SUPPORTING INFORMATION

Mechanistic Studies of a "Declick" Reaction

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I. General procedure

Materials

All materials used in the synthesis of compounds and related tests, were purchased from Sigma-Aldrich Chemical Co., Acros Organics, Tokyo Chemical Industry, etc. and used without further purification. The reactions were performed in standard glassware. Evaporation was done by rotatory evaporation using a standard rotovap equipped with dry ice condenser. NMR solvents were purchased from Cambridge Isotope Laboratories.

In the experiments described in this paper, the unpleasantness of the thiol smell released from the reactions was equivalent to or slightly worse than the odor of natural gas. However, as a precaution against even these levels of exposure, the reactions were carried out in a fume hood or in sealed cuvettes for spectra collection.

All cuvettes made by fused quartz were purchased from Starna Cells with standard screw and septum top.

Methods and instruments

Column chromatography

Column chromatography was performed using silica gel 60 (230 ± 400 mesh, 0.040 ± 0.063 mm) from Dynamic Adsorbents.

Nuclear magnetic resonance (NMR)

^{1}H and ^{13}C NMR spectra were recorded on Varian DirectDrive or Varian INOVA 400 MHz NMR spectrometers. The NMR spectra were referenced to solvent and the spectroscopic solvents ($CDCl_3$, CD_3CN, D_2O, DMSO-d_6, etc.) were purchased from Cambridge Isotope Laboratories and stored over 3 Å molecular sieves.

Liquid chromatography–mass spectrometry (LC-MS)

Finnigan MAT-VSQ 700 and DSQ spectrometers were used to obtain mass spectra. HR electrospray ionization (ESI) mass spectra were recorded using either Agilent 6530 Accurate-Mass Q-TOF LC/MS or MALDI-TOF (Vogayer, PerSeptive Biosystem).

High-resolution mass spectrometry (HRMS)

High-resolution mass spec (HRMS) analysis was conducted by the University of Texas Mass Spectrometry Facility using Agilent Technologies 6530 Accurate Mass Q-TOF LC/MS system. MALDI-TOF MS analysis was performed using an AB-Sciex Voyager-DE PRO MALDI-TOF equipped with a 337 nm nitrogen laser in linear mode using CHCA as a matrix.

UV-Vis spectroscopy

The UV-Vis absorbance spectra and kinetics were obtained in Cary 100 UV-Vis spectrophotometer from Agilent Technology. The spectra were run in Cary WinUV software: Scan, Kinetics and Scanning Kinetics, respectively.

II. pH dependence titration

Representative procedure for pH titrations: 2Ph-X (500 µM) was dissolved in 2:1 water:methanol and divided into two solutions. One solution was acidified with a drop of 12 M HCl and the other was basified with a drop of 7 M NaOH solution. The absorbance cuvette was charged with the acidic solution. The pH was measured and the absorbance was then taken. Basic solution was titrated in and absorbance spectra taken at varying pH (every 0.3-1.0 pH units). Once the pH of the solution stopped increasing, acidic solution was titrated back in to measure additional pH values in order to more accurately determine the pK_a. (Note the "bump" visible in the spectra at 345 nm is due to lamp switchover in the instrument.)

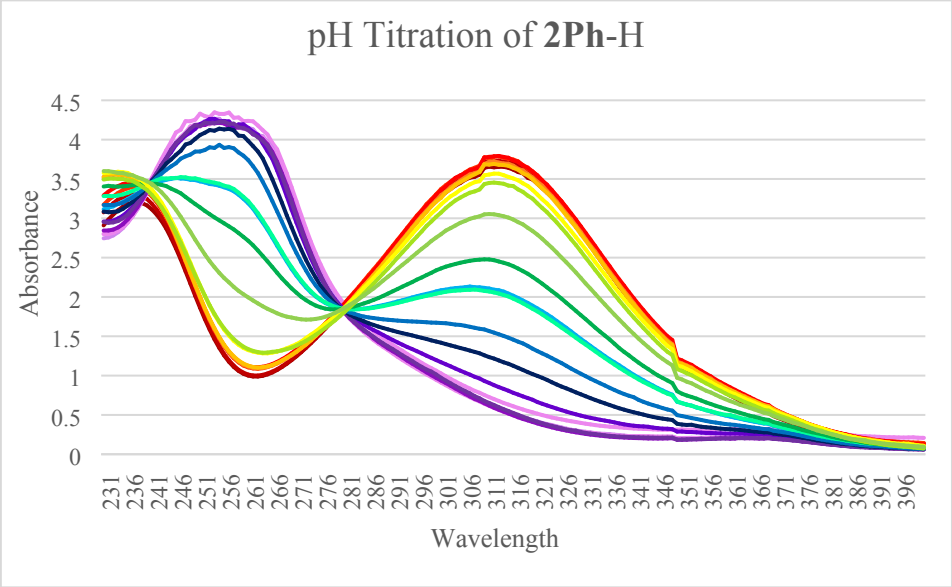


Figure S1. pH titration of 2Ph-H. Red indicates lowest pH's (0.65), purple indicates highest (13.52). Calculated pK_a = 6.02.

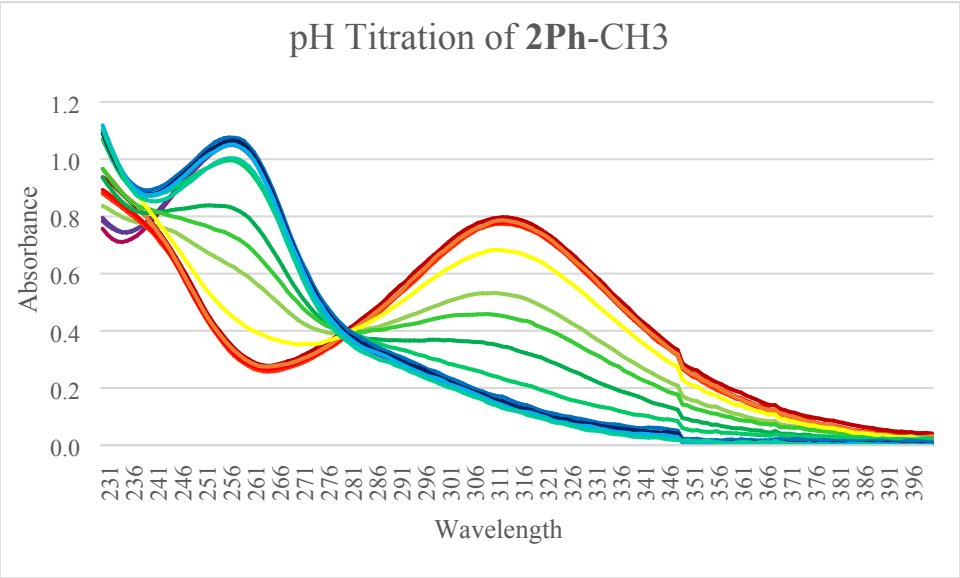


Figure S2. pH titration of 2Ph-CH_3. Red indicates lowest pH's (2.41), purple indicates highest (12.7). Calculated pK_a = 6.51.

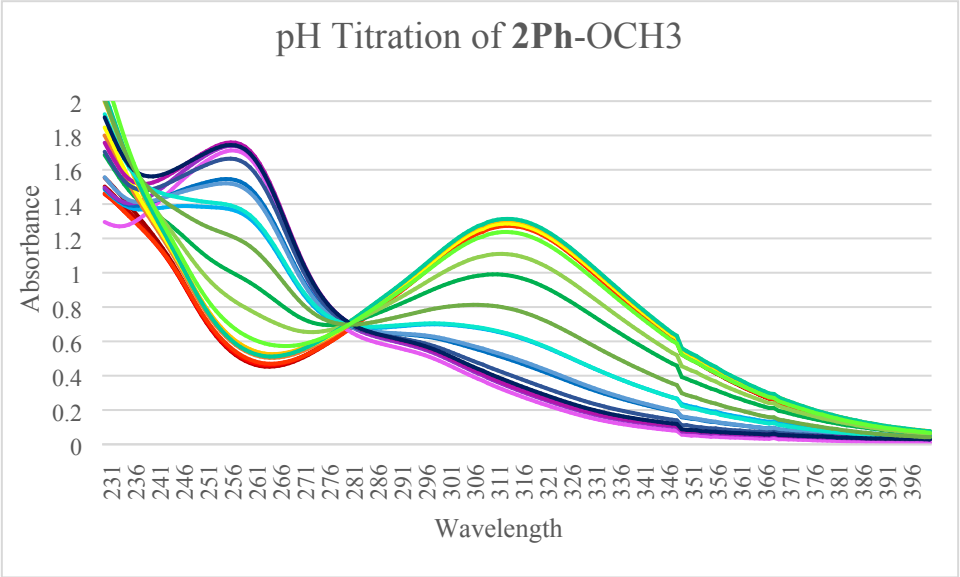


Figure S3. pH titration of 2Ph-OCH_3. Red indicates lowest pH's (0.87), purple indicates highest (11.64). Calculated pK_a = 6.54.

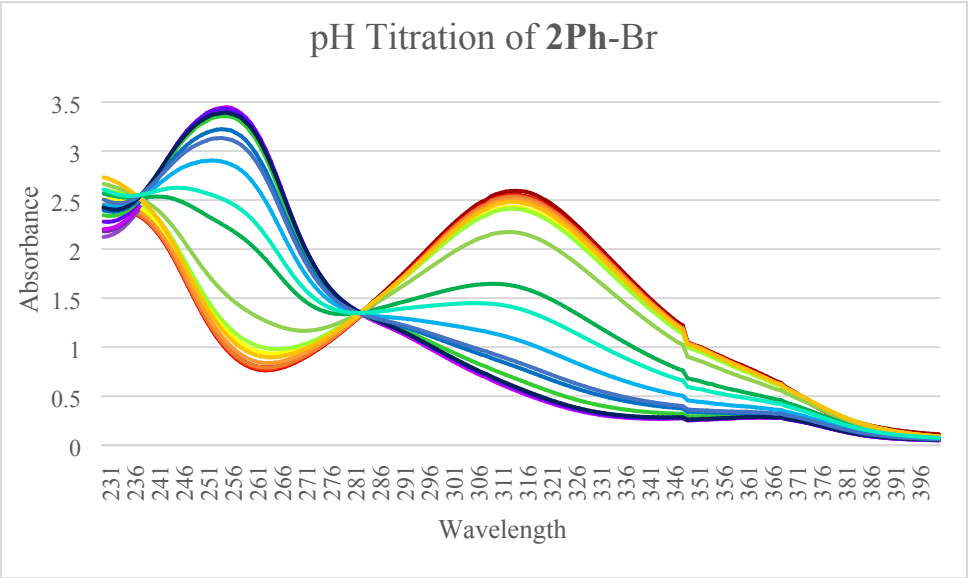


Figure S4. pH titration of 2Ph-Br. Red indicates lowest pH's (0.68), purple indicates highest (10.51). Calculated pK_a = 5.56.

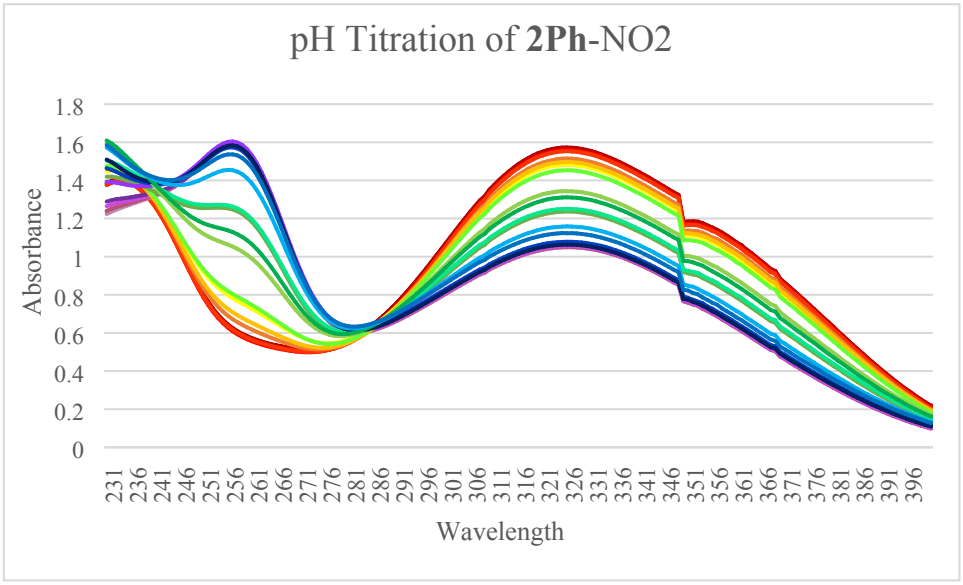


Figure S5. pH titration of 2Ph-NO_2. Red indicates lowest pH's (1.21), purple indicates highest (11.11). Calculated pK_a = 4.34.

