Supporting Information

Dithioesters: Simple, Tunable, Cysteine-Selective H_2S Donors

Matthew M. Cerda, Turner D. Newton, Yu Zhao, Brylee K. Collins, Christopher H. Hendon, Michael D. Pluth

Contact Information:
Michael D. Pluth
pluth@uoregon.edu

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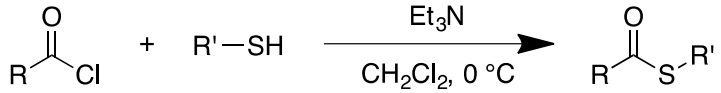
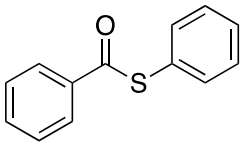
Materials and Methods.
Reagents were purchased from Tokyo Chemical Industry and/or Oakwood Chemicals and used directly as received. Deuterated solvents were purchased from Cambridge Isotope Laboratories and used as received. ^{1}H and $^{13}C\{^{1}H\}$ NMR were recorded on Bruker 500 and 600 MHz instruments. Chemical shifts are reported relative to residual protic solvent resonances. MS data was collected on a Xevo Waters ESI LC/MS instrument. Silica gel (SiliaFlash F60, Silicycle, 230-400 mesh) was used for column chromatography. All air-free manipulations were performed under an inert atmosphere using standard Schlenk technique or an Innovative Atmospheres N_2-filled glove box. UV-Vis spectra were acquired on an Agilent Cary 60 UV-Vis spectrophotometer equipped with a Quantum Northwest TC-1 temperature controller at 25 °C ± 0.05 °C.

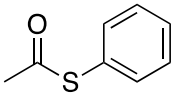
Synthesis
General Procedure for the Synthesis of Thioesters (modified from previous report[1])



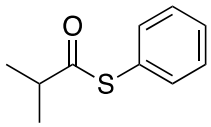
The desired thiol (1.1 equiv.) and triethylamine (1.1 equiv.) were added to anhydrous CH_2Cl_2 (20 mL) and cooled to 0 °C. Once cooled, the desired acid chloride (1.0 equiv.) was added dropwise, and the reaction was stirred at 0 °C for 1 h. The reaction was quenched with deionized H_2O (30 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic extractions were washed with brine (1 x 20 mL), dried over $MgSO_4$, and concentrated under reduced pressured. The desired product was purified by column chromatography.



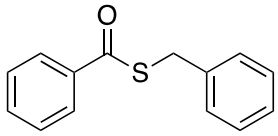
S-phenyl benzothioate.
White powder, 852 mg (96%)
R_f = 0.23 (25% CH_2Cl_2 in hexanes)
^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.04 (d, 2H), 7.61 (t, 1H), 7.55 – 7.44 (m, 7H).
$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ: 190.14, 136.63, 135.09, 133.65, 129.52, 129.24, 128.74, 127.48, 127.34.
TOF MS (ASAP$^+$) (*m/z*): $[M + H]^+$ calc'd for $C_{13}H_{10}OS$ 215.0531; found 215.0548



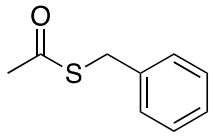
S-phenyl ethanethioate.
Clear oil, 538 mg (86%)
R_f = 0.42 (50% CH_2Cl_2 in hexanes)
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 (s, 5H), 2.43 (s, 3H).
$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ: 194.06, 134.44, 129.43, 129.19, 127.91, 30.19.
TOF MS (ASAP$^+$) (*m/z*): $[M + H]^+$ calc'd for C_8H_8OS 153.0374; found 153.0374



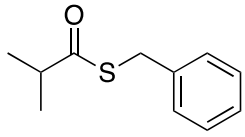
S-phenyl 2-methylpropanethioate.
Clear oil, 492 mg (66%)
R_f = 0.56 (50% CH_2Cl_2 in hexanes)
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (s, 5H), 2.87 (hept, J = 6.9, 1.9 Hz, 1H), 1.27 (d, J = 7.0, 1.8 Hz, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ: 201.85, 134.56, 129.17, 129.09, 127.87, 42.99, 19.37.
TOF MS (ASAP$^+$) (*m/z*): $[M + H]^+$ calc'd for $C_{10}H_{12}OS$ 181.0687; found 181.0705



S-benzyl benzothioate.
Clear oil, 779 mg (93%)
R_f = 0.40 (33% CH_2Cl_2 in hexanes)
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.98 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 8.0 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.29 – 7.24 (m, 1H), 4.33 (s, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ: 191.27, 137.45, 136.78, 133.42, 128.96, 128.61, 127.31, 127.28, 33.32.
TOF MS (ASAP$^+$) (*m/z*): $[M + H]^+$ calc'd for $C_{14}H_{12}OS$ 229.0687; found 229.0655

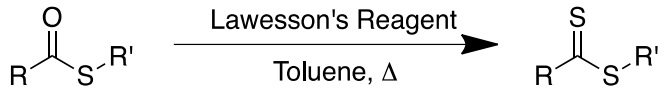


S-benzyl ethanethioate.
Clear oil, 405 mg (67%)
R_f = 0.24 (25% CH_2Cl_2 in hexanes)
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.31 – 7.27 (m, 4H), 7.27 – 7.23 (m, 1H), 4.13 (s, 2H), 2.35 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ: 195.09, 137.56, 128.77, 128.60, 127.24, 33.42, 30.29.
TOF MS (ASAP$^+$) (*m/z*): $[M + Na]^+$ calc'd for $C_9H_{10}OS$ 189.0350; found 189.0485

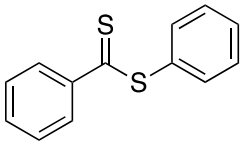


S-benzyl 2-methylpropanethioate.
Clear oil, 577 mg (66%)
R_f = 0.48 (33% CH_2Cl_2 in hexanes)
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.31 – 7.28 (m, 4H), 7.25 – 7.22 (m, 1H), 4.11 (s, 2H), 2.76 (hept, J = 6.9 Hz, 1H), 1.21 (d, J = 6.9 Hz, 6H).
^{13}C NMR (151 MHz, $CDCl_3$) δ: 203.44, 137.73, 128.79, 128.59, 127.17, 42.88, 32.89, 19.35.
TOF MS (ASAP$^+$) (*m/z*): $[M + H]^+$ calc'd for $C_{11}H_{14}OS$ 195.0844; found 195.0835

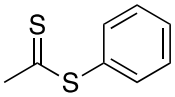
General Procedure for the Synthesis of Dithioesters (modified from previous report[1])



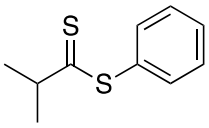
The desired thioester (1.0 equiv.) and Lawesson's Reagent (0.75 equiv.) were added to anhydrous toluene (20 mL) and heated to 120 °C under reflux. After 5.5 h, the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure, and the desired product purified by column chromatography.



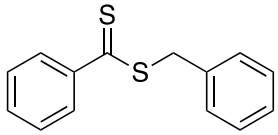
Phenyl benzodithioate (**PDTE**).
Red-violet solid, 217 mg (81%)
R_f = 0.42 (20% CH_2Cl_2 in hexanes)
^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.10 (d, J = 7.1 Hz, 1H), 7.57 (t, 1H), 7.54 – 7.47 (m, 6H), 7.45 – 7.40 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ: 228.49, 144.59, 135.38, 132.60, 131.38, 130.36, 129.66, 128.40, 126.99.
TOF MS (ASAP$^+$) (*m/z*): $[M + H]^+$ calc'd for $C_{13}H_{10}S_2$ 231.0302; found 231.0302



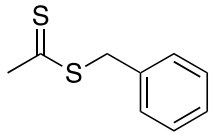
Phenyl ethanedithioate (**MPDTE**).
Burnt orange oil, 185 mg (67%)
R_f = 0.40 (20% CH_2Cl_2 in hexanes)
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.52 – 7.46 (m, 3H), 7.45 – 7.40 (m, 2H), 2.87 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ: 234.30, 134.74, 131.77, 130.36, 129.60, 38.95.
TOF MS (ASAP$^+$) (*m/z*): $[M + H]^+$ calc'd for $C_8H_8S_2$ 169.0146; found 169.0132



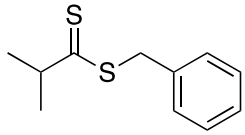
Phenyl 2-methylpropanedithioate (**iPPDTE**).
Yellow oil, 129 mg (59%)
R_f = 0.58 (25% CH_2Cl_2 in hexanes)
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.50 – 7.47 (m, 3H), 7.42 – 7.39 (m, 2H), 3.54 (hept, J = 6.7 Hz, 1H), 1.38 (d, J = 6.6 Hz, 6H).
^{13}C NMR (151 MHz, $CDCl_3$) δ: 246.77, 134.97, 130.83, 130.18, 129.51, 48.70, 24.24.
TOF MS (ASAP$^+$) (*m/z*): $[M + H]^+$ calc'd for $C_{10}H_{12}S_2$ 197.0459; found 197.0463



Benzyl benzodithioate (**PBDTE**).
Red oil, 243 mg (91%)
R_f = 0.41 (20% CH_2Cl_2 in hexanes)
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.00 (d, J = 7.7 Hz, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.42 – 7.27 (m, 8H), 4.61 (s, 2H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 227.69, 144.75, 134.97, 132.40, 129.29, 128.72, 128.34, 127.75, 126.90, 42.28.
TOF MS (ASAP$^+$) (*m/z*): $[M + H]^+$ calc'd for $C_{14}H_{12}S_2$ 245.0459; found 245.0471



Benzyl ethanedithioate (**MBDTE**).
Yellow-brown oil, 181 mg, (82%)
R_f = 0.54 (25% CH_2Cl_2 in hexanes)
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.34 – 7.26 (m, 5H), 4.46 (s, 2H), 2.85 (s, 3H).
$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ: 232.29, 135.13, 129.09, 128.67, 127.66, 41.98, 38.85.
TOF MS (ASAP$^+$) (*m/z*): $[M + Na]^+$ calc'd for $C_9H_{10}S_2$ 183.0302; found 183.0281



Benzyl 2-methylpropanedithioate (**iPBDTE**).
Orange-brown oil, 164 mg (76%)
R_f = 0.58 (25% CH_2Cl_2 in hexanes)
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.34 – 7.26 (m, 5H), 4.45 (s, 2H), 3.42 (hept, J = 6.7 Hz, 1H), 1.34 (d, J = 6.7 Hz, 7H).
$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ: 245.91, 135.22, 129.13, 128.67, 127.58, 49.35, 40.52, 24.19.
TOF MS (ASAP$^+$) (*m/z*): $[M + H]^+$ calc'd for $C_{11}H_{14}S_2$ 211.0615; found 211.0612

