Branched Montbretin A mimics allow derivatisation and potent amylase inhibition.

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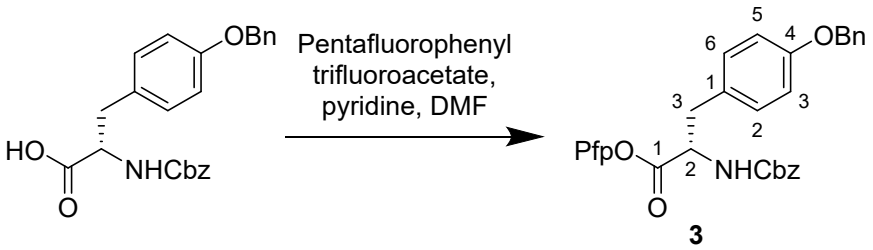
General Materials. All reagents and solvents were purchased from commercial suppliers (Sigma-Aldrich® or Thermo Fisher Scientific®) unless otherwise specified. Dichloromethane was dried by distillation with calcium hydride, tetrahydrofuran was distilled from sodium-benzophenone ketyl. Deionized water was prepared using a Millipore-Direct QTM 5 Ultrapure Water System. Analytical thin layer chromatography (TLC) was performed on Merck pre-coated 0.2 mm aluminum-backed sheets of Silica gel 60F254. TLC plates were visualized with UV light (254 nm) and stained with 1% ferric chloride in 50% water 50% methanol, or with 10% ammonium molybdate in 2 M H_2SO_4, followed by heating. Flash chromatography was performed with silica gel (pore size 60 Å, 220-440 mesh particle size) from Sigma-Aldrich. High performance liquid chromatography (HPLC) was performed on an Agilent 1260 Infinity Bio-inert Quaternary LC using an Agilent Eclipse XDB-C18 column (9.4 x 250 mm, 5 μm) at room temperature using acetonitrile and water with a flow rate of 4 mL/min. Elution of material was monitored by UV/Vis at 210, 280, and 350 nm. ^{1}H NMR, ^{13}C NMR, HMBC, and HSQC spectra were acquired on a Bruker 300 MHz or 400 MHz spectrometer. Low resolution mass spectra were acquired on a Waters ZQ Mass Detector equipped with an ESCI ion source and Waters 2695 HPLC. High resolution mass spectra were acquired on a Waters/Micromass LCT ESI-TOF. Mass spectra for high molecular weight compounds (>2,000 Da) were acquired on a Bruker Autoflex MALDI-TOF instrument.

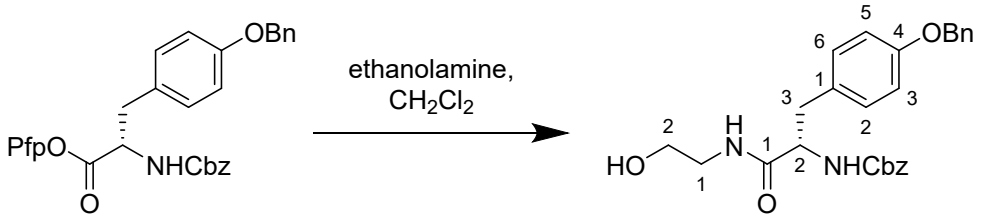
Perfluorophenyl (*S*)-2-(((benzyloxy)carbonyl)amino)-3-(4-(benzyloxy)phenyl)propanoate (**3**)



3

A solution of *N*-Cbz,*O*-Bn-tyrosine (1.013 g, 2.5 mmol) in DMF (5 mL) was treated with pyridine (0.22 mL), followed by pentafluorophenyl trifluoroacetate (0.5 mL, 0.82 g, 2.9 mmol). The reaction mixture was stirred at room temperature for 1 hour and was then diluted with ethyl acetate (100 mL) and washed with 0.1 M HCl and 5% $NaHCO_3$ (3 x 100 mL each). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the *title compound* (1.26 g, 2.2 mmol, 88%) as a colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.32 (m, 10 H, 10 x ArH), 7.12 (d, J = 8.6, 2 H, 2 x ArH), 6.93 (d, J = 8.6, 2 H, 2 x ArH), 5.19-5.12 (m, 3 H, NH + CH_2), 5.05 (s, 2 H, CH_2), 5.01-4.94 (m, 1 H, CH), 3.31-3.16 (m, 2 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (C=O), 158.5 (C=O), 155.7 (C), 137.0 (C), 136.0 (C), 130.5 (2 x CH), 128.74 (2 x CH), 128.70 (2 x CH), 128.5 (CH), 128.3 (2 x CH), 128.2 (CH), 127.6 (2 x CH), 126.8 (C), 115.4 (2 x CH), 70.2 (CH_2), 67.5 (CH_2), 54.8 (CH), 37.1 (CH_2). Pfp carbon signals not observed. HRMS (ESI-TOF): m/z calc'd for $C_{30}H_{22}NO_5F_5Na$: 594.1316 $[M+Na]^+$; found: 594.1323.

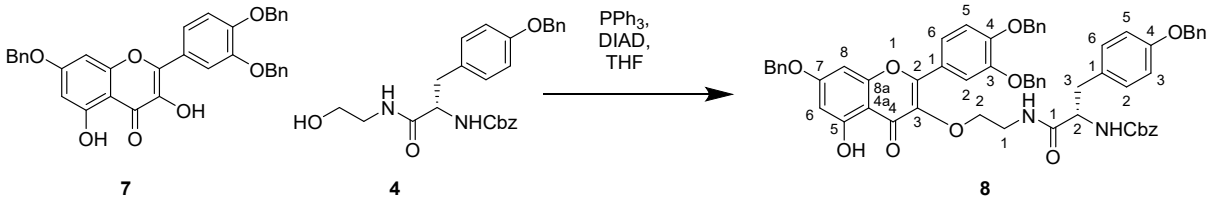
Benzyl (*S*)-(3-(4-(benzyloxy)phenyl)-1-((2-hydroxyethyl)amino)-1-oxopropan-2-yl)carbamate (**4**)



3 **4**

A solution of **3** (960 mg, 1.68 mmol) in CH_2Cl_2 (10 mL) was treated with ethanolamine (205 mg, 203 µL, 3.36 mmol) dropwise. The reaction mixture was stirred for 1.5 hours and was then diluted with ethyl acetate (100 mL). The solution was then washed with 1 M HCl (2 x 100 mL), 1 M NaOH (2 x 100 mL), water (100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the *title compound* (670 mg, 1.49 mmol, 89%) as a colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.29 (m, 10 H, 10 x ArH), 7.10 (d, J = 8.5, 2 x H, 2 x ArH), 6.89 (d, J = 8.5, 2 x H, 2 x ArH), 6.23 (bt, J = 5.6, 1 H, NH), 5.45 (bd, J = 6.7, 1 H, NH), 5.06 (s, 2 H, CH_2), 5.02 (s, 2 H, CH_2), 4.33 (app q, J = 7.2, 1 H, CH), 3.60-3.47 (m, 2 H, CH_2), 3.28 (app q, J = 5.2, 2 H, CH_2), 3.07-2.92 (m. 2 H, CH_2). In agreement with the literature.[1]

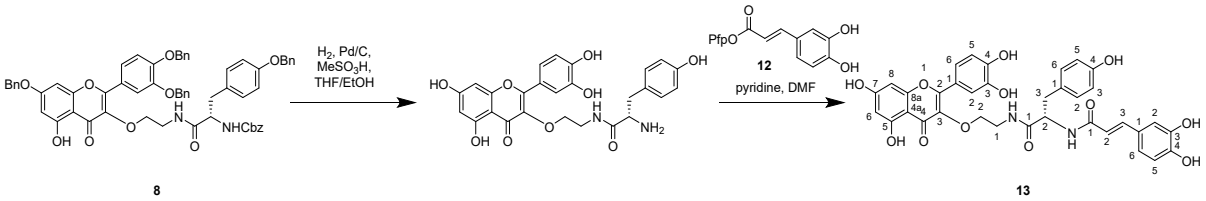
Benzyl (*S*)-(1-((2-((7-(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-5-hydroxy-4-oxo-4H-chromen-3-yl)oxy)ethyl)amino)-3-(4-(benzyloxy)phenyl)-1-oxopropan-2-yl)carbamate (**8**)



7 **4** **8**

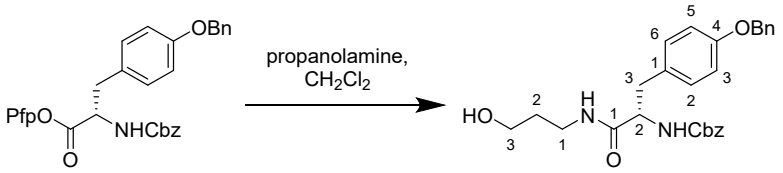
A solution of flavonol **7** (240 mg, 0.42 mmol), alcohol **4** (190 mg, 0.42 mmol) and triphenylphosphine (550 mg, 2.1 mmol) in THF (15 mL) was cooled to 0 °C and treated dropwise with DIAD (0.2 mL, 1.0 mmol). The reaction mixture was stirred at 0 °C for 2.5 hours and was diluted with ethyl acetate and saturated aqueous $NaHCO_3$ (100 mL each). The aqueous layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10 % - 20 % EtOAc in CH_2Cl_2), followed by a subsequent purification on silica gel (2:3 EtOAc:petroleum ether) gave the *title compound* (87mg, 87 µmol, 21%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1 H, OH), 7.65 (d, *J* = 1.9, 1 H, ArH), 7.61 (dd, *J* = 8.6, 1.9, 1 H, ArH), 7.51-7.26 (m, 25 H, 25 x ArH), 7.09 (d, *J* = 8.4, 2 H, 2 x ArH), 7.04 (d, *J* = 8.6, 1 H, 1 x ArH), 6.76 (d, *J* = 8.4, 2 H, 2 x ArH), 6.46 (d, *J* = 1.9, 1 H, ArH), 6.43 (d, *J* = 1.9, 1 H, ArH), 5.57 (d, *J* = 8.4, 1 H, NH), 5.27 (s, 2 H, CH_2), 5.24 (s, 2 H, CH_2), 5.20-5.08 (m, 4 H, 2 x CH_2), 4.82 (s, 2 H, CH_2), 4.52 (app q, *J* = 7.0, 1 H, CH), 3.71-3.58 (m, 2 H, CH_2), 3.38 (app q, *J* = 16.0, 2 H, CH_2), 3.15-2.99 (m, 2 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4 (C=O), 171.2 (C=O), 164.8 (C), 161.9 (C), 157.7 (C=O), 156.8 (C), 156.4 (C), 155.9 (C), 151.8 (C), 148.5 (C), 137.7 (C), 137.1 (C), 136.8 (C), 136.6 (C), 136.5 (C), 135.7 (C), 130.6 (2 x CH), 128.89 (C), 128.86 (2 x CH), 128.77 (2 x CH), 128.75 (2 x CH), 128.53 (4 x CH), 128.49 (2 x CH), 128.2 (CH), 128.13 (CH), 128.08 (CH), 128.03 (CH), 127.9 (CH), 127.5 (2 x CH), 127.32 (2 x CH), 127.30 (2 x CH), 127.2 (2 x CH), 122.84 (C), 122.80 (CH), 115.1 (CH), 114.8 (2 x CH), 113.9 (CH), 105.9 (C), 98.9 (CH), 93.3 (CH), 71.4 (CH_2), 71.3 (CH_2), 70.9 (CH_2), 70.6 (CH_2), 69.7 (CH_2), 66.9 (CH_2), 56.5 (CH), 40.3 (CH_2), 38.3 (CH_2). HRMS (ESI-TOF): m/z calc'd for $C_{62}H_{54}N_2O_{11}Na$: 1025.3625 $[M+Na]^+$; found: 1025.3622.

(*S*,*E*)-3-(3,4-dihydroxyphenyl)-*N*-(1-((2-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)ethyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)acrylamide (**13**)



A solution of **8** (40 mg, 40 μmol) in EtOH/THF (1:2, 9 mL) was treated with Pd/C (40 mg) and methanesulfonic acid (3 μL, 46 μmol). The flask was evacuated and placed under hydrogen pressure and stirred 16 h at room temperature. The reaction mixture was filtered through Celite, the filter cake was washed with ethanol (10 mL) and the filtrate treated with triethylamine (10 μL, 72 μmol). The filtrate was concentrated *in vacuo* and dissolved in DMF (1 mL). The reaction mixture was treated with pyridine (6.5 μL, 80 μmol), followed by **12** (13.8 mg, 40 μmol). After stirring for 16 h, pyridine (6.5 μL, 80 μmol) was added and the reaction mixture was stirred for a further 5 h, whereupon further **12** was added (6.9 mg, 20 μmol). After a total of 40 h stirring, the reaction mixture was quenched with water (100 μL) and was concentrated *in vacuo*. Purification by flash chromatography on silica gel (78:10:10:2 to 67:15:15:3, CH_2Cl_2:MeOH:Acetone:Water) gave the *title compound* (10.3 mg, 15 μmol, 38%) as a yellow solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.60 (d, *J* = 2.1, 1 H, ArH), 7.49 (dd, *J* = 8.6, 2.1, 1 H, ArH), 7.34 (d, *J* = 15.7, 1 H, CH), 7.07 (d, *J* = 8.5, 2 H, 2 x ArH), 6.98 (d, *J* = 1.8, 1 H, ArH), 6.91 (d, *J* = 8.6, 1 H, ArH), 6.88 (dd, *J* = 8.5, 1.8, 1 H, ArH), 6.73 (d, *J* = 8.5, 1 H, ArH), 6.64 (d, *J* = 8.5, 2 H, 2 x ArH), 6.43 (d, *J* = 15.7, 1 H, CH), 6.36 (d, *J* = 2.0, 1 H, ArH), 6.18 (d, *J* = 2.0, 1 H, ArH), 4.66 (dd, *J* = 8.3, 6.3, 1 H, CH), 4.00-3.79 (m, 2 H, CH_2), 3.49-3.44 (m, 2 H, CH_2), 3.13-2.85 (m, 2 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7 (C=O), 174.0 (C=O), 169.2 (C=O), 166.0 (C), 163.0 (C), 158.4 (C), 158.2 (C), 157.2 (C), 150.0 (C), 148.8 (C), 146.6 (C), 146.4 (C), 143.0 (CH), 138.3 (C), 131.3 (2 x CH), 129.2 (C), 128.2 (C), 122.8 (C), 122.4 (CH), 122.3 (CH), 117.9 (CH), 116.5 (2 x CH), 116.4 (CH), 116.2 (2 x CH), 115.3 (CH), 105.8 (C), 99.9 (CH), 94.8 (CH), 71.7 (CH_2), 57.1 (CH), 41.2 (CH_2), 38.3 (CH_2). HRMS (ESI-TOF): m/z calc'd for $C_{35}H_{30}N_2O_{12}Na$: 693.1696 $[M+Na]^+$; found: 693.1691.

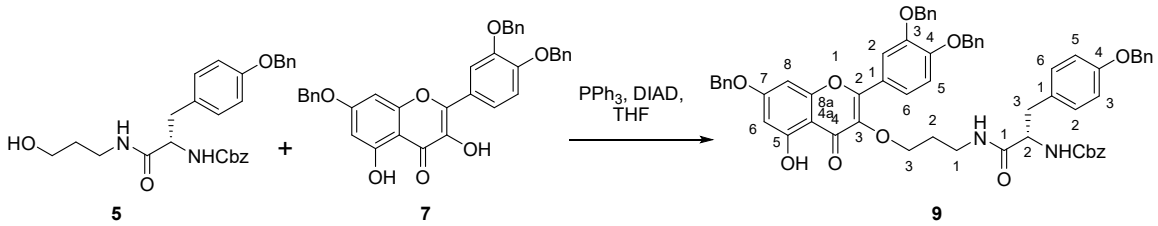
Benzyl (*S*)-(3-(4-(benzyloxy)phenyl)-1-((3-hydroxypropyl)amino)-1-oxopropan-2-yl)carbamate (**6**)



3 **6**

A solution of **3** (850 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was treated with propanolamine (230 mg, 0.23 mL, 3.0 mmol) dropwise. The reaction mixture was stirred for 1.5 hours and was then diluted with ethyl acetate (100 mL). The solution was then washed with 1 M HCl (2 x 100 mL), 1 M NaOH (2 x 100 mL), water (100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the *title compound* (620 mg, 1.3 mmol, 90 %) as a colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.29 (m, 10 H, 10 x ArH), 7.10 (d, J = 8.6, 2 x H, 2 x ArH), 6.90 (d, J = 8.6, 2 x H, 2 x ArH), 6.08 (bt, J = 5.5, 1 H, NH), 5.30 (bs, 1 H, NH), 5.09 (s, 2 H, CH_2), 5.04 (s, 2 H, CH_2), 4.30 (app q, J = 7.2, 1 H, CH), 3.47 (t, J = 5.5, 2 H, CH_2), 3.31 (app q, J = 6.1, 2 H, CH_2), 3.10-2.92 (m. 2 H, CH_2), 2.24 (bs, 1 H, OH), 1.57 (p, J = 5.7, 2 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (C=O), 158.0 (C=O), 156.1 (C), 137.0 (C), 136.2 (C), 130.5 (2 x CH), 128.72 (2 x CH), 128.69 (2 x CH), 128.4 (CH), 128.2 (2 x CH), 128.1 (CH), 127.6 (2 x CH), 115.2 (2 x CH), 70.1 (CH_2), 67.2 (CH_2), 59.7 (CH_2), 56.8 (CH), 37.8 (CH_2), 36.7 (CH_2), 31.8 (CH_2). 1 x C obscured. HRMS (ESI-TOF): m/z calc'd for $C_{27}H_{30}N_2O_5Na$: 485.2047 $[M+Na]^+$; found: 485.2054.

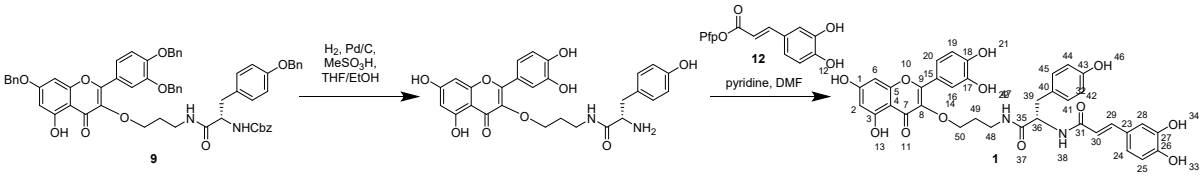
Benzyl (*S*)-(1-((3-((7-(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-5-hydroxy-4-oxo-4H-chromen-3-yl)oxy)propyl)amino)-3-(4-(benzyloxy)phenyl)-1-oxopropan-2-yl)carbamate (**9**)



5 **7** **9**

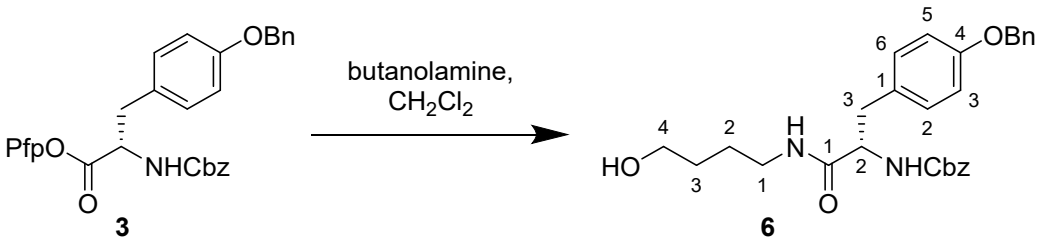
A solution of **7** (309 mg, 0.54 mmol), **5** (250 mg, 0.54 mmol) and triphenylphosphine (283 mg, 1.1 mmol) in THF (25 mL) was cooled to 0 °C and treated dropwise with DIAD (0.21 mL, 1.1 mmol). The reaction mixture was stirred at 0 °C for 2.5 hours and was diluted with ethyl acetate and saturated aqueous $NaHCO_3$ (100 mL each). The aqueous layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (2% MeOH in CH_2Cl_2) gave the *title compound* (188 mg, 0.16 mmol, 30 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (bs, 1H, NH), 7.68 (s, 1H, ArH), 7.62 (d, *J* = 8.7, 1H, ArH), 7.50-7.17 (m, 24H), 7.11 (d, *J* = 8.6, 2H, 2 x ArH), 7.01 (d, *J* = 8.6, 2H, 2 x ArH), , 6.76 (d, *J* = 8.3, 2H, 2 x H), 6.46 (bs, 2H, 2 x ArH), 5.61 (d, *J* = 8.3, 1H, NH), 5.26 (s, 2 H, CH_2), 5.21 (s, 2 H, CH_2), 5.13 (s, 2 H, CH_2), 5.12-5.02 (m, 2H, CH_2), 4.82 (s, 2 H, CH_2), 4.53 (app q, *J* = 7.1, 1 H, CH), 3.59-3.32 (m, 4H, 2 x CH_2), 3.16-2.96 (m, 2 H, CH_2), 1.64 (bs, 2 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7 (C=O), 171.0 (C=O), 164.8 (C), 161.9 (C), 157.7 (C=O), 156.7 (C), 156.3 (C), 155.8 (C), 151.7 (C), 148.5 (C), 137.7 (C), 137.1 (C), 136.9 (C), 136.5 (C), 135.7 (C), 130.6 (2 x CH), 129.04 (C), 128.85 (2 x CH), 128.73 (2 x CH), 128.70 (2 x CH), 128.5 (4 x CH), 128.4 (2 x CH), 128.2 (CH), 128.1 (CH), 128.04 (CH), 127.98 (CH), 127.9 (CH), 127.5 (2 x CH), 127.34 (2 x CH), 127.26 (4 x CH), 123.0 (C), 122.7 (CH), 114.9 (CH), 114.8 (2 x CH), 113.8 (CH), 106.0 (C), 98.9 (CH), 93.2 (CH), 71.6 (CH_2), 70.9 (CH_2), 70.6 (CH_2), 69.8 (CH_2), 69.1 (CH_2), 66.8 (CH_2), 56.6 (CH), 38.4 (CH_2), 35.7 (CH_2), 28.5 (CH_2). HRMS (ESI-TOF): m/z calc'd for $C_{63}H_{57}N_2O_{11}$: 1017.3957 $[M+H]^+$; found: 1017.3963.

(*S*,*E*)-3-(3,4-dihydroxyphenyl)-*N*-(1-((3-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)acrylamide (**1**)



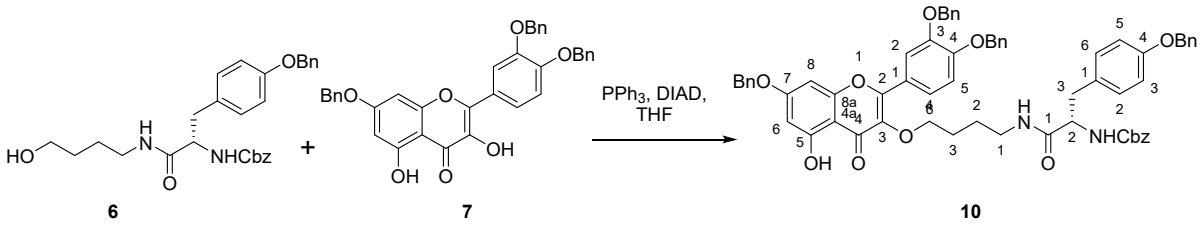
A solution of **9** (46 mg, 0.045 mmol) in EtOH/THF (1:2, 9 mL) was treated with Pd/C (40 mg) and methanesulfonic acid (3 µL, 46 µmol). The flask was evacuated and placed under hydrogen pressure and stirred 16 h at room temperature. The reaction mixture was filtered through Celite, the filter cake was washed with ethanol (10 mL) and the filtrate treated with triethylamine (10 µL, 72 µmol). The filtrate was concentrated *in vacuo* and dissolved in DMF (1 mL). The reaction mixture was treated with pyridine (6.5 µL, 80 µmol), followed by **12** (13.8 mg, 40 µmol). After stirring for 16 h, pyridine (6.5 µL, 80 µmol) was added and the reaction mixture was stirred for a further 5 h, whereupon further 12 was added (6.9 mg, 20 µmol). After a total of 40 h stirring, the reaction mixture was quenched with water (100 µL) and was concentrated *in vacuo*. Purification by flash chromatography on silica gel (78:10:10:2 to 67:15:15:3, DCM:MeOH:Acetone:Water) gave the *title compound* (11 mg, 0.016 mmol, 36 %) as a yellow solid. Analytical data as reported previously.[2]

Benzyl (*S*)-(3-(4-(benzyloxy)phenyl)-1-((4-hydroxybutyl)amino)-1-oxopropan-2-yl)carbamate (**6**)



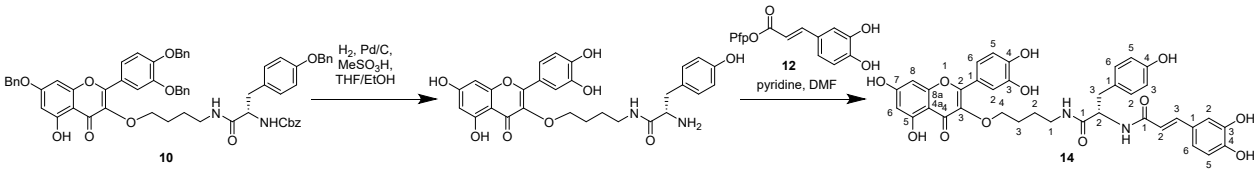
A solution of **3** (600 mg, 1.05 mmol) in dichloromethane (10 mL) was treated with butanolamine (187 mg, 0.19 mL, 2.1 mmol) dropwise. The reaction mixture was stirred for 1.5 hours and was then diluted with ethyl acetate (100 mL). The solution was then washed with 1 M HCl (2 x 100 mL), 1 M NaOH (2 x 100 mL), water (100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to yield the *title compound* (480 mg, 1.01 mmol, 96 %) as a colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.29 (m, 10 H, 10 x ArH), 7.10 (d, J = 8.5, 2 x H, 2 x ArH), 6.89 (d, J = 8.5, 2 x H, 2 x ArH), 6.11 (bt, J = 5.3, 1 H, NH), 5.45 (bd, J = 6.5, 1 H, NH), 5.07 (s, 2 H, CH_2), 5.02 (s, 2 H, CH_2), 4.29 (app q, J = 7.2, 1 H, CH), 3.54 (t, J = 5.5, 2 H, CH_2), 3.18 (app q, J = 6.1, 2 H, CH_2), 3.07-2.91 (m. 2 H, CH_2), 1.89 (bs, 1 H, OH), 1.49-1.38 (m, 4 H, 2 x CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C=O), 158.0 (C=O), 156.0 (C), 137.0 (C), 136.3 (C), 130.5 (2 x CH), 128.9 (C), 128.73 (2 x CH), 128.69 (2 x CH), 128.4 (CH), 128.2 (2 x CH), 128.1 (CH), 127.6 (2 x CH), 115.2 (2 x CH), 70.2 (CH_2), 67.2 (CH_2), 62.4 (CH_2), 56.8 (CH), 39.4 (CH_2), 38.0 (CH_2), 29.7 (CH_2), 26.0 (CH_2). HRMS (ESI-TOF): m/z calc'd for $C_{28}H_{32}N_2O_5$: 477.2384 $[M+H]^+$; found: 477.2387.

Benzyl (S)-(1-((4-((7-(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-5-hydroxy-4-oxo-4H-chromen-3-yl)oxy)butyl)amino)-3-(4-(benzyloxy)phenyl)-1-oxopropan-2-yl)carbamate (**10**)



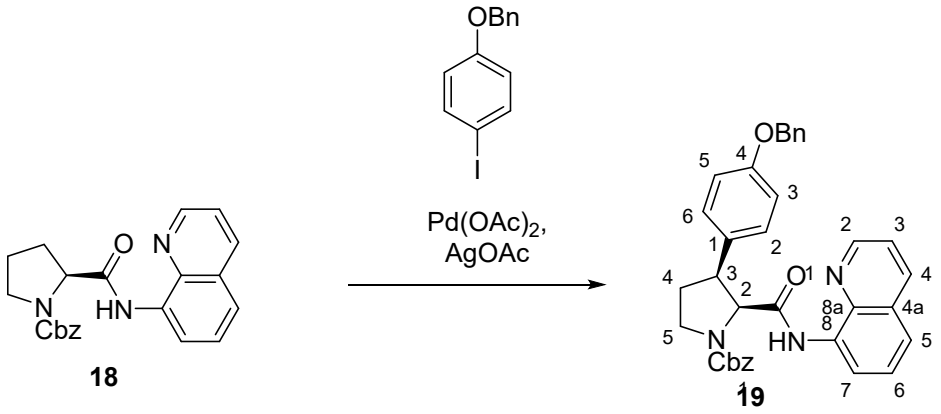
A solution of **6** (250 mg, 0.525 mmol), **7** (300 mg, 0.525 mmol) and triphenylphosphine (206.56 mg, 0.7875 mmol) in THF (25 mL) was cooled to 0 °C and treated dropwise with DIAD (0.123 mL, 0.7875 mmol). The reaction mixture was stirred at 0 °C for 2.5 hours and was diluted with ethyl acetate and saturated aqueous $NaHCO_3$ (100 mL each). The aqueous layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (2% MeOH in CH_2Cl_2) gave the *title compound* (150 mg, 0.145 mmol, 28 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.61 (m, 2 H, 2 x ArH), 7.48-7.25 (m, 25 H, 25 x ArH), 7.07-7.00 (m, 3 H, 3 x ArH), 6.78 (d, *J* = 8.1, 2 H, 2 x ArH), 6.45 (bs, 3 H, 2 x ArH, 1 x NH), 5.50 (d, *J* = 6.9, 1 H, NH), 5.24 (s, 2 H, CH_2), 5.21 (s, 2 H, CH_2), 5.13 (s, 2 H, CH_2), 5.06 (s, 2 H, CH_2), 4.90 (s, 2 H, CH_2), 4.41 (app q, *J* = 7.0, 1 H, CH), 3.83-3.68 (m, 2 H, CH_2), 3.22 (bs, 2 H, CH_2), 3.06-2.91 (m, 2 H, CH_2). 1.54 (bs, 4 H, 2 x CH_2) ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9 (C=O), 171.0 (C=O), 164.7 (C), 162.1 (C), 157.8 (C=O), 156.8 (C), 156.2 (C), 151.6 (C), 148.4 (C), 138.3 (C), 137.04 (C), 136.99 (C), 136.6 (C), 136.4 (C), 135.9 (C), 130.5 (2 x CH), 128.9 (2 x CH), 128.77 (2 x CH), 128.74 (2 x CH), 128.6 (4 x CH), 128.5 (C), 128.2 (CH), 128.1 (3 x CH), 128.0 (CH), 127.6 (2 x CH), 127.5 (2 x CH), 127.4 (2 x CH), 127.3 (2 x CH), 123.3 (C), 123.0 (CH), 115.4 (CH), 114.9 (2 x CH), 113.8 (CH), 106.2 (C), 98.8 (CH), 93.2 (CH), 72.6 (CH_2), 71.7 (CH_2), 71.0 (CH_2), 70.6 (CH_2), 69.9 (CH_2), 67.0 (CH_2), 56.5 (CH), 39.3 (CH_2), 38.4 (CH_2), 27.9 (CH_2), 25.8 (CH_2). 1 x C not observed. HRMS (ESI-TOF): m/z calc'd for $C_{64}H_{58}N_2O_{11}Na$: 1053.3938 $[M+Na]^+$; found: 1053.3925.

(*S*,*E*)-3-(3,4-dihydroxyphenyl)-*N*-(1-((4-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)butyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)acrylamide (**14**)



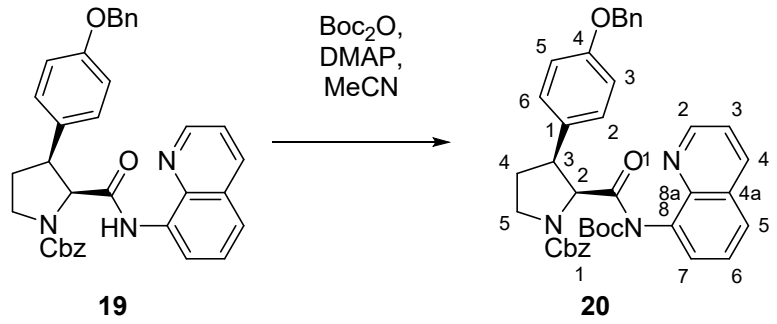
A solution of **10** (40 mg, 40 µmol) in EtOH/THF (1:2, 9 mL) was treated with Pd/C (40 mg) and methanesulfonic acid (3 µL, 46 µmol). The flask was evacuated and placed under hydrogen pressure and stirred 16 h at room temperature. The reaction mixture was filtered through Celite, the filter cake was washed with ethanol (10 mL) and the filtrate treated with triethylamine (10 µL, 72 µmol). The filtrate was concentrated *in vacuo* and dissolved in DMF (1 mL). The reaction mixture was treated with pyridine (6.5 µL, 80 µmol), followed by **12** (13.8 mg, 40 µmol). After stirring for 16 h, pyridine (6.5 µL, 80 µmol) was added and the reaction mixture was stirred for a further 5 h, whereupon further caffeate-Pfp ester was added (6.9 mg, 20 µmol). After a total of 40 h stirring, the reaction mixture was quenched with water (100 µL) and was concentrated *in vacuo*. Purification by flash chromatography on silica gel (78:10:10:2 to 67:15:15:3, CH_2Cl_2:MeOH:Acetone:Water) gave the *title compound* (11 mg, 16 µmol, 42%) as a yellow solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.57 (d, *J* = 2.0, 1 H, ArH), 7.47 (dd, *J* = 8.5, 2.1, 1 H, ArH), 7.34 (d, *J* = 15.6, 1 H, CH), 7.05 (d, *J* = 8.5, 2 H, 2 x ArH), 6.97 (d, *J* = 1.7, 1 H, ArH), 6.91-6.85 (m, 2 H, 2 x ArH), 6.73 (d, *J* = 8.1, 1 H, ArH), 6.67 (d, *J* = 8.5, 2 H, 2 x ArH), 6.42-6.36 (m, 2 H, 2 x ArH), 6.19 (d, *J* = 2.0, 1 H, ArH), 4.61 (t, *J* = 7.4, 1 H, CH), 3.85 (t, *J* = 5.4, 2 H, CH_2), 3.25-3.06 (m, 2 H, CH_2), 3.04-2.83 (m, 2 H, CH_2), 1.66-1.51 (m, 4 H, 2 x CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1 (C=O), 173.7 (C=O), 168.9 (C=O), 165.8 (C), 163.1 (C), 158.4 (C), 158.3 (C), 157.2 (C), 149.8 (C), 148.8 (C), 146.7 (C), 146.3 (C), 142.9 (CH), 138.6 (C), 131.3 (2 x CH), 129.0 (C), 128.2 (C), 123.1 (C), 122.5 (CH), 122.2 (CH), 117.9 (CH), 116.7 (CH), 116.4 (CH), 116.3 (CH), 116.2 (2 x CH), 115.1 (CH), 105.9 (C), 99.7 (CH), 94.7 (CH), 73.4 (CH_2), 56.8 (CH), 40.0 (CH_2), 38.6 (CH_2), 28.8 (CH_2), 26.7 (CH_2). HRMS (ESI-TOF): m/z calc'd for $C_{37}H_{35}N_2O_{12}$: 699.2190 $[M+H]^+$; found: 699.2191.

Benzyl (2*S*,3*S*)-3-(4-(benzyloxy)phenyl)-2-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (**19**)



A reaction vessel was charged with proline **18** (375 mg, 1.0 mmol), AgOAc (300 mg, 1.8 mmol), 4-benzyloxyphenyl iodide (558 mg, 1.8 mmol) and $Pd(OAc)_2$ (11 mg, 0.05 mmol). The reaction vessel was evacuated and back-filled with argon, then was sealed and stirred at 110 °C for 22 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), filtered through celite, and further washed with ethyl acetate (2 x 10 mL). The filtrate was concentrated *in vacuo*, and the crude residue was purified by flash chromatography on silica gel (18% EtOAc in toluene) to give the *title compound* (329 mg, 0.59 mmol, 59 %) as a colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H, NH), 8.63 (d, J = 4.5, 1 H), 8.61-8.55 (m, 1 H), 8.02 (dd, J = 15.2, 8.3, 1 H), 7.45-7.18 (m, 13 H), 7.02-6.90 (m, 2 H), 6.72-6.67 (m, 2 H), 5.30-5.09 (m, 2 H, CH_2), 4.79-4.57 (m, 3 H, CH_2 + CH), 4.19-4.06 (1 H, CH of CH_2), 3.78-3.60 (m, 2 H, CH + CH of CH_2), 2.86-2.67 (m, 1 H, CH of CH_2), 2.22-2.14 (p, J = 6.1, 1 H, CH of CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7 (C=O), 157.9 (C), 154.9 + 154.4 (C=O), 147.9 (CH), 138.1 (C), 136.7 (C), 136.3 (C), 135.9 (CH), 133.7 (C), 128.9 (2 x CH), 128.7 (CH), 128.3 (2 x CH), 127.9 (CH), 127.7 (2 x CH), 127.5 (2 x CH), 127.2 (2 x CH), 127.0 (CH), 121.4 (CH), 121.3 (CH), 116.2 (CH), 114.7 (2 x CH), 69.6 (CH_2), 67.0 (CH_2), 66.5 + 66.3 (CH), 48.0 + 47.1 (CH), 46.6 + 46.2 (CH_2), 28.6 + 27.9 (CH_2). 2 x C not observed. HRMS (ESI-TOF): m/z calc'd for $C_{35}H_{32}N_3O_4$: 558.2393 $[M+H]^+$; found: 558.2398.

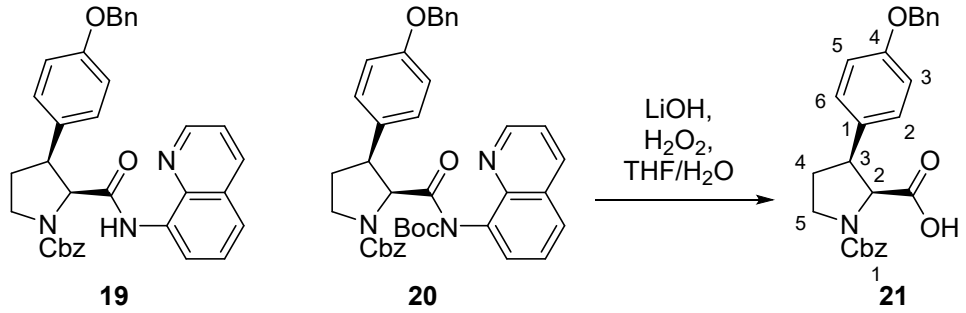
Benzyl (2*S*,3*S*)-3-(4-(benzyloxy)phenyl)-2-((tert-butoxycarbonyl)(quinolin-8-yl)carbamoyl) pyrrolidine-1-carboxylate (**20**)



19 **20**

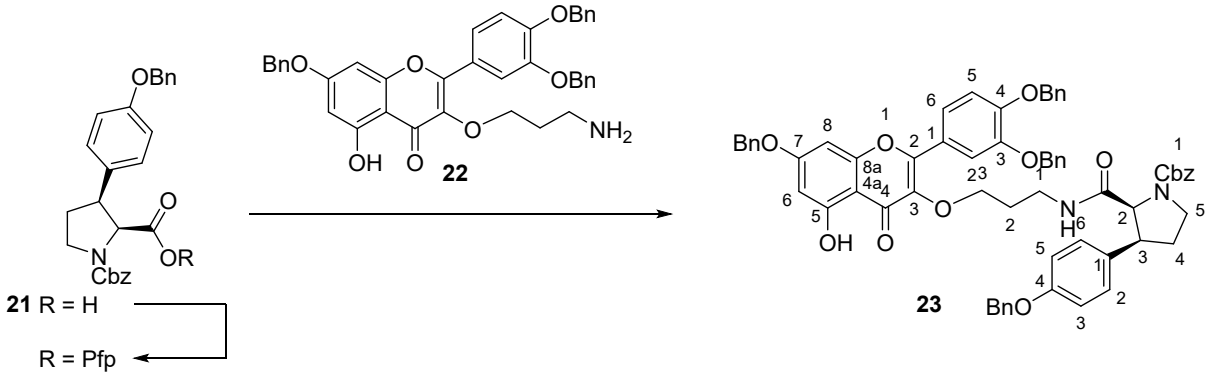
A reaction vessel was charged with proline **19** (112 mg, 0.2 mmol), Boc_2O (436 mg, 2.0 mmol) and DMAP (50 mg, 0.4 mmol), and acetonitrile (0.4 mL) was added. The reaction vessel was evacuated briefly and backfilled with argon, and was then sealed and stirred at 55 °C. Further addition of Boc_2O (3 x 200 mg) was carried out after 1.5, 22, and 26 hours, and the temperature was increased to 70 °C after 22 hours. After 44 hours the reaction mixture was cooled to rt, diluted with sat aq ammonium chloride (2 mL) and CH_2Cl_2 (2 mL). The layers were separated and the aqueous was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (20% ethyl acetate in toluene) to yield the *title compound* mixed with starting material **19**, which was used in the next step without further purification. HRMS (ESI-TOF): m/z calc'd for $C_{40}H_{40}N_3O_6$: 658.2917 $[M+H]^+$; found: 658.2915.

