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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 , $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$, ACN, H_2O , 0°C , 2 h.

Compound **1**^[1]: ^1H 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]: ^1H 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 selenocysteine(**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]: ¹H NMR (400 MHz, CDCl₃), 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); ¹³C-NMR (100MHz, CDCl₃): 28.77, 32.81, 53.05, 54.14, 80.72, 155.48, 171.73; ⁷⁷Se NMR (76.29 MHz, CDCl₃), δ (ppm): 295.8.

All these values are matching with literature values.

Figure S1. A) ¹H NMR spectrum of **21** after incubating with H₂O₂ and its comparison with authentic sample of **23**. B) HPLC chromatogram obtained for the reaction of **21** with 4 equiv. of H₂O₂. C) HPLC chromatogram obtained for the reaction of **21** with 10 equiv., of H₂O₂.

A)

B)

Figure S2. A) ^1H 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) ^1H 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. ^1H 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. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 22.

Figure S10. ¹³C NMR spectrum (100.56 MHz, CDCl₃) of compound 22.

Figure S11. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **8**.

Figure S12. ¹³C NMR spectrum (100.56 MHz, CDCl₃) of compound **8**.

Figure S13. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 17.

Figure S14. ¹³C NMR spectrum (100.56 MHz, CDCl₃) of compound 17.

Figure S15. ^1H 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. ^1H 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. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **11**.

Figure S20. ¹³C NMR spectrum (100.56 MHz, CDCl₃) of compound **11**.

Figure S21. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 19.

Figure S22. ¹³C NMR spectrum (100.56 MHz, CDCl₃) of compound 19.

Figure S23. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **20**.

Figure S24. ¹³C NMR spectrum (100.56 MHz, CDCl₃) of compound **20**.

Figure S25. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **21**.

Figure S26. ¹³C NMR spectrum (100.56 MHz, CDCl₃) of compound **21**.

Figure S27. ⁷⁷Se NMR spectrum (76.29 MHz, CDCl₃) of compound **22**.

Figure S28. ⁷⁷Se NMR spectrum (76.29 MHz, CDCl₃) of compound **17**.

Figure S29. ⁷⁷Se NMR spectrum (76.29 MHz, CDCl₃) of compound **18**.

Figure S30. ⁷⁷Se NMR spectrum (76.29 MHz, CDCl₃) of compound **21**.

Figure S31. ⁷⁷Se NMR spectrum (76.29 MHz, CDCl₃) 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**.

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