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Discovery and optimisation of 1-acyl-2-benzylpyrrolidines as potent dual orexin receptor antagonists

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Electronic supplementary information contents:

Synthetic details for the preparation of compounds:

Commercially available starting materials were used as received without further purification. Flash column chromatography was performed using Biotage SNAP cartridges (10−340 g) and elution was with a Biotage Isolera system. Merck pre-coated thin layer chromatography (TLC) plates were used for TLC analysis. Final compounds were purified to >95% purity (UV and NMR) by reverse phase preparative HPLC using a Waters XBridge column (10 μm, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% NH_4OH (25% aq.) [eluent B]; Gradient: 90% B → 5% B over 6.5 min (flow: 75 mL/min). Detection: UV/Vis + MS. Racemates can be separated into their enantiomers by chiral HPLC using a ChiralPaK IC column (5 μm, 250 x 4.6 mm). Conditions: Heptane + 0.05% DEA [eluent A]; EtOH + 0.05% DEA [eluent B]; Isocratic elution with 50% eluent B (flow: 1 mL/min), or a CHIRALCEL OZ-H column (5 μm, 250 x 4.6 mm). Conditions: CO_2 [eluent A]; EtOH + 0.1% DEA [eluent B]; Isocratic elution with 50% eluent B (flow: 4 mL/min).

Mass spectrometry data were recorded by one of the following methods:

LC-MS with acidic conditions

Method A: Agilent 1100 series with mass spectrometry detection (MS: Finnigan single quadrupole). Column: Zorbax SB-aq (3.5 μm, 4.6 x 50 mm). Conditions:

MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B → 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

Method B: Agilent 1100 series with mass spectrometry detection (MS: Finnigan single quadrupole). Column: Waters XBridge C18 (2.5 μm, 4.6 x 30 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B → 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

LC-MS with basic conditions

Method C: Agilent 1100 series with mass spectrometry detection (MS: Finnigan single quadrupole). Column: Zorbax Extend C18 (5 μm, 4.6 x 50 mm). Conditions: MeCN [eluent A]; 13 mmol/L NH_3 in water [eluent B]. Gradient: 95% B → 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

Method D: Agilent 1100 series with mass spectrometry detection (MS: Finnigan single quadrupole). Column: Waters XBridge C18 (5 μm, 4.6 x 50 mm). Conditions: MeCN [eluent A]; 13 mmol/L NH_3 in water [eluent B]. Gradient: 95% B → 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

LC−HRMS parameters were the following: analytical pump Waters Acquity binary, Solvent Manager, MS, SYNAPT G2 MS, source temperature of 150 °C, desolvation temperature of 400 °C, desolvation gas flow of 400 L/h; cone gas flow of 10 L/h, extraction cone of 4 RF; lens 0.1 V; sampling cone 30; capillary 1.5 kV; high resolution mode; gain of 1.0, MS function of 0.2 s per scan, 120−1000 amu in full scan, centroid mode. Lock spray: keucine enkephalin, 2 ng/mL (556.2771 Da), scan time of 0.2 s with interval of 10 s and average of 5 scans; DAD: Acquity UPLC PDA detector. Column was an Acquity UPLC BEH C18 1.7 μm, 2.1 mm x 50 mm from Waters, thermostated in the Acquity UPLC column manager at 60 °C. Eluents were the following: water + 0.05% formic acid; B, acetonitrile + 0.05% formic acid. Gradient was 2−98% B over 3.0 min. Flow was 0.6 mL/min. Detection was at UV 214 nm.

^{1}H NMR spectra were recorded on a Bruker (400 or 500 MHz) spectrometer in the indicated deuterated solvent. Chemical shifts are reported in ppm relative to solvent peaks as the internal reference. The substituted pyrrolidine orexin receptor

antagonists described in this manuscript exhibit complex conformations in solution, arising from hindered rotations that are slow on the NMR and LC-MS timescale. The proton spectra typically consist of broad, overlapping multiplets precluding a detailed coupling constant analysis and we feel that pictorial reproductions of the NMR spectra are more informative for comparative purposes; thus, NMR resonances of final compounds will not be listed in numerical format. Instead, we include reproductions of the ^{1}H and ^{13}C NMR spectra at 25 °C of all final compounds. In cases where final compounds appear as a mixture of conformational isomers, visible in their LC-MS spectra, the retention time of the most abundant conformer is given.

clogP values were calculated using ChemBioDraw Ultra 14.0.

Abbreviations used: aq., aqueous; DCM, dichloromethane; DEA, diethylamine; DIPEA, diisopropylethylamine; DMF, dimethylformamide; DMSO, dimethylsulfoxide; er, enantiomeric ratio; Et_2O, diethyl ether; EtOAc, ethyl acetate; EtOH, ethanol; HCl, hydrochloric acid; H_2O, water; HPLC, high performance liquid chromatography; MeCN, acetonitrile; MeOH, methanol; min, minutes; $NaHCO_3$, sodium bicarbonate; NaOH, sodium hydroxide; Na_2SO_4, sodium sulfate; $^{n}BuLi$, n-butyl-lithium; prep., preparative; py, pyridine; RT, room temperature; Soln., solution; TBME, tert-butyl methyl ether; TBTU, 2-(1*H*-benzotriazole-1-yl)-1,2,3,3-tetramethyluronium tetrafluoroborate; THF, tetrahydrofuran; t_R, retention time.

rac-(2-(3,4-dimethoxybenzyl)piperidin-1-yl)(1-ethyl-1*H*-indol-3-yl)methanone 2

A prestirred solution of 1-ethyl-1*H*-indole-3-carboxylic acid (17 mg, 0.09 mmol), TBTU (31 mg, 0.1 mmol), and DIPEA (24 μL, 0.14 mmol) in DMF (0.5 mL) was added to a RT solution of 2-(3,4-dimethoxybenzyl)piperidine hydrochloride (purchased from BioBlocks inc.) (25 mg, 0.09 mmol) and DIPEA (24 μL, 0.14 mmol) in DMF (0.5 mL) and the resulting mixture was shaken for 18 h. The reaction mixture was directly purified by prep. HPLC to give the title compound as a yellow oil (26 mg, 69%). LC-MS B: t_R = 0.92 min; $[M+H]^+$ = 407.21; LC-HRMS: t_R = 1.32 min; [M+H]/z = 407.2335, found = 407.2340.

rac-(2-(3,4-dimethoxybenzyl)piperidin-1-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone 4

The title compound was prepared from 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (prepared in analogy to the procedure described in WO2008/069997, p28) (19 mg, 0.09 mmol) and 2-(3,4-dimethoxybenzyl)piperidine hydrochloride (purchased from BioBlocks inc.) (25 mg, 0.1 mmol) in analogy to the procedure described for **2**. The product was isolated as a yellow oil (17 mg, 44%). LC-MS D: t_R = 0.87 min; $[M+H]^+$ = 421.22; LC-HRMS: t_R = 1.26 min; [M+H]/z = 421.2240, found = 421.2243.

rac-(2-(3,4-dimethoxyphenethyl)piperidin-1-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone 5

The title compound was prepared from 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (prepared in analogy to the procedure described in WO2008/069997, p28) (23 mg, 0.11 mmol) and 2-(3,4-dimethoxyphenethyl)piperidine (purchased from UkrOrgSynthesis) (25 mg, 0.1 mmol) in analogy to the procedure described for **2**. The product was isolated as a yellow oil (34 mg, 79%). LC-MS D: t_R = 0.95 min; $[M+H]^+$ = 435.19; LC-HRMS: t_R = 1.33 min; [M+H]/z = 435.2396, found = 435.2393.

rac-(2-(3-methoxyphenethyl)piperidin-1-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone 6

The title compound was prepared from 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (prepared in analogy to the procedure described in WO2008/069997, p28) (13 mg, 0.06 mmol) and 2-(3-methoxyphenethyl)piperidine (purchased from Matrix Scientific) (13 mg, 0.06 mmol) in analogy to the procedure described for **2**. The product was isolated as a yellow oil (18 mg, 77%). LC-MS D: t_R = 1.0 min; $[M+H]^+$ = 405.29; LC-HRMS: t_R = 1.42 min; [M+H]/z = 405.2291, found = 405.2298.

(*S*)-tetrahydro-3*H*-pyrrolo[1,2-*c*][1,2,3]oxathiazole 1,1-dioxide 29

A solution of sulfuryl chloride (8 mL, 99 mmol) in DCM (40 mL) was added dropwise over 1.5 h to a well stirred -78°C solution of (*S*)-(+)-2-(hydroxymethyl)pyrrolidine (10 g, 99 mmol) and pyridine (16 mL, 20 mmol) in DCM (60 mL) under argon. After 3 h the cooling bath was removed and the mixture was allowed to reach 0°C. The reaction mixture was quenched into ice water and transferred to a separating funnel. The layers were separated and the aqueous layer was extracted with DCM (2x). The combined organic extracts were washed with 1M aq. HCl soln., with water, and with

brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give a yellow solid. This was then re-dissolved in THF (50 mL), filtered through a sintered funnel to remove residual py.HCl and concentrated *in vacuo* to give the title compound as a pale yellow solid (8.8 g, 55%). ^{1}H NMR ($CDCl_3$) δ: 1.81-1.88 (m, 1 H), 1.93-2.09 (m, 2 H), 2.17-2.29 (m, 1 H), 3.26-3.35 (m, 1 H), 3.69-3.78 (m, 1 H), 4.05-4.11 (m, 1 H), 4.25-4.34 (m, 1 H), 4.55-4.61 (m, 1 H).

(*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine 30

^{n}BuLi 1.6 M in hexane (22.8 mL, 36 mmol) was added to a solution of 4-bromoveratrole (5.25 mL, 36 mmol) in THF (40 mL) under Argon at such a rate that the internal temperature remained below -70°C. After a few minutes the mixture became cloudy and a fine white to beige suspension was formed (hard to stir!). After 30 min a solution of (*S*)-tetrahydro-3*H*-pyrrolo[1,2-*c*][1,2,3]oxathiazole 1,1-dioxide **29** (4.88 g, 30 mmol) in THF (15 mL) was added keeping the internal temperature below -70°C. The cooling bath was removed and the mixture returned slowly to RT where all solids went back into solution. The brown solution was stirred for 1 h at RT and the volatiles were removed *in vacuo*. The residue was dissolved in 2 M aq. HCl (50 mL) and ethanol (50 mL) and heated to 95°C for 40 h. The reaction mixture was cooled to RT, diluted with H_2O, and the mixture washed with TBME (1x60 mL). This extract was discarded and the aqueous phase was basified with 5 M aq. NaOH and re-extracted with TBME (3x60 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give the title compound as a yellow oil (4.43 g, 67%). LC-MS B: t_R = 0.37 min; er: >99:1; $[M+H]^+$ = 222.15; ^{1}H NMR ($CDCl_3$) δ: 1.36-1.45 (m, 1 H), 1.67-1.92 (m, 4 H), 2.67-2.76 (m, 2 H), 2.81-2.87 (m, 1 H), 3.03-3.08 (m, 1 H), 3.18-3.25 (m, 1 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 6.75-6.79 (m, 2 H), 6.80-6.83 (m, 1 H).

(*S*)-2-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)methyl)pyrrolidine 31

The title compound was prepared from 6-bromo-1,4-benzodioxane (2 mL, 15 mmol) and (*S*)-tetrahydro-3*H*-pyrrolo[1,2-*c*][1,2,3]oxathiazole 1,1-dioxide **29** (2.0 g, 12 mmol) in analogy to the procedure described for **30**. The product was isolated as a brown oil (1.2 g, 45%). LC-MS A: t_R = 0.51 min; $[M+H]^+$ = 220.16.

(*S*)-2-(benzo[*d*][1,3]dioxol-5-ylmethyl)pyrrolidine 32

The title compound was prepared from 4-bromo-1,2-(methylenedioxy)benzene (1.8 mL, 15 mmol) and (*S*)-tetrahydro-3*H*-pyrrolo[1,2-*c*][1,2,3]oxathiazole 1,1-dioxide **29** (2.0 g, 12 mmol) in analogy to the procedure described for **30**. The product was isolated as a brown oil (1.86 g, 74%). LC-MS A: t_R = 0.51 min; $[M+H]^+$ = 206.18.

(*S*)-2-(3,5-dimethoxybenzyl)pyrrolidine 33

The title compound was prepared from 1-bromo-3,5-dimethoxybenzene (3.2 g, 15 mmol) and (*S*)-tetrahydro-3*H*-pyrrolo[1,2-*c*][1,2,3]oxathiazole 1,1-dioxide **29** (2.0 g, 12 mmol) in analogy to the procedure described for **30**. The product was isolated as a brown oil (0.51 g, 19%). LC-MS B: t_R = 0.45 min; $[M+H]^+$ = 222.25.

(*S*)-2-(3-chloro-4-methoxybenzyl)pyrrolidine 34

The title compound was prepared from 4-bromo-2-chloro-1-methoxybenzene (2.2 g, 10 mmol) and (*S*)-tetrahydro-3*H*-pyrrolo[1,2-*c*][1,2,3]oxathiazole 1,1-dioxide **29** (1.34 g, 8.2 mmol) in analogy to the procedure described for **30**. The product was isolated as a yellow oil (0.51 g, 28%). LC-MS A: t_R = 0.54 min; $[M+H]^+$ = 226.2.

(*S*)-2-(2-chloro-3-methoxybenzyl)pyrrolidine 35

The title compound was prepared from 1-chloro-2-methoxybenzene (1.9 g, 13.5 mmol) and (*S*)-tetrahydro-3*H*-pyrrolo[1,2-*c*][1,2,3]oxathiazole 1,1-dioxide **29** (2.0 g, 12 mmol) in analogy to the procedure described for **30**. The product was isolated as an orange oil (1.1 g, 38%). LC-MS A: t_R = 0.55 min; $[M+H]^+$ = 226.15.

(*S*)-2-(2-chloro-5-methoxybenzyl)pyrrolidine 36

The title compound was prepared from 2-bromo-1-chloro-4-methoxybenzene (2.2 g, 10 mmol) and (*S*)-tetrahydro-3*H*-pyrrolo[1,2-*c*][1,2,3]oxathiazole 1,1-dioxide **29** (1.35 g, 8.3 mmol) in analogy to the procedure described for **30**. The product was isolated as a yellow oil (0.6 g, 32%). LC-MS A: t_R = 0.57 min; $[M+H]^+$ = 225.98.

(*S*)-2-(3-chloro-4-methylbenzyl)pyrrolidine 37

The title compound was prepared from 4-bromo-2-chloro-1-methylbenzene (3.0 g, 15 mmol) and (*S*)-tetrahydro-3*H*-pyrrolo[1,2-*c*][1,2,3]oxathiazole 1,1-dioxide **29** (2.0 g, 12 mmol) in analogy to the procedure described for **30**. The product was isolated as a brown oil (1.37 g, 27%). LC-MS A: t_R = 0.60 min; $[M+H]^+$ = 210.11.

(*S*)-2-(3,4-dichlorobenzyl)pyrrolidine 38

The title compound was prepared from 1,2-dichloro-4-iodobenzene (4.1 g, 15 mmol) and (*S*)-tetrahydro-3*H*-pyrrolo[1,2-*c*][1,2,3]oxathiazole 1,1-dioxide **29** (2.0 g, 12 mmol) in analogy to the procedure described for **30**. The product was isolated as a yellow oil (0.44 g, 16%). LC-MS A: t_R = 0.59 min; $[M+H]^+$ = 230.14.

5-(benzo[*d*][1,3]dioxol-5-yl)-2-methylthiazole-4-carboxylic acid 39

Step 1: Methyl 5-bromo-2-methylthiazole-4-carboxylate (0.73 g, 3.1 mmol) and 1,3-benzodioxole-5-boronic acid (0.5 g, 3.1 mmol) were dissolved in a mixture of EtOH (20 mL) and toluene (20 mL). Freshly prepared 2 M aq. Na_2CO_3 soln. (31 mL) was added and the mixture was degassed by bubbling N_2 through the mixture for 30 s. Tetrakis(triphenylphosphine) palladium (129 mg, 0.11 mmol) was added quickly and the reaction mixture was heated to reflux for 1 h. The mixture was allowed to cool to RT and some water was added before it was filtered over a celite plug washing with additional water and EtOH. The EtOH was evaporated *in vacuo* and the remaining phases were extracted with DCM (3x). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude product was purified by flash chromatography (eluting with a gradient of 10% to 50% EtOAc in hexane) to give the methyl ester of the title compound as a pale yellow solid (0.55 g, 64%, some transesterification to the ethyl ester was observed). LC-MS B: t_R = 0.67 min; $[M+H]^+$ = 278.14.

Step 2: The ester from above (0.55 g, 2 mmol) was partitioned between MeOH (30 mL) and 2 M aq. NaOH soln. (15 mL) and heated to a gentle reflux (67°C) overnight. The MeOH was evaporated *in vacuo* and the remaining aqueous layer acidified with 1M aq. HCl before being extracted with DCM (3x). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give the title compound as a pink solid that was used further without purification (0.46 g, 88%). LC-MS B: t_R = 0.58 min; $[M+H]^+$ = 264.12; ^{1}H NMR (d_6-DMSO) δ: 2.65 (s, 3 H), 6.09 (s, 2 H), 6.93-6.99 (m, 2 H), 7.07 (d, *J* = 1.2 Hz, 1 H), 12.82 (s br, 1 H).

5-(2,3-dihydrobenzofuran-5-yl)-2-methylthiazole-4-carboxylic acid 40

The title compound was prepared from methyl 5-bromo-2-methylthiazole-4-carboxylate (0.48 g, 2 mmol) and (2,3-dihydrobenzofuran-5-yl)boronic acid (0.33 g, 2 mmol) in analogy to the two-step sequence described for **39**. The title compound

was isolated as a white solid (0.29 g, 82%). LC-MS B: t_R = 0.59 min; $[M+H]^+$ = 262.23; ^{1}H NMR (d_6-DMSO) δ: 2.65 (s, 3 H), 3.17-3.23 (m, 2H), 4.55-4.60 (m, 2 H), 6.78-6.82 (m, 1 H), 7.18-7.22 (m, 1 H), 7.34 (s br, 1 H), 12.75 (s br, 1 H).

(*S*)-(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone 7

The title compound was prepared from 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (prepared in analogy to the procedure described in WO2008/069997, p28) (184 mg, 0.90 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (200 mg, 0.90 mmol) in analogy to the procedure described for **2**. The product was isolated as a yellow solid (160 mg, 44%). LC-MS D: t_R = 0.89 min; $[M+H]^+$ = 407.23; er: >99:1; LC-HRMS: t_R = 1.21 min; [M+H]/z = 407.2083, found = 407.2084.

(*S*)-(2-(2*H*-1,2,3-triazol-2-yl)phenyl)(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)methanone 8

The title compound was prepared from 2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (256 mg, 1.36 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (300 mg, 1.36 mmol) in analogy to the procedure described for **2**. The product was isolated as a cream solid (398 mg, 75%). LC-MS D: t_R = 0.85 min; $[M+H]^+$ = 393.05; LC-HRMS: t_R = 1.15 min; [M+H]/z = 393.1927, found = 393.1931.

(*S*)-(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone 9

The title compound was prepared from 5-methyl-2-(1*H*-pyrazol-1-yl)benzoic acid (prepared in analogy to the procedure described in WO2014/057435, p92) (12 mg, 0.06 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (14 mg, 0.06 mmol) in analogy to the procedure described for **2**. The product was isolated as a white solid (7 mg, 24%). LC-MS D: t_R = 0.88 min; $[M+H]^+$ = 406.17; LC-HRMS: t_R = 1.20 min; [M+H]/z = 406.2131, found = 406.2136.

(*S*)-(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)(2-(pyrimidin-2-yl)phenyl)methanone 10

The title compound was prepared from 2-(pyrimidin-2-yl)benzoic acid (0.91 g, 4.5 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (1.0 g, 4.5 mmol) in analogy to the procedure described for **2**. The product was isolated as a white solid (0.56 g,

31%). LC-MS D: t_R = 0.83 min; $[M+H]^+$ = 404.07; LC-HRMS: t_R = 1.13 min; [M+H]/z = 404.1974, found = 404.1980.

(*S*)-(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone 11

The title compound was prepared from 6-methyl-3-(pyrimidin-2-yl)picolinic acid (prepared in analogy to the procedure described in WO2010/063662, p31) (15 mg, 0.07 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (15 mg, 0.07 mmol) in analogy to the procedure described for **2**. The product was isolated as a white solid (10 mg, 36%). LC-MS D: t_R = 0.79 min; $[M+H]^+$ = 419.13; LC-HRMS: t_R = 1.11 min; [M+H]/z = 419.2083, found = 419.2082.

(*S*)-(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)(3-(*m*-tolyl)pyrazin-2-yl)methanone 12

The title compound was prepared from 3-(*m*-tolyl)pyrazine-2-carboxylic acid (prepared in analogy to the procedure described in WO2010/38200, p48) (214 mg, 1.0 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (221 mg, 1.0 mmol) in analogy to the procedure described for **2**. The product was isolated as a cream solid (331 mg, 79%). LC-MS D: t_R = 0.88 min; $[M+H]^+$ = 418.16; LC-HRMS: t_R = 1.24 min; [M+H]/z = 418.2131, found = 418.2135.

(*S*)-(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)(2-methyl-5-(*m*-tolyl)thiazol-4-yl)methanone 13

The title compound was prepared from 2-methyl-5-(*m*-tolyl)thiazole-4-carboxylic acid (211 mg, 0.90 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (200 mg, 0.90 mmol) in analogy to the procedure described for **2**. The product was isolated as a yellow solid (167 mg, 42%). LC-MS D: t_R = 0.95 min; $[M+H]^+$ = 437.2; LC-HRMS: t_R = 1.33 min; [M+H]/z = 437.1899, found = 437.1900.

(*S*)-(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)(2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)methanone 14

The title compound was prepared from 2-(3-methyl-1,2,4-oxadiazol-5-yl)benzoic acid (281 mg, 1.38 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (305 mg, 1.38 mmol) in analogy to the procedure described for **2**. The product was isolated as a yellow solid (403 mg, 72%). LC-MS D: t_R = 0.85 min; $[M+H]^+$ = 408.1; LC-HRMS: t_R = 1.16 min; [M+H]/z = 408.1923, found = 408.1931.

(*S*)-(2-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)methyl)pyrrolidin-1-yl)(2-methyl-5-(*m*-tolyl)thiazol-4-yl)methanone 15

The title compound was prepared from 2-methyl-5-(*m*-tolyl)thiazole-4-carboxylic acid (23 mg, 0.1 mmol) and (*S*)-2-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)methyl)pyrrolidine **31** (22 mg, 0.1 mmol) in analogy to the procedure described for **2**. The product was isolated as a white solid (20 mg, 47%). LC-MS D: t_R = 0.98 min; $[M+H]^+$ = 435.07; LC-HRMS: t_R = 1.37 min; [M+H]/z = 435.1742, found = 435.1750.

(*S*)-(2-(benzo[*d*][1,3]dioxol-5-ylmethyl)pyrrolidin-1-yl)(2-methyl-5-(*m*-tolyl)thiazol-4-yl)methanone 16

The title compound was prepared from 2-methyl-5-(*m*-tolyl)thiazole-4-carboxylic acid (23 mg, 0.1 mmol) and (*S*)-2-(benzo[*d*][1,3]dioxol-5-ylmethyl)pyrrolidine **32** (21 mg, 0.1 mmol) in analogy to the procedure described for **2**. The product was isolated as a white solid (29 mg, 69%). LC-MS D: t_R = 0.99 min; $[M+H]^+$ = 421.08; LC-HRMS: t_R = 1.39 min; [M+H]/z = 421.1586, found = 421.1588.

(*S*)-(2-(3,5-dimethoxybenzyl)pyrrolidin-1-yl)(2-methyl-5-(*m*-tolyl)thiazol-4-yl)methanone 17

The title compound was prepared from 2-methyl-5-(*m*-tolyl)thiazole-4-carboxylic acid (211 mg, 0.9 mmol) and (*S*)-2-(3,5-dimethoxybenzyl)pyrrolidine **33** (200 mg, 0.9 mmol) in analogy to the procedure described for **2**. The product was isolated as a yellow solid (290 mg, 74%). LC-MS D: t_R = 1.0 min; $[M+H]^+$ = 437.11; LC-HRMS: t_R = 1.41 min; [M+H]/z = 437.1899, found = 437.1899.

(*S*)-(2-(3-chloro-4-methoxybenzyl)pyrrolidin-1-yl)(2-methyl-5-(*m*-tolyl)thiazol-4-yl)methanone 18

The title compound was prepared from 2-methyl-5-(*m*-tolyl)thiazole-4-carboxylic acid (200 mg, 0.89 mmol) and (*S*)-2-(3-chloro-4-methoxybenzyl)pyrrolidine **34** (200 mg, 0.89 mmol) in analogy to the procedure described for **2**. The product was isolated as a yellow solid (290 mg, 74%). LC-MS D: t_R = 1.02 min; $[M+H]^+$ = 441.07; LC-HRMS: t_R = 1.46 min; [M+H]/z = 441.1404, found = 441.1412.

(*S*)-(2-(2-chloro-3-methoxybenzyl)pyrrolidin-1-yl)(2-methyl-5-(*m*-tolyl)thiazol-4-yl)methanone 19

The title compound was prepared from 2-methyl-5-(*m*-tolyl)thiazole-4-carboxylic acid (23 mg, 0.1 mmol) and (*S*)-2-(2-chloro-3-methoxybenzyl)pyrrolidine **35** (23 mg, 0.1

mmol) in analogy to the procedure described for **2**. The product was isolated as a brown solid (15 mg, 33%). LC-MS D: t_R = 0.96 min; $[M+H]^+$ = 441.16; LC-HRMS: t_R = 1.42 min; [M+H]/z = 441.1404, found = 441.1410.

(*S*)-(2-(2-chloro-5-methoxybenzyl)pyrrolidin-1-yl)(2-methyl-5-(*m*-tolyl)thiazol-4-yl)methanone 20

The title compound was prepared from 2-methyl-5-(*m*-tolyl)thiazole-4-carboxylic acid (23 mg, 0.1 mmol) and (*S*)-2-(2-chloro-5-methoxybenzyl)pyrrolidine **36** (23 mg, 0.1 mmol) in analogy to the procedure described for **2**. The product was isolated as a brown solid (36 mg, 81%). LC-MS D: t_R = 1.0 min; $[M+H]^+$ = 441.16; LC-HRMS: t_R = 1.49 min; [M+H]/z = 441.1404, found = 441.1410.

(*S*)-(2-(3-chloro-4-methylbenzyl)pyrrolidin-1-yl)(2-methyl-5-(*m*-tolyl)thiazol-4-yl)methanone 21

The title compound was prepared from 2-methyl-5-(*m*-tolyl)thiazole-4-carboxylic acid (23 mg, 0.1 mmol) and (*S*)-2-(3-chloro-4-methylbenzyl)pyrrolidine **37** (21 mg, 0.1 mmol) in analogy to the procedure described for **2**. The product was isolated as a brown solid (24 mg, 57%). LC-MS D: t_R = 1.08 min; $[M+H]^+$ = 425.06; LC-HRMS: t_R = 1.59 min; [M+H]/z = 425.1454, found = 425.1460.

(*S*)-(2-(3,4-dichlorobenzyl)pyrrolidin-1-yl)(2-methyl-5-(*m*-tolyl)thiazol-4-yl)methanone 22

The title compound was prepared from 2-methyl-5-(*m*-tolyl)thiazole-4-carboxylic acid (35 mg, 0.15 mmol) and (*S*)-2-(3,4-dichlorobenzyl)pyrrolidine **38** (35 mg, 0.15 mmol) in analogy to the procedure described for **2**. The product was isolated as a yellow solid (53 mg, 79%). LC-MS D: t_R = 1.08 min; $[M+H]^+$ = 445.03; LC-HRMS: t_R = 1.59 min; [M+H]/z = 445.0908, found = 445.0910.

(*S*)-(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone 23

The title compound was prepared from 5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid (24 mg, 0.1 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (22 mg, 0.1 mmol) in analogy to the procedure described for **2**. The product was isolated as a yellow oil (27 mg, 60%). LC-MS D: t_R = 0.92 min; $[M+H]^+$ = 441.17; LC-HRMS: t_R = 1.28 min; [M+H]/z = 441.1648, found = 441.1650.

(*S*)-(5-(3-chlorophenyl)-2-methylthiazol-4-yl)(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)methanone 24

The title compound was prepared from 5-(3-chlorophenyl)-2-methylthiazole-4-carboxylic acid (prepared in analogy to the procedure described in WO2009/16560, p63) (25 mg, 0.1 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (22 mg, 0.1 mmol) in analogy to the procedure described for **2**. The product was isolated as a yellow oil (32 mg, 71%). LC-MS D: t_R = 0.96 min; $[M+H]^+$ = 457.02; LC-HRMS: t_R = 1.36 min; [M+H]/z = 457.1353, found = 457.1361.

(*S*)-(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)(5-(3-methoxyphenyl)-2-methylthiazol-4-yl)methanone 25

The title compound was prepared from 5-(3-methoxyphenyl)-2-methylthiazole-4-carboxylic acid (prepared in analogy to the procedure described in WO2010/044054, p82) (25 mg, 0.1 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (22 mg, 0.1 mmol) in analogy to the procedure described for **2**. The product was isolated as a cream solid (28 mg, 62%). LC-MS D: t_R = 0.92 min; $[M+H]^+$ = 453.12; LC-HRMS: t_R = 1.26 min; [M+H]/z = 453.1848, found = 453.1858.

(*S*)-(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)(5-(4-methoxyphenyl)-2-methylthiazol-4-yl)methanone 26

The title compound was prepared from 5-(4-methoxyphenyl)-2-methylthiazole-4-carboxylic acid (prepared in analogy to the procedure described in WO2010/044054, p82) (25 mg, 0.1 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (22 mg, 0.1 mmol) in analogy to the procedure described for **2**. The product was isolated as a cream solid (8 mg, 17%). LC-MS D: t_R = 0.91 min; $[M+H]^+$ = 452.99; LC-HRMS: t_R = 1.25 min; [M+H]/z = 453.1848, found = 453.1856.

