Photosensitizer Drug Delivery via an Optical Fiber

Matibur Zamadar, Goutam Ghosh, Adaickapillai Mahendran, Mihaela Minnis, Bonnie I. Kruft, Ashwini Ghogare, David Aebisher, and Alexander Greer

Department of Chemistry and Graduate Center, City University of New York, Brooklyn College, Brooklyn, New York 11210
Email: agreer@brooklyn.cuny.edu

Supporting Information

Table of Contents

Page

Comparison of the Absorption Spectra of Glass 1 and Pheophorbide 11.

The absorption spectrum of glass **1** had (i) an intensity increase, (ii) broadening of the Soret and Q-bands, and (iii) 4th Q-band 666 nm red shift (1 nm) and blue shift (3 nm) relative to sensitizer **11** in acetonitrile and toluene, respectively (Figure S1). Polívka et al. showed that the 4th Q-band of pheophorbide derivatives shifted red/blue region depending on the polarity of solvent, e.g., the 4th Q-band was at 665 nm in acetonitrile and at 671 nm in benzene.[1] Absorption intensity increases and red and blue shifting of Q-bands based on solvent polarity have been observed for 5,10,15,20-tetra(4-(trimethyl-ammonio)phenyl)-21H,23H-porphine tetratosylate and for 5,10,15,20-tetra(1-methyl-4-pyridyl)-21H,23H-porphine tetratosylate encapsulated in monolithic sol-gel glass,[2] and the surface polarity of a monolithic silica gel glass is suggested to be between methanol and water.[3] Thus, we concluded that the probe tip surface **1** has a polarity similar to acetonitrile.

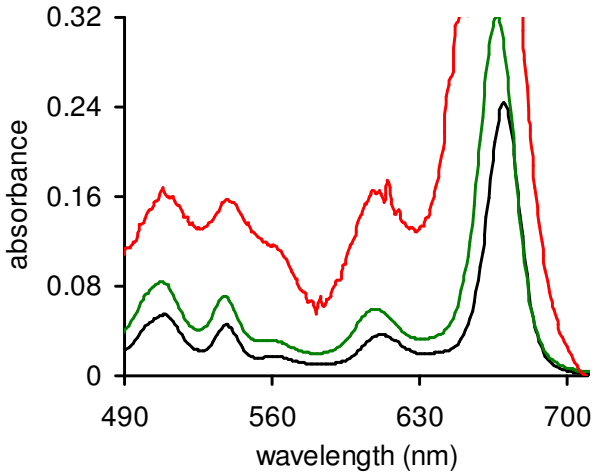


Figure S1. Normalized absorption spectra of functionalized glass **1** in air (red line), and **11** in acetonitrile (green line) and toluene (black line). The $Q_x(0,1)$, $Q_x(0,0)$, $Q_y(0,1)$, and $Q_y(0,0)$ bands can be seen (l to r).

Synthetic Procedure of Known Compounds 6-8[4]

1,2-Bis(4-bromophenoxy)ethane (6). Yield 32.7 grams (57%). To a solution of sodium hydroxide (12.4 g, 0.31 mol) in water (50 mL) was added 4-bromophenol (51.7 g, 0.3 mol). The mixture was stirred at 60-70 °C for 0.5 h followed by addition of 1,2-dibromoethane (26.3 g, 0.14 mol). The resulting mixture was then refluxed for 6 h at 100 °C. After cooling, the white solid was separated from the reaction mixture by filtration at room temperature. The solid was purified by recrystallization from ethanol and dried in vacuo (mp 130-132 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.9 Hz, 4H), 6.82 (d, *J* = 8.9 Hz, 4H), 4.27 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 132.3, 116.5, 113.4, 66.7; (lit. data for **6**, ref 4): mp 130-132 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37(d, *J* = 6.8 Hz, 4H), 6.81 (d, *J* = 6.8 Hz, 4H), 4.25 (s, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 157.5, 132.3, 116.5, 113.4, 66.7.

***meso*-1,2-Dibromo-1,2-bis(4-bromophenoxy)-ethane (*meso*-7).** Yield *meso*-**7**, 0.82 g (17%). In 50 mL of carbon tetrachloride was dissolved 3.37 g (9.06 mmol) **6**, 3.95 g (22.19 mmol) of *N*-bromosuccinimide, and 0.54 g (2.23 mmol) of benzoyl peroxide. The resulting solution was refluxed at 80 °C for 6 h. After cooling to room temperature, the mixture was filtered and the crude products obtained from the filtrate by evaporating the solvent. The crude product was purified by silica gel chromatography (230-400 mesh; 6:1 hexane/ dichloromethane) yielded pure *meso*- and *dl*-**7**. Silica gel chromatography was used to separate *meso*-**7** from *dl*-**7** (mp of *meso*-**7** 140-142 °C). mp (*meso*-**7**) 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 9.0 Hz, 4H), 7.08 (d, *J* = 9.0 Hz, 4H), 6.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 132.9, 118.9, 117.4, 85.3; (lit. data for **7**, ref 4): mp 140-142 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 8.9, 1.2 Hz, 4H), 7.08 (dd, *J* = 8.9, 1.2 Hz, 4H), 6.51 (s, *J* = 6.2 Hz, 2H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 153.7, 132.9, 118.9, 117.0, 85.3.

***cis*-1,2-Bis(4-bromophenoxy)ethene (*cis*-8)**. Yield 0.35g (95%). *Meso*-**7** (0.54 g, 1.02 mmol) was dissolved in 20 mL acetone, followed by an addition of sodium iodide (0.45 g, 3 mmol). The reaction mixture was stirred for 2 h at room temperature and developed a deep red color. The solvent was evaporated in rotary vap. followed by the addition of water (25 mL) and dichloromethane (100 mL) with continuous stirring. A saturated aqueous solution of sodium thiosulfate was added until the solution became colorless. The organic layer was separated, dried over anhydrous $NaSO_4$, and evaporated. The solid was purified by recrystallization from ethanol to obtain *cis*-**8** (mp: 102-105 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 9.0 Hz, 4H), 6.97 (d, J = 9.0, 4H), 6.11 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 132.6, 128.5, 118.0, 115.4; (lit. data for **8**, ref 4): mp 102-104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 9.0 Hz, 4H), 6.97 (d, J = 9.0, 4H), 6.11 (s, 2H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 156.3, 132.5, 128.5, 118.0, 115.4.

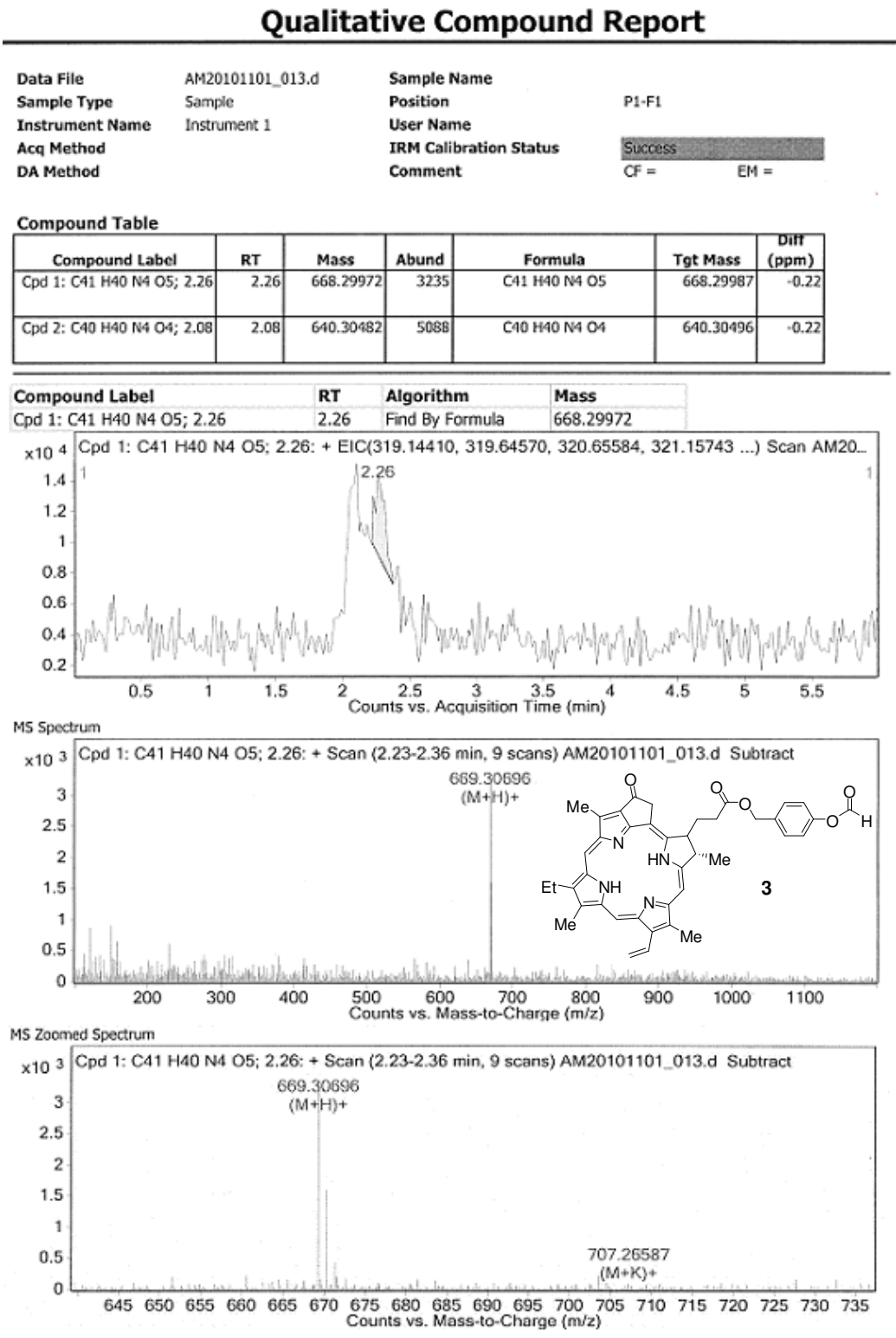
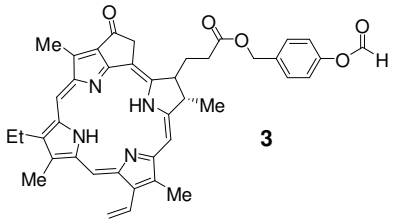


Figure S2. HRMS of 4-(formyloxy)benzyl-pyropheopheophorbide (**3**).