(2*S*,3*S*)-1-((benzyloxy)carbonyl)-3-(4-(benzyloxy)phenyl)pyrrolidine-2-carboxylic acid (**21**)



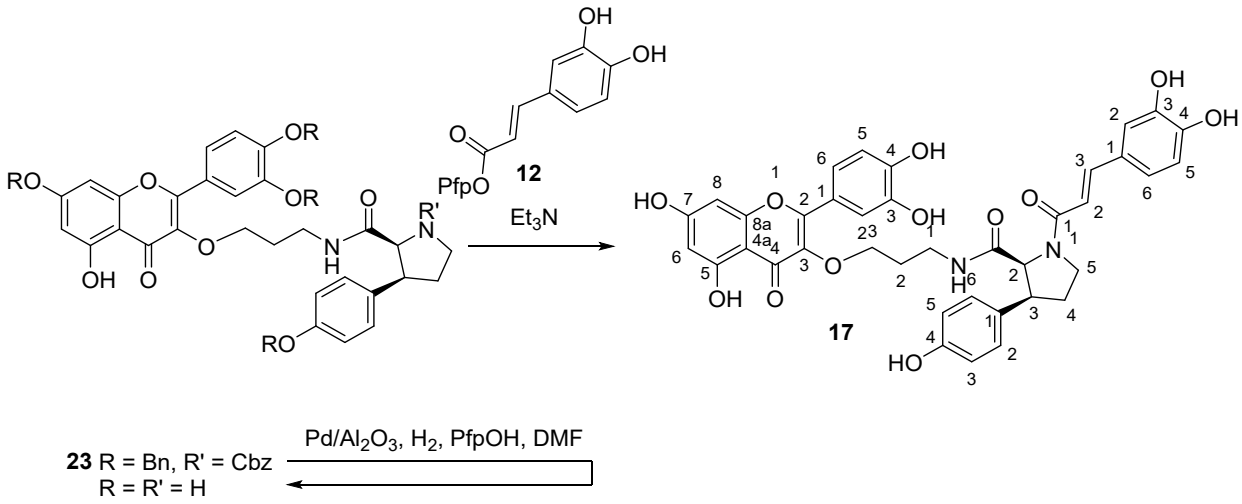
A solution of H_2O_2 (306 µL, 3.0 mmol, 30% in water) in THF (3 mL) was added to a solution of LiOH•H_2O (84 mg, 2.0 mmol) in H_2O (3 mL) at 0 °C under argon. This solution was then added to the mixture of **19** and **20** in THF (4 mL) at 0 °C under argon. The resultant solution was stirred at room temperature for 44 hours, whereupon sodium thiosulfate (10 mL) and ethyl acetate (10 mL) were added, and the solution was acidified to pH = 2 with 1 M HCl. The layers were separated and the aqueous was further extracted with ethyl acetate (3 x 10 mL), and the pooled organics dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (E = 5% methanol in dichloromethane) to yield the *title compound* (25.8 mg, 60 µmol, 30% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.23 (m, 10H), 7.13 (dd, J = 8.3, 5.4 2 H), 6.89 (d, J = 8.4, 2 H), 5.14, 5.08 (ABq, 2H, J_{AB} = 12.6), 4.98 (s, 2H), 4.52 (app dd, J = 8.7, 4.9), 3.87 (app t, J = 9.5), 3.68-3.57 (m, 1H), 3.54-3.46 (m, 1H), 2.59-2.43 (m, 1H), 2.14-2.06 (m, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6 + 175.2 (C=O), 158.34 + 158.30 (C), 155.1 + 154.4 (C=O), 137.1 + 137.0 (C), 136.6 + 136.4 (C), 129.1 + 129.0 (2 x CH), 128.7 (2 x CH), 128.6 + 128.5 (2 x CH), 128.5 + 128.3 (C), 128.2 + 128.0 (3 x CH), 127.7 (CH), 127.6 (2 x CH), 114.9 (2 x CH), 70.1 (CH_2), 67.4 + 67.3 (CH_2), 64.1 + 63.8 (CH), 47.5 + 46.5 (CH), 46.4 + 46.1 (CH_2), 28.7 + 27.7 (CH_2). HRMS (ESI-TOF): m/z calc'd for $C_{26}H_{25}NO_5Na$: 454.1625 $[M+Na]^+$; found: 454.1629.

Benzyl (2*S*,3*S*)-2-((3-((7-(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-5-hydroxy-4-oxo-4H-chromen-3-yl)oxy)propyl)carbamoyl)-3-(4-(benzyloxy)phenyl)pyrrolidine-1-carboxylate (**23**)



A solution of **21** (25.8 mg, 60 µmol) in DMF (0.2 mL) was treated with pyridine (5.3 µL, 66 µmol) and pentafluorophenyl trifluoroacetate (12 µL, 70 µmol). The reaction mixture was stirred at room temperature for 90 minutes, diluted with ethyl acetate (20 mL) and washed with 0.1 M HCl and 5% $NaHCO_3$ (3 x 20 mL each) and brine (20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude Pfp ester was then taken up in CH_2Cl_2 (1 mL) and was added to a solution of **22** (42 mg, 66 µmol) and pyridine (10 µL, 120 µmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at room temperature for three days, with further additions of amine (42 mg, t = 24h) and triethylamine (8.4 µL, 60 µmol, t = 43h and t = 66h). The reaction mixture was diluted with CH_2Cl_2 (10 mL) and was washed with 1 M HCl (3 x 5 mL) and brine (5 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (20% to 40% ethyl acetate in toluene) to yield the *title compound* (36.4 mg, 35 µmol, 58% over two steps) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.51 (s) + 12.38 (s, 1 H), 7.68 (d, *J* = 3.1, 1H), 7.62 (d, *J* = 8.3, 1H), 7.49-7.17 (m, 27H), 7.00 (d, *J* = 8.7, 1H), 6.73 (app dd, *J* = 16.4, 8.3, 2H), 6.53-6.48 (m, 2H), 5.25-5.03 (m, 8H), 4.85-4.79 (m, 2H), 4.48 (app dd, *J* = 12.1, 8.5, 1H), 3.97 (app q, *J* = 9.0), 3.65-3.13 (m, 5H), 2.98-2.89 (m, 1H), 2.73 (app sept, *J* = 11.0, 1H), 2.08 (bs, 1H), 1.52-1.22 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8 (C=O), 170.0 (C=O), 164.9 + 164.8 (C), 161.99 + 161.95 (C), 158.0 (C=O), 156.8 (C), 156.3 (C), 154.9 + 154.6 (C), 151.73 + 151.65 (C), 148.6 (C), 137.8 + 137.7 (C), 137.0 (C), 136.9 (C), 136.61 + 136.56 (C), 135.8 (C), 129.7 (2 x CH), 129.5 (CH), 128.9 (2 x CH), 128.8 (2 x CH), 128.7 (2 x CH), 128.54 (2 x CH), 128.48 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.0 (2 x CH), 127.64 (CH), 127.59 (2 x CH), 127.4 (2 x CH), 127.29 (2 x CH), 127.26 (2 x CH), 123.1 (C), 122.7 (CH), 115.0 (CH), 114.5 (2 x CH), 113.9 (CH), 106.1 (C), 99.0 (CH), 93.3 (CH), 71.63 + 71.59 (CH_2), 71.0 (CH_2), 70.6 (CH_2), 69.9 (CH_2), 68.4 + 68.3 (CH_2), 67.0 + 66.9 (CH_2), 65.7 + 65.4 (CH), 47.9 + 47.1 (CH), 46.7 + 46.3 (CH_2), 34.8 + 34.6 (CH_2), 29.0 + 28.4 + 28.1 (2 x CH_2). HRMS (ESI-TOF): m/z calc'd for $C_{65}H_{59}N_2O_{11}$: 1043.4113 $[M+H]^+$; found: 1043.4128.

(2*S*,3*S*)-*N*-(3-((2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)propyl)-1-((*E*)-3-(3,4-dihydroxyphenyl)acryloyl)-3-(4-hydroxyphenyl)pyrrolidine-2-carboxamide (**17**)

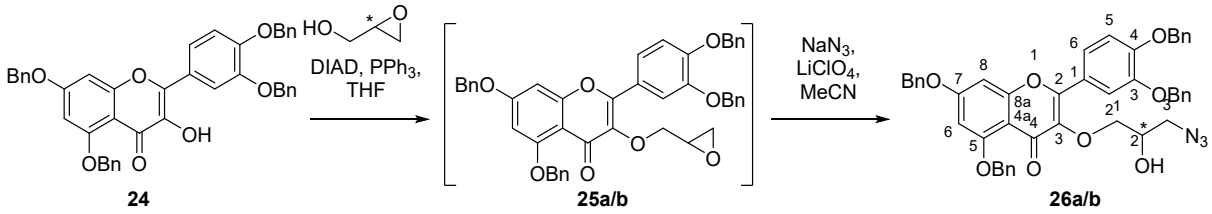


A solution of **23** (36 mg, 35 µmol) in DMF (1 mL) was treated with a solution of PfpOH (32 mg, 0.17 mmol) in DMF (1 mL) and Pd/Al_2O_3 (10 mg), placed under hydrogen pressure and stirred for 18 hours at room temperature. The reaction mixture was filtered through celite and the filter cake washed with DMF (0.5 mL). The filtrate was cooled to 0 °C and was treated with Et_3N (10 µL, 70 µmol) and **12** (24 mg, 70 µmol). The reaction mixture was then stirred at room temperature for 4 hours, cooled to 0 °C and diluted with HCl (0.1 M, 5 mL) and EtOAc (5 mL). The layers were separated and the organic layer was further washed with HCl (0.1 M, 3 x 5 mL) and brine (5 mL), and the pooled aqueous layers were extracted with EtOAc (5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (79:10:10:1 CH_2Cl_2:MeOH:Acetone:Water + 0.1% formic acid) gave the *title compound* (18.3 mg, 26 µmol, 75%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 + 7.54 (2 x d, *J* = 2.1, 1H), 7.46 + 7.45 (2 x dd, *J* = 8.4, 2.1, 1H), 7.39 + 7.38 (2 x d, *J* = 15.3, 1H), 7.12 + 7.09 (2 x d, *J* = 8.5, 1H), 6.97-6.82 (m, 3H), 6.74-6.47 (m, 4H), 6.40 + 6.33 (2 x d, *J* = 2.0, 1H), 6.23 + 6.22 (2 x d, *J* = 2.0, 1H), 4.75 + 4.66 (2 x d, *J* = 8.5, 1H), 4.12 (t, *J* = 9.0) + 4.03 (dd, *J* = 11.7, 9.0, 1H), 3.79-3.53 (m, 3H), 3.29-3.11 (m, 2H), 2.75-2.56 (m, 1H), 2.16 + 2.08 (2 x p, *J* = 6.0, 1H), 1.70-1.43 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 172.3, 167.8, 165.9, 162.9, 158.4, 158.3, 157.8, 149.9, 149.1, 146.6, 146.4, 138.5, 130.6, 128.8, 128.2, 122.9, 122.5, 122.3, 116.6, 116.5, 116.4, 116.2, 116.1, 115.6, 115.3, 115.2, 105.9, 99.8, 94.9, 70.5, 66.8, 48.0, 47.5, 36.9, 30.3, 29.8. HRMS (ESI-TOF): m/z calc'd for $C_{38}H_{34}N_2O_{12}$: 711.2185 $[M+H]^+$; found: 711.2188

(*R*)-3-(3-azido-2-hydroxypropoxy)-5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-4H-chromen-4-one (**26a**)

OR

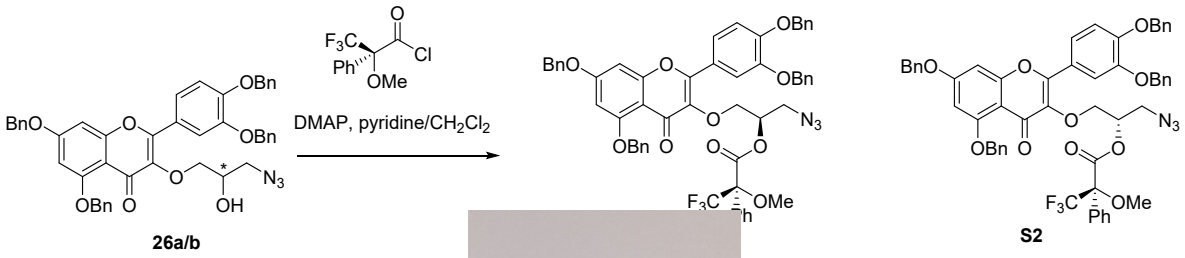
(*S*)-3-(3-azido-2-hydroxypropoxy)-5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-4H-chromen-4-one (**26b**)



A solution of **24**[3] (520 mg, 0.78 mmol), *R*-glycidol (78 μL, 1.2 mmol) and triphenylphosphine (310 mg, 1.2 mmol) in THF (15 mL) was cooled to 0 °C and treated dropwise with DIAD (0.24 mL, 1.2 mmol). The reaction mixture was stirred at 0 °C for 16 hours and was diluted with ethyl acetate and saturated aqueous $NaHCO_3$ (40 mL each). The aqueous layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was triturated with methanol (8.0 mL), filtered, and washed with methanol (5.0 mL) and dried under vacuum to provide intermediate epoxide **25b** as a pink solid, which was used in the next step without further purification.

Epoxide **25b** was taken up in acetonitrile (17 mL) and was treated with lithium perchlorate (220 mg, 2.1 mmol) and sodium azide (130 mg, 2.1 mmol) and stirred at 90 °C. Upon completion (2 h), the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL). The combined organics were washed with water (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (ethyl acetate/toluene 1:9) to provide *title compound* **26b** as a colourless solid (0.20 g, 0.26 mmol, 33%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.0 Hz, 1H, ArH), 7.64 (dd, *J* = 8.6, 2.0 Hz, 1H, ArH), 7.58 (d, *J* = 7.5, 2H, 2 x ArH), 7.50-7.30 (m, 18H, 18 x ArH), 7.05 (d, *J* = 8.6 Hz, 1 H, ArH), 6.54 (d, *J* = 2.1 Hz, 1 H, ArH), 6.48 (d, *J* = 2.1 Hz, 1 H, ArH), 6.03 (d, *J* = 3.2, 1 H, OH), 5.26 (s, 4H, 2 x CH_2), 5.23 (s, 2H, CH_2), 5.10 (s, 2H, CH_2), 4.01-3.94 (m, 1H, CH), 3.83 (d, *J* = 4.5, 2H, CH_2), 3.44-3.33 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7 (C=O), 163.4 (C), 159.9 (C), 158.9 (C), 153.8 (C), 151.3 (C), 148.7 (C), 140.1 (C), 137.1 (C), 136.7 (C), 136.2 (C), 135.6 (C), 128.9 (2 x CH), 128.8 (4 x CH), 128.7 (2 x CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.7 (2 x CH), 127.3 (4 x CH), 126.7 (2 x CH), 123.2 (C), 122.5 (CH), 114.9 (CH), 114.0 (CH), 109.5 (C), 98.4 (CH), 94.0 (CH), 75.3 (CH_2), 71.5 (CH_2), 71.02 (CH_2), 70.97 (CH_2), 70.7 (CH_2), 69.7 (CH), 53.0 (CH_2). HRMS (ESI-TOF): m/z calc'd for $C_{46}H_{39}N_3O_8Na$: 784.2635 $[M+Na]^+$; found: 784.2637.

An equivalent reaction starting with *S*-glycidol provided **26a** in 50% yield, analytical data as above.



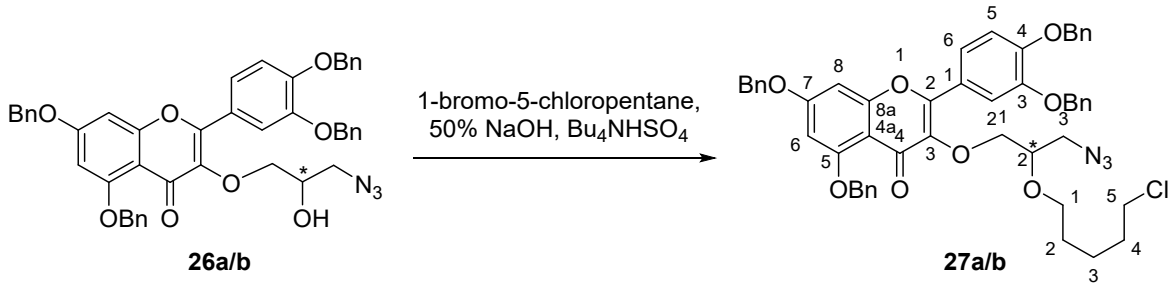
A solution of DMAP in pyridine (2 mg/r) alcohol (**26a** or **26b**, 1 µmol), followed by a solution of Mosher's acid chlori , 10 µL). Stirred for 1 hour at room temperature, analysed by TLC (20 cm l ethyl acetate in toluene, stained in 1% $FeCl_3$ in $MeOH/H_2O$ (1:1).

S1 **S2**

(*R*)-3-(3-Azido-2-((5-chloropentyl)oxy)propoxy)-5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-4H-chromen-4-one (**27a**)

OR

(*S*)-3-(3-Azido-2-((5-chloropentyl)oxy)propoxy)-5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-4H-chromen-4-one (**27b**)

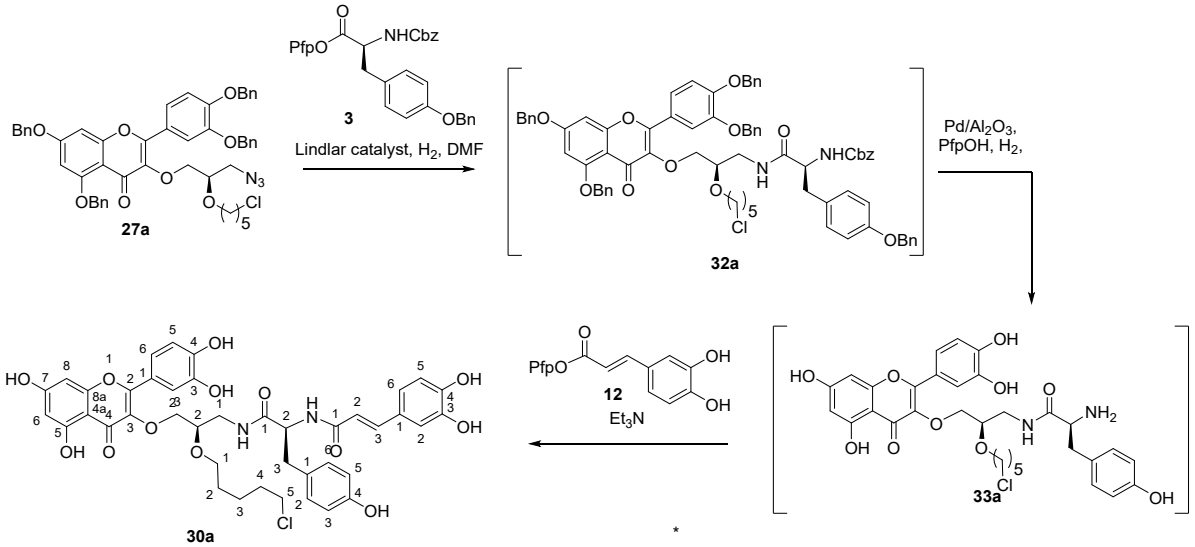


26a/b **27a/b**

A solution of **26a** (360 mg, 0.47 mmol) in bromochloropentane (1.9 mL, 14 mmol) was treated with 50% NaOH (3.4 mL) and tetrabutylammonium bisulfate (48 mg, 0.14 mmol). The biphasic mixture was stirred vigorously at room temperature for 4 hours, and then was cooled to 0 °C and was treated with water (15 mL) and CH_2Cl_2 (30 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (5% ethyl acetate in toluene) gave *title compound* **27a** (330 mg, 0.38 mmol, 81%) as a colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.64 (m, 2H, 2 x ArH), 7.58 (d, *J* = 7.7, 2H, 2 x ArH), 7.51-7.28 (m, 18H, 18 x ArH), 7.03 (d, *J* = 8.5 Hz, 1 H, ArH), 6.52 (d, *J* = 2.2 Hz, 1 H, ArH), 6.45 (d, *J* = 2.2 Hz, 1 H, ArH), 5.26 (s, 6H, 3 x CH_2), 5.09 (s, 2H, CH_2), 4.13 (dd, *J* = 4.7, 10.3) + 4.03 (dd, *J* = 10.2, 5.4, 2 H, CH_2), 3.74 (app p, *J* = 4.9, 1 H, CH), 3.57-3.33 (m, 6 H, 3 x CH_2), 1.72 (p, *J* = 7.2, 2 H, CH_2), 1.58-1.37 (m, 4 H, 2 x CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 (C=O), 162.9 (C), 159.9 (C), 158.8 (C), 152.8 (C), 151.1 (C), 148.6 (C), 140.2 (C), 137.2 (C), 136.8 (C), 136.5 (C), 135.8 (C), 128.9 (2 x CH), 128.7 (4 x CH), 128.7 (2 x CH), 128.6 (CH), 128.14 (CH), 128.06 (CH), 127.8 (CH), 127.7 (2 x CH), 127.5 (2 x CH), 127.3 (2 x CH), 126.8 (2 x CH), 123.7 (C), 122.8 (CH), 115.5 (CH), 114.0 (CH), 110.1 (C), 98.3 (CH), 94.0 (CH), 78.2 (CH), 71.7 (CH_2), 71.1 (2 x CH_2), 70.9 (CH_2), 70.6 (CH_2), 70.1 (CH_2), 52.3 (CH_2), 45.1 (CH_2), 32.6 (CH_2), 29.3 (CH_2), 23.5 (CH_2). HRMS (ESI-TOF): m/z calc'd for $C_{51}H_{49}N_3O_8Cl$: 866.3208 $[M+H]^+$; found: 866.3209.

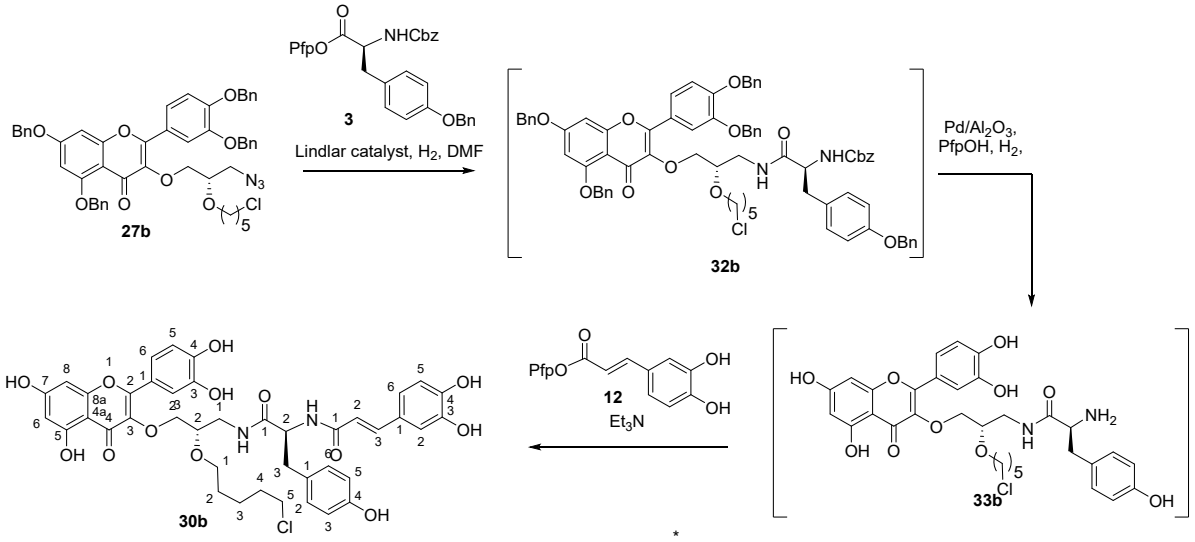
An equivalent reaction starting with **26b** provided **27b** in 91% yield, analytical data as above.

(*E*)-*N*-((*S*)-1-(((*R*)-2-((5-Chloropentyl)oxy)-3-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-3-(3,4-dihydroxyphenyl)acrylamide (**30a**)



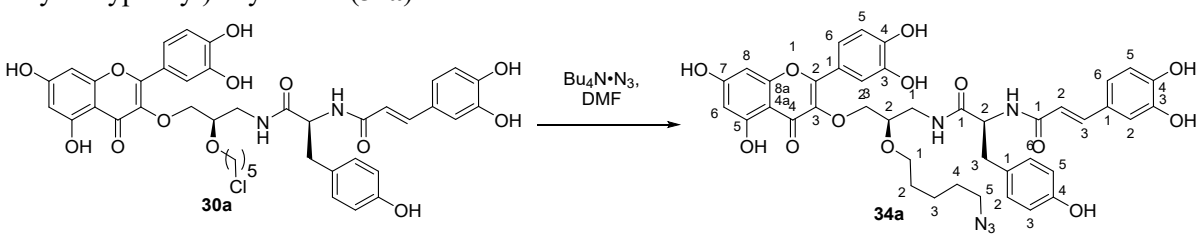
A solution of azide (**27a**) (174 mg, 0.201 mmol) and tyrosine derivative **3** (116 mg, 0.203 mol) in DMF (11.6 mL) was treated with Lindlar catalyst (174 mg), placed under hydrogen pressure (1 atm) and stirred for 16 hours at room temperature. The reaction mixture was filtered through celite, and the celite washed with DMF (2.50 mL) to give a solution of amide **32a**. This solution was treated with 5% palladium on alumina (54.0 mg) and pentafluorophenol (148 mg, 0.803 mmol), placed under hydrogen pressure (1 atm) and stirred for 16 hours at room temperature. The reaction mixture was filtered through celite, and the celite washed with DMF (5.0 mL) to give a solution of amine **33a**. This solution was evacuated-backfilled with argon, cooled to 0 °C and treated with **12** (140 mg, 0.402 mmol) and triethylamine (56.8 µL, 0.402 mmol). The reaction mixture was stirred at room temperature for 48 hours at room temperature, cooled to 0 °C and diluted with ethyl acetate (80 mL) and 0.1 M HCl (30 mL). The layers were separated and the organic layer further washed with 0.1 M HCl (30 mL) and brine (30 mL). The pooled aqueous washes were back-extracted with ethyl acetate (30 mL) and the combined organics were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (79:10:10:1 CH_2Cl_2:Acetone:MeOH:H_2O + 0.1% HCOOH to 73:12.5:12.5:2 CH_2Cl_2:Acetone:MeOH:H_2O + 0.1% HCOOH) gave the *title compound* (65.0 mg, 0.081 mmol, 40%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 2.1, 1H), 7.53 (dd, *J* = 8.6, 2.1, 1H), 7.31 (d, *J* = 15.6, 1H), 7.05 (d, *J* = 8.5, 2H), 6.92 (d, *J* = 1.8, 1H), 6.86 (d, *J* = 8.4, 1H), 6.79 (dd, *J* = 8.3, 1.8), 6.70 (d, *J* = 8.1, 1H), 6.57 (d, *J* = 8.5, 2H), 6.38 (d, *J* = 15.6, 1H), 6.30 (d, *J* = 1.7, 1H), 6.18 (d, *J* = 1.7, 1H), 4.71 (t, *J* = 7.5, 1H), 3.77-3.68 (m, 2H), 3.50 (t, *J* = 6.7, 2H), 3.44-3.37 (m, 3H), 3.24 (dd, *J* = 10.3, 2.2, 1H), 3.04 (dd, *J* = 13.6, 7.8, 1H), 2.91 (dd, *J* = 13.6, 7.5, 1H), 1.72 (p, *J* = 7.2, 2H), 1.57-1.50 (m, 2H), 1.45-1.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 174.0, 169.0, 165.8, 162.7, 158.2, 158.0, 157.2, 149.9, 148.7, 146.5, 146.4, 143.0, 138.0, 131.4 (x2), 129.0, 128.0, 122.73, 122.69, 122.2, 117.7, 116.5, 116.4, 116.3, 116.2 (x2), 115.2, 105.8, 99.9, 94.8, 77.1, 70.5, 57.3, 45.7, 40.3, 38.4, 33.6, 30.1, 24.5. HRMS (ESI-TOF): m/z calc'd for $C_{41}H_{42}ClN_2O_{13}$: 805.2370 $[M+H]^+$; found: 805.2371

(*E*)-*N*-((*S*)-1-(((*S*)-2-((5-Chloropentyl)oxy)-3-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-3-(3,4-dihydroxyphenyl)acrylamide (**30b**)



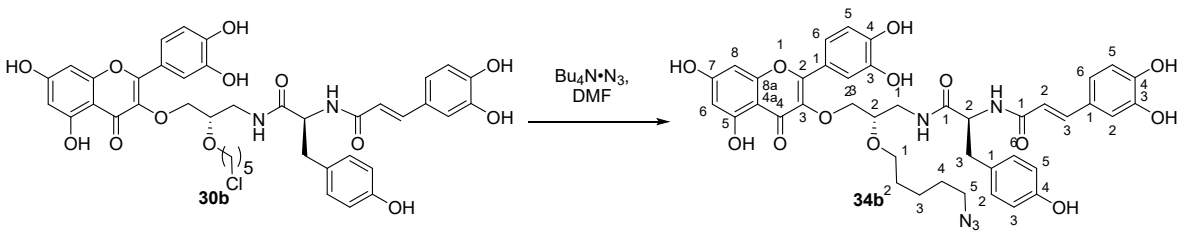
A solution of azide (**27b**) (96 mg, 0.11 mmol) and tyrosine derivative **3** (64 mg, 0.11 mol) in DMF (6.0 mL) was treated with Lindlar catalyst (96 mg), placed under hydrogen pressure (1 atm) and stirred for 16 hours at room temperature. The reaction mixture was filtered through celite, and the celite washed with DMF (2.5 mL) to give a solution of amide **32a**. This solution was treated with 5% palladium on alumina (30 mg) and pentafluorophenol (82 mg, 0.44 mmol), placed under hydrogen pressure (1 atm) and stirred for 4 hours at room temperature. The reaction mixture was filtered through celite, and the celite washed with DMF (2.5 mL) to give a solution of amine **33a**. This solution was evacuated-backfilled with argon, cooled to 0 °C and treated with **12** (77 mg, 0.22 mmol) and triethylamine (31 µL, 0.22 mmol). The reaction mixture was stirred at room temperature for 16 hours at room temperature, cooled to 0 °C and diluted with ethyl acetate (80 mL) and 0.1 M HCl (30 mL). The layers were separated and the organic layer further washed with 0.1 M HCl (30 mL) and brine (30 mL). The pooled aqueous washes were back-extracted with ethyl acetate (30 mL) and the combined organics were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (79:10:10:1 CH_2Cl_2:Acetone:MeOH:H_2O + 0.1% HCOOH to 73:12.5:12.5:2 CH_2Cl_2:Acetone:MeOH:H_2O + 0.1% HCOOH) gave the *title compound* (50 mg, 0.06 mmol, 56%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (bs, 1H), 7.52 (d, *J* = 8.3, 1H), 7.30 (d, *J* = 15.7, 1H), 7.08 (d, *J* = 8.3, 2H), 6.92 (bs, 1H), 6.85 (d, *J* = 8.4), 6.80 (d, *J* = 8.1, 1H), 6.71-6.66 (m, 3H), 6.37 (d, *J* = 15.7, 1H), 6.30 (bs, 1H), 6.16 (bs, 1H), 4.69 (t, *J* = 7.2, 1H), 3.85-3.78 (m, 2H), 3.55-3.45 (m, 5H)3.39-3.35 (m, 2H), 3.09 (dd, *J* = 13.5, 6.5, 1H), 2.92 (dd, *J* = 13.5, 8.0, 1H), 1.68 (p, *J* = 7.1, 2H), 1.53-1.45 (m, 2H), 1.42-1.36 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 174.1 + 174.0, 169.0, 165.7, 164.7, 162.8, 158.2, 157.9, 149.8, 148.7, 146.5, 146.3, 142.9, 138.1, 131.3 (x2), 129.1, 128.1, 122.8, 122.7, 122.2, 117.7, 116.6, 116.4 (x2), 116.3 (x2), 115.2, 105.8, 99.8, 94.8, 77.7, 71.8, 70.6, 57.2 + 57.1, 45.7, 40.7 + 40.6, 38.3, 33.6, 30.2, 24.5. HRMS (ESI-TOF): m/z calc'd for $C_{41}H_{42}ClN_2O_{13}$: 805.2370 $[M+H]^+$; found: 805.2368.

(*E*)-*N*-((*S*)-1-(((*R*)-2-((5-Azidopentyl)oxy)-3-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-3-(3,4-dihydroxyphenyl)acrylamide (**34a**)



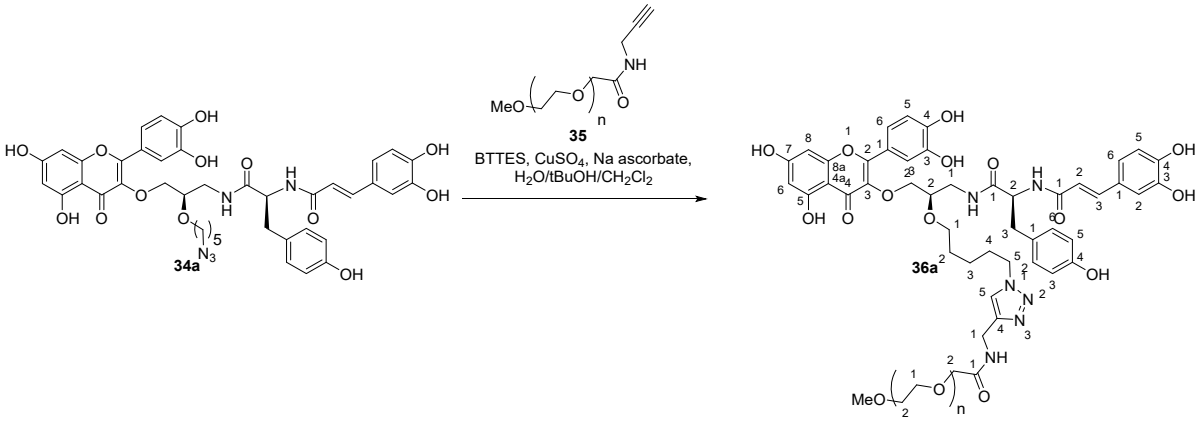
A solution of **30a** (40 mg, 50 µmol) in DMF (0.5 mL) was treated with tetrabutylammonium azide (100 mg, 350 µmol) and stirred at 60 °C for 21 hours. The reaction mixture was diluted with ethyl acetate (10 mL), washed with HCl (0.1 M, 3 x 5 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (79:10:10:1 CH_2Cl_2:Acetone:MeOH:H_2O + 0.1% HCOOH) gave the *title compound* (26.5 mg, 33 µmol, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 2.0, 1H), 7.54 (dd, *J* = 8.4, 2.1, 1H), 7.31 (d, *J* = 15.7, 1H), 7.05 (d, *J* = 8.4, 2H), 6.92 (d, *J* = 1.8, 1H), 6.87 (d, *J* = 8.4, 1H), 6.79 (dd, *J* = 8.3, 1.8, 1H), 6.70 (d, *J* = 8.2, 1H), 6.57 (d, *J* = 8.4, 2H), 6.38 (d, *J* = 15.7, 1H), 6.32 (d, *J* = 1.9, 1H), 6.19 (d, *J* = 1.9, 1H), 4.70 (t, *J* = 7.5, 1H), 3.76-3.68 (m, 2H), 3.45-3.33 (m, 4H), 3.28-3.21 (m, 3H), 3.04 (dd, *J* = 13.7, 7.6, 1H), 2.91 (dd, *J* = 13.7, 7.6, 1H), 1.61-1.50 (m, 4H), 1.41-1.33 (m, 2H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 173.9, 169.0, 165.9, 162.8, 158.3, 158.1, 157.3, 149.9, 148.8, 146.5, 146.4, 143.0, 138.1, 131.4 (x2), 129.0, 128.1, 122.8, 122.7, 122.2, 117.7, 116.6, 116.4 (x2), 116.2 (x2), 115.2, 105.8, 99.9, 94.8, 77.2, 71.2, 70.5, 57.3, 52.4, 40.3, 38.4, 30.4, 29.7, 24.4. HRMS (ESI-TOF): m/z calc'd for $C_{41}H_{42}N_5O_{13}$: 812.2774 $[M+H]^+$; found: 812.2771.

(*E*)-*N*-((*S*)-1-(((*S*)-2-((5-Azidopentyl)oxy)-3-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-3-(3,4-dihydroxyphenyl)acrylamide (**34b**)



A solution of **30b** (40 mg, 50 µmol) in DMF (0.5 mL) was treated with tetrabutylammonium azide (100 mg, 350 µmol) and stirred at 60 °C for 21 hours. The reaction mixture was diluted with ethyl acetate (10 mL), washed with HCl (0.1 M, 3 x 5 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (79:10:10:1 CH_2Cl_2:Acetone:MeOH:H_2O + 0.1% HCOOH) gave the *title compound* (29.8 mg, 37 µmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (bs, 1H), 7.52 (d, *J* = 8.3, 1H), 7.30 (d, *J* = 15.7, 1H), 7.08 (d, *J* = 8.3, 2H), 6.92 (bs, 1H), 6.85 (d, *J* = 8.4), 6.80 (d, *J* = 8.1, 1H), 6.71-6.66 (m, 3H), 6.37 (d, *J* = 15.7, 1H), 6.30 (bs, 1H), 6.16 (bs, 1H), 4.69 (t, *J* = 7.2, 1H), 3.85-3.78 (m, 2H), 3.55-3.45 (m, 5H), 3.39-3.35 (m, 2H), 3.09 (dd, *J* = 13.5, 6.5, 1H), 2.92 (dd, *J* = 13.5, 8.0, 1H), 1.68 (p, *J* = 7.1, 2H), 1.53-1.45 (m, 2H), 1.42-1.36 (m, 2H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 174.0, 169.0, 165.8, 162.9, 158.3, 158.0, 157.2 149.9, 148.8, 146.5, 146.3, 142.9, 138.2, 131.3 (x2), 129.2, 128.1, 122.8, 122.7, 122.2, 117.7, 116.6, 116.4 (x2), 116.3 (x2), 115.2, 105.8, 99.8, 94.8, 77.7, 71.9, 70.6, 57.1, 52.4, 40.6, 38.3, 30.5, 29.7, 24.3. HRMS (ESI-TOF): m/z calc'd for $C_{41}H_{42}N_5O_{13}$: 812.2774 $[M+H]^+$; found: 812.2761.

