

Supplementary Material

Synthesis of novel selenocaffeine derivatives

Augusto Konzgen, Carolina A. de Oliveira, Márcio Santos Silva, Laura Abenante,* and Eder J. Lenardão*

Centro de Ciências Químicas, Farmacêuticas e de Alimentos – CCQFA. Universidade Federal de Pelotas – UFPel. P. O. box 354, CEP 96010-900, Pelotas – RS, Brazil

Email: laura.abenante@ufpel.edu.br lenardao@ufpel.edu.br

Table of Contents

Experimental Section – General Information	S2
General procedure for the synthesis of selenocaffeine derivatives 3a-g	S2
Selected spectra of compounds 3a-g	S4

EXPERIMENTAL SECTION

General Information: The reactions were monitored by TLC carried out on pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV₂₅₄ by using UV light as visualization agent and the mixture of 5% vanillin in 10% H₂SO₄ under heating conditions as developing agent. Merck silica gel (particle size 63-200 µm) was used to flash chromatography, and PTLC Glass Plates L × W 20 cm × 20 cm, silica gel 60 F₂₅₄, 1 mm, was used in the preparative thin layer chromatography. Hydrogen nuclear magnetic resonance spectra (¹H NMR) were obtained at 400 MHz on A Bruker Ascend 400 spectrometer. The spectra were recorded in CDCl₃ solutions. The chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) as the external reference. Hydrogen coupling patterns are described as broad signal (br), singlet (s), doublet (d), triplet (t), doublet of doublets (dd), doublet of doublet of doublets (ddd) and multiplet (m). Coupling constants (*J*) are reported in Hertz. Carbon-13 nuclear magnetic resonance spectra (¹³C NMR) were obtained at 100 MHz on Bruker Nuclear Ascend 400 spectrometer. The chemical shifts are reported in ppm, referenced to the solvent peak of CDCl₃. Selenium-77 nuclear magnetic resonance spectra (⁷⁷Se NMR) were obtained at 76 MHz on Bruker Nuclear Ascend 400 spectrometer. The chemical shifts are reported in ppm, referenced to diphenyl diselenide as the external reference. The HRMS analysis was performed in a Bruker micrOTOF-QII spectrometer equipped with an APCI source operating in positive mode. The samples were solubilized in acetonitrile and analyzed by direct infusion at a constant flow rate of 180 µL/min. The acquisition parameters were capillary: 4000 V, end plate offset: -500 V, nebulizer: 1.5 bar, dry gas: 1.5 L min⁻¹, and dry heater: 180 °C. The collision cell energy was set to 5.0 eV. The mass-to-charge ratio (*m/z*) data were processed and analyzed using Bruker Daltonics software: Compass Data Analysis and Isotope Pattern. Melting point (m.p.) values were measured in a Marte PFD III instrument.

General procedure for the synthesis of the products 3a-g.

In a Schlenk tube were added caffeine **1** (0.25 mmol), diaryl diselenide **2a-g** (0.15 mmol), Cu(OAc)₂•H₂O (20 mol%), AgOAc (2 mol%; when used) and xylene (2.0 mL). The resulting mixture was stirred at 150 °C, under oxygen atmosphere (balloon) for 24 hours. After this time, the reaction was received in NH₄Cl saturated aqueous solution, extracted with ethyl acetate (3x10 mL), dried over MgSO₄, and concentrated under vacuum. Then, the crude was purified by column chromatography in a mixture of hexanes/ethyl acetate (80:20) as the eluent.

1,3,7-trimethyl-8-(phenylselanyl)-3,7-dihydro-1H-purine-2,6-dione (3a).¹ Yield: 0.070 g; 0.08 g (80%; 91%); white solid; m.p.: 153 – 156 °C (Lit.:¹ 165 °C). ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.50-7.47 (m, 2H), 7.32-7.29 (m, 3H), 3.92 (s, 3H), 3.58 (s, 3H), 3.39 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ (ppm) 154.83, 151.41, 148.54, 142.60, 132.56, 129.78, 128.46, 127.25, 109.91, 34.15, 29.84, 27.95. ⁷⁷Se (76 MHz) δ (ppm) 331.43.

1,3,7-trimethyl-8-(p-tolylselanyl)-3,7-dihydro-1H-purine-2,6-dione (3b).¹

Yield: 0.032 g; 0.036 g (36%; 40%); pale white solid; m.p.: 123 – 133 °C (Lit.:¹ 148 °C). ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.40 (d, *J* = 8 Hz, 2H), 7.12 (d, *J* = 8 Hz, 2H), 3.90 (s, 3H), 3.57 (s, 3H), 3.39 (s, 3H), 2.34 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ (ppm) 154.81, 151.43, 148.51, 143.15, 138.84, 133.08, 130.56, 123.24, 109.82, 34.10, 29.84, 27.93, 21.11. ⁷⁷Se (76 MHz) δ (ppm) 326.68.

8-((4-chlorophenyl)selanyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (3c).¹

Yield: 0.030 g; 0.054 g (31%; 56%); white solid; m.p.: 161 – 175 °C (Lit.:¹ not listed). ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.45 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 3.94 (s, 3H), 3.56 (s, 3H), 3.39 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ (ppm) 154.79, 148.56, 142.16, 134.99, 134.07, 129.93, 125.16, 109.95, 34.11, 29.83, 27.95. ⁷⁷Se (76 MHz) δ (ppm) 329.42.

8-((4-bromophenyl)selanyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (3d).

Yield: 0.026 g; 0.036 g (24%; 33%); pale white solid; m.p.: 134-136. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.45 (d, *J* = 8 Hz, 2H), 7.37 (d, *J* = 8 Hz, 2H), 3.94 (s, 3H), 3.57 (s, 3H), 3.40 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ (ppm) 154.83, 151.42, 148.59, 142.05, 134.24, 132.91, 125.95, 123.08, 110.01, 34.16, 29.88, 28.00. ⁷⁷Se (76 MHz) δ (ppm) 328.38 HRMS (APCI-QTOF) *m/z*: [M + H]⁺ Calcd for C₁₄H₁₃BrN₄O₂Se: 428.9457, found: 428.9453.

1,3,7-trimethyl-8-((3-(trifluoromethyl)phenyl)selanyl)-3,7-dihydro-1H-purine-2,6-dione (3e).

Yield: 0.030 g; 0.042 g (29%; 40%); white solid; m.p.: 162 – 177 °C. ^1H NMR (CDCl_3 , 400 MHz) δ (ppm) 7.86 (s, 1H), 7.68 (d, J = 4 Hz, 1H), 7.60 (d, J = 8 Hz, 1H), 7.45 (t, J = 8 Hz, 1H), 3.97 (s, 3H), 3.56 (s, 3H), 3.40 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz) δ (ppm) 154.82, 151.38, 148.63, 141.63, 135.73, 132.02 (d, J = 32 Hz), 130.04, 129.30 (q, J = 4 Hz), 128.24, 125.33 (q, J = 4 Hz), 123.35 (q, J = 271 Hz) 110.06, 34.13, 29.80, 27.98. ^{77}Se (76 MHz) δ (ppm) 338.25. ^{77}Se (76 MHz) δ (ppm) 338.25 HRMS (APCI-QTOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{13}\text{F}_3\text{N}_4\text{O}_2\text{Se}$: 419.0229, found: 419.0212.

8-((2-methoxyphenyl)selanyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (3f).

Yield: 0.032 g; 0.042 g (34%; 44%); pale brown solid; m.p.: 150 – 160 °C. ^1H NMR (CDCl_3 , 400 MHz) δ (ppm) 7.28-7.24 (m, 1H), 6.94-6.82 (m, 3H), 3.96 (s, 3H), 3.89 (s, 3H), 3.60 (s, 3H), 3.42 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz) δ (ppm) 156.61, 154.87, 151.43, 148.70, 141.45, 130.52, 129.00, 122.09, 117.91, 110.99, 110.07, 56.01, 34.23, 29.87, 27.97. ^{77}Se (76 MHz) δ (ppm) 338.25. ^{77}Se (76 MHz) δ (ppm) 272.38 HRMS (APCI-QTOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_3\text{Se}$: 381.0461, found: 381.0458.

8-(mesitylselanyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (3g).