Qualitative Compound Report

MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
664.50646				161		
665.51901				157		
667.59961				146		
669.30696	669.30715	-0.29		3235	C41 H41 N4 O5	(M+H)+
669.60066				175		
670.3105	670.31034	0.25		1592	C41 H41 N4 O5	(M+H)+
671.31476	671.31333	2.13		442	C41 H41 N4 O5	(M+H)+
671.53912				203		
672.59577				160		
707.26587	707.26303	4.02	1	81	C41 H40 K N4 O5	(M+K)+



3

Figure S2. contd. HRMS of 4-(formyloxy)benzyl-pyropheopheophorbide (**3**).

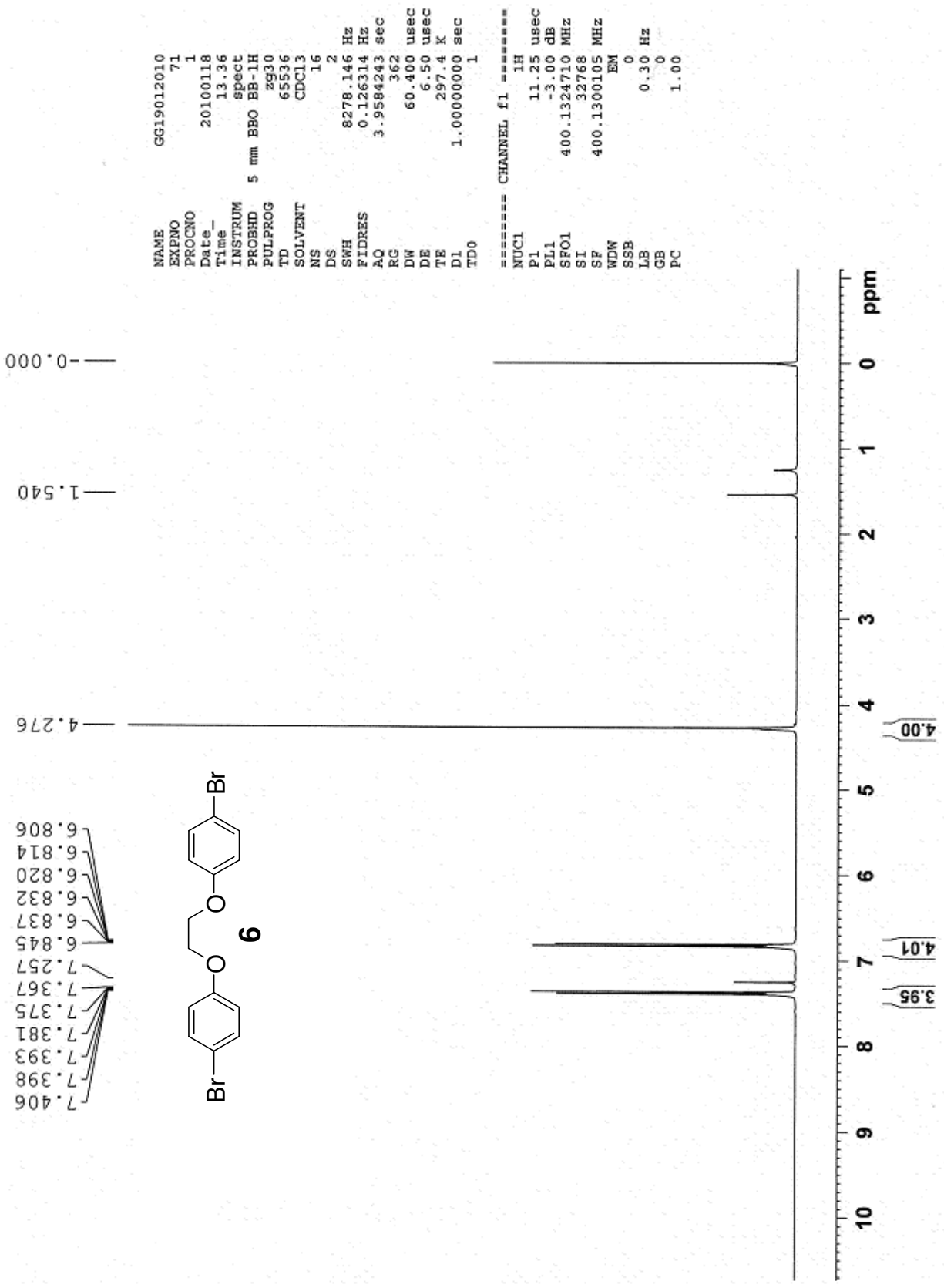


Figure S3. ^{1}H NMR of 1,2-bis(4-bromophenoxy)ethane (**6**) in $CDCl_3$.

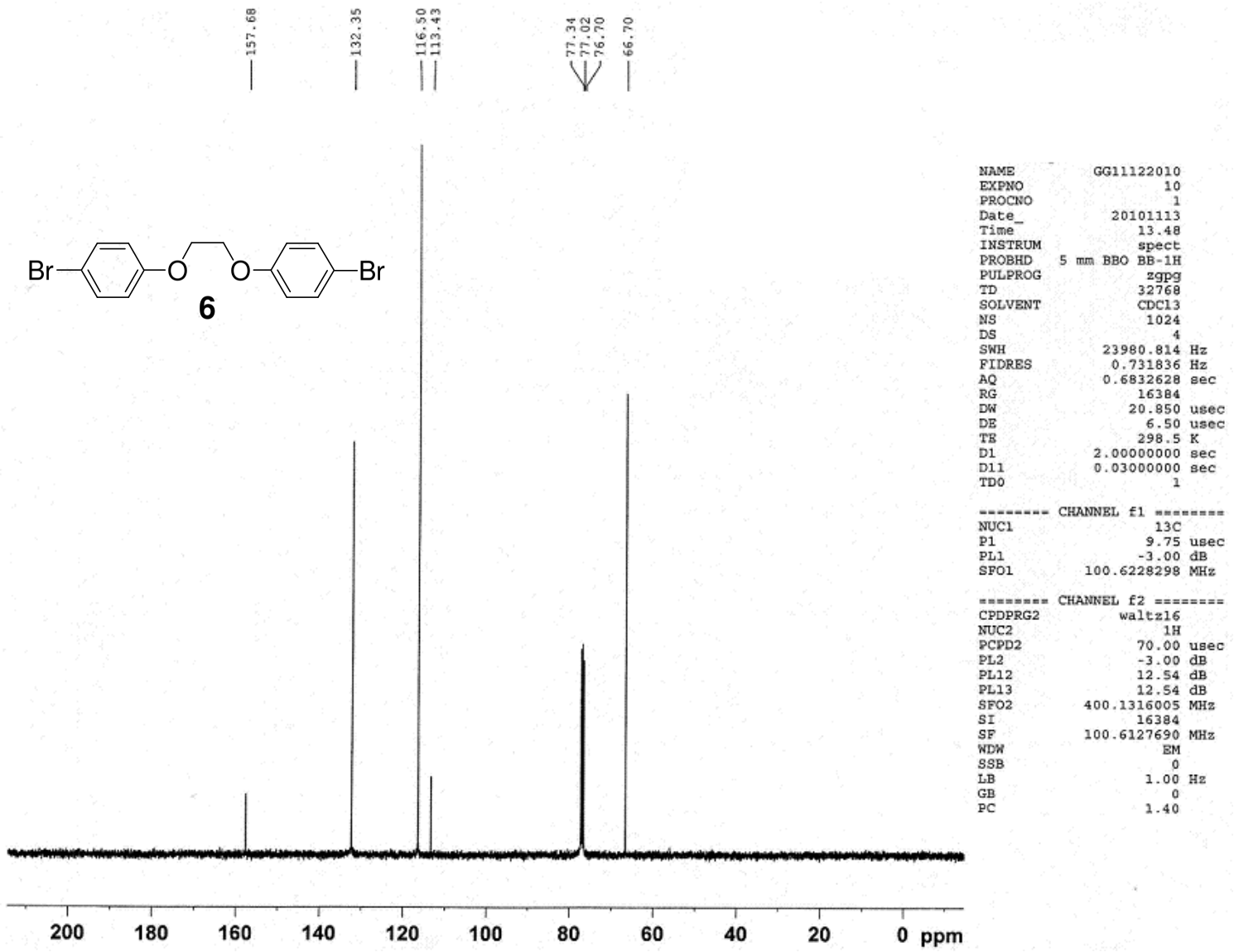


Figure S4. ^{13}C NMR of 1,2-bis(4-bromophenoxy)ethane (**6**) in $CDCl_3$.

