Supporting Information For:

Novel TPP^+ carrier to target mitochondria without uncoupling oxidative phosphorylation

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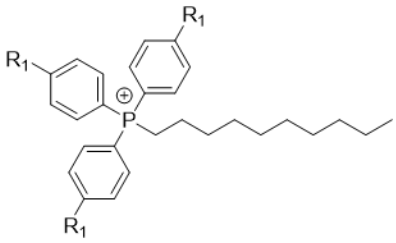
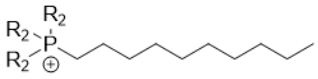
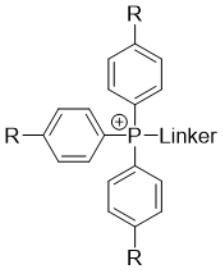
Supplemental Tables:





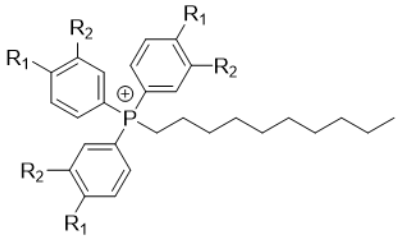
Sr. No.	R_1	Hückel charge	Sr. No.	R_2	Hückel charge
1	-H	0.326	15	Pentafluorophenyl	0.305
	Electron Withdrawing		16	4-Pyridyl	0.360
2	$-CF_3$	0.523			
3	$-NO_2$	0.388			
4	-CN	0.377			
5	-COOH	0.349			
6	$-SO_3H$	0.326			
7	$-COOCH_3$	0.349			
8	-Cl	0.328			
9	-F	0.328			
	Electron Donating				
10	$-NH_2$	0.294			
11	-OH	0.299			
12	$-OCH_3$	0.299			
13	$-CH_3$	0.310			
14	$-NHCOCH_3$	0.288			

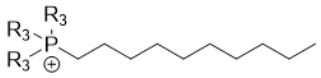
Supplemental Table S1: Hückel charge calculations for charge density on the phosphorus atom of various aryl-modified TPP^+-decyl conjugates.



Sr. No.	R	Linker	cLogP
1	$-OCH_3$	Decyl	8.399
2	$-CH_3$	Decyl	9.425
3	-H	Decyl	8.531
4	-Cl	Decyl	10.307
5	-F	Decyl	8.990
6	$-CF_3$	Decyl	11.335
7	$-OCH_3$	Butyl	5.747
8	$-CH_3$	Butyl	6.773
9	-H	Butyl	5.879
10	-Cl	Butyl	7.655
11	-F	Butyl	6.337
12	$-CF_3$	Butyl	8.683
13	$-OCH_3$	Benzyl	6.138
14	$-CH_3$	Benzyl	7.164
15	-H	Benzyl	6.270
16	-Cl	Benzyl	8.046
17	-F	Benzyl	6.729
18	$-CF_3$	Benzyl	9.074

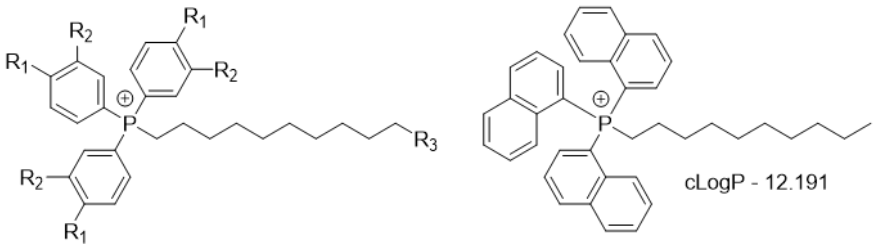
Supplemental Table S2: LogP calculation for all first generation modified TPP^+ compounds





Sr. No.	R_1	R_2	Hückel charge	Sr. No.	R_3	Hückel charge
	Electron Donating			5	Phenyl	0.326
1	$-OCH_3$	-H	0.299	6	1-Naphthyl	0.363
2	-H	$-OCH_3$	0.324			
	Electron Withdrawing					
3	-F	-H	0.328			
4	-H	-F	0.325			

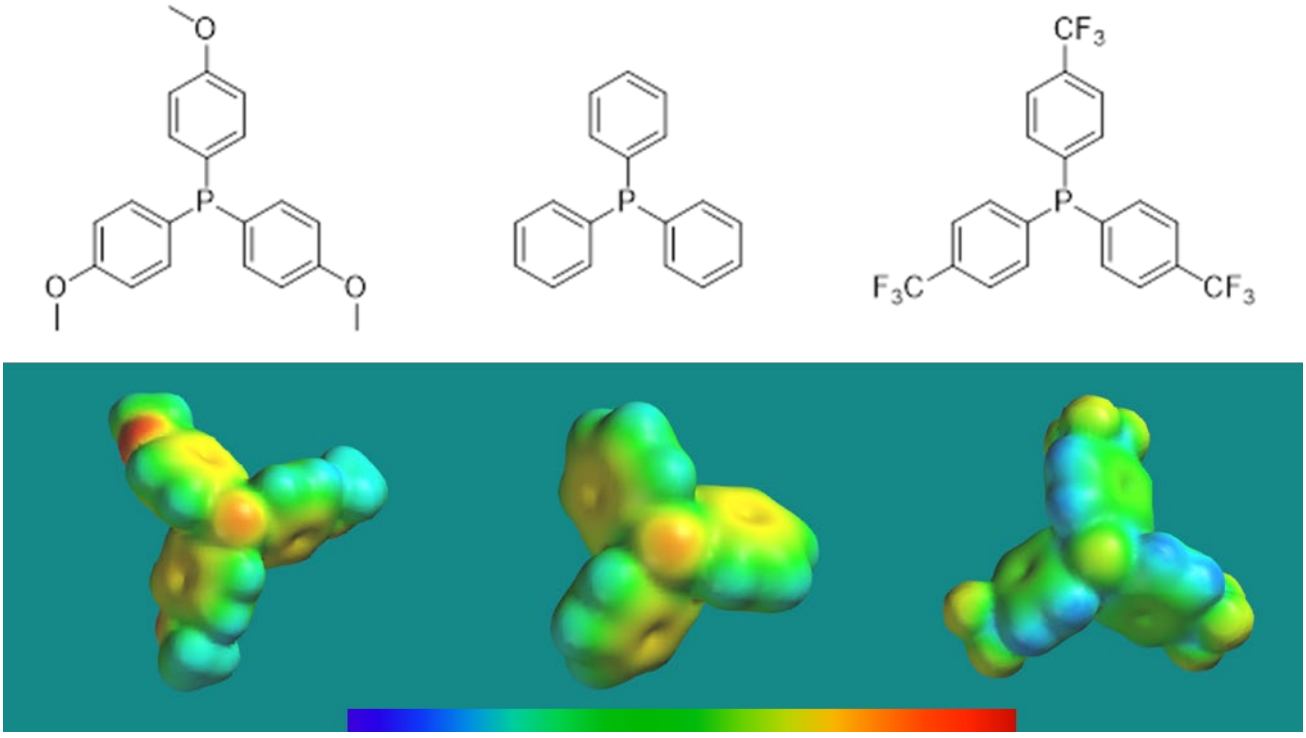
Supplemental Table S3: Hückel charge calculations for charge density on the phosphorus atom for sets of modified TPP-decyl compounds which attempt to vary either Hückel charge or lipophilicity, while keeping the other variable constant.



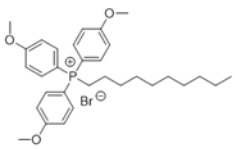
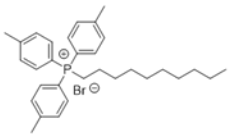
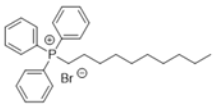
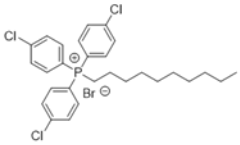
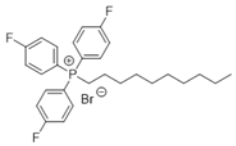
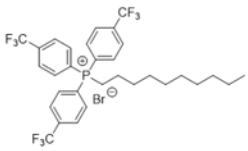
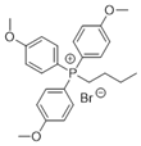
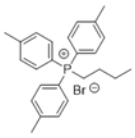
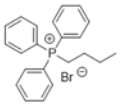
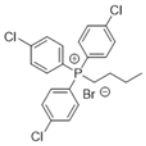
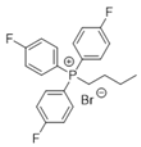
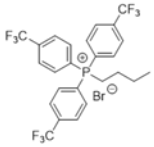
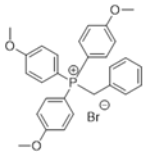
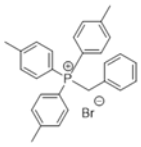
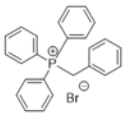
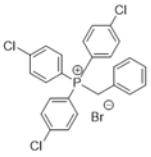
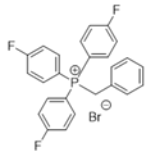
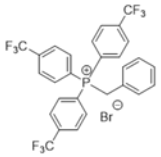
Sr. No.	R_1	R_2	R_3	cLogP
1	-H	-H	-H	8.531
2	$-OCH_3$	-H	-H	8.399
3	-H	$-OCH_3$	-H	8.510
4	-F	-H	-H	8.990
5	-H	-F	-H	9.101
6	$-OCH_3$	-H	$-NH_2$	6.970
7	-H	-H	$-NH_2$	7.102
8	$-CF_3$	-H	$-NH_2$	9.906
9	$-OCH_3$	-H	-COOH	7.479
10	-H	-H	-COOH	7.611
11	$-CF_3$	-H	-COOH	10.415

Supplemental Table S4: LogP calculation for second generation TPP^+ compounds.

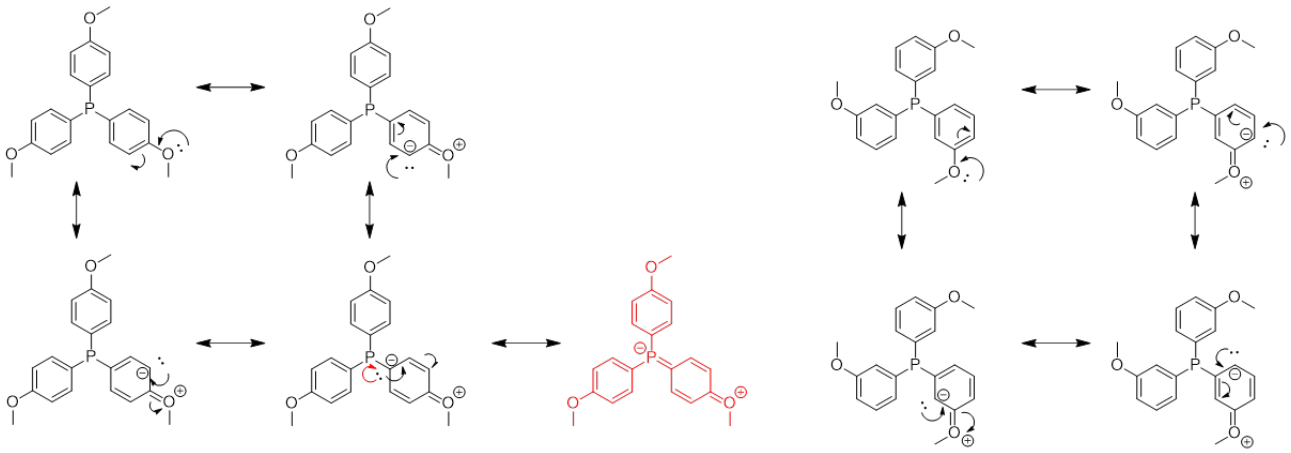
Supplementary Figures:



Supplemental Figure S1: Electrostatic potential map of triphenylphosphine with para-methoxy substitution (left), no substitution (center) and para-trifluoromethyl substitution (right). As the methoxy groups donate electrons through resonance effect, they increase the electron density on the phosphorus, thereby making the phosphorus atom electron rich, as shown by increase in the red color over triphenylphosphine. On the other hand, the trifluoromethyl groups withdraw electrons from the phosphorus, making it less electron rich (less red) than the unsubstituted triphenylphosphine.

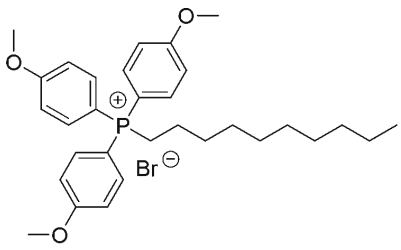
Modified TPP⁺ with electron donating substituents		Unsubstituted traditional TPP⁺		Modified TPP⁺ with electron withdrawing substituents	
					
4-OMe-TPP-DC (**9**)	4-CH_3-TPP-DC (**10**)	H-TPP-DC (**11**)	4-Cl-TPP-DC (**12**)	4-F-TPP-DC (**13**)	4-CF_3-TPP-DC (**14**)
					
4-OMe-TPP-BU (**15**)	4-CH_3-TPP-BU (**16**)	H-TPP-BU (**17**)	4-Cl-TPP-BU (**18**)	4-F-TPP-BU (**19**)	4-CF_3-TPP-BU (**20**)
					
4-OMe-TPP-BZ (**22**)	4-CH_3-TPP-BZ (**23**)	H-TPP-BZ (**24**)	4-Cl-TPP-BZ (**25**)	4-F-TPP-BZ (**26**)	4-CF_3-TPP-BZ (**27**)

Supplemental Figure S2: Panel of first-generation aryl modified TPP^+ conjugates with the decyl, butyl and benzyl linker chains.

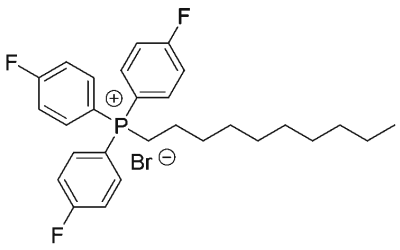


Para-methoxy substitution Meta-methoxy substitution

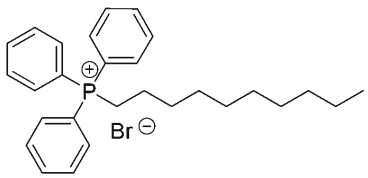
Supplemental Figure S3: Resonance of a para substituent and meta substituent and how it affects the charge density of the phosphorus atom in triphenylphosphine.



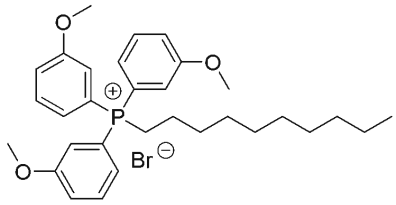
4-OMe-TPP-DC (**9**)



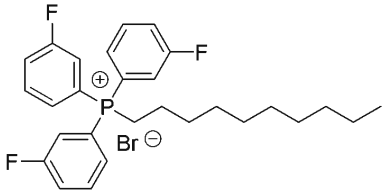
4-F-TPP-DC (**13**)



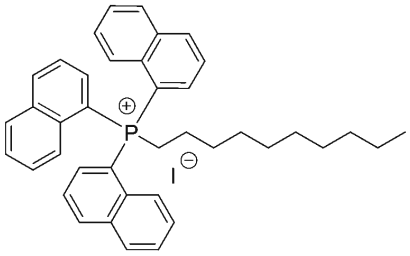
H-TPP-DC (**11**)



3-OMe-TPP-DC (**30**)

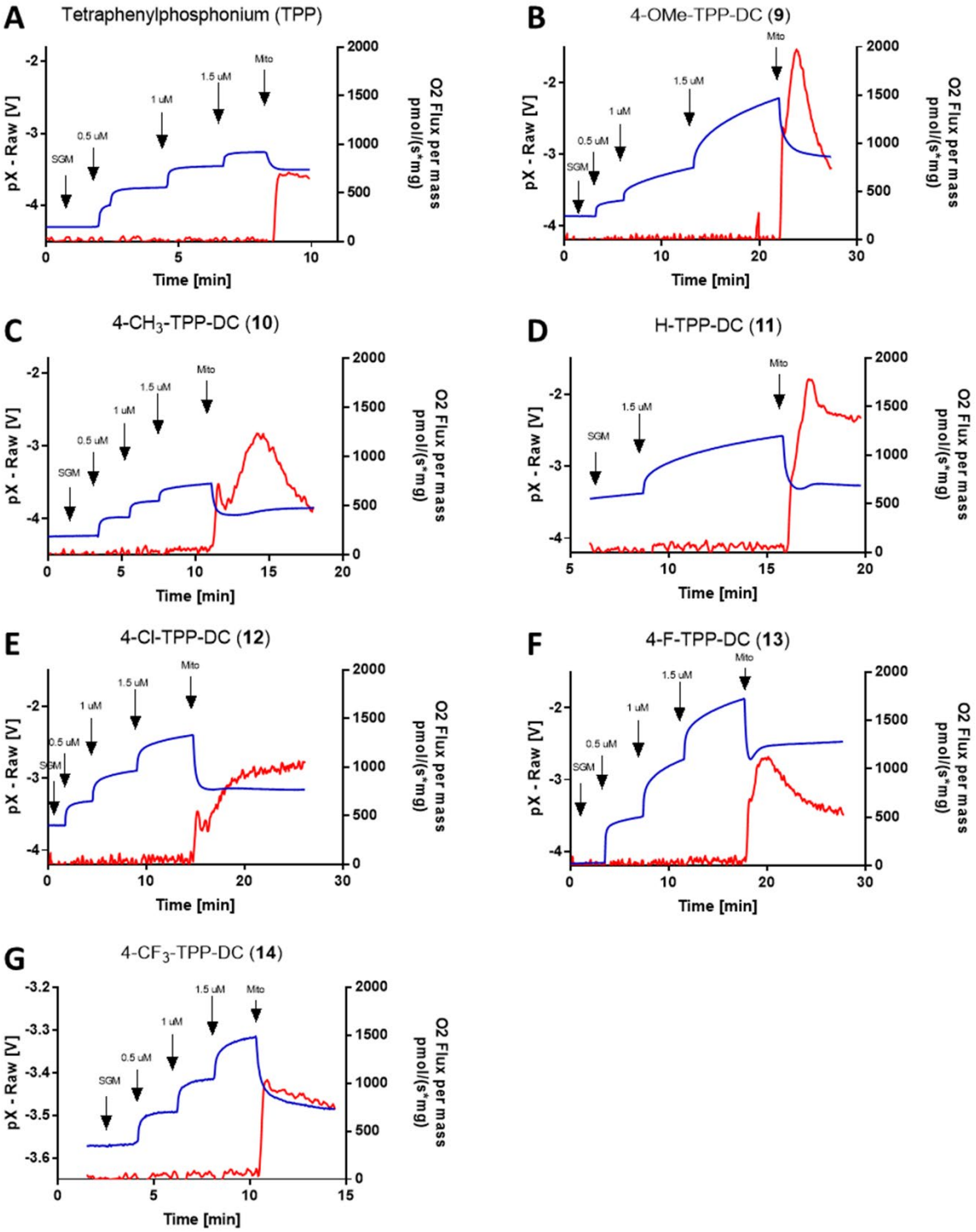


3-F-TPP-DC (**31**)



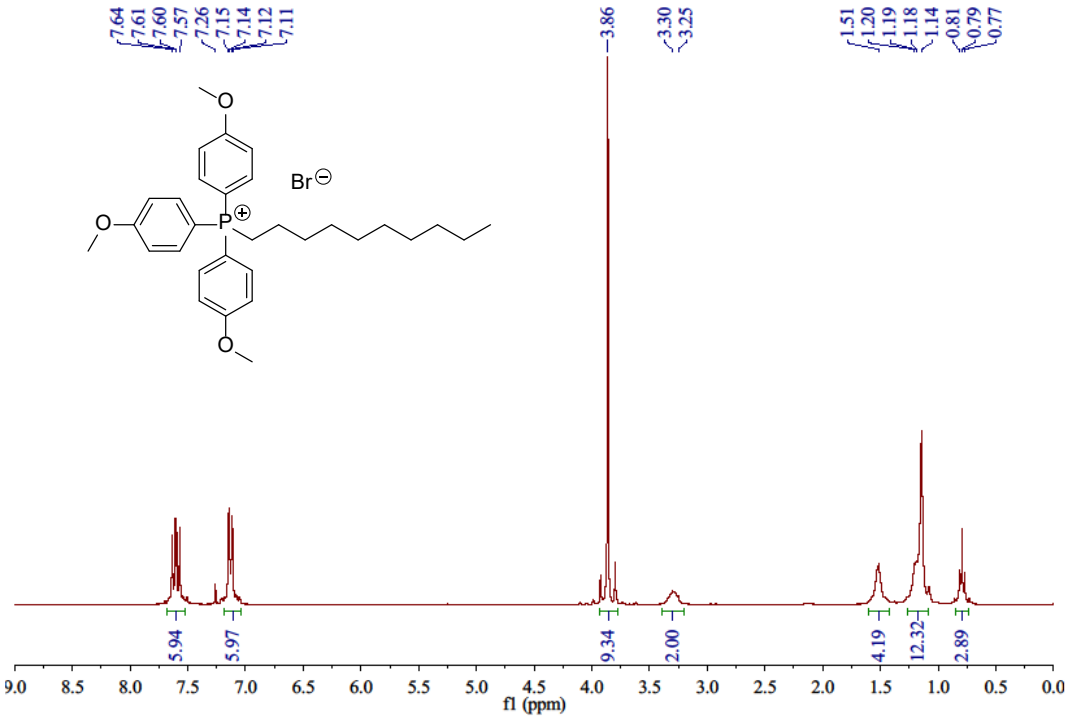
Tris(1-Napthyl)-P-DC (**33**)

Supplemental Figure S4: The second-generation aryl modified TPP^+ conjugates. Compounds **30**, **31**, **33** were designed to alter either Hückel Charge or Lipophilicity as one variable while keeping the other variable constant as compared to cognate first-generation analogs, compounds **9**, **13** and **11** respectively.

