Supporting Information

Development of Noviomimetics as C-terminal Hsp90 Inhibitors

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Contents:

Luciferase reporter assay and immunoblot analysis……...s3

General chemical methods…….……....s3

Molecular Modeling……..…….……....s3

Synthetic procedures and compound characterization…….……..….s4-s10

Luciferase Reporter Assay and Immunoblot Analysis

The luciferase reporter assay was performed using a 1.5 kb region upstream of the start codon of the human *HSPA1A* gene to drive luciferase expression as previously described. 50B11 cells[29] were grown in 10 cm dishes in maintenance medium and the cells were transfected using lipofectamine. Twenty four hours after transfection, the cells were re-seeded into 24 well plates at a density of 2 x 10^5 cells per well. After a 6 hr period to permit attachment, the cells were treated with the indicated compounds for 16 hr. Luciferase activity was assessed and normalized to the total protein concentration of each well.

50B11 cells were treated with the indicated compounds for 24 hrs and were scraped into lysis buffer containing 50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1 mM EDTA, 1% NP-40, 0.5 mM sodium orthovandate, 40 mM NaF, 10 mM β-glycerophosphate, and Complete Protease Inhibitors (Roche Diagnostics). After 15 minutes on ice, the lysates were sonicated then centrifuged at 10,000 x g for 10 min at 4ºC. The protein concentration of the supernatant was estimated using a Bio-Rad protein assay and bovine serum albumin as the standard. Following SDS-PAGE, the proteins were transferred to nitrocellulose and the membrane incubated with 5% non-fat dry milk in phosphate buffered saline containing 0.1% Tween 20 (PBST) for 1-2hr at room temperature. The blots were probed with primary antibodies recognizing Hsp70 or β-actin at 4ºC overnight. The membranes were washed with PBST and subsequently incubated with HRP-conjugated secondary antibodies and immunoreactive proteins were visualized using chemiluminescence detection

General Chemical Methods

All chemical starting materials purchased from Sigma-Aldrich, Acros Organics, TCI, and Alfa Aesar were directly used without further purification. The purity of the synthesized compounds was determined by NMR spectroscopy. The purity of the compounds used in the biological assays was ≥ 95%. ^{1}H NMR were recorded at 400 or 500 MHz (Bruker DRX-400 Bruker with a H/C/P/F QNP gradient probe) spectrometer. ^{13}C NMR spectra were recorded at 125 MHz (Bruker DRX 500 with broadband, inverse triple resonance, and high resolution magic angle spinning HR-MA probe spectrometer); chemical shifts are reported in δ (ppm) relative to the internal reference chloroform-d ($CDCl_3$, 7.27 ppm). FAB (HRMS) spectra were recorded with a LCT Premier (Waters Corp., Milford, MA). TLC was performed on glass backed silica gel plates (Uniplate) with spots visualized by UV light. All solvents were reagent grade and, when necessary, were purified and dried by standard methods. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator operating at reduced pressure.

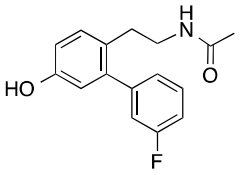
Molecular Modeling.

Docking studies were performed using Surflex-Dock in Sybyl v8.0. A homology model of Hsp90α based on the open HtpG. SAXS structure was used as the receptor, while the protomol was generated using docked Novobiocin.[34] The energy minimized molecules

were docked with 10 different starting conformations with ring flexibility allowed. Pymol was used for visual interpretation and figure preparation.

Synthesis and Compound Characterization

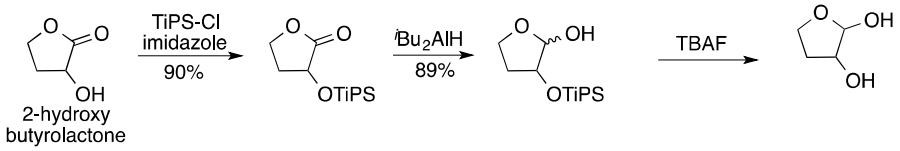
N-(2-(3'-fluoro-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 24



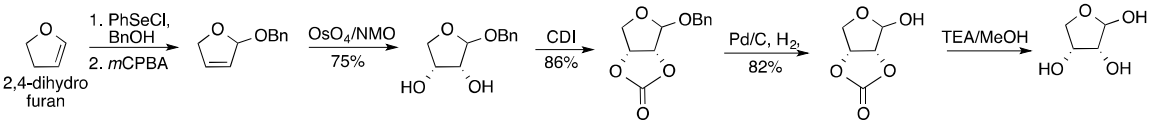
The detailed synthesis and compound characterization of aglycone **24** is described in reference 22.

Synthesis of Compounds 2, 3, 4, 7, 13 and 14

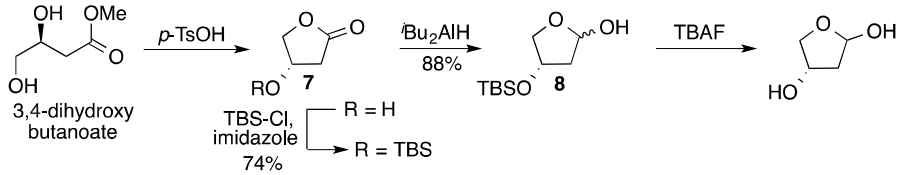
Synthesis of **2**



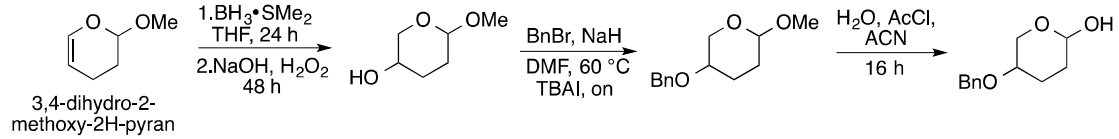
Synthesis of **3**



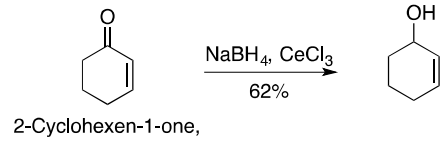
Synthesis of **4**



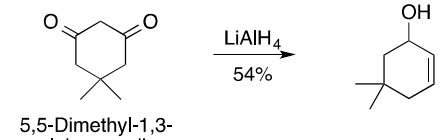
Synthesis of **7.** (see ref 27)



Synthesis of **13** (see ref 28)

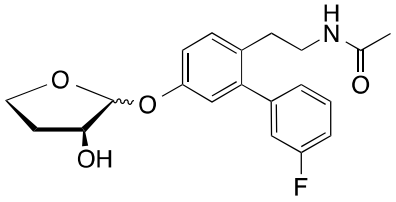


Synthesis of **14** (see ref 28)



Representative procedure for Mitsunobu coupling with sugars:

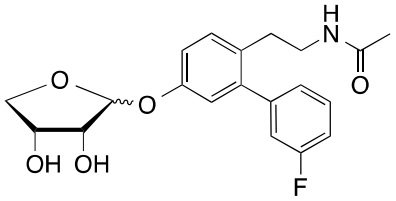
***N*-(2-(3'-fluoro-5-((3-hydroxytetrahydrofuran-2-yl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 25**



Diisopropylazodicarboxylate (90 μL, 0.46 mmol) was added slowly to a solution of aglycone, **24** (105 mg, 0.38 mmol), sugar **2** (100 mg, 0.38 mmol) (TIPS protected) and triphenylphosphine (200 mg, 0.76 mmol) in THF (3 mL) at 0 °C. The resulting mixture was stirred at rt for 2 h, quenched with water, and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified via column chromatography (SiO_2, 100:1, $CHCl_3$:MeOH) to afford TIPS protected compound (53 mg) as a mixture of diastereomers. The product was deprotected by reaction with tetrabutylammonium fluoride (0.19 mL) in THF (0.5 mL). The desired compound was obtained after column chromatography (SiO_2, 100:1, CH_2Cl_2:MeOH) in 72%, as a mixture of diastereomers:

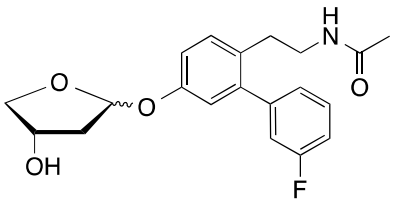
^{1}H-NMR (500 MHz, $CDCl_3$) 0.70:0.30 mixture of diastereomers δ 7.41-7.35 (m, 1H), 7.23-7.19 (m, 1H), 7.08−6.97 (m, 4H), 6.95 (d, *J* = 2.7 Hz, 0.3H), 6.89 (d, *J* = 2.7 Hz, 0.7H), 5.61 (s, 0.70H), 5.55 (s, 0.3H), 5.31 (br, s, 1H), 4.50 (d, *J* = 4 Hz, 0.70H), 4.40 (m, 0.3H), 4.21-4.15 (m, 1H), 4.15-4.08 (m, 1H), 3.28 (q, *J* = 5 Hz, 2H), 2.74 (q, *J* = *3* Hz, 2H), 2.44-2.37 (m, 0.75H), 2.36-2.29 (m, 0.39H), 2.04-2.01 (m, 0.21H), 1.99-1.93 (m, 0.8H), 1.87 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.26, 163.76, 161.80, 143.65, 142.45, 131.06, 130.14, 129.65, 125.15, 118.41, 116.29, 116.22, 114.49, 106.44, 100.25, 76.09, 72.84, 67.67, 40.74, 32.55, 32.21, 23.53. HRMS (ESI+) m/z [M+Na+] calcd for $C_{20}H_{22}FNO_4Na$ 382.1431; found 382.1423.

***N*-(2-(5-(((3*R*,4*R*)-3,4-dihydroxytetrahydrofuran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 26**



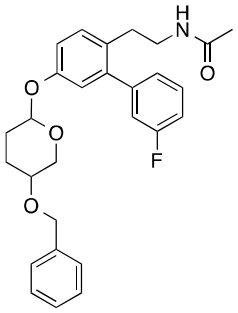
^{1}H-NMR (500 MHz, $CDCl_3$) 0.76:0.24 mixture of diastereomers δ 7.40-7.35 (m, 1H), 7.22 (d, *J* = 5 Hz, 1H), 7.09−7.05 (m, 2H), 7.01-6.98 (m, 1H), 6.90 (d, *J* = 3 Hz, 1H), 5.65 (s, 1H), 5.29 (br, s, 1H), 4.58-4.57 (m, 0.77H), 4.39-4.38 (m, 0.76H), 4.26-4.25 (m, 0.82H), 3.96 (m, 0.76H), 3.27 (q, *J* = 5 Hz, 2H), 2.75 (t, *J* = 5 Hz, 2H), 1.88 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.24, 163.77, 161.81, 155.25, 143.59, 142.39, 131.13, 130.19, 125.15, 118.32, 116.48, 116.35, 116.24, 114.40, 106.43, 73.25, 70.94, 40.74, 32.20, 29.99, 23.57. HRMS (ESI+), m/z [M+Na+] calcd for $C_{20}H_{22}FNO_5Na$ 398.1380; found 398.1370.

(R)-N-(2-(3'-fluoro-5-((4-hydroxytetrahydrofuran-2-yl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 27



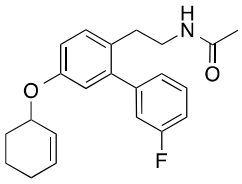
^{1}H-NMR (500 MHz, $CDCl_3$) 0.56:0.44 mixture of diastereomers δ 7.41-7.34 (m, 1H), 7.24-7.20 (m, 1H), 7.09−6.98 (m, 4H), 6.94-6.91 (m, 1H), 5.99-5.98 (m, 0.55H), 5.88-5.86 (m, 0.42H), 5.35 (br, s, 1H), 4.67 (m, 0.56H), 4.5-4.48 (m, 0.44H), 4.13-4.07 (m, 1.39H), 3.92-3.90 (m, 0.57H), 3.31-3.23 (m, 2H), 2.76-2.73 (m, 2H), 2.48-2.42 (m, 0.61H), 2.38-2.35 (m, 0.83H), 2.23 (m, 0.47H), 1.87 (s, 3H), 1.73 (m, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.20, 163.75, 161.79, 155.69, 155.13, 143.69, 142.39, 131.11, 130.13, 129.64, 125.15, 118.61, 118.44, 116.37, 103.12, 102.60, 75.09, 71.68, 71.38, 43.10, 41.99, 40.72, 32.19, 23.54. HRMS (ESI+), m/z [M+Na+] calcd for $C_{20}H_{22}FNO_4Na$ 382.1431; found 382.1419.

N-(2-(5-((5-(benzyloxy)tetrahydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 28



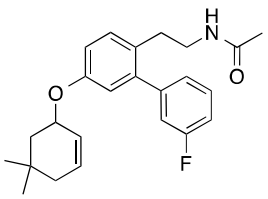
^{1}H-NMR (500 MHz, $CDCl_3$) 0.43:0.57 mixture of diastereomers δ 7.62-7.57 (m, 2H), 7.51-7.46 (m, 1H), 7.42−7.38 (m, 2H), 7.32-7.26 (m, 2H), 7.24-7.20 (m, 1H), 7.15-7.13 (m, 1H), 7.03-6.92 (m, 3H), 6.86-6.84 (m, 1H), 5.44 (t, J = 3 Hz, 0.43H), 5.37 (t, J = 2.6 Hz, 0.57H), 5.21 (br, s, 1H), 4.92 (m, 0.42H), 4.82 (m, 0.38H), 4.56-4.48 (m, 2H), 3.86 (dd, J_1 = 2 Hz, J_2 = 12 Hz, 0.44H), 3.69-3.59 (m, 1.55H), 3.53-3.47 (m, 1H), 3.20 (q, J = 5 Hz, 2H), 2.67 (t, J = 5 Hz, 2H), 2.04-1.75 (m, 4H), 1.8 (s, 3H), 1.22-1.11 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) 170.24, 163.72, 161.76, 155.74, 155.32, 143.72, 142.23, 138.64, 132.37, 132.29, 130.97, 128.84, 128.76, 128.71, 127.86, 125.15, 118.46, 116.29, 114.43, 96.17, 94.89, 72.38, 70.88, 63.47, 40.85, 40.76, 32.15, 28.95, 25.05, 23.48. HRMS (ESI+), m/z [M+Na+] calcd for $C_{28}H_{30}FNO_4Na$ 486.2057; found 486.2040.

N-(2-(5-(cyclohex-2-en-1-yloxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 29



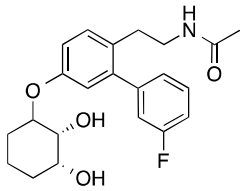
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.33-7.28 (m, 1H), 7.12 (d, J = 5 Hz, 1H), 7.01−6.92 (m, 4H), 6.84 (d, J = 5 Hz, 1H), 6.62 (d, J = 5 Hz, 1H), 6.71 (d, J = 5 Hz, 1H), 5.92-5.89 (m, 1H), 5.81-5.78 (m, 1H), 5.23 (br, s, 1H), 4.72 (br, s, 1H), 3.20 (q, J = 3 Hz, 2H), 2.66 (t, J = 3 Hz, 2H), 2.10-2.03 (m, 1H), 1.99-1.71 (m, 4H), 1.80 (s, 3H), 1.60-1.54 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.8, 163.4, 161.5, 156.2, 143.6, 142.0, 132.3, 130.8, 129.8, 128.0, 126.1, 124.8, 117.3, 116.1, 115.4, 114.1, 70.9, 40.5, 31.8, 28.3, 25.0, 23.3, 18.9. HRMS (ESI+), m/z [M+Na+] calcd for $C_{22}H_{24}FNO_2Na$ 376.1689; found 376.1639.

N-(2-(5-((5,5-dimethylcyclohex-2-en-1-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 30



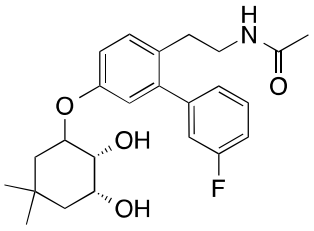
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.41-7.36 (m, 1H), 7.20 (d, J = 5 Hz, 1H), 7.10−7.00 (m, 3H), 6.90-6.87 (m, 1H), 6.77-6.75 (m, 1H), 5.85 (s, 2H), 5.35(br, s, 1H), 4.86 (br, s, 1H), 3.29 (q, J = 3 Hz, 2H), 2.74 (t, J = 3 Hz, 2H), 2.05-1.89 (m, 3H), 1.87 (s, 3H), 1.64-1.59 (m, 1H), 1.28-1.26 (m, 1H), 1.04 (s, 3H), 0.99 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.8, 161.5, 156.3, 142.0, 133.2, 130.8, 130.4, 129.8, 128.0, 126.9, 124.8, 124.7, 117.2, 116.1, 115.3, 114.1, 70.1, 40.5, 36.0, 33.8, 31.8, 23.8, 23.3, 21.5. HRMS (ESI+), m/z [M+Na+] calcd for $C_{24}H_{28}FNO_2Na$ 404.2002; found 404.2000.

N-(2-(5-(((2R,3R)-2,3-dihydroxycyclohexyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 31



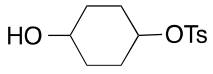
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34-7.30 (m, 1H), 7.13 (d, J = 5 Hz, 1H), 7.02−6.84 (m, 4H), 6.72 (d, J = 5 Hz, 1H), 5.71 (br, s, 1H), 4.41-4.36 (m, 1H), 4.12 (br, s, 1H), 3.70-3.67 (m, 1H), 3.20 (q, J = 3 Hz, 2H), 2.66 (t, J = 3 Hz, 2H), 2.24 (m, 1H), 2.33 (br, s, 1H), 2.18 (br, s, 1H), 2.08-2.04 (m, 1H), 1.88-1.84 (m, 1H), 1.80 (s, 3H), 1.68-1.63 (m, 2H), 1.51-1.42 (m, 2H), 1.28-1.26 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.8, 163.5, 161.5, 156.1, 143.3, 142.1, 130.9, 129.8, 128.8, 124.8, 117.5, 116.1, 115.6, 114.1, 74.5, 79.4, 40.4, 31.9, 29.9, 28.3, 23.3, 18.2. HRMS (ESI+), m/z [M+Na+] calcd for $C_{22}H_{26}FNO_4Na$ 410.1744; found 410.1726.

N-(2-(5-(((2R,3R)-2,3-dihydroxy-5,5-dimethylcyclohexyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 32



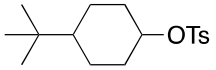
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.41-7.36 (m, 1H), 7.20 (d, J = 5 Hz, 1H), 7.09−6.98 (m, 3H), 6.92-6.89 (m, 1H), 6.79 (m, 1H), 5.39 (br, s, 1H), 4.66-4.60(m, 1H), 4.23-4.20 (m, 1H), 3.78-3.76 (m, 1H), 3.28 (q, J = 3 Hz, 2H), 2.73 (t, J = 3 Hz, 2H), 2.84-2.28 (br, s, 2H), 1.92-1.71 (m, 2H), 1.87 (s, 3H), 1.47-1.33 (m, 2H), 1.18 (s, 3H), 0.99 (s, 3H), 0.99 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 23.54, 32.17, 32.34, 32.36, 40.76, 40.79, 41.14, 41.90, 69.69, 75.66, 114.55, 115.28, 116.42, 117.99, 125.09, 128.98, 130.21, 131.19, 142.47, 143.69, 156.39, 161.80, 163.77, 170.23. HRMS (ESI+), m/z [M+Na+] calcd for $C_{24}H_{30}FNO_4Na$ 438.2057; found 438.2093.

