Electronic Supplementary Material (ESI) for RSC Advances

SUPPORTING INFORMATION

Microwave-assisted hydrolysis: efficient synthesis of α-substituted cysteines on multi-gram scale

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General Information

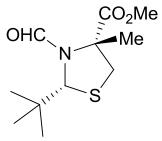
Unless specified, all non-aqueous reactions were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.[1] All glassware was stored in the oven and/or was flame-dried prior to use under an inert atmosphere of gas. Anhydrous solvents were obtained either by filtration through drying columns (THF, Et_2O, CH_2Cl_2, benzene, DMF, CH_3CN, toluene, hexane, methanol) on a GlassContour system (Irvine, CA) or by distillation over calcium hydride (Et_3N, diisopropylamine). Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F254). Visualization of the developed chromatogram was performed by UV absorbance or aqueous potassium permanganate. Flash column chromatography was performed using 230-400 mesh silica (EM Science or Silicycle) of the indicated solvent system according to standard technique.[2] Melting points were obtained on a Buchi melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin Elmer Spectrum One FTIR and are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra (^1H, ^{13}C, DEPT 135) were recorded either on a Bruker AV 300 or AV 400 spectrometer. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.27 ppm, water, δ 4.79 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz and assignation. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (77.16 ppm) as the internal standard. All spectra were obtained with complete proton decoupling. Optical rotations were determined with a Perkin-Elmer 341 polarimeter at 589 nm. Data are reported as follows: [α]λtemp, concentration (*c* in g/100 mL), and solvent. High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal.

Reagents: Unless otherwise stated, commercial reagents were used without purification.

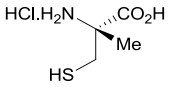
Systems: MARS5 express (#907300) and Discover (#908005) is a trademark of CEM Corporation and Iniator EXP US (#355302, 10458-277) is a trademark of Biotage Company

[1] D. F. Shriver, M. A. Drezdzon, *The Manipulation of Air-Sensitive Compounds*; 2nd ed.; Wiley: New York, 1986.
[2] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem*. 1978, **43,** 2923.

Experimental Procedures and Characterization Data



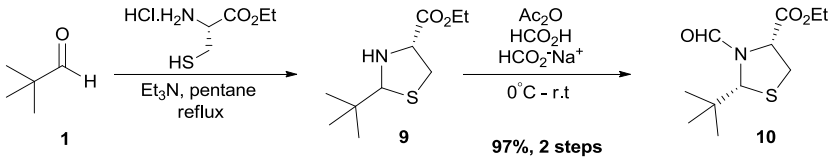
Methyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-3-formyl-4-methyl-1,3-thiazolidine-4-carboxylate (**4a**): Synthesized according to reported procedure[3] Analysis matched the reported data in literature
mp 46-48 °C; lit.: **mp** 49-50 °C[3]
[α]$_D^{20}$ = - 96.0 (*c* 1.39.in $CHCl_3$); lit.: **[α]$_D$** = - 100.2 (*c* 1.39.in $CHCl_3$)[3]
^{1}H NMR ($CHCl_3$, 400 MHz) 2.3:1 mixture of rotamers - Major: δ 8.30 (1H, s, C*H*O), 4.68 (1H, s, $(CH_3)_3CH$), 3.79 (3H, s, , CO_2CH_3), 3.35 (1H, d, *J* = 10.0 Hz, SCH_2), 2.75 (1H, d, *J* = 10.0 Hz, SCH_2), 1.79 (3H, s, CCH_3), 1.10 (9H, s, $(CH_3)_3CH$)



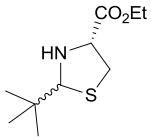
2-Methyl-L-cysteine hydrochloride (**5a**) : Hydroscopic beige solid. The general procedure for the microwave-assisted hydrolysis was followed. 95% isolated yield. Analysis matched the reported data in literature.
mp 159-161 °C; lit.: **mp** 157-159 °C (decomp.)[3]
[α]$_D^{20}$ = + 9.1 (*c* 1.58 in H_2O); lit.: **[α]$_D$** = + 8.13 (*c* 1.58.in H_2O)[3]
^{1}H NMR (D_2O, 400 MHz): δ 3.16 (1H, d, *J* = 16.0 Hz, $HSCH_2$), 2.87 (1H, d, *J* = 16.0 Hz, $HSCH_2$), 1.57 (3H, s, CCH_3)
^{13}C NMR (D_2O, 75 MHz): δ 173.3, 62.0, 30.9, 21.9
FTIR (cm-1) (neat): 3480, 3314-2439 (br), 1717, 1493, 1220, 1189, 887
HRMS (ESI, Pos) calcd for $C_4H_{10}ClNO_2S$ [M-HCl]$^+$: 135.0349 *m/z*, found 135.0348 *m/z*.

[3] G. Pattenden, S. M. Thom and M. F. Jones, *Tetrahedron*, 1993, **49**, 2131.

Synthesis of thiazolidines 8



Scheme 1 Procedure for the synthesis of thiazolidine **10**



Ethyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-1,3-thiazolidine-4-carboxylate (**9**): To a stirred solution of ethyl cysteine ester hydrochloride (20.00 g, 107.72 mmol) in pentane (258.5 mL) was added trimethylacetaldehyde **1** (11.13 g, 129.26 mmol) and triethylamine (13.08 g, 129.26 mmol). After stirring overnight at reflux, the mixture was filtered and concentrated under reduced pressure to yield **9** as a clear oil. The crude product was used the next step without further purification.

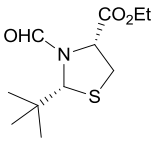
$[\alpha]_D^{20}$ = - 89.2 (*c* 1.225.in $CHCl_3$); $\mathbf{R_f}$ = 0.47 (15% EtOAc/Hexanes)

^{1}H NMR ($CHCl_3$, 300 MHz) 2:1 mixture of diastereoisomers - Major: δ 4.43 (1H, s, $(CH_3)_3CH$), 4.26-4.12 (2H, m, CO_2CH_2), 3.77 (1H, dd, *J* = 10.5, 8.5 Hz, SCH_2), 3.23 (1H, dd, *J* = 10.5, 8.5 Hz, SCH_2), 3.23 (1H, t, *J* = 8.5 Hz, $CHCO_2Et$), 2.38 (1H, br s, *NH*), 1.26 (3H, t, *J* = 8.5 Hz, $CO_2CH_2CH_3$), 1.04 (9H, s, $(CH_3)_3CH$) – Minor: δ 4.50 (1H, s $(CH_3)_3CH$), 4.26-4.12 (2H, m, CO_2CH_2), 4.07 (1H, t, J = 6.0 Hz, $CHCO_2Et$), 3.10 (1H, J = 10.5, 6.0 Hz, SCH_2), 2.97 (dd, J = 10.5, 6.0 Hz, 1H, SCH_2), 2.38 (1H, br s, *NH*), 1.26 (3H, t, J = 8.5 Hz, $CO_2CH_2CH_3$), 0.94 (9H, s, $(CH_3)_3CH$)

^{13}C NMR ($CHCl_3$, 75 MHz) mixture of diastereoisomers - Major: δ 171.4, 81.9, 65.5, 61.5, 37.5, 33.9, 27.0, 14.1– Minor: δ 171.9, 79.8, 65.1, 61.3, 37.1, 36.0, 26.6, 14.1

FTIR (cm^{-1}) (neat): 3316, 2955, 2868, 1736, 1182, 802

HRMS (ESI, Pos) calcd for $C_{10}H_{19}NO_2S$ $[M+H]^+$: 218.1209 *m/z*, found 218.1212 *m/z*.



Ethyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-3-formyl-1,3-thiazolidine-4-carboxylate (**10**): To a stirred solution of **9** (107.72 mmol) in formic acid (148.5 mL) was added sodium formate (8.06 g, 118.49 mmol). This solution was cooled to 0°C and acetic anhydride (35.52g, 323.16 mmol) was added dropwise over 90 min. After stirring overnight at room temperature, the solution was concentrated under reduced pressure. The resulting oily residue was carefully quenched with a saturated $NaHCO_3$ aqueous solution until no gas formation was observed. The aqueous solution was extracted with Et_2O (4 x 500mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield **10** as a clear oil (25.67 g, 97% over 2 steps). The crude product used to the next step without any further purification.

$[\alpha]_D^{20}$ = - 124.3 (*c* 0.967.in $CHCl_3$); **R_f** = 0.21 (15% EtOAc/Hexanes)

^{1}H NMR ($CHCl_3$, 300 MHz) 5.6:1 mixture of rotamers - Major: δ 8.32 (1H, s, C*H*O), 4.81 (1H, t, *J* = 9.0 Hz, 1H,C*H*CO_2), 4.71 (1H, s $(CH_3)_3$C*H*), 4.19 (2H, q, *J* = 7.5 Hz, CO_2*C*$H_2$$CH_3$), 3.30 (1H, dd, *J* = 12.0, 9.0 Hz, SC*H*$_2$), 3.22 (1H, dd, *J* = 12.0, 9.0 Hz, SC*H*$_2$), 1.25 (3H, t, *J* = 7.5 Hz, CO_2CH_2C*H*$_3$), 1.00 (9H, s, (*C*H$_3$)$_3$CH)

^{13}C NMR ($CHCl_3$, 75 MHz) mixture of rotamers - Major: δ 169.5, 162.5, 75.1, 61.6, 61.6, 38.6, 32.9, 26.3, 14.1

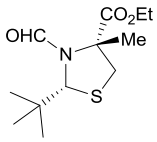
FTIR (cm^{-1}) (neat): 2958, 2871, 1741, 1671, 1394, 1180, 1025

HRMS (ESI, Pos) calcd for $C_{11}H_{19}NO_3S$ $[M+Na]^+$: 268.0978 *m/z*, found 268.0973 *m/z*.

Synthesis of quaternary cysteines

General procedure for the synthesis of hydrolysis precursors

To a solution of diisopropylamine (0.42 mL, 3.06 mmol) in THF (9.26 mL) at -78 °C were slowly added a 2.5 M solution of *n*-butyllithium in hexanes (0.86 mL, 2.14 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1.36 mL). After stirring 1 hour at -78 °C, the solution was cooled to -90 °C (internal temperature) and thiazolidine **10** (0.500 g, 2.04 mmol) in THF (0.33 mL) was added dropwise while maintaining the internal temperature below -90 °C. After stirring for 1 hour at -90 °C, the electrophile (2.45 mmol) was added dropwise. After stirring for 2 hours at -90°C, the reaction mixture was allowed to warm to room temperature over 20 minutes and then concentrated under reduced pressure. The oily residue was quenched by the addition of brine (20 mL) and extracted with Et_2O (4 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography with 0-15% EtOAc in hexanes afforded the desired alkylated thiazolidine **7**.



Ethyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-3-formyl-4-methyl-1,3-thiazolidine-4-carboxylate (**7a**): To a solution of diisopropylamine (20.59 mL, 150.95 mmol) in THF (457.0 mL) at -78 °C were slowly added a 2.5 M solution of *n*-butyllithium in hexanes (42.27 mL, 105.67) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (67.0 mL). sAfter stirring 1 hour at -78 °C, the solution was cooled to -90 °C (internal temperature) and thiazolidine **10** (24.69 g, 100.64 mmol) in THF (16.5 mL) was added dropwise while maintaining the internal temperature below -90 °C. After stirring 1 hour at -90 °C, iodomethane (7.53 mL, 120.76 mmol) was added dropwise. After stirring 2 hours at -90 °C, the reaction mixture was allowed to warm to room temperature over 45 minutes then concentrated under reduced pressure. The oily residue was quenched by the addition of brine (500 mL) and extracted with Et_2O (3 x 500 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography with 0-15% EtOAc in hexanes afforded the desired alkylated thiazolidine **7a** as a yellowish oil (19.17 g, 73%).

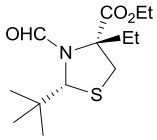
$[\alpha]_D^{20}$ = -93.3 (*c* 0.933.in $CHCl_3$); **R_f** = 0.34 (15% EtOAc/Hexanes)

^{1}H NMR ($CHCl_3$, 300 MHz) 2:1 mixture of rotamers - Major: δ 8.25 (1H, s, C*H*O), 4.64 (1H, s, $(CH_3)_3CH$), 4.19 (2H, q, *J* = 7.2 Hz, CO_2CH_2), 3.29 (1H, d, *J* = 12.0 Hz, SCH_2), 2.69 (1H, d, *J* = 12.0 Hz, SCH_2), 1.72 (3H, s, CCH_3), 1.24 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 1.04 (9H, s, $(CH_3)_3CH$)

^{13}C NMR ($CHCl_3$, 75 MHz) mixture of rotamers - Major: δ 171.4, 161.0, 74.3, 70.0, 61.7, 41.5, 39.4, 26.7, 20.6, 14.0

FTIR (cm^{-1}) (neat): 2959, 2873, 1736, 1669, 1308, 1138, 731

HRMS (ESI, Pos) calcd for $C_{12}H_{21}NO_3S$ $[M+Na]^+$: 282.1134 *m/z*, found 282.11344 *m/z*.



Ethyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-4-ethyl-3-formyl-1,3-thiazolidine-4-carboxylate (**7b**) : Clear oil. The general procedure for the synthesis of hydrolysis precursors was followed. 25% isolated yield.

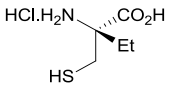
[α]$_D^{20}$ = - 81.9 (*c* 0.717.in $CHCl_3$); **R_f** = 0.30 (15% EtOAc/Hexanes)

^{1}H NMR ($CHCl_3$, 300 MHz) 3.6:1 mixture of rotamers - Major: δ 8.46 (1H, s, C*H*O), 5.41 (1H, s, $(CH_3)_3CH$), 4.33-4.16 (2H, m, $CO_2CH_2CH_3$), 3.73 (1H, dd, *J* = 12.0 Hz, SCH_2), 2.99 (1H, dd, *J* = 12.0 Hz, SCH_2), 2.18-2.03 (2H, m, CCH_2CH_3), 1.30 (3H, t, *J* = 6.0 Hz, CO_2CH_2), 0.99 (3H, t, *J* = 7.5 Hz, CCH_2CH_3), 0.97 (9H, s, $(CH_3)_3CH$)

^{13}C NMR ($CHCl_3$, 75 MHz): δ 172.6, 162.8, 73.2, 71.9, 62.4, 40.1, 38.7, 33.5, 27.1, 14.1, 8.2

FTIR (cm^{-1}) (neat): 2959, 2872, 1733, 1671, 1362, 1314, 1024

HRMS (ESI, Pos) calcd for $C_{13}H_{23}NO_3S$ $[M+H]^+$: 274.1471 *m/z*, found 274.1470 *m/z*.

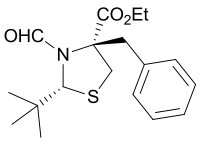


2'-Sulfanyl-D-isovaline hydrochloride (**8b**): White solid. The general procedure for microwave-assisted hydrolysis was followed. 95% isolated yield. Analysis matched the previously reported data in literature.

mp 214-218°C; lit.: **mp** 220-224 °C (decomp.)[3]

[α]$_D^{20}$ = + 7.8 (*c* 0.317.in H_2O); lit.: **[α]$_D$** = + 2.24 (*c* 0.8.in H_2O)[3]

^{1}H NMR (D_2O, 300 MHz): δ 3.11 (1H, d, *J* = 15.0 Hz, $HSCH_2$), 2.81 (1H, d, *J* = 15.0 Hz, $HSCH_2$), 1.99-1.76 (2H, m, CCH_2CH_3), 0.88 (3H, t, *J* = 7.5 Hz, CCH_2CH_3)



Ethyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-3-formyl-4-(phenylmethyl)-1,3-thiazolidine-4-carboxylate (**7c**): Clear oil. The general procedure for the synthesis of hydrolysis precursors was followed. 55% isolated yield.

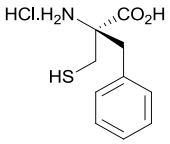
[α]$_D^{20}$ = - 53.7 (*c* 0.350.in $CHCl_3$); **R_f** = 0.33 (15% EtOAc/Hexanes)

^{1}H NMR ($CHCl_3$, 300 MHz) 1.6:1 mixture of rotamers - Major: δ 8.67 (1H, s, C*H*O) 7.35-7.24 (3H, m, CH_{Ar}), 7.17-7.11 (2H, m, CH_{Ar}), 5.37 (1H, s, $(CH_3)_3CH$), 4.33-4.19 (2H, m, CO_2CH_2), 3.62-3.56 (2H, m,CH_2), 3.40 (1H, d, *J* = 15.0 Hz, CH_2), 3.07 (1H, d, *J* = 15.0 Hz, CH_2), 1.27 (3H, t, *J* = 7.5 Hz, $CO_2CH_2CH_3$), 0.96 (9H, s, $(CH_3)_3CH$)

^{13}C NMR ($CHCl_3$, 75 MHz) mixture of rotamers - Major: δ 163.5, 134.8, 130.3, 128.7, 126.8, 75.0, 73.6, 71.9, 62.4, 45.9, 40.4, 37.7, 27.3, 14.0

FTIR (cm^{-1}) (neat): 2958, 2871, 1732, 1671, 1361, 1236, 1038, 739

HRMS (ESI, Pos) calcd for $C_{18}H_{25}NO_3S$ $[M+H]^+$: 336.1628 *m/z*, found 336.1633 *m/z*.

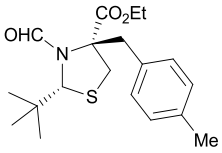


α-(Sulfanylmethyl)-D-phenylalanine hydrochloride (**8c**): Gummy white solid. The general procedure for microwave-assisted hydrolysis was followed (2 hours). 81% isolated yield. Analysis matched the previously reported data in literature.

mp 110-114°C (decomp.)

[α]$_D^{20}$ = + 9.0 (*c* 1.167.in H_2O); lit.: **[α]$_D$ =** + 7.07 (*c* 1.07.in H_2O)[3]

^{1}H NMR (D_2O, 400 MHz): δ 7.34-7.26 (3H, m, CH_{Ar}), 7.20-7.14 (2H, m, CH_{Ar}, 3.26 (2H, dd, *J*= 20.0, 4.0 Hz, C*H*$_2$), 3.08 (1H, d, *J*= 20.0 Hz, C*H*$_2$), 2.86 (1H, d, *J*= 20.0 Hz, C*H*$_2$)



Ethyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-3-formyl-4-[(4-methylphenyl)methyl]-1,3-thiazolidine-4-carboxylate (**7d**): Clear oil. The general procedure for the synthesis of hydrolysis precursors was followed. 48% isolated yield.

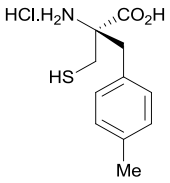
[α]$_D^{20}$ = - 43.0 (*c* 0.733.in $CHCl_3$); **R$_f$** = 0.27 (15% EtOAc/Hexanes)

^{1}H NMR ($CHCl_3$, 300 MHz) 2:1 mixture of rotamers - Major: δ 8.65 (1H, s, C*H*O), 7.11 (2H, d, *J* = 7.5 Hz, C*H*$_{Ar}$), 7.02 (2H, d, *J*=7.5 Hz, C*H*$_{Ar}$), 5.37 (1H, s, $(CH_3)_3CH$), 4.33-4.20 (2H, m, CO_2CH_2), 3.63-3.51 (2H, m, C*H*$_2$), 3.29 (1H, d, *J* = 13.5 Hz, C*H*$_2$), 3.07 (1H, d, *J* = 13.5 Hz, C*H*$_2$), 2.33 (3H, s, ArC*H*$_3$), 1.28 (3H, t, *J* = 9.0 Hz, $CO_2CH_2CH_3$), 0.96 (9H, s, $(CH_3)_3CH$)

^{13}C NMR ($CHCl_3$, 75 MHz) mixture of rotamers - Major: δ 171.4, 163.5, 137.4, 131.6, 130.1, 129.4, 73.7, 71.9, 62.3, 45.5, 40.1, 37.9, 27.3, 21.1, 14.1

FTIR (cm-1) (neat): 2957, 2870, 1733, 1671, 1307, 1235, 1041

HRMS (ESI, Pos) calcd for $C_{19}H_{27}NO_3S$ $[M+H]^+$: 350.1784 *m/z*, found 350.1788 *m/z*.



4-Methyl-α-(sulfanylmethyl)-D-phenylalanine hydrochloride (**8d**): White solid. The general procedure for the microwave-assisted hydrolysis was followed (10 hours). 84% isolated yield.

mp 86-88 °C

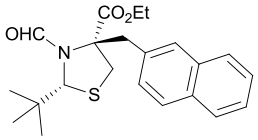
[α]$_D^{20}$ = + 24.7 (*c* 0.425.in H_2O)

^{1}H NMR (D_2O, 300 MHz): δ 7.15 (2H, d, *J* = 7.5 Hz, CH_{Ar}), 7.06 (2H, d, *J* = 7.5 Hz, CH_{Ar}), 3.23 (2H, dd, *J* = 13.5, 4.5 Hz, C*H*$_2$), 3.04 (1H, d, *J* = 15.0 Hz, C*H*$_2$), 2.84 (1H, d, *J* = 15.0 Hz C*H*$_2$), 2.22 (3H, s, ArC*H*$_3$)

^{13}C NMR (D_2O, 75 MHz): δ 171.8, 138.5, 130.0, 129.7, 129.3, 65.9, 40.3, 29.0, 20.1

FTIR (cm^{-1}) (neat): 3285-2522 (br), 2200, 1724, 1559, 1376, 1201, 816

HRMS (ESI, Pos) calcd for $C_{11}H_{15}ClNO_2S$ $[M-HCl+H]^+$: 226.0896 *m/z*, found 226.0887 *m/z*.



Ethyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-3-formyl-4-(naphthalen-2-ylmethyl)-1,3-thiazolidine-4-carboxylate (**7e**): Clear oil. The general procedure for the synthesis of hydrolysis precursors was followed. 58% isolated yield.

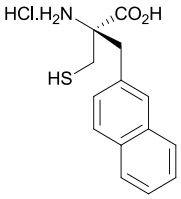
[α]$_D^{20}$ = - 7.5 (*c* 0.983.in $CHCl_3$); **R_f** = 0.19 (15% EtOAc/Hexanes)

^{1}H NMR ($CHCl_3$, 300 MHz) 1.4:1 mixture of rotamers - Major: δ 8.49 (1H, s, C*H*O), 7.86-7.73 (4H, m, CH_{Ar}), 7.63 (1H, s, CH_{1Ar}), 7.53-7.41(4H, m, CH_{Ar}), 5.42 (1H, s, $(CH_3)_3CH$), 4.36-4.20 (2H, m, CO_2CH_2), 3.63 (1H, d, *J* = 9.0 Hz, CH_2Ph), 3.59 (1H, d, *J* =9.0 Hz, CH_2), 3.50 (1H, d, *J* = 12.0 Hz, CH_2), 3.14 (1H, d, *J* = 12.0 Hz, CH_2), 1.24 (3H, t, *J* = 7.5 Hz, $CO_2CH_2CH_3$), 0.98 (9H, s, $(CH_3)_3$CH)

^{13}C NMR ($CHCl_3$, 75 MHz) mixture of rotamers - Major: δ 171.5, 163.4, 133.3, 132.7, 132.3, 129.5, 128.3, 127.7, 127.7, 127.6, 126.4, 125.9, 73.7, 71.9, 62.5, 46.1, 40.4, 37.7, 27.3, 14.1

FTIR (cm^{-1}) (neat): 3057, 2960, 2873, 1733, 1663, 1308, 1194, 729

HRMS (ESI, Pos) calcd for $C_{22}H_{27}NO_3S$ $[M+H]^+$: 386.1784 *m/z*, found 386.1781 *m/z*.



(2*R*)-2-Amino-3-naphthalen-2-yl-2-(sulfanylmethyl)propanoic acid hydrochloride (**8e**): White solid. The general procedure for the microwave-assisted hydrolysis was followed (10 hours). 73% isolated yield.

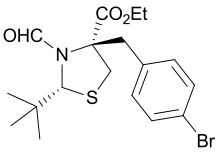
mp 164-166 °C;**[α]$_D^{20}$** = + 18.9 (*c* 0.417 in 1M HCl in H_2O)

^{1}H NMR (D_2O, 300 MHz): δ 7.89-7.83 (3H, m), 7.72 (1H, s), 7.53-7.48 (2H, m), 7.32 (1H, d, *J* = 12.0 Hz), 3.44 (1H, d, *J* = 16.0 Hz, CH_2), 3.28 (1H, d, *J* = 16.0 Hz, CH_2), 3.23 (1H, d, *J* = 16.0 Hz, CH_2), 2.88 (1H, d, *J* = 16.0 Hz, CH_2)

^{13}C NMR (1M HCl in D_2O, 75 MHz): δ 171.0, 132.5, 132.0, 129.4, 128.8, 128.3, 127.3, 127.2, 127.1, 126.3, 126.2, 65.2, 40.3, 28.5

FTIR (cm^{-1}) (neat): 3161-2605 (br), 2559, 2174, 1737, 1537, 1213, 862, 747, 476

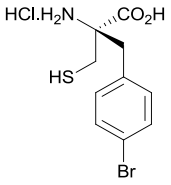
HRMS (ESI, Pos) calcd for $C_{14}H_{16}ClNO_2S$ $[M-HCl]^+$: 261.0818 *m/z*, found 261.0818 *m/z*.



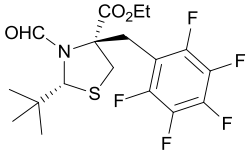
Ethyl (2*R*,4*R*)-4-[(4-bromophenyl)methyl]-2-(1,1-dimethylethyl)-3-formyl-1,3-thiazolidine-4-carboxylate (**7f**): Clear oil. The general procedure for the synthesis of hydrolysis precursors was followed. 64% isolated yield.

[α]$_D^{20}$ = - 10.4 (*c* 1.067 in $CHCl_3$); **R_f** = 0.32 (15% EtOAc/Hexanes)

^{1}H NMR ($CHCl_3$, 300 MHz) 1.15:1 mixture of rotamers - Major: δ 8.40 (1H, s, C*H*O) 7.37 (2H, d, *J* = 9.0 Hz, CH_{Ar}), 7.18 (2H, d, *J* = 9.0 Hz, CH_{Ar}), 4.50 (1H, s, $(CH_3)_3CH$), 4.31-4.16 (2H, m, CO_2CH_2), 3.53 (1H, d, *J* = 12.8 Hz, CH_2), 3.32 (1H, d, *J* = 12.8 Hz, CH_2), 2.96 (1H, d, *J* = 12.8 Hz, CH_2), 2.88 (1H, d, *J* = 12.8 Hz, CH_2), 1.27 (3H, t, *J* = 7.5 Hz, $CO_2CH_2CH_3$), 1.03 (9H, s, $(CH_3)_3CH$)
^{13}C NMR ($CHCl_3$, 75 MHz) mixture of rotamers - Major: δ 163.5, 134.8, 130.3, 128.7, 126.8, 75.0, 73.6, 71.9, 62.4, 45.9, 40.4, 37.7, 27.3, 14.0
FTIR (cm^{-1}) (neat): 2958, 2871, 1734, 1669, 1486, 1305, 1073, 732
HRMS (ESI, Pos) calcd for $C_{18}H_{25}ClBrNO_3S$ $[M–HCl+Na]^+$: 436.0553 *m/z*, found 436.0536 *m/z*.

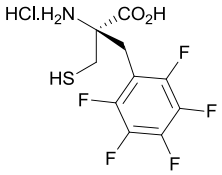


4-Bromo-α-(sulfanylmethyl)-D-phenylalanine hydrochloride (**8f**): White solid. The general procedure for the microwave-assisted hydrolysis was followed (10 hours). 81% isolated yield.
mp 106-108 °C
$[\alpha]_D^{20}$ = +41.5 (*c* 0.542.in 1M HCl in H_2O)
^{1}H NMR (D_2O, 300 MHz): δ 7.48 (2H, d, *J* = 9.0 Hz, CH_{Ar}), 7.09 (2H, d, *J* = 9.0 Hz, CH_{Ar}), 3.27 (1H, d, *J* = 15.0 Hz, CH_2), 3.25 (1H, d, *J* = 13.5 Hz, CH_2), 3.05 (1H, d, *J* = 14.2 Hz, CH_2), 2.84 (1H, d, *J* = 13.5 Hz, CH_2)
^{13}C NMR (D_2O, 75 MHz): δ 172.2, 132.9, 132.7, 132.3, 122.6, 66.4, 40.9, 29.8,
FTIR (cm^{-1}) (neat): 3161-2561 (br), 2173, 1724, 1488, 1442, 1202, 1071, 1011, 818, 509
HRMS (ESI, Pos) calcd for $C_{10}H_{13}BrClNO_2S$ $[M+H]^+$: 289.9845 *m/z*, found 289.9844 *m/z*.



Ethyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-3-formyl-4-[(pentafluorophenyl)methyl]-1,3-thiazolidine-4-carboxylate (**7g**): Clear oil. The general procedure for the synthesis of hydrolysis precursors was followed. 59% isolated yield.
$[\alpha]_D^{20}$ = + 45.2 (*c* 0.967.in $CHCl_3$); **R_f** = 0.31 (15% EtOAc/Hexanes)
^{1}H NMR ($CHCl_3$, 300 MHz) 6.7:1 mixture of rotamers - Major: δ 8.37 (1H, s, C*H*O), 4.52 (1H, s, $(CH_3)_3CH$), 4.28 (2H, q, *J* = 6.0 Hz, CO_2CH_2), 4.00 (1H, d, *J* = 13.5 Hz, CH_2), 3.61 (1H, d, *J* = 13.5 Hz, CH_2), 3.28 (1H, d, *J* = 12.0 Hz, CH_2), 2.98 (1H, d, *J* = 12.0 Hz, CH_2), 1.31 (3H, t, *J* = 6.0 Hz, $CO_2CH_2CH_3$), 1.05 (9H, s, $(CH_3)_3CH$)
^{13}C NMR ($CHCl_3$, 75 MHz) mixture of rotamers - Major: δ 170.3, 161.4, 148.0-148.5 (m), 145.0-144.5 (m), 142.2-141.7 (m), 139.4-138.2 (m), 136.1-135.5 (m), 111.2-110.6 (m), 74.4, 71.8, 62.5, 39.6, 38.2, 26.7, 25.3, 14.0
^{19}F NMR ($CDCl_3$, 282 MHz) mixture of rotamers - Major: δ -141.50 (2F, dd, *J*= 22.6, 8.5 Hz), -155.80 (1F, t, *J*= 22.6 Hz), -162.61 (2F, td, *J*= 22.6, 8.5 Hz)
FTIR (cm^{-1}) (neat): 2961, 2874, 1737, 1521, 1501, 1241, 1097, 971, 732

HRMS (ESI, Pos) calcd for $C_{18}H_{20}F_5NO_3S$ $[M+Na]^+$: 448.0976 *m/z*, found 448.0957 *m/z*.



2,3,4,5,6-Pentafluoro-α-(sulfanylmethyl)-D-phenylalanine hydrochloride (**8g**): Greenish solid. The general procedure for the microwave-assisted hydrolysis was followed (10 hours). 67% isolated yield. Compounds is 95% pure (contains disulfide dimer)

mp 138-140 °C

$[\alpha]_D^{20}$ = - 3.7 (*c* 0.267.in 1M HCl in H_2O)

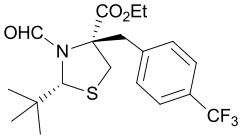
^{1}H NMR (D_2O, 400 MHz): δ 3.29 (2H, s, CC*H*$_2$Ar), 3.19 (1H, d, *J* = 16.0 Hz, HSC*H*$_2$), 2.72 (1H, d, *J* = 16.0 Hz, HSC*H*$_2$)

^{13}C NMR (1M HCl in D_2O, 75 MHz): δ 170.2, 146.9 (CF), 143.8(CF), 142.5(CF), 138.9(CF), 135.7(CF), 106.0, 64.4, 28.0, 27.9

^{19}F NMR (D_2O, 282 MHz): δ – - 140.45 (2F, dd, *J* = 22.6, 8.5 Hz), - 153.84 (1F, t, *J* = 21.2 Hz), - 162.03- -162.21 (2F, m)

FTIR (cm^{-1}) (neat): 3291-2814 (br), 1740, 1522, 1503, 1208, 1033

HRMS (ESI, Pos) calcd for $C_{10}H_9BrClF_5NO_2S$ $[M-HCl]^+$: 372.116301.0190 *m/z*, found 301.0199*m/z*.



Ethyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-3-formyl-4-[(pentafluorophenyl)methyl]-1,3-thiazolidine-4-carboxylate (**7g**): White solid. The general procedure for the synthesis of hydrolysis precursors was followed. 79% isolated yield

mp 48-50°C

$[\alpha]_D^{20}$ = - 7.8 (*c* 0.983.in $CHCl_3$); **R_f** = 0.34 (15% EtOAc/Hexanes)

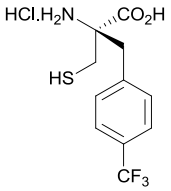
^{1}H NMR ($CDCl_3$, 300 MHz) 1.5:1 mixture of rotamers - Major: δ 8.44 (1H, s, C*H*O), 7.54 (2H, d, *J* = 9.0 Hz, C*H*$_{Ar}$), 7.46 (2H, d, *J* = 9.0 Hz, C*H*$_{Ar}$), 4.53 (1H, s, $(CH_3)_3CH$), 4.36-4.20 (2H, m, CO_2CH_2), 3.72 (1H, d, *J* = 12.0 Hz, C*H*$_2$), 3.61 (1H, d, *J* = 12.0 Hz, C*H*$_2$), 3.26 (1H, d, *J* = 12.0 Hz, SC*H*$_2$), 2.90 (1H, d, *J* = 12.0 Hz, C*H*$_2$), 1.31 (3H, t, *J* = 6.0 Hz, $CO_2CH_2CH_3$), 1.07 (9H, s, $(CH_3)_3$CH)

^{13}C NMR ($CDCl_3$, 75 MHz) mixture of rotamers - Major: δ 170.9, 161.6, 140.9, 131.2, 129.0 125.6, 124.9 (q, *J*= 3.5Hz, CF_3), 74.8, 73.0, 62.1, 45.4, 39.5, 38.0, 26.8, 14.0

^{19}F NMR ($CDCl_3$, 282 MHz) mixture of rotamers - Major: δ - 62.35

FTIR (cm^{-1}) (neat): 2965, 2875, 1744, 1661, 1320, 1017, 803, 643

HRMS (ESI, Pos) calcd for $C_{19}H_{24}F_3NO_3S$ $[M+Na]^+$: 426.1321 *m/z*, found 426.1306 *m/z*.



α-(Sulfanylmethyl)-4-(trifluoromethyl)-D-phenylalanine hydrochloride (**8h**): Greenish solid. The general procedure for the microwave-assisted hydrolysis was followed (10 hours). 79% isolated yield. Compounds is 95% pure (contains disulfide dimer)

mp 218-222°C

$[\alpha]_D^{20}$ = + 48.7 (*c* 0.283.in 1M HCl in H_2O)

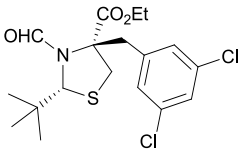
^{1}H NMR (D_2O, 300 MHz): δ 7.54 (2H, d, *J* = 6.9 Hz, CH_{Ar}), 6.94 (2H, d, *J* = 6.9 Hz, CH_{Ar}), 3.04 (1H, d, *J* = 14.2 Hz, C*H*$_2$), 2.93 (1H, d, *J* = 15.0 Hz, C*H*$_2$), 2.88 (1H, d, *J* = 14.2 Hz, C*H*$_2$), 2.61 (1H, d, *J* = 15.0 Hz, C*H*$_2$)

^{13}C NMR (1M HCl in D_2O, 75 MHz): δ 170.7, 169.7, 137.7, 130.4, 130.0, 129.1, 65.2, 40.2, 28.7

^{19}F NMR (D_2O, 282 MHz): δ - 62.62

FTIR (cm^{-1}) (neat): 3349-2584 (br), 2286, 1686, 1574, 1380, 1226, 1183, 700

HRMS (ESI, Pos) calcd for $C_{11}H_{13}ClF_3NO_2S$ $[M\text{-}HCl]^+$: 279.0535 *m/z*, found 279.0540 *m/z*.



Ethyl (2*R*,4*R*)-4-[(3,5-dichlorophenyl)methyl]-2-(1,1-dimethylethyl)-3-formyl-1,3-thiazolidine-4-carboxylate (**7i**): White solid. The general procedure for the synthesis of hydrolysis precursors was followed. 82% isolated yield.

mp 78-80 °C

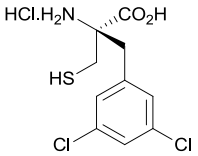
$[\alpha]_D^{20}$ = + 7.3 (*c* 1.092.in $CHCl_3$); **R_f** = 0.35 (15% EtOAc/Hexanes)

^{1}H NMR ($CDCl_3$, 300 MHz) 1.6:1 mixture of rotamers - Major: δ 8.46 (1H, s, C*H*O), 7.35-7.12 (3H, m, C*H*$_{Ar}$), 4.40 (1H, s, $(CH_3)_3CH$), 4.33-4.21 (2H, m, CO_2CH_2), 3.83 (1H, d, *J* = 15.0 Hz, C*H*$_2$), 3.75 (1H, d, *J* = 15.0 Hz, C*H*$_2$), 3.32 (1H, d, *J* = 12.0 Hz, C*H*$_2$), 3.25 (1H, d, *J* = 12.0 Hz, C*H*$_2$), 1.31 (3H, t, *J* = 6.0 Hz, $CO_2CH_2CH_3$), 1.05 (9H, s, $(CH_3)_3CH$)

^{13}C NMR ($CDCl_3$, 75 MHz) mixture of rotamers - Major: δ 170.7, 161.6, 137.2, 134.0, 132.4, 131.6, 130.4, 128.2, 75.0, 73.4, 62.3, 39.6, 38.9, 34.2, 26.9, 14.0

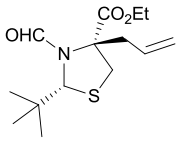
FTIR (cm-1) (neat): 2961, 2870, 1727, 1656, 1393, 1308, 1251, 744, 511

HRMS (ESI, Pos) calcd for $C_{18}H_{23}Cl_2NO_3S$ $[M+H]^+$: 404.0849 *m/z*, found 404.0834 *m/z*.