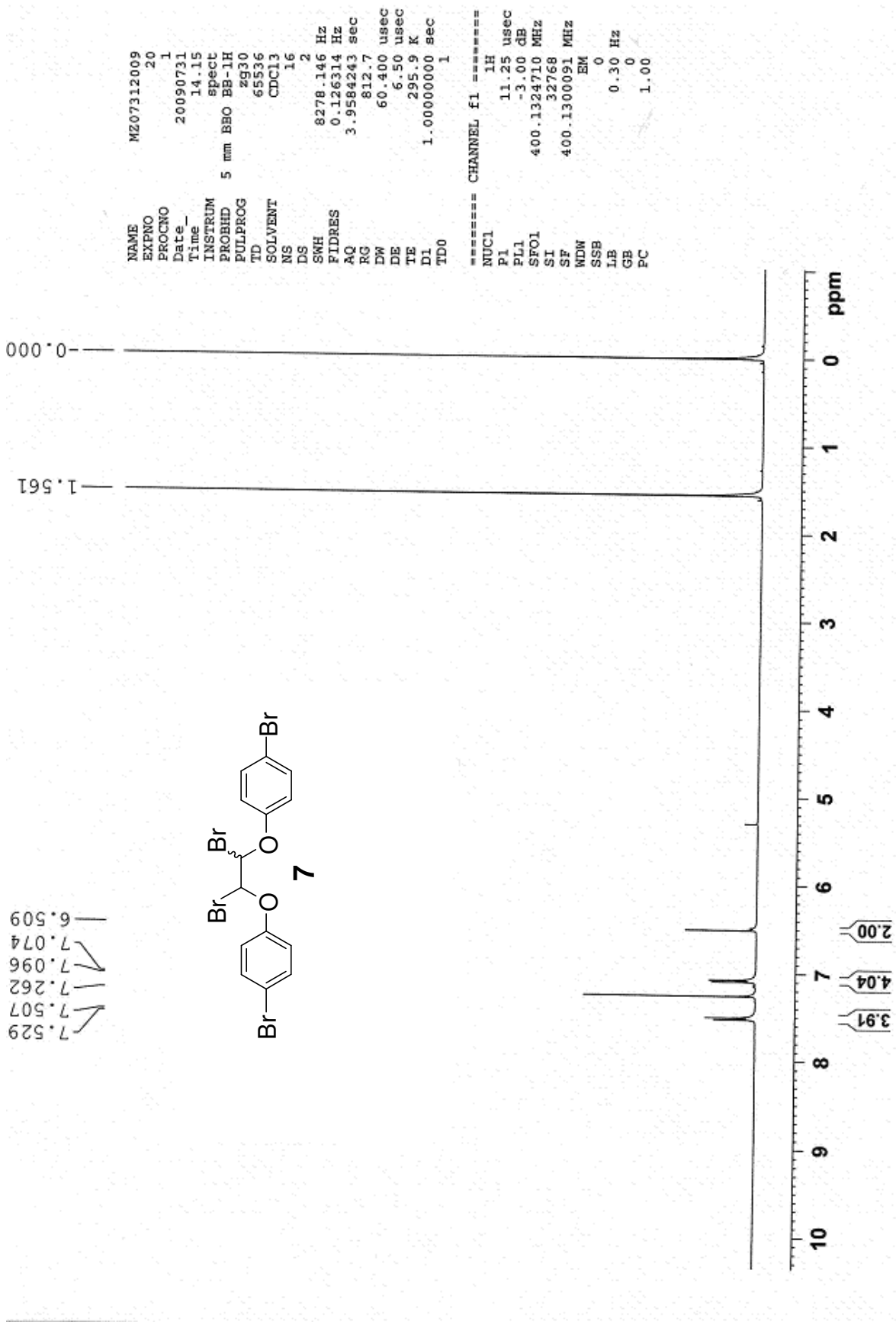


Figure S5. ^{1}H NMR of *meso*-1,2-dibromo-1,2-bis(4-bromophenoxy)-ethane (**7**) in $CDCl_3$.

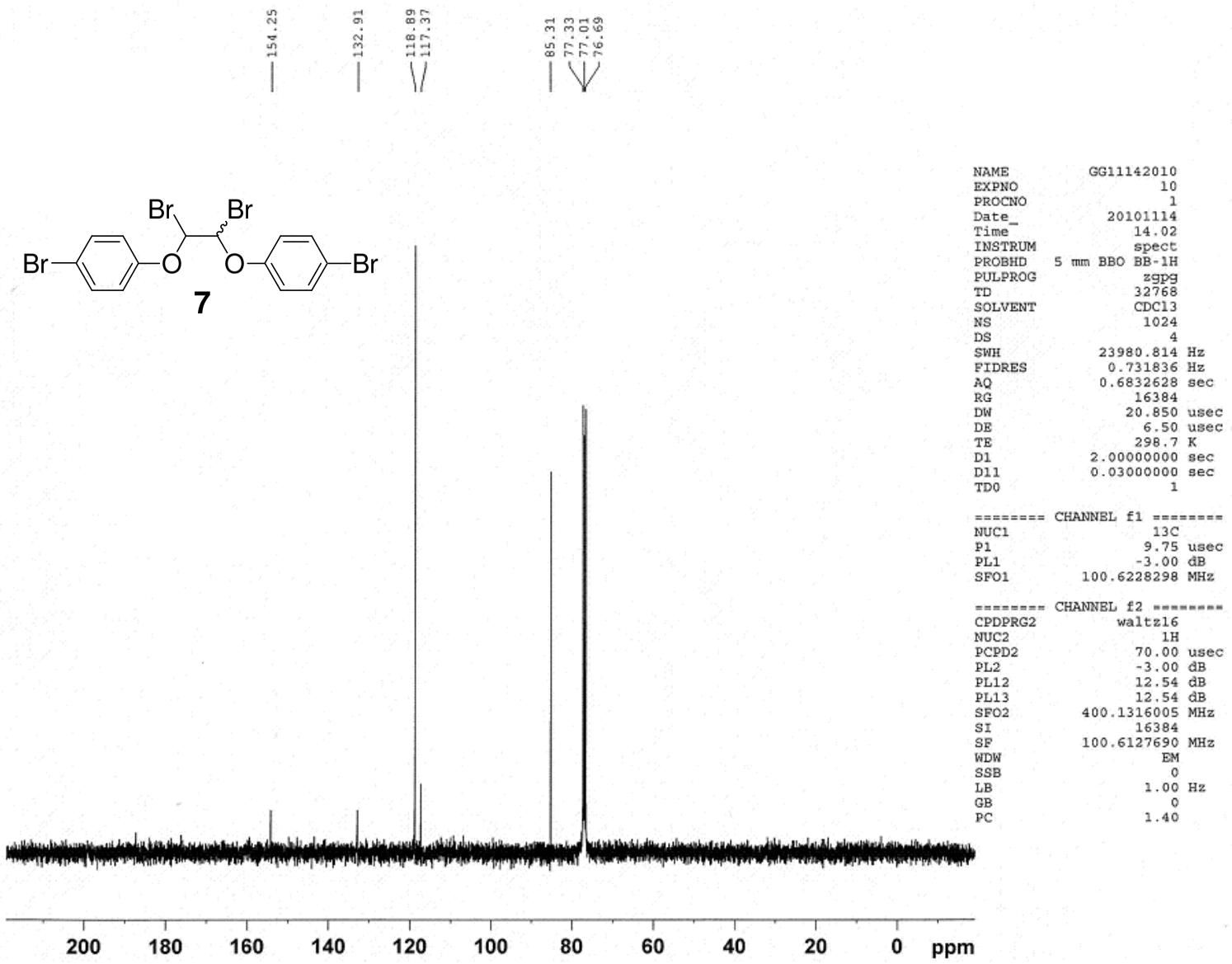


Figure S6. ^{13}C NMR of *meso*-1,2-dibromo-1,2-bis(4-bromophenoxy)-ethane (**7**) in $CDCl_3$.

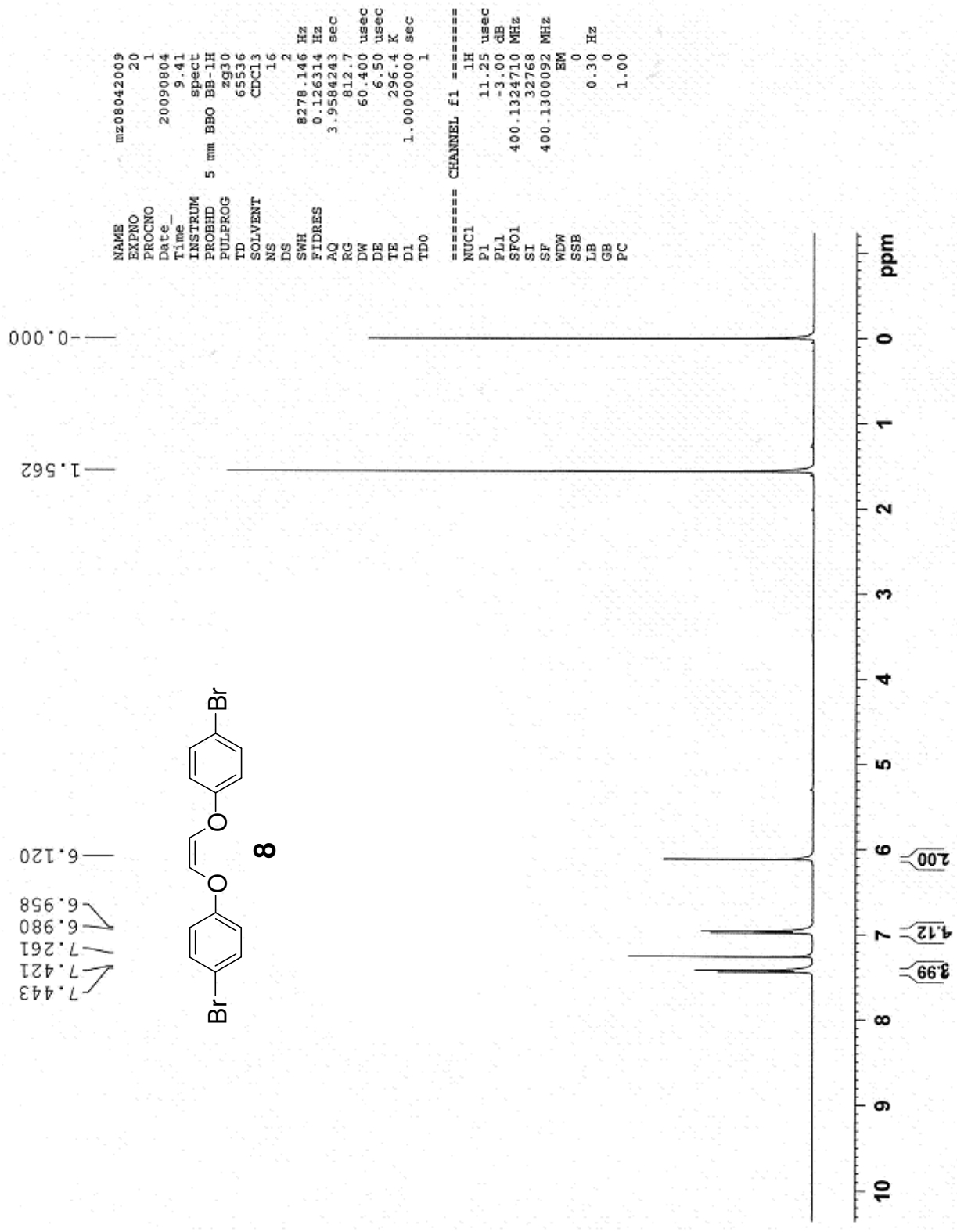


Figure S7. ^{1}H NMR of *cis*-1,2-bis(4-bromophenoxy)ethene (**8**) in $CDCl_3$.

