Synthesis and Initial Structure–Activity Relationships of Modified Salicylihalamides

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Supporting Information

I. General techniques

Unless noted otherwise, commercially available materials were used without further purification. All solvents used were of HPLC- or ACS-grade. Solvents used for moisture sensitive operations were distilled from drying agents under a nitrogen atmosphere: Et_2O and THF from sodium benzophenone ketyl; benzene and toluene from sodium; CH_2Cl_2, CH_3CN, NEt_3 and pyridine from CaH_2.
All moisture sensitive reactions were carried out under a nitrogen atmosphere with magnetic stirring. Flash chromatography (FC) was performed using *E Merck* silicagel 60 (240-400 mesh) according to the protocol of Still, Kahn, and Mitra (*J. Org. Chem.* **1978**, *43*, 2923). Thin Layer chromatography was performed using precoated plates purchased from *E. Merck* (silicagel 60 PF254, 0.25 mm) that were visualized using a $KMnO_4$ or Ce(IV) stain.

Nuclear magnetic resonance (NMR) spectra were recorded on either a *Varian Inova-400* or *Mercury-300* spectrometer at operating frequencies of 400 / 300 MHz (^{1}H NMR) or 100 / 75 MHz (^{13}C NMR). Chemical shifts (δ) are given in ppm relative to residual solvent (usually chloroform; δ 7.27 for ^{1}H NMR or δ 77.25 for proton decoupled ^{13}C NMR), and coupling constants (*J*) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplet, whereby the prefix *app* is applied in cases where the true multiplicity is unresolved, and *br* when the signal in question is broadened.

Infrared spectra were recorded on a *Perkin-Elmer 1000* series FTIR with wavenumbers expressed in cm^{-1} using samples prepared as thin films between salt plates. Mass spectra were recorded on a Finnigan SSQ700 [Chemical Ionization (CI) or Electron Impact (EI)] or a *Micromass Quattro II* mass spectrometer [Electro-Spray (ES)]. High-resolution mass spectra (HRMS) were recorded at the NIH regional mass spectrometry facility at the University of Washington, St. Louis, MO.

II. Experimental procedures

*1. Procedure for acyl azide formation from acid **9***

To a stirred solution of acid **9** (52 mg, 0.0883 mmol) and $(PhO)_2P(O)N_3$ (77.3 µL; 0.353 mmol) in benzene (4 mL) was added Et_3N (58 µL) at RT. After stirring for 14 h at RT, the solvent was removed and the residue was purified by FC (silicagel, 2.5% EtOAc in hexanes). The corresponding acyl azide was obtained in 92% yield (50 mg).

*2. Curtius rearrangement and preparation of **1**, **11-13***

The acyl azide derived from **9** (12 mg; 0.0195 mmol) in benzene (1 mL) was stirred at 75ºC for 6 h, after which the solvent was removed and the residue (isocyanate **10**) dissolved in diethyl ether (1 mL). In a separate flask, a 0.15 M solution of 1-lithio-1,3-hexadiene was prepared by the addition of *t*-BuLi (2.05 equiv with respect to the bromide) to a solution of the corresponding bromide in THF at -78ºC. After stirring for 45 min at -78ºC and warming to RT, the organolithium (0.15 M in THF; 143 µL; 0.0215 mmol) was added dropwise to the ethereal solution of isocyanate **10** at -78ºC. The mixture was allowed to reach 0ºC over a 1 h period followed by the addition of pH 7.0 phosphate buffer. Extraction with diethyl ether (3×), drying (Na_2SO_4), concentration and rapid purification by FC (silicagel, 6% EtOAc in hexanes containing 0.2% Et_3N) gave 3.7 mg of a less polar product **i** and 5.9 mg of a more polar product **ii**.

The less polar product **i** was treated with 250 µL of a solution prepared from 0.5 g commercial HF·pyridine in 1.25 mL pyridine and 6.75 mL THF. The more polar product **ii** was similarly treated with 410 µL of the same solution. After stirring for 48 h at RT, the reactions were quenched with a phosphate buffer (pH 7.0; 10 mL), extracted with EtOAc (4×), dried (Na_2SO_4) and concentrated. The product derived from deprotection of **ii** was purified by normal-phased semi-preparative HPLC (5µ Luna silicagel; 250 × 10 mm column; 25% acetone in hexanes, t_R = 25 min) yielding 1.7 mg of a 1:1 mixture of salicylihalamide A (**1**) and the corresponding geometrical isomer **11** (20% from acyl azide). The product derived from deprotection of **i** provided two fractions after HPLC purification (35% acetone in hexanes): 1.5 mg of **13** (t_R = 25.7 min; 10% yield from acyl azide) and 1.5 mg of **12** (t_R = 26.7 min; 10% yield from acyl azide). The combined overall yield for **1**, **11-13** from acyl azide is 40%.

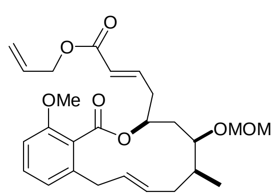
3. Curtius rearrangement and preparation of ***14*** *and* ***15***

Following the procedure described above, acyl azide (9.0 mg; 0.0146 mmol) was converted to isocyanate **10**, followed by the addition of *n*-hexyllithium (0.15 M in THF; prepared from the bromide as described above). Workup and rapid purification by FC (silicagel, 15% EtOAc in hexanes containing 0.2% Et_3N) gave 4.0 mg of a less polar product **i** and 4.2 mg of a more polar product **ii.** Deprotection and purification by semi-preparative HPLC as described above yielded 1.4 mg (22%) of **14** (derived from **ii**) and 1.6 mg (14%) of the corresponding dimer **15** (derived from **i**) respectively.

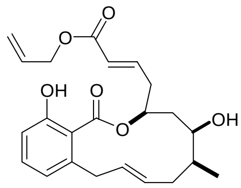
4. Curtius rearrangement and preparation of carbamate ***16***

A solution of the acyl azide derived from acid **9** (10.0 mg; 0.0163 mmol) and 1-pentanol (11 µL; 0.1019 mmol) in benzene (1 mL) was stirred for 8 h at 80°C. After removal of the solvent, the residue was treated with 780 µL of a solution prepared from 0.5 g commercial HF·pyridine in 1.25 mL pyridine and 6.75 mL THF. After stirring for 24 h at RT, the reaction were quenched with a phosphate buffer (pH 7.0; 10 mL), extracted with EtOAc (4×), dried (Na_2SO_4) and concentrated. Purification by FC (silicagel; 25% acetone in hexanes) yielded 3.4 mg of carbamate **16** (0.00763 mmol; 47%).

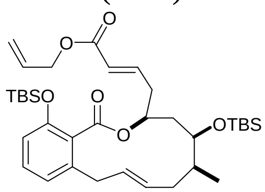
III. Characterization data



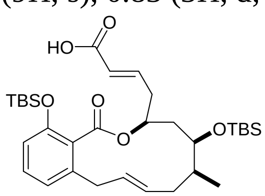
6: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (1H, *app*.t, *J* = 8.0 Hz), 7.14 (1H, ddd, *J* = 6.0, 8.0, 15.6 Hz), 6.81 (1H, d, *J* = 8.4 Hz), 6.75 (1H, d, *J* = 7.2 Hz), 5.95 (1H, d, *J* = 15.6 Hz), 5.90-6.00 (1H, m), 5.32-5.52 (3H, m), 5.33 (1H, td, *J* = 1.2, 17.0 Hz), 5.24 (1H, td, *J* = 1.2, 10.4 Hz), 4.89 (1H, d, *J* = 6.8 Hz), 4.81 (1H, d, *J* = 6.8 Hz), 4.64 (2H, dd, *J* = 1.2, 5.6 Hz), 4.16 (1H, dd, *J* = 3.6, 9.6 Hz), 3.85 (3H, s), 3.71 (1H, dd, *J* = 9.6, 16.4 Hz), 3.45 (3H, s), 3.32 (1H, *br* d, *J* = 16.4 Hz), 2.65 (1H, ddd, *J* = 6.0, 7.6, 15.6 Hz), 2.47 (1H, ddd, *J* = 4.0, 8.0, 15.6 Hz), 2.27-2.36 (1H, m), 2.08-2.19 (1H, m), 1.76 (1H, dd, *J* = 8.8, 15.6), 1.70 (1H, *app*.dt, *J* = 11.6, 14.0 Hz), 1.44 (1H, dd, *J* = 9.6, 15.6 Hz), 0.86 (3H, d, *J* = 6.4 Hz).



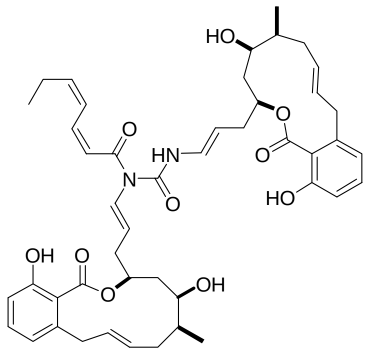
7: $[\alpha]_D$ = +4.32 (*c* 0.88, $CHCl_3$); IR 3407, 3172, 2959, 1731, 1690, 1656, 1590 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.0 (1H, s), 7.31 (1H, dd, *J* = 7.6, 8.4 Hz), 7.01 (1H, *app*.dt, *J* = 7.2, 15.6 Hz), 6.89 (1H, dd, *J* = 0.8, 8.4 Hz), 6.71 (1H, dd, *J* = 0.8, 7.6 Hz), 5.97 (1H, d, *J* = 15.6 Hz), 5.95 (1H, ddt, *J* = 5.6, 10.4, 15.6 Hz), 5.64 (1H, *app*.dt, *J* = 5.2, 11.2 Hz), 5.44-5.52 (1H, m), 5.33 (1H, *app*.qd, *J* = 1.2, 15.6 Hz), 5.24 (1H, *app*.qd, *J* = 1.2, 10.4 Hz), 5.02-5.13 (1H, m), 4.65 (1H, *app*.td, *J* = 1.2, 5.6 Hz), 3.74 (1H, dd, *J* = 5.6, 16.4 Hz), 3.62 (1H, dd, *J* = 3.2, 8.8 Hz), 3.38 (1H, *br* d, *J* = 16.4 Hz), 2.56-2.69 (2H, m), 2.31-2.40 (1H, m), 2.03 (1H, dd, *J* = 11.2, 15.2), 1.79-1.97 (2H, m), 1.52-1.72 (1H, m), 1.44 (1H, ddd, *J* = 1.2, 8.4, 14.8 Hz), 0.93 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 165.9, 163.1, 143.7, 142.5, 134.5, 133.2, 132.3, 126.5, 124.5, 123.9, 118.5, 116.9, 113.1, 73.2, 70.5, 65.3, 39.3, 38.6, 38.0, 37.5, 35.6, 13.9; MS (CI) *m/z* (%): 401 (28), 383 (30), 343 (37), 325 (100); HRMS (FAB) Calcd for $C_{23}H_{29}O_6$ (MH^+): 401.1964. Found: 401.1973.



