Supporting Information for

A bioorthogonal quadricyclane ligation

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Table of Contents

Finding a reaction partner for quadricyclane

Scheme S1. Synthesis of quadricyclane.

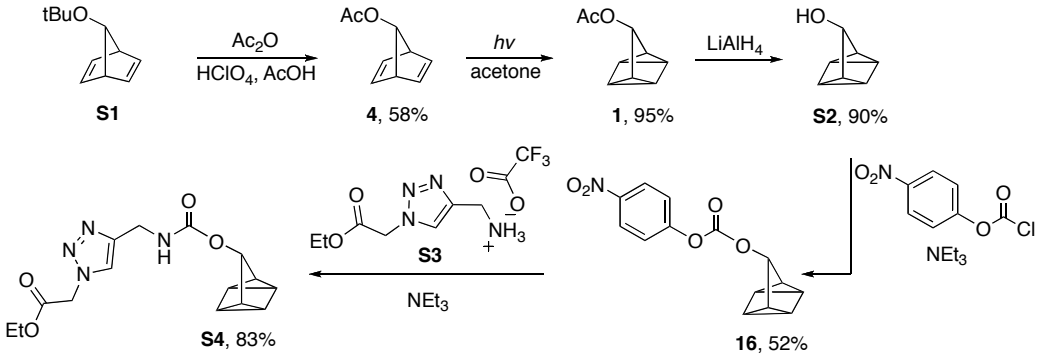
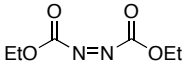
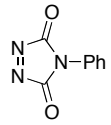
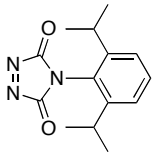


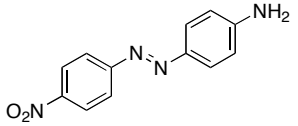
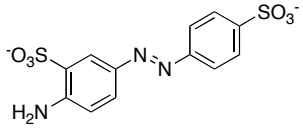
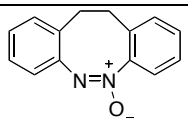
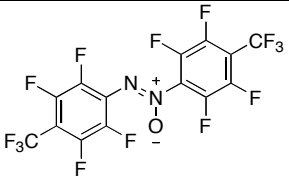
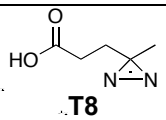
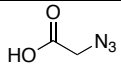
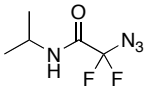
Table S1. Compounds screened for reactivity with quadricyclane. An initial screen with quadricyclane **1** and potential reaction partners was performed and monitored by TLC and mass spectrometry over the course of a week. Any reaction partners that appeared promising by the TLC/MS assay were further analyzed by NMR.

Entry	Compound	Comments
1[1]	 **T1**	**1** (5 mg) plus **T1** (7 mg) in DCM (0.2 mL) yields only a small amount of product after 3 d at 37 °C. DEAD shows some degradation in H_2O and MeOH.
2[2]	 **T2**	$k = 4 \times 10^{-3}$ $M^{-1}s^{-1}$ in CD_3CN (by NMR kinetics with 50 mM each reagent). PTAD (**T2**) is not stable to protic solvent or water.[3]
3[4]	 **T3**	**T3** was reactive with quadricyclane but bis(isopropyl) PTAD (**T3**) was still not stable enough to water to act as a bioorthogonal reaction partner.

[1] (a) Domingo, L.R.; Saez, J.A.; Zaragoza, R.J.; Arno, M. *J. Org. Chem.* **2008**, *73*, 8791-8799. (b) Rieber, N.; Alberta, J.; Lipsky, J.A.; Lemal, D.M. *J. Am. Chem. Soc.* **1969**, *91*, 5668-5669.

[2] LeBlanc, B.F.; Sheridan, R.S. *J. Am. Chem. Soc.* **1985**, *107*, 4554-4556.

[3] Keana, J.F.W.; Guzikowski, A.P.; Ward, D.D.; Morat, C.; Van Nice, F.L. *J. Org. Chem.* **1983**, *48*, 2654-2660.

4	 **T4**	12.5 mM **S4** + 125 mM **T4** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
5	 **T5**	12.5 mM **S4** + 125 mM **T5** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
6[5]	 **T6**	No reaction by NMR with 50 mM **T6** and 50 mM **S2**. Solvent mixture was 4:1:1 MeOD/D_2O/$CDCl_3$.
7[6]	 **T7**	12.5 mM **S4** + 125 mM **T7** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
8[7]	 **T8**	12.5 mM **S4** + 125 mM **T8** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
9	 **T9**	12.5 mM **S4** + 125 mM **T9** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
10[8]	 **T10**	12.5 mM **S4** + 125 mM **T10** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.

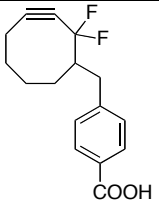
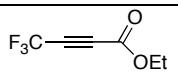
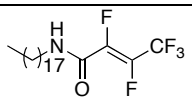
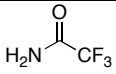
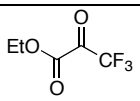
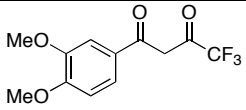
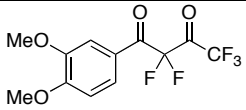
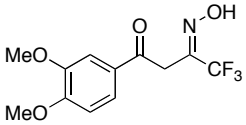
[4] For preparation of **T3** see: Keana, J.F.W.; Guzikowski, A.P.; Ward, D.D.; Morat, C.; Van Nice, F.L. *J. Org. Chem.* **1983**, *48*, 2654-2660.

[5] For preparation of **T6** see: Smith, M.A.; Weinstein, B.; Greene, F.D. *J. Org. Chem.* **1980**, *45*, 4597-4602.

[6] For preparation of **T7** see: Korobeinicheva, I.K.; Fugaeva, O.M.; Furin, G.G. *Izvestia Akademii nauk SSSR, Seria himiceskaa* **1986**, *7*, 1537-1544.

[7] For preparation of **T8** see: Bond, M.R.; Zhang, H.; Vu, P.D.; Kohler, J.J. *Nat. Protocols* **2009**, *4*, 1044-1063.

[8] **T10** was synthesized by subjecting ethyl difluoroazidoacetate to 1 equivalent of isopropyl amine in dimethylformamide (0.5 M reactants) at 0 ^oC for 1.5 h. Extraction with ether and distillation afforded pure **T10**. Ethyl difluoroazidoacetate was prepared according to the procedure of Koppes and Chaykovsky. Koppes, W.M.; Chaykovsky, M. "Preparation of 2-azido-2,2-difluoroethanol" US Patent 5276171, **1994.**

11[9]	 **T11**	12.5 mM **S4** + 125 mM **T11** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
12[10]	 **T12**	LCMS assay indicated reaction occurred; however, polymerization/product stability appeared problematic. The reaction was also monitored by NMR with 50 mM **T12** and 50 mM **S2** in 4:1:1 MeOD/D_2O/$CDCl_3$. There was still starting material after 5 d at rt.
13[11]	 **T13**	12.5 mM **S4** + 125 mM **T13** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
14[12]	 **T14**	12.5 mM **S4** + 125 mM **T14** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
15[12]	 **T15**	12.5 mM **S4** + 125 mM **T15** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
16	 **T16**	No reaction by NMR with 50 mM **T16** and 50 mM **S2**. The solvent mixture was 4:1:1 MeOD/D_2O/$CDCl_3$.
17[13]	 **T17**	12.5 mM **S4** + 125 mM **T17** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
18[14]	 **T18**	12.5 mM **S4** + 125 mM **T18** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.

[9] For preparation of **T11** see: Codelli, J.A.; Baskin, J.M.; Agard, N.J.; Bertozzi, C.R. *J. Am. Chem. Soc.* **2008**, *130*, 11486-11493.

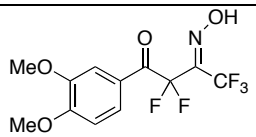
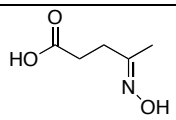
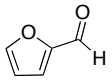
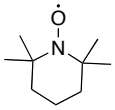
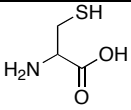
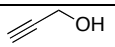
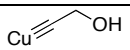
[10] For reactivity with fluoroacetylenes see: Barlow, M.G.; Suliman, N.E.; Tipping, A.E. *J. Fluorine Chem.* **1995**, *73*, 61-67.

[11] For reactivity with fluoroolefins see: Petrov, V.A.; Davidson, F.; Krusic, P.J.; Marchione, A.A.; Marshall, W.J. *J. Fluorine Chem.* **2005**, *126*, 601-610.

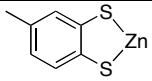
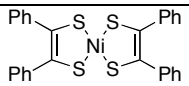
[12] For reactivity with fluorinated carbonyl compounds see: Petrov, V.A.; Davidson, F.; Smart, B.E. *J. Fluorine Chem.* **2004**, *125*, 1543-1552.

[13] **T17** was prepared from **T16** by treatment with Cs_2CO_3 and Selectfluor™. See ref 9.

[14] **T18** was prepared from **T16** by treatment with hydroxylamine.

19[15]	 **T19**	12.5 mM **S4** + 125 mM **T19** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
20[16]	 **T20**	12.5 mM **S4** + 125 mM **T20** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
21	 **T21**	12.5 mM **S4** + 125 mM **T21** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
22	 **T22**	12.5 mM **S4** + 125 mM **T22** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
23	 **T23**	12.5 mM **S4** + 125 mM **T23** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
24	 **T24**	12.5 mM **S4** + 125 mM **T24** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
25	 **T25**	12.5 mM **S4** + 125 mM **T25** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
26	 **T26**	12.5 mM **S4** + 125 mM **T26** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
27	 **T27**	12.5 mM **S4** + 125 mM **T27** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
28	 **T28**	12.5 mM **S4** + 125 mM **T28** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
29	 **T29**	12.5 mM **S4** + 125 mM **T29** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.
30	 **T30**	12.5 mM **S4** + 125 mM **T30** and **T31** in 3:1 MeOH/H_2O; A small amount of DTT adduct was evident by LCMS after multiple days.
31	 **T31**	12.5 mM **S4** + 125 mM **T31** in 3:1 MeOH/H_2O; nothing promising by LCMS or TLC over multiple days at rt.

[15] **T19** was prepared from **T17** by treatment with hydroxylamine.
[16] **T19** was prepared by the oxime ligation of levulinic acid and hydroxylamine.

32	DTT + AIBN **T30 + T31**	12.5 mM **S4** + 125 mM **T30** and **T31** in 3:1 MeOH/H_2O; A small amount of DTT adduct was evident by LCMS after multiple days.
33	 **T32**	No reaction by NMR in 6:1 DMSO/MeOD at 14 mM. LCMS assay (12.5 mM **S4** + 125 mM **T32** in 3:1 MeOH/H_2O) also did not seem promising.
34	 **2**	Limited solubility prevented good kinetics by ^{1}H-NMR but reaction is clean. LCMS assay (12.5 mM **S4** + 125 mM **2** in 3:1 MeOH/H_2O) shows product formation.

Stability of quadricyclane

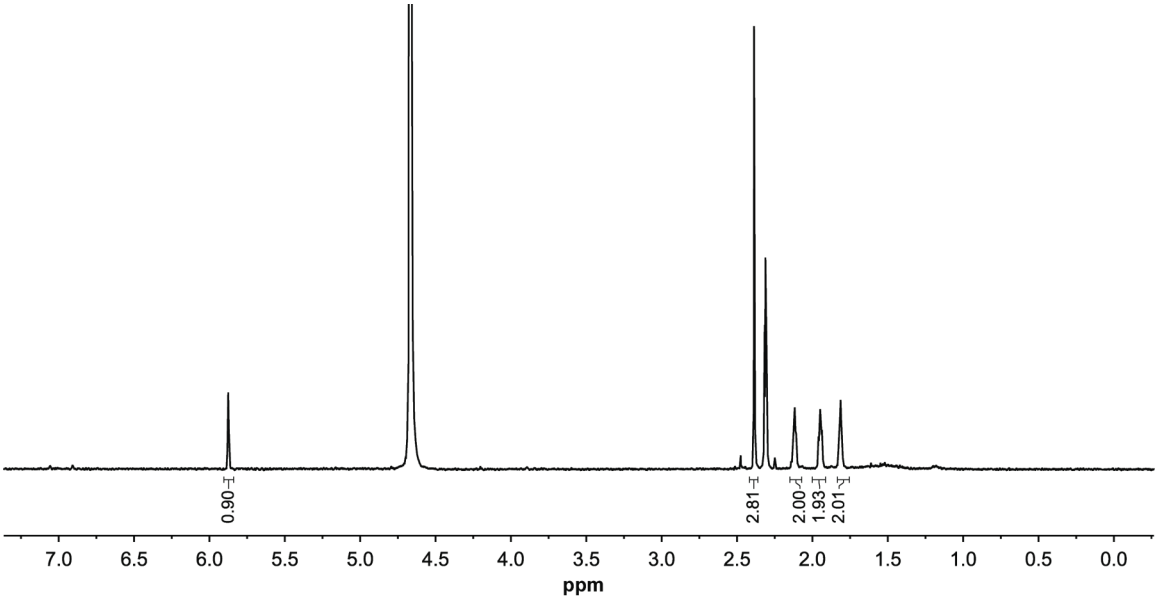


Figure S1. Quadricyclane is stable in phosphate buffered saline (PBS, pH 7.4). 7-Acetoxy quadricyclane (**1**, 2 mg) was dissolved in 0.4 mL of CD_3CN. To this solution, 0.4 mL of deuterated PBS was added. The NMR spectrum above was taken 2.5 months after the described solution was prepared.

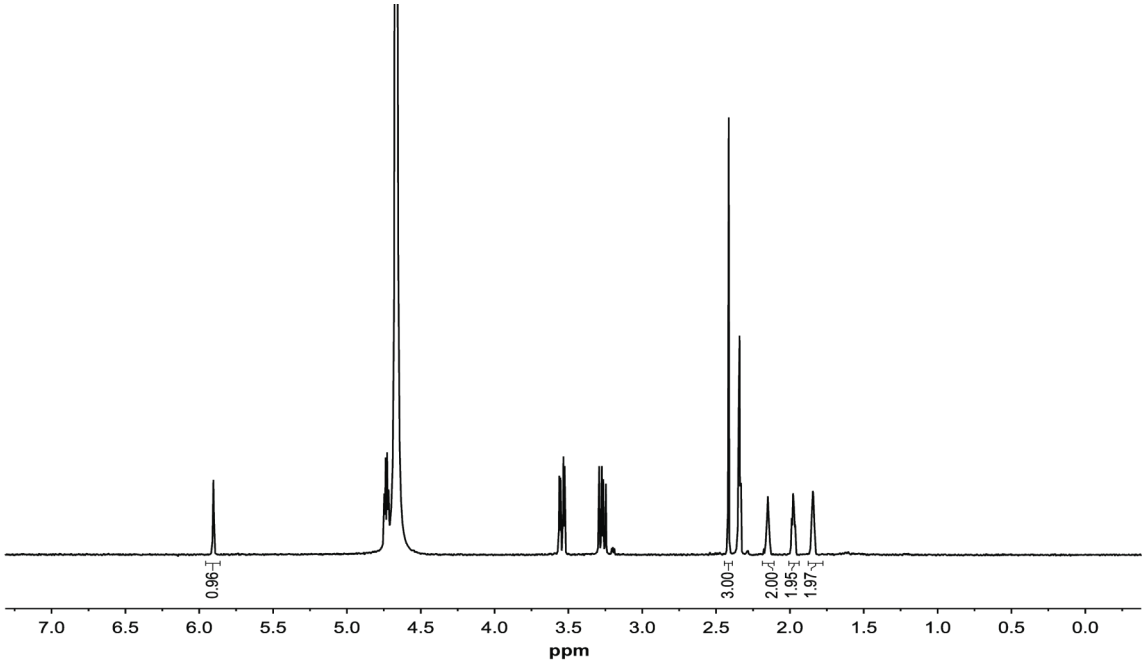


Figure S2. Quadricyclane is stable to cysteine. 7-Acetoxy quadricyclane (**1**, 2 mg) was dissolved in 0.4 mL of CD_3CN. To this solution, 0.4 mL of deuterated PBS and 3 mg of cysteine were added. The NMR spectrum above was taken 2.5 months after the described solution was prepared.

Photodegradation study of 3

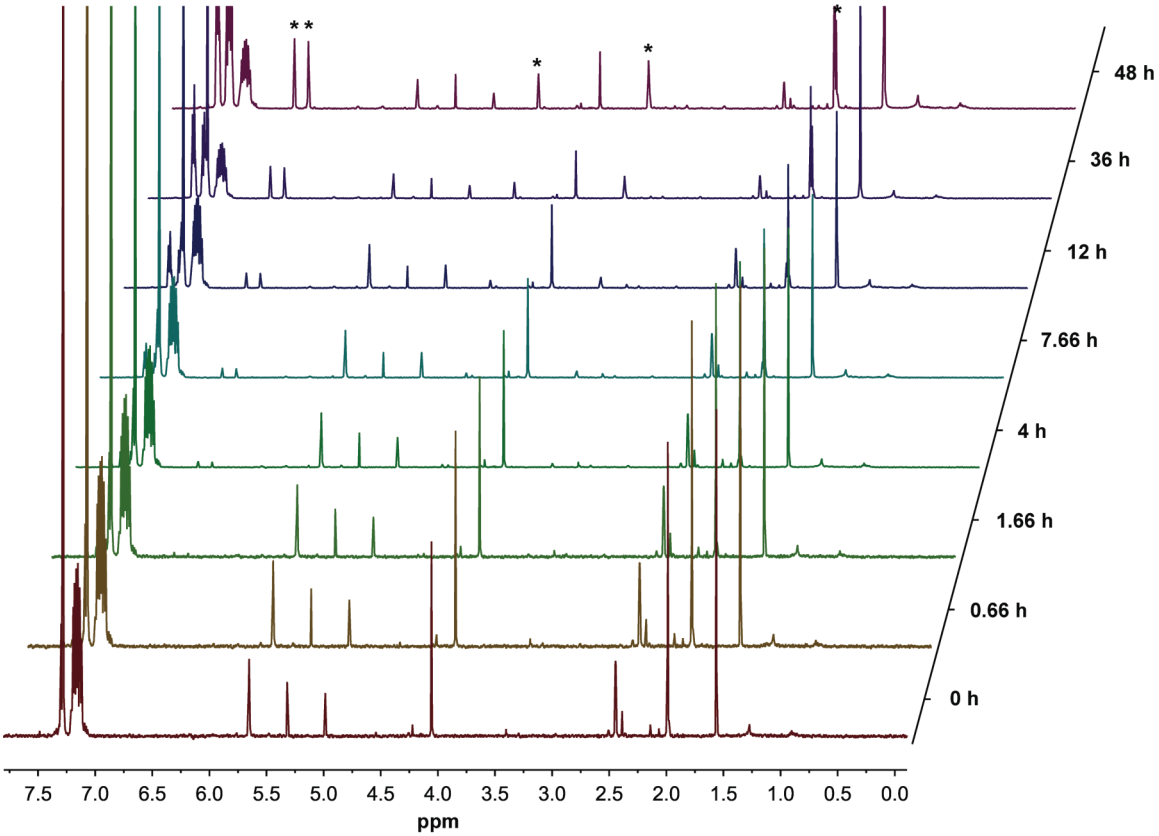


Figure S3. Complex **3** is photo-labile. Complex **3** (2.2 mg) was dissolved in $CDCl_3$ (~0.75 mL) and placed in an NMR tube on the bench continually exposed to ambient light. NMR spectra were periodically obtained. The asterisks indicate the chemical shifts for 7-acetoxy norbornadiene (**4**). At the 36 h time point, there is a 1:1.1 ratio of **3**:**4** as judged by integration of the olefin peaks. The calculated half-life based on all integration data is 34.8 h.

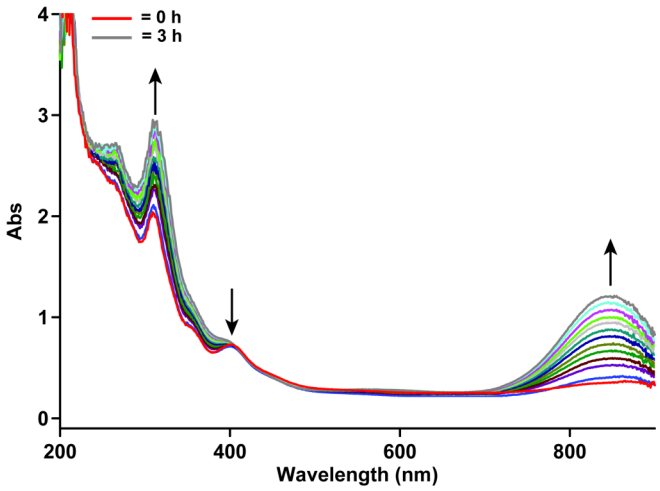


Figure S4. Complex **3** is photo-labile. Using an NMR assay degradation of **3** over the first few hours is not evident. However, using UV/Vis/NIR spectroscopy, which has greater sensitivity than NMR, the formation of **2** from **3** is evident at early timepoints. A solution of **3** was prepared in CH_3CN and left in ambient light. A UV/Vis/NIR spectrum was obtained every 15 min. The NIR absorption band at 850 nm characteristic of **2** is growing in.[17]

Table S2. Additives tested to prevent photodegradation of complex **3**. A solution containing 200 μM **3** and 1.25 mM additive in 3:1 CH_3CN/H_2O was left in ambient light and monitored for formation of **2** by UV/Vis/NIR spectroscopy. Some additives were able to reduce compound **2** to the anionic state as evident by a peak centered at ~900 nm in the UV/Vis/NIR spectra.

Entry	Compound	Result
1	No additive	Photodegradation; **2** precipitates from solution. See Figure S5.
2[18]	1,2-diaminocylohexane tetraacetate	Photodegradation; **2** precipitates from solution.
3	Triphenylphosphine	Photodegradation and reduction to anionic species (abs band ~ 900 nm).
4	Histidine	Photodegradation and some reduction of **2** to anionic species but also some precipitate observed.

[17] Kajitani, M.; Kohara, M.; Kitayama, T.; Asano, Y.; Sugimori, A. *Chem. Lett.* **1986**, 2109-2112.
[18] Tandon, S.K.; Mathur, A.K. *Acta Pharmacol. Et. Toxicol.* **1976**, *38*, 401-408.

5[18]	Ethylenediaminetetraacetate	Photodegradation; **2** precipitates from solution.
6[18]	Diethyldithiocarbamate	Complex **3** present after 20 h in light. See Figure S5.
7	Cysteine	Photodegradation and reduction of **2** to anionic species (abs band ~ 900 nm). See Figure S5.
8	Dithiothreitol	Photodegradation and reduction to anionic species (abs band ~ 900 nm).
9[19]	Methyl iodide*	Photodegradation; **2** precipitates from solution.

* Methyl iodide experiment performed in 100% CH_3CN

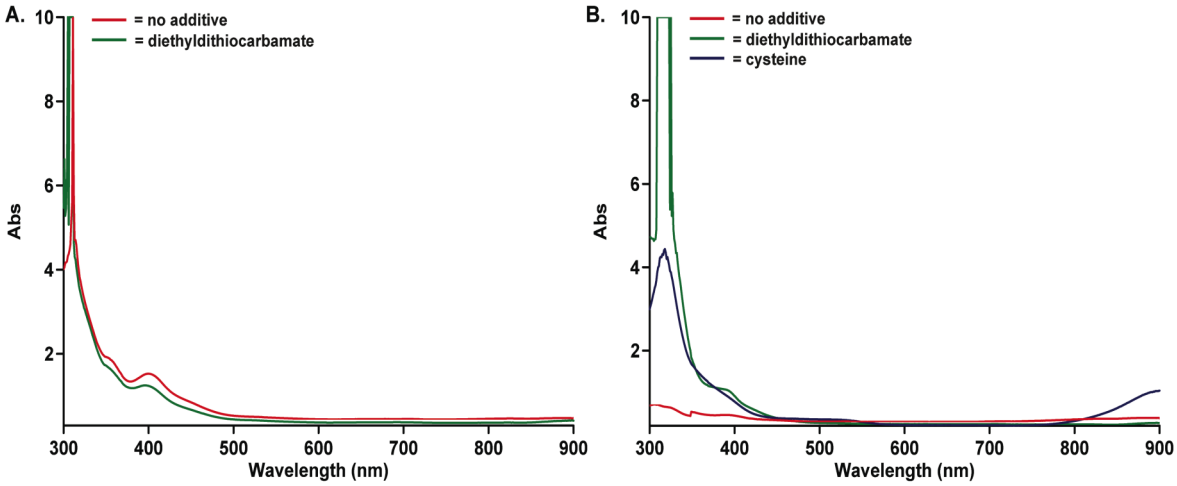
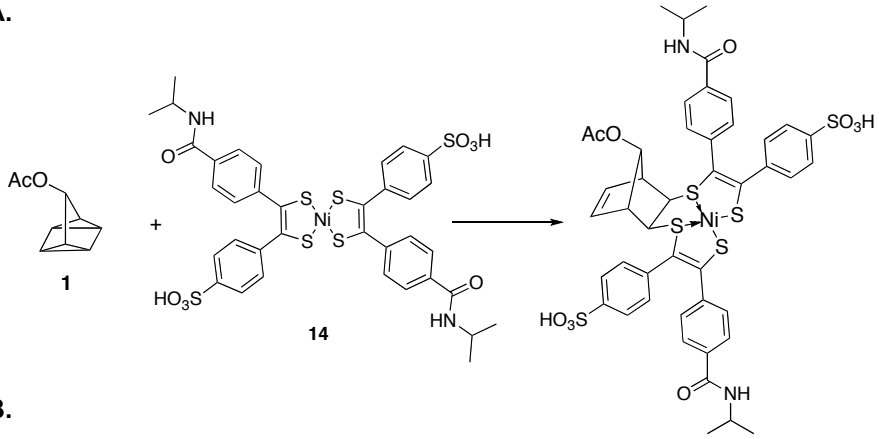


Figure S5. Diethyldithiocarbamate (**5**) prevents the photo-degradation of complex **3**. A solution containing 200 μM **3** and 0 (red) or 1.25 (green) mM **5** in 3:1 CH_3CN/H_2O was prepared and left in ambient light continually. A. UV/Vis/NIR spectra of the described solutions taken before being exposed to light. B. UV/Vis/NIR spectra of the described solutions taken after 20 h of exposure to light. The red line contains little absorbance due to the low solubility of **2** in acetonitrile. If **2** is reduced to the anionic state by cysteine (1.25 mM, blue line) solubility in acetonitrile is improved and evidence of photodegradation can be seen. The diethyldithiocarbamate treated sample remains unaltered after exposure to light indicating no photodegradation occurred.

[19] Schrauzer, G.N.; Ho, R.K.Y.; Murillo, R.P. *J. Am. Chem. Soc.* **1970**, *92*, 3508-3509.

Kinetic analysis of the reaction between 1 and 14

A.



B.

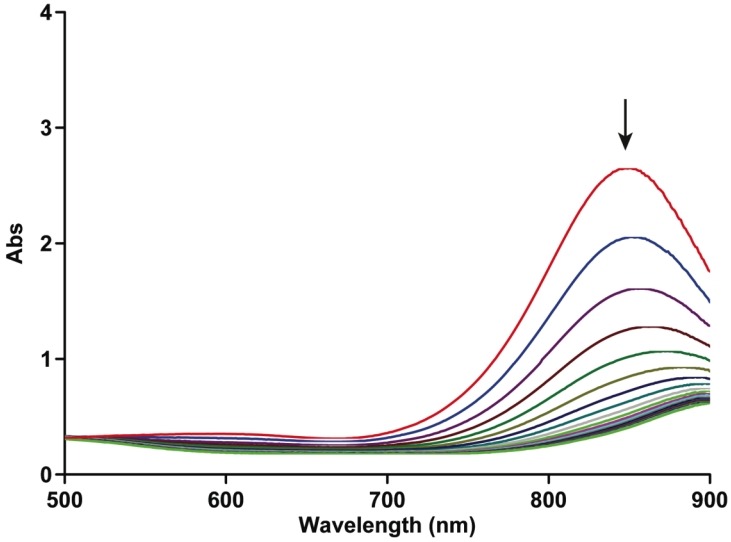


Figure S6. A. The reaction between **1** and **14**. B. A series of UV/Vis/NIR spectra taken as the reaction in part A is proceeding. A solution of **14** (400 μM in PBS) was combined with **1** (20 mM in EtOH) and a UV/Vis/NIR spectrum was taken every 30 seconds.

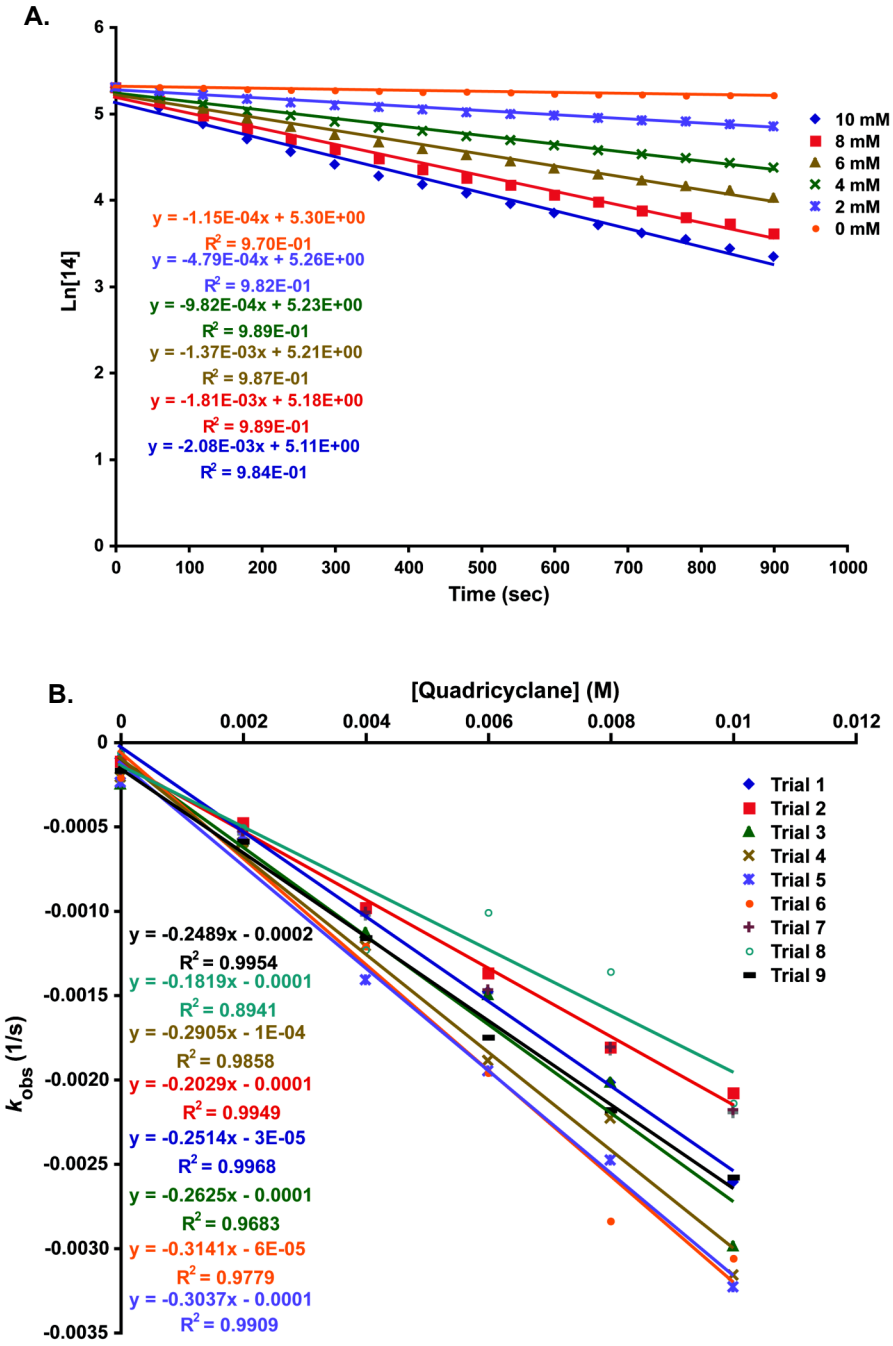


Figure S7. The second-order rate constant for the reaction of **1** and **14** was determined using pseudo-first order kinetics. A solution of 400 μM **14** in PBS was combined with various solutions of quadricyclane **1** (20 mM, 16 mM, 12 mM, 8 mM, 4 mM, or 0 mM in EtOH) in a 1:1 ratio (total volume = 100 μL). The reaction was monitored by the absorbance at 850 nm for 15 min. The absorbance values were correlated to the concentration of **14** using a standard curve. A plot of Ln[**14**] verses time resulted in a series of first-order rate constants (k_{obs}). Plotting each k_{obs} value vs. [**1**] yields a linear

regression with the slope of the line indicating the second-order rate constant. The average of nine trials resulted in a second-order rate constant of 0.25 $\pm$ 0.05 $M^{-1}s^{-1}$. A. A representative plot to determine k_{obs}. B. Plot of k_{obs} vs. [**1**] for each trial.