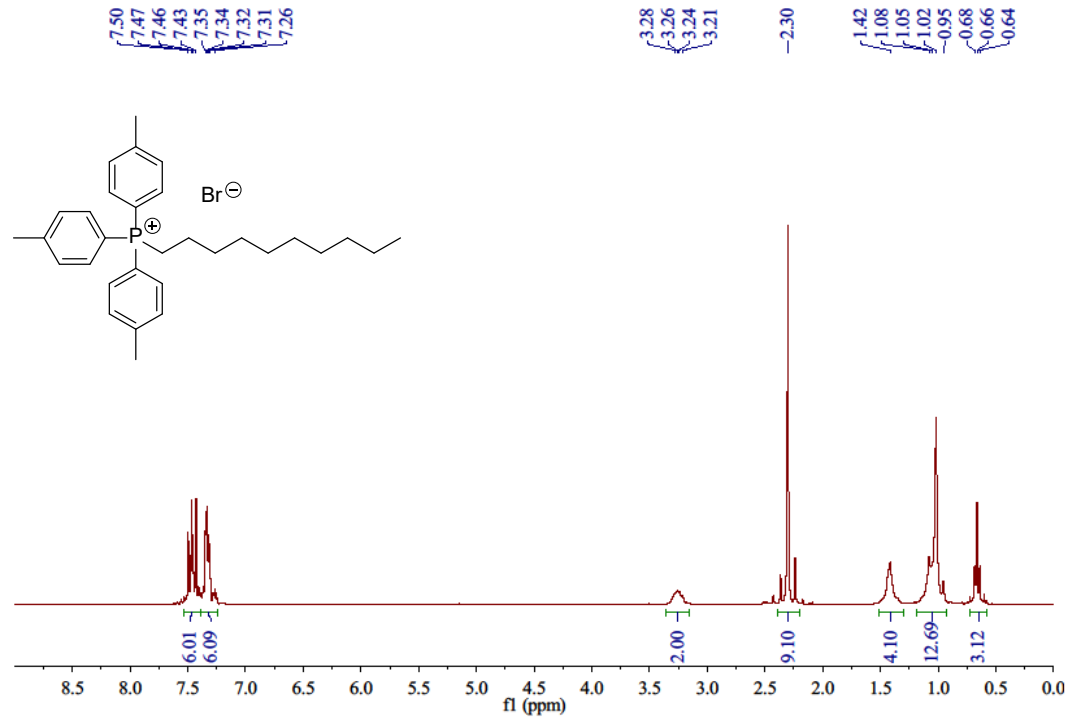


Supplemental Figure S5: Mitochondrial accumulation of first-generation aryl modified TPP^+-decyl analogs assessed by TPP^+ ion-selective electrode measurements. Mitochondrial substrate combination (SGM) was added to the chamber first. Then TPP^+ electrode response (blue trace; plotted on left Y-axis) was calibrated with 3 × 0.5 µM additions of the investigated compound, followed by addition of mouse liver mitochondria

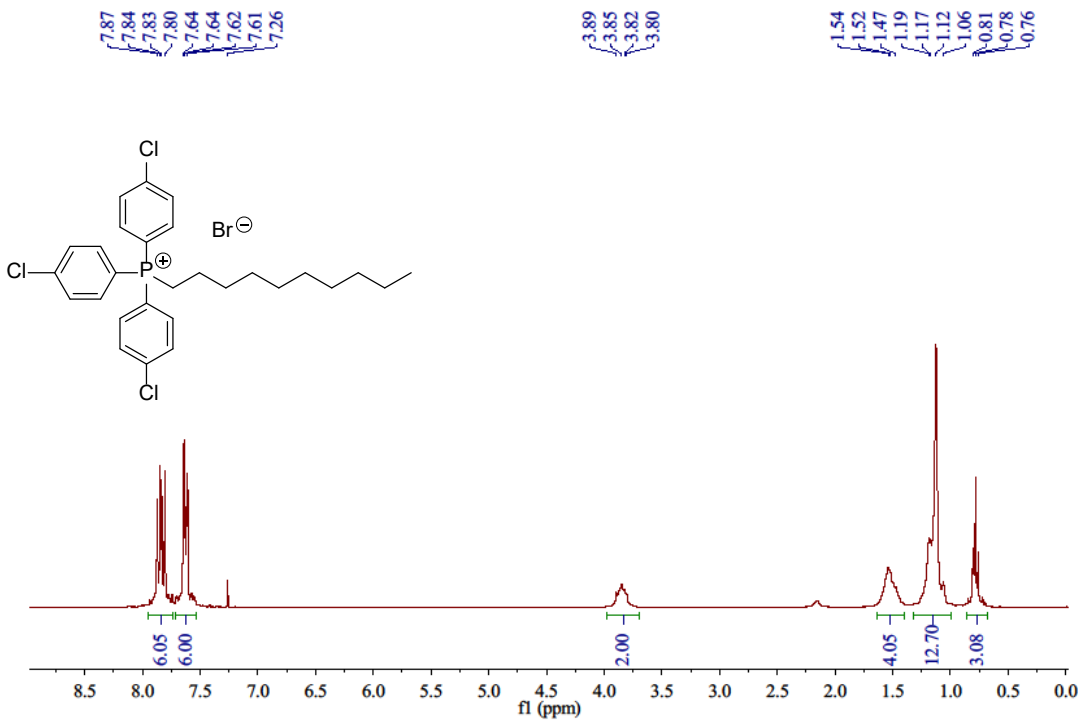
(mito) (0.1 mg/mL) and the experiment terminated when steady state reading was achieved. Corresponding oxygen consumption per unit mass (red trace; plotted on right Y-axis) was recorded with Clark-type oxygen electrode. The compounds tested were (A) tetraphenylphosphonium chloride (TPP); (B) 4-OMe-TPP-DC (**9**); (C) 4-CH_3-TPP-DC (**10**); (D) H-TPP-DC (**11**); (E) 4-Cl-TPP-DC (**12**); (F) 4-F-TPP-DC (**13**); (G) 4-CF_3-TPP-DC (**14**).



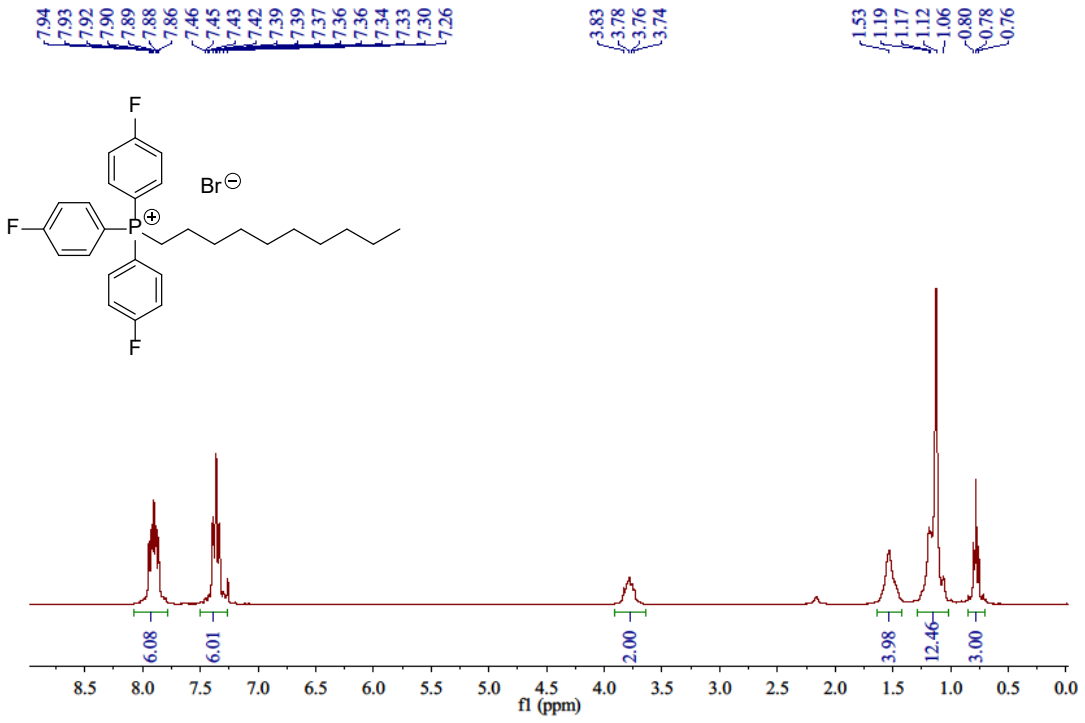
Supplemental Figure S6: ^{1}H NMR of 4-OMe-TPP-DC (**9**)



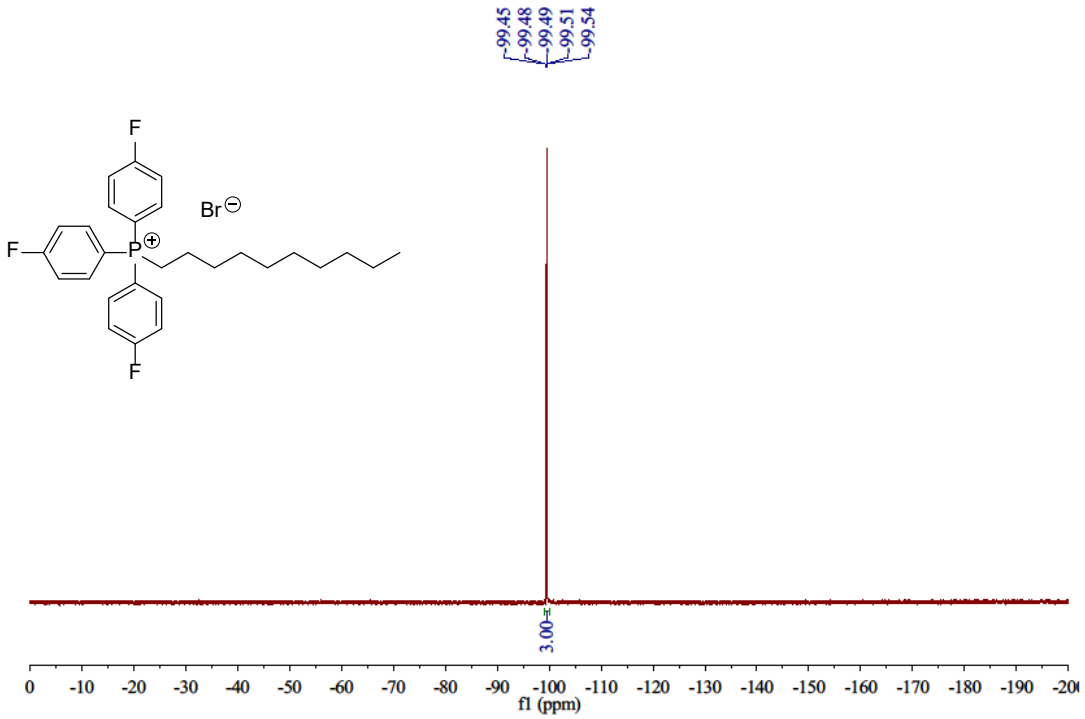
Supplemental Figure S7: ^{1}H NMR of 4-CH_3-TPP-DC (**10**)



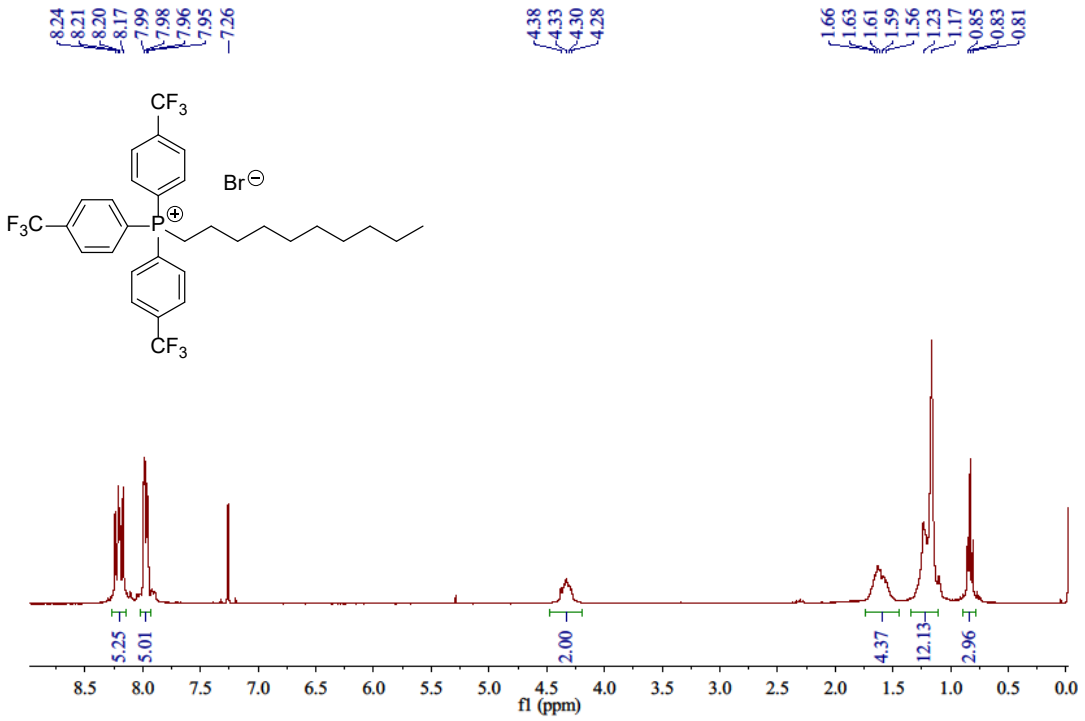
Supplemental Figure S8: ^{1}H NMR of 4-Cl-TPP-DC (**12**)



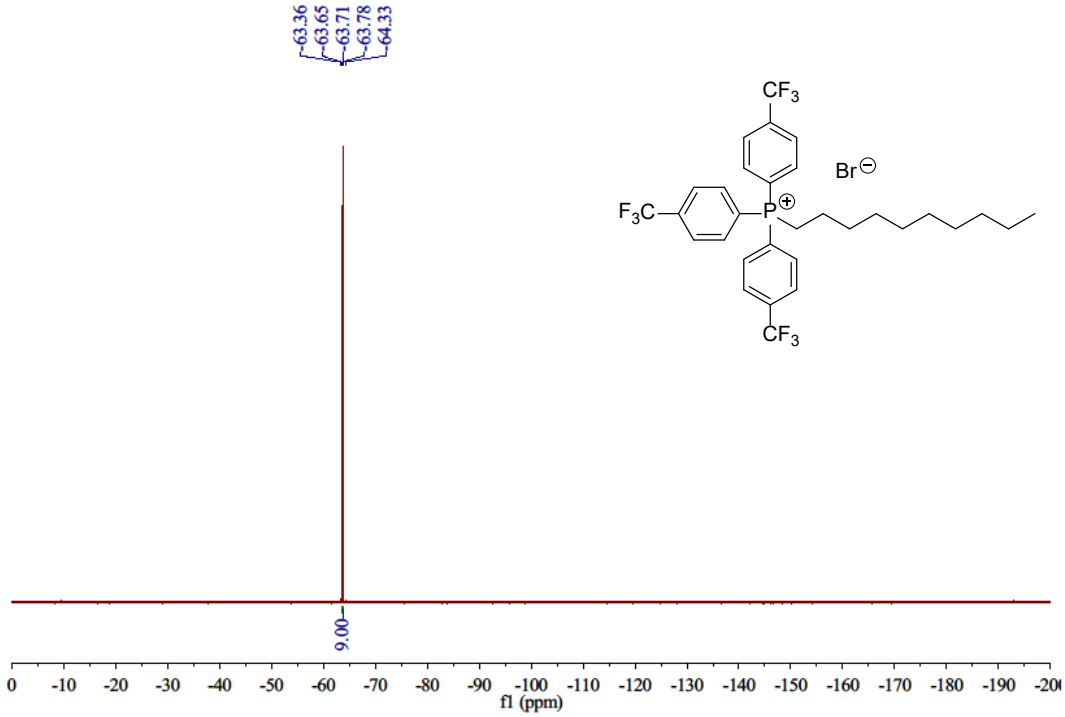
Supplemental Figure S9: ^{1}H NMR of 4-F-TPP-DC (**13**)



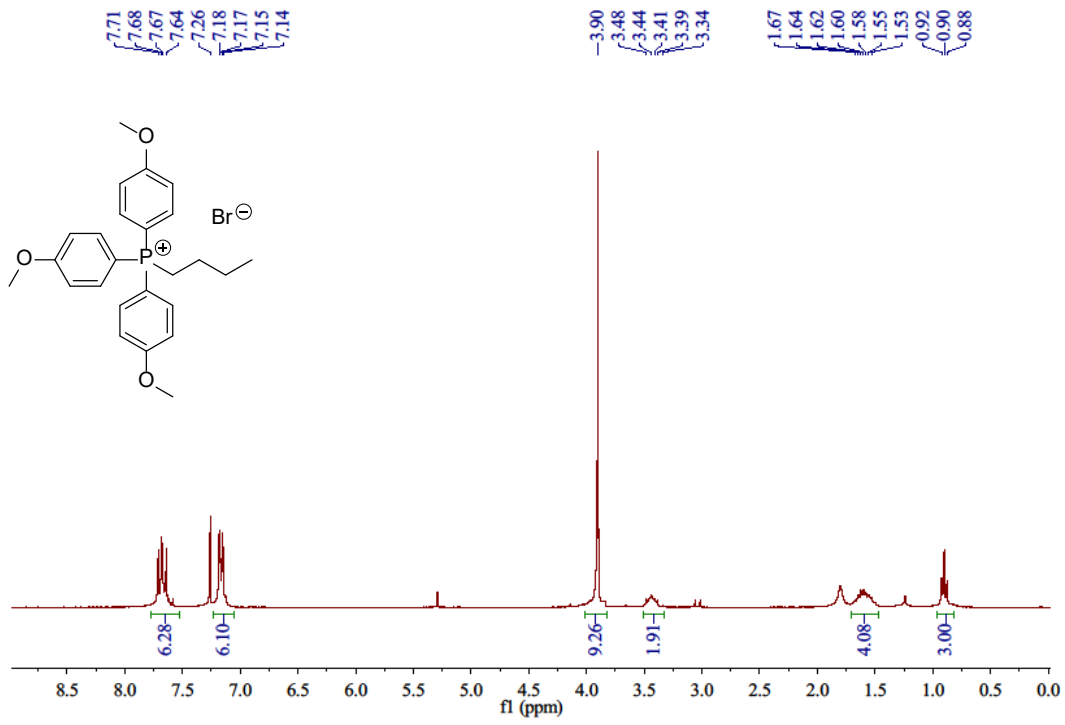
Supplemental Figure S10: ^{19}F NMR of 4-F-TPP-DC (**13**)