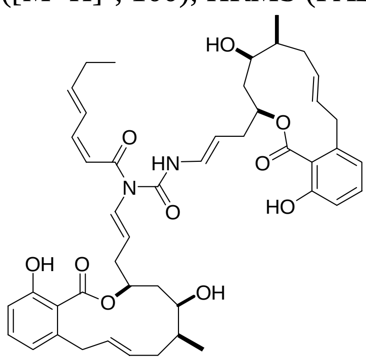
8: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (1H, *app*.t, *J* = 8.0 Hz), 6.93 (1H, *app*.dt, *J* = 7.2, 15.6 Hz), 6.75 (1H, d, *J* = 7.6 Hz), 6.72 (1H, d, *J* = 8.0 Hz), 5.95 (1H, ddt, *J* = 6.0, 10.4, 17.2 Hz), 5.94 (1H, d, *J* = 15.6 Hz), 5.29-5.46 (3H, m), 5.33 (1H, *app*.qd, *J* = 1.6, 17.2 Hz), 5.24 (1H, *app*.qd, *J* = 1.6, 10.4 Hz), 4.64 (2H, dd, *J* = 1.6, 5.6 Hz), 4.26 (1H, dd, *J* = 3.2, 8.8 Hz), 3.65 (1H, dd, *J* = 8.8, 16.4 Hz), 3.32 (1H, *br* d, *J* = 16.4 Hz), 2.55-2.60 (2H. m), 2.22-2.30 (1H, m), 1.76-1.85 (1H, m), 1.65-1.75 (1H, m), 1.67 (1H, dd, *J* = 8.8, 15.6 Hz), 1.41 (1H, dd, *J* = 8.8, 15.6 Hz), 0.96 (9H, s), 0.90 (9H, s), 0.83 (3H, d, *J* = 6.4 Hz), 0.22 (3H, s), 0.20 (3H, s), 0.15 (3H, s), 0.12 (3H, s).



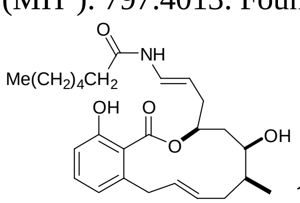
9: $[\alpha]_D$ = +2.0 (*c* 1.84, $CHCl_3$); IR 2956, 2930, 2858, 1728, 1700, 1652, 1582, 1457 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (1H, *app*.t, *J* = 8.0 Hz), 7.02 (1H, *app*.dt, *J* = 7.2, 15.6 Hz), 6.75 (1H, d, *J* = 7.6 Hz), 6.72 (1H, d, *J* = 8.0 Hz), 5.93 (1H, d, *J* = 15.6 Hz), 5.30-5.46 (3H, m), 4.26 (1H, dd, *J* = 3.2, 8.8 Hz), 3.66 (1H, dd, *J* = 8.8, 16.0 Hz), 3.32 (1H, *br* d, *J* = 16.0 Hz), 2.60 (2H, *app*.t, *J* = 6.8 Hz), 2.21-2.30 (1H, m), 1.75-1.86 (1H, m), 1.35-1.45 (1H, m), 0.96 (9H, s), 0.91 (9H, s), 0.83 (3H, d, *J* = 6.4 Hz), 0.22 (3H, s), 0.20 (3H, s), 0.15 (3H, s), 0.12 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 168.4, 152.9, 146.5, 138.9, 131.6, 129.8, 128.5, 127.5, 123.8, 123.4, 118.0, 72.5, 72.2, 38.7, 38.3, 38.2, 37.3, 36.5, 26.1, 25.9, 18.5, 18.2, 13.2, -3.9, -4.19, -4.24, -4.3; MS (ES) *m/z* (%): 589 (10), 531 (21), 457 (18), 367 (40), 115 (78), 73 (100); HRMS (FAB) Calcd for $C_{32}H_{53}O_6Si_2$ (MH^+): 589.3381. Found: 589.3391.



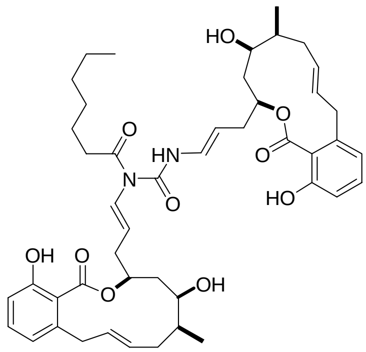
12: ^{1}H NMR (400 MHz, CD_3OD) δ 7.14 (1H, *app*.t, *J* = 8.0 Hz), 7.13 (1H, *app*.t, *J* = 8.0 Hz), 7.06 (1H, *app*.t, *J* = 11.2 Hz), 6.75 (1H, d, *J* = 8.0 Hz), 6.72 (1H, d, *J* = 14.0 Hz), 6.71 (1H, d, *J* = 8.0 Hz), 6.68 (1H, d, *J* = 7.6 Hz), 6.67 (1H, d, *J* = 7.6 Hz), 6.61 (1H, *app*.t, *J* = 12.0 Hz), 6.44 (1H, d, *J* = 14.0 Hz), 6.09 (1H, d, *J* = 11.6 Hz), 5.81-5.90 (2H, m), 5.51 (1H, ddd, *J* = 6.4, 8.4, 14.8 Hz), 5.23-5.48 (6H, m), 4.18 (1H, dd, *J* = 3.6, 9.6 Hz), 4.17 (1H, dd, *J* = 3.6, 9.6 Hz), 3.62 (1H, dd, *J* = 8.8, 15.6 Hz), 3.58 (1H, dd, *J* = 8.8, 15.6 Hz), 3.37 (2H, *br* d, *J* = 15.6 Hz), 2.42-2.61 (3H, m), 2.25-2.40 (3H, m), 2.15-2.24 (2H, m), 1.84-1.95 (2H, m), 1.68-1.87 (4H, m), 1.30-1.43 (2H, m), 0.97 (3H, t, *J* = 7.2 Hz), 0.87 (6H, d, *J* = 6.8 Hz); MS (ES) *m/z* (%): 819.33 ($[M+Na]^+$, 35), 797.34 ($[M+H]^+$, 100); HRMS (FAB) Calcd for $C_{46}H_{57}N_2O_{10}$ (MH^+): 797.4013. Found: 797.4015.



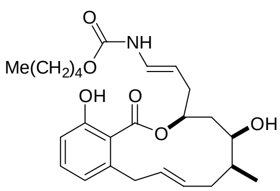
13: ^{1}H NMR (400 MHz, CD_3OD) δ 7.21 (1H, dd, *J* = 11.2, 15.2 Hz), 7.14 (1H, *app*.t, *J* = 8.0 Hz), 7.13 (1H, *app*.t, *J* = 7.6 Hz), 6.75 (1H, d, *J* = 7.6 Hz), 6.74 (1H, d, *J* = 13.6 Hz), 6.71 (1H, d, *J* = 8.0 Hz), 6.68 (1H, d, *J* = 7.2 Hz), 6.67 (1H, d, *J* = 7.6 Hz), 6.45 (1H, d, *J* = 13.6 Hz), 6.29 (1H, *app*.t, *J* = 11.2 Hz), 6.07 (1H, dt, *J* = 6.8, 15.2 Hz), 5.99 (1H, d, *J* = 11.6 Hz), 5.84 (1H, *app*.dt, *J* = 6.8, 14.0 Hz), 5.51 (1H, ddd, *J* = 6.4, 8.0, 14.4 Hz), 5.23-5.47 (6H, m), 4.18 (1H, dd, *J* = 4.4, 8.8 Hz), 4.17 (1H, dd, *J* = 4.4, 8.8 Hz), 3.61 (1H, dd, *J* = 8.8, 16.8 Hz), 3.58 (1H, dd, *J* = 8.4, 16.4 Hz), 3.37 (2H, *br* d, *J* = 16.4 Hz), 2.42-2.55 (3H, m), 2.25-2.40 (3H, m), 2.15-2.24 (2H, m), 1.84-1.95 (2H, m), 1.69-1.87 (4H, m), 1.32-1.43 (2H, m), 1.04 (3H, t, *J* = 7.2 Hz), 0.87 (6H, d, *J* = 6.8 Hz); MS (ES) *m/z* (%): 819.30 ($[M+Na]^+$, 60), 797.34 ($[M+H]^+$, 100); HRMS (FAB) Calcd for $C_{46}H_{57}N_2O_{10}$ (MH^+): 797.4013. Found: 797.4021.



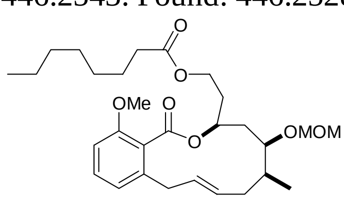
14: ^{1}H NMR (400 MHz, CD_3OD) δ 7.15 (1H, *app*.t, *J* = 8.0 Hz), 6.76 (1H, d, *J* = 14.0 Hz), 6.74 (1H, d, *J* = 8.0 Hz), 6.67 (1H, d, *J* = 7.2 Hz), 5.25-5.44 (4H, m), 4.13 (1H, dd, *J* = 3.2, 8.8 Hz), 3.57 (1H, dd, *J* = 8.0, 16.4 Hz), 3.37 (1H, *br* d, *J* = 16.4 Hz), 2.25-2.46 (3H, m), 2.22 (2H, t, *J* = 7.2 Hz), 1.84-1.95 (1H, m), 1.71-1.83 (2H, m), 1.57-1.66 (2H, m), 1.28-1.42 (7H, m), 0.91 (3H, t, *J* = 7.2 Hz), 0.87 (3H, d, *J* = 6.8 Hz); MS (ES) *m/z* (%): 466.24 ($[M+Na]^+$, 17), 444.26 ($[M+H]^+$, 100); HRMS (FAB) Calcd for $C_{26}H_{38}NO_5$ (MH^+): 444.2750. Found: 444.2759.



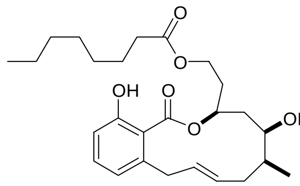
15: ^{1}H NMR (400 MHz, CD_3OD) δ 7.14 (1H, *app*.t, *J* = 7.6 Hz), 7.12 (1H, *app*.t, *J* = 7.2 Hz), 6.75 (1H, d, *J* = 8.4 Hz), 6.73 (1H, d, *J* = 14.4 Hz), 6.72 (1H, d, *J* = 8.8 Hz), 6.67 (2H, d, *J* = 7.2 Hz), 6.35 (1H, d, *J* = 14.0 Hz), 6.00 (1H, *app*.dt, *J* = 7.6, 14.4 Hz), 5.50 (1H, ddd, *J* = 6.4, 8.4, 14.4 Hz), 5.25-5.46 (6H, m), 4.19 (1H, dd, *J* = 3.2, 9.2 Hz), 4.16 (1H, dd, *J* = 3.2, 8.8 Hz), 3.60 (1H, dd, *J* = 8.0, 16.0 Hz), 3.59 (1H, dd, *J* = 7.6, 16.0 Hz), 3.37 (2H, *br* d, *J* = 16.0 Hz), 2.63 (1H, *app*.dt, *J* = 7.6, 16.8 Hz), 2.40-2.56 (4H, m), 2.24-2.39 (3H, m), 1.70-1.95 (6H, m), 1.47-1.57 (2H, m), 1.21-1.43 (8H, m), 0.87 (3H, d, *J* = 6.8 Hz), 0.86 (3H, d, *J* = 6.8 Hz), 0.86 (3H, t, *J* = 7.2 Hz); MS (ES) *m/z* (%): 823.33 ($[M+Na]^+$, 50), 801.37 ($[M+H]^+$, 100); HRMS (FAB) Calcd for $C_{46}H_{61}N_2O_{10}$ (MH^+): 801.4326. Found: 801.4334.