Stability of Ni bis(dithiolene) 14

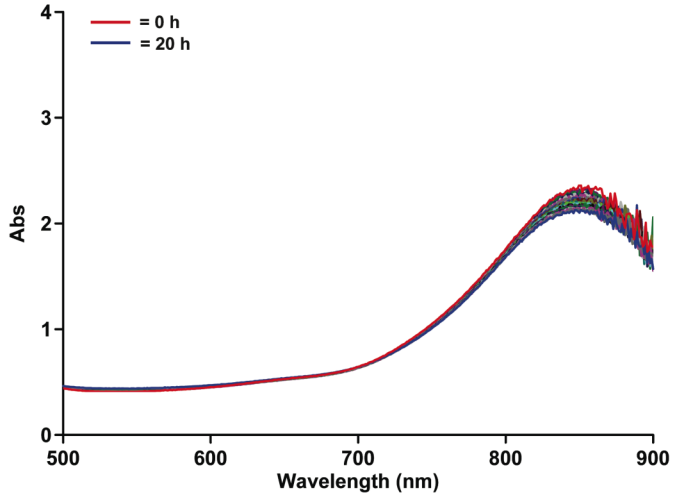


Figure S8. Ni bis(dithiolene) **14** is stable to PBS. Ni bis(dithiolene) **14** was dissolved in PBS. The absorption of the NIR band was monitored for changes over 20 h. A UV/Vis/NIR spectrum was taken every hour. Only slight reduction in signal is evident.

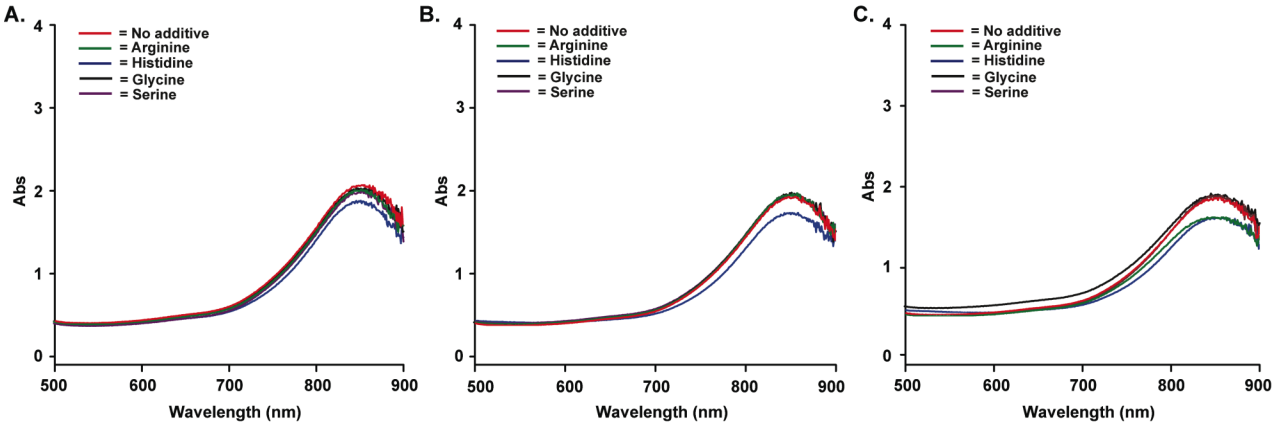


Figure S9. Ni bis(dithiolene) **14** is moderately stable to excess of free amino acids. A solution of 400 μM **14** in PBS was combined with solutions of 50 mM of the indicated amino acid in a 1:1 ratio. The absorbance of each solution was monitored over time. A. The UV/Vis/NIR spectra taken after approximately 15 min. B. The UV/Vis/NIR spectra taken after 1 h. C. The UV/Vis/NIR spectra taken after 2 h. Red = no amino acid present. Green = arginine. Blue = histidine. Black = glycine. Purple = serine.

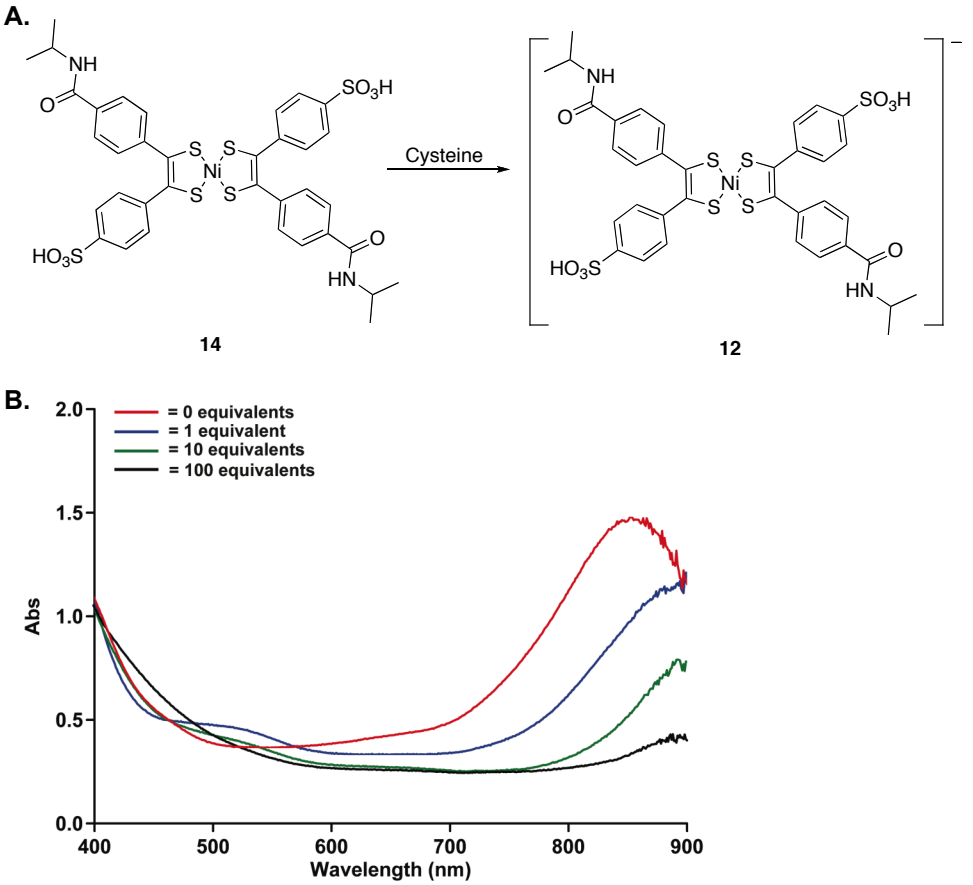


Figure S10. Ni bis(dithiolene) **14** is not stable to cysteine. A. Schematic for the reduction of **14** to **12** by free cysteine. B. UV/Vis/NIR analysis of the reaction between **14** and cysteine. A solution of 125 μM **14** in PBS was prepared with 0 (red), 1 (blue), 10 (green) or 100 (black) equivalents of cysteine. All the mixtures instantly turned orange upon addition of cysteine and displayed the UV/Vis/NIR spectra shown above. A smaller, red-shifted NIR absorption band is consistent with reduction of **14** to **12**.[20]

[20] (a) Nakazumi, H.; Takamura, R.; Kitao, T. *J. Soc. Dyers Colour.* **1991**, *107*, 459-462. (b) Nomura, M.; Takayama, C.; Kajitani, M. *Inorg. Chim. Acta* **2004**, *357*, 2294-2300.

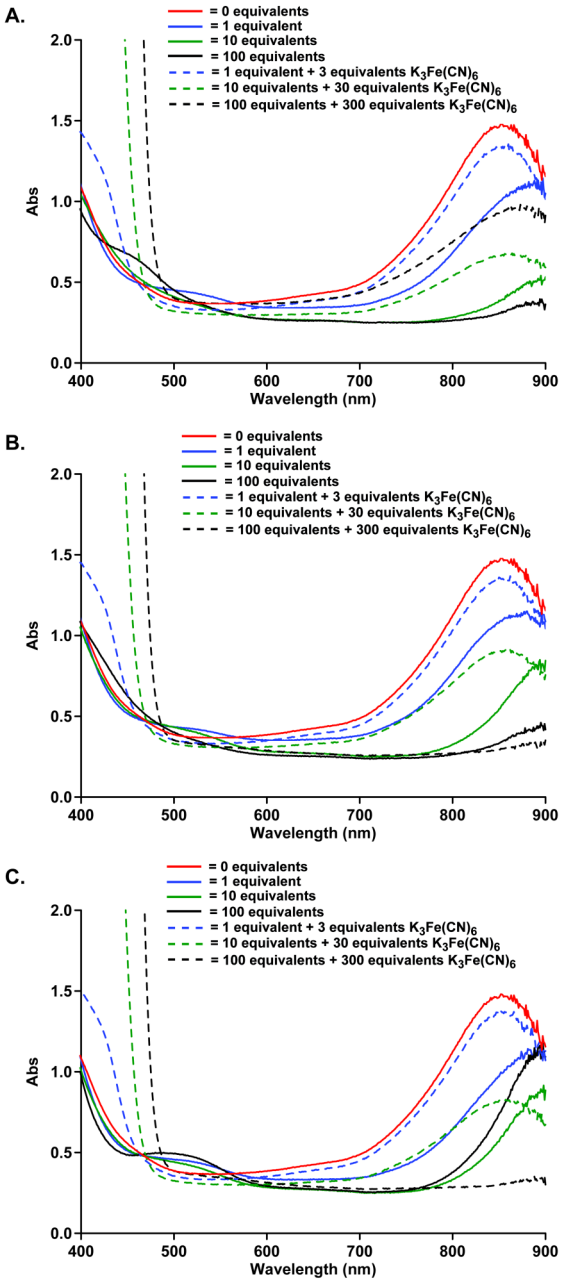


Figure S11. Ni bis(dithiolene) **14** is not stable to reducing agents. A solution of 125 μM **14** in PBS was prepared with 0 (red), 1 (blue, solid), 10 (green, solid) or 100 (black, solid) equivalents of β-mercaptoethanol (BME, A), tris(carboxyethyl)phosphine (TCEP, B), or *N*-acetyl cysteine (**C**). All the mixtures instantly turned orange upon addition of reducing agent and displayed the UV/Vis/NIR spectra shown above. A smaller, red-shifted NIR absorption band is consistent with reduction of **14** to **12**.[20] For the cases of 1 and 10 equivalents of reducing agent, **14** could be recovered by the addition of 3 equivalents or 30 equivalents of potassium ferricyanide ($K_3Fe(CN)_6$), respectively (blue or green dashed lines). However, the addition of 300 equivalents of $K_3Fe(CN)_6$ did not restore **14** when **14** was subjected to 100 equivalents of reducing agent (black dashed line).

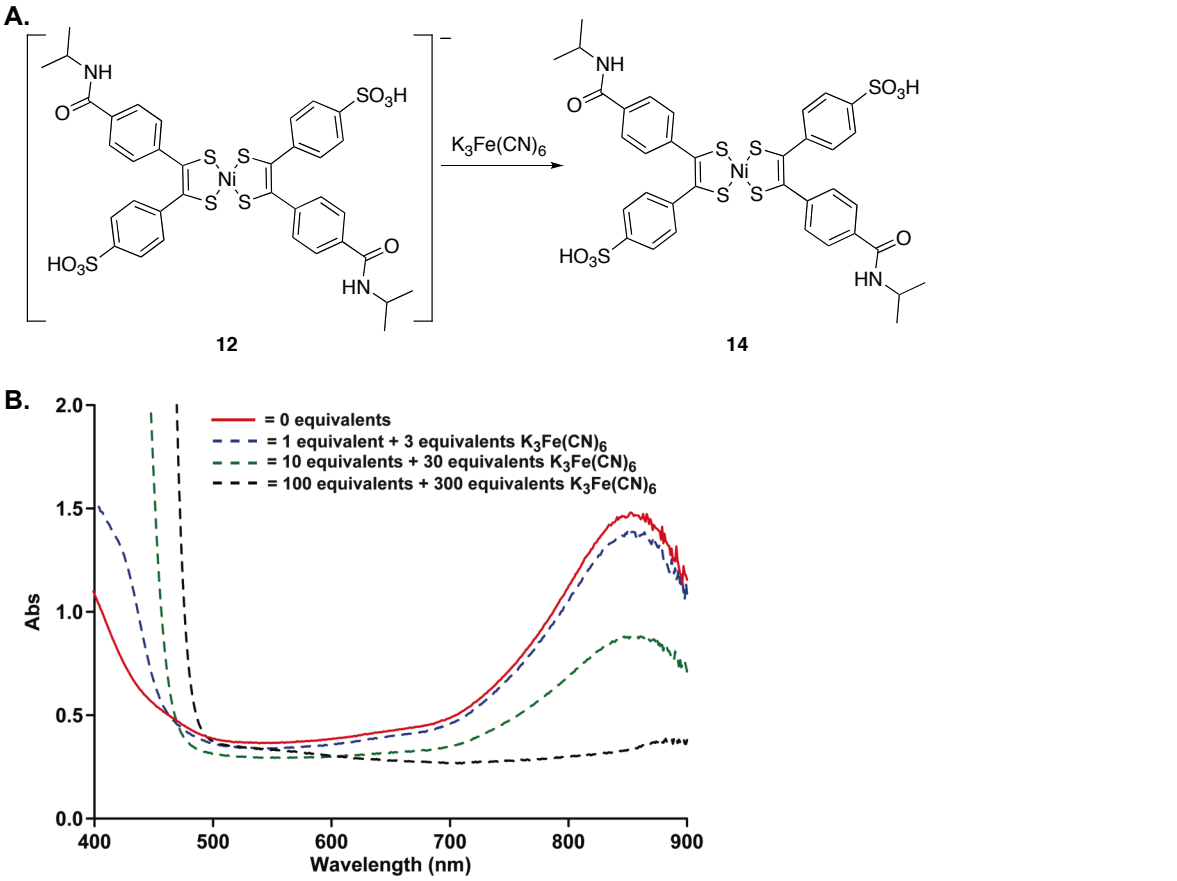


Figure S12. Ni bis(dithiolene) **14** can be rescued by addition of $K_3Fe(CN)_6$. A. Schematic for the oxidation of **12** to **14**. B. UV/Vis/NIR analysis of the oxidation. A solution of 125 μM **14** in PBS was treated with 1, 10, or 100 equivalents of cysteine followed by 3, 30, or 300 equivalents of $K_3Fe(CN)_6$, respectively (blue, green, black dashed lines). After 1 h, UV/Vis/NIR spectra were collected. The red line represents 125 μM **14** with no treatment.

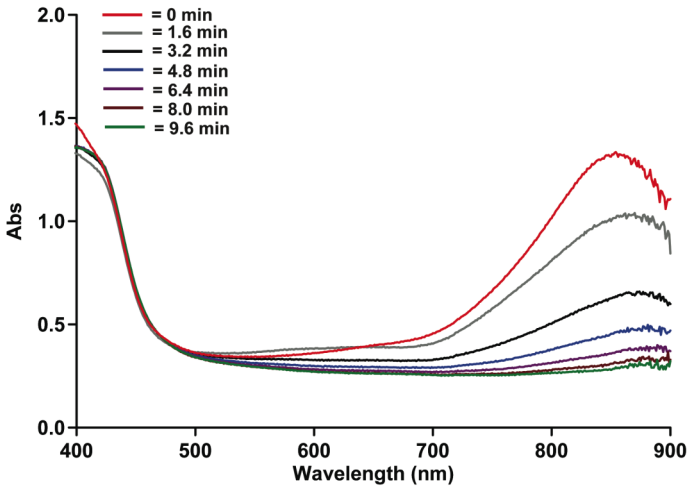


Figure S13. Ni bis(dithiolene) **14** rescued by the addition of $K_3Fe(CN)_6$ reacts with quadricyclane. A solution of 125 μM **14** in PBS was treated with 1 equivalent of cysteine followed by 3 equivalents of $K_3Fe(CN)_6$. Quadricyclane was added and a UV/Vis/NIR spectrum was immediately recorded (red line). UV/Vis/NIR spectra were then collected every 1 min and 40 sec. The observed reduction in signal is consistent with the quadricyclane ligation occurring (See Figure S6).

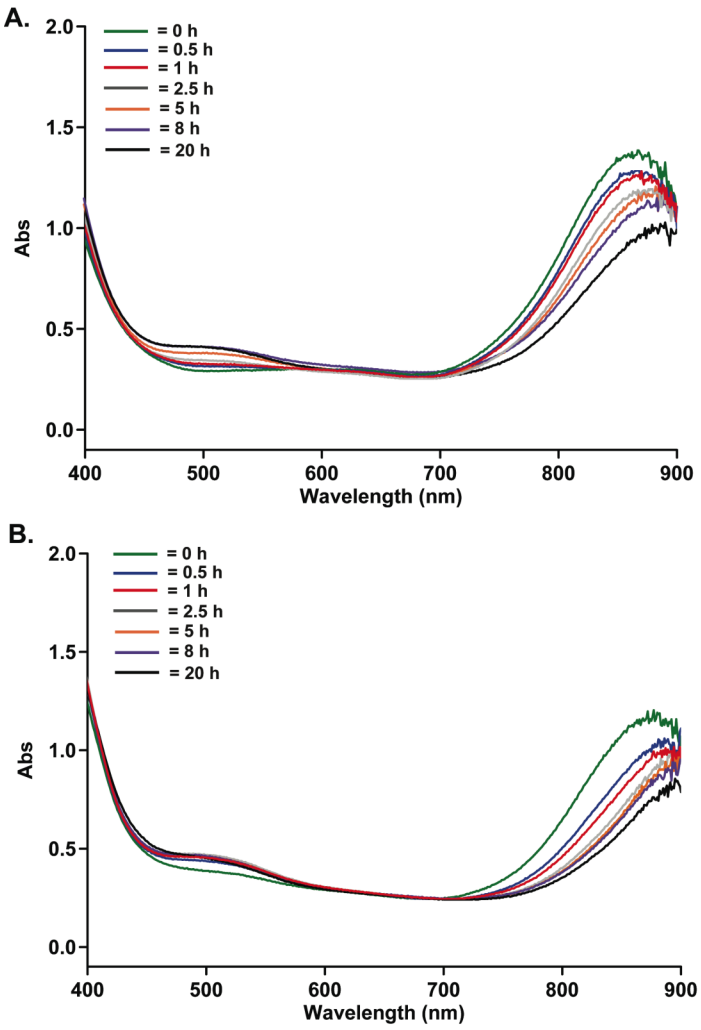


Figure S14. Ni bis(dithiolene) **14** is reduced by bovine serum albumin (BSA). A solution containing **14** (100 μM) and BSA (1.2 equivalents (A) or 12 equivalents (B)) was monitored by UV/Vis/NIR spectroscopy at various timepoints over 20 h. UV/Vis/NIR spectra were normalized to each other at 650 nm. An Ellman's test for sulfhydryl groups indicated 30-40% of the predicted free cysteine residues on commercial BSA were available for disulfide exchange.

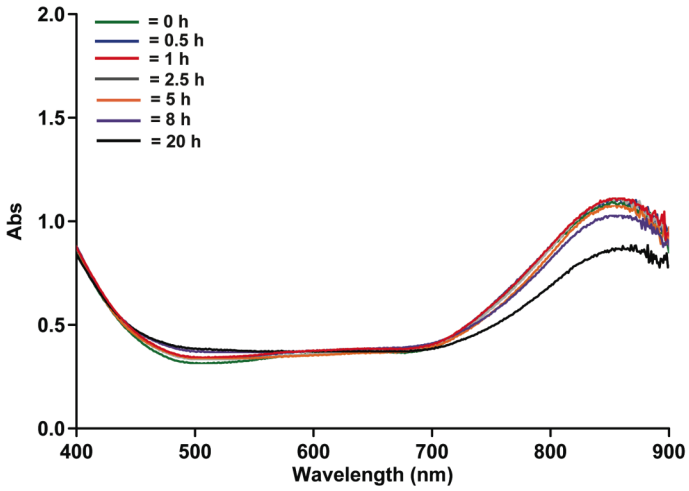


Figure S15. Ni bis(dithiolene) **14** is stable to oxidized insulin over multiple hours. A solution containing **14** (100 μM) and oxidized insulin (1.2 equivalents) was monitored by UV/Vis/NIR spectroscopy at various timepoints over 20 h. UV/Vis/NIR spectra were normalized to each other at 650 nm.

Preparation of QC-BSA

Bovine serum albumin (100 mg, Sigma) was dissolved in PBS (5 mL). Quadricyclane *p*-nitrophenyl carbonate **16** (5 mg, 0.02 mmol) was dissolved in DMSO (300 μL) with a small amount of DMF (60 μL). A portion of the BSA solution (0.5 mL) was combined with the quadricyclane solution (100 μL) and DMSO (200 μL). The mixture instantly turned yellow indicating release of *p*-nitrophenol. After 3 h, the protein was purified on a NAP-5 column. The column was pre-equilibrated with PBS (10 mL). A portion of the protein mixture (350 μL) was added to the column and eluted with PBS (500 μL per fraction). Four fractions were collected with the second fraction containing the most protein. Protein concentrations were assayed by a NanoDrop2000 (Thermo Scientific) and a BioRAD D_c assay.

Western Blot Procedures

Figure 2

The described protein mixtures were quenched with diethyldithiocarbamate **5** and quadricyclane **1** (3-15 mM). 4X SDS-loading buffer (with BME) was added and the protein mixtures were loaded onto a 12% BisTris gel (BioRAD, Criterion). The gel was run at 200 V in MES buffer. Proteins were transferred to nitrocellulose (0.45 μm, BioRAD) over 90 min at 75 V. The nitrocellulose was then treated with Ponceau stain and incubated in blocking buffer (5% BSA in PBS with 0.1% Tween 20) for 2 h at rt. Anti-biotin conjugated to horse-radish peroxidase (α-biotin-HRP, Jackson Labs) was added to the blocking buffer (1:100,000 dilution) and incubated at rt for 1 h. The blot was washed with PBST (PBS with 0.1% Tween 20, 3 x 10 min) and detection was

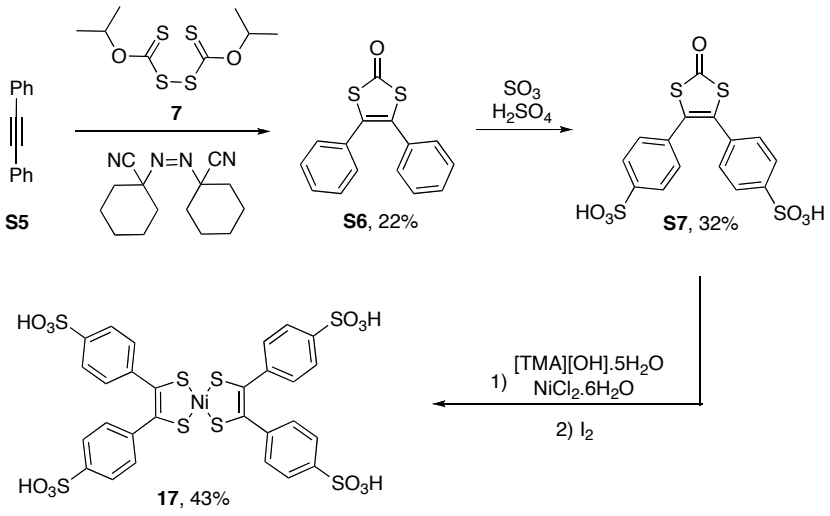
performed by chemiluminescence using Pierce SuperSignal West Pico Chemiluminescent Substrate.

Figure 3

The described protein mixture was quenched with diethyldithiocarbamate **5** (9.6 mM), quadricyclane **1** (9.6 mM), 2-azidoethanol (14.5 mM), and excess 850 mM tris buffer pH 7.2 until the pH was neutralized. 4X SDS loading buffer (with BME) was added and the mixture was separated into three equal portions and loaded onto a 4-12% BisTris gel (BioRAD, Criterion). The gel was run at 150 V in MES buffer. Proteins were transferred to nitrocellulose (0.45 μm, BioRAD) over 120 min at 50 V. The nitrocellulose was then treated with Ponceau stain and separated into three sections. Two sections were incubated in BSA blocking buffer (5% BSA in PBST) and the third was incubated with milk blocking buffer (5% non-fat milk in PBST) for 2 h at rt. One BSA-blocked blot was incubated with α-biotin-HRP (1:100,000, Jackson Labs). The other BSA-blocked blot was incubated with α-fluorescein-HRP (1:100,000, Invitrogen) and the milk-blocked blot was incubated with α-FLAG-HRP (1:100,000, Sigma, M2 monoclonal). All incubations were performed for 1 h at rt and followed by washing with PBST (3 x 10 min). Detection was performed by chemiluminescence using Pierce SuperSignal West Pico Chemiluminescent Substrate.

Supporting figures and schemes for protein labeling experiments

Scheme S2. Synthesis of tetrasulfonated Ni bis(dithiolene) **17**.



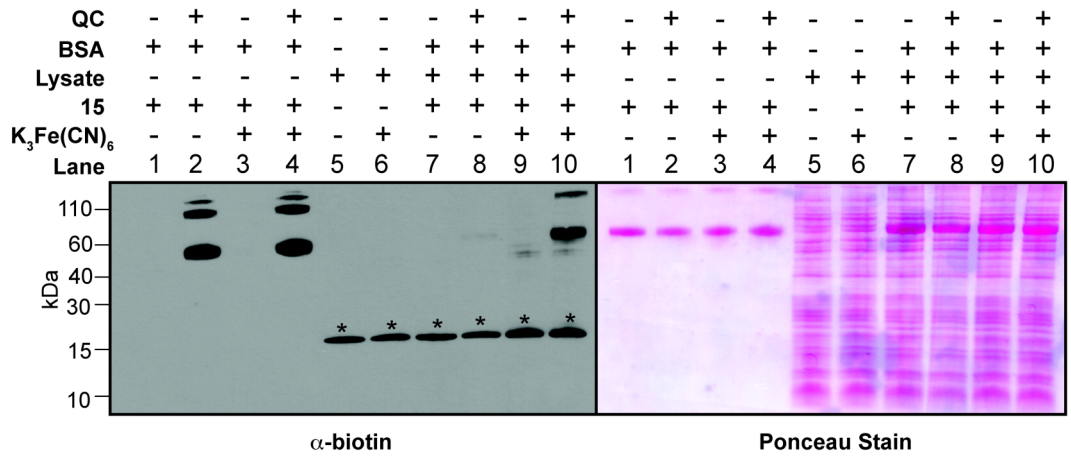
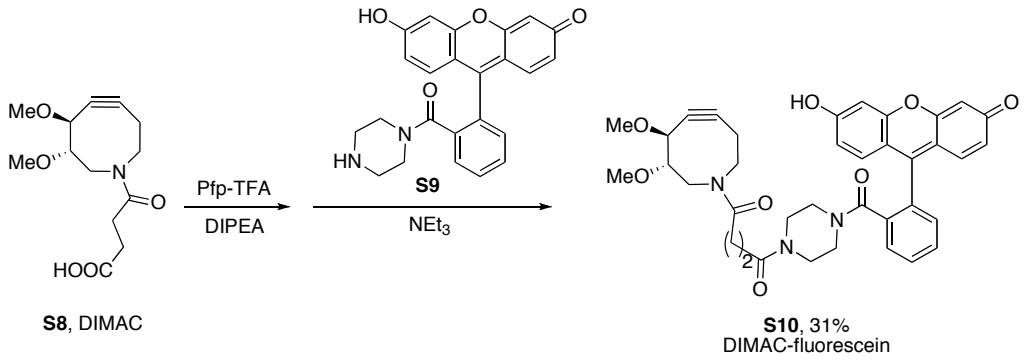


Figure S16. Oxidizing agent increases the efficiency of labeling of QC-BSA by **15**. BSA (1.5 μg, lanes 1,3) or QC-BSA (1.5 μg, lanes 2,4) were combined with **15** (50 μM) for 30 min in the presence (lanes 3-4) or absence (lanes 1-2) of 1 mM $K_3Fe(CN)_6$. Lysate from *E. coli* (25 μg) was combined with (lane 6) or without (lane 5) 1 mM $K_3Fe(CN)_6$ for 30 min. Lysate (25 μg) and BSA (1.5 μg, lanes 7,9) or QC-BSA (1.5 μg, lanes 8,10) were combined with **15** (50 μM) for 30 min in the presence (lanes 9,10) or absence (lanes 7,8) of 1 mM $K_3Fe(CN)_6$. After 30 min, all reaction mixtures were quenched with excess **1** and **5** and analyzed by Western blot probing with α-biotin-HRP. Protein loading was verified by Ponceau Stain. The bands denoted with an asterisk represent an endogenously biotinylated *E. coli* protein.

Scheme S3. Synthesis of DIMAC-fluorescein.



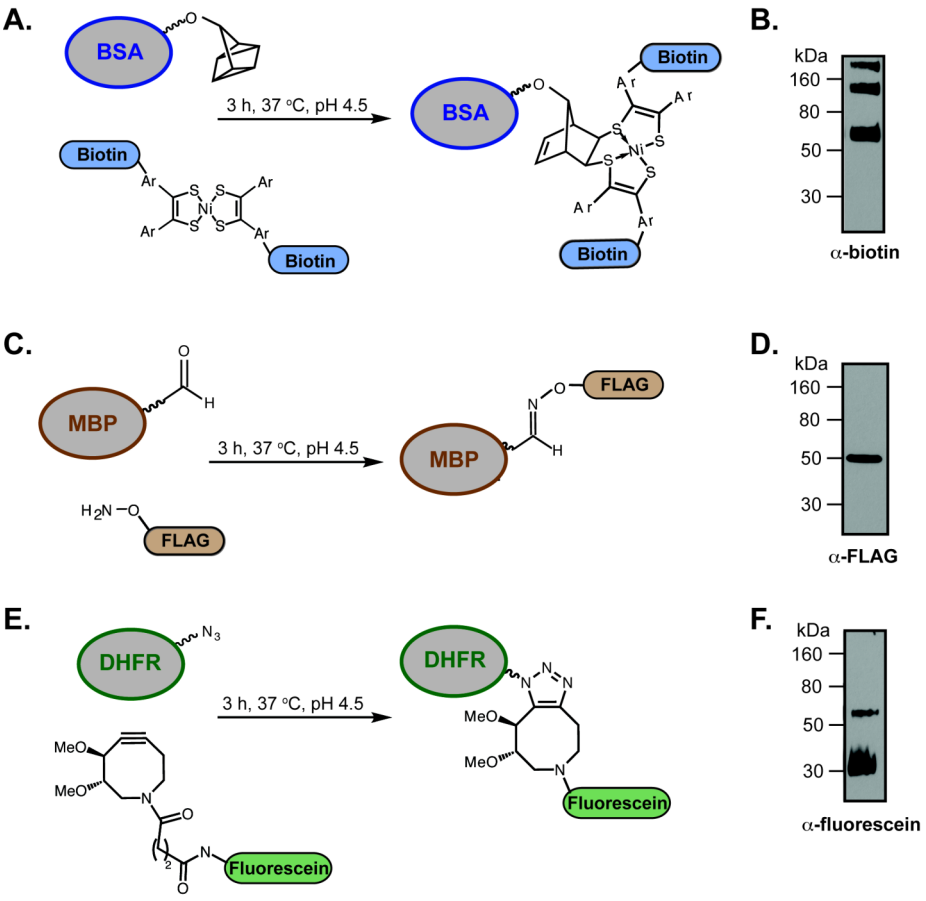


Figure S17. Controls for the banding patterns seen in Figure 3B. A/B. QC-BSA (8 μg) and **15** (150 μM) were combined at 37 °C, pH 4.5. After 3 h, this mixture was basified with 850 mM tris buffer and quenched with excess **1**, **5**, and 2-azidoethanol. It was then analyzed by Western blot probing with an α-biotin-HRP antibody (B). C/D. CHO-MBP (8 μg) and H_2NO-FLAG (1 mM) were combined at 37 °C, pH 4.5. After 3 h, this mixture was basified with 850 mM tris buffer and quenched with excess **1**, **5**, and 2-azidoethanol. It was then analyzed by Western blot probing with an α-FLAG-HRP antibody (D). E/F. AzDHFR (8 μg) and DIMAC-fluor (250 μM) were combined at 37 °C, pH 4.5. After 3 h, this mixture was basified with 850 mM tris buffer and quenched with excess **1**, **5**, and 2-azidoethanol. It was analyzed by Western blot probing with an α-fluorescein-HRP antibody (F).

