Hg(II)-mediated intramolecular cyclization reaction in aqueous media and its application as Hg(II) selective indicator

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Contents

General Experiments

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields of synthesized compounds were measured after chromatographic purification. UV-vis spectra were recorded on a UV 1800 (Shimadzu) spectrophotometer. Proton and ^{13}C-NMR spectra were measured at 25 ºC using Varian Unity Innova 400 and 500 instruments. The electrospray ionization (ESI) source was coupled to a hybrid quadrupole orthogonal time-of-flight (Q-TOF) mass spectrometer (SYNAPT G2, Waters, MS Technologies, Manchester, U.K.) was used to mass spectra acquirement in positive- and negative-ion mode. A capillary and cone voltage of ± 3.0kV and 30 V, and capillary temperature of 120 °C were used for both polarities, respectively. The desolvation source conditions were as follows; for the desolvation gas 800 L/h was used and the desolvation temperature was kept at 600 °C. Data acquisition took place over the mass range of m/z 50 to m/z 1200 for MS modes. The sample was introduced into the ESI source at a constant flow rate of 20 µl/min by using an external syringe pump (HARVARD 11Plus, Holliston, MA, USA).

Stock solutions of all of the compounds studied were made up in DMSO with the final concentrations being between 1.3×10^{-5} M and 9.5×10^{-6} M. ACS grade solvents were purchased and used without purification. The stock solutions were appropriately diluted with the solvents for the ensuing studies.

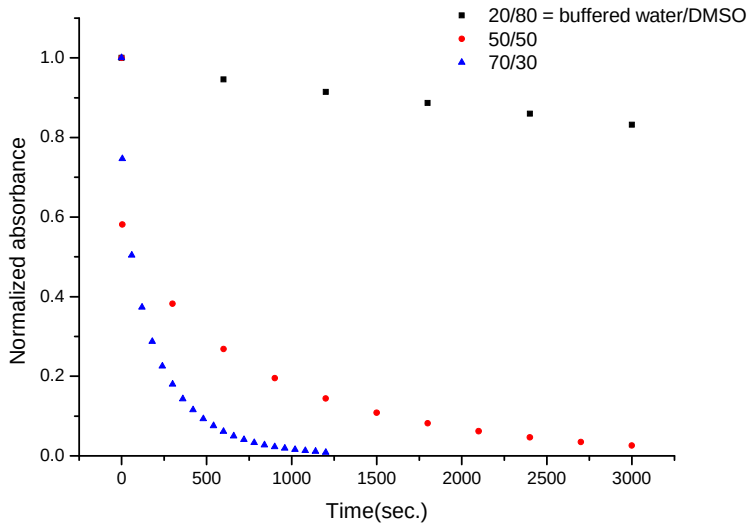


Figure S1. Plots of absorbance change of **6** (1.1×10^{-5} M) at 608 nm as a function of time with 2 equiv of Hg(II) in various percentages of buffered water and DMSO (v/v) (10 mM PBS buffer, pH = 7.0).

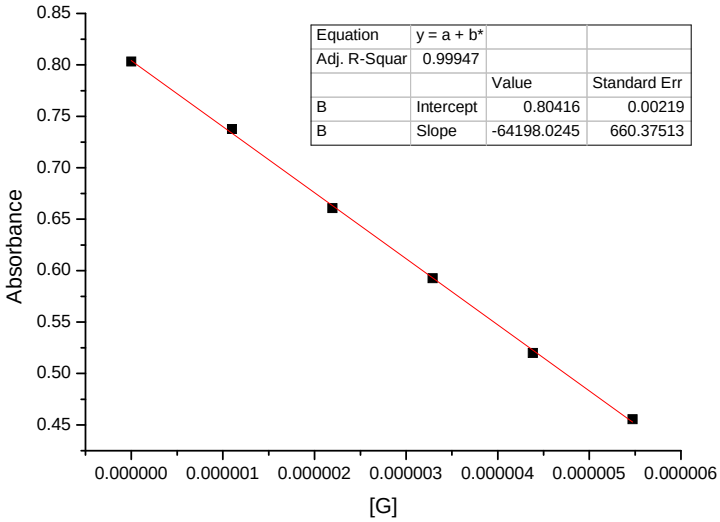


Figure S2. Plot of absorbance change of **6** (9.56×10^{-6} M) at 608 nm as a function of Hg(II) concentration in DMSO/water (3:7, v/v) (10 mM PBS buffer, pH = 7.0). Data were acquired 20 min. after the addition of a given amount of Hg(II) from 0 to 5.5 μM.

Table 1. Crystal data and structure refinement for **5a**

Identification code	**5a**	
Empirical formula	C13 H14 Cl Hg N O3	
Formula weight	468.29	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.98880(10) Å	α= 92.8870(10)°.
	b = 10.8795(2) Å	β= 91.0330(10)°.
	c = 19.1331(4) Å	γ = 90.1320(10)°.
Volume	1452.69(5) $Å^3$	
Z	4	
Density (calculated)	2.141 g/cm^3	
Absorption coefficient	10.781 mm^{-1}	
F(000)	880	
Crystal size	0.220 x 0.180 x 0.050 mm^3	
Theta range for data collection	1.07 to 28.29°.	
Index ranges	-9<=h<=9, -14<=k<=14, -25<=l<=25	
Reflections collected	38046	
Independent reflections	7193 [R(int) = 0.0555]	
Completeness to theta = 28.29°	99.3 %	
Absorption correction	'SADABS'	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7193 / 21 / 293	
Goodness-of-fit on F^2	1.014	
Final R indices [I>2sigma(I)]	R1 = 0.0453, wR2 = 0.1227	
R indices (all data)	R1 = 0.0773, wR2 = 0.1459	
Largest diff. peak and hole	1.793 and -1.211 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for cho. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Hg(1)	-71(1)	-1524(1)	2987(1)	50(1)
Hg(2)	4903(1)	6156(1)	2978(1)	49(1)
Cl(1)	-19(5)	-3616(2)	2770(2)	71(1)
Cl(2)	4982(5)	8213(2)	2751(2)	70(1)
N(1)	2000(12)	2300(8)	5360(4)	53(2)
N(2)	7008(11)	2765(8)	5347(4)	50(2)
O(1)	4339(10)	2301(6)	2624(3)	53(2)
O(2)	7082(12)	3786(7)	5632(4)	64(2)
O(3)	7458(13)	1808(8)	5648(4)	75(2)
O(4)	-639(10)	2252(6)	2621(4)	52(2)
O(5)	2100(13)	1322(7)	5636(4)	68(2)
O(6)	2503(13)	3299(7)	5651(4)	73(2)
C(1)	-766(15)	1005(10)	2486(5)	53(2)
C(2)	-135(13)	342(8)	3024(5)	44(2)
C(3)	360(12)	1234(8)	3583(5)	42(2)
C(4)	20(12)	2379(8)	3302(5)	42(2)
C(5)	351(13)	3516(9)	3666(6)	50(2)
C(6)	1013(12)	3470(8)	4341(5)	45(2)
C(7)	1273(12)	2315(8)	4628(5)	41(2)
C(8)	977(12)	1198(8)	4267(5)	41(2)
C(9)	-1548(18)	638(12)	1779(6)	70(3)
C(10)	-140(30)	770(20)	1197(13)	170(10)
C(11)	1380(30)	-230(20)	1159(13)	150(8)
C(12)	3020(60)	-460(50)	670(30)	400(30)
C(13)	3430(60)	-1810(40)	750(20)	290(20)
C(14)	4245(14)	3561(9)	2461(5)	47(2)
C(15)	4821(14)	4303(8)	3025(5)	45(2)
C(16)	5313(12)	3499(8)	3578(5)	41(2)
C(17)	5972(12)	3664(8)	4263(5)	42(2)
C(18)	6320(12)	2590(8)	4618(5)	42(2)
C(19)	6025(12)	1429(8)	4334(5)	47(2)
C(20)	5375(14)	1260(8)	3655(5)	49(2)

C(21)	5022(13)	2290(8)	3300(5)	45(2)
C(22)	3455(17)	3788(11)	1766(6)	69(3)
C(23)	4780(20)	3520(18)	1181(9)	113(6)
C(24)	6530(30)	4270(20)	1193(14)	162(9)
C(25)	6470(40)	5470(30)	930(20)	115(11)
C(26)	8420(50)	5930(40)	800(20)	290(20)
C(25')	7850(60)	4660(30)	660(20)	154(16)

Experimental Section

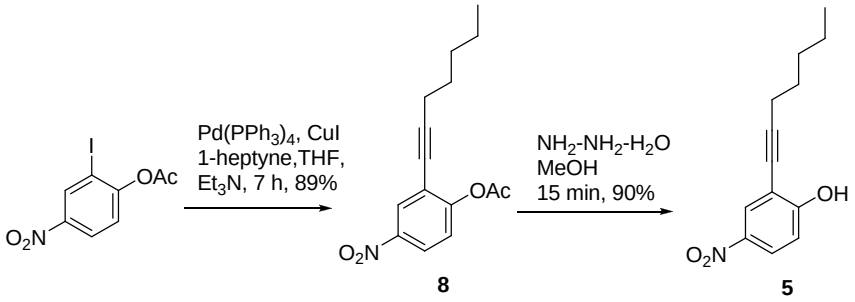
General procedure for synthesis of benzofuran derivative by Hg(II)

To a well-stirred solution of 2-alkynylhydroxybenzene (0.086 mmol) in DMSO (4.1 mL) was added $HgCl_2$ (1.03 mL, 0.17 M in H_2O). The reaction mixture was stirred at room temperature. The reaction mixture was poured into H_2O, and the product was extracted with Et_2O/EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and then filtered; the filtrate was concentrated under reduced pressure to obtain the residue. The residue was purified over silica gel to afford the benzofuran derivative.