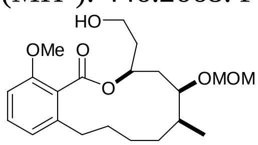
16: $[\alpha]_D$ = -18.8 (*c* 0.17, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.14 (1H, *app*.t, *J* = 8.0 Hz), 6.73 (1H, d, *J* = 8.0 Hz), 6.67 (1H, d, *J* = 7.2 Hz), 6.49 (1H, d, *J* = 14.4 Hz), 5.26-5.44 (3H, m), 5.18 (1H, *app*.dt, *J* = 7.2, 14.4 Hz), 4.13 (1H, dd, *J* = 3.6, 9.2 Hz), 4.07 (2H, t, 6.4 Hz), 3.57 (1H, dd, *J* = 8.4, 16.4 Hz), 3.36 (1H, *br* d, *J* = 16.4 Hz), 2.25-2.44 (3H, m), 1.84-1.95 (1H, m), 1.71-1.82 (2H, m), 1.60-1.69 (2H, m), 1.33-1.41 (5H, m), 0.93 (3H, t, *J* = 7.6 Hz), 0.87 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 171.2, 157.2, 156.6, 140.8, 131.83, 131.76, 127.8, 123.2, 122.6, 115.4, 106.9, 76.4, 72.1, 66.4, 39.1, 38.9, 38.7, 37.5, 36.6, 29.9, 29.3, 23.5, 14.5, 13.7; MS (ES) *m/z* (%): 468.20 ($[M+Na]^+$, 26), 446.23 ($[M+H]^+$, 100); HRMS (FAB) Calcd for $C_{25}H_{36}NO_6$ (MH^+): 446.2543. Found: 446.2528.



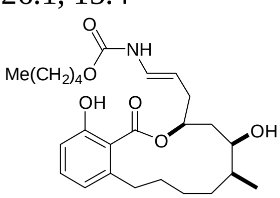
17: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (1H, *app*.t, *J* = 8.4 Hz), 6.80 (1H, d, *J* = 8.4 Hz), 6.75 (1H, d, *J* = 7.6 Hz), 5.42-5.53 (2H, m), 5.35 (1H, *app*.ddt, *J* = 2.4, 9.6, 15.2 Hz), 4.90 (1H, d, *J* = 6.8 Hz), 4.82 (1H, d, *J* = 6.8), 4.27 (1H, ddd, *J* = 4.8, 7.6, 11.2 Hz), 4.22 (1H, ddd, *J* = 6.4, 8.8, 11.2 Hz), 4.18 (1H, dd, *J* = 3.6, 9.2 Hz), 3.18 (3H, s), 3.72 (1H, dd, *J* = 9.6, 16.4 Hz), 3.47 (3H, s), 3.32 (1H, dddd, *J* = 2.0, 2.0, 4.4, 16.4 Hz), 2.27-2.36 (1H, m), 2.29 (2H, t, *J* = 7.2 Hz), 2.07-2.18 (1H, m), 1.87-2.06 (2H, m), 1.78 (1H, dd, *J* = 8.8, 15.6 Hz), 1.71 (1H, *app*.dt, *J* = 11.6, 14.4 Hz), 1.53-1.67 (2H, m), 1.43 (1H, dd, *J* = 9.2, 15.2 Hz), 1.22-1.34 (8H, m), 0.87 (3H, d, *J* = 6.8 Hz), 0.87 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 168.5, 156.7, 139.2, 131.6, 130.3, 128.7, 124.5, 122.9, 109.3, 97.1, 79.4, 71.5, 61.1, 55.8, 55.6, 38.0, 37.9, 36.1, 35.4, 34.6, 34.2, 31.9, 29.3, 29.1, 25.2, 22.8, 14.3, 13.5.



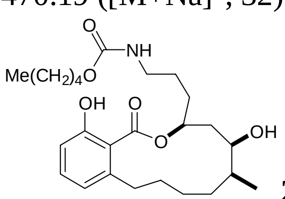
18: $[\alpha]_D$ = -3.72 (*c* 0.2, $CHCl_3$); IR 3412, 3152, 2918, 2850, 1738, 1686, 1591, 1467 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.0 (1H, *br* s), 7.30 (1H, dd, *J* = 7.6, 8.4 Hz), 6.90 (1H, dd, *J* = 0.8, 8.4 Hz), 6.71 (1H, dd, *J* = 0.8, 7.6 Hz), 5.62 (1H, *app*.ddt, *J* = 0.8, 6.0, 12.0 Hz), 5.49 (1H, *br* d, *J* = 15.6 Hz), 5.03-5.13 (1H, m), 4.24 (1H, *app*.dt, *J* = 6.0, 6.4, 11.6 Hz), 4.18 (1H, *app*.dt, *J* = 6.0, 11.6 Hz), 3.76 (1H, dd, *J* = 6.0, 17.2 Hz), 3.64 (1H, dd, *J* = 3.6, 8.8 Hz), 3.39 (1H, *br* d, *J* = 17.2 Hz), 2.30-2.40 (1H, m), 2.27 (2H, t, *J* = 7.2 Hz), 1.99-2.09 (3H, m), 1.78-1.97 (2H, m), 1.54-1.64 (2H, m), 1.39 (1H, ddd, *J* = 0.8, 8.8, 15.2 Hz), 1.20-1.34 (8H, m), 0.93 (3H, d, *J* = 6.8 Hz), 0.88 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 171.2, 162.8, 142.4, 134.3, 133.1, 126.6, 123.8, 117.0, 113.4, 72.3, 70.6, 60.8, 39.3, 38.6, 37.5, 34.7, 34.5, 31.9, 29.9, 29.3, 29.1, 25.1, 22.8, 14.3, 13.9; MS (CI) *m/z* (%): 447 (30), 429 (70), 303 (36), 285 (75), 145 (100); HRMS (FAB) Calcd for $C_{26}H_{38}O_6$ (MH^+): 446.2668. Found: 446.2658.



20: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, t, *J* = 8.0 Hz), 6.79 (1H, d, *J* = 7.6 Hz), 6.79 (1H, d, *J* = 8.4 Hz), 5.52 (1H, *app*.q, *J* = 8.0 Hz), 4.76 (2H, s), 5.83 (3H, s), 3.70-84 (3H, m), 3.44 (3H, s), 2.80-2.91 (1H, m), 2.42-2.51 (2H, m), 1.98-2.06 (1H, m), 1.87-1.95 (3H, m), 1.60-1.78 (3H, m), 1.42-1.56 (2H, m), 1.18-1.30 (2H, m), 0.91 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 156.5, 141.5, 130.8, 123.6, 122.4, 109.0, 96.7, 71.6, 58.9, 56.07, 55.97, 39.0, 35.8, 34.1, 31.8, 26.1, 15.4

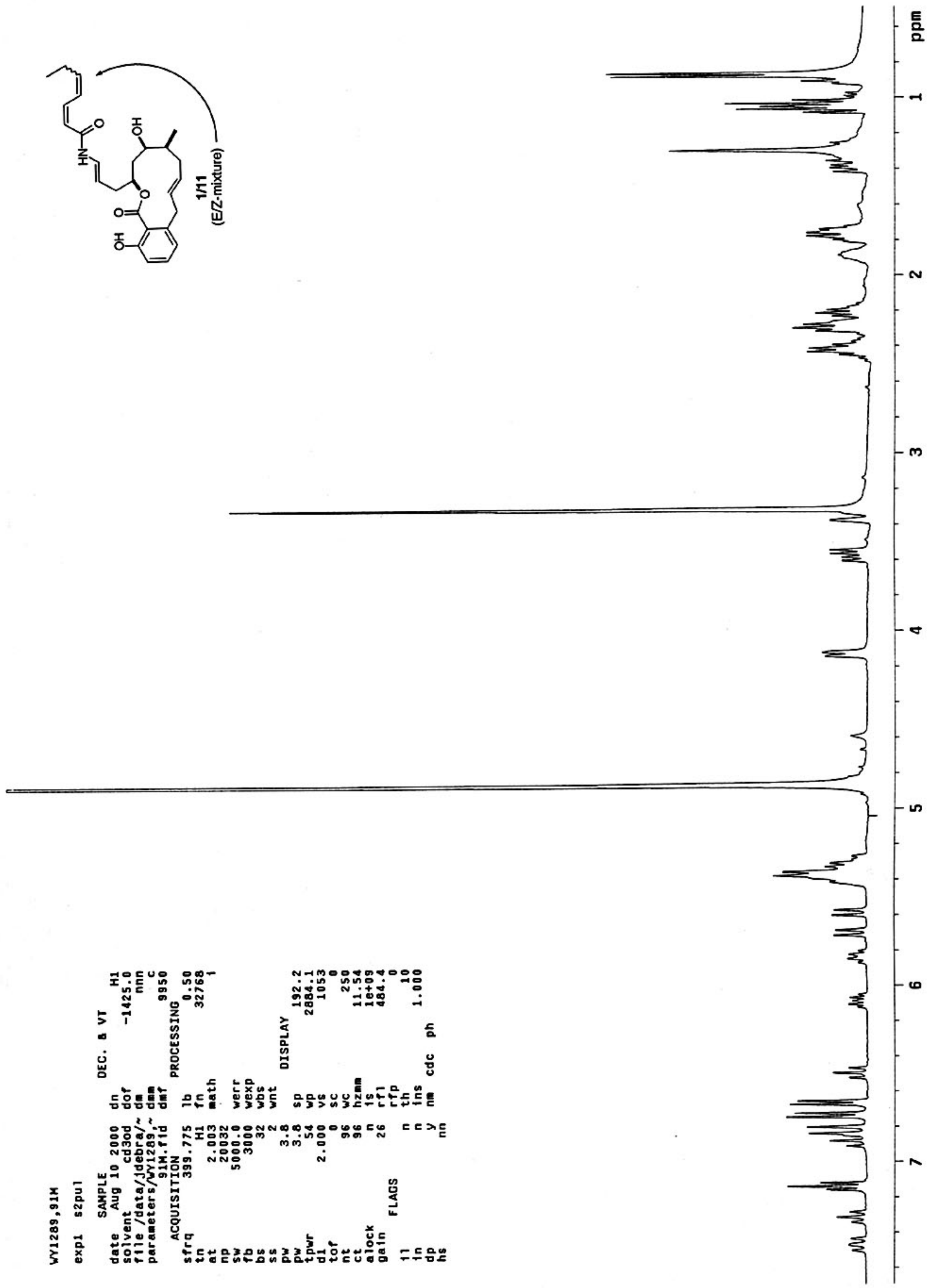


21: ^{1}H NMR (400 MHz, CD_3OD) δ 7.25 (1H, *app*.t, *J* = 7.6 Hz), 6.75 (1H, d, *J* = 8.4 Hz), 6.73 (1H, d, *J* = 7.6 Hz), 6.44 (1H, d, *J* = 14.0 Hz), 5.14-5.22 (1H, m), 5.05 (1H, *app*.dt, *J* = 7.6, 14.0 Hz), 4.04 (2H, t, *J* = 6.4 Hz), 3.82-3.88 (1H, m), 3.66 (1H, ddd, 3.6, 12.4, 12.4 Hz), 2.39 (2H, *app*.t, *J* = 6.6 Hz), 2.21 (1H, ddd, *J* = 6.4, 12.4, 12.4 Hz), 2.10-2.20 (1H, m), 1.40-1.80 (9H, m), 1.30-1.40 (5H, m), 0.95 (3H, d, *J* = 6.8 Hz), 0.92 (3H, t, *J* = 6.4 Hz); MS (ES) *m/z* 448.20 ($[M+H]^+$, 100), 470.19 ($[M+Na]^+$, 32).



22: ^{1}H NMR (400 MHz, CD_3OD) δ 7.24 (1H, *app*.t, *J* = 8.0 Hz), 6.75 (1H, d, *J* = 8.4 Hz), 6.73 (1H, d, *J* = 7.2 Hz), 5.24-5.32 (1H, m), 3.99 (2H, t, *J* = 6.8 Hz), 3.86-3.92 (1H, m), 3.55 (1H, ddd, 3.6, 12.4, 12.4 Hz), 3.11 (2H, *app*.t, *J* = 6.8 Hz), 2.11-2.30 (2H, m), 1.45-1.77 (13H, m), 1.28-1.38 (5H, m), 0.94 (3H, d, *J* = 6.8 Hz), 0.91 (3H, t, *J* = 7.6 Hz); MS (ES) *m/z* 450.24 ($[M+H]^+$, 100), 472.24 ($[M+Na]^+$, 67).

