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Supporting Information

# Modelling the Inhibition of Selenoproteins by Small Molecules Using Cysteine and Selenocysteine Derivatives

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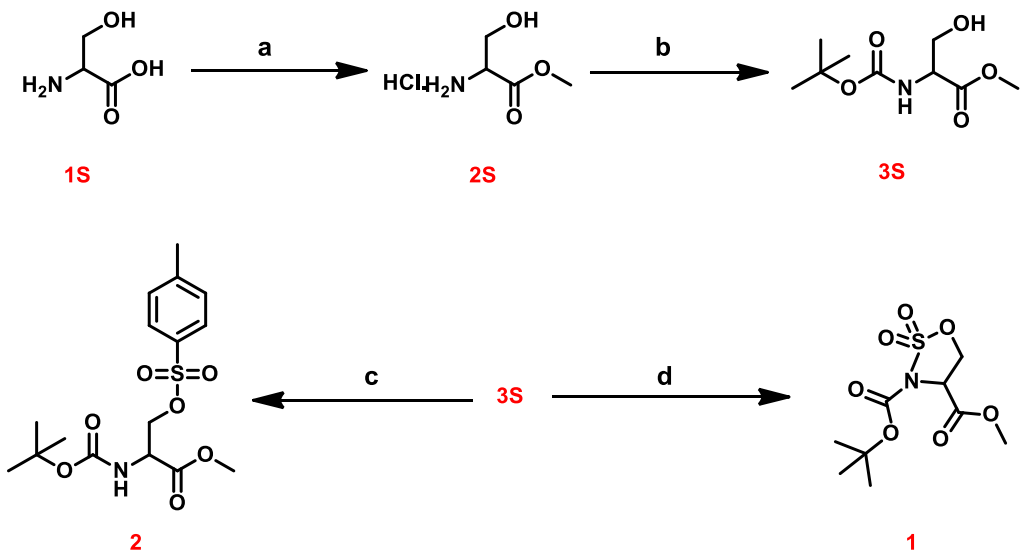
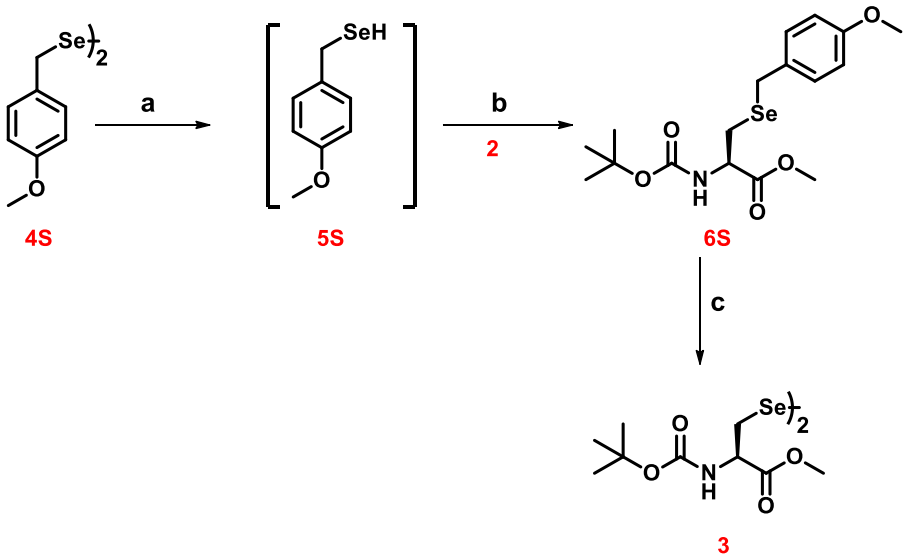



**Scheme S1**. Synthetic route to starting materials **1** and **2** used for the synthesis of aryl cysteine and selenocysteine derivatives. a) $SOCl_2$, MeOH, reflux, 4 h, b) Boc anhydride, aqu., $NaHCO_3$, Dioxane, 27 °C, c) TsCl, Pyridine, 27 °C, d) i) $SOCl_2$, pyridine, dry ACN, -40 °C, 3 h, ii) $NaIO_4$, $RuCl_3$. $3H_2O$, ACN, $H_2O$, 0 °C, 2 h.

Compound **1**[1]: $^1$H NMR ($CDCl_3$), δ (ppm): 1.55 (s, 9H), 3.86 (s, 1H), 4.68-4.71 (d, 1H), 4.77-4.83 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$), δ (ppm): 28.15, 53.91, 58.00, 68.18, 86.49, 148.45, 168.01.

Compound **2**[2]: $^1$H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.42 (s, 9H), 2.45 (s, 3H), 3.70 (s,3H),4.29 (dd, 1H), 4.40 (dd, 1H), 4.51 (dt, 1H),5.32 (d, 1H),7.36 (d, 2H),7.76 (d, 2H); $^{13}$C-NMR (100MHz, $CDCl_3$): 21.6, 28.2, 52.85, 52.90, 69.5, 80.4, 128.0, 129.9, 132.3, 145.1, 154.9, 168.9.




**Scheme S2**. Synthetic route to protected selenocystine(**3**) starting from *p*Mob diselenide and o-tosyl serine (**2**). a) $NaBH_4$, DMF, b) compound **2** in DMF, c) $I_2$ in MeOH & $H_2O$.

Compound **3**[3]:$^{1}$H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.43 (s, 9H), 3.35-3.39 (m, 2H), 3.75 (s, 3H), 4.58-4.63 (m, 1H), 5.38-5.40 (bd, 1H); $^{13}$C-NMR (100MHz, $CDCl_3$): 28.77, 32.81, 53.05, 54.14, 80.72, 155.48, 171.73; $^{77}$Se NMR (76.29 MHz, $CDCl_3$), δ (ppm): 295.8.

All these values are matching with literature values.

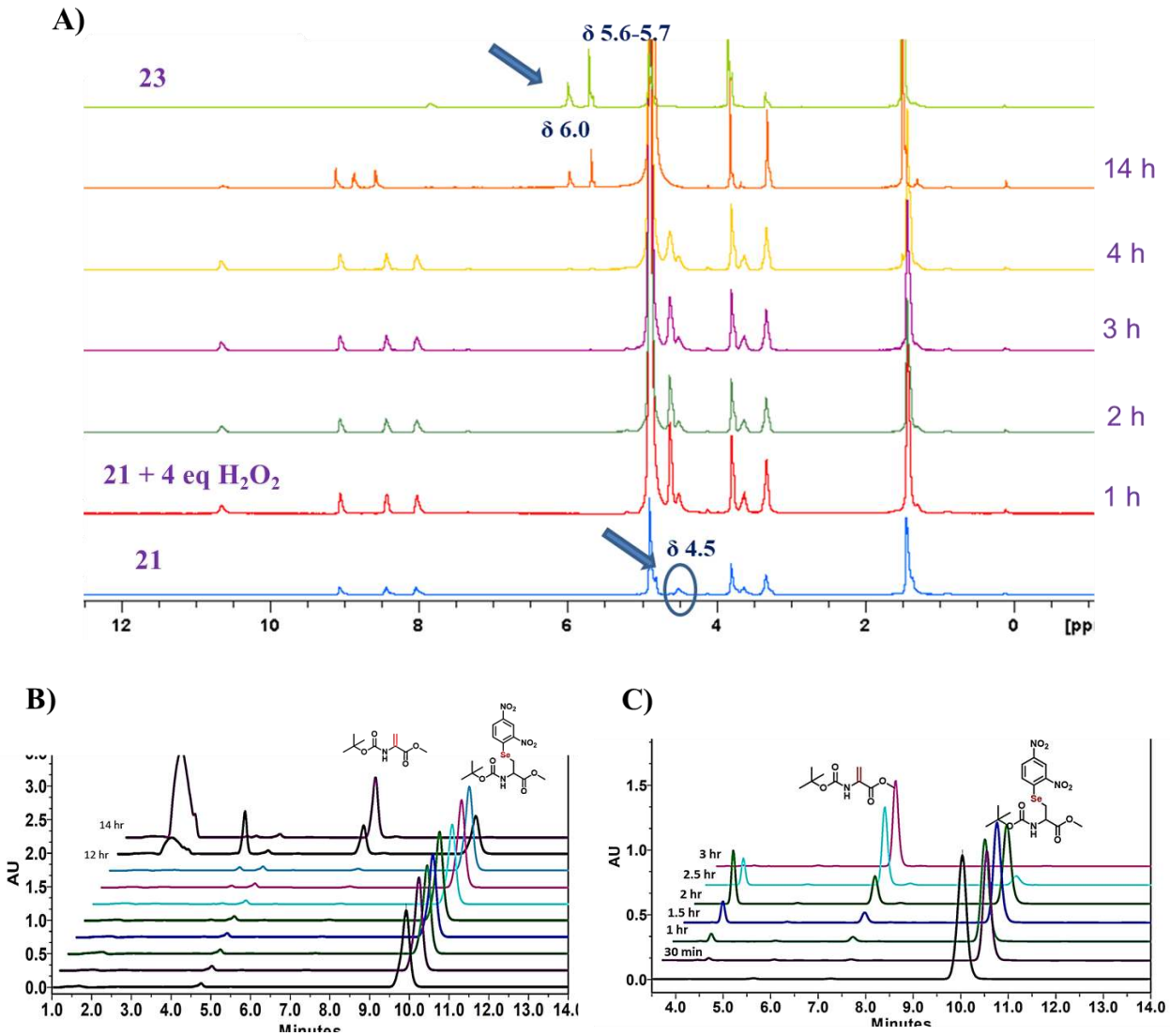
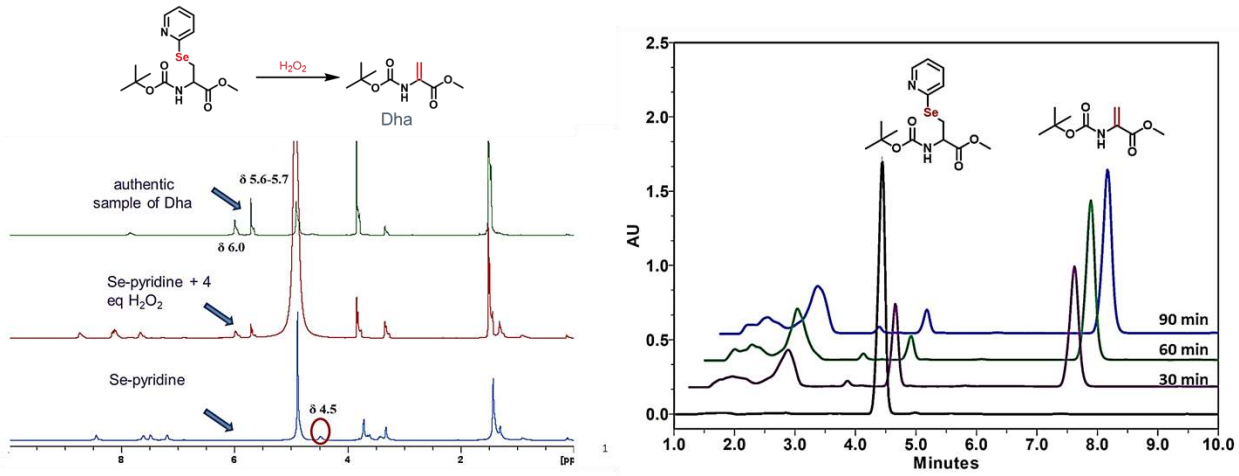



**Figure S1.** A) $^{1}$H NMR spectrum of **21** after incubating with $H_2O_2$ and its comparison with authentic sample of **23**. B) HPLC chromatogram obtained for the reaction of **21** with 4 equiv. of $H_2O_2$. C) HPLC chromatogram obtained for the reaction of **21** with 10 equiv., of $H_2O_2$.