(5-nitro-2-phenylbenzofuran-3-yl)mercury(II) chloride (3a)
By following the general procedure, the reaction of **3** (20.6 mg, 0.086 mmol) yielded **3a** (37.9 mg, 93% yield). ^{1}H NMR (400 MHz, DMSO) δ 9.17 (d, *J* = 2.5 Hz, 1H), 8.19 (dd, *J* = 9.0, 2.5 Hz, 1H), 8.08 (m, 2H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.54 (m, 3H). HRMS–ESI: m/z $[M + Cl]^+$ calcd for $C_{14}H_8HgNO_3$: 509.9587; found:509.9564.

2-((3-nitrophenyl)ethynyl)phenol (4)

1-Iodo-3-nitrobenzene (0.21 g, 0.85 mmol) was added to the solution of 2-ethynylphenol (0.10 g, 0.85 mmol) in anhydrous THF (7 mL) and triethylamine (0.7 mL), and the resulting mixture was flushed with argon and then $Pd(PPh_3)_2Cl_2$ (0.018 g, 0.025 mmol) and CuI (0.003 g, 0.013 mmol) were added to the solution. The resulting mixture was heated at 60 °C for 3 h. After cooling to room temperature, the reaction mixture was poured into an aqueous saturated solution of NaCl and the product was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and then filtered; the filtrate was concentrated under reduced pressure to obtain the residue. The residue was purified over silica gel to afford **4** (0.142 g, 70%).^{1}H-NMR (400 MHz, $CDCl_3$) [ppm] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 1.8, 1.8 Hz, 1H), 8.21 (ddd, *J* = 8.3, 2.3, 1.0 Hz, 1H), 7.83 (m, 1H), 7.56 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.45 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.32 (ddd, *J* = 8.3, 7.4, 1.7 Hz, 1H), 7.00 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.94 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H), 5.74 (s, 1H).^{13}C-NMR (100 MHz, DMSO-d_6) [ppm] ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.93, 148.40, 137.35, 132.29, 131.52, 129.77, 126.55, 124.53, 123.56, 120.89, 115.35, 108.78, 93.70, 86.15. HRMS–ESI: m/z $[M - H]^-$ calcd for $C_{14}H_8NO_3$: 238.0503; found: 238.0503.



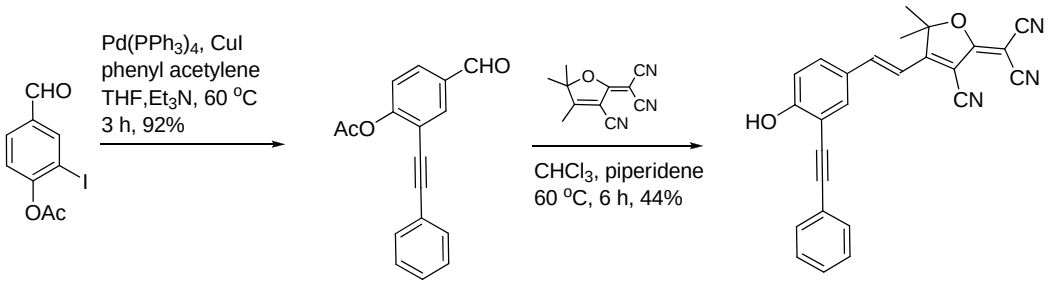
Scheme S1. Synthetic scheme of **5**.

2-(hept-1-ynyl)-4-nitrophenyl acetate (**8**).
To a well stirred solution of 2-iodo-4-nitrophenyl acetate (0.20 g, 0.65 mmol) in THF (6 mL) and Et_3N (0.6 mL) were added $Pd(PPh_3)_4$ (.012 g, 0.01 mmol), 1-heptyne (0.13 mL, 0.98 mmol). After 5-10 min. CuI (0.004 g, 0.02 mmol) was added and the resulting solution was stirred at room temperature for 7 h. Then the reaction mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na2SO4 then filtered, and the filtrate was concentrated under reduced pressure to afford a residue. The residue was purified over silica gel to afford 8 (0.19 g, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$) [ppm] 8.31 (d, *J* = 2.8 Hz, 1H), 8.14 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.25 (d, *J* = 8.9 Hz, 1H), 2.44 (t, *J* = 7.1 Hz, 2H), 2.37 (s, 3H), 1.61 (m, 2H), 1.40 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] 168.1, 156.3, 145.5, 128.7, 123.8, 123.3, 120.0, 98.9, 74.1, 31.2, 28.3, 22.4, 21.0, 19.7, 14.1. HRMS–ESI: m/z $[M – CH_3CO]^-$ calcd for $C_{13}H_{14}NO_3$: 232.0974; found: 232.0976.

2-(hept-1-ynyl)-4-nitrophenol (5)

Compound **8** (0.065 g, 0.23 mmol) was dissolved in MeOH (7 mL). After the addition of hydrazine monohydrate (0.016 mL, 0.34 mmol), the reaction mixture was stirred at room temperature for 15 min. After completion of reaction dil HCl was added and the solvent was removed under reduced pressure to afford a residue. The residue was purified over silica gel to afford **5** (0.05 g, 90%).
^{1}H-NMR (400 MHz, $CDCl_3$) [ppm] 8.22 (d, *J* = 2.8 Hz, 1H), 8.10 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.01 (d, *J* = 9.1 Hz, 1H), 6.48 (bs, 1H), 2.50 (t, *J* = 7.2 Hz, 2H), 1.66 (m, 2H), 1.39 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H), ^{13}C-NMR (100 MHz, $CDCl_3$) [ppm] 161.6, 141.3, 127.8, 125.7, 114.9, 111.5, 100.9, 72.8, 31.3, 28.3, 22.4, 19.7, 14.1. HRMS–ESI: m/z $[M - H]^-$ calcd for $C_{13}H_{14}NO_3$: 232.0974; found: 232.0975.

(5-nitro-2-pentylbenzofuran-3-yl)mercury(II) chloride (5a)
By following the general procedure, the reaction of **5** (20.0 mg, 0.086 mmol) yielded **5a** (38.2 mg, 95% yield). ^{1}H-NMR (400 MHz, DMSO) [ppm] 8.87 (d, *J* = 2.2 Hz, 1H), 8.09 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.67 (dd, *J* = 9.0, 0.4 Hz, 1H), 2.85 (t, *J* = 7.5 Hz, 2H), 1.70 (dd, *J* = 14.6, 7.5 Hz, 2H), 1.30 (m, 4H), 0.87 (t, *J* = 7.2 Hz, 3H), HRMS–ESI: m/z $[M + Cl]^-$ calcd for $C_{13}H_{14}Cl_2HgNO_3$: 504.0057; found: 504.0060.



Scheme S2. Synthetic scheme of **7**.