Toxicity analyses

Jurkat cells (human T-cell lymphoma) were maintained in RPMI-1640 media (Invitrogen Life Technologies) supplemented with 10% fetal bovine serum (FBS), penicillin (100 units/mL), and streptomycin (0.1 mg/mL) in a 5% CO_2 water-saturated atmosphere. The cells were maintained at densities between 1×10^5 and 1.6×10^6 cells/mL.

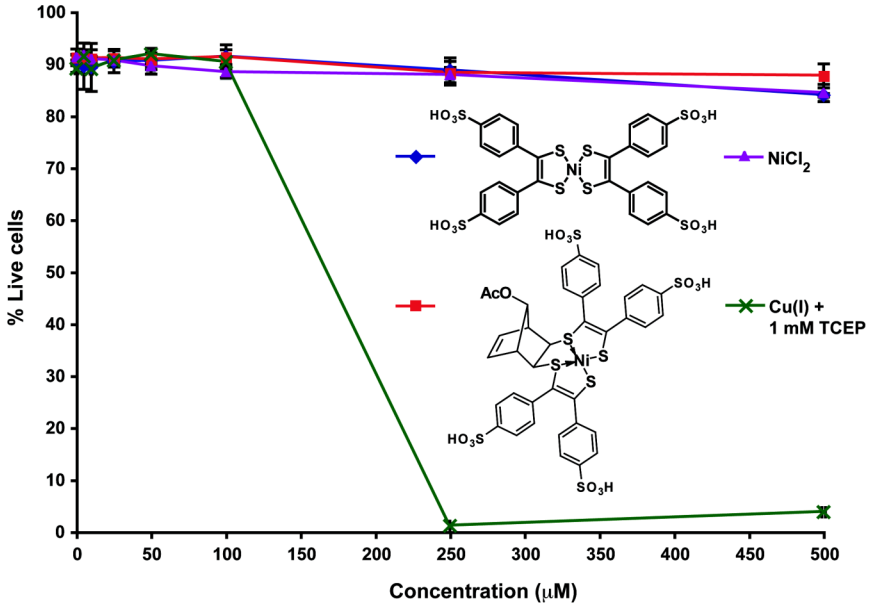


Figure S18. Cytotoxicity of **17** and the adduct of **1** and **17** in relation to $NiCl_2$ and Cu(I). Jurkat cells were washed twice with FACS buffer (PBS with 1% FBS) and placed in a 96-well plate with ~400,000 cells/well (pellet 2500 x *g*, 3 min, 4 °C). The cells were treated with at 0, 10, 25, 50, 100, 250, or 500 μM of **17** (blue diamond), the product of **1** and **17** (red square), $NiCl_2$ (purple triangle), or $CuSO_4$ in the presence of 1 mM TCEP (green cross) for 1 h. The cells were washed three times by resuspension in FACS buffer (200 μL) followed by concentration by centrifugation (2500 x *g*, 3 min, 4 °C). Following the third wash, the cells were resuspended in 100 μL of 1X binding buffer containing 5 μL of 7-AAD and 5 μL of FITC-AnnexinV (buffer and reagents from BD Pharmingen™). The cells were incubated at rt in the dark for 15 min, diluted to 500 μL with binding buffer and analyzed by flow cytometry (FL1 vs. FL3) on a BD Biosciences FACSCalibur flow cytometer equipped with a 488-nm argon laser. Plotted is the percentage of cells that do not stain with either 7-AAD or FITC-Annexin-V. The error bars represent the standard deviation of three replicate samples.

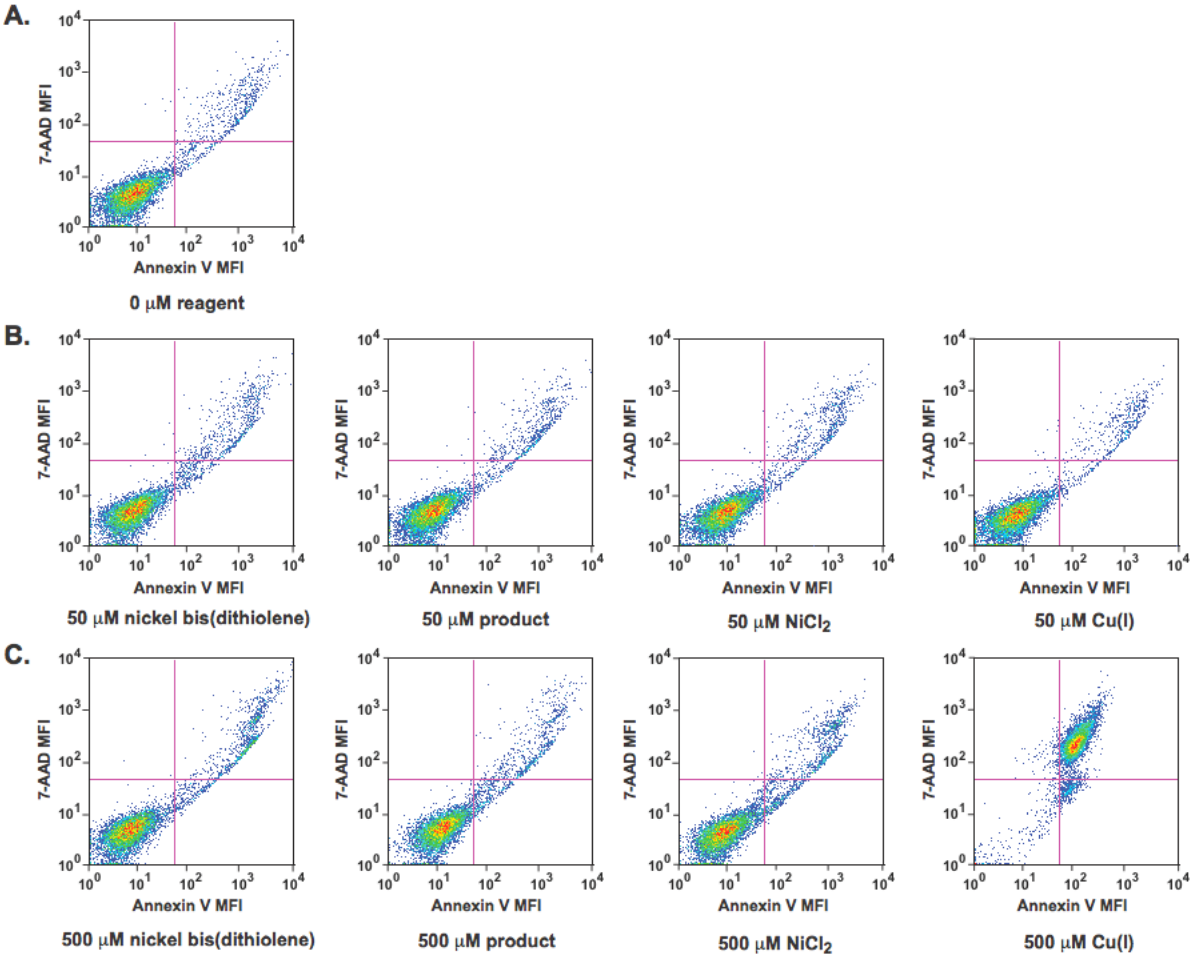


Figure S19. Representative dot plots for the experiment in Figure S18. A. Cells treated with no reagent. B. Cells treated with 50 μM of reagent. C. Cells treated with 500 μM reagent. The percentage of cells in the bottom left quadrant is what is plotted in Figure S18. MFI = mean fluorescence intensity (arbitrary units).

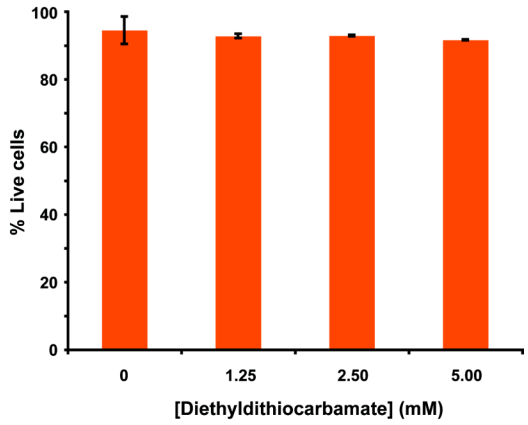


Figure S20. Cytotoxicity of diethyldithiocarbamate (**5**). Jurkat cells were washed twice with FACS buffer (PBS with 1% FBS) and placed in a 96-well plate with ~500,000 cells/well (pellet 2500 x *g*, 3 min, 4 °C). The cells were treated with 0, 1.25, 2.50, or 5.00 mM of **5** for 1 h. The cells were washed three times by resuspension in FACS buffer (200 μL) followed by concentration by centrifugation (2500 x *g*, 3 min, 4 °C). Following the third wash, the cells were resuspended in 100 μL of 1X binding buffer and 7.5 μL of 7-AAD and 5 μL of AnnexinV-PE were added (buffer and reagents from BD Pharmingen™). The cells were incubated at rt in the dark for 15 min, diluted to 500 μL with binding buffer and analyzed by flow cytometry (FL2 vs. FL3) on a BD Biosciences FACSCalibur flow cytometer equipped with a 488-nm argon laser. Plotted is the percentage of cells that do not stain with either 7-AAD or AnnexinV-PE. The error bars represent the standard deviation of three replicate samples.

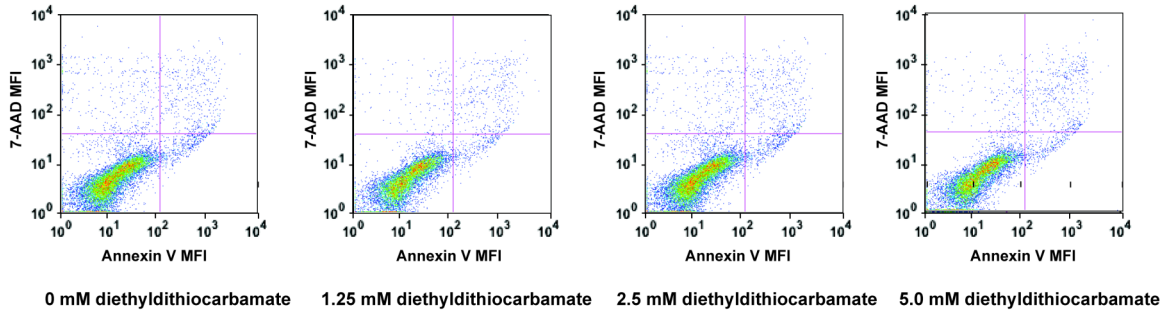
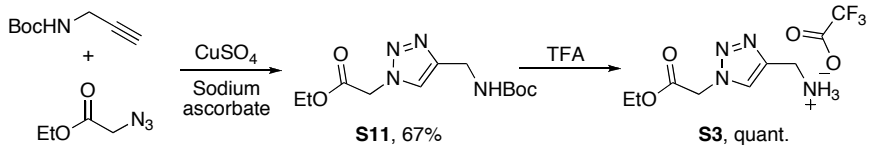


Figure S21. Representative dot plots for the experiment in Figure S20. The percentage of cells in the bottom left quadrant is what is plotted in Figure S20. MFI = mean fluorescence intensity (arbitrary units).

Scheme S4. Synthesis of triazole linker.



General Experimental Procedure

All chemical reagents were purchased from Sigma-Aldrich, Acros or TCI and used without purification unless noted otherwise. Anhydrous DMF and MeOH were purchased from Aldrich or Acros in sealed bottles; all other solvents were purified as described by Pangborn *et al.*[21] In all cases, solvent was removed by reduced pressure with a Buchi Rotovapor R-114 equipped with a Welch self-cleaning dry vacuum. Products were further dried by reduced pressure with an Edwards RV5 high vacuum. Lyophilization was performed on a LABCONCO FreeZone® instrument equipped with an Edwards RV2 pump. Thin layer chromatography was performed with EMD 60 Å silica gel plates. Flash chromatography was performed using Silicycle® 60 Å 230-400 mesh silica. All ^{1}H and ^{13}C spectra are reported in ppm and referenced to solvent peaks. Spectra were obtained on Bruker AVQ-400, AVB-400, DRX-500, AV-500, or AV-600 instruments. UV/Vis/NIR spectra were acquired on a CARY 100 Bio UV-Visible Spectrophotometer with a range of 200-900 nm. Electron impact (EI) and electrospray ionization (ESI) mass spectra were obtained from the UC Berkeley Mass Spectrometry Facility. HPLC was performed on a Varian Pro Star or Varian Prep Star instrument with a C18 column.

Experimental Procedures

Complex 3. Bis(dithiobenzil)nickel(II) (**2**, 50 mg, 0.092 mmol, 1.0 equiv.) was combined with 7-acetoxy quadricyclane **1** (30 mg, 0.20 mmol, 2.2 equiv.) in dichloromethane (1 mL) for 5 days in the dark. The reaction was evaporated to ~200 mL and methanol (1 mL) was added. This mixture was placed in the fridge until brown precipitate formed. The precipitate was collected and washed with minimal amounts of methanol to yield 40 mg of **3** (0.058 mmol, 63%) Some product was left in the mother liquor. The crude ^{1}H NMR showed ~90% conversion of **2** to **3**. R_f = 0.1 in 1:3 hexanes/dichloromethane. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28-7.26 (m, 4H) , 7.19-7.10 (m, 16H), 5.63 (s, 2H), 4.97 (s, 1H), 4.04 (s, 2H), 2.43 (apparent q, J = 1.7 Hz, 2H), 1.97 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 162.2, 140.1, 137.4, 133.0, 129.9, 129.1, 128.7, 128.4, 128.1, 127.5, 118.0, 85.4, 62.0, 53.6, 49.5, 21.1. HRMS (EI): calcd. for $C_{37}H_{20}O_2NiS_4^+$ $[M]^+$, 692.0482; found, 692.0485.

Methyl 4-(phenylethynyl)benzoate (6). Phenyl acetylene (1.5 mL, 14 mmol, 1.3 equiv.) and methyl-4-iodobenzoate (3.0 g, 11 mmol, 1.0 equiv.) were dissolved in THF (90 mL,

[21] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

anhydrous). To this solution, CuI (300 mg, 1.5 mmol, 0.14 equiv.), $PdCl_2(PPh_3)_2$ (450 mg, 0.64 mmol, 0.06 equiv), and NEt_3 (6.0 mL, 43 mmol, 3.9 equiv.) were added. Upon NEt_3 addition, the reaction mixture turned dark black. The mixture was stirred at rt until the solution was no longer dark (~ 2 h), at which point the reaction was quenched with methanol (25 mL), evaporated to dryness, and purified by silica gel chromatography with hexanes/ethyl acetate (200:1, 100:1, 50:1, 25:1, 10:1, 8:1, 6:1). This procedure yielded pure **6** in 99% yield (2.7 g, 11 mmol). R_f = 0.5 in 8:1 hexanes/ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.1 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.56-7.54 (m, 2H), 7.38-7.36 (m, 3H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 131.9, 131.7, 129.7, 129.7, 129.0, 128.6, 128.2, 122.9, 92.6, 88.8, 52.4. HRMS (EI): calcd. for $C_{16}H_{12}O_2^+$ $[M]^+$, 236.0837; found, 236.0841.

Methyl 4-(2-oxo-5-phenyl-1,3-dithiol-4-yl)benzoate (8). Methyl 4-(phenylethynyl)benzoate **6** (250 mg, 1.1 mmol, 1.0 equiv.) was combined with diisopropyl xanthogen disulfide[22] **7** (290 mg, 1.1 mmol, 1.0 equiv.) and 1,1'-azobis(cyclohexanecarbonitrile) (110 mg, 0.48 mmol, 0.45 equiv.) in *m*-xylene (2.2 mL, anhydrous). The mixture was heated to reflux for 20 h, at which point the reaction mixture was evaporated to dryness and **8** was purified by silica gel chromatography eluting with hexanes/ethyl acetate (40:1). This procedure resulted in 130 mg of **8** (0.40 mmol, 37%). R_f = 0.5 in 6:1 hexanes/ethyl acetate. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.1 Hz, 2H), 7.31-7.30 (m, 1H), 7.29-7.26 (m, 4H), 7.20-7.19 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.2, 166.5, 136.5, 131.6, 131.0, 130.4, 130.2, 129.8, 129.7, 129.4, 129.2, 127.6, 52.5. HRMS (EI): calcd. for $C_{17}H_{12}O_3S_2^+$ $[M]^+$, 328.0228; found, 328.0222.

4-(2-Oxo-5-(4-sulfophenyl)-1,3-dithiol-4-yl)benzoic acid (9). Compound **8** (700 mg, 2.1 mmol, 1.0 equiv.) was dissolved in sulfuric acid (8 mL, 18 M) and fuming sulfuric acid (80 μL, 20% in H_2SO_4) was added. This mixture was heated to 90 ^{o}C overnight. The following day it was cooled to rt, neutralized with NaOH and $NaHCO_3$ and evaporated. The resulting solid was subjected to methanol (~100 mL) and sonicated. This solution was then filtered and the filtrate was evaporated to dryness. The remaining solid was purified by silica gel chromatography with an acetonitrile/methanol solvent system (15:1, 10:1) to result in 620 mg of pure **9** (1.6 mmol, 74%). R_f = 0.5 in 9:1 acetonitrile/water. ^{1}H NMR (600 MHz, MeOD): δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.35 (dd, *J* = 13.9, 8.4 Hz, 4H). ^{13}C NMR (150 MHz, MeOD): δ 190.9, 169.2, 147.1, 137.1, 134.6, 132.9, 131.3, 130.9, 130.85, 130.4, 130.0, 127.8. HRMS (ESI): calcd. for $C_{16}H_9O_6S_3^-$ $[M-H]^-$ 392.9567; found 392.9565.

4-(5-(4-(Isopropylcarbamoyl)phenyl)-2-oxo-1,3-dithiol-4-yl)benzenesulfonic acid (10). Compound **9** (130 mg, 0.33 mmol, 1.0 equiv.) was dissolved in dimethylformamide (5 mL, anhydrous). To this solution, isopropyl amine (30 μL, 0.037 mol, 1.1 equiv.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl, 96 mg, 0.50 mmol, 1.5 equiv.), hydroxybenzotriazole hydrate (HOBt, 65 mg, 0.42 mmol, 1.3 equiv.), and NEt_3 (90 μL, 0.65 mmol, 1.9 equiv.) were added. The mixture was stirred at rt for 5

[22] Jamir, L.; Yella, R.; Patel, B.K. *J. Sulfur Chem.* **2009**, *30*, 128-134.

h, at which point it was evaporated to dryness. Compound **10** was purified by HPLC using a water/methanol solvent system with a gradient of 30-95% methanol over 25 min. The desired product elutes at 14 min. This procedure resulted in pure **10** (56 mg, 0.13 mmol, 39 %). ^{1}H NMR (600 MHz, MeOD): δ 7.75-7.72 (m, 4H), 7.34-7.31 (m, 4H), 4.17 (sep, *J* = 6.6 Hz, 1H), 1.22 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (150 MHz, MeOD): δ 191.0, 168.5, 147.3, 136.8, 135.8, 134.7, 131.0, 130.9, 130.3, 130.1, 129.1, 127.8, 43.4, 22.6. HRMS (ESI): calcd. for $C_{19}H_{16}O_5N_1S_3^-$ $[M-H]^-$ 434.0196; found, 434.0193.

Ni bis(dithiolene) 14. 4-(5-(4-(isopropylcarbamoyl)phenyl)-2-Oxo-1,3-dithiol-4-yl)benzenesulfonic acid **10** (45 mg, 0.10 mmol, 1.0 equiv.) was dissolved in a mixture of THF/MeOH (1 mL/0.7 mL). Tetramethyl ammonium hydroxide pentahydrate (40 mg, 0.22 mmol, 2.2 equiv.) was dissolved in MeOH (0.2 mL) and added to the solution with compound **10**. The mixture turned a light orange color. After 30 min, $NiCl_2 \cdot 6H_2O$ (12 mg, 0.050 mmol, 0.50 equiv.) was added and the mixture turned dark red. This mixture was stirred at rt overnight. The following morning, iodine (12 mg, 0.047 mmol, 0.051 equiv.) was added and the mixture became dark blue. After 2 h stirring at rt, the mixture was evaporated to dryness and purified by silica gel chromatography eluting with acetonitrile/water (25:1, 10:1, 5:1). This procedure resulted in 40 mg of **14** as a blue solid (0.046 mmol, 90%). R_f = 0.2 in 9:1 acetonitrile/water. ^{1}H NMR (600 MHz, MeOD): δ 7.88 (d, *J* = 6.4 Hz, 4H), 7.68 (d, *J* = 7.8 Hz, 4H), 7.54 (d, *J* = 7.1 Hz, 4H), 7.22 (s, 4H), 4.32- 4.11 (m, 2H), 1.30 (d, *J* = 6.5 Hz, 12H). The NMR was taken in the presence of I_2 to keep all of **14** in the neutral oxidation state. The anionic form is paramagnetic which prevents a spectrum form being obtained. Due to this difficulty, we have characterized the sulfonated Ni bis(dithiolenes) by UV/Vis/NIR, HRMS, and HPLC instead of NMR. UV/Vis/NIR (water): 851 nm (1.2 au), 638 nm (0.4 au), 312 nm (3.1 au), 282 nm (3.3 au), 209 nm (5.1 au), 206 nm (4.7 au). HRMS (ESI): calcd. for $C_{36}H_{32}O_8N_2NiS_6^{-2}$ $[M - 2H]^{-2}$, 434.9924; found, 434.9918.

Compound 11. 4-(2-Oxo-5-(4-sulfophenyl)-1,3-dithiol-4-yl)benzoic acid **9** (20 mg, 0.046 mmol, 1 equiv.) was dissolved in dimethylformamide (1 mL, anhydrous). To this solution, biotin-$(PEG)_3$-amine[23] (23 mg, 0.056 mmol, 1.1 equiv.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl, 15 mg, 0.078 mmol, 1.7 equiv.), hydroxybenzotriazole (HOBt, 10 mg, 0.065 mmol, 1.4 equiv.), and NEt_3 (15 μL, 0.11 mmol, 2.0 equiv.) were added. The mixture was stirred at rt overnight. The following morning the mixture was evaporated to dryness and purified by HPLC using water/methanol solvent system. Compound **11** eluted at 32 min when a gradient of 0 to 100% methanol over 45 min was used. This procedure resulted in pure **11** (17 mg, 0.021 mol, 45 %). R_f = 0.4 in 4:1 acetonitrile/methanol. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.9 Hz, 4H), 7.31 (t, *J* = 7.6 Hz, 4H), 4.53- 4.50 (m, 1H), 4.34- 4.32 (m, 1H), 3.57-3.52 (m, 8H), 3.49-3.48 (m, 2H), 3.42 (dd, *J* = 10.2, 5.9 Hz, 4H), 3.23-3.16 (m, 4H), 3.11-3.07 (m, 1H), 2.89 (dd, *J* = 12.8, 4.8 Hz, 1H), 2.69 (d, *J* = 12.8 Hz, 1H), 2.18 (t, *J* = 7.3 Hz, 2H), 1.83-1.81 (m, 2H), 1.72-1.58 (m, 6H), 1.41-1.37 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.8, 176.4, 167.0, 166.0, 147.3, 136.4, 135.9, 134.7, 131.1, 131.0,

[23] Wilbur, D.S.; Hamlin, D.K.; Vessella, R.L.; Stray, J.E.; Buhler, K.R.; Stayton, P.S.; Klumb, L.A.; Pathare, P.M.; Weerawarna, S.A. *Bioconjugate Chem.* **1996**, *7*, 689-702.

130.3, 130.0, 129.1, 127.8, 71.6, 71.4, 71.3, 70.4, 70.0, 64.0, 62.4, 57.0, 50.0, 43.5, 41.0, 39.0, 38.2, 36.7, 30.4, 29.9, 29.5, 27.0. HRMS (ESI): cacld. For $C_{36}H_{45}O_{10}N_4S_4^-$ $[M-H]^-$, 821.2024; found, 821.2036.

Ni bis(dithiolene) 15. Ligand precursor **11** (24 mg, 0.029 mmol, 1.0 equiv.) was dissolved in a mixture of THF/H_2O (0.4 mL/0.4 mL). Tetramethyl ammonium hydroxide pentahydrate (11 mg, 0.061 mmol, 2.1 equiv.) in MeOH (60 μL) was added to the solution with compound **11**. The mixture turned a yellow/orange color. After 30 min, $NiCl_2 \cdot 6H_2O$ (3.5 mg, 0.015 mmol, 0.50 equiv.) was added and the solution turned a dark reddish brown. This mixture was stirred at rt overnight. The following morning, iodine (3.5 mg, 0.014 mmol, 0.48 equiv.) was added and the mixture turned dark blue in color. After 3 h stirring at rt, the mixture was purified by silica gel chromatography eluting with acetonitrile/water (10:1, 5:1, 2:1). This procedure resulted in 20 mg of **15** as a blue solid (0.024 mmol, 84%). $R_f = 0.3$ in 3:1 acetonitrile/water. UV/Vis/NIR (water): 868 nm (0.6 au), 349 nm (0.9 au), 315 nm (1.5 au), 276 nm (1.7 au), 201 nm (3.9 au). HRMS (ESI): calcd. for $C_{70}H_{90}O_{18}N_8NiS_8^{2-}$ $[M-2H]^{2-}$, 822.1752; found, 822.1749.

7-Acetoxy-2,5-norbornadiene (4). 7-*tert*-Butoxy-2,5-norbornadiene **S1**[24] (1.7 g, 10 mmol, 1.0 equiv.) was combined with acetic anhydride (3.4 mL, 36 mmol, 3.6 equiv.) and acetic acid (16.9 mL) at 0 °C. This solution was poured into precooled perchloric acid (2.3 mL, 60%). The yellow reaction mixture was stirred for 1 min at 0 °C and then poured onto ice water (~50 mL). Additional water was added until no yellow color remained. The aqueous solution was extracted with dichloromethane (3 x 50 mL). The organic layers were combined, dried, decanted, and evaporated to dryness. The crude product was purified by silica gel chromatography eluting with 25:1 hexanes/ether. This procedure resulted in 910 mg of pure **4** as a colorless oil (6.1 mmol, 58%). $R_f = 0.5$ in 10:1 hexanes/ethyl acetate. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.63 (s, 2H), 6.50 (s, 2H), 4.50 (s, 1H), 3.53 (s, 2H), 1.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 140.4, 137.9, 99.4, 52.5, 21.3. HRMS (EI): calcd. for $C_9H_{10}O_2^+$ $[M]^+$, 150.0681; found, 150.0638.

7-Acetoxy quadricyclane (1). 7-Acetoxy-2,5-norbornadiene **4** (400 μL, 3.9 mmol, 1.0 equiv.) was dissolved in hexane (150 mL, degassed) and placed in a quartz round bottom flask containing a small amount of acetone (~0.5 mL). The mixture was irradiated with a 450W Mercury Arc lamp for 5 h. Throughout the irradiation process, the reaction was kept under a nitrogen atmosphere. Following irradiation, sat $AgNO_3$ (5 mL) was added and the mixture was vigorously stirred in the dark for 15 min to complex any remaining **4**. The hexane was removed and the aqueous solution was filtered and extracted with hexanes (2 x 10 mL). The hexanes were combined, dried, decanted, and evaporated to dryness to result in pure **5** as a wet, colorless solid (560 mg, 3.7 mmol, 95%). $R_f = 0.7$ in

[24] Commercially available from Sigma or can be prepared from norbornadiene in low yield, see: Story, P.R.; Fahrenholtz, S.R. *Org. Syn.* **1964**, *44*, 12. Extreme caution should be taken as explosions have occurred during preparation of 7-*tert*-butoxynorbornadiene. See: Baxter, A.D.; Binns, F.; Javed, T.; Roberts, S.M.; Sadler, P.; Scheinmann, F.; Wakefield, B.J.; Lynch, M. *J. Chem. Soc. Perkin Trans.* **1986**, 889-900.

5:1 hexanes/ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.62 (t, J = 1.7 Hz, 1H), 2.11 (s, 3H), 1.83-1.80 (m, 2H), 1.62- 1.59 (m, 2H), 1.53- 1.51 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 82.4, 25.8, 21.5, 16.1, 14.8. HRMS (EI): calcd. for $C_9H_{10}O_2^+$ $[M]^+$, 150.0681; found, 150.0638.

7-Hydroxy quadricyclane (S2). 7-Acetoxy quadricyclane **1** (325 mg, 2.2 mmol, 1.0 equiv.) was dissolved in ether (1.0 mL, anhydrous). This solution was added to lithium aluminum hydride (1.2 mL, 1.2 mmol, 0.55 equiv., 1 M in diethyl ether) precooled to 0 ^{o}C. The mixture was warmed to rt and stirred for 15 min, at which point the reaction was quenched with aqueous Rochelle's salt (~ 5 mL). The mixture was stirred until the aluminum was sufficiently complexed and two layers formed in the flask. The aqueous layer was extracted with ether (3 x 20 mL) and the organic layers were combined, dried with $MgSO_4$, filtered, and evaporated to dryness. This procedure resulted in ~90% pure **S2** as a volatile, colorless oil (210 mg, 1.8 mmol, 80% yield). Note: If this compound is purified by silica gel chromatography and aldehyde byproduct is formed resulting in a less pure product than that obtained from the crude reaction. R_f = 0.2 in 5:1 hexanes/ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.87 (t, J = 1.8 Hz, 1H), 1.77-1.74 (m, 2H), 1.56-1.53 (m, 2H), 1.38-1.36 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 79.5, 29.0, 15.9, 14.9 HRMS (EI): calcd. for $C_7H_8O^+$ $[M]^+$, 108.0575; found, 108.0574.

***p*-Nitrophenyl carbonate quadricyclane 16**. 7-Hydroxy quadricyclane **S2** (20 mg, 0.19 mmol, 1.0 equiv.) was dissolved in dichloromethane (7 mL, anhydrous) and cooled to 0 ^{o}C. Pyridine (90 μL, 1.1 mmol, 5.8 equiv., anhydrous) was added followed by *p*-nitrophenyl chloroformate (87 mg, 0.44 mmol, 2.3 equiv.). The reaction mixture was warmed to rt over 3 h, at which point it was quenched with water and extracted with dichloromethane (3 x 15 mL). The organic layers were combined, dried with $MgSO_4$, decanted, and evaporated to dryness. The crude product was purified by silica gel chromatography with hexanes/ether (9:1, 4:1, 2:1). This procedure resulted in 27 mg of pure **16** as a white solid (0.010 mmol, 52%). R_f = 0.7 in 7:1 hexanes/ethyl acetate. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.28 (d, J = 9.0 Hz, 2H), 7.43 (d, J = 9.0 Hz, 2H), 5.71 (s, 1H), 1.93-1.91 (m, 2H), 1.70-1.68 (m, 2H), 1.65-1.64 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.9, 152.9, 145.5, 125.5, 122.0, 88.0, 25.8, 16.4, 15.3. HRMS (EI): calcd. for $C_{14}H_{11}O_5N^+$ $[M]^+$, 273.0637; found, 273.0634.

4,5-Diphenyl-1,3-dithiol-2-one (S6). Diphenylacetylene **S5** (2.5 g, 13.9 mmol, 1.0 equiv.) was combined with 1,1'-azobis(cyclohexane)carbonitrile (1.5 g, 6.1 mmol, 0.44 equiv.), diisopropyl xanthogen disulfide **7** (4.3 g, 15.9 mmol, 1.1 equiv.) in *m*-xylene (30 mL, anhydrous). The reaction mixture was heated to reflux overnight. The following day, the reaction mixture was cooled to rt, evaporated to dryness, and purified by silica gel chromatography with a hexane/toluene solvent system (10:1, 8:1, 6:1). This procedure resulted in 830 mg of **S6** (3.1 mmol, 22% yield). R_f = 0.6 in 10:1 hexanes/ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35- 7.25 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 131.8, 129.6, 128.93, 128.89, 128.8. HRMS (EI): calcd. for $C_{15}H_{10}OS_2^+$ $[M]^+$, 270.0173; found, 270.0179.