IV. ^{1}H NMR spectra of compounds 1/11, ent-1, ent-11, 6-9, 12-18 and 20-22.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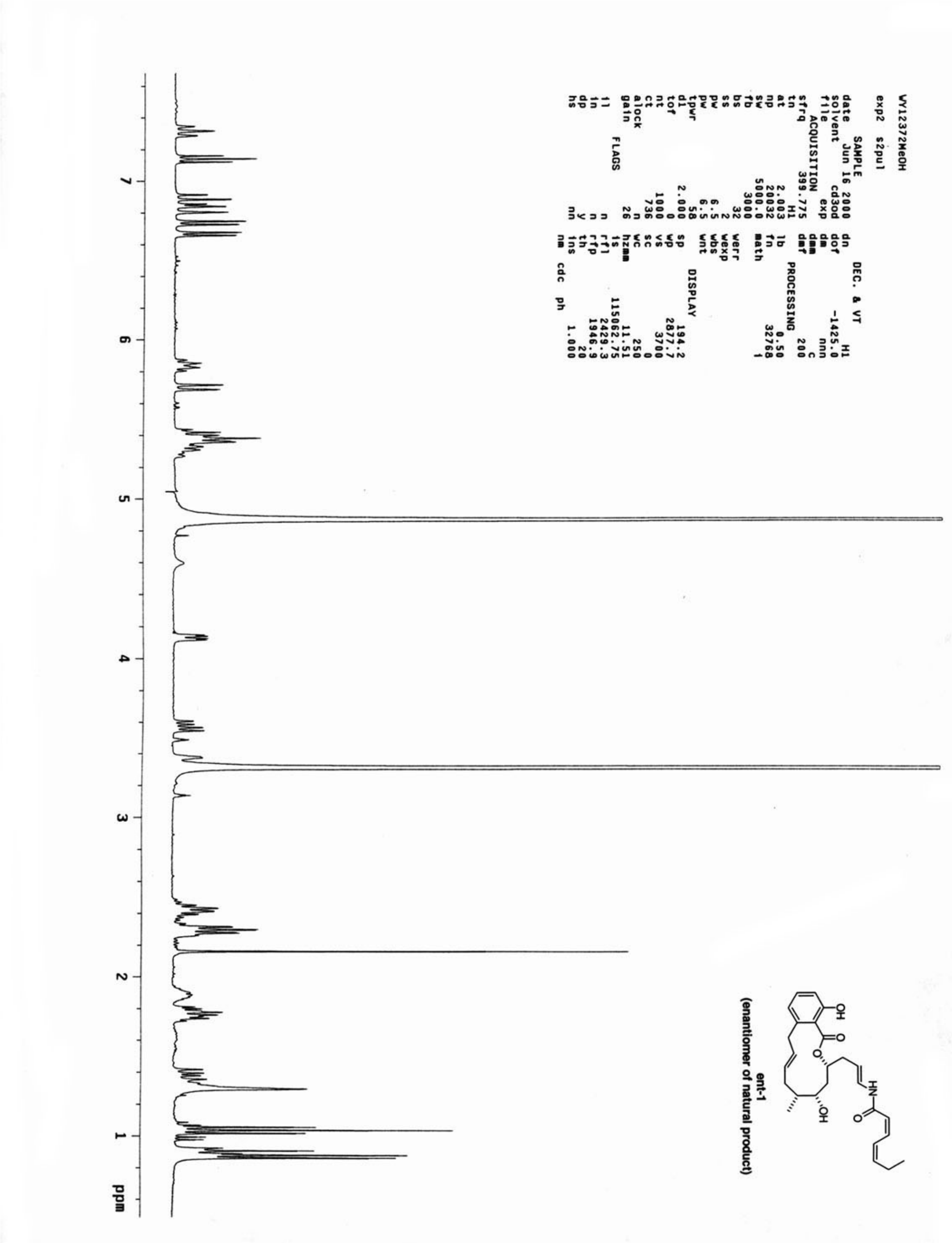
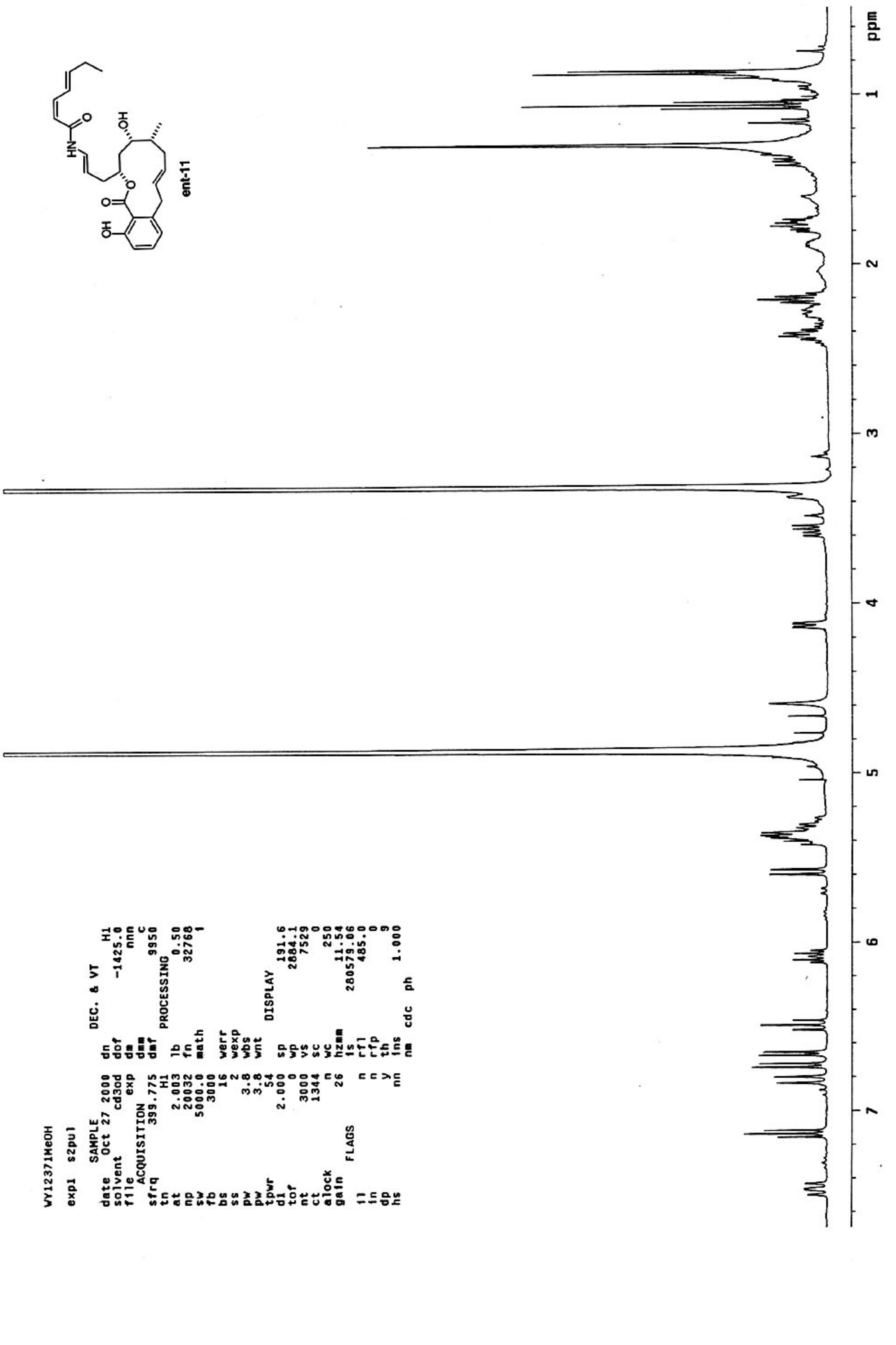