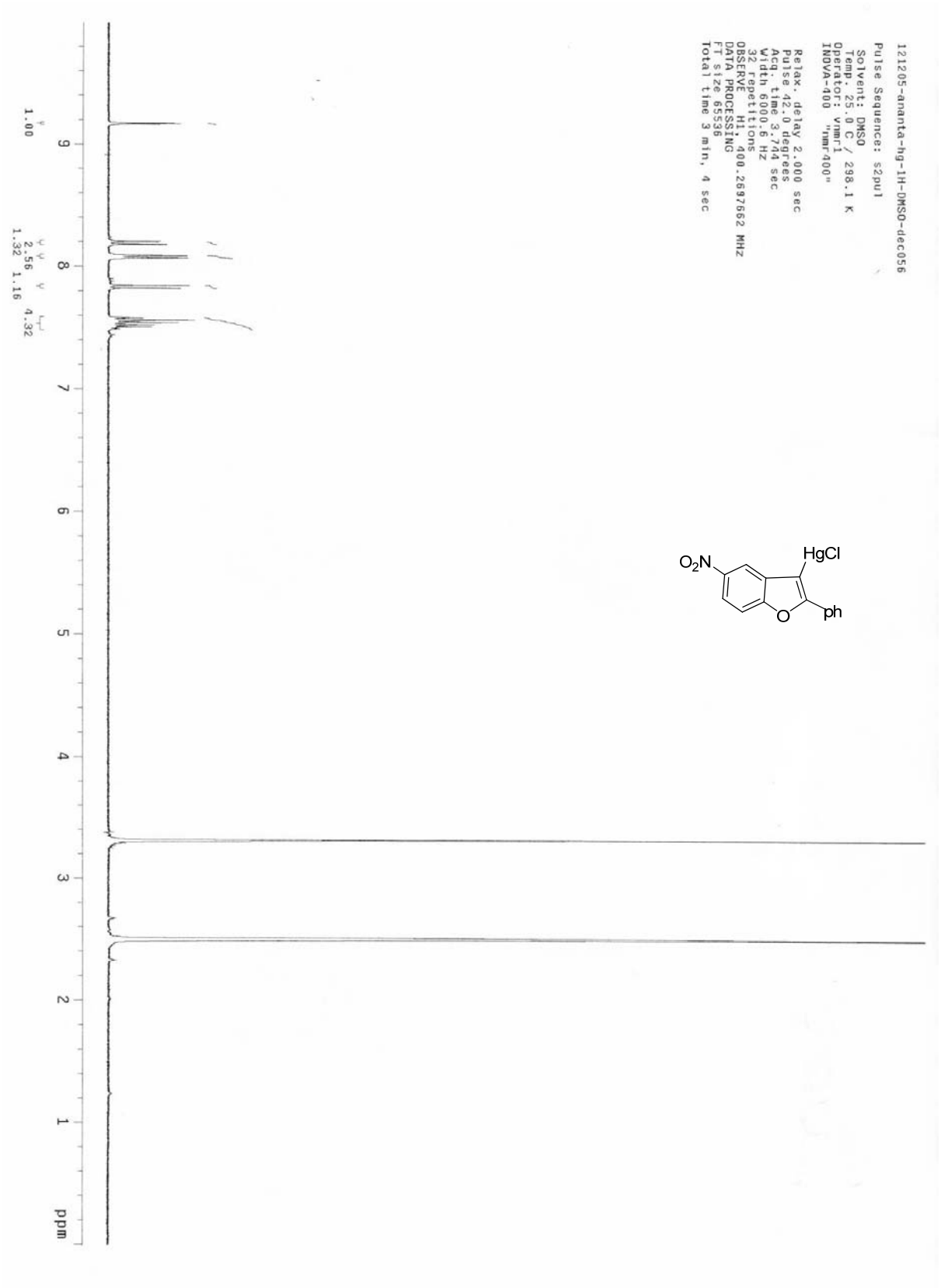
4-formyl-2-(phenylethynyl)phenyl acetate (6)
To a well-stirred solution of iodoaldehyde acetate (0.205 g, 0.71 mmol) in THF (8 mL) and Et_3N (0.8 mL) were added phenyl acetylene (0.16 mL, 1.06 mmol), $Pd(PPh_3)_4$ (.025 g, 0.021 mmol), and CuI (0.002 g, 0.011 mmol). The resulting mixture was heated at 60 °C for 3 h. After cooling to room temperature, the reaction mixture was poured into an aqueous saturated solution of NaCl and the product was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and then filtered; the filtrate was concentrated under reduced pressure to obtain the residue. The residue was purified over silica gel to afford **6** (0.174 g, 92%).
^{1}H NMR (400 MHz, $CDCl_3$) [ppm] 9.99 (d, *J* = 0.4 Hz, 1H), 8.10 (dd, *J* = 7.9, 0.4 Hz, 1H), 7.88 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.40 – 7.35 (m, 3H), 7.32 (ddd, *J* = 8.3, 0.4, 0.4 Hz, 1H), 2.41 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] 190.5, 168.4, 156.1, 134.9, 134.3, 131.9, 130.4, 129.3, 128.7, 123.5, 122.5, 119.0, 95.9, 83.2, 21.1. HRMS–ESI: m/z $[M – CH_3CO]^-$ calcd for $C_{15}H_9O_2$: 221.0608; found: 221.0610.

(E)-2-(3-cyano-4-(4-hydroxy-3-(phenylethynyl)styryl)-5,5-dimethylfuran-2(5H)-ylidene)malononitrile (7)
In a round-bottom flask fitted with a reflux condenser, compound **6** (0.1 g, 0.38 mmol) and 2-dicyanomethylene-3-cyano-4,5,5-trimethyl-2,5-dihydrofuran (TCF) (0.68 g, 0.34 mmol) were dissolved in $CHCl_3$ (4 mL). Piperidine (cat.) was added to the mixture, which was then stirred at reflux for 6 h. After cooling to room temperature, the mixture was concentrated under reduced pressure to afford a residue. The residue was purified over silica gel to afford **7** (0.067 g, 44%).^{1}H NMR (400 MHz, DMSO) δ 11.20 (s, 1H), 8.08 (d, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 16.3 Hz, 1H), 7.83 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.55 (m, 2H), 7.44 (m, 3H), 7.10 (d, *J* = 16.3 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 1.79 (s, 6H), ^{13}C NMR (100 MHz, DMSO) δ 177.2, 175.6, 162.3, 147.1, 135.3, 131.9, 131.2, 128.8, 125.9, 122.5, 116.5, 112.83, 112.80, 112.0, 111.1, 111.0, 99.2, 97.4, 93.3, 85.4, 53.6, 25.2. HRMS–ESI: m/z $[M + Na]^+$ calcd for $C_{26}H_{17}N_3NaO_2$: 426.1218; found:426.1210.

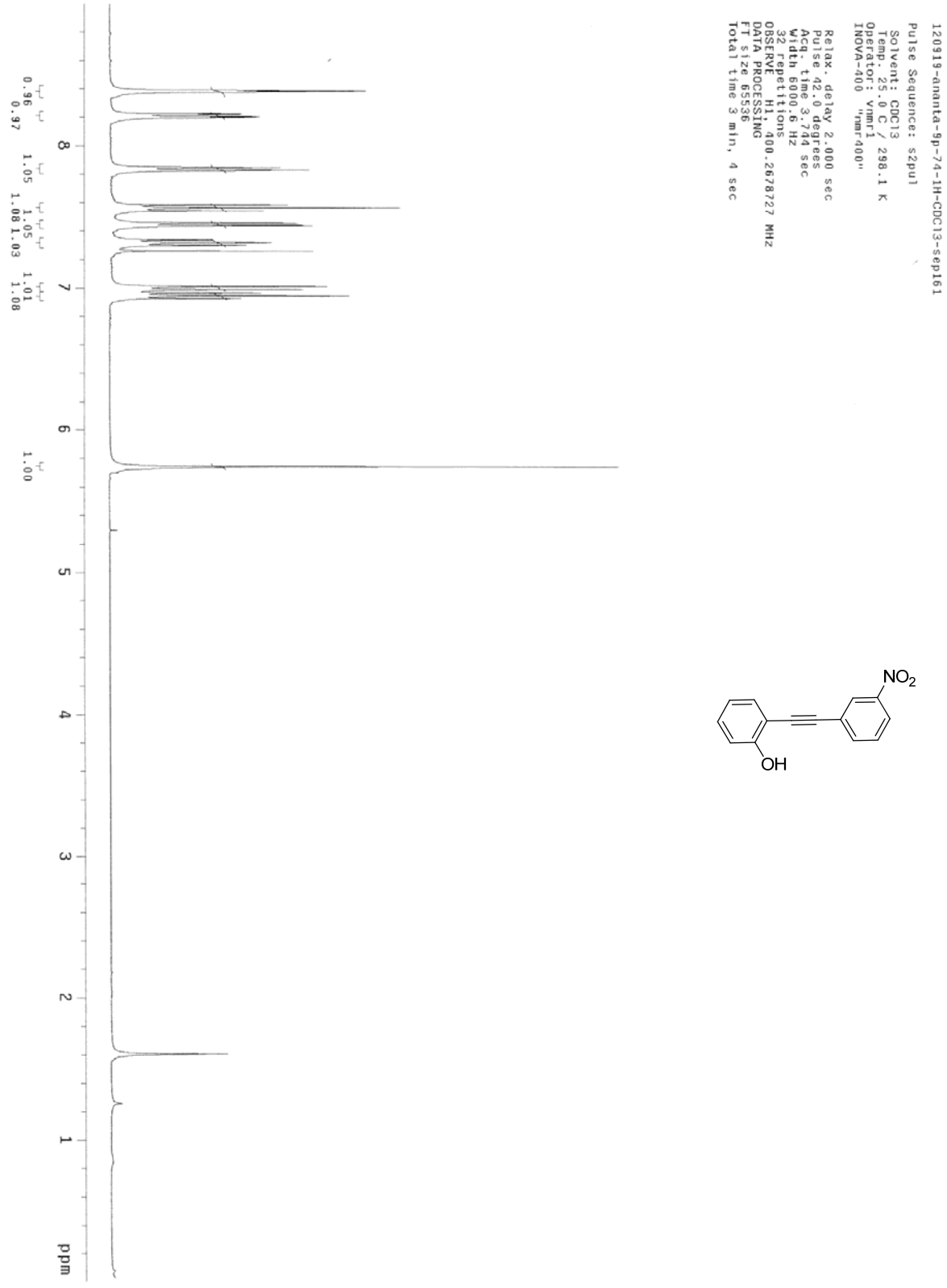
(E)-(5-(2-(4-cyano-5-(dicyanomethylene)-2,2-dimethyl-2,5-dihydrofuran-3-yl)vinyl)-2-phenylbenzofuran-3-yl)mercury(II) chloride (7a)
By following the general procedure, the reaction of **7** (34.7 mg, 0.086 mmol) yielded 7a (43.9 mg, 80% yield). ^{1}H NMR (400 MHz, DMSO) δ 8.49 (s, 1H), 8.04 (m, 2H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H),