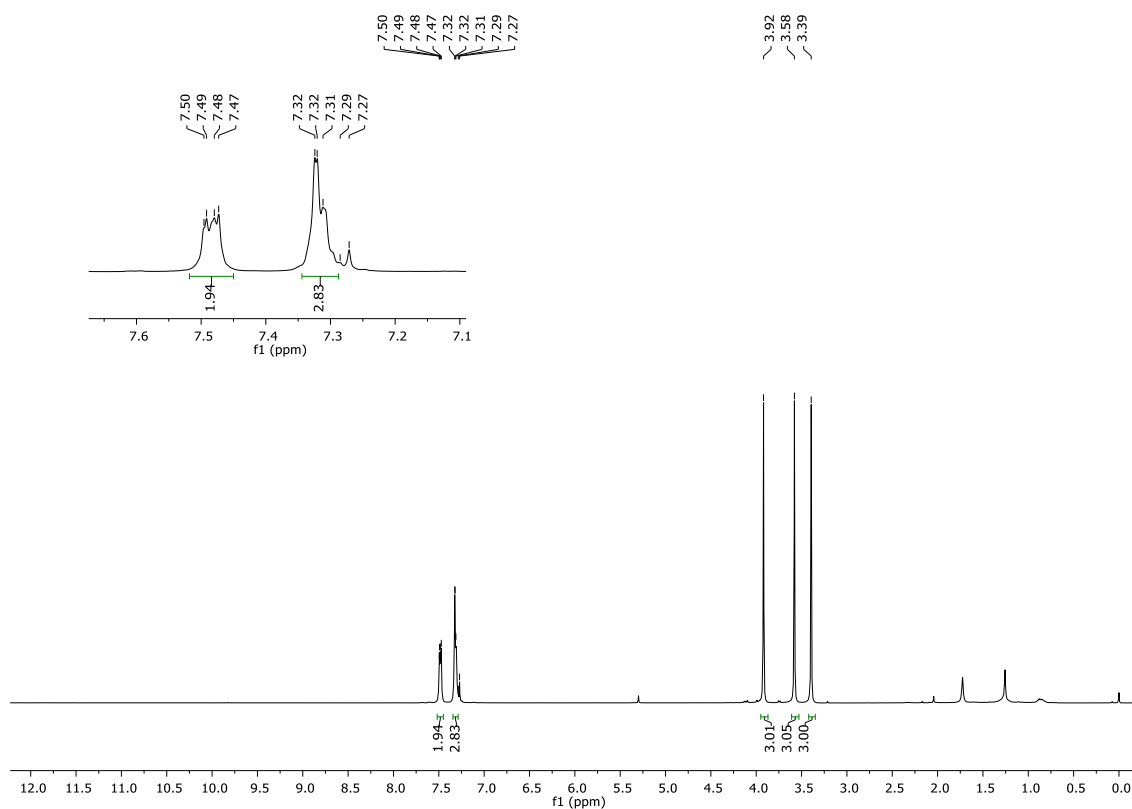
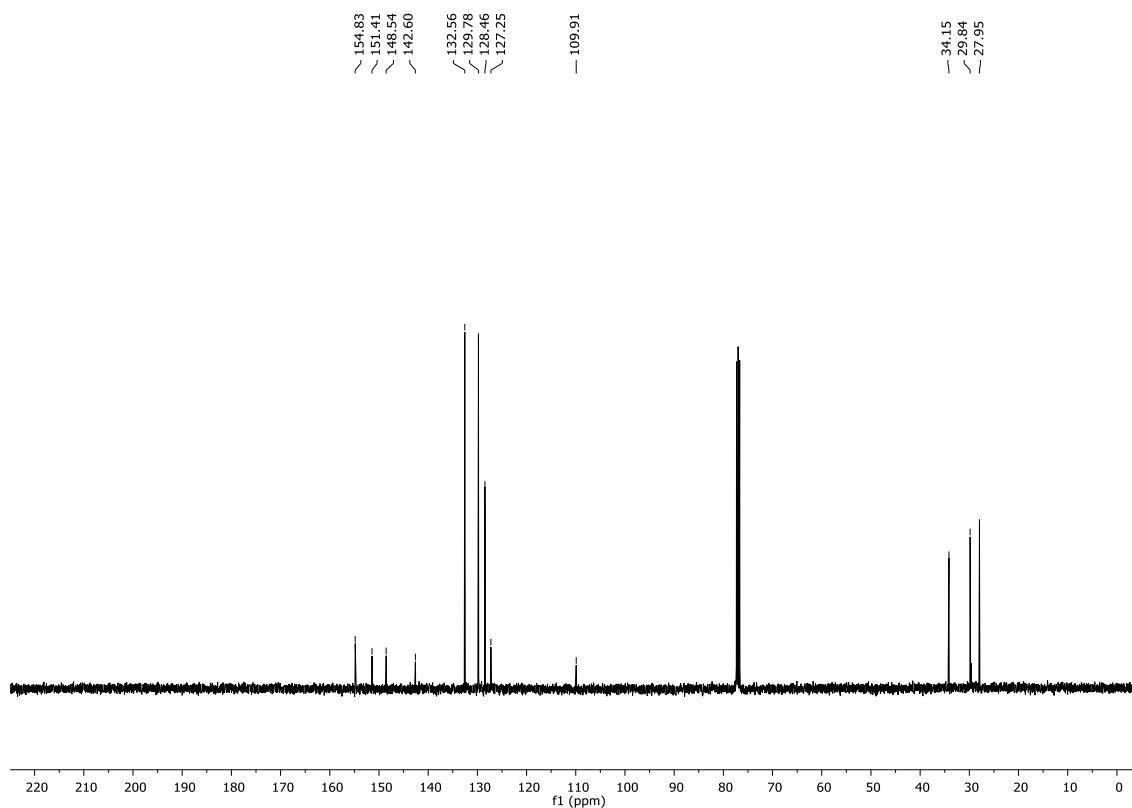
Yield: 0.032 g; 0.040 g (33%; 41%); pale brown solid; m.p.: 190 – 210 °C. ^1H NMR (CDCl_3 , 400 MHz) δ (ppm) 6.97 (s, 2H), 3.78 (s, 3H), 3.47 (s, 3H), 3.36 (s, 3H), 2.45 (s, 6H), 2.29 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz) δ (ppm) 154.65, 151.47, 148.70, 144.93, 142.70, 139.79, 129.28, 124.41, 109.31, 33.45, 29.78, 27.84, 24.24, 20.96. ^{77}Se (76 MHz) δ (ppm) 338.25. ^{77}Se (76 MHz) δ (ppm) 246.98 HRMS (APCI-QTOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{20}\text{N}_4\text{O}_2\text{Se}$: 393.0825, found: 393.0819.

REFERENCE

1. Holthausen, C.; Carlos, I. B. R.; Gomes, S. Q.; Granja, I. J. A.; Silva, S. S.; Silva, A. C.; Junca, E.; Zimmermann, M. V. G.; Raitz, I.; Federico, L. B.; Braga, A. L.; Rafique, J.; Saba, S.; Frizon, T. E. A. *Org. Biomol. Chem.* **2026**, *24*, 5846-5848.

<https://doi.org/10.1039/d6ob00464d>

SELECTED SPECTRA

Figure S1. ¹H NMR (CDCl₃ 400 MHz) of compound 3a.Figure S2. ¹³C NMR (CDCl₃ 100 MHz) of compound 3a.

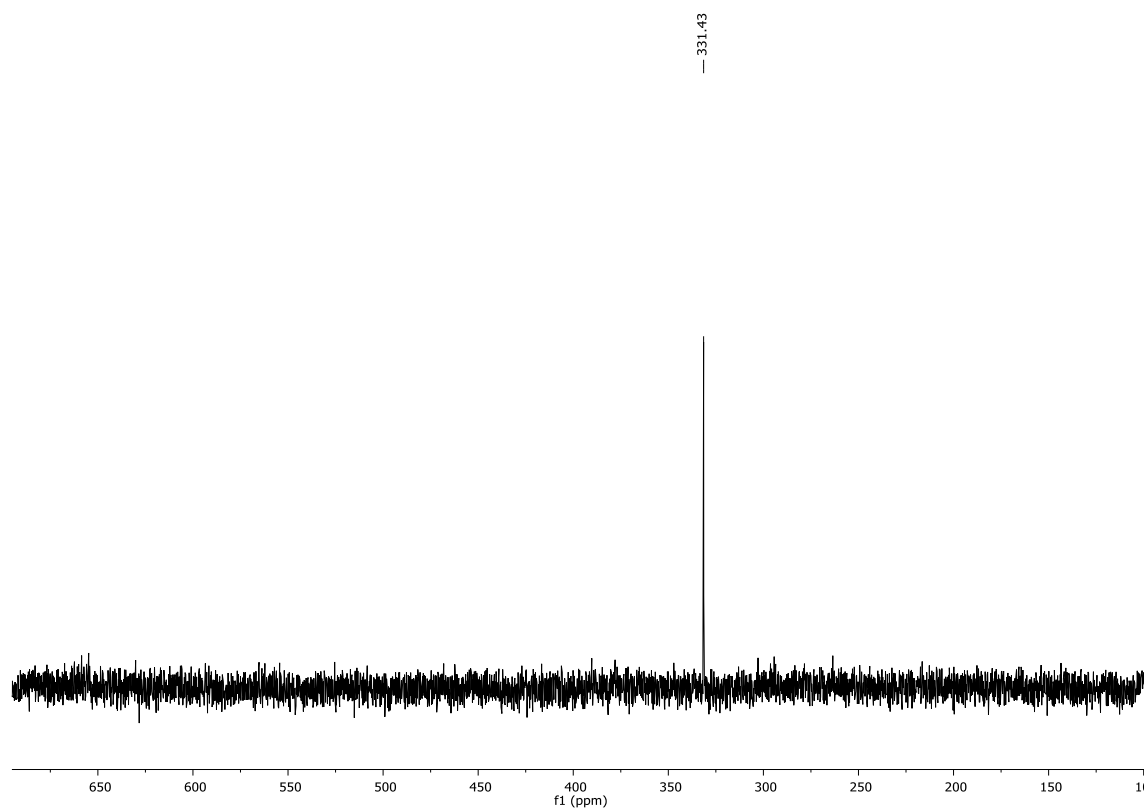


Figure S3. ^{77}Se NMR (CDCl_3 76 MHz) of compound **3a**.