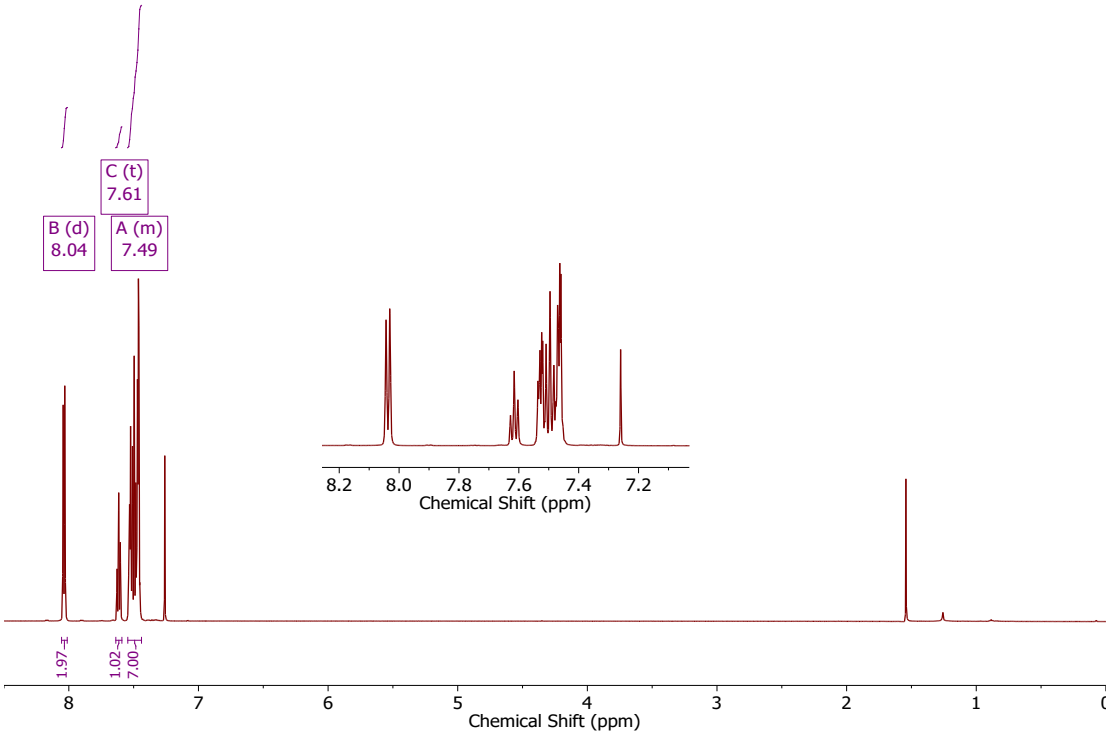


Figure S1. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of *S*-phenyl benzothioate

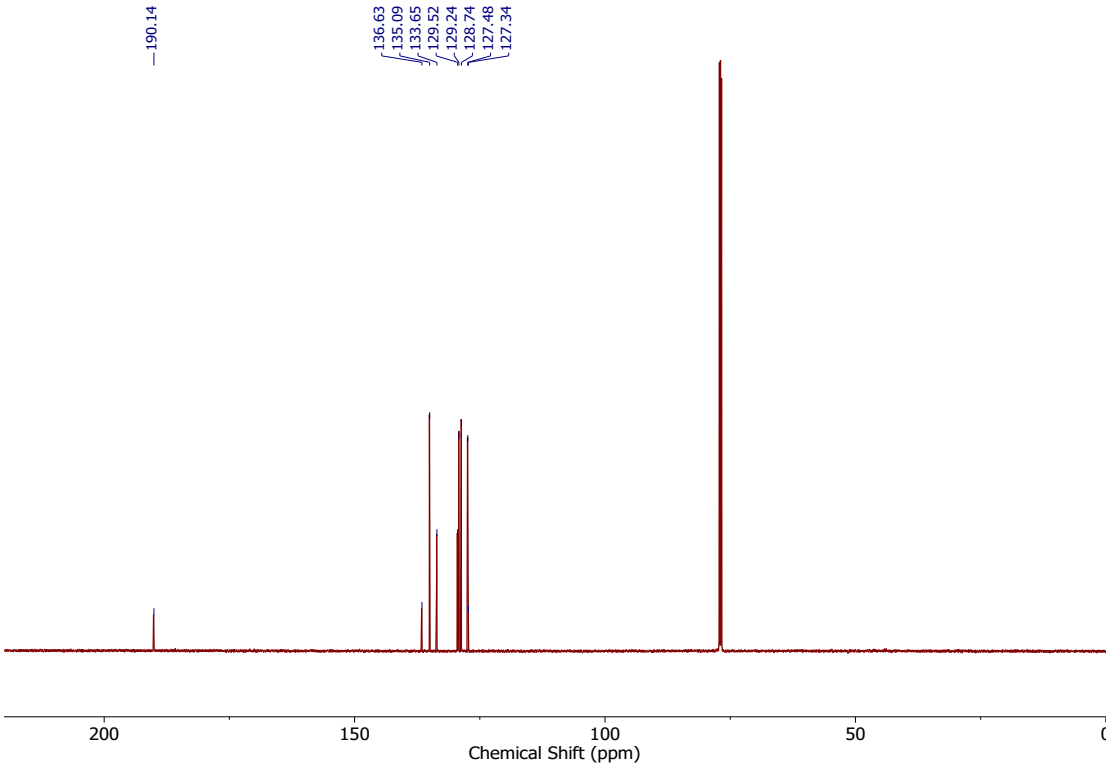


Figure S2. $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of *S*-phenyl benzothioate

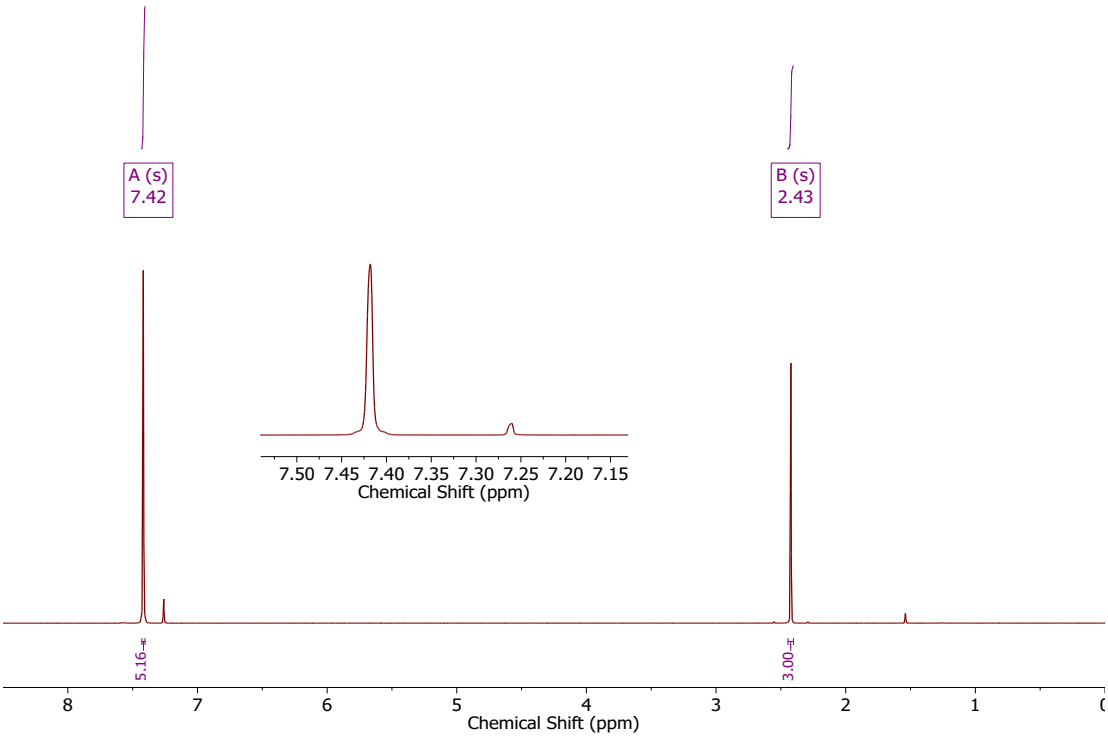


Figure S3. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *S*-phenyl ethanethioate

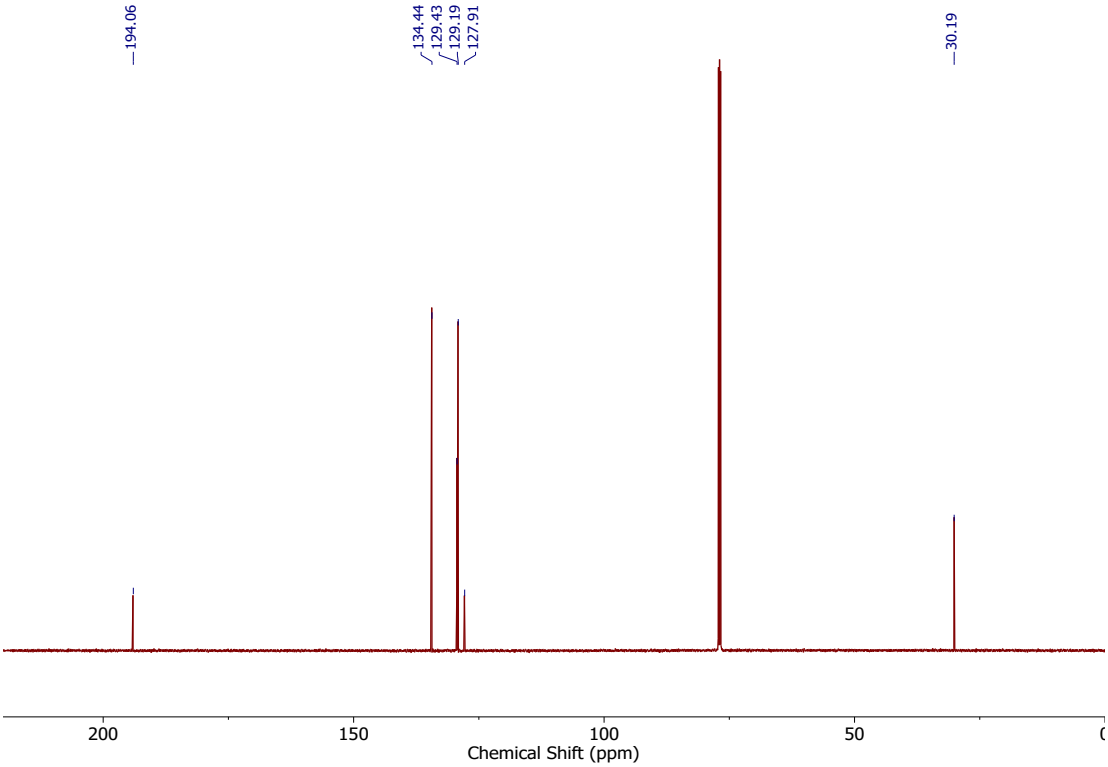


Figure S4. $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of *S*-phenyl ethanethioate

