

Supporting Information

Engineering an Antibiotic to Fight Cancer: Optimization of the Novobiocin Scaffold to Produce Anti-Proliferative Agents

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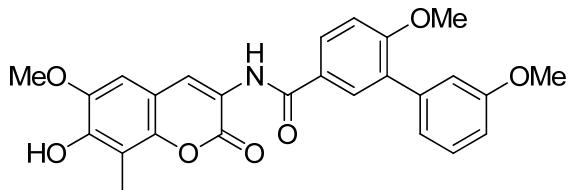
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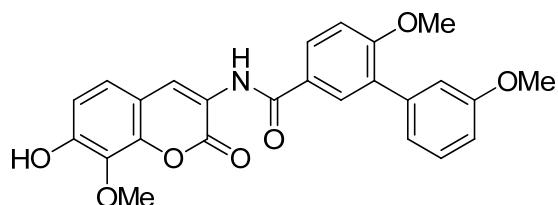
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^1H NMR of 83b	S356

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General. The purity of all compounds was determined to be >95% as determined by ¹H and ¹³C NMR spectra, unless otherwise noted. The most active 15 compounds were further verified for >95% purity based on HPLC analyses.

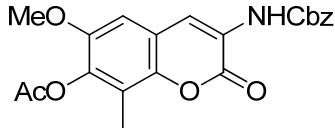


N-(7-hydroxy-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (6b**):** A solution of **10b** (174 mg, 0.35 mmol) in methanol (3.5 mL) at rt was treated with triethylamine (0.35 mL). After 12 h, the solvent was removed and the residue purified via column chromatography (SiO₂, 10:1, CH₂Cl₂:acetone) to afford **1b** as a yellow amorphous solid (158 g, 99%): ¹H NMR (CDCl₃, 500 MHz) δ 8.79 (s, 1H), 8.71 (s, 1H), 7.92 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.89 (d, *J* = 2.5 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.14–7.06 (m, 3H), 6.94–6.92 (m, 1H), 6.81 (s, 1H), 6.11 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 2.37 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 165.7, 159.9, 159.7, 159.5, 146.2, 144.5, 144.2, 138.8, 131.1, 130.1, 129.3, 128.3, 126.3, 124.7, 122.2, 122.0, 115.4, 113.3, 112.3, 111.9, 111.1, 104.5, 56.5, 56.0, 55.5, 8.3; IR (film) ν_{max} 3408, 2980, 2843, 2359, 2341, 1636, 1533, 1356, 1244, 1015, 918; HRMS (ESI⁺) *m/z*: [M + H⁺] calcd for C₂₆H₂₄NO₇, 462.1553; found, 462.1529.

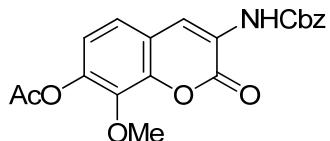


N-(7-hydroxy-8-methoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (6c**):** A solution of **12c** (63 mg, 0.13 mmol) in methanol (1.3 mL) at rt was treated

with triethylamine (0.13 mL). After 12 h, the solvent was removed and the residue purified via column chromatography (SiO_2 , 10:1, CH_2Cl_2 :acetone) to afford **6c** as a yellow amorphous solid (57 mg, 99%): ^1H NMR (CDCl_3 , 500 MHz) δ 8.82 (s, 1H), 8.66 (s, 1H), 7.92 (dd, J = 8.5, 2.5 Hz, 1H), 7.88 (d, J = 2.5 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.13–7.07 (m, 3H), 6.97–6.92 (m, 2H), 6.03 (bs, 1H), 4.13 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 165.7, 160.0, 159.5, 158.7, 150.4, 143.1, 138.7, 133.7, 131.2, 130.1, 129.4, 128.3, 126.1, 124.8, 123.3, 122.1, 121.7, 115.4, 114.1, 113.3, 113.1, 111.2, 62.1, 56.1, 55.5; IR (film) ν_{max} 3348, 3038, 2970, 2847, 2093, 1643, 1014, 795; HRMS (ESI $^+$) m/z : [M + H $^+$] calcd for $\text{C}_{25}\text{H}_{22}\text{NO}_7$, 448.1396; found, 448.1381.



3-((benzyloxy)carbonyl)amino-6-methoxy-8-methyl-2-oxo-2H-chromen-7-yl acetate (8b): A solution of **7b**¹ (195 mg, 0.55 mmol) in anhydrous pyridine (3.0 mL) was treated with acetic anhydride (1.0 mL). After 12 h, the solvent was removed and the residue purified via column chromatography (SiO_2 , 100:1, CH_2Cl_2 :acetone) to afford **8b** as a colorless amorphous solid (216 mg, 99%): ^1H NMR ($(\text{CD}_3)_2\text{CO}$, 400 MHz) δ 8.31 (s, 1H), 8.22 (bs, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.42–7.33 (m, 3H), 7.25 (s, 1H), 5.26 (s, 2H), 3.89 (s, 3H), 2.33 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 168.6, 158.5, 153.2, 148.8, 142.6, 139.7, 135.6, 128.8 (2C), 128.7, 128.4 (2C), 124.0, 121.3, 120.6, 117.6, 106.2, 67.7, 56.3, 20.5, 9.3; IR (film) ν_{max} 3306, 2924, 2853, 1759, 1703, 1531, 1393, 1205, 1088, 1026, 914, 764, 698; HRMS (ESI $^+$) m/z : [M + H $^+$] calcd for $\text{C}_{21}\text{H}_{20}\text{NO}_7$, 398.1240; found, 398.1258.



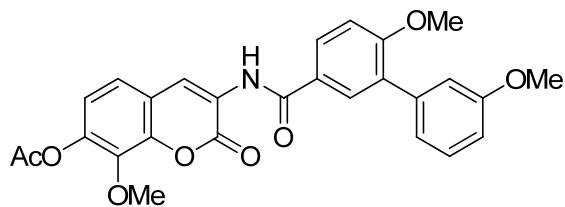
3-((benzyloxy)carbonyl)amino-8-methoxy-2-oxo-2H-chromen-7-yl acetate (8c): A solution of **7c**¹ (60 mg, 0.18 mmol) in anhydrous pyridine (2.25 mL) was treated with acetic anhydride (0.75 mL). After 12 h, the solvent was removed and the residue purified via column chromatography (SiO₂, 40:1, CH₂Cl₂:acetone) to afford **8c** as a colorless amorphous solid (67 mg, 99%): ¹H NMR (CDCl₃, 500 MHz) δ 8.29 (s, 1H), 7.59 (s, 1H), 7.42–7.34 (m, 5H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 5.23 (s, 2H), 4.01 (s, 3H), 2.36 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 168.9, 157.6, 153.2, 144.0, 143.5, 139.5, 135.5, 128.8 (2C), 128.7, 128.4 (2C), 123.8, 121.8, 121.2, 119.8, 119.2, 67.8, 61.8, 20.8; IR (film) ν_{max} 3409, 3352, 3312, 3088, 3038, 2945, 2837, 2359, 2332, 1765, 1710, 1533, 1383, 1366, 1238, 1202, 1045, 698; HRMS (ESI⁺) *m/z*: [M + Na⁺] calcd for C₂₀H₁₇NNaO₇, 406.0903; found, 406.0928.



3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-6-methoxy-8-methyl-2-oxo-2H-chromen-7-yl acetate (12b): Palladium on carbon (10%, 43 mg) was added to **8b** (216 mg, 0.54 mmol) in anhydrous THF (3.6 mL) and the solution was placed under an atmosphere of H₂. After 12 h, the solution was filtered through SiO₂ (40:1, CH₂Cl₂:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (142 mg, 99%).

A solution of 3',6-dimethoxy-[1,1'-biphenyl]-3-carbonyl chloride² (130 mg, 0.47 mmol), in anhydrous THF (2.7 mL), was added to a solution of the amine (123 mg, 0.47 mmol) and

anhydrous triethylamine (0.13 mL, 0.94 mmol) in anhydrous THF (2.7 mL). After 12 h, the solvent was removed and the residue purified via column chromatography (SiO₂, 40:1, CH₂Cl₂:acetone) to afford **12b** as a colorless amorphous solid (129 mg, 55%): ¹H NMR (CD₂Cl₂, 400 MHz) δ 8.84 (s, 1H), 8.80 (s, 1H), 7.97 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.92 (d, *J* = 2.5 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.16–7.11 (m, 3H), 7.01 (s, 1H), 6.97–6.95 (m, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 2.38 (s, 3H), 2.32 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 168.6, 165.8, 160.0, 159.5, 159.2, 148.9, 142.8, 140.0, 138.7, 131.2, 130.2, 129.3, 128.4, 126.0, 124.2, 123.3, 122.2, 120.6, 117.8, 115.4, 113.3, 111.2, 106.6, 56.4, 56.1, 55.5, 20.6, 9.3; IR (film) ν_{max} 3404, 2926, 2853, 1765, 1713, 1670, 1603, 1522, 1385, 1242, 1204, 1180, 1094, 1022, 571; HRMS (ESI⁺) *m/z*: [M + H⁺] calcd for C₂₈H₂₆NO₈, 504.1658; found, 504.1625.

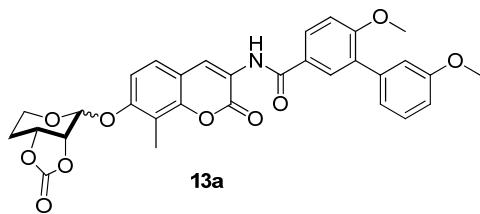


3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methoxy-2-oxo-2H-chromen-7-yl acetate (12c): Palladium on carbon (10%, 5 mg) was added to **8c** (25 mg, 0.065 mmol) in anhydrous THF (0.44 mL) and the solution was placed under an atmosphere of H₂. After 12 h, the solution was filtered through SiO₂ (40:1, CH₂Cl₂:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (16 mg, 99%).

A solution of 3',6-dimethoxy-[1,1'-biphenyl]-3-carbonyl chloride² (18 mg, 0.064 mmol), in anhydrous THF (0.37 mL), was added to a solution of the amine (16 mg, 0.064 mmol) and anhydrous triethylamine (18 μL, 0.13 mmol), dissolved in anhydrous THF (0.37 mL). After 12 h, the solvent was removed and the residue purified via column chromatography (SiO₂, 40:1, CH₂Cl₂:acetone) to afford **12c** as a colorless amorphous solid (16 mg, 50%): ¹H NMR (CDCl₃,

500 MHz) δ 8.83 (s, 1H), 8.75 (s, 1H), 7.92 (dd, J = 8.5, 2.5 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.13–7.02 (m, 4H), 6.94–6.92 (m, 1H), 4.04 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 169.0, 165.8, 160.1, 159.5, 158.3, 144.3, 143.7, 139.6, 138.6, 131.3, 130.2, 129.4, 128.4, 125.9, 124.0, 123.2, 122.3, 122.1, 120.0, 119.4, 115.4, 113.3, 111.2, 61.8, 56.0, 55.5, 20.9; IR (film) ν_{max} 3398, 3097, 2993, 2926, 2853, 2357, 2339, 1765, 1666, 1599, 1520, 1456, 1362, 1244, 1202, 1078, 1022, 905, 802, 734; HRMS (ESI $^+$) m/z : [M + 2H $^+$] calcd for $\text{C}_{27}\text{H}_{25}\text{NO}_8$, 491.1580; found, 491.1537.

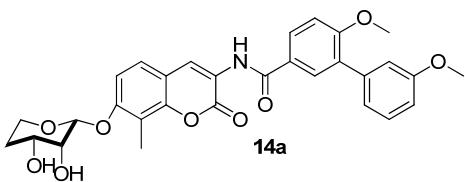
Representative procedure for Mitsunobu coupling with sugars:



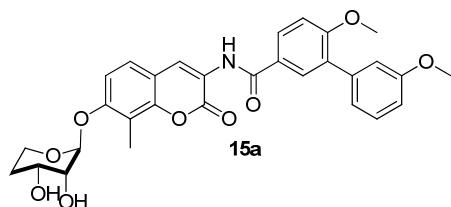
3',6-dimethoxy-N-(8-methyl-2-oxo-7-((3aR,7aR)-2-oxotetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yloxy)-2H-chromen-3-yl)biphenyl-3-carboxamide (13a):

Diisopropylazodicarboxylate (90 μL , 0.46 mmol) was added slowly to a solution of phenol **6** (100 mg, 0.23 mmol), sugar **F** (48 mg, 0.28 mmol) and triphenylphosphine (122 mg, 0.46 mmol) in THF (3 mL) at rt. The resulting reaction mixture was stirred at rt for 2 h, quenched with water and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with saturated sodium chloride solution, 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 compound **13a** (117 mg, 88%) as a mixture of diastereomers.

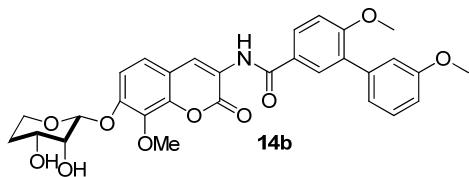
Representative procedure for cyclic carbonate hydrolysis:



N-(7-((2R,3R,4R)-3,4-dihydroxytetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (14a): A solution of **13a** (117 mg, 0.20 mmol) in THF:H₂O:MeOH (3:1:1, 2 mL) was treated with LiOH (26 mg, 0.61 mmol). The resulting reaction mixture was stirred at rt for 2 h, cooled to 0°C, then acidified to pH ~4 with 5% aqueous HCl. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with saturated sodium chloride solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified via column chromatography (SiO₂, 100:5, CH₂Cl₂:MeOH) to yield diastereomers **14a** and **15a**. Compound **14a** (59 mg, 53%) was obtained as a colorless amorphous solid. ¹H NMR (500 MHz, CDCl₃) δ 8.81 (s, 1H), 8.72 (bs, 1H), 7.92 (dd, *J* = 2.3, 8.6 Hz, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 2.4 Hz, 1H), 7.07 (d, *J* = 8.9 Hz, 1H), 6.94 (dd, *J* = 1.9, 7.6 Hz, 1H), 5.48 (d, *J* = 3.1 Hz, 1H), 4.14 (m, 1H), 4.03 (dt, *J* = 3.3, 11.7 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.62 (dt, *J* = 3.7, 12.0 Hz, 1H), 2.77 (d, *J* = 9.3 Hz, 1H), 2.68 (d, *J* = 9.4 Hz, 1H), 2.40 (s, 3H), 2.02 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 165.5, 160.0, 159.4, 156.1, 149.0, 138.5, 131.1, 130.0, 129.2, 128.2, 126.0, 125.9, 123.8, 122.4, 122.0, 115.2, 113.2, 112.3, 111.0, 99.4, 77.2, 68.4, 67.8, 55.9, 55.6, 55.3, 31.0, 8.7; IR (film) ν_{max} 3303, 3288, 2921, 2851, 1705, 1672, 1604, 1526, 1504, 1485, 1367, 1240, 1132, 1074, 1051, 1024, 999 cm⁻¹; HRMS (FAB) *m/z*: [M + Na⁺] calcd for C₃₀H₂₉NNaO₉, 570.1740; found, 570.1744.

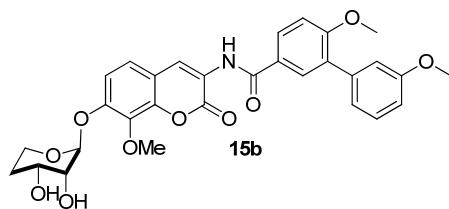


N-(7-((2S,3R,4R)-3,4-dihydroxytetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (15a): Compound **15a** (40 mg, 35%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.77 (s, 1H), 8.70 (s, 1H), 7.91 (dd, $J = 2.4, 8.5$ Hz, 1H), 7.89 (d, $J = 2.3$ Hz, 1H), 7.36 (t, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 8.6$ Hz, 1H), 7.12 (dt, $J = 1.5, 7.6$ Hz, 1H), 7.09 (m, 2H), 7.06 (d, $J = 8.6$ Hz, 1H), 6.93 (ddd, $J = 0.6, 2.5, 8.3$ Hz, 1H), 5.52 (d, $J = 4.0$ Hz, 1H), 4.26 (m, 1H), 3.95 (t, $J = 3.7$ Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.84 (m, 1H), 3.79 (m, 1H), 2.79 (bs, 1H), 2.53 (bs, 1H), 2.33 (s, 3H), 1.97 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 159.9, 159.5, 159.4, 155.8, 149.1, 138.7, 131.1, 130.1, 129.3, 128.3, 126.0, 125.9, 124.2, 122.2, 122.1, 115.4, 115.0, 114.7, 113.2, 112.4, 111.8, 111.1, 98.8, 77.4, 70.0, 66.3, 60.0, 56.0, 55.4, 29.8, 8.5; IR (film) ν_{max} 3400, 3387, 2954, 2924, 2851, 1713, 1668, 1605, 1526, 1504, 1481, 1367, 1265, 1242, 1205, 1078, 1051, 1033, 1002, 999 cm^{-1} ; HRMS (FAB) m/z : [M + Na⁺] calcd for C₃₀H₂₉NNaO₉, calcd 570.1740; found, 570.1733.

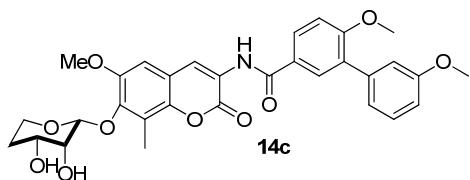


N-(7-((2R,3R,4R)-3,4-dihydroxytetrahydro-2H-pyran-2-yloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (14b): Compound **14b** (36 mg, 38%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.81 (s, 1H), 8.72 (s, 1H), 7.91 (dd, $J = 2.4, 8.6$ Hz, 1H), 7.88 (d, $J = 2.4$ Hz, 1H), 7.37 (t, $J = 7.6$ Hz, 1H), 7.23 (d, $J = 8.8$ Hz, 1H), 7.27 (d, $J = 8.9$ Hz, 1H), 7.12 (dt, $J = 1.2, 7.9$ Hz, 1H), 7.09 (m, 1H), 7.07 (d, $J =$

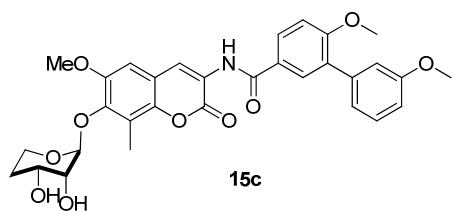
8.6 Hz, 1H), 6.93 (dd, J = 1.0, 2.9, 7.9 Hz, 1H), 5.40 (d, J = 4.8 Hz, 1H), 4.29 (m, 1H), 4.02 (s, 3H), 3.93 (m, 1H), 3.90 (s, 3H), 3.88 (m, 1H), 3.86 (s, 3H), 2.82 (bs, 1H), 2.38 (bs, 1H), 1.95 (m, 1H), 1.88 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 160.0, 159.4, 158.8, 150.9, 144.0, 138.6, 137.6, 131.1, 130.1, 129.3, 128.3, 125.9, 123.7, 122.8, 122.7, 122.1, 116.4, 115.4, 114.1, 113.3, 111.2, 100.5, 66.4, 62.1, 60.5, 56.0, 55.5, 29.8; IR (film) ν_{max} 3411, 3301, 2989, 2985, 1716, 1668, 1605, 1524, 1502, 1483, 1462, 1436, 1365, 1274, 1247, 1182, 1118, 1070, 997 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{30}\text{H}_{29}\text{NNaO}_{10}$, calcd 586.1689; found, 586.1683.



N-(7-((2S,3R,4R)-3,4-dihydroxytetrahydro-2H-pyran-2-yloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (15b): Compound **15b** (21 mg, 22%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.78 (s, 1H), 8.70 (s, 1H), 7.87 (m, 2H), 7.35 (t, J = 7.7 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.00–7.15 (m, 4H), 6.92 (d, J = 7.9 Hz, 1H), 5.56 (s, 1H), 4.17 (m, 1H), 4.04 (s, 3H), 4.01 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.57 (d, J = 10.5 Hz, 1H), 3.42 (m, 1H), 1.99 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 160.0, 159.4, 158.5, 150.3, 143.8, 138.6, 137.3, 131.1, 130.1, 129.3, 128.3, 125.8, 123.6, 122.8, 122.1, 116.2, 115.3, 114.0, 113.2, 111.1, 99.6, 68.4, 67.7, 62.2, 56.0, 55.5, 55.4, 31.3; IR (film) ν_{max} 3400, 3386, 2935, 2896, 2839, 1707, 1670, 1605, 1521, 1500, 1367, 1274, 1245, 1120, 1081, 1054, 952 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{30}\text{H}_{29}\text{NNaO}_{10}$, calcd 586.1689; found, 586.1689.

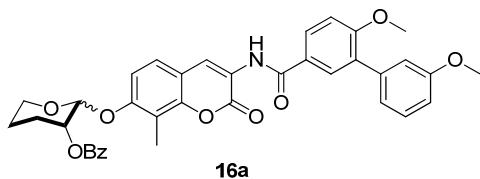


N-(7-((2R,3R,4R)-3,4-dihydroxytetrahydro-2H-pyran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (14c): Compound **14c** (37 mg, 44%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.81 (s, 1H), 8.80 (s, 1H), 7.93 (dd, $J = 2.4, 8.6$ Hz, 1H), 7.90 (d, $J = 2.4$ Hz, 1H), 7.38 (t, $J = 8.0$ Hz, 1H), 7.13 (dt, $J = 1.5, 7.6$ Hz, 1H), 7.10 (t, $J = 2.5$ Hz, 1H), 7.08 (d, $J = 8.8$ Hz, 1H), 6.94 (ddd, $J = 0.9, 2.7, 8.0$ Hz, 1H), 6.89 (s, 1H), 5.03 (d, $J = 6.9$ Hz, 1H), 4.28 (m, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.75–3.90 (m, 3H), 3.60 (bs, 1H), 2.64 (bs, 1H), 2.47 (s, 3H), 1.90 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.6, 159.9, 159.3, 159.2, 149.1, 146.0, 143.3, 138.5, 131.1, 130.0, 129.2, 128.2, 125.9, 123.6, 123.3, 122.1, 122.0, 116.3, 115.3, 113.1, 111.0, 106.3, 104.1, 71.8, 66.7, 61.1, 56.2, 55.9, 55.4, 30.1, 9.9; IR (film) ν_{max} 3401, 3363, 3001, 2952, 1701, 1670, 1605, 1589, 1501, 1423, 1367, 1230, 1191, 1110, 1053, 997 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{31}\text{H}_{31}\text{NNaO}_{10}$, calcd 600.1841; found, 600.1846.



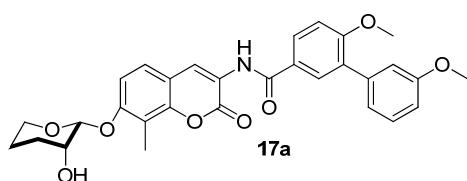
N-(7-((2S,3R,4R)-3,4-dihydroxytetrahydro-2H-pyran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (15c): Compound **15c** (24 mg, 29%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.75 (s, 1H), 8.73 (s, 1H), 7.86–7.90 (m, 2H), 7.35 (t, $J = 7.8$ Hz, 1H), 7.11 (dt, $J = 1.5, 8.0$ Hz, 1H), 7.08 (t, $J = 2.4$ Hz, 1H), 7.03 (d, $J = 9.6$ Hz, 1H), 6.92 (ddd, $J = 1.2, 8.7$ Hz, 1H), 6.81 (s, 1H), 5.20

(d, $J = 3.3$ Hz, 1H), 4.35 (td, $J = 3.1, 11.5$ Hz, 1H), 4.09 (s, 1H), 3.93 (d, $J = 6.5$ Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.55 (dt, $J = 4.4, 11.5$ Hz, 1H), 3.19 (d, $J = 5.2$ Hz, 1H), 2.44 (s, 3H), 1.94 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.6, 159.9, 159.4, 159.1, 149.2, 146.1, 143.3, 138.6, 132.2, 132.1, 130.1, 129.2, 128.6, 128.3, 125.9, 123.6, 123.1, 116.2, 115.4, 113.1, 111.0, 106.3, 103.6, 69.2, 67.3, 56.8, 56.2, 55.9, 55.4, 30.6, 9.9; IR (film) ν_{max} 3400, 3377, 2952, 2867, 1711, 1670, 1605, 1587, 1500, 1427, 1369, 1227, 1138, 1120, 1054, 997 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{31}\text{H}_{31}\text{NNaO}_{10}$, calcd 600.1844; found, 600.1846.



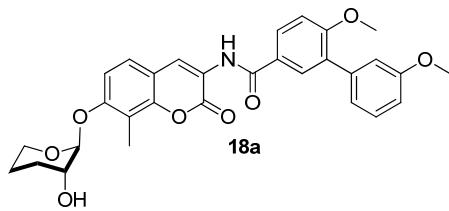
(R)-2-(3'-(3',6-dimethoxybiphenyl-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yloxy)tetrahydro-2H-pyran-3-yl benzoate (16a): Compound **16a** was obtained as a colorless amorphous solid and carried on without further purification.

Sodium metal (20 mg, 0.86 mmol) was added to a solution of **16a** (110 mg, 0.17 mmol) in MeOH (5 mL) at 0 °C. The resulting reaction mixture was stirred for 5 min at 0 °C, then quenched with water and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated sodium chloride solution, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via column chromatography (SiO_2 , 100:1, $\text{CH}_2\text{Cl}_2:\text{MeOH}$) to afford **17a** and **18a** (62 mg, 64%) as a mixture diastereomers.



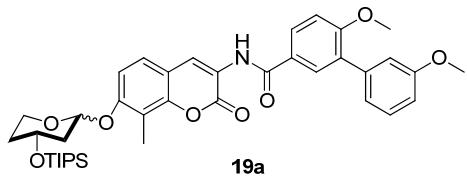
N-(7-((2R,3R)-3-hydroxytetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (17a): Compound **17a** (35 mg, 36%) was obtained

as an amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.81 (s, 1H), 8.72 (bs, 1H), 7.92 (dd, $J = 2.4, 8.6$ Hz, 1H), 7.89 (d, $J = 2.4$ Hz, 1H), 7.37 (t, $J = 8.1$ Hz, 1H), 7.36 (d, $J = 8.8$ Hz, 1H), 7.17 (d, $J = 8.8$ Hz, 1H), 7.13 (dt, $J = 1.2, 7.8$ Hz, 1H), 7.09 (m, 1H), 7.07 (d, $J = 8.4$ Hz, 1H), 6.94 (ddd, $J = 0.9, 2.6, 8.3$ Hz, 1H), 5.55 (d, $J = 3.2$ Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.70 (m, 1H), 3.61 (m, 1H), 2.41 (s, 3H), 2.06 (m, 1H), 1.91 (m, 2H), 1.80 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 159.9, 159.5, 159.4, 156.0, 149.2, 138.7, 131.2, 130.1, 129.3, 128.3, 126.2, 126.0, 124.2, 122.3, 122.1, 115.4, 115.1, 114.7, 113.3, 112.2, 111.1, 97.6, 68.4, 60.5, 56.0, 55.5, 27.9, 24.2, 8.6; IR (film) ν_{max} 3402, 2935, 2879, 2851, 1705, 1670, 1605, 1527, 1500, 1367, 1242, 1207, 1180, 1126, 1068, 987, 970 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{30}\text{H}_{29}\text{NNaO}_8$, calcd 554.1791; found, 554.1788.



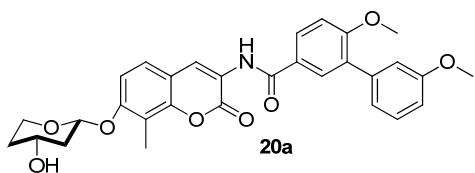
N-(7-((2S,3R)-3-hydroxytetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (18a): Compound **18a** (27 mg, 28%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.81 (s, 1H), 8.71 (bs, 1H), 7.92 (dd, $J = 2.4, 8.6$ Hz, 1H), 7.89 (d, $J = 2.3$ Hz, 1H), 7.37 (t, $J = 7.9$ Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.08–7.14 (m, 3H), 7.07 (d, $J = 8.8$ Hz, 1H), 6.93 (ddd, $J = 0.7, 2.6, 8.3$ Hz, 1H), 5.16 (d, $J = 4.6$ Hz, 1H), 3.92 (m, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.62 (m, 1H), 2.38 (s, 3H), 2.23 (m, 2H), 1.90 (m, 1H), 1.74 (m, 1H), 1.63 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 159.9, 159.5, 159.4, 156.1, 149.2, 138.7, 131.2, 130.1, 129.3, 128.3, 126.2, 124.2, 122.3, 122.1, 115.4, 115.2, 114.7, 113.3, 112.1, 111.1, 100.4, 67.8, 63.4, 56.0, 55.5, 27.5, 22.1, 21.9, 8.6; IR (film) ν_{max}

3404, 2923, 2845, 1711, 1670, 1606, 1526, 1502, 1369, 1242, 1205, 1178, 1115, 1057, 995, 974 cm⁻¹; HRMS (FAB) *m/z*: [M + Na⁺] calcd for C₃₀H₂₉NNaO₈, calcd 554.1791; found, 554.1803.



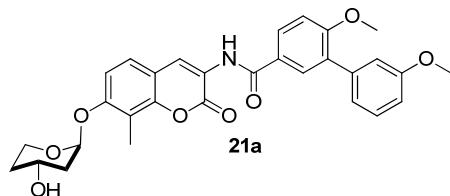
(R)-3',6-dimethoxy-N-(8-methyl-2-oxo-7-(4-(triisopropylsilyloxy)tetrahydro-2H-pyran-2-yloxy)-2H-chromen-3-yl)biphenyl-3-carboxamide (19a): Compound **19a** (158 mg, 78%) was obtained as a colorless amorphous solid and used without further purification.

Tetrabutylammonium fluoride (0.5 mL, 0.50 mmol) was added dropwise to a solution of **19a** (158 mg, 0.23 mmol) in THF (4 mL) at rt. The resulting reaction mixture was stirred at rt for 1 h, then quenched with water and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated sodium chloride solution, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified via column chromatography (SiO₂, 100:1, CH₂Cl₂:MeOH) to afford **20a** and **21a** (120 mg, 72%) as a mixture of diastereomers.

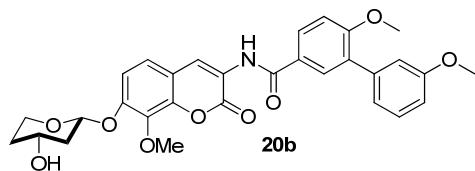


N-(7-((2R,4R)-4-hydroxytetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (20a): Compound **20a** (68 mg, 41%) was obtained as a colorless amorphous solid. ¹H NMR (500 MHz, CDCl₃) δ 8.81 (s, 1H), 8.71 (s, 1H), 7.92 (dd, *J* = 2.4, 8.6 Hz, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 7.12 (m, 1H), 7.09 (m, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.93 (ddd, *J* = 0.8, 2.6, 8.27 Hz, 1H), 5.77 (t, *J* = 2.8 Hz, 1H), 4.37 (m, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.81 (d, *J* = 2.5 Hz, 1H), 3.80 (t, *J* = 2.1 Hz, 1H), 2.35 (s, 3H), 2.33 (m, 1H), 2.01 (m, 1H), 1.80 (m,

1H), 1.70 (m, 1H), 1.64 (bs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 159.9, 159.6, 159.5, 156.1, 149.2, 138.7, 131.2, 130.1, 129.3, 128.3, 126.2, 125.8, 124.4, 122.1, 122.0, 115.4, 114.8, 114.3, 113.3, 111.7, 111.1, 96.8, 63.9, 59.8, 56.0, 55.5, 39.5, 34.9, 8.5; IR (film) ν_{max} 3477, 2967, 2923, 1713, 1668, 1606, 1525, 1502, 1369, 1242, 1205, 1178, 1114, 1057, 974 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{30}\text{H}_{29}\text{NNaO}_8$, calcd 554.1791; found, 554.1794.

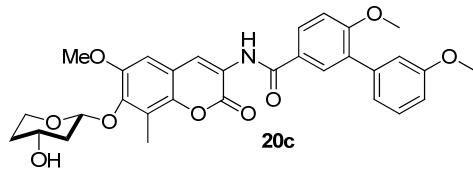


N-(7-((2S,4R)-4-hydroxytetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (21a): Compound **21a** (52 mg, 31%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.81 (s, 1H), 8.71 (s, 1H), 7.92 (dd, $J = 2.4, 8.6$ Hz, 1H), 7.89 (d, $J = 2.4$ Hz, 1H), 7.36 (t, $J = 7.9$ Hz, 1H), 7.35 (d, $J = 8.6$ Hz, 1H), 7.14 (d, $J = 8.7$ Hz, 1H), 7.12 (m, 1H), 7.09 (m, 1H), 7.07 (d, $J = 8.5$ Hz, 1H), 6.93 (ddd, $J = 0.8, 2.5, 8.5$ Hz, 1H), 5.55 (t, $J = 3.4$ Hz, 1H), 4.15 (m, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.64 (dt, $J = 4.4, 12.1$ Hz, 1H), 2.86 (d, $J = 6.4$ Hz, 1H), 2.37 (s, 3H), 2.23 (dt, $J = 3.6, 14.1$ Hz, 1H), 2.10 (m, 1H), 1.99 (m, 1H), 1.77 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 159.9, 159.5, 159.4, 156.2, 149.1, 138.7, 131.2, 130.1, 129.3, 128.3, 126.1, 125.9, 124.1, 122.3, 122.1, 115.4, 114.9, 114.7, 113.3, 112.0, 111.1, 97.6, 64.1, 57.3, 56.0, 55.5, 37.2, 32.7, 8.7; IR (film) ν_{max} 3443, 2964, 2923, 1712, 1667, 1606, 1525, 1502, 1370, 1247, 1205, 1178, 1114, 1057, 974 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{30}\text{H}_{29}\text{NNaO}_8$, calcd 554.1791; found, 554.1800.



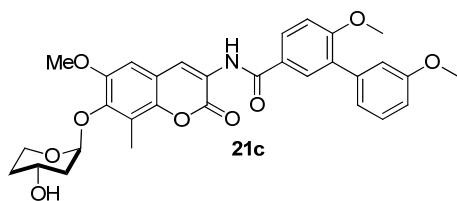
N-(7-((2R,4R)-4-hydroxytetrahydro-2H-pyran-2-yloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (20b):

Compound **20b** (36 mg, 66%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.68 (s, 1H), 8.59 (s, 1H), 7.78 (dd, $J = 2.4, 8.6$ Hz, 1H), 7.75 (d, $J = 2.4$ Hz, 1H), 7.23 (t, $J = 7.9$ Hz, 1H), 7.10 (d, $J = 8.8$ Hz, 1H), 6.97 (m, 3H), 6.80 (dd, $J = 2.2, 7.9$ Hz, 1H), 5.58 (t, $J = 3.0$ Hz, 1H), 4.04 (bs, 1H), 3.98 (dt, $J = 3.0, 11.9$ Hz, 2H), 3.91 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 3.47 (dd, $J = 3.1, 11.9$ Hz, 1H), 2.04 (m, 1H), 1.86 (s, 1H), 1.67 (m, 2H). ^1H NMR (125 MHz, CDCl_3) δ 165.7, 160.0, 159.5, 158.8, 150.1, 144.1, 138.7, 137.3, 131.2, 130.1, 129.3, 128.3, 126.0, 123.8, 122.8, 122.7, 122.1, 116.0, 115.4, 114.0, 138.8, 113.3, 111.2, 97.5, 63.5, 62.0, 56.6, 56.0, 55.5, 36.2, 32.4; IR (film) ν_{max} 3403, 2937, 2848, 1708, 1670, 1606, 1527, 1502, 1367, 1242, 1205, 1113, 1109, 1057, 996, 974 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{30}\text{H}_{29}\text{NNaO}_9$, calcd 570.1740; found, 570.1733.

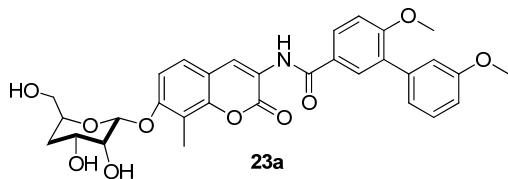
**N-(7-((2R,4R)-4-hydroxytetrahydro-2H-pyran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (20c):**

Compound **20c** (36 mg, 38%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.79 (s, 1H), 8.76 (s, 1H), 7.92 (dd, $J = 2.5, 8.6$ Hz, 1H), 7.89 (d, $J = 2.4$ Hz, 1H), 7.37 (t, $J = 8.2$ Hz, 1H), 7.12 (dt, $J = 1.5, 7.61$ Hz, 1H), 7.09 (t, $J = 2.5$ Hz, 1H), 7.07 (d, $J = 8.5$ Hz, 1H), 6.93 (ddd, $J = 1.5, 2.5, 8.5$ Hz, 1H), 6.86 (s, 1H), 5.33 (t, $J = 3.5$ Hz, 1H), 4.40 (m, 1H), 4.11 (m, 1H), 3.90 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.56 (dt, $J = 4.8, 11.9$ Hz, 1H), 2.99 (bs, 1H), 2.45 (s, 3H), 2.12–2.25 (m, 2H), 1.93 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 160.0, 159.5, 159.4, 150.1, 146.2, 143.4, 138.7, 131.2, 130.2, 129.4, 128.4, 126.1, 123.7, 123.5, 122.2, 121.0, 116.1, 115.4,

113.3, 111.2, 106.6, 101.9, 64.4, 58.3, 56.3, 56.1, 55.6, 37.5, 33.0, 10.1; IR (film) ν_{max} 3398, 2999, 2935, 2833, 1701, 1670, 1602, 1527, 1500, 1483, 1400, 1358, 1275, 1242, 1207, 1180, 1078, 1053, 1022, 916 cm^{-1} ; HRMS (FAB) m/z : [M + Na⁺] calcd for C₃₁H₃₁NNaO₉, calcd 584.1897; found, 584.1899.



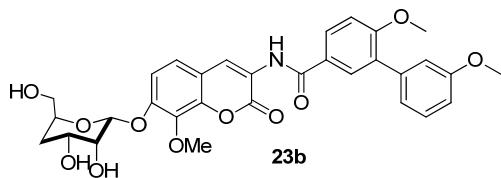
N-(7-((2S,4R)-4-hydroxytetrahydro-2H-pyran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (21c): Compound **21c** (29 mg, 29%) was obtained as a colorless amorphous solid. ¹H NMR (500 MHz, CDCl₃) δ 8.79 (s, 1H), 8.75 (s, 1H), 7.92 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.12 (dt, *J* = 1.5, 7.8 Hz, 1H), 7.09 (t, *J* = 2.7 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.93 (ddd, *J* = 1.2, 2.6, 8.6 Hz, 1H), 6.85 (s, 1H), 5.64 (t, *J* = 2.9 Hz, 1H), 4.35 (m, 1H), 4.13 (dt, *J* = 2.7, 11.1 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.82 (dt, *J* = 3.6, 11.1 Hz, 1H), 2.46 (m, 1H), 2.42 (s, 3H), 2.02 (m, 1H), 1.77 (td, *J* = 3.5, 10.3 Hz, 1H), 1.67 (m, 1H), 1.59 (d, *J* = 4.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 165.7, 160.0, 159.5, 159.5, 150.1, 146.5, 143.5, 138.7, 131.2, 130.1, 129.3, 128.3, 126.1, 123.8, 123.2, 122.1, 120.5, 115.7, 115.4, 113.3, 111.1, 106.7, 101.4, 63.9, 60.7, 56.2, 56.0, 55.5, 39.7, 34.9, 9.8; IR (film) ν_{max} 3401, 2992, 2847, 1709, 1670, 1605, 1527, 1501, 1367, 1242, 1205, 1182, 1113, 1057, 997, 974 cm^{-1} ; HRMS (FAB) m/z : [M + Na⁺] calcd for C₃₁H₃₁NNaO₉, calcd 584.1897; found, 584.1903.



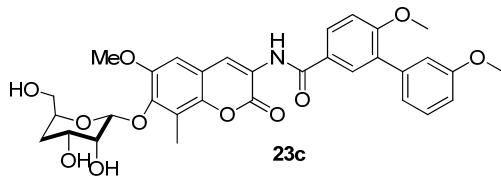
N-(7-((2R,3R,4R,6S)-3,4-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (23a): Compound **22** (237 mg, 82%) was obtained as a colorless amorphous solid and used without further purification.

Pyridinium *p*-toluenesulfonate (16 mg, 0.16 mmol) was added to a solution of **22** (230 mg, 0.33 mmol) in methanol (4 mL) at rt. The reaction mixture was stirred at rt for 48 h, quenched with saturated sodium bicarbonate, then solvent was removed. The residue was diluted with water and extracted with ethyl acetate (3 x 5 mL), and then the combined organic layers were washed with saturated sodium chloride solution, dried over anhydrous Na₂SO₄ and concentrated. The crude residue) was carried on to deprotection without further purification.

Palladium on carbon (10%, 30 mg) was added to the crude intermediate in ethanol (5 mL) and the solution was placed under an atmosphere of H₂. After 48 h, the solution was purified via column chromatography (SiO₂, 100:8, CH₂Cl₂:MeOH) to yield triol **23a** as a colorless amorphous solid (112 mg, 60%). ¹H NMR (500 MHz, CDCl₃) δ 8.72 (s, 1H), 8.67 (s, 1H), 7.91 (d, *J* = 2.4 Hz, 1H), 7.89 (m, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.07–7.14 (m, 3H), 7.04 (d, *J* = 8.8 Hz, 1H), 6.92 (ddd, *J* = 0.9, 2.7, 8.2 Hz, 1H), 5.57 (d, *J* = 3.6 Hz, 1H), 4.16 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.84 (m, 1H), 3.75 (m, 1H), 3.67 (d, *J* = 10.9 Hz, 1H), 3.55 (m, 1H), 3.26 (d, *J* = 8.7 Hz, 1H), 2.99 (d, *J* = 7.5 Hz, 1H), 2.32 (s, 3H), 1.90 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 165.7, 160.0, 159.4, 159.3, 156.2, 149.0, 138.7, 131.1, 130.1, 129.3, 128.4, 126.0, 124.0, 122.4, 122.1, 115.5, 115.4, 115.1, 113.2, 112.4, 111.1, 99.3, 73.0, 68.0, 67.6, 65.0, 64.9, 56.0, 55.4, 33.7, 8.7; IR (film) ν_{max} 3398, 3352, 2923, 2871, 2852, 1708, 1629, 1605, 1577, 1527, 1500, 1483, 1431, 1369, 1245, 1207, 1124, 1076, 985 cm⁻¹; HRMS (FAB) *m/z*: [M + Na⁺] calcd for C₃₁H₃₁NNaO₁₀, calcd 600.1846; found, 600.1840.

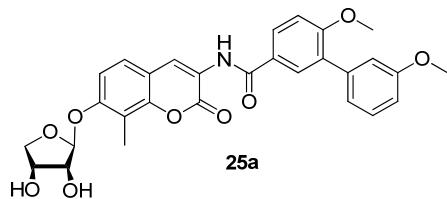


N-(7-((2R,3R,4R,6S)-3,4-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (23b): Compound **23b** (26 mg, 57%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.72 (s, 1H), 8.65 (s, 1H), 7.83 (dd, $J = 2.4, 8.6$ Hz, 1H), 7.81 (d, $J = 2.4$ Hz, 1H), 7.30 (t, $J = 8.2$ Hz, 1H), 7.16 (d, $J = 8.9$ Hz, 1H), 6.94–7.07 (d, $J = 2.4, 8.9$ Hz, 1H), 7.05 (dt, $J = 1.7, 8.2$ Hz, 1H), 7.02 (t, $J = 2.6$ Hz, 1H), 7.00 (d, $J = 8.6$ Hz, 1H), 6.86 (ddd, $J = 0.9, 2.6, 8.3$ Hz, 1H), 5.60 (d, $J = 3.4$ Hz, 1H), 4.16 (m, 1H), 4.09 (m, 1H), 3.98 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.72 (m, 1H), 3.60 (bs, 1H), 3.56 (t, $J = 4.1$ Hz, 1H), 3.50 (m, 1H), 3.27 (d, $J = 9.5$ Hz, 2H), 1.88 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.6, 159.9, 159.3, 158.4, 150.0, 143.7, 138.5, 137.5, 131.0, 130.0, 129.2, 128.3, 125.7, 123.5, 122.9, 122.8, 122.0, 116.4, 115.3, 114.0, 113.1, 111.0, 99.7, 68.0, 67.6, 65.1, 64.8, 61.8, 55.9, 55.4, 32.8; IR (film) ν_{max} 3402, 3390, 2937, 2837, 1714, 1670, 1605, 1527, 1502, 1483, 1461, 1367, 1274, 1246, 1207, 1180, 1081, 1051, 976 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{31}\text{H}_{31}\text{NNaO}_{11}$, calcd 616.1794; found, 616.1786.



N-(7-((2R,3R,4R,6S)-3,4-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (23c): Compound **23c** (33 mg, 63%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.70 (s, 1H), 8.69 (s, 1H), 7.84 (d, $J = 2.4, 8.4$ Hz, 2H), 7.82 (d, $J = 2.4$ Hz, 1H), 7.30 (t, $J = 7.8$ Hz, 1H), 7.05 (dt, $J = 1.8, 8.2$ Hz, 1H), 7.02 (t, $J = 2.2$ Hz, 1H), 6.96 (d, $J = 7.8$ Hz,

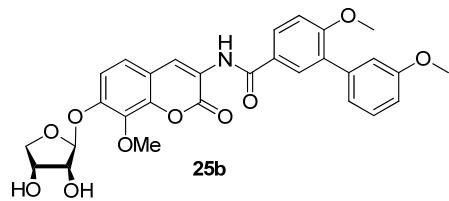
1H), 6.87 (dd, $J = 2.7, 8.7$ Hz, 1H), 6.79 (s, 1H), 5.25 (d, $J = 4.1$ Hz, 1H), 4.58 (m, 1H), 4.15 (m, 1H), 4.01 (d, $J = 6.4$ Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.70 (m, 2H), 3.56 (m, 1H), 3.08 (d, $J = 6.3$ Hz, 1H), 2.41 (s, 3H), 1.94 (m, 1H), 1.77 (m, 1H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.6, 159.9, 159.3, 159.0, 148.9, 146.2, 143.3, 138.5, 131.0, 130.0, 129.2, 128.3, 125.7, 123.7, 123.0, 122.0, 121.1, 116.3, 115.3, 113.1, 111.0, 106.3, 104.0, 68.7, 67.0, 65.6, 64.5, 56.1, 55.9, 55.4, 32.3, 10.0; IR (film) ν_{max} 3400, 3390, 2938, 2844, 1713, 1670, 1606, 1529, 1500, 1483, 1460, 1369, 1273, 1247, 1205, 1180, 1081, 1051, 976 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{32}\text{H}_{33}\text{NNaO}_{11}$, calcd 630.1951; found, 630.1953.



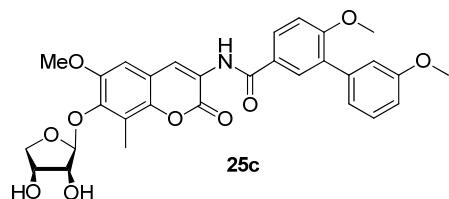
N-(7-((2S)-3,4-dihydroxytetrahydrofuran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (25a): Compound **24a** (98 mg, 80%) was obtained as a colorless amorphous solid and used without further purification.

A solution of **24a** (90 mg, 0.16 mmol) in THF:H₂O:MeOH (3:1:1, 3 mL) was treated with LiOH (20 mg, 0.48 mmol), then stirred at rt for 2 h. The resulting reaction mixture was stirred at rt for 2 h, cooled to 0°C, then acidified to pH ~4 with 5% aqueous HCl. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified via column chromatography (SiO₂, 100:5, CH₂Cl₂:MeOH) to yield diol **25a** as a colorless amorphous solid (72 mg, 84%). ^1H NMR (500 MHz, CDCl_3) δ 8.76 (s, 1H), 8.70 (s, 1H), 7.90 (dd, $J = 2.4, 8.5$ Hz, 1H), 7.88 (d, $J = 2.3$ Hz, 1H), 7.36 (t, $J = 7.9$ Hz, 1H), 7.30 (d, $J = 8.6$ Hz, 1H), 7.12 (dt, $J = 1.2, 7.8$ Hz, 1H), 7.09 (t, $J = 2.4$ Hz, 1H) 7.08 (d, $J =$

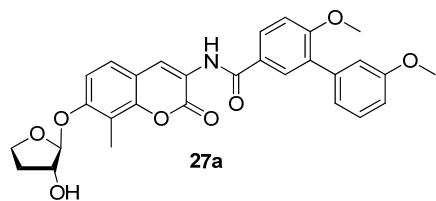
8.8 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 6.93 (dd, J = 2.4, 8.3 Hz, 1H), 5.68 (s, 1H), 4.59 (m, 1H), 4.46 (d, J = 4.7 Hz, 1H), 4.23 (dd, J = 5.0, 10.0 Hz, 1H), 4.00 (dd, J = 3.2, 10.0 Hz, 1H) 3.89 (s, 3H), 3.86 (s, 3H), 3.33 (bs, 1H), 2.88 (bs, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 159.8, 159.4, 159.3, 156.0, 149.0, 138.6, 131.0, 129.9, 129.2, 128.2, 125.9, 125.7, 124.3, 122.0, 121.9, 115.3, 115.0, 114.3, 113.1, 111.9, 111.0, 106.5, 76.5, 73.2, 70.7, 55.9, 55.3, 8.4; IR (film) ν_{max} 3409, 3401, 2938, 2838, 1712, 1670, 1605, 1526, 1483, 1367, 1274, 1246, 1205, 1181, 1054, 1020, 972 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{29}\text{H}_{27}\text{NNaO}_9$, calcd 556.1584; found, 556.1692.



N-(7-((2S)-3,4-dihydroxytetrahydrofuran-2-yloxy)-8-methoxy-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (25b): Compound **25b** (39 mg, 68%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.81 (s, 1H), 8.73 (s, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.90 (s, 1H), 7.38 (t, J = 8.4 Hz, 1H), 7.28 (d, J = 9.2 Hz, 1H), 7.24 (s, 1H), 7.15 (t, J = 10.4 Hz, 1H), 7.11 (s, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 5.67 (d, J = 4.1 Hz, 1H), 4.30 (m, 3H), 4.13 (d, J = 10.1 Hz, 1H), 4.07 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H), 3.52 (bs, 1H), 3.14 (bs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.6, 159.9, 159.4, 158.5, 150.0, 143.7, 138.6, 138.0, 131.1, 130.0, 129.2, 128.2, 125.8, 123.5, 122.9, 122.7, 122.0, 116.5, 115.4, 115.3, 113.2, 111.1, 101.6, 74.7, 73.2, 69.4, 62.1, 55.9, 55.3; IR (film) ν_{max} 3479, 3406, 2938, 2837, 1713, 1670, 1605, 1525, 1481, 1367, 1274, 1244, 1207, 1180, 1053, 1020, 972 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{29}\text{H}_{27}\text{NNaO}_{10}$, calcd 572.1533; found, 572.1523.



N-(7-((2S)-3,4-dihydroxytetrahydrofuran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (25c): Compound **25c** (44 mg, 81%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.99 (s, 1H), 8.71 (s, 1H), 8.00 (dt, $J = 2.3, 8.6$ Hz, 1H), 7.94 (t, $J = 2.3$ Hz, 1H), 7.36 (t, $J = 7.4$ Hz, 1H), 7.27 (d, $J = 8.8$ Hz, 1H), 7.20 (s, 1H), 7.14 (s, 1H), 7.14 (dt, $J = 2.4, 10.4$ Hz, 1H), 6.95 (dd, $J = 2.4, 8.3$ Hz, 1H), 5.66 (s, 1H), 4.65 (m, 1H), 4.33 (d, $J = 4.5$ Hz, 1H), 4.24 (m, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.84 (s, 3H), 3.78 (dd, $J = 5.2, 8.9$ Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.9, 160.4, 159.3, 150.8, 145.8, 144.0, 139.9, 131.4, 130.8, 129.9, 129.3, 127.0, 124.4, 124.2, 124.1, 122.7, 121.3, 116.6, 116.2, 113.5, 112.3, 110.2, 107.9, 76.6, 73.7, 71.1, 56.5, 56.3, 55.5, 9.5; IR (film) ν_{max} 3400, 3375, 2937, 2840, 1707, 1670, 1602, 1577, 1526, 1500, 1483, 1458, 1382, 1242, 1207, 1180, 1095, 1081, 1022, 960 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{30}\text{H}_{29}\text{NNaO}_{10}$, calcd 586.1689; found, 586.1697.



N-(7-((2R)-3-hydroxytetrahydrofuran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (27a): Compound **26a** (144 mg, 88%) was obtained as a colorless amorphous solid and used without further purification.

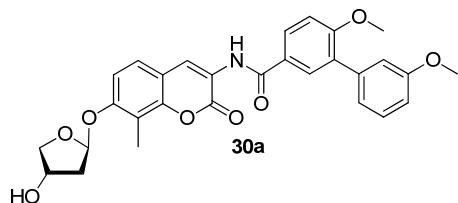
TBAF (1.0 M in THF, 0.4 mL, 0.4 mmol) was added dropwise to a solution of **27a** (130 mg, 0.2 mmol) in THF (3 mL) at rt. The resulting mixture was stirred at rt for 1 h, quenched with

water and extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with saturated sodium chloride solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified via column chromatography (SiO_2 , 100:1, $\text{CH}_2\text{Cl}_2:\text{MeOH}$) to yield **27a** and **28a** (97 mg, 74%) as a mixture of diastereomers in a 7:6 ratio, respectively. Compound **27a** (52 mg, 40%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.80 (s, 1H), 8.72 (s, 1H), 7.93 (dd, $J = 2.4, 8.5$ Hz, 1H), 7.91 (d, $J = 2.3$ Hz, 1H), 7.39 (t, $J = 7.9$ Hz, 1H), 7.33 (d, $J = 8.6$ Hz, 1H), 7.13 (dt, $J = 3.4, 4.0$ Hz, 3H), 7.09 (d, $J = 8.6$ Hz, 1H), 6.95 (dd, $J = 2.2, 7.9$ Hz, 1H), 5.69 (s, 1H), 4.61 (t, $J = 4.7$ Hz, 1H), 4.25 (dd, $J = 8.0, 16.0$ Hz, 1H), 4.14 (td, $J = 4.1, 8.9$ Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 2.46 (dt, $J = 6.8, 13.6$ Hz, 1H), 2.29 (s, 3H), 2.24 (d, $J = 5.3$ Hz, 1H), 2.05 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 159.9, 159.6, 159.5, 156.1, 149.2, 138.7, 131.2, 129.3, 128.3, 126.2, 125.8, 125.2, 124.4, 122.1, 122.1, 115.4, 115.2, 114.3, 113.3, 112.1, 111.2, 106.6, 76.1, 67.8, 56.0, 55.5, 32.5, 8.5; IR (film) ν_{max} 3404, 2951, 2939, 2902, 1712, 1670, 1649, 1629, 1605, 1527, 1502, 1481, 1369, 1265, 1207, 1105, 1065, 1033, 993, 962 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{29}\text{H}_{27}\text{NNaO}_8$, calcd 540.1634; found, 540.1622.



N-(7-((2S)-3-hydroxytetrahydrofuran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (28a): Compound **28a** (45 mg, 34%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.77 (s, 1H), 8.70 (bs, 1H), 7.91 (dd, $J = 2.4, 8.5$ Hz, 1H), 7.89 (d, $J = 2.4$ Hz, 1H), 7.36 (t, $J = 7.9$ Hz, 1H), 7.30 (d, $J = 8.7$ Hz, 1H), 7.08–7.14 (m, 3H), 7.06 (d, $J = 8.7$ Hz, 1H), 6.93 (ddd, $J = 0.9, 2.6, 8.4$ Hz, 1H), 5.66 (s, 1H), 4.58 (t, $J = 5.1$ Hz, 1H), 4.24 (q, $J = 8.2$ Hz, 1H), 4.11 (dt, $J = 4.3, 9.1$ Hz, 1H), 3.89 (s, 3H),

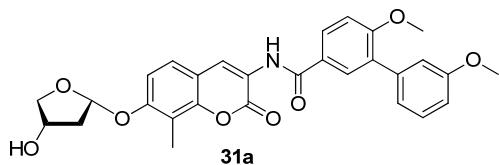
3.86 (s, 3H), 2.43 (m, 1H), 2.28 (d, $J = 4.1$ Hz, 1H), 2.26 (s, 3H), 2.02 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 159.9, 159.6, 159.4, 156.0, 149.2, 138.7, 131.1, 130.0, 129.3, 128.3, 126.1, 125.8, 124.4, 122.1, 122.0, 115.4, 115.1, 114.3, 113.3, 112.1, 111.1, 106.5, 76.1, 67.8, 56.0, 55.5, 32.4, 8.5; IR (film) ν_{max} 3400, 2948, 2942, 2889, 1711, 1668, 1649, 1605, 1527, 1505, 1484, 1370, 1267, 1204, 1106, 1067, 1034, 993, 963 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{29}\text{H}_{27}\text{NNaO}_8$, calcd 540.1634; found, 540.1627.



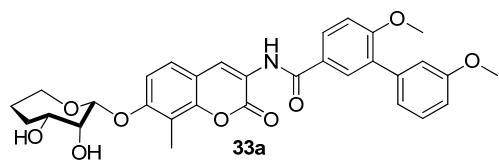
N-(7-((2R)-4-hydroxytetrahydrofuran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (30a): Compound **29a** (160 mg, 82%) was obtained as a colorless amorphous solid and used without further purification.

TBAF (1.0M in THF, 0.5 mL, 0.5 mmol) was added dropwise to solution of **29a** (157 mg, 0.25 mmol) in THF (4 mL) at rt. The reaction mixture was stirred at rt for 1 h, quenched with water and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated sodium chloride solution, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude residue was purified via column chromatography (SiO_2 , 100:1, $\text{CH}_2\text{Cl}_2:\text{MeOH}$) to yield **30a** and **31a** (96 mg, 75%) as a mixture of diastereomers in a 4:3 ratio, respectively. Compound **30a** (55 mg, 43%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.80 (s, 1H), 8.71 (bs, 1H), 7.91 (dd, $J = 2.4, 8.6$ Hz, 1H), 7.89 (d, $J = 2.4$ Hz, 1H), 7.36 (t, $J = 7.9$ Hz, 1H), 7.35 (d, $J = 8.6$ Hz, 1H), 7.19 (d, $J = 8.8$ Hz, 1H), 7.12 (dt, $J = 1.78, 8.0$ Hz, 1H), 7.09 (t, $J = 2.6$ Hz, 1H), 7.1 (d, $J = 8.8$ Hz, 1H), 6.93 (ddd, $J = 0.8, 2.6, 8.3$ Hz, 1H), 6.03 (dd, $J = 2.7, 5.6$ Hz, 1H), 4.73 (m, 1H), 4.11 (dd, $J = 4.3, 9.9$ Hz, 1H), 3.95 (dt, $J = 1.4, 9.9$ Hz, 1H),

3.90 (s, 3H), 3.86 (s, 3H), 2.54 (ddd, $J = 3.0, 6.3, 14.6$ Hz, 1H), 2.41 (m, 1H), 2.30 (s, 3H), 2.29 (bs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 159.9, 159.4, 156.7, 149.2, 138.7, 131.1, 130.1, 129.3, 128.3, 126.2, 125.8, 125.2, 124.4, 122.1, 122.1, 115.4, 115.2, 114.4, 113.3, 112.4, 111.1, 102.9, 75.1, 71.6, 56.0, 55.5, 43.1, 8.5; IR (film) ν_{max} 3404, 2923, 2845, 1711, 1670, 1606, 1526, 1502, 1369, 1242, 1205, 1178, 1115, 1057, 995, 974 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{29}\text{H}_{27}\text{NNaO}_8$, calcd 540.1634; found, 540.1629.



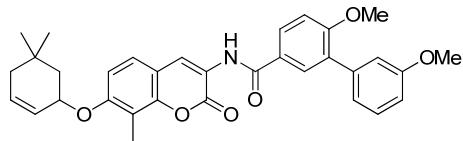
N-(7-((2S)-4-hydroxytetrahydrofuran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (31a): Compound **31a** (41 mg, 32%) was obtained as a colorless amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 8.80 (s, 1H), 8.72 (bs, 1H), 7.91 (dd, $J = 2.5, 8.6$ Hz, 1H), 7.89 (d, $J = 2.3$ Hz, 1H), 7.36 (t, $J = 7.9$ Hz, 1H), 7.35 (d, $J = 8.6$ Hz, 1H), 7.16 (d, $J = 8.6$ Hz, 1H), 7.12 (dt, $J = 1.5, 7.7$ Hz, 1H), 7.09 (t, $J = 2.6$ Hz, 1H), 7.07 (d, $J = 8.6$ Hz, 1H), 6.93 (ddd, $J = 0.8, 2.6, 8.4$ Hz, 1H), 5.59 (d, $J = 4.3$ Hz, 1H), 4.47 (m, 1H), 4.18 (dt, $J = 4.1, 8.9$ Hz, 1H), 3.98 (q, $J = 8.3$ Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.45 (d, $J = 9.8$ Hz, 1H), 2.39 (m, 1H), 2.36 (s, 3H), 2.09 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.7, 159.9, 159.4, 153.9, 149.1, 138.7, 131.1, 130.1, 129.3, 128.3, 126.1, 125.9, 125.1, 124.1, 122.4, 122.1, 115.6, 115.4, 114.9, 113.2, 113.2, 111.1, 100.6, 73.0, 66.6, 56.0, 55.4, 31.7, 8.7; IR (film) ν_{max} 3400, 2925, 2845, 1707, 1670, 1605, 1527, 1500, 1367, 1242, 1205, 1180, 1113, 1077, 1034, 987, 974 cm^{-1} ; HRMS (FAB) m/z : [M + Na $^+$] calcd for $\text{C}_{29}\text{H}_{27}\text{NNaO}_8$, calcd 540.1634; found, 540.1632.



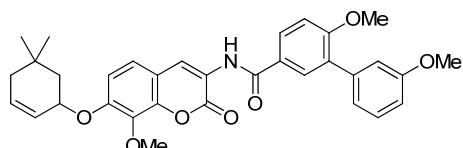
N-(7-((2R,3R,4R)-3,4-dihydroxyoxepan-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (33a): Compound **32a** (180 mg, 78%) was obtained as a colorless amorphous solid and used without further purification.

A solution of **32a** (172 mg, 0.29 mmol) in THF:H₂O:MeOH (3:1:1, 5 mL) was treated with LiOH (37 mg, 0.88 mmol) at rt. The reaction mixture stirred at rt for 2 h, cooled to 0°C, then acidified to pH ~4 with 5% aqueous HCl. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with saturated sodium chloride solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified via column chromatography (SiO₂, 100:5, CH₂Cl₂:MeOH) to yield diol **33a** (118 mg, 68%) as a colorless amorphous solid. ¹H NMR (500 MHz, CDCl₃) δ 8.74 (s, 1H), 8.65 (s, 1H), 7.85 (dd, *J* = 2.5, 8.6 Hz, 1H), 7.82 (d, *J* = 2.6 Hz, 1H), 7.30 (t, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 7.05 (dt, *J* = 1.2, 9.1 Hz, 1H), 7.03 (t, *J* = 2.4 Hz, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.86 (ddd, *J* = 0.9, 2.7, 8.3 Hz, 1H), 5.39 (d, *J* = 2.7 Hz, 1H), 4.22 (m, 1H), 3.95 (dd, *J* = 3.1, 8.8 Hz, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.58 (dd, *J* = 3.1, 10.5 Hz, 1H), 2.88 (d, *J* = 5.3 Hz, 1H), 2.32 (s, 3H), 2.20 (d, *J* = 6.5 Hz, 1H), 2.10 (m, 1H), 1.87 (m, 1H), 1.76 (m, 1H), 1.65 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 165.6, 159.8, 159.3, 155.8, 149.0, 138.6, 131.1, 130.0, 129.2, 128.2, 126.0, 125.8, 123.9, 122.4, 122.0, 116.2, 115.6, 115.3, 114.9, 113.1, 112.7, 111.0, 98.8, 75.8, 71.5, 65.3, 55.9, 55.3, 29.9, 25.7, 8.7; IR (film) ν_{max} 3402, 3350, 2931, 2877, 2834, 1697, 1670, 1606, 1531, 1504, 1369, 1238, 1207, 1182, 1097, 1076, 995, 970 cm⁻¹; HRMS (FAB) *m/z*: [M + Na⁺] calcd for C₃₁H₃₁NO₉Na, calcd 584.1897; found, 584.1884.

Representative procedure for Mitsunobu coupling with sugar mimics:

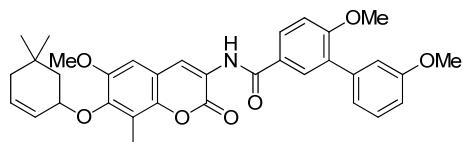


N-(7-(5,5-dimethylcyclohex-2-enyloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (40a). Diisopropylazodicarboxylate (231 mg, 1.14 mmol) was added to a solution of allylic alcohol **37** (72 mg, 0.57 mmol), phenol **6a** (247 mg, 0.57 mmol) and triphenylphosphine (299 mg, 1.14 mmol) in anhydrous THF (10 mL). After 2 h, the solvent was removed and the residue purified via column chromatography (SiO_2 , 100:1, CH_2Cl_2 :acetone) to afford compound **40a** as a colorless amorphous solid (143 mg, 47 %). ^1H NMR (400 MHz, CDCl_3) δ 8.81 (s, 1H), 8.72 (s, 1H), 7.95–7.92 (m, 2H), 7.40–7.28 (m, 2H), 7.16–7.07 (m, 3H), 6.96–6.93 (m, 2H), 5.92–5.85 (m, 2H), 4.95 (m, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.32 (s, 3H), 2.07–1.67 (m, 4H), 1.09 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.6, 159.9, 159.7, 159.5, 157.9, 149.6, 138.8, 131.1, 130.5, 130.1, 129.3, 128.3, 126.3, 125.7, 125.0, 124.6, 122.2, 121.6, 115.4, 115.2, 113.32, 113.28, 111.1, 110.4, 73.0, 56.0, 55.5, 41.6, 39.2, 30.7, 30.5, 27.2, 8.5. IR (film) ν_{max} 3405, 3031, 2950, 2927, 2868, 1710, 1672, 1605, 1524, 1500, 1367, 1267, 1242, 1205, 1180, 1101, 1022 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{33}\text{H}_{34}\text{NO}_6$, 540.2386; found 540.2382.

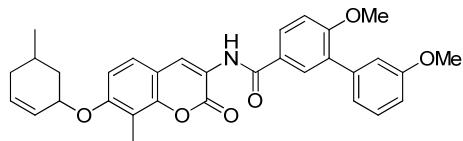


N-(7-(5,5-dimethylcyclohex-2-enyloxy)-8-methoxy-2-oxochromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (40b). Compound **40b** was obtained as a white amorphorous solid (32 mg, 71%). ^1H NMR (400 MHz, CDCl_3) δ 8.73 (s, 1H), 8.64 (s, 1H), 7.85–7.81 (m, 2H), 7.29 (t, J = 8.1 Hz, 1H), 7.14 (d, J = 8.7 Hz, 1H), 7.06–6.99 (m, 3H), 6.91 (d, J =

8.7 Hz, 1H), 6.87–6.85 (m, 1H), 5.83–5.75 (m, 2H), 4.89 (m, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 1.96–1.61 (m, 4H), 0.99 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.3, 159.0, 152.6, 144.3, 138.6, 137.4, 131.0, 130.4, 130.0, 129.2, 128.2, 126.0, 124.8, 124.0, 122.4, 122.1, 122.0, 115.2, 114.5, 113.2, 1112.8, 111.0, 74.0, 61.5, 55.9, 55.3, 41.4, 39.0, 30.9, 30.6, 26.7. IR (film) ν_{max} 3402, 3085, 3025, 2920, 2847, 1714, 1670, 1603, 1522, 1500, 1367, 1278, 1246, 1148, 1099, 1082, 1022 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for $\text{C}_{33}\text{H}_{33}\text{NO}_7\text{Na}$, 578.2155; found 578.2150.

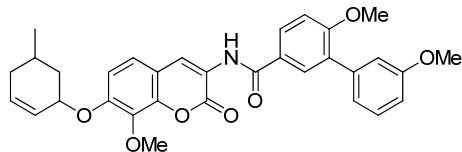


N-(7-(5,5-dimethylcyclohex-2-enyloxy)-6-methoxy-8-methyl-2-oxochromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (40c). Compound **40c** was obtained as a white amorphorous solid (73 mg, 88%). ^1H NMR (400 MHz, CDCl_3) δ 8.78 (s, 1H), 8.75 (s, 1H), 7.95–7.90 (m, 2H), 7.36 (t, J = 8.2 Hz, 1H), 7.14–7.05 (m, 3H), 6.93 (d, J = 8.1 Hz 1H), 6.84 (s, 1H), 5.82–5.78 (m, 2H), 4.76 (m, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 2.38 (s, 3H), 2.09–1.67 (m, 4H), 1.04 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.4, 159.3, 150.4, 147.8, 143.5, 138.6, 131.0, 130.0, 129.2, 129.0, 128.2, 126.6, 126.1, 123.8, 122.8, 122.0, 120.8, 115.3, 115.1, 113.1, 111.0, 106.5, 78.1, 56.0, 55.9, 55.3, 42.4, 39.1, 31.3, 30.9, 26.2, 9.9. IR (film) ν_{max} 3406, 3084, 3028, 2999, 2943, 2899, 2864, 1697, 1672, 1605, 1580, 1535, 1501, 1371, 1279, 1234, 1207, 1180, 1099, 1016 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for $\text{C}_{34}\text{H}_{35}\text{NO}_7\text{Na}$, 592.2311; found 592.2324.



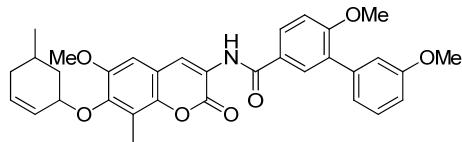
3',6-dimethoxy-N-(8-methyl-7-(5-methylcyclohex-2-enyloxy)-2-oxo-2H-chromen-3-yl)biphenyl-3-carboxamide (41a).

Compound **41a** was obtained as a white amorphous solid (180 mg, 55%). ^1H NMR (400 MHz, CDCl_3) δ 8.81 (s, 1H), 8.72 (s, 1H), 7.94–7.92 (m, 2H), 7.40–7.33 (m, 2H), 7.16–7.07 (m, 3H), 6.97–6.95 (m, 2H), 6.08–5.92 (m, 2H), 4.86 (m, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.35 (s, 3H), 2.33–2.28 (m, 1H), 2.09–1.60 (m, 4H), 1.07 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.6, 159.9, 159.7, 159.5, 157.8, 149.6, 138.8, 133.7, 131.1, 130.1, 129.3, 128.3, 126.3, 125.7, 124.6, 124.4, 122.1, 121.6, 115.4 (2C), 113.4, 113.3, 111.1, 110.8, 71.4, 56.0, 55.5, 36.6, 33.9, 24.1, 21.7, 8.6. IR (film) ν_{max} 3402, 3032, 2980, 2906, 2826, 1713, 1676, 1607, 1554, 1375, 1251, 1093 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{32}\text{H}_{32}\text{NO}_6$, 516.2230; found 526.2229.

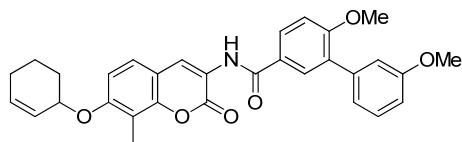
**3',6-dimethoxy-N-(8-methoxy-7-(5-methylcyclohex-2-enyloxy)-2-oxochromen-3-yl)biphenyl-3-carboxamide (41b).**

Compound **41b** was obtained as a white amorphous solid (38 mg, 81%). ^1H NMR (500 MHz, CDCl_3) δ 8.73 (s, 1H), 8.64 (s, 1H), 7.85–7.81 (m, 2H), 7.29 (t, $J = 8.3$ Hz, 1H), 7.13 (d, $J = 8.2$ Hz, 1H), 7.06–7.02 (m, 3H), 6.91 (d, $J = 8.2$ Hz, 1H), 6.87–6.85 (m, 1H), 6.01–5.99 (m, 1H), 5.87–5.83 (m, 1H), 4.80 (m, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 2.19–2.15 (m, 1H), 2.10–1.98 (m, 2H), 1.64–1.57 (m, 1H), 1.44–1.38 (m, 1H), 0.95 (d, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.5, 159.8, 159.3, 159.0, 152.6, 144.2, 138.6, 137.6, 133.8, 131.0, 130.0, 129.2, 128.2, 126.0, 124.1, 124.0, 122.4, 122.05, 122.00, 115.2, 114.5, 113.2, 113.1, 111.0, 72.2, 61.5, 55.9, 55.3, 36.3, 33.8, 23.9, 12.5. IR (film) ν_{max} 3398, 3085, 3028, 2947, 2908, 2833, 1713, 1672, 1605, 1574, 1522, 1502, 1462, 1367, 1275, 11246, 1207,

1180, 1024 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for C₃₂H₃₁NO₇Na, 564.1999; found 564.1983.

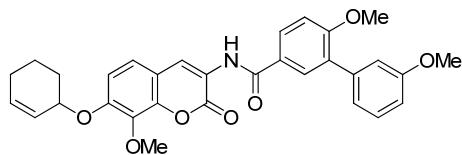


3',6-dimethoxy-N-(6-methoxy-8-methyl-7-(5-methylcyclohex-2-enyloxy)-2-oxochromen-3-yl)biphenyl-3-carboxamide (41c). Compound **41c** was obtained as a white amorphous solid (64 mg, 96%). ¹H NMR (400 MHz, CDCl₃) δ 8.73 (s, 1H), 8.68 (s, 1H), 7.86–7.83 (m, 2H), 7.30 (t, J = 8.3 Hz, 1H), 7.07–6.99 (m, 3H), 6.87–6.85 (m, 1H), 6.78 (s, 1H), 5.95–5.91 (m, 1H), 5.80–5.74 (m, 1H), 4.67 (bs, 1H), 3.83 (s, 6H), 3.79 (s, 3H), 2.30 (s, 3H), 2.22–2.15 (m, 2H), 1.97–1.65 (m, 1H), 1.65–1.54 (m, 1H), 1.36–1.25 (m, 1H), 0.95 (d, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 159.8, 159.5, 159.3, 150.5, 147.6, 143.5, 138.6, 133.0, 131.0, 130.0, 129.2, 128.2, 126.1, 125.5, 123.9, 122.8, 122.0, 120.9, 115.2, 115.0, 113.1, 111.0, 106.5, 75.5, 56.0, 55.9, 55.3, 37.1, 34.0, 23.9, 21.7, 9.7. IR (film) ν_{max} 3408, 3084, 3028, 2943, 2899, 2867, 1697, 1672, 1605, 1580, 1531, 1501, 1371, 1234, 1207, 1178, 1099, 1016 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₃₃H₃₄NO₇, 556.2335; found 556.2325.

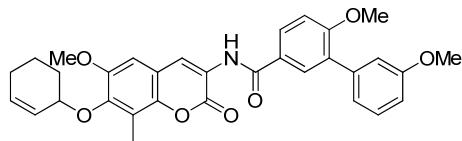


N-(7-(cyclohex-2-enyloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (42a). Compound **42a** was obtained as a colorless amorphous solid (103 mg, 56%). ¹H NMR (400 MHz, CDCl₃) δ 8.81 (s, 1H), 8.72 (s, 1H), 7.95–7.92 (m, 2H), 7.40–7.28 (m, 2H), 7.16–7.07 (m, 3H), 6.97–6.93 (m, 2H), 6.03–5.90 (m, 2H), 4.88 (m, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.33 (s, 3H), 2.30–2.24 (m, 2H), 2.06–1.90 (m, 3H), 1.81–1.72 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 159.9, 159.7, 159.5, 157.8, 149.6, 138.8, 132.8, 131.1, 130.1, 129.3,

128.3, 126.3, 126.0, 125.7, 124.6, 122.2, 121.6, 115.4, 115.3, 113.4, 113.3, 111.1, 110.8, 72.1, 56.0, 55.5, 28.7, 25.3, 19.1, 8.6. IR (film) ν_{max} 3404, 3041, 2934, 2835, 1709, 1670, 1605, 1526, 1502, 1369, 1267, 1244, 1205, 1180, 1101, 1022 cm^{-1} . HRMS (ESI $^+$) m/z : [M + H $^+$] calcd for C₃₁H₃₀NO₆, 512.2073; found 512.2077.



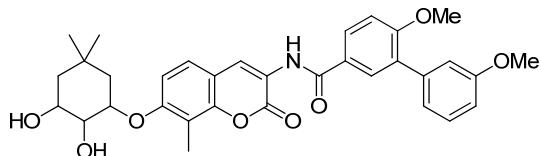
N-(7-(cyclohex-2-enyloxy)-8-methoxy-2-oxochromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (42b). Compound **42b** was obtained as a white amorphous solid (44 mg, 88%).
¹H NMR (400 MHz, CDCl₃) δ 8.82 (s, 1H), 8.74 (s, 1H), 7.94–7.92 (m, 2H), 7.39 (t, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 1H), 7.15–7.08 (m, 3H), 7.00–6.95 (m, 2H), 6.03–5.90 (m, 2H), 4.91 (m, 1H), 4.01 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 2.19–2.16 (m, 1H), 2.09–1.91 (m, 3H), 1.71–1.66 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 159.8, 159.3, 159.0, 152.5, 144.2, 138.6, 137.5, 132.9, 131.1, 130.0, 129.2, 128.2, 126.0, 125.6, 124.0, 122.4, 122.1, 122.0, 115.3, 114.6, 113.2 (2C), 111.0, 72.9, 61.5, 55.9, 55.3, 28.5, 25.1, 18.9. IR (film) ν_{max} 3398, 3083, 3025, 2949, 2918, 2906, 2870, 1713, 1672, 1603, 1574, 1522, 1502, 1462, 1366, 1277, 1248, 1207, 1145, 1022 cm^{-1} . HRMS (ESI $^+$) m/z : [M + Na $^+$] calcd for C₃₁H₂₉NO₇Na 550.1842; found 550.1844.



N-(7-(cyclohex-2-enyloxy)-6-methoxy-8-methyl-2-oxochromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (42c). Compound **42c** was obtained as a white amorphous solid (59 mg, 80%). ¹H NMR (400 MHz, CDCl₃) δ 8.80 (s, 1H), 8.77 (s, 1H), 7.94–7.92 (m, 2H), 7.38 (t, *J*=7.9, 1H), 7.15–7.06 (m, 3H), 6.95 (d, *J*=8.1, 1H), 6.85 (s, 1H), 5.97–5.88

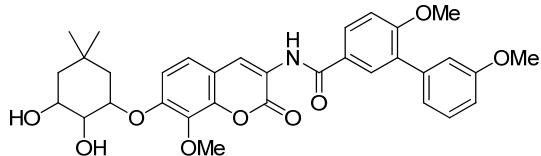
(m, 2H), 4.77 (bs, 1H), 3.91 (s, 6H), 3.87 (s, 3H), 2.40 (s, 3H), 2.19–2.15 (m, 1H), 2.04–1.81 (m, 4H), 1.66–1.63 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.4, 159.3, 150.5, 147.5, 143.5, 138.6, 131.9, 131.0, 130.0, 129.2, 128.2, 127.1, 126.1, 123.9, 122.8, 122.0, 120.9, 115.3, 115.0, 113.1, 111.0, 106.5, 76.1, 56.0, 55.9, 55.3, 29.2, 25.2, 19.0, 9.8. IR (film) ν_{max} 3403, 3086, 3021, 2935, 2867, 1709, 1670, 1603, 1580, 1524, 1501, 1383, 1242, 1207, 1180, 1094, 1051, 1022 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for $\text{C}_{32}\text{H}_{31}\text{NO}_7\text{Na}$, 564.1999; found 564.1990.

Representative procedure for olefin dihydroxylation:

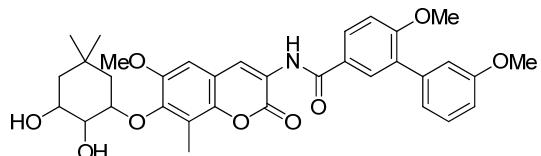


N-(7-((1R,2R,3R)-2,3-dihydroxy-5-methylcyclohexyloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (43a). A solution of **40a** (40 mg, 0.074 mmol) in acetone (3 mL) was treated with *N*-Methylmorpholine-*N*-oxide (17.6 mg, 0.15 mmol), followed by an aqueous solution of OsO₄ (4%, 47 μL). After 12 h, the solvent was removed and the residue was purified via column chromatography (SiO_2 , 20:1, CH_2Cl_2 :acetone) to afford compound **43a** as a white amorphorous solid (34 mg, 80%). ^1H NMR (400 MHz, CDCl_3) δ 8.79 (s, 1H), 8.72 (s, 1H), 7.95–7.92 (m, 2H), 7.41–7.33 (m, 2H), 7.16–7.08 (m, 3H), 6.97–6.94 (m, 2H), 4.80–4.70 (m, 1H), 4.26 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.78–3.75 (m, 1H), 2.90 (bs, 1H), 2.50 (bs, 1H), 2.48 (s, 3H), 1.90–1.84 (m, 2H), 1.51–1.39 (m, 2H), 1.23 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.7, 160.0, 159.6, 159.5, 157.4, 149.5, 138.8, 131.2, 130.2, 129.4, 128.4, 126.2, 125.9, 124.5, 122.2, 121.8, 115.4, 115.2, 113.7, 113.3, 111.2, 110.5, 76.6, 74.2, 69.6, 56.1, 55.5, 41.8, 41.2, 32.2, 31.1, 29.3, 8.6. IR (film) ν_{max} 3485, 3402, 2928,

2891, 1710, 1664, 1605, 1531, 1495, 1404, 1371, 1353, 1258, 1095, 1045 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for C₃₃H₃₅NO₈Na, 596.2260; found 596.2263.



N-(7-(2,3-dihydroxy-5,5-dimethylcyclohexyloxy)-8-methoxy-2-oxochromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (43b). Compound **43b** was obtained as a white amorphous solid (28 mg, 82%). ^1H NMR (500 MHz, CDCl₃) δ 8.74 (s, 1H), 8.65 (s, 1H), 7.85 (dd, J = 8.6, 2.4, 1H), 7.82 (d, J = 2.4 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.06–7.04 (m, 1H), 7.02–7.01 (m, 2H), 6.90 (d, J = 8.8 Hz, 1H), 6.88–6.85 (m, 1H), 4.51–4.47 (m, 1H), 4.18–4.17 (m, 1H), 3.96 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.77–3.74 (m, 1H), 3.24 (bs, 1H), 2.37 (bs, 1H), 1.89–1.85 (m, 1H), 1.76–1.72 (m, 1H), 1.45–1.37 (m, 2H), 1.14 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (125 MHz, CDCl₃) δ 165.6, 159.9, 159.3, 158.7, 152.7, 144.1, 138.6, 137.8, 131.1, 130.0, 129.2, 128.2, 125.9, 123.7, 122.8, 122.5, 122.0, 115.5, 115.3, 114.4, 113.1, 111.0, 79.5, 74.8, 69.8, 61.9, 55.9, 55.3, 42.3, 41.6, 32.7, 32.3, 28.6. IR (film) ν_{max} 3480, 3407, 2930, 2870, 1713, 1670, 1605, 1524, 1502, 1461, 1367, 1277, 1244, 1207, 1180, 1049, 1035 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for C₃₃H₃₅NO₉Na, 612.2210; found 612.2203.

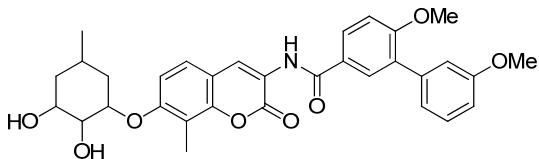


N-(7-(2,3-dihydroxy-5,5-dimethylcyclohexyloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (43c). Compound **43c** was obtained as a white amorphous solid (52 mg, 83%). ^1H NMR (500 MHz, CDCl₃) δ 8.81 (s, 1H), 8.77 (s, 1H), 7.94–7.90 (m, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.14–7.04 (m, 3H), 6.96–6.93 (m, 1H), 6.89 (s, 1H), 4.40–

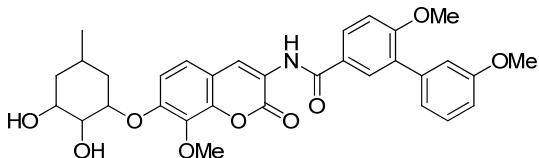
4.39 (m, 1H), 4.20 (m, 1H), 4.09 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.80–3.77 (m, 1H), 2.67 (s, 1H), 2.41 (s, 3H), 1.82–1.73 (m, 2H), 1.53–1.40 (m, 2H), 1.07 (S, 3H), 0.97 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 165.6, 159.9, 159.32, 159.26, 149.4, 146.9, 143.6, 138.6, 131.1, 130.0, 129.2, 128.2, 125.9, 123.5, 123.2, 122.0, 121.0, 115.5, 115.3, 113.1, 111.0, 106.5, 81.8, 75.8, 70.0, 56.1, 55.9, 55.3, 43.7, 41.3, 33.5, 32.3, 28.0, 10.0. IR (film) ν_{max} 3497, 3404, 2955, 2930, 2860, 1716, 1670, 1602, 1580, 1524, 1501, 1464, 1382, 1277, 1245, 1207, 1137, 1074 cm^{-1} .

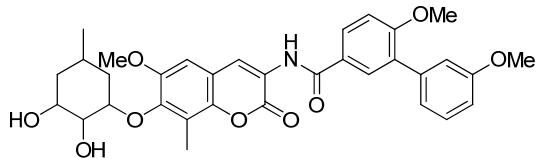
^1H HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for $\text{C}_{34}\text{H}_{37}\text{NO}_9\text{Na}$, 626.2366; found 626.2369.



N-(7-((1R,2R,3R)-2,3-dihydroxy-5-methylcyclohexyloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (44a). Compound **44a** was obtained as a white amorphorous solid (21 mg, 79%). ^1H NMR (400 MHz, CDCl_3) δ 8.78 (s, 1H), 8.70 (s, 1H), 7.93–7.89 (m, 2H), 7.37 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0, 1H), 7.14–7.06 (m, 3H), 6.95–6.93 (m, 2H), 4.77–4.76 (m, 1H), 4.10–4.05 (m, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 2.69 (bs, 1H), 2.29 (s, 3H), 2.11 (bs, 1H), 1.93–1.86 (m, 1H), 1.85–1.71 (m, 2H), 1.56–1.51 (m, 1H), 1.45–1.38 (m, 1H), 0.96 (d, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.7, 160.0, 159.7, 159.5, 156.8, 149.6, 138.8, 131.2, 130.2, 129.4, 128.4, 126.2, 125.9, 124.5, 122.2, 121.8, 115.5, 115.0, 113.6, 113.3, 111.2, 109.9, 76.2, 69.5, 69.0, 56.1, 55.5, 36.7, 32.4, 25.5, 21.9, 8.6. IR (film) ν_{max} 3471, 3407, 2950, 2927, 2869, 1713, 1681, 1605, 1526, 1495, 1404, 1371, 1353, 1259, 1076 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for $\text{C}_{32}\text{H}_{33}\text{NO}_8\text{Na}$, 582.2104; found 582.2097.



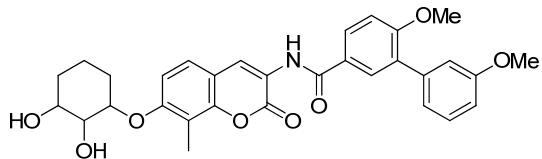
N-(7-(2,3-dihydroxy-5-methylcyclohexyloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (44b). Compound **44b** was obtained as a white amorphorous solid (28 mg, 68%). ^1H NMR (500 MHz, CDCl_3) δ 8.72 (s, 1H), 8.64 (s, 1H), 7.85–7.81 (m, 2H), 7.29 (t, J = 7.9 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.06–6.99 (m, 3H), 6.90–6.87 (m, 2H), 4.66–4.64 (m, 1H), 4.09–4.04 (m, 1H), 4.00–3.98 (m, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 2.47 (bs, 1H), 1.89 (m, 1H), 1.77–1.67 (m, 2H), 1.51–1.54 (m, 1H), 1.39–1.31 (m, 1H), 0.92–0.90 (d, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.6, 159.8, 159.3, 158.9, 151.86, 144.3, 138.6, 137.4, 131.1, 130.0, 129.2, 128.2, 125.9, 123.8, 122.6, 122.3, 122.0, 115.3, 114.9, 113.1, 112.8, 111.0, 77.6, 69.5, 68.7, 61.6, 55.9, 55.3, 36.4, 32.5, 25.3, 21.7. IR (film) ν_{max} 3462, 3404, 2930, 2868, 1713, 1670, 1605, 1576, 1524, 1502, 1462, 1367, 1277, 1246, 1207, 1180, 1049, 1024 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for $\text{C}_{32}\text{H}_{33}\text{NO}_9\text{Na}$, 598.2053; found 598.2053.



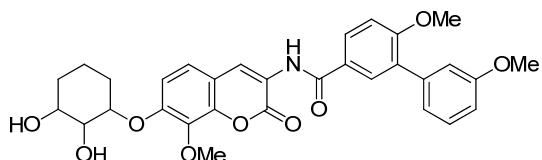
N-(7-(2,3-dihydroxy-5-methylcyclohexyloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (44c). Compound **44c** was obtained as a white amorphous solid (42 mg, 93%). ^1H NMR (500 MHz, CDCl_3) δ 8.80 (s, 1H), 8.76 (s, 1H), 7.94–7.90 (m, 2H), 7.38 (t, J = 7.9 Hz, 1H), 7.14–7.09 (m, 3H), 6.95–6.93 (m, 1H), 6.86 (s, 1H), 4.48–4.45 (m, 1H), 4.24–4.22 (m, 1H), 4.06–4.05 (m, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 2.56 (bs, 1H), 2.07–2.05 (m, 1H), 1.99 (bs, 1H), 1.83–1.75 (m, 2H), 1.52–1.44 (m, 2H), 1.02–1.01 (d, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.8, 160.0, 159.6, 159.5, 150.1, 147.7, 143.6, 138.8, 131.3, 130.2, 129.4, 128.4, 1126.2, 123.9, 123.2, 122.2, 120.3, 115.5, 115.4, 113.3, 111.2, 106.7, 82.1, 71.0, 69.2, 56.2, 56.1, 55.5, 36.6, 34.2, 26.0, 22.0, 9.9. IR (film) ν_{max} 3512, 3404,

2957, 2930, 2860, 1716, 1670, 1602, 1580, 1523, 1464, 1383, 1277, 1246, 1207, 1074 cm⁻¹.

HRMS (ESI⁺) m/z: [M + Na⁺] calcd for C₃₃H₃₅NO₉Na, 612.2210; found 612.2192.

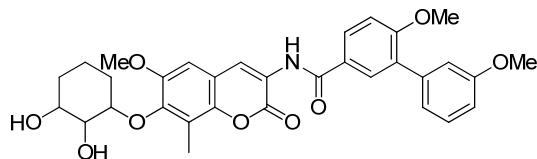


N-(7-((1R,2R,3R)-2,3-dihydroxycyclohexyloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (45a). Compound **45a** as a colorless amorphous solid (41 mg, 85%). ¹H NMR (400 MHz, CDCl₃) δ 8.78 (s, 1H), 8.72 (s, 1H), 7.95–7.91 (m, 2H), 7.41–7.32 (m, 2H), 7.16–7.08 (m, 3H), 6.98–6.94 (m, 2H), 4.65–4.55 (m, 1H), 4.23–4.22 (m, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.85 (m, 1H), 2.34 (s, 3H), 2.11–2.08 (m, 1H), 1.95–1.90 (m, 1H), 1.63–1.50 (m, 3H), 1.45–1.42 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 165.7, 160.0, 159.7, 159.6, 157.4, 149.5, 138.8, 131.3, 130.2, 129.4, 128.4, 126.3, 125.8, 124.4, 122.2, 122.0, 115.5 (2C), 114.0, 113.4, 111.24, 111.15, 78.5, 74.5, 69.7, 56.1, 55.5, 29.9, 28.6, 18.4, 8.6. IR (film) ν_{max} 3484, 3405, 2949, 2843, 1707, 1639, 1601, 1547, 1531, 1454, 1377, 1274, 1265, 1051, 1014 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₃₁H₃₂NO₈, 546.2128; found 546.2127.

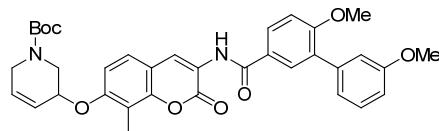


N-(7-(2,3-dihydroxycyclohexyloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (45b). Compound **45b** was obtained as a white amorphorous solid (41 mg, 87%). ¹H NMR (500 MHz, CDCl₃) δ 8.72 (s, 1H), 8.64 (s, 1H), 7.85–7.81 (m, 2H), 7.29 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.06–6.99 (m, 3H), 6.94 (d, J = 8.0 Hz, 1H), 6.87–6.86 (m, 1H), 4.32 (m, 1H), 4.14 (m, 1H), 3.96 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.73–3.71 (m, 1H), 3.35 (bs, 1H), 2.41 (bs, 1H), 2.10 (m, 1H), 1.85 (m, 1H), 1.67 (m, 1H),

1.56 (m, 1H), 1.50–1.40 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.6, 159.9, 159.3, 158.7, 152.7, 144.0, 138.5, 137.8, 131.1, 130.0, 129.2, 128.2, 125.9, 123.7, 122.7, 122.5, 122.0, 115.6, 115.3, 114.9, 113.1, 111.0, 81.5, 74.8, 69.6, 61.9, 55.9, 55.8, 55.3, 29.6, 18.3. IR (film) ν_{max} 3458, 3407, 2930, 2858, 1709, 1668, 1603, 1524, 1501, 1367, 1267, 1244, 1101, 1076, 1018 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for $\text{C}_{31}\text{H}_{31}\text{NO}_9\text{Na}$, 584.1897; found 584.1904.

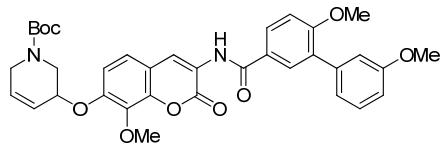


N-(7-(2,3-dihydroxycyclohexyloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (45c). Compound **45c** was obtained as a white amorphous solid (39 mg, 78%). ^1H NMR (500 MHz, CDCl_3) δ 8.70 (s, 1H), 8.67 (s, 1H), 7.84–7.81 (m, 2H), 7.29 (t, $J = 7.9$ Hz, 1H), 7.06–7.01 (m, 2H), 6.99 (d, $J = 8.5$ Hz, 1H), 6.84–6.84 (m, 1H), 6.77 (s, 1H), 4.14–4.12 (m, 1H), 4.12–4.10 (m, 1H) 3.96 (bs, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.73–3.71 (dd, $J = 8.9, 2.9$ Hz, 1H), 2.63 (bs, 1H), 2.30 (s, 3H), 1.88–1.83 (m, 2H), 1.55–1.39 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.6, 159.8, 159.3, 159.2, 149.4, 146.7, 143.4, 138.6, 131.0, 130.0, 129.2, 128.2, 125.9, 123.4, 123.2, 122.0, 121.1, 115.5, 115.3, 113.1, 111.0, 106.3, 83.7, 75.6, 69.4, 56.0, 55.9, 55.3, 30.5, 29.4, 18.4, 9.9. IR (film) ν_{max} 3463, 3408, 2937, 2860, 1717, 1672, 1601, 1524, 1502, 1383, 1339, 1236, 1205, 1182, 1051 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for $\text{C}_{32}\text{H}_{33}\text{NO}_9\text{Na}$, 598.2053; found 598.2054.

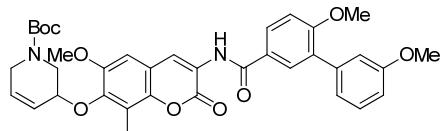


Tert-butyl 5-(3-(3',6-dimethoxybiphenyl-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yloxy)-5,6-dihdropyridine-1(2H)-carboxylate (47a). Compound **47a** was obtained as a light

yellow amorphous solid (1.57 g, 79%). ^1H NMR (400 MHz, CDCl_3) δ 8.82 (s, 1H), 8.72 (s, 1H), 7.94–7.90 (m, 2H), 7.40–7.36 (m, 2H), 7.14–6.93 (m, 3H), 6.96–6.94 (m, 2H), 6.02–5.80 (m, 2H), 4.87 (m, 1H), 4.20–3.99 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.77–3.42 (m, 2H), 2.32 (s, 3H), 1.49 (s, 3H), 1.41 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.5, 159.3, 156.9, 154.6, 149.4, 138.6, 131.0, 130.0, 129.2, 128.8, 128.2, 126.1, 125.6, 125.3, 124.4, 124.2, 122.0, 121.8, 115.2, 113.8, 113.1, 111.0, 110.1, 80.2, 70.0, 69.5, 55.9, 55.3, 44.9, 43.7, 43.0, 28.4, 22.0, 21.8, 8.4. IR (film) ν_{max} 3400, 3067, 2976, 2935, 2837, 1705, 1670, 1605, 1526, 1500, 1367, 1244, 1205, 1180, 1103, 1024 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{35}\text{H}_{37}\text{N}_2\text{O}_8$, 613.2550; found, 613.2533.

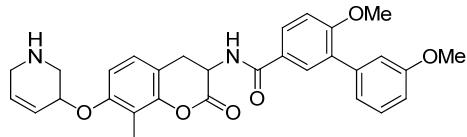


Tert-Butyl 5-(3-(3',6-dimethoxybiphenyl-3-ylcarboxamido)-8-methoxy-2-oxo-2H-chromen-7-yloxy)-5,6-dihydropyridine-1(2H)-carboxylate (47b). Compound **47b** was obtained as a light yellow amorphorous solid (236 mg, 74%). ^1H NMR (400 MHz, CDCl_3) δ 8.81 (s, 1H), 8.70 (s, 1H), 7.93–7.89 (m, 2H), 7.37 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.14–7.07 (m, 3H), 6.95–6.93 (m, 1H), 6.03–5.98 (m, 2H), 4.89 (m, 1H), 4.11–4.01 (m, 1H), 3.99 (s, 3H), 3.98–3.95 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.84–3.72 (m, 2H), 1.48–1.46 (m, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.6, 159.8, 159.3, 158.8, 154.6, 151.8, 144.2, 138.6, 137.7, 131.1, 130.0, 129.2, 129.0, 128.2, 126.0, 125.0, 124.3, 123.8, 122.4, 122.0, 115.2, 113.7, 113.4, 113.1, 111.0, 80.3, 70.9, 70.0, 61.5, 55.9, 55.3, 43.6, 28.4. IR (KBr) ν_{max} 3425, 3070, 2959, 2930, 2872, 2860, 1728, 1693, 1680, 1600, 1462, 1381, 1273, 1122, 1072 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for $\text{C}_{35}\text{H}_{36}\text{N}_2\text{O}_9\text{Na}$, 651.2318; found, 651.2321.



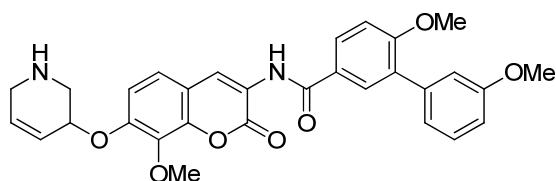
Tert-butyl 5-(3-(3',6-dimethoxybiphenyl-3-ylcarboxamido)-6-methoxy-8-methyl-2-oxo-2H-chromen-7-yloxy)-5,6-dihydropyridine-1(2H)-carboxylate (47c). Compound **47c** was obtained as a light yellow amorphous solid (154 mg, 69%). ¹H NMR (400 MHz, CDCl₃) δ 8.80 (s, 1H), 8.76 (s, 1H), 7.94–7.90 (m, 2H), 7.37 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 7.10–7.07 (m, 2H), 6.94 (dd, J = 8.2, 2.4 Hz, 1H), 6.86 (s, 1H), 5.95–5.83 (m 2H), 4.85 (m, 1H), 4.06–3.96 (m, 1H), 3.92 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 2.36 (s, 3H), 1.47 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 159.8, 159.3 (2C), 154.9, 150.1, 146.7, 143.4, 138.6, 131.0, 130.0, 129.2, 128.2, 127.4, 126.0, 125.1, 123.6, 123.0, 122.0, 120.8, 115.3, 113.1, 111.0, 106.4, 80.1, 73.4, 56.0, 55.9, 55.3, 28.4, 21.7, 9.4. IR (KBr) ν_{max} 3398, 3090, 3074, 2964, 2931, 2849, 2837, 1701, 1676, 1664, 1603, 1521, 1483, 1413, 1242, 1170 cm⁻¹. HRMS (ESI⁺) m/z: [M + Na⁺] calcd for C₃₆H₃₈N₂O₉Na, 665.2475; found, 665.2468.

Representative procedure for Boc deprotection:

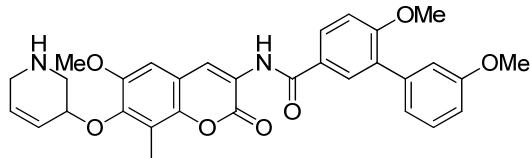


3',6-dimethoxy-N-(8-methyl-2-oxo-7-(1,2,3,6-tetrahydropyridin-3-yloxy)-2H-chromen-3-yl)biphenyl-3-carboxamide (48a): A solution of compound **48a** (470 mg, 0.78 mmol) in methylene chloride (20 mL) was treated with TFA (2 mL). The solution was stirred at rt overnight and concentrated to dryness, then the residue was purified via column chromatography (SiO₂, 10:1, CH₂Cl₂:MeOH) to afford compound **48a** as a white amorphous solid (349 mg, 88%). ¹H NMR (400 MHz, CDCl₃) δ 8.77 (s, 1H), 8.72 (s, 1H), 7.92–7.90 (m, 2H), 7.38–7.29

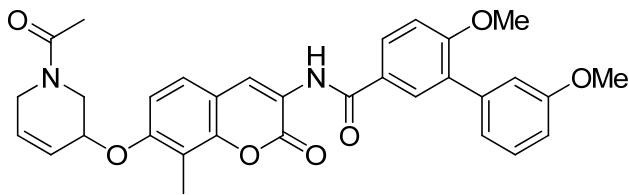
(m, 2H), 7.14–7.04 (m, 3H), 6.94–6.88 (m, 2H), 6.10–5.99 (m, 2H), 4.70 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.46–3.31 (m, 2H), 2.32 (m, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.4, 159.7, 159.4, 159.3, 157.2, 149.4, 138.6, 133.3, 130.9, 130.0, 129.2, 128.2, 126.1, 125.6, 124.4, 124.2, 122.0, 121.7, 115.3, 115.1, 113.6, 113.1, 111.0, 110.5, 69.4, 55.9, 55.3, 47.7, 44.8, 8.5. IR (film) ν_{max} 3400, 3083, 3008, 2968, 2837, 1703, 1668, 1601, 1523, 1504, 1367, 1201, 1132, 1105 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{30}\text{H}_{29}\text{N}_2\text{O}_6$, 513.2026; found, 513.2024.



3',6-dimethoxy-N-(8-methoxy-2-oxo-7-(1,2,3,6-tetrahydropyridin-3-yloxy)-2H-chromen-3-yl)biphenyl-3-carboxamide (48b). Compound **48b** was obtained as a white amorphous solid (61 mg, 81%). ^1H NMR (500 MHz, CDCl_3) δ 8.81 (s, 1H), 8.73 (s, 1H), 7.94–7.91 (m, 2H), 7.38 (t, $J = 7.9$ Hz, 1H), 7.22 (d, $J = 8.7$ Hz, 1H), 7.14–7.07 (m, 3H), 6.98 (d, $J = 8.7$ Hz, 1H), 6.94 (dd, $J = 8.3, 2.1$ Hz, 1H), 6.14–6.04 (m, 2H), 5.06 (m, 1H), 4.01 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.84–3.72 (m, 2H), 3.60 (m, 1H), 3.48 (m, 1H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.5, 159.9, 159.3, 158.4, 150.6, 144.0, 138.6, 138.3, 131.0, 130.0, 129.2, 128.2, 126.0, 125.8, 124.9, 123.3, 122.9, 122.7, 122.0, 116.5, 115.5, 115.3, 113.1, 111.0, 68.3, 61.9, 55.9, 55.2, 44.7, 41.7. IR (KBr) ν_{max} 3404, 2956, 2849, 1677, 1608, 1527, 1458, 1439, 1369, 1205, 1140 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{30}\text{H}_{29}\text{N}_2\text{O}_7$, 529.1975; found, 529.1979.



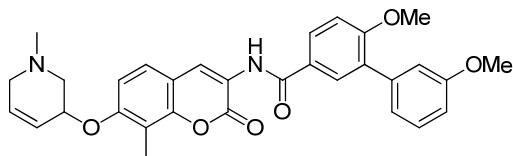
3',6-dimethoxy-N-(6-methoxy-8-methyl-2-oxo-7-(1,2,3,6-tetrahydropyridin-3-yloxy)-2H-chromen-3-yl)biphenyl-3-carboxamide (48c). Compound **48c** was obtained as a light brown amorphorous solid (371 mg, 79%). ¹H NMR (400 MHz, DMSO-*d*₆) 9.64 (s, 1H), 9.06 (s, 1H), 8.00–7.92 (m, 2H), 7.39–7.33 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.12–7.10 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.17–6.05 (m, 2H), 4.72 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.73–3.69 (m, 2H), 3.45–3.42 (m, 2H), 2.32 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 165.6, 159.6, 159.4, 158.5, 149.7, 146.5, 143.8, 139.1, 130.5, 129.9, 129.6 (2C), 127.8, 126.1, 126.0, 125.5, 123.5, 122.2, 119.8, 115.8, 115.7, 113.0, 112.0, 108.0, 71.2, 56.6, 56.3, 55.6, 45.0, 41.7, 9.8. IR (KBr) *v*_{max} 3418, 3004, 2984, 2841, 1685, 1664, 1604, 1529, 1433, 1381, 1242, 1138 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₃₁H₃₁N₂O₇, 543.2131; found, 543.2130.



N-(7-(1-acetyl-1,2,3,6-tetrahydropyridin-3-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (50a). A solution of compound **48a** (45 mg, 0.088 mmol) in pyridine (3 mL) was treated with acetic anhydride (1 mL) and stirred at rt for 2 h. After 2 h, the solvent was removed and the residue purified via column chromatography (SiO₂, 4:1, CH₂Cl₂:acetone) to afford compound **50a** as a white amorphous solid (43 mg, 88%). ¹H NMR (400 MHz, CDCl₃) δ 8.81 (s, 1H), 8.72 (s, 1H), 7.94–7.91 (m, 2H), 7.39–7.29 (m, 2H), 7.15–7.08 (m, 3H), 7.00–6.92 (m, 2H), 6.12–5.96 (m, 2H), 4.91–4.89 (m, 1H), 4.51–4.34 (m, 1H), 4.09–4.03 (m, 1H), 3.93–3.90 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.76–3.51 (m, 1H), 2.30 (3H), 2.17 (3H). ¹³C NMR (100 MHz, CDCl₃) δ 170.0, 165.69, 165.65, 160.00, 159.95, 159.6, 159.5, 157.0, 156.6, 149.6, 149.5, 138.79, 138.77, 131.22, 131.19, 130.9, 130.1, 129.3, 128.3, 127.5, 126.8,

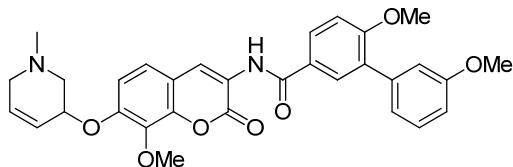
126.3, 126.2, 125.89, 125.85, 124.4, 124.1, 123.6, 122.2, 122.1, 115.6, 115.5, 115.46, 115.41, 114.21, 114.17, 113.33, 113.30, 111.2, 111.0, 110.2, 70.1, 69.6, 56.1, 55.5, 47.9, 45.7, 42.5, 41.9, 21.9, 21.4, 8.54, 8.51. IR (film) ν_{max} 3409, 3049, 2933, 2839, 1712, 1686, 1628, 1605, 1526, 1433, 1373, 1246, 1136, 1097, 1022 cm⁻¹. HRMS (ESI⁺) m/z: [M + Na⁺] calcd for C₃₂H₃₀N₂O₇Na, 577.1950; found, 577.1947.

Representative procedure for synthesis of compounds 51a–c.

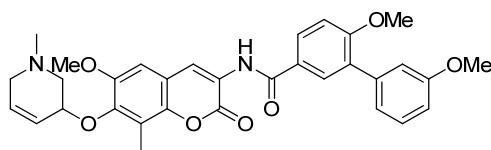


3',6-dimethoxy-N-(8-methyl-7-(1-methyl-1,2,3,6-tetrahydropyridin-3-yloxy)-2-oxo-2H-chromen-3-yl)biphenyl-3-carboxamide (51a). A solution of compound **49a** (249 mg, 0.49 mmol) in THF (3 mL) was treated with potassium carbonate (132 mg, 0.97 mmol) at 0°C, followed by methyl iodide (30 µL, 0.49 mmol). The reaction was quenched with saturated ammonium chloride solution, and extracted with methylene chloride (2 x 30 mL). The combined organic layers were dried over magnesium sulfate, concentrated to dryness and purified via column chromatography (SiO₂, 10:1, CH₂Cl₂:MeOH) to afford compound **51a** as a light brown amorphorous solid (84 mg, 33%). ¹H NMR (400 MHz, CDCl₃) δ 8.82 (s, 1H), 8.73 (s, 1H), 7.95–7.92 (m, 2H), 7.41–7.35 (m, 2H), 7.16–7.08 (m, 3H), 6.95 (m, 2H), 6.04–5.94 (m, 2H), 4.99 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.09–2.98 (m, 3H), 2.67–2.63 (m, 1H), 2.44 (s, 3H), 2.36 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 159.9, 159.7, 159.5, 157.6, 149.6, 138.8, 131.2, 130.2, 130.1, 129.3, 128.3, 126.2, 125.8, 124.5, 124.4, 122.2, 121.9, 115.6, 115.4, 113.8, 113.3, 111.2, 110.9, 72.3, 56.8, 56.0, 55.5, 54.4, 45.8, 8.6. IR (film) ν_{max} 3404, 3090, 3049, 2935, 2839, 1697,

1662, 1634, 1606, 1524, 1500, 1369, 1236, 1097, 1018 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₃₁H₃₁N₂O₆, 527.2182; found, 527.2178.

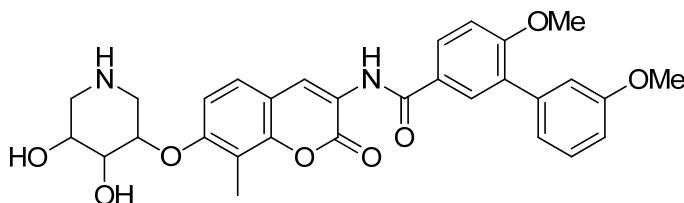


3',6-dimethoxy-N-(8-methoxy-7-(1-methyl-1,2,3,6-tetrahydropyridin-3-yloxy)-2-oxo-2H-chromen-3-yl)biphenyl-3-carboxamide (51b). Compound **51b** was obtained a light brown amorphous solid (68 mg, 30%). ¹H NMR (500 MHz, MeOD) δ 8.58 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.83 (s, 1H), 7.32–7.28 (m, 2H), 7.16–7.14 (m, 2H), 7.07–7.05 (m, 2H), 6.90 (m, 1H), 6.26–6.13 (m, 2H), 5.14 (m, 1H), 3.97 (s, 3H), 3.95–3.93 (m, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.80–3.73 (m, 2H), 3.61–3.58 (m, 1H), 3.02 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 165.5, 159.8, 159.3, 158.8, 152.2, 144.2, 138.6, 137.8, 131.0, 130.1, 130.0, 129.2, 128.2, 125.9, 124.2, 123.8, 122.4, 122.3, 122.0, 115.3, 115.1, 113.8, 113.1, 111.0, 72.9, 61.5, 56.4, 55.9, 55.3, 54.1, 45.5. IR (KBr) ν_{max} 3404, 2954, 2845, 1689, 1643, 1607, 1573, 1529, 1502, 1277, 1205, 1140, 1099, 1022 cm⁻¹. HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₃₁H₃₁N₂O₇, 543.2131; found 543.2126.

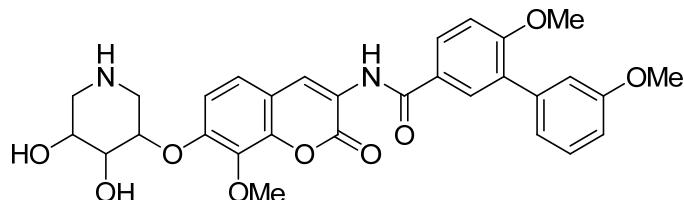


3',6-dimethoxy-N-(6-methoxy-8-methyl-7-(1-methyl-1,2,3,6-tetrahydropyridin-3-yloxy)-2-oxo-2H-chromen-3-yl)biphenyl-3-carboxamide (51c). Compound **51c** was obtained a light brown amorphous solid (59 mg, 21%). ¹H NMR (400 MHz, CDCl₃) δ 8.82 (s, 1H), 8.78 (s, 1H), 7.96–7.92 (m, 2H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.16–7.08 (m, 3H), 6.95 (dd, *J* = 8.0, 2.3 Hz, 2H), 6.87 (s, 1H), 6.00–5.97 (m, 2H), 4.78 (m, 1H), 3.92 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 3.09 (d, *J* = 7.0 Hz, 1H), 2.92 (d, *J* = 7.0 Hz, 1H), 2.77–2.70 (m, 2H), 2.44 (s, 3H), 2.41 (s, 3H). ¹³C NMR

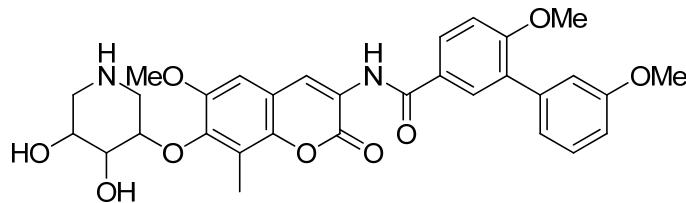
(100 MHz, CDCl₃) δ 165.6, 159.8, 159.4, 159.3, 150.3, 147.5, 143.5, 138.6, 131.1, 130.0, 129.7, 129.2, 128.2, 126.0, 125.3, 123.8, 123.0, 122.0, 121.0, 115.3 (2C), 113.1, 111.0, 106.4, 76.0, 57.1, 56.0, 55.9, 55.3, 54.4, 45.8, 9.6. IR (KBr) ν_{max} 3403, 3112, 3072, 2954, 2929, 2854, 1716, 1649, 1605, 1502, 1458, 1366, 1248, 1207, 1180, 1086 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₃₂H₃₃N₂O₇, 557.2288; found, 527.2300.



N-(7-(4,5-dihydroxypiperidin-3-yloxy)-8-methyl-2-oxochromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (52a). Compound **52a** was obtained as a colorless amorphorous solid (32 mg, 53%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.66 (s, 1H), 8.48 (s, 1H), 8.01 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.93 (d, *J* = 2.3, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.18 (d, *J* = 8.8, 1H), 7.13–7.10 (m, 2H), 6.97–6.95 (m, 1H), 4.96 (d, *J* = 5.2, 1H), 4.61 (d, *J* = 4.2, 1H), 4.45–4.41 (m, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.73 (bs, 1H), 3.68 (bs, 1H), 3.08–3.04 (m, 1H), 2.76–2.72 (m, 1H), 2.60–2.57 (m, 1H), 2.48–2.44 (m, 1H), 2.24 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 165.6, 159.6, 159.4, 158.8, 158.6, 150.1, 139.2, 130.4, 129.92, 129.85, 129.7, 129.6, 126.5, 126.3, 122.2, 121.5, 115.7, 113.9, 113.1, 113.0, 112.0, 111.3, 77.9, 72.1, 69.2, 56.4, 55.6, 49.5, 47.1, 8.6. IR (film) ν_{max} 3317 (broad), 2950, 2918, 2849, 1705, 1674, 1607, 1541, 1533, 1375, 1253, 1204, 1136, 1103 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₃₀H₃₁N₂O₈, 547.2080; found, 547.2083.

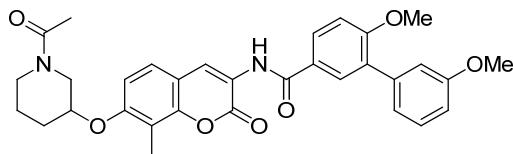


N-(7-(4,5-dihydroxypiperidin-3-yloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (52b). Compound **52b** was obtained as a colorless amorphorous solid (48 mg, 92%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 8.48 (s, 1H), 7.99 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.92 (d, *J* = 2.4 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.23 (t, *J* = 9.0 Hz, 1H), 7.12–7.09 (m 2H), 6.96–6.94 (m, 1H), 5.02 (s, 1H), 4.76 (s, 1H), 4.48–4.44 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.77 (s, 3H), 3.72 (m, 1H), 3.70–3.69 (m, 1H), 3.17–3.09 (m, 2H), 2.81–2.77 (m, 1H), 2.66–2.63 (m, 1H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 165.2, 159.2, 159.0, 157.9, 153.2, 144.5, 138.7, 136.0, 130.0, 129.4, 129.20, 129.16 (2C), 125.8, 122.8, 121.7, 121.6, 115.3, 113.7, 112.6, 112.5, 111.6, 77.5, 71.6, 68.7, 60.9, 55.9, 55.1, 48.9, 46.5. IR (KBr) *v*_{max} 3417 (broad), 2947, 2846, 1682, 1645, 1602, 1519, 1434, 1389, 1206, 1141 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₃₀H₃₁N₂O₉, 563.2030; found, 563.2029.

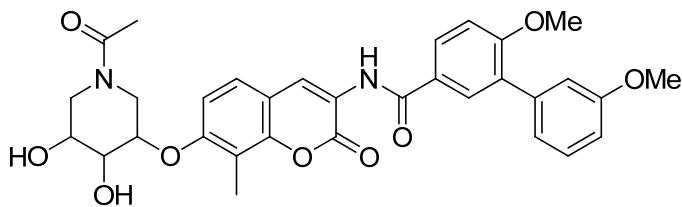


N-(7-(4,5-dihydroxypiperidin-3-yloxy)-6,8-dimethoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (52c). Compound **52c** was obtained as a colorless amorphous solid (42 mg, 59%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.65 (s, 1H), 8.53 (s, 1H), 7.99 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.92 (d, *J* = 2.4 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.28 (s, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.12–7.09 (m 2H), 6.96–6.94 (m, 1H), 4.16 (m, 1H), 3.87 (s, 6H), 3.80 (m, 1H), 3.76 (s, 3H), 3.75 (m, 1H), 3.04–3.01 (m, 1H), 2.78–2.74 (m, 1H), 2.70–2.65 (m, 2H), 2.32 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 165.1, 159.1, 158.9, 158.1, 149.3, 147.4, 143.6, 138.6, 130.0, 129.4, 129.1 (2C), 128.1, 125.7, 122.5, 121.7, 119.0, 115.2, 114.4, 112.5, 111.5, 107.3, 80.7, 71.5, 67.5, 56.1, 55.9, 55.1, 47.8, 45.9, 9.3. IR (KBr) *v*_{max} 3402 (broad), 2974, 2939,

2835, 1666, 1631, 1604, 1523, 1502, 1462, 1429, 1366, 1267, 1244, 1091, 1022 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₃₁H₃₃N₂O₉, 577.2186; found, 577.2180.

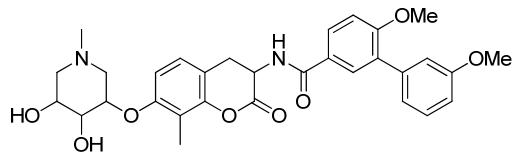


N-(7-(1-acetyl-4,5-dihydroxypiperidin-3-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6'-dimethoxybiphenyl-3-carboxamide (53a). Palladium on carbon (10%, 5 mg) was added to **50** (36 mg, 0.07 mmol) in anhydrous THF (3 mL) and the solution was placed under an atmosphere of H₂. After 12 h, the solution was filtered through SiO₂ (40:1, CH₂Cl₂:acetone) and the eluent was concentrated to afford **53a** as a colorless amorphous solid (32 mg, 89%). ¹H NMR (400 MHz, CDCl₃) δ 8.80 (s, 1H), 8.72 (s, 1H), 7.94-7.90 (m, 2H), 7.40-7.34 (m, 2H), 7.15-7.07 (m, 3H), 6.99-6.86 (m, 2H), 4.60-4.30 (m, 1H), 4.25-3.95 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.76-3.39 (m, 3H), 2.32-2.04 (3H), 1.98-1.82 (m, 3H), 1.70-1.50 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 169.5, 169.4, 165.5 (2C), 159.8, 159.7, 159.5, 159.4, 159.3, 156.7, 156.1, 149.5, 149.4, 138.6 (2C), 131.0, 130.0, 129.2, 128.2, 126.1, 126.0, 125.7, 124.3, 124.0, 122.0, 121.7, 115.4, 115.3, 115.2, 113.8, 113.7, 113.2, 113.1, 111.0, 110.5, 109.8, 72.0, 71.4, 55.9, 55.3, 50.3, 46.6, 45.5, 42.0, 30.0, 28.8, 23.3, 21.5, 21.4, 21.2, 8.3. IR (film) ν_{max} 3406, 2934, 2835, 1701, 1666, 1628, 1539, 1369, 1234, 1093, 1022 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₃₂H₃₂N₂O₇, 557.2288; found 557.2291.

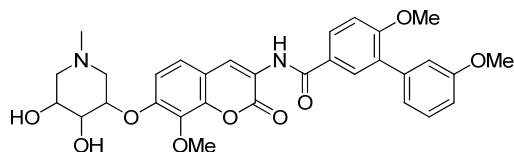


N-(7-(1-acetyl-4,5-dihydroxypiperidin-3-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6'-dimethoxybiphenyl-3-carboxamide (54a). Compound **54a** was obtained as a white

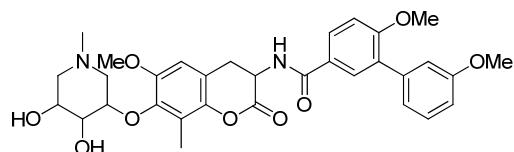
amorphorous solid (22 mg, 81%). ^1H NMR (400 MHz, CDCl_3) δ 8.71–8.67 (m, 2H), 7.92–7.87 (M, 2H), 7.37–7.36 (t, $J=8.0$, 1H), 7.31–7.25 (m, 1H), 7.25–7.04 (m, 3H), 6.95–6.92 (m, 1H), 4.66–3.97 (m, 4H), 3.90–3.85 (m, 6H), 3.79–2.82 (m, 3H), 2.26–2.01 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.6, 170.4, 165.7, 160.0, 159.5, 159.3, 157.1, 156.1, 149.4, 149.3, 138.8, 131.2, 130.2, 129.4, 128.4, 126.2, 126.0, 124.4, 123.9, 122.2, 121.9, 115.5, 115.1, 114.9, 114.3, 114.1, 113.3, 111.2, 110.6, 109.6, 74.6, 73.3, 69.5, 68.4, 65.9, 56.1, 55.5, 49.8, 45.9, 43.2, 43.1, 21.6, 21.5, 8.5, 8.4. IR (film) ν_{max} 3400, 3365 (broad), 2931, 2839, 1712, 1628, 1607, 1526, 1502, 1369, 1267, 1244, 1105, 1034 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for $\text{C}_{32}\text{H}_{32}\text{N}_2\text{O}_9\text{Na}$, 611.2005; found, 611.2011.



N-(7-(4,5-dihydroxy-1-methylpiperidin-3-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (55a). Compound **55a** was obtained as light brown amorphorous solid (27 mg, 60%). ^1H NMR (400 MHz, CDCl_3) δ 8.79 (s, 1H), 8.72 (s, 1H), 7.95–7.92 (m, 2H), 7.41–7.33 (m, 2H), 7.16–7.05 (m, 4H), 6.97–6.95 (m, 1H), 4.61 (m, 1H), 4.10 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.78–3.76 (m, 1H), 3.11–2.99 (m, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 2.12–2.08 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.4, 159.3, 157.4, 149.3, 138.6, 131.0, 130.0, 129.2, 128.2, 126.0, 125.7, 124.2, 122.0, 121.9, 115.5, 115.3, 114.0, 113.2, 111.2, 111.0, 73.5, 68.6, 59.1, 57.0, 55.9, 55.3, 45.5, 8.4. IR (film) ν_{max} 3402, 2927, 2852, 1707, 1653, 1605, 1526, 1502, 1369, 1267, 1242, 1207, 1107 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{31}\text{H}_{33}\text{N}_2\text{O}_8$, 561.2237; found, 561.2239.

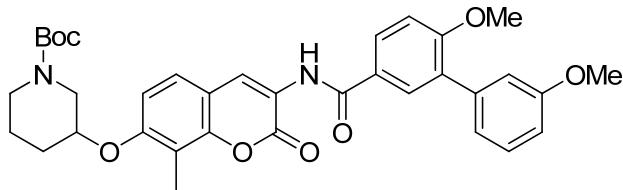


N-(7-(4,5-dihydroxy-1-methylpiperidin-3-yloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (55b). Compound **55b** was obtained as a light brown amorphorous solid (9.8 mg, 39%). ^1H NMR (500 MHz, CDCl_3) δ 8.82 (s, 1H), 8.74 (s, 1H), 7.95–7.91 (m, 2H), 7.39 (t, J = 8.7 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 7.15–7.08 (m, 3H), 6.96 (dd, J = 8.7, 2.2 Hz, 1H), 4.48 (m, 1H), 4.10 (m, 1H), 4.06 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 3.79–3.78 (m, 1H), 3.16–3.14 (m, 1H), 3.02–2.99 (m, 1H), 2.37 (s, 3H), 2.33 (t, J = 12.2 Hz, 1H), 2.18 (t, J = 12.2 Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.5, 159.9, 159.4, 158.7, 152.6, 145.2, 144.1, 138.6, 138.0, 131.1, 130.0, 129.2, 128.2, 125.9, 123.6, 122.7, 122.0, 115.9, 115.3, 115.0, 113.2, 111.1, 79.3, 76.1, 68.6, 62.0, 59.0, 57.4, 55.9, 55.3, 45.5. IR (KBr) ν_{max} 3410 (broad), 2927, 2870, 2835, 1710, 1664, 1603, 1524, 1502, 1460, 1366, 1275, 1244, 1086 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{31}\text{H}_{33}\text{N}_2\text{O}_9$, 577.2186; found, 577.2180.

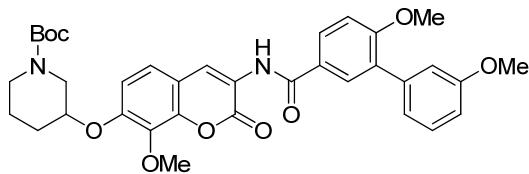


N-(7-(4,5-dihydroxy-1-methylpiperidin-3-yloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (55c). Compound **55c** was obtained as light brown amorphous solid (38 mg, 61%). ^1H NMR (400 MHz, CDCl_3) δ 8.81 (s, 1H), 8.78 (s, 1H), 7.95–7.92 (m, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.16–7.08 (m, 3H), 6.96 (dd, J = 8.0, 2.1 Hz, 1H), 6.89 (s, 1H), 4.40 (m, 1H), 4.08 (m, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 3.79 (m, 1H), 2.97 (m, 2H), 2.41 (s, 3H), 2.33 (s, 3H), 2.25–2.16 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.6, 159.9, 159.34, 159.25, 149.3, 146.7, 143.4, 138.6, 131.1, 130.0, 129.2, 128.2, 126.0,

123.5, 123.3, 122.0, 120.8, 115.7, 115.3, 113.1, 111.0, 106.4, 80.7, 77.2, 68.4, 58.7, 58.0, 56.1, 55.9, 55.3, 45.7, 9.6. IR (KBr) ν_{max} 3405 (broad), 2959, 2930, 2854, 1682, 1647, 1605, 1439, 1385, 1207, 1138, 1022 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₃₂H₃₅N₂O₉, 591.2342; found, 591.2326.

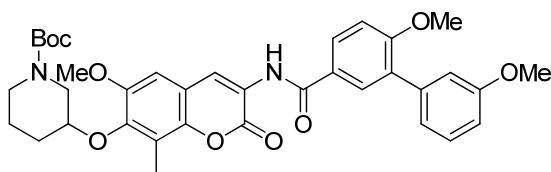


Tert-butyl 3-(3-(3',6-dimethoxybiphenyl-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yloxy)piperidine-1-carboxylate (56a). Compound **56a** was obtained as a light brown amorphorous solid (643 mg, 67%). ¹H NMR (400 MHz, CDCl₃) δ 8.82 (s, 1H), 8.69 (s, 1H), 7.95–7.91 (m, 2H), 7.41–7.35 (m, 2H), 7.16–7.08 (m, 3H), 6.97–6.94 (m, 2H), 4.42 (m, 1H), 3.892 (s, 3H), 3.88 (s, 3H), 3.74–3.40 (m, 4H), 2.33 (s, 3H), 2.07–1.92 (m, 3H), 1.62–1.58 (m, 1H), 1.48 (bs, 3H), 1.28 (bs, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 165.5, 159.8, 159.5, 159.3, 156.8, 154.7, 149.4, 138.6, 131.0, 130.0, 129.2, 128.2, 126.1, 125.6, 124.3, 122.0, 121.7, 115.2, 115.0, 113.6, 113.2, 111.0, 109.9, 79.8, 77.3, 71.5, 55.9, 55.3, 47.3, 29.9, 28.3, 21.7, 8.3. IR (film) ν_{max} 3403, 2980, 2937, 1707, 1653, 1676, 1605, 1524, 1502, 1464, 1367, 1242, 1178, 1109, 1041 cm⁻¹. HRMS (ESI⁺) m/z: [M + Na⁺] calcd for C₃₅H₃₈N₂O₈Na, 637.2526; found, 637.2524.

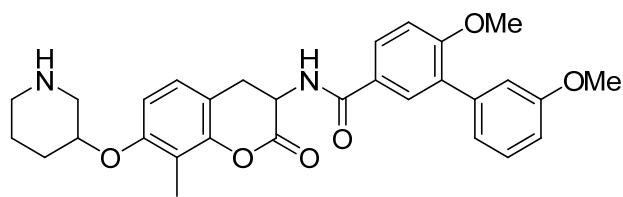


Tert-butyl 3-(3-(3',6-dimethoxybiphenyl-3-ylcarboxamido)-8-methoxy-2-oxo-2H-chromen-7-yloxy)piperidine-1-carboxylate (56b). Compound **56b** was obtained as a light

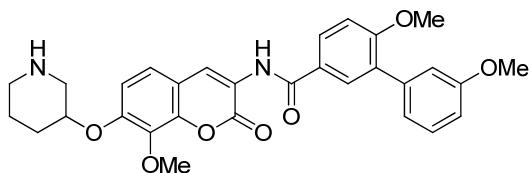
brown amorphorous solid (174 mg, 82%). ^1H NMR (400 MHz, CDCl_3) δ 8.79 (s, 1H), 8.72 (s, 1H), 7.92–7.89 (m, 2H), 7.36 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.13–6.99 (m, 3H), 6.97–6.91 (m, 2H), 4.38 (m, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.85–3.39 (m, 4H), 2.05 (m, 1H), 1.88 (m, 2H), 1.56 (m, 1H), 1.41 (bs, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.3, 158.9, 154.7, 151.7, 144.2, 138.6, 137.4, 131.0, 130.0, 129.2, 128.2, 125.9, 123.8, 122.3, 122.0, 115.2, 114.9, 113.1, 113.0, 112.8, 111.0, 79.8, 72.9, 61.5, 55.9, 55.3, 47.7, 43.8, 30.9, 29.9, 28.4. IR (KBr) ν_{max} 3407, 2943, 2837, 1676, 1630, 1605, 1521, 1431, 1205, 1136 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{35}\text{H}_{39}\text{N}_2\text{O}_9$, 631.2656; found 631.2661.



Tert-butyl 3-(3'-(3,6-dimethoxybiphenyl-3-yl)carboxamido)-6-methoxy-8-methyl-2-oxo-2H-chromen-7-yloxy)piperidine-1-carboxylate (56c). Compound **56c** was obtained as a light brown amorphous solid (135 mg, 95%). ^1H NMR (400 MHz, CDCl_3) δ 8.78 (s, 1H), 8.76 (s, 1H), 7.93–7.91 (m, 2H), 7.37 (t, J = 8.0 Hz, 1H), 7.14–7.06 (m, 3H), 6.94 (m, 1H), 6.85 (s, 1H), 4.32 (m, 1H), 3.94 (s, 6H), 3.86 (s, 3H), 3.82–3.59 (m, 2H), 3.21 (m, 2H), 2.38 (s, 3H), 2.06–1.77 (m, 3H), 1.51–1.48 (m, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.3, 154.8, 150.1, 146.5, 143.5, 138.6, 131.0, 130.0, 129.2, 128.2, 126.1, 123.7, 123.0, 122.9, 122.0, 120.6, 115.3, 115.2, 113.1, 111.0, 106.5, 79.6, 76.4, 56.0, 55.9, 55.3, 30.9, 30.6, 29.3, 28.4, 21.7, 9.4. IR (KBr) ν_{max} 3402, 3333, 2976, 2931, 2868, 1713, 1680, 1632, 1604, 1529, 1425, 13666, 1232, 1201, 1167, 1095 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for $\text{C}_{36}\text{H}_{40}\text{N}_2\text{O}_9\text{Na}$, 667.2632; found, 667.2629.

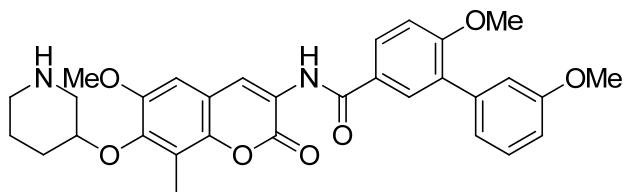


3',6-dimethoxy-N-(8-methyl-2-oxo-7-(piperidin-3-yloxy)-2H-chromen-3-yl)biphenyl-3-carboxamide (57a). Compound **57a** was obtained as white amorphous solid (23 mg, 79%). ¹H NMR (400 MHz, CDCl₃) δ 8.68 (s, 1H), 8.64 (s, 1H), 7.86–7.84 (m, 2H), 7.33–7.30 (m, 2H), 7.09–6.88 (m, 5H), 4.50 (bs, 1H), 4.06–3.90 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.63–3.50 (m, 4H), 2.20 (s, 3H), 1.41 (bs, 3H), 1.22 (bs, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 165.5, 159.9, 159.4, 159.3, 155.6, 149.3, 138.7, 131.0, 130.1, 129.3, 128.3, 126.0, 125.8, 123.8, 122.3, 122.2, 115.6, 115.4, 114.4, 113.2, 111.1, 110.3, 69.3, 56.0, 55.4, 46.8, 43.8, 28.0, 19.5, 8.7. IR (film) ν_{max} 3404, 2939, 2837, 1709, 1670, 1607, 1526, 1502, 1369, 1269, 1242, 1103, 1031 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₃₀H₃₁N₂O₆, 515.2182; found, 515.2186.

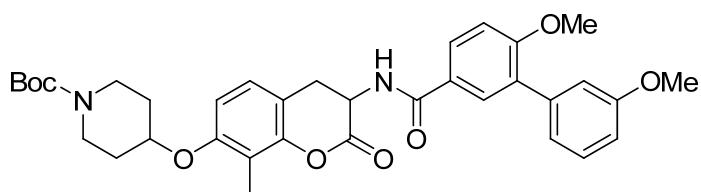


3',6-dimethoxy-N-(8-methoxy-2-oxo-7-(piperidin-3-yloxy)-2H-chromen-3-yl)biphenyl-3-carboxamide (57b). Compound **57b** was obtained as white amorphous solid (93 mg, 84%). ¹H NMR (400 MHz, MeOD) δ 8.37 (s, 1H), 7.69–7.66 (m, 2H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.96–6.82 (m, 4H), 6.82 (dd, *J* = 8.2 Hz, 2.3, 1H), 4.66 (m, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.42–3.37 (m, 2H), 3.23–3.19 (m, 2H), 2.15–2.10 (m, 2H), 2.02–1.98 (m, 2H). ¹³C NMR (100 MHz, MeOD) δ 164.5, 158.4, 158.0, 156.8, 149.3, 142.8, 137.3, 136.3, 129.0, 128.5, 127.3, 126.8, 124.1, 123.2, 121.4, 121.0, 120.3, 114.5, 113.8, 113.0, 111.0, 109.6, 69.9, 59.6, 53.6, 53.1, 45.1, 42.3, 24.8, 16.6. IR (KBr) ν_{max} 3400, 2980, 2948, 2843, 1693, 1634,

1607, 1571, 1531, 1504, 1371, 1207, 1140, 1101 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₃₀H₃₁N₂O₇, 531.2131; found, 531.2129.

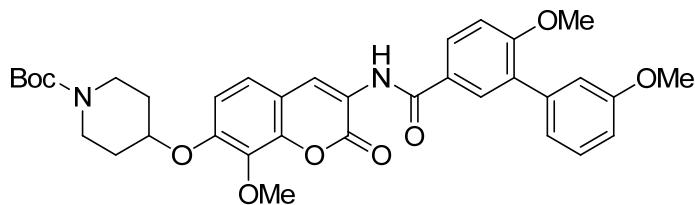


3',6-dimethoxy-N-(6-methoxy-8-methyl-2-oxo-7-(piperidin-3-yloxy)-2H-chromen-3-yl)-[1,1'-biphenyl]-3-carboxamide (57c). Compound **57c** was obtained as white amorphous solid (83 mg, 73%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.65 (s, 1H), 8.56 (s, 1H), 8.99 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.92 (s, 1H), 7.39–7.33 (m, 2H), 7.25 (d, *J* = 9.1 Hz, 1H), 7.12–7.10 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 4.36 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.36–3.10 (m, 4H), 2.31 (s, 3H), 2.01–1.68 (m, 4H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 165.6, 159.6, 159.4, 158.5, 149.8, 146.4, 143.8, 139.1, 130.5, 129.9, 129.6, 127.9, 126.1, 123.5, 122.2, 119.7, 118.8, 115.7, 115.68, 113.0, 112.0, 108.0, 75.0, 56.6, 56.4, 55.6, 46.9, 43.4, 28.2, 19.5, 9.7. IR (KBr) ν_{max} 3398, 2976, 2867, 1677, 1642, 1460, 1535, 1502, 1205, 1142 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₃₁H₃₃N₂O₇, 545.2288; found, 545.2282.

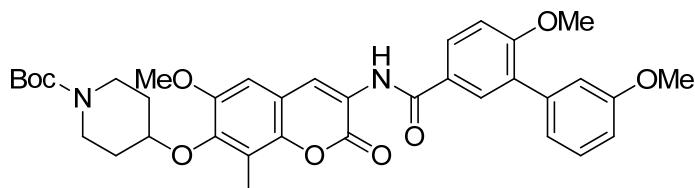


Tert-butyl 4-(3',6-dimethoxybiphenyl-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yloxy)piperidine-1-carboxylate (58a). Compound **58a** was obtained a light brown amorphorous solid (220 mg, 72%). ¹H NMR (400 MHz, CDCl₃) δ (CDCl₃) 8.77 (s, 1H), 8.70 (s, 1H), 7.91–7.89 (m, 2H), 7.38–7.28 (m, 2H), 7.14–7.04 (m, 3H), 6.94–6.86 (m, 2H), 4.60 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.67–3.63 (m, 2H), 3.47–3.46 (m, 2H), 2.33 (s, 3H), 1.93–1.81

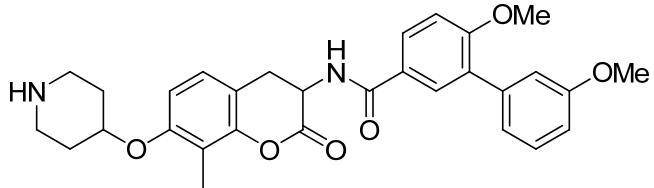
(m, 4H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.5, 159.4, 156.7, 154.9, 149.5, 138.7, 131.0, 130.0, 129.2, 128.2, 126.1, 125.7, 124.2, 122.1, 121.8, 115.33, 115.29, 113.6, 113.2, 111.1, 110.5, 79.8, 72.8, 56.0, 55.4, 30.6, 28.5, 22.0, 21.8, 8.4. IR (film) ν_{max} 3400, 2980, 2864, 1717, 1699, 1683, 1635, 1558, 1521, 1386, 1244, 1105 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for $\text{C}_{35}\text{H}_{38}\text{N}_2\text{O}_8\text{Na}$, 637.2526; found, 637.2523.



Tert-butyl 4-(3'-(3',6-dimethoxybiphenyl-3-ylcarboxamido)-8-methoxy-2-oxochromen-7-yloxy)piperidine-1-carboxylate (58b). Compound **58b** was obtained as a light brown amorphorous solid (156 mg, 85%). ^1H NMR (500 MHz, CDCl_3) δ 8.81 (s, 1H), 8.73 (s, 1H), 7.93–7.90 (m, 2H), 7.37 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 8.7 Hz, 1H), 7.14–7.07 (m, 3H), 6.96–6.93 (m, 2H), 4.61–4.58 (m, 1H), 4.01 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.77–3.72 (m, 2H), 3.42 (m, 2H), 2.00–1.96 (m, 2H), 1.85–1.82 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.3, 158.8, 154.8, 151.7, 144.3, 138.6, 137.8, 131.0, 130.0, 129.2, 128.2, 125.9, 123.7, 122.4, 122.3, 122.0, 115.3, 115.1, 113.6, 113.1, 111.0, 79.7, 74.5, 61.5, 55.9, 55.3, 53.5, 30.7, 28.4, 21.7. IR (KBr) ν_{max} 3404, 2978, 2935, 1701, 1637, 1605, 1521, 1431, 1389, 1373, 1232, 1207, 1180, 1086 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{35}\text{H}_{39}\text{N}_2\text{O}_9$, 631.2656; found, 631.2652.

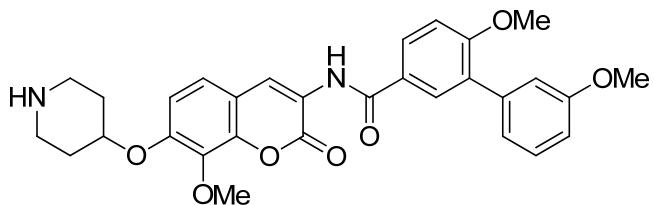


Tert-butyl 4-(3-(3',6-dimethoxybiphenyl-3-ylcarboxamido)-6-methoxy-8-methyl-2-oxochromen-7-yloxy)piperidine-1-carboxylate (58c). Compound **58c** was obtained as a light brown amorphorous solid (120 mg, 69%). ^1H NMR (400 MHz, CDCl_3) δ 8.76 (s, 1H), 8.75 (s, 1H), 7.92–7.89 (m, 2H), 7.36 (t, J = 8.0 Hz, 1H), 7.13–7.04 (m, 3H), 6.94–6.91 (m, 1H), 6.83 (s, 1H), 4.37–4.33 (m, 1H), 3.88 (s, 6H), 3.86 (s, 3H), 3.90–3.86 (m, 2H), 3.11–3.06 (m, 2H), 2.37 (s, 3H), 1.90 (m, 2H), 1.75–1.71 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.32, 159.28, 154.8, 150.3, 146.7, 143.4, 138.6, 131.0, 130.0, 129.2, 128.2, 126.0, 123.6, 123.0, 122.0, 120.6, 115.28, 115.23, 113.1, 111.0, 106.5, 79.6, 78.6, 56.0, 55.9, 55.3, 31.7 (2C), 28.5, 21.7 (2C), 9.7. IR (KBr) ν_{max} 3404, 2939, 2860, 1697, 1674, 1636, 1605, 1522, 1500, 1382, 1242, 1207, 1176, 1026 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{36}\text{H}_{41}\text{N}_2\text{O}_9$, 645.2812; found, 645.2810.

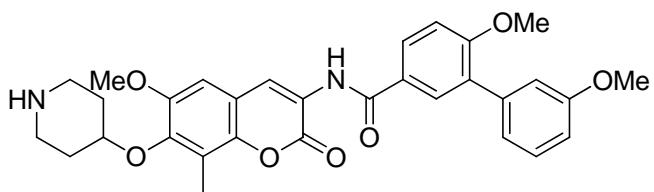


3',6-dimethoxy-N-(8-methyl-2-oxo-7-(piperidin-4-yloxy)-2H-chromen-3-yl)biphenyl-3-carboxamide (59a). Compound **59a** was obtained as a white amorphous solid (41 mg, 68%). ^1H NMR (400 MHz, CDCl_3) δ (CDCl₃) 8.82 (s, 1H), 8.73 (s, 1H), 7.95–7.91 (m, 2H), 7.41–7.35 (m, 2H), 7.15–7.08 (m, 3H), 6.95 (d, J = 4.0 Hz, 1H), 6.88 (d, J = 4.8 Hz, 1H), 4.66 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.27 (m, 2H), 3.04 (m, 2H), 2.38 (s, 3H), 2.19–2.16 (m, 2H), 1.99 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ (CDCl₃) 165.7, 160.0, 159.6, 159.5, 156.5, 149.6, 138.8, 131.2, 130.2, 129.4, 128.4, 126.2, 125.8, 124.3, 122.2, 122.1, 115.5, 115.4, 113.9, 113.3, 111.2, 110.5, 71.5, 56.1, 55.5, 42.0 (2C), 29.8 (2C), 8.6. IR (film) ν_{max} 3400, 2933, 2833, 1699, 1668, 1601,

1522, 1499, 1366, 1236, 1204, 1134, 1101, 1028 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₃₀H₃₁N₂O₆, 515.2182; found, 515.2189.

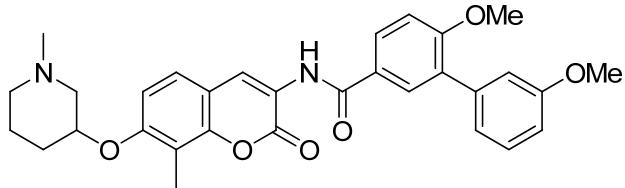


3',6-dimethoxy-N-(8-methoxy-2-oxo-7-(piperidin-4-yloxy)chromen-3-yl)biphenyl-3-carboxamide (59b). Compound **59b** was obtained as a white amorphorous solid (145 mg, 93%).
¹H NMR (500 MHz, CDCl₃) δ 8.37 (s, 1H), 7.69–7.66 (m, 2H), 7.21 (t, J = 8.5 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.96–6.92 (m, 4H), 6.82–6.80 (m, 1H), 4.66 (m, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.42–3.37 (m, 2H), 3.23–3.19 (m, 2H), 2.15–2.10 (m, 2H), 2.02–1.98 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 167.1, 161.2, 160.8, 159.7, 152.4, 145.6, 140.1, 138.8, 131.7, 131.3, 130.1, 129.5, 126.8, 126.1, 124.1, 123.5, 123.1, 116.6, 116.5, 114.8, 113.8, 112.3, 72.1, 62.1, 56.4, 55.9, 41.8, 28.5. IR (KBr) ν_{max} 3414, 2966, 2927, 1680, 1632, 1610, 1410, 1371, 1277, 1205, 1142 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₃₀H₃₁N₂O₇, 531.2131; found, 531.2120.



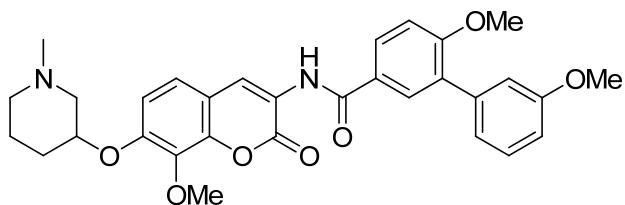
3',6-dimethoxy-N-(6-methoxy-8-methyl-2-oxo-7-(piperidin-4-yloxy)-2H-chromen-3-yl)-[1,1'-biphenyl]-3-carboxamide (59c). Compound **59c** was obtained as a white amorphous solid (74 mg, 88%). ¹H NMR (400 MHz, CDCl₃) δ (DMSO-*d*₆) 9.66 (s, 1H), 8.54 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.31 (s, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.12–7.10 (m, 2H), 6.96 (d, J = 8.0 Hz, 1H), 4.38 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.80 (s,

3H), 3.31 (m, 2H), 3.06 (m, 2H), 2.28 (s, 3H), 2.04 (m, 2H), 1.89 (m, 2H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 165.6, 159.6, 159.4, 158.2, 150.1, 146.5, 143.9, 139.1, 130.5, 129.9, 129.6, 128.3, 126.1, 123.3, 122.2, 119.7, 119.0, 115.7, 115.4, 113.0, 112.0, 107.9, 75.6, 56.6, 56.4, 49.0, 41.3, 28.7, 9.7. IR (KBr) ν_{max} 3400, 2970, 2849, 1678, 1632, 1605, 1433, 1385, 1205, 1138, 1026 cm⁻¹. HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₃₁H₃₃N₂O₇, 545.2288; found, 545.2288.

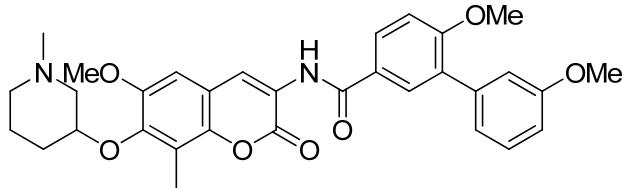


3',6-dimethoxy-N-(8-methyl-7-(1-methylpiperidin-3-yloxy)-2-oxo-2H-chromen-3-yl)biphenyl-3-carboxamide (60a).

Compound **60a** was obtained as a light brown amorphous solid (35 mg, 41%). ^1H NMR (400 MHz, CDCl₃) δ 8.82 (s, 1H), 8.72 (s, 1H), 7.96–7.91 (m, 2H), 7.41–7.34 (m, 2H), 7.15–7.08 (m, 3H), 6.98–6.94 (m, 2H), 4.47 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.09–3.07 (m, 1H), 2.76–2.74 (m, 1H), 2.36 (s, 3H), 2.34 (s, 3H), 2.20–2.07 (m, 2H), 1.90–1.86 (m, 1H), 1.72–1.64 (m, 2H), 1.54–1.50 (m, 1H). ^{13}C NMR (100 MHz, CDCl₃) δ 165.4, 159.8, 159.5, 159.3, 157.3, 149.4, 138.6, 131.0, 130.0, 129.2, 128.1, 126.1, 125.6, 124.3, 122.0, 121.6, 115.3, 115.2, 113.5, 113.1, 111.0, 110.9, 74.2, 59.9, 55.9, 55.4, 55.3, 46.3, 29.8, 23.3, 8.4. IR (film) ν_{max} 3406, 2939, 2839, 1705, 1674, 1605, 1526, 1502, 1367, 1269, 1242, 1205, 1182, 1138, 1105, 1036 cm⁻¹. HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₃₁H₃₃N₂O₆, 529.2339; found, 529.2335.



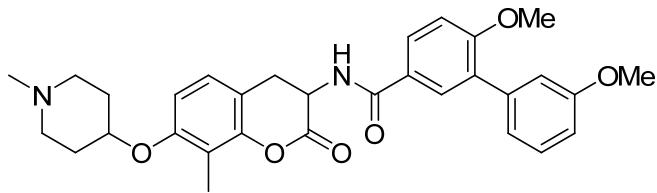
3',6-dimethoxy-N-(8-methoxy-7-(1-methylpiperidin-3-yloxy)-2-oxo-2H-chromen-3-yl)biphenyl-3-carboxamide (60b). Compound **60b** was obtained a light brown amorphorous solid (16 mg, 52%). ^1H NMR (400 MHz, CDCl_3) δ 8.81 (s, 1H), 8.72 (s, 1H), 7.94–7.90 (m, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 7.15–7.07 (m, 3H), 6.98 (d, J = 8.7 Hz, 1H), 6.95 (dd, J = 8.0, 2.4 Hz, 1H), 4.48 (m, 1H), 4.01 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.06 (d, J = 10.0 Hz, 1H), 2.71 (d, J = 10.0 Hz, 1H), 2.34 (s, 3H), 2.10 (t, J = 9.7 Hz, 1H), 2.13–2.06 (m, 2H), 1.89–1.69 (m, 1H), 1.69–1.66 (m, 1H), 1.55–1.52 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.3, 158.9, 152.1, 144.2, 138.6, 137.6, 131.1, 130.0, 129.2, 128.2, 126.0, 123.9, 122.4, 122.2, 122.0, 115.3, 114.8, 113.3, 113.2, 111.0, 74.9, 61.5, 59.8, 55.9, 55.3 (2C), 46.3, 29.6, 23.2. IR (KBr) ν_{max} 3407, 2939, 2870, 2850, 1711, 1673, 1605, 1529, 1367, 1244, 1278, 1090 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{31}\text{H}_{33}\text{N}_2\text{O}_7$, 545.2288; found, 545.2298.



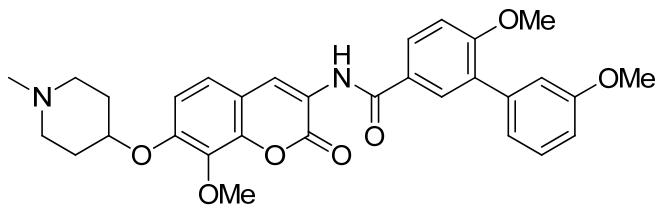
3',6-dimethoxy-N-(6-methoxy-8-methyl-7-(1-methylpiperidin-3-yloxy)-2-oxo-2H-chromen-3-yl)biphenyl-3-carboxamide (60c). Compound **60c** was obtained a light brown amorphous solid (47 mg, 60 %). ^1H NMR (400 MHz, CDCl_3) δ 8.81 (s, 1H), 8.77 (s, 1H), 7.95–7.91 (m, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.15–7.08 (m, 3H), 6.95 (dd, J = 8.0, 2.4 Hz, 1H), 6.85 (s, 1H), 4.35 (m, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.00 (d, J = 8.0 hz, 1H), 2.69 (d, J = 8.0 Hz, 1H), 2.41 (s, 3H), 2.34 (s, 3H), 2.24 (t, J = 8.0 Hz, 1H), 2.09–2.01 (m, 3H), 1.88–1.85 (m, 1H), 1.63–1.49 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.4, 159.3, 150.4, 147.0, 143.4, 138.6, 131.1, 130.0, 129.2, 128.2, 126.1, 123.8, 122.9, 122.0, 120.8, 115.3, 115.2, 113.1, 111.0, 106.3, 78.2, 60.5, 56.0, 55.9, 55.4, 55.3, 46.4, 30.3, 23.4, 9.6. IR (KBr) ν_{max}

3408, 2978, 2934, 2874, 2858, 1713, 1633, 1603, 1520, 1467, 1373, 1288, 1226, 1203, 1105 cm⁻¹.

¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₃₂H₃₅N₂O₇, 559.2444; found, 559.2446.

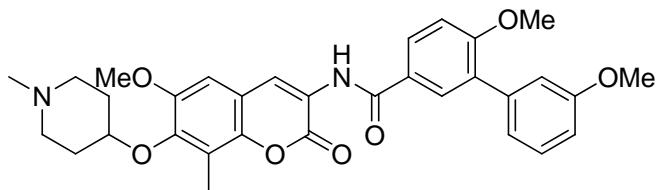


3',6-dimethoxy-N-(8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)biphenyl-3-carboxamide (61a). Compound **61a** was obtained a light brown amorphorous solid (56 mg, 46 %). ¹H NMR (400 MHz, CDCl₃) δ 8.76 (s, 1H), 8.67 (s, 1H), 7.92–7.86 (m, 2H), 7.36–7.33 (m, 2H), 7.11–7.08 (m, 3H), 6.93–6.89 (m, 2H), 4.54 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 2.80–2.76 (m, 2H), 2.57 (m, 2H), 2.41 (s, 3H), 2.33 (s, 3H), 2.19–2.12 (m, 2H), 1.97–1.95 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 165.1, 159.7, 159.4, 159.3, 157.0, 149.4, 138.9, 130.8, 130.8, 129.8, 128.1, 126.1, 125.5, 123.9, 121.9, 121.7, 115.3, 115.0, 113.2, 112.8, 111.0, 110.5, 73.1, 55.8, 55.3, 52.5, 46.0 (2C), 30.9 (2C), 8.1. IR (film) ν_{max} 3406, 2939, 2839, 1705, 1674, 1605, 1526, 1502, 1367, 1242, 1205, 1182, 1138, 1105, 1036 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₃₁H₃₃N₂O₆, 529.2339; found, 529.2334.

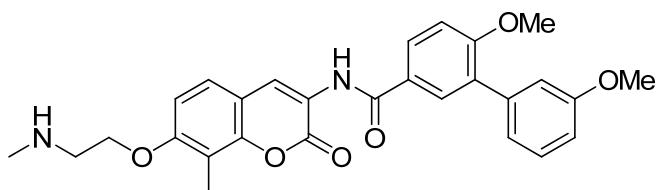


3',6-dimethoxy-N-(8-methoxy-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-[1,1'-biphenyl]-3-carboxamide (61b). Compound **61b** was obtained a light brown amorphous solid (47 mg, 66 %). ¹H NMR (400 MHz, CDCl₃) δ 8.82 (s, 1H), 8.74 (s, 1H), 7.94–7.88 (m, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.14–7.08 (m, 3H), 6.98–6.94 (m, 2H), 4.78 (m, 1H), 4.03 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 3.56–3.53 (m, 2H), 3.35–3.30 (m, 2H), 2.92

(s, 3H), 2.38–2.20 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.9, 160.0, 159.3, 158.5, 150.4, 144.3, 138.5, 138.2, 131.1, 130.0, 129.2, 128.3, 125.6, 123.7, 123.1, 122.8, 122.0, 116.2, 115.3, 114.3, 113.1, 111.1, 68.8, 61.8, 55.9, 55.3, 49.9 (2C), 44.1, 27.2 (2C). IR (KBr) ν_{max} 406, 2941, 2928, 2853, 1713, 1666, 1605, 1526, 1502, 1462, 1367, 1277, 1244, 1207, 1086, 1045 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{31}\text{H}_{33}\text{N}_2\text{O}_7$, 545.2288; found, 545.2281.