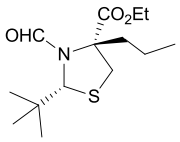


3,5-dichloro-α-(sulfanylmethyl)-D-phenylalanine hydrochloride (**8i**): White solid. The general procedure for the microwave-assisted hydrolysis precursors was followed (10 hours). 82% isolated yield. Compound is 95% pure (contains disulfide dimer).

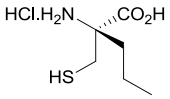
mp 119-123°C
[α]$_D^{20}$ = - 7.3 (*c* 0.325.in 1M HCl in H_2O)
^{1}H NMR (D_2O, 400 MHz): δ 7.33-7.28 (1H, m, CH_{Ar}), 7.25-7.19 (2H, m, CH_{Ar}), 3.37 (1H, d, *J* = 12.0 Hz, C*H*$_2$), 3.22 (2H, dd, *J* = 14.0, 2.0 Hz, C*H*$_2$), 2.82 (1H, d, *J* = 12.0 Hz, C*H*$_2$)
^{13}C NMR (1M HCl in D_2O, 75 MHz): δ 173.9, 135.7, 135.1, 134.8, 134.3, 133.7, 132.3, 68.4, 40.1, 31.4
FTIR (cm^{-1}) (neat): 3271-2162 (br), 1723, 1541, 1470, 1197, 1100, 1046, 885, 813
HRMS (ESI, Pos) calcd for $C_{10}H_{12}Cl_3NO_2S$ [M-HCl]$^+$: 278.9882 *m/z*, found 278.9892 *m/z*.



Ethyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-3-formyl-4-prop-2-en-1-yl-1,3-thiazolidine-4-carboxylate (**7j**): Clear oil. The general procedure for the synthesis of hydrolysis precursors was followed. 63% isolated yield.
[α]$_D^{20}$ = - 91.4 (*c* 1.025.in $CHCl_3$); **R$_f$** = 0.26 (15% EtOAc/Hexanes)
^{1}H NMR ($CDCl_3$, 300 MHz) 1.3:1 mixture of rotamers - Major: δ 8.52 (1H, s, C*H*O), 5.86-5.69 (1H, m, CCH_2CH=CH_2), 5.37 (1H, s, $(CH_3)_3CH$), 5.22-5.07 (2H, m, CCH_2CH=C*H*$_2$), 4.33-4.22 (2H, m, CO_2CH_2), 3.70 (1H, d, *J* = 12.0 Hz, SC*H*$_2$), 3.07 (1H, d, *J* = 12.0 Hz, SC*H*$_2$), 2.85-279 (2H, m, CCH_2CH=C*H*$_2$), 1.32 (3H, t, *J* = 7.5 Hz, $CO_2CH_2CH_3$), 0.93 (9H, s, $(CH_3)_3CH$)
^{13}C NMR ($CDCl_3$, 75 MHz) mixture of rotamers - Major: δ 171.8, 162.8, 130.5, 121.0, 72.2, 72.0, 62.5, 44.8, 40.2, 38.9, 27.1, 14.1
FTIR (cm^{-1}) (neat): 2960, 2872, 1733, 1671, 1363, 1236, 1039, 920
HRMS (ESI, Pos) calcd for $C_{14}H_{23}NO_3S$ [M+H]$^+$: 286.1471 *m/z*, found 286.1458 *m/z*.



Ethyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-3-formyl-4-propyl-1,3-thiazolidine-4-carboxylate (**11j**): A solution of thiazolidine **8l** (256 mg, 0.898 mmol) and 10% palladium on carbon (191 mg, 0.180 mmol) in EtOH (8.98 mL) was stirred under a hydrogen atmosphere for 2.5 hours. The solution was filtered over a silica pad and eluted with DCM. Flash chromatography with 0-15% EtOAc in hexanes afforded the desired alkylated thiazolidine **11j** as a clear oil (251 mg, 97%).
[α]$_D^{20}$ = - 69.4 (*c* 1.117.in $CHCl_3$); **R$_f$** = 0.26 (15% EtOAc/Hexanes)
^{1}H NMR ($CDCl_3$, 300 MHz) 3.6:1 mixture of rotamers - Major: δ – 8.45 (1H, s, C*H*O), 5.39 (1H, s, $(CH_3)_3CH$), 4.31-4.16 (2H, m, CO_2CH_2), 3.73 (1H, d, *J* = 12.0 Hz, SC*H*$_2$), 3.00 (1H, d, *J* = 12.0 Hz, SC*H*$_2$), 2.01 (2H, t, *J* = 10.5 Hz, $CCH_2CH_2CH_3$), 1.56-1.33 (2H, m, $CCH_2CH_2CH_3$), 1.30 (3H, t, *J* = 7.5 Hz, $CO_2CH_2CH_3$), 0.93 (9H, s, $(CH_3)_3CH$), 0.93-0.86 (3H, m, $CCH_2CH_2CH_3$)
^{13}C NMR ($CDCl_3$, 75 MHz) mixture of rotamers - Major: δ 172.6, 162.8, 72.7, 71.8, 62.3, 42.7, 40.1, 39.3, 27.0, 17.0, 14.2, 14.0
FTIR (cm^{-1}) (neat): 2959, 2873, 1733, 1671, 1465, 1362, 1302, 1230, 1025
HRMS (ESI, Pos) calcd for $C_{14}H_{25}NO_3S$ [M+Na]$^+$: 310.1447 *m/z*, found 310.1448 *m/z*.



2-(Sulfanylmethyl)-D-norvaline hydrochloride (**8j**): White solid. The general procedure for the hydrolysis precursors was followed. 78% isolated yield.

mp 198-200°C

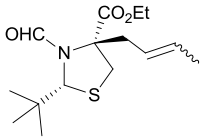
[α]$_D^{20}$ = + 26.2 (*c* 0.392.in H_2O)

^{1}H NMR (D_2O, 300 MHz): δ 3.12 (1H, d, *J* = 16.5 Hz, HSC*H*$_2$), 2.84 (1H, d, *J* = 16.5 Hz, HSC*H*$_2$), 1.82 (2H, qu, *J* = 6.8 Hz, C*H*$_2$), 1.47-1.27 (1H, m, C*H*$_2$), 1.27-1.10 (1H, m, C*H*$_2$), 0.84 (3H, t, *J* = 6.8 Hz, $CCH_2CH_2CH_3$)

^{13}C NMR (D_2O, 75 MHz): δ 172.8, 65.4, 37.3, 29.5, 16.8, 13.0

FTIR (cm^{-1}) (neat): 3292-2627 (br), 2164, 1734, 1575, 1393, 1206, 814

HRMS (ESI, Pos) calcd for $C_6H_{14}ClNO_2S$ [M-HCl]$^+$: 163.0662 *m/z*, found 163.0664 *m/z*.



Ethyl (2*R*,4*R*)-4-[(2*E*)-but-2-en-1-yl]-2-(1,1-dimethylethyl)-3-formyl-1,3-thiazolidine-4-carboxylate (**7k**): Clear oil The general procedure for the synthesis of hydrolysis precursors was followed. 55% isolated yield.

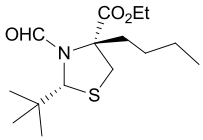
[α]$_D^{20}$ = - 55.4 (*c* 0.675.in $CHCl_3$); **R$_f$** = 0.32 (15% EtOAc/Hexanes)

^{1}H NMR ($CDCl_3$, 300 MHz) 7.7:1 mixture of rotamers and 1.5:1 mixture of conformer trans:cis - Major: δ 8.31 (1H, s, C*H*O), 5.56-5.18 (2H, m, C*H*=C*H*), 5.17 (1H, s, $(CH_3)_3CH$), 4.15-3.97 (2H, m, CO_2CH_2), 3.50 (1H, d, *J* = 16.0 Hz, SC*H*$_2$), 2.89 (1H, d, *J* = 16.0 Hz, SC*H*$_2$), 2.60-2.53 (2H, m, C*H*$_2$CH=CH), 1.54-1.42 (3H, m, CH_3CH=CH), 1.13 (3H, t, *J* = 7.5 Hz, $CO_2CH_2CH_3$), 0.76 (9H, s, $(CH_3)_3CH$)

^{13}C NMR ($CDCl_3$, 75 MHz) mixture of rotamers - Major: δ 171.7, 162.7, 131.4, 123.1, 72.2, 71.6, 62.1, 43.4, 40.0, 38.6, 26.9, 17.9, 14.0,

FTIR (cm^{-1}) (neat): 2959, 2872, 1734, 1671, 1393, 1237, 1035

HRMS (ESI, Pos) calcd for $C_{15}H_{25}NO_3S$ [M+H]$^+$: 300.1628 *m/z*, found 300.1629 *m/z*.



Ethyl (2*R*,4*R*)-4-butyl-2-(1,1-dimethylethyl)-3-formyl-1,3-thiazolidine-4-carboxylate (**11k**): A solution of thiazolidine **8k** (269 mg, 0.898 mmol) and 10% palladium on carbon (191 mg, 0.180 mmol) in EtOH (8.98 mL) was stirred under a hydrogen atmosphere for 2.5 hours. The solution was filtered over a silica pad and eluted with DCM. Flash chromatography with 0-15% EtOAc in hexanes afforded the desired alkylated thiazolidine **11k** as a clear oil (249 mg, 92%).

[α]$_D^{20}$ = - 55.0 (*c* 0.800.in $CHCl_3$); **R$_f$** = 0.32 (15% EtOAc/Hexanes)

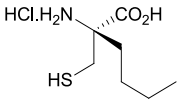
^{1}H NMR ($CDCl_3$, 300 MHz) 3.6:1 mixture of rotamers - Major: δ 8.39 (1H, s, C*H*O), 5.33 (1H, s, $(CH_3)_3CH$), 4.25-4.14 (2H, m, CO_2CH_2), 3.68 (1H, d, *J* = 15.0 Hz, SC*H*$_2$), 2.94 (1H, d, *J* = 15.0 Hz, SC*H*$_2$), 2.01-1.93 (2H, m, $CCH_2CH_2CH_2CH_3$), 1.46-1.11 (4H, m, $CCH_2CH_2CH_2CH_3$), 1.24

(3H, t, *J* = 6.0 Hz, $CO_2CH_2CH_3$), 0.96 (9H, s, $(CH_3)_3CH$), 0,83 (3H, t, *J* = 6.0 Hz, $CCH_2CH_2CH_2CH_3$)

^{13}C NMR ($CDCl_3$, 75 MHz) mixture of rotamers - Major: δ 172.5, 162.7, 72.5, 71.7, 62.2, 40.1, 40.0, 39.1, 27.0, 25.6, 22.6, 14.1, 13.7

FTIR (cm^{-1}) (neat): 2957, 2871, 1733, 1671, 1299, 1234, 1032, 731

HRMS (ESI, Pos) calcd for $C_{15}H_{27}NO_3S$ $[M+H]^+$: 302.1784 *m/z*, found 302.1779 *m/z*.



2-(Sulfanylmethyl)-D-norleucine hydrochloride (**8k**): White solid. The general procedure for the microwave-assisted hydrolysis was followed. 83% isolated yield.

mp 202-204°C

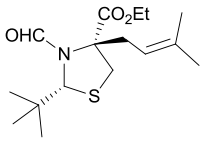
$[\alpha]_D^{20}$ = + 7.5 (*c* 0.333.in H_2O)

^{1}H NMR (D_2O, 300 MHz): δ 3.13 (1H, d, *J* = 15.0 Hz, $HSCH_2$), 2.84 (1H, d, *J* = 15.0 Hz, $HSCH_2$), 1.92-1.74 (2H, m, $CCH_2CH_2CH_2CH_3$), 1.37-1.09 (4H, m, $CCH_2CH_2CH_2CH_3$), 0.78 (3H, t, *J* = 7.5 Hz, $CCH_2CH_2CH_2CH_3$)

^{13}C NMR (D_2O, 75 MHz): δ 172.8, 65.4, 34.9, 29.5, 25.3, 22.0, 13.0

FTIR (cm^{-1}) (neat): 3271-2582 (br), 2163, 1729, 1497, 1382, 1207, 1157, 1052, 792

HRMS (ESI, Pos) calcd for $C_7H_{16}ClNO_2S$ $[M-HCl]^+$: 177.0818 *m/z*, found 177.0820 *m/z*.



Ethyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-3-formyl-4-(3-methylbut-2-en-1-yl)-1,3-thiazolidine-4-carboxylate (**7l**): Clear oil. The general procedure for the synthesis of hydrolysis precursors was followed. 67% isolated yield.

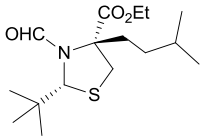
$[\alpha]_D^{20}$ = - 48.3 (*c* 0.892.in $CHCl_3$); **R_f** = 0.34 (15% EtOAc/Hexanes)

^{1}H NMR ($CDCl_3$, 300 MHz) 3:1 mixture of rotamers - Major: δ 8.51 (1H, s, C*H*O), 5.37 (s, 1H, $(CH_3)_3CH$), 5.10 (1H, br t, *J* = 6.0 Hz, $CH=(CH_3)_2$), 4.34-4.16 (2H, m, CO_2CH_2), 3.67 (1H, d, *J* = 12.0 Hz, SCH_2), 3.00 (1H, d, *J* = 12.0 Hz, SCH_2), 2.77 (2H, d, *J* = 6.0 Hz, $CH_2CH=(CH_3)_2$), 1.71 (3H, s, $CH_2CH=(CH_3)_2$), 1.61 (3H, s, $CH_2CH=(CH_3)_2$), 1.31 (3H, t, *J* = 7.5 Hz, $CO_2CH_2CH_3$), 0.94 (9H, s, $(CH_3)_3CH$)

^{13}C NMR ($CDCl_3$, 75 MHz) mixture of rotamers - Major: δ 172.0, 162.9, 137.7, 116.6, 72.8, 71.9, 62.3, 40.1, 39.1, 38.9, 27.1, 25.9, 18.1, 14.1

FTIR (cm^{-1}) (neat): 2959, 2871, 1734, 1672, 1362, 1228, 1050

HRMS (ESI, Pos) calcd for $C_{16}H_{27}NO_3S$ $[M+H]^+$: 314.1784 *m/z*, found 314.1784 *m/z*.



Ethyl (2*R*,4*R*)-2-(1,1-dimethylethyl)-3-formyl-4-(3-methylbutyl)-1,3-thiazolidine-4-carboxylate (**11l**): A solution of thiazolidine **8l** (150 mg, 0.479 mmol) and 10% palladium on carbon (102 mg, 0.096 mmol) in EtOH (4.79 mL) was stirred under a hydrogen atmosphere for 16 hours. The solution was filtered over a silica pad and eluted with DCM. Flash chromatography with 0-15% EtOAc in hexanes afforded the desired alkylated thiazolidine **11l** as a clear oil (150 mg, 99%).

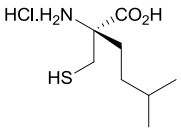
$[\alpha]_D^{20}$ = - 56.2 (*c* 0.992.in $CHCl_3$); **R_f** = 0.34 (15% EtOAc/Hexanes)

^{1}H NMR ($CDCl_3$, 300 MHz) 3.7:1 mixture of rotamers - Major: δ 8.43 (1H, s, C*H*O), 5.37 (1H, s, $(CH_3)_3CH$), 4.24 (2H, q, *J* = 8.0 Hz, CO_2CH_2), 3.72 (1H, d, *J* = 12.0 Hz, SCH_2), 2.95 (1H, d, *J* =12.0 Hz, SCH_2), 2.01 (2H, t, *J* = 9.0 Hz, $CCH_2CH_2CH(CH_3)_2$) 1.52-1.41 (1H, m, $CCH_2CH_2CH(CH_3)_2$), 1.28 (3H, t, *J* = 8.0 Hz, $CO_2CH_2CH_3$), 1.28-1.16 (2H, m, $CCH_2CH_2CH(CH_3)_2$), 0.91 (9H, s, $(CH_3)_3CH$), 0,86 (6H, br d, *J* = 6.0 Hz, $CCH_2CH_2CH(CH_3)_2$)

^{13}C NMR ($CDCl_3$, 75 MHz) mixture of rotamers - Major: δ 172.5, 162.8, 72.7, 71.9, 62.4, 40.1, 39.0, 38.4, 32.2, 28.1, 26.7, 22.4, 14.1

FTIR (cm^{-1}) (neat): 2956, 2870, 1733, 1672, 1362, 1298, 1032

HRMS (ESI, Pos) calcd for $C_{16}H_{29}NO_3S$ $[M+H]^+$: 316.1941 *m/z*, found 316.1948 *m/z*.



5-Methyl-2-(sulfanylmethyl)-D-norleucine hydrochloride (**8l**): White solid. The general procedure for microwave-assisted hydrolysis precursors was followed

mp 178-180°C

$[\alpha]_D^{20}$ = +18.0 (*c* 0.316.in H_2O)

^{1}H NMR (D_2O, 400 MHz): δ 3.09 (1H, d, *J* = 14.0 Hz, $HSCH_2$), 2.82 (1H, d, *J* = 14.0 Hz, $HSCH_2$), 1.94-1.73 (2H, m, $CCH_2CH_2CH(CH_3)_2$), 1.50-1.38 (1H, m, $CCH_2CH_2CH(CH_3)_2$), 1.26-1.13 (1H, m, $CCH_2CH_2CH(CH_3)_2$), 1.09-0.95 (1H, m, $CCH_2CH_2CH(CH_3)_2$), 0.76 (6H, d, *J* = 4.0 Hz, $CCH_2CH_2CH(CH_3)_2$)

^{13}C NMR (D_2O, 75 MHz): δ 172.8, 65.4, 33.3, 31.6, 29.0, 27.4, 21.5

FTIR (cm^{-1}) (neat):3221-2625 (br), 2195, 1731, 1560, 1388, 1210, 1057

HRMS (ESI, Pos) calcd for $C_8H_{18}ClNO_2S$ $[M-HCl]^+$: 191.0975 *m/z*, found 191.0975 *m/z*.

Multi-gram synthesis of 5a

Procedure using CEM Stop-flow Voyager

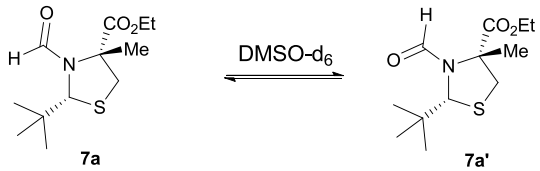
Thiazolidine **7a** (5.00 g, 19.28 mmol) was added to a 1 L bottle and purged with argon for 15 minutes. A solution of aqueous HCl 5N (64 mL), previously degassed by bubbling argon for 30 min, was added. This inlet bottle was sealed under an atmosphere of argon and the solution was vigorously stirred to create a suspension. The reaction was then performed with 2 cycles (2 x 35 mL) at 160 °C for 1 hour. The inlet bottle was washed with a solution HCl 5 N (20 mL) and a last cycle was performed at 160 °C for 1 hour. The combined aqueous phases were washed with EtOAc (3 x 40 ml) then the acidic aqueous phase was concentrated under reduced pressure to afford the desired (*R*)-α-alkylcysteine **5a** as a highly hygroscopic beige solid (3.18 g, 96%). The inlet bottle was extracted with DCM (3x 25 mL) to recover 350 mg of starting material as a clear oil (Quantitative yield based on recovered starting material)

Procedure using CEM Microwave-Accelerated Reaction System (MARS)

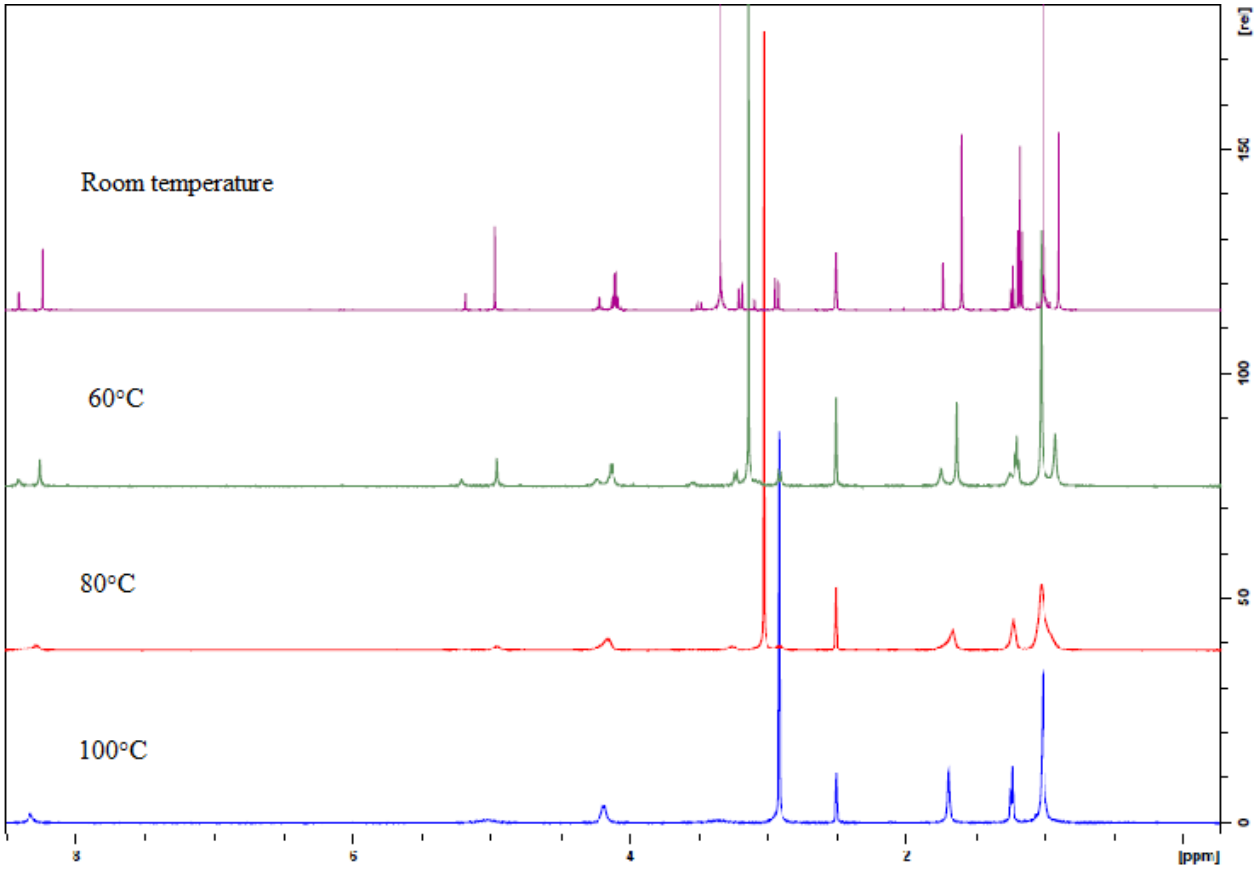
Thiazolidine **7a** (10.0 g, 38.55 mmol) was added to 5 different closed vessels (5 x 2.0 g) and purged with argon for 15 minutes. A solution of aqueous HCl 5N (5 x 25 mL), previously degassed by bubbling argon for 30 minutes, was added to each vessel which were rapidly sealed under an atmosphere of argon. The solutions were heated at 160 °C for 1 hour using MARS digestion system. The combined aqueous phases were washed with EtOAc (3 x 75 ml) then the acidic aqueous was concentrated under reduced pressure to afford the desired (*R*)-α-alkylcysteine **5a** as a highly hygroscopic beige solid (6.60 g, 99%).

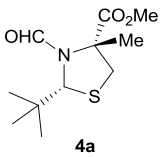
^{1}H NMR and ^{13}C NMR Spectra

High temperature ^{1}H NMR Experiment with 7a

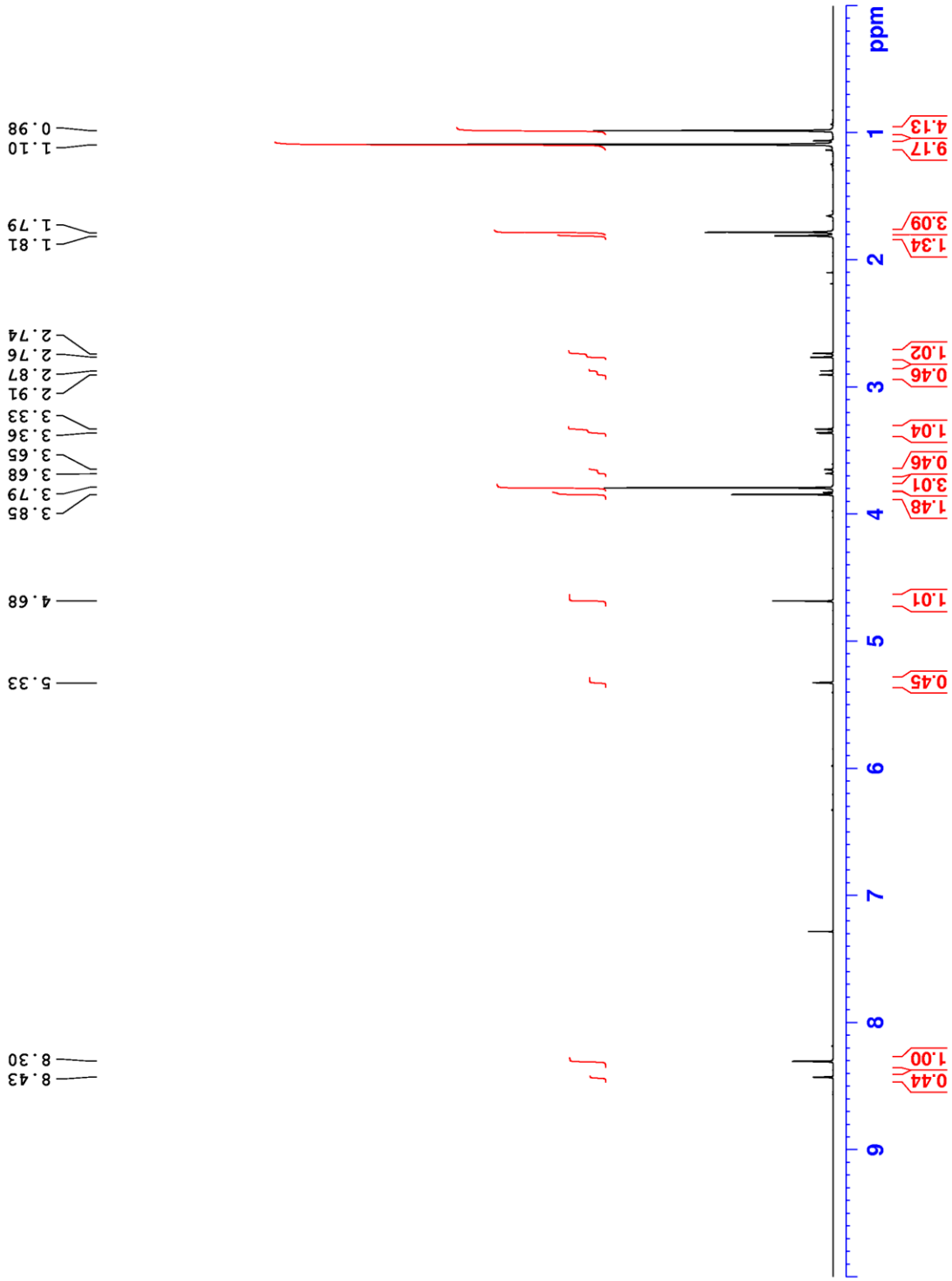


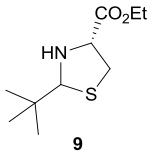
7a 7a'





4a

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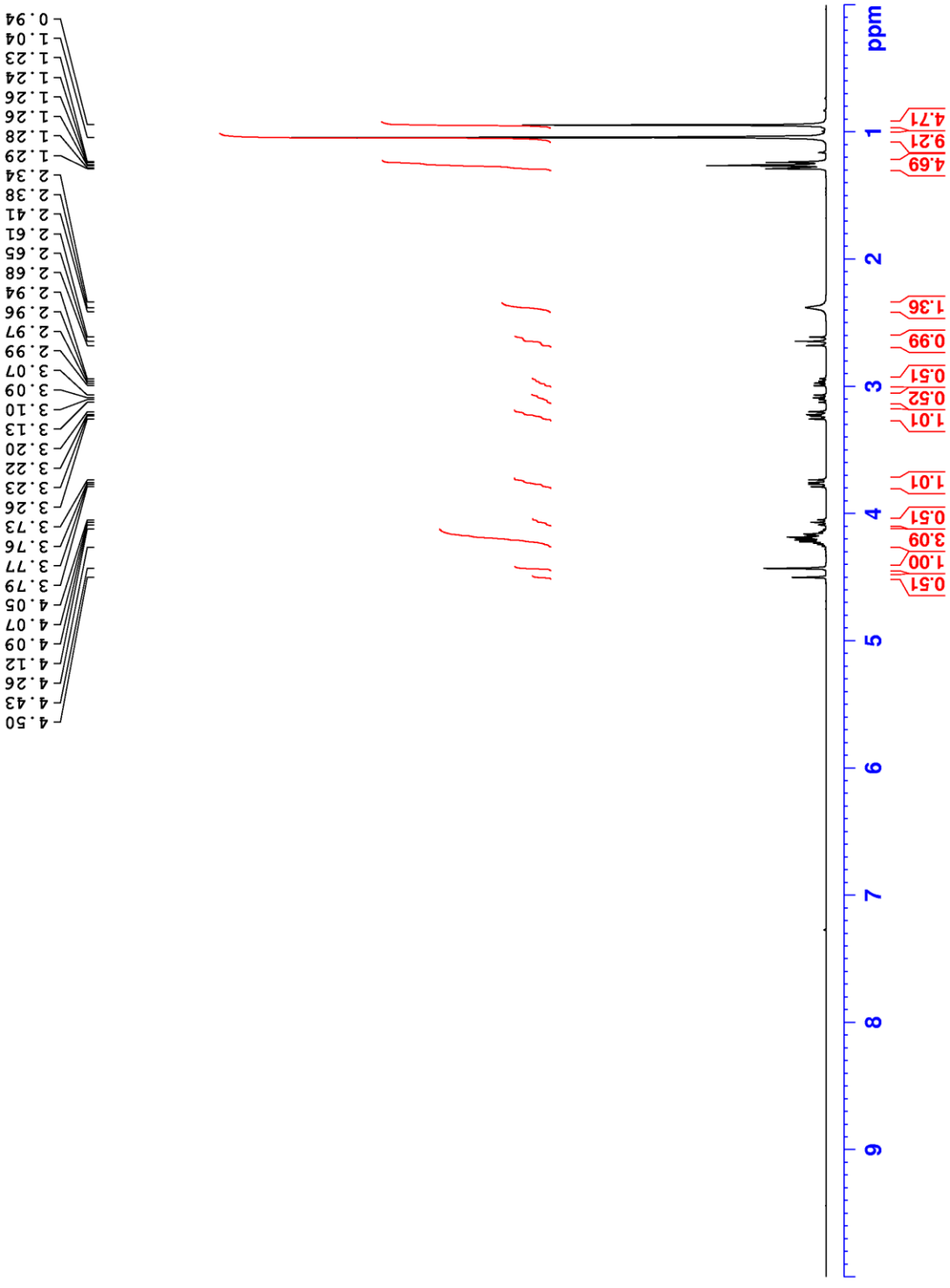
HN
S

9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2.68
2.94
2.96
2.97
2.99
3.07
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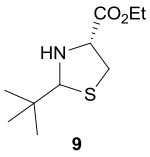
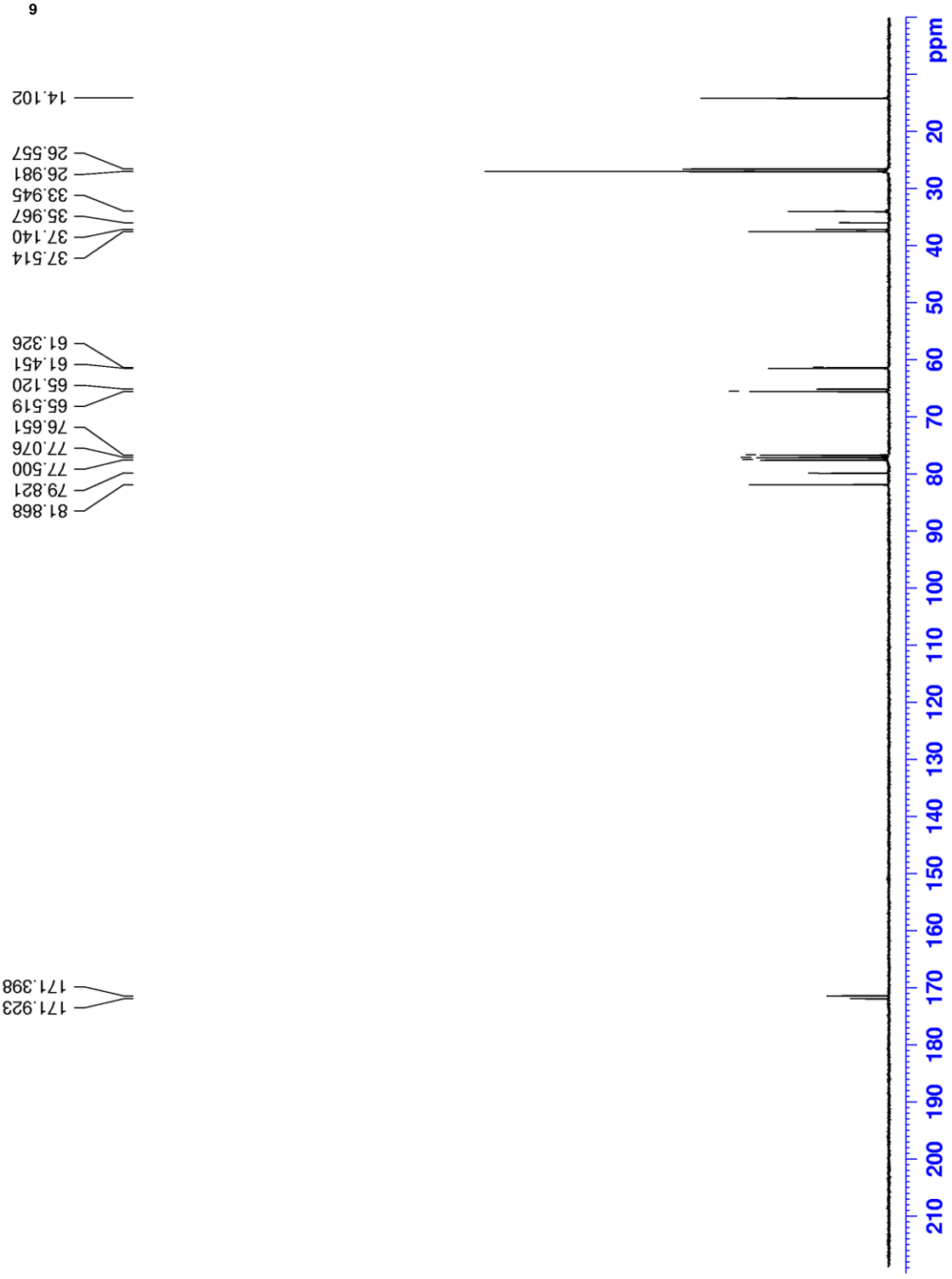

CO2Et
HN
S

9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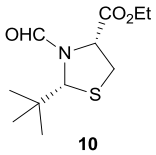
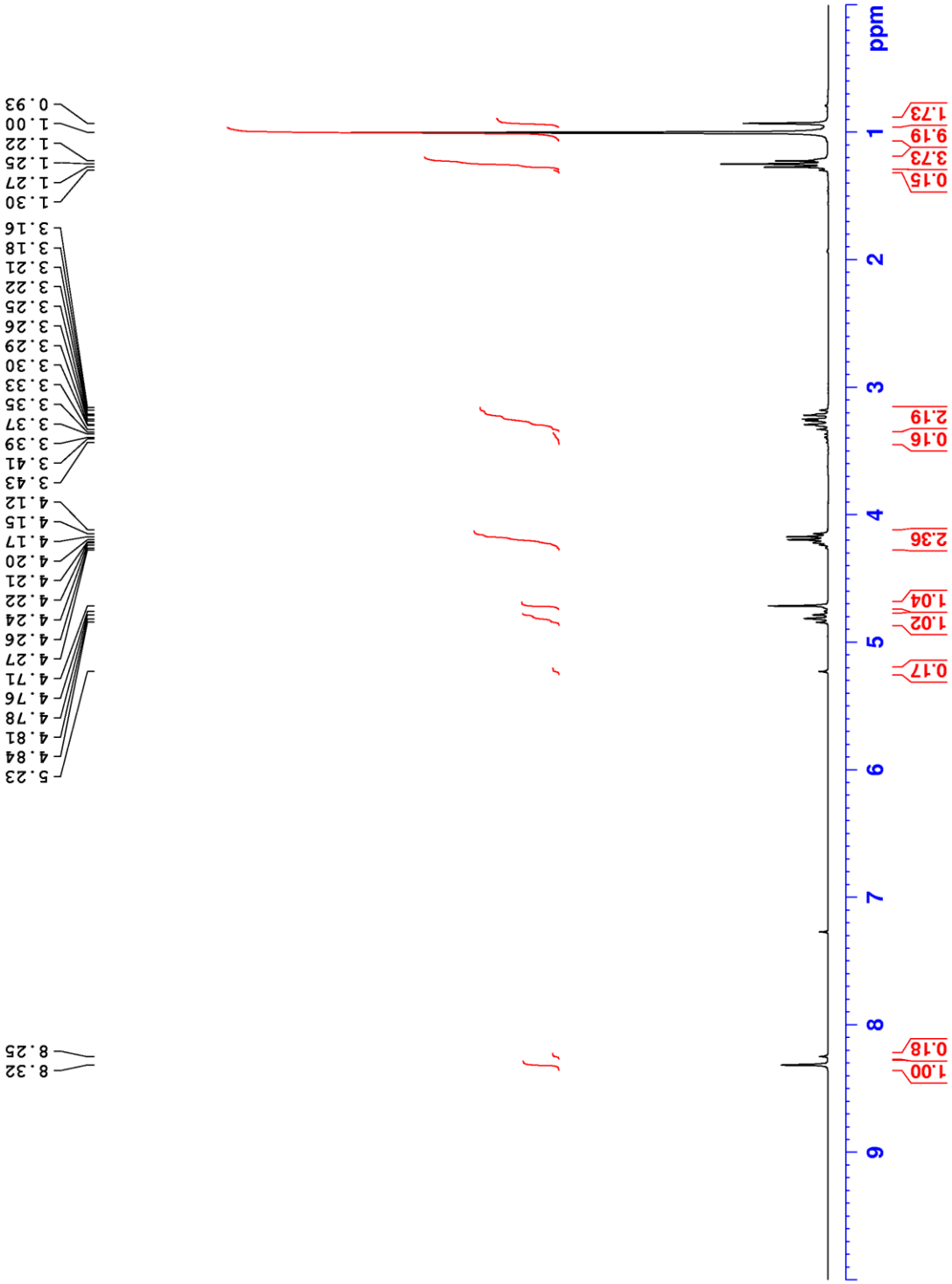
ppm