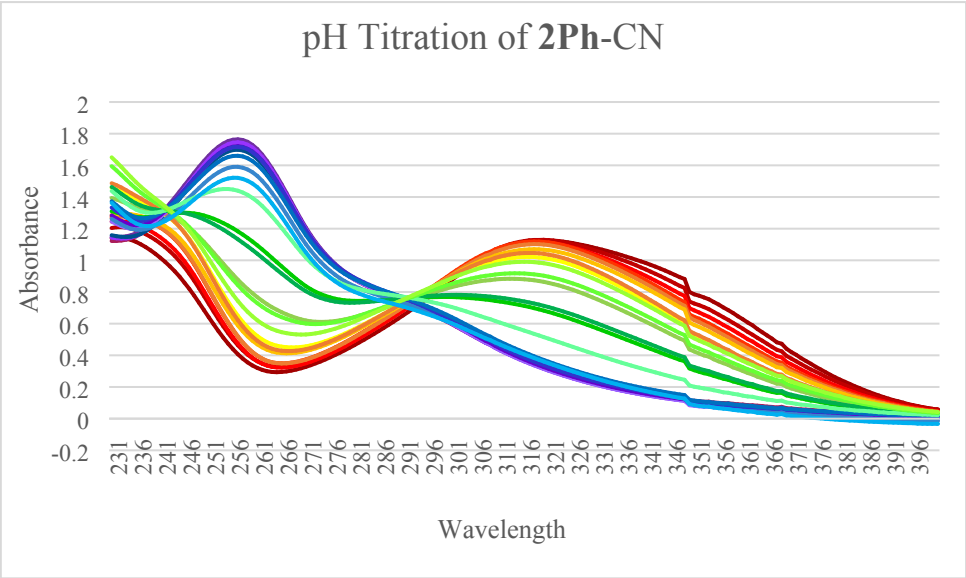
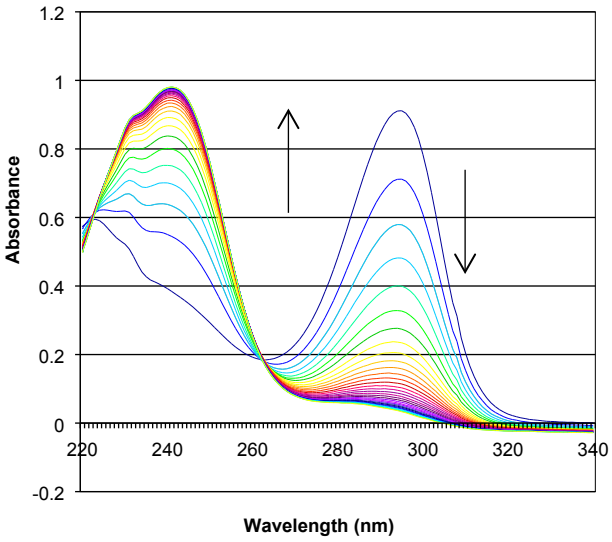


Figure S6. pH titration of 2Ph-CN. Red indicates lowest pH's (0.85), purple indicates highest (11.33). Calculated pK_a = 4.54.

A



B

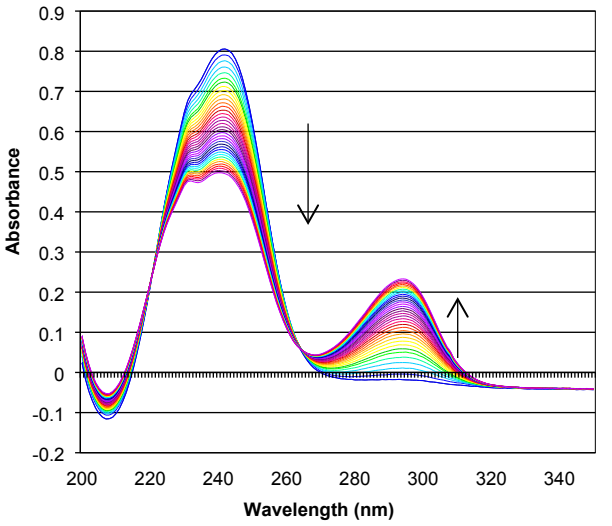


Figure S7. Acid/base induced reversibility of 3 and 7 (50 µM). (A) adjusted to pH 7.5 through adding aqueous sodium hydroxide (2 N) and then measured every 4 mins. (B) adjusted to pH 2.3 through adding aqueous hydrogen chloride (2 N) and then measured every 20 mins. UV-Vis time kinetics were carried out in (2:1) H2O/MeOH solvent mixture.

III. Reaction between 2Ph-X and β-mercaptoethanol

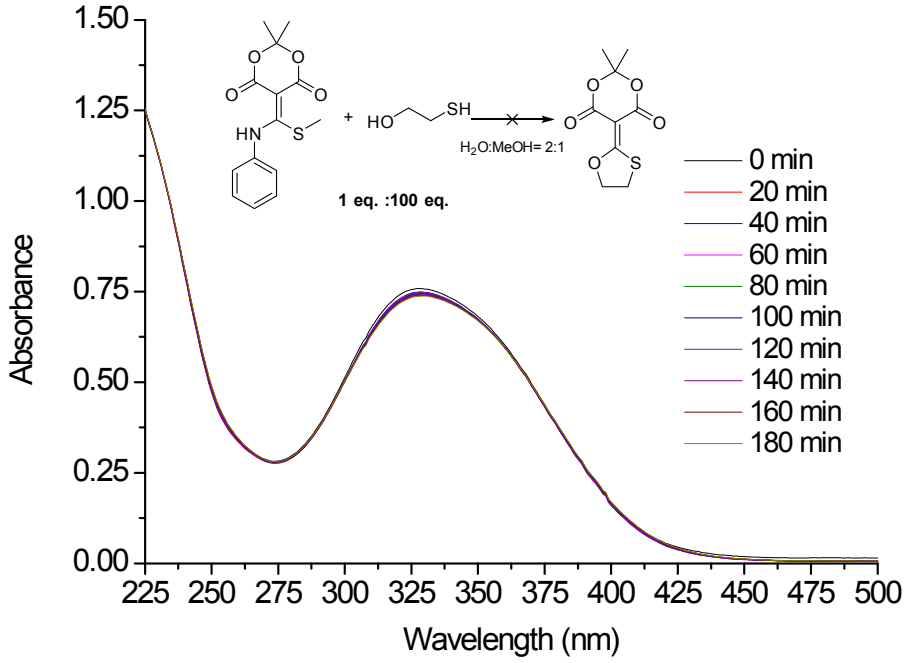


Figure S8. Time kinetics for UV-Vis absorbance of **2Ph**-H (50 μM) with 100 eq. β-mercaptoethanol in 2:1 H_2O:MeOH mixture.

IV. Time kinetics for 3 and 7

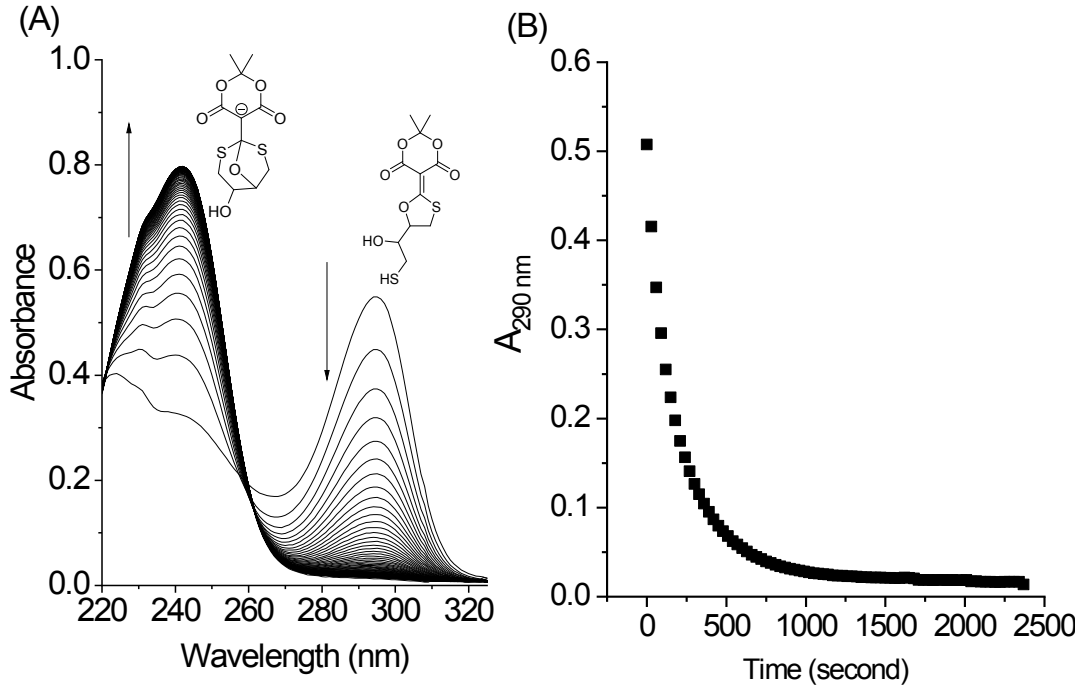


Figure S9. (A) Time kinetics for UV-Vis absorbance spectra of **3** (50 μM) (B) Time-kinetic curve for absorbance at 290 nm, referring to A. The detection was carried out in 2:1 H_2O:MeOH mixture.

V. Stability of 5

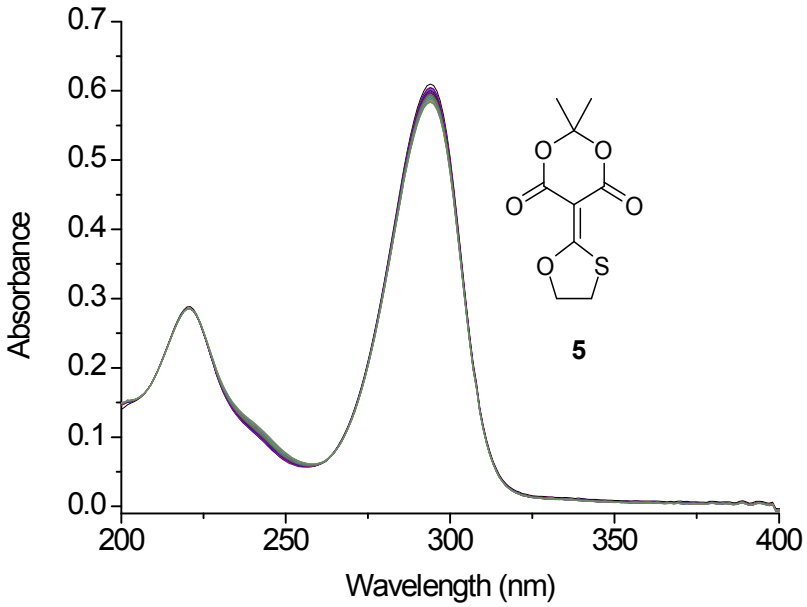


Figure S10. UV-Vis absorbance and stability test (0 – 120 mins) of **5** (50 μM) in 2:1 H_2O:MeOH mixture. Compound **5** is referred to as CABME.

VI. ^{1}H NMR time kinetics

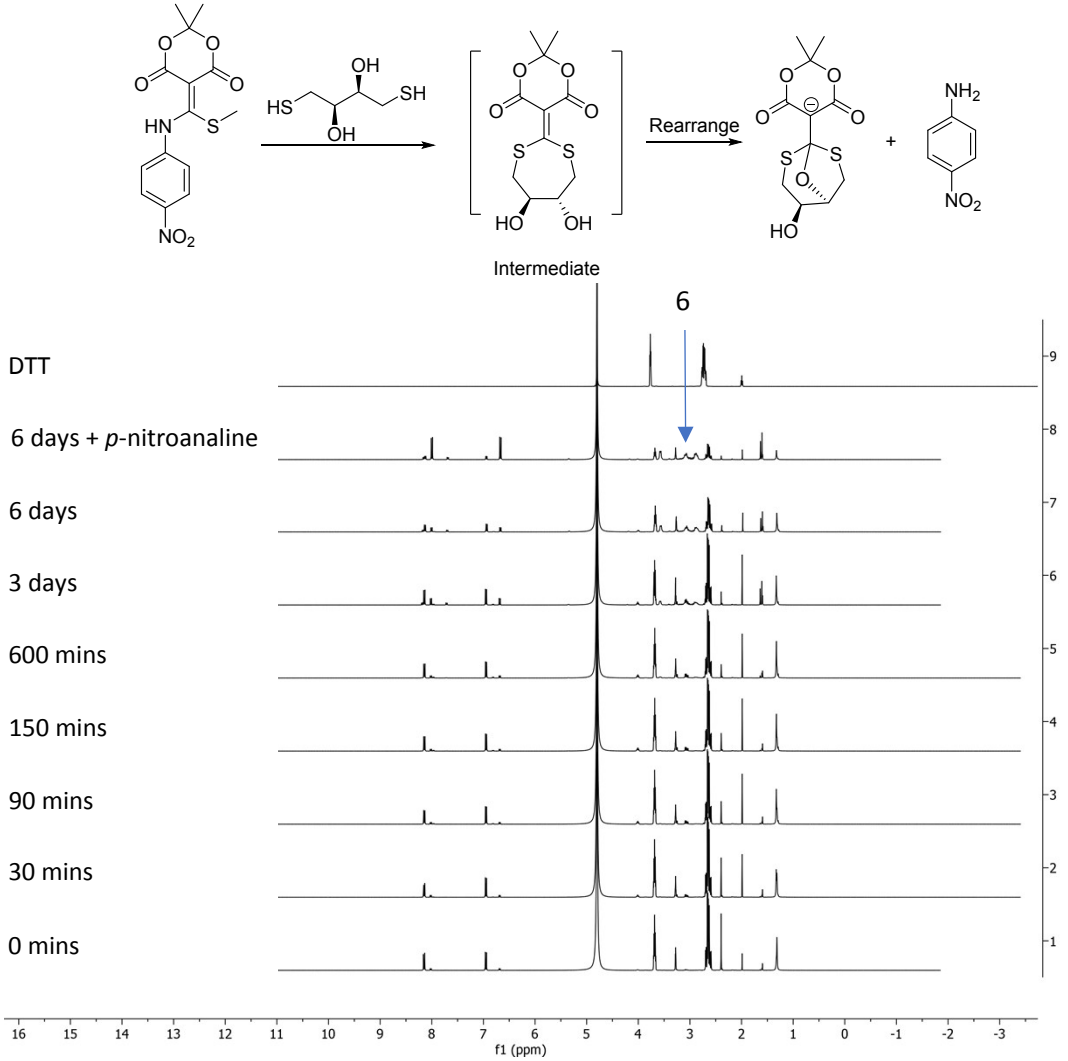
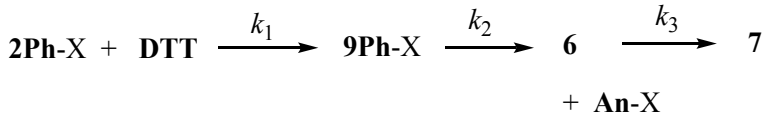