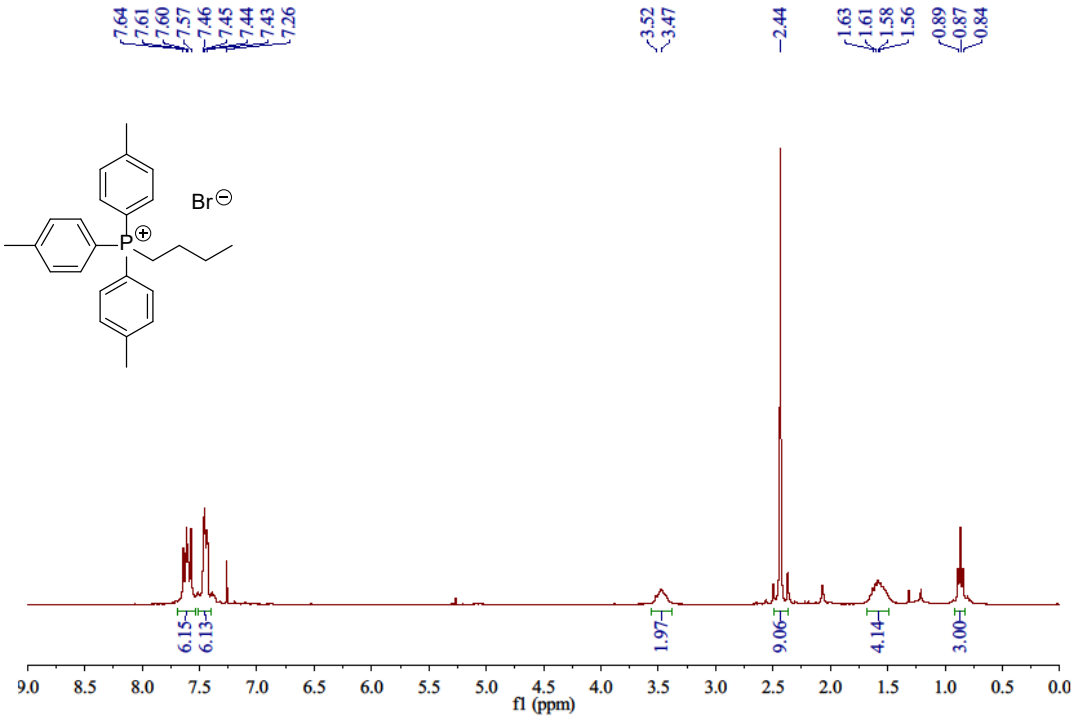
Supplemental Figure S11: ^{1}H NMR of 4-CF_3-TPP-DC (**14**)



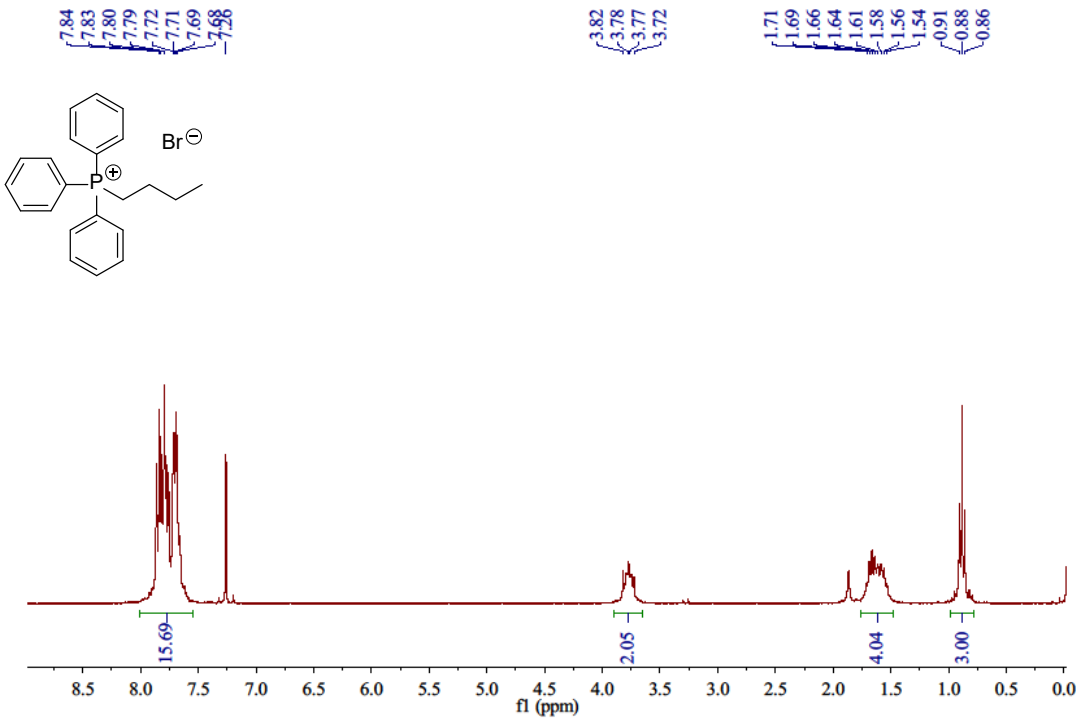
Supplemental Figure S12: ^{19}F NMR of 4- CF_3-TPP-DC (**14**)



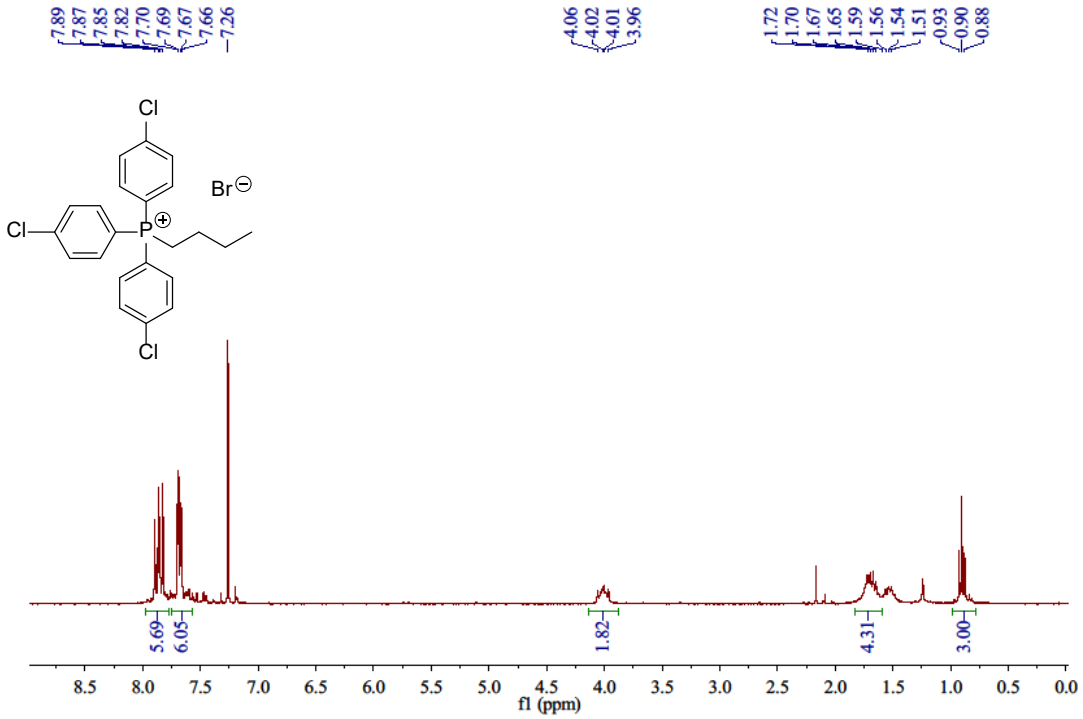
Supplemental Figure S13: ^{1}H NMR of 4-OMe-TPP-BU (**15**)



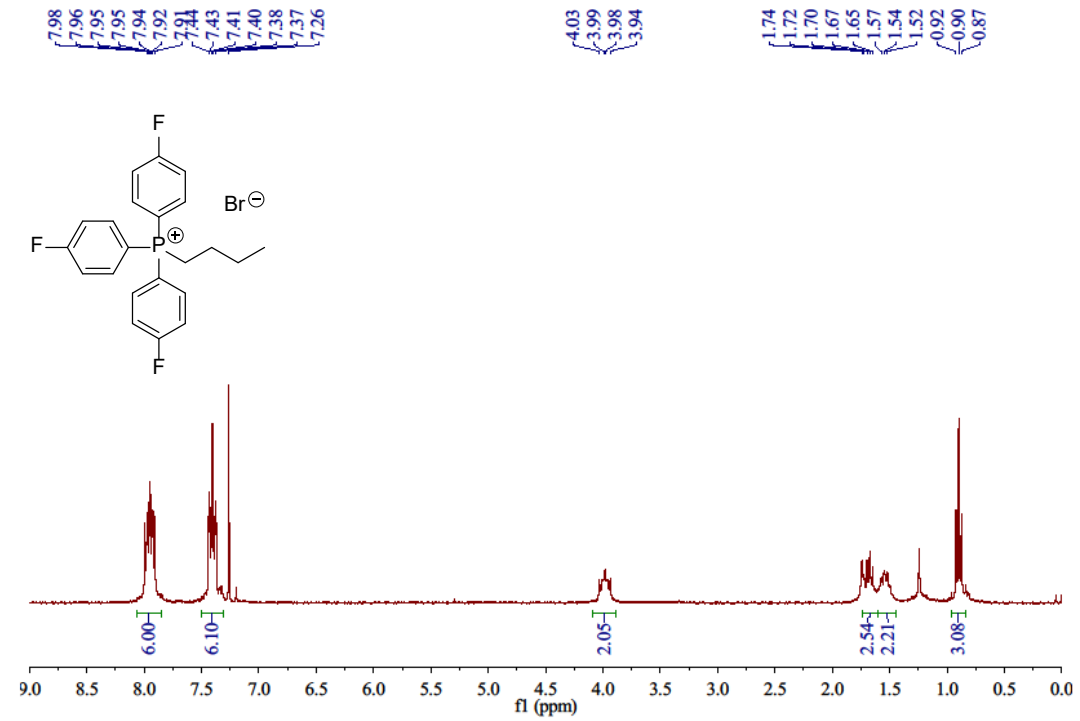
Supplemental Figure S14: ^{1}H NMR of 4-CH_3-TPP-BU (**16**)



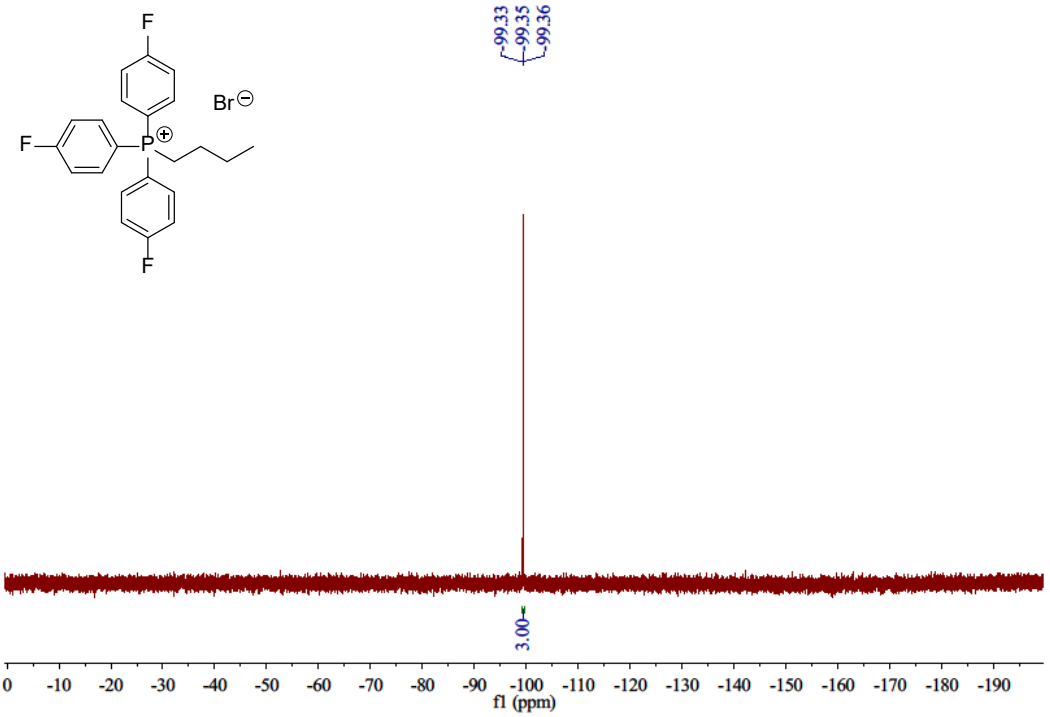
Supplemental Figure S15: ^{1}H NMR of H-TPP-BU (**17**)



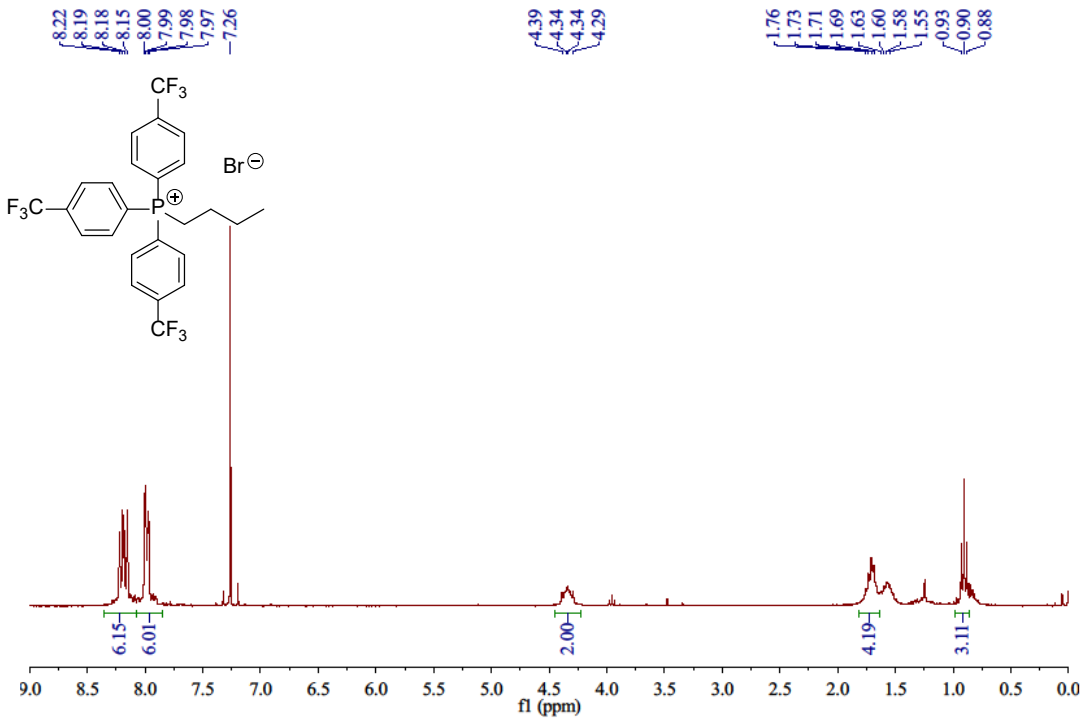
Supplemental Figure S16: ^{1}H NMR of 4-Cl-TPP-BU (**18**)



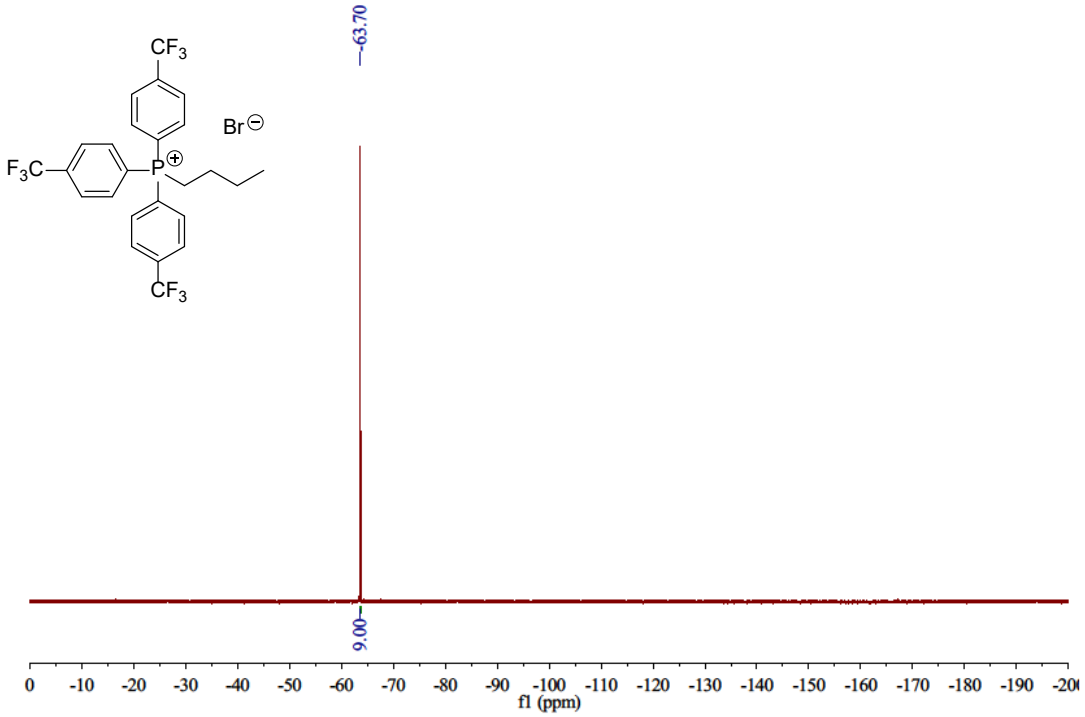
Supplemental Figure S17: ^{1}H NMR of 4-F-TPP-BU (**19**)



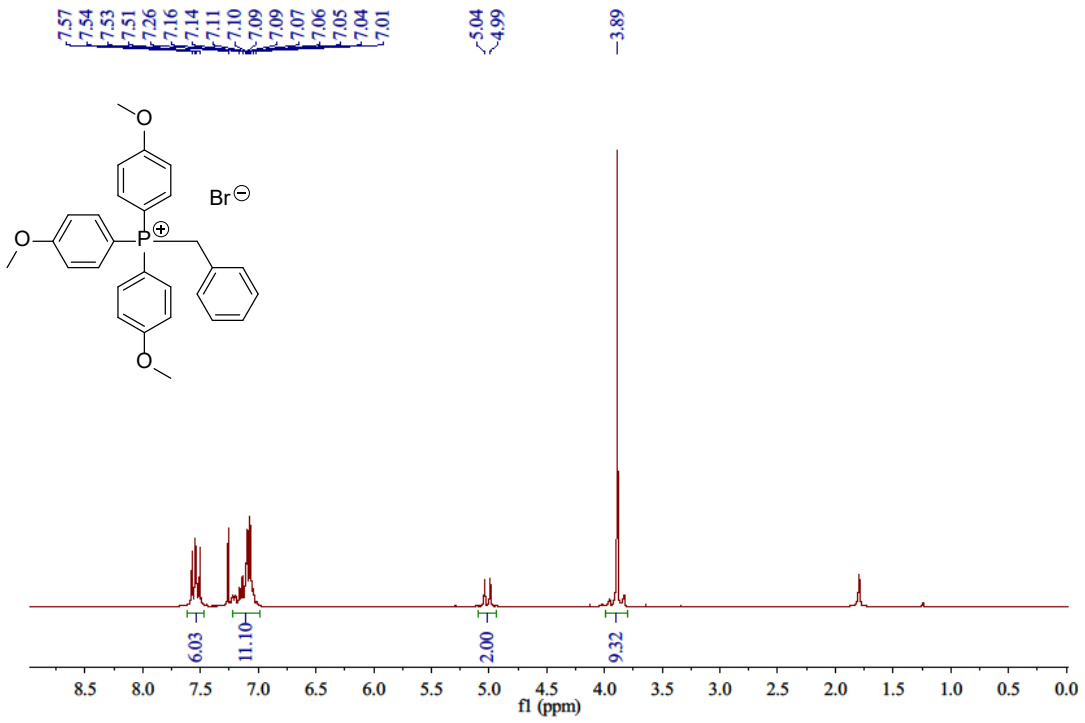
Supplemental Figure S18: ^{19}F NMR of 4-F-TPP-BU (**19**)



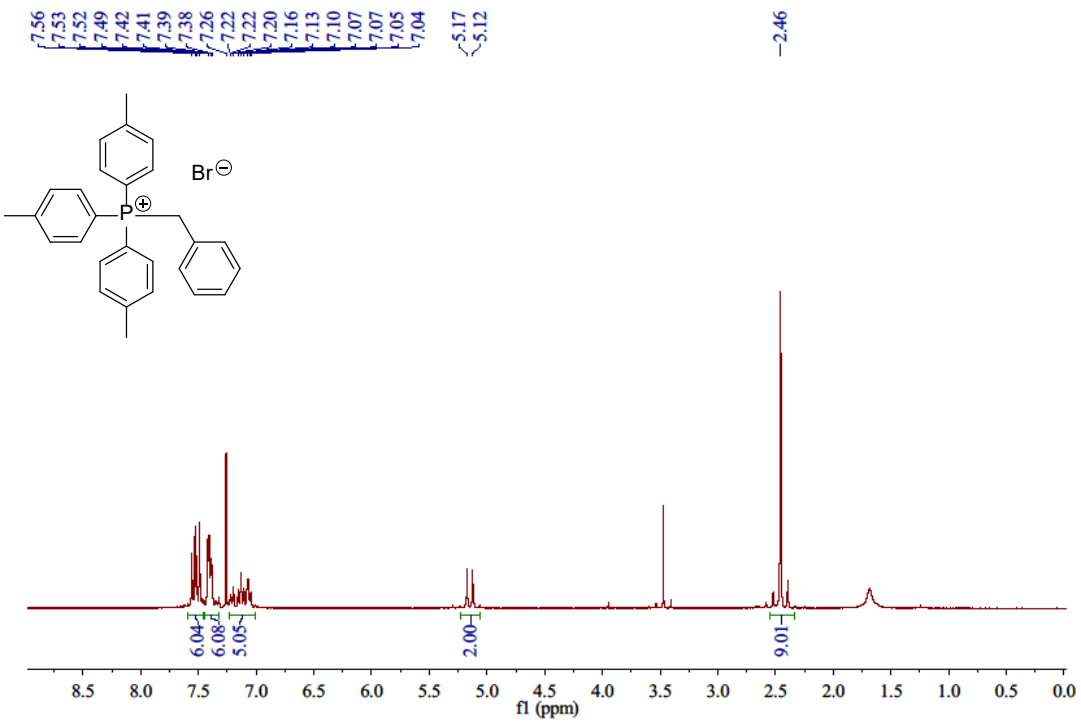
Supplemental Figure S19: ^{1}H NMR of 4-CF_3-TPP-BU (**20**)