A)

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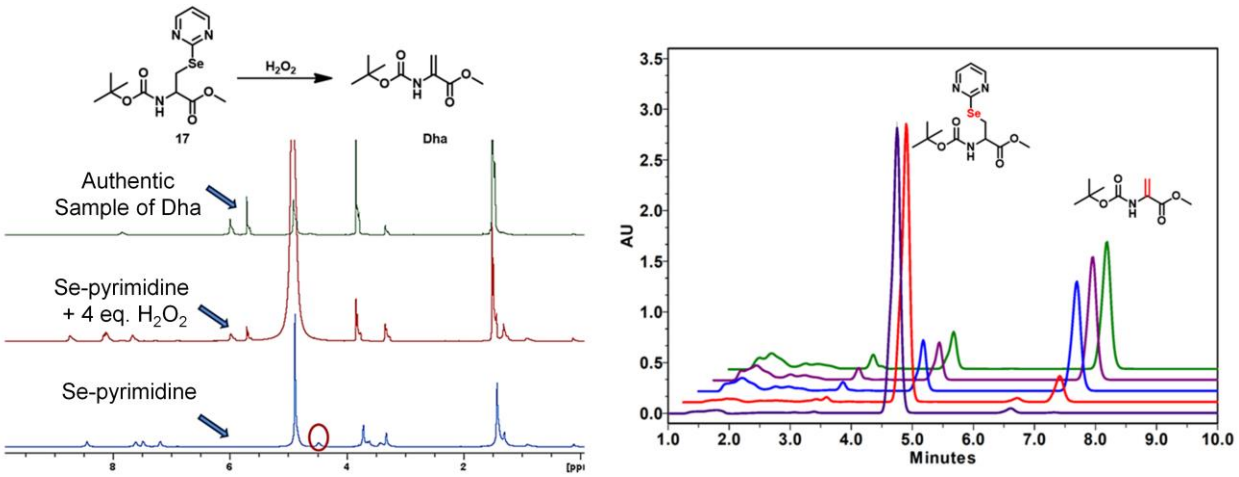


**Figure S2.** A) $^1$H NMR spectrum of **17** after incubating with $H_2O_2$ and HPLC chromatogram obtained for the reaction of **17** with 4 equiv. of $H_2O_2$ indicating the formation of Dha. B) $^1$H NMR spectrum of **18** after incubating with $H_2O_2$ and HPLC chromatogram obtained for the reaction of **18** with 4 equiv., of $H_2O_2$, indicating the formation of Dha.

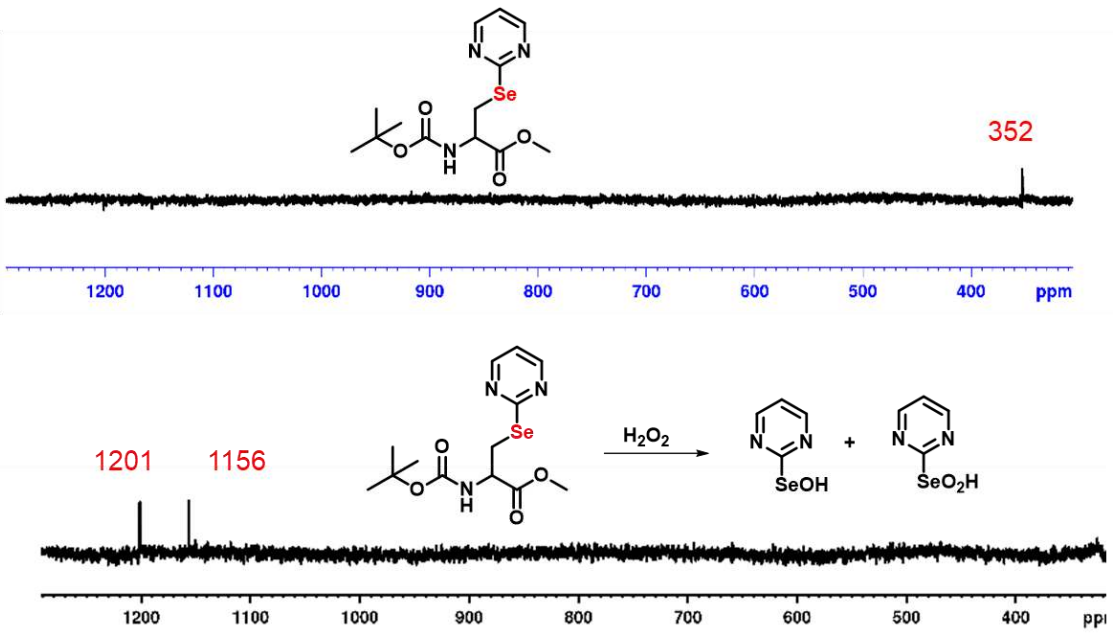


**Figure S3.** $^{77}$Se spectrum obtained for the reaction of **18** with $H_2O_2$, indicating the generation of selenenic acid **31** and seleninic acid **43**.

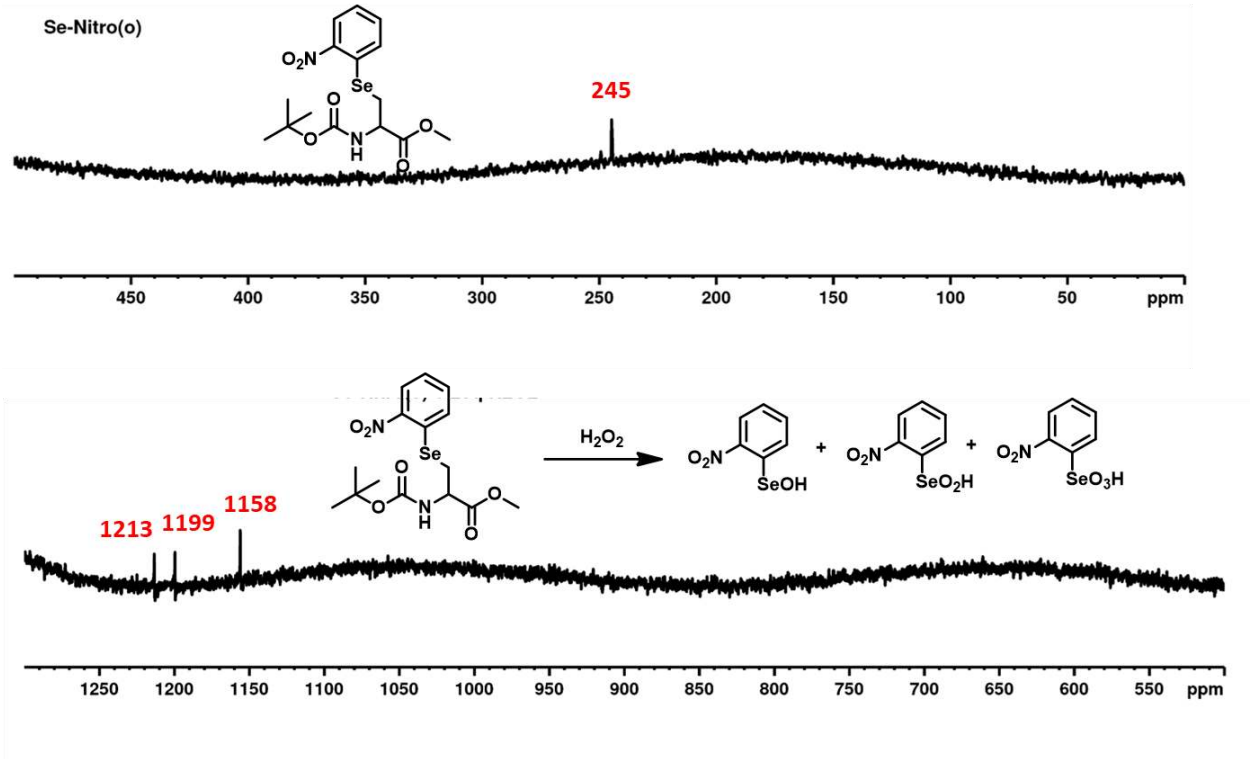


**Figure S4.** $^{77}$Se spectrum obtained for the reaction of **19** with $H_2O_2$, indicating the generation of selenenic acid **32**, seleninic acid **44** and selenonic acid **50**.

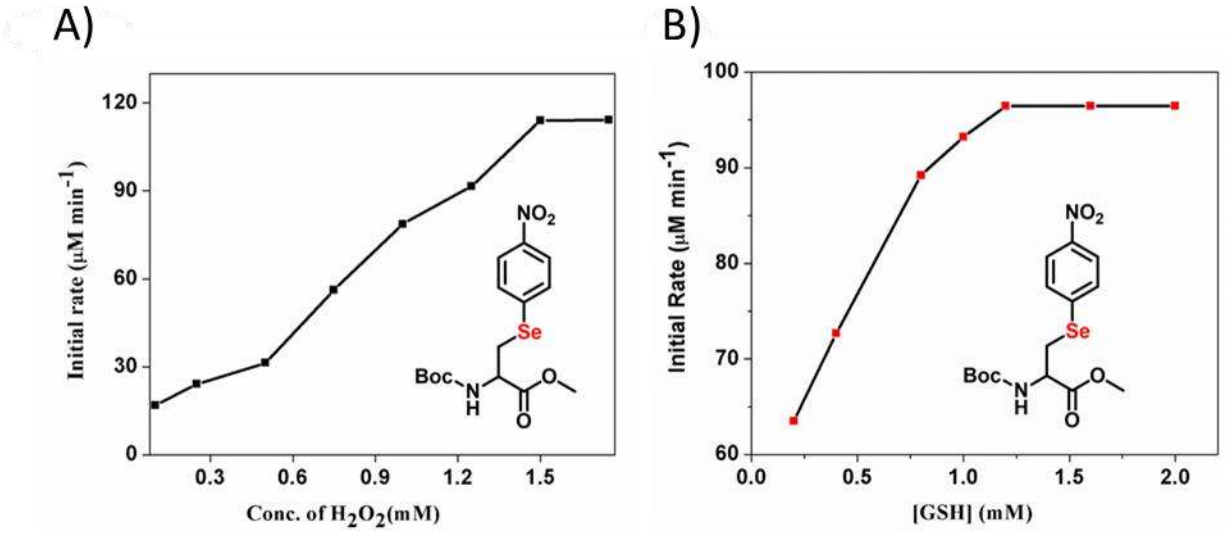


**Figure S5.** (A) Effect of hydrogen peroxide concentration on the initial rate for compound **20**. Phosphate buffer, 2mM GSH, 0.4 mM of NADPH, 1.74 U GR, 0.1 mM of compound and 0.1 mM to 1.5 mM of $H_2O_2$. (B) Effect of GSH concentration on the initial rate for compound **20**. Phosphate buffer, 0.2 mM to 2 mM GSH, 0.4 mM of NADPH, 1.74 U GR, 0.1 mM of compound and 1.5 mM of $H_2O_2$.