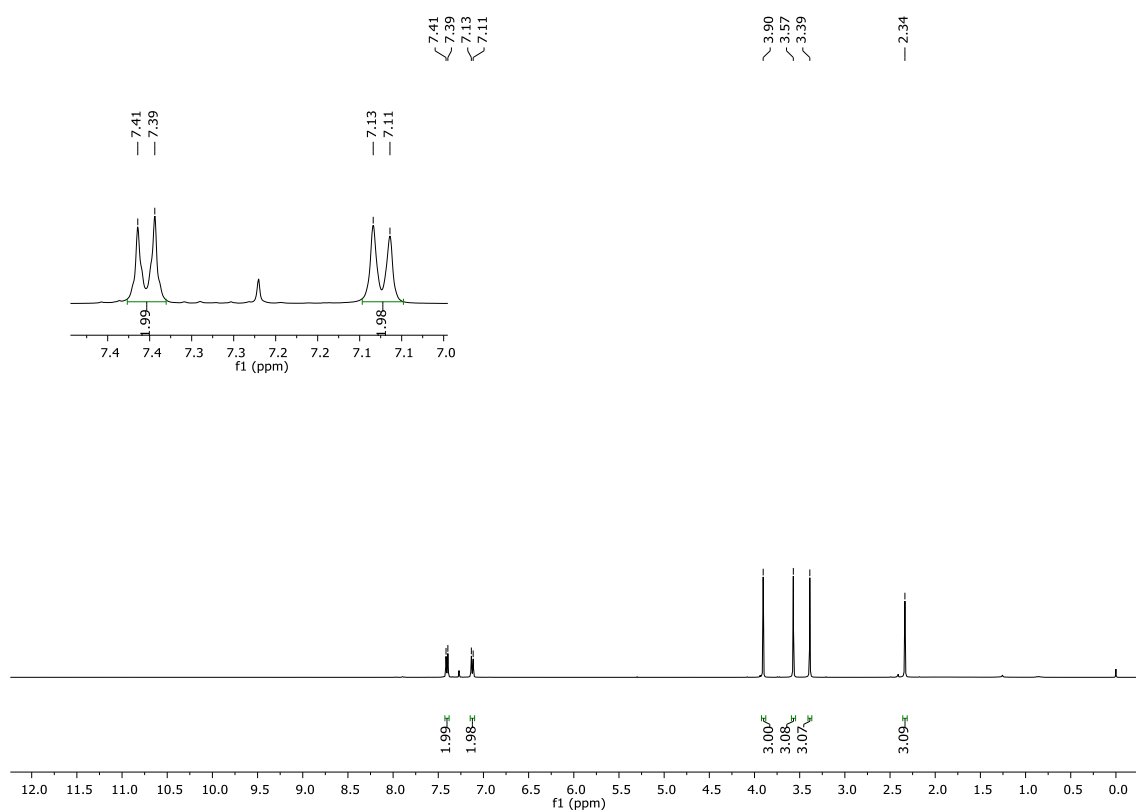
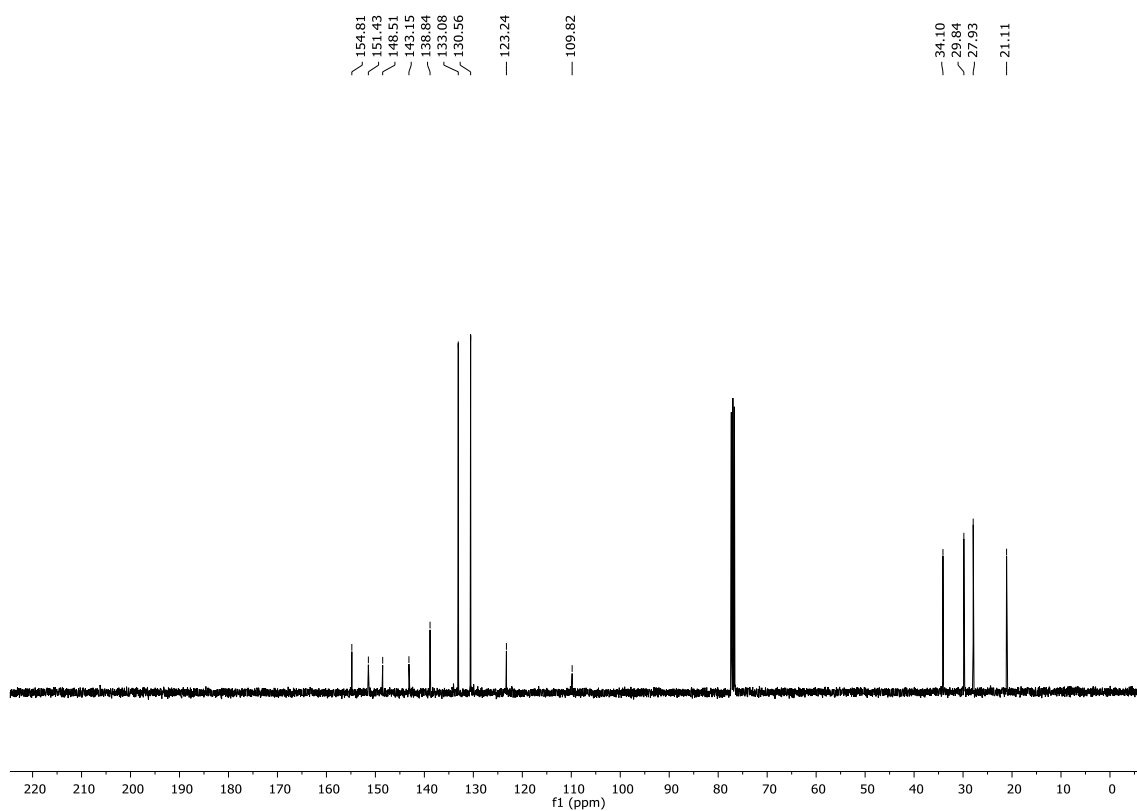
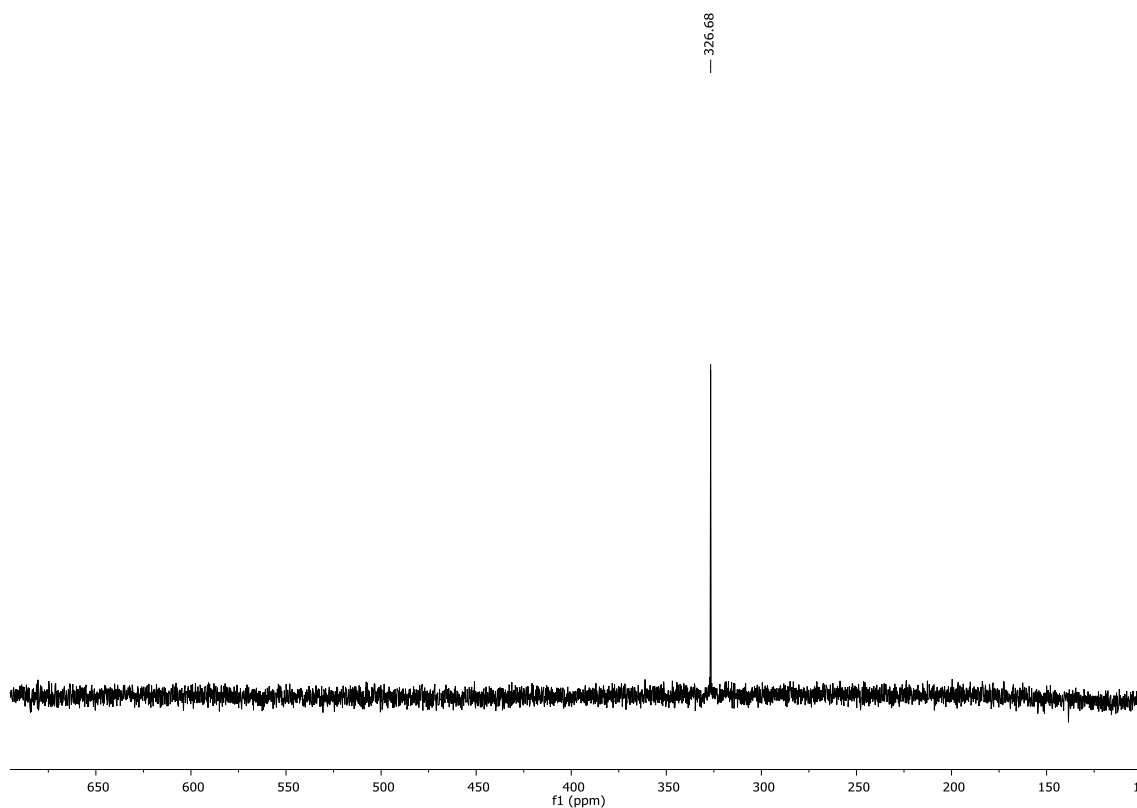


Figure S4. ^1H NMR (CDCl_3 400 MHz) of compound **3b**.