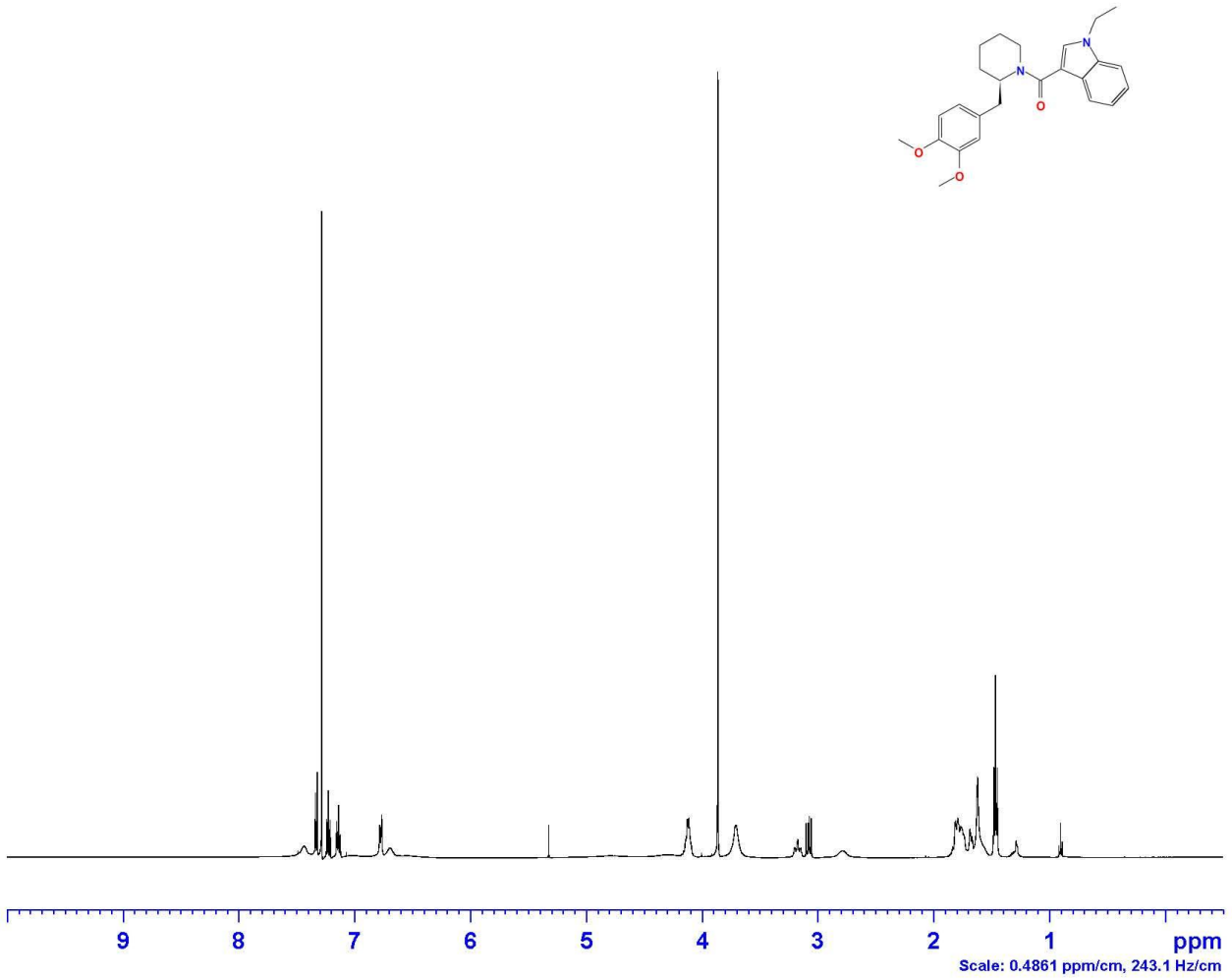
(*S*)-(5-(benzo[*d*][1,3]dioxol-5-yl)-2-methylthiazol-4-yl)(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)methanone 27

The title compound was prepared from 5-(benzo[*d*][1,3]dioxol-5-yl)-2-methylthiazole-4-carboxylic acid **39** (238 mg, 0.9 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (200 mg, 0.9 mmol) in analogy to the procedure described for **2**. The product was isolated as a white solid (252 mg, 60%). LC-MS D: t_R = 0.89 min; $[M+H]^+$ = 466.99; LC-HRMS: t_R = 1.23 min; [M+H]/z = 467.1641, found = 467.1652.

(*S*)-(5-(2,3-dihydrobenzofuran-5-yl)-2-methylthiazol-4-yl)(2-(3,4-dimethoxybenzyl)pyrrolidin-1-yl)methanone 28

The title compound was prepared from 5-(2,3-dihydrobenzofuran-5-yl)-2-methylthiazole-4-carboxylic acid **40** (26 mg, 0.1 mmol) and (*S*)-2-(3,4-dimethoxybenzyl)pyrrolidine **30** (22 mg, 0.1 mmol) in analogy to the procedure described for **2**. The product was isolated as a yellow oil (33 mg, 71%). LC-MS D: t_R = 0.90 min; $[M+H]^+$ = 464.98; LC-HRMS: t_R = 1.25 min; [M+H]/z = 465.1848, found = 465.1855.

^{1}H & ^{13}C NMR spectra of final compounds:

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PROCNO                1

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TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                200.03
DW                50.000 usec
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NUC1                 1H
P1                  9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
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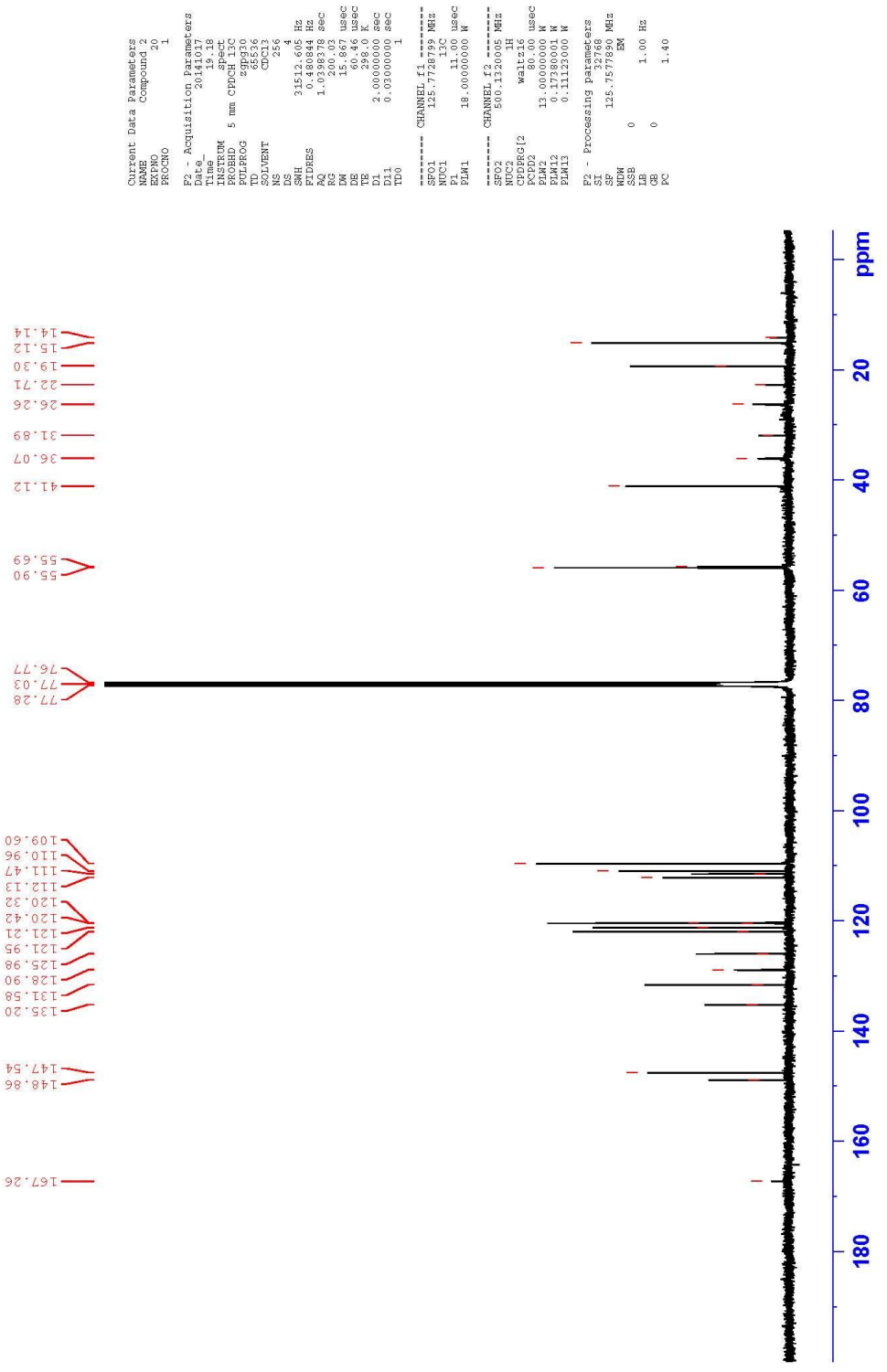
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TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
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NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
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NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
F2 - Processing parameters
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LB 1.00 Hz
GB 0
PC 1.40
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19.30
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125.98
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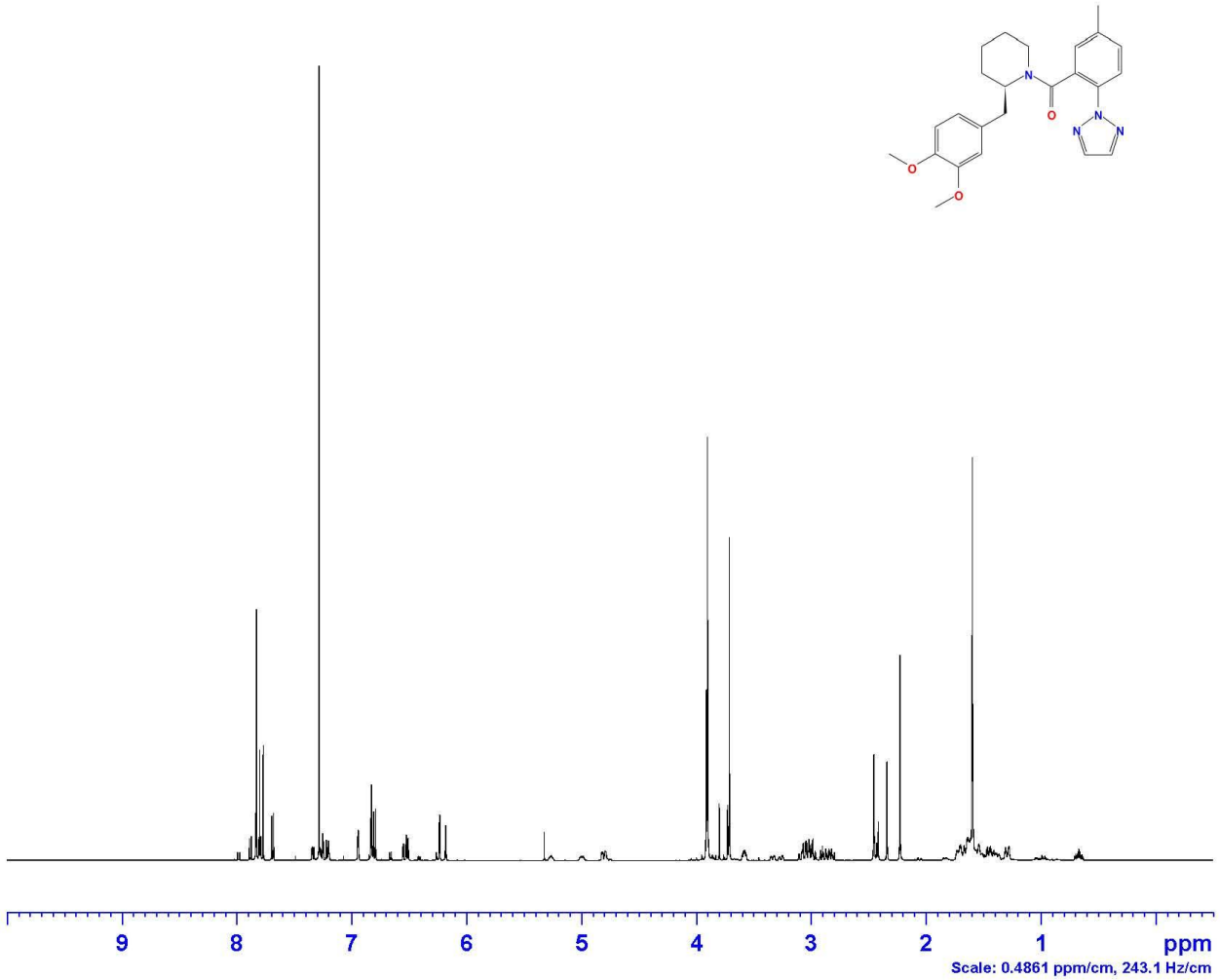


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PROCNO                1

F2 - Acquisition Parameters
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PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                200.03
DW                50.000 usec
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TE                298.0 K
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NUC1                 1H
P1                 9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
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WDW                 EM
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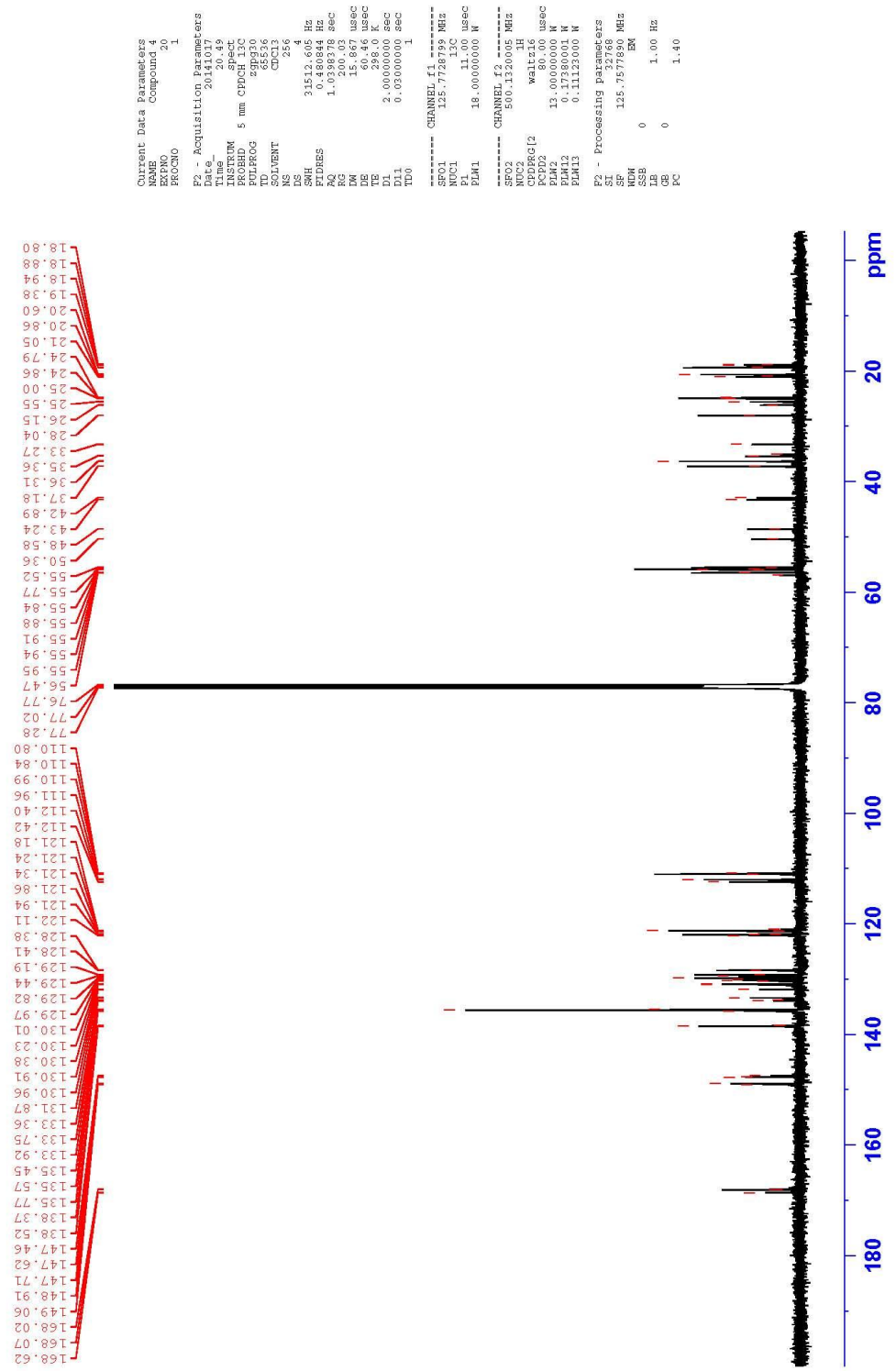
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PROCNO 1
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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 60.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
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NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
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NUC2 1H
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PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
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GB 0
PC 1.40
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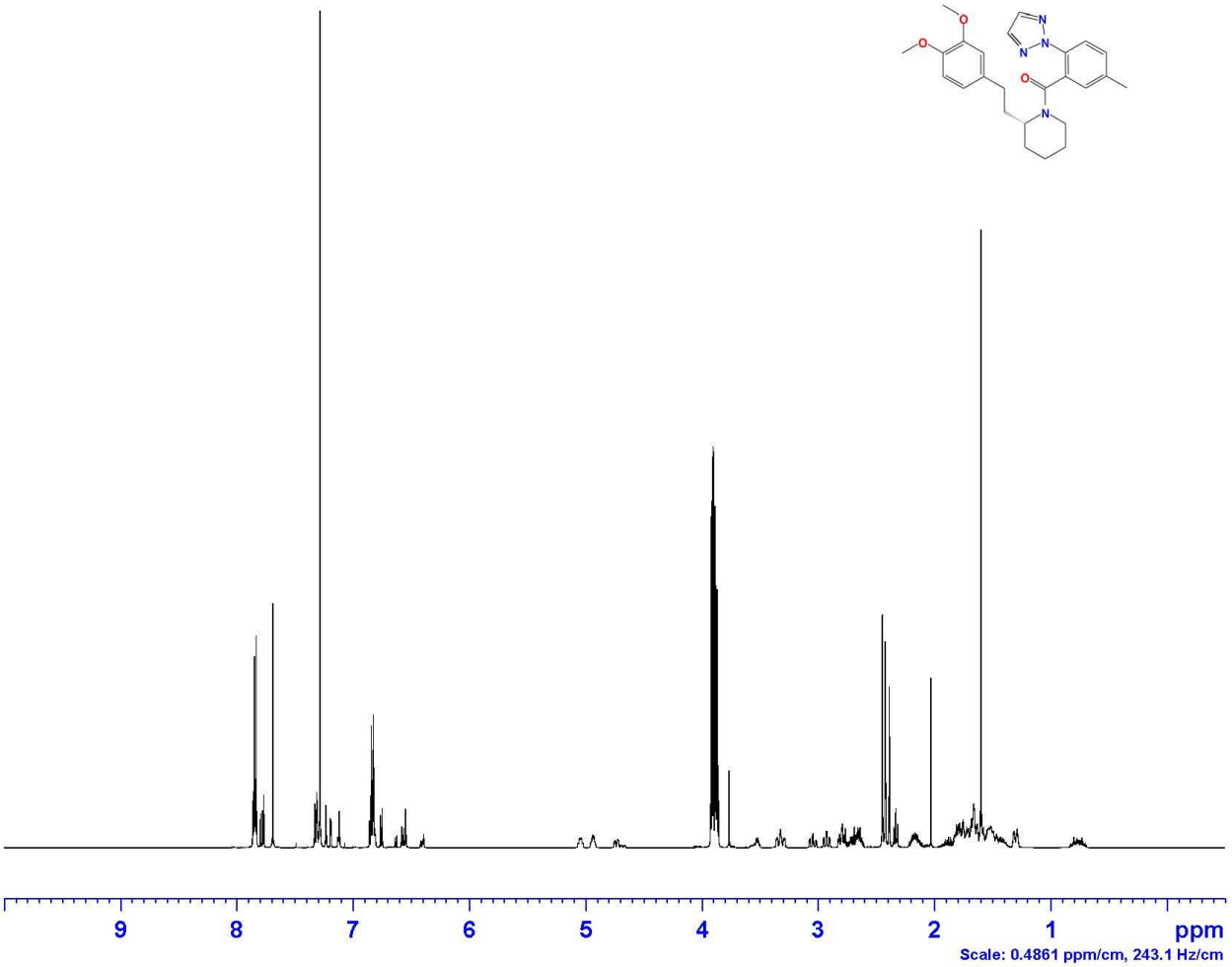


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Current Data Parameters
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EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
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Time              20.53
INSTRUM           spect
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PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                200.03
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                 9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
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SF           500.1300000 MHz
WDW                 EM
SSB       0
LB                0.30 Hz
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PC                1.00
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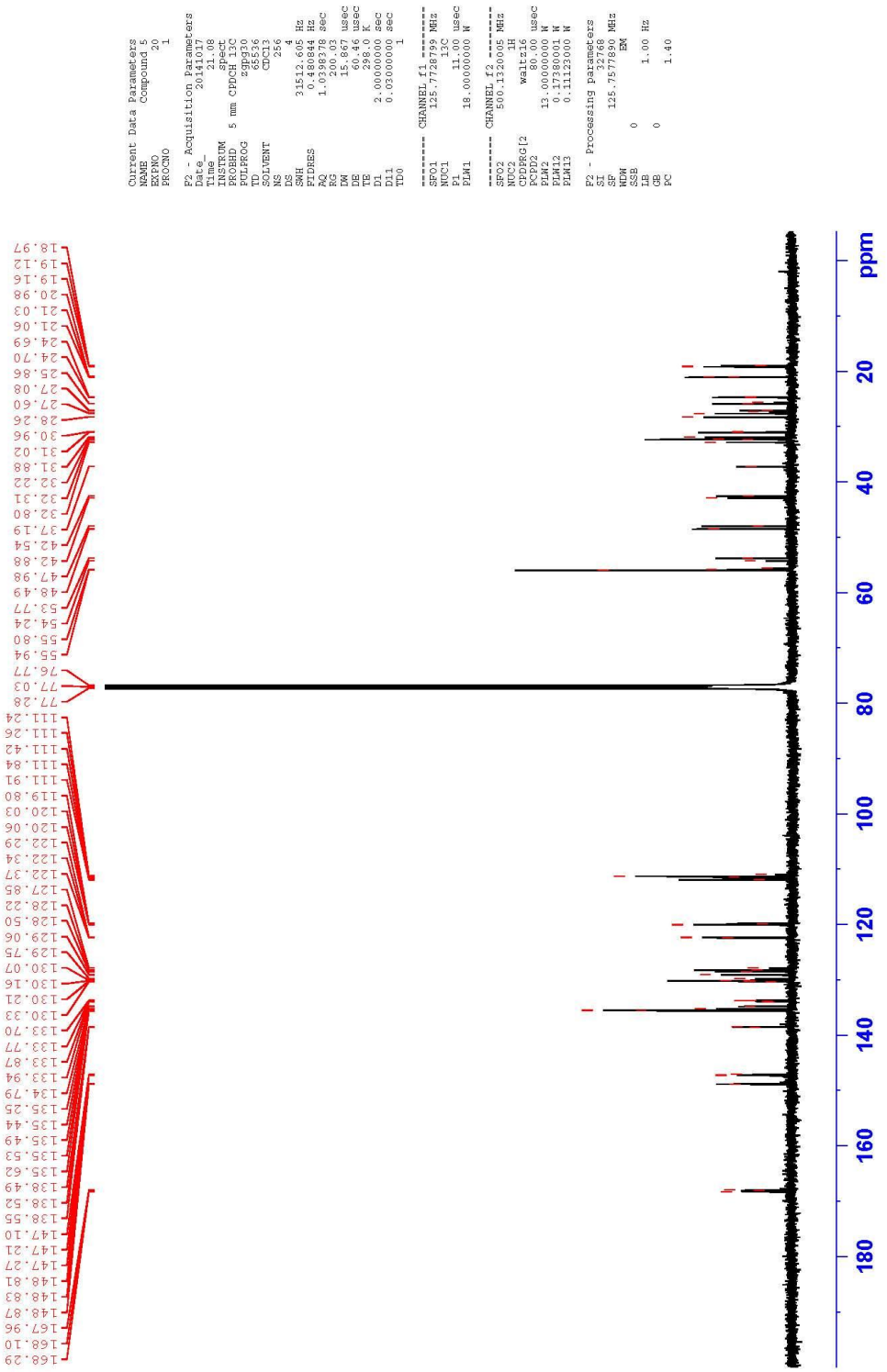
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PROCNO 1
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Time 21.08
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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
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NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
CHANNEL f2
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
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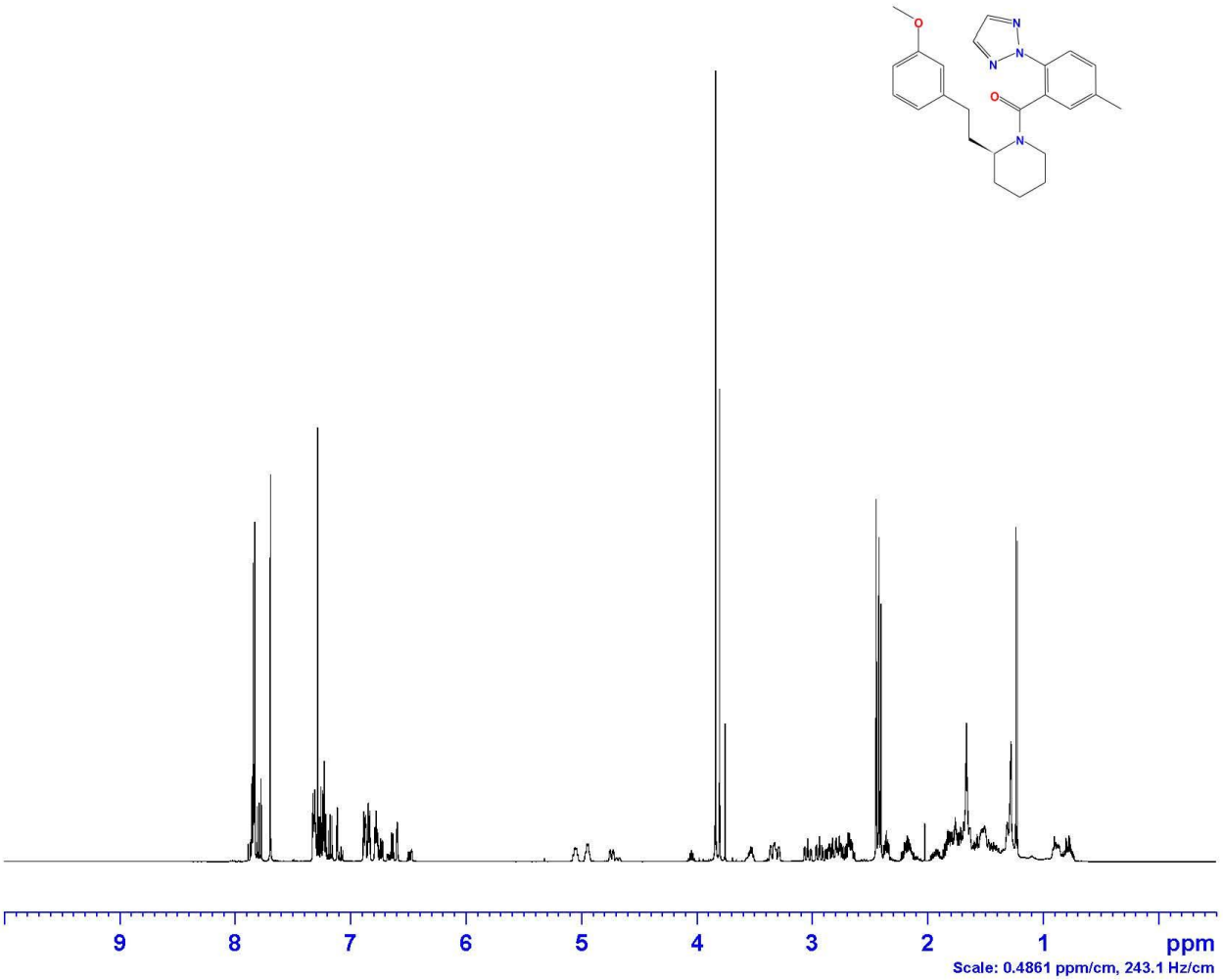


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EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
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PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                114.07
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
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SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
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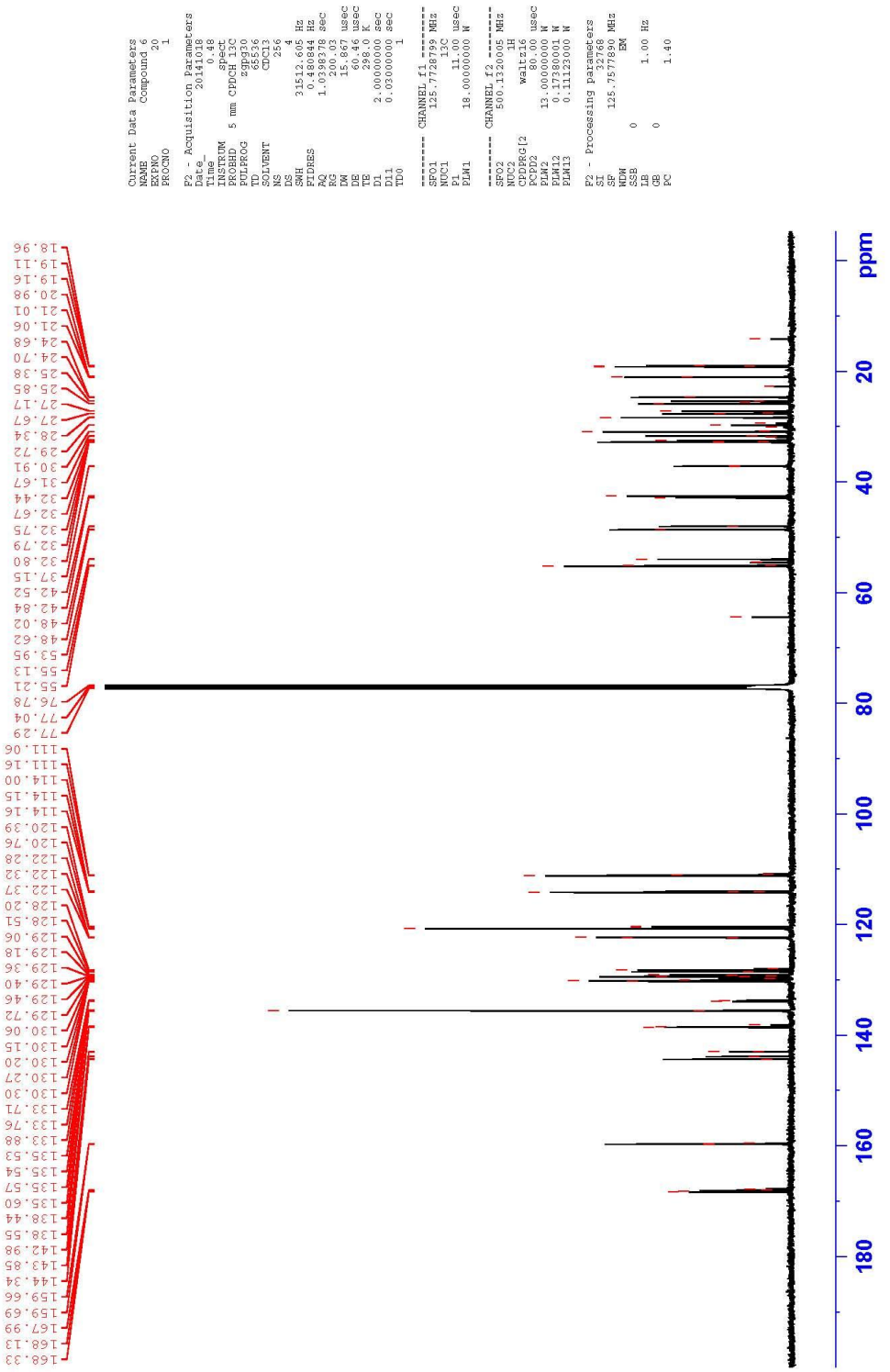
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TD 65536
SOLVENT CDCl3
NS 256
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FIDRES 0.480844 Hz
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RG 200.03
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DE 6.46 usec
TE 298.0 K
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D11 0.03000000 sec
TD0 1
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NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
CHANNEL f2
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NUC2 1H
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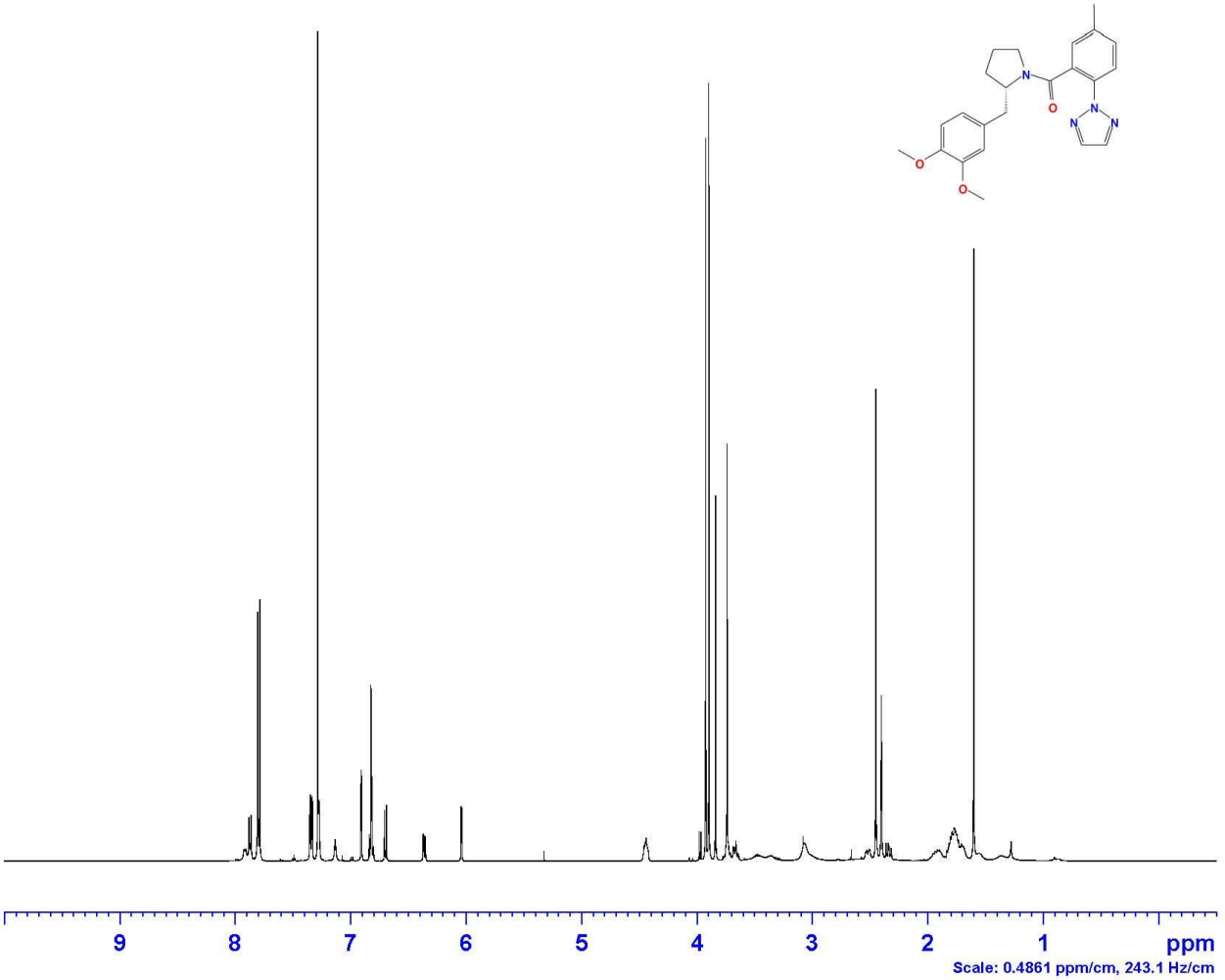