7.51 (m, 4H), 7.18 (d, J = 16.3 Hz, 1H), 1.79 (s, 6H), HRMS–ESI: m/z [M +Cl]$^-$ calcd for $C_{26}H_{16}Cl_2HgN_3O_2$: 674.0326; found: 674.0316.

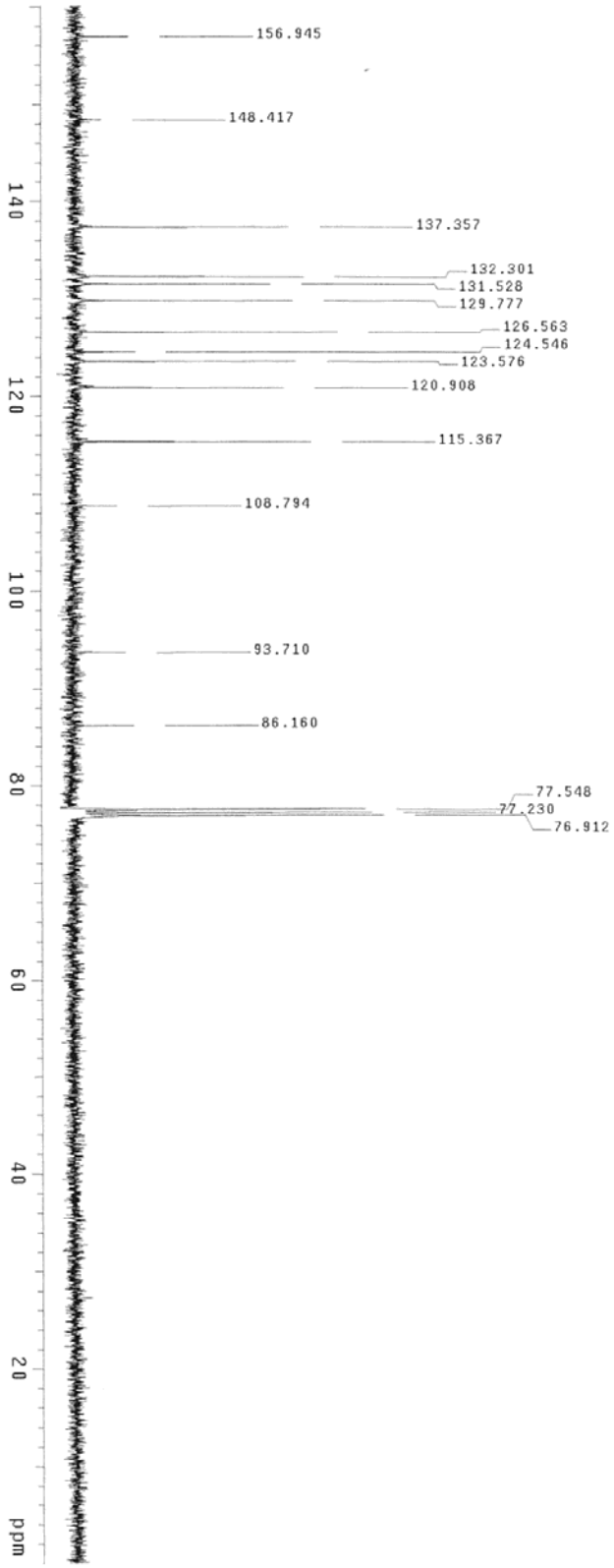
NMR Spectra



^{1}H NMR spectrum of **3a** recorded in $CDCl_3$



^{1}H NMR spectrum of **4** recorded in $CDCl_3$



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Operator: vnmr1
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Pulse 80.0 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
440 repetitions
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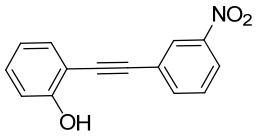
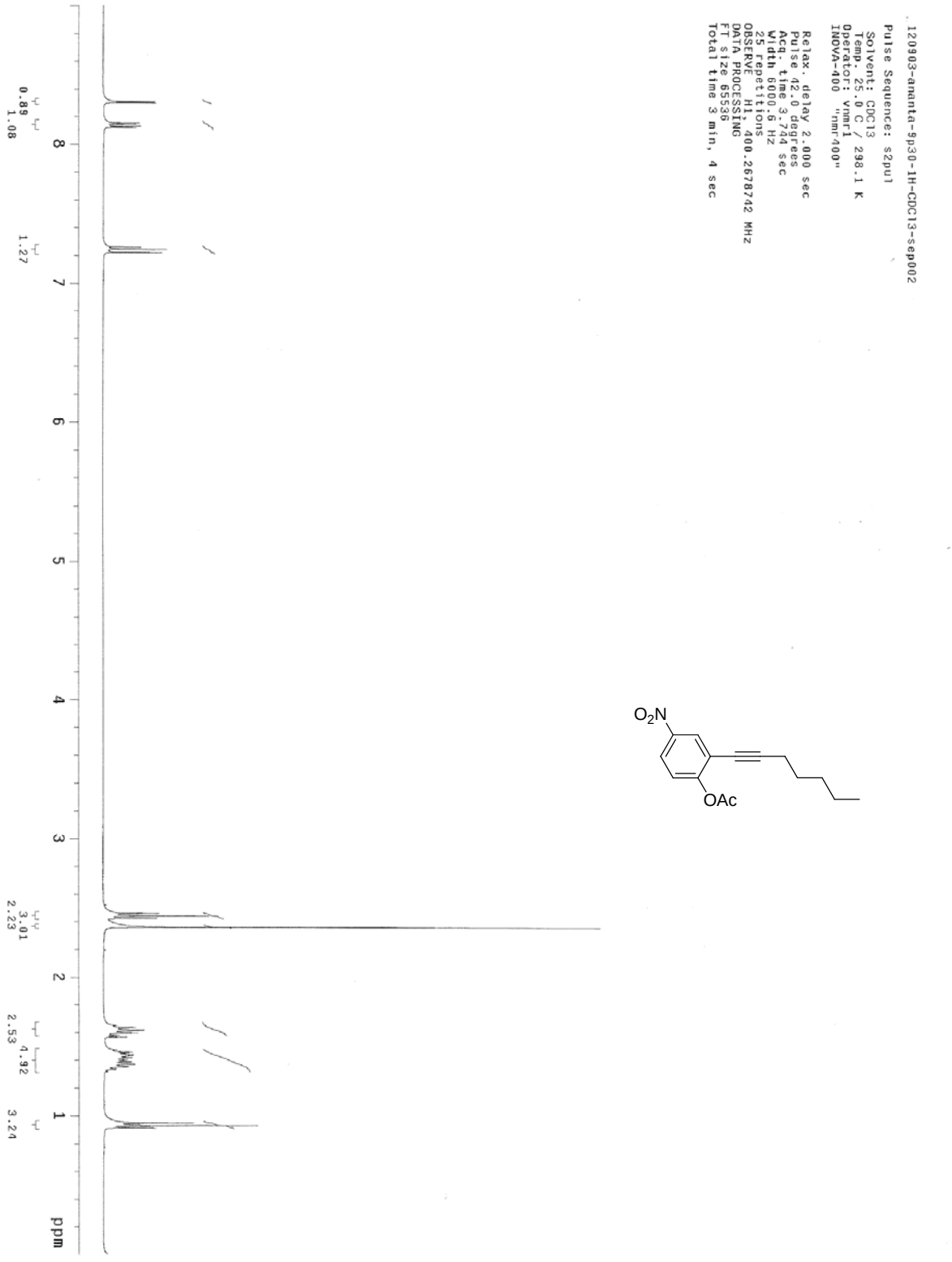
DECOUPLE H1, 400.2691977 MHz
Power 41 dB
on during acquisition
off during delay
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 2 hr, 20 min, 16 sec