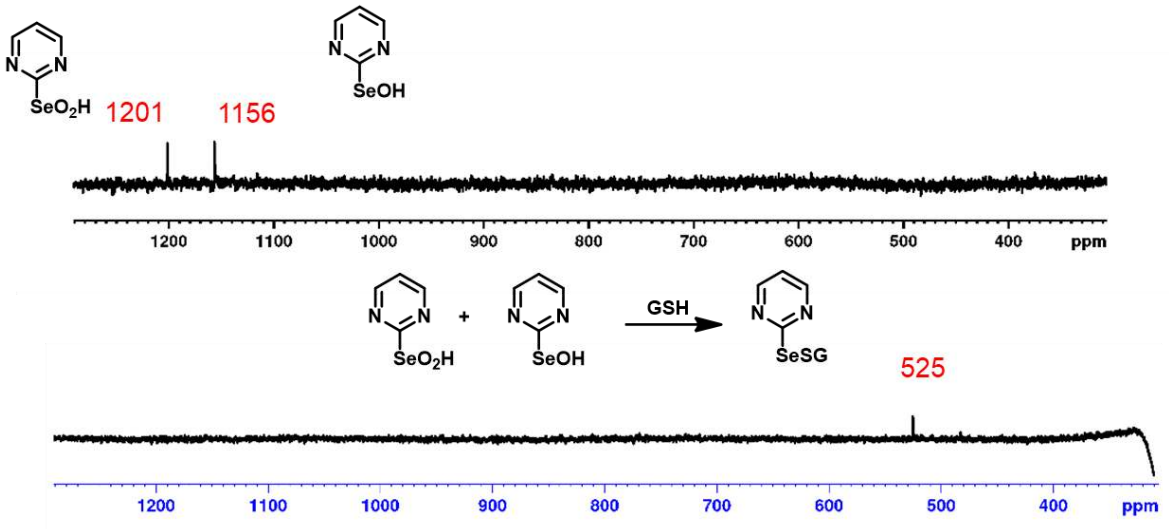


**Figure S6.** $^{77}$Se spectrum obtained for the reaction of **18** with $H_2O_2$, indicating the generation of selenenic acid **31** and seleninic acid **43**. The subsequent reaction with GSH to produces the selenenyl sulphide **54**.

