Supporting Information

Visible-Light-Driven Electrophilic Chalcogen Species: Integration of Sustainable Synthesis, Green Metrics, and Computational Discovery of Antioxidants

Filipe. T. Coelho[a], Leonardo V. E. Guimarães[a], Camila P. Ebersol[a], Larissa G. Velasco[a], Pâmella da Costa[b], Cristiani F. Bortolatto[b], Wendell T. Coltro[a], Luciano M. Lião[a], Felipe L. Coelho[c]* and José S. S. Neto[a]*

[a] SustenSin - Instituto de Química, Universidade Federal de Goiás, 74690-900 Goiânia – GO, Brasil.

[b] LABIONEM - Centro de Ciências Químicas, Farmacêuticas e de Alimentos, Universidade Federal de 96010-900, Pelotas – RS, Brasil.

[c] Instituto de Química, Universidade Federal do Rio grande do Sul, 91501 – 970, Porto Alegre – RS, Brasil.

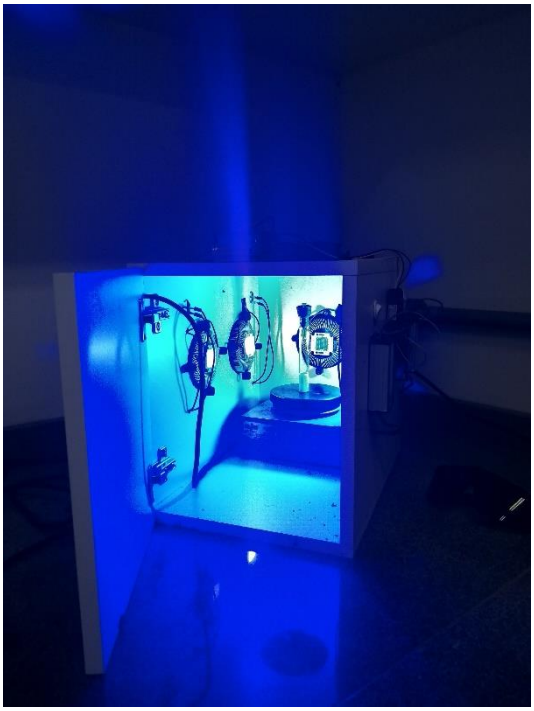
TABLE OF CONTENTS

1. General Information

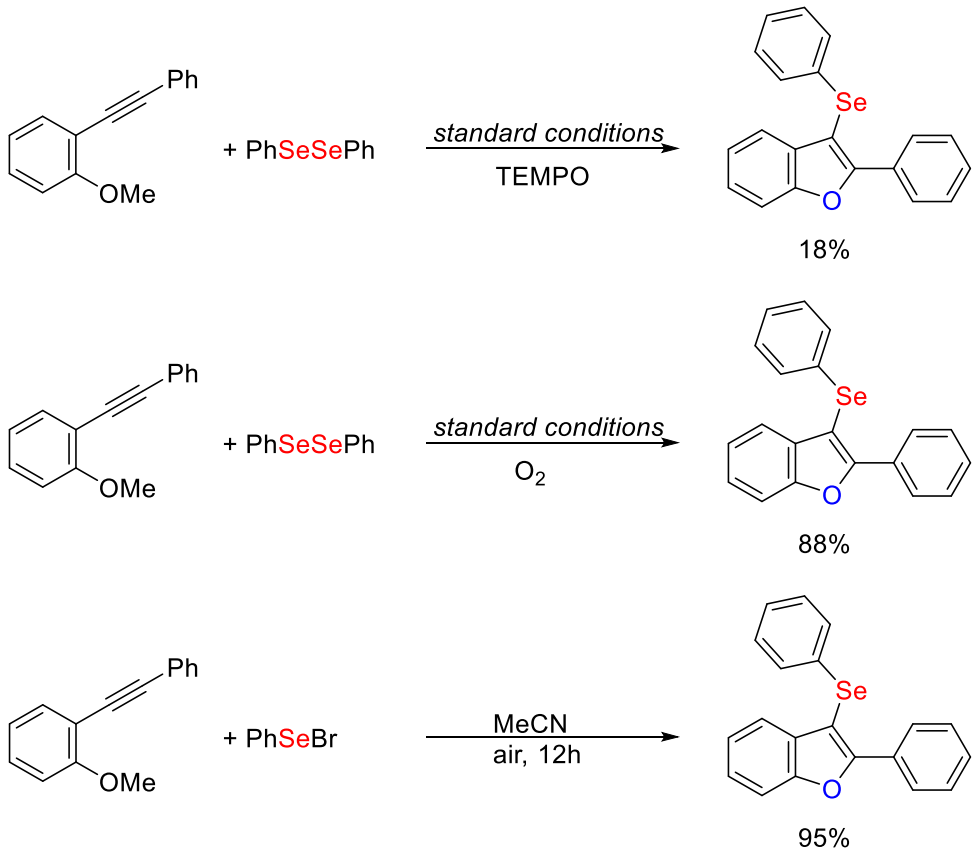
The reactions were monitored by TLC carried out on Merck silica gel (60 F254) by using UV light as visualizing agent and 5% vanillin in 10% H_2SO_4 and heat as developing agents. Nuclear magnetic resonance spectra (^{1}H NMR) were acquired on a Bruker Avance III 500 spectrometer (Bruker, Rheinstetten, Germany) operating at 11.75 Tesla, fitted with a broadband inverse (BBI) probe at 25 °C. ^{1}H NMR spectra were acquired by zg30 pulse program (Bruker) in 64k points with an acquisition time of 3.27 s, a relaxation delay of 1s and 16 scans. ^{13}C NMR spectra were acquired by zgpg30 pulse program (Bruker) in 64k points with an acquisition time of 0.91s, a relaxation delay of 0.5 s and 2048 scans. Chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) as the external reference. Coupling constants (J) are reported in Hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), dt (doublet of triplet), t (triplet), q (quartet), quint (quintet), sext (sextet), m (multiplet) and brd (broad doublet). Chemical shifts (δ) are given in parts per million from the peak of tetramethylsilane (δ = 0.00 ppm) as the internal standard in ^{1}H NMR or from the solvent peak of $CDCl_3$ (d = 77.00 ppm) in ^{13}C NMR. Triethylamine and carbon tetrabromide were purchased from commercial suppliers and used as received.

2. Photoreactor

The home-made photoreactor used in the experiments, illustrated above, consists of five irradiation units mounted inside an MDF box. The box has a width of 24 cm, with the sample positioned approximately 12 cm from the irradiation source. A cooling fan was installed at the top of the box to regulate the internal temperature, which is monitored with a digital thermometer. Each irradiation unit is equipped with either a 50 W blue or a 50 W white chip LED coupled to a processor cooler. For this study, a single 50 W blue LED unit was employed. The reaction mixture was stirred with a magnetic stirrer positioned inside the photoreactor.



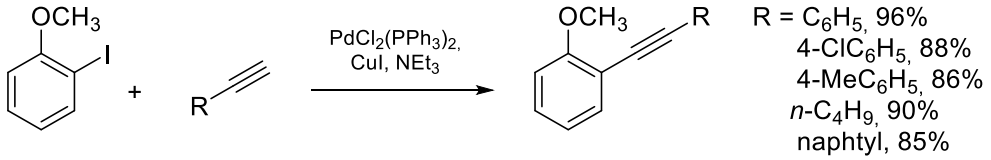
3. Controlled Experiments



Scheme 1. Controlled experiments performed to investigate the reaction mechanism.

4. Synthetic procedures

4.1 General procedure for 1-methoxy-2-(arylethynyl)benzene derivatives[1]



In Schlenk tube, a mixture of 2-iodoanisole (650 μL, 5.0 mmol), arylacetylene derivative (5.0 mmol), $PdCl_2(PPh_3)_2$ (3 mol%, 109 mg, 0.15 mmol) and CuI (3 mol%, 28 mg, 0.15 mmol) in triethylamine (20 mL) was stirred under argon at room temperature overnight. The reaction mixture was filtered through a layer of Celite and concentrated in vacuo. The residue was dissolved in ethyl acetate (50 mL) and washed with water (2 x 20 mL). The organic layer was dried over $MgSO_4$, the solvent was evaporated under reduced pressure and the crude product was purified on a silica gel column using hexane as eluent.

4.2.General procedure for the synthesis of diorganyl dichalcogenides 2.

4.2.1. General Procedure for the Synthesis of Organic Diselenides (RSeSeR)[2]

Under an inert atmosphere of nitrogen, a dry round-bottom flask equipped with a magnetic stirrer was charged with magnesium turnings (1.0 equiv) and anhydrous diethyl ether. The corresponding organic halide (R–X, 2.0 equiv) was added dropwise, and the mixture was stirred until complete formation of the organomagnesium reagent was achieved. Powdered elemental selenium (1.0 equiv) was then added portionwise at 0 °C, and the reaction mixture was allowed to warm to room temperature and stirred for an additional 1–2 h.

After completion, the reaction was quenched by careful addition of saturated aqueous ammonium chloride solution, and the resulting mixture was stirred under air for 4–6 h to promote oxidative coupling of the intermediate organoselenium species. The biphasic mixture was then extracted with ethyl acetate, and the combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and

---

[1] Jablonkai, I.; Bogner, M. M.; Zsignár-Nagy, B.; Simon, J.; London, G. *Eur. J. Org. Chem.* **2025,** *28*, e202401114.

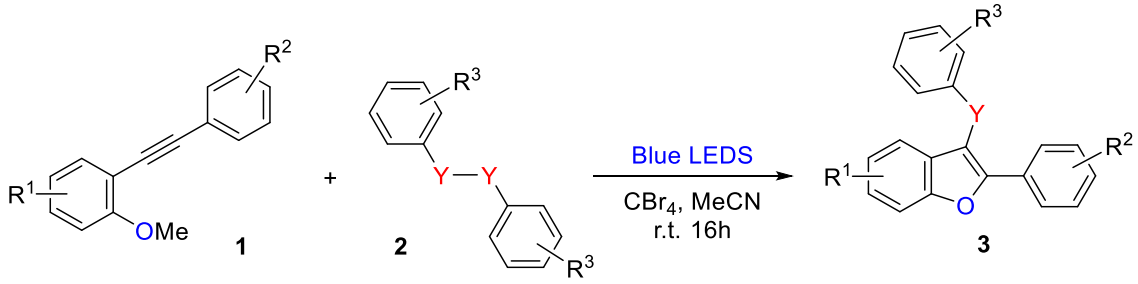
[2] H. J. Reich, M. L. Cohen and P. S. Clark, *Reagents for Synthesis of Organoselenium Compounds: Diphenyl Diselenide and Benzeneselenenyl Chloride*, *Org. Synth.*, **1979**, *59*, 141.

concentrated under reduced pressure. The crude product was purified by recrystallization from hexane to afford the corresponding organic diselenide (RSeSeR).