ent-1
(enantiomer of natural product)
ppm


ent-11
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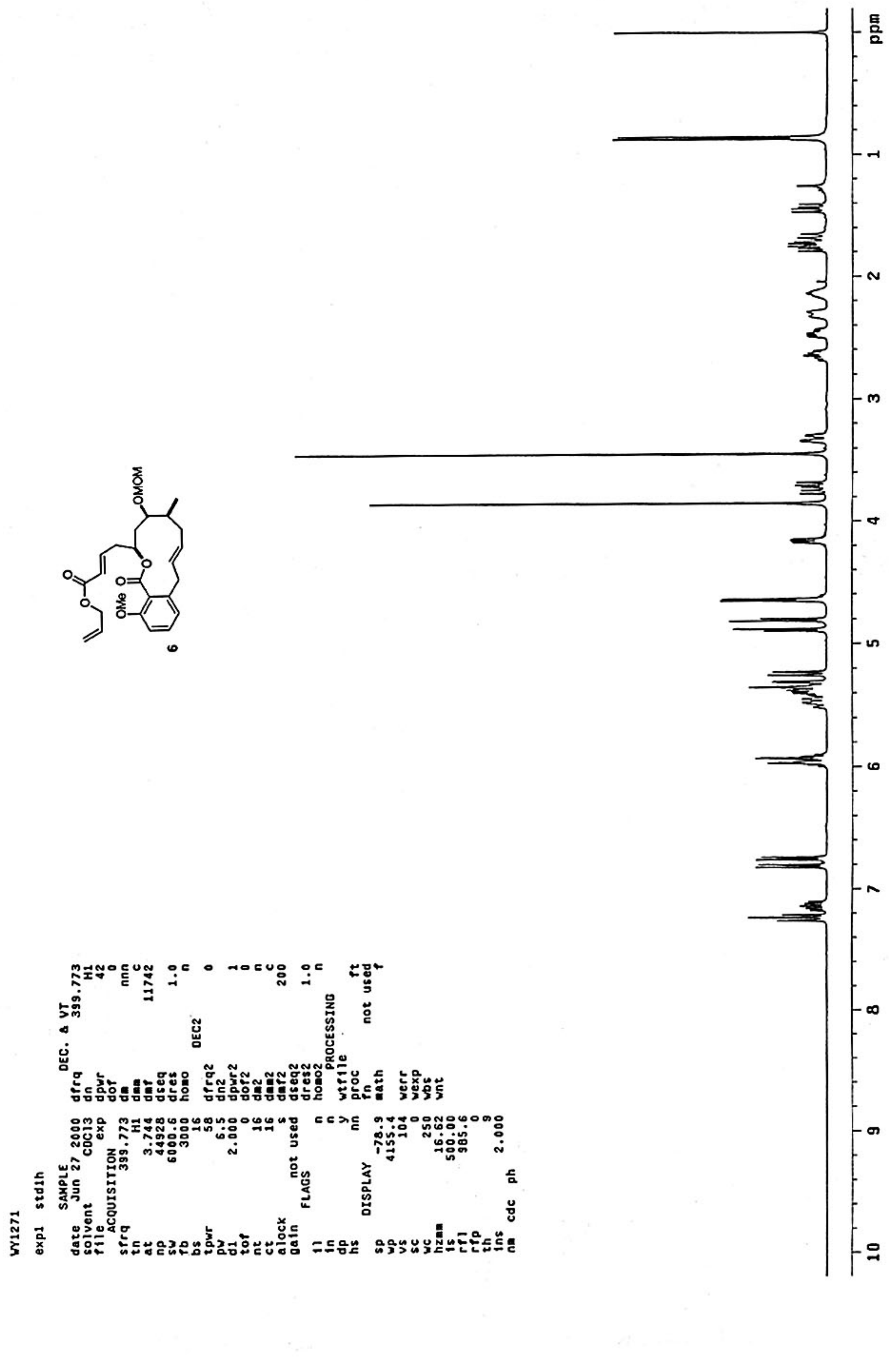
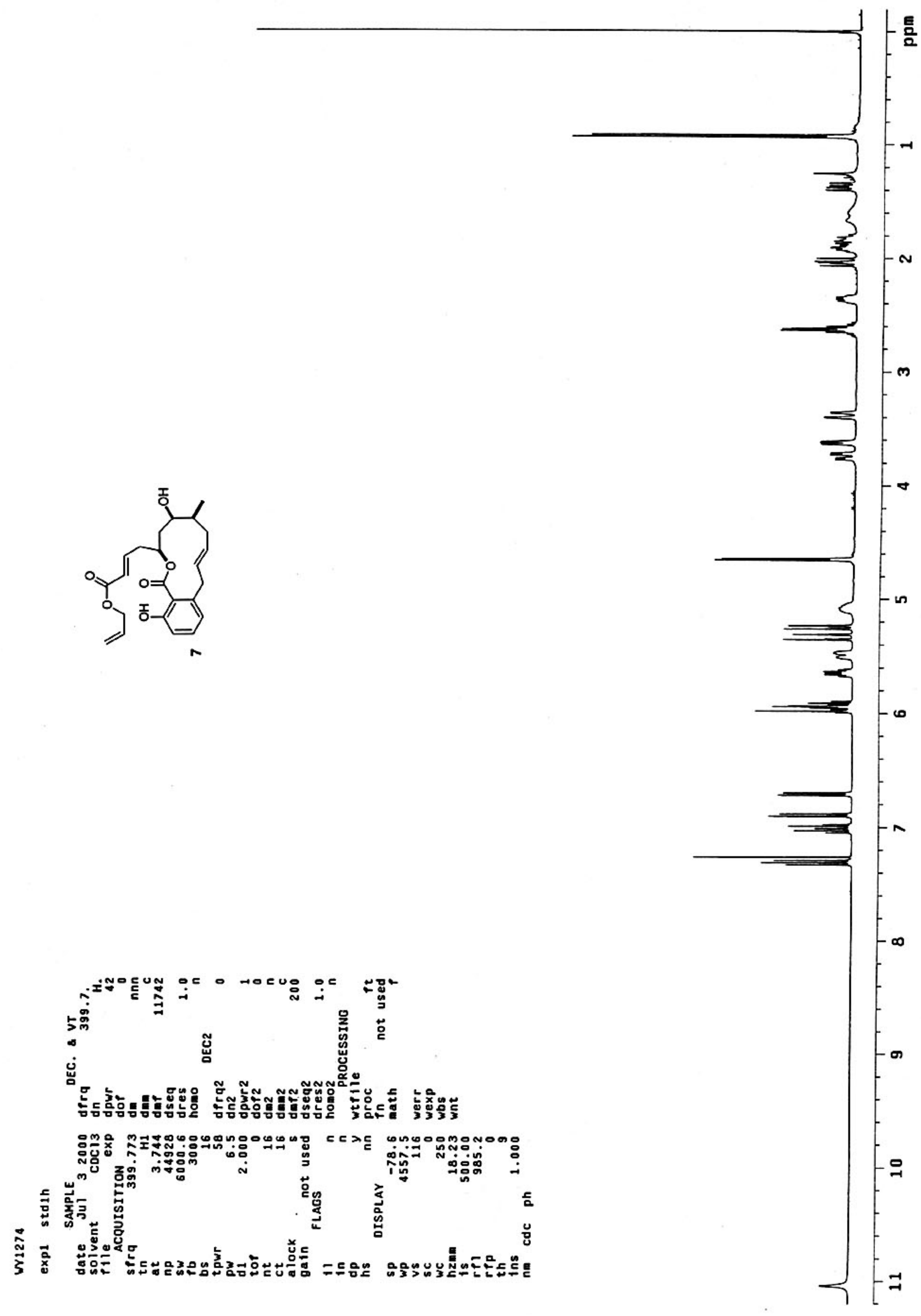
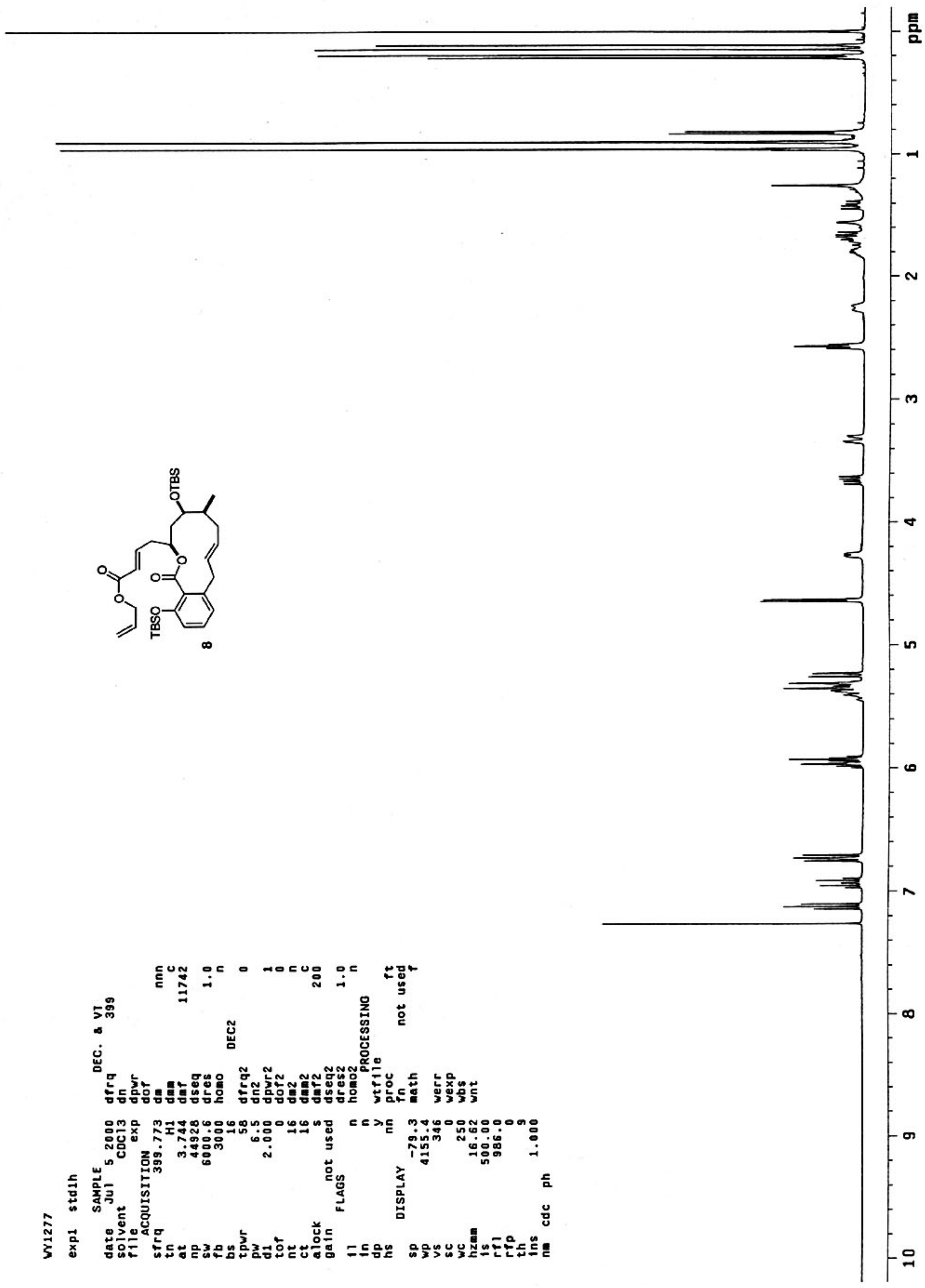
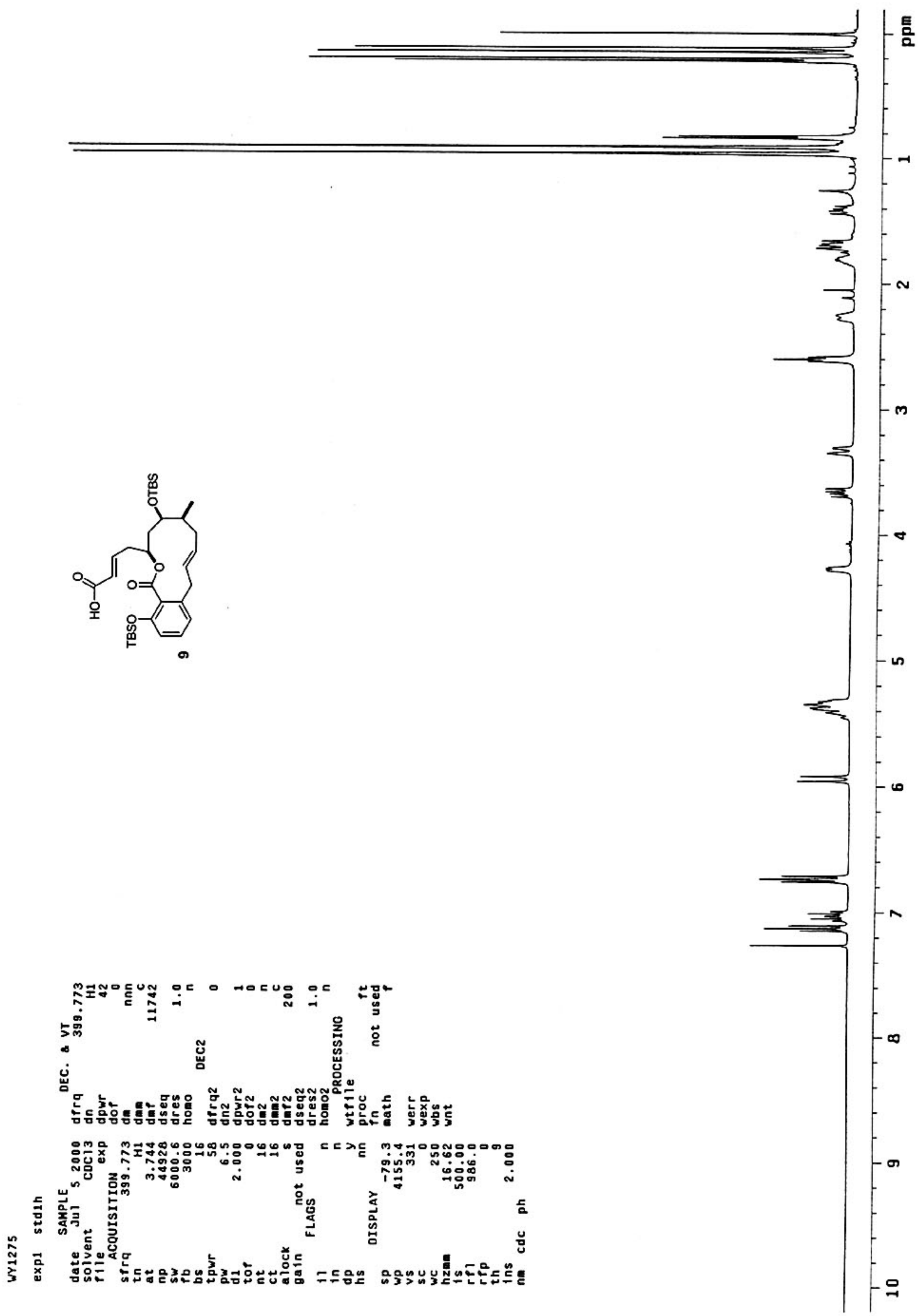