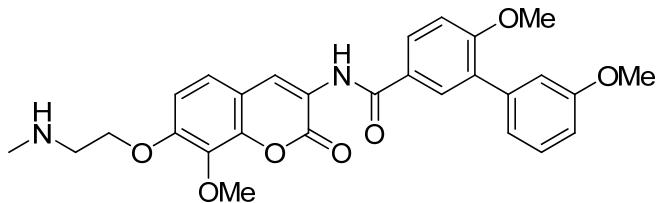


3',6-dimethoxy-N-(6-methoxy-8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-[1,1'-biphenyl]-3-carboxamide (61c). Compound **61c** was obtained a light brown amorphorous solid (43 mg, 74%). ^1H NMR (400 MHz, CDCl_3) δ 8.80 (s, 1H), 8.77 (s, 1H), 7.95–7.91 (m, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.15–7.08 (m, 3H), 6.95 (dd, J = 8.0, 2.4 Hz, 1H), 6.86 (s, 1H), 4.30 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 2.97 (m, 2H), 2.52–2.46 (m, 5H), 2.40 (s, 3H), 2.11 (m, 2H), 2.00 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.6, 159.8, 159.33, 159.31, 150.2, 146.8, 143.5, 138.6, 131.1, 130.0, 129.2, 128.2, 126.0, 123.6, 123.1, 122.0, 120.6, 115.34, 115.28, 113.1, 111.0, 106.5, 77.3, 56.0, 55.9, 55.3, 52.4 (2C), 45.3, 30.8 (2C), 9.7. IR (KBr) ν_{max} 3404, 2937, 2841, 1718, 1649, 1602, 1577, 1477, 1465, 1371, 1249, 1207, 1180, 1138, 1083 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{32}\text{H}_{35}\text{N}_2\text{O}_7$, 559.2444; found, 559.2448.



3',6-dimethoxy-N-(8-methyl-7-(2-(methylamino)ethoxy)-2-oxo-2H-chromen-3-yl)biphenyl-3-carboxamide (64a).

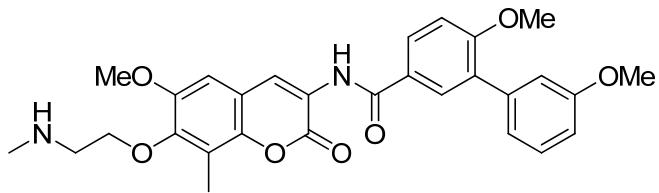
Compound **64a** was obtained after acidic deprotection of **63a** as a light brown amorphous solid (174 mg, 65% over 2 steps). ¹H NMR (400 MHz, CD₃OD) δ 8.61 (s, 1H), 7.93 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.87 (d, *J* = 2.2 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.32 (t, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 7.09–7.05 (m, 3H), 6.91 (dd, *J* = 8.2, 1.5 Hz, 1H), 4.38 (t, *J* = 8.0 Hz, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 3.53 (t, *J* = 8.0 Hz, 2H), 2.85 (s, 3H), 2.35 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 165.3, 159.3, 159.1, 158.4, 157.7, 149.7, 138.8, 130.1, 129.6, 129.5, 129.3, 126.4, 125.9, 121.9, 121.5, 118.8, 115.8, 115.4, 113.2, 113.0, 111.7, 109.2, 65.3, 56.0, 55.2, 48.0, 33.7, 8.1. IR (KBr) *v*_{max} 3433 (broad), 2924, 2851, 1691, 1652, 1601, 1462, 1382, 1209, 1145, 1020 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₂₈H₂₉N₂O₆, 489.2026; found, 489.2020.



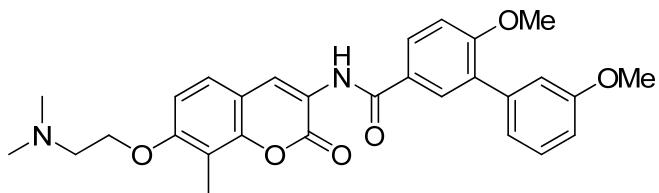
3',6-dimethoxy-N-(8-methoxy-7-(2-(methylamino)ethoxy)-2-oxo-2H-chromen-3-yl)biphenyl-3-carboxamide (64b).

Compound **64b** was obtained after acidic deprotection of **63b** as a light yellow amorphous solid (112 mg, 89% over 2 steps). ¹H NMR (400 MHz, CD₃OD) δ 8.59 (s, 1H), 7.90 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.85 (d, *J* = 2.4 Hz, 1H), 7.32–7.29 (m, 2H), 7.16 (d, *J* = 8.6 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 7.07–7.06 (m, 2H), 6.91–6.89 (m, 1H), 4.40 (t, *J* = 4.9 Hz, 2H), 3.98 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.52 (t, *J* = 4.9 Hz, 2H), 2.85 (s, 3H). ¹³C NMR (100 MHz, CD₃OD) δ 168.0, 161.5, 161.0, 159.9, 153.7, 145.8, 140.3, 138.0, 132.2, 131.4, 130.2, 129.8, 127.2, 127.0, 124.4, 123.9, 123.1, 117.0, 116.5, 113.9, 113.1, 112.5, 66.7, 62.4, 56.5, 55.9, 49.6, 34.2. IR (KBr) *v*_{max} 3402 (broad), 2926, 2851, 1702, 1678, 1601, 1479, 1383,

1248, 1209, 1146, 1099, 1020 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₂₈H₂₉N₂O₇, 505.1975; found, 505.1977.

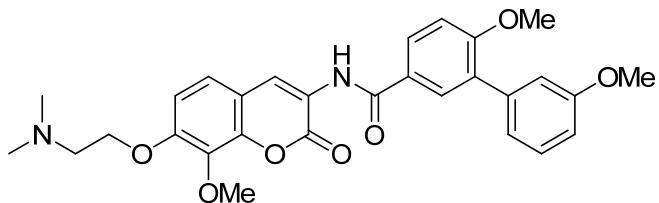


3',6-dimethoxy-N-(6-methoxy-8-methyl-7-(2-(methylamino)ethoxy)-2-oxo-2H-chromen-3-yl)biphenyl-3-carboxamide (64c). Compound **64c** was obtained after acidic deprotection of **63c** as a light yellow amorphous solid (59 mg, 47% over 2 steps). ^1H NMR (400 MHz, CD₃OD) δ 8.53 (s, 1H), 7.84–7.79 (m, 2H), 6.98 (t, J = 8.0 Hz, 1H), 6.78–6.74 (m, 3H), 6.59 (s, 1H), 6.58 (dd, J = 8.0, 1.5 Hz, 1H), 3.89 (t, J = 4.5 Hz, 2H), 3.56 (s, 3H), 3.11 (t, J = 4.5 Hz, 2H), 3.05 (s, 3H), 3.01 (s, 3H), 2.53 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (100 MHz, CD₃OD) δ 170.0, 163.8, 163.3, 162.7, 153.7, 150.4, 147.0, 142.6, 134.4, 133.7, 132.6, 132.1, 129.4, 128.6, 127.0, 125.5, 123.7, 120.0, 119.0, 116.2, 114.8, 110.6, 71.3, 59.1, 58.8, 58.3, 52.8, 36.3, 11.4. IR (KBr) ν_{max} 3450 (broad), 2924, 2845, 1708, 1678, 1602, 1464, 1383, 1277, 1209, 1146, 1020 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₂₉H₃₁N₂O₇, 519.2131; found, 519.2128.

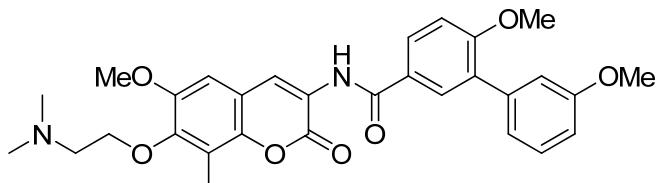


N-(7-(2-(dimethylamino)ethoxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (65a). Compound **65a** was obtained as colorless amorphous solid (52 mg, 66%). ^1H NMR (400 MHz, CDCl₃) δ 8.80 (s, 1H), 8.70 (s, 1H), 7.93–7.89 (m, 2H), 7.39–7.34 (m, 2H), 7.14–7.06 (m, 3H), 6.94 (dd, J = 8.2, 2.4 Hz, 1H), 6.88 (d, J = 8.7, 1H), 4.17 (t, J = 5.8 Hz, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 2.81 (t, J = 5.8 Hz, 2H), 2.38 (s,

6H), 2.34 (s, 3H). $^{13}\text{CNMR}$ (100 MHz, CDCl_3) δ 165.5, 159.8, 159.6, 159.3, 158.3, 149.2, 138.6, 131.0, 130.0, 129.2, 128.2, 126.1, 125.7, 124.4, 122.0, 121.6, 115.2, 114.2, 113.5, 113.2, 11.0, 108.9, 67.5, 58.3, 55.9, 55.3, 46.2, 8.4. IR (KBr) ν_{max} 3406, 2926, 2851, 1709, 1667, 1605, 1582, 1500, 1441, 1367, 1269, 1246, 1207, 1180, 1140, 1113 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{29}\text{H}_{31}\text{N}_2\text{O}_6$, 503.2182; found, 503.2181.

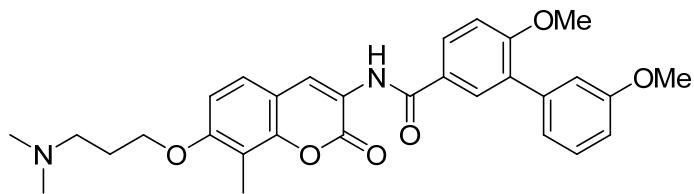


N-(7-(2-(dimethylamino)ethoxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (65b). Compound **65b** was obtained as a light yellow amorphous solid (47 mg, 70%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.80 (s, 1H), 8.71 (s, 1H), 7.93–7.89 (m, 2H), 7.37 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.13–7.06 (m, 3H), 6.95–6.92 (m, 2H), 4.21 (t, J = 5.9 Hz, 2H), 4.00 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 2.82 (t, J = 5.9 Hz, 2H), 2.38 (s, 6H). $^{13}\text{CNMR}$ (100 MHz, CDCl_3) δ 165.5, 159.8, 159.3, 158.9, 153.3, 144.0, 138.6, 136.7, 131.1, 130.0, 129.2, 128.2, 126.0, 123.9, 122.5, 122.1, 122.0, 115.3, 114.7, 113.2, 111.2, 111.0, 68.0, 61.6, 58.1, 55.9, 55.3, 46.0. IR (KBr) ν_{max} 3404, 2928, 2853, 1693, 1648, 1605, 1479, 1367, 1248, 1207, 1113, 1032, 1022 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{29}\text{H}_{31}\text{N}_2\text{O}_7$, 519.2131; found, 519.2135.



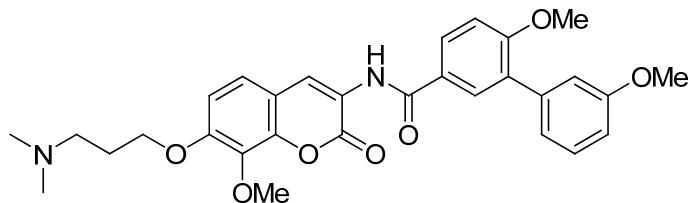
N-(7-(2-(dimethylamino)ethoxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (65c). Compound **65c** was obtained as a white amorphous

solid (41 mg, 64%). ^1H NMR (400 MHz, CDCl_3) δ 8.80 (s, 1H), 8.77 (s, 1H), 7.94–7.91 (m, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.15–7.08 (m, 3H), 6.96–6.94 (m, 1H), 6.86 (s, 1H), 4.15 (t, J = 5.7 Hz, 2H), 3.91 (s, 6H), 3.88 (s, 3H), 2.83 (t, J = 5.7 Hz, 2H), 2.47 (s, 3H), 2.45 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.4 (2C), 150.3, 148.1, 143.4, 138.6, 131.1, 130.0, 129.2, 128.2, 126.0, 123.7, 123.1, 122.0, 120.4, 115.5, 115.3, 113.1, 111.0, 106.5, 70.5, 59.0, 56.0, 55.9, 55.3, 45.6, 9.0. IR (KBr) ν_{max} 3398, 2954, 2847, 1706, 1674, 1605, 1582, 1529, 1502, 1468, 1381, 1246, 1207, 1144, 1022 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_7$, 533.2288; found, 533.2291.

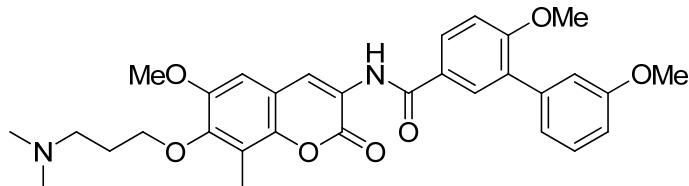


N-(7-(3-(dimethylamino)propoxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (66a).

Compound **66a** was obtained as a light brown amorphous solid (65 mg, 70%). ^1H NMR (400 MHz, CDCl_3) δ 8.81 (s, 1H), 8.71 (s, 1H), 7.95–7.91 (m, 2H), 7.40–7.34 (m, 2H), 7.15–7.08 (m, 3H), 6.95 (dd, J = 8.2, 2.0 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H), 4.14 (t, J = 6.2 Hz, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 2.61 (t, J = 6.2 Hz, 2H), 2.37 (s, 6H), 2.34 (s, 3H), 2.11–2.06 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.6, 159.3, 158.4, 149.2, 138.6, 131.0, 130.0, 129.2, 128.2, 126.1, 125.7, 124.5, 122.0, 121.5, 115.2, 114.1, 113.4, 113.2, 111.0, 108.9, 66.8, 56.3, 55.9, 55.3, 45.3, 27.2, 8.2. IR (KBr) ν_{max} 3400, 2924, 2854, 1708, 1670, 1607, 1528, 1367, 1242, 1205, 1111, 1022 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_6$, 517.2339; found, 517.2342.

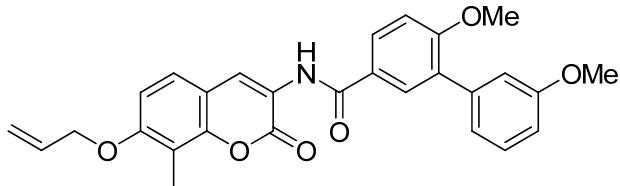


N-(7-(3-(dimethylamino)propoxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (66b). Compound **66b** was obtained as a light yellow amorphous solid (36 mg, 72%). ^1H NMR (400 MHz, CDCl_3) δ 8.79 (s, 1H), 8.70 (s, 1H), 7.92–7.88 (m, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.13–7.06 (m, 3H), 6.94–6.90 (m, 2H), 4.17 (t, J = 6.2 Hz, 2H), 4.02 (s, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 2.65 (t, J = 6.2 Hz, 2H), 2.39 (s, 6H), 2.12 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.4, 158.9, 153.4, 144.0, 138.6, 136.5, 131.1, 130.0, 129.2, 128.2, 126.0, 124.0, 122.6, 122.1, 122.0, 115.3, 114.6, 113.2, 111.0, 111.95, 67.5, 61.5, 56.1, 55.9, 55.3, 45.1, 27.0. IR (KBr) ν_{max} 3404, 2941, 2837, 1709, 1666, 1602, 1582, 1501, 1462, 1379, 1244, 1207, 1180, 1093 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_7$, 533.2288; found, 533.2291.



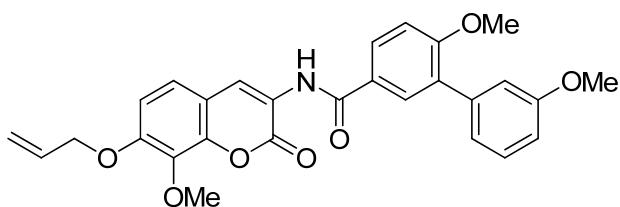
N-(7-(3-(dimethylamino)propoxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (66c). Compound **66c** was obtained as a white amorphous solid (57 mg, 76%). ^1H NMR (400 MHz, CDCl_3) δ 8.78 (s, 1H), 8.75 (s, 1H), 7.92–7.90 (m, 2H), 7.37 (t, J = 8.0 Hz, 1H), 7.14–7.06 (m, 3H), 6.95–6.92 (m, 1H), 6.84 (s, 1H), 4.06 (t, J = 6.2 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 2.74 (t, J = 6.2 Hz, 2H), 2.44 (s, 6H), 2.39 (s, 3H), 2.11–2.05 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 159.8, 159.3, 158.30, 158.29, 150.3, 148.0, 143.3, 138.6, 131.0, 130.0, 129.2, 126.0, 123.7, 123.1, 122.0, 120.3, 115.5, 115.3, 113.1,

111.0, 106.5, 71.3, 56.3, 56.0, 55.9, 55.3, 44.9, 27.7, 9.0. IR (KBr) ν_{max} 3404, 2941, 2837, 1709, 1672, 1603, 1582, 1526, 1501, 1464, 1377, 1242, 1205, 1093, 1034 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₃₁H₃₅N₂O₇, 547.2444; found, 547.2449.

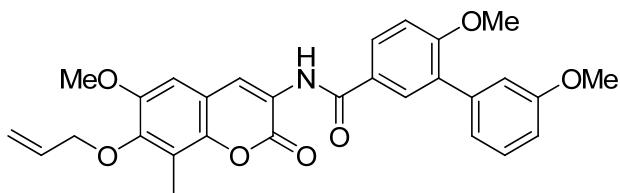


N-(7-(allyloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (67a).

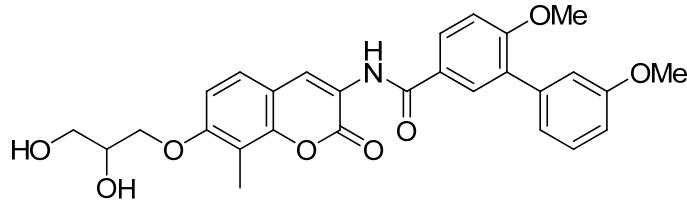
A solution of compound **6a** (149 mg, 0.35 mmol) in THF (5 mL) was treated with potassium carbonate (238 mg, 1.73 mmol) and allylbromide (84 mg, 0.69 mmol). The resulting mixture was refluxed for 8 h, quenched with aqueous ammonium chloride and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was purified via column chromatography (SiO₂, 40:1, CH₂Cl₂:acetone) to give compound **67a** as a white amorphous solid (144 mg, 88%). ¹H NMR (500 MHz, CDCl₃) δ 8.77 (s, 1H), 8.70 (s, 1H), 7.92–7.90 (m, 2H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.16–7.12 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.95 (dd, *J* = 8.0 Hz, 1.5, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.61–6.04 (m, 1H), 5.47 (dd, *J* = 7.1, 1.5 Hz, 1H), 5.33 (dt, *J* = 10.2, 1.1 Hz, 1H), 4.61 (d, *J* = 5.0 Hz, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 2.35 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 165.3, 159.7, 159.5, 159.4, 158.0, 149.2, 138.6, 132.8, 131.0, 130.0, 129.2, 128.1, 126.1, 125.6, 124.2, 122.0, 121.6, 117.6, 115.3, 114.3, 113.5, 113.1, 111.0, 109.2, 69.3, 55.9, 55.3, 8.2. IR (KBr) ν_{max} 3400, 3085, 3025, 2939, 2835, 1711, 1672, 1605, 1524, 1502, 1462, 1367, 1281, 1246, 1207, 1180, 1103, 1022 cm⁻¹. HRMS (ESI⁺) m/z calcd for [M+Na⁺] C₂₈H₂₄NO₆Na, 494.1580; found, 494.1583.



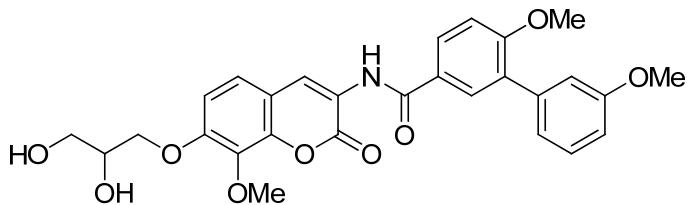
N-(7-(allyloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (67b). A solution of compound **6b** (61 mg, 0.14 mmol) in DMF (5 mL) was treated with sodium hydride (60%, 8.4 mg, 0.21 mmol) and allylbromide (34 mg, 0.28 mmol). The resulting mixture was refluxed for 8 h, quenched with aqueous ammonium chloride and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was purified via column chromatography (SiO₂, 40:1, CH₂Cl₂:acetone) to afford compound **67b** as a white amorphous solid (57 mg, 84%). ¹H NMR (500 MHz, CDCl₃) δ 8.81 (s, 1H), 8.72 (s, 1H), 7.92 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.13 (td, *J* = 7.6, 1.0 Hz, 1H), 7.10–7.08 (m, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.95–6.92 (m, 2H), 6.13–6.05 (m, 1H), 5.46 (dd, *J* = 7.2, 1.5 Hz, 1H), 5.34 (dt, *J* = 5.0, 1.1 Hz, 1H), 4.69 (dd, *J* = 5.0, 1.0 Hz, 2H), 4.02 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 165.8, 160.0, 159.5, 159.1, 153.2, 144.2, 138.8, 136.8, 132.8, 131.3, 130.2, 129.4, 128.4, 126.2, 124.2, 122.7, 122.4, 122.2, 118.5, 115.5, 114.9, 113.4, 111.5, 111.2, 70.3, 61.8, 56.1, 55.5. IR (KBr) *v*_{max} 3400, 3084, 3000, 2937, 2835, 1713, 1672, 1607, 1526, 1502, 1462, 1367, 1283, 1245, 1207, 1103, 1022 cm⁻¹. HRMS (ESI⁺) m/z calcd for [M+Na⁺] C₂₈H₂₅NO₇Na, 510.1529; found, 510.1521.



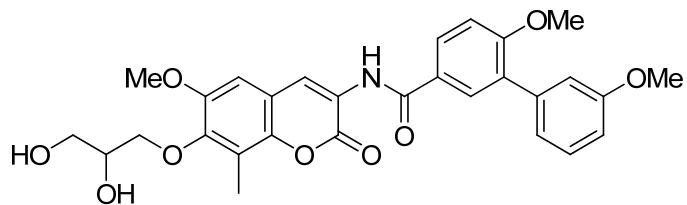
N-(7-(allyloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (67c). Compound **67c** was obtained as a white amorphous solid (34 mg, 76%). ¹H NMR (500 MHz, CDCl₃) δ 8.77 (s, 1H), 8.74 (s, 1H), 7.90 (dd, *J* = 10.8, 2.3 Hz, 1H), 7.88 (d, *J* = 2.3 Hz, 1H), 7.34 (t, *J* = 10.8 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 7.05 (d, *J* = 8.5, Hz, 1H), 6.92 (d, *J* = 8.5, 1H), 6.83 (s, 1H), 6.12–6.04 (m, 1H), 5.35 (d, *J* = 7.2, 1.5 Hz, 1H), 5.23 (d, *J* = 10.3 Hz, 1H), 4.54 (dd, *J* = 6.0, 1.0 Hz, 2H), 3.89 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.37 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 165.8, 160.0, 159.6, 159.5, 150.6, 148.0, 143.5, 138.8, 134.0, 131.2, 130.2, 129.4, 128.4, 126.2, 123.9, 123.2, 122.2, 120.8, 118.4, 115.7, 115.5, 113.3, 111.2, 106.7, 74.4, 56.2, 56.1, 55.5, 9.4. IR (KBr) *v*_{max} 3402, 3084, 3002, 2939, 2835, 1713, 1670, 1605, 1526, 1502, 1462, 1367, 1283, 1246, 1207, 1103, 1022 cm⁻¹. HRMS (ESI⁺) m/z calcd for [M+Na⁺] C₂₉H₂₇NO₇Na, 524.1685; found, 524.1684.



N-(7-(2,3-Dihydroxypropoxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (68a). Compound **68a** was obtained as a white amorphous powder (58 mg, 90%). ¹H NMR (400 MHz, CDCl₃) δ 8.82 (s, 1H), 8.72 (s, 1H), 7.95–7.91 (m, 2H), 7.41–7.36 (m, 2H), 7.16–7.08 (m, 3H), 6.97–6.90 (m, 2H), 4.22–4.16 (m, 3H), 3.99 (s, 3H), 3.92 (s, 3H), 3.91–3.81 (2H), 2.59 (s, 1H), 2.36 (s, 3H), 2.02 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 159.5, 159.4, 158.9, 158.8, 150.0, 139.2, 130.4, 129.8, 129.6, 129.5, 129.3, 126.7, 126.2, 122.2, 121.5, 115.7, 113.1, 113.0 (2C), 112.0, 109.6, 70.9, 70.4, 63.1, 56.4, 55.6, 8.4. IR (KBr) *v*_{max} 3256 (broad), 3030, 2980, 2939, 1735, 1691, 1526, 1382, 1256, 1178, 1109, 1051, 1020 cm⁻¹. HRMS (ESI⁺) m/z: [M + Na⁺] calcd for C₂₈H₂₇NO₈Na, 528.1634; found, 528.1630.

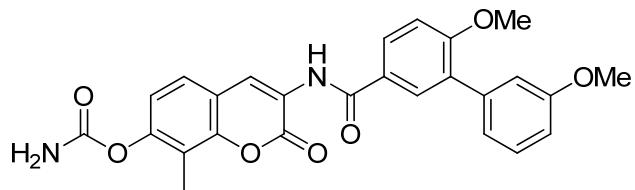


N-(7-(2,3-dihydroxypropoxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (68b). Compound **68b** was obtained as a white amorphous powder (26 mg, 74%). ^1H NMR (500 MHz, DMSO- d_6) δ 9.68 (s, 1H), 8.48 (s, 1H), 7.99 (dd, J = 8.6, 2.3 Hz, 1H), 7.92 (d, J = 2.3 Hz, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.26 (d, J = 8.6, 1H), 7.12 (t, J = 8.8 Hz, 1H), 7.10 (d, J = 2.6 Hz, 1H), 6.96 (dd, J = 8.3, 2.1 Hz, 1H), 5.05 (bs, 1H), 4.73 (t, J = 5.7 Hz, 1H), 4.15 (dd, J = 10.0, 4.1 Hz, 1H), 4.04 (dd, J = 10.0, 2.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 3.50 (t, J = 5.6 Hz, 2H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 165.1, 159.1, 158.9, 157.9, 153.6, 144.2, 138.7, 135.3, 130.0, 129.3, 129.2, 129.1 (2C), 125.7, 122.9, 121.7, 121.5, 115.2, 113.6, 112.5, 111.5, 110.8, 70.7, 69.8, 62.6, 60.8, 55.9, 55.1. IR (KBr) ν_{max} 3294 (broad), 2982, 2937, 1711, 1678, 1538, 1502, 1468, 1375, 1232, 1109, 1047, 1020 cm^{-1} . HRMS (ESI $^+$) m/z: [M + Na $^+$] calcd for C₂₈H₂₇NO₉Na, 544.1583; found, 544.1581.



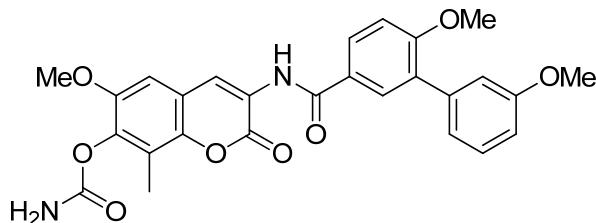
N-(7-(2,3-dihydroxypropoxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (68c). Compound **68c** was obtained as a white amorphous powder (18 mg, 67%). ^1H NMR (500 MHz, DMSO- d_6) δ 9.65 (s, 1H), 8.54 (s, 1H), 8.00 (dd, J = 8.7, 2.4 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.29 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.12–7.09 (m, 2H), 6.96 (dd, J = 8.6, 2.6 Hz, 1H), 4.89 (s, OH, 1H), 4.62 (t, J = 5.7 Hz,

1H), 4.05 (dd, $J = 10.0, 4.2$, 1H), 3.98–3.92 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.79–3.74 (m, 1H), 3.44 (t, $J = 5.6$ Hz, 2H). 2.31 (s, 3H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 165.2, 159.1, 159.0, 158.2, 149.6, 148.1, 143.5, 138.7, 130.0, 129.4, 129.1 (2C), 128.1, 125.7, 122.6, 121.7, 119.0, 115.2, 114.6, 112.6, 111.6, 107.6, 75.0, 70.7, 62.9, 56.1, 55.9, 55.1, 8.8. IR (KBr) ν_{max} 3284 (broad), 2980, 2842, 1709, 1694, 1524, 1483, 1375, 1251, 1178, 1146, 1109, 1051, 1020 cm⁻¹. HRMS (ESI⁺) m/z: [M + Na⁺] calcd for C₂₉H₂₉NO₉Na, 558.1740; found, 558.1733.



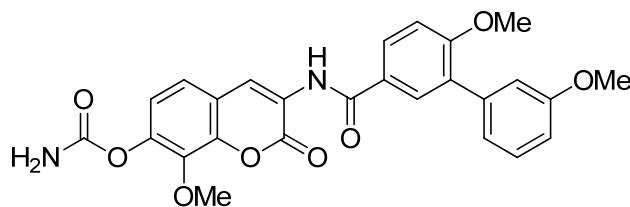
3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yl carbamate (69a):

A solution of sulfurisocyanatidic chloride (6.0 μL , 0.070 mmol), dissolved in anhydrous CH₂Cl₂ (0.20 mL), was slowly added to **6a**³ (30 mg, 0.070 mmol) in anhydrous CH₂Cl₂ (1.20 mL) at rt. After 2 h, the solvent was removed and the residue was stirred with cold H₂O overnight. The solid was collected by filtration, washing with H₂O, and thoroughly dried to afford **69a** as a yellow amorphous solid (19 mg, 56%): ^1H NMR (DMSO- d_6 , 500 MHz) δ 9.77 (s, 1H), 8.59 (s, 1H), 8.01 (dd, $J = 9.0, 2.5$ Hz, 1H), 7.93 (d, $J = 2.5$ Hz, 1H), 7.62 (d, $J = 8.5$ Hz, 1H), 7.43 (bs, 1H), 7.37 (t, $J = 8.0$ Hz, 1H), 7.27 (d, $J = 9.0$ Hz, 1H), 7.14–7.09 (m, 4H), 6.97–6.94 (m, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (DMSO- d_6 , 125 MHz) δ 168.5, 165.3, 159.2, 159.0, 154.2, 149.1, 138.7, 136.7, 130.1, 129.4, 129.3, 129.2, 127.9, 125.7, 125.6, 123.2, 121.8, 119.8, 118.4, 116.6, 115.3, 112.6, 111.6, 56.0, 55.2, 8.7; IR (film) ν_{max} 3053, 2986, 2305, 1713, 1603, 1522, 1421, 1367, 1265, 897, 748; HRMS (ESI⁺) m/z: [M + 2H⁺] calcd for C₂₆H₂₄N₂O₇, 476.1584; found, 476.1514.



3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-6-methoxy-8-methyl-2-oxo-2H-chromen-7-yl carbamate (69b):

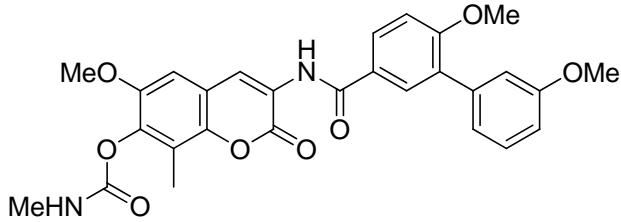
A solution of sulfurisocyanatidic chloride (3.8 μ L, 0.043 mmol), dissolved in anhydrous CH_2Cl_2 (0.12 mL), was slowly added to **6b** (20 mg, 0.043 mmol) in anhydrous CH_2Cl_2 (0.75 mL) at rt. After 2 h, the solvent was removed and the residue was stirred with cold H_2O overnight. The solid was collected by filtration, washing with H_2O , and thoroughly dried to afford **69b** as a yellow amorphous solid (11 mg, 50%): ^1H NMR (CDCl_3 , 500 MHz) δ 8.81 (s, 1H), 8.78 (s, 1H), 7.92 (dd, J = 8.5, 2.5 Hz, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.14–7.07 (m, 4H), 6.95–6.93 (m, 1H), 6.91 (s, 1H), 3.90 (s, 6H), 3.86 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 165.8, 160.0, 159.5, 159.2, 153.8, 149.6, 142.8, 139.7, 138.7, 131.2, 130.2, 129.3, 128.4, 126.1, 124.1, 123.3, 122.1, 121.3, 117.8, 115.4, 113.3, 111.1, 106.6, 56.5, 56.0, 55.5, 9.2; IR (film) ν_{max} 3053, 2986, 2684, 2305, 1421, 1265, 895, 750, 706; HRMS (ESI $^+$) m/z : [M + 2H $^+$] calcd for $\text{C}_{27}\text{H}_{26}\text{N}_2\text{O}_8$, 506.1689; found, 506.1637.



3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methoxy-2-oxo-2H-chromen-7-yl carbamate (69c):

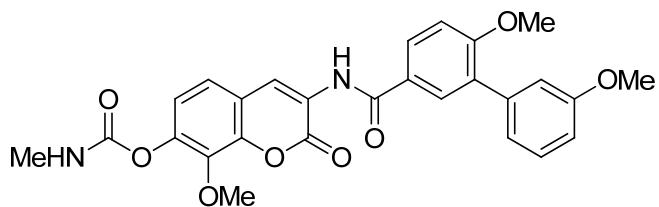
A solution of sulfurisocyanatidic chloride (11 μ L, 0.13 mmol), dissolved in anhydrous CH_2Cl_2 (0.4 mL), was slowly added to **6c** (30 mg, 0.066 mmol) in anhydrous CH_2Cl_2 (1.6 mL) at rt. After 2 h, the solvent was removed and the residue was stirred with cold H_2O

overnight. The solid was collected by filtration, washing with H_2O , and thoroughly dried to afford **69c** as a colorless amorphous solid (22 mg, 68%): ^1H NMR ($\text{DMSO}-d_6$, 500 MHz) δ 9.78 (s, 1H), 8.58 (s, 1H), 8.01 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.93 (d, $J = 2.5$ Hz, 1H), 7.49 (d, $J = 8.5$ Hz, 1H), 7.46 (bs, 1H), 7.37 (t, $J = 8.0$ Hz, 1H), 7.27 (d, $J = 8.5$ Hz, 1H), 7.16–7.10 (m, 4H), 6.97–6.94 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 165.8, 160.1, 159.5, 158.4, 154.1, 144.3, 143.7, 140.0, 138.7, 131.3, 130.1, 129.3, 128.4, 125.9, 123.9, 123.2, 122.2, 122.1, 120.3, 119.3, 115.4, 113.3, 111.2, 62.0, 56.1, 55.5; IR (film) ν_{max} 3406, 3271, 3053, 2986, 2359, 2339, 1715, 1672, 1603, 1531, 1502, 1366, 1265, 1082, 897, 737, 704; HRMS (ESI $^+$) m/z : [M + H $^+$] calcd for $\text{C}_{26}\text{H}_{23}\text{N}_2\text{O}_8$, 491.1454; found, 491.1432.

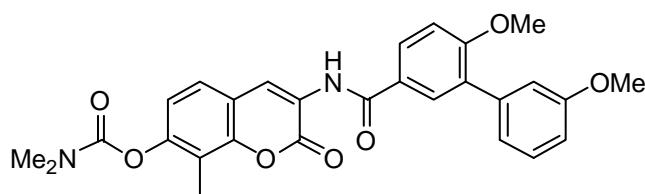


3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-6-methoxy-8-methyl-2-oxo-2H-chromen-7-yl methylcarbamate (70b): A solution of **6b** (20 mg, 0.043 mmol) in anhydrous pyridine (2.1 mL) was treated with methylcarbamic chloride (4.4 mg). After 12 h, the solvent was removed and the residue purified via column chromatography (SiO_2 , 40:1, CH_2Cl_2 :acetone) to afford **70b** as a yellow amorphous solid (21 mg, 95%): ^1H NMR (CDCl_3 , 500 MHz) δ 8.79 (s, 1H), 8.71 (s, 1H), 7.92 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.89 (d, $J = 2.5$ Hz, 1H), 7.37 (t, $J = 8.0$ Hz, 1H), 7.13–7.06 (m, 3H), 6.95–6.92 (m, 1H), 6.81 (s, 1H), 6.11 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.37 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 165.7, 159.9, 159.7, 159.4, 146.1, 144.5, 144.2, 138.7 (2C), 131.1, 130.1, 129.3, 128.3, 126.3, 124.7, 122.1, 122.0, 115.4, 113.3, 112.2, 111.9, 111.1, 105.0, 56.4, 56.0, 55.5, 29.6, 8.3; IR (film) ν_{max} 3053, 2986,

2685, 2359, 2341, 2307, 1684, 1421, 1265, 1022, 897, 746, 704; HRMS (ESI⁺) *m/z*: [M + H⁺] calcd for C₂₈H₂₇N₂O₈, 519.1767; found, 519.1839.

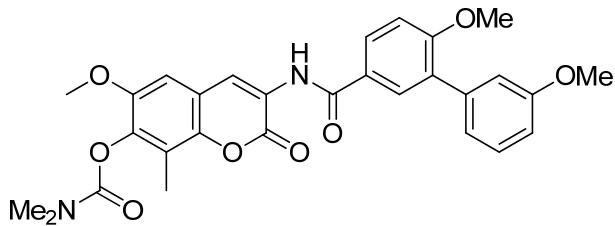


3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methoxy-2-oxo-2H-chromen-7-yl methylcarbamate (70c): A solution of **6c** (33 mg, 0.074 mmol) in anhydrous pyridine (3.5 mL) was treated with methylcarbamic chloride (7.4 mg). After 12 h, the solvent was removed and the residue purified via column chromatography (SiO₂, 40:1, CH₂Cl₂:acetone) to afford **70c** as a yellow amorphous solid (34 mg, 90%): ¹H NMR (CDCl₃, 500 MHz) δ 8.81 (s, 1H), 8.65 (bs, 1H), 7.97 (bs, 1H), 7.92 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.88 (d, *J* = 2.5 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.13–7.07 (m, 3H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.95–6.93 (m, 1H), 4.12 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 165.7, 160.0, 159.5, 158.7, 150.4, 143.1, 141.6, 138.7, 133.7, 131.2, 130.1, 129.3, 128.3, 126.1, 124.8, 123.3, 122.1, 121.7, 115.4, 114.1, 113.3, 113.1, 111.2, 62.1, 56.0, 55.5, 29.9; IR (film) ν_{max} 3030, 2851, 2284, 1693, 1668, 1599, 1520, 1495, 1487, 1371, 1342, 1231, 1161, 1078, 964, 901, 856, 795; HRMS (ESI⁺) *m/z*: [M + Na⁺] calcd for C₂₇H₂₄N₂NaO₈, 527.1430; found, 527.1403.



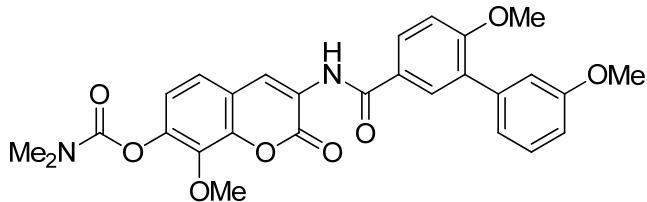
3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yl dimethylcarbamate (71a): A solution of **6a** (30 mg, 0.070 mmol) in pyridine (3.0 mL) at rt was

treated with dimethylcarbamyl chloride (1.0 mL). After 12 h, the solvent was removed and the residue purified via column chromatography (SiO_2 , 40:1, CH_2Cl_2 :acetone) to afford **71a** as a colorless amorphous solid (31 mg, 89%): ^1H NMR (CDCl_3 , 500 MHz) δ 8.84 (s, 1H), 8.75 (s, 1H), 7.93 (dd, J = 8.5, 2.5 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.40–7.35 (m, 2H), 7.14–7.07 (m, 4H), 6.95–6.92 (m, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.17 (s, 3H), 3.05 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 165.8, 160.0, 159.5, 159.3, 154.2, 151.0, 148.9, 138.7, 131.2, 130.1, 129.3, 128.4, 126.1, 125.5, 123.6, 123.5, 122.2, 119.9, 119.3, 117.4, 115.4, 113.3, 111.2, 56.1, 55.5, 37.0, 36.7, 9.1; IR (film) ν_{max} 3053, 2986, 2305, 1724, 1421, 1265, 1163, 895, 746, 706; HRMS (ESI $^+$) m/z : [M + 2H $^+$] calcd for $\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_7$, 504.1897; found, 504.1822.

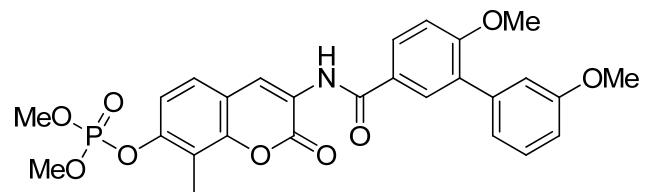


3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-6-methoxy-8-methyl-2-oxo-2H-chromen-7-yl dimethylcarbamate (71b): A solution of **6b** (25 mg, 0.054 mmol) in pyridine (2.25 mL) at rt was treated with dimethylcarbamyl chloride (0.75 mL). After 12 h, the solvent was removed and the residue purified via column chromatography (SiO_2 , 40:1, CH_2Cl_2 :acetone) to afford **71b** as a yellow amorphous solid (25 mg, 85%): ^1H NMR (CDCl_3 , 500 MHz) δ 8.81 (s, 1H), 8.77 (s, 1H), 7.92 (dd, J = 8.5, 2.5 Hz, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.14–7.07 (m, 3H), 6.95–6.92 (m, 1H), 6.89 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.18 (s, 3H), 3.04 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 165.7, 160.0, 159.5, 159.3, 154.0, 149.7, 143.0, 140.8, 138.7, 131.2, 130.2, 129.3, 128.4, 126.1, 123.9, 123.6, 122.2, 121.1, 117.3, 115.4, 113.3, 111.1, 106.5, 56.5, 56.0, 55.5, 37.1, 36.8, 9.3; IR (film) ν_{max} 3053,

2986, 2305, 1724, 1713, 1672, 1603, 1522, 1501, 1421, 1383, 1267, 1163, 897, 739, 704; HRMS (ESI⁺) *m/z*: [M + H⁺] calcd for C₂₉H₂₉N₂O₈, 533.1924; found, 533.1841.

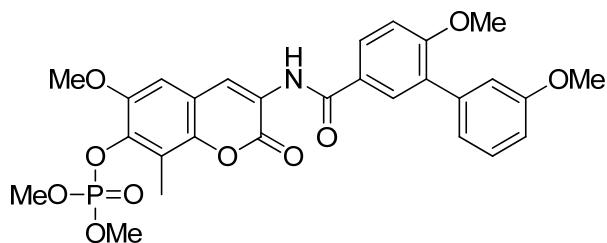


3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methoxy-2-oxo-2H-chromen-7-yl dimethylcarbamate (71c): A solution of **6c** (25 mg, 0.056 mmol) in pyridine (2.25 mL) at rt was treated with dimethylcarbamyl chloride (0.75 mL). After 12 h, the solvent was removed and the residue purified via column chromatography (SiO₂, 40:1, CH₂Cl₂:acetone) to afford **71c** as a colorless amorphous solid (19 mg, 65%): ¹H NMR (CDCl₃, 500 MHz) δ 8.84 (s, 1H), 8.74 (s, 1H), 7.92 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.90 (d, *J* = 2.5 Hz, 1H), 7.38–7.35 (m, 2H), 7.13–7.07 (m, 4H), 6.95–6.93 (m, 1H), 4.05 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H), 3.16 (s, 3H), 3.05 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 165.8, 160.0, 158.6, 156.5, 153.0, 149.9, 145.5, 144.0, 142.6, 140.0, 135.6, 130.1, 129.3, 128.4 (2C), 126.0, 123.5, 122.1, 120.5, 118.9, 115.4, 113.3, 111.2, 61.9, 56.0, 55.5, 36.8 (2C); IR (film) ν_{max} 3053, 2986, 2930, 2685, 2305, 1603, 1421, 1265, 1157, 1024, 895, 737, 704; HRMS (ESI⁺) *m/z*: [M + H⁺] calcd for C₂₈H₂₇N₂O₈, 519.1767; found, 519.1750.



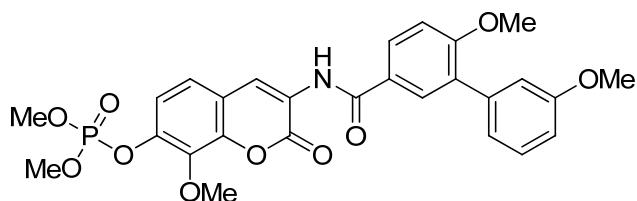
3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yl dimethyl phosphate (72a): Dimethyl phosphorochloridate (6.3 μL, 0.058 mmol) was slowly added to **6a** (25 mg, 0.058 mmol) and 4-dimethylaminopyridine (7.1 mg, 0.058 mmol) in

anhydrous CH₂Cl₂ (1.2 mL) at rt. After 12 h, the solvent was removed and the residue purified via column chromatography (SiO₂, 40:1 → 10:1 CH₂Cl₂:acetone) to afford **72a** as a colorless amorphous solid (17 mg, 54%): ¹H NMR (CDCl₃, 500 MHz) δ 8.83 (s, 1H), 8.74 (s, 1H), 7.93 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.39–7.36 (m, 2H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.13–7.07 (m, 3H), 6.95–6.93 (m, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 2.44 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 165.7, 160.0, 159.5, 159.1, 149.9, 149.8, 149.0, 138.7, 131.2, 130.1, 129.3, 128.4, 125.9, 125.8, 123.5, 123.3, 122.1, 118.1, 117.2, 115.4, 113.3, 111.2, 56.0, 55.5, 55.3 (2C), 9.0; IR (film) ν_{max} 3404, 3053, 2986, 2930, 2854, 2305, 1715, 1674, 1605, 1522, 1501, 1421, 1366, 1265, 1055, 897, 725, 704; HRMS (ESI⁺) *m/z*: [M + 2H⁺] calcd for C₂₇H₂₈NO₉P, 541.1502; found, 541.1454.

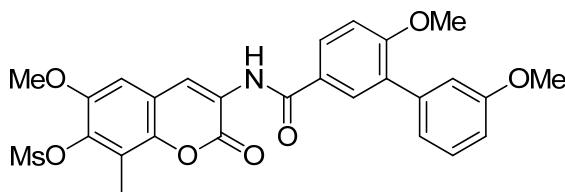


3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-6-methoxy-8-methyl-2-oxo-2H-chromen-7-yl dimethyl phosphate (72b): Dimethyl phosphorochloridate (7.0 μL, 0.065 mmol) was slowly added to **6b** (30 mg, 0.065 mmol) and 4-dimethylaminopyridine (8 mg, 0.065 mmol) in anhydrous CH₂Cl₂ (1.3 mL) at rt. After 12 h, the solvent was removed and the residue purified via column chromatography (SiO₂, 40:1 → 10:1 CH₂Cl₂:acetone) to afford **72b** as a colorless amorphous solid (14 mg, 41%): ¹H NMR (CDCl₃, 500 MHz) δ 8.79 (s, 1H), 8.77 (s, 1H), 7.92 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.89 (d, *J* = 2.5 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.13–7.06 (m, 3H), 6.94–6.92 (m, 1H), 6.90 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 2.46 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 165.8, 160.0, 159.5, 159.2, 148.9 (2C), 138.7,

131.2, 130.2, 129.3, 128.4, 126.0, 124.0, 123.2, 122.1, 120.4, 117.1 (2C), 115.4, 113.3, 111.1, 106.9, 56.5, 56.0, 55.5, 55.3, 55.2, 9.7; IR (film) ν_{max} 3053, 2986, 2685, 2305, 1713, 1522, 1501, 1421, 1385, 1265, 897, 746, 704; HRMS (ESI⁺) *m/z*: [M + Na⁺] calcd for C₂₈H₂₈NNaO₁₀P, 592.1349; found, 592.1341.

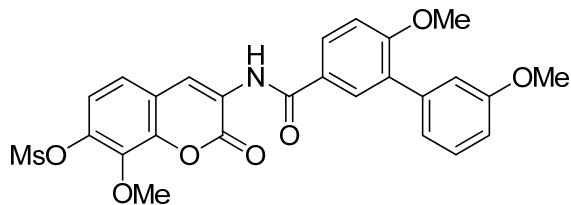


3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methoxy-2-oxo-2H-chromen-7-yl dimethyl phosphate (72c): Dimethyl phosphorochloridate (4.0 μ L, 0.038 mmol) was slowly added to **6c** (17 mg, 0.038 mmol) and 4-dimethylaminopyridine (5 mg, 0.038 mmol) in anhydrous CH₂Cl₂ (0.8 mL) at rt. After 12 h, the solvent was removed and the residue purified via column chromatography (SiO₂, 40:1) to afford **72c** as a yellow amorphous solid (6.0 mg, 30%): ¹H NMR (CDCl₃, 500 MHz) δ 8.82 (s, 1H) 8.74 (s, 1H), 7.92 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.88 (d, *J* = 2.5 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.25–7.23 (m, 1H), 7.13–7.07 (m, 3H), 6.95–6.93 (m, 1H) 4.09 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 165.7, 160.1, 159.5, 158.4, 144.4, 144.0, 138.6, 131.3, 130.1, 129.3, 128.4, 125.8, 123.8, 123.1, 122.4, 122.1, 118.6, 118.5, 118.4, 115.4, 113.3, 111.2, 62.2, 56.0, 55.5, 55.3 (2C); IR (film) ν_{max} 3053, 2959, 2928, 2854, 2361, 2307, 1718, 1674, 1605, 1522, 1501, 1462, 1366, 1265, 1207, 1180, 1038, 1024, 916, 858, 735, 704; HRMS (ESI⁺) *m/z*: [M + Na⁺] calcd for C₂₇H₂₆NNaO₁₀P, 578.1192; found, 578.1147.



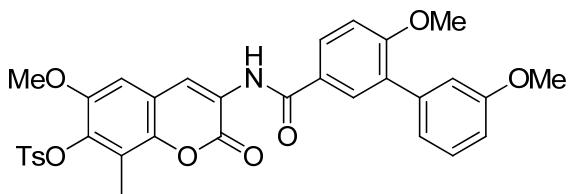
3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-6-methoxy-8-methyl-2-oxo-2H-chromen-7-yl methanesulfonate (73b):

Methanesulfonyl chloride (10 μ L, 0.13 mmol) was added to **6b** (15 mg, 0.033 mmol) in anhydrous pyridine (0.20 mL) at 0° C. The resulting solution was warmed to rt and stirred overnight, then diluted with H₂O. The desired product was extracted with EtOAc (3 \times 10 mL); combined organic fractions were dried (Na₂SO₄), filtered, and concentrated. The residue was purified via column chromatography (SiO₂, 40:1, CH₂Cl₂:acetone) to afford **73b** as a yellow amorphous solid (13 mg, 97%): ¹H NMR (DMSO-*d*₆, 500 MHz) δ 9.77 (s, 1H), 8.64 (s, 1H), 8.01 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.92 (d, *J* = 2.5 Hz, 1H), 7.49 (s, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 7.12–7.10 (m, 2H), 6.97–6.95 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.54 (s, 3H), 2.36 (s, 3H); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 165.4, 159.3, 159.0, 157.7, 149.2, 148.9, 139.1, 138.7, 130.1, 129.3, 129.2, 128.9, 126.2, 124.6, 121.8, 121.2, 118.1, 115.3 (2C), 112.6, 111.5, 108.0, 55.1 (2C), 54.8, 29.1, 10.0; IR (film) ν_{max} 3053, 2986, 2928, 2685, 2305, 1717, 1601, 1421, 1383, 1265, 1153, 895, 737, 704; HRMS (ESI⁺) *m/z*: [M + H⁺] calcd for C₂₇H₂₆NO₉S, 540.1328; found, 540.1395.

**3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methoxy-2-oxo-2H-chromen-7-yl methanesulfonate (73c):**

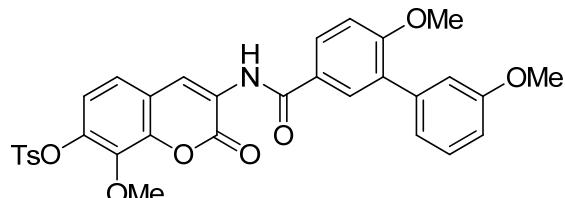
Methanesulfonyl chloride (17 μ L, 0.22 mmol) was added to **6b** (25 mg, 0.056 mmol) in anhydrous pyridine (0.40 mL) at 0° C. The resulting solution was warmed to rt and stirred overnight, then diluted with H₂O. The desired product was extracted with EtOAc (3 \times 10 mL); combined organic fractions were dried (Na₂SO₄), filtered, and concentrated. The residue was purified via column chromatography (SiO₂, 40:1, CH₂Cl₂:acetone) to afford **73c** as a

yellow amorphous solid (29 mg, 99%): ^1H NMR (CDCl_3 , 500 MHz) δ 8.80 (s, 1H), 8.73 (s, 1H), 7.88 (dd, J = 8.5, 2.0 Hz, 1H), 7.85 (d, J = 2.5 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.26–7.23 (m, 2H), 7.09–7.04 (m, 3H), 6.91–6.89 (m, 1H), 4.09 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.23 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 165.7, 160.2, 159.5, 158.0, 143.6, 142.4, 140.0, 138.6, 131.2, 130.1, 129.3, 128.4, 125.7, 124.6, 122.5 (2C), 122.1, 121.1, 120.6, 115.4, 113.2, 111.2, 62.6, 56.0, 55.4, 38.6; IR (film) ν_{max} 2928, 2359, 2341, 1720, 1676, 1603, 1521, 1501, 1464, 1364, 1242, 1180, 1078, 970, 860; HRMS (ESI $^+$) m/z : [M + H $^+$] calcd for $\text{C}_{26}\text{H}_{24}\text{NO}_9\text{S}$, 526.1172; found, 526.1179.

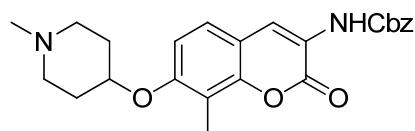


3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-6-methoxy-8-methyl-2-oxo-2H-chromen-7-yl 4-methylbenzenesulfonate (74b): 4-methylbenzene-1-sulfonyl chloride (50 μL , 0.26 mmol) was added to **6b** (30 mg, 0.065 mmol) in anhydrous pyridine (0.40 mL) at 0° C. The resulting solution was warmed to rt and stirred overnight, then diluted with H_2O (10 mL). The desired product was extracted with EtOAc (3×10 mL); combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2 , 40:1, CH_2Cl_2 :acetone) to afford **74b** as a yellow amorphous solid (39 mg, 98%): ^1H NMR (CDCl_3 , 500 MHz) δ 8.79 (s, 1H), 8.78 (s, 1H), 7.92 (dd, J = 8.5, 2.5 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.39–7.36 (m, 3H), 7.13–7.07 (m, 3H), 6.95–6.93 (m, 1H), 6.81 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.59 (s, 3H), 2.49 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 165.8, 160.0, 159.4, 159.0, 149.8, 145.3, 142.6, 138.7, 138.6, 134.3, 131.2, 130.2, 129.7 (2C), 129.3, 128.5 (2C), 128.4, 125.8, 124.6, 123.0, 122.7, 122.1, 118.6, 115.4,

113.2, 111.1, 106.6, 56.0, 55.9, 55.4, 21.9, 10.4; IR (film) ν_{max} 3053, 2986, 2685, 2305, 1713, 1601, 1421, 1383, 1265, 1163, 895, 739, 706; HRMS (ESI⁺) m/z : [M + H⁺] calcd for C₃₃H₃₀NO₉S, 616.1641; found, 616.1676.

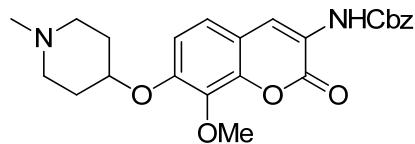


3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methoxy-2-oxo-2H-chromen-7-yl 4-methylbenzenesulfonate (74c): 4-methylbenzene-1-sulfonyl chloride (43 μ L, 0.22 mmol) was added to **6c** (25 mg, 0.056 mmol) in anhydrous pyridine (0.40 mL) at 0° C. The resulting solution was warmed to rt and stirred overnight, then diluted with H₂O (10 mL). The desired product was extracted with EtOAc (3 \times 10 mL); combined organic fractions were dried (Na₂SO₄), filtered, and concentrated. The residue was purified via column chromatography (SiO₂, 40:1, CH₂Cl₂:acetone) to afford **74c** as a colorless amorphous solid (33 mg, 99%): ¹H NMR (CDCl₃, 500 MHz) δ 8.80 (s, 1H), 8.74 (s, 1H), 7.91 (dd, J = 8.5, 2.5 Hz, 1H), 7.88 (d, J = 2.5 Hz, 1H), 7.81–7.79 (m, 2H), 7.38–7.34 (m, 3H), 7.19 (d, J = 8.5 Hz, 1H), 7.12–7.07 (m, 4H), 6.95–6.92 (m, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 2.47 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 165.7, 160.2, 159.5, 158.1, 145.9, 143.5, 142.6, 140.5, 138.6, 132.9, 131.3, 130.0 (2C), 129.3, 128.6 (2C), 128.4, 125.7, 124.4, 122.7, 122.1, 121.9, 120.5, 120.2, 115.4, 113.3, 111.2, 62.1, 56.0, 55.5, 21.9; IR (film) ν_{max} 3053, 2927, 2359, 2341, 1720, 1676, 1603, 1522, 1501, 1462, 1364, 1265, 1178, 1078, 1007, 858, 818, 737, 706; HRMS (ESI⁺) m/z : [M + H⁺] calcd for C₃₂H₂₈NO₉S, 602.1485; found, 602.1494.

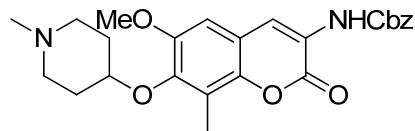


Benzyl 8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-ylcarbamate (75a).

Compound **75a** was obtained as a white amorphous solid (60 mg, 58%). ^1H NMR (400 MHz, CDCl_3) δ 8.25 (s, 1H), 7.55 (s, 1H), 7.40–7.34 (m, 5H), 7.24 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.22 (s, 2H), 4.48 (m, 1H), 2.71 (m, 2H), 2.52–2.49 (m, 2H), 2.38 (s, 3H), 2.11–2.07 (m, 2H), 1.98–1.89 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 158.8, 156.5, 153.2, 149.2, 135.6, 128.7, 128.5, 128.2, 125.1, 122.2, 121.4, 115.2, 113.0, 110.4, 72.4, 67.4, 52.0 (2C), 46.0, 30.3 (2C), 8.4. IR (film) ν_{max} 3406, 3319, 2939, 2849, 2791, 1711, 1609, 1524, 1366, 1271, 1227, 1204, 1103, 1038, 1024 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_5$, 423.1920; found 423.1920.

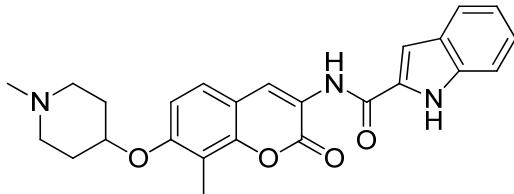
**Benzyl 8-methoxy-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-ylcarbamate (75b).**

Compound **75b** was obtained as light brown oil (63 mg, 89%). ^1H NMR (400 MHz, CDCl_3) δ 8.25 (s, 1H), 7.58 (s, 1H), 7.40–7.34 (m, 5H), 7.13 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.22 (s, 2H), 4.46 (m, 1H), 3.98 (s, 3H), 2.80–2.77 (m, 2H), 2.51–2.40 (m, 2H), 2.39 (s, 3H), 2.12–2.08 (m, 2H), 1.98–1.88 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 158.2, 153.2, 151.5, 144.0, 137.8, 135.6, 128.7, 128.5, 128.2, 122.1, 122.0, 121.8, 114.8, 113.5, 72.3, 67.5, 61.5, 52.1 (2C), 45.8, 30.4 (2C). IR (film) ν_{max} 3406, 3331, 2974, 2941, 2893, 1720, 1703, 1607, 1553, 1502, 1462, 1367, 1240, 1070. cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_6$, 439.1869; found 439.1867.



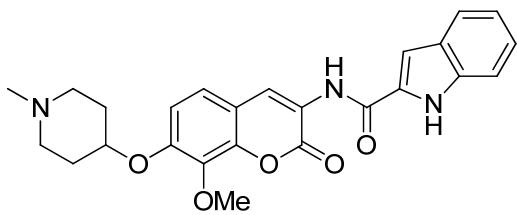
Benzyl 6-methoxy-8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-ylcarbamate (75c). Compound **75c** was obtained as light brown oil (134 mg, 88%). ¹H NMR (400 MHz, CDCl₃) δ 8.25 (s, 1H), 7.59 (s, 1H), 7.42–7.35 (m, 5H), 6.77 (s, 1H), 5.23 (s, 2H), 4.23–4.22 (m, 1H), 3.86 (s, 3H), 2.85–2.82 (m, 2H), 2.36 (s, 3H), 2.33 (s, 2H), 2.28–2.20 (m, 2H), 2.01–1.97 (m, 2H), 1.93–1.86 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 158.9, 153.4, 150.5, 146.8, 143.4, 135.7, 128.9, 128.7, 128.4, 122.9, 121.9, 120.9, 115.2, 106.3, 78.1, 67.7, 56.2, 53.3 (2C), 46.1, 31.8 (2C), 9.9. IR (film) ν_{max} 3404, 3312, 2937, 2864, 1710, 1693, 1609, 1529, 1466, 1385, 1367, 1288, 1240, 1211, 1109, 1078, 1031 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₂₅H₂₉N₂O₆, 435.2026; found, 453.2021.

Representative procedure for the preparation of compounds 77, 78, 81 and 82:



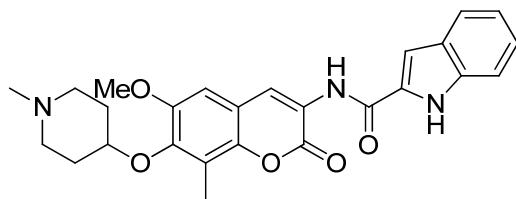
N-(8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)-1H-indole-2-carboxamide (78a). Compound **75a** (60 mg, 0.14 mmol) and Pd/C mixture were suspended in THF (2 mL) and stirred under hydrogen overnight. The mixture was filtered and the filtrate was concentrated and dried under vacuum for 2 h. The residue was dissolved in methylene chloride (2 mL) and treated with freshly prepared indole carboxylic chloride (25.5 mg, 0.14 mmol) and pyridine (0.1 mL). The resulting mixture was stirred at rt for 2 h, then purified via column chromatography (SiO₂, CH₂Cl₂:MeOH, 10:1) to yield compound **78a** (31 mg, 51%). ¹H NMR (500 MHz, CD₃CD-CDCl₃) δ 8.50 (s, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 1H), 7.09 (t, *J* = 8.1 Hz, 1H), 7.00 (s, 1H), 6.92 (t, *J* = 7.9 Hz, 1H), 6.72 (d,

J = 8.7 Hz, 1H), 4.54 (m, 1H), 2.53 (m, 2H), 2.35 (m, 2H), 2.18 (s, 3H), 2.13 (s, 3H), 1.85 (m, 2H), 1.75 (m, 2H). ^{13}C MNR (125 MHz, CD₃CD-CDCl₃) δ 160.5, 159.4, 156.7, 149.4, 137.3, 129.8, 127.2, 125.6, 125.3, 124.8, 122.0, 120.9, 120.5, 114.9, 113.2, 112.0, 110.4, 104.6, 77.4, 51.5 (2C), 45.3, 29.7 (2C), 7.9. IR (film) ν_{max} 3391, 3292, 2958, 2851, 1709, 1643, 1605, 1537, 1385, 1263, 1236, 1211, 1107, 1036, 731 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₂₅H₂₆N₃O₄, 432.1923; found 432.1927. This material was determined to be 100% pure (Retention time = 8.37 min) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H₂O (0.2% H₃PO₄)/30% MeCN → 52% H₂O (0.2% H₃PO₄)/48% MeCN → 95% H₂O (0.2% H₃PO₄)/5% MeCN → 70% H₂O (0.2% H₃PO₄)/30% MeCN, flow rate 1.0 mL/min.

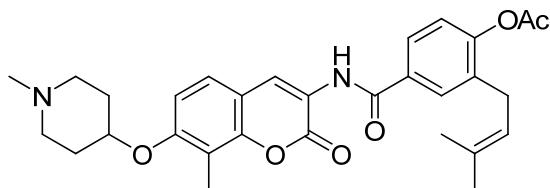


N-(8-methoxy-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)-1H-indole-2-carboxamide (78b). Compound **78b** was obtained as a light brown amorphous solid (28 mg, 38%). ^1H MNR (500 MHz CDCl₃/MeOD) δ 8.66 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.24 (t, *J* = 8.2 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.13 (s, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 4.45 (m, 1H), 3.93 (s, 3H), 2.71 (m, 2H), 2.45 (m, 2H), 2.32 (s, 3H), 2.15–2.11 (m, 2H), 2.00–1.91 (m, 2H). ^{13}C MNR (125 MHz CDCl₃/MeOD) δ 160.4, 158.7, 151.75, 144.2, 137.5, 137.2, 129.7, 127.4, 125.2, 124.3, 122.5, 122.3, 121.7, 120.8, 114.7, 113.4, 112.1, 104.7, 77.3, 61.5, 51.7 (2C), 45.6, 29.6 (2C). IR (film) ν_{max} 3390, 3312, 3292, 2928, 2851, 1711, 1653, 1607, 1535, 1383, 1264, 1236, 1211, 1107, 1036, 738 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₂₅H₂₆N₃O₅, 448.1873; found 448.1886. This material was determined to be 99% pure (Retention time = 9.04) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting

with 70% H₂O (0.2% H₃PO₄)/30% MeCN → 52% H₂O (0.2% H₃PO₄)/48% MeCN → 95% H₂O (0.2% H₃PO₄)/5% MeCN → 70% H₂O (0.2% H₃PO₄)/30% MeCN, flow rate 1.0 mL/min.

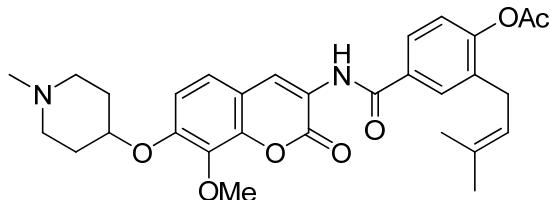


N-(6-methoxy-8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)-1H-indole-2-carboxamide (78c). Compound **78c** was obtained as a light brown amorphous solid (19 mg, 53%). ¹H MNR (500 MHz DMSO-*d*₆) 11.91 (s, 1H), 9.56 (s, 1H), 8.55 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.42 (s, 1H), 7.30 (s, 1H), 7.25 (t, *J* = 8.1 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 4.24–4.21 (m, 1H), 3.85 (s, 3H), 2.86 (m, 2H), 2.33 (s, 3H), 2.50 (m, 2H), 2.29 (s, 3H), 1.92–1.90 (m, 2H), 1.79–1.77 (m, 2H). ¹³C MNR (125 MHz DMSO-*d*₆) δ 160.0, 158.0, 149.7, 146.4, 143.5, 137.1, 130.3, 127.6, 126.9, 124.3, 122.3, 122.0, 120.1, 119.2, 114.6, 112.4, 107.4, 105.1, 77.1, 56.9, 52.1 (2C), 44.7, 30.7 (2C), 9.4. IR (film) ν_{max} 3379, 3312, 2924, 2851, 1713, 1659, 1582, 1543, 1468, 1392, 1292, 1136, 1084, 1036 739 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₂₄H₂₆N₃O₅, 462.2029; found 462.2032. This material was determined to be 99% pure (Retention time = 8.70) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H₂O (0.2% H₃PO₄)/30% MeCN → 52% H₂O (0.2% H₃PO₄)/48% MeCN → 95% H₂O (0.2% H₃PO₄)/5% MeCN → 70% H₂O (0.2% H₃PO₄)/30% MeCN, flow rate 1.0 mL/min.



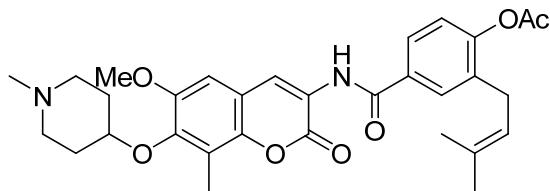
4-(8-Methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-ylcarbamoyl)-2-(3-methylbut-2-enyl)phenyl acetate (79a). Compound **79a** was obtained as white amorphous solid

(76 mg, 73%). ^1H NMR (500MHz, CDCl_3), δ 8.79 (s, 1H), 8.71 (s, 1H), 7.81 (d, J = 2.1 Hz, 1H), 7.77 (dd, J = 8.3 Hz, 2.1, 1H), 7.34(d, J = 8.6 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 5.25 (m, 1H), 4.52 (m, 1H), 3.33 (d, J = 7.2 Hz, 2H), 2.76–2.70 (m, 2H), 2.55–2.45 (m, 2H), 2.40 (s, 3H), 2.35 (s, 6H), 2.15–2.09 (m, 2H), 1.97–1.92 (m, 2H), 1.78 (s, 3H), 1.74 (s, 3H). ^{13}C NMR δ (125MHz, CDCl_3) 169.1, 165.6, 159.6, 157.1, 152.3, 149.7, 134.8, 134.5, 131.8, 129.5, 126.1, 125.8, 124.8, 123.1, 121.7, 120.8, 115.4, 113.5, 110.6, 77.4, 52.3 (2C), 46.2, 30.5 (2C), 29.0, 25.9, 21.1, 18.1, 8.6. IR (film) ν_{max} 3400, 3087, 2922, 2851, 1765, 1711, 1672, 1607, 1526, 1493, 1369, 1248, 1202, 1175, 1099, 1040 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{30}\text{H}_{35}\text{N}_2\text{O}_6$, 519.2495; found, 519.2485. This material was determined to be 95% pure (Retention time = 14.3) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H_2O (0.2% H_3PO_4)/30% MeCN → 52% H_2O (0.2% H_3PO_4)/48% MeCN → 95% H_2O (0.2% H_3PO_4)/5% MeCN → 70% H_2O (0.2% H_3PO_4)/30% MeCN, flow rate 1.0 mL/min.



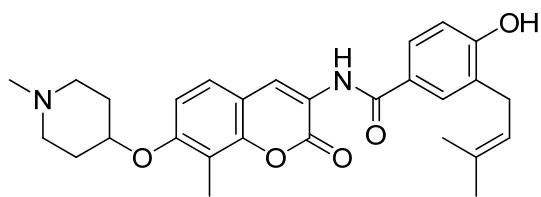
4-(8-methoxy-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-ylcarbamoyl)-2-(3-methylbut-2-enyl)phenyl acetate (79b). Compound **79b** was obtained as white amorphous solid (85 mg, 61%). ^1H NMR (500MHz, CDCl_3) δ 8.70 (s, 1H), 8.64 (s, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.68 (dd, J = 8.3, 2.3 Hz, 1H), 7.14 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 5.15 (m, 1H), 4.49 (m, 1H), 3.93 (s, 3H), 3.24 (d, J = 7.2 Hz, 2H), 2.90–2.85 (m, 2H), 2.68–2.65 (m, 2H), 2.46 (s, 3H), 2.26 (s, 3H), 2.19–2.16 (m, 2H), 1.98–1.94(m, 2H), 1.69 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (125MHz, CDCl_3) δ 169.0, 165.6, 158.8, 152.3, 151.6, 144.4, 137.9, 134.8, 134.4, 131.5, 129.5, 126.0, 124.1, 123.1, 122.8, 122.4, 120.7, 115.2, 113.8, 72.1, 61.7,

51.5 (2C), 45.3, 29.5 (2C), 28.9, 25.8, 21.0, 18.0. IR (film) ν_{max} 3406, 3084, 2962, 2937, 2831, 1731, 1711, 1666, 1604, 1529, 1502, 1462, 1366, 1258, 1178, 1103, 1036 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₃₀H₃₅N₂O₇, 535.2444; found, 535.2442.

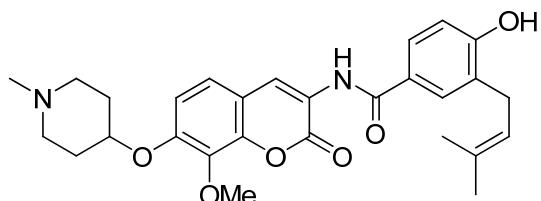


4-(6-methoxy-8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-ylcarbamoyl)-2-(3-methylbut-2-enyl)phenyl acetate (79c). Compound **79c** was obtained as white amorphous solid (81mg, 70%). ¹H NMR (500MHz, CDCl₃) δ 8.78 (s, 1H), 8.75 (s, 1H), 7.81 (d, *J* = 2.2 Hz, 1H), 7.77 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.85 (s, 1H), 5.25 (m, 1H), 4.32 (m, 1H), 3.89 (s, 3H), 3.32 (d, *J* = 7.2 Hz, 2H), 3.07–3.04 (m, 2H), 2.82–2.65 (m, 2H), 2.54 (s, 3H), 2.39 (s, 3H), 2.35 (s, 3H), 2.19–2.16 (m, 2H), 2.11–2.02 (m, 2H), 1.77 (s, 3H), 1.74 (s, 3H). ¹³C NMR (125MHz, CDCl₃) δ 169.2, 165.8, 159.4, 152.4, 150.4, 147.1, 143.8, 134.9, 134.6, 131.7, 129.6, 126.2, 124.1, 123.2, 120.9, 120.8, 115.5, 106.8, 77.5, 56.3, 52.3 (2C), 45.3, 30.6 (2C), 29.1, 26.0, 21.1, 18.1, 10.0. IR (film) ν_{max} 3404, 3086, 2935, 2852, 1721, 1711, 1672, 1605, 1529, 1383, 1250, 1177, 1085, 1034 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₃₁H₃₇N₂O₇, 549.2601; found, 549.2604. This material was determined to be 98% pure (Retention time = 13.9) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H₂O (0.2% H₃PO₄)/30% MeCN → 52% H₂O (0.2% H₃PO₄)/48% MeCN → 95% H₂O (0.2% H₃PO₄)/5% MeCN → 70% H₂O (0.2% H₃PO₄)/30% MeCN, flow rate 1.0 mL/min).

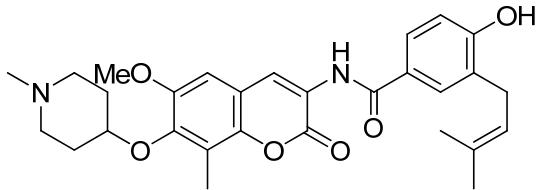
Representative procedure for the preparation of compounds **80** and **84**:



4-Hydroxy-N-(8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)-3-(3-methylbut-2-enyl)benzamide (80a). Compound **79a** (52 mg, 0.1 mmol) was dissolved in 10% triethylamine/methanol (3 mL). The solution was stirred at rt overnight and concentrated. The residue was purified via column chromatography (SiO₂, CH₂Cl₂:MeOH, 10:1) to afford **80a** as a white amorphous solid (37 mg, 73%). ¹H NMR (500MHz, DMSO-*d*₆) δ 9.22 (s, 1H), 8.47 (s, 1H), 7.68–7.66 (m, 2H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.11 (d, *J* = 8.9 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 5.30 (m, 1H), 4.57 (m, 1H), 3.27 (d, *J* = 7.3 Hz, 2H), 2.62–2.54 (m, 2H), 2.34–2.28 (m, 2H), 2.22 (s, 3H), 2.21 (s, 3H), 1.96–1.92 (m, 2H), 1.76–1.72(m, 2H), 1.71 (s, 3H), 1.69 (s, 3H). ¹³C NMR (125MHz, DMSO-d₆) δ 165.3, 158.8, 158.4, 156.6, 149.5, 131.9, 129.2, 127.8, 127.7, 126.8, 126.0, 124.0, 122.3, 121.3, 114.6, 113.4, 112.7, 110.8, 72.1, 51.8 (2C), 45.7, 30.2 (2C), 27.9, 25.6, 17.7, 8.2. IR (film) ν_{max} 3421, 3081, 2938, 2856, 1703, 1666, 1601, 1528, 1504, 1366, 1248, 1178, 1150, 1094, 1040 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₂₈H₃₃N₂O₅, 477.2389; found, 477.2397. This material was determined to be 98% pure (Retention time = 13.5) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H₂O (0.2% H₃PO₄)/30% MeCN → 52% H₂O (0.2% H₃PO₄)/48% MeCN → 95% H₂O (0.2% H₃PO₄)/5% MeCN → 70% H₂O (0.2% H₃PO₄)/30% MeCN, flow rate 1.0 mL/min.

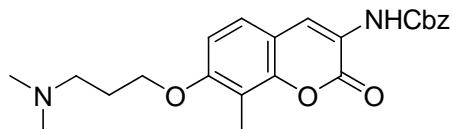


4-hydroxy-N-(8-methoxy-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)-3-(3-methylbut-2-enyl)benzamide (80b). Compound **80b** was obtained as white amorphous solid (24 mg, 75%). ¹H NMR (500MHz, CDCl₃) δ 9.26 (s, 1H), 8.49 (s, 1H), 7.68–7.66 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 9.0 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 1H), 5.30 (m, 1H), 4.58 (m, 1H), 3.88 (s, 3H), 3.27 (d, *J* = 7.2 Hz, 2H), 2.76–2.69 (m, 2H), 2.48–2.39 (m, 2H), 2.32 (s, 3H), 2.04–1.95 (m, 2H), 1.83–1.74 (m, 2H), 1.71 (s, 3H), 1.69 (s, 3H). ¹³C NMR (125MHz, CDCl₃) δ 165.3, 158.8, 157.9, 151.5, 144.3, 136.3, 131.9, 129.2, 127.7, 127.4, 126.9, 123.9, 122.8, 122.3, 121.9, 114.6, 114.0, 112.7, 72.7, 60.9, 51.7 (2C), 45.1, 29.9 (2C), 27.9, 25.5, 17.7. IR (film) ν_{max} 3406, 3317 (broad), 3086, 3053, 2941, 2833, 1711, 1666, 1605, 1527, 1502, 1460, 1365, 1265, 1178, 1080, 1034, 739 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₂₈H₃₃N₂O₆, 493.2339; found; 493.2337.



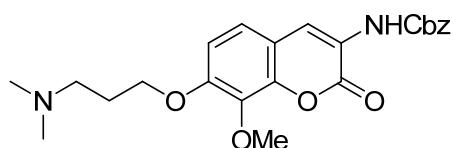
4-hydroxy-N-(6-methoxy-8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)-3-(3-methylbut-2-enyl)benzamide (80c). Compound **80c** was obtained as white amorphous solid (21mg, 81%). ¹H NMR (500MHz, DMSO-*d*₆) δ 10.2 (s, 1H), 9.23 (s, 1H), 8.54 (s, 1H), 7.68–7.66 (m, 2H), 7.28 (s, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 5.30 (m, 1H), 4.21 (m, 1H), 3.85 (s, 3H), 3.35–3.30 (m, 2H), 3.28 (d, *J* = 7.2 Hz, 2H), 2.90–2.81 (m, 2H), 2.32–2.29 (m, 2H), 2.28 (s, 3H), 2.25 (s, 3H), 1.93–1.88 (m, 2H), 1.78–1.71 (m, 2H), 1.71 (s, 3H), 1.70 (s, 3H). ¹³C NMR (125MHz, DMSO-*d*₆) δ 165.4, 158.9, 158.3, 149.8, 146.2, 143.3, 131.9, 129.2, 127.7, 126.9, 126.5, 123.9, 122.8, 122.3, 119.2, 114.8, 114.6, 107.4, 77.3, 56.1, 52.2 (2C), 44.8, 30.8 (2C), 27.9, 25.5, 17.7, 9.4. IR (film) ν_{max} 3406, 3088, 3045, 2931, 2853, 1709, 1657, 1601, 1529, 1500,

1381, 1250, 1178, 1086, 1034 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₂₉H₃₅N₂O₆, 507.2495; found, 507.2494. This material was determined to be 99% pure (Retention time = 13.2) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H₂O (0.2% H₃PO₄)/30% MeCN → 52% H₂O (0.2% H₃PO₄)/48% MeCN → 95% H₂O (0.2% H₃PO₄)/5% MeCN → 70% H₂O (0.2% H₃PO₄)/30% MeCN, flow rate 1.0 mL/min.



Benzyl 7-(3-(dimethylamino)propoxy)-8-methyl-2-oxo-2H-chromen-3-yl carbamate (81a).

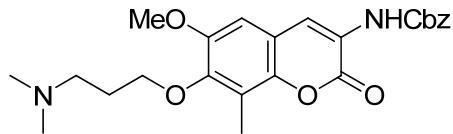
Compound **81a** was obtained as colorless oil (670 mg, 72%). ¹H NMR (400MHz, CDCl₃) δ 8.11 (s, 1H), 7.45 (s, 1H), 7.29–7.23 (m, 5H), 7.11 (d, *J* = 8.6 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 5.10 (s, 2H), 3.97 (t, *J* = 5.8 Hz, 2H), 2.46 (t, *J* = 5.8 Hz, 2H), 2.22 (s, 6H), 2.17 (s, 3H), 1.93 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 159.0, 158.2, 153.3, 149.0, 135.8, 128.8 (2C), 128.6, 128.4 (2C), 125.3, 122.5, 121.4, 114.0, 113.3, 108.9, 67.5, 66.8, 56.4, 45.4 (2C), 27.4, 8.2. IR (film) ν_{max} 3404, 3323, 2978, 2943, 2816, 2768, 1713, 1610, 1524, 1381, 1366, 1273, 1227, 1204, 1109, 1022 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₂₃H₂₆N₂O₅, 411.1920; found, 411.1918.



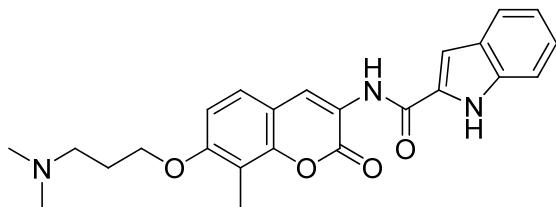
Benzyl 7-(3-(dimethylamino)propoxy)-8-methoxy-2-oxo-2H-chromen-3-ylcarbamate (81b).

Compound **81b** was obtained as a brown white amorphous foam (39 mg, 92%). ¹H NMR (400MHz, CDCl₃): δ 8.25 (s, 1H), 7.55 (s, 1H), 7.41–7.30 (m, 5H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 5.23 (s, 2H), 4.16 (t, *J* = 5.8 Hz, 2H), 3.97 (s, 3H), 2.68 (t, *J* = 5.8 Hz, 2H), 2.41 (s, 6H), 2.13 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 158.3, 153.2, 153.0, 143.8, 136.4, 135.6, 128.7 (2C), 128.5, 128.2 (2C), 122.1, 121.93, 121.86, 114.4, 110.9, 67.5, 67.4, 61.5, 56.1,

45.0 (2C), 26.9. IR (film) ν_{max} 3406, 3310, 2937, 2813, 2766, 1697, 1631, 1608, 1537, 1271, 1229, 1213, 1113, 1024. cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₂₃H₂₇N₂O₆, 427.1869; found, 427.1861.

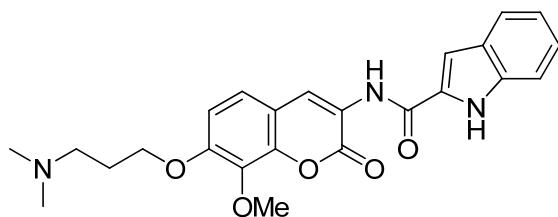


Benzyl 7-(3-(dimethylamino)propoxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-ylcarbamate (81c). Compound **81c** was obtained as a white amorphous solid (77 mg, 60%). ^1H NMR (400MHz, CDCl₃): δ 8.20 (s, 1H), 7.62 (s, 1H), 7.37–7.31 (m, 5H), 6.72 (s, 1H), 5.19 (s, 2H), 4.01 (t, J = 5.7 Hz, 2H), 3.83 (s, 3H), 2.55 (t, J = 5.7 Hz, 2H), 2.32 (s, 3H), 2.29 (s, 6H), 199–1.96 (m, 2H). ^{13}C NMR (100 MHz, CDCl₃) δ 158.7, 153.1, 150.2, 147.9, 143.0, 135.6, 128.6 (2C), 128.5, 128.2 (2C), 122.8, 121.7, 120.2, 115.2, 106.1, 71.6, 67.4, 56.4, 55.9, 45.3 (2C), 28.3, 8.9. IR (film) ν_{max} 3404, 3313, 2953, 2820, 2770, 1709, 1524, 1464, 1389, 1298, 1229, 1204, 1090, 1024 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for C₂₄H₂₉N₂O₆, 441.2026; found, 441.2018.

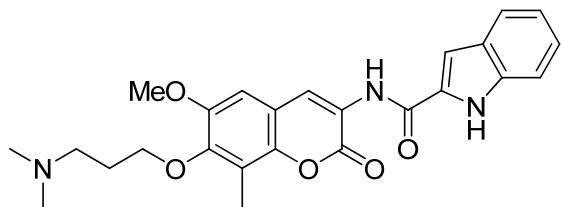


N-(7-(3-(dimethylamino)propoxy)-8-methyl-2-oxo-2H-chromen-3-yl)-1H-indole-2-carboxamide (82a). Compound **82a** was obtained a brown amorphous solid (21 mg, 36%). ^1H NMR (500 MHz, DMSO-*d*₆) δ 11.89 (s, 1H), 9.60 (s, 1H), 8.49 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.42 (s, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.11–7.07 (m, 2H), 4.14 (t, J = 6.2 Hz, 2H), 2.62 (m, 2H), 2.32 (s, 6H), 2.24 (s, 3H), 2.00–1.90 (m, 2H). ^{13}C NMR (125 MHz, DMSO-*d*₆) δ 160.0, 158.22, 158.19, 149.5, 137.1, 130.5, 129.3, 127.0,

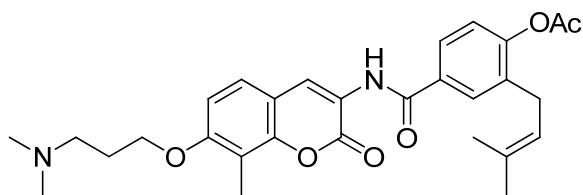
126.3, 124.2, 122.0, 120.8, 120.1, 112.7, 112.49, 112.46, 109.2, 105.0, 66.5, 55.2, 44.4 (2C), 26.1, 8.0. IR (film) ν_{max} 3375, 3319, 2926, 2854, 1711, 1649, 1580, 1535, 1412, 1390, 1327, 1265, 1111, 1063, 789 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₂₄H₂₆N₃O₄, 420.1923; found, 420.1920. This material was determined to be 100% pure (Retention time = 12.1) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H₂O (0.2% H₃PO₄)/30% MeCN → 52% H₂O (0.2% H₃PO₄)/48% MeCN → 95% H₂O (0.2% H₃PO₄)/5% MeCN → 70% H₂O (0.2% H₃PO₄)/30% MeCN, flow rate 1.0 mL/min.



N-(7-(3-(dimethylamino)propoxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-1H-indole-2-carboxamide (82b). Compound **82b** was obtained a brown amorphous solid (28 mg, 70%). ¹H NMR (500 MHz, CDCl₃-CD₃OD) δ 8.50 (s, 1H), 7.47 (m, 1H), 7.28 (m, 1H), 7.11–7.04 (m, 2H), 7.00 (s, 1H), 6.94–6.91 (m, 1H), 6.79–6.76 (m, 1H), 3.95 (t, *J* = 4.7 Hz, 2H), 3.78 (s, 3H), 2.52 (m, 2H), 2.23 (s, 3H), 2.22 (s, 3H), 1.92–1.88 (m, 2H). ¹³C NMR (125 MHz, CDCl₃/CD₃OD) δ 164.5, 162.7, 157.3, 147.9, 141.4, 140.0, 133.8, 131.3, 128.9, 128.8, 126.8, 126.1, 125.5, 124.6, 118.4, 116.1, 114.8, 108.7, 71.1, 65.3, 59.9, 48.4 (2C), 30.4. IR (film) ν_{max} 3379, 3321, 2943, 2853, 1712, 1662, 1583, 1542, 1421, 1391, 1291, 1207, 1138, 1030, 739 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₂₄H₂₆N₃O₅, 436.1873; found, 436.1867. This material was determined to be 100% pure (Retention time = 8.25) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H₂O (0.2% H₃PO₄)/30% MeCN → 52% H₂O (0.2% H₃PO₄)/48% MeCN → 95% H₂O (0.2% H₃PO₄)/5% MeCN → 70% H₂O (0.2% H₃PO₄)/30% MeCN, flow rate 1.0 mL/min.

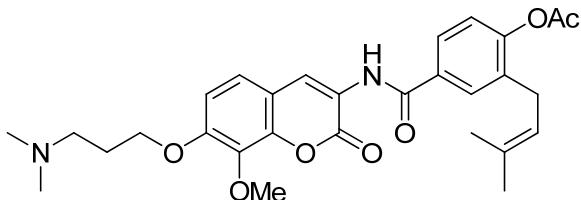


N-(7-(3-(dimethylamino)propoxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-1H-indole-2-carboxamide (82c). Compound **82c** was obtained a brown amorphous solid (41 mg, 83%). ^1H NMR (500 MHz, CDCl_3 - CD_3OD) δ 8.37 (s, 1H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.17 (d, $J = 8.0$ Hz, 1H), 6.97 (t, $J = 8.0$ Hz, 1H), 6.89 (s, 1H), 6.81 (t, $J = 8.0$ Hz, 1H), 6.60 (s, 1H). 3.74 (t, $J = 5.6$ Hz, 2H), 3.60 (s, 3H), 2.67 (t, $J = 5.6$ Hz, 2H), 2.29 (s, 6H), 1.80 (s, 3H), 1.80 (m, 2H). ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 164.5, 163.1, 154.1, 151.7, 147.2, 141.4, 133.8, 131.3, 128.8, 128.4, 126.5, 125.9, 124.4, 123.9, 119.5, 116.0, 110.5, 108.6, 74.7, 60.1, 59.6, 47.7 (2C), 30.6, 12.3. IR (film) ν_{max} 3381, 3315, 2943, 2833, 1722, 1657, 1543, 1467, 1394, 1292, 1086, 1030, 739 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{25}\text{H}_{28}\text{N}_3\text{O}_5$, 450.2029; found, 450.2031. This material was determined to be 96% pure (Retention time = 7.92) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H_2O (0.2% H_3PO_4)/30% MeCN \rightarrow 52% H_2O (0.2% H_3PO_4)/48% MeCN \rightarrow 95% H_2O (0.2% H_3PO_4)/5% MeCN \rightarrow 70% H_2O (0.2% H_3PO_4)/30% MeCN, flow rate 1.0 mL/min.



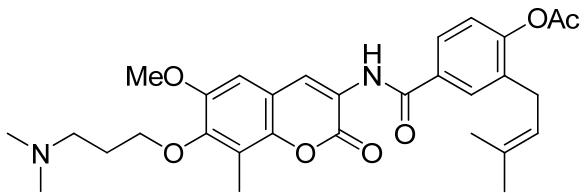
4-(7-(3-(Dimethylamino)propoxy)-8-methyl-2-oxo-2H-chromen-3-ylcarbamoyl)-2-(3-methylbut-2-enyl)phenyl acetate (83a). Compound **83a** was obtained as a white amorphous solid (79 mg, 77%). ^1H NMR (500MHz, CDCl_3) δ 8.79 (s, 1H), 8.70 (s, 1H), 7.81 (s, 1H), 7.77 (d, $J = 8.3$ Hz, 1H), 7.34 (d, $J = 8.6$ Hz, 1H), 7.18 (d, $J = 8.3$ Hz, 1H), 6.88 (d, $J = 8.6$ Hz,

1H), 5.25 (m, 1H), 4.15 (t, $J = 6.0$ Hz, 2H), 3.32 (d, $J = 7.2$ Hz, 2H), 2.77 (t, $J = 7.4$ Hz, 2H), 2.49 (s, 6H), 2.35 (s, 3H), 2.33 (s, 3H), 2.17 (m, 2H), 1.77 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.1, 165.6, 159.7, 158.4, 152.3, 149.4, 134.8, 134.5, 131.8, 129.6, 126.09, 126.05, 124.9, 123.1, 121.7, 120.9, 114.3, 113.6, 109.1, 66.7, 56.4, 45.0 (2C), 29.0, 26.8, 26.0, 21.1, 18.2, 8.4. IR (film) ν_{max} 3400, 3086, 3054, 2922, 2851, 1765, 1711, 1672, 1607, 1526, 1493, 1369, 1248, 1202, 1175, 1099, 1040 cm^{-1} . HRMS (ESI $^+$) m/z: [M + H $^+$] calcd for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_6$, 507.2495; found, 507.2501. This material was determined to be 100% pure (Retention time = 10.0) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H_2O (0.2% H_3PO_4)/30% MeCN \rightarrow 52% H_2O (0.2% H_3PO_4)/48% MeCN \rightarrow 95% H_2O (0.2% H_3PO_4)/5% MeCN \rightarrow 70% H_2O (0.2% H_3PO_4)/30% MeCN, flow rate 1.0 mL/min.

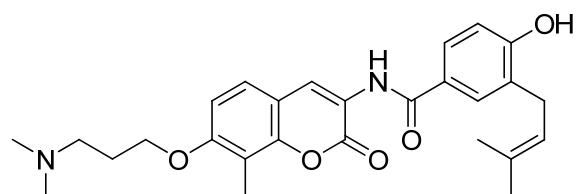


4-(7-(3-(dimethylamino)propoxy)-8-methoxy-2-oxo-2H-chromen-3-ylcarbamoyl)-2-(3-methylbut-2-enyl)phenyl acetate (83b). Compound **83b** was obtained as white amorphous solid (48 mg, 54%). ^1H NMR (500 MHz, CDCl_3) δ 8.79 (s, 1H), 8.70 (s, 1H), 7.80 (d, $J = 2.3$ Hz, 1H), 7.76 (dd, $J = 8.4$ Hz, 2.3 Hz, 1H), 7.22 (d, $J = 8.8$ Hz, 1H), 7.18 (d, $J = 8.4$ Hz, 1H), 6.95 (d, $J = 8.8$ Hz, 1H), 5.24 (m, 1H), 4.17 (t, $J = 6.3$ Hz, 2H), 3.99 (s, 3H), 3.32 (d, $J = 7.2$ Hz, 2H), 2.66 (t, $J = 7.2$ Hz, 2H), 2.40 (s, 6H), 2.37 (s, 3H), 2.12 (m, 2H), 1.77 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.1, 165.7, 159.1, 153.7, 152.3, 144.3, 136.6, 134.9, 134.5, 131.7, 129.6, 126.1, 124.5, 123.1, 122.9, 122.1, 120.8, 114.6, 111.1, 67.6, 61.8, 56.3, 45.3 (2C), 29.0, 27.1, 25.9, 21.1, 18.2. IR (film) ν_{max} 3408, 3084, 3024, 2937, 2858, 1711, 1666, 1605, 1529,

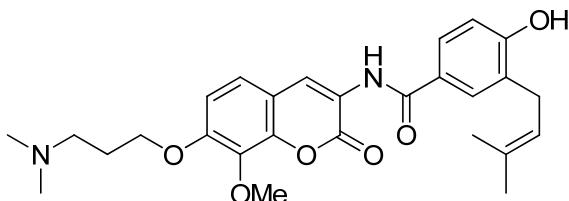
1502, 1462, 1367, 1259, 1178, 1105, 1082, 1034 cm⁻¹. HRMS (ESI⁺) m/z calcd for [M+H⁺] C₂₉H₃₅NO₇, 523.2444; found, 523.2450.



4-(7-(3-(dimethylamino)propoxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-ylcarbamoyl)-2-(3-methylbut-2-enyl)phenyl acetate (83c). Compound **83c** was obtained as white amorphous solid (81 mg, 70%). ¹H NMR (500 MHz, CDCl₃) δ 8.78 (s, 1H), 8.75 (s, 1H), 7.81 (d, *J* = 2.2 Hz, 1H), 7.77 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.84 (s, 1H), 5.24 (m, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.90 (s, 3H), 3.32 (d, *J* = 7.2 Hz, 2H), 2.89 (t, *J* = 7.5 Hz, 2H), 2.55 (s, 6H), 2.37 (s, 3H), 2.35 (s, 3H), 2.15 (m, 2H), 1.77 (s, 3H), 1.73 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 169.1, 165.7, 159.5, 152.3, 150.4, 148.1, 143.6, 134.9, 134.5, 131.7, 129.6, 126.1, 124.1, 123.17, 123.14, 120.8, 120.6, 115.7, 106.7, 71.1, 56.5, 56.2, 44.7 (2C), 29.0, 27.4, 25.9, 21.1, 18.2, 9.2. IR (film) *v*_{max} 3404, 3082, 2935, 2854, 1765, 1711, 1672, 1605, 1527, 1492, 1382, 1249, 1177, 1088, 1034 cm⁻¹. HRMS (ESI⁺) m/z calcd for [M+H⁺] C₃₀H₃₇NO₇, 537.2601; found, 537.2595. This material was determined to be 99% pure (Retention time = 10.8) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H₂O (0.2% H₃PO₄)/30% MeCN → 52% H₂O (0.2% H₃PO₄)/48% MeCN → 95% H₂O (0.2% H₃PO₄)/5% MeCN → 70% H₂O (0.2% H₃PO₄)/30% MeCN, flow rate 1.0 mL/min).

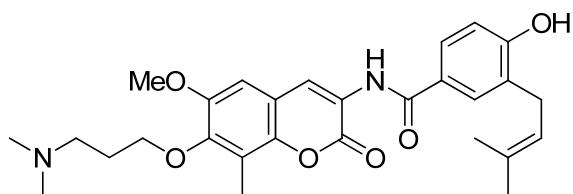


N-(7-(3-(Dimethylamino)propoxy)-8-methyl-2-oxo-2H-chromen-3-yl)-4-hydroxy-3-(3-methylbut-2-enyl)benzamide (84a). Compound **84a** was obtained as a white, amorphous solid (22 mg, 69%). ^1H NMR (500MHz, DMSO- d_6) δ 10.19 (s, 1H), 9.24 (s, 1H), 8.47 (s, 1H), 7.68–7.66 (m, 2H), 7.56 (d, J = 8.7 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H), 5.31 (m, 1H), 4.13 (t, J = 6.2 Hz, 2H), 3.27 (d, J = 7.2 Hz, 2H), 2.47 (t, J = 6.9 Hz, 2H), 2.22 (s, 6H), 2.21 (s, 3H), 1.92 (m, 2H), 1.71 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (125MHz, DMSO- d_6) δ 165.3, 158.7, 158.4, 158.1, 149.3, 131.8, 129.2, 128.1, 127.6, 126.8, 126.1, 124.0, 122.3, 121.2, 114.5, 112.7, 112.4, 109.1, 66.6, 55.5, 45.0 (2C), 27.9, 26.6, 25.5, 17.7, 7.9. IR (film) ν_{max} 3408, 2961, 2928, 1709, 1666, 1607, 1529, 1504, 1367, 1256, 1178, 1109 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₂₇H₃₃N₂O₅, 465.2389; found, 465.2388. This material was determined to be 100% pure (Retention time = 9.83) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H₂O (0.2% H₃PO₄)/30% MeCN → 52% H₂O (0.2% H₃PO₄)/48% MeCN → 95% H₂O (0.2% H₃PO₄)/5% MeCN → 70% H₂O (0.2% H₃PO₄)/30% MeCN, flow rate 1.0 mL/min.



N-(7-(3-(dimethylamino)propoxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-4-hydroxy-3-(3-methylbut-2-enyl)benzamide (84b). Compound **84b** was obtained as a white amorphous solid (16 mg, 79%). ^1H NMR (500MHz, DMSO- d_6) δ 10.23 (bs, 1H), 9.27 (s, 1H), 8.48 (s, 1H), 7.68–7.66 (m, 2H), 7.44 (d, J = 8.9 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 5.30 (m, 1H), 4.16 (t, J = 6.2 Hz, 2H), 3.87 (s, 3H), 3.27 (d, J = 7.2 Hz, 2H), 2.62 (m, 2H), 2.31 (s, 6H), 1.76 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (125MHz, DMSO- d_6) δ 165.4, 158.8, 158.0, 153.1, 144.1, 135.3, 131.9, 129.3, 127.7, 126.9, 123.9, 122.9, 122.3 (2C), 121.8, 114.6, 113.8, 110.9,

66.9, 60.9, 55.2, 44.5 (2C), 27.9, 26.1, 25.5, 17.7. IR (film) ν_{max} 3410, 3319, 3086, 2960, 2878, 1711, 1666, 1605, 1529, 1504, 1462, 1367, 1259, 1178, 1105, 1084 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₂₇H₃₃N₂O₆, 481.2339; found, 481.2338. This material was determined to be 100% pure (Retention time = 9.11) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H₂O (0.2% H₃PO₄)/30% MeCN → 52% H₂O (0.2% H₃PO₄)/48% MeCN → 95% H₂O (0.2% H₃PO₄)/5% MeCN → 70% H₂O (0.2% H₃PO₄)/30% MeCN, flow rate 1.0 mL/min.



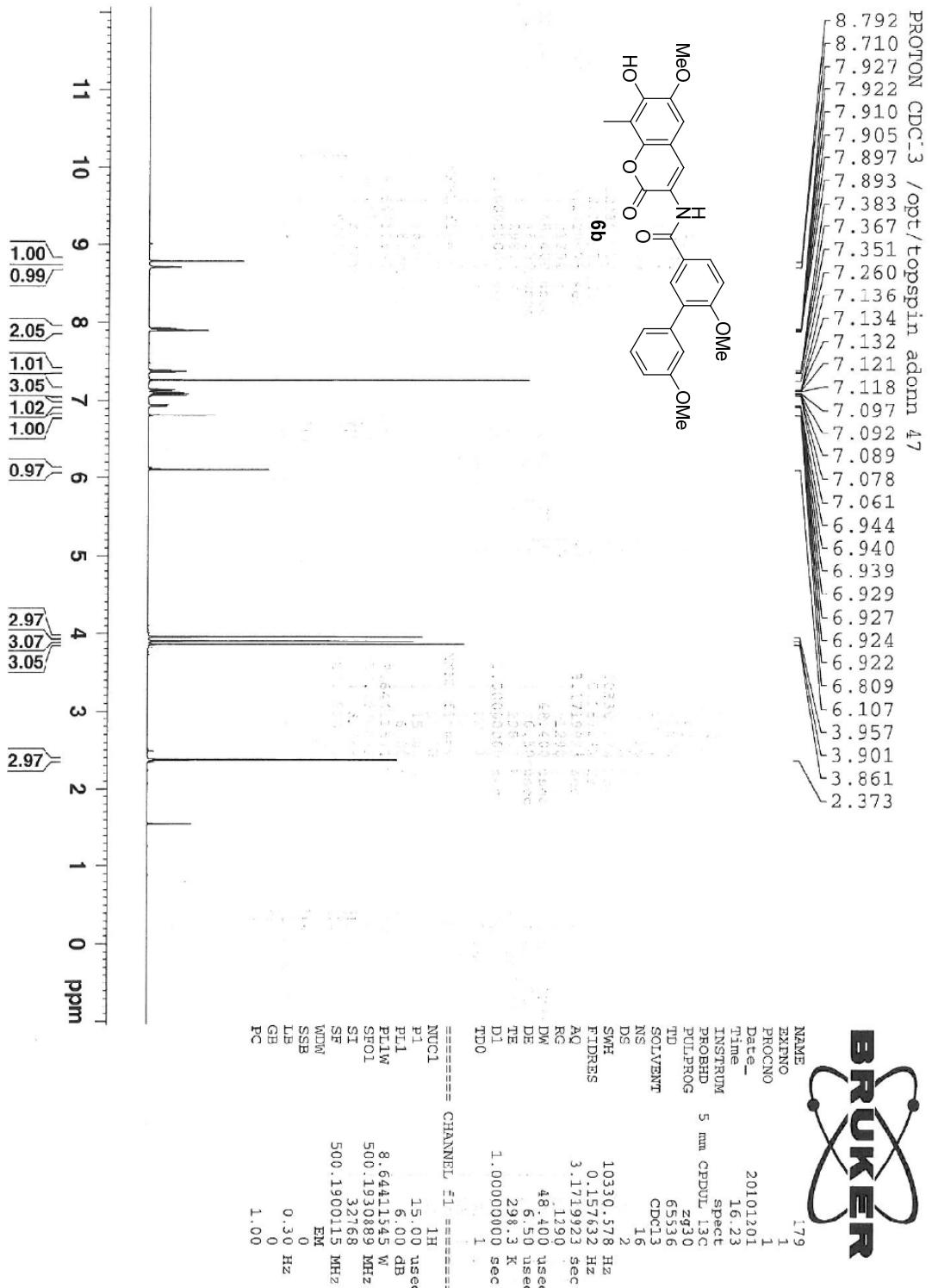
N-(7-(3-(dimethylamino)propoxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-4-hydroxy-3-(3-methylbut-2-enyl)benzamide (84c). Compound **84c** was obtained as a white amorphous solid (23 mg, 58%). ¹H NMR (500MHz, DMSO-d₆) δ 10.25 (bs, 1H), 9.22 (s, 1H), 8.54 (s, 1H), 7.67–7.66 (m, 2H), 7.27 (s, 1H), 6.92 (dd, *J* = 6.5, 2.4 Hz, 1H), 5.30 (m, 1H), 3.98 (t, *J* = 6.3 Hz, 2H), 3.85 (s, 3H), 3.27 (d, *J* = 7.2 Hz, 2H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.27 (s, 3H), 2.26 (s, 6H), 1.89 (m, 2H), 1.71 (s, 3H), 1.70 (s, 3H). ¹³C NMR (125MHz, DMSO-d₆) δ 165.3, 158.9, 158.3, 149.7, 147.5, 143.2, 131.9, 129.1, 127.7, 126.9, 126.4, 123.9, 122.9, 122.3, 118.9, 114.9, 114.6, 107.5, 70.9, 56.0, 55.4, 44.6 (2C), 27.9, 27.3, 25.5, 17.7, 8.7. IR (film) ν_{max} 3406, 3082 (broad), 2962, 2856, 1709, 1670, 1603, 1526, 1502, 1378, 1257, 1176, 1090, 1043, 758 cm⁻¹. HRMS (ESI⁺) m/z: [M + H⁺] calcd for C₂₈H₃₅N₂O₆, 495.2495; found, 495.2498. This material was determined to be 100% pure (Retention time = 8.48) by HPLC (ZORBAX Eclipse Plus 4.6 x 150 mm column eluting with 70% H₂O (0.2% H₃PO₄)/30% MeCN → 52% H₂O (0.2%

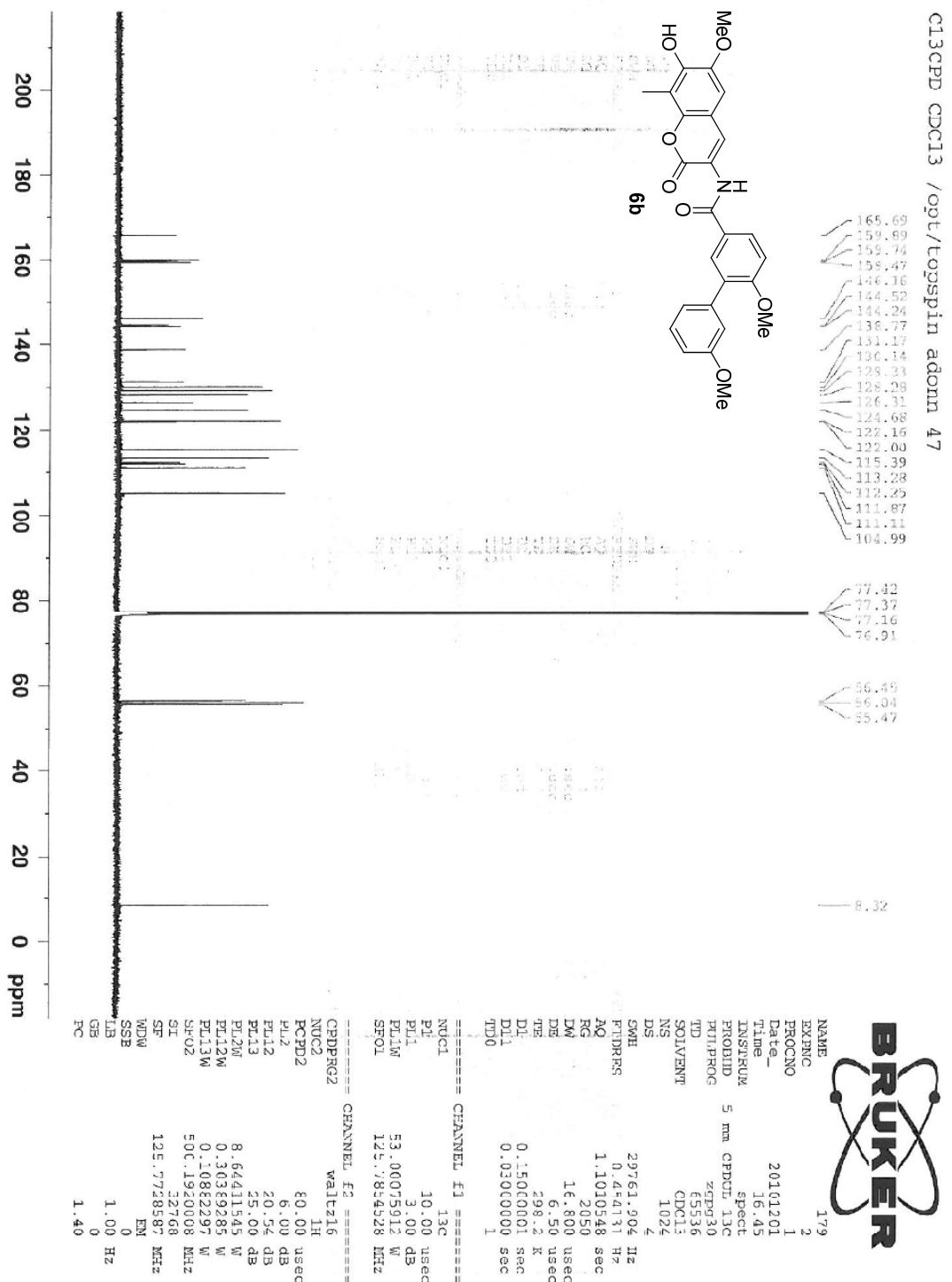
H_3PO_4)/48% MeCN → 95% H_2O (0.2% H_3PO_4)/5% MeCN → 70% H_2O (0.2% H_3PO_4)/30% MeCN, flow rate 1.0 mL/min.

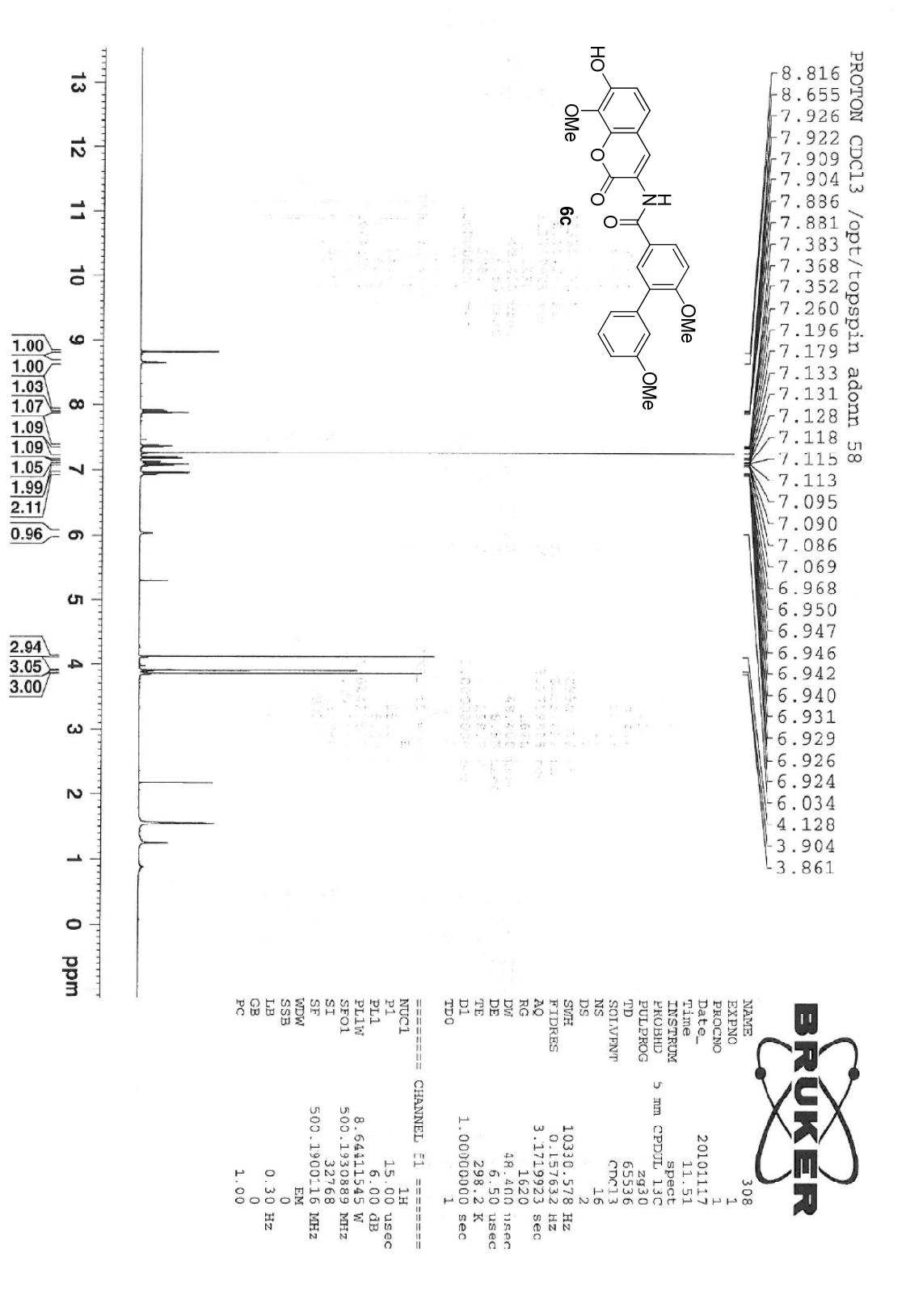
Anti-proliferation assays. Cells were maintained in a 1:1 mixture of Advanced DMEM/F12 (Gibco) supplemented with non-essential amino acids, L-glutamine (2 mM), streptomycin (500 $\mu\text{g}/\text{mL}$), penicillin (100 units/mL), and 10% FBS. Cells were grown to confluence in a humidified atmosphere (37° C , 5% CO_2), seeded (2000/well, 100 μL) in 96-well plates, and allowed to attach overnight. Compound or GDA at varying concentrations in DMSO (1% DMSO final concentration) was added, and cells were returned to the incubator for 72 h. At 72 h, the number of viable cells was determined using an MTS/PMS cell proliferation kit (Promega) per the manufacturer's instructions. Cells incubated in 1% DMSO were used at 100% proliferation, and values were adjusted accordingly. IC_{50} values were calculated from separate experiments performed in triplicate using GraphPad Prism.

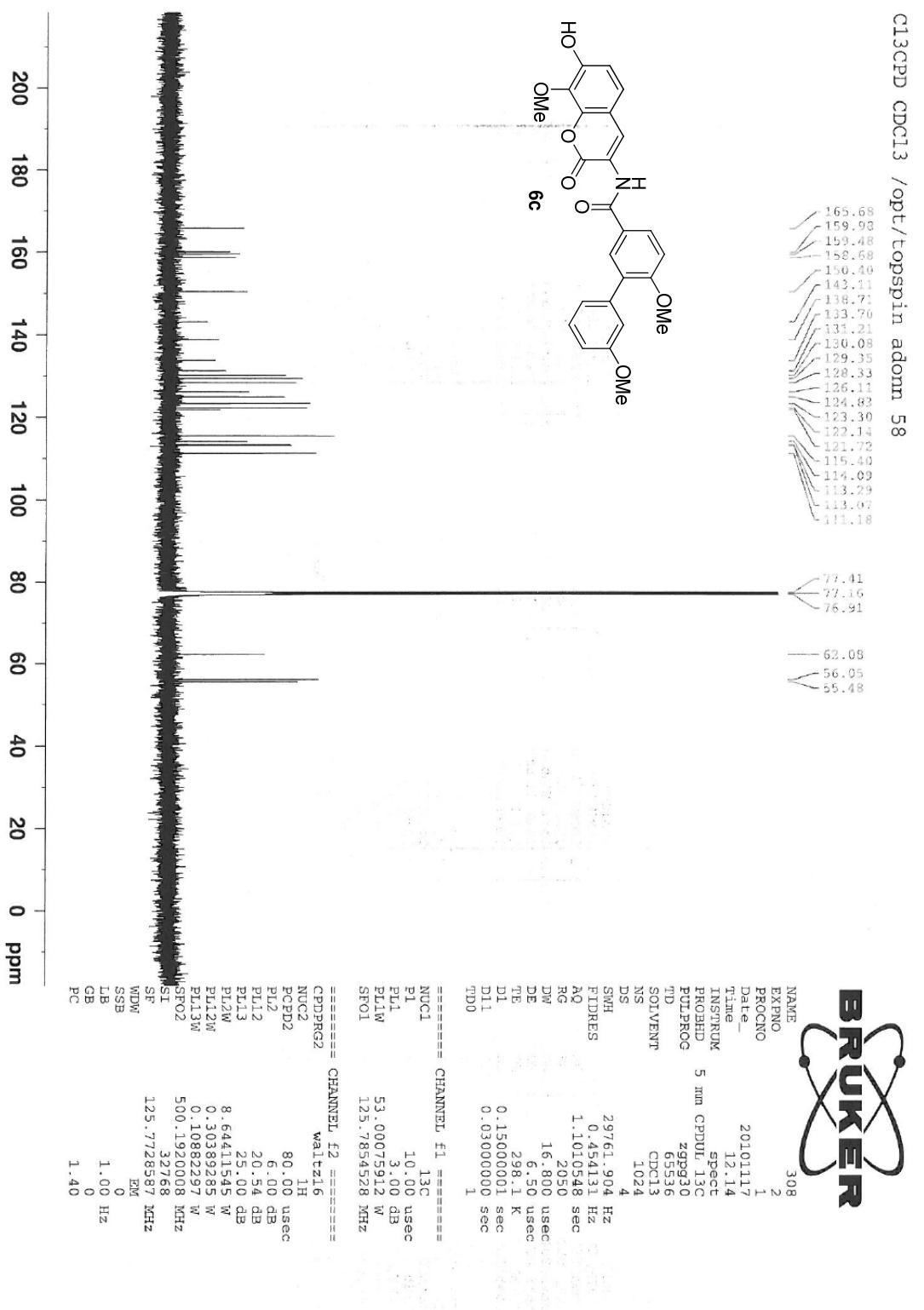
Western blot Analyses. MCF-7 cells were cultured as described above and treated with various concentrations of drug, GDA in DMSO (1% DMSO final concentration), or vehicle (DMSO) for 24 h. Cells were harvested in cold PBS and lysed in RIPA lysis buffer containing 1 mM PMSF, 2 mM sodium orthovanadate, and protease inhibitors on ice for 1 h. Lysates were clarified at 14000g for 10 min at 4° C . Protein concentrations were determined using the Pierce BCA protein assay kit per the manufacturer's instructions. Equal amounts of protein (20 μg) were electrophoresed under reducing conditions, transferred to a nitrocellulose membrane, and immunoblotted with the corresponding specific antibodies. Membranes were incubated with an

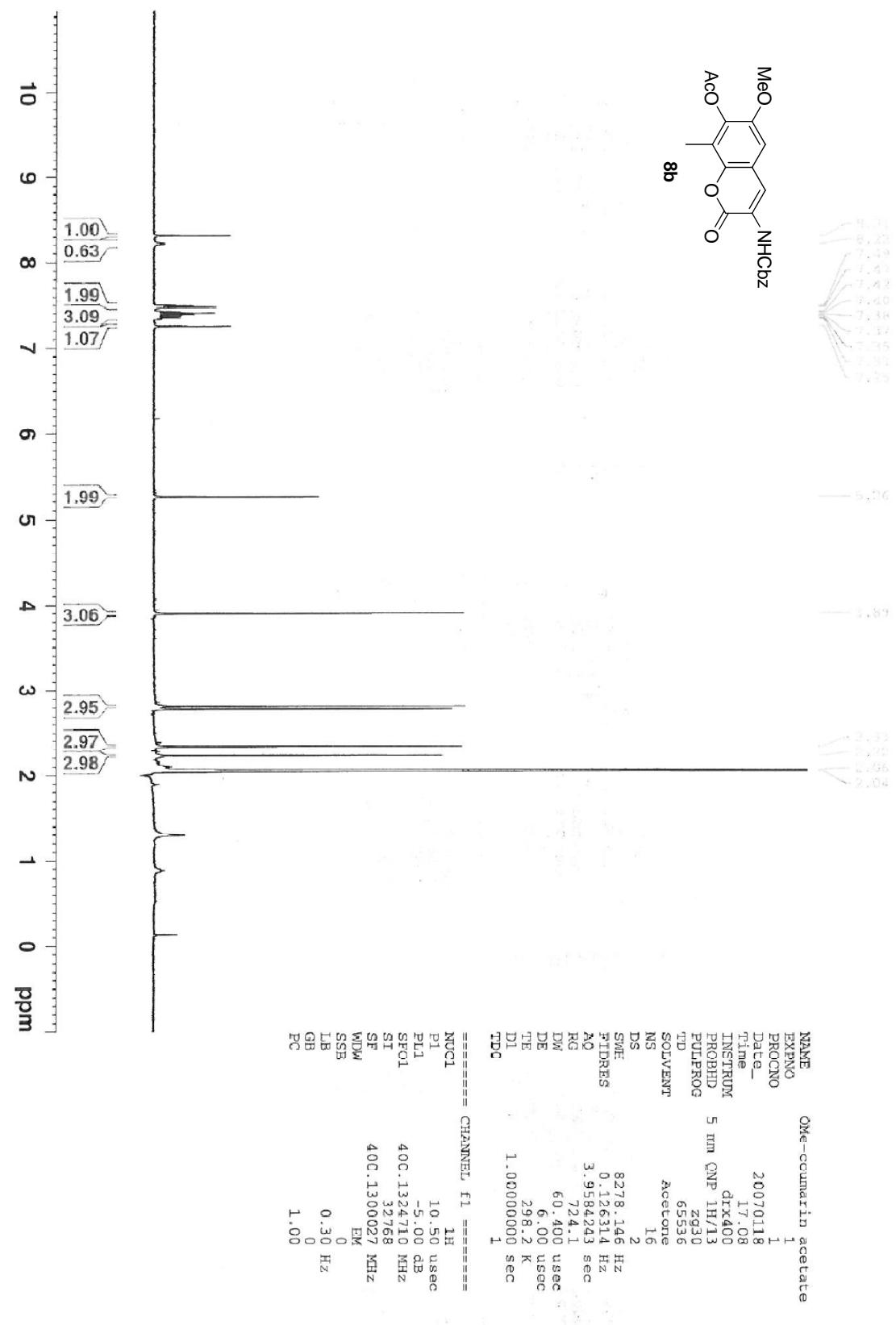
appropriate horseradish peroxidase-labeled secondary antibody, developed with a chemiluminescent substrate, and visualized.