OHC
N
CO2Et
S

10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3.30
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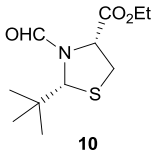
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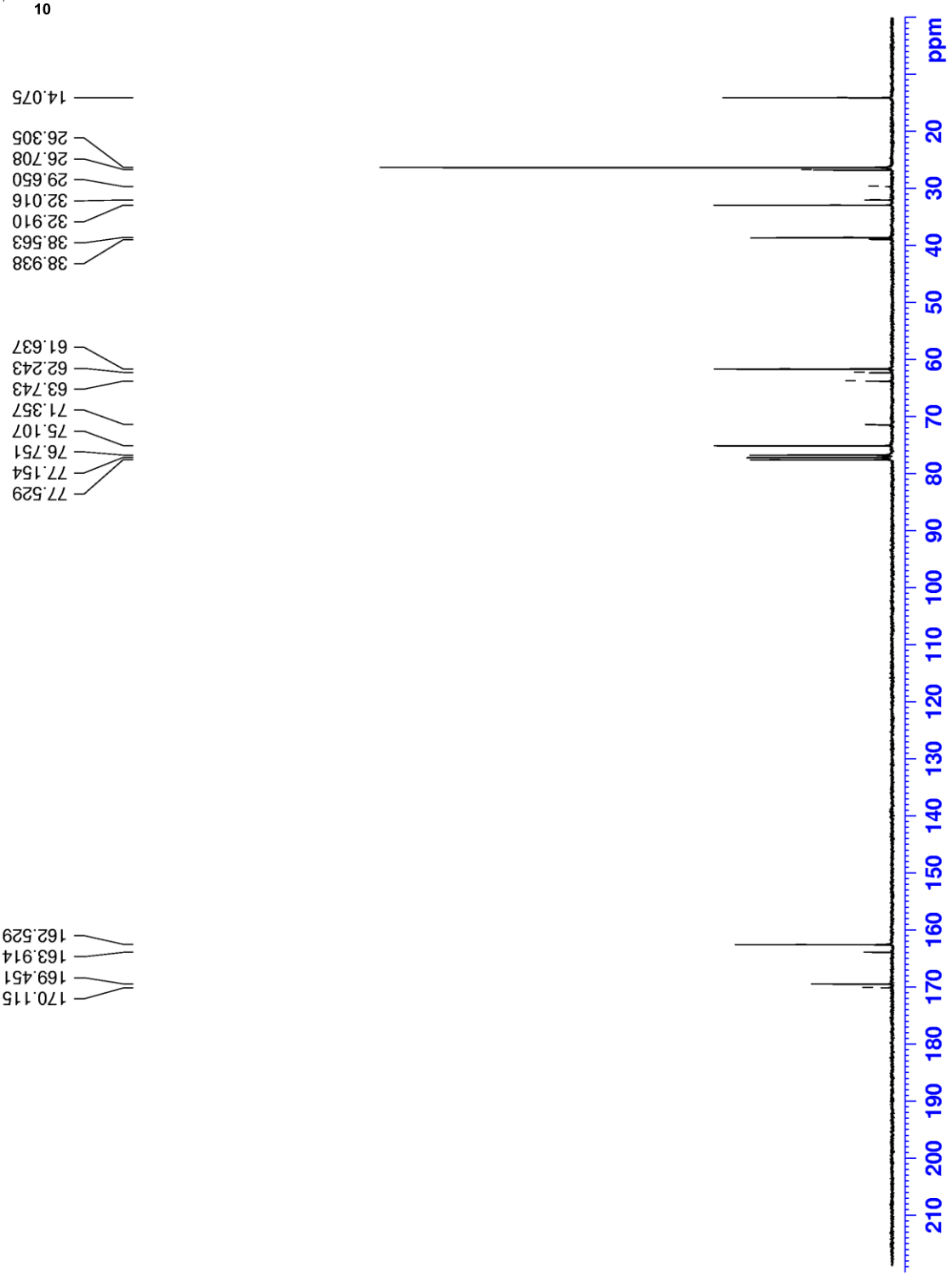
N
S
CO2Et

10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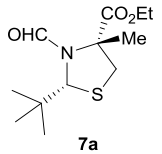
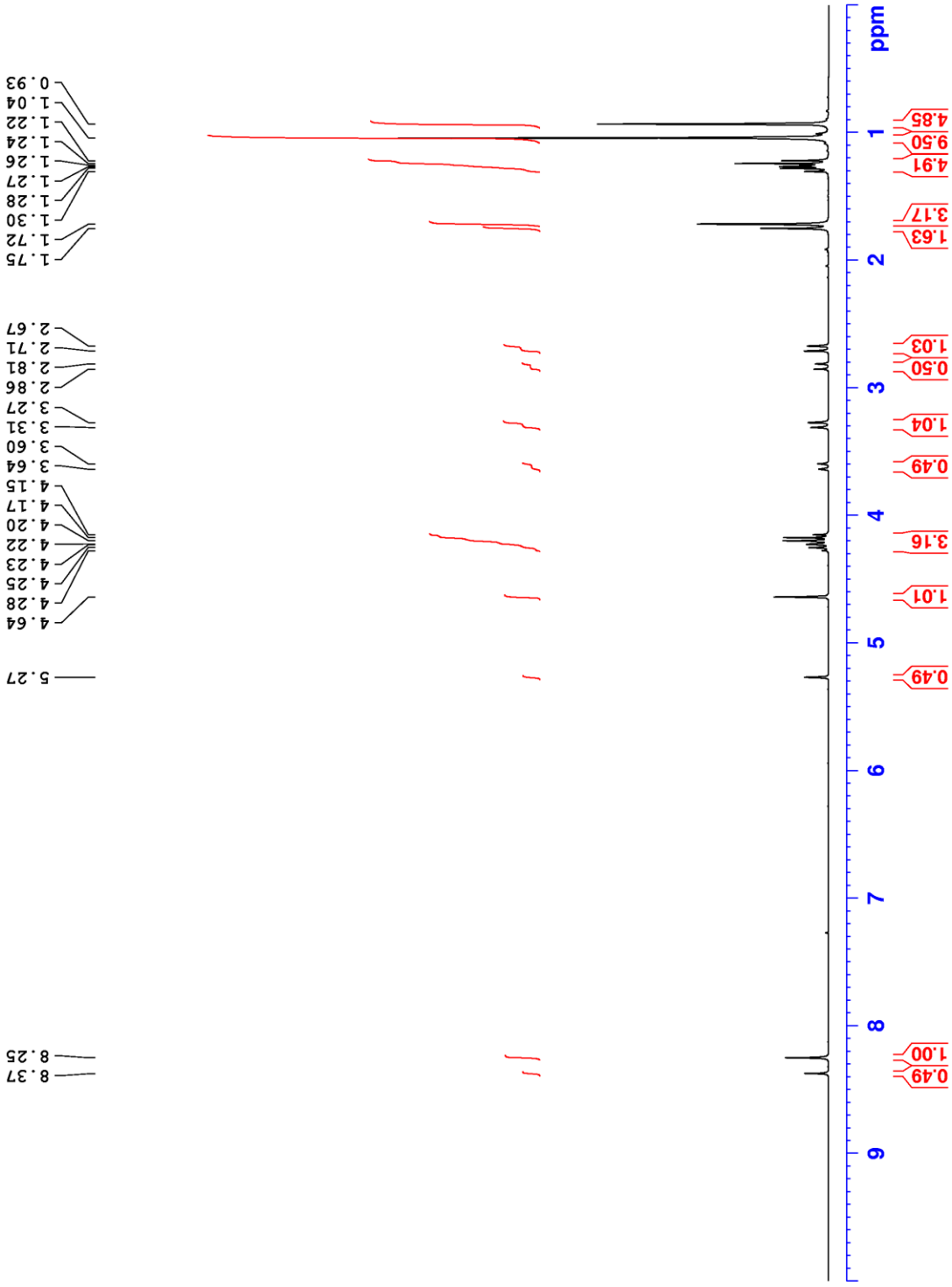

CO2Et
OHC
N
Me
S

7a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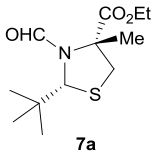
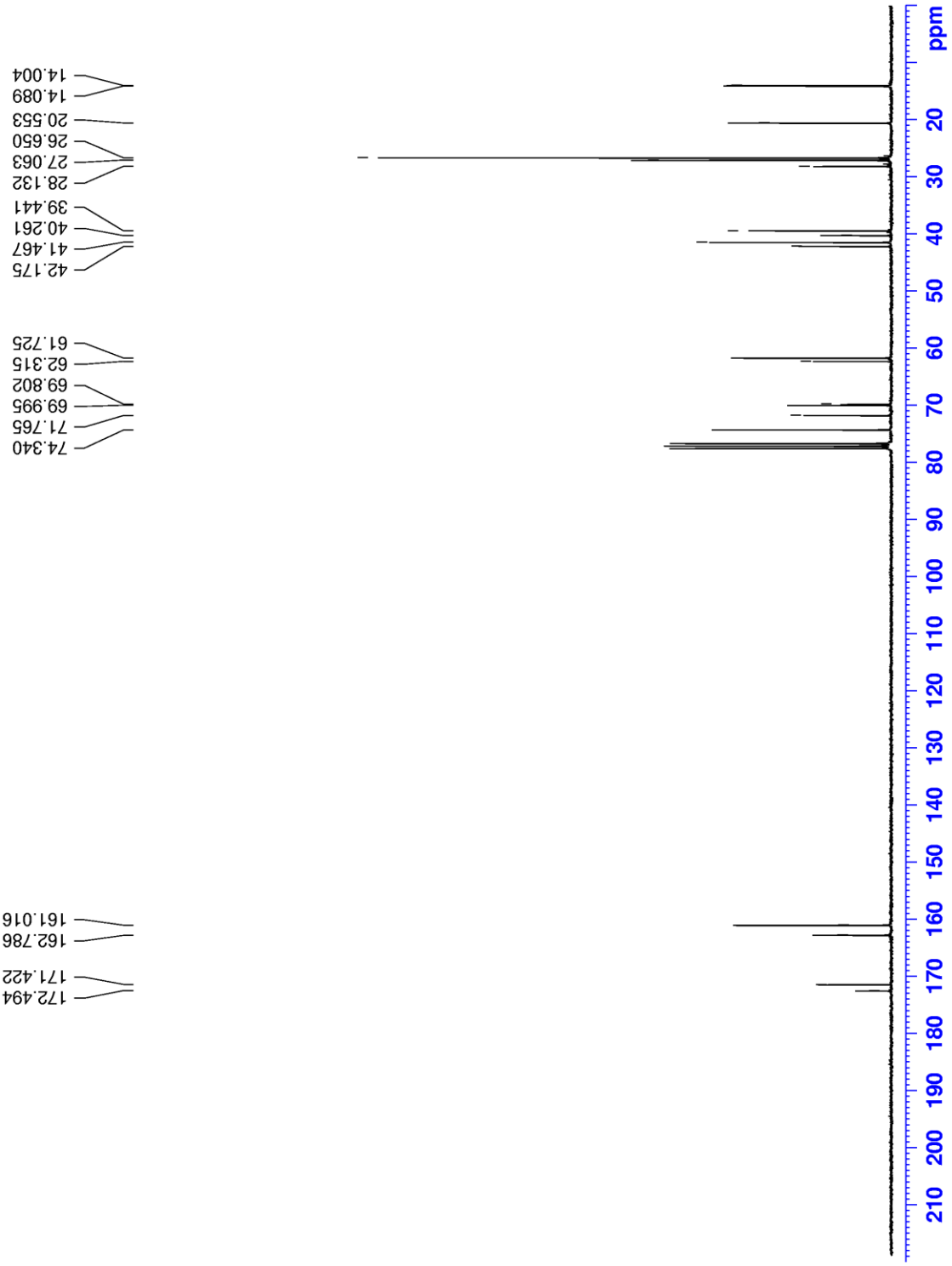
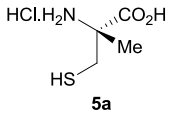
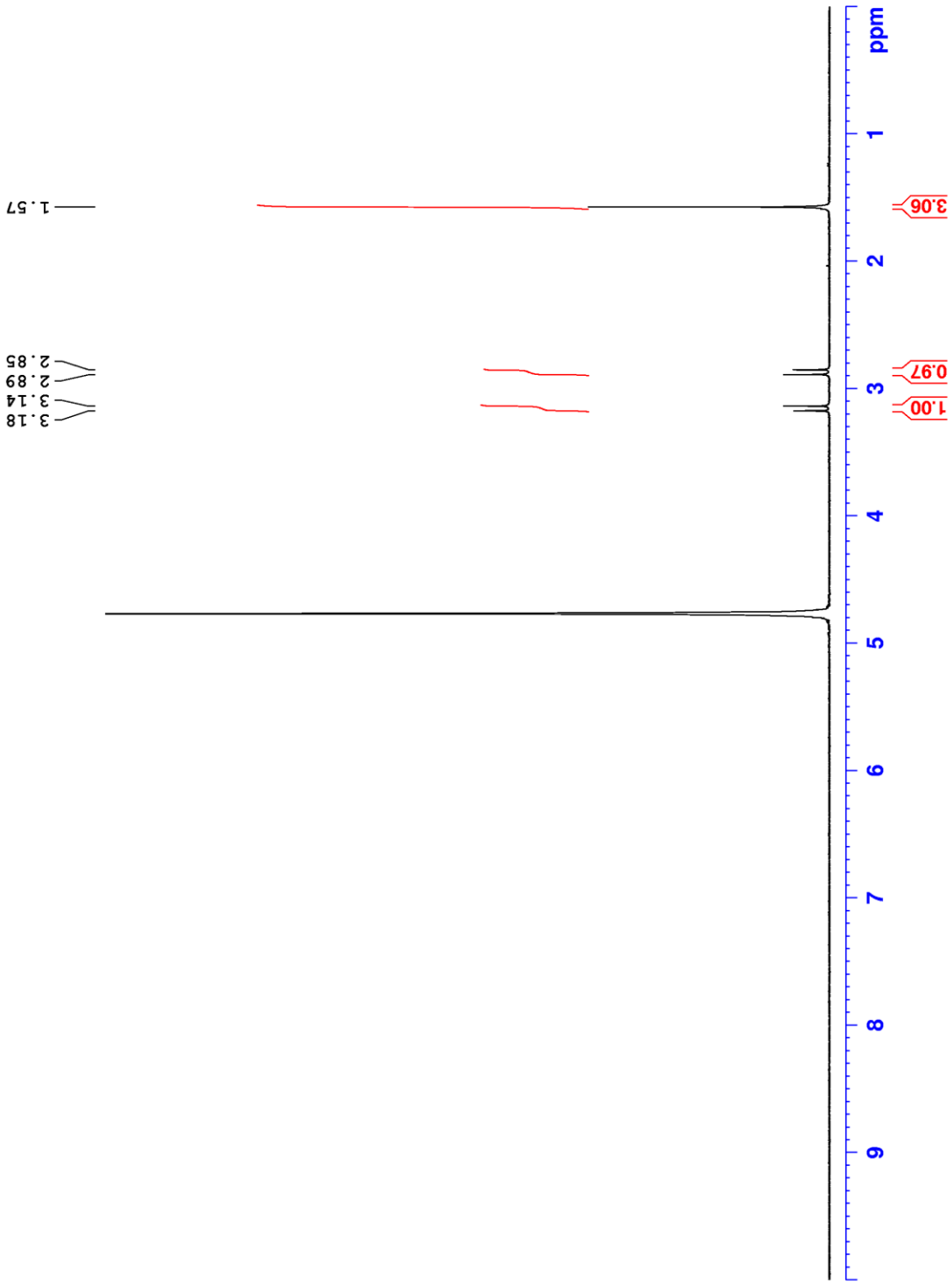


7a




HCl.H2N
CO2H
Me
HS

5a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2.85
2.89
3.14
3.18
3.06
0.97
1.00
ppm
1
2
3
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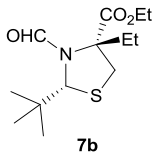
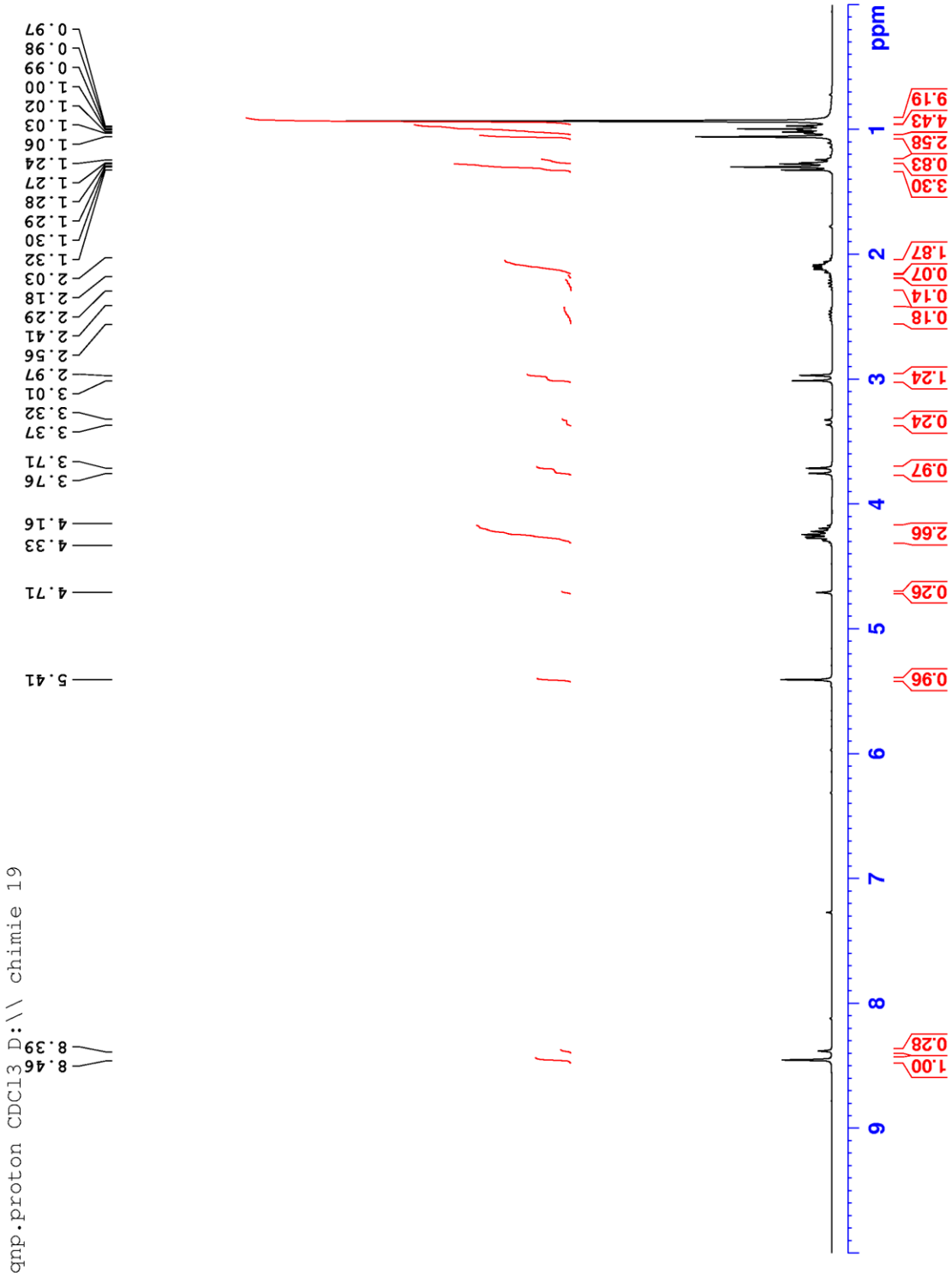
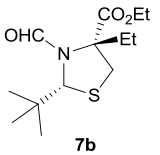
6
7
8
9



7b





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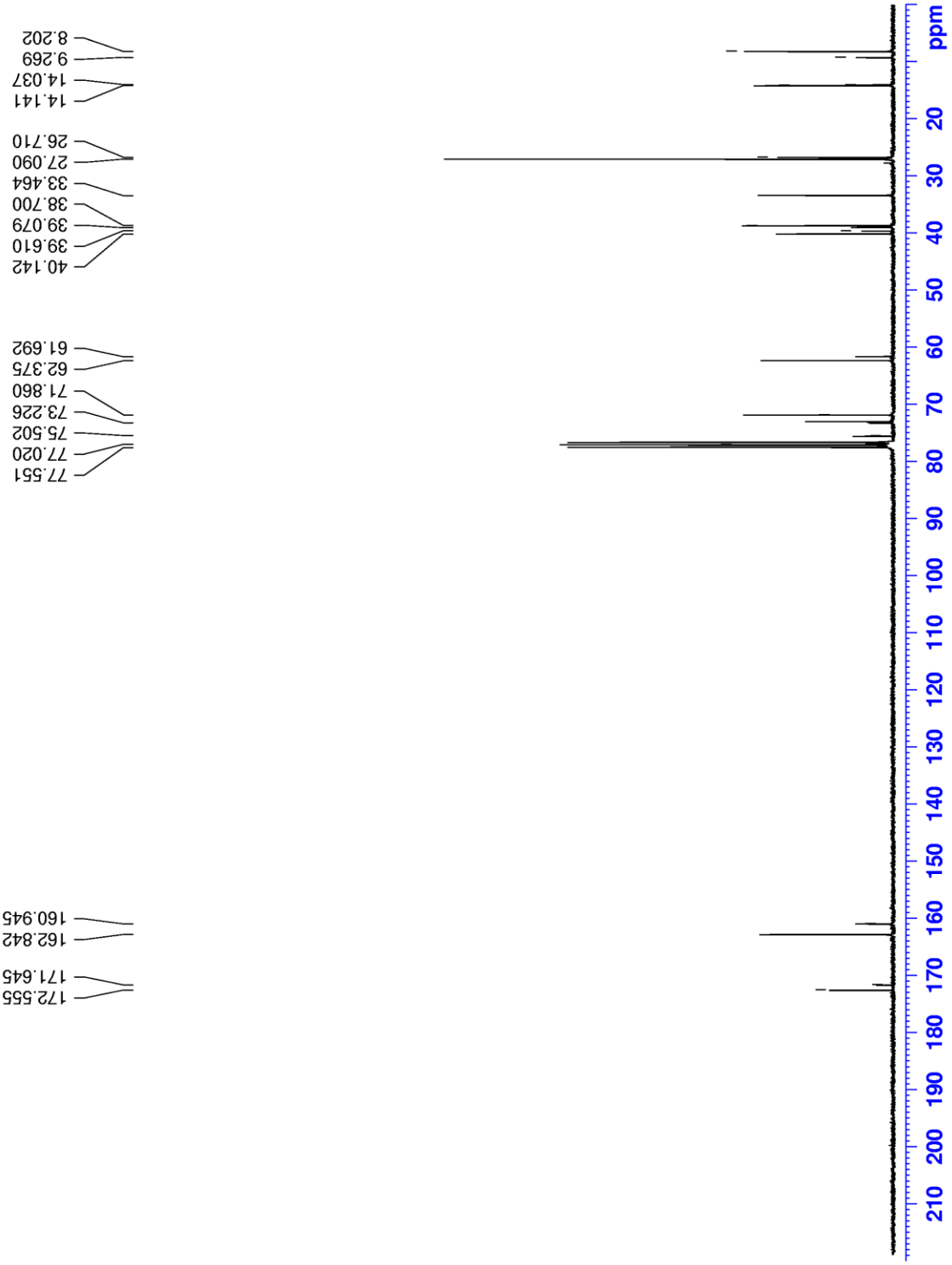
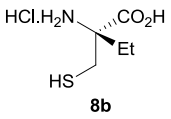
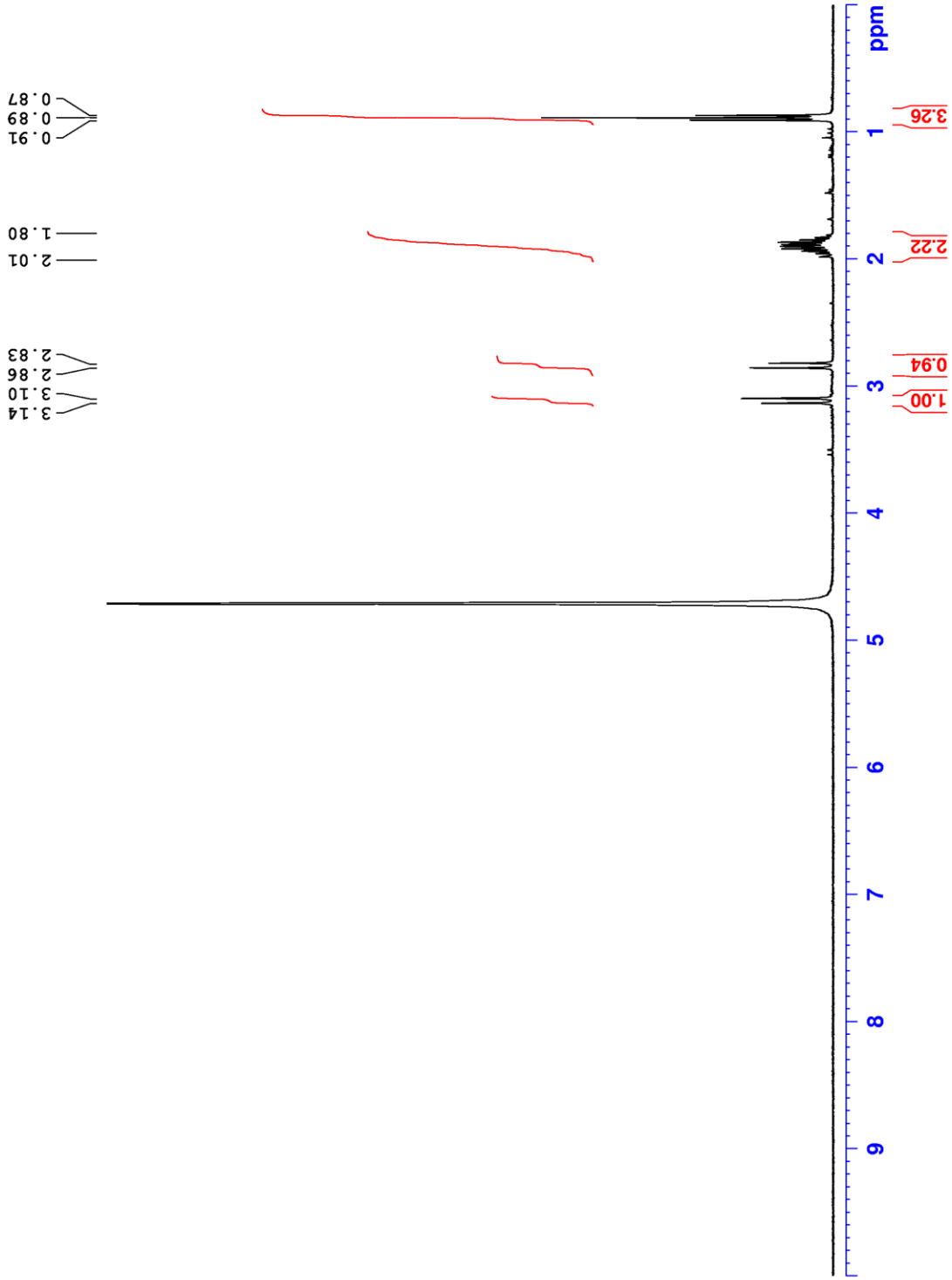



HCl.H2N
CO2H
Et
HS

8b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2.83
2.86
3.10
3.14
3.26
2.22
0.94
1.00
ppm
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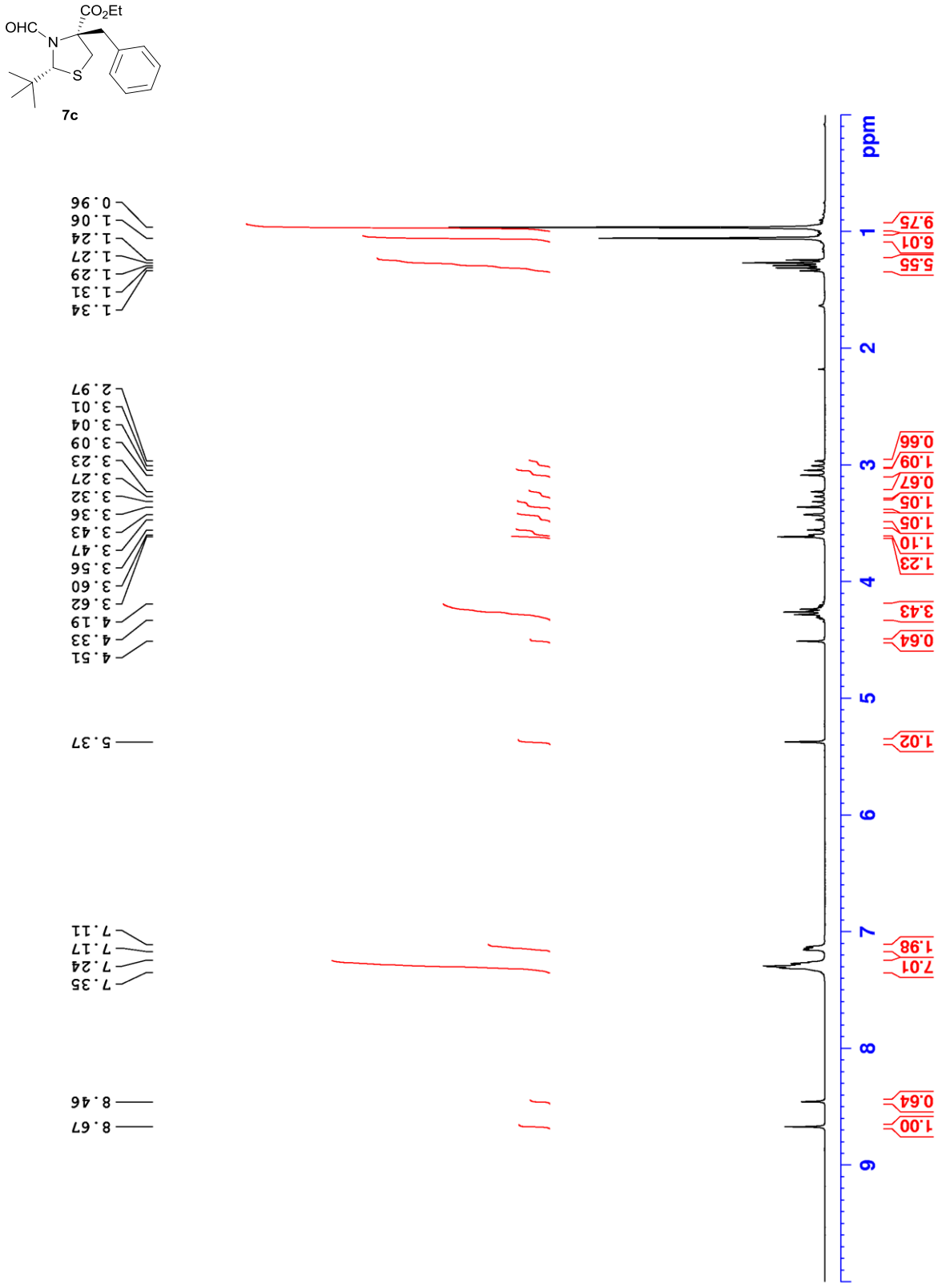
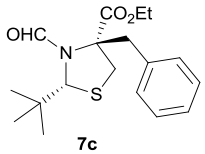
2
3
4
5
6
7
8
9





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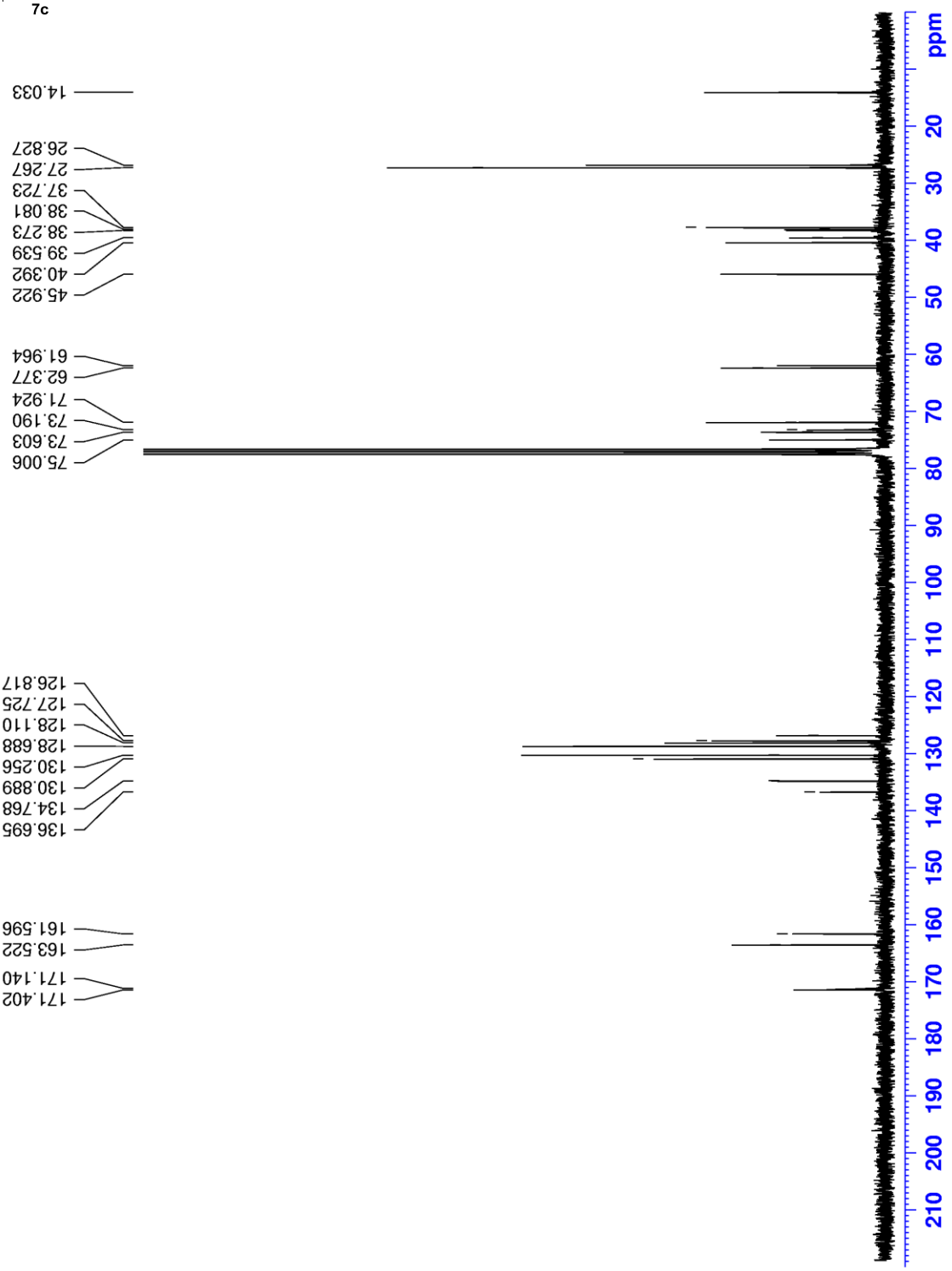
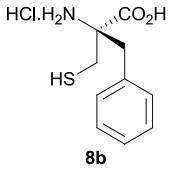
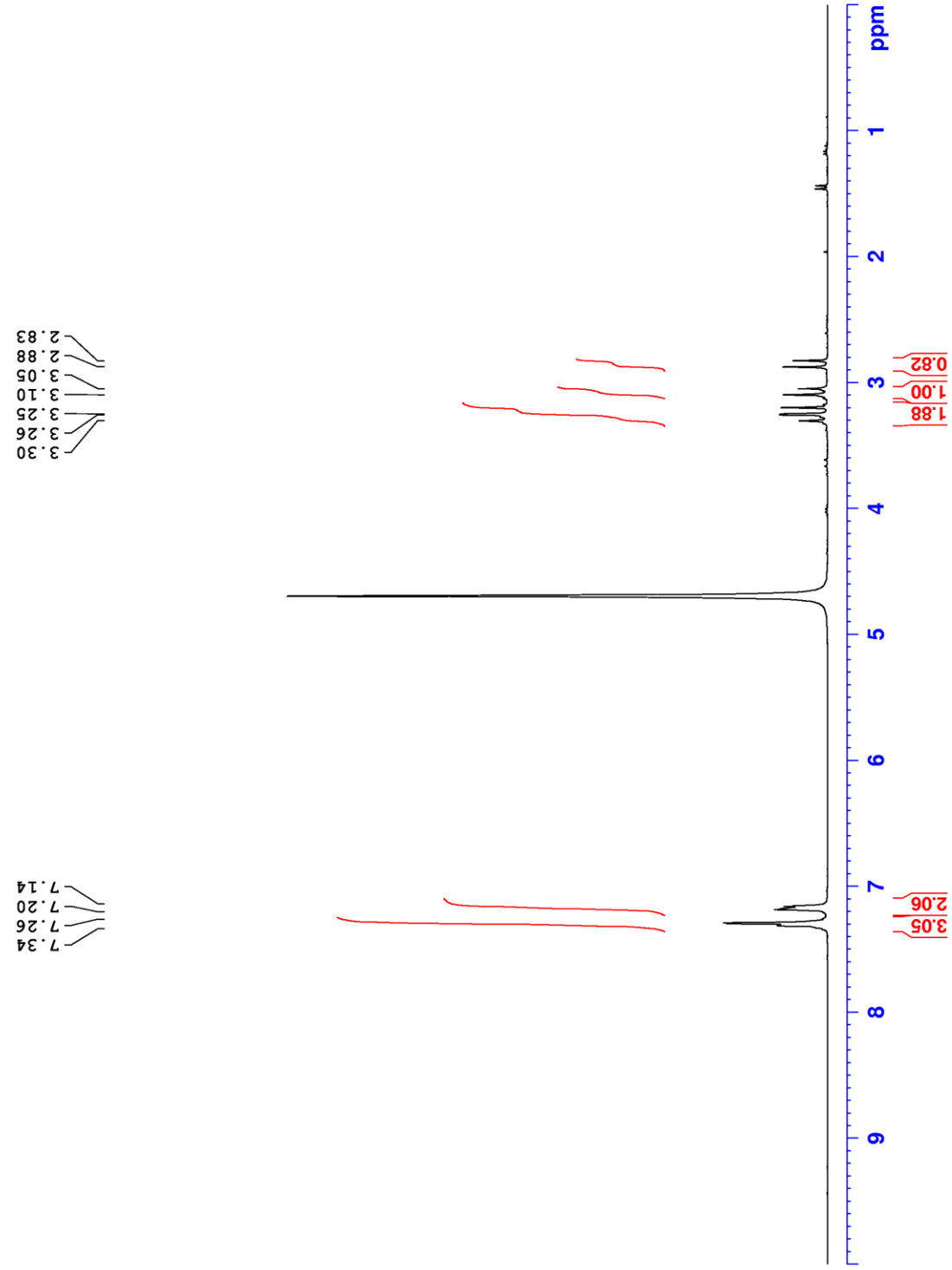
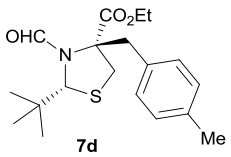