Figure S11. Time kinetics for ^{1}H-NMR spectra between **2Ph-NO$_2$** and DTT in 2:1 D_2O/MeOD mixture. Postulated the indicated resonances correspond to intermediate **6**.

VII. Kinetic Analysis in Detail

Although there are software packages that will do numerical integration of rate equations (DynaFit, Berkeley Madonna, Copasi) there are none that include SVD analysis of time resolved spectra. Applied Photophysics and OLIS offer software for SVD analysis based on using analytic solutions of rate equations and cannot be used to globally fit spectra collected at multiple concentrations, and suffer from the errors inherent in fitting data to multiple exponentials. It does not seem appropriate to reference alternative software that falls short of the needs for this study. Note that KinTek Explorer was modified to enable global fitting of data collected at multiple concentrations of DTT specifically for this study, and this extensive modification was paid for by KAJ through KinTek Corp.

Here we provide a summary of the data supporting the Hammett plot (Figure 6). We monitored the reaction of each derivative with DTT by measuring spectra as a function of time, as described in the main text for **2Ph**-H. The time-dependent spectra were resolved by singular value decomposition (SVD) analysis (1,2). The SVD amplitudes were then fit to a minimal model by nonlinear regression analysis based on numerical integration of the rate equations using KinTek Explorer (KinTek Corporation, Austin, TX).



Experiments performed at 1, 2, 5, and 10 mM DTT were fit simultaneously with the known spectra of the aniline derivatives (products of the reaction) included. However, unlike the case for **2Ph**-H, we did not include data to define the spectra of the products of the reaction. The value of k_3 was not well defined, so it was locked at 0.0002 s^{-1}. The purpose of this analysis was only to derive estimates for the values of k_1 and k_2 for each derivative. In achieving the best fit possible, we fit the SVD amplitude data, but also fit data directly to the spectra by deriving an extinction coefficient at each wavelength for each species. Alternating between the two methods helped to find the solution for the best fit to data. In each case, below we show the results of fitting the SVD amplitude vectors, which are weighted by their significance values.

By globally fitting the time-dependent spectra over a range of concentrations, the data provided good definition of the two rate constants, k_1 and k_2. However, there may be some limitations to the data because the absorption spectrum of **DTT** was subtracted from each data set and the high levels of absorbance at lower wavelengths may have exceeded the linear response range of the spectrophotometer. Thus, we were unable to provide reliable spectra for ***6*** and ***7*** and in some cases the best-fit predicted negative absorbance. Again because we are only using these data to obtained estimates for k_1 and and k_2, this was not considered to be a serious problem.

For each **2Ph**-X derivative below, we present the results of fitting the time-resolved spectra at 5 mM **DTT** as representative of data over the range of concentrations; that is, we show the fit to the SVD amplitude vectors, the predicted time dependence of species and the reconstituted spectra at 5 mM **DTT**. The predicted spectra of individual species are derived from the global fit to data at all concentrations.

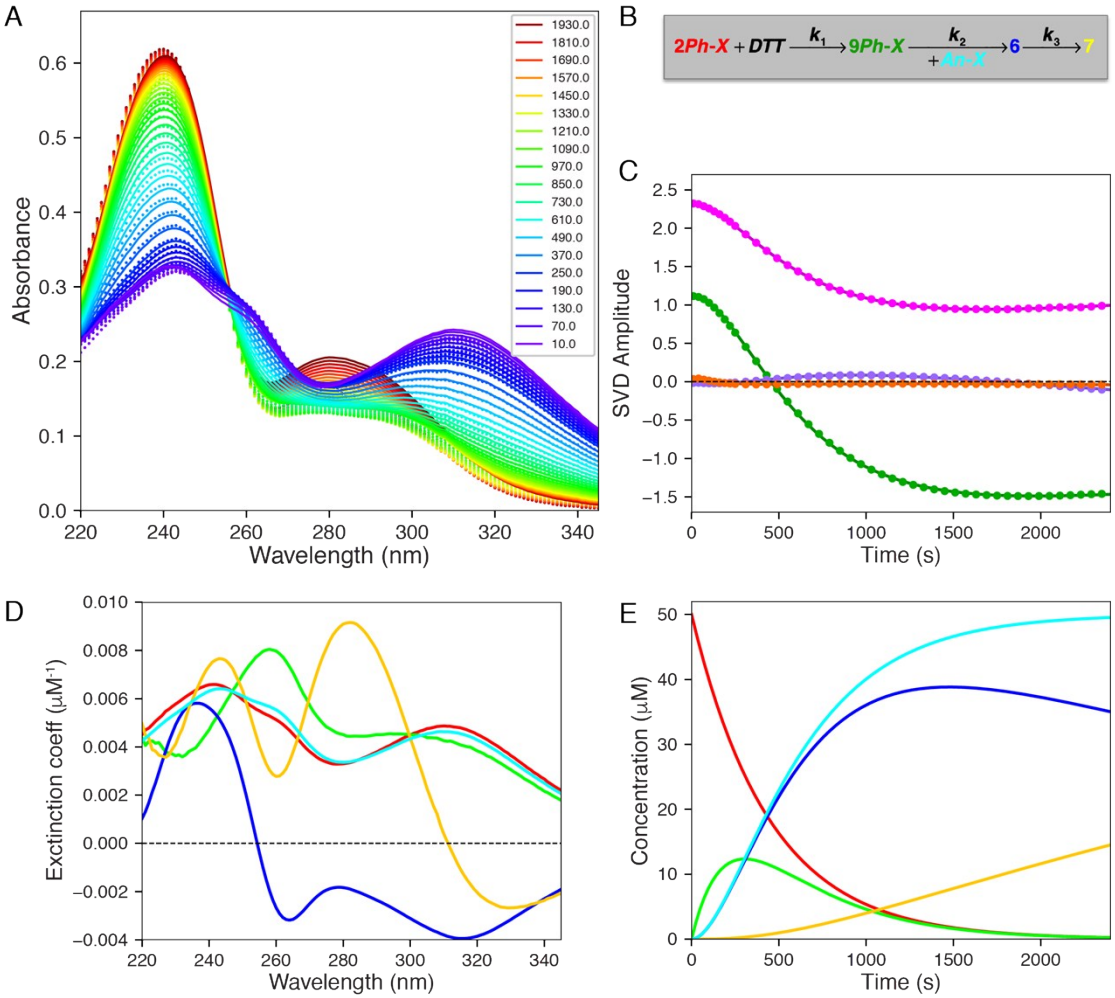


Figure S12. **Fitting time-resolved spectra for 2Ph-OH.** A. The reconstituted time-dependent spectra are shown (smooth lines) superimposed on the data (points). B. The reaction sequence with color-coding for each species in panels D and E. C. The fit to the SVD amplitude vectors at 5 mM DTT; note the colors do not correspond to any species. D. Predicted spectra of each species color coded at shown in B. E. Time dependence of each species, color-coded as in B. Note the matrix for the reconstituted spectra are a product of vectors in panels D and E.

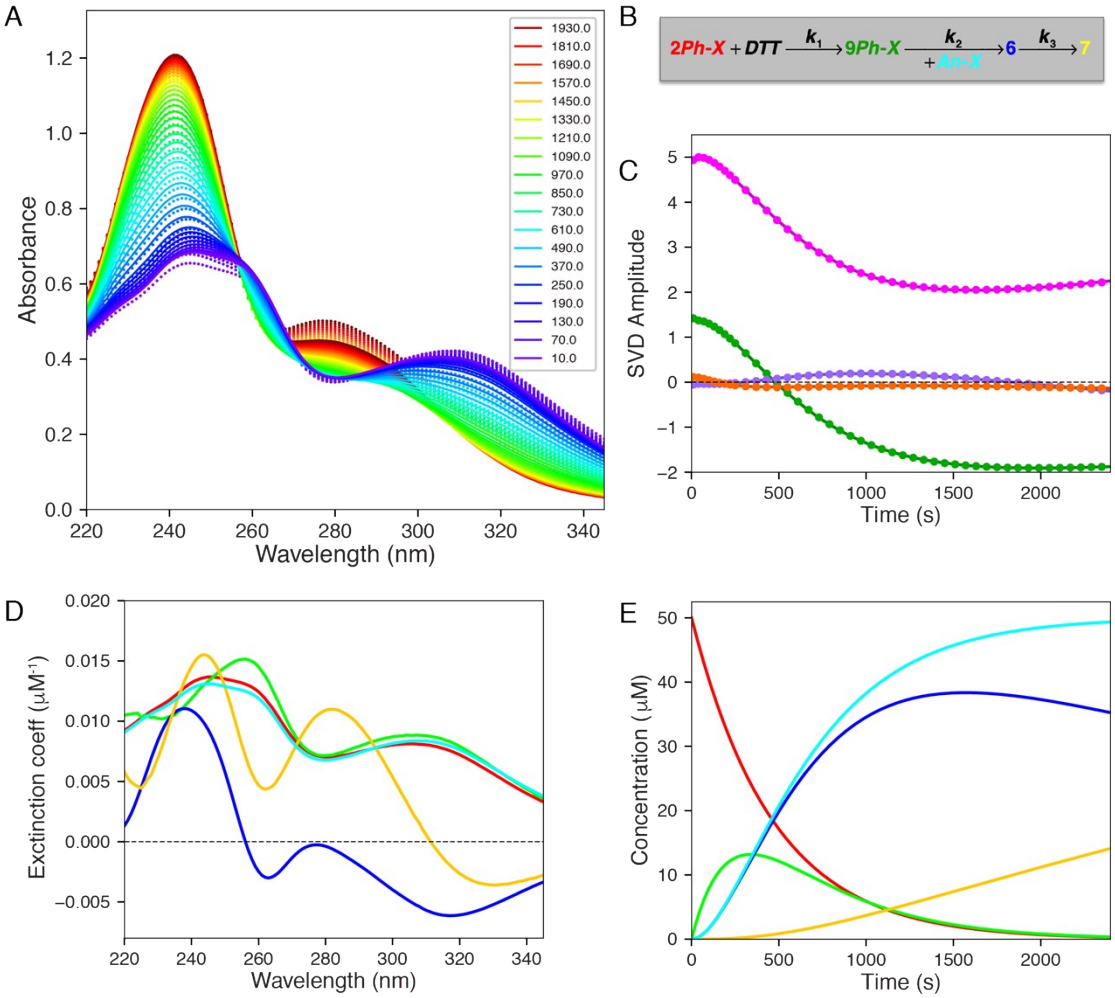


Figure S13. **Fitting time-resolved spectra for 2Ph-OMe.** A. The reconstituted time-dependent spectra are shown (smooth lines) superimposed on the data (points). B. The reaction sequence with color-coding for each species in panels D and E. C. The fit to the SVD amplitude vectors at 5 mM DTT; note the colors do not correspond to any species. D. Predicted spectra of each species color coded at shown in B. E. Time dependence of each species, color-coded as in B. Note the matrix for the reconstituted spectra are a product of vectors in panels D and E.