^{13}C NMR spectrum of **4** recorded in DMSO-d_6



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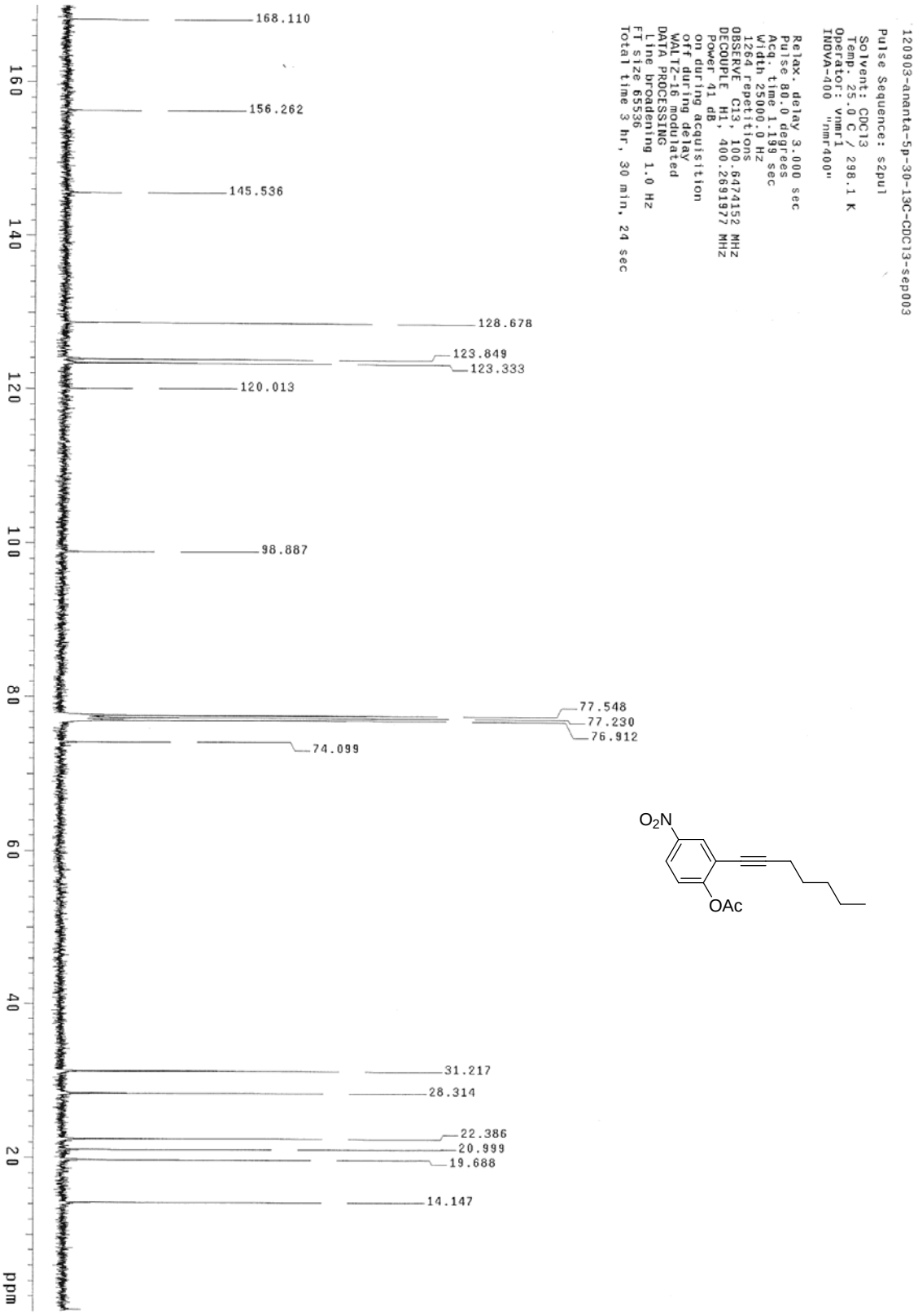
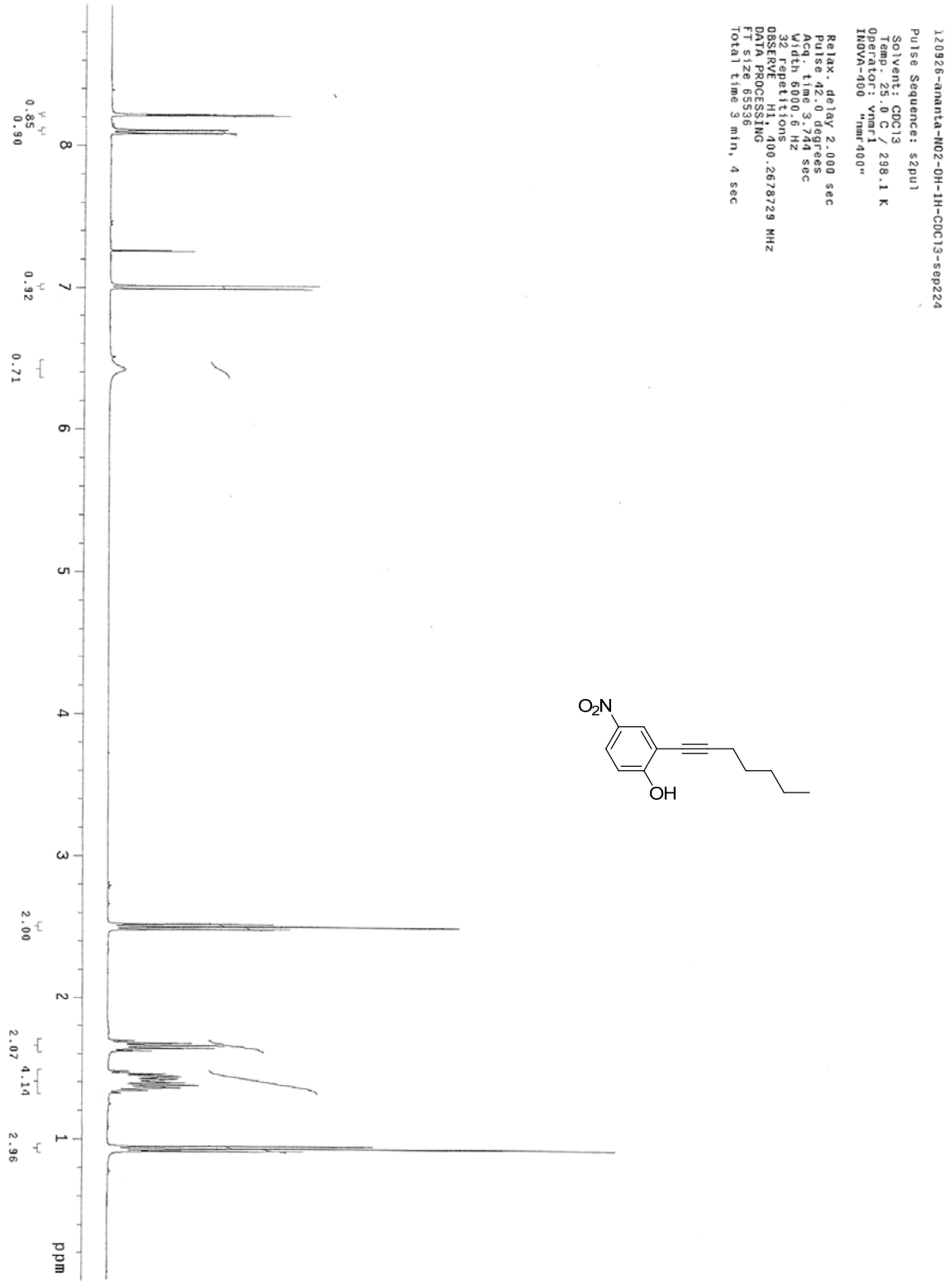
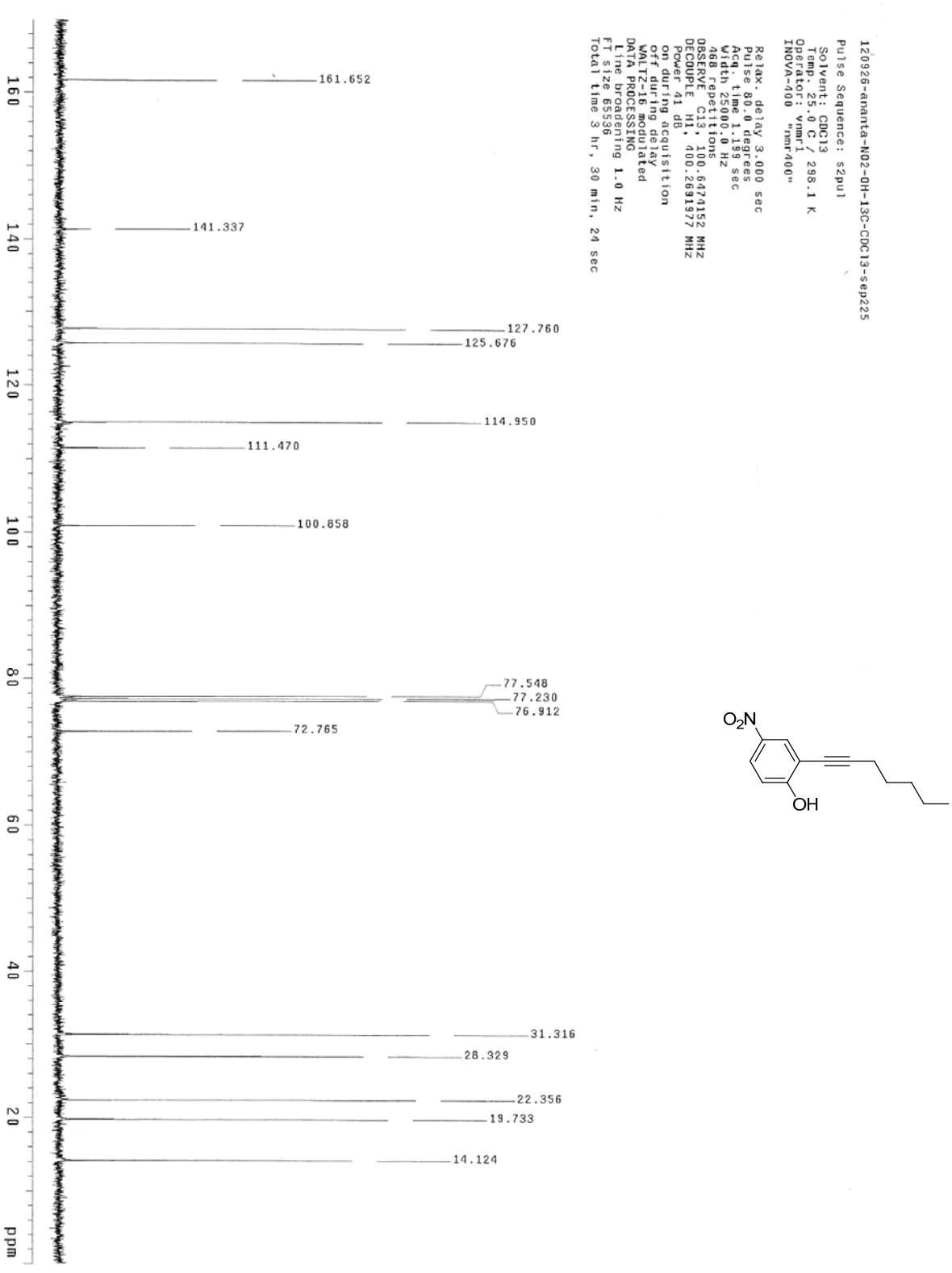