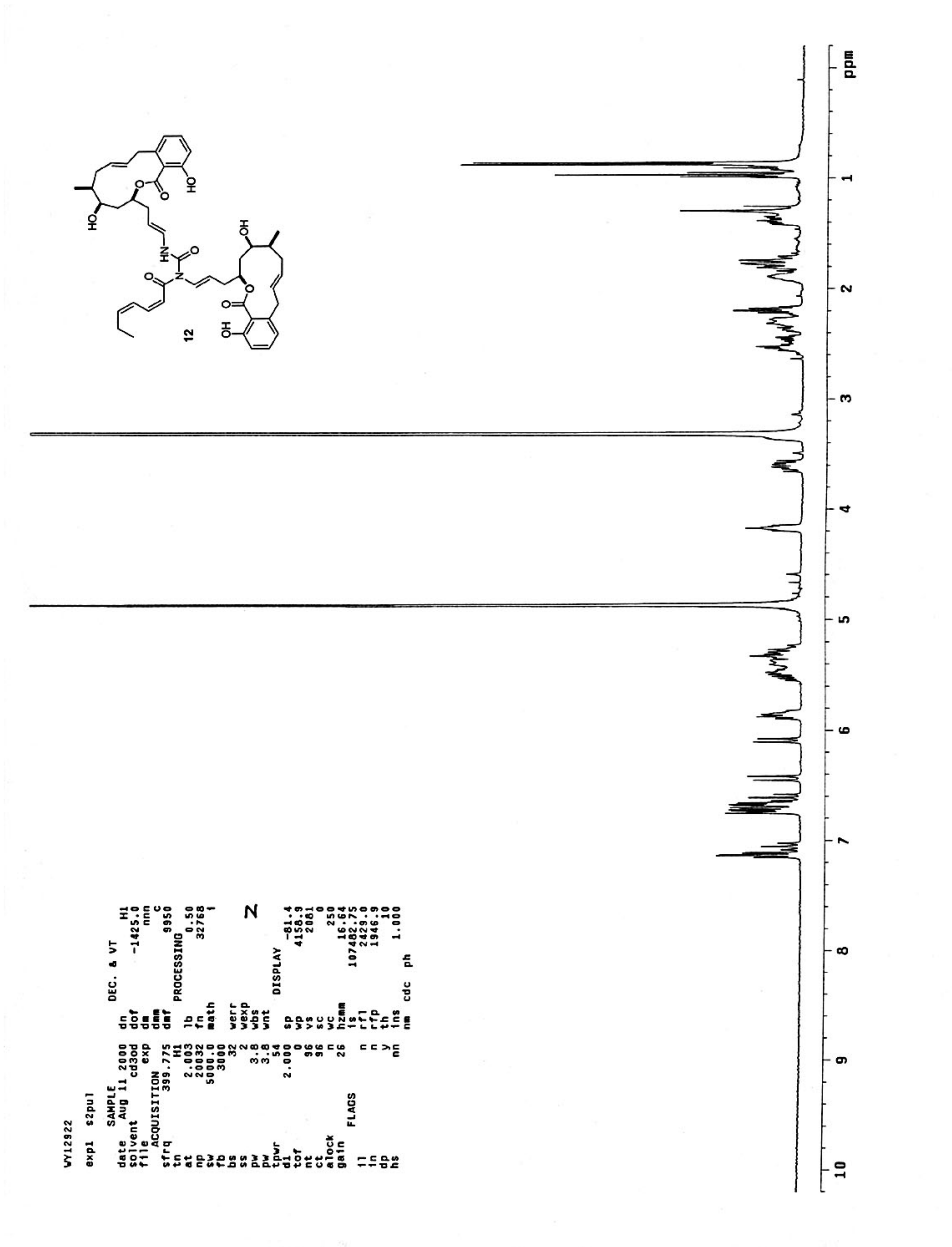




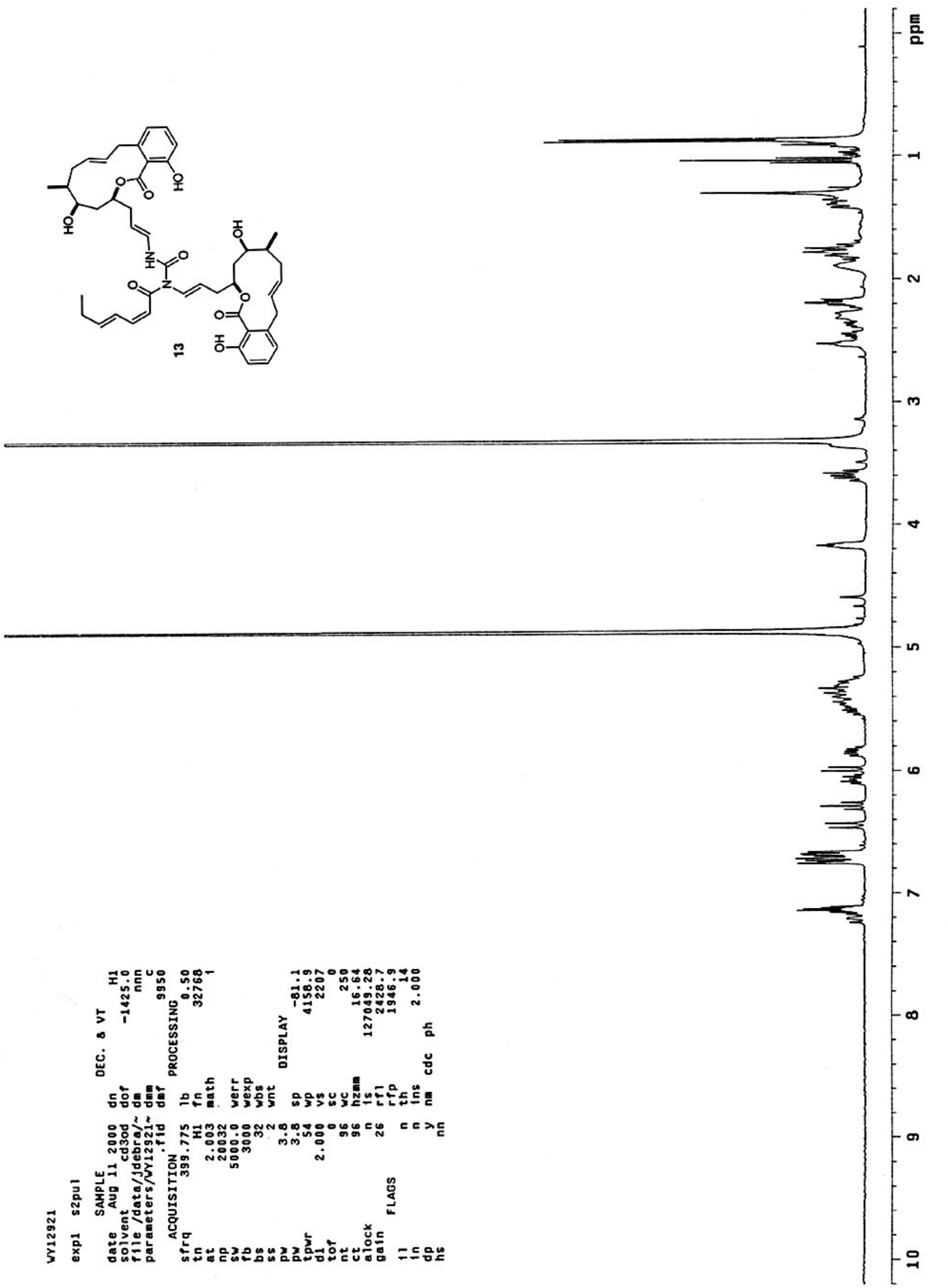
Wu, Y.; Seguil, O. R.; De Brabander, J. K. “Synthesis and Initial Structure–Activity Relationships of Modified Salicylihalamides.”

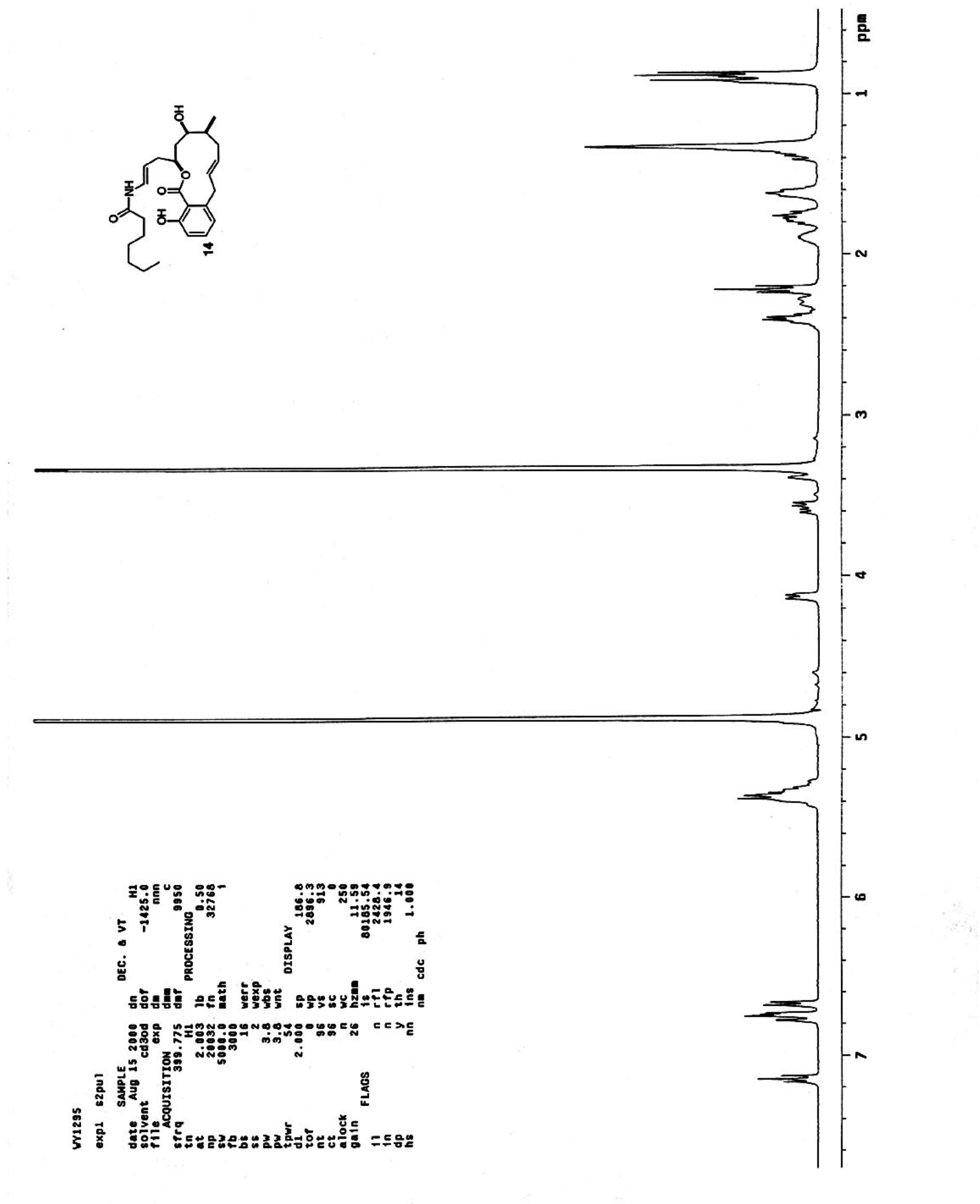


Wu, Y.; Seguil, O. R.; De Brabander, J. K. "Synthesis and Initial Structure–Activity Relationships of Modified Salicylihalamides."

