In vitro Cytostatic and Cytocidal Activity of Quinoline Antimalarial Drugs vs. Inhibition of Hemozoin Crystal Growth

Supplemental Information Available: Propionate buffer optimization, lipid catalyst concentration optimization, physical and pharmacokinetic properties, antiplasmodial IC_{50} and LD_{50}, and BHIA IC_{50} for all antiplasmodial drugs and drug analogues; ^{1}H and ^{13}C NMR spectra for compounds synthesized in this study (**6**-**9**).

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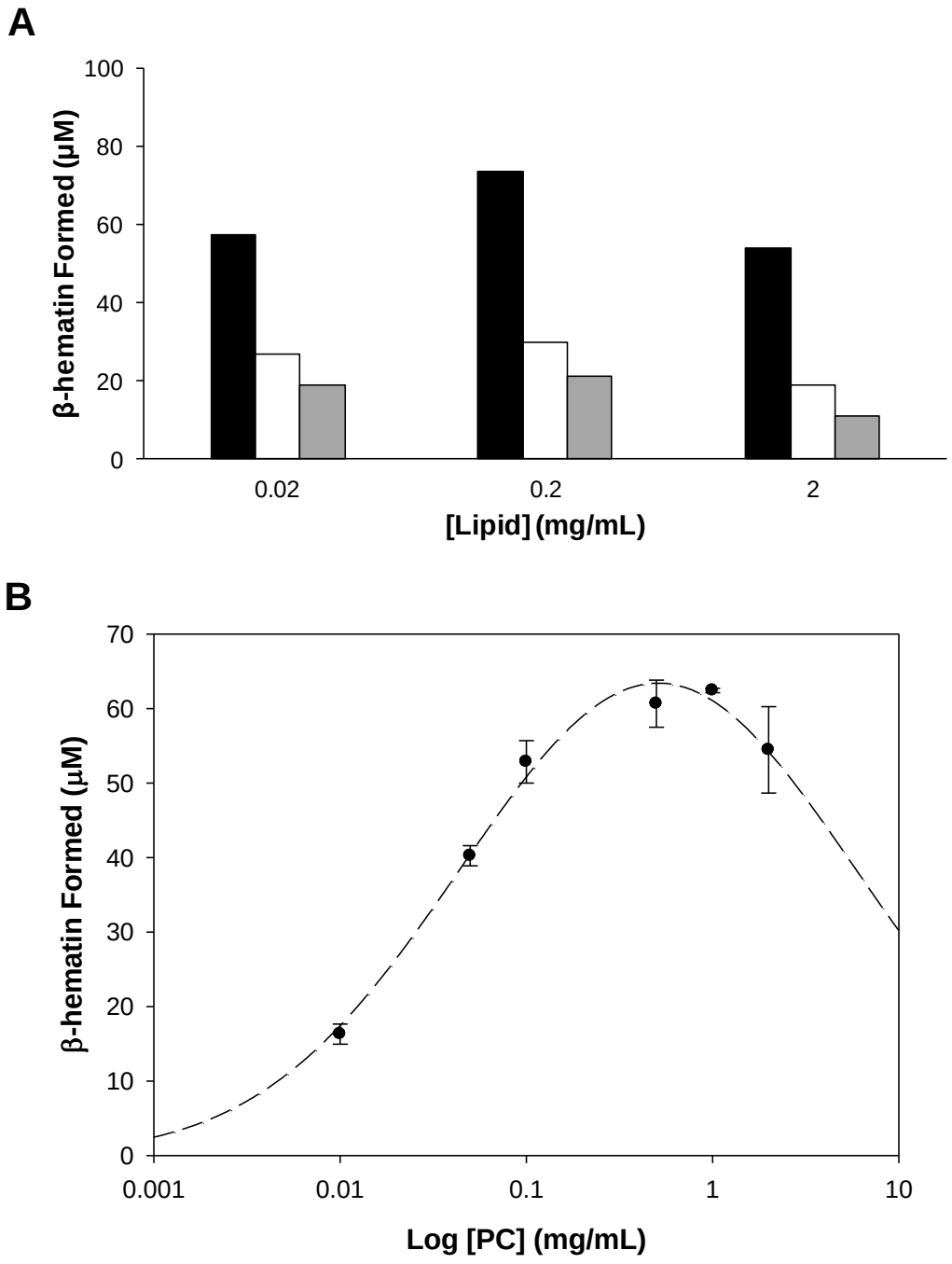