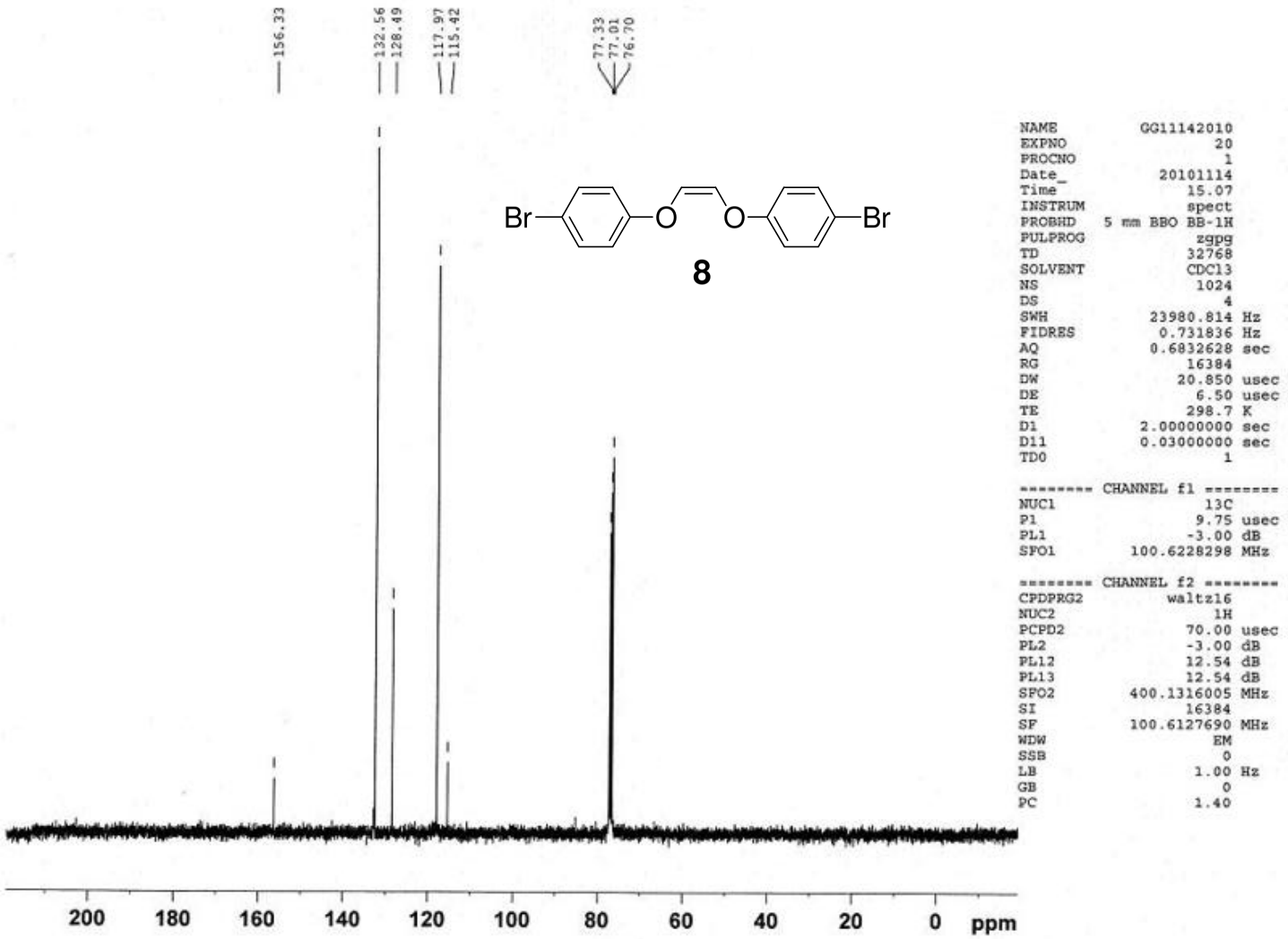


Figure S8. ^{13}C NMR of *cis*-1,2-bis(4-bromophenoxy)ethene (**8**) in $CDCl_3$.

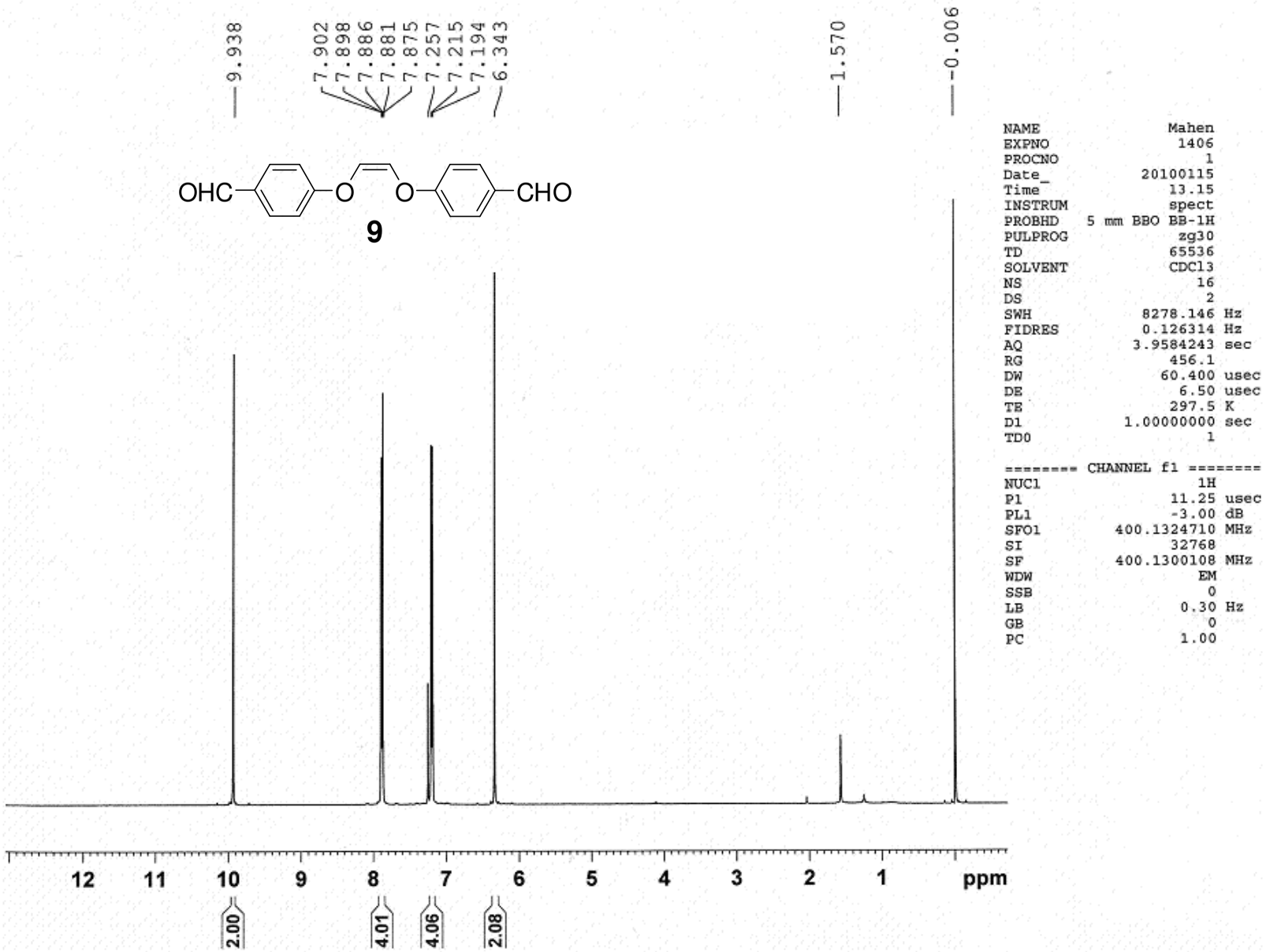


Figure S9. ^{1}H NMR of (Z)-4,4'-(ethene-1,2-diylbis(oxy))dibenzaldehyde (**9**) in $CDCl_3$.