4.2.2. General Procedure for the Synthesis of Organic Disulfides (RSSR)[3]

A round-bottom flask equipped with a magnetic stirrer was charged with the corresponding thiol (R–SH, 2.0 equiv) and an appropriate solvent. Aqueous hydrogen peroxide (30%, 1.0 equiv) was added dropwise at room temperature, and the reaction mixture was stirred under air for 3 h. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by recrystallization from hexane to afford the corresponding organic disulfide (RSSR).

4.3.General procedure for the synthesis of compounds 3a-ae:

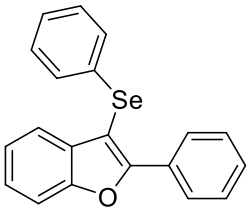


In a 5.0 mL glass tube, the corresponding 2-alynylanisole (0.25 mmol) and diorganyl chalcogenide (0.137 mmol) was added to a solution of CBr_4 (83 mg; 0.25 mmol) in acetonitrile under air. The reaction mixture was irradiated with blue light for 16h in the photoreactor. After completion of the reaction, the crude residue was concentrated under reduced pressure and adsorbed onto silica gel (~1.0 g). The mixture was dried under vacuum to afford a free-flowing powder, which was applied as a dry layer to the top of the prepacked silica gel column. Elution with hexane afforded the purified product.

[3] M. Kirihara, Y. Asai, S. Ogawa, T. Noguchi, A. Hatano and Y. Hirai, *Synthesis*, **2007**, 3286–3289.

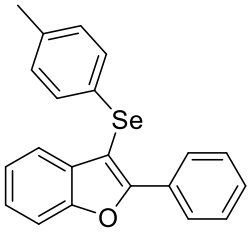
1. Spectral data of the products 3a-ad:

Compound 3a: 2-phenyl-3-(phenylselanyl)benzo[*b*]furan.[4]



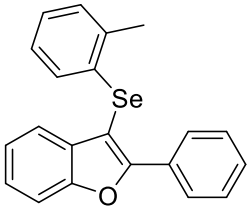
White solid. **Yield**: 86 mg, 98%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.2 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.24 – 7.21 (m, 1H), 7.18 – 7.10 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.4, 154.3, 132.1, 131.5, 130.3, 129.5, 129.3, 128.6, 127.9, 126.4, 125.4, 123.6, 121.4, 111.3, 99.8.

Compound 3b: 2-phenyl-3-(*p*-tolylselanyl)benzo[*b*]furan.[13]



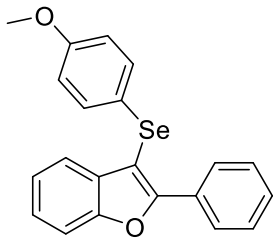
Yellow solid. **Yield:** 81 mg, 89%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.4 Hz, 2H), 7.52 (t, *J* = 8.2 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.22 – 7.19 (m, 3H), 6.96 (d, *J* = 8.1 Hz, 2H), 2.22 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.1, 154.2, 136.3, 132.1, 130.2, 129.7, 129.3, 128.6, 127.9, 127.6, 125.3, 123.5, 121.4, 111.2, 100.3, 21.1.

Compound 3c: 2-phenyl-3-(*o*-tolylselanyl)benzo[*b*]furan.[13]



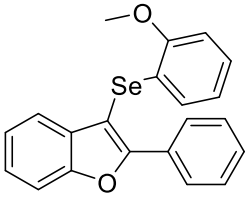
Pallid oil. **Yield:** 82 mg, 91%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.18 – 8.16 (m, 2H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.47 – 7.41 (m, 3H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.33 – 7.31 (m, 1H), 7.23 – 7.21 (m, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 2.47 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.7, 154.4, 136.9, 132.2, 132.1, 130.3, 130.2, 129.4, 128.6, 128.5, 127.9, 126.9, 126.2, 125.4, 123.6, 121.4, 111.3, 99.3, 21.6.

Compound 3d: 3-((*p*-methoxyphenyl)selanyl)-2-phenylbenzo[*b*]furan.[13]



Pallid yellow solid. **Yield**: 91 mg, 96%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.5 Hz, 2H), 7.57 – 7.55 (m, 2H), 7.52 – 7.49 (m, 2H), 7.45 – 7.42 (m, 1H), 7.37 – 7.32 (m, 3H), 7.29 – 7.24 (m, 1H), 6.76 (d, *J* = 8.4 Hz, 2H), 3.76 (s, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.9, 156.6, 154.2, 132.1, 132.0, 130.4, 129.3, 128.6, 127.9, 125.2, 123.5, 121.4, 121.2, 115.2, 111.3, 101.1, 55.4.

Compound 3e: 3-((2-methoxyphenyl)selanyl)-2-phenylbenzofuran.[13]

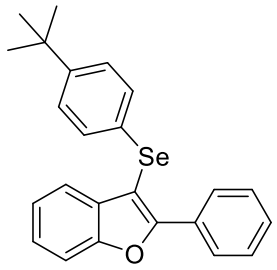


Yellow oil. **Yield:** 85 mg, 90%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.3 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7,44 – 7,41 (m, 2H), 7.38 – 7.33 (m, 2H), 7.25 – 7,22 (m, 1H), 7.13 – 7,10 (m, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.78 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.66 (t, *J* = 7.3 Hz, 1H), 3.95 (s, 3H). **^{13}C NMR** (125 MHz,

[4] G. B. Blödorn, L. F. B. Duarte, J. A. Roehrs, M. S. Silva, J. S. S. Neto and D. Alves, *Eur. J. Org. Chem.*, **2022**, *2022*, e202200775.

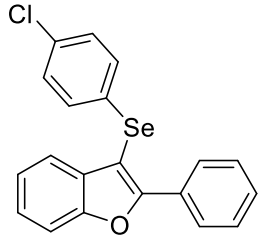
$CDCl_3$) δ 158.2, 156.0, 154.4, 132.3, 130.3, 129.4, 128.6, 128.3, 127.9, 126.9, 125.4, 123.6, 121.9, 121.5, 111.3, 110.4, 98.0, 56.0.

Compound 3f: 3-((4-(tert-butyl)phenyl)selanyl)-2-phenylbenzo[*b*]furan.[5]



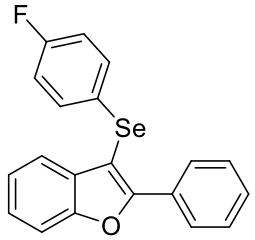
White solid. **Yield:** 23 mg, 23%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.8 Hz, 2H), 7.56 – 7.53 (m, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.40 – 7.37 (m, 1H), 7.35 – 7.31 (m, 1H), 7.25 – 7.22 (m, 3H), 7.18 (d, *J* = 8.4 Hz, 2H), 1.23 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.3, 154.3, 149.6, 132.3, 131.5, 130.4, 129.4, 129.3, 128.6, 127.9, 127.8, 126.6, 125.3, 123.5, 121.5, 111.3, 100.1, 34.5, 31.4.

Compound 3g: 3-((4-chlorophenyl)selanyl)-2-phenylbenzofuran.[13]



Yellow solid. Yield: 78 mg, 82%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.4 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.49 – 7.43 (m, 3H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.35 – 7.32 (m, 1H), 7.25 – 7.19 (m, 3H), 7.12 (d, *J* = 8.5 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.5, 154.3, 132.5, 131.7, 130.6, 130.1, 129.7, 129.6, 129.5, 128.7, 127.9, 125.5, 123.7, 121.2, 111.4, 99.5.

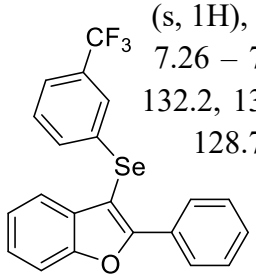
Compound 3h: 3-((4-fluorophenyl)selanyl)-2-phenylbenzo[*b*]furan.[13]



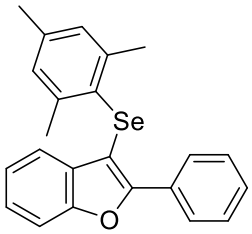
White solid. **Yield:** 67 mg, 73%. %. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.20 – 8.18 (m, 2H), 7.53 (brd, *J* = 8.2 Hz, 1H), 7.48 (brd, *J* = 8.3 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.39 – 7.36 (m, 1H), 7.32 – 7.29 (m, 1H), 7.27 – 7.25 (m, 2H), 7.23 – 7.20 (m, 1H), 6.86 – 6.83 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.0 (d, *J* = 246.2 Hz), 157.2, 154.3, 131.8, 131.5 (d, *J* = 7.6 Hz), 130.2, 129.5, 128.6, 127.9, 125.7 (d, *J* = 3.2 Hz), 125.4, 123.6, 121.2, 116.6 (d, *J* = 21.8 Hz), 111.4, 100.3.

Compound 3i: 2-phenyl-3-((3-(trifluoromethyl)phenyl)selanyl)benzo[*b*]furan.[13]

White solid. **Yield:** 84 mg, 81%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.18 – 8.16 (m, 2H), 7.60 (s, 1H), 7.57 (brd, *J* = 8.2 Hz, 1H), 7.49 – 7.43 (m, 3H), 7.41 – 7.33 (m, 4H), 7.26 – 7.20 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.9, 154.3, 132.9, 132.2, 131.6, 131,7 (q, J_2 = 32.7 Hz), 131.5, 130.0, 129.7 (d, J_3 = 9.8 Hz), 128.7, 127.9, 125.7 (q, J_4 = 4.4 Hz), 125.6, 123.8, 123.6 (q, J_1 = 272.9 Hz), 123.2 (q, J_4 = 3.3 Hz), 121.0, 111.5, 98.9.