(*E*)-3-(3,4-dihydroxyphenyl)-N-((*S*)-1-(((*S*)-3-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)-2-((5-(4-((2-(methoxyPEG)acetamido)methyl)-1H-1,2,3-triazol-1-yl)pentyl)oxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)acrylamide (**36a**)



A suspension of **34a** (6.5 mg, 8 µmol), PEG-5000 alkyne **35**[4] (20 mg, 4 µmol), and BTTES ligand (0.2 mg, 0.4 µmol) in CH_2Cl_2 (0.2 mL) and tBuOH (0.4 mL) treated with a solution of $CuSO_4$•$5H_2O$ (0.1 mg, 0.4 µmol) in water (0.1 mL) and sodium ascorbate (0.86 mg, 4.8 µmol) in water (0.1 mL). Stirred at room temperature for 39 hours and concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (1 mL), filtered through celite and concentrated *in vacuo*. The residue was dissolved in DMF (0.5 mL), cooled to 0 °C and precipitated with Et_2O. The precipitate was collected by centrifugation and washed with ice-cold Et_2O (2 x 1 mL) to give a pale yellow solid (22.8 mg, 98% from **35**).

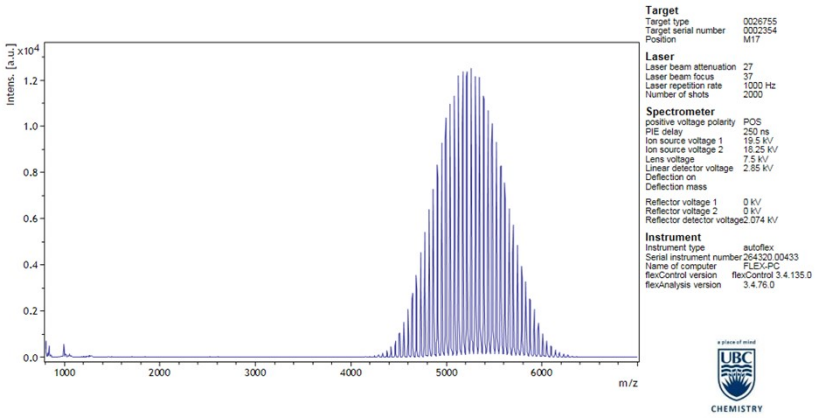


*Figure 1: MALDI-TOF analysis of **35***

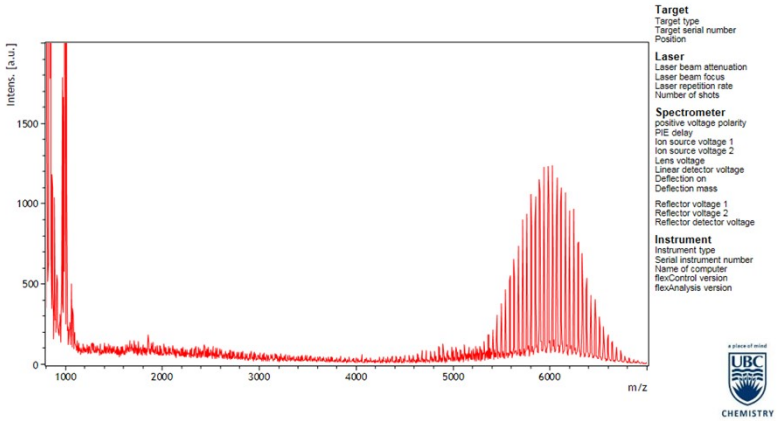
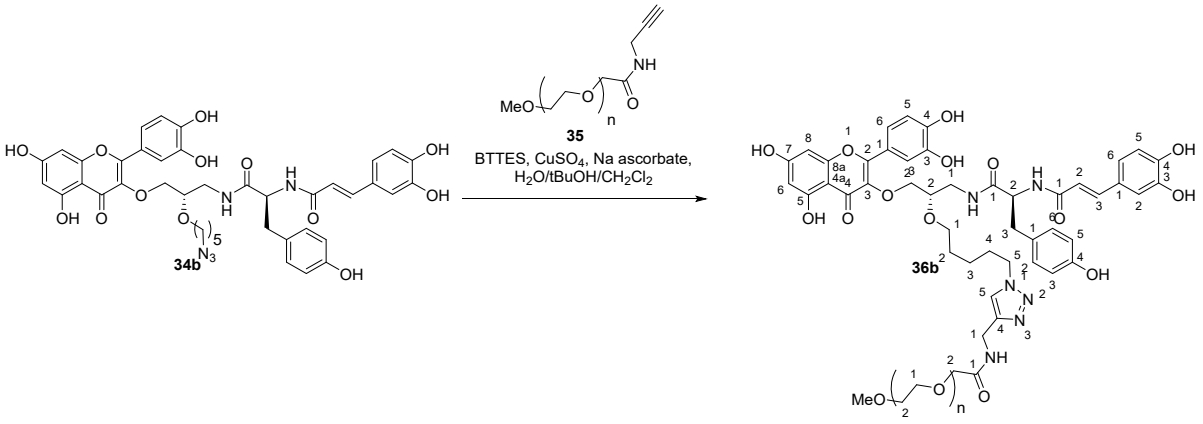


*Figure 2: MALDI-TOF analysis of **36a***

(*E*)-3-(3,4-dihydroxyphenyl)-N-((*S*)-1-(((*S*)-3-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)-2-((5-(4-((2-(methoxyPEG)acetamido)methyl)-1H-1,2,3-triazol-1-yl)pentyl)oxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)acrylamide (**36b**)



A suspension of **34b** (6.5 mg, 8 µmol), PEG-5000 alkyne **35** (20 mg, 4 µmol), and BTTES ligand (0.2 mg, 0.4 µmol) in CH_2Cl_2 (0.2 mL) and tBuOH (0.4 mL) treated with a solution of $CuSO_4 \bullet 5H_2O$ (0.1 mg, 0.4 µmol) in water (0.1 mL) and sodium ascorbate (0.86 mg, 4.8 µmol) in water (0.1 mL). Stirred at room temperature for 19 hours and concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (1 mL), filtered through celite and concentrated *in vacuo*. The residue was dissolved in DMF (0.5 mL), cooled to 0 °C and precipitated with Et_2O. The precipitate was collected by centrifugation and washed with ice-cold Et_2O (2 x 1 mL) to give a pale yellow solid (18 mg, 77% from **35**).

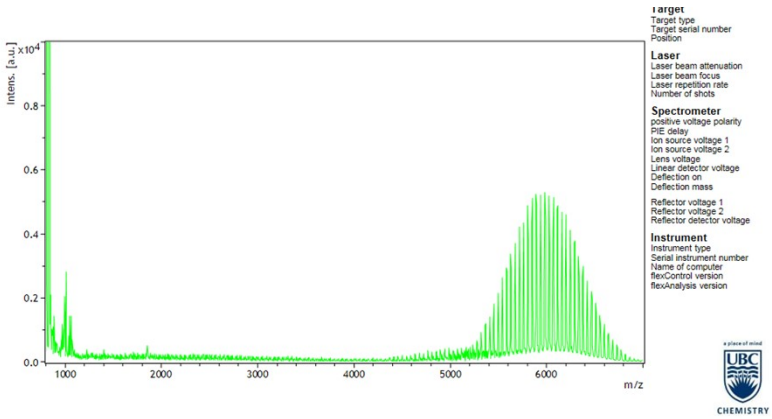
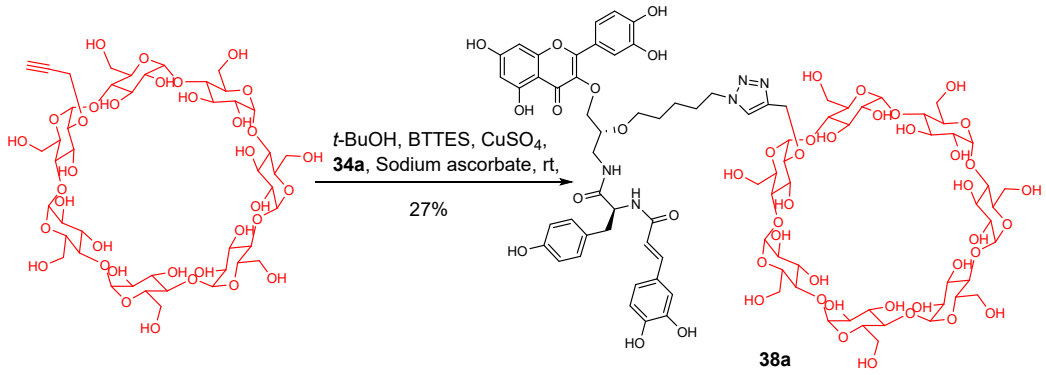


*Figure 3: MALDI-TOF analysis of **36b***

(*E*)-3-(3,4-dihydroxyphenyl)-N-((*S*)-1-(((*S*)-3-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)-2-((5-(4-((2-(methoxyPEG)amino)methyl)-1H-1,2,3-triazol-1-yl)pentyl)oxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-1H-1,2,3-triazol-1-yl-(2-*O*-methyl)-α-D-cycloheptoglucose (**38a**)



A suspension of β-CD alkyne **37** (23 mg, 19.6 µmol), **34a** (16 mg, 19.7 µmol), and BTTES ligand (12 mg, 24.3 µmol) in *t*-BuOH (4.8 mL) was treated with a solution of $CuSO_4$•$5H_2O$ (40 mg, 0.16 mmol) in water (1.2 mL) and sodium ascorbate (16 mg, 80 µmol) in water (1.2 mL). The mixture was stirred for 6 days at room temperature. The solution was concentrated *in vacuo*, re-dissolved in H_2O (5.0 mL), and lyophilized. The solid was dissolved in MeOH (1.0 mL), filtered and washed with MeOH to remove the solids, and the filtrate was concentrated *in vacuo*. Purification by flash chromatography on silica gel (9:1, 5:1 & 3:1 CH_3CN:H_2O with 1% HCOOH) gave the *title compound* (10.7 mg, 5.4 µmol, 27%). ^{13}C NMR (151 MHz, d_6-DMSO) δ 177.69, 171.64, 165.43, 163.92, 160.82, 156.33, 155.73, 155.52, 148.45, 147.10, 145.20, 144.98, 143.47, 139.73, 136.58, 129.99, 127.93, 126.25, 123.95, 121.16, 120.82, 120.51, 117.87, 115.64, 115.46, 115.35, 114.76, 113.93, 104.06, 101.86, 101.83, 101.57, 100.08, 98.53, 93.66, 81.96, 81.45, 81.34, 81.19, 79.32, 76.34, 72.87, 72.45, 72.11, 71.94, 71.67, 71.59, 71.14, 69.70, 68.74, 64.27, 59.76, 54.68, 49.35, 39.52, 39.38, 39.24, 39.10, 38.96, 38.82, 38.68, 36.86, 29.58, 28.90, 28.73, 28.59, 22.44, 22.03. MS (MALDI): m/z calc'd for $C_{86}H_{113}N_5O_{48}$: 2007.8 $[M+Na]^+$; found: 2007.8.

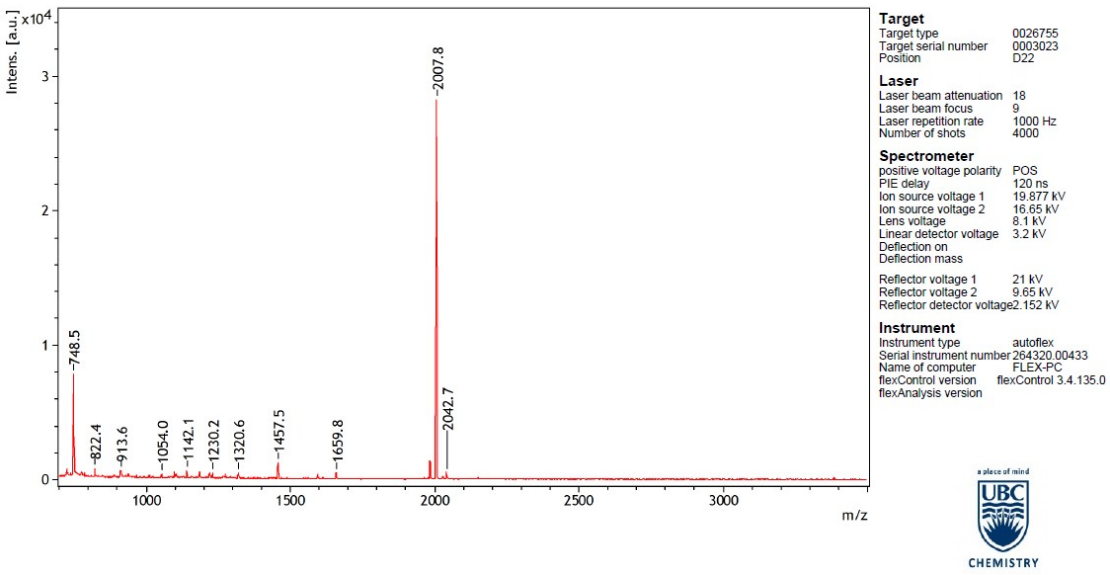
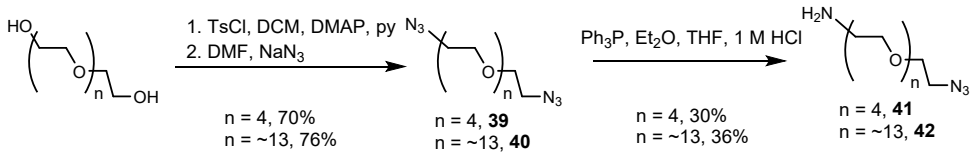


Figure 4: ***38a*** *MALDI*

(2-(polyethyleneglycolyl)azidoethyl)aminoethane **41**, & **42** (PEG600 {n = ~13} **42** as an example)



A solution of TsCl (3.33 g, 17.5 mmol) in CH_2Cl_2 (10 mL) was added slowly over 30 min to a mixture of pyridine (5 mL), PEG600 (2.1 g, 3.5 mmol) and DMAP (0.3 g) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate (300 mL), washed with 1M HCl (2 x 100 mL), saturated $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residual was purified by flash column chromatography on silica gel (50:1 and 25:1 DCM:MeOH) to afford the tosylated PEG as an oil (2.69 g, 2.96 mmol, 84%). The tosylated PEG was then dissolved in DMF (30 mL), and NaN_3 (0.87 g, 13.4 mmol) was added. The mixture was stirred overnight at 50 °C, before cooling to room temperature. The mixture was diluted with ethyl acetate (200 mL), washed with water (2 x 50 mL) and brine (50 mL). The aqueous phase was extracted with ethyl acetate (4 x 100 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography on silica gel (15:1 DCM:MeOH) gave the di-azido-PEG derivatives **40** (1.742 g, 2.68 mmol, 91%). To the di-azido-PEG derivatives **40** (1.742 g) in ether (3.5 mL)/THF (0.8 mL)/1M HCl (3.5 mL) with vigorously stirring at room temperature, was added PPh_3 (702 mg, 2.68 mmol) in Et_2O (16 mL) slowly dropwise over the course of 2.5 h. The mixture was then stirred for an additional 24 h at room temperature. Upon completion, water (20 mL) was added, and the two layers were separated. The aqueous layer was extracted with ether (3 x 10 mL). The aqueous phase was cooled with an ice bath, and solid NaOH was added until the pH was >12, extracted with DCM (3 x 30 mL). The organic phase was washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated. The resulting residual was purified by flash column chromatography on silica gel (9:1 DCM:MeOH, with 1% v/v 1M NH_4OH) to afford the product **42** as an oil (597 mg, 0.96 mmol, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (brs), 3.79 (t, J 4.88 Hz), 3.62 (brd, J 4.96 Hz), 3.55 (m), 3.28 (t, J 4.92 Hz), 3.09 (brd, J 4.60 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.69, 70.66, 70.63, 70.56, 70.51, 70.47, 70.45, 70.41, 70.39, 70.34, 70.21, 70.19, 70.13, 70.05, 70.00, 69.93, 66.81, 50.72, 40.28. Product **41**was obtained as a slightly yellow oil in 62% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68-3.62 (m, 12 H), 3.52 (t, 2 H, J 5.20 Hz), 3.39 (t, 2 H, J 5.04 Hz), 2.87 (t, 2 H, J 5.20 Hz), 1.74 (brs, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.34, 70.67, 70.63, 70.26, 70.02, 50.66, 41.76. ESI-MS: m/z calc'd for $C_8H_{18}N_4O_3$: 219.1 $[M+H]^+$; found: 219.2.

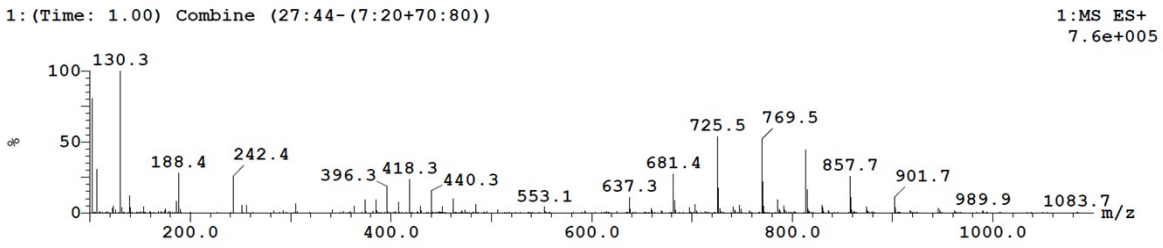
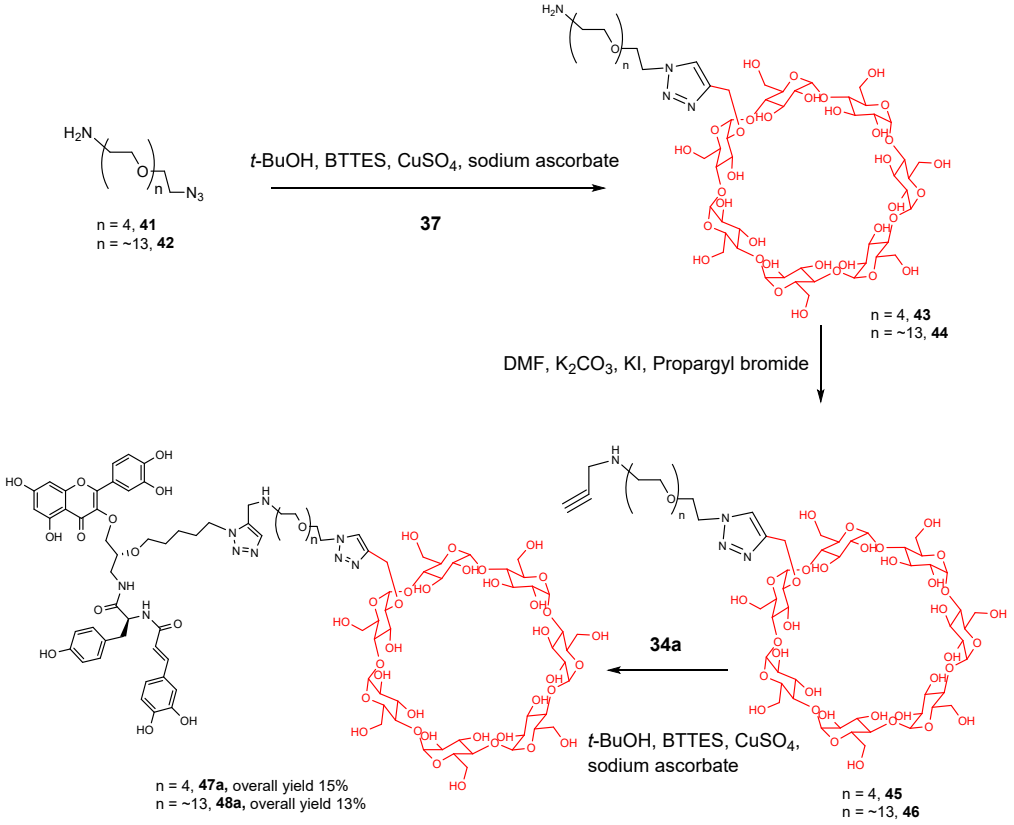


*Figure 5: **42** ESI-MS*

(*E*)-3-(3,4-dihydroxyphenyl)-N-((*S*)-1-(((*S*)-3-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)-2-((5-(4-((2-(polyethyleneglycolyl)amino)methyl)-1H-1,2,3-triazol-1-yl)pentyl)oxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-1H-1,2,3-triazol-1-yl-(2-*O*-methyl)-α-D-cycloheptoglucose (**47a**, **48a**, & **47a** used as an example)



A suspension of β-CD alkyne **37** (126 mg, 0.11mmol), PEG-200 azide **41** (70 mg, 0.32 mmol), and BTTES ligand (73 mg, 0.15 mmol) in *t*-BuOH (10 mL) was treated with aqueous solutions of $CuSO_4$ (0.133 M, 7 mL) and sodium ascorbate (0.066 M, 7 mL), and the mixture was stirred for 24 h at room temperature. After evaporation, the resulting residue was purified by flash column chromatography on silica gel (4:1:1, CH_3CN:H_2O:NH_4OH), the fractions were combined and evaporated, redissolved in water and lyophilized to afford an off-white solid (**43**, 183 mg, not pure). The solid (117 mg) was dissolved in dry DMF (20 mL) under N_2 at room temperature, and then were added anhydrous K_2CO_3 (70 mg, 0.51 mmol), KI (2 mg, 12 μmmol) and propargyl bromide (80% in toluene) (9 μL, 83.5 μmol), the reaction mixture was stirred for 24 h in the dark at room temperature under N_2, filtered through Celite and concentrated. The resulting residues was purified by flash column chromatography on silica gel (5:1:1, 4.5:1:1, 4:1:1, CH_3CN:H_2O:NH_4OH) to give by-product, product (**45**, 21 mg) and starting material respectively. A suspension of **45** (12 mg, 8.4 μmmol), **34a** (4.6 mg, 5.7 μmmol) and BTTES (3.5 mg, 7.1 μmol) in *t*-BuOH (1.6 mL) was treated with $CuSO_4$•$5H_2O$ (0.133 M, 0.41 mL) and sodium ascorbate (0.066 M, 0.41 mL), and the reaction mixture was stirred for 19 h at room temperature. The product was precipitated out on the wall of flask, solution was poured out and washed with MeOH. The precipitate was dissolved water, loaded on SepPak (C_{18}), eluted with water, MeOH and MeOH with 1% HCOOH. The fractions were combined and evaporated. The residue was redissolved in water and lyophilized to afford the desired product (**47a**, 5.7 mg, 2.5 μmmol, 45%). Overall yield based on alkyne: **47a**, 15%; **48a**, 13%.

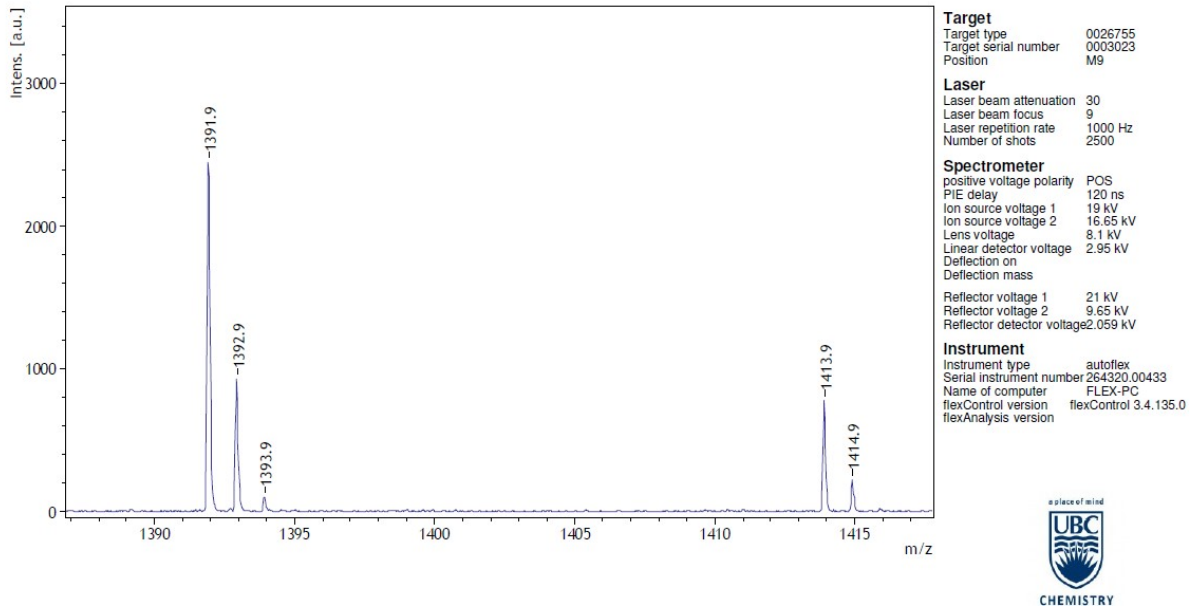


Figure 6: ***43*** *MALDI*

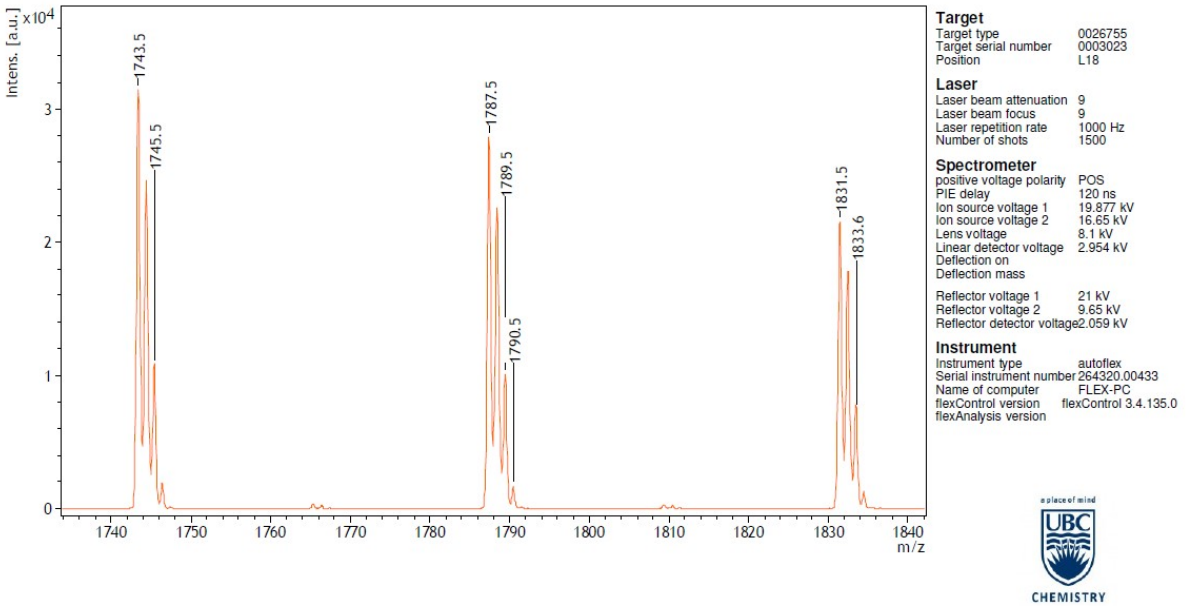


Figure 7: ***44*** *MALDI*

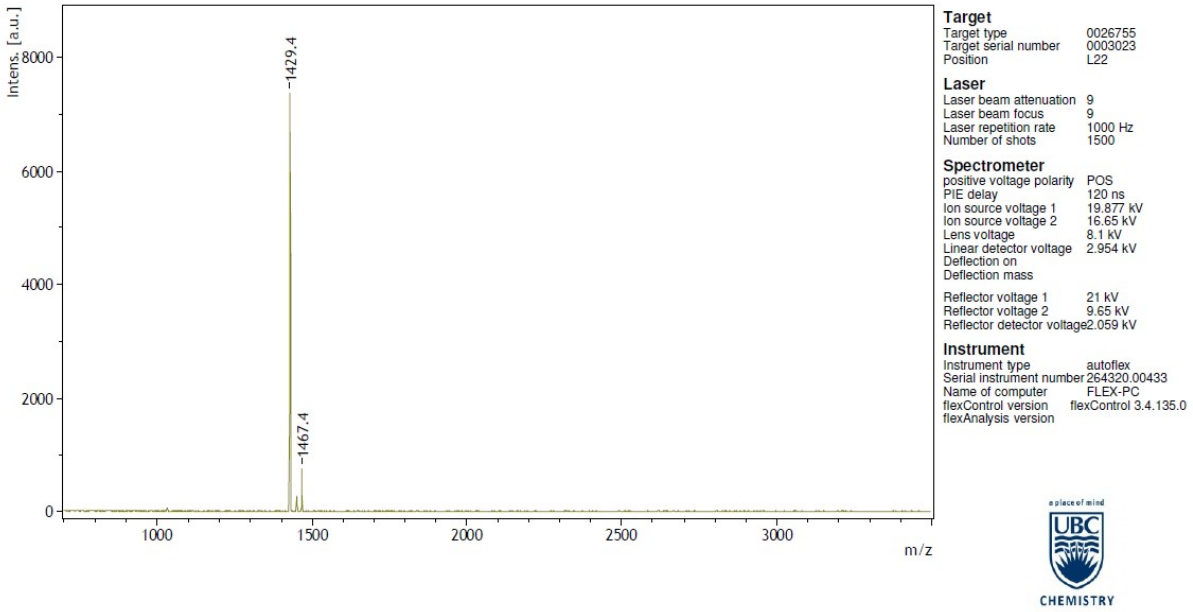


Figure 8: ***45*** *MALDI*

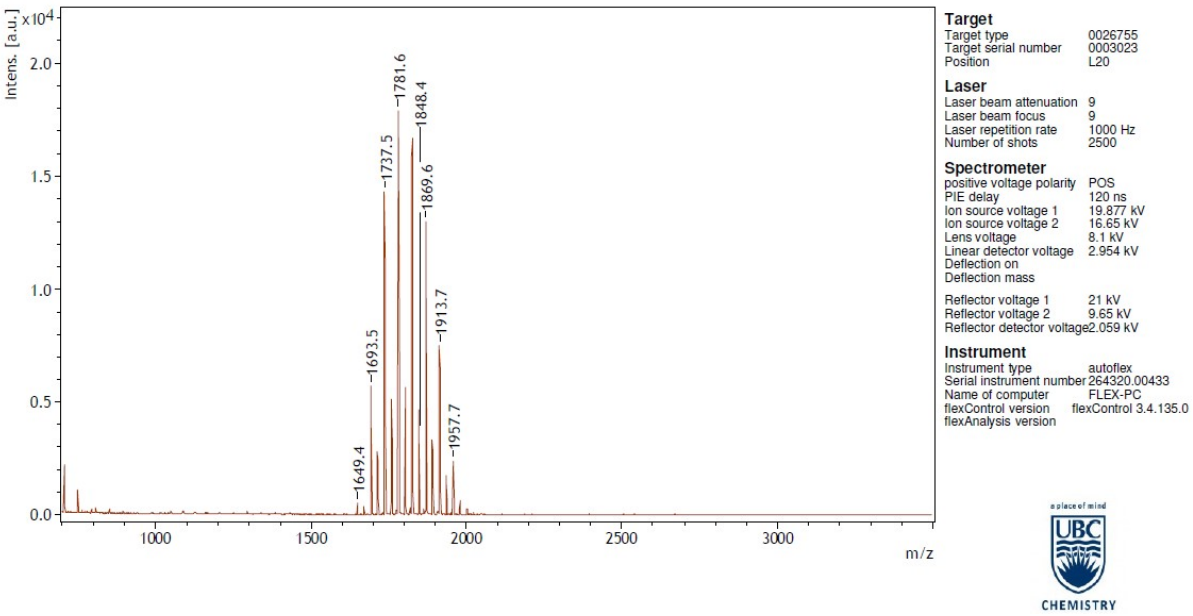


Figure 9: ***46*** *MALDI*

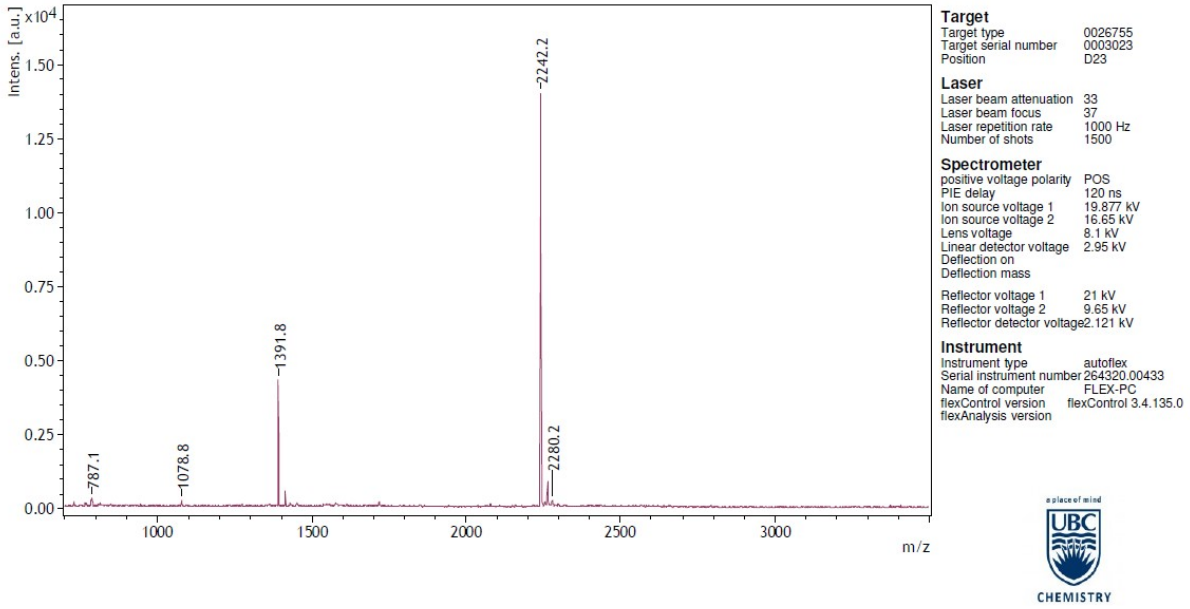


Figure 10: ***47a*** *MALDI*

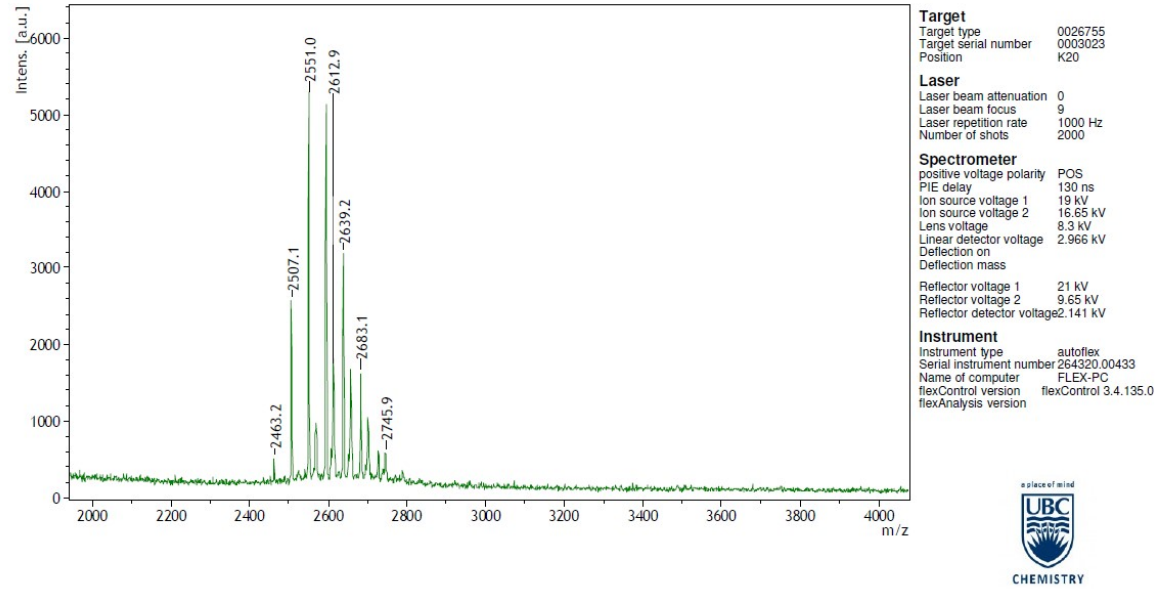
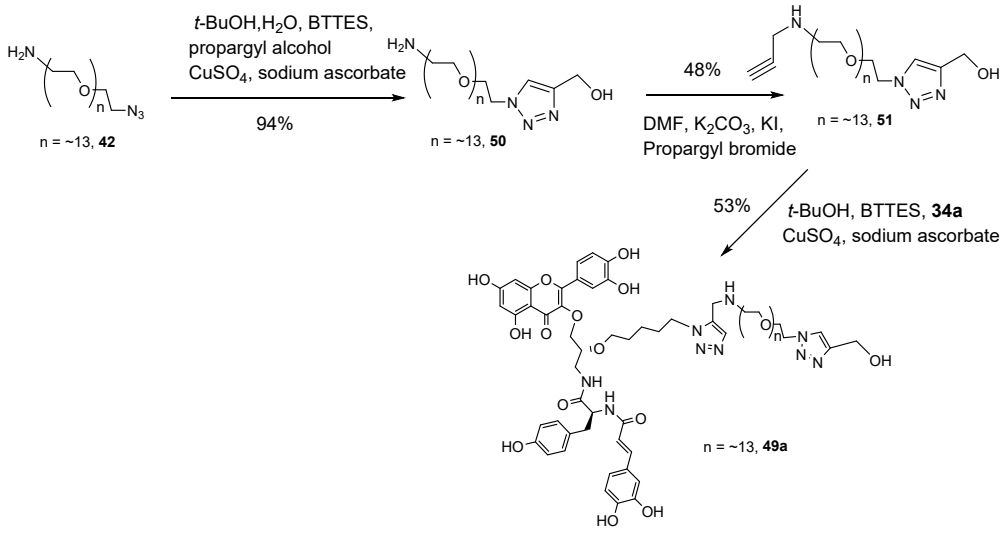


Figure 11: ***48a*** *MALDI*

(E)-3-(3,4-dihydroxyphenyl)-N-((S)-1-(((R)-3-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)-2-((5-(5-(((2-(2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)ethoxy)polyethyleneglycolyl)amino)methyl)-1H-1,2,3-triazol-1-yl)pentyl)oxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)acrylamide **49a**



A suspension of **42** (80 mg, 0.13 mmol), propargyl alcohol (13 µL, 0.22 mmol), and BTTES ligand (6.5 mg, 13 µmol) in *t*-BuOH (1.3 mL) and water (1.3 mL) was treated with $CuSO_4$•$5H_2O$ (0.133 M, 0.3 mL) and sodium ascorbate (0.066 M, 0.3 mL), and the mixture was stirred for 36 h at room temperature. The reaction mixture was evaporated and co-evaporated with toluene three times, the resulting residue was purified by flash column chromatography on silica gel (6:1, DCM:MeOH, with 1% 1M NH_4OH) to afford **50** as an oil (82 mg, 0.12 mmol, 94%). A suspension of the solid (82 mg, 0.12 mmol), anhydrous K_2CO_3 (51 mg, 0.37 mmol), KI (2 mg, 12 µmmol) and propargyl bromide (80% in toluene) (13 µL, 0.12 mmol) in dry DMF (6mL) was stirred overnight in the dark under N_2 at room temperature, and the reaction mixture was filtered through Celite and concentrated. The resulting residues was purified by flash column chromatography on silica gel (9:1 and 7:1, DCM:MeOH, with 1% 1M NH_4OH) to afford the product as a foam (**51**, 27 mg, 38.1 µmmol, 32%) (48% based on the consumed starting material, 29 mg of starting material was recovered). A suspension of **51** (7 mg, 9.9 µmmol), **34a** (6 mg, 7.4 µmmol) and BTTES (5 mg, 10.1 µmol) in *t*-BuOH (2.4 mL) was treated with $CuSO_4$•$5H_2O$ (0.133 M, 0.6 mL) and sodium ascorbate (0.066 M, 0.6 mL), and the reaction mixture was stirred overnight at room temperature. The product was precipitated out on the wall of flask, solution was poured out and washed with MeOH and water respectively. The precipitate was dissolved in minimum amount of DMSO, and diluted with water, lyophilized to afford the product **49a** a yellow solid (5.91 mg, 3.9 µmmol, 53%).