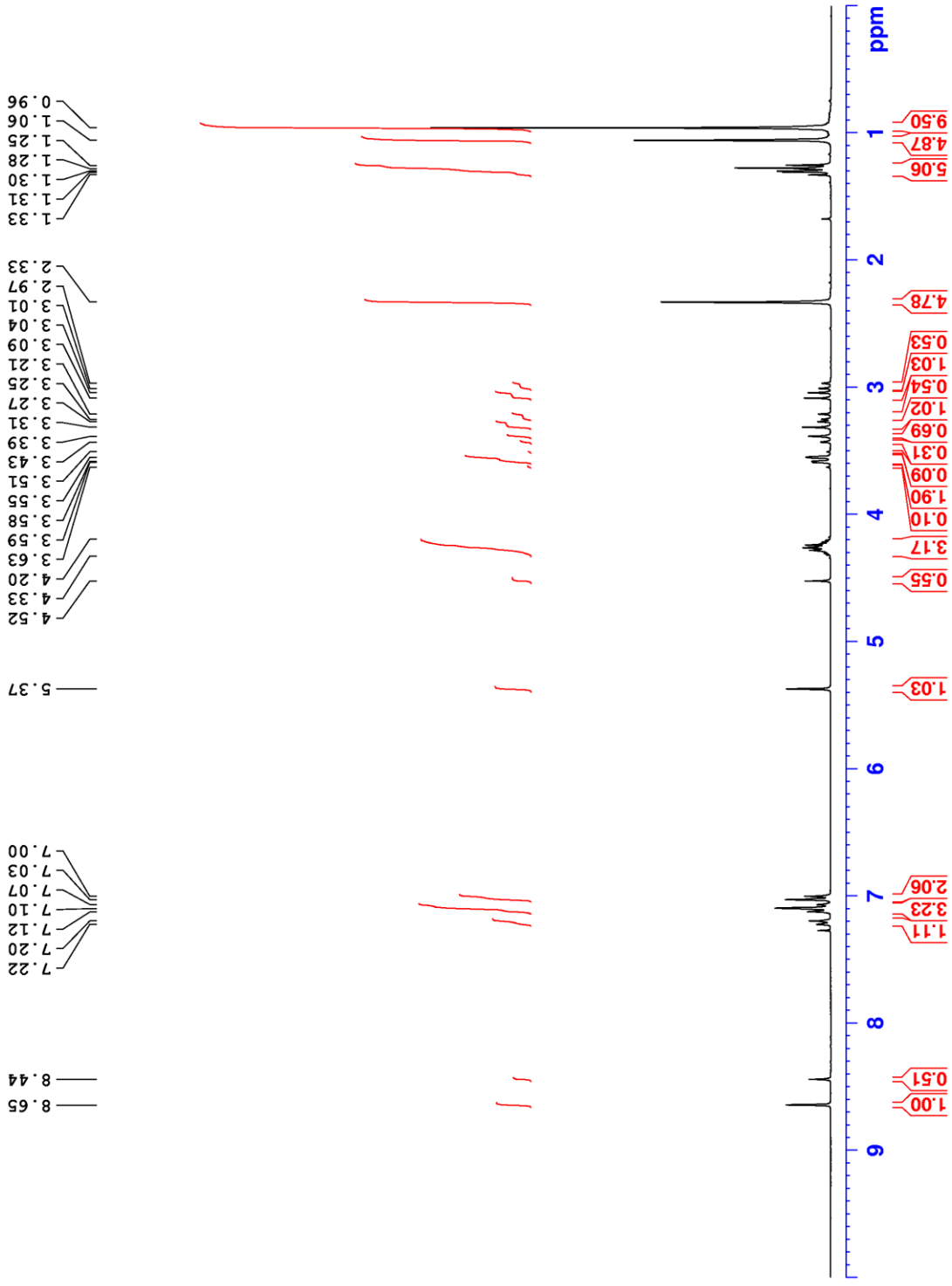


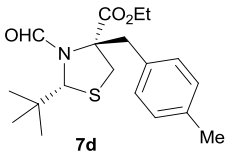
8b



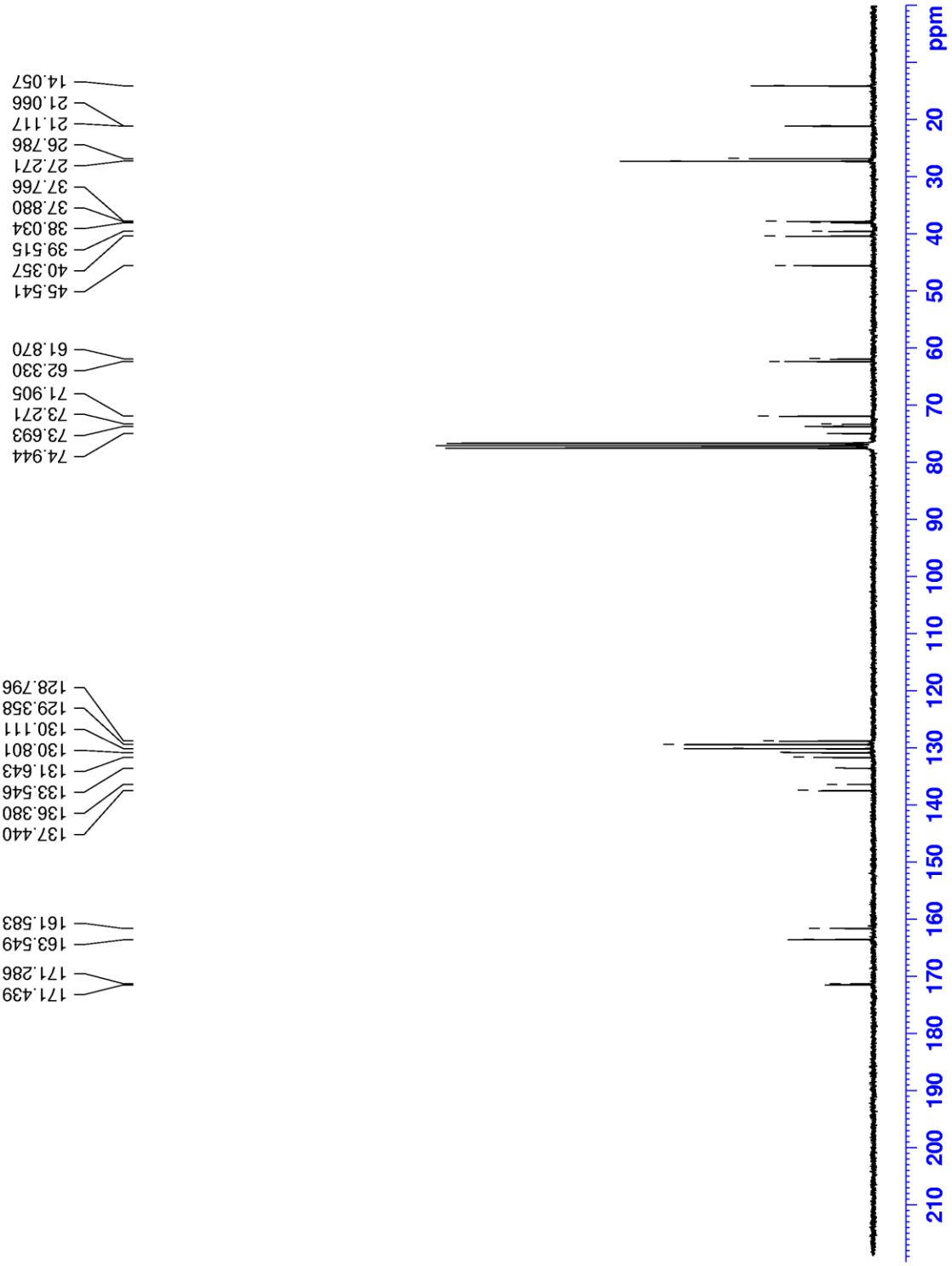


7d




CO2Et
OHC
N
S
Me

7d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21.117
26.786
27.271
37.766
37.880
38.034
39.515
40.357
45.541
61.870
62.330
71.905
73.271
73.693
74.944
128.796
129.358
130.111
130.801
131.643
133.546
136.380
137.440
161.583
163.549
171.286
171.439
ppm
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60
70
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90
100
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120
130
140
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180
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200
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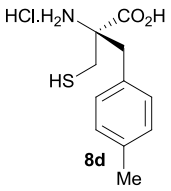
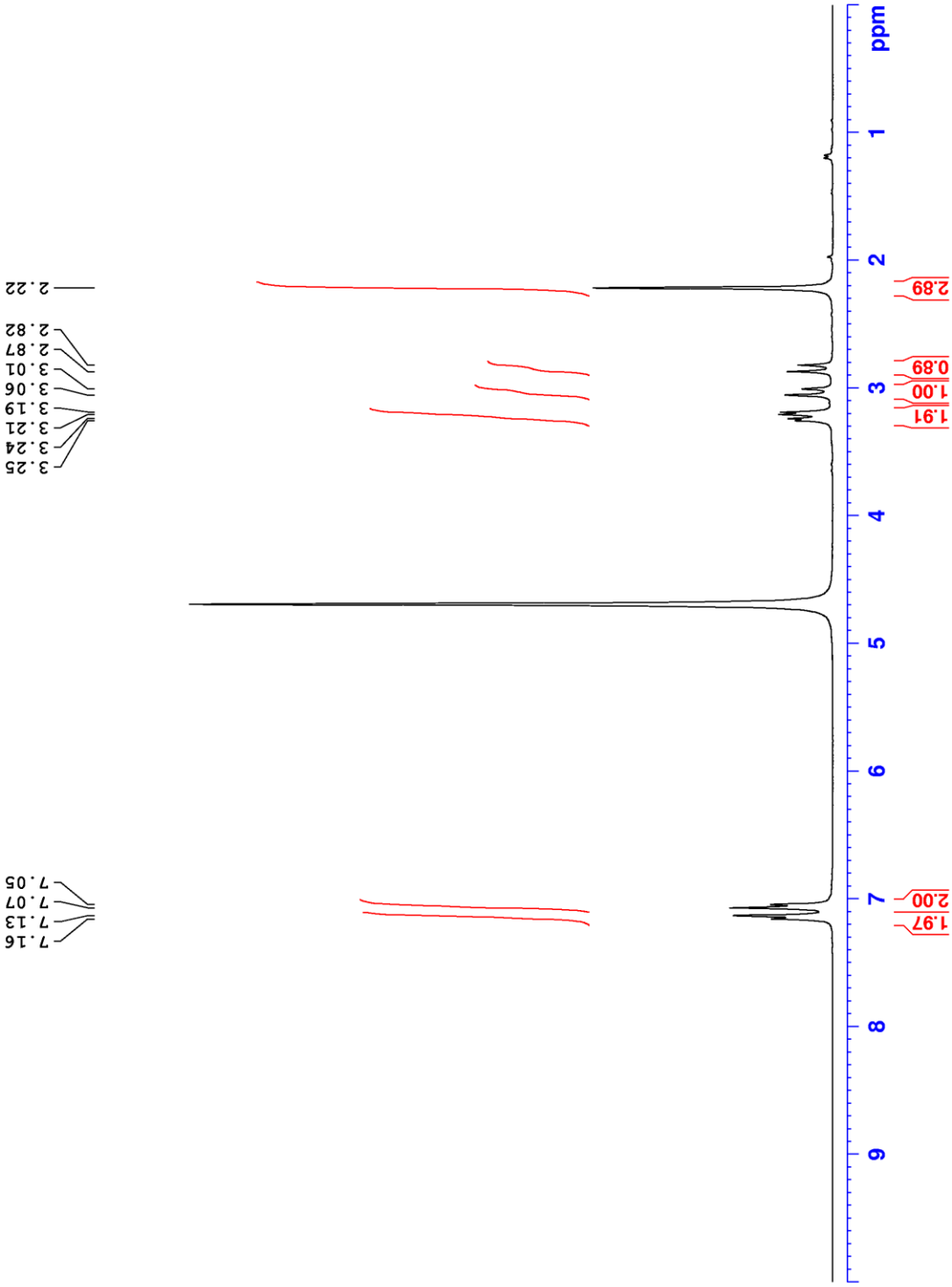
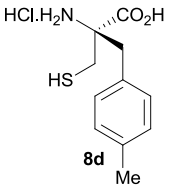
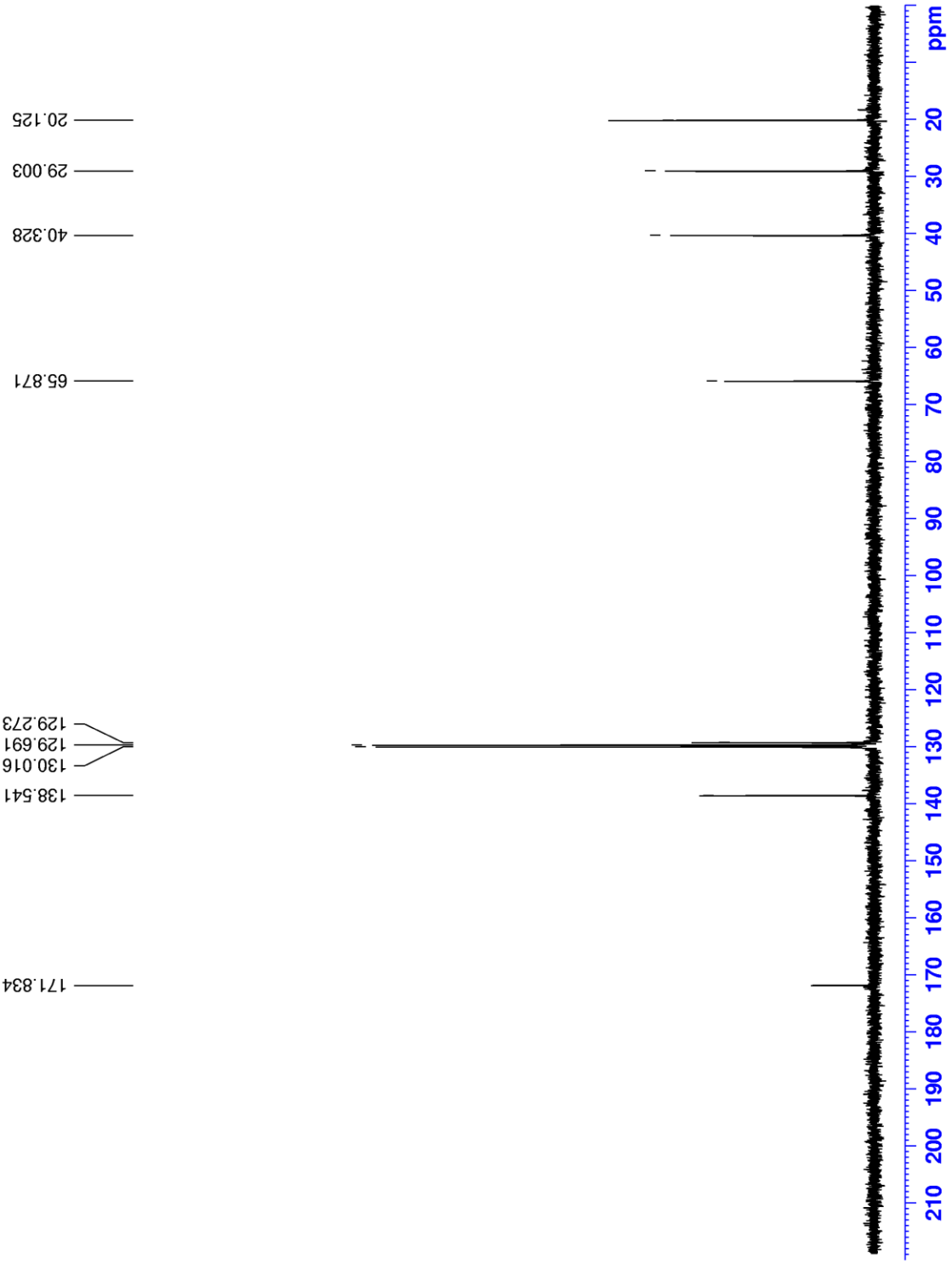





HCl.H2N
CO2H
HS
8d
Me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129.691
130.016
138.541
171.834
ppm
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60
70
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100
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140
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180
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200
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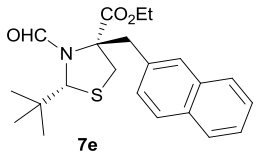
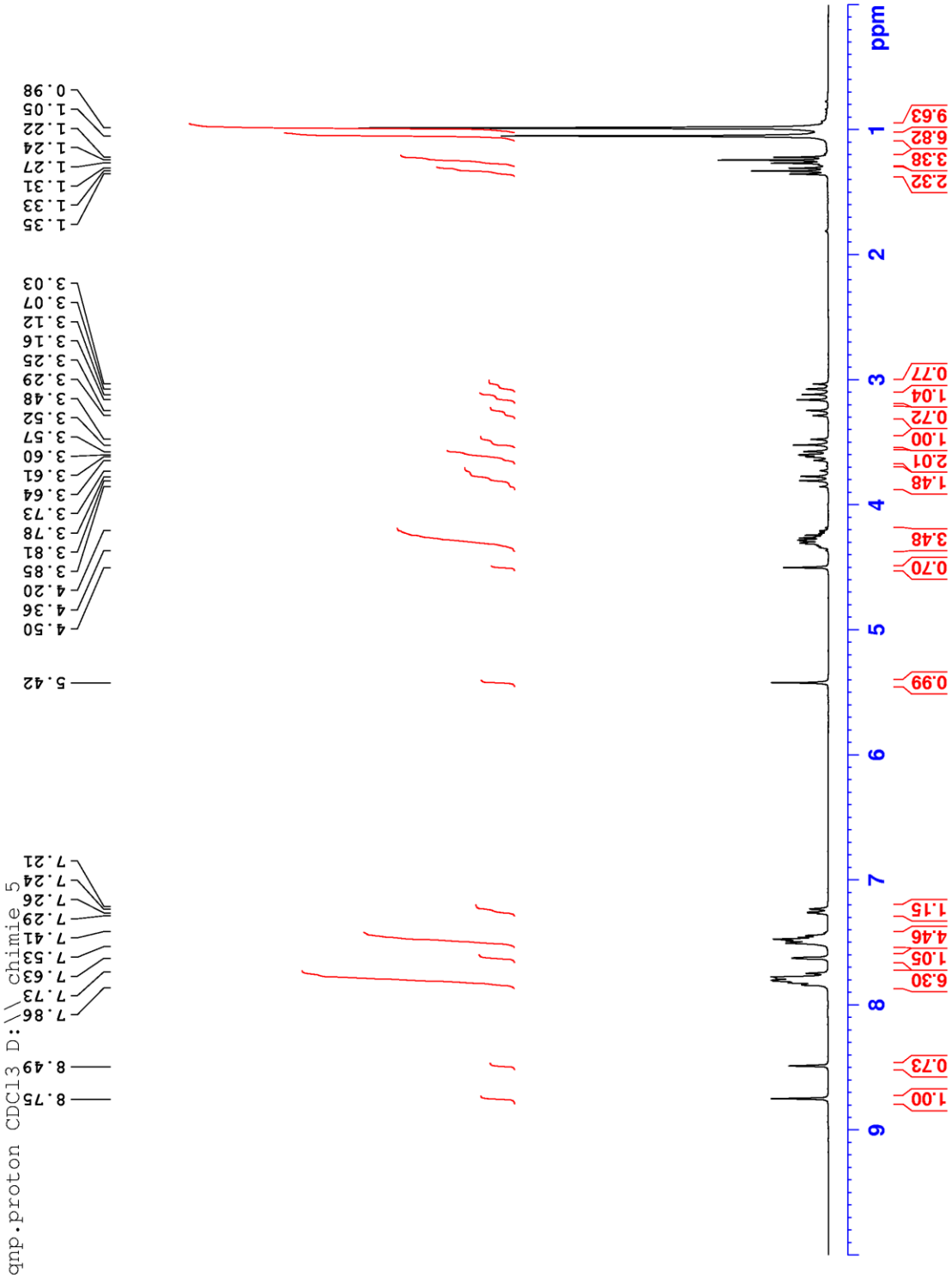
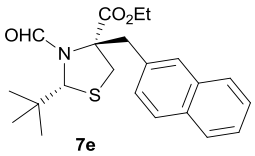
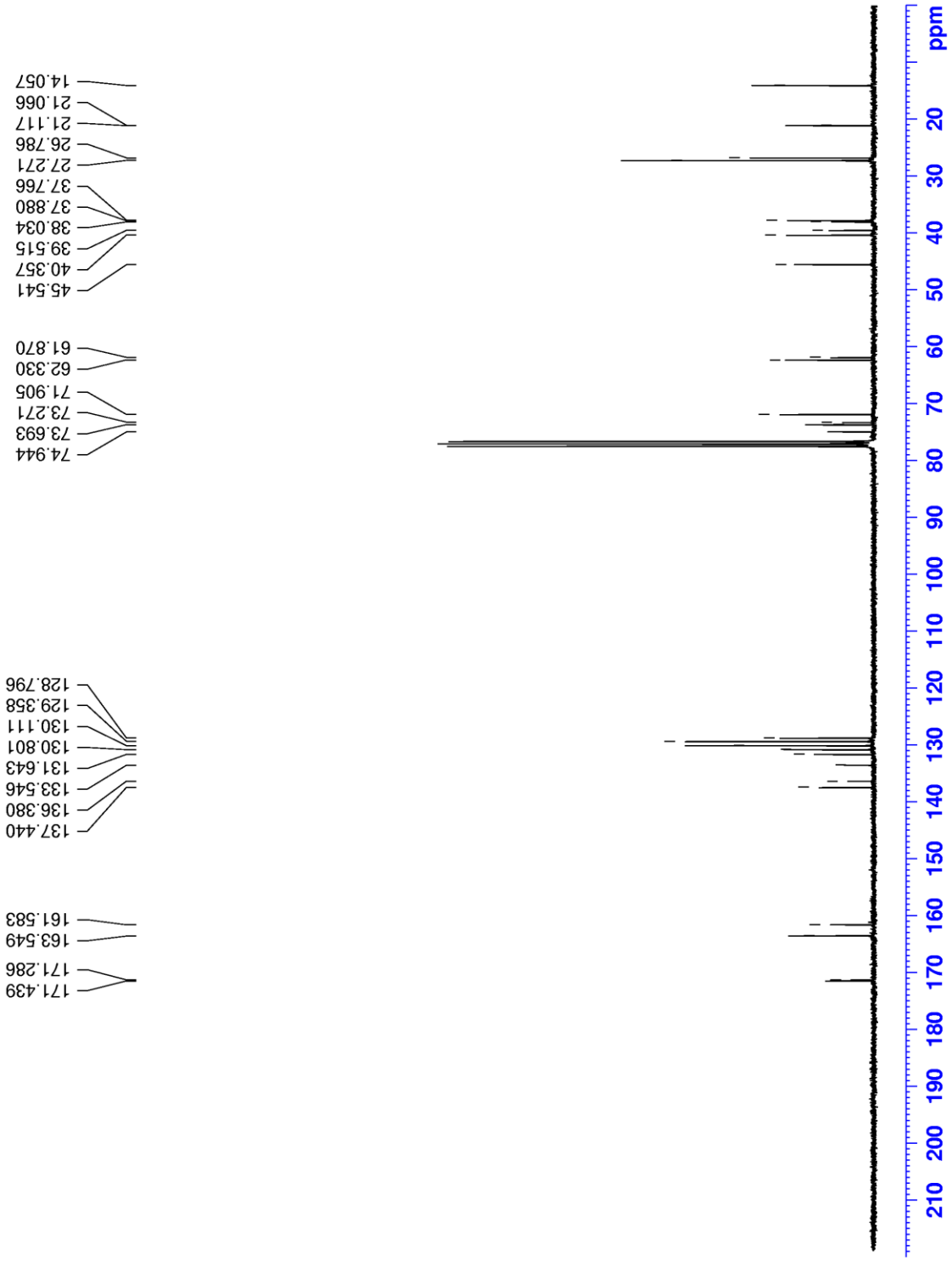


7e




OHC
N
S
CO2Et

7e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21.117
26.786
27.271
37.766
37.880
38.034
39.515
40.357
45.541
61.870
62.330
71.905
73.271
73.693
74.944
128.796
129.358
130.111
130.801
131.643
133.546
136.380
137.440
161.583
163.549
171.286
171.439
ppm
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60
70
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90
100
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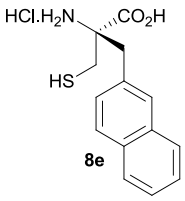
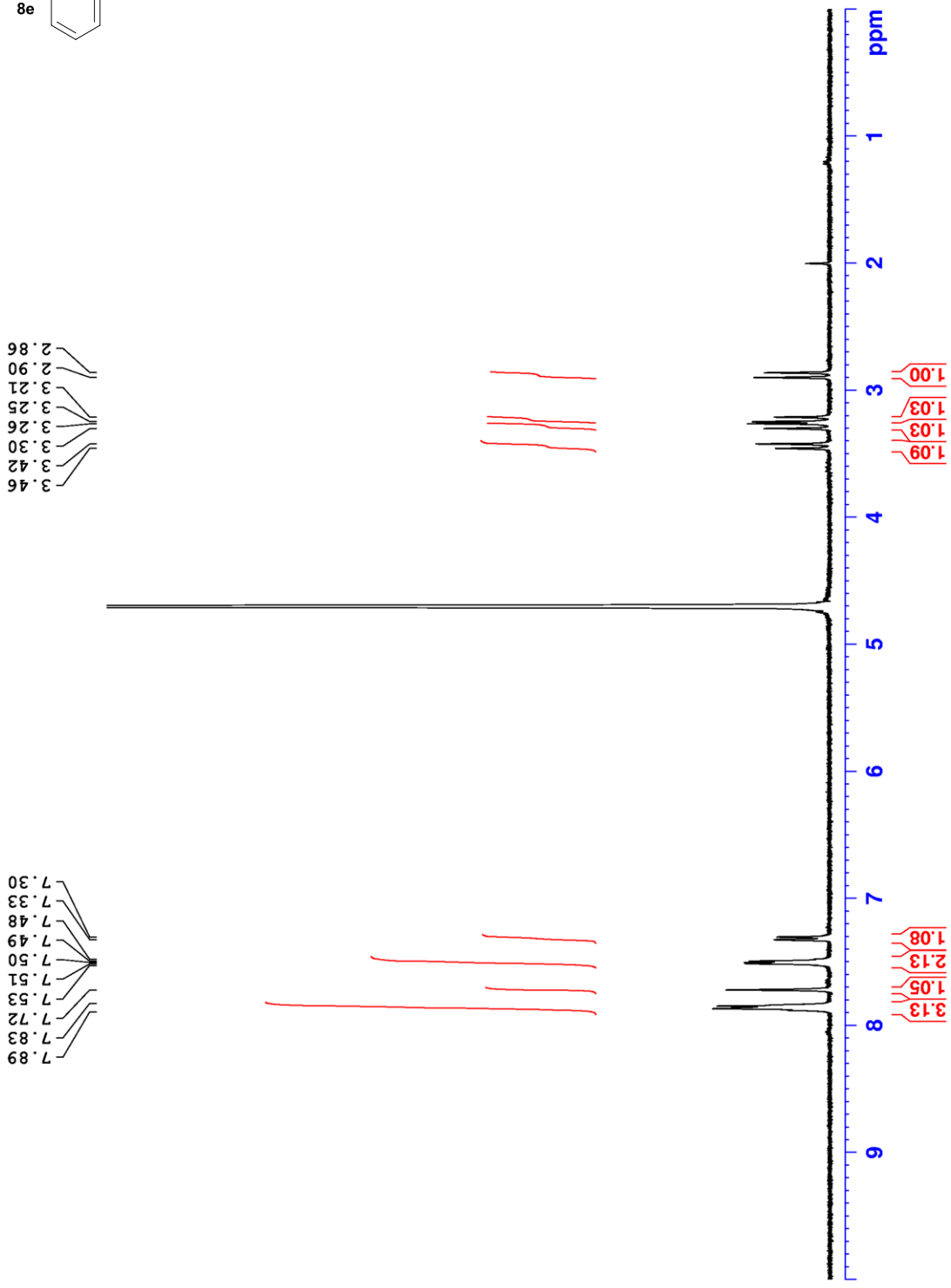
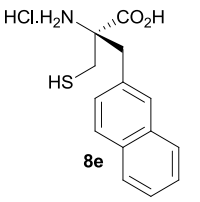
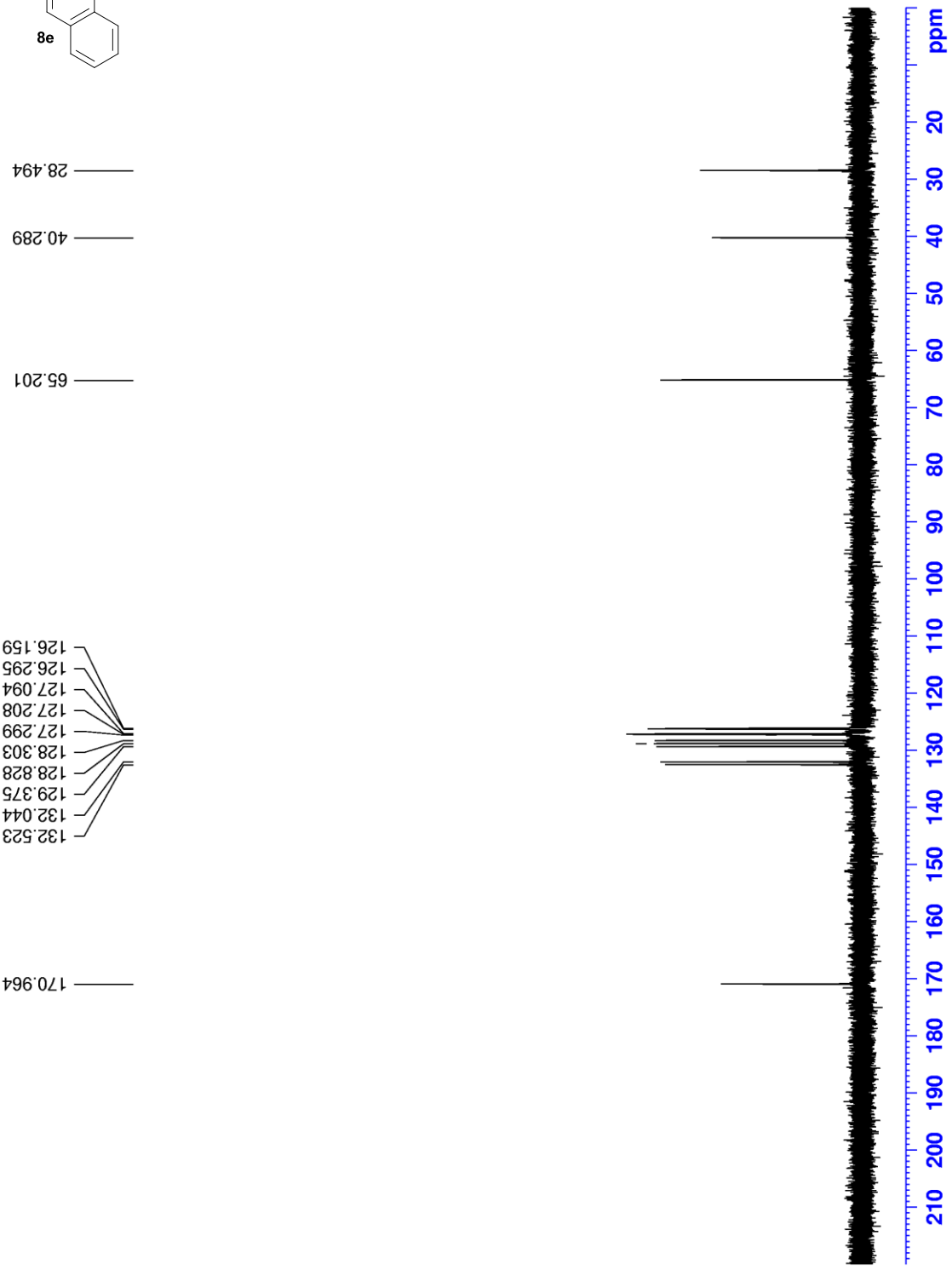
200
210



8e




HCl.H2N
CO2H
HS
8e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126.295
127.094
127.208
127.299
128.303
128.828
129.375
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170.964
ppm
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30
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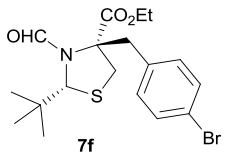
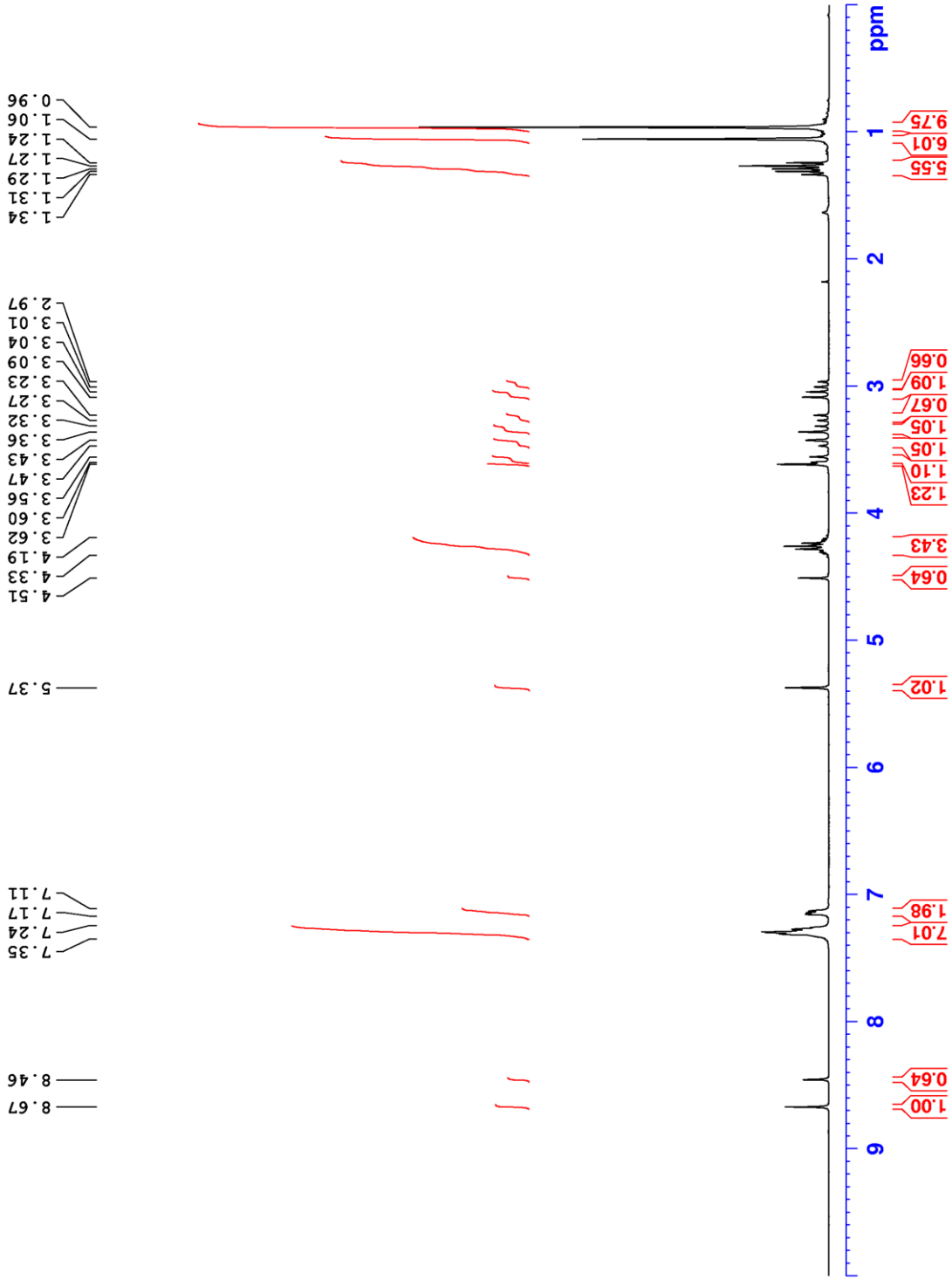
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