Figure S1. Optimization of lipid catalyst concentration. A) Effect of PC (solid bars), 1-monopalmitin (pMAG, open bars), and 1-monostearin (sMAG, shaded bars) on Hz yield; B) Effect of PC concentration on Hz yield. Hz yield was measured in the presence of 100 μM FPIX, 1 M propionate buffer (pH 5.2) at 37 ^{o}C over a 4 h period. Error bars represent the standard error of the mean resulting from three replicate measurements.

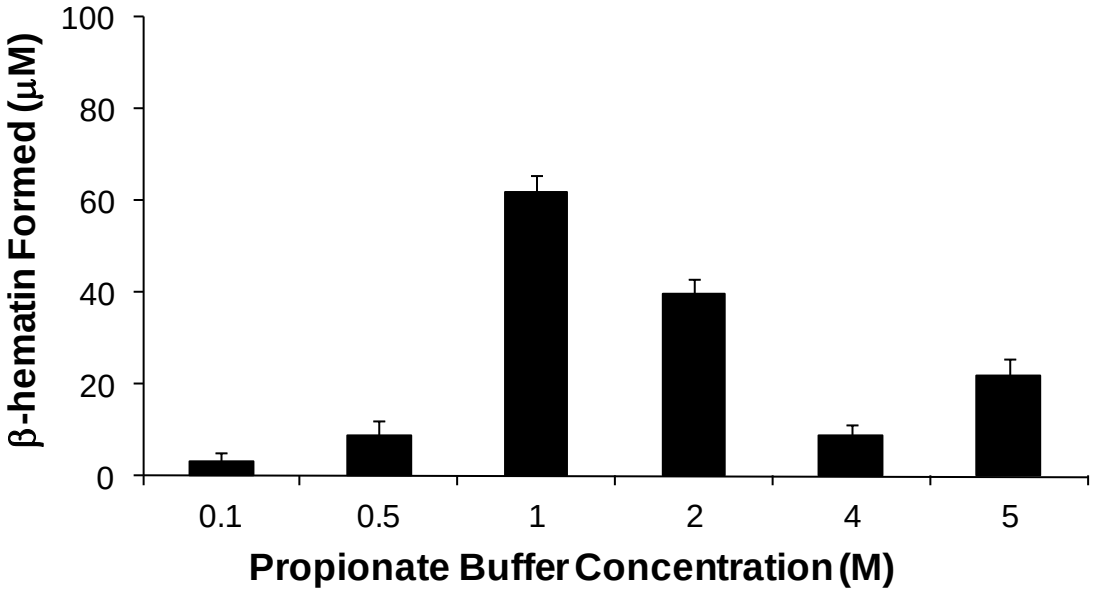


Figure S2. Optimization of propionate buffer concentration. The effect of propionate buffer concentration on Hz yield was measured at pH 5.2 in the presence of 100 μM FPIX and 0.5 mg/mL PC at 37 ^{o}C using the 16 h assay described in the Methods. Error bars represent the standard error of the mean resulting from three replicate measurements.

Table S1. Physical and pharmacokinetic properties, antiplasmodial IC_{50} and LD_{50}, and BHIA IC_{50} for antimalarial drugs and drug analogues used in this work.