Figure S5. ^{13}C NMR (CDCl_3 100 MHz) of compound **3b**.Figure S6. ^{77}Se NMR (CDCl_3 76 MHz) of compound **3b**.

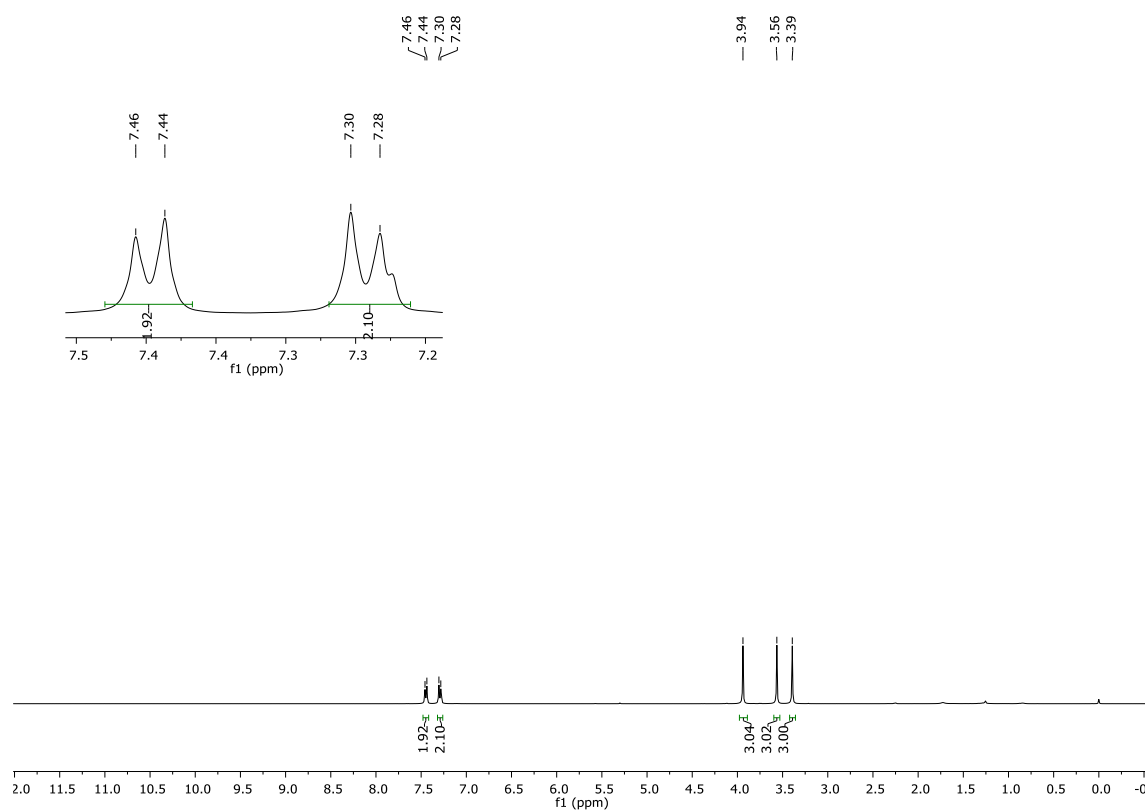


Figure S7. ^1H NMR (CDCl_3 400 MHz) of compound **3c**.

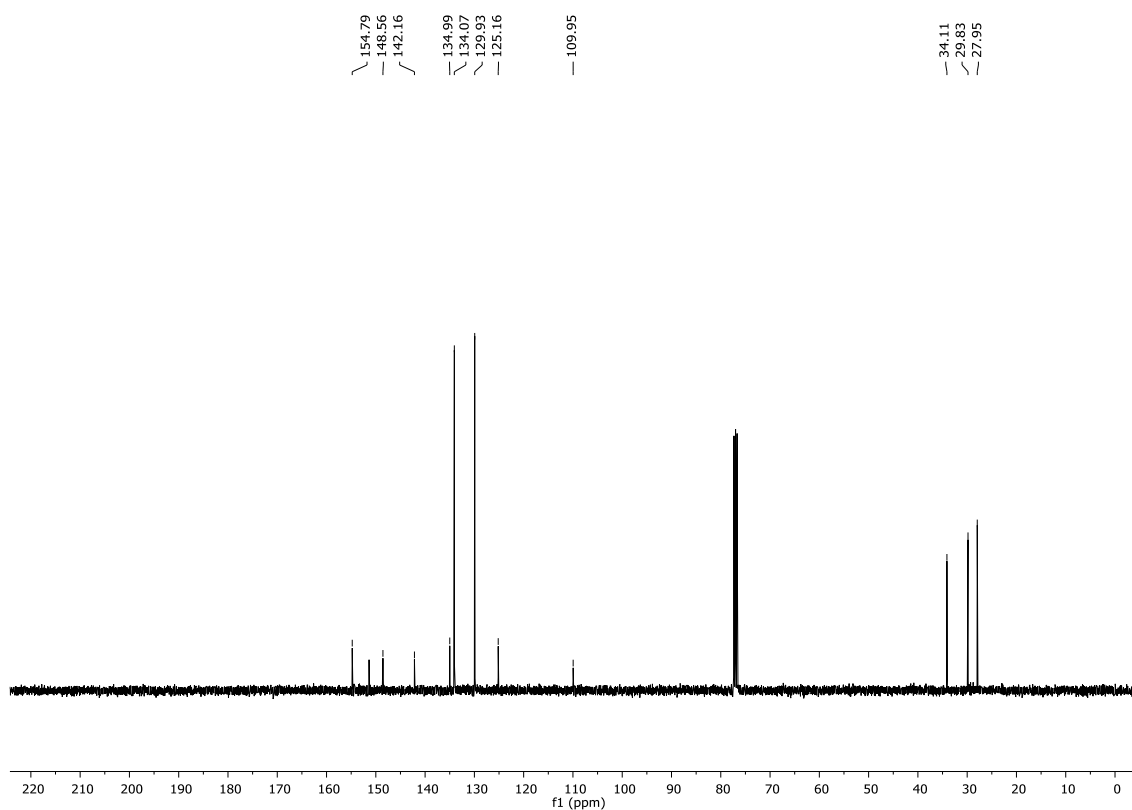


Figure S8. ^{13}C NMR (CDCl_3 100 MHz) of compound **3c**.

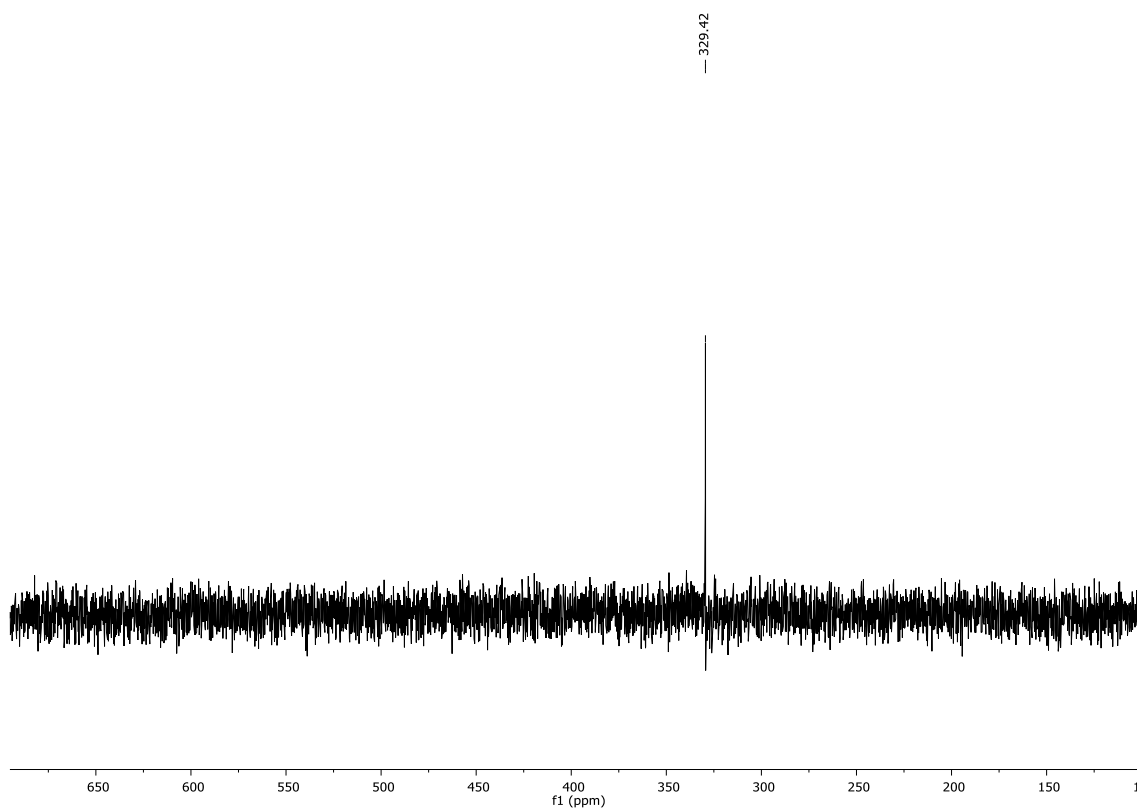


Figure S9. ^{77}Se NMR (CDCl_3 76 MHz) of compound **3c**.