CO2Et
OHC
N
S
Br

7f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3
4
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6
7
8
9
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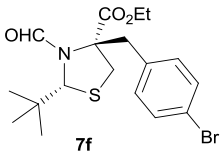
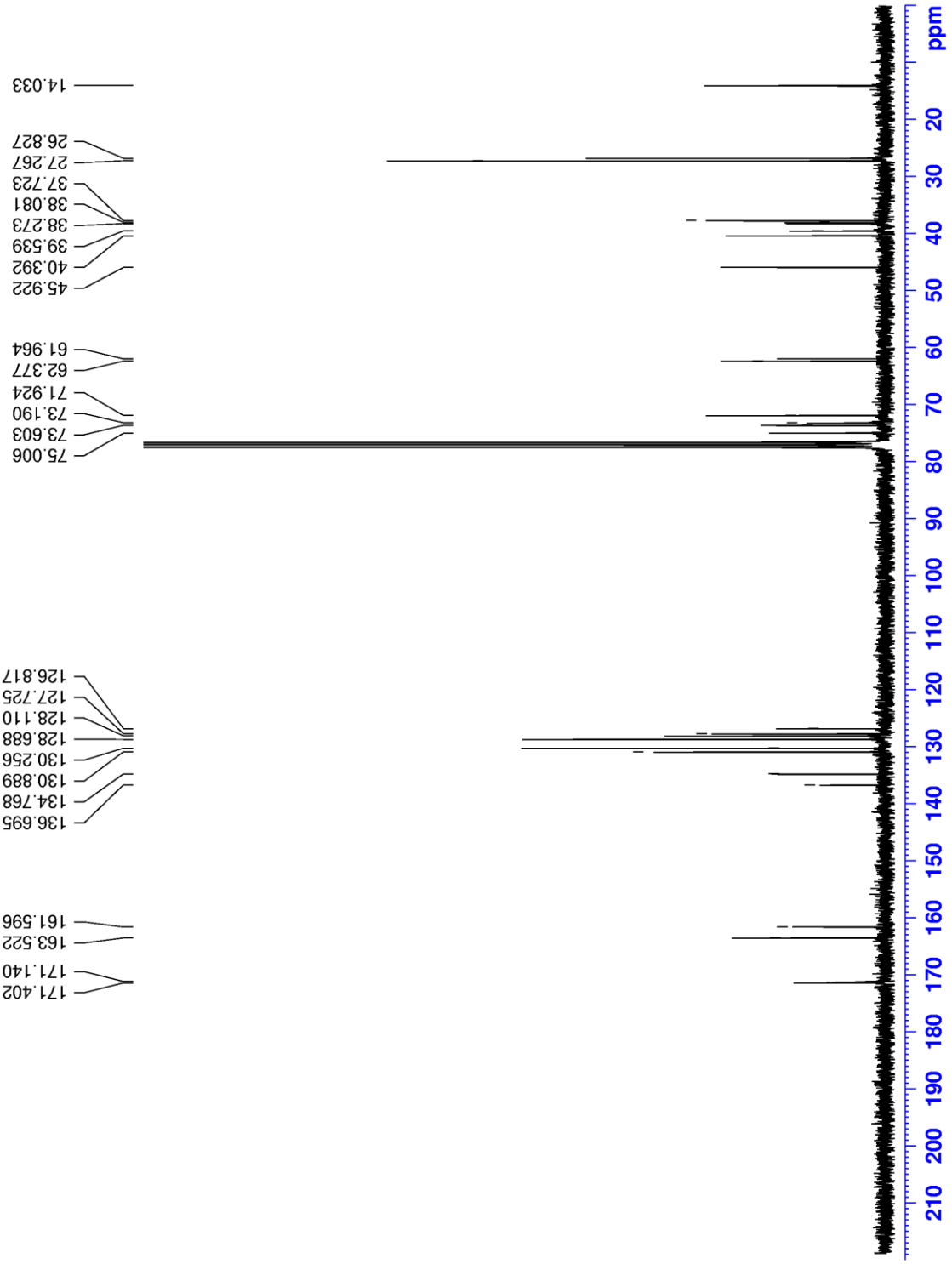
6.01
5.55
0.66
1.09
0.67
1.05
1.05
1.10
1.23
3.43
0.64
1.02
1.98
7.01
1.00
0.64
0.96
1.06
1.24
1.27
1.29
1.31
1.34
2.97
3.01
3.04
3.09
3.23
3.27
3.32
3.36
3.43
3.47
3.56
3.60
3.62
4.19
4.33
4.51
5.37
7.11
7.17
7.24
7.35
8.46
8.67


CO2Et
OHC
N
S
Br

7f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27.267
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38.081
38.273
39.539
40.392
45.922
61.964
62.377
71.924
73.190
73.603
75.006
126.817
127.725
128.110
128.688
130.256
130.889
134.768
136.695
161.596
163.522
171.140
171.402
ppm
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30
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60
70
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90
100
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200
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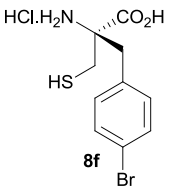
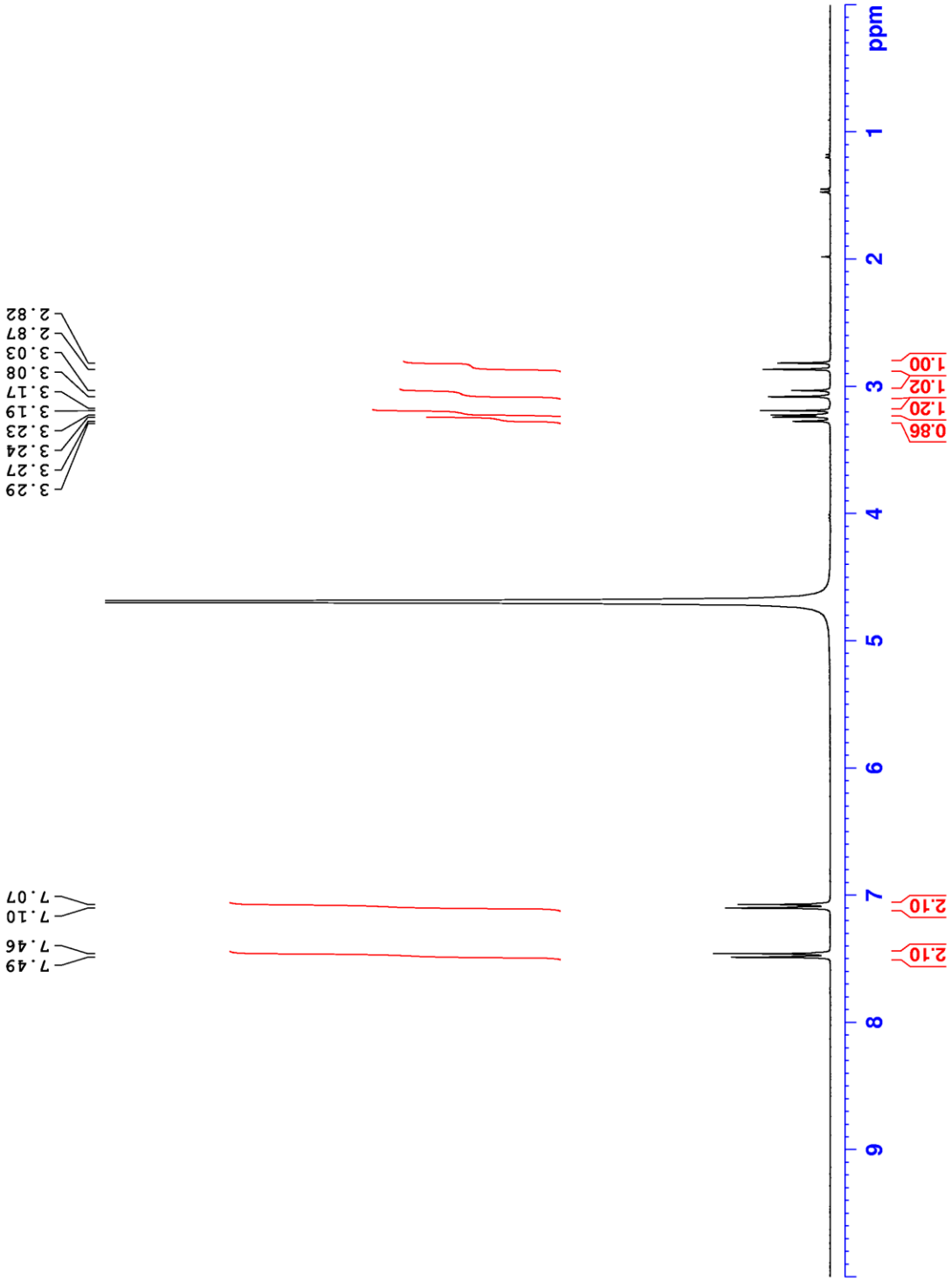
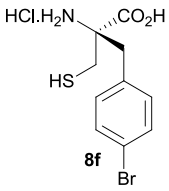
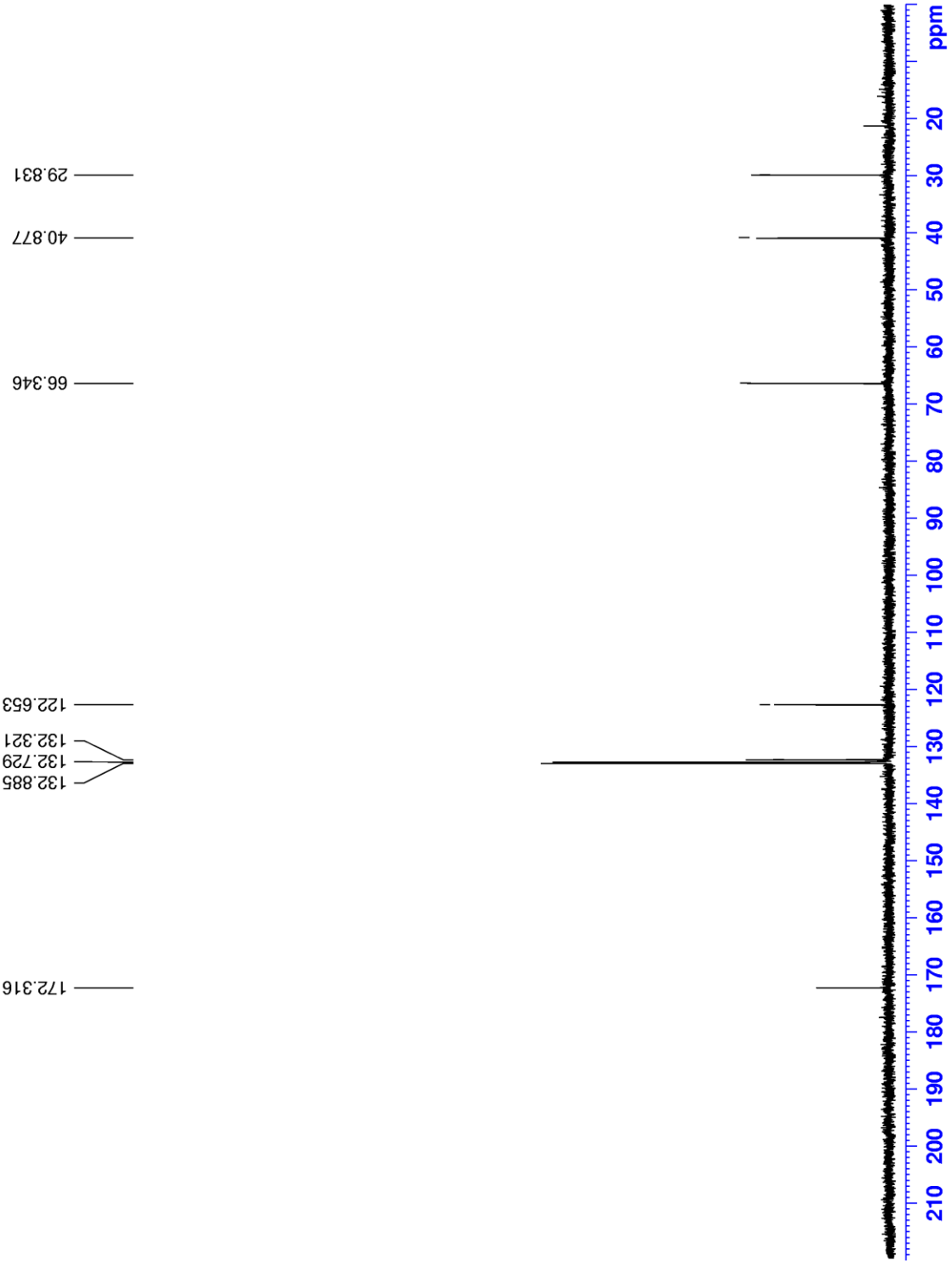





HCl.H2N
CO2H
HS
8f
Br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132.729
132.885
172.316
ppm
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70
80
90
100
110
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140
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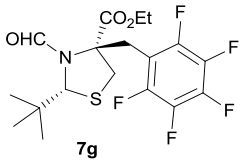
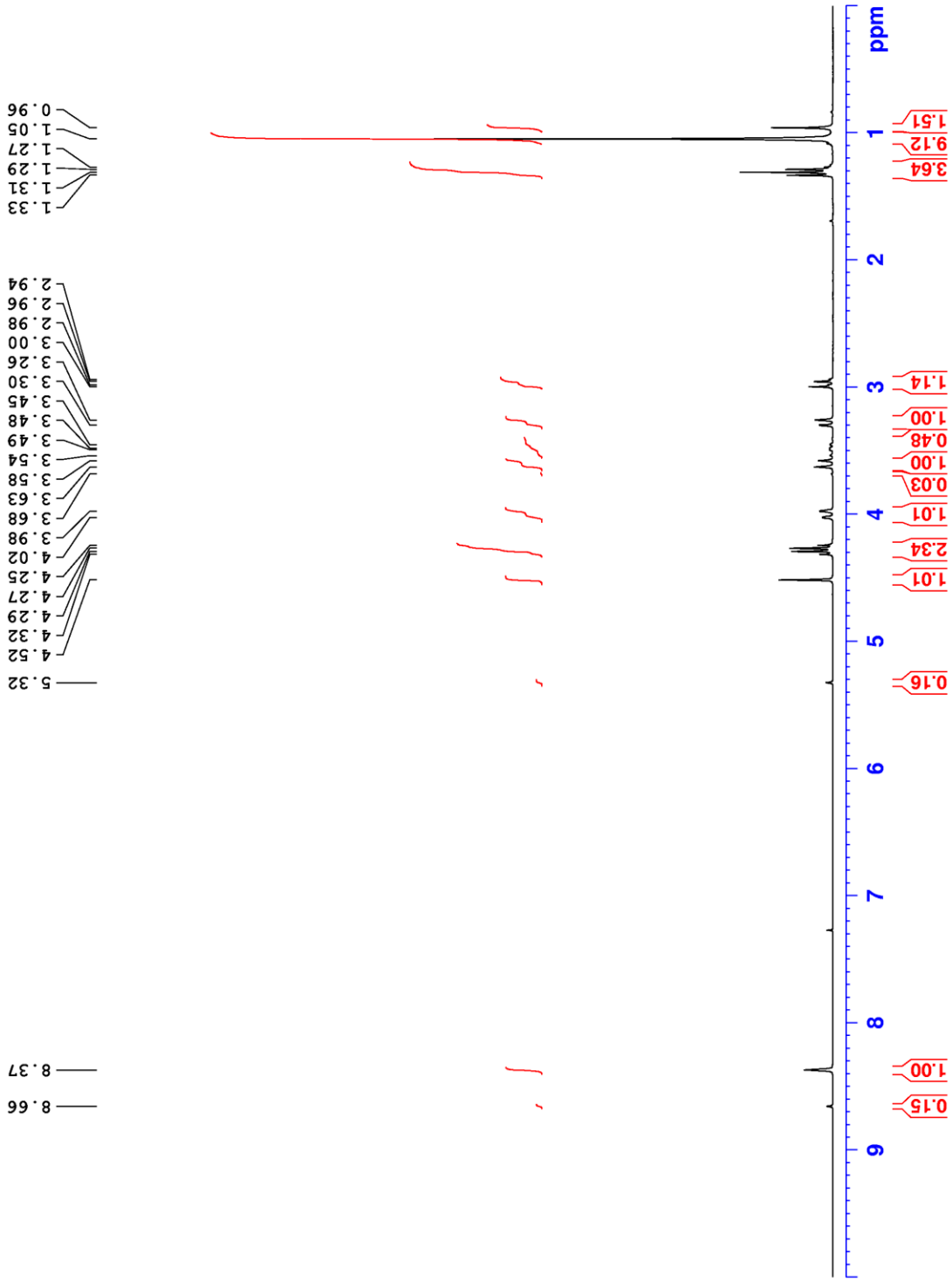
200
210


CO2Et
F
OHC
N
F
F
S
F
F

7g


ppm
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3
4
5
6
7
8
9
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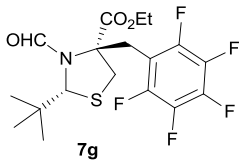
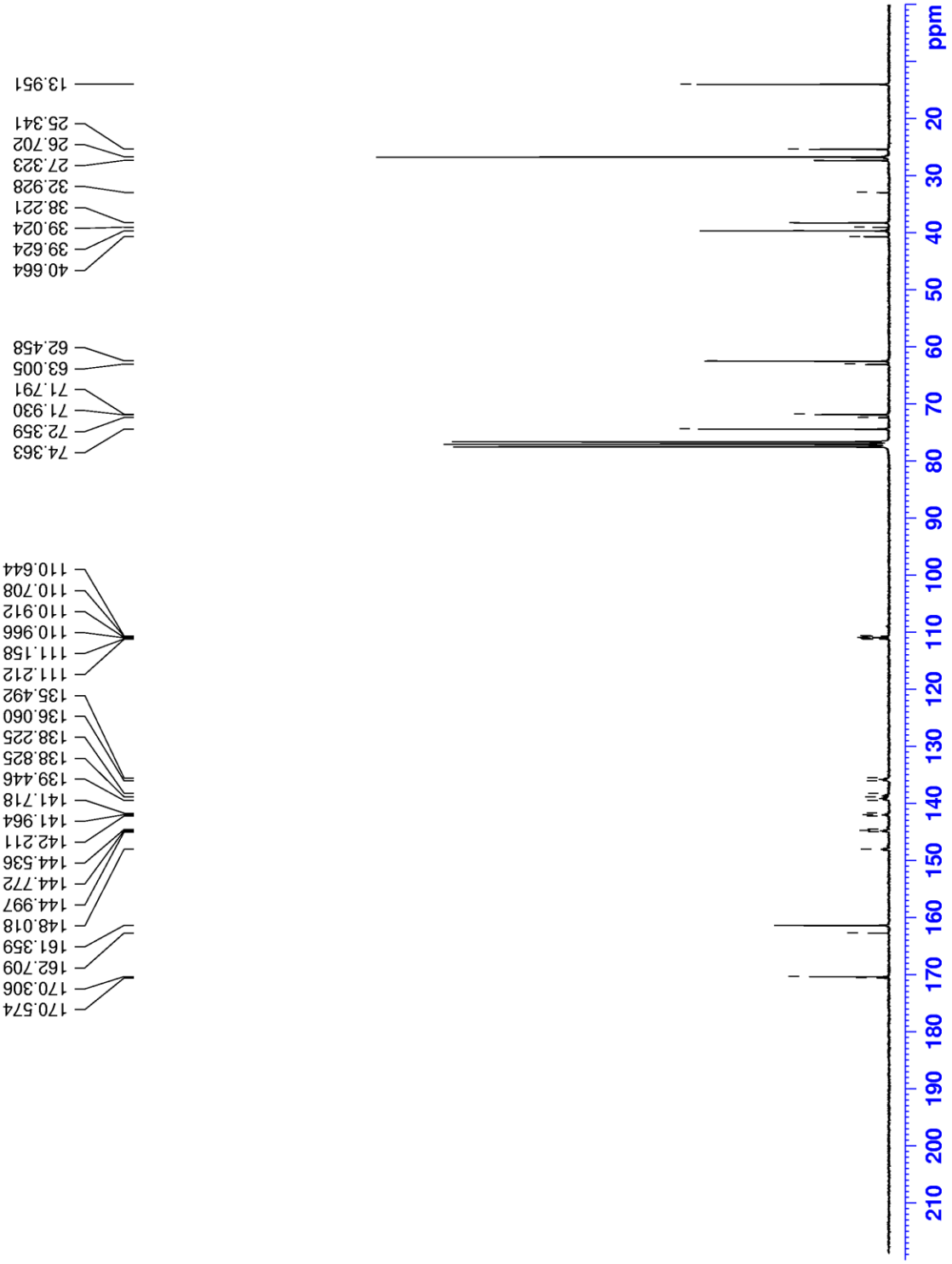
9.12
3.64
1.14
1.00
0.48
1.00
0.03
1.01
2.34
1.01
0.16
1.00
0.15
0.96
1.05
1.27
1.29
1.31
1.33
2.94
2.96
2.98
3.00
3.26
3.30
3.45
3.48
3.49
3.54
3.58
3.63
3.68
3.98
4.02
4.25
4.27
4.29
4.32
4.52
5.32
8.37
8.66


OHC
N
CO2Et
S
F
F
F
F
F

7g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71.930
72.359
74.363
110.644
110.708
110.912
110.966
111.158
111.212
135.492
136.060
138.225
138.825
139.446
141.718
141.964
142.211
144.536
144.772
144.997
148.018
161.359
162.709
170.306
170.574
ppm
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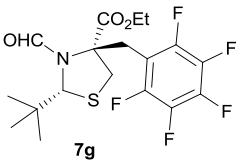
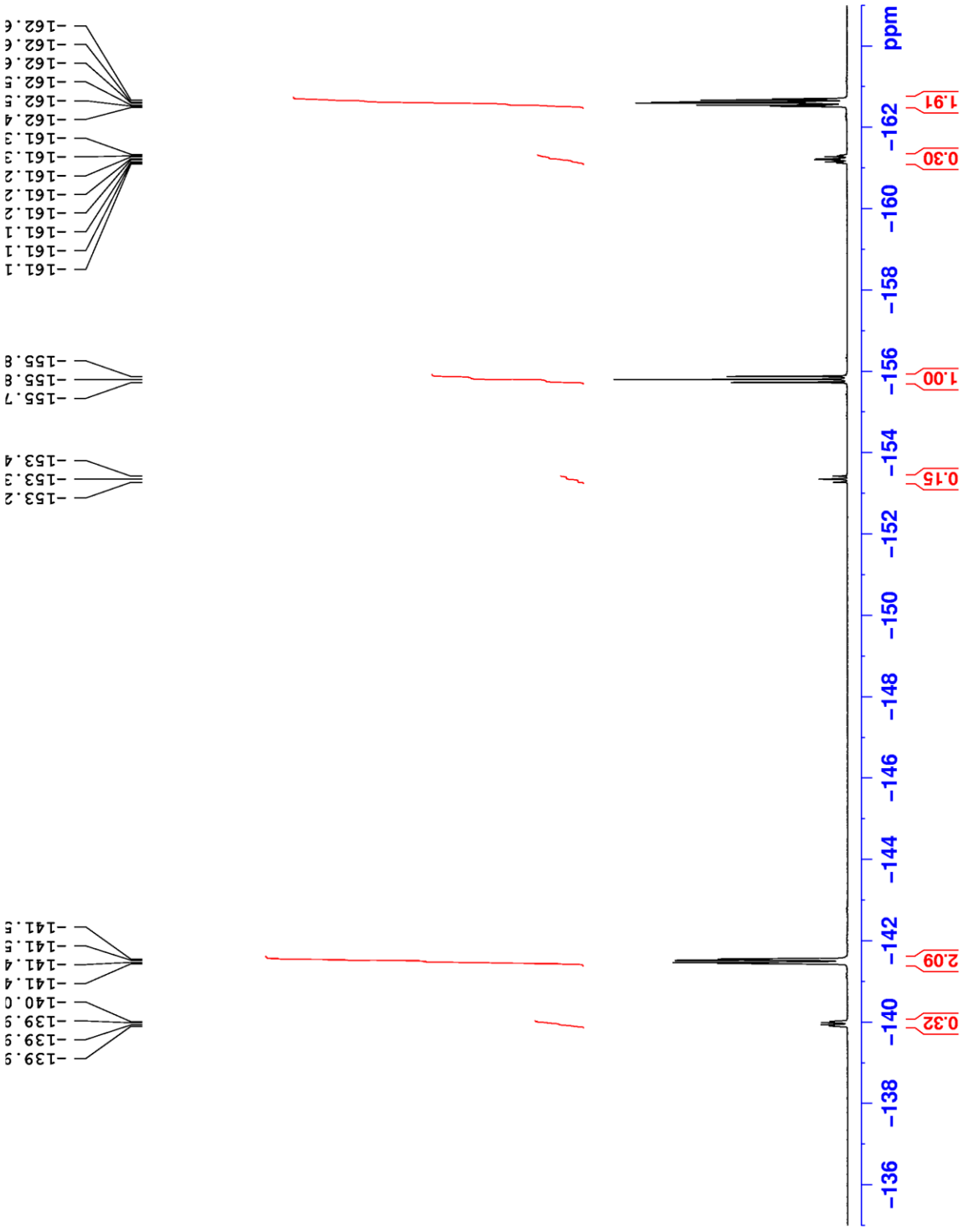

OHC
N
CO2Et
S
F
F
F
F
F

7g


-162.6
-162.6
-162.6
-162.5
-162.5
-162.4
-161.3
-161.3
-161.2
-161.2
-161.2
-161.1
-161.1
-161.1
-155.8
-155.8
-155.7
-153.4
-153.3
-153.2
-141.5
-141.5
-141.4
-141.4
-140.0
-139.6
-139.6
-139.6
ppm
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-154
-152
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-140
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-136
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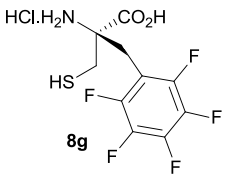
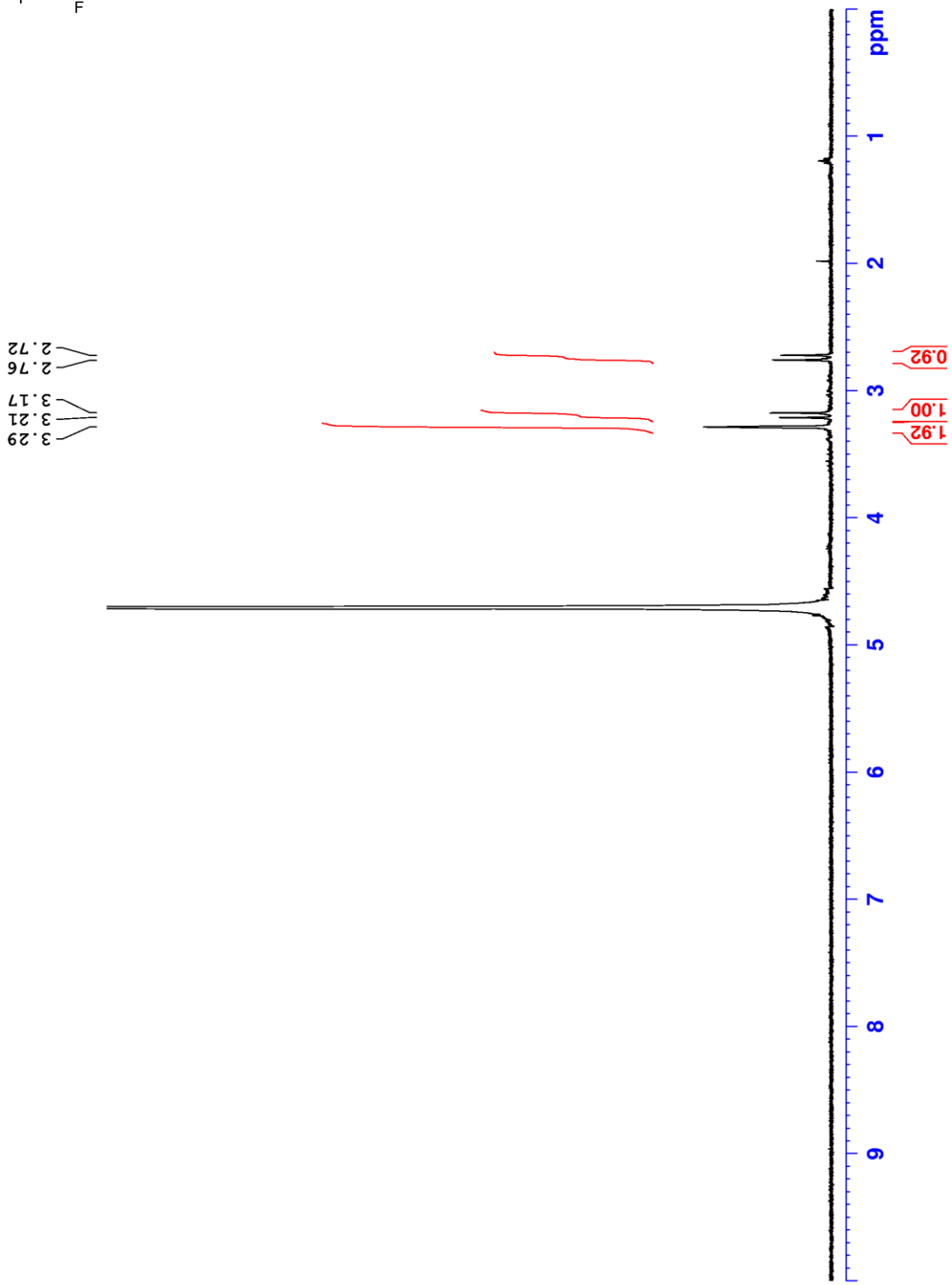
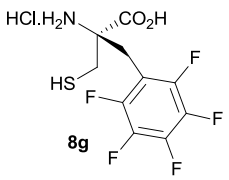
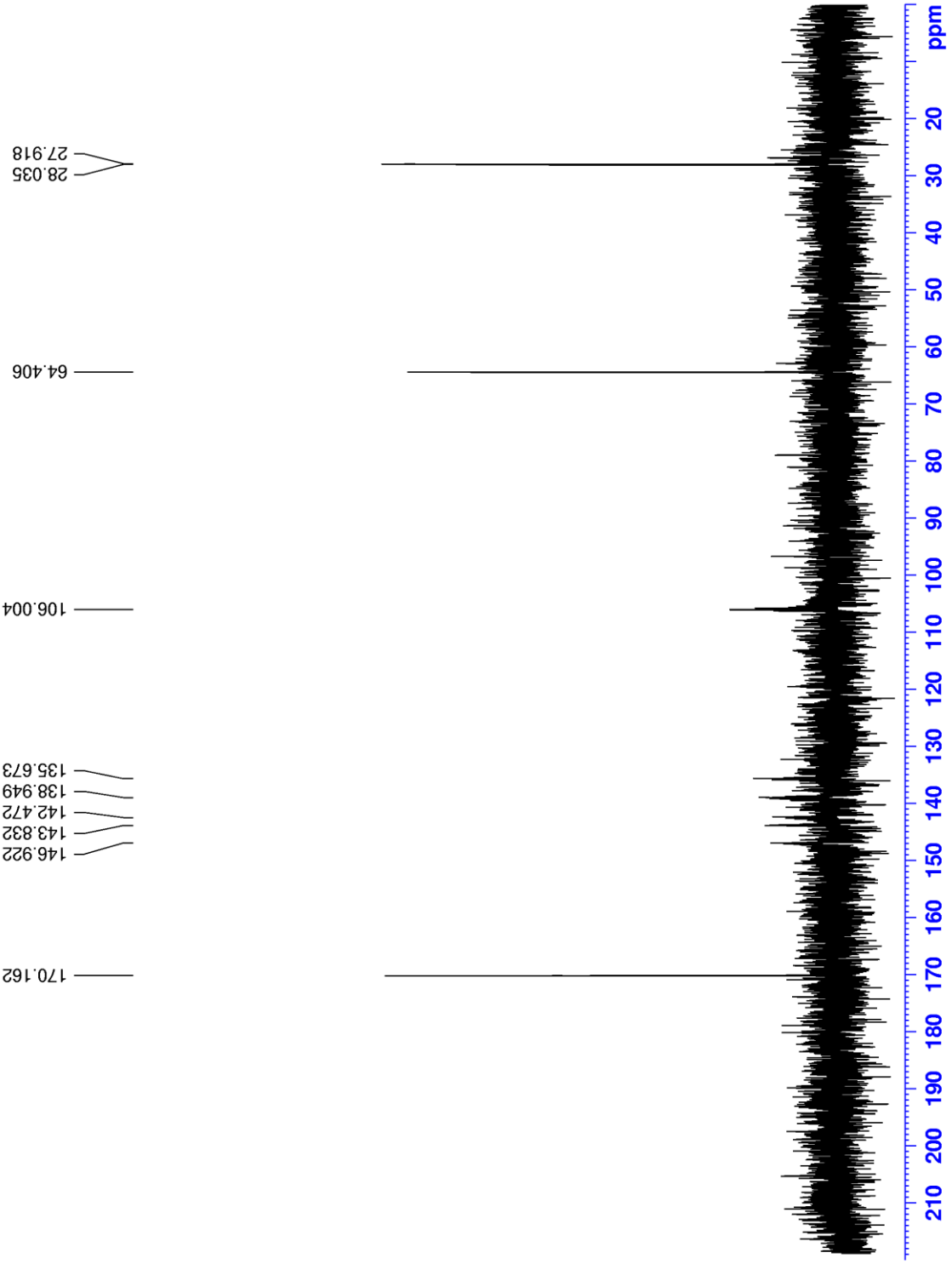
2.09
0.32


HCl.H2N
CO2H
HS
F
F
F
F
F

8g


2.72
2.76
3.17
3.21
3.29
0.92
1.00
1.92
ppm
1
2
3
4
5
6
7
8
9


HCl.H2N
CO2H
HS
F
F
F
F
F
8g


27.918
28.035
64.406
106.004
135.673
138.949
142.472
143.832
146.922
170.162
ppm
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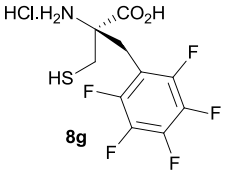
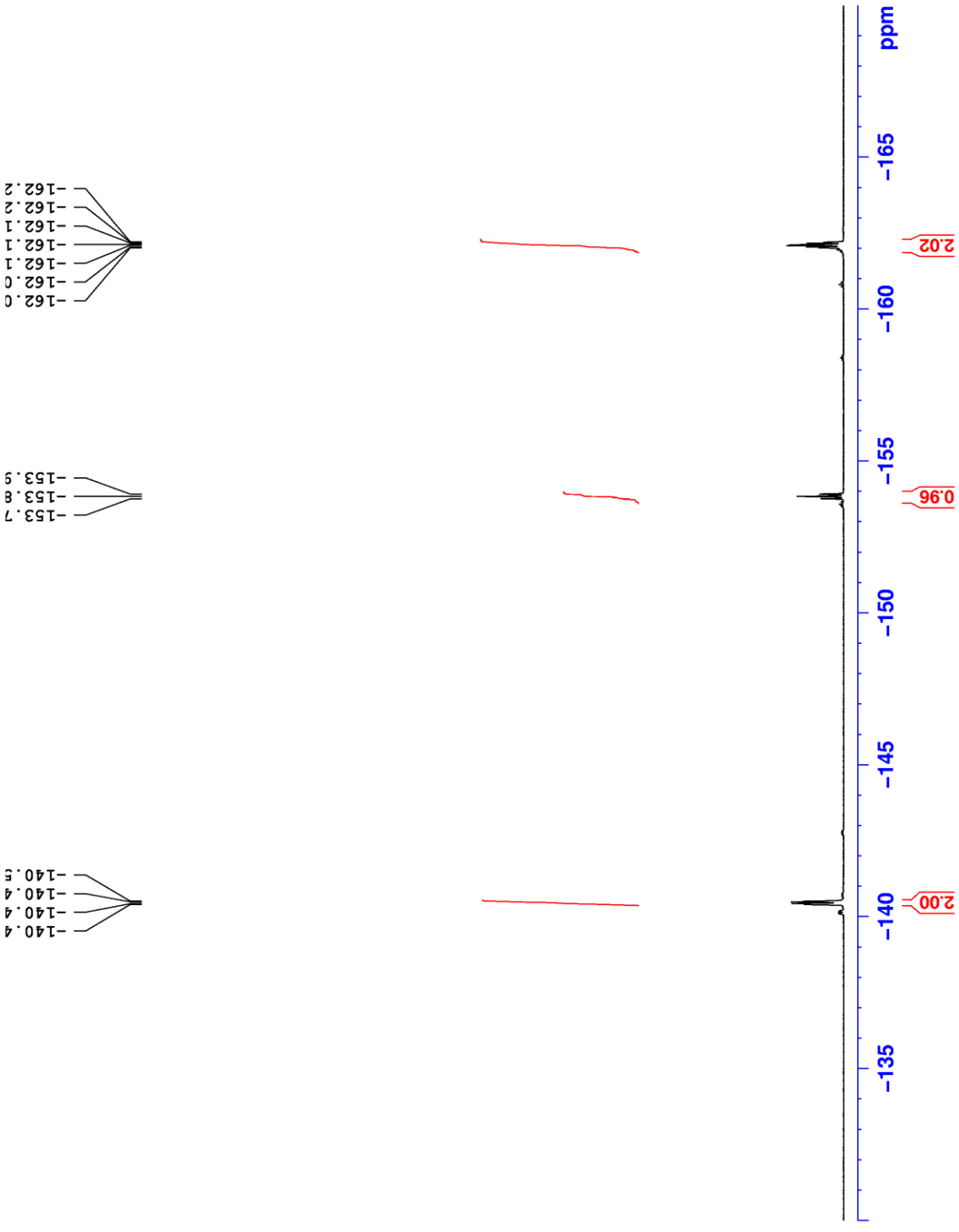
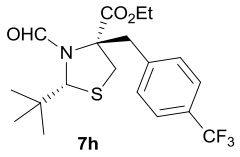
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