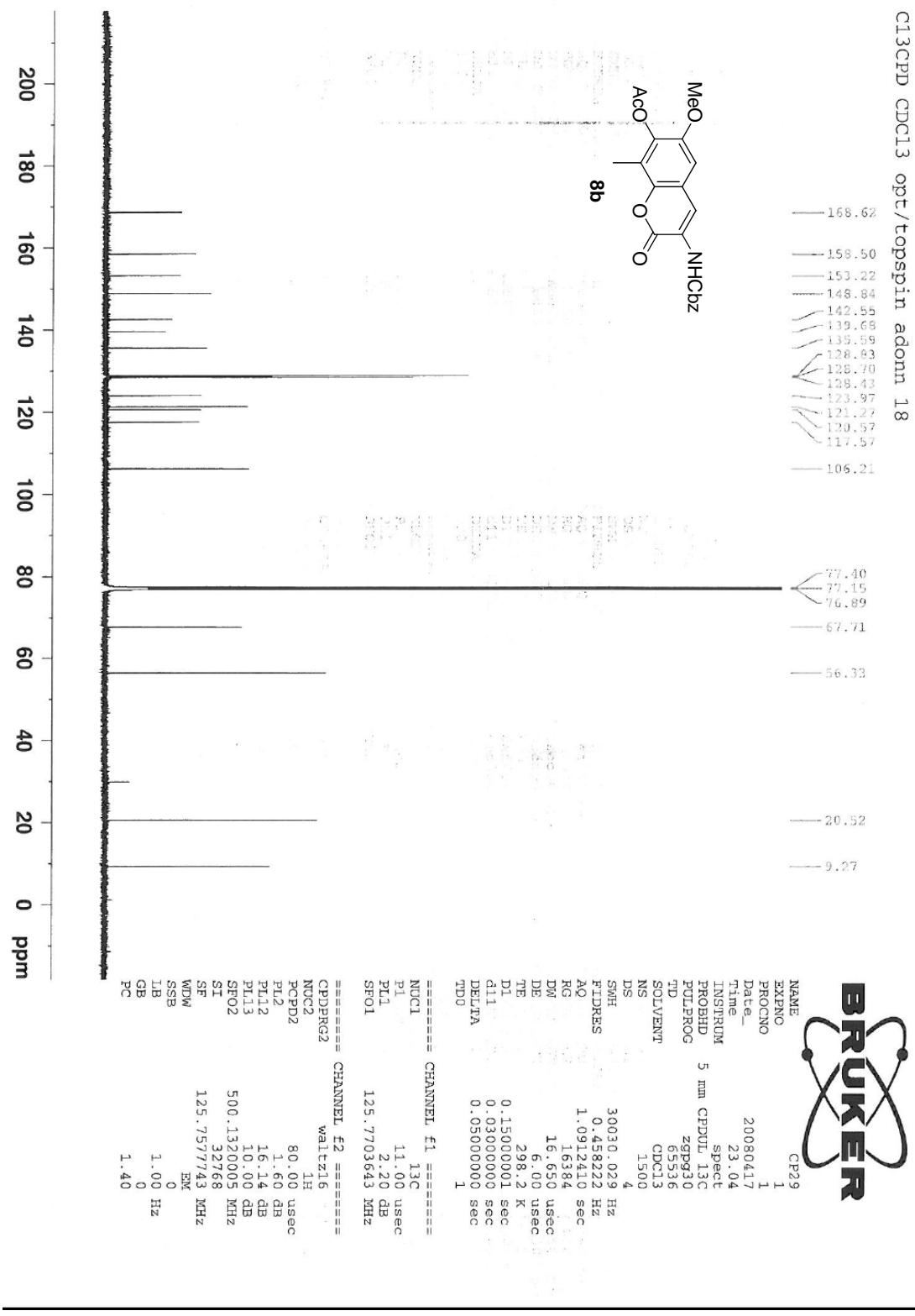


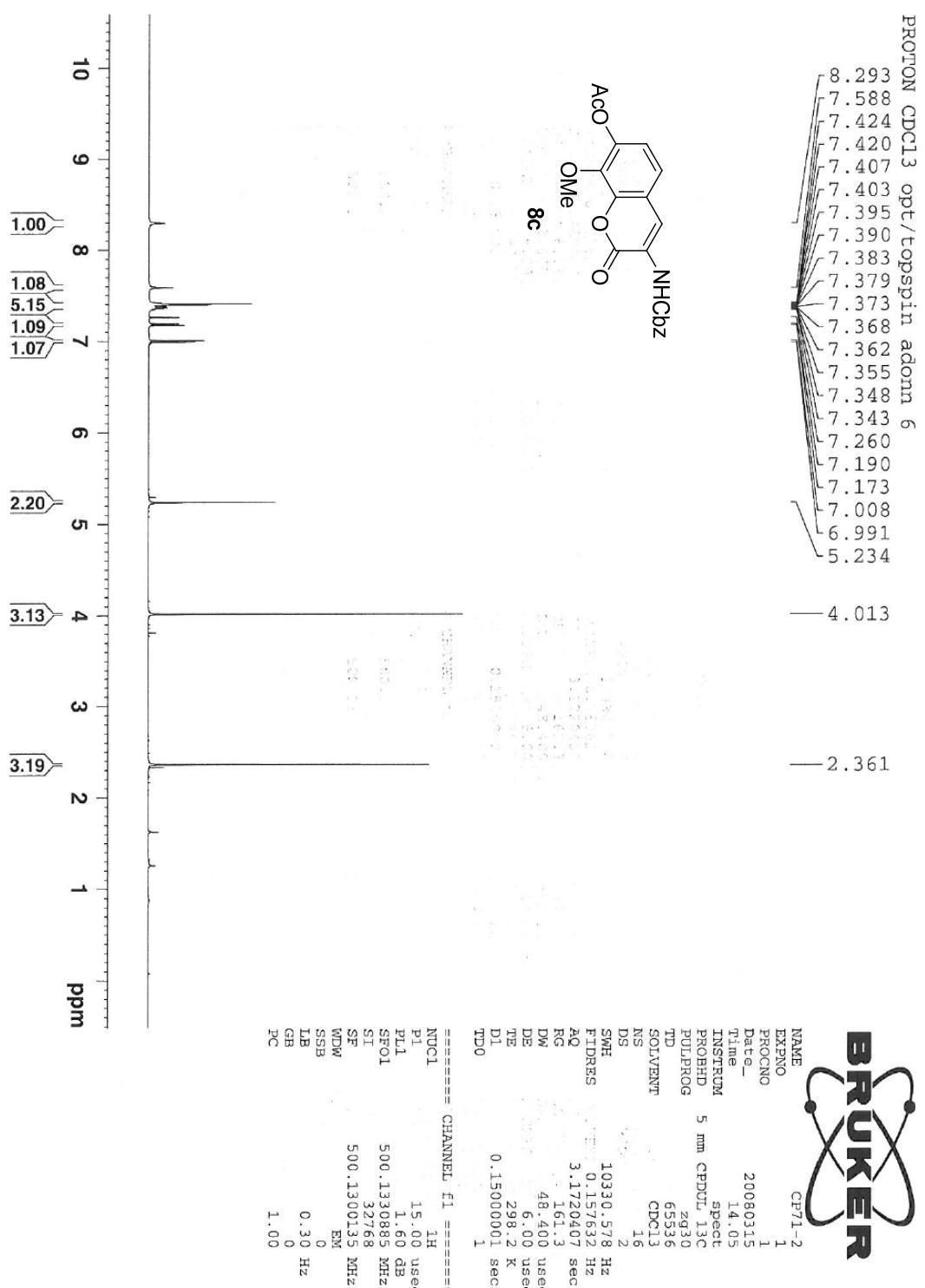


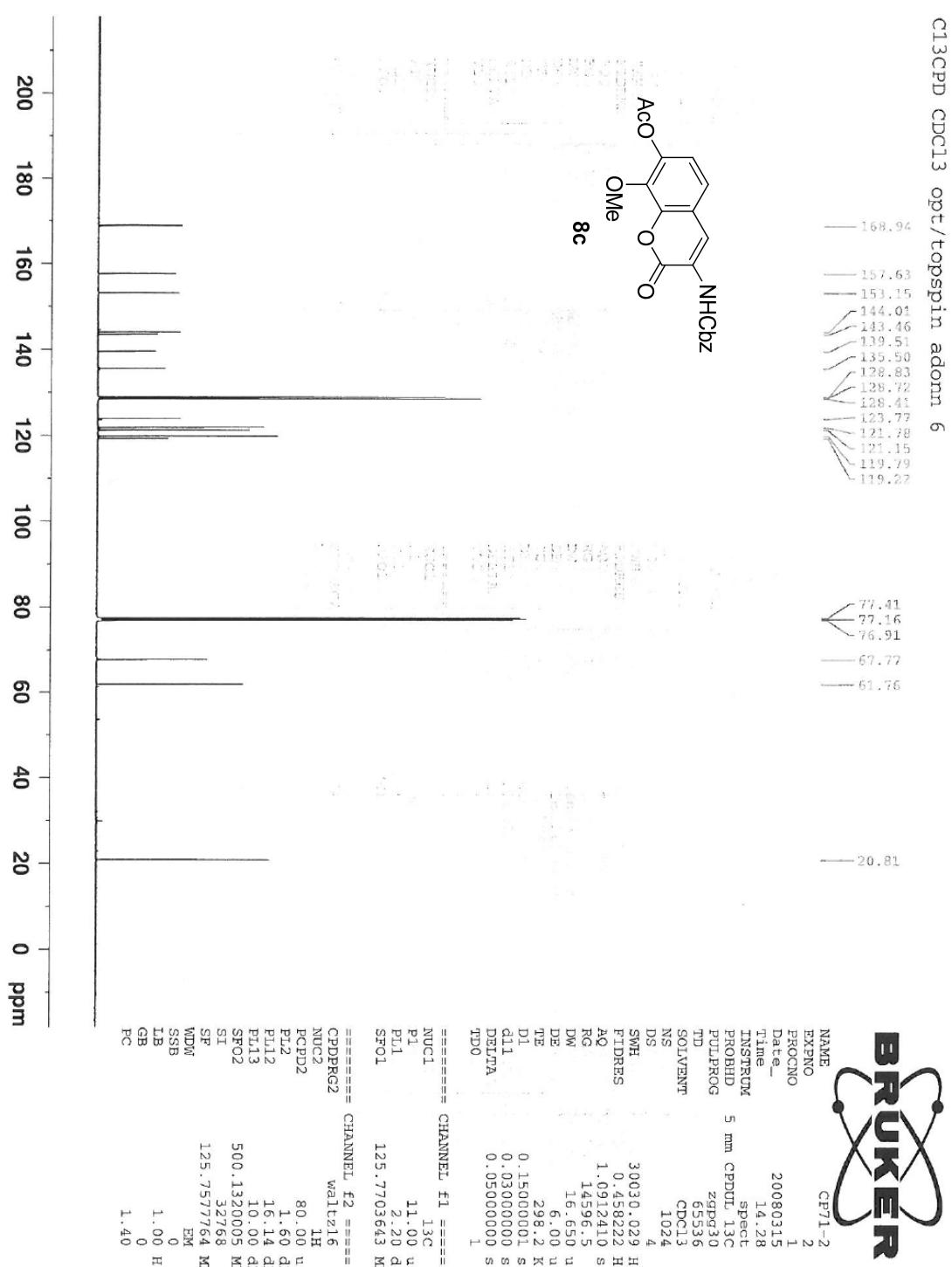


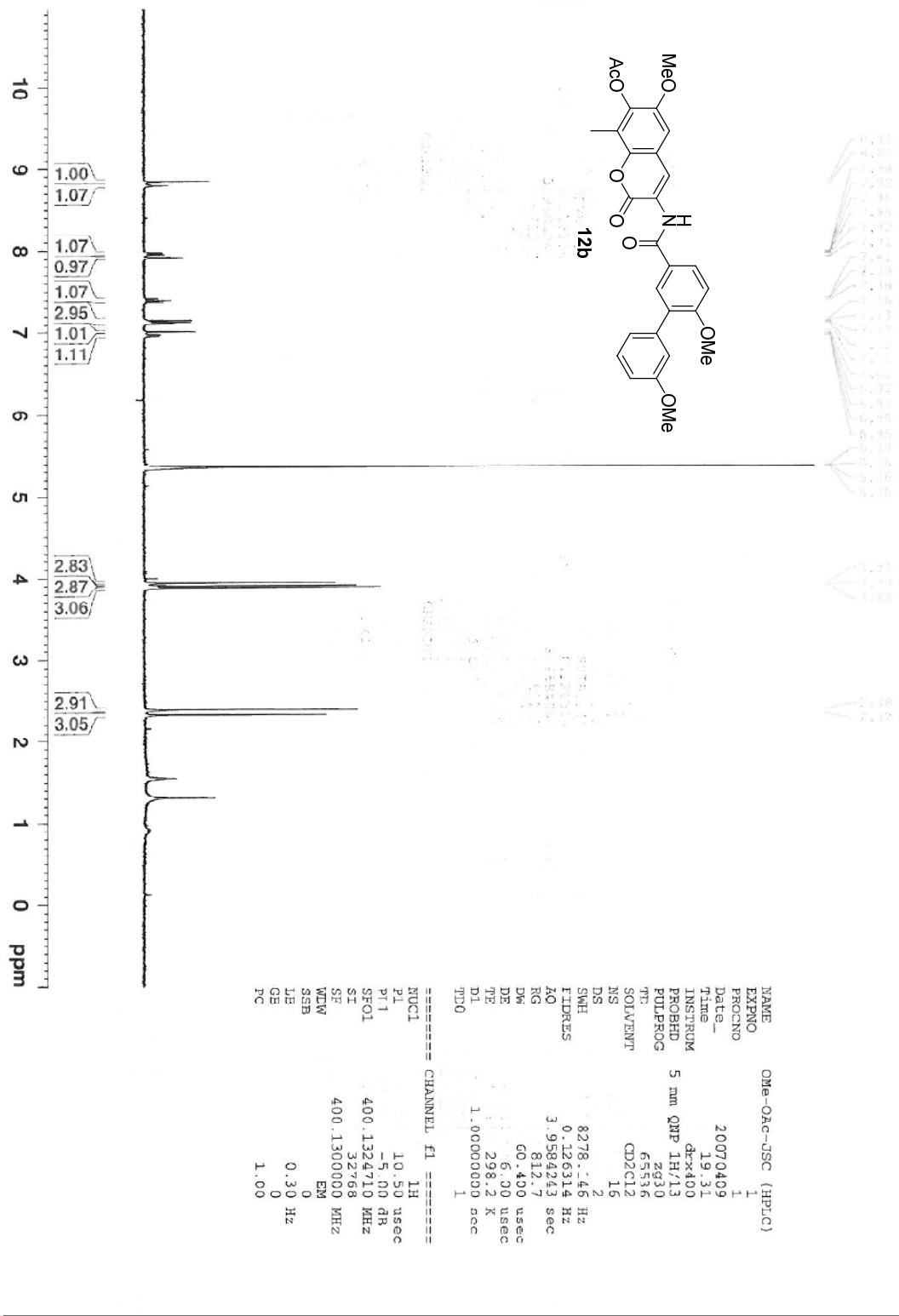


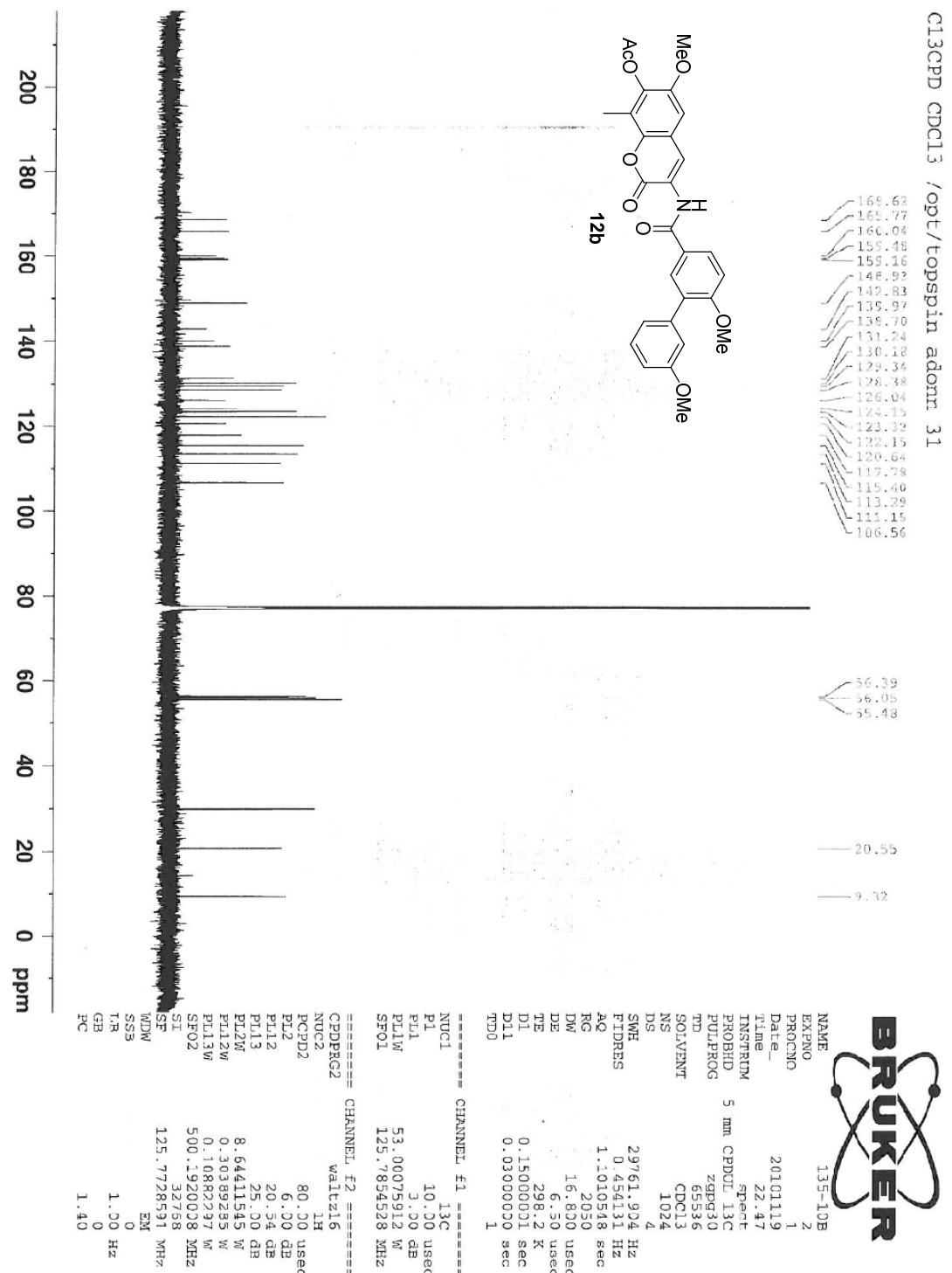


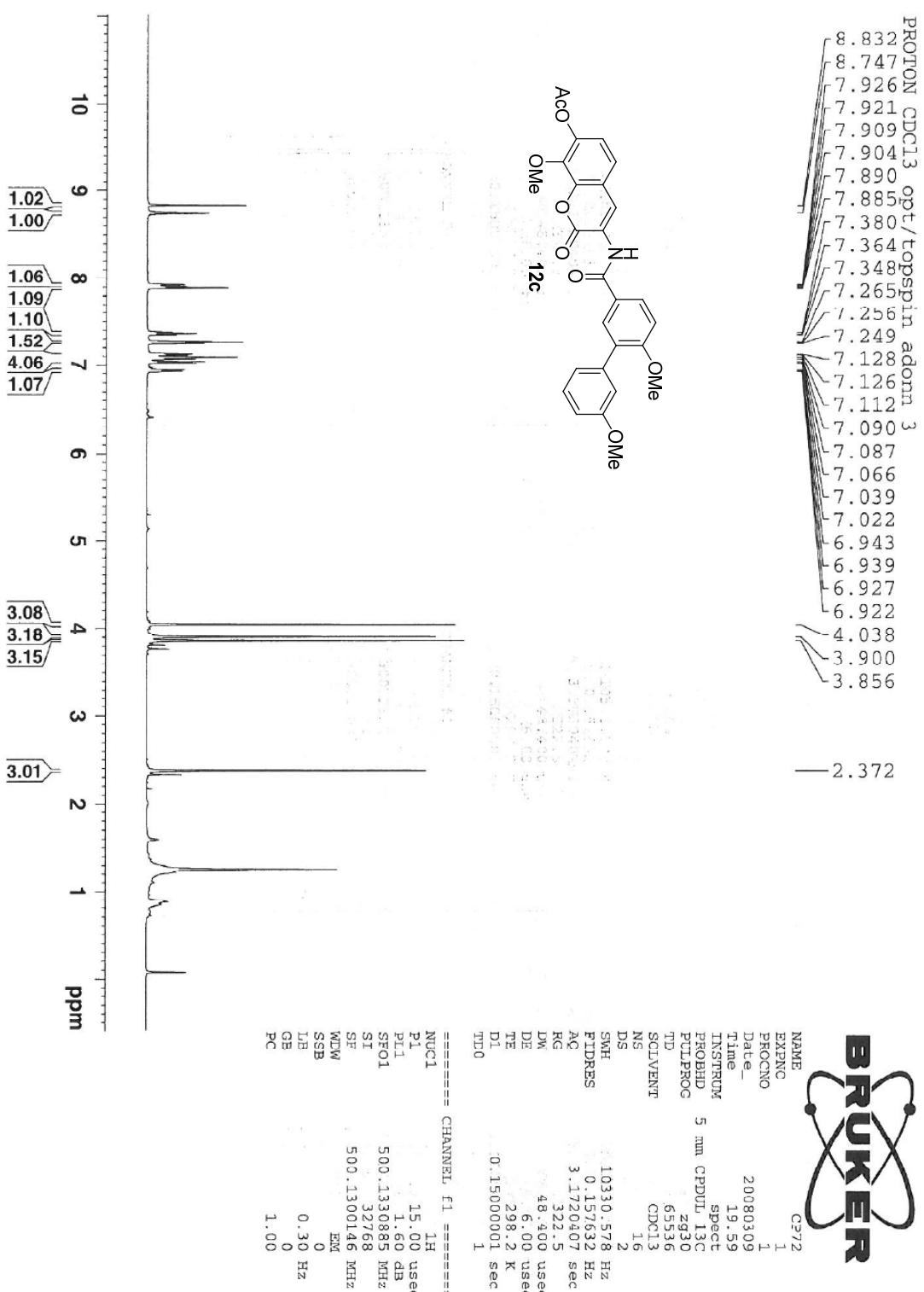


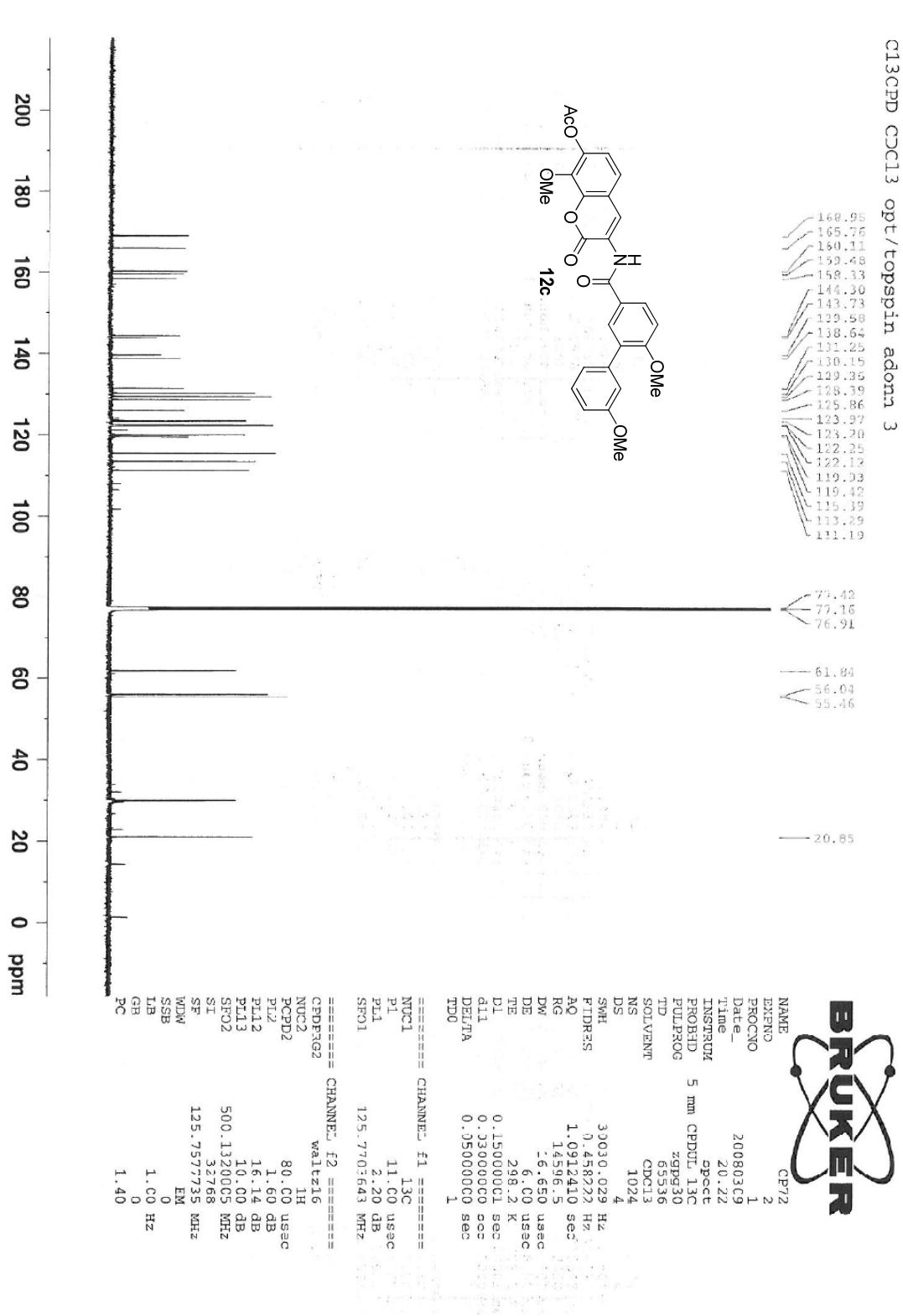


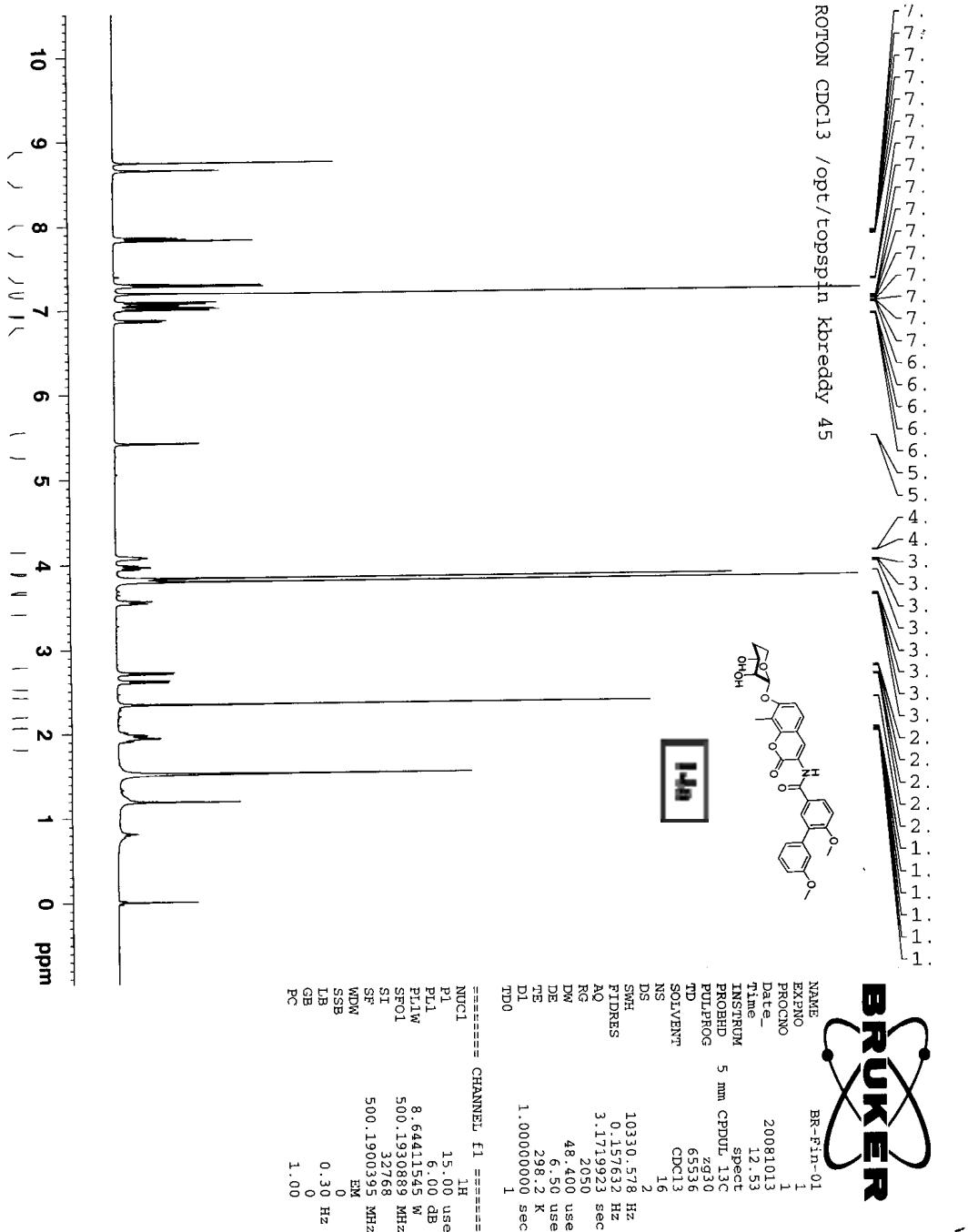


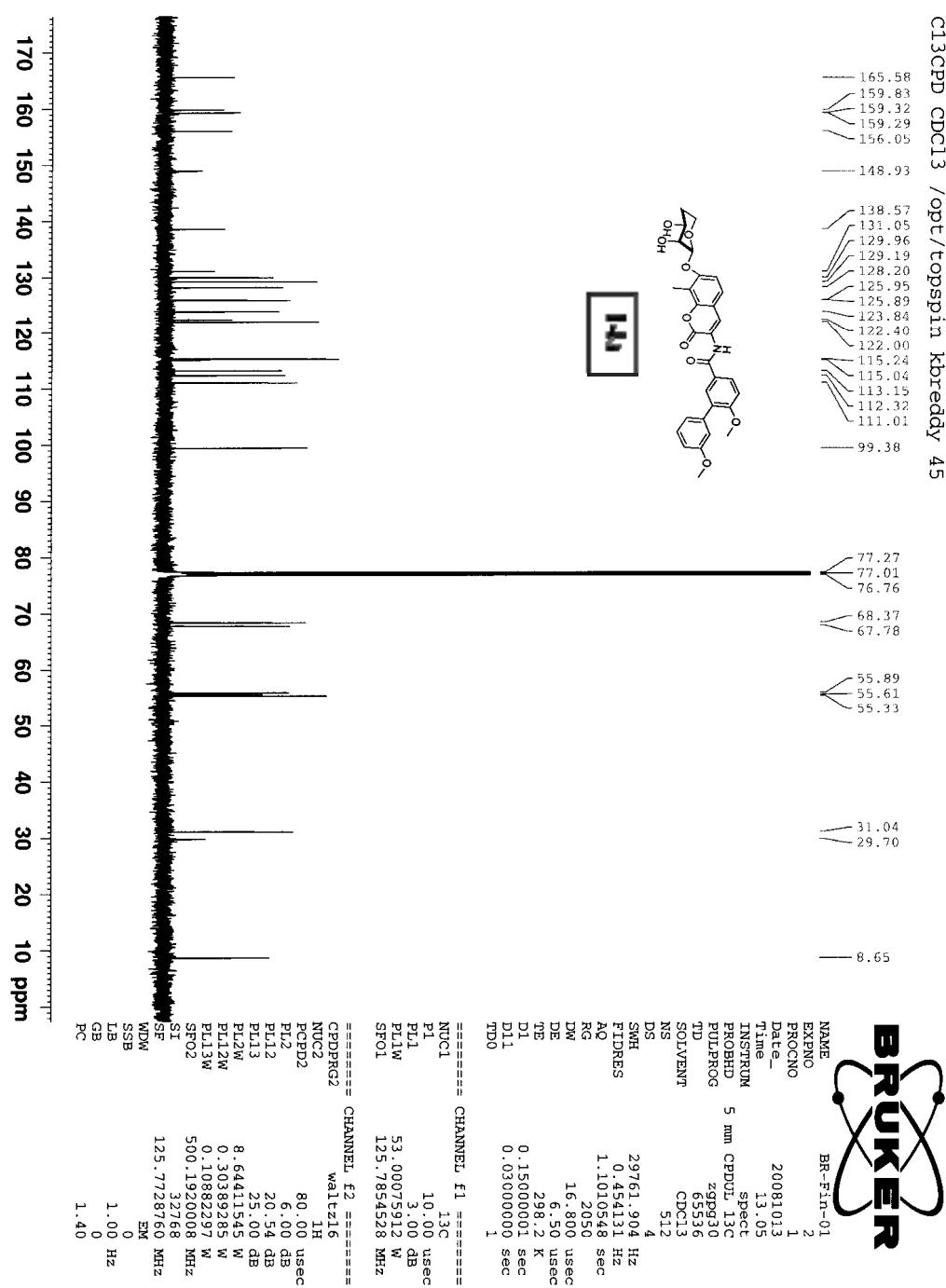


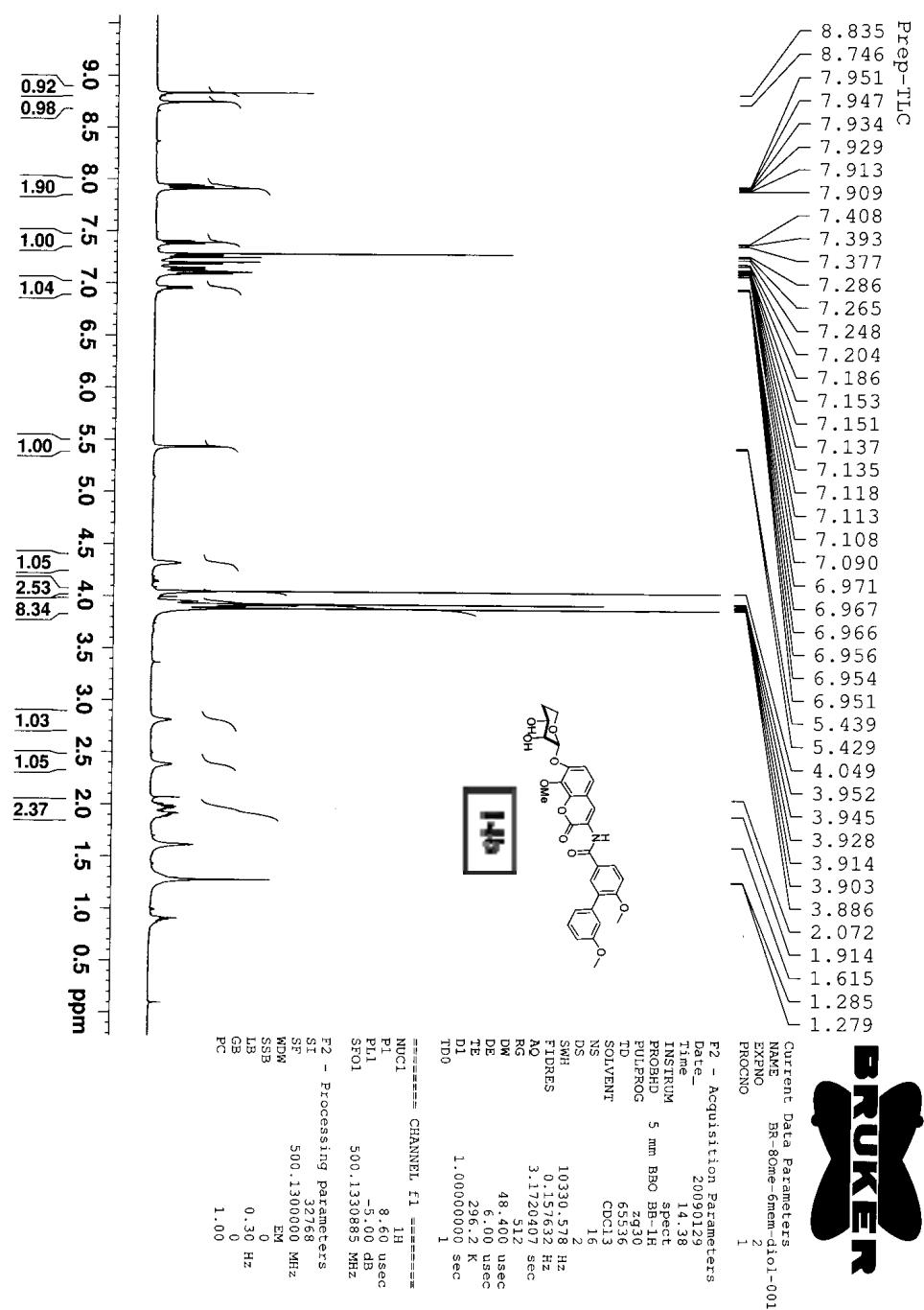


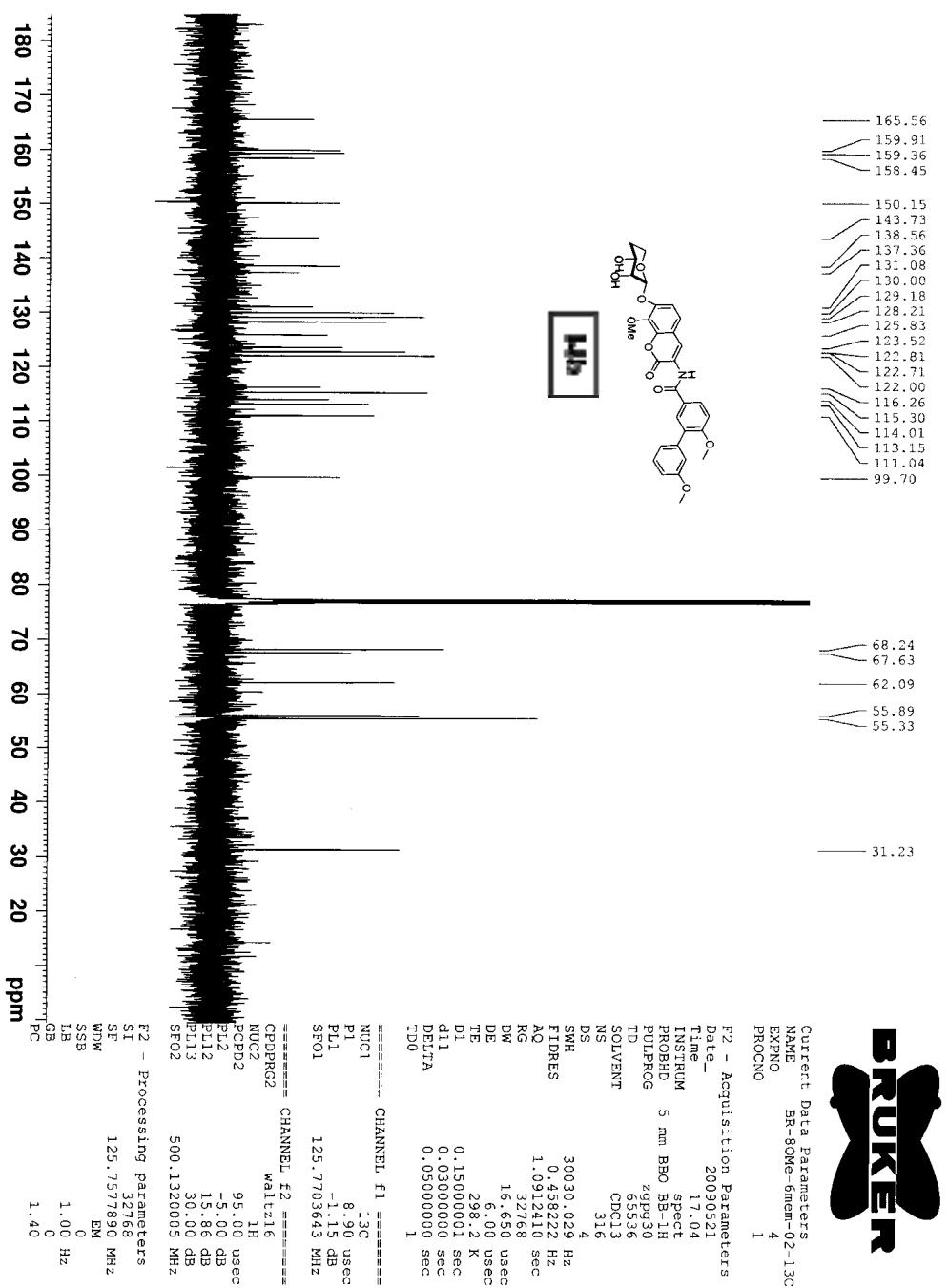


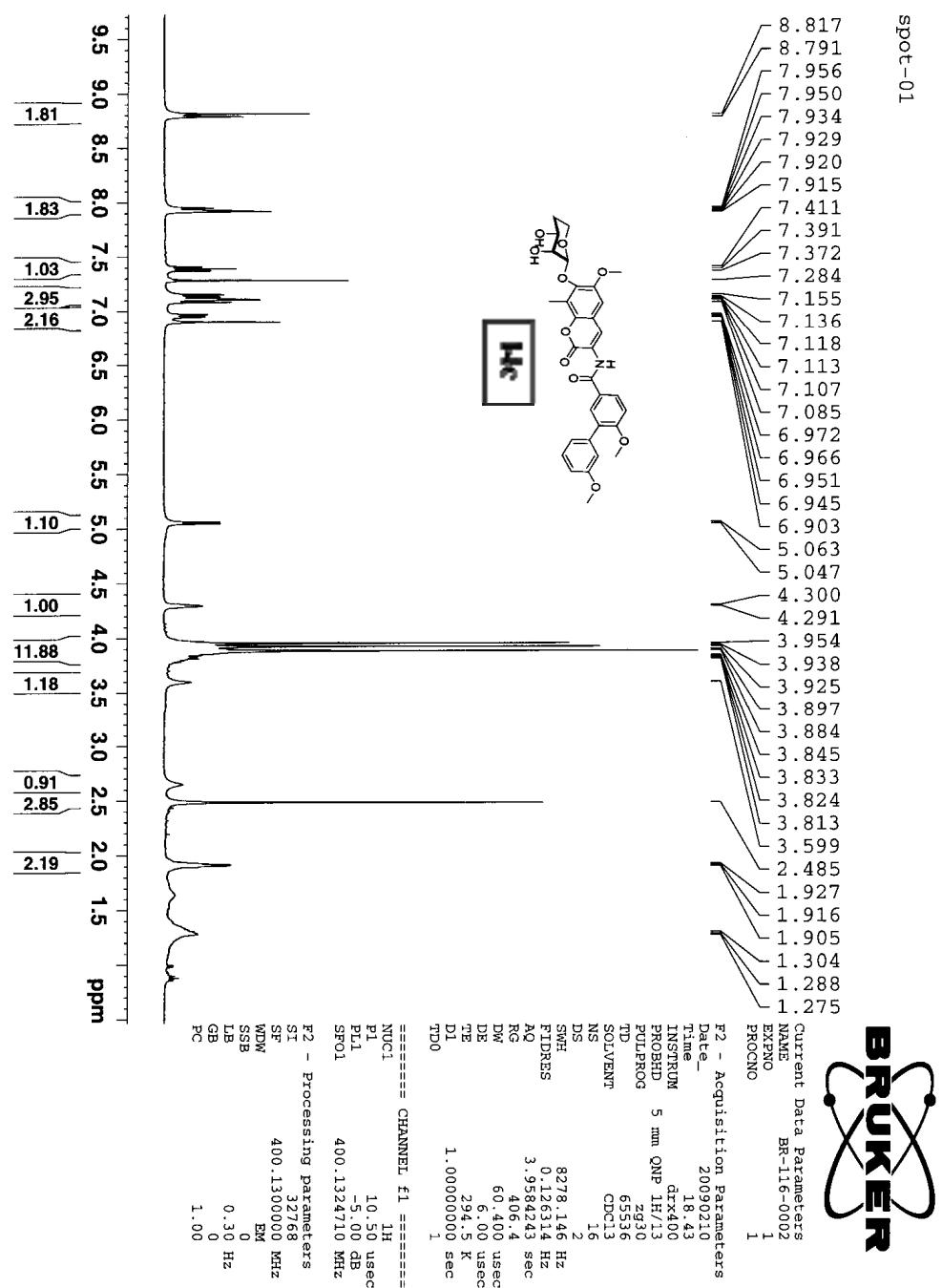


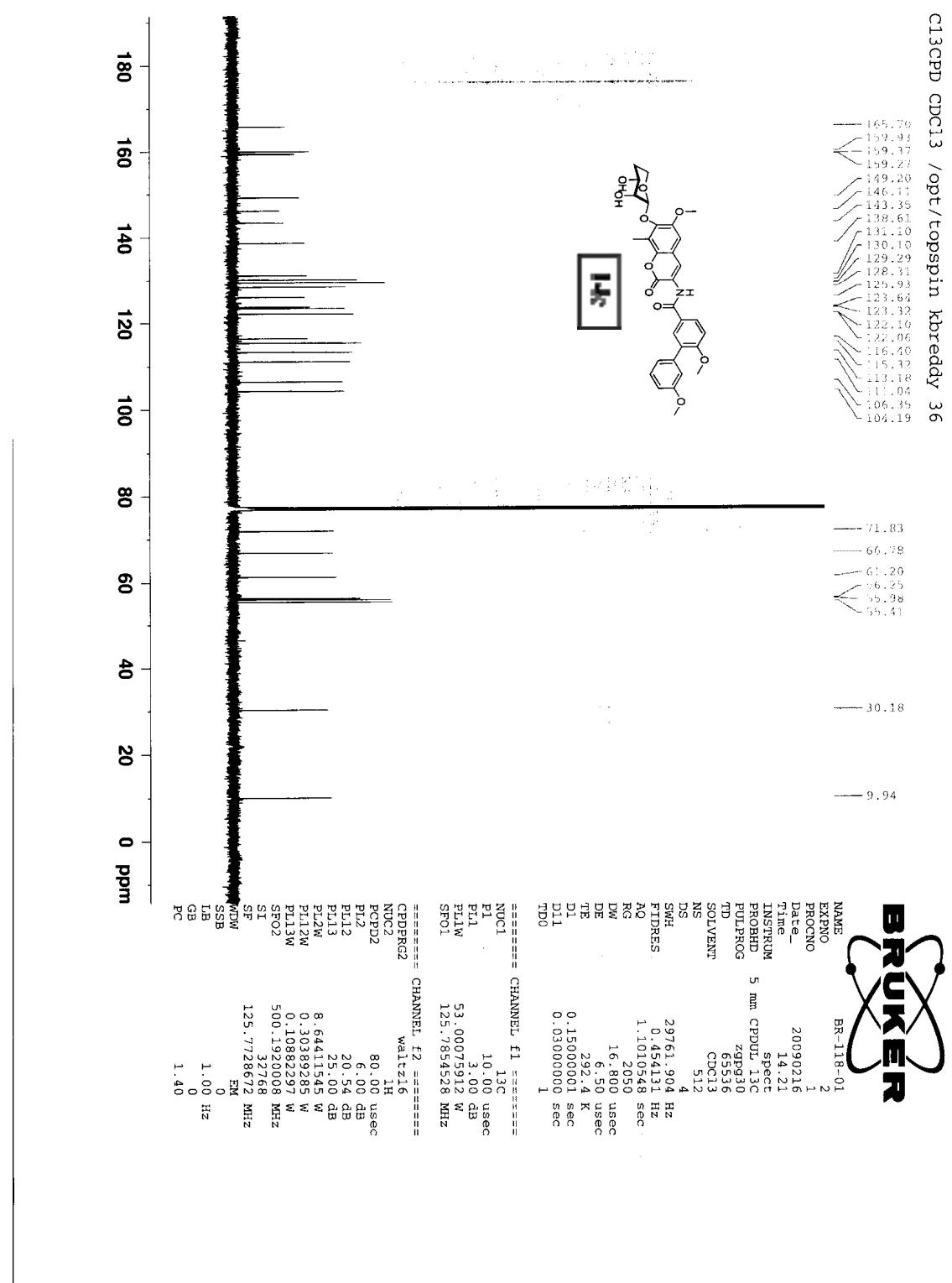


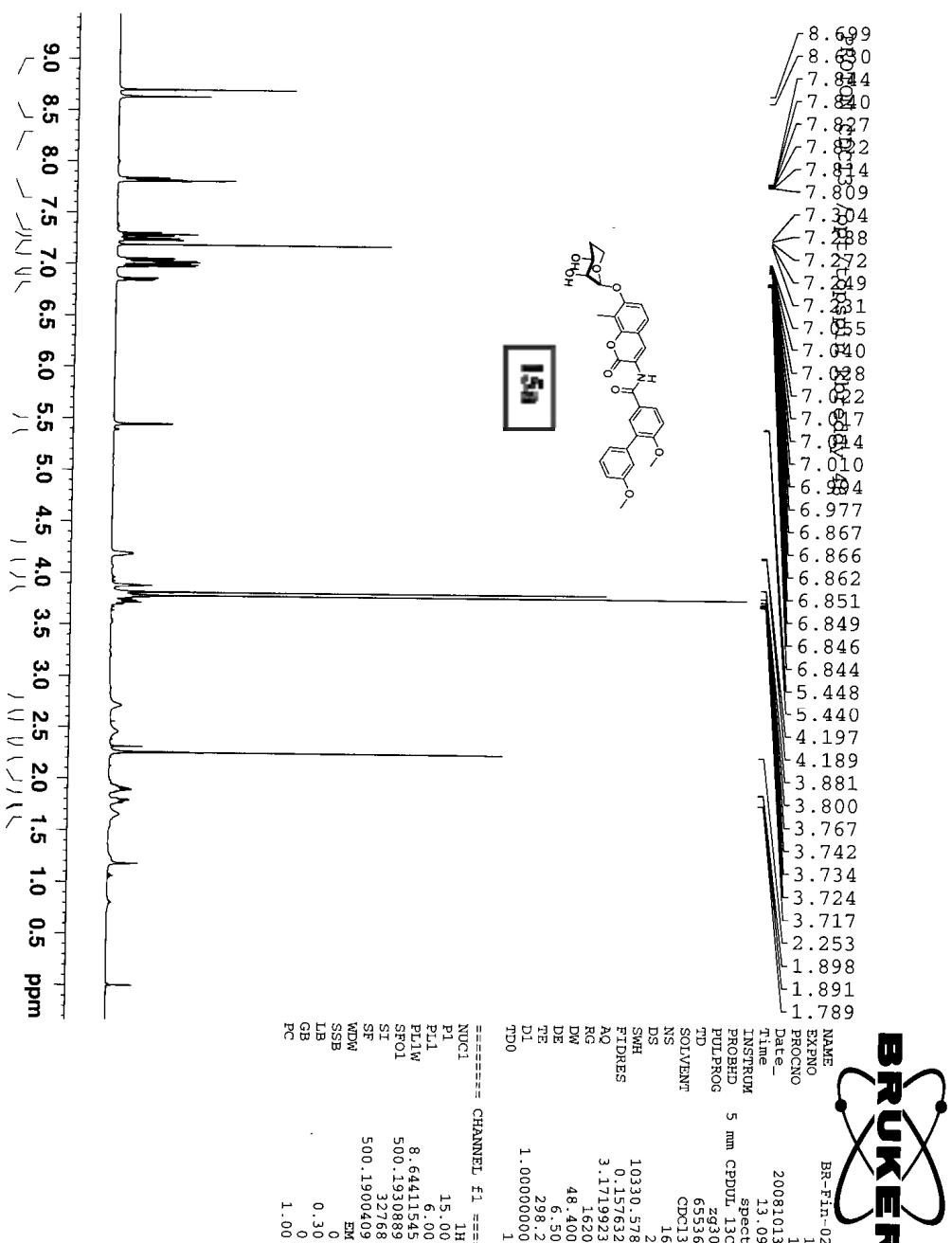


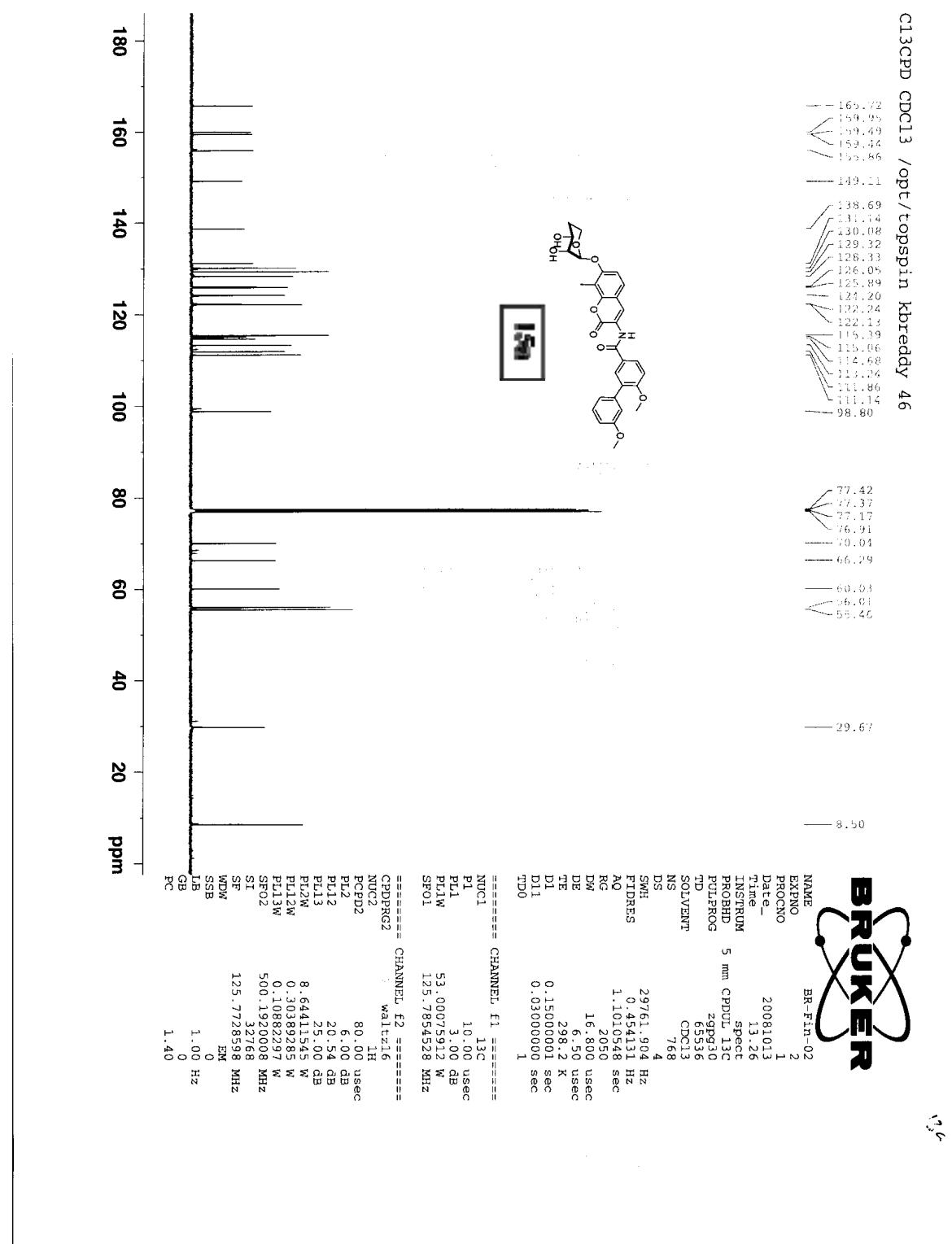


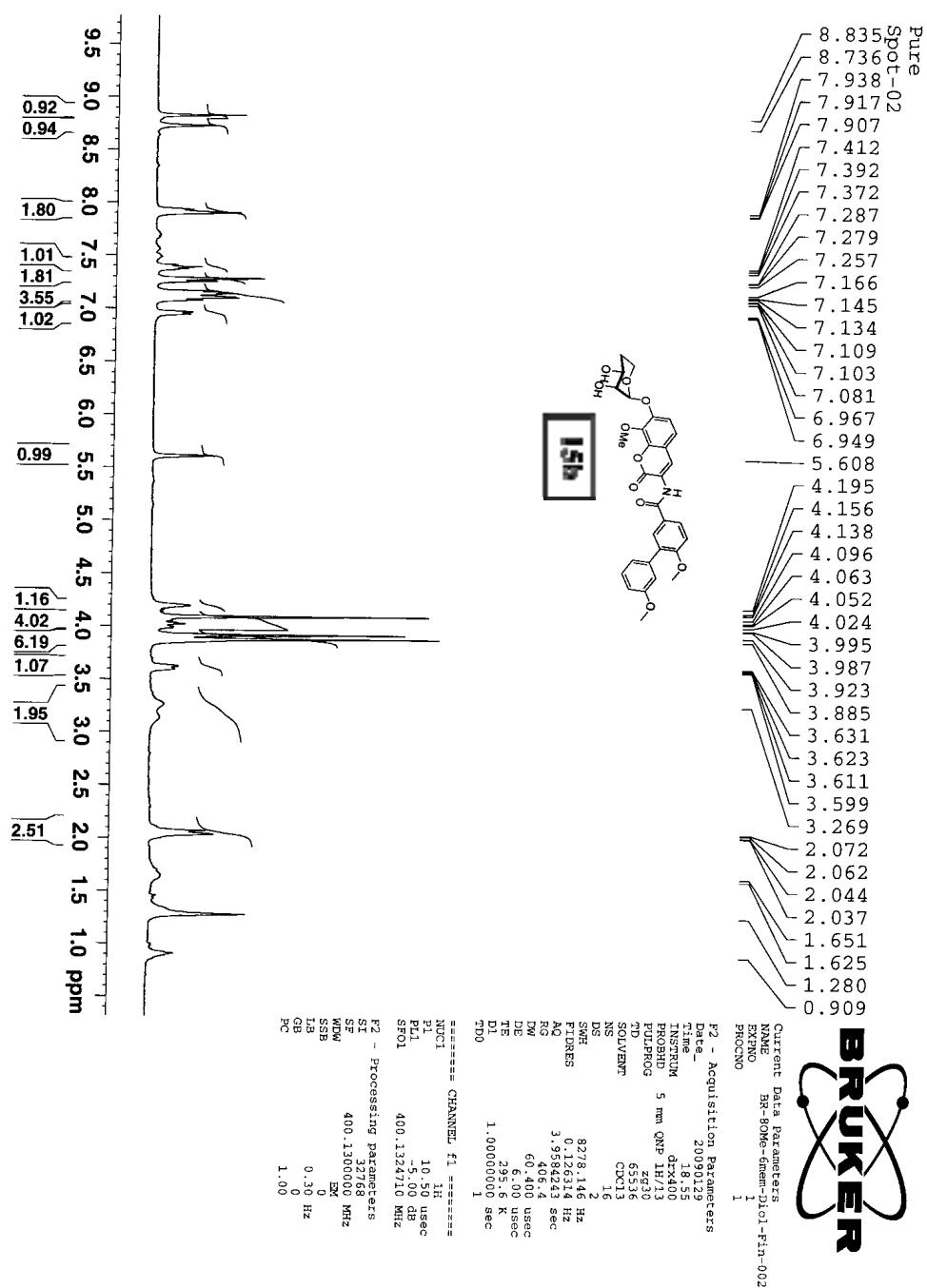


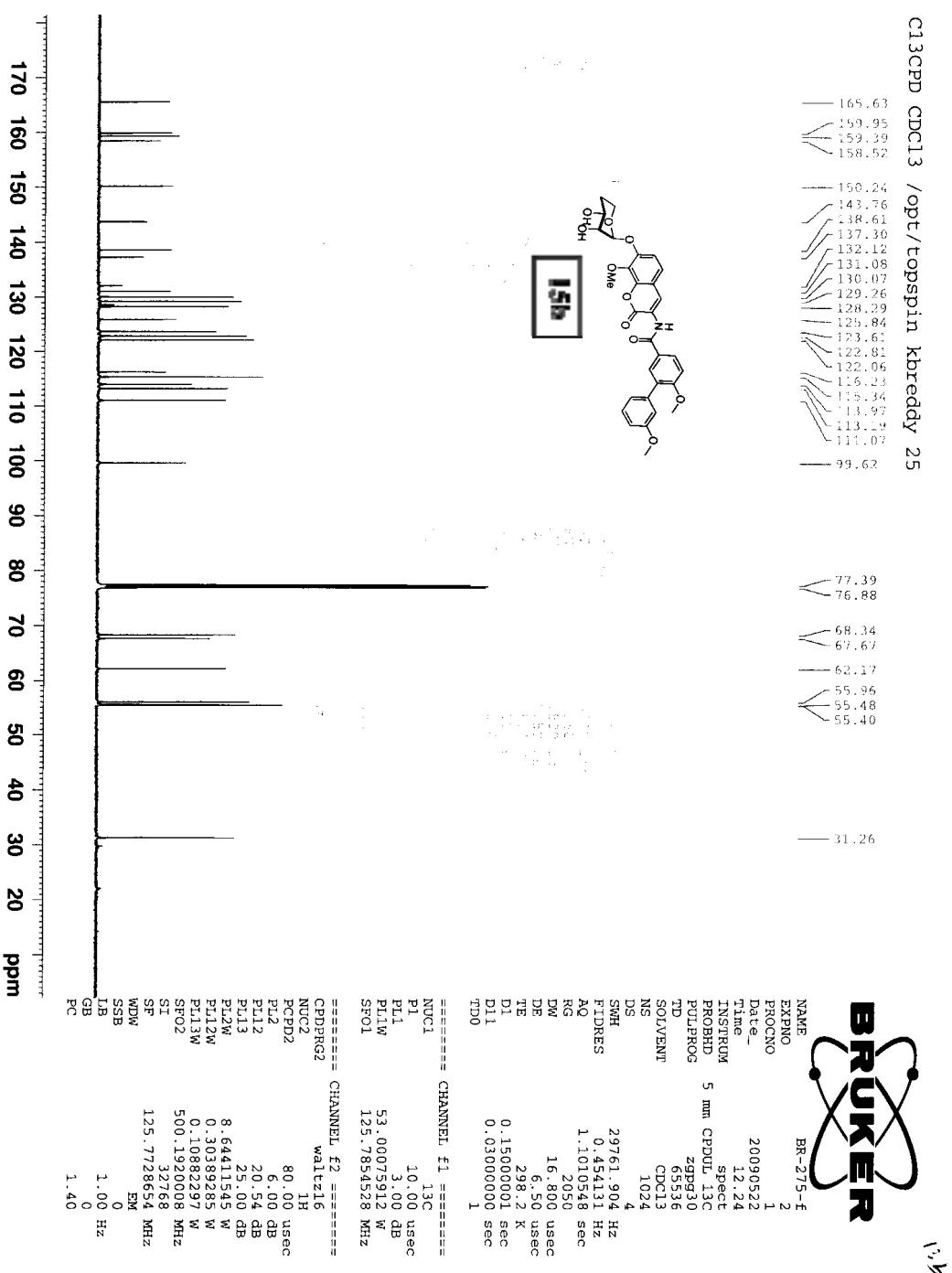


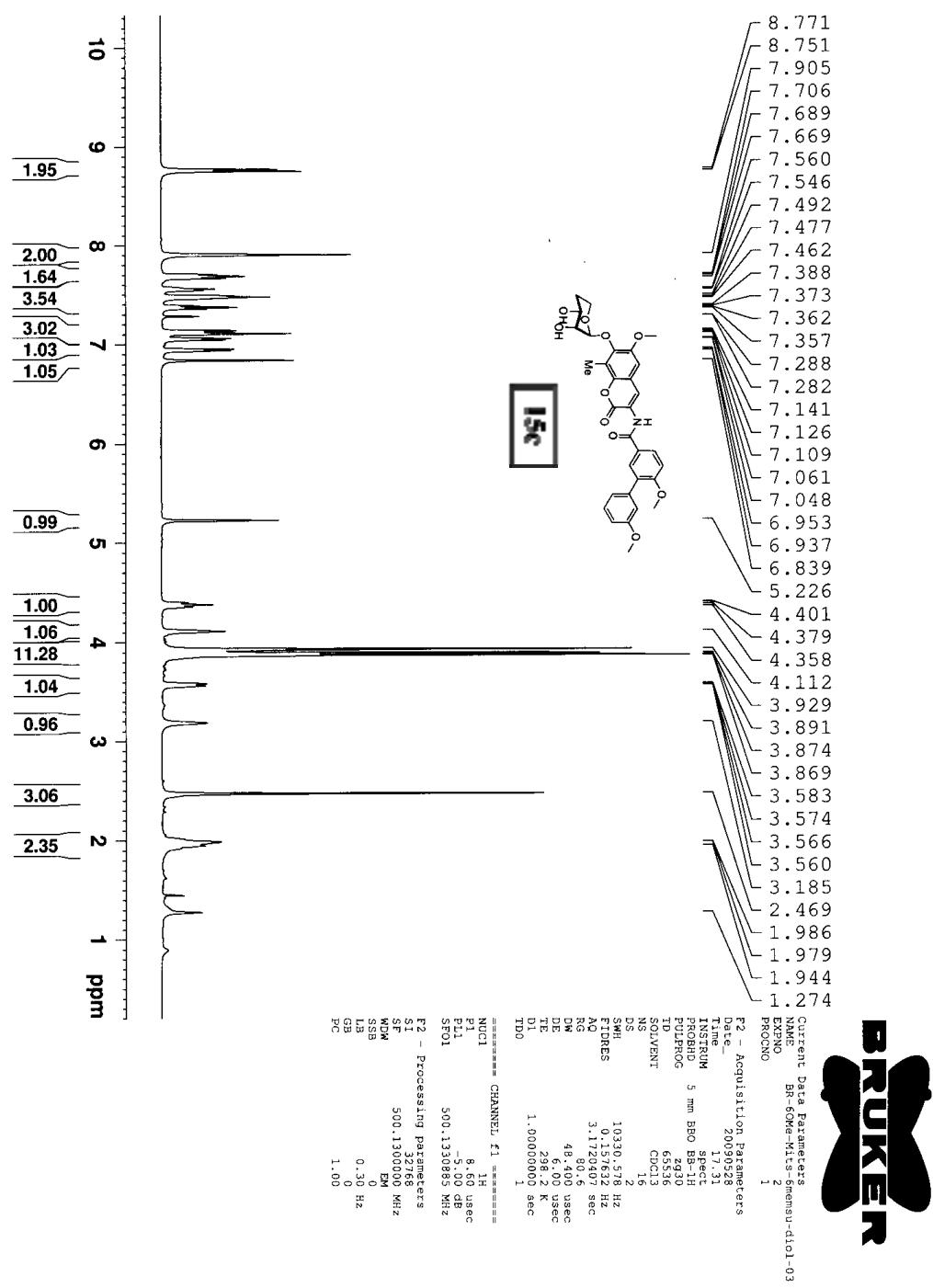


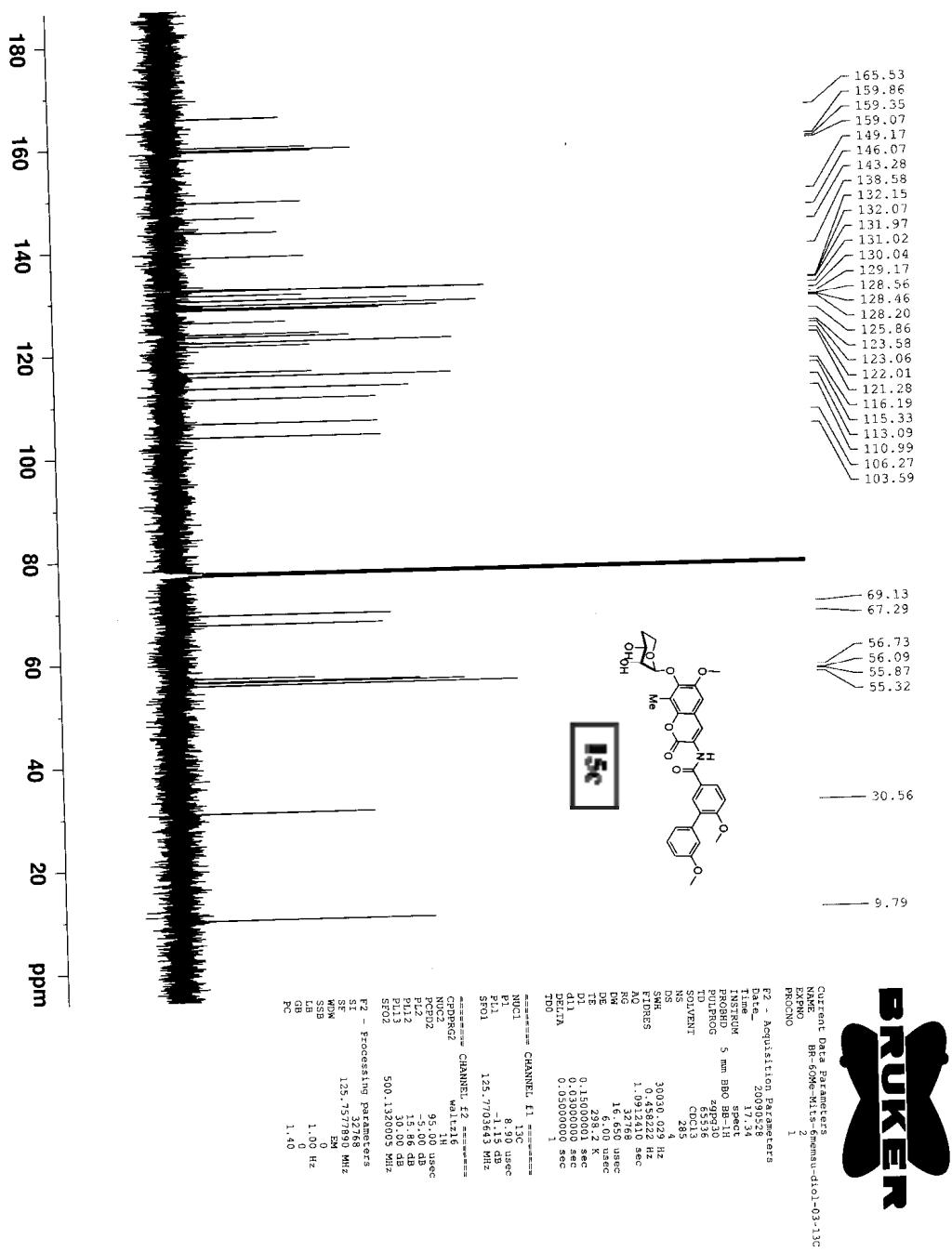






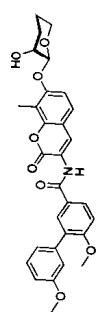
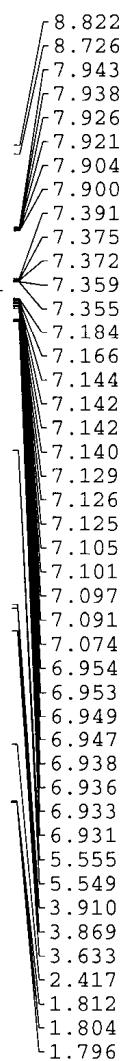




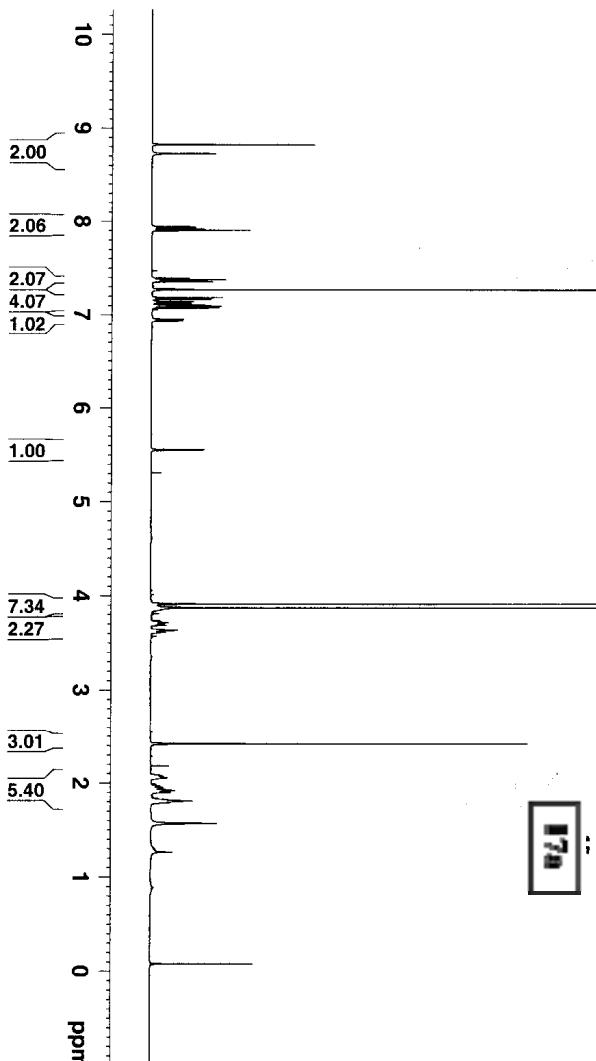


PROTON CDCl₃ /opt/topspin kreddy 9

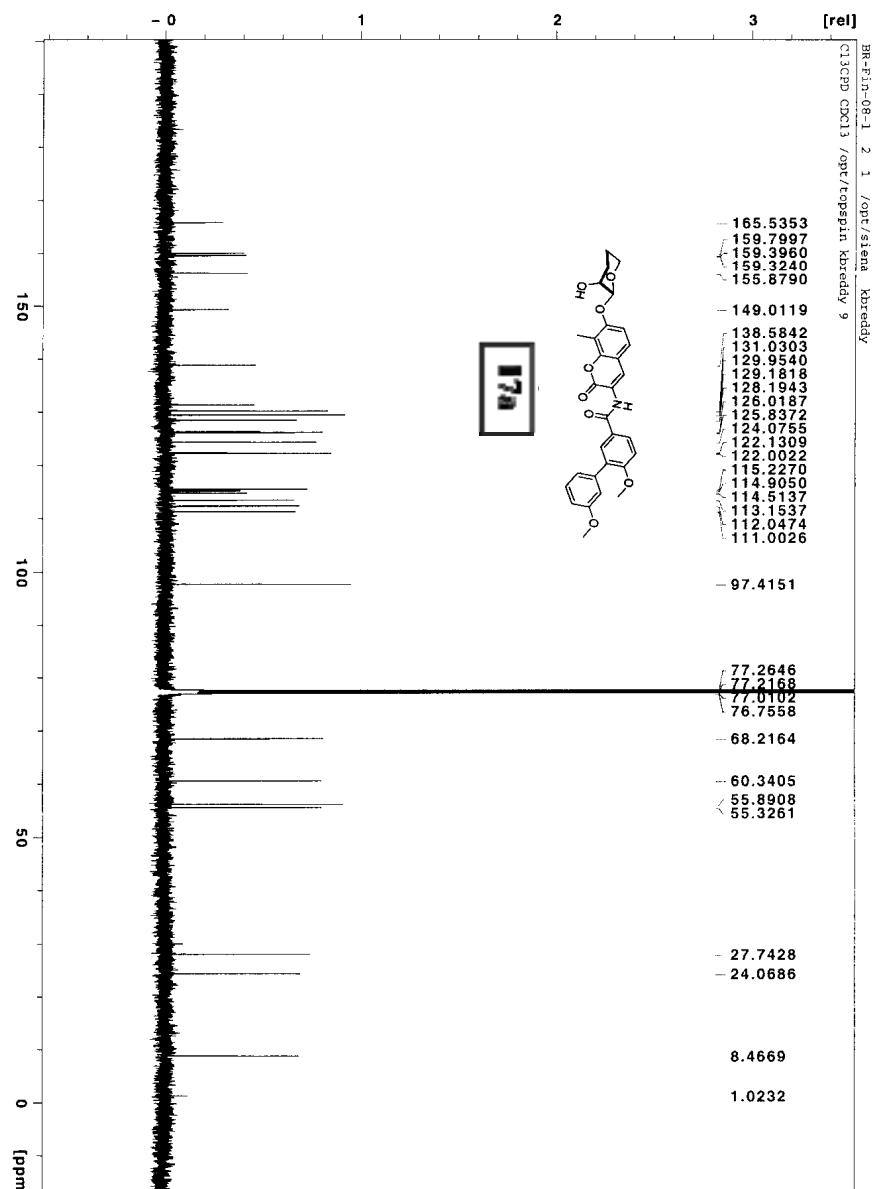
16a



17a



```
=====
CHANNEL f1 =====
NUC1      1H
P1        15.00 usec
PL1       6.00 dB
PL1W     8.64411545 W
SP01      500.1930889 MHz
SI        32768
SF      500.1900012 MHz
WDW      EM
SSB       0
LB        0.30 Hz
GB       0
PC        1.00
```



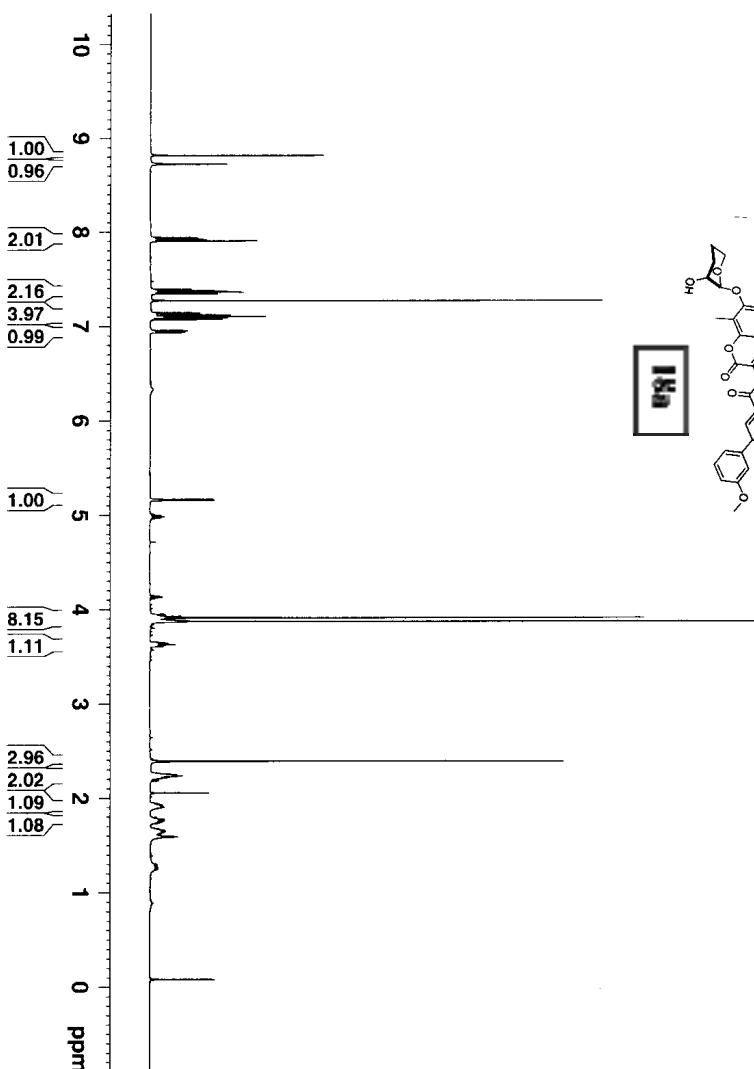
PROTON CDCl₃ /opt/topspin kbready 10

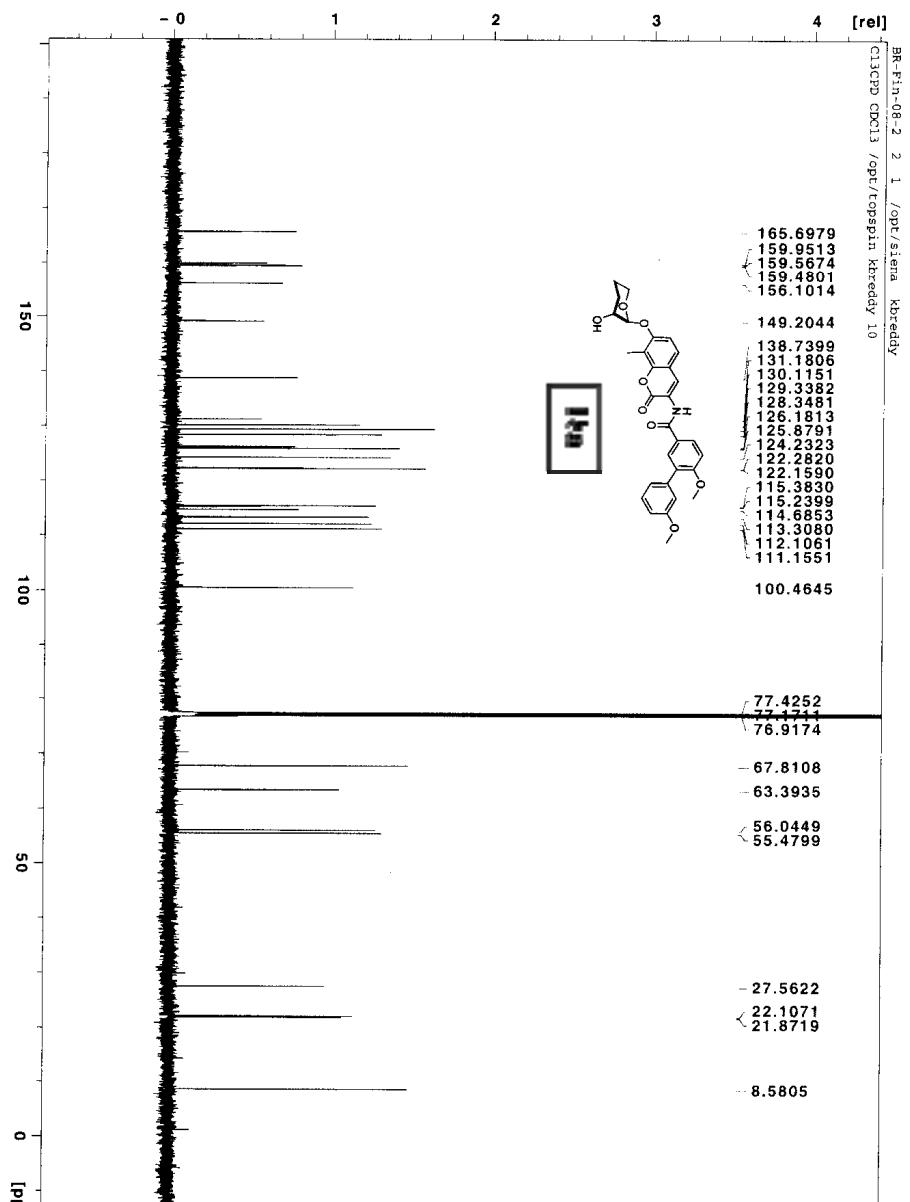
BRUKER

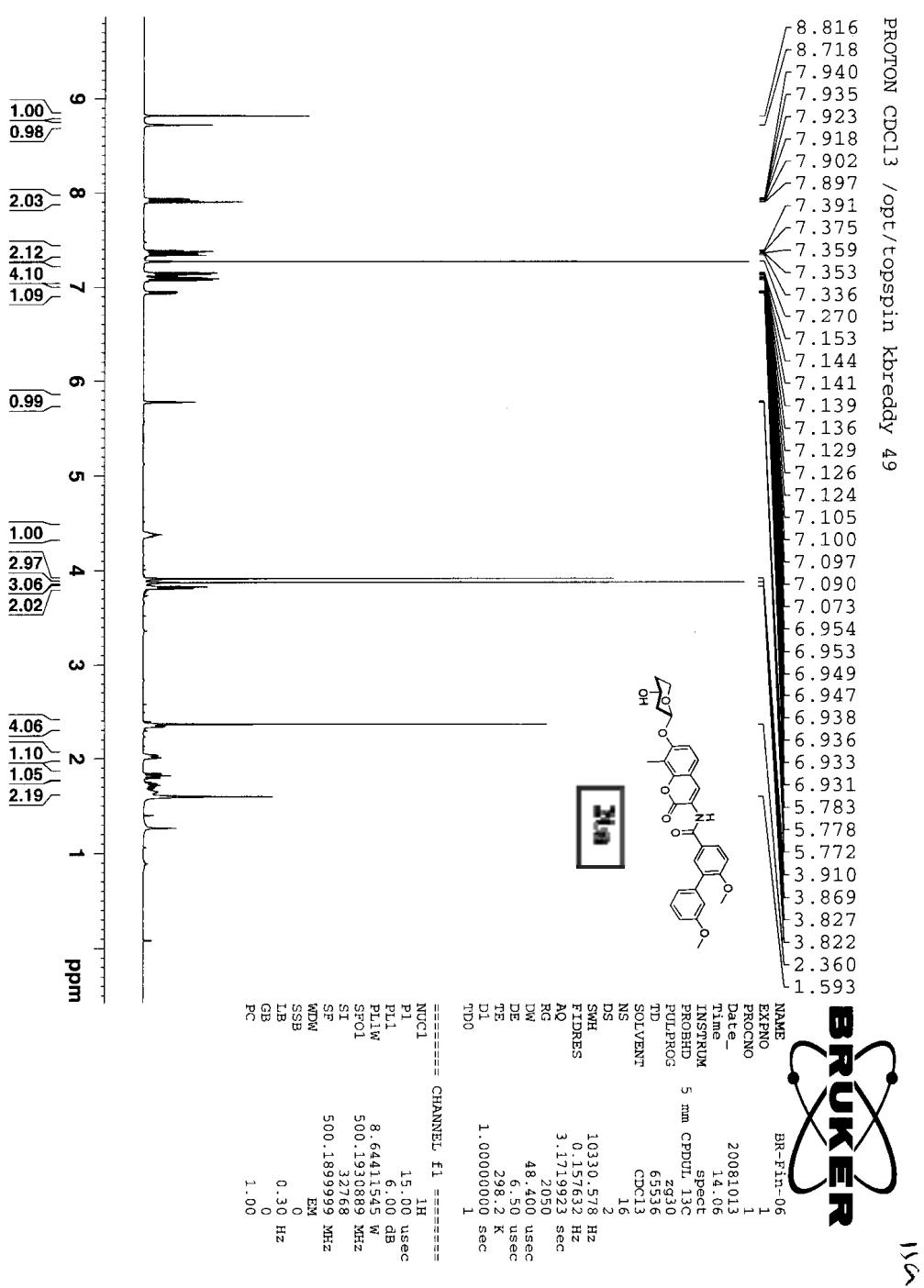
NAME BR-Fin-08-2
EXPGO 1
PROCNO 1
Date 2008/01/4
Time 14:25
INSTRUM Spect
PROBHD 5 mm CPDUL_13C
PULPROG zg30
TD 65536

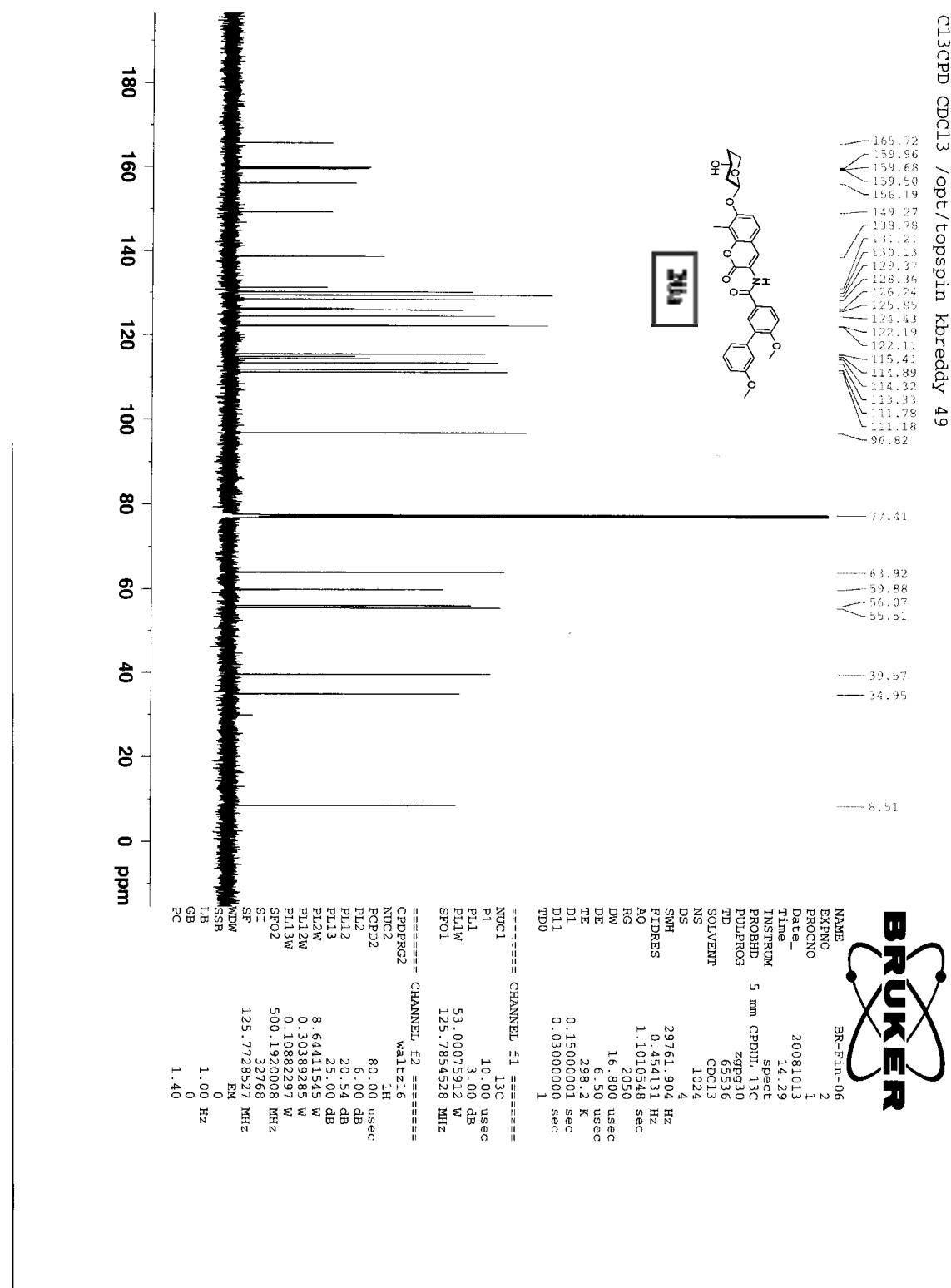
SOLVENT CDCl₃
NS 16
DS 2
SWH 10330.578 Hz
ETR 0.157632 Hz
FIDRES 3.171923 sec
AO 2050
RG 48.400 usec
DW 6.50 usec
DE 298.2 K
TE 1.0000000 sec
D1 1
TDO 1

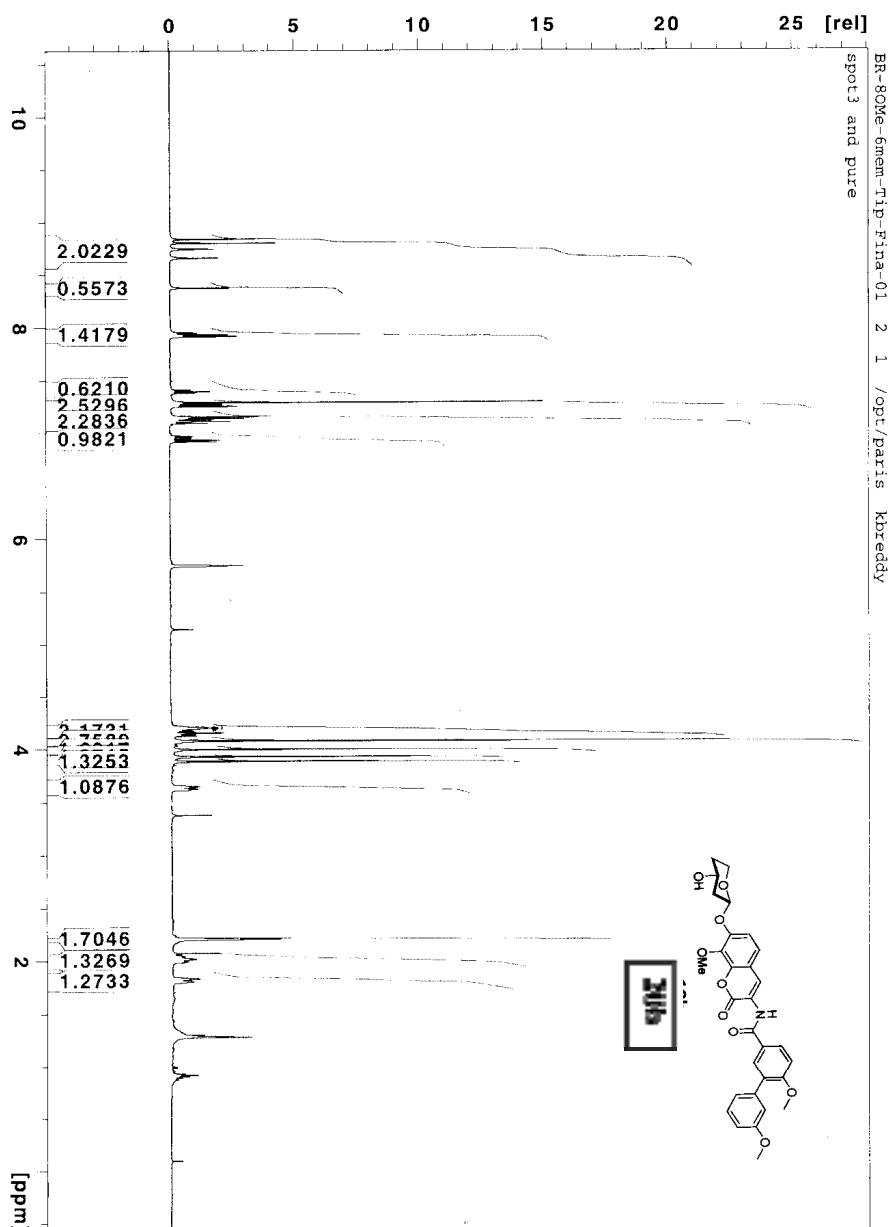
===== CHANNEL f1 =====
NUC1 1H
P1 15.00 usec
PL 6.00 dB
PLW 8.64411545 W
SP1W 500.1930889 MHz
SI 3.7768
SF 500.1900002 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



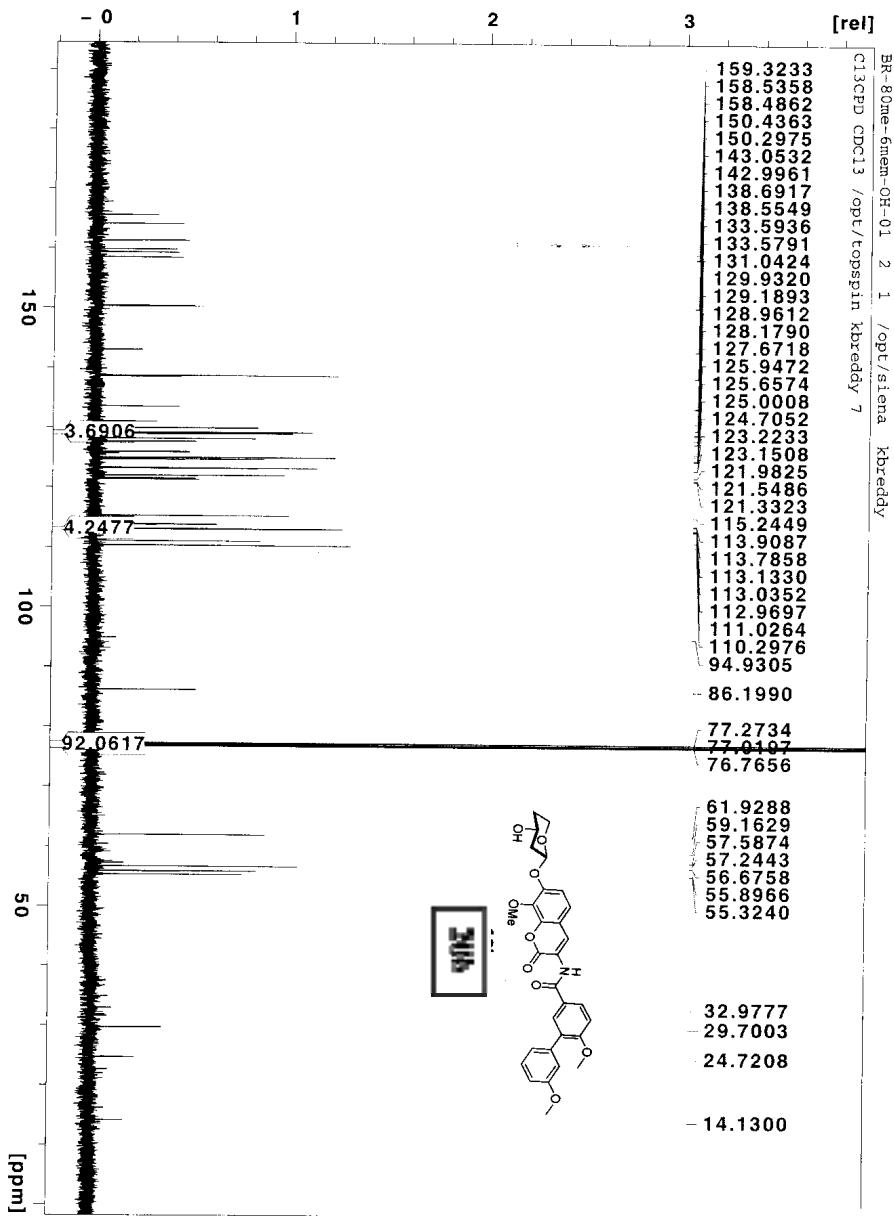


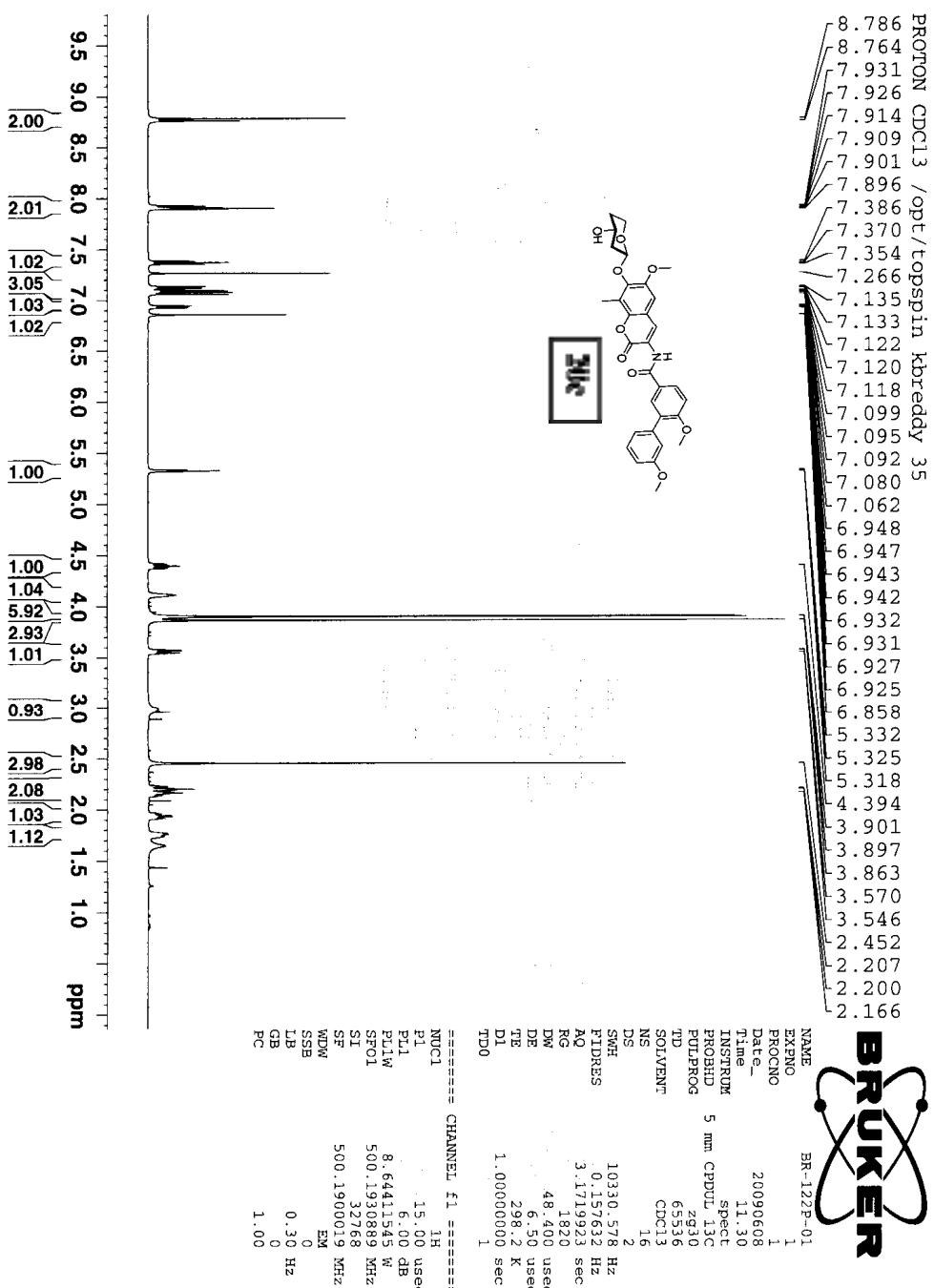


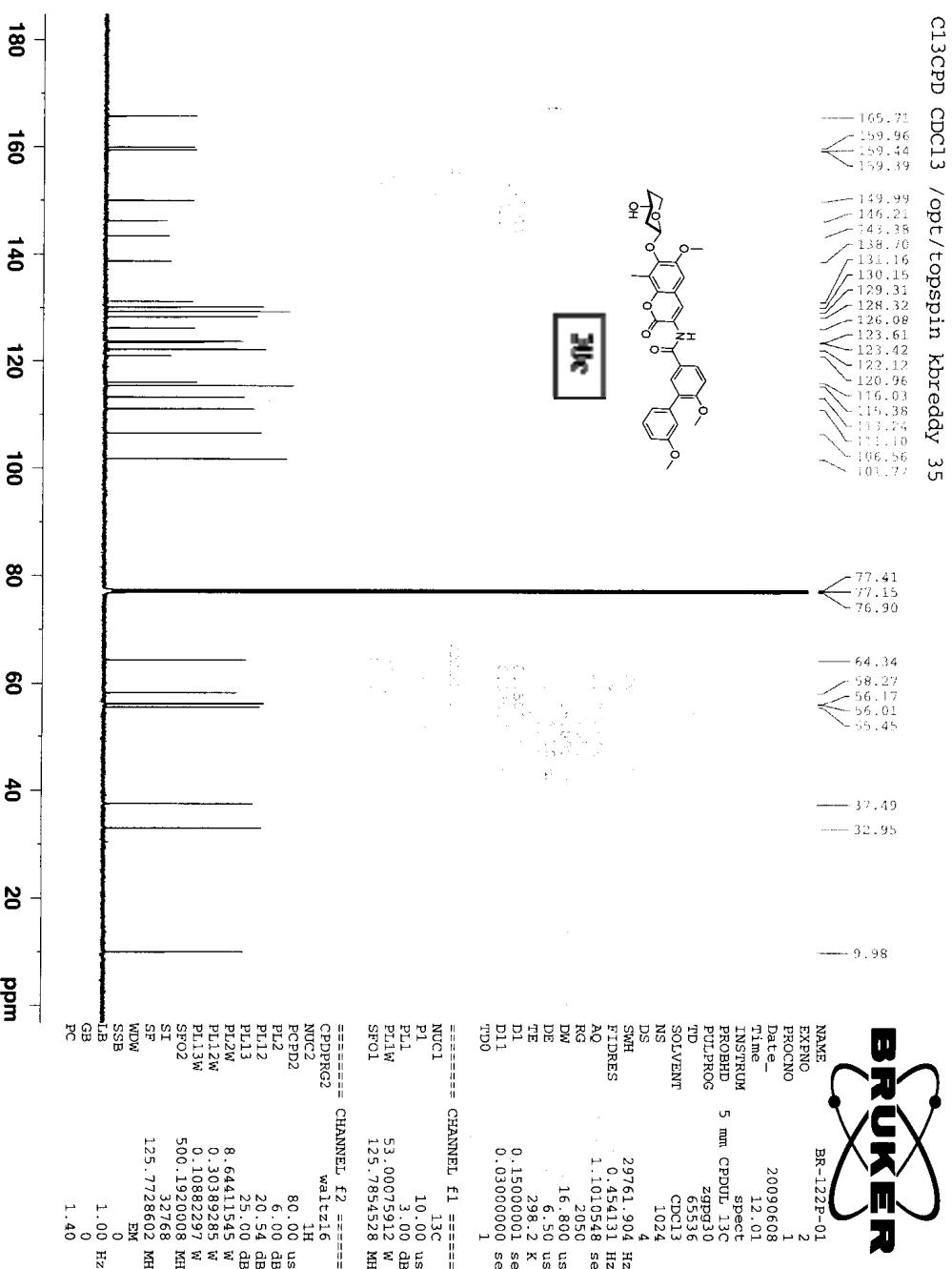


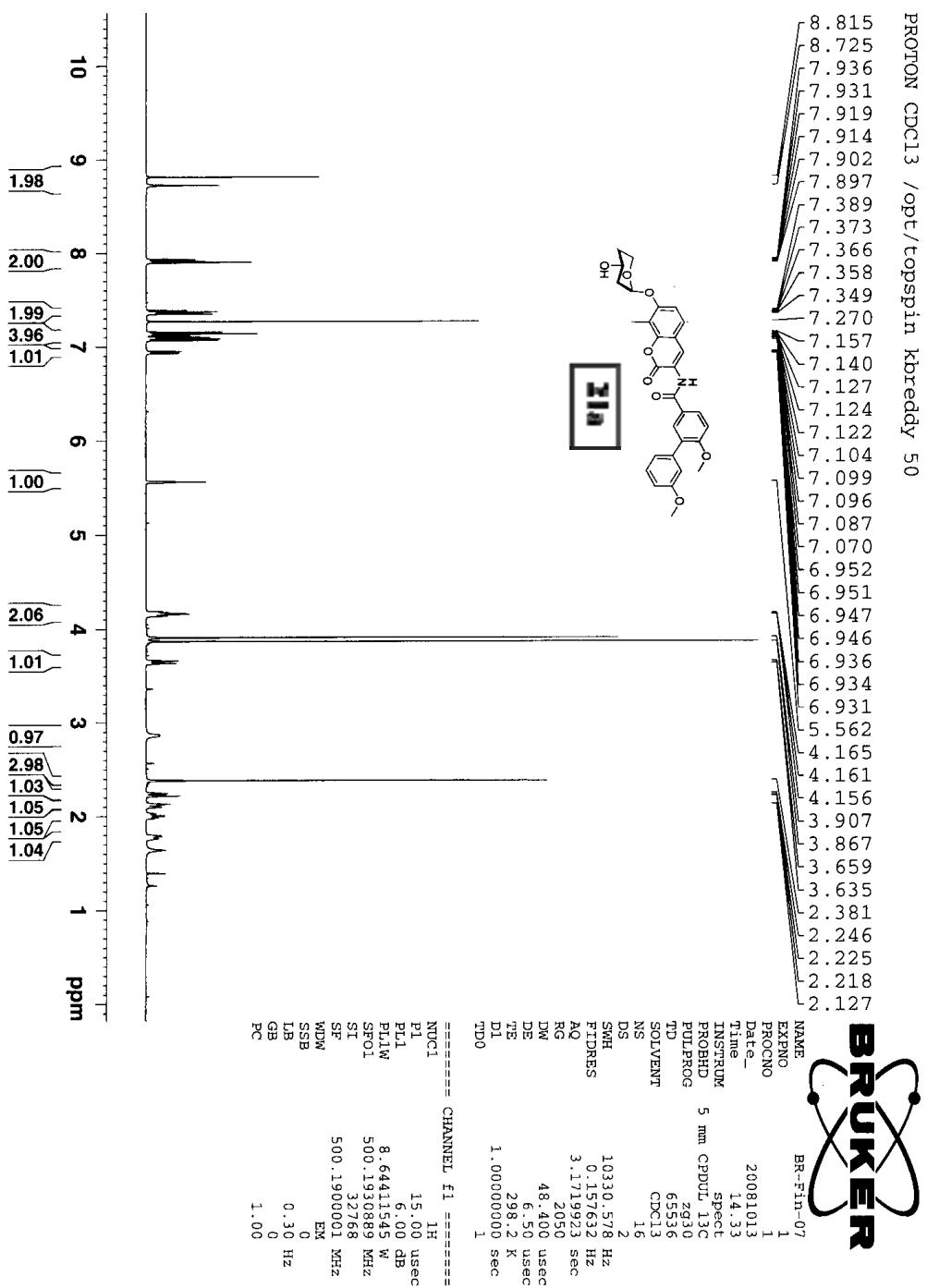


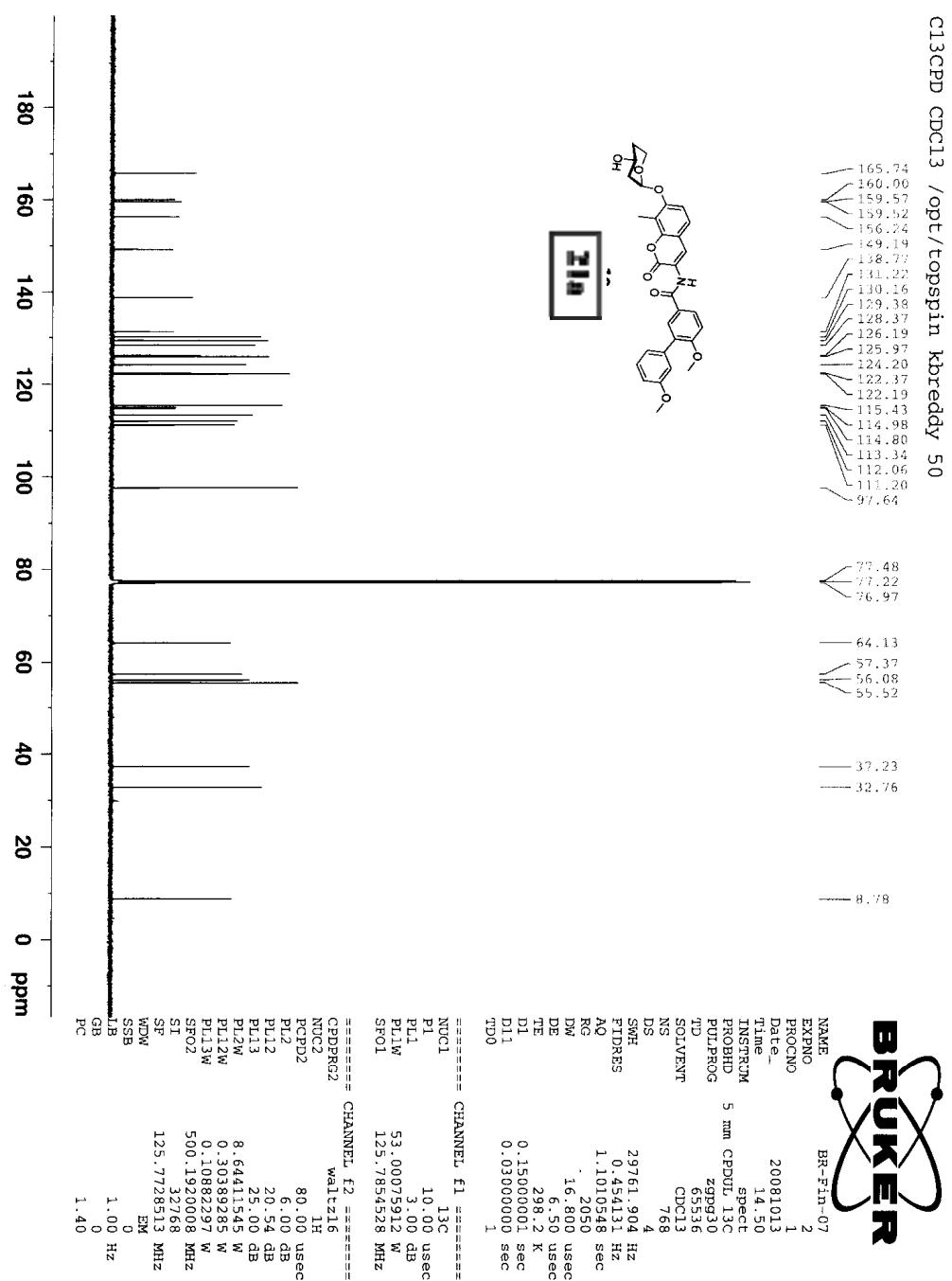
二







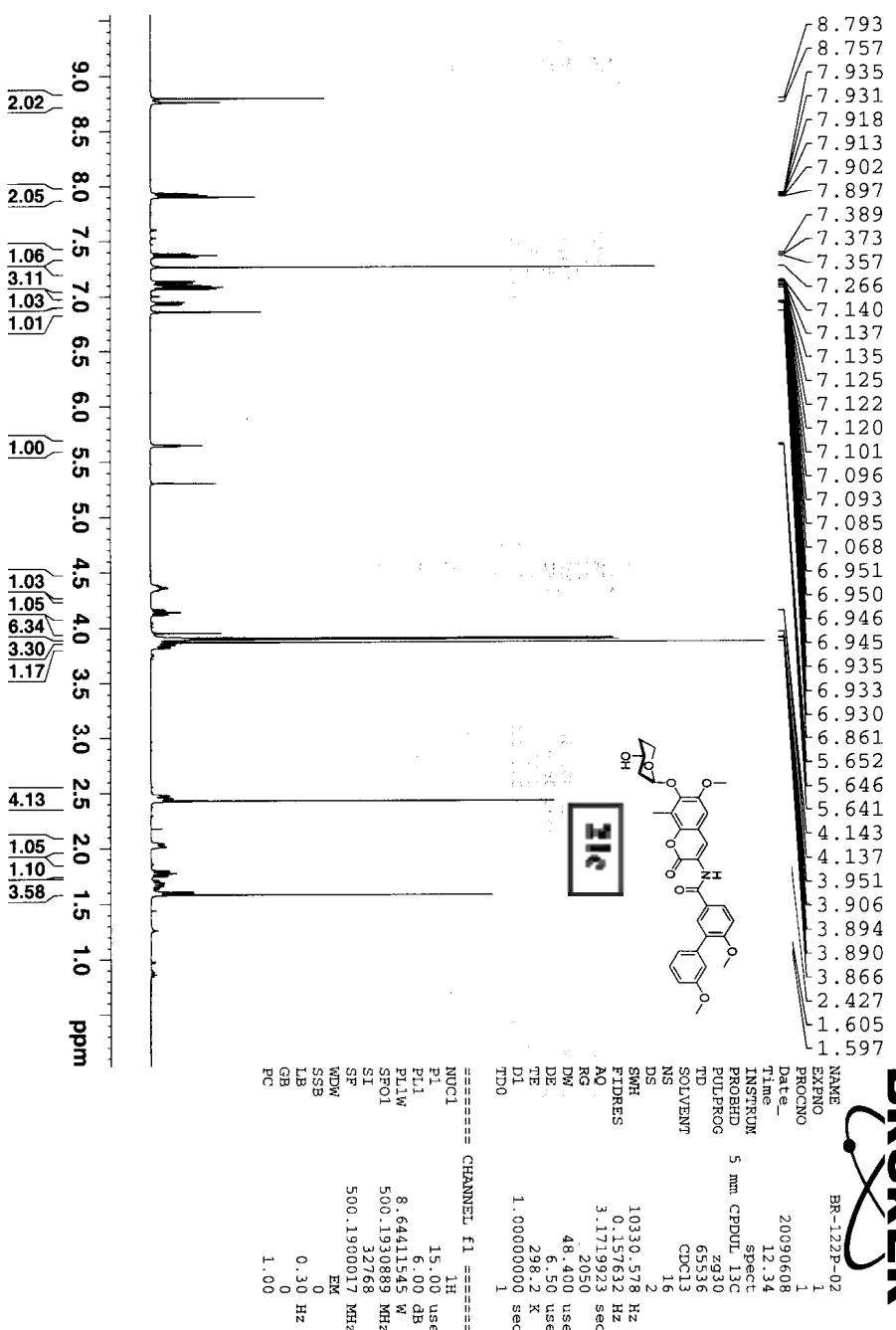


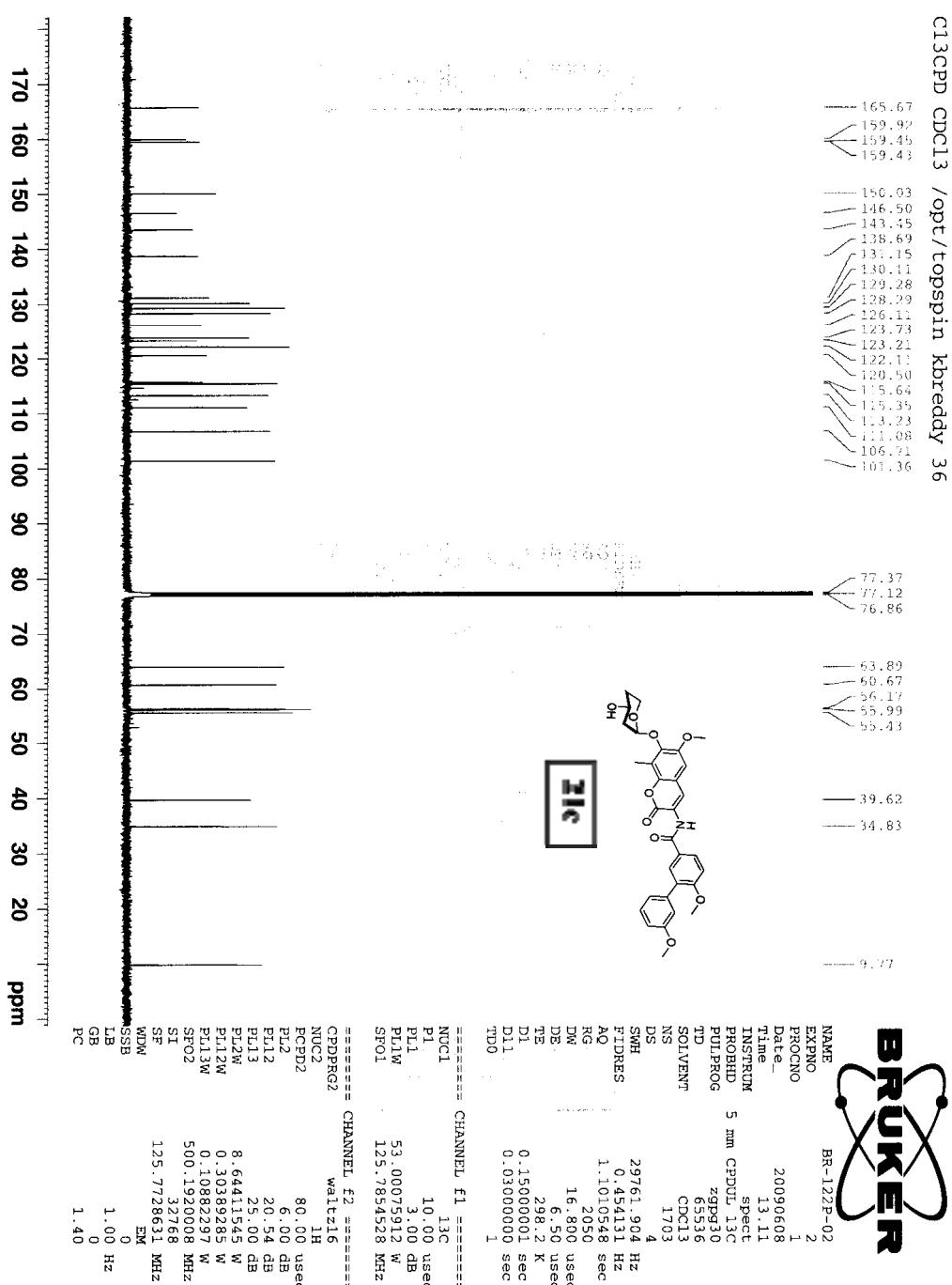


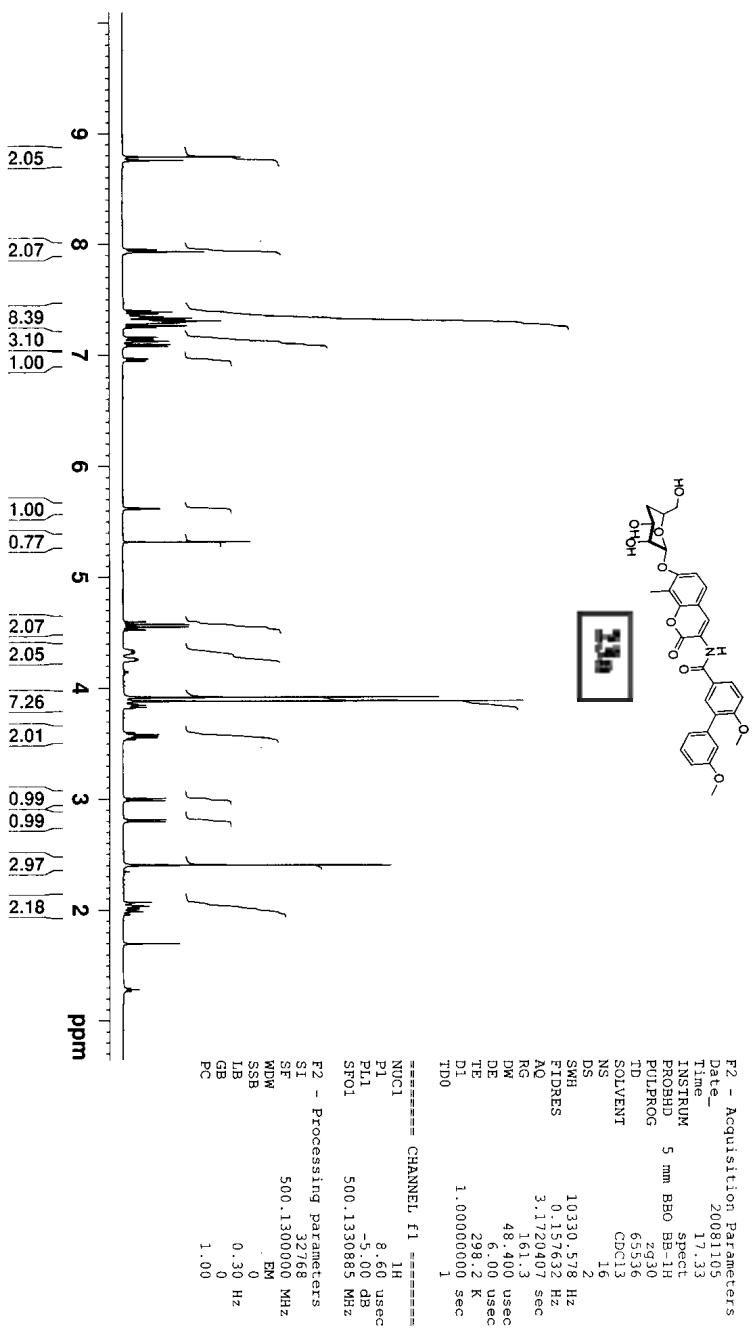
PROTON CDCl₃ /opt/topspin kbreddy 36

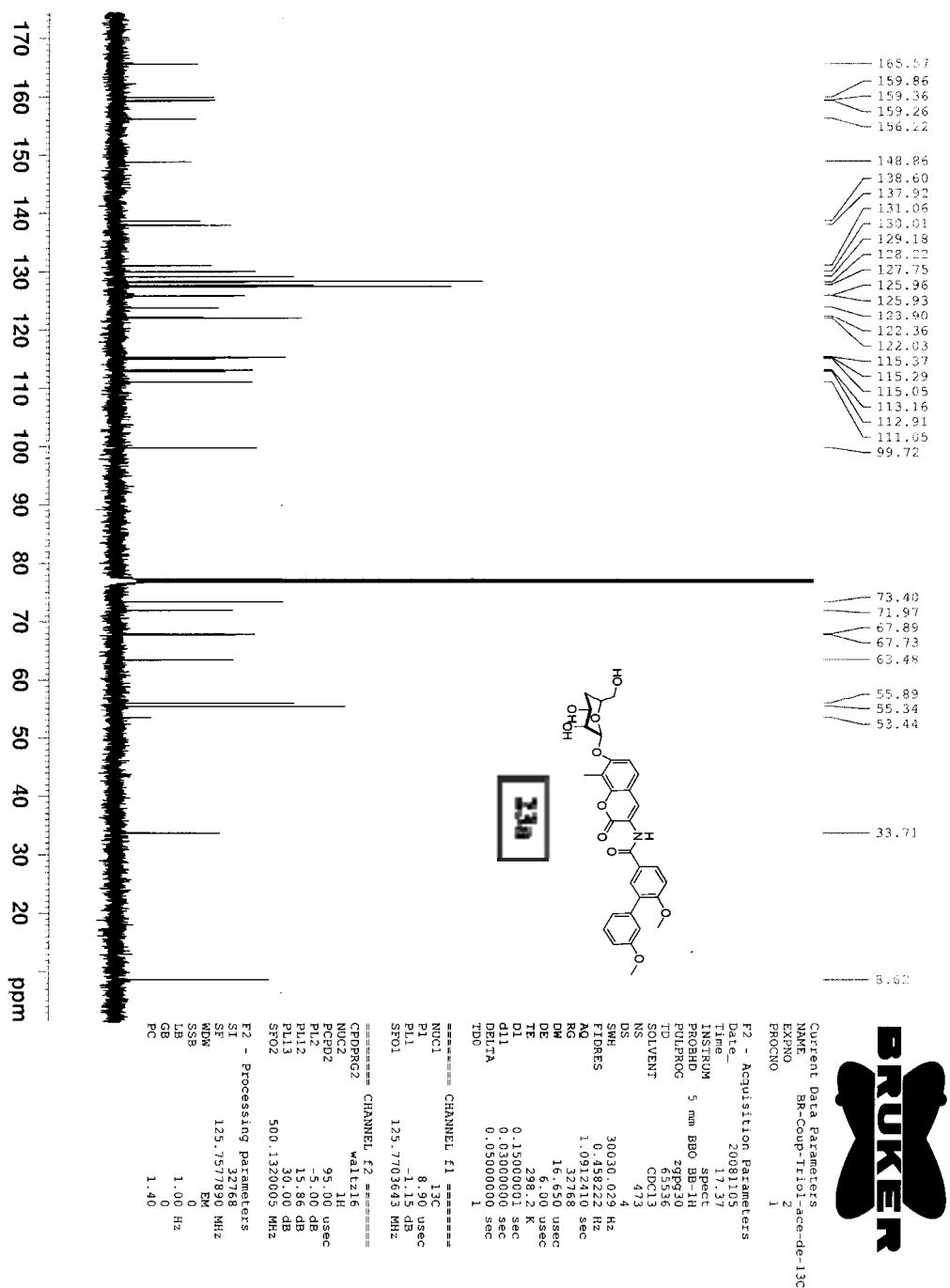


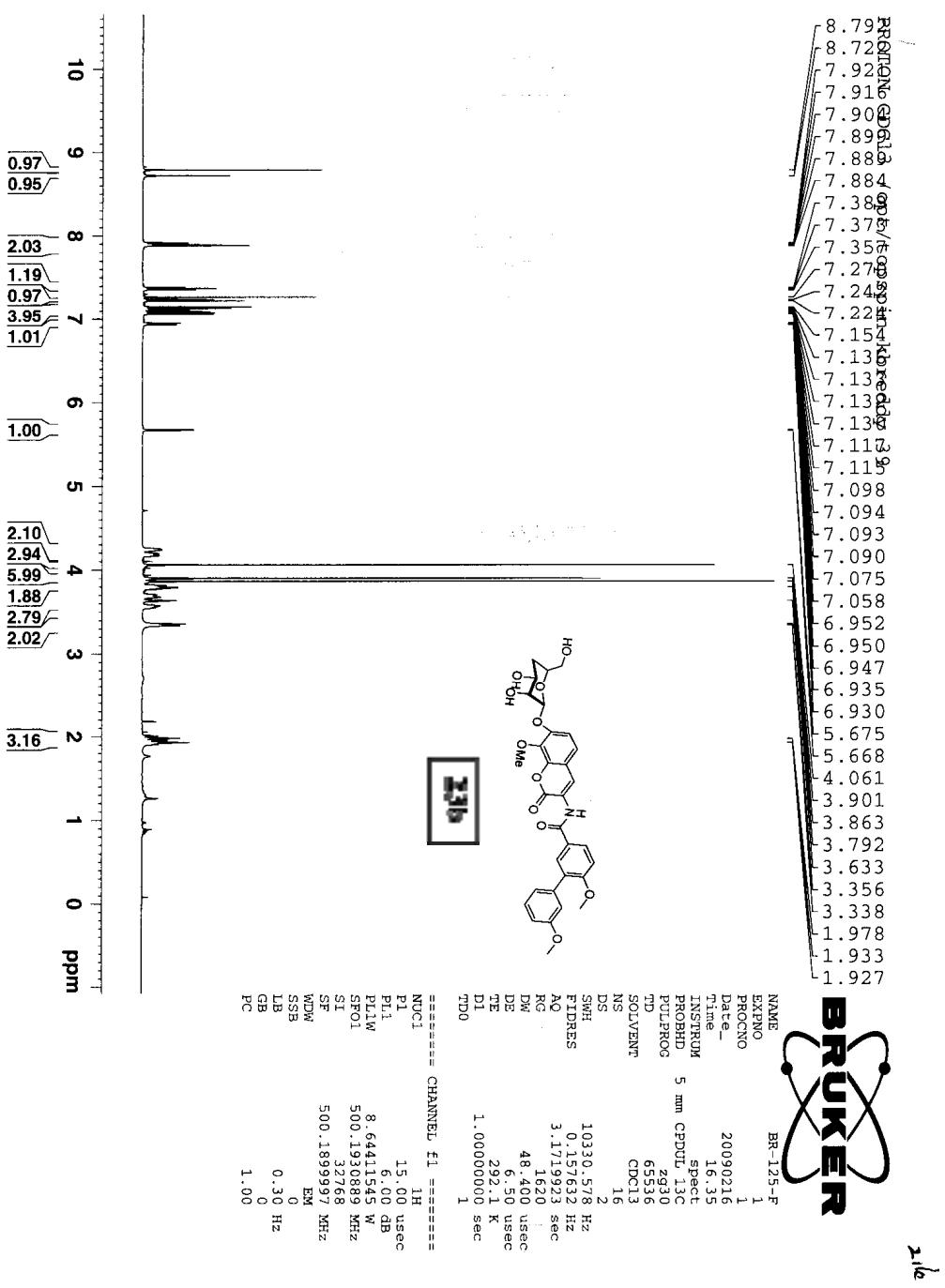
WU



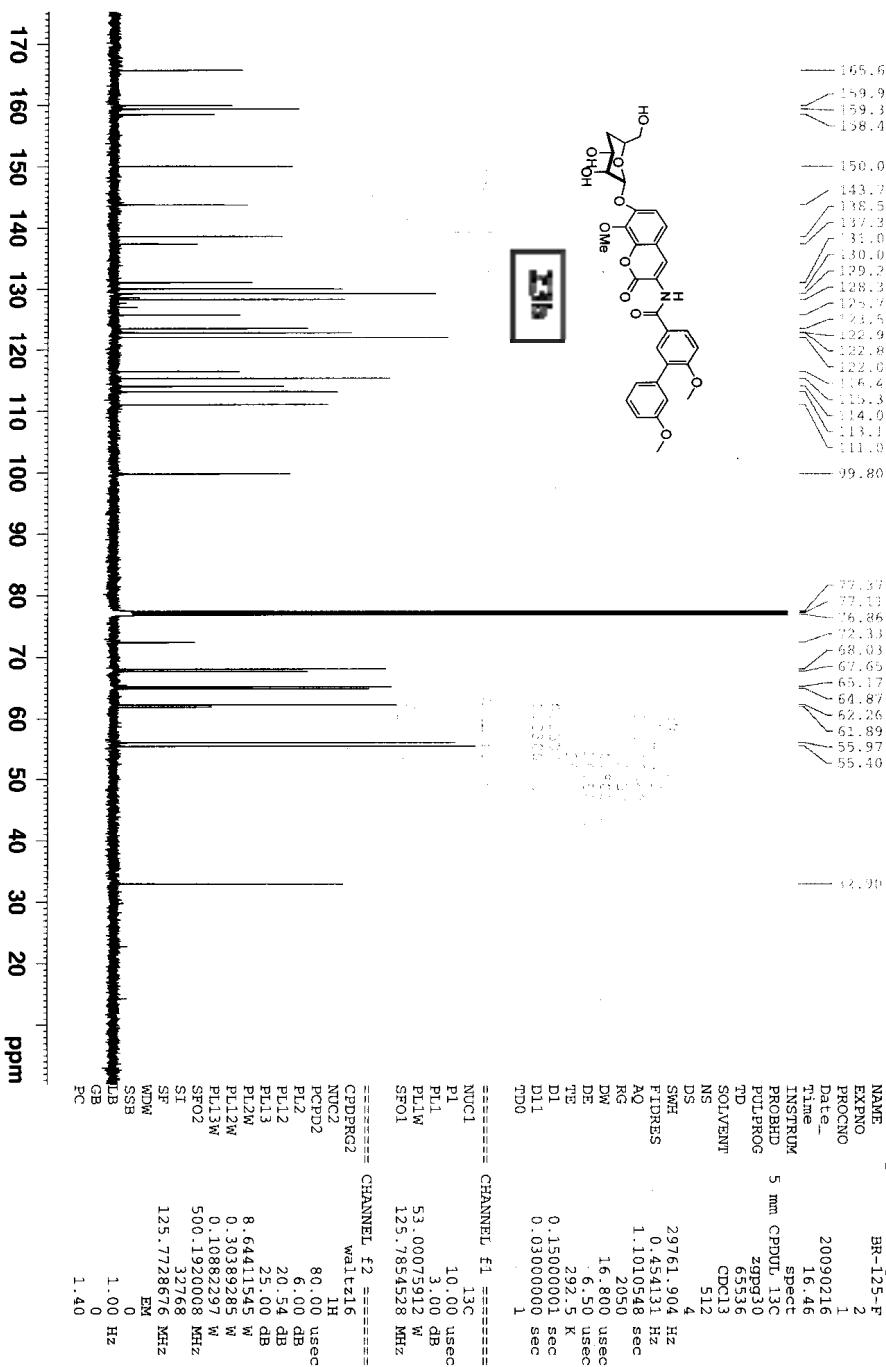


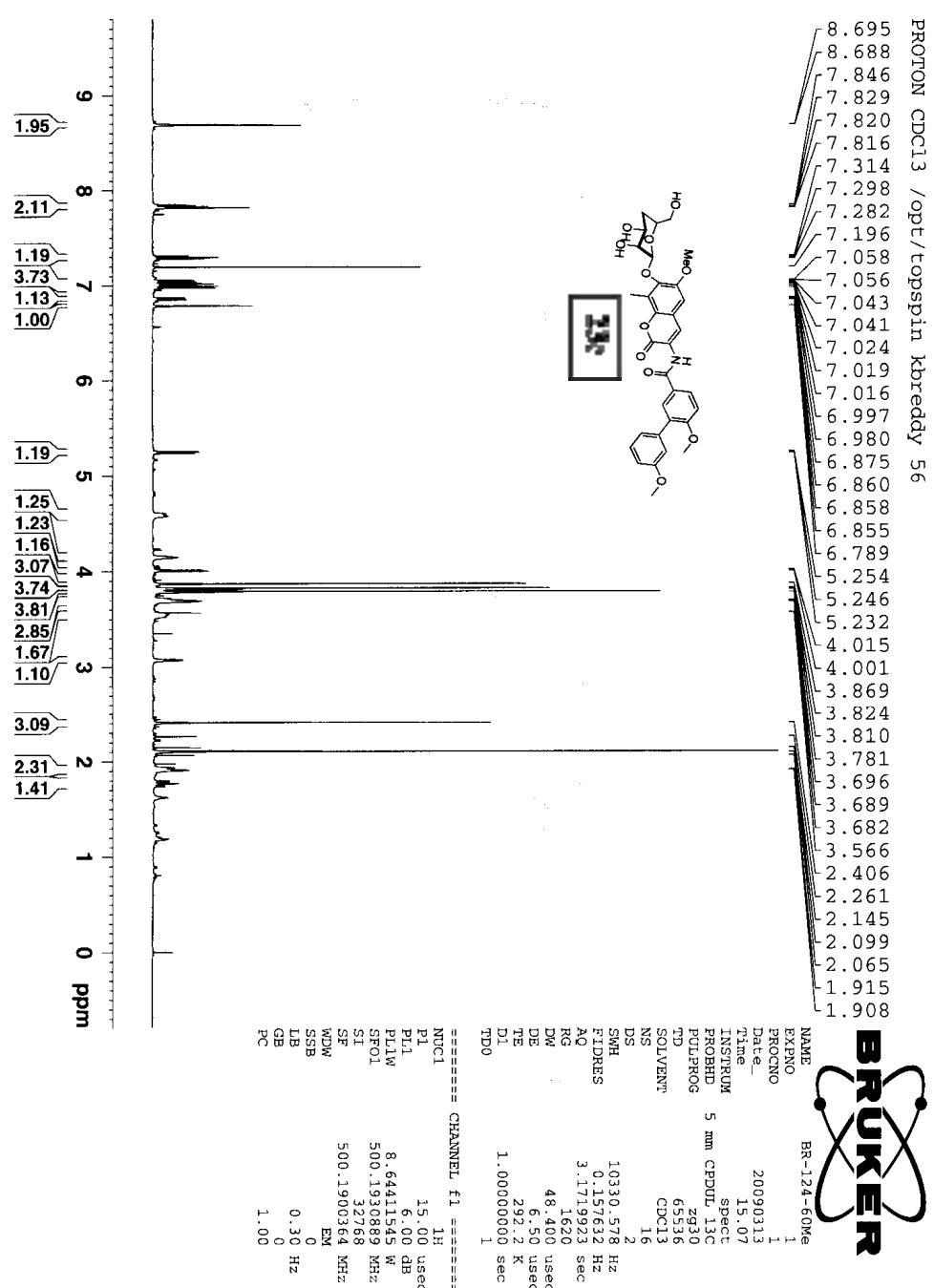


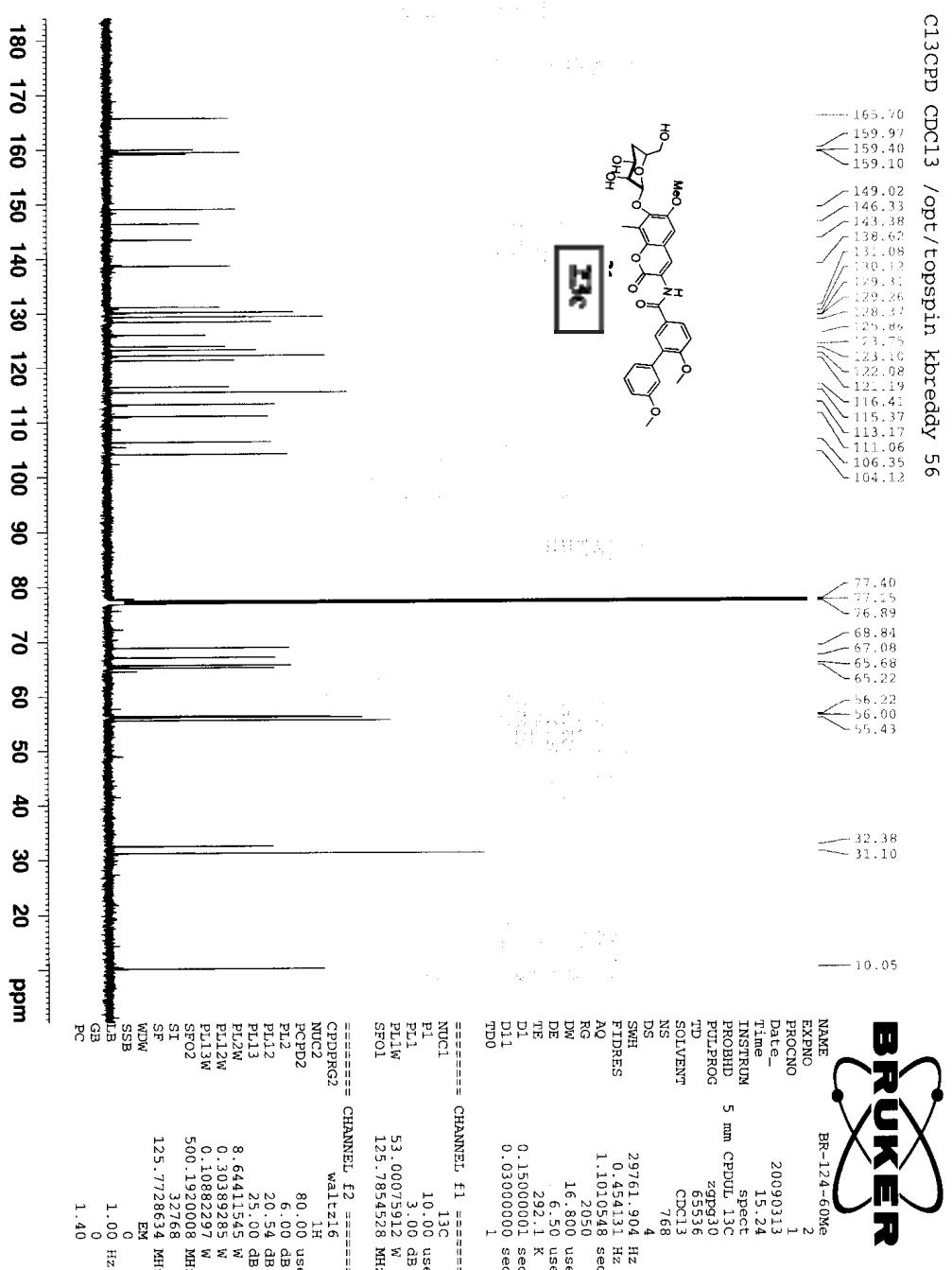


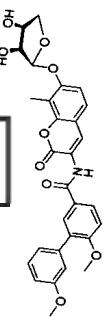


C13CPD CDC13 /opt/topspin kbreddy 39







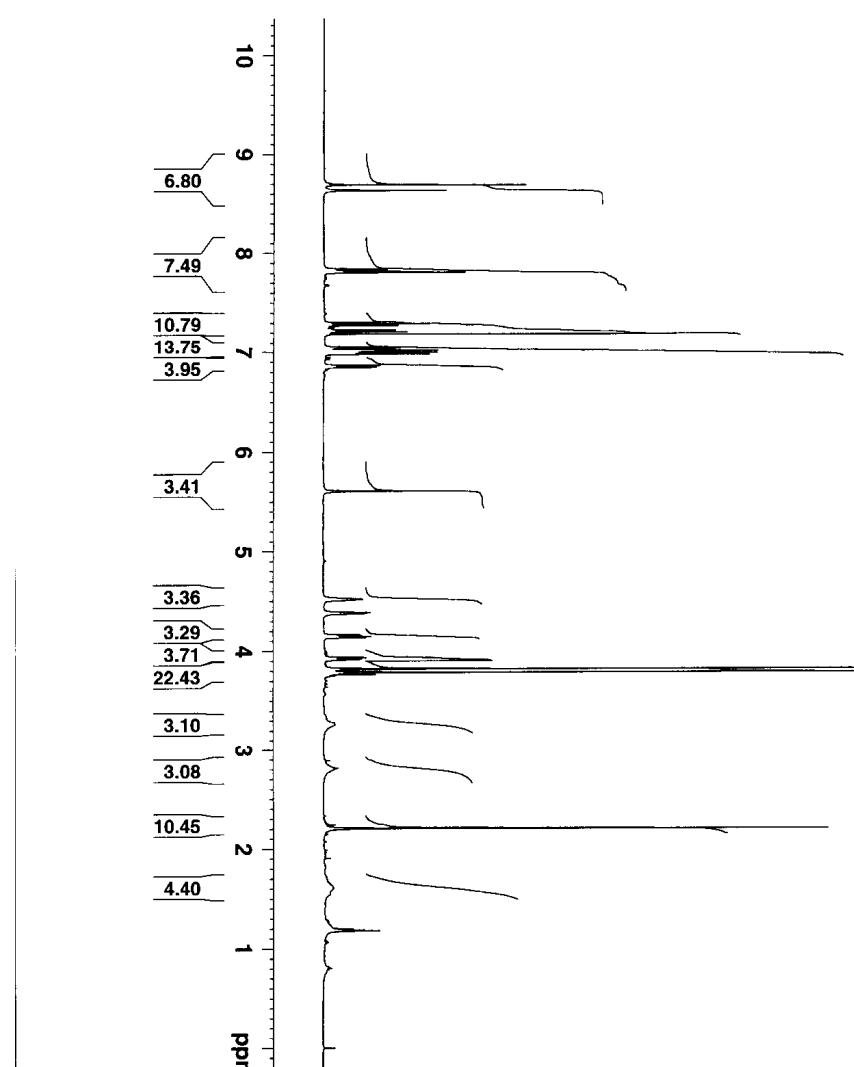
PROTON CDCl₃ / optw/topspin kbreddy 47

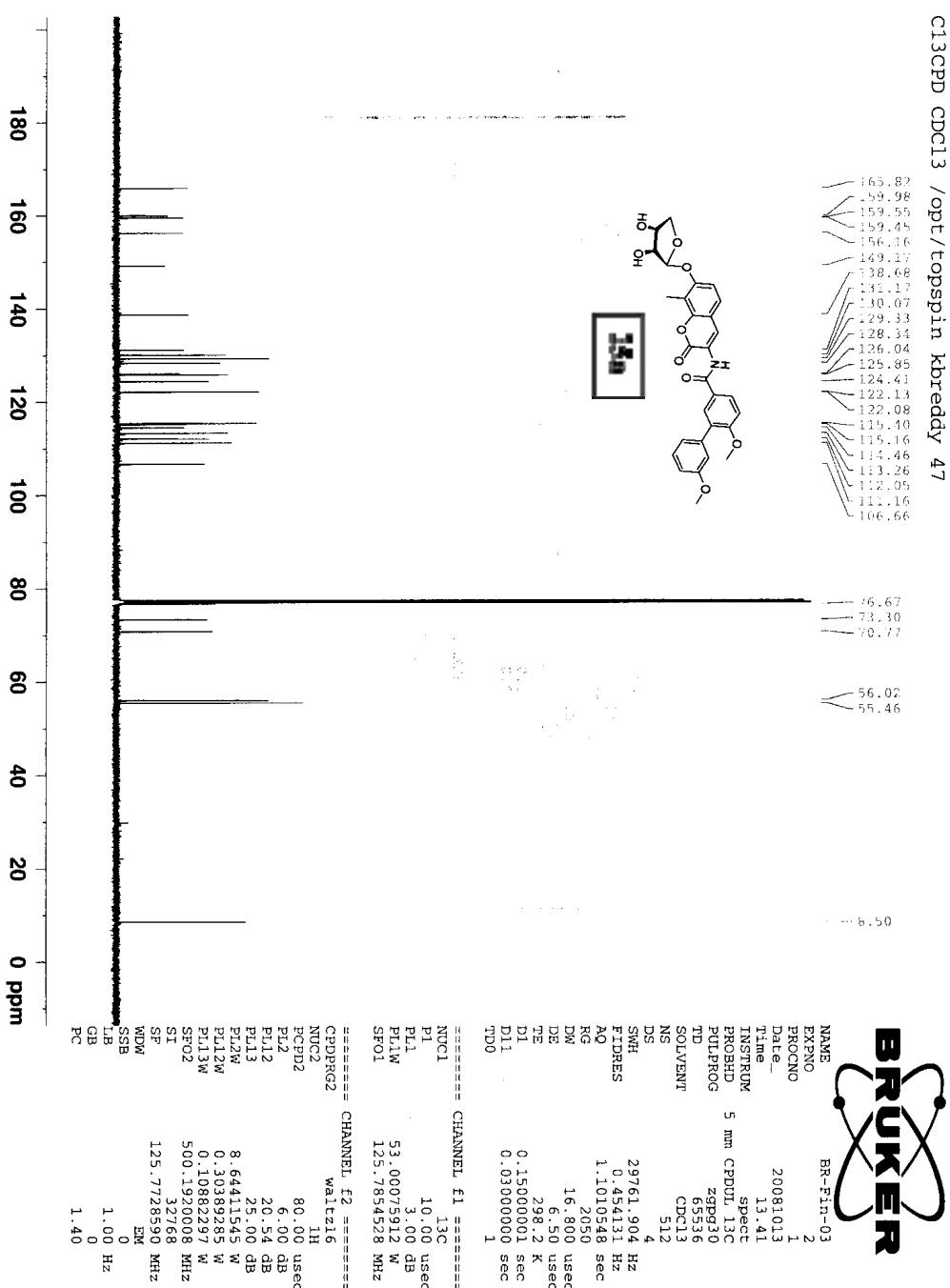
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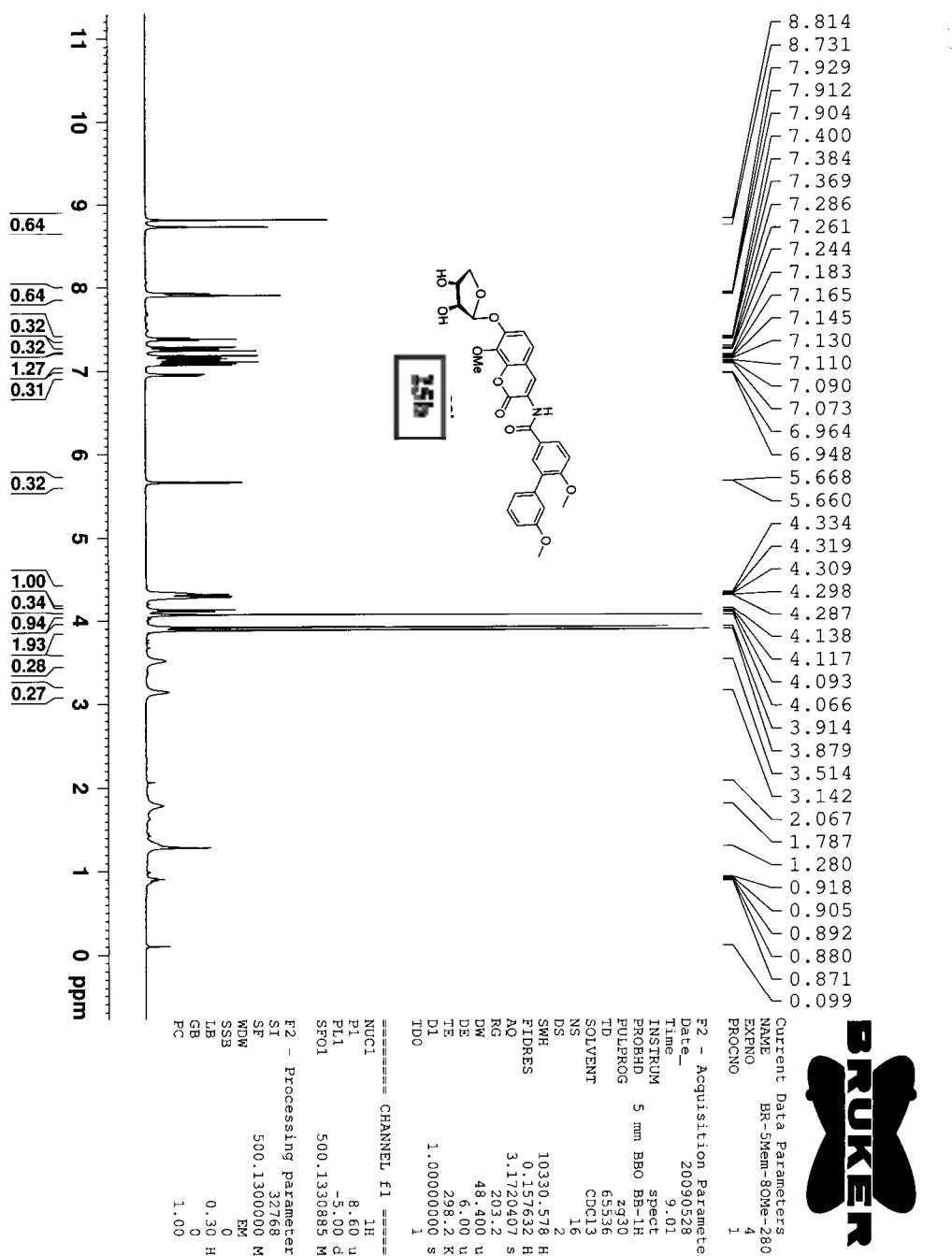
NAME          BR-Fin-03
EXPNO         1
PROCNO        1
Date_        20081013
Time       13:30
INSTRUM      spect
PROBHD      5 mm CPTDUL 13C
PULPROG      zg30
TD        65536
SOLVENT      CDCl3
NS           16
DS            2
SWH       10330.578 Hz
FIDRES     0.157632 Hz
AQ        3.171923 sec
RG          2050
RG          48.400 usec
DW           6.50 usec
DE          298.2 K
TE          298.2 K
D1        1.00000000 sec
TDO