					Antiplasmodial IC_{50} (nM)[d]		Antiplasmodial LD_{50} (µM)[e]		BHIA IC_{50} (µM)[d]	
Cpd ID	**MW (g/mol)**	**pKa[a]**	**ClogP[b]**	**Diffusion Coefficient (x 10^{-6} cm^2/s)[c]**	**HB3**	**Dd2**	**HB3**	**Dd2**	**pH 5.6**	**pH 5.2**
CQ	318.19	7.65 9.86	4.65	5.00	19.6 (0.4)	201.5 (9.1)	0.12 (0.01)	16.5 (2.1)	52.9 (8.0)	194.9 (5.6)
QN	324.42	5.69 9.10	3.26	5.00	107.2 (12.4)	265.6 (14.6)	9.1 (0.4)	36.3 (9.1)	42.5 (8.3)	255.4 (22.7)
QD	324.42	5.69 9.10	3.26	5.00	41.9 (6.0)	174.2 (3.1)	0.43 (0.1)	33.6 (0.1)	27.2 (2.7)	176.2 (4.9)
AQ	355.86	5.84 9.88	4.09	4.82	10.0 (3.3)	27.7 (2.9)	0.04 (0.007)[f]	0.05 (0.004)[f]	22.1 (0.9)	70.1 (1.3)
1	294.95	5.11 8.59	4.58	5.26	9530.0 (39.5)	5500.0 (28.2)	79.9 (0.1)	94.4 (0.8)	39.6 (2.2)	312.6 (10.1)
2	305.90	7.50 9.81	4.34	4.99	6.0 (0.7)	26.0 (3.5)	0.23 (0.01)	0.52 (0.01)	8.2 (0.9)	37.8 (6.2)
3	319.90	7.56 9.48	4.82	4.82	12.0 (0.9)	199.0 (11.1)	3.8 (0.1)	15.7 (1.0)	11.2 (2.0)	65.2 (8.1)
4	363.92	4.93 7.48 9.58	5.16	4.45	95.0 (10.6)	169.0 (16.2)	7.1 (0.1)	41.3 (0.1)	17.0 (2.5)	117.0 (12.6)

5	362.90	7.70 9.35	3.15	4.48	79.0 (5.9)	94.0 (10.7)	0.80 (0.01)	51.5 (5.1)	7.2 (1.2)	142.4 (14.9)
6	249.74	7.65 10.04	2.44	5.97	2990.0 (31.8)	2390.0 (33.4)	45.2 (0.1)	17.4 (1.3)	44.5 (7.5)	209.0 (17.1)
7	292.92	7.44 9.17	4.40	4.46	> 10000	3720.0 (42.5)	2.8 (0.02)	2.7 (0.01)	53.0 (8.2)	96.0 (12.4)
8	451.00	7.64 8.05	4.39	4.13	1680.0 (23.5)	6970.0 (51.2)	2.8 (0.02)	3.9 (0.07)	52.5 (6.1)	172.5 (16.3)
9	350.89	7.64 8.99 9.55	1.40	4.82	1390.0 (19.5)	8070.0 (62.3)	8.6 (0.05)	2.8 (0.01)	117.5 (19.2)	121.5 (18.3)

[a]Calculated using the SPARC online calculator (sparc.chem.uga.edu/sparc/liqpka/index.cfm?ionize=N13). pKas are for the quinolinyl and side chain aliphatic nitrogens, respectively, with the former listed from left to right beginning at the quinoline branch point (see Figure 5).

[b] Calculated for octanol/water using the SPARC online calculator.