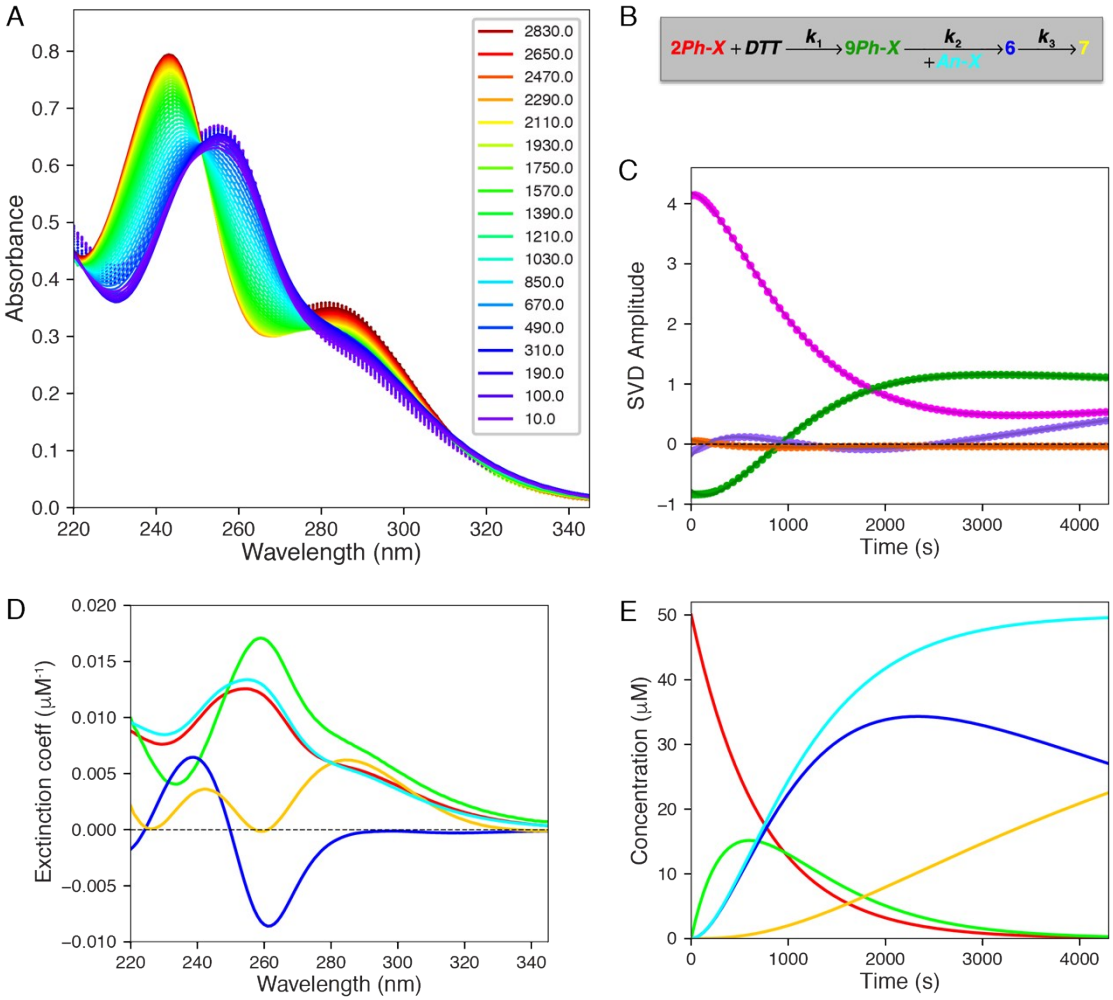


Figure S14. Fitting time-resolved spectra for 2Ph-Br. A. The reconstituted time-dependent spectra are shown (smooth lines) superimposed on the data (points). B. The reaction sequence with color-coding for each species in panels D and E. C. The fit to the SVD amplitude vectors at 5 mM DTT; note the colors do not correspond to any species. D. Predicted spectra of each species color coded at shown in B. E. Time dependence of each species, color-coded as in B. Note the matrix for the reconstituted spectra are a product of vectors in panels D and E.

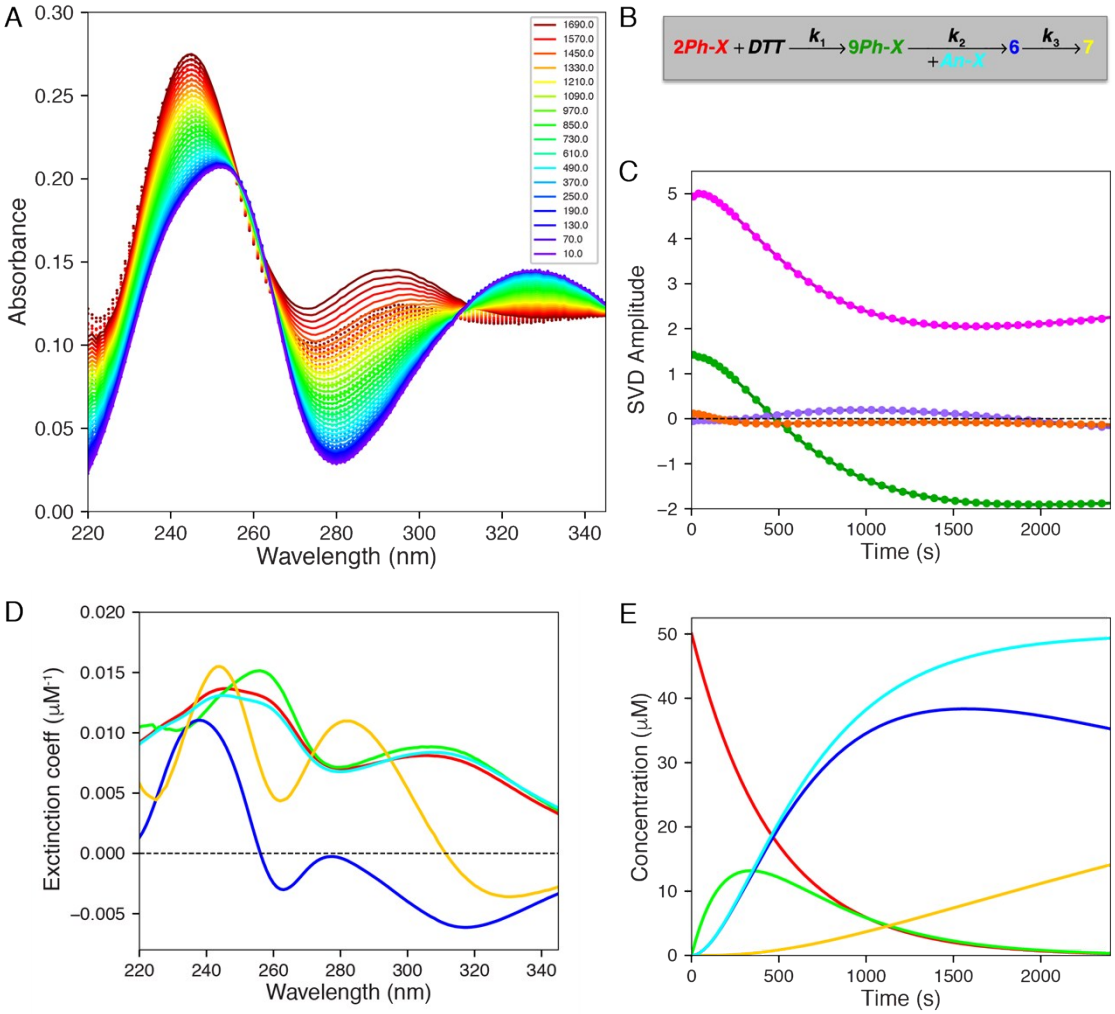


Figure S15. Fitting time-resolved spectra for 2Ph-NO_2. A. The reconstituted time-dependent spectra are shown (smooth lines) superimposed on the data (points). B. The reaction sequence with color-coding for each species in panels D and E. C. The fit to the SVD amplitude vectors at 5 mM DTT; note the colors do not correspond to any species. D. Predicted spectra of each species color coded at shown in B. E. Time dependence of each species, color-coded as in B. Note the matrix for the reconstituted spectra are a product of vectors in panels D and E.

VIII. Time kinetics for 2Ph-X with DTT

Representative procedure for kinetics experiments: 2Ph-X was dissolved in 2:1 water:methanol (50 µM). **DTT** was added to the solution and the vial sealed. The solution was scanned every 30 min for 240 min then every 60 min until 2400 total minutes had passed, unless otherwise specified. In each spectra t=0 is red.

2Ph-H:

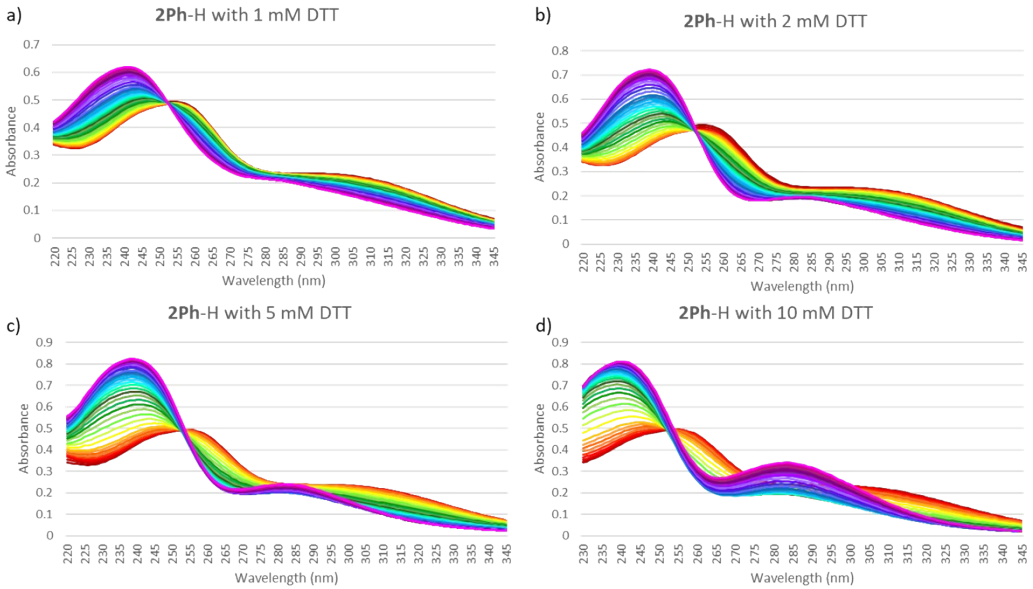


Figure S16. Time-kinetic experiment for reaction between **2Ph**-H and **DTT** with various amounts of concentration.

2Ph-OCH_3:

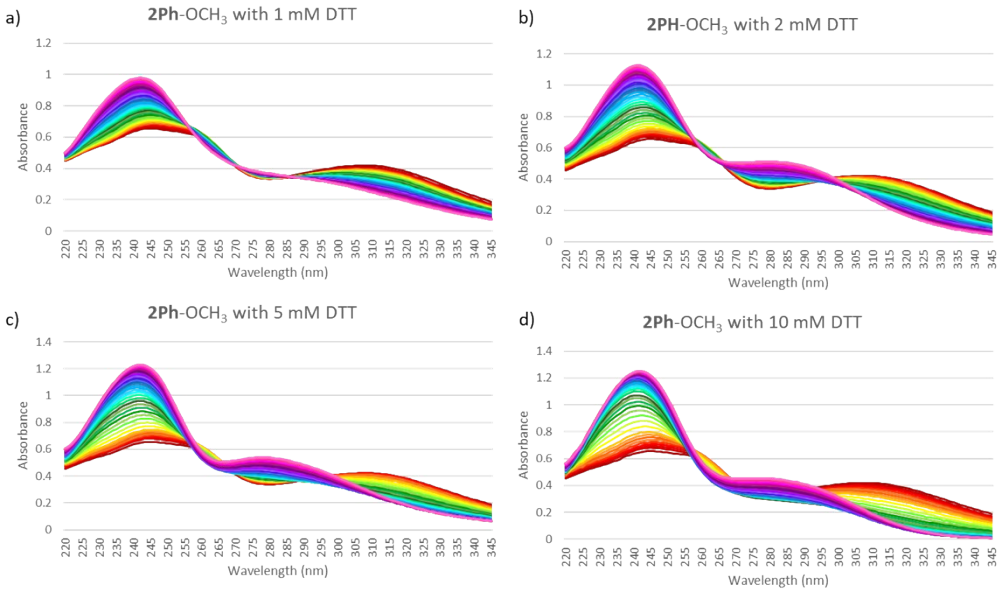


Figure S17. Time-kinetic experiment for reaction between **2Ph**-OCH_3 and **DTT** with various amounts of concentration.

