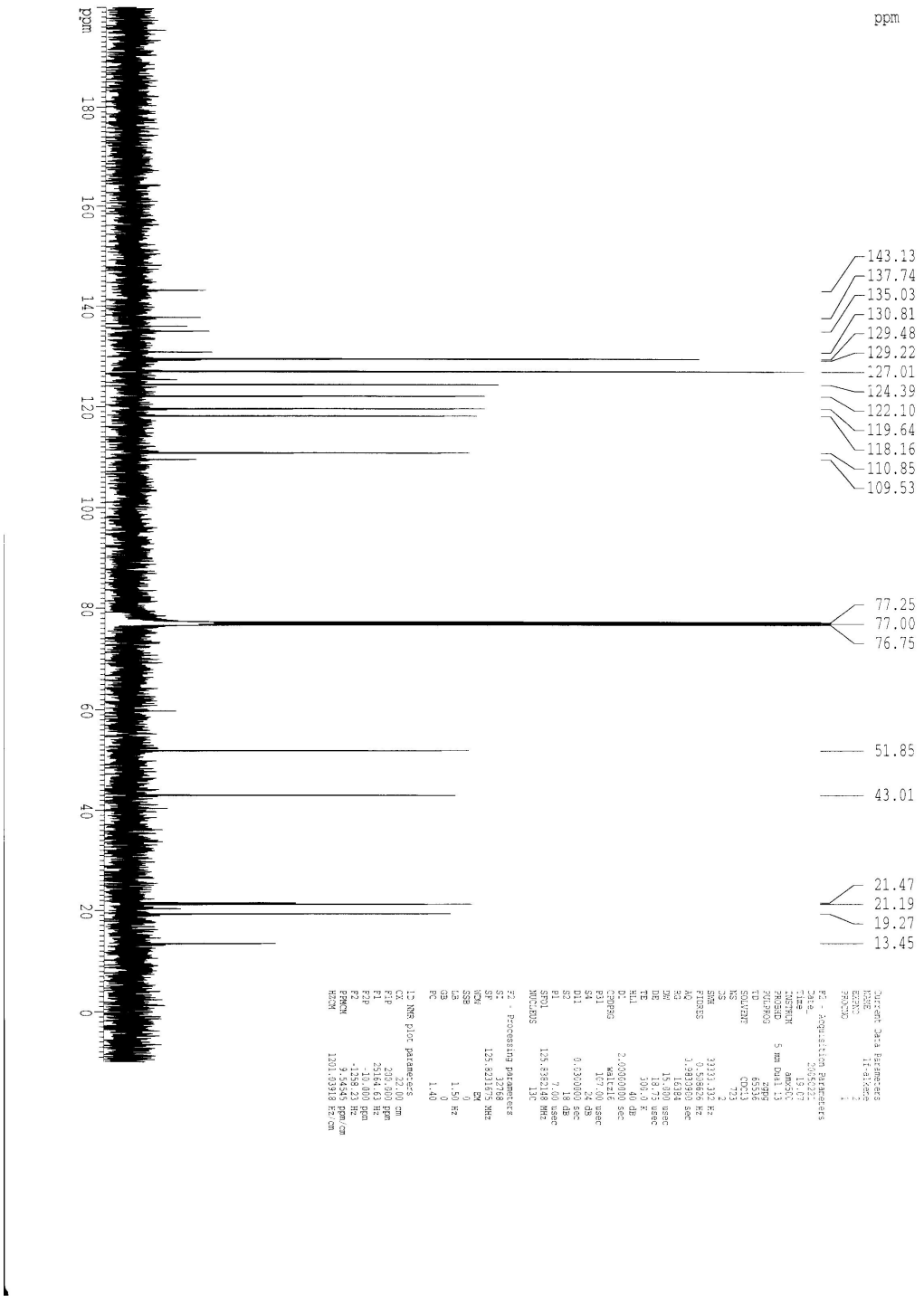
^{1}H NMR spectrum of Compound **4i**.



^{13}C NMR Spectrum of Compound **4i.**



^{1}H NMR spectrum of Compound **4j**.



^{13}C NMR spectrum of Compound **4j**.