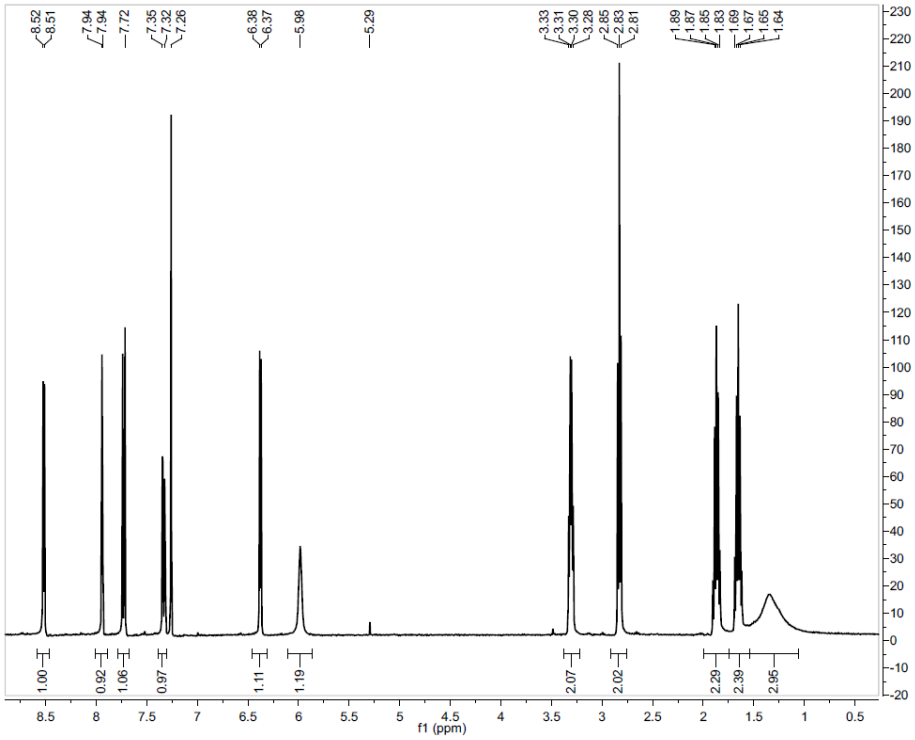
[c]Calculated for water diffusion using the SPARC online calculator.

[d]IC_{50} values are an average of three independent trials, each performed in triplicate (9 replicates total). SEM is shown in parentheses.

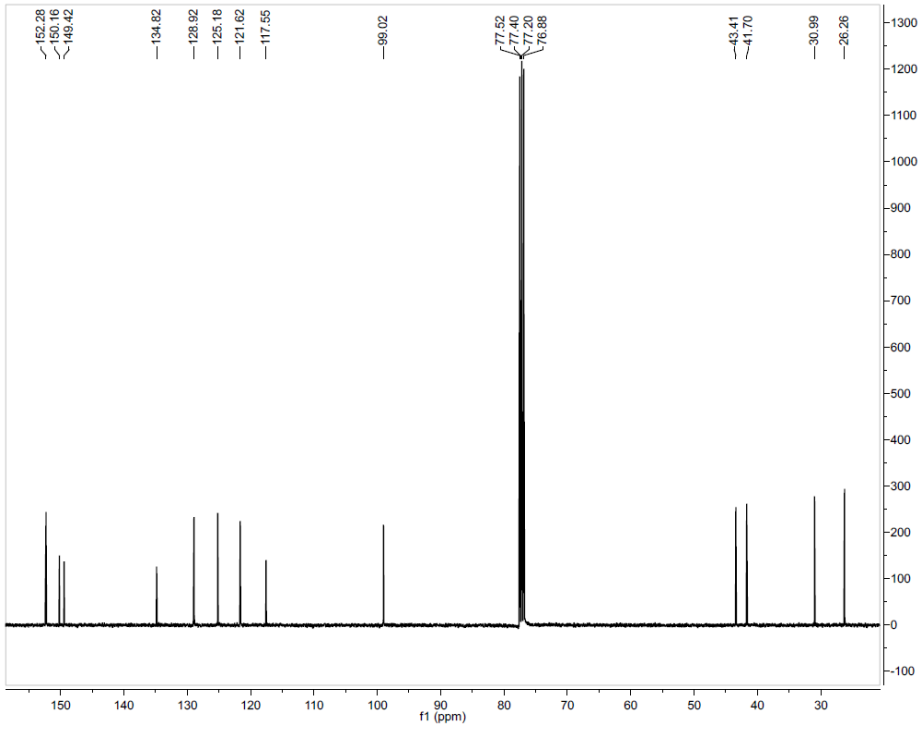
[e]LD_{50} values are an average of two independent trials, each performed in triplicate (6 replicates total). SEM is shown in parentheses.