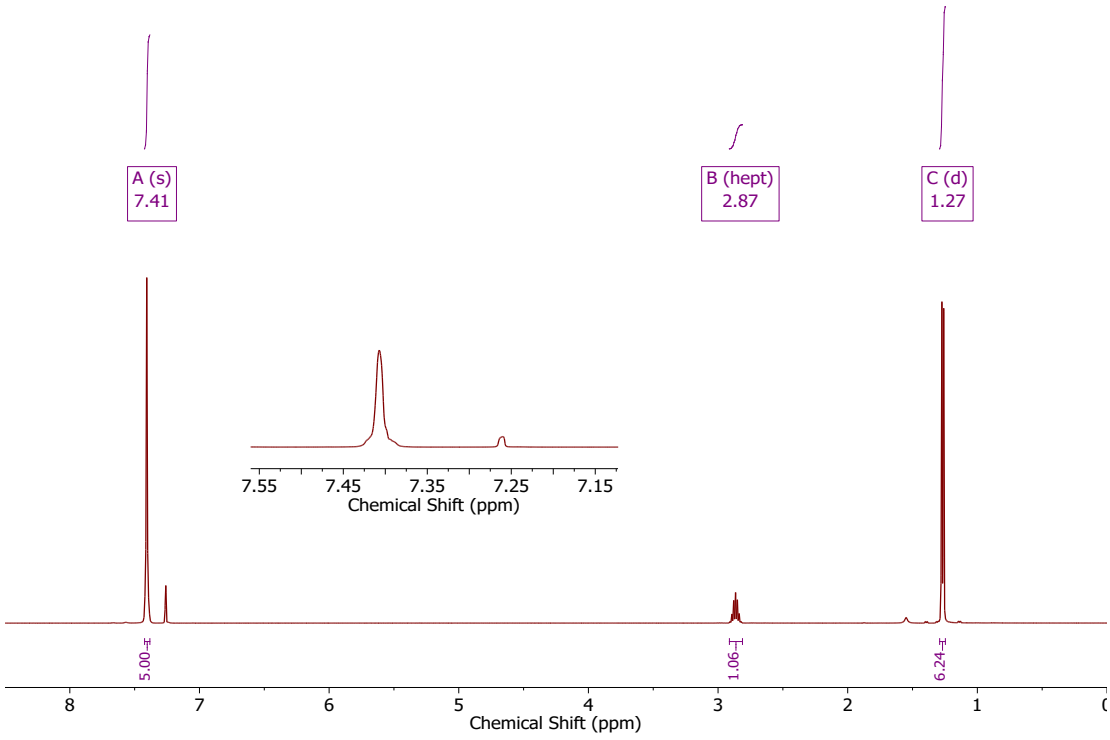


Figure S5. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *S*-phenyl 2-methylpropanethioate

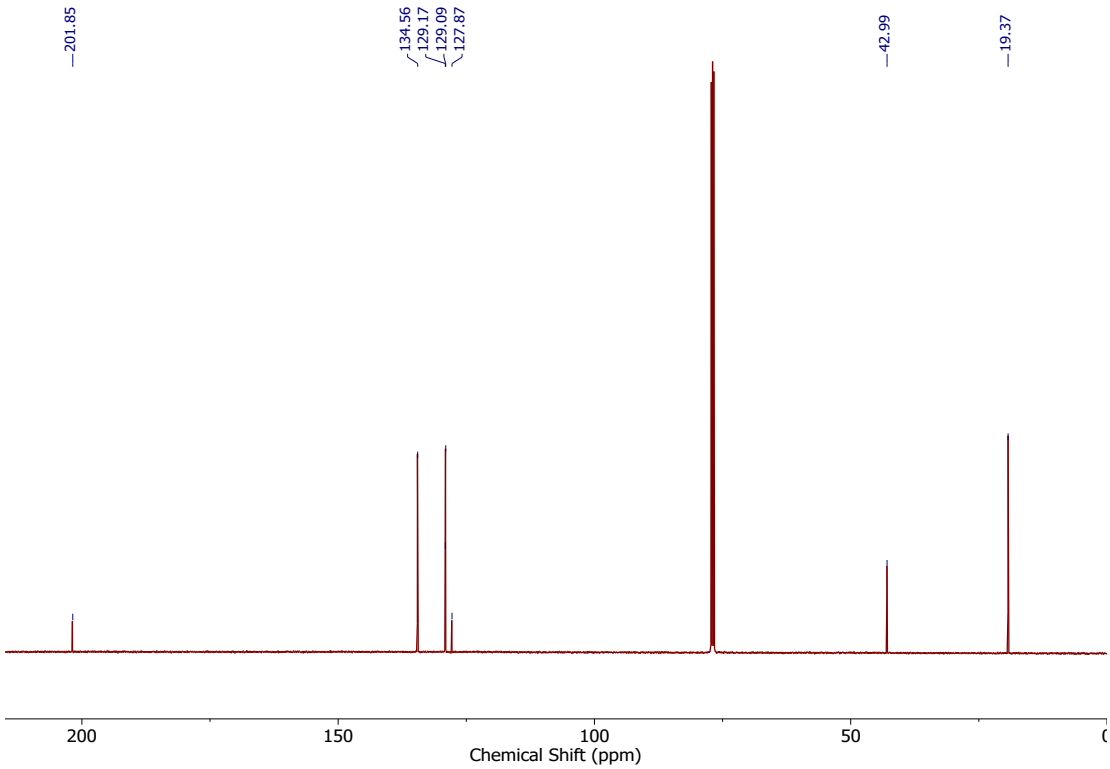


Figure S6. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) spectrum of *S*-phenyl 2-methylpropanethioate

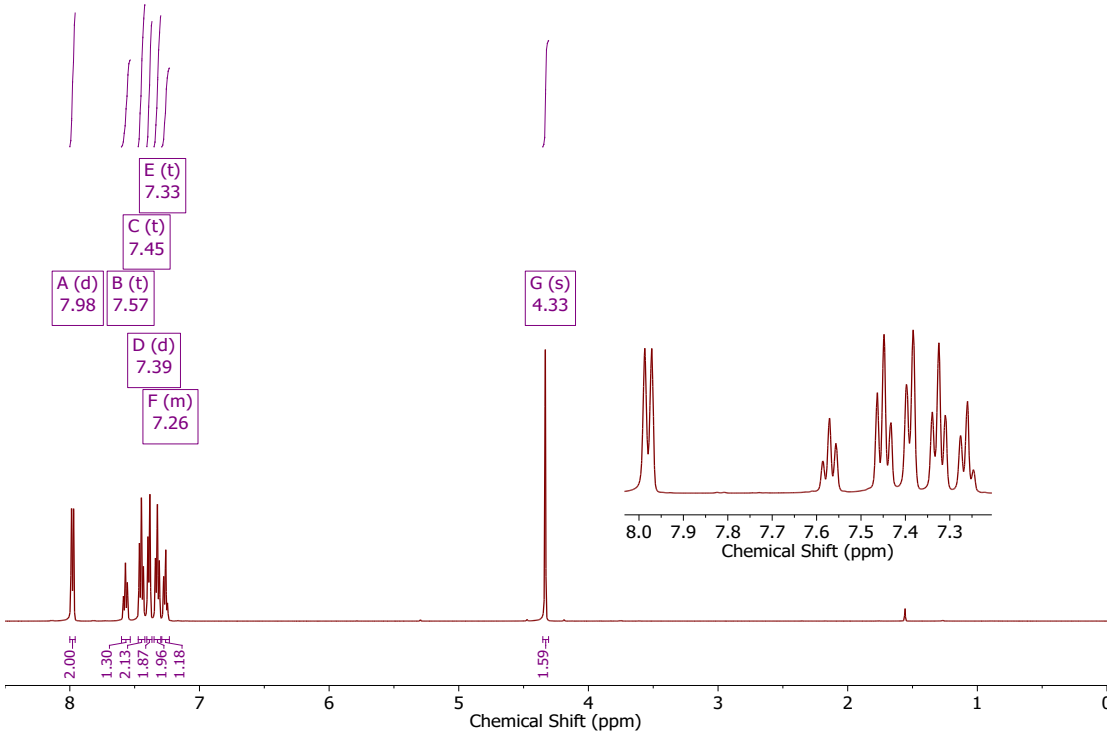


Figure S7. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *S*-benzyl benzothioate

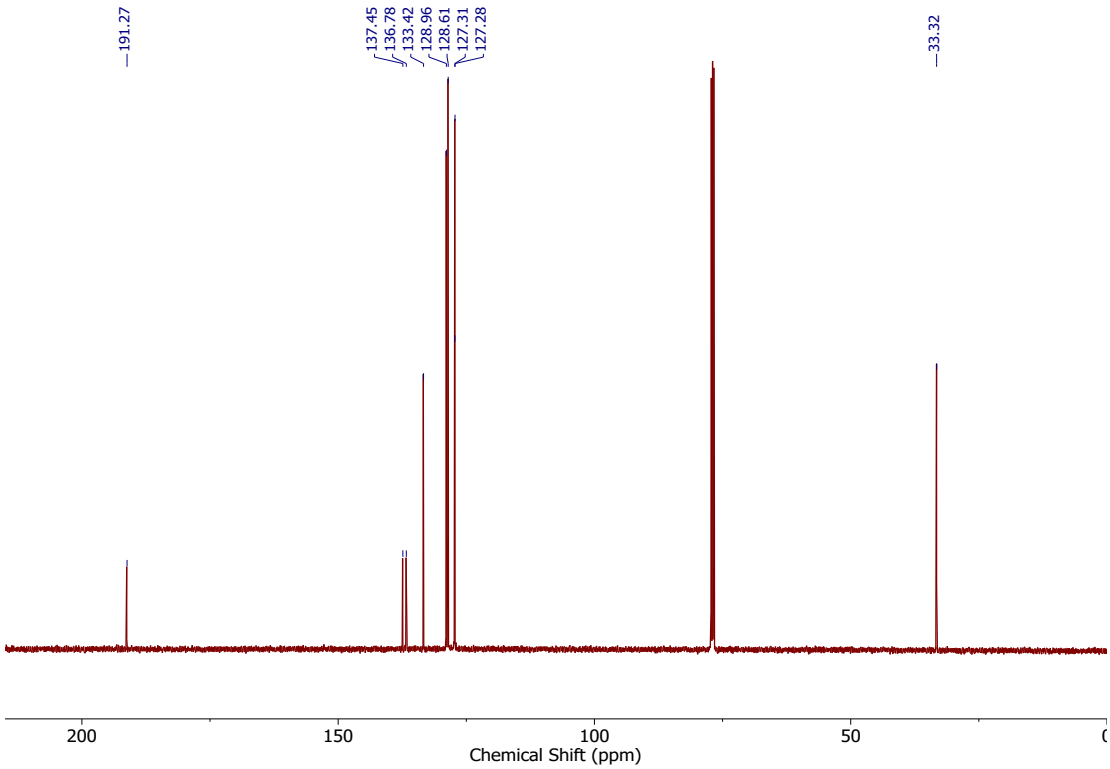


Figure S8. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) spectrum of *S*-benzyl benzothioate