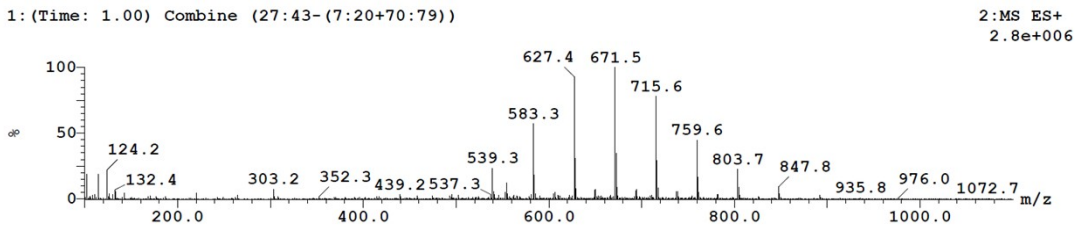


*Figure 12: **50** ESI-MS*

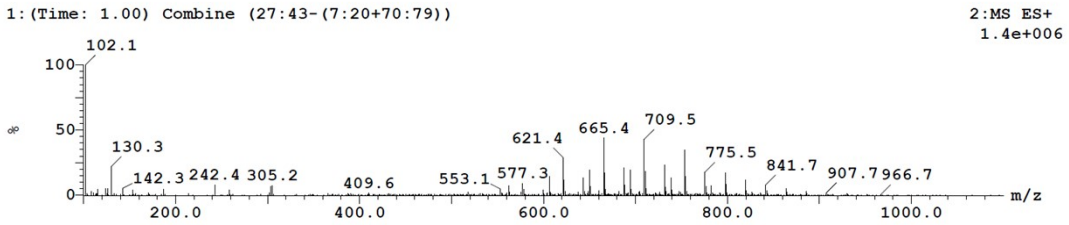


Figure 13: ***51*** *ESI-MS*

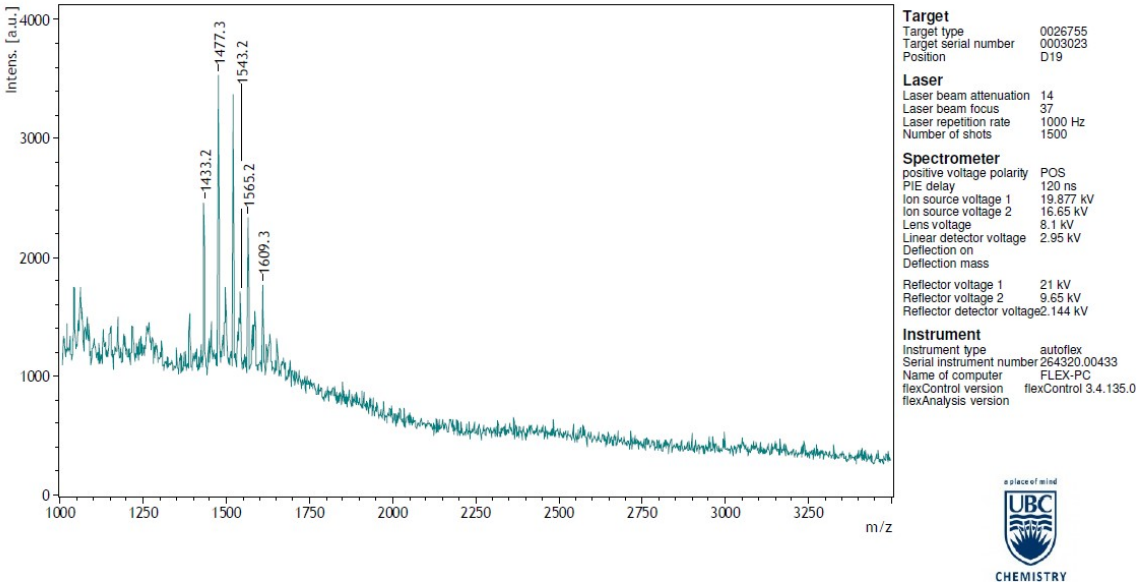


Figure 14: ***49a*** *MALDI*

NMR Data

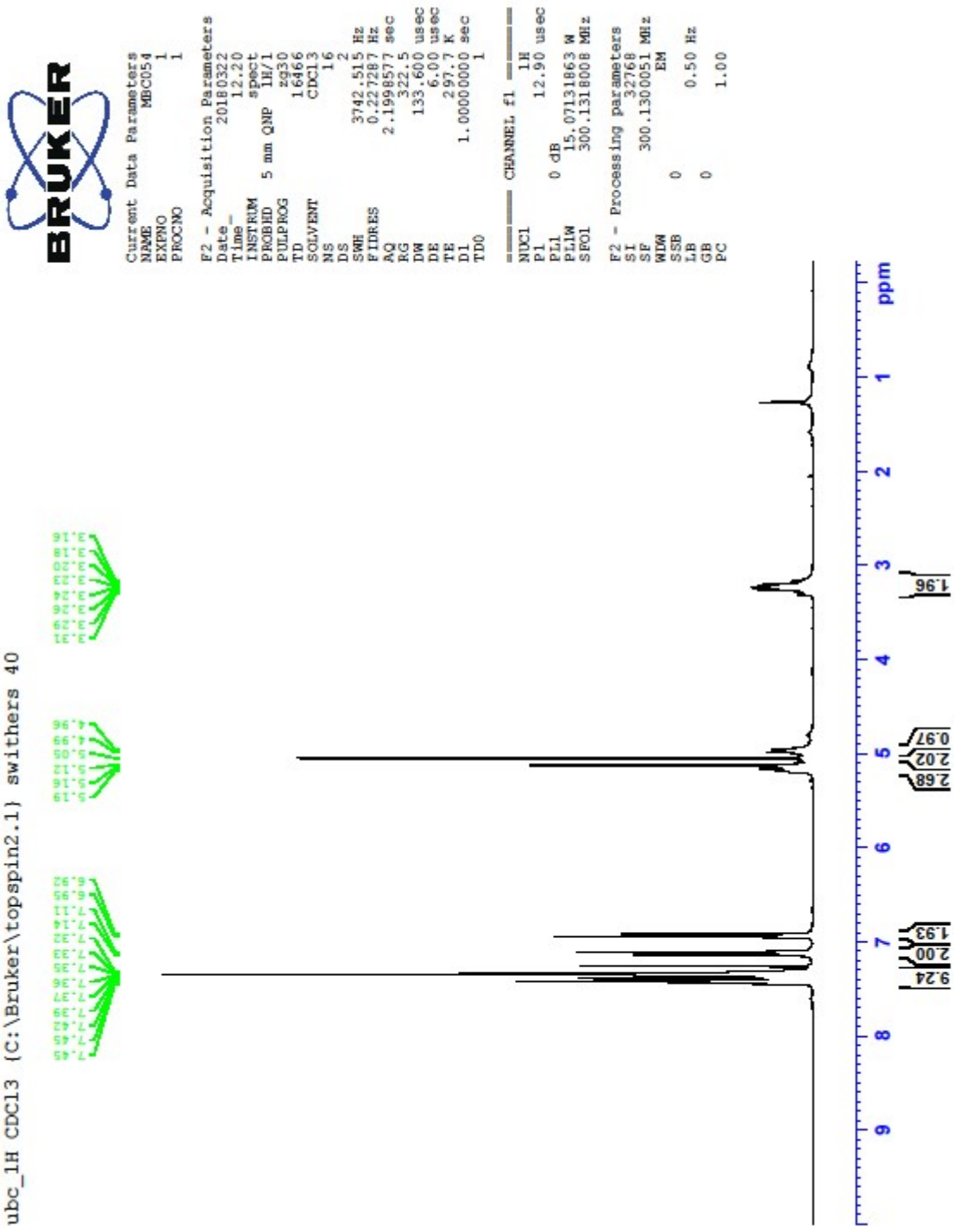


*Figure 4: ^{1}H NMR **(3)***

Figure 5: ^{13}C NMR (3)

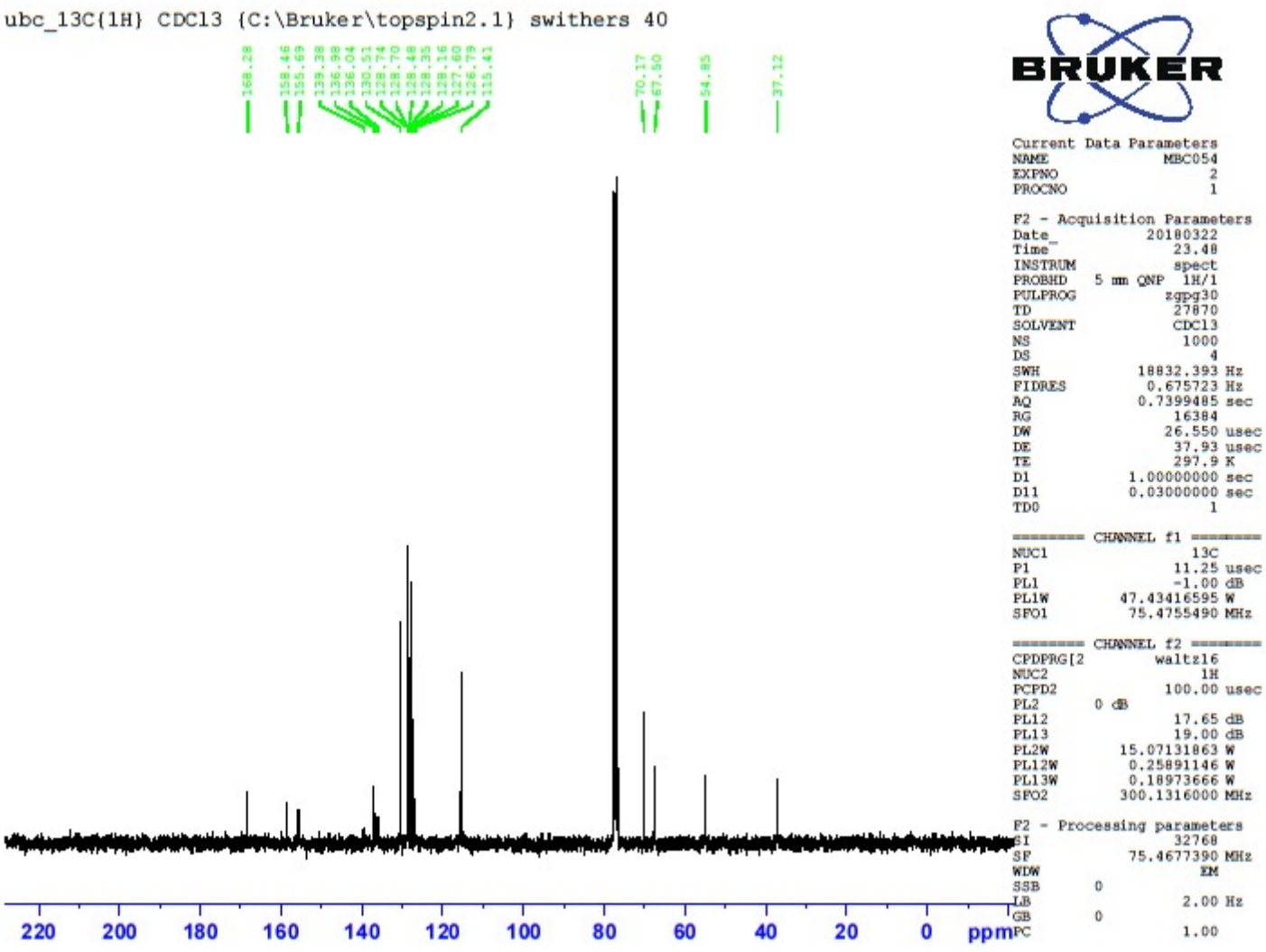


Figure 6: ^{1}H NMR (4)

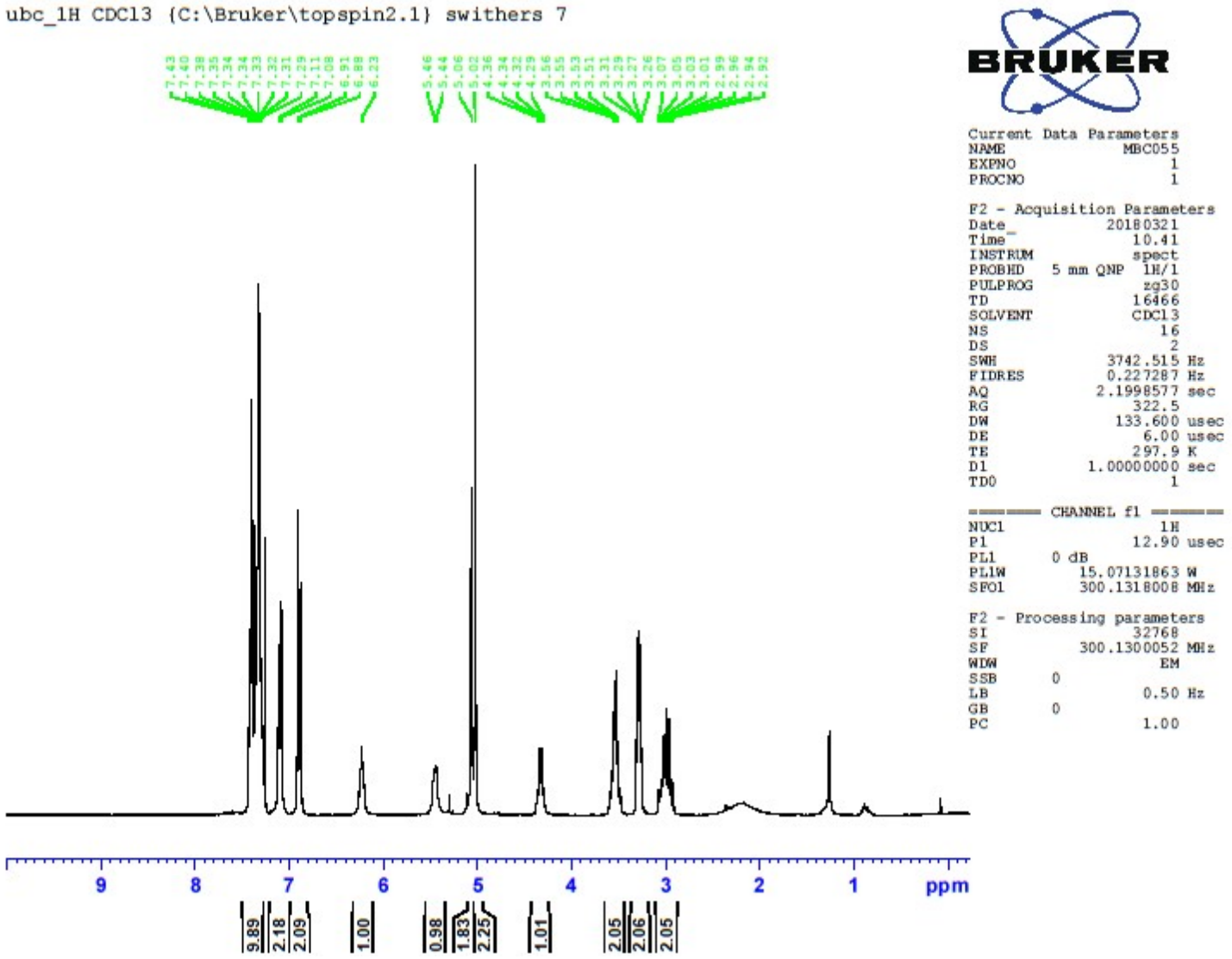


Figure 7: ^{13}C NMR (4)

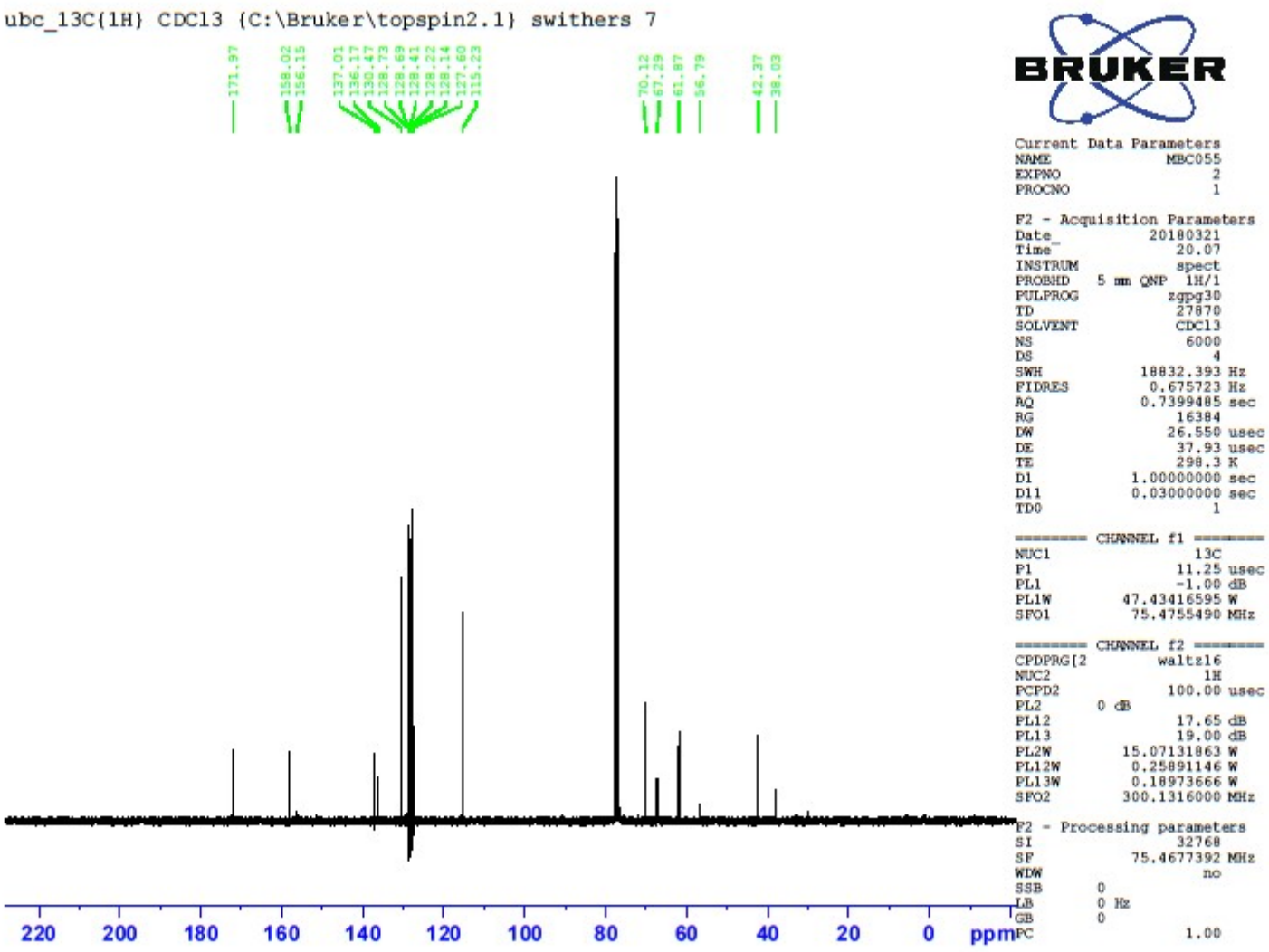


*Figure 8: ^1H NMR (**8**)*

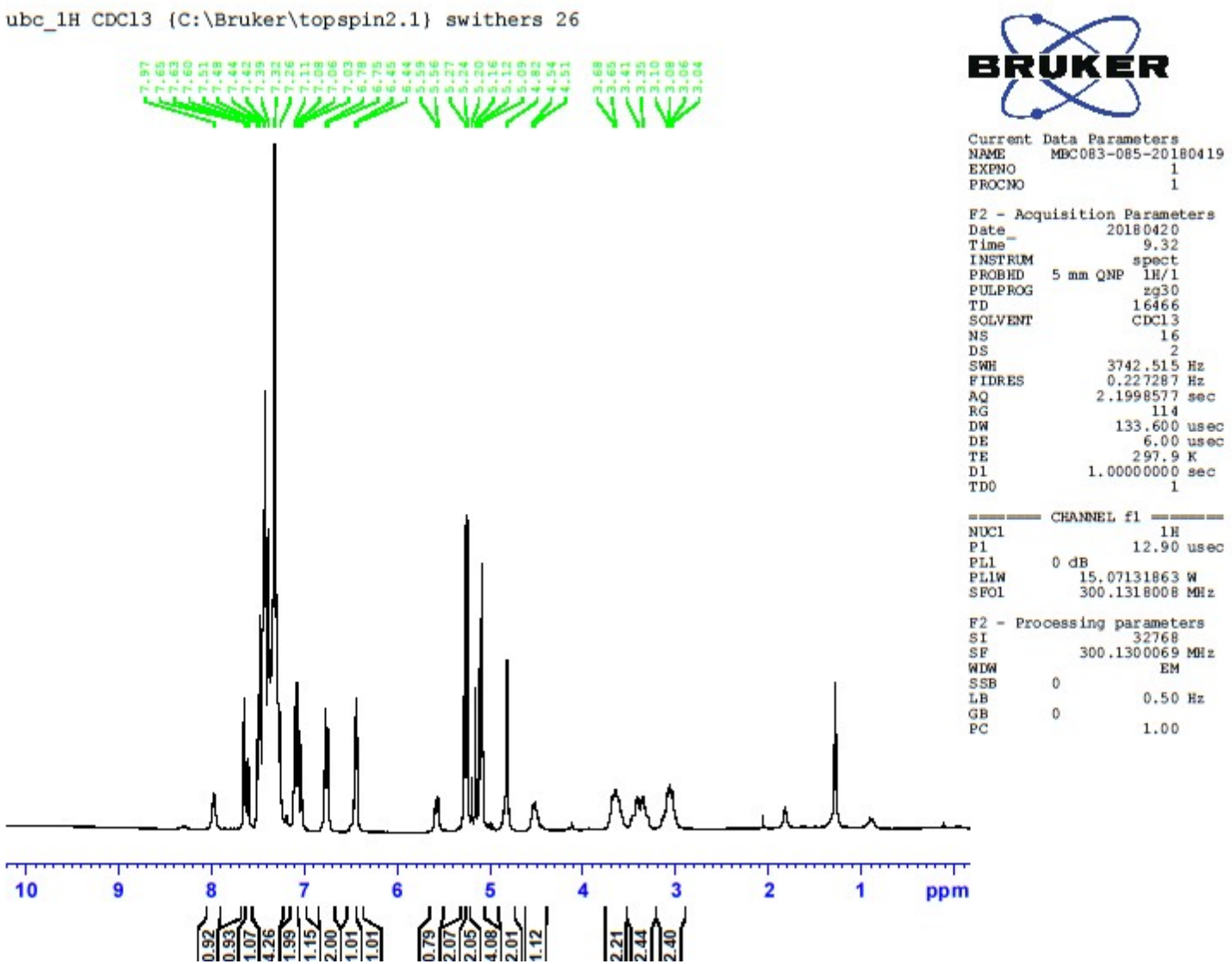


Figure 9: ^{13}C NMR (8)

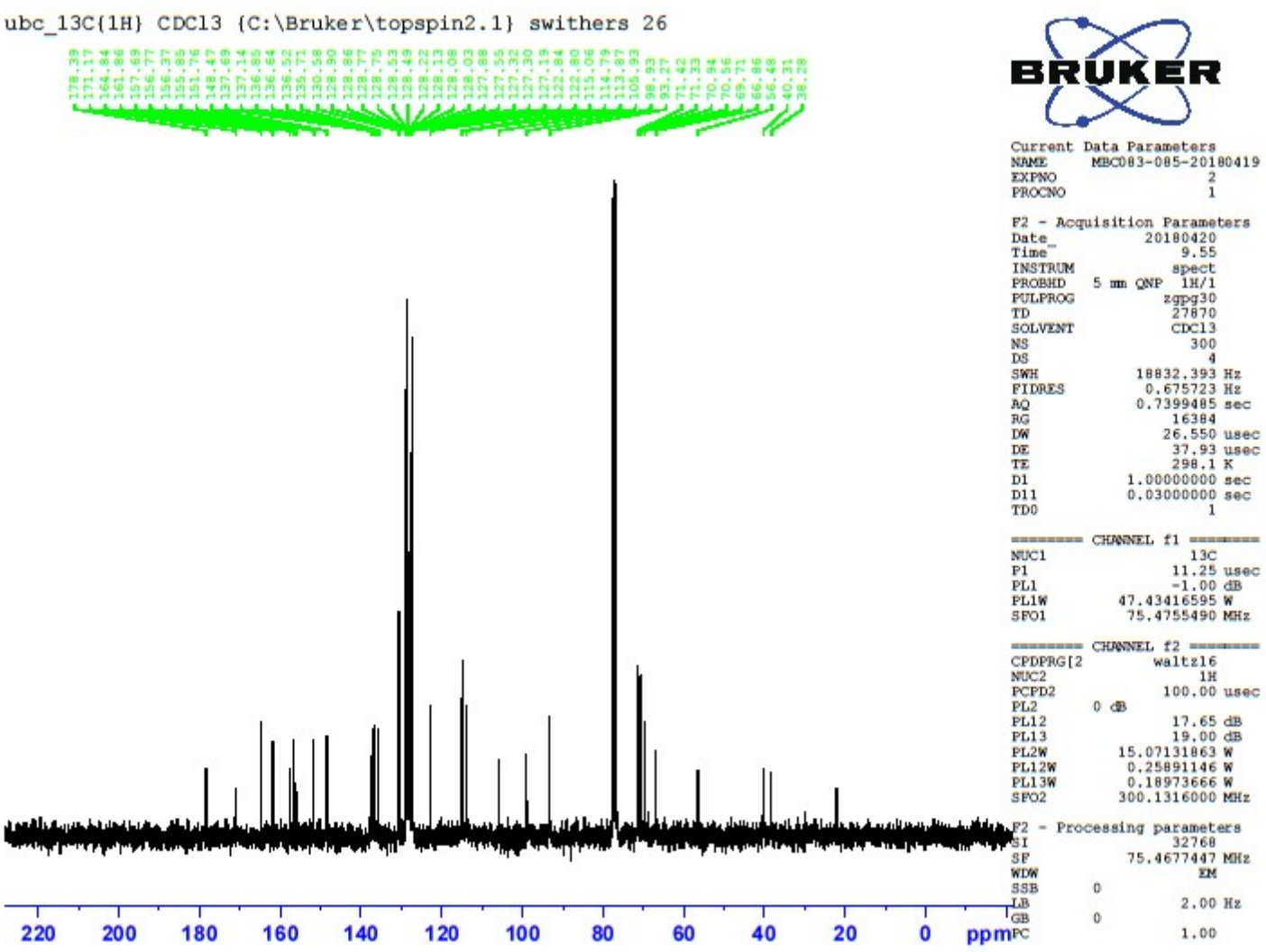
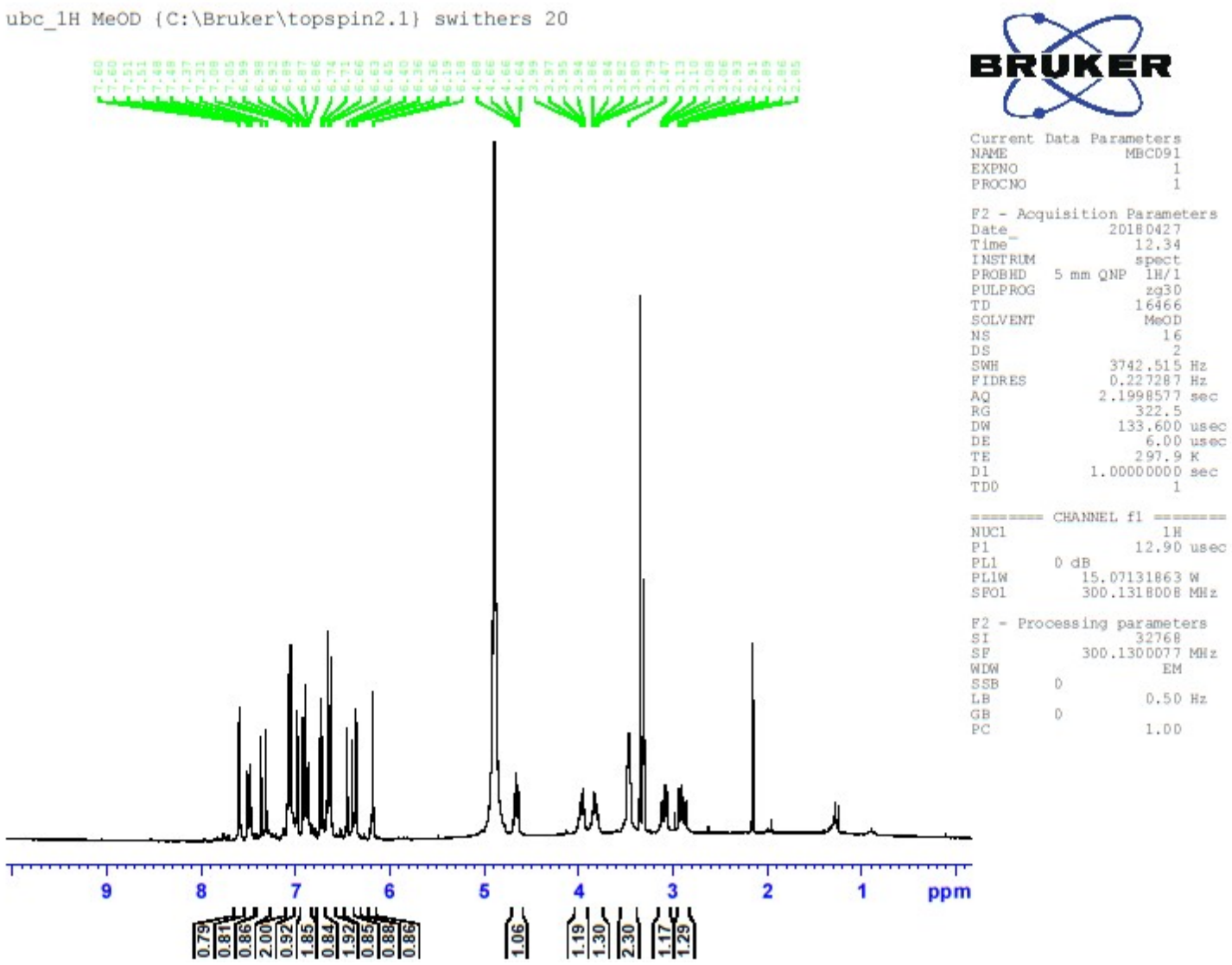


Figure 10: ^{1}H NMR (13)



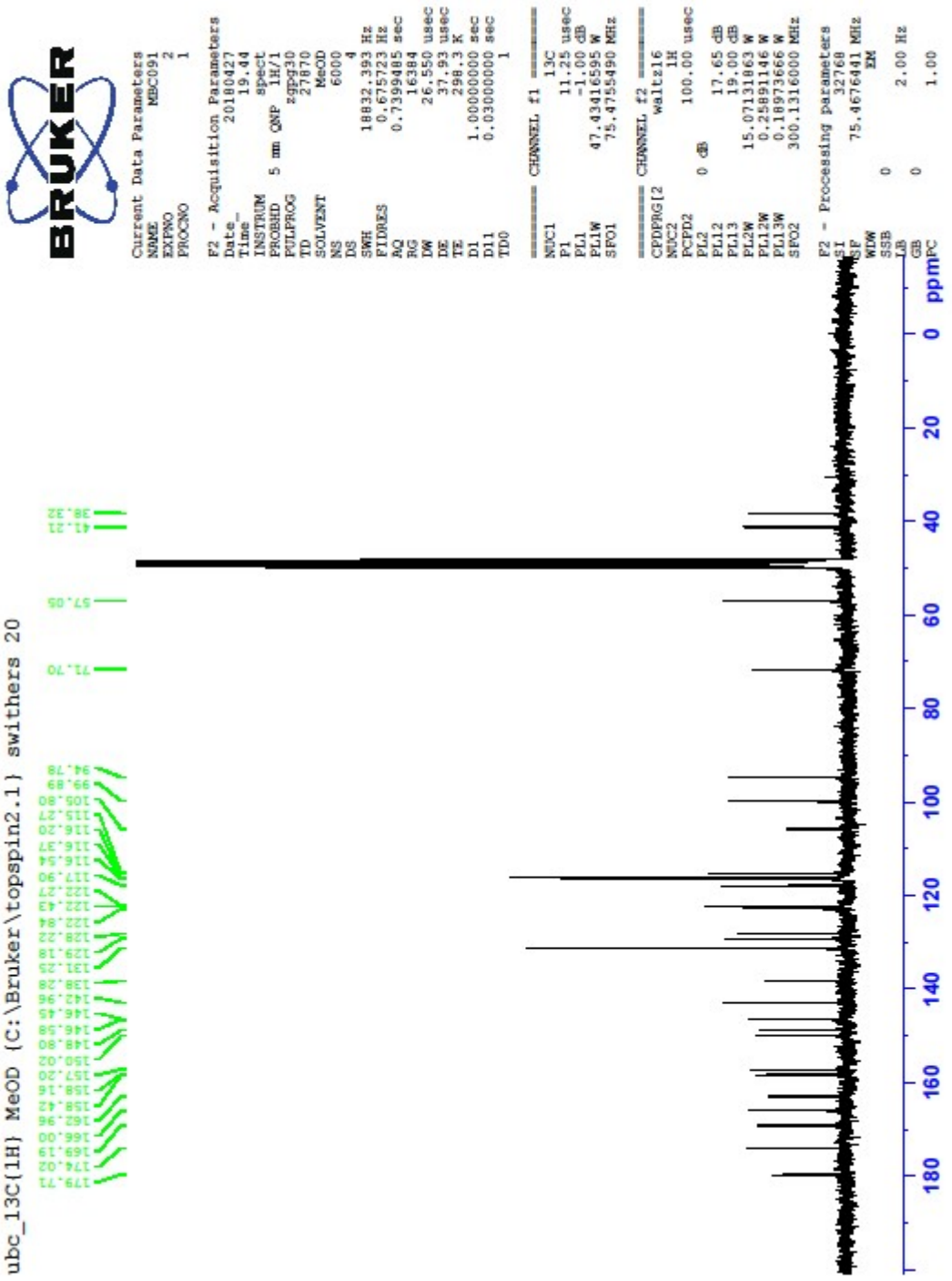


Figure 11: ^{13}C NMR (**13**)

Figure 12: ^1H NMR (6)

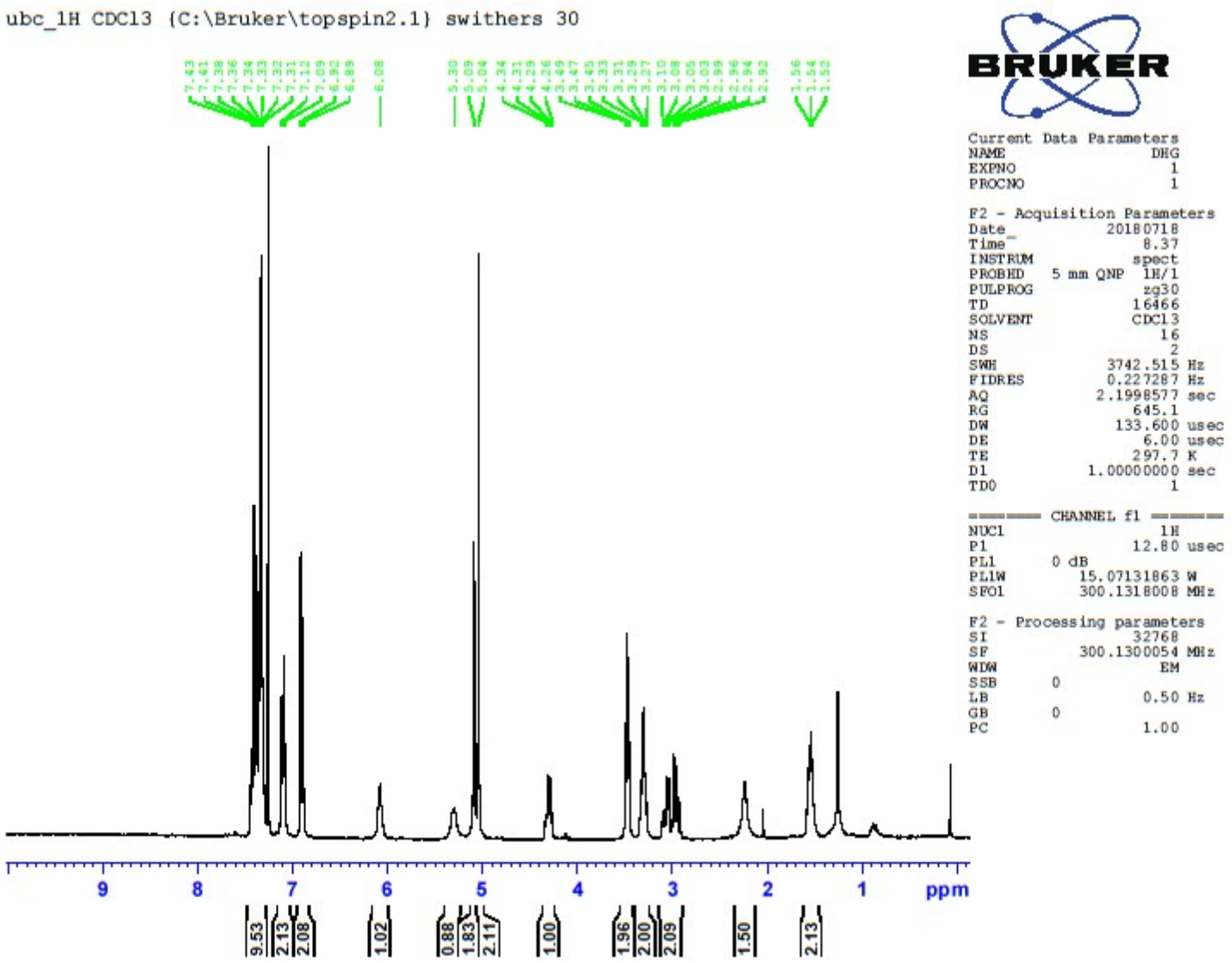


Figure 13: ^{13}C NMR (6)