4,4'-(2-Oxo-1,3-dithiole-4,5-diyl)dibenzenesulfonic acid (S7). 4,5-diphenyl-1,3-dithiol-2-one **S6** (830 mg, 3.1 mmol, 1.0 equiv.) was dissolved in sulfuric acid (10 mL, 18 M). Fuming sulfuric acid (150 μL, 20% in sulfuric acid) was added and the reaction mixture was heated to 90 ^{o}C overnight. The following morning the mixture was cooled to 0 ^{o}C and neutralized first with NaOH then with $NaHCO_3$. Once neutral, methanol (100 mL) was added, the solution was filtered, and the filtrate evaporated to dryness. The solid was again dissolved in methanol (100 mL), filtered, and the filtrate evaporated to dryness. The residue was then dissolved in water (50 mL) and washed with hexane (3 x 50 mL). The water layer was evaporated to dryness and the crude product was purified by HPLC on a C18 column with a water/acetonitrile solvent system (0 to 30% acetonitrile over 30 min). The product elutes at 10 min. This procedure resulted in 430 mg of pure **S7** (1.0 mmol, 32% yield). ^{1}H NMR (600 MHz, MeOD): δ 7.76 (d, J = 8.3 Hz, 4H), 7.33 (d, J = 8.4 Hz, 4H). ^{13}C NMR (151 MHz, MeOD): δ 191.0, 147.1, 134.6, 130.8, 130.1, 127.8. HRMS (ESI): calcd. for $C_{15}H_9O_7S_4^-$ $[M-H]^-$ 428.9237; found, 428.9238.

Ni bis(dithiolene) 17. 4,4'-(2-Oxo-1,3-dithiole-4,5-diyl)dibenzenesulfonic acid **S7** (33 mg, 0.075 mmol, 1.0 equiv.) was dissolved in a mixture of methanol (0.5 mL), THF (0.7 mL), and water (0.75 mL). Tetramethyl ammonium hydroxide pentahydrate (28 mg, 0.15 mmol, 2.1 equiv.) was dissolved in MeOH (0.15 mL) and added to the solution with compound **S7**. The mixture turned a yellow color. After 30 min, $NiCl_2{\cdot}6H_2O$ (8.5 mg, 0.036 mmol, 0.48 equiv.) was added and stirred for 6 h, at which point iodine (8.5 mg, 0.033 mmol, 0.45 equiv.) was added and the blue mixture was stirred overnight at rt. The following morning, TLC indicated that some reduced complex may be present and more iodine (5 mg, 0.020 mmol, 0.26 equiv.) was added. After stirring for an additional 30 min, the reaction was evaporated to dryness and purified by silica gel chromatography eluting with acetonitrile/water (25:1, 9:1). This procedure resulted in 28 mg of **17** (0.033 mmol, 43% yield). UV/Vis/NIR: 832 nm (1.1 au), 591 nm (0.3 au), 349 nm (1.0 au), 315 nm (2.0 au), 272 nm (1.7 au). HRMS (ESI): calcd. for $C_{28}H_{16}O_{12}NiS_8^{4-}$ $[M-4H]^{4-}$, 214.4446; found, 214.4447.

DIMAC-fluorescein (S10). DIMAC[25] (**S8**, 8.0 mg, 0.030 mmol, 1.0 equiv.) was dissolved in CH_3CN (1 mL, anhydrous) and cooled to 0 ^{o}C. DIPEA (10 μL, 0.057 mmol, 1.9 equiv.) was added and the mixture was stirred for 10 min, at which point pentafluorophenyltrifluoroacetate (15 μL, 0.087 mmol, 2.9 equiv.) was added. The reaction was warmed to rt and stirred for 1.5 h. It was then evaporated to dryness and purified by silica gel chromatography eluting with toluene/ether (7:1, 5:1, 3:1, anhydrous solvents used for chromatography). This procedure resulted in DIMAC-pentafluorophenyl ester (13 mg, 0.030 mmol, quant.). Half of the DIMAC-pentafluorophenyl ester (6.5 mg, 0.015 mmol, 1.0 equiv.) was dissolved in dimethylformamide (0.5 mL, anhydrous). In a separate flask, fluorescein-piperazine **S9**[26] (11 mg, 0.028 mmol, 1.8 equiv.) was dissolved in dimethylformamide (0.5 mL, anhydrous) and DIPEA (~10 μL, 0.06 mmol, 4 equiv.). The DIMAC solution was added to the fluorescein-piperazine solution at 0 ^{o}C. The reaction was warmed to rt over 5 h, at

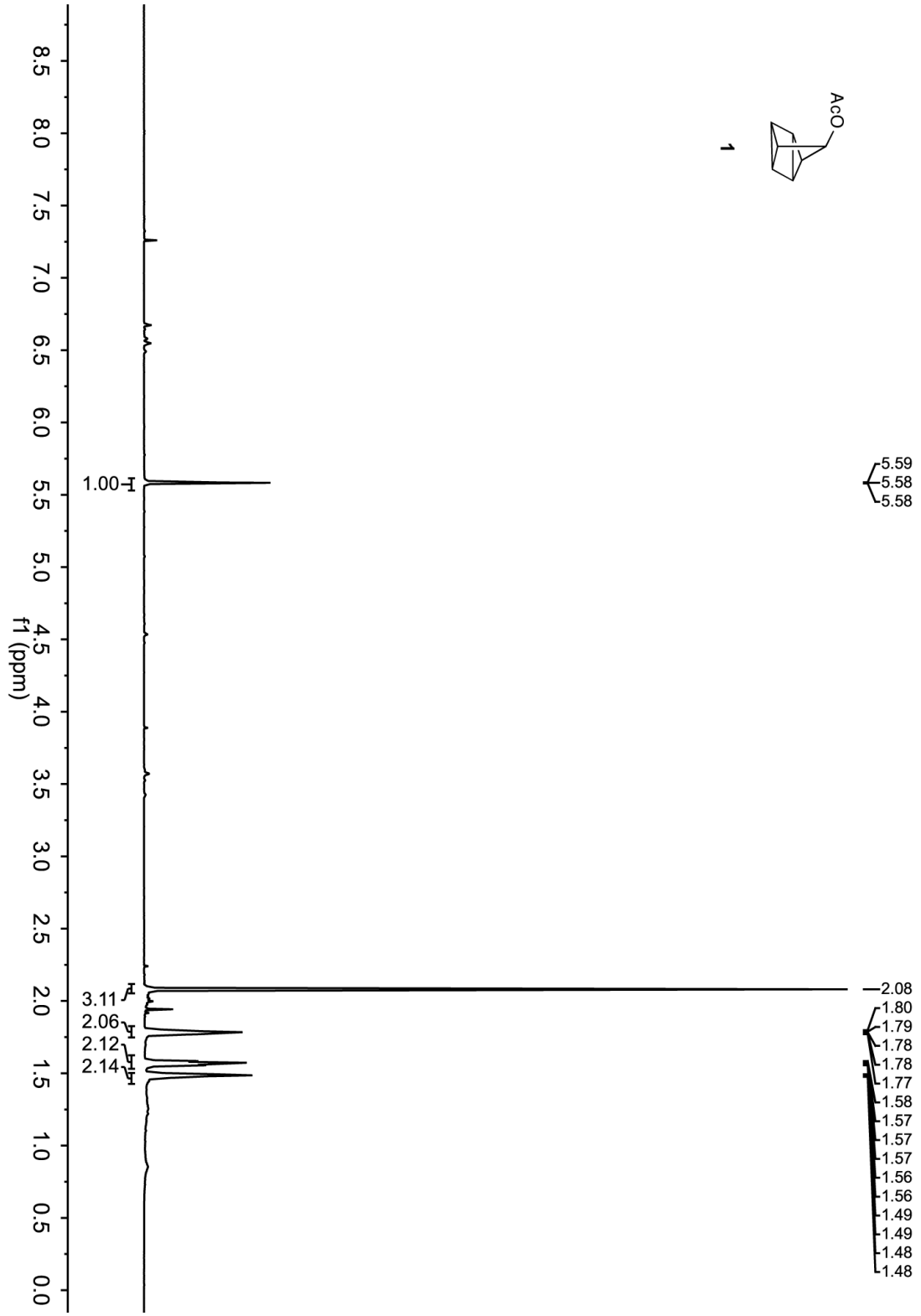
[25] Sletten, E.M.; Bertozzi, C.R. *Org. Lett.* **2008**, *10*, 3097-3099.
[26] Hangauer, M.J.; Bertozzi, C.R. *Angew. Chem. Int. Ed.* **2008**, *47*, 2394-2397.

which point it was evaporated to dryness and purified first by silica gel chromatography (5:3:1 EtOAc/MeOH/H_2O) then by HPLC (C18 column, with methanol/water, 40-100% methanol over 25 min, elutes at 15 min). This procedure resulted in pure DIMAC-fluorescein (3 mg, 0.005 mmol, 31% yield). R_f = 0.7 in 5:3:1 ethyl acetate/methanol/water. HRMS (ESI): calcd. for $C_{37}H_{37}O_8N_3Na$ $[M+Na]^+$, 674.2473; found, 674.2478.

Ethyl 2-(4-((*tert*-butoxycarbonylamino)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (S11). Ethyl azidoacetate (120 mg, 0.930 mmol, 1.00 equiv.) and *N*-boc propargyl amine (146 mg, 0.942 mmol, 1.02 equiv.) were dissolved in a mixture of ethanol (1.8 mL) and water (1.8 mL). To this solution, $CuSO_4$ (2 mg, 0.01 mmol, 0.1 equiv.) and sodium ascorbate (50 μL of 2M solution in water, 0.1 mmol, 1 equiv.) were added. The mixture was stirred overnight at rt. The following morning, the ethanol was removed by evaporation and the product was extracted into ethyl acetate (3 x 50 mL). The ethyl acetate was dried with $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by silica gel chromatography with hexanes/ethyl acetate (5:1, 3:1, 1:1, 1:2). This procedure resulted in 178 mg of pure **S11** (0.627 mmol, 67%). R_f = 0.7 in ethyl acetate. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 (s, 1H), 5.34 (s, 1H), 5.08 (s, 2H), 4.34 (d, *J* = 6.0 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.37 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.3, 155.9, 145.9, 123.4, 79.5, 62.3, 50.8, 36.0, 28.3, 14.0. HRMS (ESI): calcd. for $C_{12}H_{21}O_4N_4$ $[M+H]^+$, 285.1563; found, 285.1556.

(1-(2-Ethoxy-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)methanaminium 2,2,2-trifluoroacetate (S3). Boc-protected triazole **S11** (178 mg, 0.627 mmol, 1 equiv.) was dissolved in dichlorometane (8 mL, anhydrous). Trifluoroacetic acid (2 mL) was added and this mixture was stirred for 1 h at rt, at which point the reaction mixture was evaporated to dryness to yield pure **S3** (200 mg, 0.67 mmol, quant.). R_f = 0.7 in 5:3:1 ethyl acetate/methanol/water. ^{1}H NMR (600 MHz, MeOD): δ 8.15 (s, 1H), 5.34 (s, 2H), 4.31 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, MeOD): δ 168.6, 161.3 (q, *J* = 38.3 Hz), 141.5, 127.4, 117.2 (q, *J* = 287.3 Hz), 63.6, 52.0, 35.6, 14.4. HRMS (ESI): calcd. for $C_7H_{13}O_2N_4$ $[M+H]^+$, 185.1039; found, 185.1033.

Quadricyclane S4. Triazole **S3** (45 mg, 0.15 mmol, 1.5 equiv.) and DIPEA (165 μL, 0.95 mmol, 10 equiv.) were combined in dichloromethane (2 mL, anhydrous) and cooled to 0 ^{o}C. *p*-Nitrophenyl carbonate quadricyclane **16** (27 mg, 0.099 mmol, was dissolved in dichloromethane (1 mL, anhydrous) and added to the solution containing triazole **S3**. The reaction mixture was warmed to rt overnight. The following morning, the mixture was evaporated to dryness and purified by silica gel chromatography to yield **S4** (26 mg, 0.082 mmol, 83%). R_f = 0.1 in 1:1 hexanes/ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 5.60 (s, 1H), 5.39 (bs, 1H), 5.13 (s, 2H), 4.50 (d, *J* = 6.3 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.79-1.77 (m, 2H), 1.58 (bs, 2H), 1.49 (bs, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 157.1, 145.8, 123.7, 83.1, 62.7, 51.1, 36.6, 26.0, 16.1, 14.8, 14.3. HRMS (ESI): calcd. for $C_{15}H_{19}O_4N_4$ $[M+H]^+$, 319.1401; found, 319.1404.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7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.00
3.11
2.06
2.12
2.14
5.59
5.58
5.58
2.08
1.80
1.79
1.78
1.78
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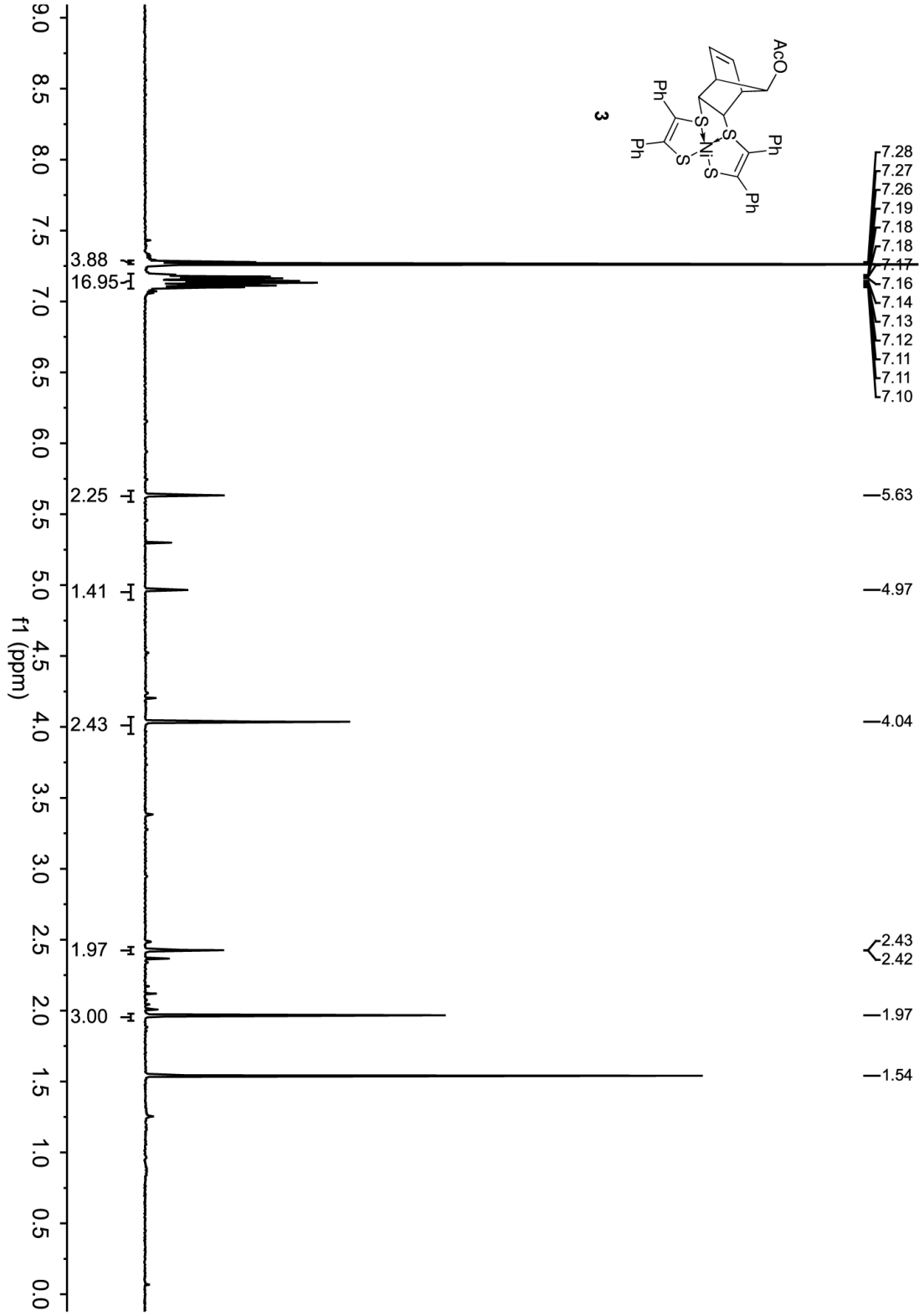
1.56
1.56
1.49
1.49
1.48
1.48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AcO
Ph
Ph
Ph
Ph
S
S
Ni
S
S
3.88
16.95
2.25
1.41
2.43
1.97
3.00
7.28
7.27
7.26
7.19
7.18
7.18
7.17
7.16
7.14
7.13
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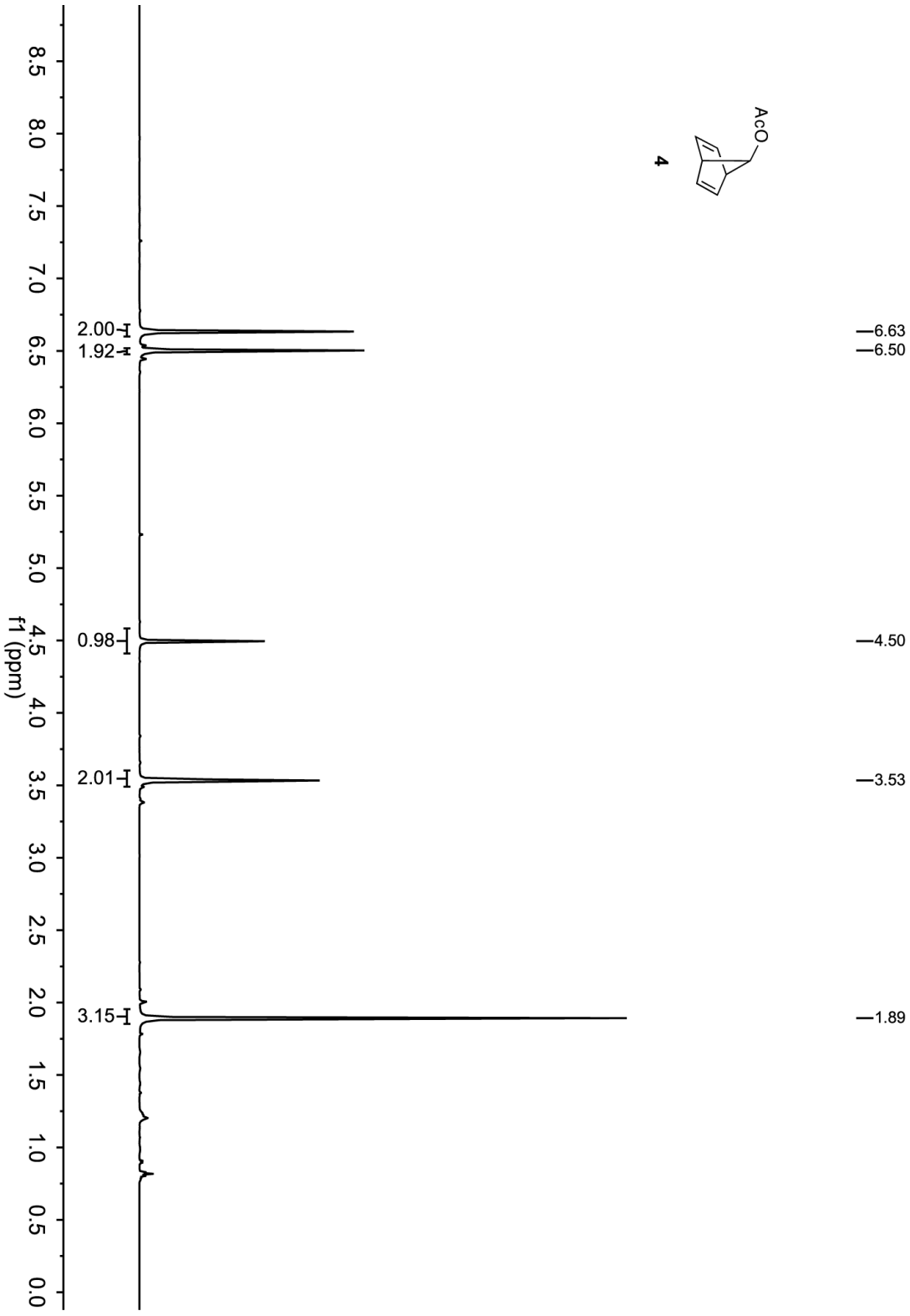
2.42
1.97
1.54
f1 (ppm)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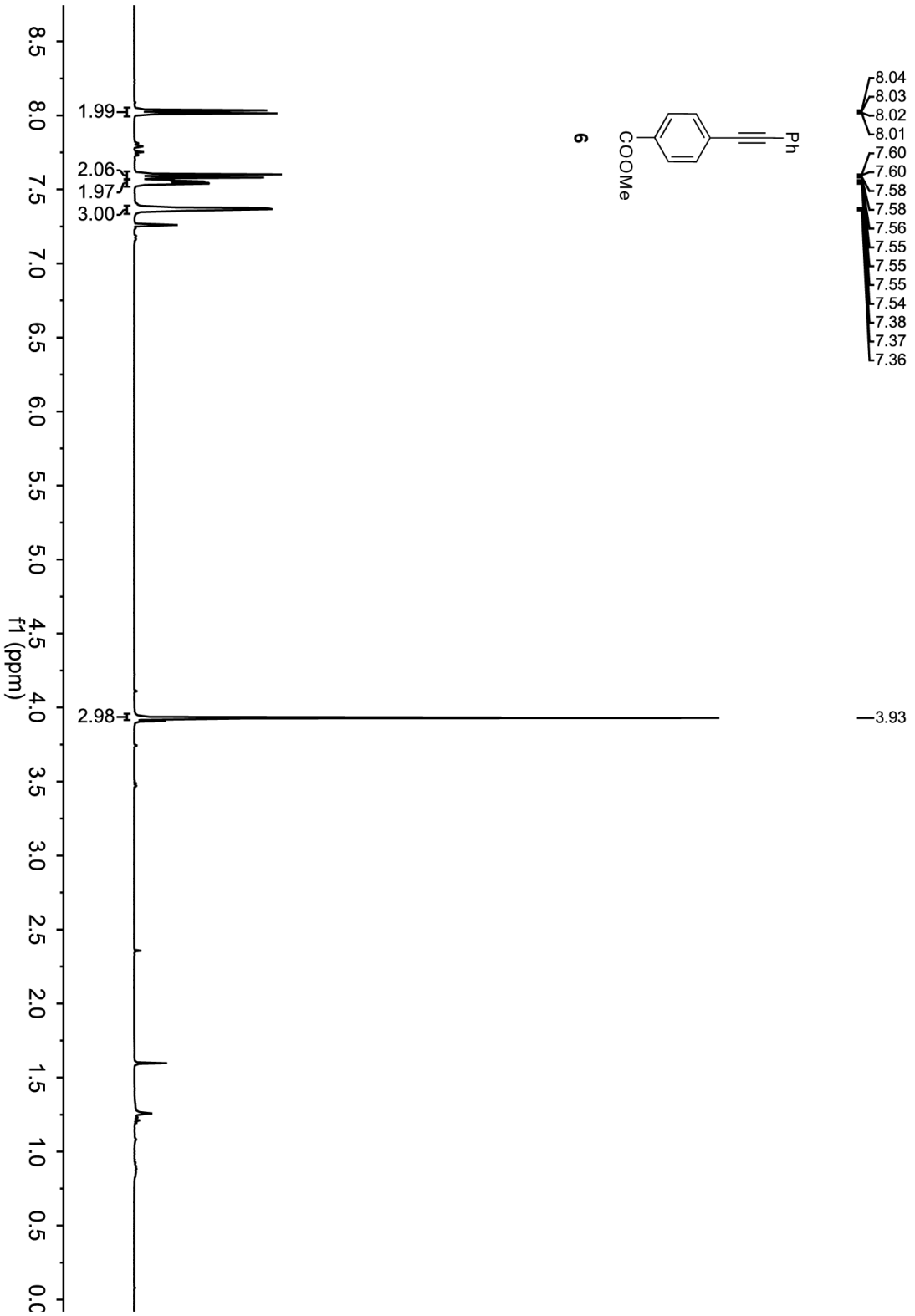
6.50
4.50
3.53
1.89
f1 (ppm)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7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
1.99
2.06
1.97
3.00
2.98
6
COOMe
Ph
8.04
8.03
8.02
8.01
7.60
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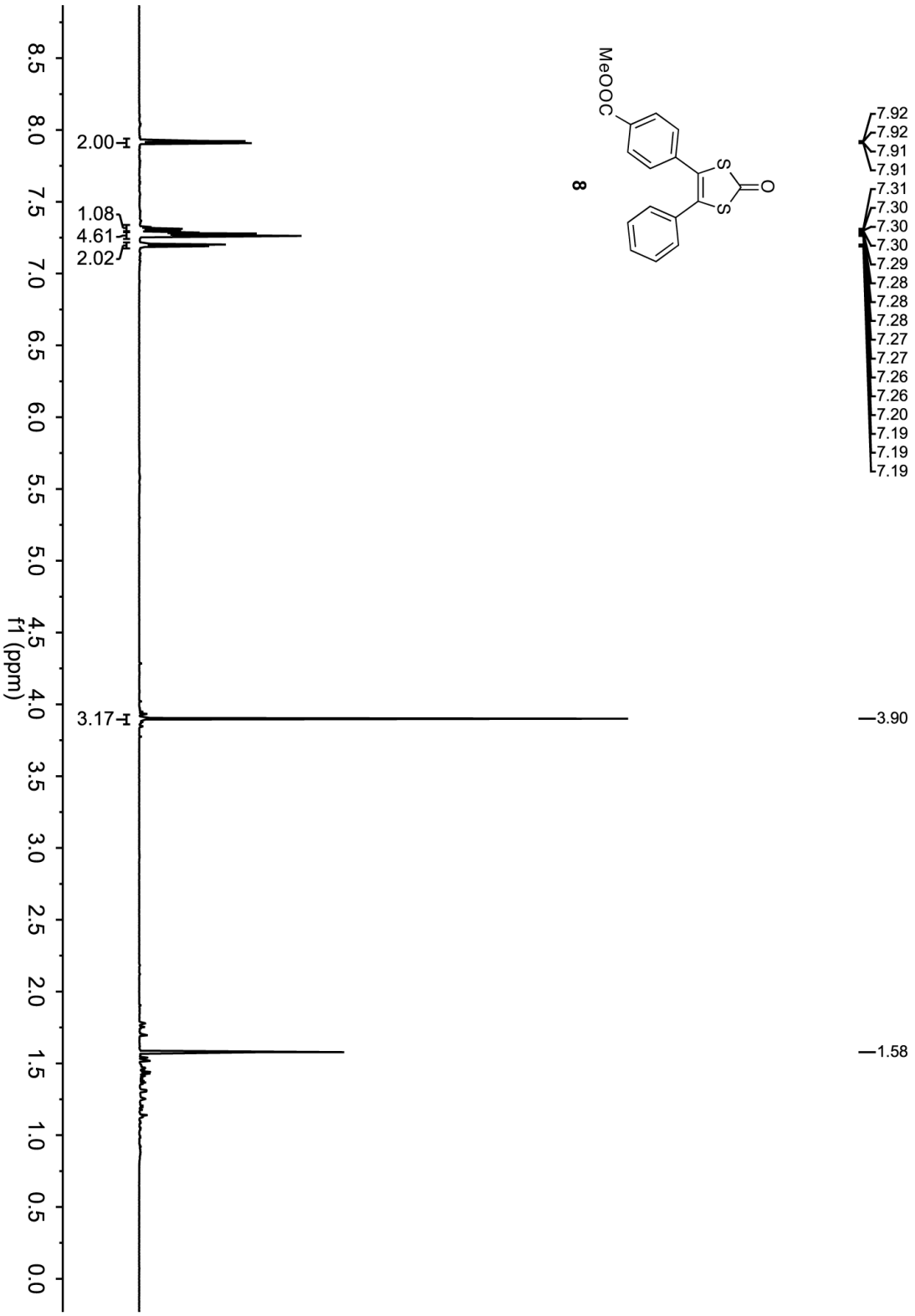
7.55
7.54
7.38
7.37
7.36
3.93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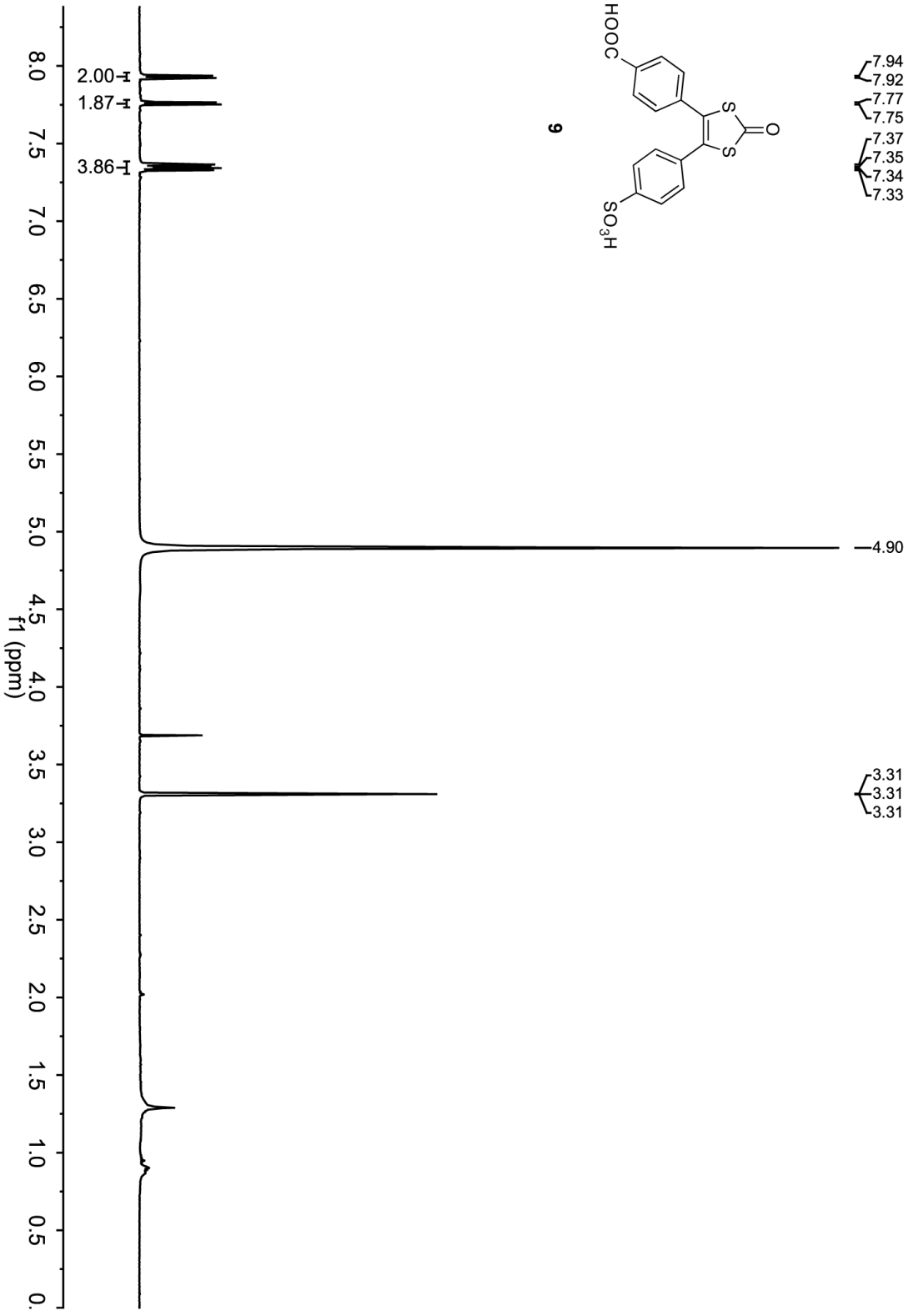
S
S
O
8
7.92
7.92
7.91
7.91
7.31
7.30
7.30
7.30
7.29
7.28
7.28
7.28
7.27
7.27
7.26
7.26
7.20
7.19
7.19
7.19
3.90
1.58
2.00
1.08
4.61
2.02
3.17
f1 (ppm)