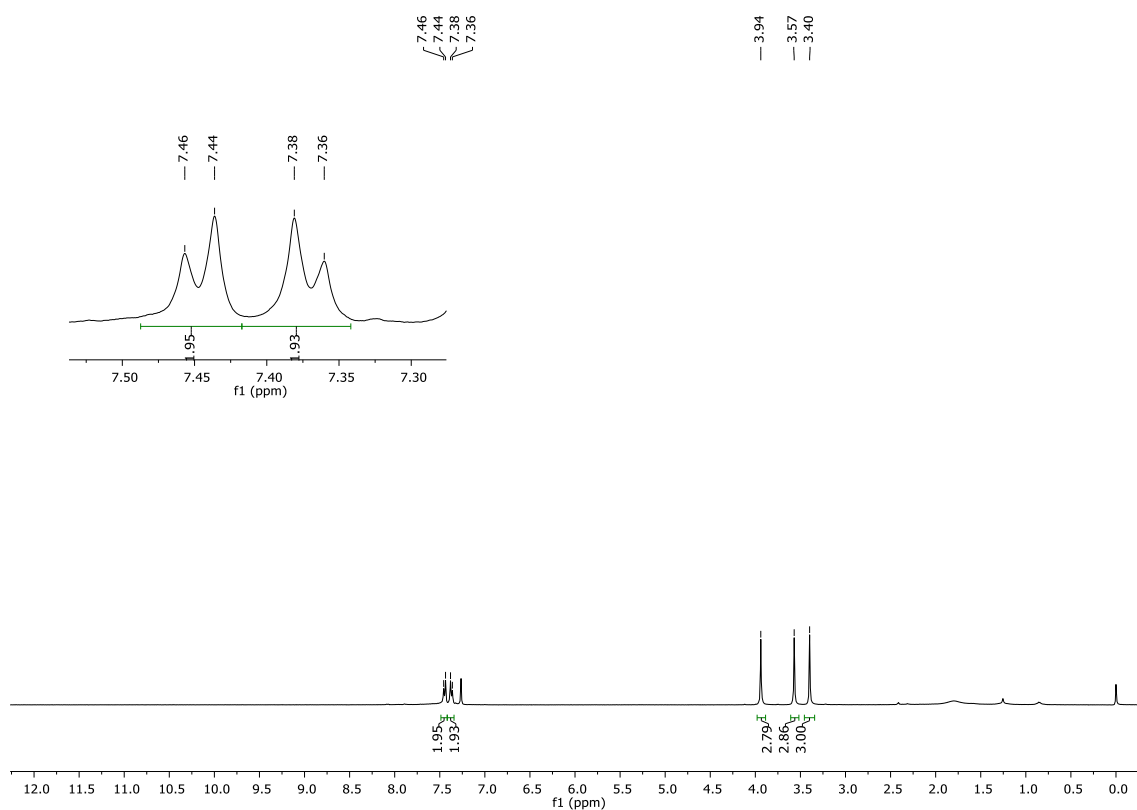


Figure S10. ^1H NMR (CDCl_3 400 MHz) of compound **3d**.

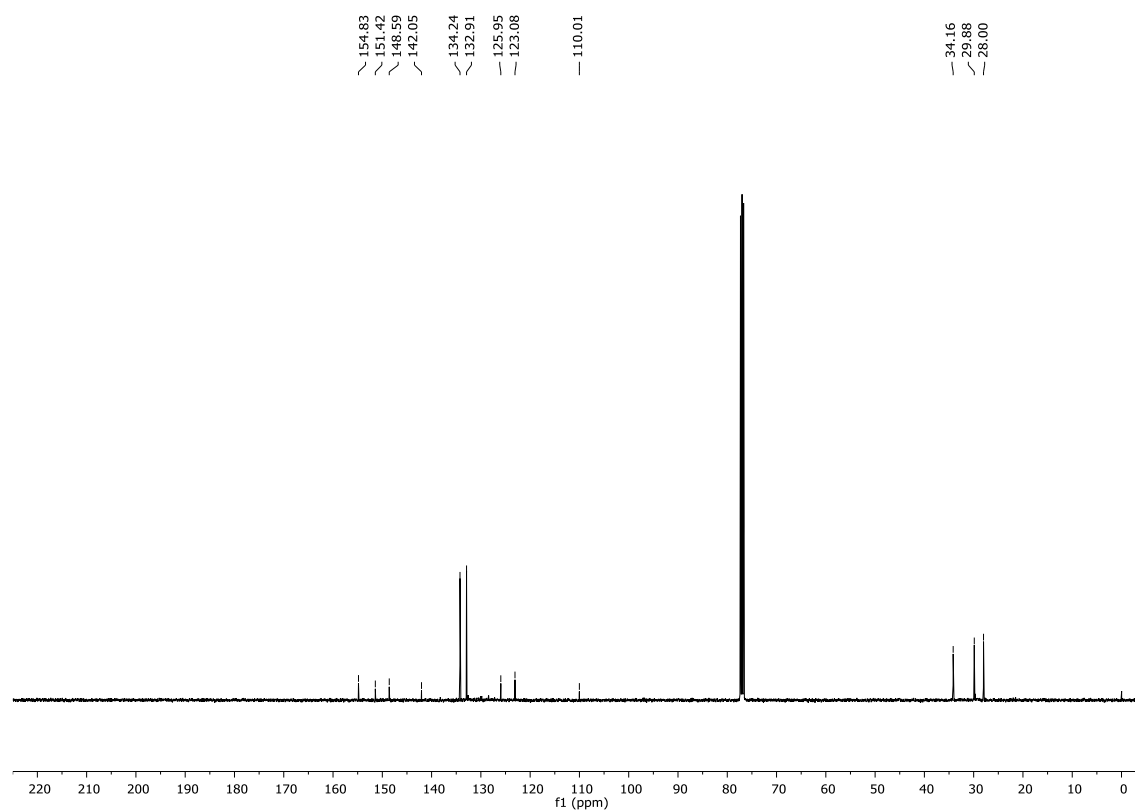


Figure S11. ^{13}C NMR (CDCl_3 100 MHz) of compound **3d**.