4-hydroxycyclohexyl 4-methylbenzenesulfonate



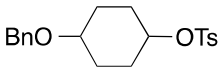
The detailed synthesis and compound characterization of the title compound is described in reference 30

4-(*tert*-butyl)cyclohexyl 4-methylbenzenesulfonate



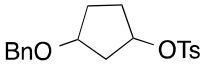
The detailed synthesis and compound characterization of the title compound is described in reference 32

4-(benzyloxy)cyclohexyl 4-methylbenzenesulfonate



The detailed synthesis and compound characterization of the title compound is described in reference 31

3-(benzyloxy)cyclopentyl 4-methylbenzenesulfonate

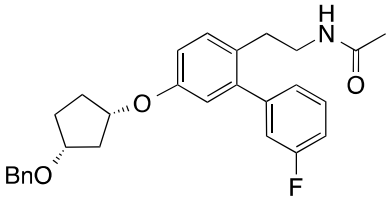


The detailed synthesis and compound characterization of the title compound is described in reference 33

Representative procedure for S_N2 coupling:

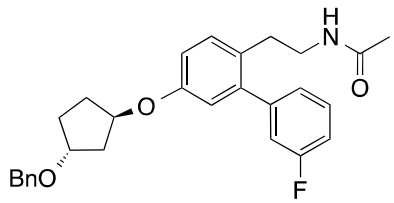
To a solution of aglycone **24** (50 mg, 0.16 mmol) in DMF (1 mL) was added potassium carbonate (27 mg, 0.19 mmol), 3-(benzyloxy)cyclopentyl 4-methylbenzenesulfonate (70 mg, 0.2 mmol) and TBAI (7 mg, 0.016 mmol). The resulting mixture was heated to 90 °C for 10 h. Upon cooling to r.t., distilled water (5 mL) was added and the organic layer extracted into ethyl acetate (2x5mL). The organic layer was concentrated and the cis and trans isomers were separated by column chromatography (SiO_2, 40% EtOAc/hexanes):

N-(2-(5-(((1S,3R)-3-(benzyloxy)cyclopentyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 33



^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.39-7.18 (m, 6H), 7.11 (d, J = 5 Hz, 1H), 6.98−6.91 (m, 2H), 6.79 (d, J = 5 Hz, 1H), 6.66 (s, 1H), 5.30 (br, s, 1H), 4.62 (m, 1H), 4.42 (s, 2H), 3.95 (m, 1H), 3.19 (q, J = 3 Hz, 2H), 2.65 (t, J = 3 Hz, 2H), 2.27 (dt, J = 2.3 Hz, 1H), 1.98-1.95 (m, 1H), 1.92-1.81 (m, 5H), 1.79 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.9, 163.5, 161.5, 156.4, 143.7, 141.9, 138.6, 130.7, 129.8, 128.3, 127.4, 124.8, 117.0, 116.2, 115.1, 113.9, 78.8, 70.9, 40.5, 38.8, 31.8, 30.7, 23.3. HRMS (ESI+), m/z [M+Na+] calcd for $C_{28}H_{30}FNO_3Na$ 470.2108; found 470.2074.

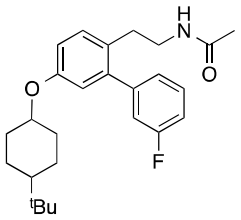
N-(2-(5-(((1R,3R)-3-(benzyloxy)cyclopentyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 34



^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34-7.26 (m, 4H), 7.23-7.19 (m, 2H), 7.12 (d, J = 5Hz, 1H), 7.02−6.92 (m, 2H), 6.77 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1H), 6.65 (d, J = 2 Hz, 1H), 5.22 (br, s, 1H), 4.82 (m, 1H), 4.46-4.39 (m, 2H), 4.16-4.14 (m, 1H), 3.22 (q, J = 5 Hz, 2H), 2.66 (t, J = 5 Hz, 2H), 2.14-1.93 (m, 4H), 1.83-1.77 (m, 2H), 1.80 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.12, 163.77, 161.81, 156.54, 143.91, 142.29, 138.82, 131.06, 128.68, 128.16, 127.90,

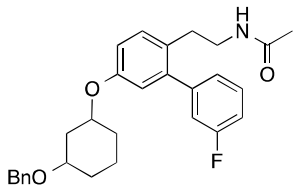
127.83, 125.14, 117.29, 116.47, 116.30, 115.25, 114.47, 114.30, 79.74, 78.12, 71.26, 40.80, 40.12, 30.74, 30.47, 23.58. HRMS (ESI+), m/z [M+Na+] calcd for $C_{28}H_{30}FNO_3Na$ 470.2108; found 470.2061.

***N*-(2-(5-((4-(*tert*-butyl)cyclohexyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 35**



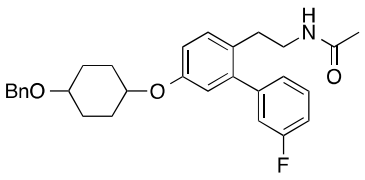
^{1}H-NMR (500 MHz, $CDCl_3$) 0.79:0.21 mixture of diastereomers δ 7.44-7.31 (m, 2H), 7.19 (d, J = 5 Hz, 1H), 7.09-7.03 (m, 2H), 7.03-6.95 (m, 1H), 6.89 (dd, J_1 = 2.7 Hz, J_2 = 8.5 Hz, 1H), 6.77 (d J = 2.8 Hz), 5.27 (br, s, 0.86H), 5.07 (s, 0.23H), 4.52 (s, 0.79H), 4.32 (d, J = 5.5 Hz, 0.21H), 3.28 (q, J = 3 Hz, 2H), 2.73 (t, J = 3 Hz, 2H), 2.12-2.09 (m 2H), 1.86 (s, 3H), 1.57-1.38 (m, 5H), 1.10-1.01 (m, 1H), 0.87 (s, 9H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.8, 163.4, 161.5, 156.1, 143.7, 141.9, 130.7, 129.7, 128.6, 127.7, 124.9, 117.7, 116.2, 116.0, 115.5, 113.9, 71.4, 47.7, 40.5, 32.5, 31.9, 30.3, 27.5, 23.3, 21.4. HRMS (ESI+), m/z [M+Na+] calcd for $C_{26}H_{34}FNO_2Na$ 434.2472; found 434.2445.

***N*-(2-(5-((3-(benzyloxy)cyclohexyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 36**



^{1}H-NMR (500 MHz, $CDCl_3$) 0.28:0.72 mixture of diastereomers δ 7.42-7.27 (m, 6H), 7.20 (d, J = 5 Hz, 1H), 7.09-7.00 (m, 3H), 6.89-6.86 (m, 1H), 6.78-6.74 (m, 1H), 5.25 (br, s, 1H), 4.61-4.56 (m, 0.32H), 4.51-4.41 (m, 2H), 4.10-4.02 (m, 0.81H), 3.81-3.75 (m, 0.28H), 3.37-3.29 (m, 0.75H), 3.19 (q, J = 3 Hz, 2H), 2.74 (t, J = 3 Hz, 2H), 2.52-2.45 (m, 0.78H), 2.07-2.00 (m, 1.44H), 1.96-1.86 (m, 0.61H), 1.83-1.72 (m, 4H), 1.64-1.52 (m, 2H), 1.40 (q, J = 11 Hz, 0.79H), 1.31-1.13 (m, 2.59H) ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.09, 163.78, 161.82, 156.25, 143.88, 142.34, 138.92, 131.11, 130.17, 128.69, 127.84, 125.15, 117.80, 116.49, 115.92, 114.49, 75.67, 75.01, 74.21, 73.16, 70.41, 70.34, 40.79, 38.79, 36.59, 32.17, 31.82, 23.60, 20.85.2 HRMS (ESI+), m/z [M+Na+] calcd for $C_{29}H_{32}FNO_3Na$ 484.2264; found 484.1877.

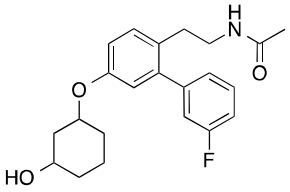
***N*-(2-(5-((4-(benzyloxy)cyclohexyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 37**



^{1}H NMR (500 MHz, $CDCl_3$) 0.46:0.54 mixture of diastereomers δ 7.32-7.25 (m, 5H), 7.50-7.46 (m, 1H), 7.11 (d, *J* = 5 Hz, 1H), 7.01-6.96 (m, 3H), 6.81-6.79 (dd, J_1 = 10 Hz, J_2 = 5 Hz, 1H), 6.68 (d, *J* = 5 Hz, 1H), 5.29 (br, s, 1H), 4.48 (s, 2H), 4.35 (m, 0.46H), 4.30 (m, 0.54H) 3.45-3.41 (m, 1H), 3.19 (q, *J* = 6.7 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.07-1.97 (m, 4H), 1.79 (s, 1H), 1.52-1.49 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 163.4, 161.5, 156.1, 155.9,

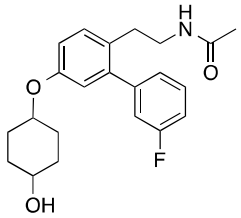
143.6, 142.0, 139.0, 132.1, 131.9 130.8, 129,8, 128.5, 128.3, 128.1, 127.4, 124.8, 117.5, 116.2, 116.0, 115.6, 114.2, 114.0, 75.4, 74.5, 72.8, 70.1, 69.7, 40.5, 31.8, 30.9, 28.4, 27.4, 23.3. HRMS (ESI+), m/z [M+Na+] calcd for $C_{29}H_{32}FNO_3Na$ 484.2264; found 484.2249.

***N*-(2-(3'-fluoro-5-((3-hydroxycyclohexyl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 38**

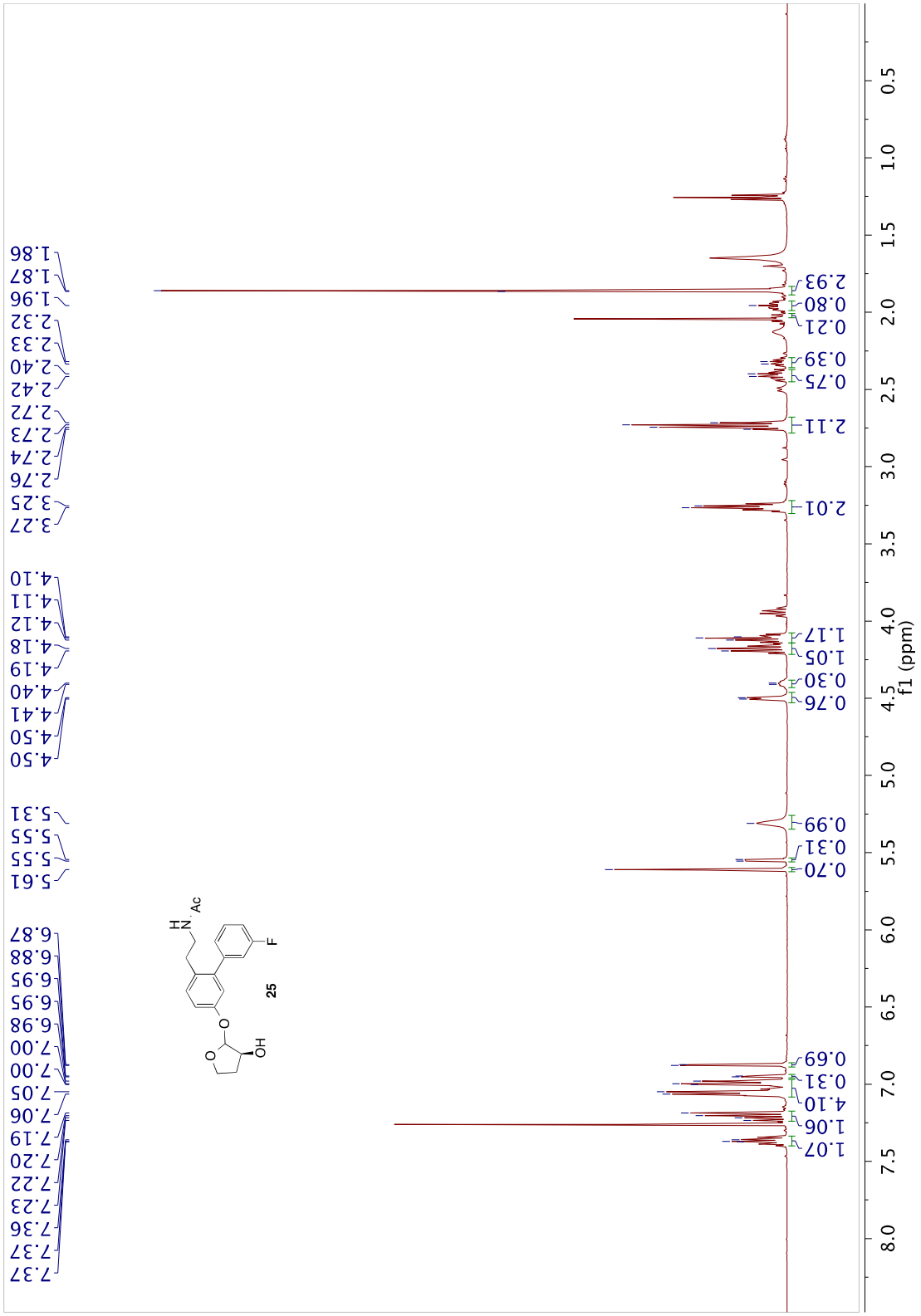


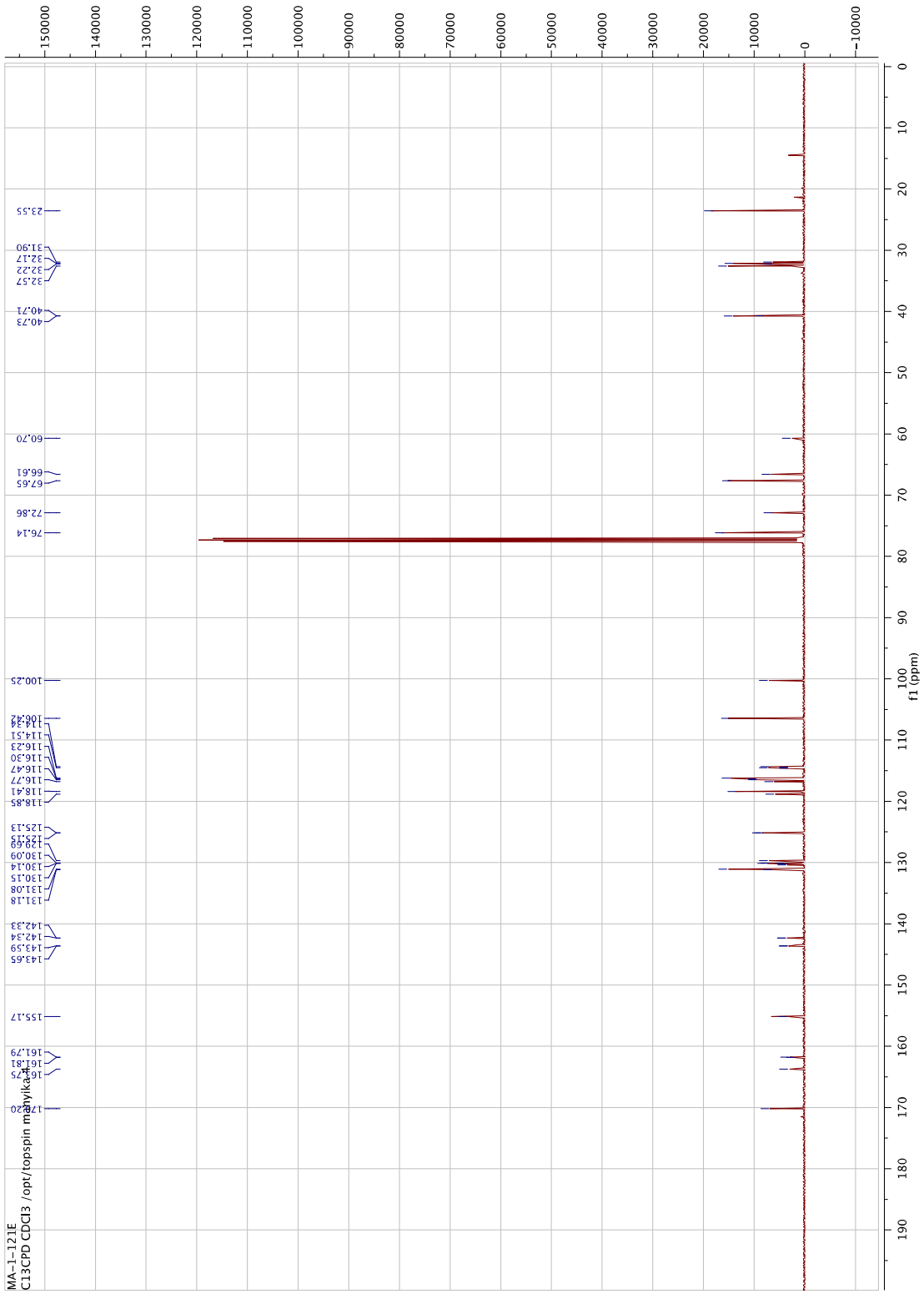
^{1}H-NMR (500 MHz, $CDCl_3$) 0.49:0.51 mixture of diastereomers δ 7.41-7.36 (m, 1H), 7.21-7.7.19 (m, 1H), 7.09-7.05 (m, 2H), 7.02-6.99 (m, 1H), 6.90-6.88 (m, 1H), 6.77-6.76 (m, 1H), 5.30 (br, s, 1H), 4.67 (s, 0.49H), 4.36-4.31 (m, 1H), 4.16-4.12 (m, 0.51H), 3.82-3.77 (m, 1H), 3.28 (q, *J* = 5 Hz, 2H), 2.73 (t, *J* = 5 Hz, 2H), 2.31-2.26 (m, 1H), 2.13-2.05 (m, 1H), 1.99-1.85 (2 H), 1.88 (s, 3H), 1.78-1.52 (m, 4H), 1.48-1.40 (m, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 19.30, 23.58, 30.24, 30.77, 32.17, 34.49, 39.11, 40.78, 67.15, 68.60, 72.99, 74.70, 114.36, 114.53, 115.93, 116.47, 117.75, 125.14, 128.84, 130.19, 131.16, 142.40, 143.73, 156.15, 161.81, 163.77, 170.14. HRMS (ESI+), m/z [M+Na+] calcd for $C_{22}H_{26}FNO_3Na$ 394.1795; found 394.1771.