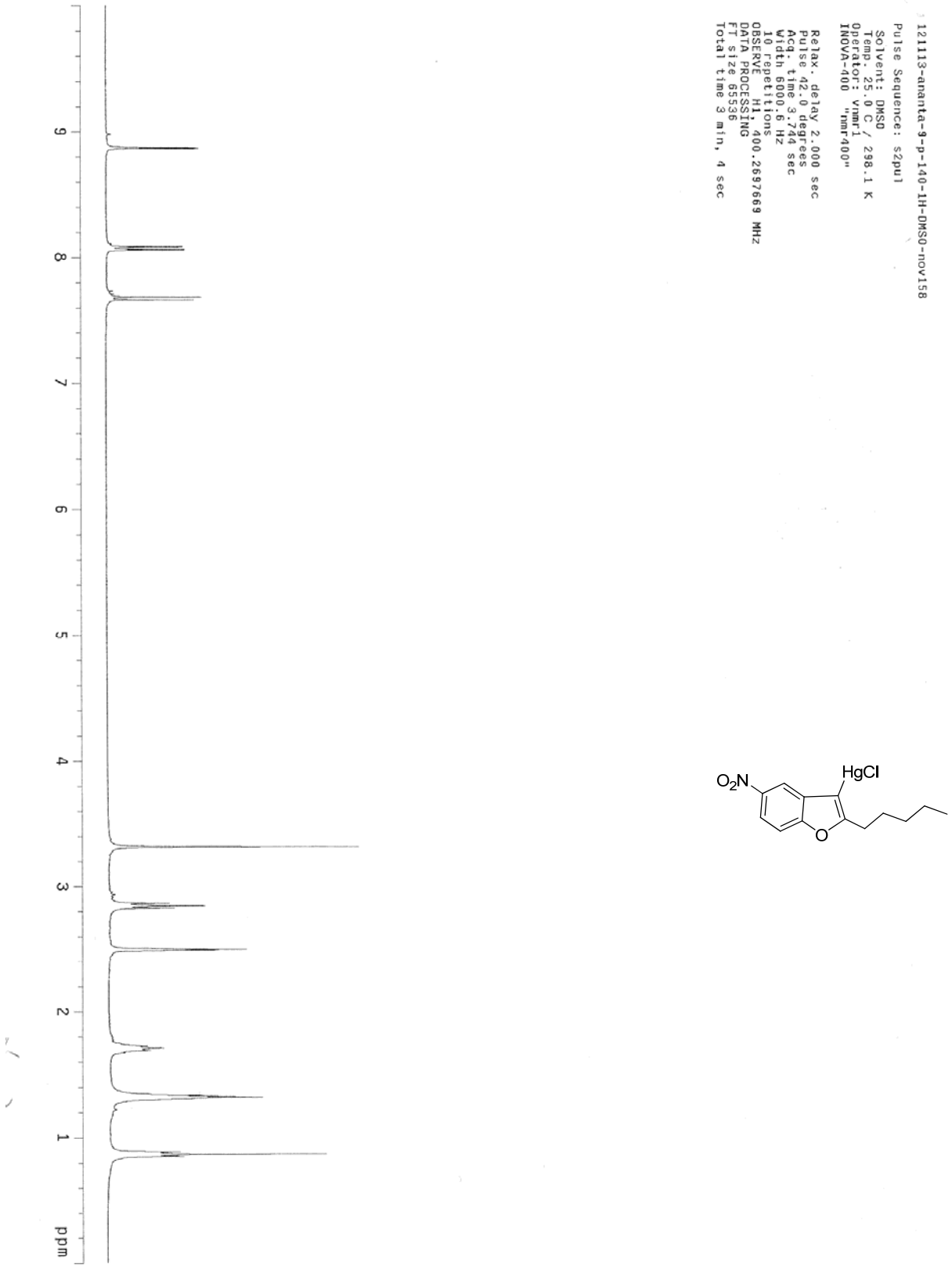
^{13}C NMR spectrum of **8** recorded in $CDCl_3$



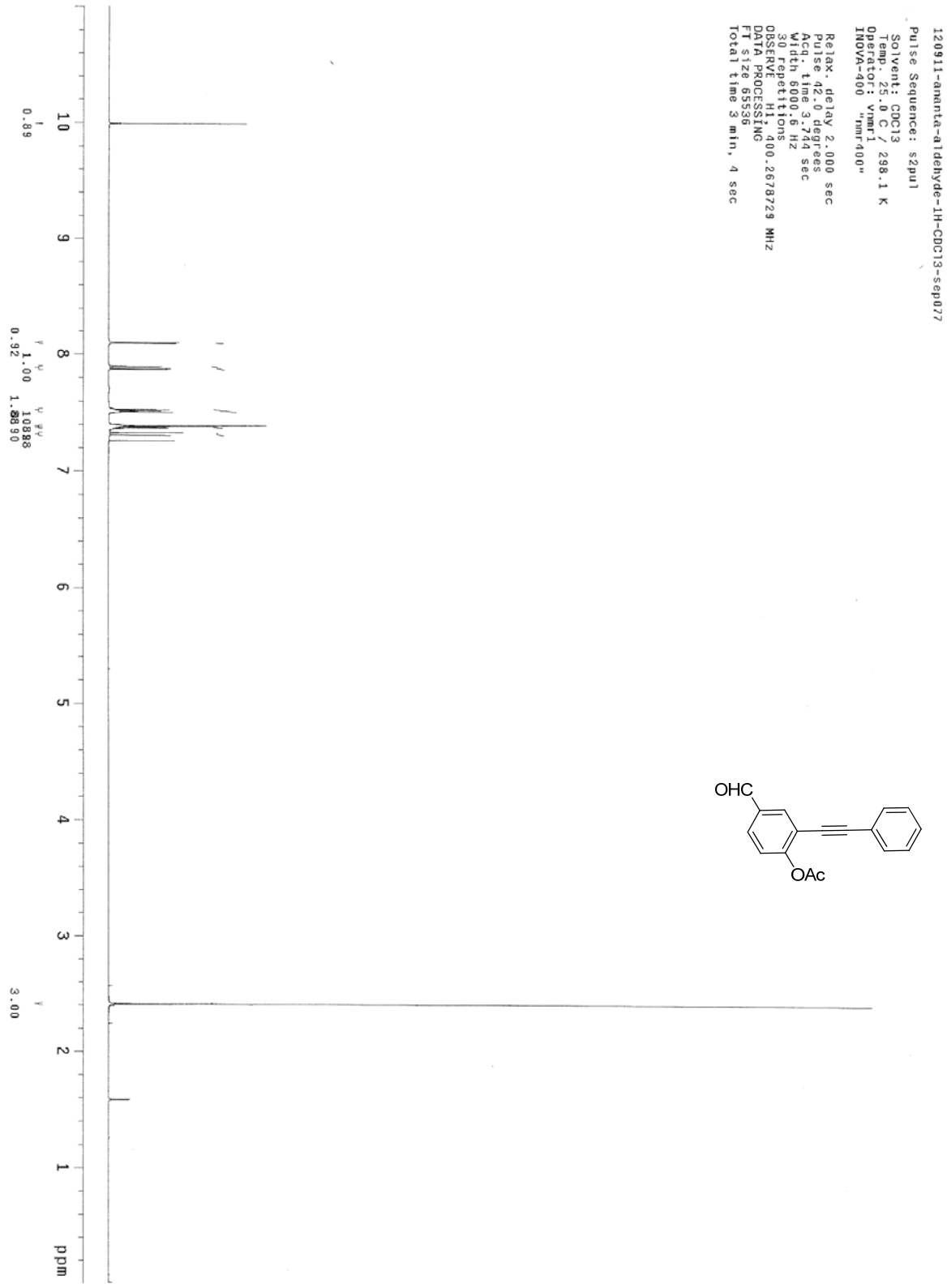
^{1}H NMR spectrum of **5** recorded in $CDCl_3$