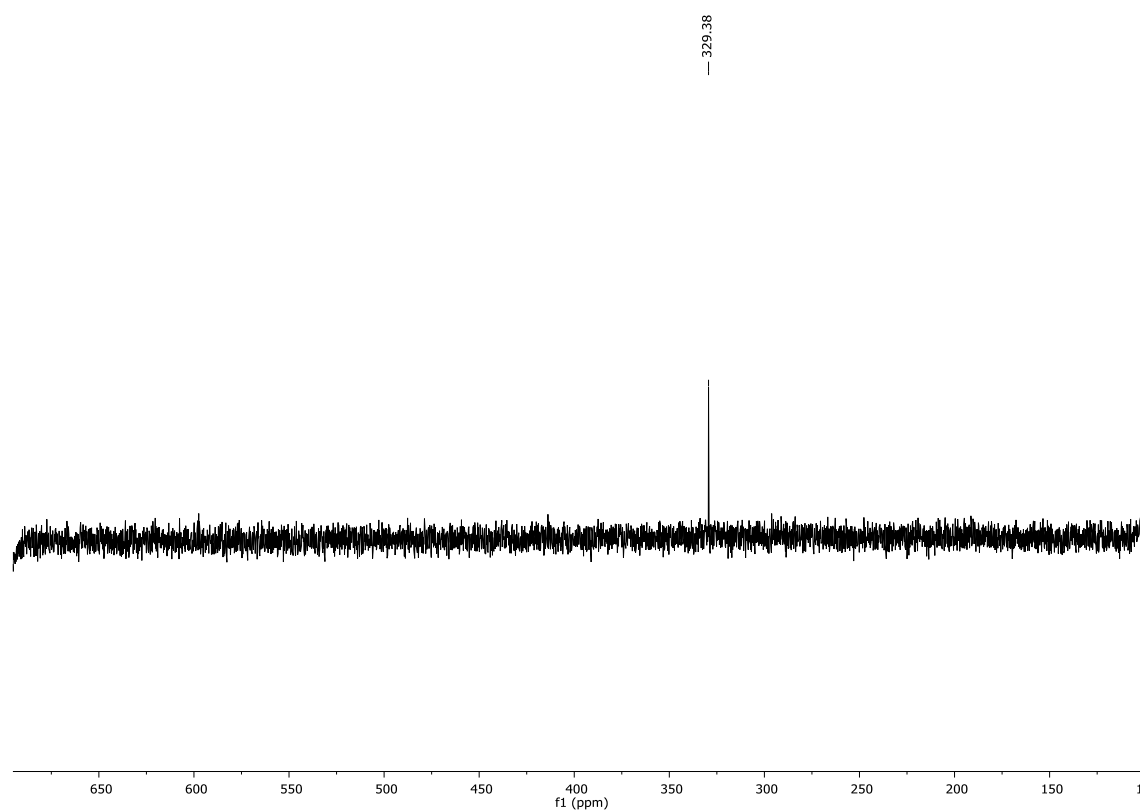
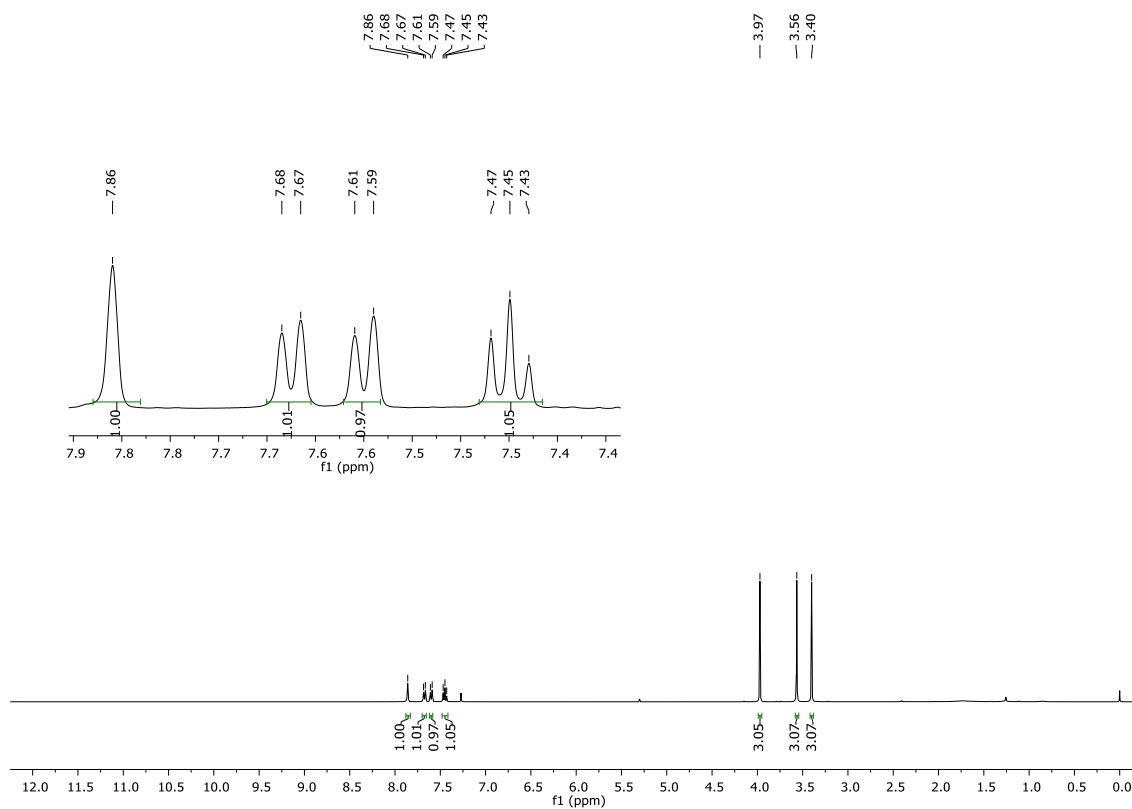
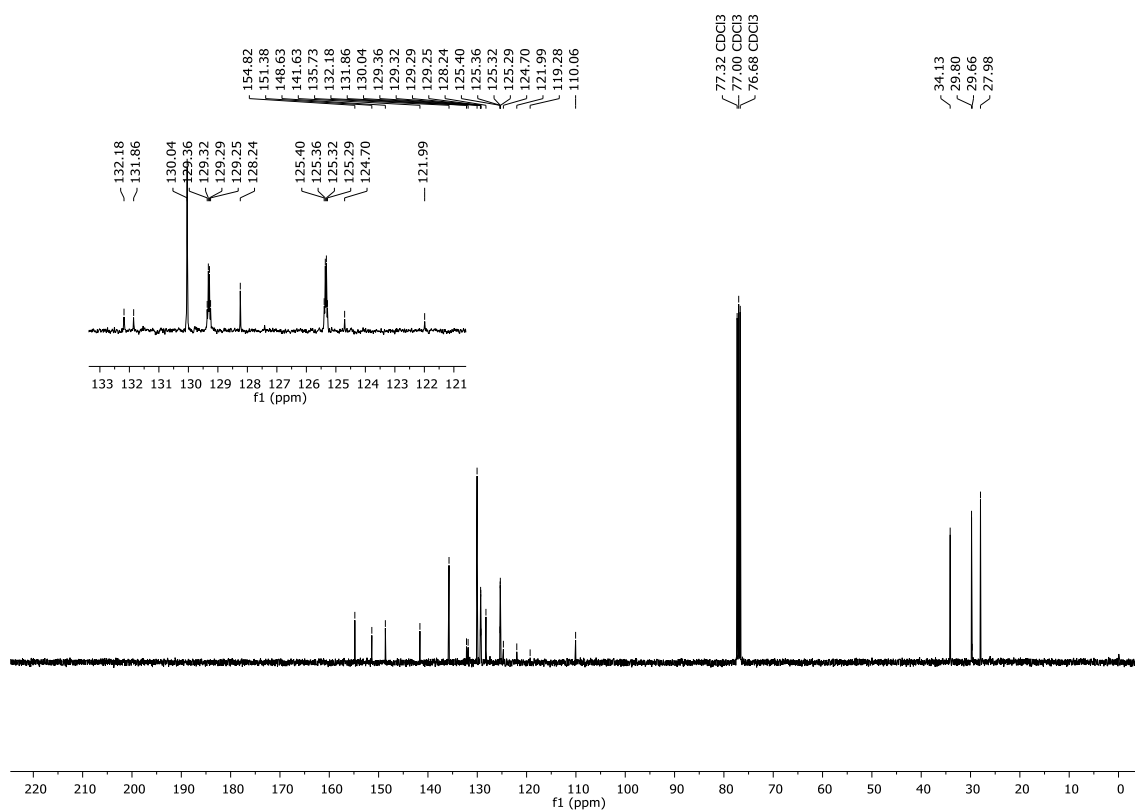


Figure S12. ^{77}Se NMR (CDCl_3 76 MHz) of compound **3d**.

Figure S13. ¹H NMR (CDCl₃ 400 MHz) of compound **3e**.Figure S14. ¹³C NMR (CDCl₃ 76 MHz) of compound **3e**.

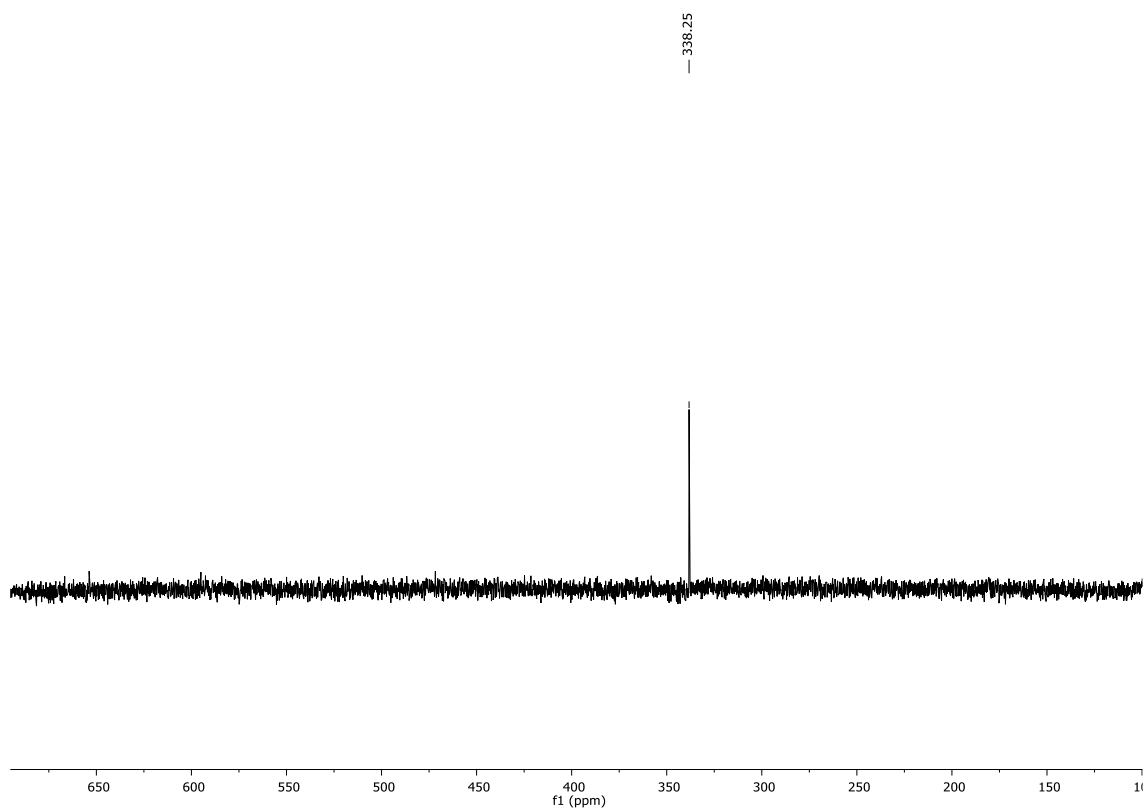


Figure S15. ^{77}Se NMR (CDCl₃ 76 MHz) of compound **3e**.