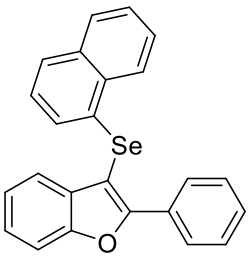
Compound 3j: 3-(mesitylselanyl)-2-phenylbenzofuran.[13] White solid. **Yield:** 65 mg, 66%.**^{1}H NMR** (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.18 – 8.04 (m, 2H), 7.46 (dt, *J* = 14.1, 7.9 Hz, 3H), 7.41 – 7.35 (m, 1H), 7.25 – 7.16 (m, 1H), 7.05 – 6.98 (m, 1H), 6.97 – 6.92 (m, 1H), 6.85 (s, 2H), 2.39 (s, 6H), 2.22 (s, 3H).**^{13}C NMR** (125 MHz, $CDCl_3$) δ



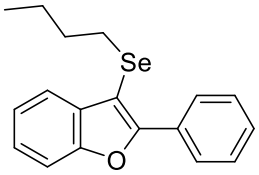
[5] M. H. Shaw, J. Twilton and D. W. C. MacMillan, *J. Org. Chem.*, 2016, **81**, 6898.

154.0, 153.5, 142.2, 138.2, 131.6, 130.7, 128.9, 128.6, 128.4, 127.47, 127.4, 126.4, 124.6, 122.8, 120.7, 111.0, 102.3, 24.1, 20.9.

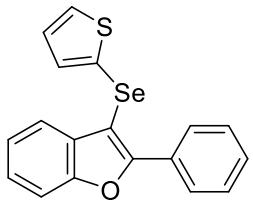
Compound 3k: 3-(naphthalen-1-ylselanyl)-2-phenylbenzo[*b*]furan.[6]



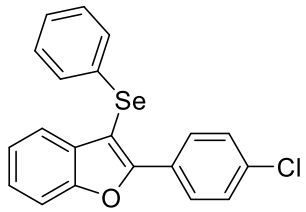
White solid. **Yield:** 83 mg, 83%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.22 – 8.19 (m, 3H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.55 – 7.44 (m, 4H), 7.41 – 7.38 (m, 2H), 7.36 – 7.33 (m, 1H), 7.31 – 7.28 (m, 1H), 7.25 - 7.23 (m, 1H), 7.18 – 7.10 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.8, 154.4, 134.2, 132.6, 132.3, 132.0, 130.2, 129.5, 128.8, 128.6, 127.9, 127.2, 126.9, 126.6, 126.4, 126.3, 125.7, 125.4, 123.6, 121.4, 111.4, 99.2.



Compound 3l: 3-(butylselanyl)-2-phenylbenzofuran.[13] Yellow Oil. **Yield:** 61mg, 74%.**^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.0 Hz, 2H), 7.69 – 7.66 (m, 1H), 7.51 – 7.47 (m, 1H), 7.44 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.31 – 7.25 (m, 2H), 2.76 (t, *J* = 7.4 Hz, 2H), 1.53 (quint, *J* = 7.4 Hz, 2H), 1.31 (sext, *J* = 7.4 Hz, 2H), 0.76 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 155.9, 153.90 132.7, 130.7, 128.9, 128.39, 127.7, 124.9, 123.1, 121.0, 111.3, 100.4, 32.4, 28.3, 22.7, 13.5.



Compound 3m: 2-phenyl-3-(thiophen-2-ylselanyl)benzofuran.[13] Pallid yellow solid.**Yield** = 56 mg, 63%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ δ 8.25 (d, *J* = 7.4 Hz, 2H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 3H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.22 (d, *J* = 3.5 Hz, 1H), 6.89 (dd, *J* = 5.3, 3.5 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.1, 153.8, 133.5, 131.6, 130.1, 129.8, 129.9, 128.4, 128.0, 127.7, 125.1, 124.5, 123.3, 121.0, 111.1, 102.1.

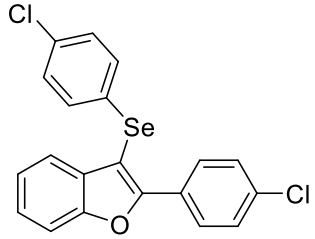


Compound 3n: 2-(4-chlorophenyl)-3-(phenylselanyl)benzo[*b*]furan.[7] Yellow solid. **Yield:** 55 mg, 57%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.6 Hz, 2H), 7.52 (t, *J* = 7.1 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.34 – 7.31 (m, 1H), 7.26 – 7.25 (m, 2H), 7.24 – 7.21 (m, 1H), 7.16 – 7.12 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.1, 154.2, 135.4, 131.9, 131.2, 129.5, 129.4, 129.1, 128.9, 128.7, 126.6, 125.6, 123.7, 121.4, 111.3, 100.4.

[6] Y. Murata, N. Otake, M. Sano, M. Matsumura and S. Yasuike, *Asian J. Org. Chem.*, 2021, **10**, 2975–2981.

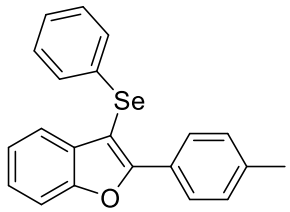
[7] C. V. Doerner, M. R. Scheide, C. R. Nicoleti, D. C. Durigon, V. D. Idiarte, M. J. A. Sousa, S. R. Mendes, S. Saba, J. S. S. Neto, G. M. Martins, J. Rafique and A. L. Braga, *Front. Chem.*, 2022, **10**, 880099.

Compound 3p: 2-(4-chlorophenyl)-3-((4-chlorophenyl)selanyl)benzo[*b*]furan.[16]



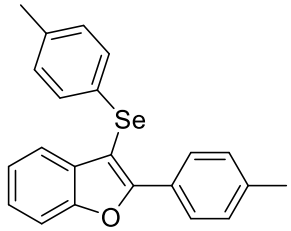
White solid. **Yield:** 83 mg, 79%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 – 8.12 (m, 2H), 7.55 (d, *J* = 8.2 Hz, 1H), 7,51 – 7, 48 (m, 1H), 7.44 – 7.42 (m, 2H), 7.38 – 7.34 (m, 1H), 7.28 – 7.24 (m, 1H), 7.21 – 7.18 (m, 2H), 7.15 – 7.12 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.9, 154.3, 135.6, 133.5, 132.7, 131.7, 130.7, 129.7, 129.5, 129.1, 128.9, 128.6, 125.8, 123.9, 121.2, 111.5, 100.1.

Compound 3q: 3-(phenylselanyl)-2-(*p*-tolyl)benzo[*b*]furan.[16]



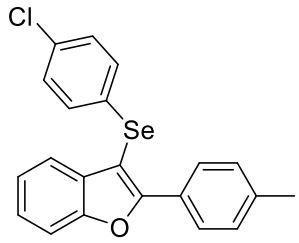
White solid. **Yield:** 80 mg, 88%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.1 Hz, 2H)**,** 7.54 – 7.49 (m, 2H), 7.32 – 7.27 (m, 3H), 7.25 – 7. 20 (m, 3H), 7.16 – 7.11 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.7, 154.2, 139.6, 132.2, 131.7, 129.4, 129.3, 129.2, 127.9, 127.5, 126.3, 125.1, 123.5, 121.2, 111.2, 99.1, 21.6.

Compound 3r: 2-(*p*-tolyl)-3-(*p*-tolylselanyl)benzo[*b*]furan.[16]

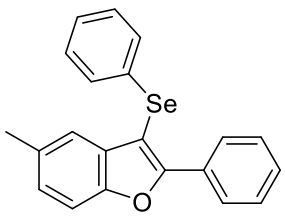


Yellow oil. **Yield:** 73 mg, 77%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 2H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.30 – 7.27 (m, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.21 – 7.18 (m, 3H), 6.95 (d, *J* = 8.0 Hz, 2H), 2.37 (s, 3H), 2.22 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.4, 154.2, 139.5, 136.3, 133.1, 132.2, 130.2, 129.6, 129.3, 127.8, 127.6, 125.0, 123.4, 121.2, 111.2, 99.5, 21.6, 21.1.

Compound 3s: 3-((4-chlorophenyl)selanyl)-2-(*p*-tolyl)benzo[*b*]furan.[16]



Yellow oil. **Yield:** 77 mg, 78%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.26 – 7.23 (m, 3H), 7.20 – 7.18 (m, 2H), 7.11 (d, *J* = 8.6 Hz, 2H), 2.39 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.9, 154.2, 139.8, 132.4, 131.9, 130.5, 129.9, 129.5, 129.4, 127.8, 127.3, 125.3, 123.6, 121.0, 111.3, 98.8, 21.6.

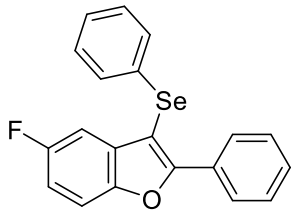


Compound 3t: 5-methyl-2-phenyl-3-(phenylselanyl)benzo[*b*]furan.[8]

White solid. **Yield:** 71 mg, 78%. White solid. **Yield: ^{1}H NMR** (500 MHz, $CDCl_3$) δ (d, *J* = 7.4 Hz, 2H), 7.42 (ddd, *J* = 7.9, 5.1, 2.4 Hz, 3H), 7.39 – 7.34 (m, 1H), 7.31 (d, *J* = 1.7 Hz, 1H), 7.30 –

[8] Rafaela M. Gay, Flávia Manarin, Caroline C. Schneider, Daniela A. Barancelli, Michael D. Costa, Gilson Zeni *J. Org. Chem.* 2010, **75**, 5701–5706

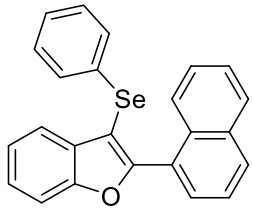
7.26 (m, 2H), 7.18 – 7.07 (m, 4H), 2.39 (s, 2H). **^{3}C NMR** (125 MHz, $CDCl_3$) δ 157.5, 152.5, 133.0, 132.0, 131.6, 130.2, 129.3, 129.2, 128.9, 128.4, 127.7, 126.5, 126.10, 120.9, 110.7, 99.2, 21.3.