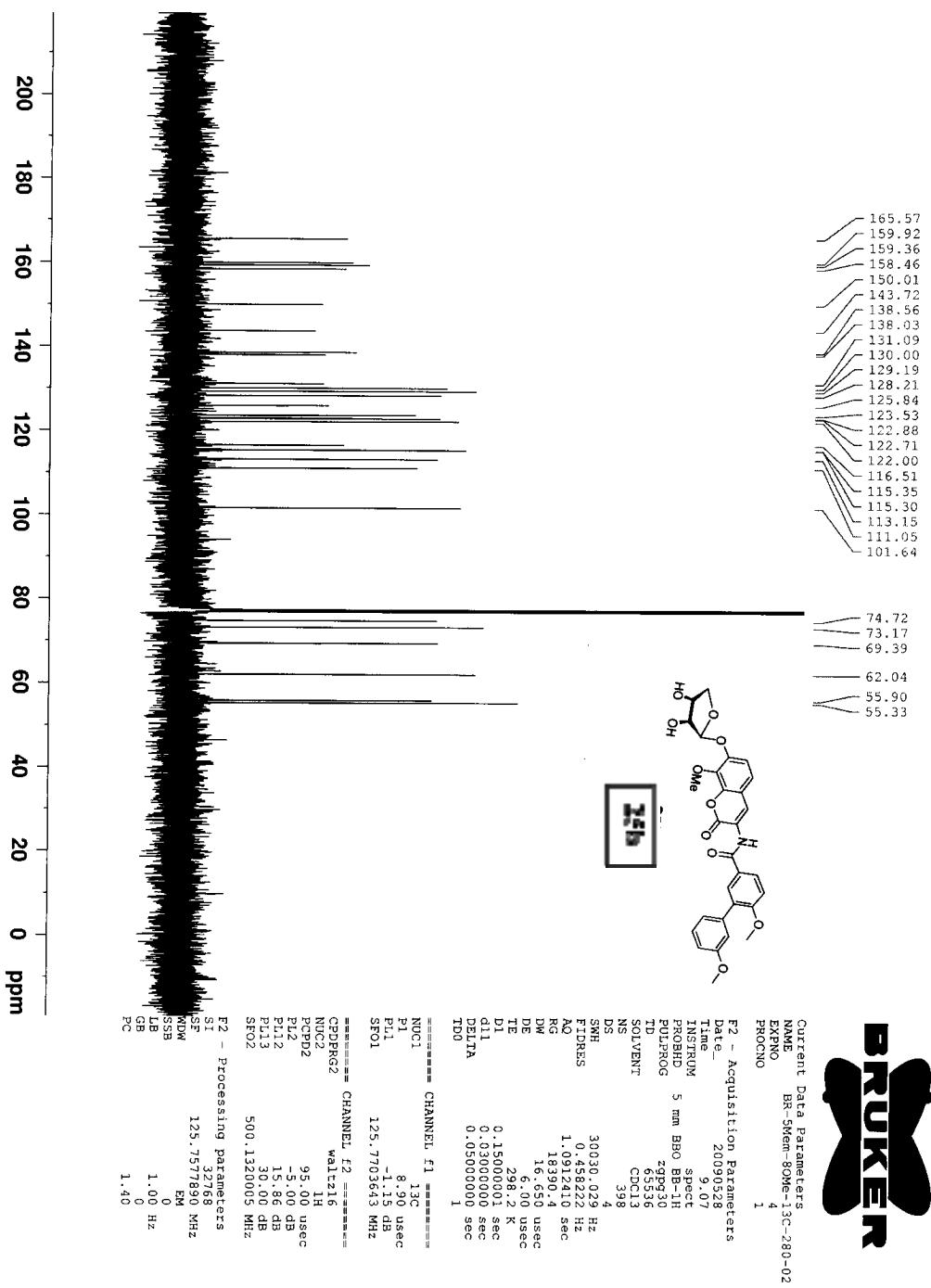
===== CHANNEL f1 =====
NUC1          1H
PL1          15.00 usec
PL1W         6.00 dB
PL1W         8.64411545 W
SP01        500.193089 MHz
SF          500.1900404 MHz
WDW          EM
SSB          0
LB          0.30 Hz
GB          0
PC          1.00

```

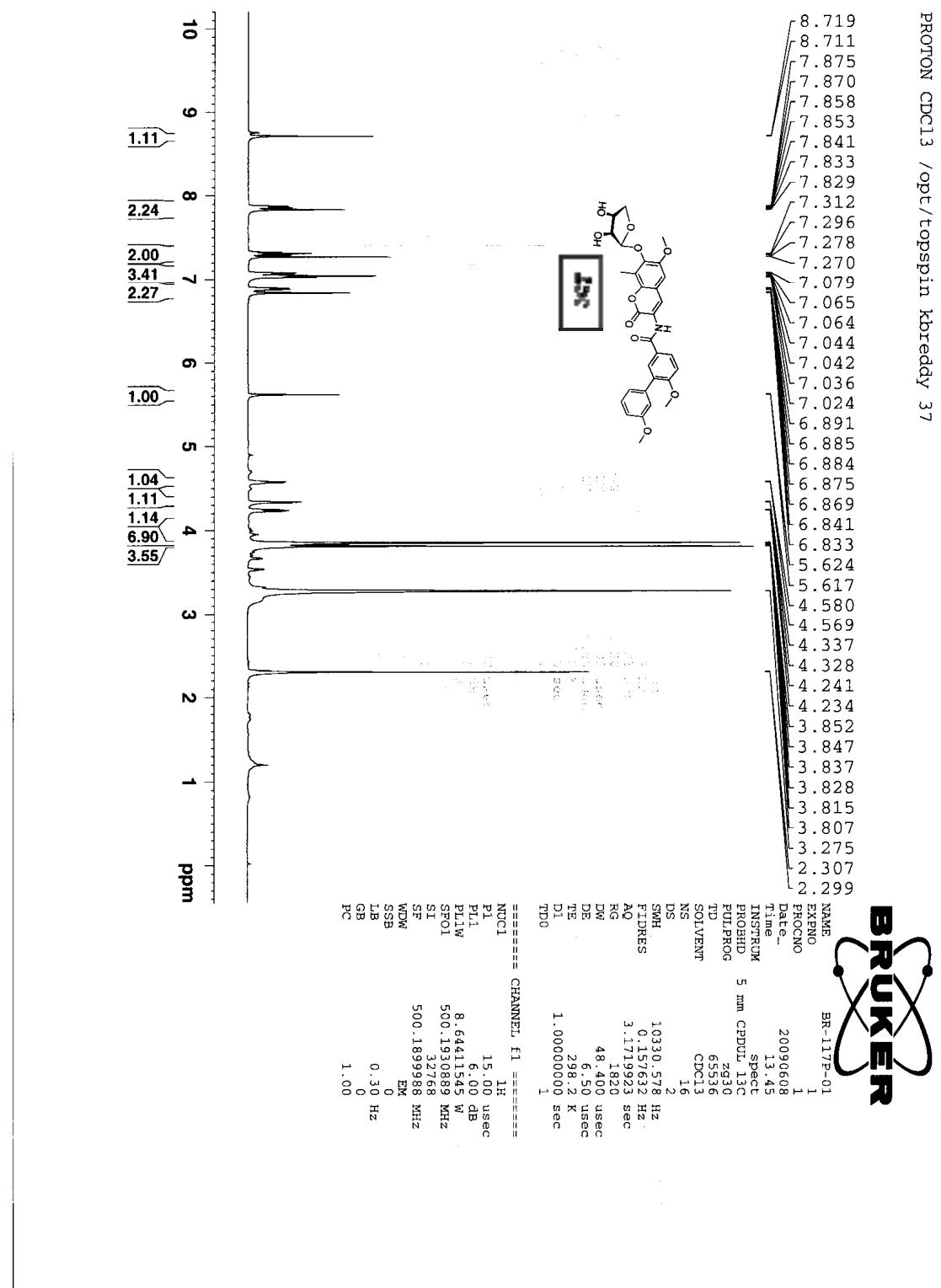


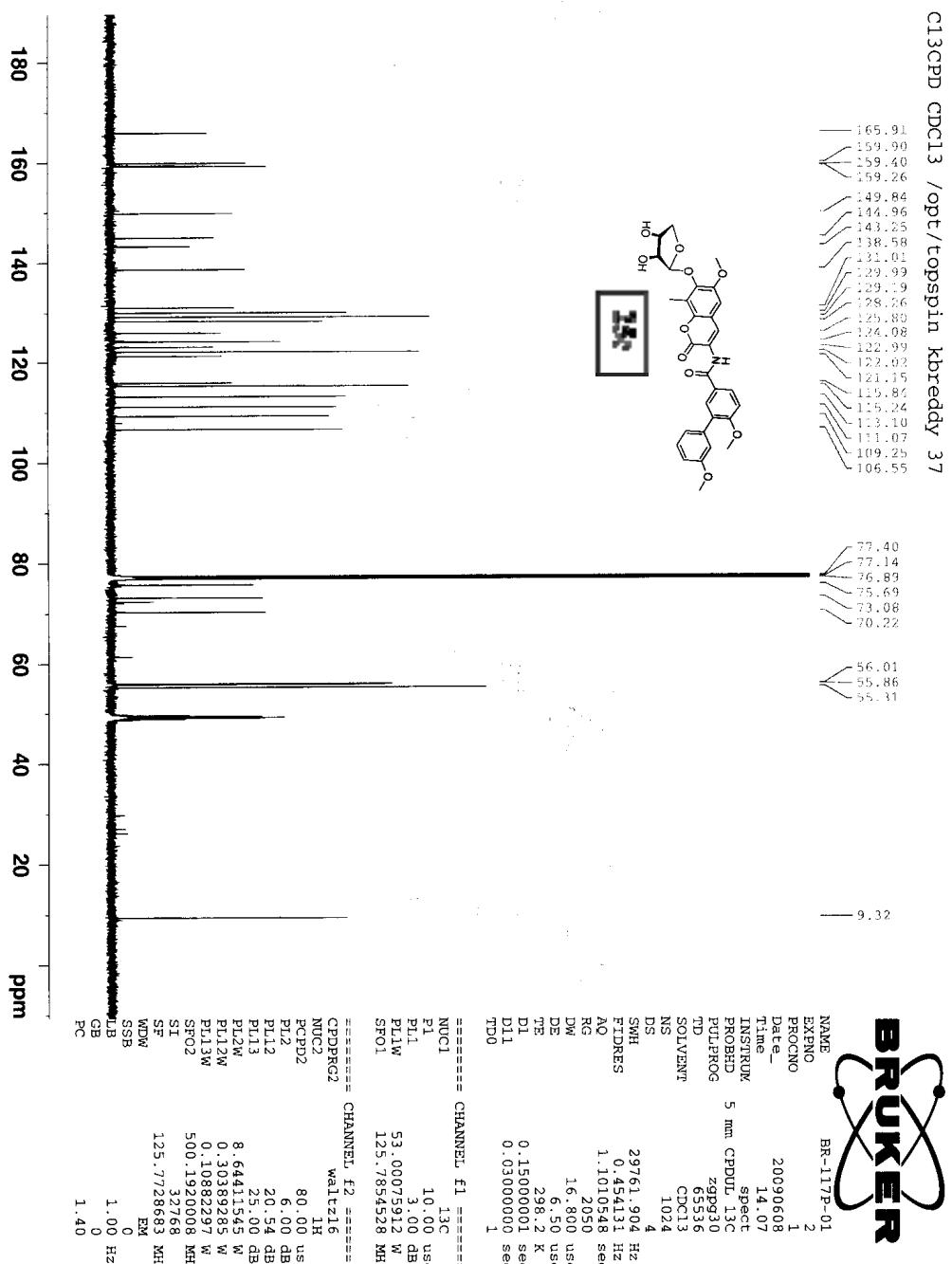


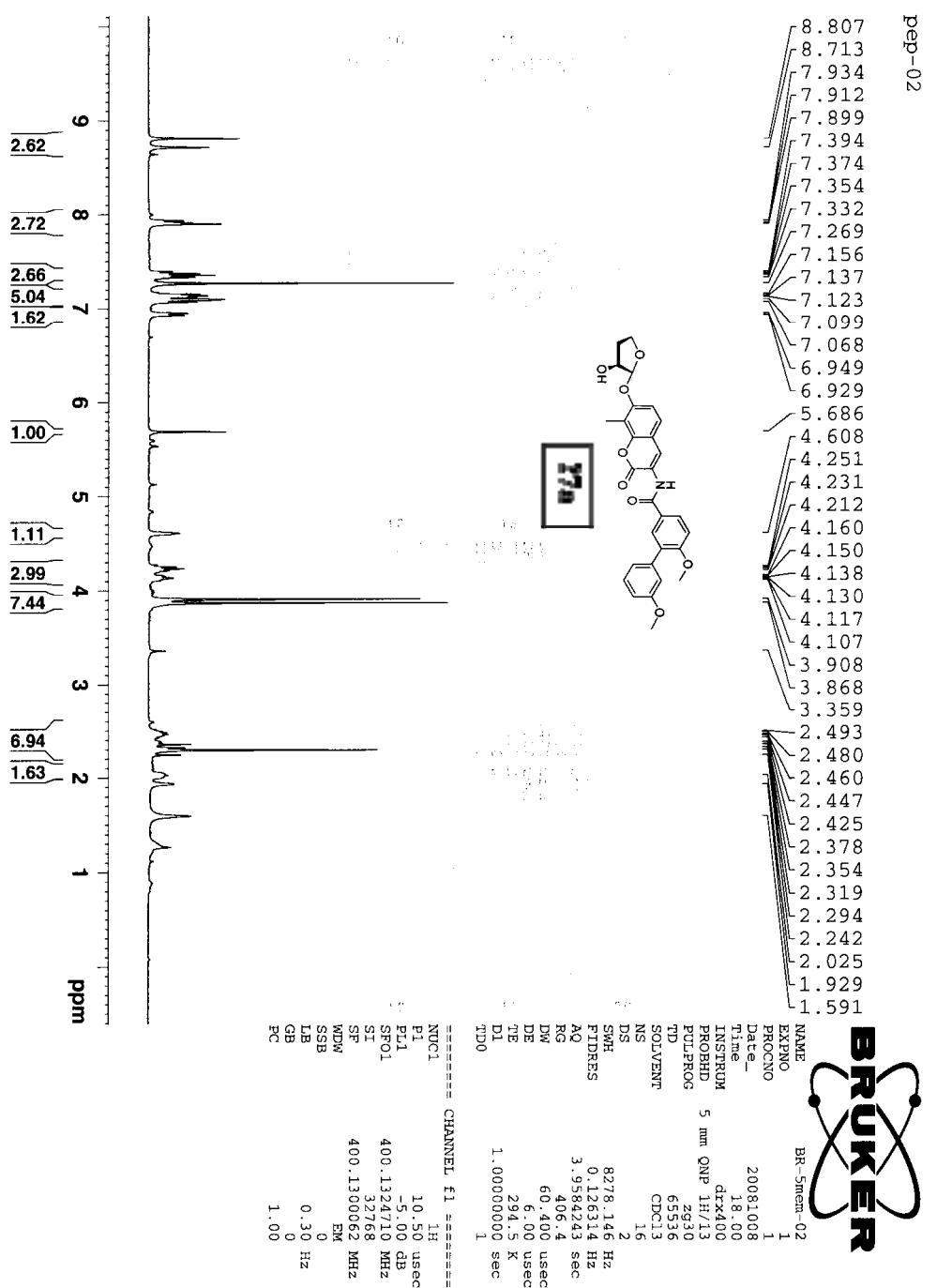


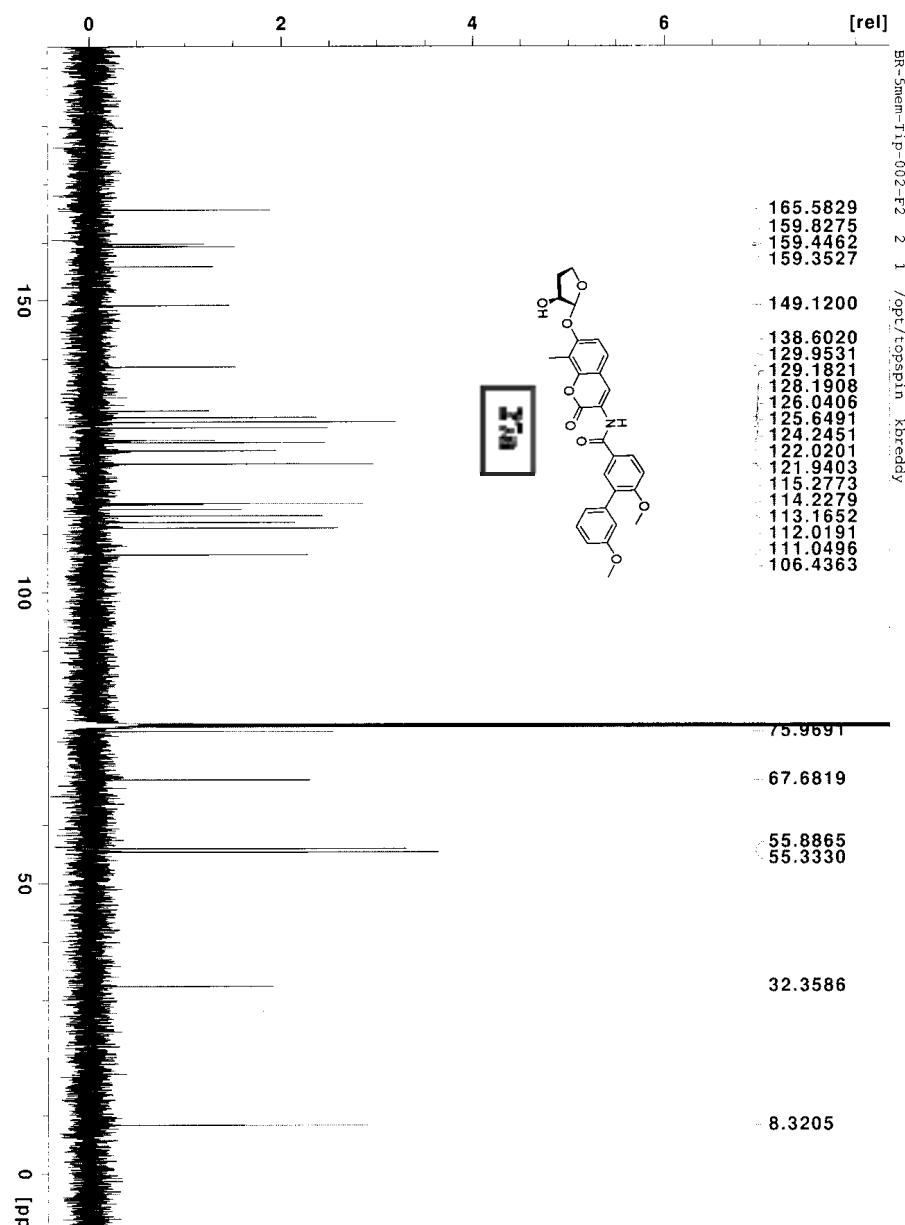


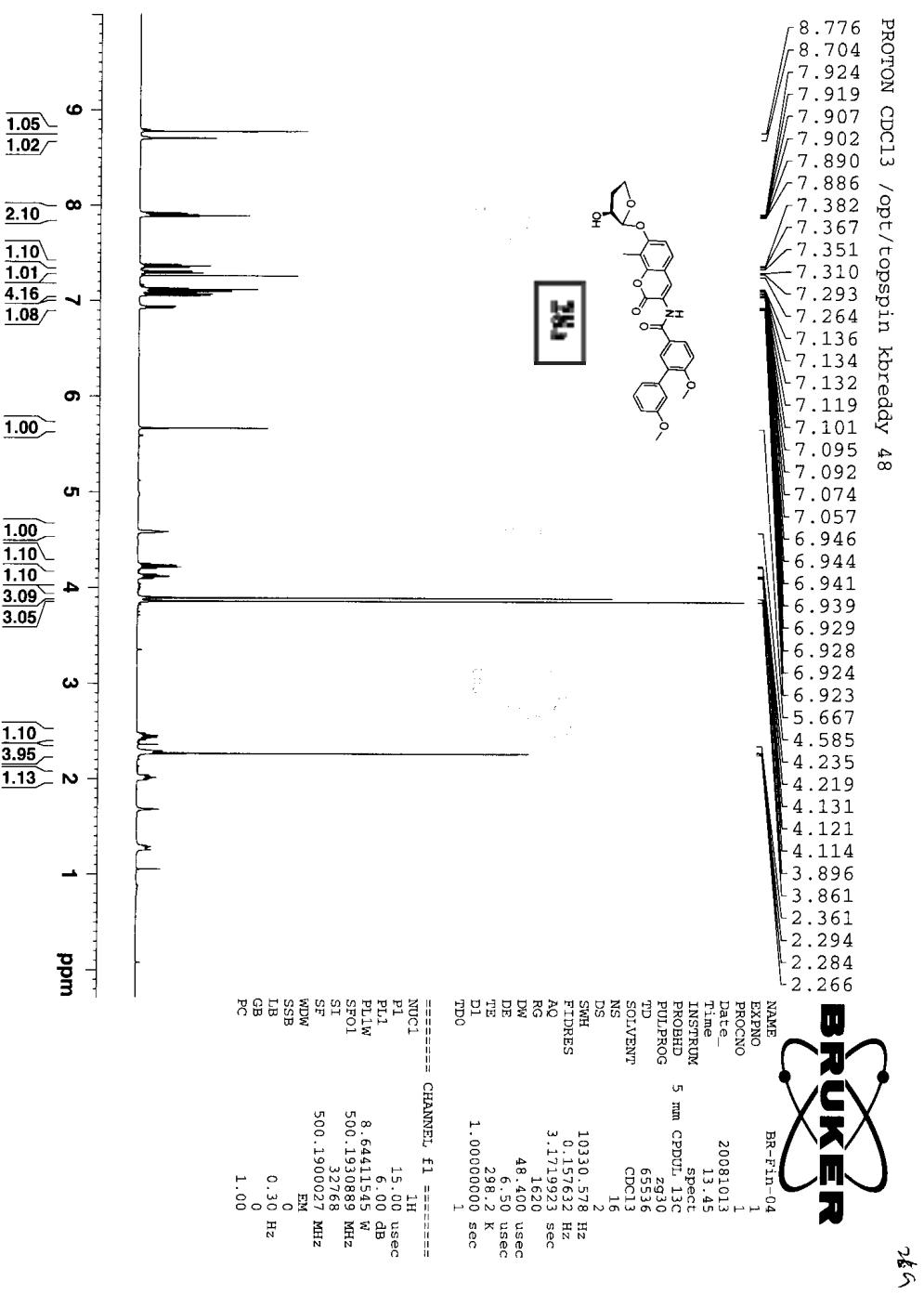
PROTON CDC13 /opt/topspin kbreddy 37

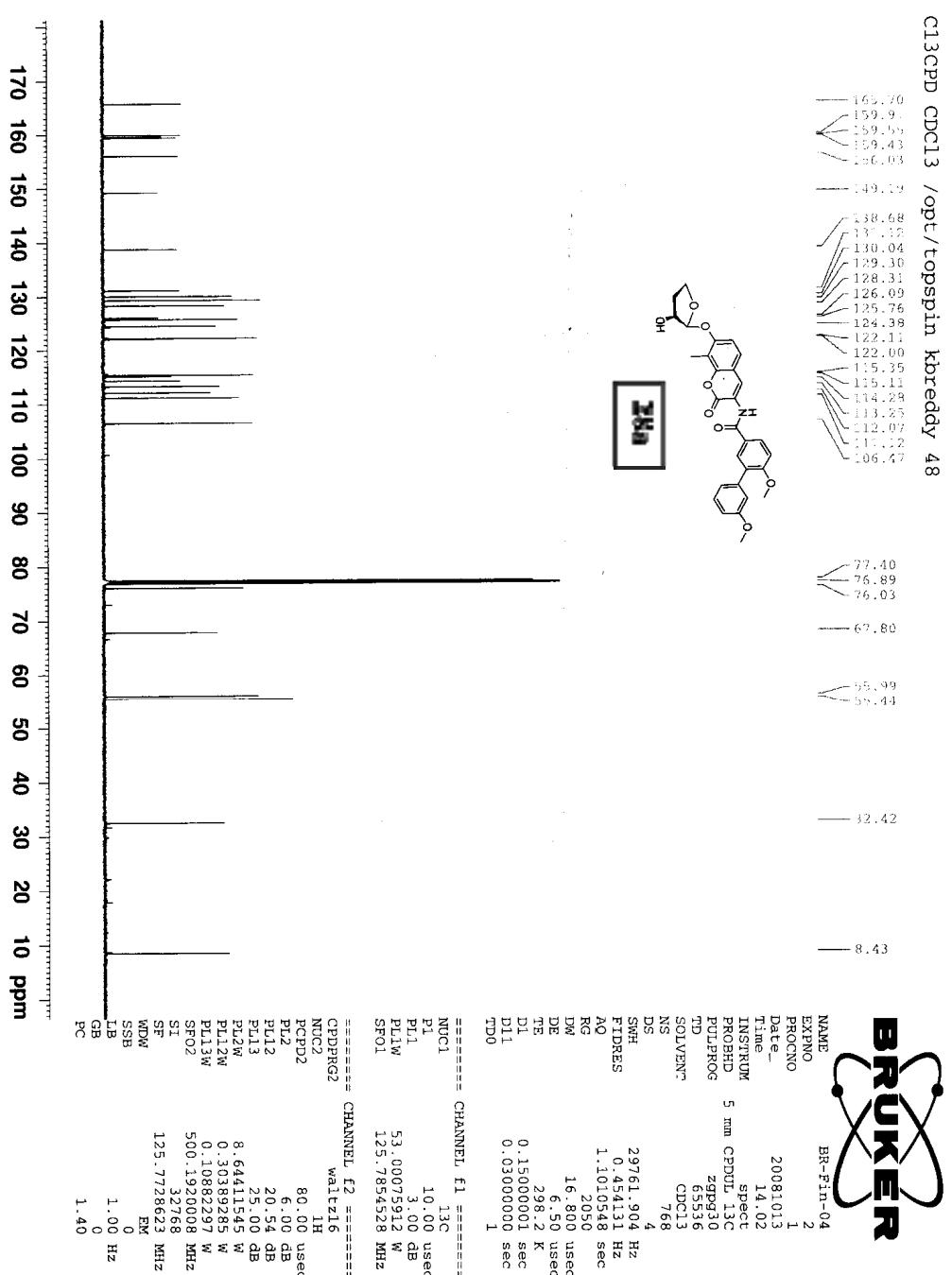


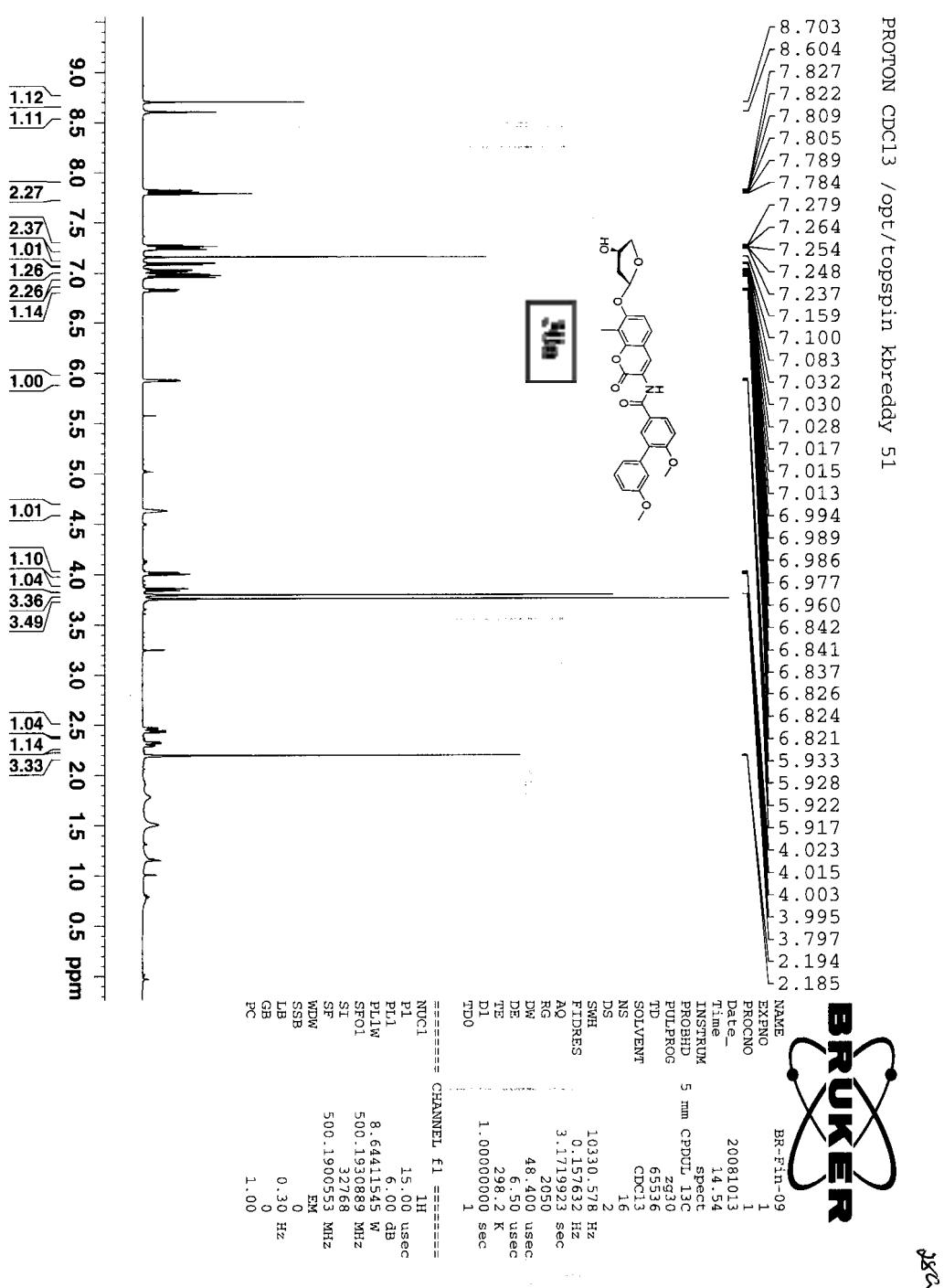


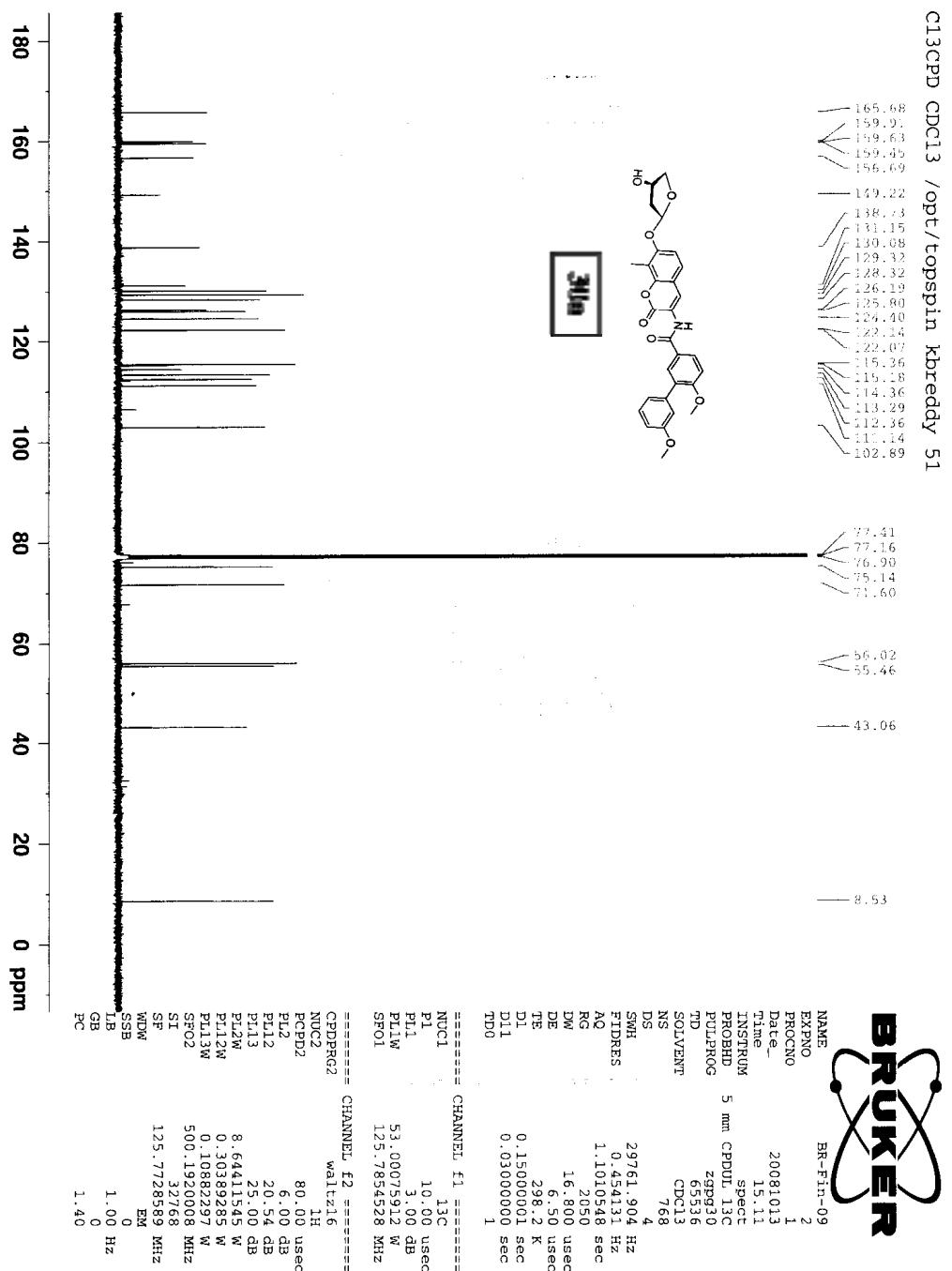








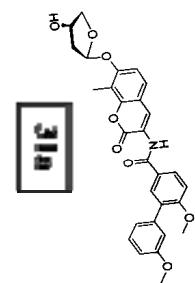




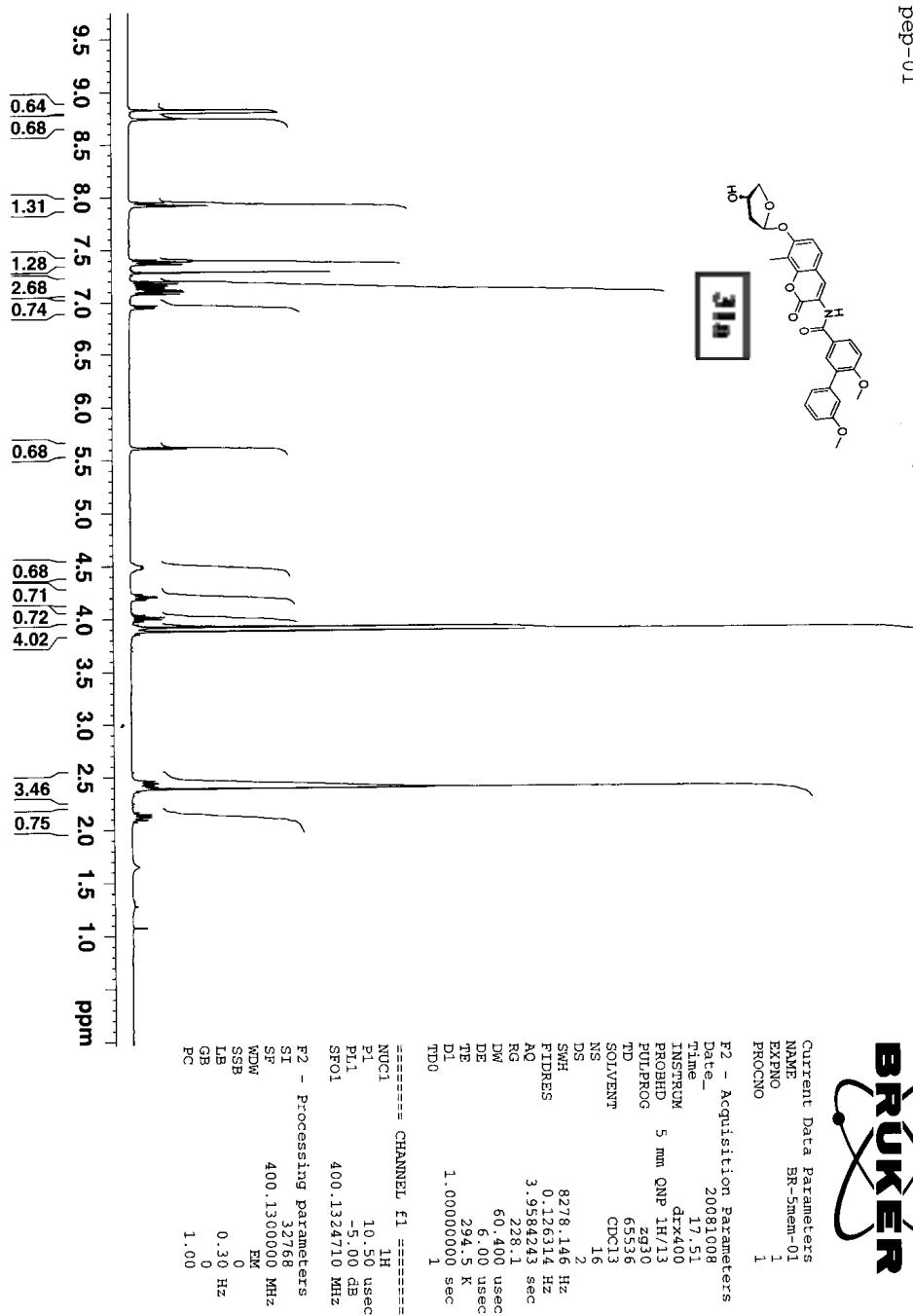
pep-01

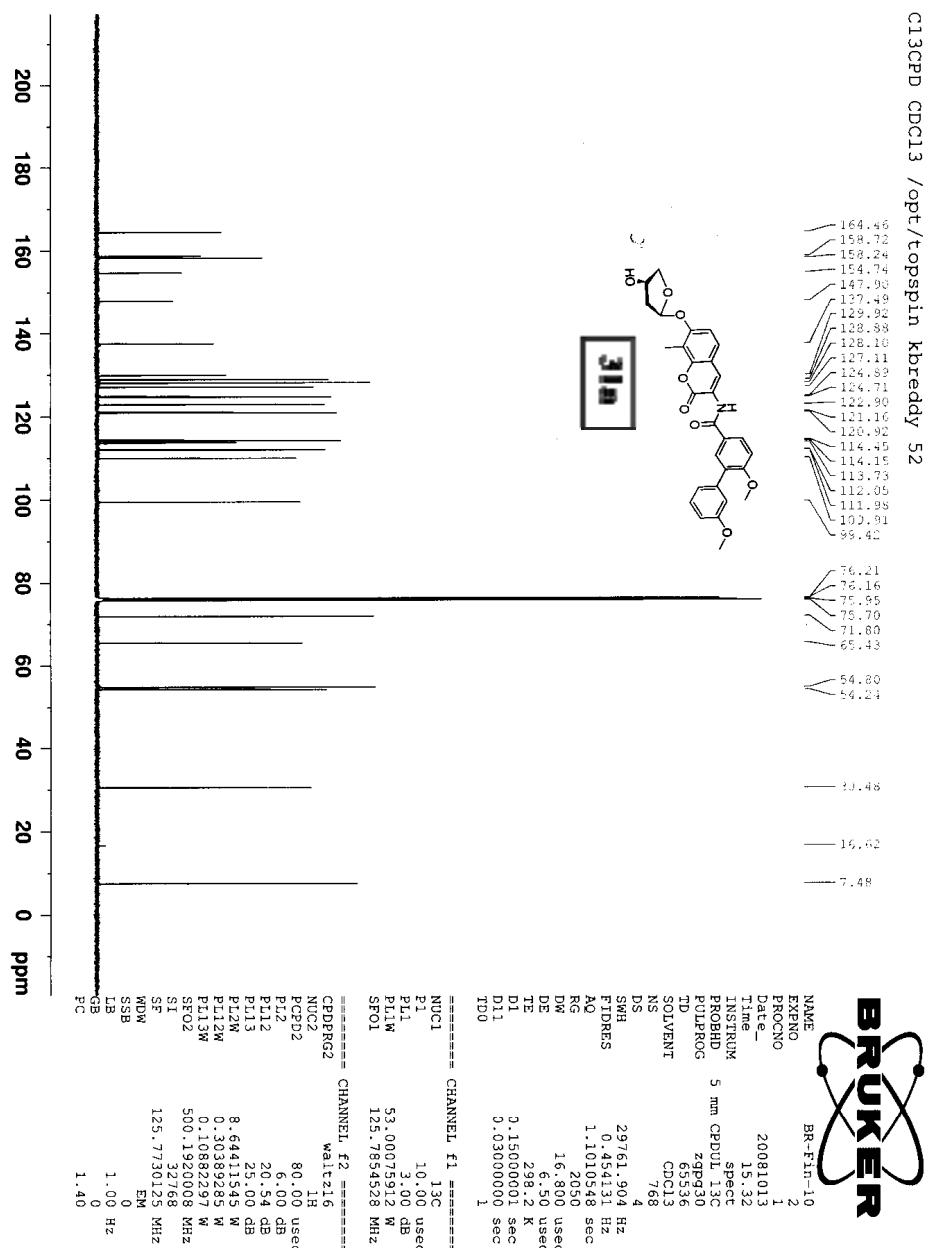
BRUKER

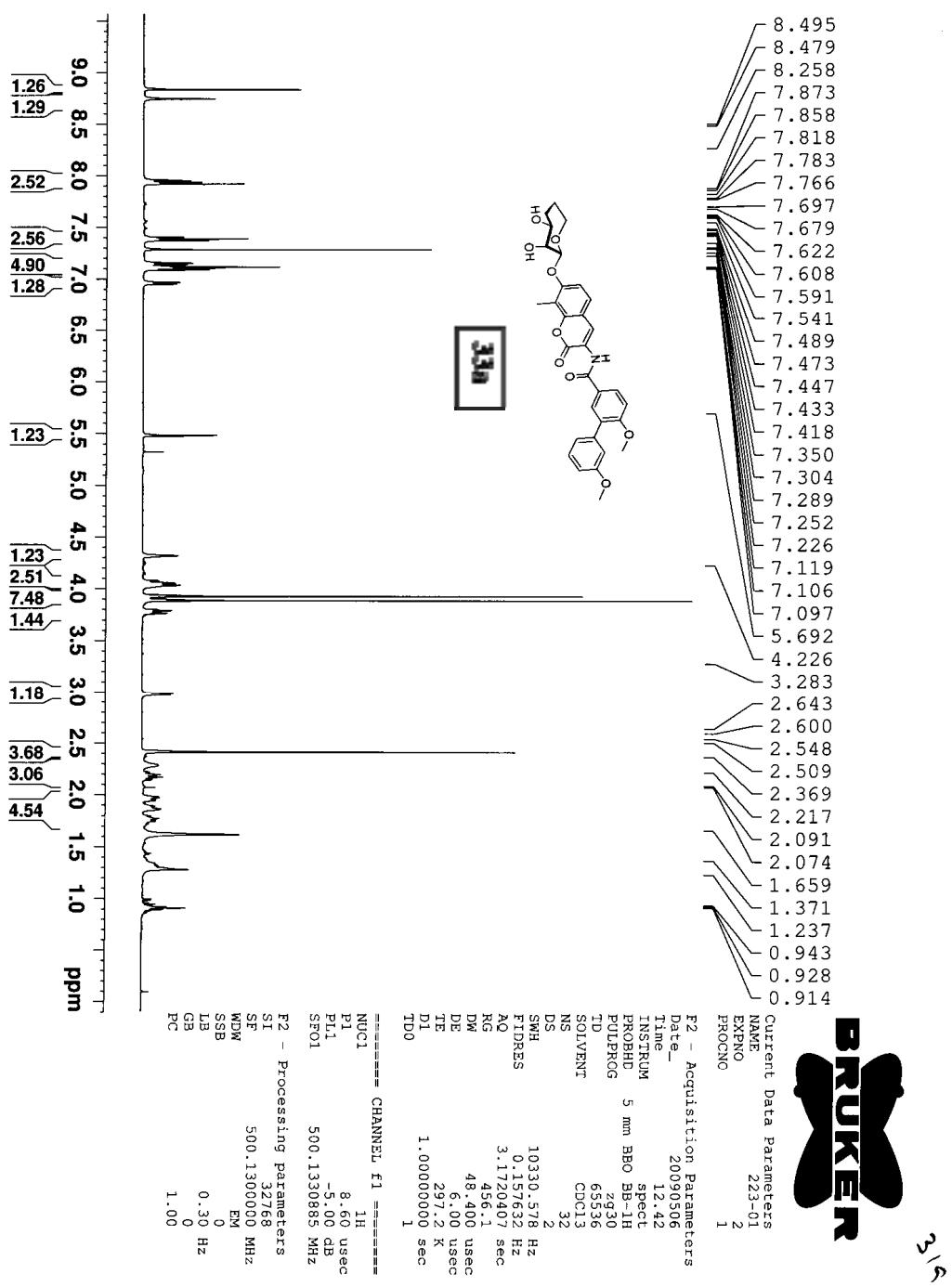
294

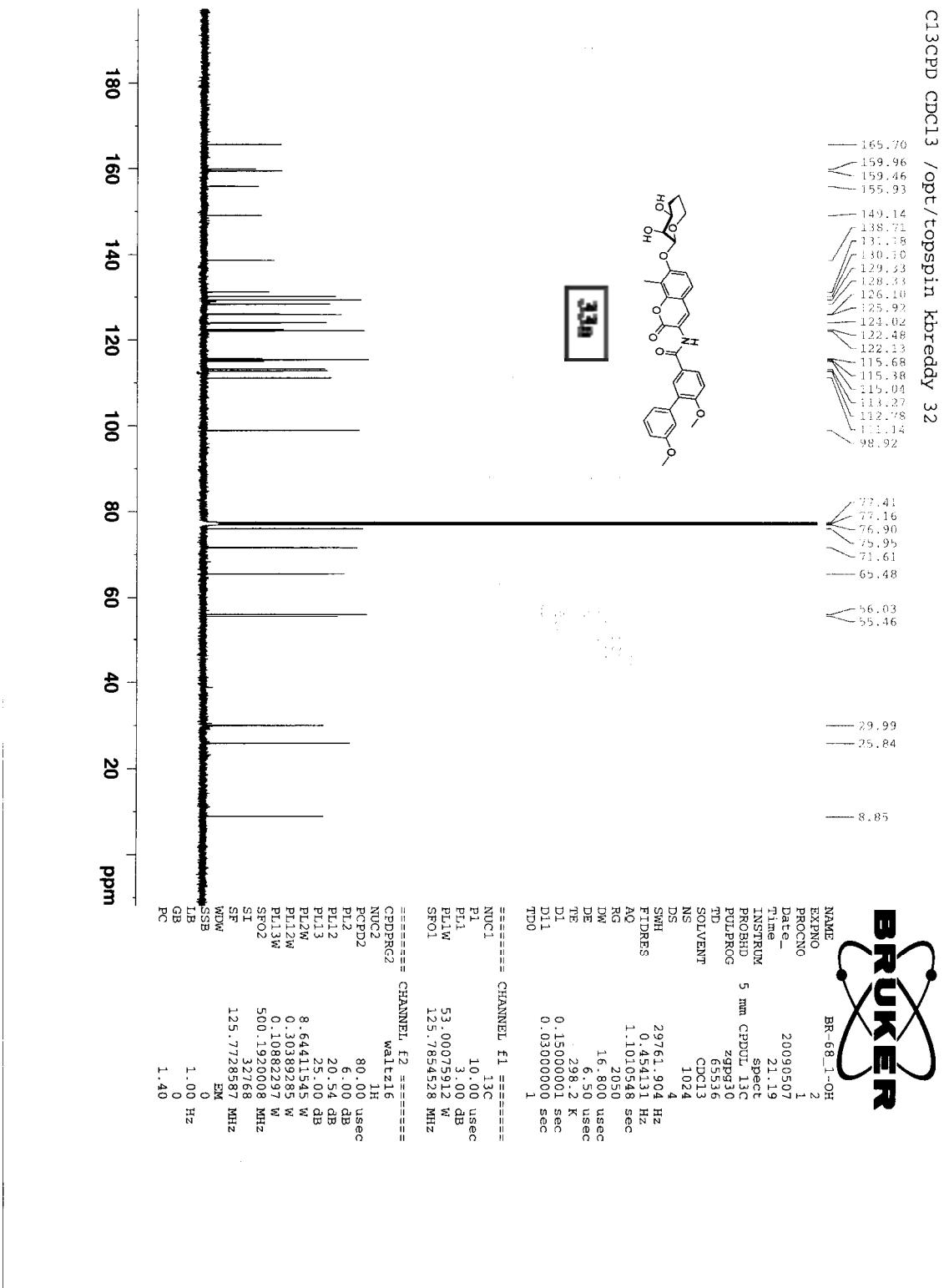


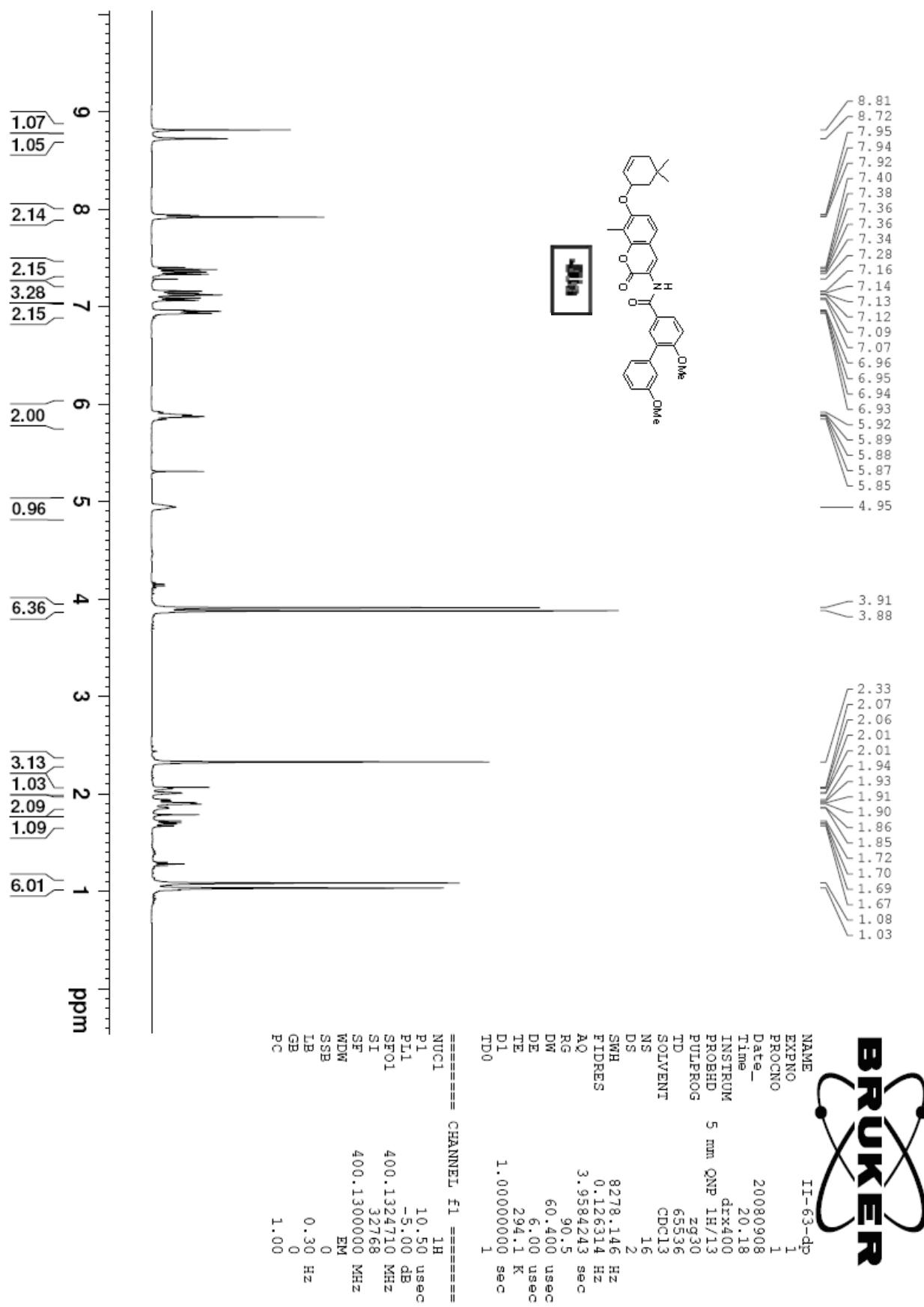
31a

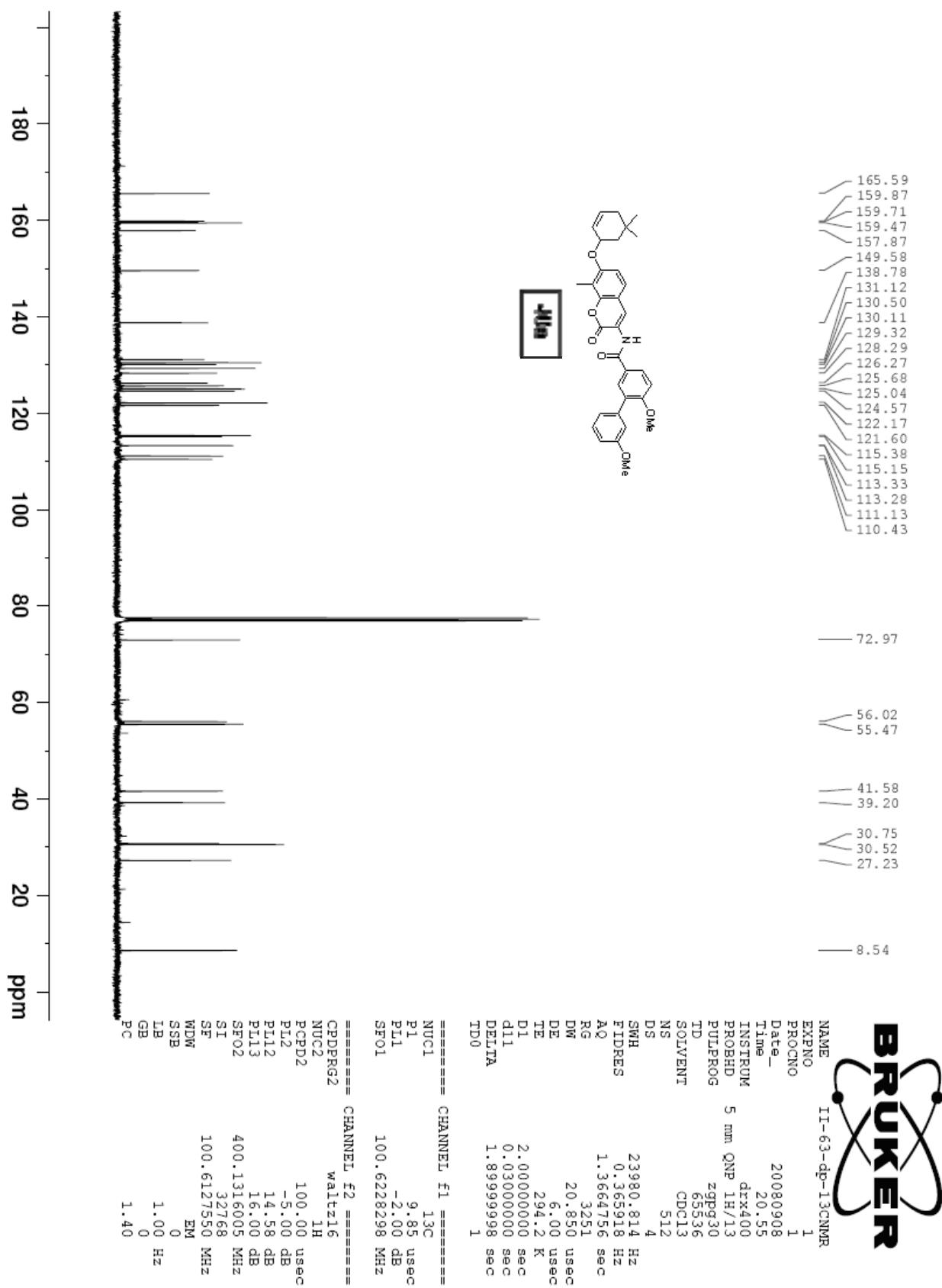


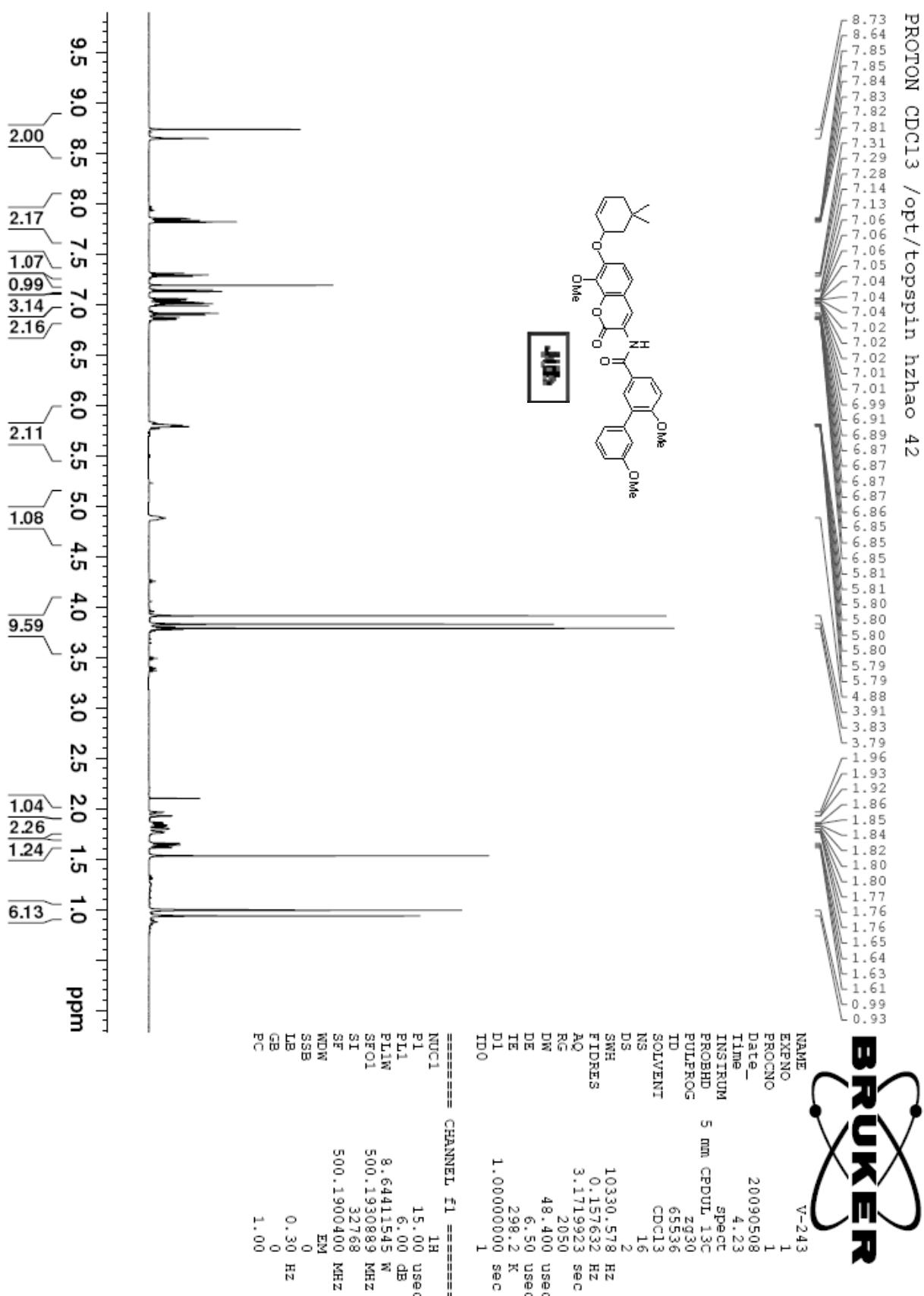


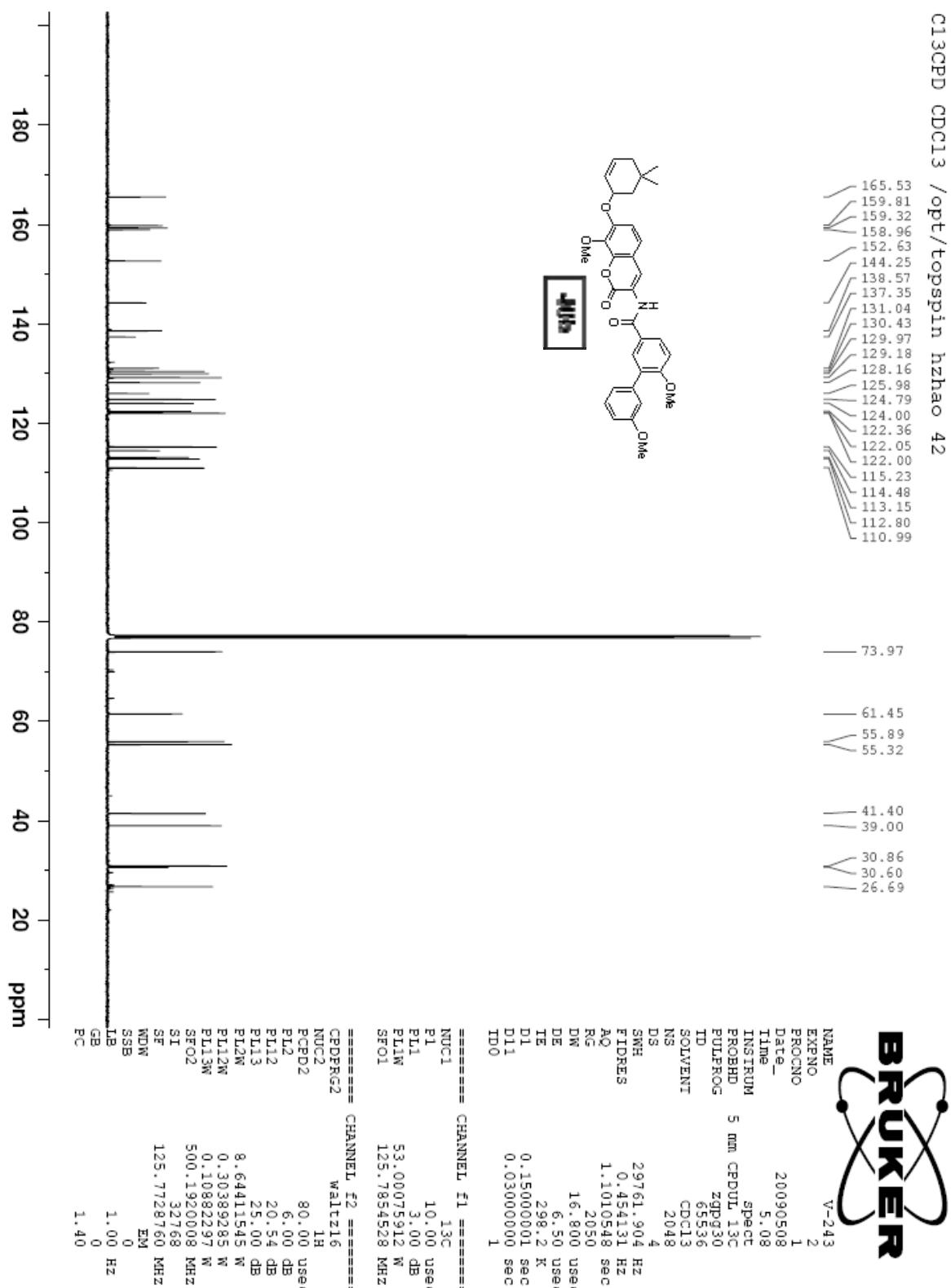


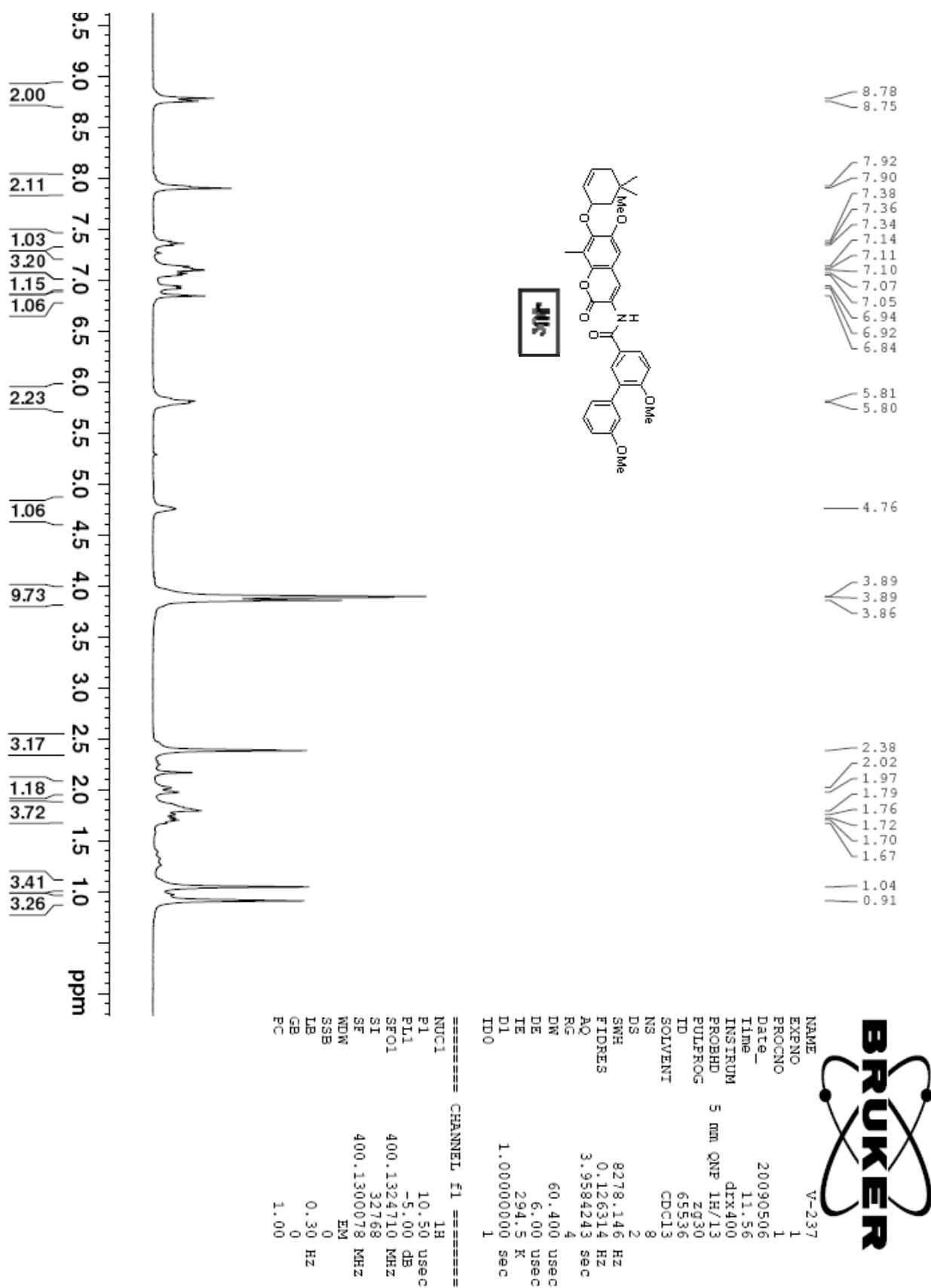


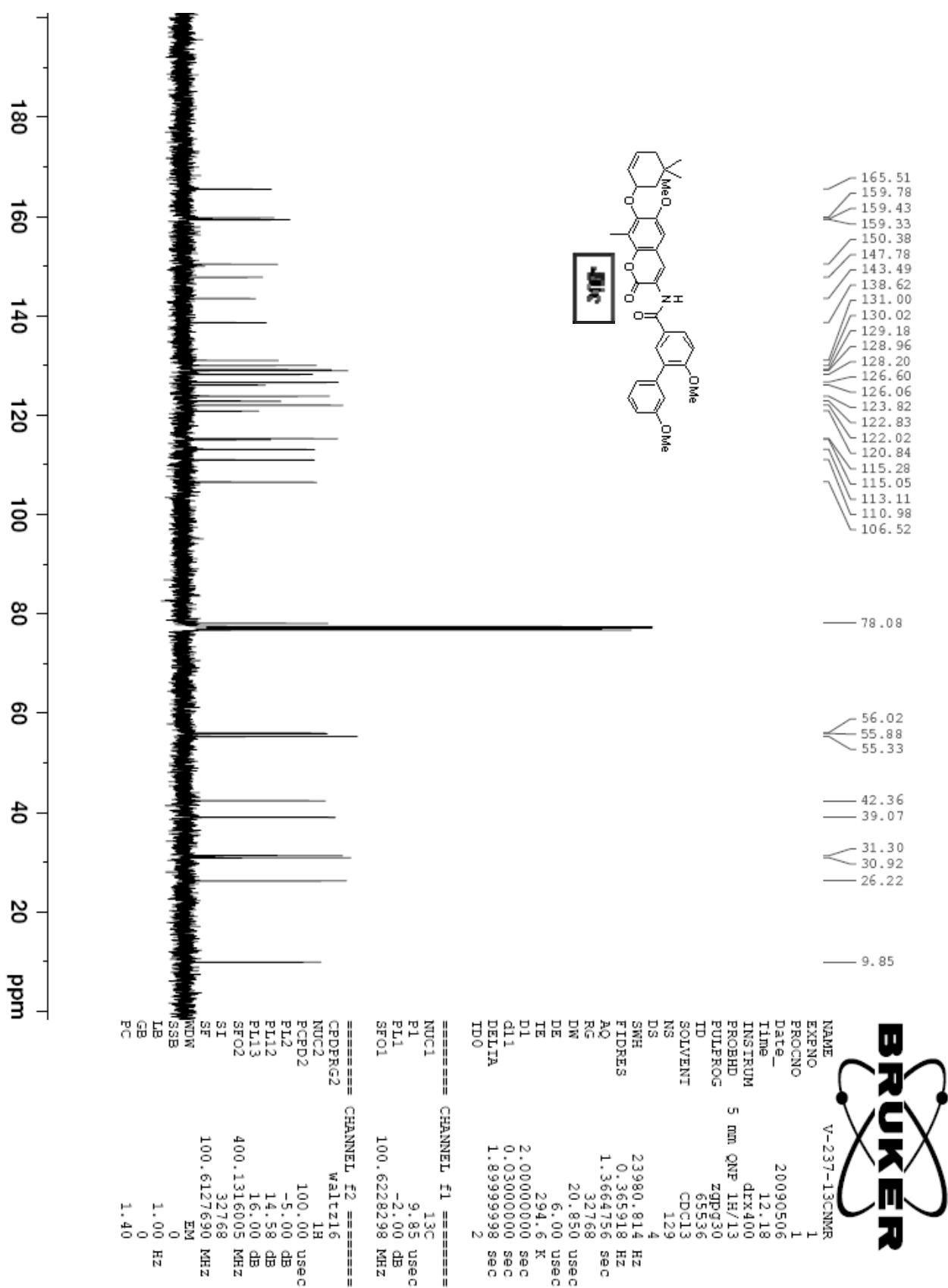


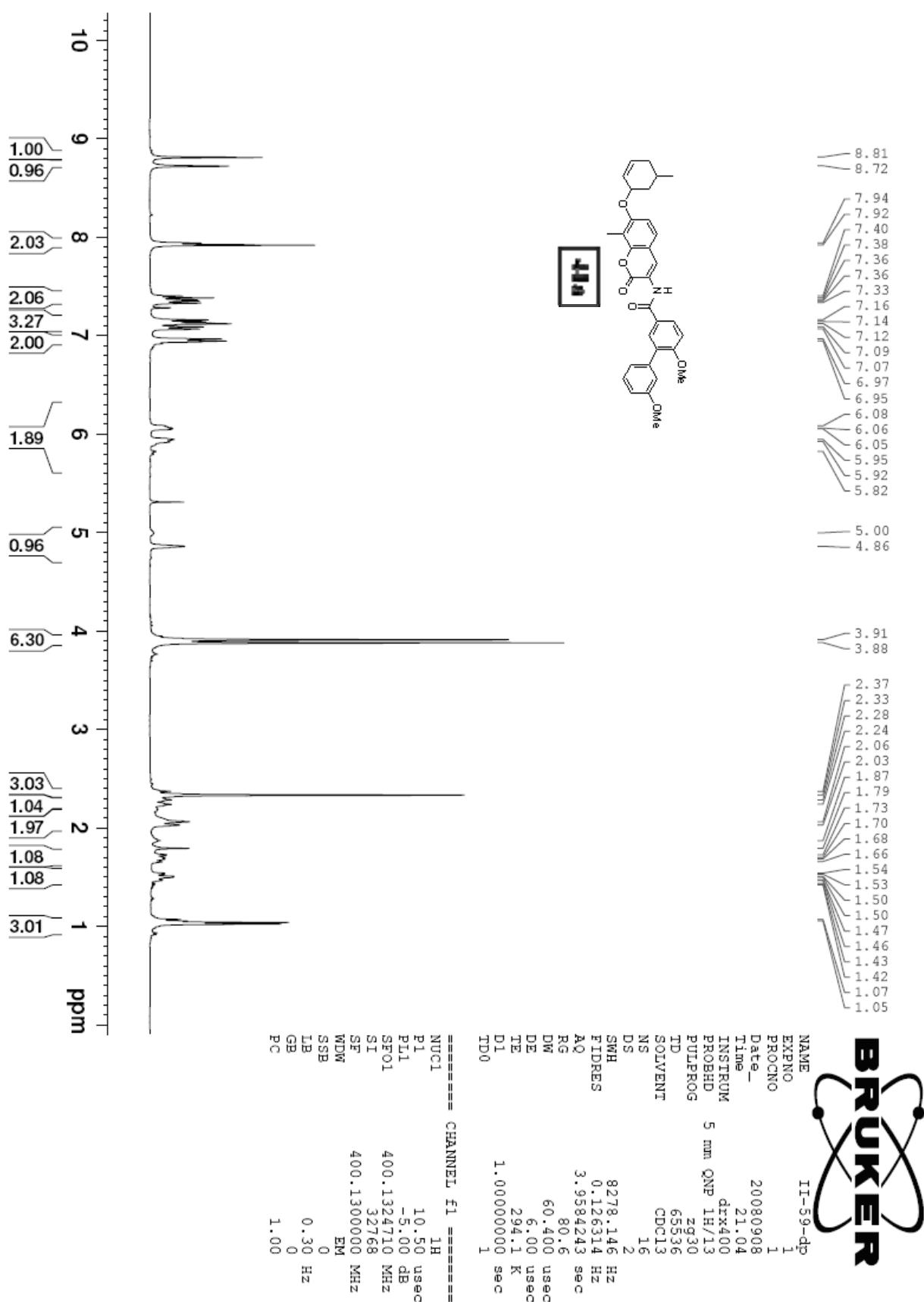


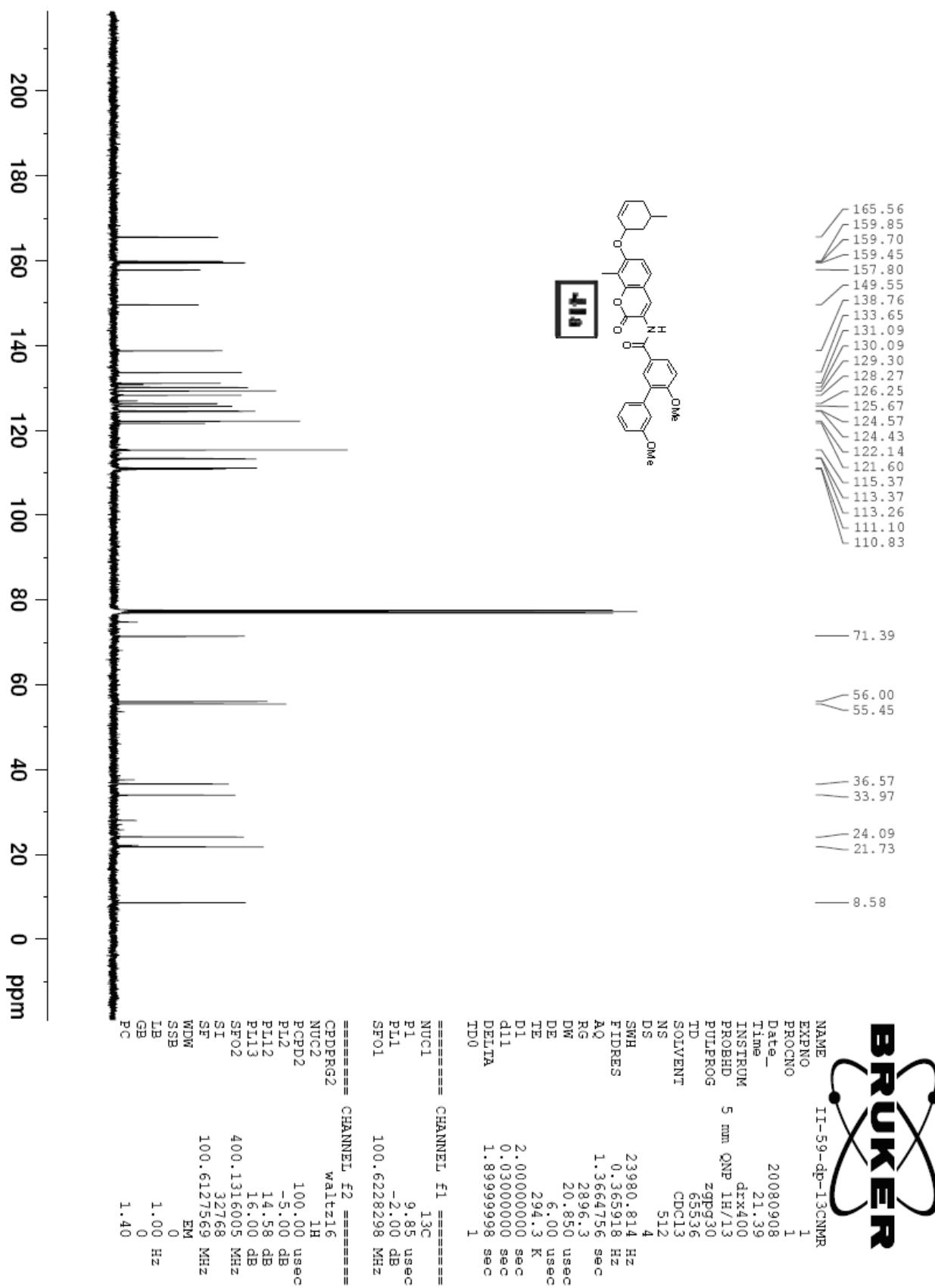


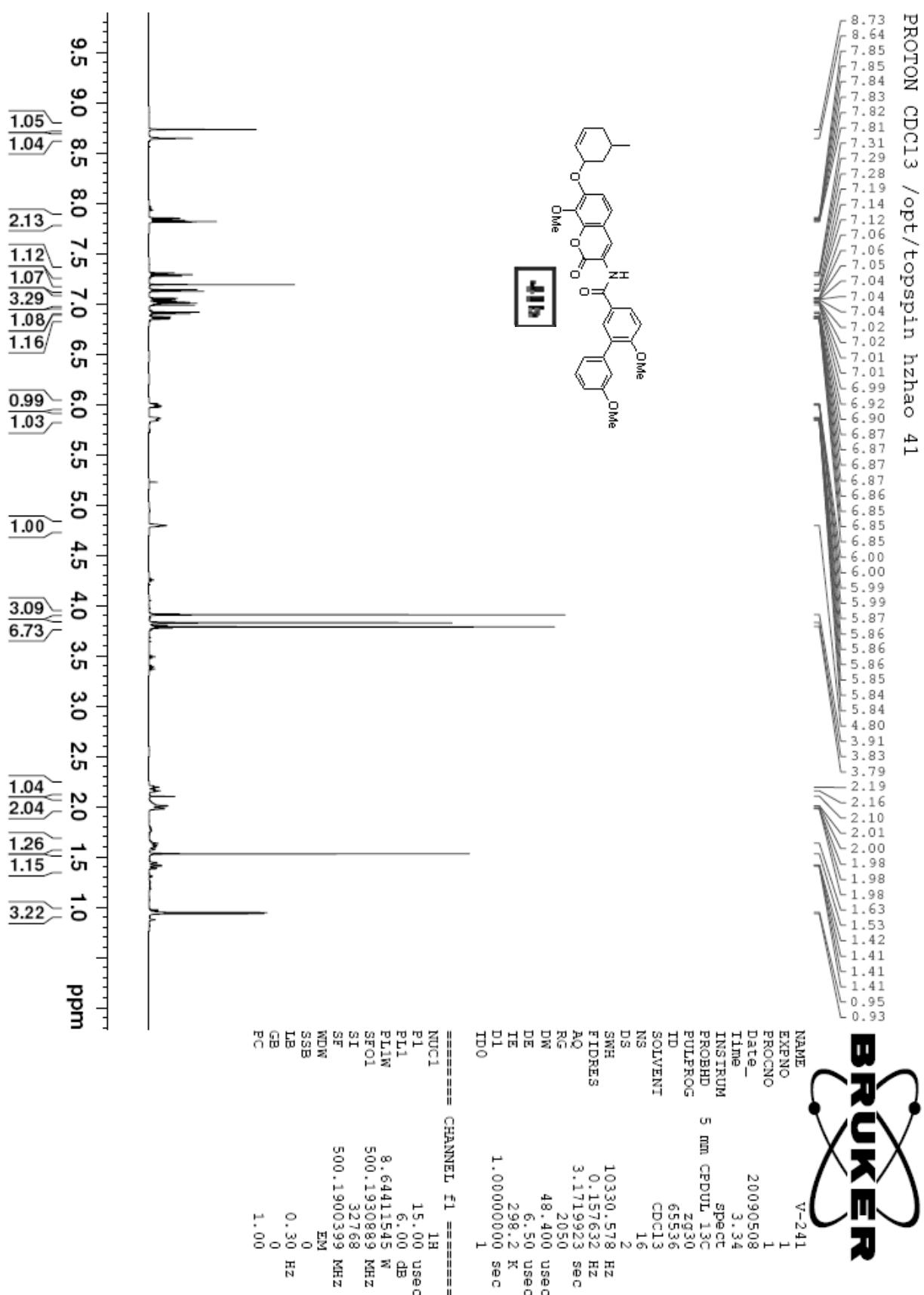


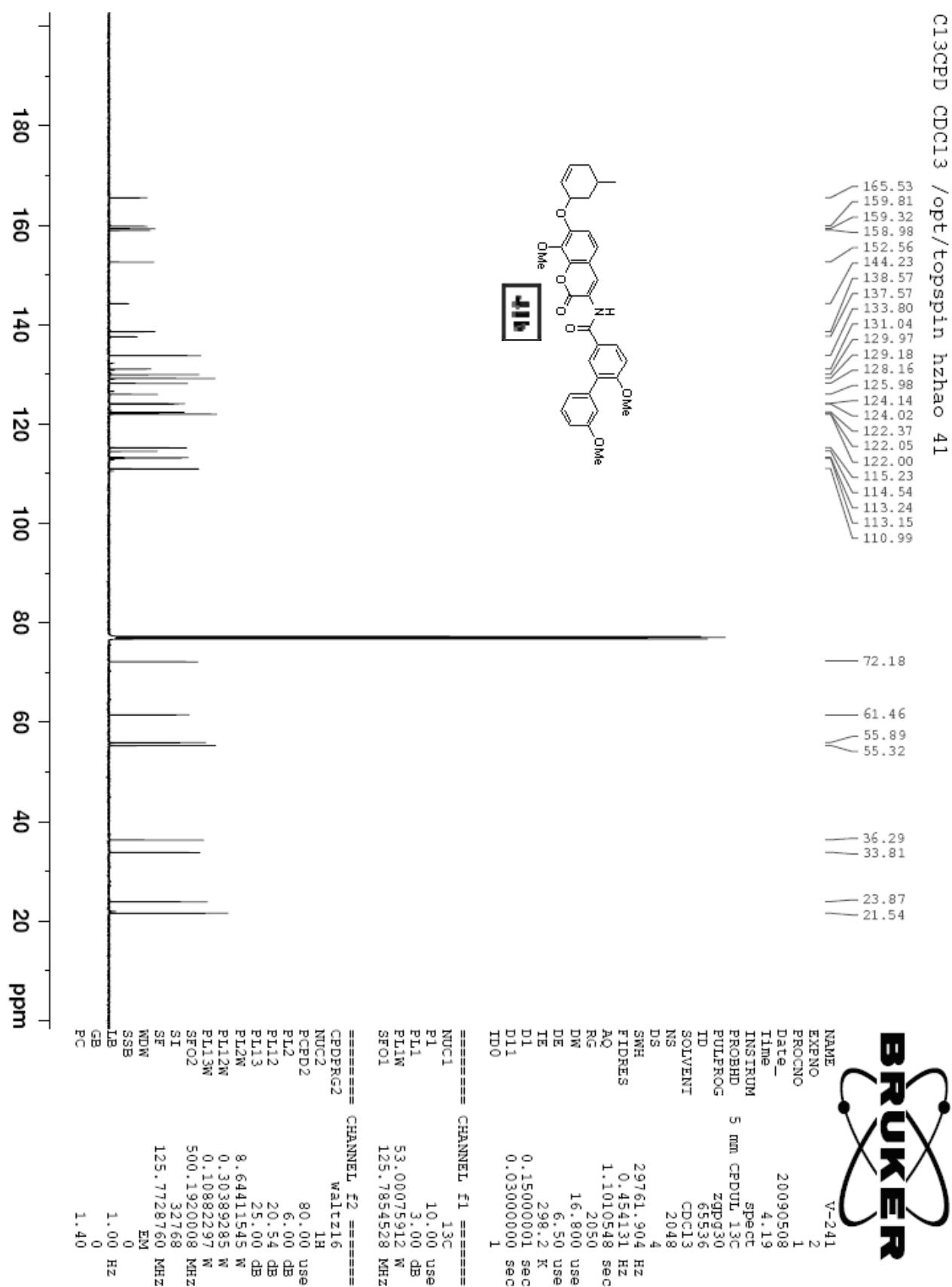


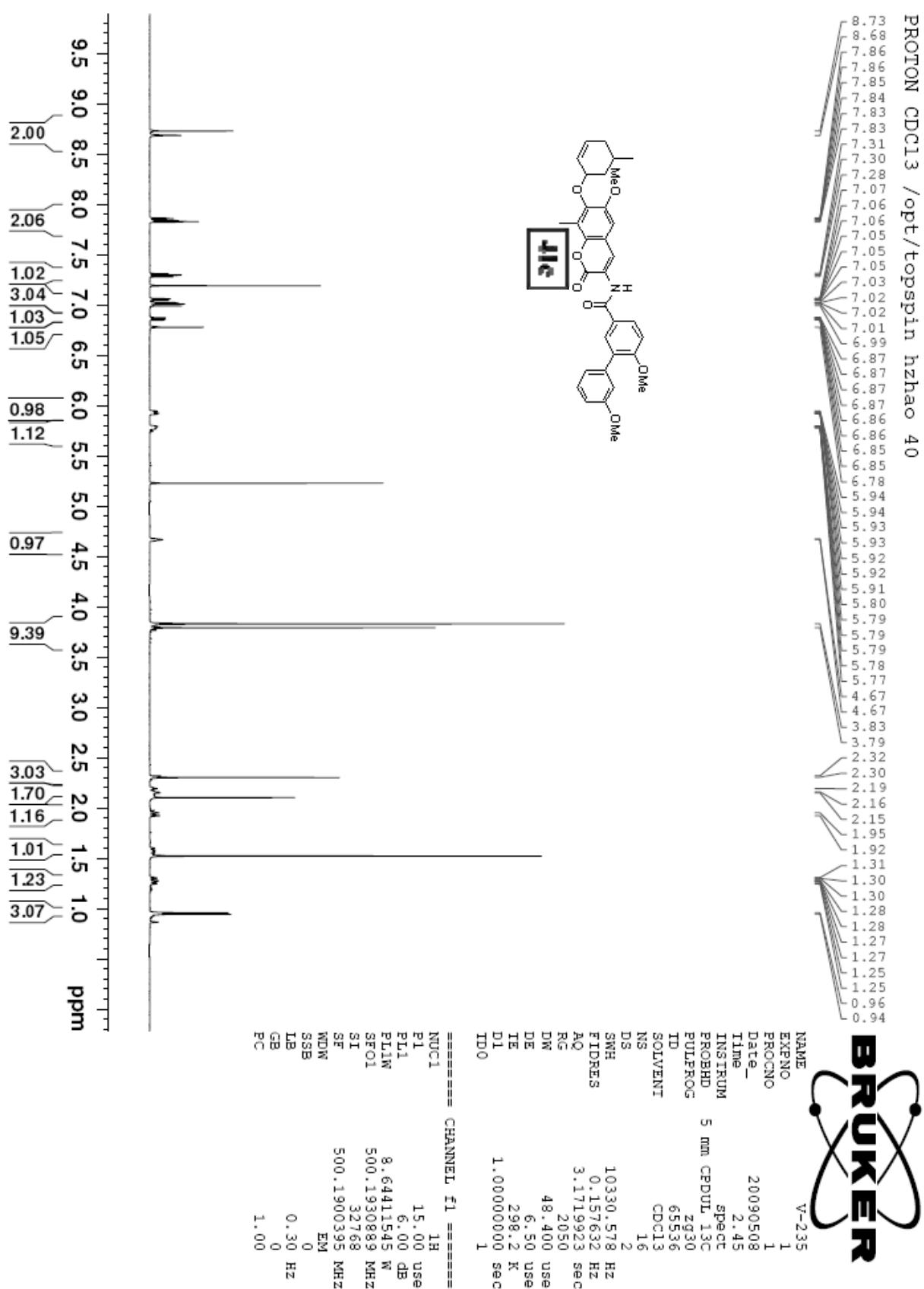


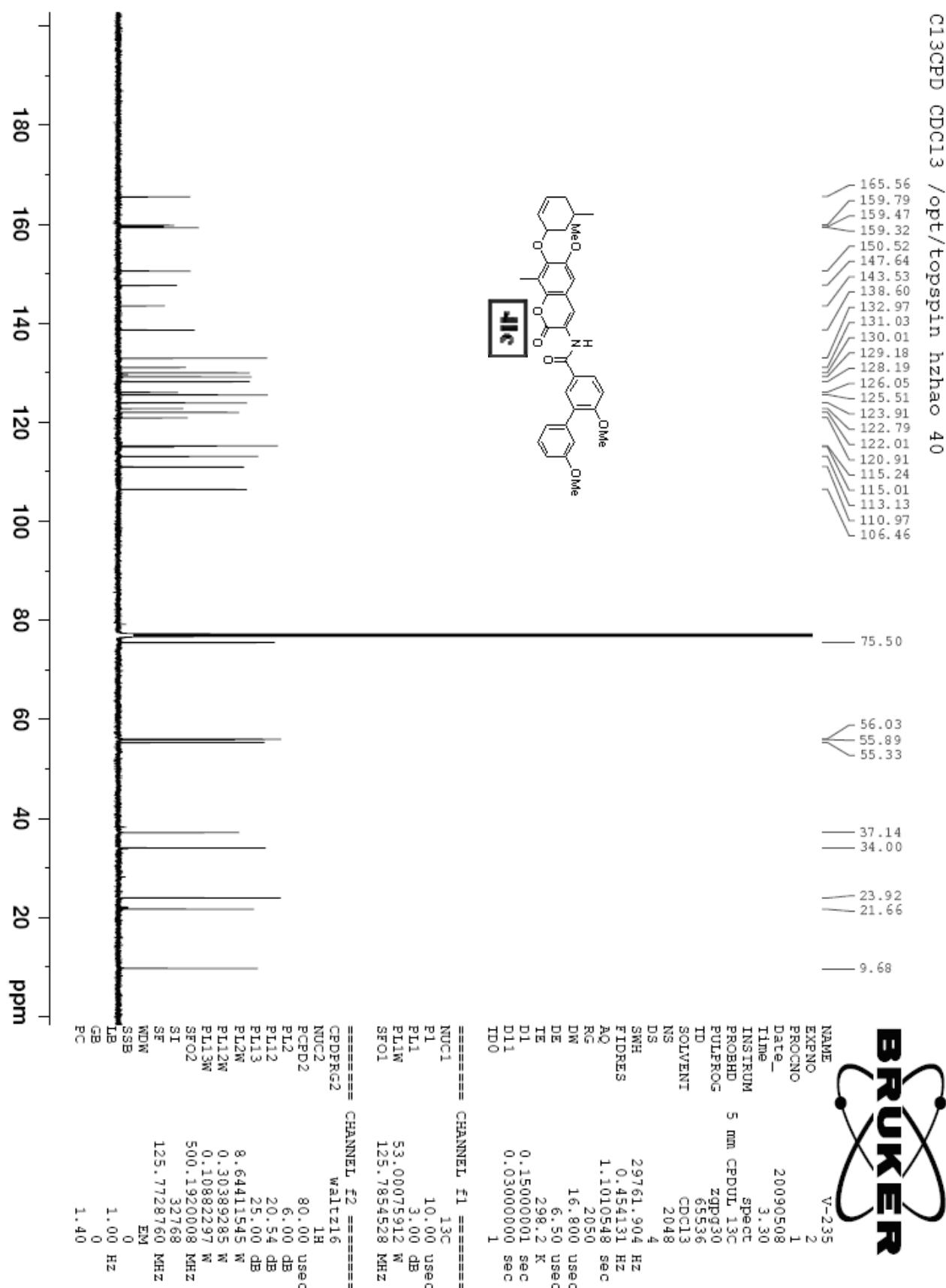


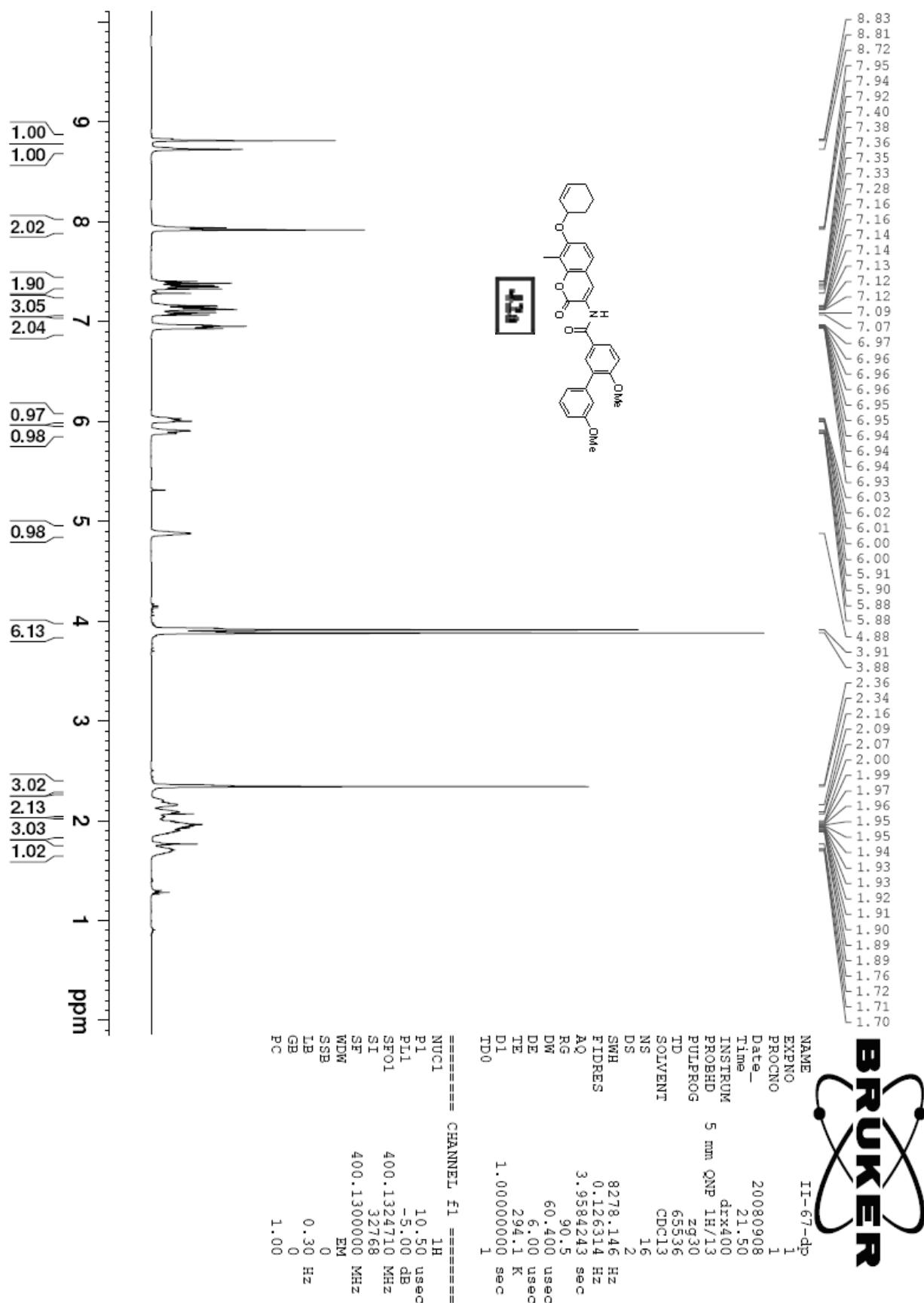


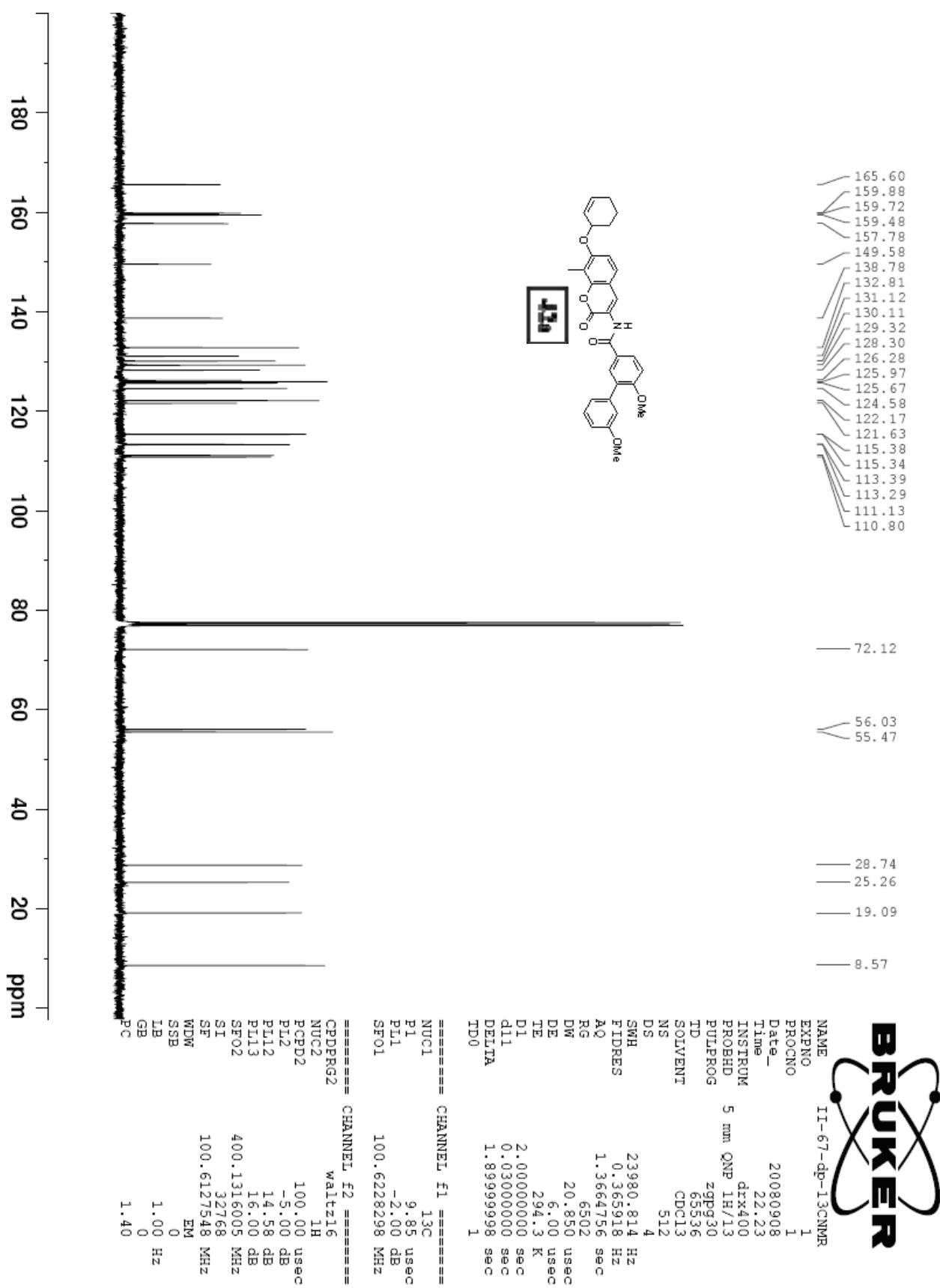


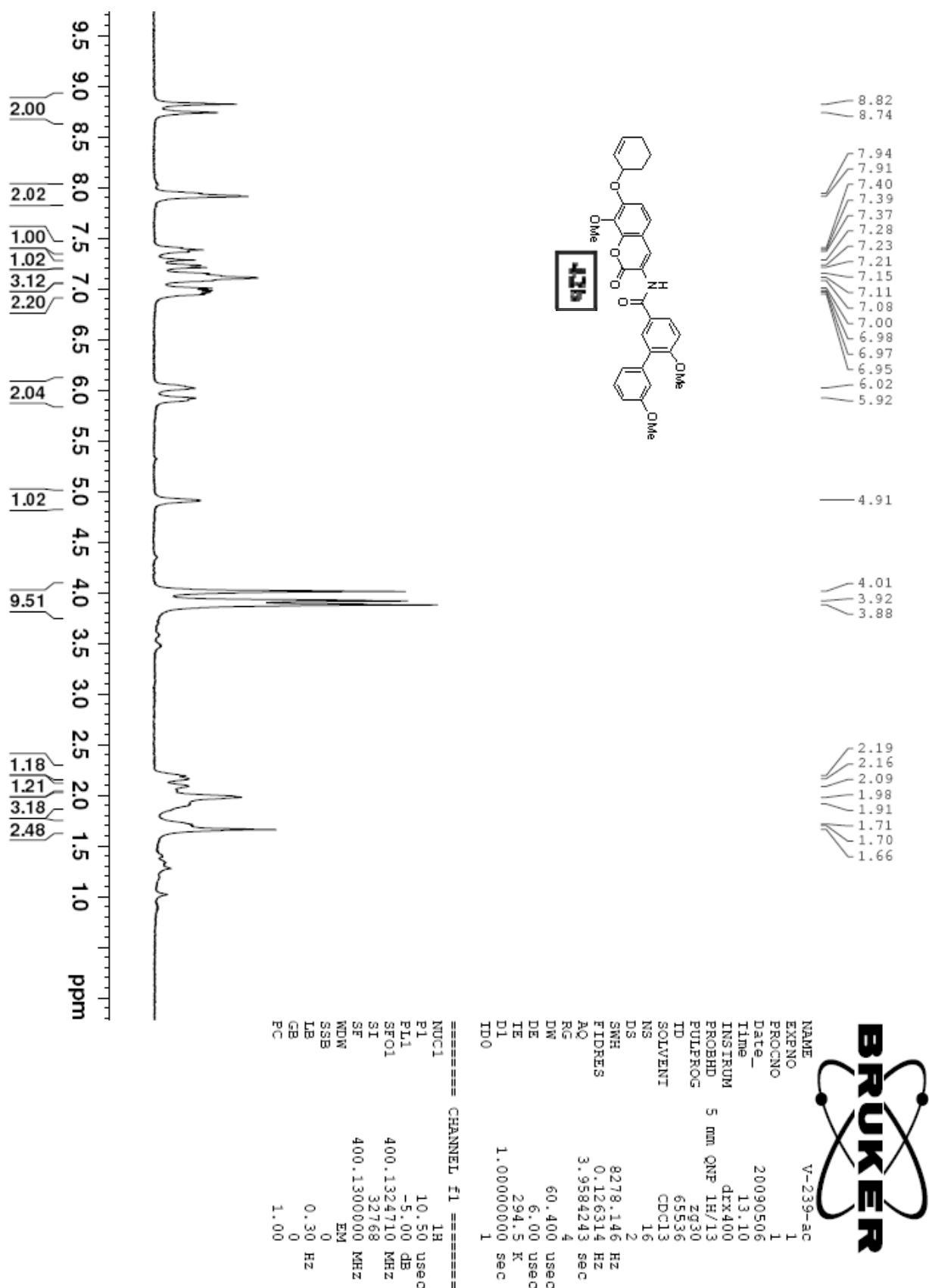


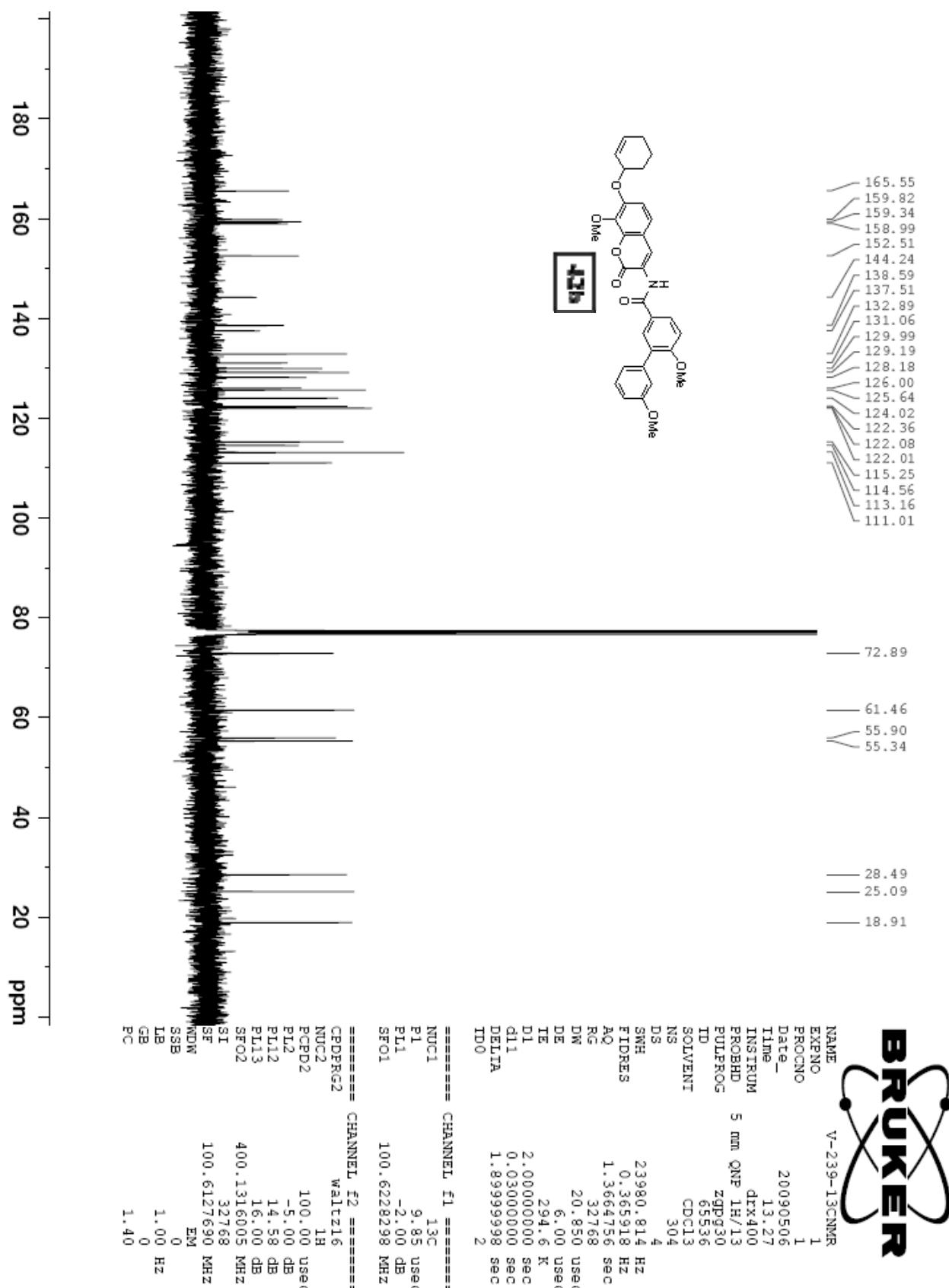


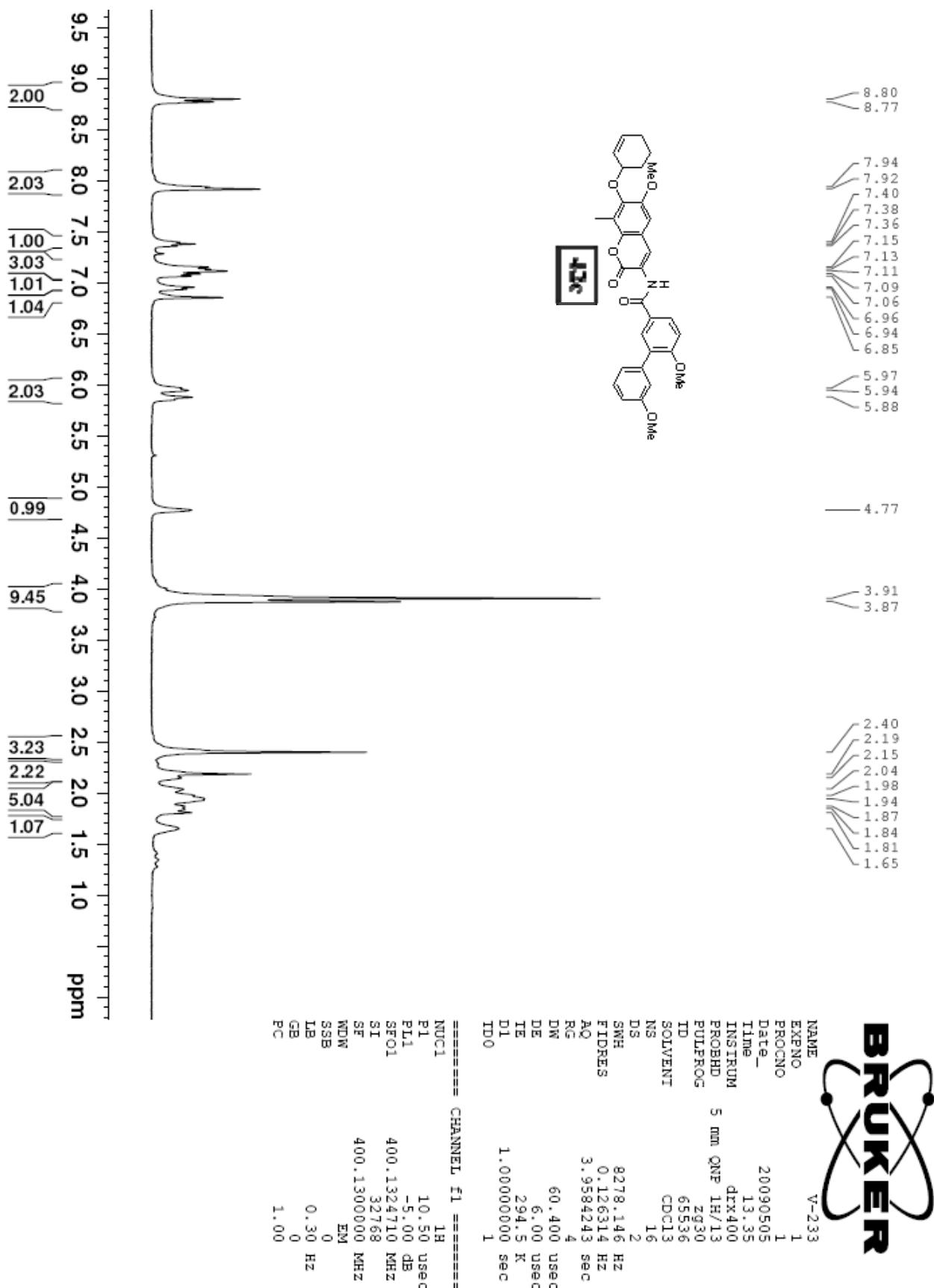


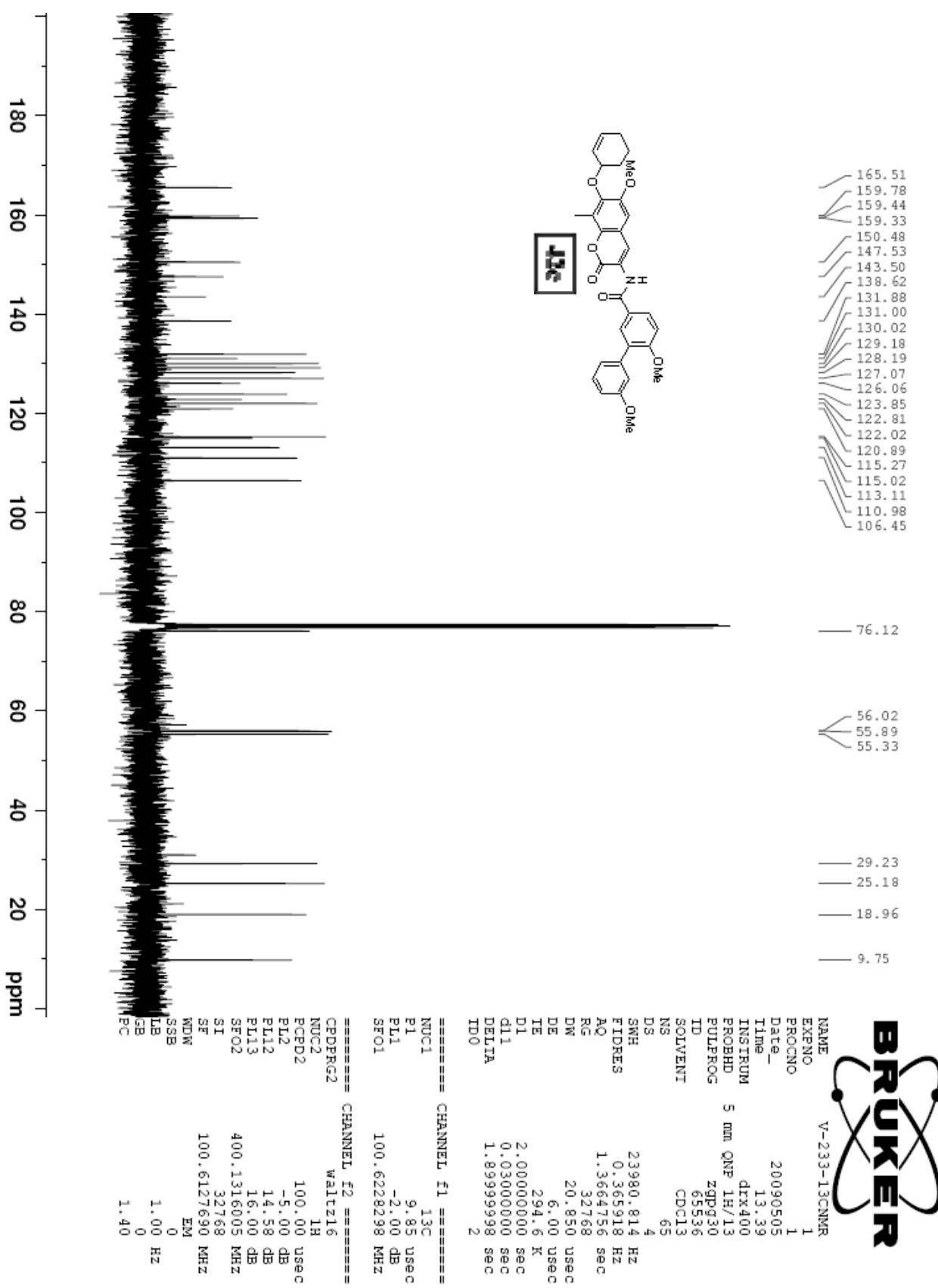


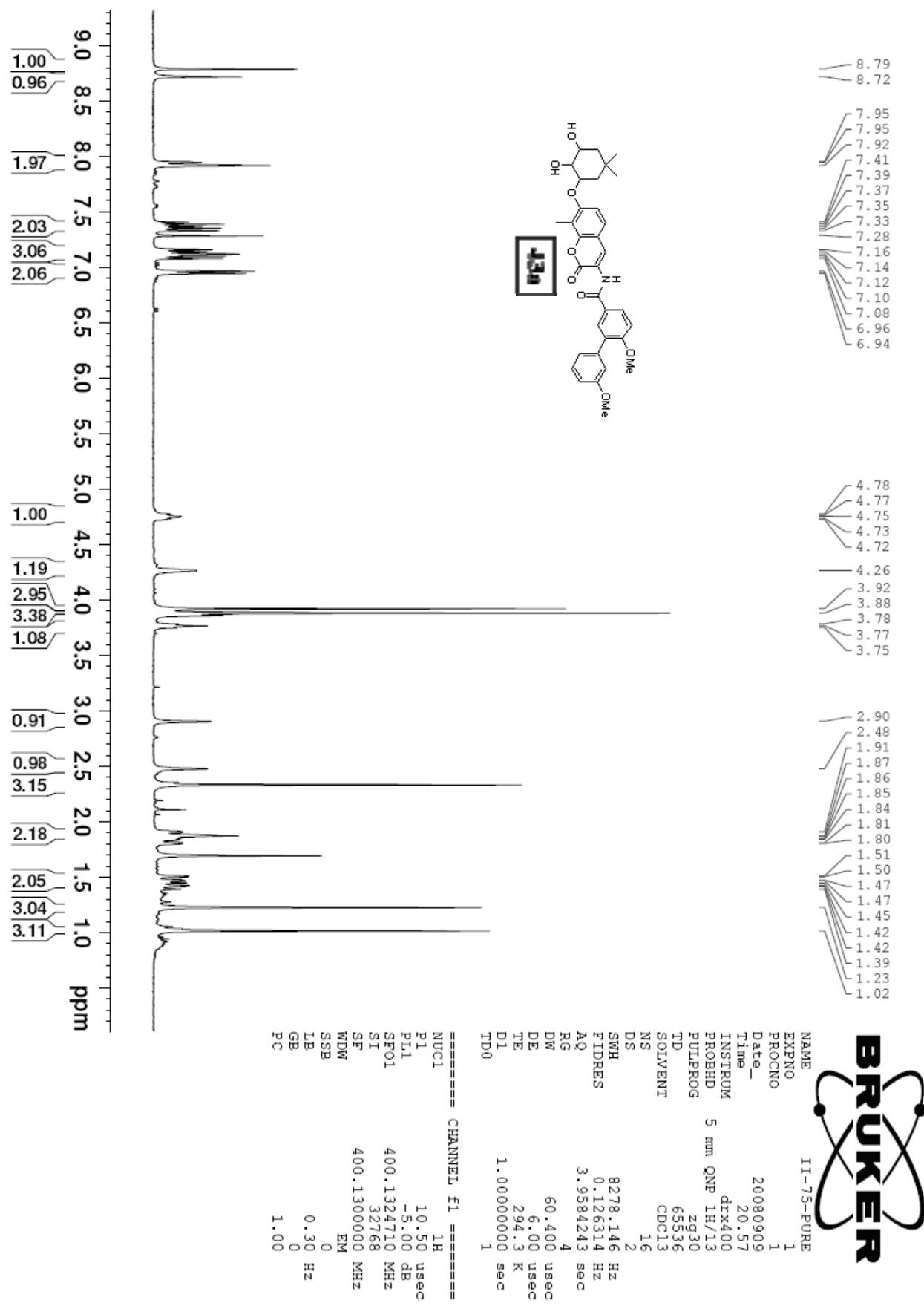


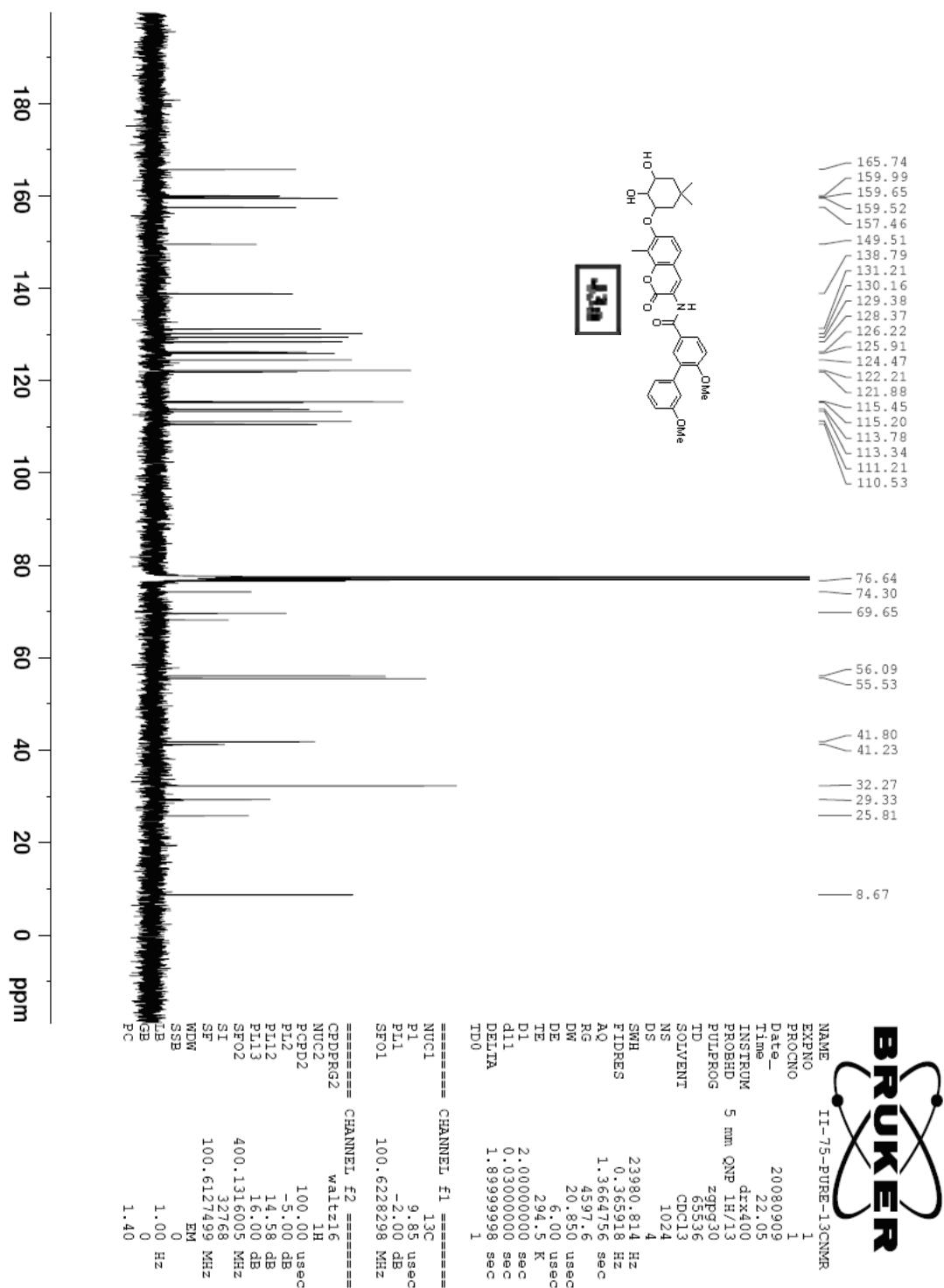


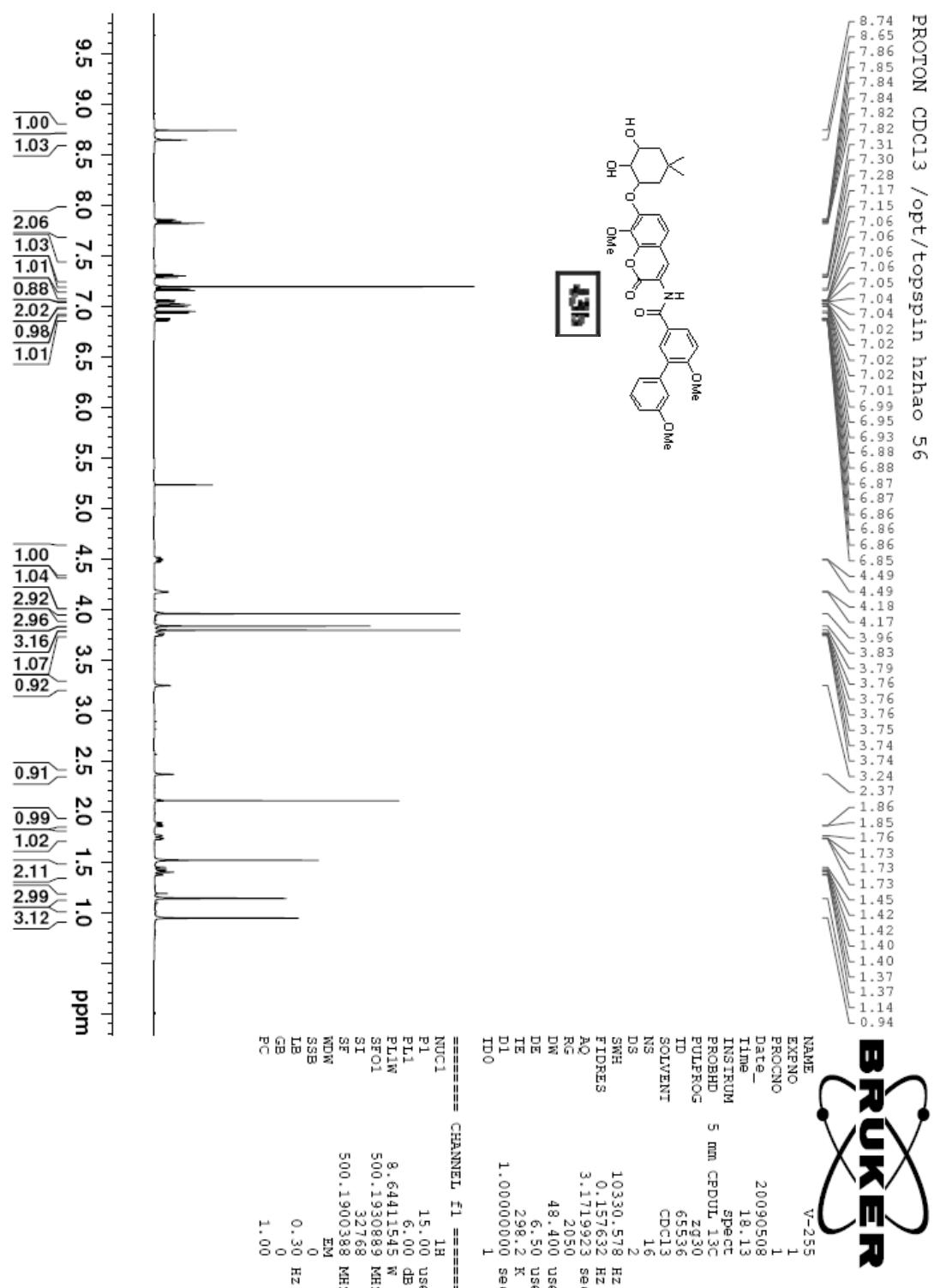


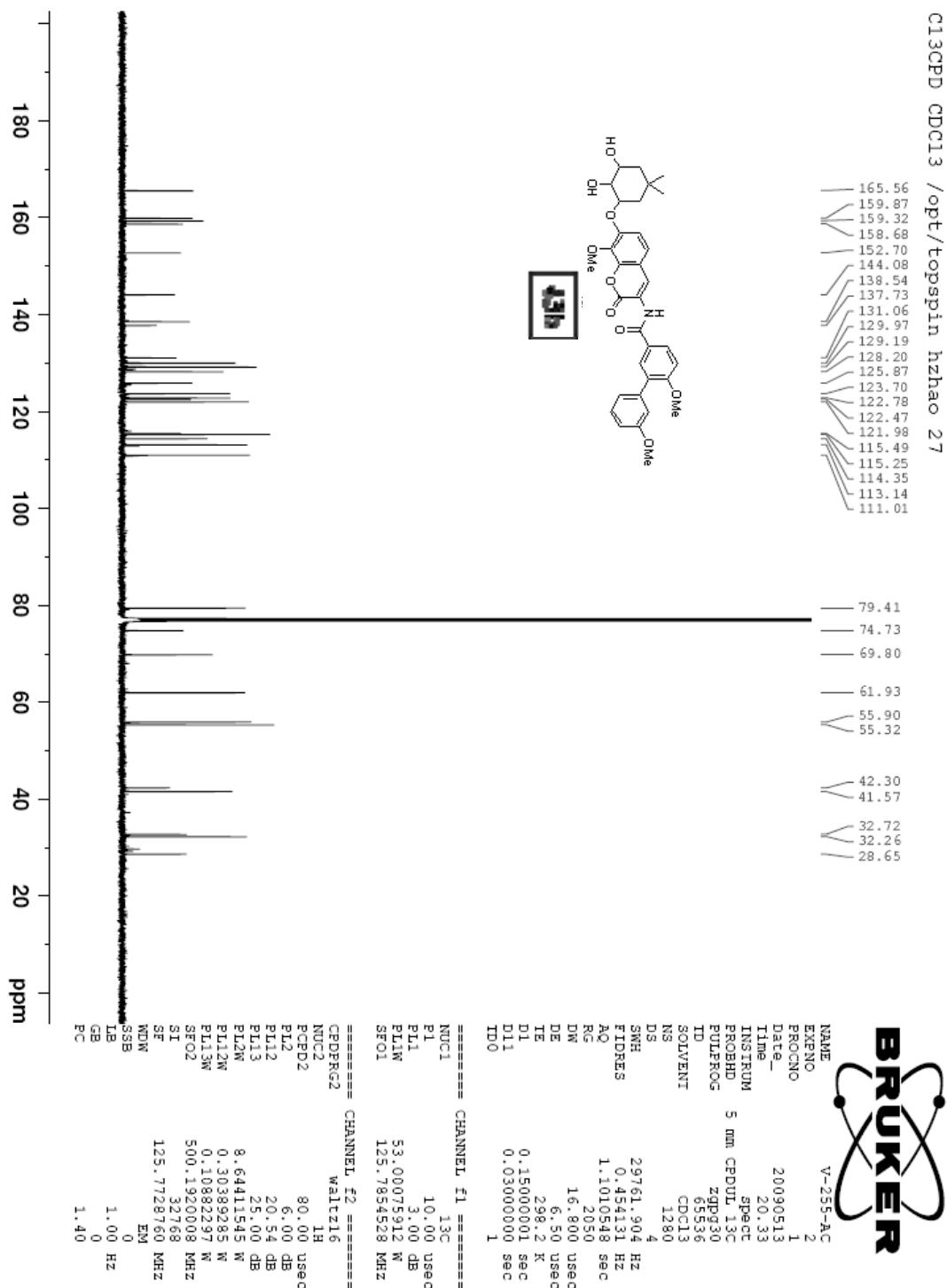


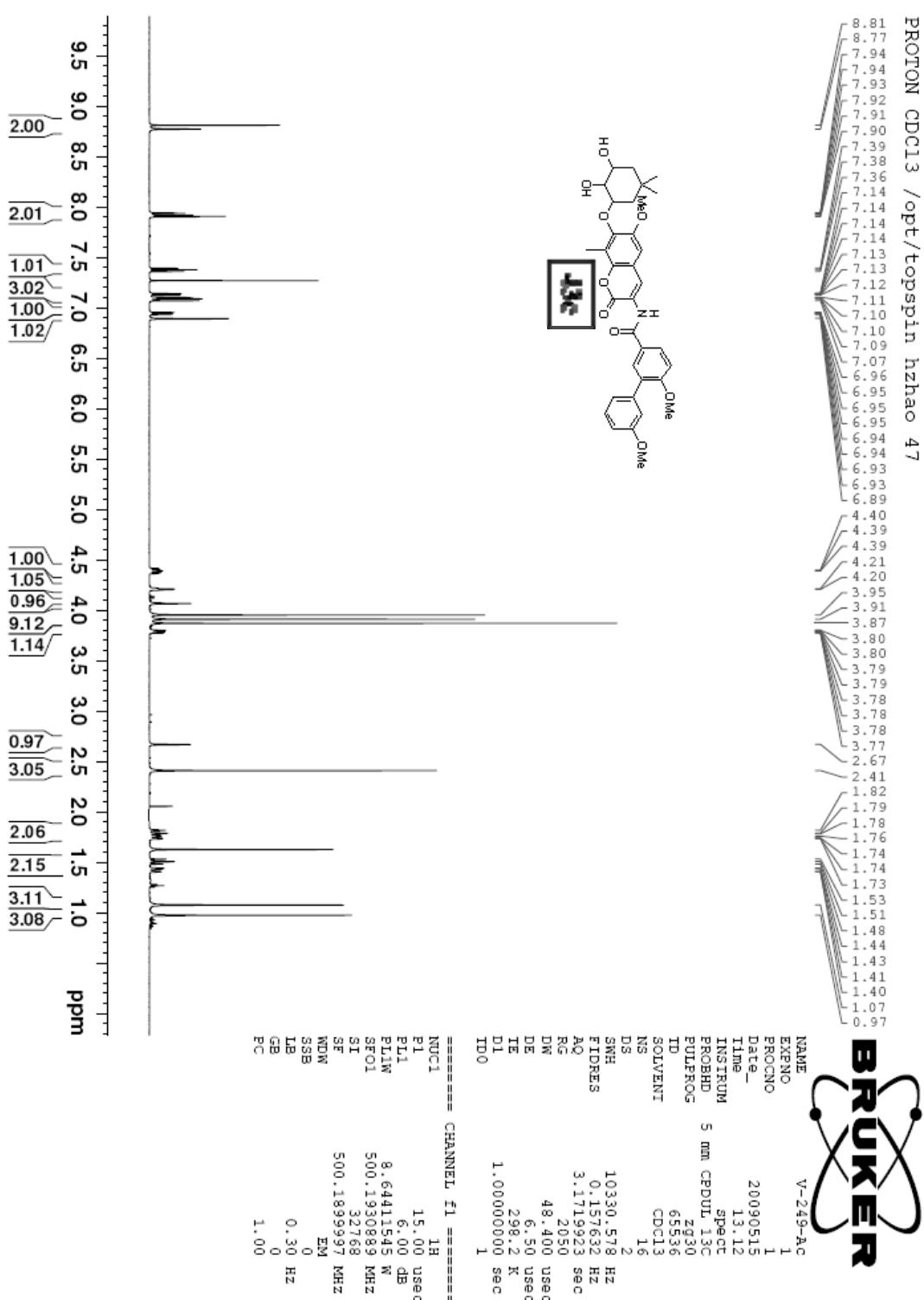


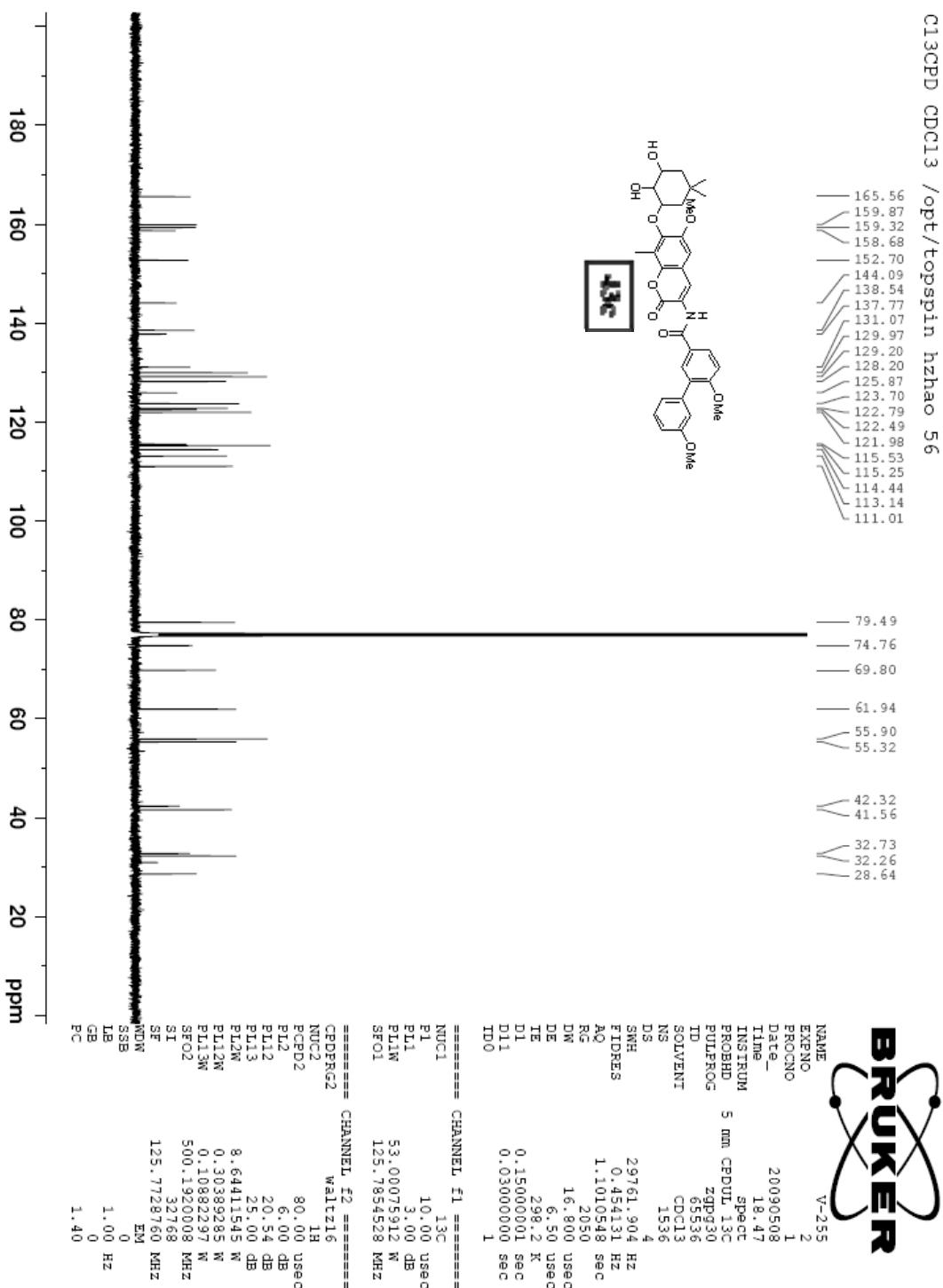


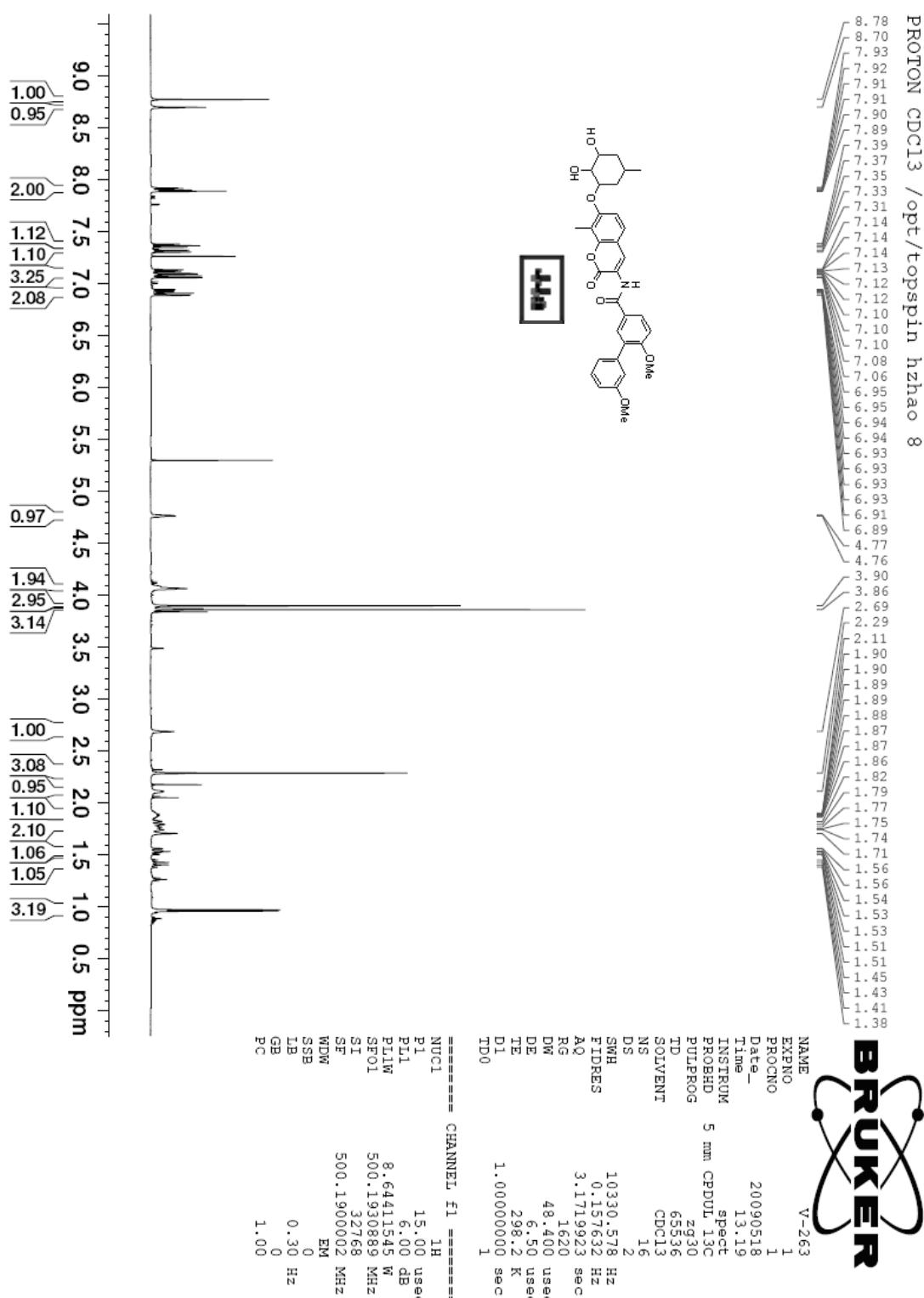


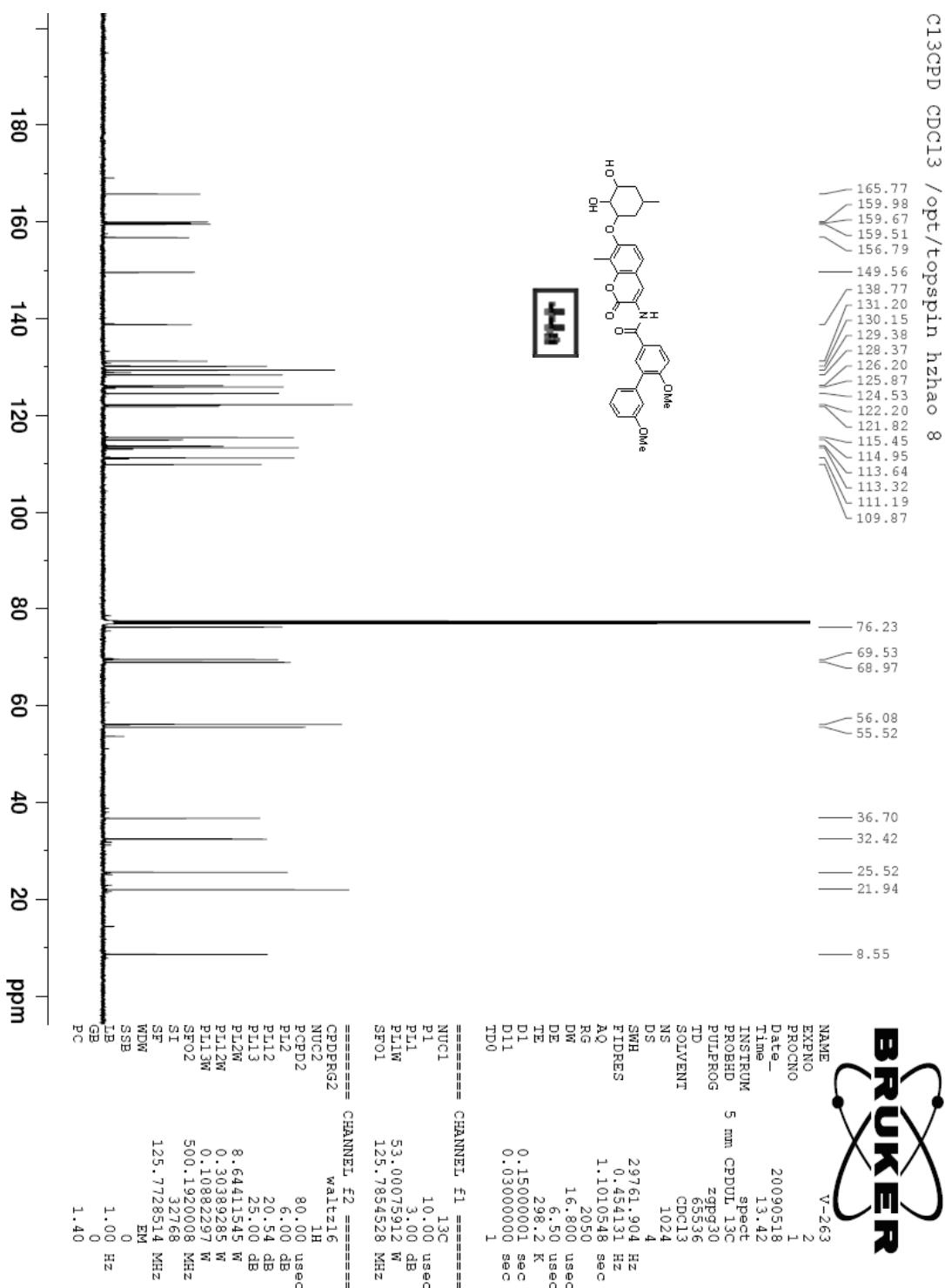


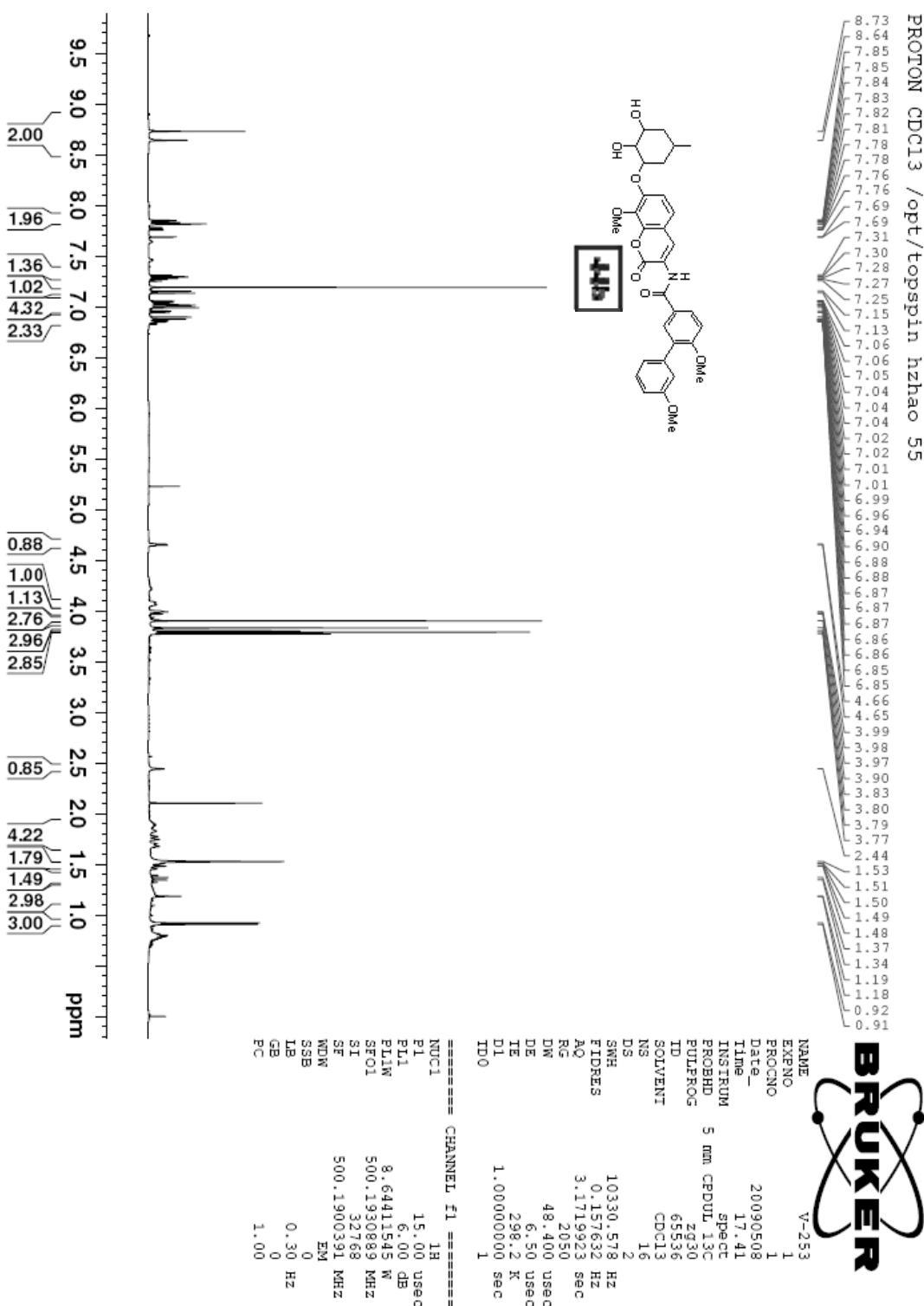


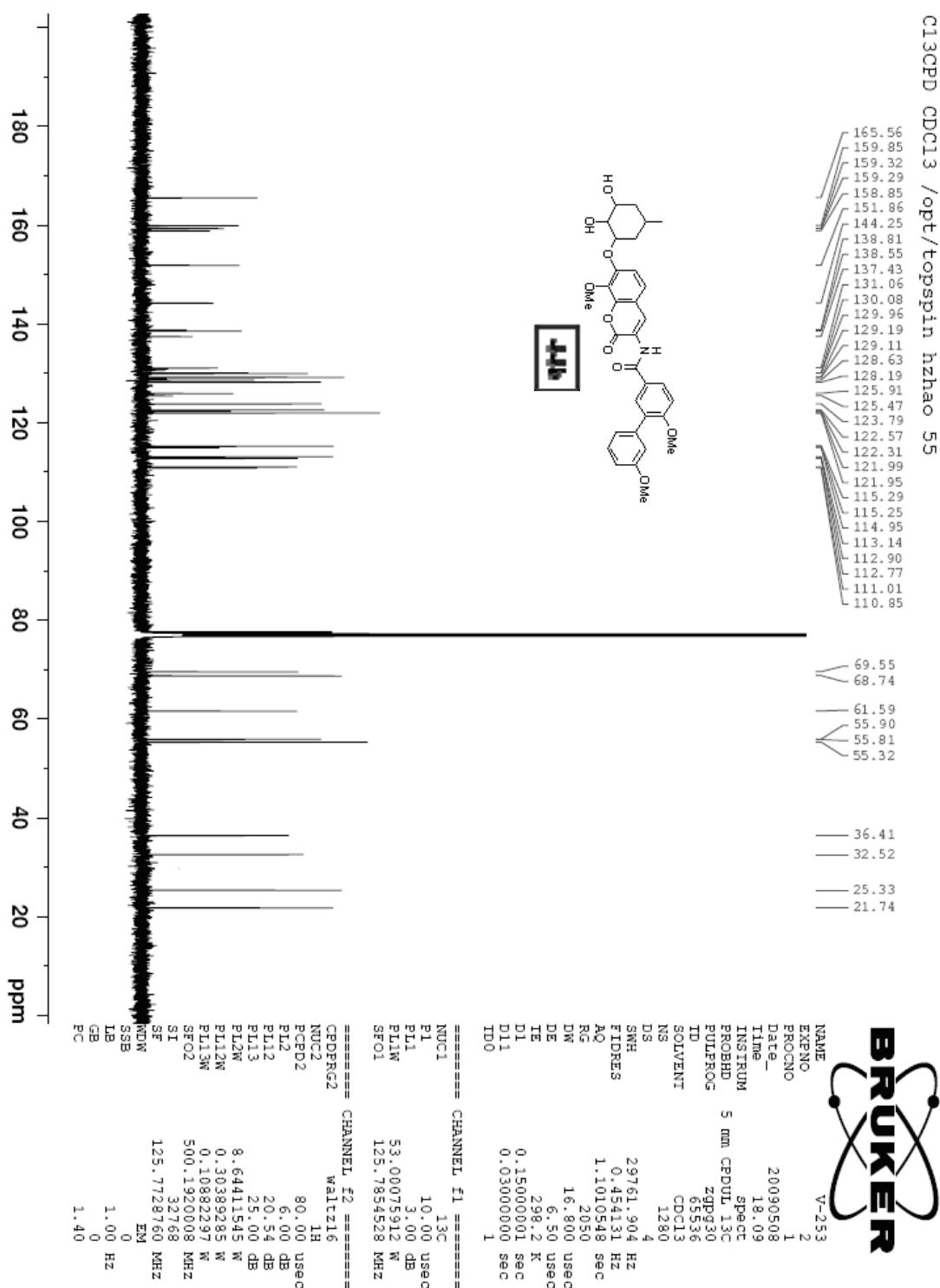


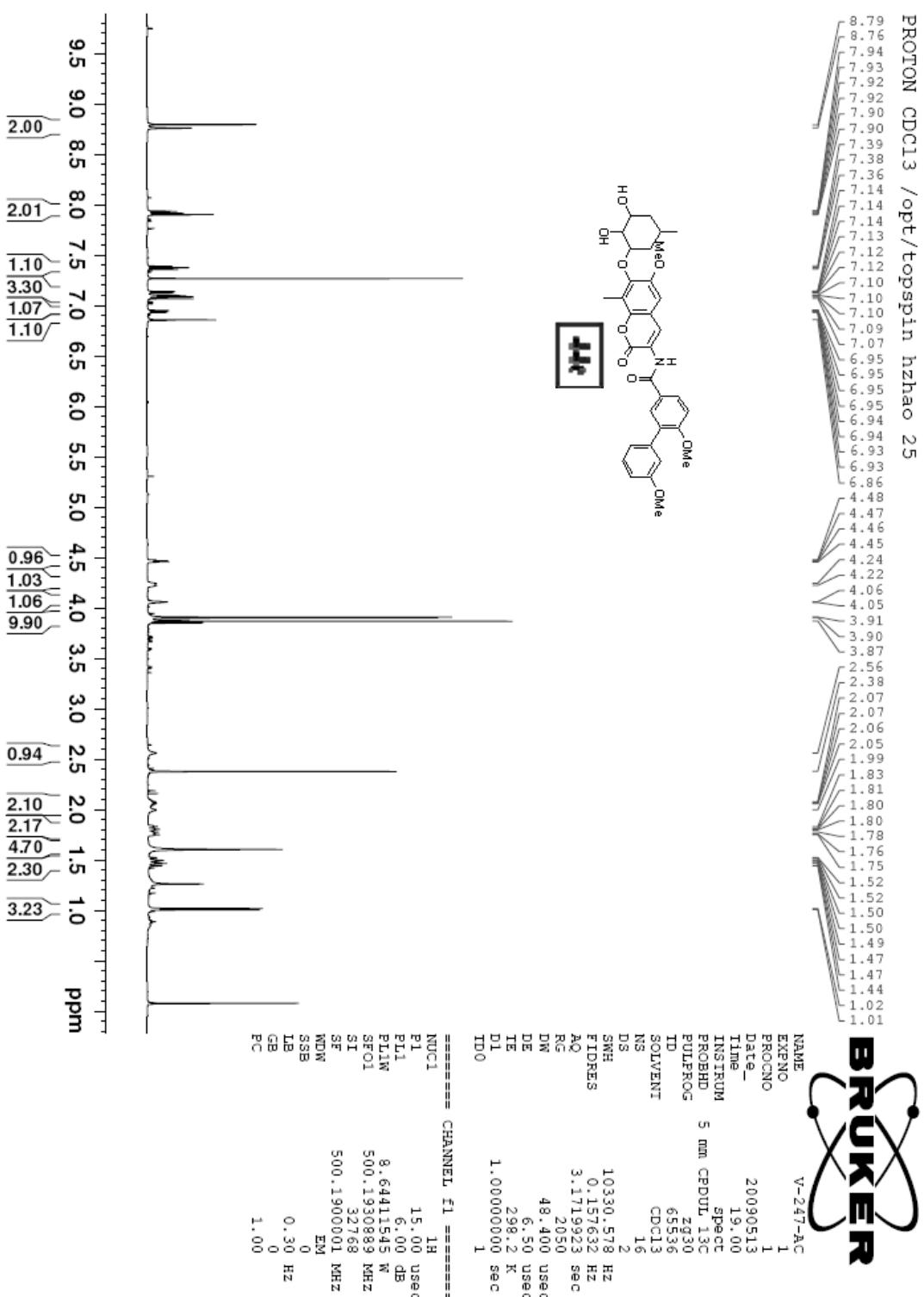


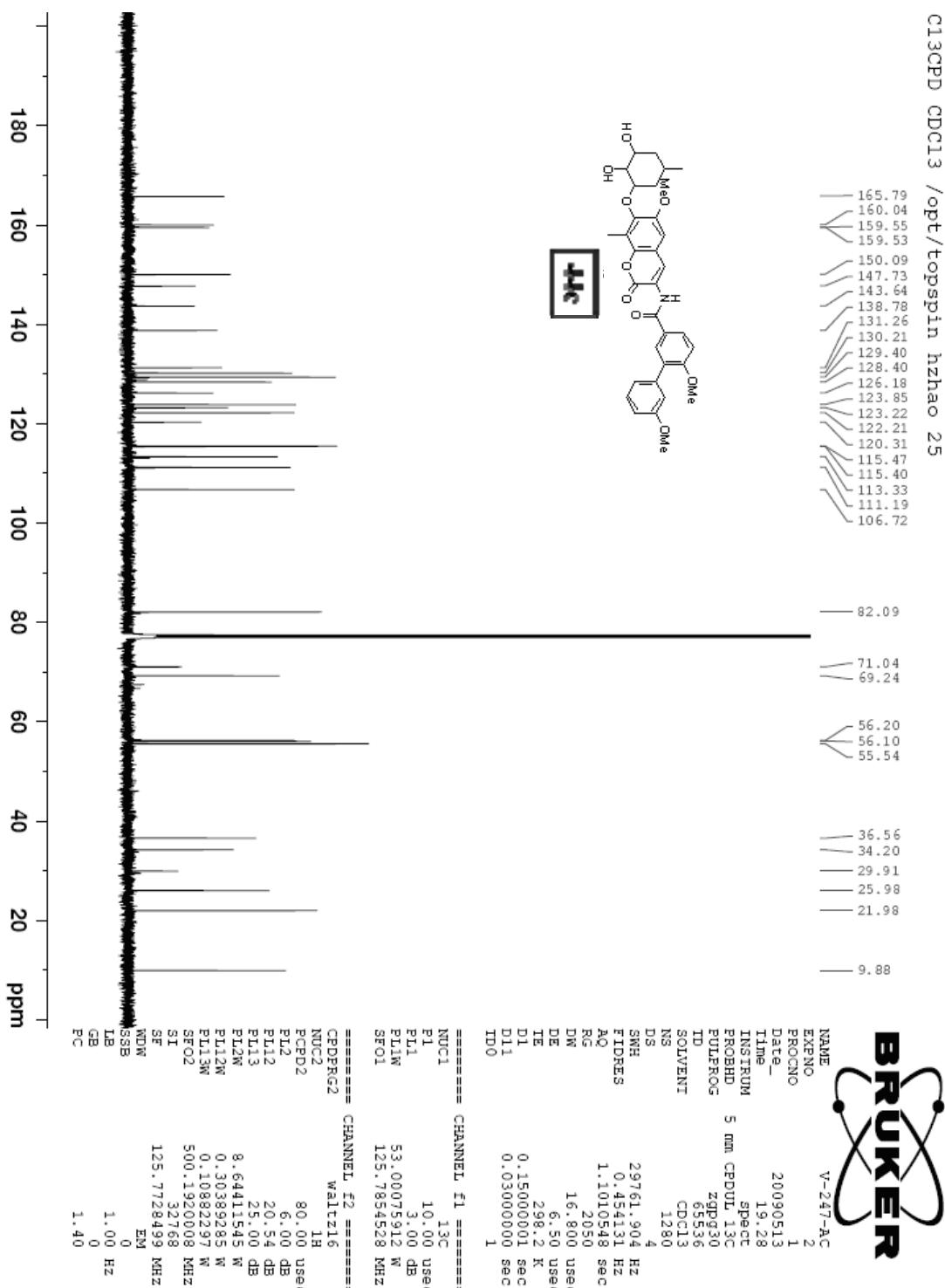


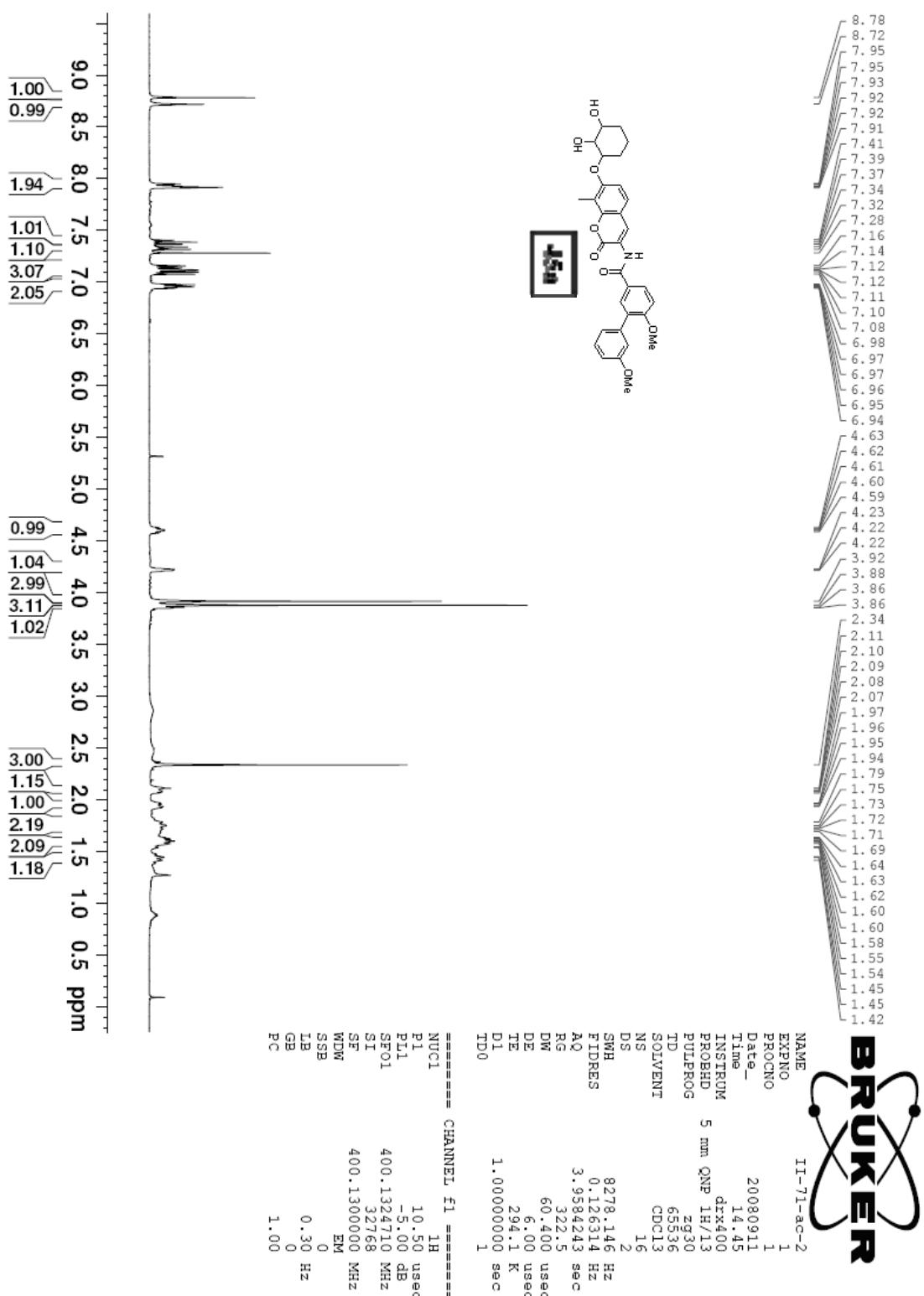


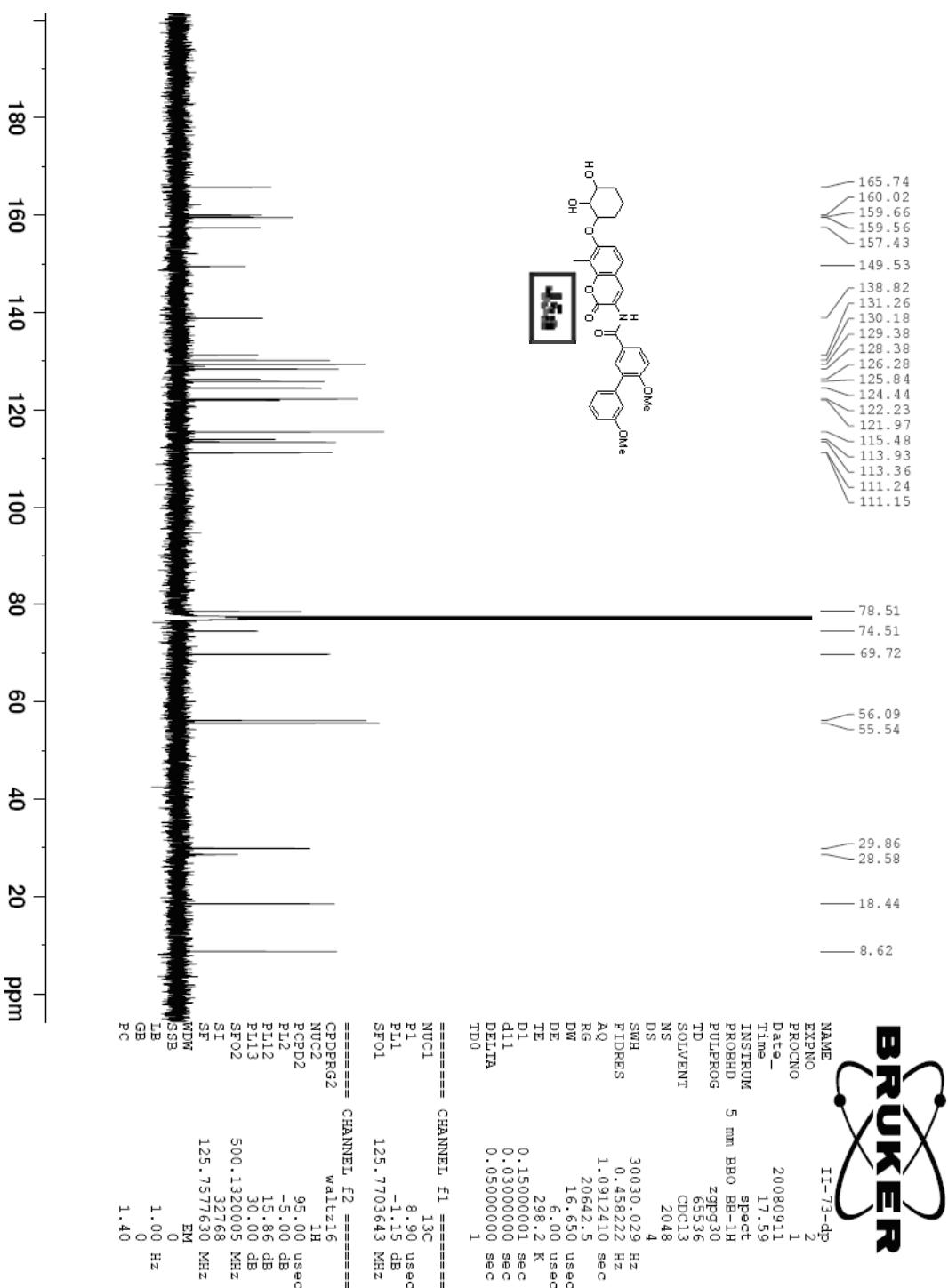


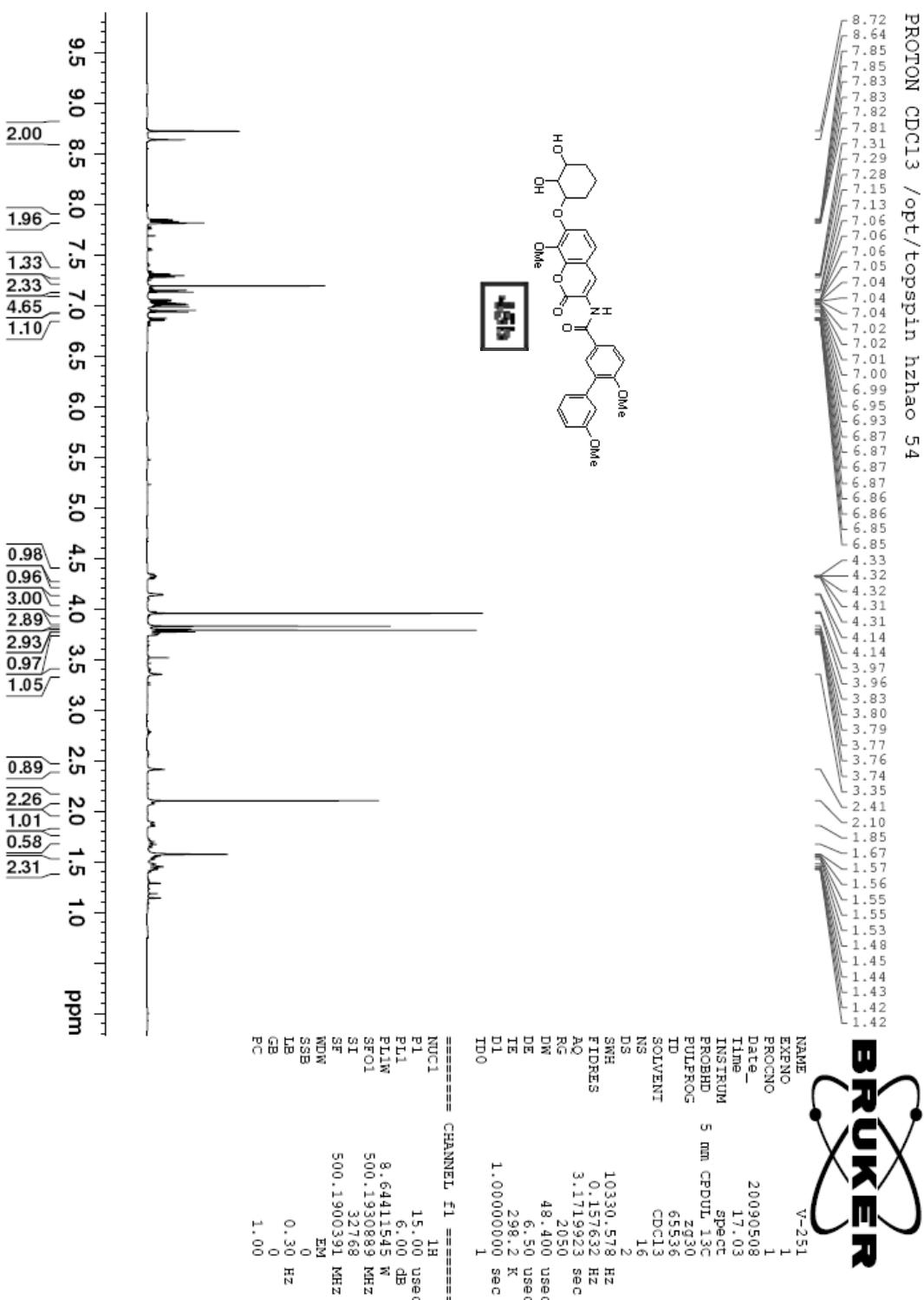


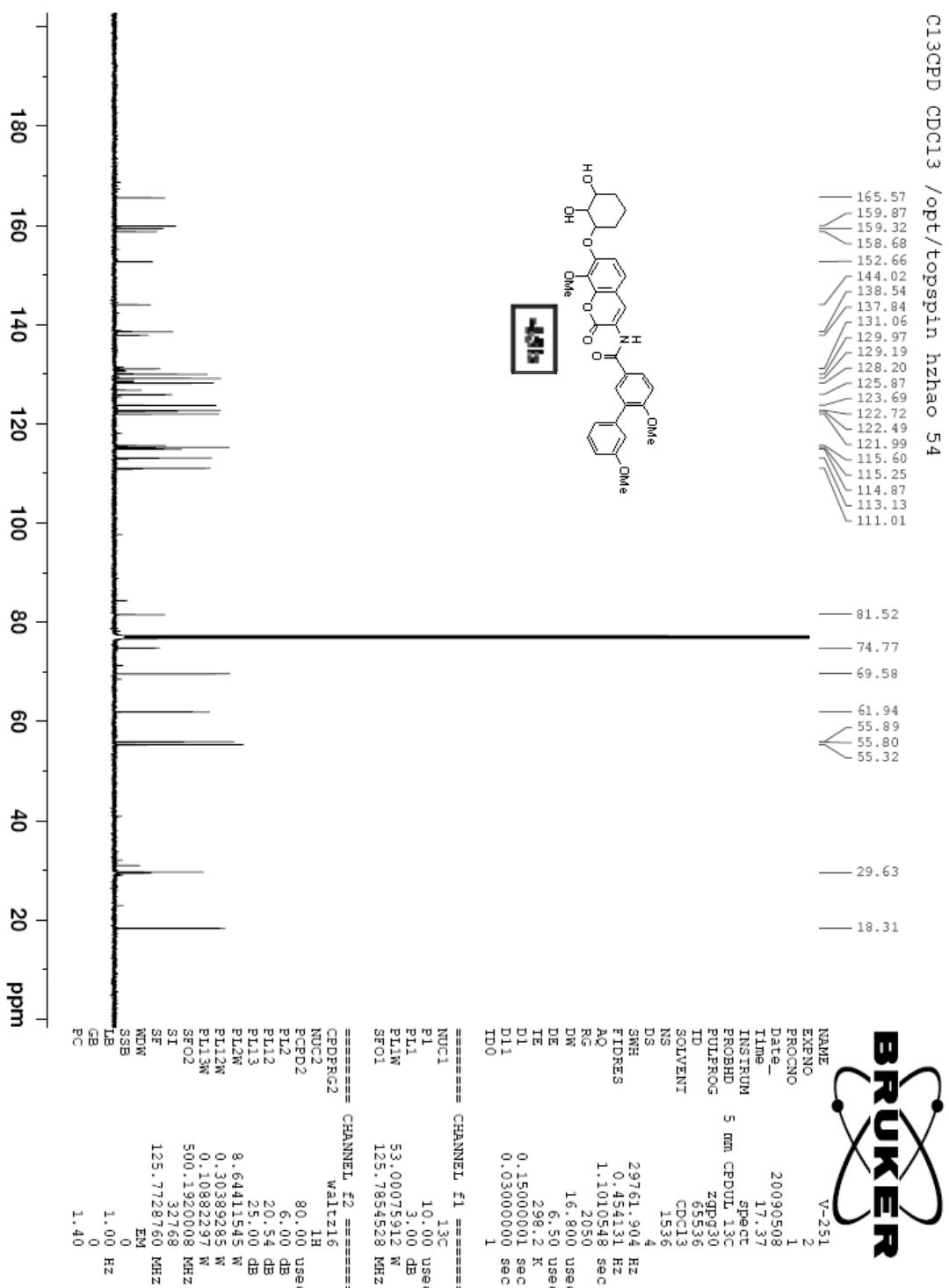


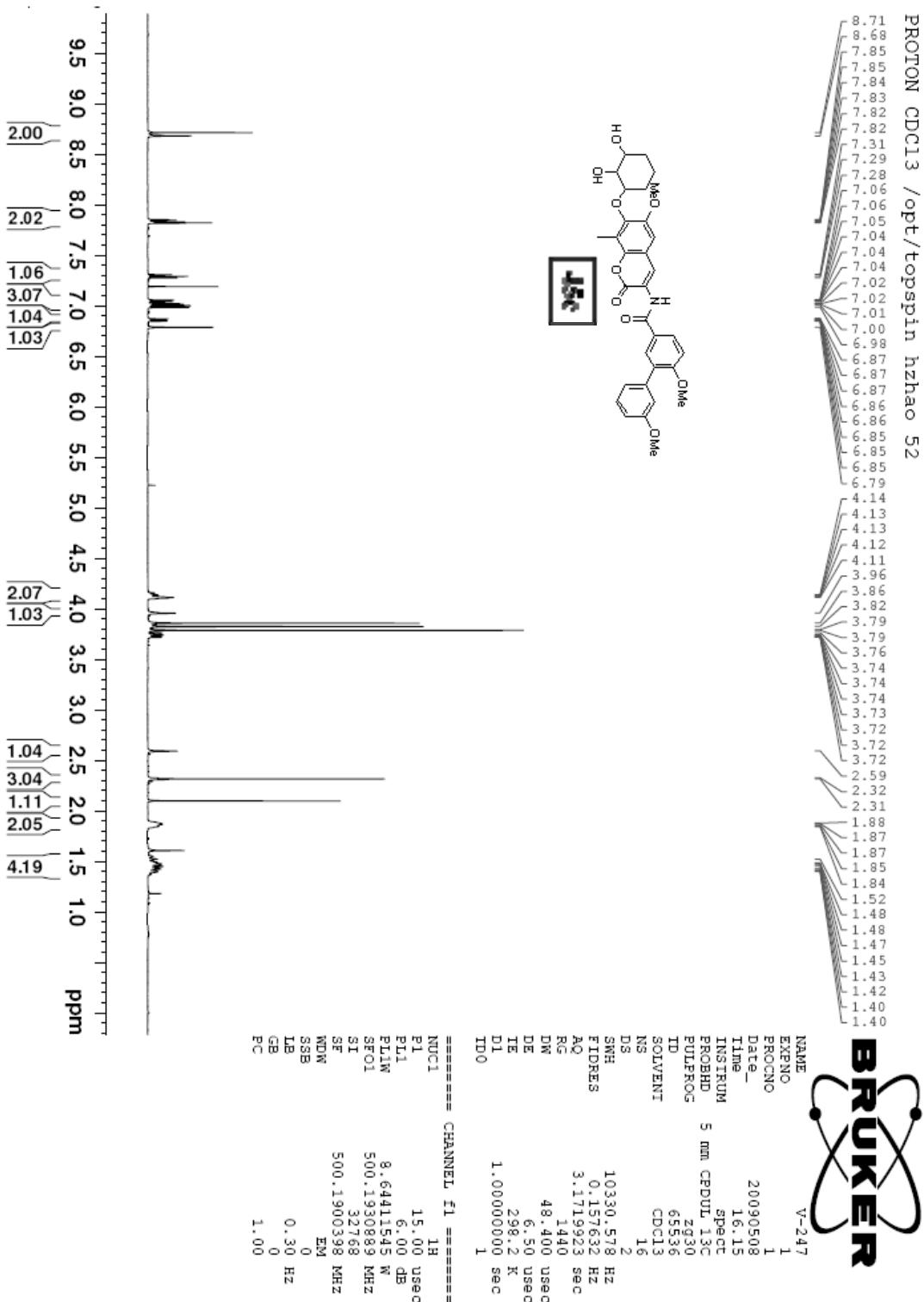


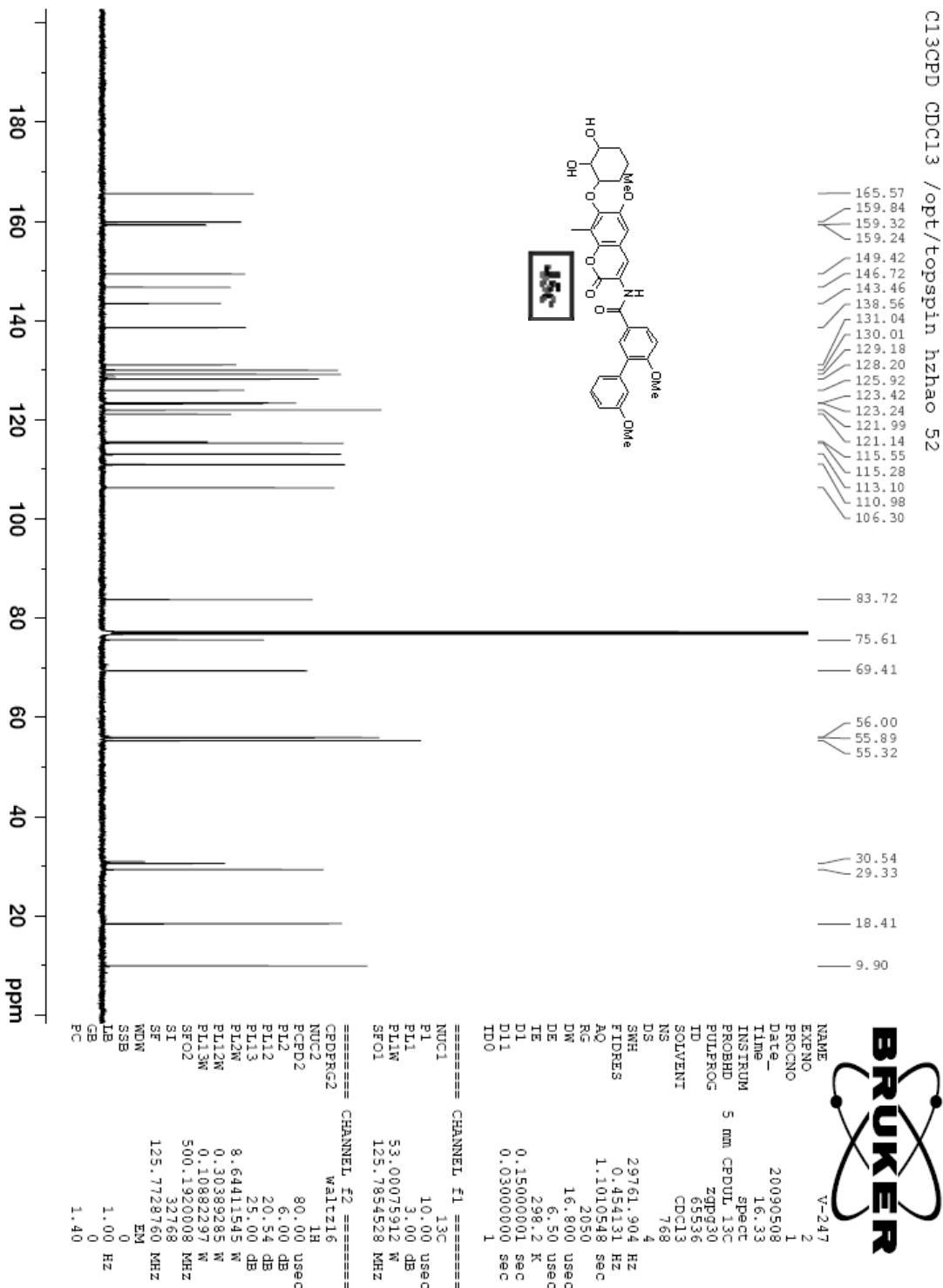


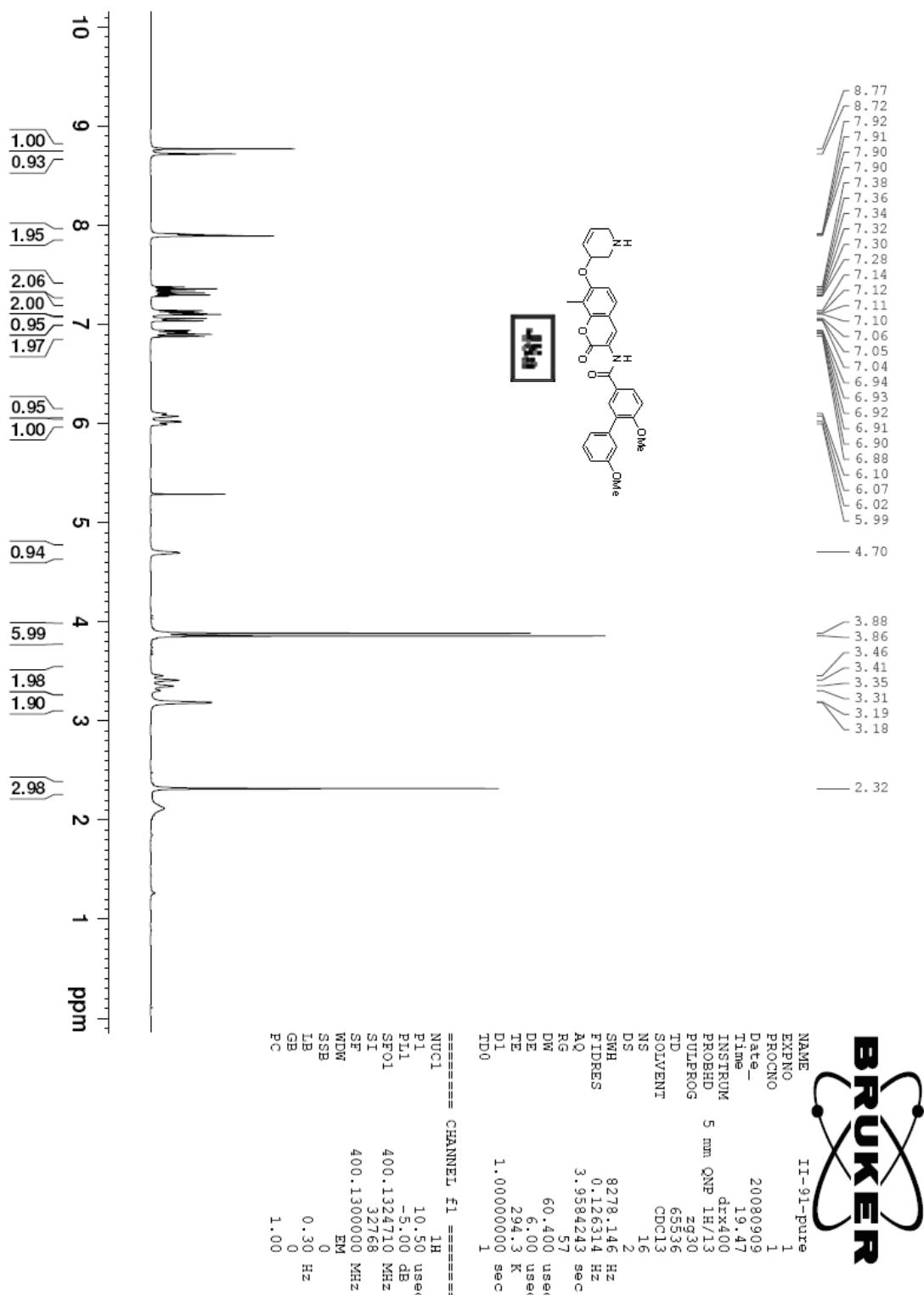