[f]Paguio MF, Bogle KL, Roepe PD. 2011. ***Plasmodium falciparum*** **resistance to cytocidal versus cytostatic effects of chloroquine.** Mol. Biochem. Parasitol. **178:**1-6.

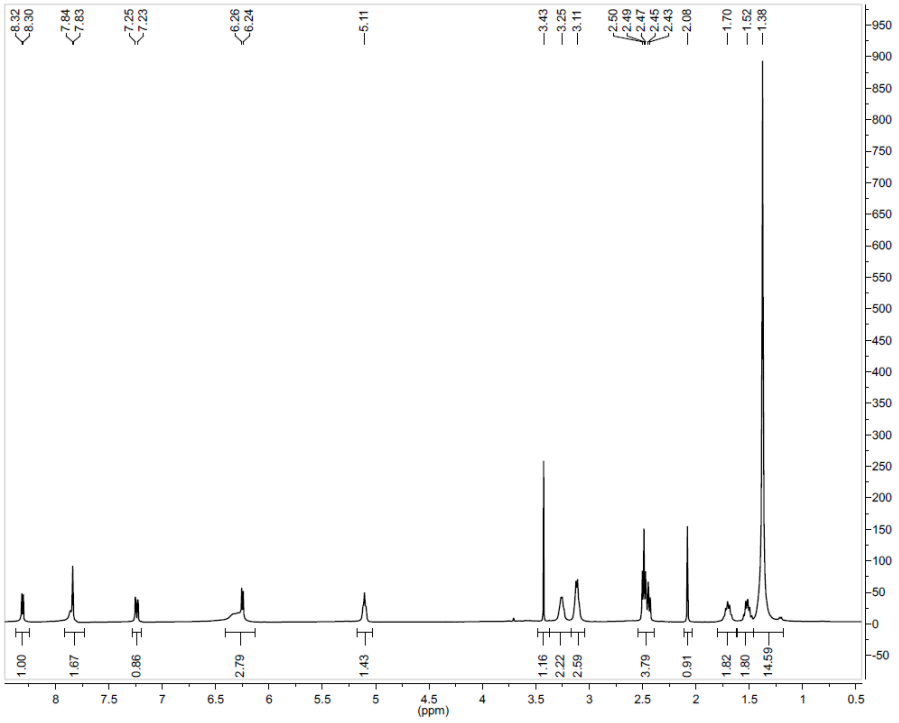
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) for 6



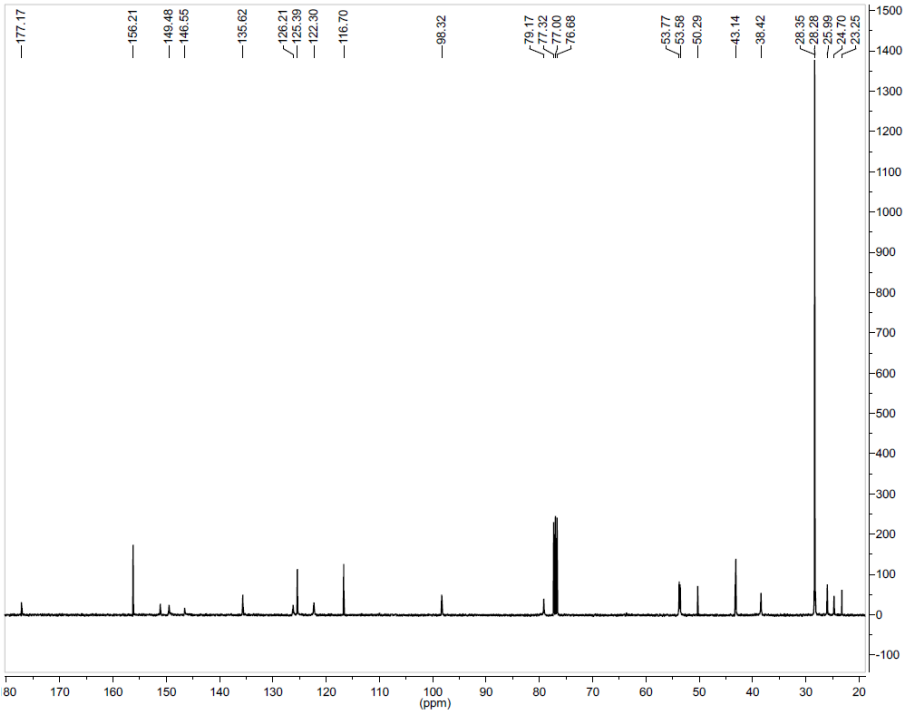
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) for 6