Compound 3u: 5-fluoro-2-phenyl-3-(phenylselanyl)benzo[*b*]furan.[17]

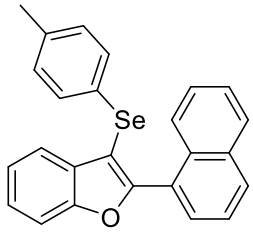
White solid. **Yield:** 59 mg, 64%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ8.19 (d, *J* = 7.6 Hz, 2H), 7.49 – 7.38 (m, 4H), 7.28 (dd, *J* = 7.3, 2.1 Hz, 2H), 7.16 (td, *J* = 6.2, 5.6, 2.3 Hz, 4H), 7.03 (td, *J* = 9.0, 2.6 Hz, 1H).. **^{3}C NMR** (125 MHz, $CDCl_3$) δ 159.7 (d, *J* = 239.5 Hz), 159.0, 133.2 (d, *J* = 10.8 Hz), 131.5, 130.9, 129.8, 129.6, 129.40, 129.3, 128.5, 127.8, 126.5, 112.9 (d, *J* = 26.3 Hz), 111.9 (d, *J* = 9.4 Hz), 106.8 (d, *J* = 25.6 Hz) ·99.8 (d, *J* = 3.9 Hz).

Compound 3v: 2-(naphthalen-1-yl)-3-(phenylselanyl)benzo[*b*]furan.[9]



White solid. **Yield:** 79 mg**,** 79%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (t, *J* = 7.4 Hz, 2H)**,** 7.91 (d, *J* = 7.7 Hz, 1H), 7.68 (dd, *J* = 7.1, 1.0 Hz, 1H), 7.97 (t, *J* = 7.4 Hz, 1H), 7.56 – 7.46 (m, 4H), 7.40 – 7.37 (m, 1H), 7.31 – 7.35 (m, 3H), 7.13 – 7.11 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.1, 155.1, 133.8, 132.3, 131.4, 130.9, 130.6, 129.9,192.9, 129.3, 128.6, 127.4, 126.9, 126.4, 126.3, 126.0, 125.3, 125.0, 123.6, 121.5, 111.6, 103.8.

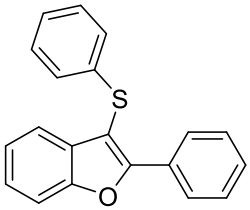
Compound 3w: 2-(naphthalen-1-yl)-3-(p-tolylselanyl)benzo[*b*]furan.[10]



White solid. **Yield:** 87 mg, 84%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 16.5, 8.2 Hz, 2H) , 7.88 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.0 Hz, 1H), 7.56 (dd, *J* = 14.6, 7.9 Hz, 2H), 7.51 – 7.44 (m, 3H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 2.21 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.8, 155.0, 136.4, 133.8, 132.3, 131.0, 130.5, 130.4, 130.1, 130.0, 128.5, 127.5,127.4,126.9, 126.3, 126.1,125.2, 125.0, 123.6, 121.5, 111.6, 104.6, 21.1.

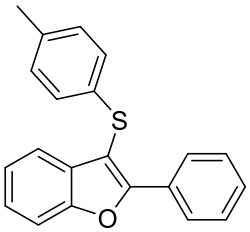
Compound 3z: 2-phenyl-3-(phenylthio)benzo[*b*]furan.[13]

[9] J. C. Kazmierczak, A. M. S. Recchi, F. Gritzenco, E. B. Balbom, T. Barcellos, A. Sperança and B. Godoi, *Eur. J. Org. Chem.*, 2017, **2017**, 6382–6389.



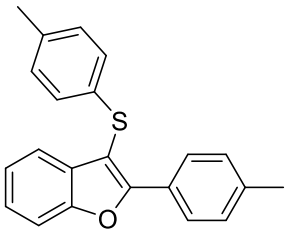
Pallid oil**. Yield:** 74 mg, 98%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.49 – 7.43 (m, 3H), 7.40 – 7.38 (m, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.22 – 7.19 (m, 5H), 7.12 – 7.09 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.6, 154.1, 136.3, 130.9, 129.9, 129.5, 129.2, 128.7, 127.6, 126.7, 125.7, 125.4, 123.6, 120.6, 111.5, 104.9.

Compound 3ab: 2-phenyl-3-(*p*-tolylthio)benzo[*b*]furan.[11]



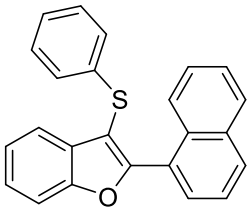
Pallid yellow solid. **Yield:** 55 mg, 70%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.26 – 8.24 (m, 2H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.49 – 7.45 (m, 3H), 7.42 -7.40 (m, 1H), 7.35 – 7.32 (m, 1H), 7.24 - 7.21 (m, 1H), 7.12 (brd, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 2.27 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.3, 154.1, 135.7, 132.6, 131.1, 129.9, 129.5, 128.7, 127.5, 127.1, 125.3, 123.5, 120.6, 111.4, 21.0.

Compound 3ac: 2-(*p*-tolyl)-3-(*p*-tolylthio)benzo[*b*]furan.[20]



Pallid oil. **Yield:** 63 mg, 77%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.46 (brd, *J* = 8.3 Hz, 1H), 7.30 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H), 7.26 – 7.23 (m, 2H), 7.20 (dd, *J* = 11.1, 3.9 Hz, 1H), 7.10 (brd, *J* = 8.2 Hz, 2H), 6.99 (brd, *J* = 8.1 Hz, 2H), 2.38 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.7, 153.9, 139.7, 135.5, 132.8, 131.2, 129.9, 129.4, 127.5, 127.2, 126.9, 125.1, 123.5, 120.4, 111.3, 104.6, 21.6, 21.0.

Compound 3ad: 2-(naphthalen-1-yl)-3-(phenylthio)benzo[*b*]furan.[20]



White Solid. **Yield:** 54 mg, 61%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (brd, *J* = 7.8 Hz, 1H), 7.94 (brd, *J* = 8.3 Hz, 1H), 7.90 – 7.89 (m, 1H), 7.72 (d, *J* = 7.1 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.52 – 7.49 (m, 4H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.16 – 7.15 (m, 4H), 7.09 – 7.05 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.3, 154.9, 136.4, 133.9, 132.1, 130.6, 129.8, 129.8, 129.1, 128.6, 127.0, 126.9, 126.8, 126.3, 126.0, 125.6, 125.4, 125.1, 123.7, 120.8, 111.8, 108.2.

[11] J. S. Han, Y. Shao, X.-H. Zhang and P. Zhong, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2013, **188**, 1599–1610.

2. Green Chemistry Metrics

Table 1. Experimental data for calculation of Reaction yield, E-factor, Atom economy, Atom efficiency, Carbon efficiency, Reaction Mass Efficiency, stoichiometric factor, Material Recovery Potential.

PART 1: RAW MATERIALS USAGE								
(A) REACTION STAGE:								
Reaction Scale	2.50E-04							
(i) REAGENTS	MW (g/mol)	*Theorical Stoich*	MW (g/mol)	Used Stoich	MW (g/mol)	Moles	Mass (g)	Carbon number
2-(phenylethynyl) alkynylanisole	208.25	1	208.25	1	208.25	2.50E-04	0.0521	15
1,2-diphenyl diselenide	312.13	0.5	156.065	0.55	171.6715	1.38E-04	0.0429	6
Tetrabromomethane	331.62	1	331.62	1	331.62	2.50E-04	0.0829	1
TOTAL REAGENTS			695.935		711.5415		0.1779	**22**
(ii) SOLVENTS			Density (g/mL)	Volume (mL)		Mass (g)		
Acetonitrile			0.786	1		0.786		
TOTAL SOLVENTS						0.786		
Reaction Materials Subtotals						0.9639		
(B) WORK-UP STAGE:								
MATERIAL USED			Density (g/mL)	Volume (mL)		Mass (g)		
TOTAL WORK-UP MATERIALS						0		
(C) PURIFICATION STAGE:								
MATERIAL			Density (g/mL)	Volume (mL)		Mass (g)		
Silica						5		
Hexane			0.661	80		52.88		
					Total	57.88		
Material recycled			Density (g/mL)	Volume (mL)		Mass (g)		
Hexane			0.661	68		44.948		
					Total	44.948		
TOTAL PURIFICATION MATERIALS					12.932			
Post-reaction Materials Subtotals					12.932			
					Mass (g)			
TOTAL INPUT MATERIALS (reclaiming)					13.90			
TOTAL INPUT MATERIALS (no reclaiming)					58.84			

(E) PRODUCT INFORMATION			**Mass (g)**	**MW (g/mol)**	**Moles**	**Mol (Limiting)**	Carbon number
selenylbenzo[b]furan			0.08557	349.29	0.00024	2.50E-04	20

PART 2: GREEN METRICS ANALYSIS

		Obtained	Ideal			
(i) Reaction yield	Rx Yield	0.980	1			
(ii) E-factor	E-factor	162.39				
(iii) Atom economy	AE	0.502	1	without CBr4	0.959	
(iv) Atom efficiency	Atom efficiency	0.492	1			
(v) Carbon efficiency	Carbon efficiency	0.909	1			
(vi) Reaction Mass Efficiency (RME)	RME	0.481	1			
(vii) stoichiometric factor (SF)	SF	1.022	1			
(viii) Material Recovery Potential (MRP)	MRP	0.764	1			

Table 2. Calculation of EcoScale parameter.