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Current Data Parameters
NAME         Compound 7
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
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Time              20.17
INSTRUM           spect
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PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES        0.152588 Hz
AQ            3.2767999 sec
RG               200.03
DW               50.000 usec
DE               40.00 usec
TE               298.0 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                 9.25 usec
PLW1        13.00000000 W

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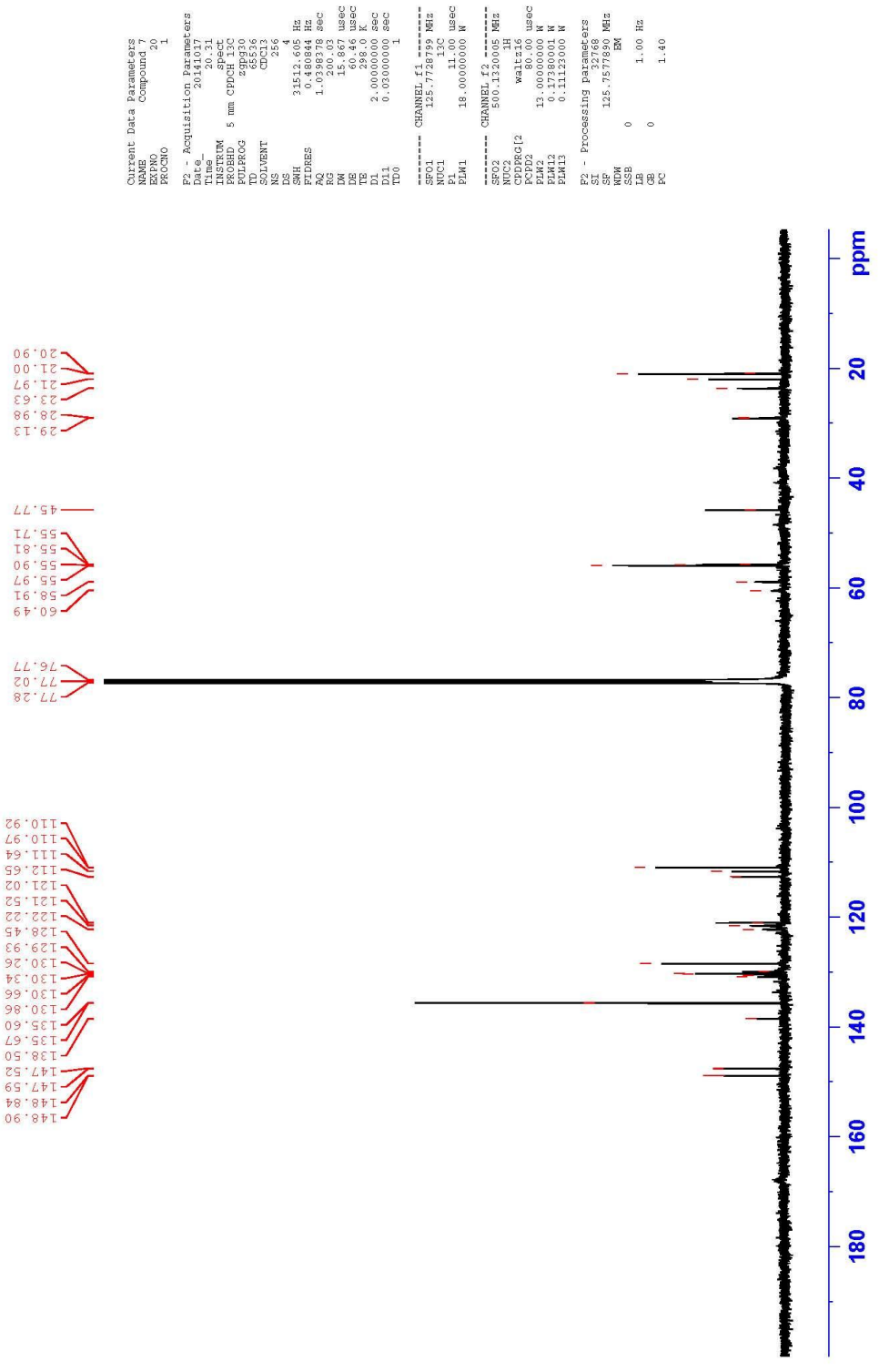
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FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
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D11 0.03000000 sec
TD0 1
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NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
CHANNEL f2
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
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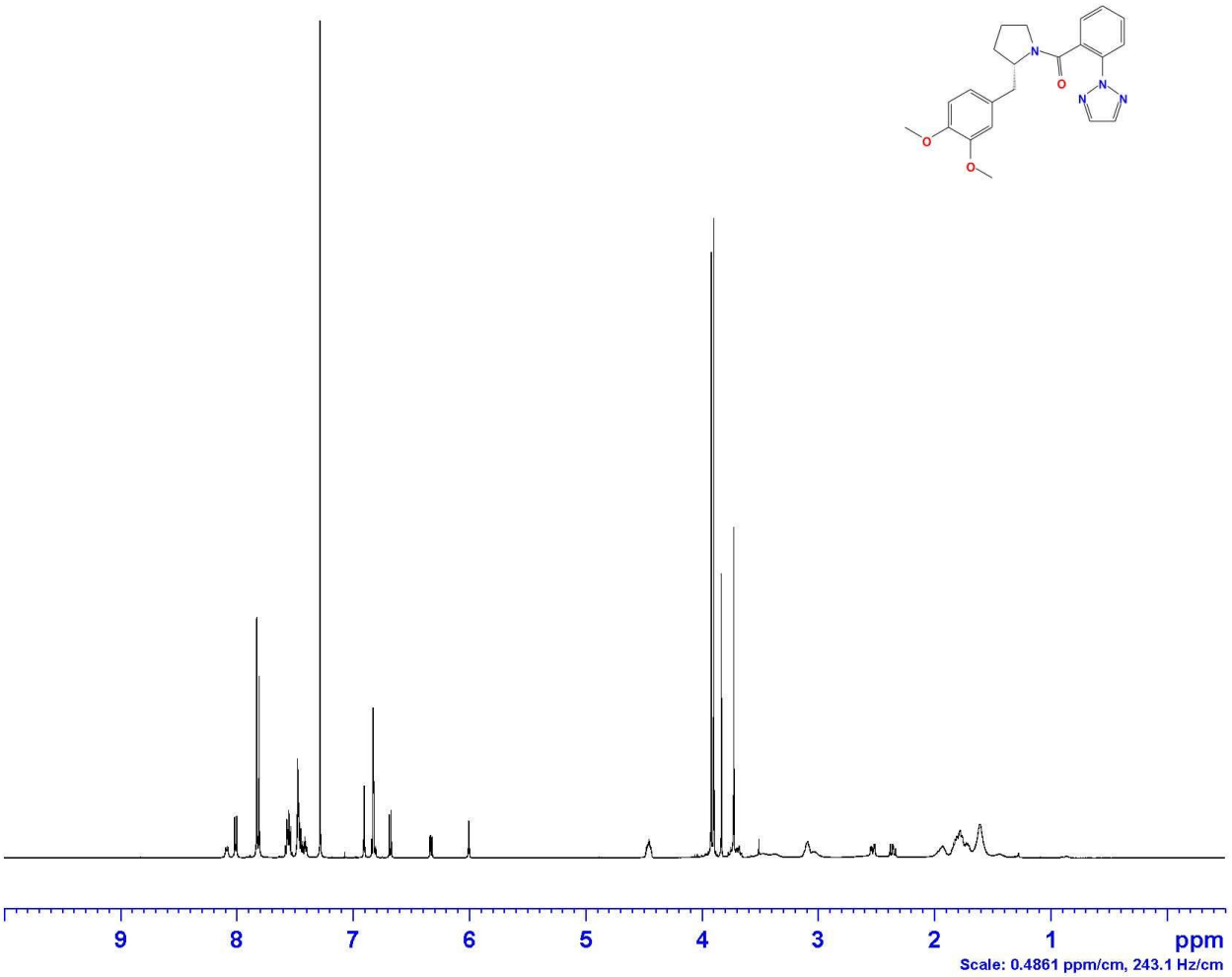


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PROCNO                1

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TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
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RG                200.03
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DE                40.00 usec
TE                298.0 K
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TD0                   1

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P1                 9.25 usec
PLW1         13.00000000 W

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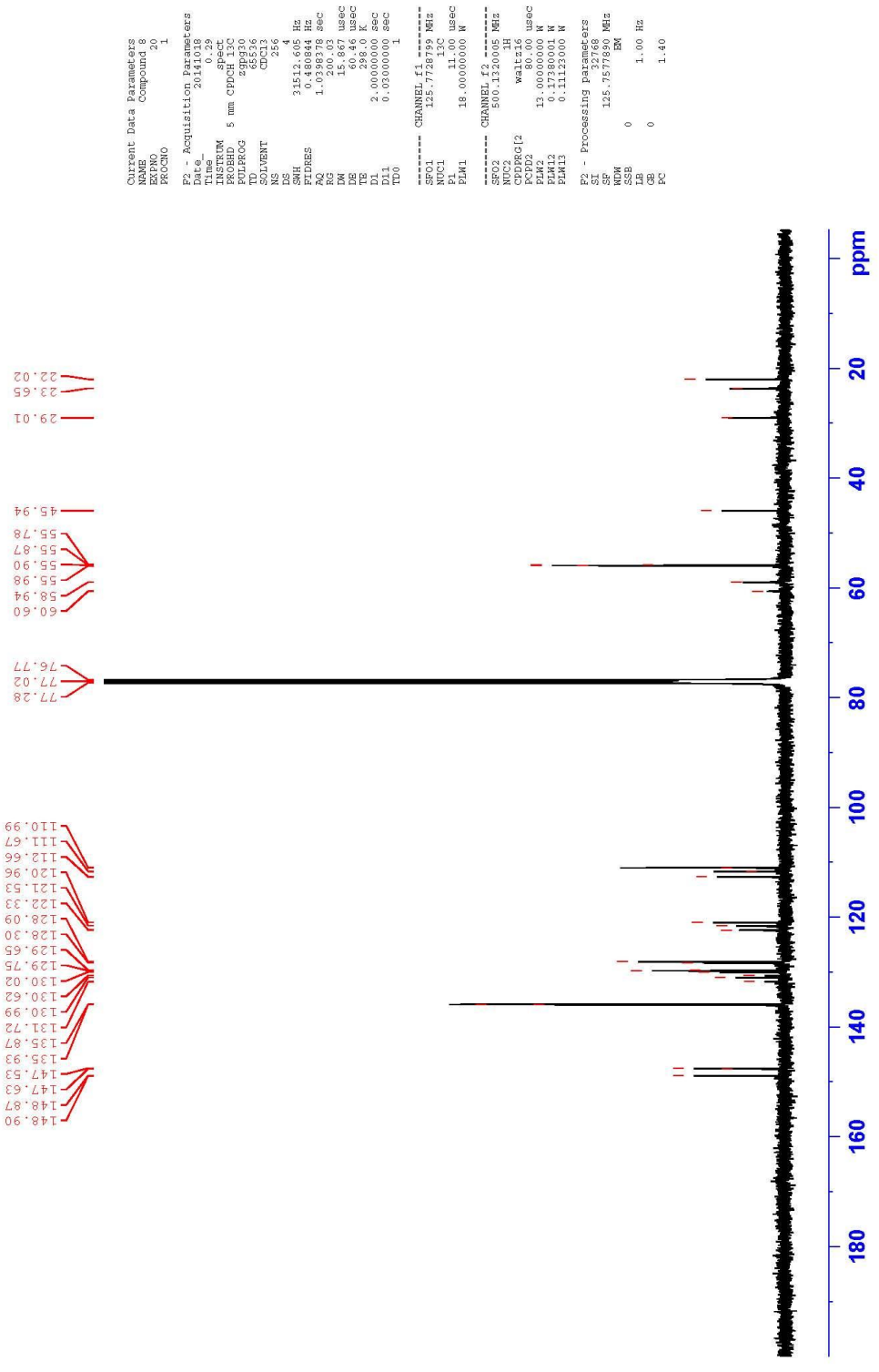
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SOLVENT CDCl3
NS 256
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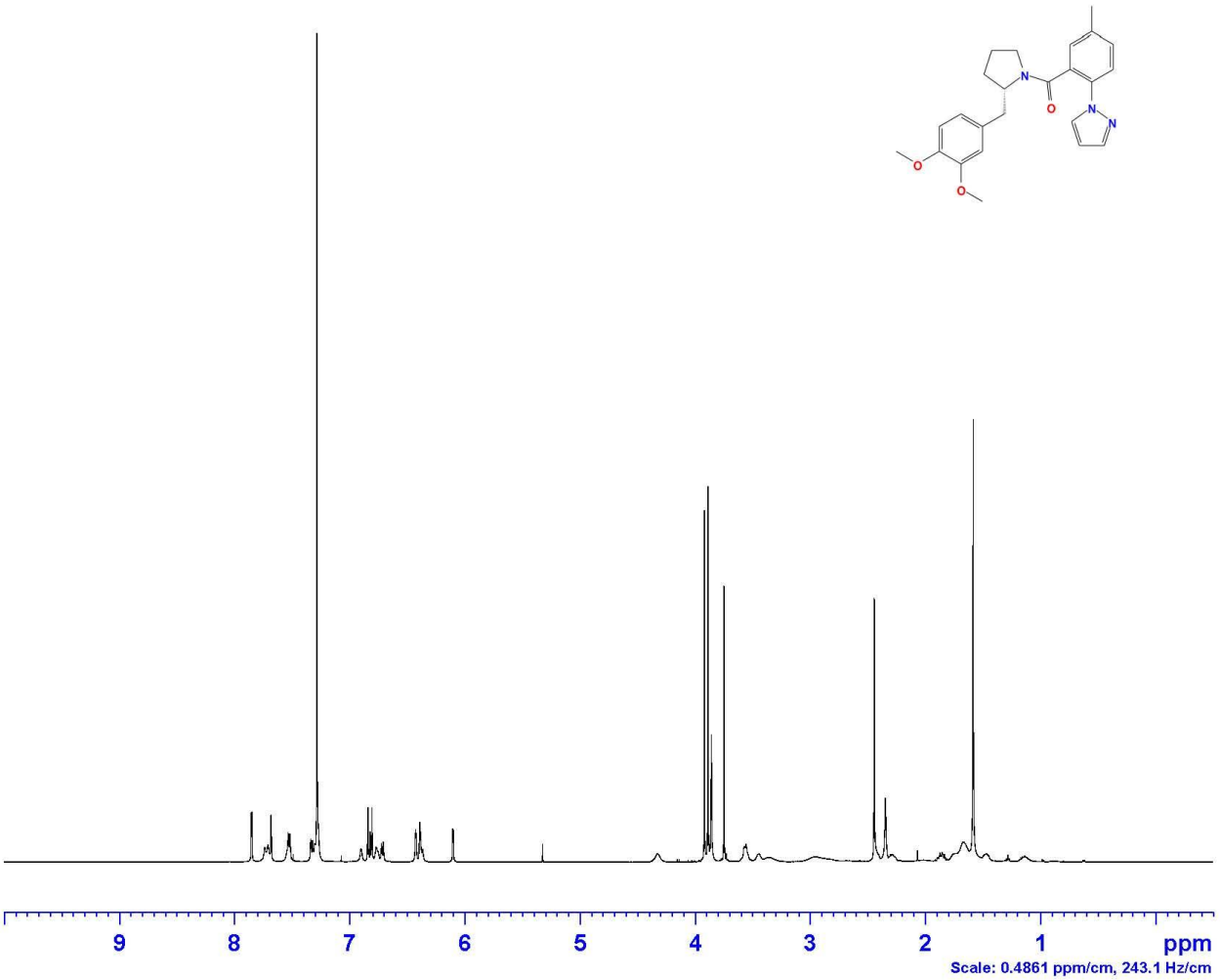
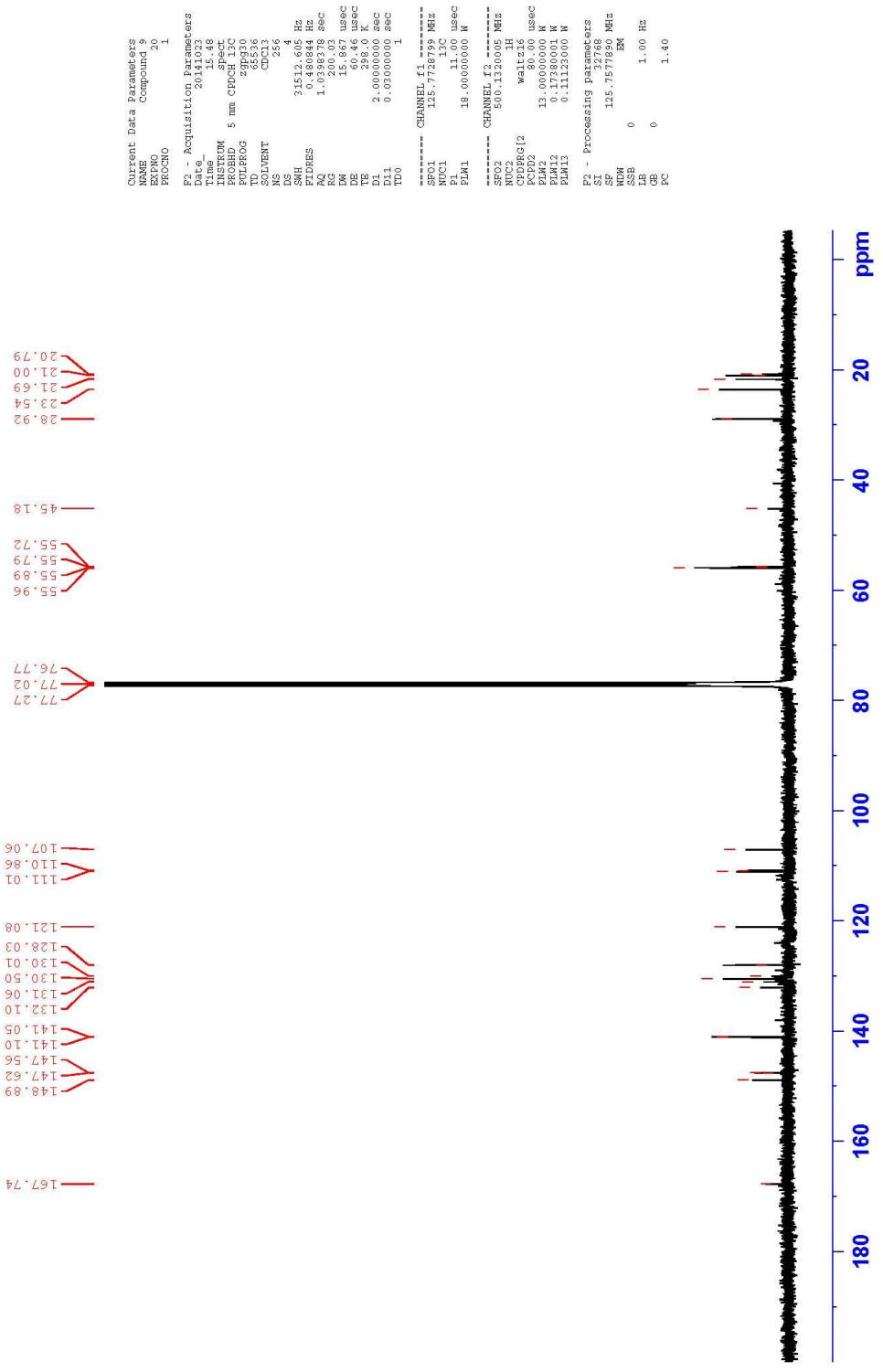
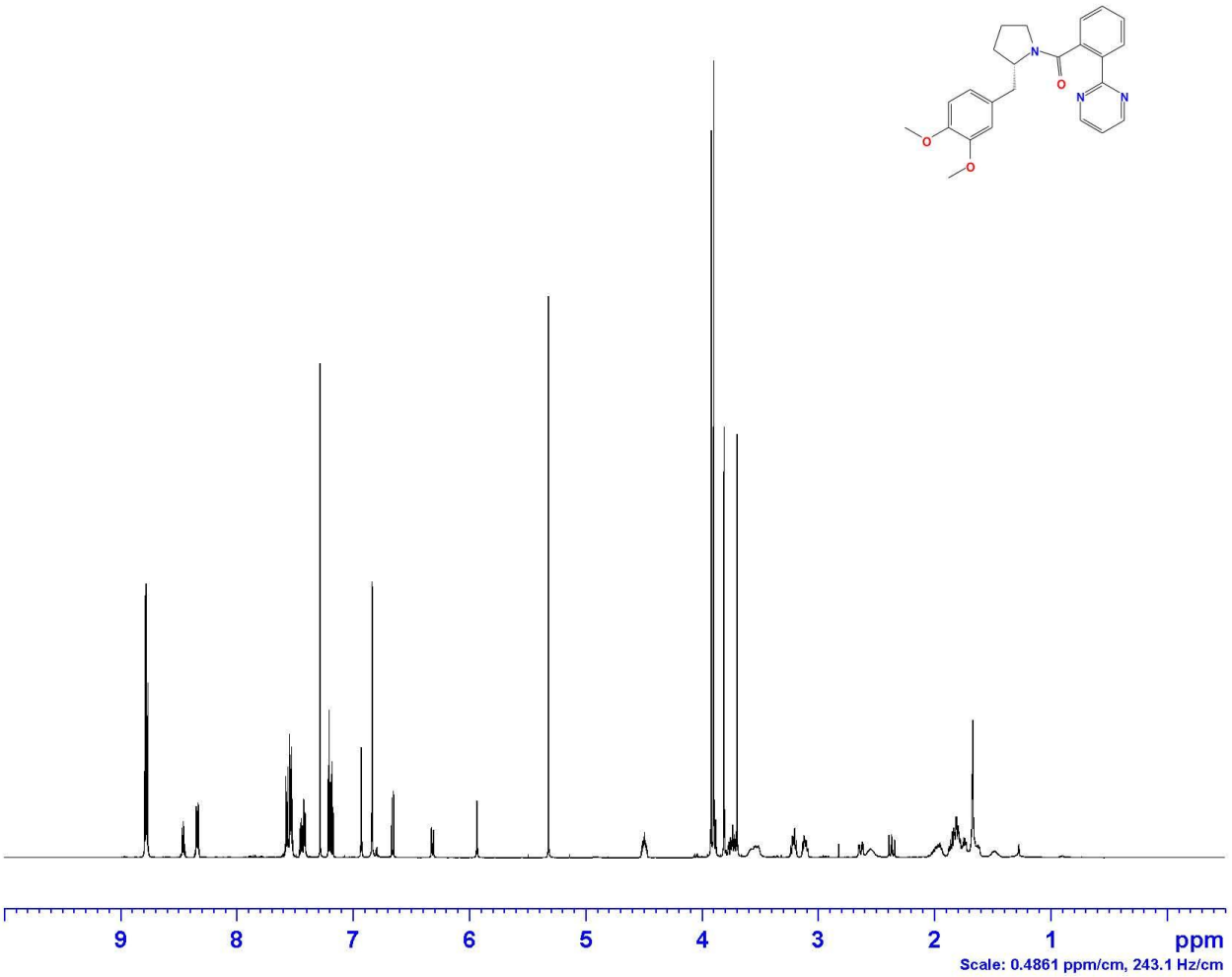
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
CHANNEL f2
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
P2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
22.02
23.65
29.01
45.94
55.78
55.87
55.90
55.98
58.94
60.60
76.77
77.02
77.28
110.99
111.67
112.66
120.96
121.53
122.33
128.09
128.30
129.65
129.75
130.02
130.62
130.99
131.72
135.87
135.93
147.53
147.63
148.87
148.90
ppm
20
40
60
80
100
120
140
160
180