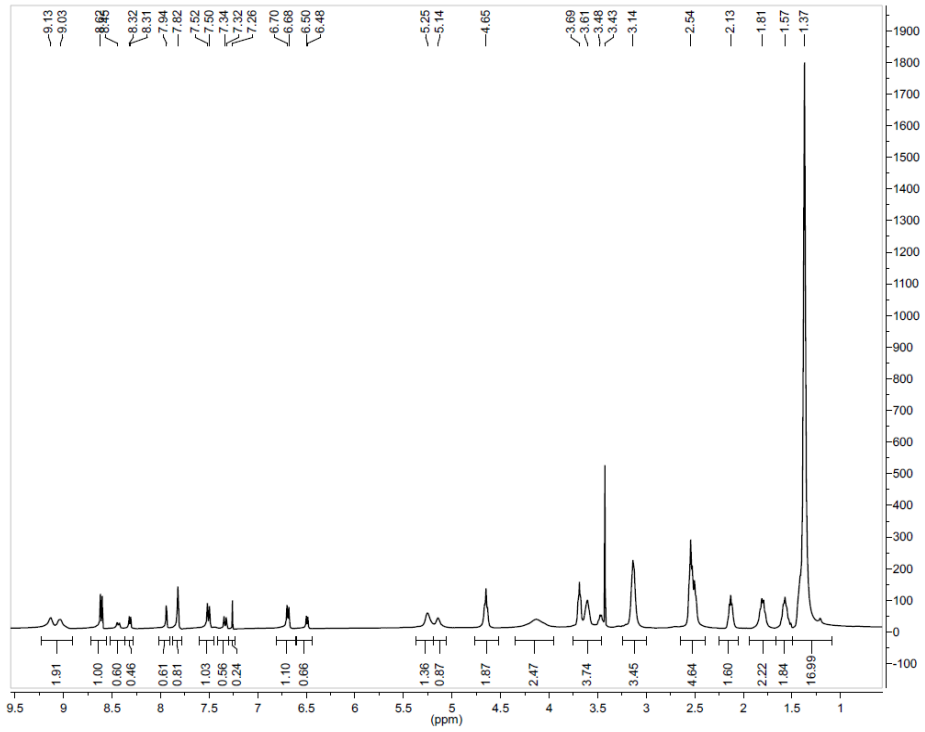
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) for 7