HOOC
S
S
O
SO3H
9
7.94
7.92
7.77
7.75
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7.33
4.90
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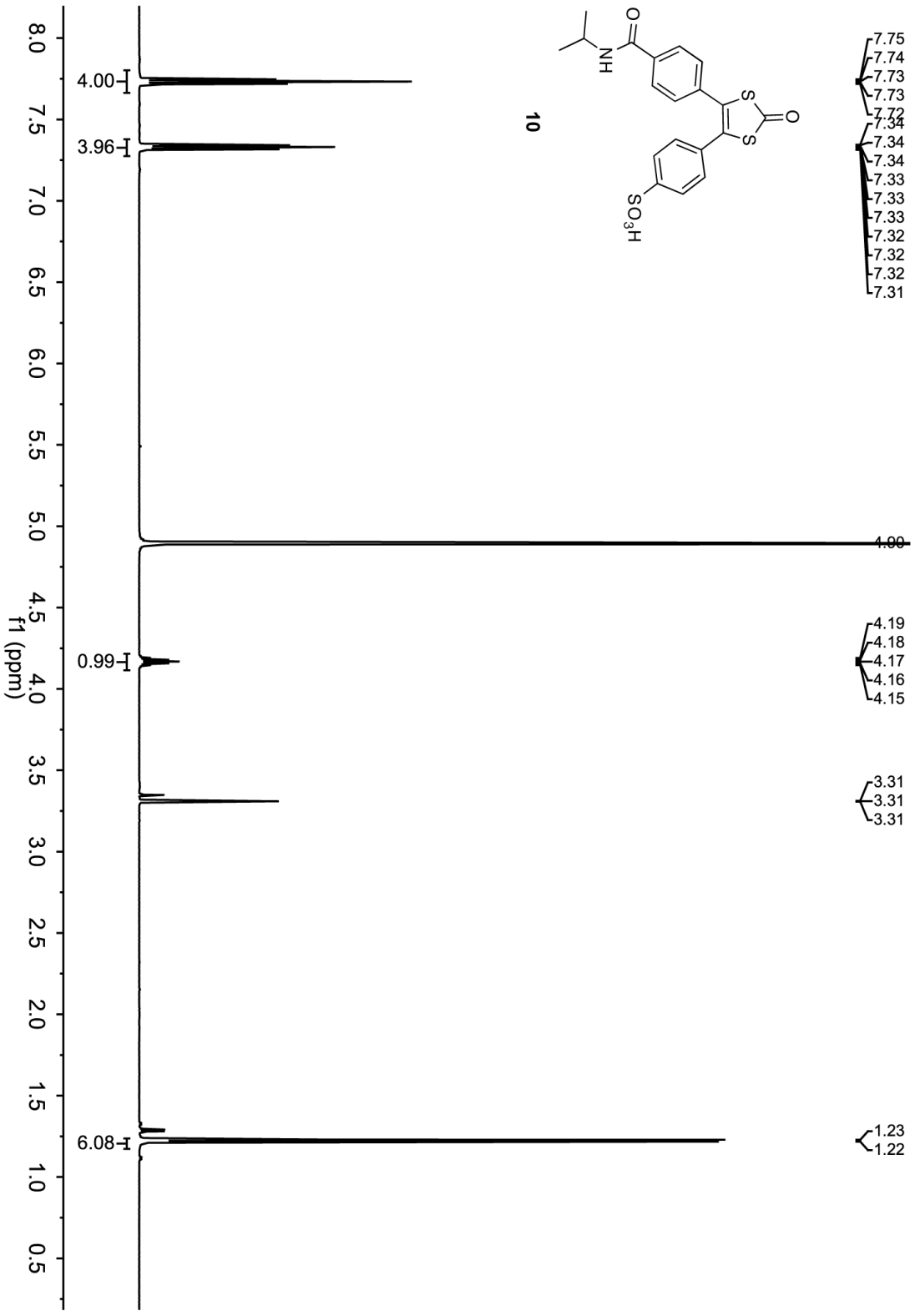
3.31
3.31
2.00
1.87
3.86
f1 (ppm)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NH
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S
S
O
SO3H
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7.73
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7.72
7.34
7.34
7.34
7.33
7.33
7.33
7.32
7.32
7.32
7.31
4.00
3.96
4.00
0.99
4.19
4.18
4.17
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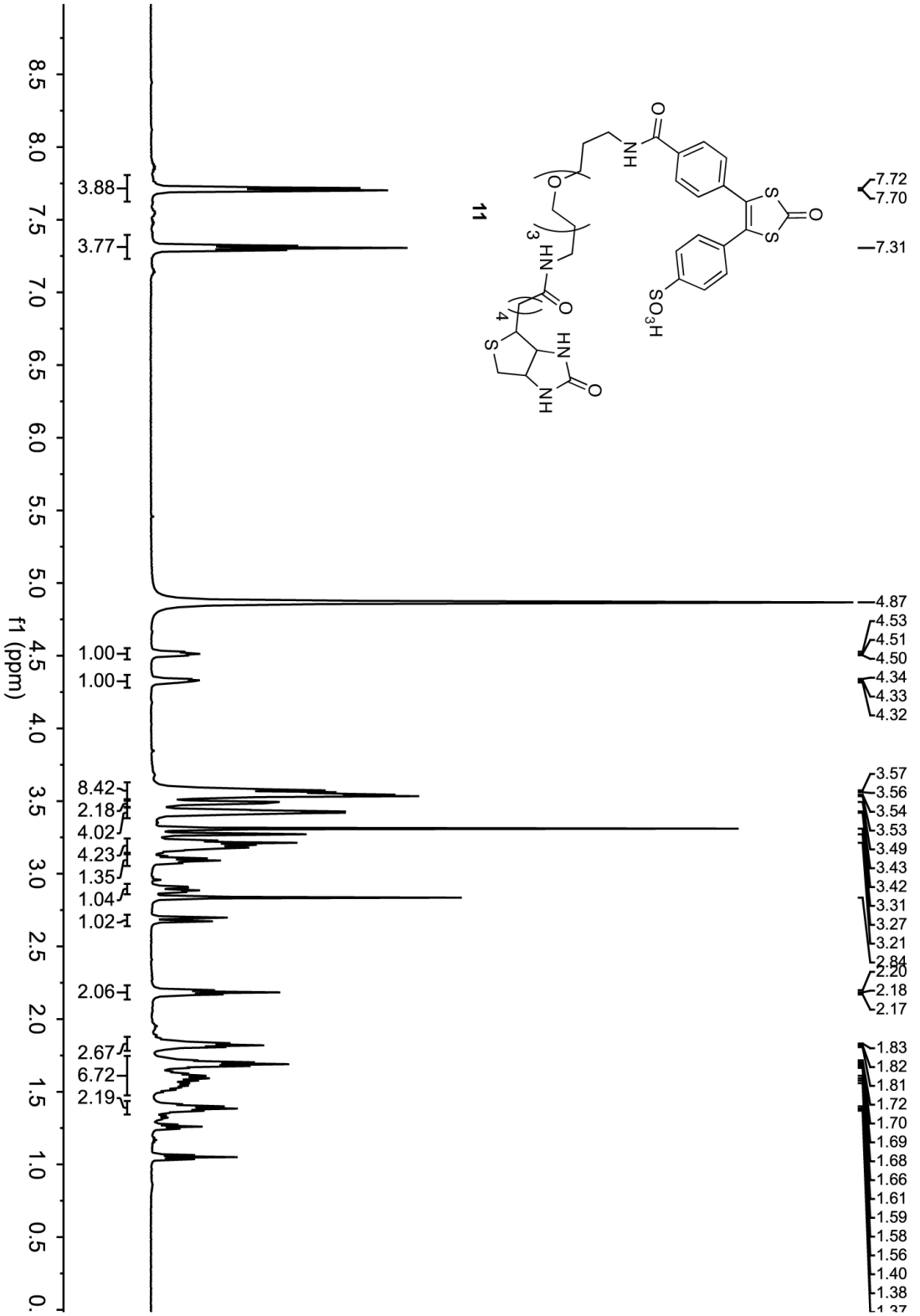
4.15
3.31
3.31
3.31
6.08
1.23
1.22
f1 (ppm)


11
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1.00
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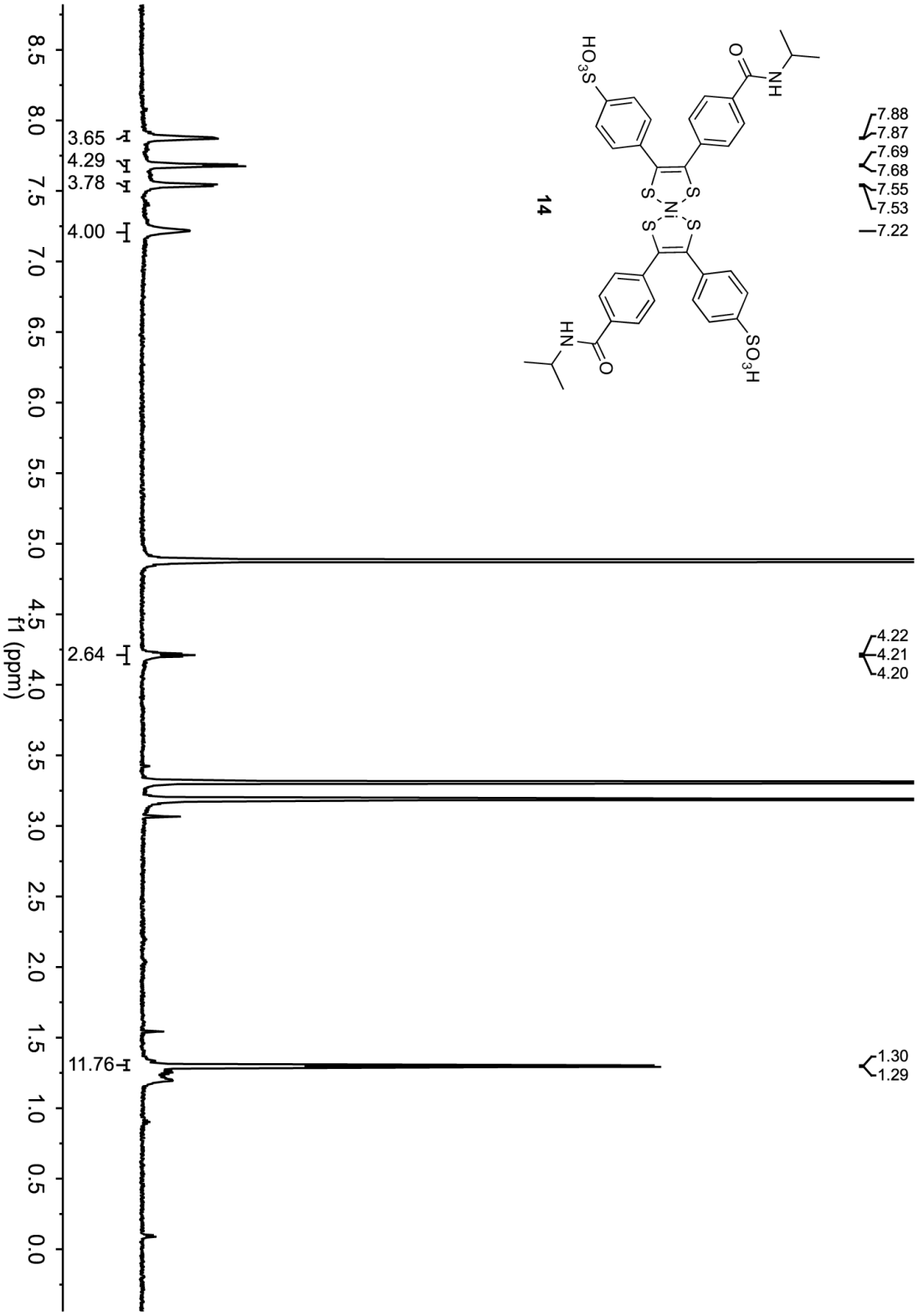
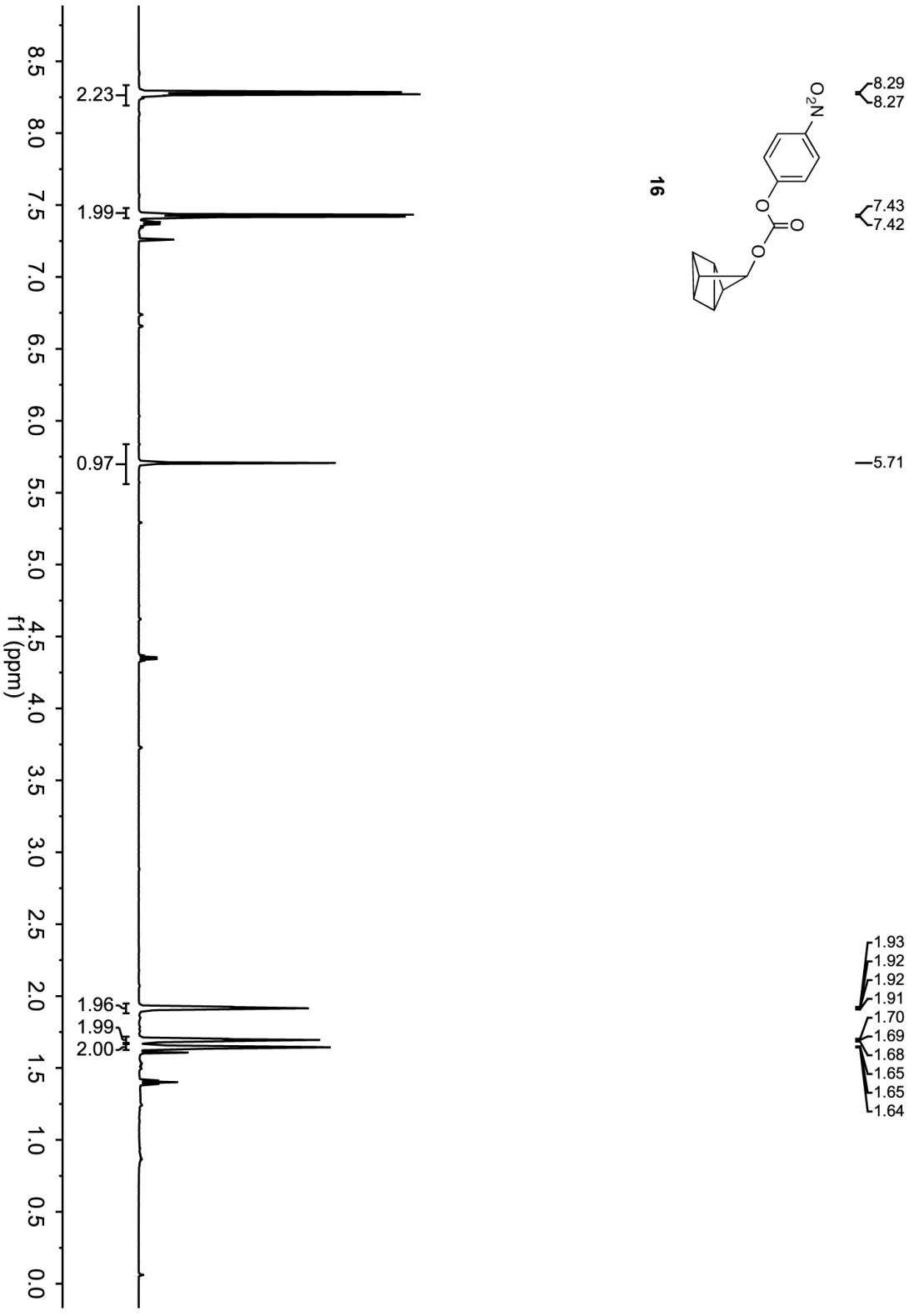
4.23
1.35
1.04
1.02
2.06
2.67
6.72
2.19
7.72
7.70
7.31
4.87
4.53
4.51
4.50
4.34
4.33
4.32
3.57
3.56
3.54
3.53
3.49
3.43
3.42
3.31
3.27
3.21
2.84
2.20
2.18
2.17
1.83
1.82
1.81
1.72
1.70
1.69
1.68
1.66
1.61
1.59
1.58
1.56
1.40
1.38


14
HO3S
SO3H
NH
HN
O
Ni
S
7.88
7.87
7.69
7.68
7.55
7.53
7.22
4.22
4.21
4.20
1.30
1.29
3.65
4.29
3.78
4.00
2.64
11.76
f1 (ppm)


16
O2N
8.29
8.27
7.43
7.42
5.71
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1.92
1.92
1.91
1.70
1.69
1.68
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1.65
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2.23
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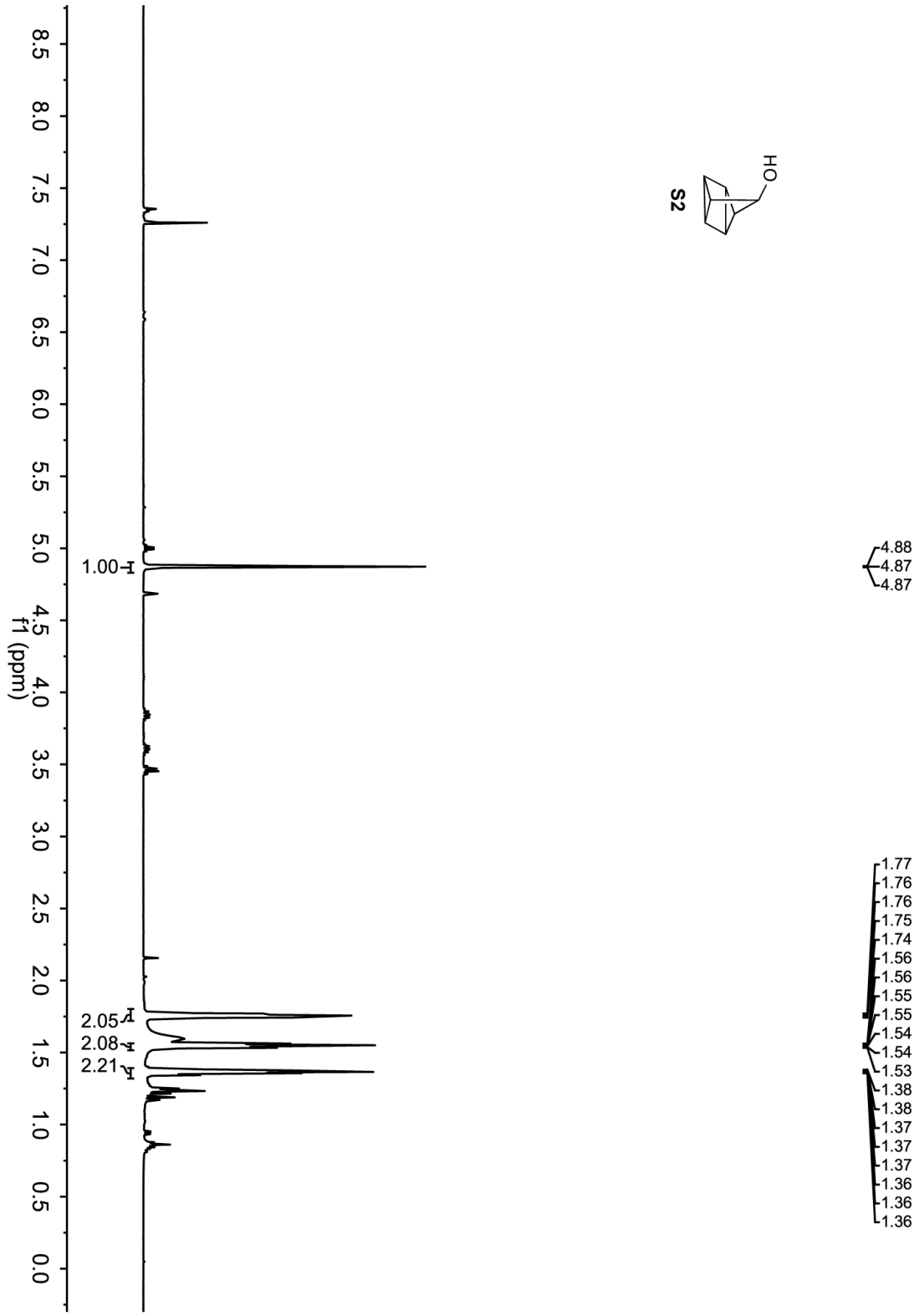
1.96
1.99
2.00
f1 (ppm)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6.5
6.0
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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
1.00
2.05
2.08
2.21
S2
OH
4.88
4.87
4.87
1.77
1.76
1.76
1.75
1.74
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1.56
1.55
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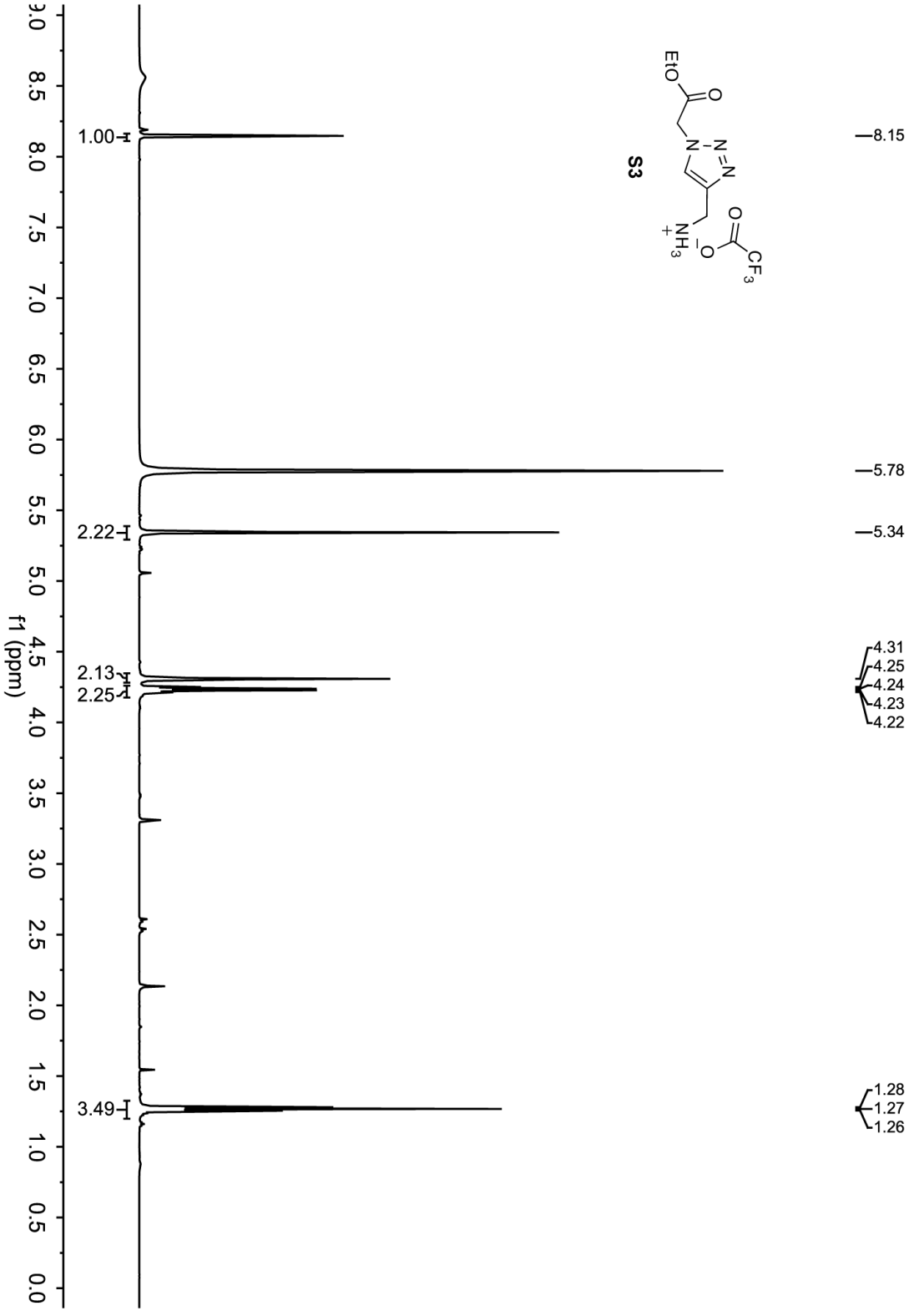
1.37
1.37
1.37
1.36
1.36
1.36


S3
EtO
O
N
N
N
O
NH3
O
O
CF3
8.15
5.78
5.34
4.31
4.25
4.24
4.23
4.22
1.28
1.27
1.26
1.00
2.22
2.13
2.25
3.49
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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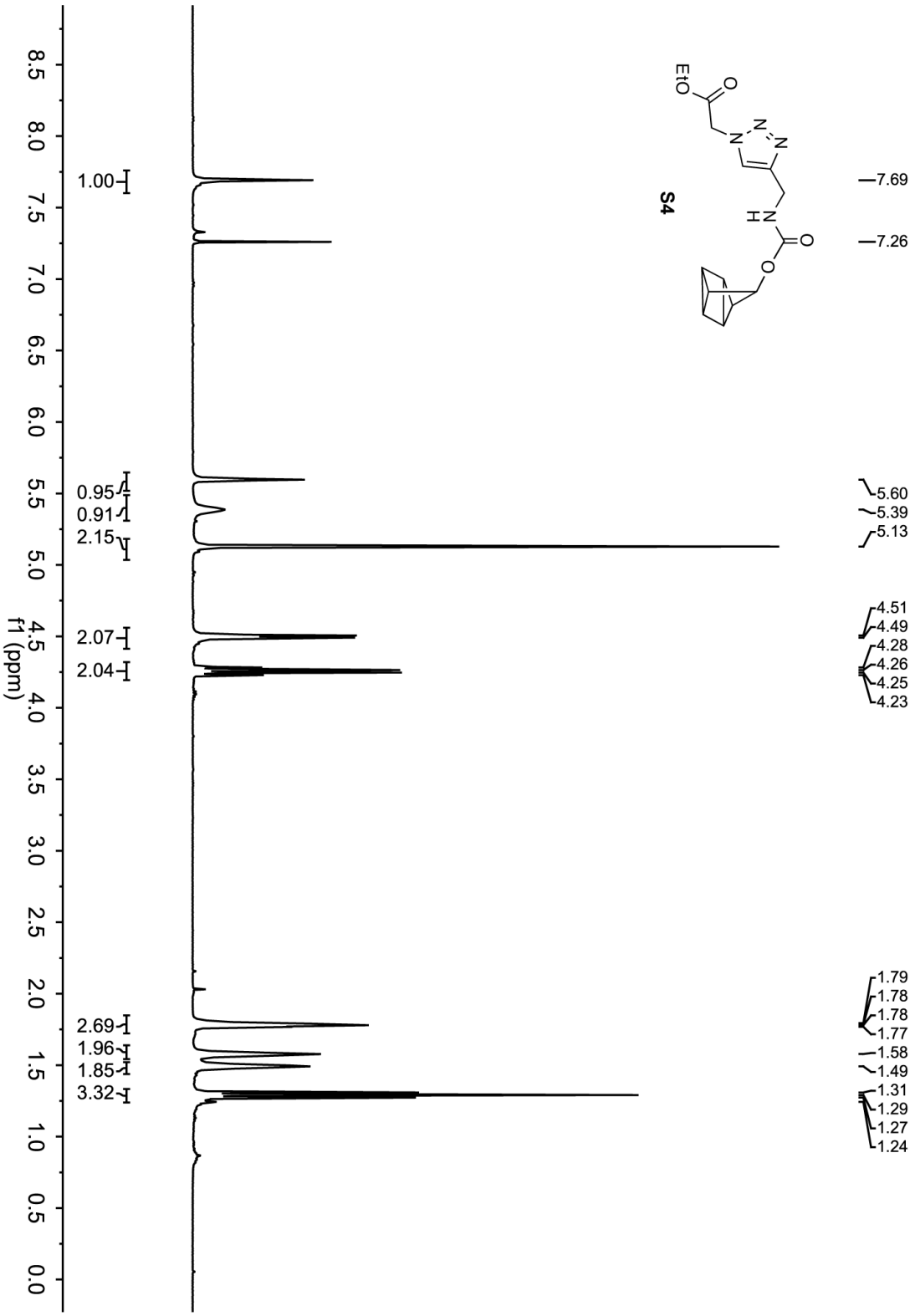
0.0


S4
EtO
O
N
N
N
H
N
O
O
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0.95
0.91
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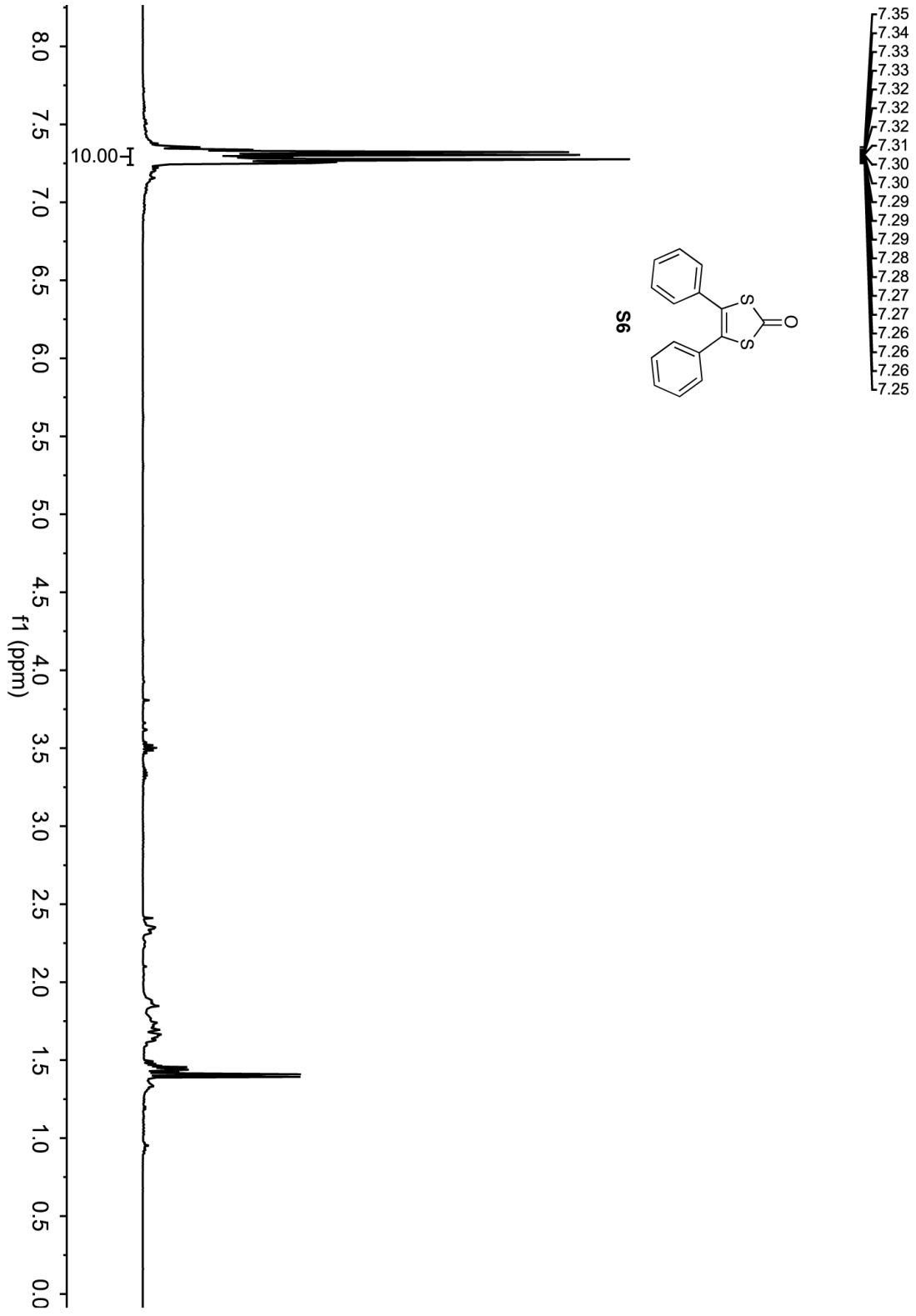
2.07
2.04
2.69
1.96
1.85
3.32
7.69
7.26
5.60
5.39
5.13
4.51
4.49
4.28
4.26
4.25
4.23
1.79
1.78
1.78
1.77
1.58
1.49
1.31
1.29
1.27
1.24
f1 (ppm)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7.33
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7.32
7.32
7.32
7.31
7.30
7.30
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7.29
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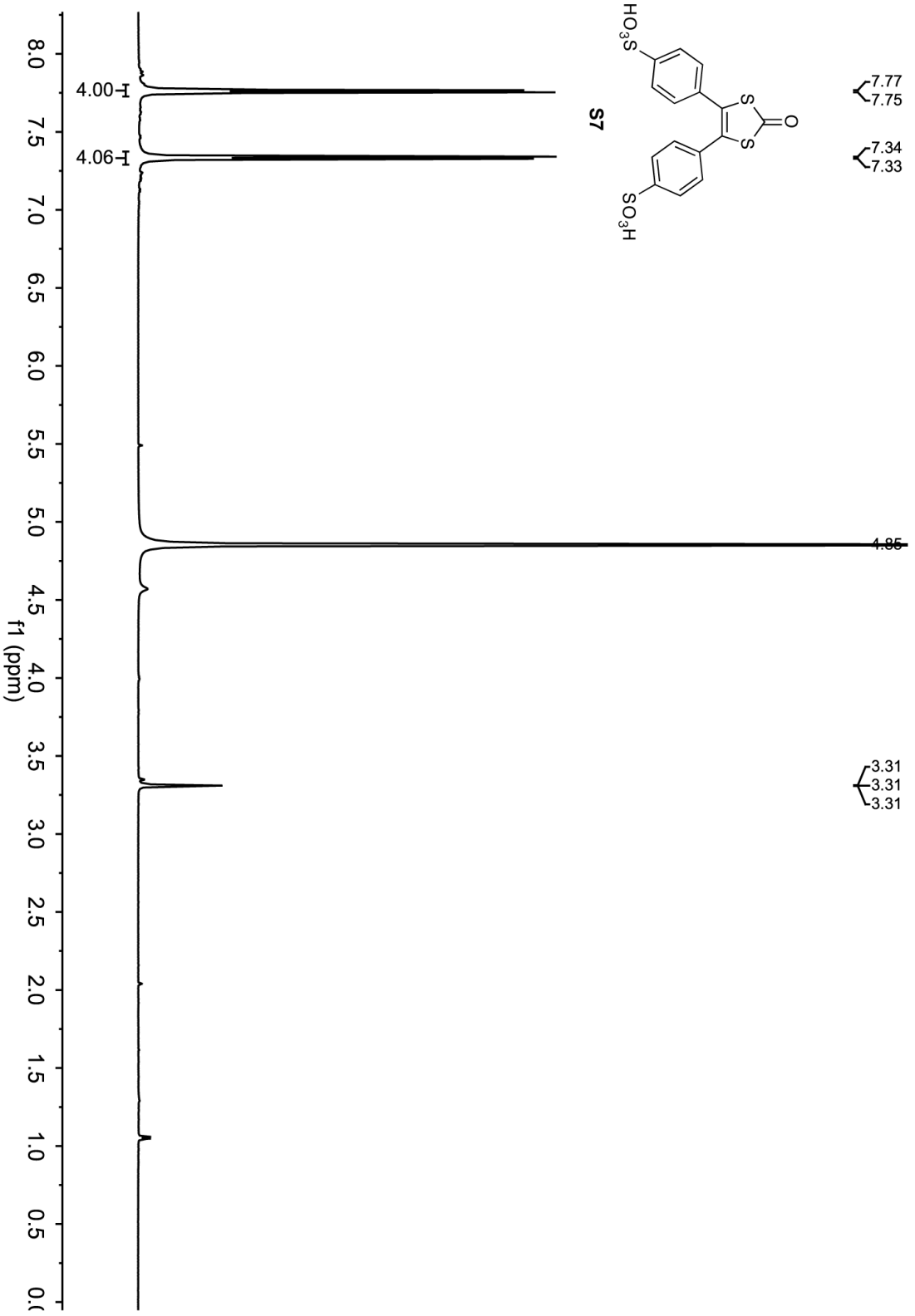
7.28
7.28
7.27
7.27
7.26
7.26
7.26
7.25
S
S
O
S6
10.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