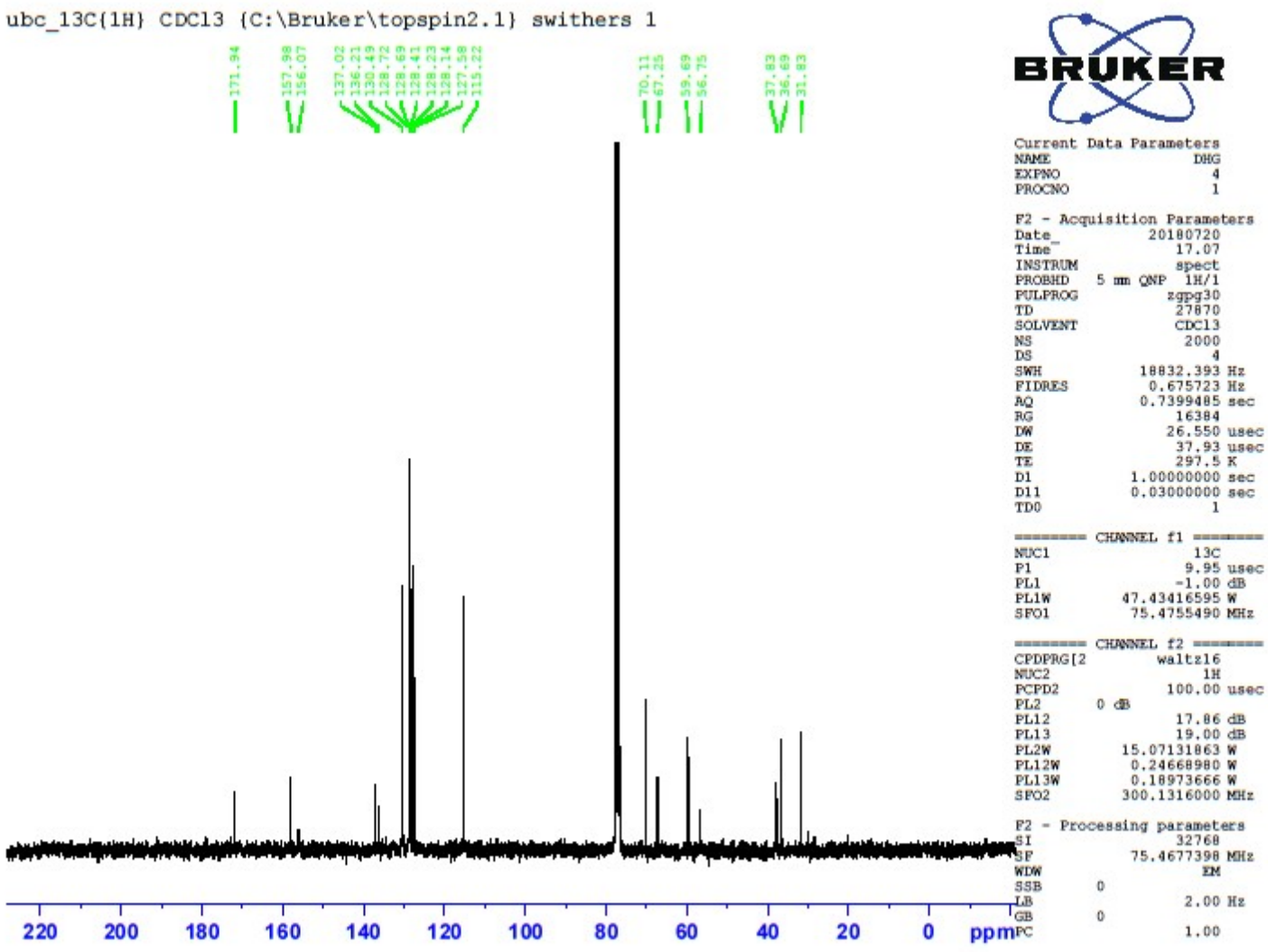


Figure 14: ^1H NMR (9)

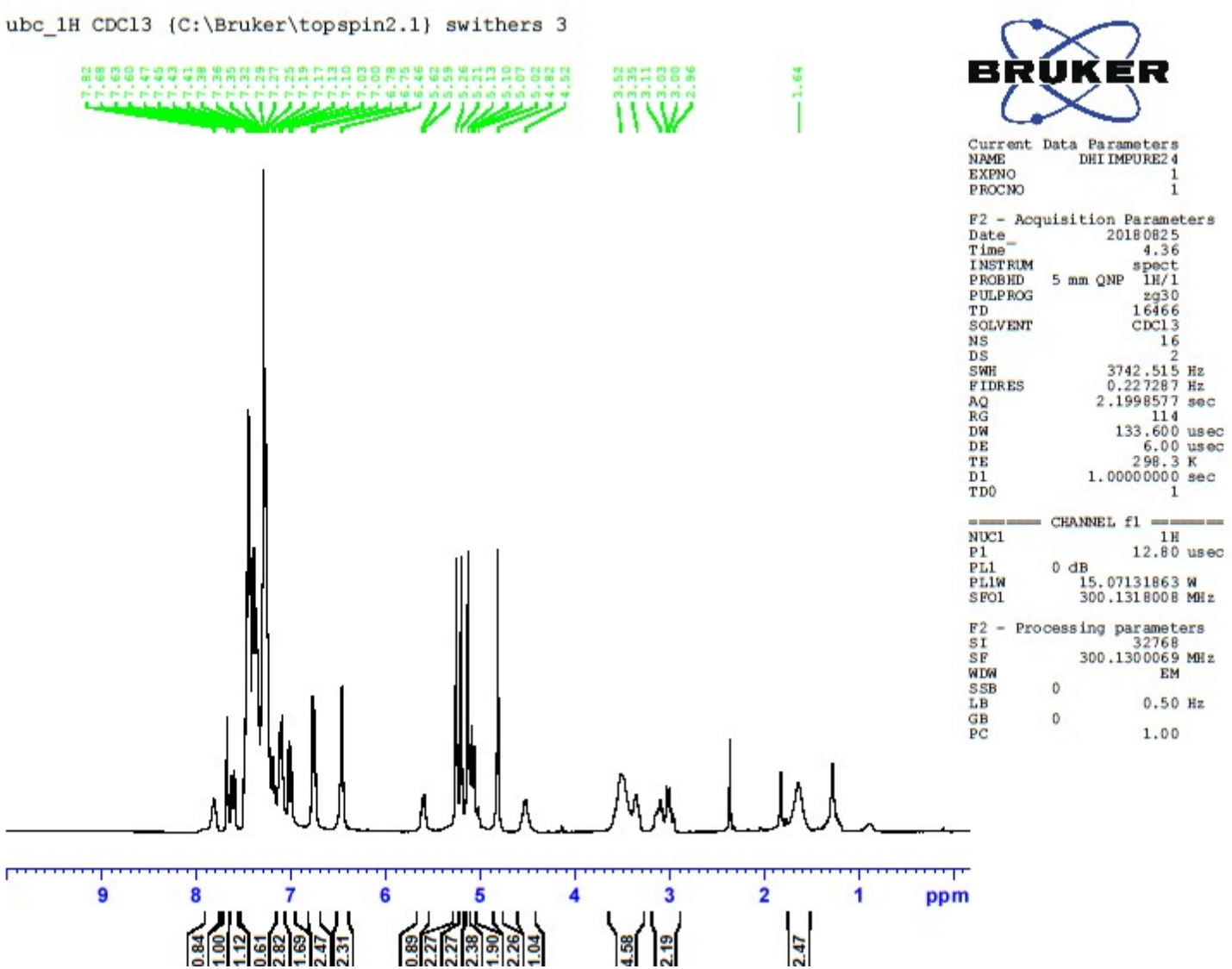


Figure 15: ^{13}C NMR (9)

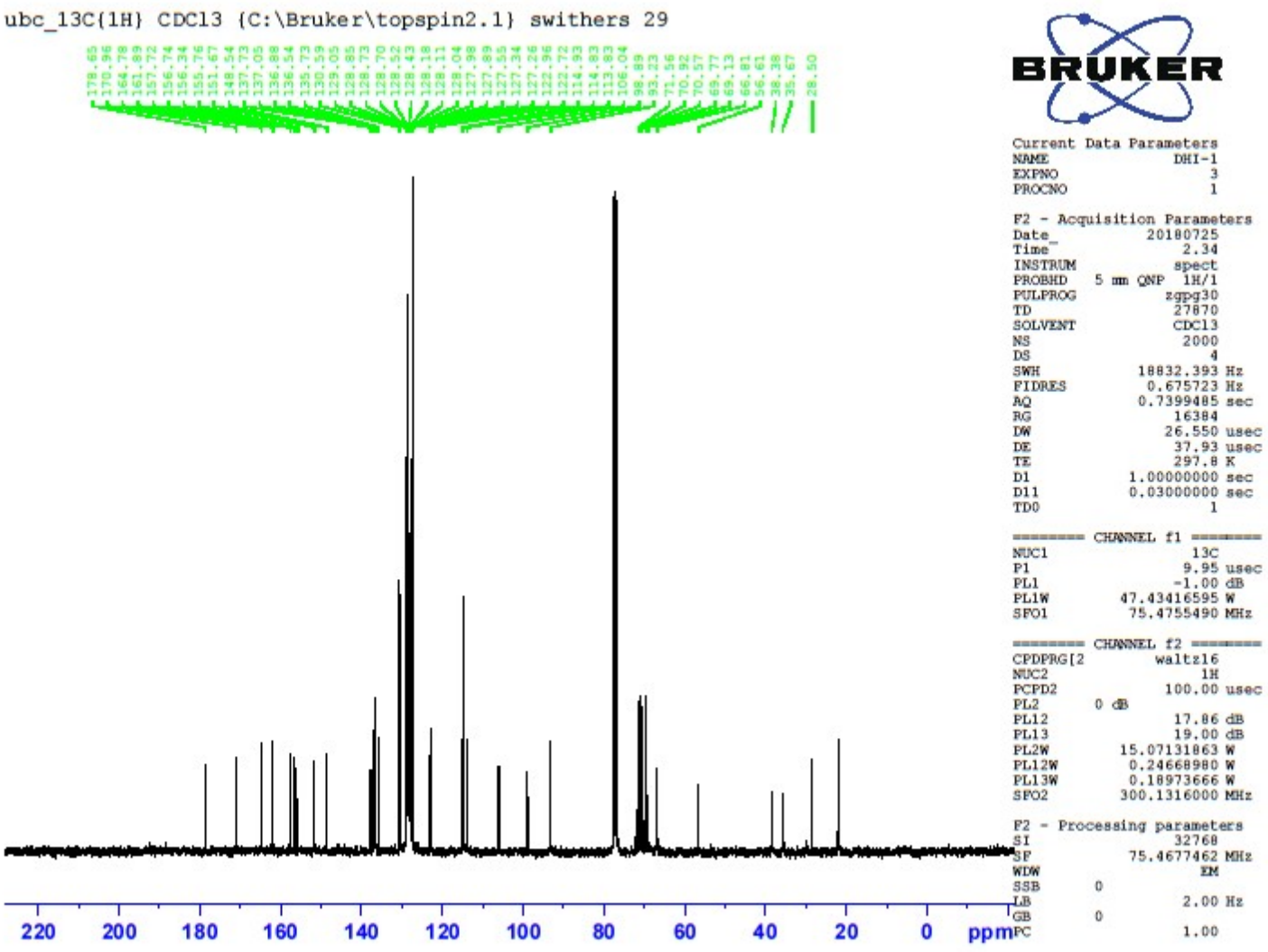
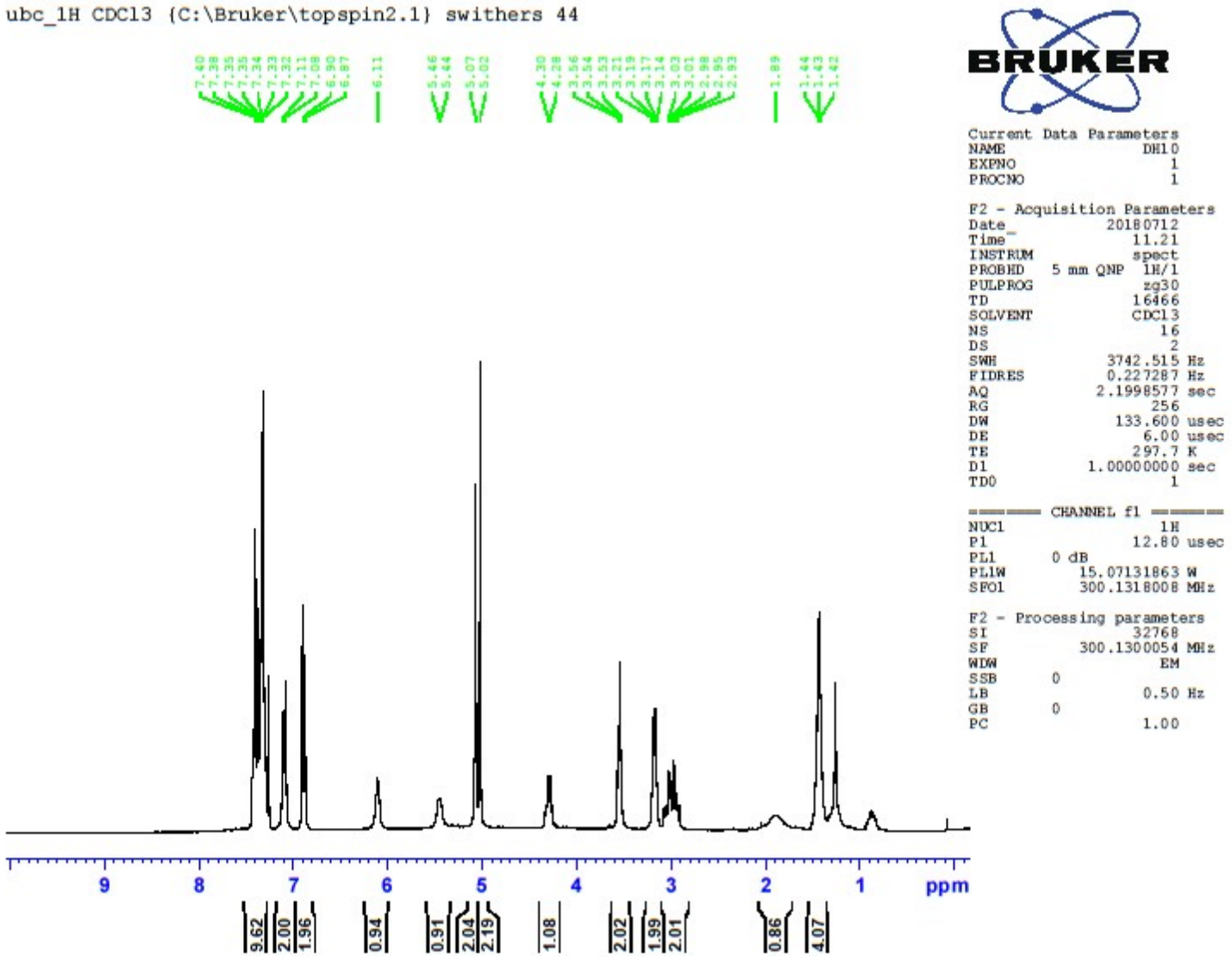


*Figure 16: ^1H NMR (**6**)*



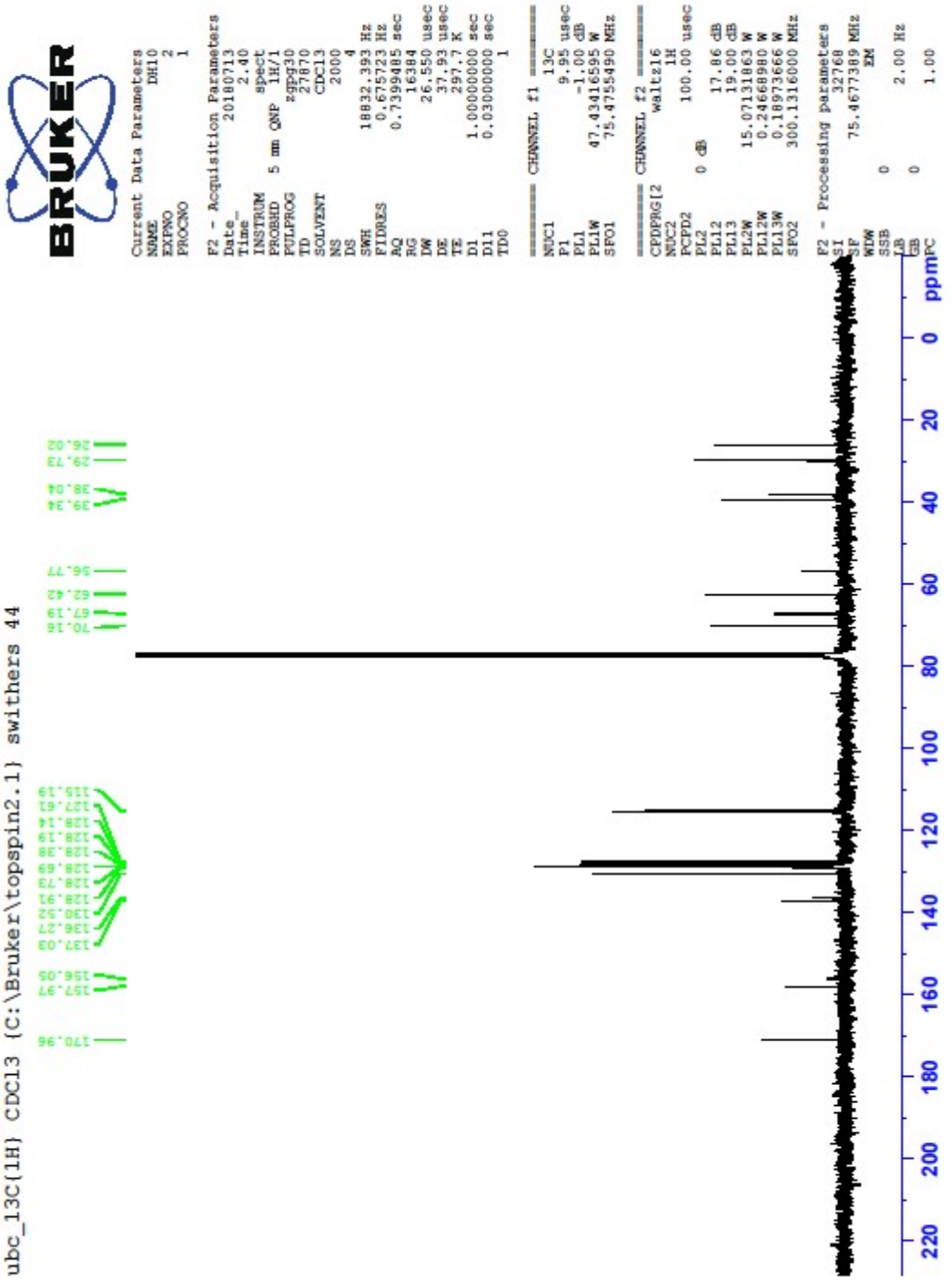


Figure 17: ^{13}C NMR (**6**)

*Figure 18: ^1H NMR (**10**)*

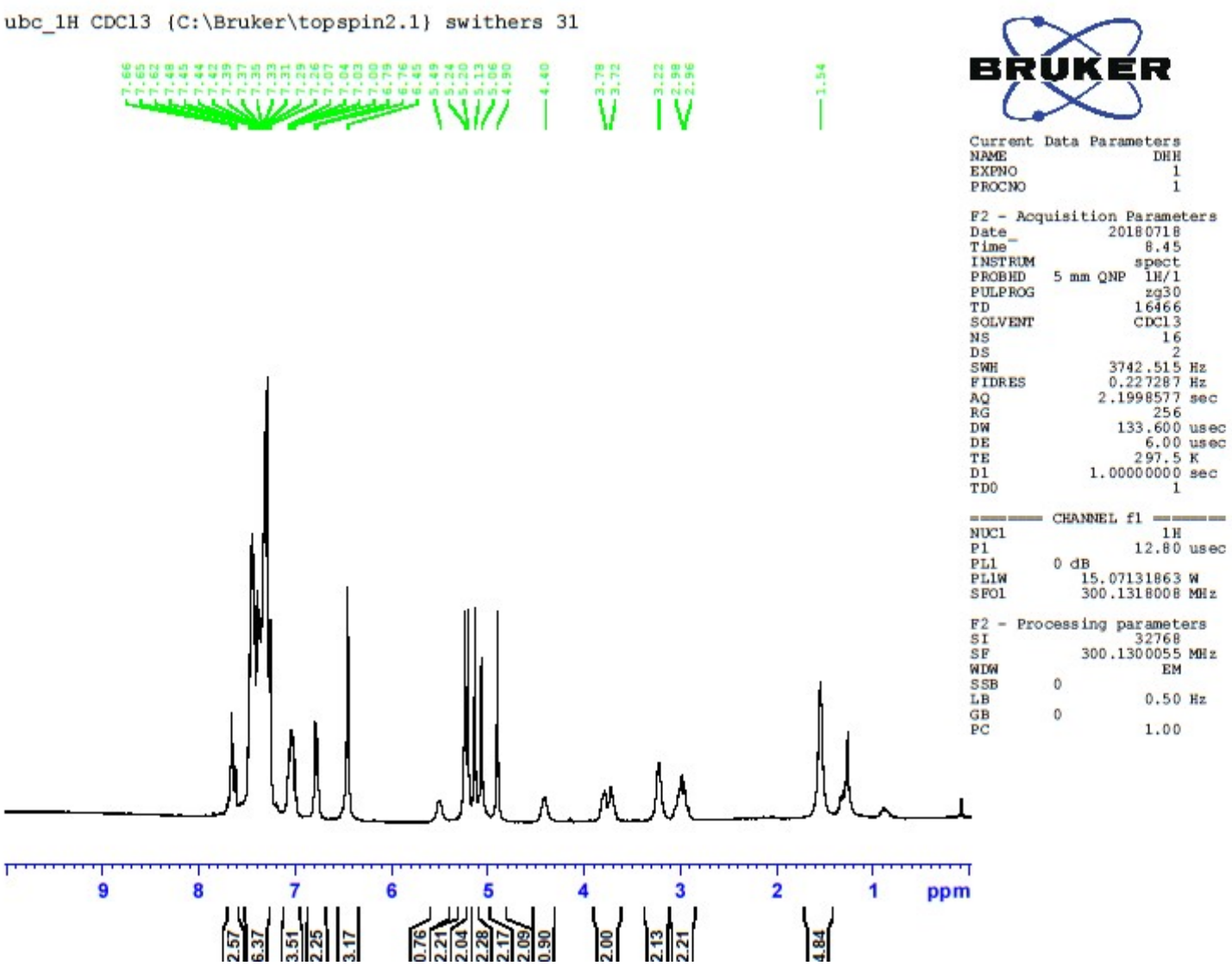


*Figure 19: ^{13}C NMR (**10**)*

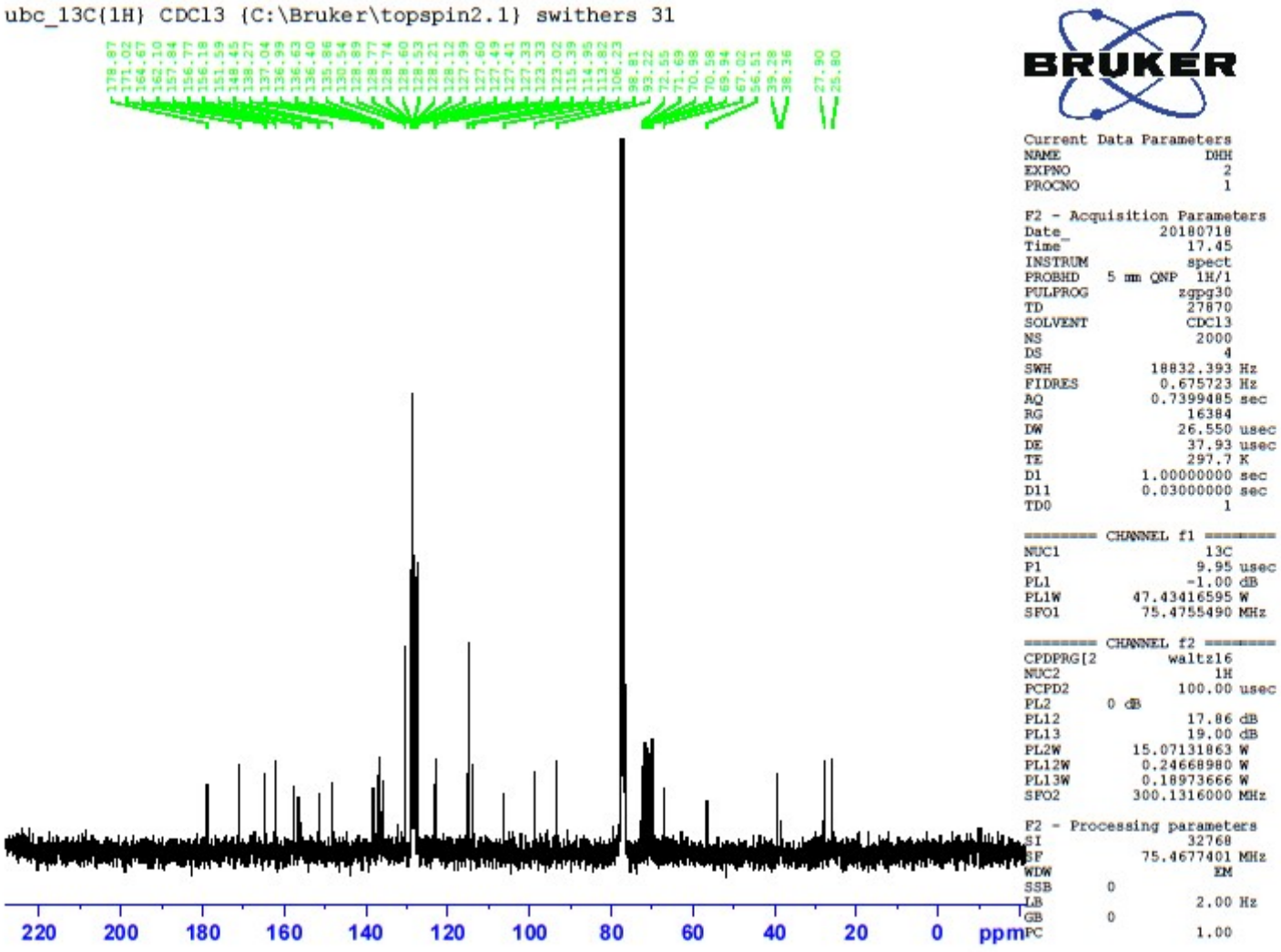


Figure 20: ^{1}H NMR (14)

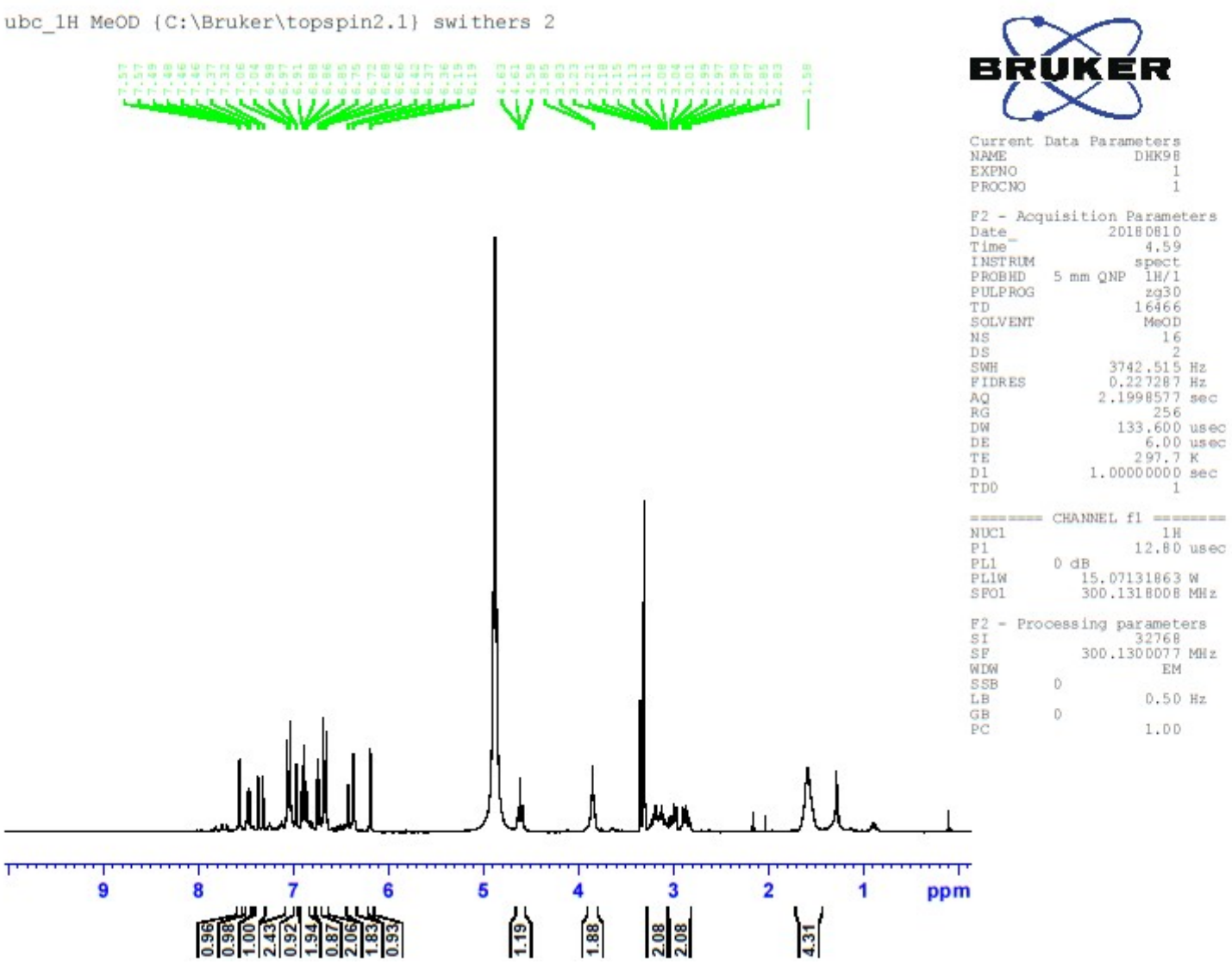


Figure 21: ^{13}C NMR (14)

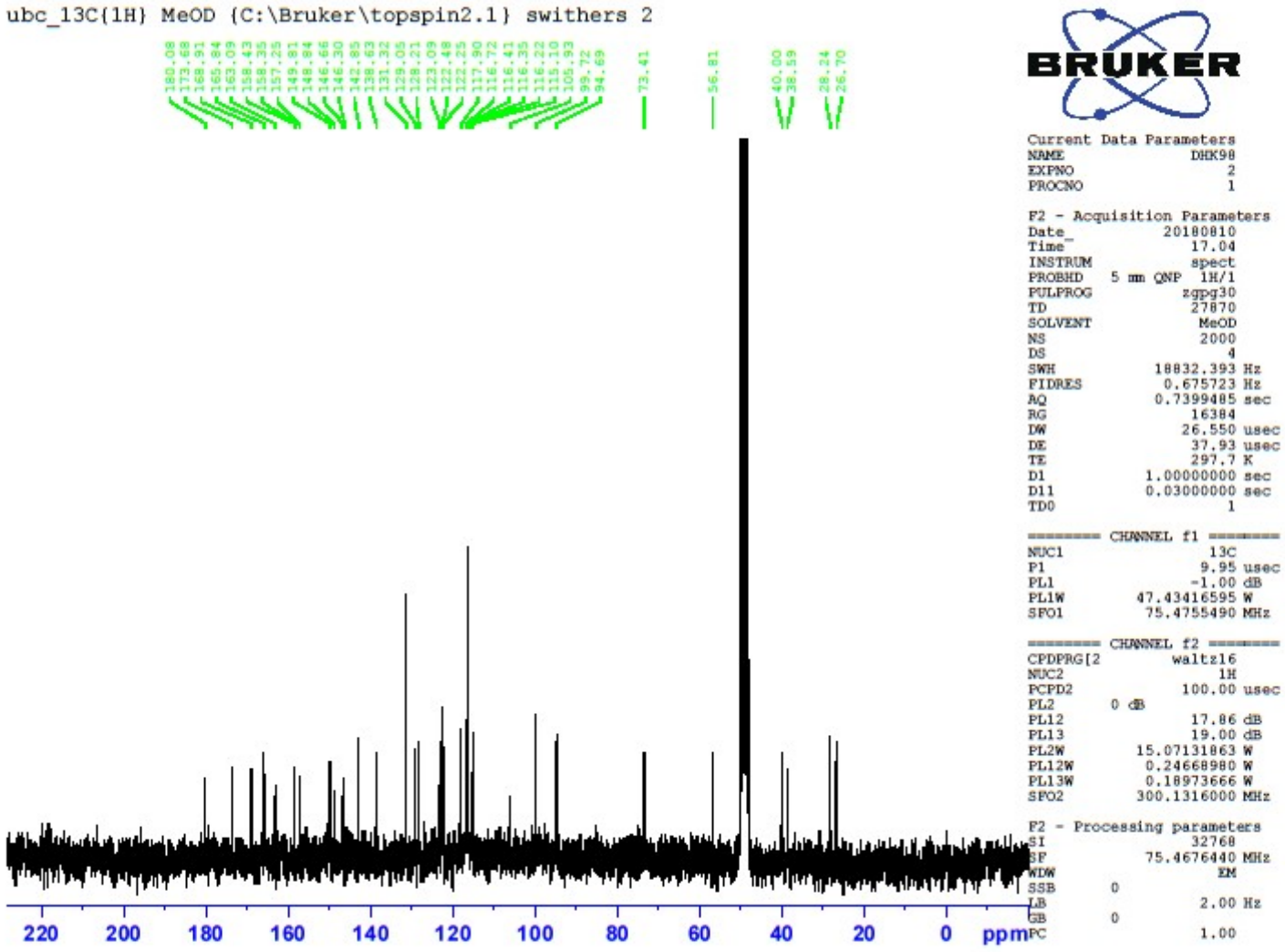


*Figure 22: ^1H NMR (**19**)*

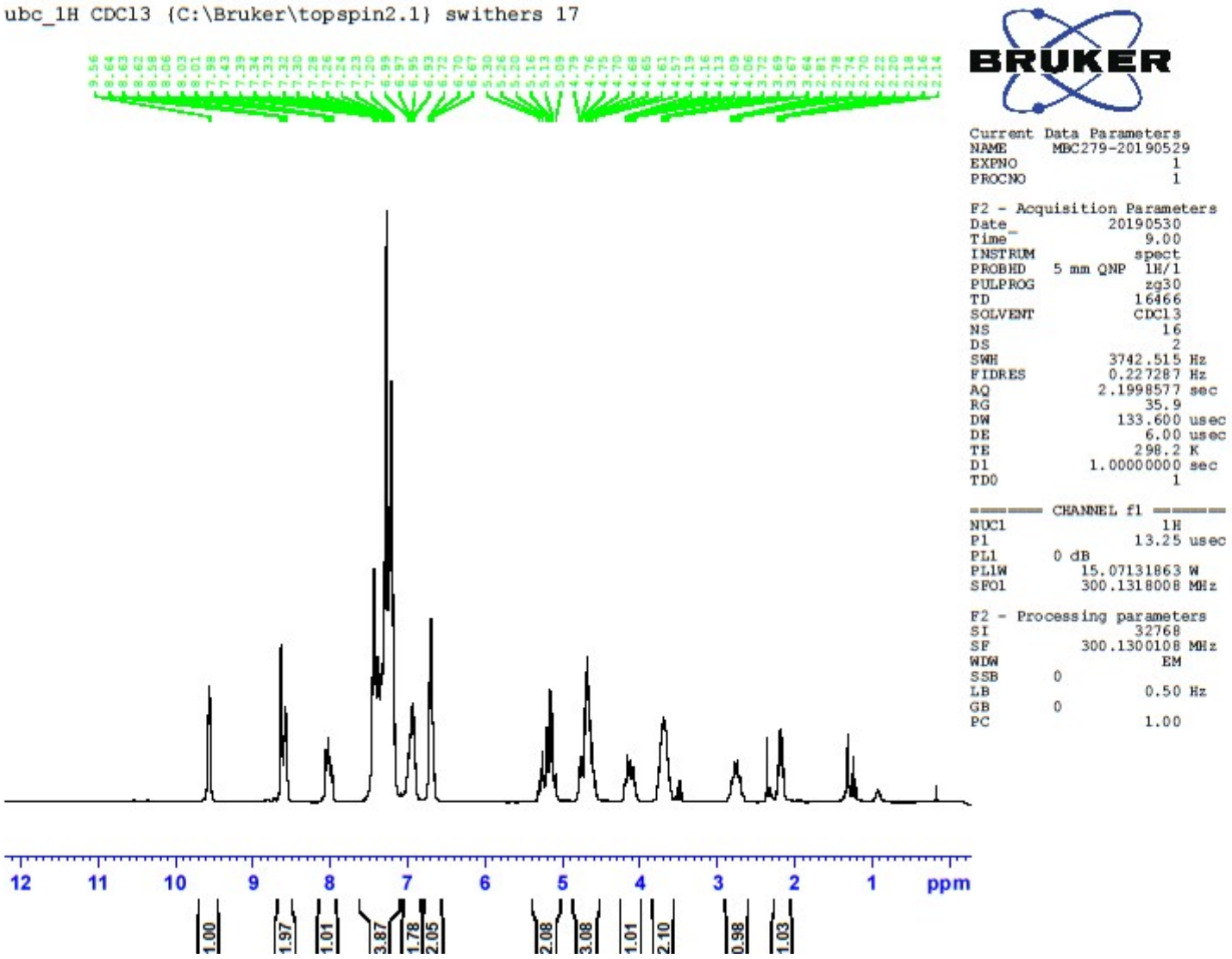


*Figure 23: ^{13}C NMR (**19**)*

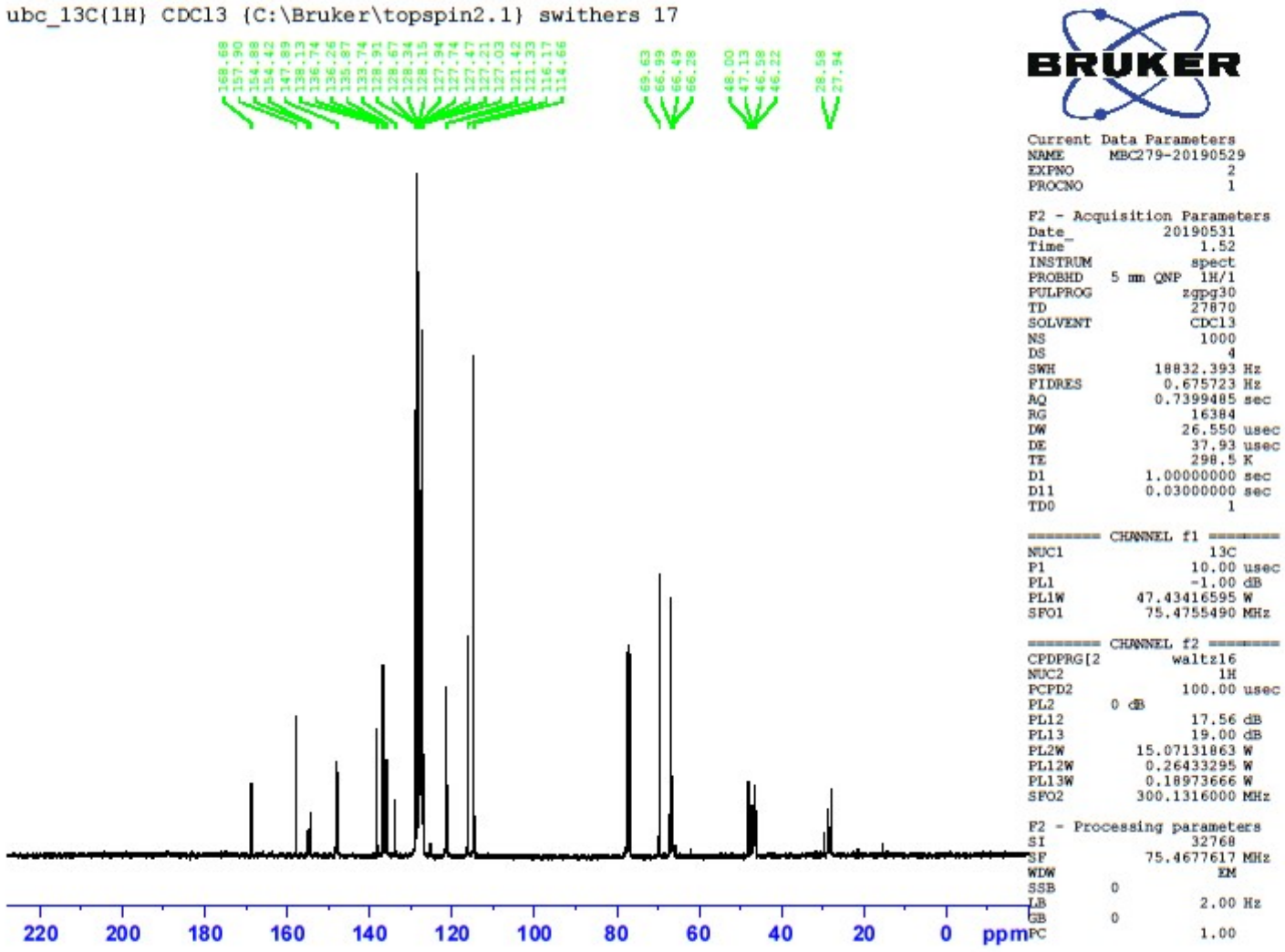
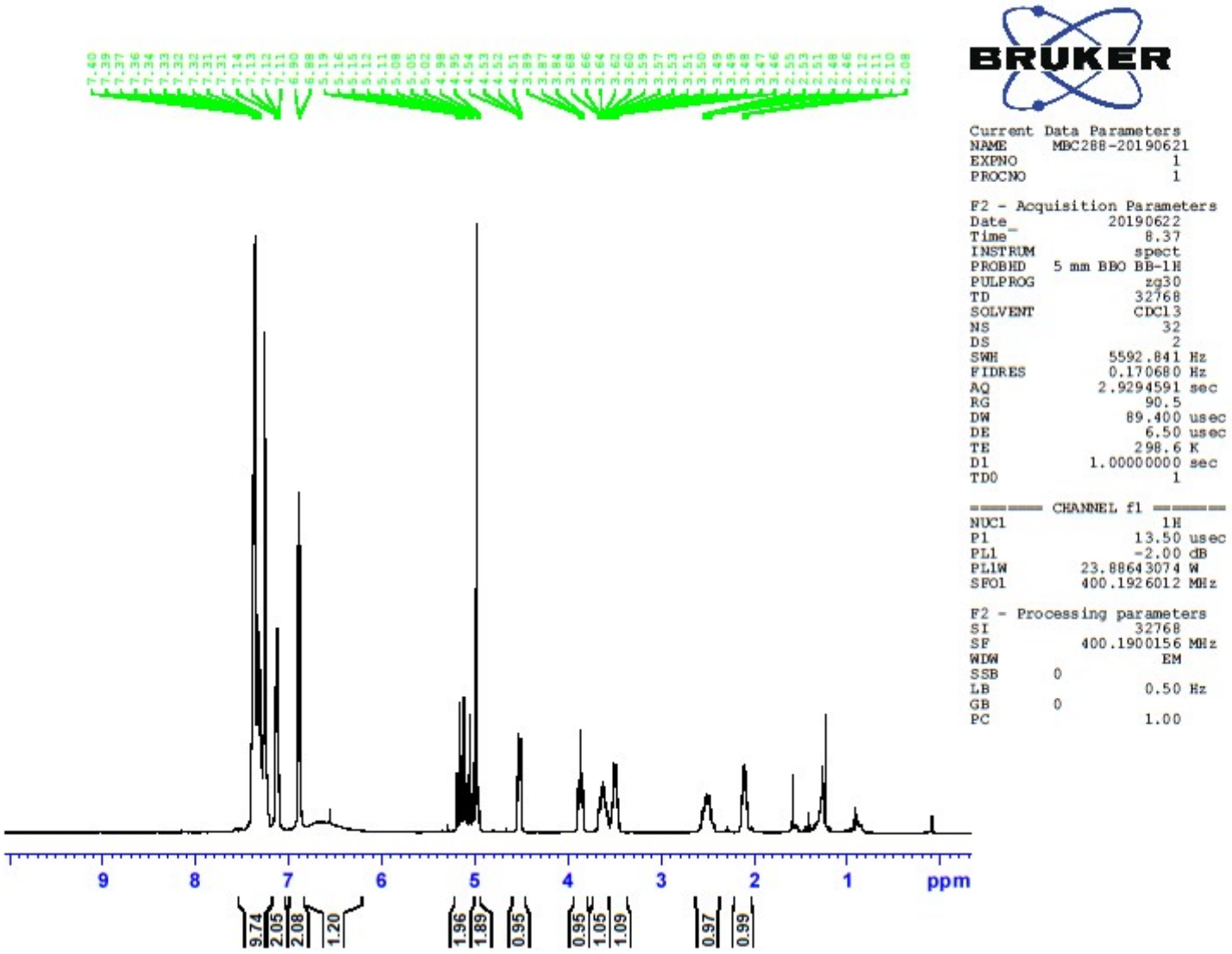