The penalty points to calculate the EcoScale			
		for **3a**	for **3z**
Parameter		Penalty points	Penalty points
1. Yield		1	1
2. Price of reaction components (10 mmol scale)			
	Expensive (< $30)	3	3
3. Safety			
Acetonitrile, Diphenyldiselenide			
	N (dangerous for environment)	5	5
	T (toxic)	5	0
	F (highly flammable)	5	5
4. Technical setup			
		0	0
5. Temperature/time			
	Room temperature, < 24 h	1	1
6. Workup and purification			
	Classical chromatography	10	10
	Ecoscale	70	75

3. NMR Characterization

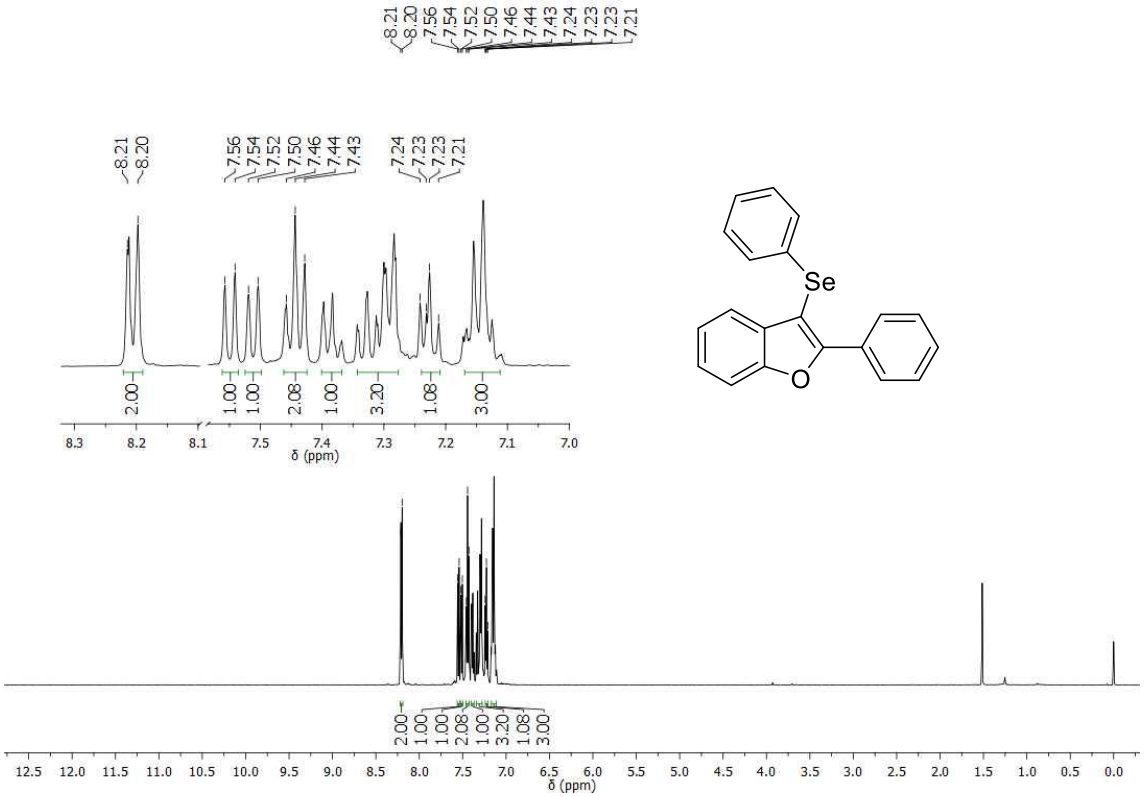


Figure S1: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3a**

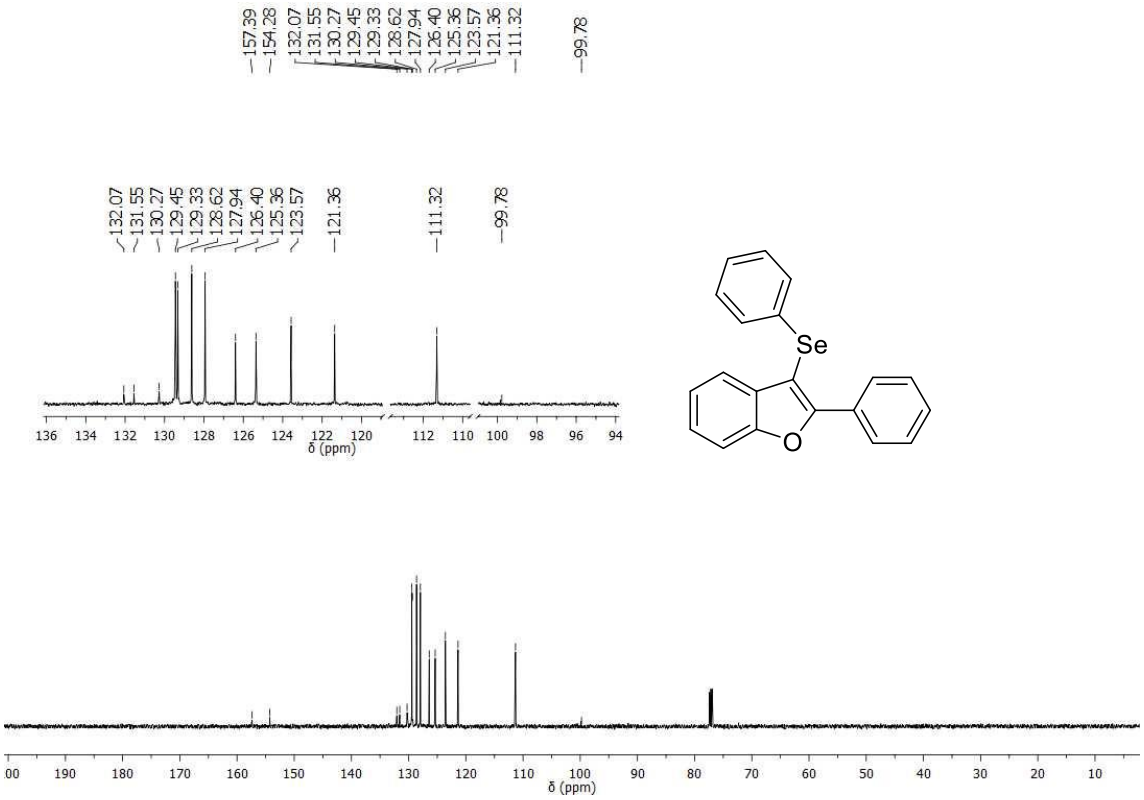


Figure S2: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3a**

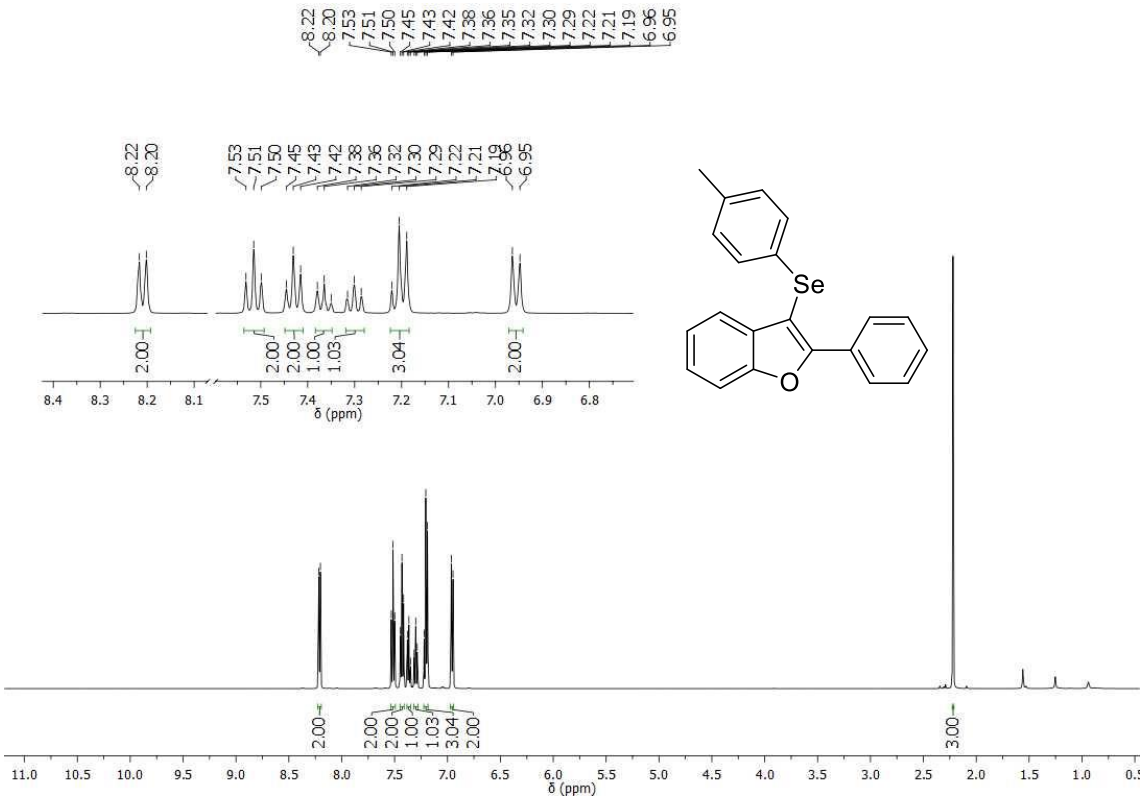


Figure S3: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3b**

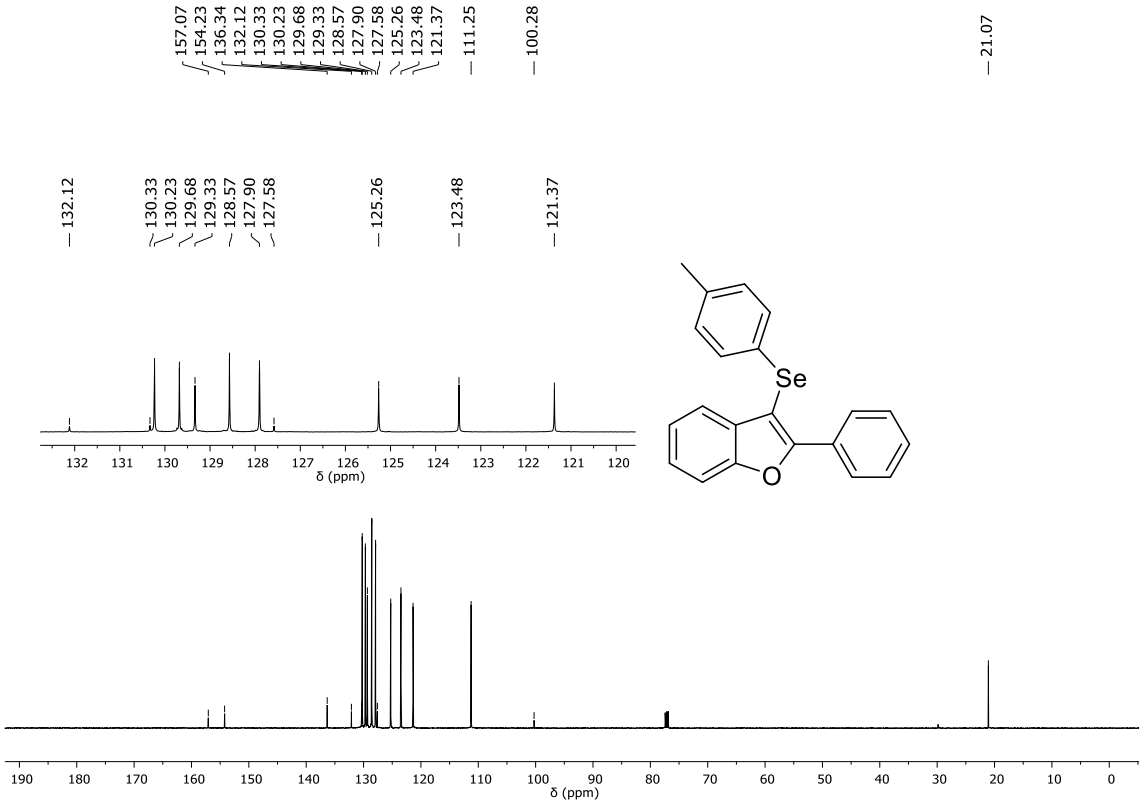


Figure S4: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3b**

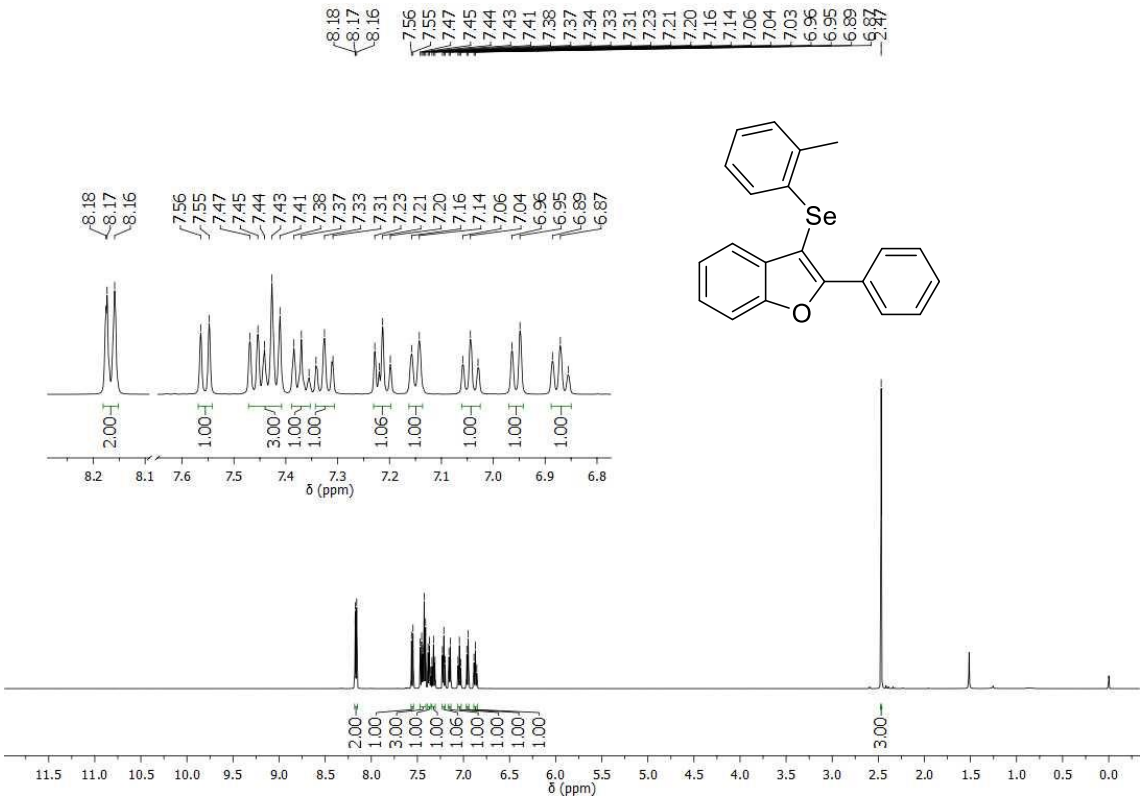


Figure S5: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3c**