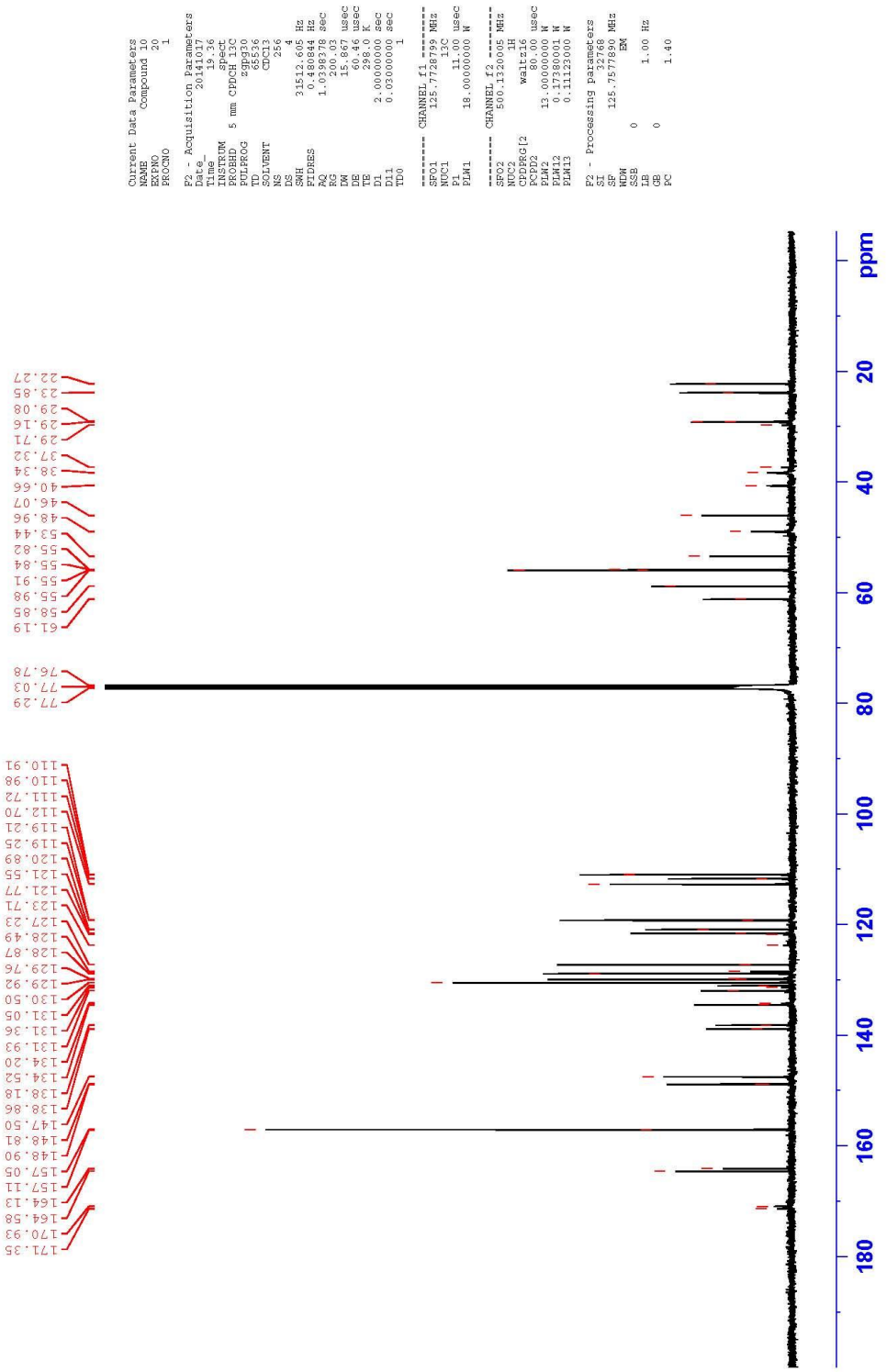


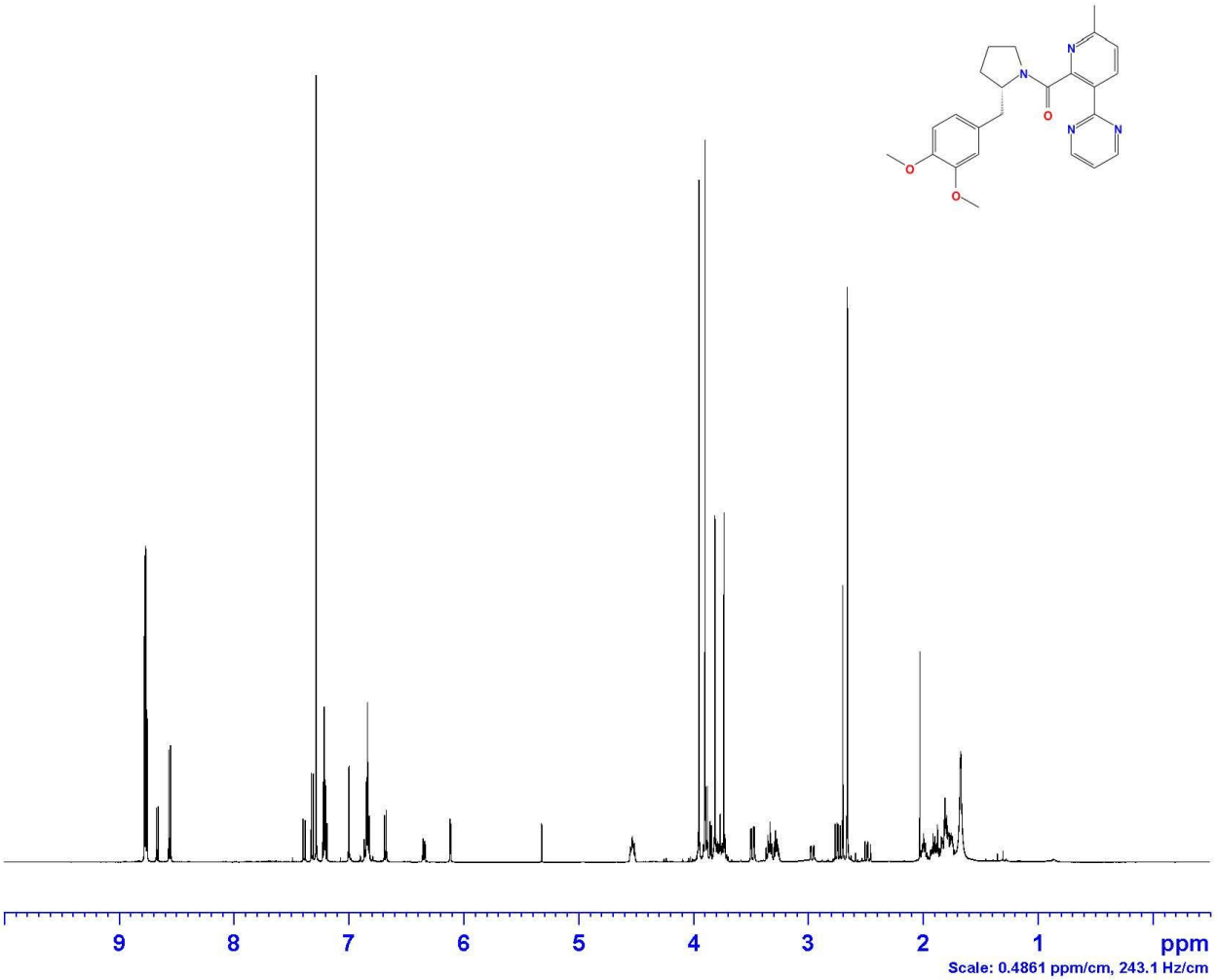

```
Current Data Parameters
NAME         Compound 9
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141023
Time              15.33
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH          10000.000 Hz
FIDRES           0.152588 Hz
AQ           3.2767999 sec
RG                200.03
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1           1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                  9.25 usec
PLW1        13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 9
EXPNO 20
PROCNO 1
P2 - Acquisition Parameters
Date_ 20141202
Time 15.48
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
P2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
167.74
148.89
147.62
147.56
141.10
141.05
132.10
131.06
130.50
130.01
128.03
121.08
111.01
110.86
107.06
77.27
77.02
76.77
55.96
55.89
55.79
55.72
45.18
28.92
23.54
21.69
21.00
20.79
ppm
20
40
60
80
100
120
140
160
180

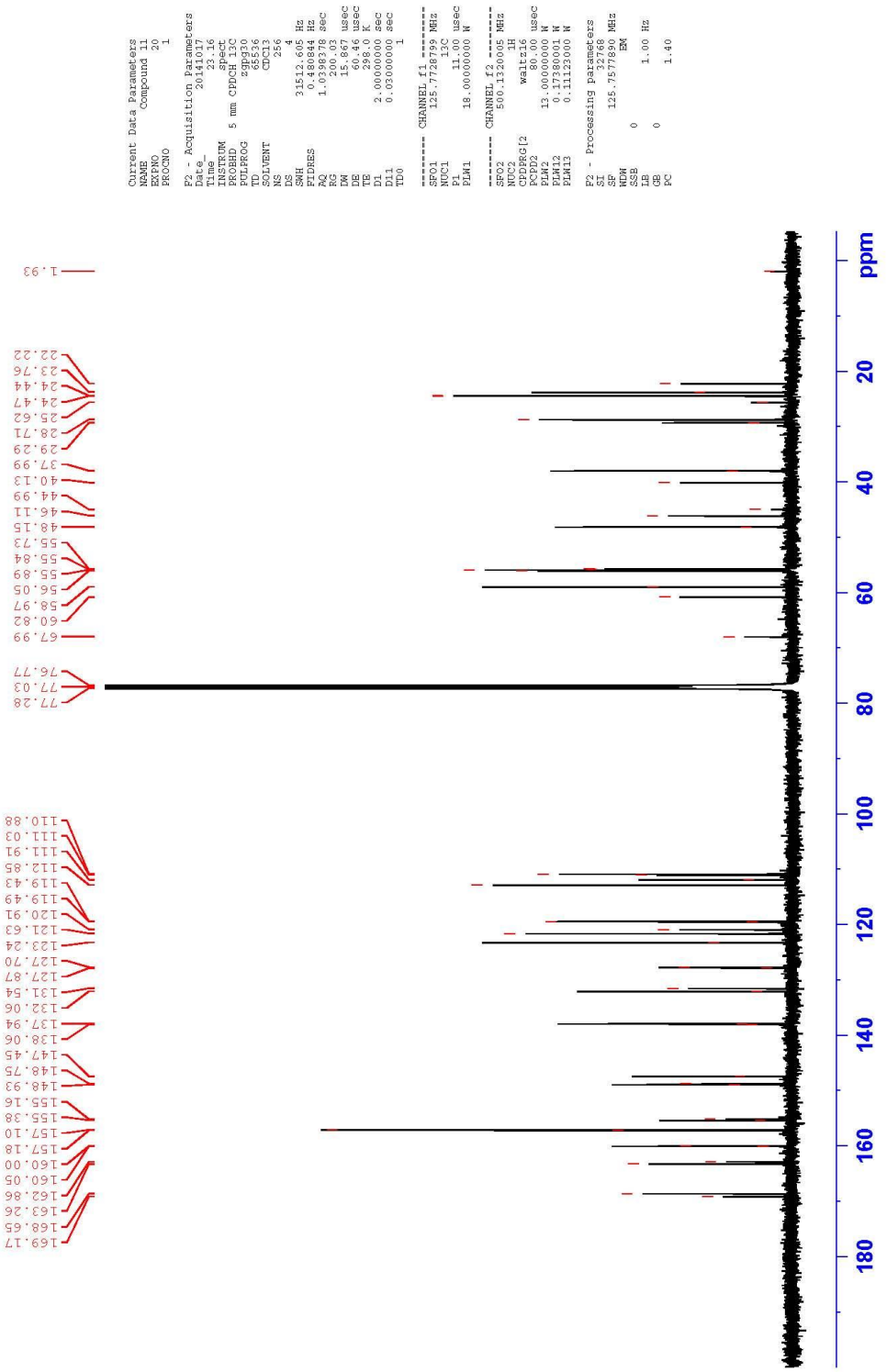


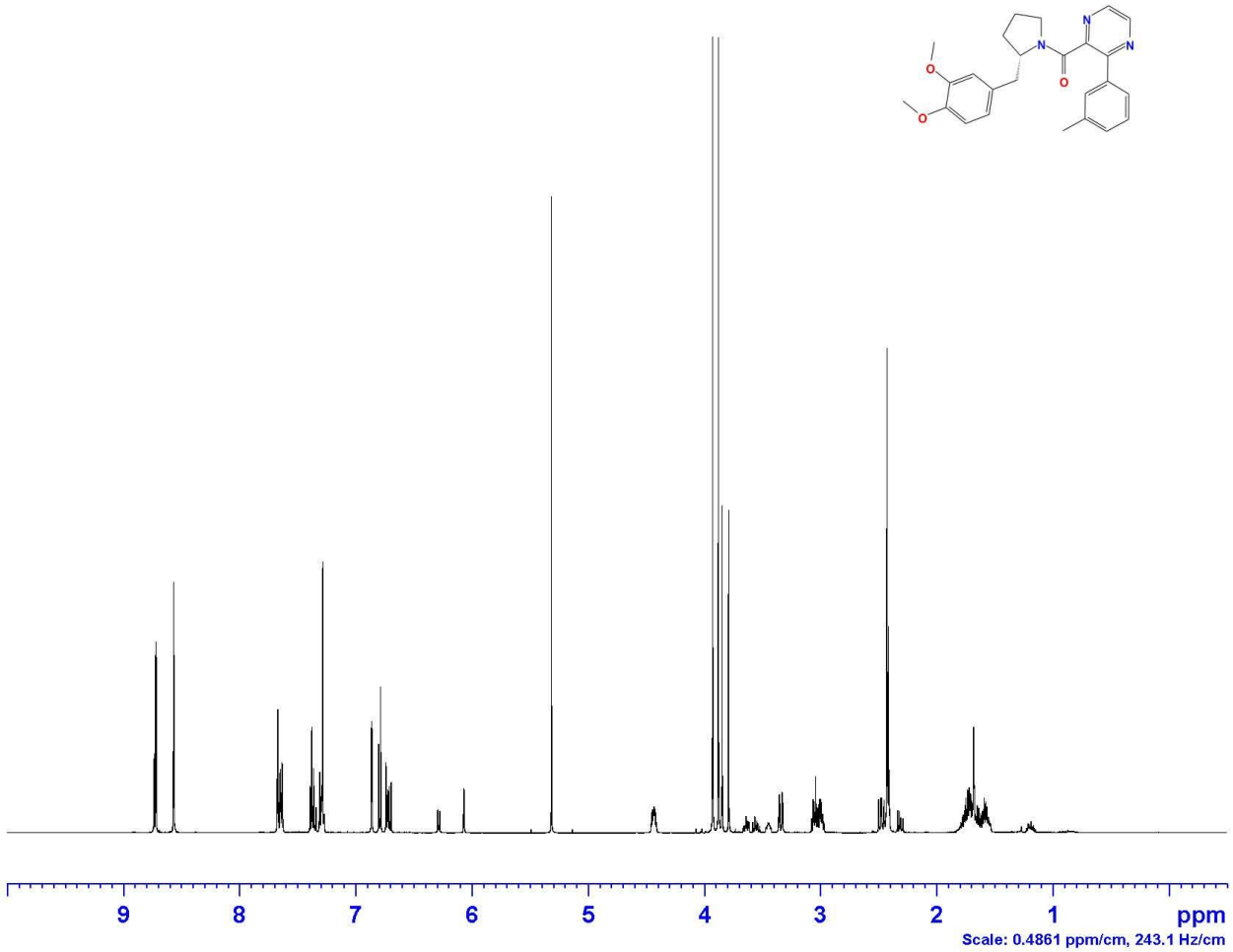

```
Current Data Parameters
NAME        Compound 10
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time               19.22
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                114.07
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                 9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```


Current Data Parameters
NAME Compound 10
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141017
Time 19.36
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 60.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm
20
40
60
80
100
120
140
160
180
22.27
23.85
29.08
29.16
29.71
37.32
38.34
40.66
46.07
48.96
53.44
55.82
55.84
55.91
55.98
58.85
61.19
76.78
77.03
77.29
110.91
110.98
111.72
112.70
119.21
119.25
120.89
121.55
121.77
123.71
127.23
128.49
128.87
129.76
129.92
130.50
131.05
131.36
131.93
134.20
134.52
138.18
138.86
147.50
148.81
148.90
157.05
157.11
164.13
164.58
170.93
171.35

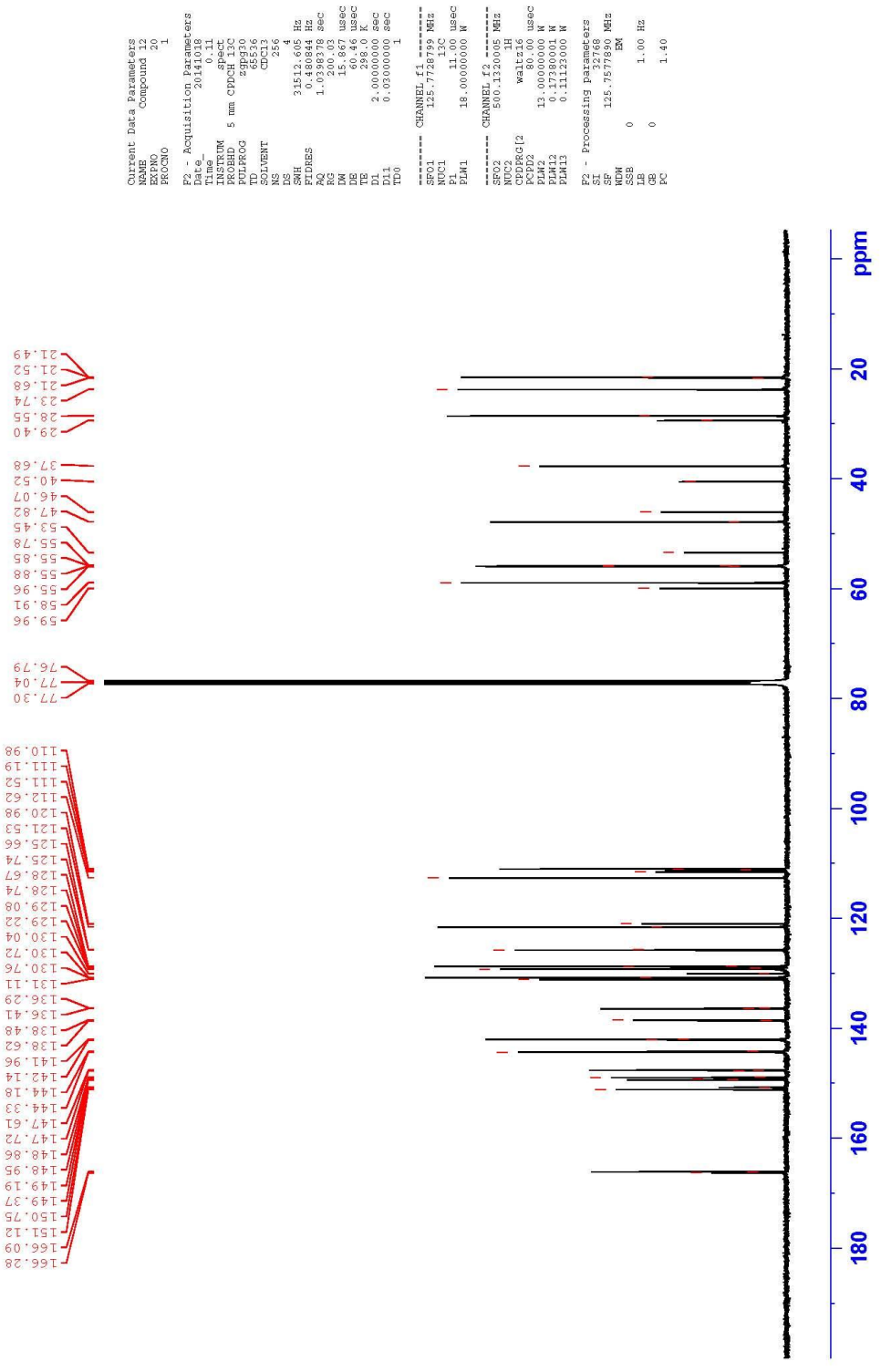


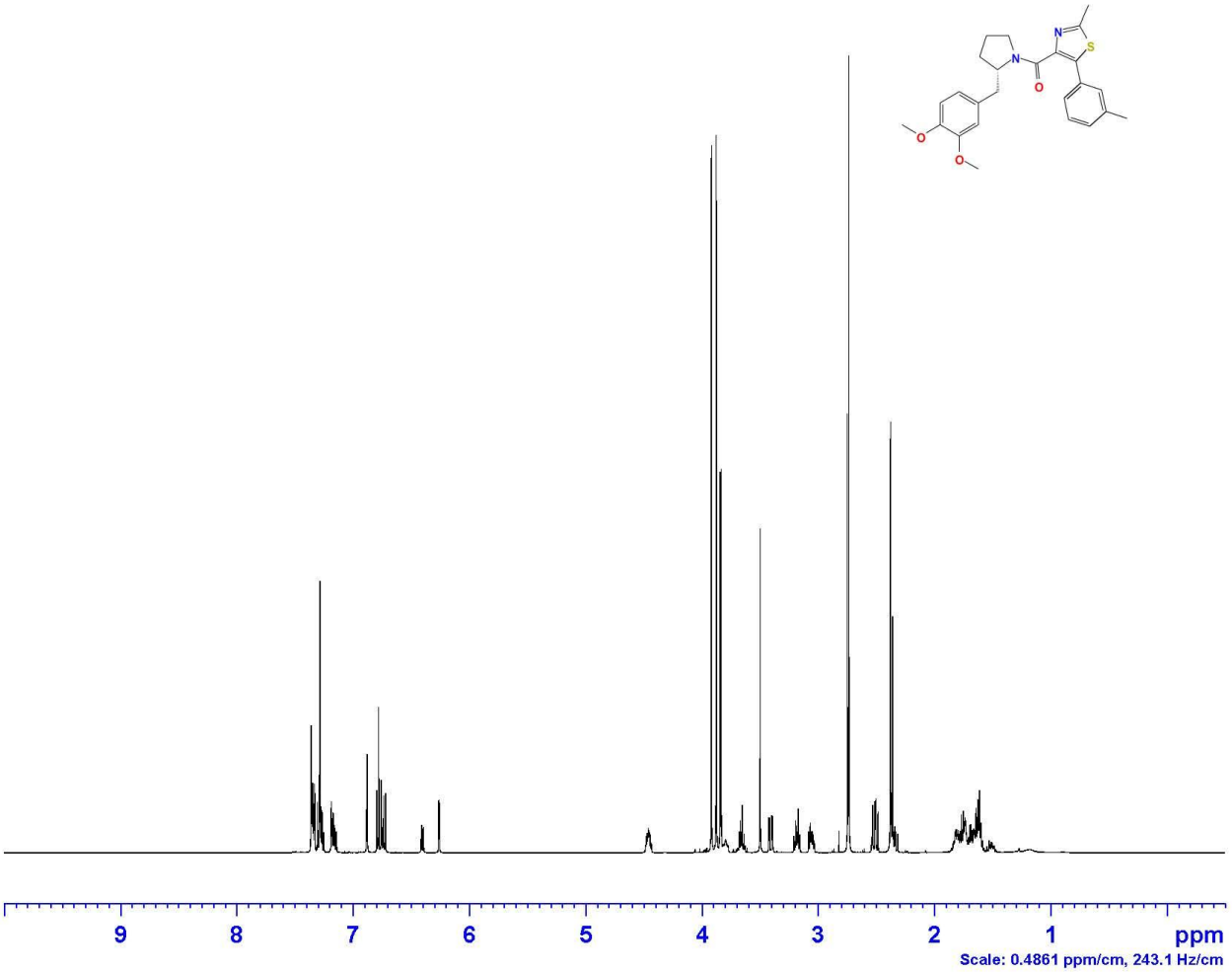

```
Current Data Parameters
NAME        Compound 11
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time              23.02
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                200.03
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                  9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 11
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161017
Time 23 16
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 60.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
CHANNEL f2
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1.93
22.22
23.76
24.44
24.47
25.62
28.71
29.29
37.99
40.13
44.99
46.11
48.15
55.73
55.84
55.89
56.05
58.97
60.82
67.99
76.77
77.03
77.28
110.88
111.03
111.91
112.85
119.43
119.49
120.91
121.63
123.24
127.70
127.87
131.54
132.06
137.94
138.06
147.45
148.75
148.93
155.16
155.38
157.10
157.18
160.00
160.05
162.86
163.26
168.65
169.17
ppm
20
40
60
80
100
120
140
160
180

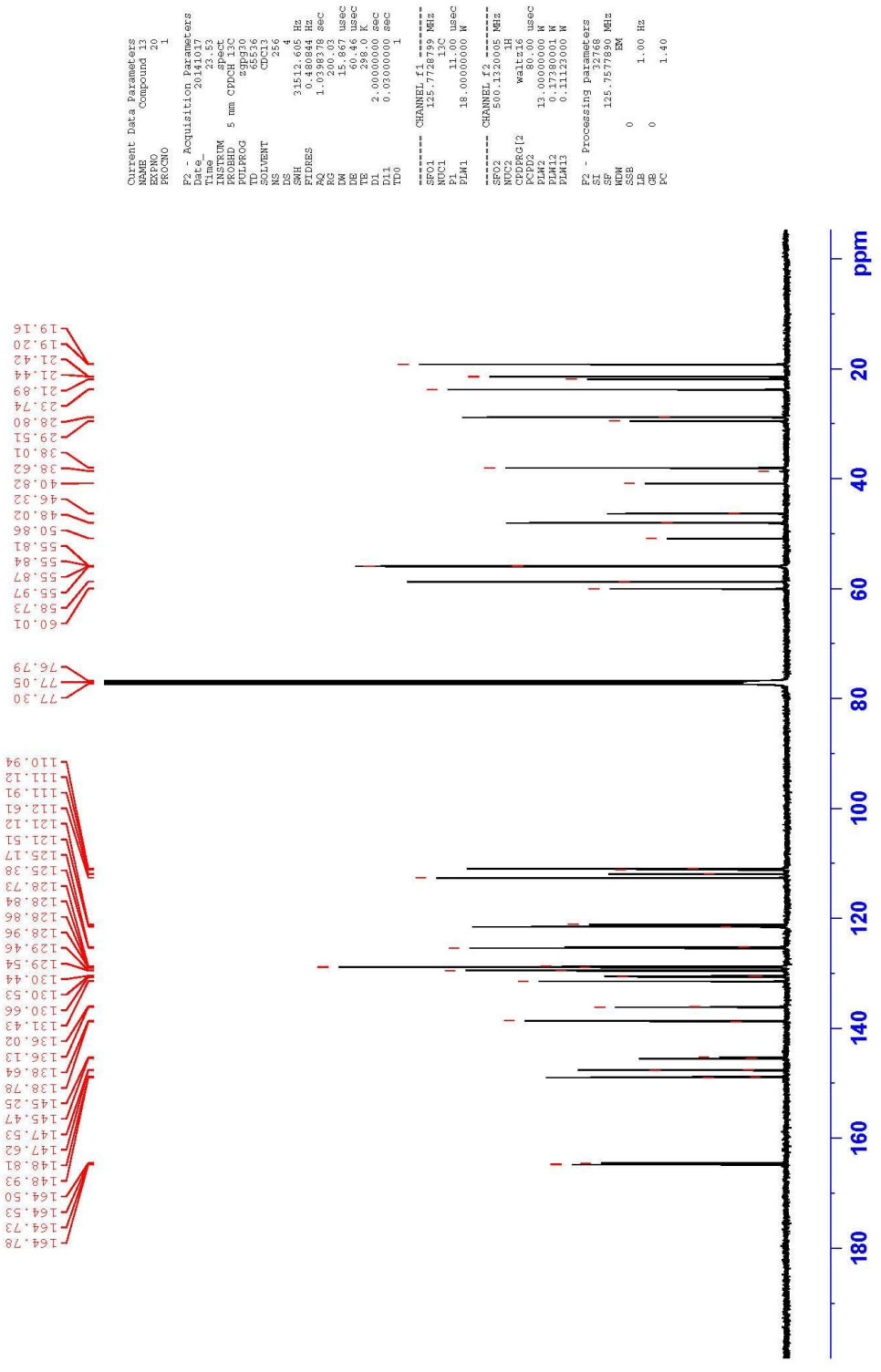


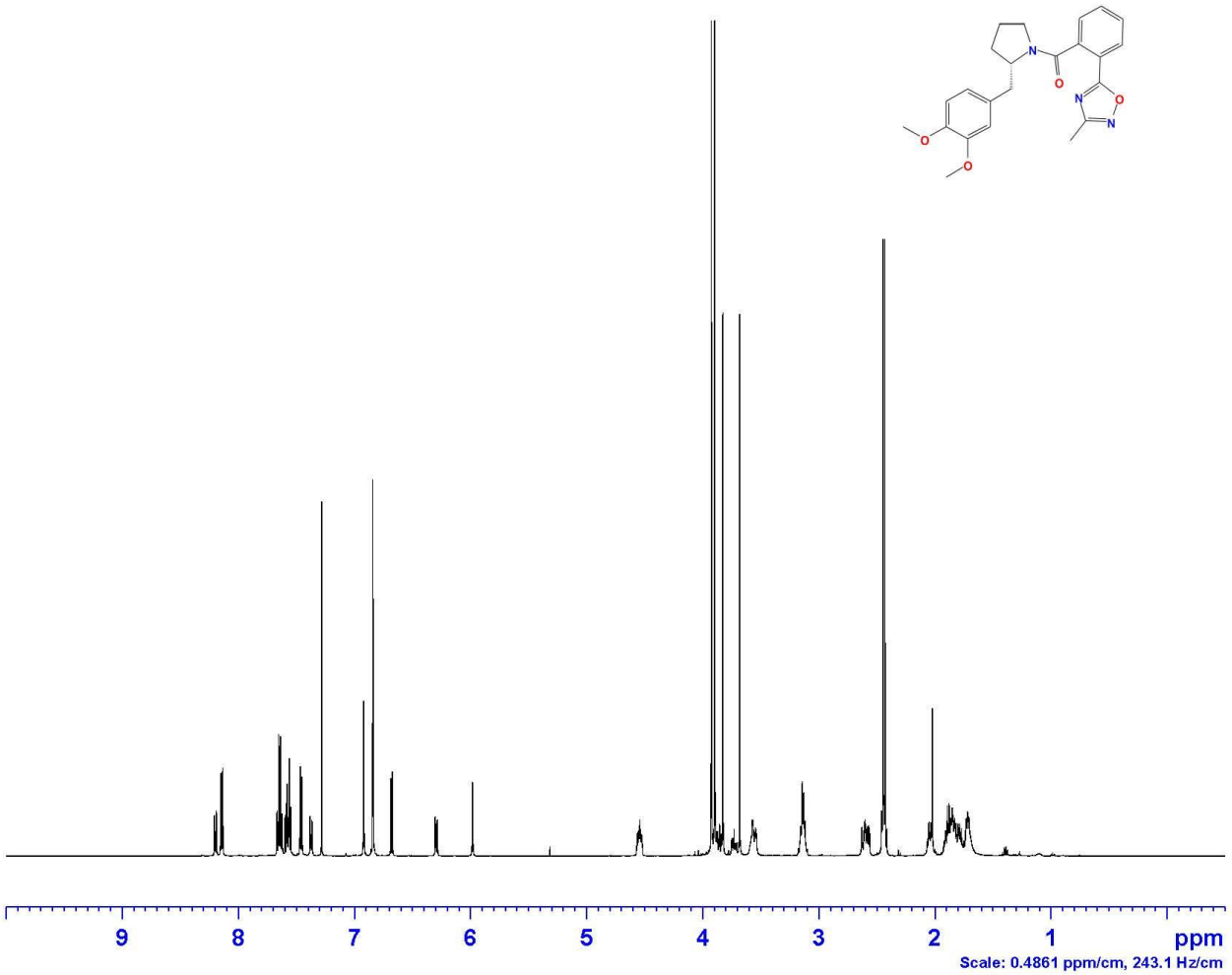

```
Current Data Parameters
NAME        Compound 12
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time              23.57
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                114.07
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1             1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                  9.25 usec
PLW1          13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 12
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141018
Time 0.11
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 60.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm
20
40
60
80
100
120
140
160
180
21.49
21.52
21.68
23.74
28.55
29.40
37.68
40.52
46.07
47.82
53.45
55.78
55.85
55.88
55.96
58.91
59.96
76.79
77.04
77.30
110.98
111.19
111.52
112.62
120.98
121.53
125.66
125.74
128.67
128.74
129.08
129.22
130.04
130.72
130.76
131.11
136.29
136.41
138.48
138.62
141.96
142.14
144.18
144.33
147.61
147.72
148.86
148.95
149.19
149.37
150.75
151.12
166.09
166.28

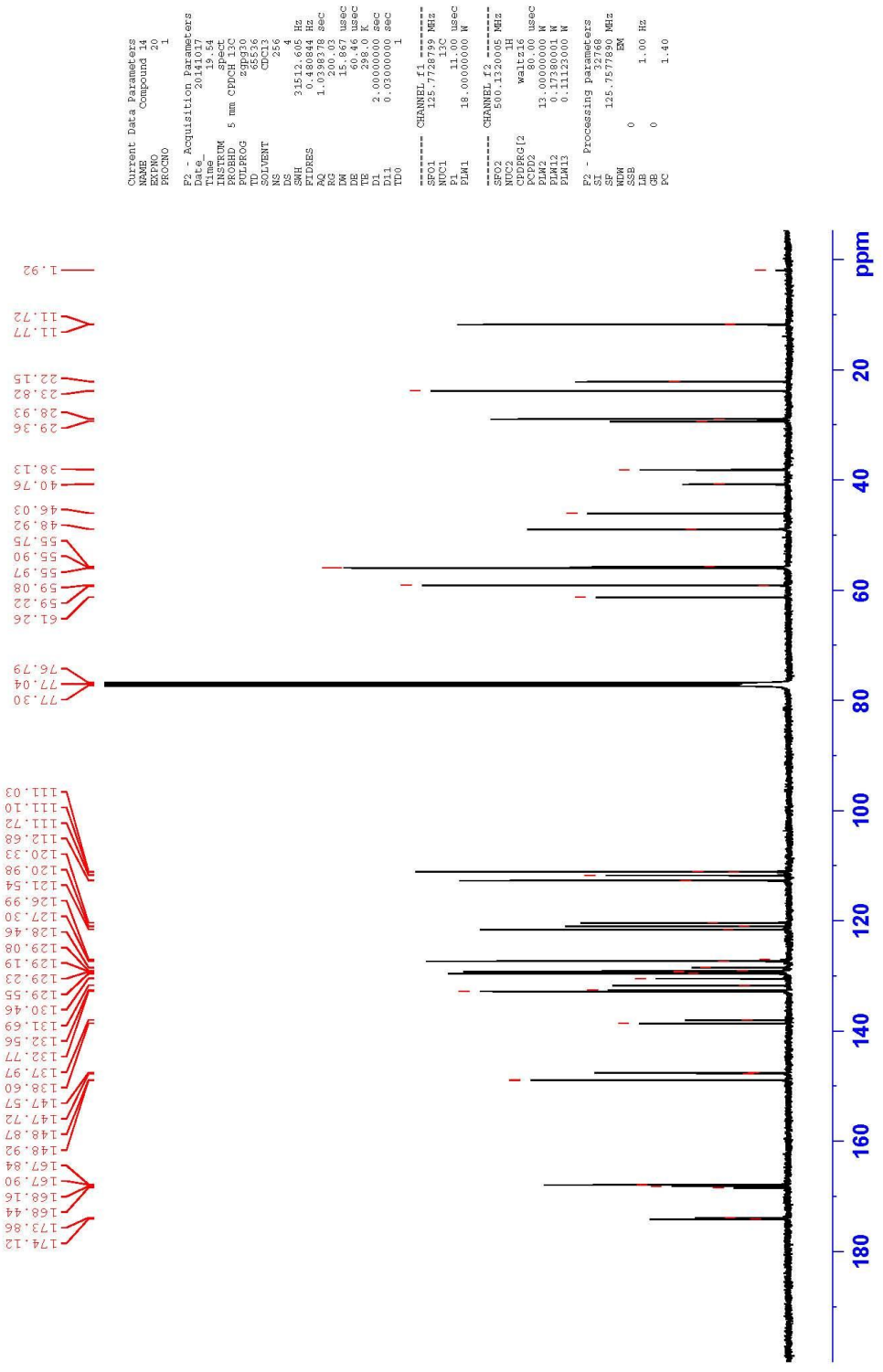


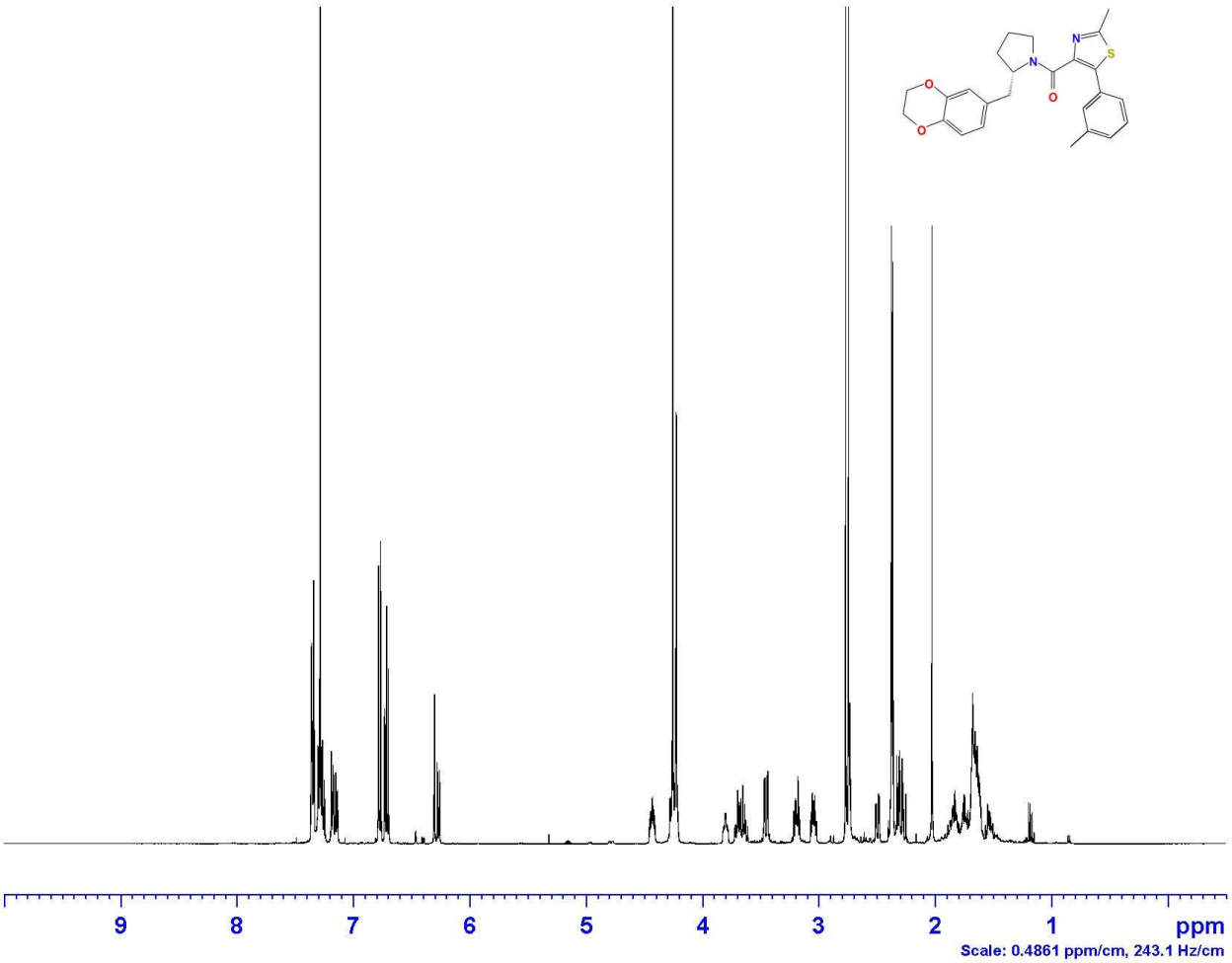

```
Current Data Parameters
NAME        Compound 13
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time               23.38
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES             0.152588 Hz
AQ              3.2767999 sec
RG                 114.07
DW                 50.000 usec
DE                 40.00 usec
TE                 298.0 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                   1H
P1                   9.25 usec
PLW1          13.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1300000 MHz
WDW                   EM
SSB        0
LB                 0.30 Hz
GB         0
PC                 1.00
```