HO3S
SO3H
S
S
O
S7
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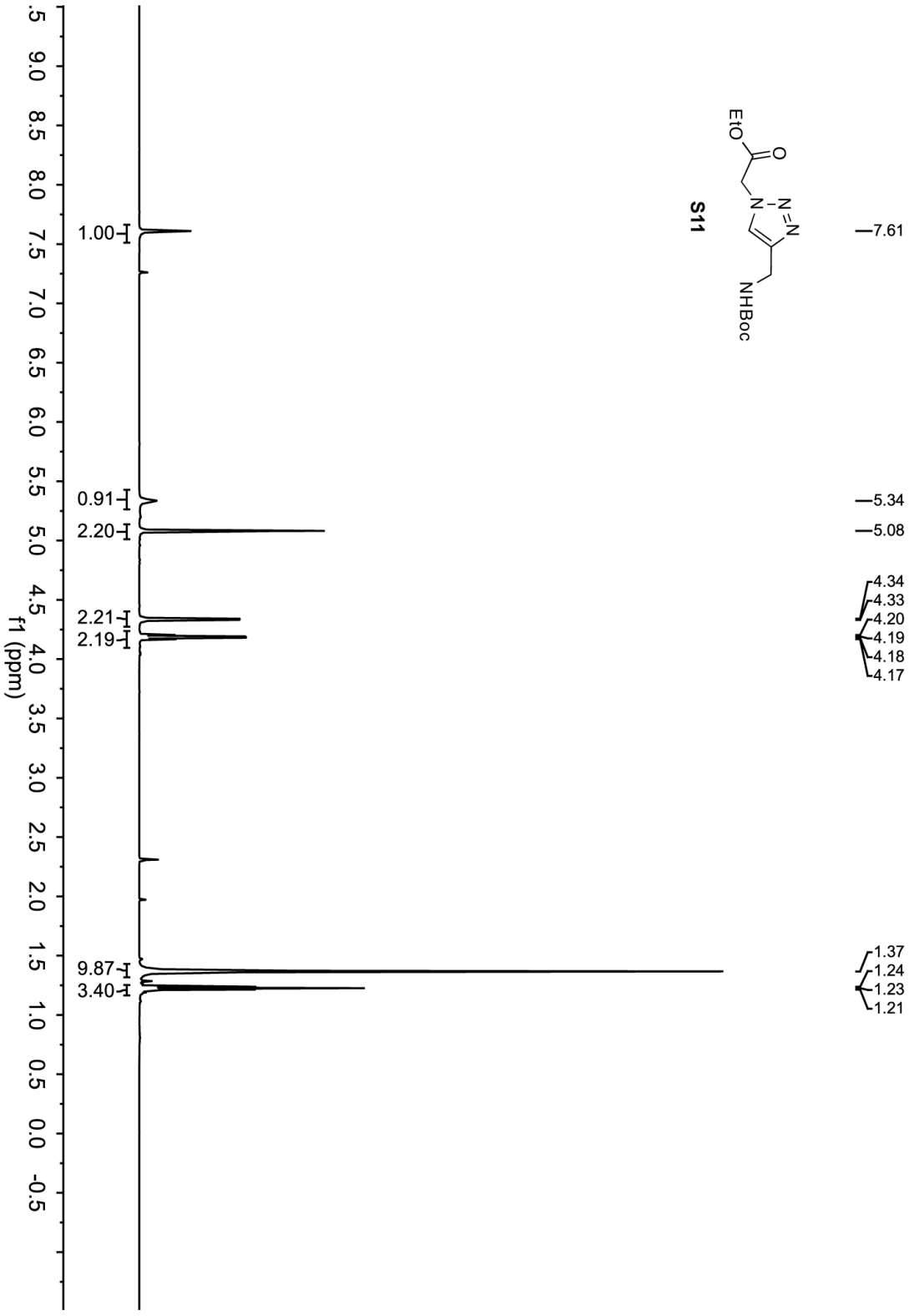
3.31
3.31
3.31
4.00
4.06
f1 (ppm)


S11
EtO
O
N
N
N
NHBoc
7.61
5.34
5.08
4.34
4.33
4.20
4.19
4.18
4.17
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1.21
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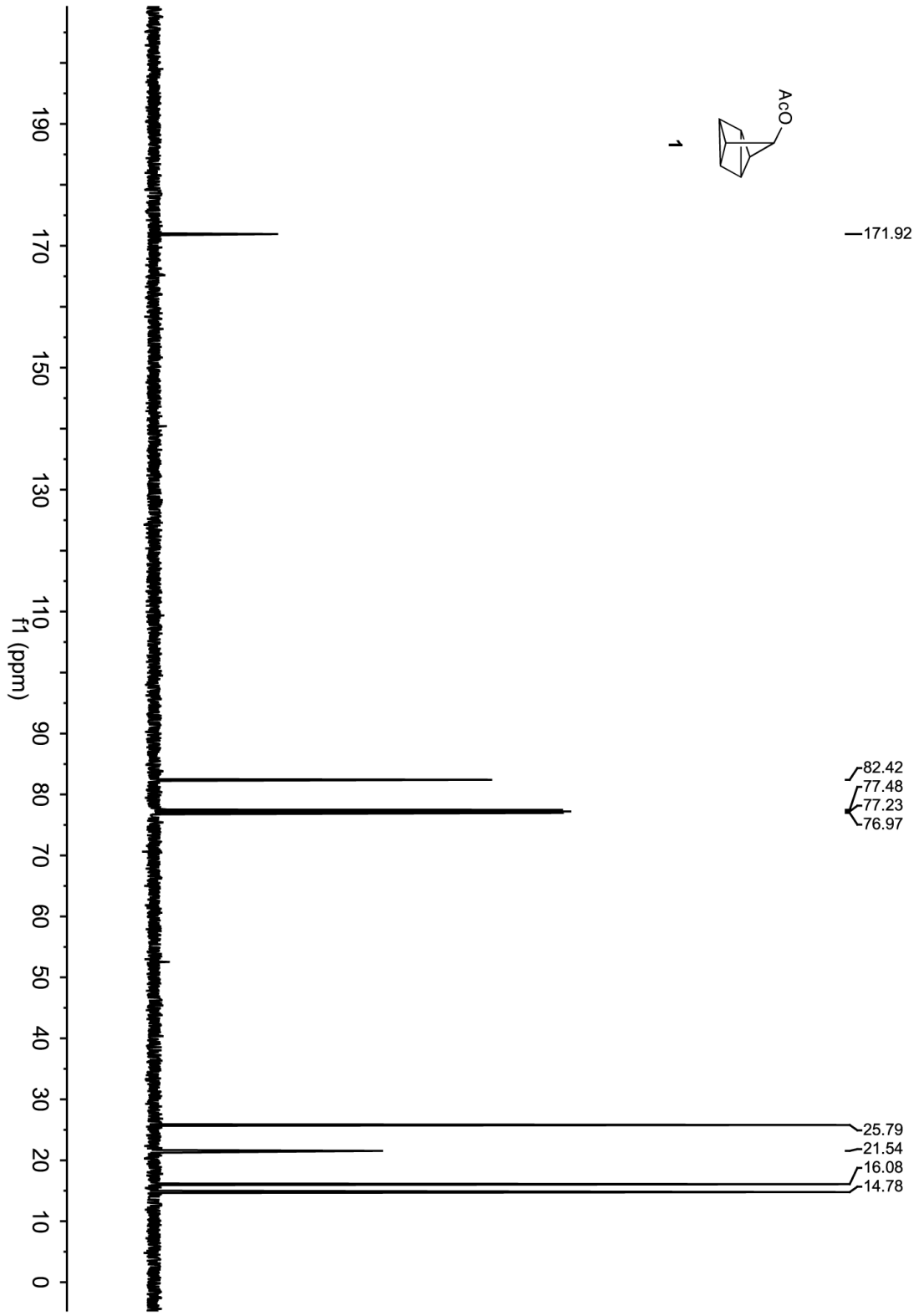
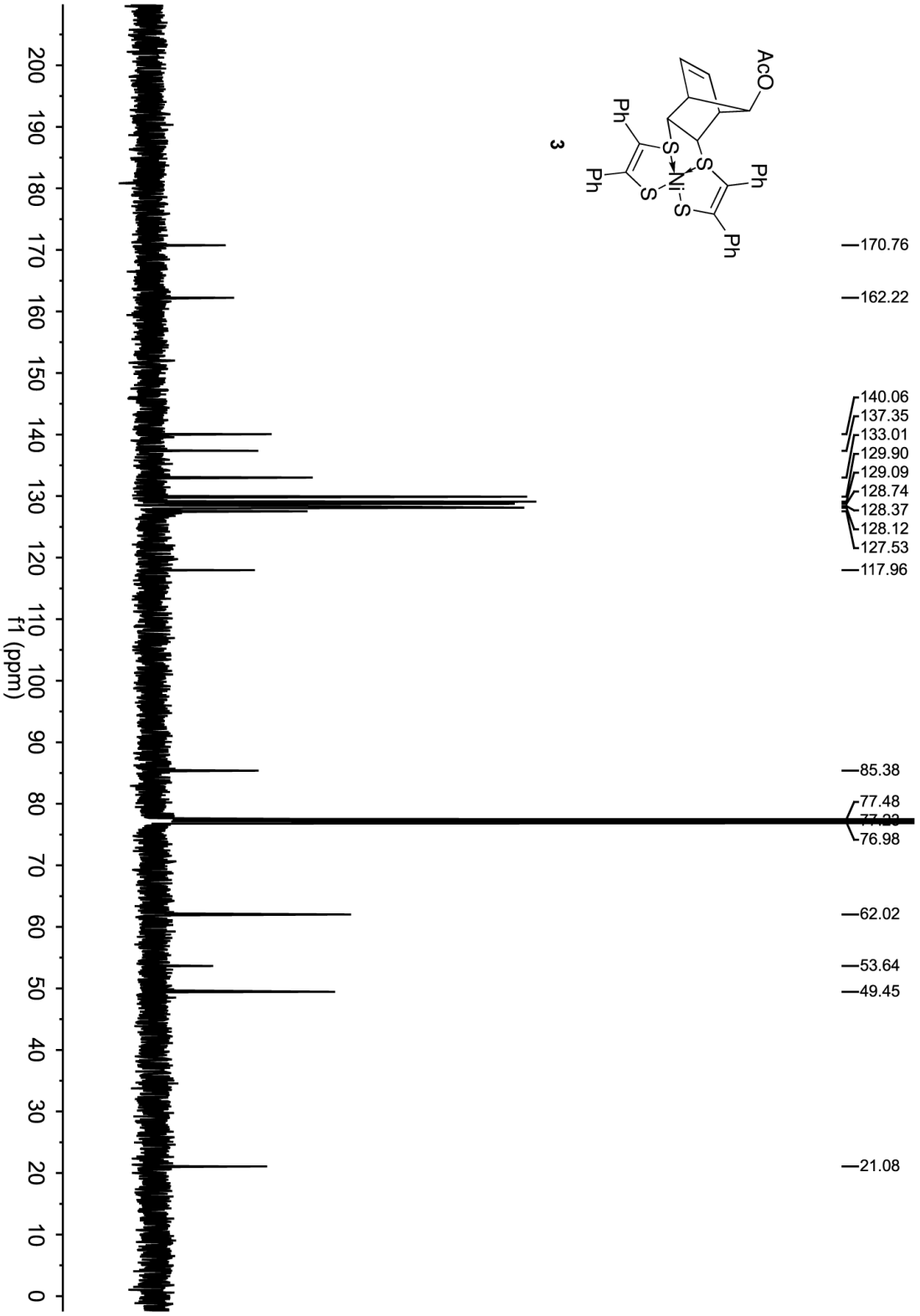
2.20
2.21
2.19
9.87
3.40
f1 (ppm)


AcO
1
171.92
82.42
77.48
77.23
76.97
25.79
21.54
16.08
14.78
f1 (ppm)
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0


3
AcO
Ph
Ph
S
S
Ni
S
S
Ph
Ph
170.76
162.22
140.06
137.35
133.01
129.90
129.09
128.74
128.37
128.12
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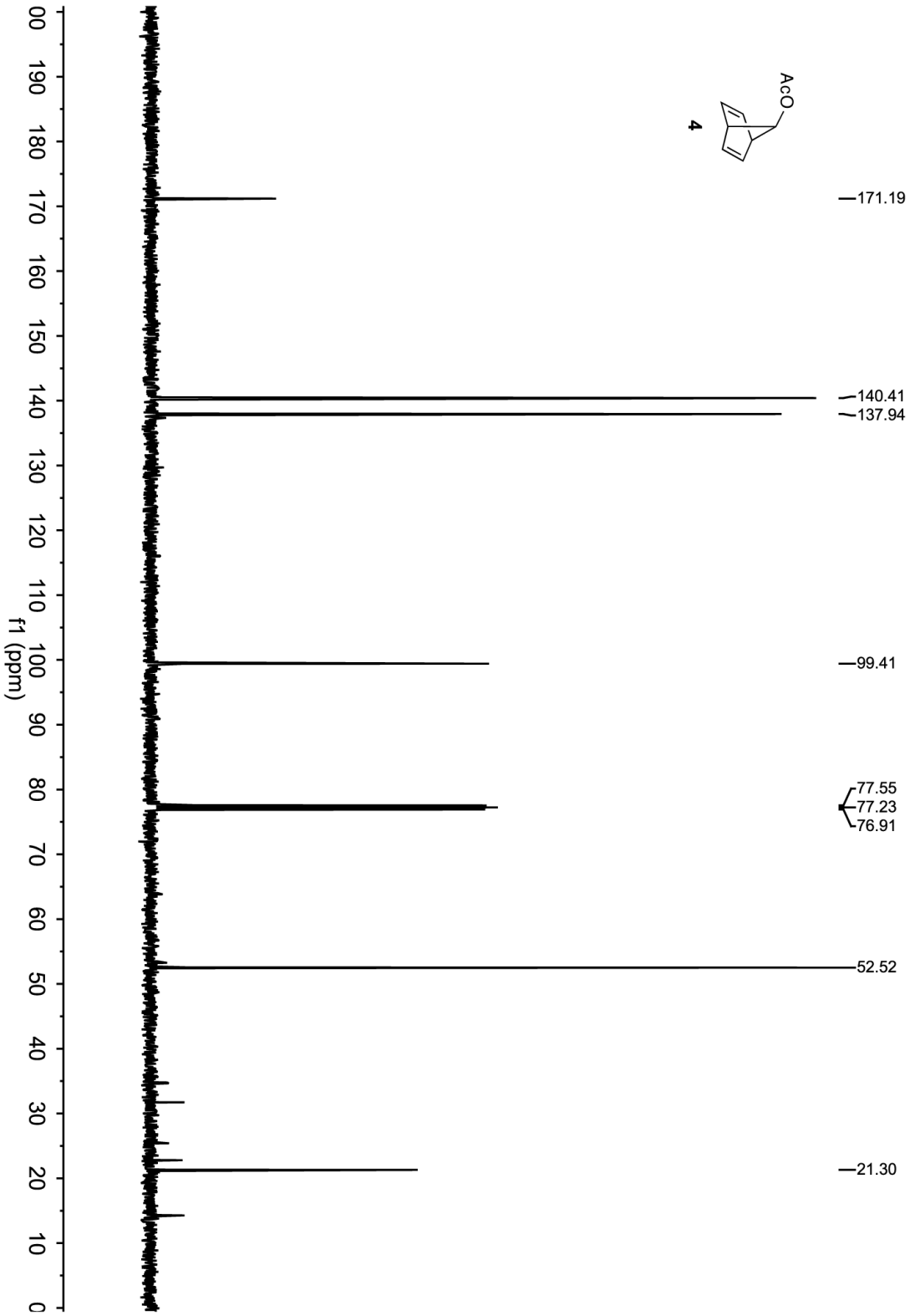
117.96
85.38
77.48
76.98
62.02
53.64
49.45
21.08
f1 (ppm)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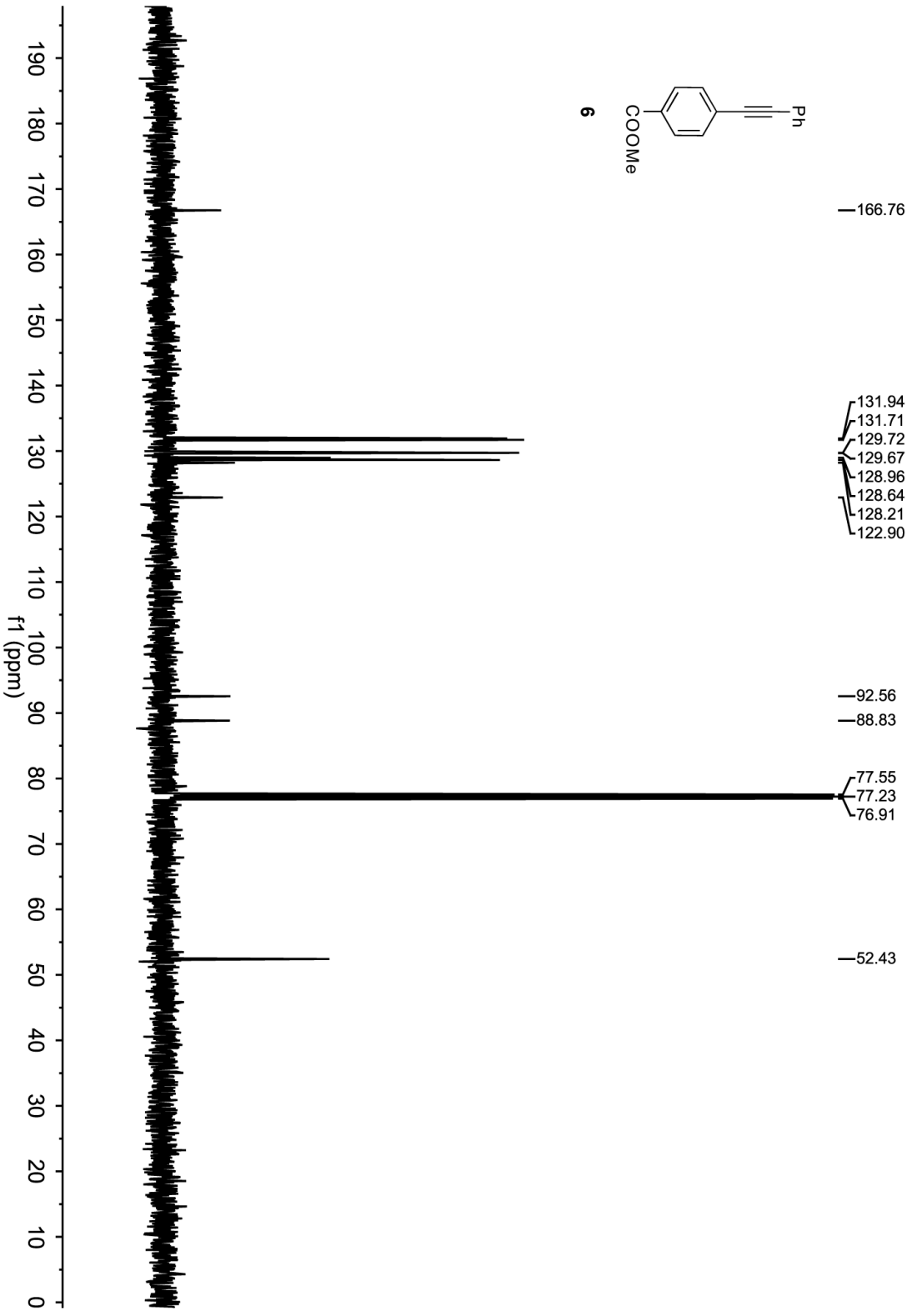
99.41
77.55
77.23
76.91
52.52
21.30
f1 (ppm)


6
COOMe
Ph
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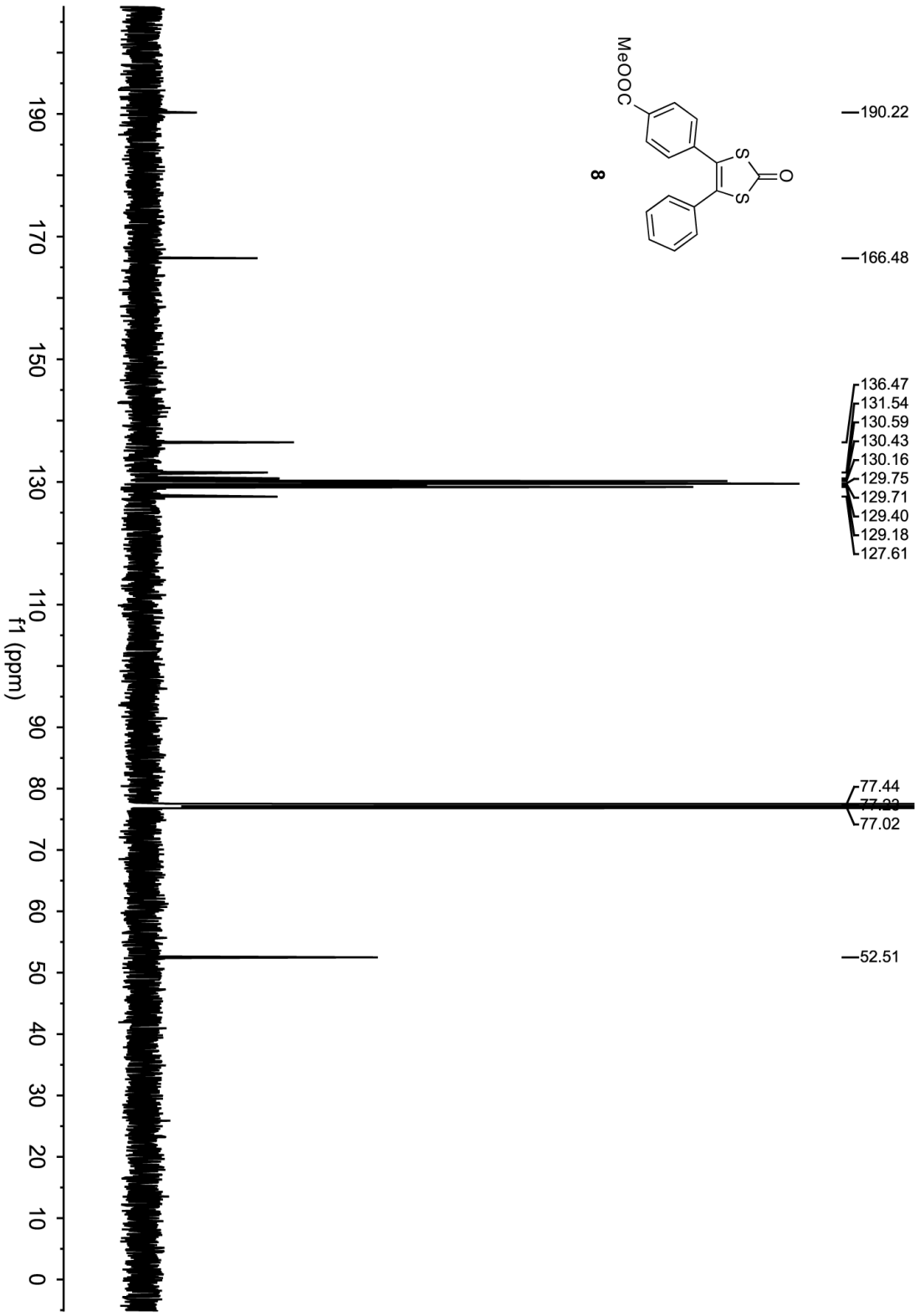
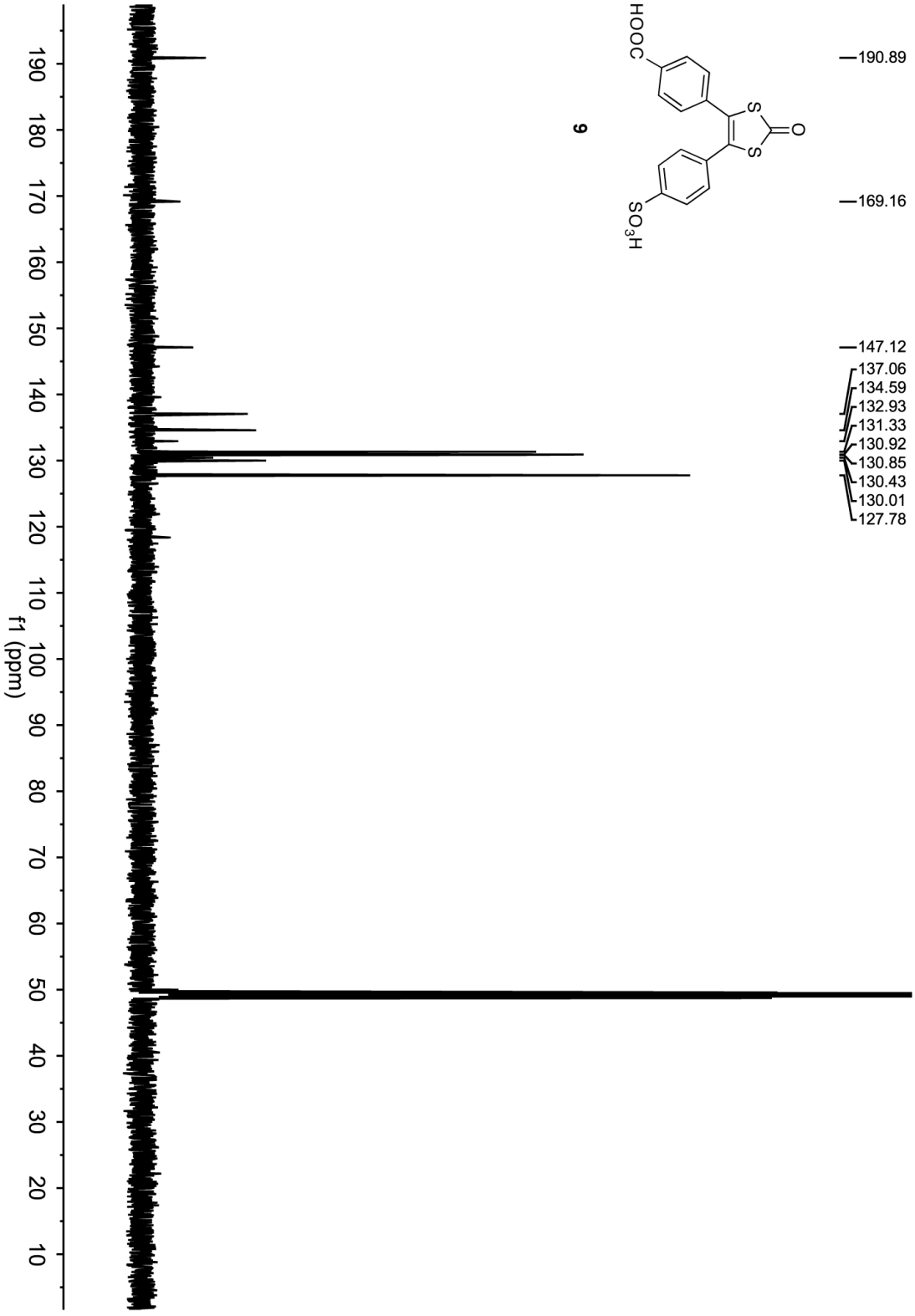
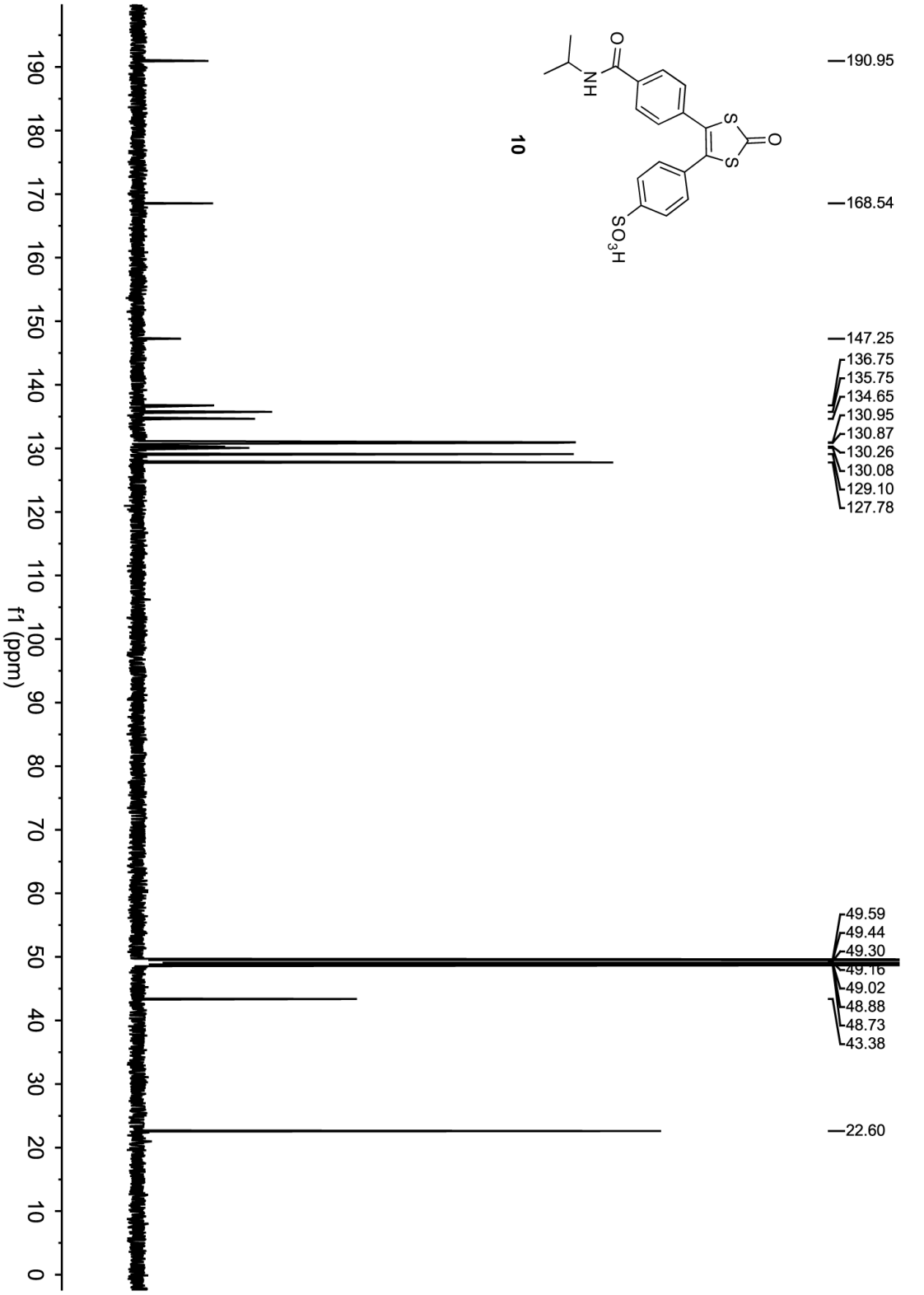
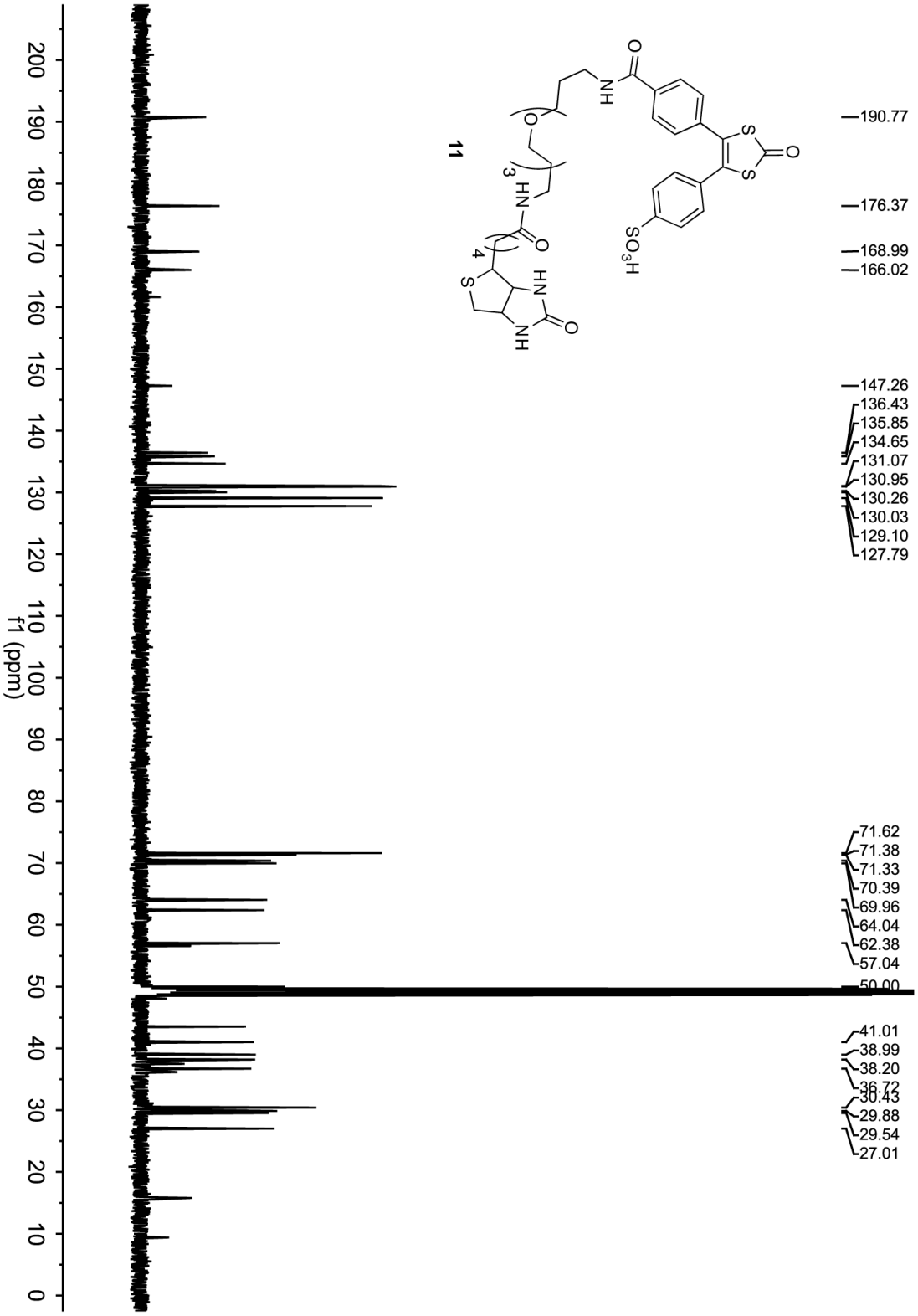
131.94
131.71
129.72
129.67
128.96
128.64
128.21
122.90
92.56
88.83
77.55
77.23
76.91
52.43
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