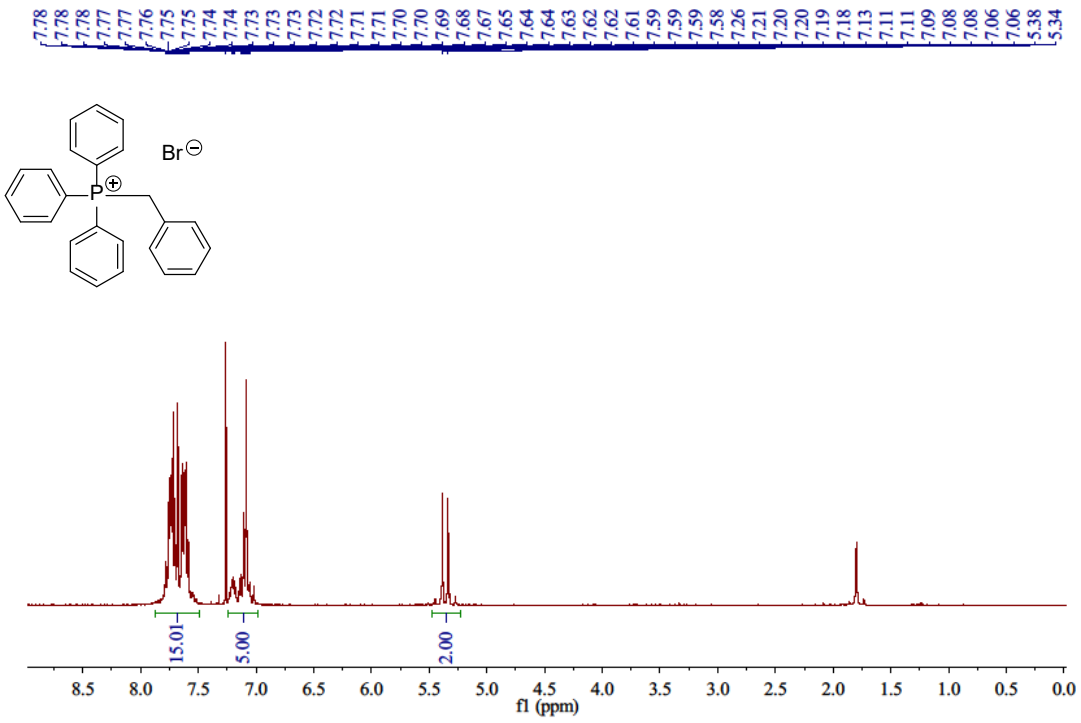
Supplemental Figure S20: ^{19}F NMR of 4- CF_3-TPP-BU (**20**)



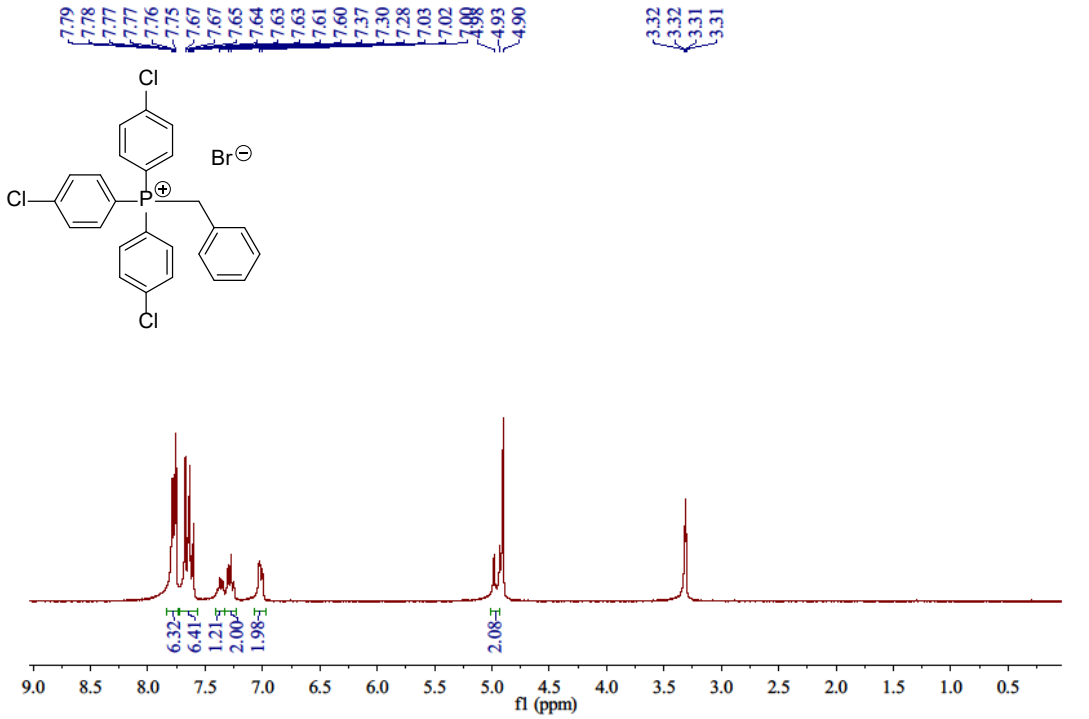
Supplemental Figure S21: ^{1}H NMR of 4-OMe-TPP-BZ (**22**)



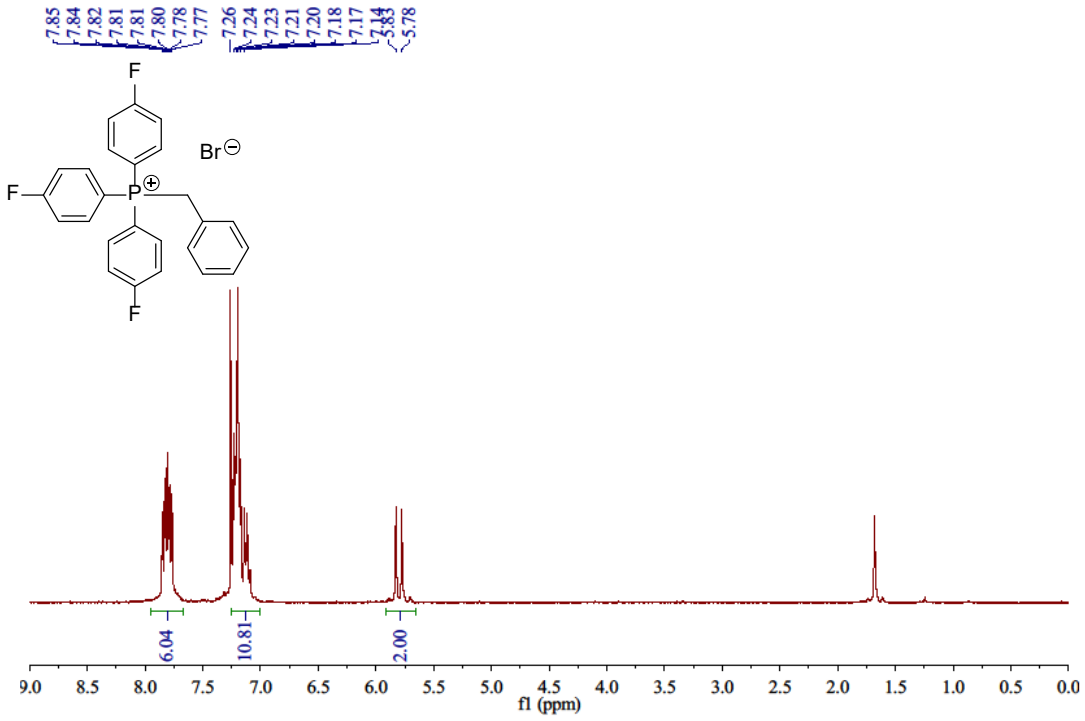
Supplemental Figure S22: ^{1}H NMR of 4-CH_3-TPP-BZ (**23**)



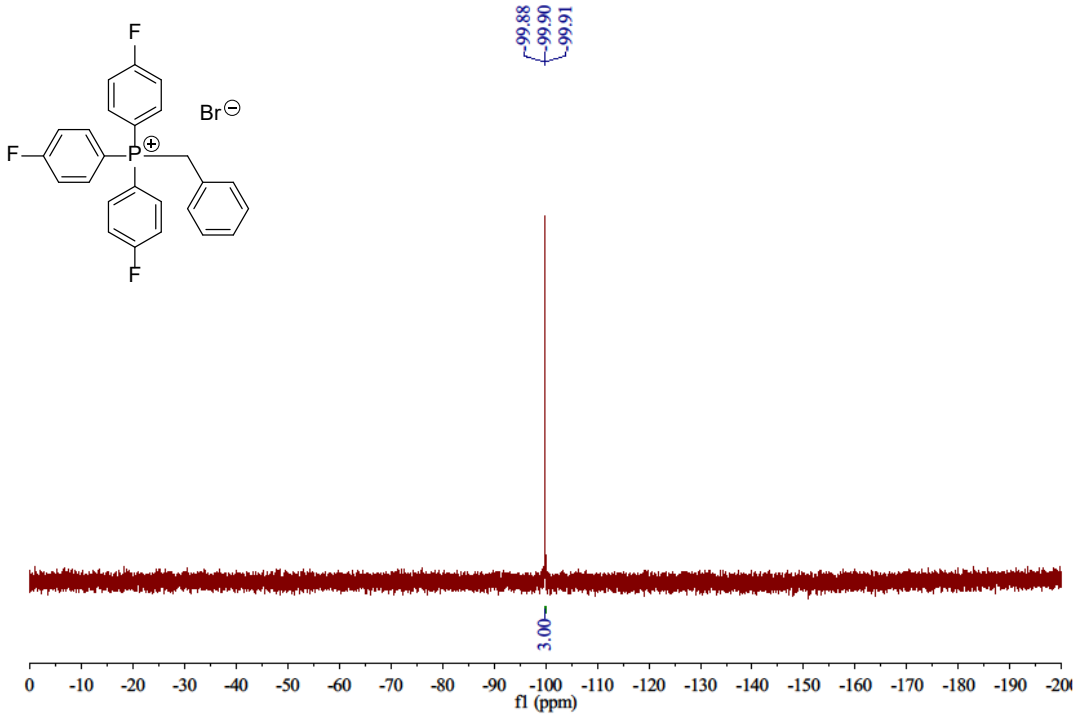
Supplemental Figure S23: ^{1}H NMR of H-TPP-BZ (**24**)



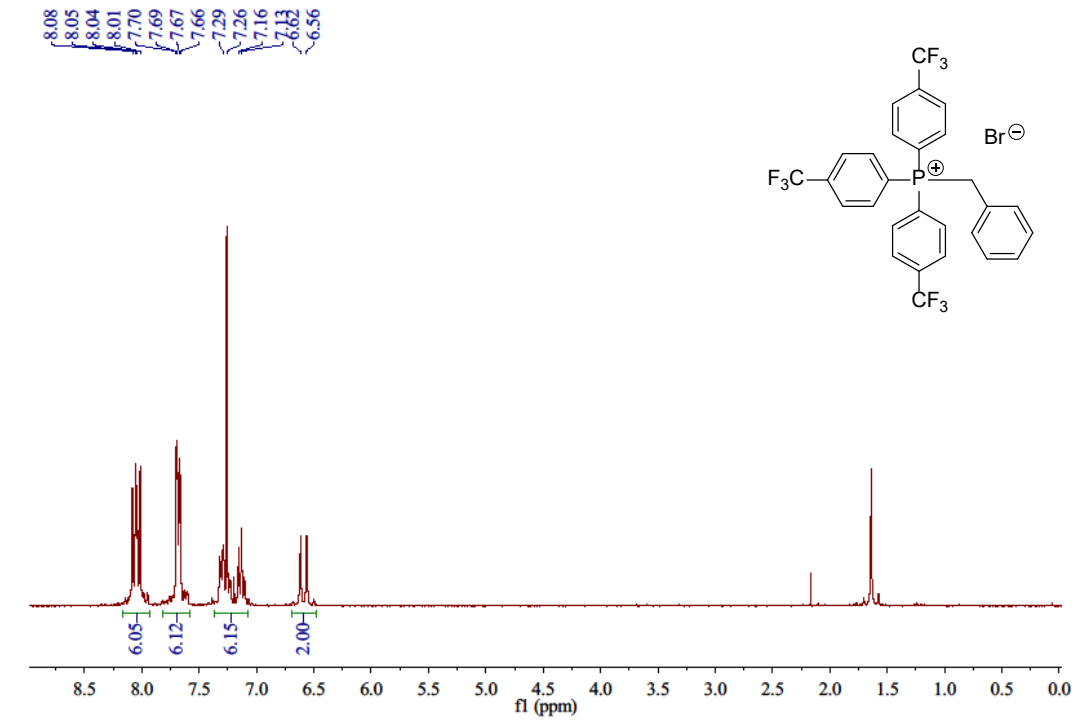
Supplemental Figure S24: ^{1}H NMR of 4-Cl-TPP-BZ (**25**)



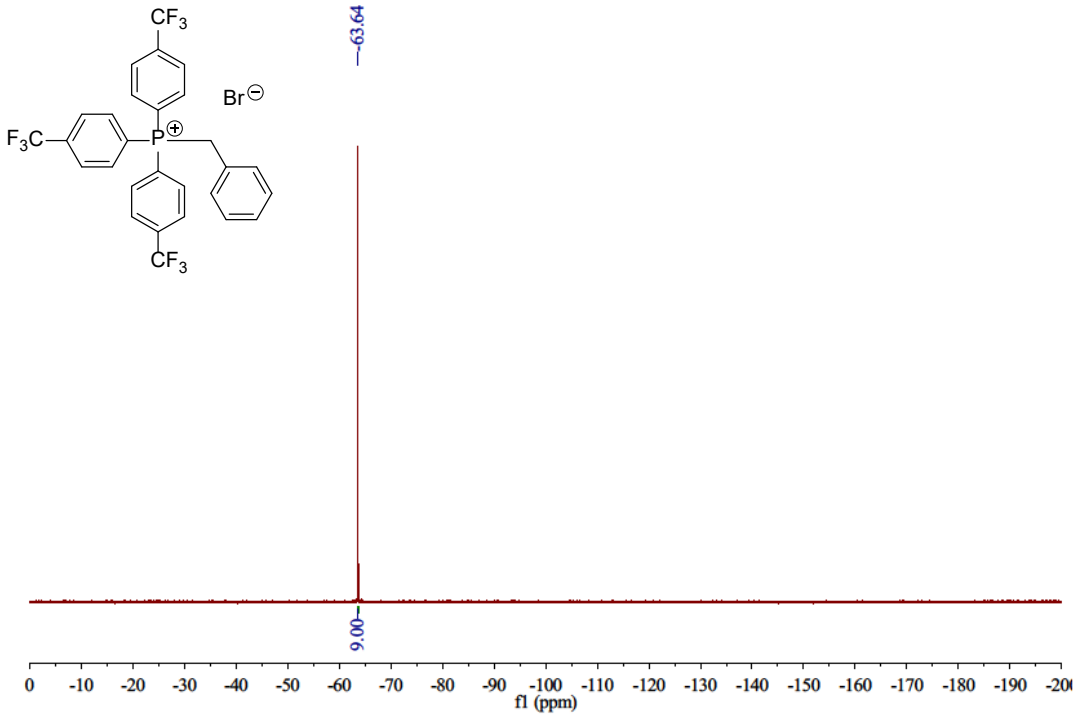
Supplemental Figure S25: ^{1}H NMR of 4-F-TPP-BZ (**26**)



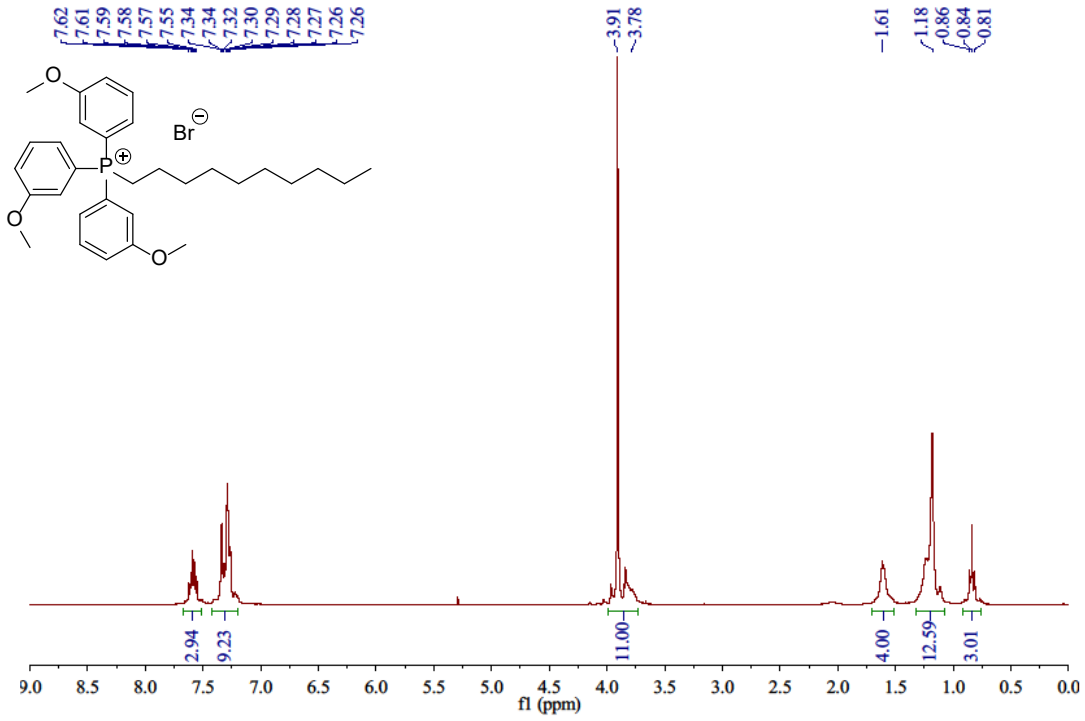
Supplemental Figure S26: ^{19}F NMR of 4-F-TPP-BZ (**26**)



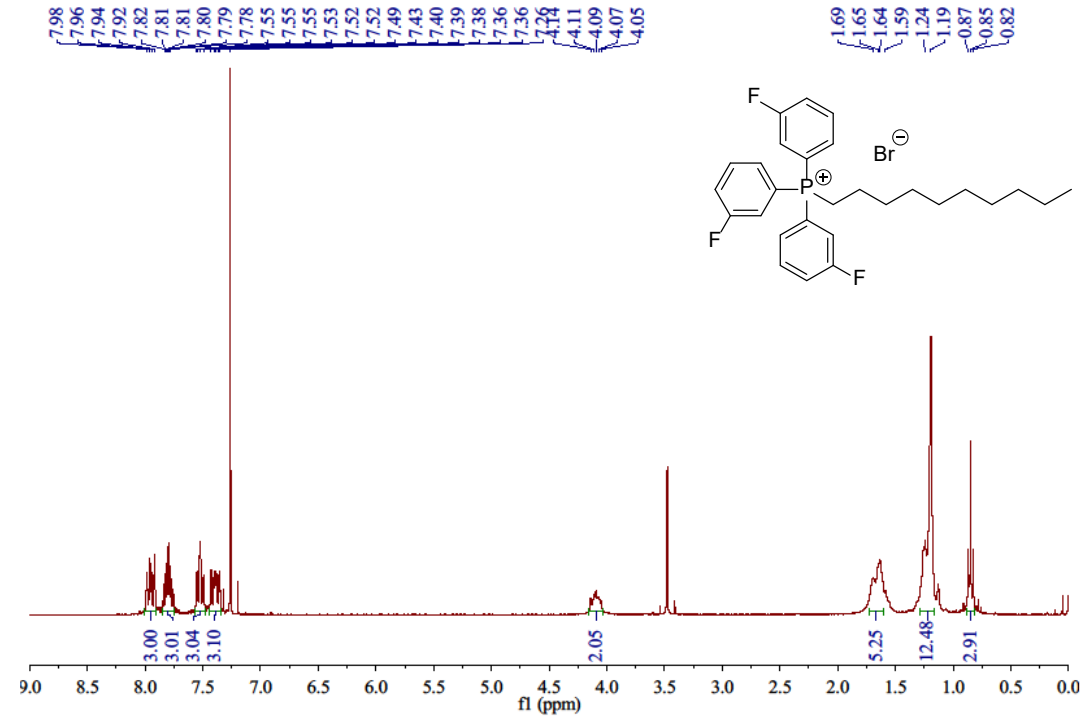
Supplemental Figure S27: ^{1}H NMR of 4-CF_3-TPP-BZ (**27**)