N-(2-(3'-fluoro-5-((4-hydroxycyclohexyl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)acetamide, 39



^{1}H-NMR (500 MHz, $CDCl_3$) 0.49:0.51 mixture of diastereomers δ 7.41-7.37 (m, 1H), 7.21-7.7.19 (m, 1H), 7.09-7.05 (m, 2H), 7.02-7.00 (m, 1H), 6.91-6.87 (m, 1H), 6.78-6.75 (m, 1H), 5.32 (br, s, 1H), 4.41-4.39 (m, 1H), 4.29-4.25 (m, 1H), 3.83-3.78 (m, 1H), 3.29 (q, *J* = 5 Hz, 2H), 2.74 (t, *J* = 5 Hz, 2H), 2.15-2.01 (m, 3H), 1.88 (s, 3H), 1.78-1.54 (m, 4H), 1.48-1.41 (m, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.14, 163.77, 161.81, 156.34, 143.91, 142.34, 131.10, 130.17, 128.48, 125.14, 117.81, 116.47, 115.81, 114.49, 114.32, 74.85, 69.29, 40.80, 32.27, 30.61, 28.83, 27.78, 23.57. HRMS (ESI+), m/z [M+Na+] calcd for $C_{22}H_{26}FNO_3Na$ 394.1795; found 394.1767.


1.86
1.87
1.96
2.32
2.33
2.40
2.42
2.72
2.73
2.74
2.76
3.25
3.27
4.10
4.11
4.12
4.18
4.19
4.40
4.41
4.50
4.50
5.31
5.55
5.55
5.61
6.87
6.88
6.95
6.95
6.98
7.00
7.00
7.05
7.06
7.19
7.20
7.22
7.23
7.36
7.37
7.37
0.69
0.31
4.10
1.06
1.07
0.99
0.31
0.70
0.76
0.30
1.05
1.17
2.01
2.11
0.75
0.39
0.21
0.80
2.93
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)
H
N
Ac
F
O
O
OH
25


MA-1-121E
C13CPD CDCl3 /opt/topspin manyika 1
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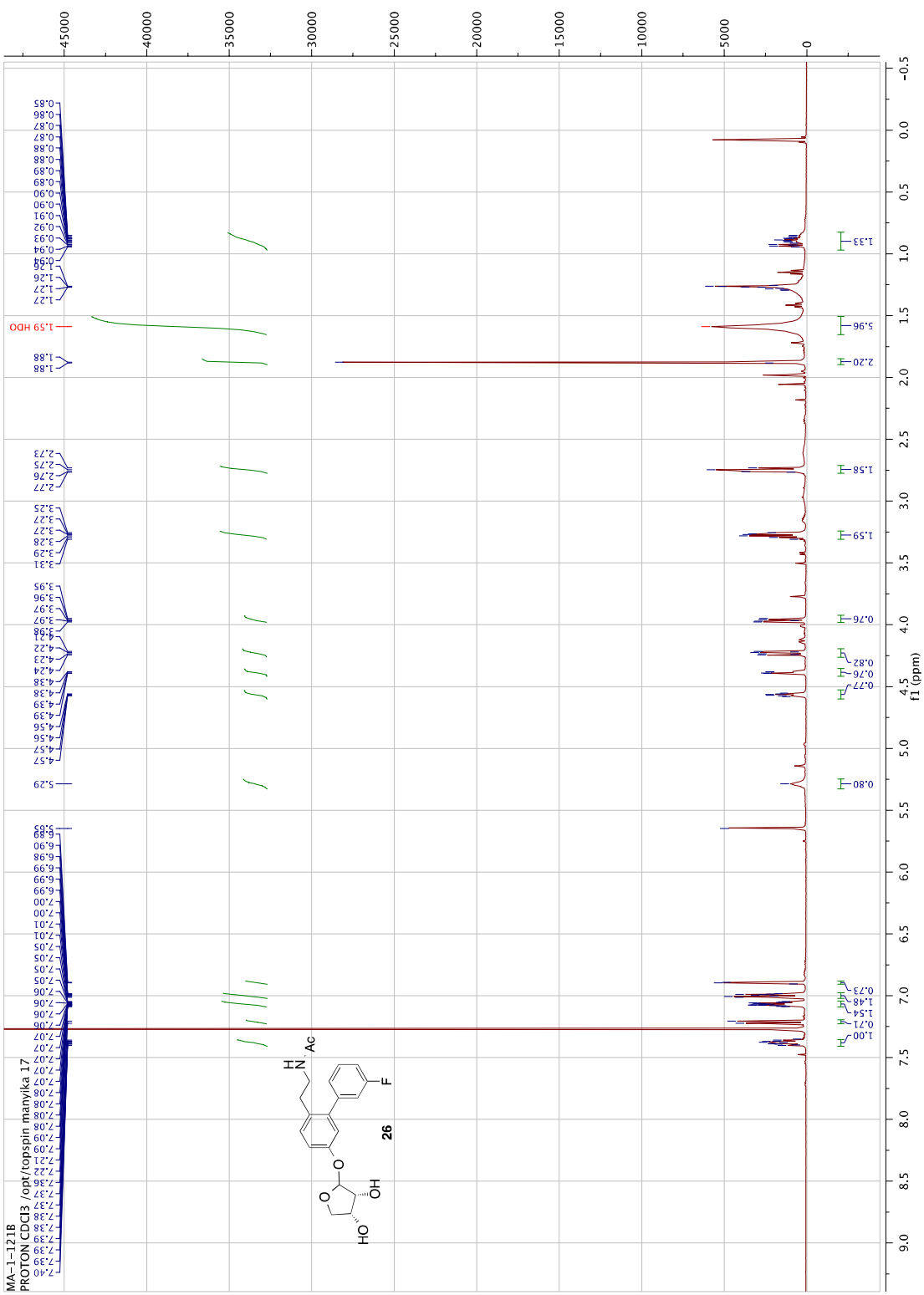
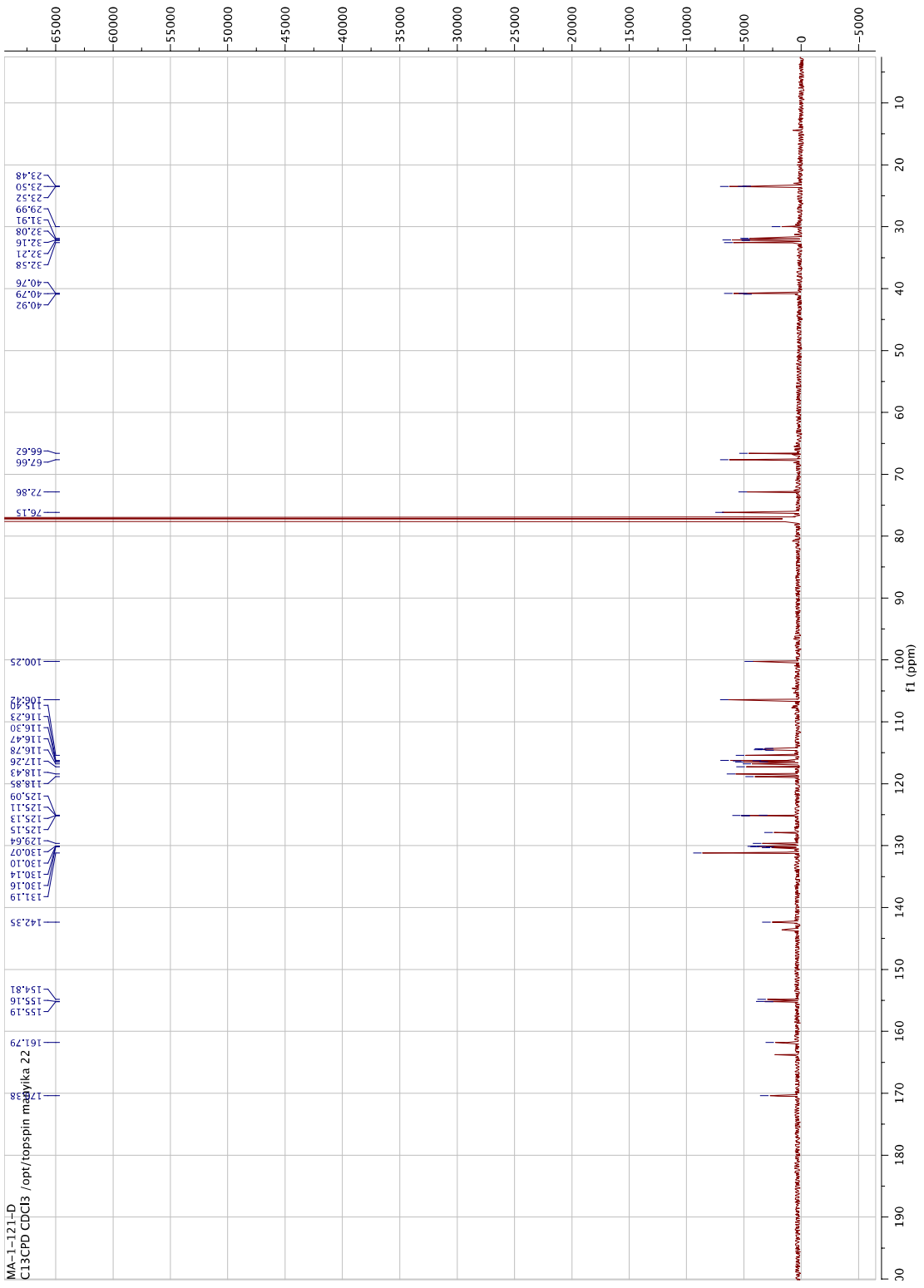
32.17
32.22
32.57
40.71
40.73
60.70
66.61
67.65
72.86
76.14
100.25
106.42
114.34
114.51
116.23
116.30
116.47
116.77
118.41
118.85
125.13
125.75
129.69
130.09
130.14
130.15
131.08
131.18
142.33
142.34
143.59
143.65
155.17
161.79
161.81
162.75
172.20
f1 (ppm)


MA-1-121B
PROTON CDCl3 /opt/topspin manyika 17
26
f1 (ppm)


MA-1-121-D
C13CPD CDCl3 /opt/topspin mavyka 22
f1 (ppm)
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23.50
23.52
29.99
31.91
32.08
32.16
32.21
32.58
40.76
40.79
40.92
66.62
67.66
72.86
76.15
100.25
106.42
115.40
116.23
116.30
116.47
116.78
117.26
118.43
118.85
125.09
125.11
125.13
125.15
129.64
130.07
130.10
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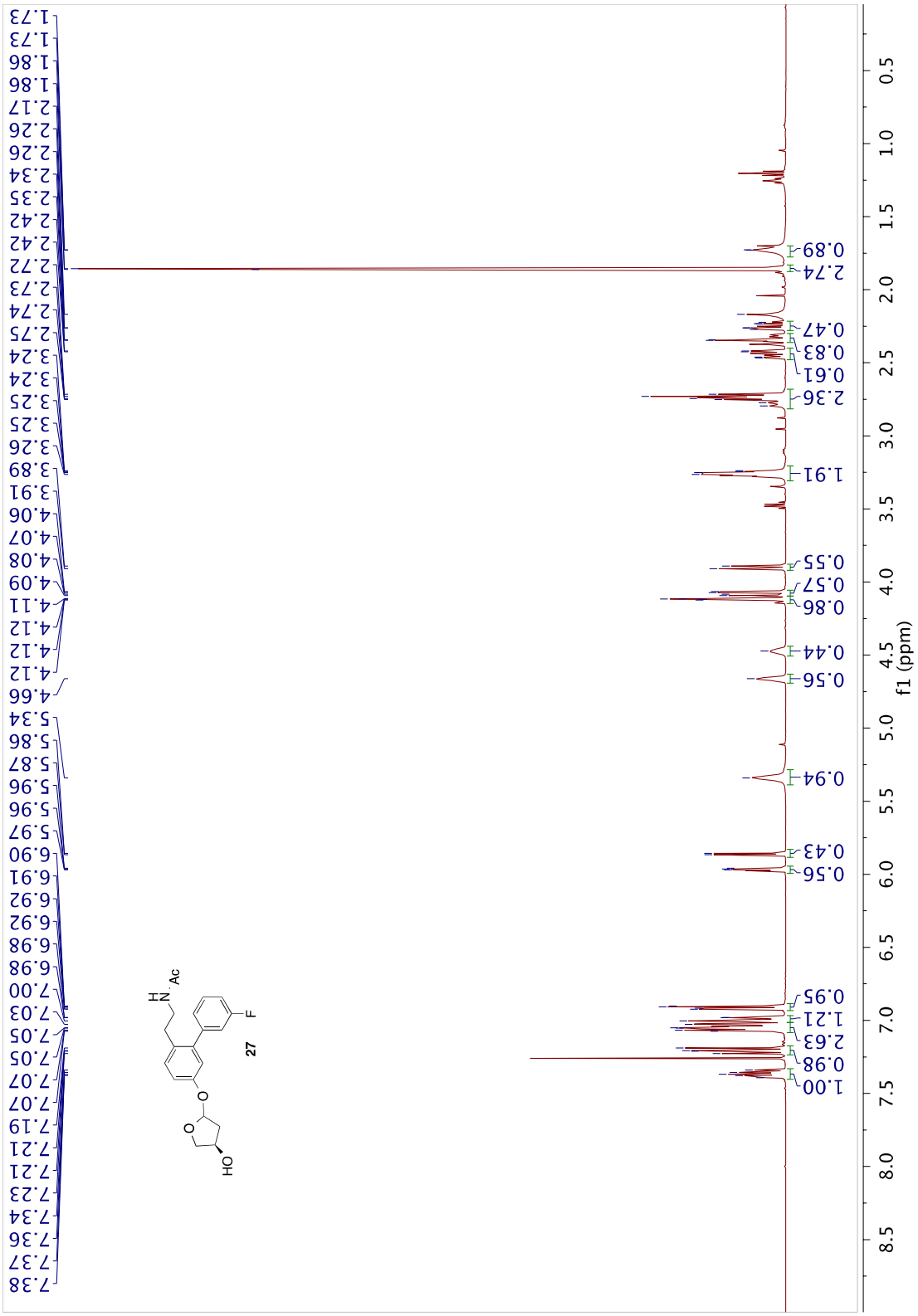
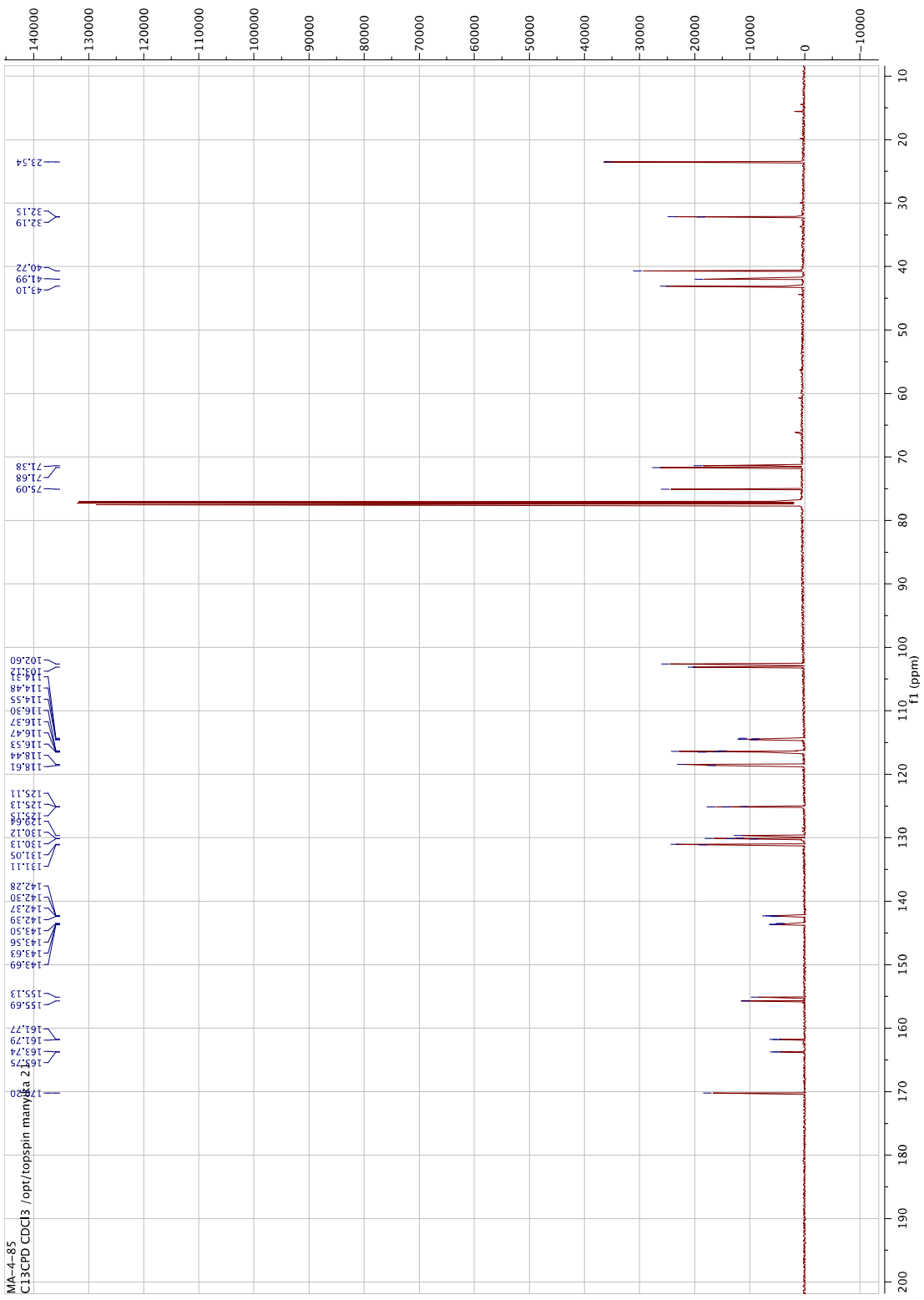
142.35
154.81
155.16
155.19
161.79
172.38