Figure 24: ^1H NMR (21)



BRUKER

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PROCNO 1

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FIDRES 0.170680 Hz
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DW 89.400 usec
DE 6.50 usec
TE 298.6 K
D1 1.00000000 sec
TD0 1

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PL1 -2.00 dB
PL1W 23.88643074 W
SFO1 400.1926012 MHz

F2 - Processing parameters
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LB 0.50 Hz
GB 0
PC 1.00

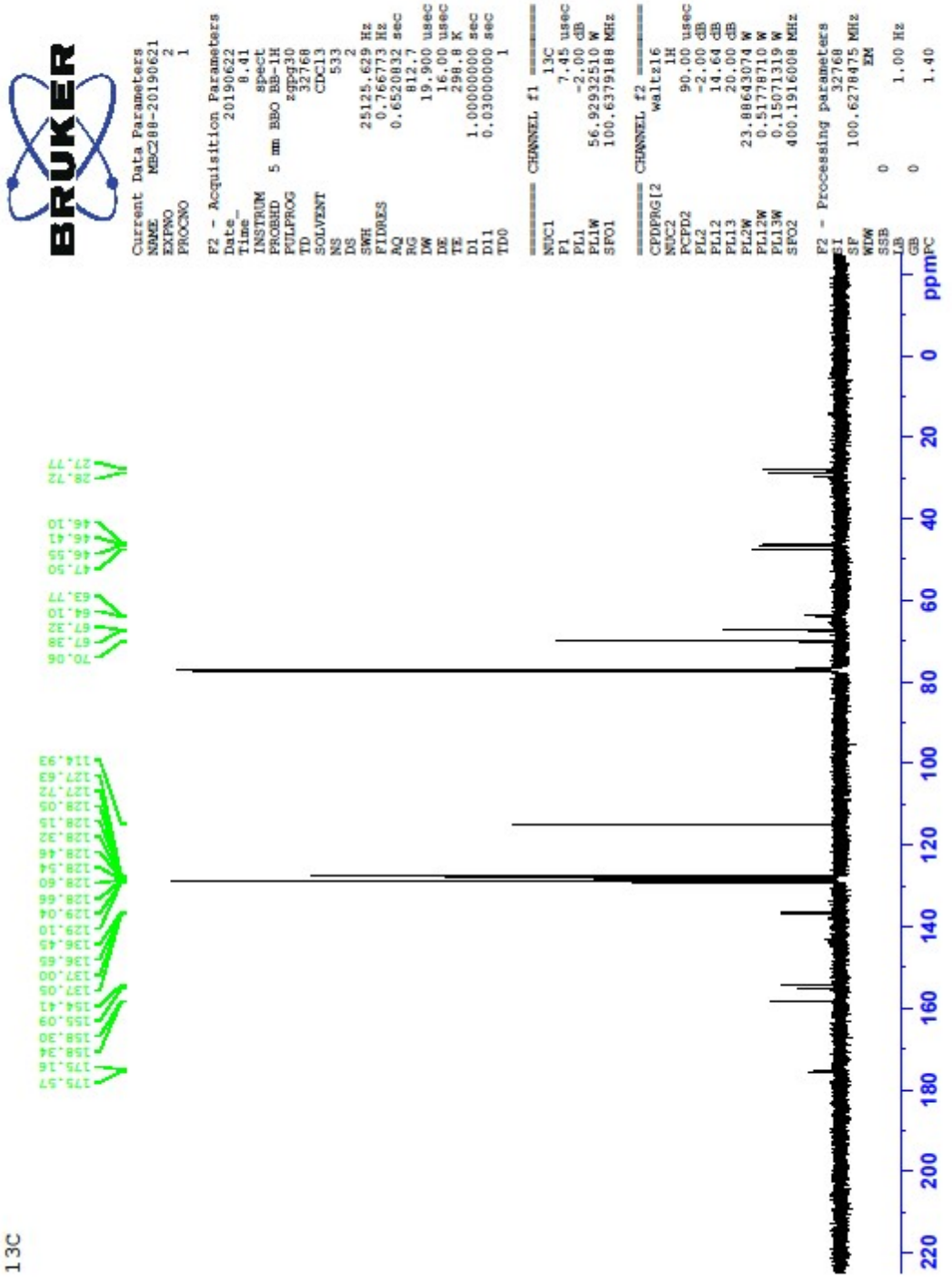


*Figure 25: ^{13}C NMR (**21**)*

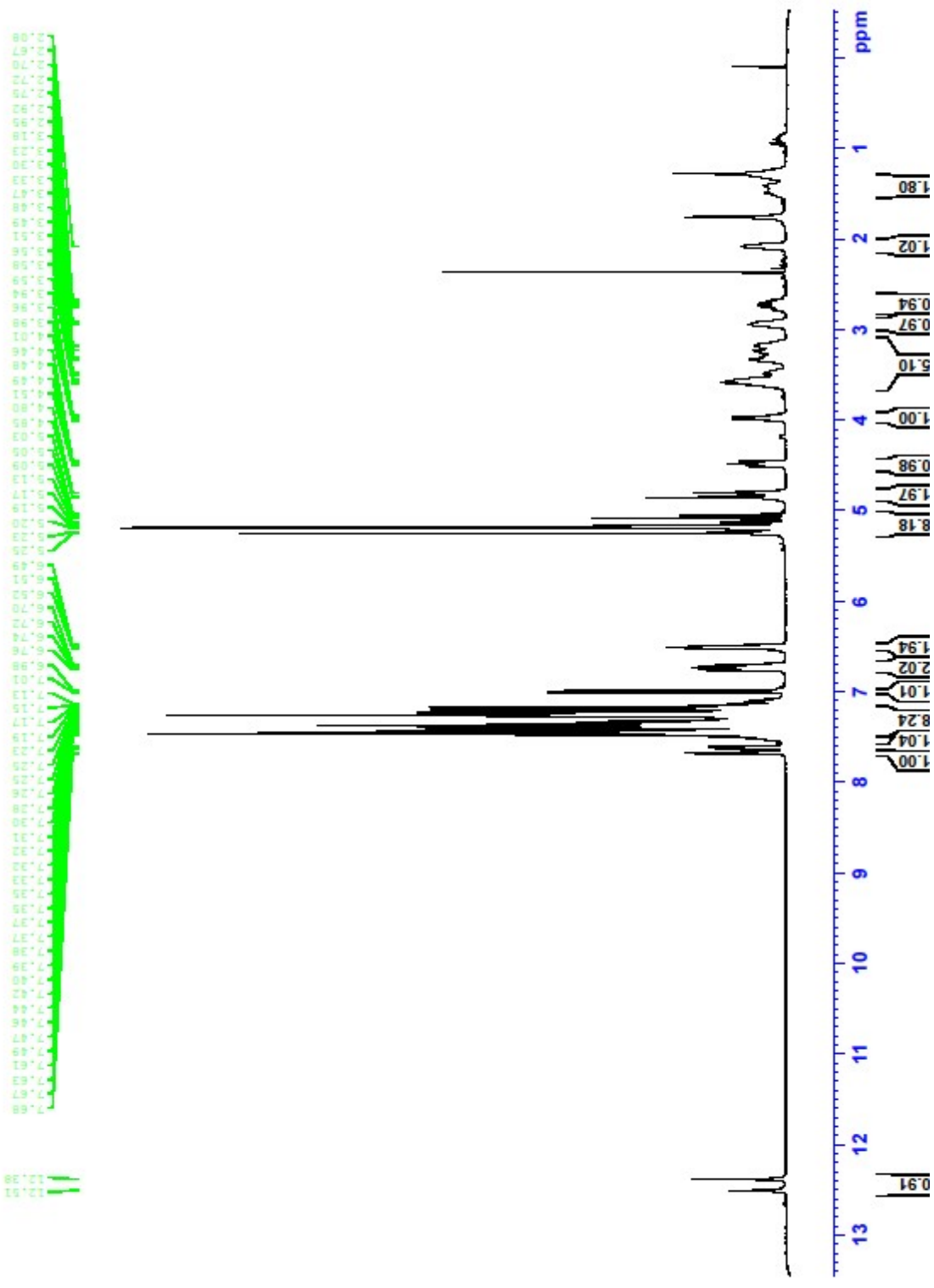


*Figure 26: [1]H NMR **(23)***

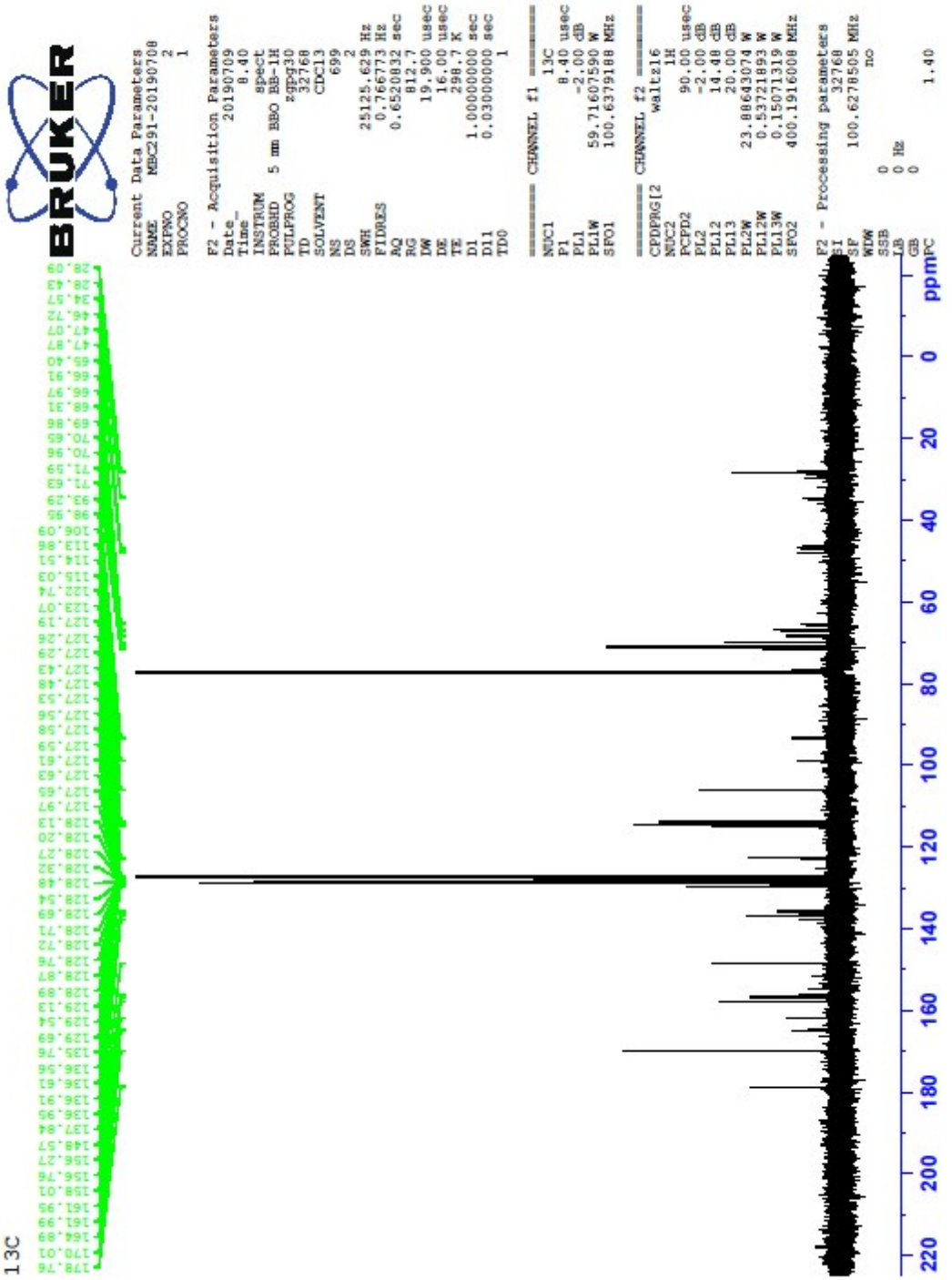


*Figure 27: ^{13}C NMR (**23**)*

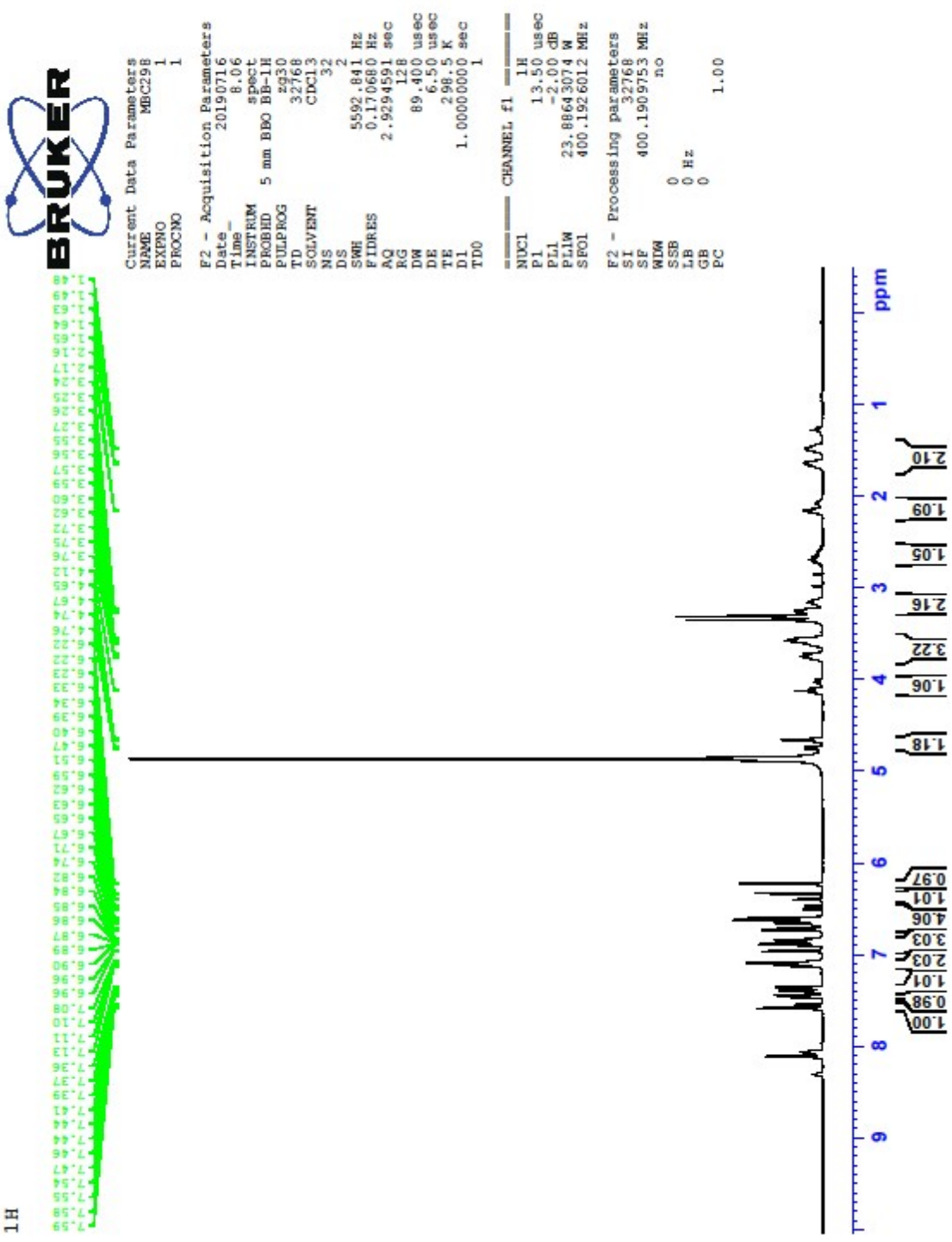


*Figure 28: [1]H NMR (**17**)*

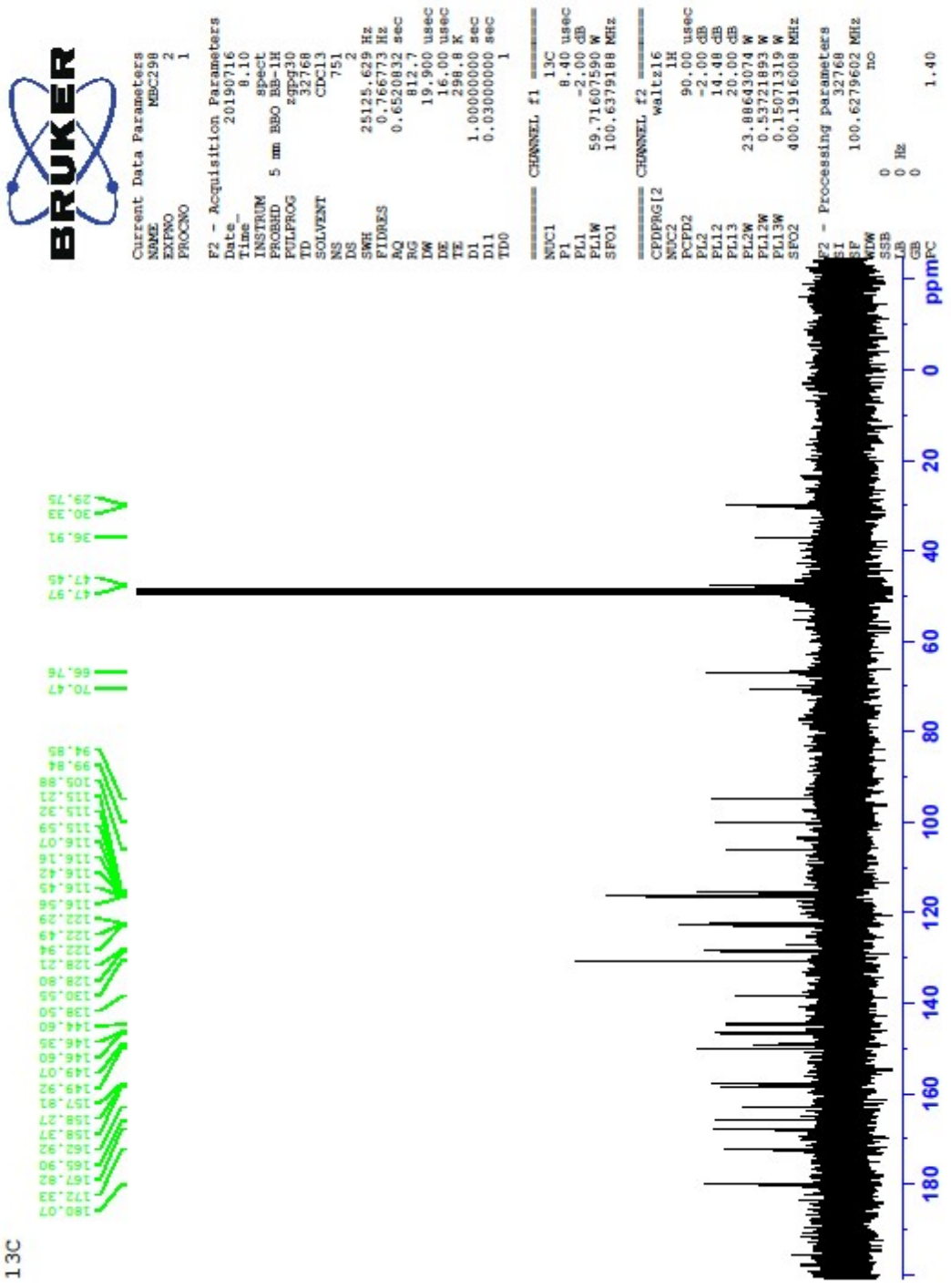


*Figure 29: ^{13}C NMR (**17**)*

*Figure 30: ^{1}H NMR (**26**)*

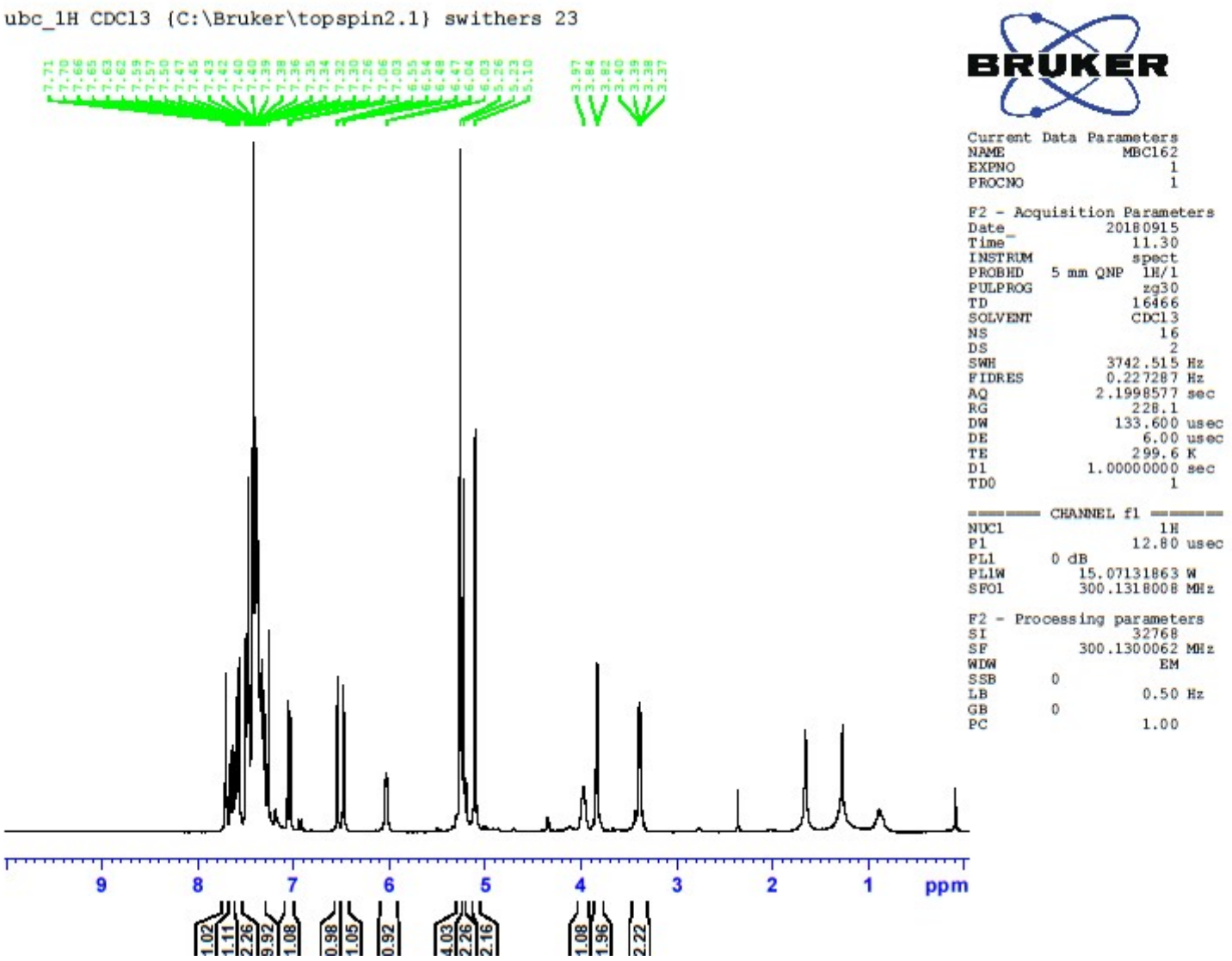


*Figure 31: ^{13}C NMR (**26**)*

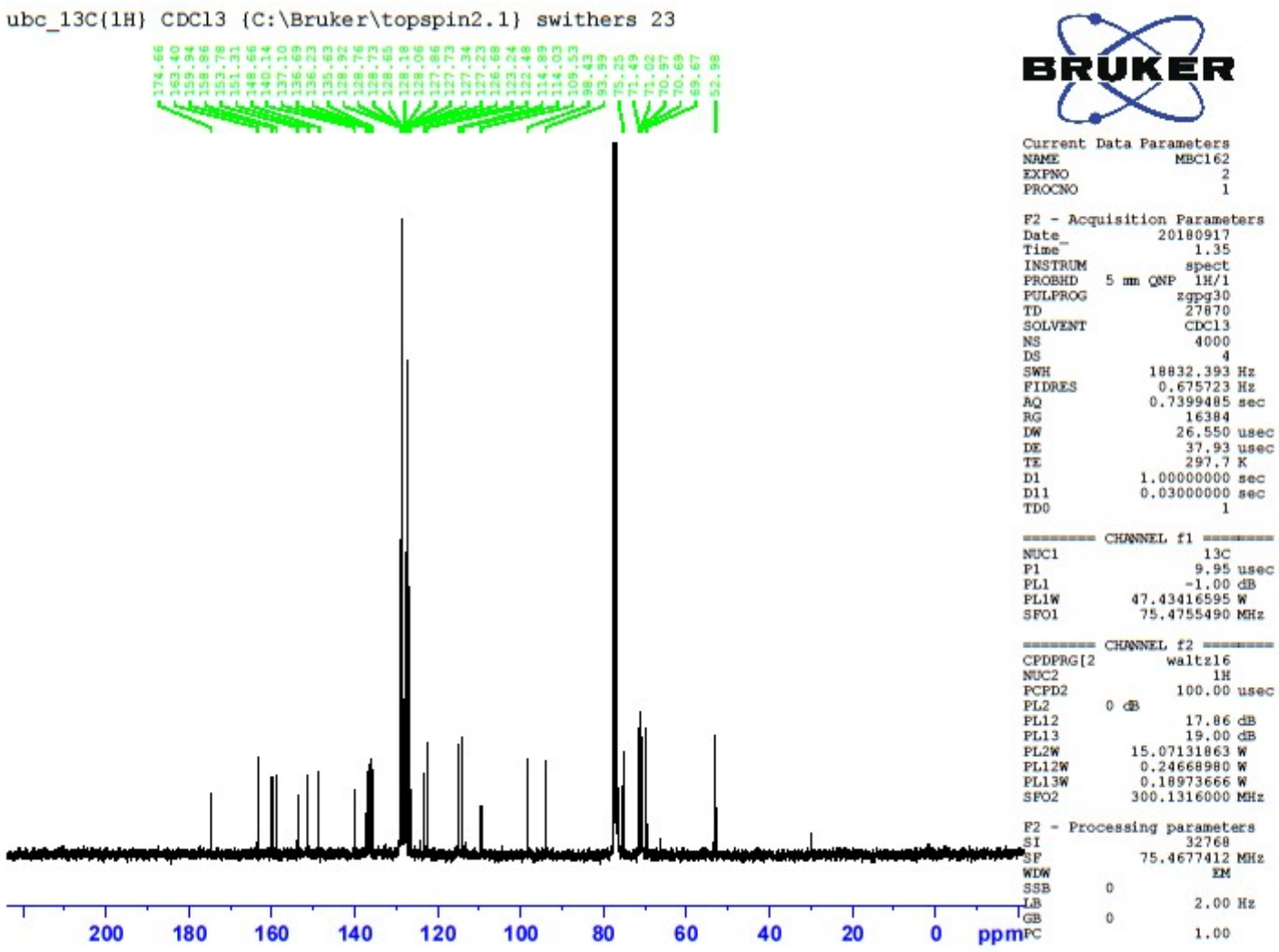


Figure 32: ^{1}H NMR (27)

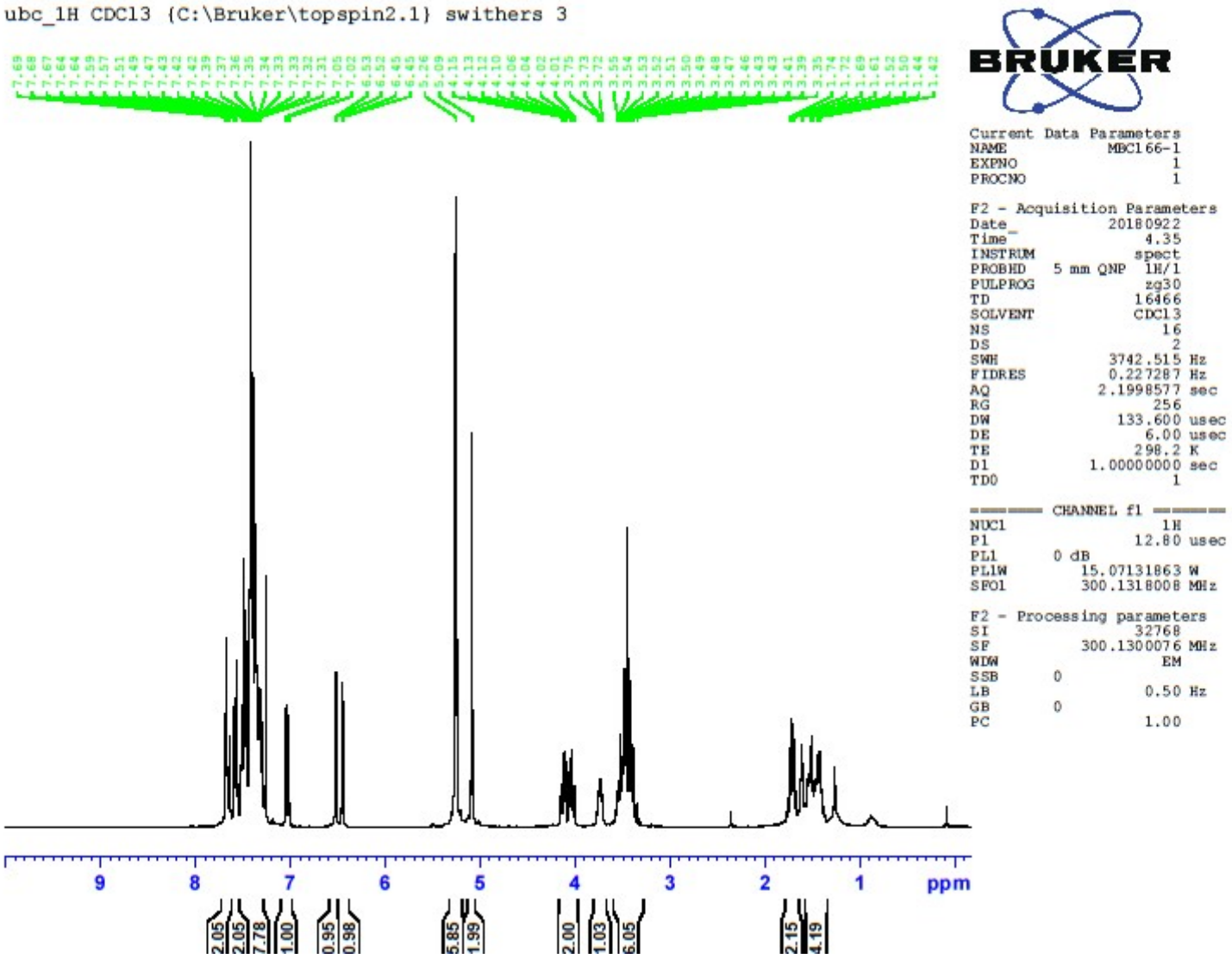
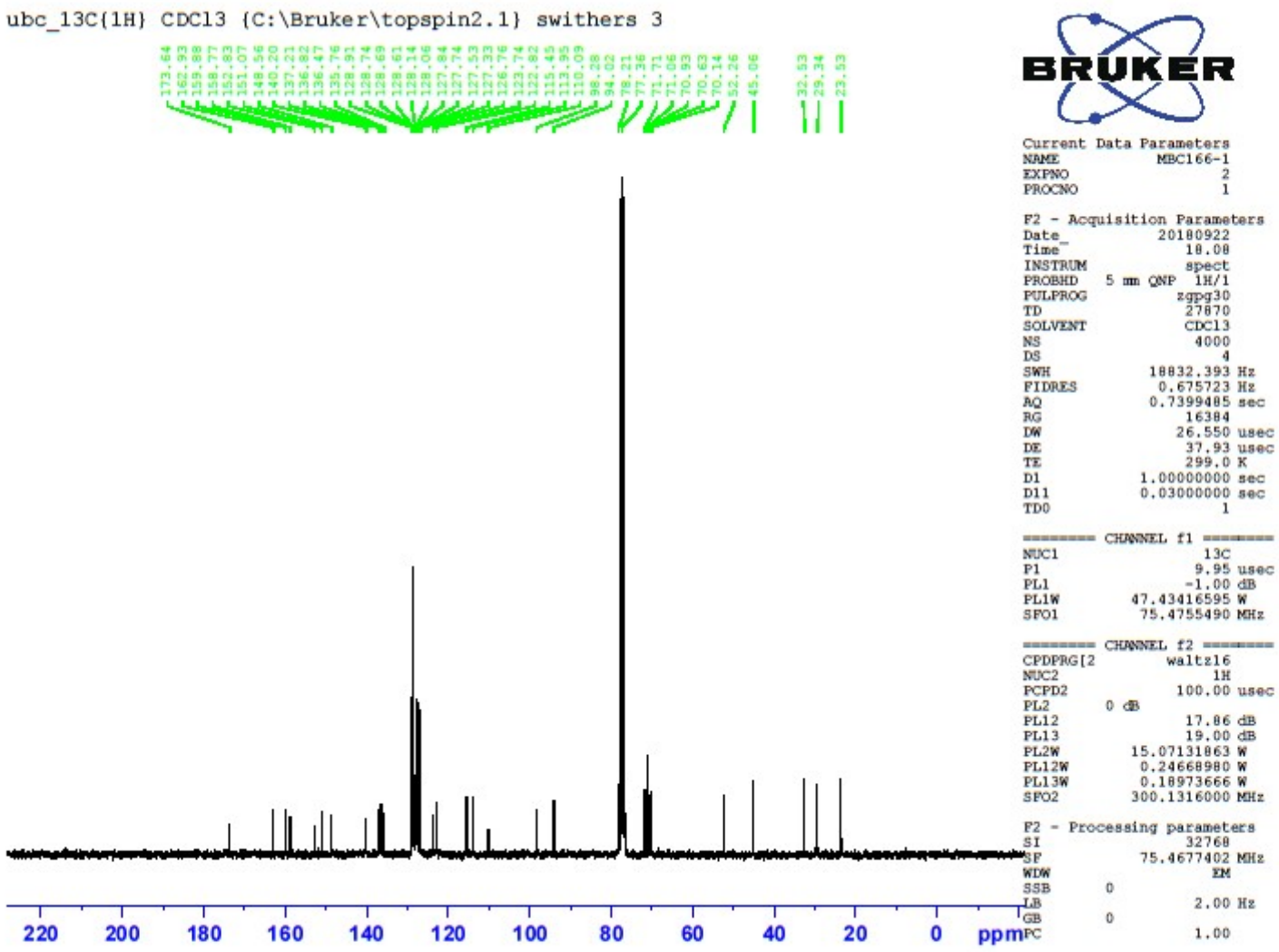


Figure 33: ^{13}C NMR (27)