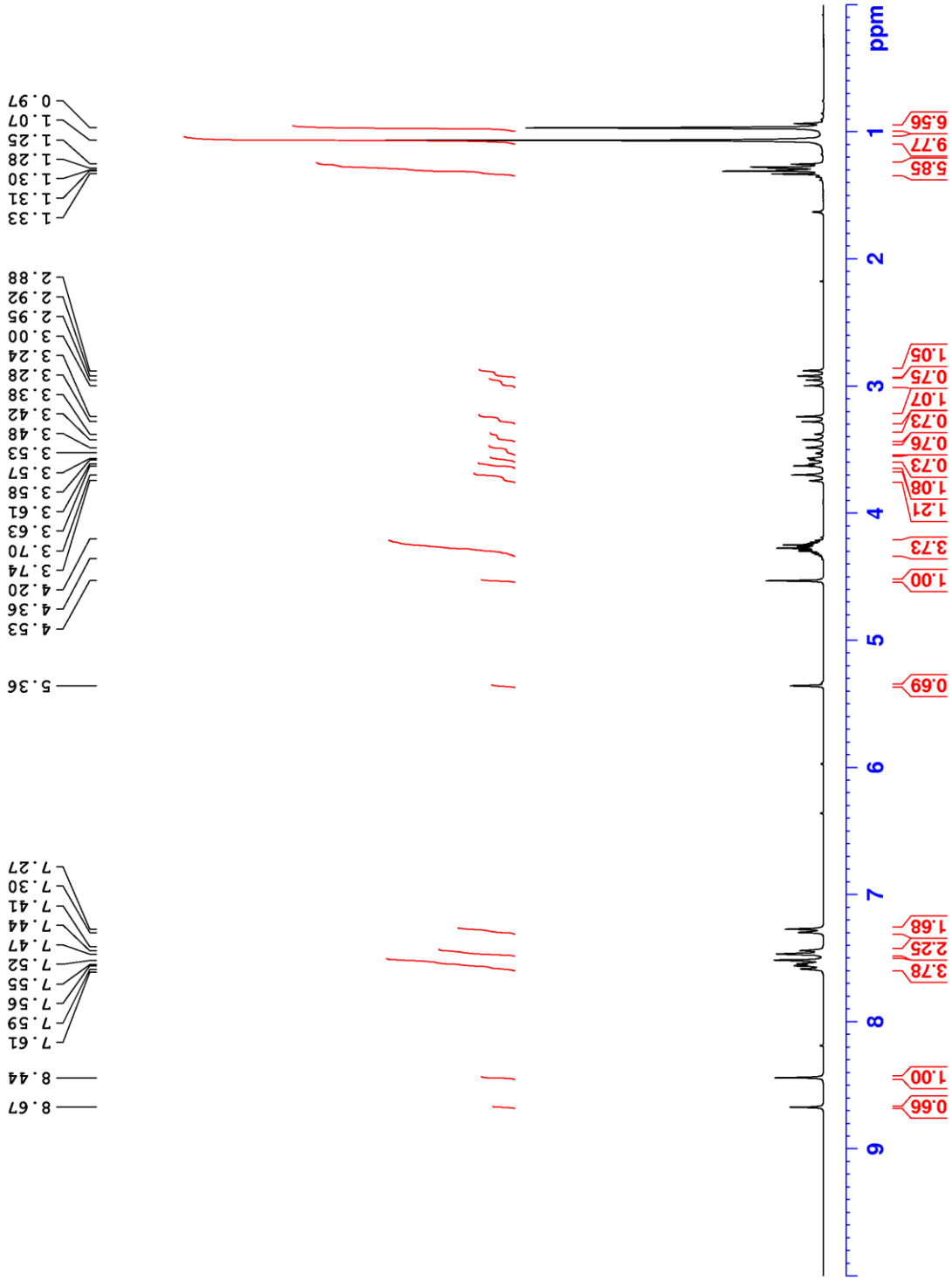

HCl.H2N
CO2H
HS
F
F
F
F
F

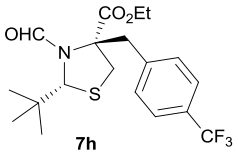
8g


-162.2
-162.2
-162.1
-162.1
-162.1
-162.0
-162.0
-153.9
-153.8
-153.7
-140.5
-140.4
-140.4
-140.4
ppm
-165
-160
-155
-150
-145
-140
-135
2.02
0.96
2.00

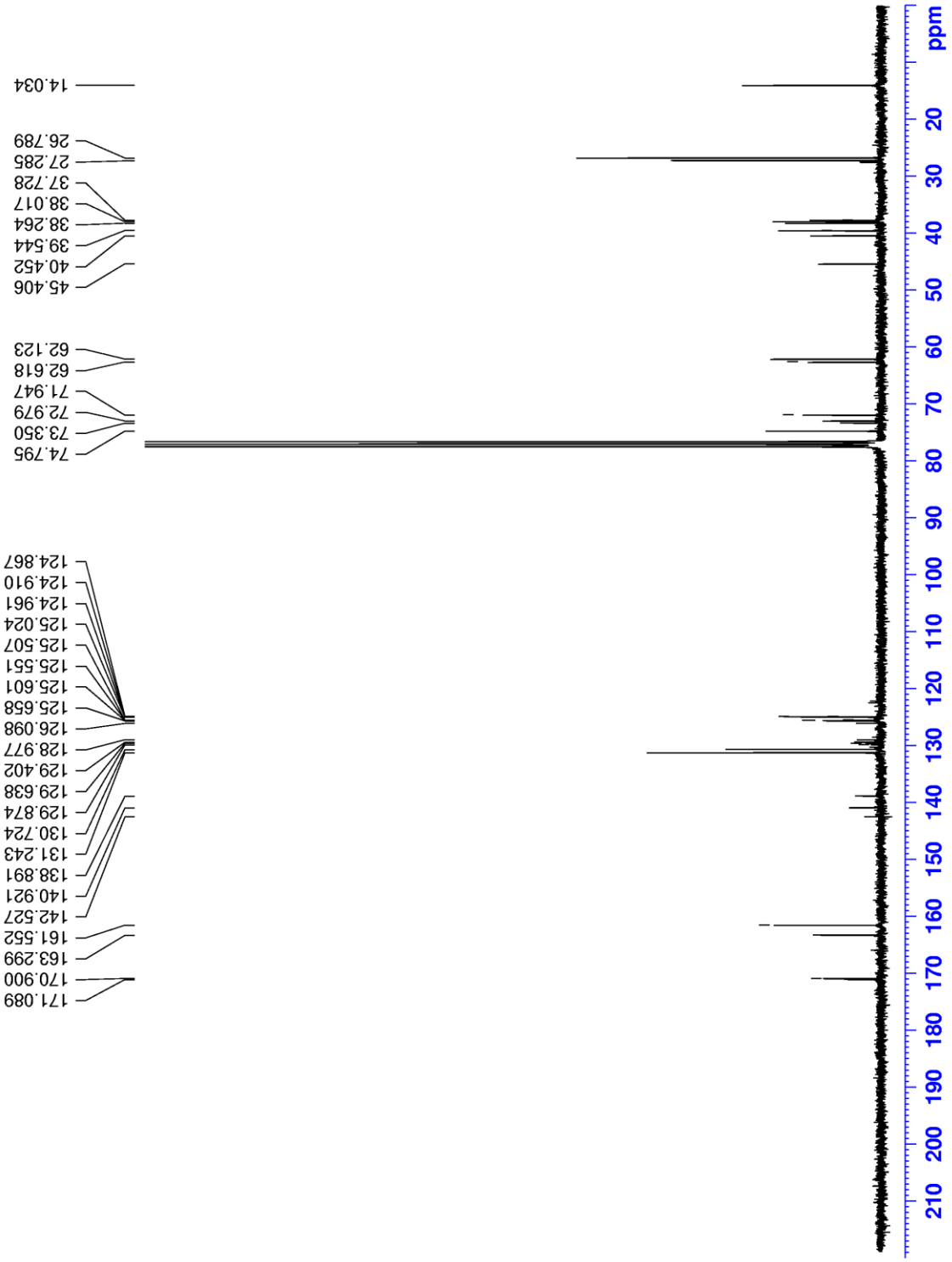

CO2Et
OHC
N
S
CF3

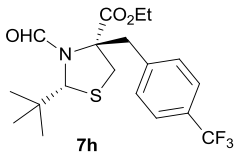
7h


ppm
1
2
3
4
5
6
7
8
9
6.56
9.77
5.85
1.05
0.75
1.07
0.73
0.76
0.73
1.08
1.21
3.73
1.00
0.69
3.78
2.25
1.68
1.00
0.66
0.97
1.07
1.25
1.28
1.30
1.31
1.33
2.88
2.92
2.95
3.00
3.24
3.28
3.38
3.42
3.48
3.53
3.57
3.58
3.61
3.63
3.70
3.74
4.20
4.36
4.53
5.36
7.27
7.30
7.41
7.44
7.47
7.52
7.55
7.56
7.59
7.61
8.44
8.67

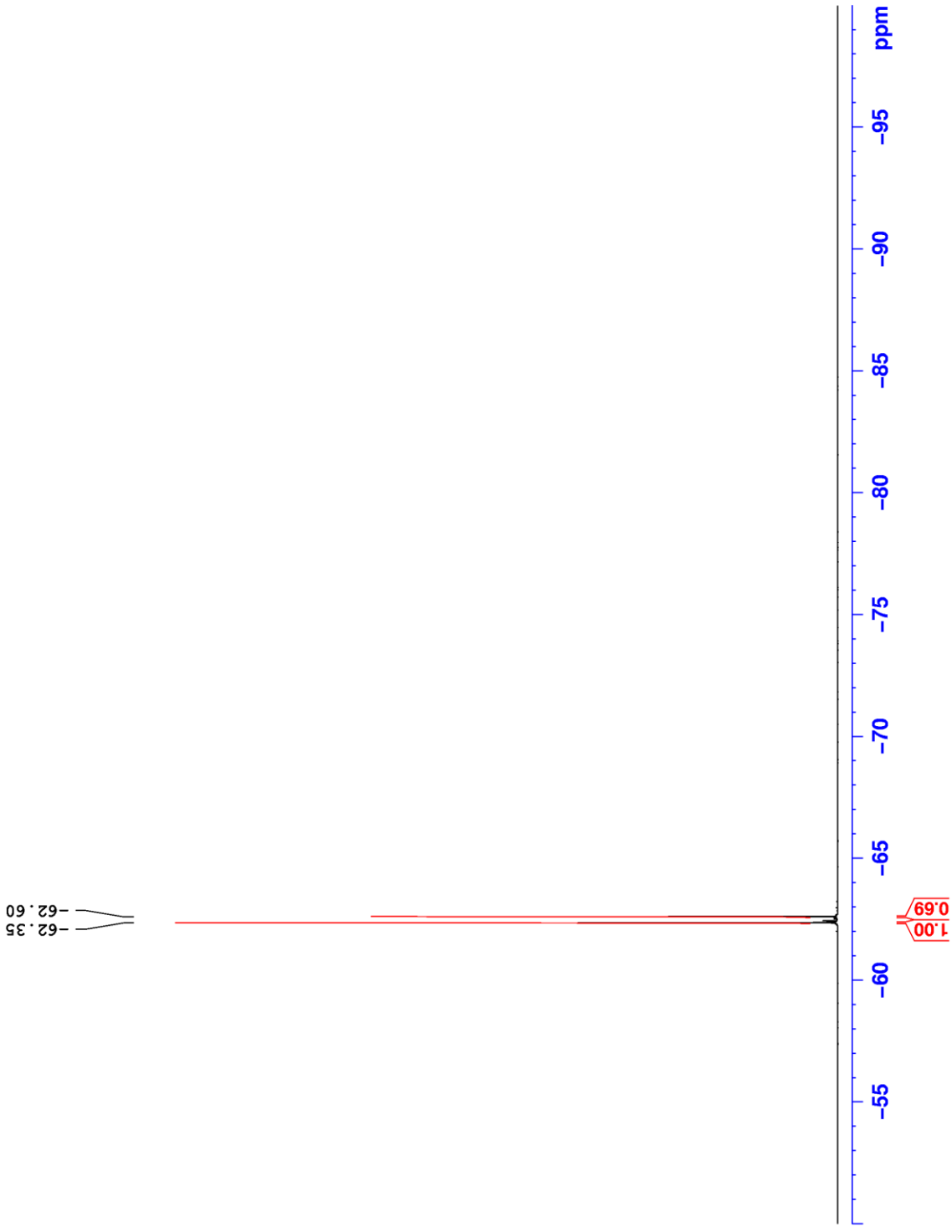

CO2Et
OHC
N
S
CF3

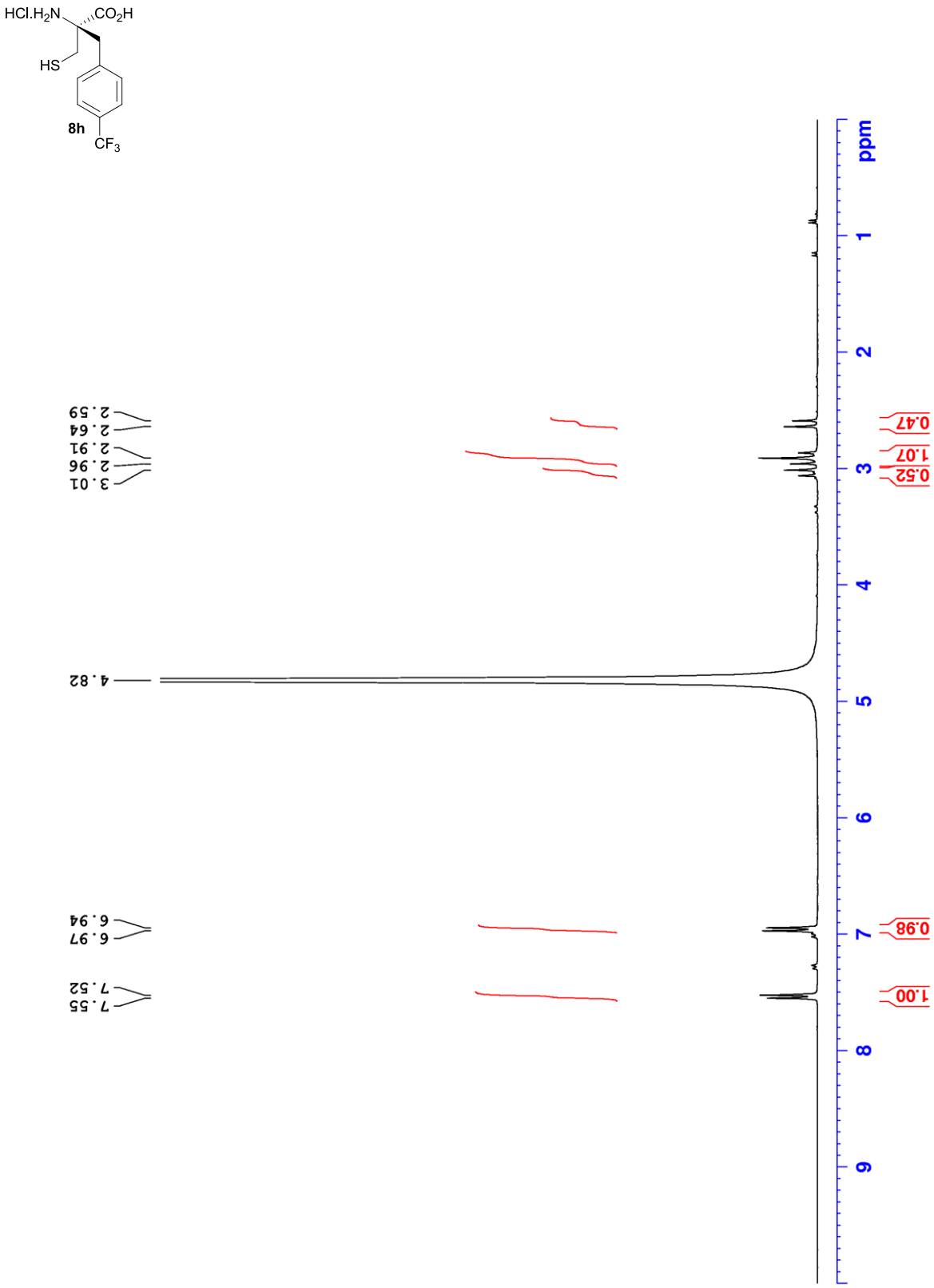
7h

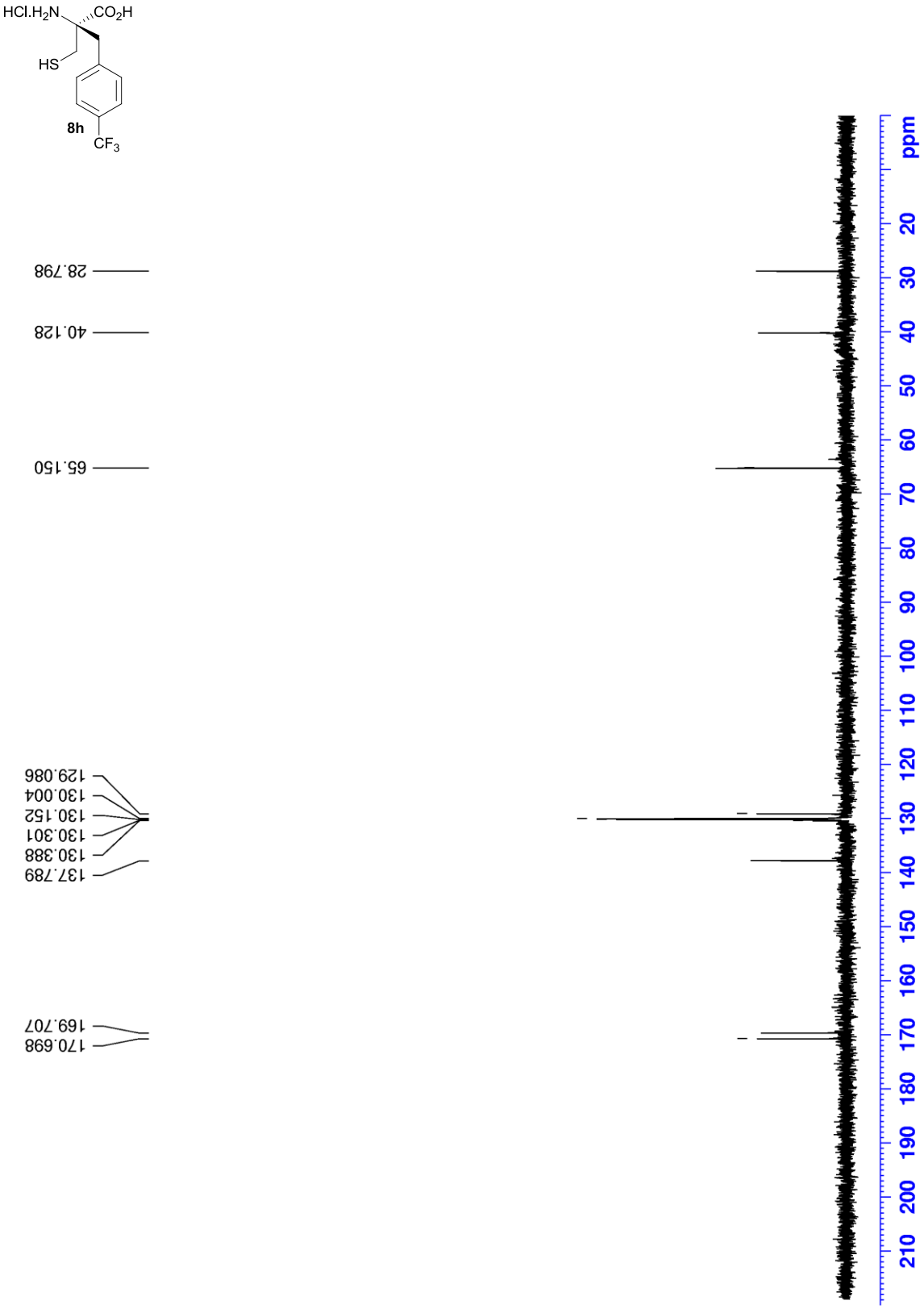

14.034
26.789
27.285
37.728
38.017
38.264
39.544
40.452
45.406
62.123
62.618
71.947
72.979
73.350
74.795
124.867
124.910
124.961
125.024
125.507
125.551
125.601
125.658
126.098
128.977
129.402
129.638
129.874
130.724
131.243
138.891
140.921
142.527
161.552
163.299
170.900
171.089
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

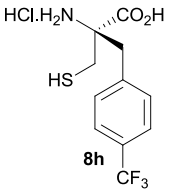


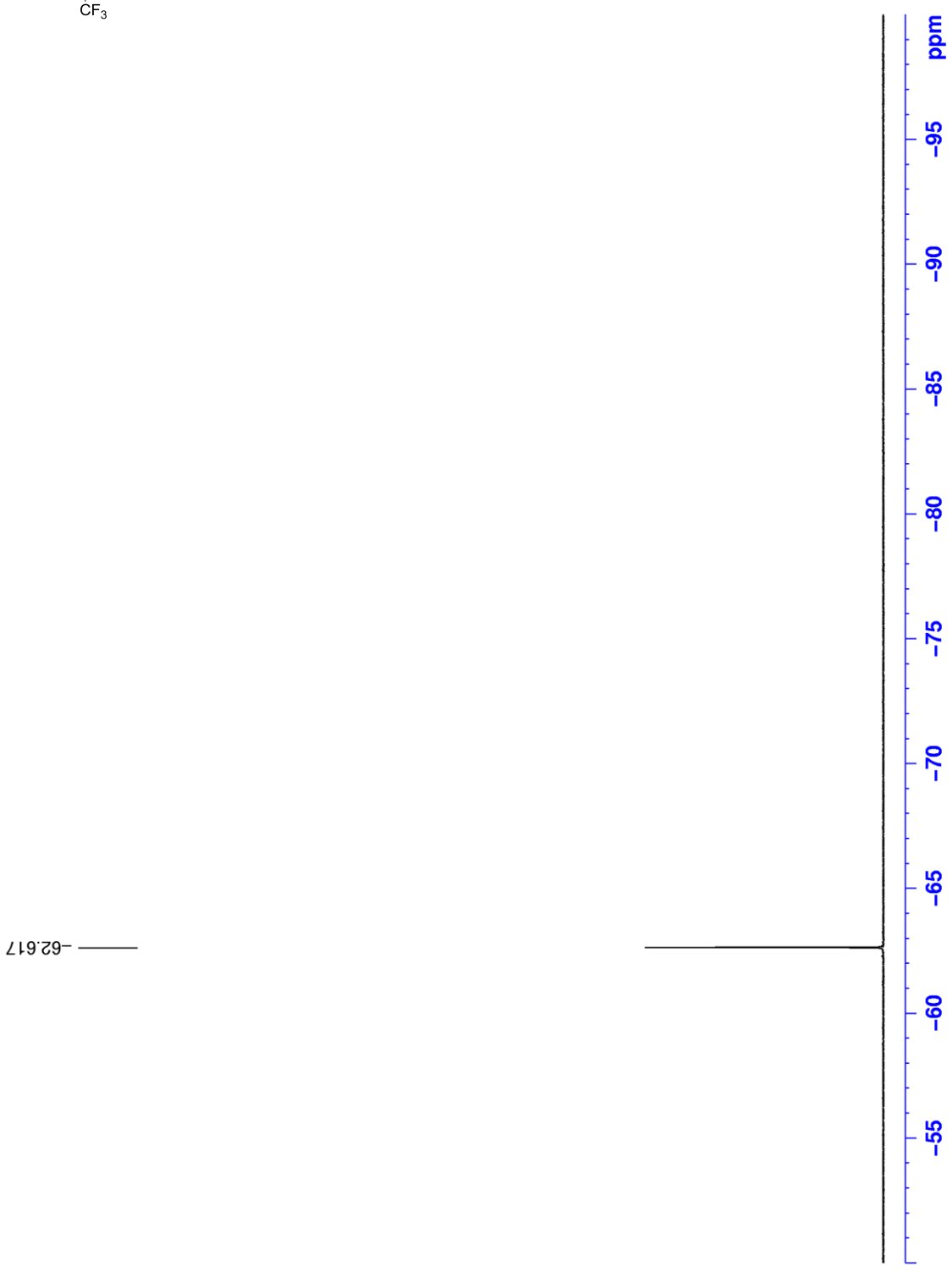
7h






HCl.H2N
CO2H
HS
8h
CF3
28.798
40.128
65.150
129.086
130.004
130.152
130.301
130.388
137.789
169.707
170.698
ppm


HCl.H2N
CO2H
HS
8h
CF3


ppm
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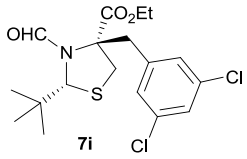
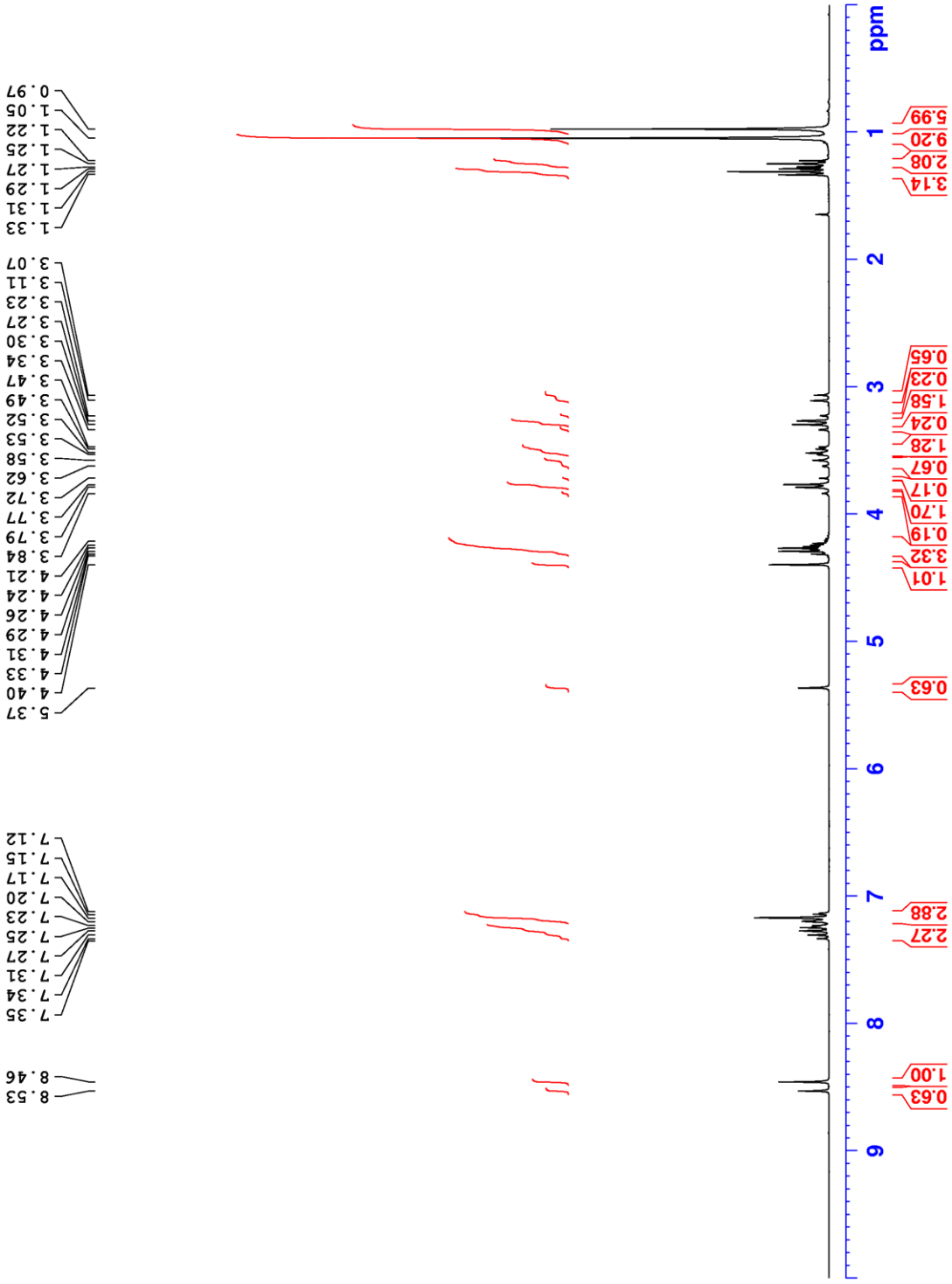
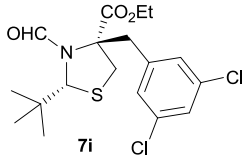
-90
-85
-80
-75
-70
-65
-60
-55
-62.617

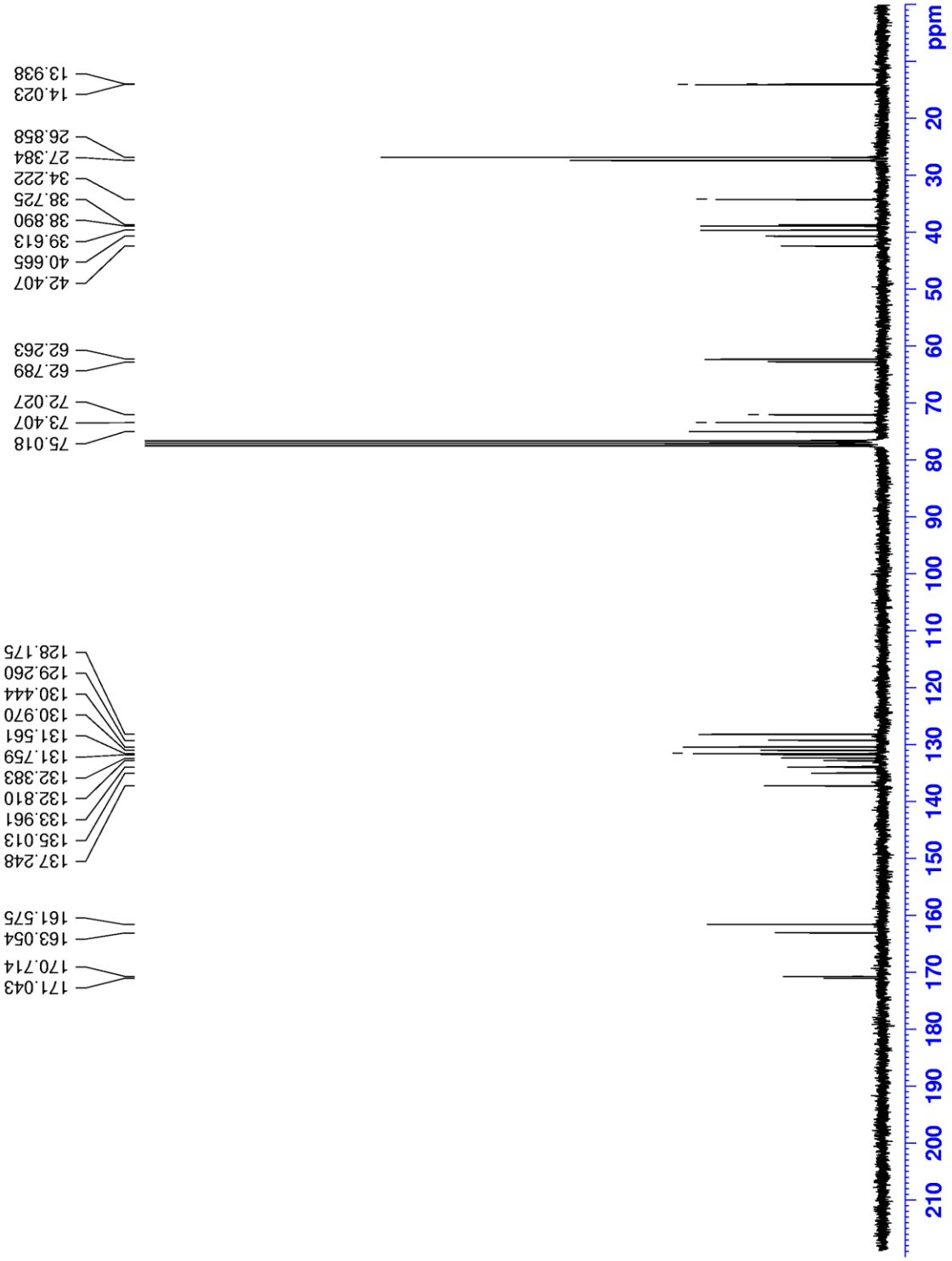

CO2Et
OHC
N
S
Cl
Cl

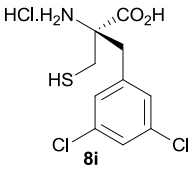
7i


ppm
1
2
3
4
5
6
7
8
9
5.99
9.20
2.08
3.14
0.65
0.23
1.58
0.24
1.28
0.67
0.17
1.70
0.19
3.32
1.01
0.63
2.88
2.27
1.00
0.63
0.97
1.05
1.22
1.25
1.27
1.29
1.31
1.33
3.07
3.11
3.23
3.27
3.30
3.34
3.47
3.49
3.52
3.53
3.58
3.62
3.72
3.77
3.79
3.84
4.21
4.24
4.26
4.29
4.31
4.33
4.40
5.37
7.12
7.15
7.17
7.20
7.23
7.25
7.27
7.31
7.34
7.35
8.46
8.53

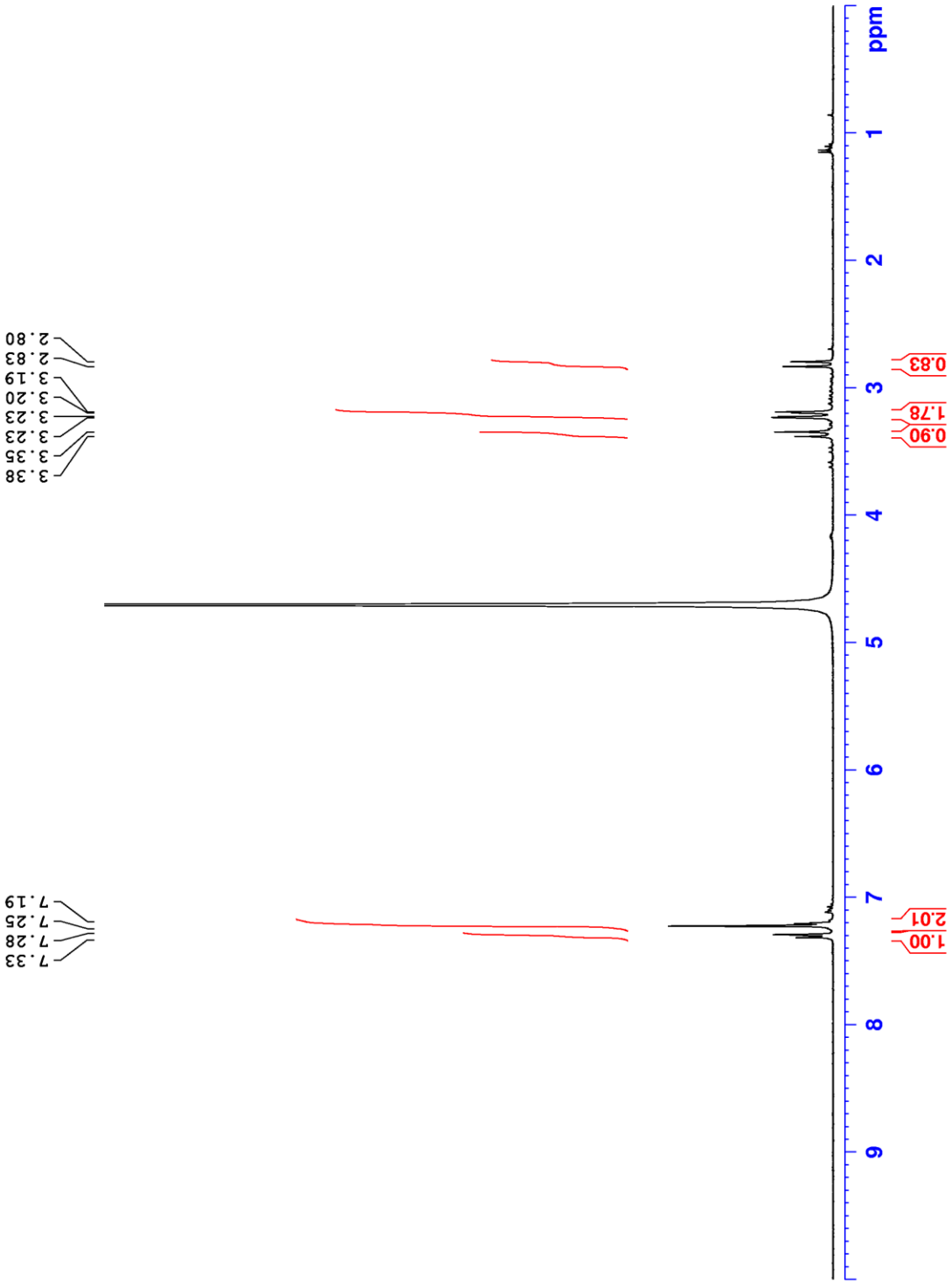

CO2Et
OHC
N
S
Cl
Cl

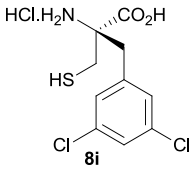
7i


13.938
14.023
26.858
27.384
34.222
38.725
38.890
39.613
40.665
42.407
62.263
62.789
72.027
73.407
75.018
128.175
129.260
130.444
130.970
131.561
131.759
132.383
132.810
133.961
135.013
137.248
161.575
163.054
170.714
171.043
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