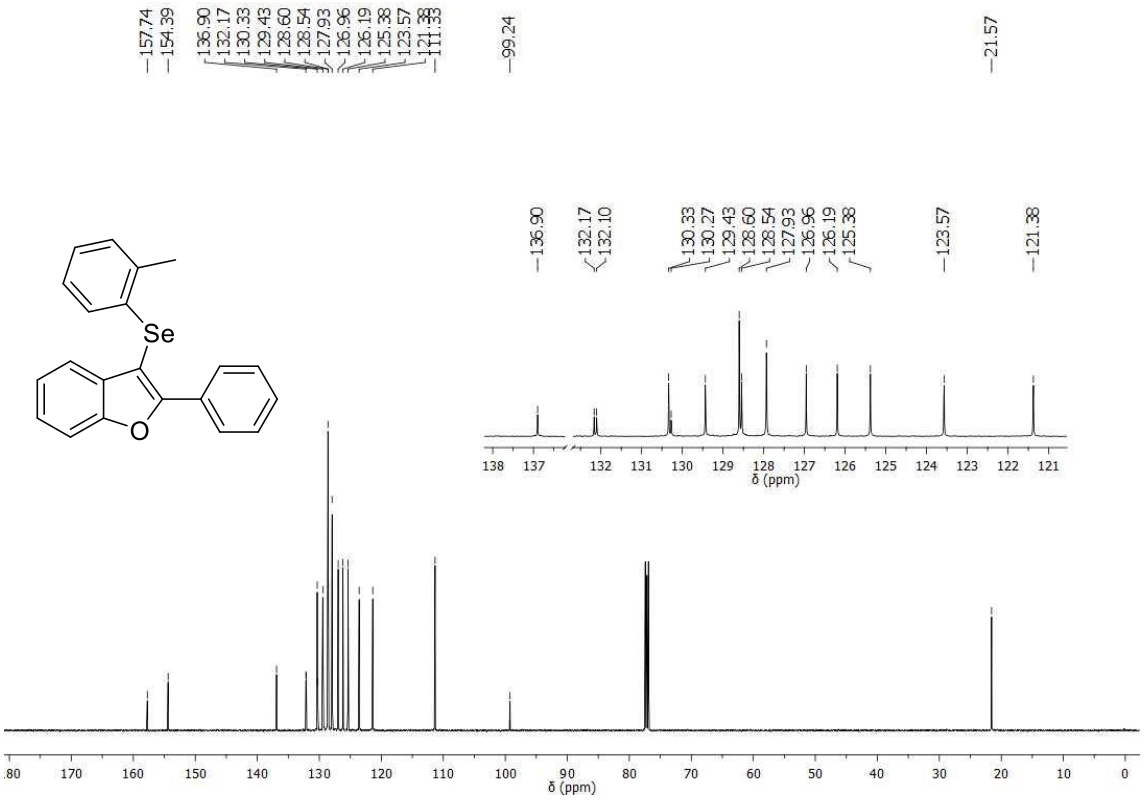


Figure S6: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3c**

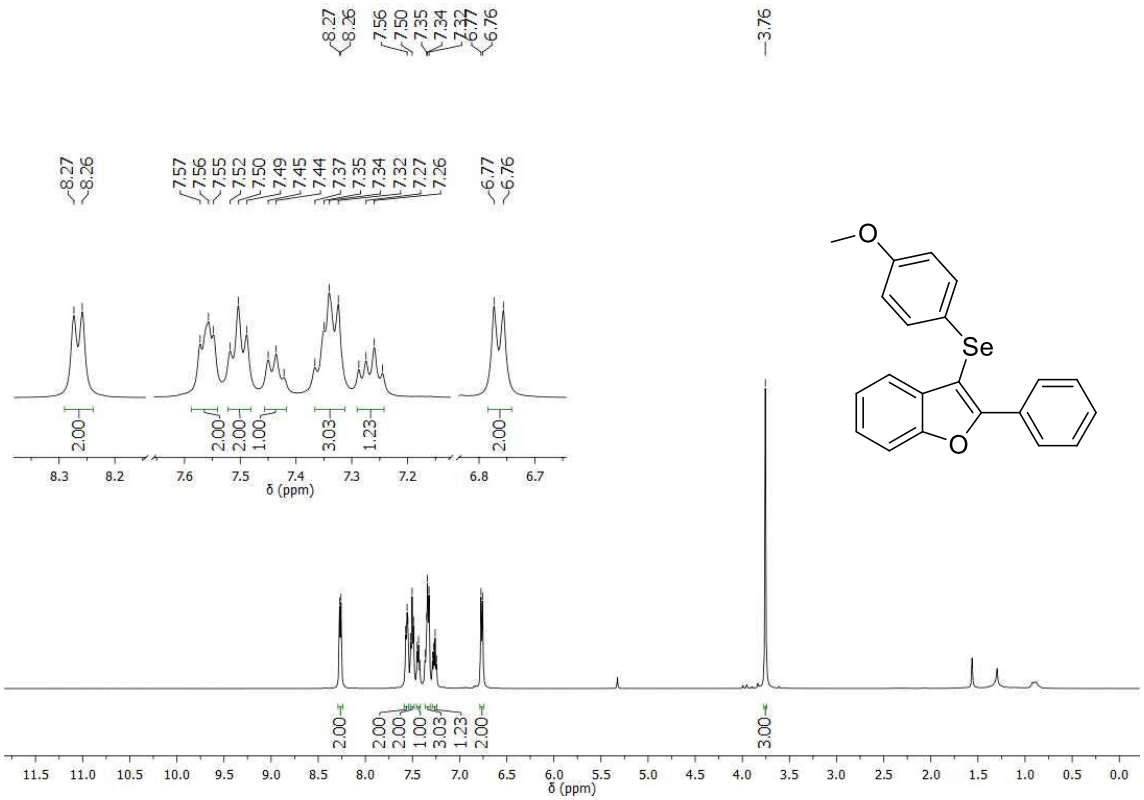


Figure S7: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3d**

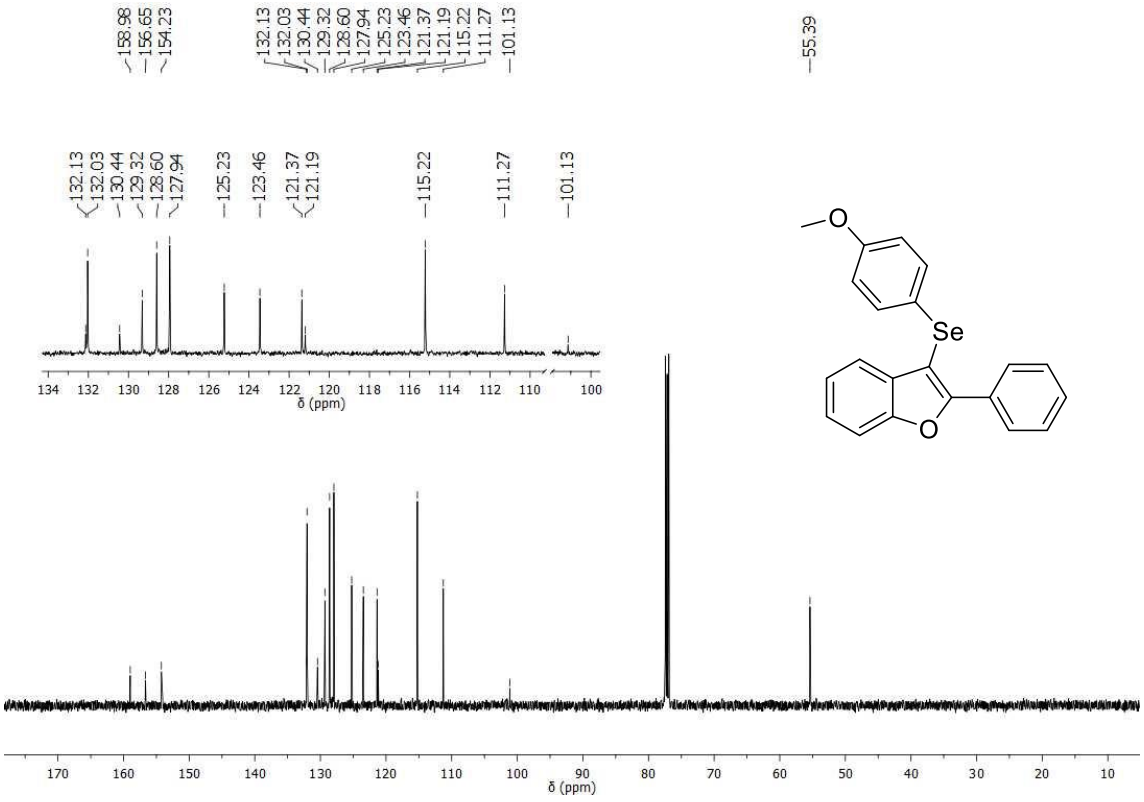


Figure S8: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3d**

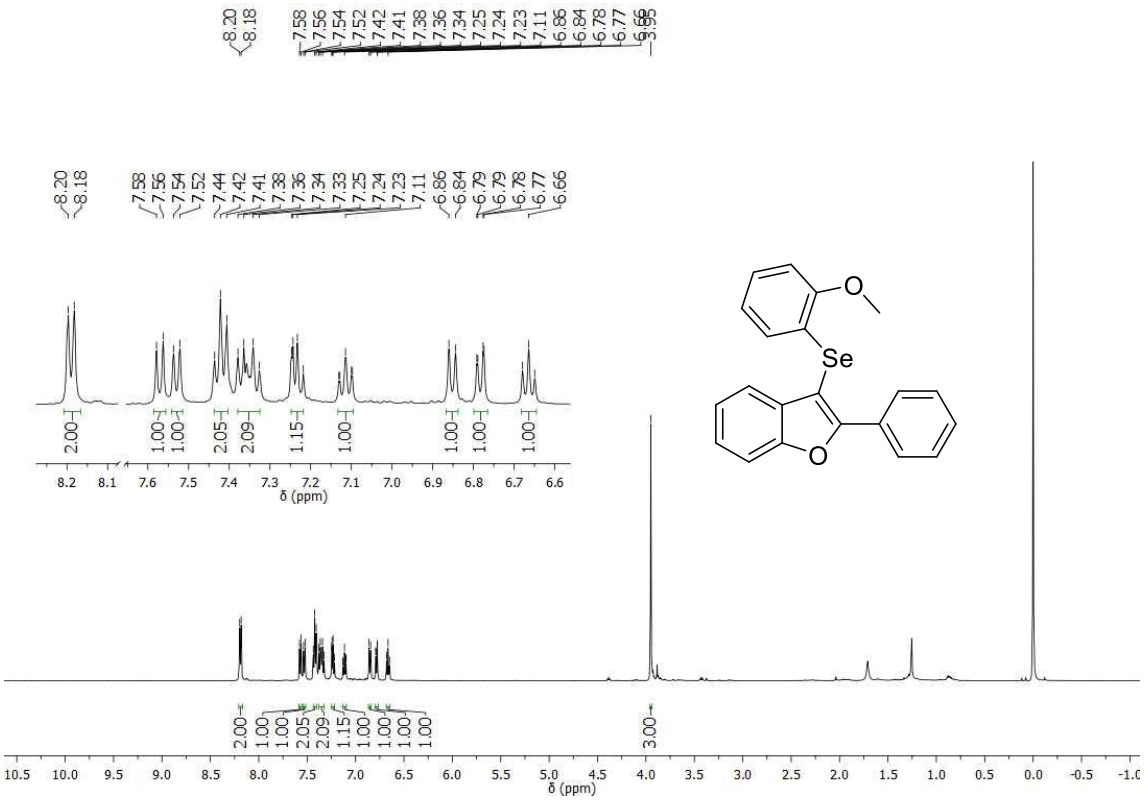


Figure S9: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3e**

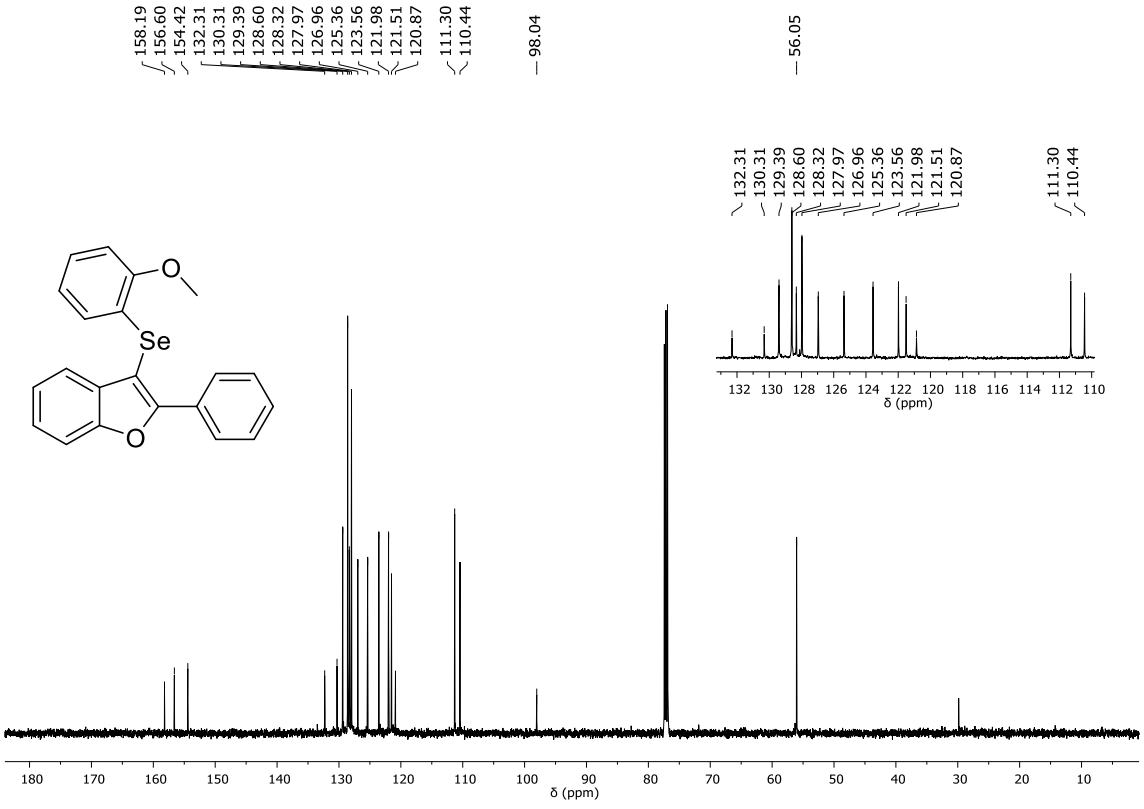