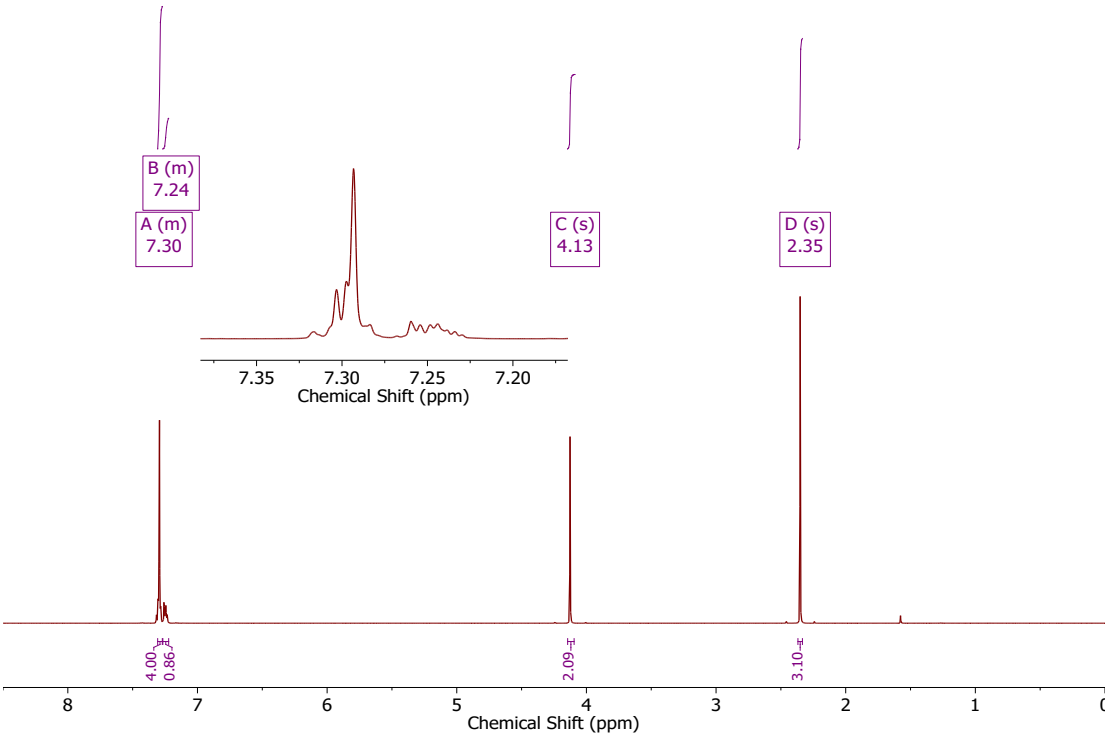


Figure S9. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of *S*-benzyl ethanethioate

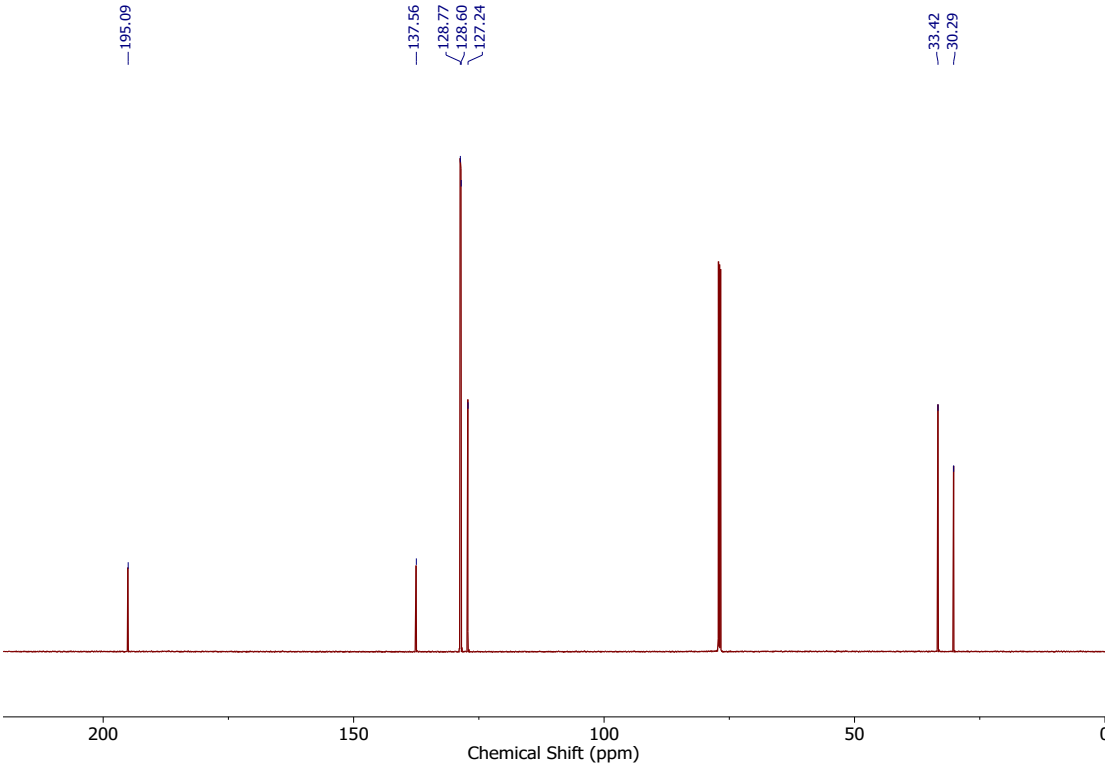


Figure S10. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) spectrum of *S*-benzyl ethanethioate

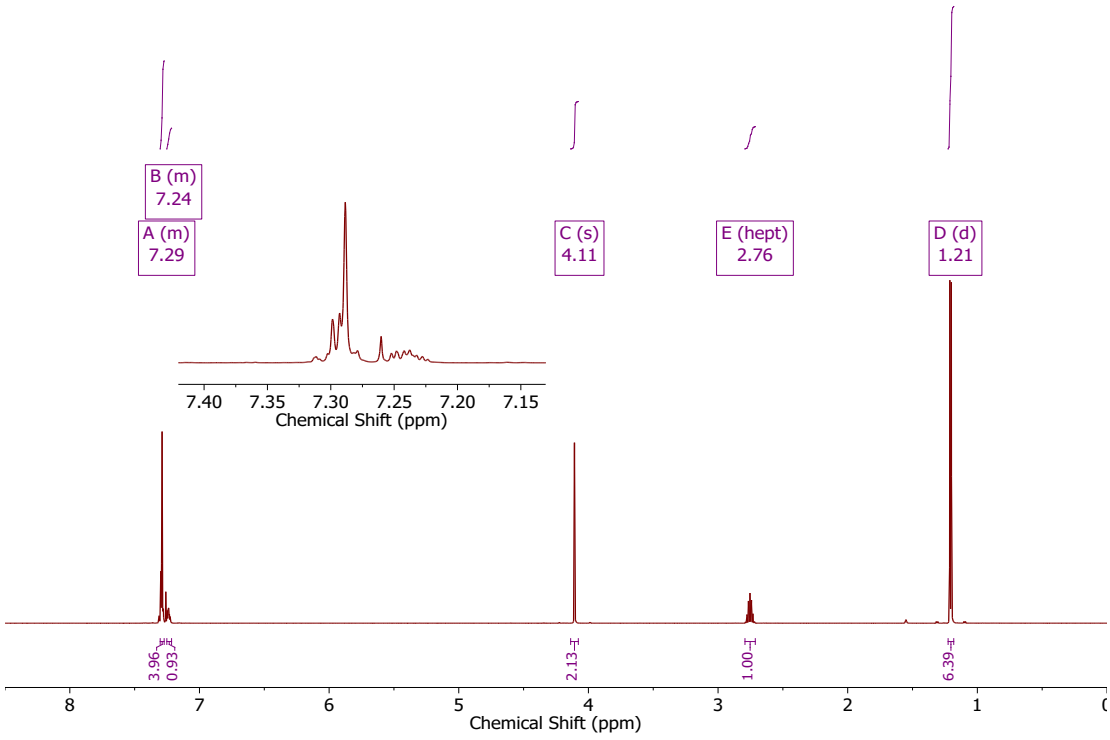


Figure S11. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of *S*-benzyl 2-methylpropanethioate

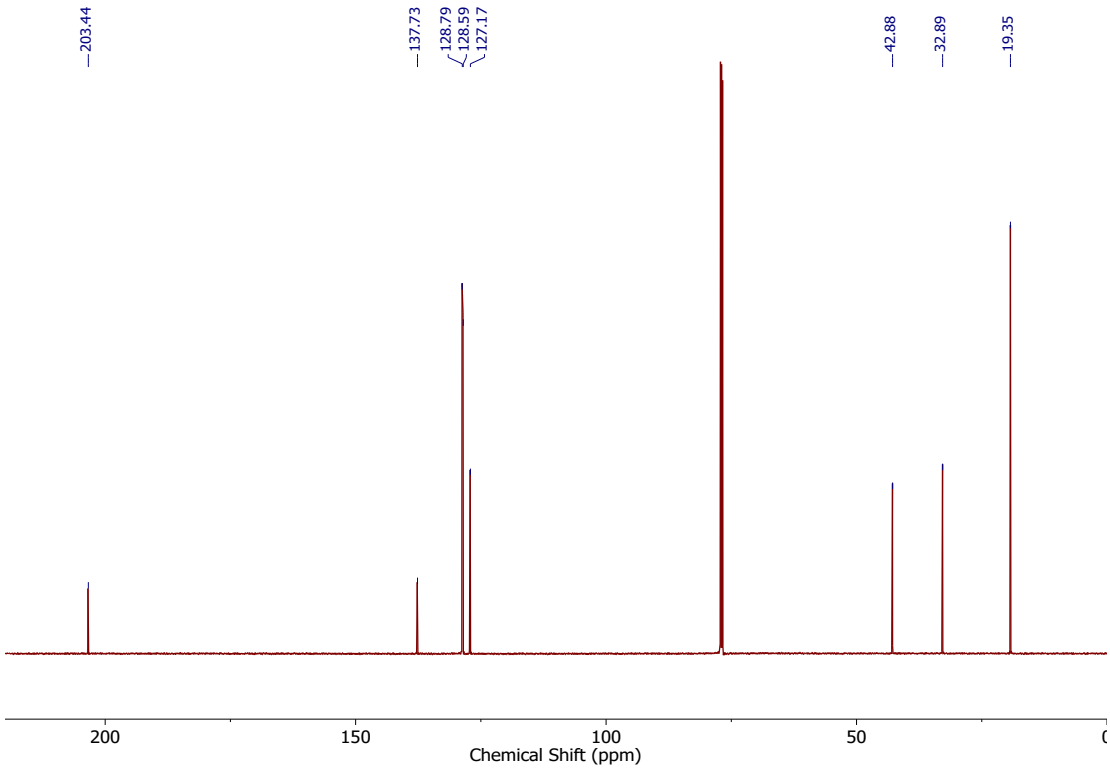


Figure S12. $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of *S*-benzyl 2-methylpropanethioate