2Ph-OH:

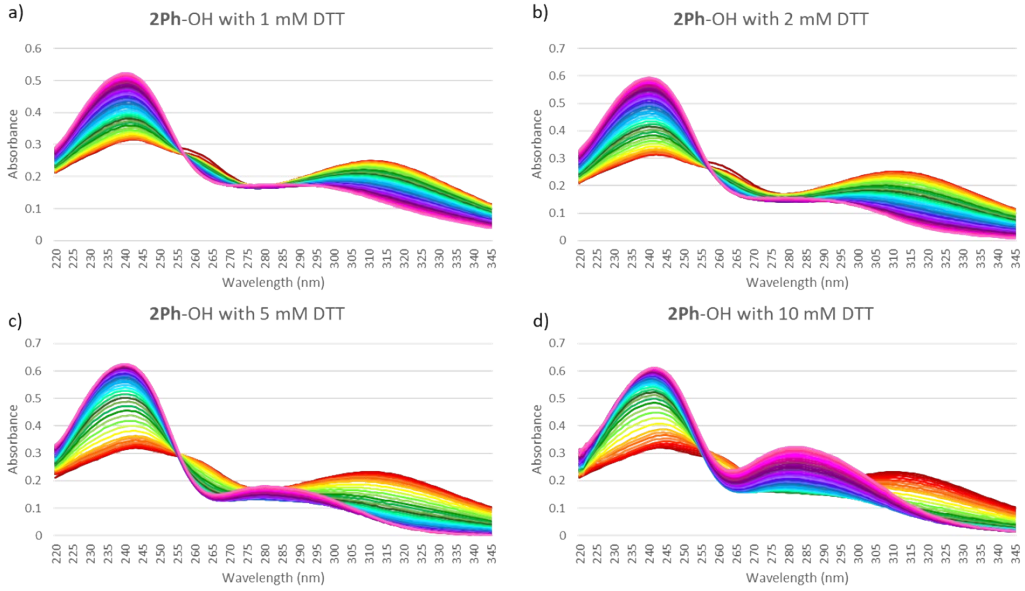


Figure S18. Time-kinetic experiment for reaction between **2Ph**-OH and **DTT** with various amounts of concentration.

2Ph-Br: **2Ph**-Br did not show enough product formation at 2400 min for kinetic analysis so experiment was extended to 4320 min. Additionally the experiment with 10 mM DTT showed too much background absorbance from the DTT for clean analysis and was omitted from final analysis.

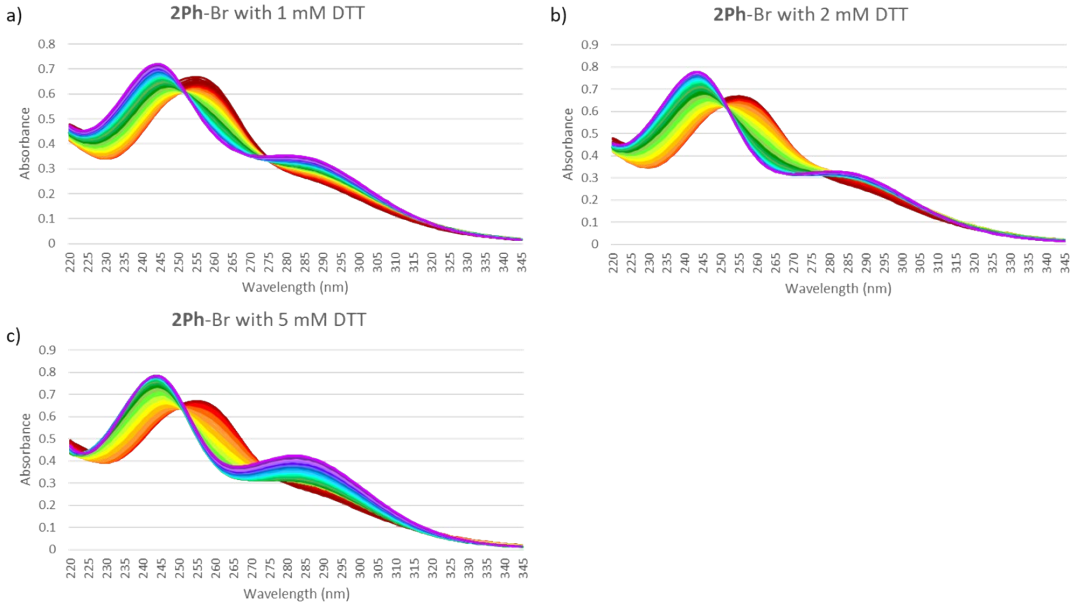


Figure S19. Time-kinetic experiment for reaction between **2Ph**-Br and **DTT** with various amounts of concentration.

2Ph-NO_2: **2Ph**-NO_2 did not show enough product formation with 1 mM **DTT** for kinetic analysis so the 1 mM **DTT** experiment was excluded.

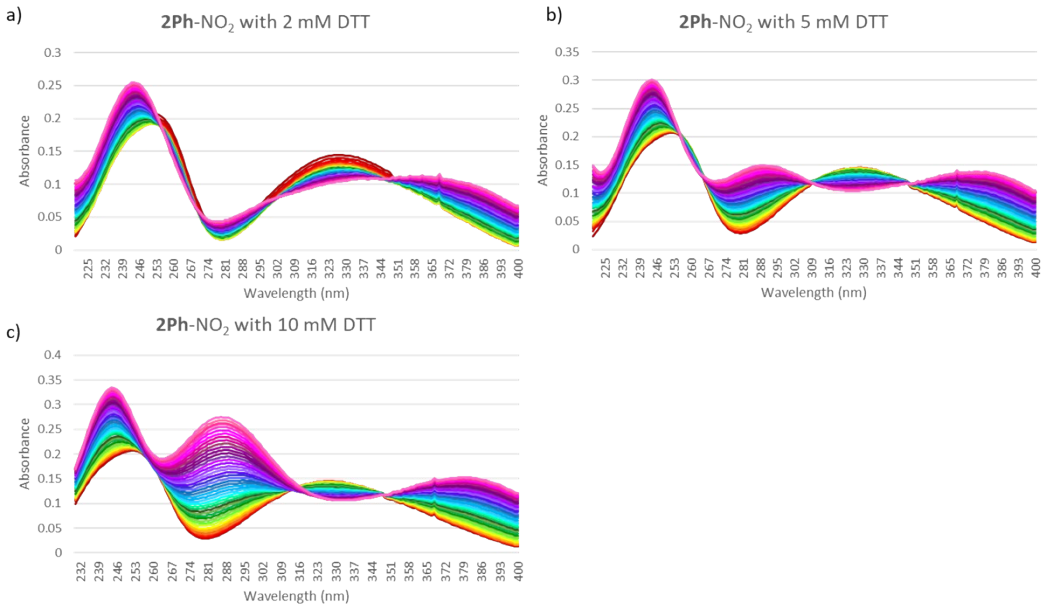


Figure S20. Time-kinetic experiment for reaction between **2Ph**-NO_2 and **DTT** with various amounts of concentration.

IX. Synthetic procedure

Representative procedure for the synthesis of compounds **2Ph-X**: 1 (0.0805 mmol, 20 mg) is dissolved in 9.6 mL 5:1 pH 7.2 phosphate buffer:acetonitrile. Aniline (0.0805 mmol) was added to the reaction mixture and a nitrogen sparged through for 16 hours. The reaction mixture was purified by reverse phase chromatography (acetonitrile:water).

2Ph-H: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.45 (m, 2H), 7.37 (m, 1H), 7.32 (m, 2H), 2.28 (s, 3H), 1.77 (s, 6H). HRMS (ESI): m/z calculated for C11H16NO4 $[M+Na]^+$: 244.1118, found 244.1116.

2Ph-CH_3: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, 2H, J = 8.12 Hz), 7.18 (m, 2H), 2.39 (s, 3H), 2.29 (s, 3H), 1.76 (s, 6H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 178.11, 138.25, 134.56, 130.05, 125.19, 103.07, 85.83, 26.35, 21.13, 18.89. HRMS (ESI): m/z calculated for C15H17NO4S $[M-H]^-$: 306.08060, found 306.0801.

2Ph-OCH_3: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.20 (m, 2H), 6.93 (m, 2H), 3.83 (s, 3H), 2.30 (s, 3H), 1.75 (s, 6H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 178.35, 159.19, 129.81, 126.81, 114.57, 103.05, 85.49, 55.52, 26.34, 18.87. HRMS (ESI): m/z calculated for C15H17NO5S $[M+Na]^+$: 346.07200, found 346.0721.

2Ph-Br: ^{1}H-NMR (400 MHz, CD_3CN): δ = 7.32 (d, 2H, J = 8.52 Hz), 6.81 (d, 2H, J = 8.02 Hz), 2.35 (s, 3H), 1.38 (s, 6H). ^{13}C-NMR (400 MHz, CD_3CN): δ = 132.70, 126.91, 121.72, 103.32, 86.78, 26.41, 19.07, 8.59. HRMS (ESI): m/z calculated for C14H14NO4SBr $[M-H]^-$: 369.97540 and 371.97340, found 369.9753 and 371.9734.

2Ph-NO_2: ^{1}H-NMR (400 MHz, CD_3OD): δ = 8.01 (m, 2H), 6.93 (m, 2H), 2.31 (m, 3H), 1.31 (s, 6H). ^{13}C-NMR (400 MHz, CD_3OD): δ = 164.99, 143.41, 123.71, 121.38, 102.10, 24.50, 13.71. HRMS (ESI): m/z calculated for C14H14N2O6S $[M-H]^-$: 337.05000, found 337.0500.

2Ph-CO_2H: ^{1}H-NMR (400 MHz, CD_3OD): δ = 8.52 (m, 2H), 7.55 (m, 2H), 3.05 (s, 3H), 2.04 (s, 6H). ^{13}C-NMR (400 MHz, CD_3OD): δ = 175.03, 165.73, 131.68, 130.66, 129.68, 120.16, 114.94, 103.67, 78.73, 14.07. HRMS (ESI): m/z calculated for C15H15NO6S $[M-H]^-$: 336.05470, found 336.0538.

2Ph-$N(CH_3)_2$: ^{1}H-NMR (400 MHz, CD3OD): δ = 7.13 (m, 2H), 6.79 (m, 2H), 2.97 (s, 6H), 2.35 (s, 3H), 1.71 (s, 6H). ^{13}C-NMR (400 MHz, CD3OD): δ = 164.29, 125.59, 112.10, 109.99, 102.82, 39.24, 29.25, 24.92. HRMS (ESI): m/z calculated for C16H20N2O4S [M-H]-: 335.10710, found 335.1069.

2Ph-CN: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, 2H, J = 8.44 Hz), 7.41 (d, 2H, J = 8.21 Hz), 2.29 (s, 3H), 1.72 (s, 6H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 192.66, 159.93, 133.43, 125.16, 103.50, 103.21, 103.01, 26.80, 26.45, 21.45, 19.02. HRMS (ESI): m/z calculated for C15H14N2O4S $[M-H]^-$: 317.06020, found 317.0604.

2Ph-OH: HRMS (ESI): m/z calculated for C14H15NO5S $[M-H]^-$: 308.05980, found 308.0595.

X. NMR spectra

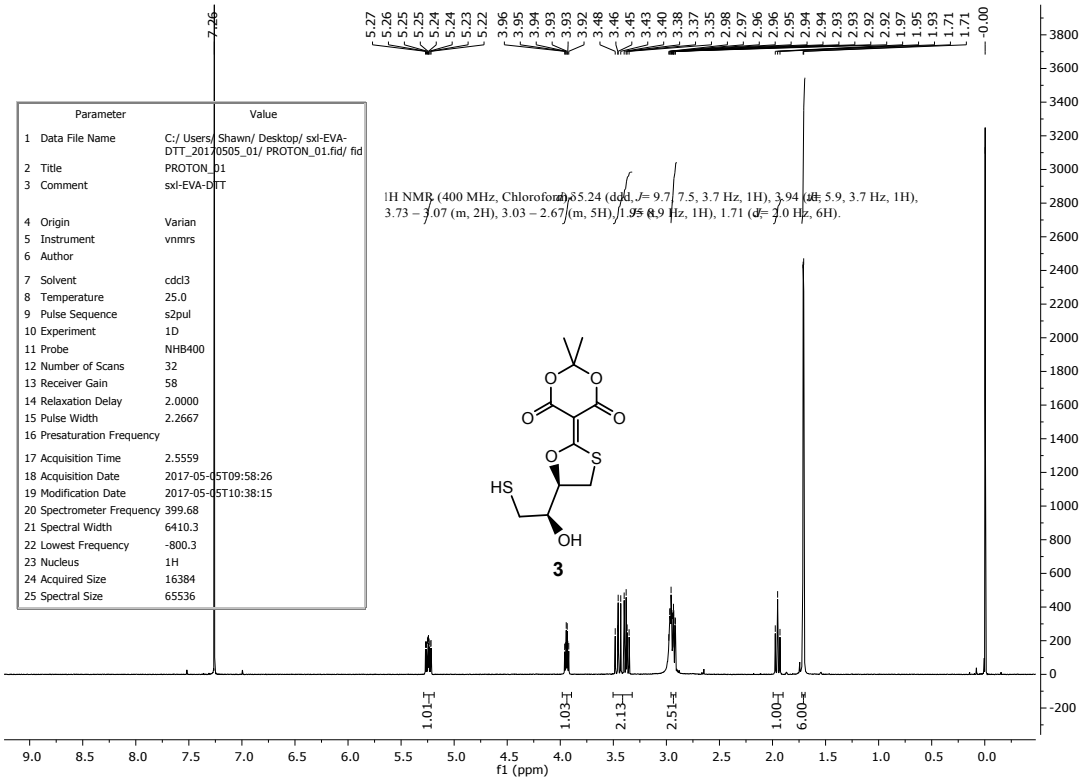


Figure S21. ^{1}H NMR for compound **3** in $CDCl_3$.