f1 (ppm)
27


MA-4-85
C13CPD CDCl3 /opt/topspin manyata 2
f1 (ppm)
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40.72
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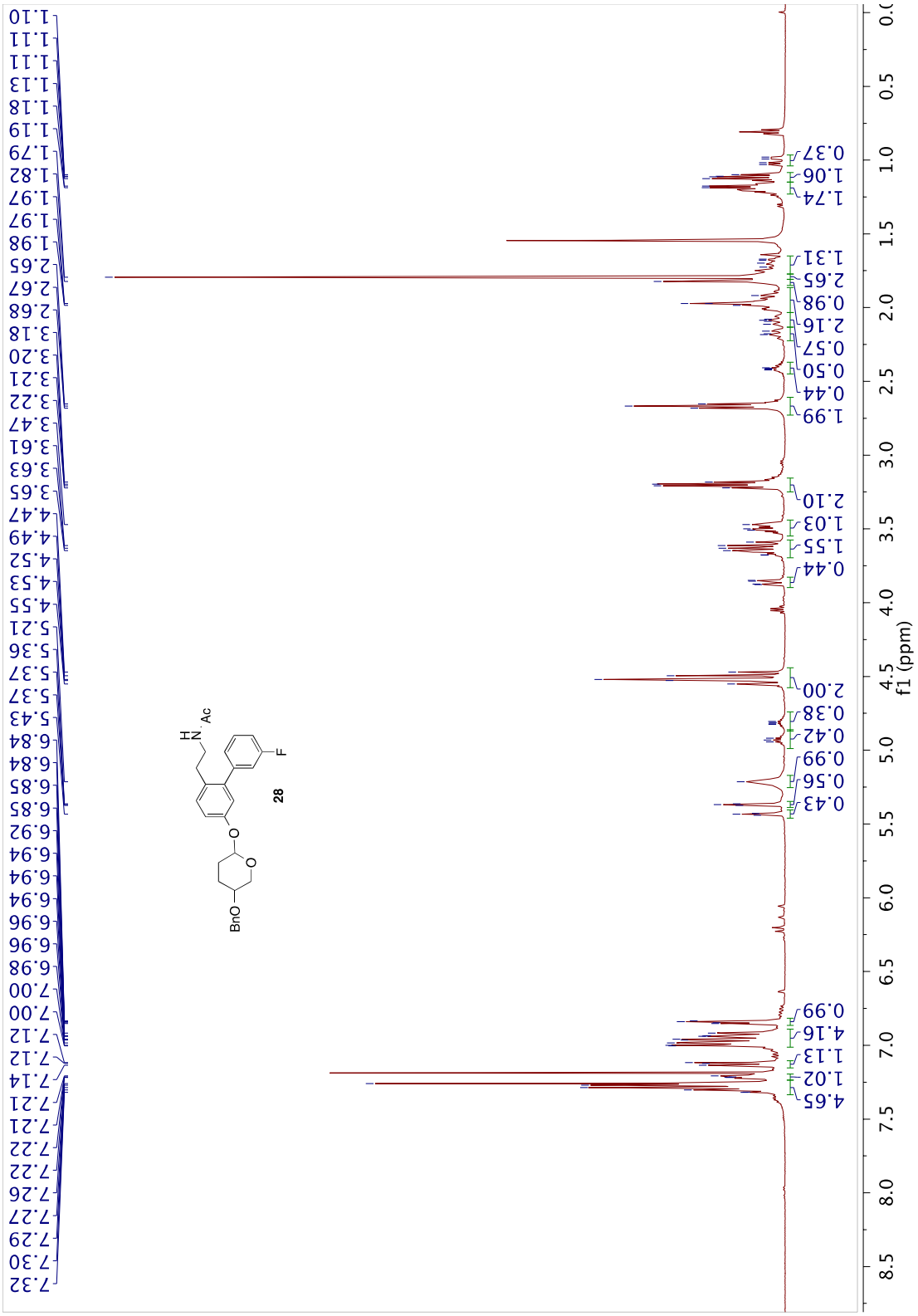
71.38
71.68
75.09
102.60
105.12
114.31
114.48
114.55
116.30
116.37
116.47
116.53
118.44
118.61
125.11
125.13
128.64
128.75
130.12
130.13
131.05
131.11
142.28
142.30
142.37
142.59
143.50
143.56
143.63
143.69
155.13
155.69
161.77
161.79
163.74
163.75
172.80


f1 (ppm)
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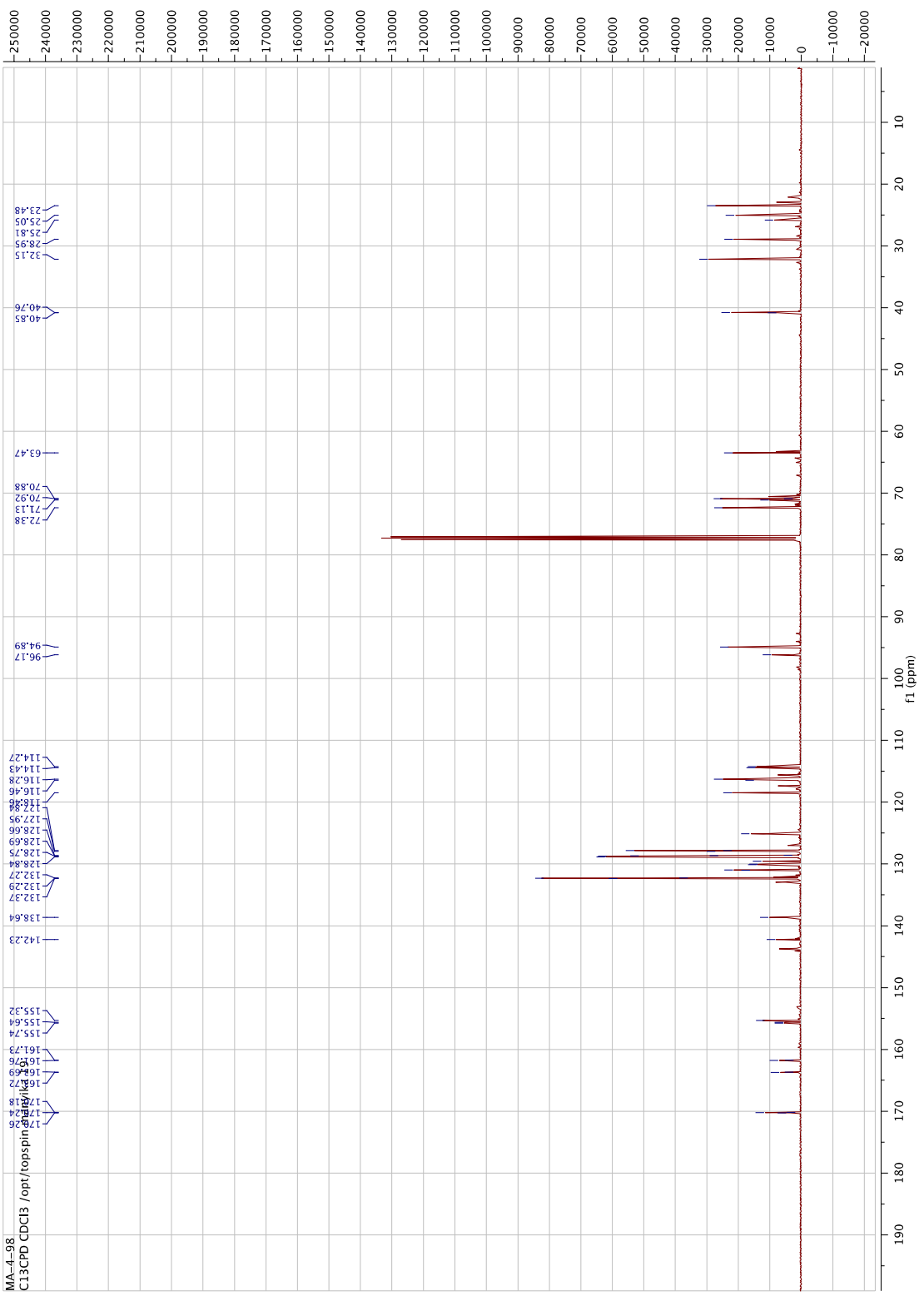
O
O
H
N
Ac
F


MA-4-98
C13CPD CDCl3 /opt/topspin4pl6/data/MA
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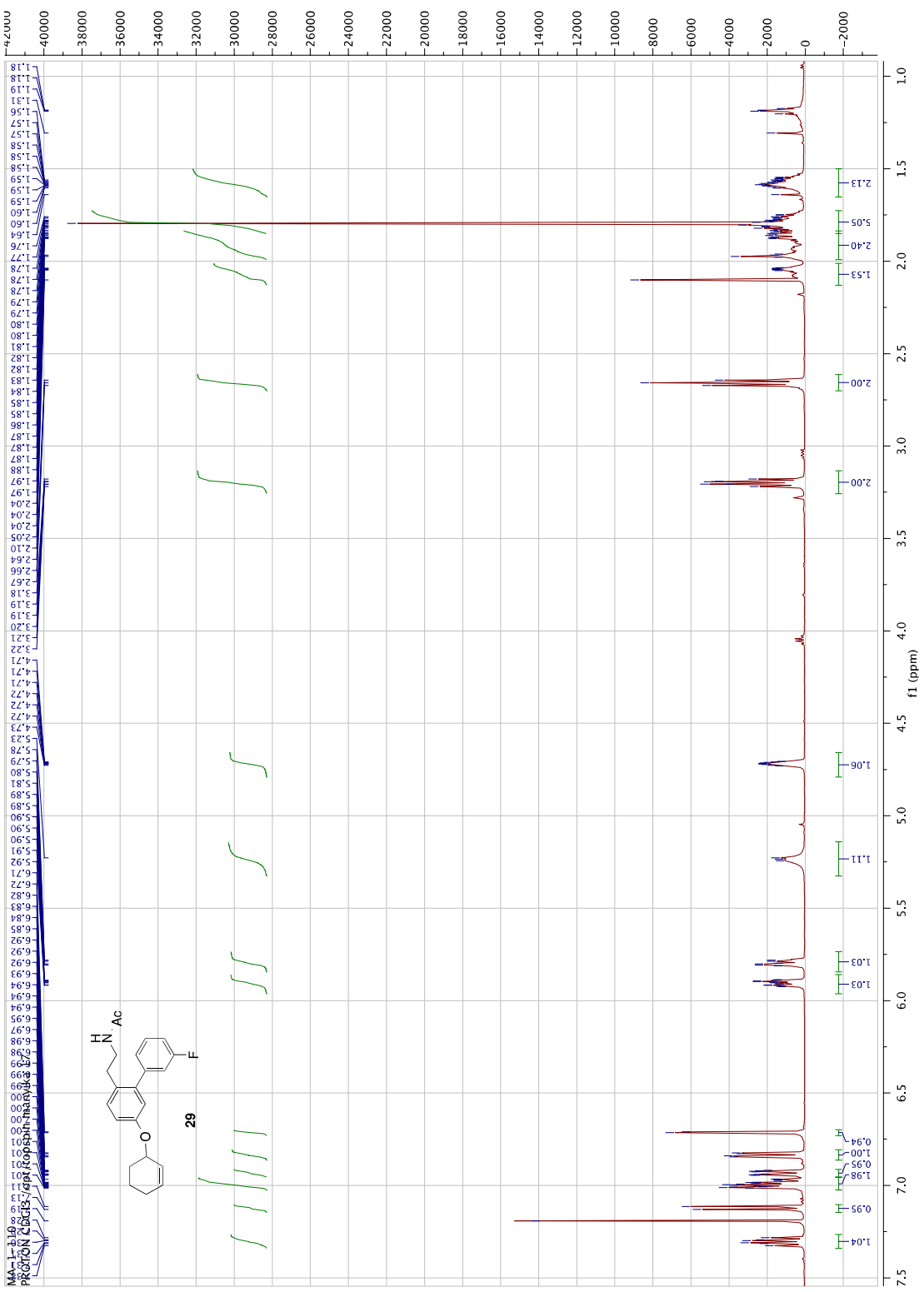
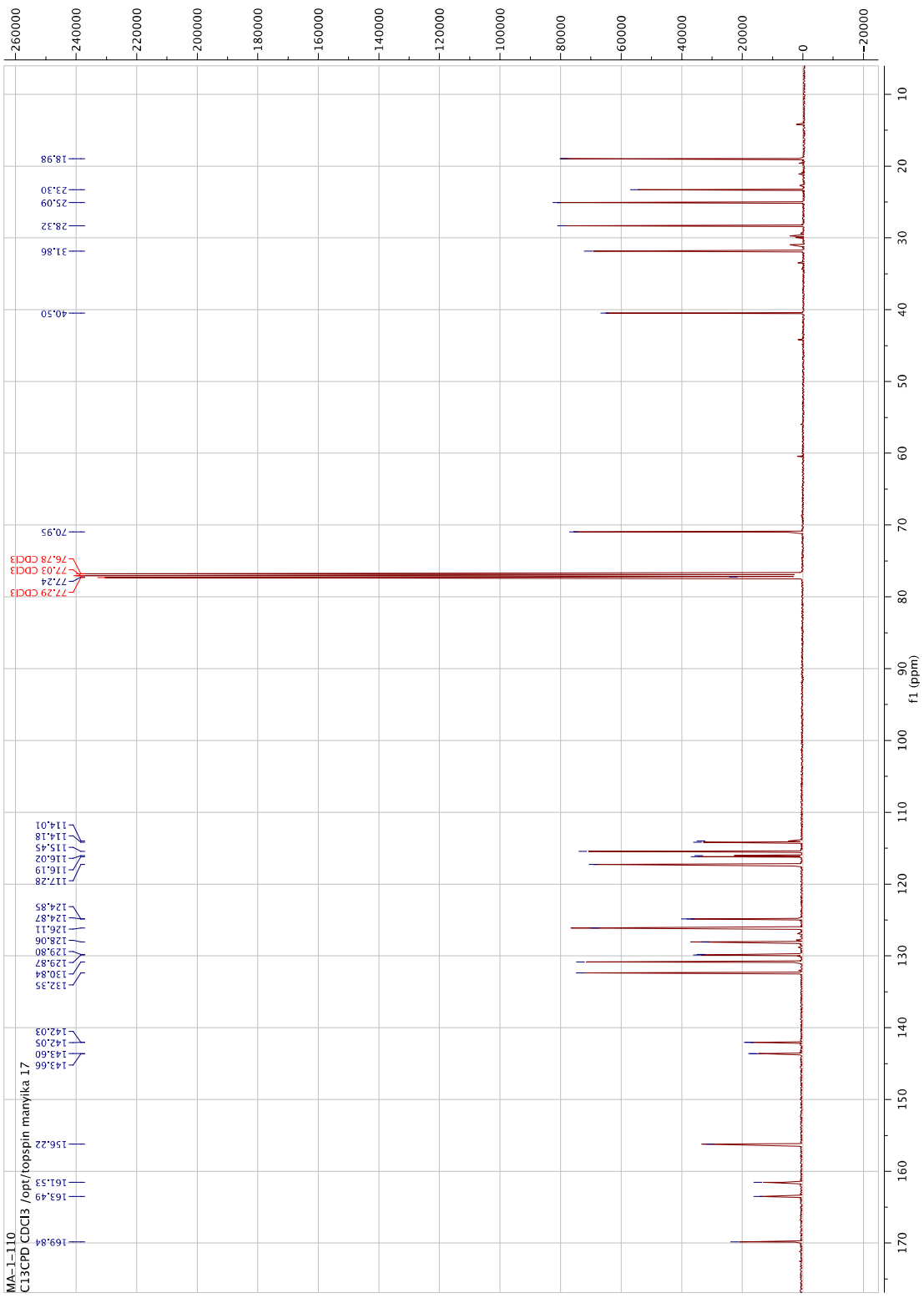
25.81
28.95
32.15
40.76
40.85
63.47
70.88
70.92
71.13
72.38
94.89
96.17
114.27
114.43
116.28
116.46
127.84
127.95
128.66
128.69
128.75
128.84
132.27
132.29
132.37
138.64
142.23
155.32
155.64
155.74
161.73
162.76
168.69
169.72
172.18
172.24
172.26
f1 (ppm)


29
f1 (ppm)