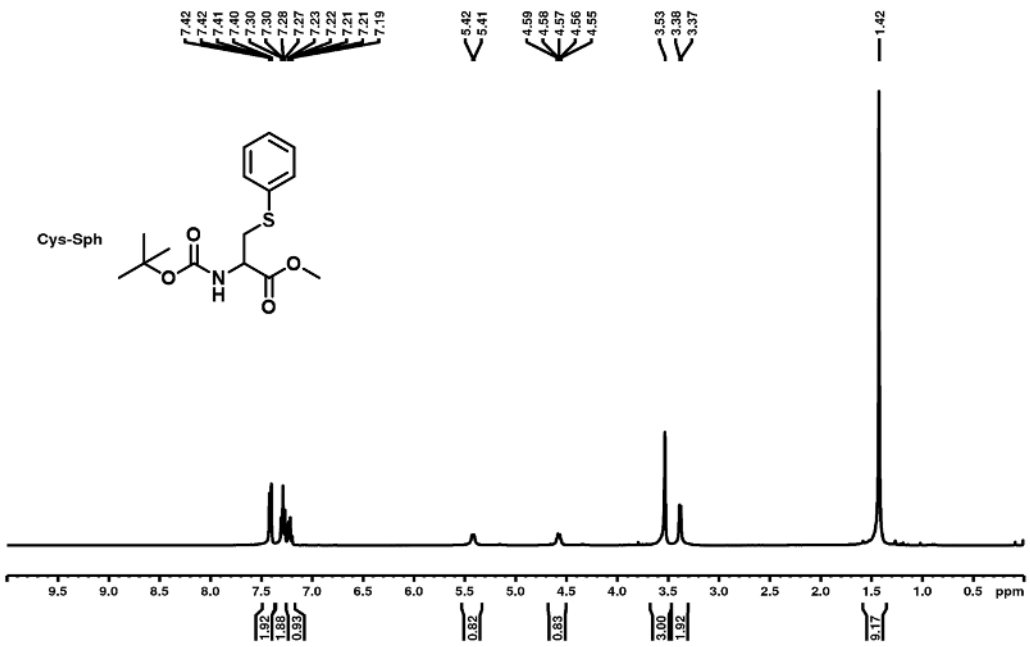


**Figure S7.** $^{1}H$ NMR spectrum (400 MHz, $CDCl_3$) of compound **7**.

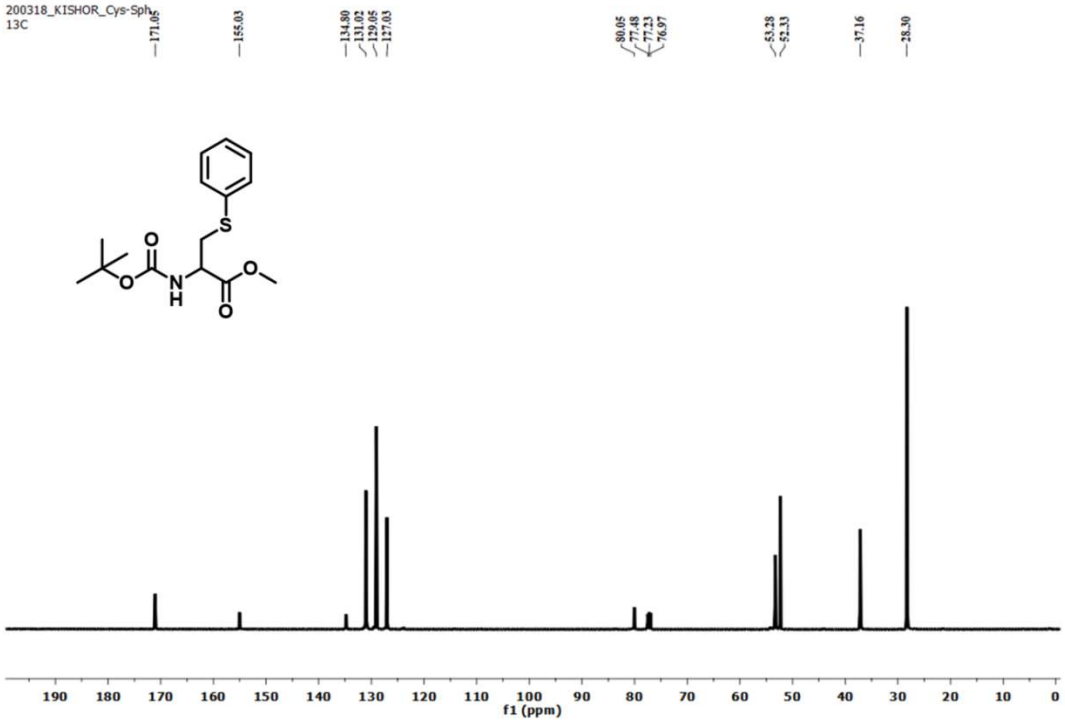


**Figure S8.** $^{13}C$ NMR spectrum (100.56 MHz, $CDCl_3$) of compound **7**.

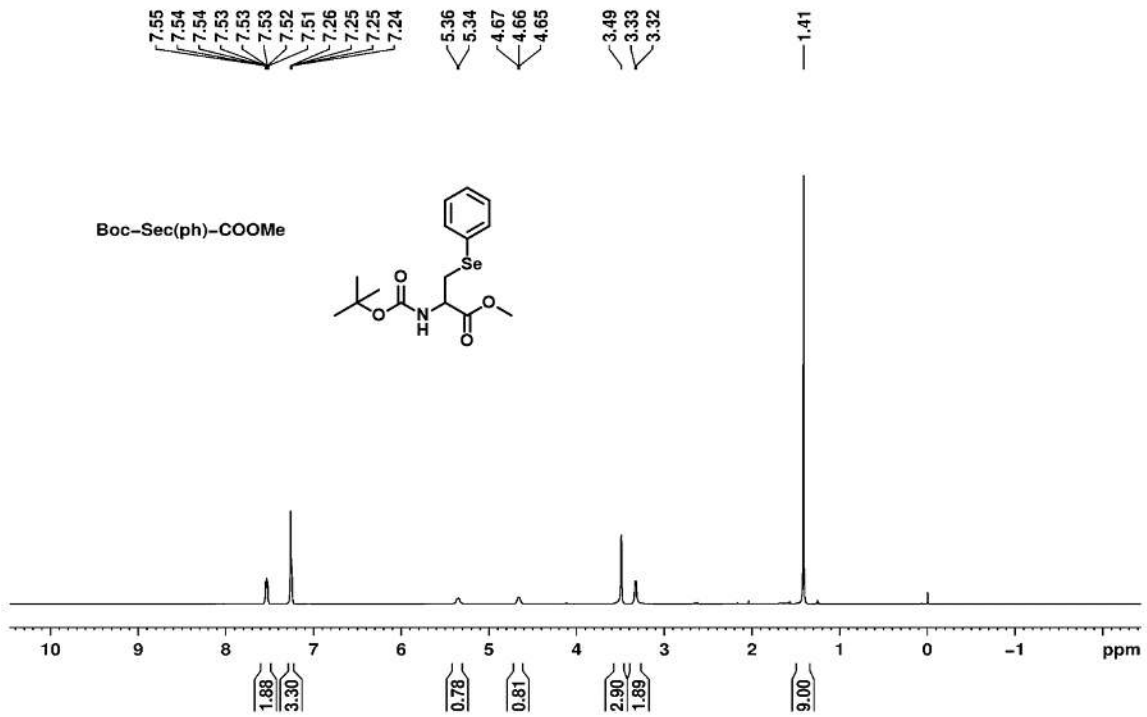


**Figure S9.** $^{1}H$ NMR spectrum (400 MHz, $CDCl_3$) of compound **22**.

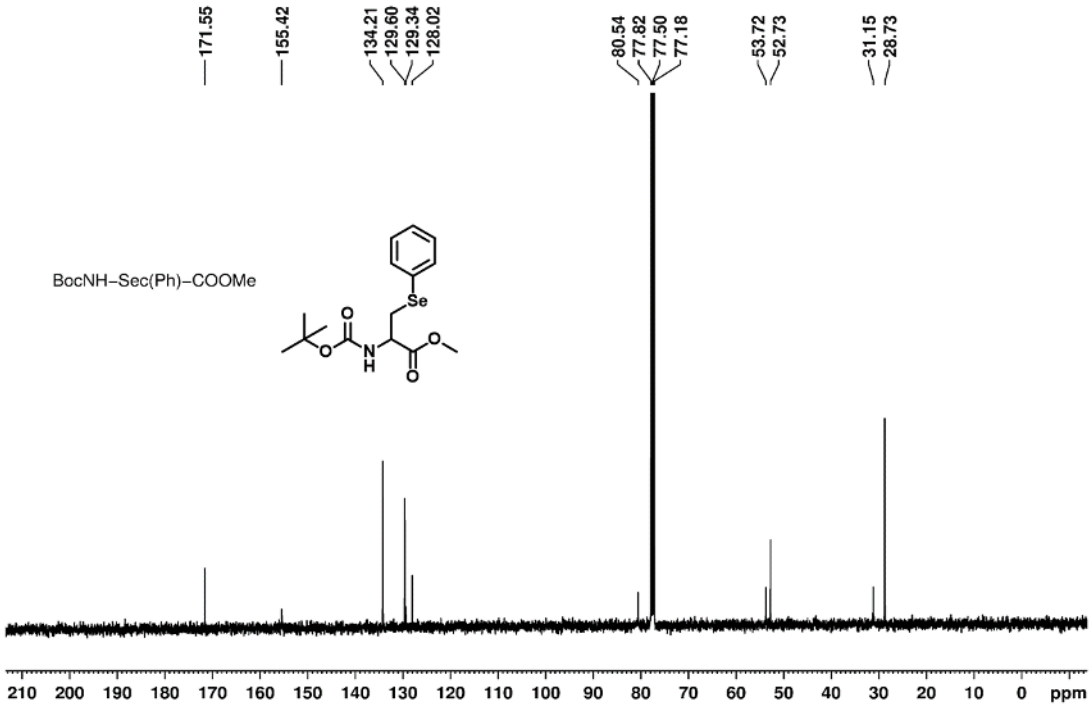


**Figure S10.** $^{13}C$ NMR spectrum (100.56 MHz, $CDCl_3$) of compound **22**.

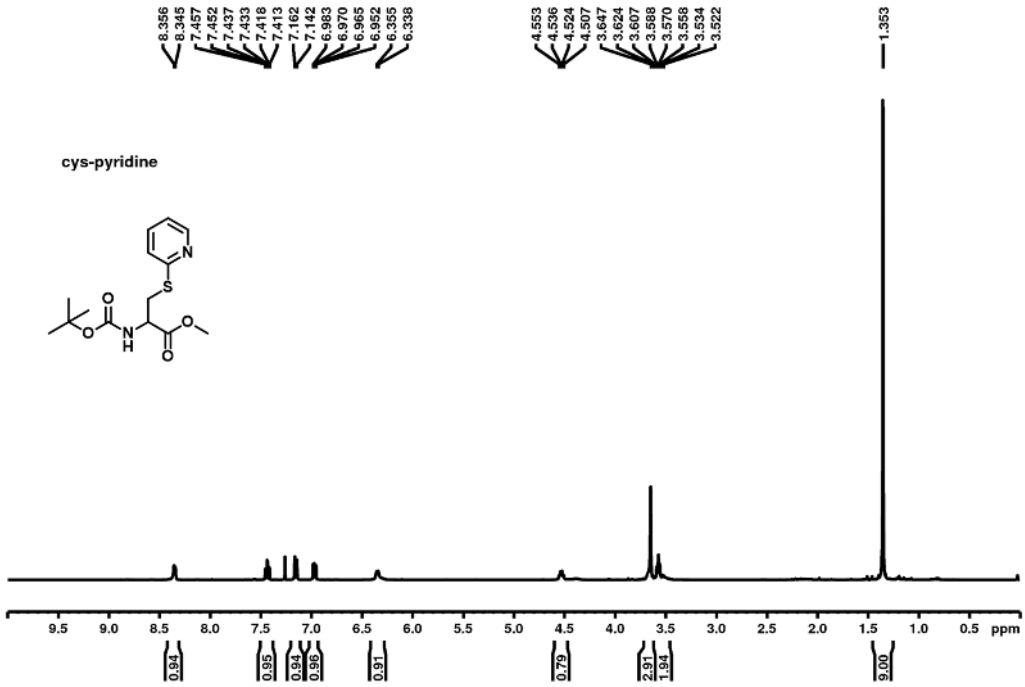


**Figure S11.** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound **8**.

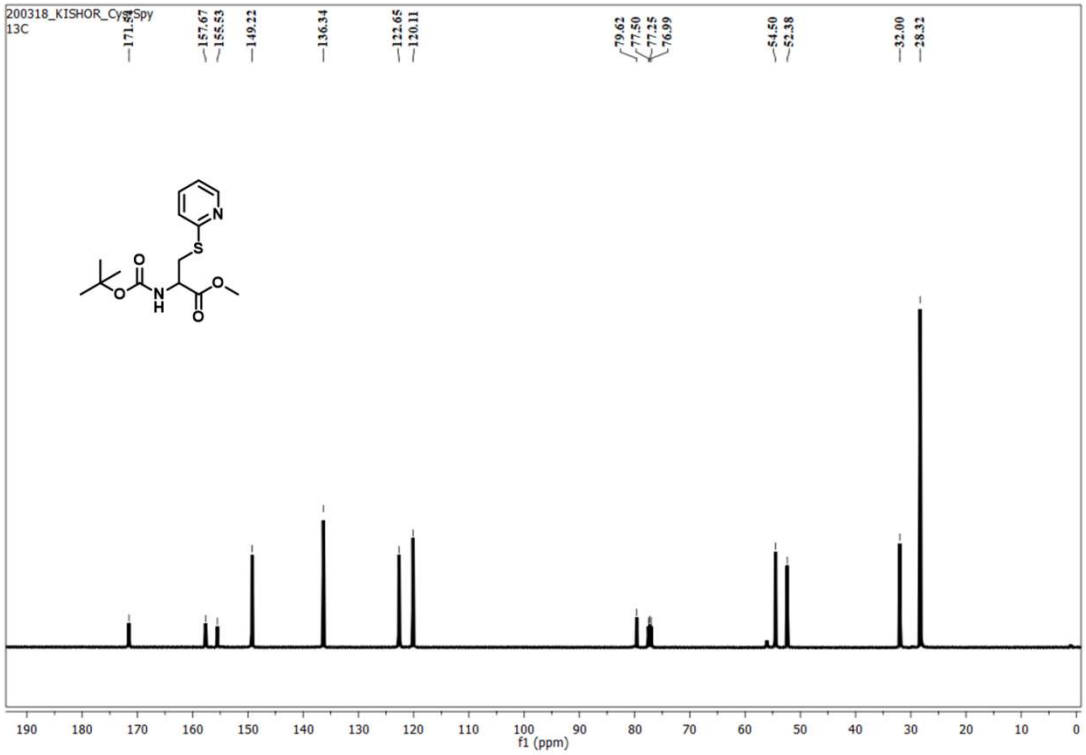


**Figure S12**. $^{13}$C NMR spectrum (100.56 MHz, $CDCl_3$) of compound **8**.

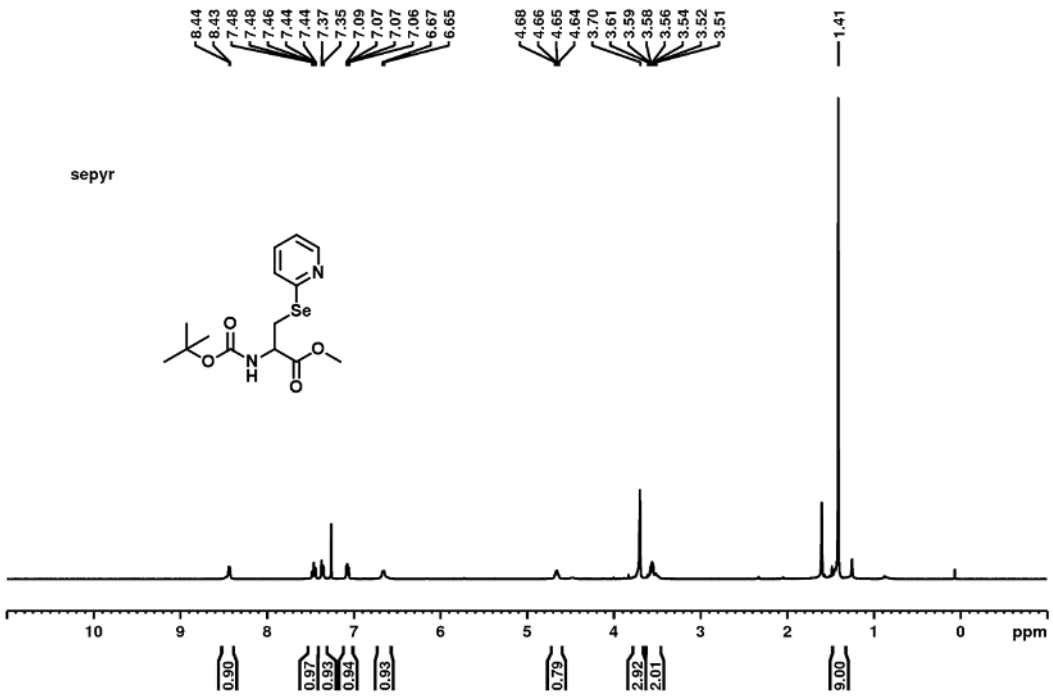