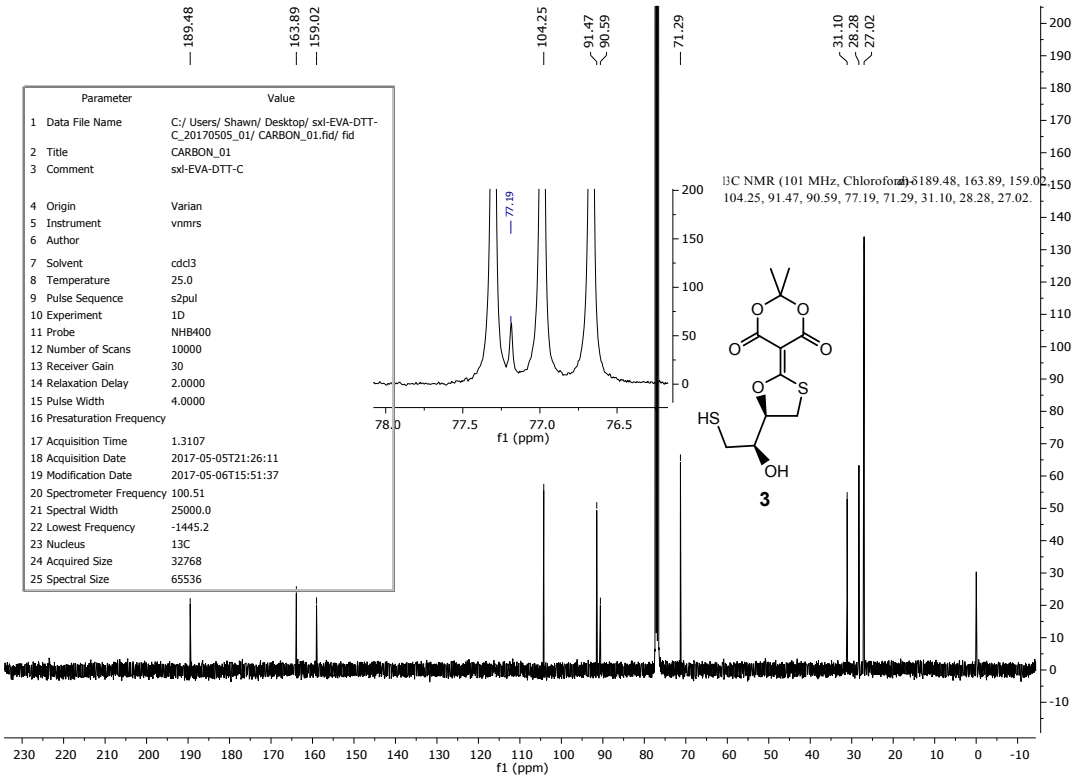
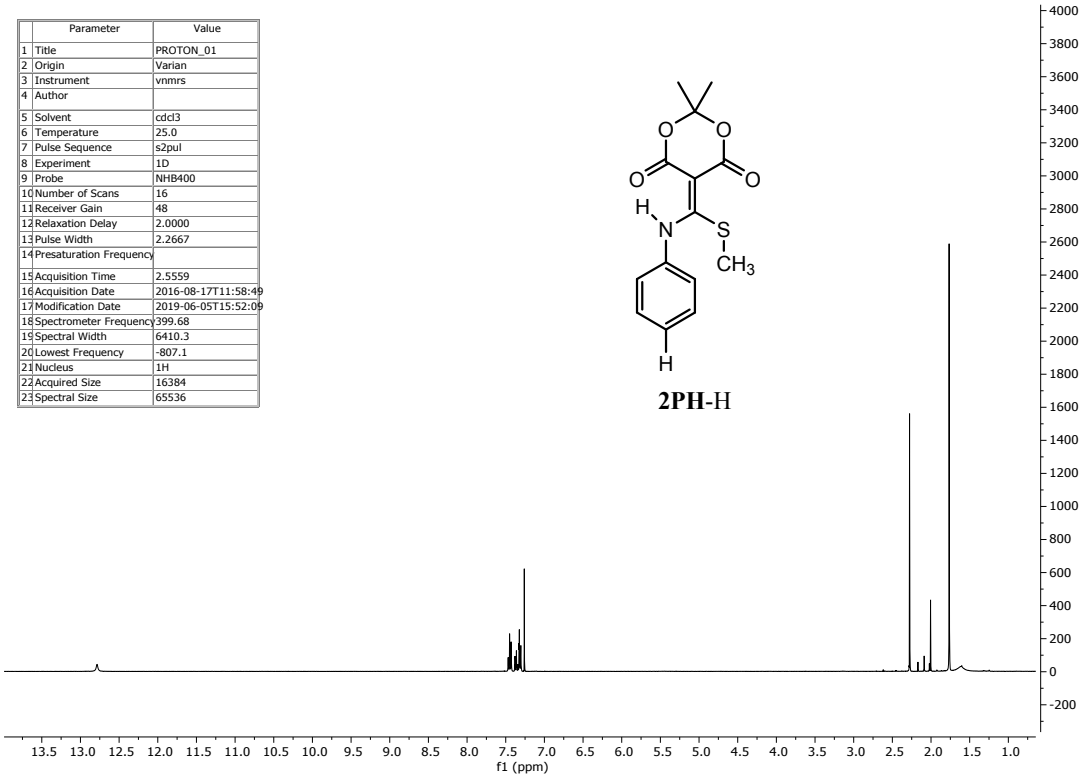


Figure S22. ^{13}C NMR for compound **3** in $CDCl_3$.



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4	Author	
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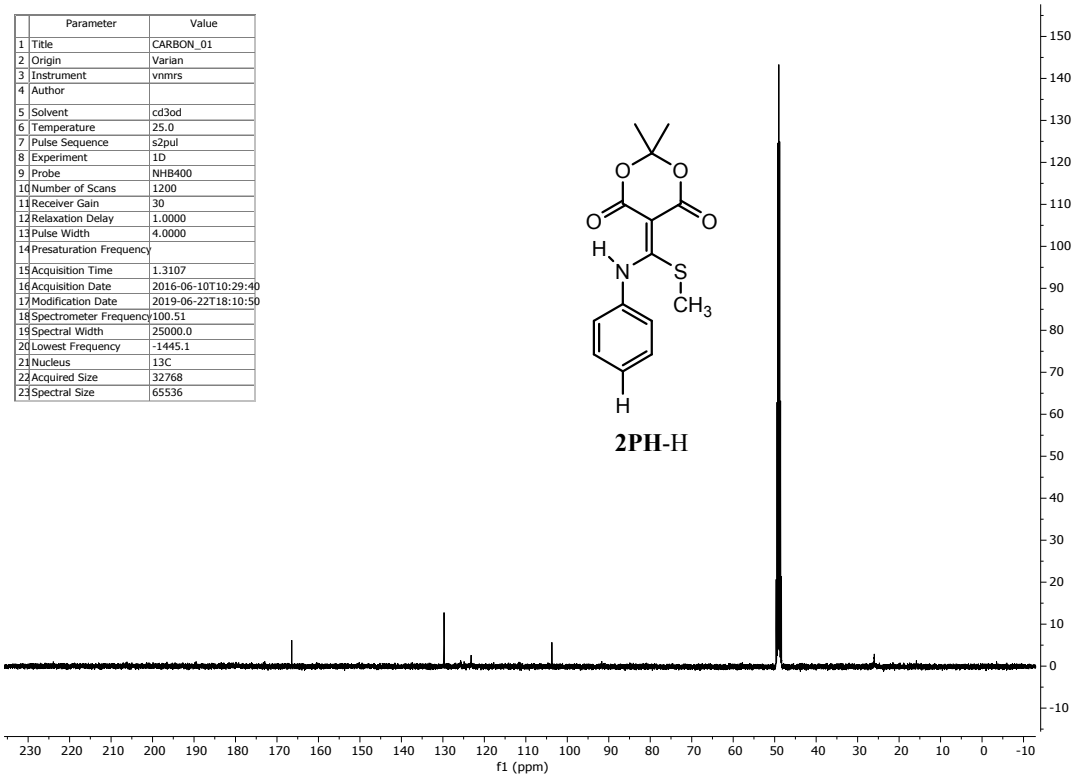
15	Acquisition Time	2.5559
16	Acquisition Date	2016-08-17T11:58:49
17	Modification Date	2019-06-05T15:52:09
18	Spectrometer Frequency	399.68
19	Spectral Width	6410.3
20	Lowest Frequency	-807.1
21	Nucleus	1H
22	Acquired Size	16384
23	Spectral Size	65536

Figure S23. ^{1}H NMR for compound **2PH-H** in $CDCl_3$.



	Parameter	Value
1	Title	CARBON_01
2	Origin	Varian
3	Instrument	vnmrs
4	Author	
5	Solvent	cd3od
6	Temperature	25.0
7	Pulse Sequence	s2pul
8	Experiment	1D
9	Probe	NHB400
10	Number of Scans	1200
11	Receiver Gain	30
12	Relaxation Delay	1.0000
13	Pulse Width	4.0000
14	Presaturation Frequency	
15	Acquisition Time	1.3107
16	Acquisition Date	2016-06-10T10:29:40
17	Modification Date	2019-06-22T18:10:50
18	Spectrometer Frequency	100.51
19	Spectral Width	25000.0
20	Lowest Frequency	-1445.1
21	Nucleus	13C
22	Acquired Size	32768
23	Spectral Size	65536

Figure S24. ^{13}C NMR for compound **2Ph-H** in CD_3OD.

	Parameter	Value
1	Title	PROTON_01
2	Origin	Varian
3	Instrument	vnmrs
4	Author	
5	Solvent	cdcl3
6	Temperature	25.0
7	Pulse Sequence	s2pul
8	Experiment	1D
9	Probe	NHB400
10	Number of Scans	32
11	Receiver Gain	40
12	Relaxation Delay	2.0000
13	Pulse Width	2.2667
14	Presaturation Frequency	
15	Acquisition Time	2.5559
16	Acquisition Date	2016-07-13T11:21:40
17	Modification Date	2019-06-05T15:52:15
18	Spectrometer Frequency	399.68
19	Spectral Width	6410.3
20	Lowest Frequency	-807.1
21	Nucleus	1H
22	Acquired Size	16384
23	Spectral Size	65536

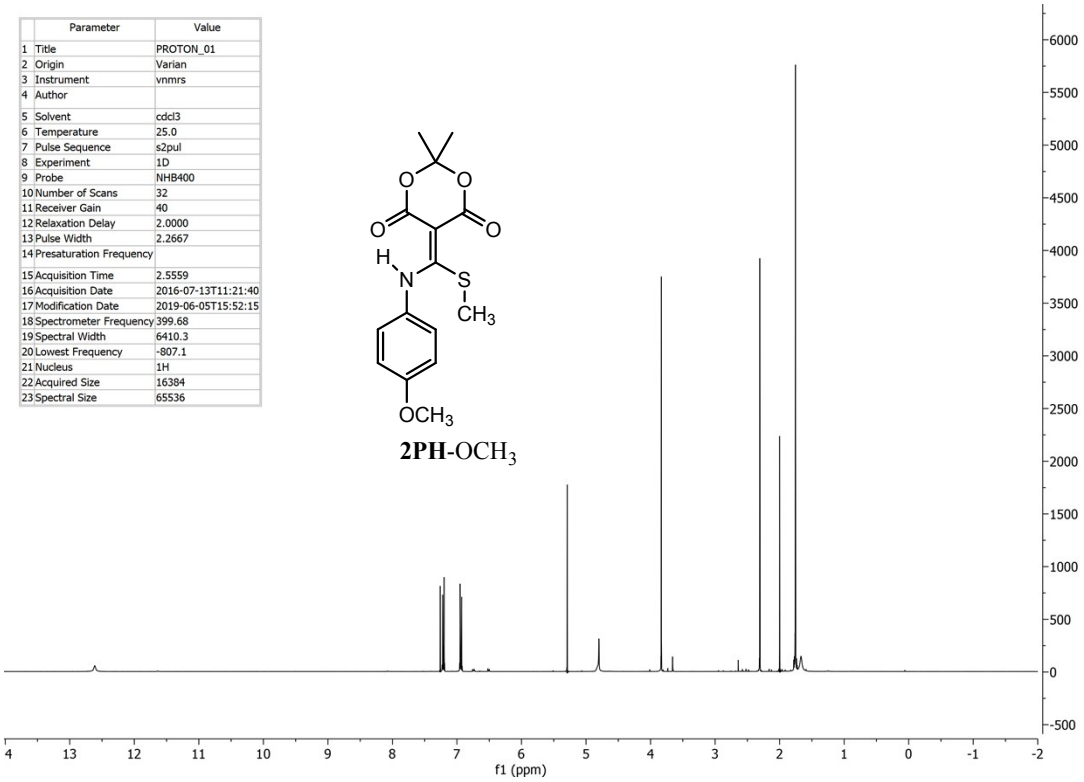


Figure S25. ^{1}H NMR for compound **2PH-OCH$_3$** in $CDCl_3$.