MA-1-110
C13CPD CDCl3 /opt/topspin manyika 17
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23.30
25.09
28.32
31.86
40.50
70.95
76.78 CDCl3
77.03 CDCl3
77.24
77.29 CDCl3
114.01
114.18
115.45
116.02
116.19
117.28
124.85
124.87
126.11
128.06
129.80
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130.84
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142.03
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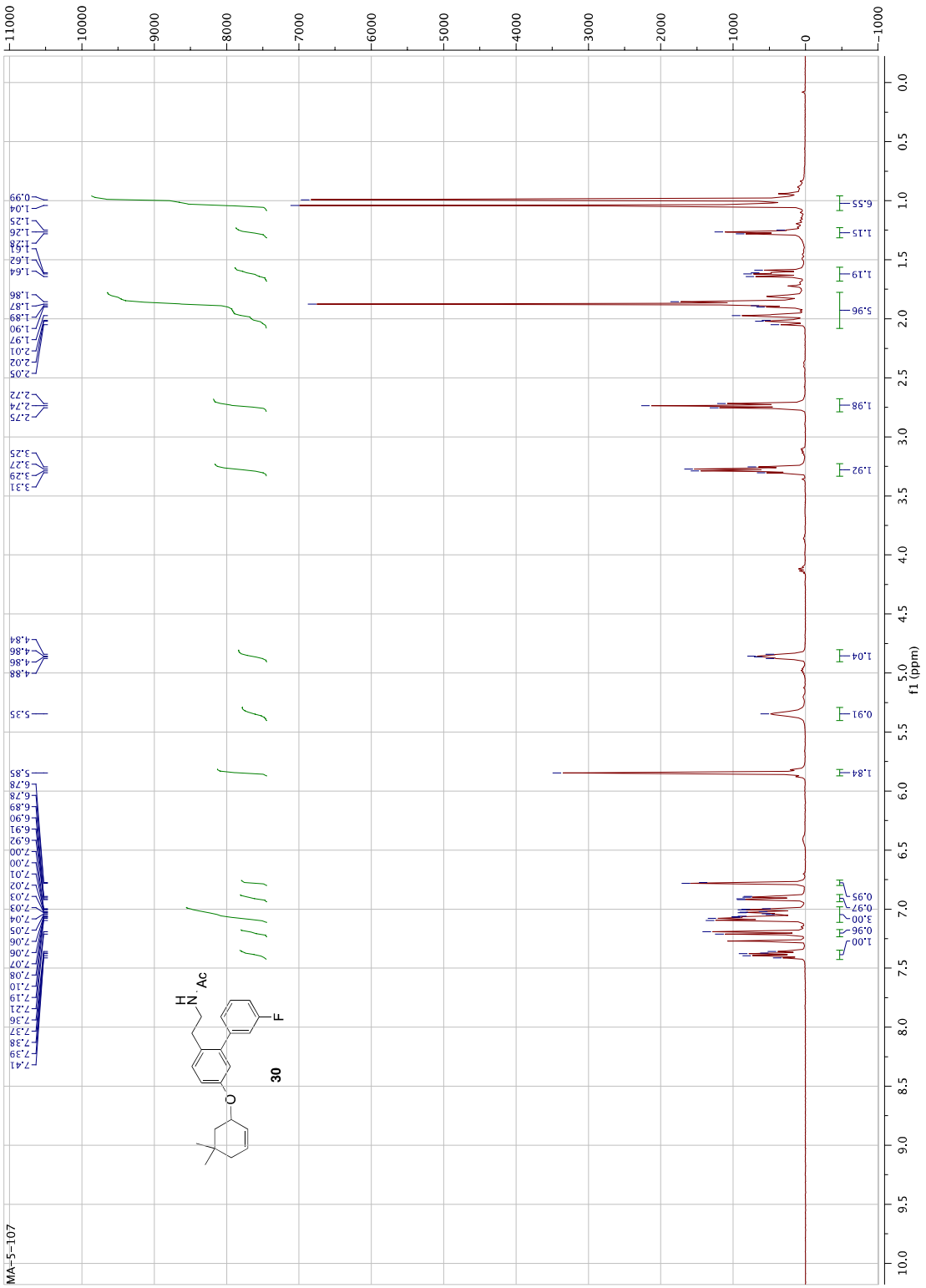
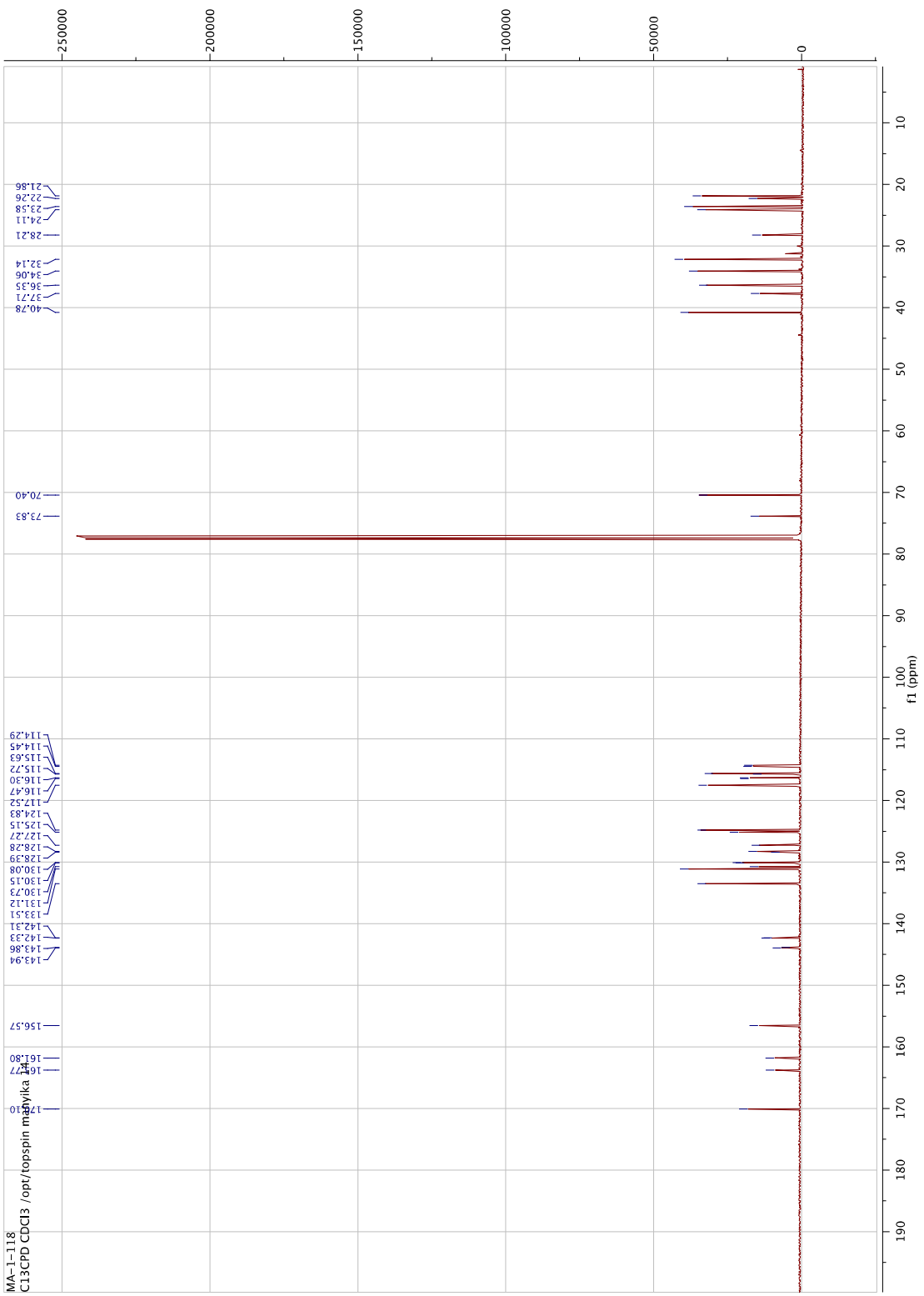
143.60
143.66
156.22
161.53
163.49
169.84


MA-5-107
30
f1 (ppm)


MA-1-118
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50000
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22.26
23.58
24.11
28.21
32.14
34.06
36.35
37.71
40.78
70.40
73.83
114.29
114.45
115.63
115.72
116.30
116.47
117.52
124.83
125.15
127.27
128.28
128.39
130.08
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131.12
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142.33
143.86
143.94
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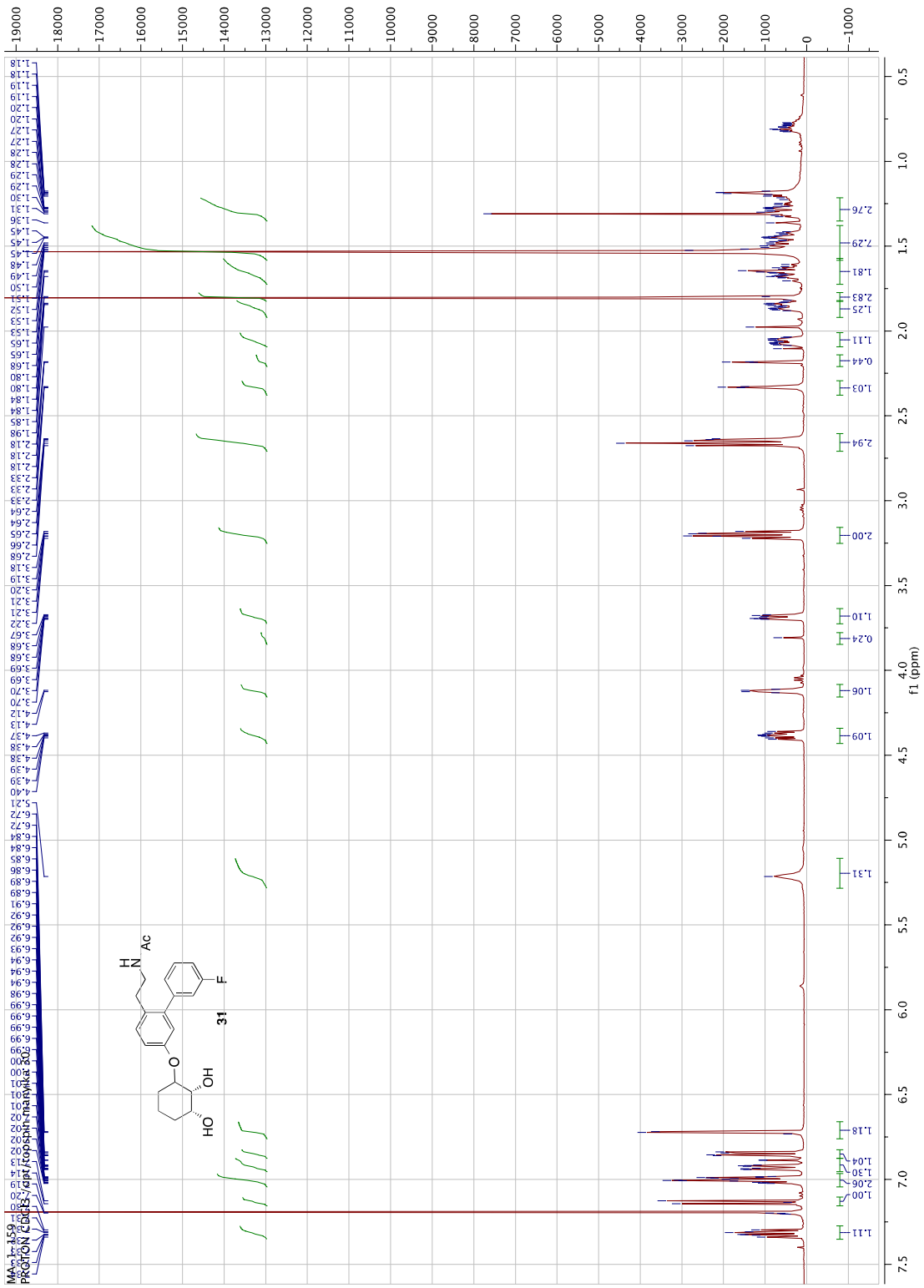
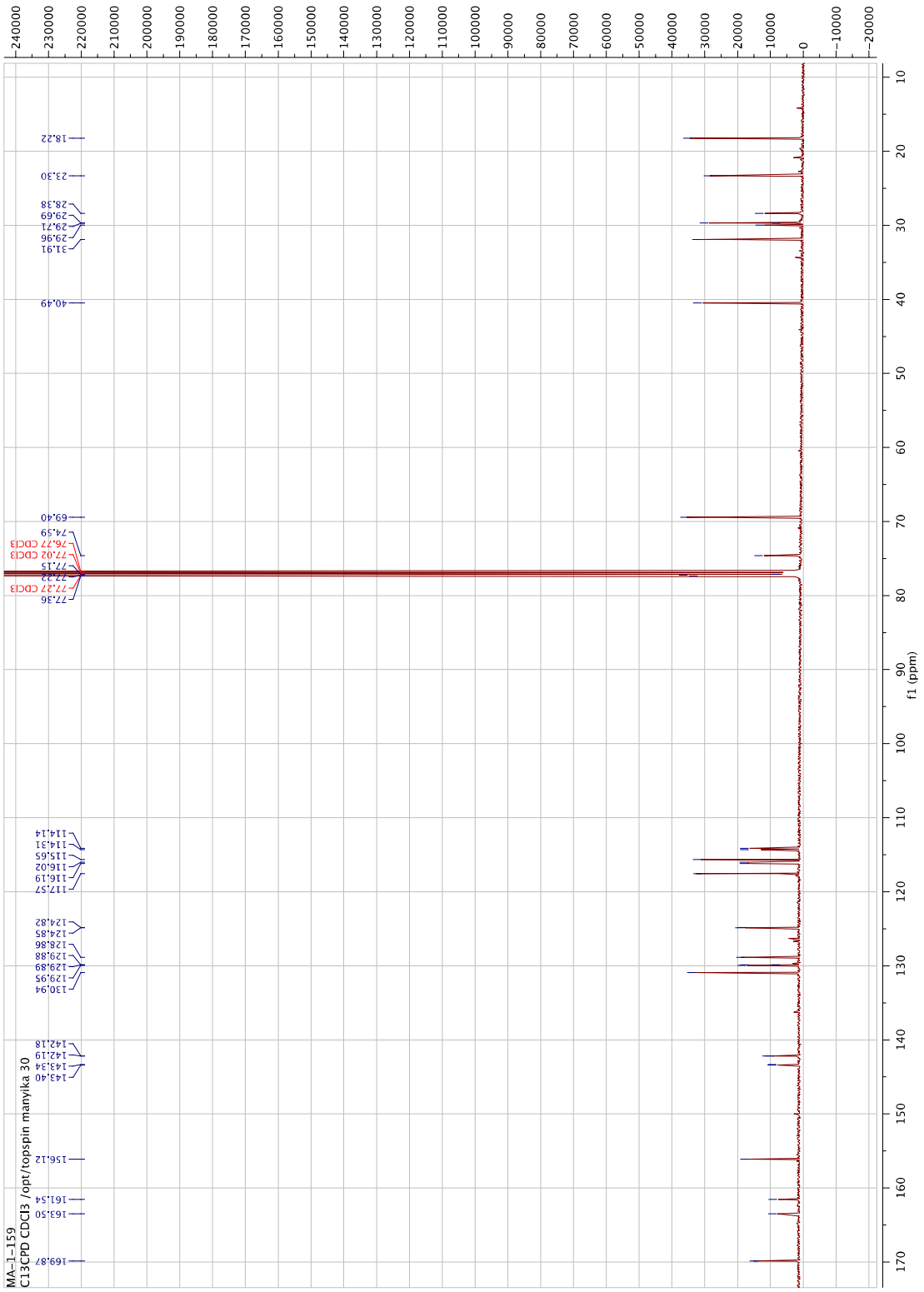
161.80
161.77
170.10