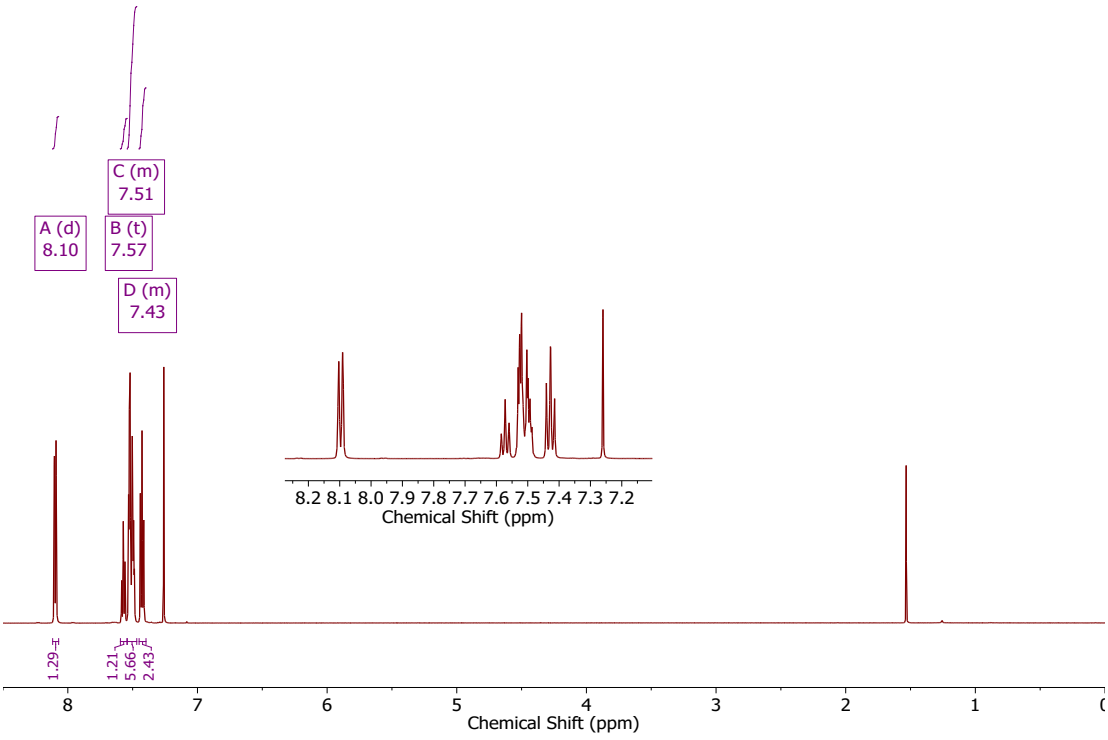


Figure S13. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **PDTE**

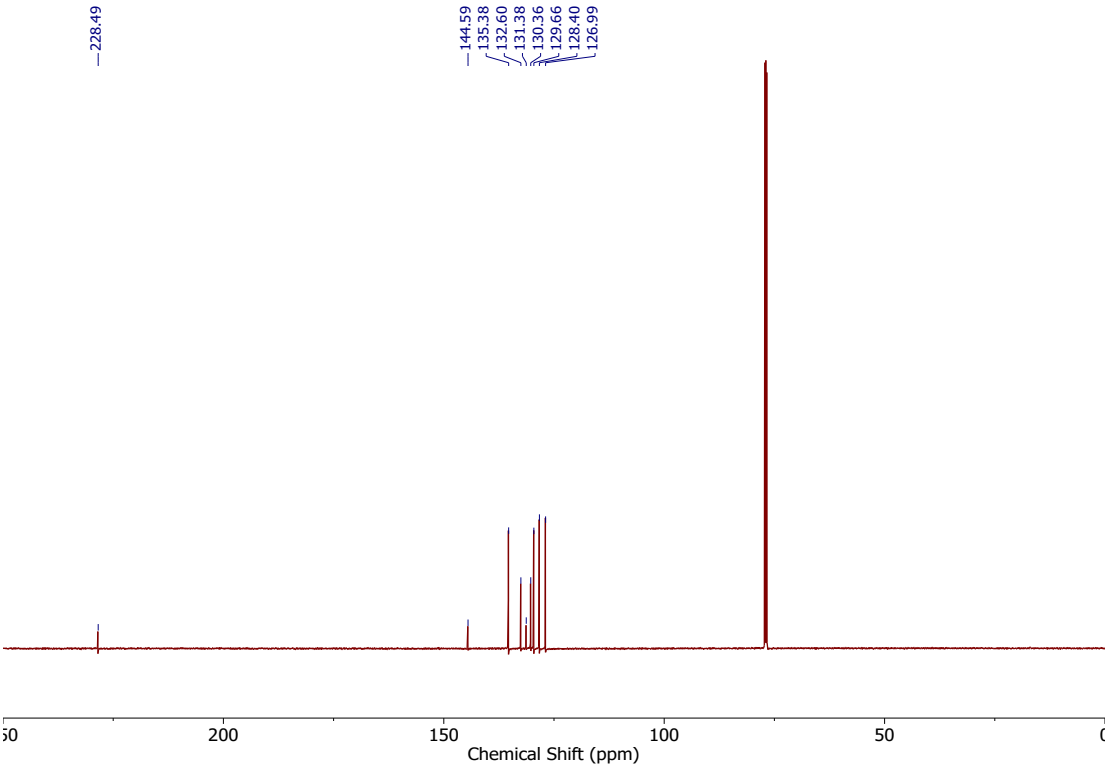


Figure S14. $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of **PDTE**

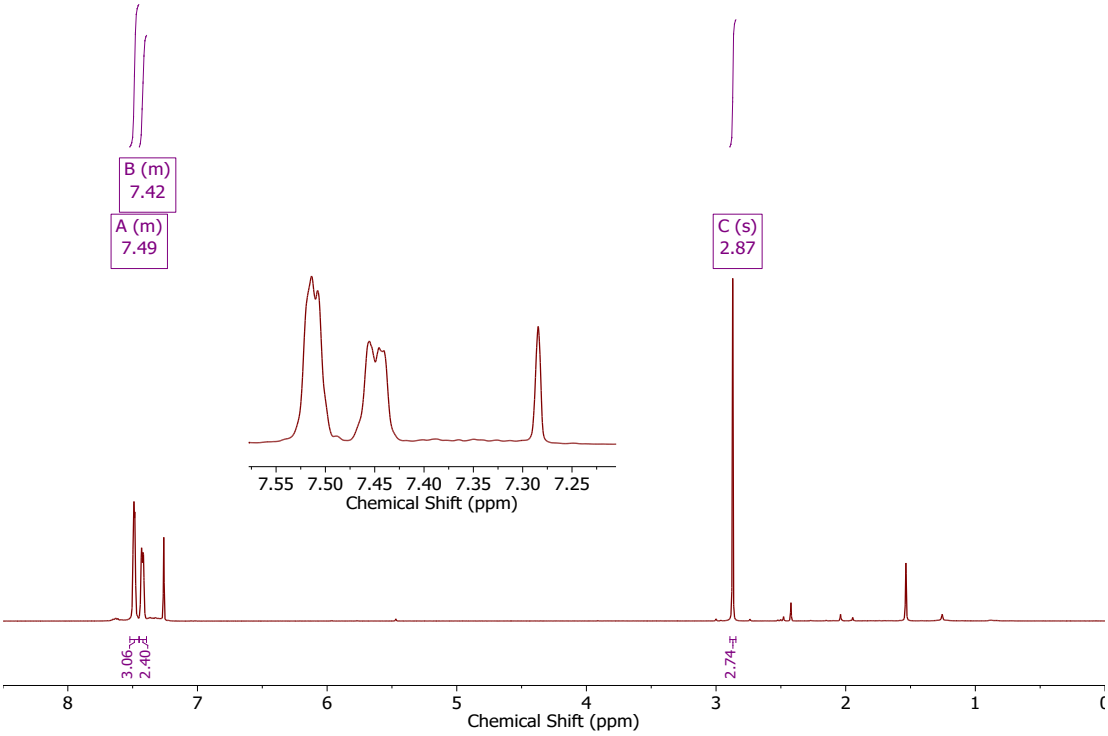


Figure S15. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **MPDTE**

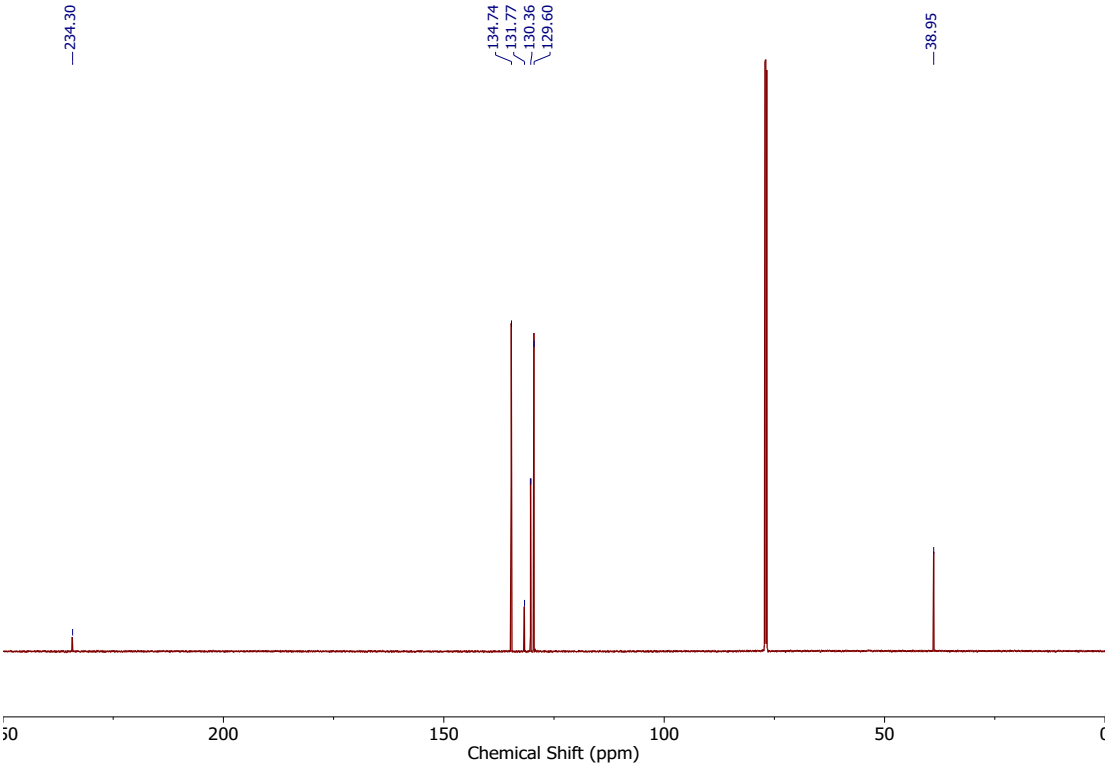


Figure S16. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) spectrum of **MPDTE**