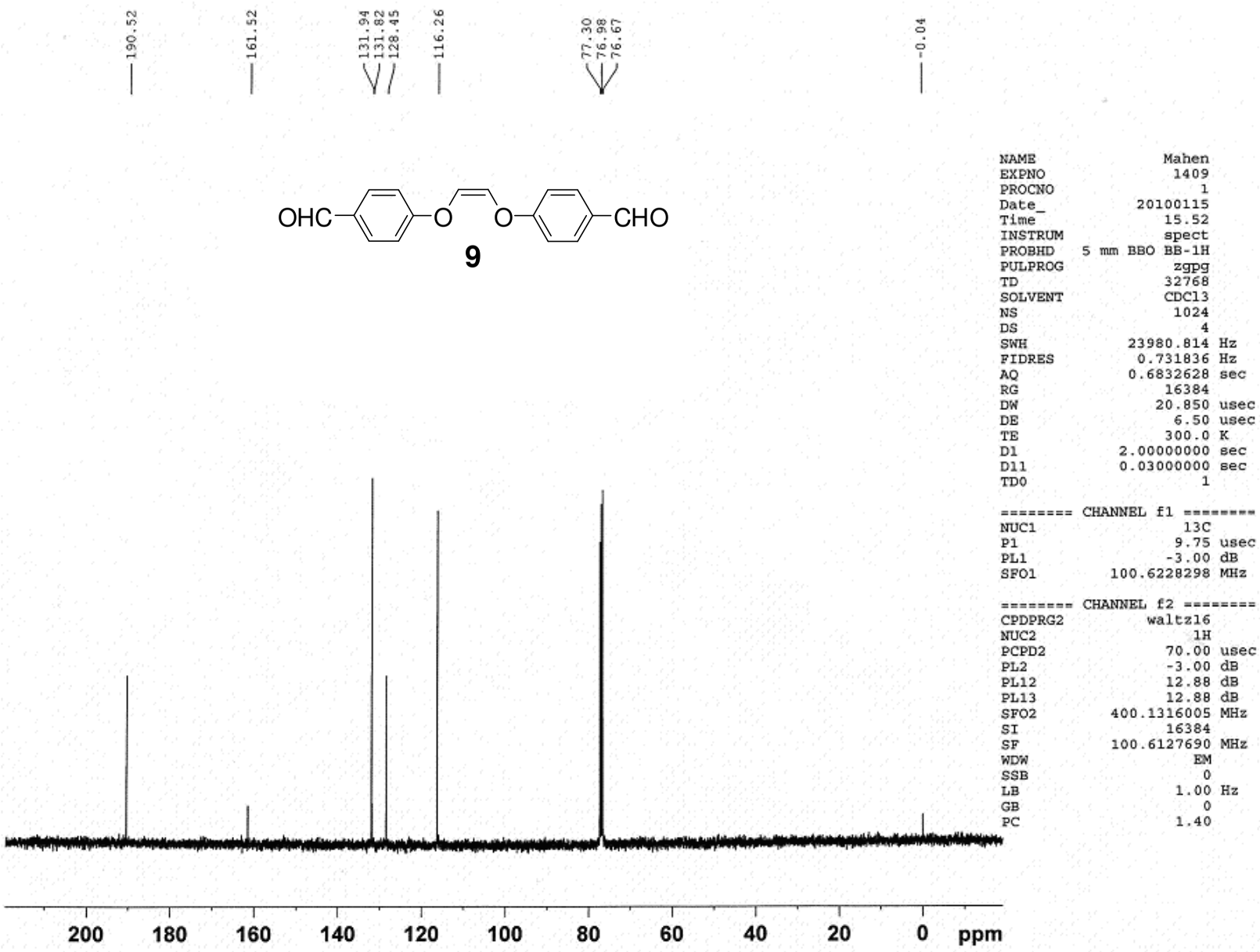


Figure S10. ^{13}C NMR of (Z)-4,4'-(ethene-1,2-diylbis(oxy))dibenzaldehyde (**9**) in $CDCl_3$.

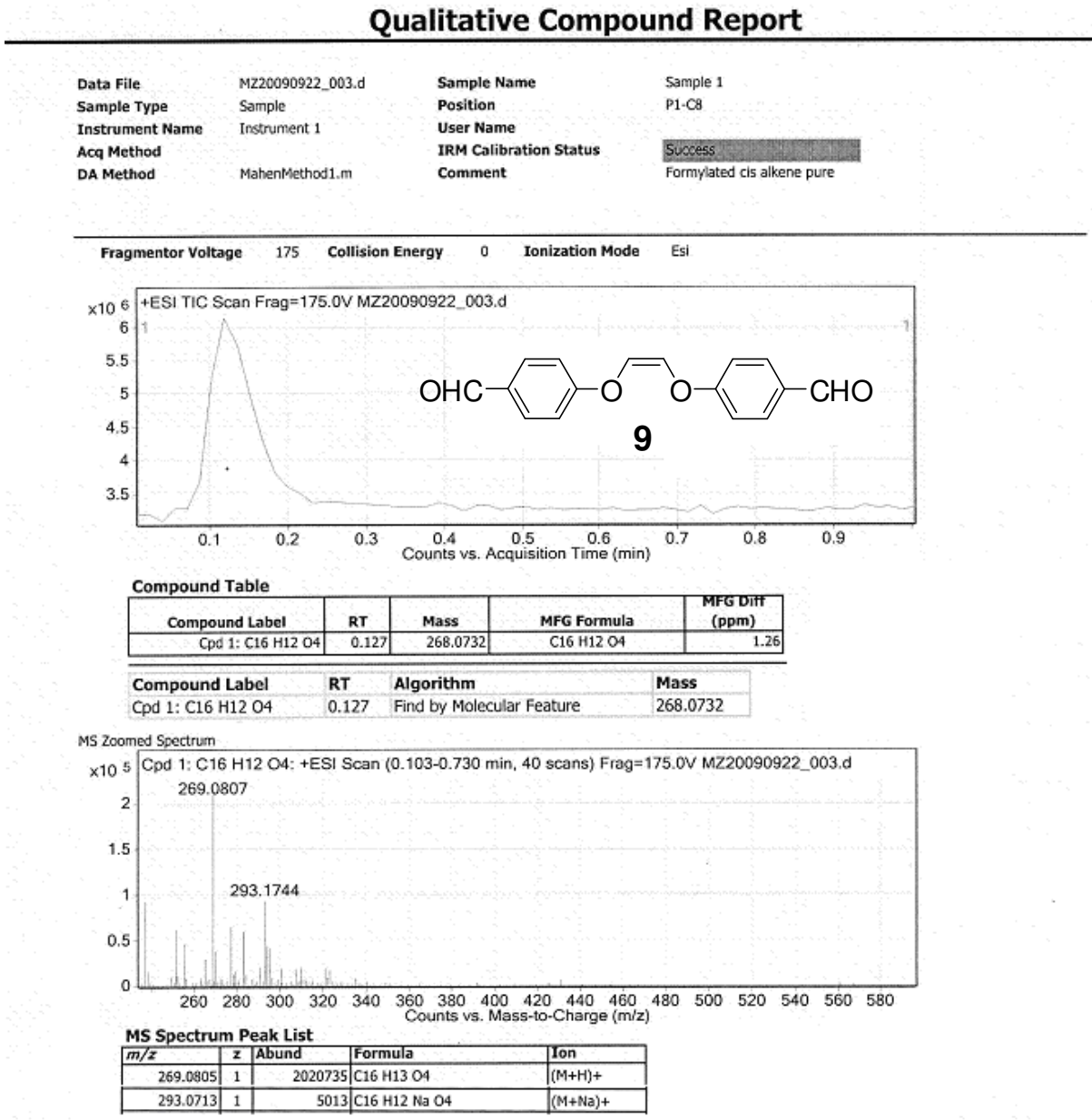


Figure S11. HRMS of (Z)-4,4'-(ethene-1,2-diylbis(oxy))dibenzaldehyde (**9**).

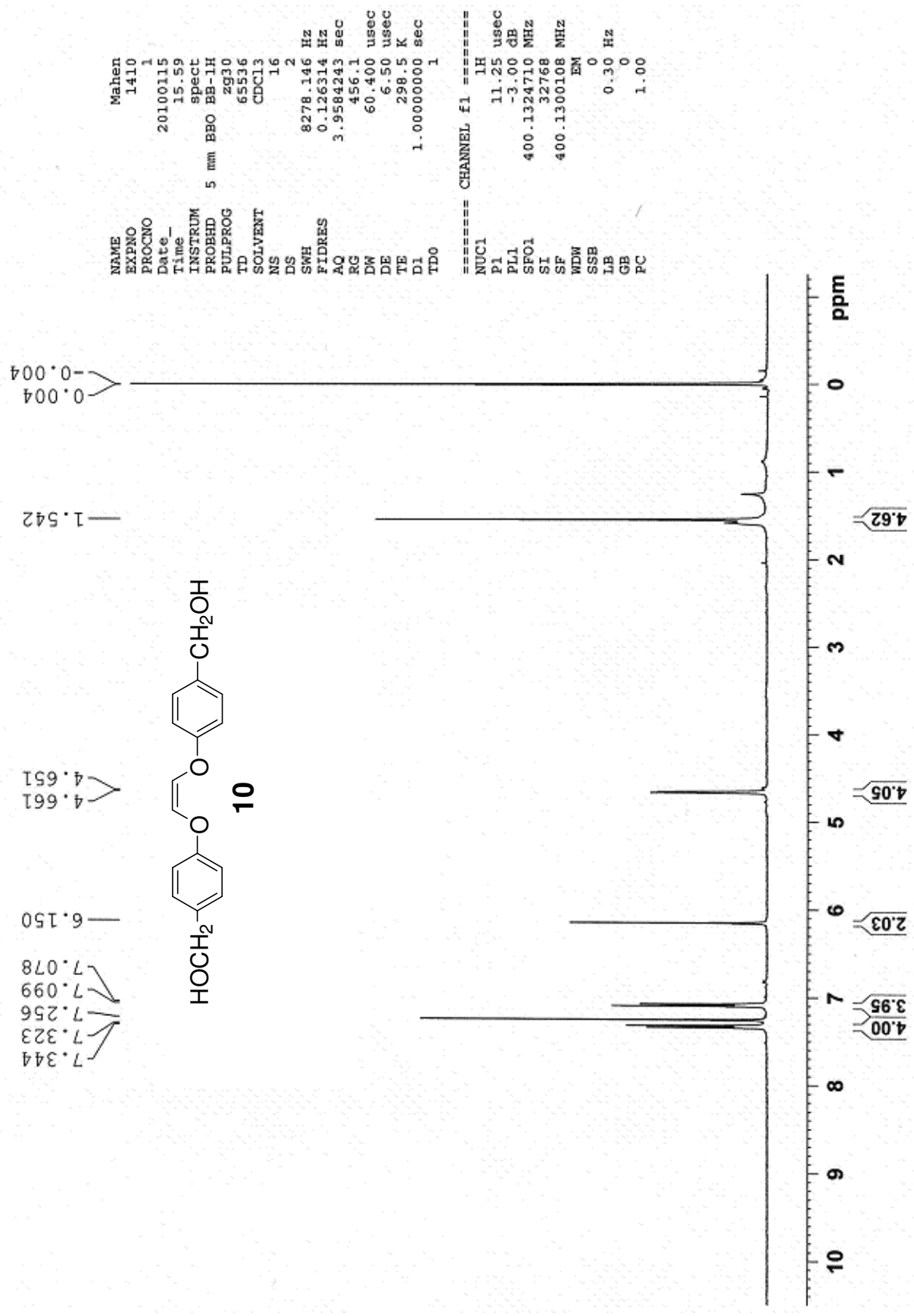


Figure S12. ^{1}H NMR of (*Z*)-(4,4'-(ethene-1,2-diylbis(oxy))bis(1,4-phenylene))-dimethanol (**10**) in $CDCl_3$.