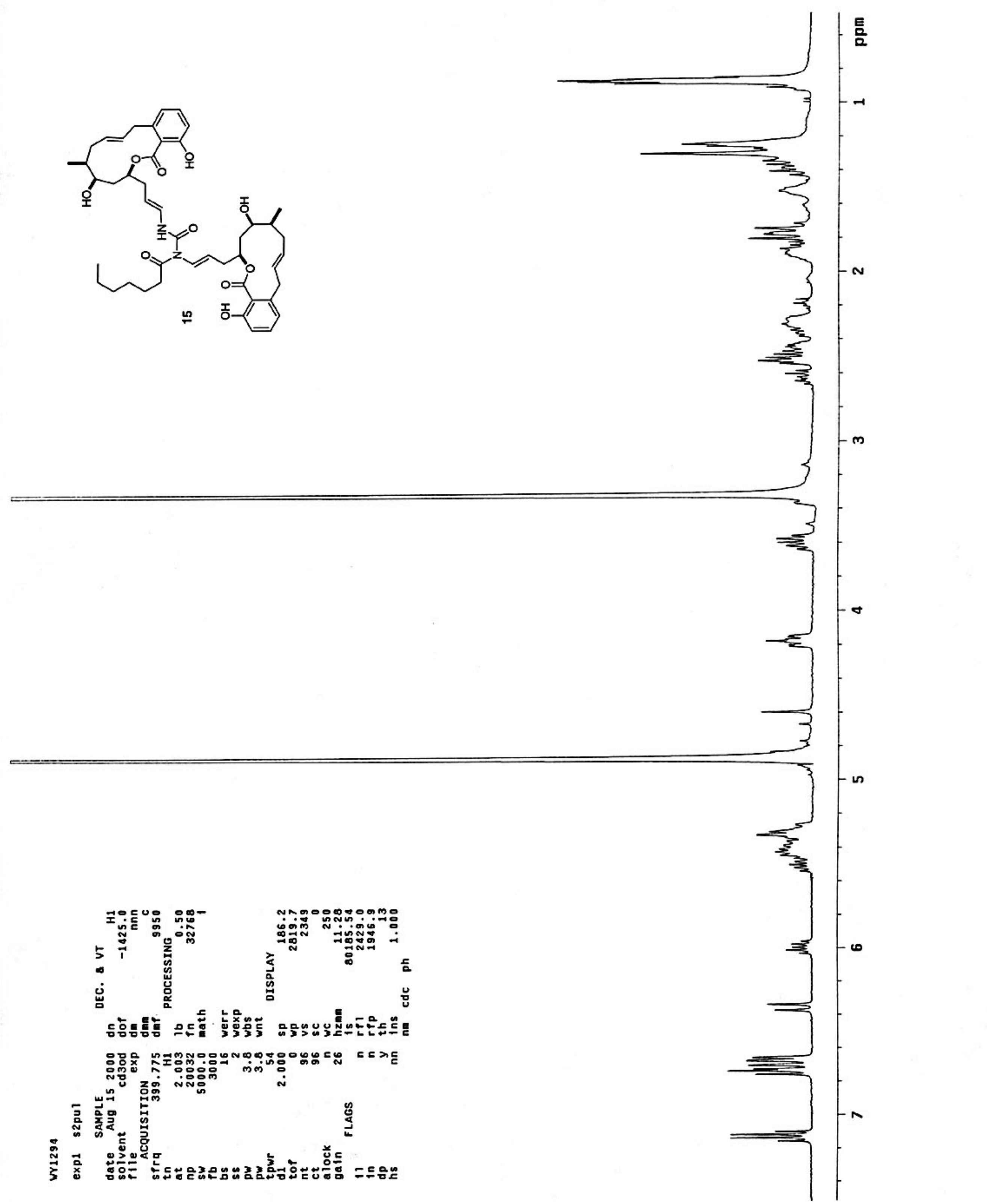


Wu, Y.; Seguil, O. R.; De Brabander, J. K. “Synthesis and Initial Structure–Activity Relationships of Modified Salicylihalamides.”

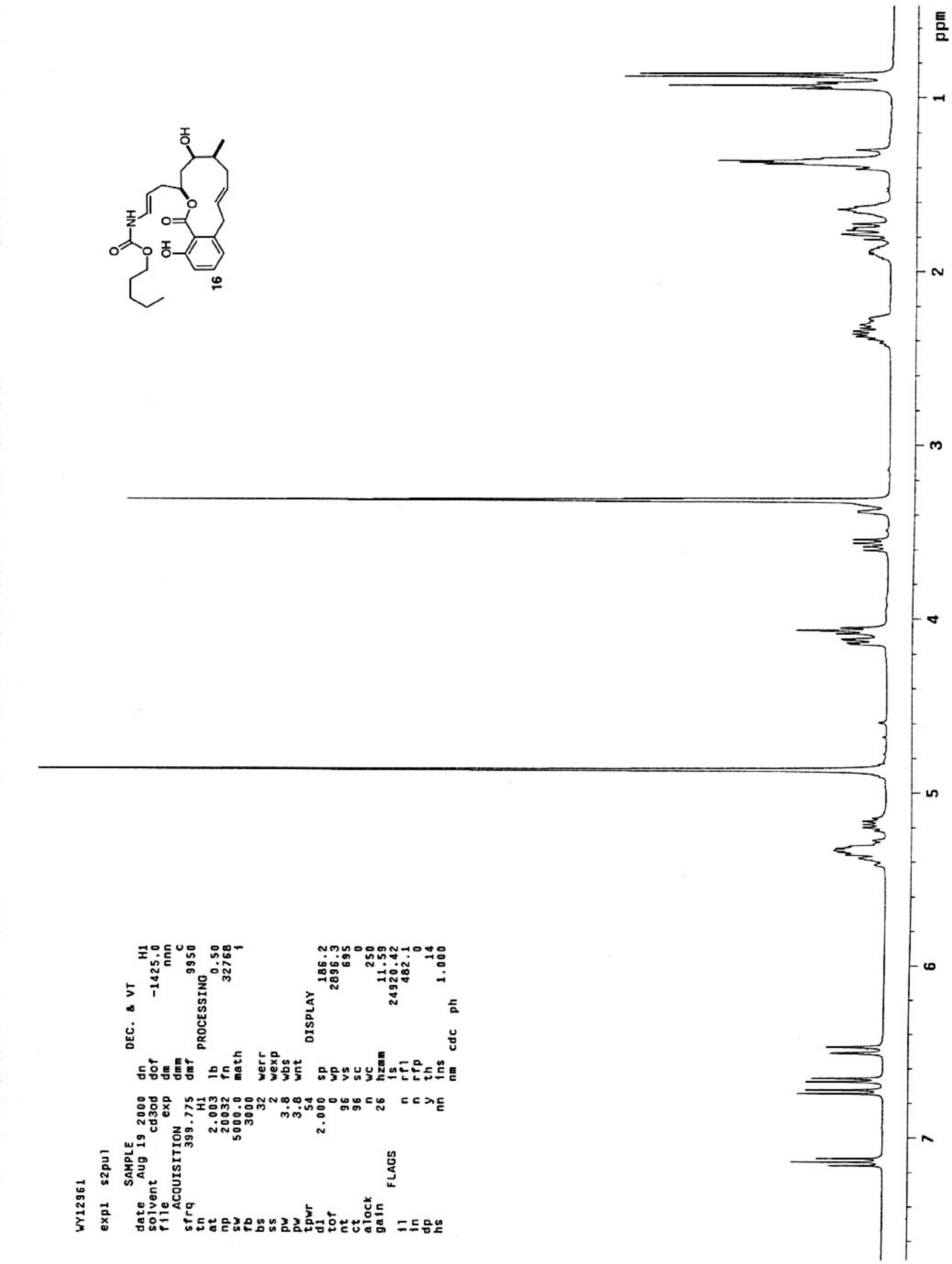


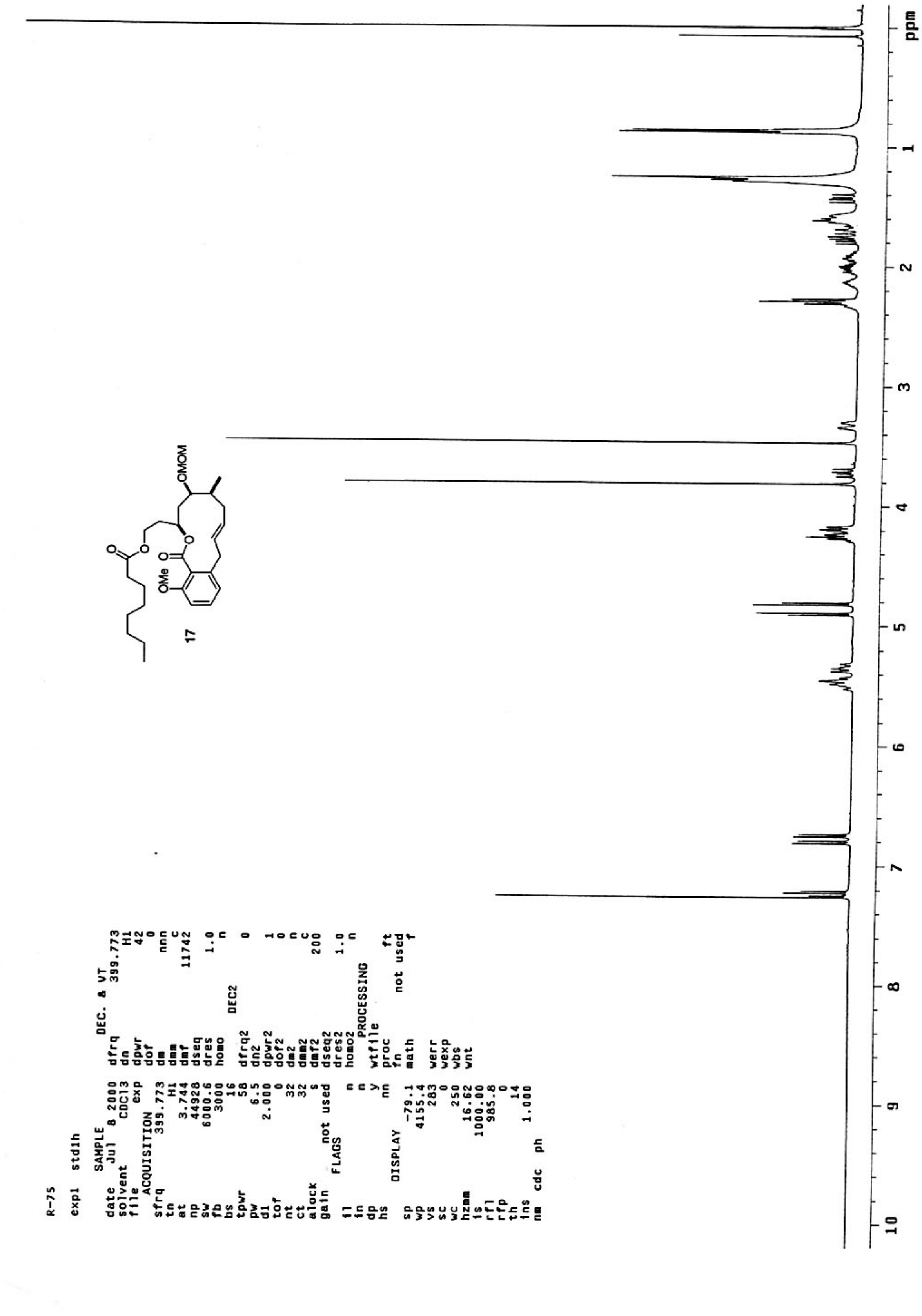


Wu, Y.; Seguil, O. R.; De Brabander, J. K. "Synthesis and Initial Structure–Activity Relationships of Modified Salicylihalamides."



Wu, Y.; Seguil, O. R.; De Brabander, J. K. “Synthesis and Initial Structure–Activity Relationships of Modified Salicylihalamides.”