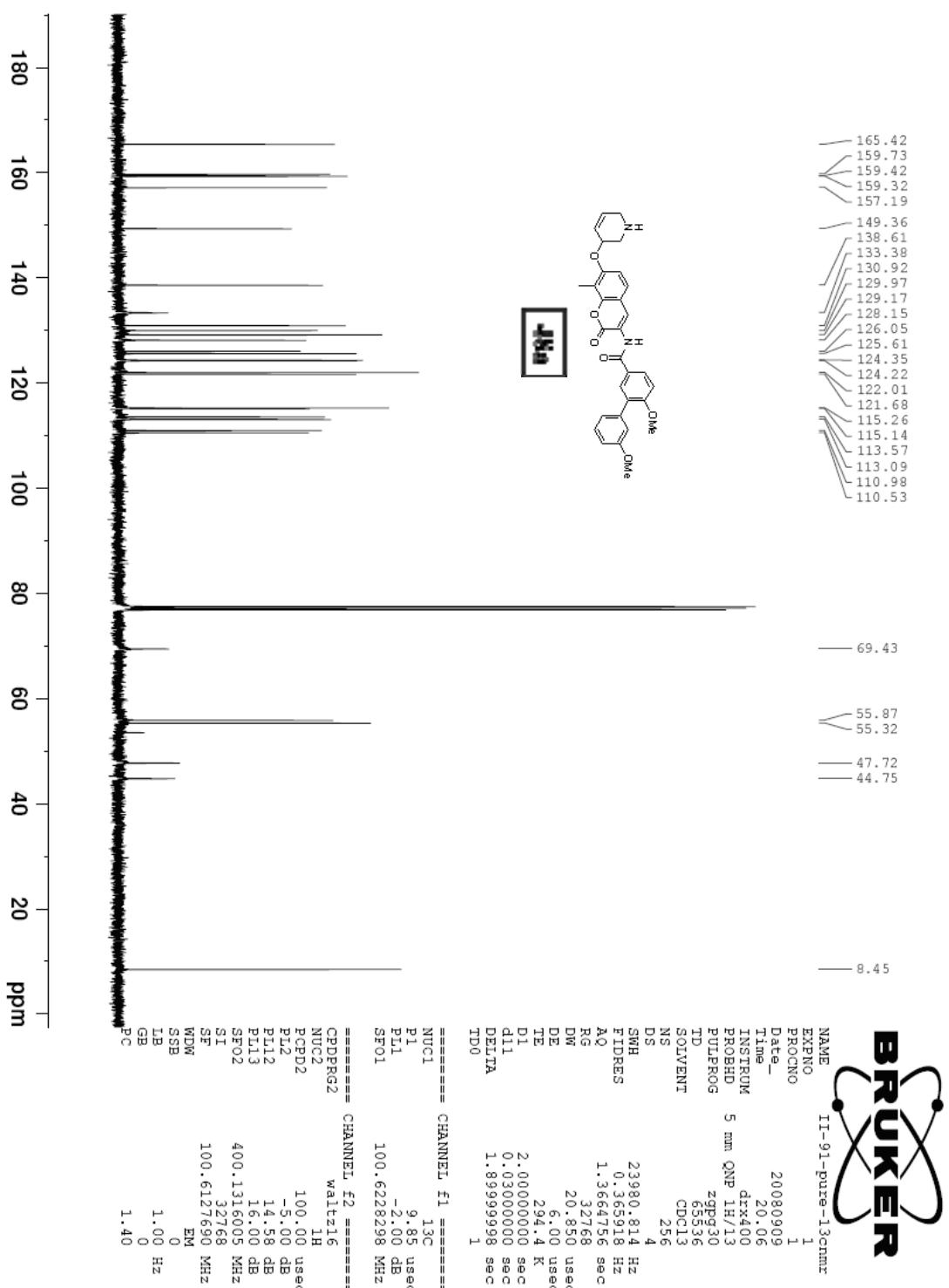


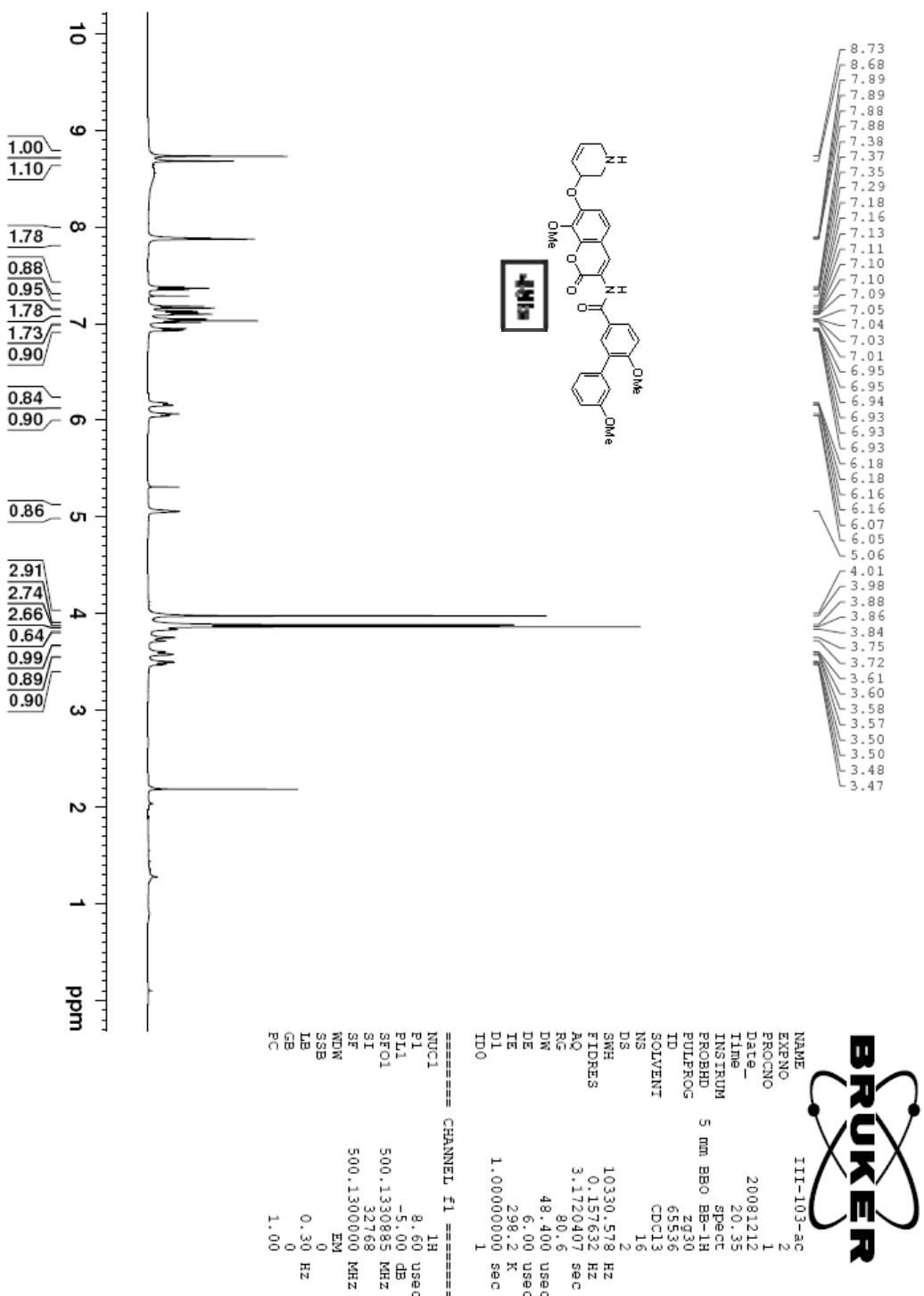


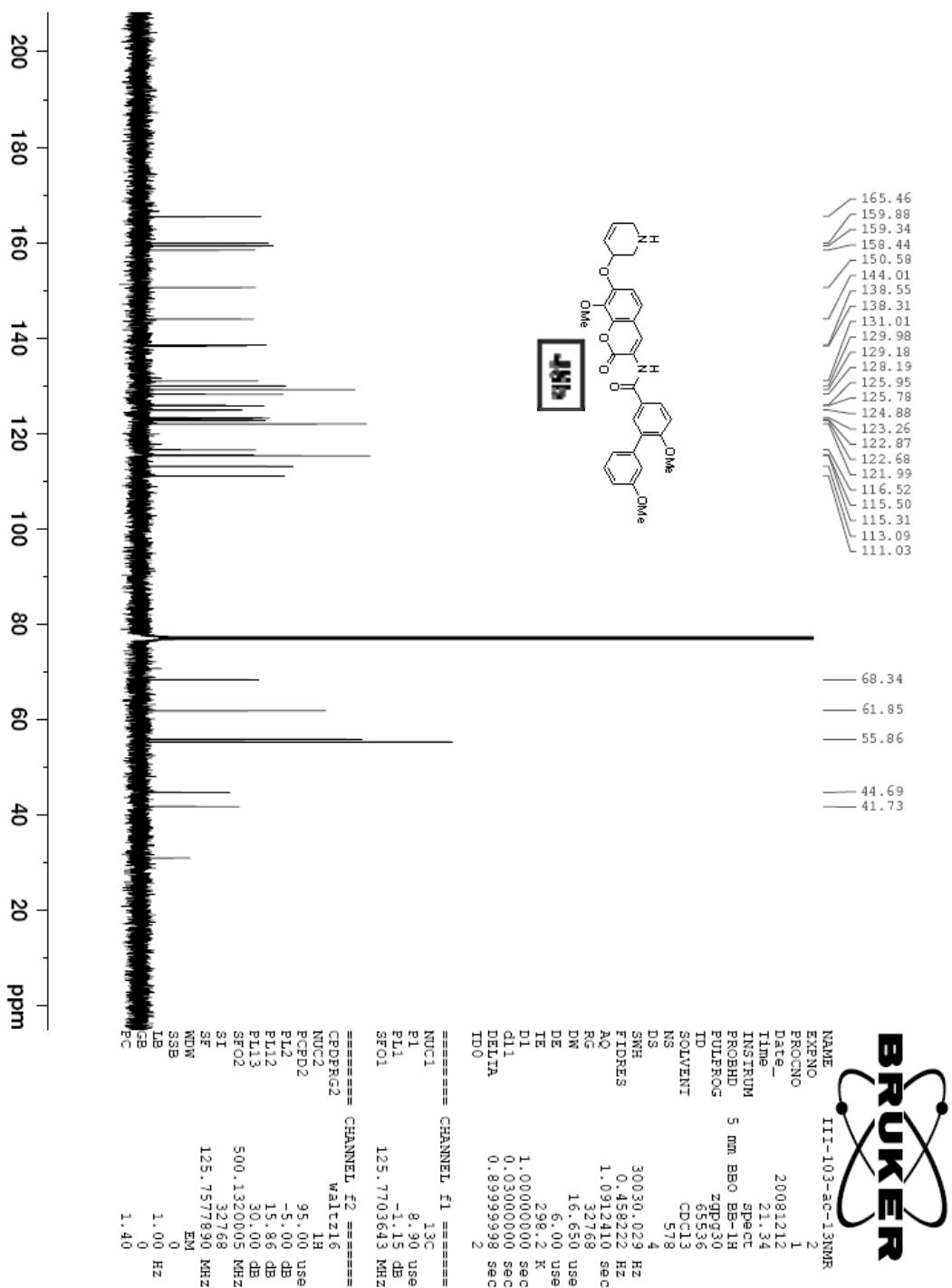


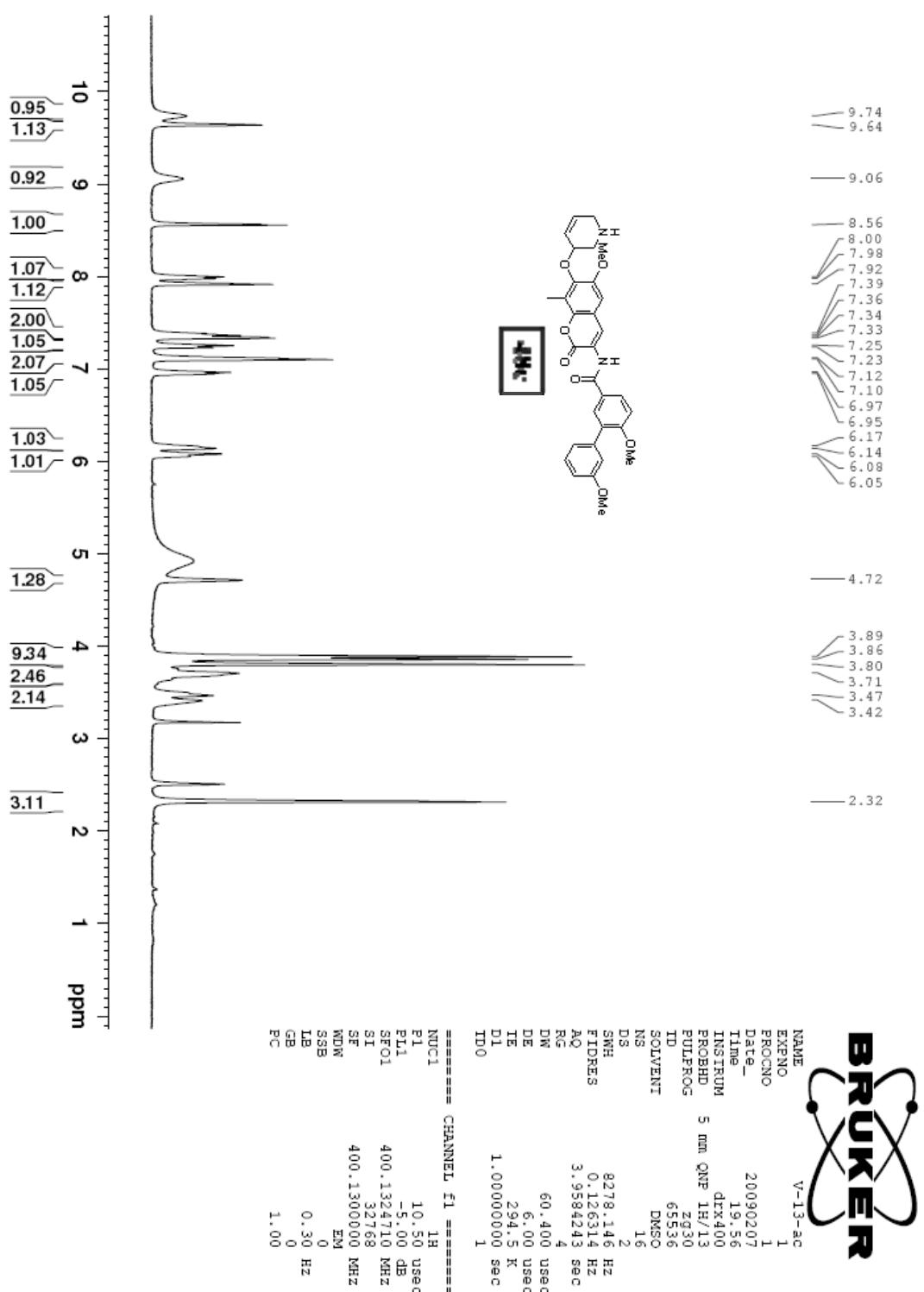


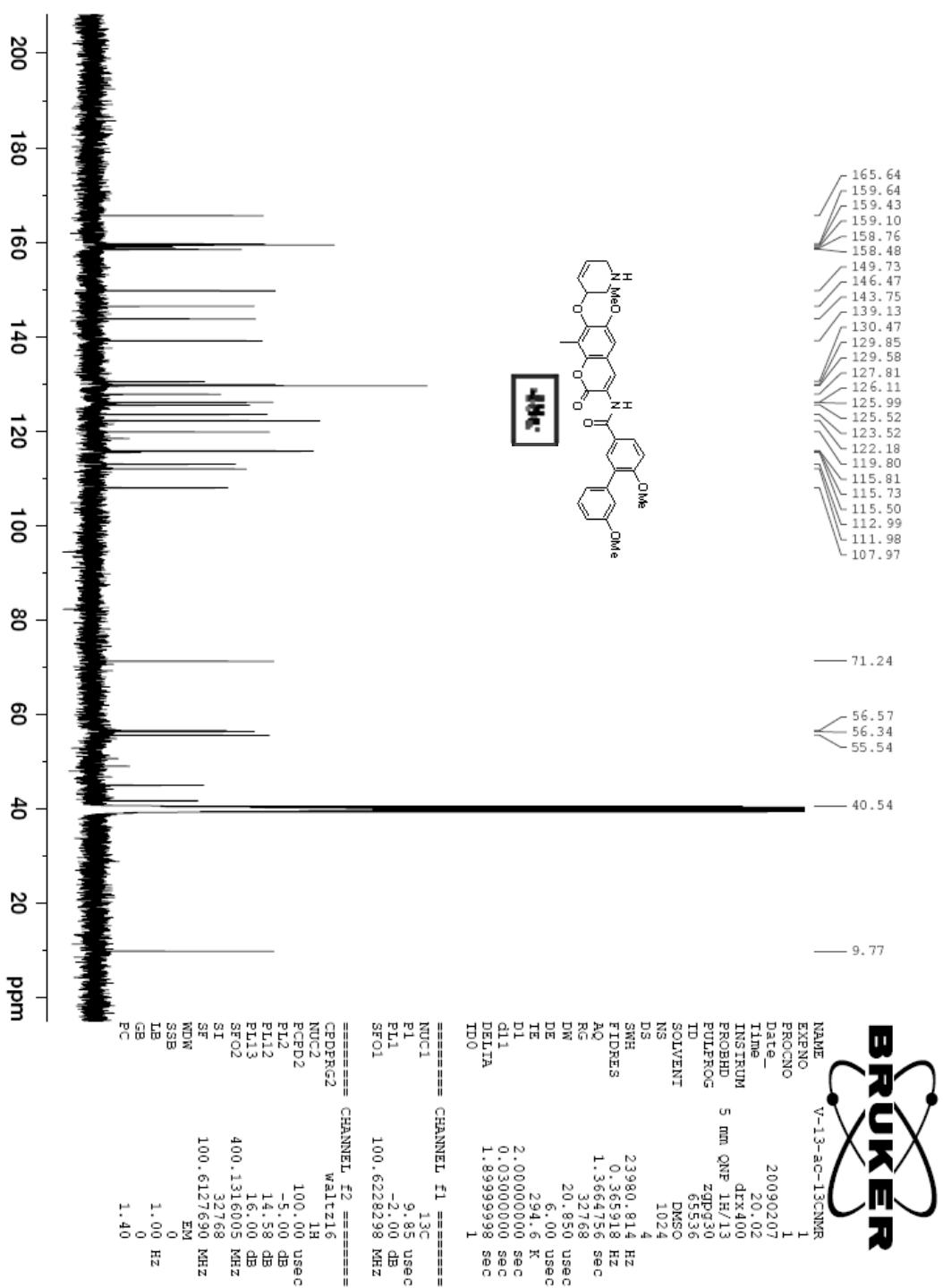


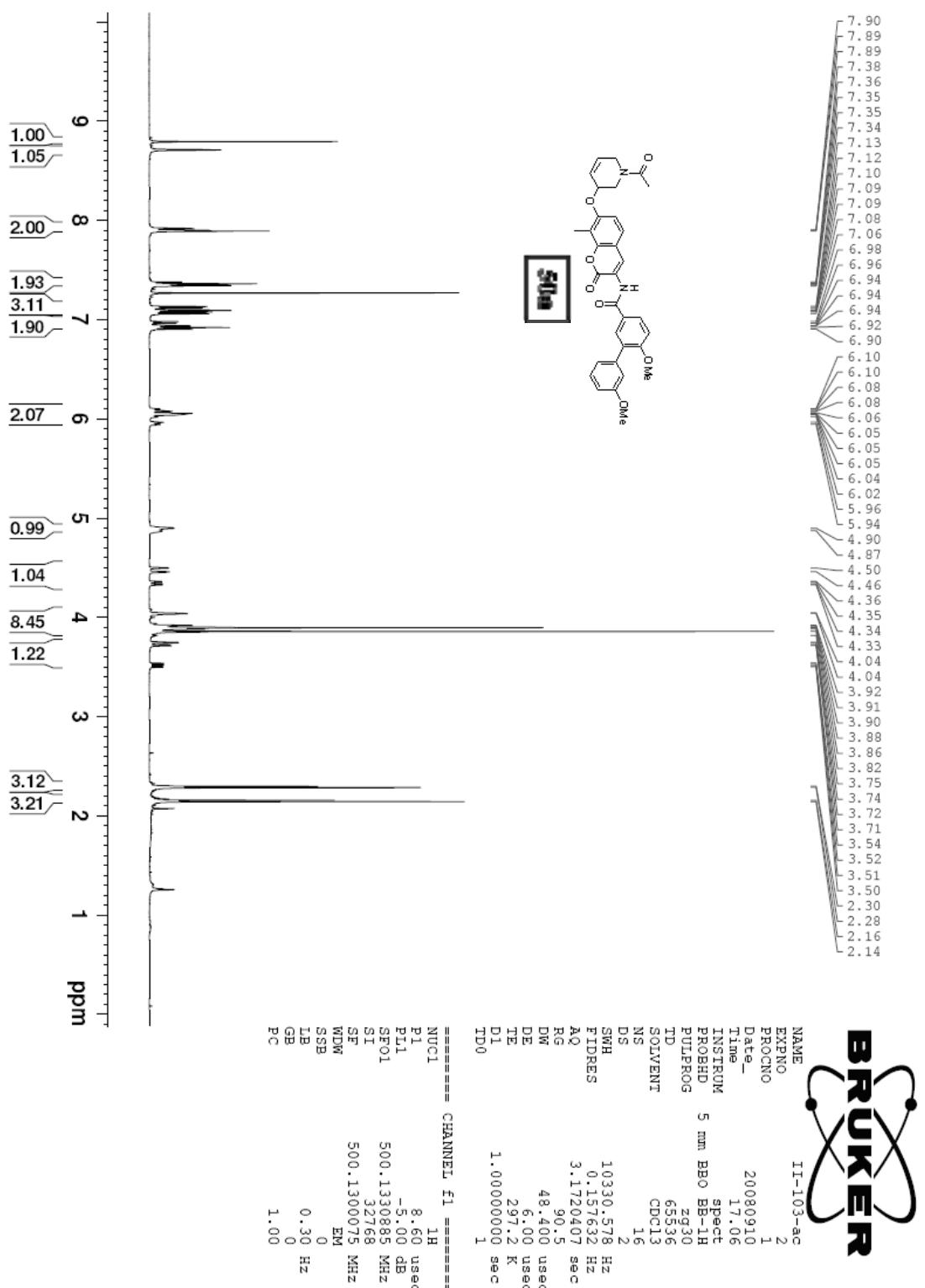


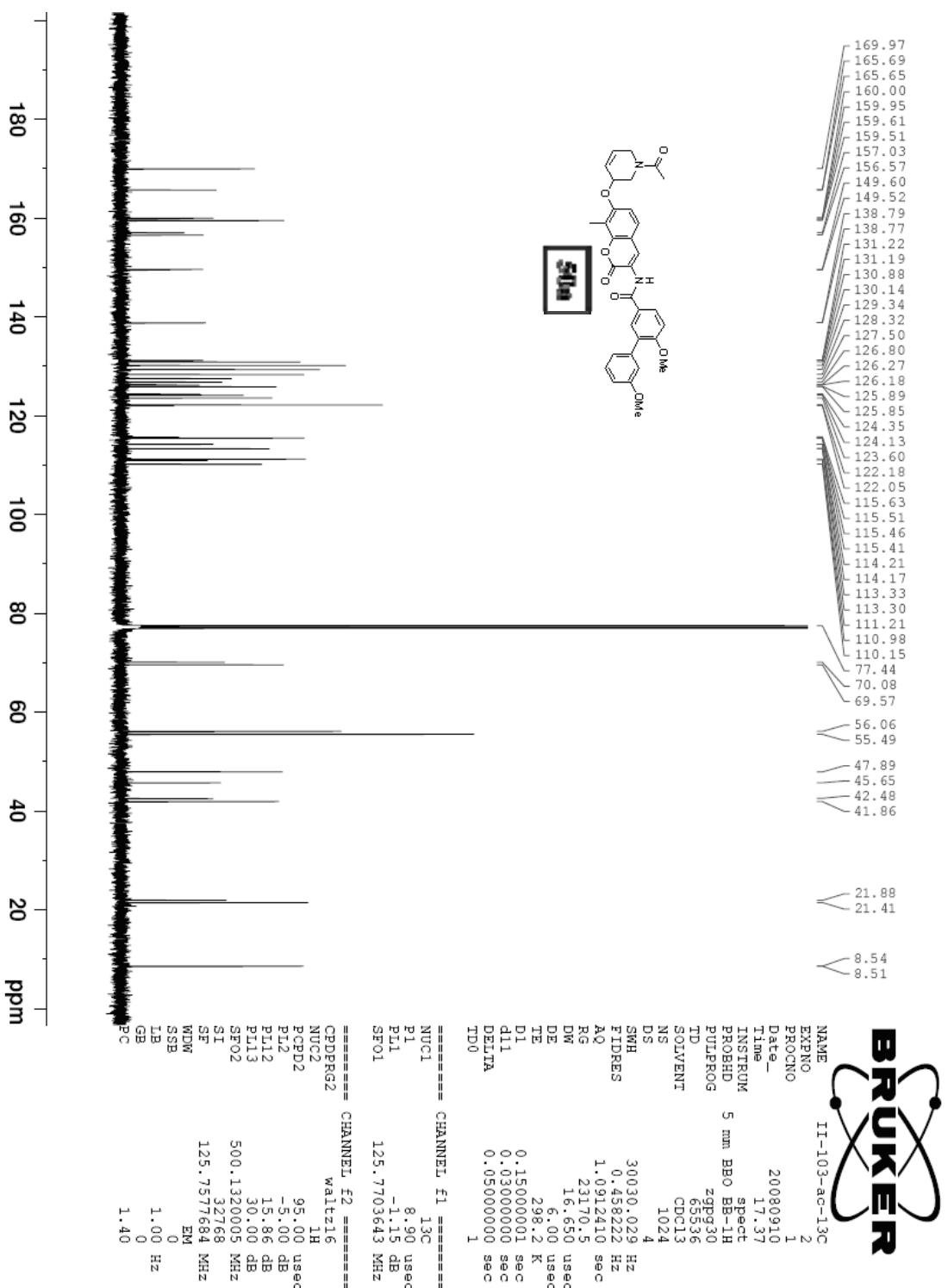


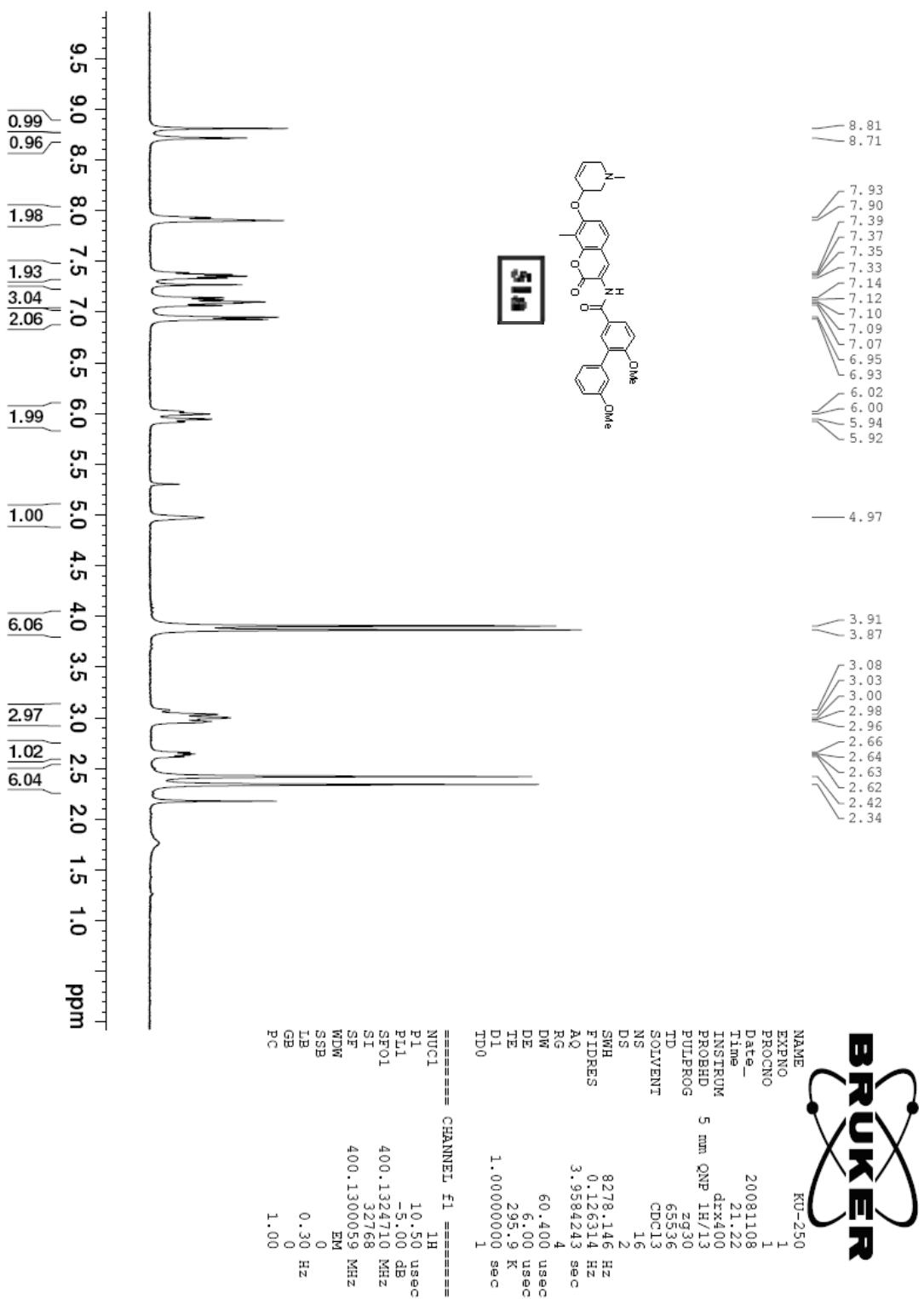


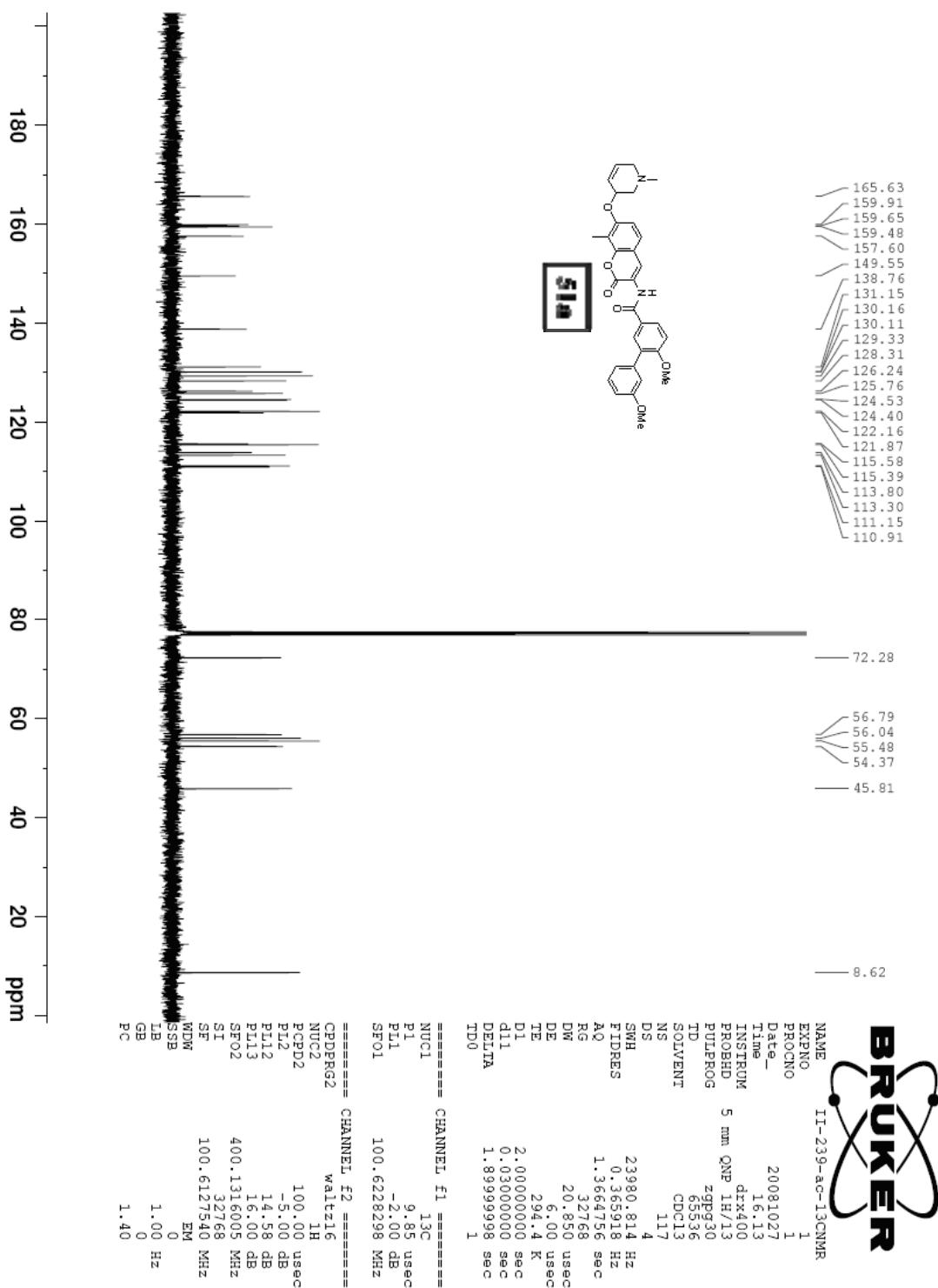


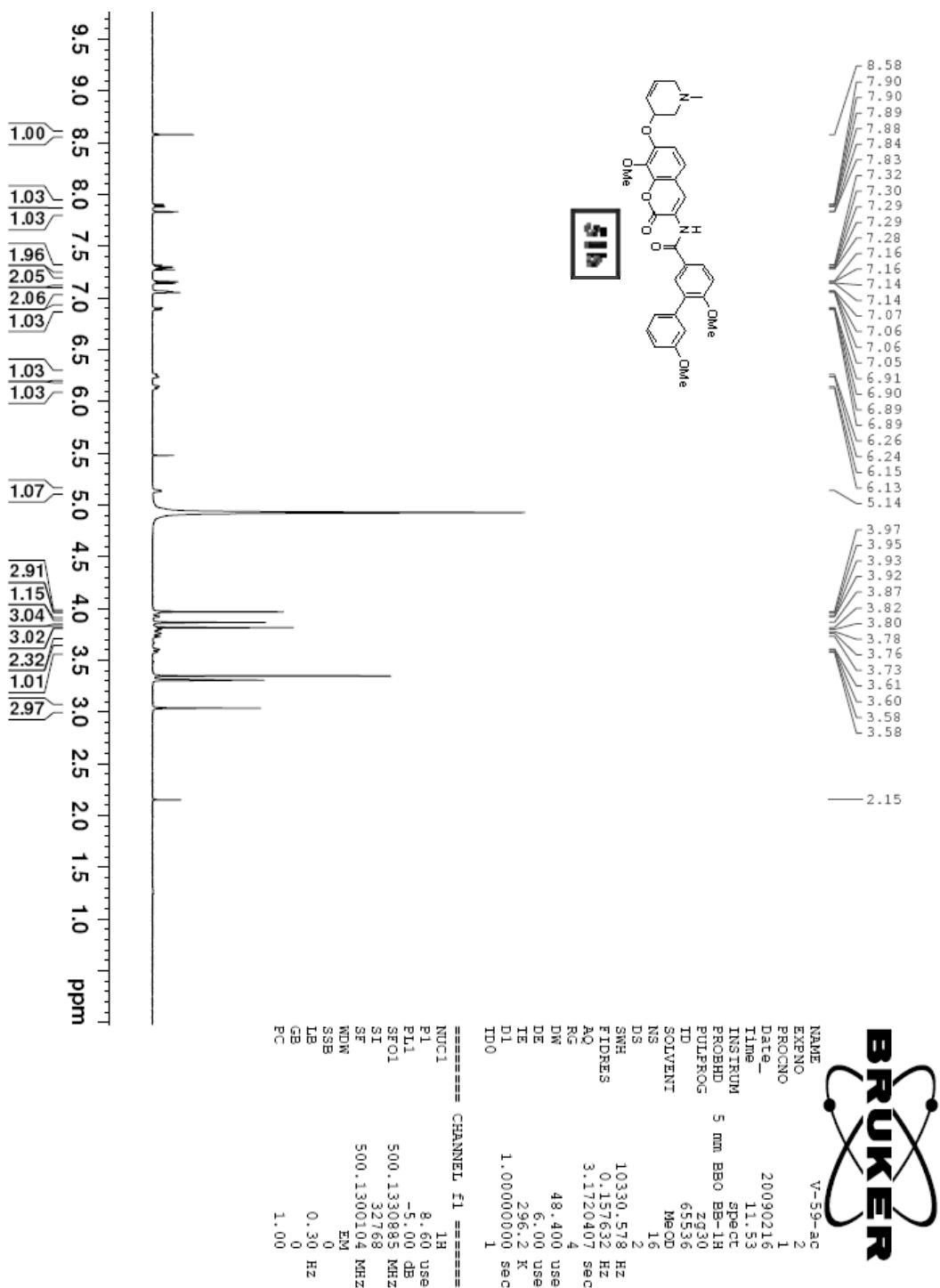


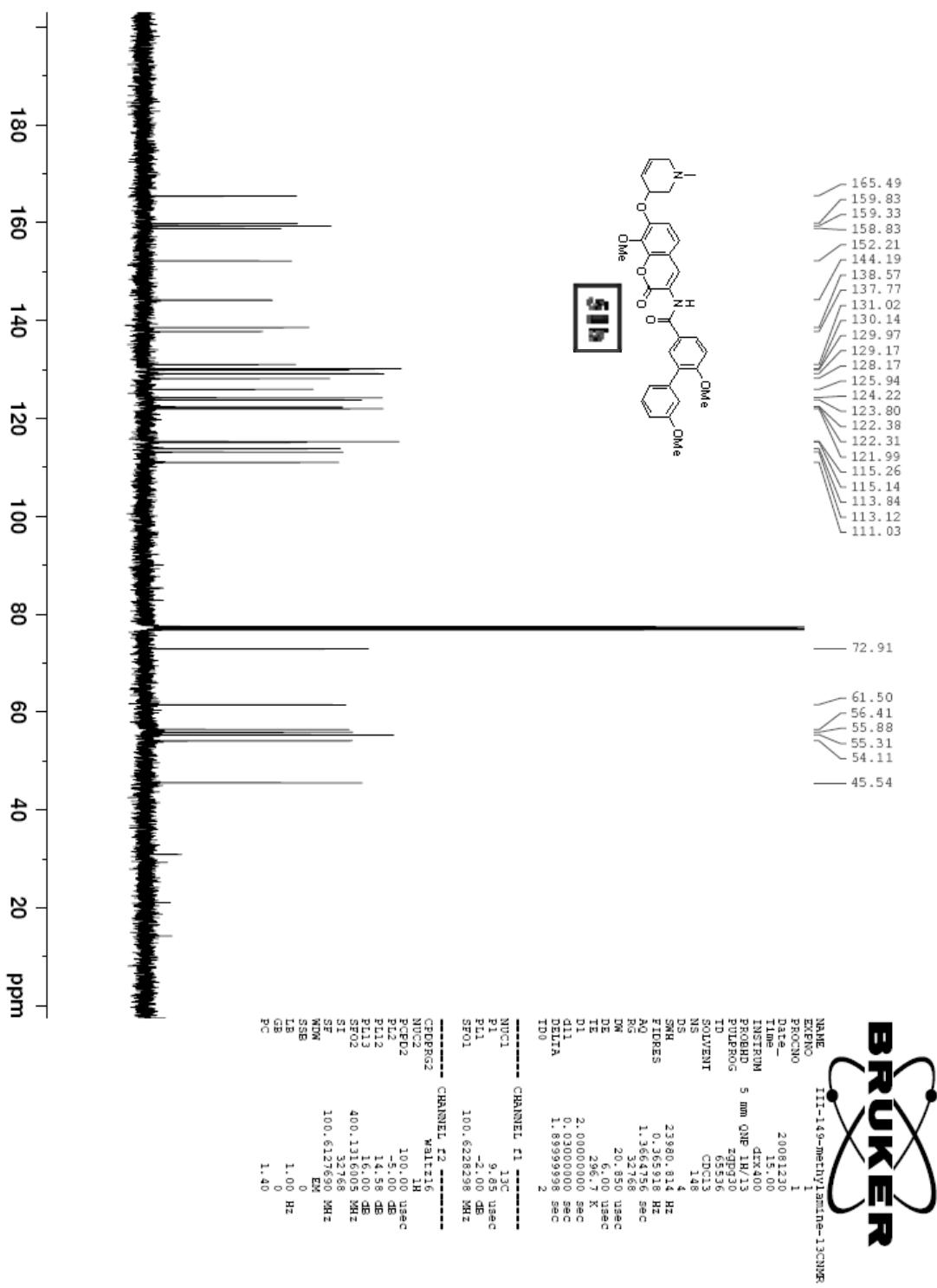


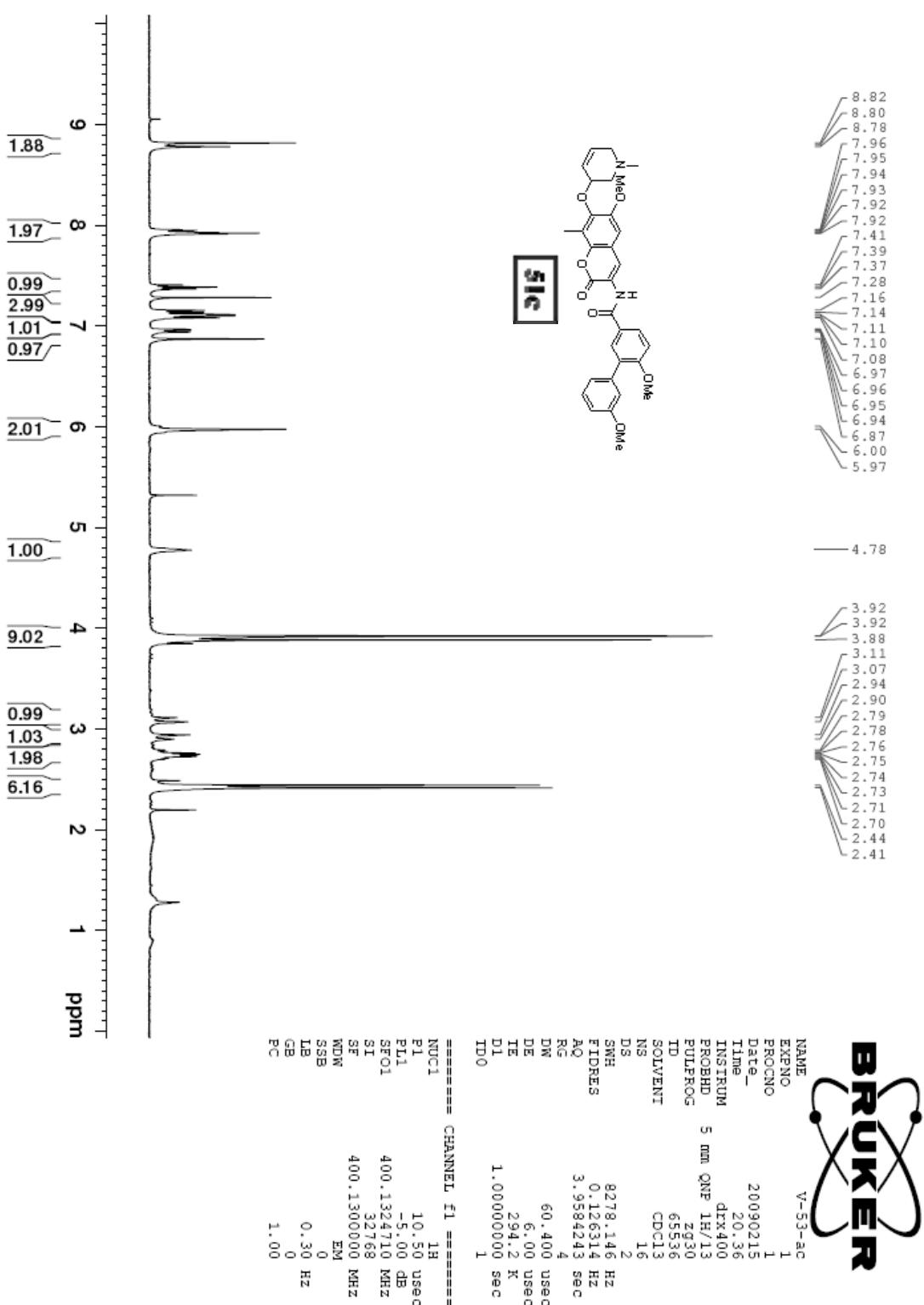


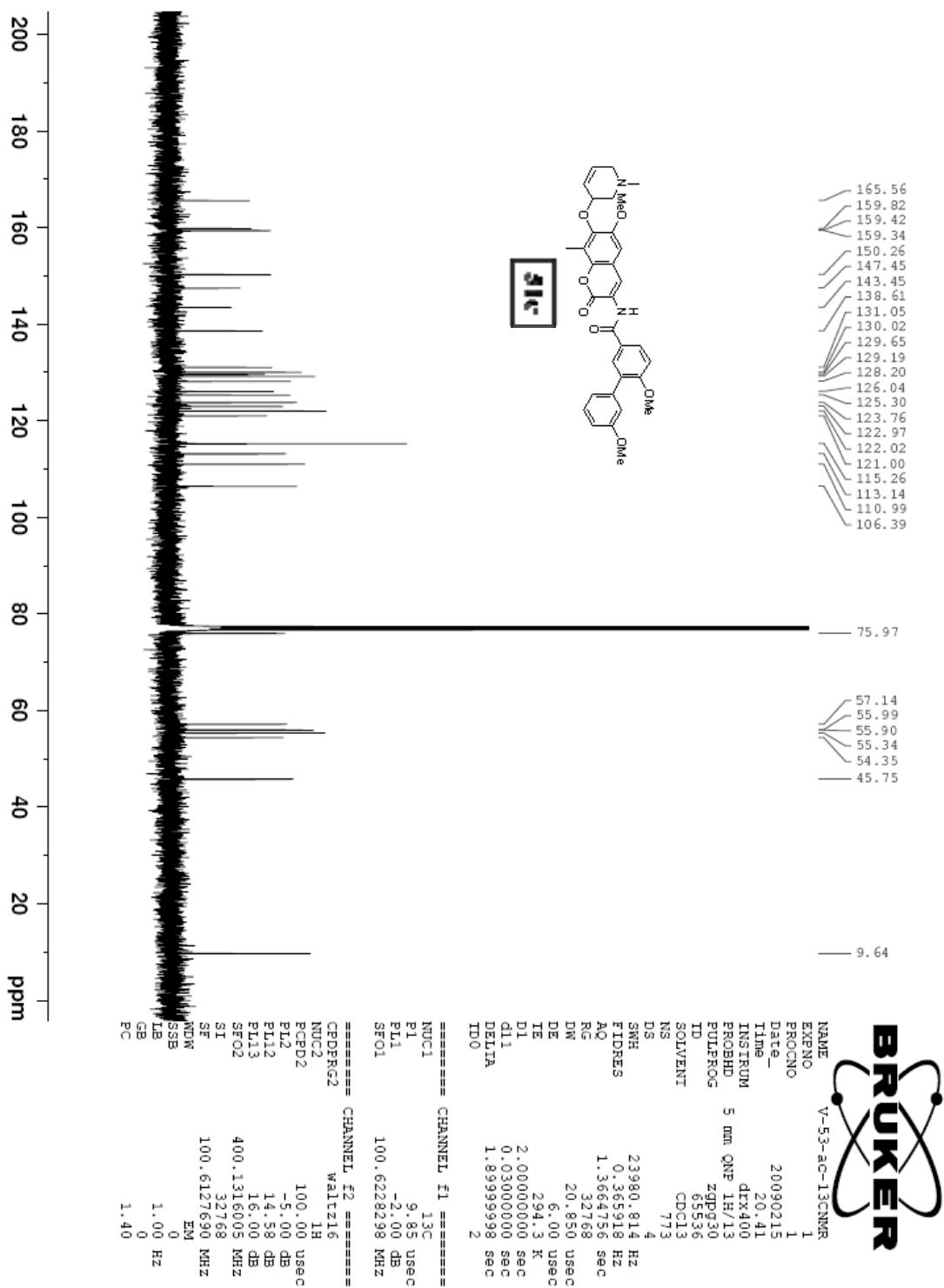


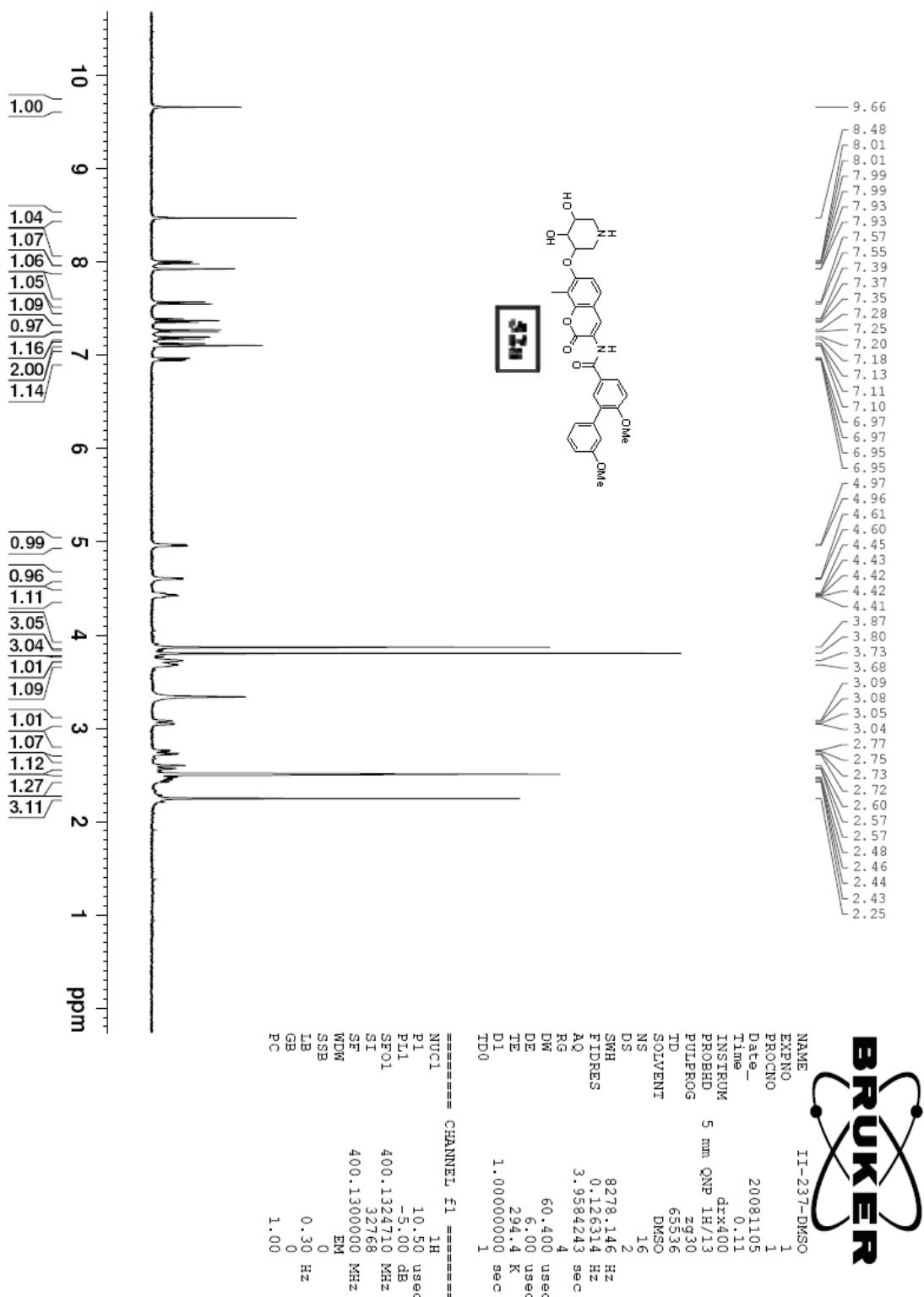


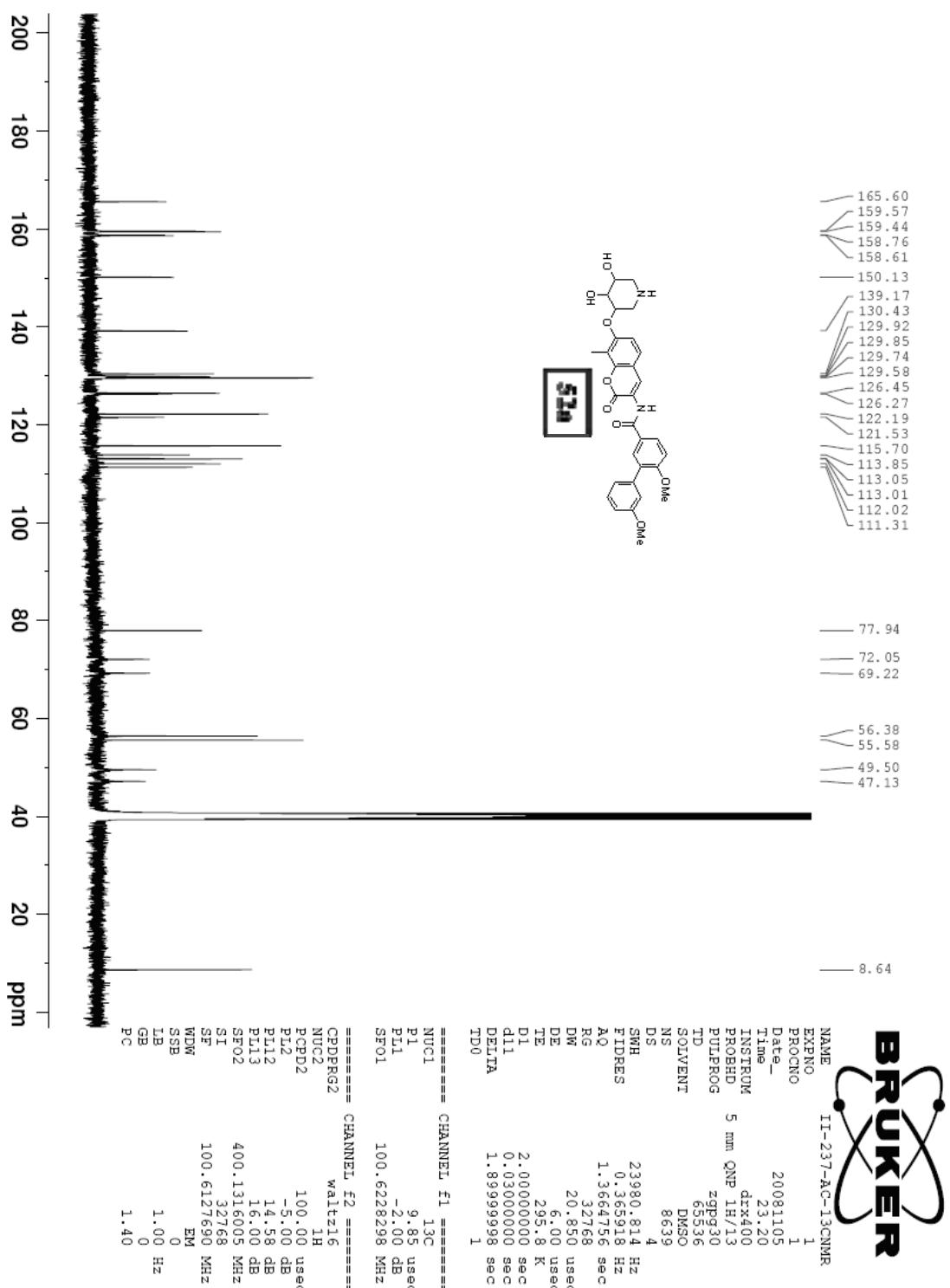


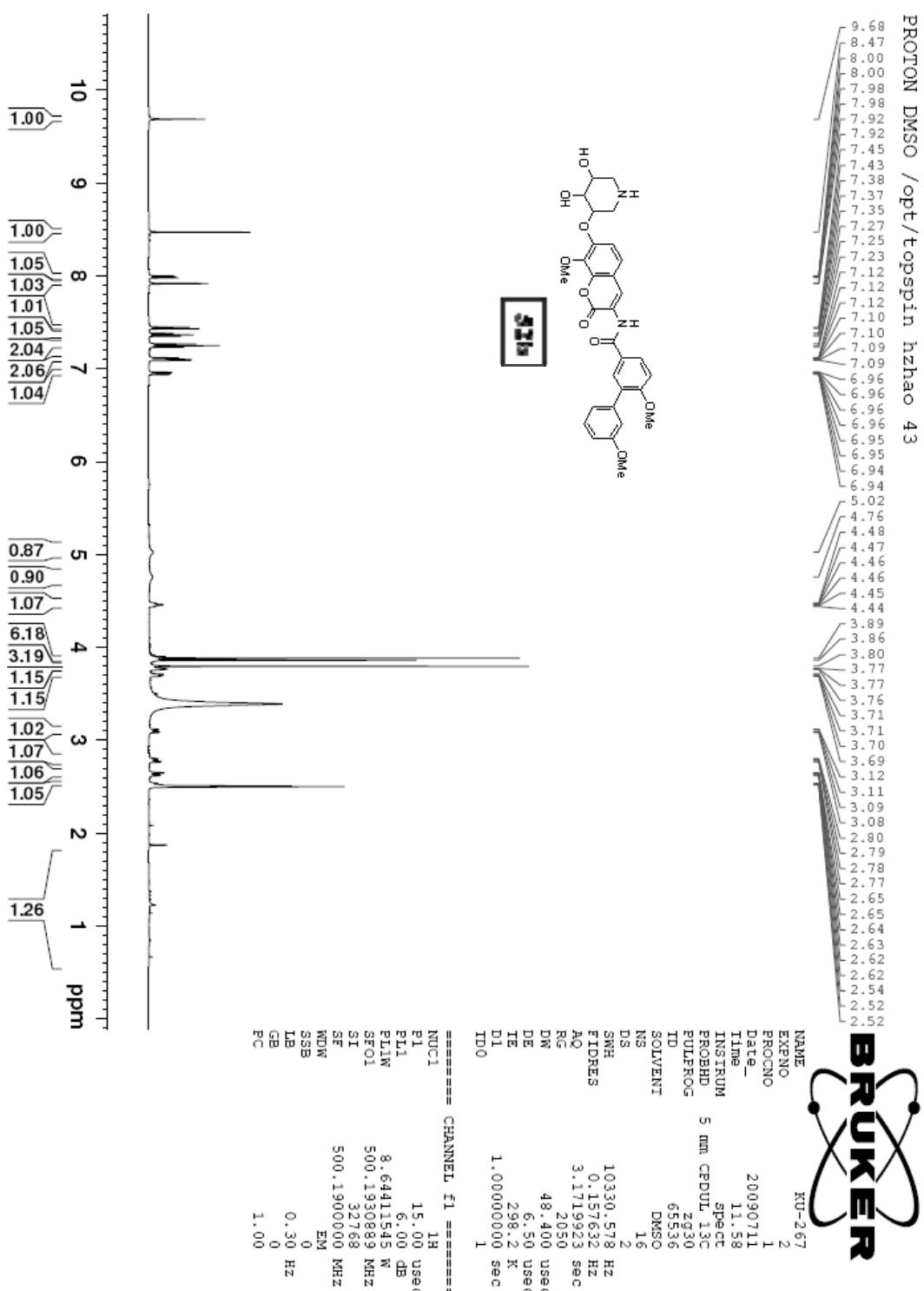


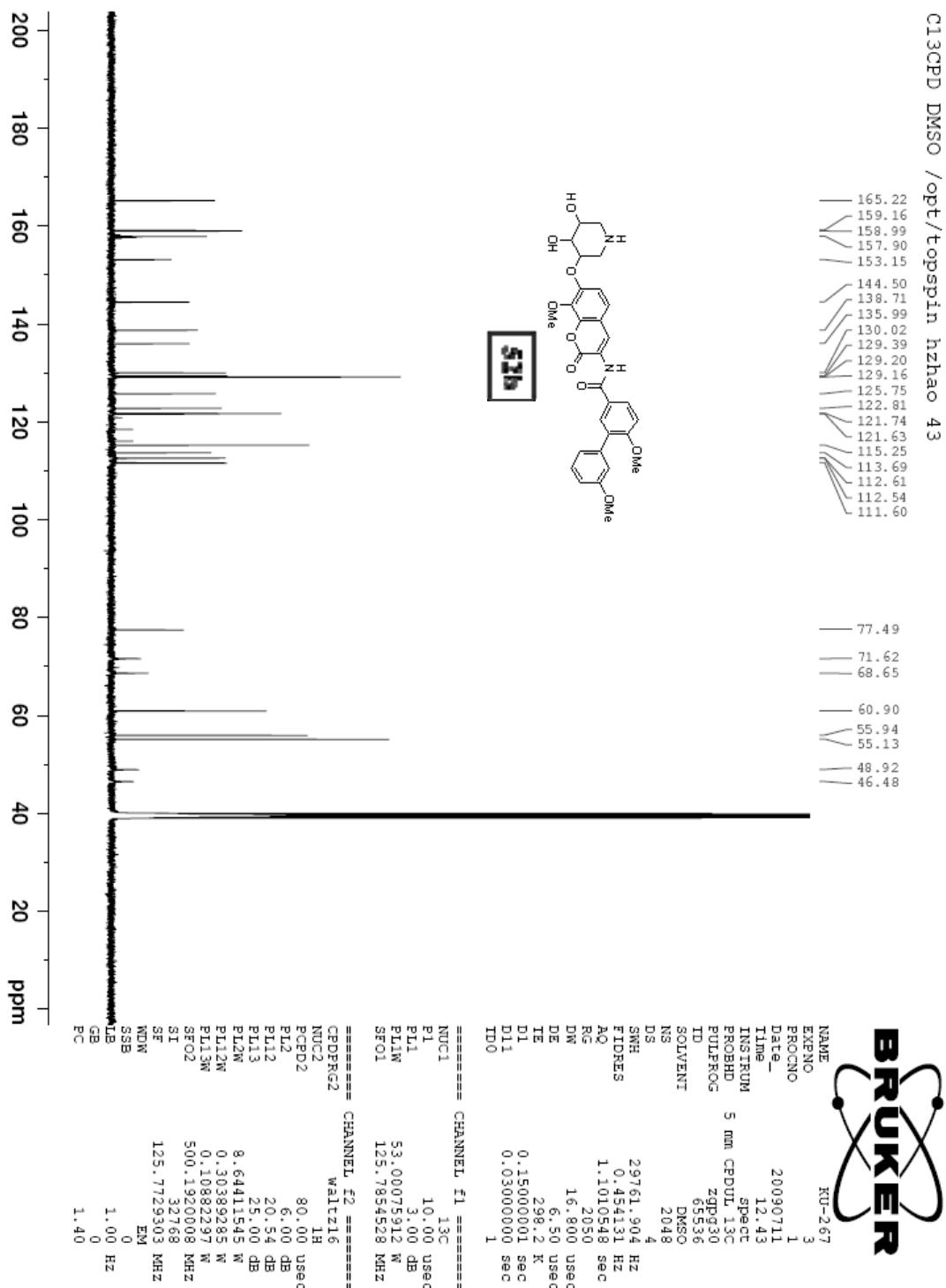


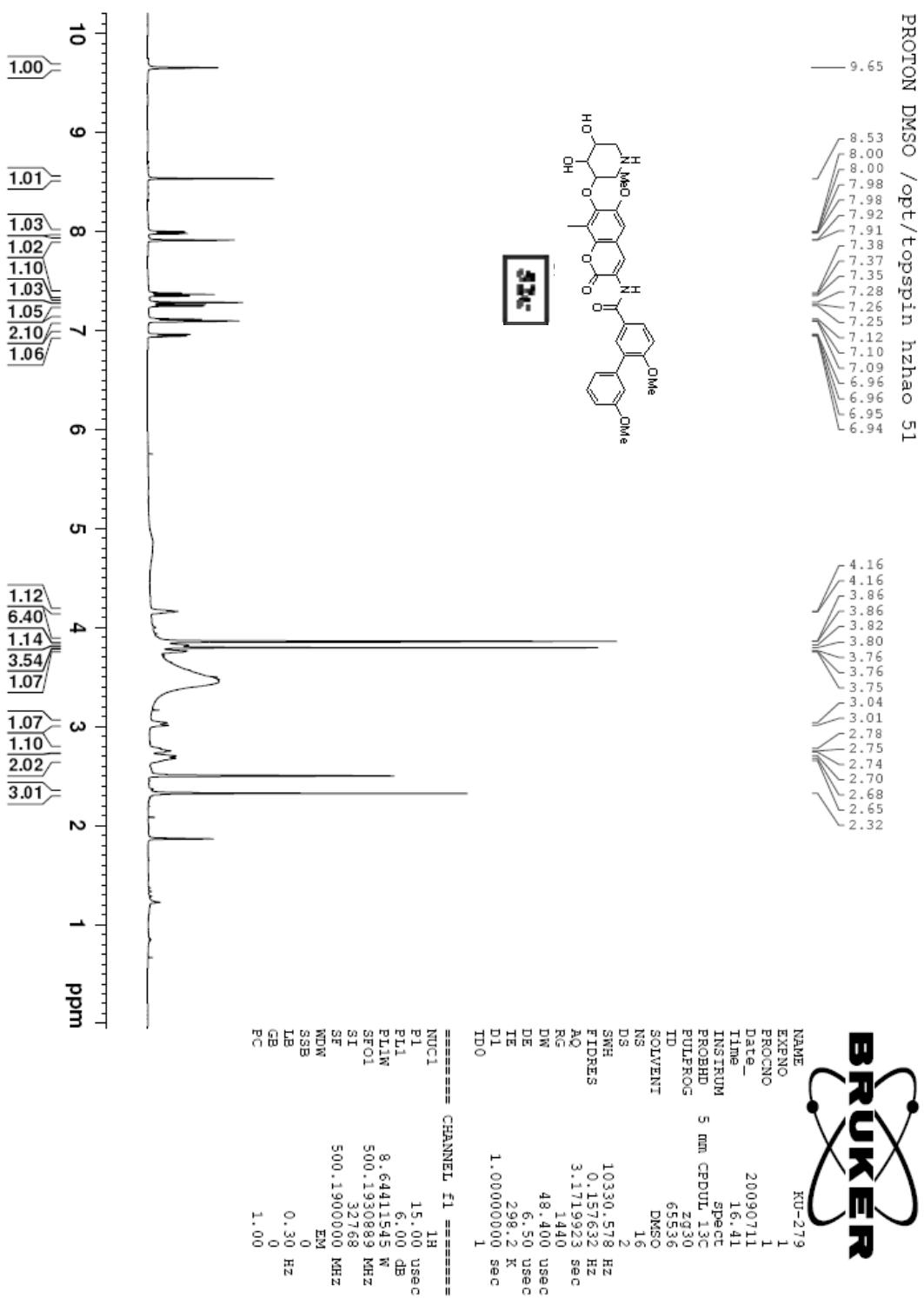


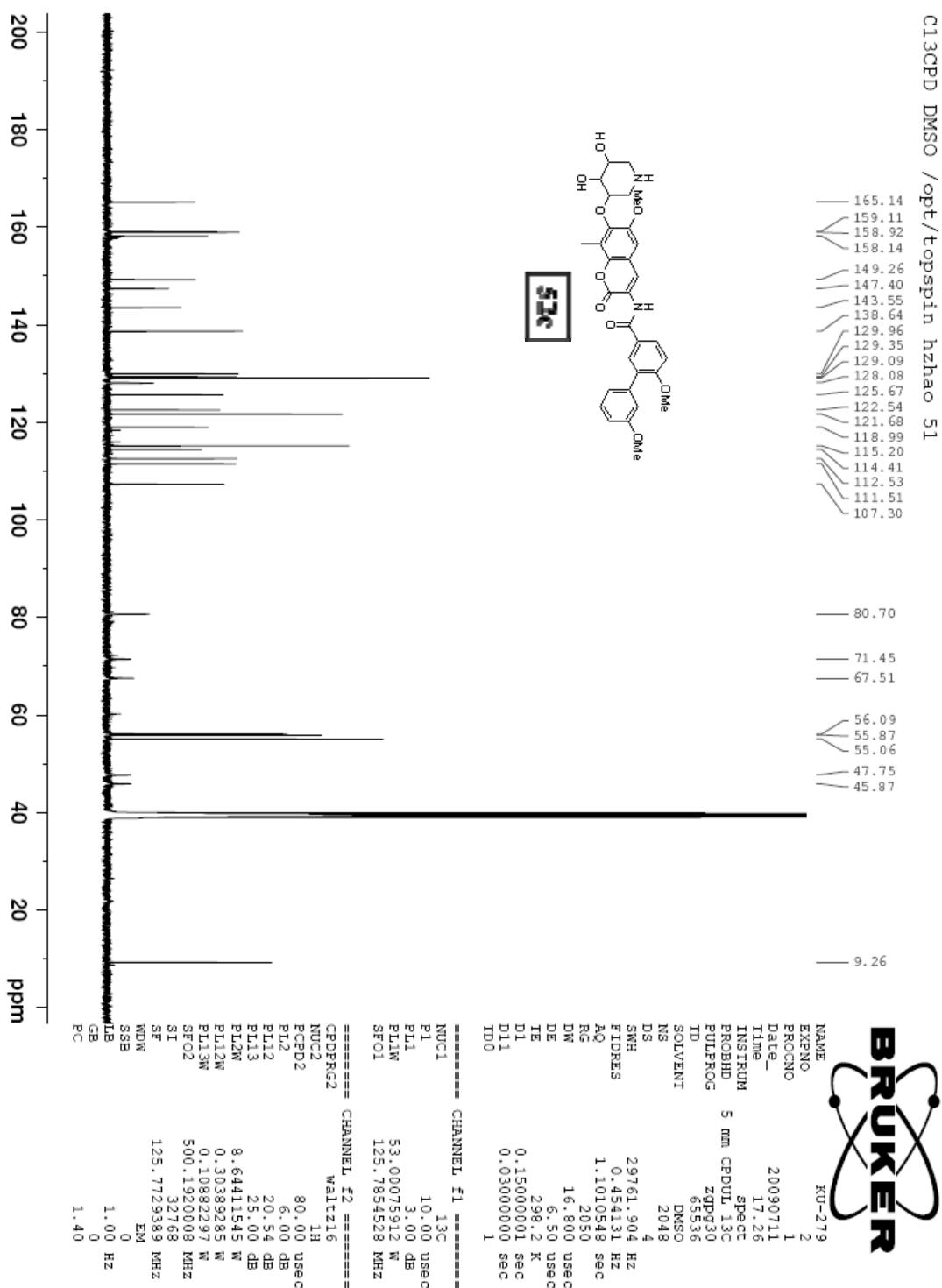


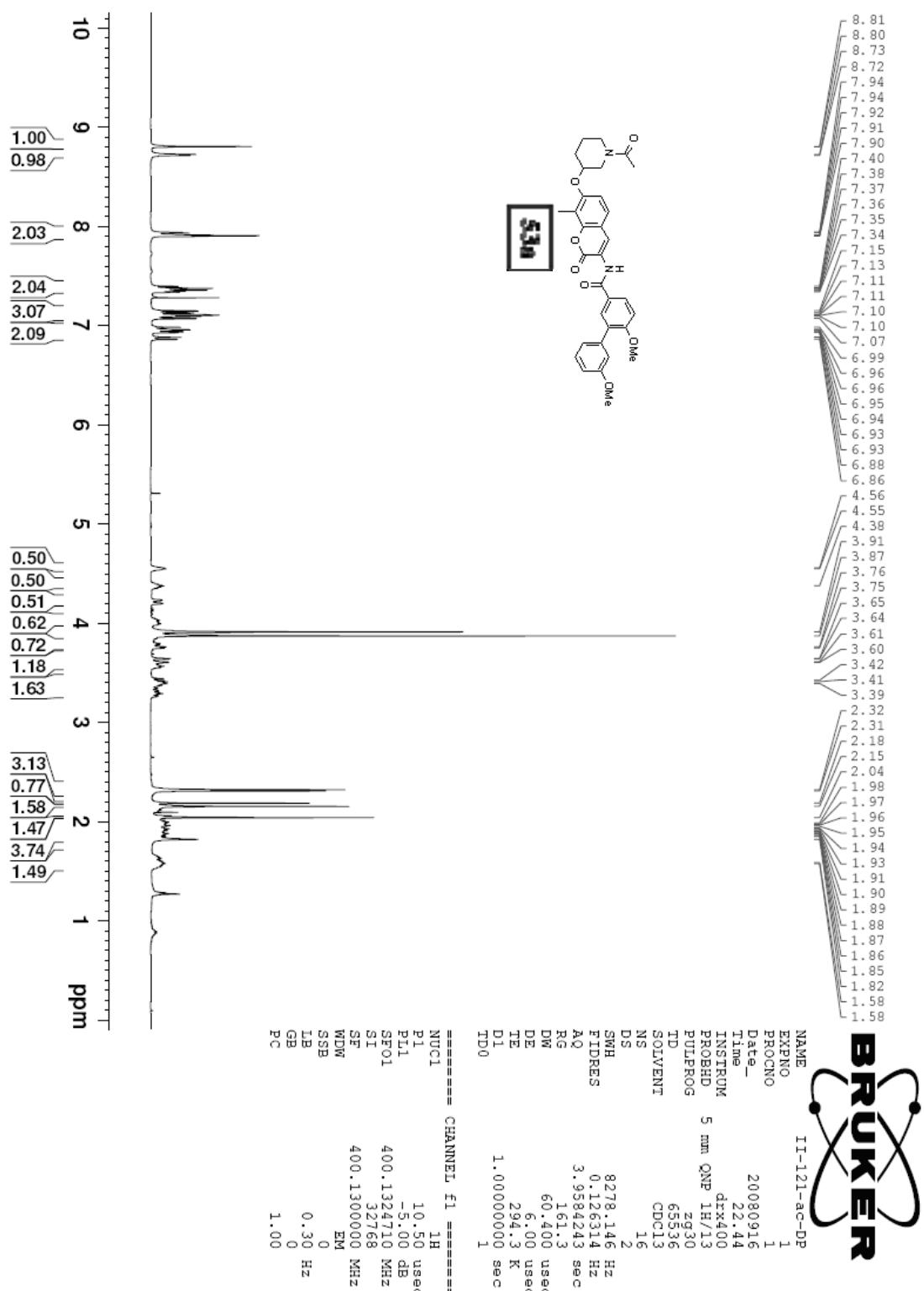


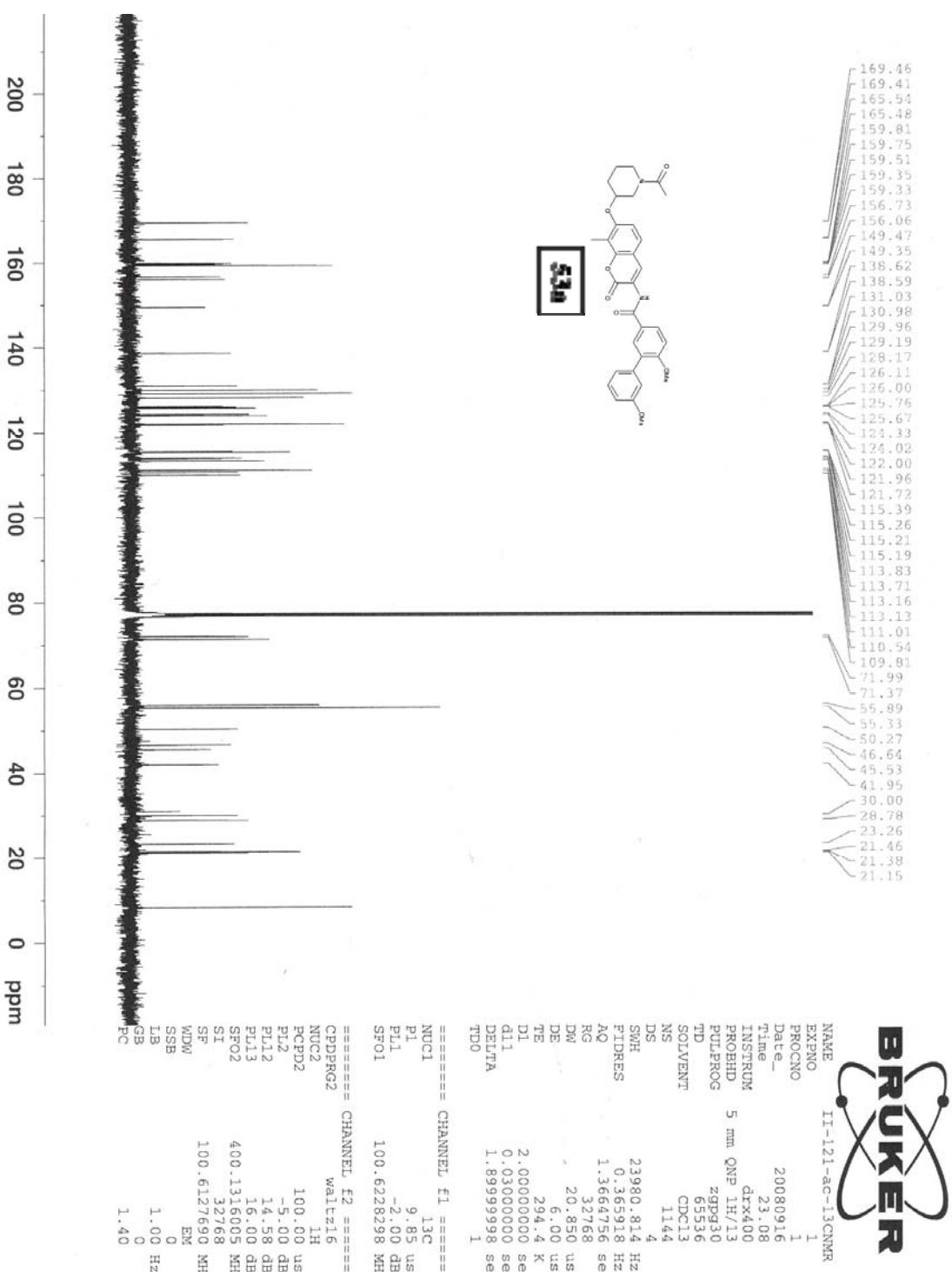


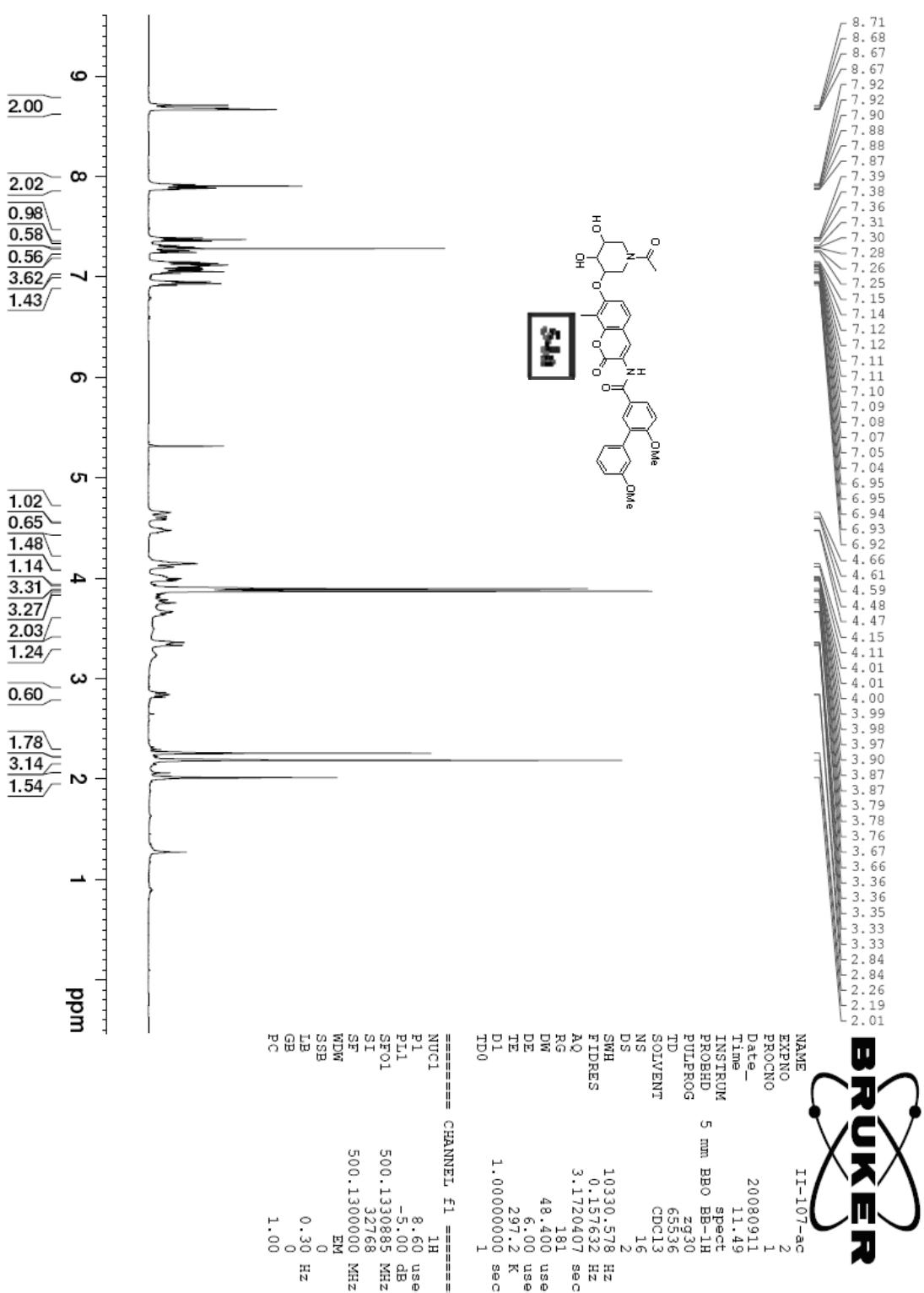


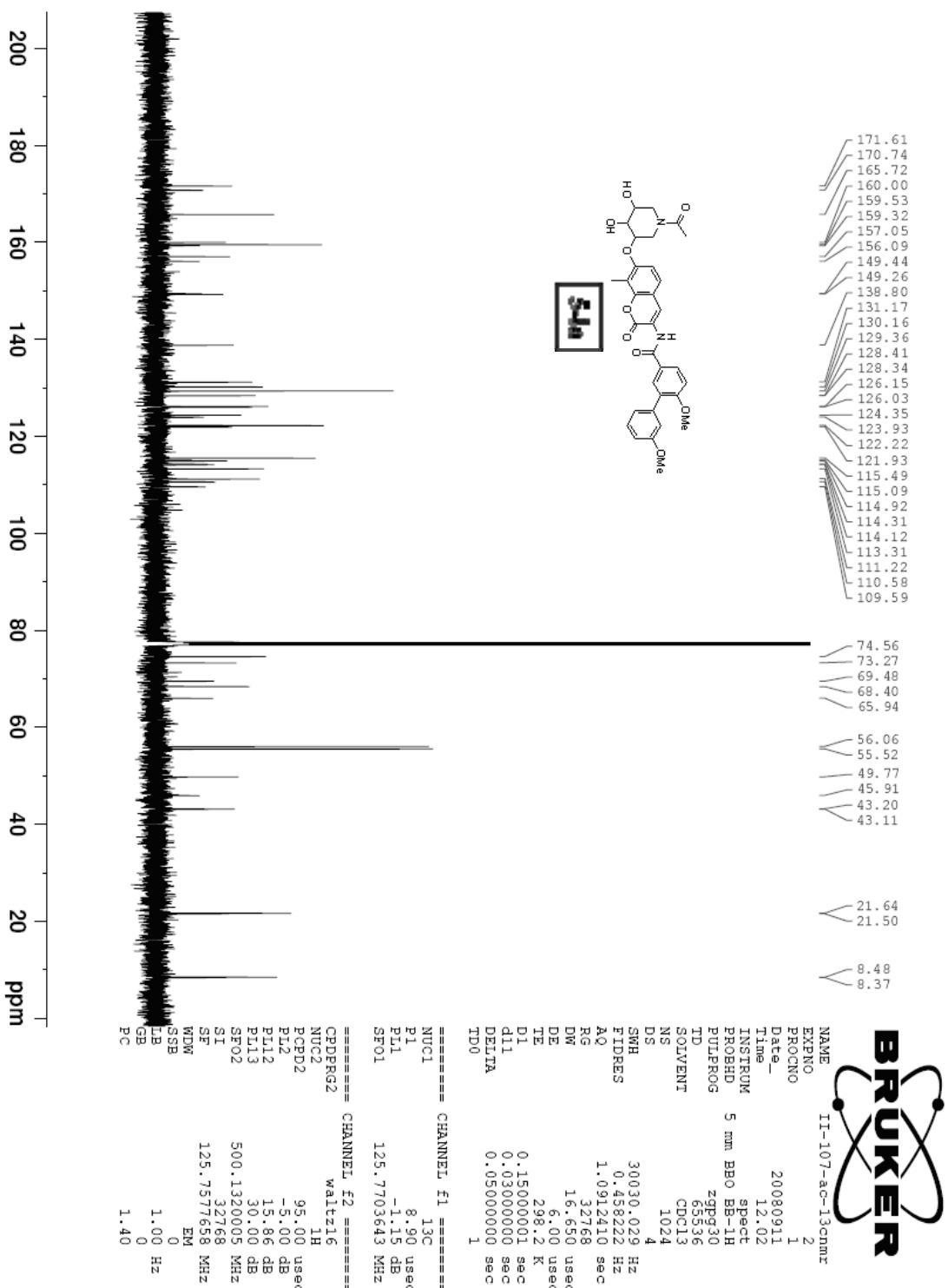


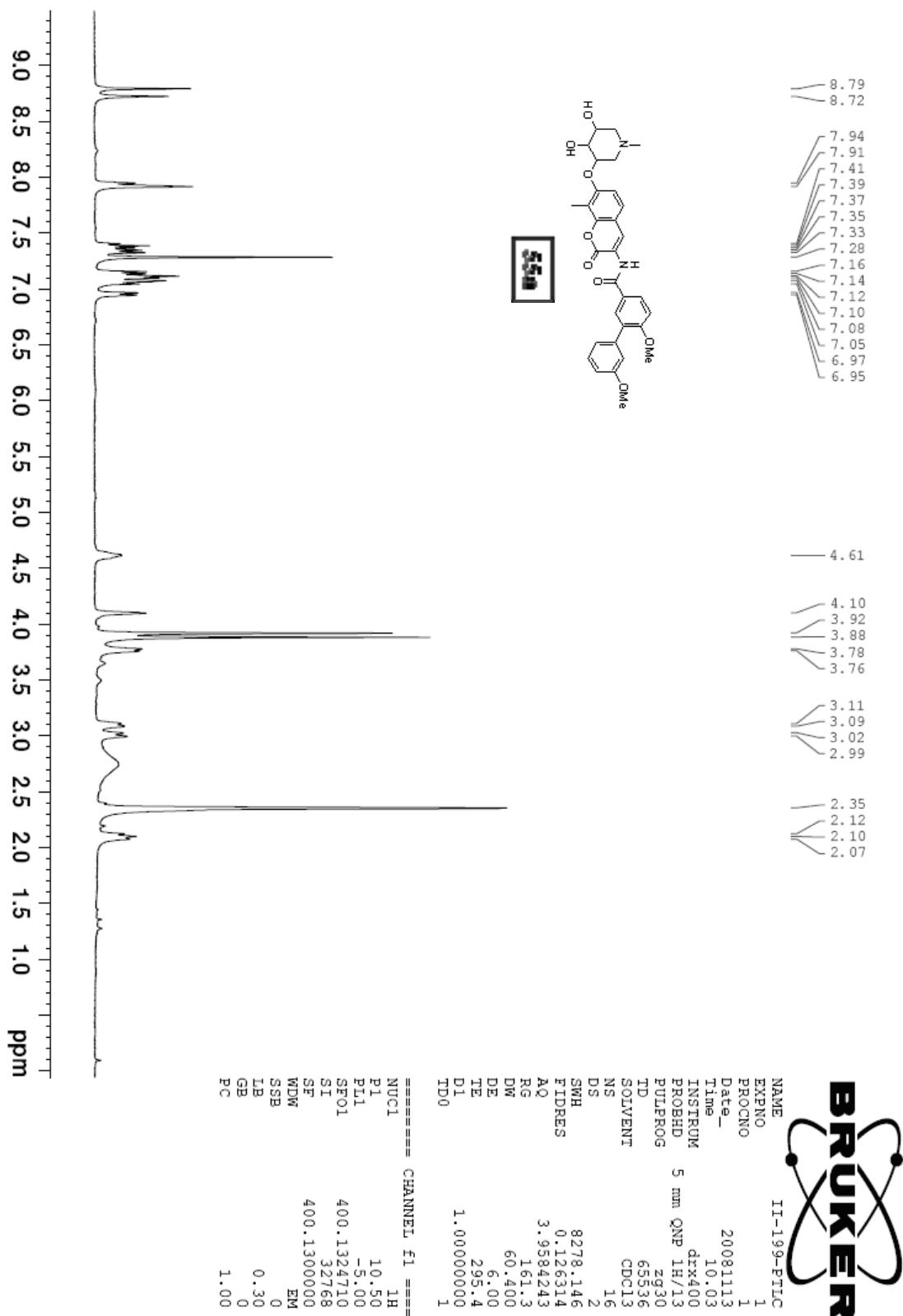


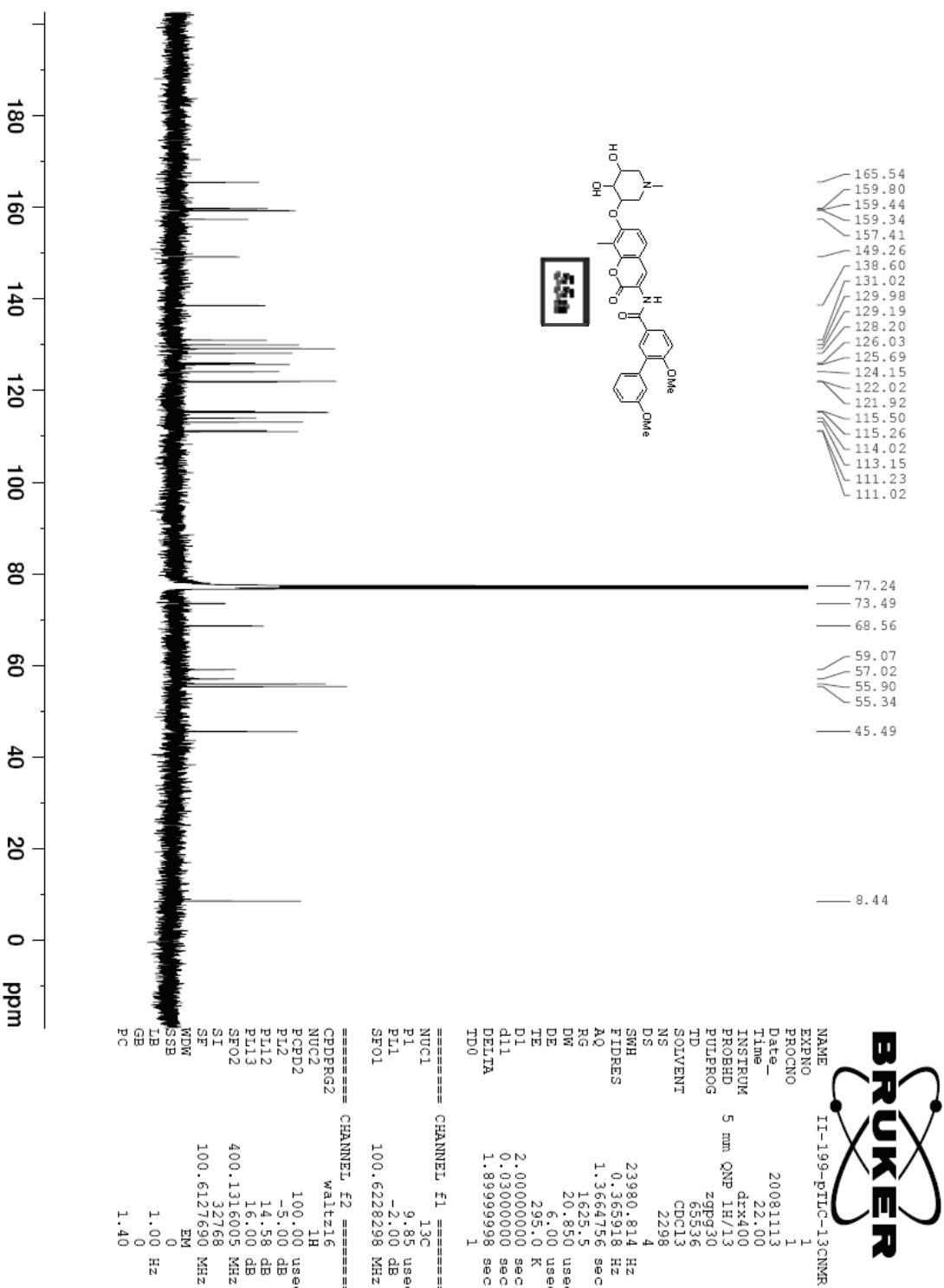


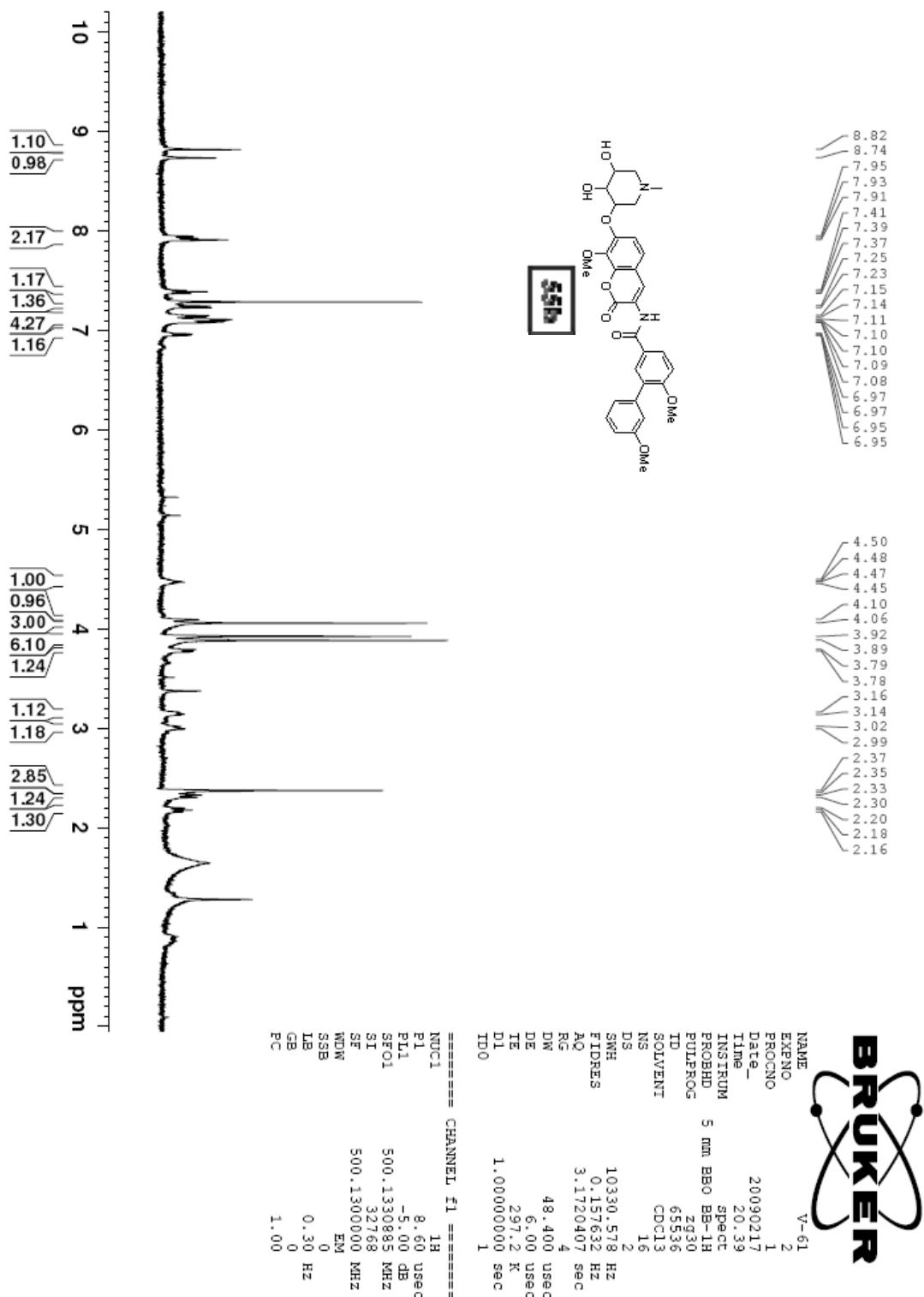


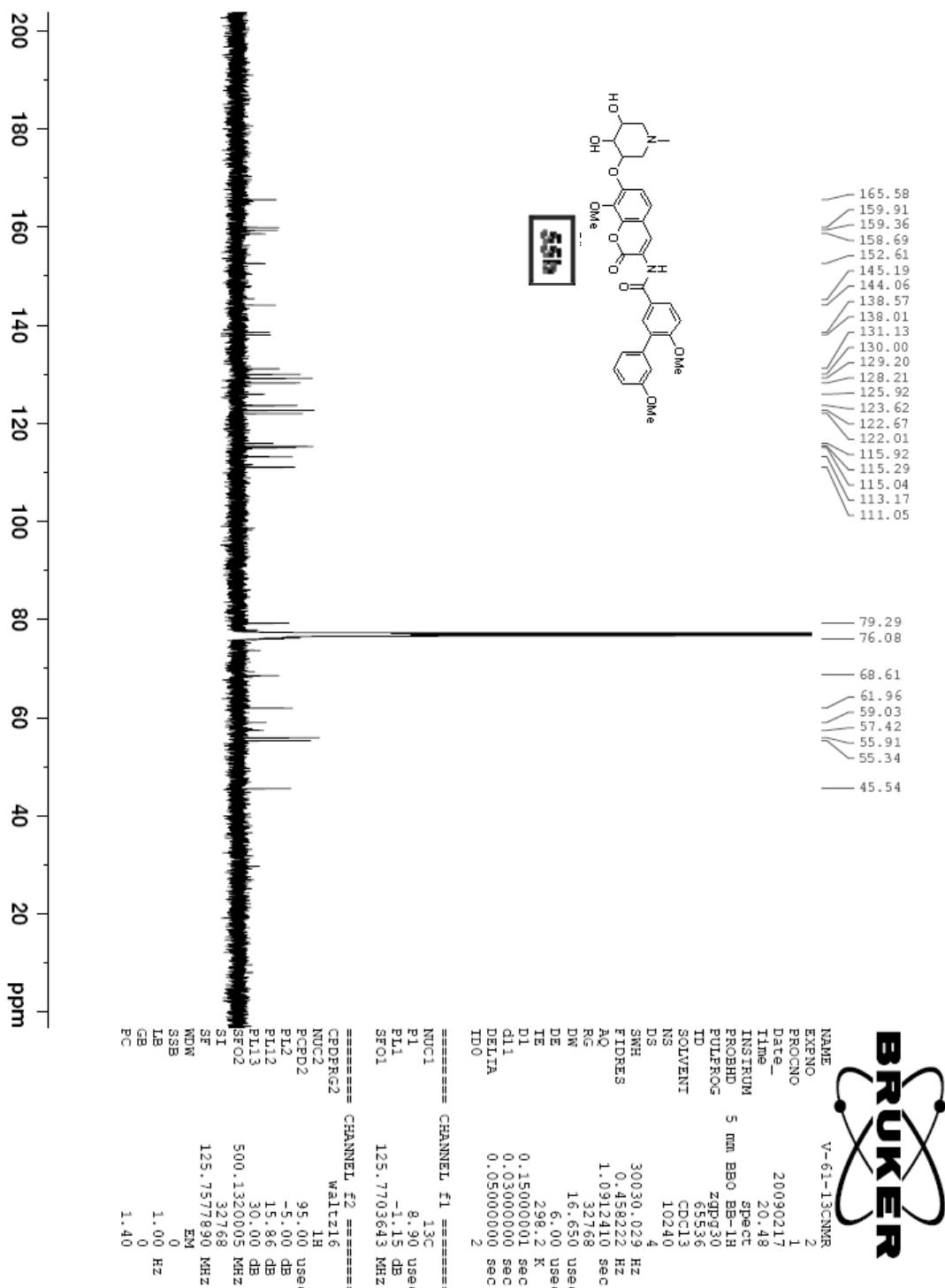


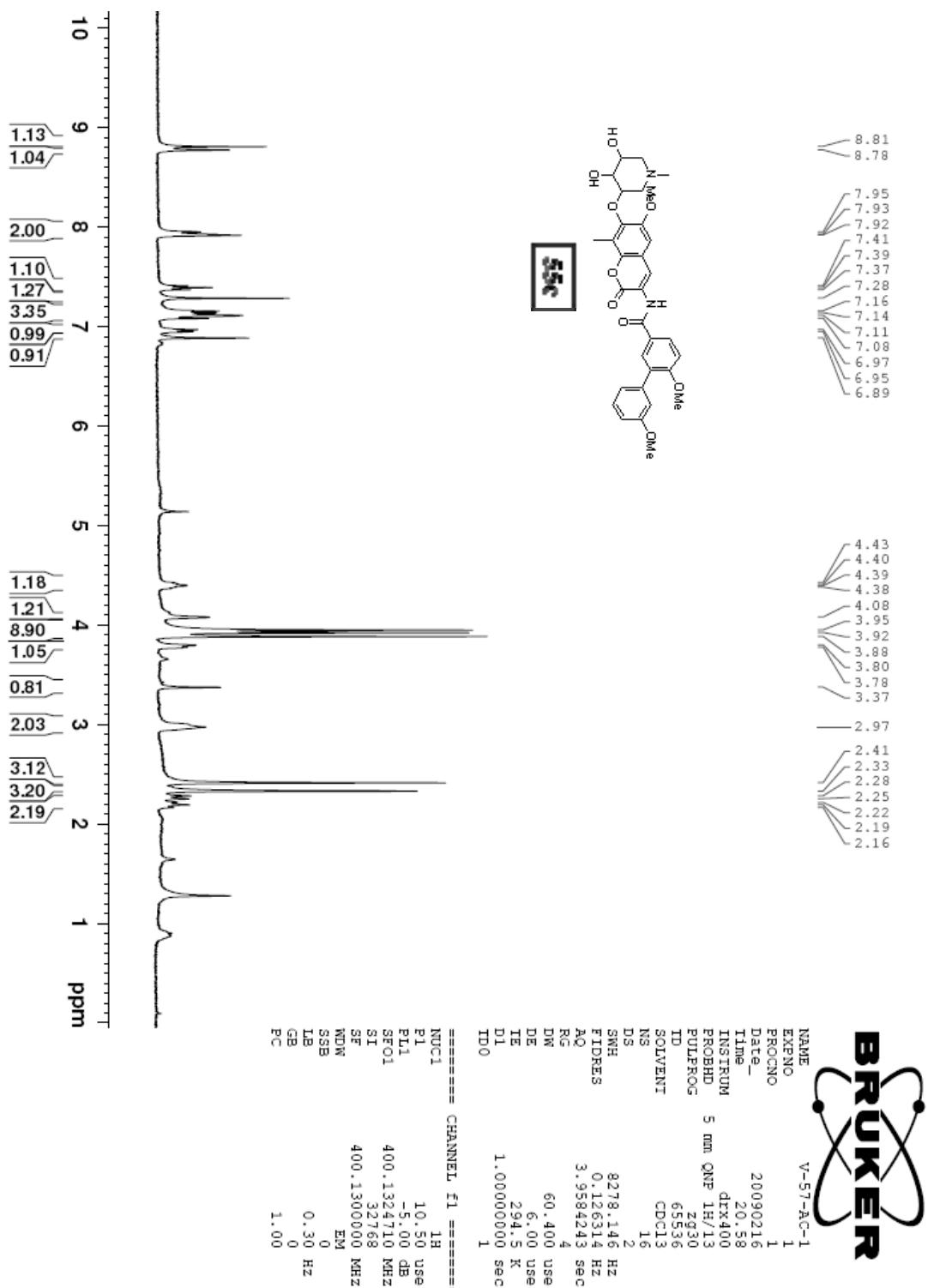


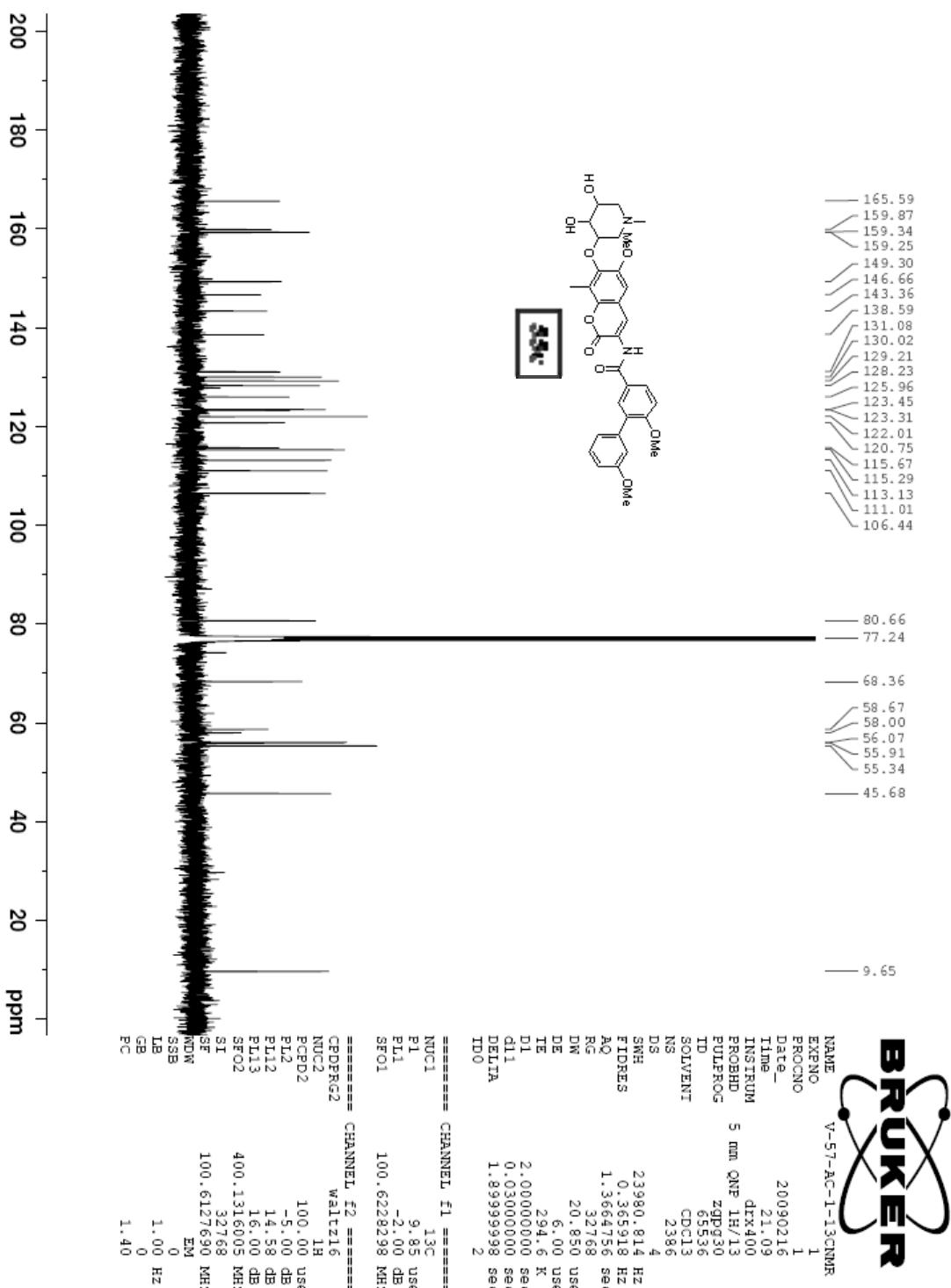


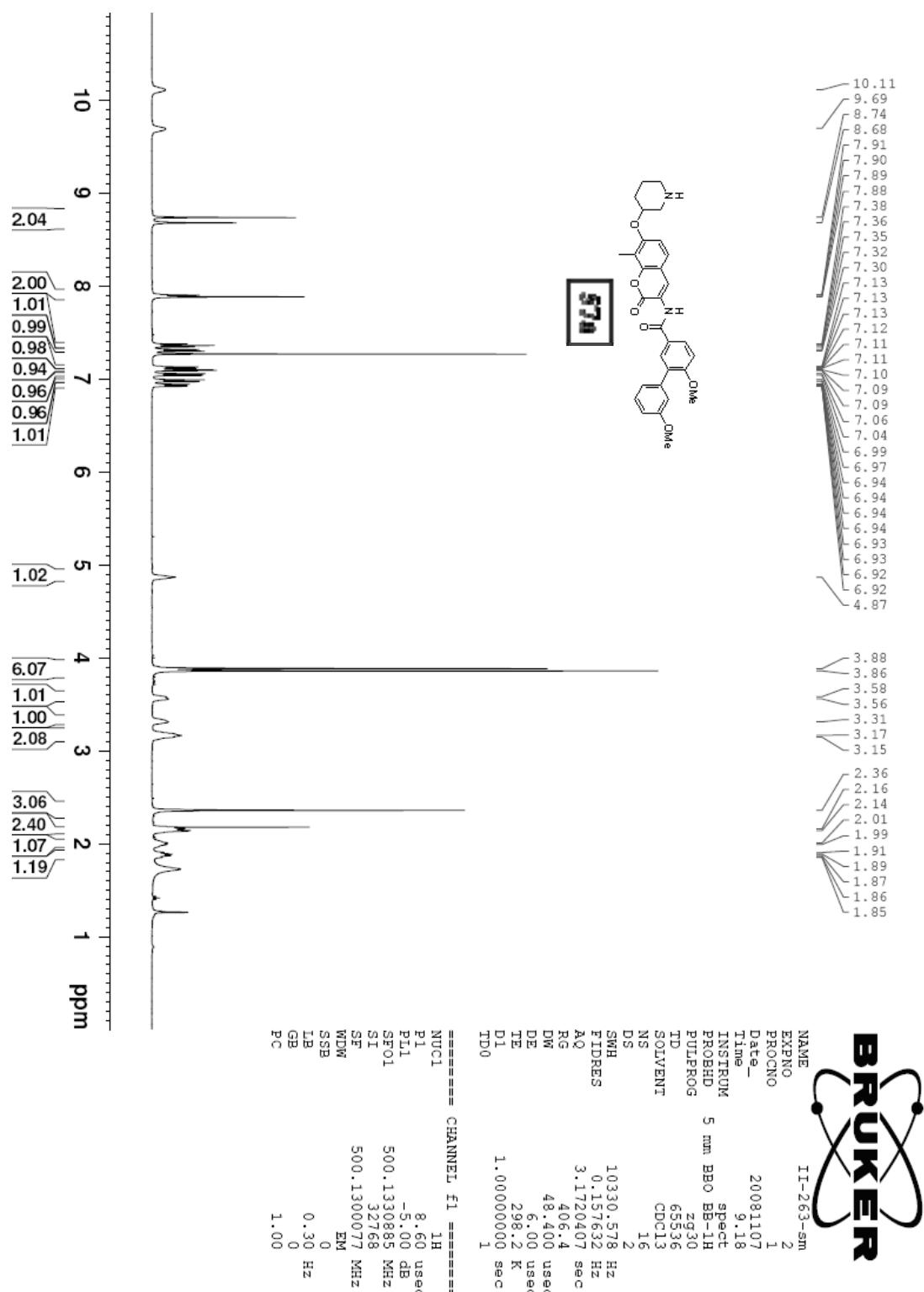


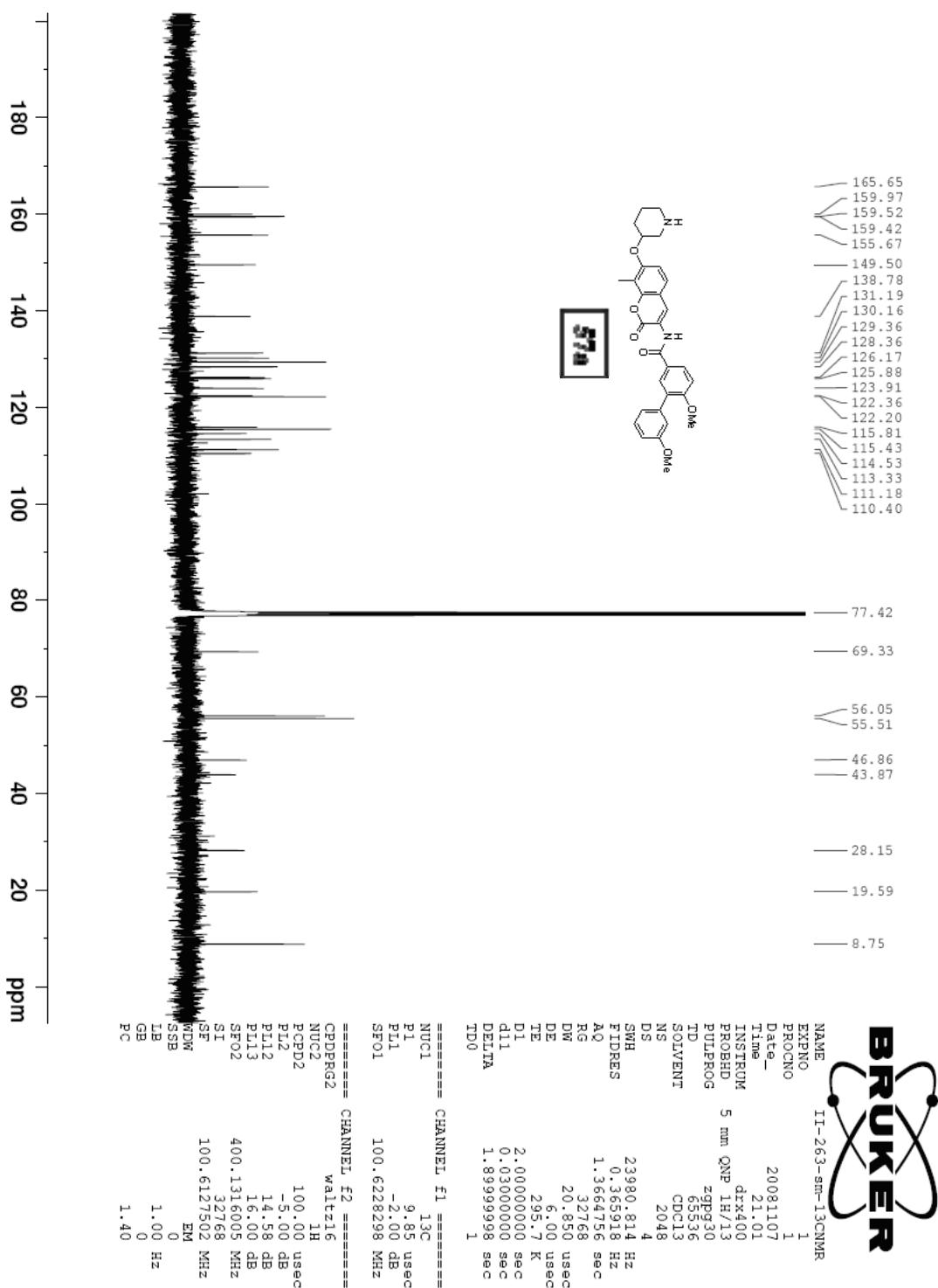


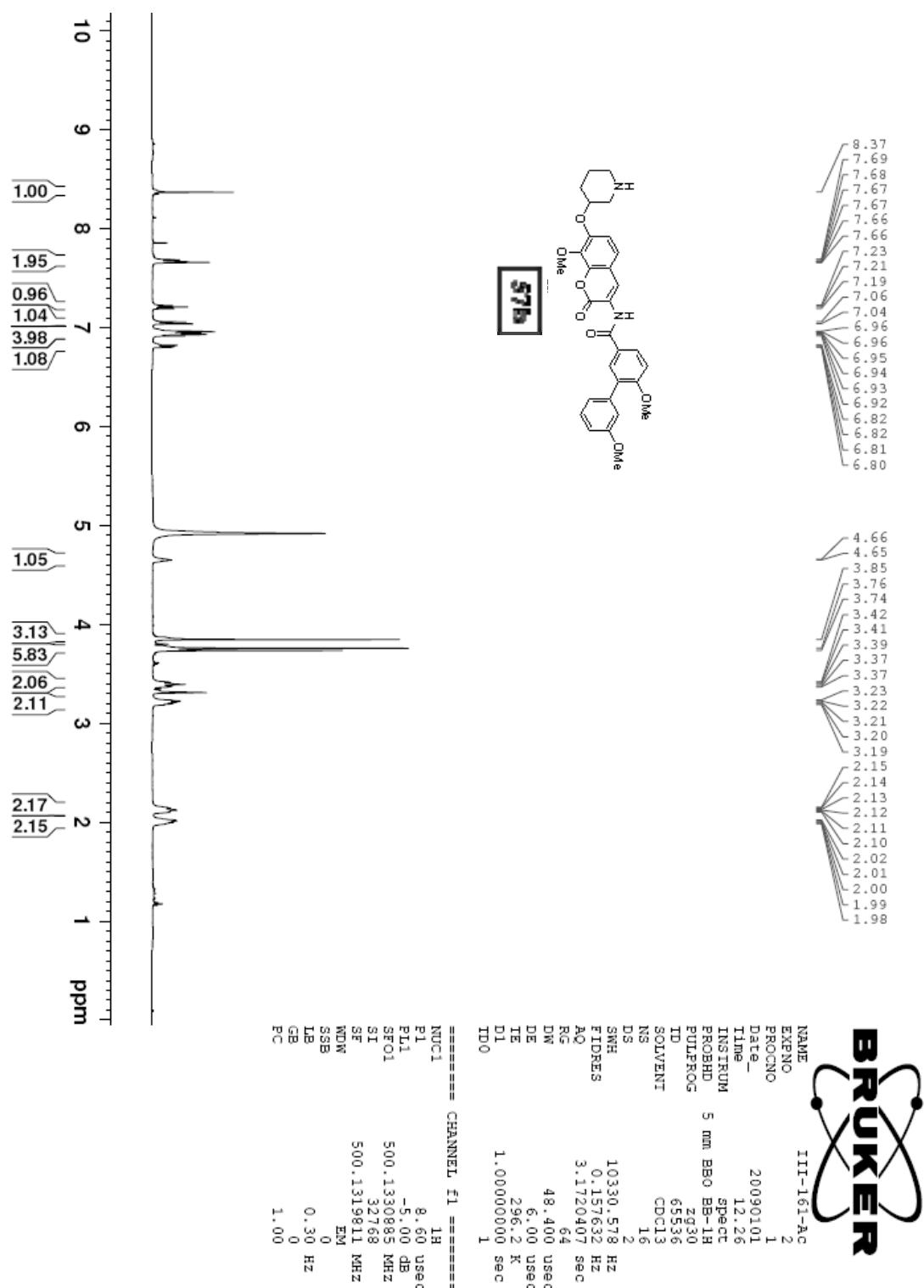


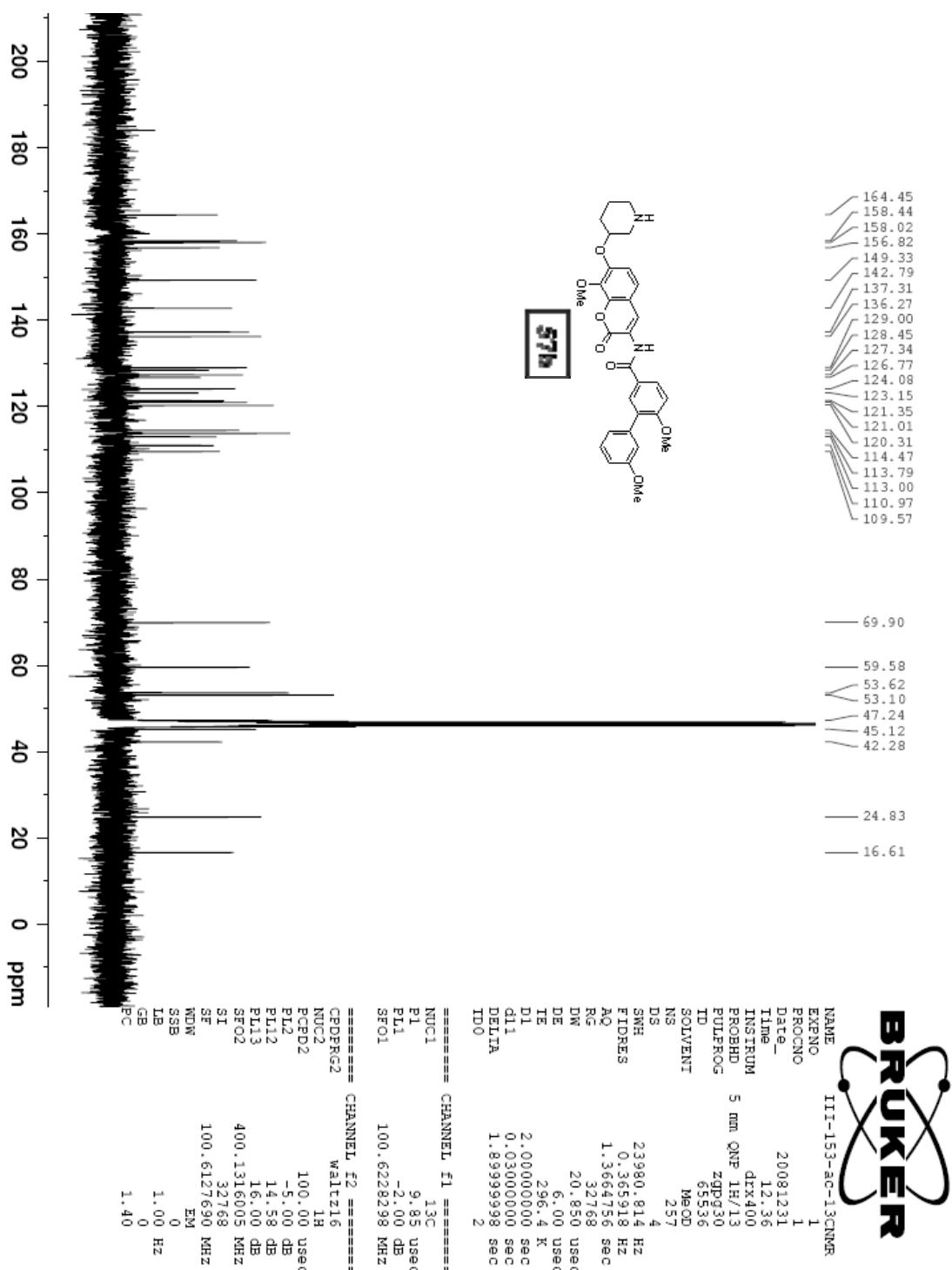


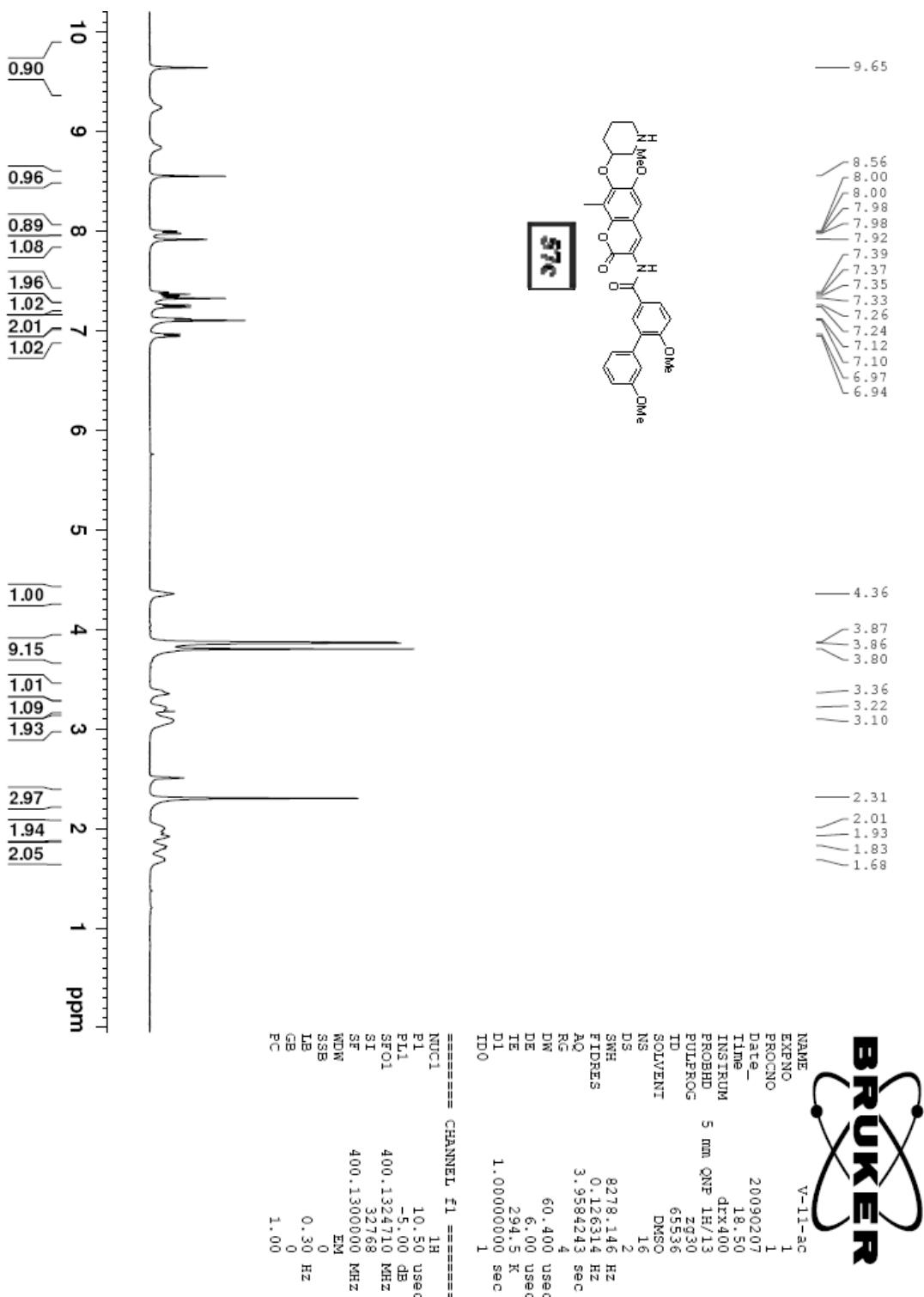


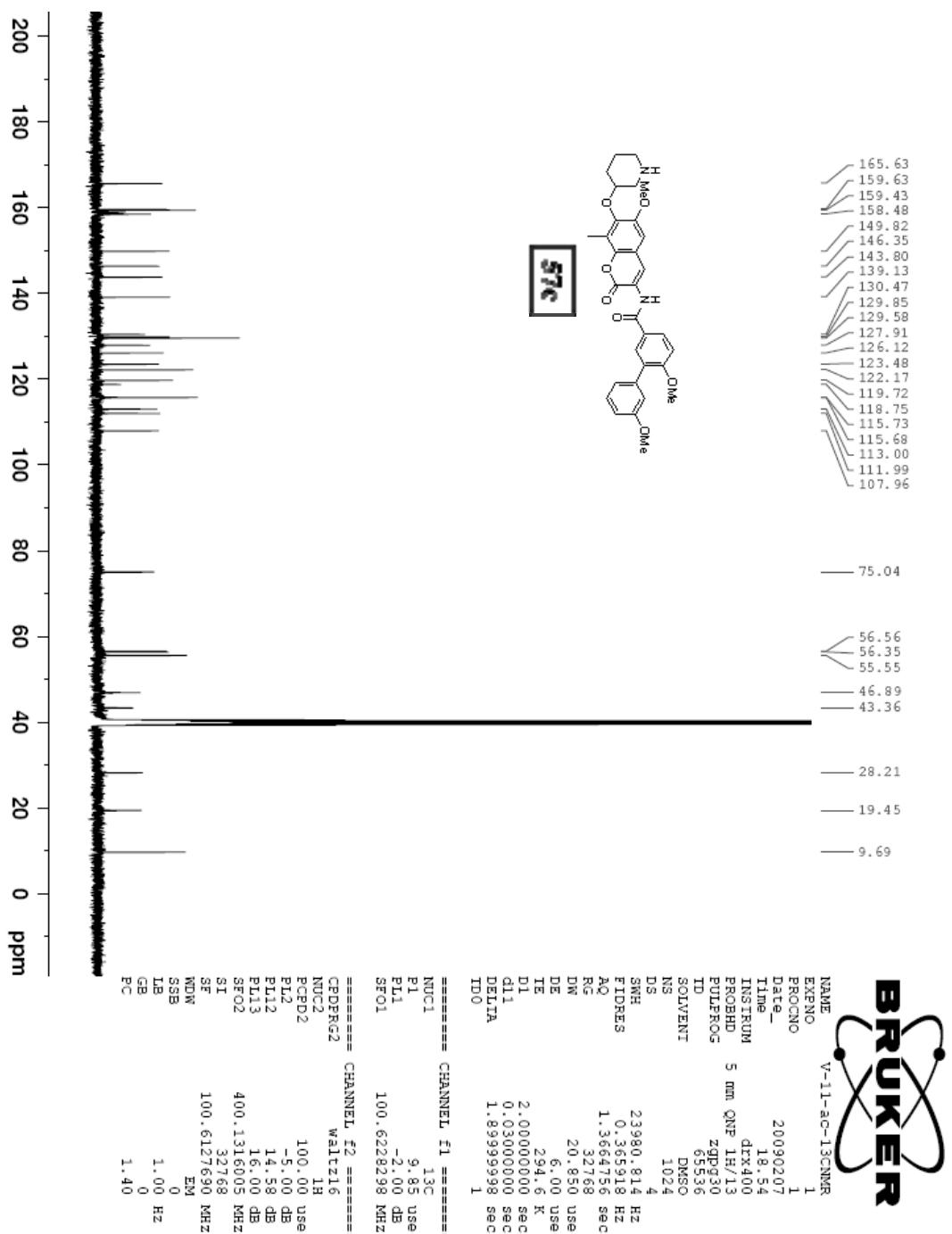


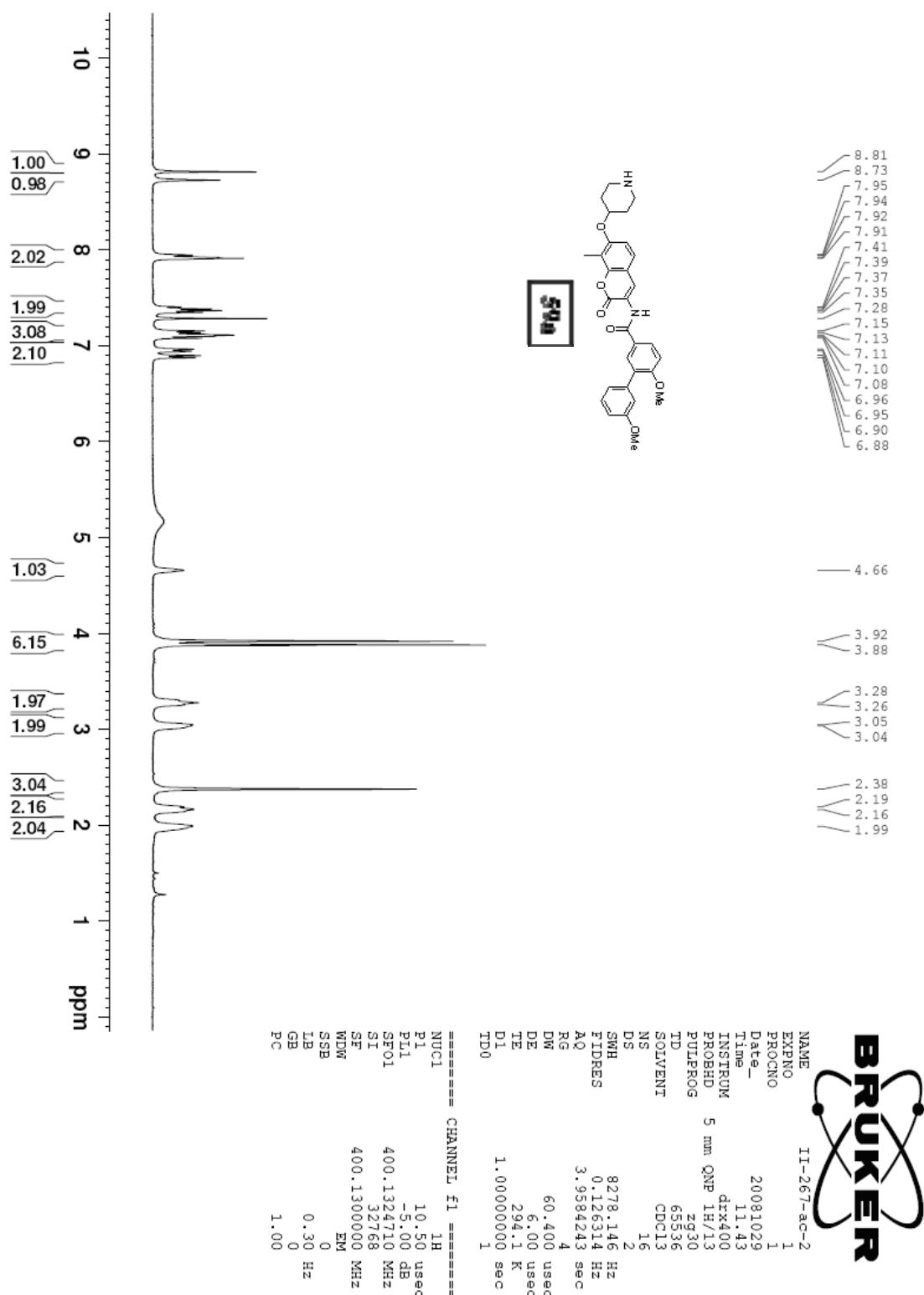


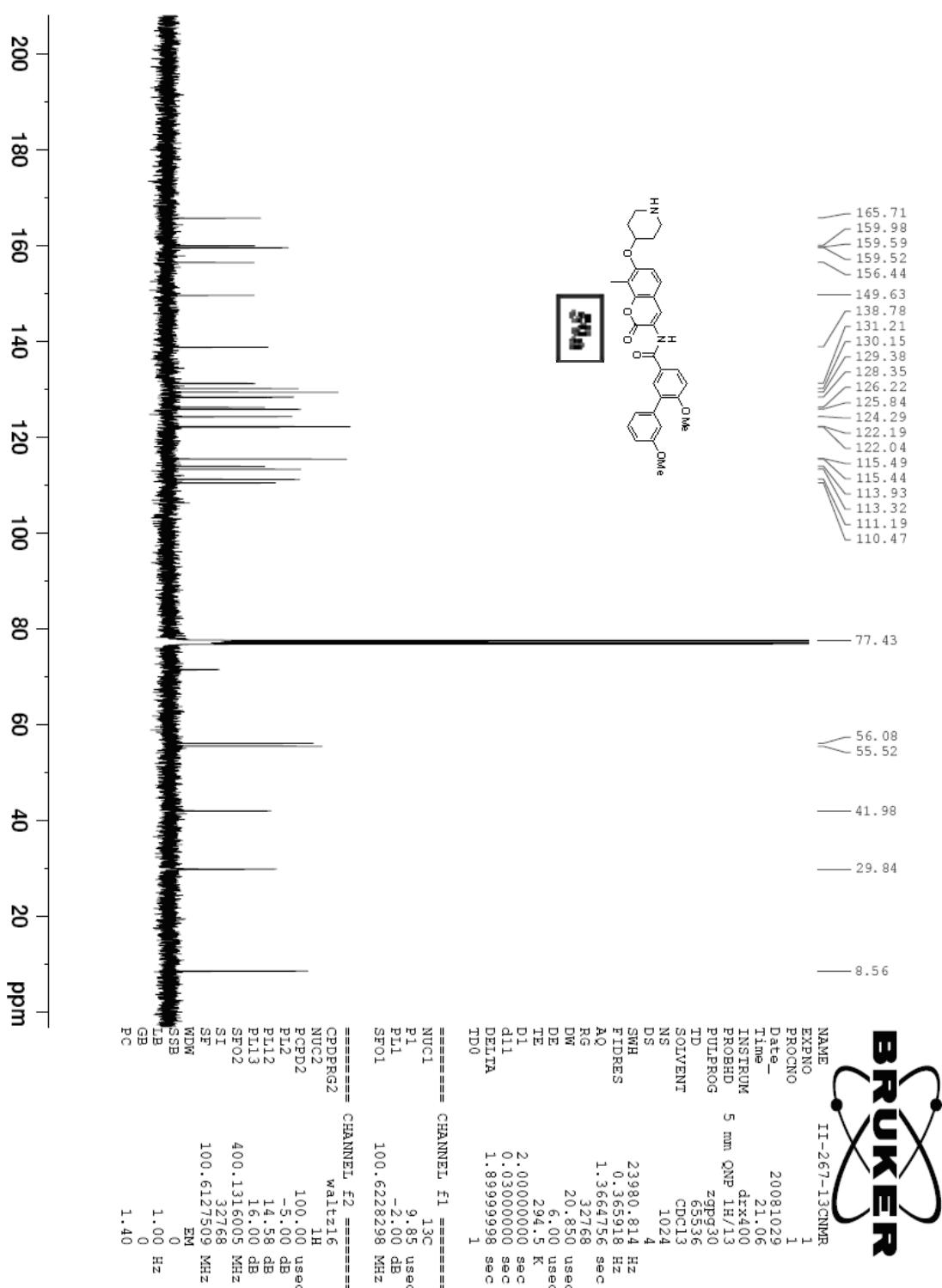


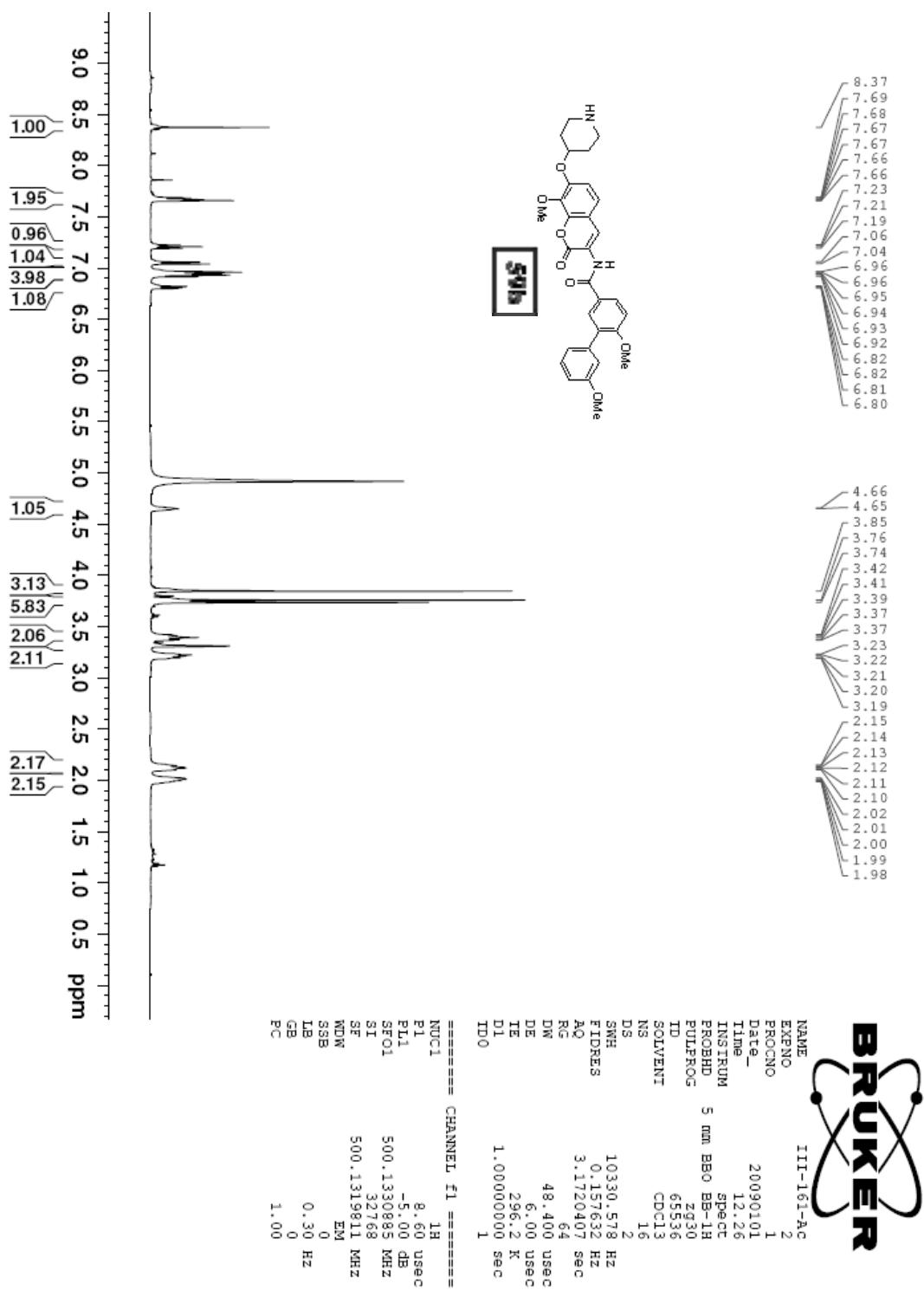


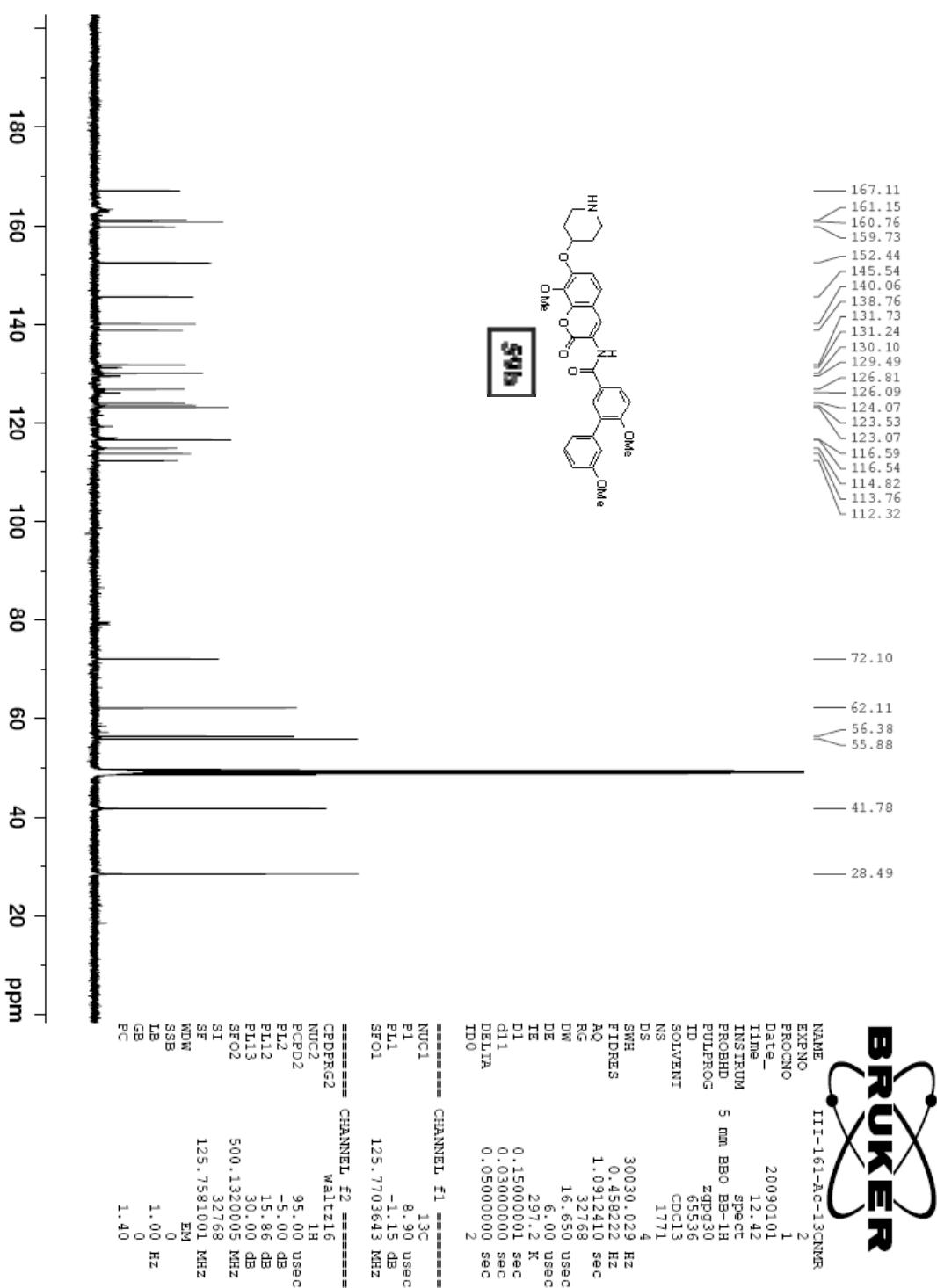


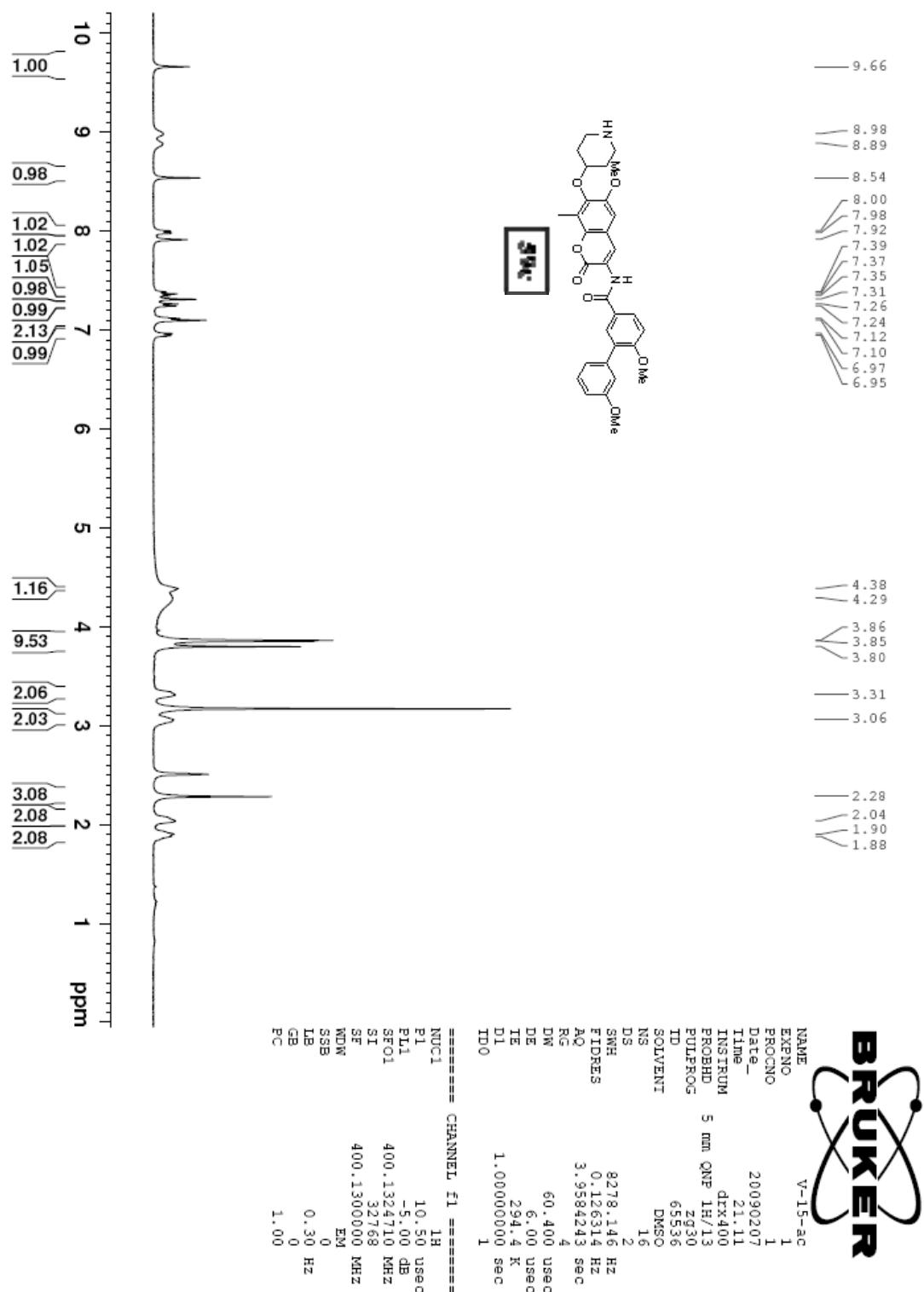


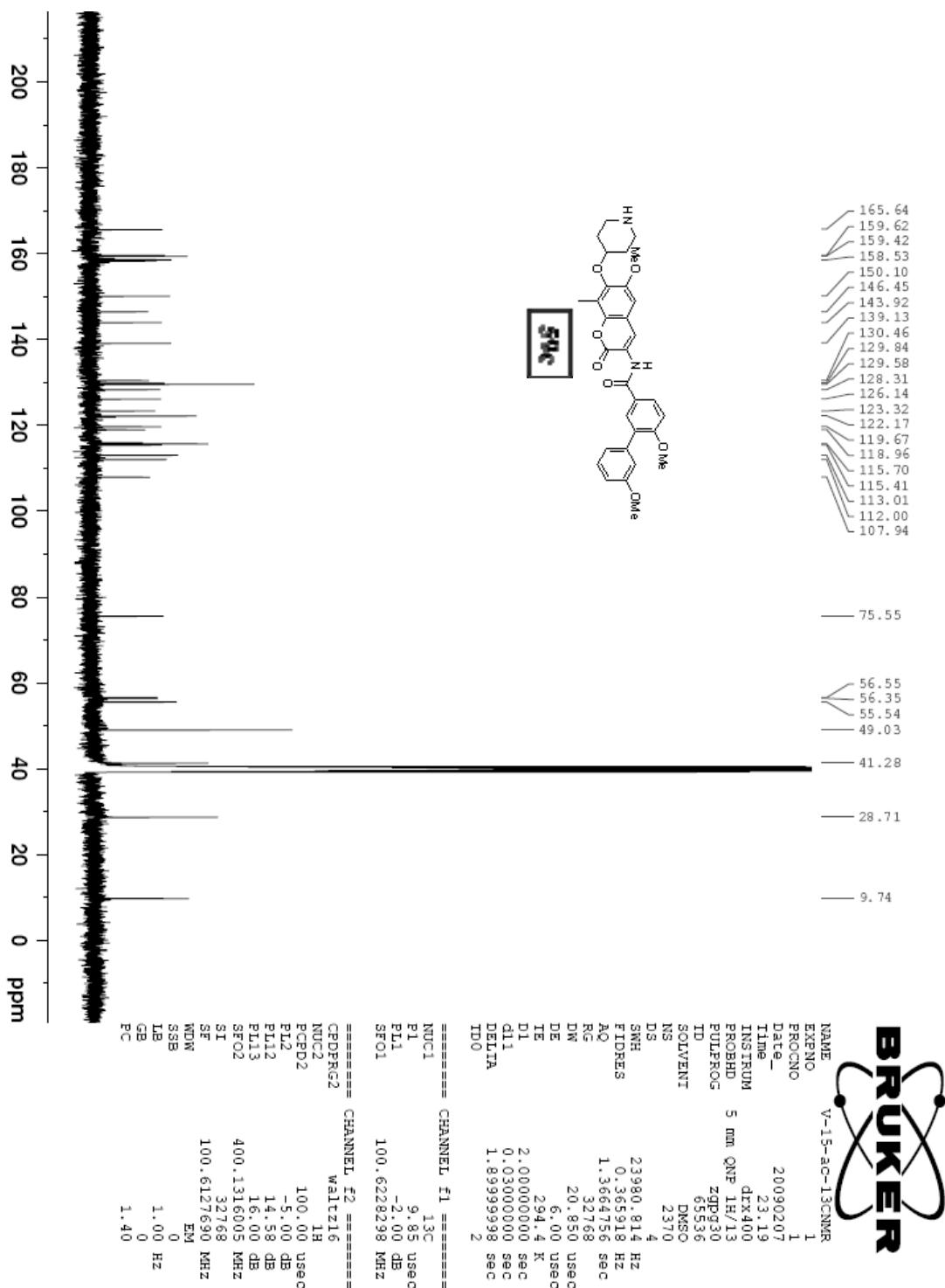


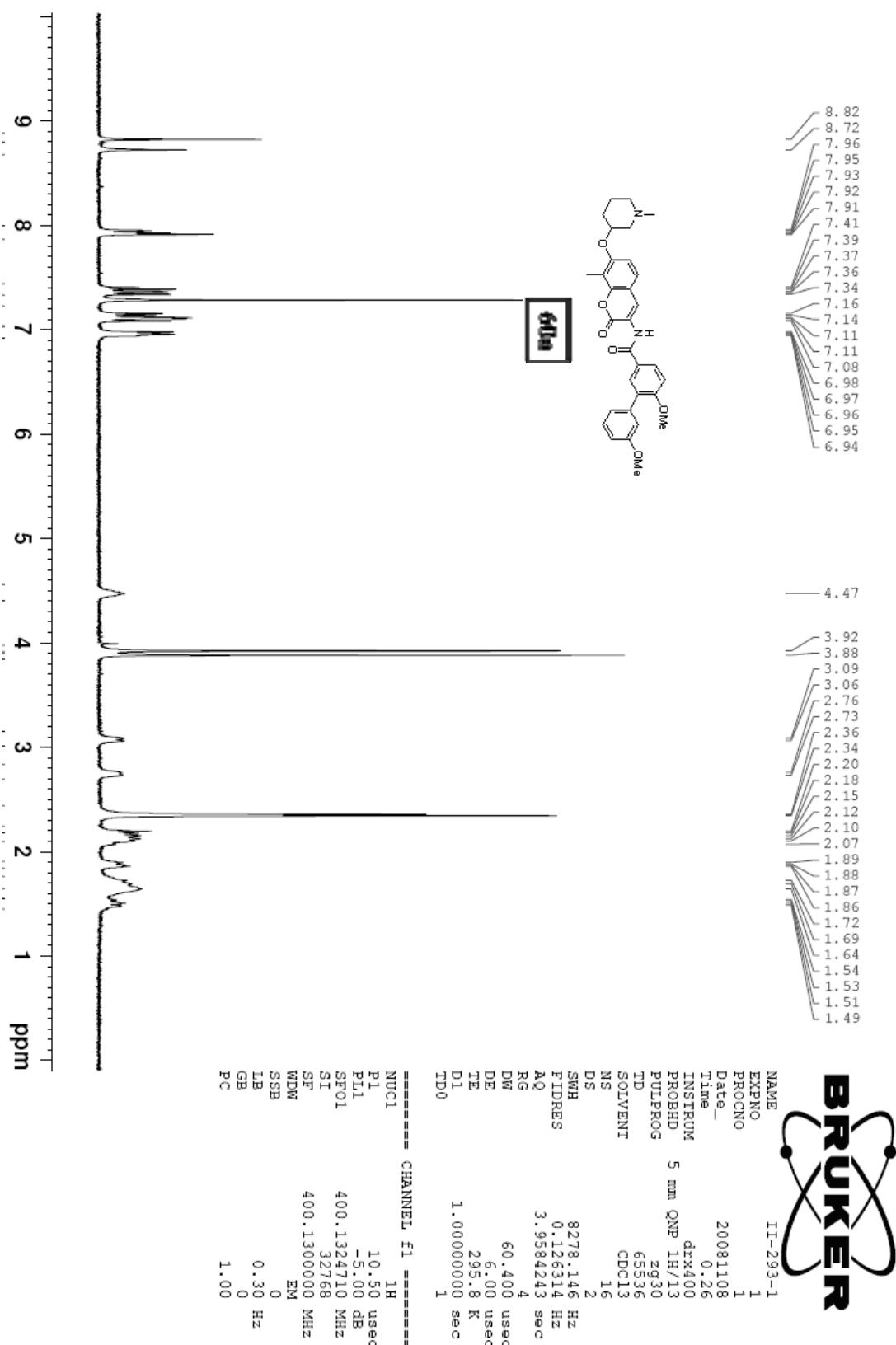


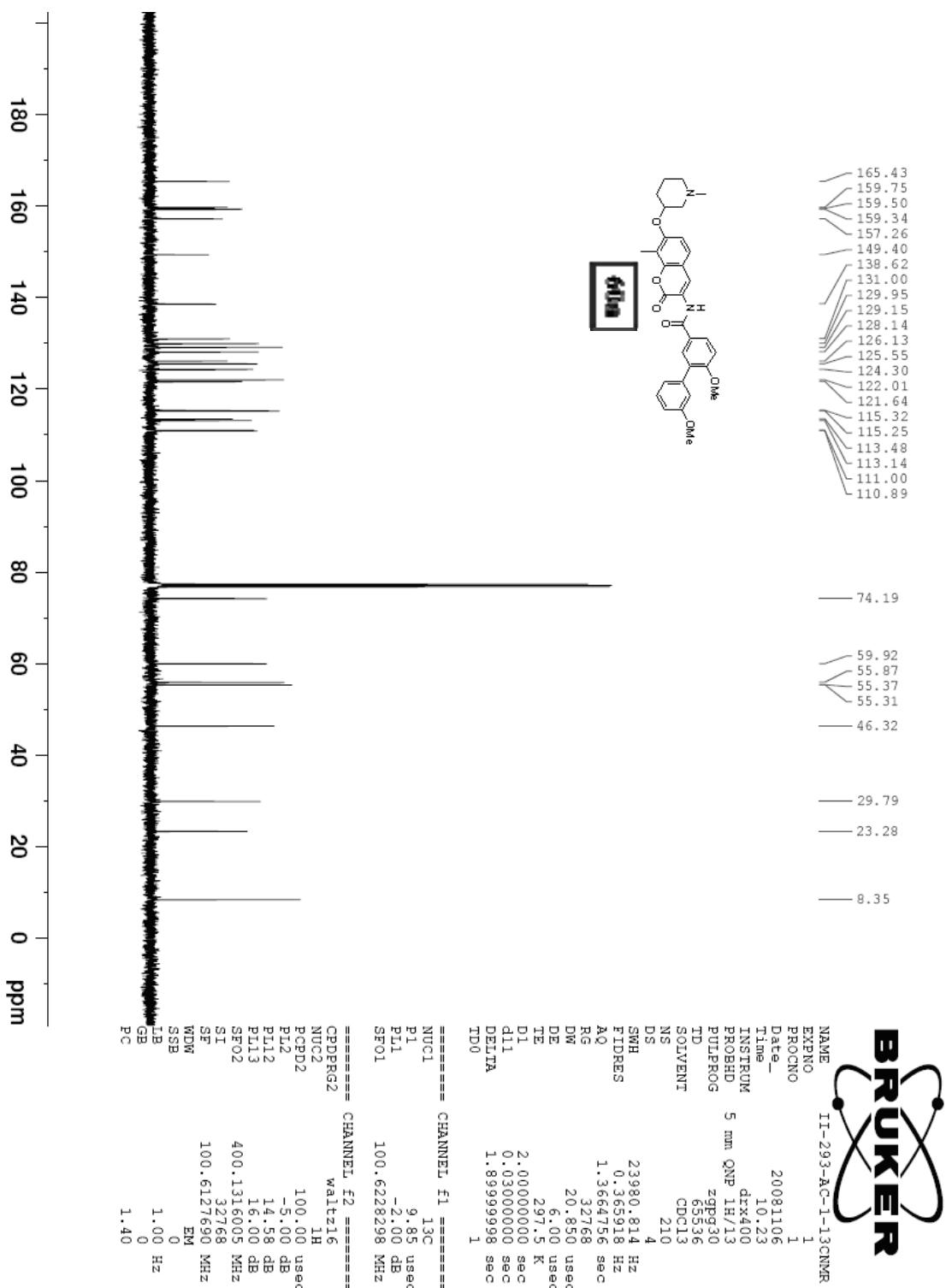


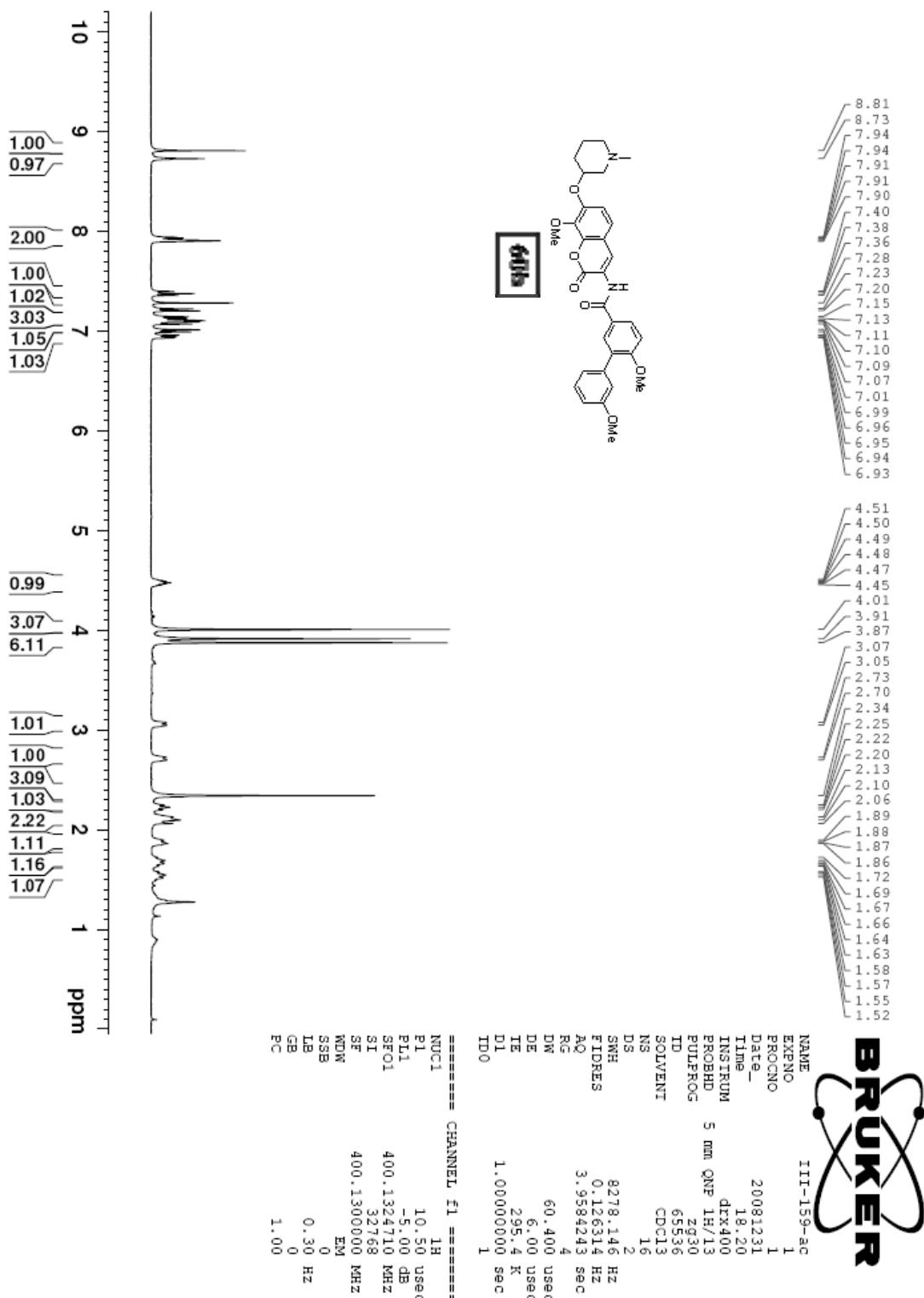


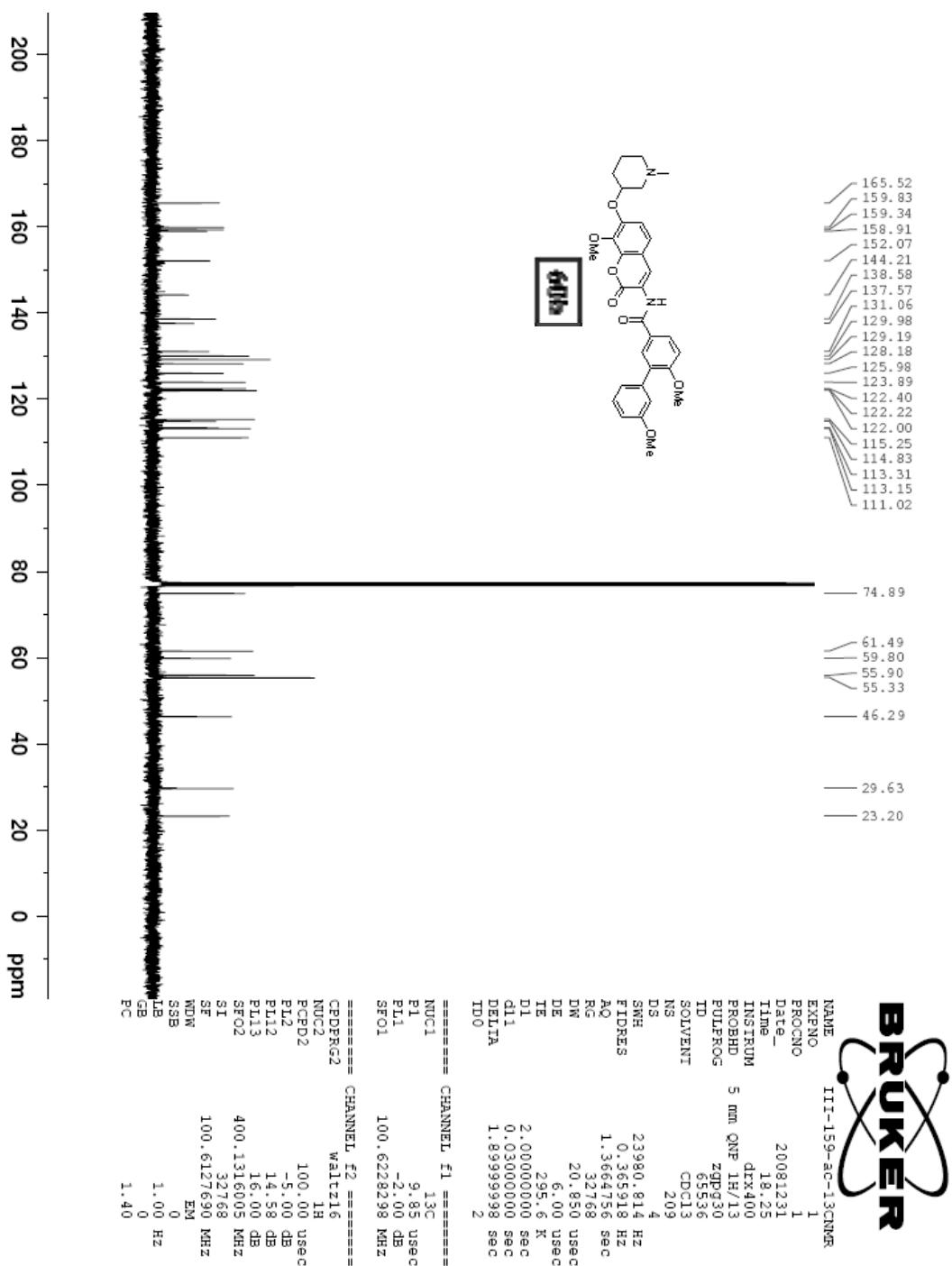


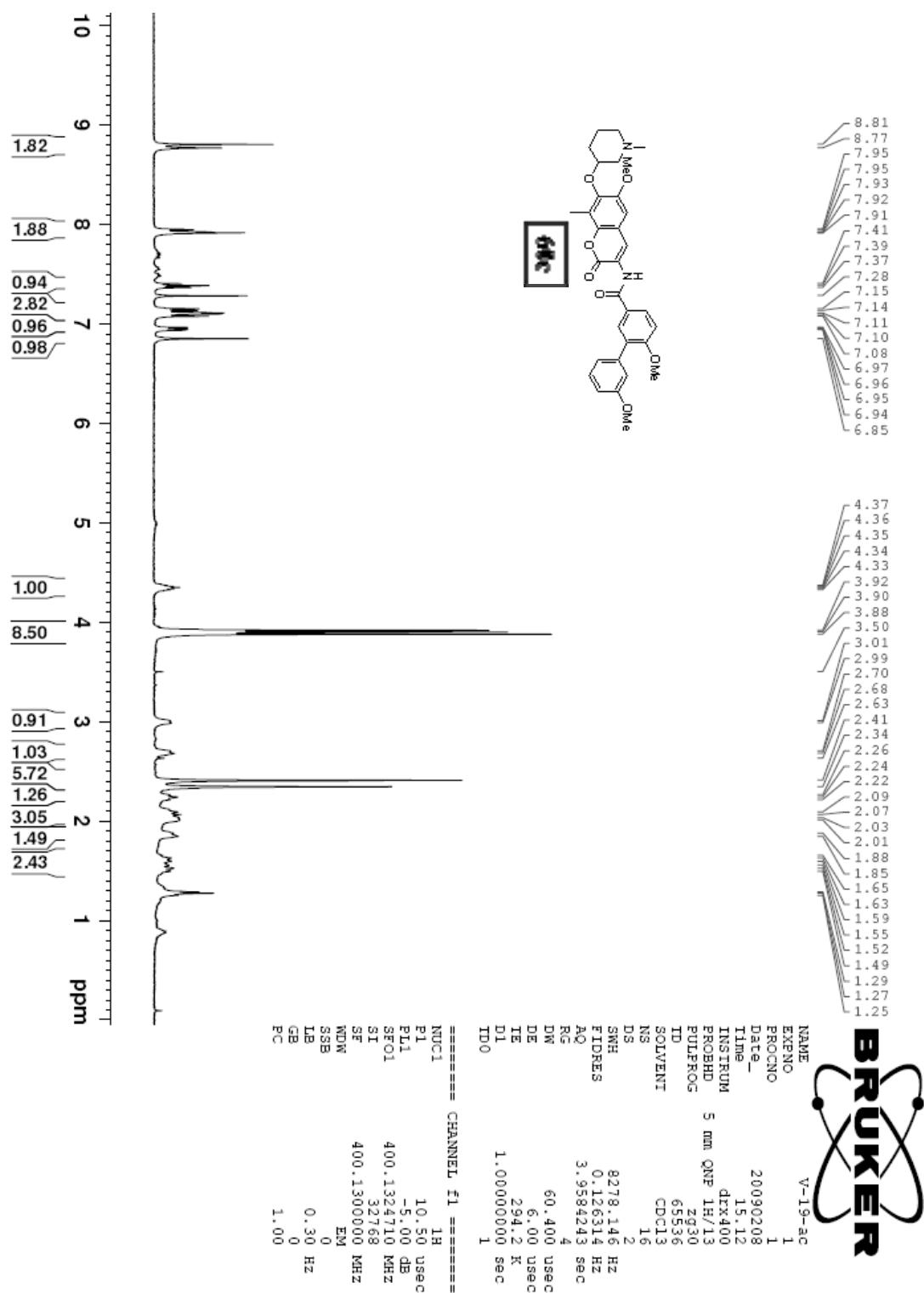


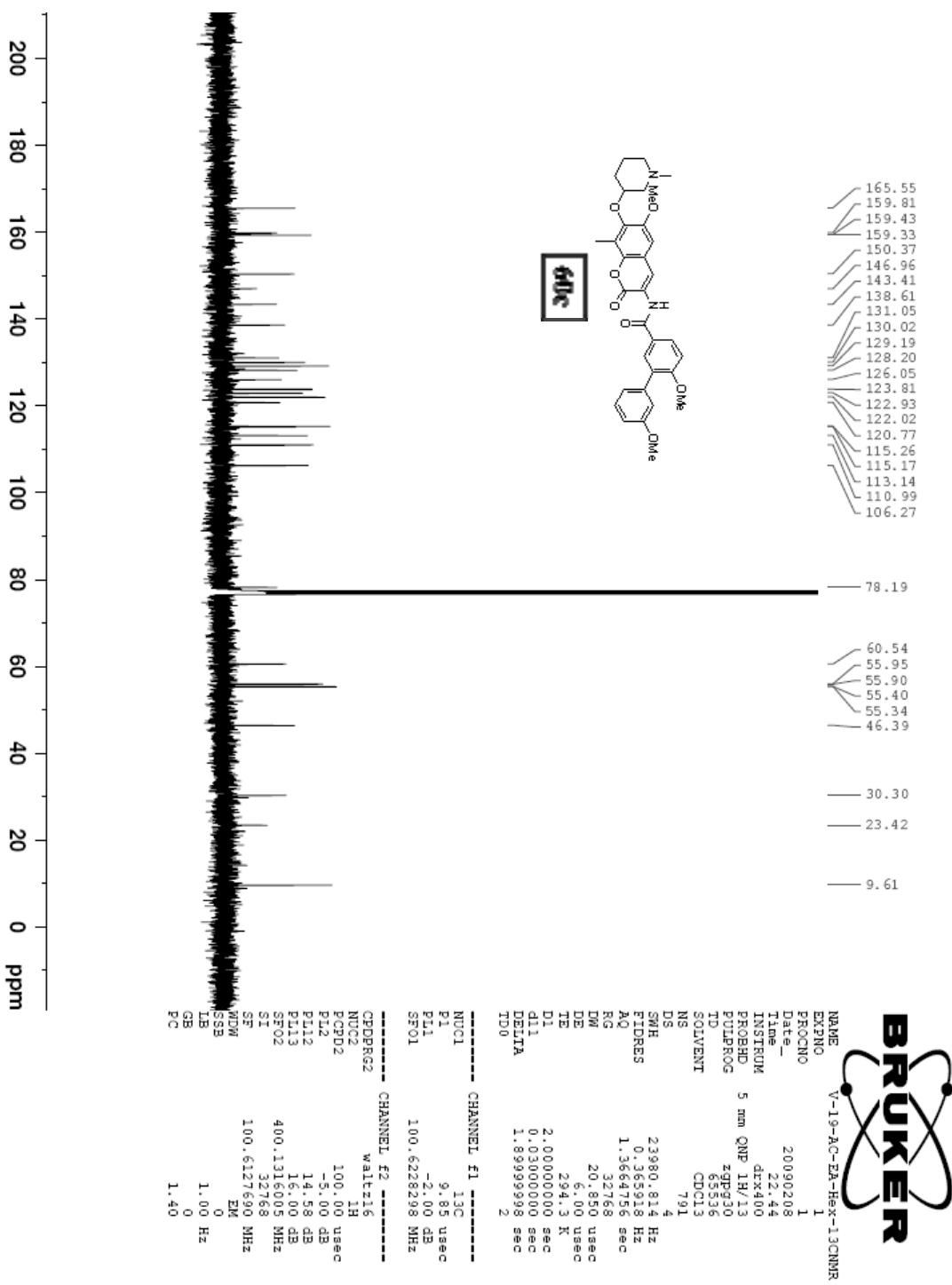


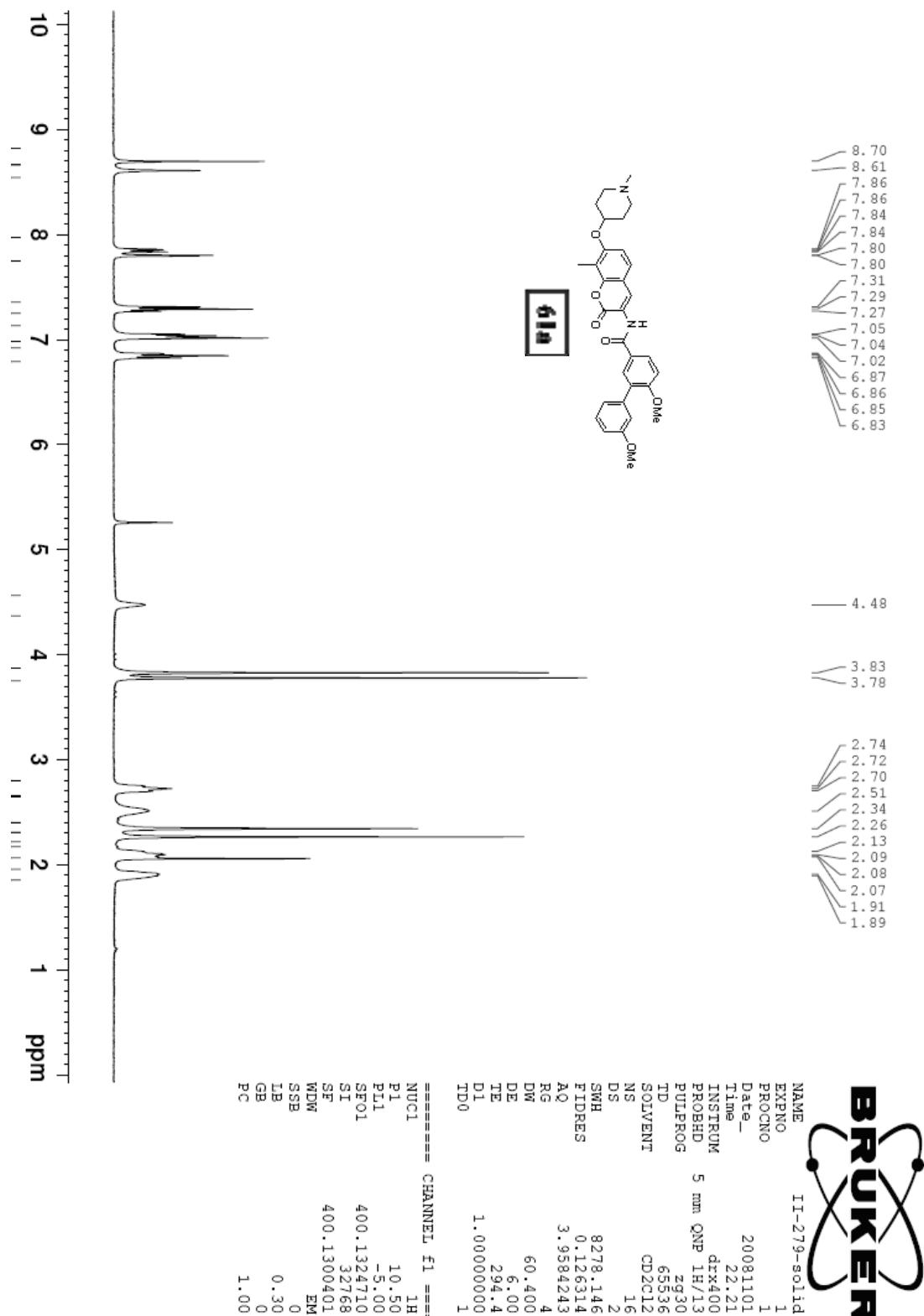


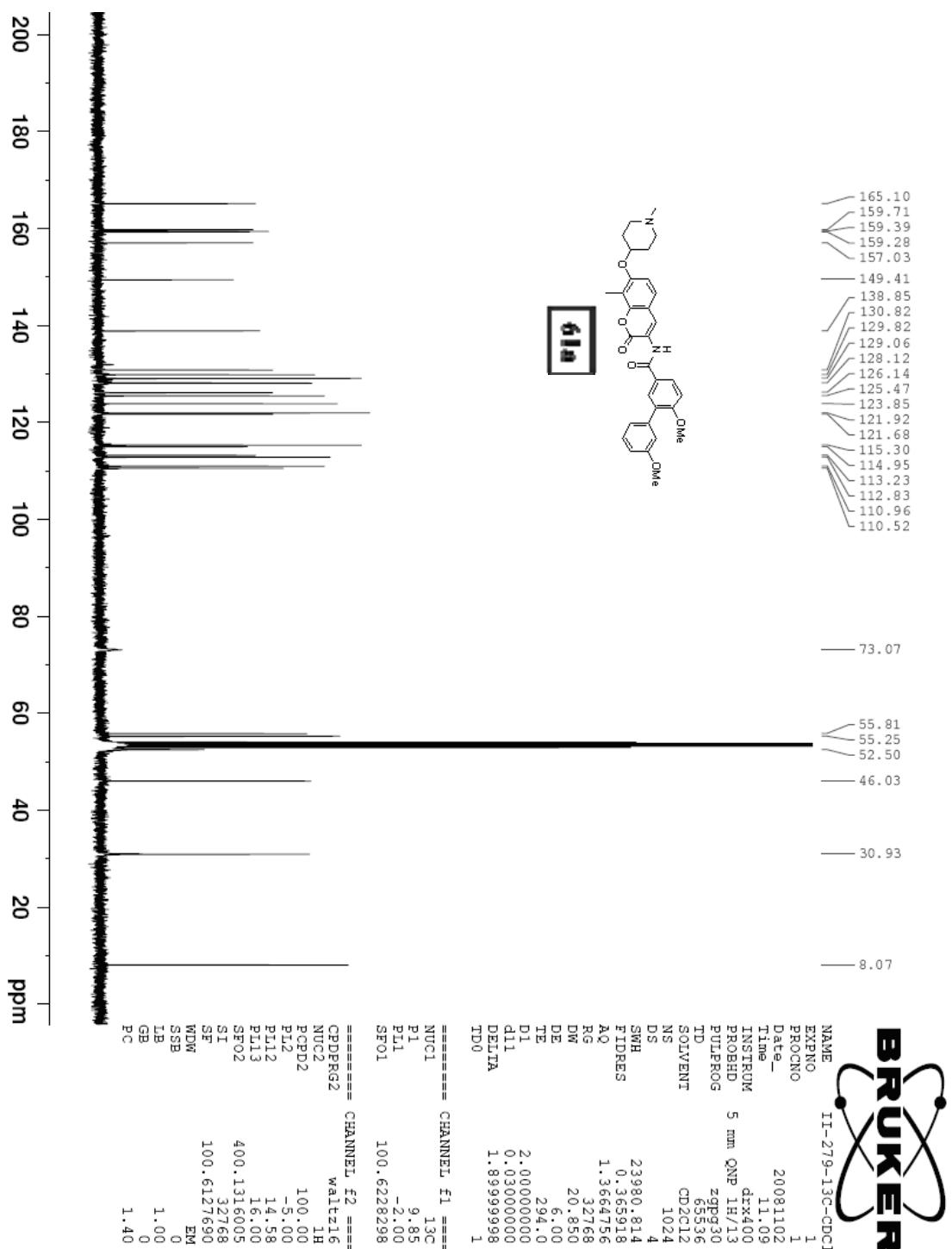


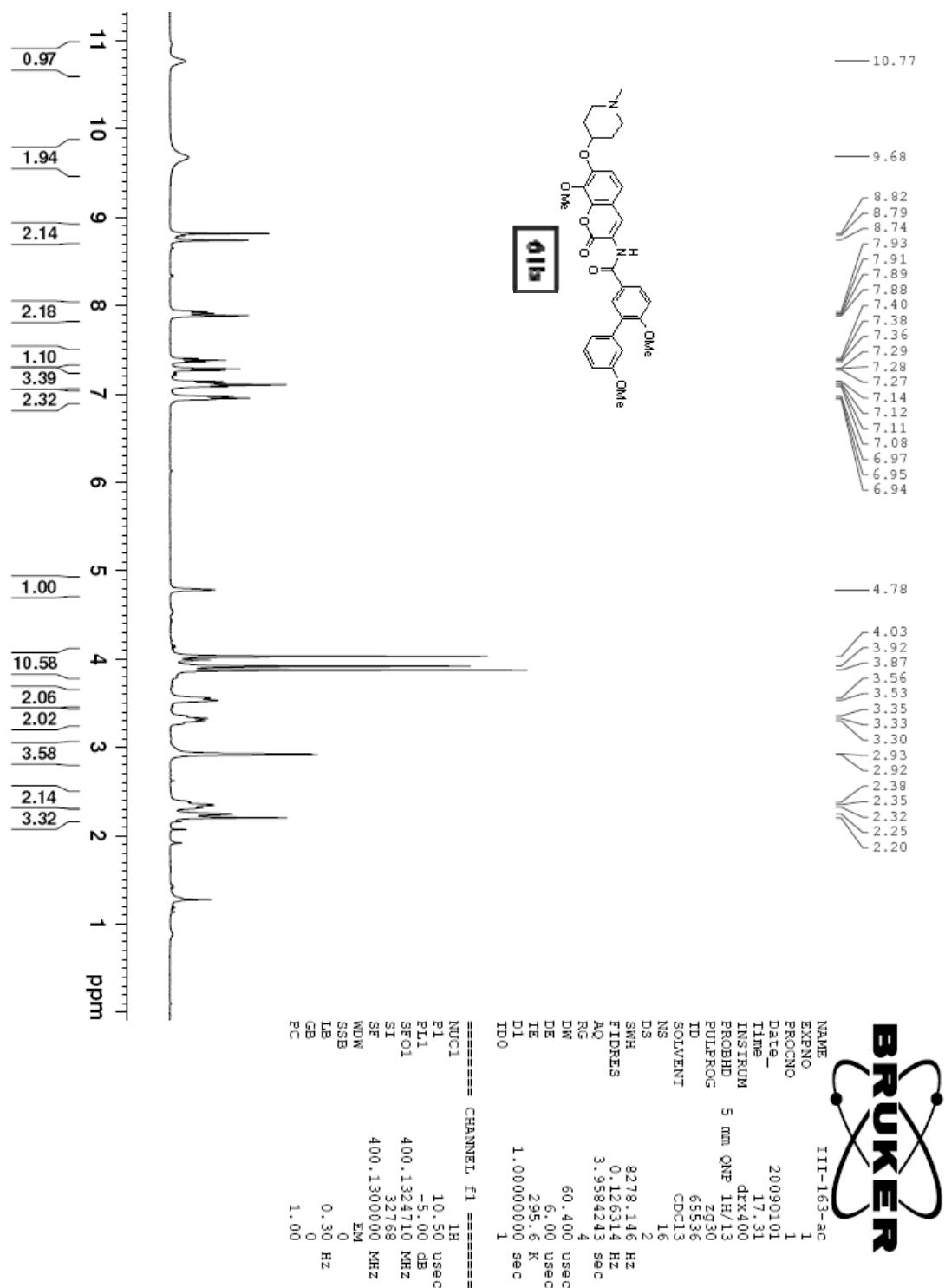


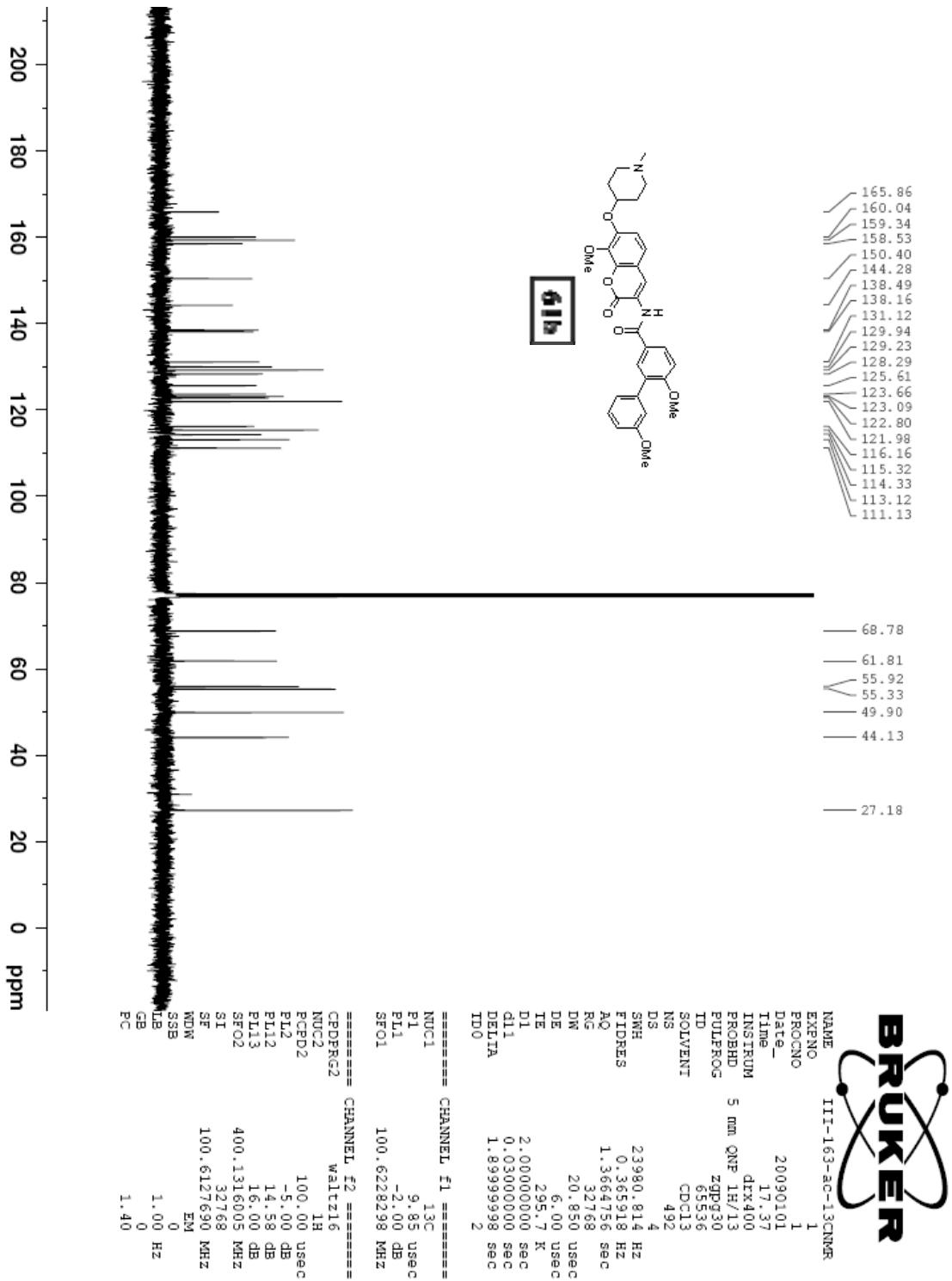


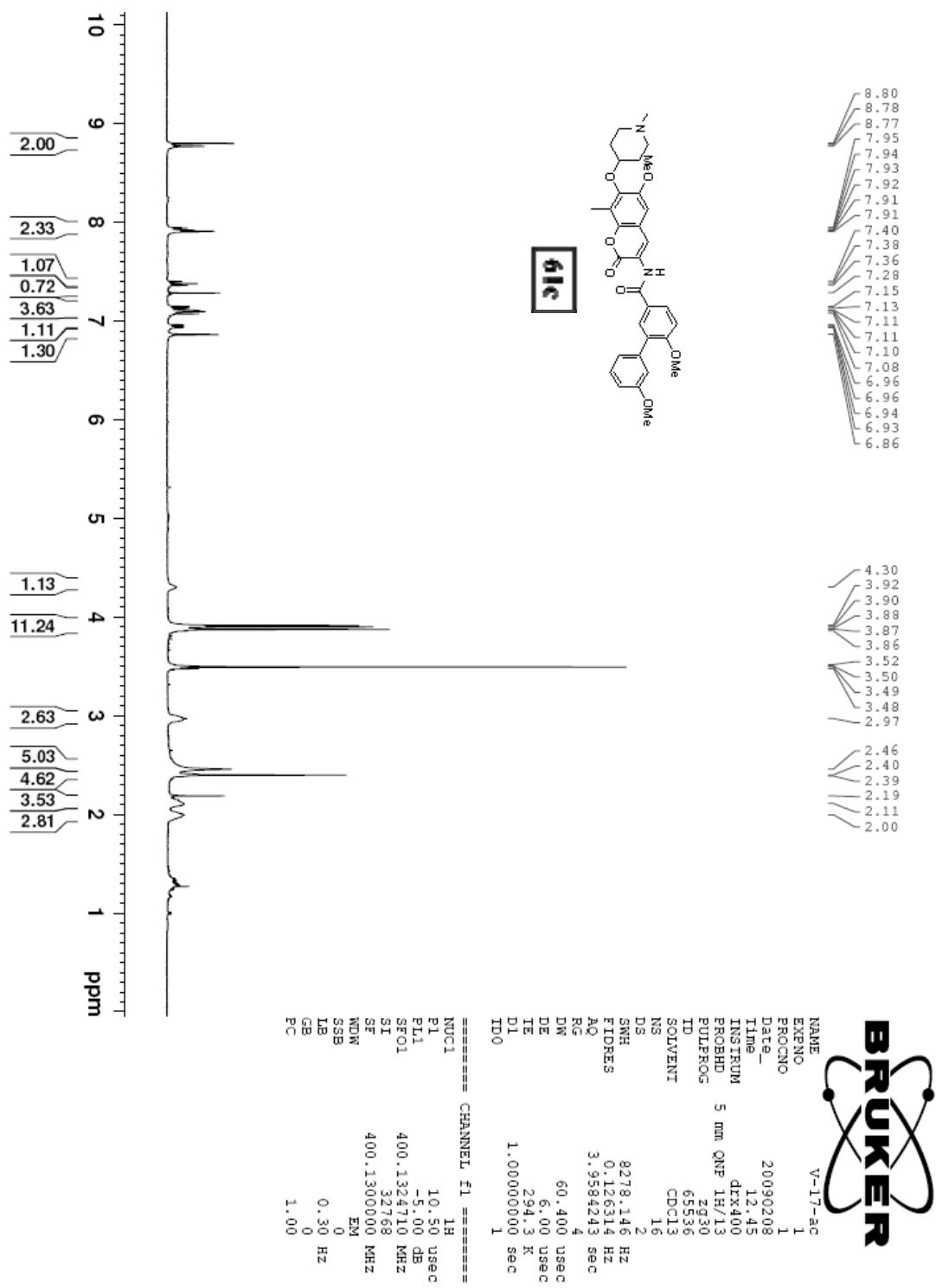


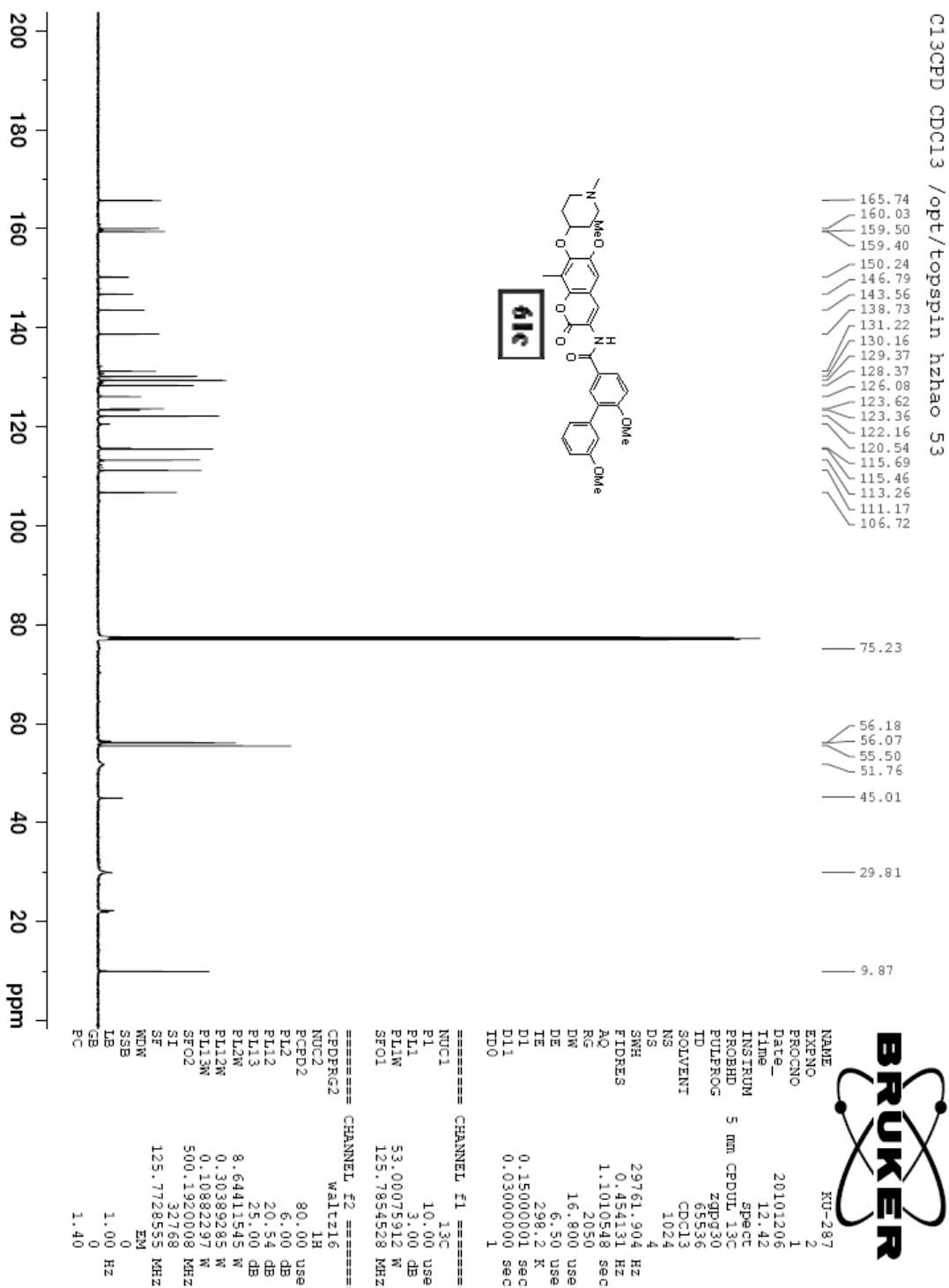


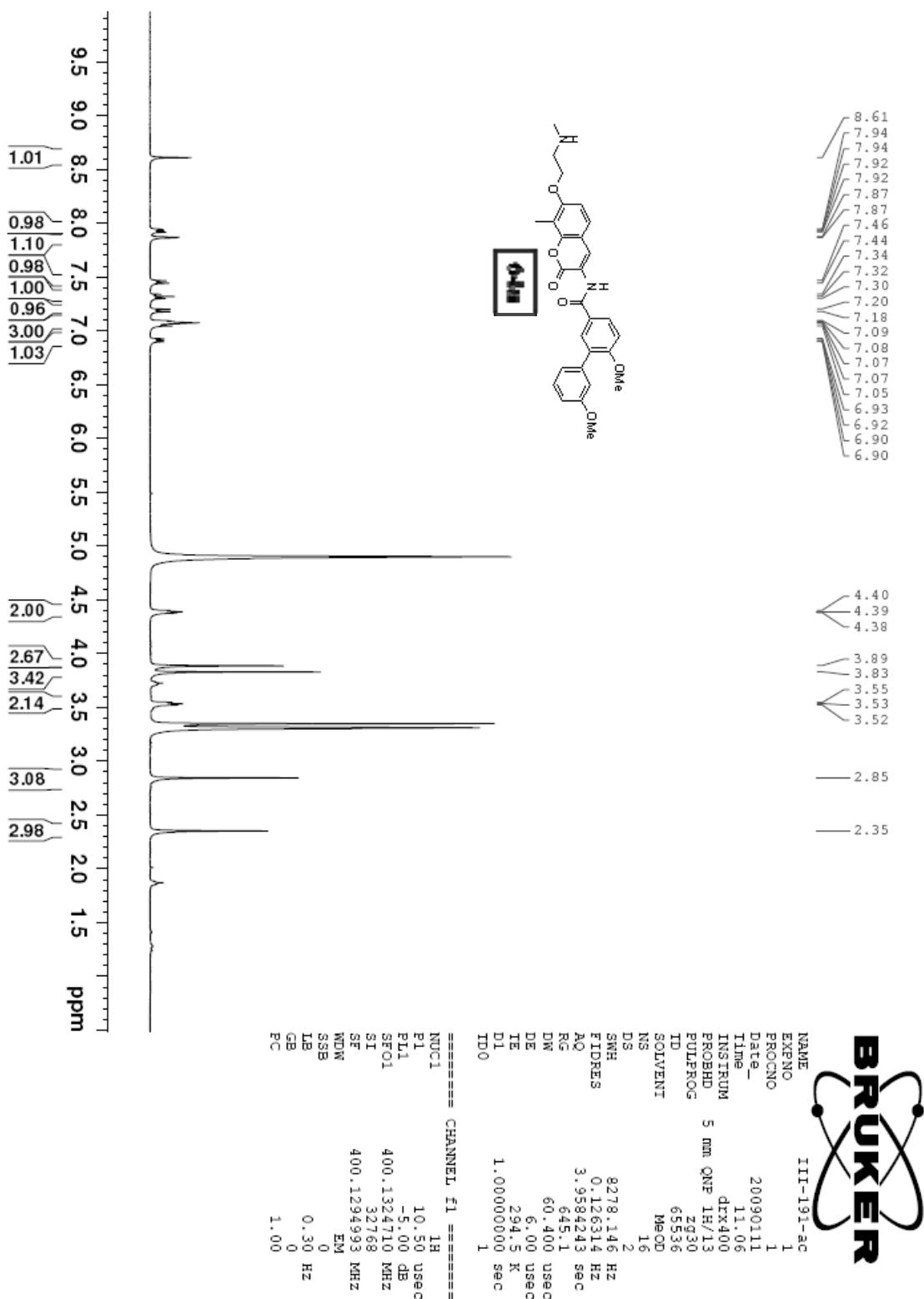


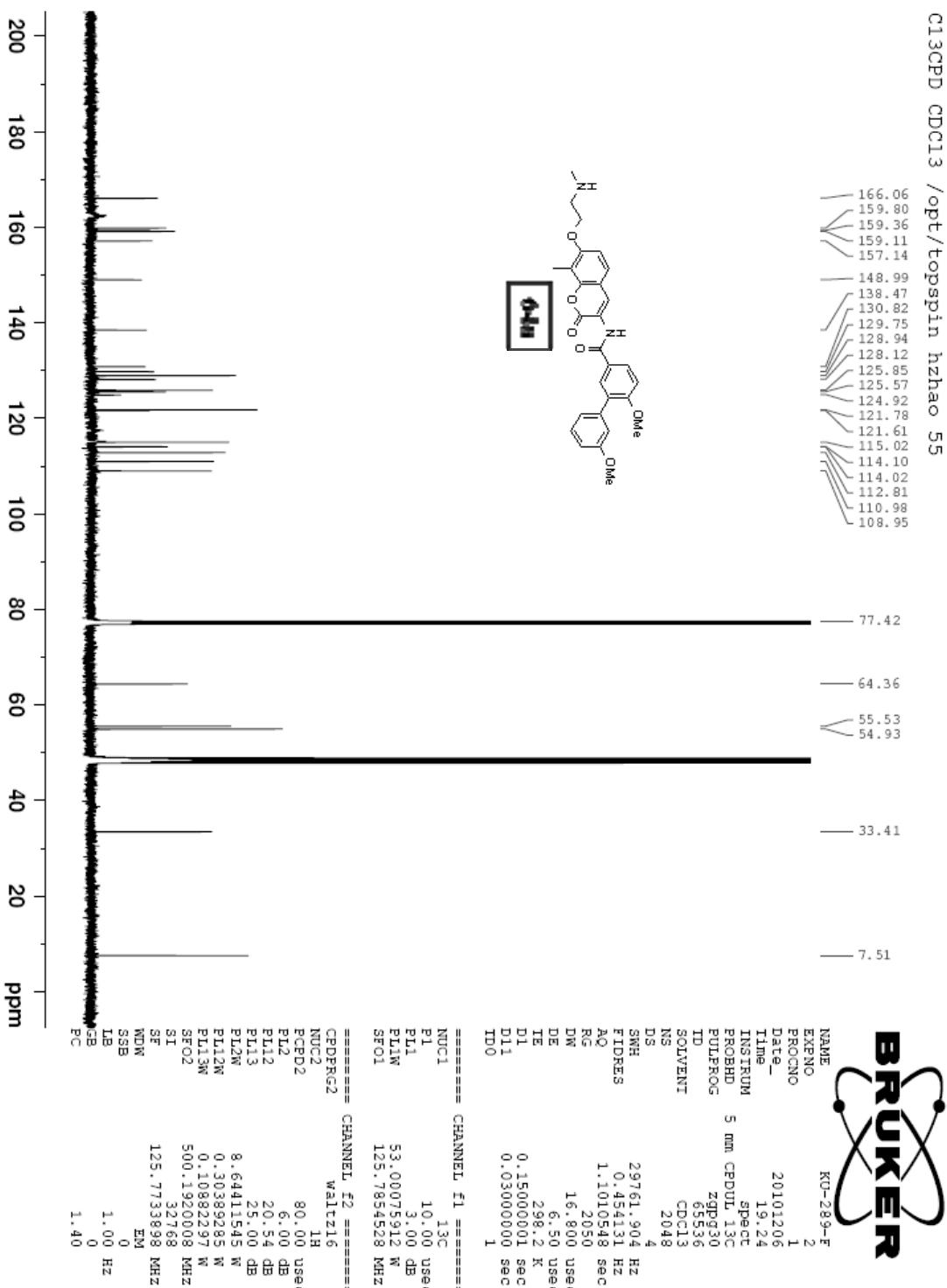


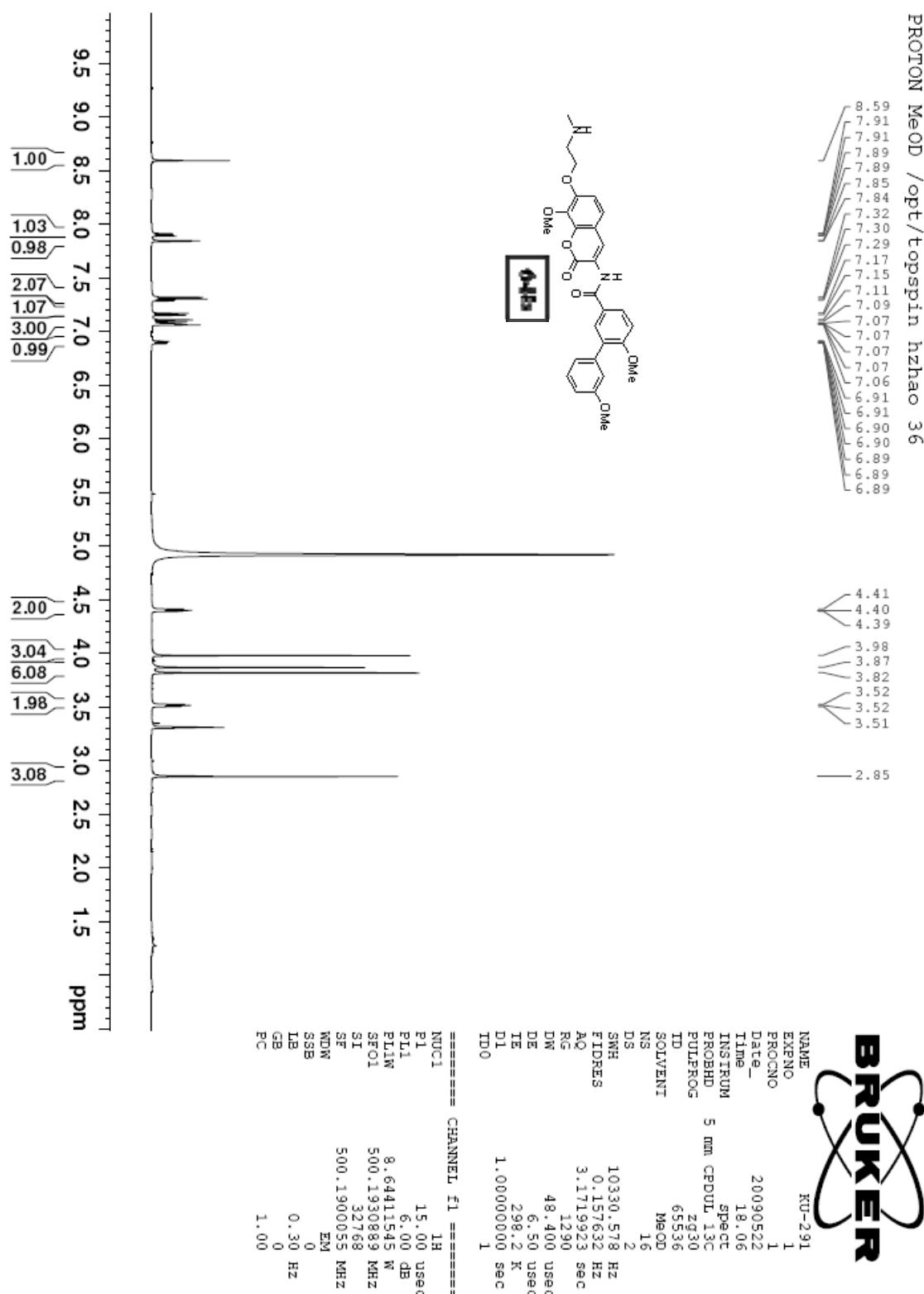


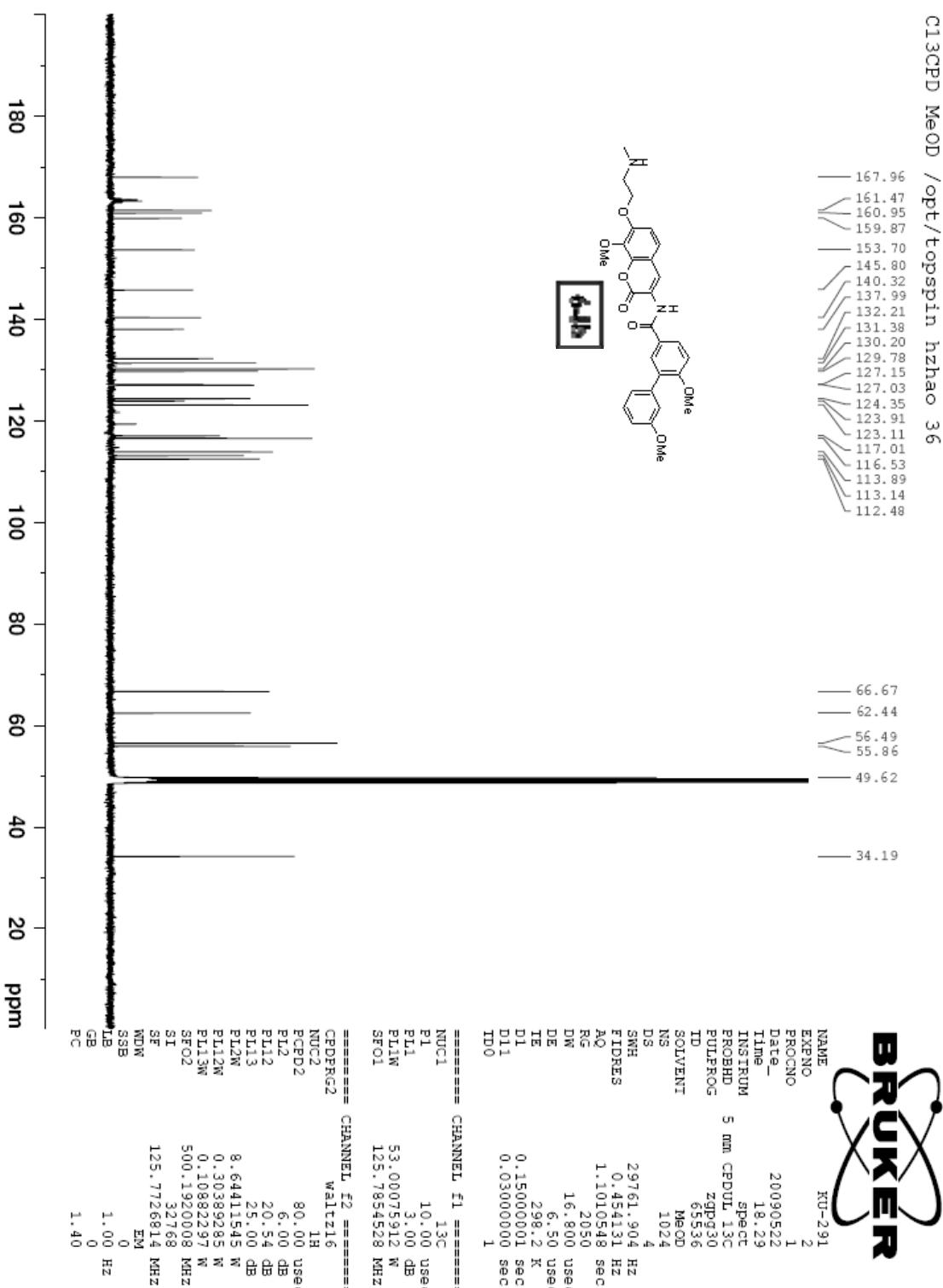


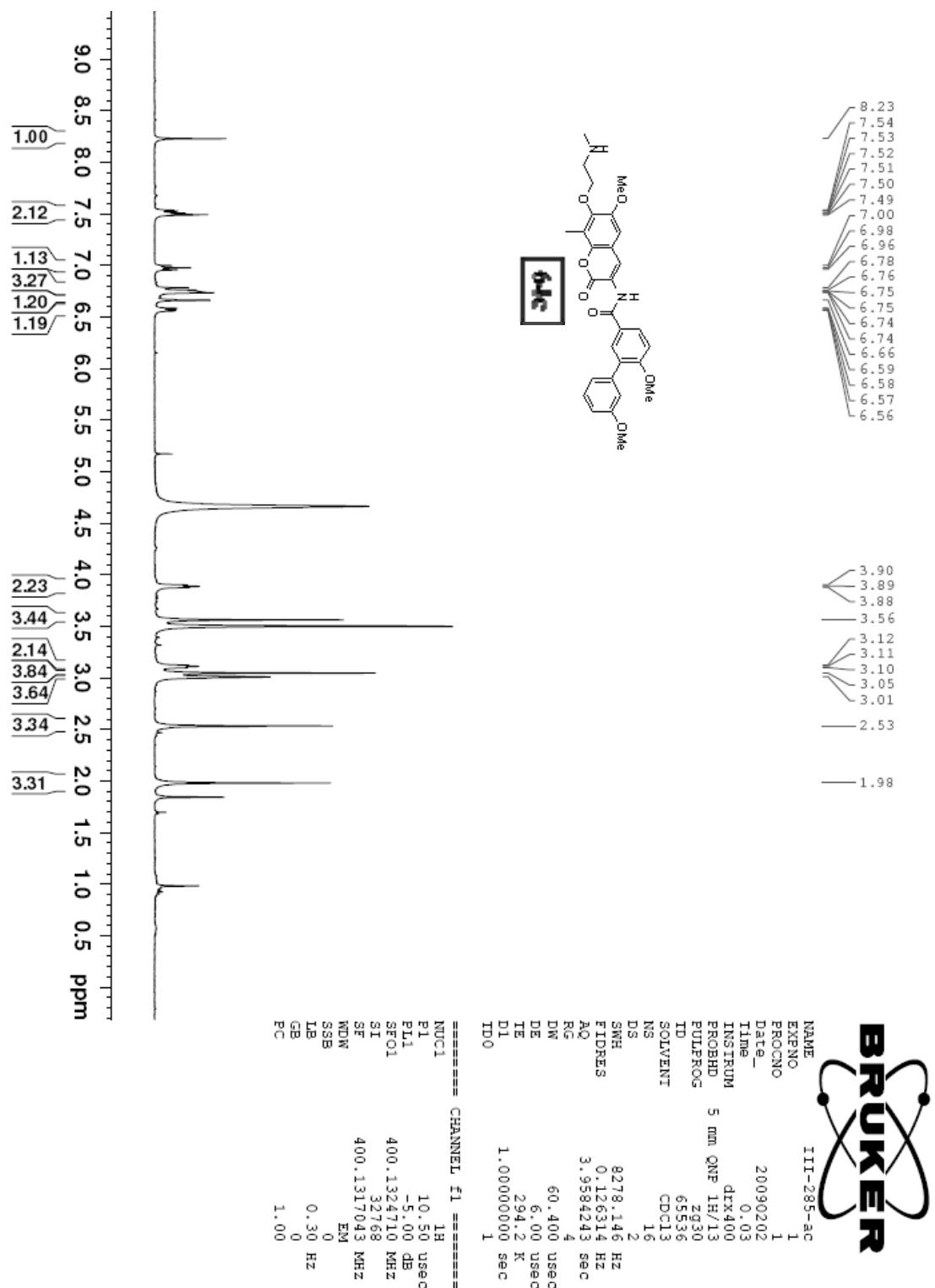


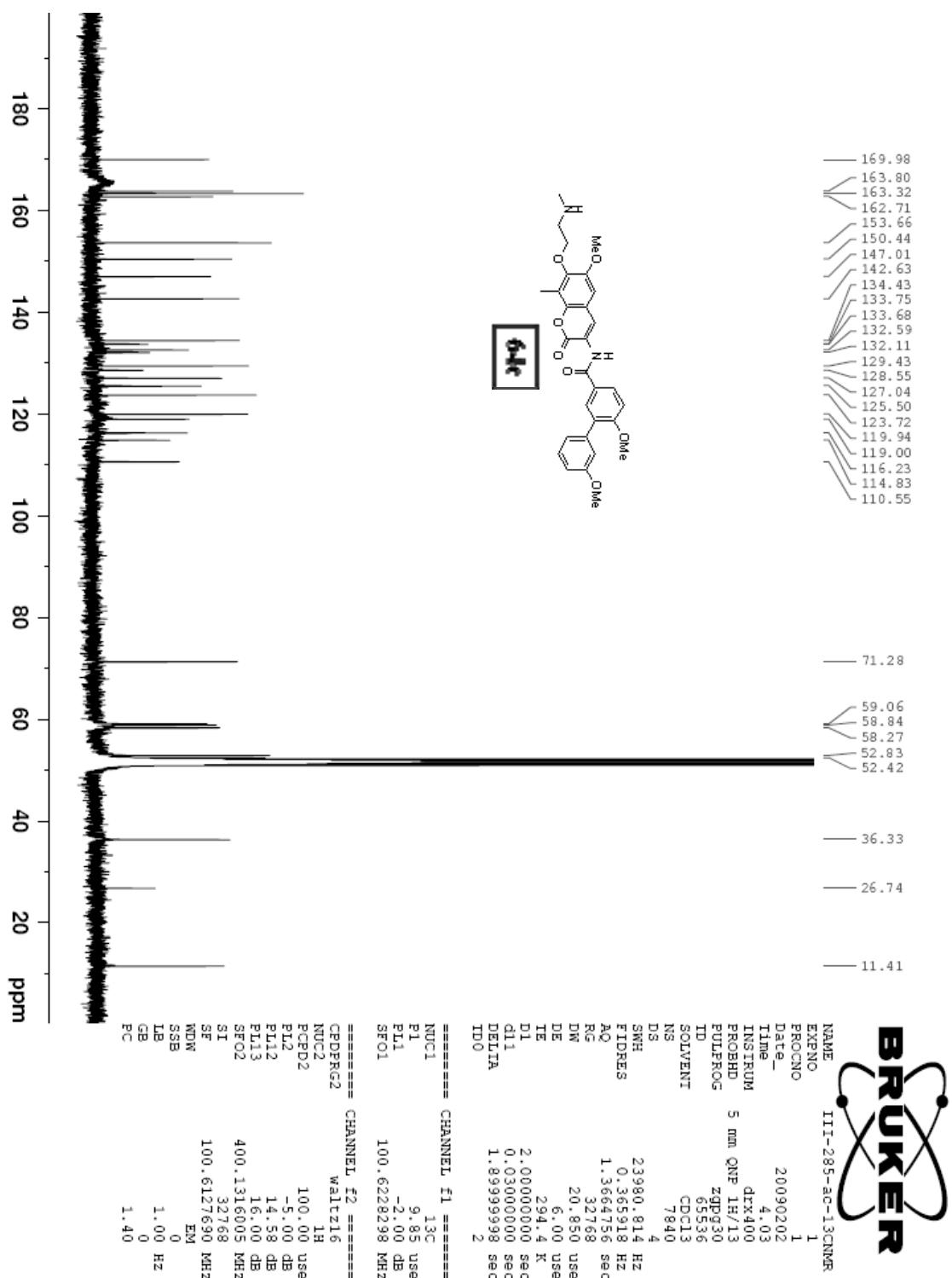