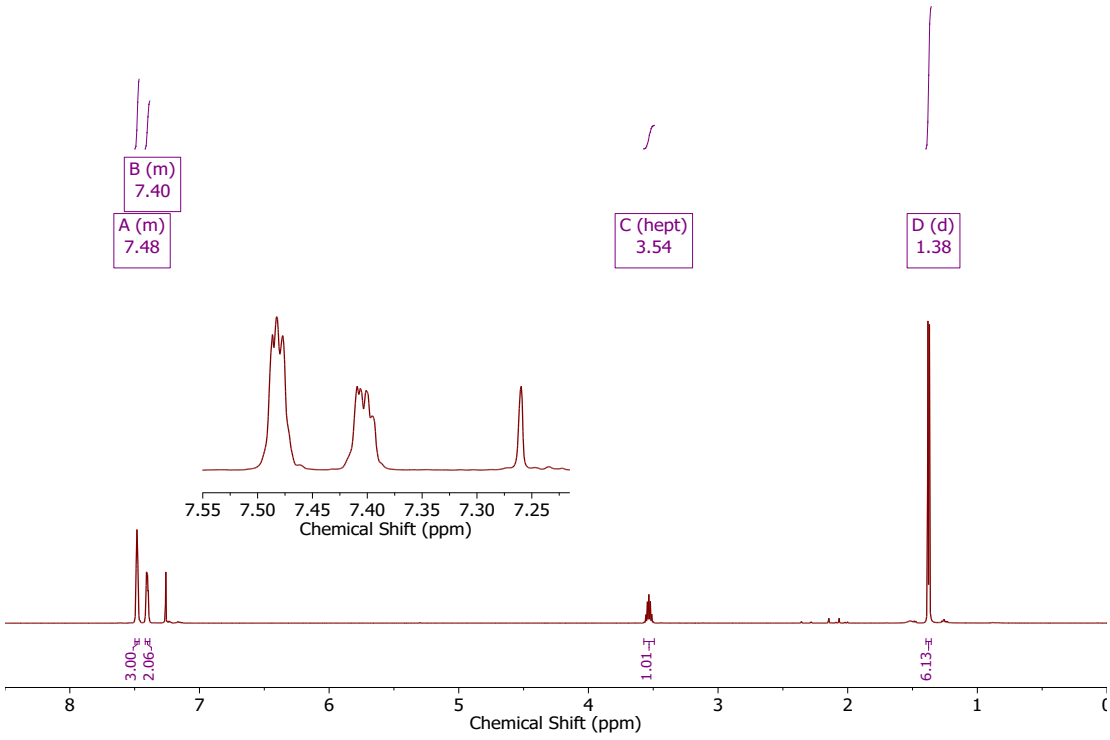


Figure S17. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **iPPDTE**

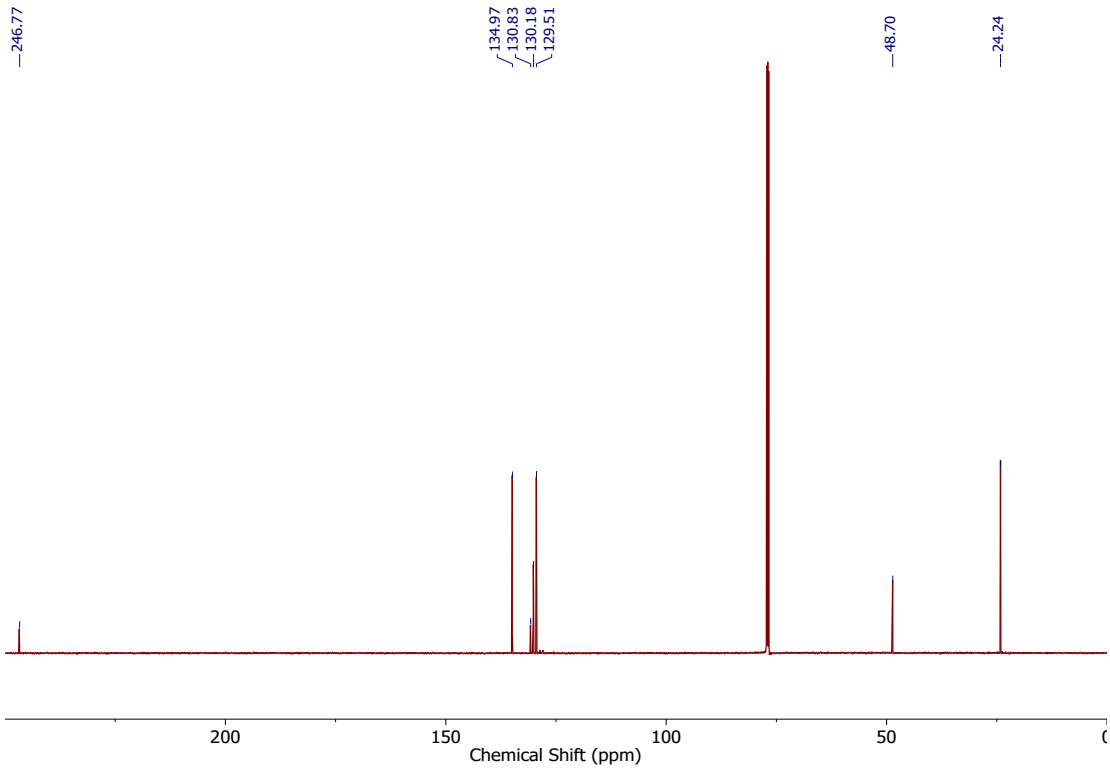


Figure S18. $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of **iPPDTE**

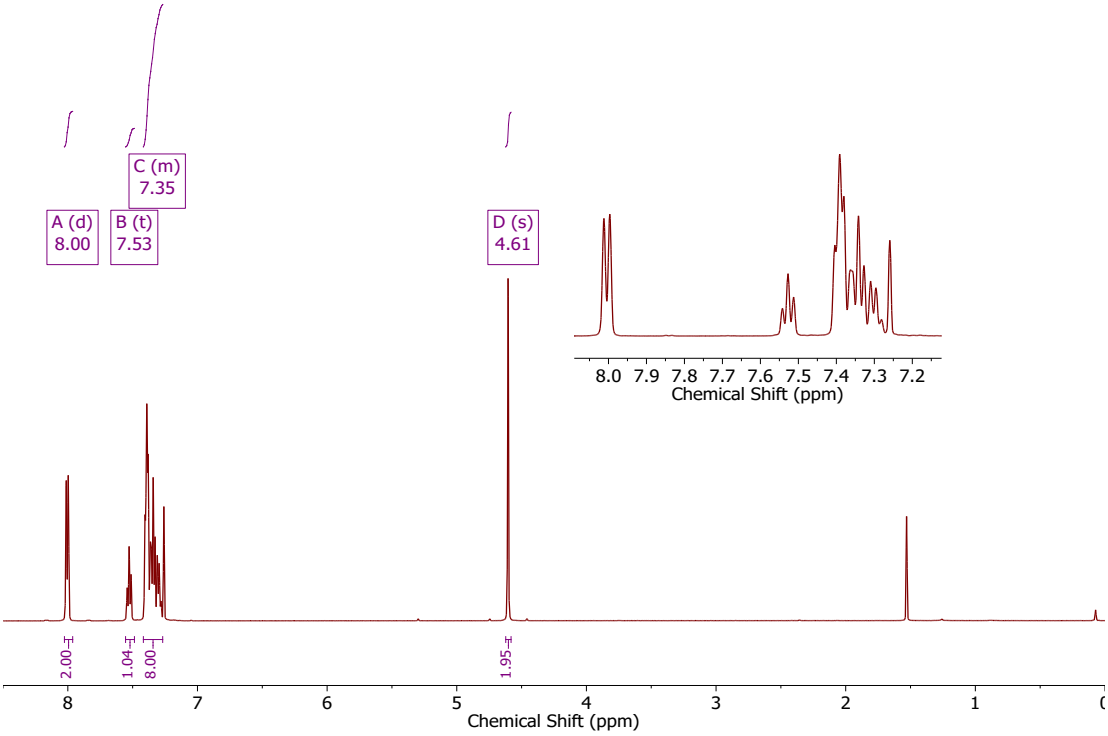


Figure S19. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **PBDTE**

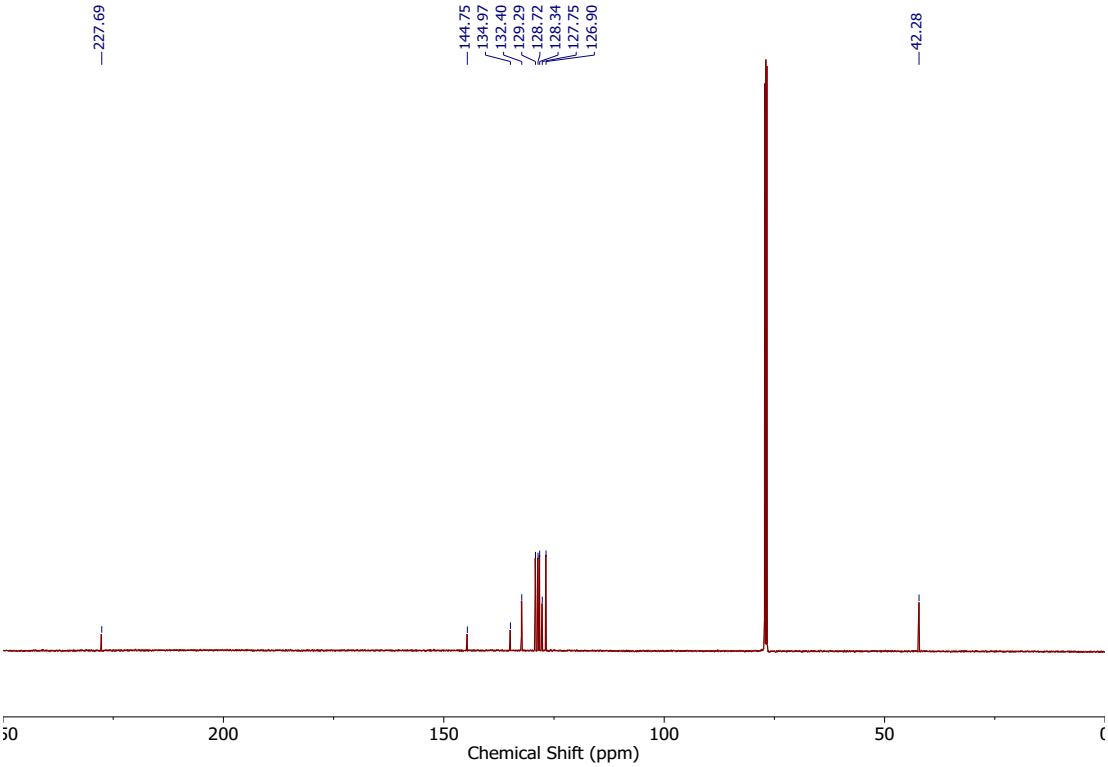


Figure S20. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) spectrum of **PBDTE**