**Figure S13.** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound **17**.

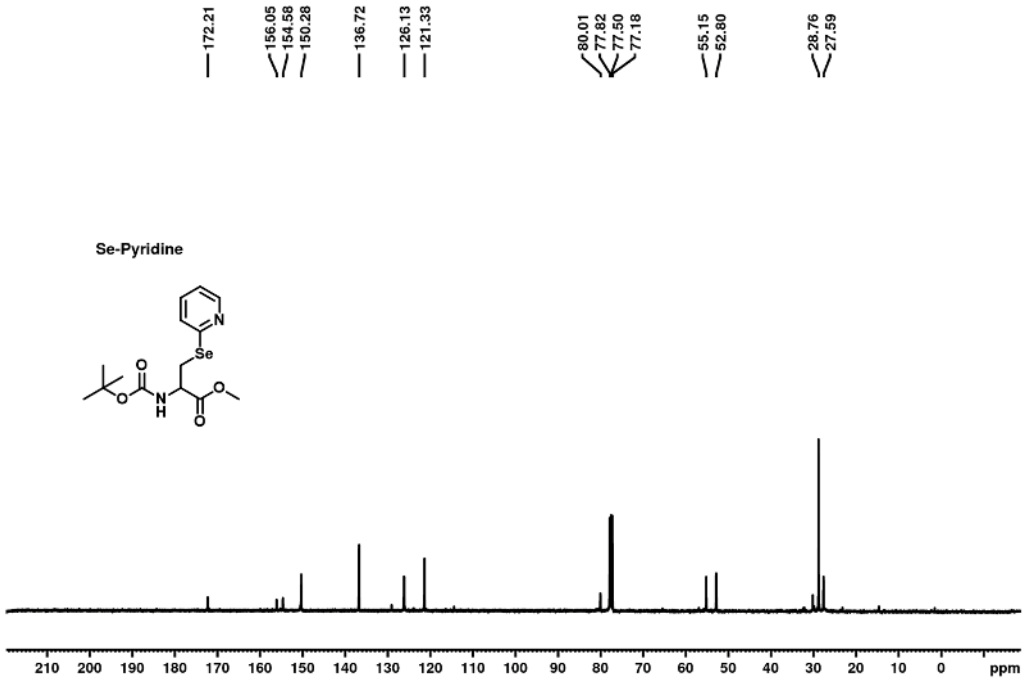


**Figure S14.** $^{13}$H NMR spectrum (100.56 MHz, $CDCl_3$) of compound **17**.

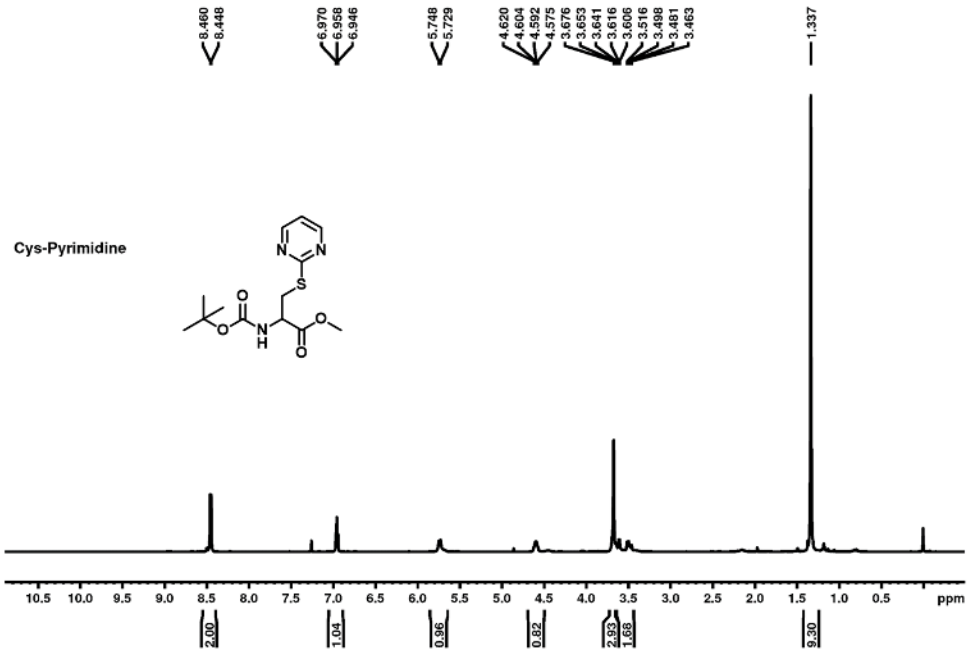


**Figure S15.** $^{1}H$ NMR spectrum (400 MHz, $CDCl_3$) of compound **9**.

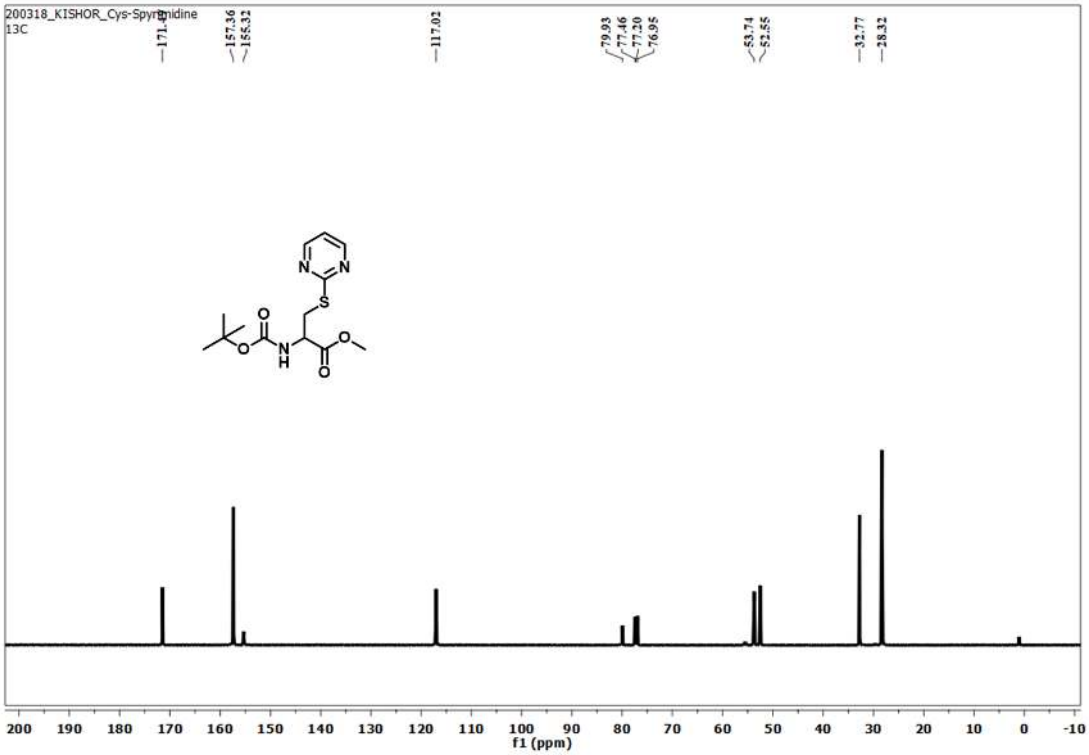


**Figure S16.** $^{13}C$ NMR spectrum (100.56 MHz, $CDCl_3$) of compound **9.**

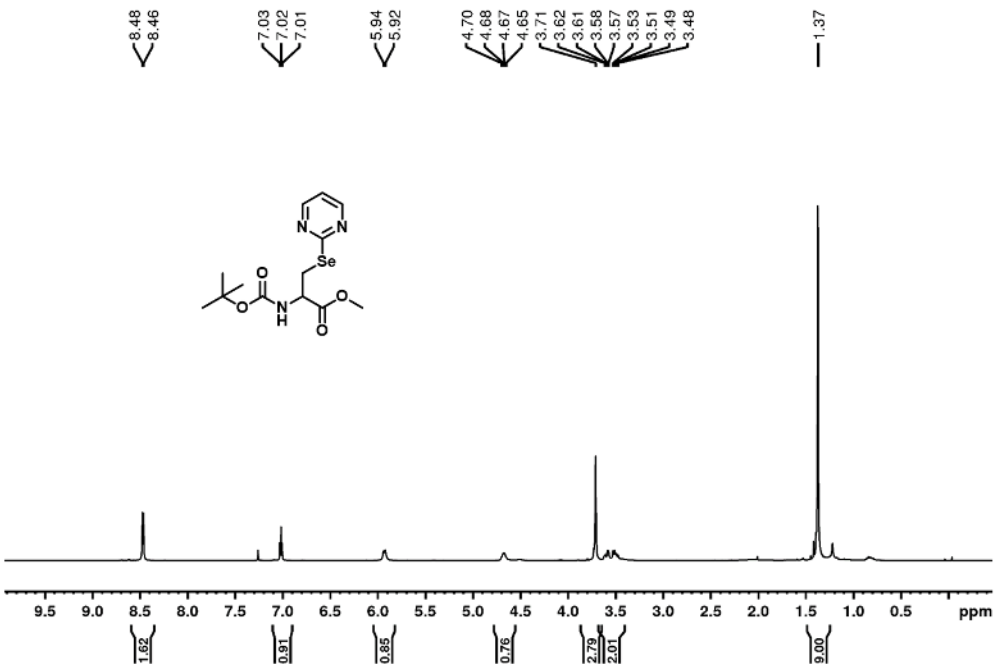


**Figure S17.** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound **18.**

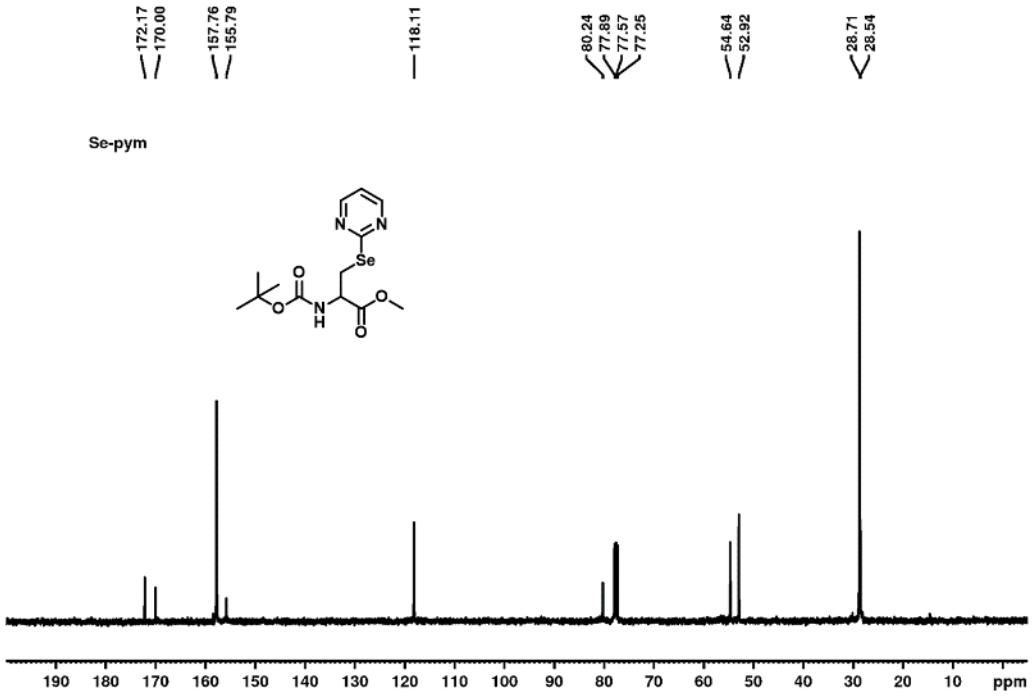


**Figure S18.** $^{13}$C NMR spectrum (100.56 MHz, $CDCl_3$) of compound **18.**

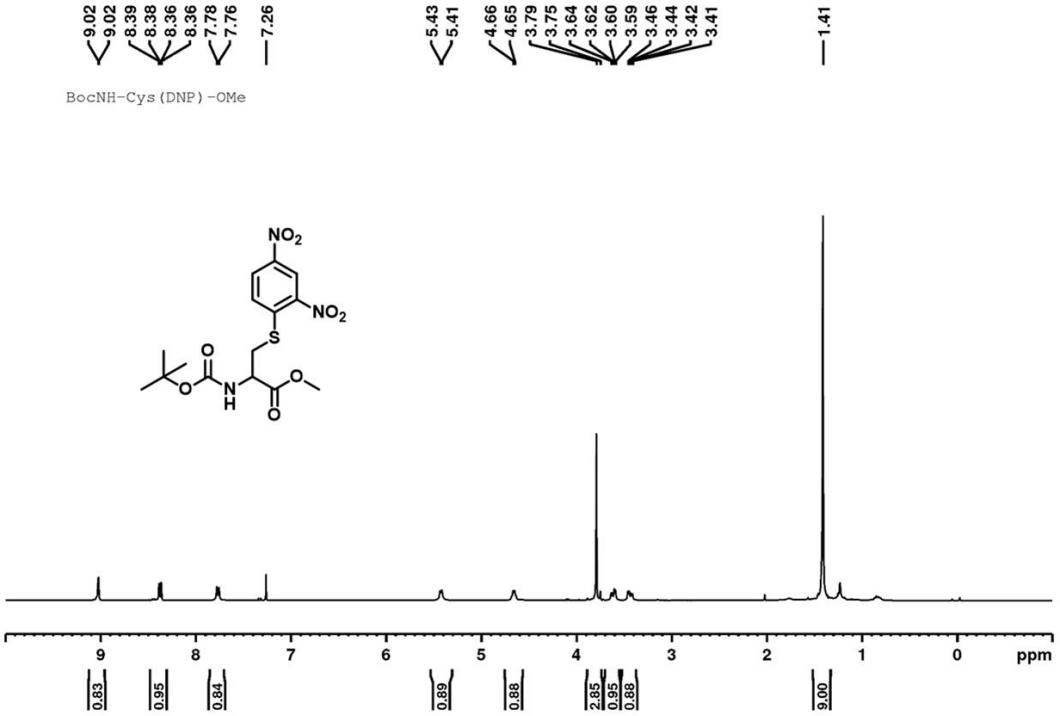


**Figure S19.** $^{1}H$ NMR spectrum (400 MHz, $CDCl_3$) of compound **11.**

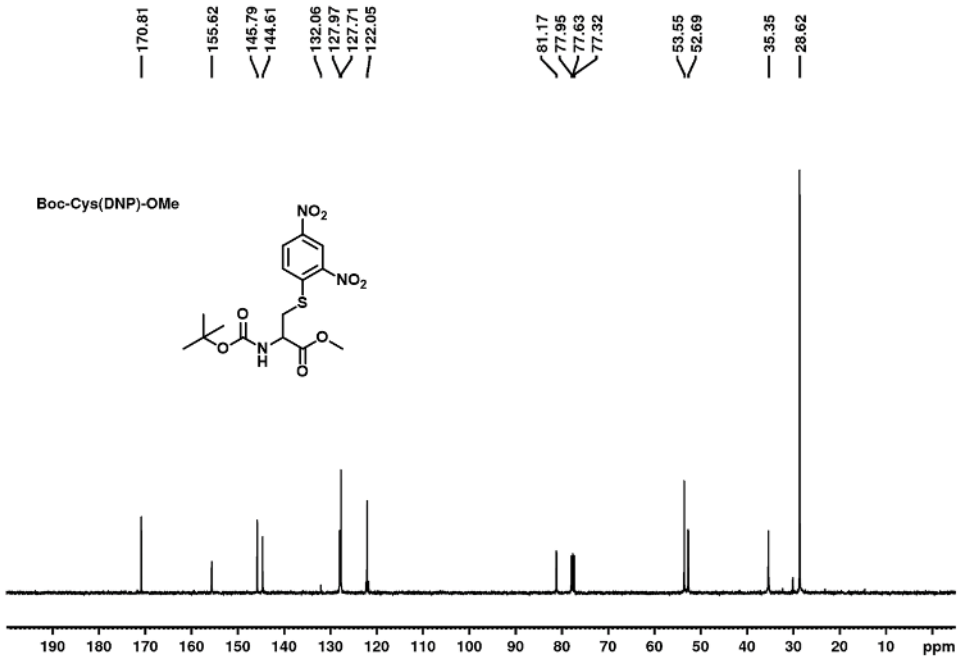