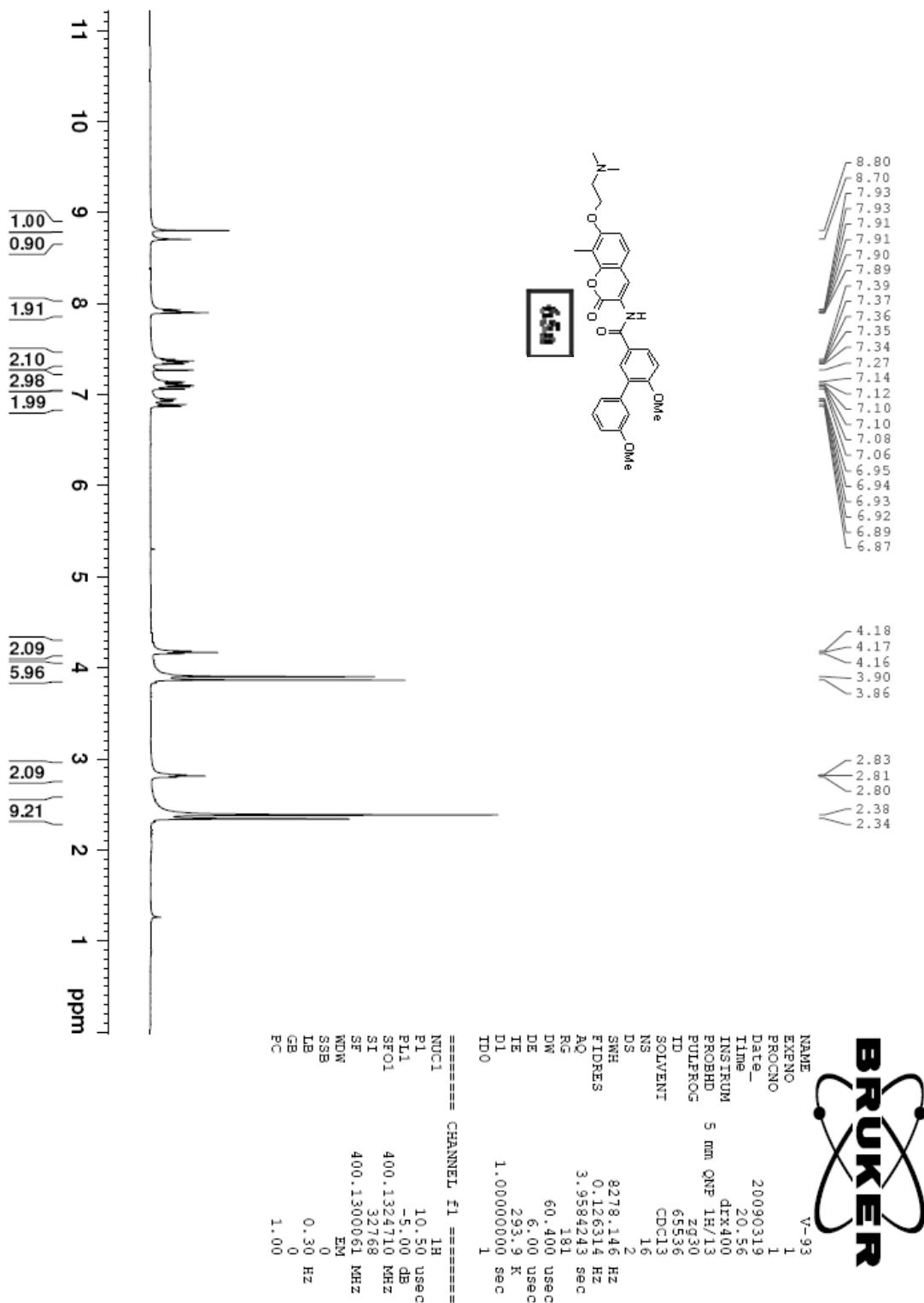


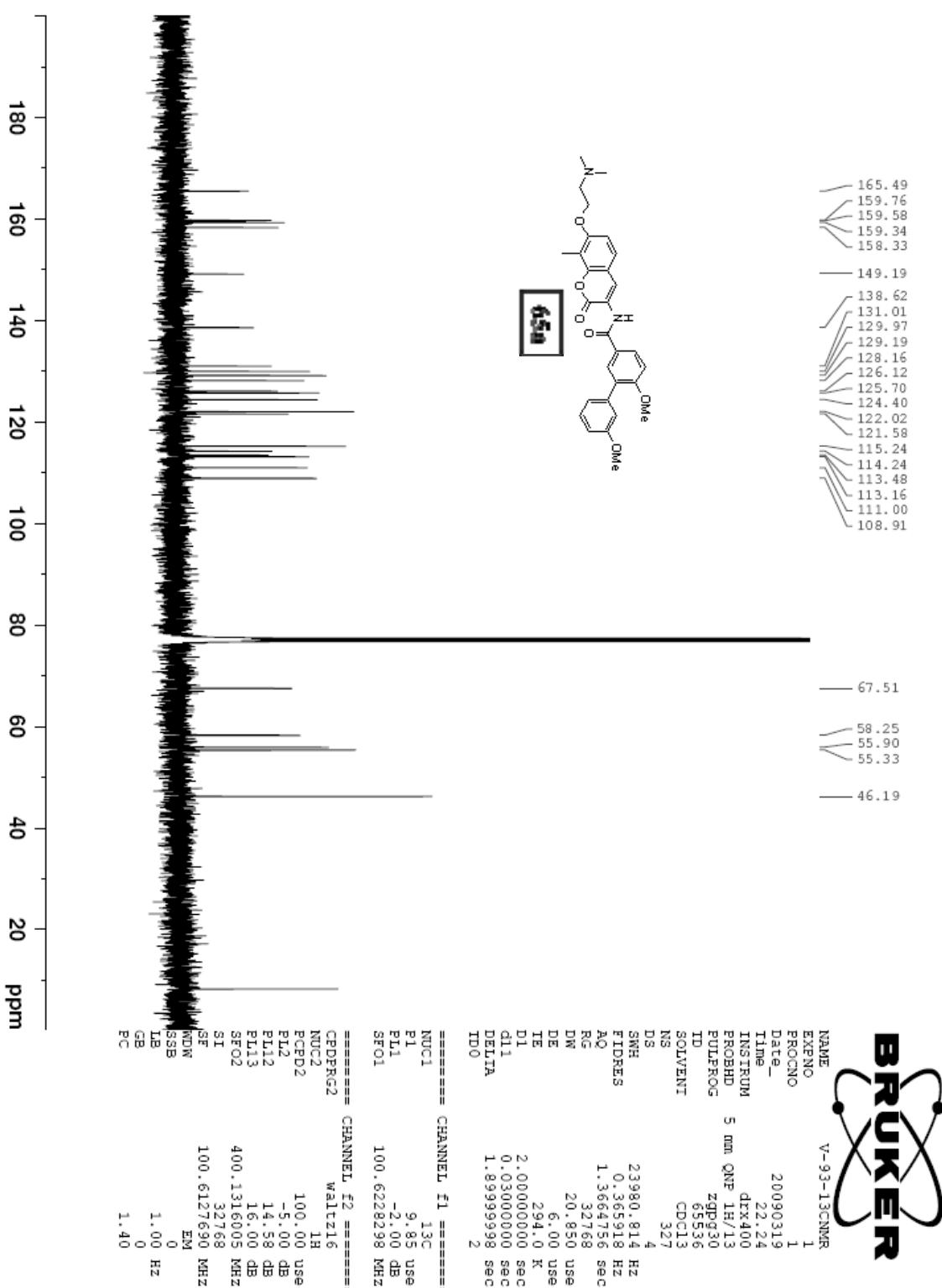


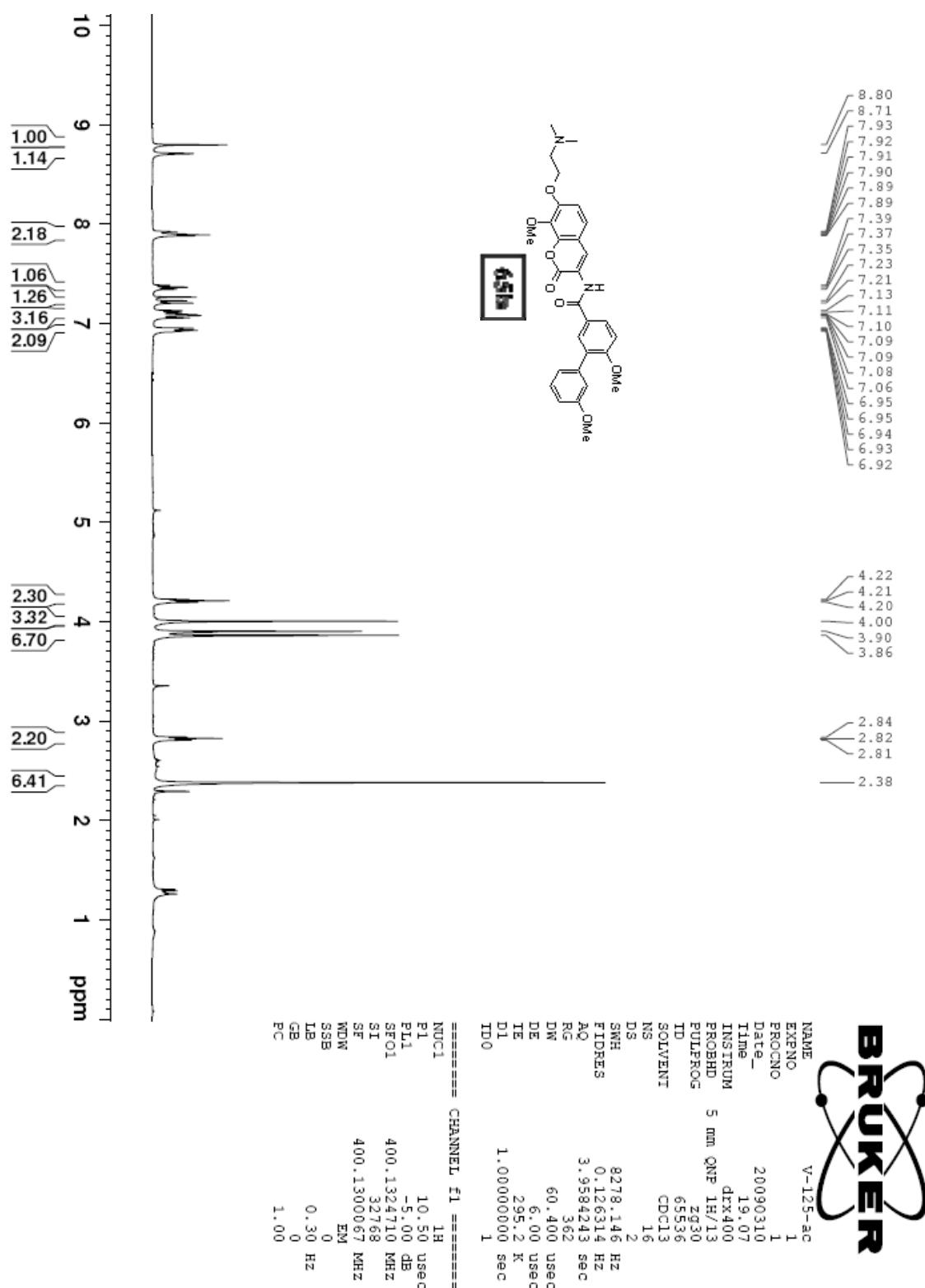


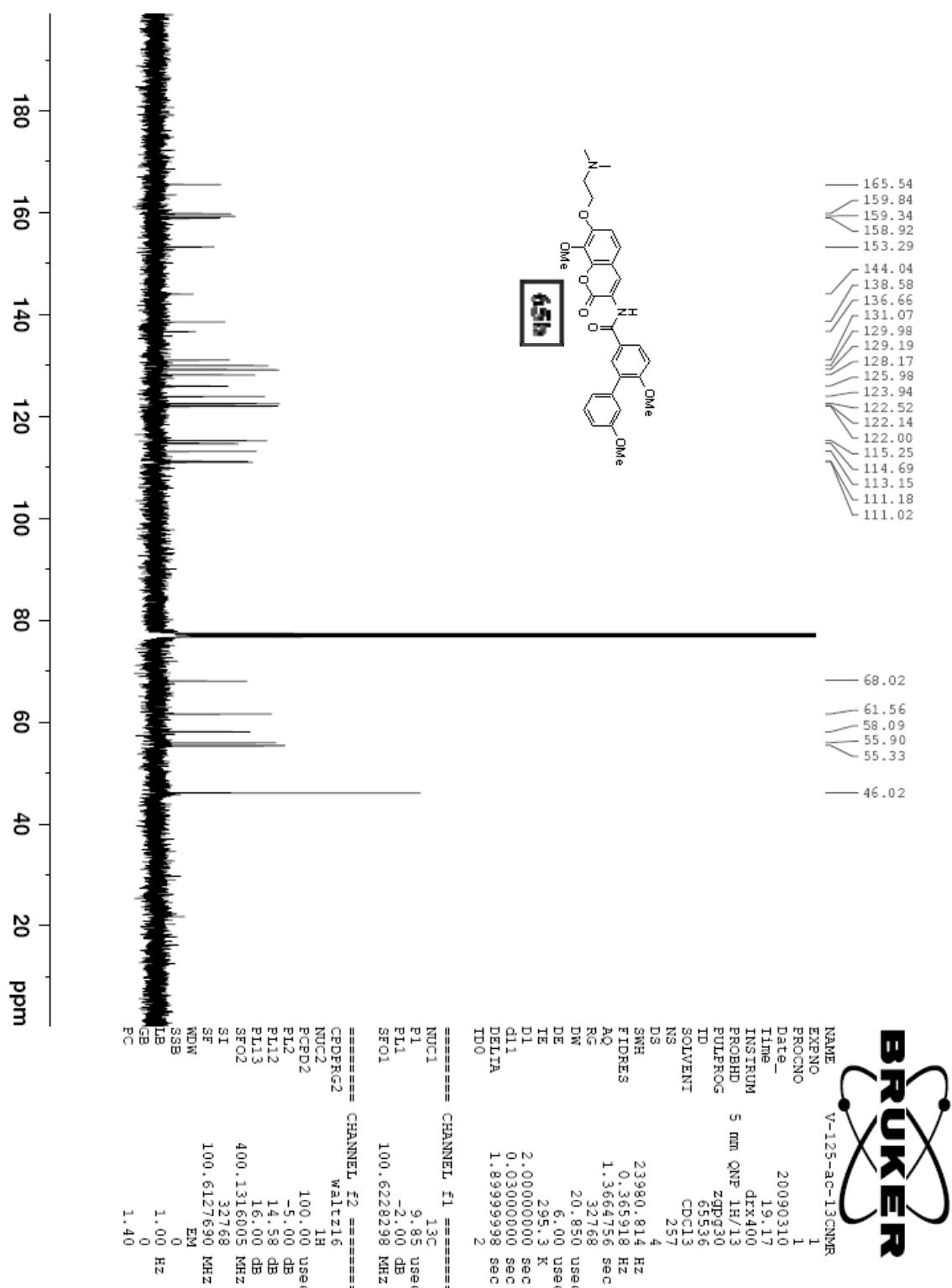


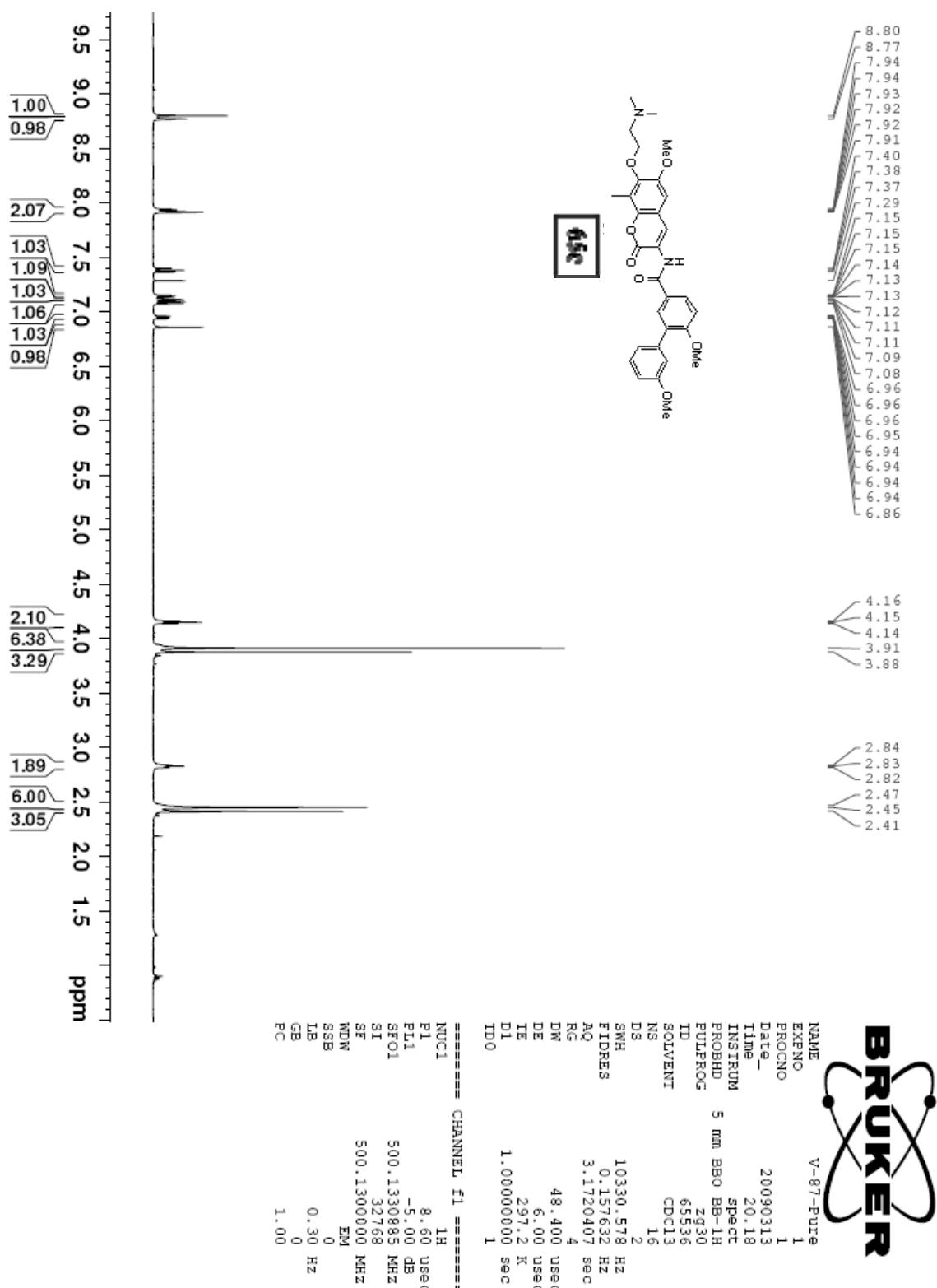


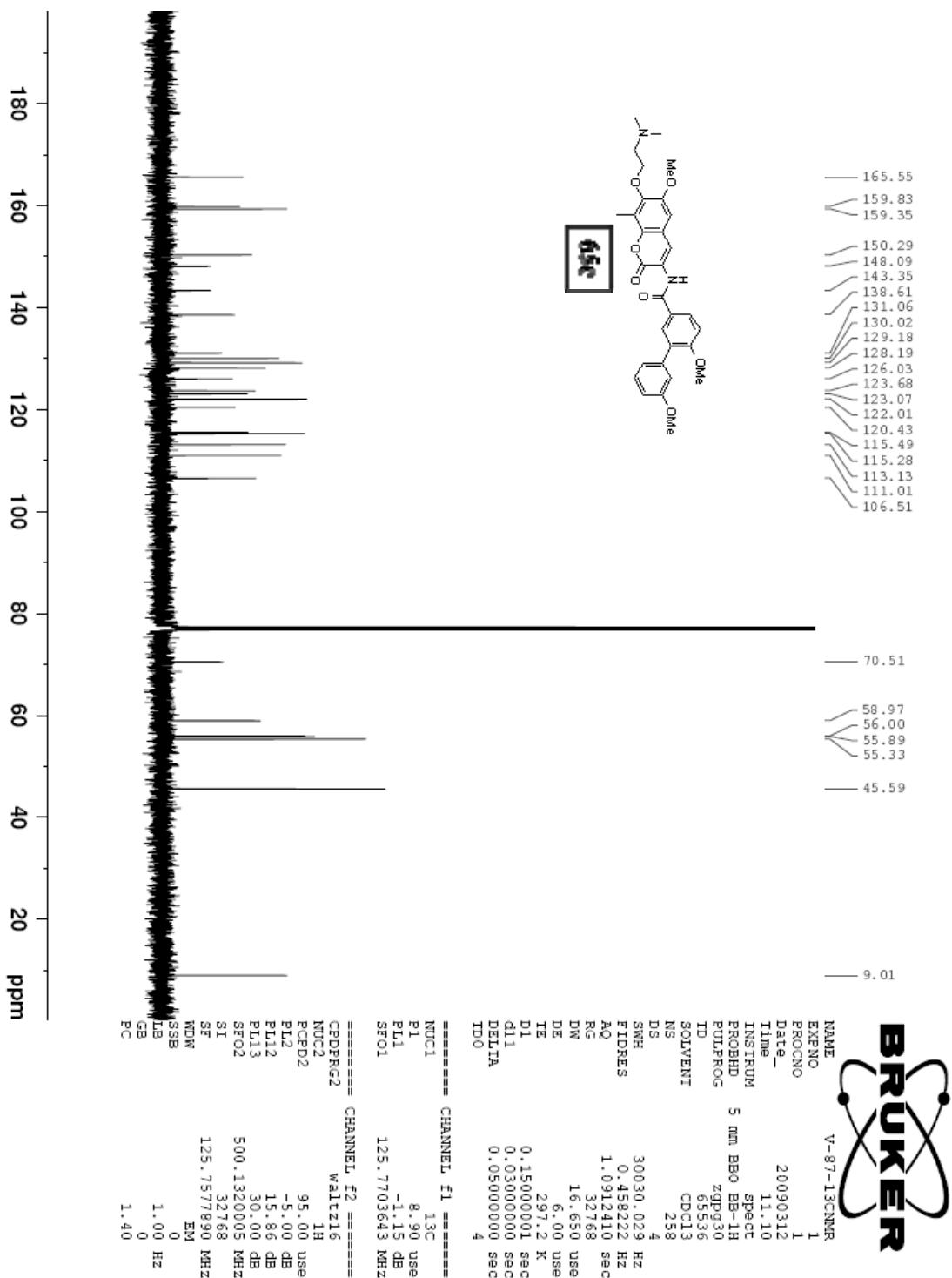


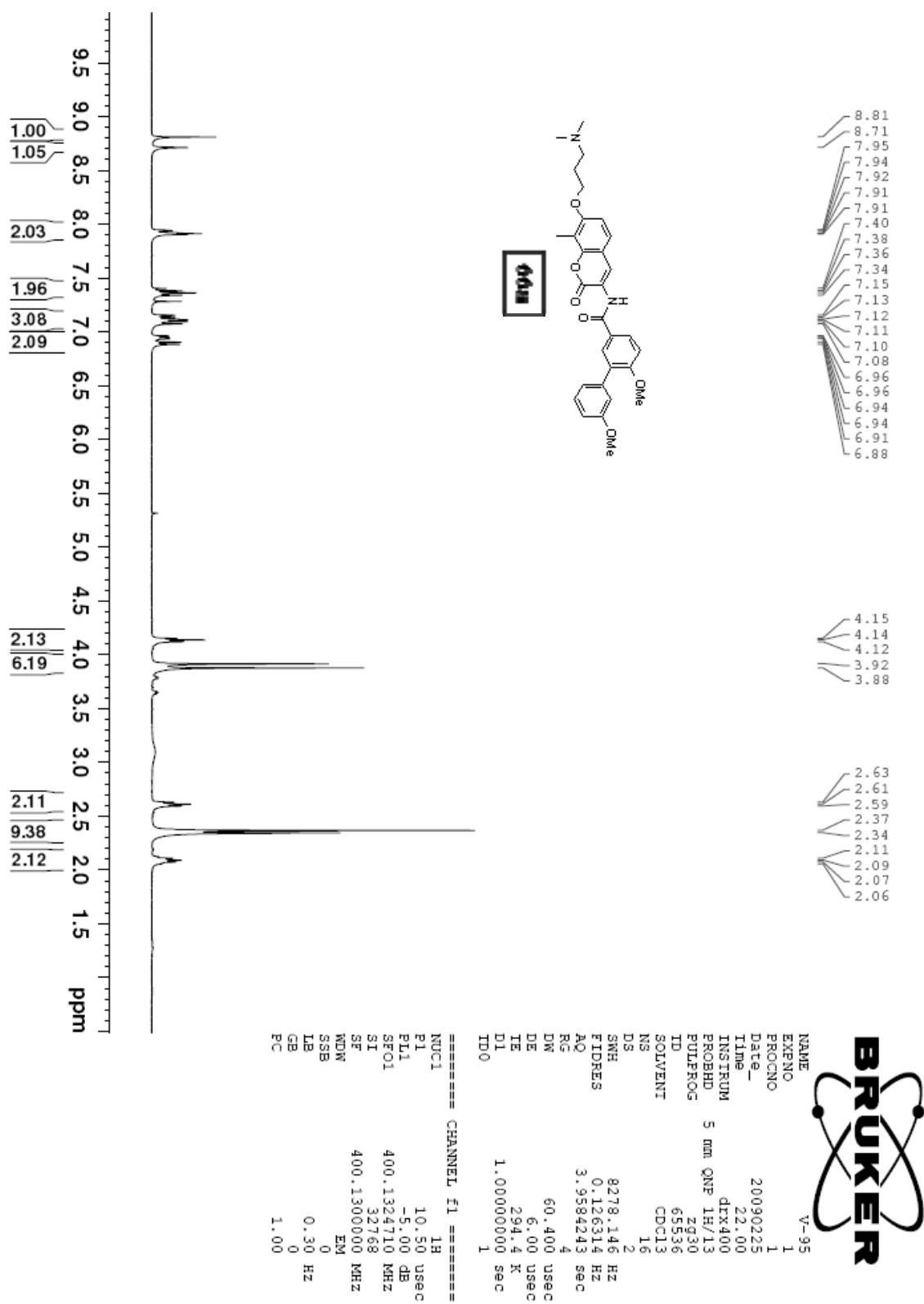


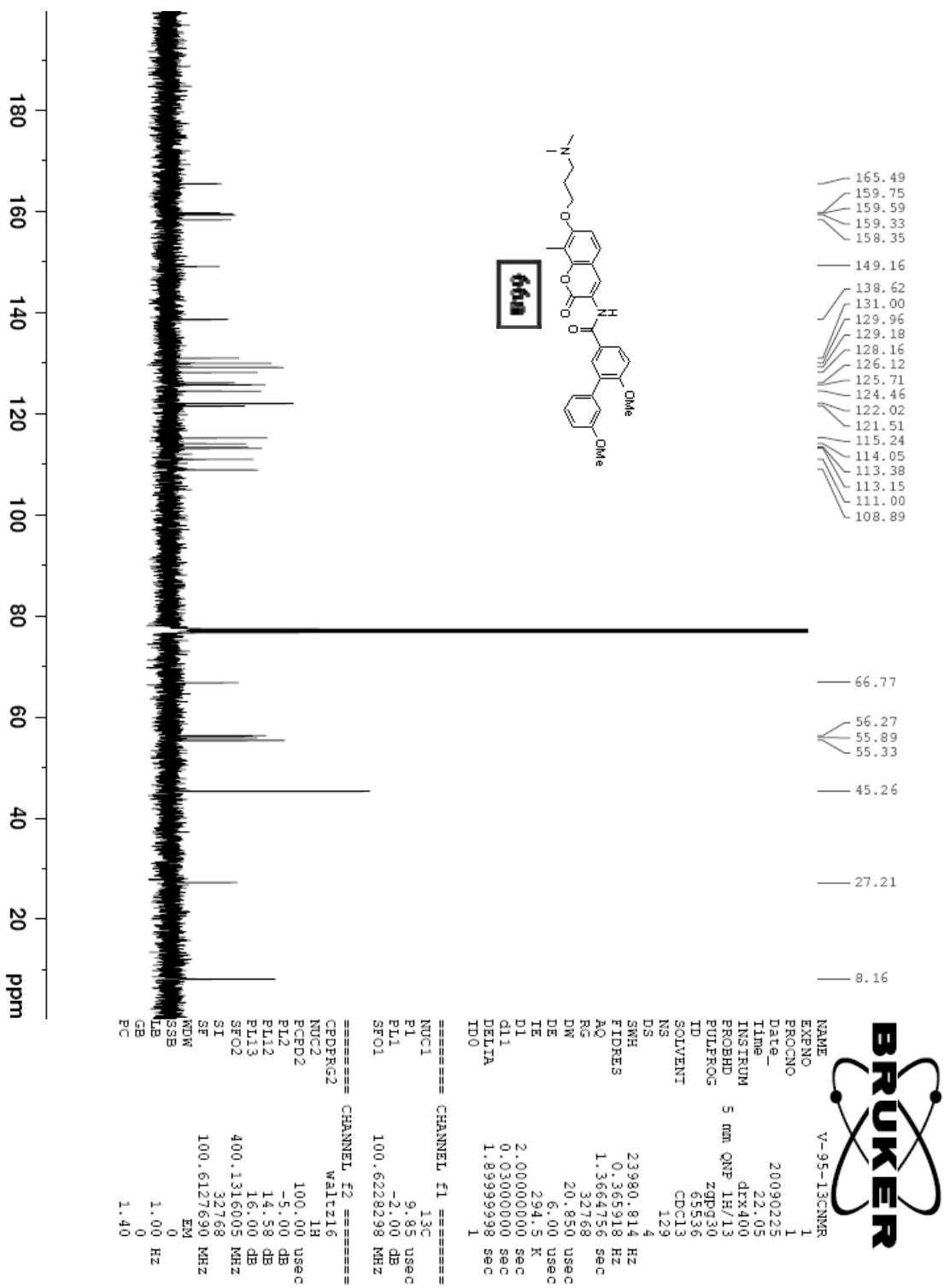


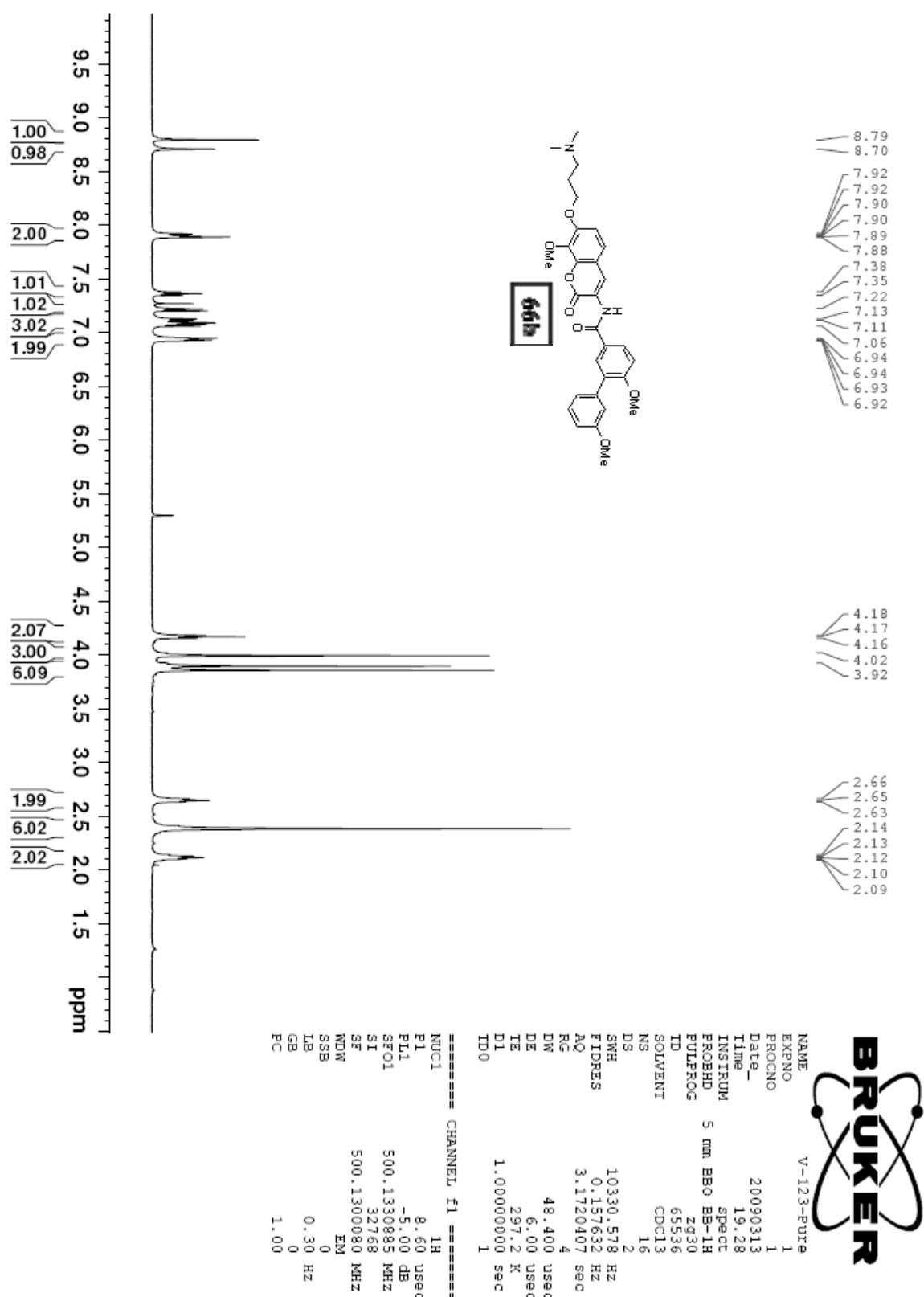


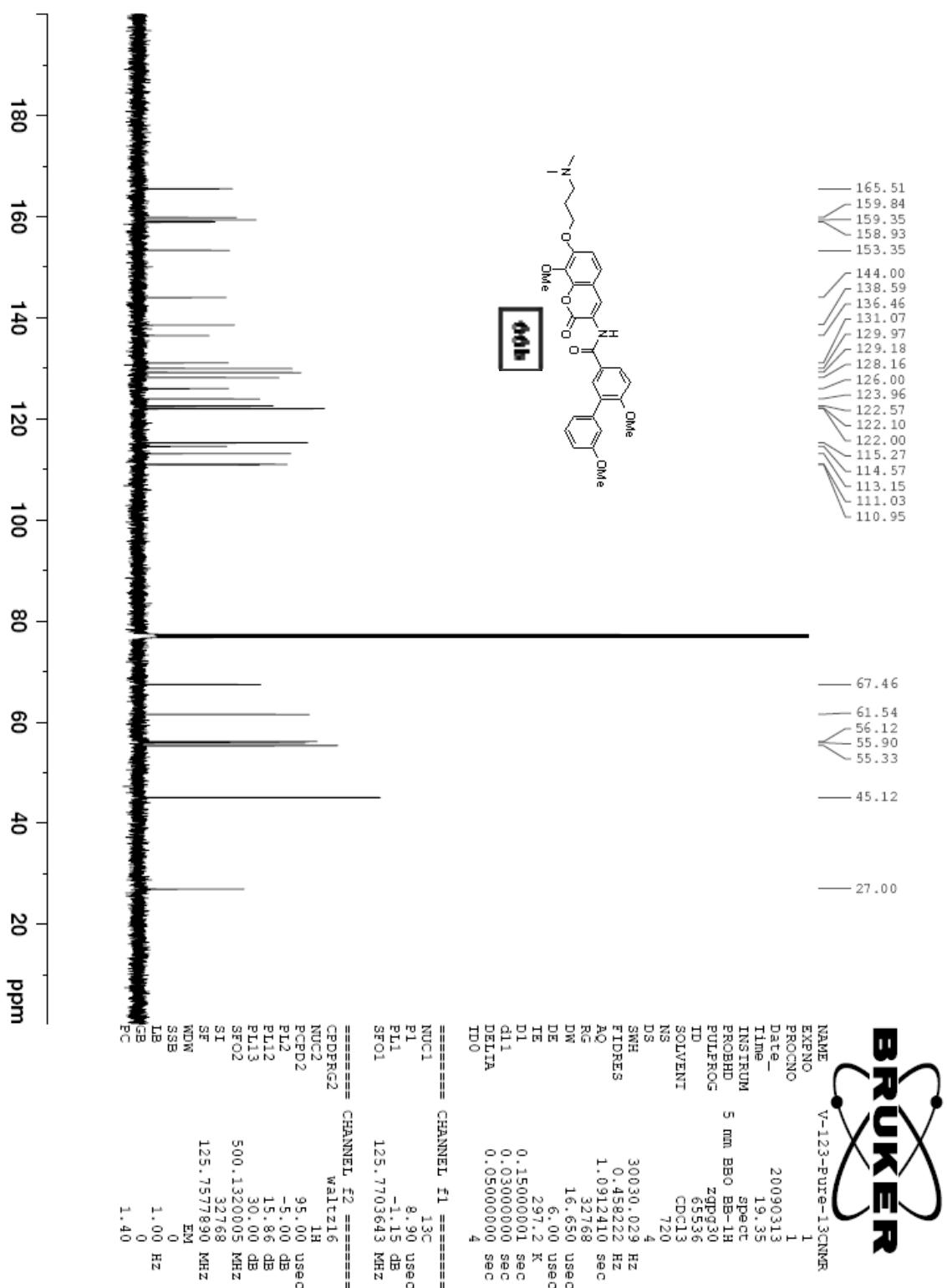


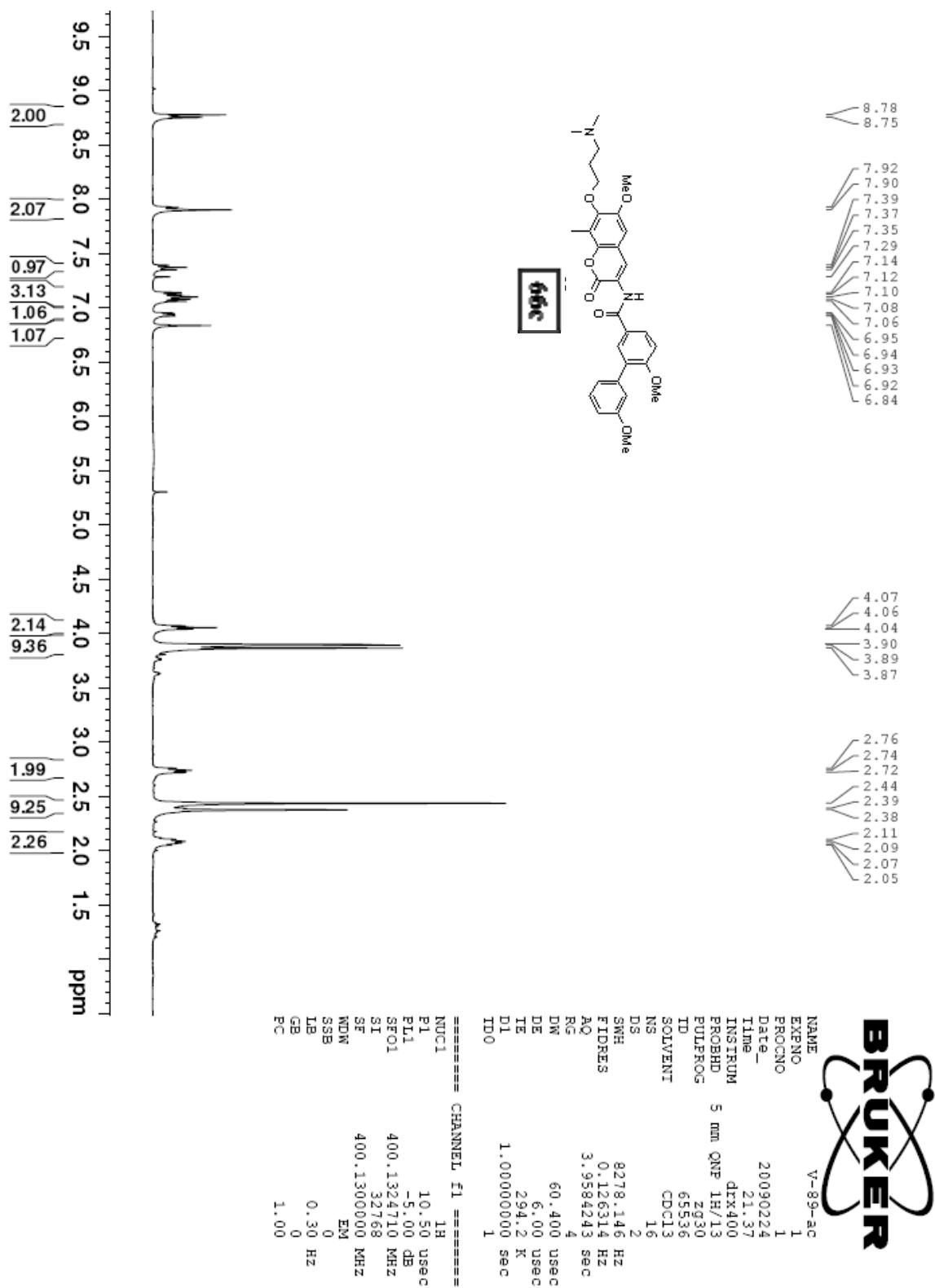


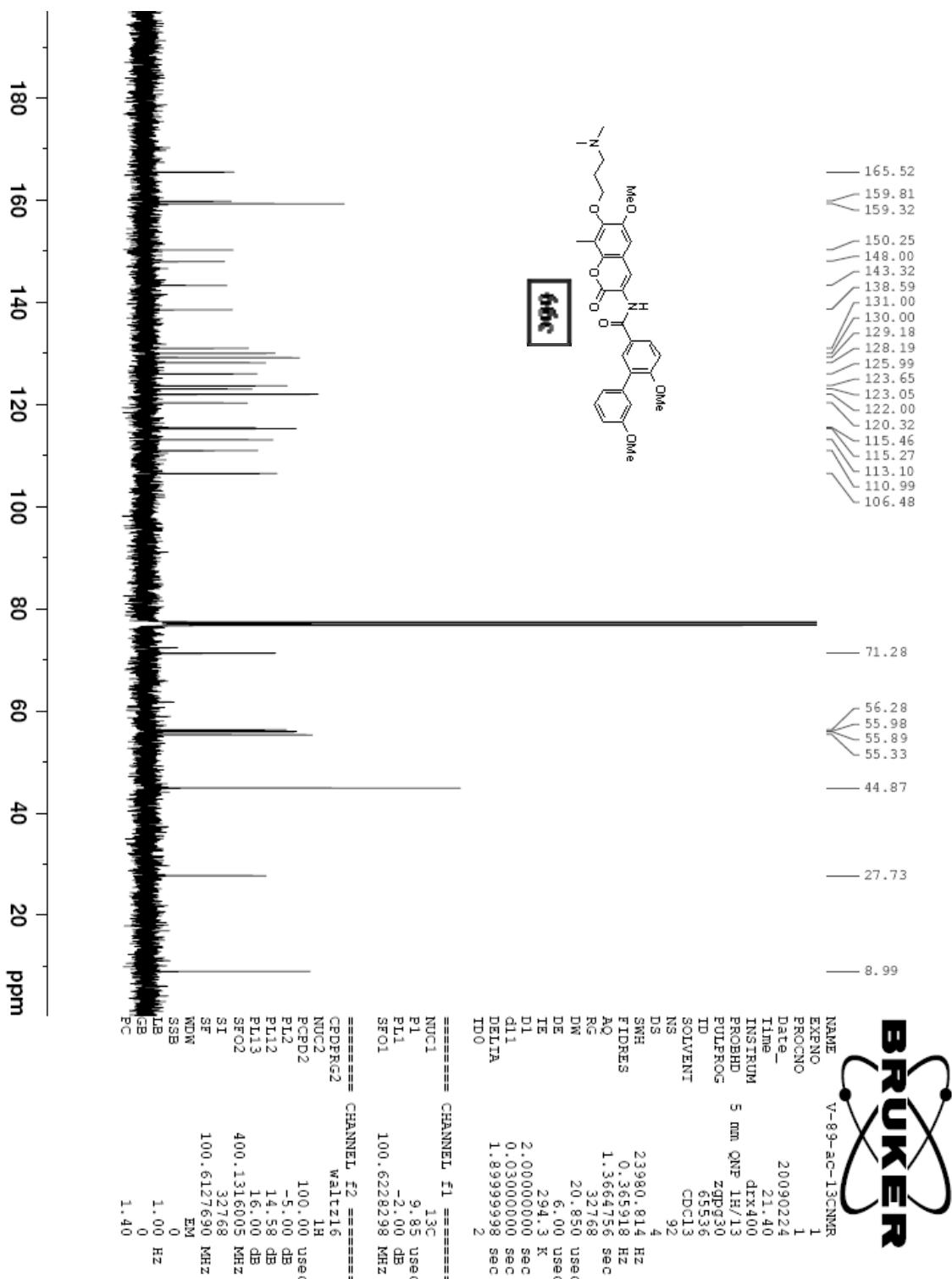


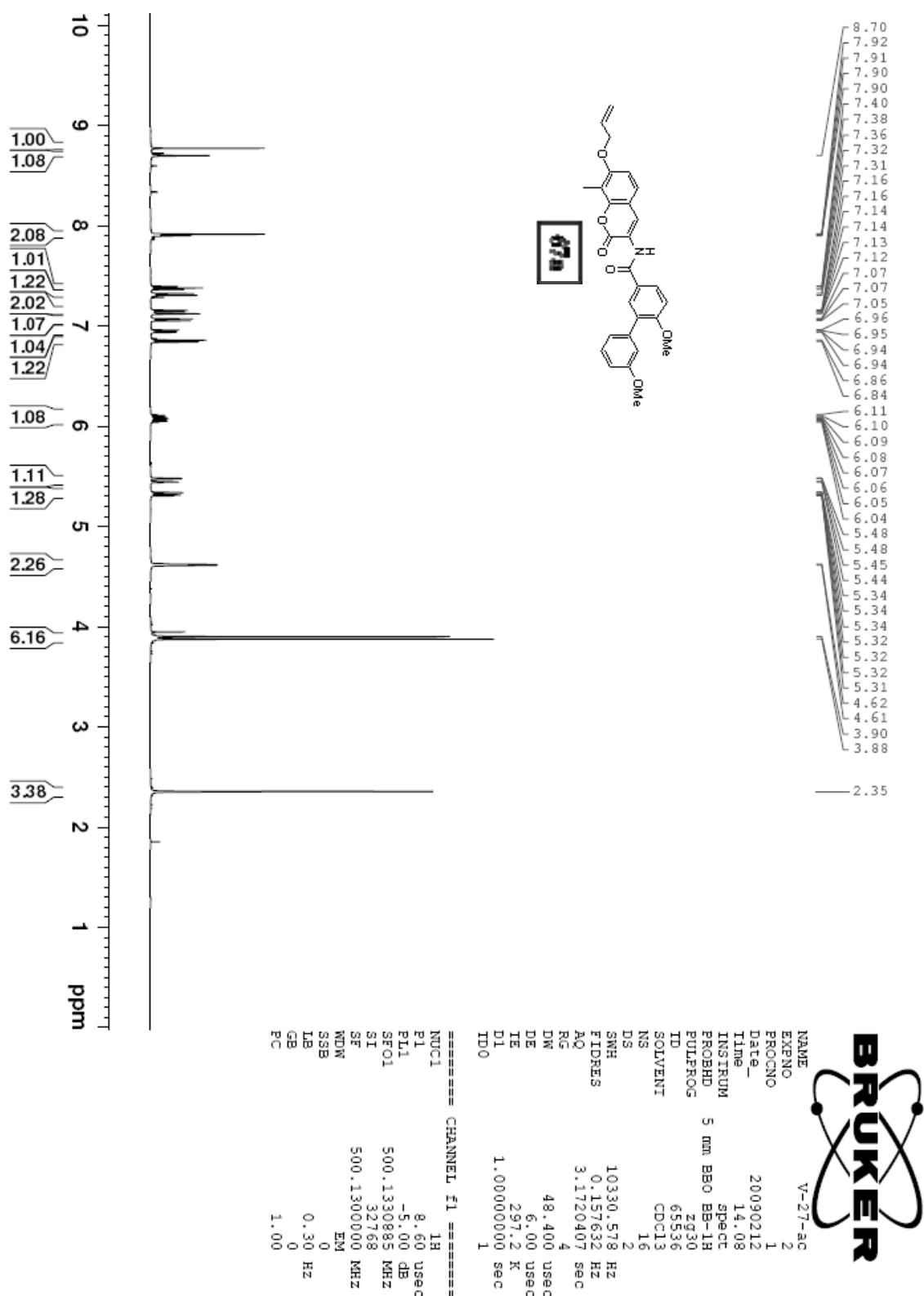


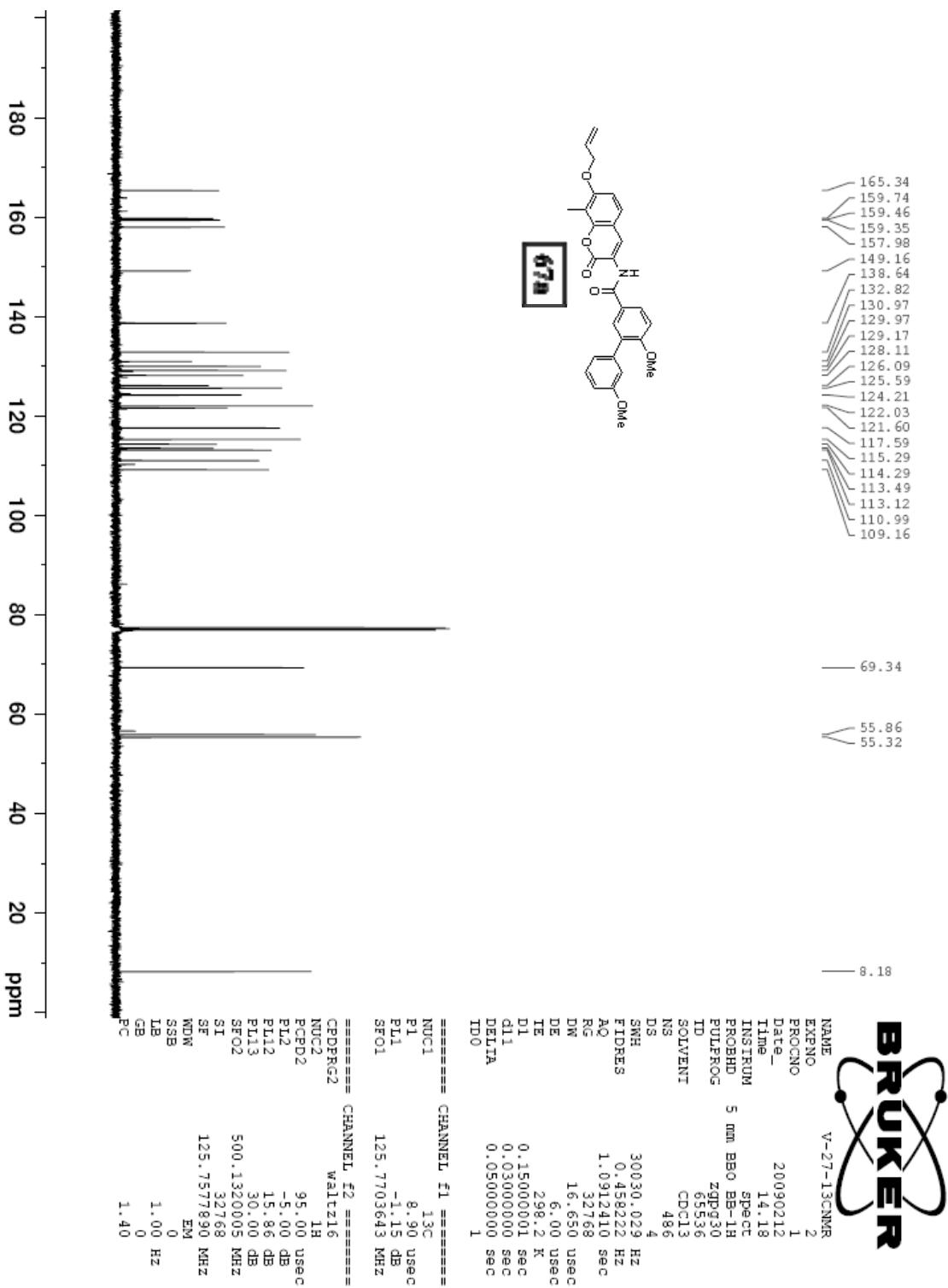


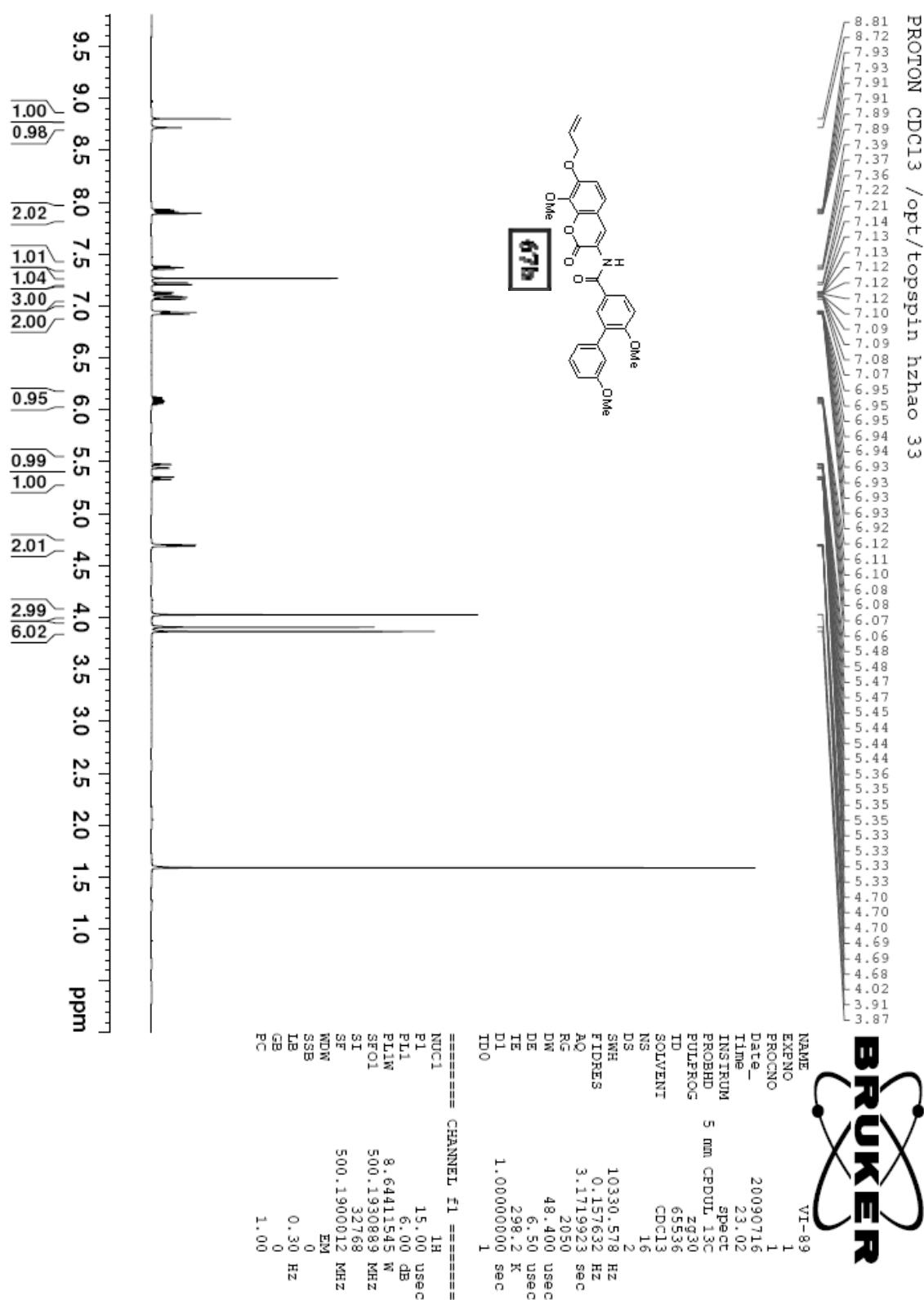


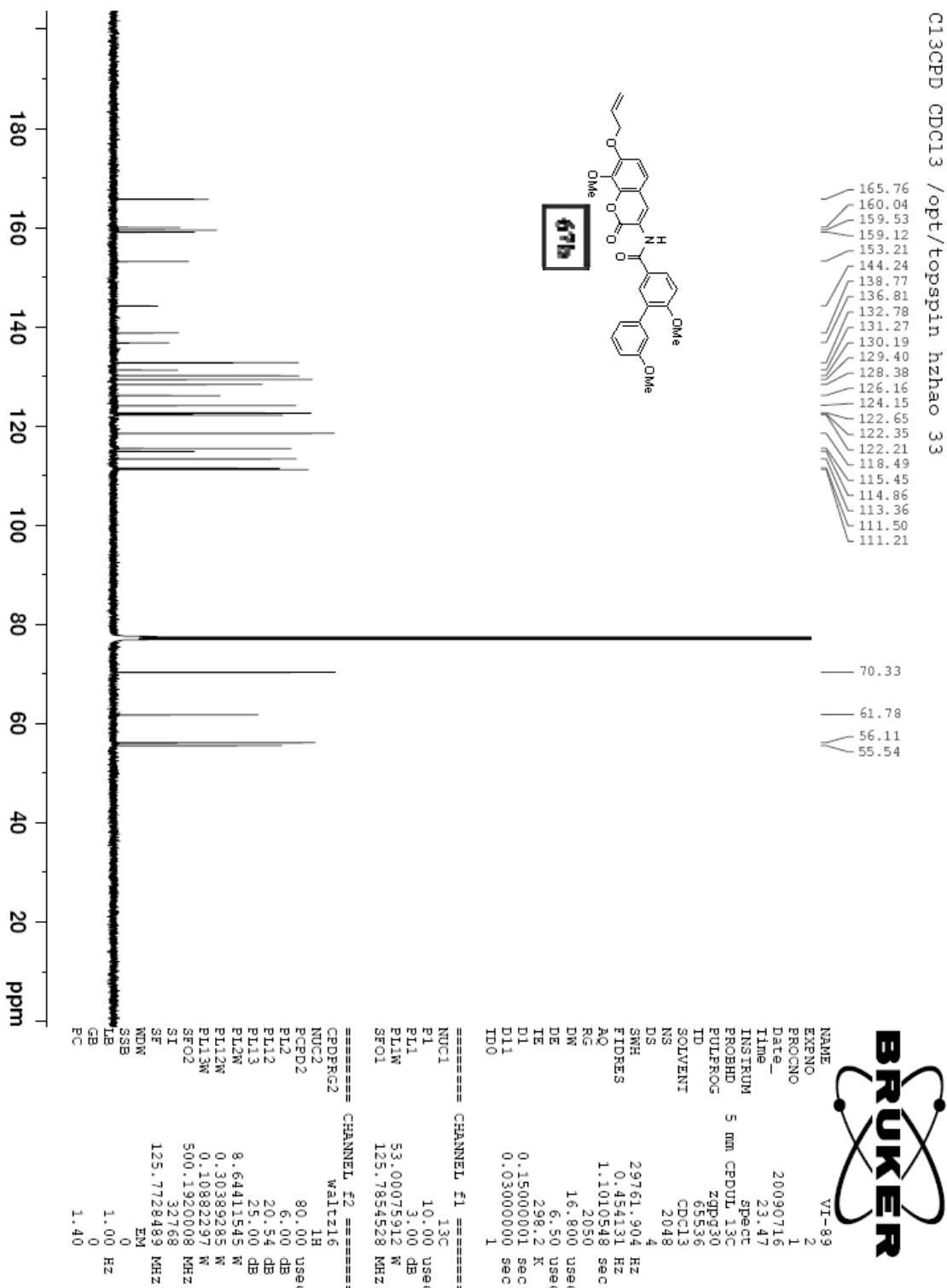


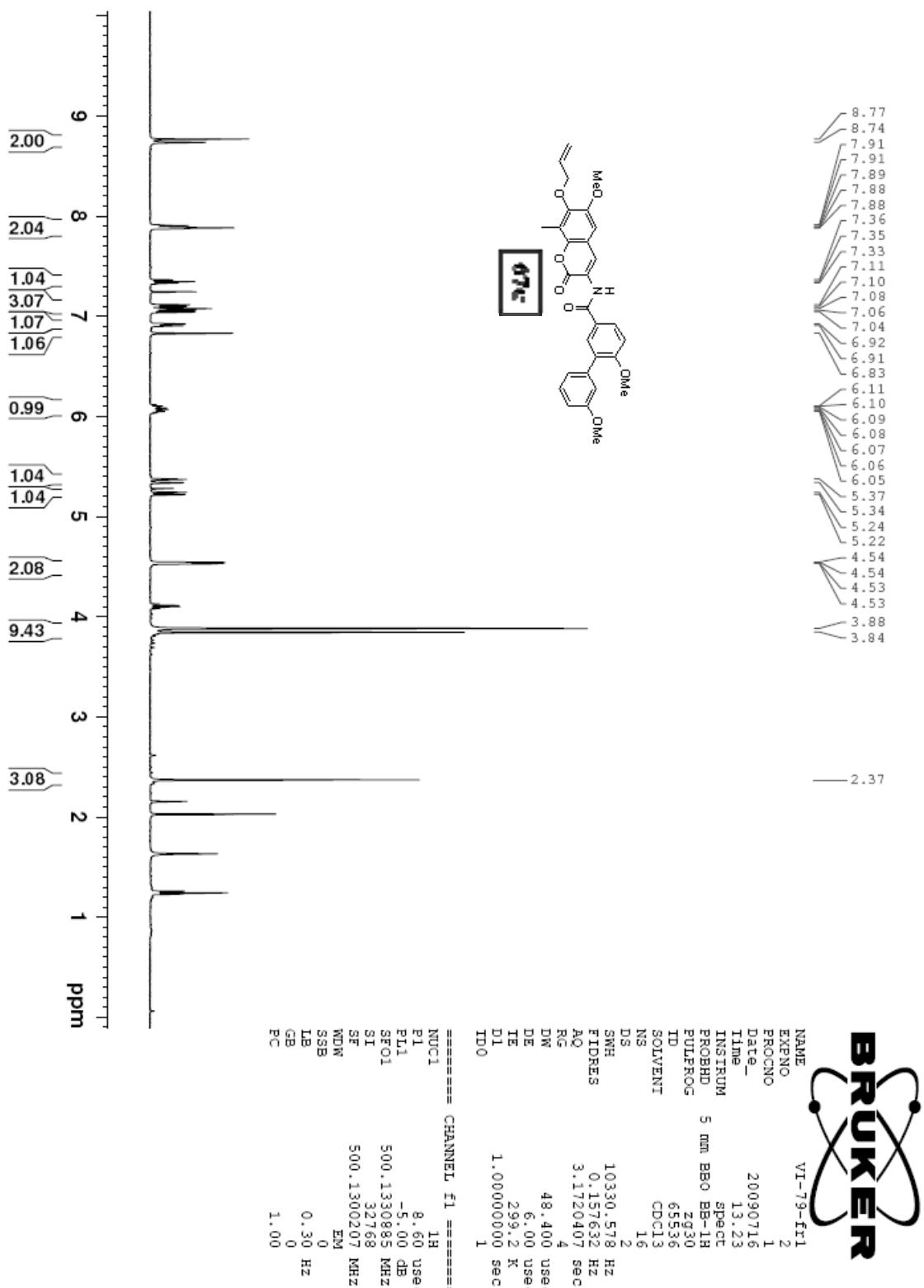


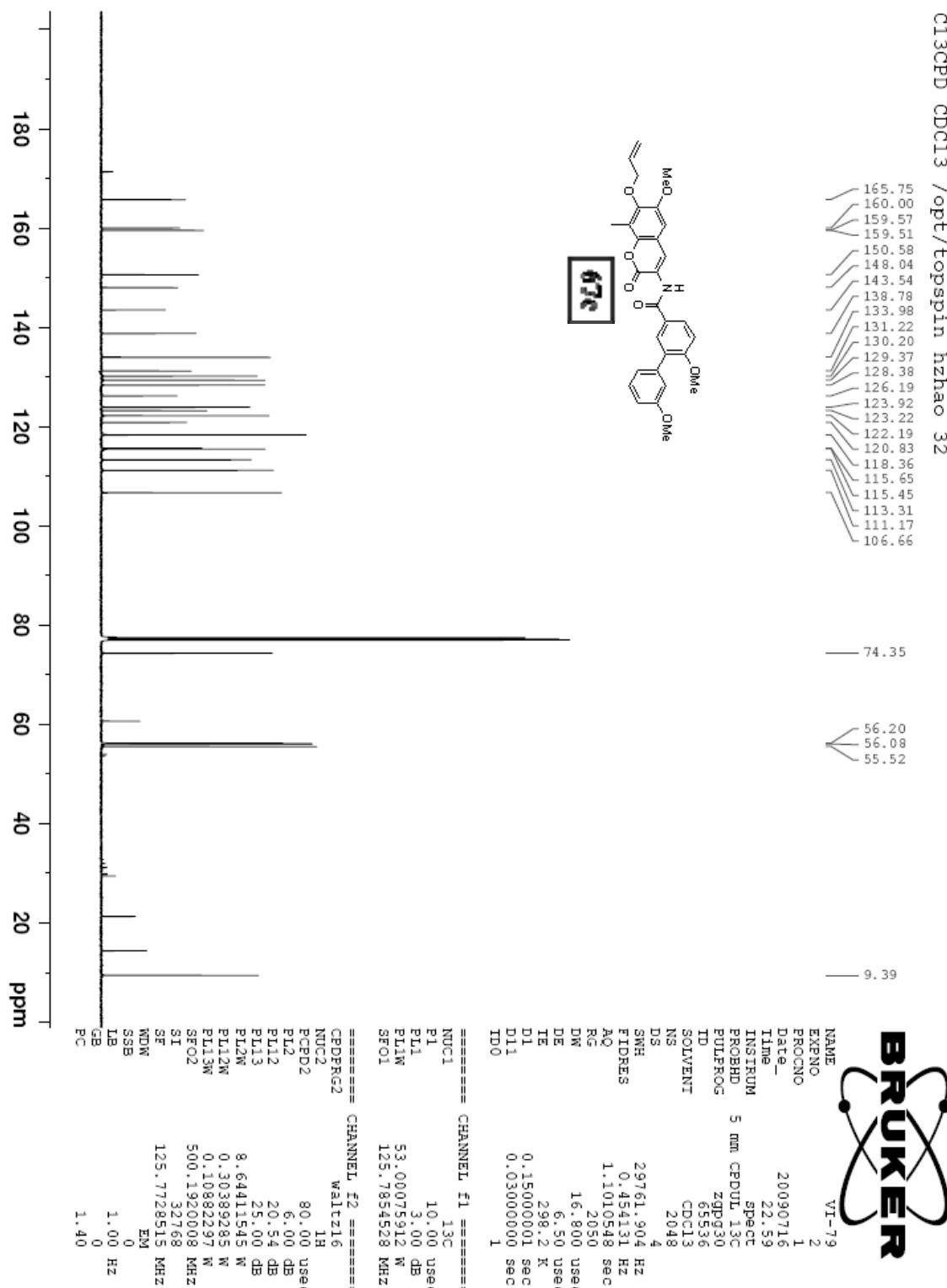


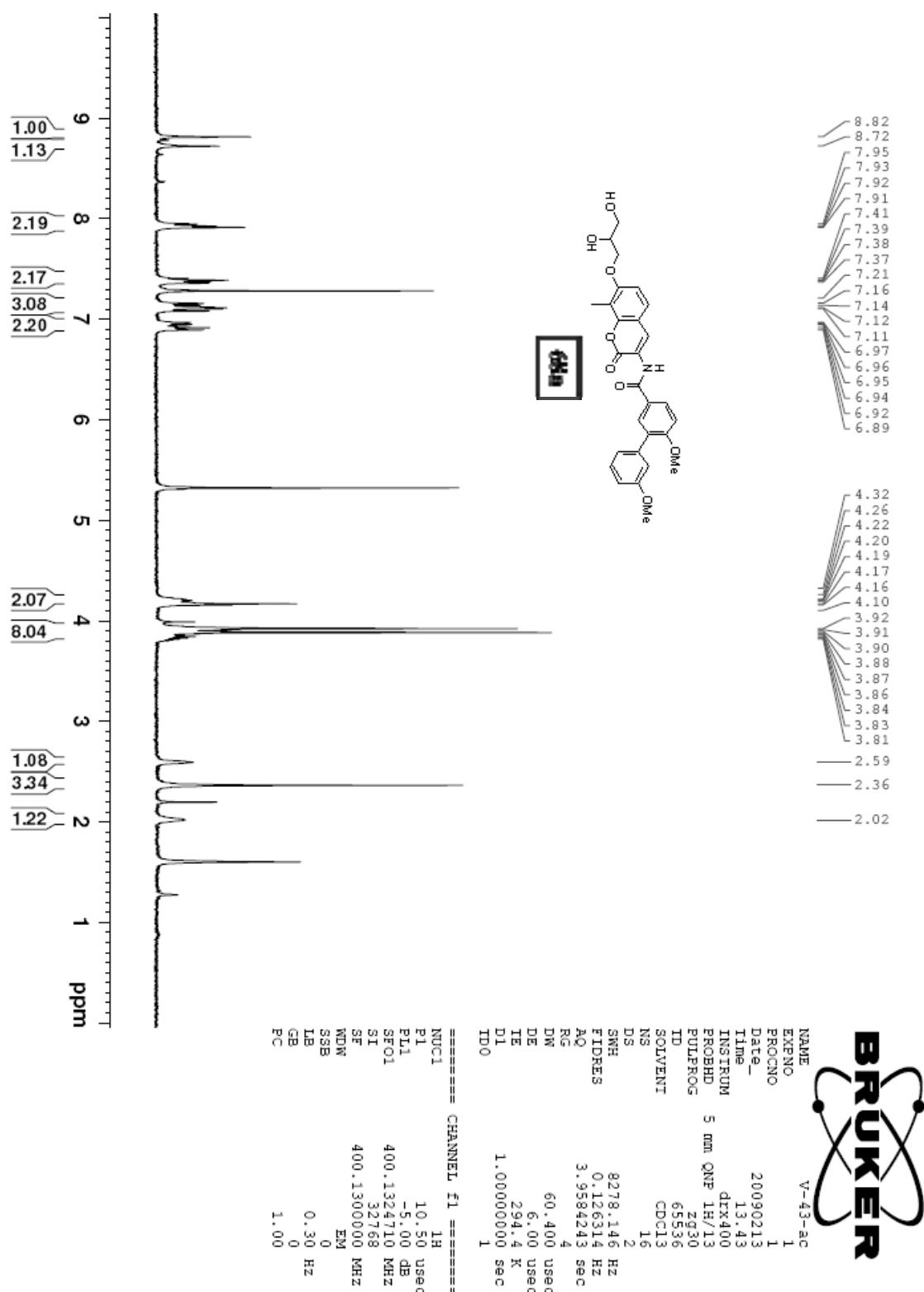


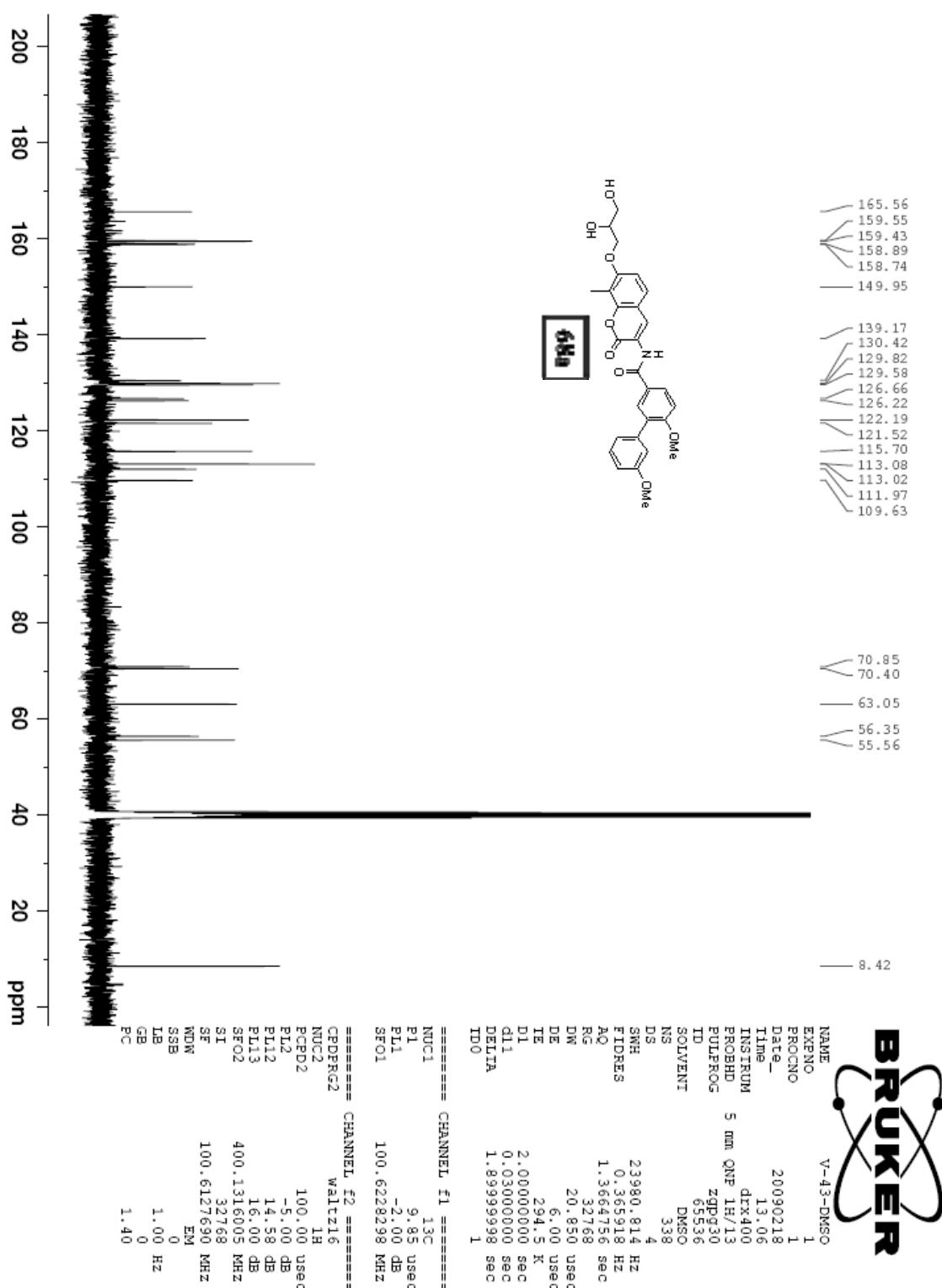


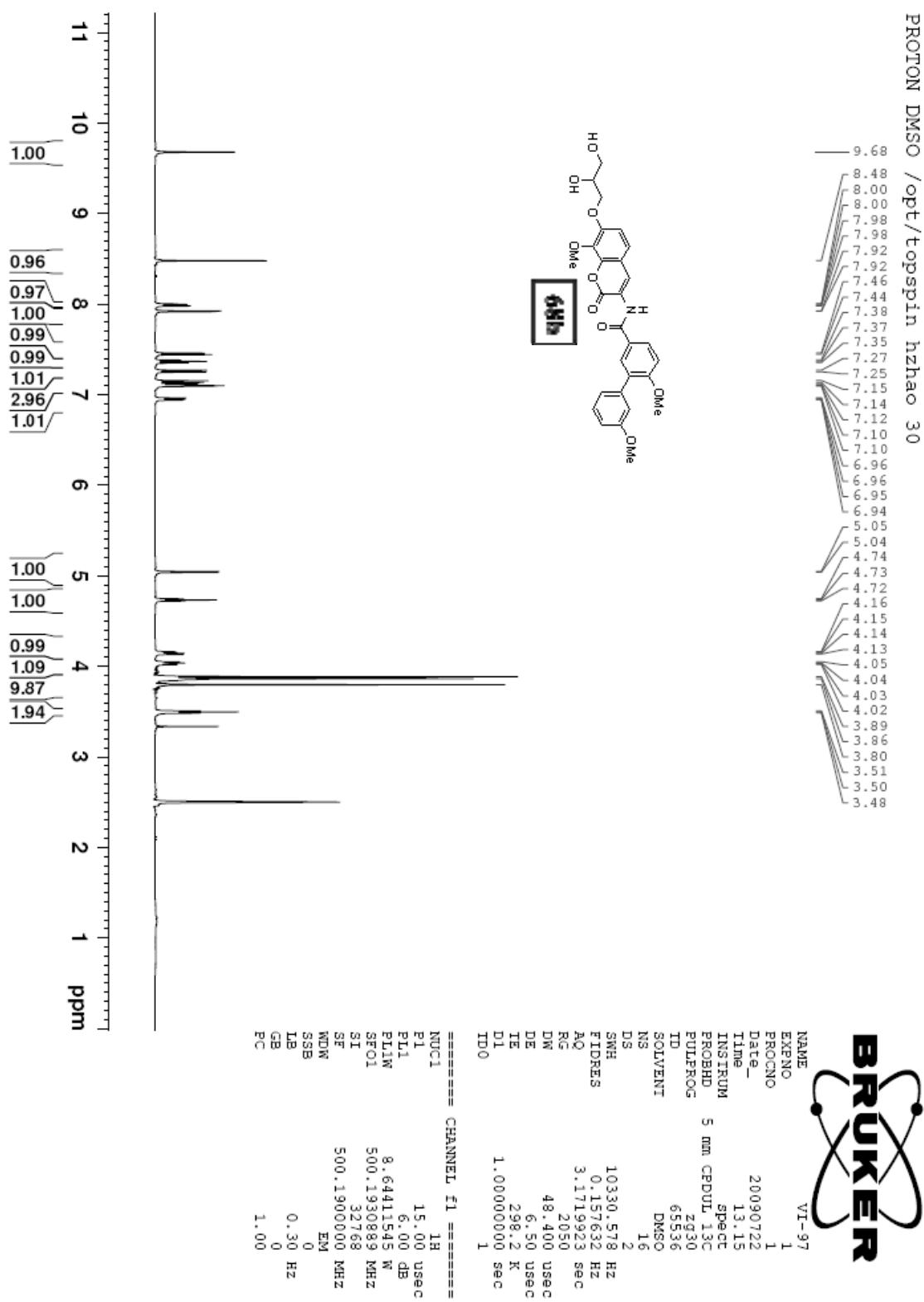


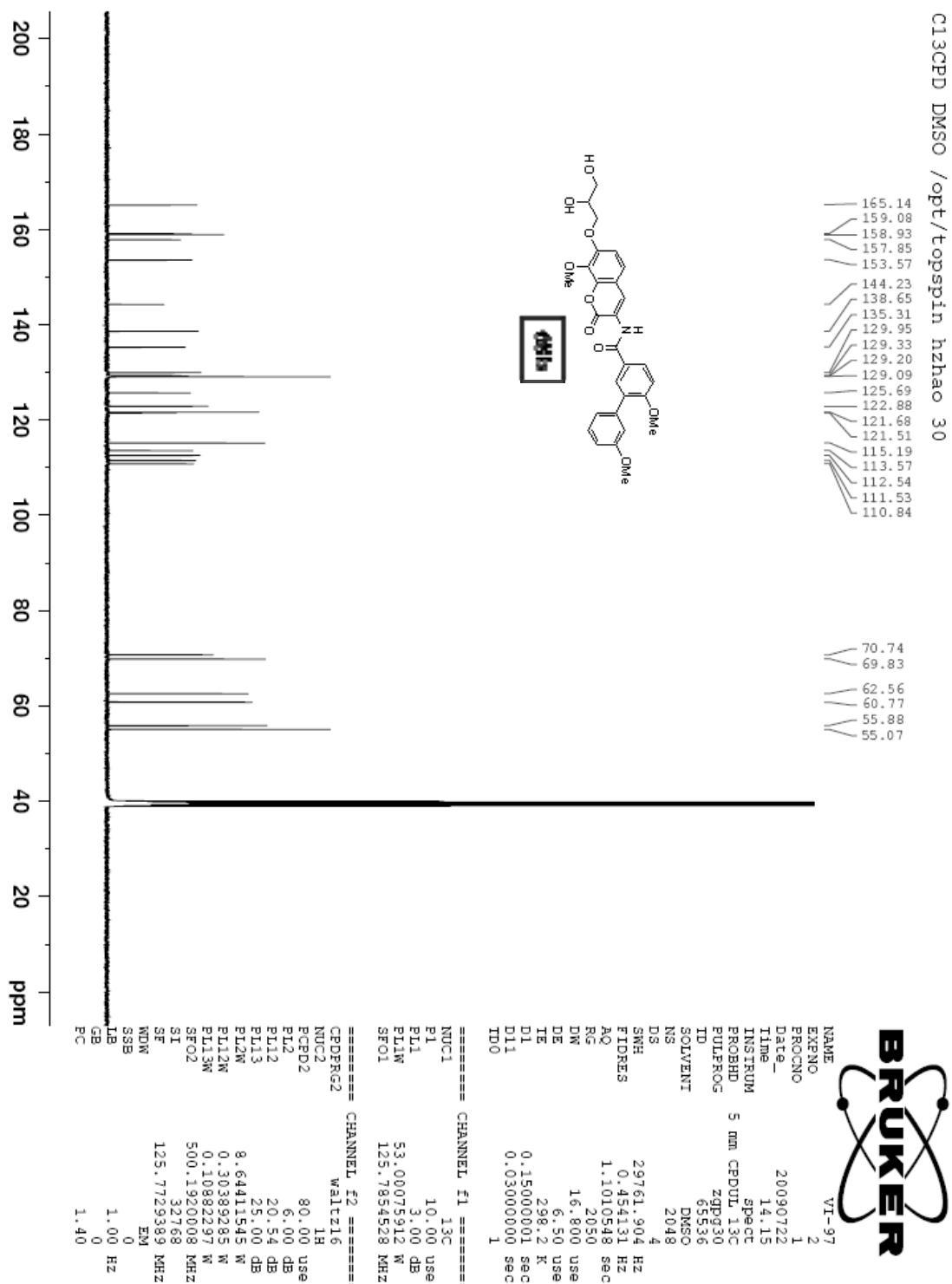


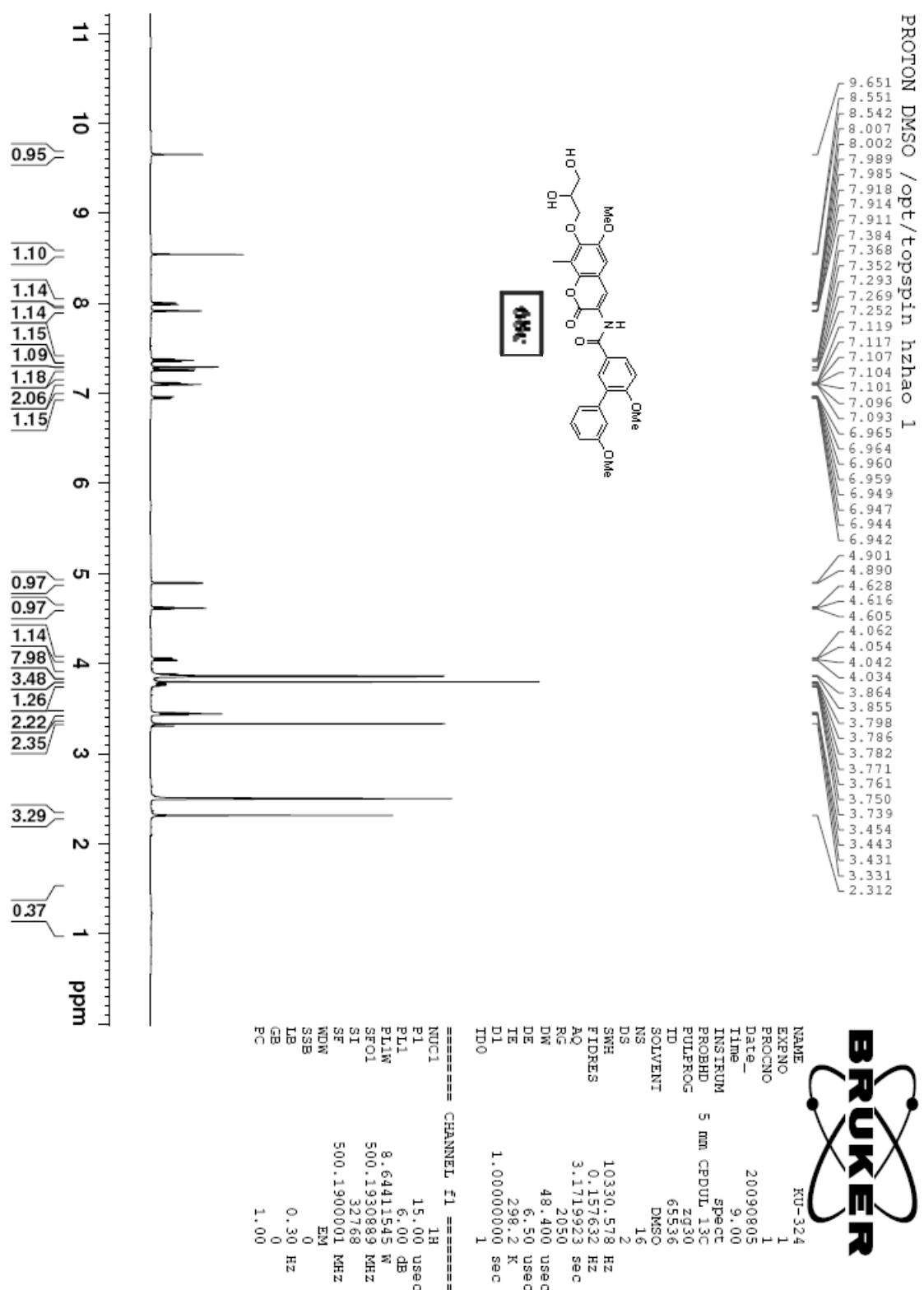


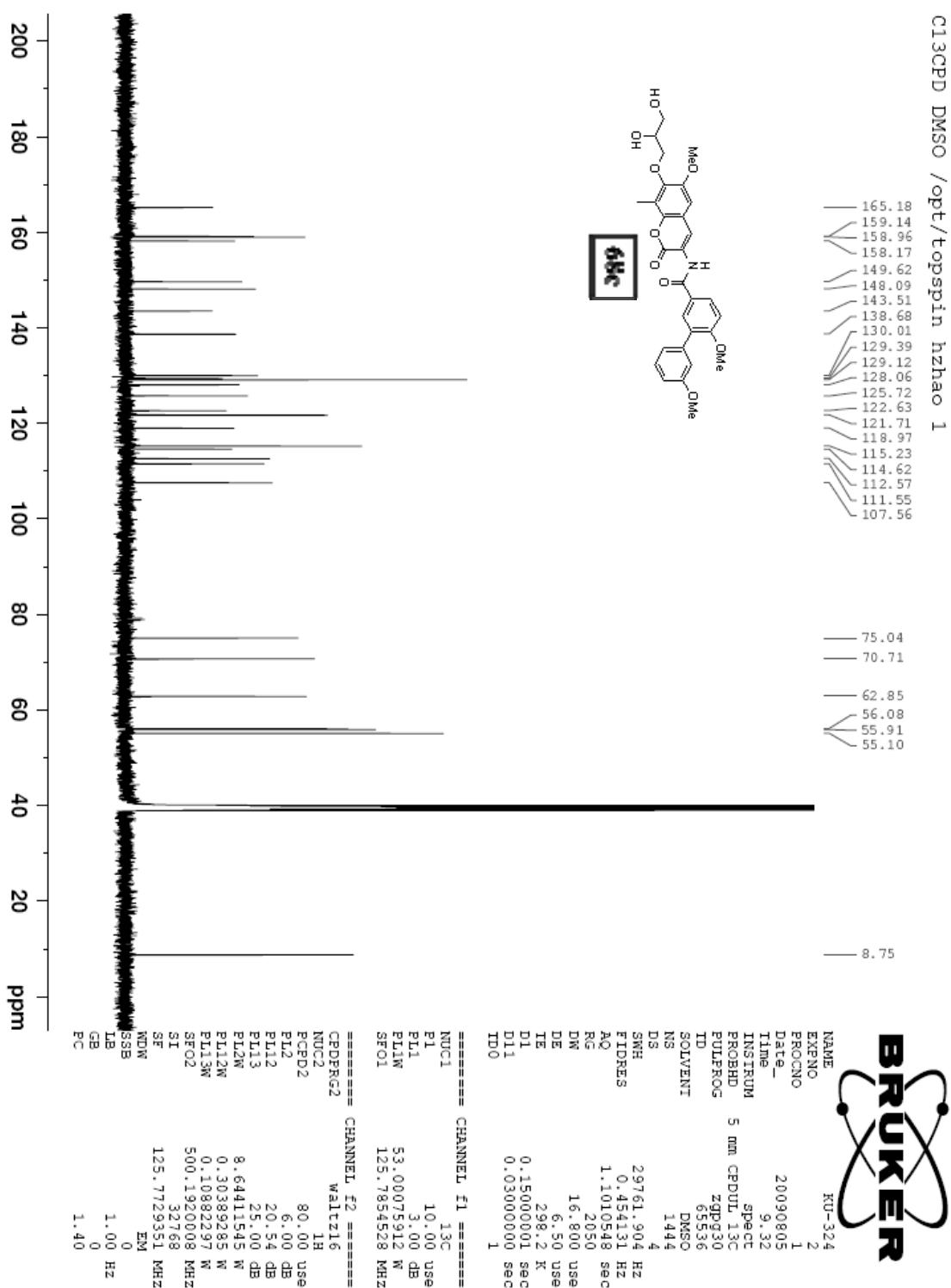


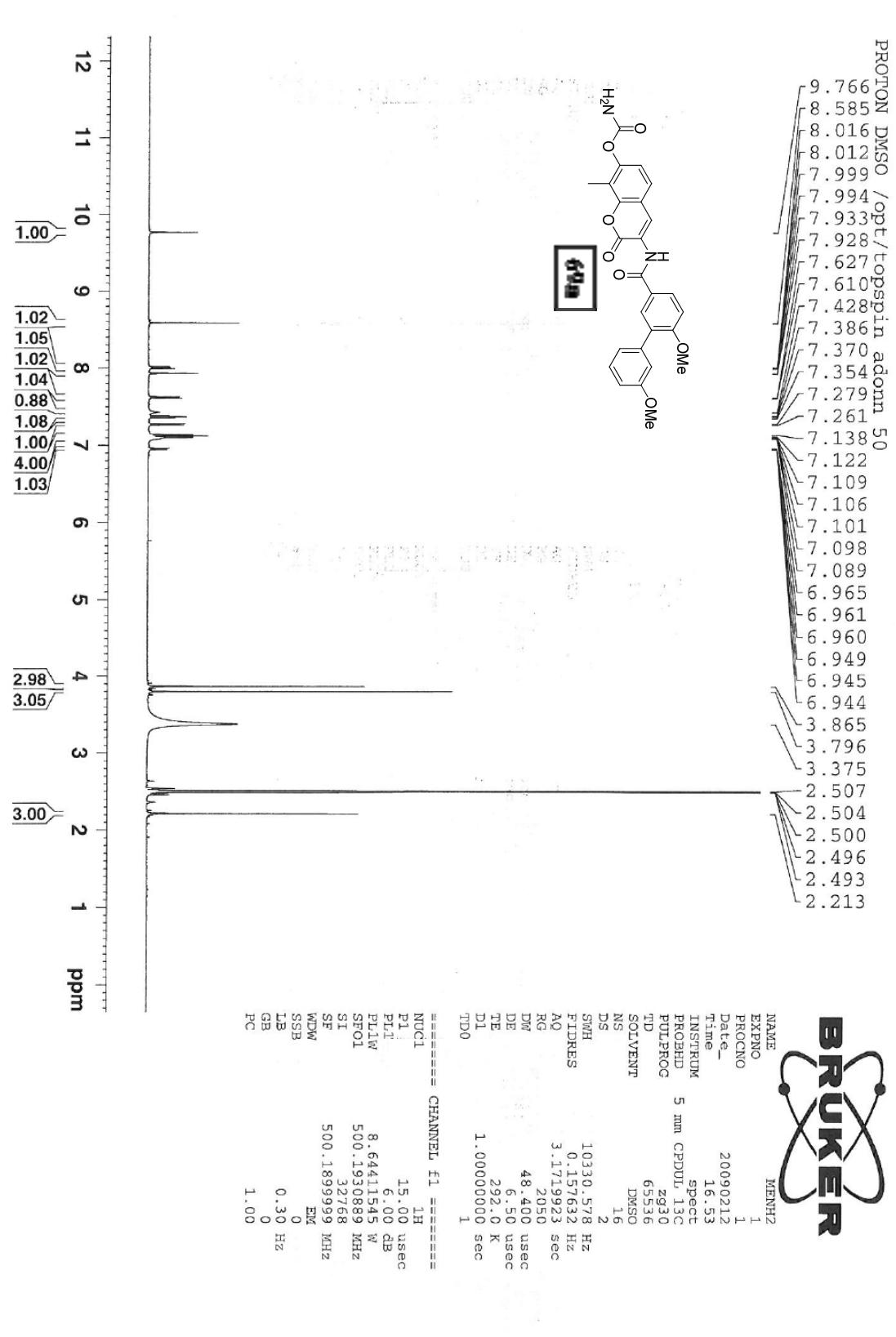


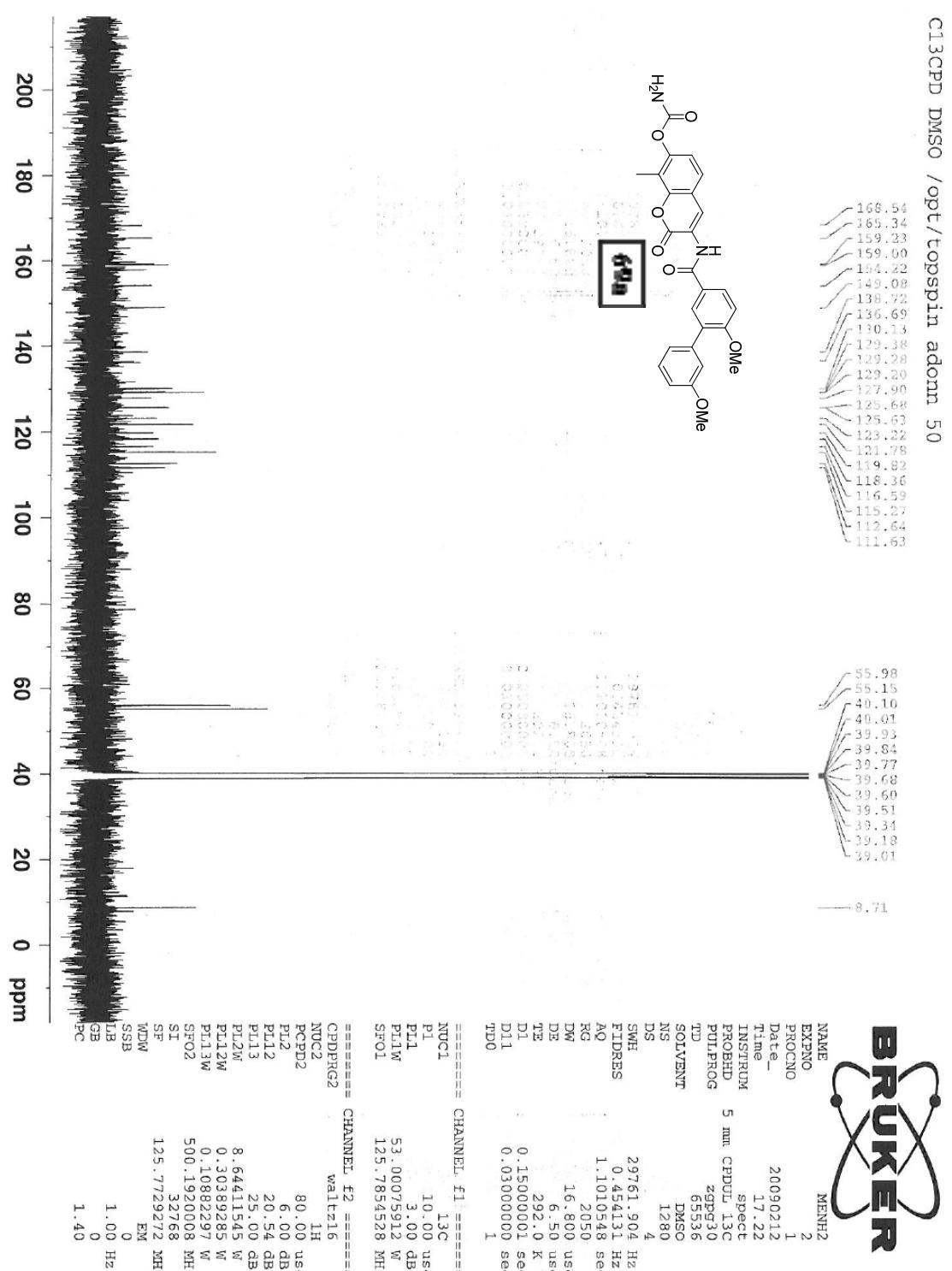


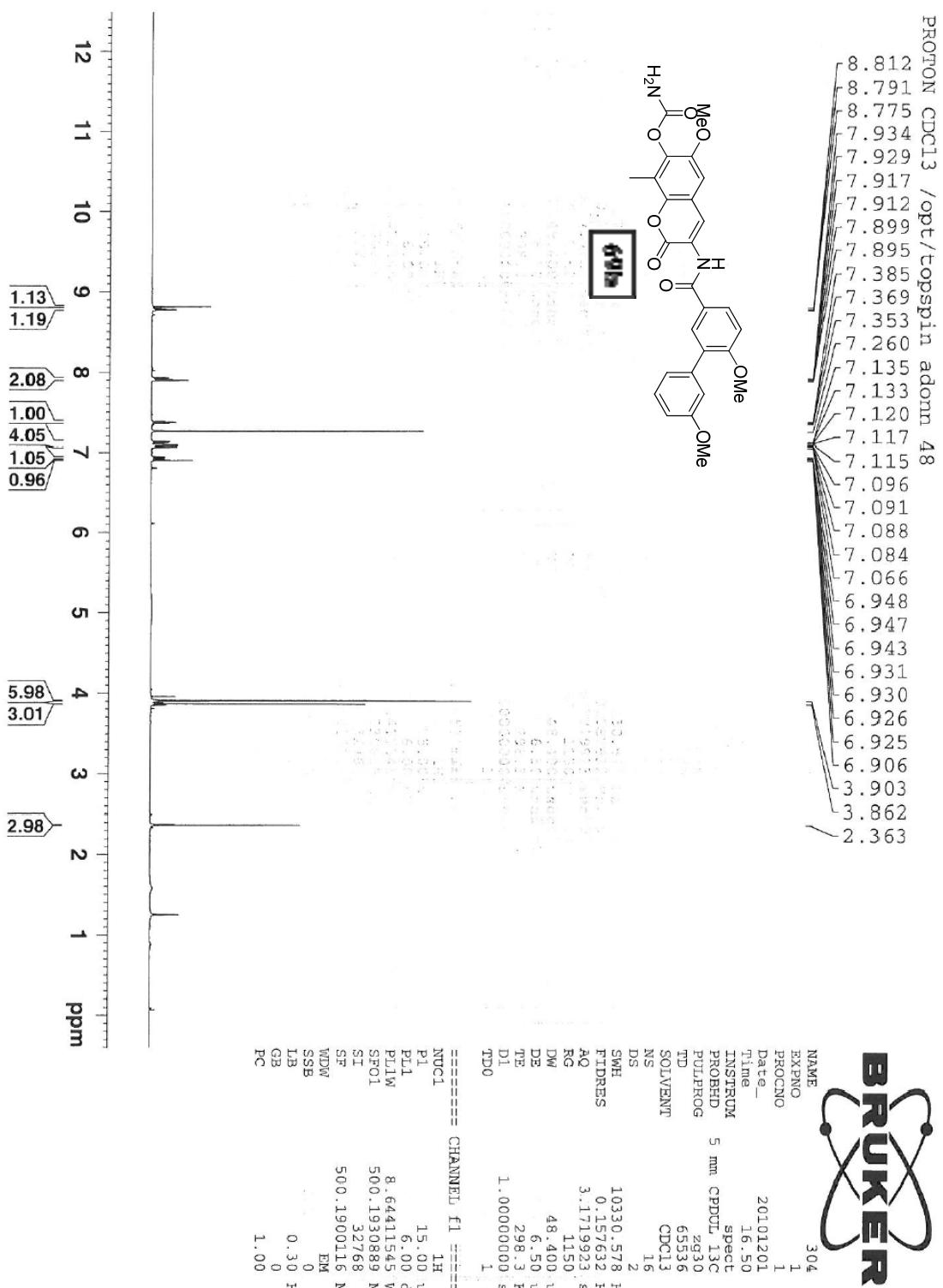


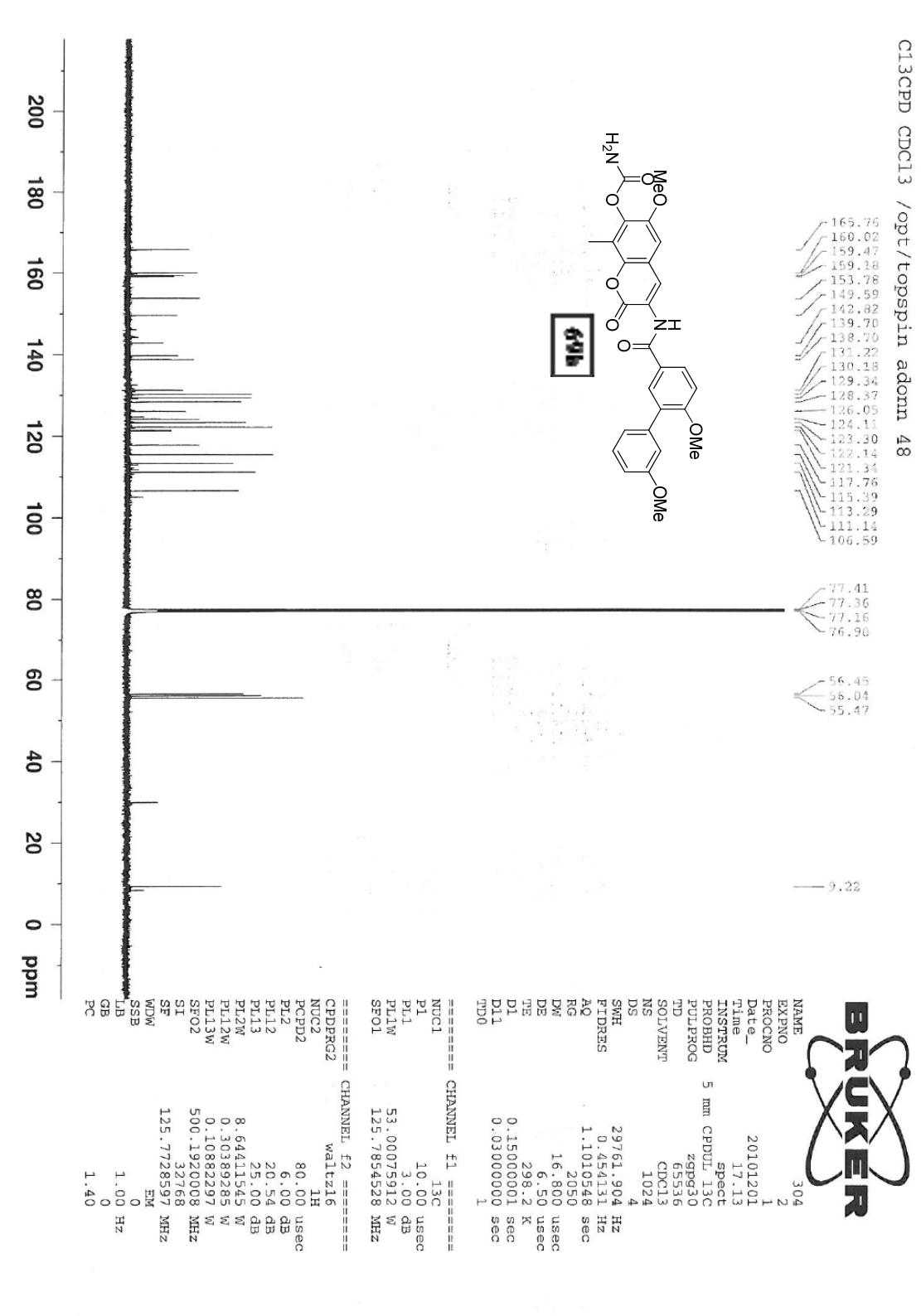


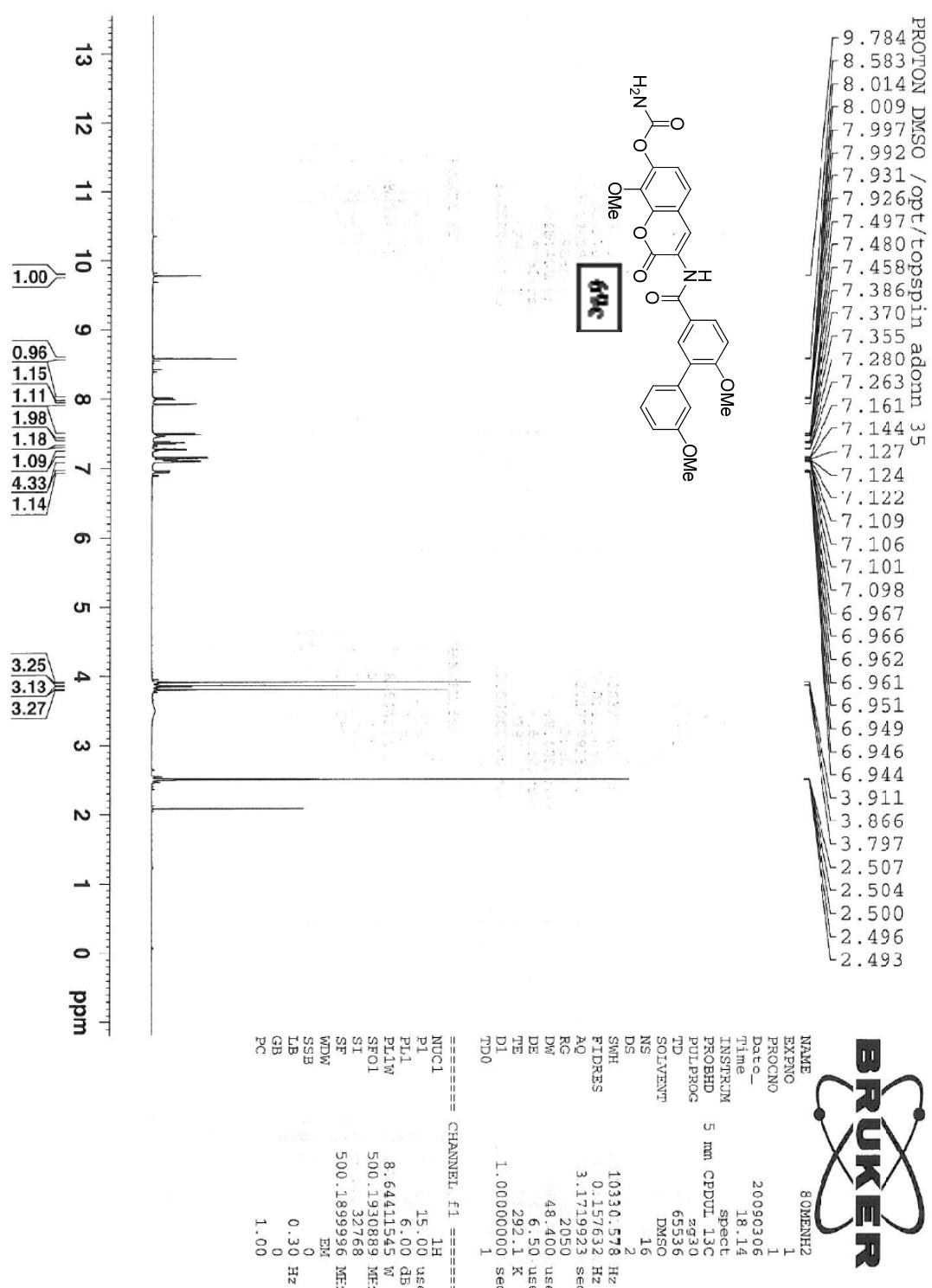


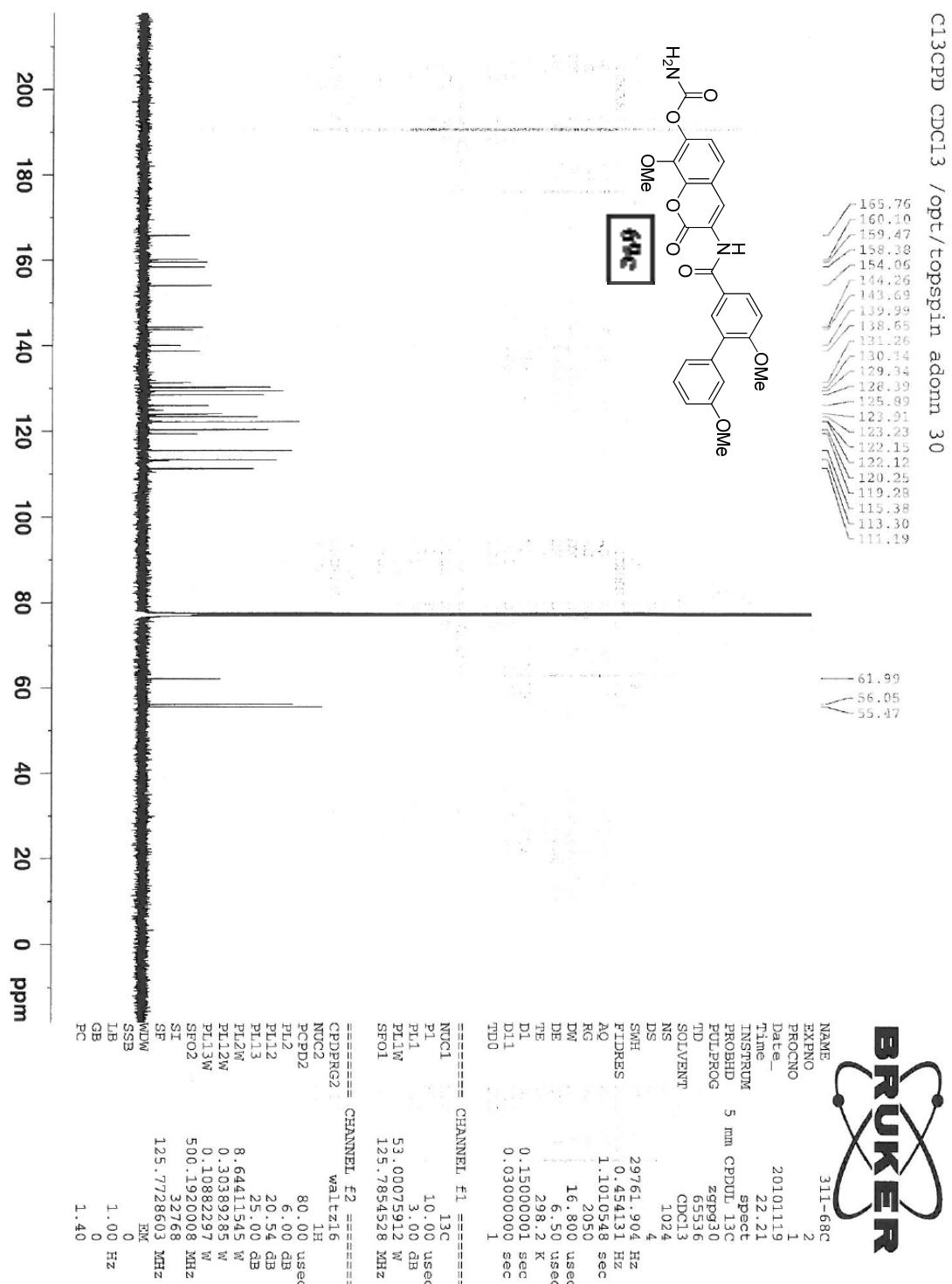


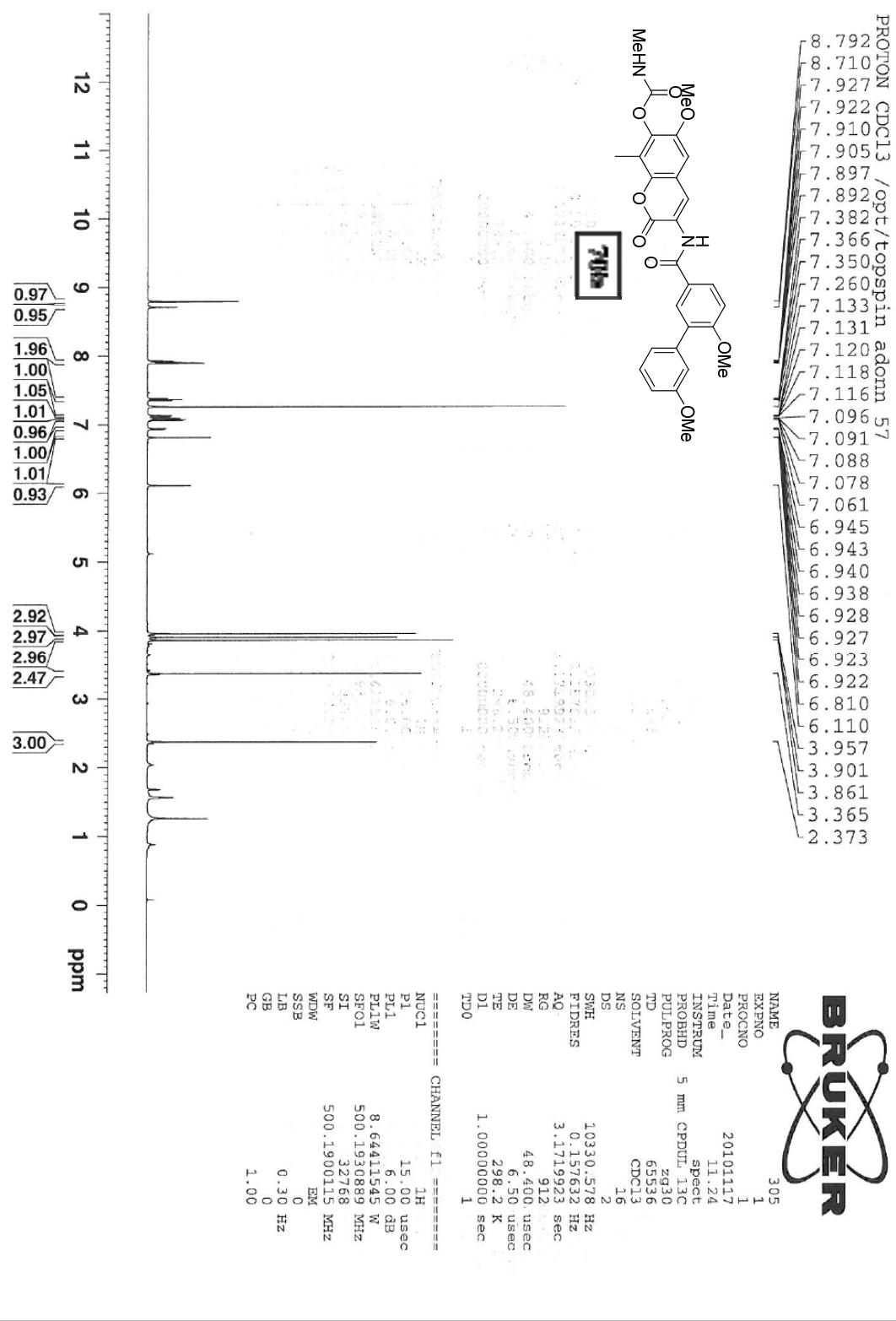


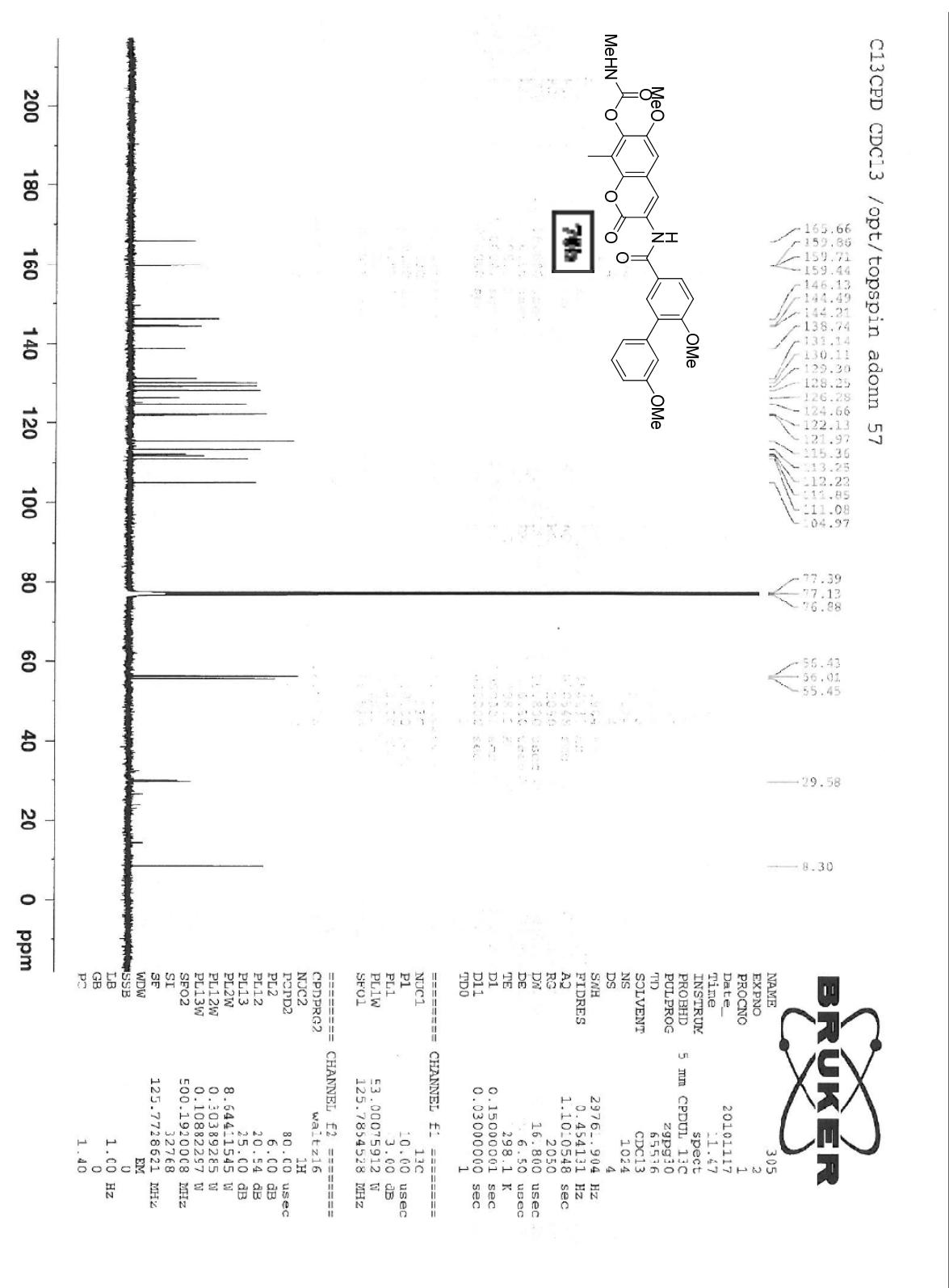


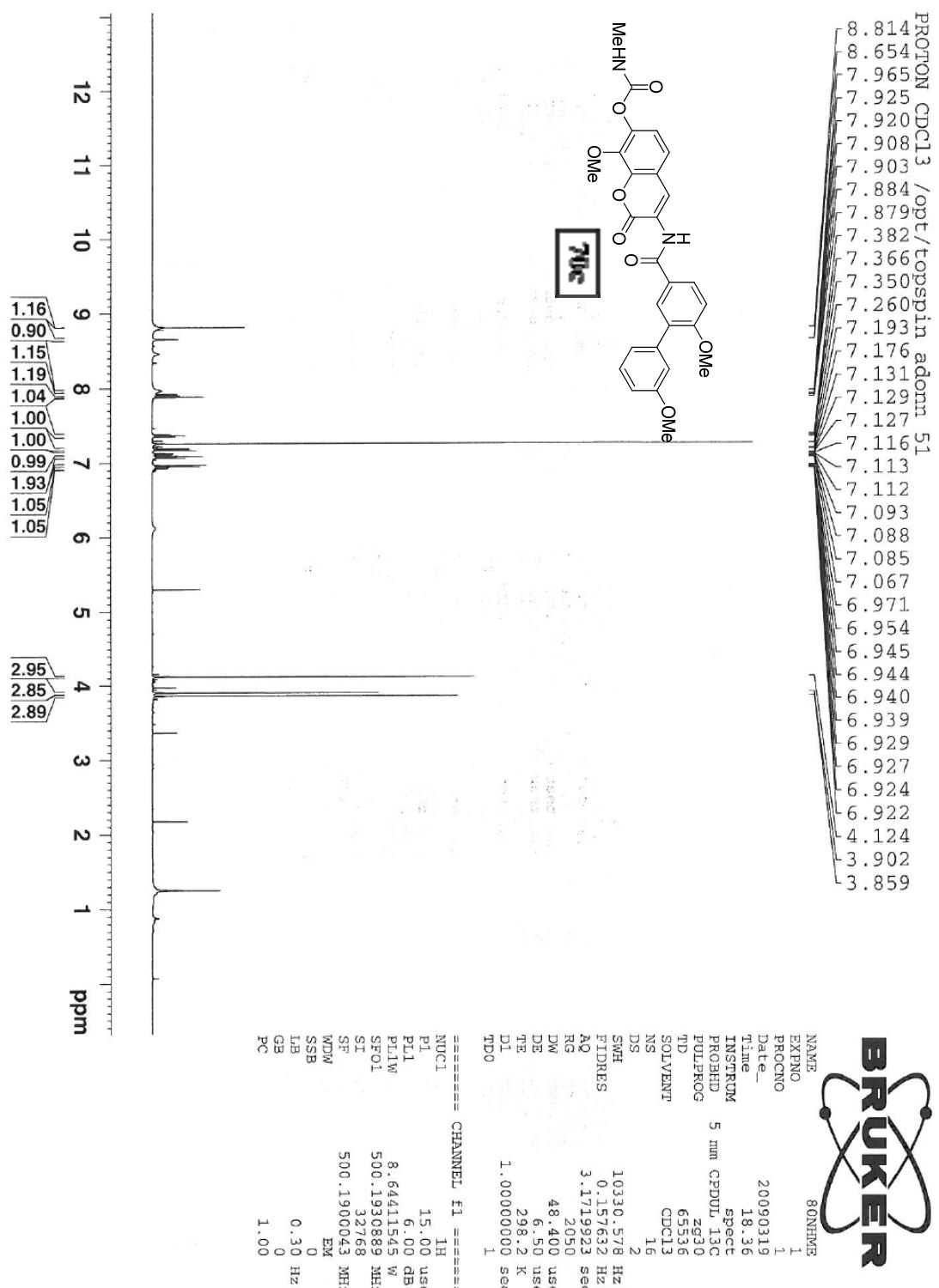


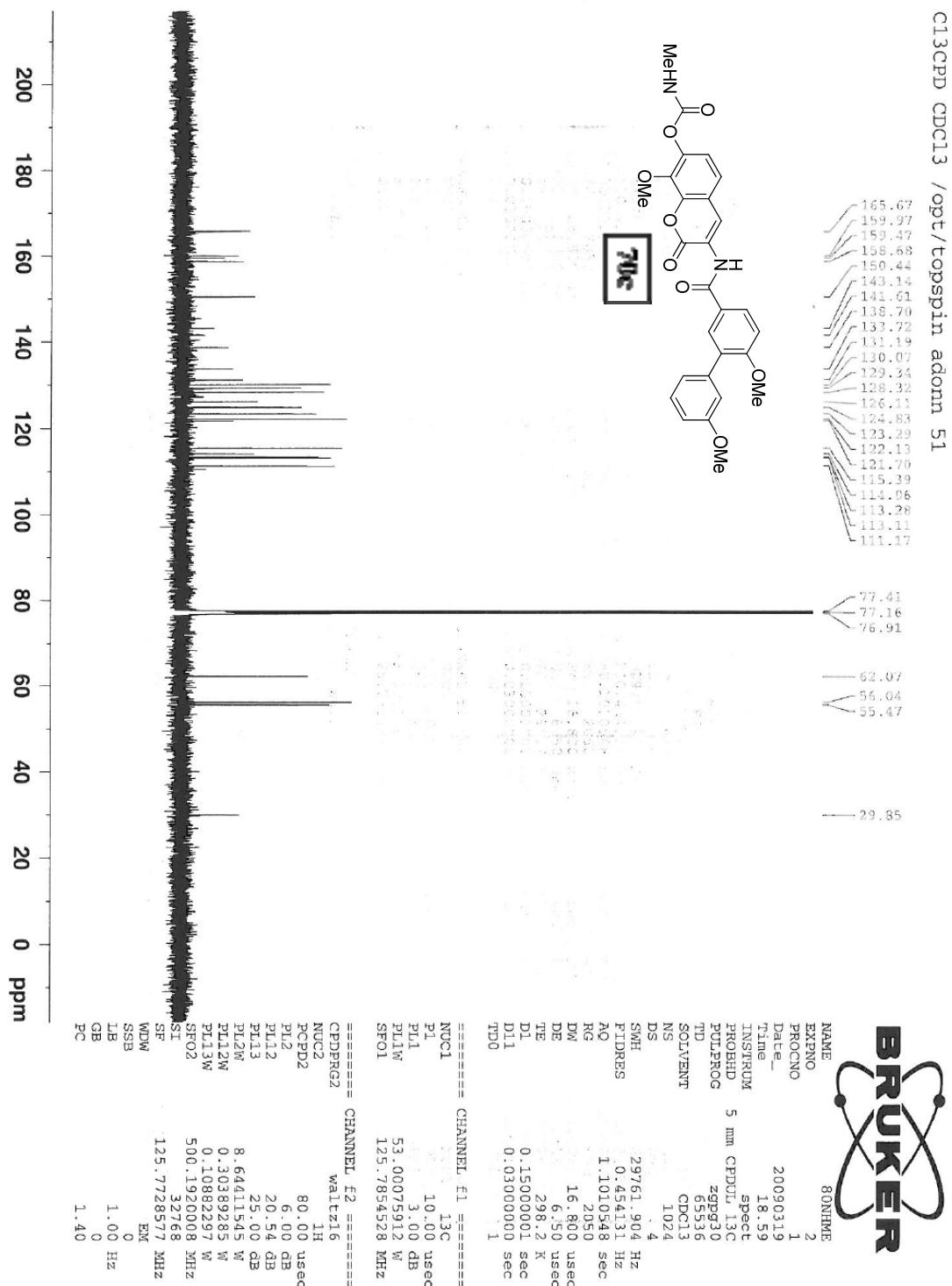


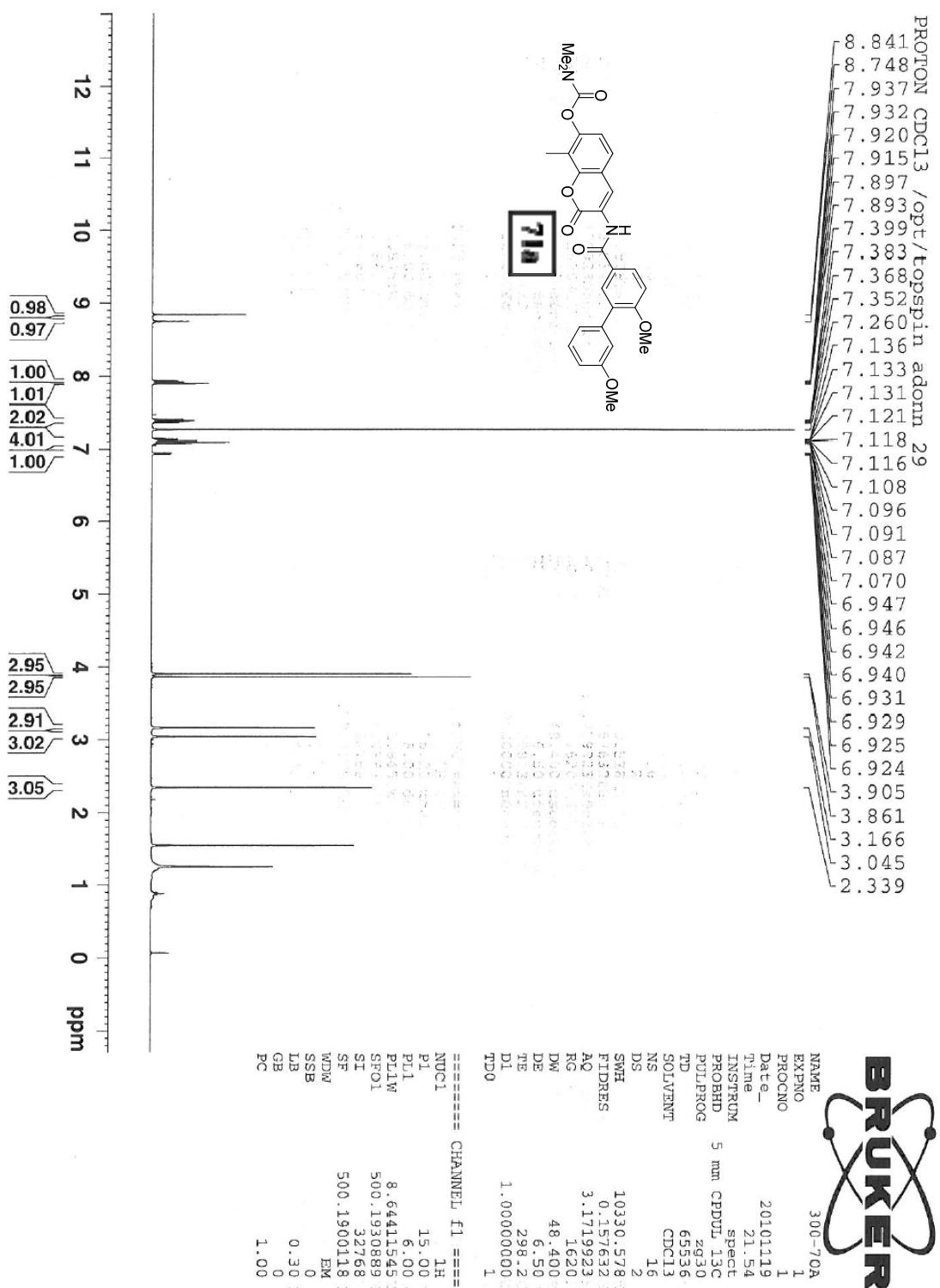


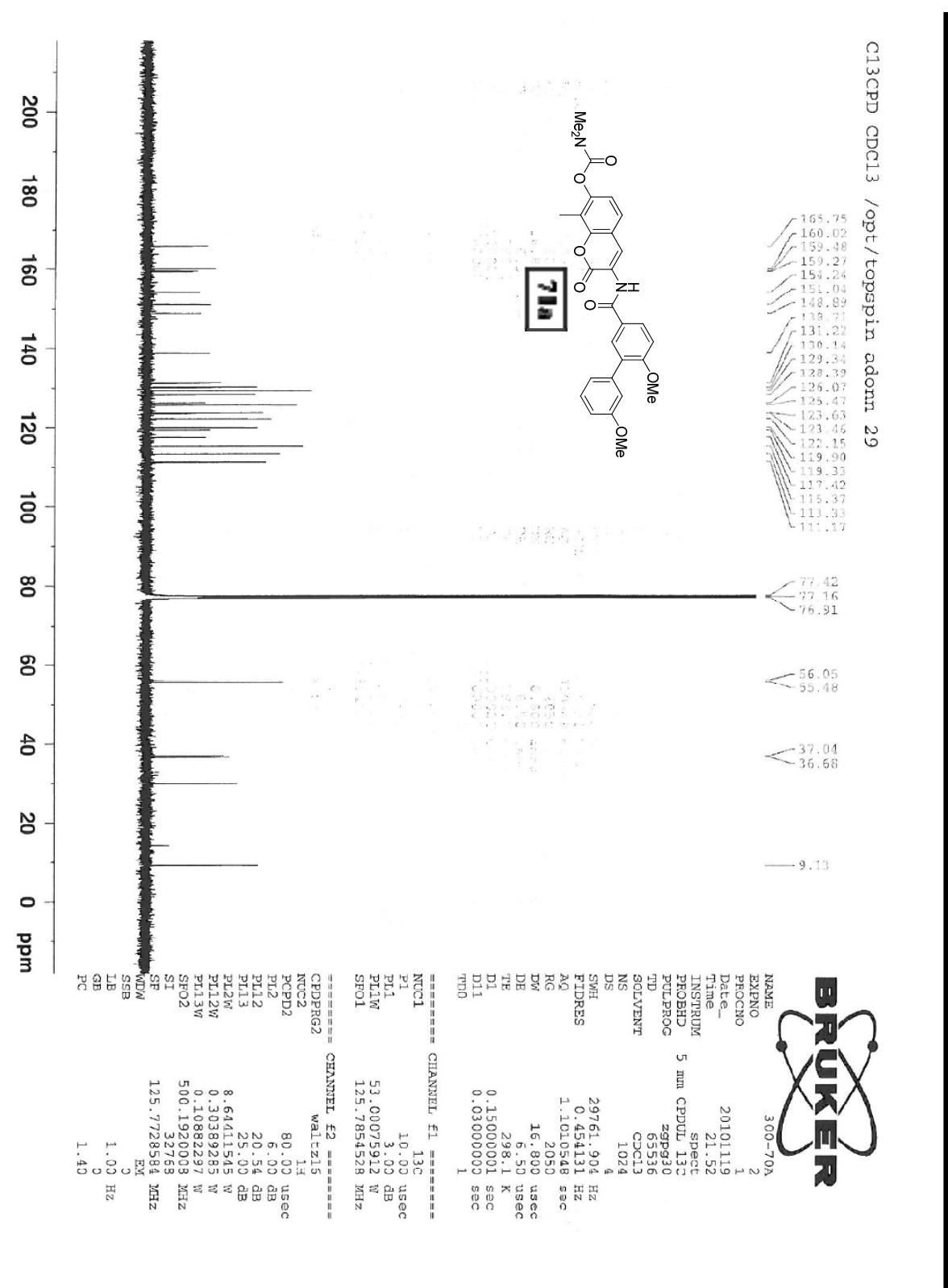


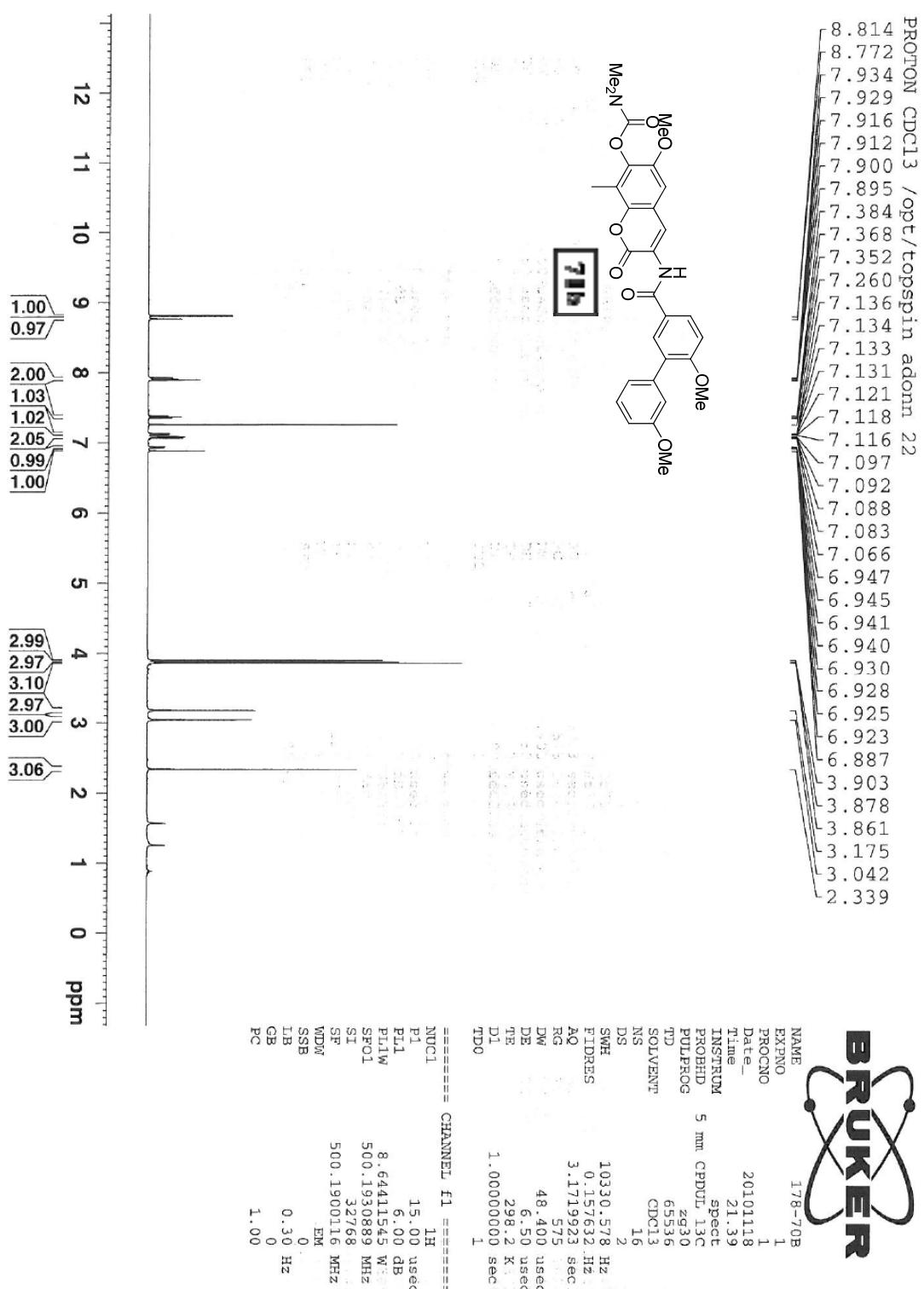


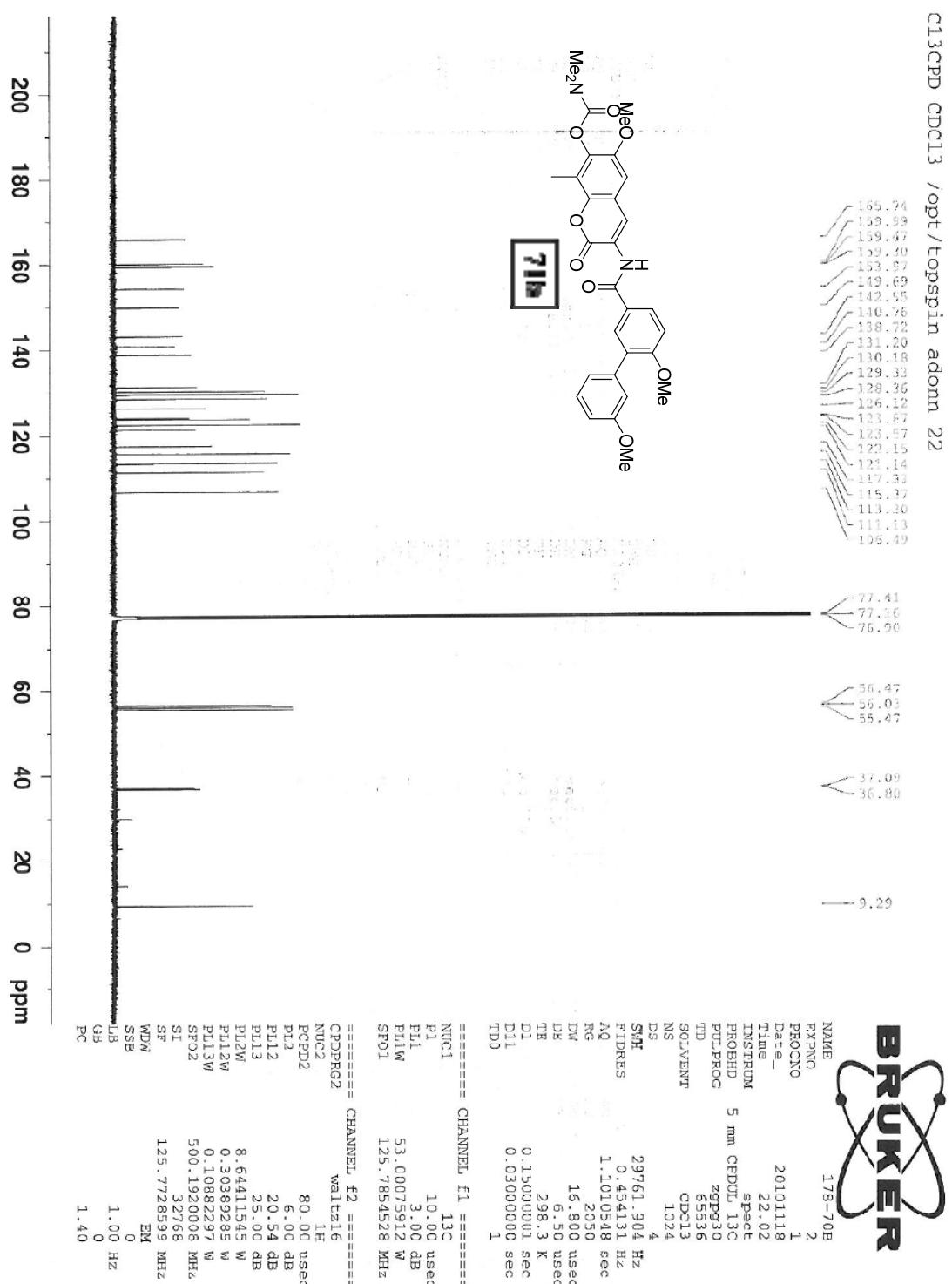


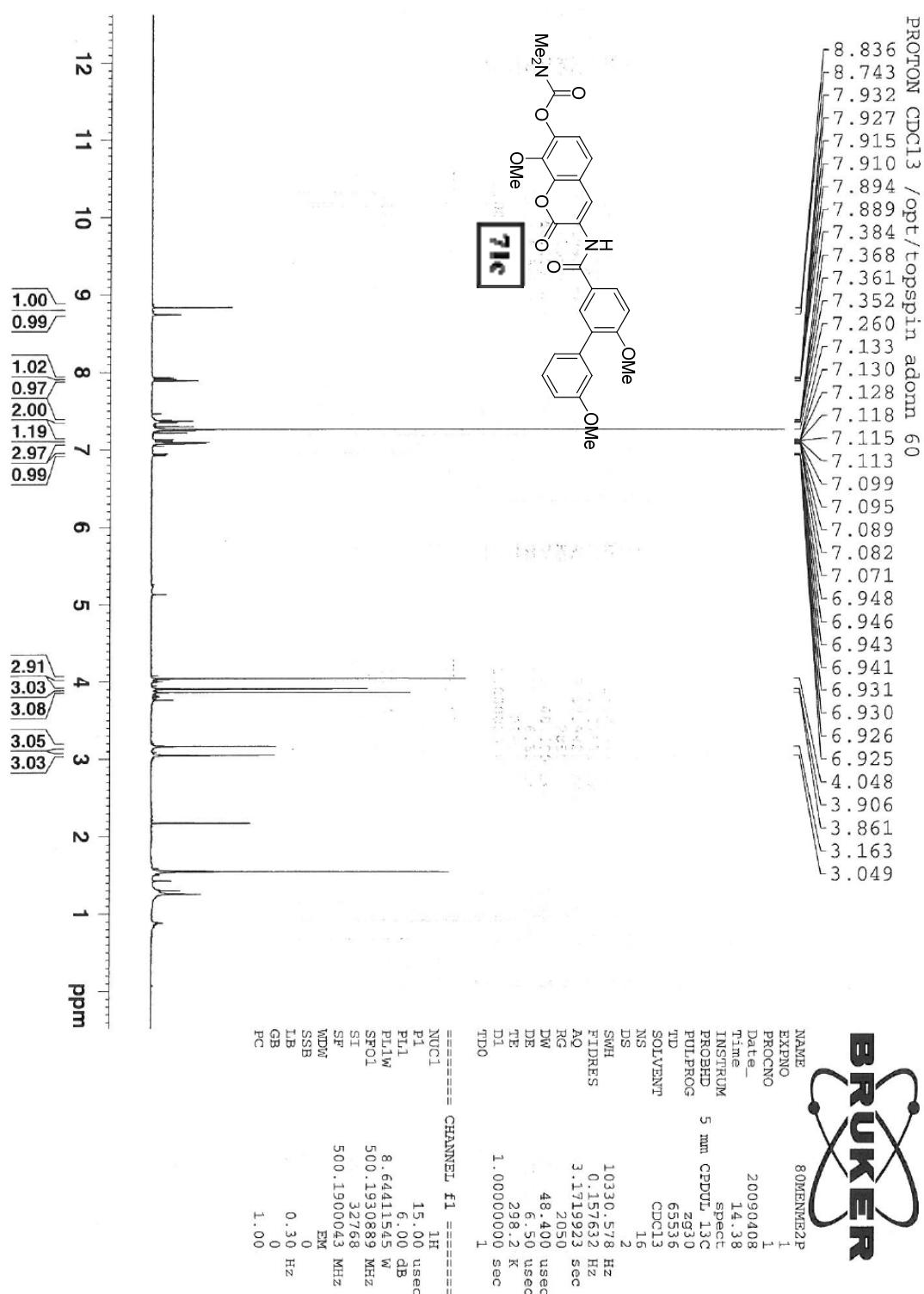


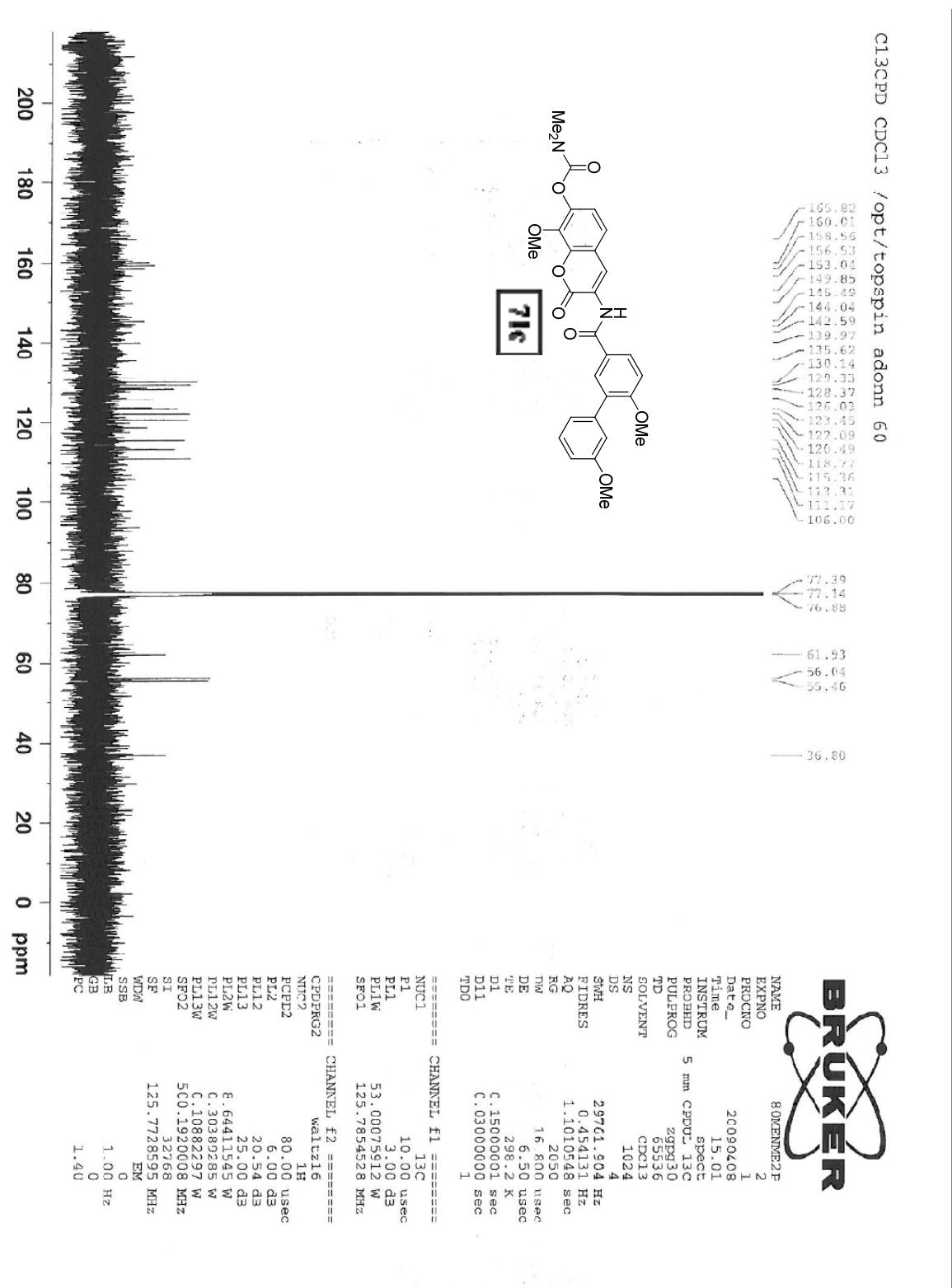


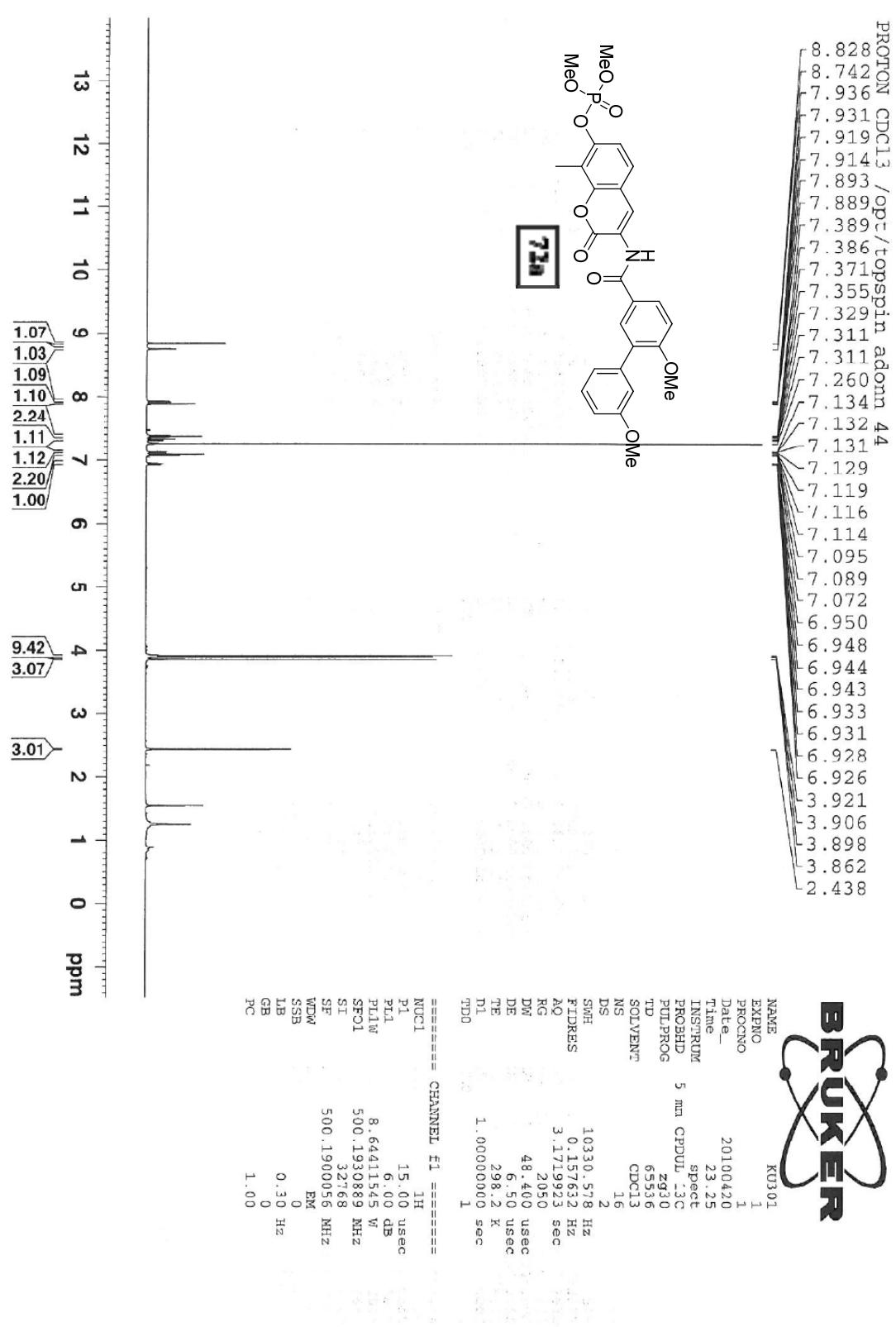


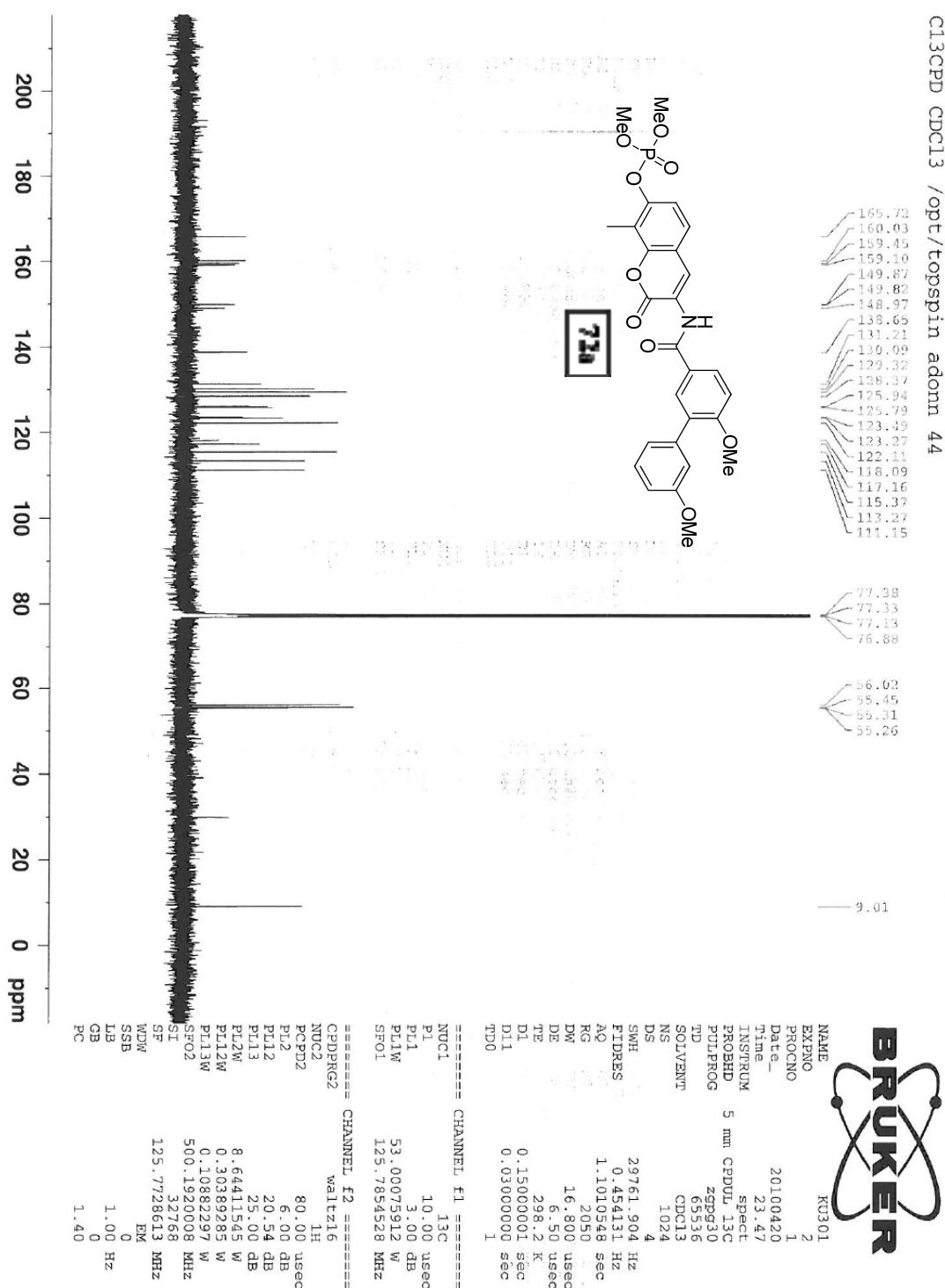


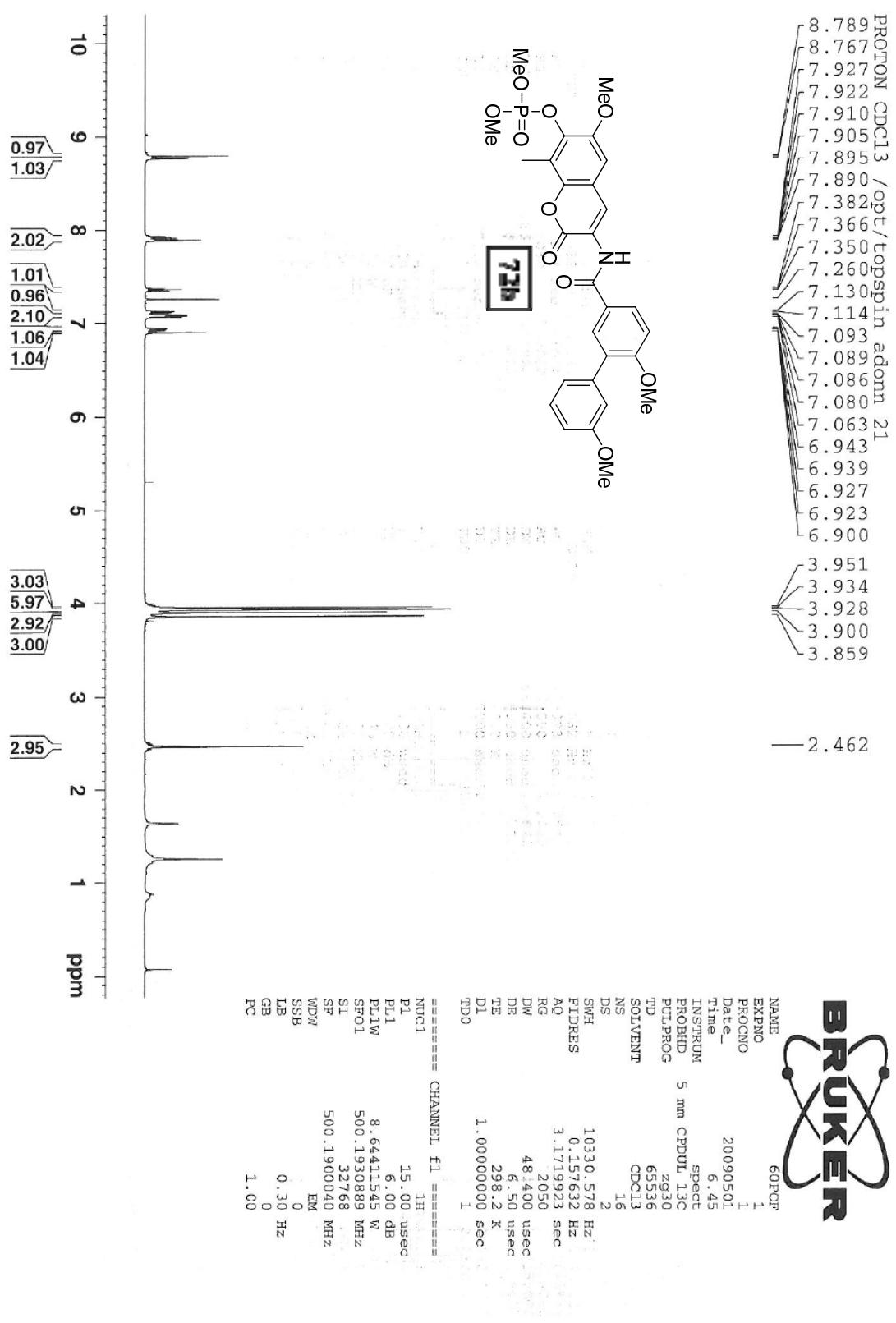


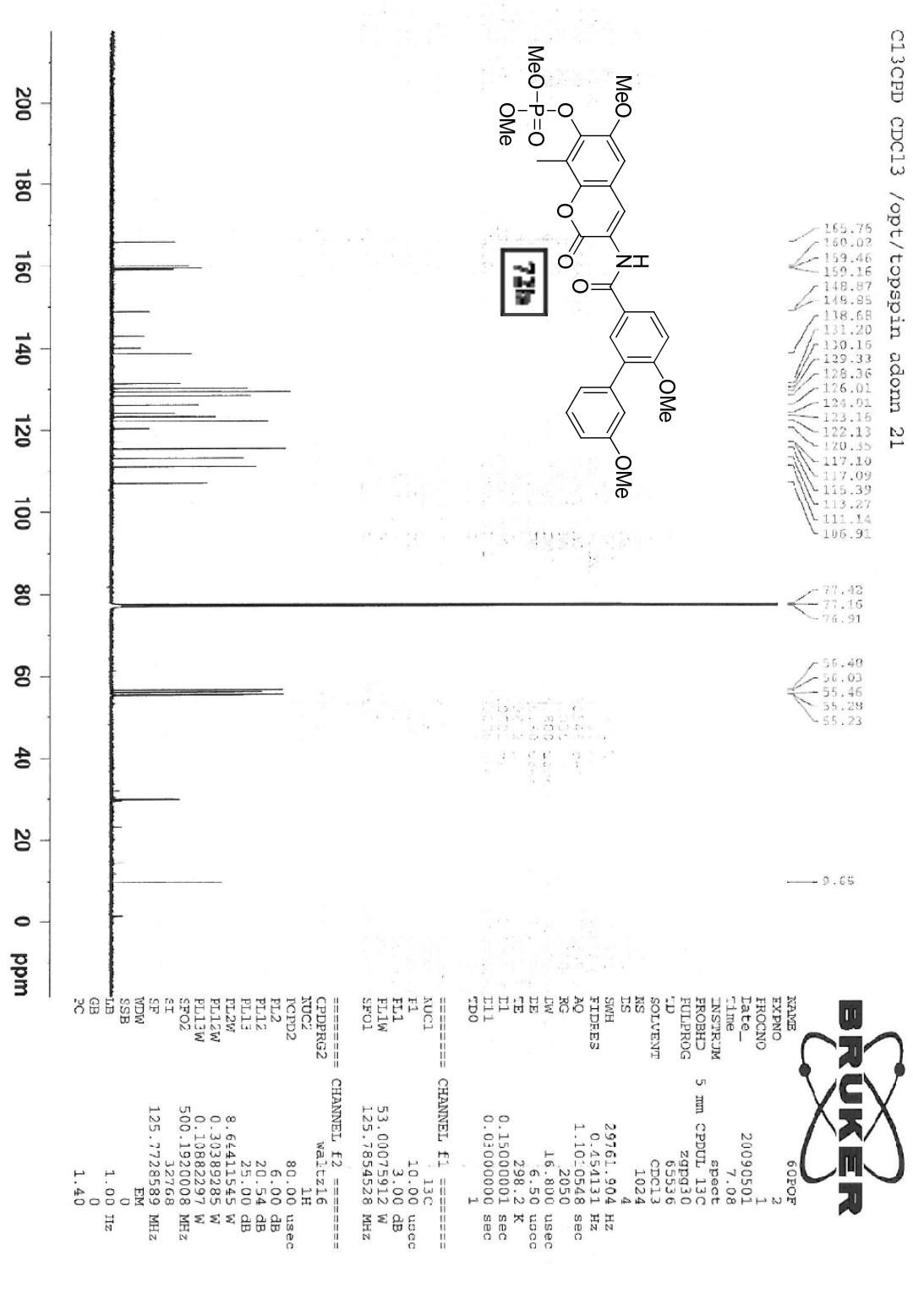


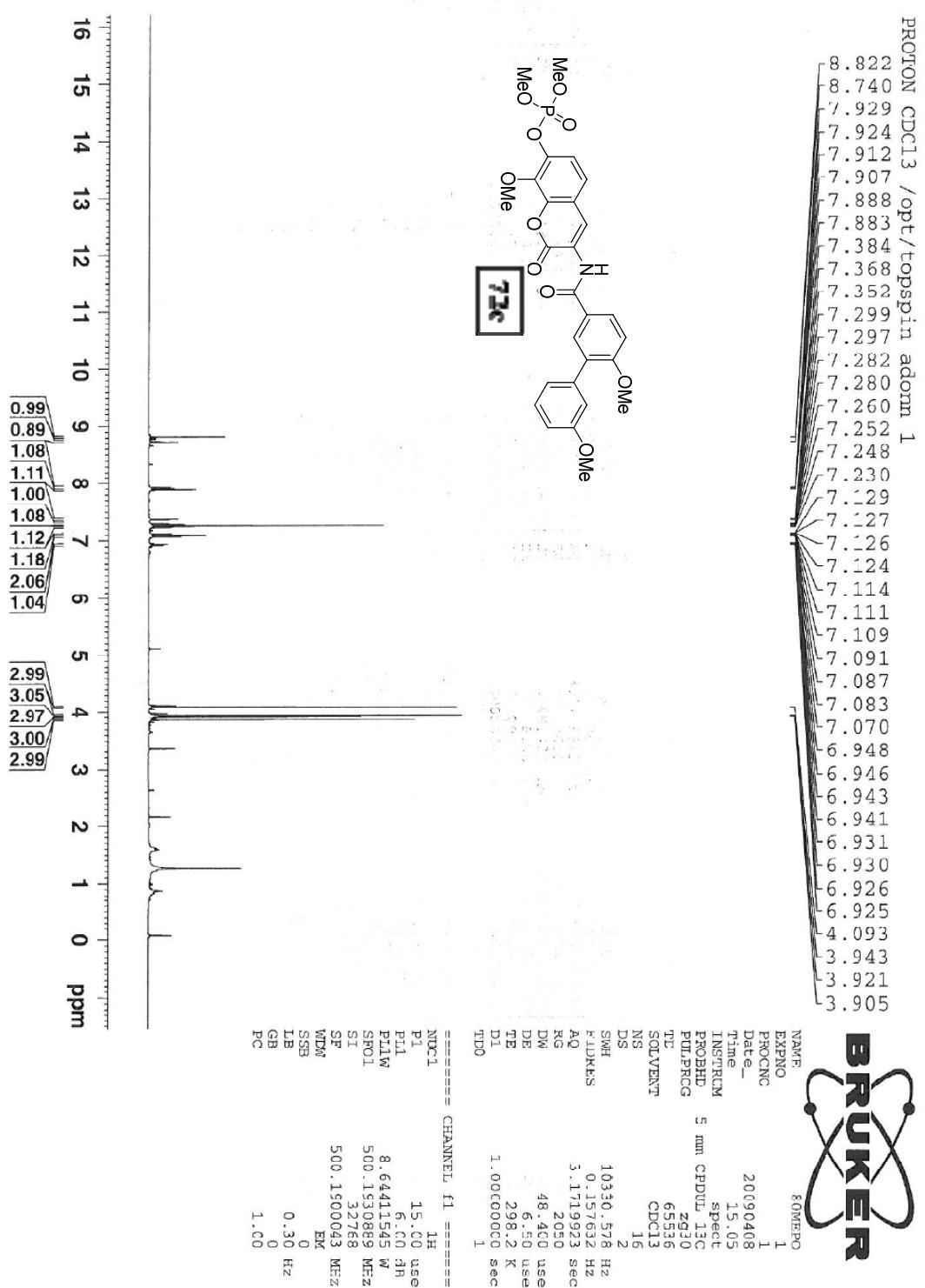


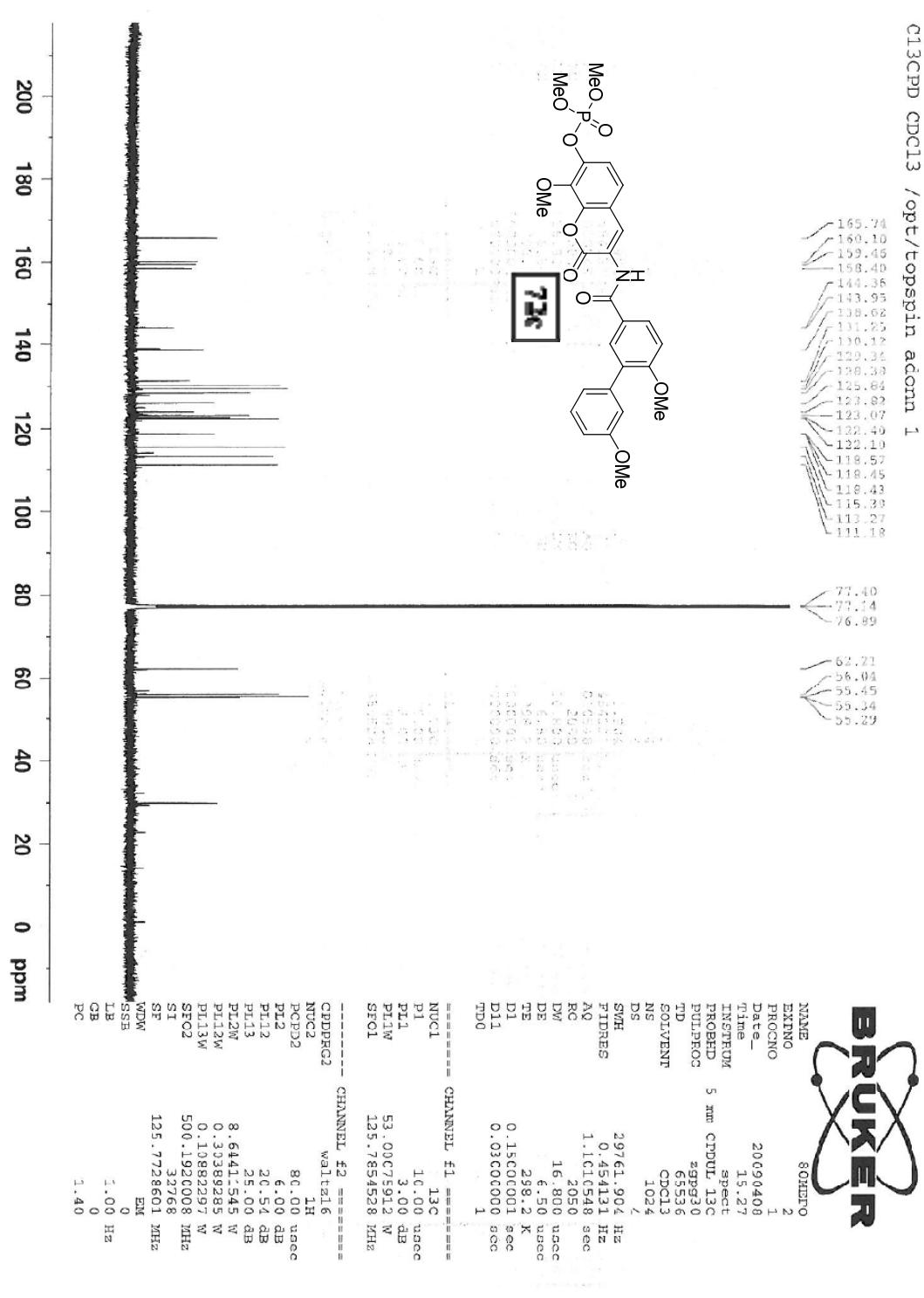


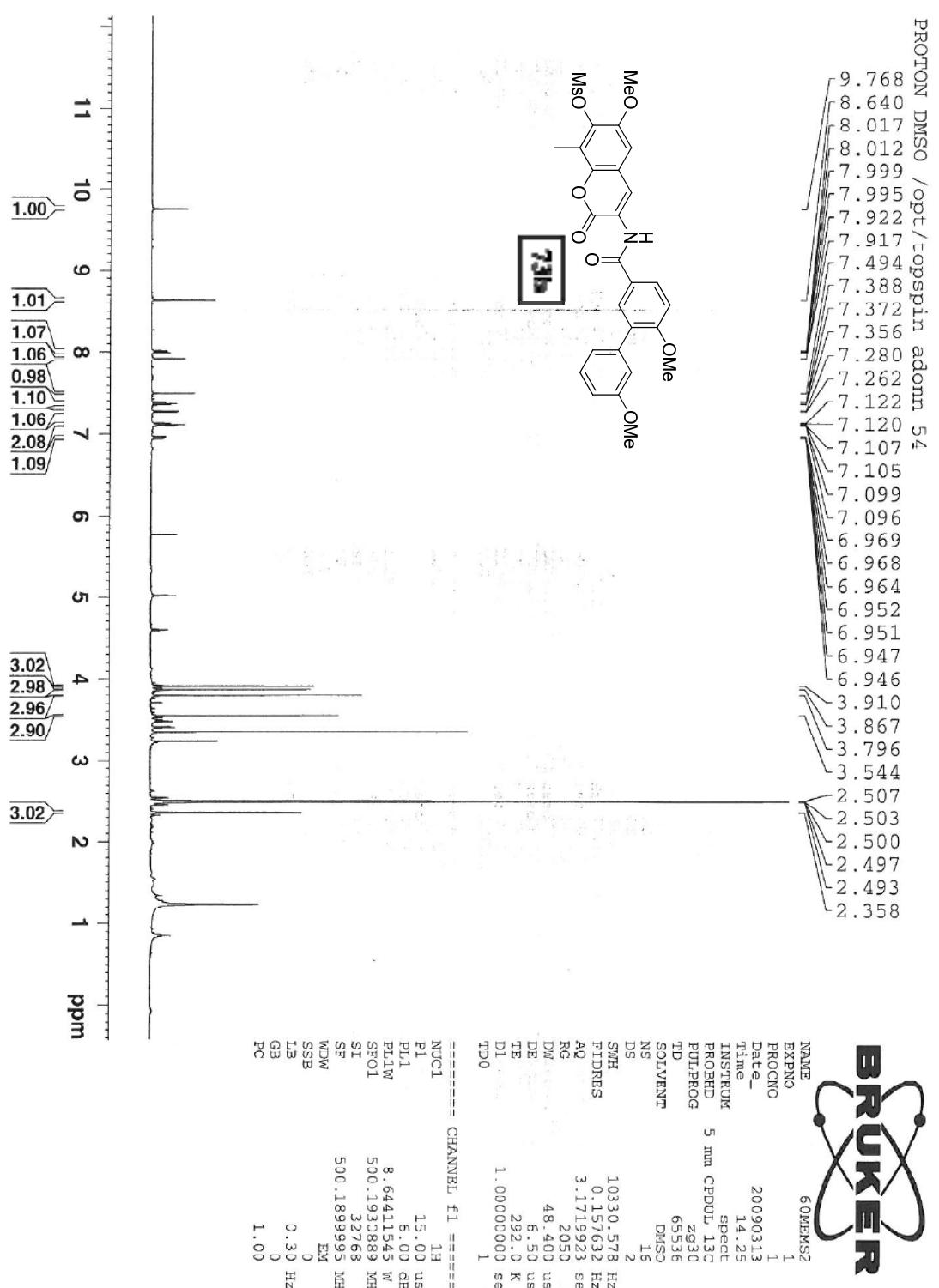


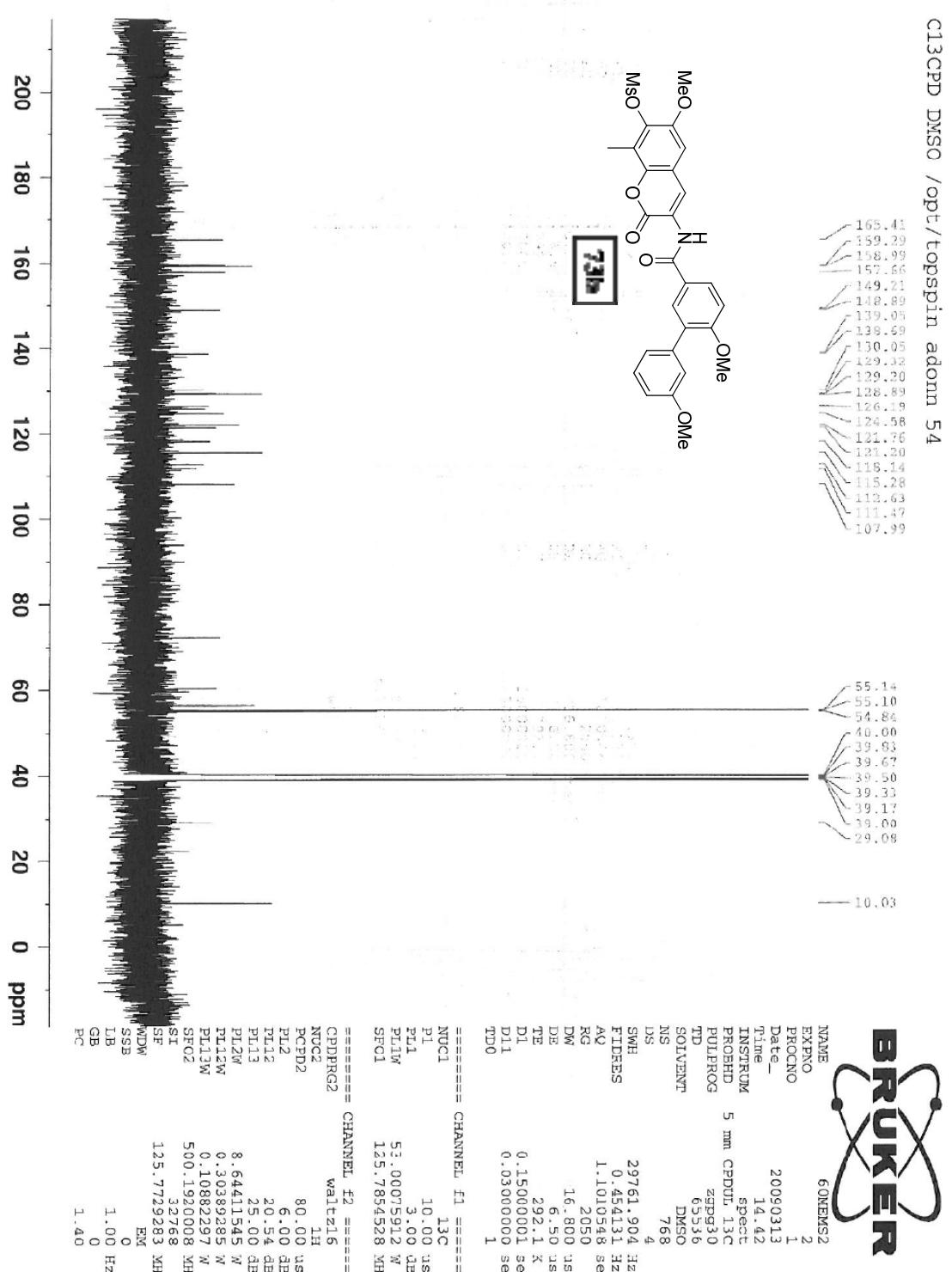


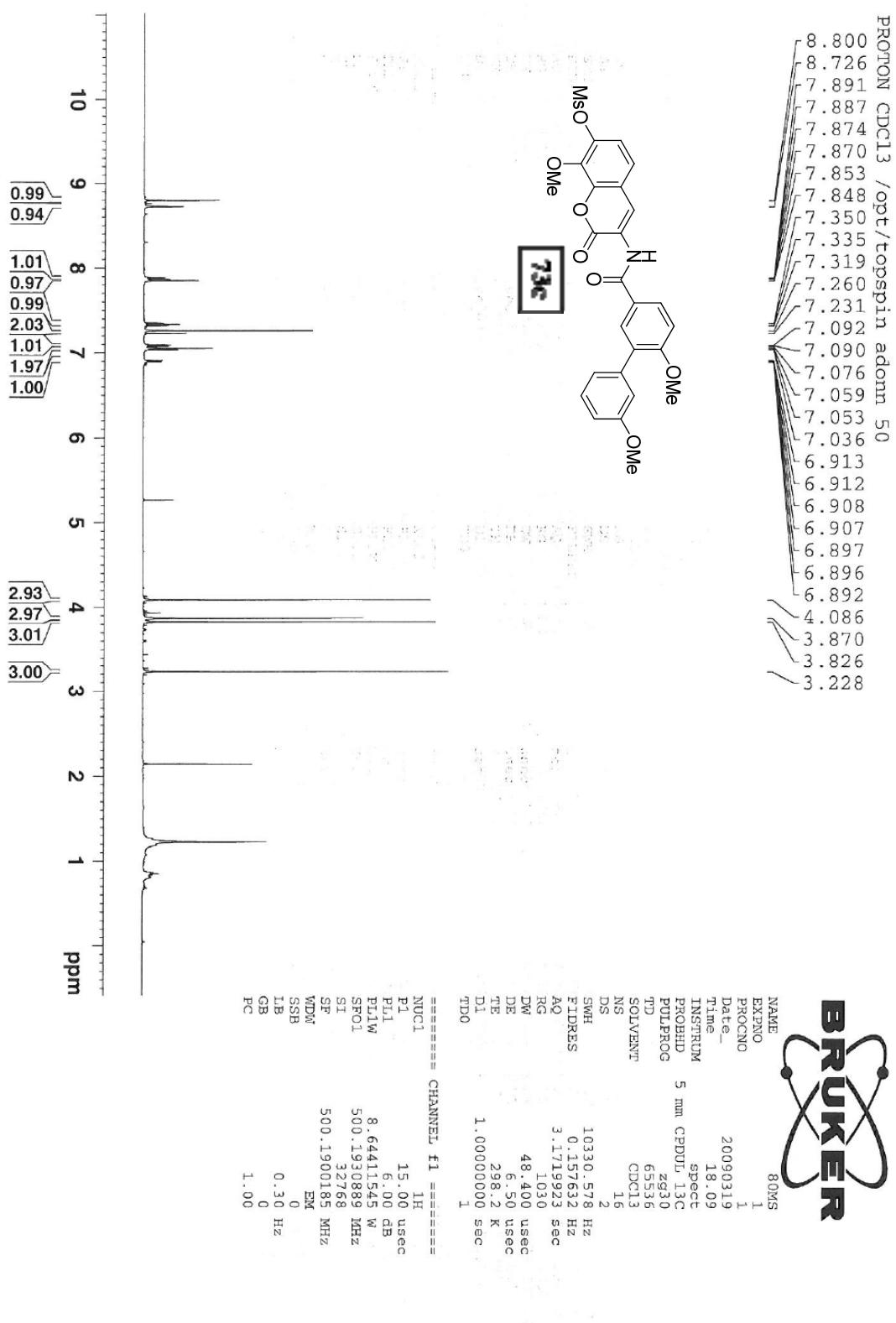


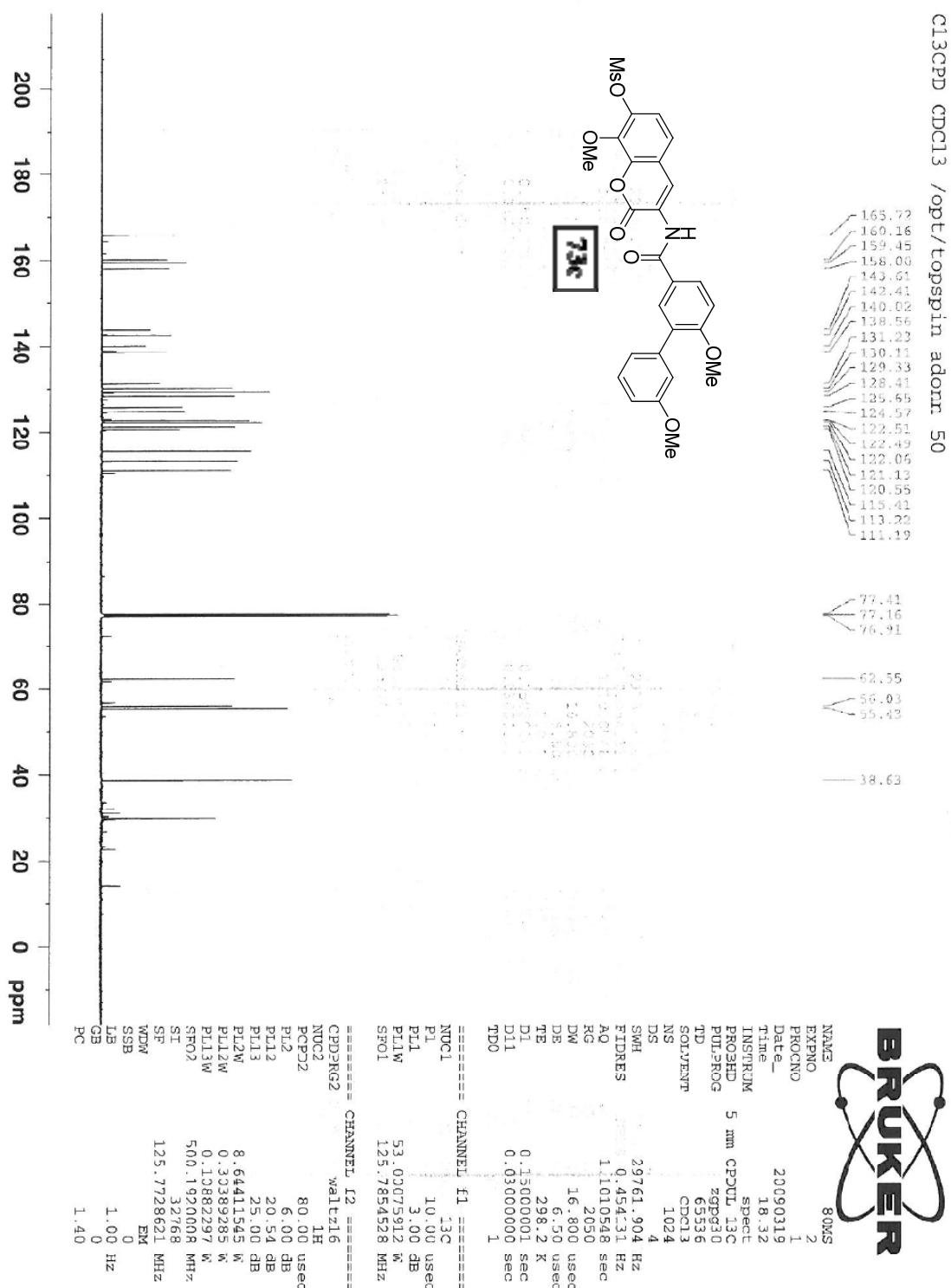


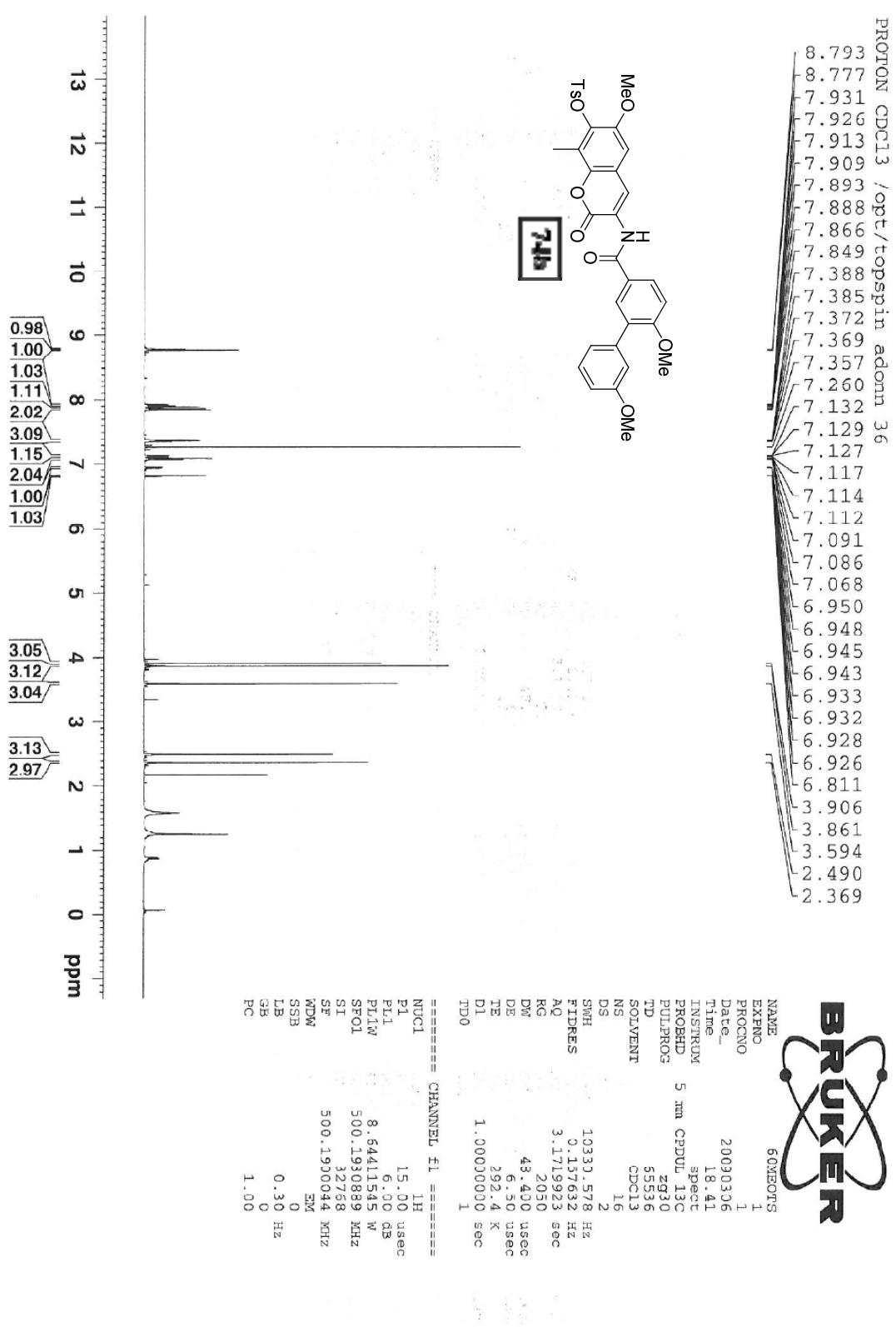


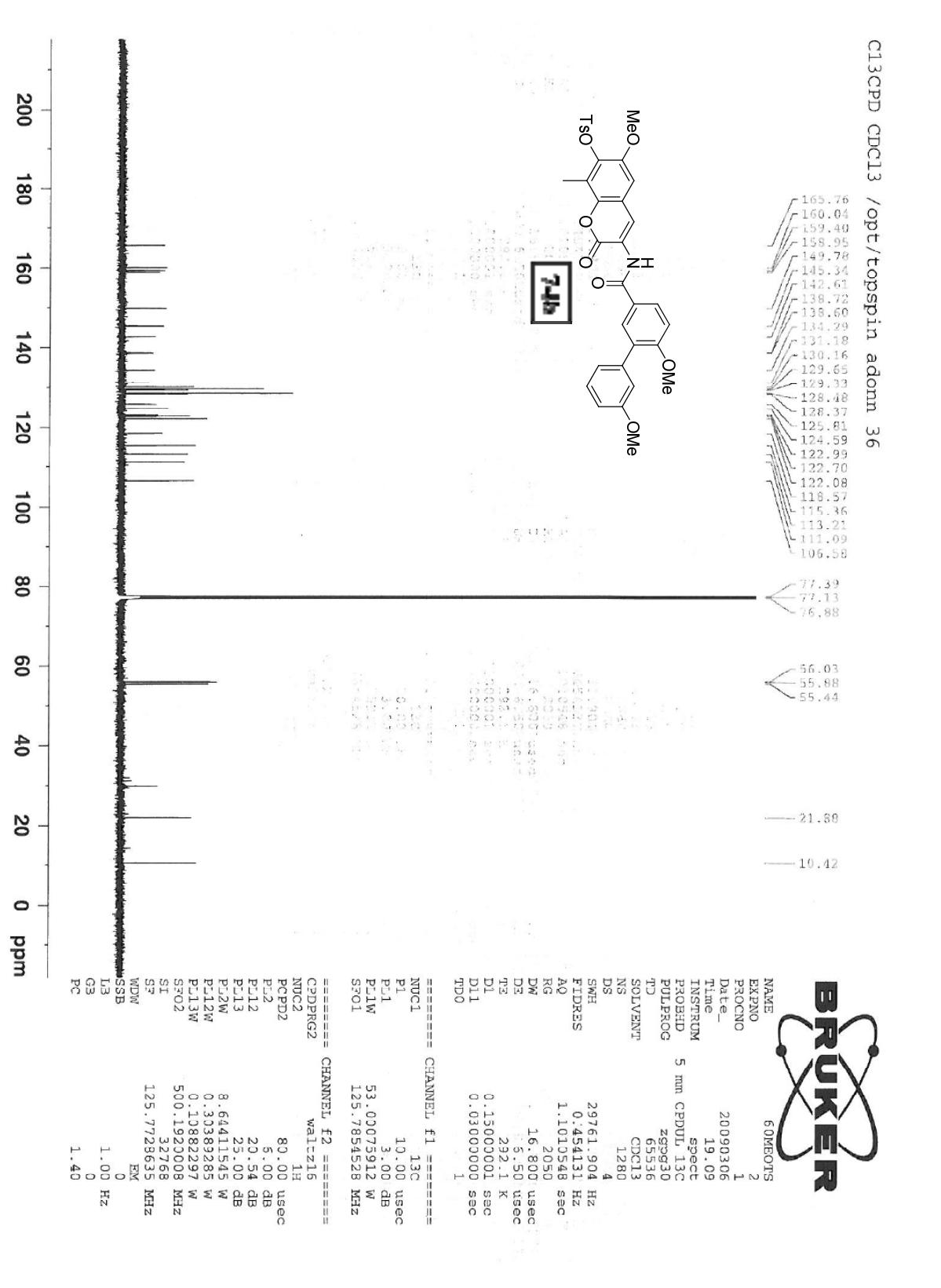


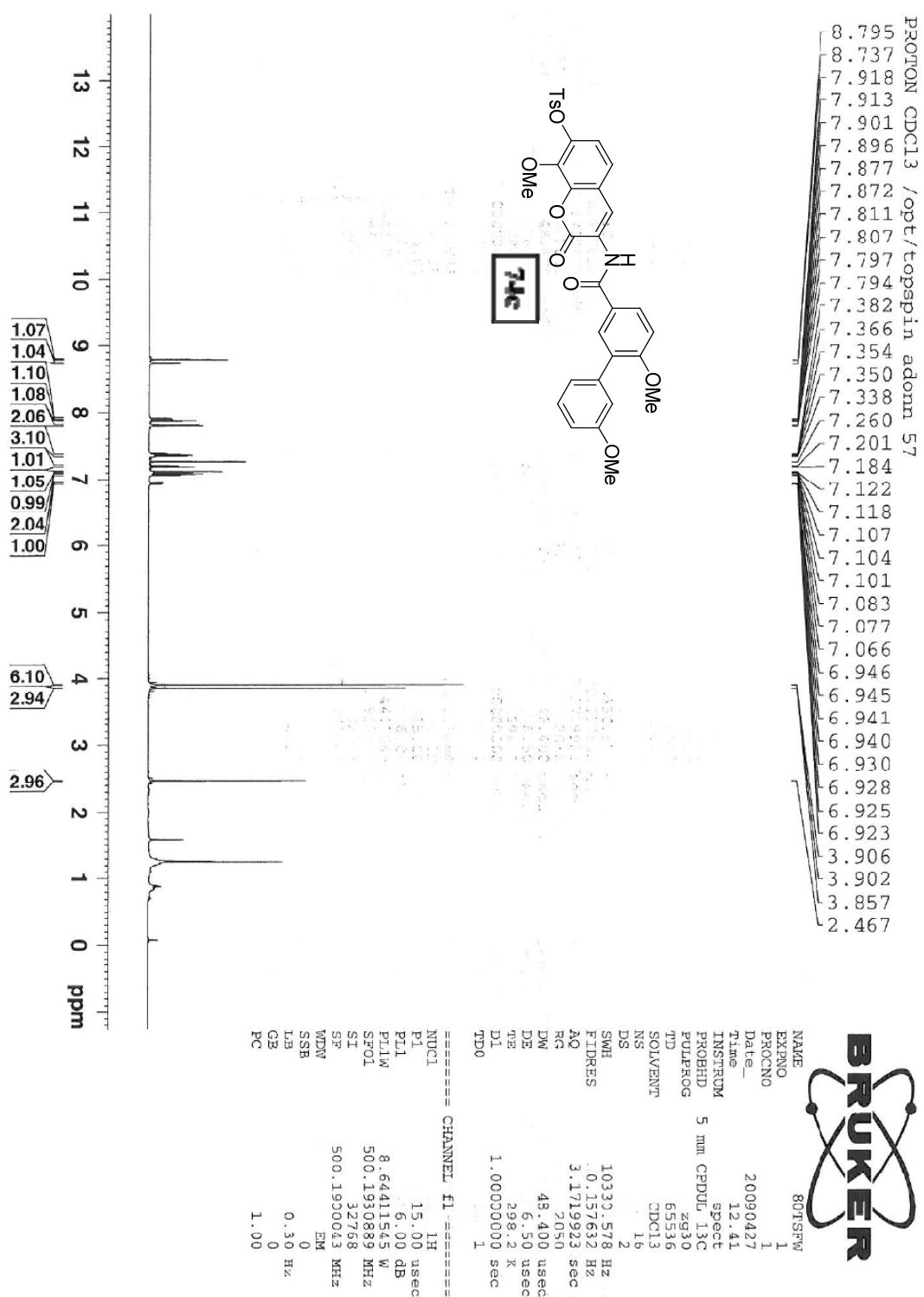


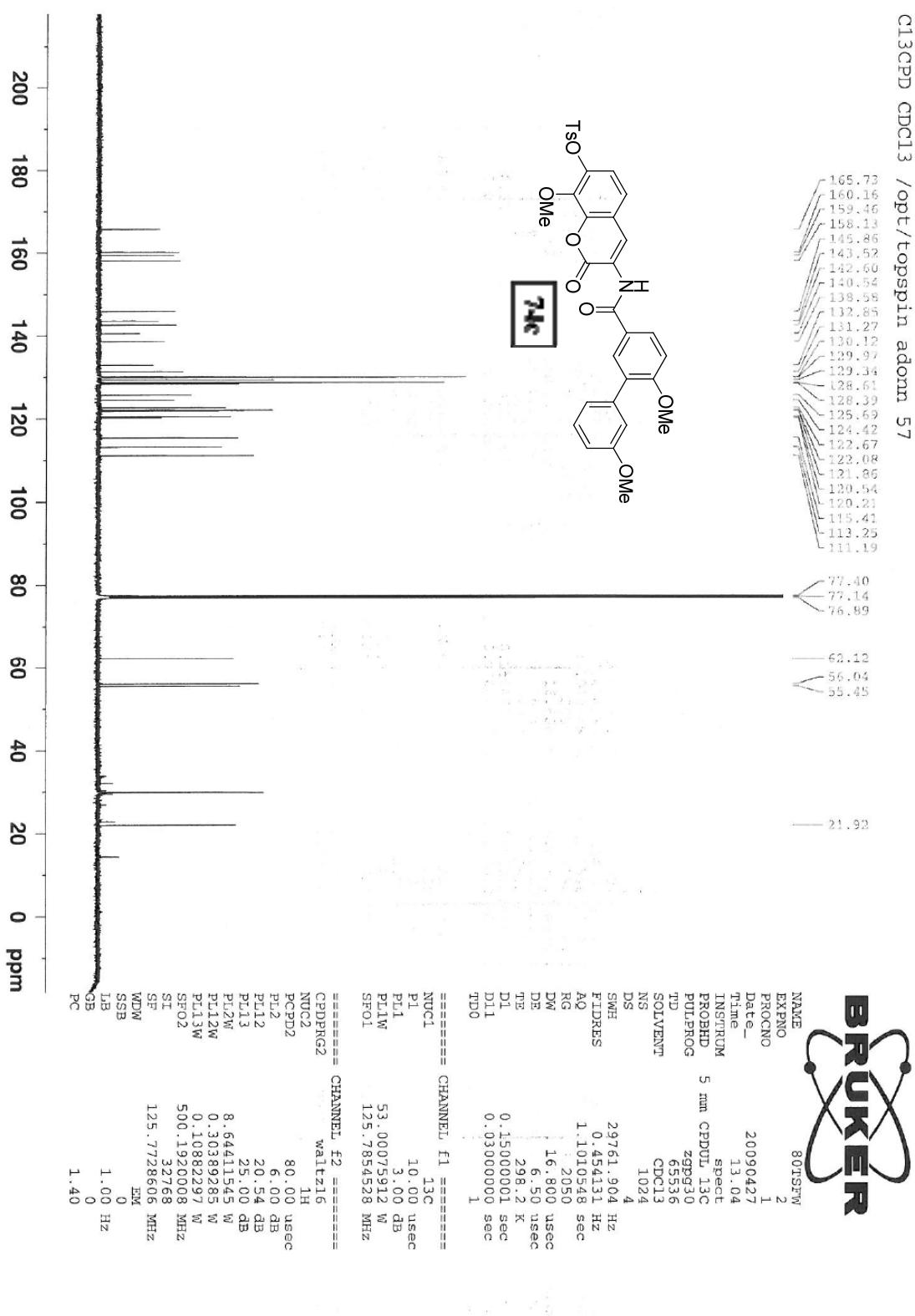


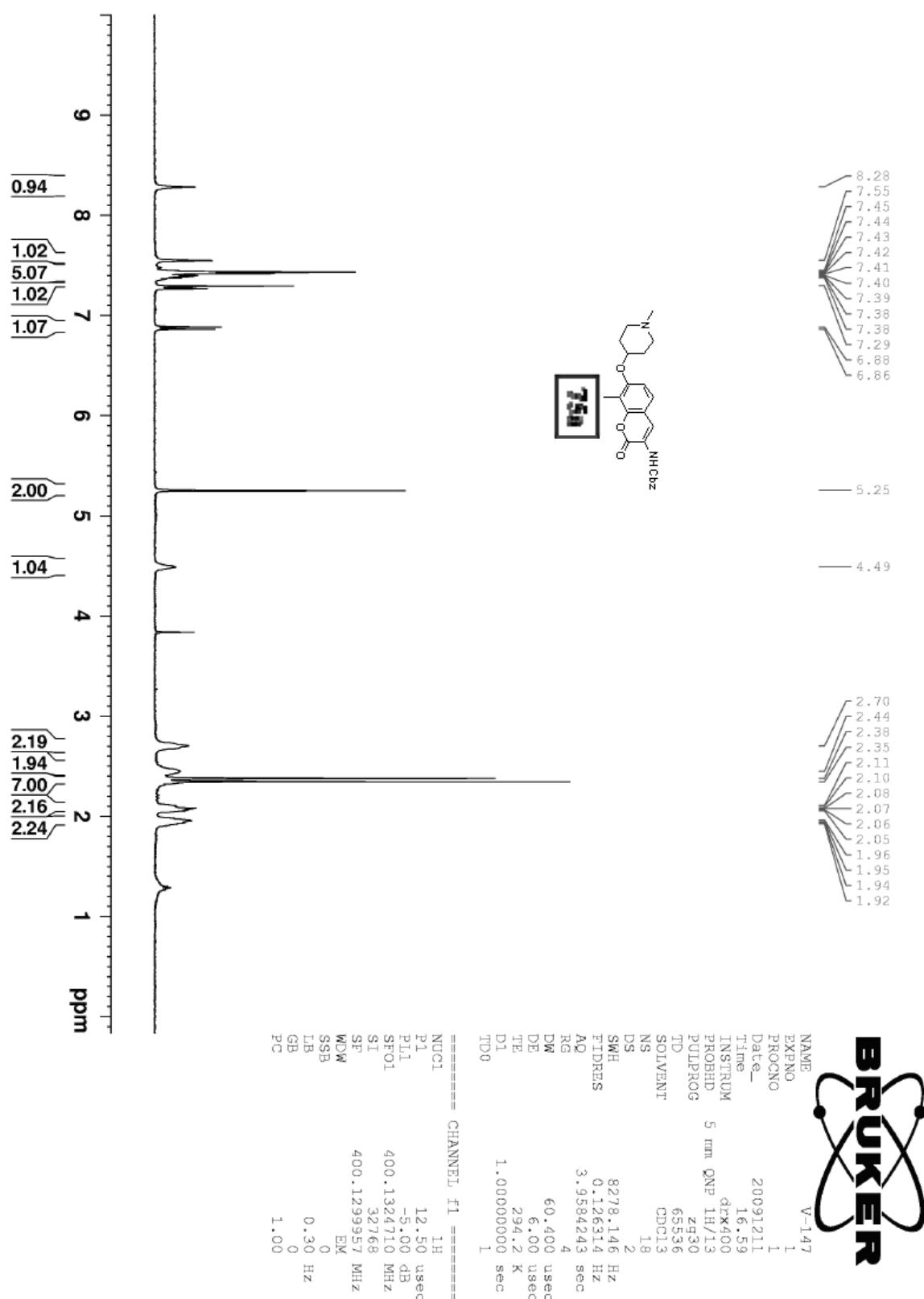


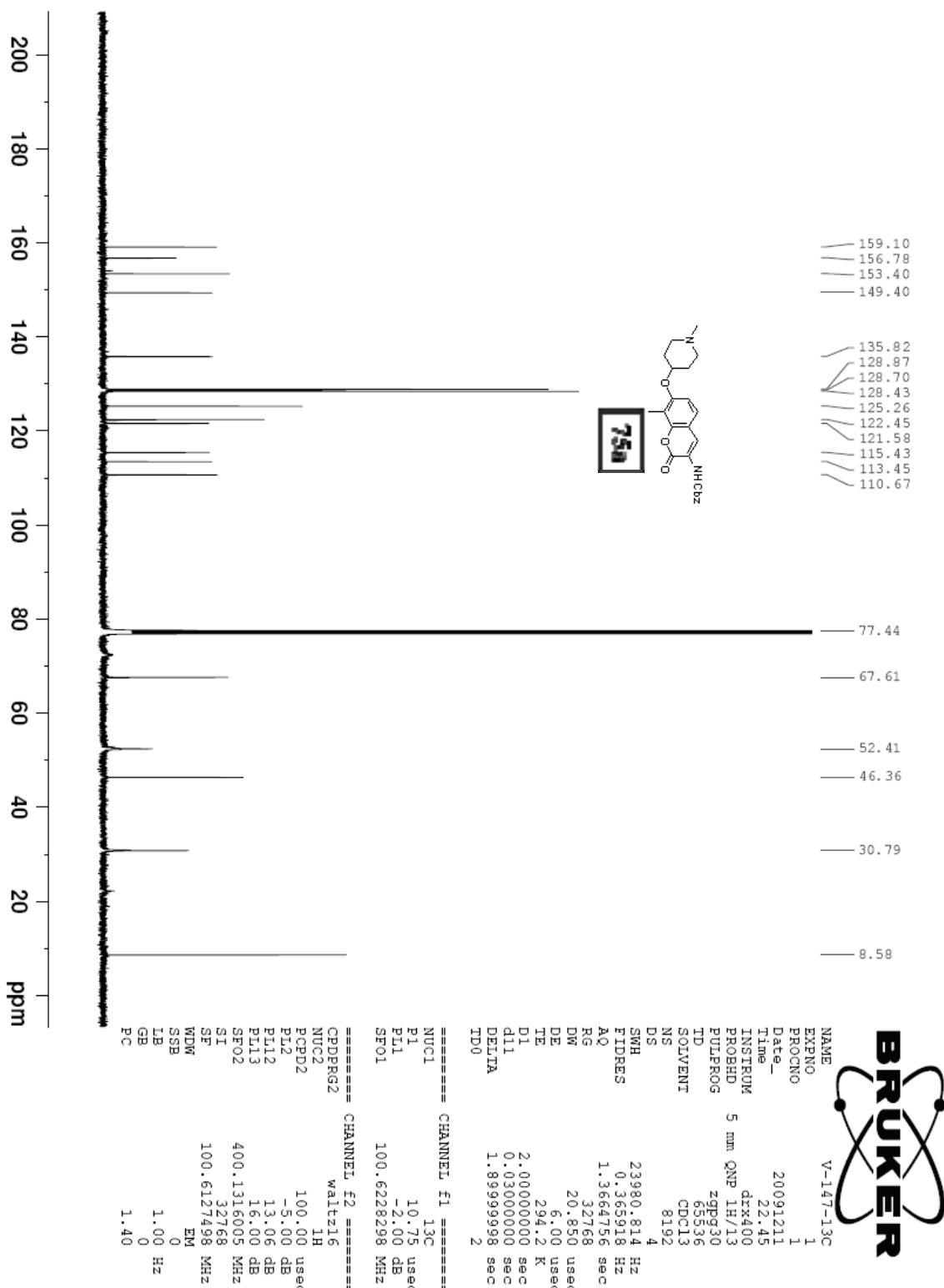


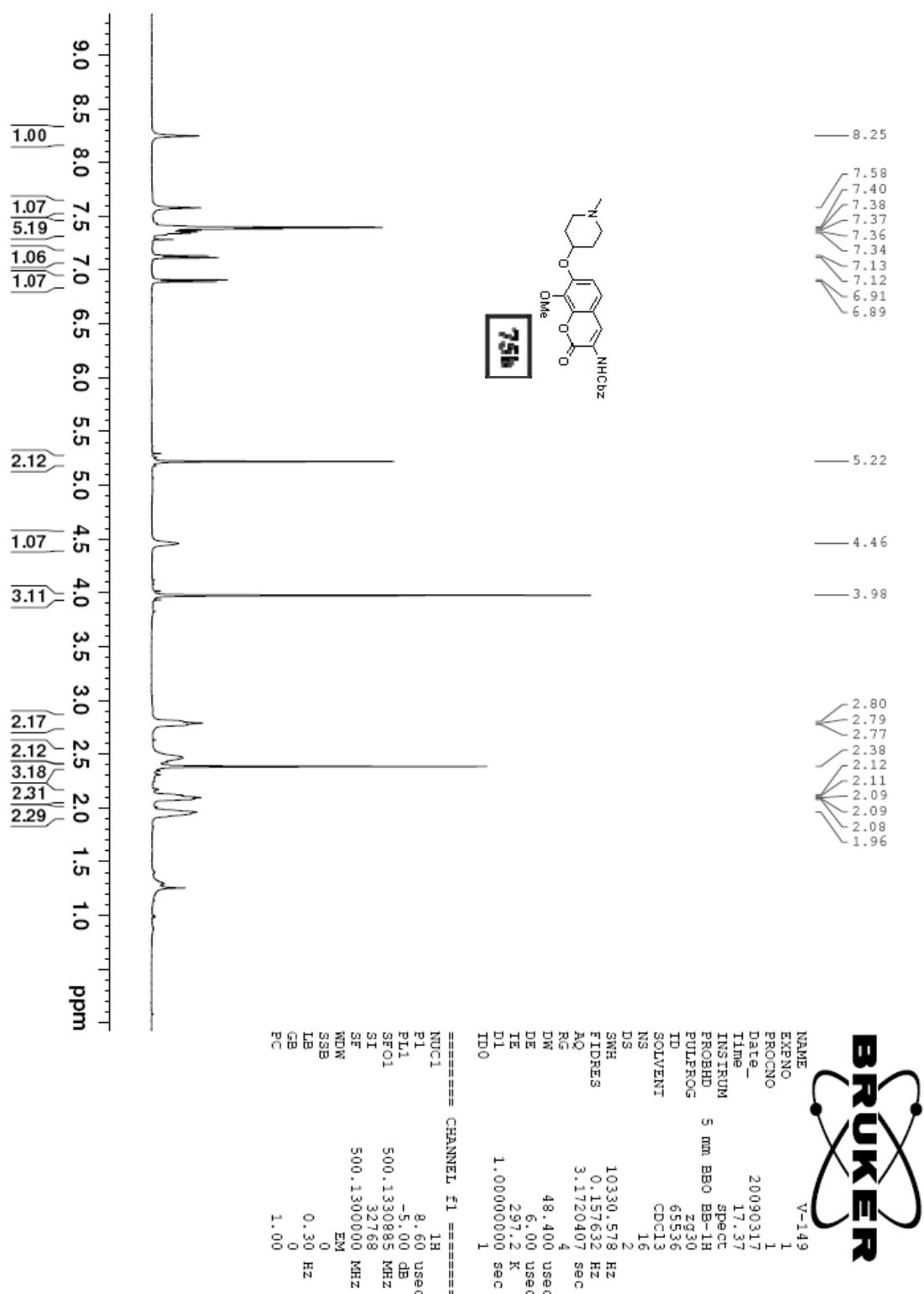


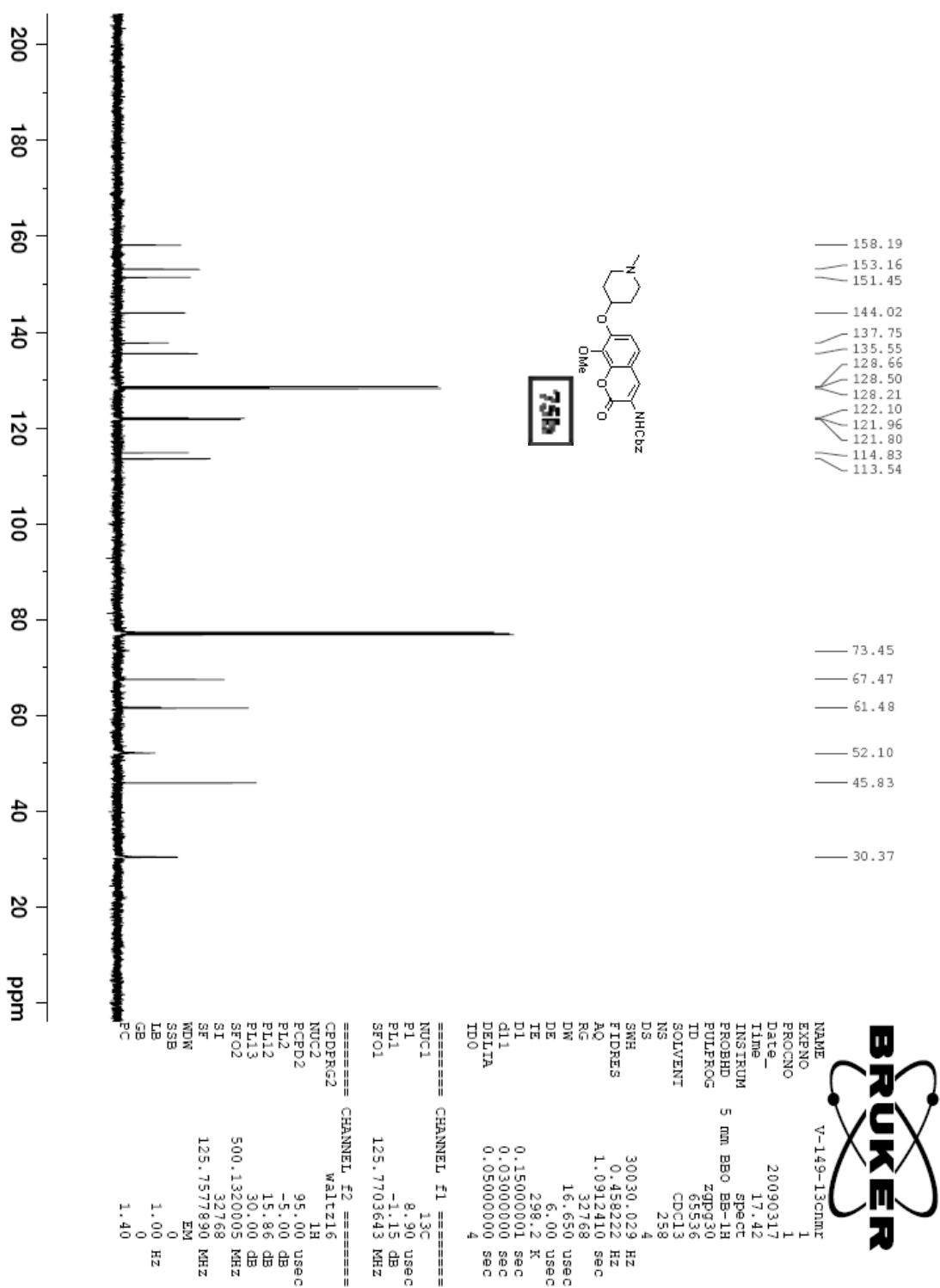


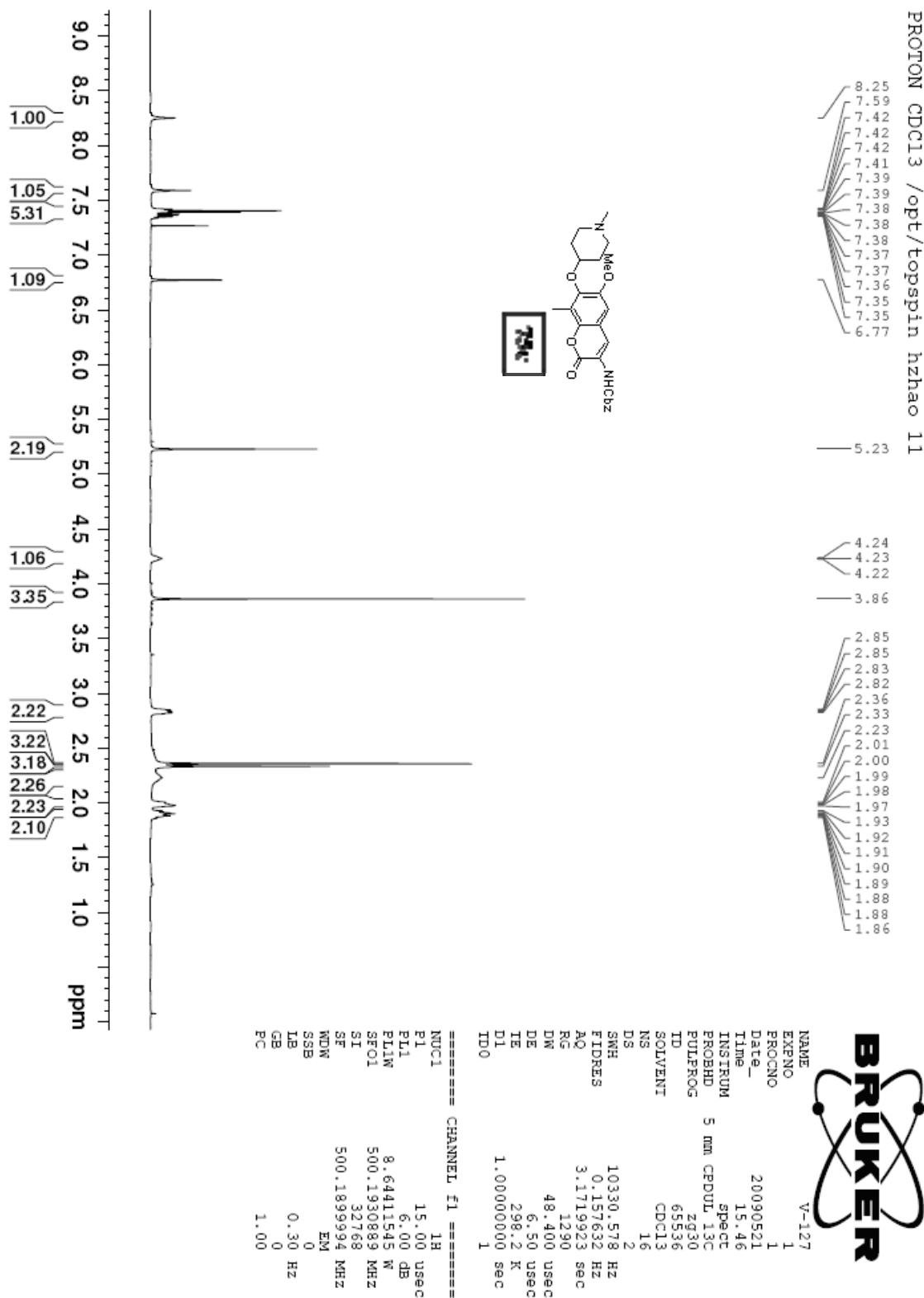