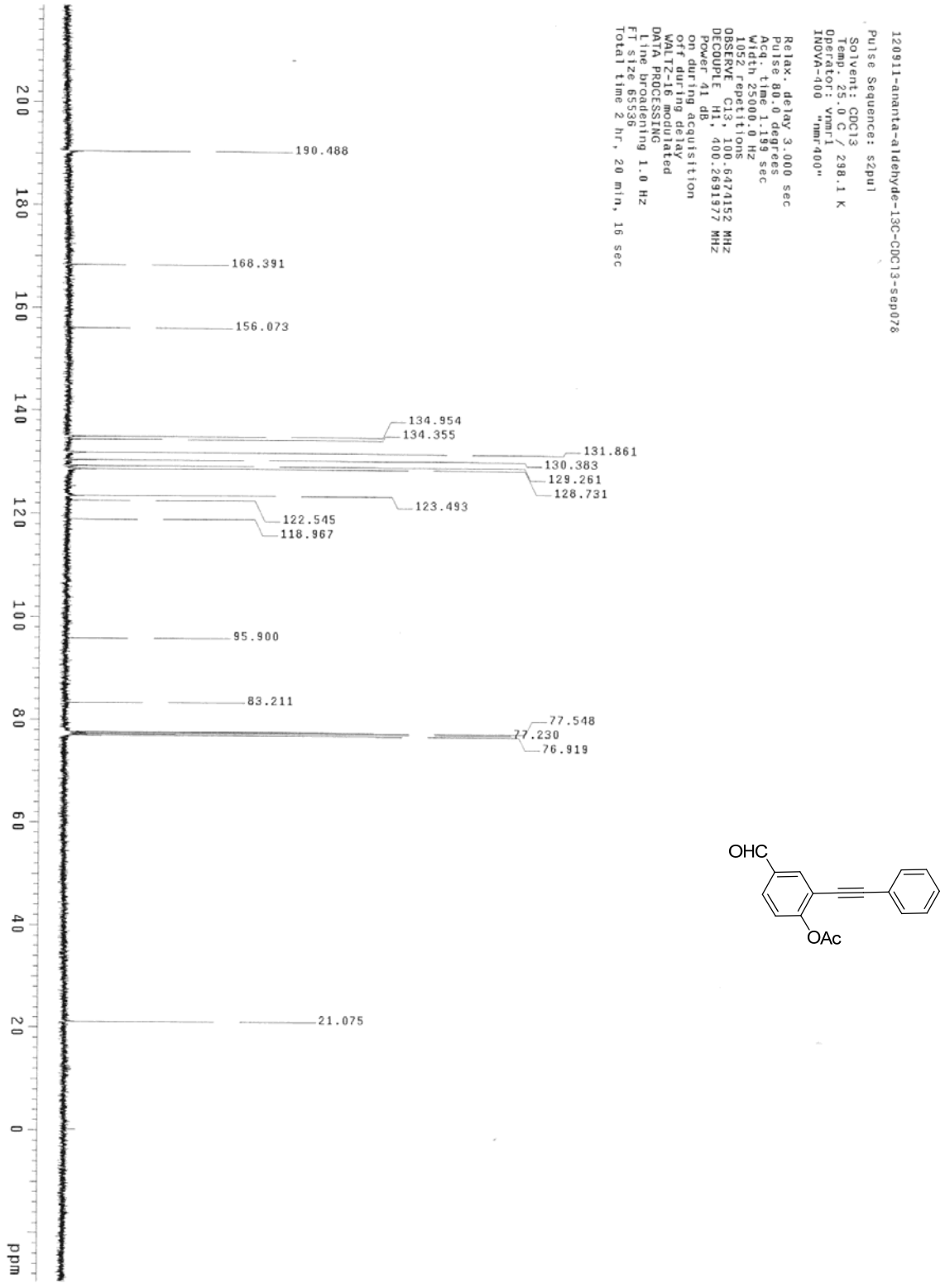
^{13}C NMR spectrum of **5** recorded in $CDCl_3$



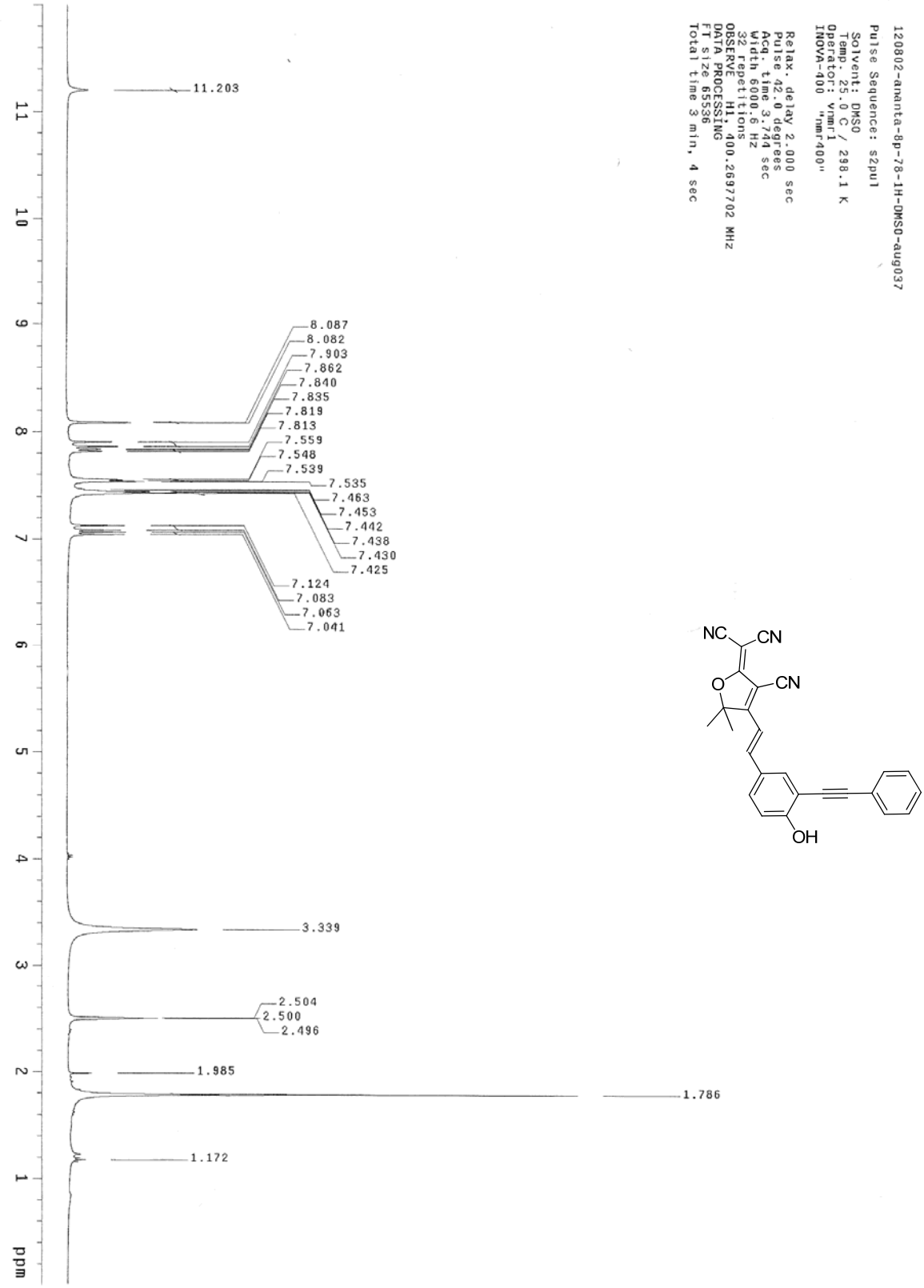
^{1}H NMR spectrum of **5a** recorded in DMSO-d_6