**Figure S20.** $^{13}C$ NMR spectrum (100.56 MHz, $CDCl_3$) of compound **11.**

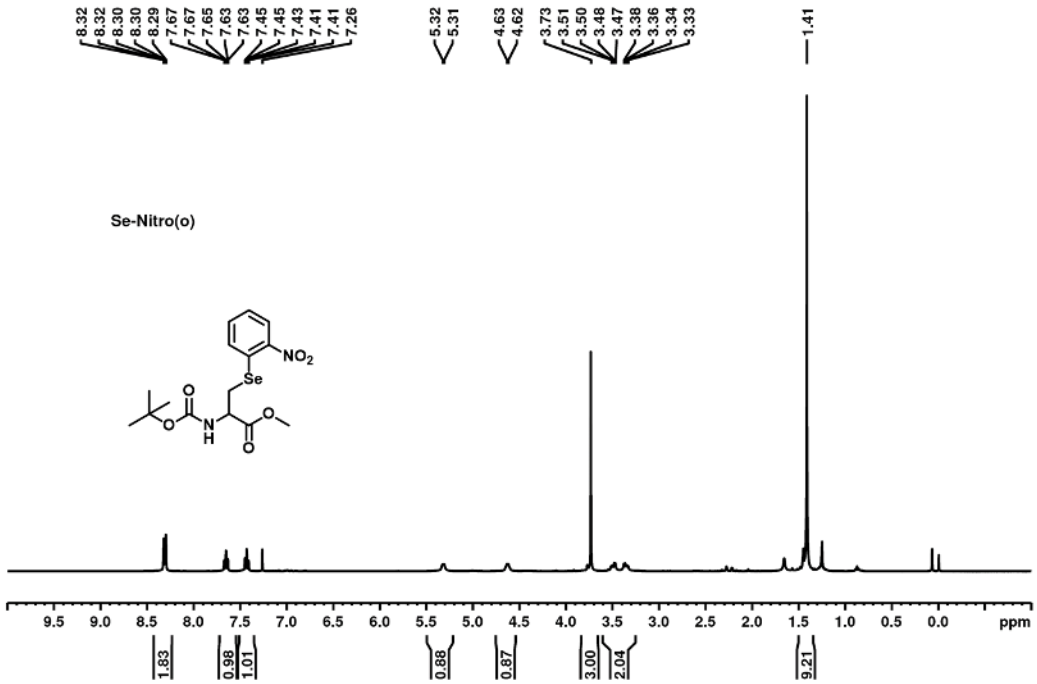


**Figure S21.** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound **19.**

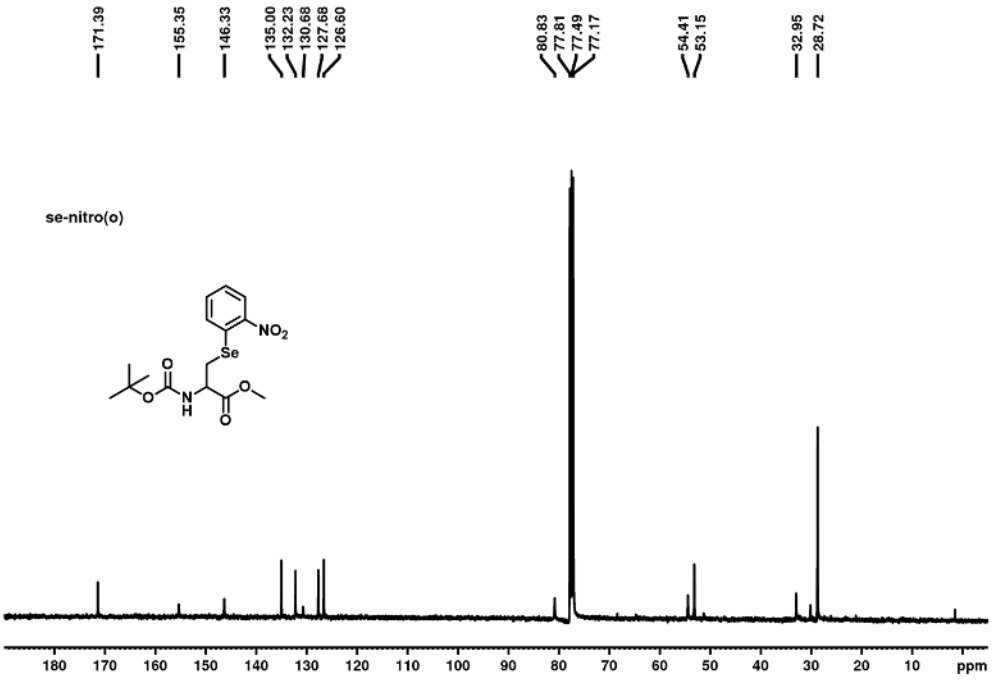


**Figure S22.** $^{13}$C NMR spectrum (100.56 MHz, $CDCl_3$) of compound **19.**

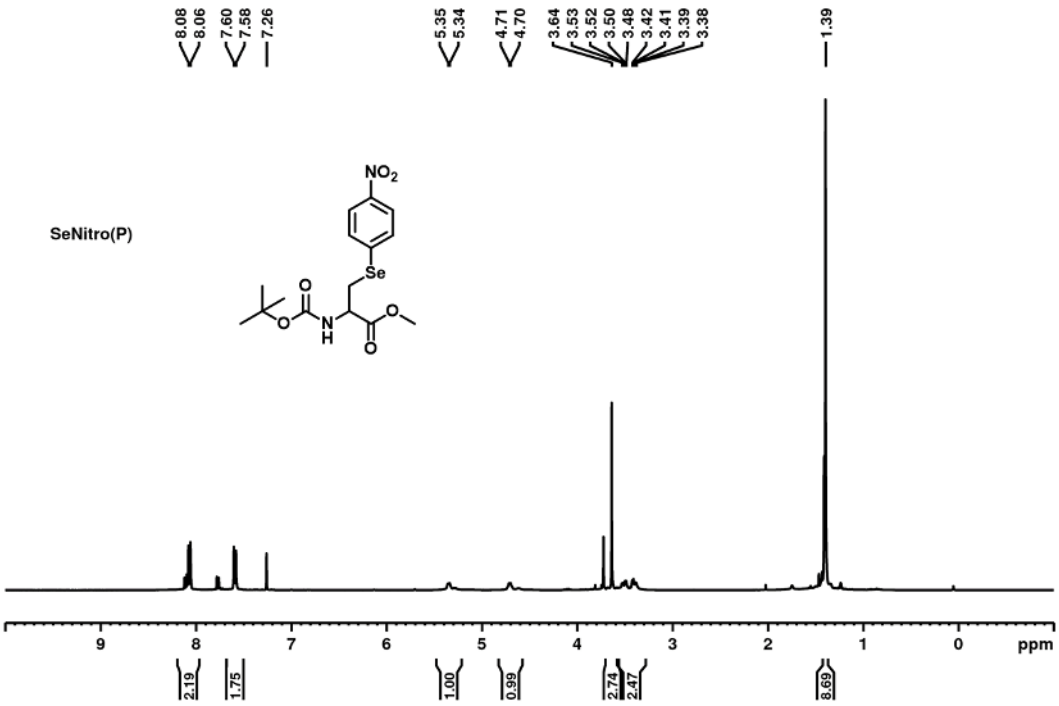


**Figure S23.** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound **20.**

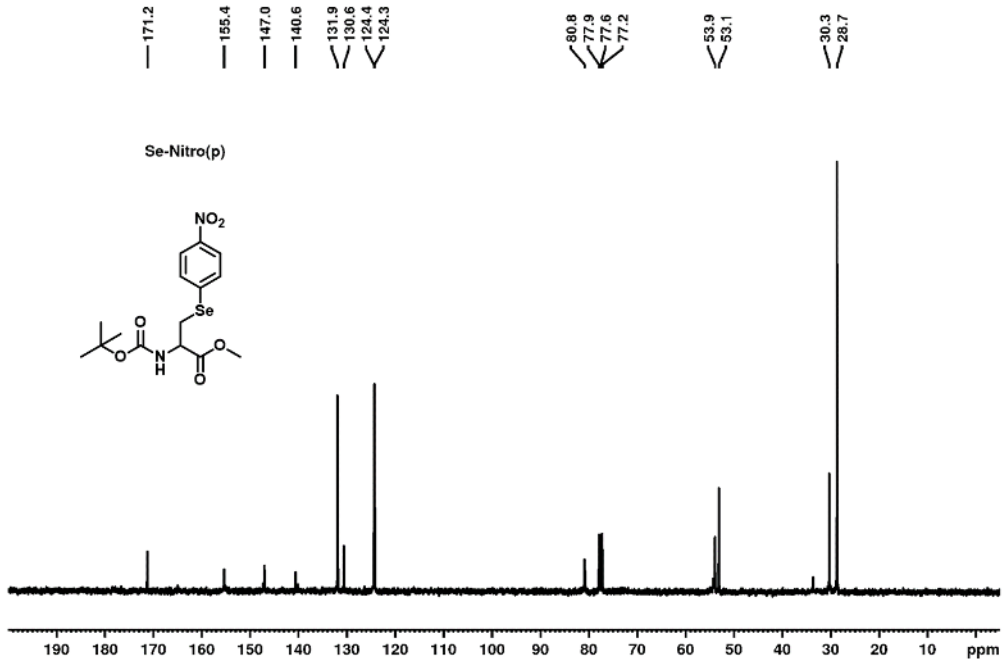


**Figure S24.** $^{13}$C NMR spectrum (100.56 MHz, $CDCl_3$) of compound **20.**

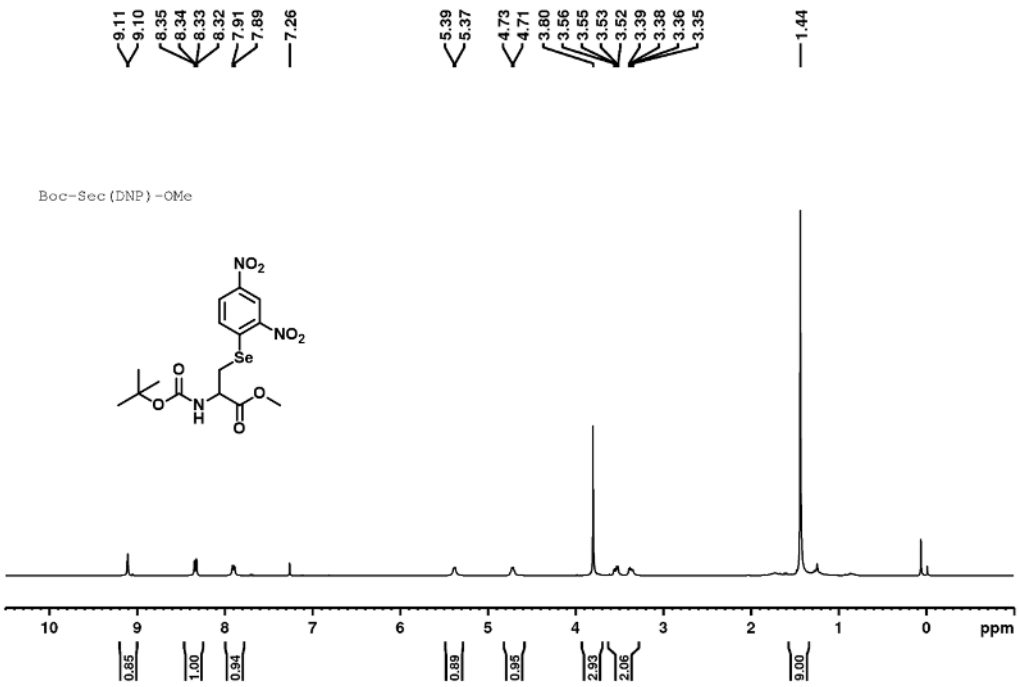


**Figure S25.** $^{1}H$ NMR spectrum (400 MHz, $CDCl_3$) of compound **21.**

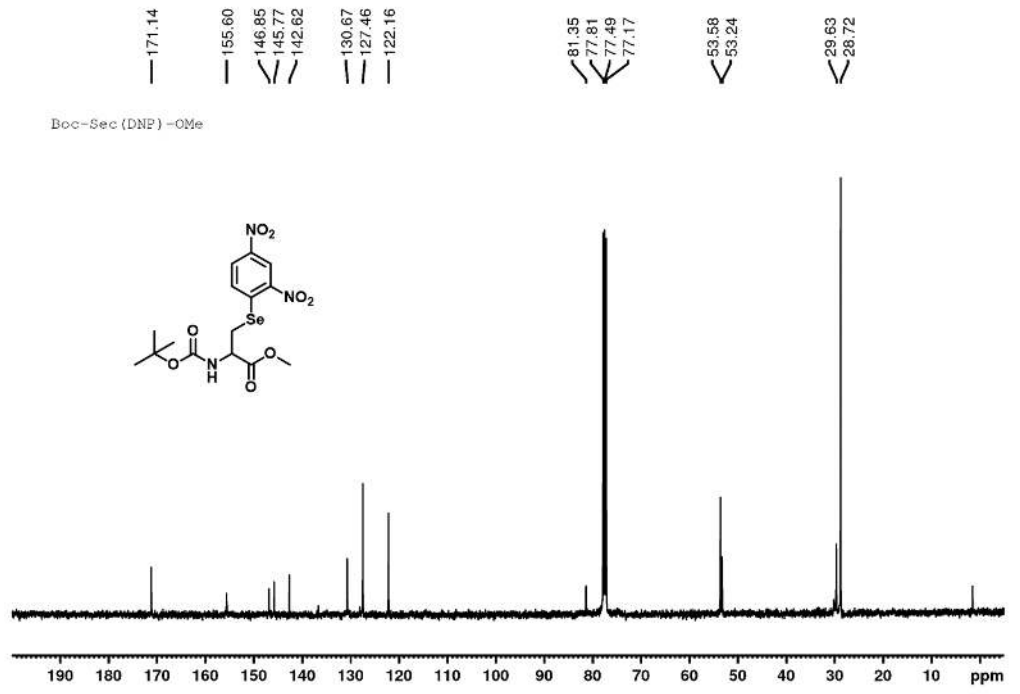


**Figure S26.** $^{13}C$ NMR spectrum (100.56 MHz, $CDCl_3$) of compound **21.**

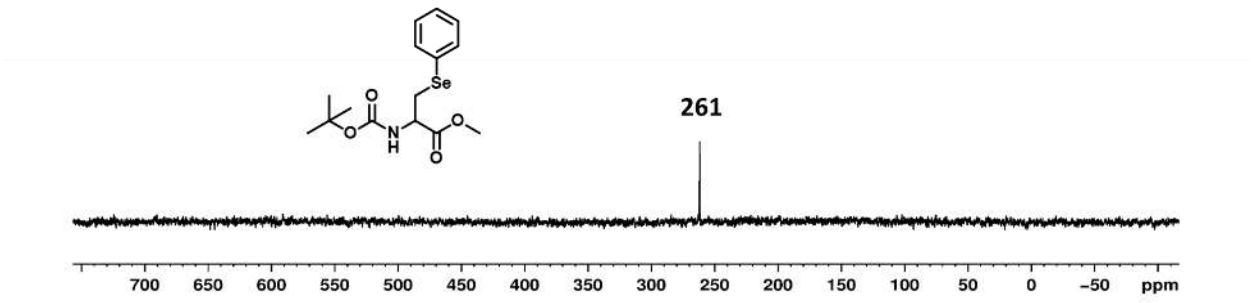