MeOOC
S
S
O
8
190.22
166.48
136.47
131.54
130.59
130.43
130.16
129.75
129.71
129.40
129.18
127.61
77.44
77.02
52.51
f1 (ppm)
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0


HOOC
S
S
O
SO3H
9
190.89
169.16
147.12
137.06
134.59
132.93
131.33
130.92
130.85
130.43
130.01
127.78
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


10
190.95
168.54
147.25
136.75
135.75
134.65
130.95
130.87
130.26
130.08
129.10
127.78
49.59
49.44
49.30
49.16
49.02
48.88
48.73
43.38
22.60
f1 (ppm)


11
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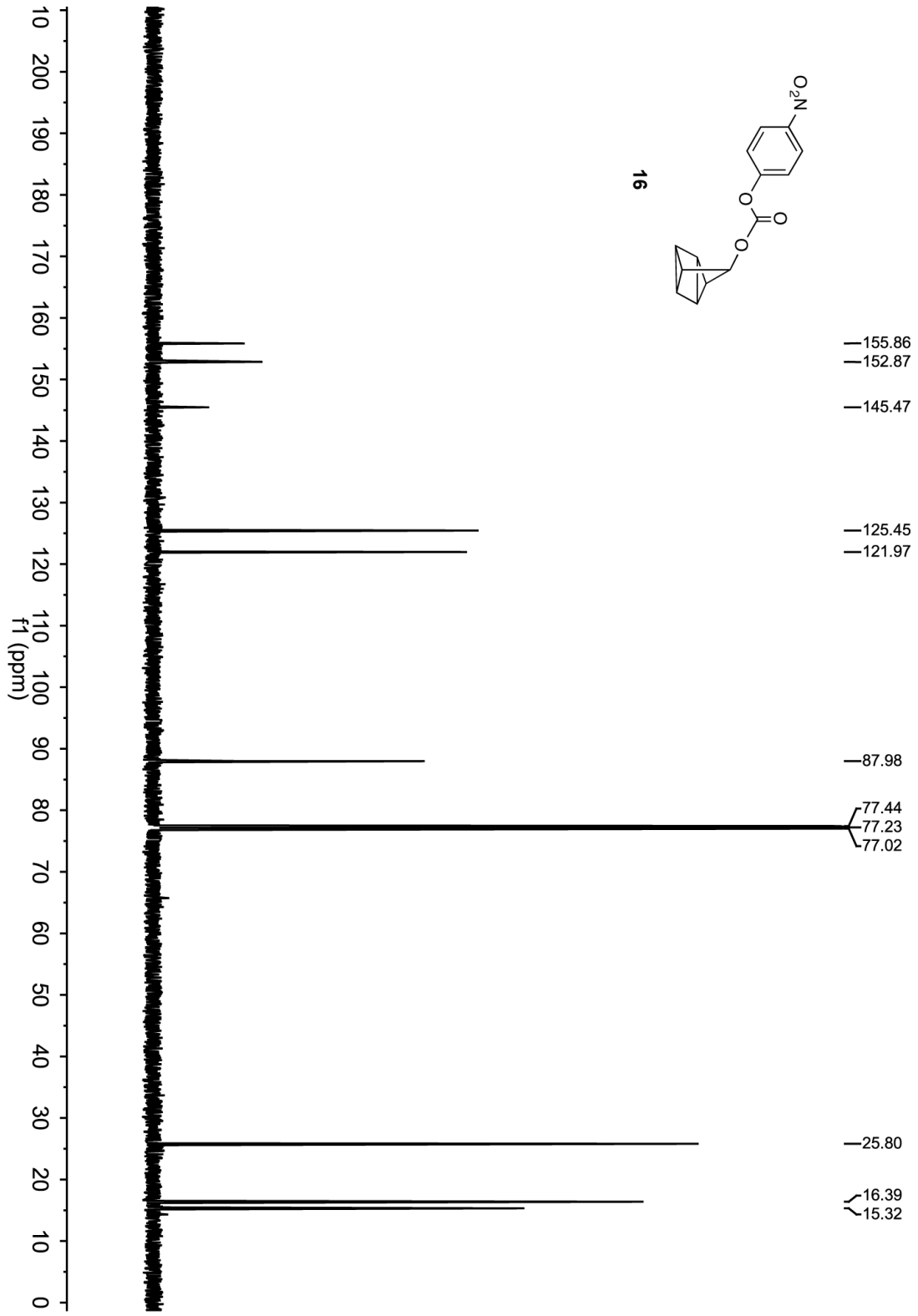
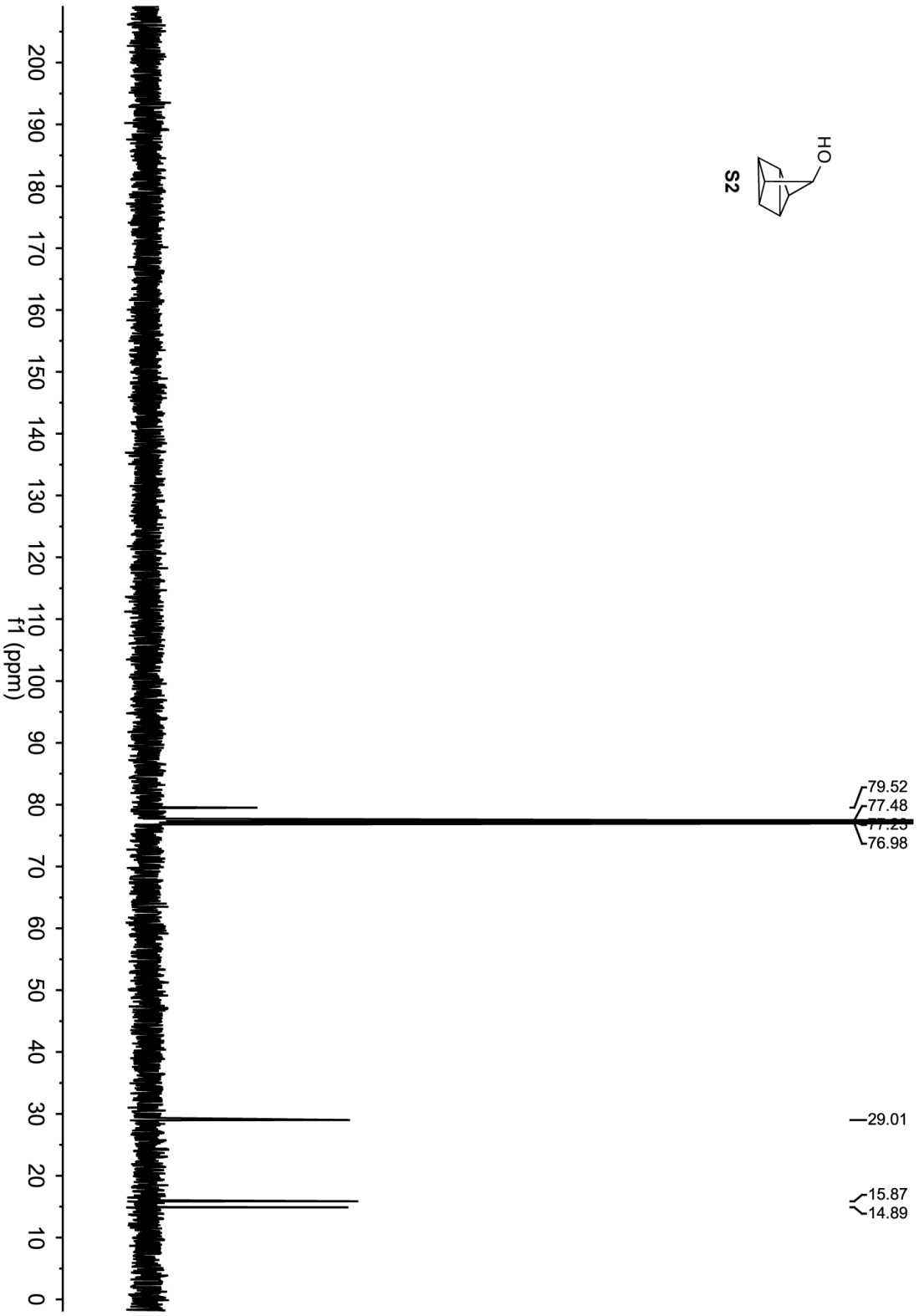
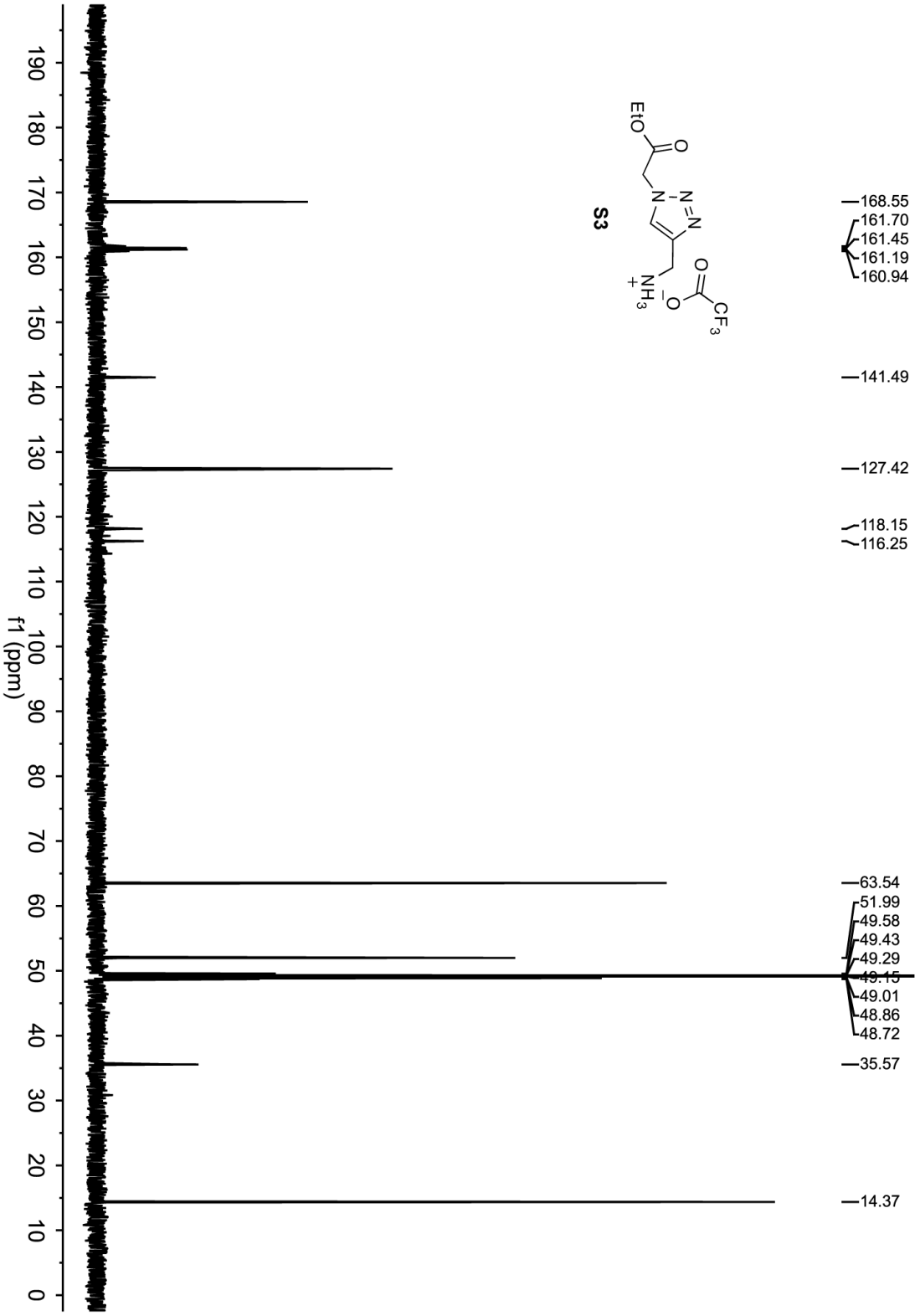
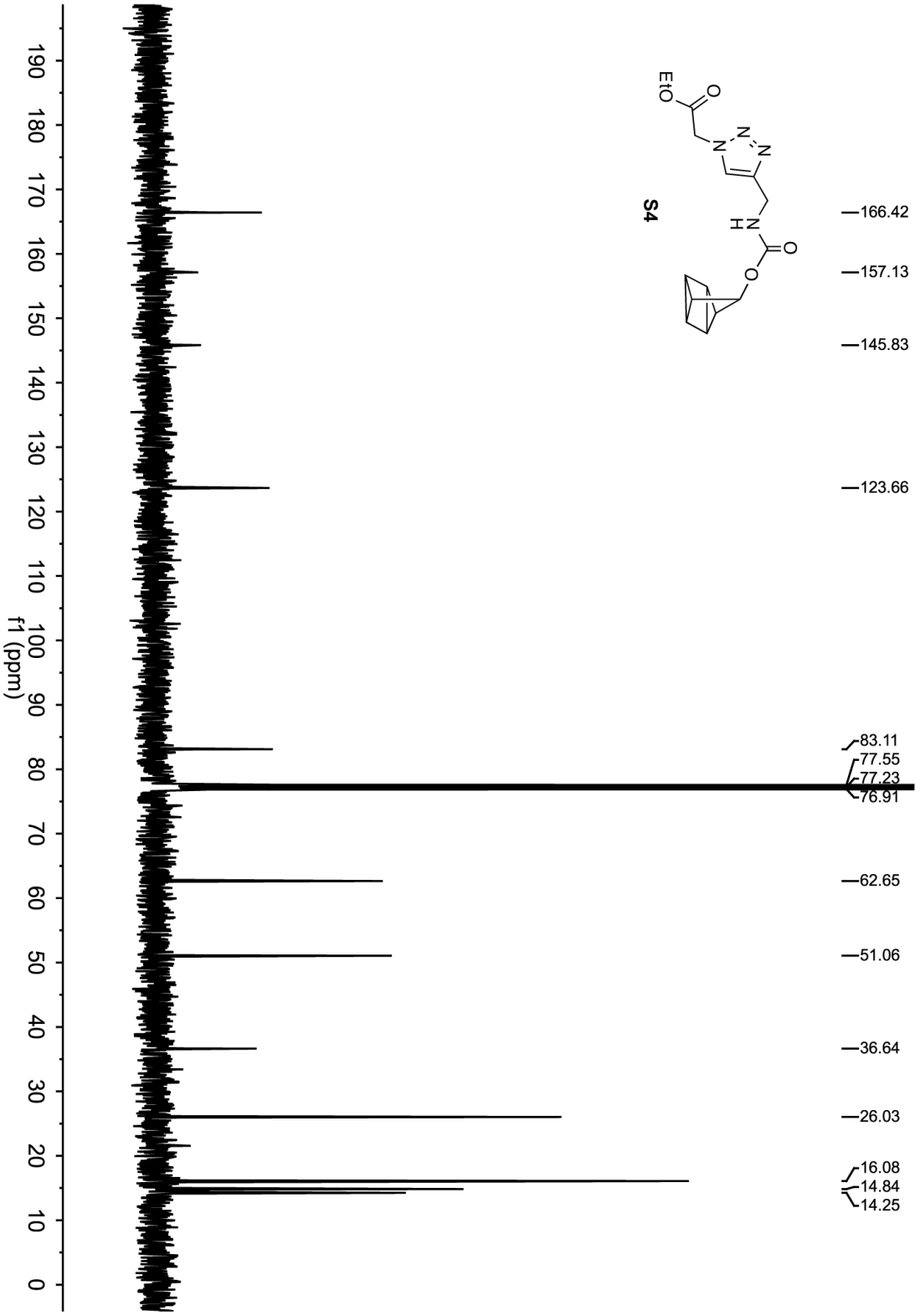
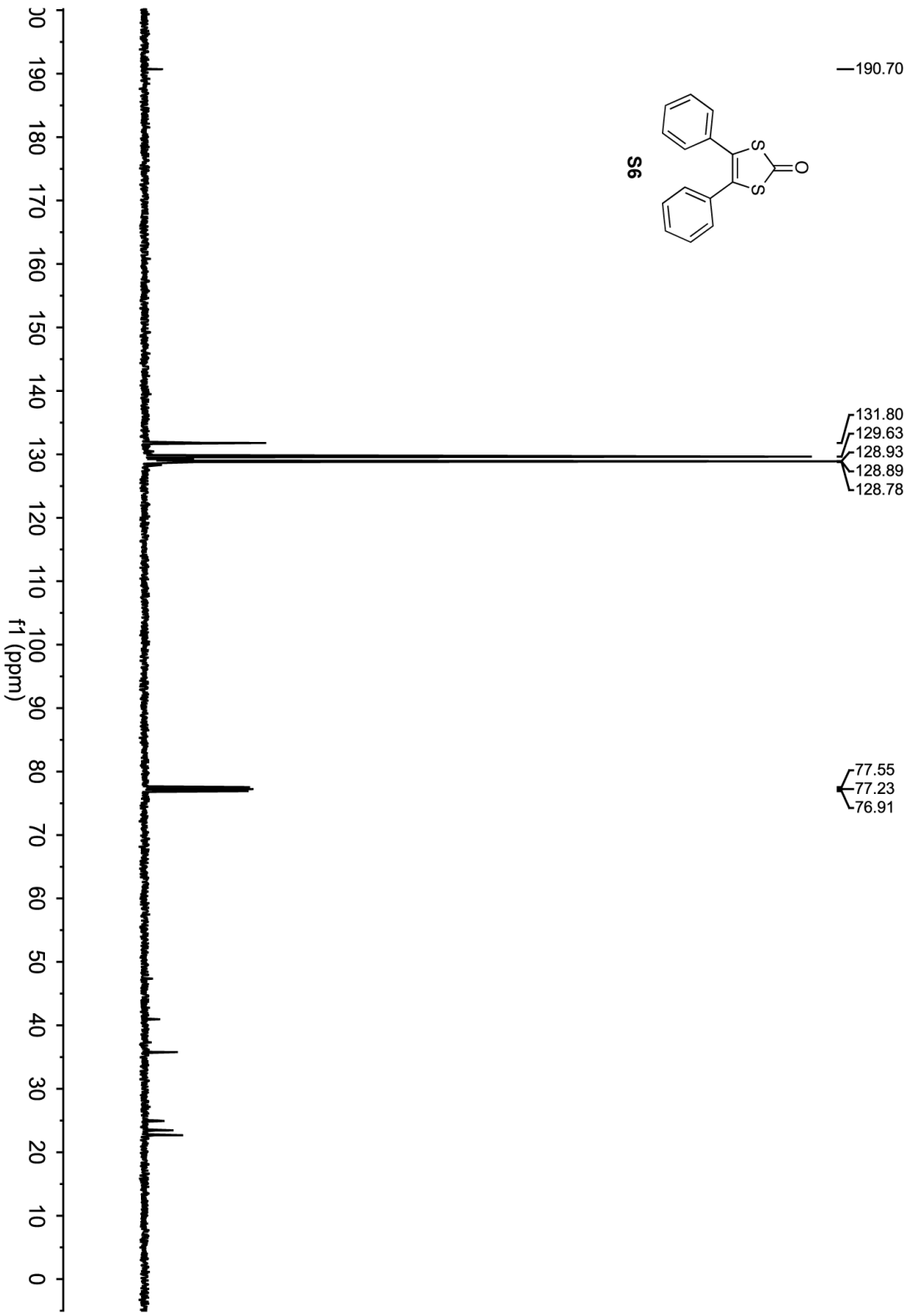
168.99
166.02
147.26
136.43
135.85
134.65
131.07
130.95
130.26
130.03
129.10
127.79
71.62
71.38
71.33
70.39
69.96
64.04
62.38
57.04
50.00
41.01
38.99
38.20
36.72
30.43
29.88
29.54
27.01
f1 (ppm)

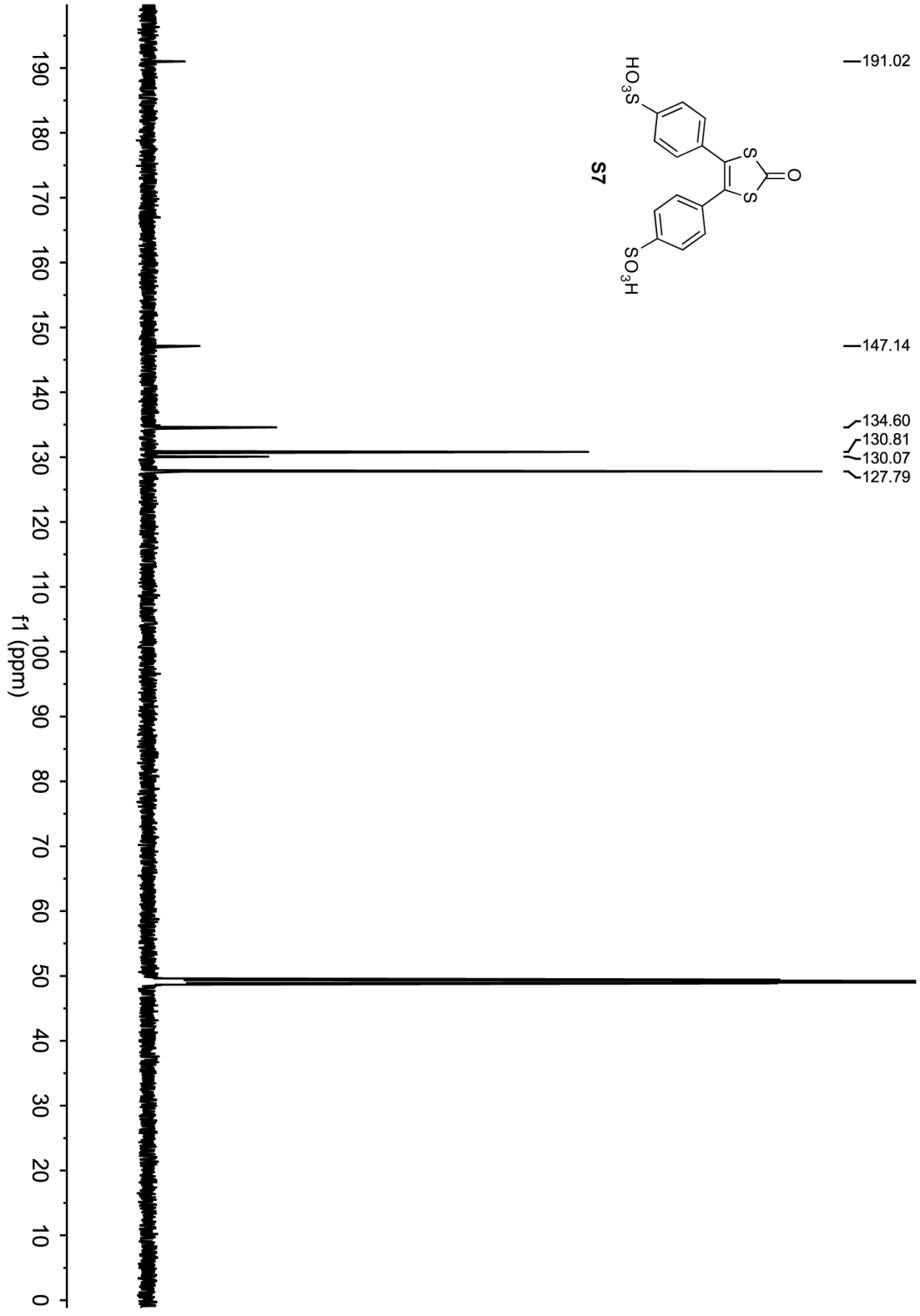

16
O2N
O
O
O
155.86
152.87
145.47
125.45
121.97
87.98
77.44
77.23
77.02
25.80
16.39
15.32
f1 (ppm)
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

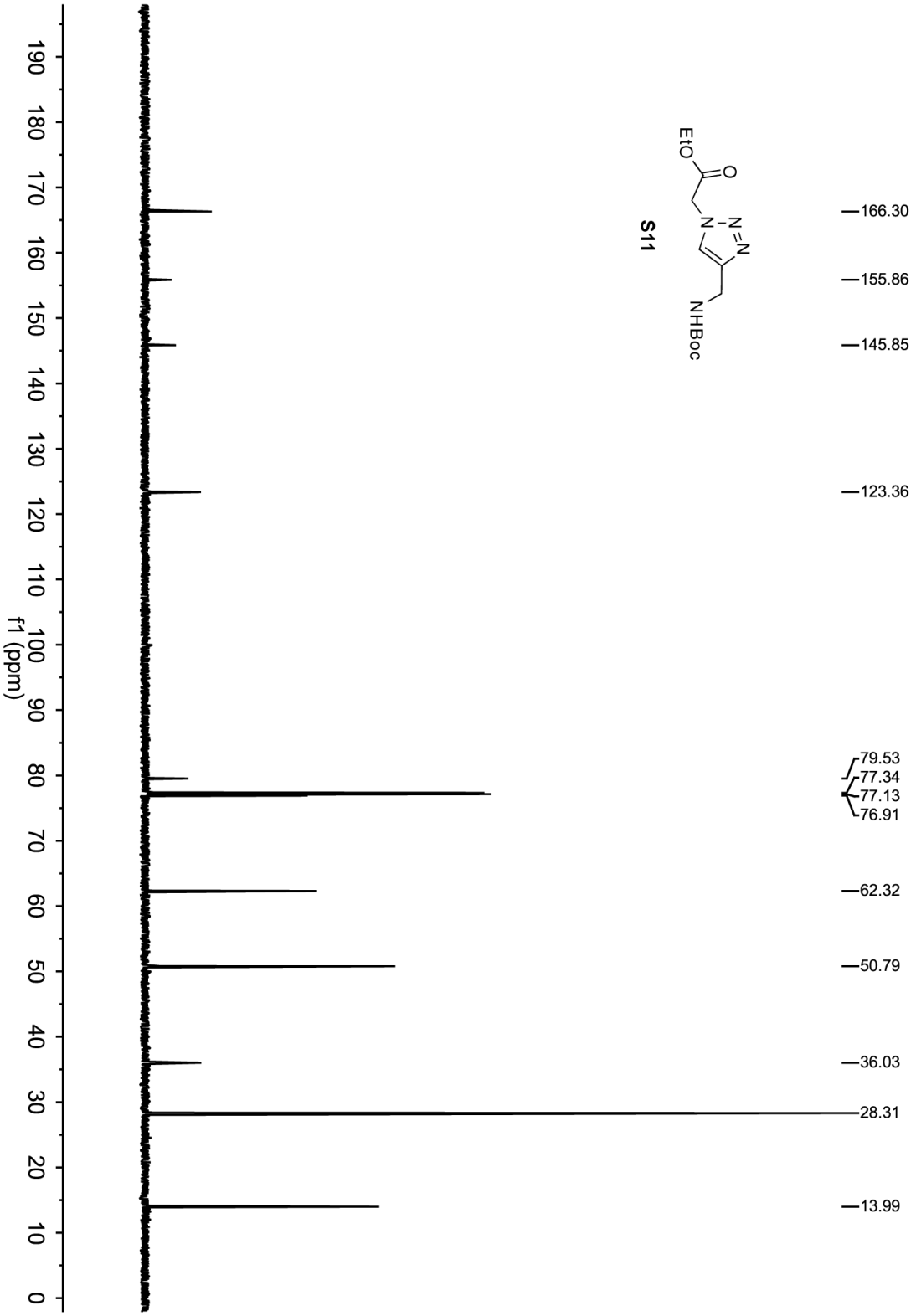

S2
OH
79.52
77.48
77.23
76.98
29.01
15.87
14.89
f1 (ppm)