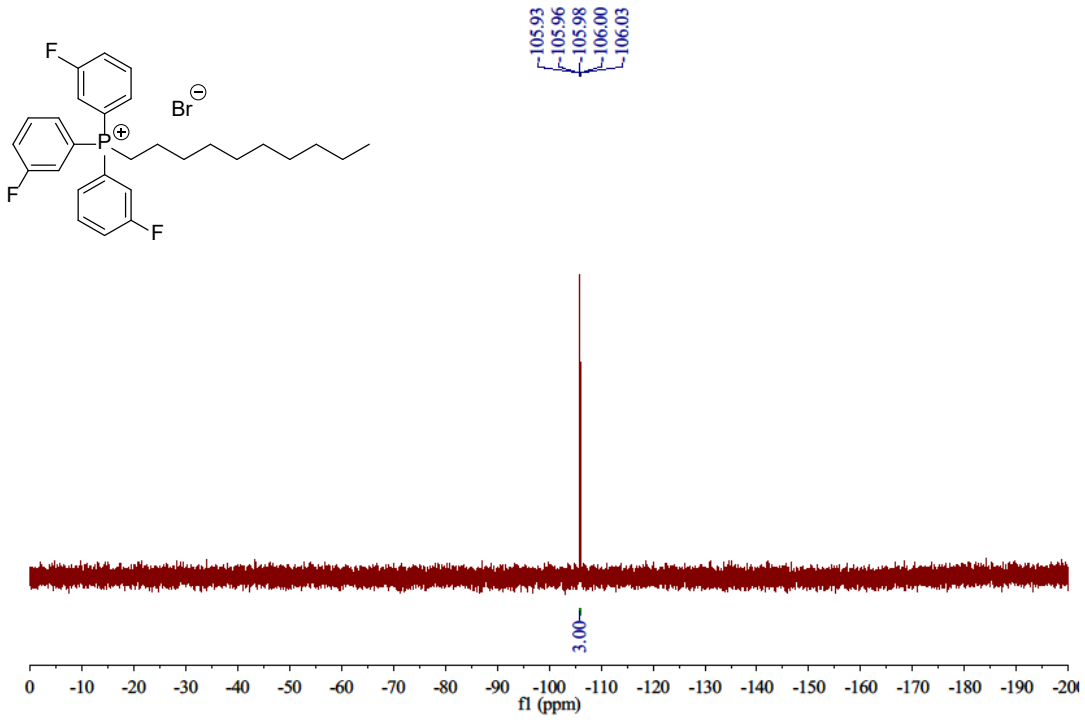
Supplemental Figure S28: ^{19}F NMR of 4- CF_3-TPP-BZ (**27**)



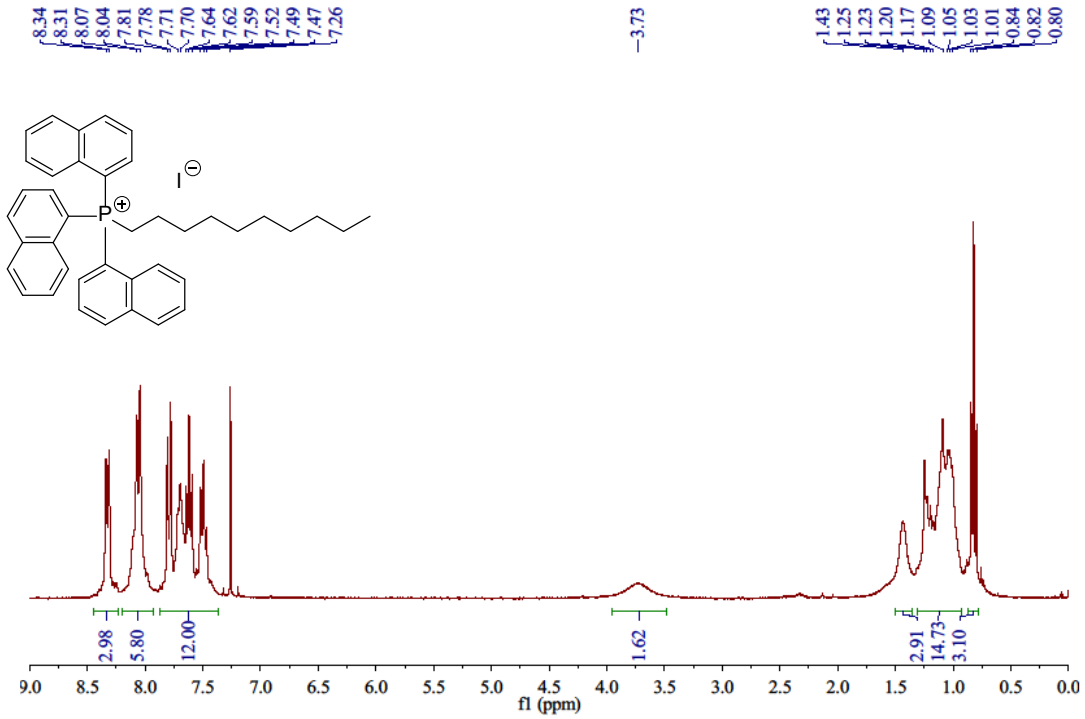
Supplemental Figure S29: ^{1}H NMR of 3-OMe-TPP-DC (**30**)



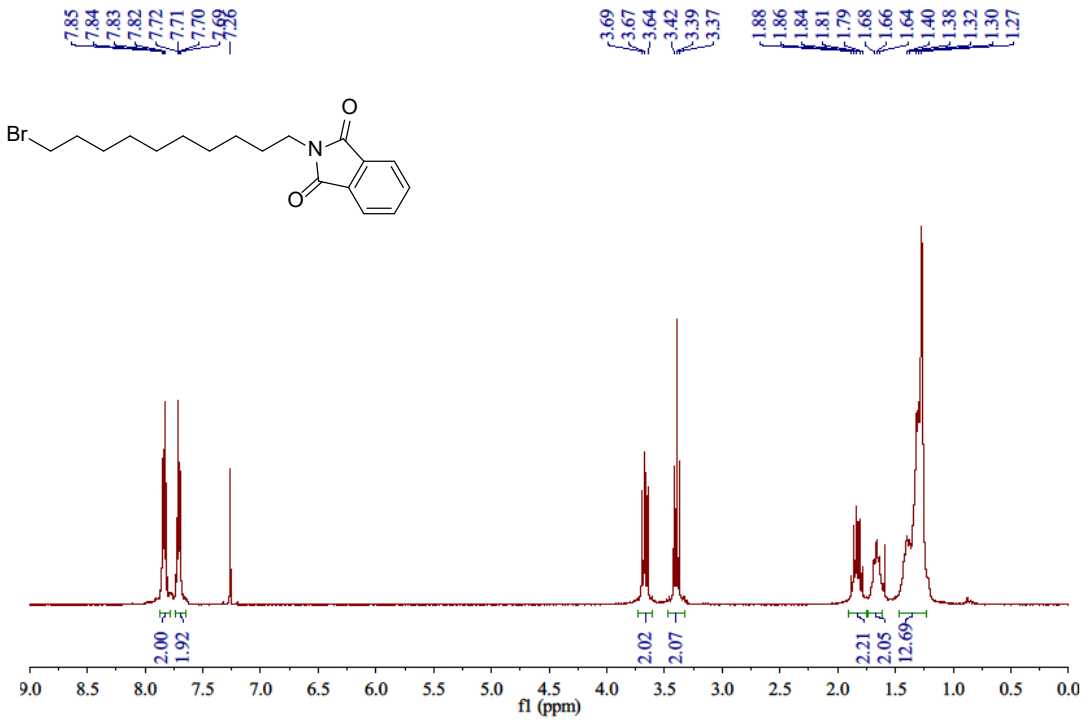
Supplemental Figure S30: ^{1}H NMR of 3-F-TPP-DC (**31**)



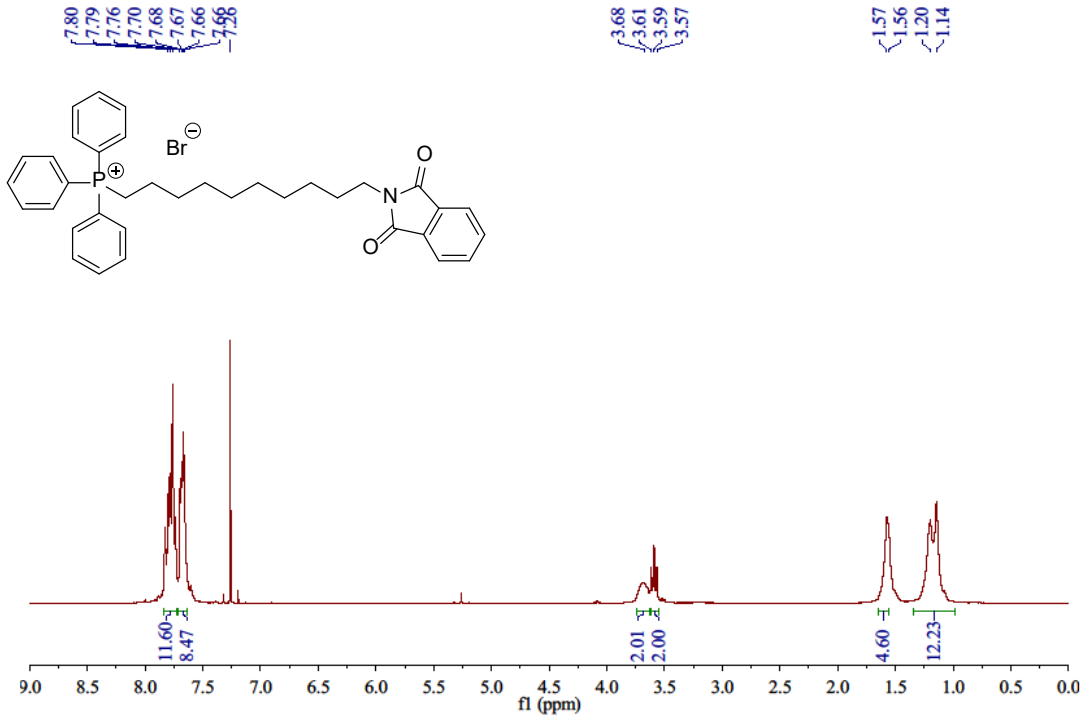
Supplemental Figure S31: ^{19}F NMR of 3-F-TPP-DC (**31**)



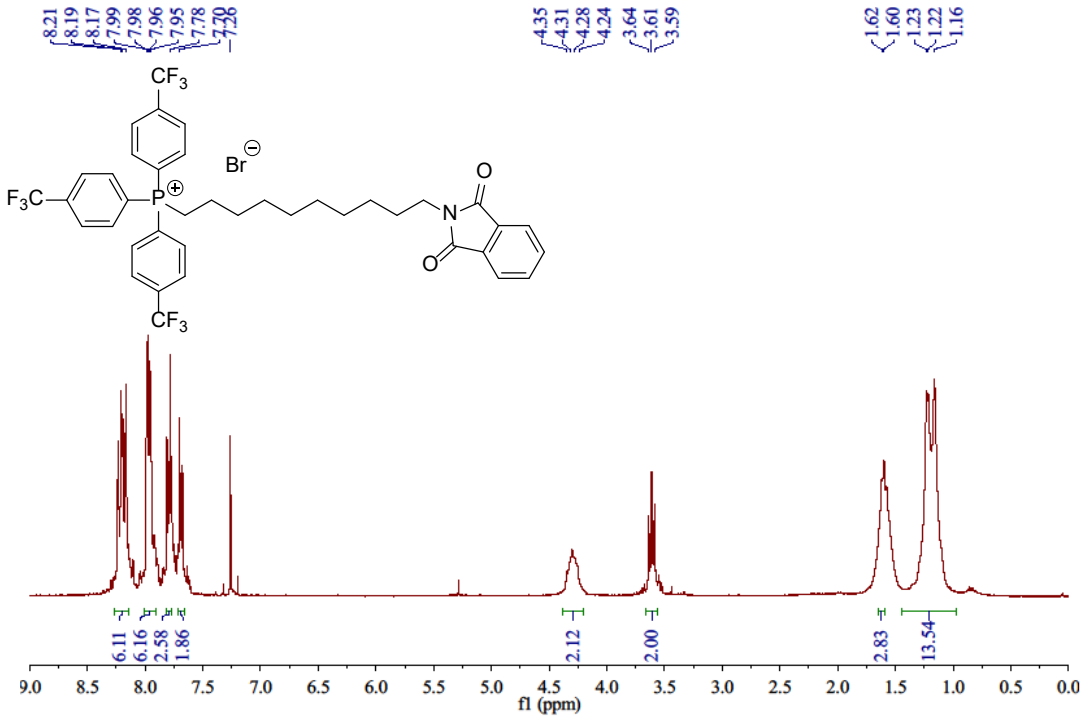
Supplemental Figure S32: ^{1}H NMR of Tri-Nap-P-DC-I (**33**)



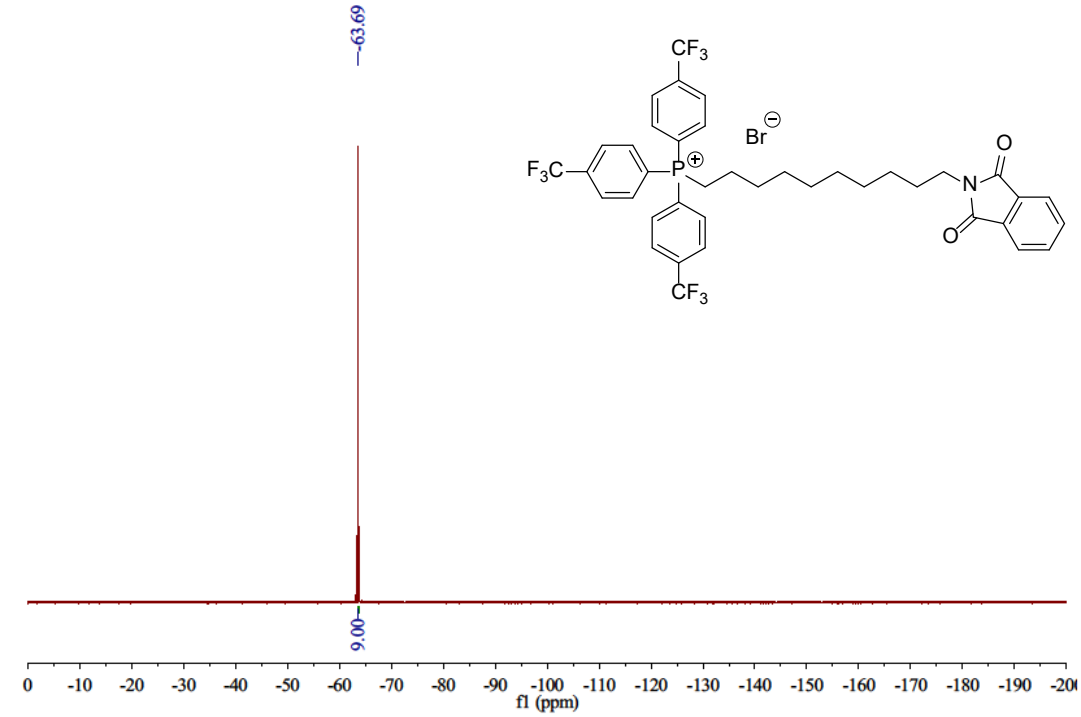
Supplemental Figure S33: ^{1}H NMR of Br-DC-Phthalimide (**36**)



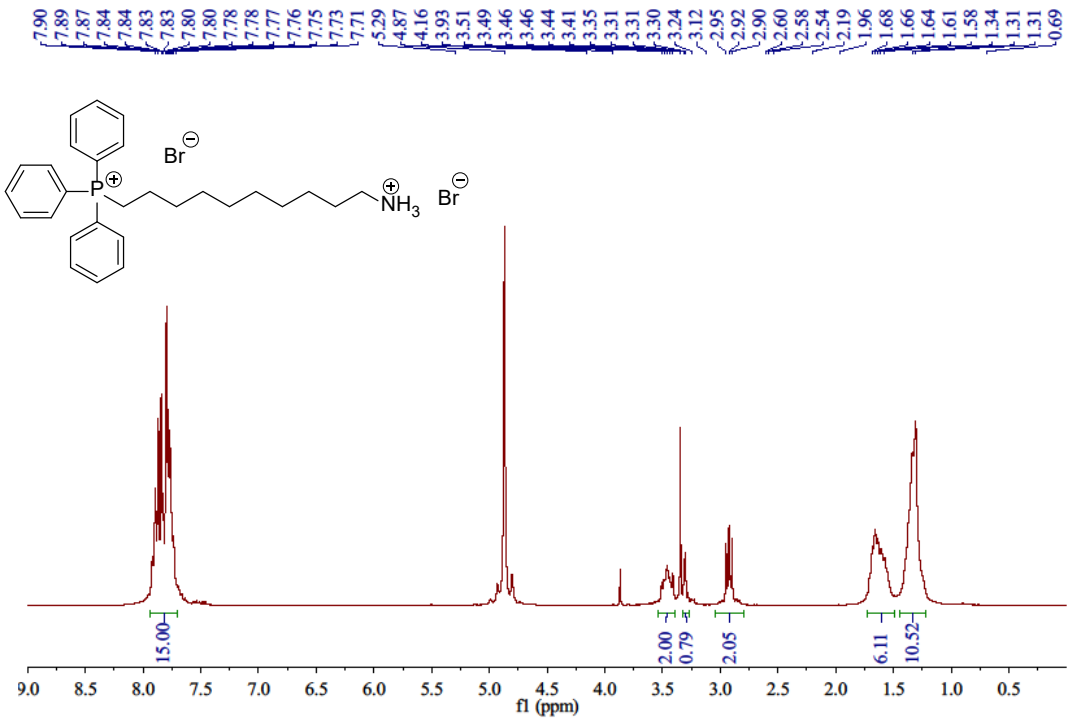
Supplemental Figure S34: ^{1}H NMR of H-TPP-DC-Pthalimide (**37**)



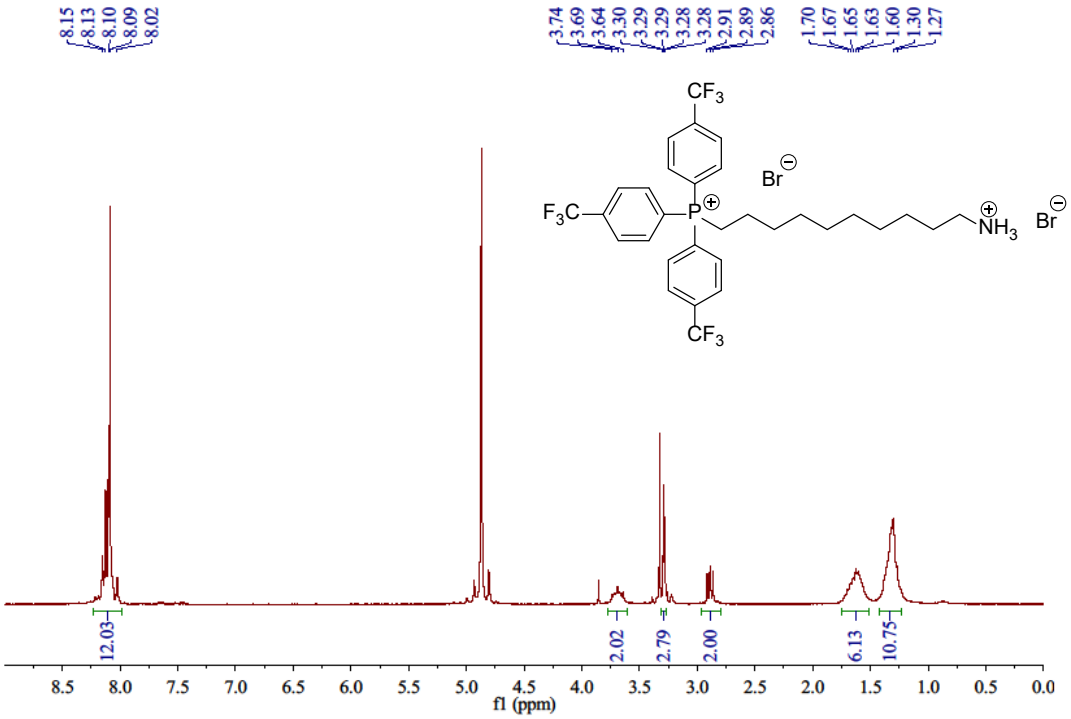
Supplemental Figure S35: ^{1}H NMR of 4-CF_3-TPP-DC-Pthalimide (**38**)