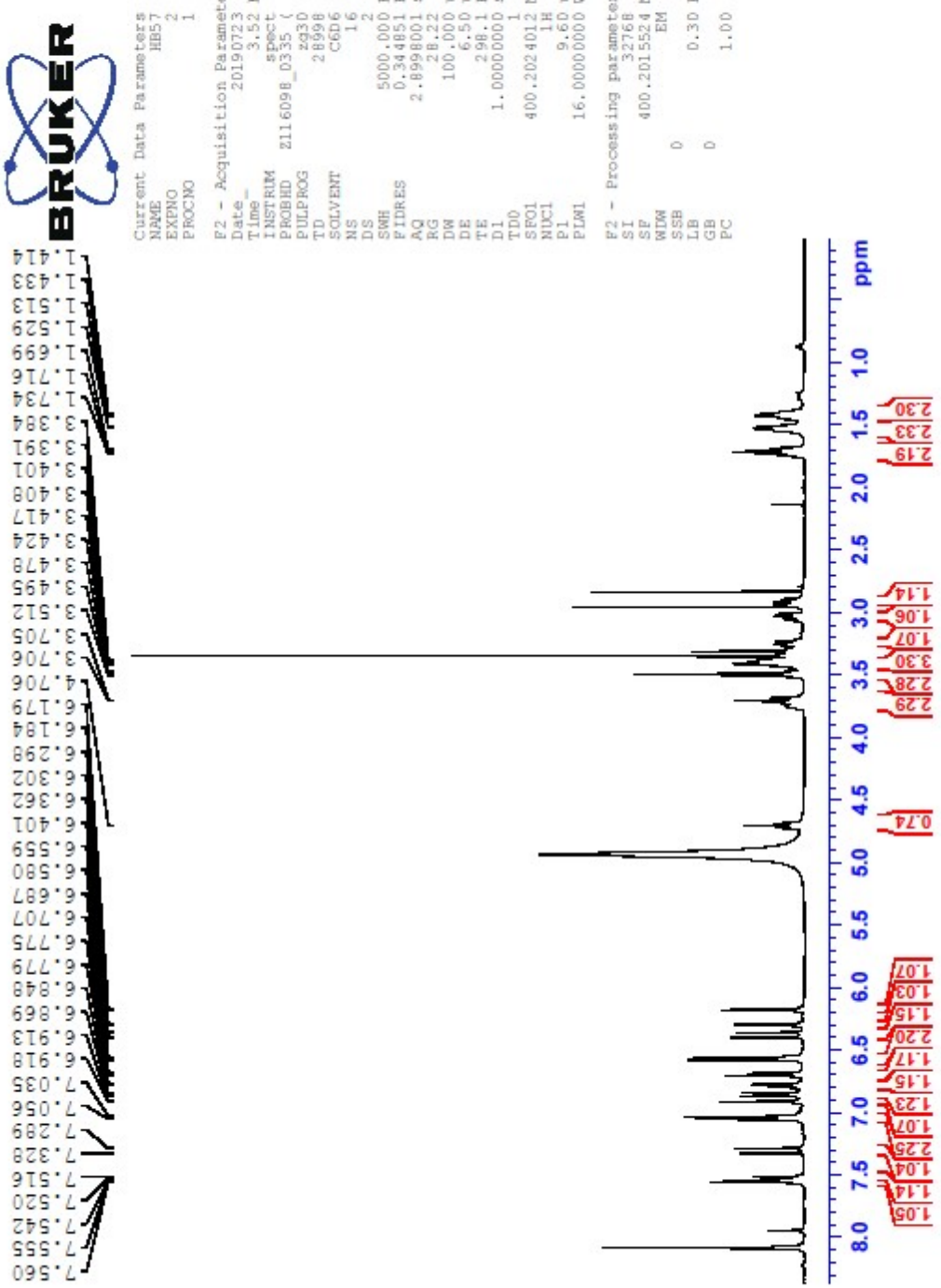


*Figure 34: [1]H NMR **(30a)***

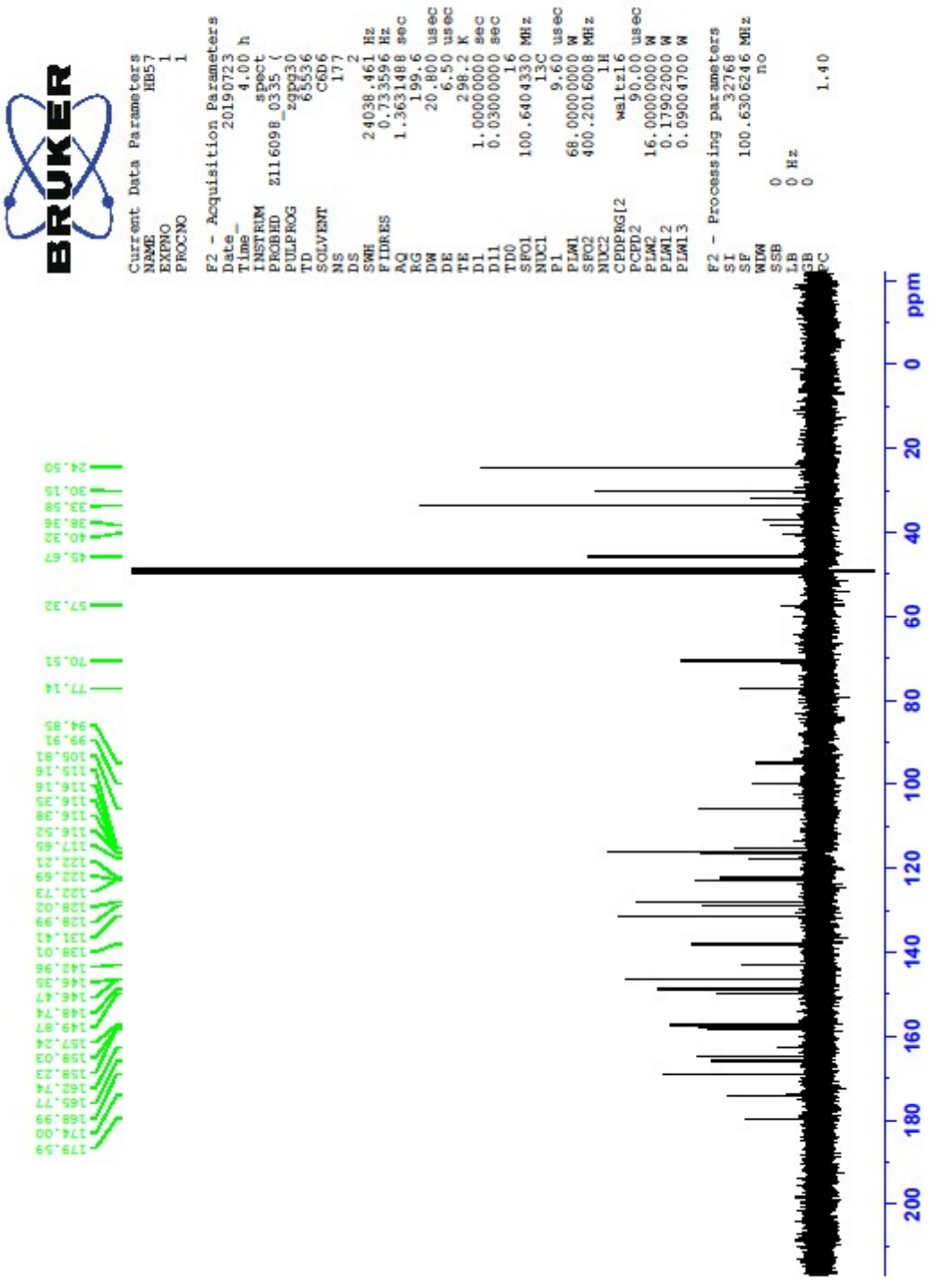
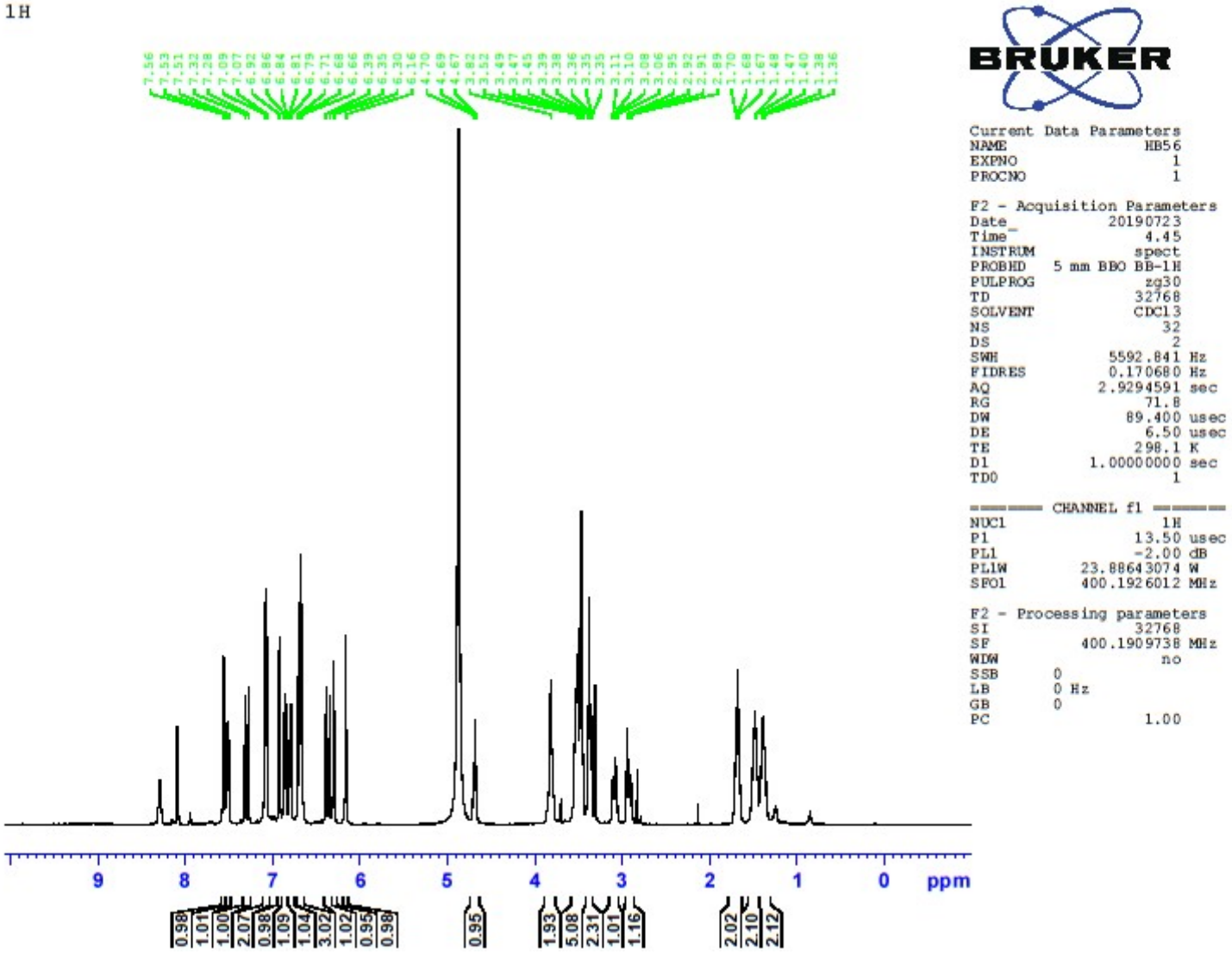


*Figure 35: ^{13}C NMR (**30a**)*

*Figure 36: ^1H NMR (**30b**)*



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PROCNO 1

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SWH 5592.841 Hz
FIDRES 0.170680 Hz
AQ 2.9294591 sec
RG 71.8
DW 89.400 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1

CHANNEL f1
NUC1 1H
P1 13.50 usec
PL1 -2.00 dB
PL1W 23.88643074 W
SFO1 400.1926012 MHz

F2 - Processing parameters
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SF 400.1909738 MHz
WDW no
SSB 0
LB 0 Hz
GB 0
PC 1.00

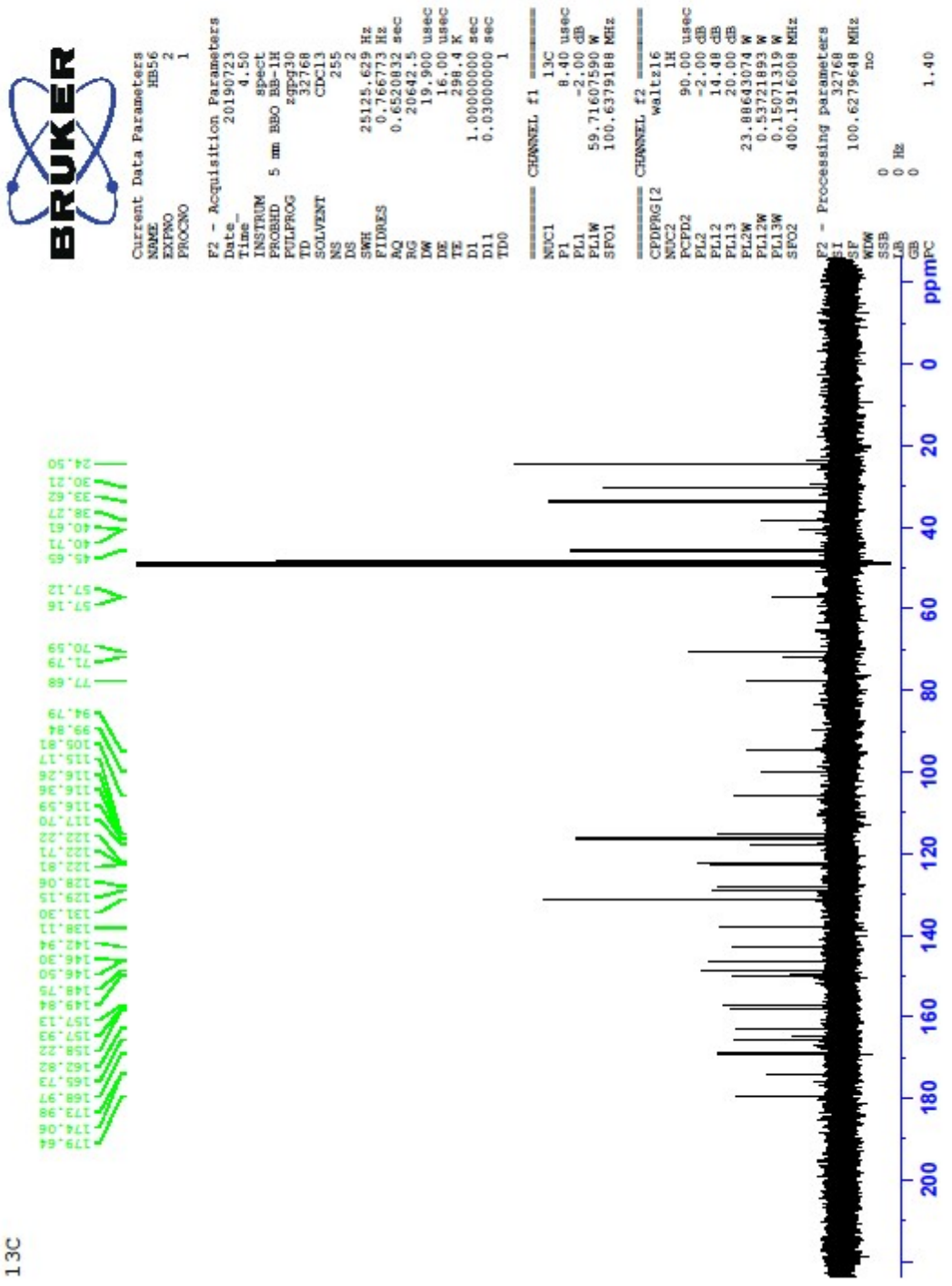
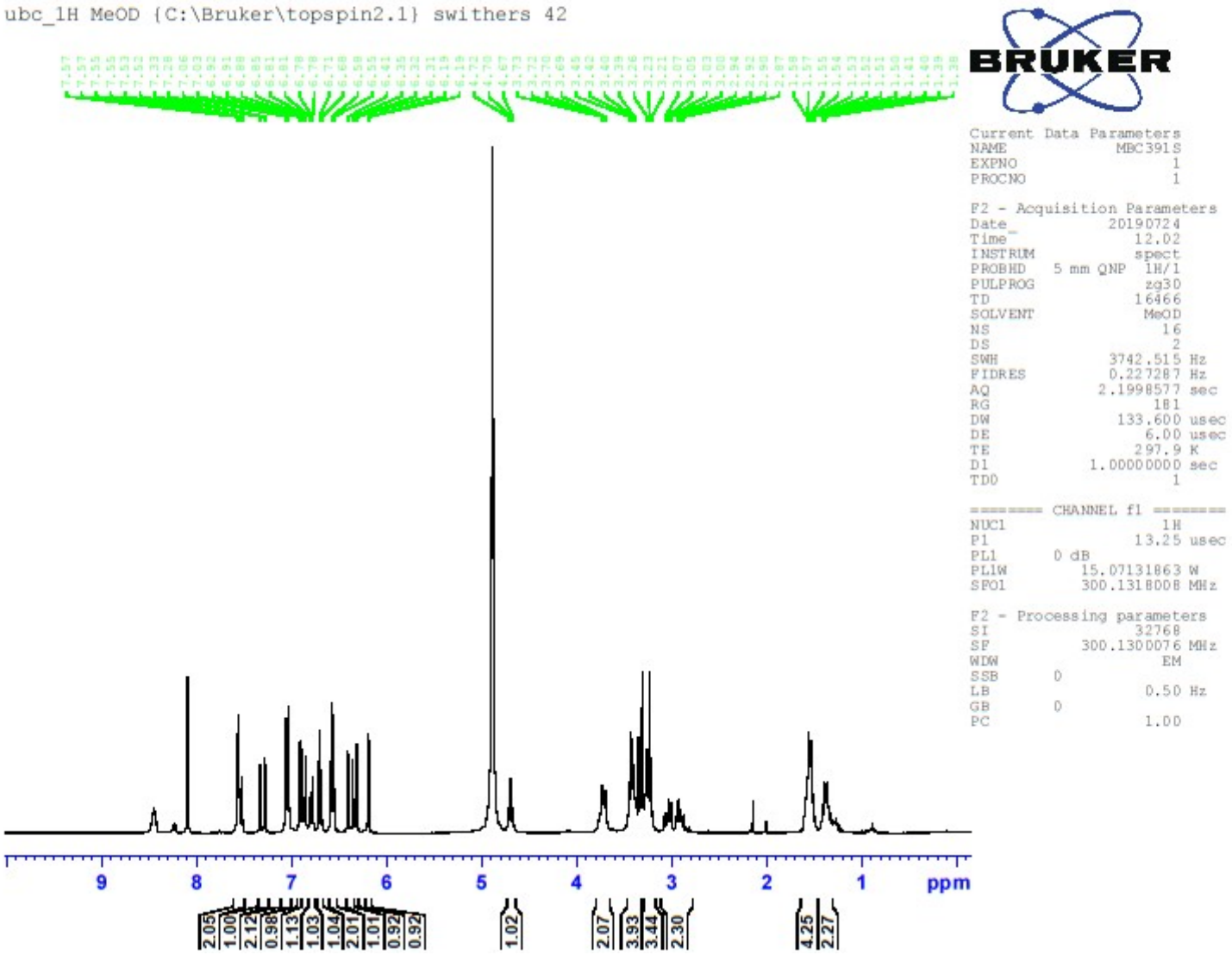


*Figure 37: ^{13}C NMR (**30b**)*

*Figure 38: ^{1}H NMR (**34a**)*



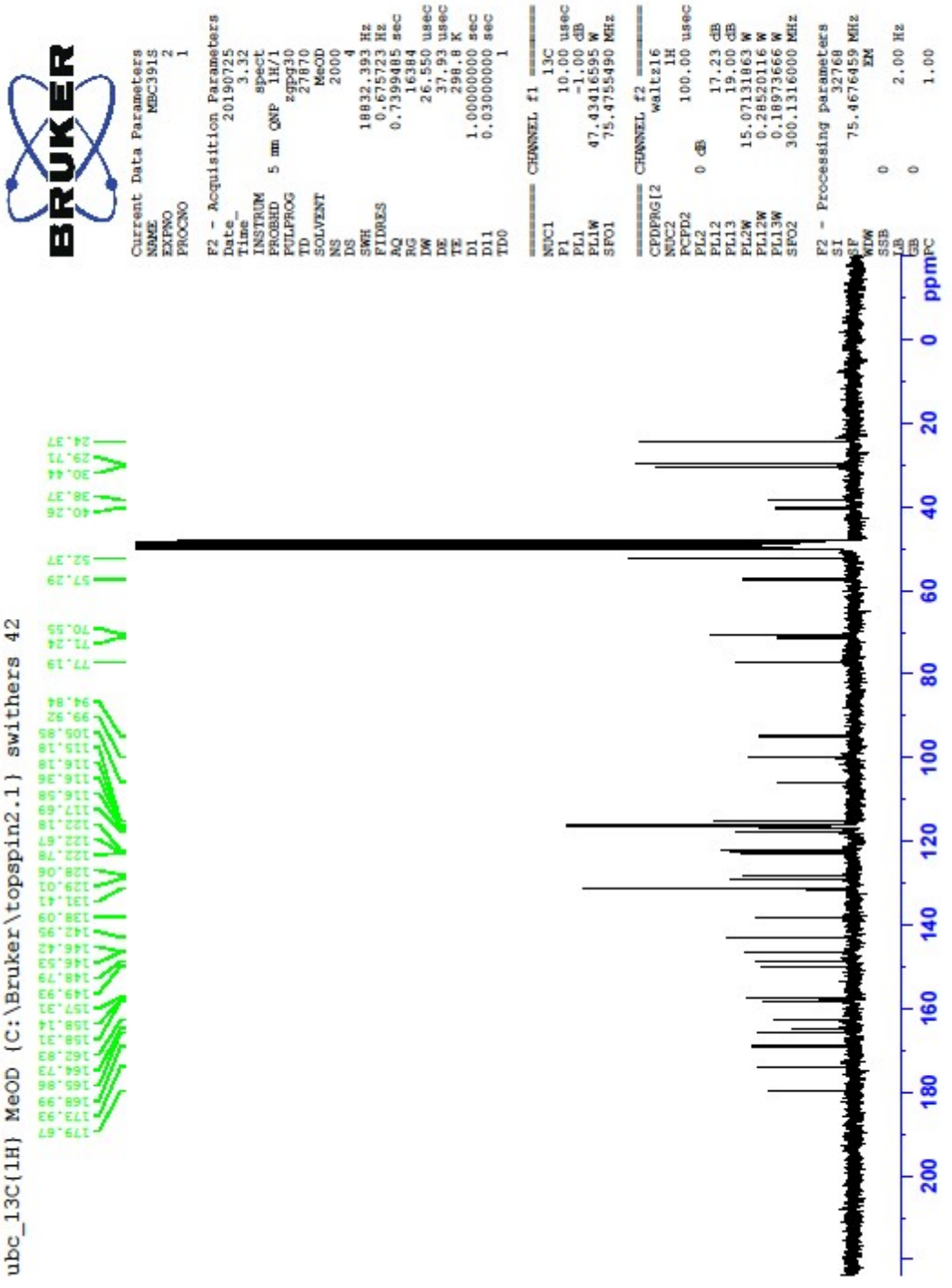


*Figure 39: ^{13}C NMR **(34 a)***

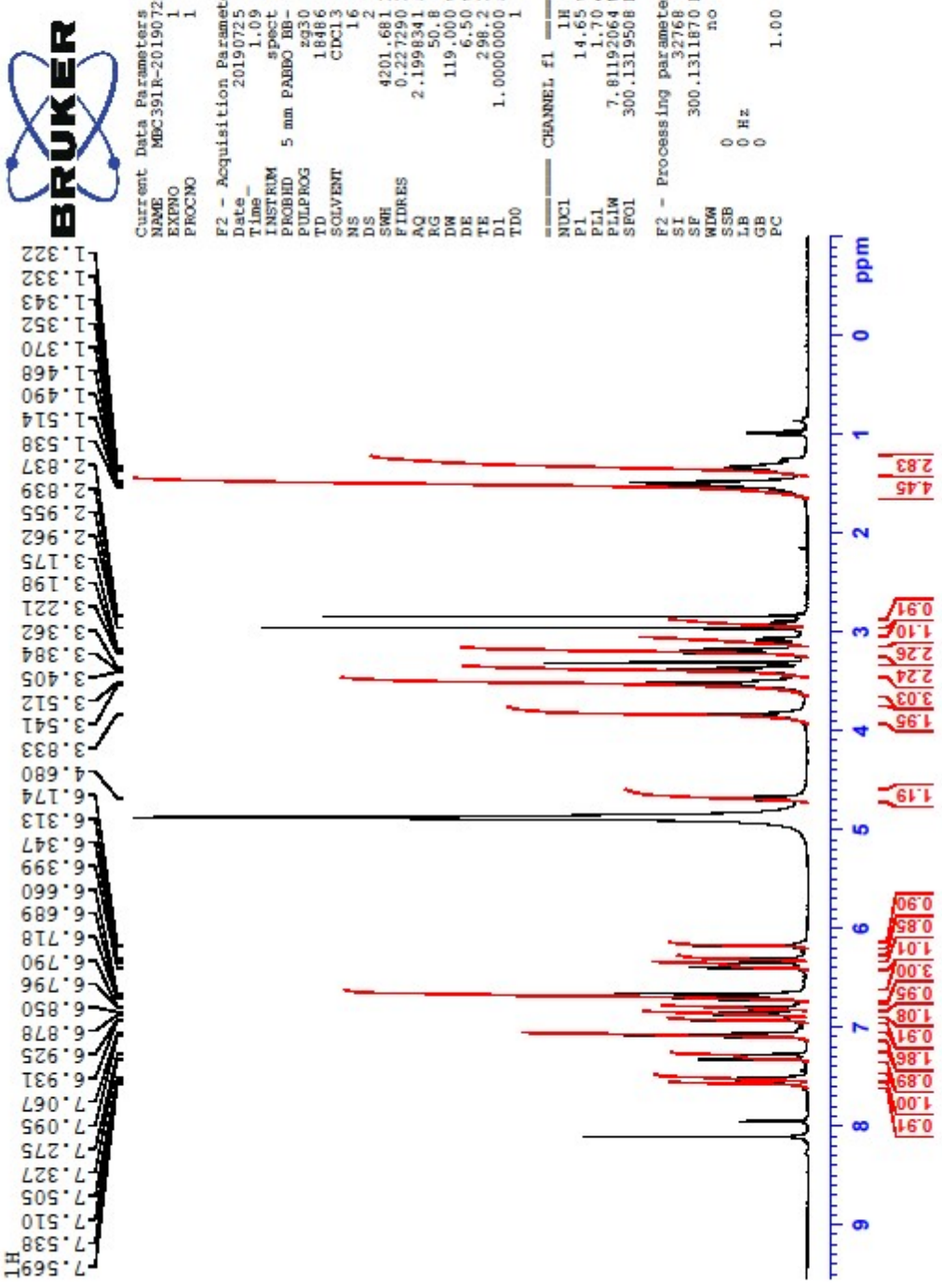


*Figure 40: [1]H NMR **(34b)***

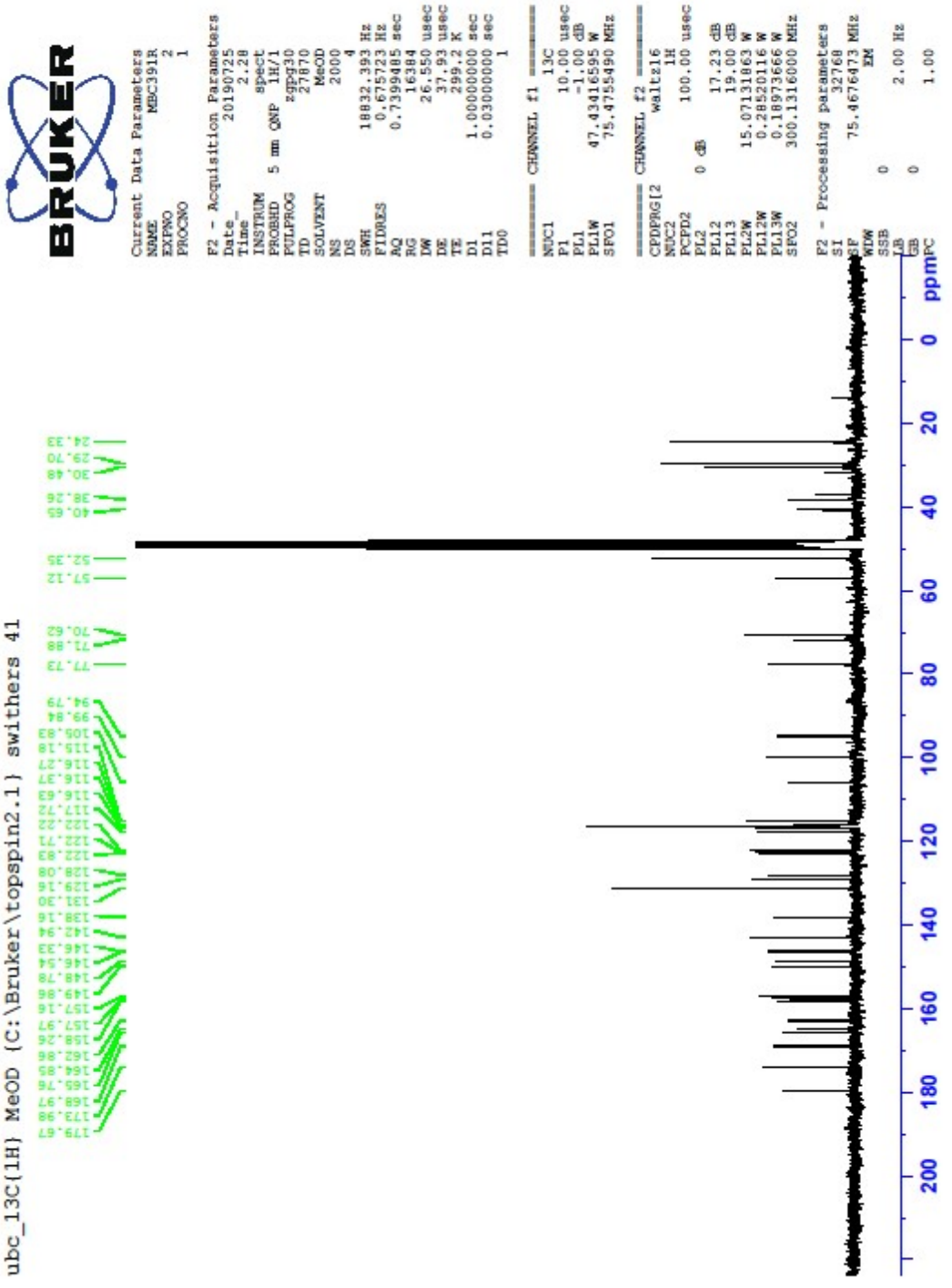


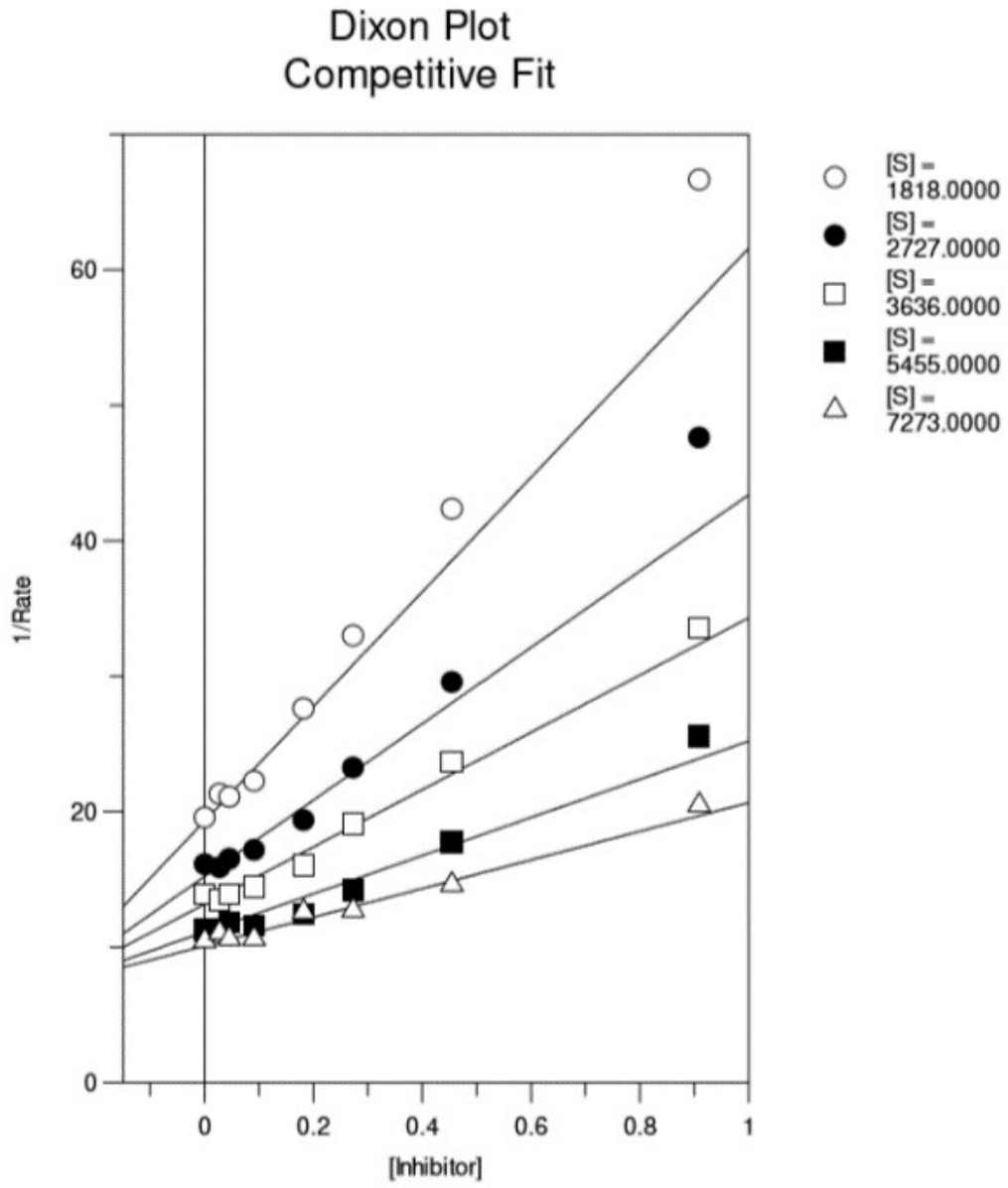
*Figure 41: ^{13}C NMR (**34b**)*

Kinetic Analysis of Inhibitors

Human pancreatic alpha-amylase (HPA) was expressed in *Pichia pastoris* and purified as described in some detail previously[2]. 2-Chloro-4-nitrophenyl α-maltotrioside (CNPG3) was purchased from Sekisui Enzymes. Incubation of this substrate with HPA leads to the release of 2-chloro-nitrophenol, and this was monitored by measuring the absorbance of the reaction solutions at 400 nm.

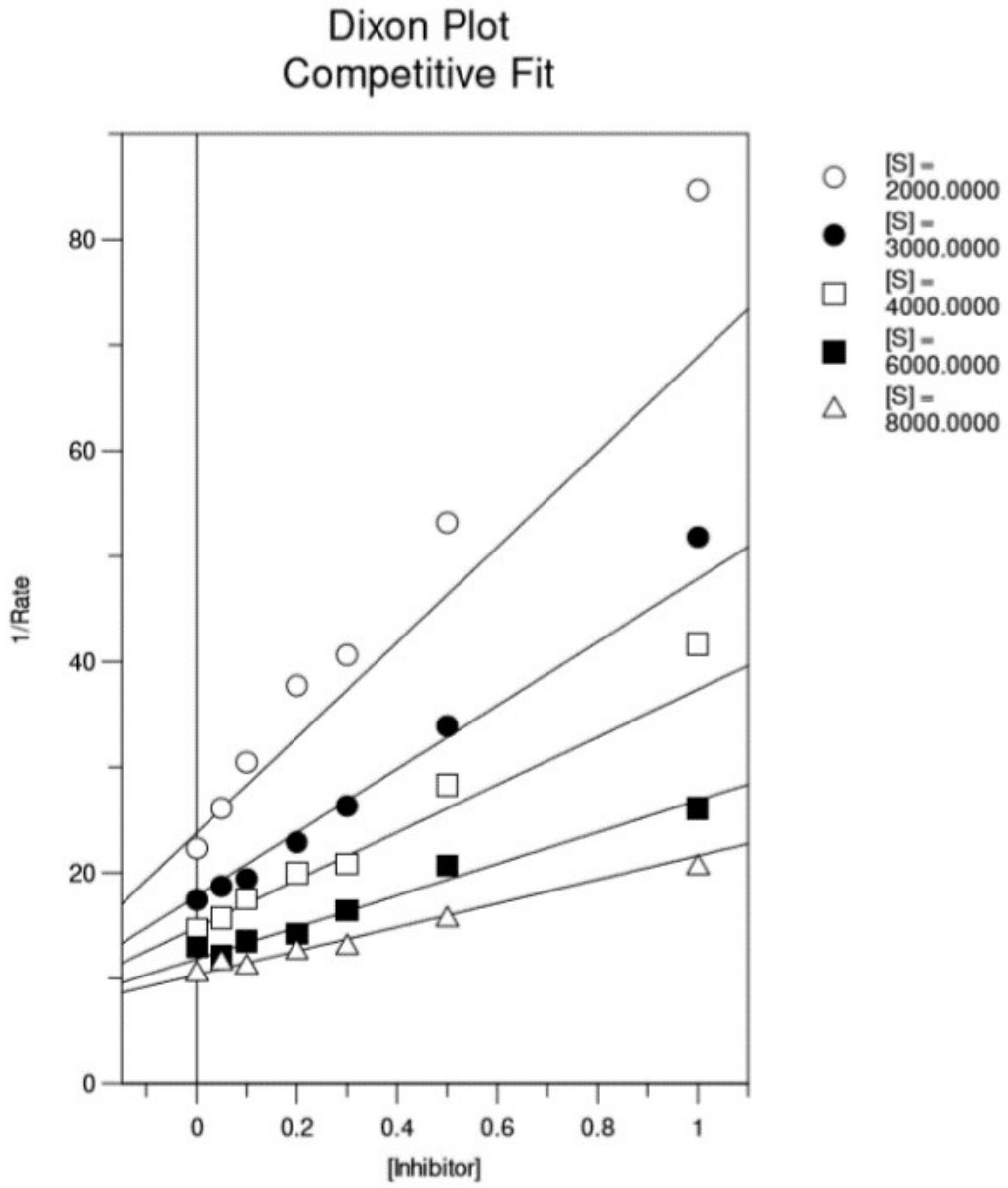
The assays were performed with either a Varian Cary 4000 UV/Vis spectrophotometer or a BioTek Synergy H1 plate reader. After the start of the reactions by addition of the substrates, the absorbance of the solutions were monitored over 5 minutes to measure the initial reaction rate. Reactions were run at 30°C in 50 mM sodium phosphate including 100 mM sodium chloride (pH 7.0). The assays were performed using two to five different [CNPG3] (2 mM and 4 mM; 2 mM, 4 mM, and 6 mM; 2 mM, 3 mM, 4 mM, 6 mM and 8 mM) for each range of inhibitor concentrations. Inhibitor concentrations generally ranging from 1/5 to 5x K_I were used. For each reaction, HPA was incubated with varying [*I*] at 30°C for at least 1 minute prior to addition of CNGP3 substrates. The resulting initial rate data were fit to a competitive inhibition model using nonlinear regression analysis, as performed by the GraFit 7.0 program to provide a value for K_I. Dixon and Lineweaver-Burke plots of each data set validated the use of a competitive inhibition model.