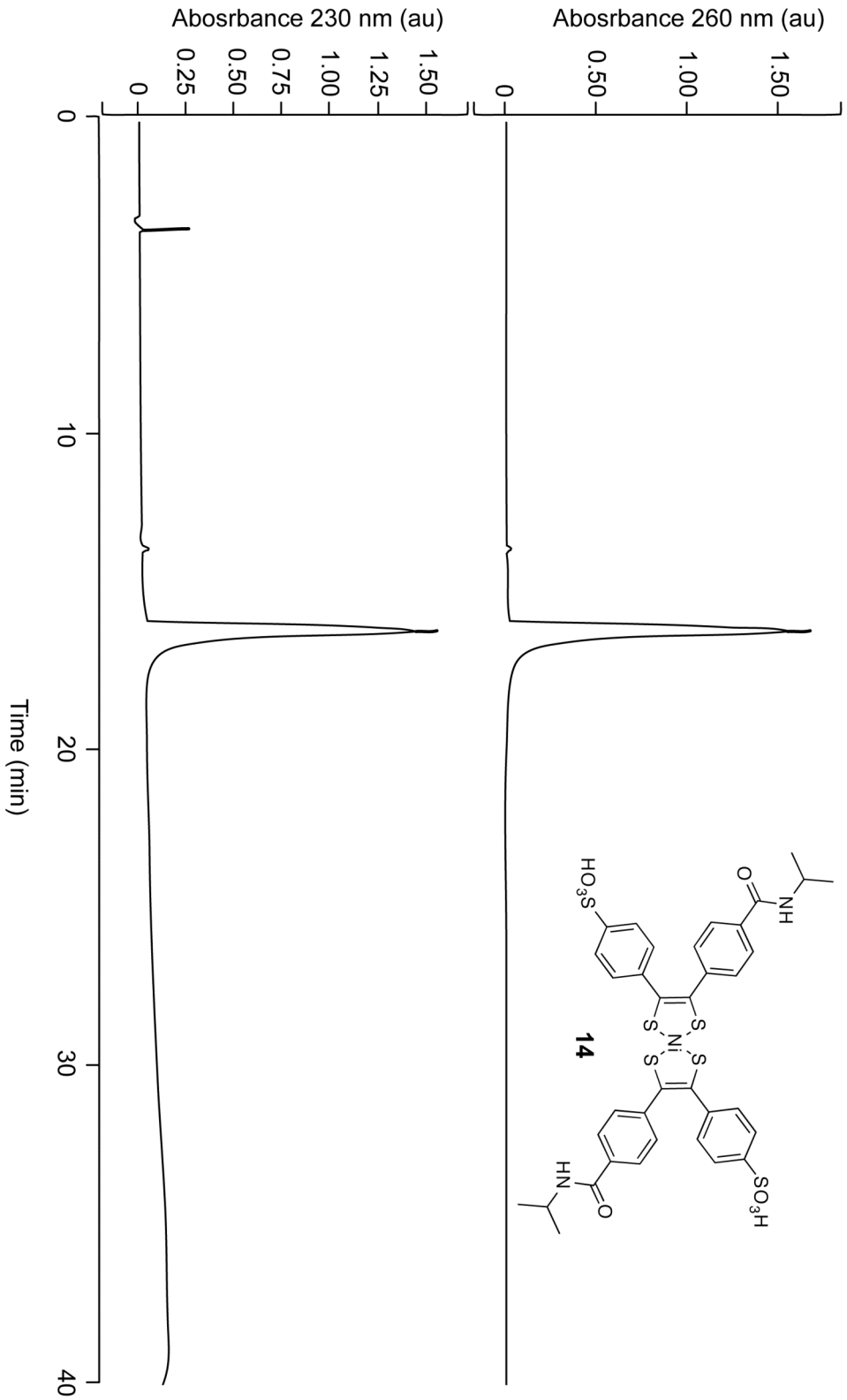

f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
EtO
O
N
N
N
NH3
O
O
CF3
S3
168.55
161.70
161.45
161.19
160.94
141.49
127.42
118.15
116.25
63.54
51.99
49.58
49.43
49.29
49.15
49.01
48.86
48.72
35.57
14.37

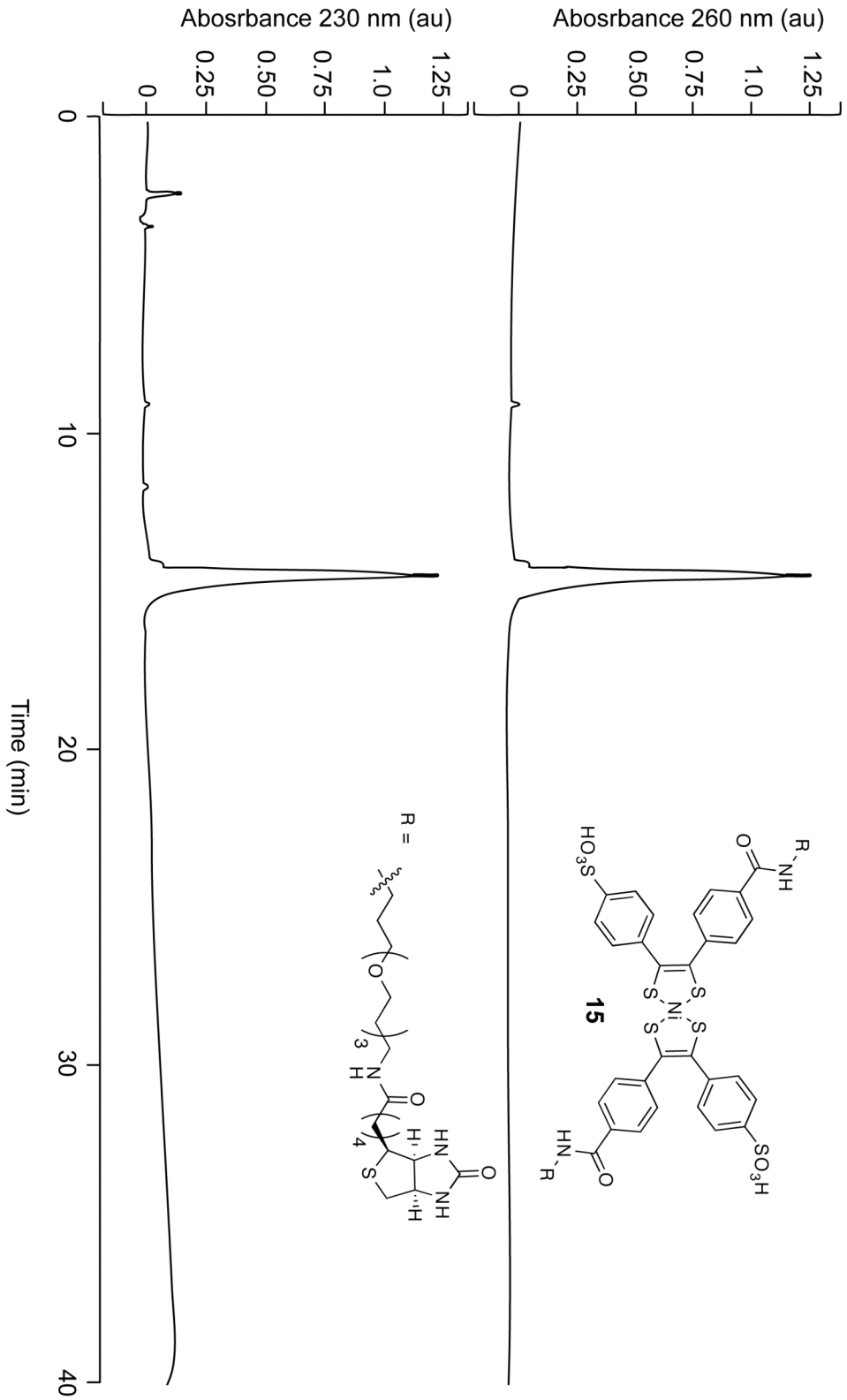

f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
EtO
O
N
N
N
H
N
O
O
S4
166.42
157.13
145.83
123.66
83.11
77.55
77.23
76.91
62.65
51.06
36.64
26.03
16.08
14.84
14.25

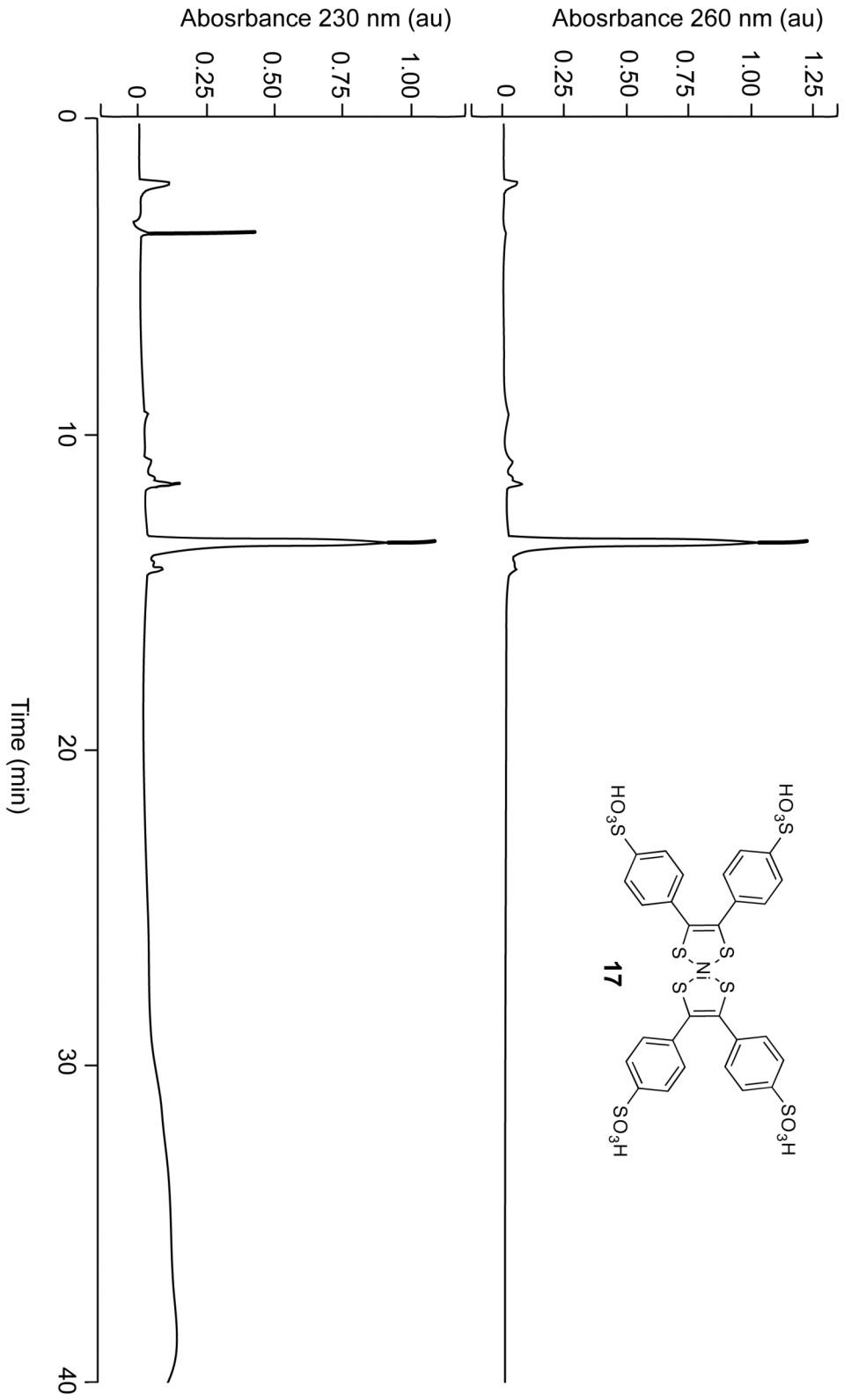

S6
190.70
131.80
129.63
128.93
128.89
128.78
77.55
77.23
76.91
f1 (ppm)

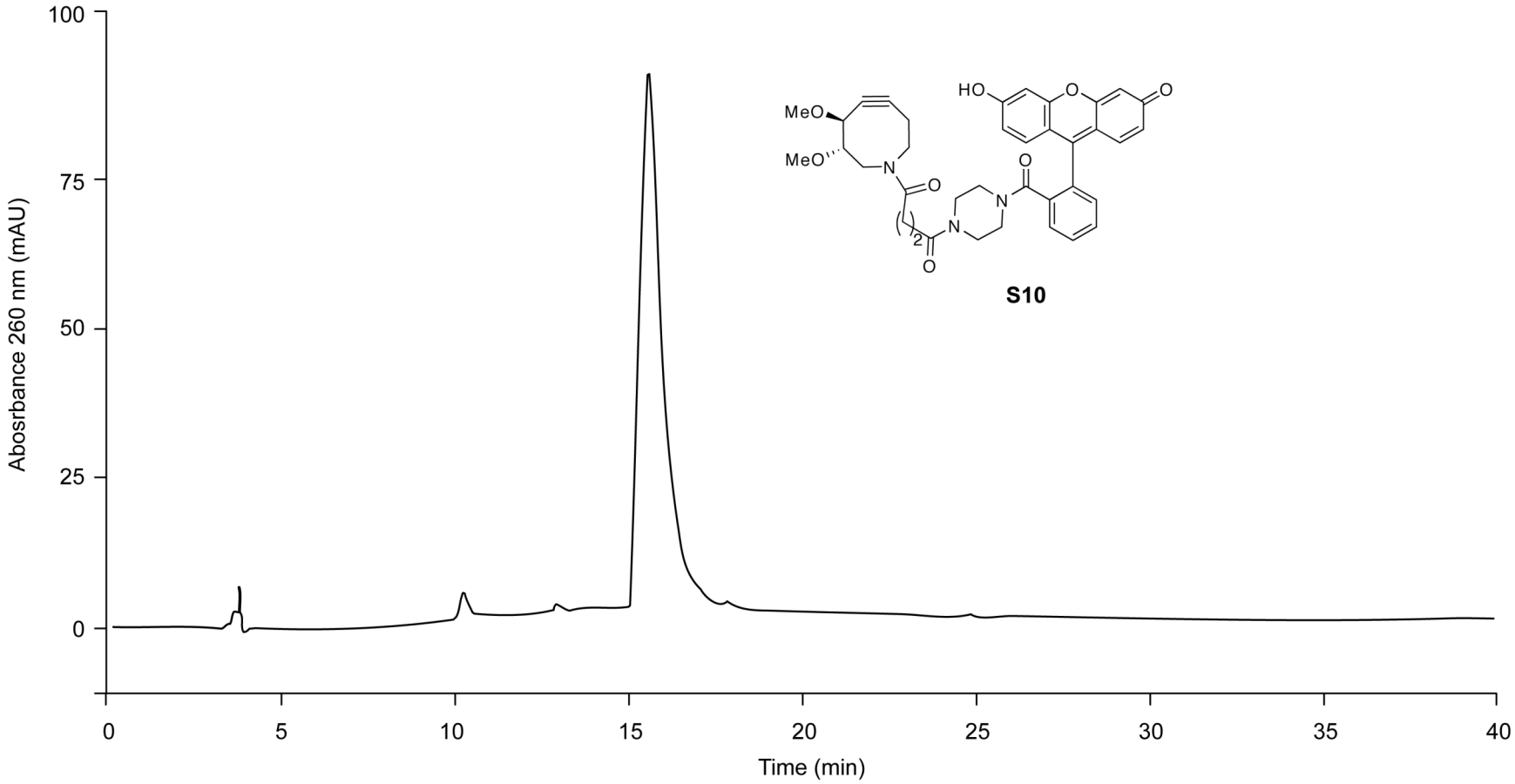

191.02
147.14
134.60
130.81
130.07
127.79
S7
HO3S
SO3H
S
S
O
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


S11
EtO
O
N
N
N
NHBoc
166.30
155.86
145.85
123.36
79.53
77.34
77.13
76.91
62.32
50.79
36.03
28.31
13.99
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

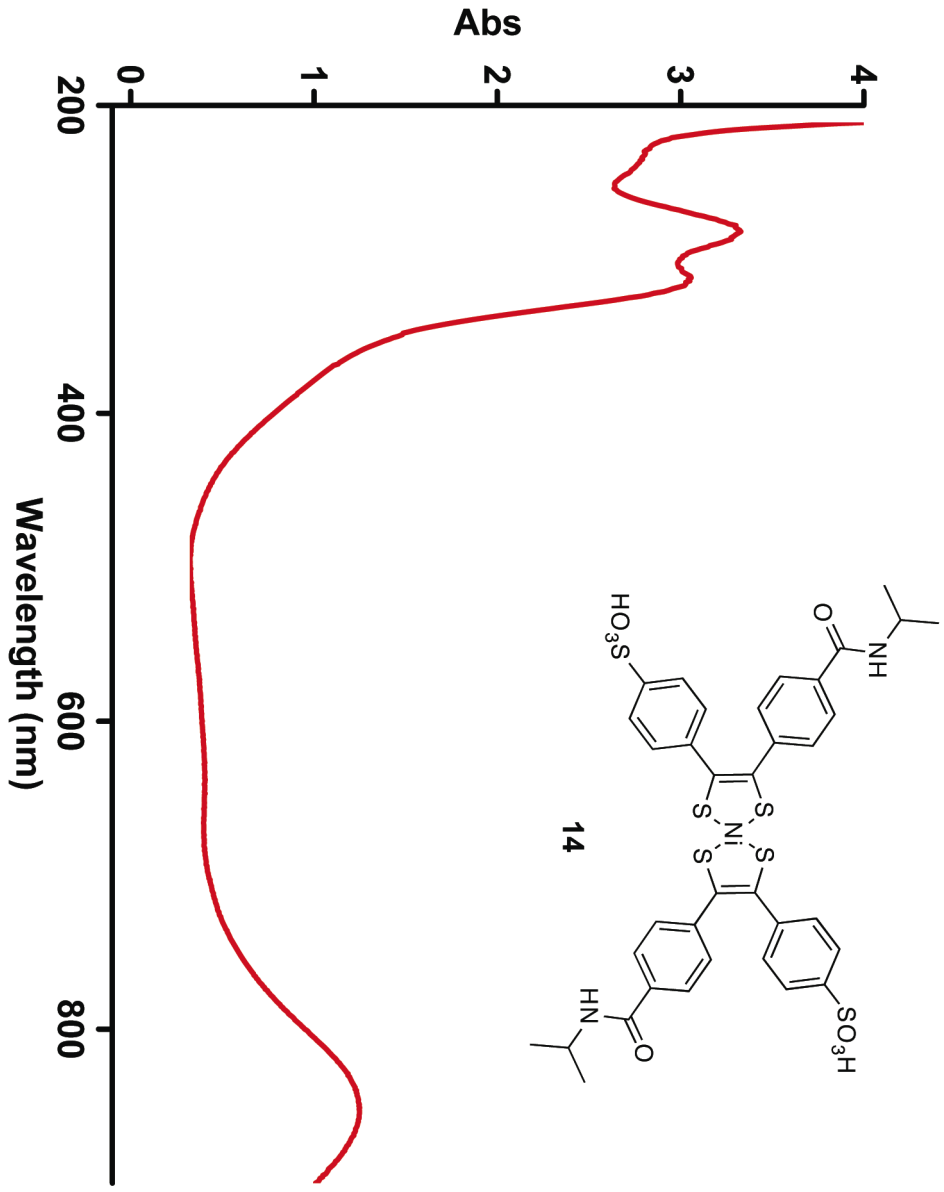

Abosrbance 230 nm (au)
0
0.25
0.50
0.75
1.00
1.25
1.50
Abosrbance 260 nm (au)
0
0.50
1.00
1.50
0
10
20
30
40
Time (min)
14
HO3S
NH
O
S
Ni
S
S
S
HN
O
SO3H

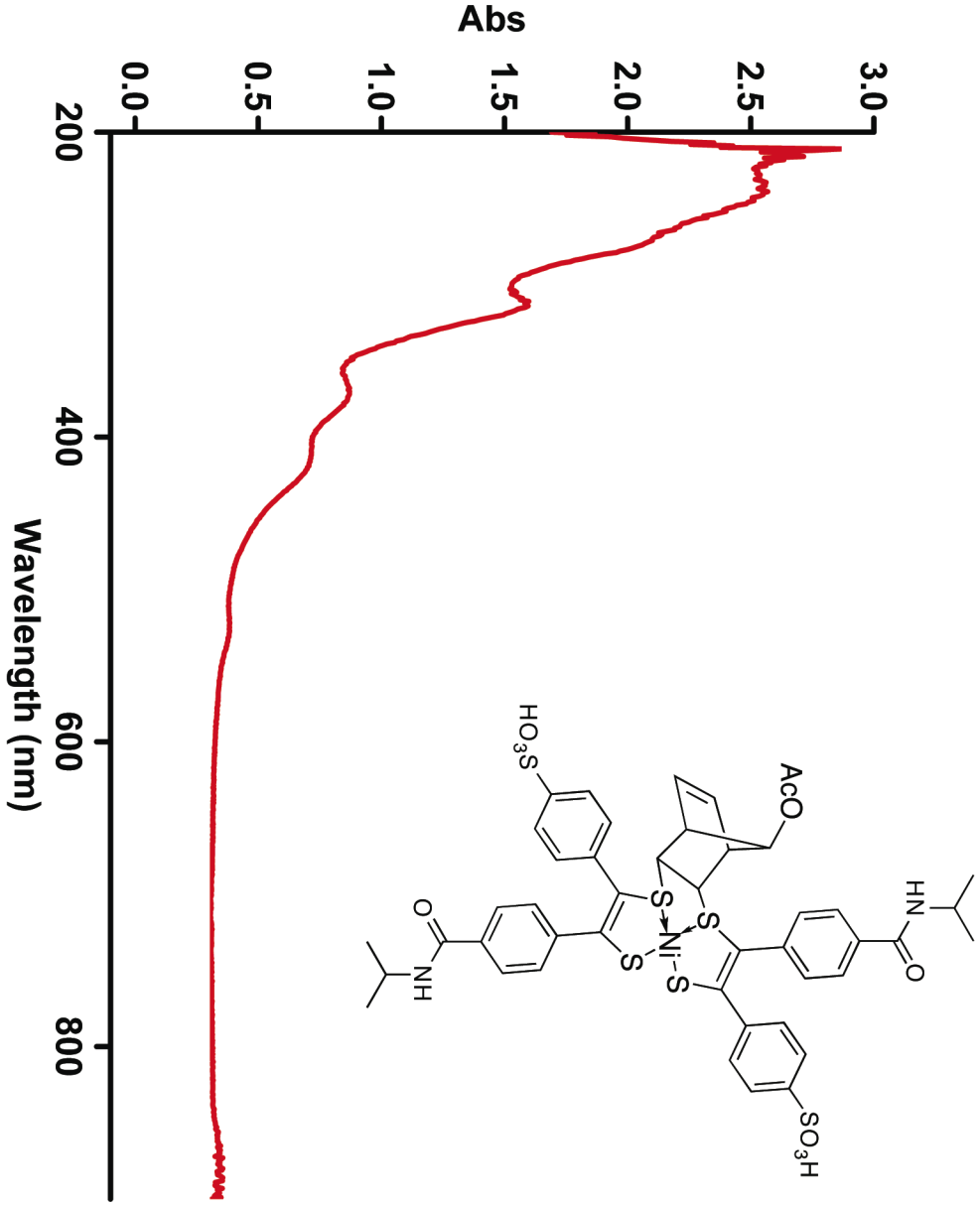

Abosrbance 230 nm (au)
Abosrbance 260 nm (au)
0
0.25
0.50
0.75
1.0
1.25
0
10
20
30
40
Time (min)
15
R =

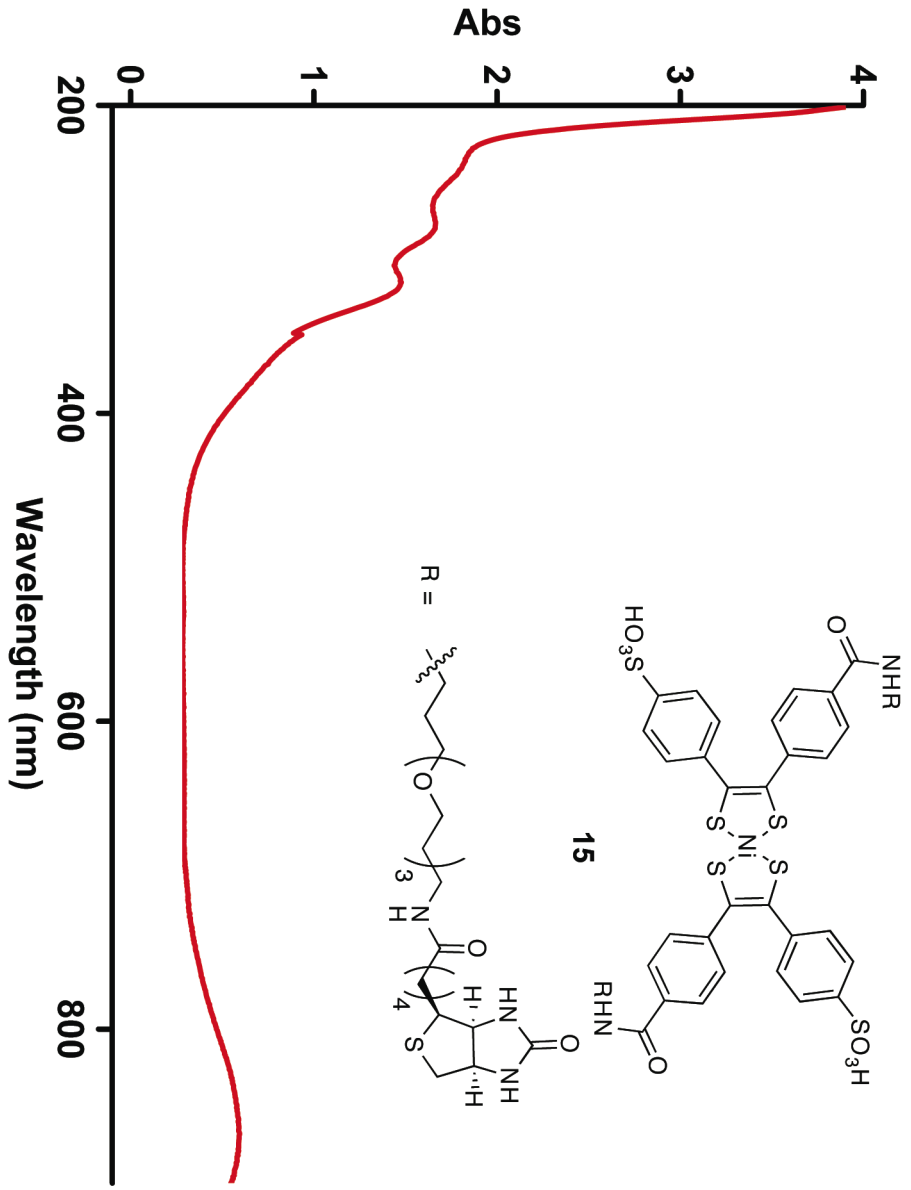

Abosrbance 230 nm (au)
Abosrbance 260 nm (au)
0
0.25
0.50
0.75
1.00
1.25
0
10
20
30
40
Time (min)
HO3S
SO3H
Ni
S
17

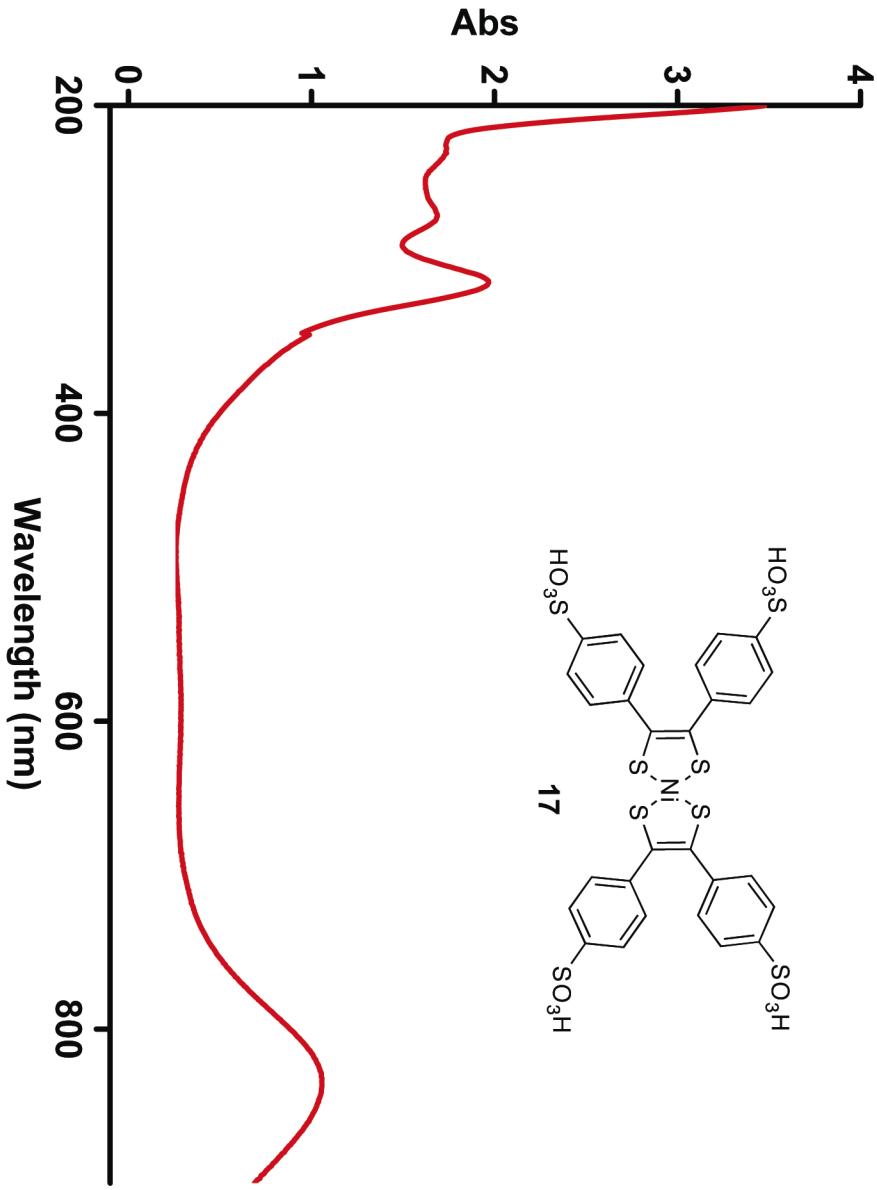

100
75
50
25
0
Abosrbance 260 nm (mAU)
0
5
10
15
20
25
30
35
40
Time (min)
MeO
MeO
N
O
2
O
N
N
O
O
HO
O
O

S10


Abs
0
1
2
3
4
200
400
600
800
Wavelength (nm)
HO3S
NH
O
S
S
Ni
S
S
HN
O
SO3H
14


Abs
0.0
0.5
1.0
1.5
2.0
2.5
3.0
200
400
600
800
Wavelength (nm)
HO3S
AcO
HN
O
NH
O
S
S
Ni
S
S
SO3H


Abs
0
1
2
3
4
200
400
600
800
Wavelength (nm)
15
R =
NHR
RHN
HO_3S
SO_3H
Ni
S
O
N
H
HN
NH


Abs
0
1
2
3
4
200
400
600
800
Wavelength (nm)
HO3S
HO3S
S
S
Ni
S
S
SO3H
SO3H

17