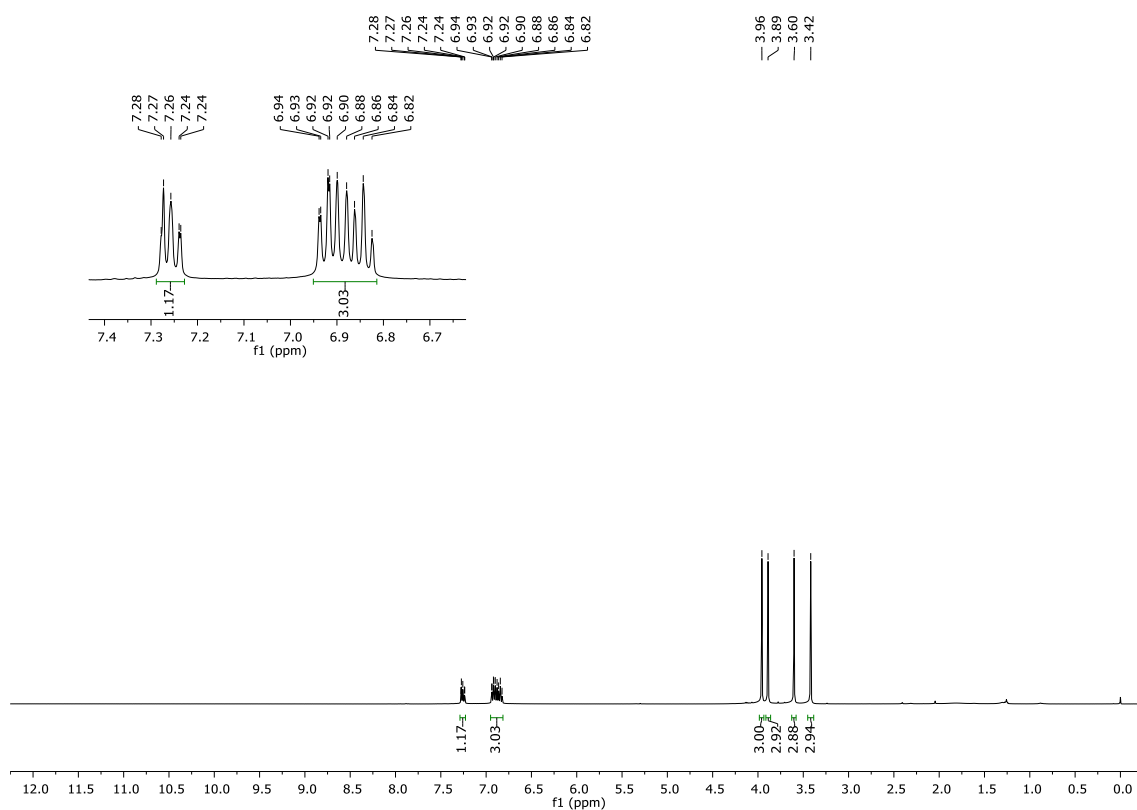


Figure S16. ^1H NMR (CDCl₃ 400 MHz) of compound **3f**.

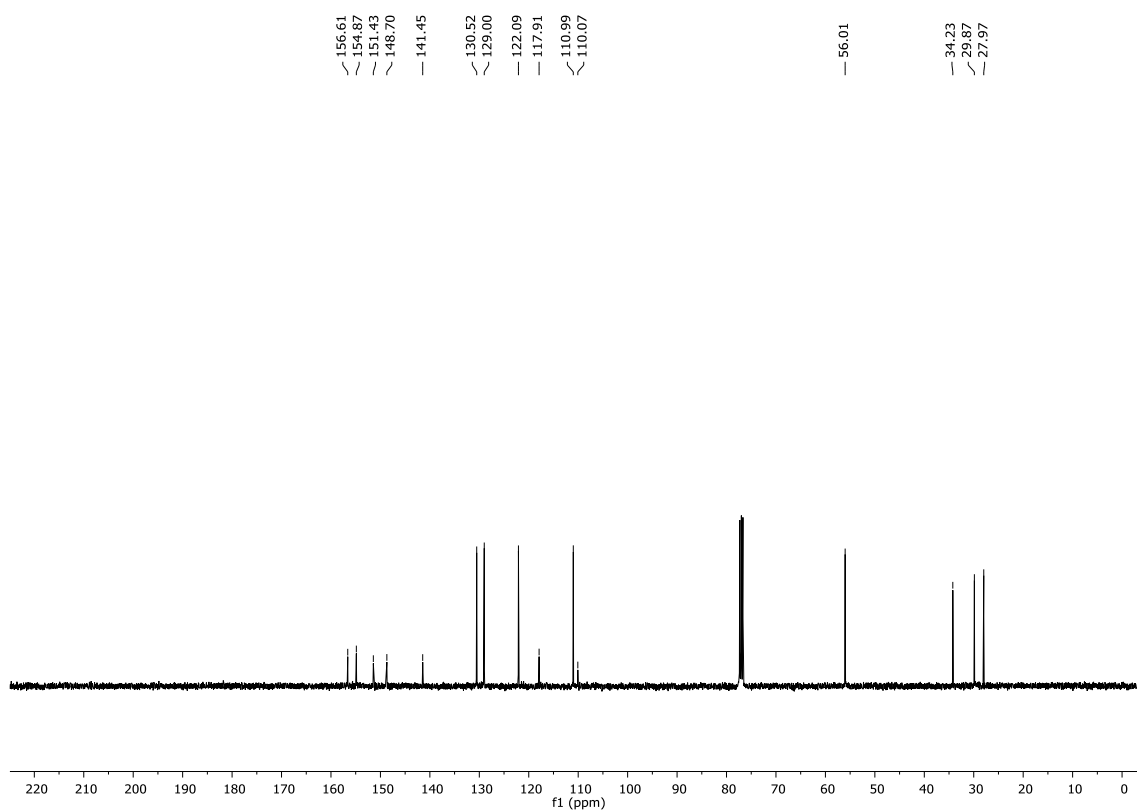


Figure S17. ^{13}C NMR (CDCl_3 100 MHz) of compound **3f**.

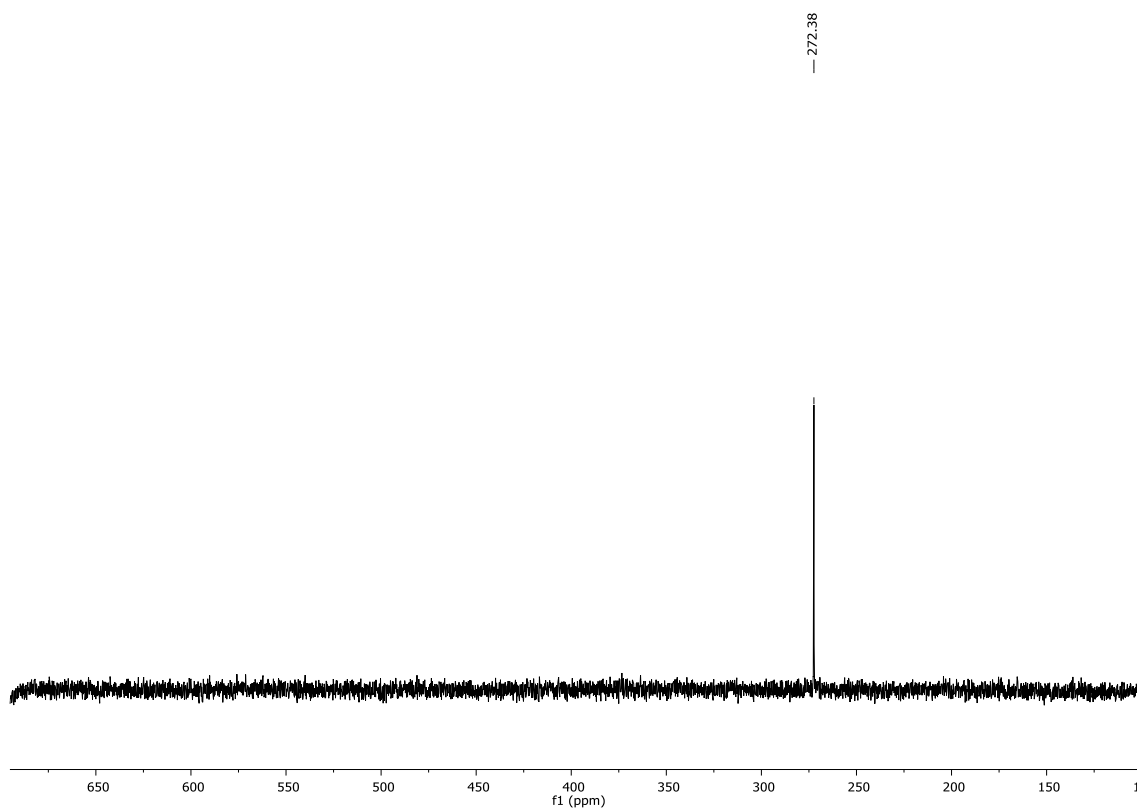


Figure S18. ^{77}Se NMR (CDCl_3 76 MHz) of compound **3f**.