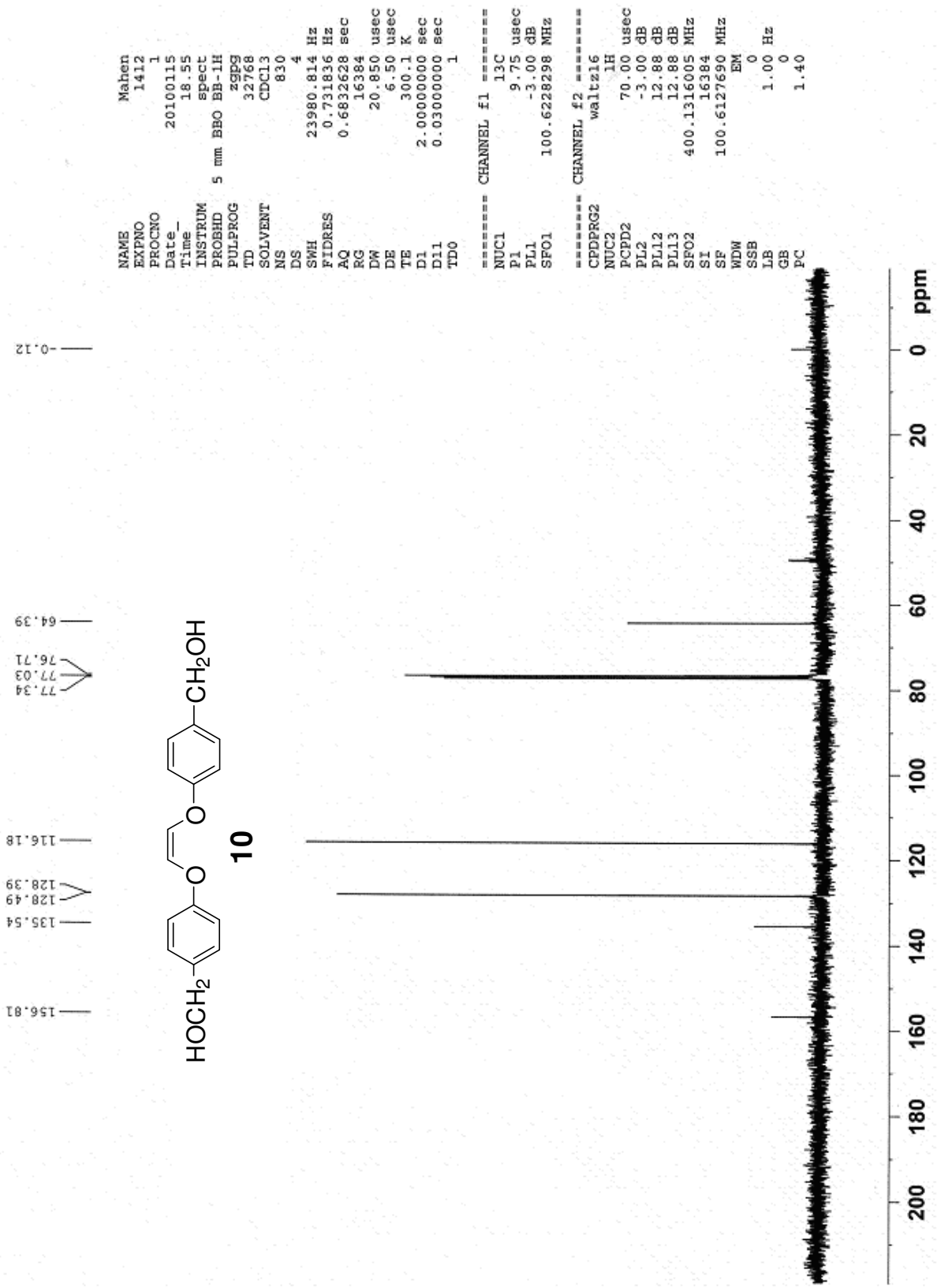
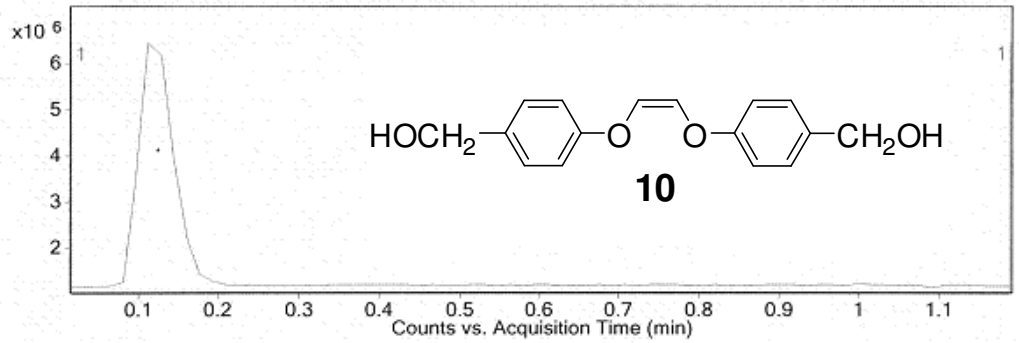


Figure S13. ^{13}C NMR of (Z)-(4,4'-(ethene-1,2-diylbis(oxy))bis(1,4-phenylene))-dimethanol (**10**) in $CDCl_3$.

Qualitative Compound Report

Data File	MZ20091105_004.d	**Sample Name**	Sample 3 (10 mg scale)
Sample Type	Sample	**Position**	P1-F3
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	Success
DA Method	Default.m	**Comment**	EM=272.10 CF=C16H16O4

Fragmentor Voltage 175 **Collision Energy** 0 **Ionization Mode** Esi



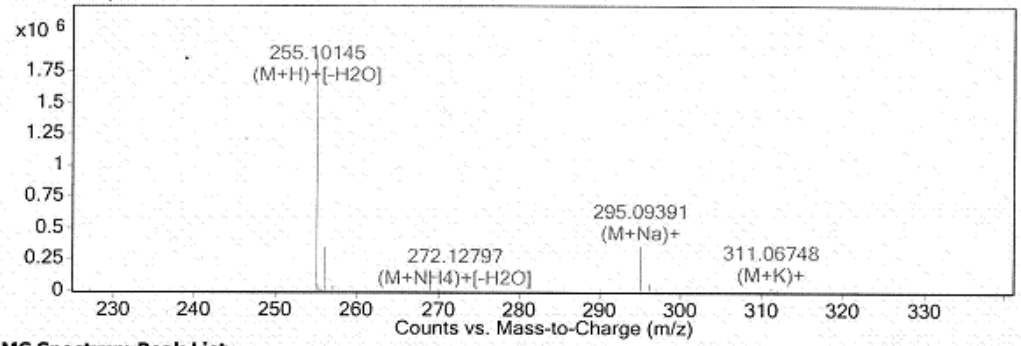
10

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C16 H16 O4	0.1	272.10474	1881770	C16 H16 O4	272.10486	-0.43

Compound Label	RT	Algorithm	Mass
Cpd 1: C16 H16 O4	0.1	Find By Formula	272.10474

MS Zoomed Spectrum



MS Spectrum Peak List

m/z	Calc m/z	Diff(ppm)	z	Abund	Formula	Ion
255.10145	255.10157	-0.46		1881770	C16 H15 O3	(M+H)+[-H2O]
255.24356				55872		
255.30133				21580		
256.1049	256.10496	-0.23		347501	C16 H15 O3	(M+H)+[-H2O]
257.10814	257.1076	2.1		43492	C16 H15 O3	(M+H)+[-H2O]
272.12797	272.12812	-0.55	1	1081	C16 H18 N O3	(M+NH4)+[-H2O]
290.13822	290.13868	-1.61	1	12161	C16 H20 N O4	(M+NH4)+
295.09391	295.09408	-0.57	1	360920	C16 H16 Na O4	(M+Na)+
296.09698	296.09747	-1.66	1	62600	C16 H16 Na O4	(M+Na)+
311.06748	311.06802	-1.72	1	31090	C16 H16 K O4	(M+K)+

--- End Of Report ---

Figure S14. HRMS of (Z)-(4,4'-(ethene-1,2-diylbis(oxy))bis(1,4-phenylene))- dimethanol (**10**).