**Figure S27.** $^{77}$Se NMR spectrum (76.29 MHz, $CDCl_3$) of compound **22**.

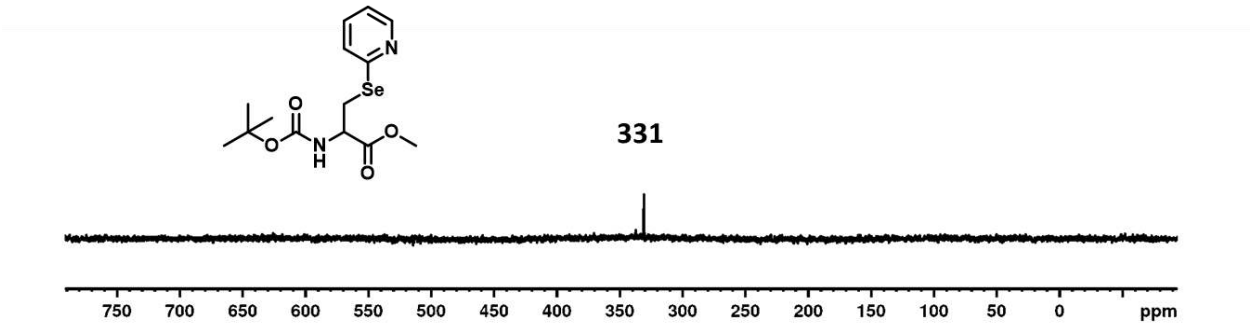


**Figure S28.** $^{77}$Se NMR spectrum (76.29 MHz, $CDCl_3$) of compound **17.**

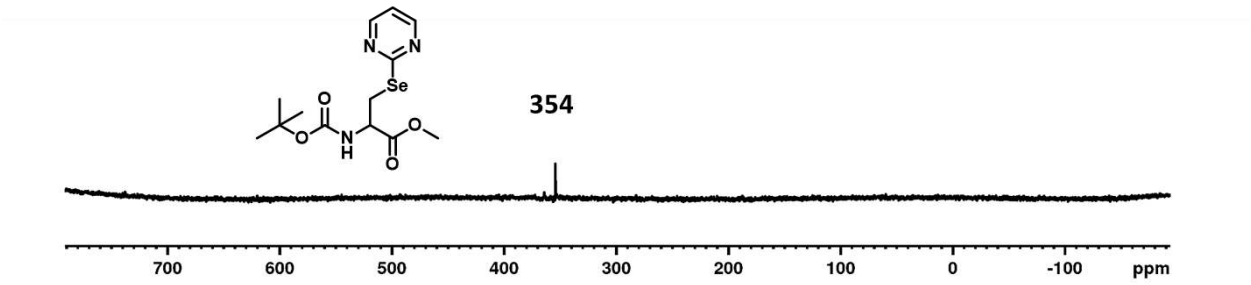


**Figure S29.** $^{77}$Se NMR spectrum (76.29 MHz, $CDCl_3$) of compound **18.**

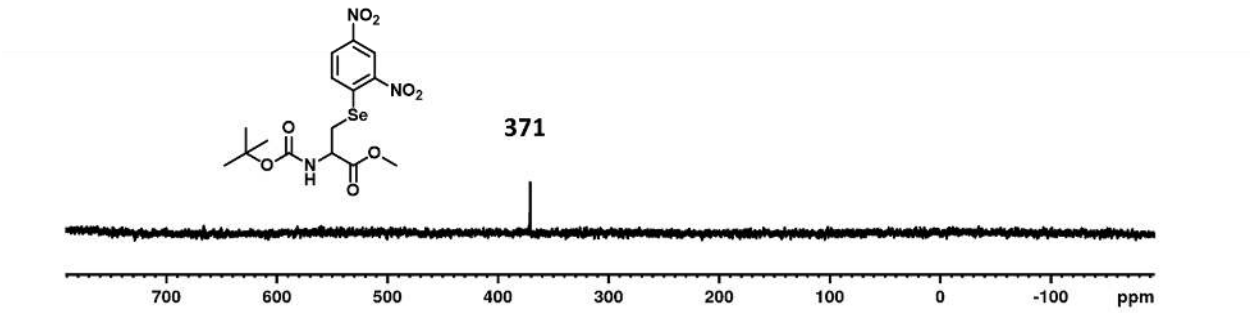


**Figure S30.** $^{77}Se$ NMR spectrum (76.29 MHz, $CDCl_3$) of compound **21**.

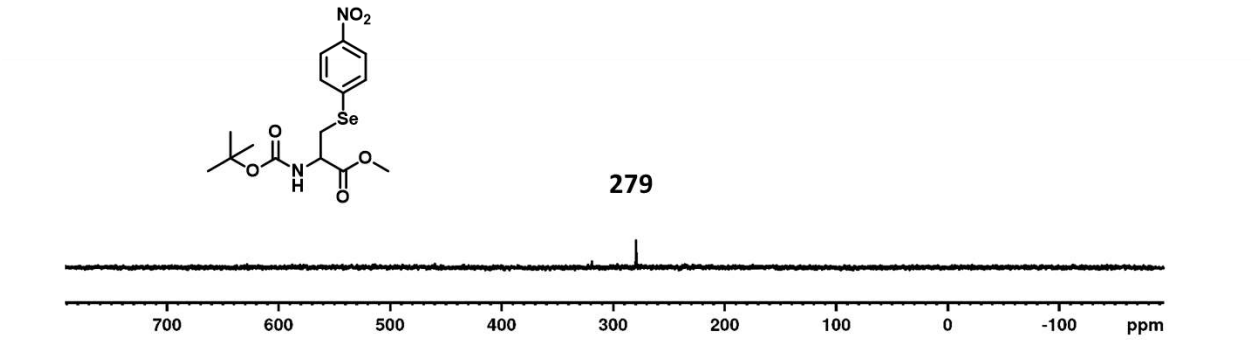


**Figure S31.** $^{77}Se$ NMR spectrum (76.29 MHz, $CDCl_3$) of compound **20.**

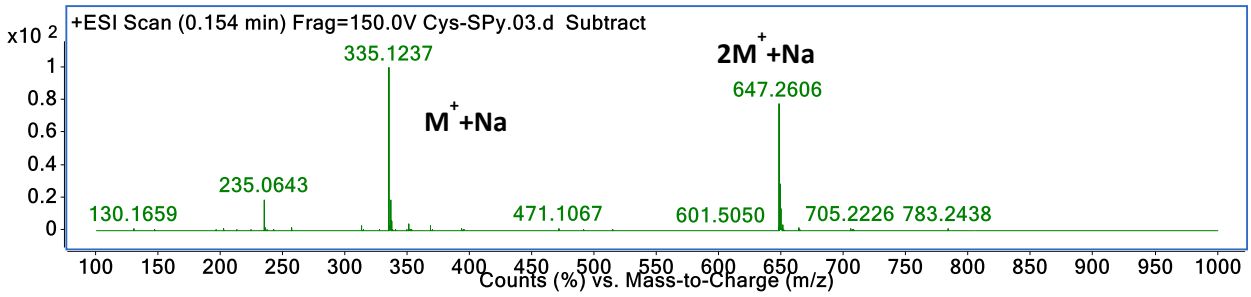


**Figure S32.** ESI-MS data of compound **8**.

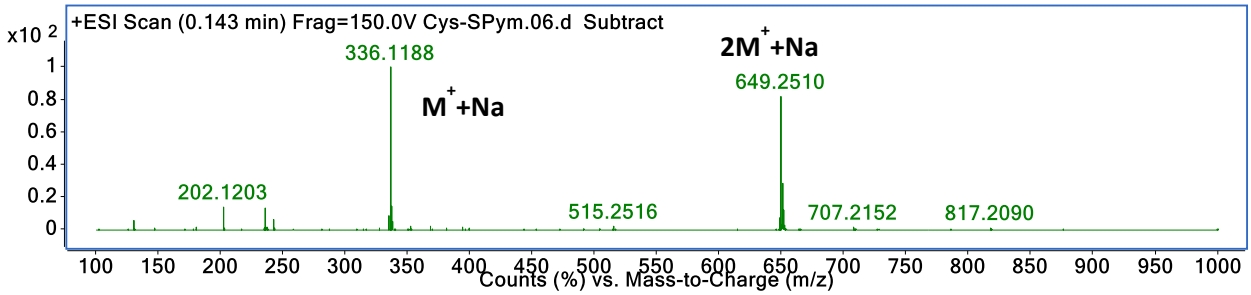


**Figure S33.** ESI-MS data of compound **9**.

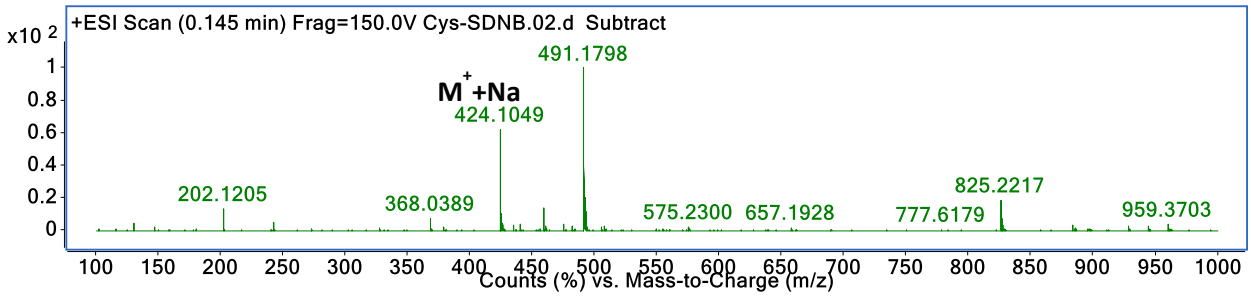