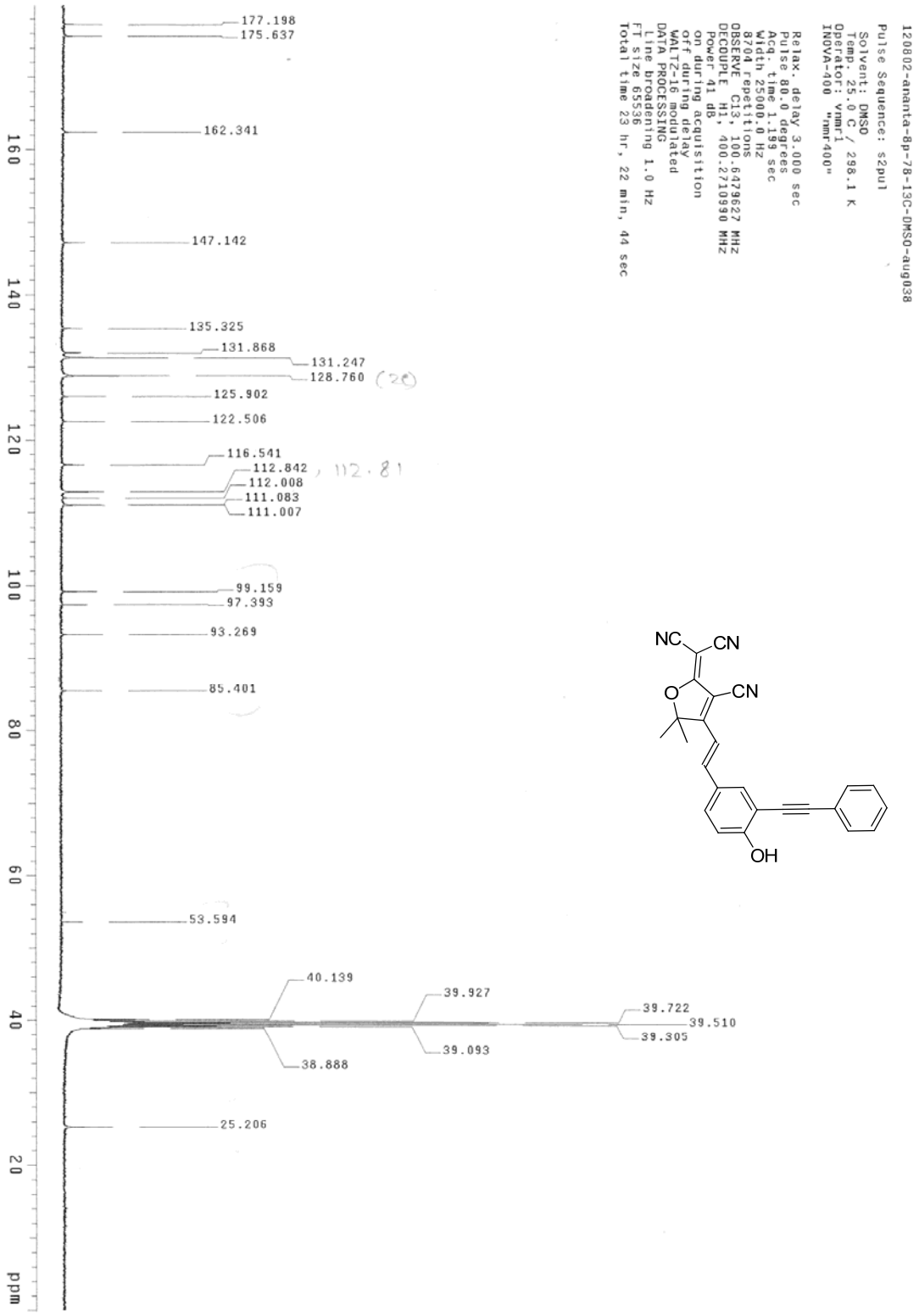
^{1}H NMR spectrum of **6** recorded in $CDCl_3$



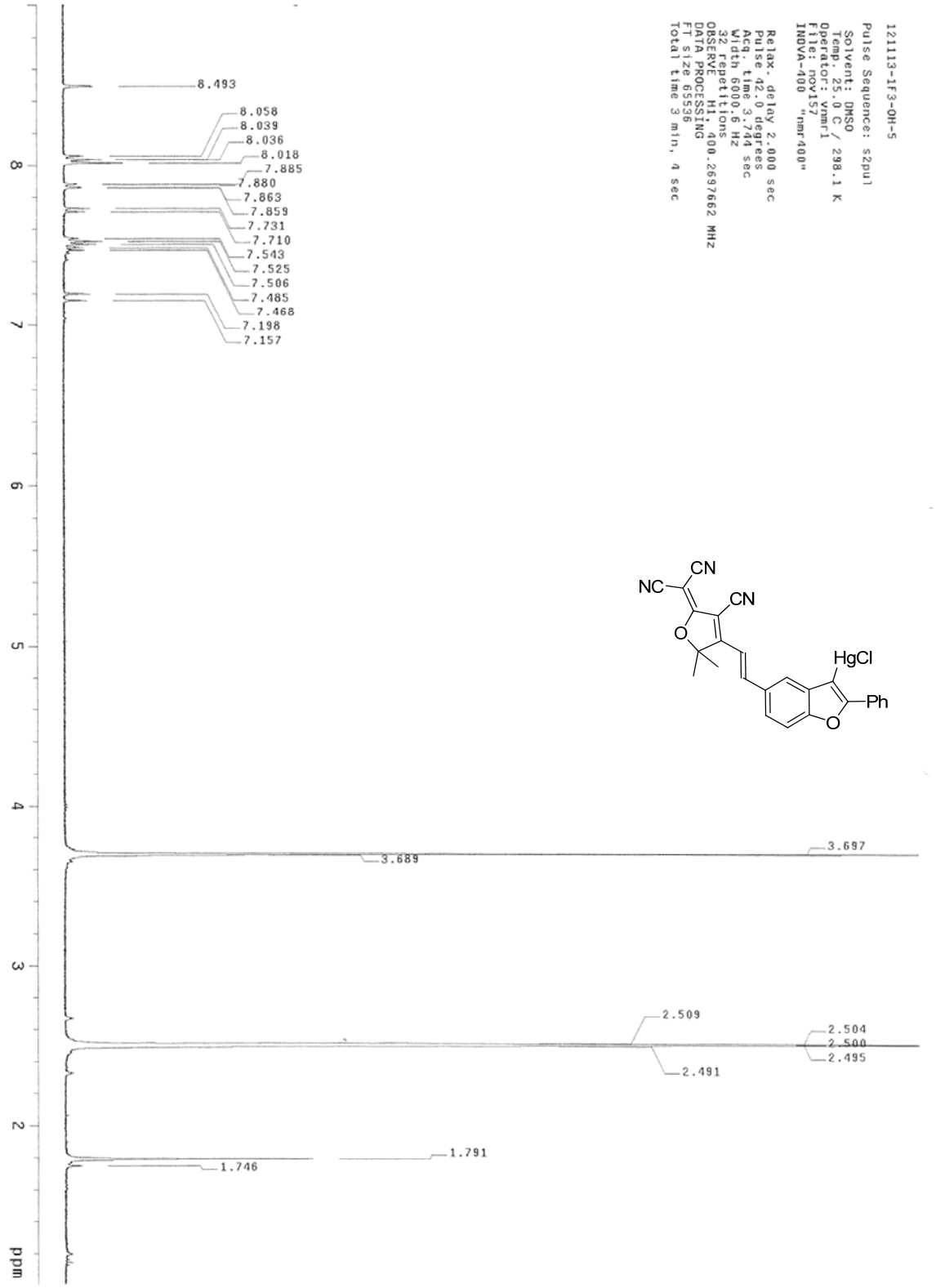
^{13}C NMR spectrum of **6** recorded in $CDCl_3$



^{1}H NMR spectrum of **7** recorded in $CDCl_3$



^{13}C NMR spectrum of **7** recorded in $CDCl_3$



^{1}H NMR spectrum of **7a** recorded in DMSO