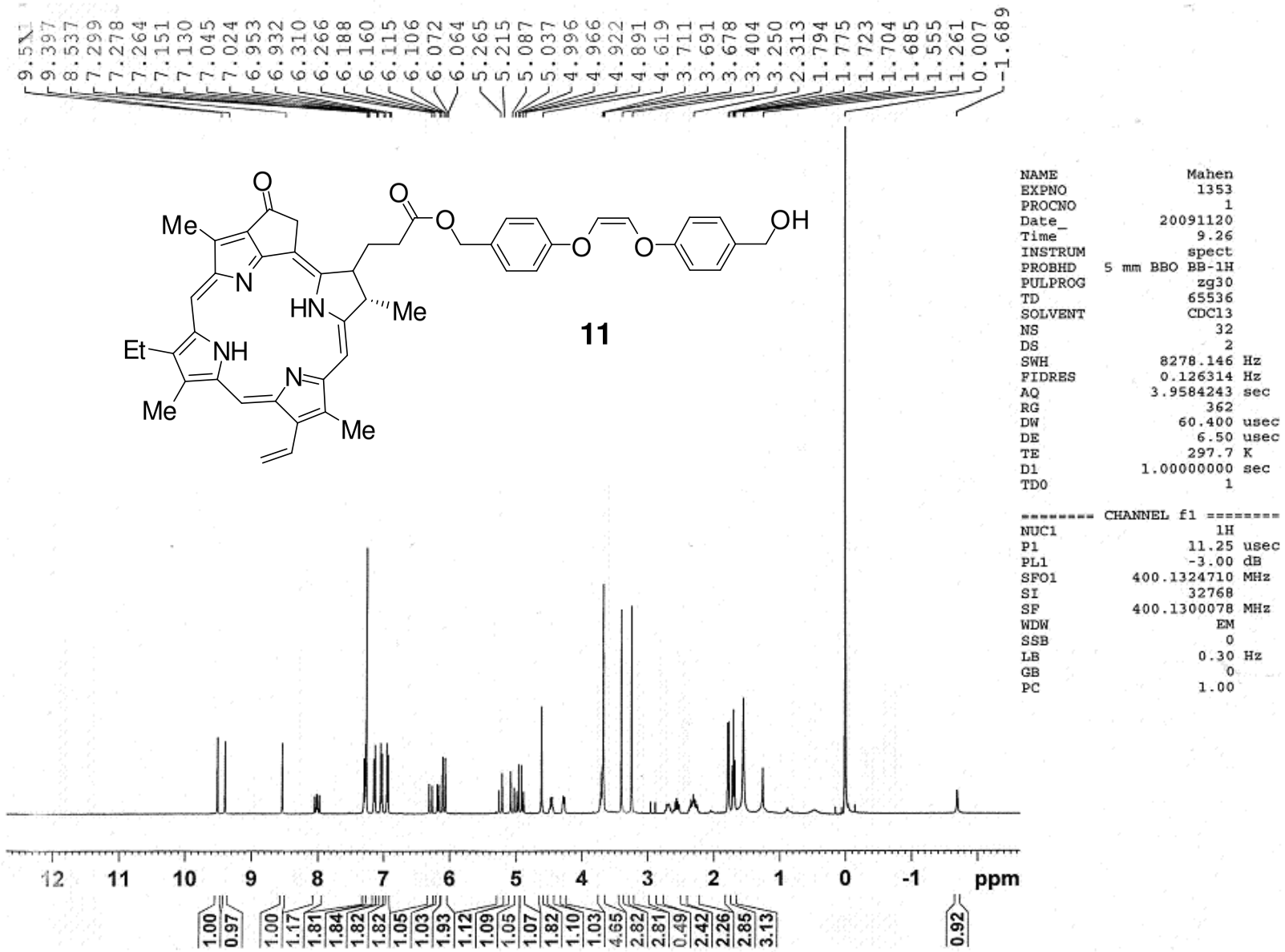


Figure S15. ^{1}H NMR of (Z)-4-[2-(4-hydroxymethyl-phenoxy)-vinyloxy]-benzyl-pyropheophorbide (**11**) in $CDCl_3$.

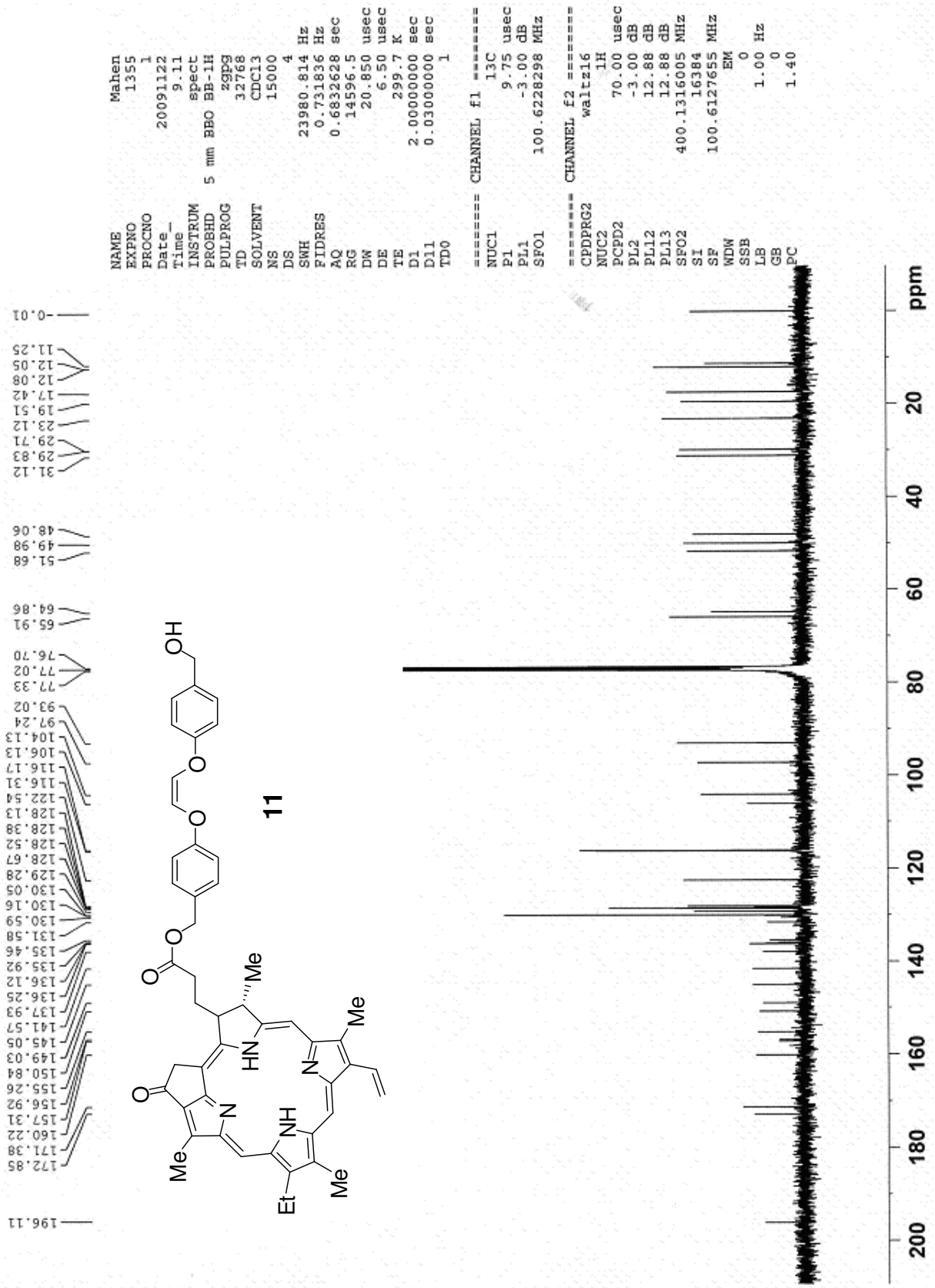
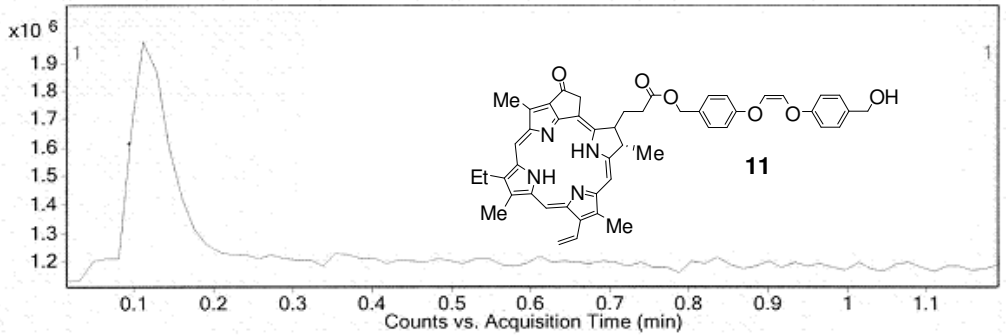


Figure S16. ^{13}C NMR of (Z)-4-[2-(4-hydroxymethyl-phenoxy)-vinyloxy]-benzyl-pyropheophorbide (**11**) in $CDCl_3$.

Qualitative Compound Report

Data File	MZ20091105_003.d	**Sample Name**	Sample 2 (10 mg scale)
Sample Type	Sample	**Position**	P1-F2
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	Success
DA Method	Default.m	**Comment**	EM=788.3574 CF=C49H48N4O6

Fragmentor Voltage 175 **Collision Energy** 0 **Ionization Mode** Esi

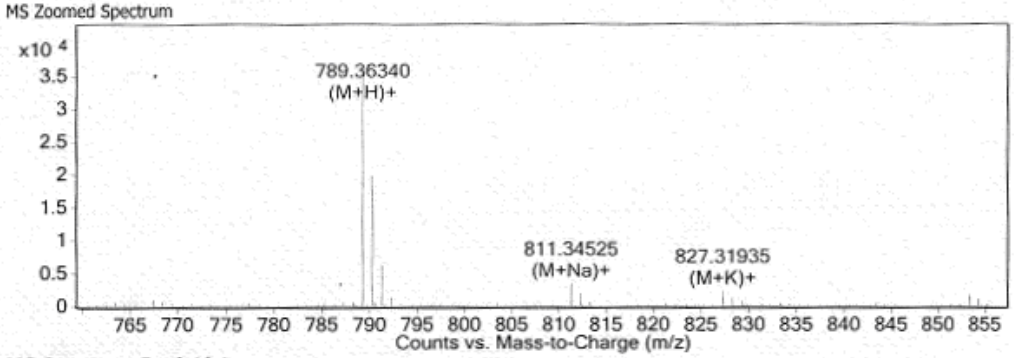


Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C49 H48 N4 O6	0.1	788.35616	35578	C49 H48 N4 O6	788.35739	-1.55

Compound Label	RT	Algorithm	Mass
Cpd 1: C49 H48 N4 O6	0.1	Find By Formula	788.35616