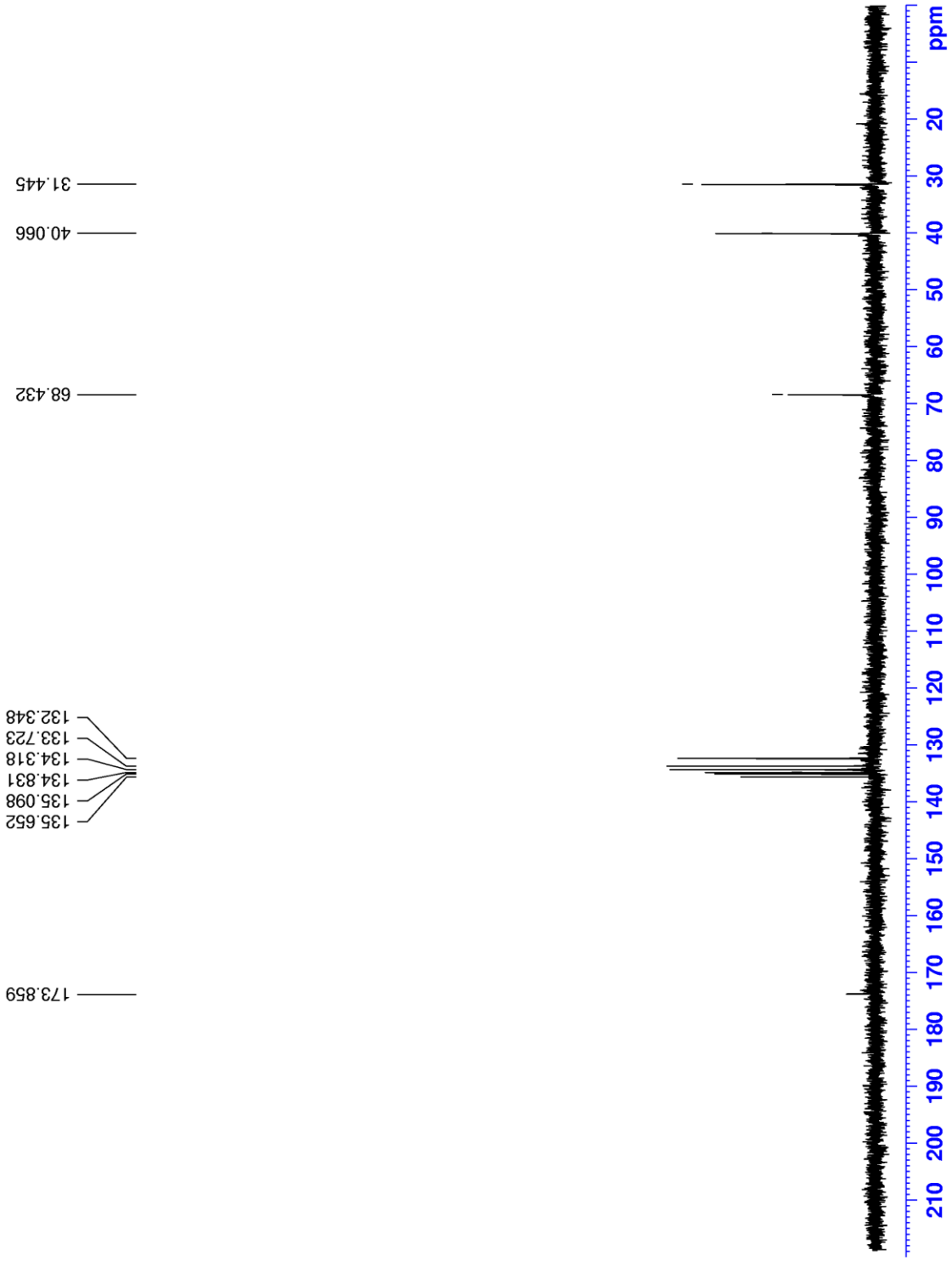


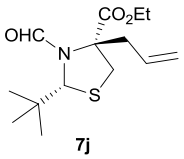
8i



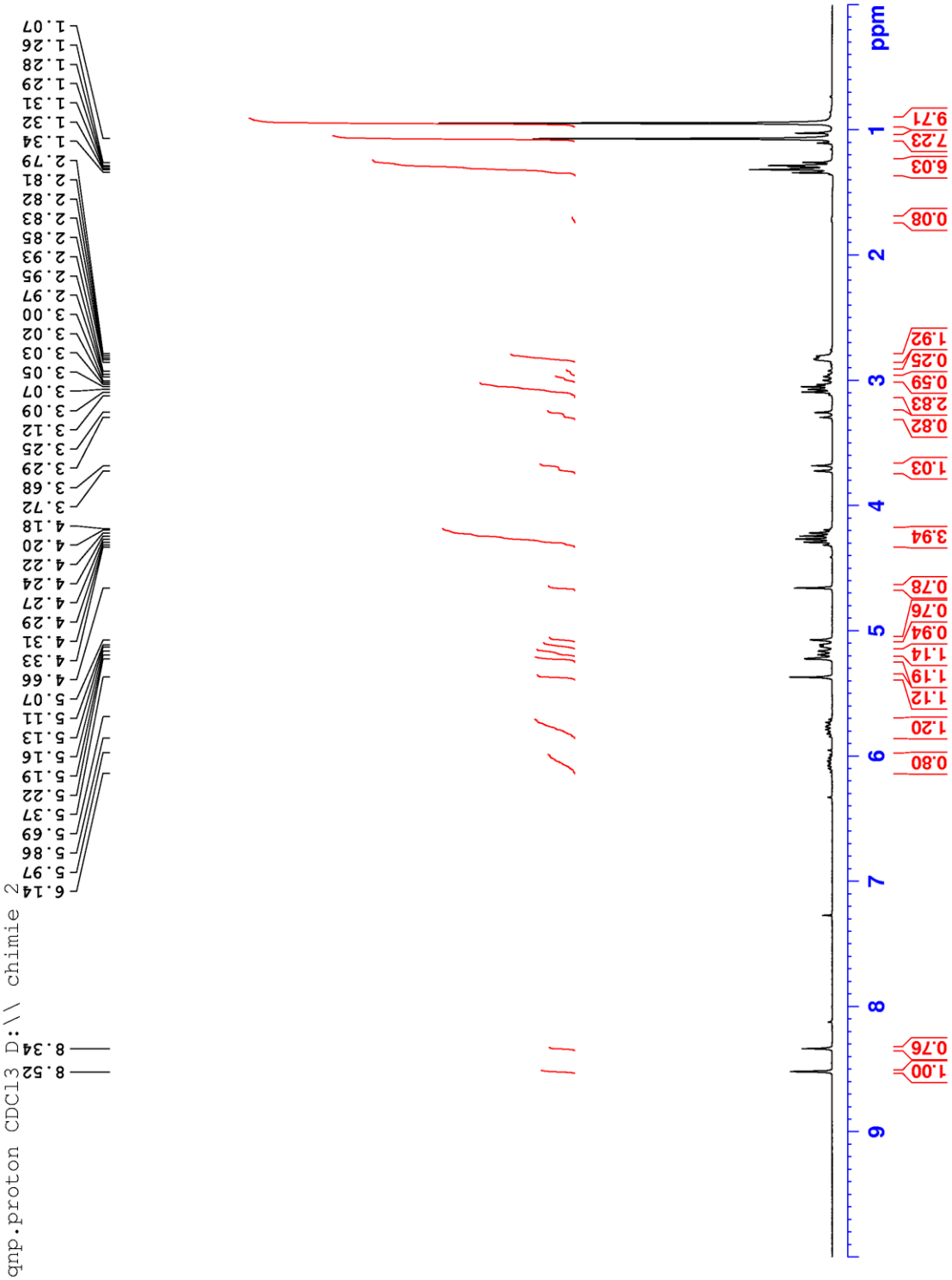

HCl.H2N
CO2H
HS
Cl
Cl

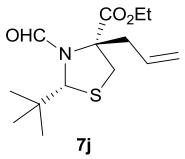
8i


31.445
40.066
68.432
132.348
133.723
134.318
134.831
135.098
135.652
173.859
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

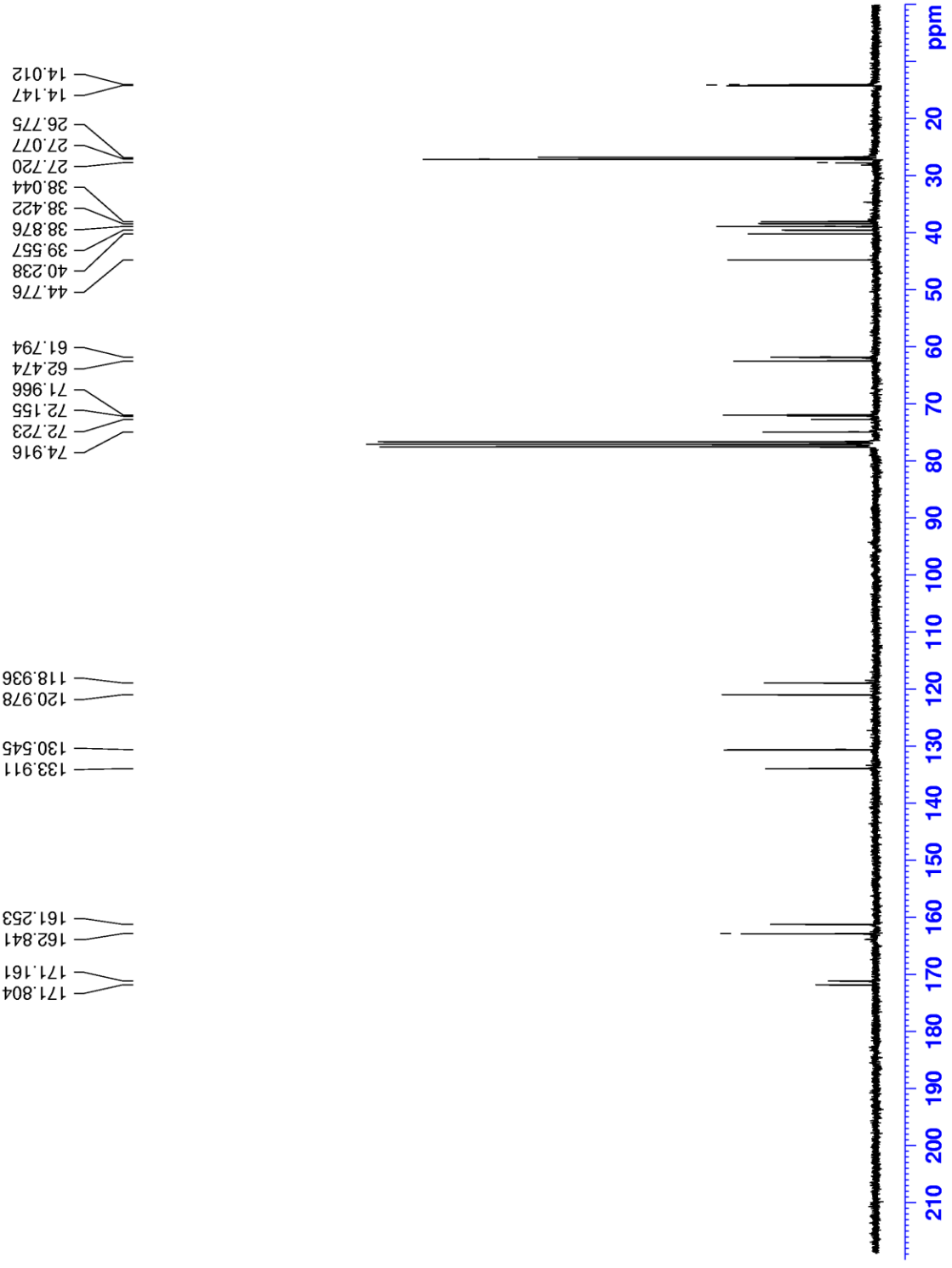

OHC
N
CO2Et
S

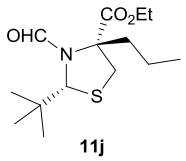
7j


qnp.proton CDC13 D:\\ chimie 2
ppm
1
2
3
4
5
6
7
8
9
9.71
7.23
6.03
0.08
1.92
0.25
0.59
2.83
0.82
1.03
3.94
0.78
0.76
0.94
1.14
1.19
1.12
1.20
0.80
1.00
0.76

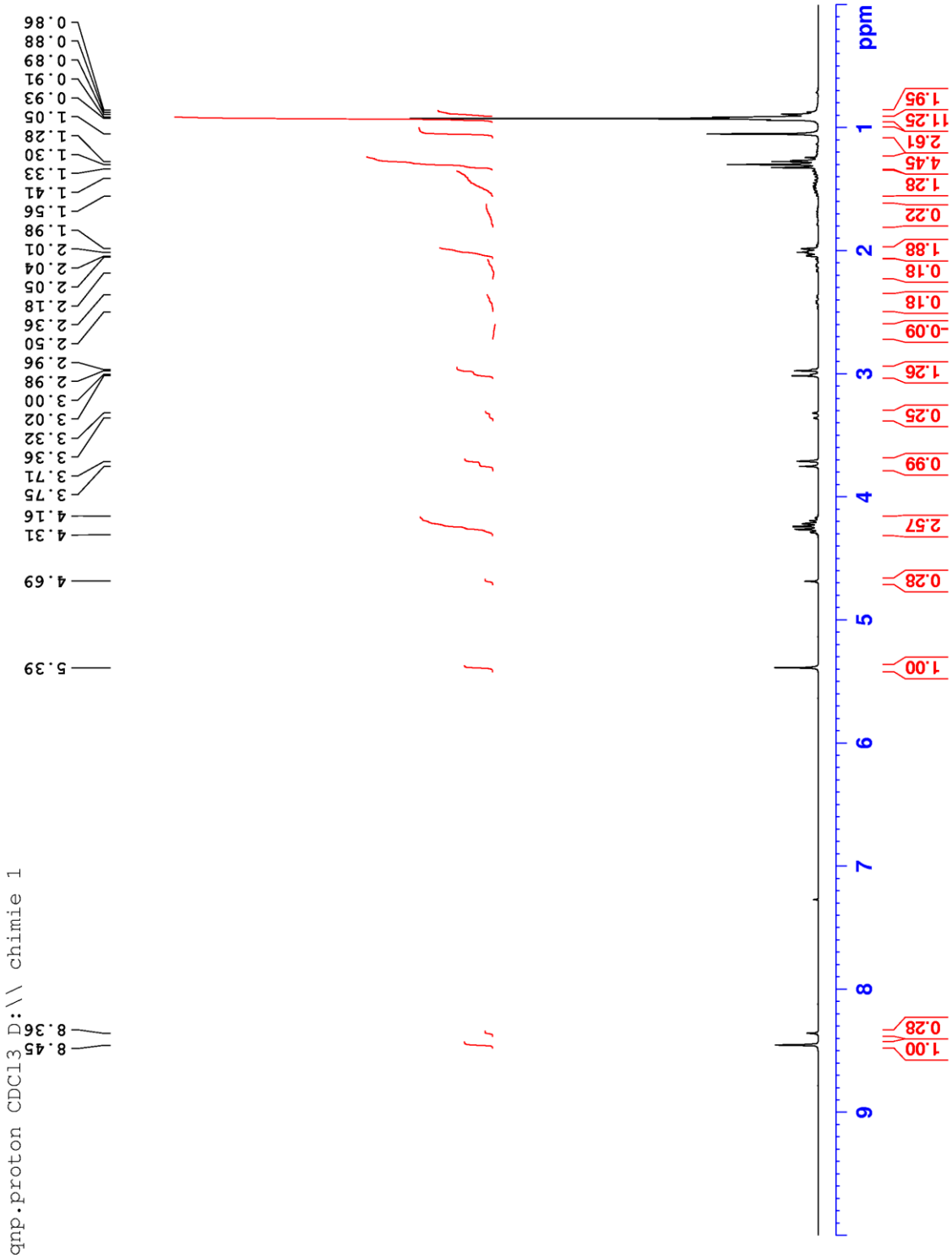


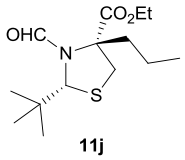
7j



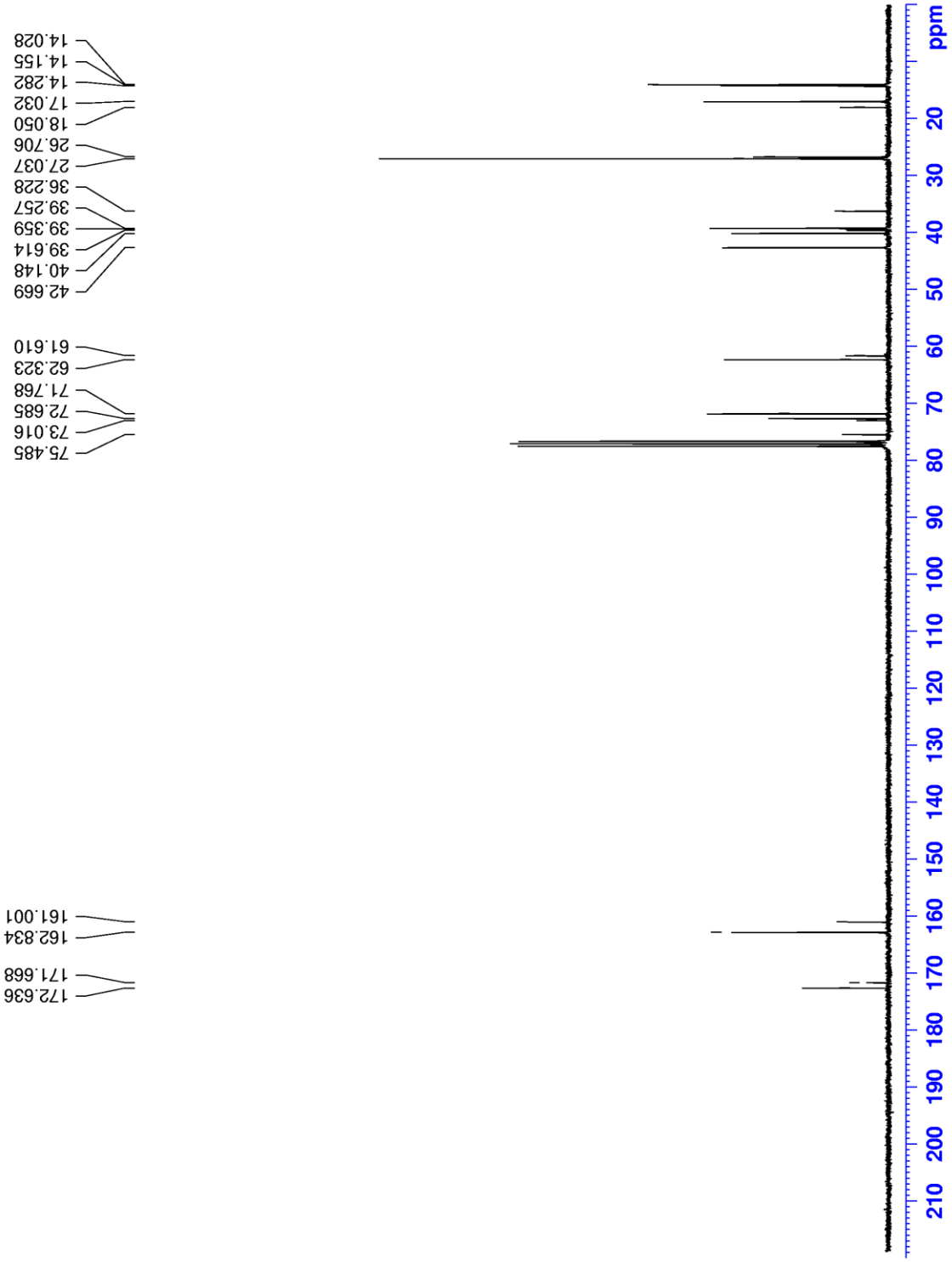

OHC
N
CO2Et
S

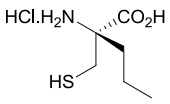
11j


qnp.proton CDCl3 D:\\ chimie 1
ppm
0.86
0.88
0.89
0.91
0.93
1.05
1.28
1.30
1.33
1.41
1.56
1.98
2.01
2.04
2.05
2.18
2.36
2.50
2.96
2.98
3.00
3.02
3.32
3.36
3.71
3.75
4.16
4.31
4.69
5.39
8.36
8.45
1.95
11.25
2.61
4.45
1.28
0.22
1.88
0.18
0.18
0.09
1.26
0.25
0.99
2.57
0.28
1.00
0.28
1.00