f1 (ppm)
31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C13CPD CDCl3 /opt/topspin manyika 30
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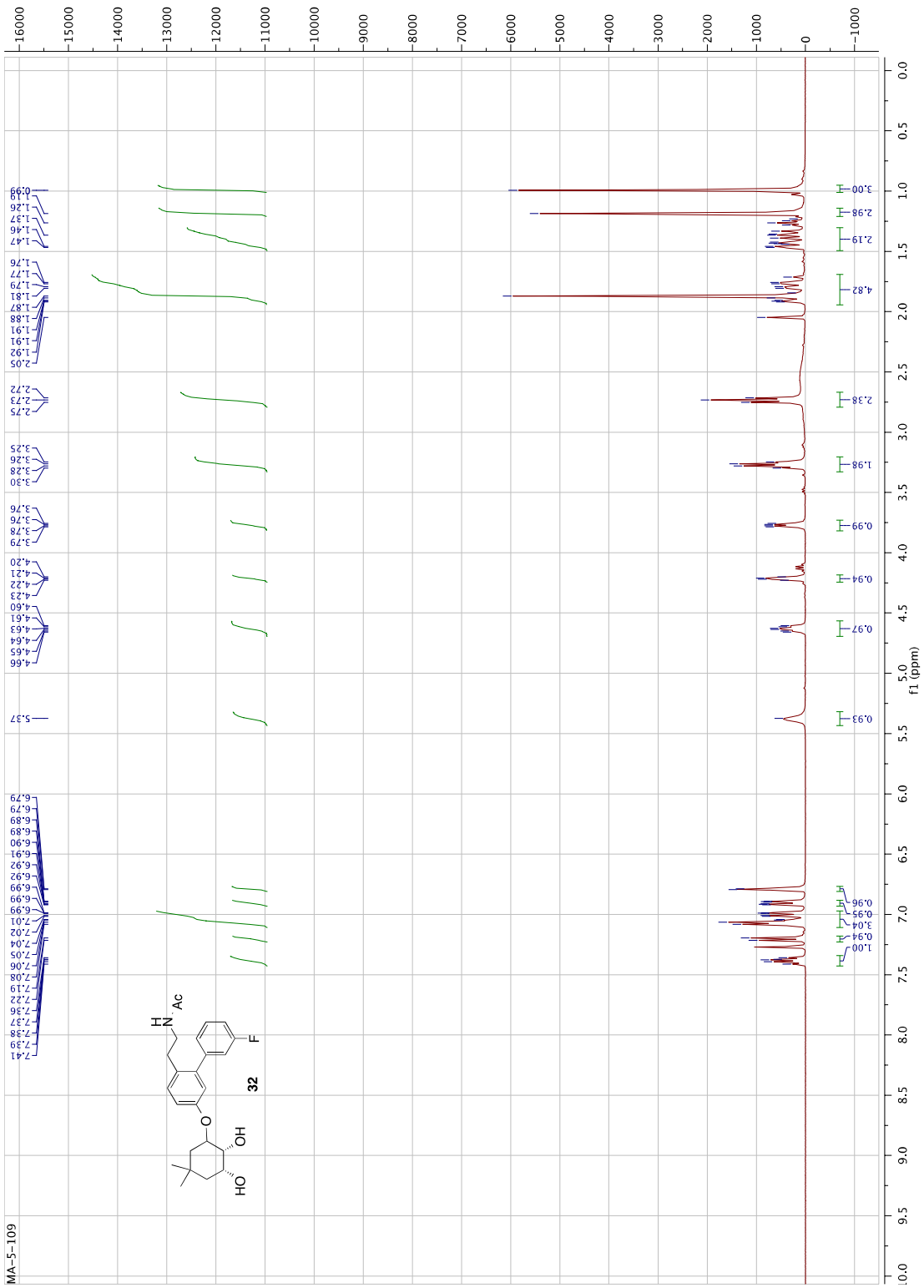
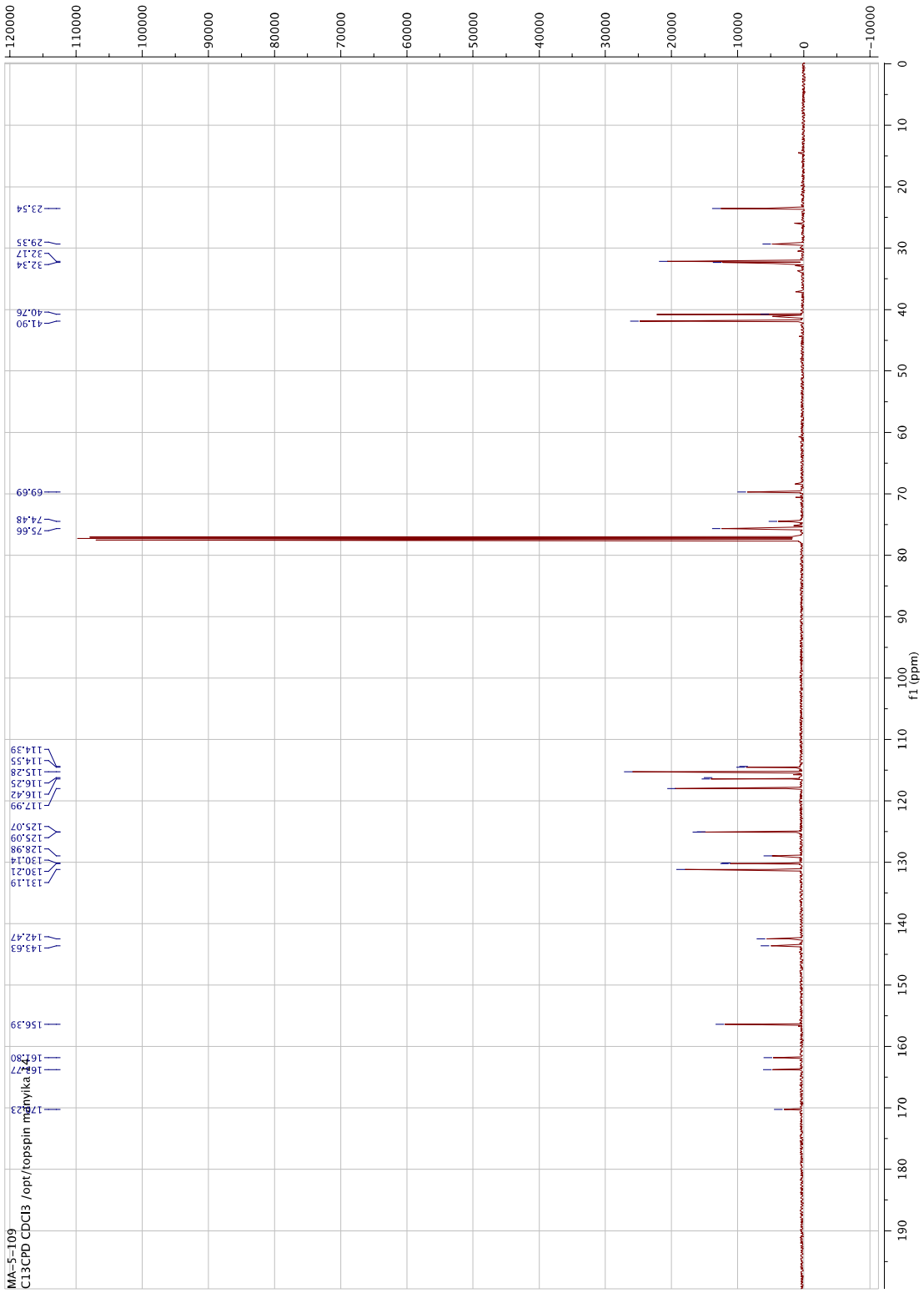
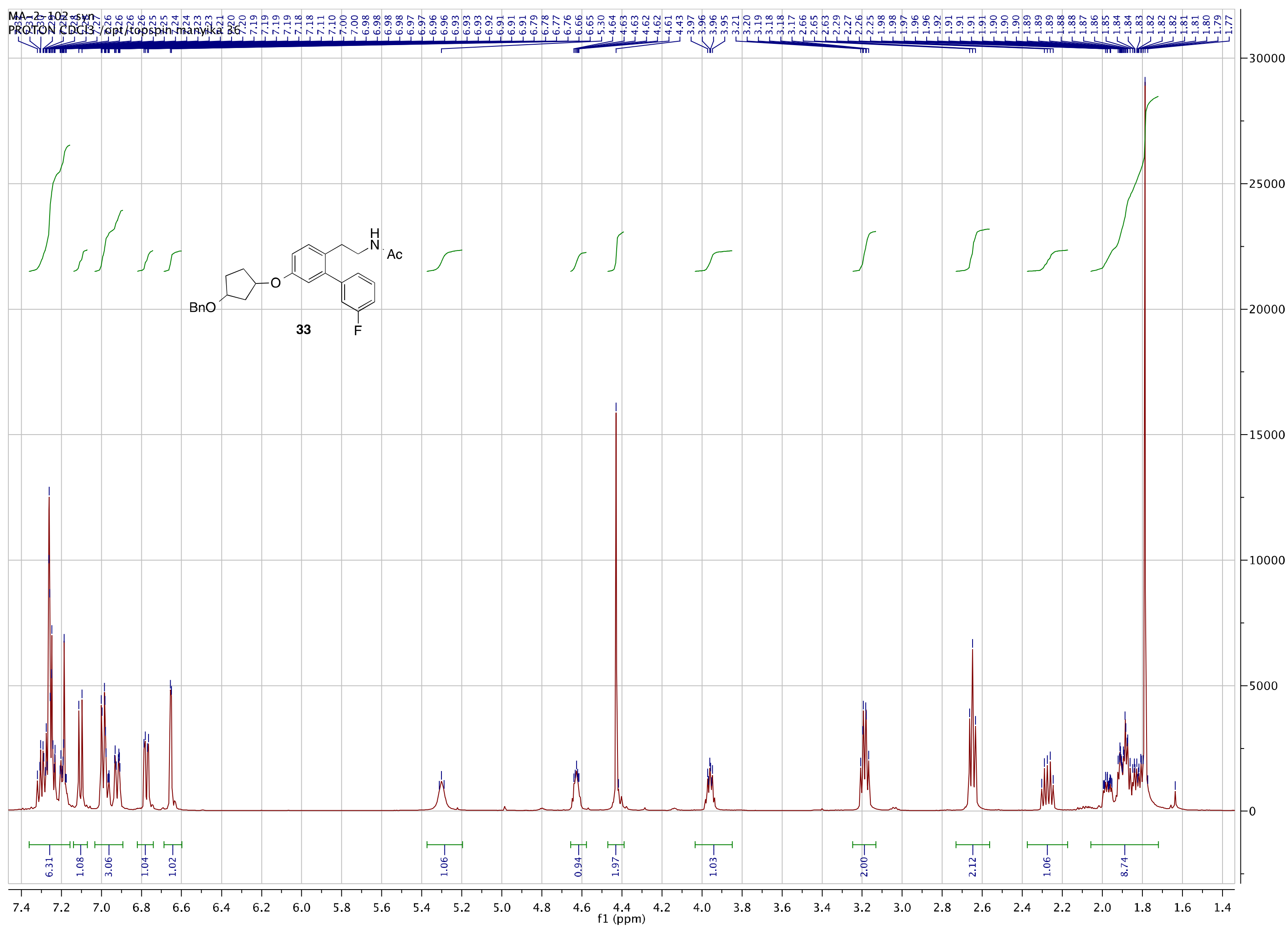
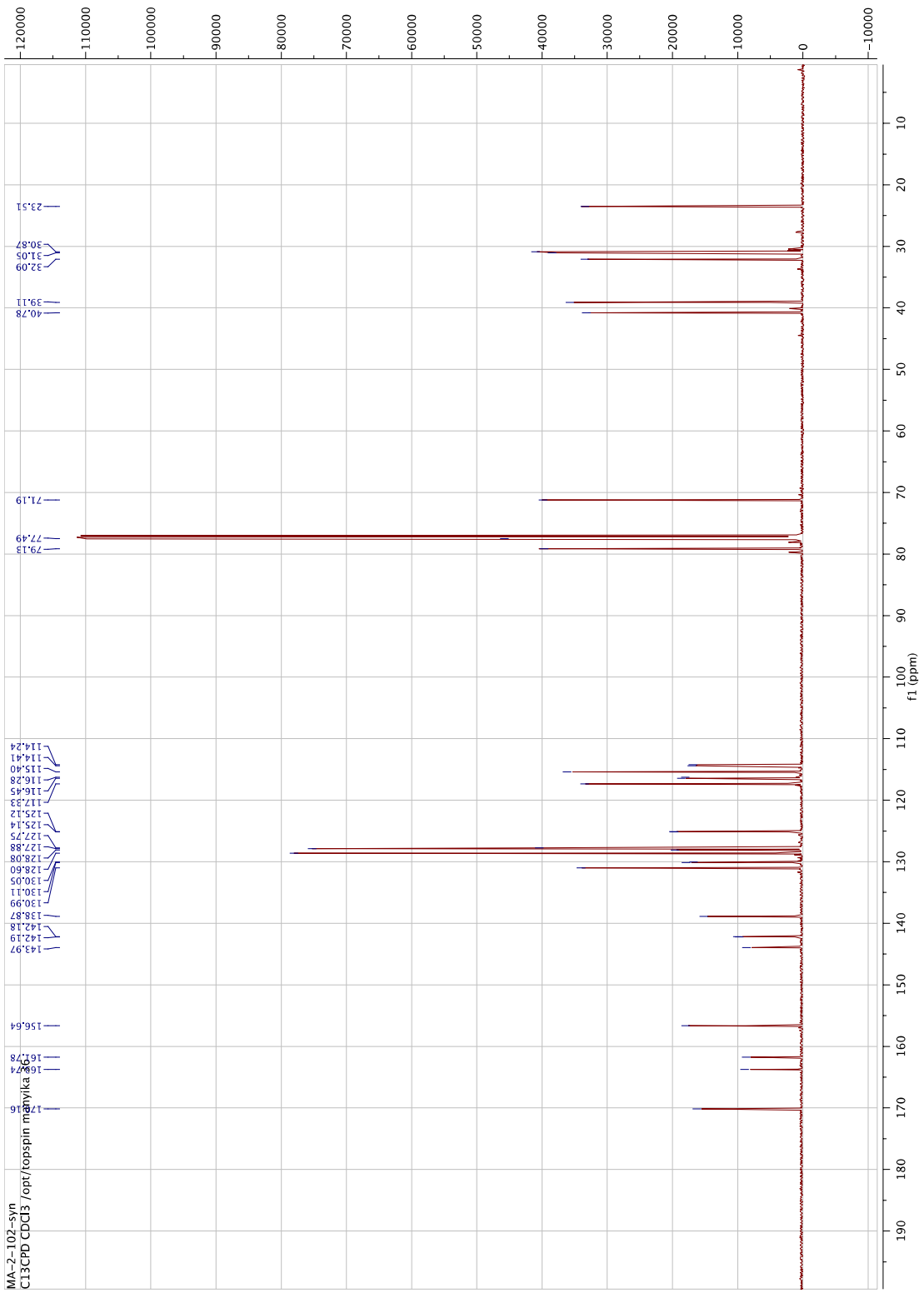
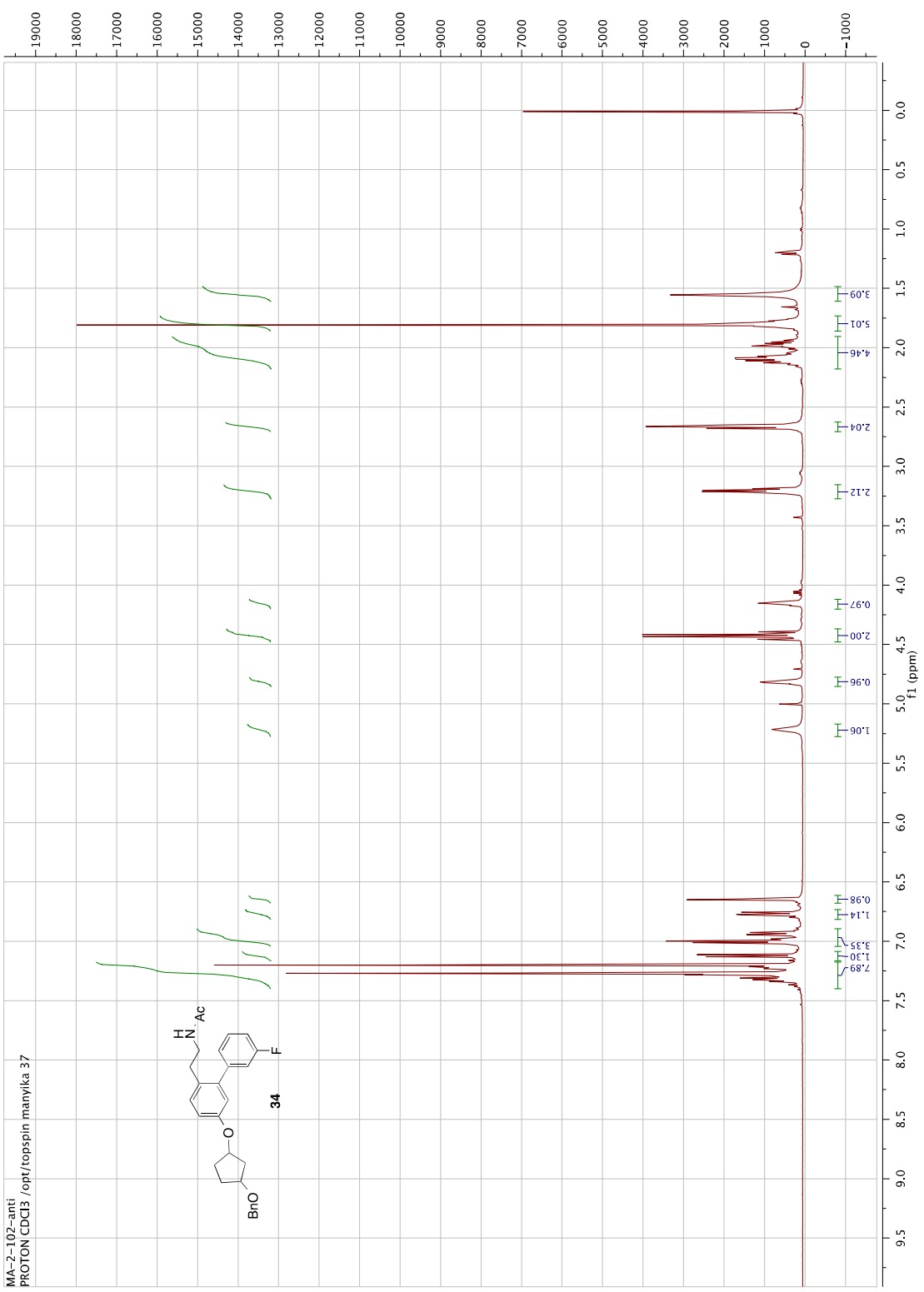
129.89
129.88
128.86
124.85
124.82
117.57
116.19
115.65
114.31
114.14
77.36
77.27 CDCl3
77.02 CDCl3
76.77 CDCl3
74.59
69.40
40.49
31.91
29.96
29.71
29.69
28.38
23.30
18.22
f1 (ppm)

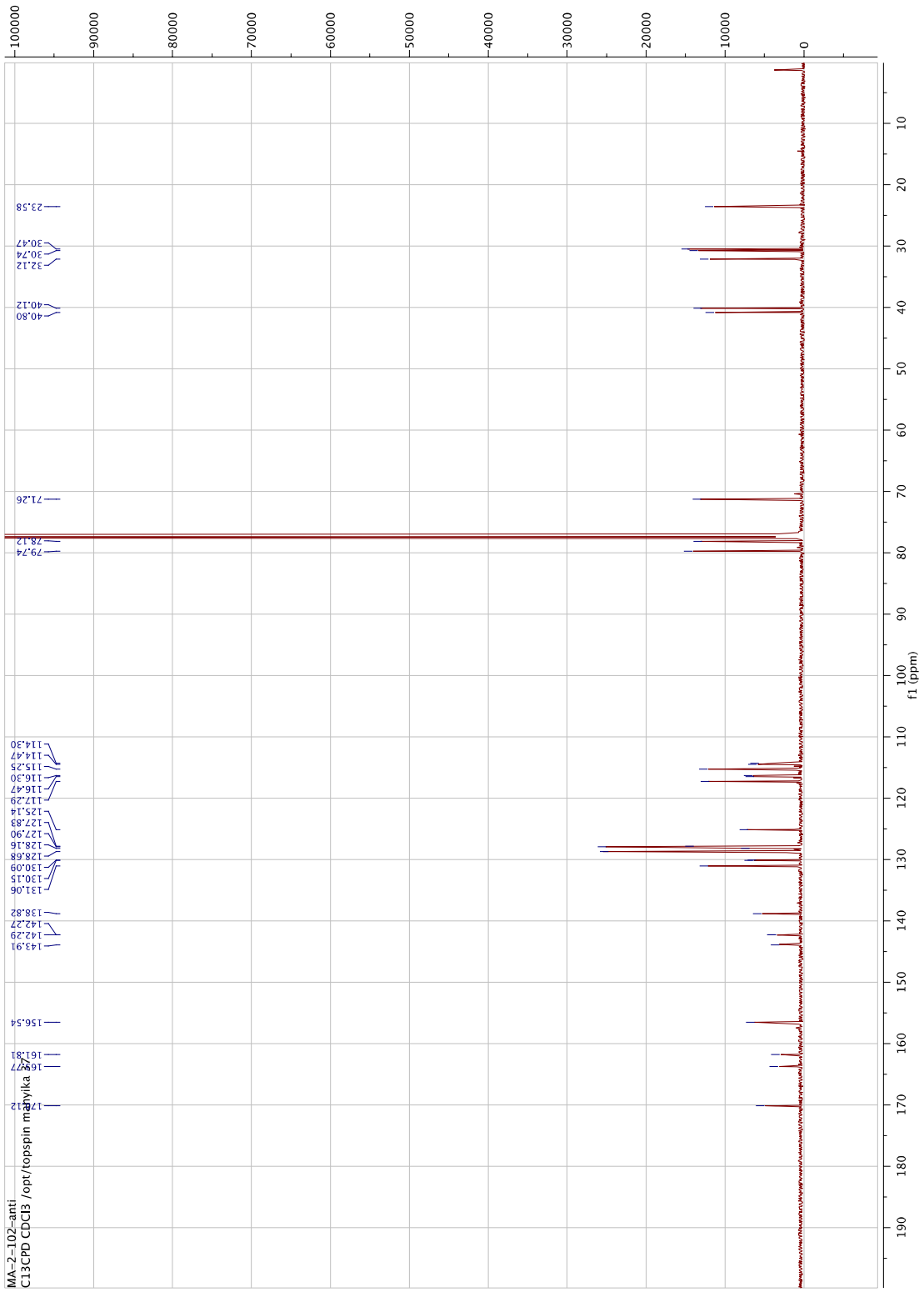

MA-5-109
f1 (ppm)
32
HO
OH
O
F
H
N
Ac

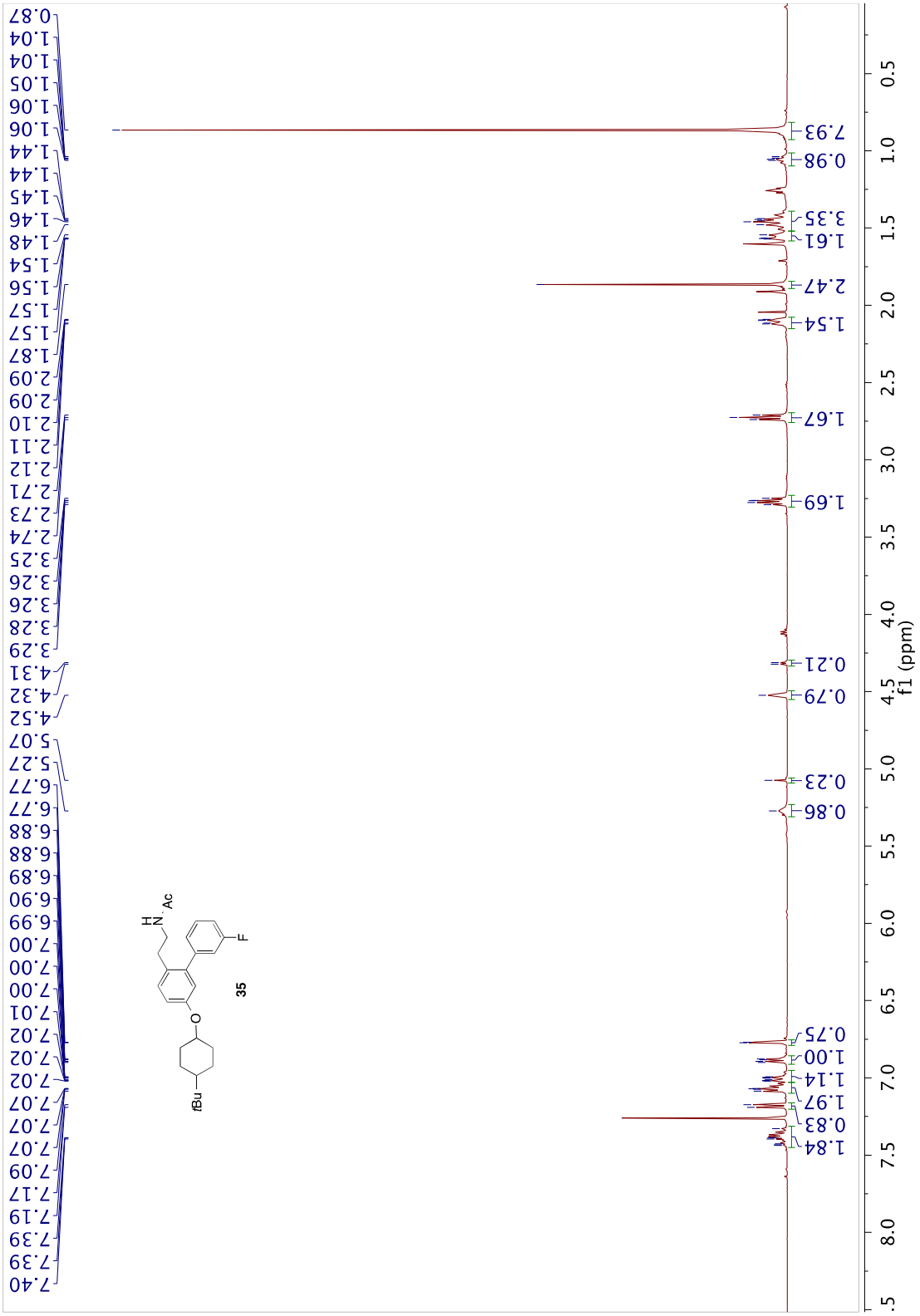

MA-5-109
C13CPD CDCl3 /opt/topspin manyika 7
f1 (ppm)
23.54
29.35
32.17
32.34
40.76
41.90
69.69
74.48
75.66
114.39
114.55
115.28
116.25
116.42
117.99
125.07
125.09
128.98
130.14
130.21
131.19
142.47
143.63
156.39
167.77
167.80
172.23