MS Zoomed Spectrum

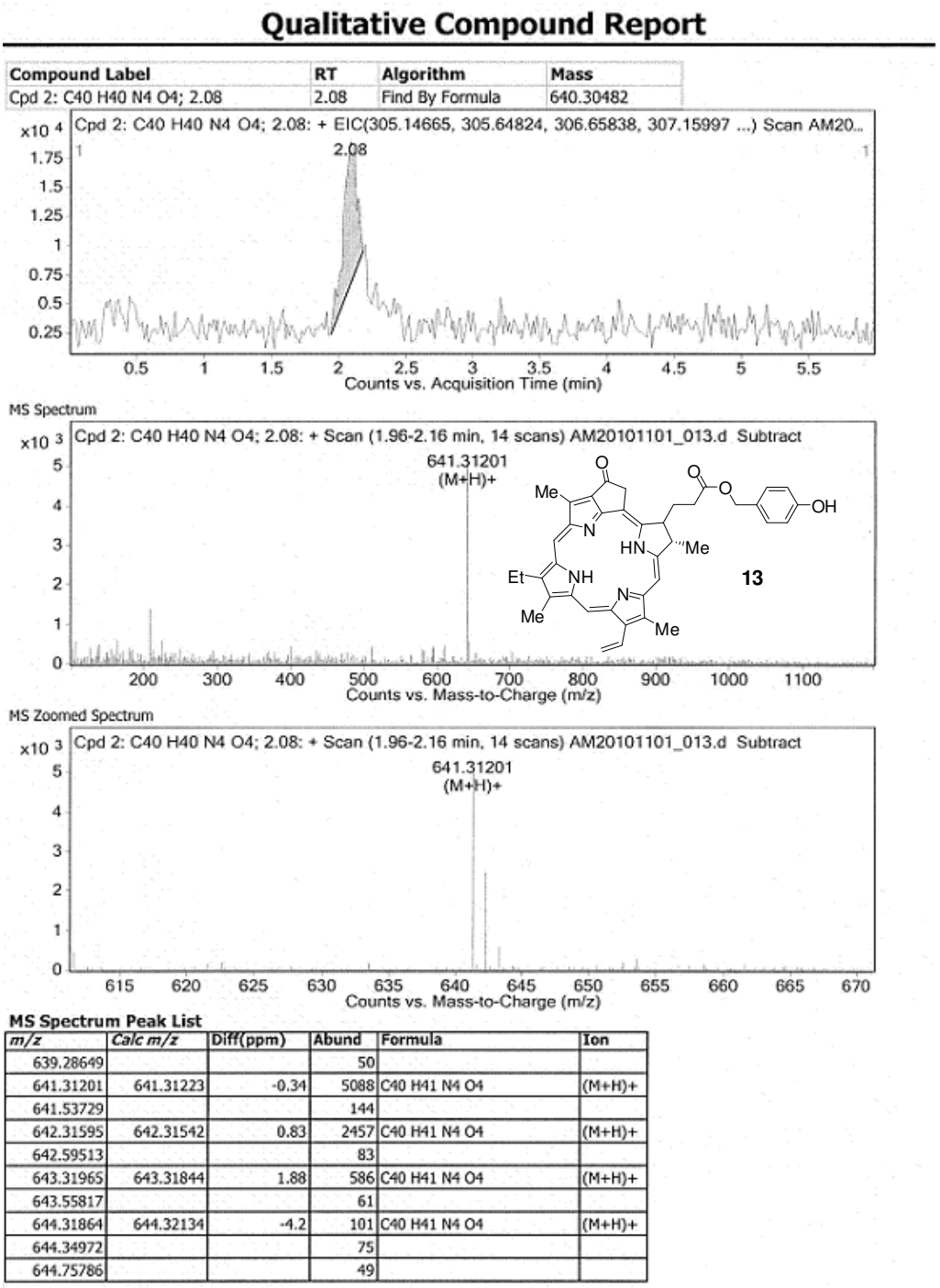


MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
787.38112				669		
789.3634	789.36466	-1.6		35578	C49 H49 N4 O6	(M+H)+
790.36687	790.36788	-1.29		19757	C49 H49 N4 O6	(M+H)+
791.3704	791.37093	-0.67		6178	C49 H49 N4 O6	(M+H)+
792.37633	792.37387	3.1		1377	C49 H49 N4 O6	(M+H)+
811.34525	811.34661	-1.68	1	3380	C49 H48 N4 Na O6	(M+Na)+
812.34956	812.34983	-0.33	1	1986	C49 H48 N4 Na O6	(M+Na)+
827.31935	827.32054	-1.44	1	2256	C49 H48 K N4 O6	(M+K)+
828.32549	828.32376	2.09	1	1141	C49 H48 K N4 O6	(M+K)+
829.32356	829.3243	-0.89	1	799	C49 H48 K N4 O6	(M+K)+

--- End Of Report ---

Figure S17. HRMS of (Z)-4-[2-(4-hydroxymethyl-phenoxy)-vinyloxy]-benzyl-pyropheophorbide (**11**).



MS Spectrum Peak List

m/z	Calc m/z	Diff(ppm)	Abund	Formula	Ion
639.28649			50		
641.31201	641.31223	-0.34	5088	C40 H41 N4 O4	(M+H)+
641.53729			144		
642.31595	642.31542	0.83	2457	C40 H41 N4 O4	(M+H)+
642.59513			83		
643.31965	643.31844	1.88	586	C40 H41 N4 O4	(M+H)+
643.55817			61		
644.31864	644.32134	-4.2	101	C40 H41 N4 O4	(M+H)+
644.34972			75		
644.75786			49		

Figure S18. HRMS of 4-hydroxybenzyl-pyropheophorbide (**13**).

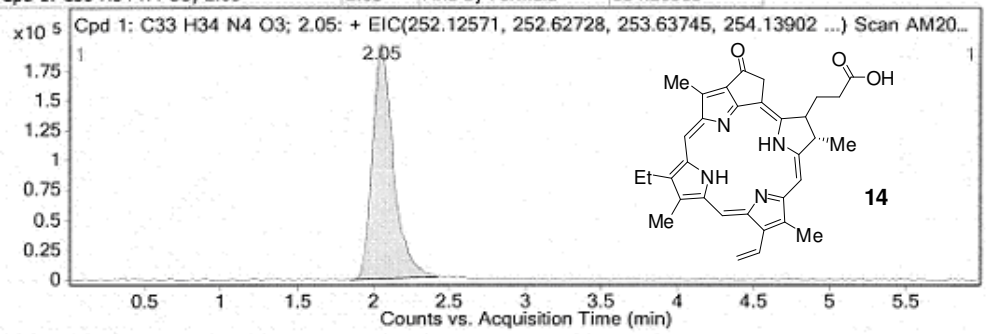
Qualitative Compound Report

Data File	AM20101027_009.d	**Sample Name**	Photocleaved product in MeOH pH=8 after 24 hrs
Sample Type	Sample	**Position**	P1-F5
Instrument Name	Instrument 1	**User Name**	
Acq Method	MahencolumnPhotocleavage.m	**IRM Calibration Status**	Success
DA Method	MahenJAD_DNA.m	**Comment**	

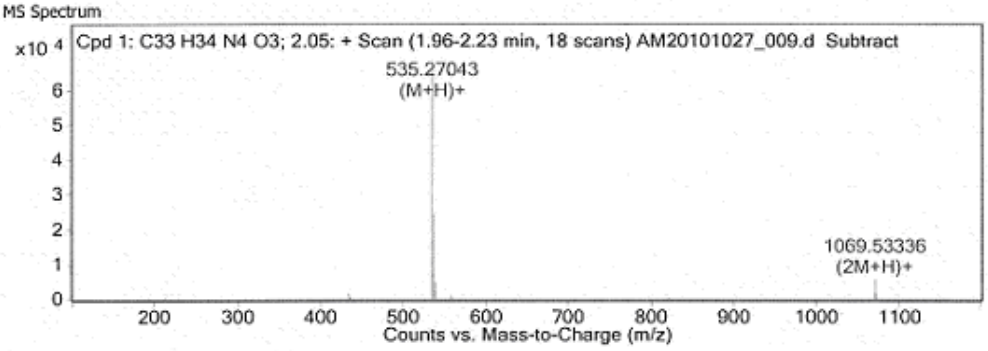
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C33 H34 N4 O3; 2.05	2.05	534.26313	65577	C33 H34 N4 O3	534.26309	0.08

Compound Label	RT	Algorithm	Mass
Cpd 1: C33 H34 N4 O3; 2.05	2.05	Find By Formula	534.26313



MS Spectrum



MS Spectrum Peak List

m/z	Calc m/z	Diff(ppm)	z	Abund	Formula	Ion
534.26191				614		
535.27043	535.27037	0.12		65577	C33 H35 N4 O3	(M+H)+
536.27306	536.27351	-0.83		24393	C33 H35 N4 O3	(M+H)+
537.27605	537.27648	-0.8		4994	C33 H35 N4 O3	(M+H)+
538.27683	538.27933	-4.64		846	C33 H35 N4 O3	(M+H)+
557.25077	557.25231	-2.77	1	994	C33 H34 N4 Na O3	(M+Na)+
1069.53336	1069.53346	-0.09	1	5542	C66 H69 N8 O6	(2M+H)+
1070.53796	1070.5366	1.27	1	4008	C66 H69 N8 O6	(2M+H)+
1071.53962	1071.53965	-0.03	1	1616	C66 H69 N8 O6	(2M+H)+
1091.51579	1091.5154	0.36	1	132	C66 H68 N8 Na O6	(2M+Na)+

--- End Of Report ---

Figure S19. HRMS of pyropheophorbide-a (**14**).

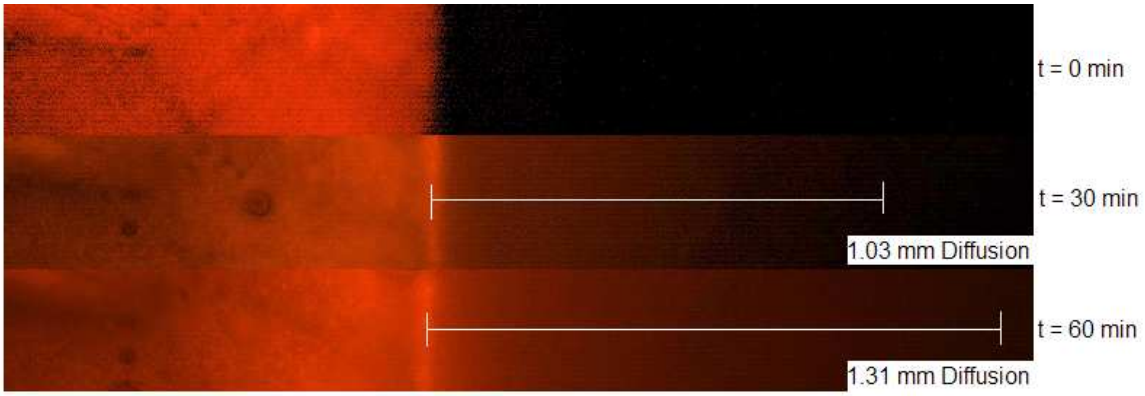


Figure S20. Images taken at 4× magnification with the epifluorescence microscope of the diffusion of photosensitizer **3** away from glass cap into petrolatum at 65 ºC at 0, 30 and 60 min with white light irradiation through the fiber optic device.

References

1. Polívka, T.; Pellnor, M.; Melo, E.; Pascher, T.; Sundström, V.; Osuka, A.; Naqvi, R. K. *J. Phys. Chem. C* **2007**, *111*, 467-476.
2. Dargiewicz, J.; Makarska, M.; Radzki, S. *Colloids Surface A: Physicochem. Eng. Aspects* **2002,** *208*, 159-165.
3. Anvir, D.; Levy, D.; Reisfed, R. *J. Phys. Chem.* **1984**, *88*, 5956-5959.
4. Yang, J.; Bauld, N. L. *J. Org. Chem.* **1999**, *64*, 9251-9253.