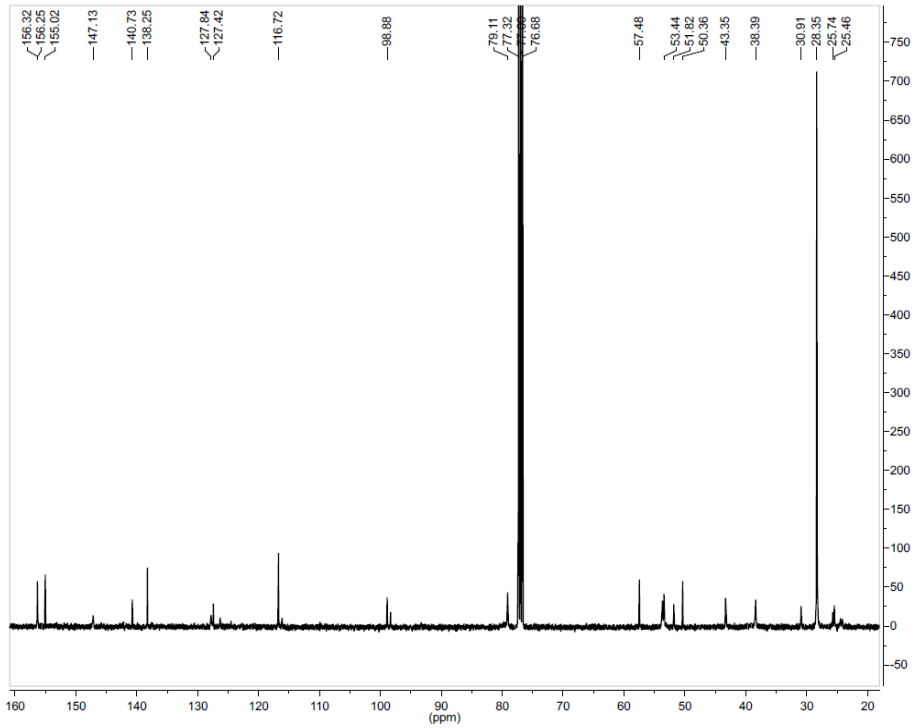
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) for 7



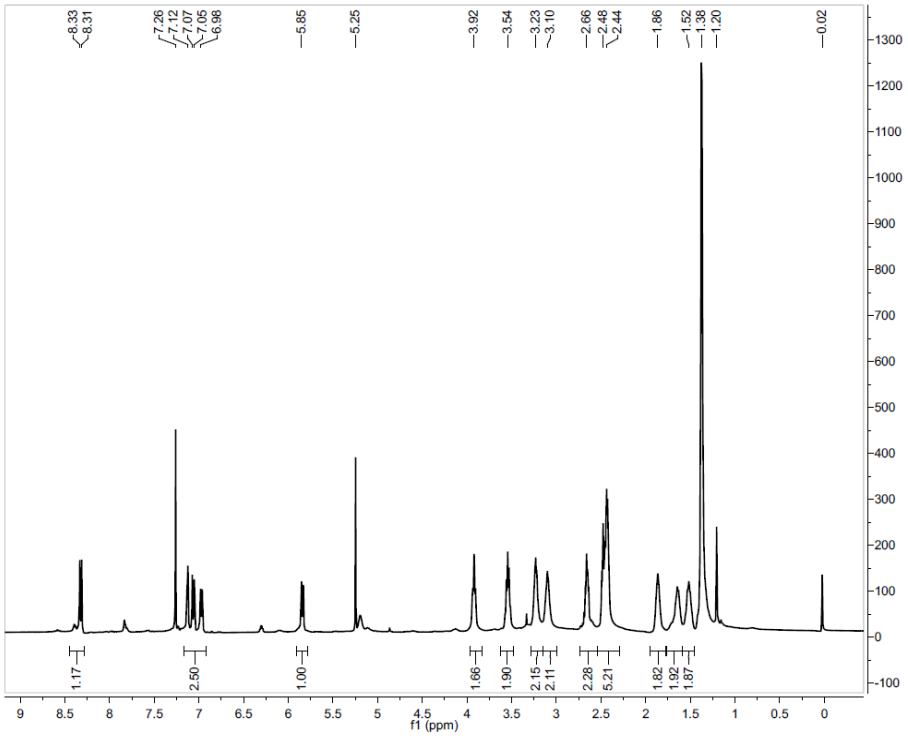
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) for 8



^{13}C NMR Spectrum (100 MHz, $CDCl_3$) for 8



^{1}H NMR Spectrum (400 MHz, $CDCl_3$) for 9



^{13}C NMR Spectrum (100 MHz, $CDCl_3$) for 9