Current Data Parameters
NAME Compound 13
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141017
Time 23.53
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
CHANNEL f2
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
F2 - Processing parameters
SI 32768
SF 125.7577880 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm
20
40
60
80
100
120
140
160
180
19.16
19.20
21.42
21.44
21.89
23.74
28.80
29.51
38.01
38.62
40.82
46.32
48.02
50.86
55.81
55.84
55.87
55.97
58.73
60.01
76.79
77.05
77.30
110.94
111.12
111.91
112.61
121.12
121.51
125.17
125.38
128.73
128.84
128.86
128.96
129.46
129.54
130.44
130.53
130.66
131.43
136.02
136.13
138.64
138.78
145.25
145.47
147.53
147.62
148.81
148.93
164.50
164.53
164.73
164.78

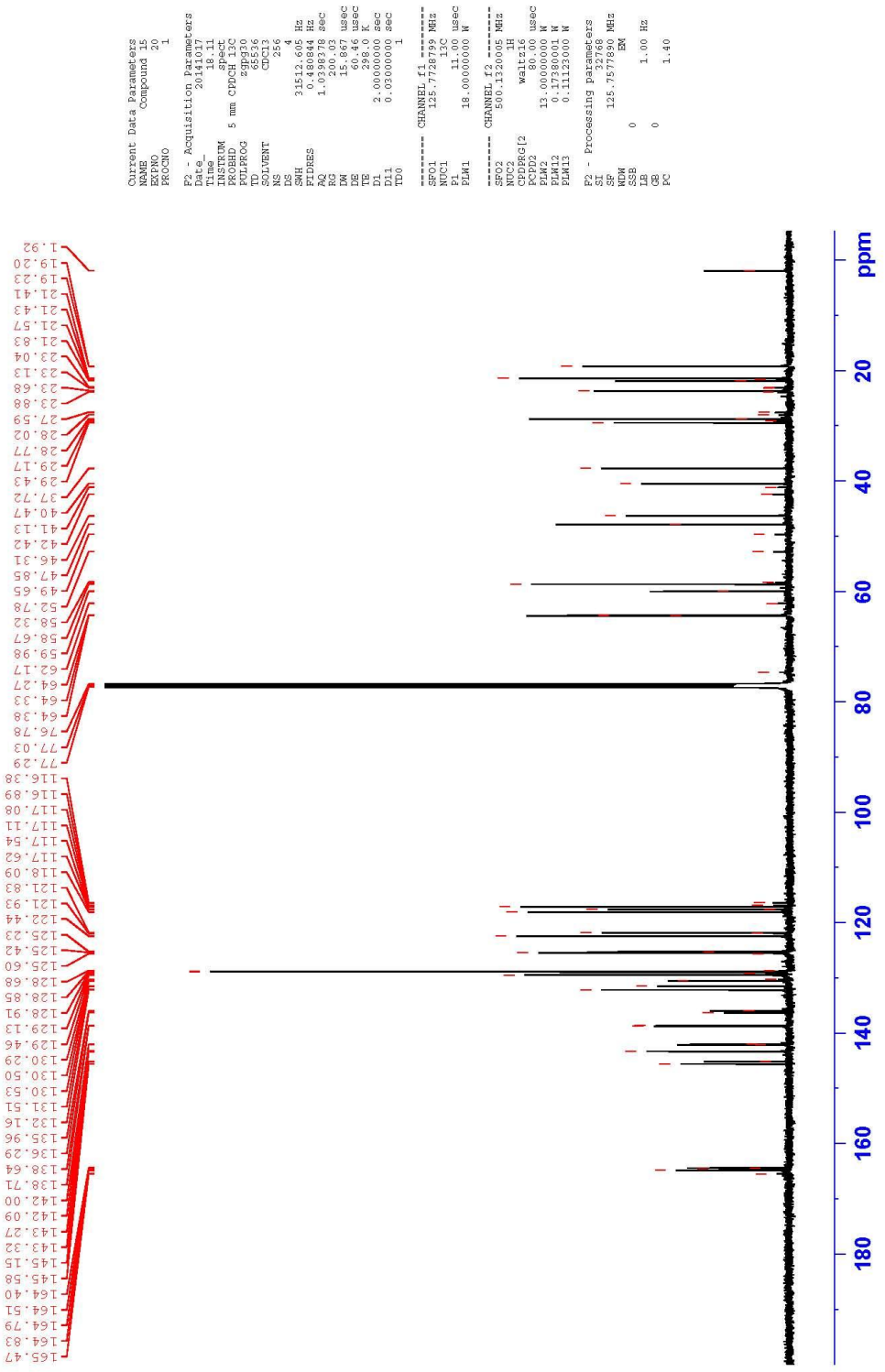


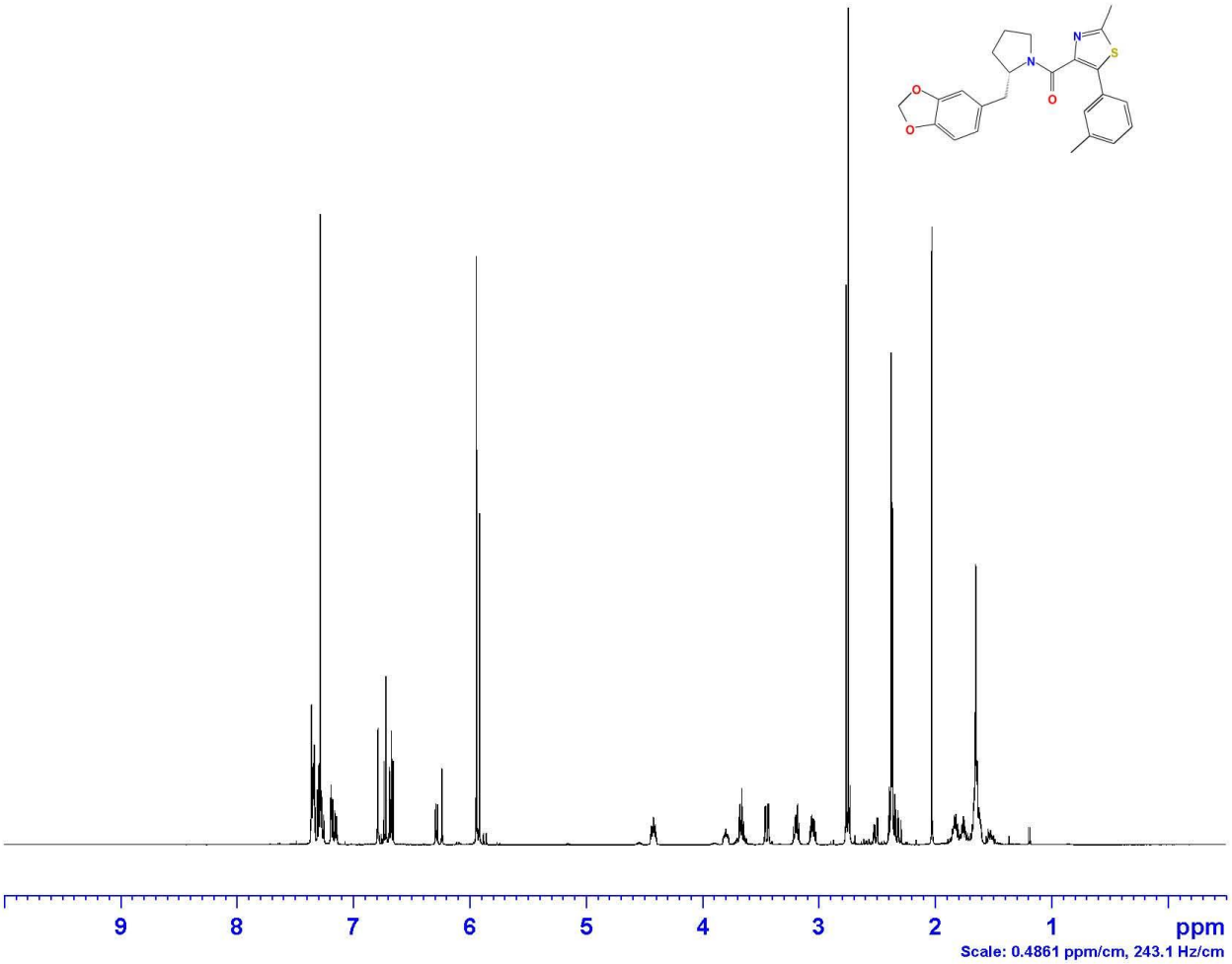

```
Current Data Parameters
NAME        Compound 14
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time               19.40
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                114.07
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                  9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 14
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141017
Time 19.54
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1.92
11.72
11.77
22.15
23.82
28.93
29.36
38.13
40.76
46.03
48.92
55.75
55.90
55.97
59.08
59.22
61.26
76.79
77.04
77.30
111.03
111.10
111.72
112.68
120.33
120.98
121.54
126.99
127.30
128.46
129.08
129.19
129.23
129.55
130.46
131.69
132.56
132.77
137.97
138.60
147.57
147.72
148.87
148.92
167.84
167.90
168.16
168.44
173.86
174.12
ppm
20
40
60
80
100
120
140
160
180

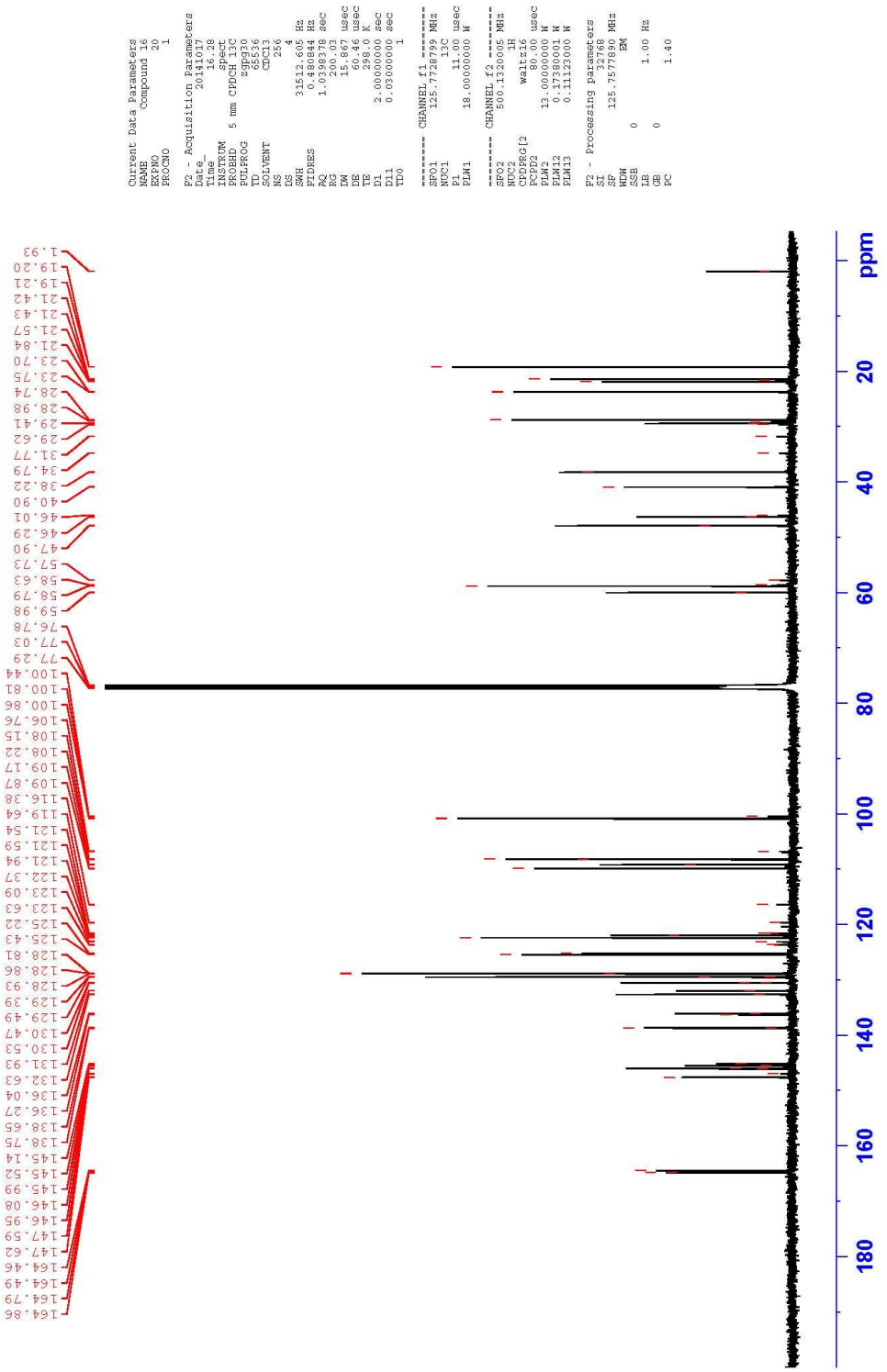


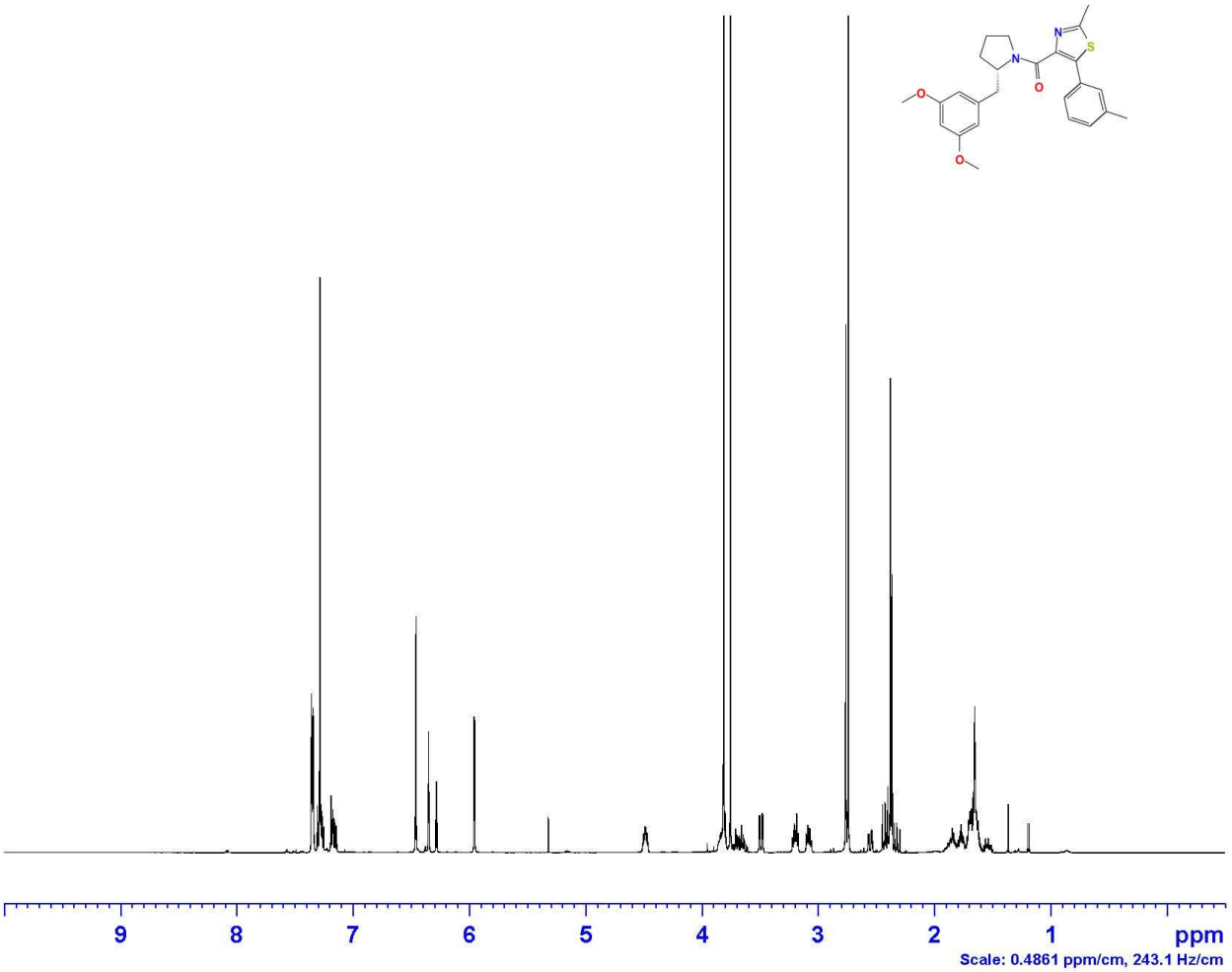

```
Current Data Parameters
NAME        Compound 15
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time              17.56
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                114.07
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1             1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1          500.1330885 MHz
NUC1                 1H
P1                  9.25 usec
PLW1          13.00000000 W

F2 - Processing parameters
SI               65536
SF            500.1300000 MHz
WDW                 EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 15
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20111017
Time 18.11
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
F2 - Processing parameters
SI 32768
SF 125.7577880 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm
20
40
60
80
100
120
140
160
180

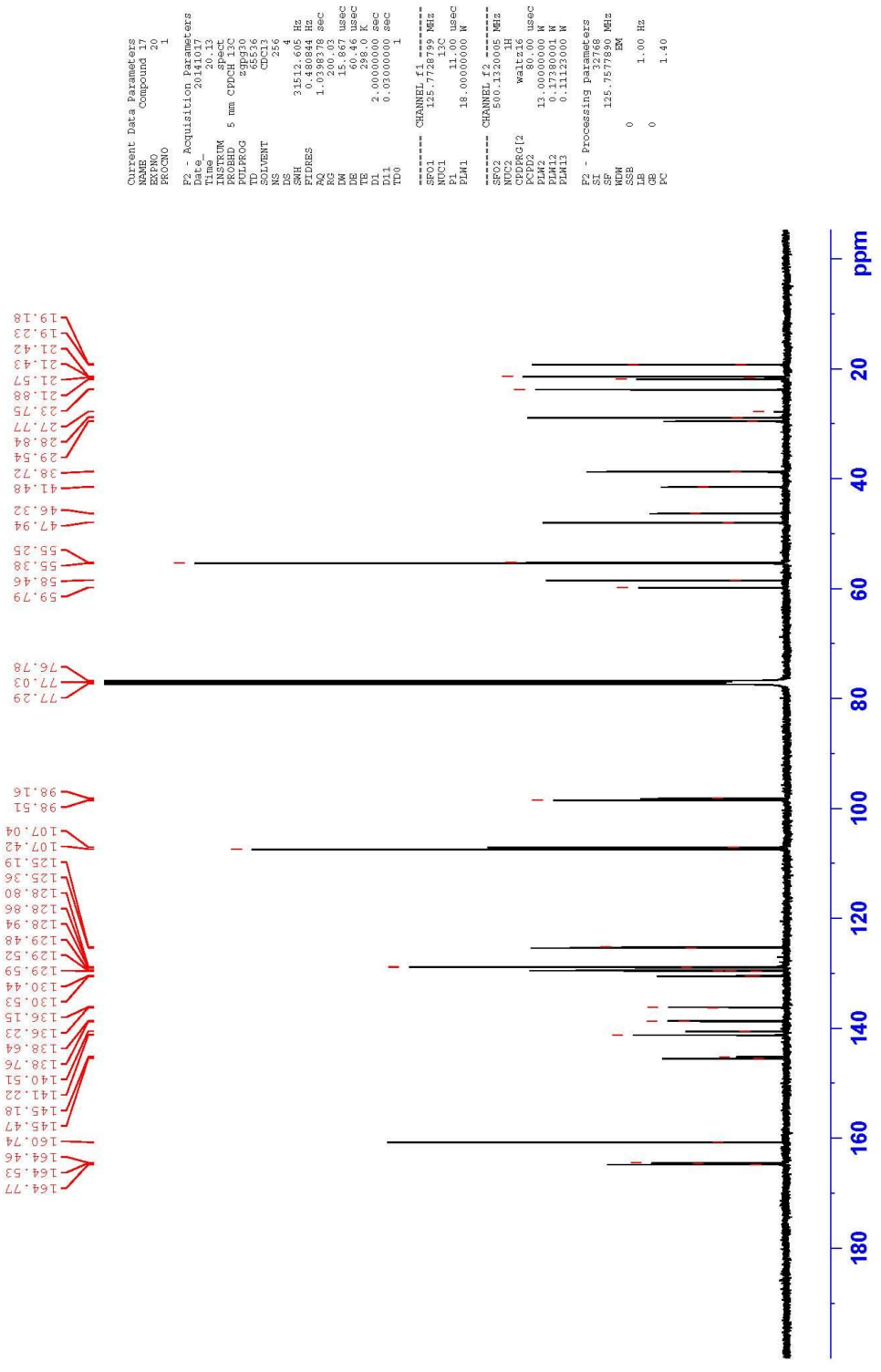


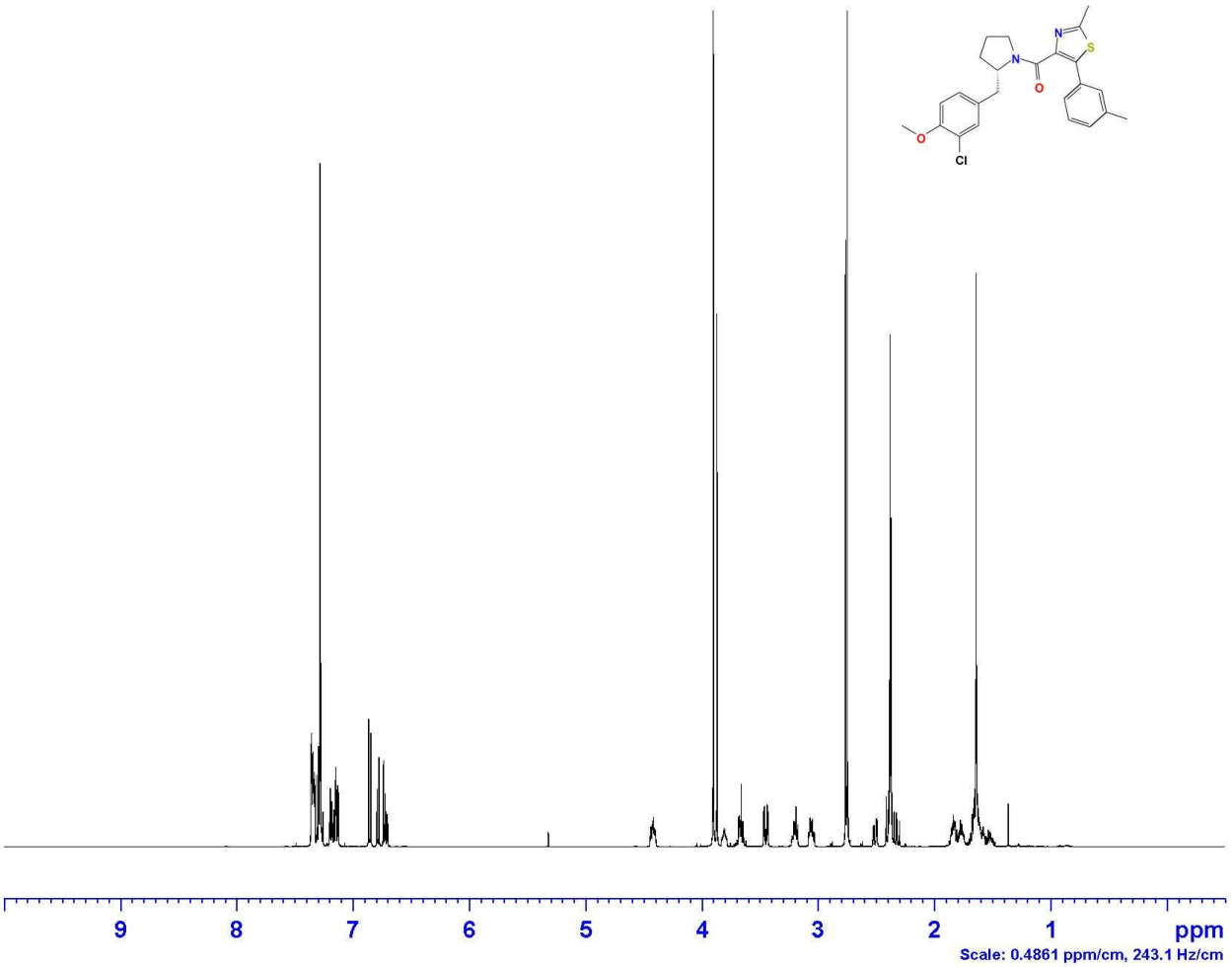

```
Current Data Parameters
NAME        Compound 16
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time              16.14
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           10000.000 Hz
FIDRES        0.152588 Hz
AQ            3.2767999 sec
RG               114.07
DW               50.000 usec
DE               40.00 usec
TE               298.0 K
D1           1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                9.25 usec
PLW1        13.00000000 W

F2 - Processing parameters
SI               65536
SF          500.1300000 MHz
WDW                 EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 16
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141017
Time 16.28
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
F2 - Processing parameters
SI 32768
SF 125.7577880 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm
20
40
60
80
100
120
140
160
180
1.93
19.20
19.21
21.42
21.43
21.57
21.84
23.70
23.75
28.74
28.98
29.41
29.62
31.77
34.79
38.22
40.90
46.01
46.29
47.90
57.73
58.63
58.79
59.98
76.78
77.03
77.29
100.44
100.81
100.86
106.76
108.15
108.22
109.17
109.87
116.38
119.64
121.54
121.59
121.94
122.37
123.09
123.63
125.22
125.43
128.81
128.86
128.93
129.39
129.49
130.47
130.53
131.93
132.63
136.04
136.27
138.65
138.75
145.14
145.52
145.99
146.08
146.95
147.59
147.62
164.46
164.49
164.79
164.86

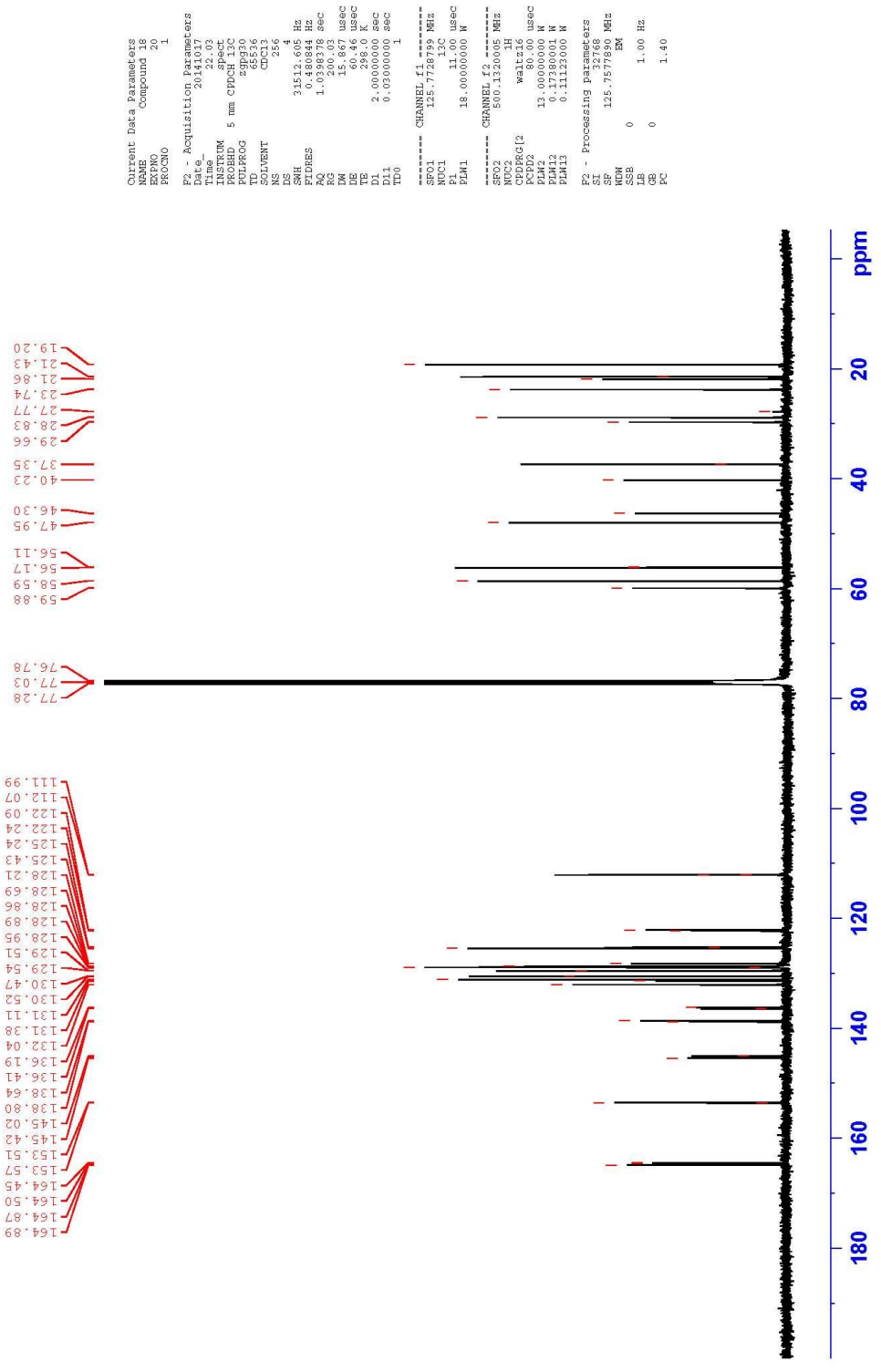


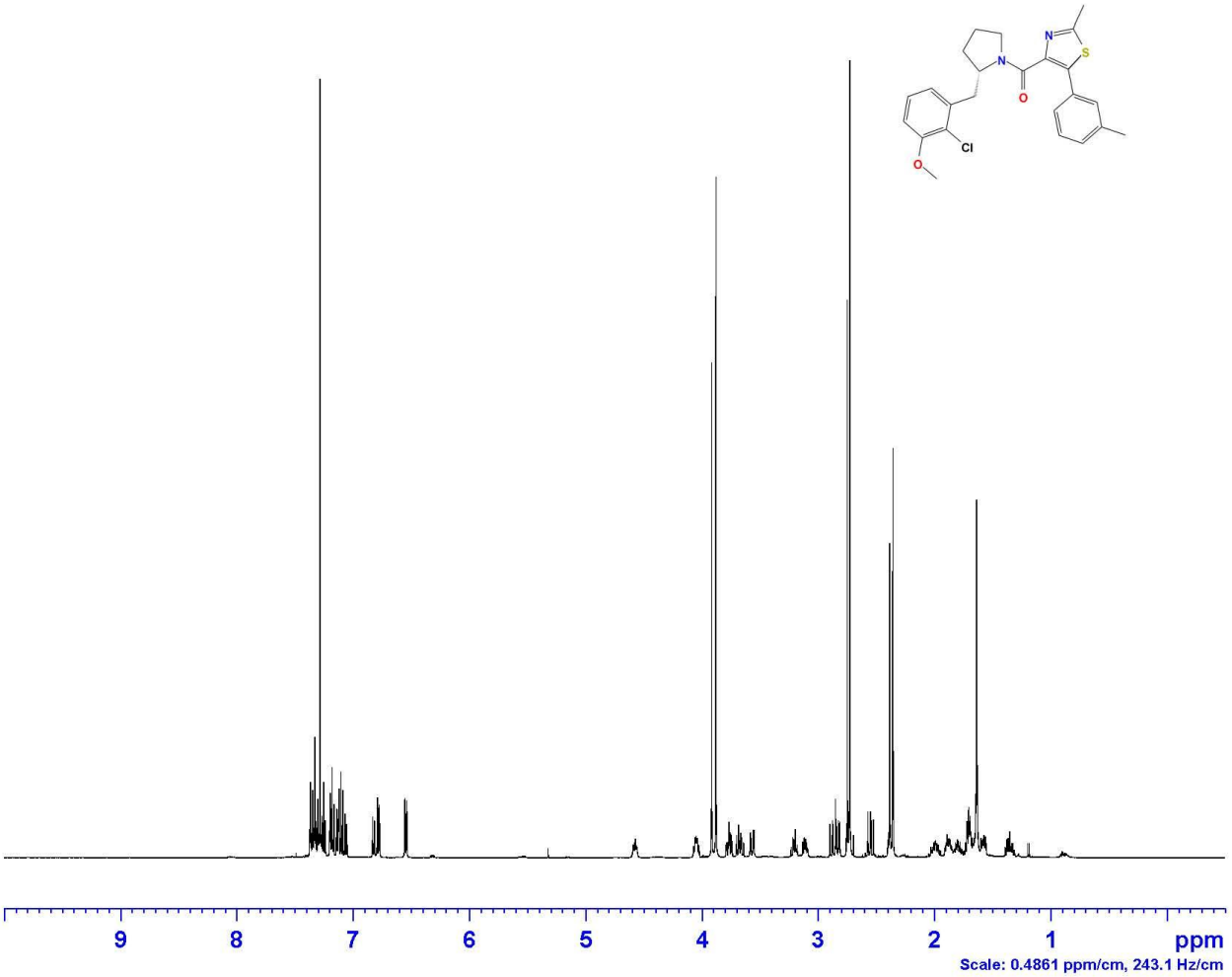