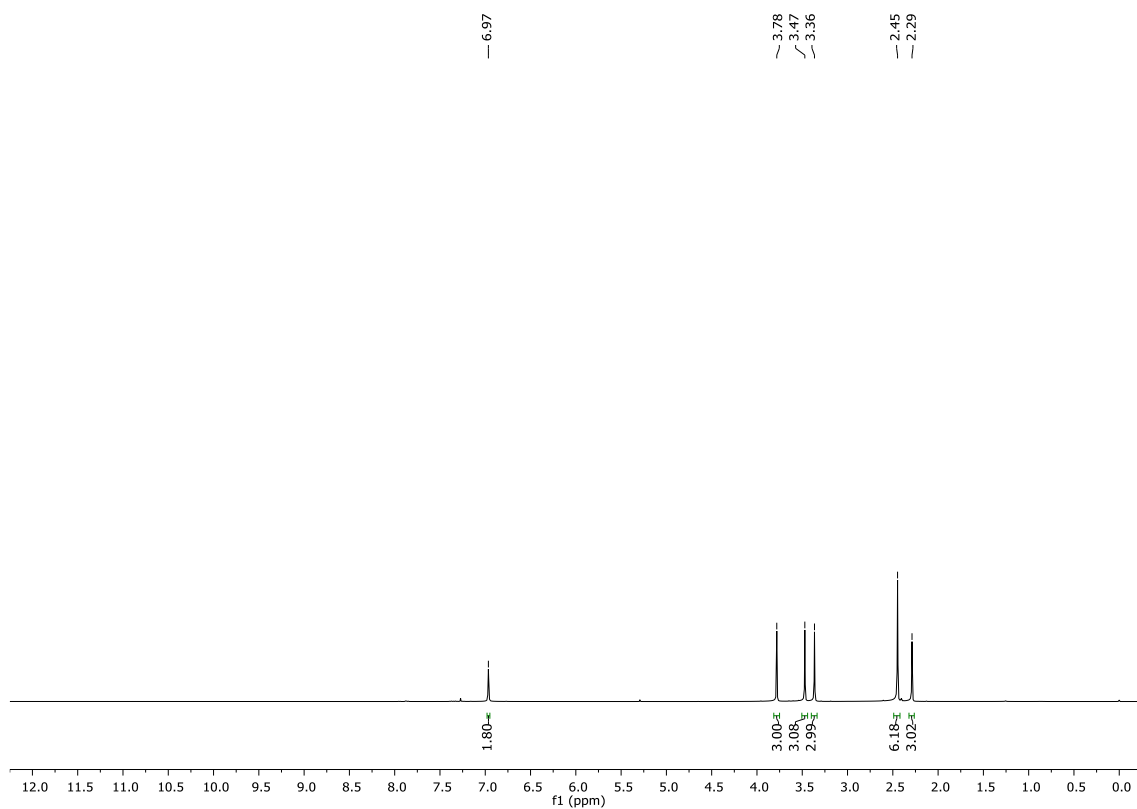


Figure S19. ^1H NMR (CDCl_3 400MHz) of compound **3g**.

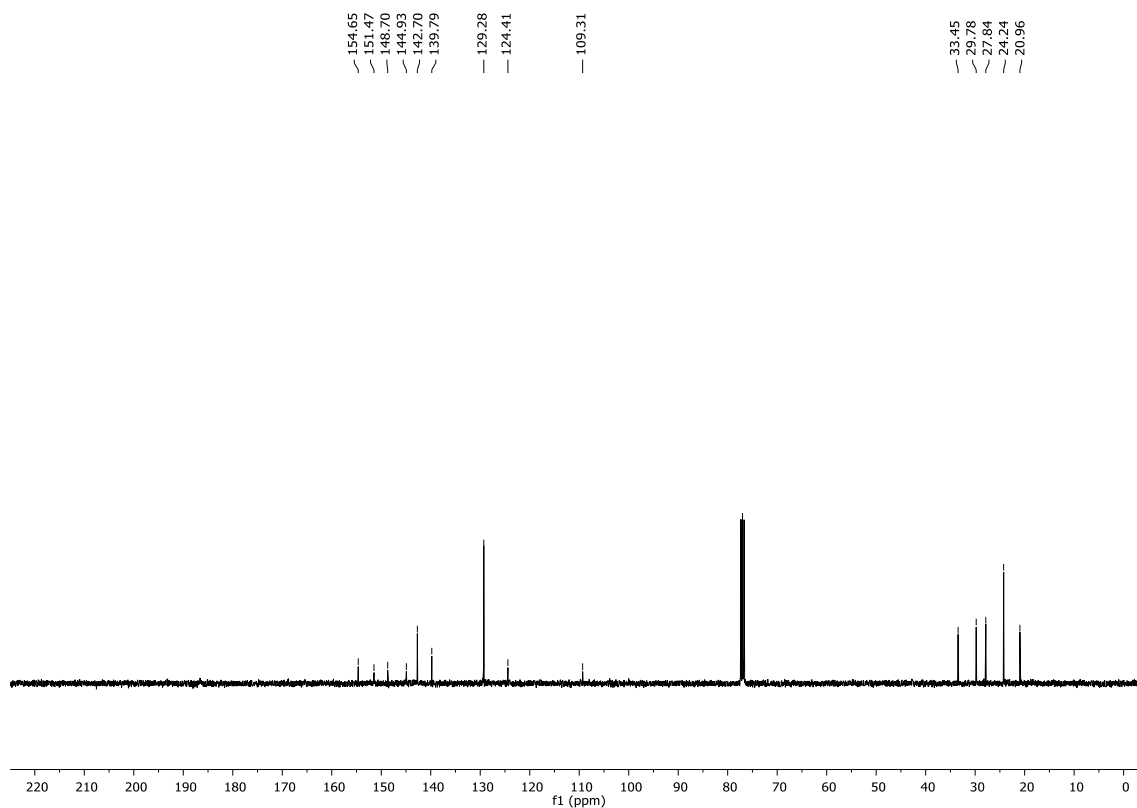


Figure S20. ^{13}C NMR (CDCl_3 100 MHz) of compound **3g**.

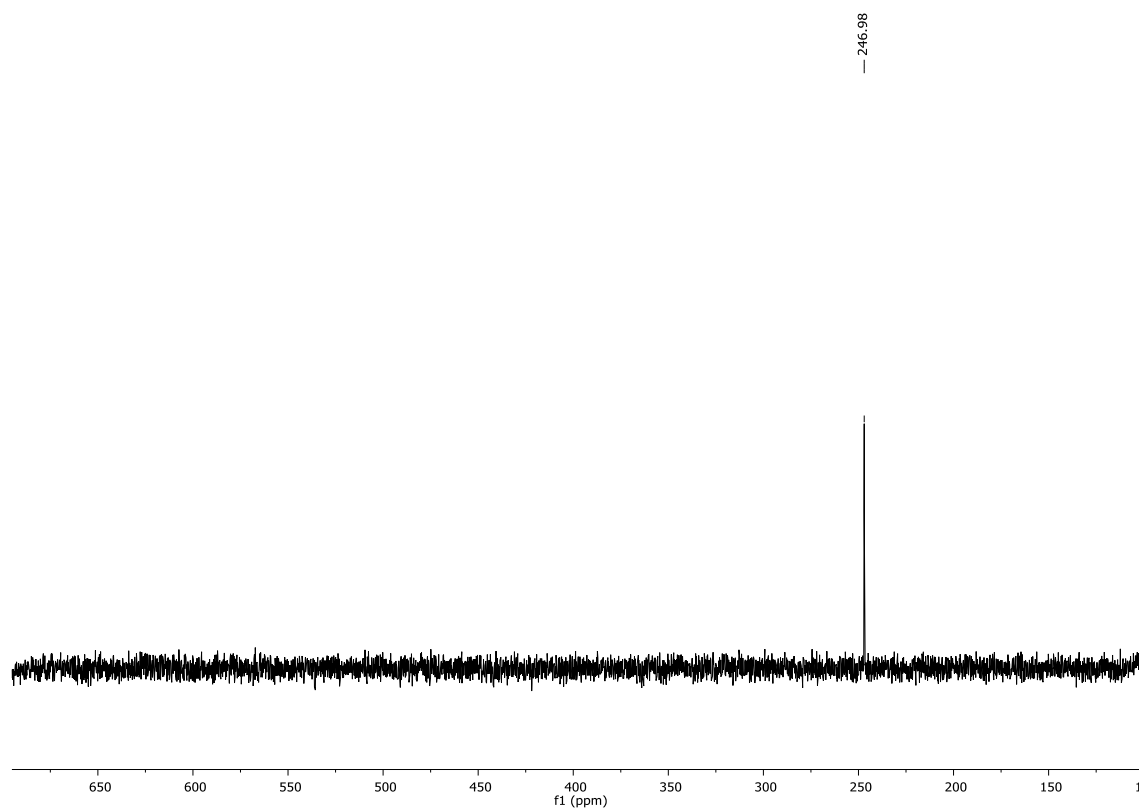


Figure S21. ^{77}Se NMR (CDCl_3 76 MHz) of compound **3g**.