	Parameter	Value
1	Title	CARBON_01
2	Origin	Varian
3	Instrument	vnmrs
4	Author	
5	Solvent	cdcl3
6	Temperature	25.0
7	Pulse Sequence	s2pul
8	Experiment	1D
9	Probe	NHB400
10	Number of Scans	1200
11	Receiver Gain	30
12	Relaxation Delay	1.0000
13	Pulse Width	4.0000
14	Presaturation Frequency	
15	Acquisition Time	1.3107
16	Acquisition Date	2016-07-13T15:01:12
17	Modification Date	2019-06-05T15:52:15
18	Spectrometer Frequency	100.51
19	Spectral Width	25000.0
20	Lowest Frequency	-1445.2
21	Nucleus	13C
22	Acquired Size	32768
23	Spectral Size	65536

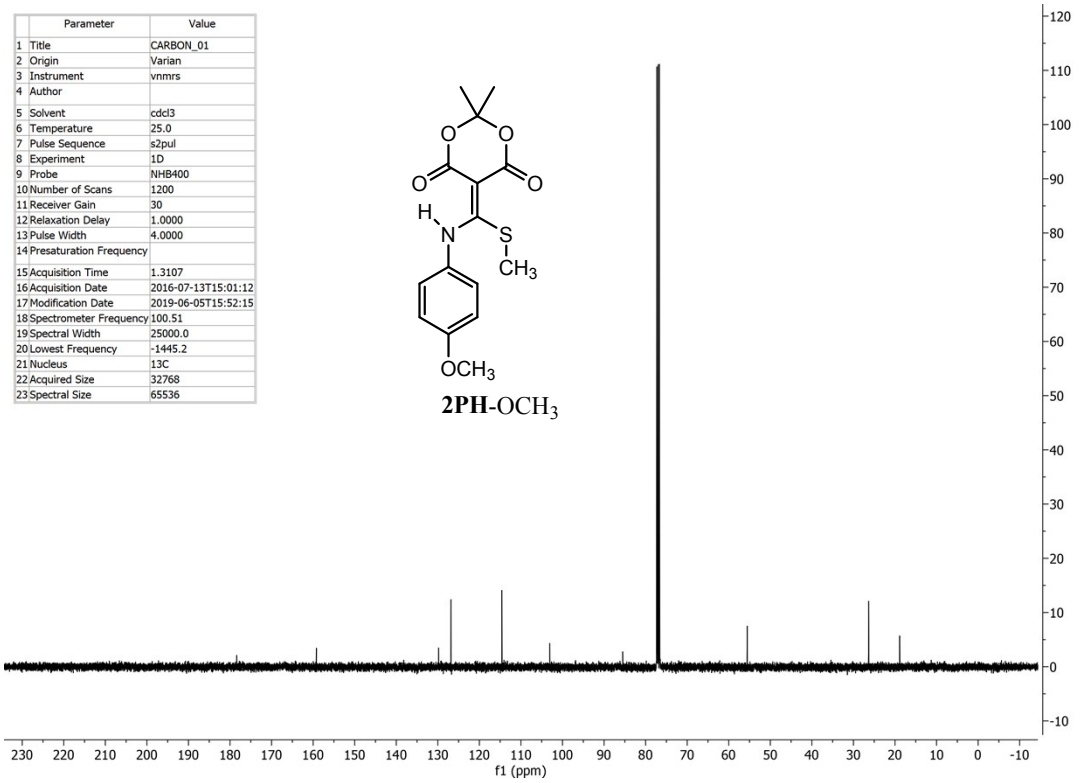
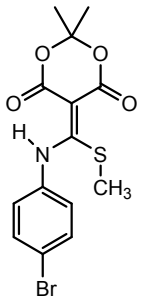


Figure S26. ^{13}C NMR for compound **2Ph-OCH$_3$** in $CDCl_3$.

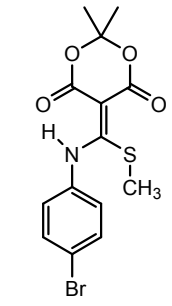
	Parameter	Value
1	Title	PROTON_01
2	Origin	Varian
3	Instrument	vnmrs
4	Author	
5	Solvent	cd3od
6	Temperature	25.0
7	Pulse Sequence	s2pul
8	Experiment	1D
9	Probe	robo_2dec2014
10	Number of Scans	32
11	Receiver Gain	50
12	Relaxation Delay	2.0000
13	Pulse Width	2.0667
14	Presaturation Frequency	
15	Acquisition Time	2.5559
16	Acquisition Date	2016-06-21T10:09:09
17	Modification Date	2019-06-05T15:52:08
18	Spectrometer Frequency	400.09
19	Spectral Width	6410.3
20	Lowest Frequency	-804.6
21	Nucleus	1H
22	Acquired Size	16384
23	Spectral Size	65536



2PH-Br

Figure S27. ^{1}H NMR for compound **2PH-Br** in CD_3OD.

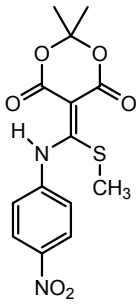
	Parameter	Value
1	Title	CARBON_01
2	Origin	Varian
3	Instrument	vnmrs
4	Author	
5	Solvent	cdcl3
6	Temperature	25.0
7	Pulse Sequence	s2pul
8	Experiment	1D
9	Probe	robo_2dec2014
10	Number of Scans	800
11	Receiver Gain	30
12	Relaxation Delay	1.0000
13	Pulse Width	2.2333
14	Presaturation Frequency	
15	Acquisition Time	1.3107
16	Acquisition Date	2016-09-01T11:03:20
17	Modification Date	2019-06-05T15:52:08
18	Spectrometer Frequency	100.61
19	Spectral Width	25000.0
20	Lowest Frequency	-1433.8
21	Nucleus	13C
22	Acquired Size	32768
23	Spectral Size	65536



2PH-Br

Figure S28. ^{13}C NMR for compound **2Ph-Br** in $CDCl_3$.

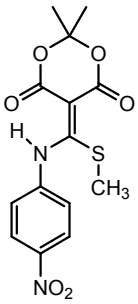
	Parameter	Value
1	Title	PROTON_01
2	Origin	Varian
3	Instrument	vnmrs
4	Author	
5	Solvent	cd3od
6	Temperature	25.0
7	Pulse Sequence	s2pul
8	Experiment	1D
9	Probe	NHB400
10	Number of Scans	16
11	Receiver Gain	42
12	Relaxation Delay	2.0000
13	Pulse Width	2.2667
14	Presaturation Frequency	
15	Acquisition Time	2.5559
16	Acquisition Date	2016-08-31T09:38:48
17	Modification Date	2019-06-05T15:52:11
18	Spectrometer Frequency	399.68
19	Spectral Width	6410.3
20	Lowest Frequency	-807.0
21	Nucleus	1H
22	Acquired Size	16384
23	Spectral Size	65536



2PH-NO_2

Figure S29. ^{1}H NMR for compound **2PH-NO_2** in CD_3OD.

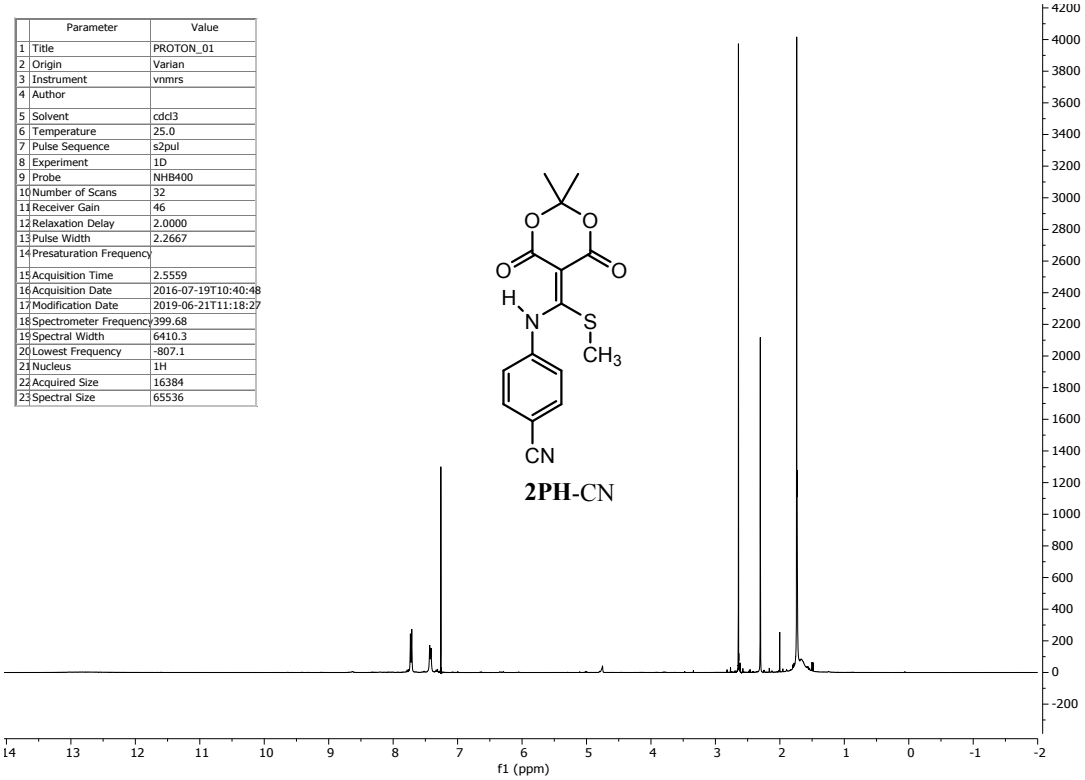
	Parameter	Value
1	Title	CARBON_01
2	Origin	Varian
3	Instrument	vnmrs
4	Author	
5	Solvent	cd3od
6	Temperature	25.0
7	Pulse Sequence	s2pul
8	Experiment	1D
9	Probe	NHB400
10	Number of Scans	800
11	Receiver Gain	30
12	Relaxation Delay	1.0000
13	Pulse Width	4.0000
14	Presaturation Frequency	
15	Acquisition Time	1.3107
16	Acquisition Date	2016-08-31T10:39:17
17	Modification Date	2019-06-05T15:52:11
18	Spectrometer Frequency	100.51
19	Spectral Width	25000.0
20	Lowest Frequency	-1445.1
21	Nucleus	13C
22	Acquired Size	32768
23	Spectral Size	65536



2PH-NO_2

Figure S30. ^{13}C NMR for compound **2Ph-NO_2** in CD_3OD.

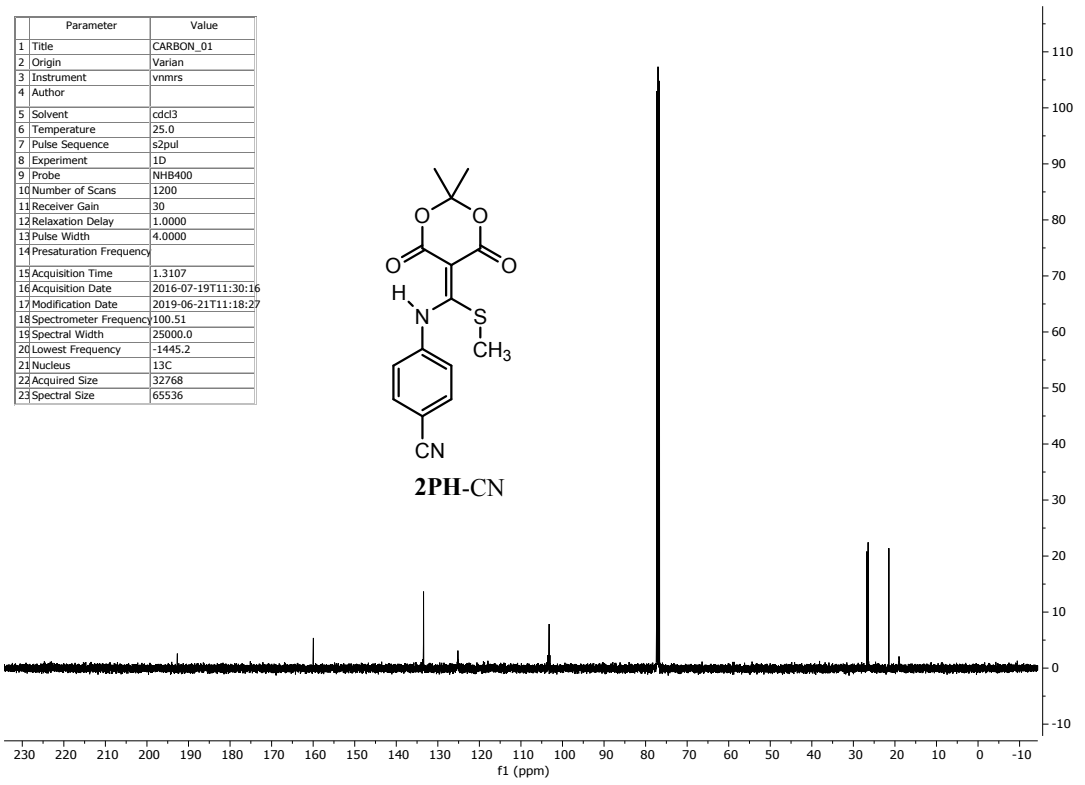
	Parameter	Value
1	Title	PROTON_01
2	Origin	Varian
3	Instrument	vnmrs
4	Author	
5	Solvent	cdcl3
6	Temperature	25.0
7	Pulse Sequence	s2pul
8	Experiment	1D
9	Probe	NHB400
10	Number of Scans	32
11	Receiver Gain	46
12	Relaxation Delay	2.0000
13	Pulse Width	2.2667
14	Presaturation Frequency	
15	Acquisition Time	2.5559
16	Acquisition Date	2016-07-19T10:40:48
17	Modification Date	2019-06-21T11:18:27
18	Spectrometer Frequency	399.68
19	Spectral Width	6410.3
20	Lowest Frequency	-807.1
21	Nucleus	1H
22	Acquired Size	16384
23	Spectral Size	65536



2PH-CN

Figure S31. ^{1}H NMR for compound **2PH-CN**in $CDCl_3$.