```
Current Data Parameters
NAME        Compound 17
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time               19.58
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                114.07
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                  9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 17
EXPNO 20
PROCNO 1
P2 - Acquisition Parameters
Date_ 20141017
Time_ 20 13
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
CHANNEL f2
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
P2 - Processing parameters
SI 32768
SF 125.7577880 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm
20
40
60
80
100
120
140
160
180
19.18
19.23
21.42
21.43
21.57
21.88
23.75
27.77
28.84
29.54
38.72
41.48
46.32
47.94
55.25
55.38
58.46
59.79
76.78
77.03
77.29
98.16
98.51
107.04
107.42
125.19
125.36
128.80
128.86
128.94
129.48
129.52
129.59
130.44
130.53
136.15
136.23
138.64
138.76
140.51
141.22
145.18
145.47
160.74
164.46
164.53
164.77

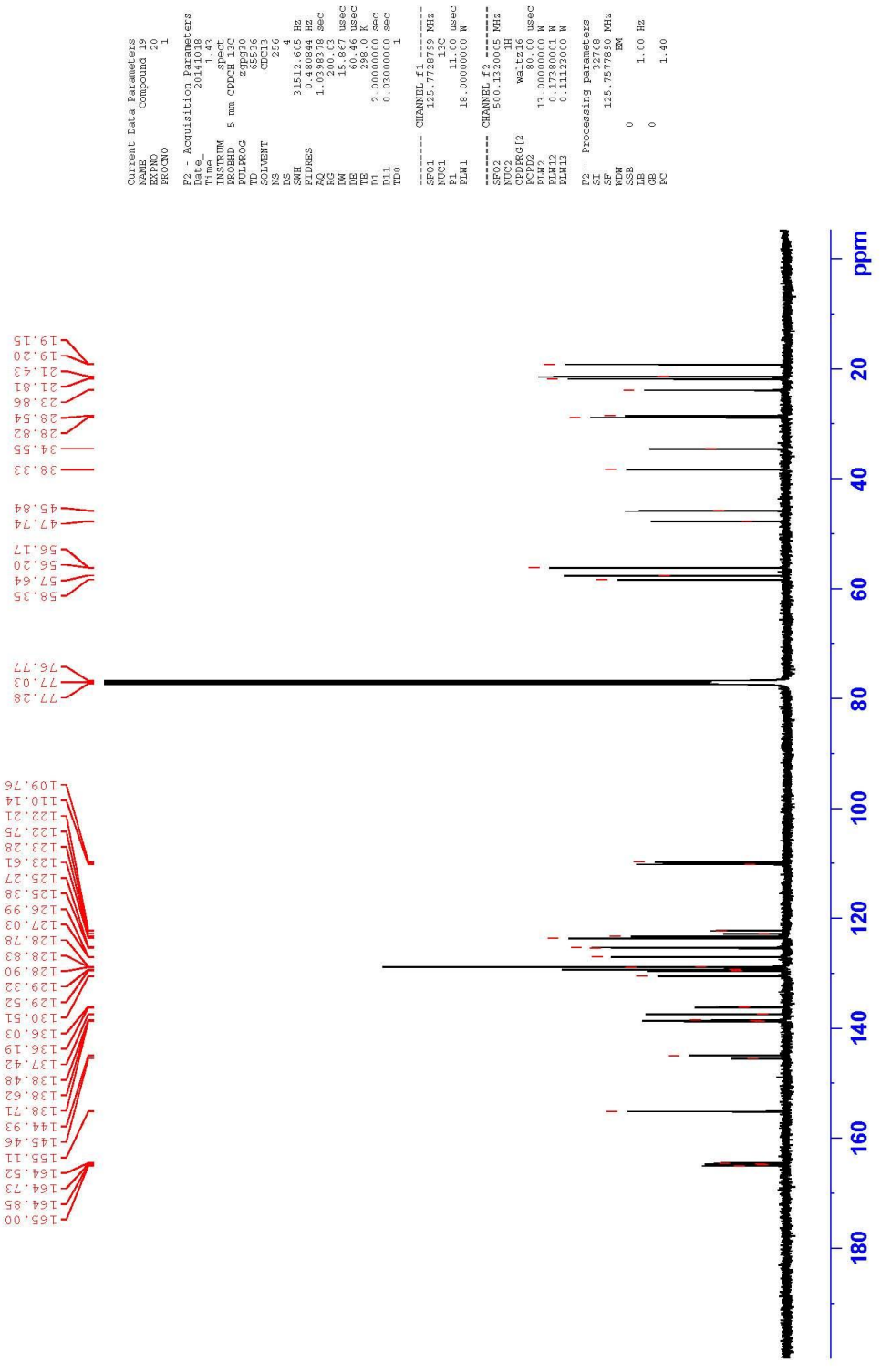


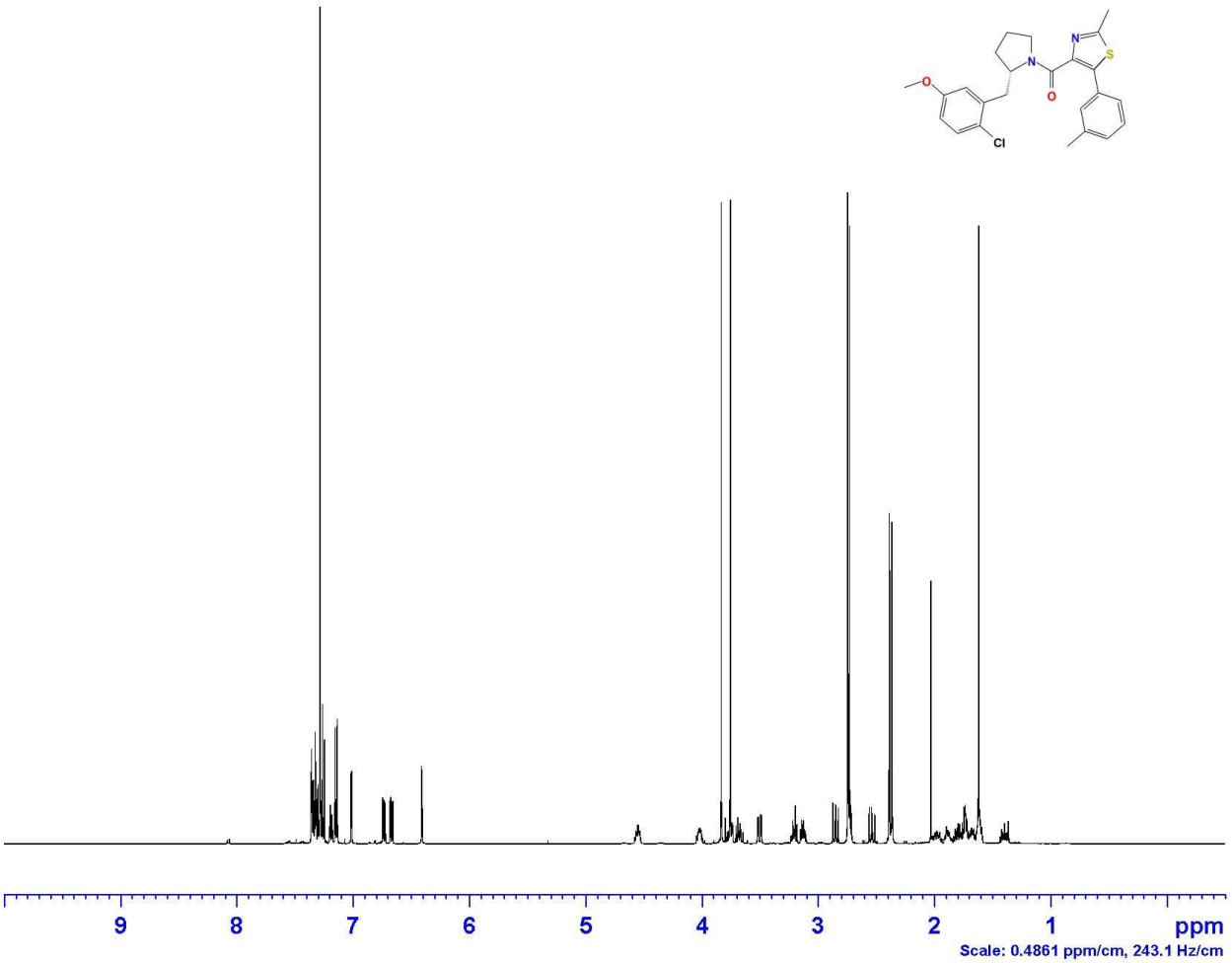

```
Current Data Parameters
NAME        Compound 18
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time              21.48
INSTRUM           spect
PROBHD    5 mm CPDCH 13C
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                114.07
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                 9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 18
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141017
Time 22.03
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
19.20
21.43
21.86
23.74
27.77
28.83
29.66
37.35
40.23
46.30
47.95
56.11
56.17
58.59
59.88
76.78
77.03
77.28
111.99
112.07
122.09
122.24
125.24
125.43
128.21
128.69
128.86
128.89
128.95
129.51
129.54
130.47
130.52
131.11
131.38
132.04
136.19
136.41
138.64
138.80
145.02
145.42
153.51
153.57
164.45
164.50
164.87
164.89
ppm
20
40
60
80
100
120
140
160
180

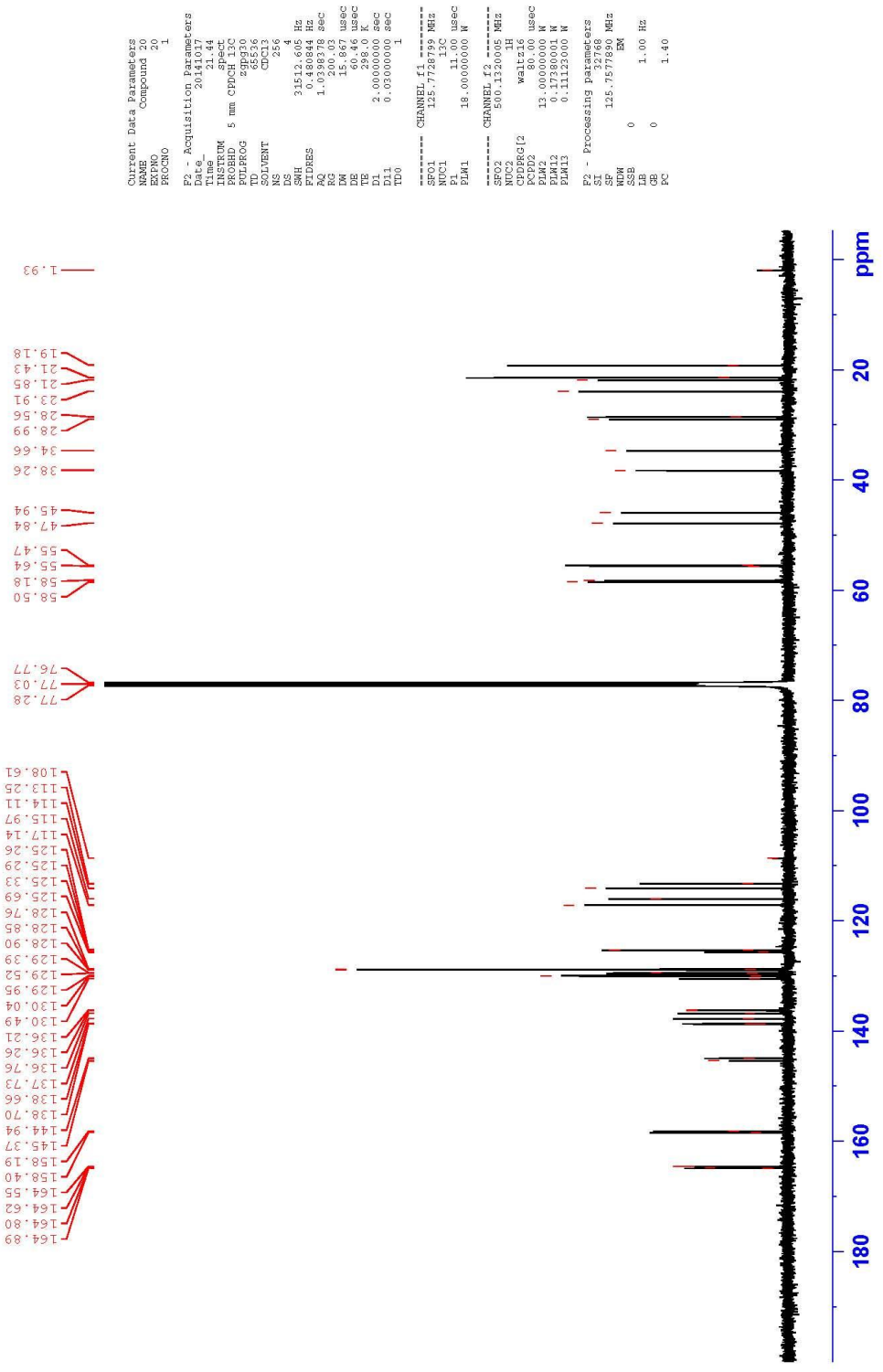


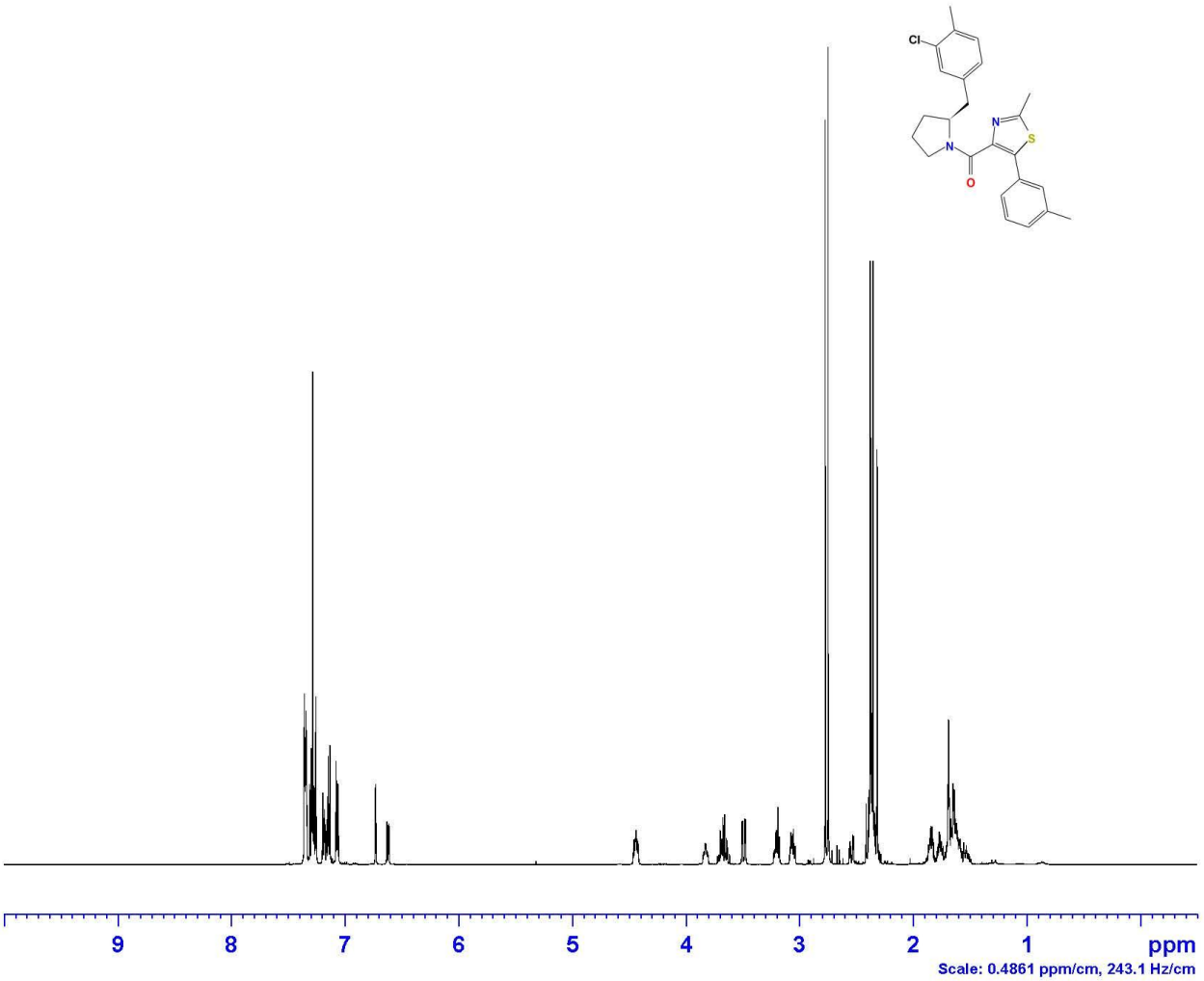

```
Current Data Parameters
NAME        Compound 19
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141018
Time               1.28
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                200.03
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                 9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 19
EXPNO 20
PROCNO 1
P2 - Acquisition Parameters
Date_ 20141013
Time 1.43
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 60.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
CHANNEL f2
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
P2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm
20
40
60
80
100
120
140
160
180
19.15
19.20
21.43
21.81
23.86
28.54
28.82
34.55
38.33
45.84
47.74
56.17
56.20
57.64
58.35
76.77
77.03
77.28
109.76
110.14
122.21
122.75
123.28
123.61
125.27
125.38
126.99
127.03
128.78
128.83
128.90
129.32
129.52
130.51
136.03
136.19
137.42
138.48
138.62
138.71
144.93
145.46
155.11
164.52
164.73
164.85
165.00