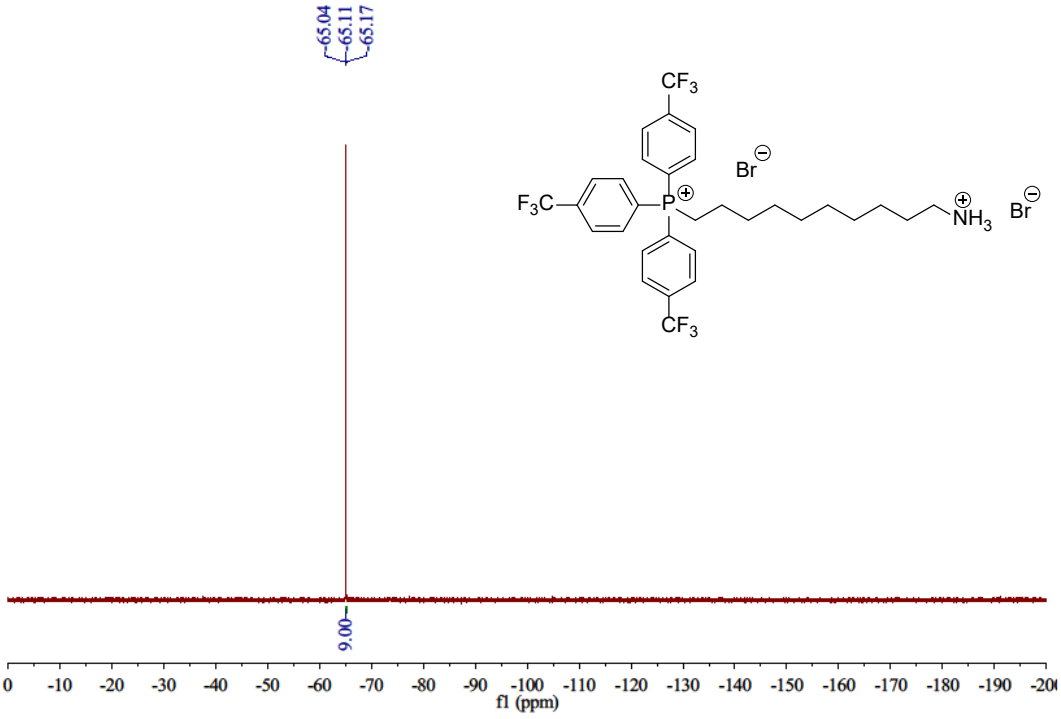
Supplemental Figure S36: ^{19}F NMR of 4-CF_3-TPP-DC-Pthalimide (**38**)



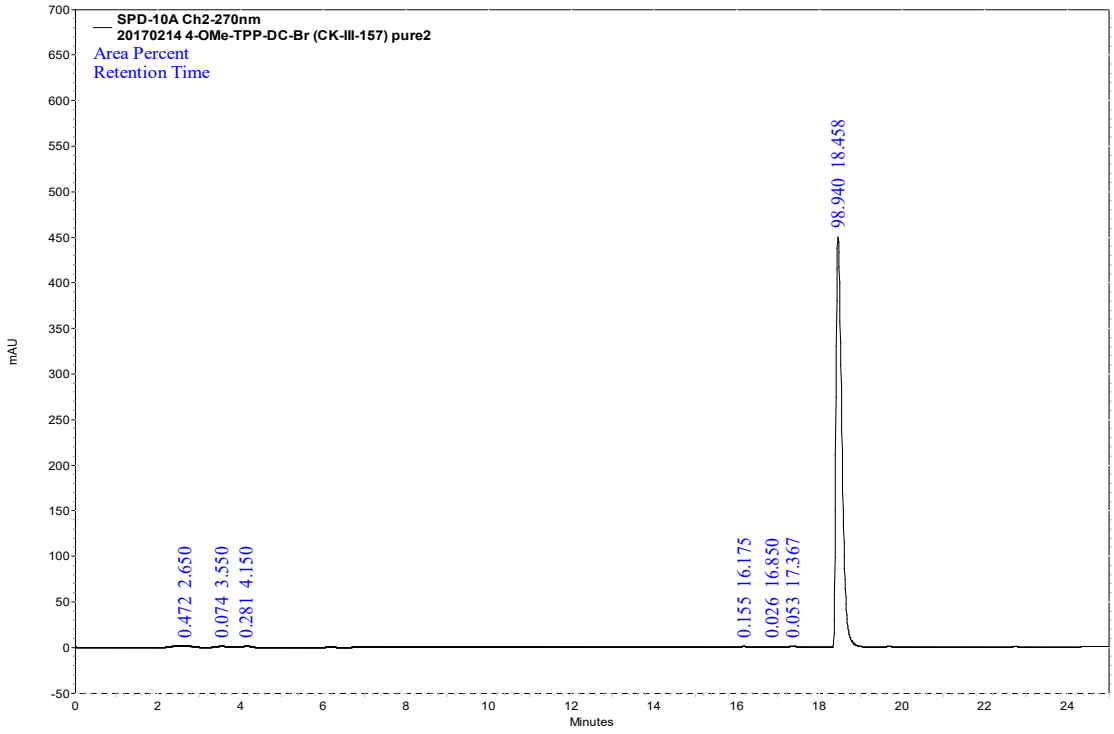
Supplemental Figure S37: ^{1}H NMR of H-TPP-DC-NH_2 (**39**)



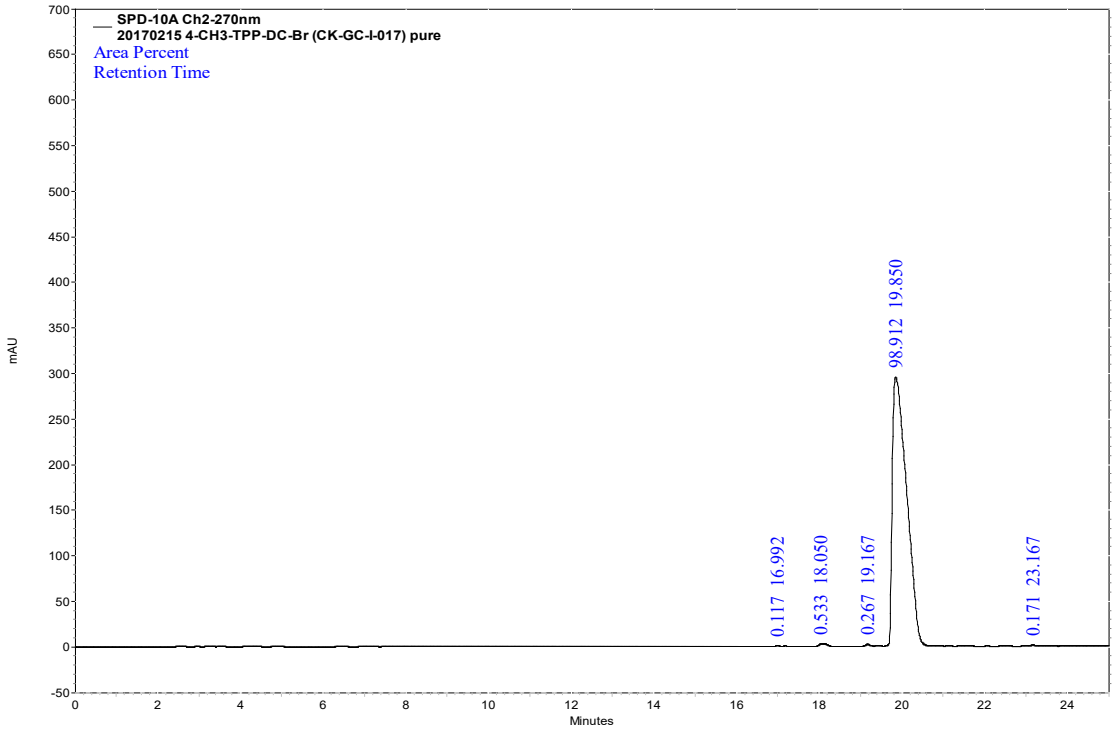
Supplemental Figure S38: ^{1}H NMR of 4-CF_3-TPP-DC-NH_2 (**40**)



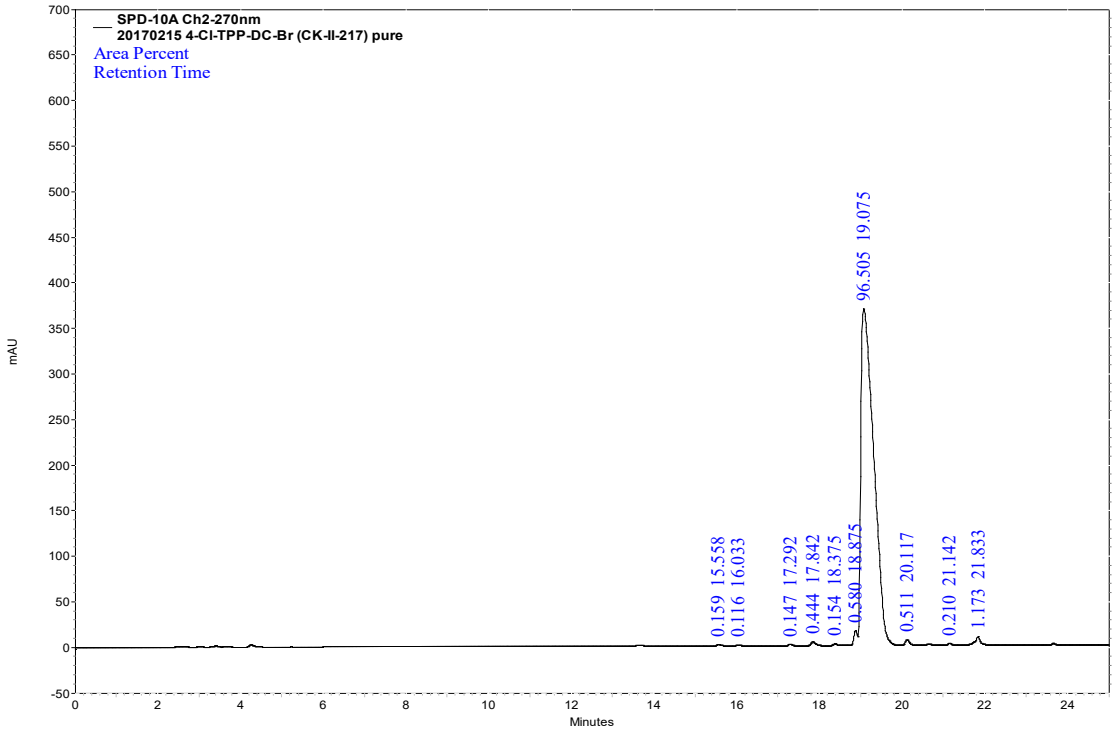
Supplemental Figure S39: ^{19}F NMR of 4-CF_3-TPP-DC-NH_2 (**40**)



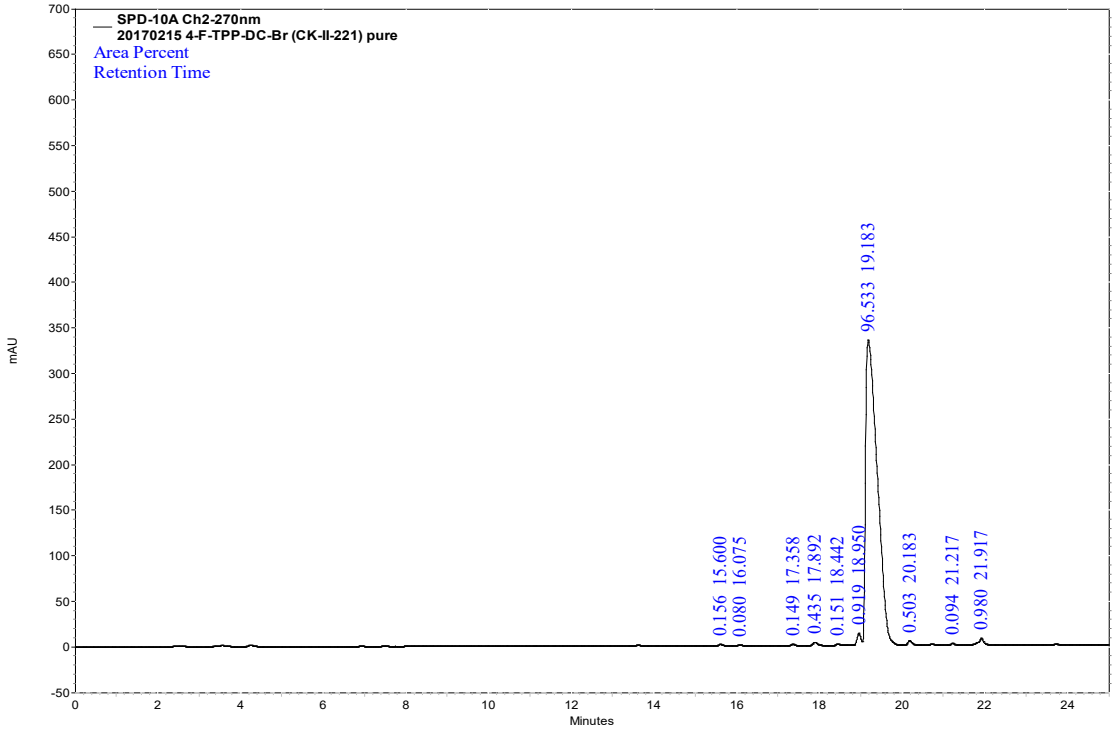
Supplemental Figure S40: HPLC chromatogram of 4-OMe-TPP-DC (**15**)



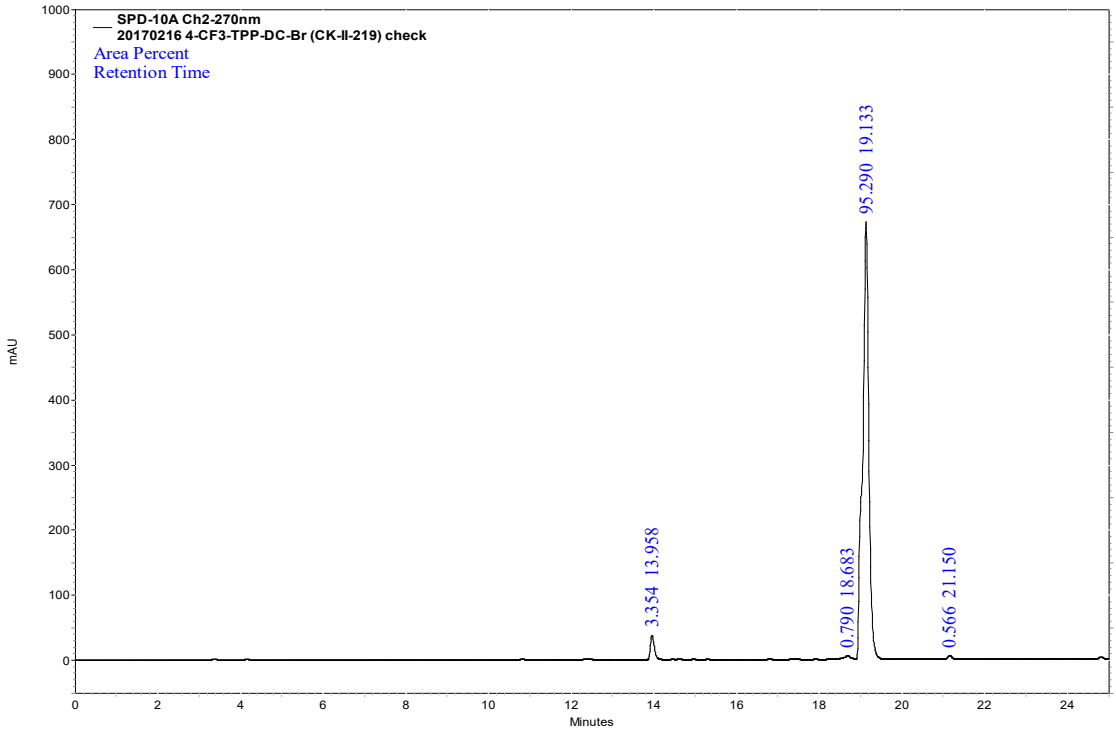
Supplemental Figure S41: HPLC chromatogram of 4-CH_3-TPP-DC (**10**)



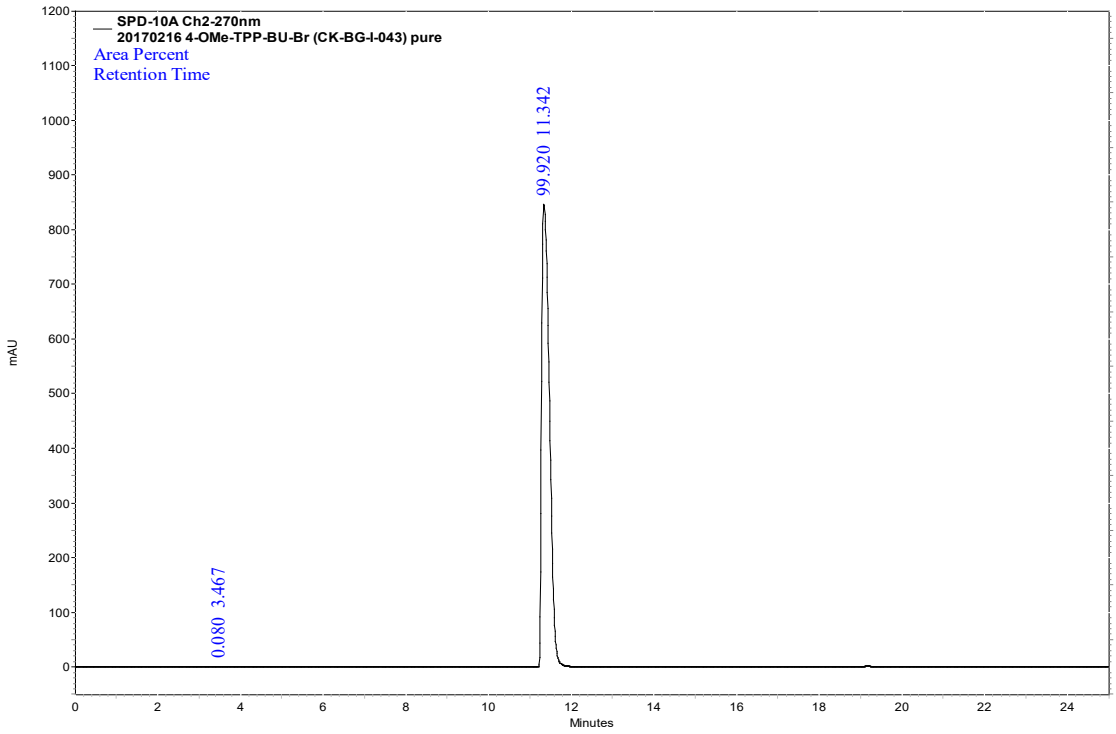
Supplemental Figure S42: HPLC chromatogram of 4-Cl-TPP-DC (**12**)



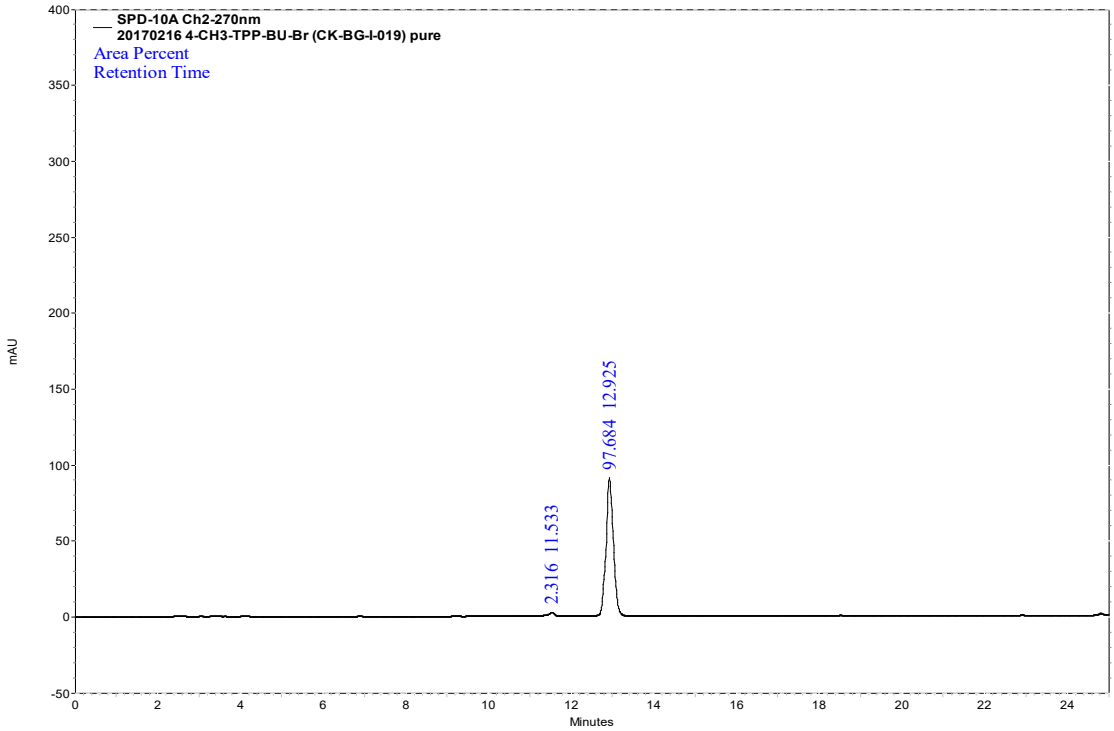
Supplemental Figure S43: HPLC chromatogram of 4-F-TPP-DC (**13**)