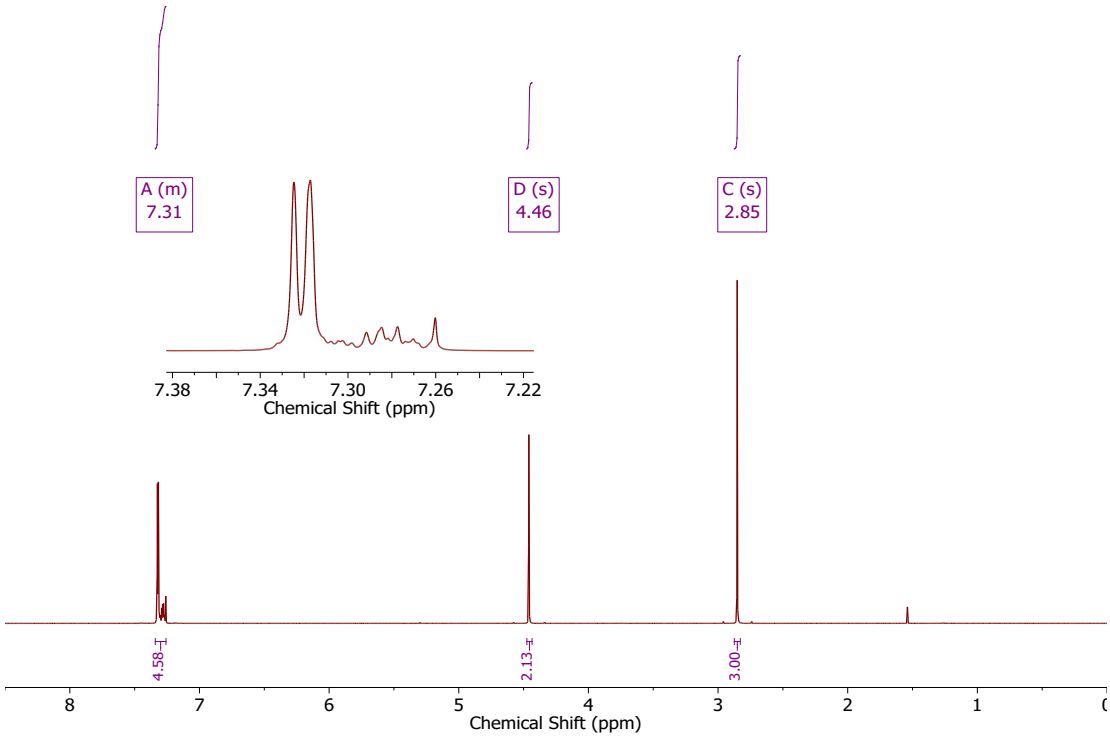


Figure S21. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **MBDTE**

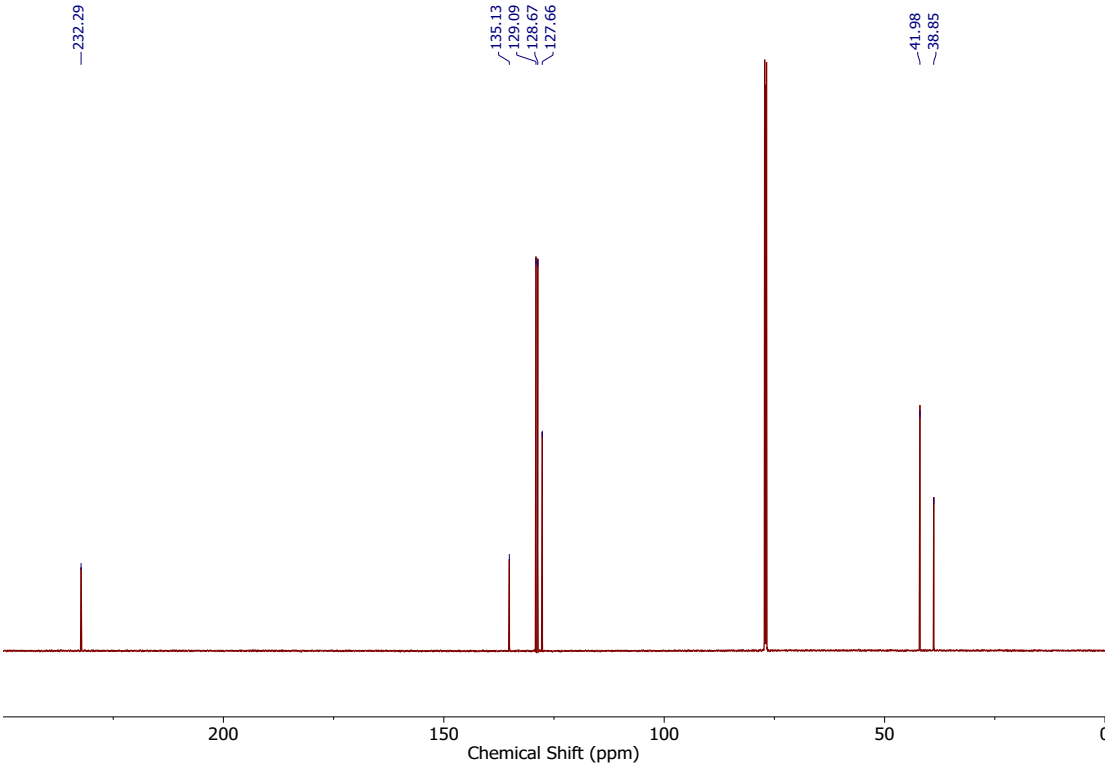


Figure S22. $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of **MBDTE**

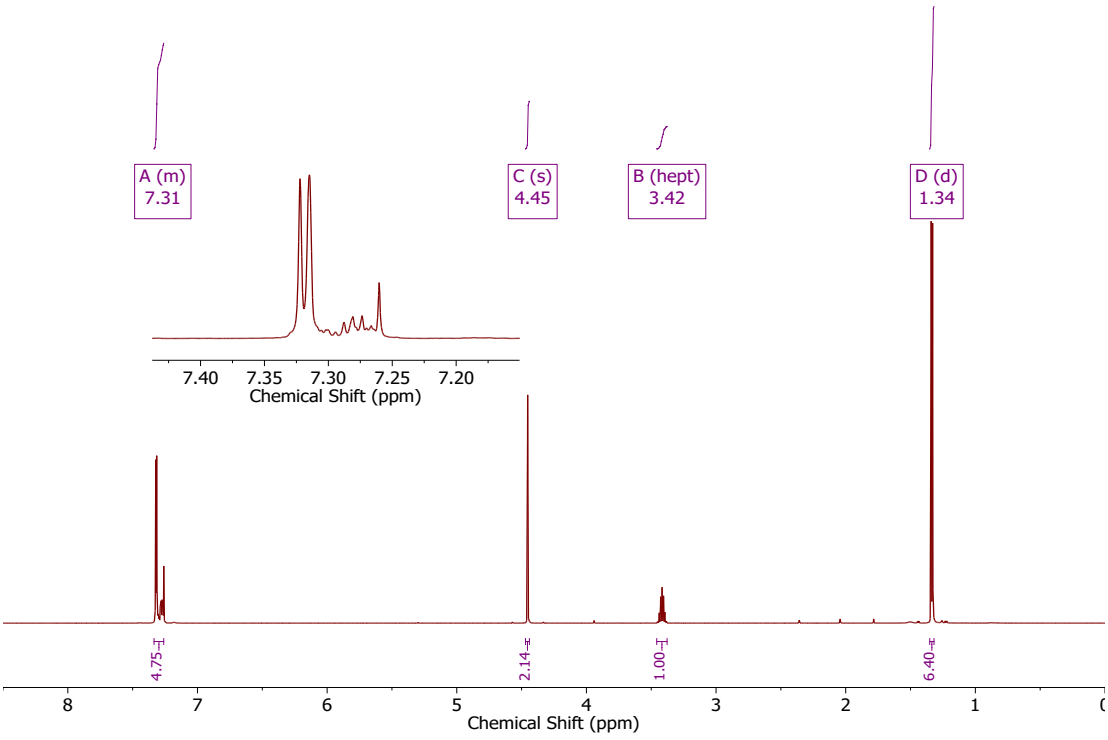


Figure S23. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **iPBDTE**

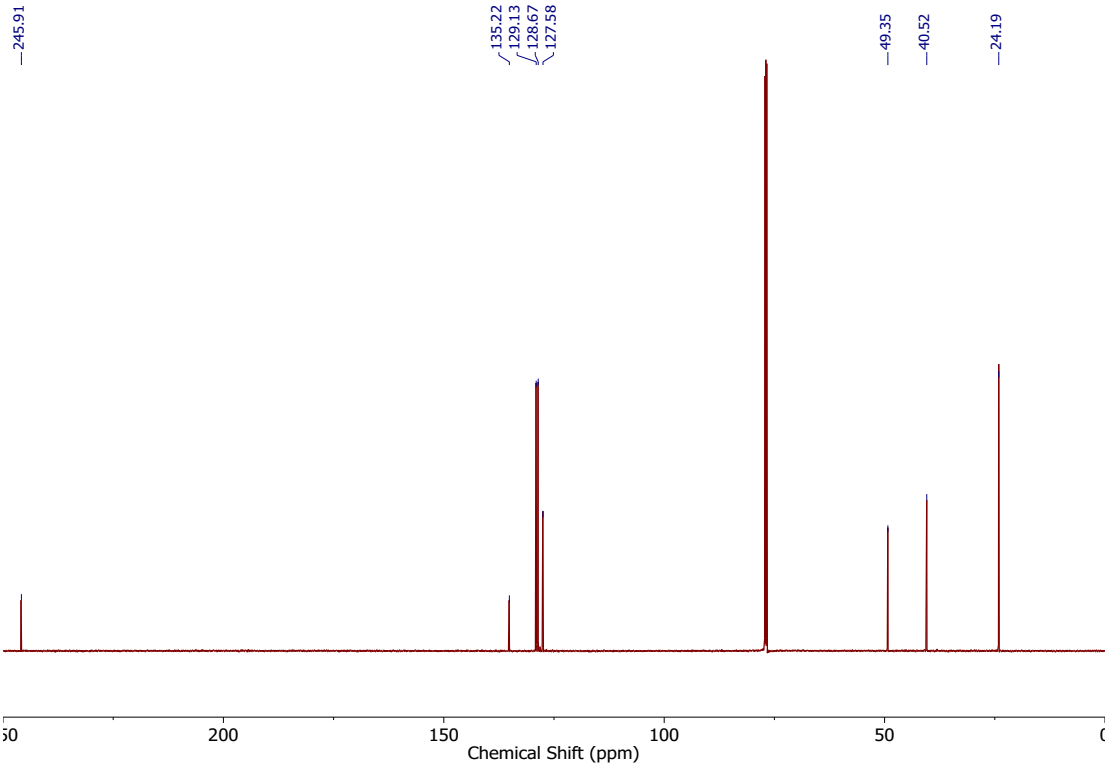


Figure S24. $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of **iPBDTE**

H_2S Detection Materials and Methods Phosphate buffered saline (PBS) tablets (1X, CalBioChem) were used to prepare buffered solutions (140 mM NaCl, 3 mM KCl, 10 mM phosphate, pH 7.4) in deionized water. Buffer solutions were sparged with N_2 to remove dissolved oxygen and stored in an N_2-filled glovebox. Donor stock solutions (in DMSO) were prepared inside an N_2-filled glovebox and stored at -25 °C until immediately before use. Trigger stock solutions (in PBS) were freshly prepared in an N_2-filled glovebox immediately before use.