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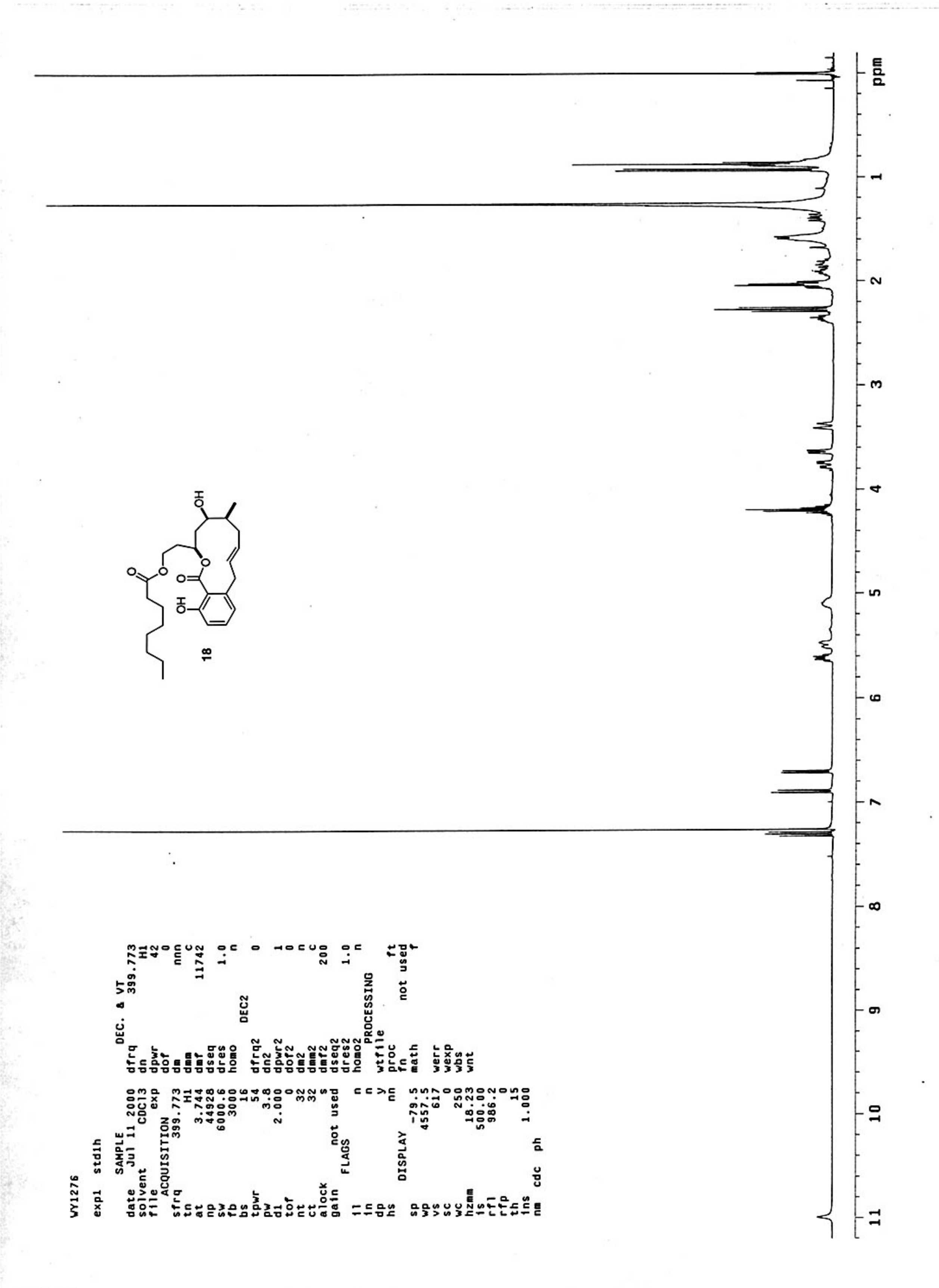
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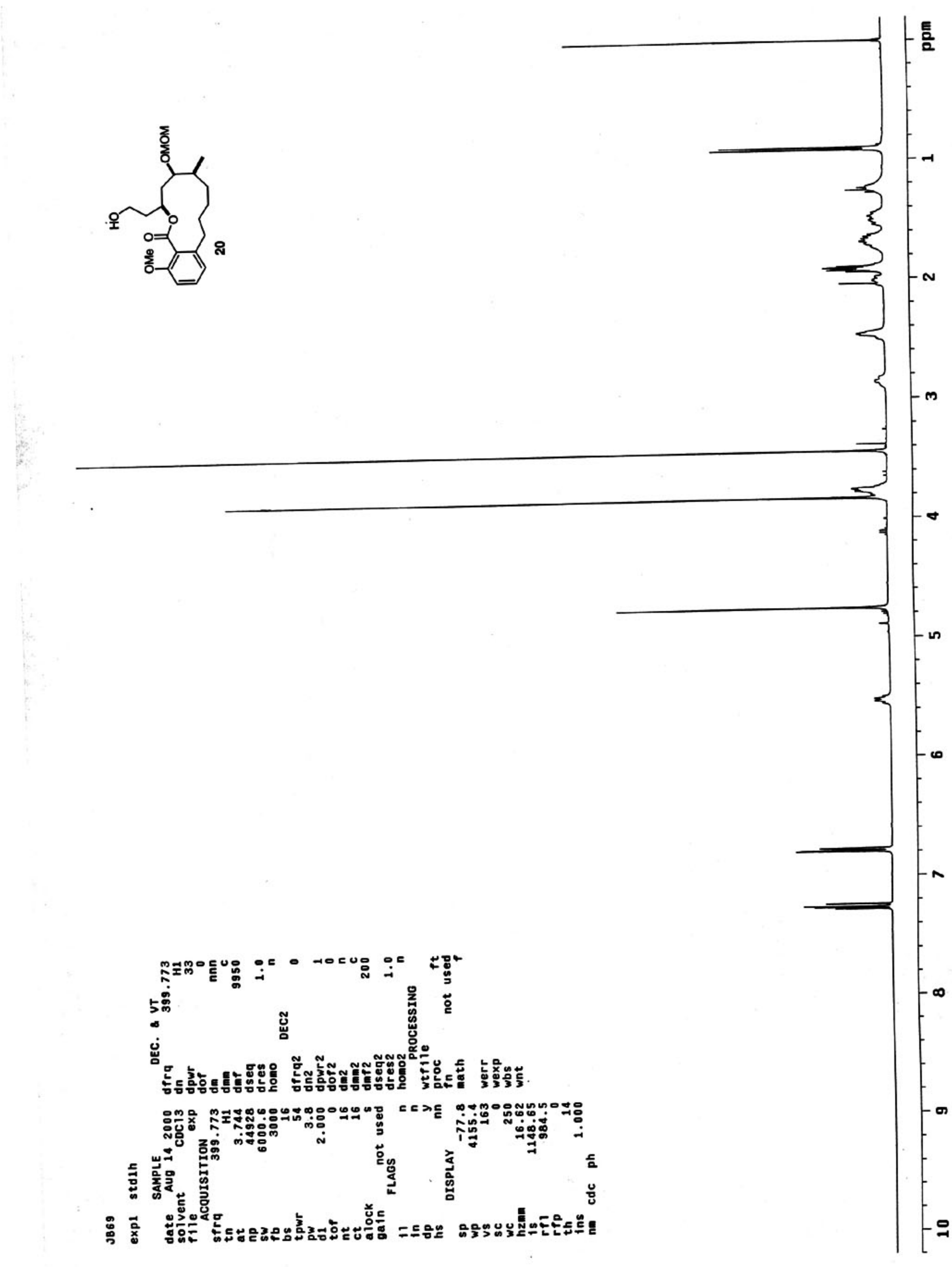
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dmf 9950
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dres 1.0
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dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
dres2 1.0
homo2 n
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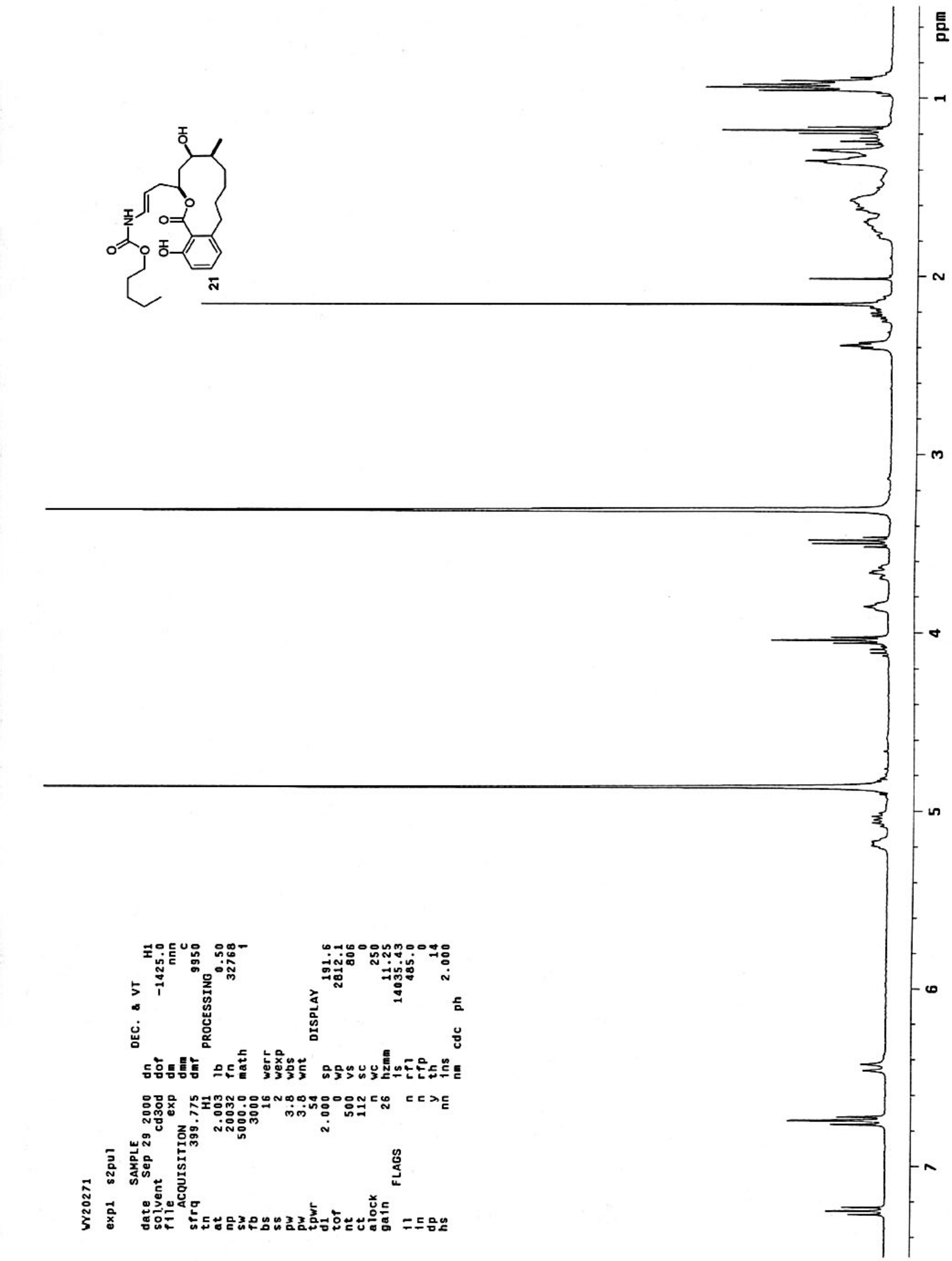
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