**Figure S34.** ESI-MS data of compound **11** [BocNH-Cys(DNB)-OMe]

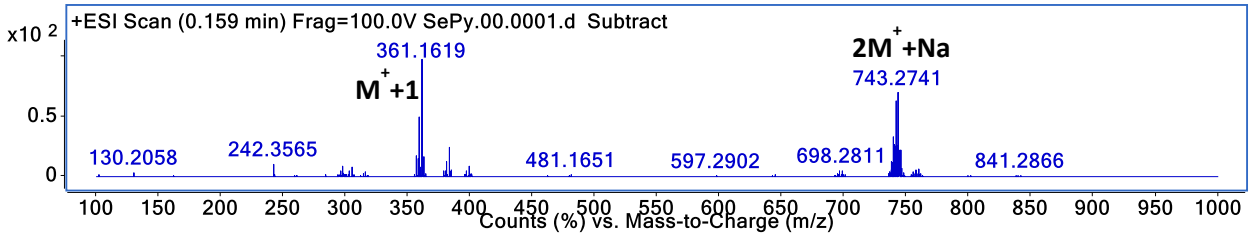


**Figure S35.** ESI-MS data of compound **17**.

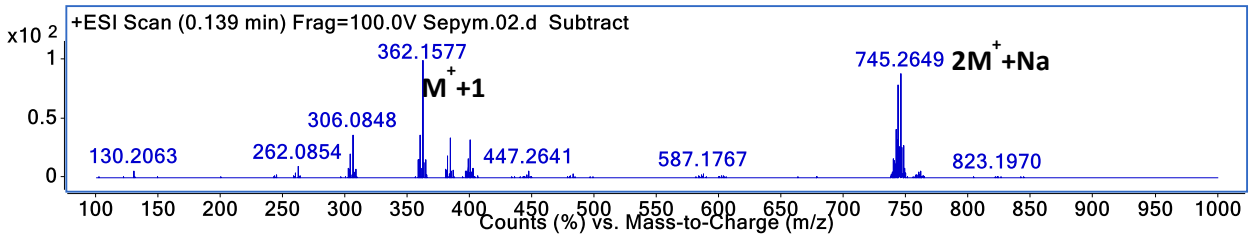


**Figure S36.** ESI-MS data of compound **18**.

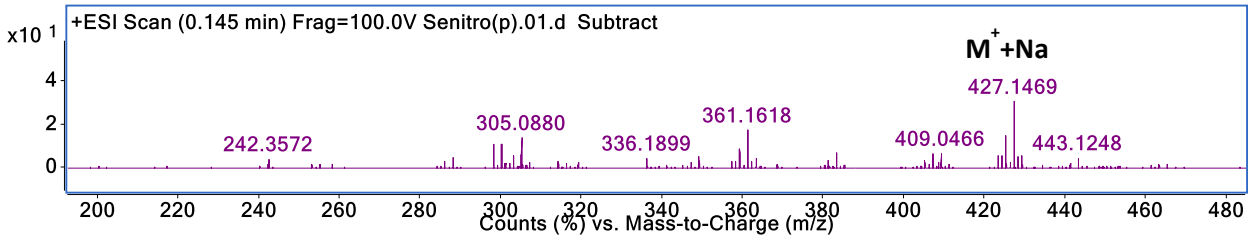


**Figure S37.** ESI-MS data of compound **20**.

## References:


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2. (a) J. Roy, W. Gordon, I. L. Schwartz and R. Walter, *J. Org. Chem.*, **1970**, *35*, 510. (b) L. A. Pete Silks, III, *Phosphorus, Sulfur and Silicon*, **1998**, *136, 137&138*, 611; (c) N. L. Brock, A. Nikolay and J. S. Dickschat, *Chem. Commun.*, **2014**, *50*, 5487.

3. (a) M. D. Gieselman, L. Xie, and W. A. van der Donk, *Org. Lett.*, **2001**, *3*, 1331. (b) Y. A. Lin, J. M. Chalker, and B. G. Davis, *J. Am. Chem. Soc.*, **2010**, *132*, 16805.