General Procedure for Measuring H_2S Release via Methylene Blue Assay (MBA). Scintillation vials containing 20 mL of PBS were prepared in an N_2-filled glovebox. To these solutions, 20 µL of 500 mM analyte stock solution (in PBS) was added for a final concentration of 500 µM. While stirring, the solutions were allowed to thermally equilibrate in heating block at the desired temperature for approximately 20-30 min. Immediately prior to donor addition, 0.5 mL solutions of methylene blue cocktail were prepared in disposable 1.5 mL cuvettes. The methylene blue cocktail solution contains: 200 µL of 30 mM $FeCl_3$ in 1.2 M HCl, 200 µL of 20 mM *N*,*N*-dimethyl-*p*-phenylene diamine in 7.2 M HCl, and 100 µL of 1% (w/v) $Zn(OAc)_2$. To begin an experiment, 20 µL of 25 mM donor stock solution (in DMSO) was added for a final concentration of 25 µM. At set time points after the addition of donor, 500 µL reaction aliquots were added to the methylene blue cocktail solutions and incubated for 1 h at room temperature shielded from light. Absorbance values at 670 nm were measured 1 h after addition of reaction aliquot. Each experiment was performed in quadruplicate unless stated otherwise.

MBA Calibration Curve. Solutions containing 0.5 mL of the methylene blue cocktail and 0.5 mL PBS containing 500 µM cysteine were freshly prepared in disposable cuvettes (1.5 mL). Under inert conditions, a 10 mM stock solution of NaSH (Strem Chemicals) in PBS was prepared and diluted to 1 mM. Immediately after dilution, 1 mM NaSH was added to 1.0 mL solutions for final concentrations of 10, 20, 30, 40, and 50 µM. Solutions were mixed thoroughly, incubated at room temperature for 1 h, and shielded from light. Absorbance values at 670 nm were measured after 1 h.

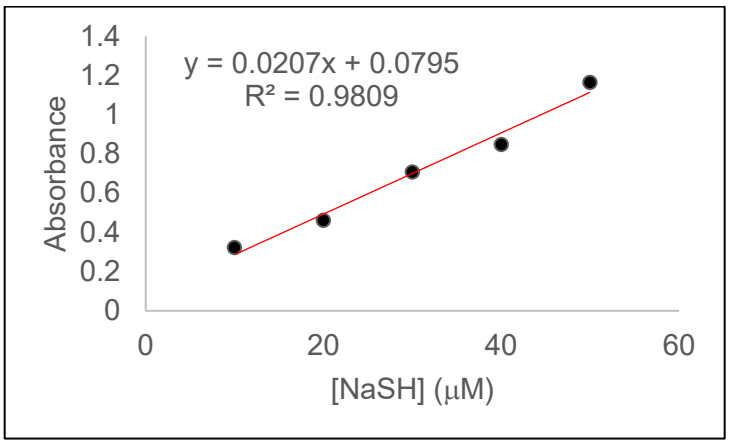
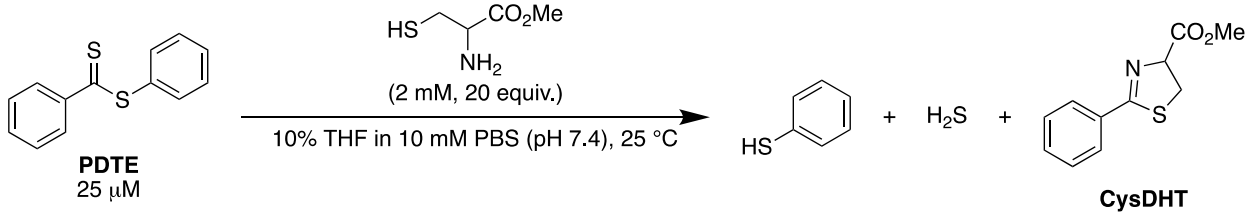


Figure S25. MBA calibration curve generated using known concentrations of NaSH.

Reaction Product Analysis via HPLC



To a 20 mL solution of 10% THF in PBS (10 mM, pH 7.4) containing 2 mM L-cysteine methyl ester (20 equiv.), 20 mL of 100 mM **PDTE** in THF was added for 100 mM **PDTE** and stirred at room temperature. After 1 h, a 1 mL reaction aliquot was analyzed by HPLC. HPLC analysis was performed on an Agilent 1260 HPLC instrument with a Poroshell 120 EC-C18 4.6x100 mm column and monitored at 280 nm. Solvent A: 95% H_2O, 5% MeOH, Solvent B: 100% MeCN. Gradient: 35% Solvent A/65% Solvent B for 2 min. Change to 100% Solvent B over 4 min and hold for 6.5 min. Change to 35% Solvent A/65% Solvent B over 0.5 min and hold for 4.5 min. Flow Rate: 0.5 mL/min, 2 μL injection. The concentration of **CysDHT** present at the end of the reaction was determined by measurement against calibration curves for each compound.

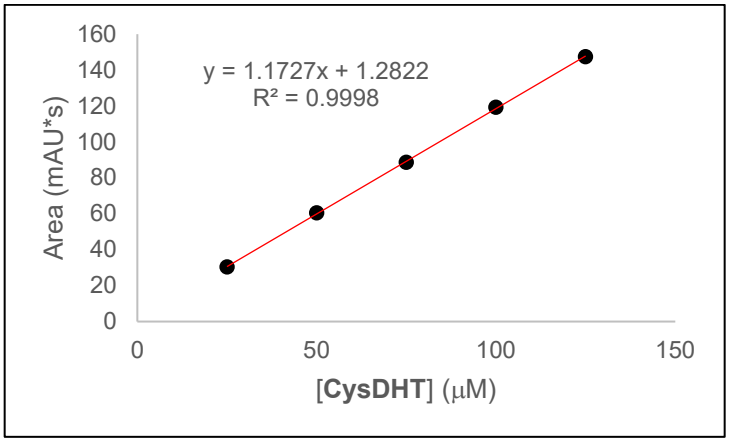


Figure S26. HPLC Calibration Curve of **CysDHT**

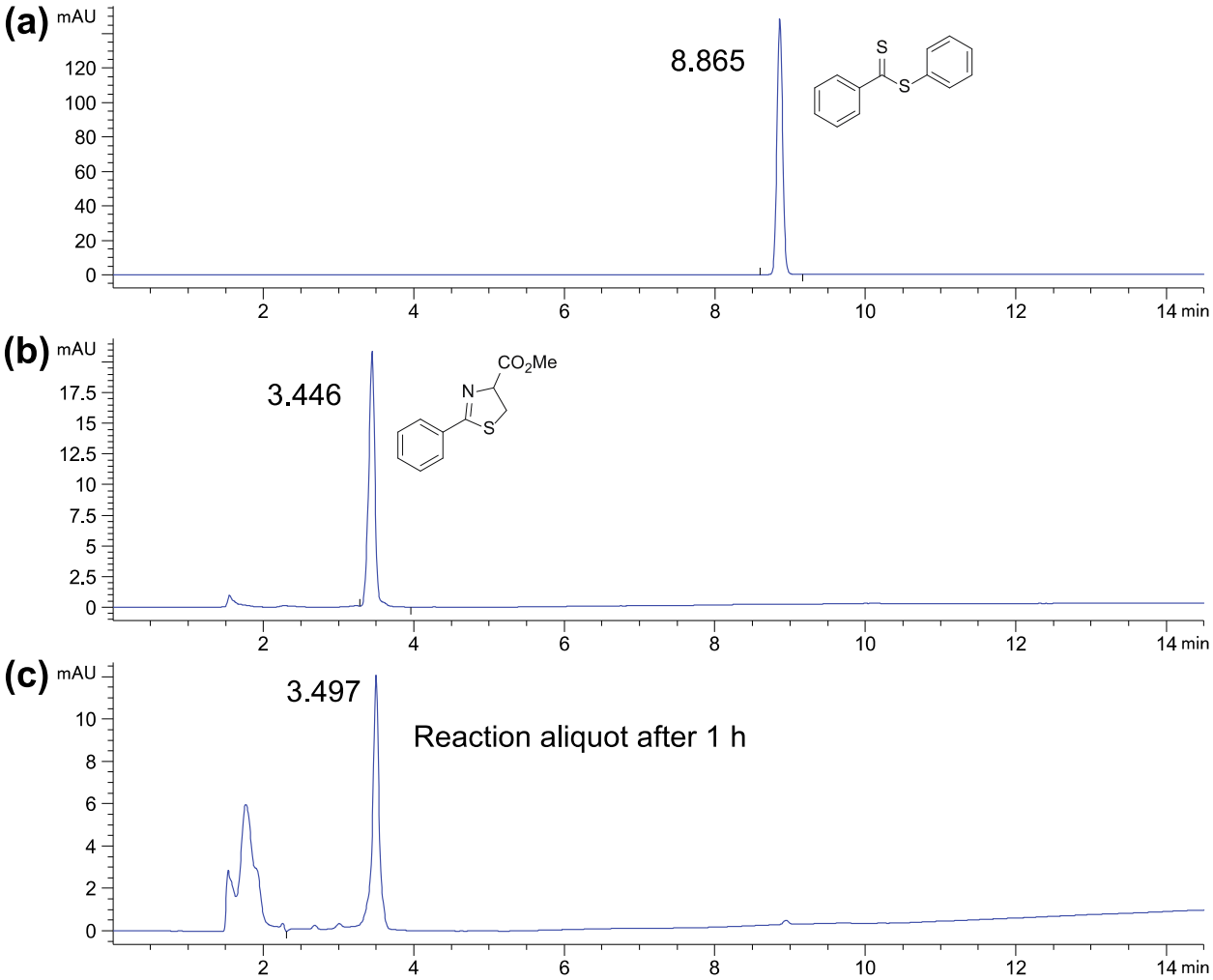


Figure S27. a) 100 ppm **PDTE** in Hexanes b) 100 µM **CysDHT** in 10 mM PBS (pH 7.4) with 10% THF c) Reaction aliquot after 1 h.

Computational Details and Geometries

Structures were initially constructed in Avogadro and optimized using the UFF force field. These resultant structures were then further geometrically optimized using a hybrid GGA functional, B3LYP, with a large triple zeta basis, 6-311++G**, that includes diffuse and polarization functions for all atoms. A pseudosolvent polarizable continuum model was used (water), to partially account for solvent stabilization. VeryTight convergence criteria for forces and displacements, as implemented in Gaussian 09.[2] Energetics were compared to a double zeta basis, 6-31+G*, which showed similar trends and energies.

Transition states were located using i) a potential energy surface scan with the modredundant feature to locate a good starting point for ii) a transition state search. The transition states were confirmed using vibrational analysis as evidenced by a single imaginary frequency corresponding to the direction of bond making / breaking.

Tabulated Geometries

C	1.70029	-0.18587	0.00410
O	2.16621	0.71750	-0.74113
O	2.24049	-1.25398	0.36123
C	0.24551	0.04002	0.50182
H	0.15410	-0.20191	1.55976
C	-0.76968	-0.78330	-0.31959
N	-0.08866	1.49368	0.33415
H	-0.50406	-0.72089	-1.37906
S	-2.51123	-0.20405	-0.08952
H	-0.66366	-1.82437	-0.01519
H	0.12530	2.04941	1.16026
H	-1.11583	1.53814	0.13329
H	0.49401	1.83539	-0.44455

C	4.31392	-0.07254	-1.03428
C	4.57404	-1.29007	-0.39442
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H	1.60761	-0.28009	1.10571
H	2.79529	0.41726	0.14130
S	-0.46667	-0.26808	1.78310

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