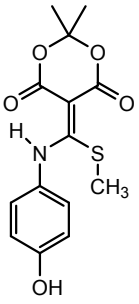
	Parameter	Value
1	Title	CARBON_01
2	Origin	Varian
3	Instrument	vnmrs
4	Author	
5	Solvent	cdcl3
6	Temperature	25.0
7	Pulse Sequence	s2pul
8	Experiment	1D
9	Probe	NHB400
10	Number of Scans	1200
11	Receiver Gain	30
12	Relaxation Delay	1.0000
13	Pulse Width	4.0000
14	Presaturation Frequency	
15	Acquisition Time	1.3107
16	Acquisition Date	2016-07-19T11:30:16
17	Modification Date	2019-06-21T11:18:27
18	Spectrometer Frequency	100.51
19	Spectral Width	25000.0
20	Lowest Frequency	-1445.2
21	Nucleus	13C
22	Acquired Size	32768
23	Spectral Size	65536



2PH-CN

Figure S32. ^{13}C NMR for compound **2Ph-CN** in $CDCl_3$.

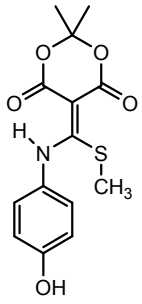
	Parameter	Value
1	Title	PROTON_01
2	Origin	Varian
3	Instrument	vnmrs
4	Author	
5	Solvent	cdcl3
6	Temperature	25.0
7	Pulse Sequence	s2pul
8	Experiment	1D
9	Probe	NHB400
10	Number of Scans	16
11	Receiver Gain	46
12	Relaxation Delay	2.0000
13	Pulse Width	2.2667
14	Presaturation Frequency	
15	Acquisition Time	2.5559
16	Acquisition Date	2015-12-08T11:02:44
17	Modification Date	2019-06-05T15:52:13
18	Spectrometer Frequency	399.68
19	Spectral Width	6410.3
20	Lowest Frequency	-800.2
21	Nucleus	1H
22	Acquired Size	16384
23	Spectral Size	65536



2PH-OH

Figure S33. ^{1}H NMR for compound **2PH-OH** in $CDCl_3$.

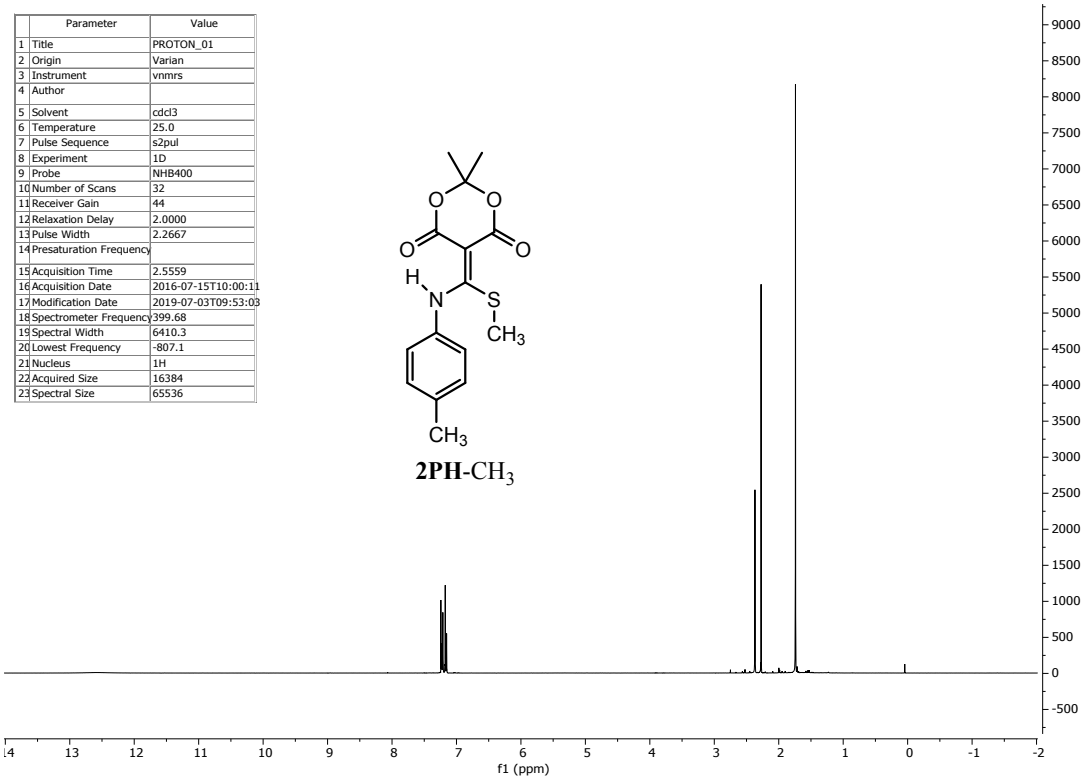
	Parameter	Value
1	Title	CARBON_01
2	Origin	Varian
3	Instrument	vnmrs
4	Author	
5	Solvent	cdcl3
6	Temperature	25.0
7	Pulse Sequence	s2pul
8	Experiment	1D
9	Probe	NHB400
10	Number of Scans	2000
11	Receiver Gain	30
12	Relaxation Delay	1.0000
13	Pulse Width	4.0000
14	Presaturation Frequency	
15	Acquisition Time	1.3107
16	Acquisition Date	2015-12-09T23:18:47
17	Modification Date	2019-06-05T15:52:13
18	Spectrometer Frequency	100.51
19	Spectral Width	25000.0
20	Lowest Frequency	-1445.2
21	Nucleus	13C
22	Acquired Size	32768
23	Spectral Size	65536



2PH-OH

Figure S34. ^{13}C NMR for compound **2Ph-OH** in $CDCl_3$.

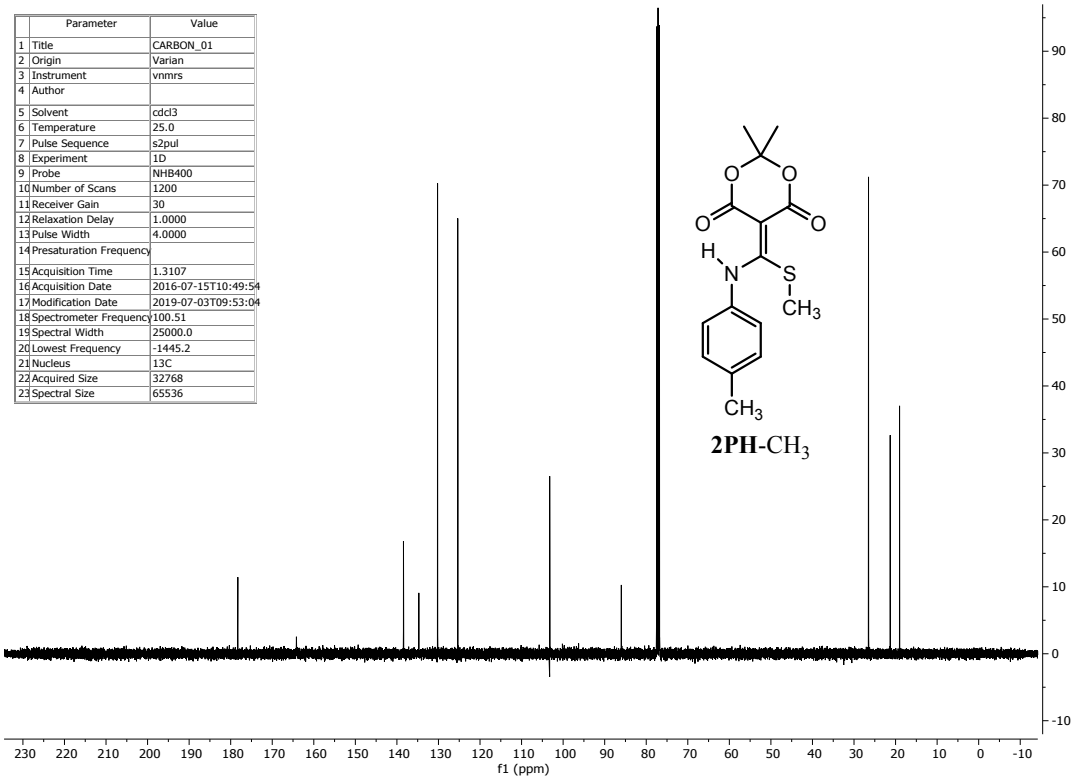
	Parameter	Value
1	Title	PROTON_01
2	Origin	Varian
3	Instrument	vnmrs
4	Author	
5	Solvent	cdcl3
6	Temperature	25.0
7	Pulse Sequence	s2pul
8	Experiment	1D
9	Probe	NHB400
10	Number of Scans	32
11	Receiver Gain	44
12	Relaxation Delay	2.0000
13	Pulse Width	2.2667
14	Presaturation Frequency	
15	Acquisition Time	2.5559
16	Acquisition Date	2016-07-15T10:00:11
17	Modification Date	2019-07-03T09:53:03
18	Spectrometer Frequency	399.68
19	Spectral Width	6410.3
20	Lowest Frequency	-807.1
21	Nucleus	1H
22	Acquired Size	16384
23	Spectral Size	65536



2PH-CH_3

Figure S35. ^{1}H NMR for compound **2PH-CH_3** in $CDCl_3$.

	Parameter	Value
1	Title	CARBON_01
2	Origin	Varian
3	Instrument	vnmrs
4	Author	
5	Solvent	cdcl3
6	Temperature	25.0
7	Pulse Sequence	s2pul
8	Experiment	1D
9	Probe	NHB400
10	Number of Scans	1200
11	Receiver Gain	30
12	Relaxation Delay	1.0000
13	Pulse Width	4.0000
14	Presaturation Frequency	
15	Acquisition Time	1.3107
16	Acquisition Date	2016-07-15T10:49:54
17	Modification Date	2019-07-03T09:53:04
18	Spectrometer Frequency	100.51
19	Spectral Width	25000.0
20	Lowest Frequency	-1445.2
21	Nucleus	13C
22	Acquired Size	32768
23	Spectral Size	65536



2PH-CH_3

Figure S36. ^{13}C NMR for compound **2Ph-CH_3** in $CDCl_3$.

XI. Derivation of Eq. 3

Assuming SSA on **10**.

$$\frac{d[10]}{dt} = 0 = k_a[2PhX][DTT] + k_{-b}[8PhX][MeSH] - k_{-a}[10] - k_b[10]$$

Solving for **10**, and making the MeSH step irreversible.

$$[10] = \frac{k_a[2PhX][DTT] + k_{-b}[8PhX][MeSH]}{k_{-a} + k_b}$$

Assuming SSA on **8Ph**-X

$$\frac{d[8PhX]}{dt} = 0 = k_b[10] + k_{-c}[9PhX] - k_{-b}[8PhX][MeSH] - k_c[8PhX]$$

Solving for 8Ph-X, and making the MeSH step irreversible

$$[8PhX] = \frac{k_b[10] + k_{-c}[9PhX]}{k_{-b}[MeSH] + k_c}$$

The rate of formation of **9Ph**-X.

$$\frac{d[9PhX]}{dt} = k_c[8PhX]$$

Plugging in for **8Ph**-X

$$\frac{d[9PhX]}{dt} = \frac{k_b[10]k_c}{k_c}$$

Plugging in for **10**

$$\frac{d[9PhX]}{dt} = \frac{k_a k_b[2PhX][DTT]}{k_{-a} + k_b}$$

Acid dissociation function for **2Ph**-X

$$K_a = \frac{[H_3O^+][2PhX-]}{[2PhX]}$$

Final Equation, after pluggin in for **2Ph**-X

$$\frac{d[9PhX]}{dt} = \frac{k_a k_b[2PhX-][DTT][H_3O^+]}{K_a(k_{-a} + k_b)}$$

1. Hendler, R. W., and Shrager, R. I. (1994) Deconvolutions based on singular value decomposition and the pseudoinverse: a guide for beginners. *J. Biochem. and Biophys. Methods* **28**, 1-33
2. Henry, E. R., and Hofrichter, J. (1992) Singular Value Decomposition: Application to Analysis of Experimental Data. *Methods Enzymol.* **210**, 129-192