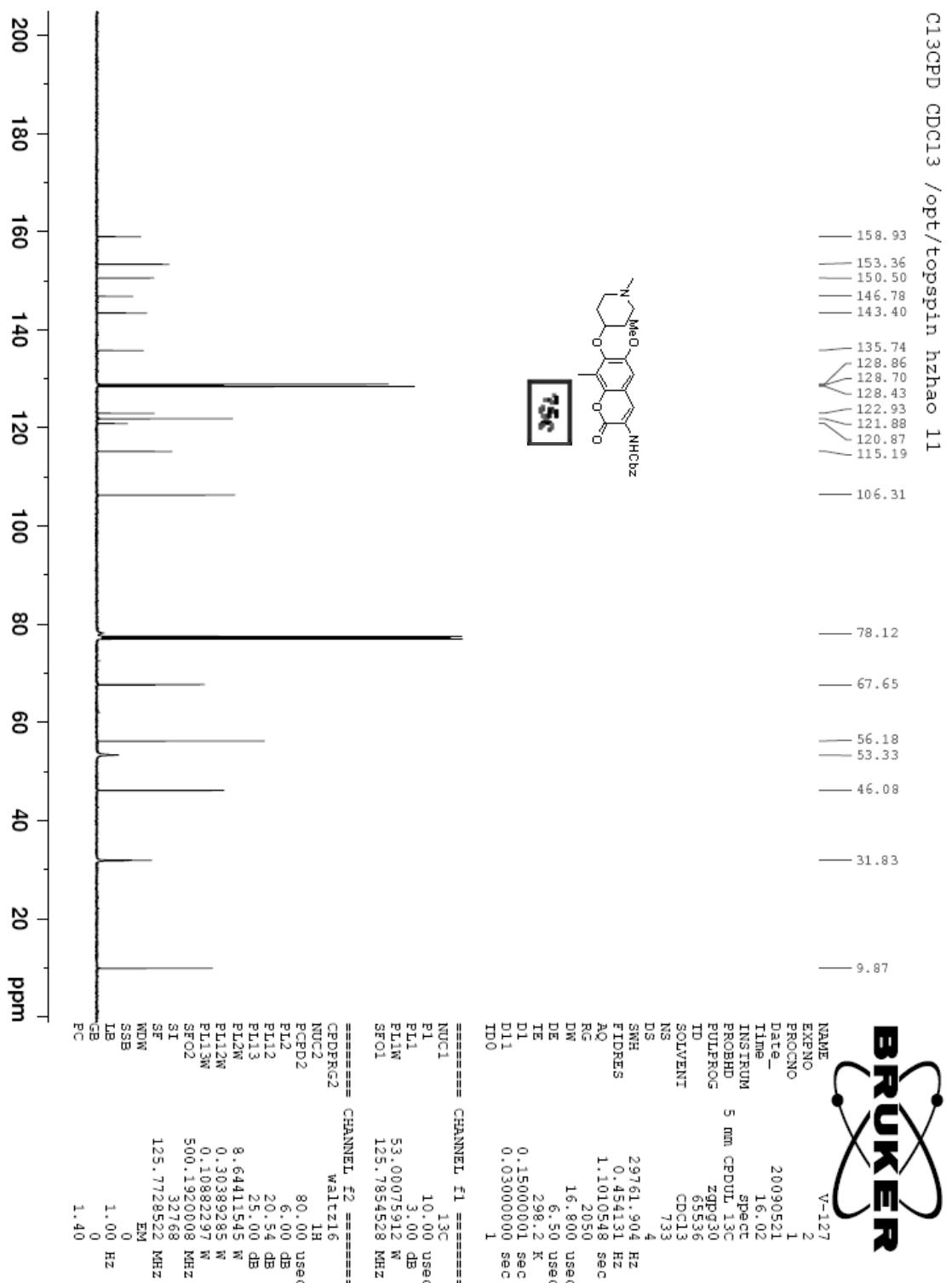


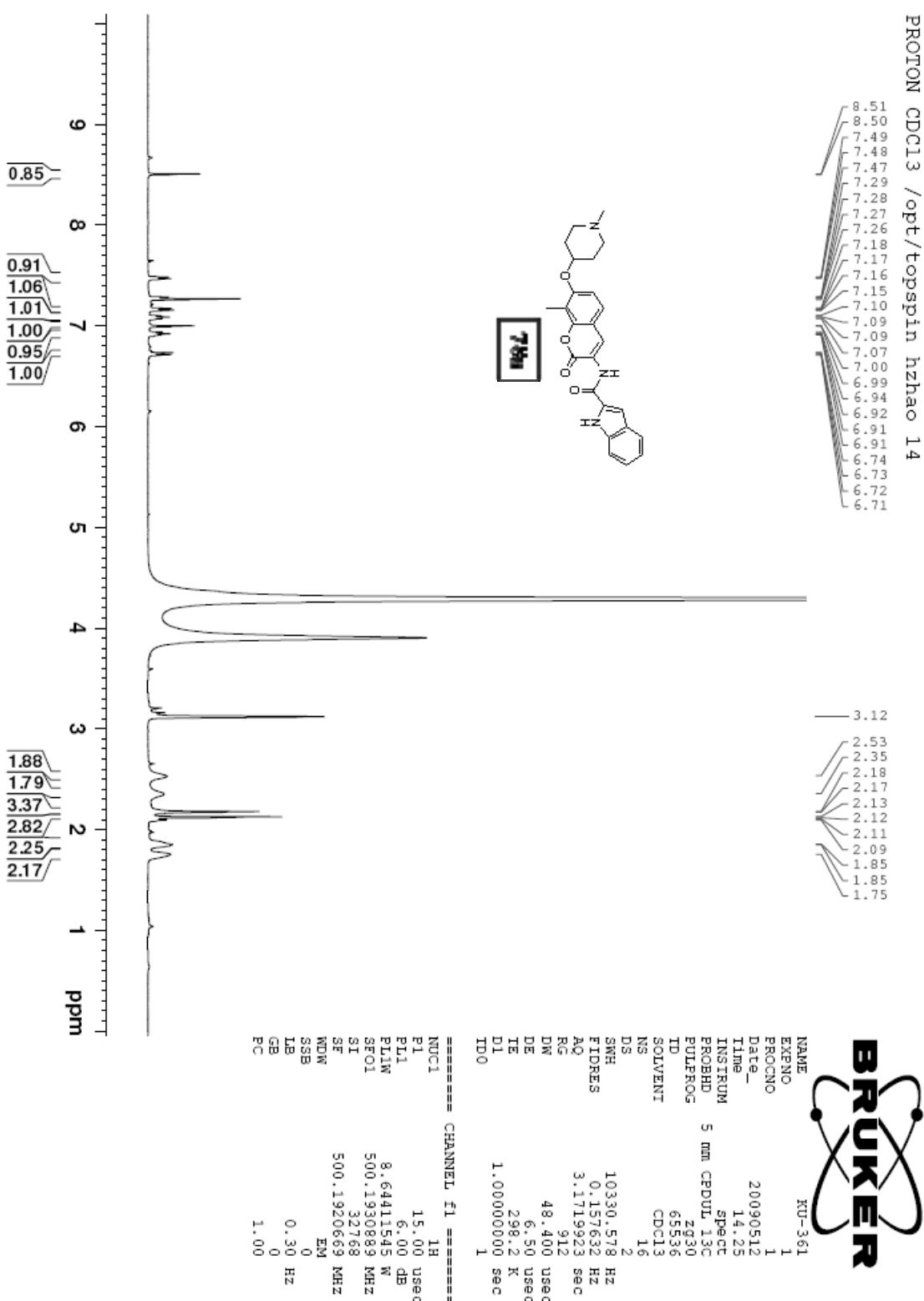


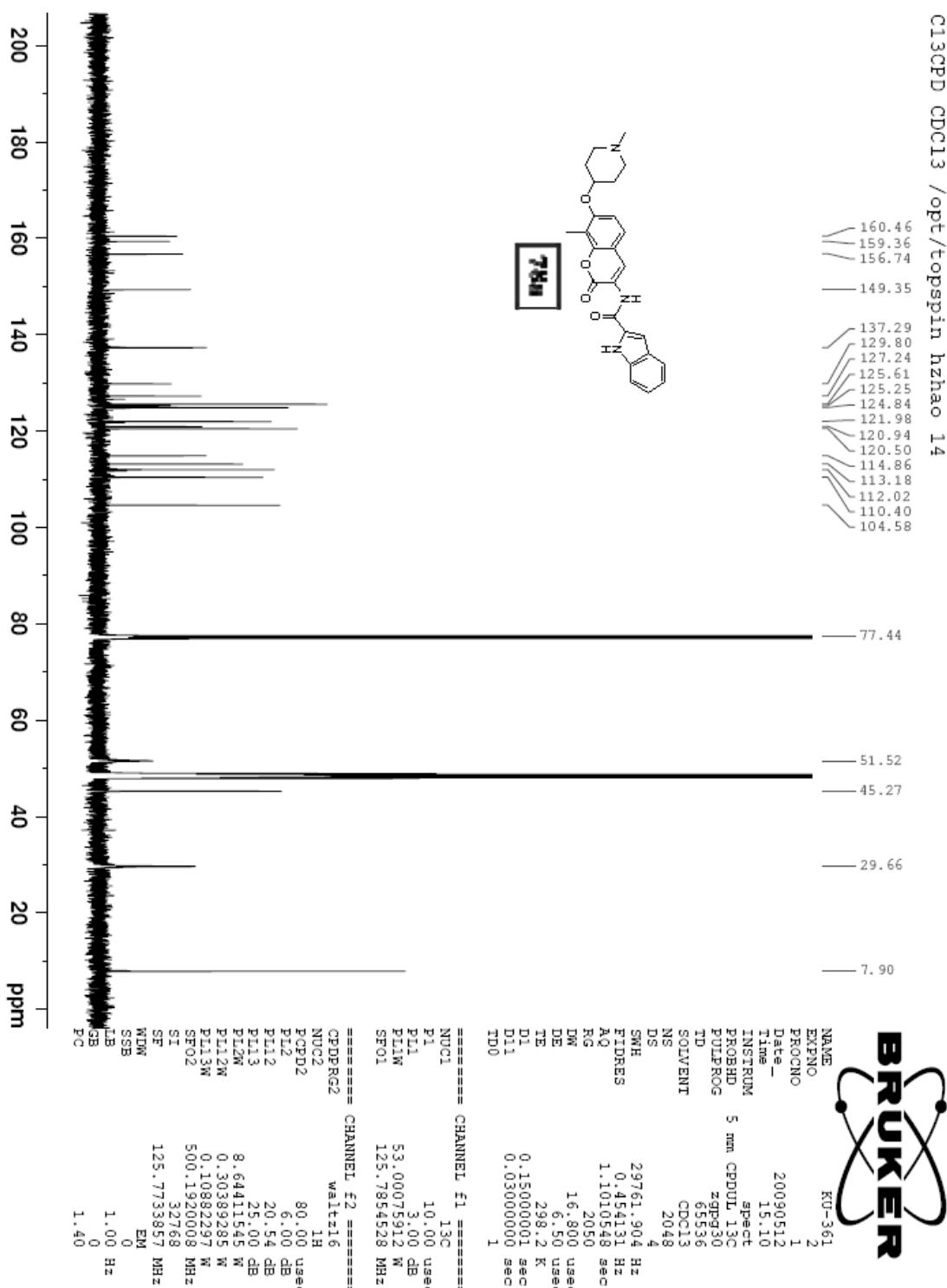


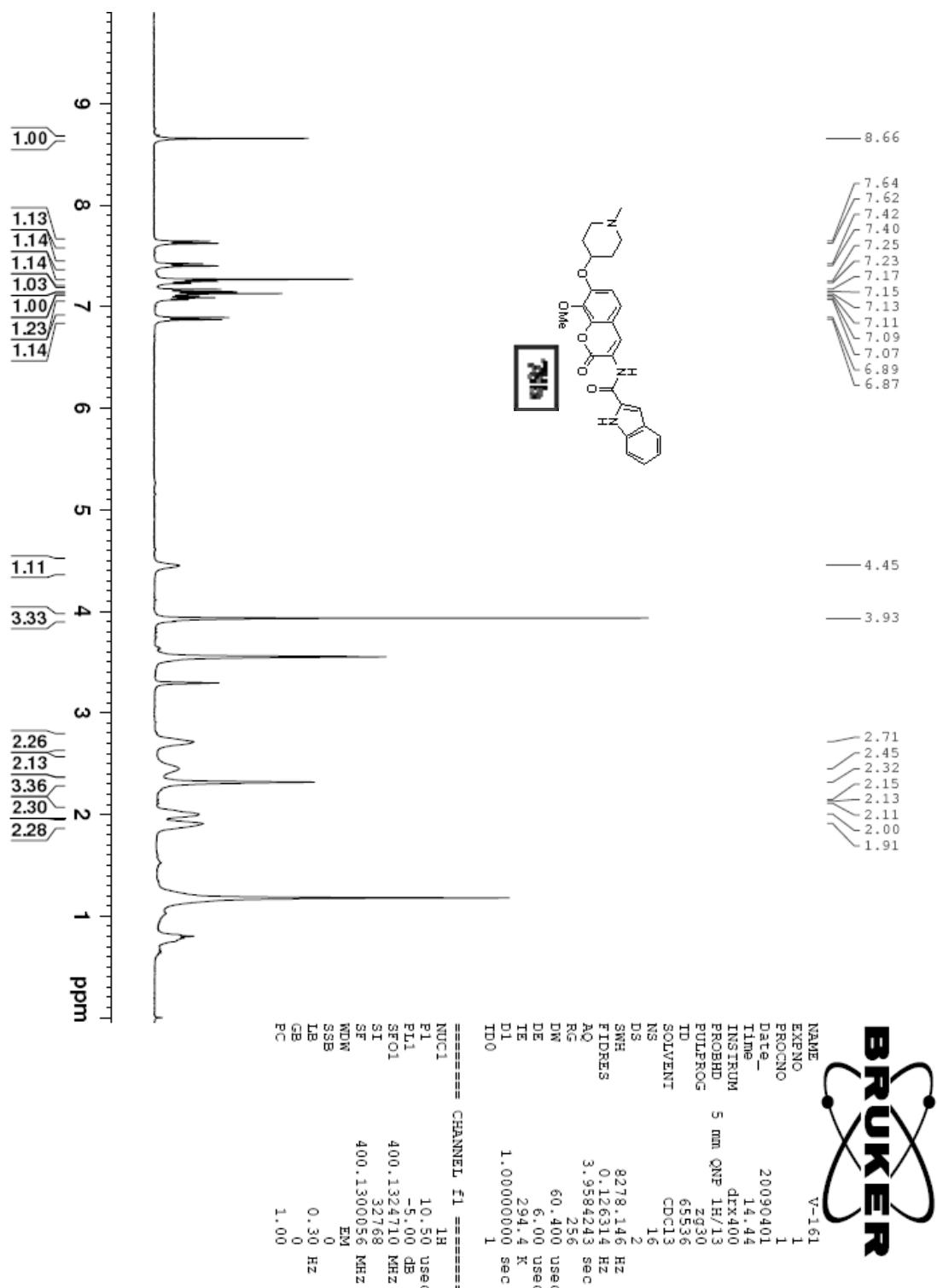


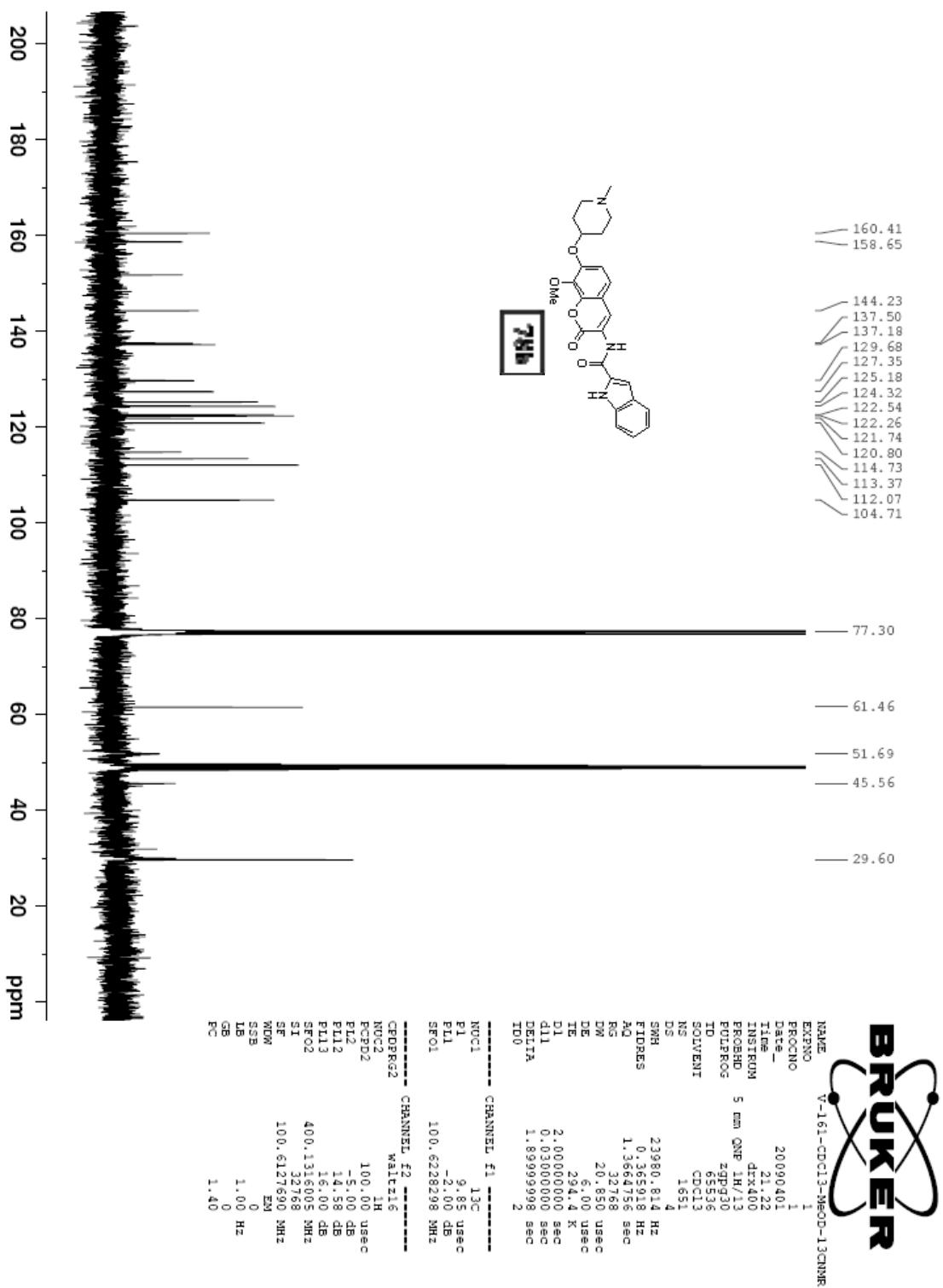


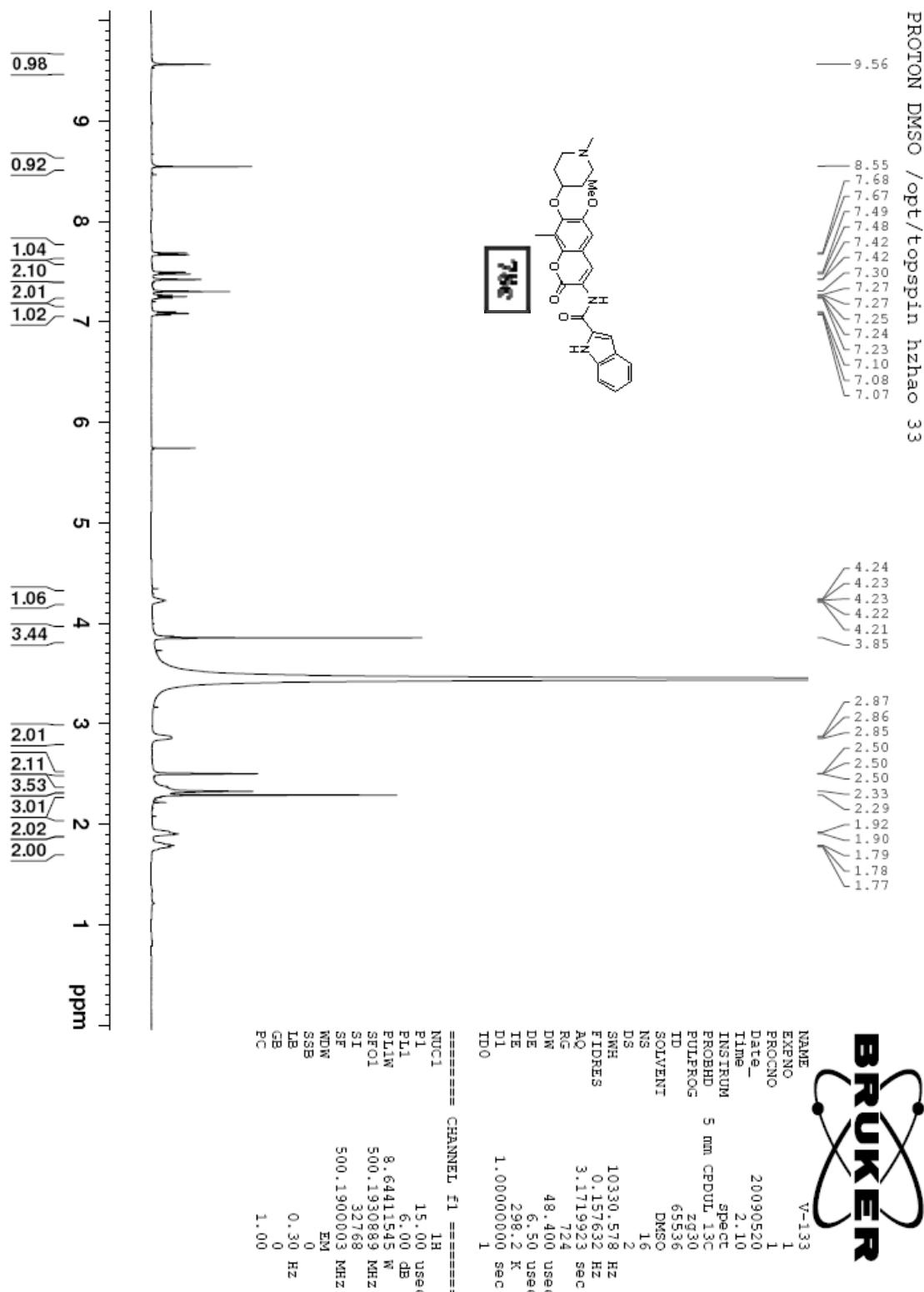


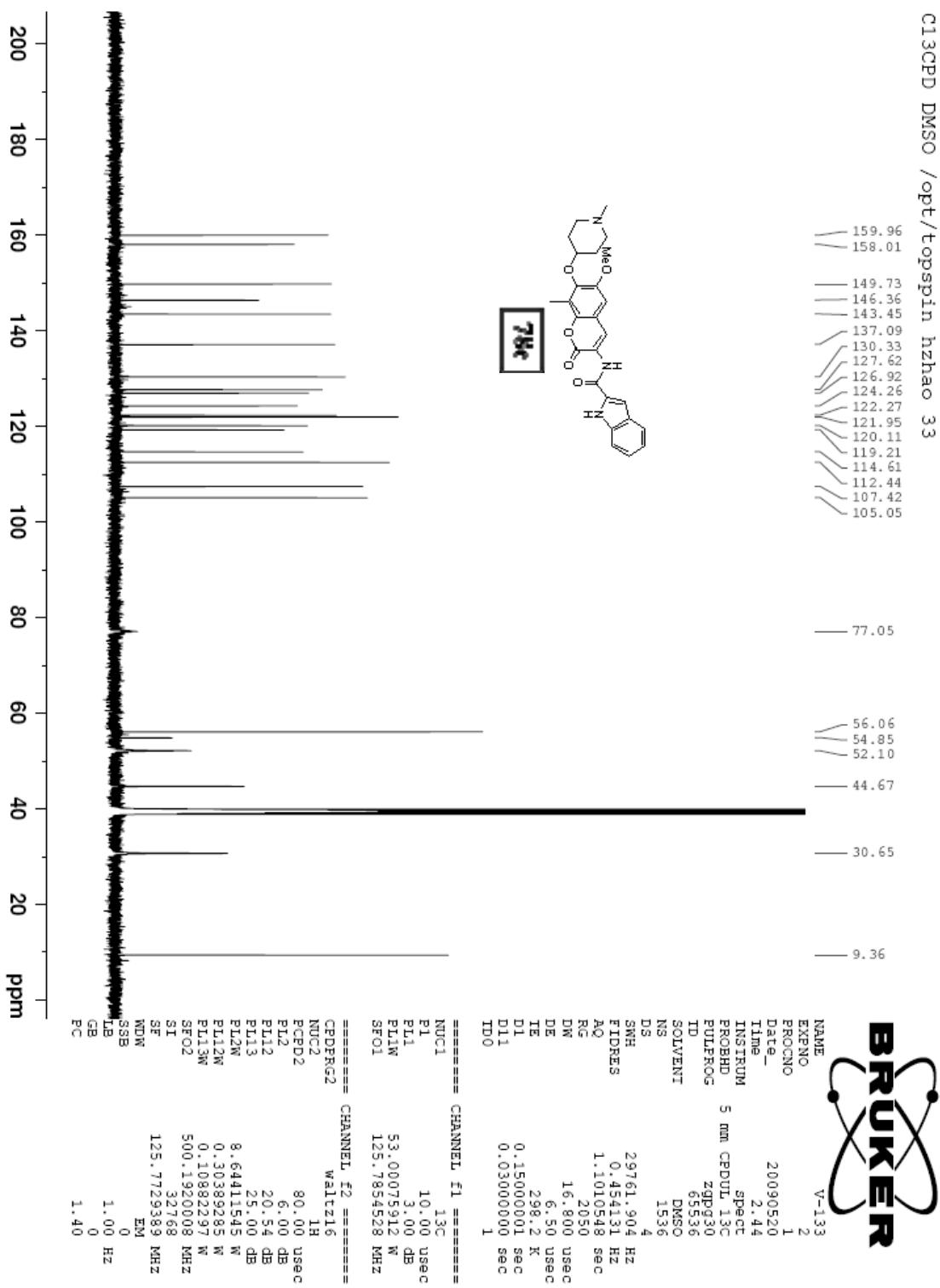


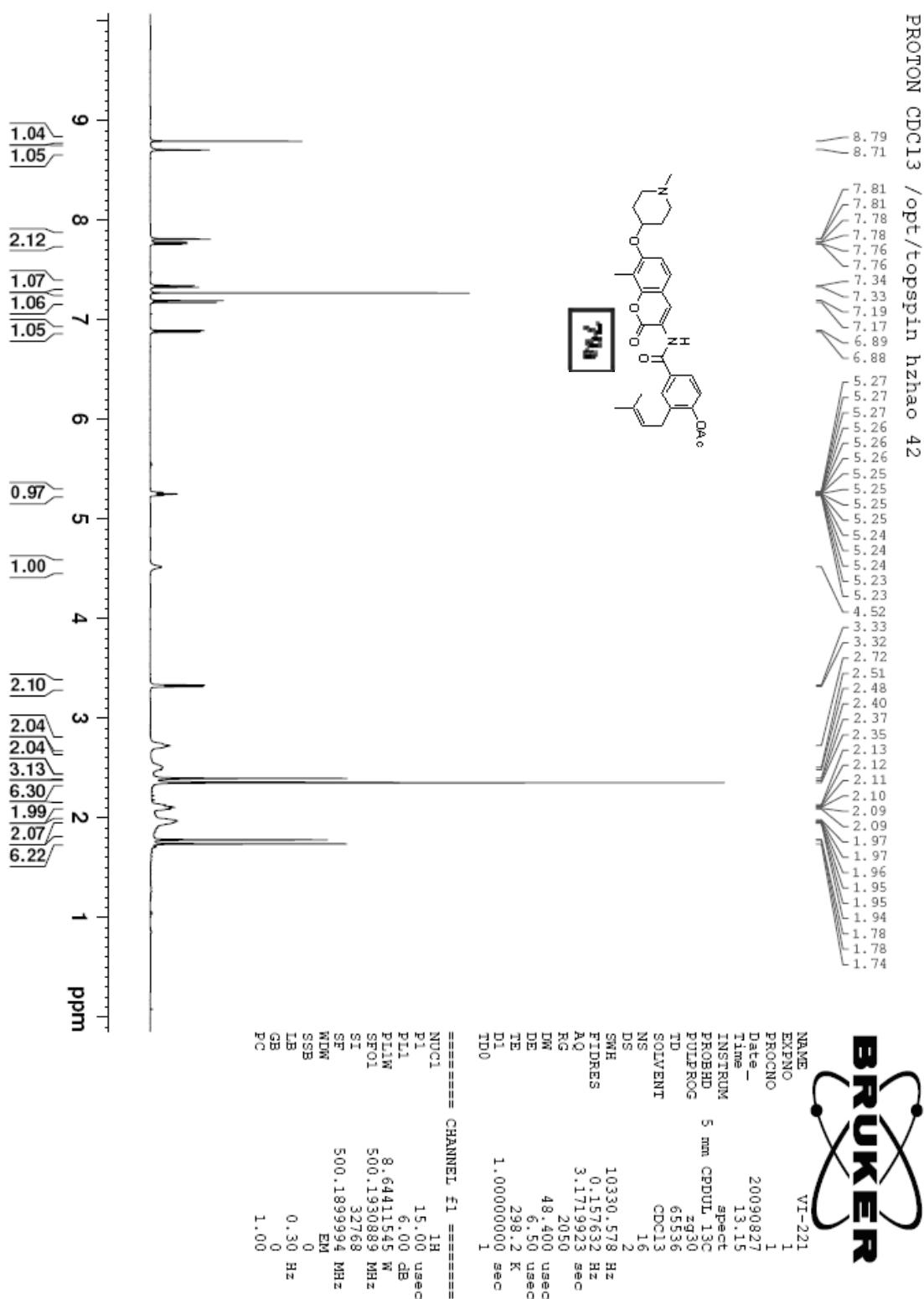


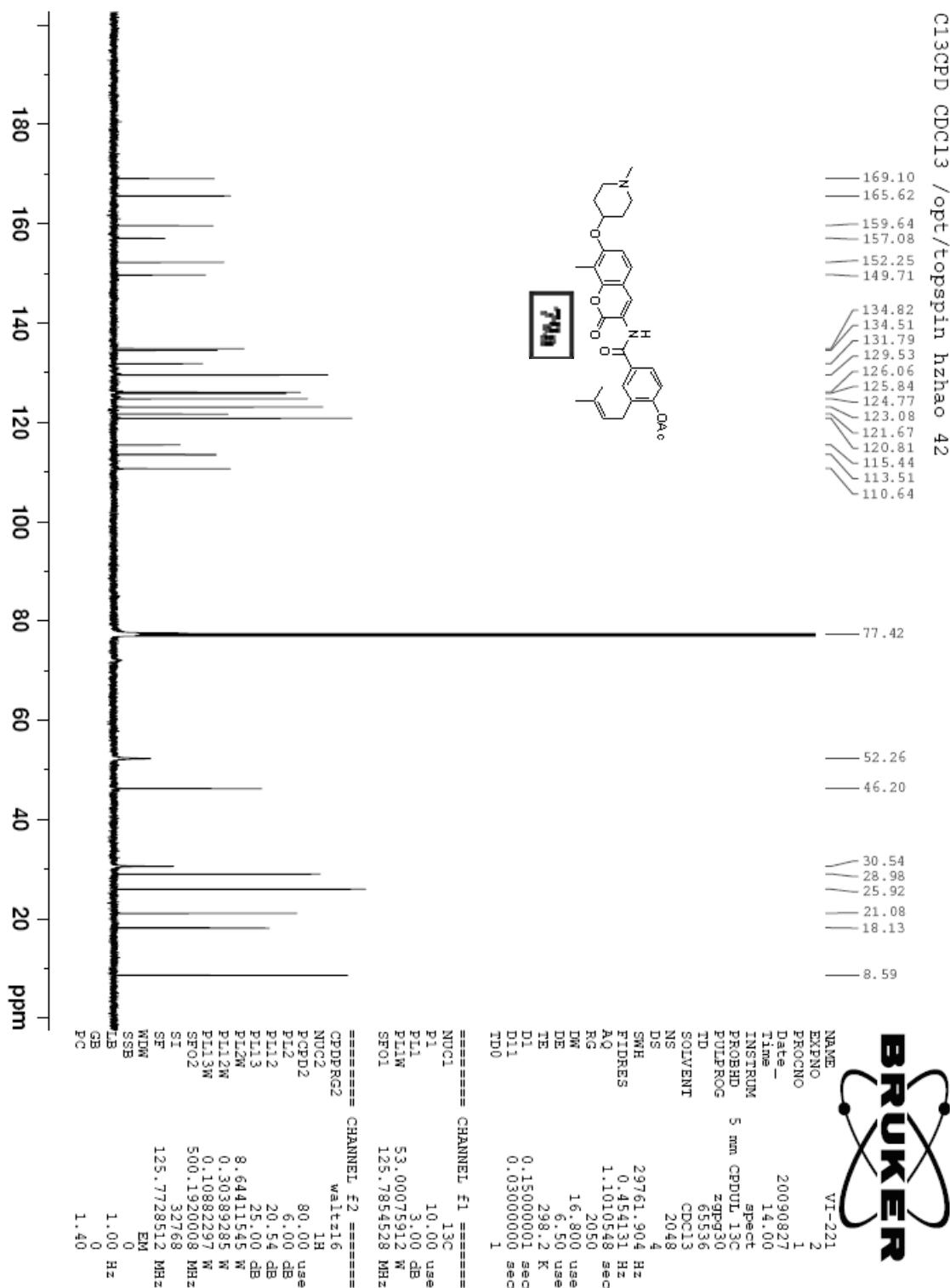


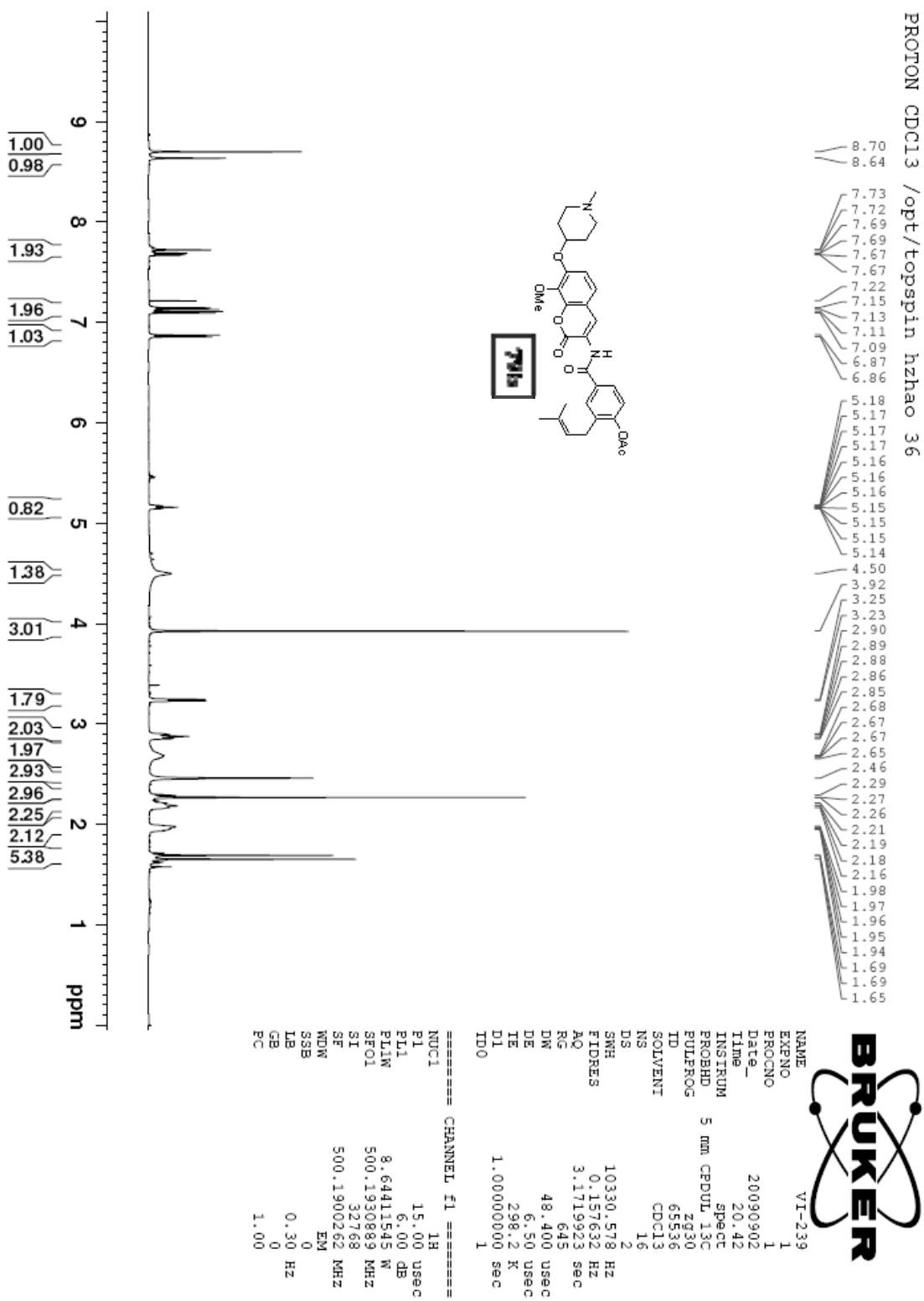


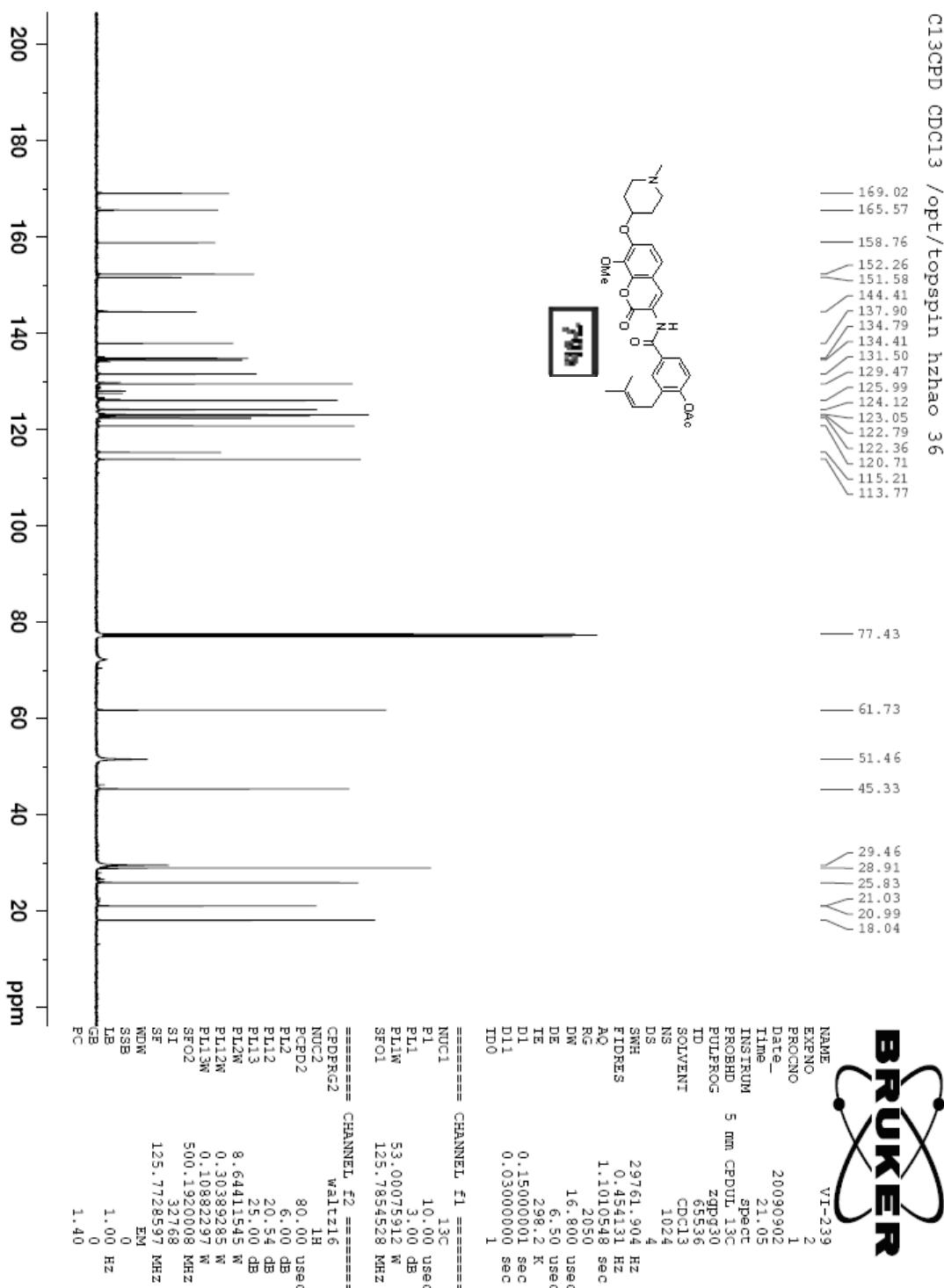


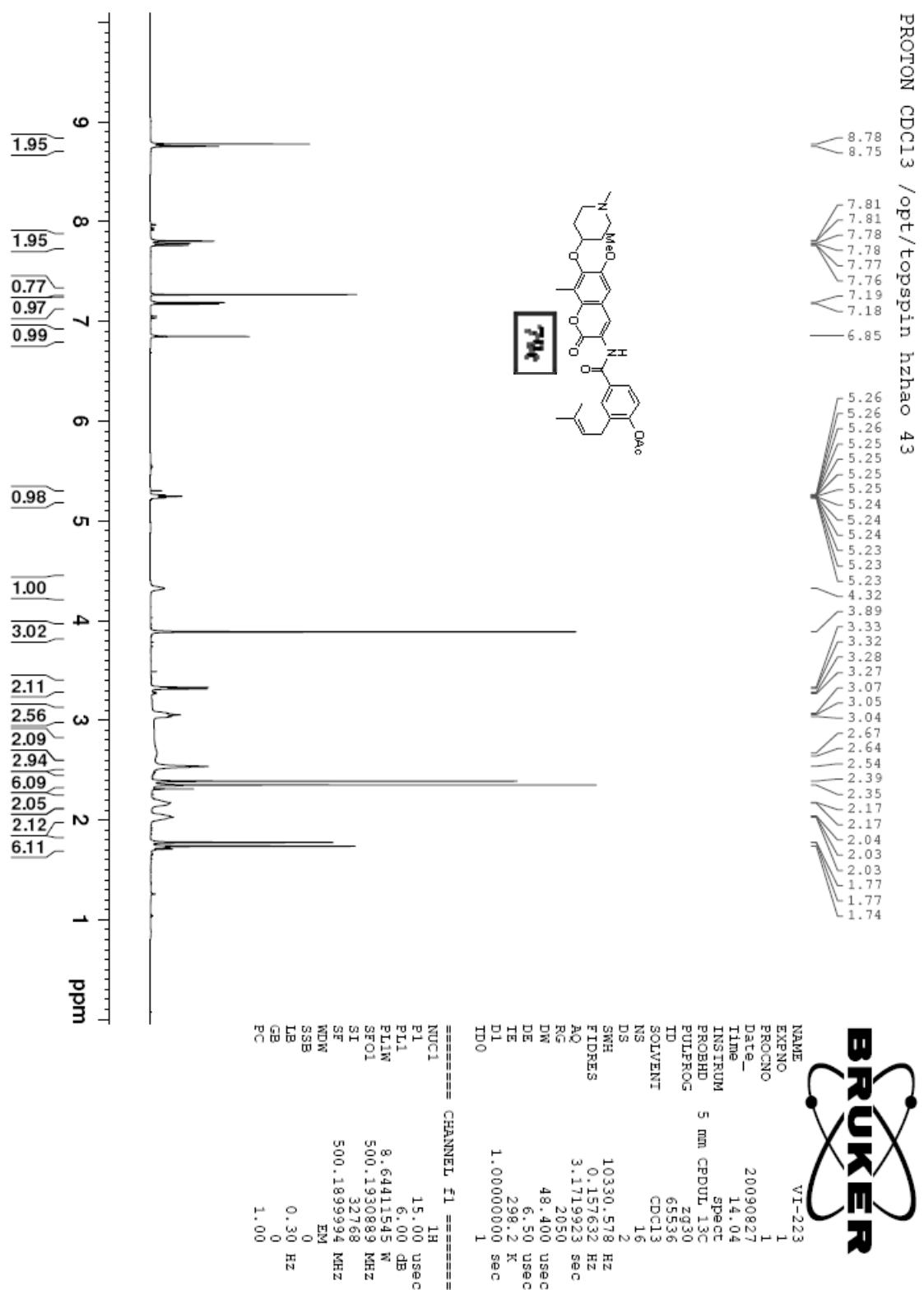


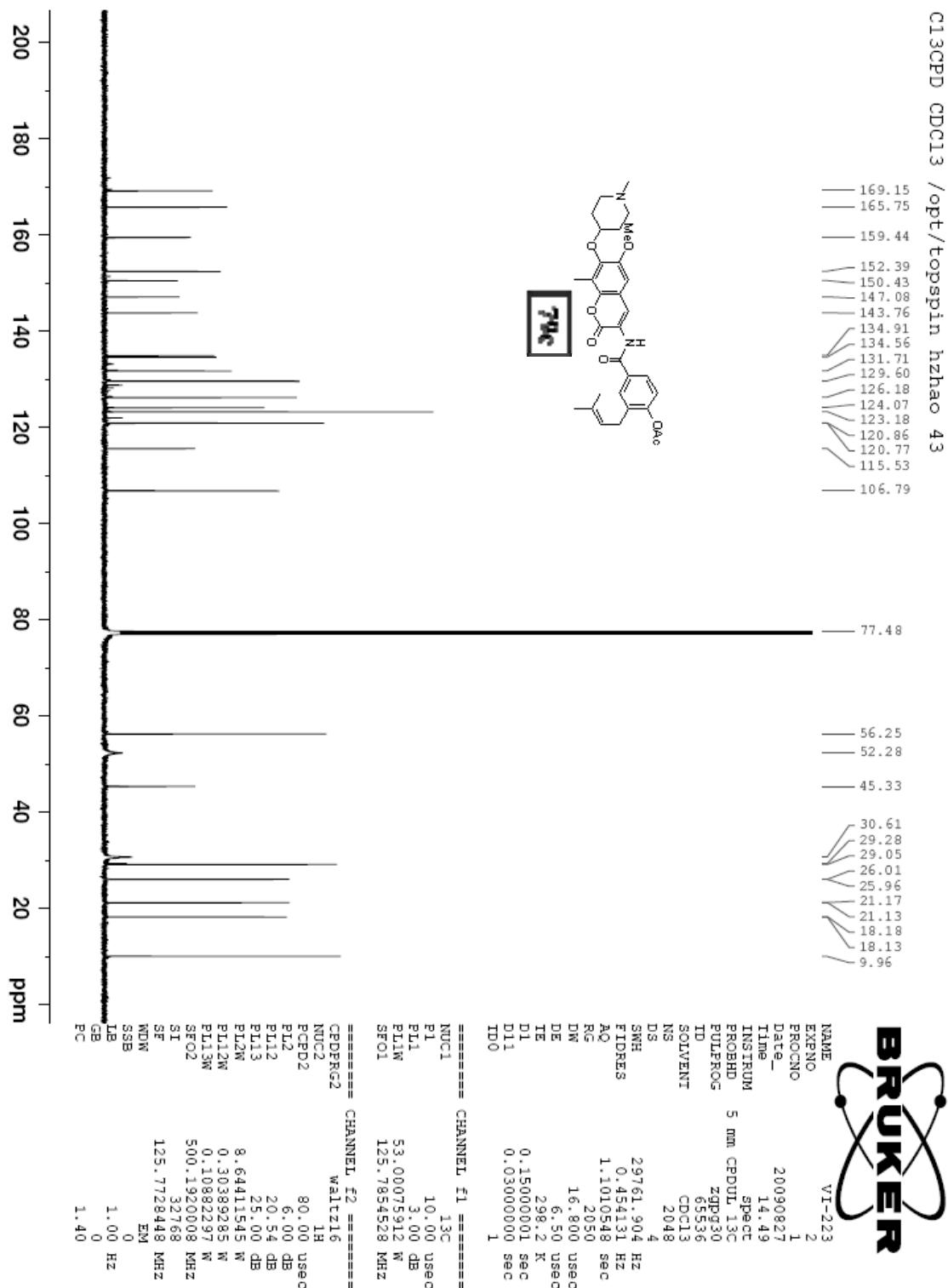


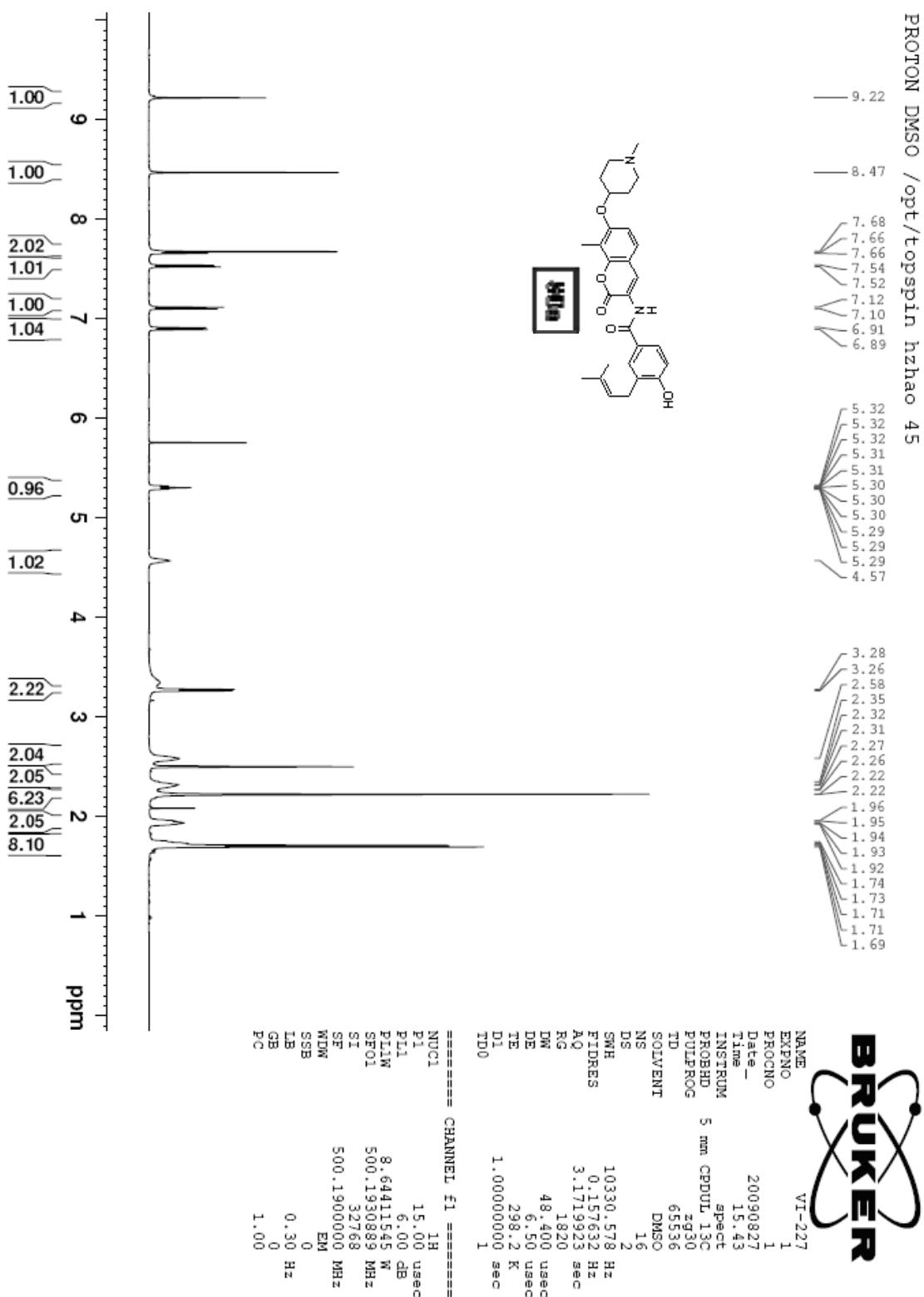


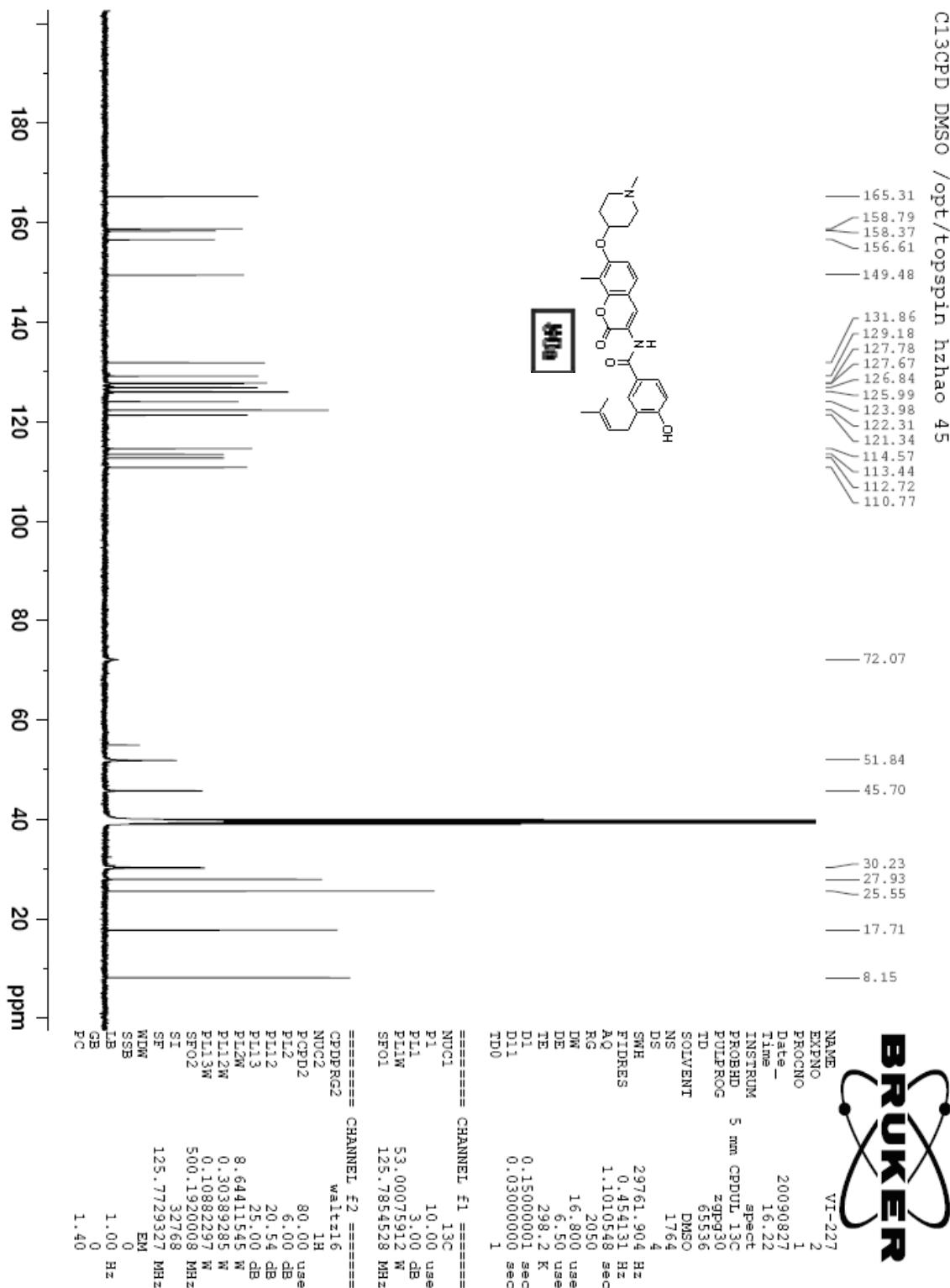


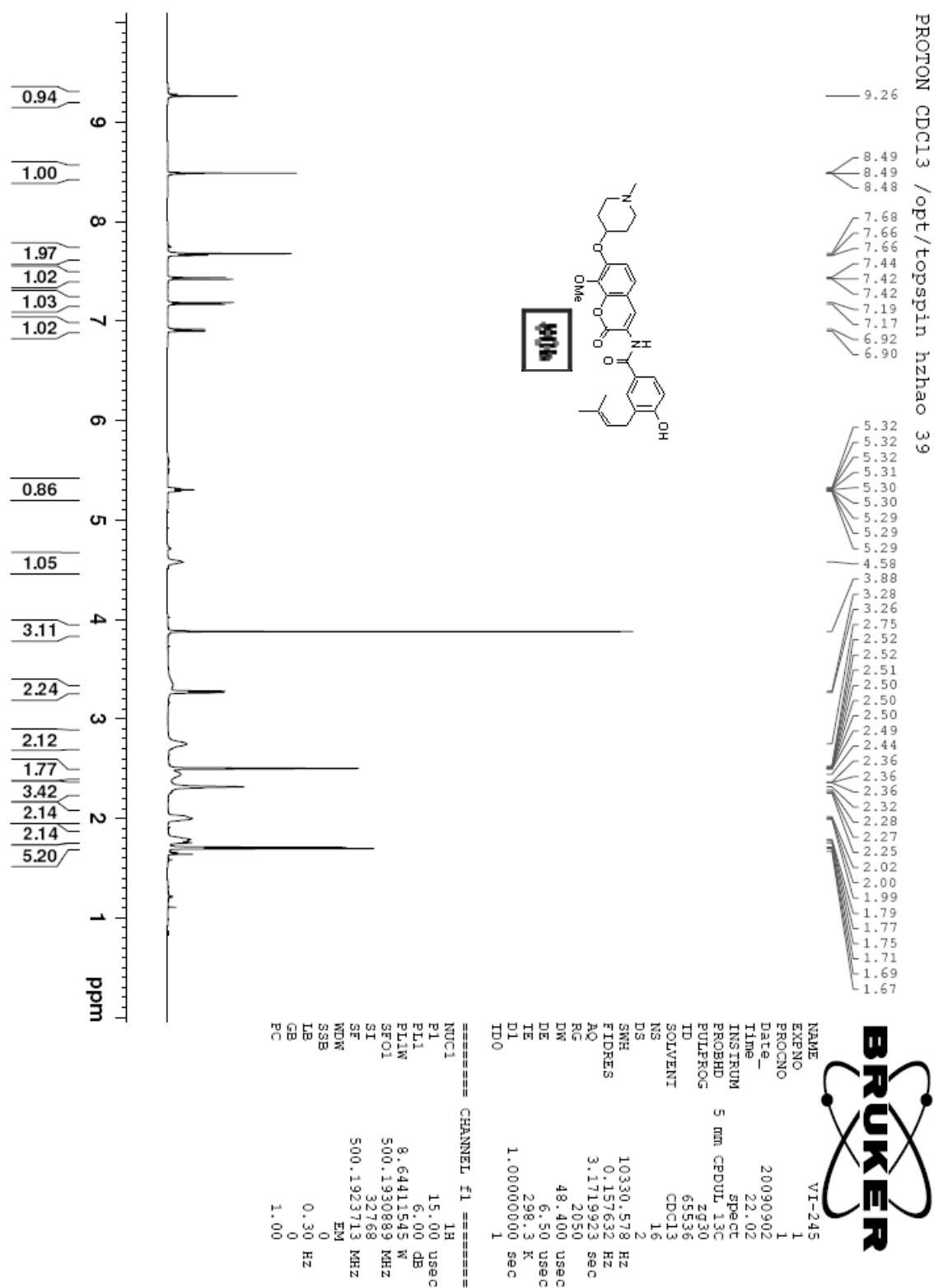


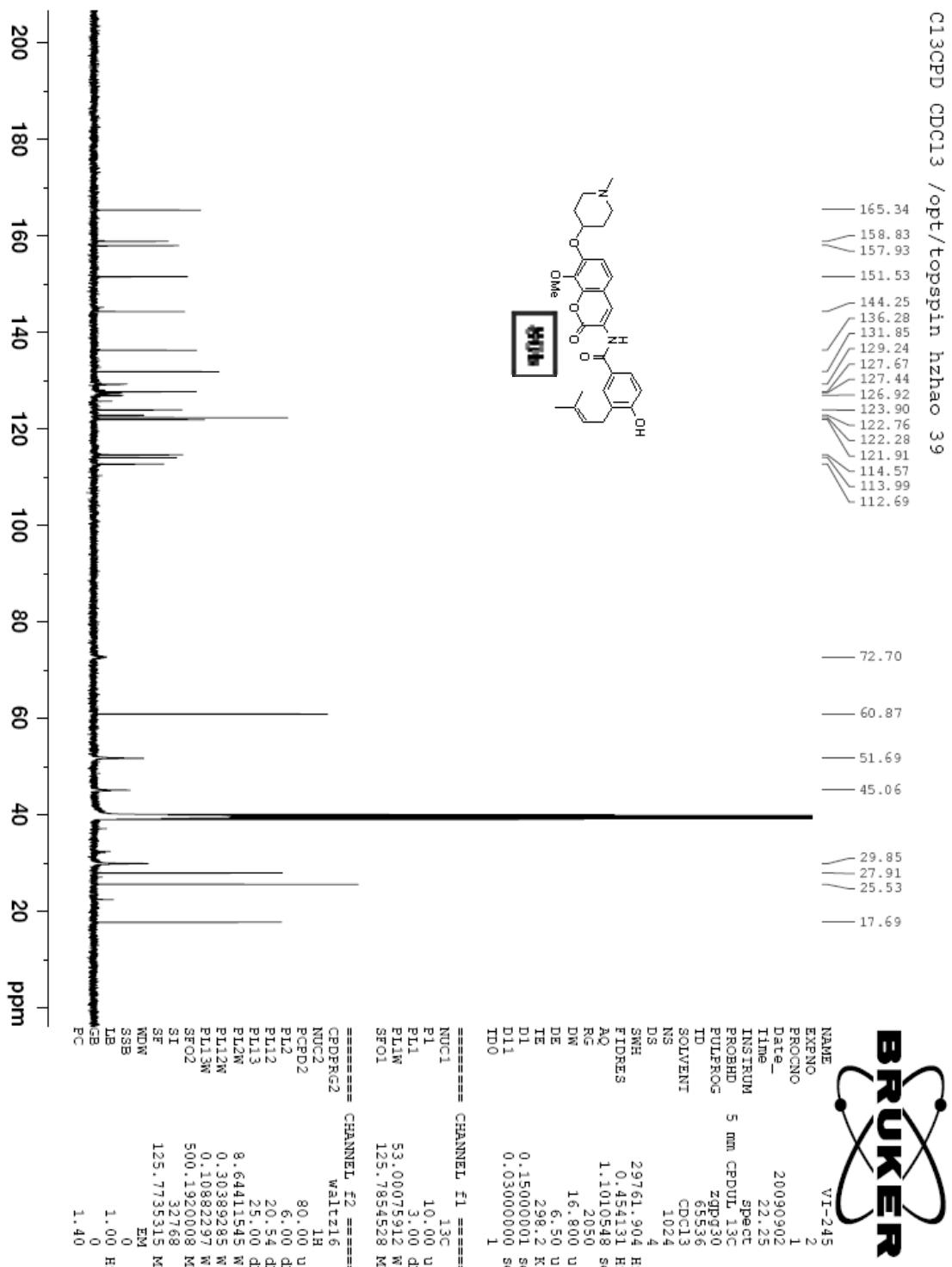


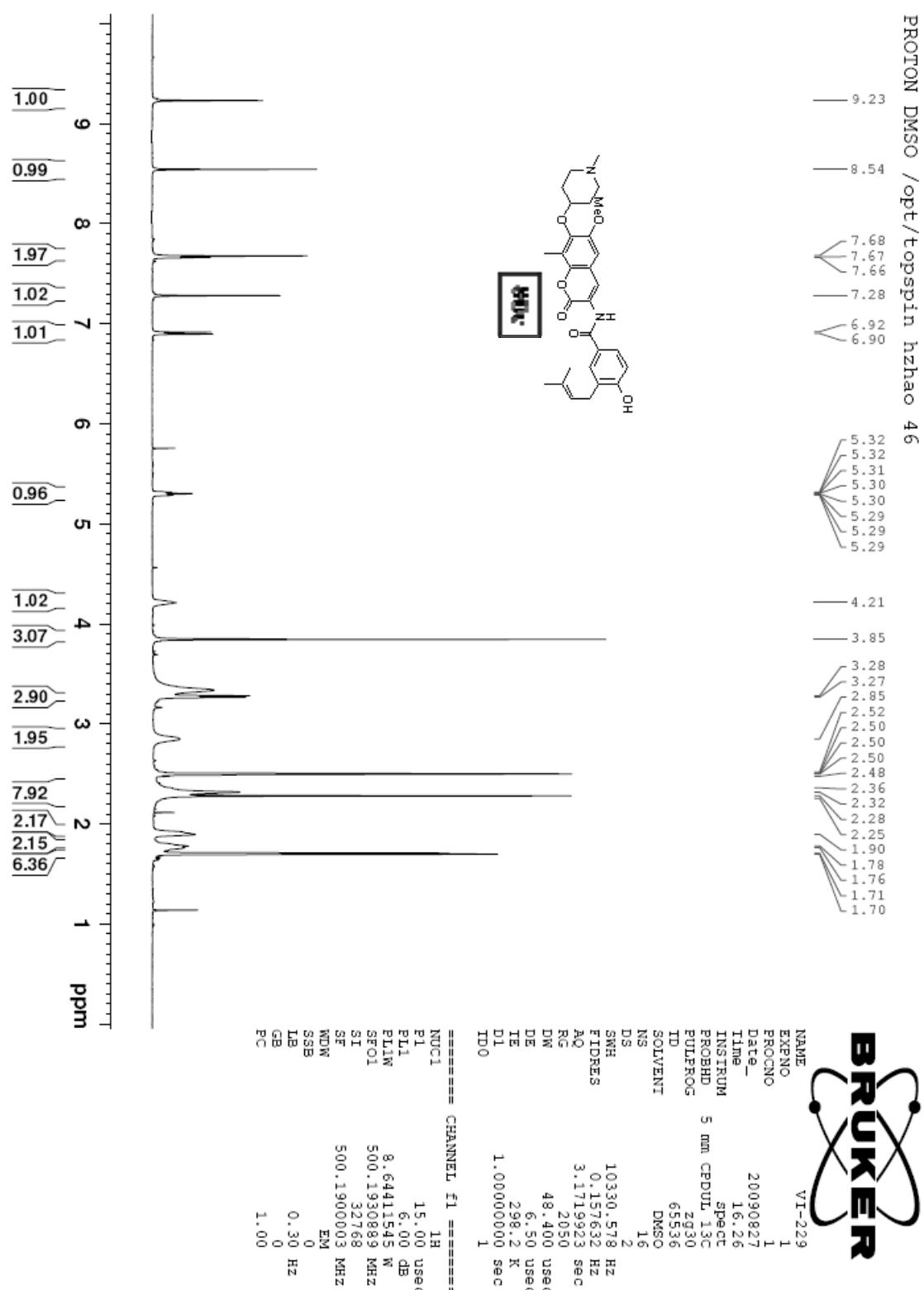


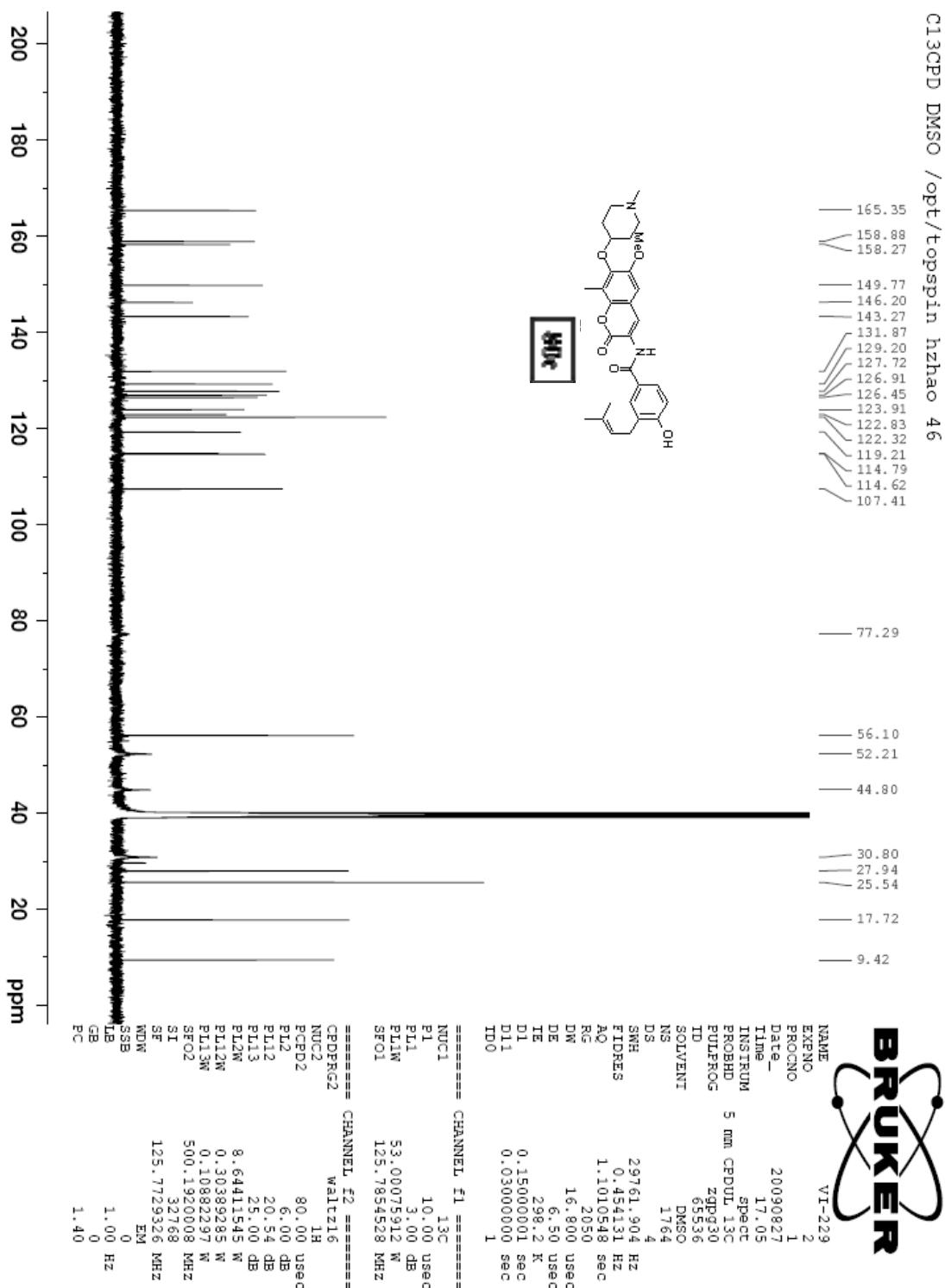


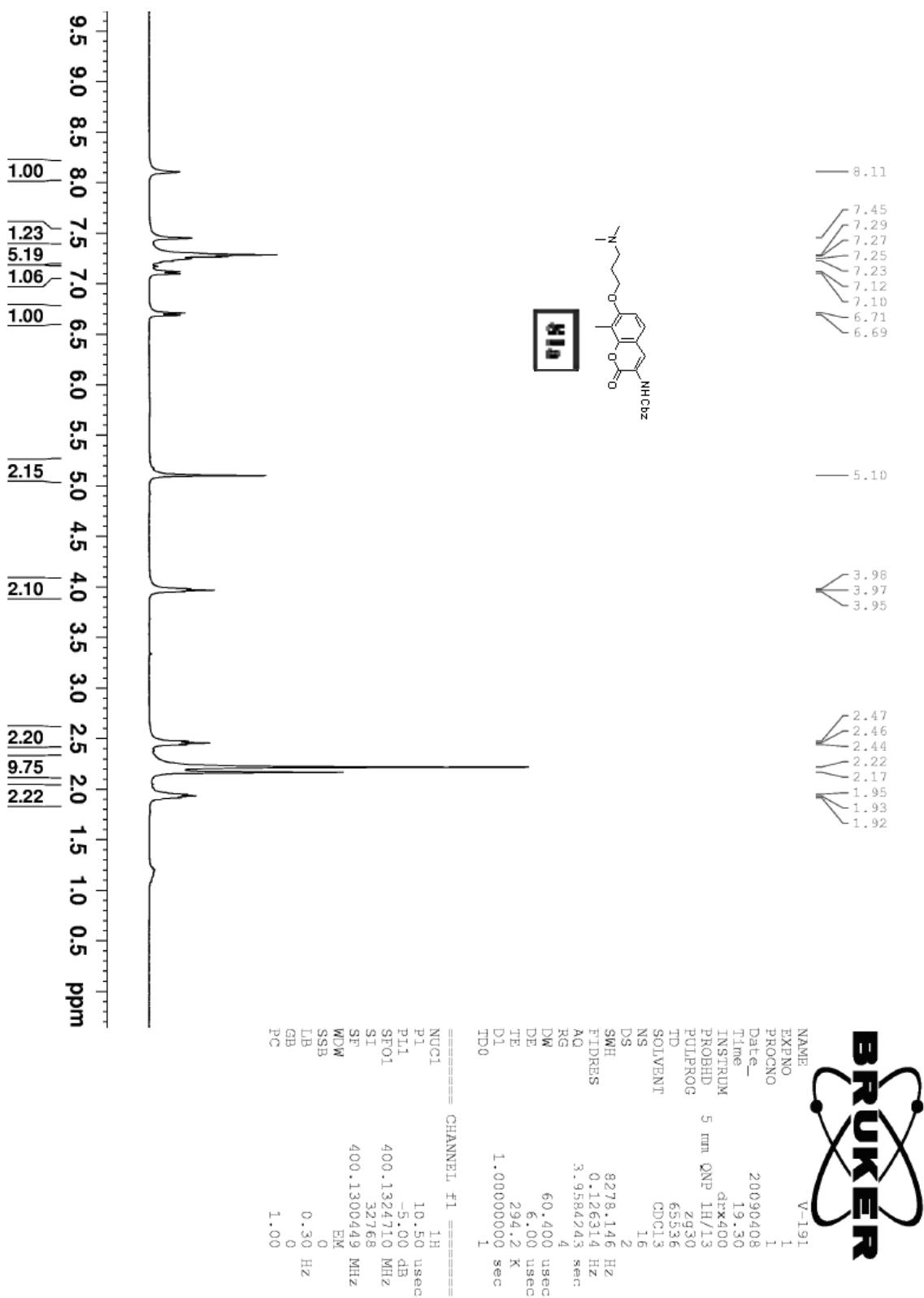


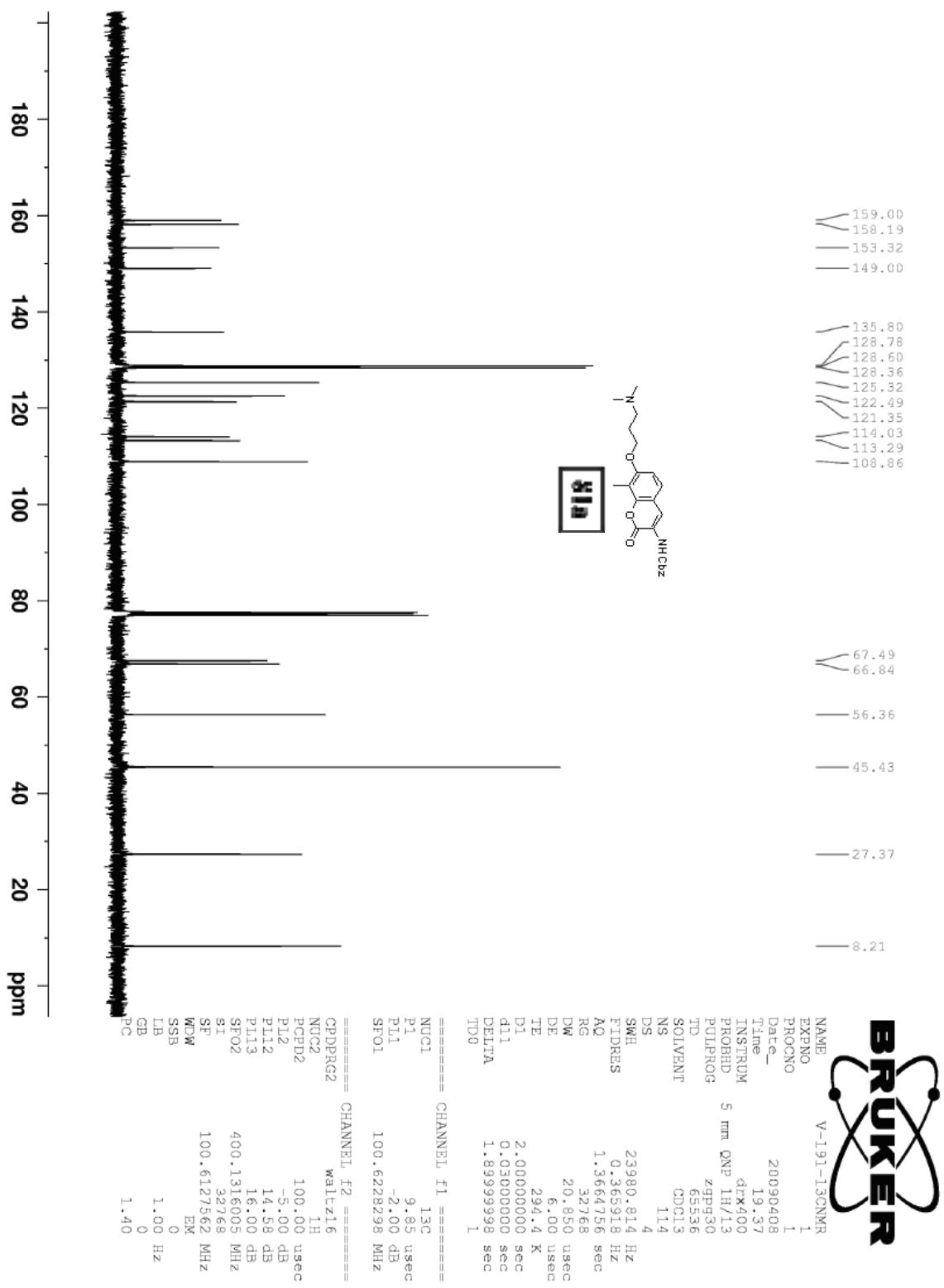


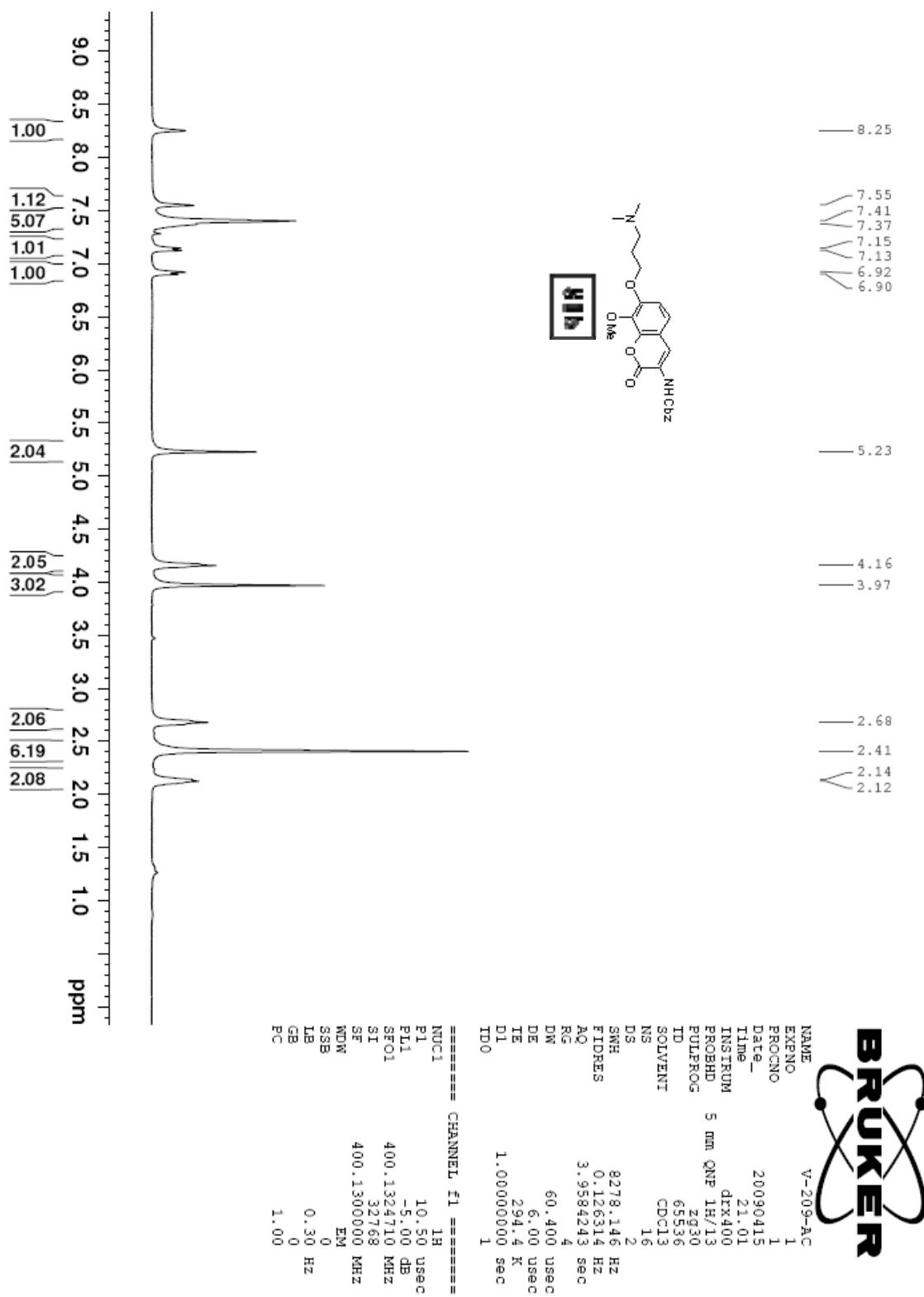


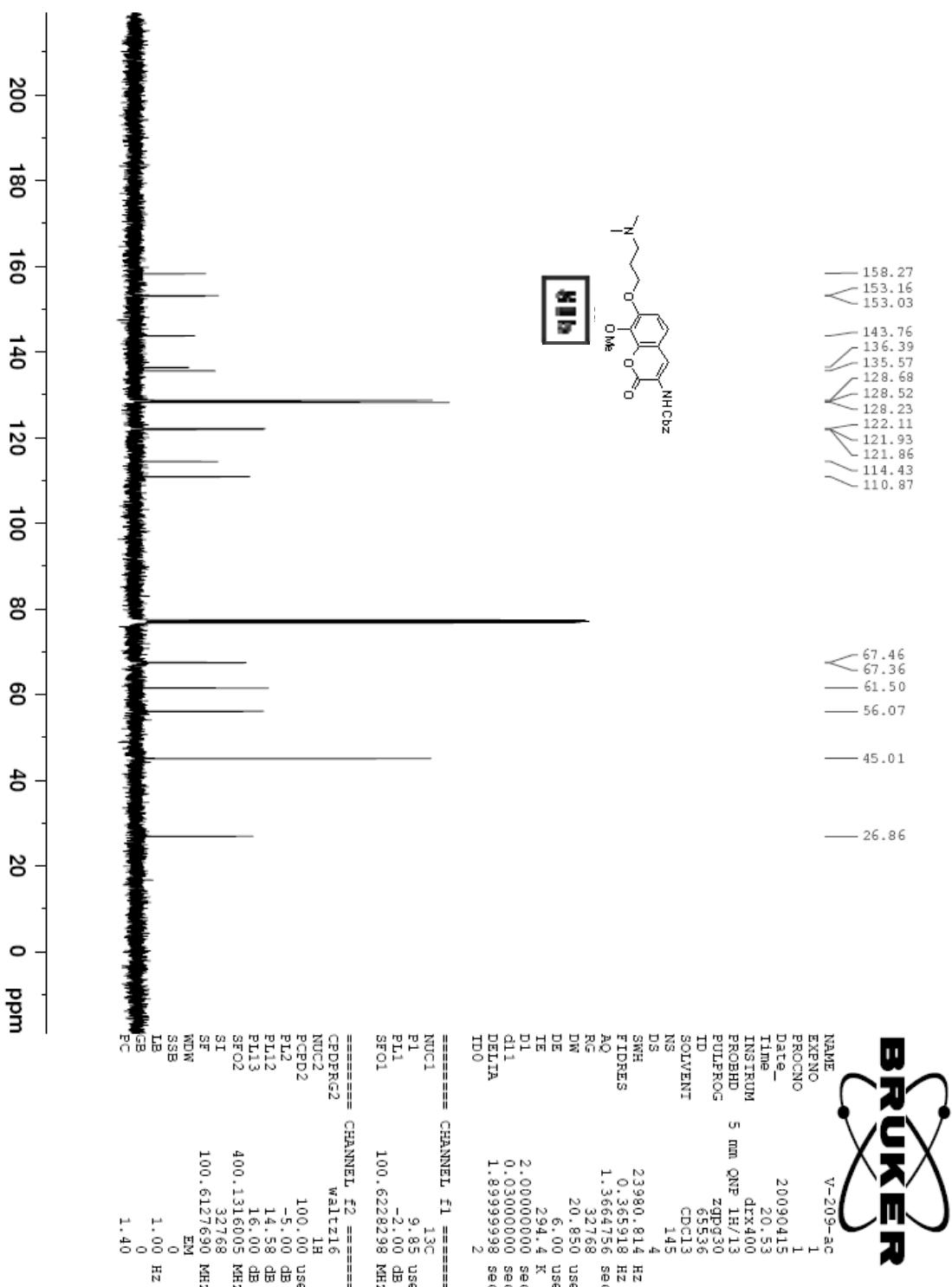


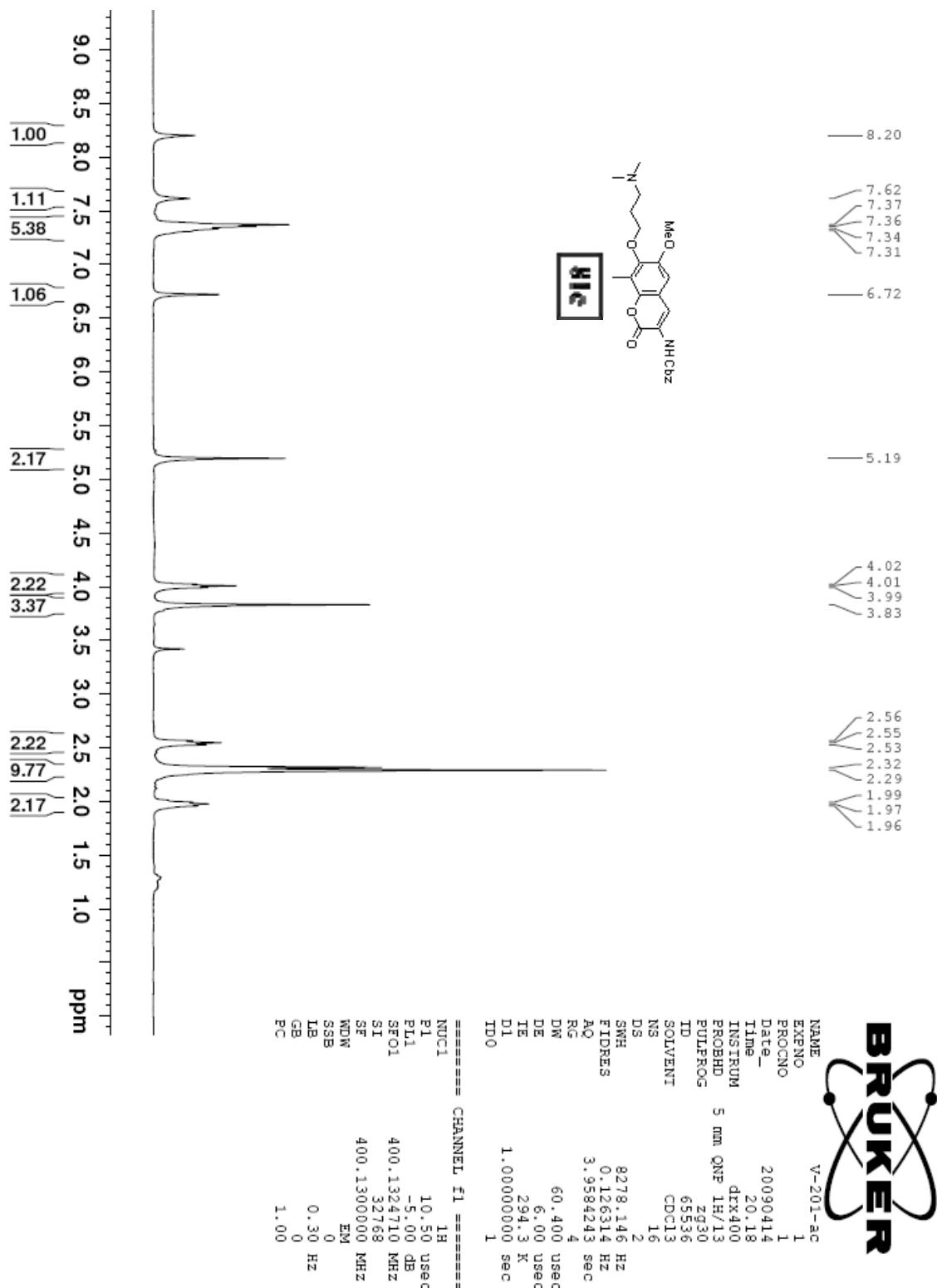


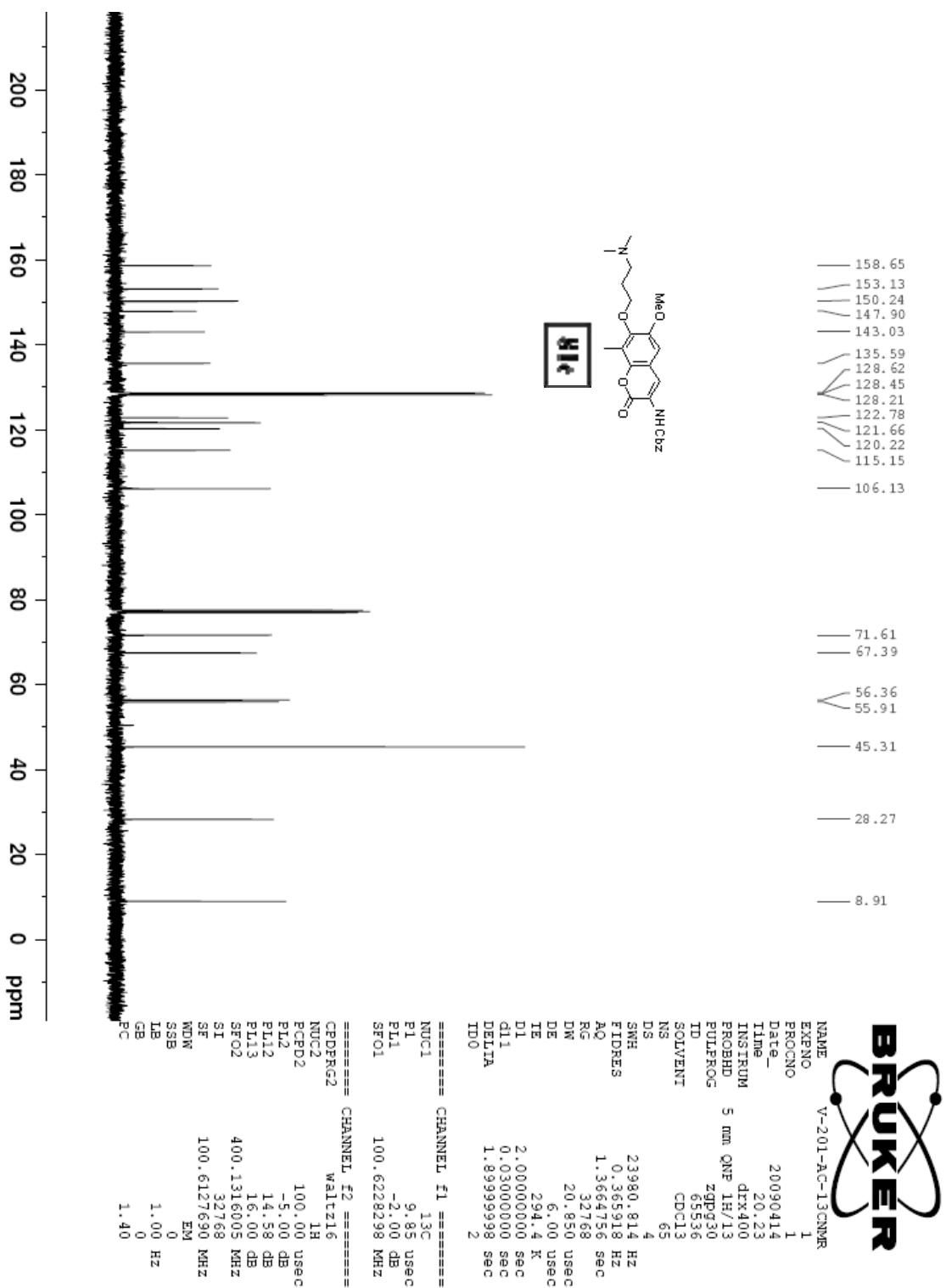


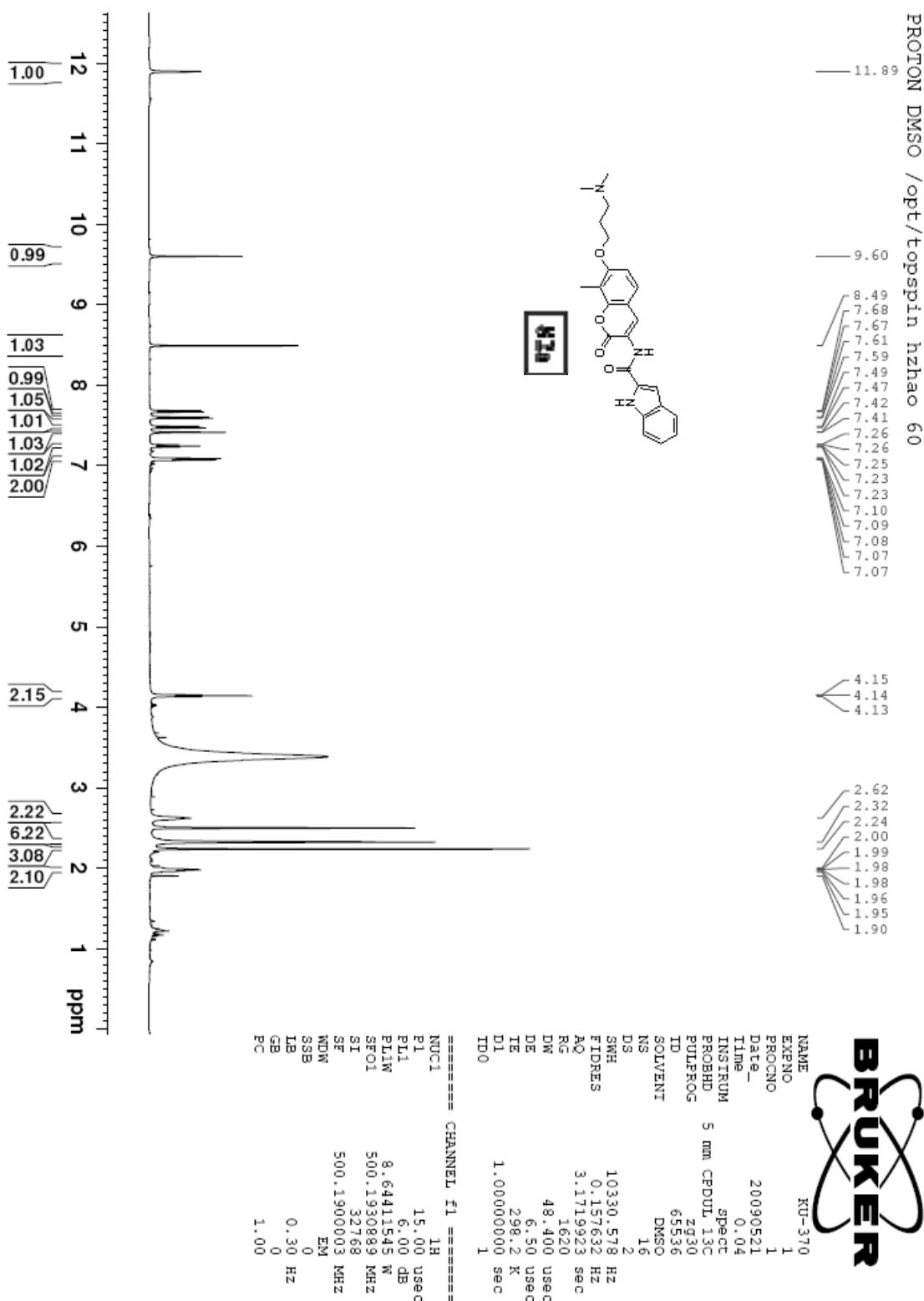


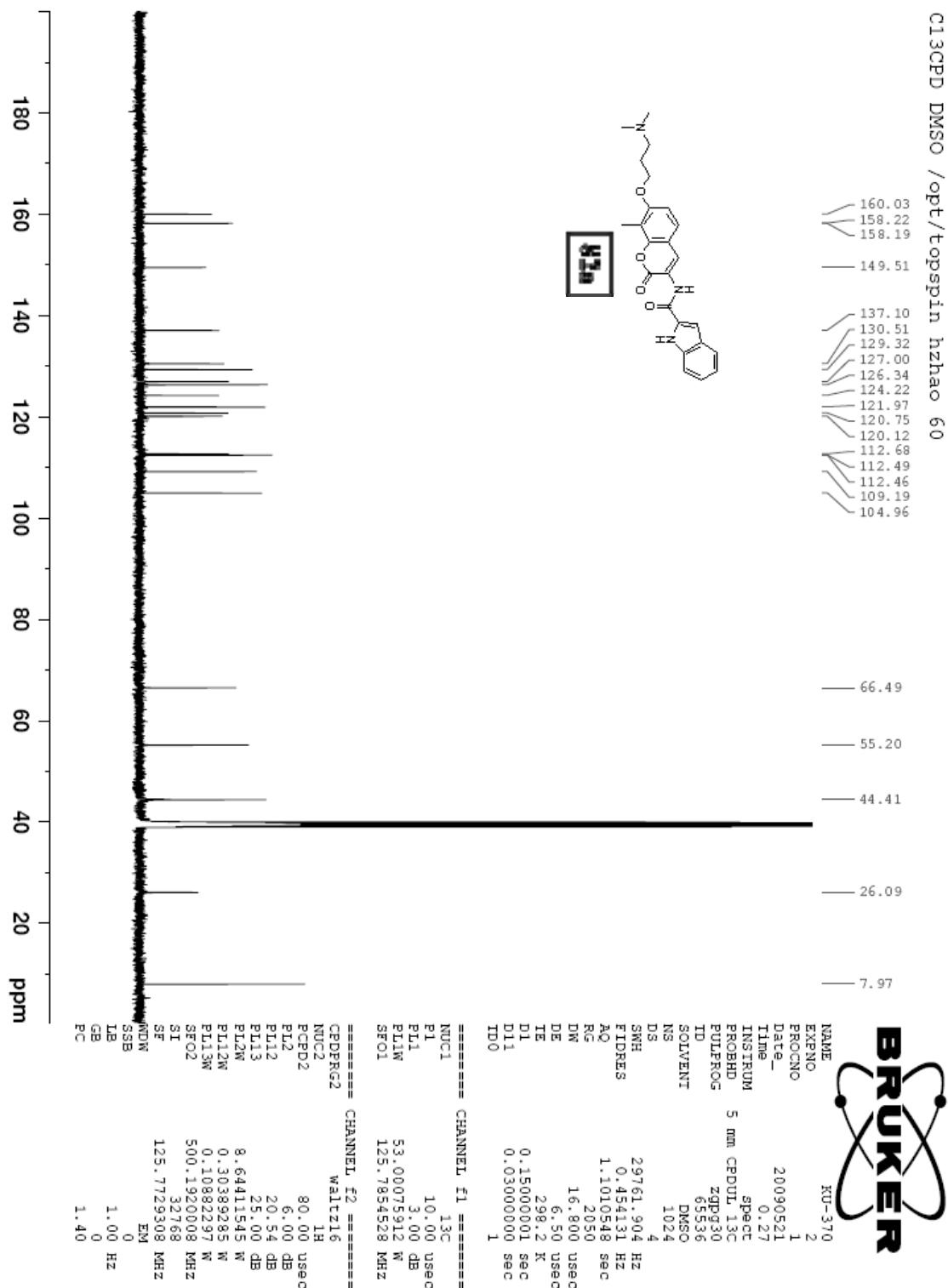


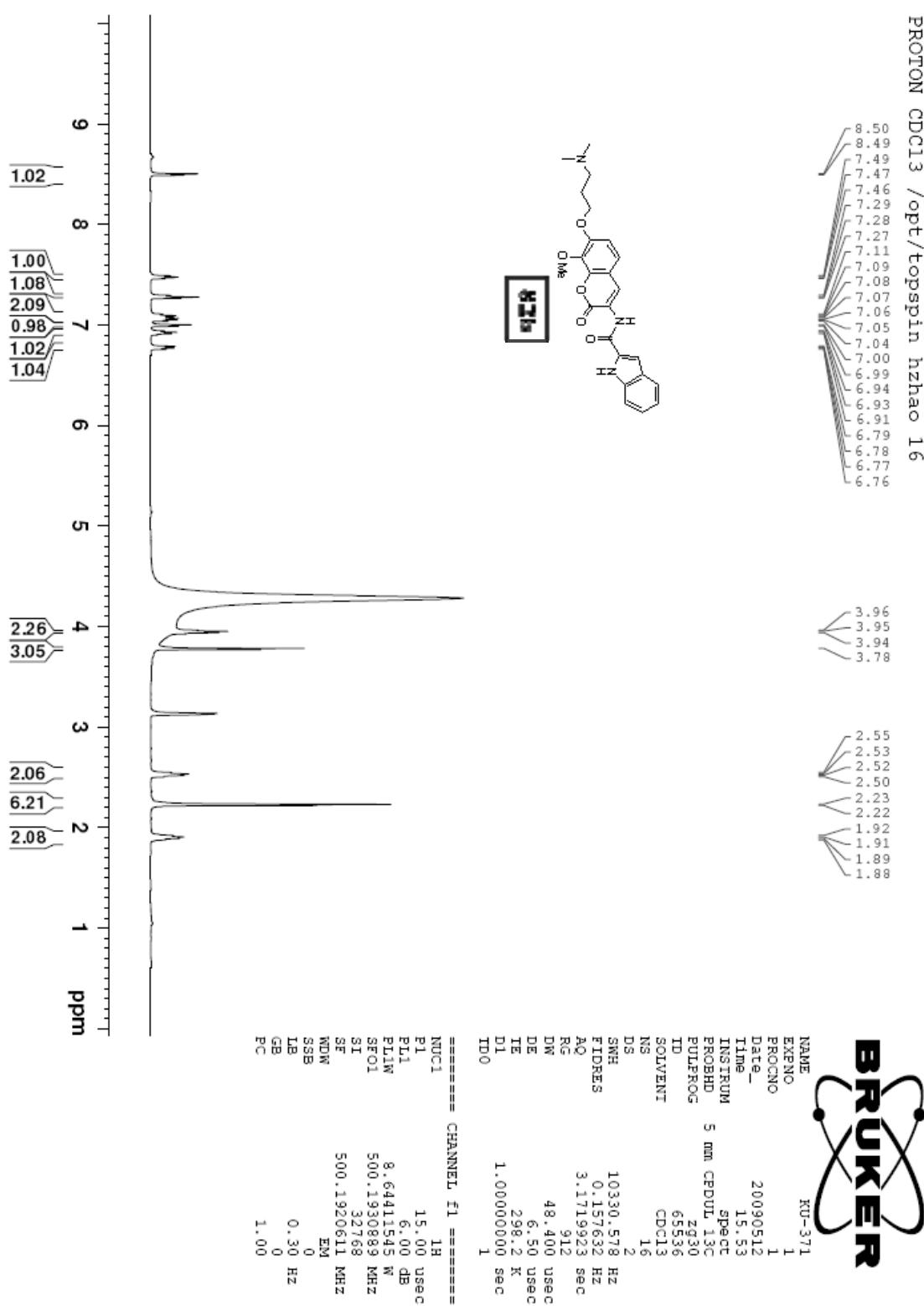


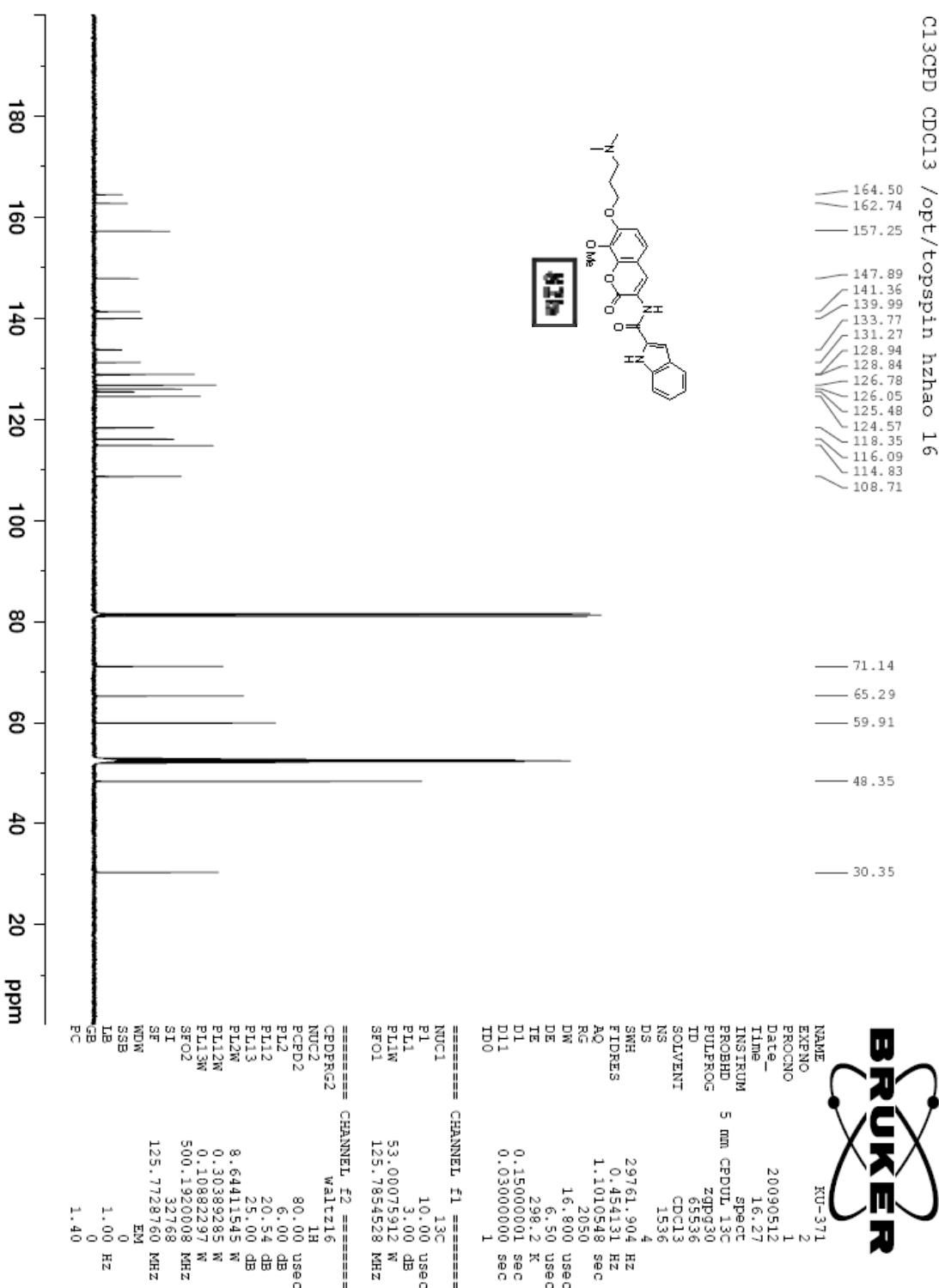


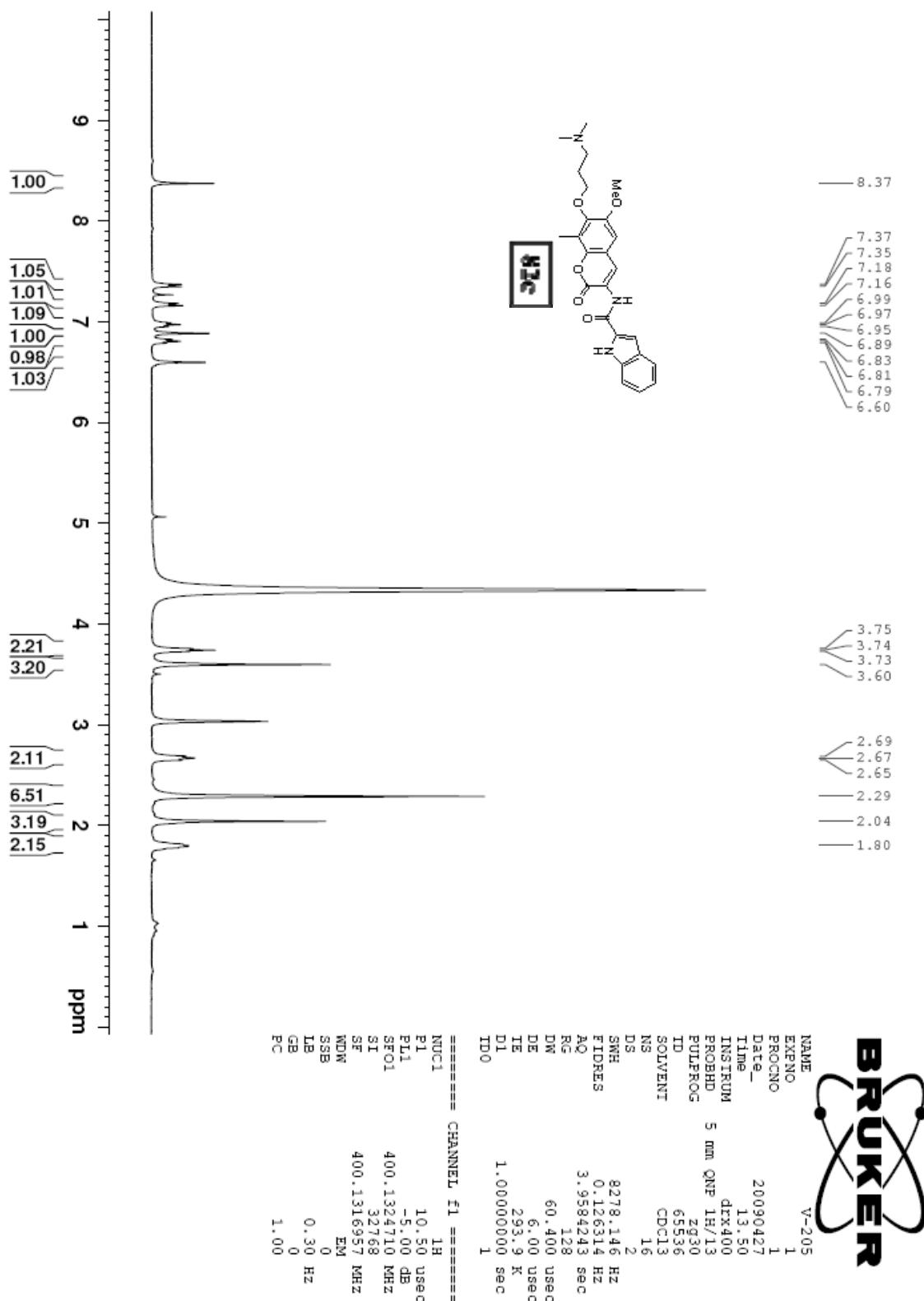


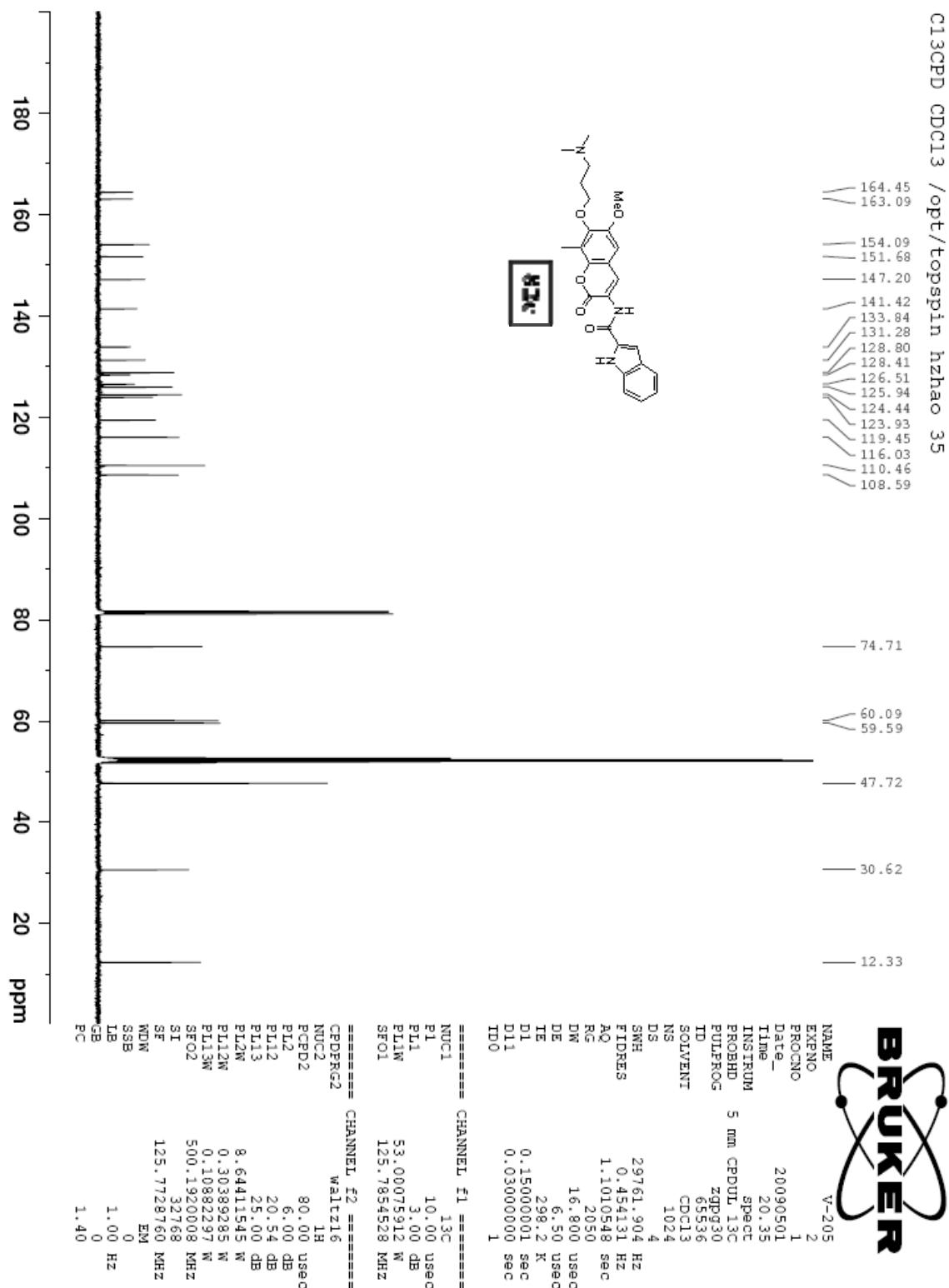


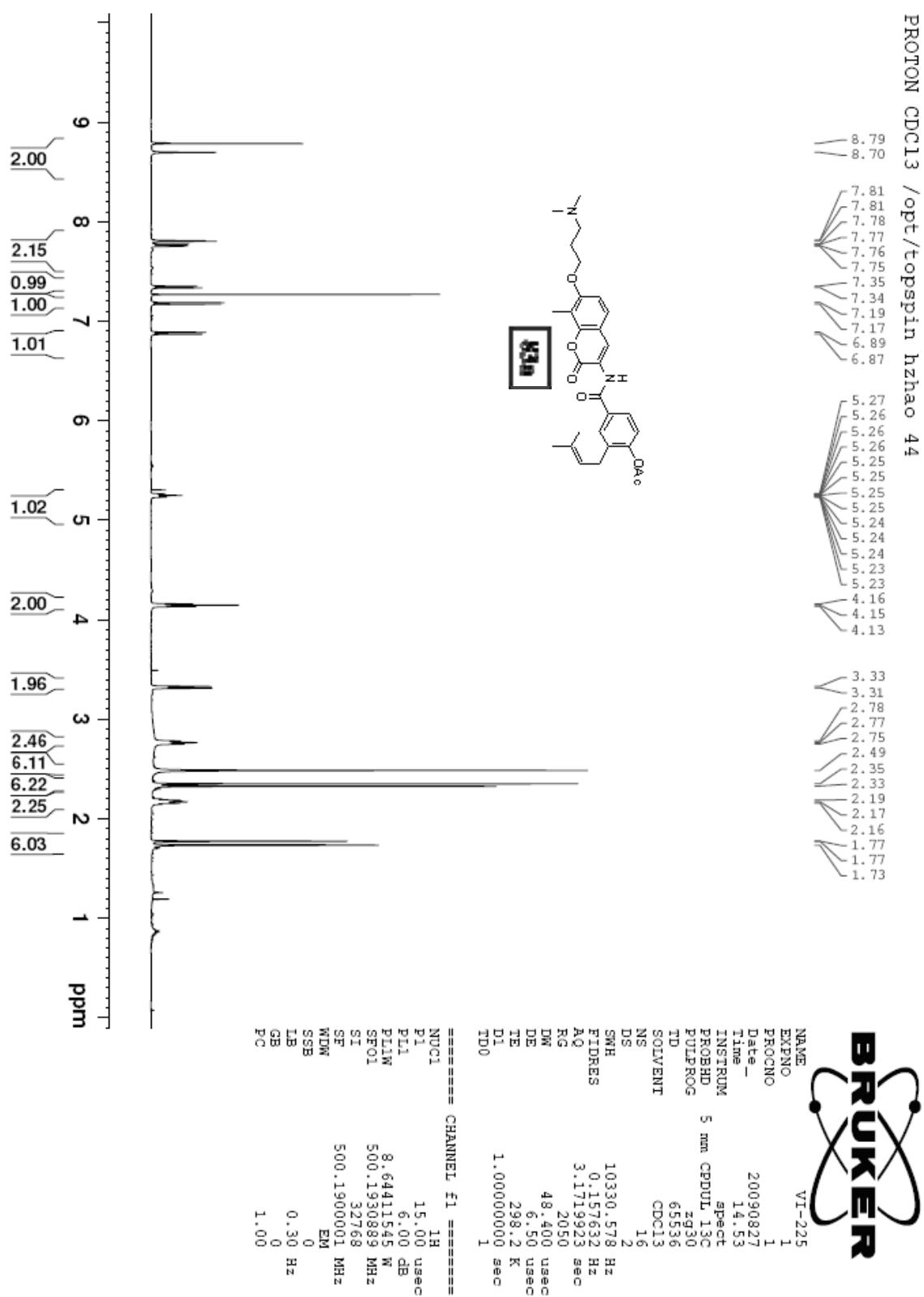


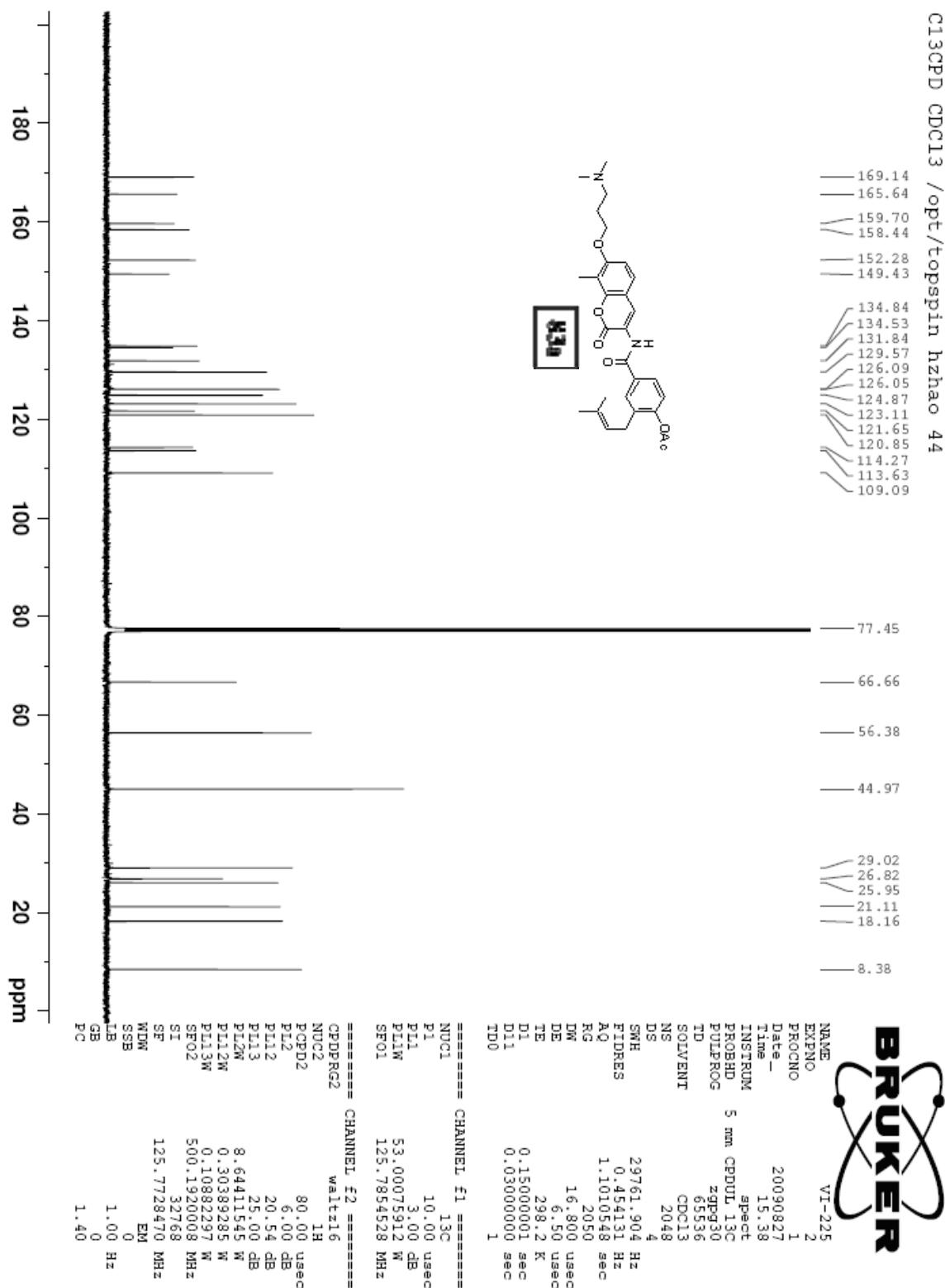


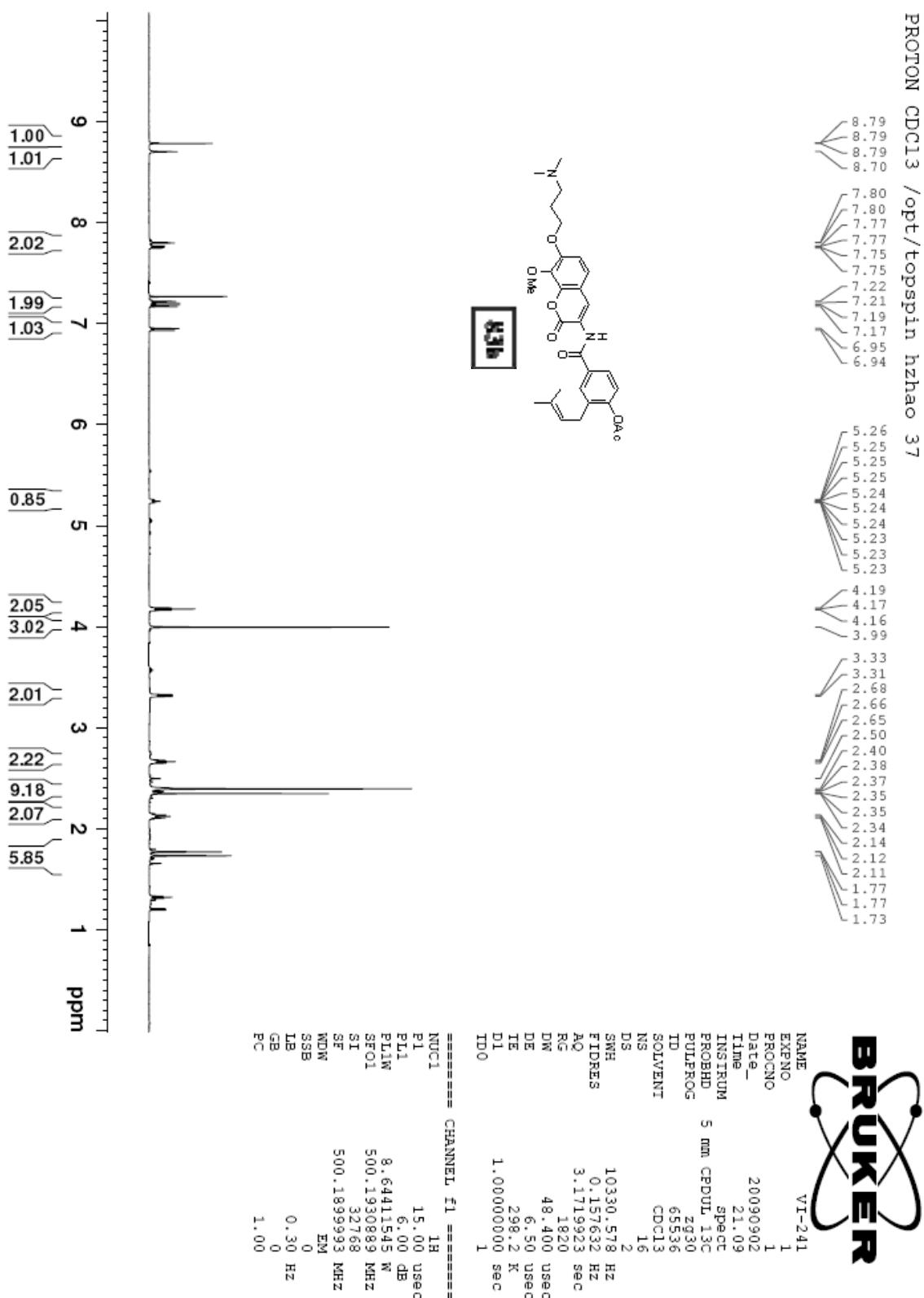


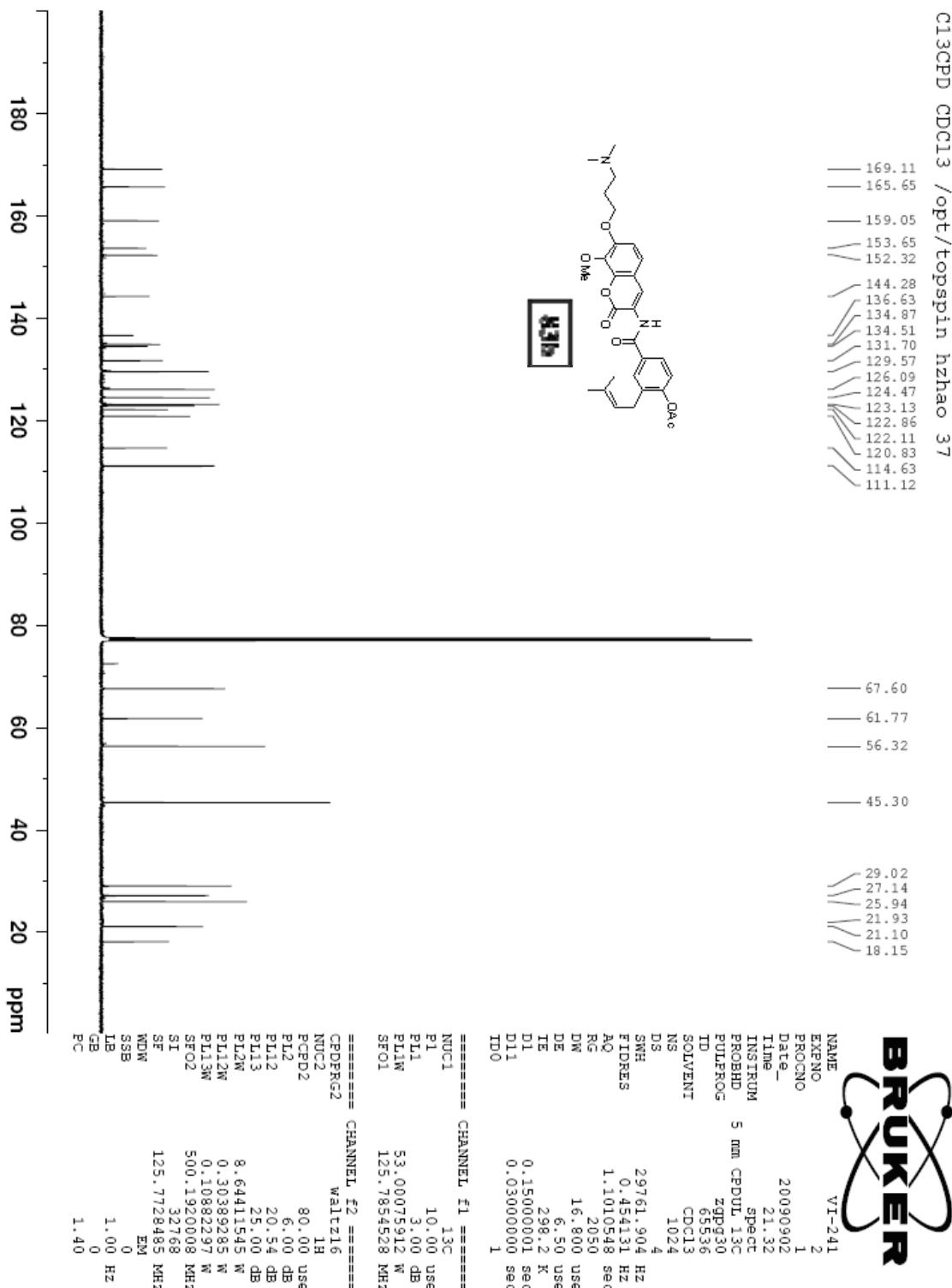


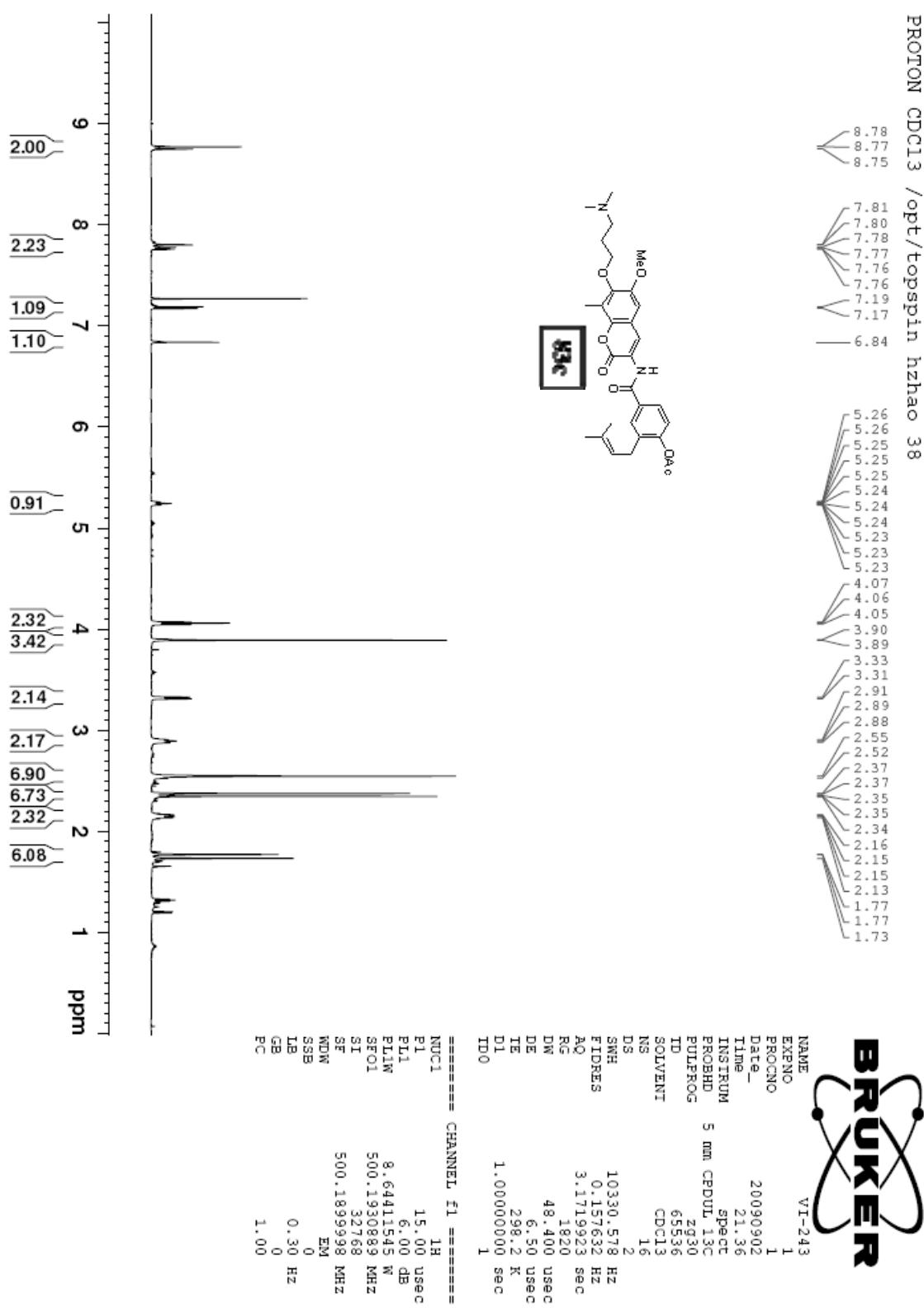


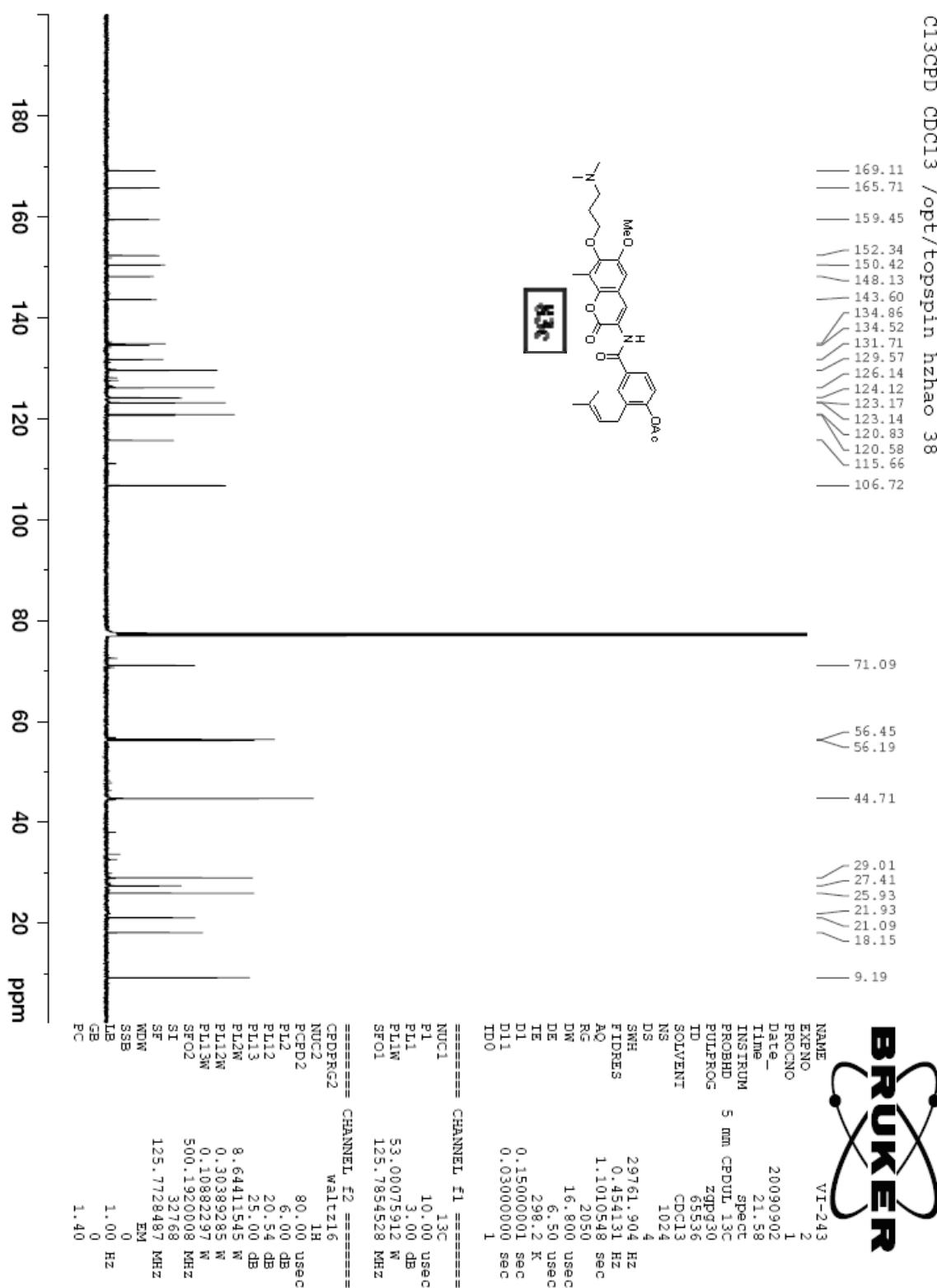


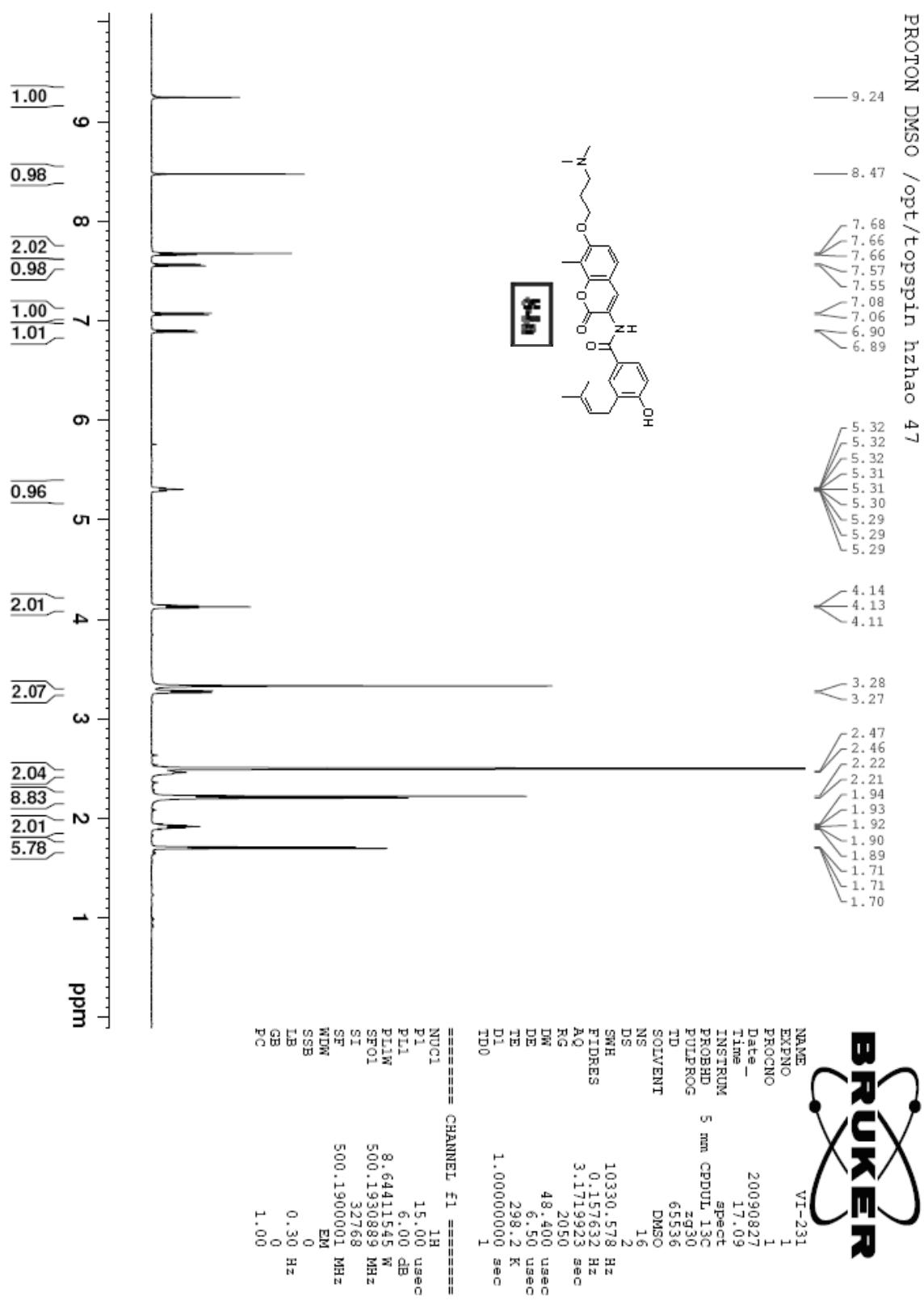


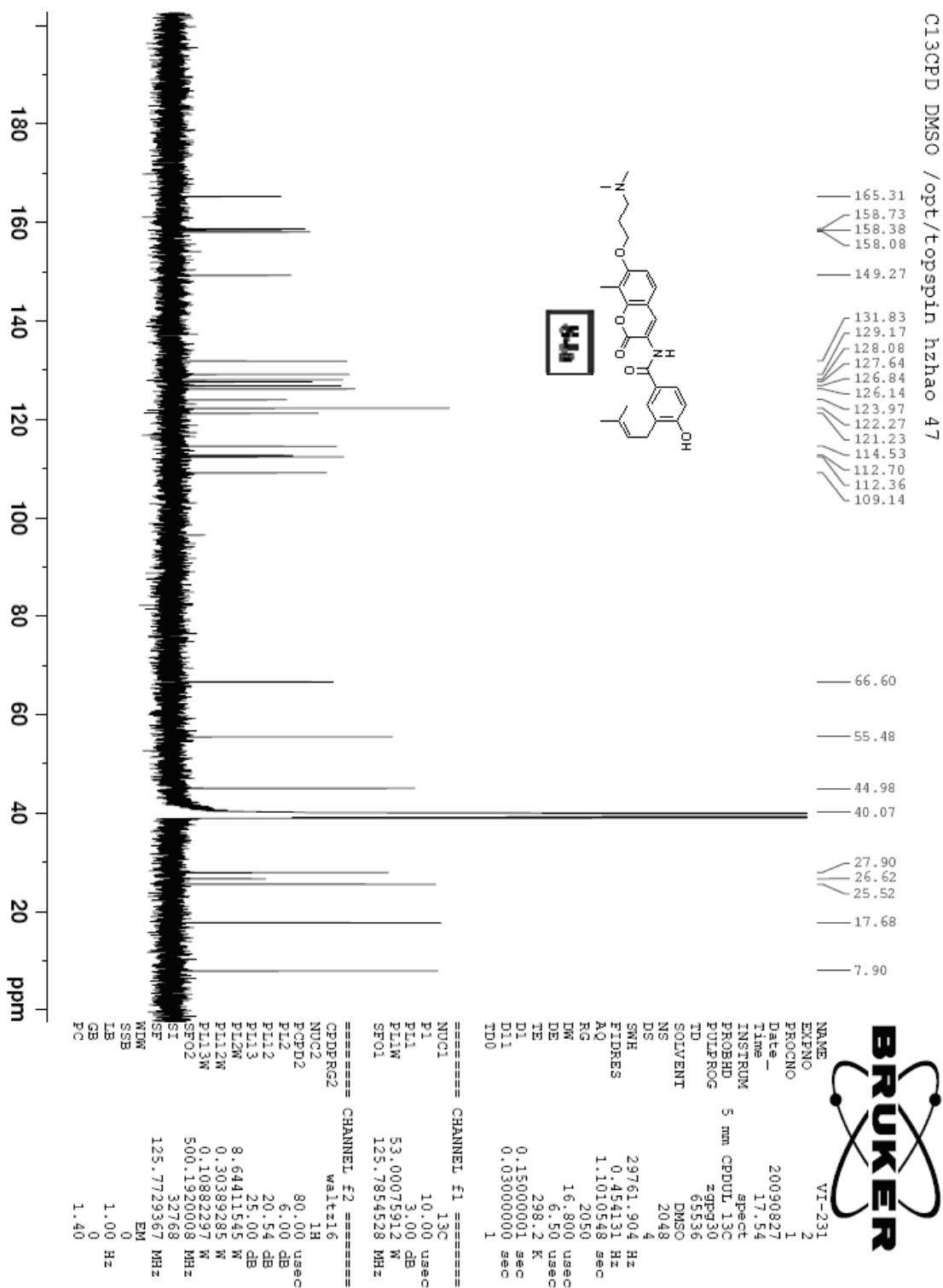


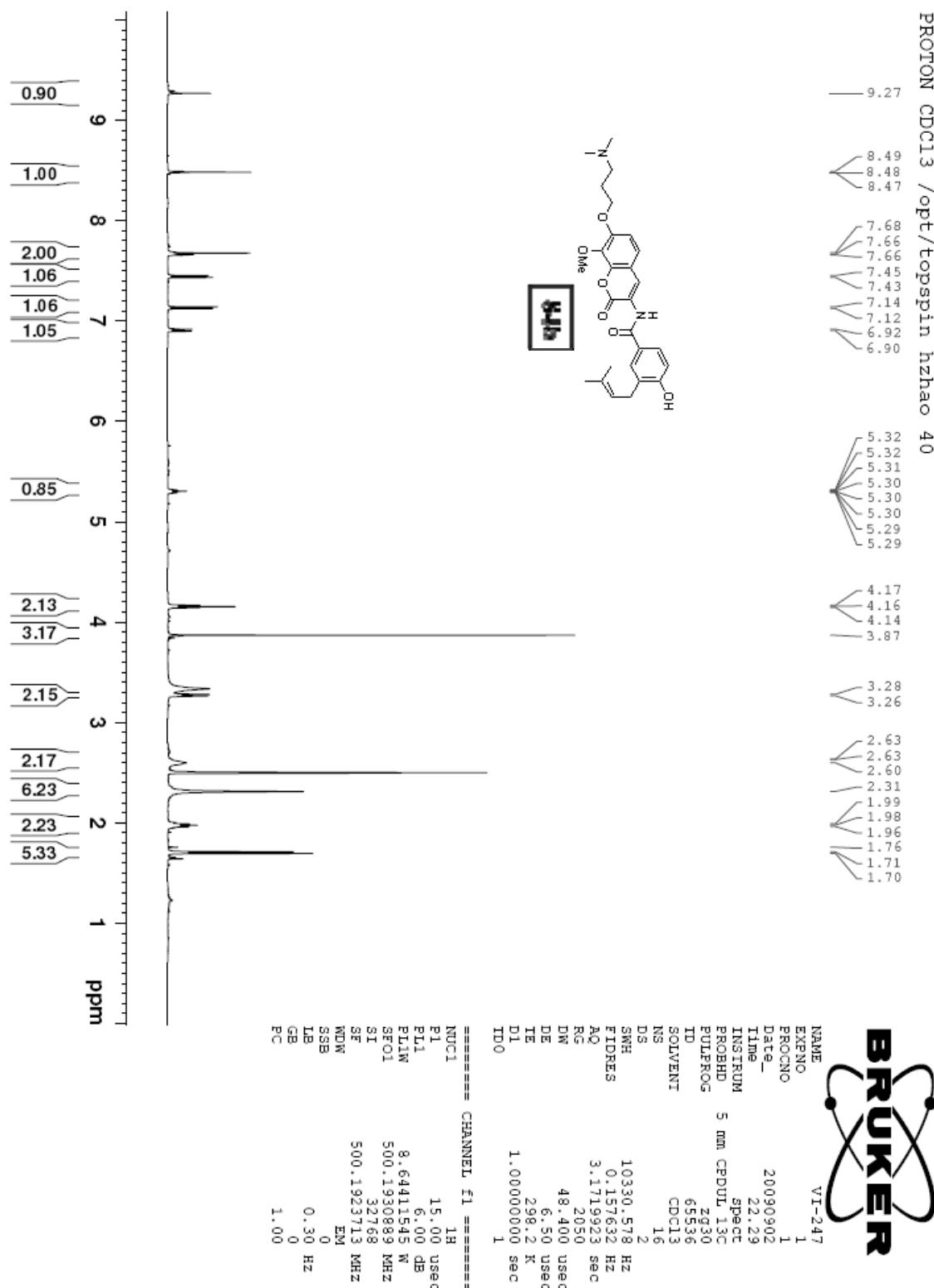


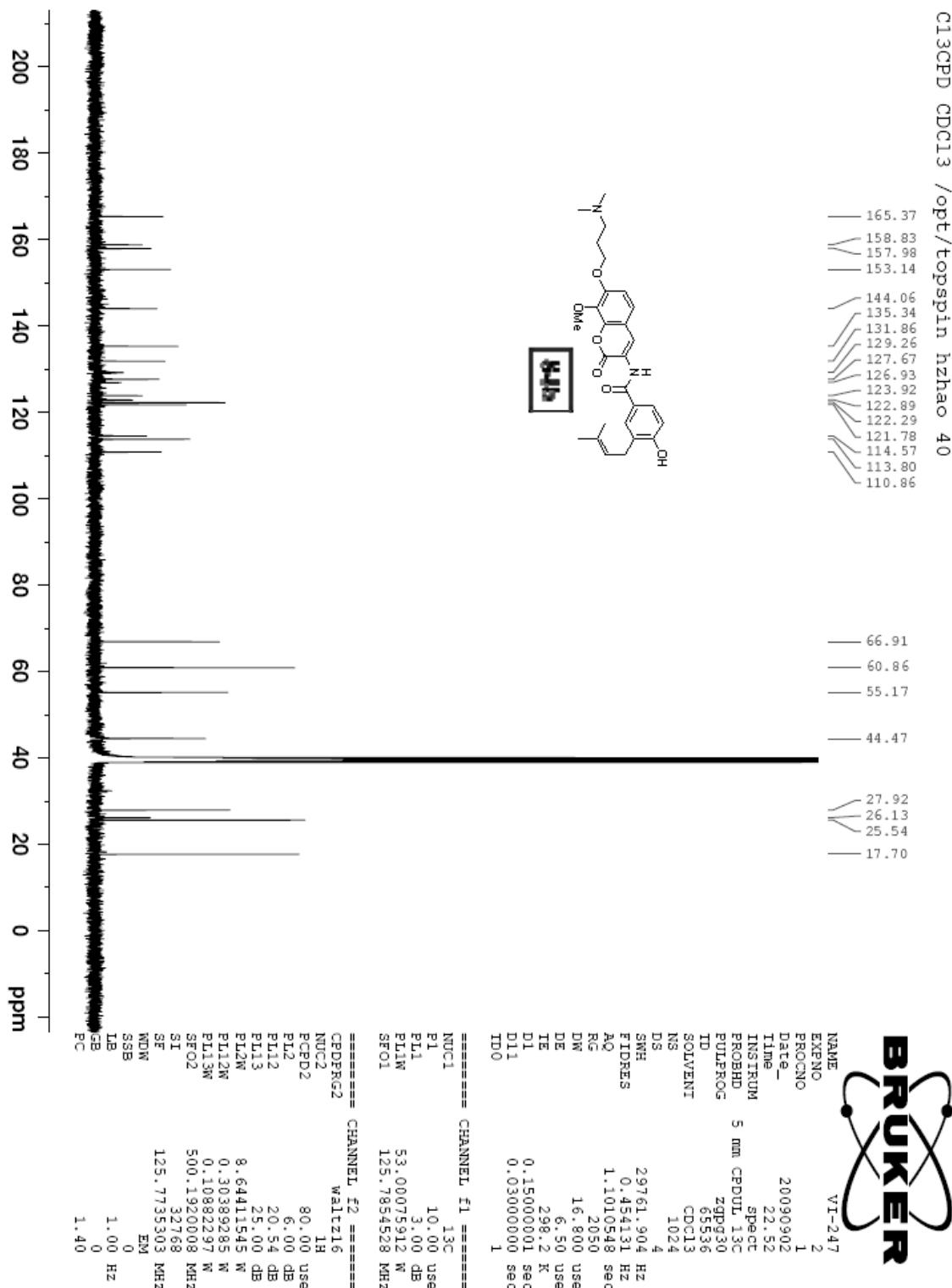


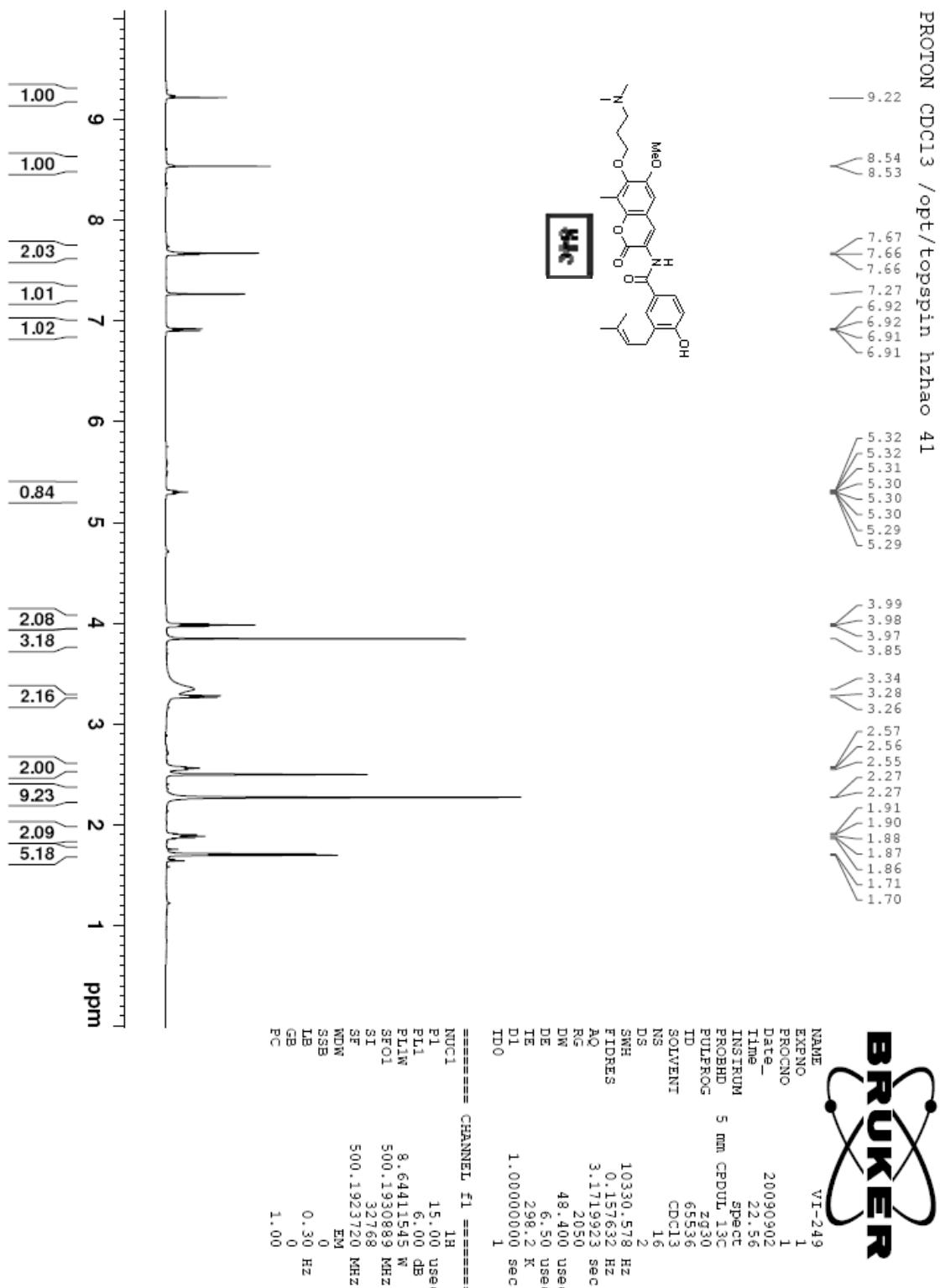


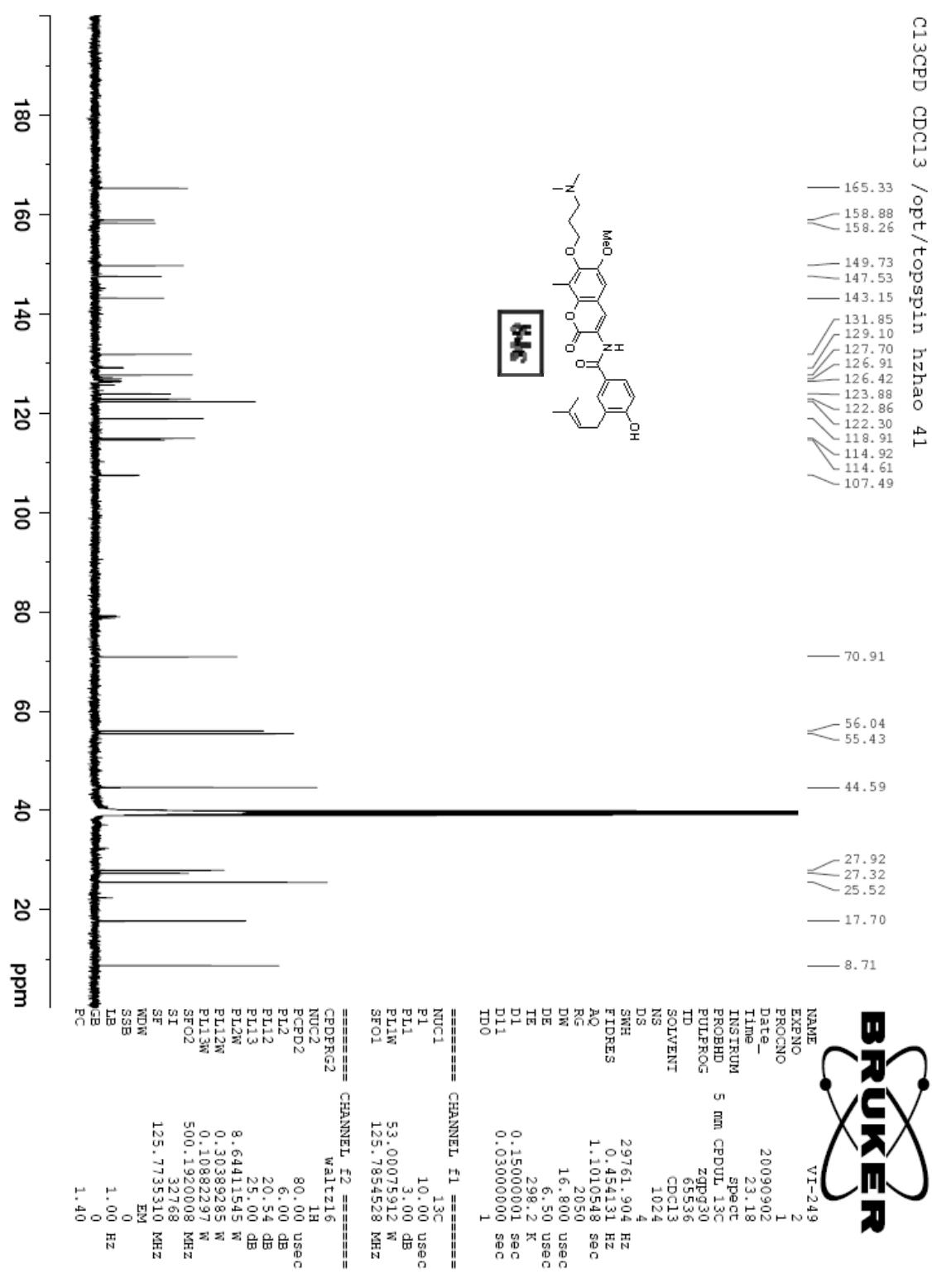












Analytical reverse HPLC

Instrument: Agilent 1260

Detector: Diode array detection

Wavelength: 254 nm

Column: ZORBAX Eclipse Plus (150 mm

X 4.6 mm, 5 μ m)

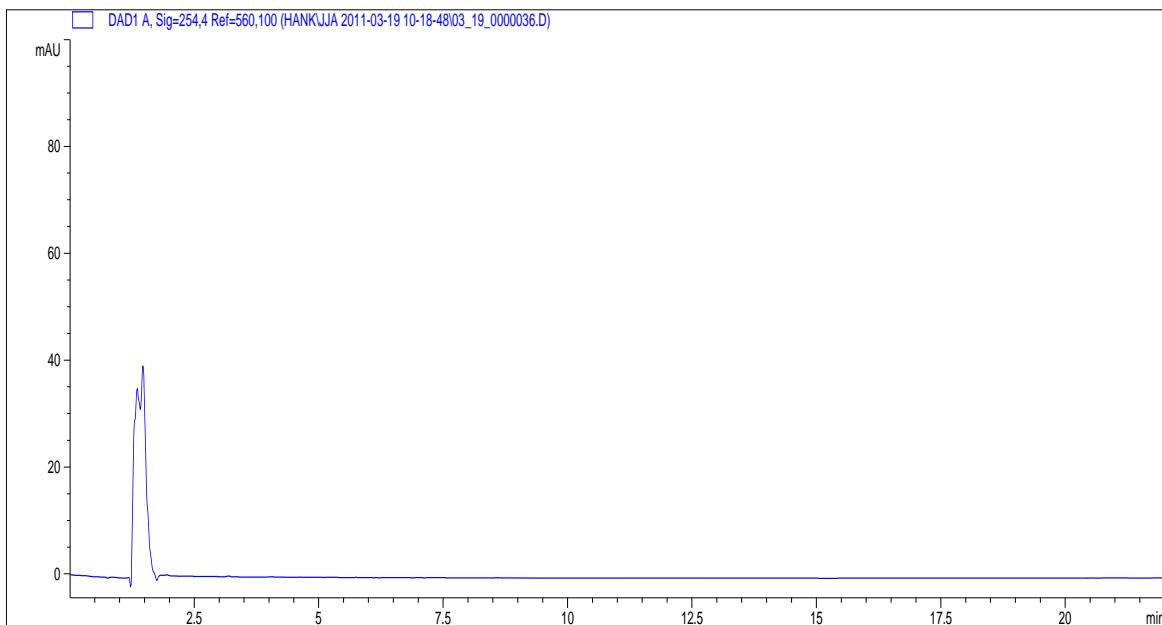
Temperture: 27 °C

Solvent system: **A**: H₂O (0.2% H₃PO₄) **B**:

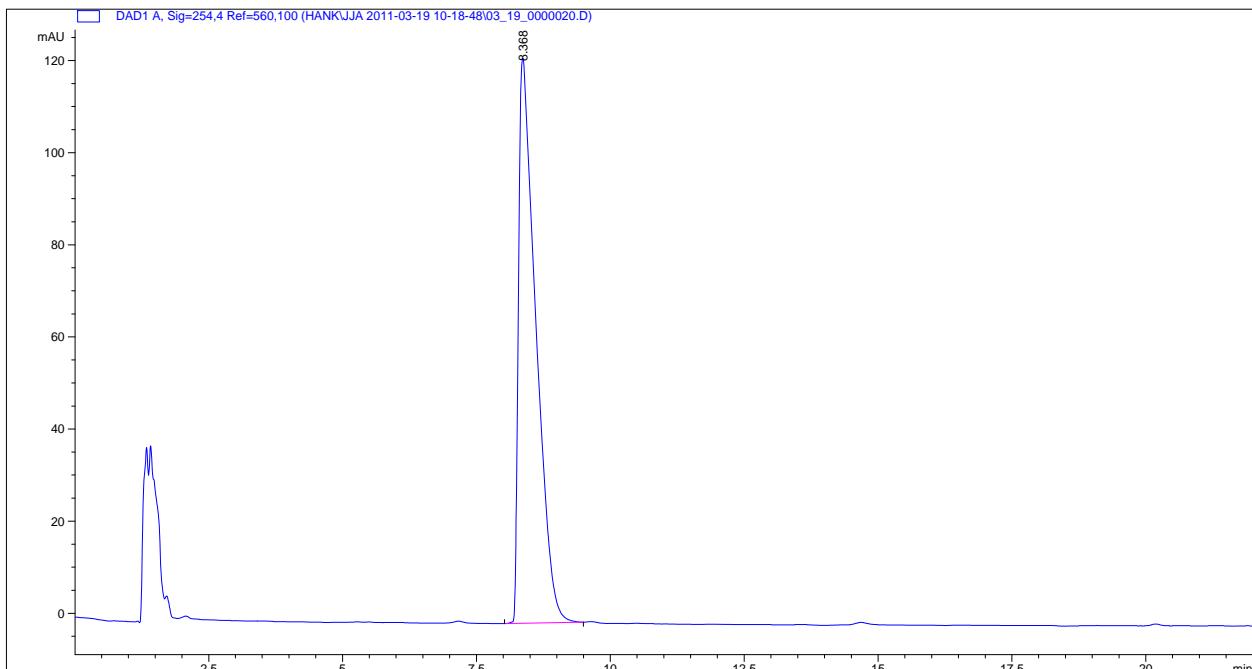
acetonitrile

Flow rate: 1.0 mL/min

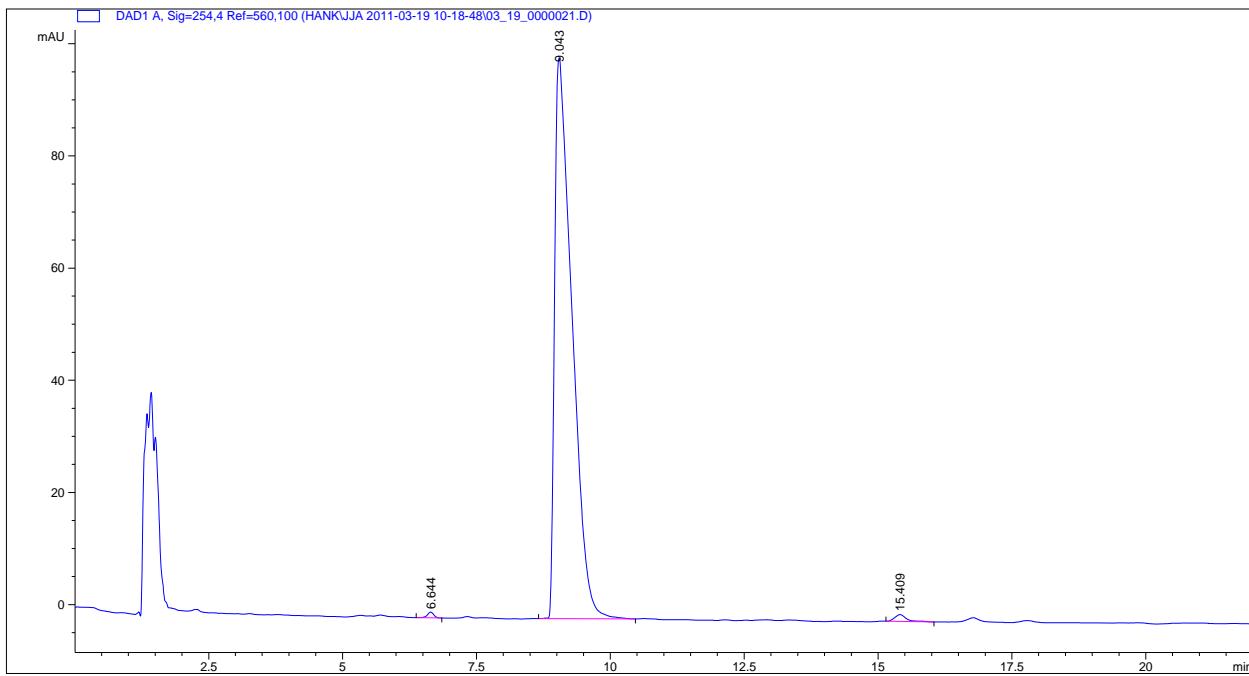
	A	B
0 min	70%	30%
18min	52%	48%
19min	95%	5%
22min	95%	5%
23min	70%	30%



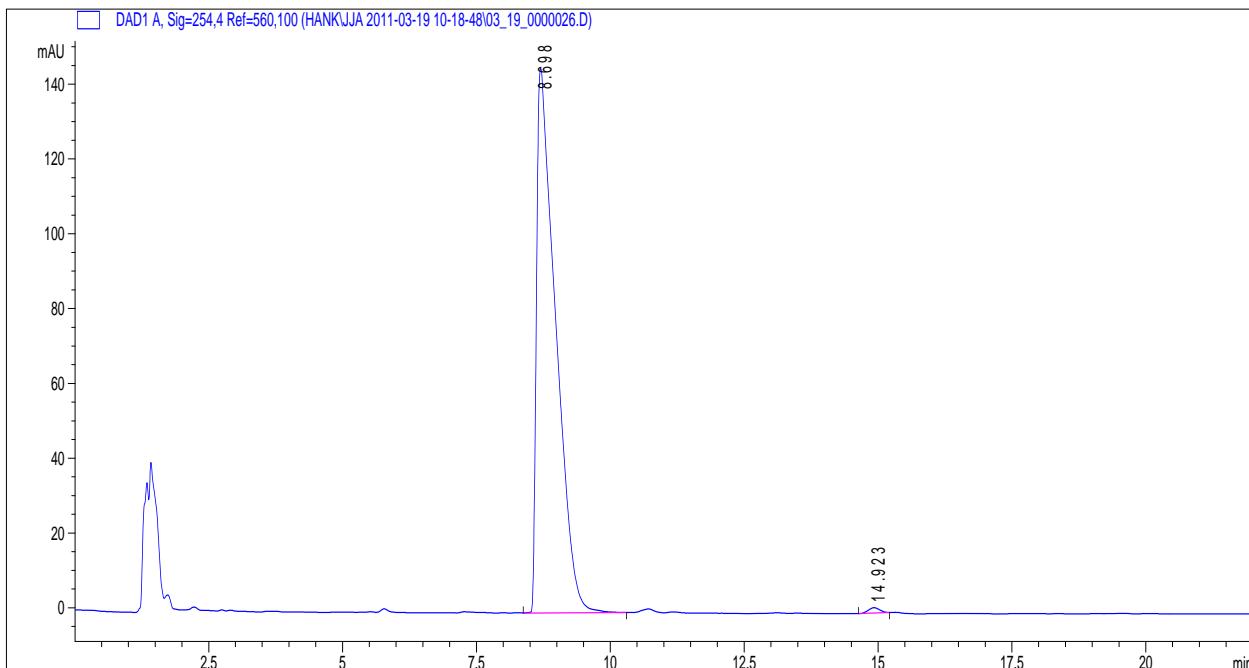
Analytical reverse-phase HPLC profile of Dimethylsulfoxide (DMSO) as background
(used as solvent to dissolve the novobiocin analogues)



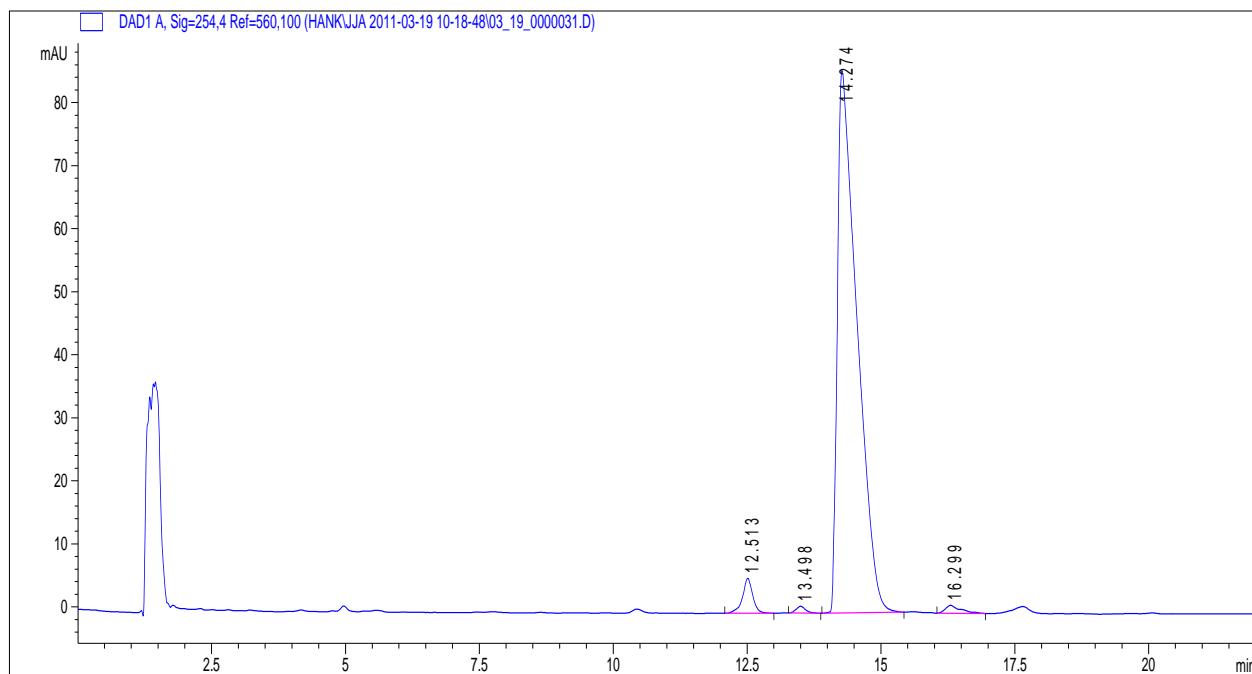