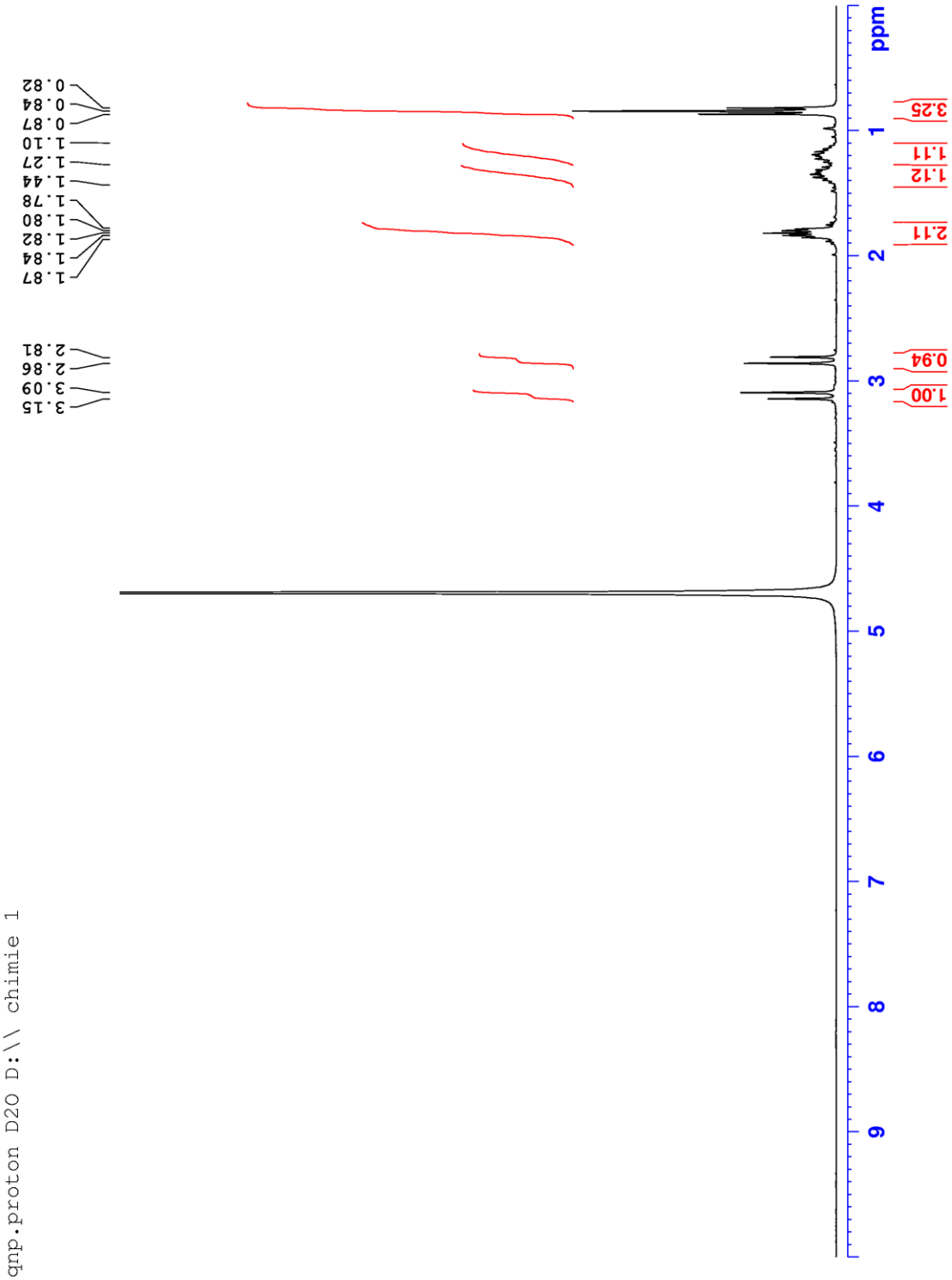


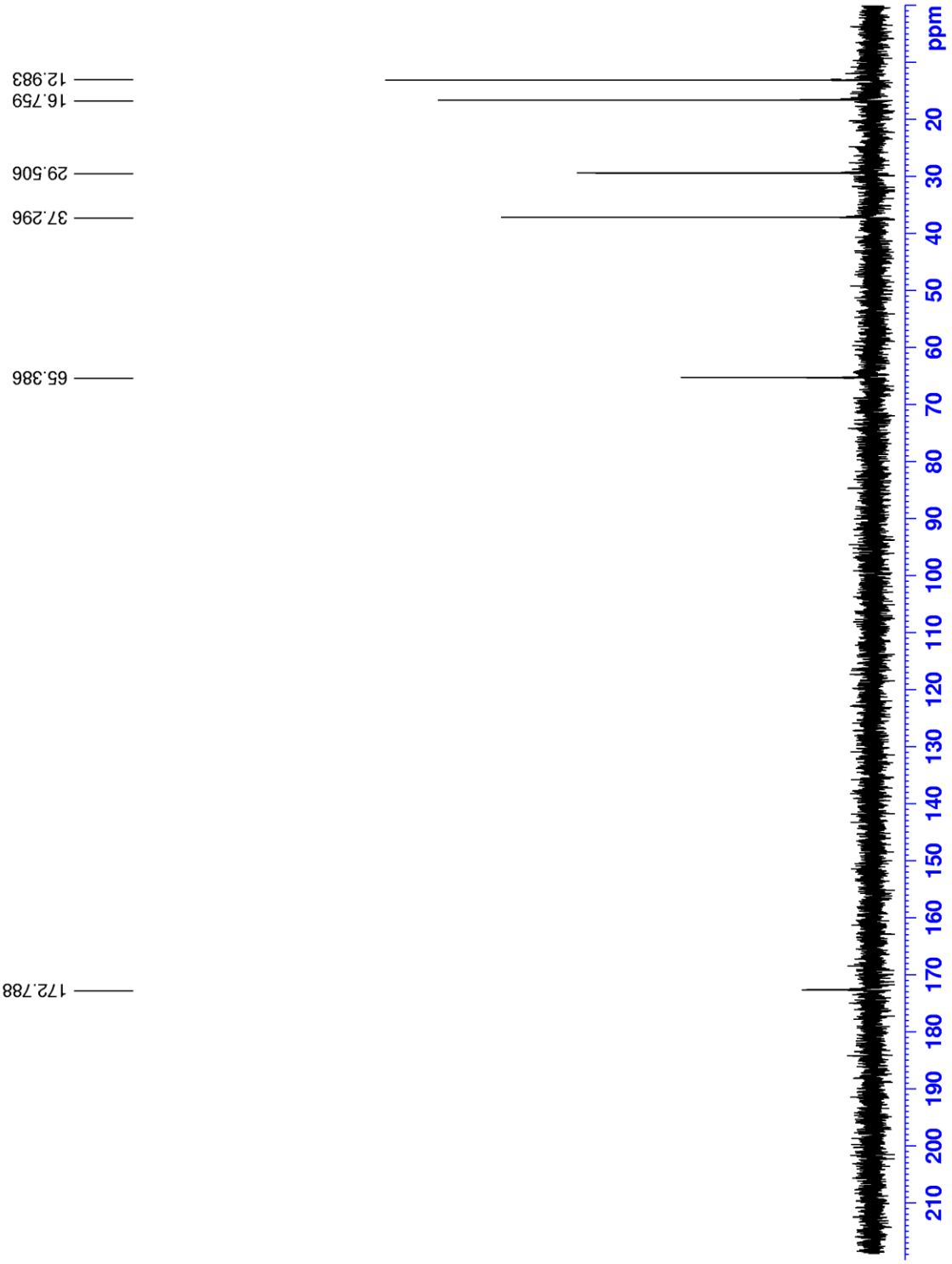
11j

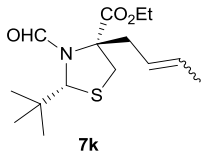




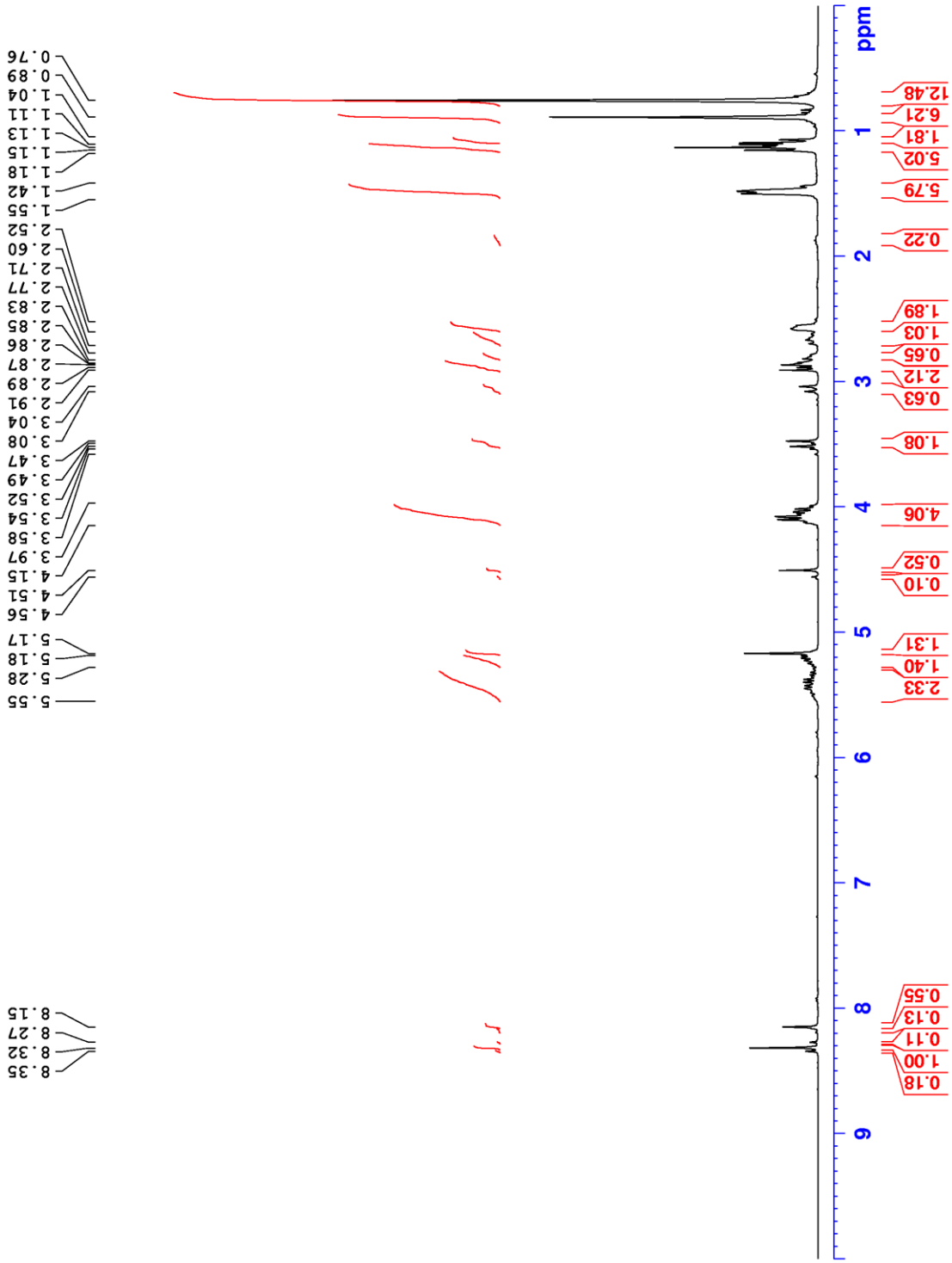
8j

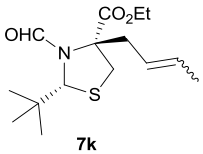




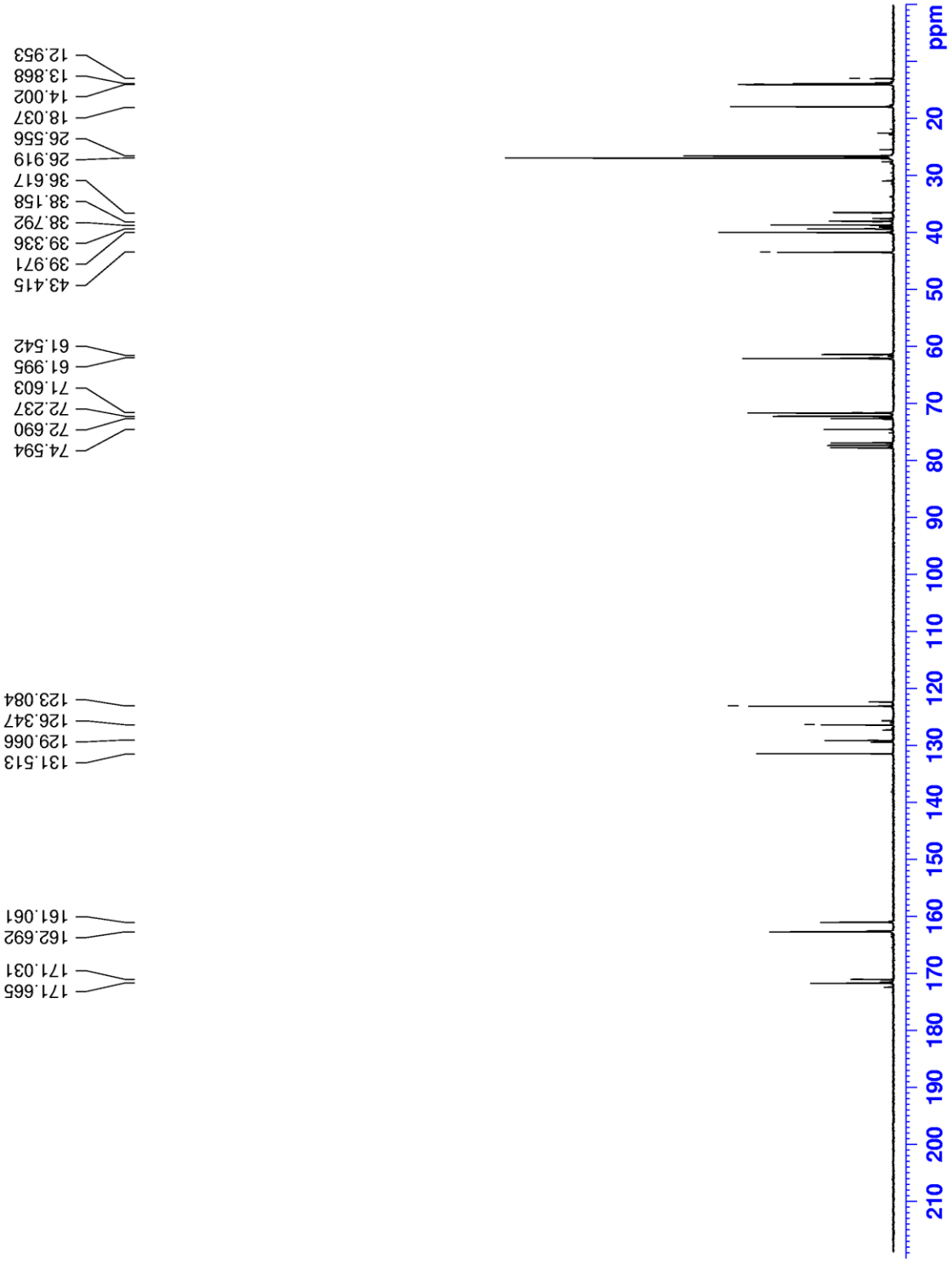


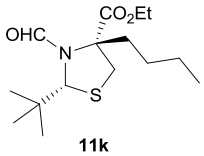
7k



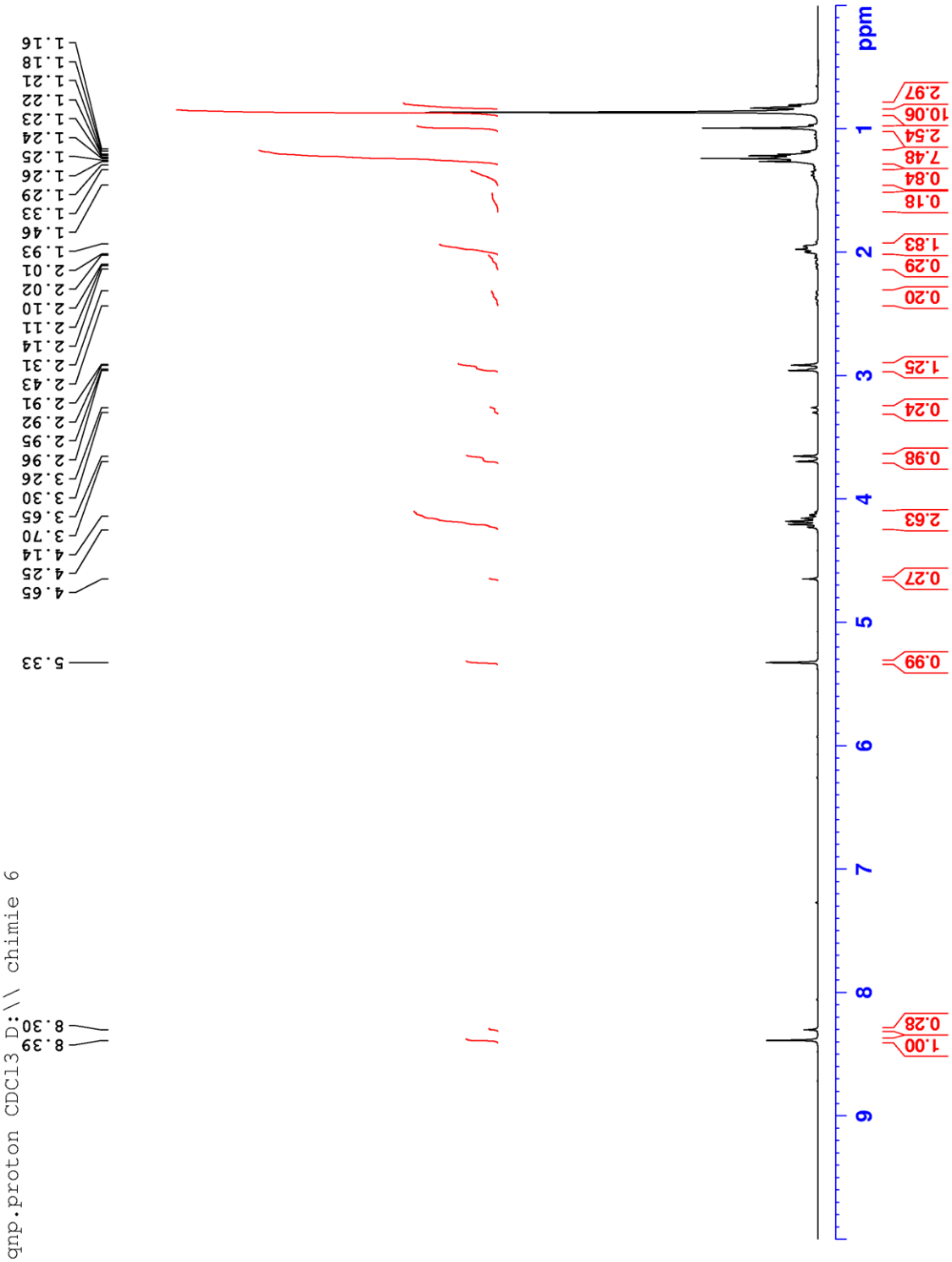


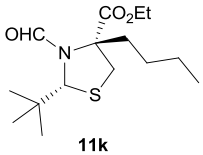
7k



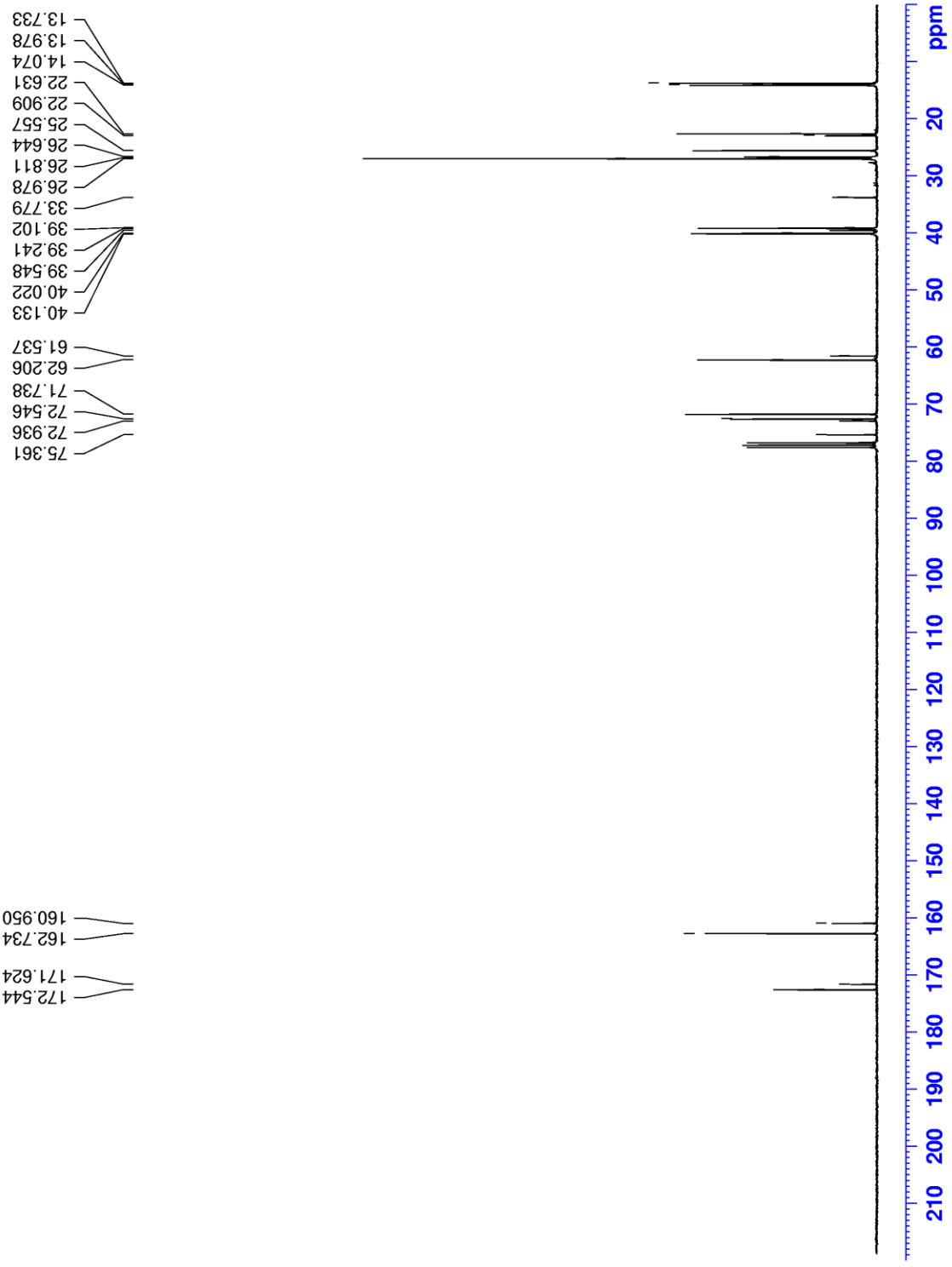

CO2Et
OHC
N
S

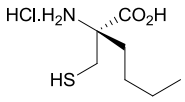
11k


qnp.proton CDCl3 D:\\ chimie 6
ppm
1.16
1.18
1.21
1.22
1.23
1.24
1.25
1.26
1.29
1.33
1.46
1.93
2.01
2.02
2.10
2.11
2.14
2.31
2.43
2.91
2.92
2.95
2.96
3.26
3.30
3.65
3.70
4.14
4.25
4.65
5.33
8.30
8.39
2.97
10.06
2.54
7.48
0.84
0.18
1.83
0.29
0.20
1.25
0.24
0.98
2.63
0.27
0.99
0.28
1.00



11k





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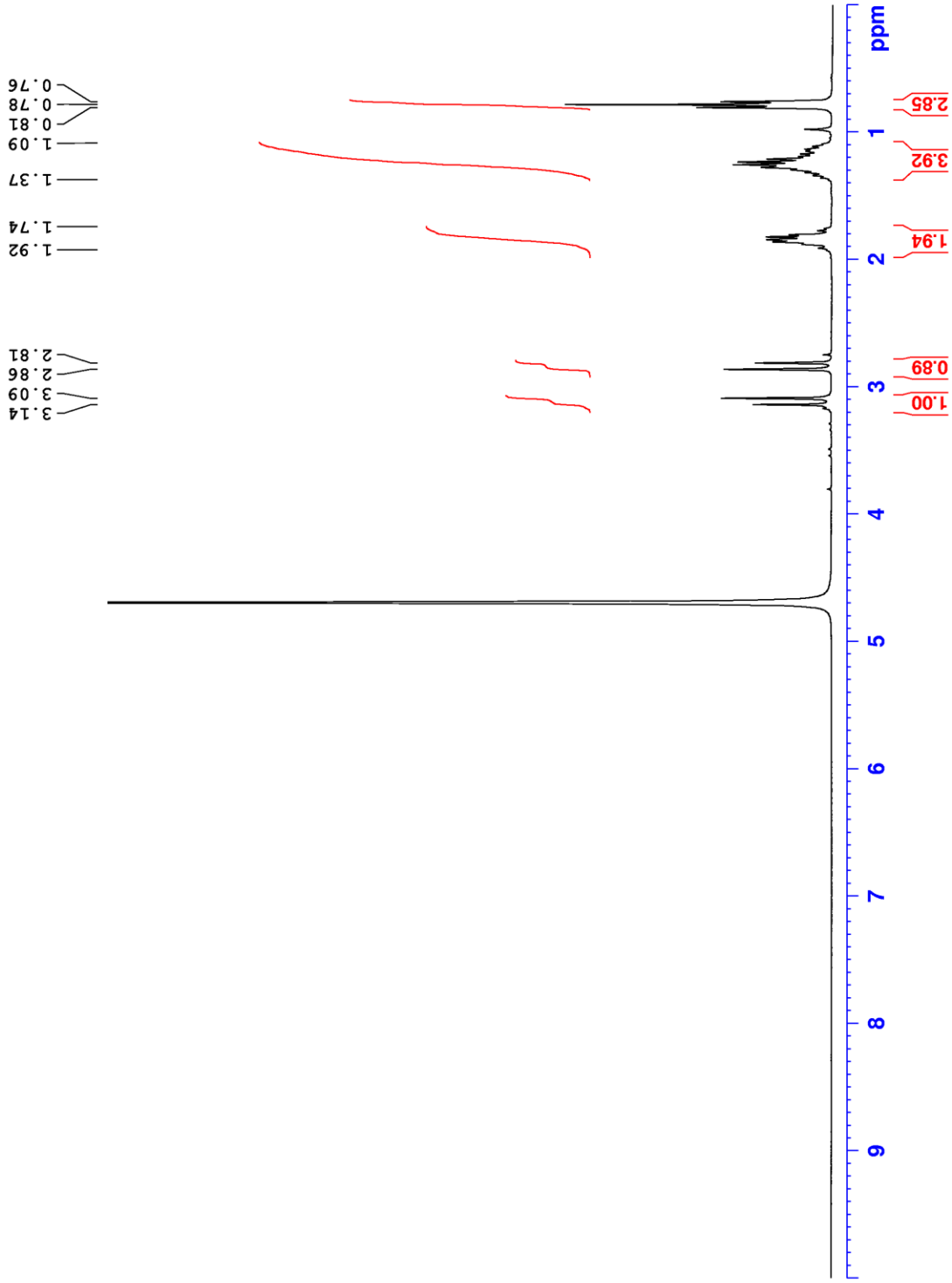

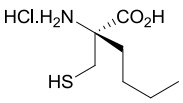

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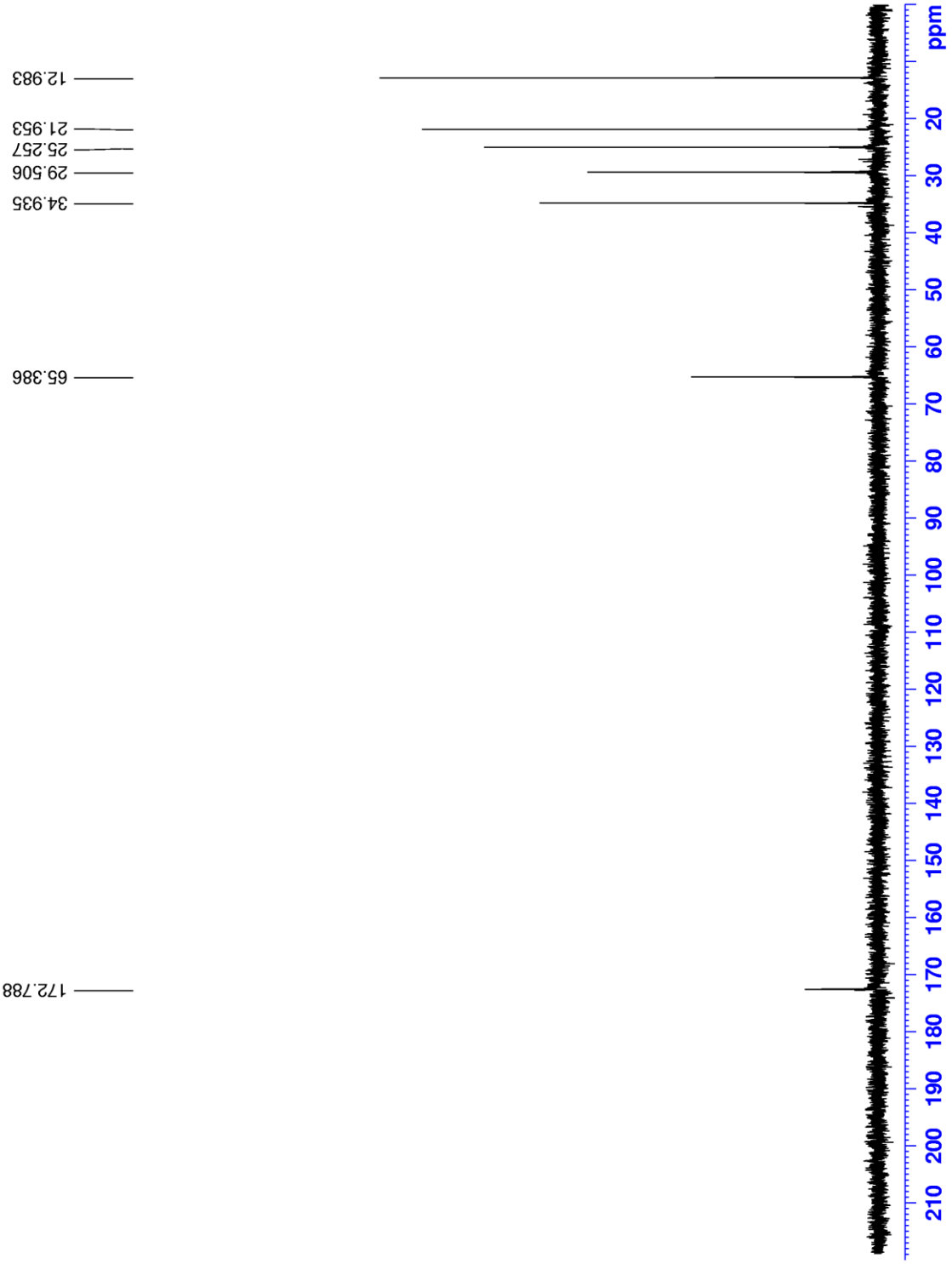
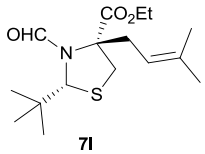
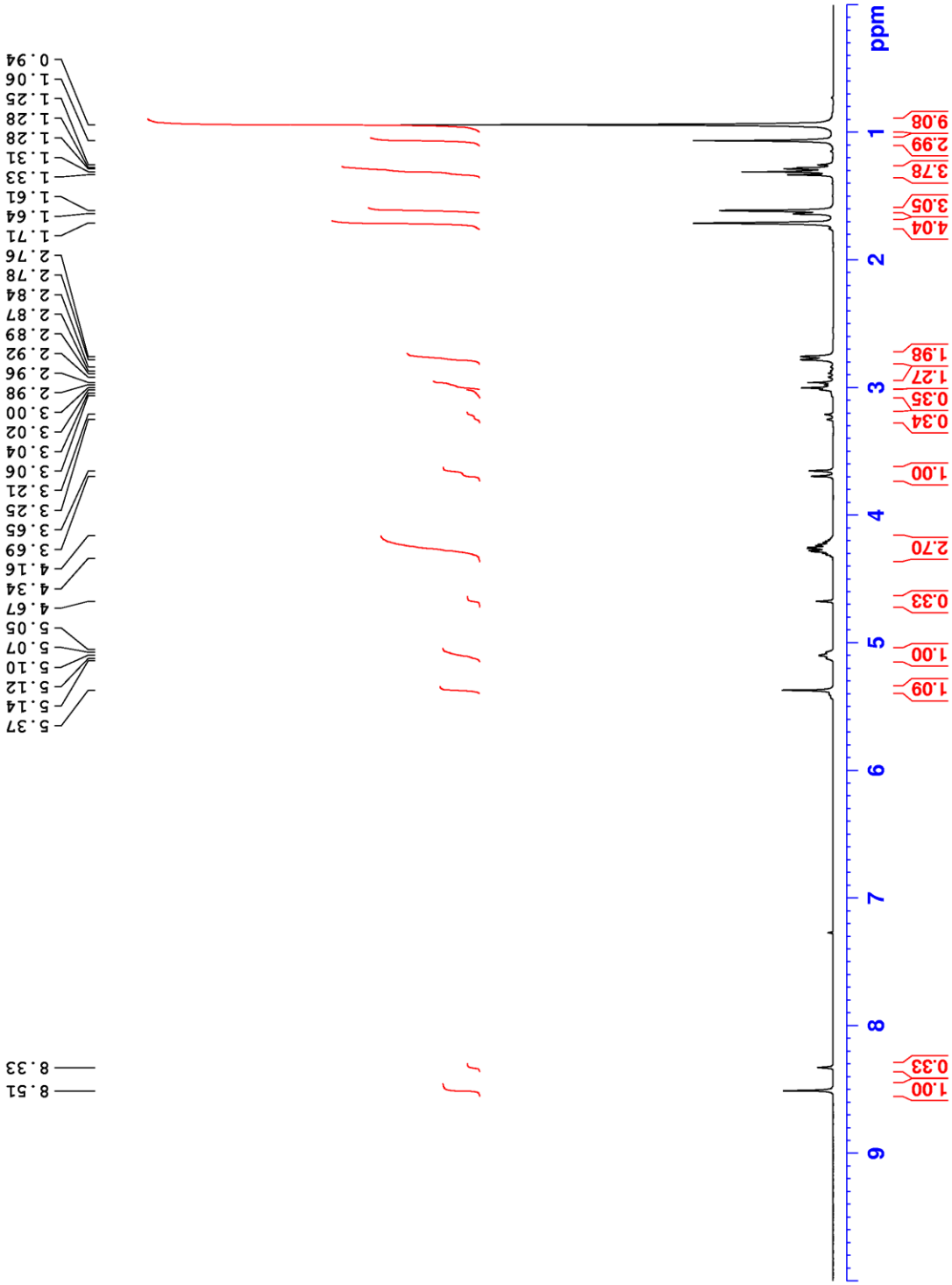
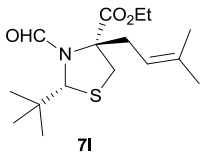




7l





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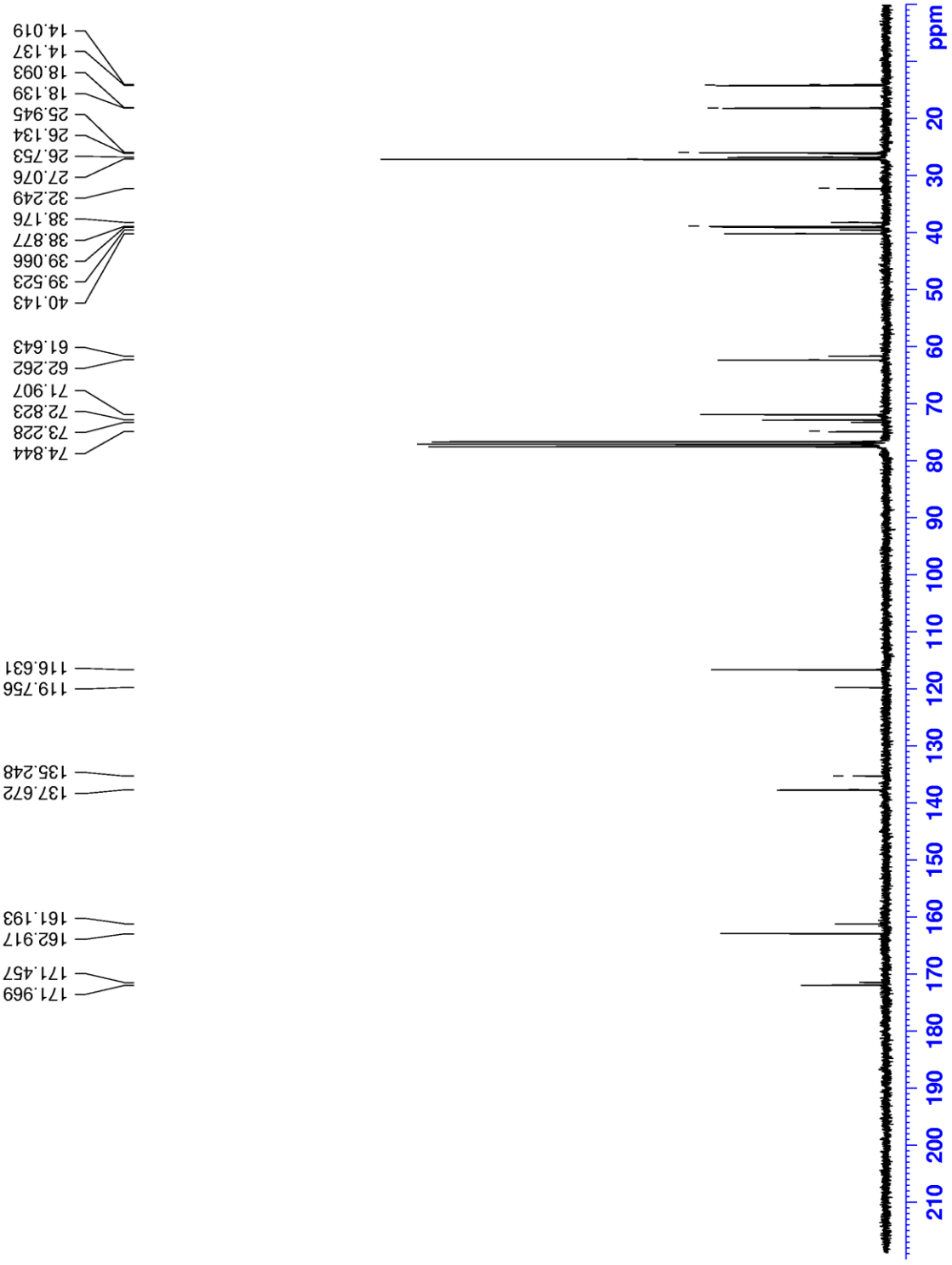
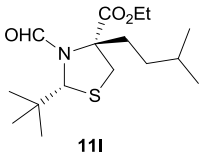
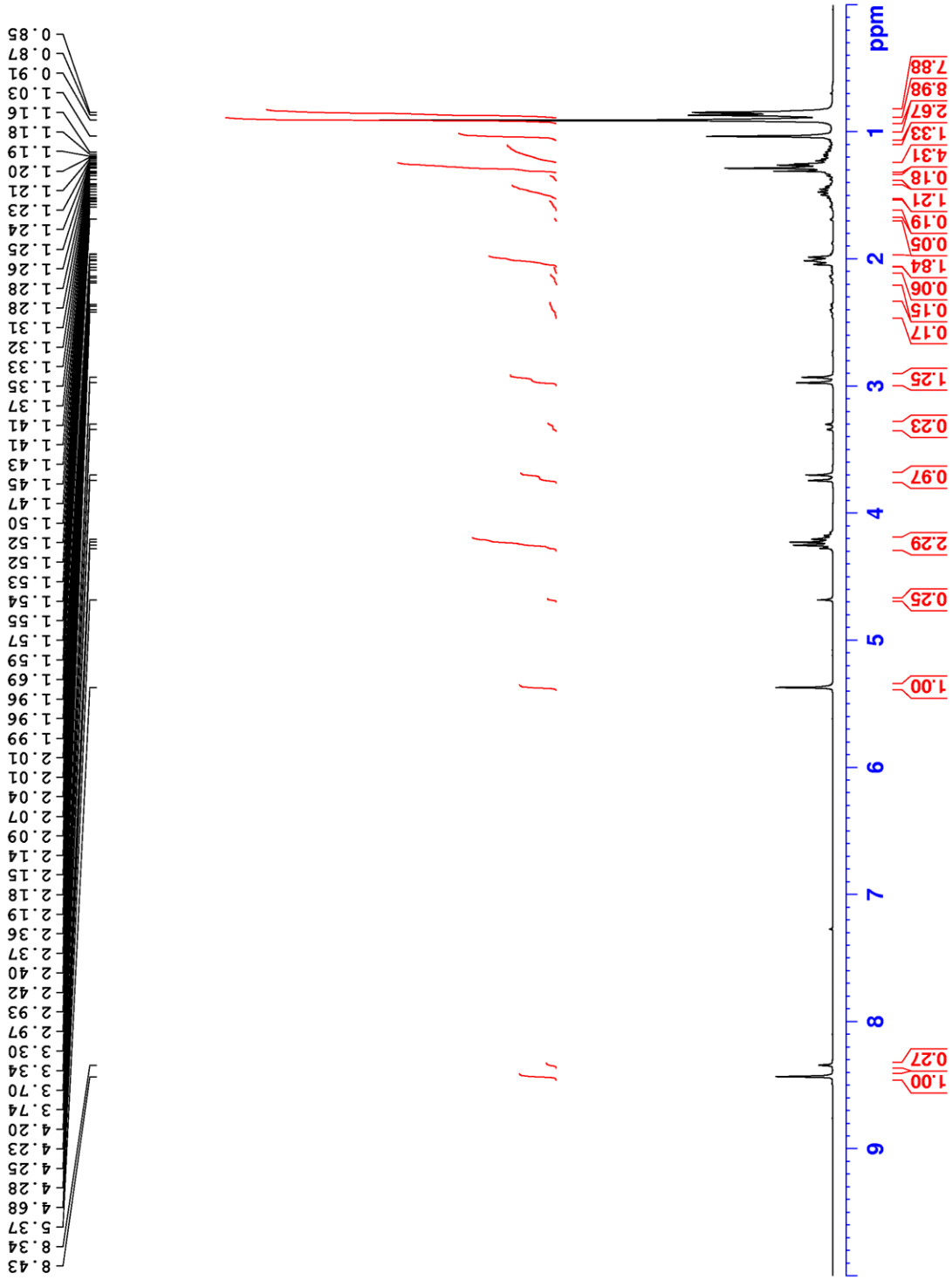
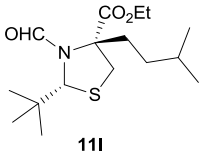


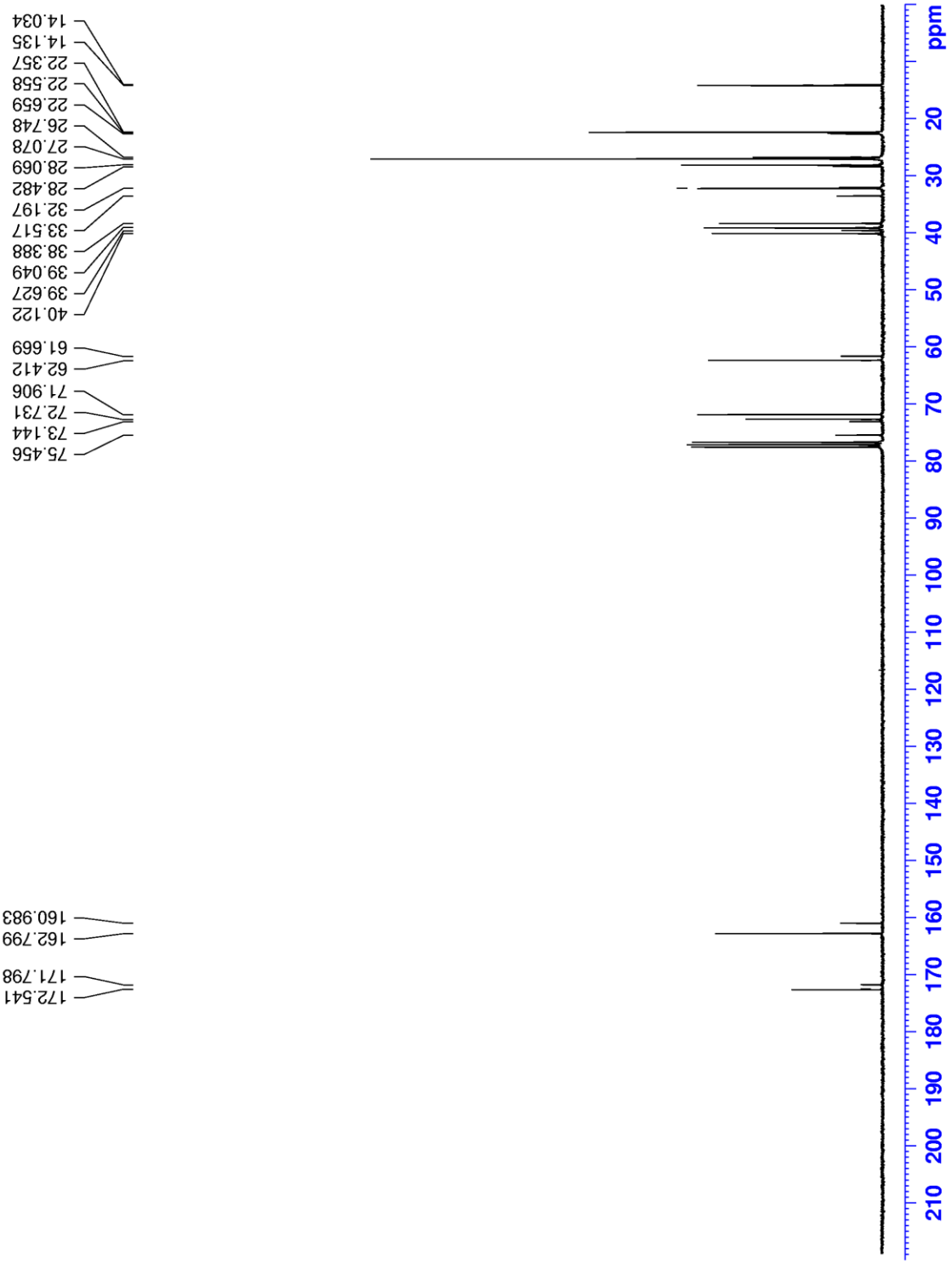

CO2Et
OHC
N
S

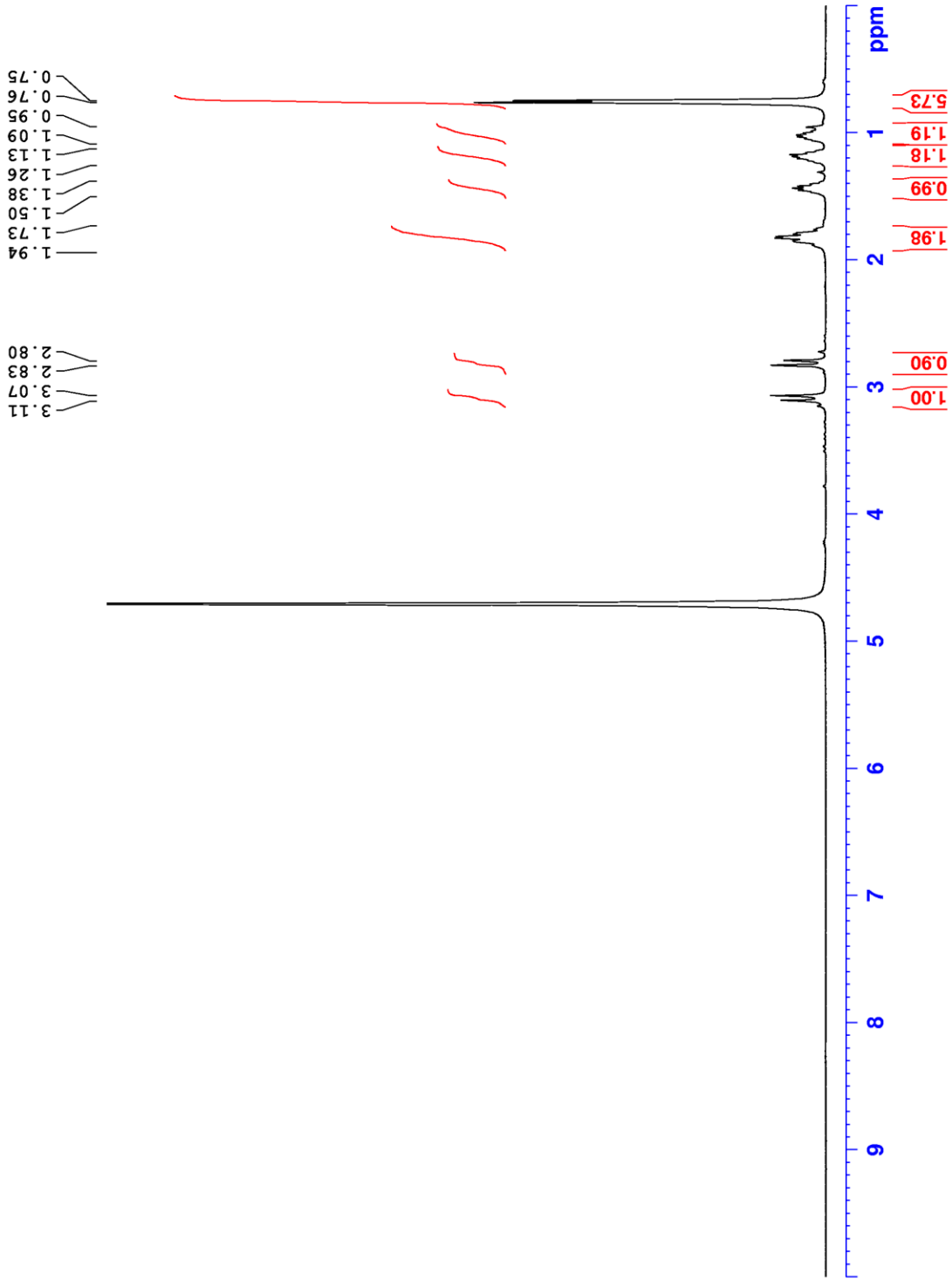
11l

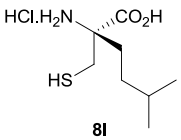

ppm
1
2
3
4
5
6
7
8
9
7.88
8.98
2.67
1.33
4.31
0.18
1.21
0.19
0.05
1.84
0.06
0.15
0.17
1.25
0.23
0.97
2.29
0.25
1.00
0.27
1.00



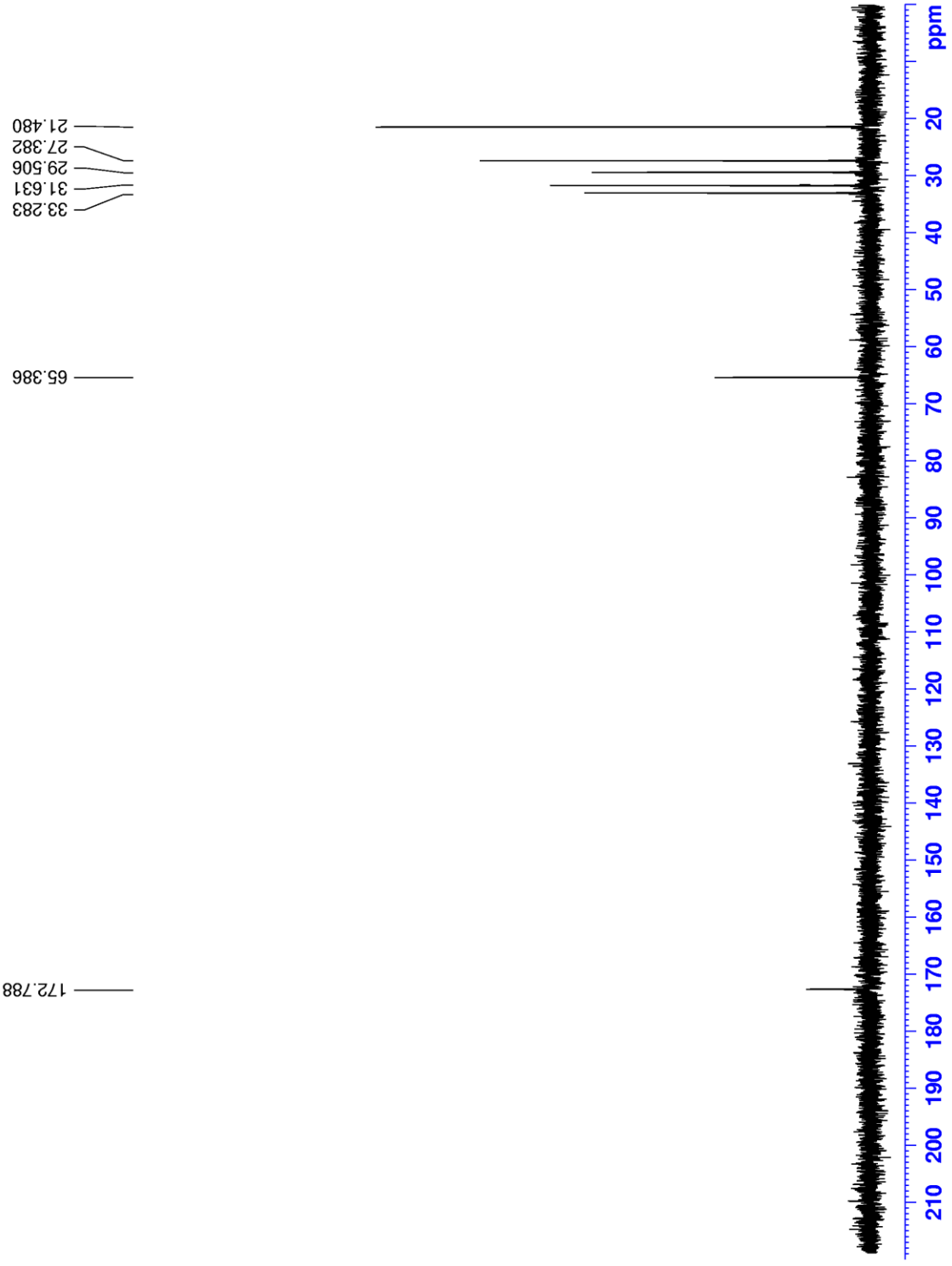
11l






HCl.H2N
CO2H
HS

8l


21.480
27.382
29.506
31.631
33.283
65.386
172.788
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210