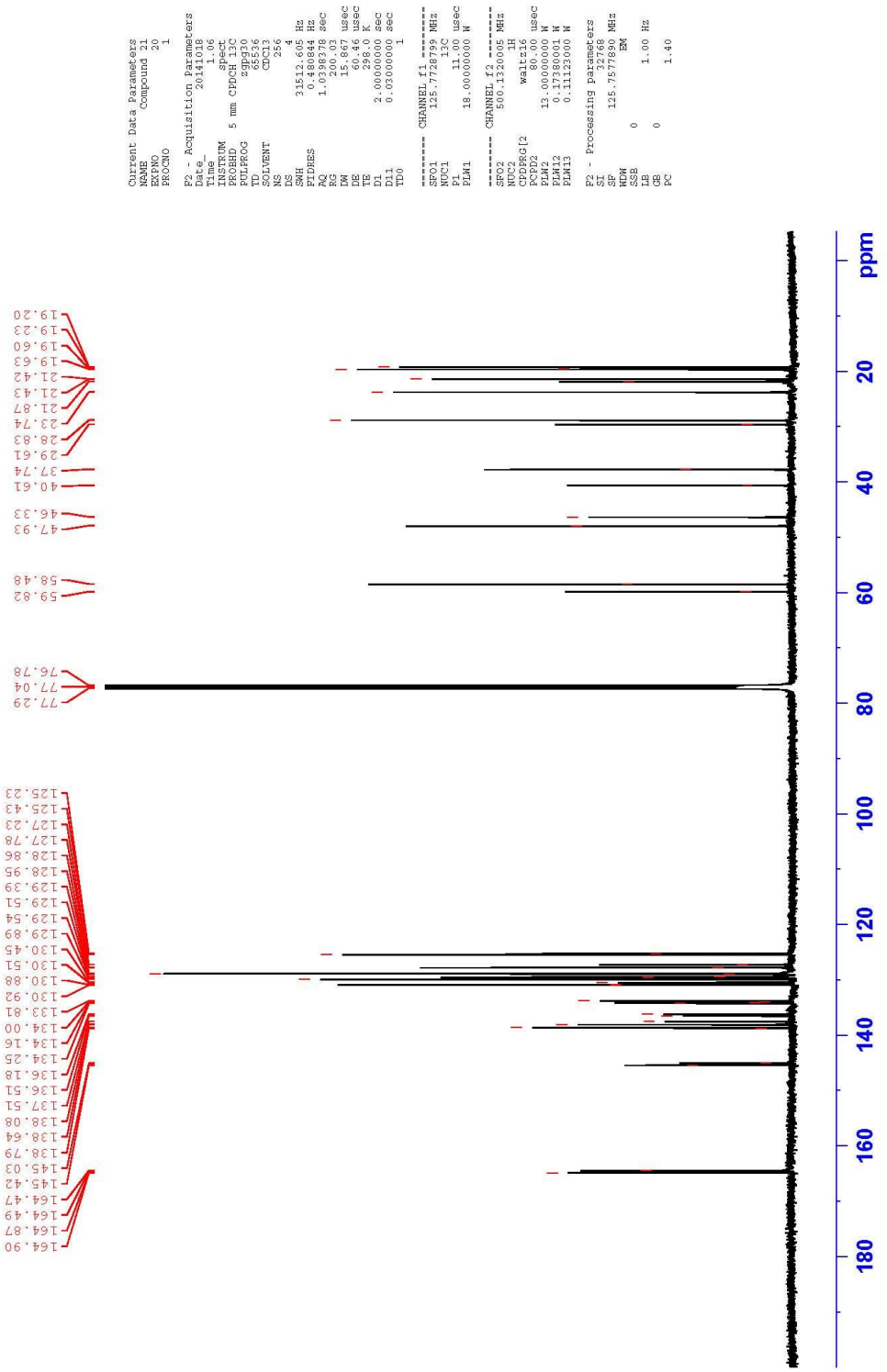


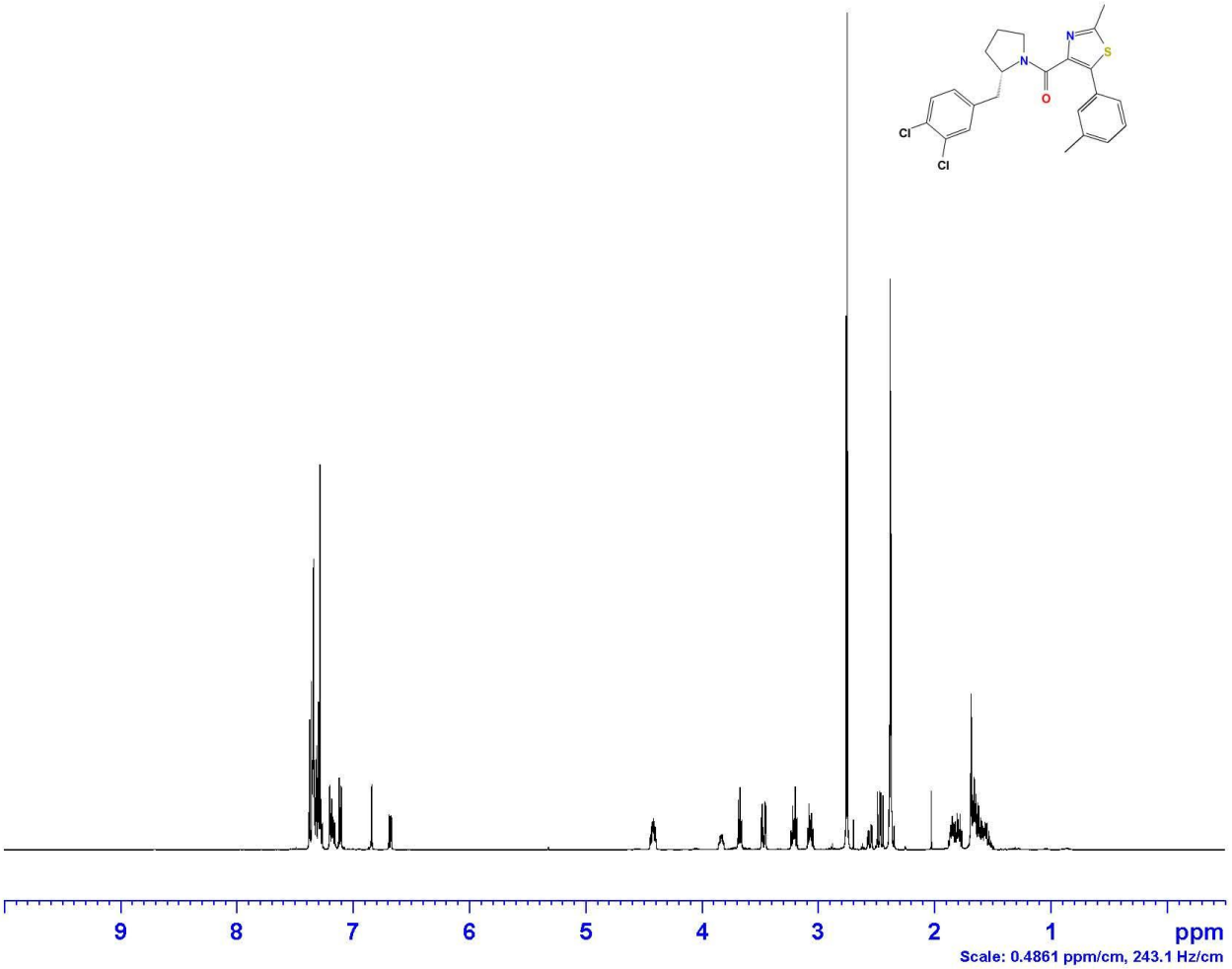

```
Current Data Parameters
NAME        Compound 20
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time               21.30
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                200.03
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                 9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 20
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161017
Time 21.44
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1.93
19.18
21.43
21.85
23.91
28.56
28.99
34.66
38.26
45.94
47.84
55.47
55.64
58.18
58.50
76.77
77.03
77.28
108.61
113.25
114.11
115.97
117.14
125.26
125.29
125.33
125.69
128.76
128.85
128.90
129.39
129.52
129.95
130.04
130.49
136.21
136.26
136.76
137.73
138.66
138.70
144.94
145.37
158.19
158.40
164.55
164.62
164.80
164.89
ppm
20
40
60
80
100
120
140
160
180

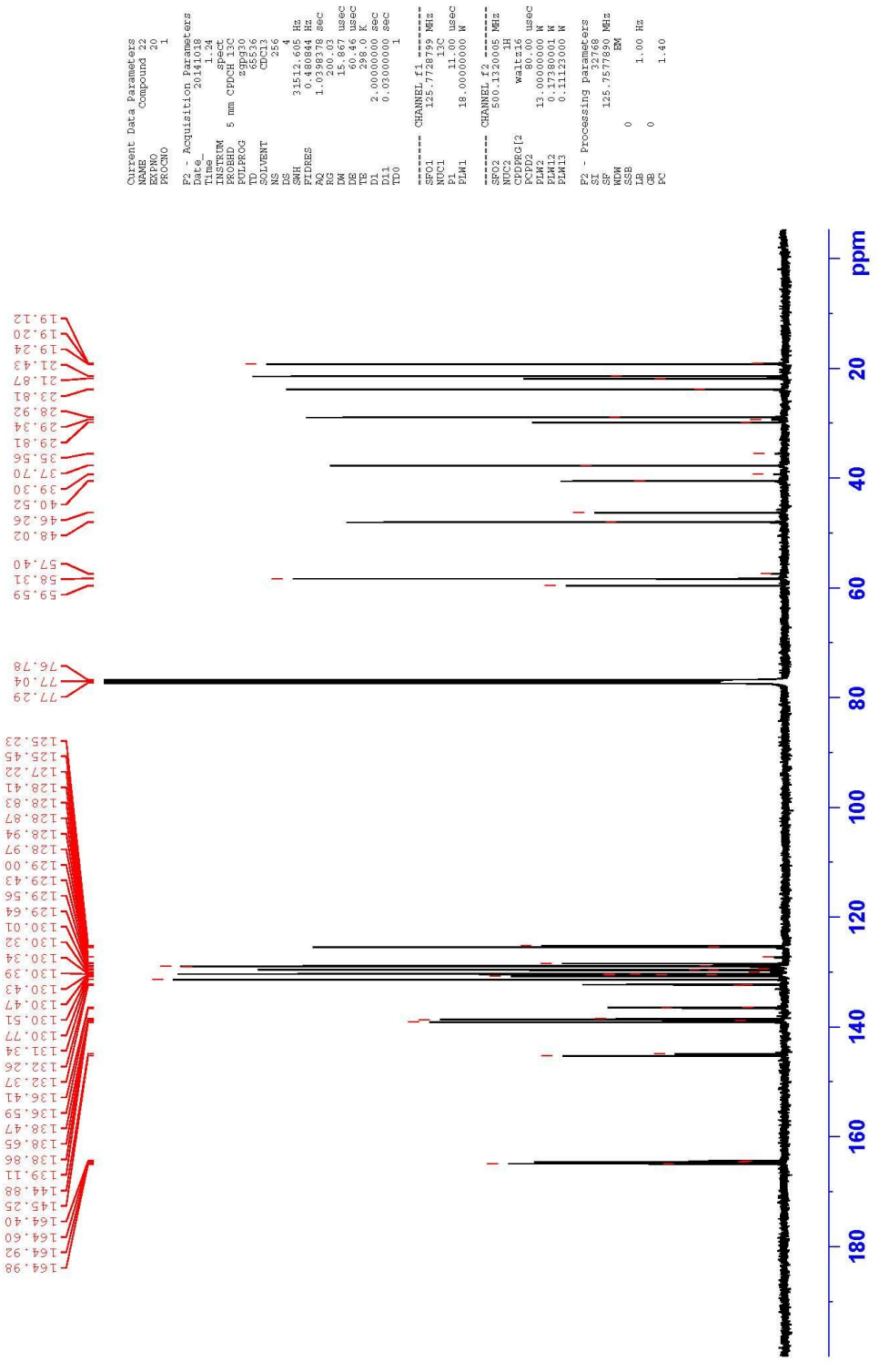


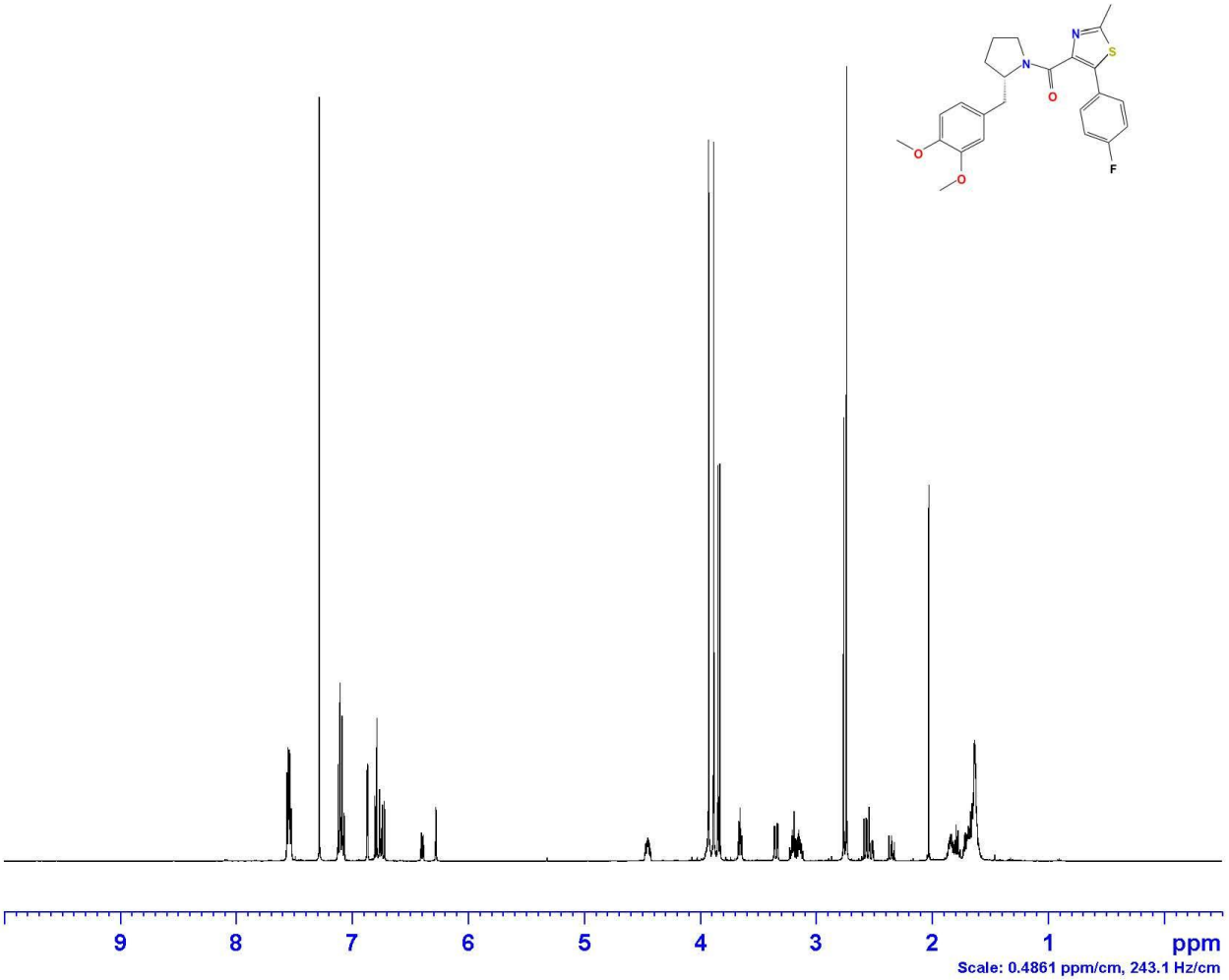

```
Current Data Parameters
NAME        Compound 21
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141018
Time               0.52
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES        0.152588 Hz
AQ            3.2767999 sec
RG               114.07
DW               50.000 usec
DE               40.00 usec
TE               298.0 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                9.25 usec
PLW1        13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 21
EXPNO 20
PROCNO 1
P2 - Acquisition Parameters
Date_ 20141018
Time_ 1.06
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
P2 - Processing parameters
SI 32768
SF 125.7577880 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm
20
40
60
80
100
120
140
160
180
19.20
19.23
19.60
19.63
21.42
21.43
21.87
23.74
28.83
29.61
37.74
40.61
46.33
47.93
58.48
59.82
76.78
77.04
77.29
125.23
125.43
127.23
127.78
128.86
128.95
129.39
129.51
129.54
129.89
130.45
130.51
130.88
130.92
133.81
134.00
134.16
134.25
136.18
136.51
137.51
138.08
138.64
138.79
145.03
145.42
164.47
164.49
164.87
164.90

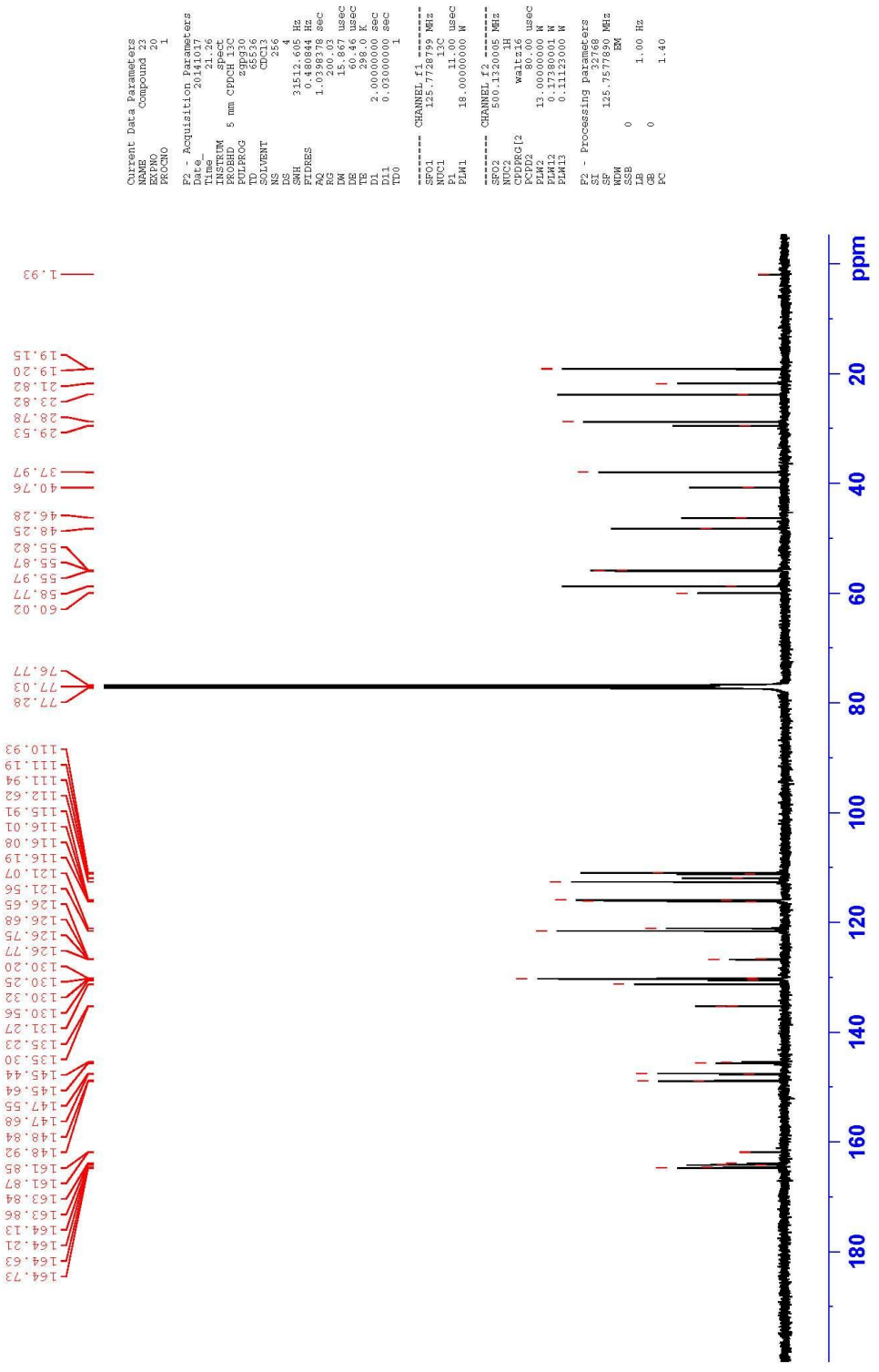


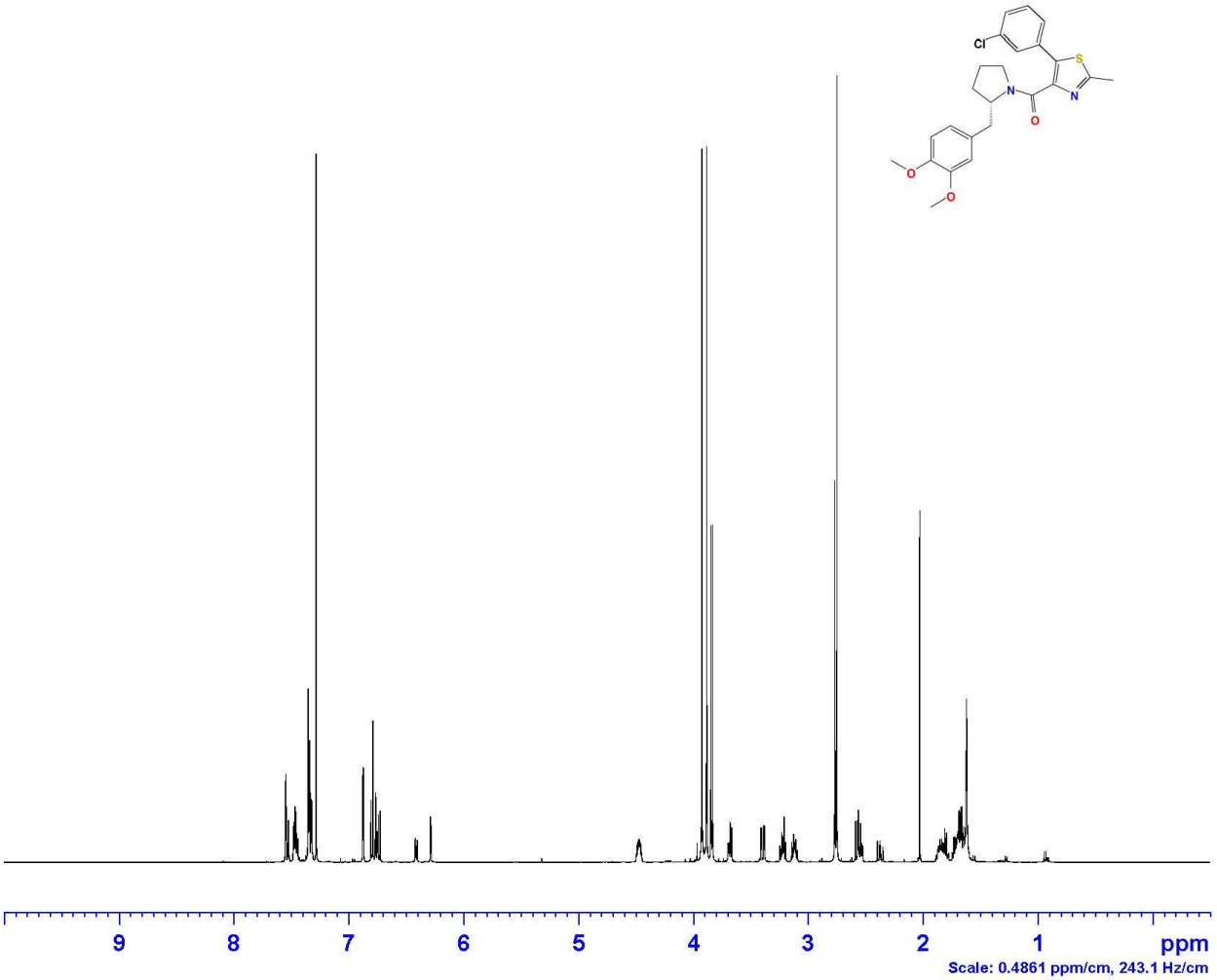

```
Current Data Parameters
NAME        Compound 22
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141018
Time               1.10
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                114.07
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                 9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```


Current Data Parameters
NAME Compound 22
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141018
Time 1.24
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 60.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
CHANNEL f2
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm
20
40
60
80
100
120
140
160
180
19.12
19.20
19.24
21.43
21.87
23.81
28.92
29.34
29.81
35.56
37.70
39.30
40.52
46.26
48.02
57.40
58.31
59.59
76.78
77.04
77.29
125.23
125.45
127.22
128.41
128.83
128.87
128.94
128.97
129.00
129.43
129.56
129.64
130.01
130.32
130.34
130.39
130.43
130.47
130.51
130.77
131.34
132.26
132.37
136.41
136.59
138.47
138.65
138.86
139.11
144.88
145.25
164.40
164.60
164.92
164.98

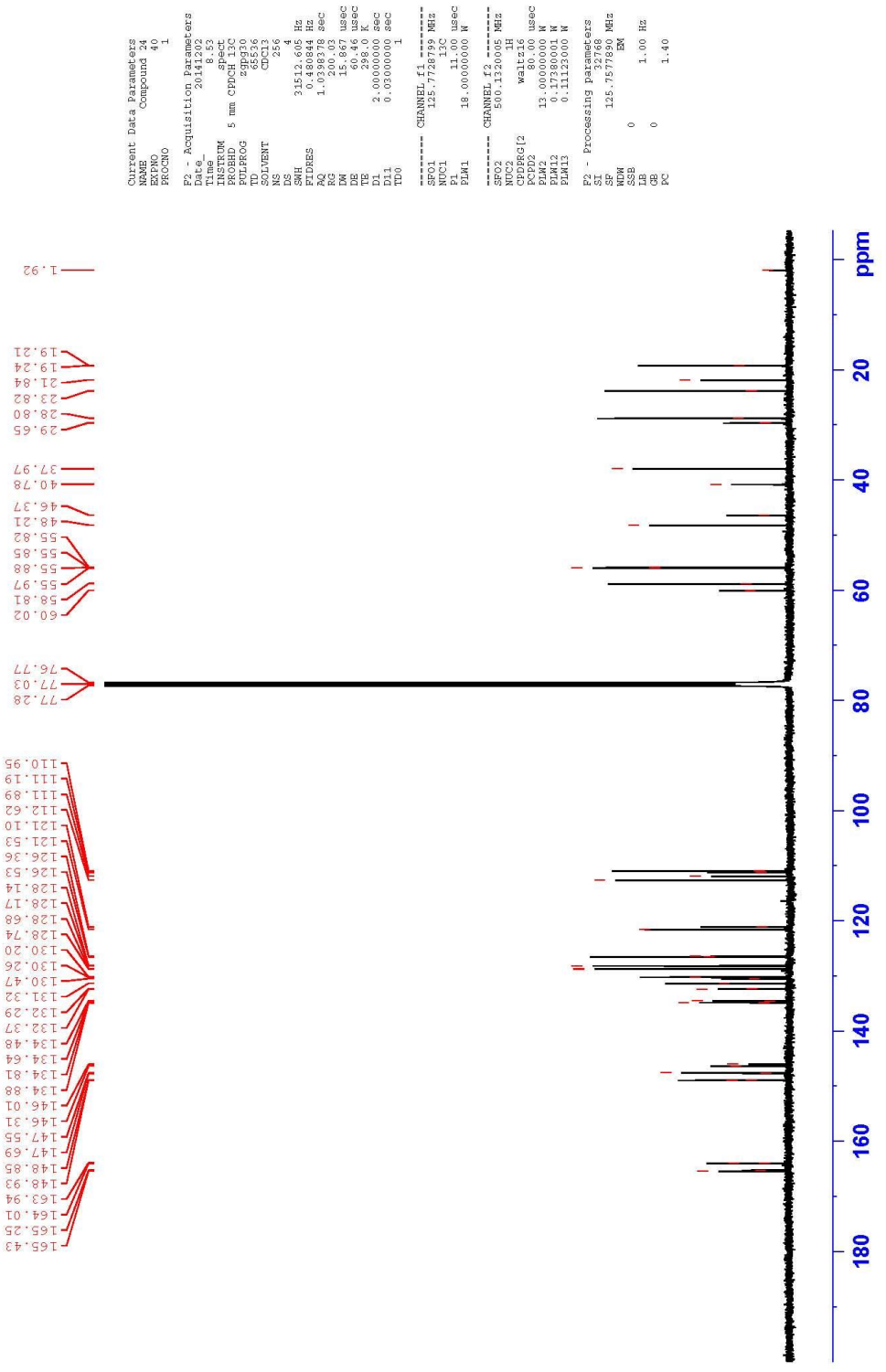


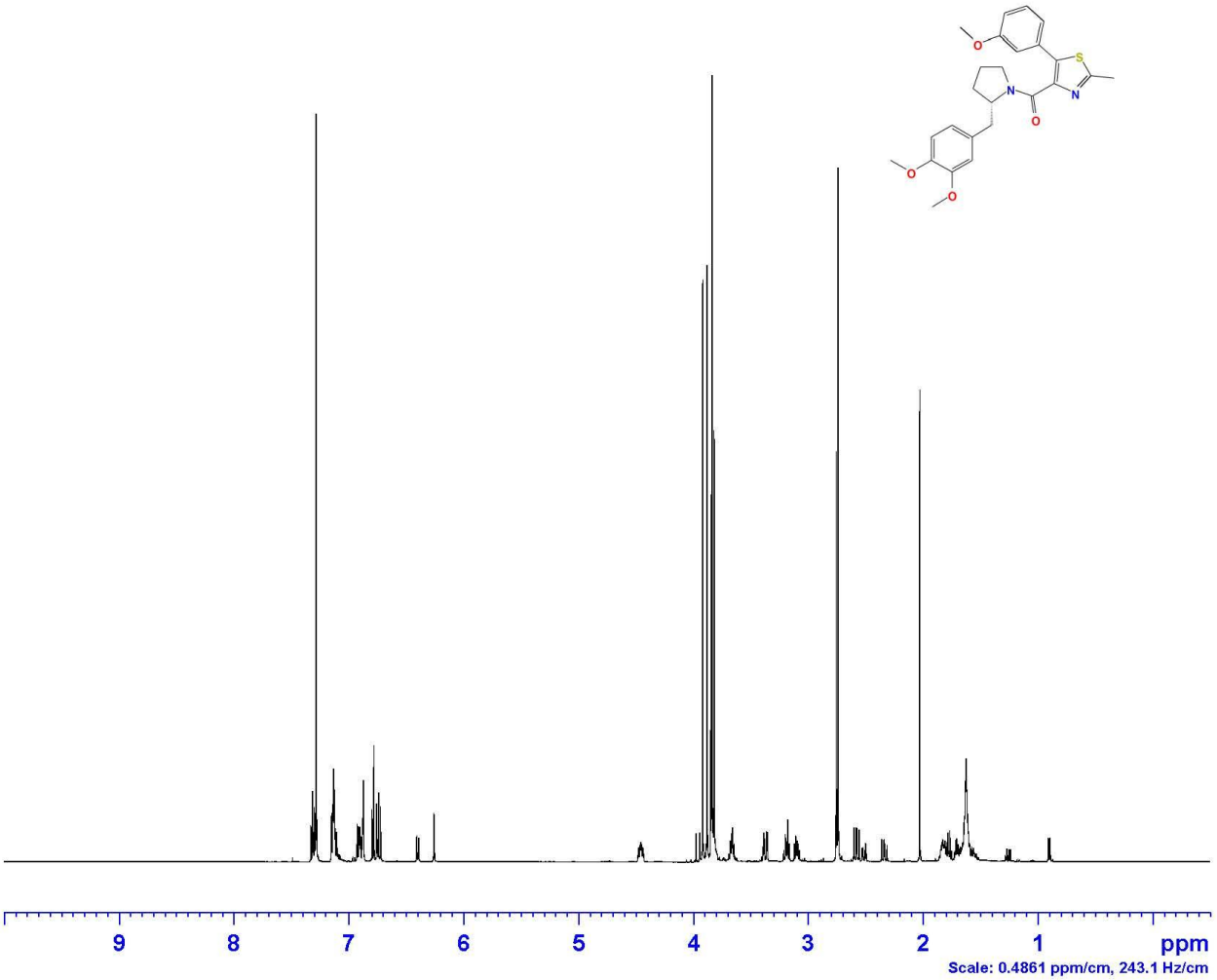

```
Current Data Parameters
NAME        Compound 23
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time              21.12
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           10000.000 Hz
FIDRES        0.152588 Hz
AQ            3.2767999 sec
RG               200.03
DW               50.000 usec
DE               40.00 usec
TE               298.0 K
D1           1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                 9.25 usec
PLW1        13.00000000 W

F2 - Processing parameters
SI               65536
SF          500.1300000 MHz
WDW                 EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 23
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141017
Time 21 26
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 60.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1.93
19.15
19.20
21.82
23.82
28.78
29.53
37.97
40.76
46.28
48.25
55.82
55.87
55.97
58.77
60.02
76.77
77.03
77.28
110.93
111.19
111.94
112.62
115.91
116.01
116.08
116.19
121.07
121.56
126.65
126.68
126.75
126.77
130.20
130.25
130.32
130.56
131.27
135.23
135.30
145.44
145.64
147.55
147.68
148.84
148.92
161.85
161.87
163.84
163.86
164.13
164.21
164.63
164.73
ppm
20
40
60
80
100
120
140
160
180

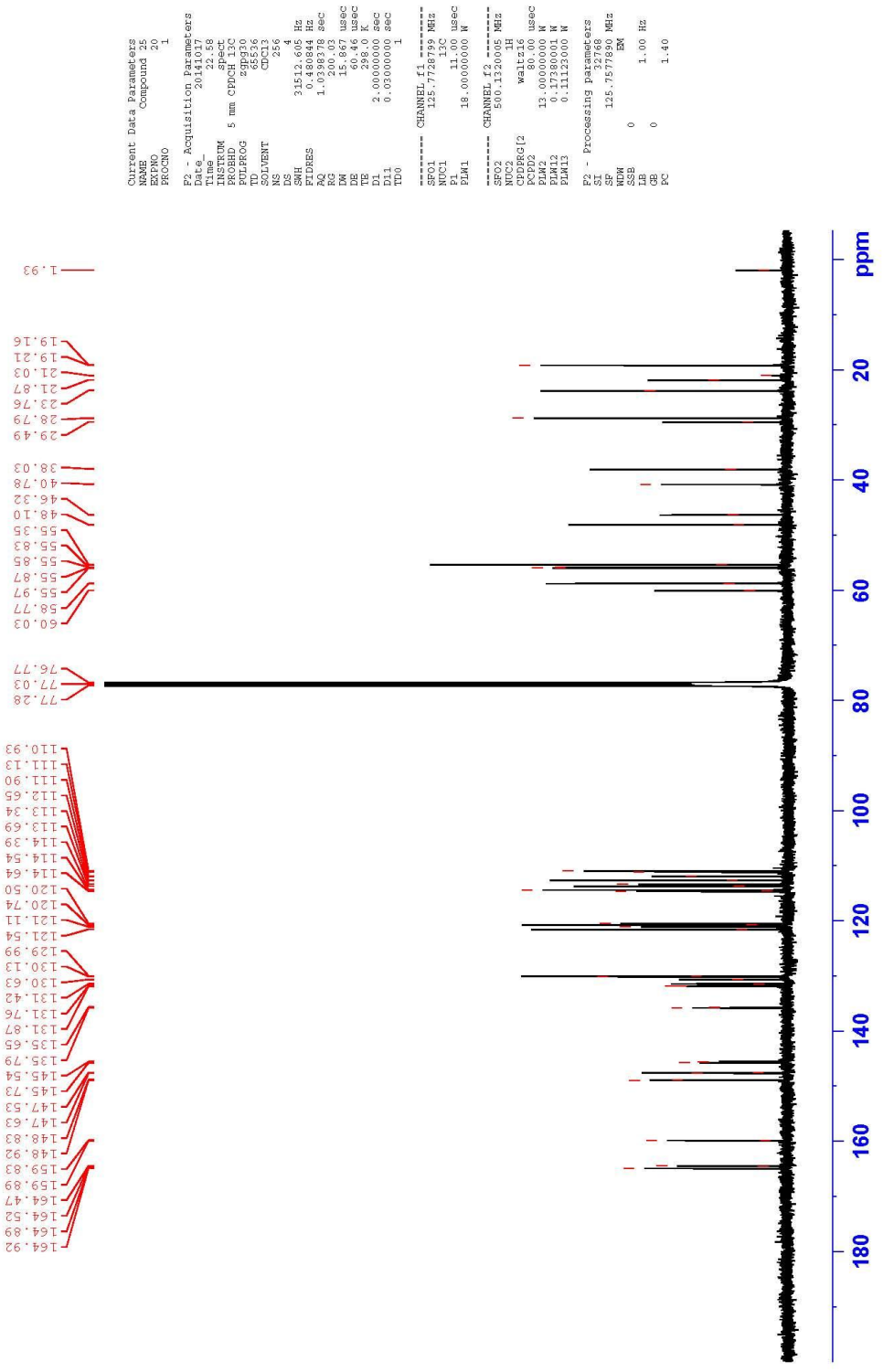


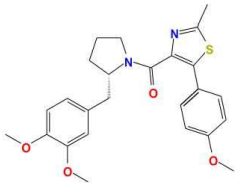

```
Current Data Parameters
NAME        Compound 24
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time               17.01
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                200.03
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                 9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

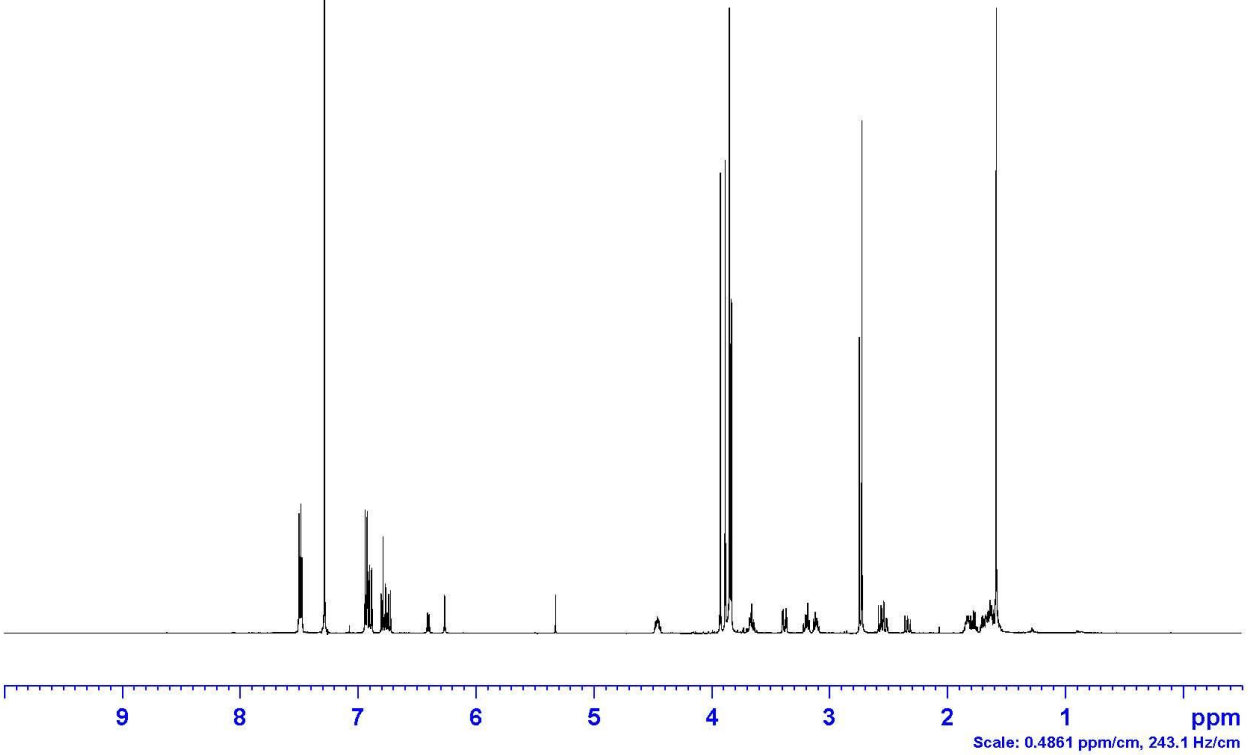

Current Data Parameters
NAME Compound 24
EXPNO 40
PROCNO 1
P2 - Acquisition Parameters
Date_ 20141102
Time 8.53
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
P2 - Processing parameters
SI 32768
SF 125.7577880 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1.92
19.21
19.24
21.84
23.82
28.80
29.65
37.97
40.78
46.37
48.21
55.82
55.85
55.88
55.97
58.81
60.02
76.77
77.03
77.28
110.95
111.19
111.89
112.62
121.10
121.53
126.36
126.53
128.14
128.17
128.68
128.74
130.20
130.26
130.47
131.32
132.29
132.37
134.48
134.64
134.81
134.88
146.01
146.31
147.55
147.69
148.85
148.93
163.94
164.01
165.25
165.43
ppm
20
40
60
80
100
120
140
160
180



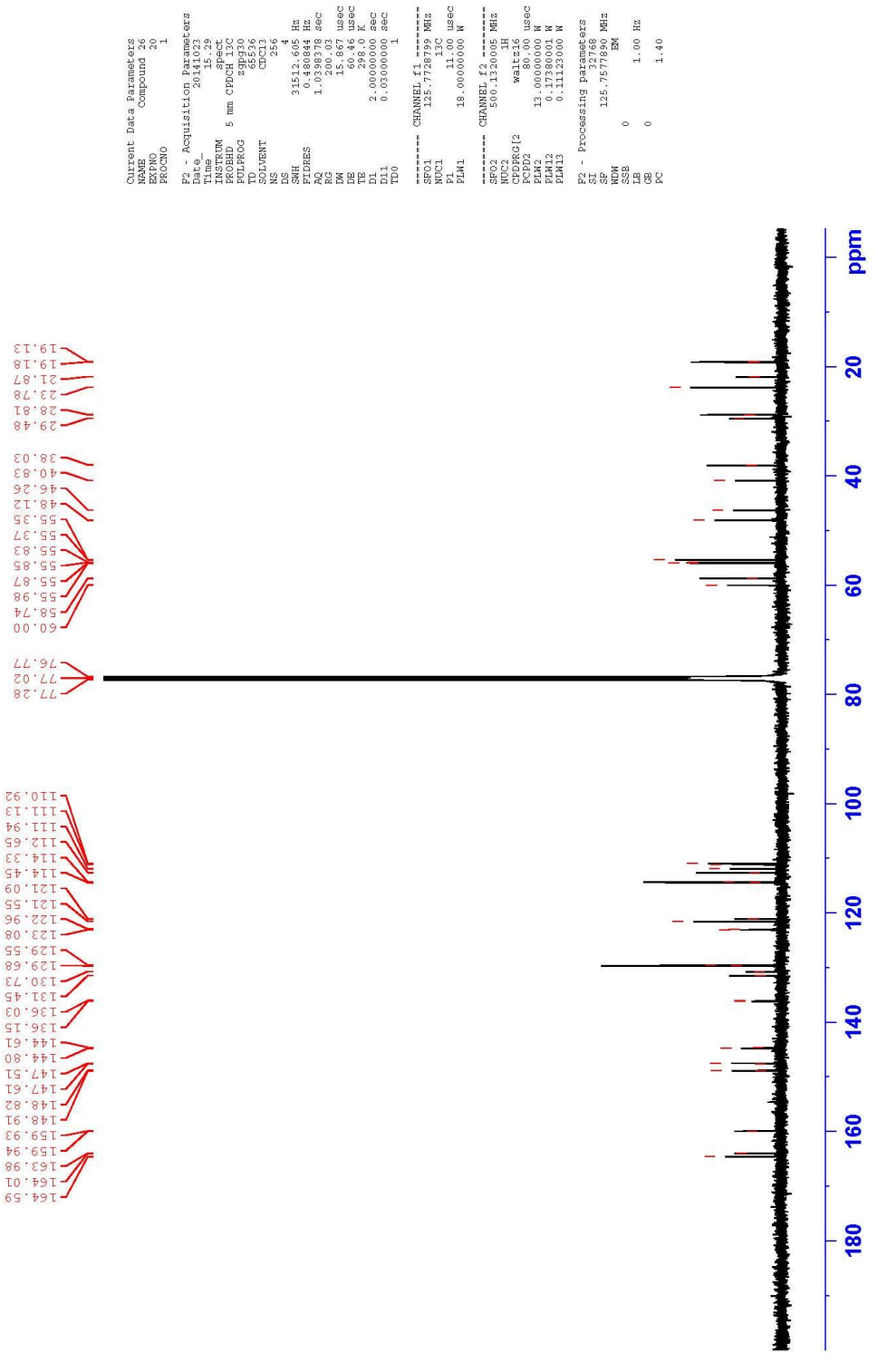