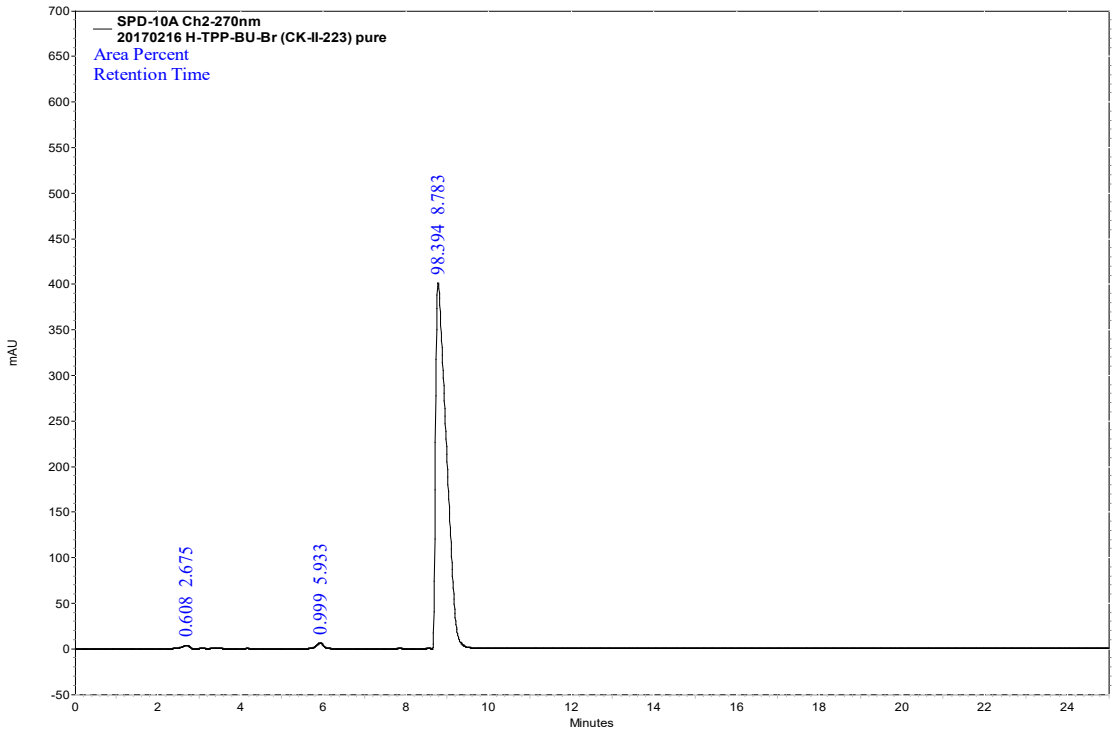
Supplemental Figure S44: HPLC chromatogram of 4-CF_3-TPP-DC (**14**)



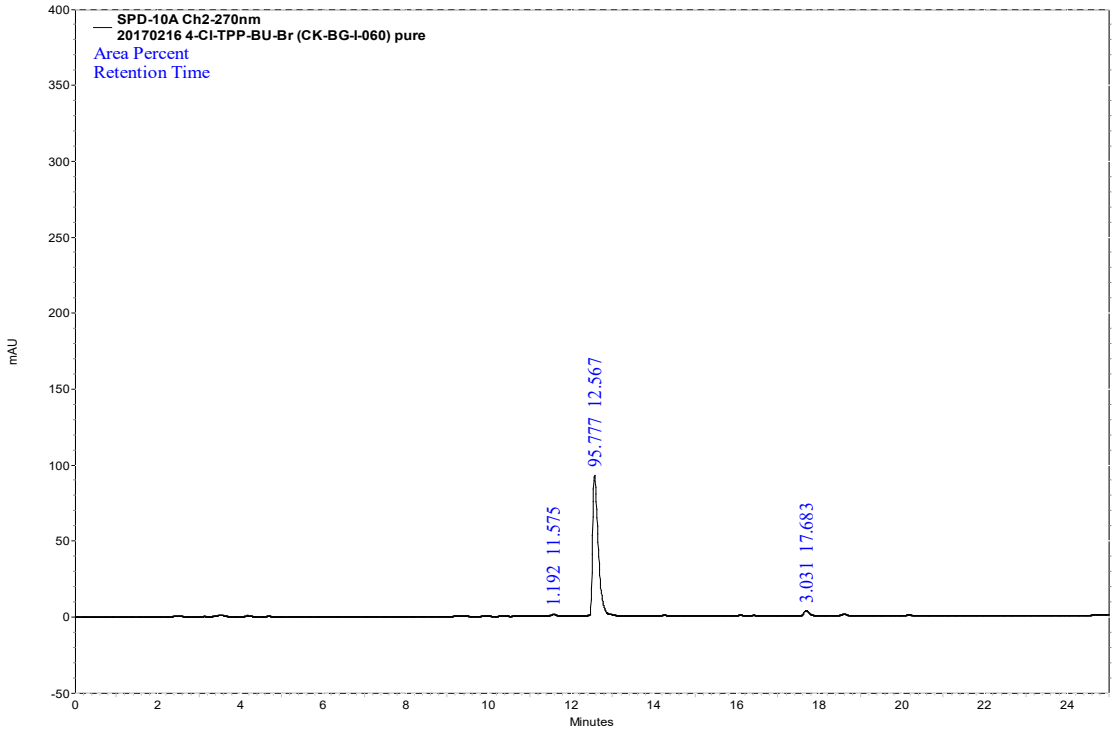
Supplemental Figure S45: HPLC chromatogram of 4-OMe-TPP-BU (**15**)



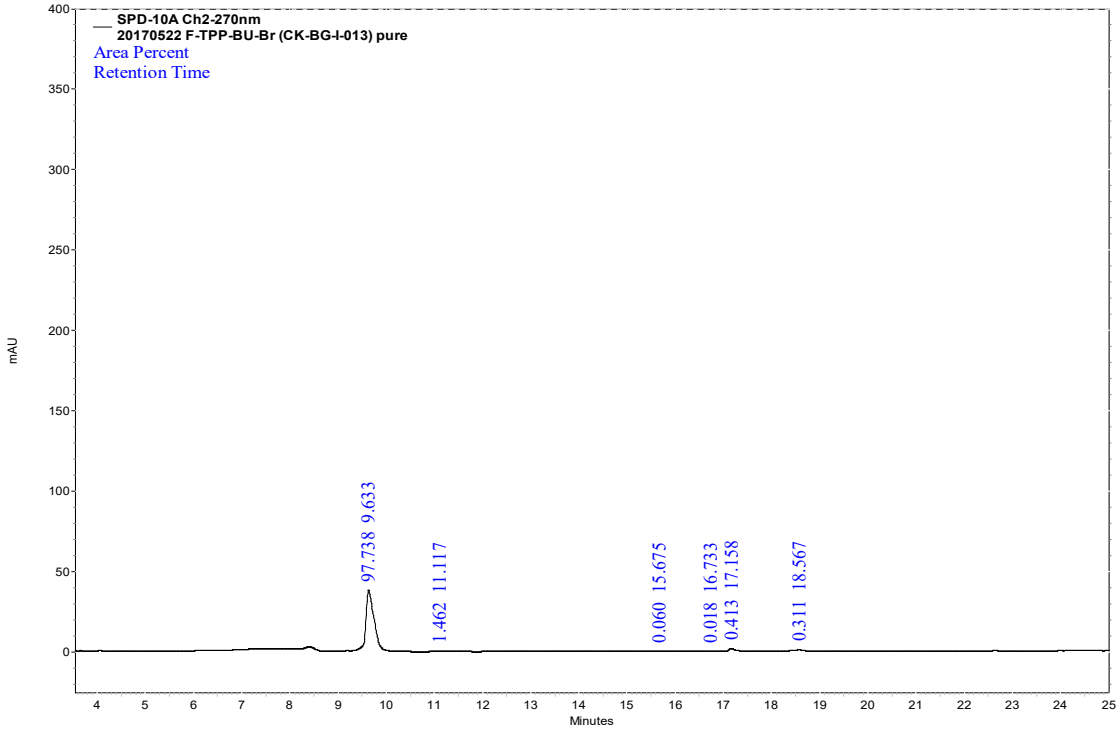
Supplemental Figure S46: HPLC chromatogram of 4-CH_3-TPP-BU (**16**)



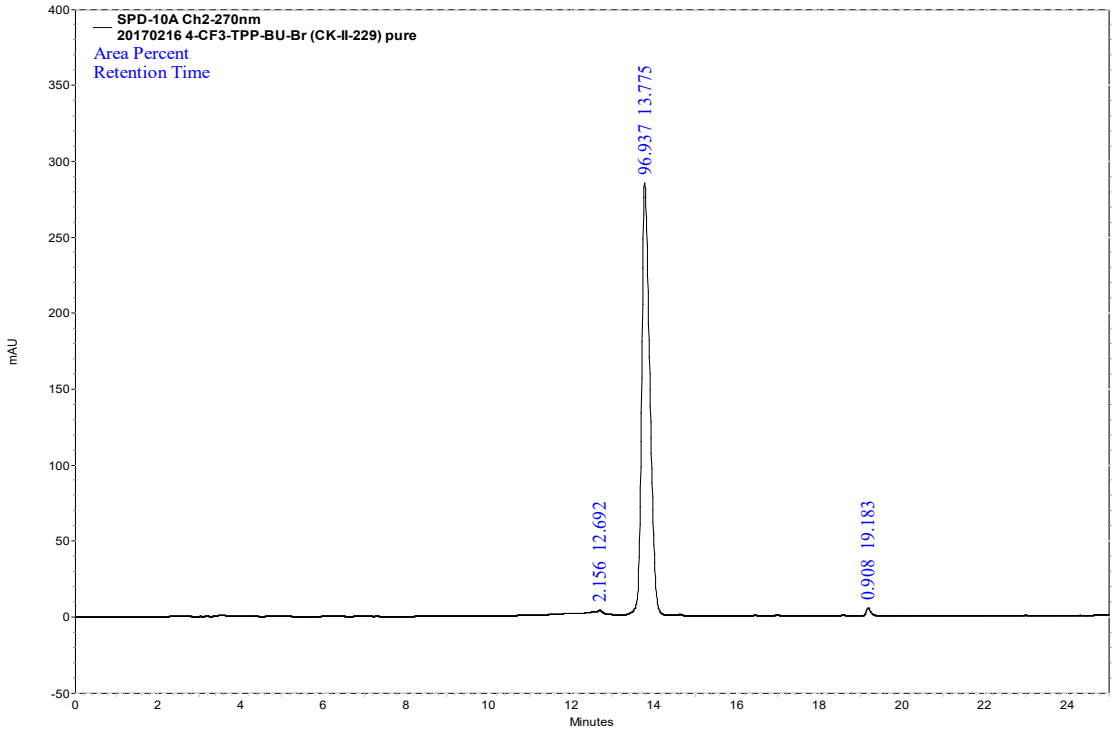
Supplemental Figure S47: HPLC chromatogram of H-TPP-BU (**17**)



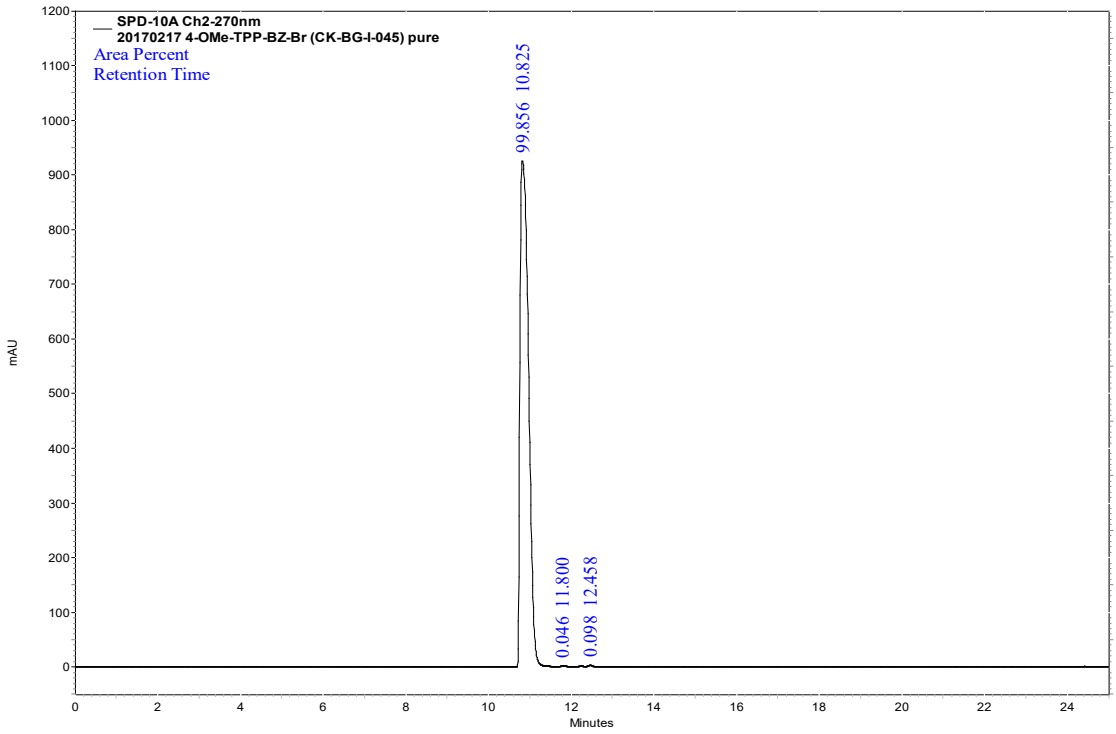
Supplemental Figure S48: HPLC chromatogram of 4-Cl-TPP-BU (**18**)



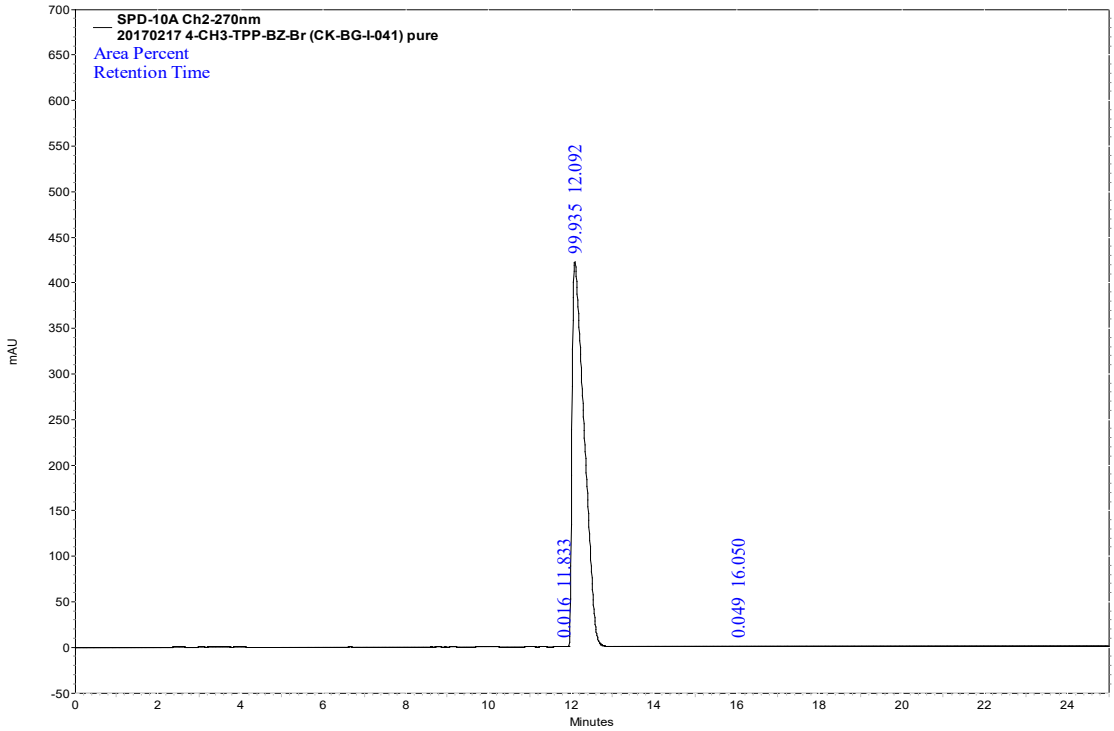
Supplemental Figure S49: HPLC chromatogram of 4-F-TPP-BU (**19**)



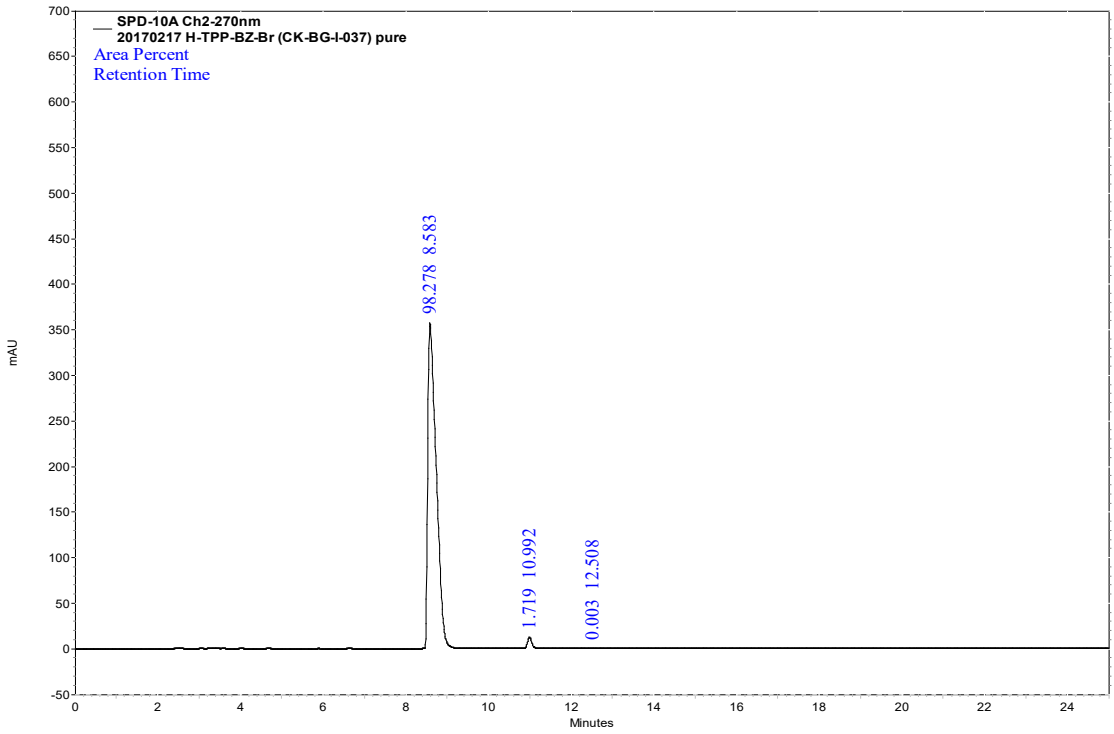
Supplemental Figure S50: HPLC chromatogram of 4-CF_3-TPP-BU (**20**)