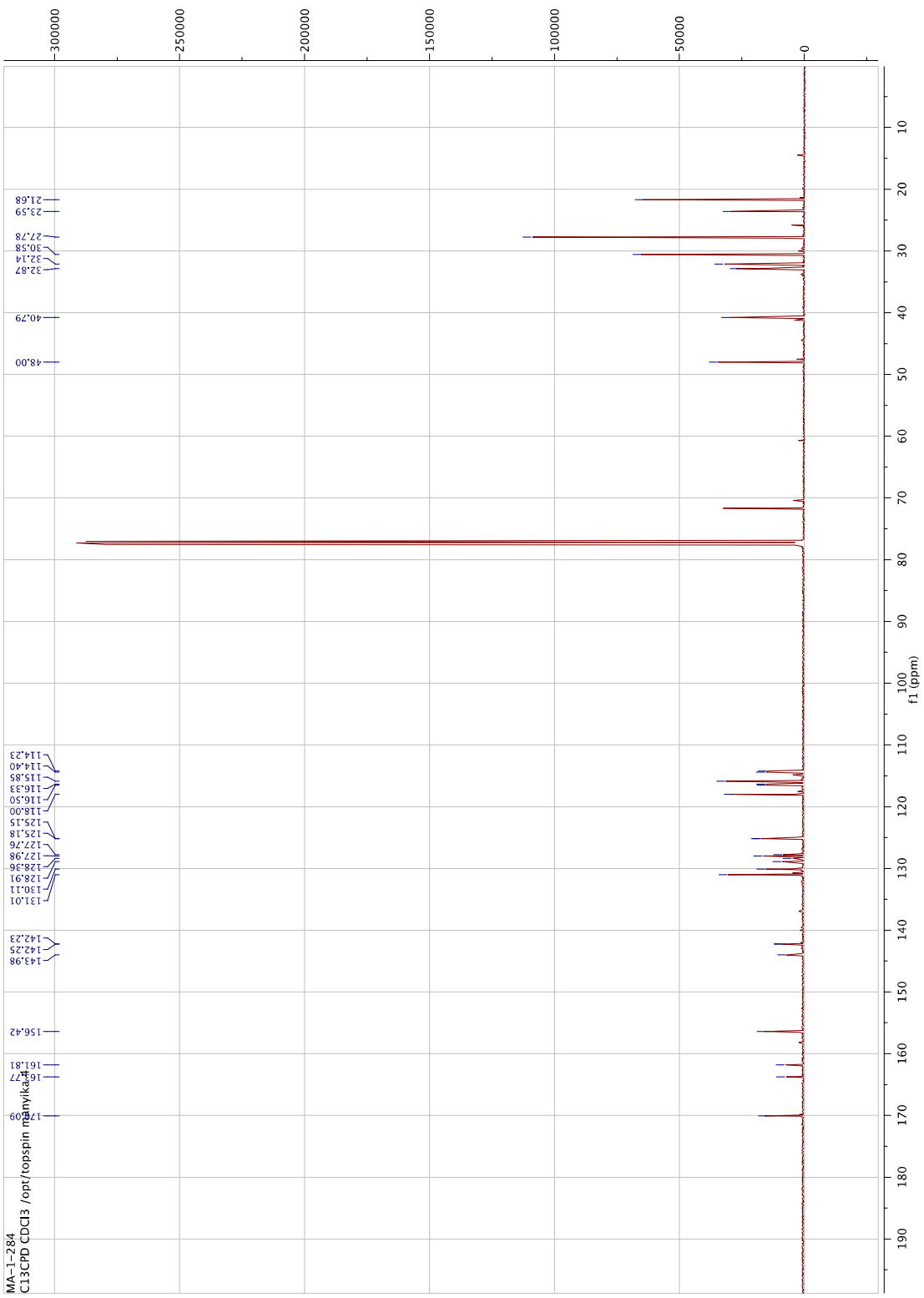

MA-2-102-syn
PROTON CDCl3 /opt/topspin manyika 36
BnO
O
H
N
Ac
F
33
6.31
1.08
3.06
1.04
1.02
1.06
0.94
1.97
1.03
2.00
2.12
1.06
8.74
f1 (ppm)

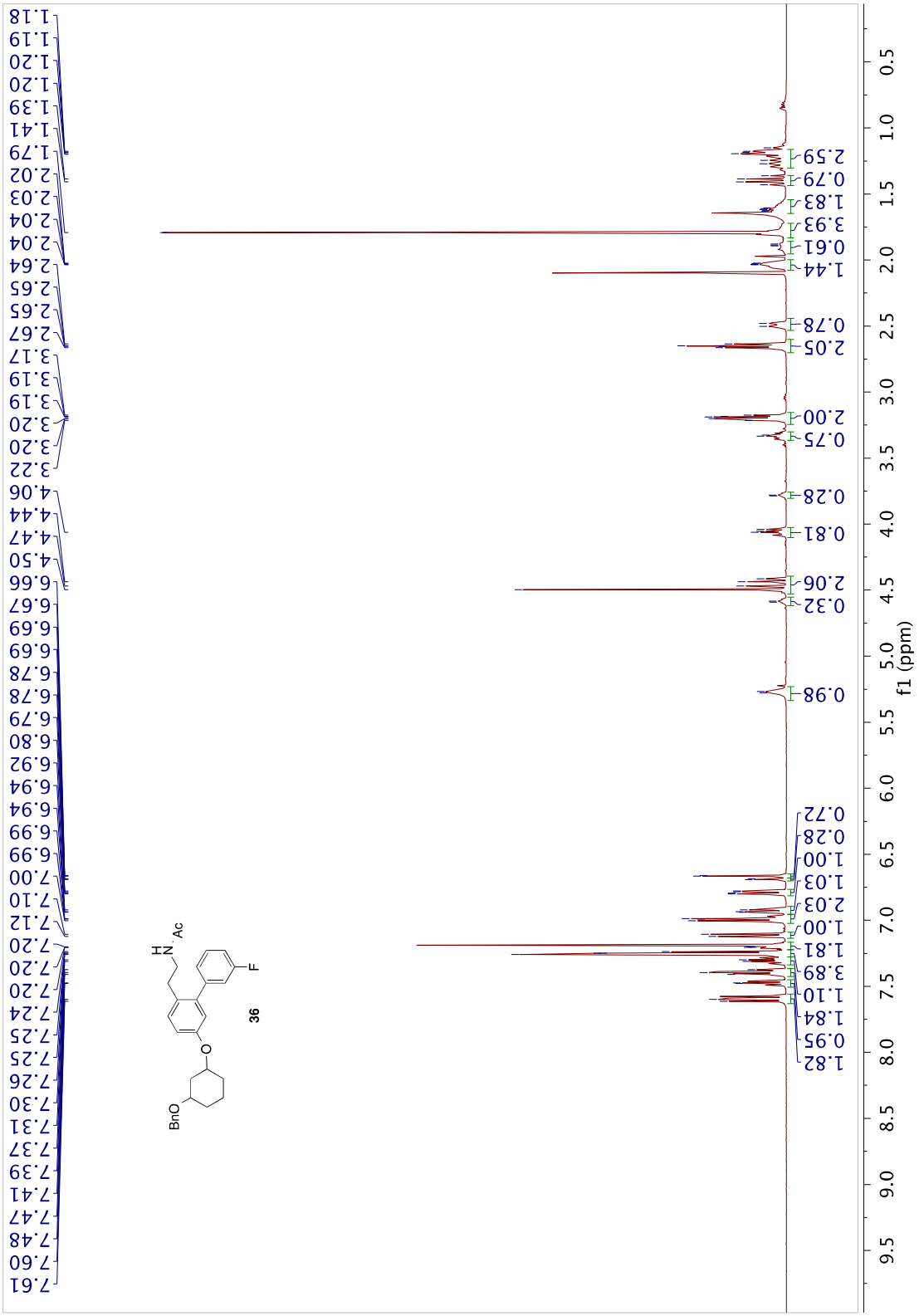

MA-2-102-syn
C13CPD CDCl3 /opt/topspin manyika 36
f1 (ppm)
23.51
30.87
31.05
32.09
39.11
40.78
71.19
77.49
79.13
114.24
114.41
115.40
116.28
116.45
117.33
125.12
125.14
127.75
127.88
128.08
128.60
130.05
130.11
130.99
138.87
142.18
142.19
143.97
156.64
161.78
166.74
172.16

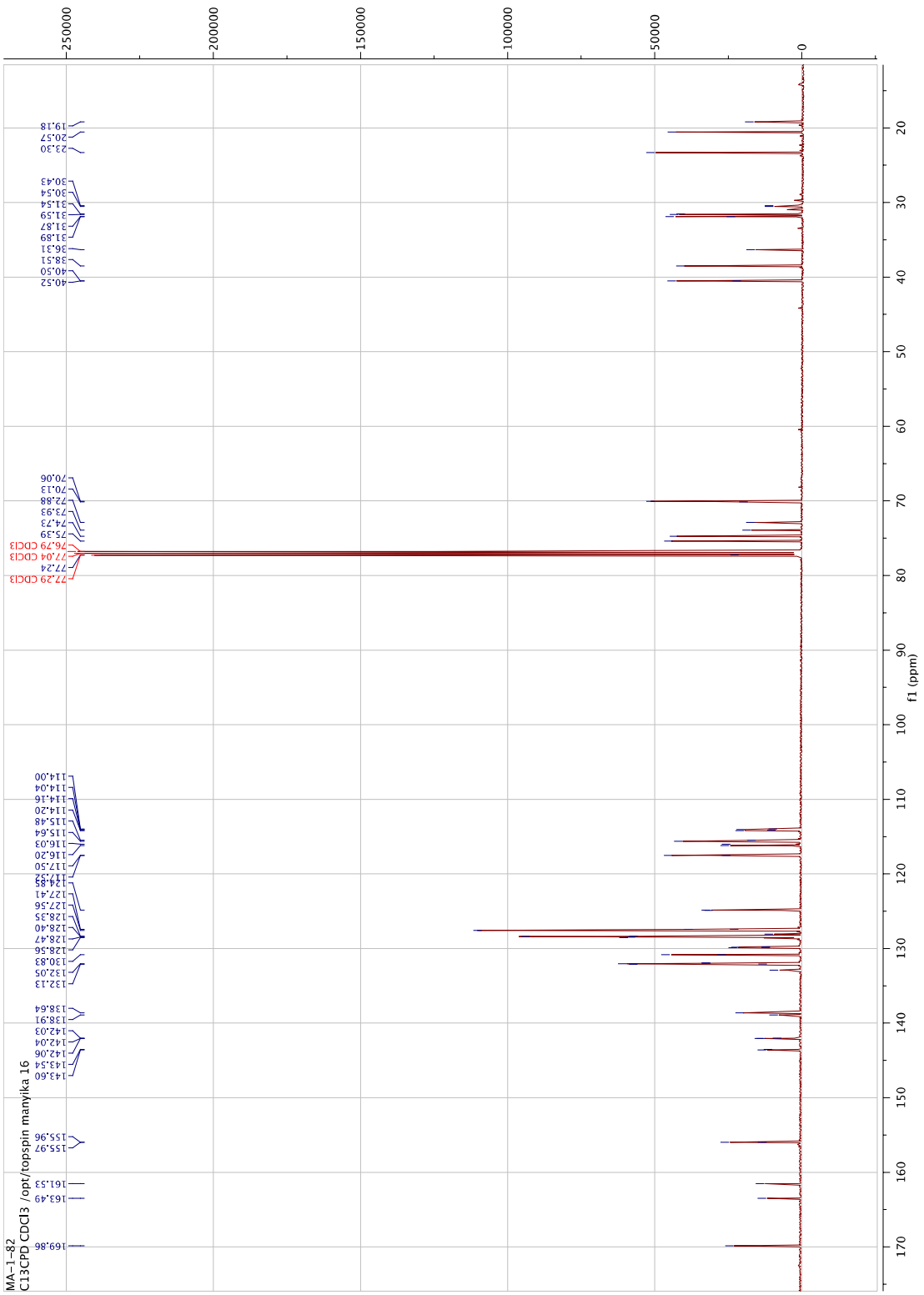

MA-2-102-anti
PROTON CDCl3 /opt/topspin manyika 37
34
BnO
O
H
N
Ac
F
f1 (ppm)
3.09
5.01
4.46
2.04
2.12
0.97
2.00
0.96
1.06
0.98
1.14
3.35
1.30
7.89

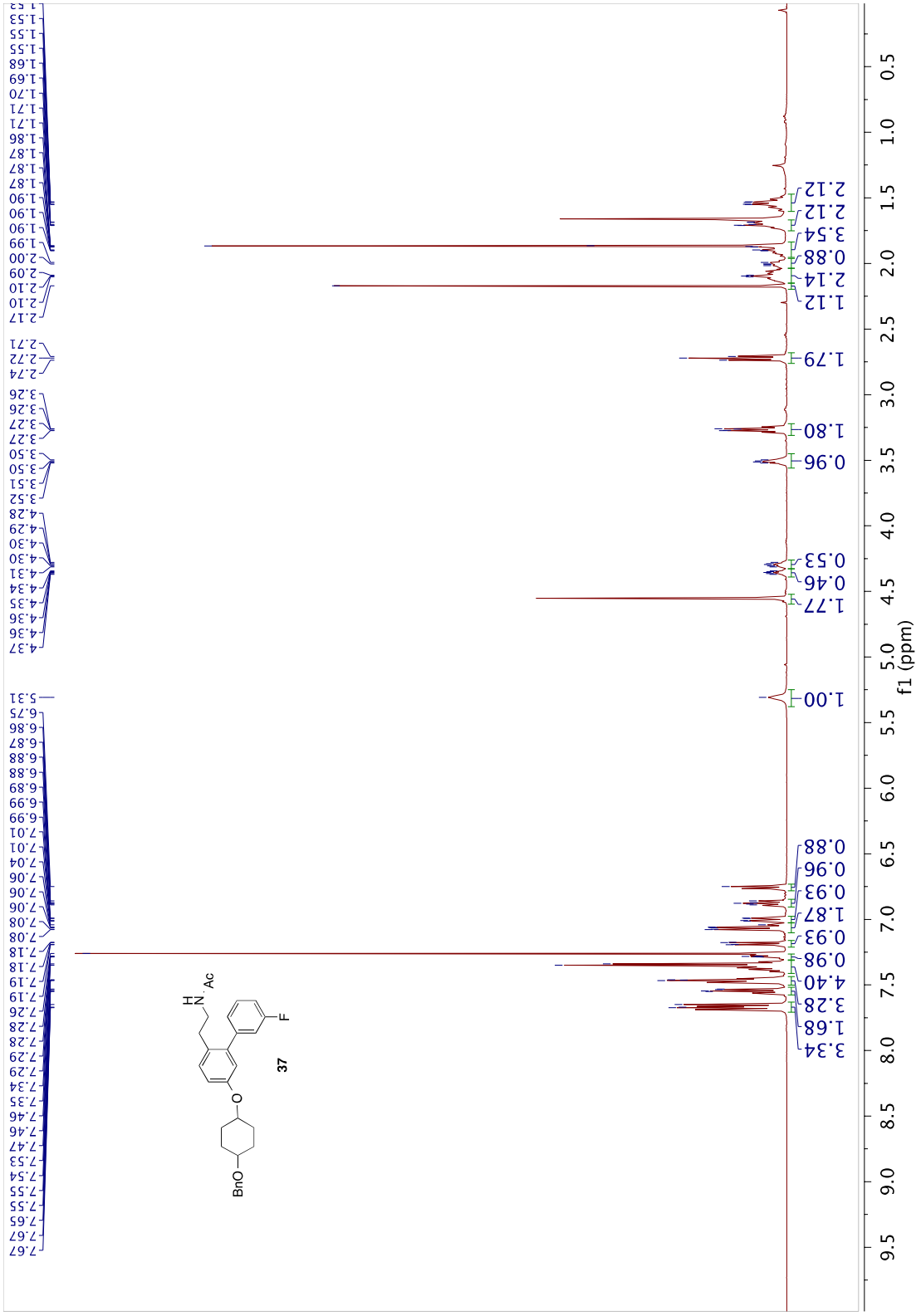

MA-2-102-anti
C13CPD CDCl3 /opt/topspin mathvika
23.58
30.47
30.74
32.12
40.12
40.80
71.26
78.12
79.74
114.30
114.47
115.25
116.30
116.47
117.29
125.14
127.83
127.90
128.16
128.68
130.09
130.15
131.06
138.82
142.27
142.29
143.91
156.54
161.81
162.77
172.12
f1 (ppm)