```
Current Data Parameters
NAME        Compound 25
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time               22.44
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                200.03
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                  9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

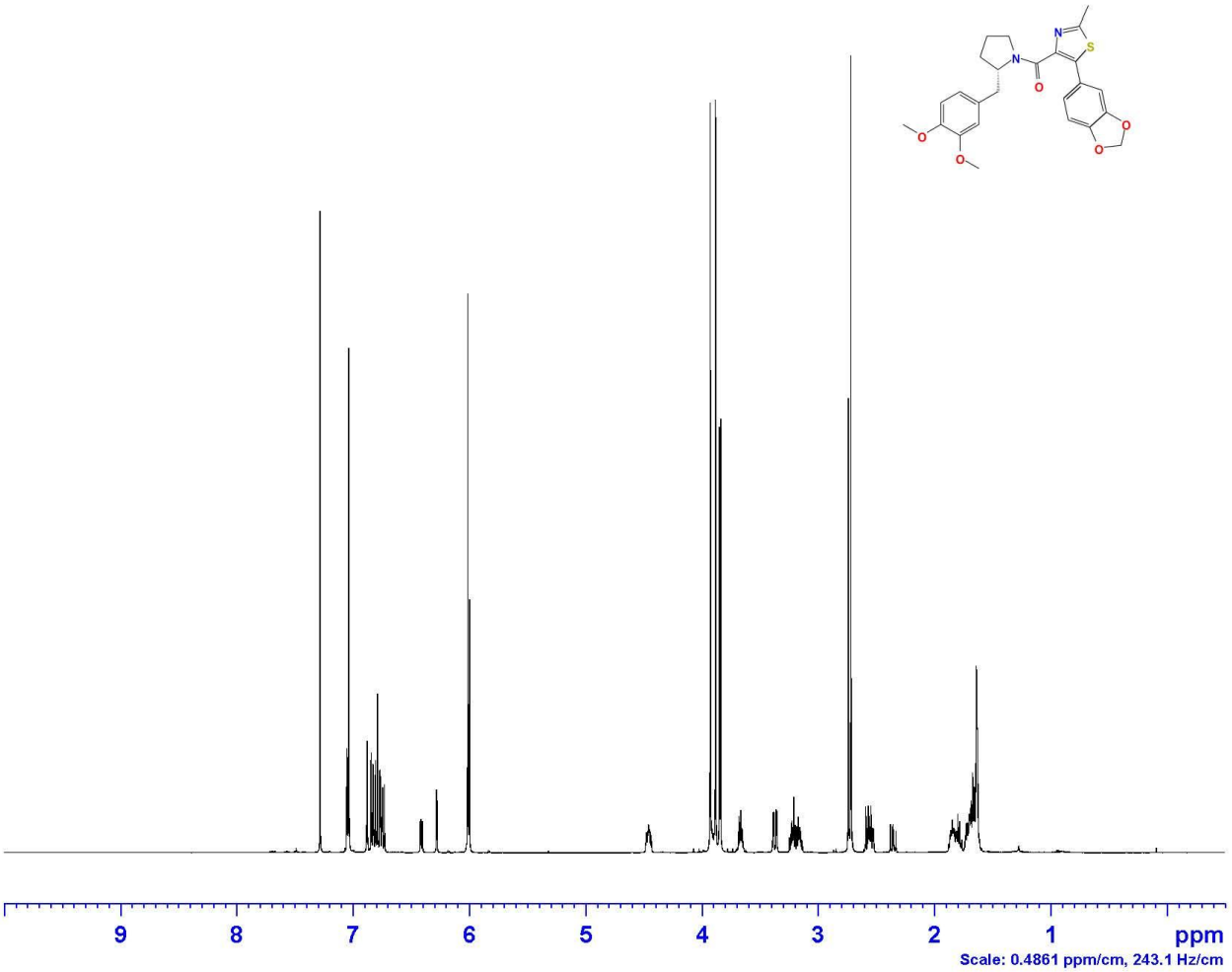

Current Data Parameters
NAME Compound 25
EXPNO 20
PROCNO 1
P2 - Acquisition Parameters
Date_ 20141017
Time 22.58
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
CHANNEL f2
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
P2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1.93
19.16
19.21
21.03
21.87
23.76
28.79
29.49
38.03
40.78
46.32
48.10
55.35
55.83
55.85
55.87
55.97
58.77
60.03
76.77
77.03
77.28
110.93
111.13
111.90
112.65
113.34
113.69
114.39
114.54
114.64
120.50
120.74
121.11
121.54
129.99
130.13
130.63
131.42
131.76
131.87
135.65
135.79
145.54
145.73
147.53
147.63
148.83
148.92
159.83
159.89
164.47
164.52
164.89
164.92
ppm
20
40
60
80
100
120
140
160
180



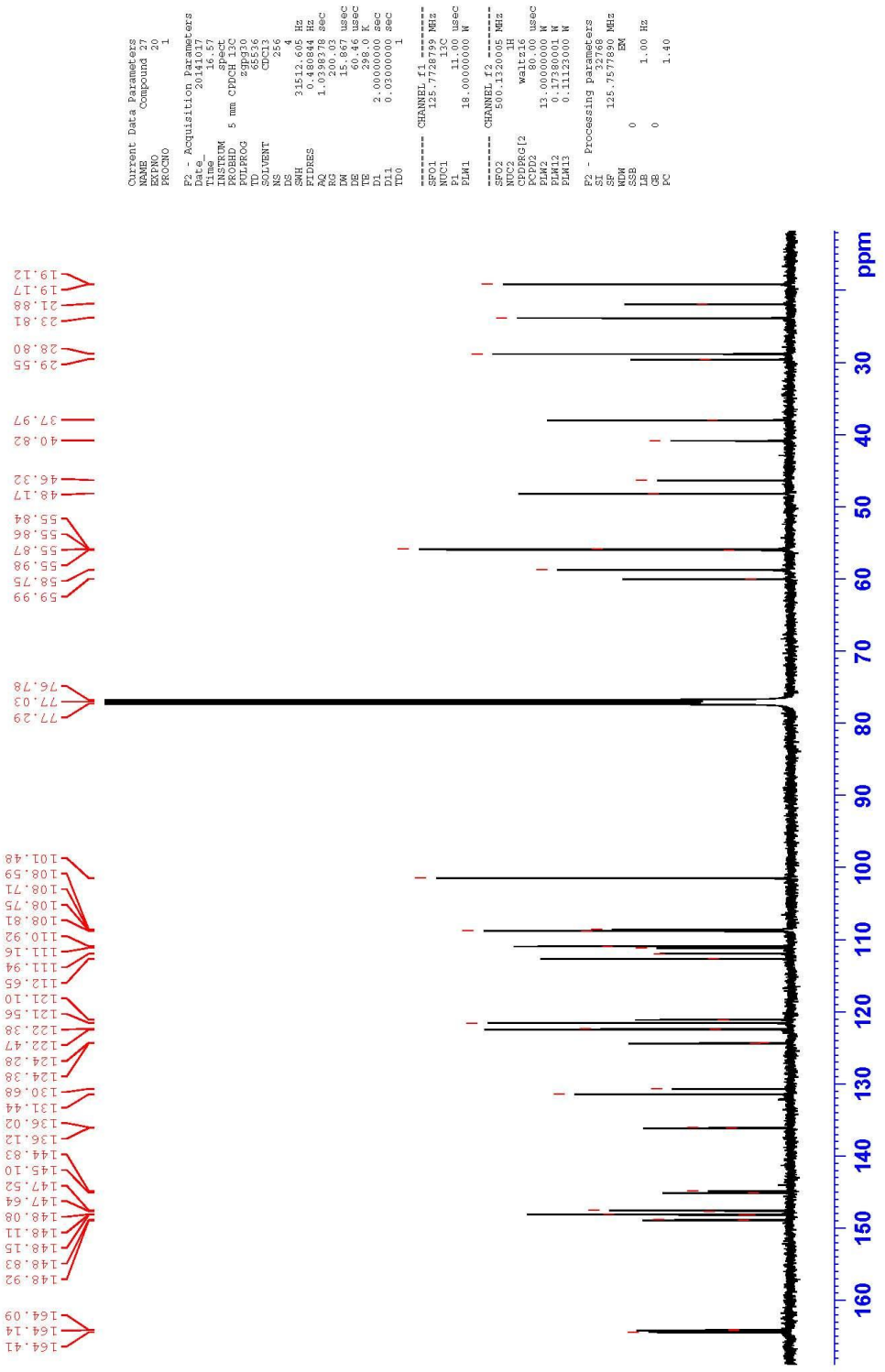


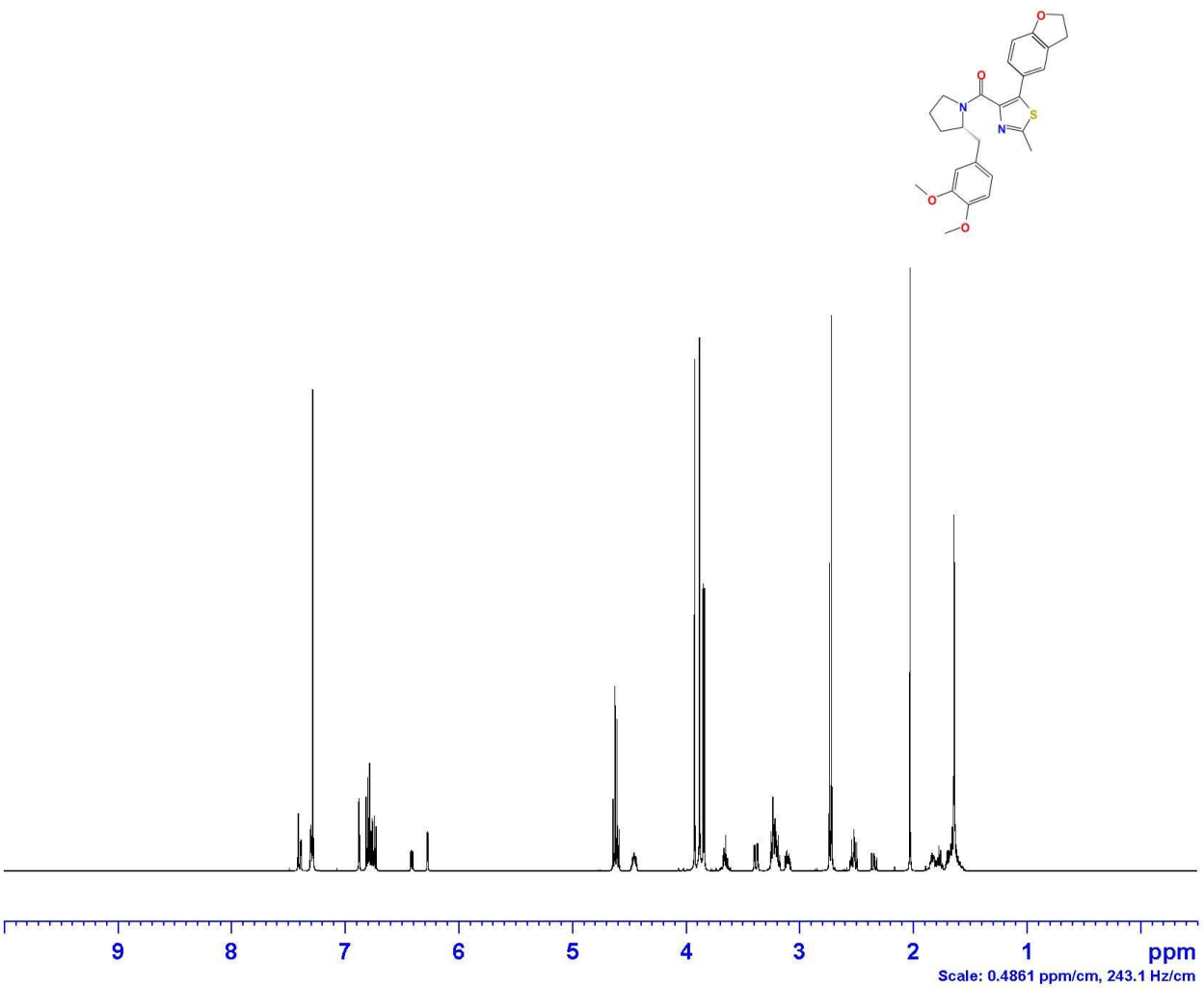

```
Current Data Parameters
NAME        Compound 26
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141023
Time              15.15
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                200.03
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                  9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 26
EXPNO 20
PROCNO 1
P2 - Acquisition Parameters
Date_ 20111202
Time 15.29
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 60.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
CHANNEL f2
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
P2 - Processing parameters
SI 32768
SF 125.7577880 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm
20
40
60
80
100
120
140
160
180
19.13
19.18
21.87
23.78
28.81
29.48
38.03
40.83
46.26
48.12
55.35
55.37
55.83
55.85
55.87
55.98
58.74
60.00
76.77
77.02
77.28
110.92
111.13
111.94
112.65
114.33
114.45
121.09
121.55
122.96
123.08
129.55
129.68
130.73
131.45
136.03
136.15
144.61
144.80
147.51
147.61
148.82
148.91
159.93
159.94
163.98
164.01
164.59

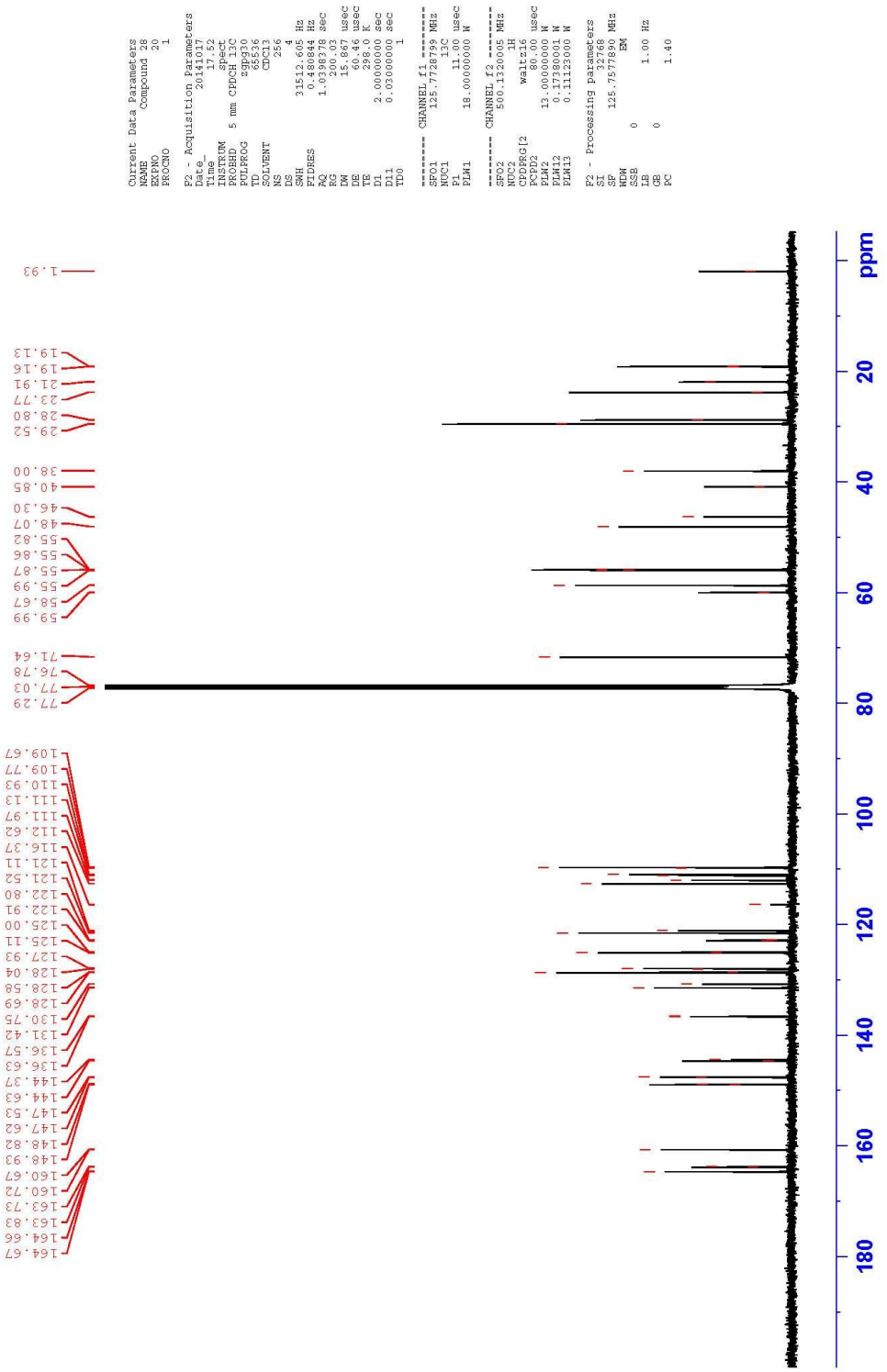



```
Current Data Parameters
NAME        Compound 27
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time              16.43
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                114.07
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1             1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1          500.1330885 MHz
NUC1                 1H
P1                  9.25 usec
PLW1          13.00000000 W

F2 - Processing parameters
SI                65536
SF            500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 27
EXPNO 20
PROCNO 1
P2 - Acquisition Parameters
Date_ 20141107
Time 16.57
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 6.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
CHANNEL f2
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
P2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm




```
Current Data Parameters
NAME        Compound 28
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20141017
Time               17.38
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                179.95
DW                50.000 usec
DE                40.00 usec
TE                298.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                 1H
P1                  9.25 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```


Current Data Parameters
NAME Compound 28
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20111017
Time 17.52
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 31512.605 Hz
FIDRES 0.480844 Hz
AQ 1.0398378 sec
RG 200.03
DW 15.867 usec
DE 60.46 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 125.7728799 MHz
NUC1 13C
P1 11.00 usec
PLW1 18.00000000 W
======== CHANNEL f2 ========
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 13.00000000 W
PLW12 0.17380001 W
PLW13 0.11123000 W
F2 - Processing parameters
SI 32768
SF 125.7577880 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1.93
19.13
19.16
21.91
23.77
28.80
29.52
38.00
40.85
46.30
48.07
55.82
55.86
55.87
55.99
58.67
59.99
71.64
76.78
77.03
77.29
109.67
109.77
110.93
111.13
111.97
112.62
116.37
121.11
121.52
122.80
122.91
125.00
125.11
127.93
128.04
128.58
128.69
130.75
131.42
136.57
136.63
144.37
144.63
147.53
147.62
148.82
148.93
160.67
160.72
163.73
163.83
164.66
164.67
ppm
20
40
60
80
100
120
140
160
180

Biological protocols:

Intracellular calcium release assays

Chinese hamster ovary (CHO) cells expressing the human or rat orexin-1 receptor or orexin-2 receptor, respectively, were grown in culture medium (Ham F-12 with L-Glutamine) containing 300 μg/mL G418, 100 U/mL penicillin, 100 μg/mL streptomycin and 10% heat inactivated fetal calf serum (FCS). The cells were seeded at 20,000 cells / well into 384-well black clear bottom sterile plates (Greiner). The seeded plates were incubated overnight at 37°C in 5% CO_2.

Orexin-A as an agonist was prepared as 1 mM stock solution in MeOH: water (1:1), diluted in Hanks balanced salt solution (HBSS) containing 0.1% bovine serum albumin (BSA), $NaHCO_3$: 0.375 g/L and 20 mM HEPES for use in the assay at a final concentration of 5 nM (EC_{70}).

Antagonists were prepared as 10 mM stock solution in DMSO, then diluted in 384-well plates using DMSO followed by a transfer of the dilutions into HBSS containing 0.1% bovine serum albumin (BSA), $NaHCO_3$: 0.375 g/L and 20 mM HEPES. On the day of the assay, 50 μL of staining buffer (HBSS containing 1% FCS, 20 mM HEPES, $NaHCO_3$: 0.375 g/L, 5 mM probenecid (Sigma) and 3 μM of the fluorescent calcium indicator fluo-4 AM (1 mM stock solution in DMSO, containing 10% pluronic) was added to each well. The 384-well cell-plates were incubated for 50 min at 37°C in 5% CO_2 followed by equilibration at RT for 30 - 120 min before measurement.

Within the Fluorescent Imaging Plate Reader (FLIPR Tetra, Molecular Devices), antagonists were added to the plate in a volume of 10 μL/well, incubated for 120 min, and finally 10 μL/well of agonist was added. Fluorescence was measured for each well at 1 second intervals, and the height of each fluorescence peak was compared to the height of the fluorescence peak induced by an EC_{70} of orexin A with vehicle in place of antagonist. The IC_{50} value (the concentration of compound needed to inhibit 50% of the agonistic response) was determined using the proprietary IC_{50}witch software.

For the determination of apparent K_b values, a dilution series of **27** was incubated with the recombinant OX receptor expressing cells for 120 min and then stimulated with a dilution series of orexin-A (OxA) to obtain a set of agonist concentration-response curves in the presence of different fixed antagonist concentrations. The obtained concentration-response curves demonstrated insurmountable antagonism.

To calculate the apparent K_b values, the EC_{50} values and Hill slopes for OxA were calculated using the proprietary IC_{50} Witch software (settings=curve-intrinsic minima and maxima were used). Then, the IC_{50} values of the antagonists at approximate $EC_{50\text{-}70}$ of OxA (1.6 nM for human OX_1, human OX_2, rat OX_2 and 8 nM for rat OX_1) were determined using the IC_{50}witch software (settings=curve-intrinsic minima and maxima were used). From this IC_{50} value, the on-day OxA EC_{50} value and the slope (n) of the OxA CRC, the apparent K_b was calculated using the generalised Cheng-Prusoff equation:[1, 2]

$$K_b = \frac{IC_{50}}{(2 + ([OxA_{stim}]/EC_{50OxA})^n)^{1/n} - 1}$$

For the determination of receptor occupancy half-life ($ROt_{1/2}$) values of **27**, cells were supplemented with 10 µL of antagonist dilution series and incubated at RT for 120 min. Then, cells were either stimulated in the FLIPR by the addition of 10 µL of 7x concentrated OxA (final assay concentration EC_{50}– EC_{70}), or cells were washed twice with 50 µL/well assay buffer (HBSS containing 0.1% BSA, 20 mM HEPES, 0.375 g/L $NaHC0_3$, 2.5 mM probenecid, pH 7.4). After 5, 15, 20 and 30 min of incubation at RT, cells were stimulated with an EC_{50}–EC_{70} of OxA by the addition of 10 µL of a 7x concentrated OxA stock in assay buffer. Calcium release was monitored for 3 min. For the estimation of $ROt_{1/2}$, the apparent K_b values were calculated via the generalised Cheng-Prusoff equation using on-plate generated EC_{50} values of OxA, and the earliest time point with a K_b value significantly shifted versus the non-washed control K_b value (K_{b0min}) was used. Significant change from K_{b0min} ($p<0.05$) was determined using the one-way ANOVA test including Dunnett's post test using GraphPadPrism software and is indicated with an asterisk in Fig. **2**. An approximate $ROt_{1/2}$ was then calculated assuming first order dissociation kinetics: $t_{1/2} = t_x/[\log_2 (K_{bxmin}/K_{b0min})]$ with x= time point of first significant change in K_b after wash-out.

Table 1 Inhibitory potency of 27 on OX_1 and OX_2-mediated intracellular Ca^{2+} release

Test system	Recombinant CHO cells expressing human or rat OX_1 or OX_2.
Assay	Inhibition of orexin-A-induced calcium mobilization, measured as increase in fluorescence of calcium-sensitive dye

Receptor	apparent K_b [σ_g]	
	OX_1	OX_2
Human	5.3 nM [1.3]	1.4 nM [1.8]
Rat	7.3 nM [1.7]	1.7 nM [1.7]

Apparent K_b values were calculated from IC_{50} values at 1.6 nM OxA (human OX_1, human OX_2, rat OX_2) or 8 nM OxA (rat OX_1) via the generalised Cheng-Prusoff equation. Apparent K_b values are expressed as the geometric means of n = 4 values determined from three independent experiments. The geometric standard deviation σg is displayed in brackets. CHO, Chinese hamster ovary; IC_{50}, concentration that causes 50% inhibition; K_b, equilibrium dissociation constant of a ligand determined by means of a functional assay; OX_1, orexin receptor 1; OX_2, orexin receptor 2; OxA, orexin-A.

Pharmacology protocols:

Experiments were conducted on male, adult Wistar (RccHan:WIST; Harlan, Horst, The Netherlands) rats, which were maintained under standard lab conditions (temperature 20 ± 2°C, relative humidity 55–70%, food and water *ad libitum*) under a regular 12 h light–dark cycle (lights on 06:00). After arrival rats were allowed at least one week of habituation to Actelion's animal facility before experiments commenced. Experimental procedures were approved by the Basel-Landschaft Veterinary Office and strictly adhered to Swiss federal regulations on animal experimentation. Unless noted otherwise, rats were socially housed in groups of four in standard plastic rodent cages, and all tests were conducted during the light phase (08:00 to 18:00) under illumination of > 600 lx, where not otherwise specified.

For telemetric transmitter implantation (EEG/EMG monitoring)

Rats were equipped with telemetric transmitters (TL11M2-F20-EET; Data Science International, St Paul, MN, USA) that allowed the noninvasive detection of electroencephalograms (EEG), electromyograms (EMG) and activity via signal transmission to a receiver. The surgical transmitter implantation was performed under aseptic conditions. The rat was placed and secured in a stereotaxic apparatus. The body of the transmitter was placed subcutaneously along the dorsal flank of the rat with the leads routed subcutaneously to an incision accessing the cranium. For EEG recordings, two trepanations were placed in the skull, 2 mm from either side of the midline and 2 mm anterior to the lambda suture for placement of one differential

pair of electrodes. Two other superficial trepanations were drilled for screws as support for cementing the electrodes. The EMG leads were inserted in either side of the muscles of the neck and sutured into place.

Sleep/wake cycle evaluation

Sleep/wake cycles were evaluated via radiotelemetry technology in rats. EEG, EMG and home cage activity were recorded from singly housed Wistar rats while under free moving conditions in their home cages. At the start of the experiment rats were placed together with their home cages in ventilated sound attenuating boxes, on a regular 12 h light/dark cycle for 3 days of acclimation before recordings started. Experiments were done in a crossover design, i.e. animals were alternatively treated with drug and vehicle. Recordings started by 24 h baseline (preceding the treatment), the 12 h night-period following the treatment, 36 h of recovery (wash out period) followed by the crossover. Oral administrations occurred at the transition from the day to the night phase (17:45 to 18:00). Sleep and wake stages were evaluated automatically using the Somnologica Science software (Medcare, Embla, USA). The recording is divided into user definable (10 s) contiguous epochs. The scoring is based on frequency estimation for EEG and amplitude discrimination for the EMG and the locomotor activity. Using these measurements, the software determines the probabilities that the EEG and EMG components within each epoch best represent waking, quiet waking, non-REM sleeping or REM sleeping. Essentially, wake consists of low-amplitude EEG activity with relatively greater power in the higher frequency bands such as alpha, from (10–13 Hz), accompanied by moderate to high-level EMG activity. The locomotor activity and the amplitude of the EMG allow the differentiation between wake and quiet wake. Non-REM sleep is defined by high amplitude EEG activity with greater power in the delta frequency band (0.5–5 Hz), and by low EMG activity. REM sleep is characterized by low amplitude EEG activity focused in the theta frequency band (6–9 Hz). There is no EMG activity present during REM sleep.

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2. Y. Cheng and W. H. Prusoff, *Biochem Pharmacol*, 1973, **22**, 3099-3108.