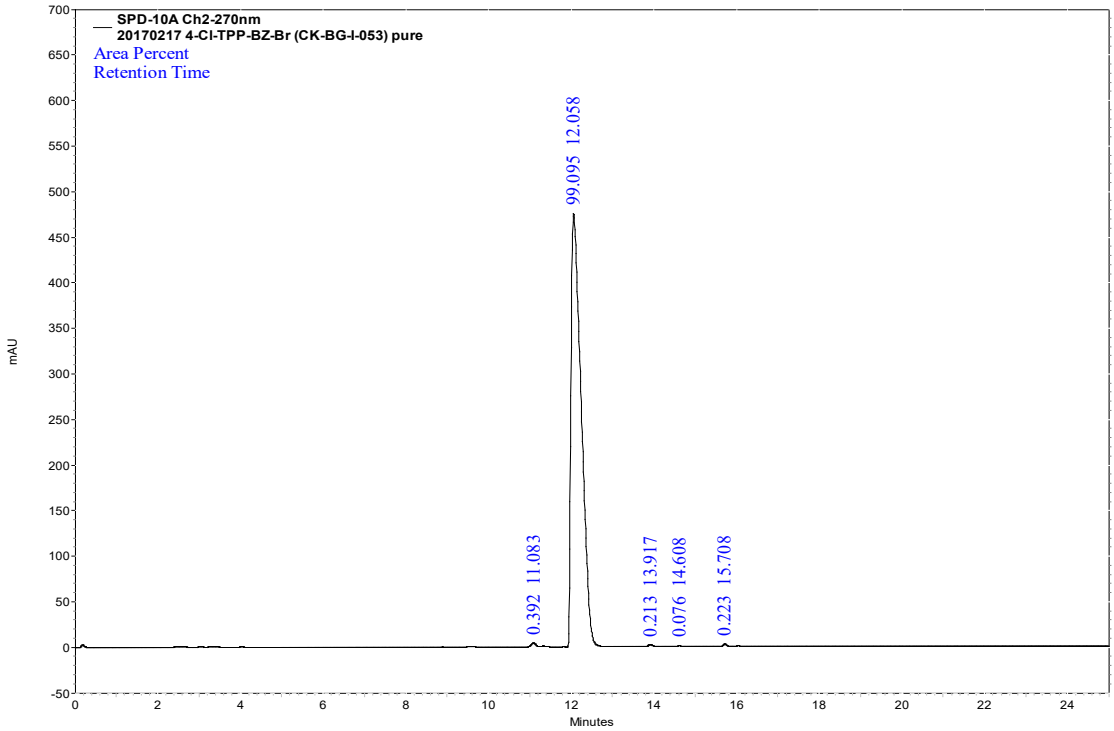
Supplemental Figure S51: HPLC chromatogram of 4-OMe-TPP-BZ (**22**)



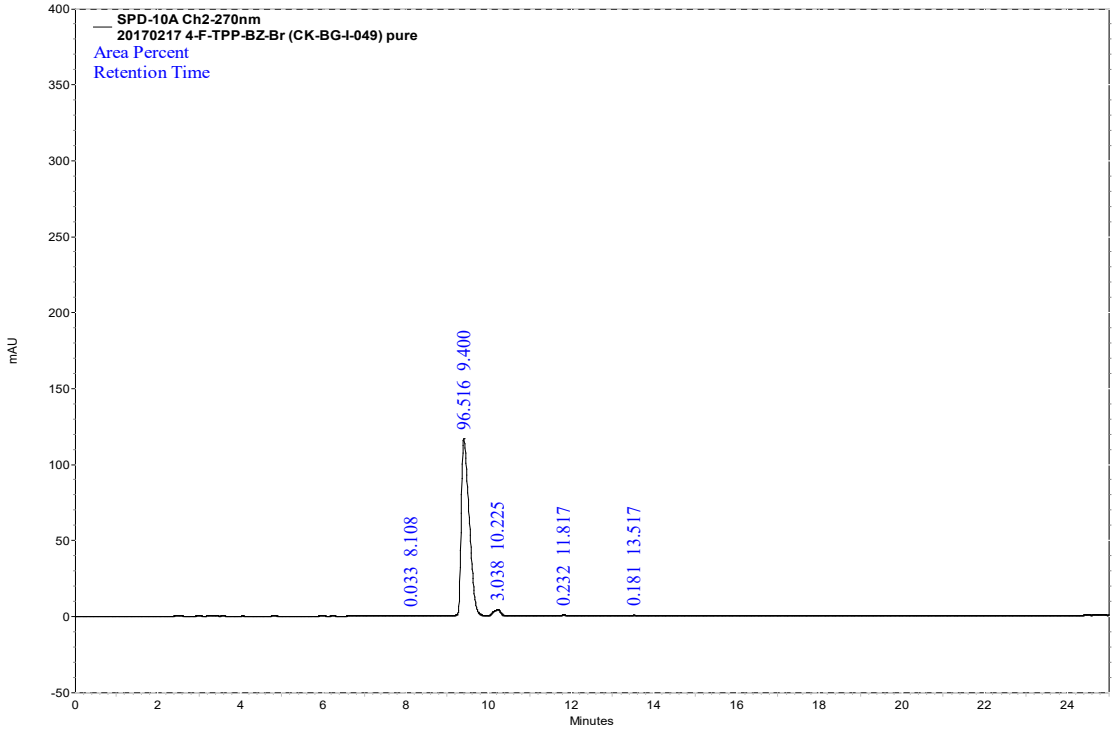
Supplemental Figure S52: HPLC chromatogram of 4-CH_3-TPP-BZ (**23**)



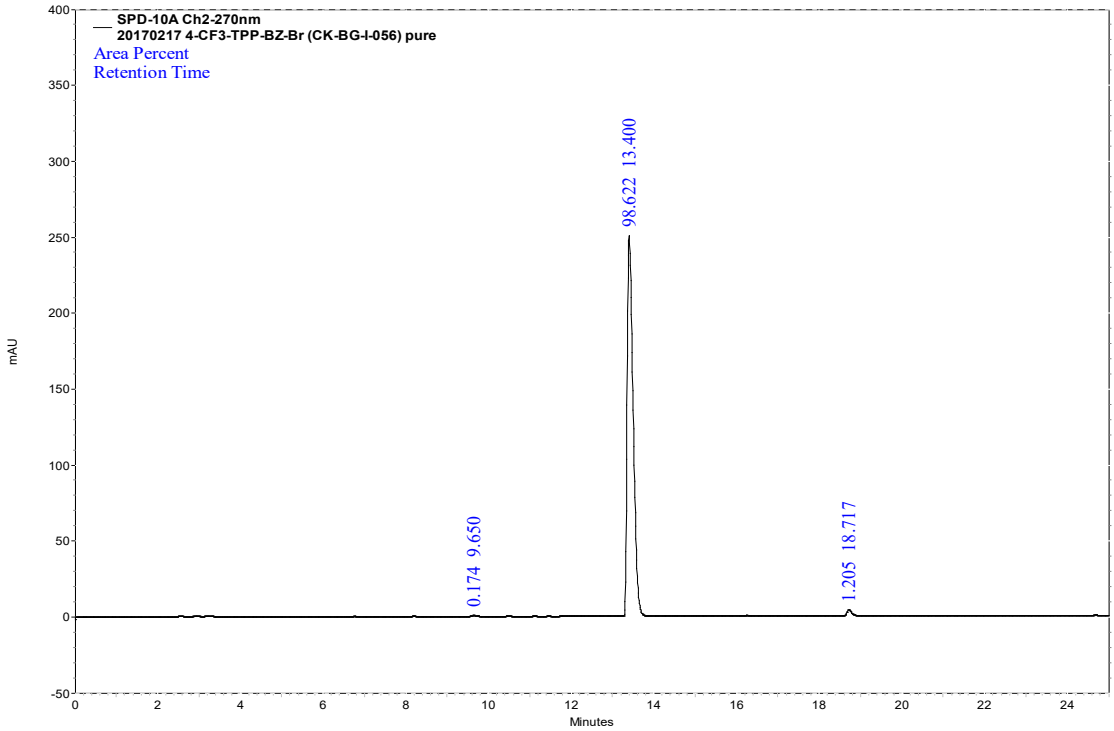
Supplemental Figure S53: HPLC chromatogram of H-TPP-BZ (**24**)



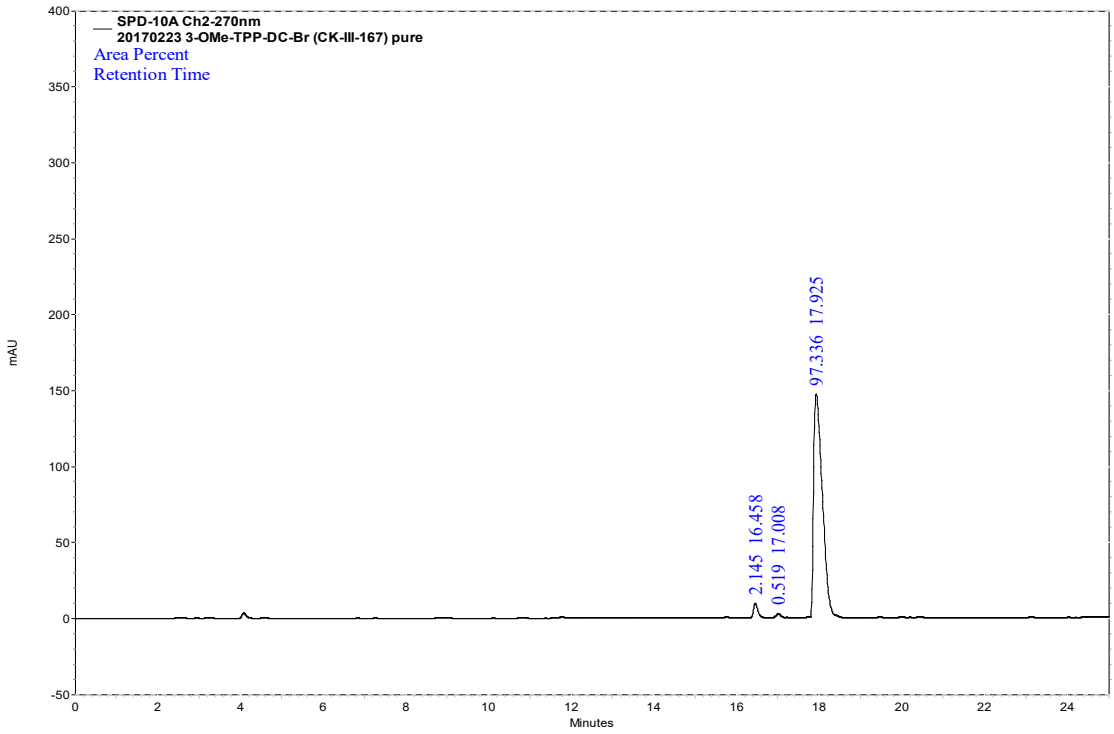
Supplemental Figure S54: HPLC chromatogram of 4-Cl-TPP-BZ (**25**)



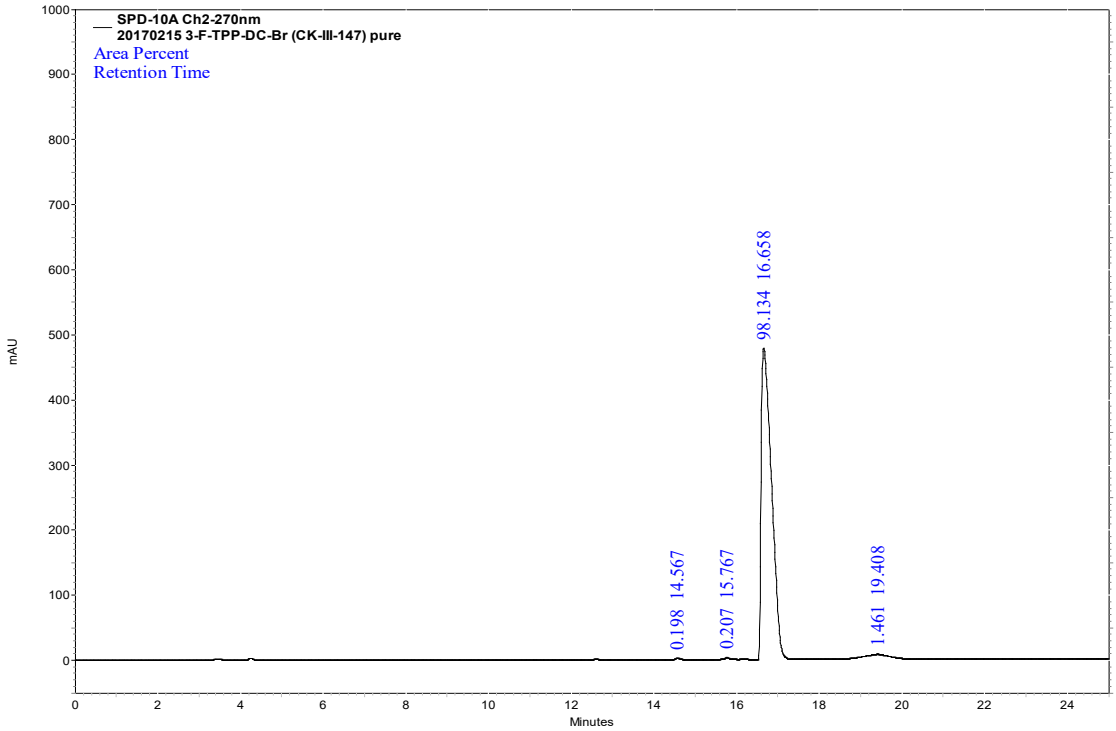
Supplemental Figure S55: HPLC chromatogram of 4-F-TPP-BZ (**26**)



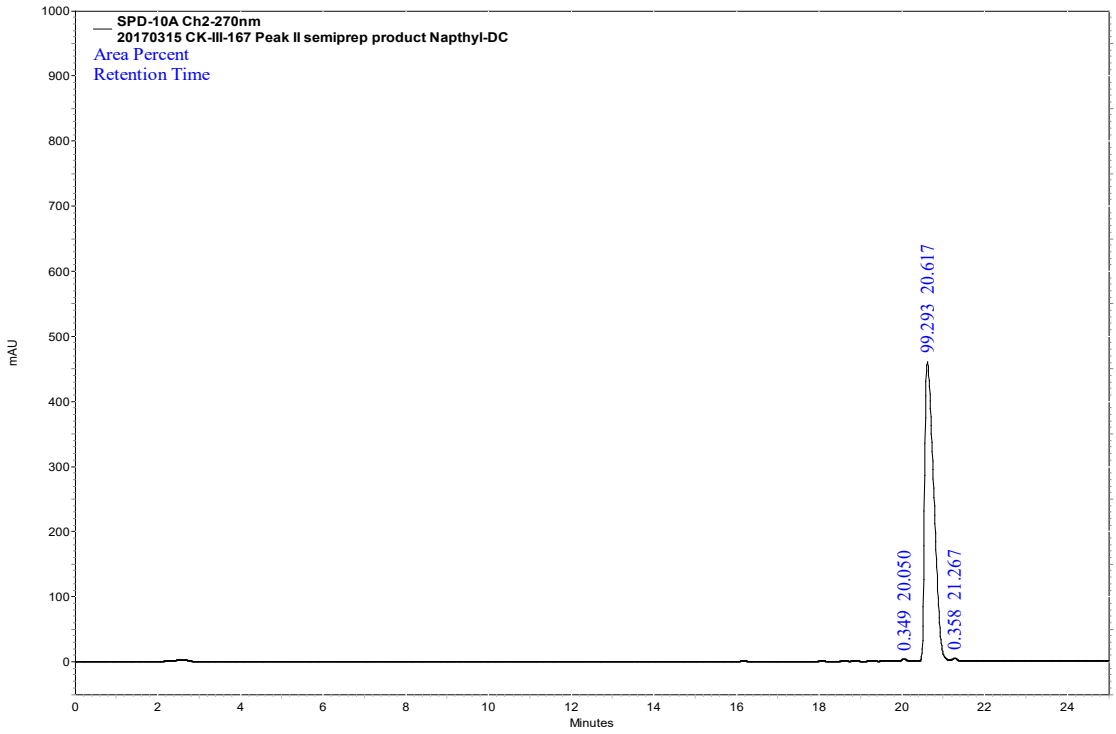
Supplemental Figure S56: HPLC chromatogram of 4-CF_3-TPP-BZ (**27**)



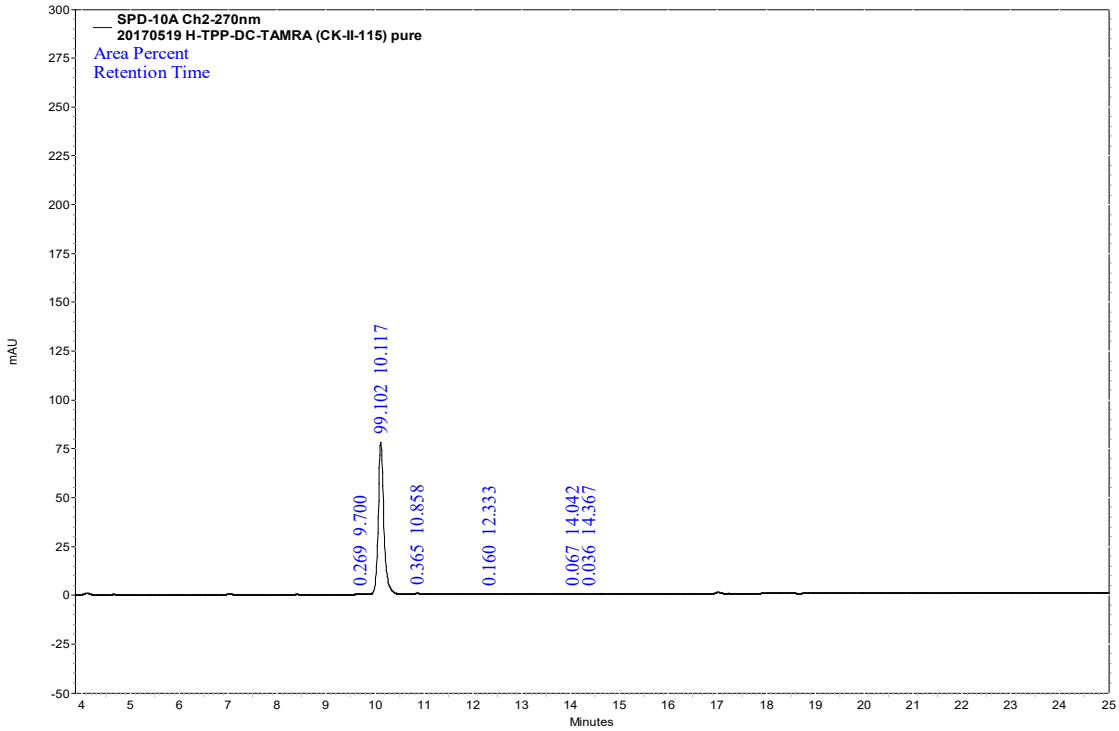
Supplemental Figure S57: HPLC chromatogram of 3-OMe-TPP-DC (**30**)



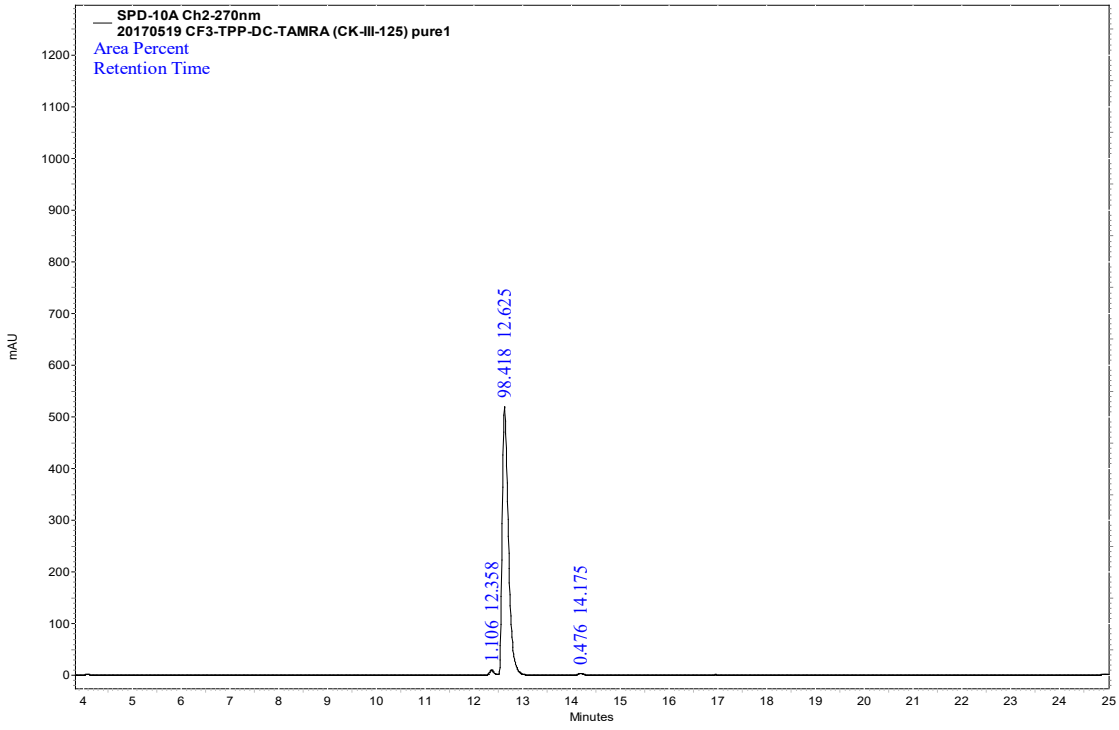
Supplemental Figure S58: HPLC chromatogram of 3-F-TPP-DC (**31**)



Supplemental Figure S59: HPLC chromatogram of Tri-Nap-P-DC-I (**33)**



Supplemental Figure S60: HPLC chromatogram of H-TPP-DC-TAMRA (**42**)



Supplemental Figure S61: HPLC chromatogram of 4-CF_3-TPP-DC-TAMRA (**43**)