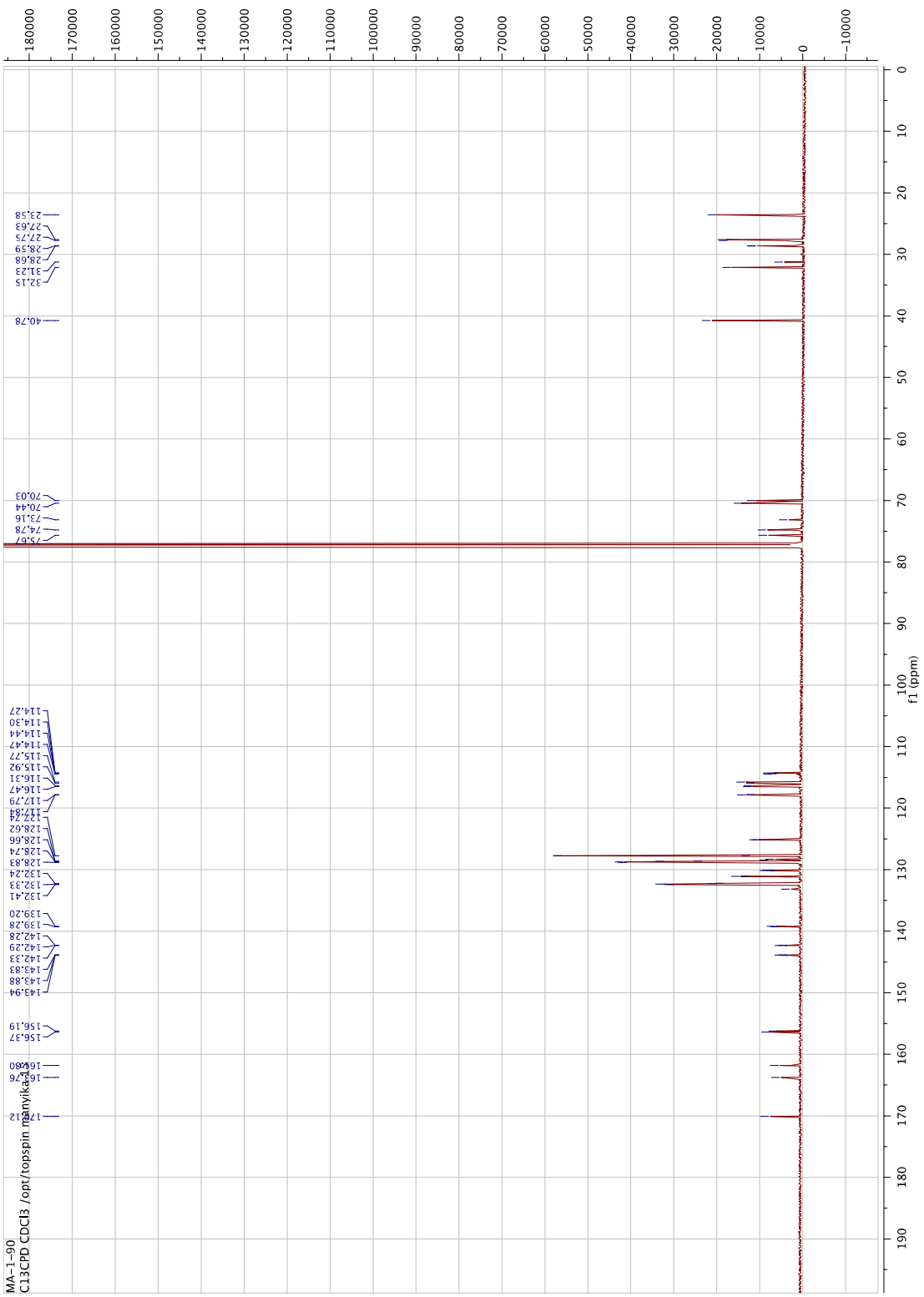

7.93
0.98
3.35
1.61
2.47
1.54
1.67
1.69
0.21
0.79
0.23
0.86
0.75
1.00
1.14
1.97
0.83
1.84
f1 (ppm)
35
Ac
F
tBu

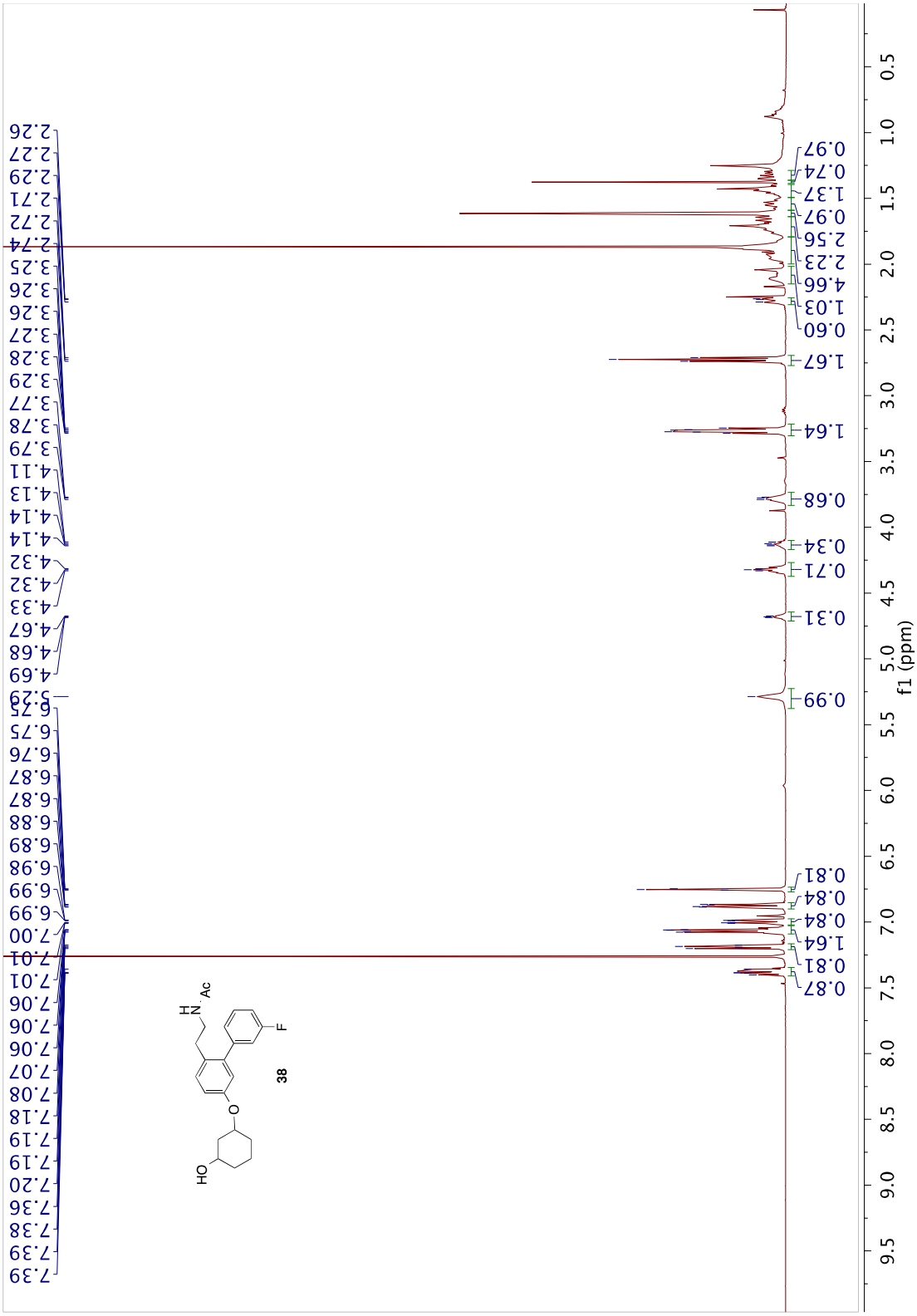

MA-1-284
C13CPD CDCl3 /opt/topspin manyika 1
f1 (ppm)
21.68
23.59
27.78
30.58
32.14
32.87
40.79
48.00
114.23
114.40
115.85
116.33
116.50
118.00
125.15
125.18
127.76
127.98
128.36
128.91
130.11
131.01
142.23
142.25
143.98
156.42
161.81
162.77
172.09

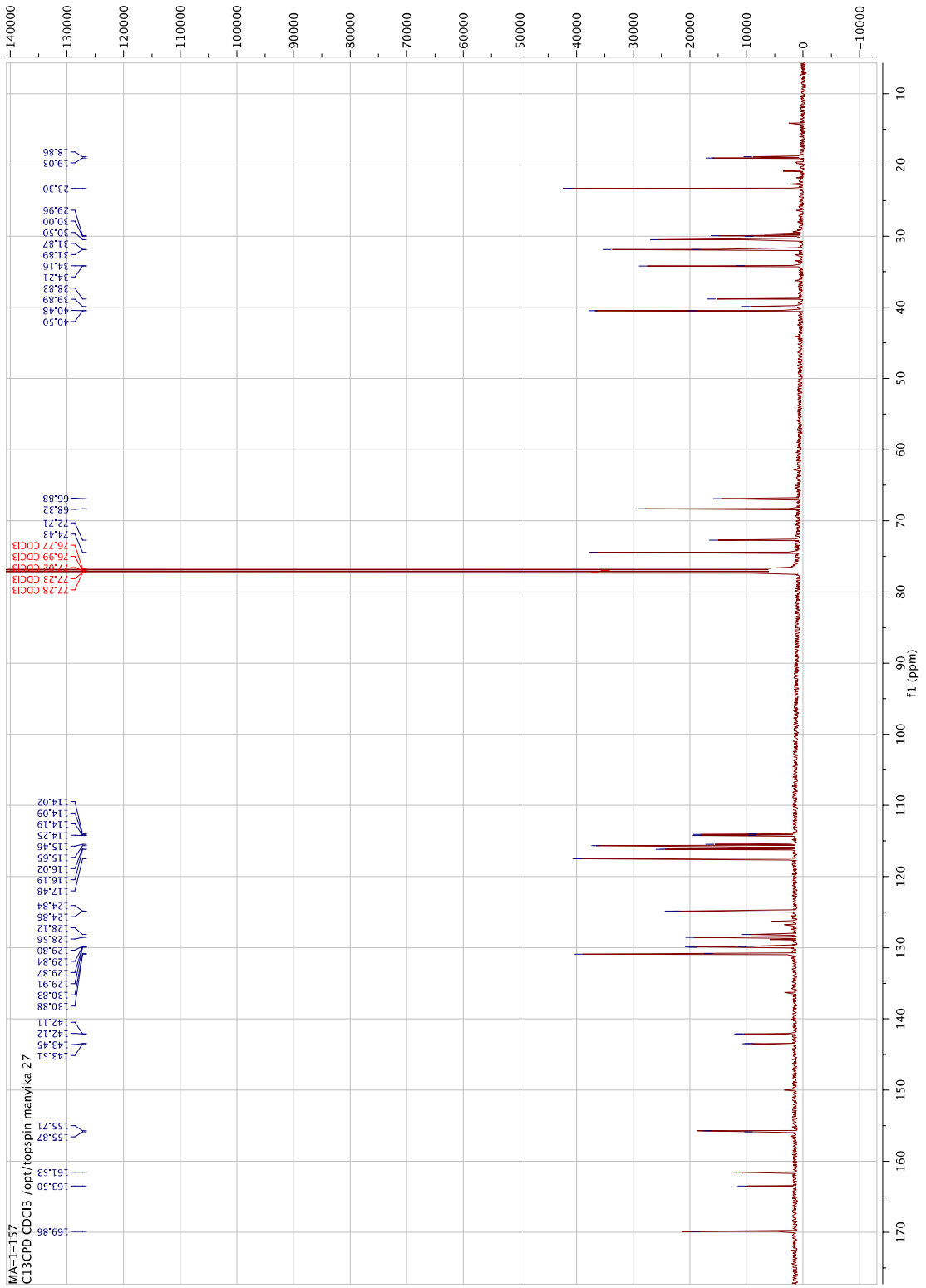

f1 (ppm)
36
BnO
Ac
F

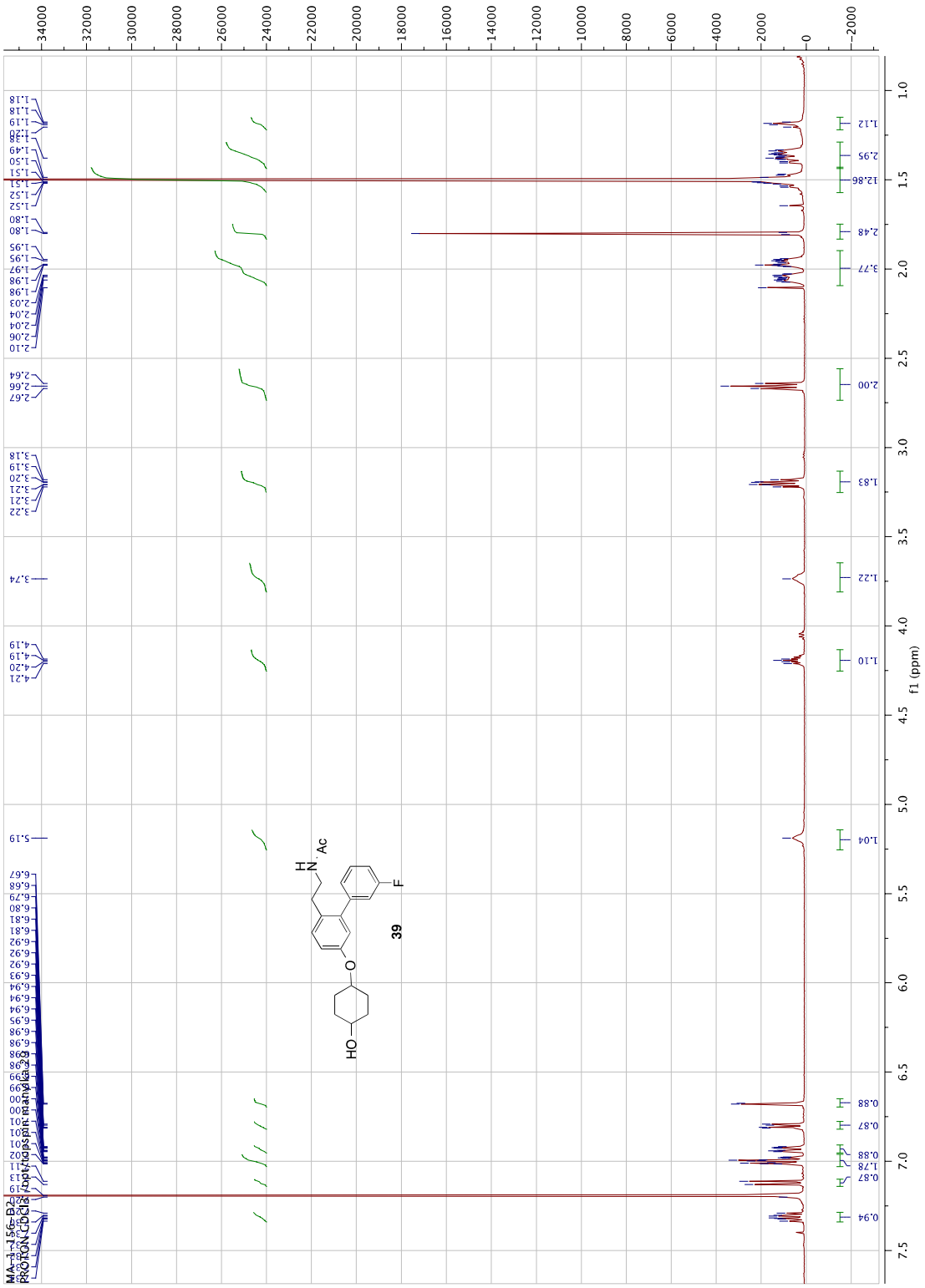

MA-1-82
C13CPD CDCl3 /opt/topspin manyika 16
f1 (ppm)

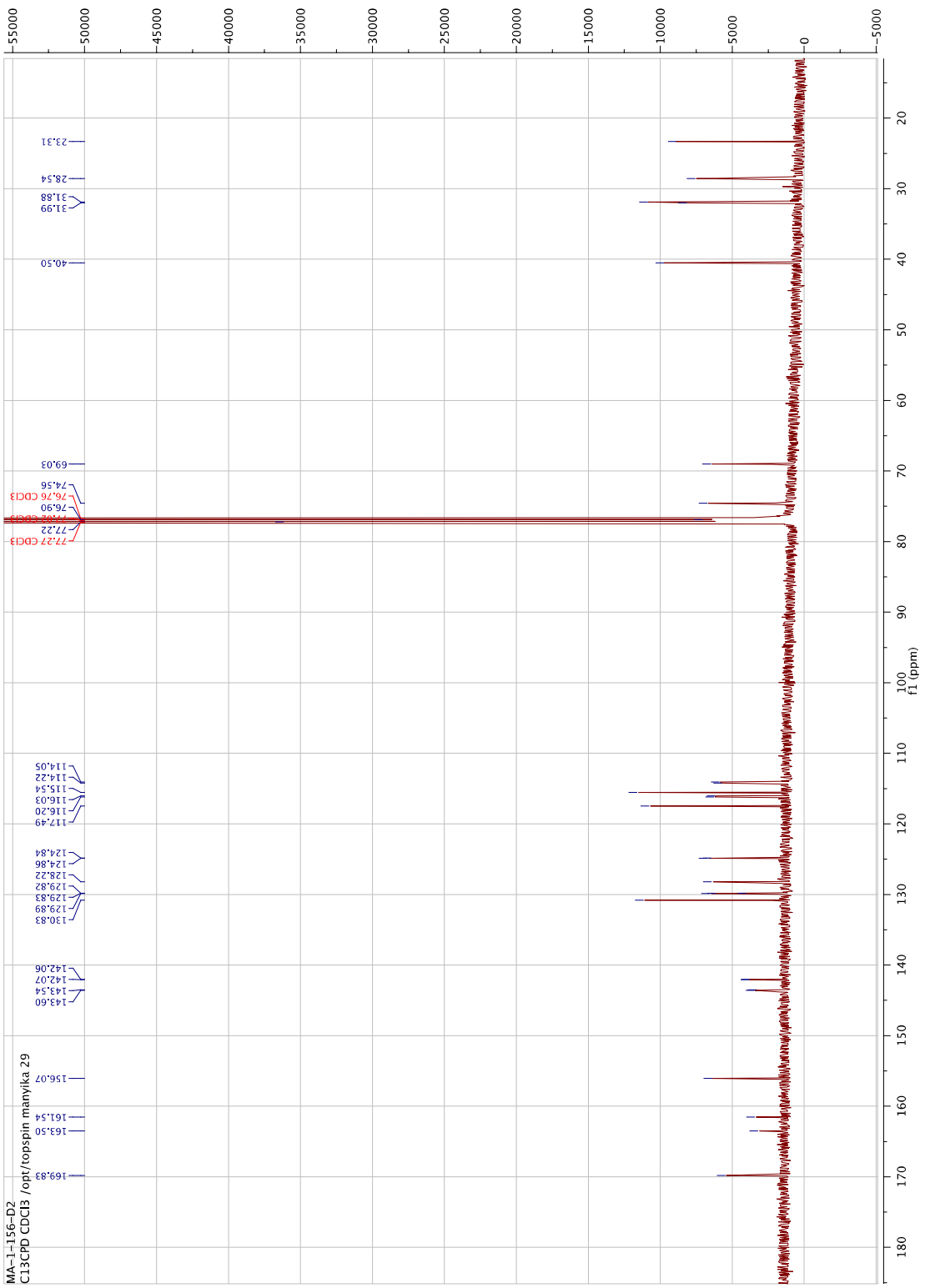

f1 (ppm)
BnO
O
H
N
Ac
F
37


MA-1-90
C13CPD CDCl3 /opt/topspin manyika 2
f1 (ppm)


38
f1 (ppm)


MA-1-157
C13CPD CDCl3 /opt/topspin manyika 27
f1 (ppm)


f1 (ppm)
39


MA-1-156-D2
C13CPD CDCl3 /opt/topspin manyika 29
169.83
163.50
161.54
156.07
143.60
143.54
142.07
142.06
130.83
129.89
129.83
129.82
128.22
124.86
124.84
117.49
116.20
116.03
115.54
114.22
114.05
77.27 CDCl3
77.22
76.76 CDCl3
76.90
74.56
69.03
40.50
31.99
31.88
28.54
23.31
f1 (ppm)