Analytical reverse-phase HPLC profile of compound **78a** prior to bioassay. Retention time = 8.37 min. Purity = 100%. Absorbance wavelength = 254 nm.



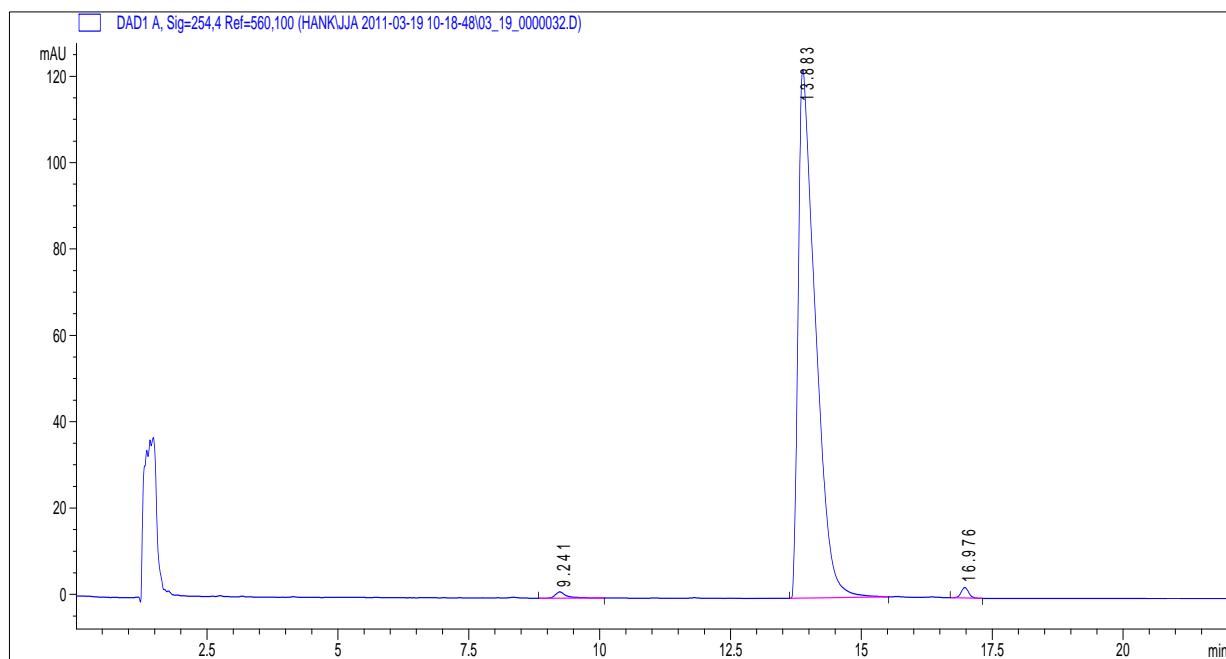
Analytical reverse-phase HPLC profile of compound **78b** prior to bioassay. Retention time = 9.04 min. Purity = 98.8%. Absorbance wavelength = 254 nm.



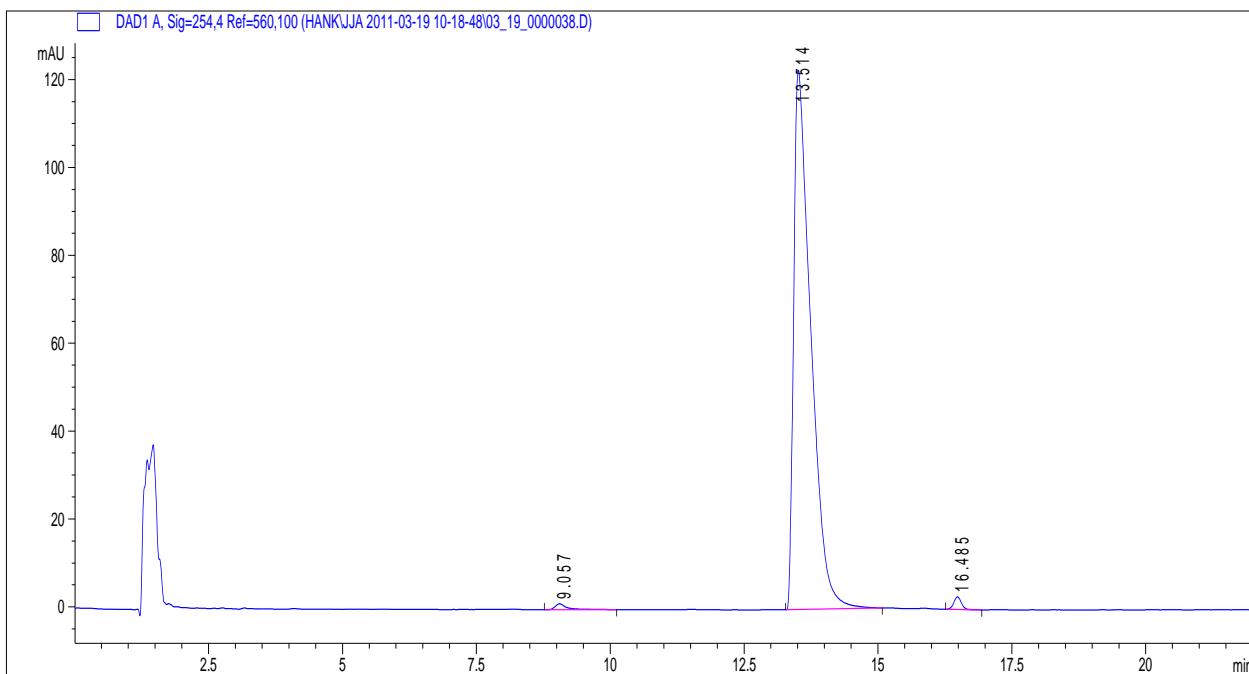
Analytical reverse-phase HPLC profile of compound **78c** prior to bioassay. Retention time = 8.70 min. Purity = 99.4%. Absorbance wavelength = 254 nm.



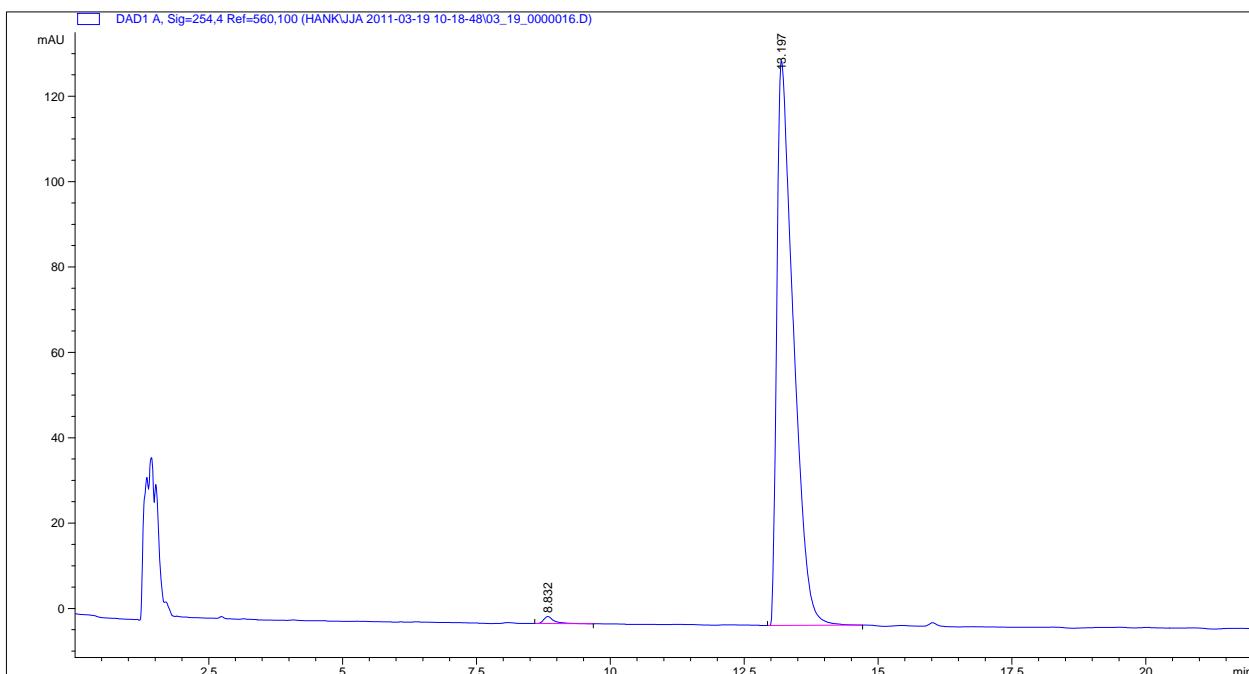
Analytical reverse-phase HPLC profile of compound **79a** prior to bioassay. Retention time = 14.3 min. Purity = 95.2%. Absorbance wavelength = 254 nm.



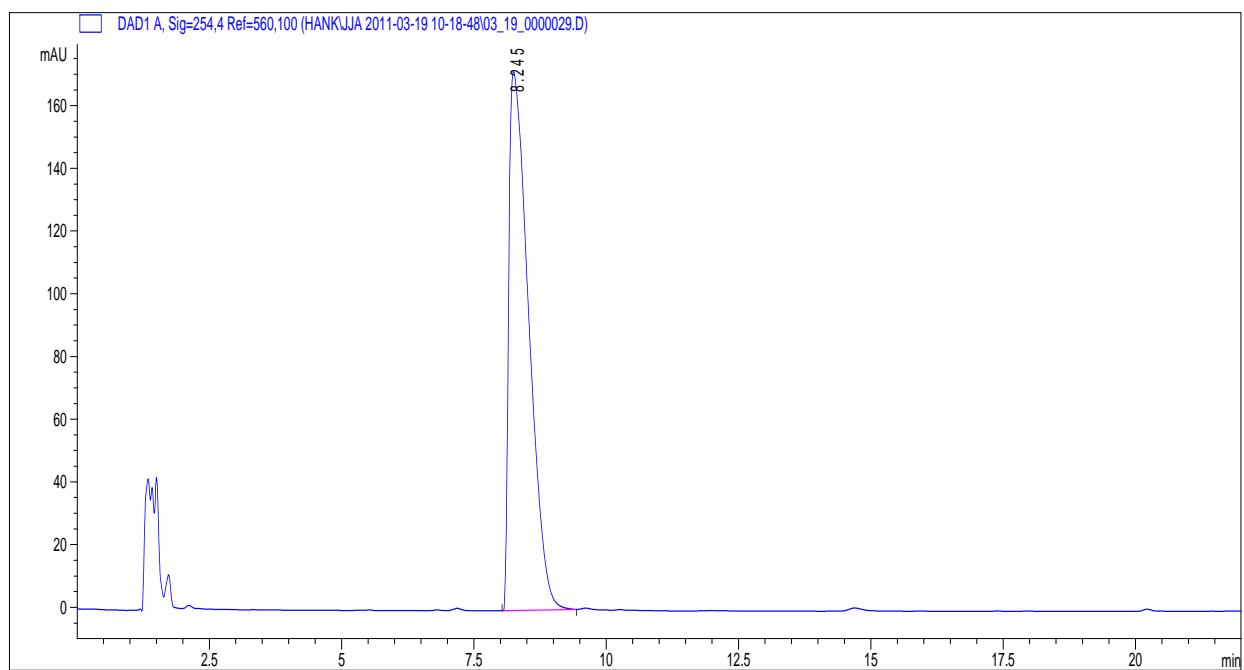
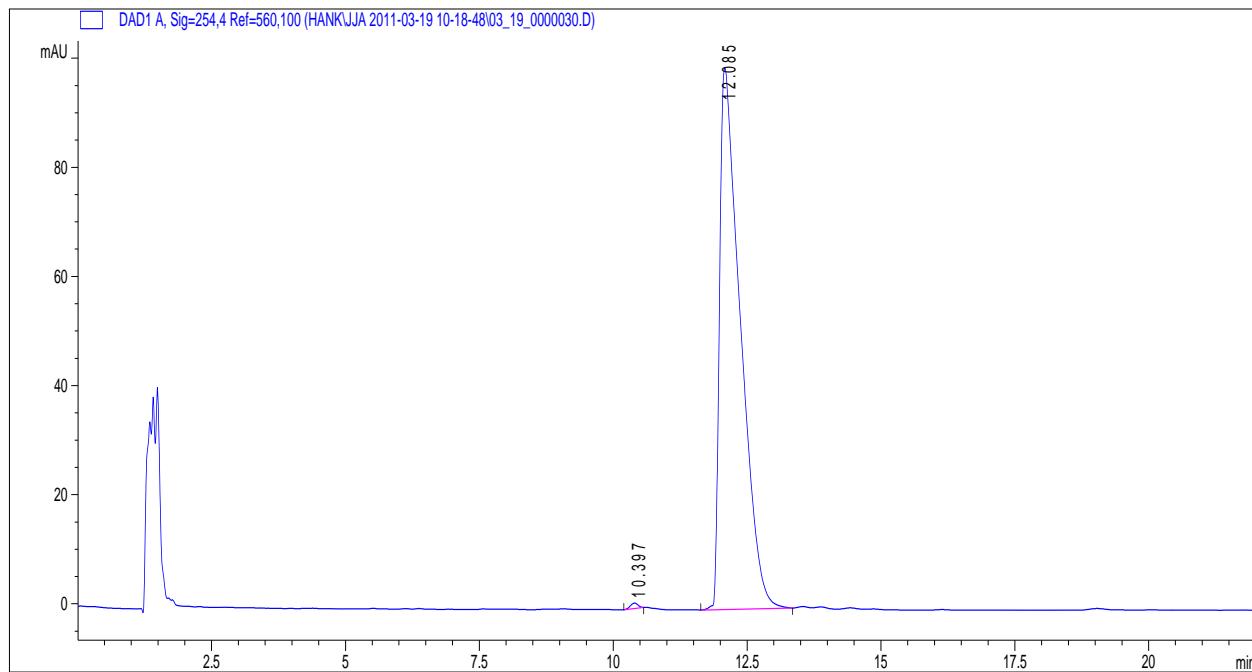
Analytical reverse-phase HPLC profile of compound **79c** prior to bioassay. Retention time = 13.9 min. Purity = 98.4%. Absorbance wavelength = 254 nm.

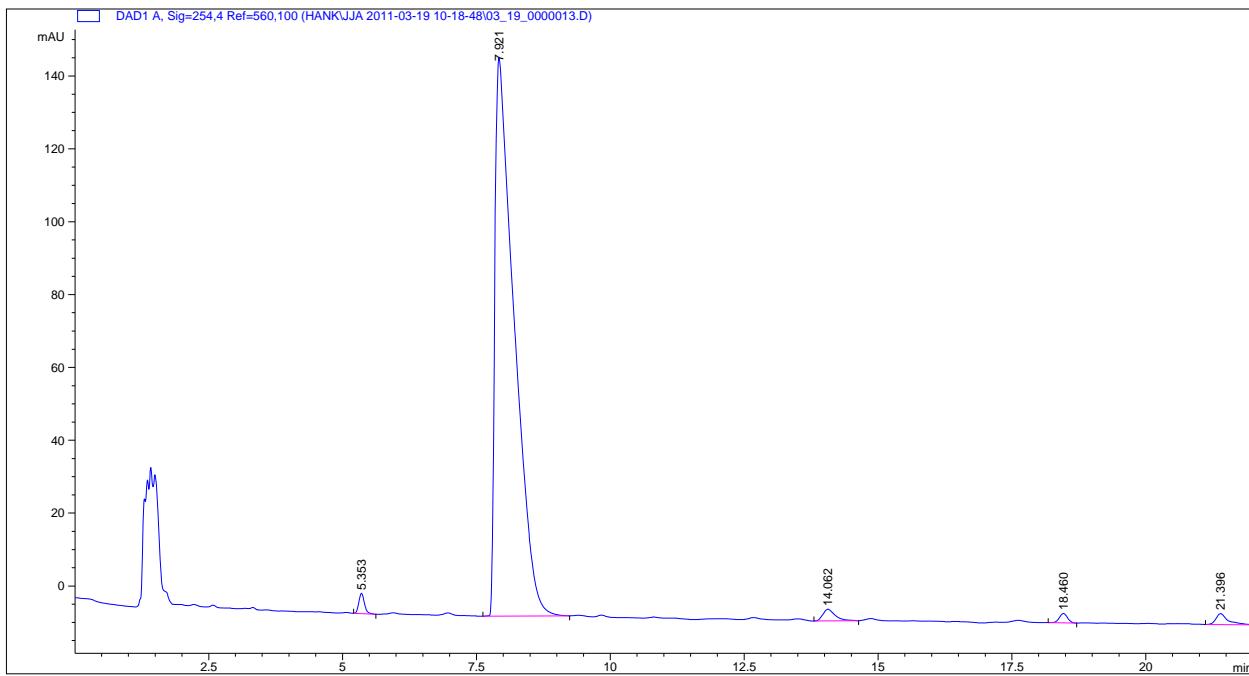


Analytical reverse-phase HPLC profile of compound **80a** prior to bioassay. Retention time = 13.5 mim. Purity = 98.2%. Absorbance wavelength = 254 nm.

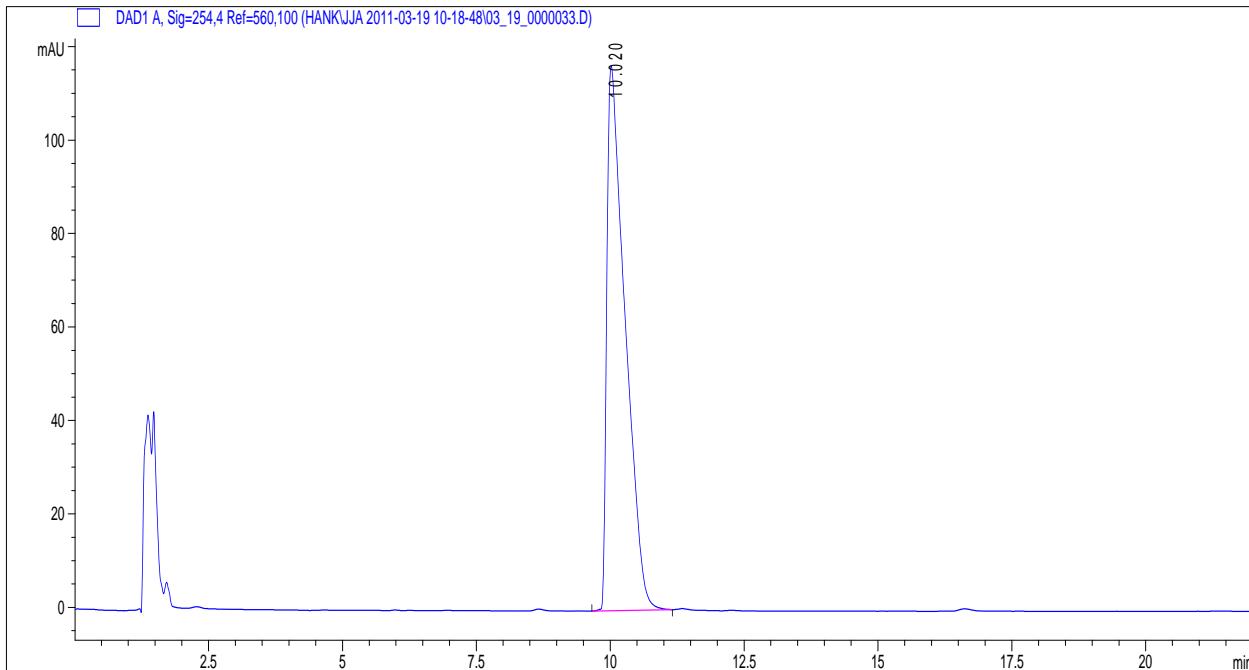


Analytical reverse-phase HPLC profile of compound **80c** prior to bioassay. Retention time = 13.2 min. Purity = 99.2%. Absorbance wavelength = 254 nm.

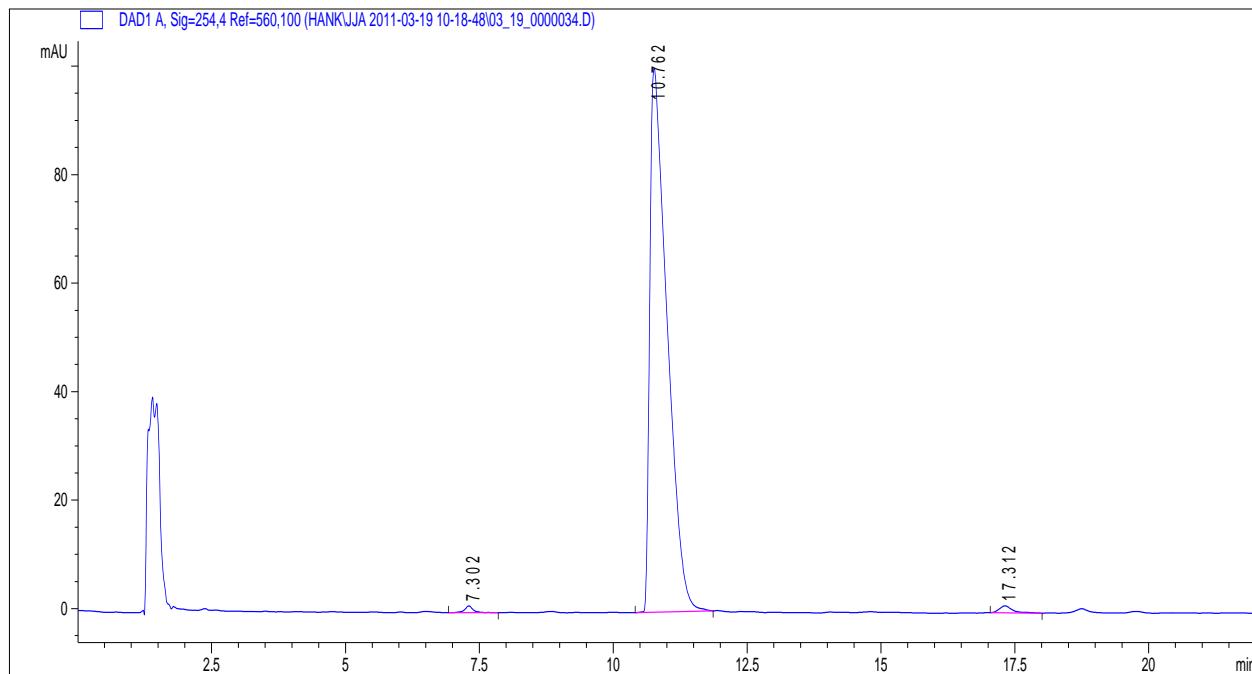




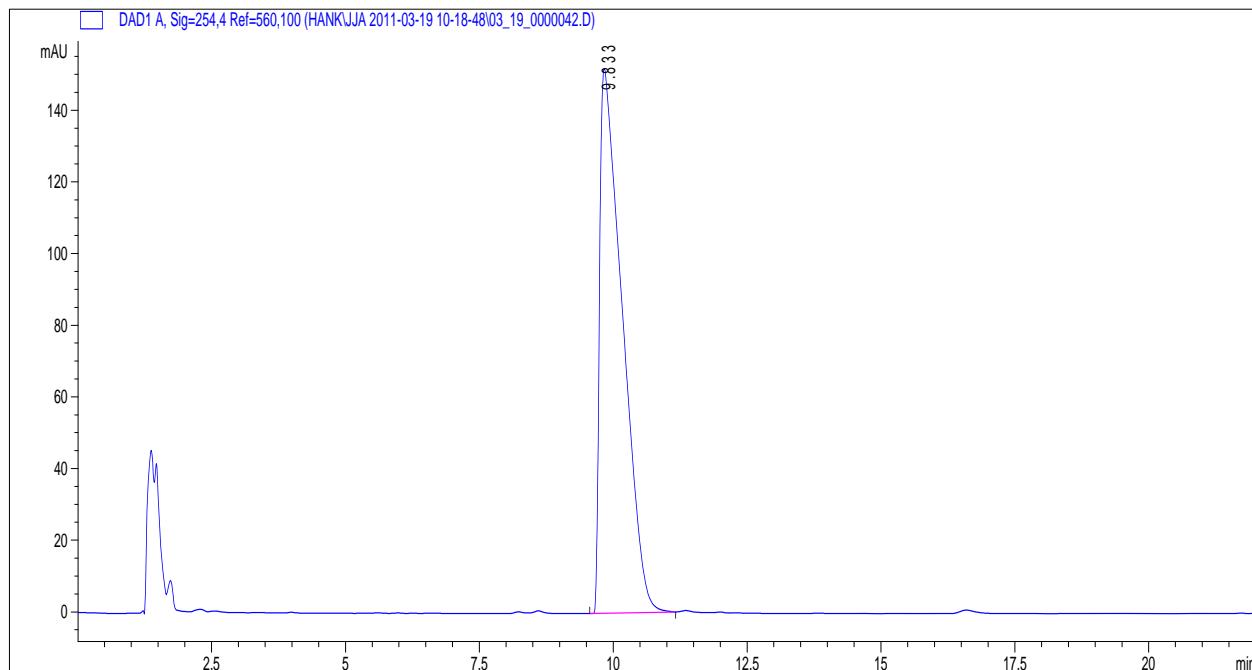
Analytical reverse-phase HPLC profile of compound **82c** prior to bioassay. Retention time = 7.92 min. Purity = 95.9%. Absorbance wavelength = 254 nm.



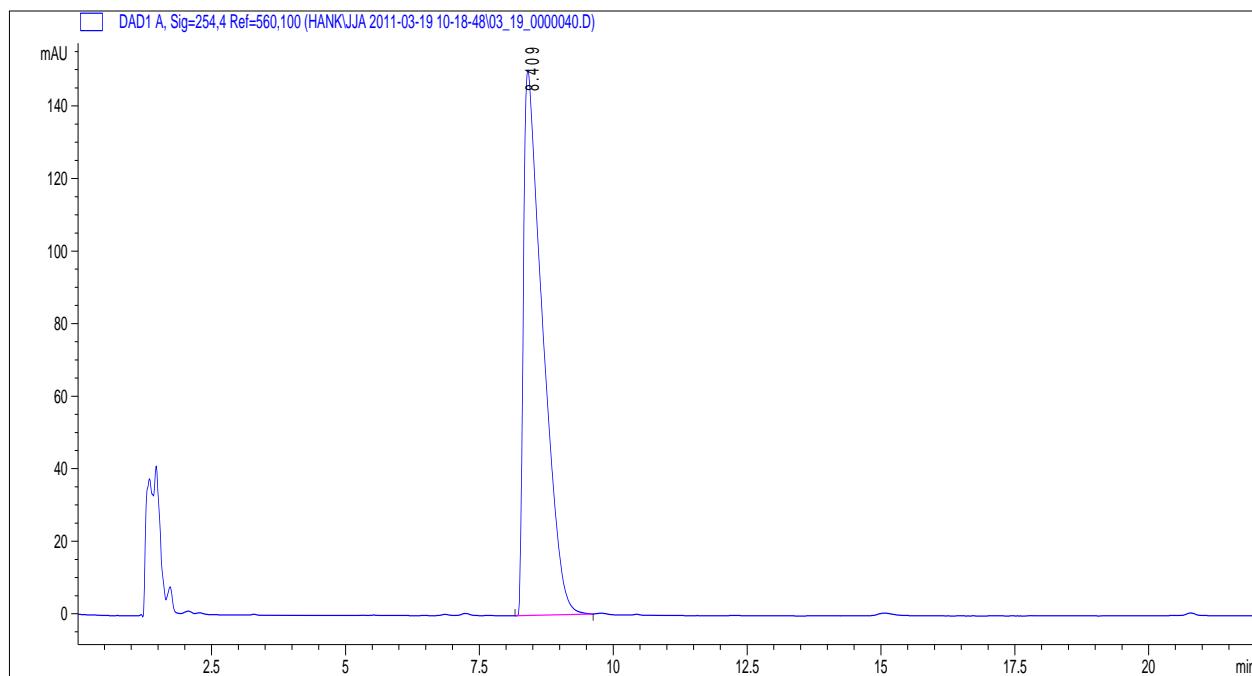
Analytical reverse-phase HPLC profile of compound **83a** prior to bioassay. Retention time = 10.0 mim. Purity = 100%. Absorbance wavelength = 254 nm.



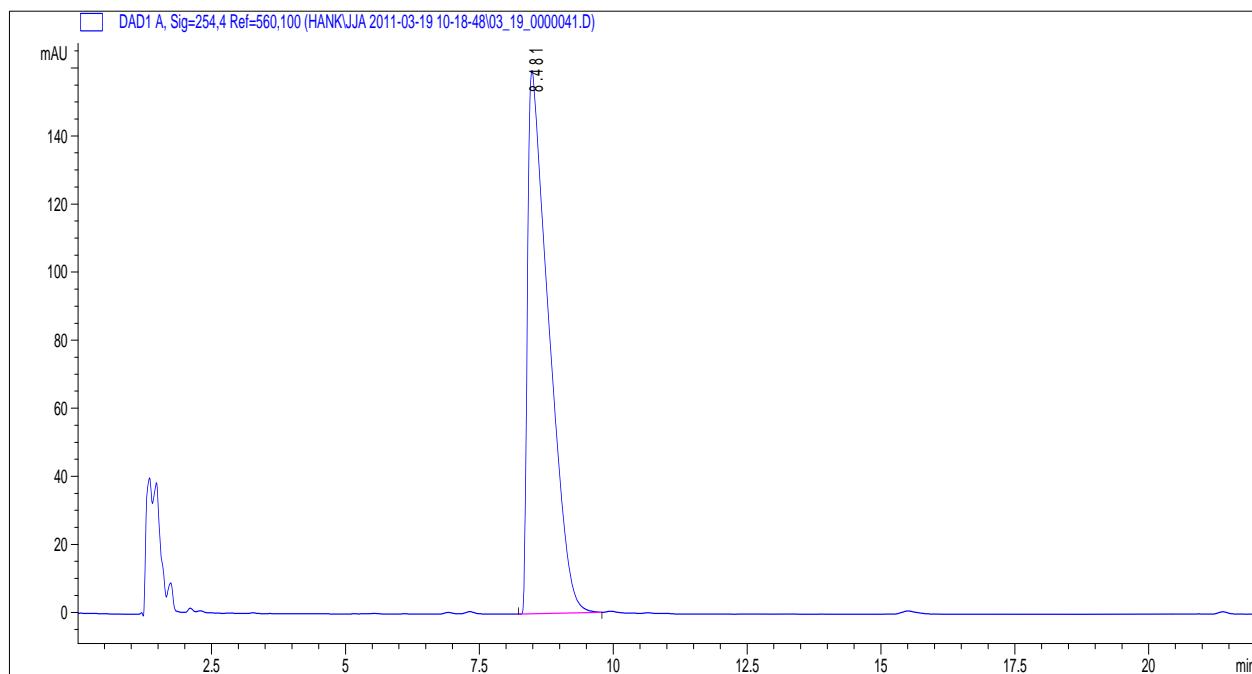
Analytical reverse-phase HPLC profile of compound **83c** prior to bioassay. Retention time = 10.8 mim. Purity = 98.5%. Absorbance wavelength = 254 nm.



Analytical reverse-phase HPLC profile of compound **84a** prior to bioassay. Retention time = 9.83 min. Purity = 100%. Absorbance wavelength = 254 nm.



Analytical reverse-phase HPLC profile of compound **84b** prior to bioassay. Retention time = 9.11 min. Purity = 100%. Absorbance wavelength = 254 nm.



Analytical reverse-phase HPLC profile of compound **84c** prior to bioassay. Retention time = 8.48 min. Purity = 100%. Absorbance wavelength = 254 nm.

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