Compound	K_I (μM)
13	0.29 ± 0.02
14	0.40 ± 0.02
17	0.10 ± 0.01
30a	0.07 ± 0.03
30b	0.20 ± 0.06
36a	0.34 ± 0.02
36b	1.2 ± 0.18
38a	1.56 ± 0.25
47a	11 ± 1.5
48a	0.76 ± 0.08
49a	~50 ± 12
Mini-MbA	0.39 ± 0.05



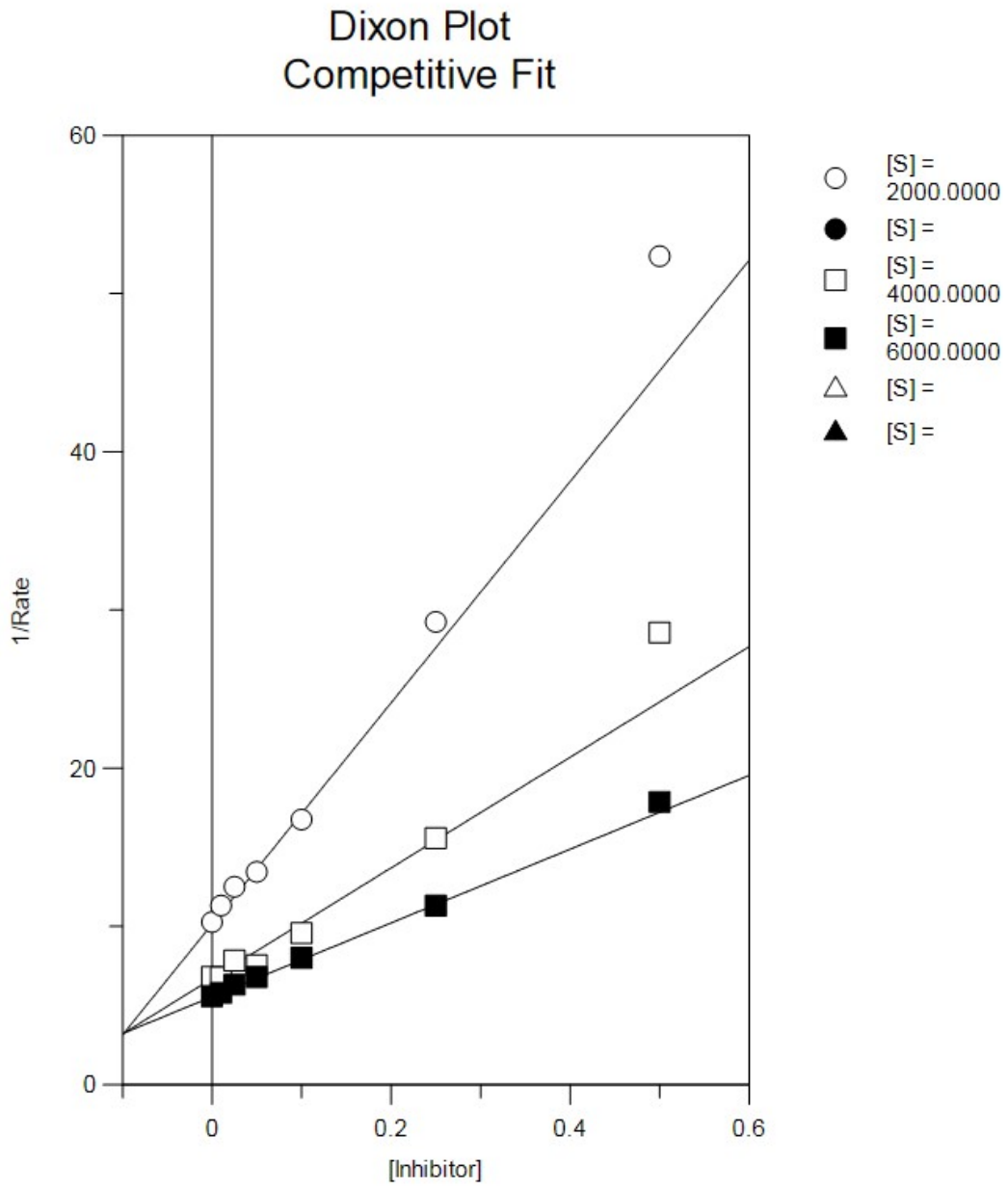
Parameter	Value	Std. Error
Vmax	0.1424	0.0046
Km	3184.0156	246.3102
Ki	0.2910	0.0206

*Figure 42: Dixon plot for **13.** All concentrations in uM*



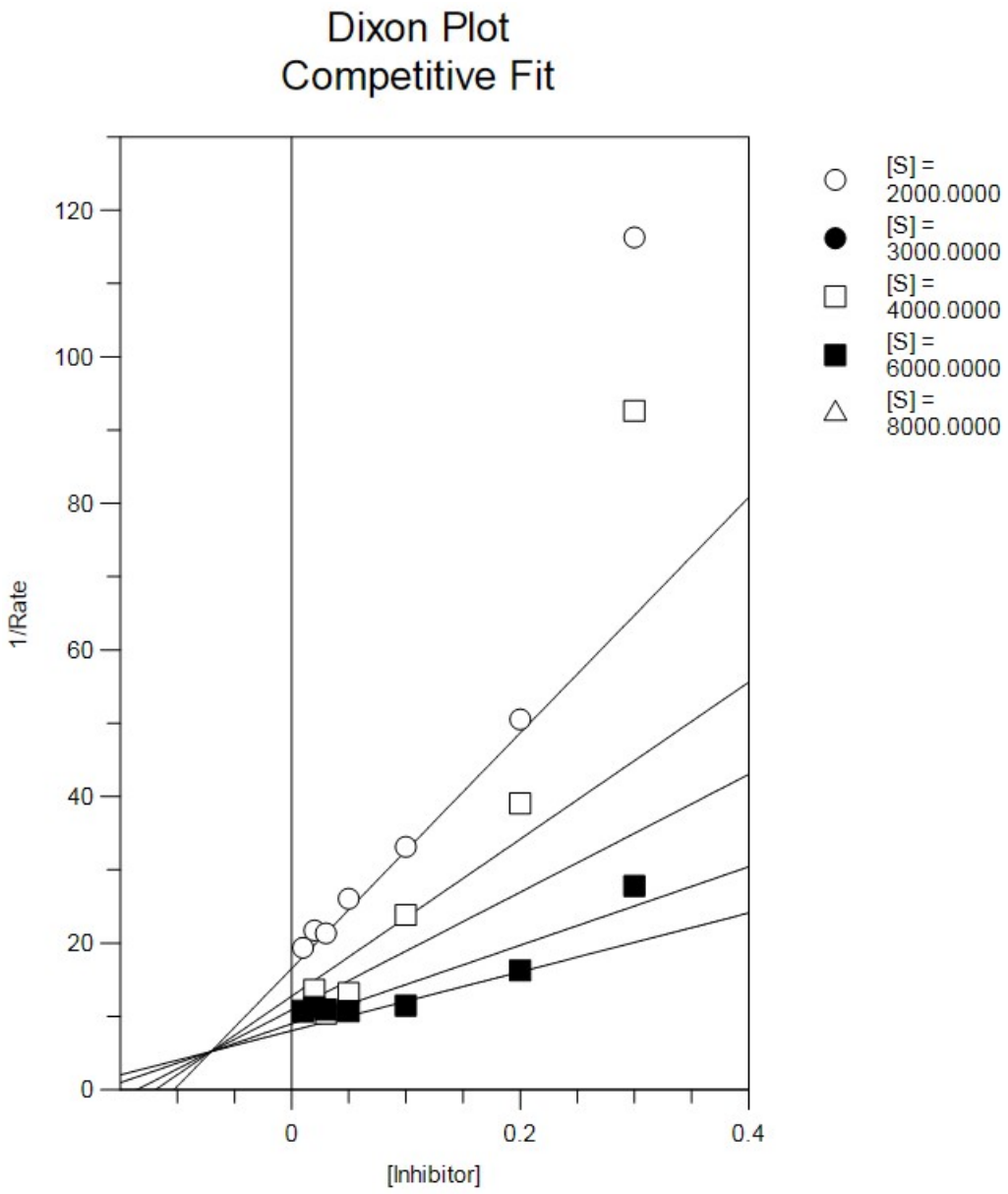
Parameter	Value	Std. Error
Vmax	0.1711	0.0089
Km	6142.1852	594.4200
Ki	0.3979	0.0292

*Figure 43: Dixon plot for **14.** All concentrations in uM.*



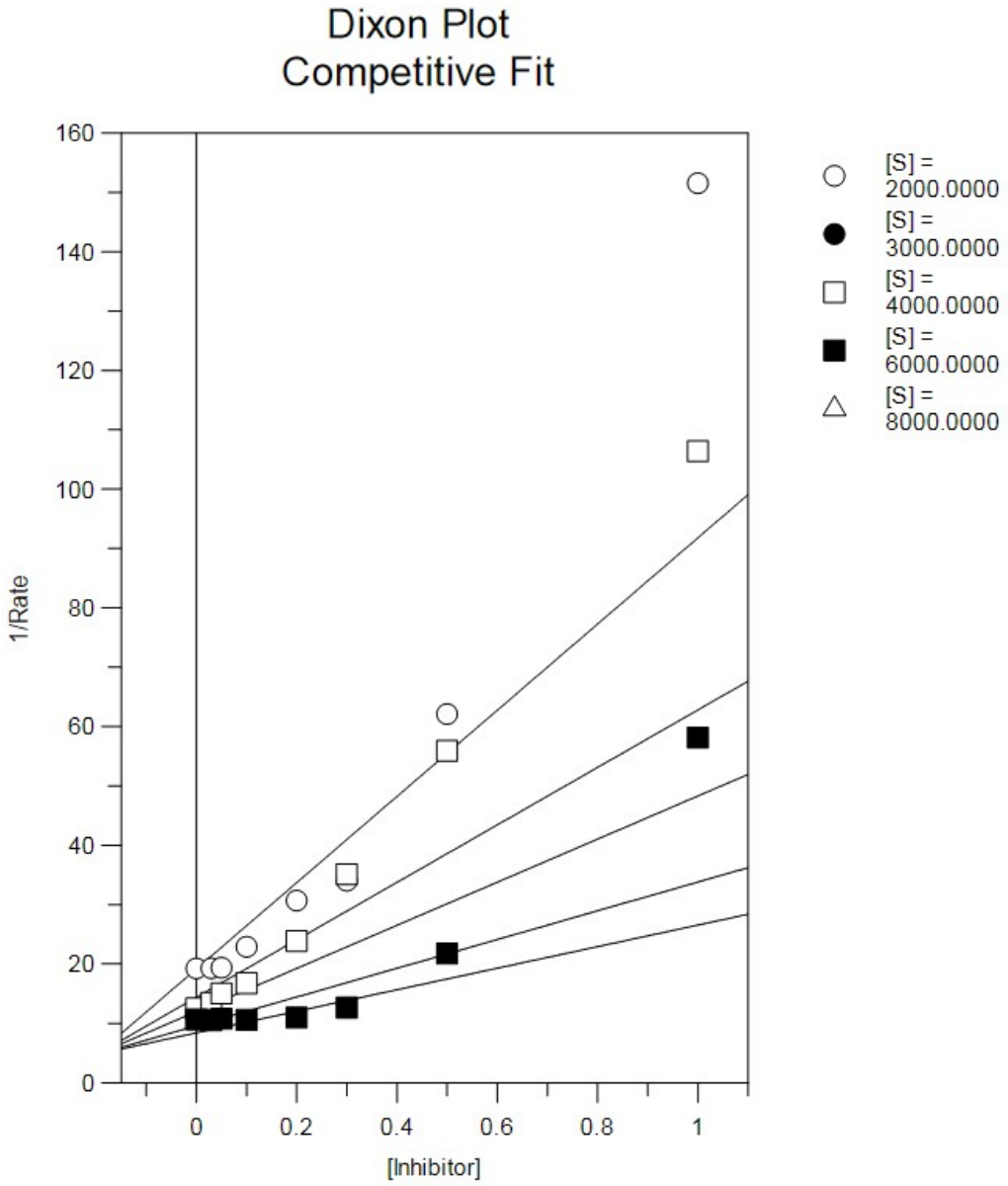
Parameter	Value	Std. Error
Vmax	0.3061	0.0182
Km	4214.9682	510.4367
Ki	0.0985	0.0086

*Figure 44: Dixon plot for **17.** All concentrations in uM.*



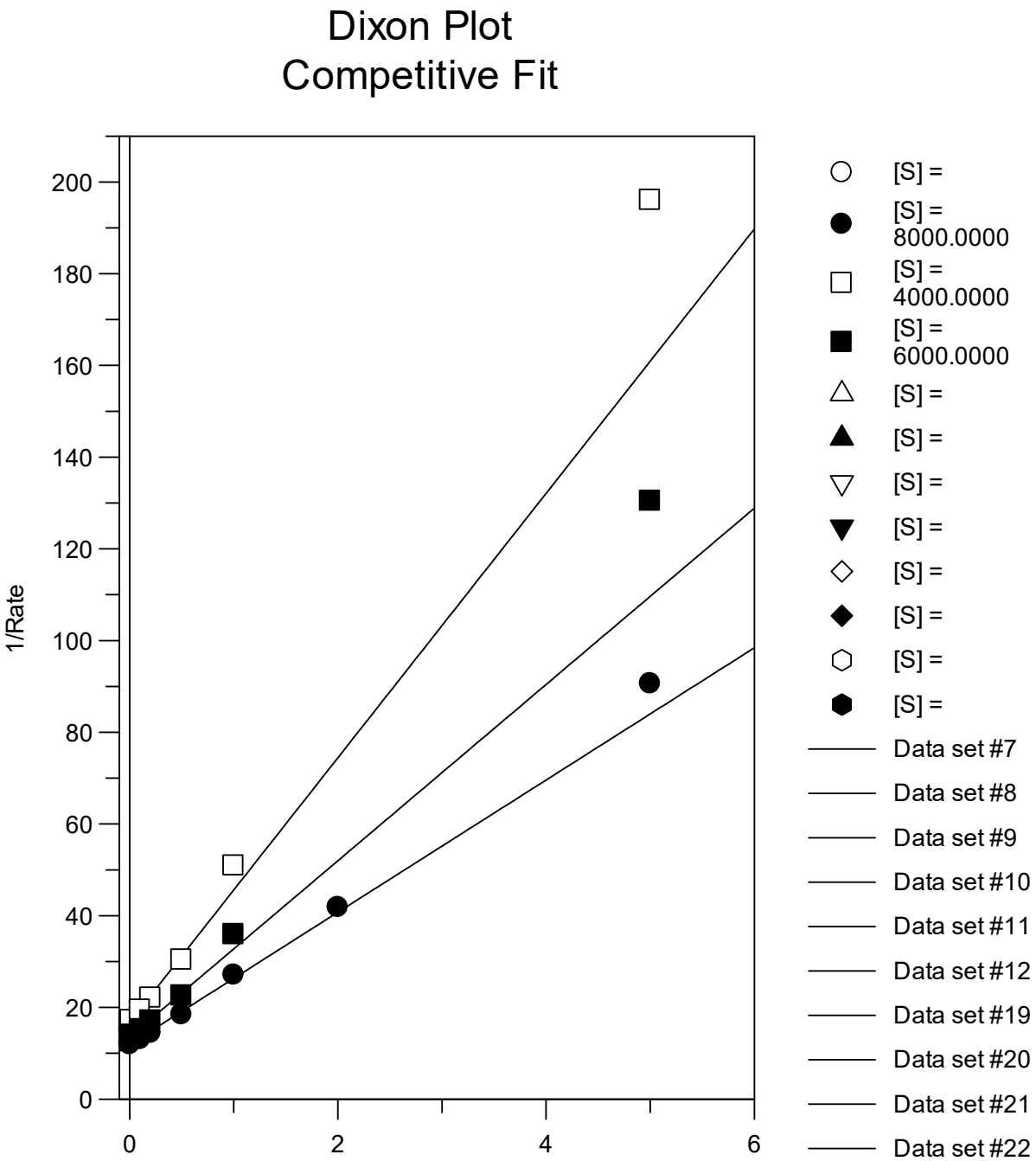
Parameter	Value	Std. Error
Vmax	0.1919	0.0496
Km	4345.2807	2277.9619
Ki	0.0705	0.0256

*Figure 45: Dixon plot for **30a.** All concentrations in uM.*



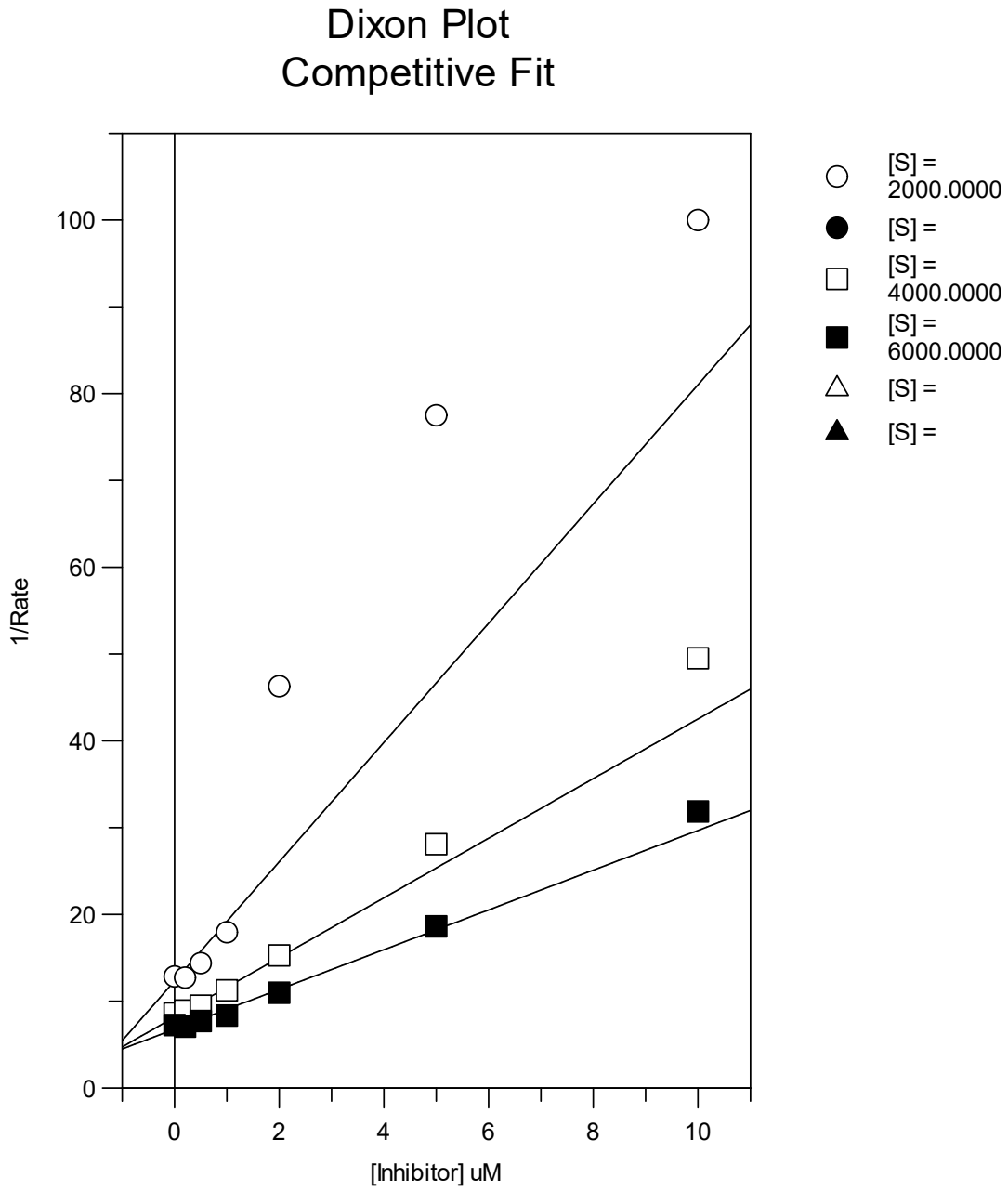
Parameter	Value	Std. Error
Vmax	0.2078	0.0551
Km	5977.6560	2782.7603
Ki	0.1981	0.0587

*Figure 46: Dixon plot for **30b**. All concentrations in uM.*



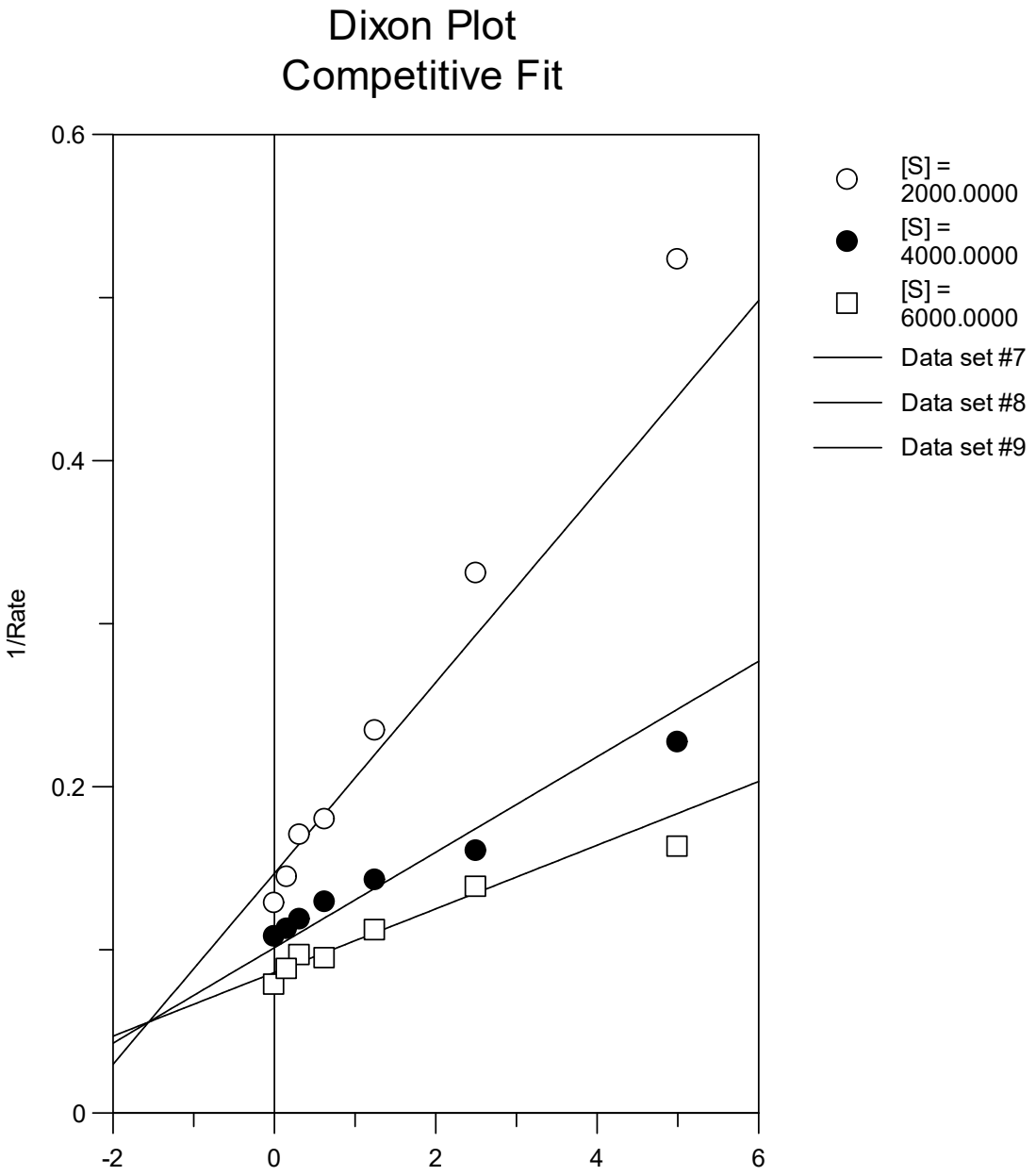
Parameter	Value	Std. Error
Vmax	0.1415	0.0073
Km	5496.1706	598.3113
Ki	0.3368	0.0230

*Figure 47: Dixon plot for **36a.** All concentrations in uM.*



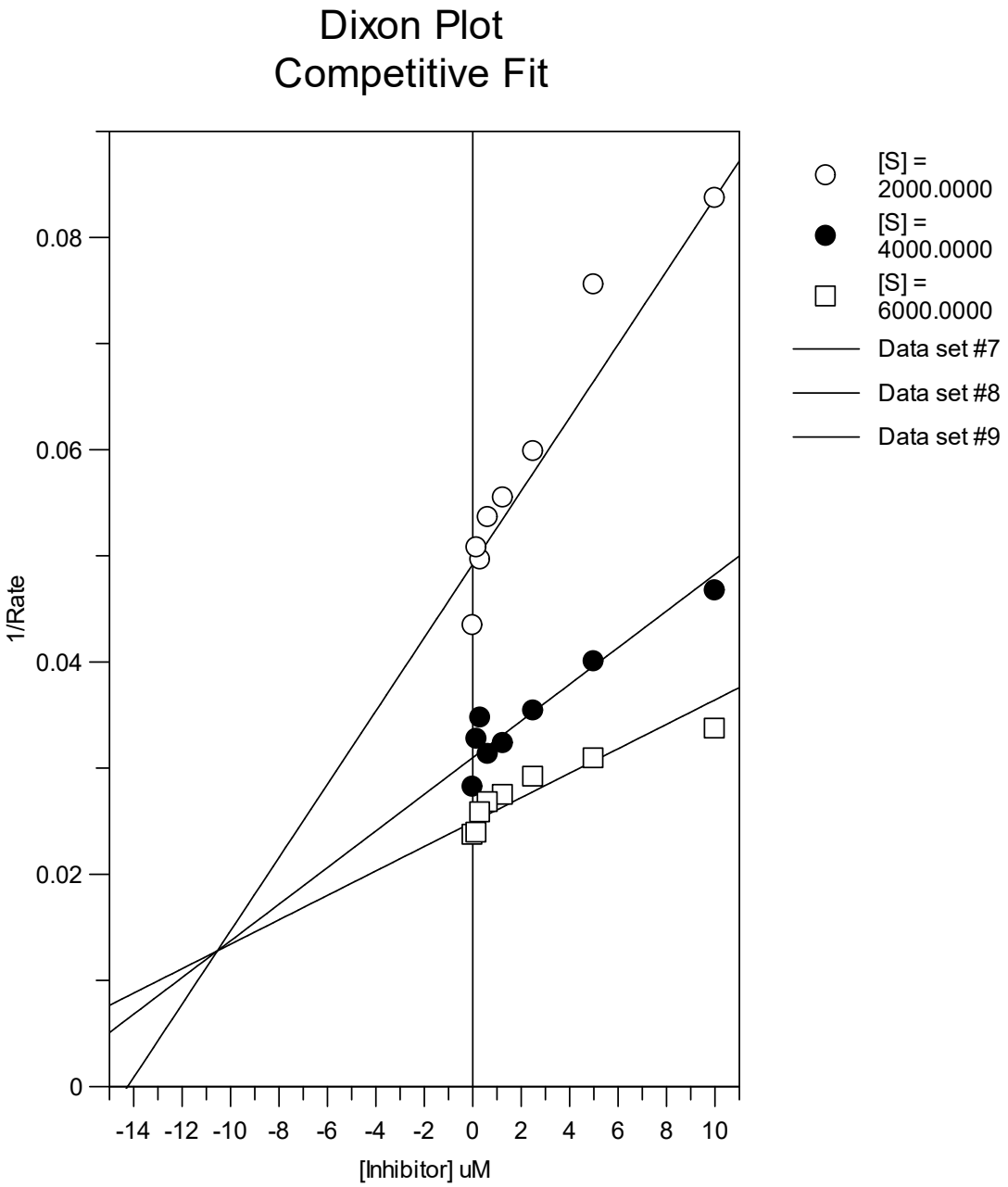
Parameter	Value	Std. Error
Vmax	0.2503	0.0266
Km	4166.1719	908.1948
Ki	1.2109	0.1806

*Figure 48: Dixon Plot for **36b**. All concentrations in uM.*



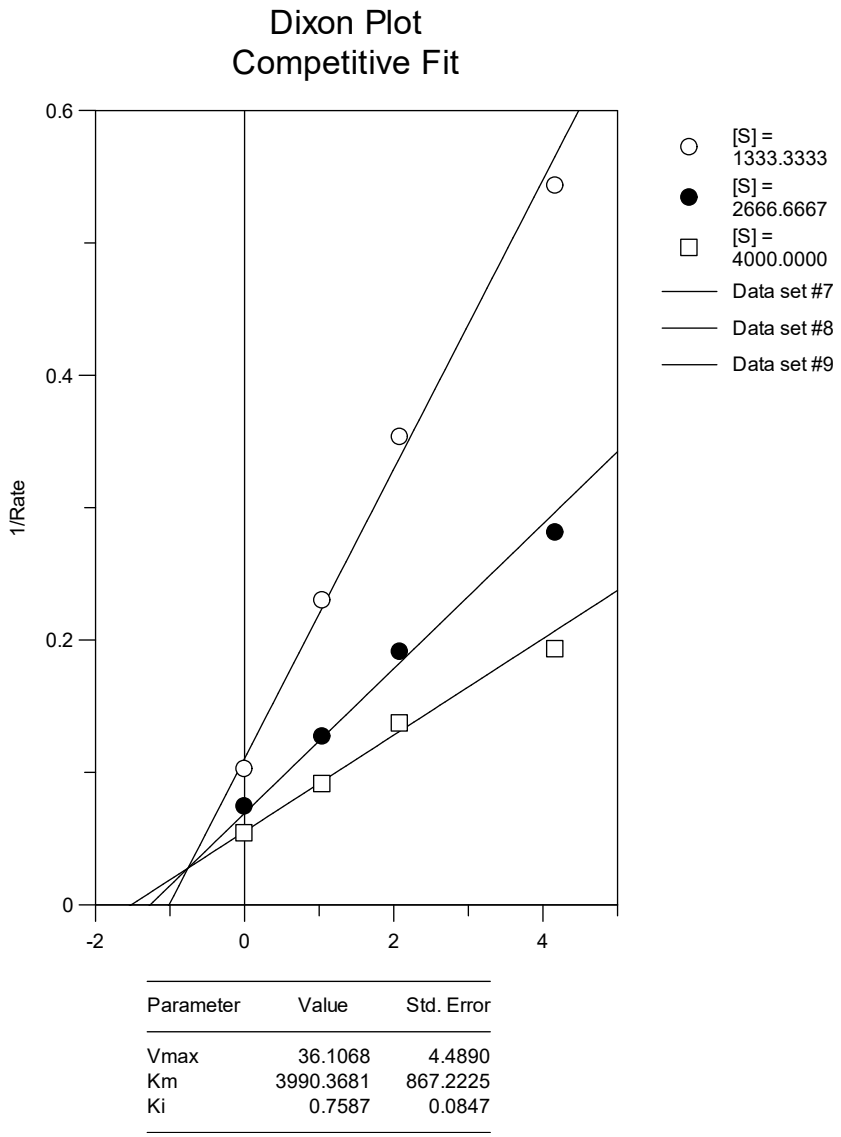
Parameter	Value	Std. Error
Vmax	17.9529	1.5178
Km	3274.0189	634.0382
Ki	1.5575	0.2458

*Figure 49: Dixon plot for **38a**. All concentrations in uM*



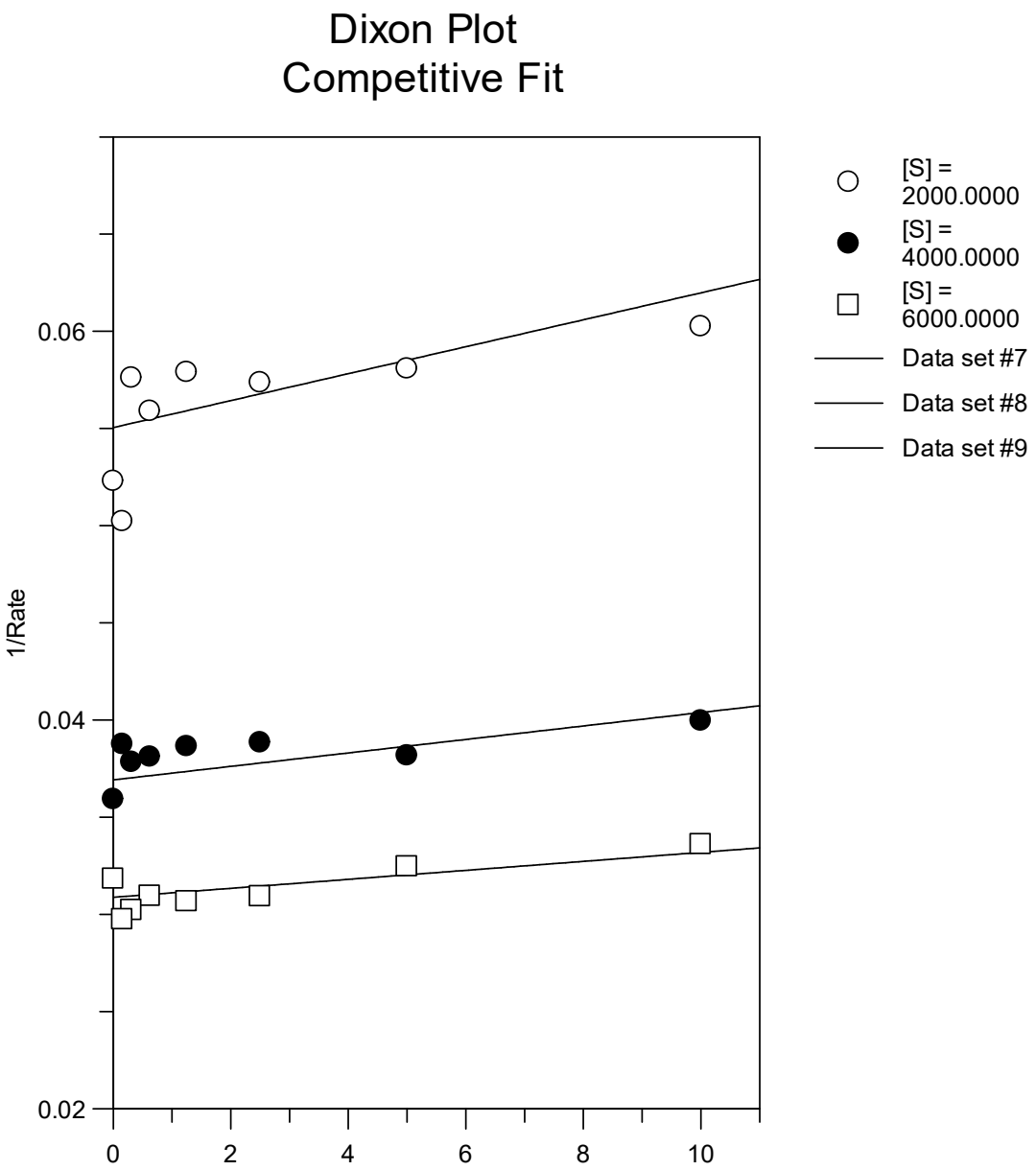
Parameter	Value	Std. Error
Vmax	78.2885	6.3829
Km	5703.8952	831.2312
Ki	10.5456	1.4661

*Figure 50: Dixon plot for **47a** All concentrations in uM.*



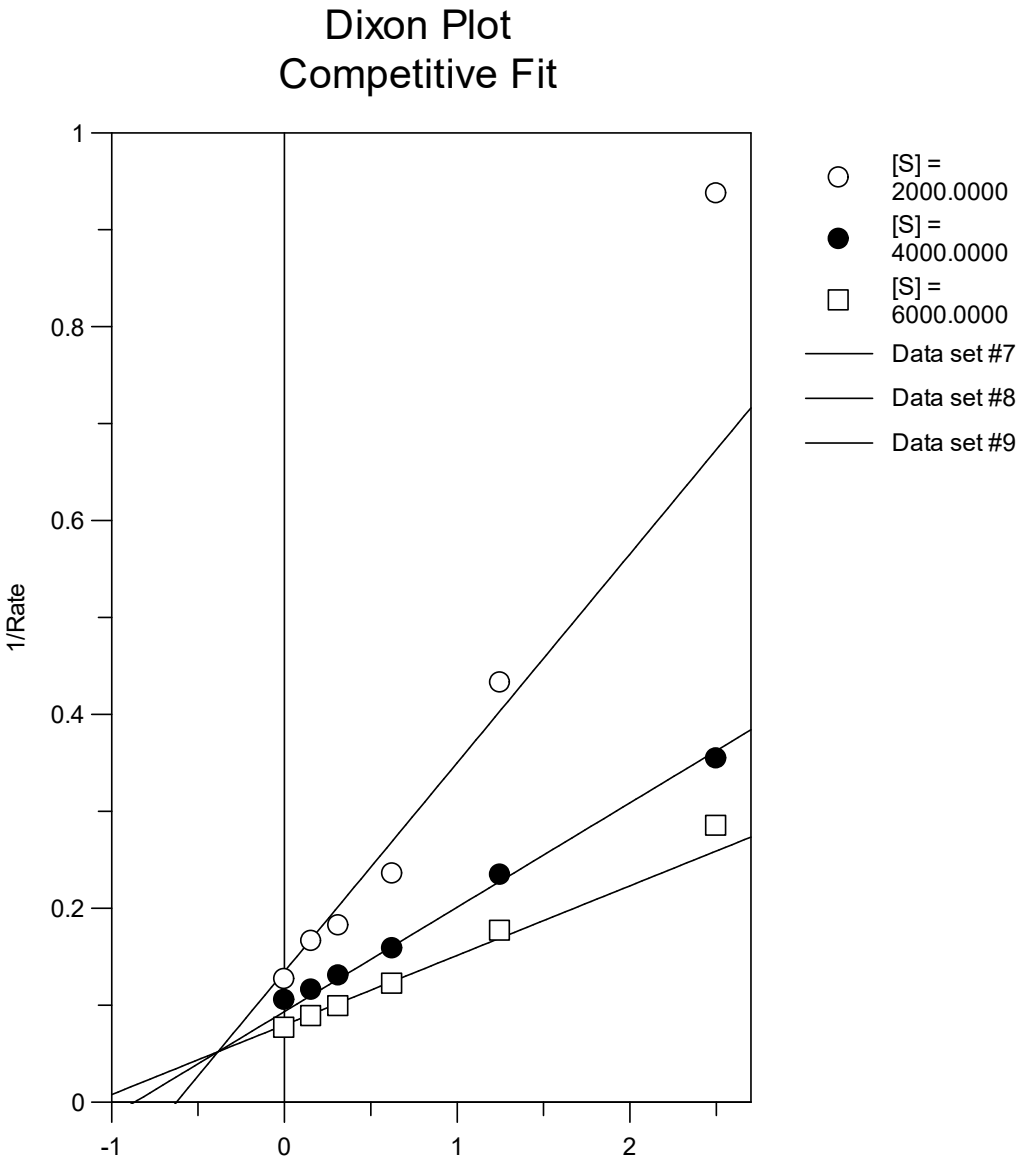
Parameter	Value	Std. Error
Vmax	36.1068	4.4890
Km	3990.3681	867.2225
Ki	0.7587	0.0847

*Figure 51: Dixon plot for **48a**. All concentrations in uM.*



Parameter	Value	Std. Error
Vmax	53.2159	1.7681
Km	3858.5909	271.3948
Ki	52.2972	12.2007

*Figure 52: Dixon plot for **49a**. All concentrations in uM.*



Parameter	Value	Std. Error
Vmax	19.2595	1.6741
Km	3185.4885	644.8151
Ki	0.3839	0.0554

*Figure 53: Dixon plot for **mini MbA**. All concentrations in uM.*

(1) Smith, R. M.; Weiner, D. P.; Chaturvedi, N. C.; Thimblin, M. D.; Raymond, S. J.; Hansen, D. E. *Bioorganic Chemistry* **1995**, *23*, 397.

(2) Tysoe, C. R.; Caner, S.; Calvert, M. B.; Win-Mason, A.; Brayer, G. D.; Withers, S. G. *Chem Sci* **2019**, *10*, 11073.

(3) Villaume, S. A.; Fu, J.; N'Go, I.; Liang, H.; Lou, H.; Kremer, L.; Pan, W.; Vincent, S. P. *Chemistry – A European Journal* **2017**, *23*, 10423.

(4) Ban, H.; Nagano, M.; Gavrilyuk, J.; Hakamata, W.; Inokuma, T.; Barbas, C. F. *Bioconjugate Chemistry* **2013**, *24*, 520.