Figure S10: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3e**

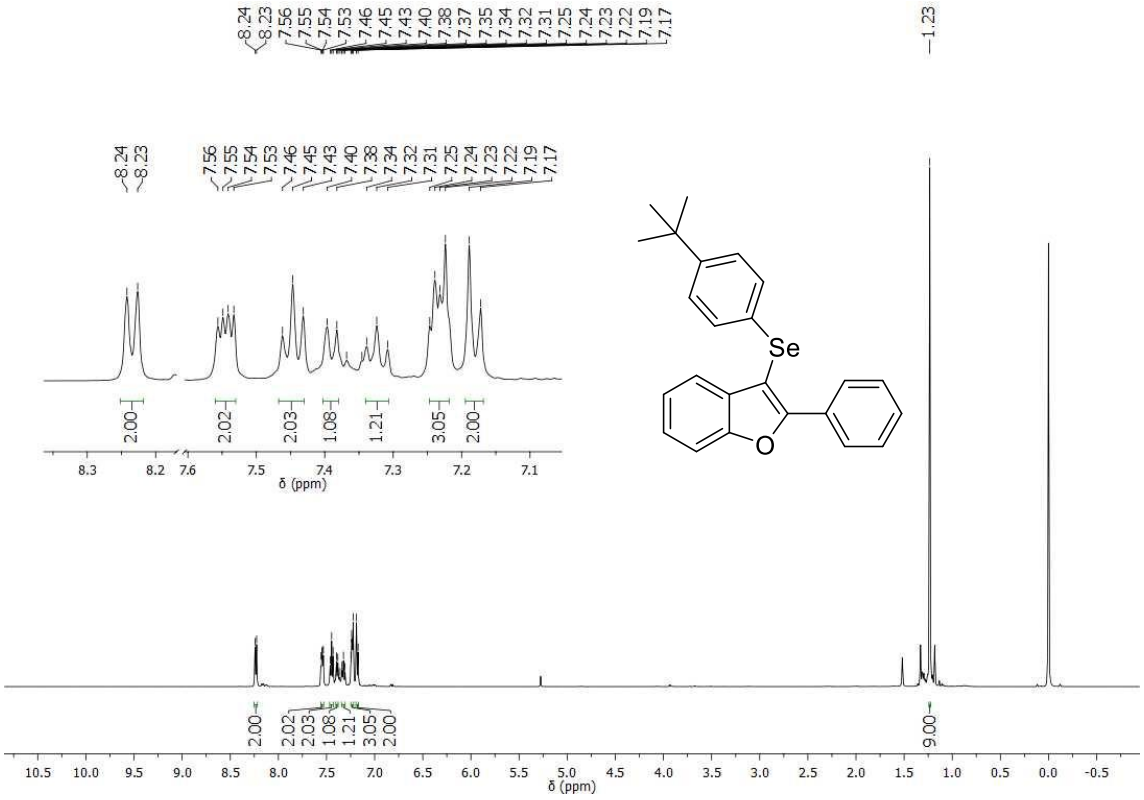


Figure S11: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3f**

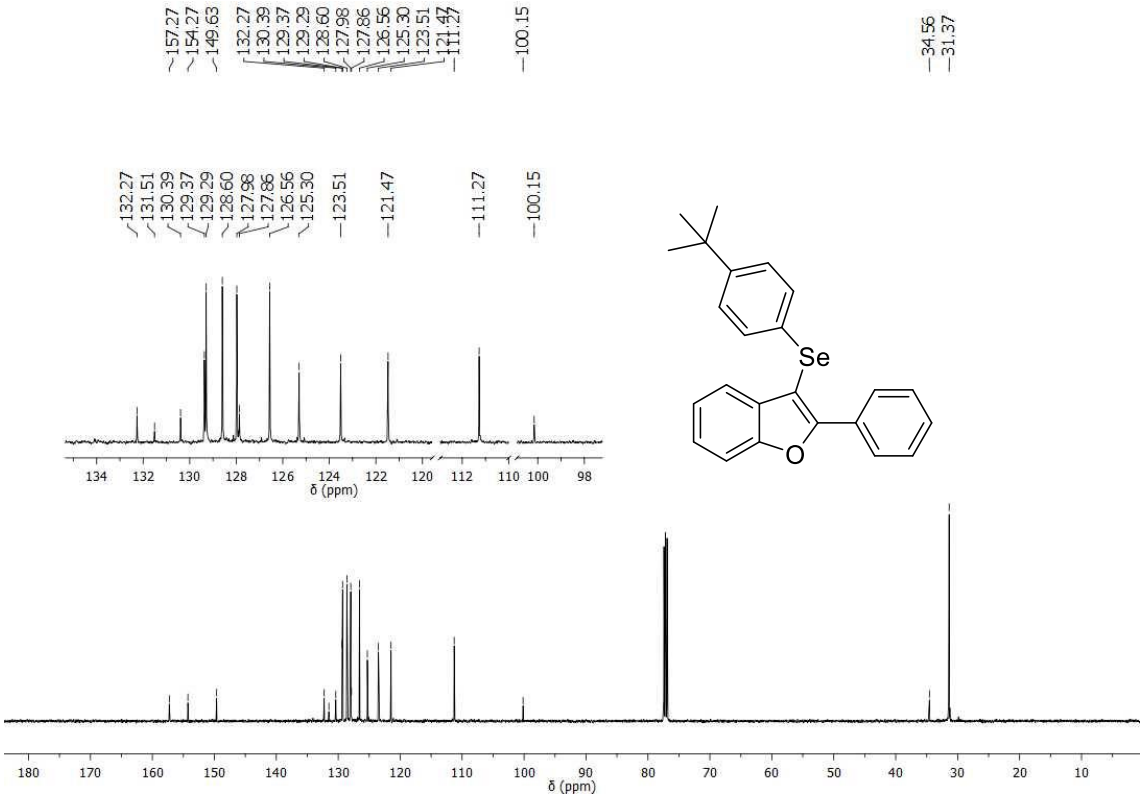


Figure S12: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3f**

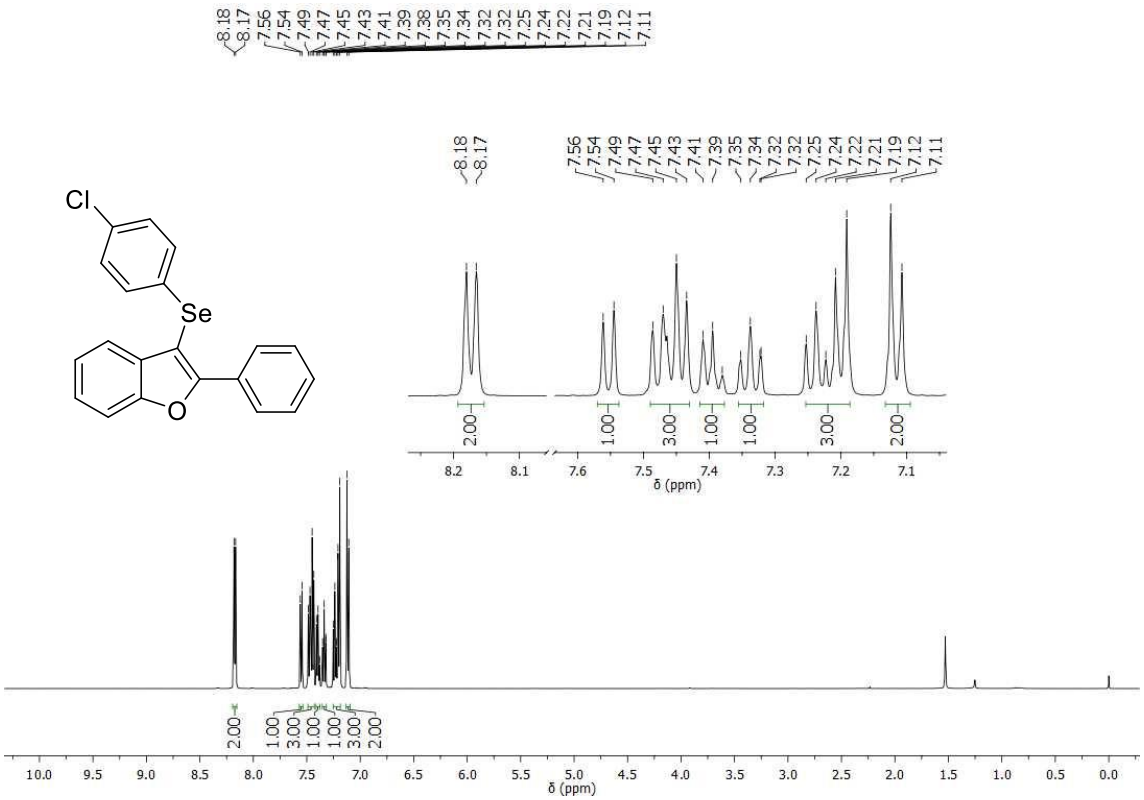


Figure S13: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3g**

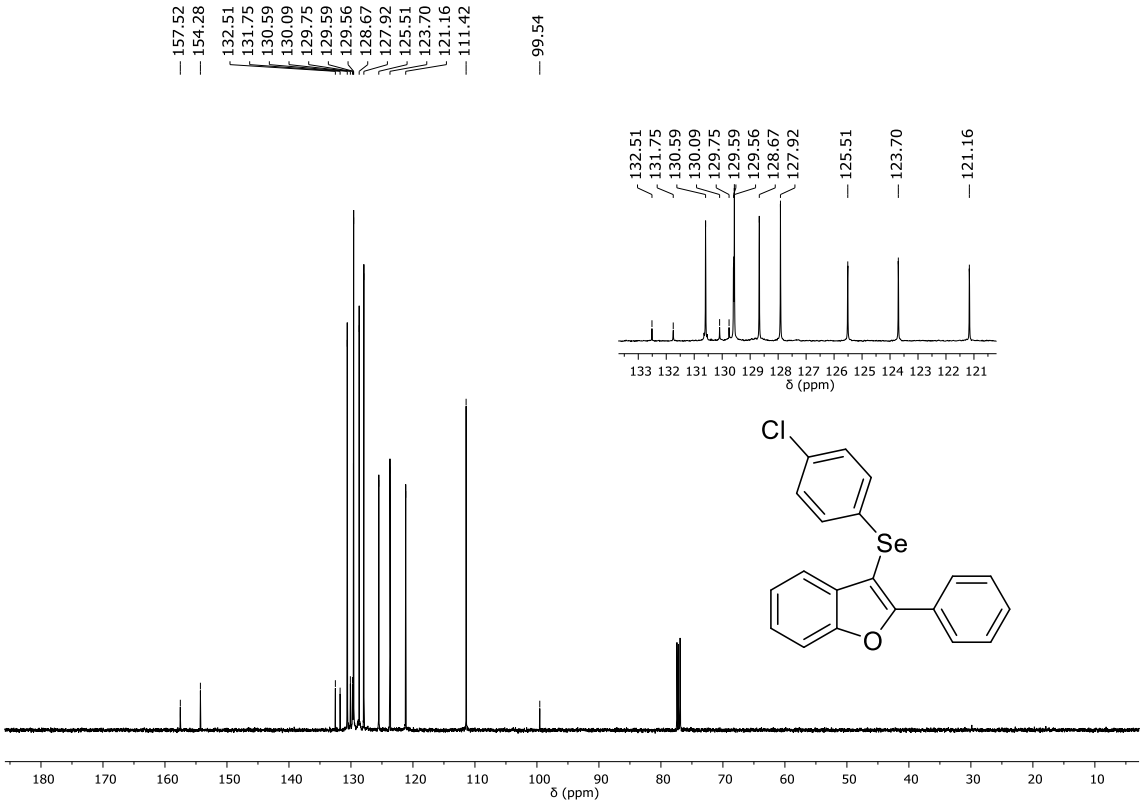


Figure S14: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3g**

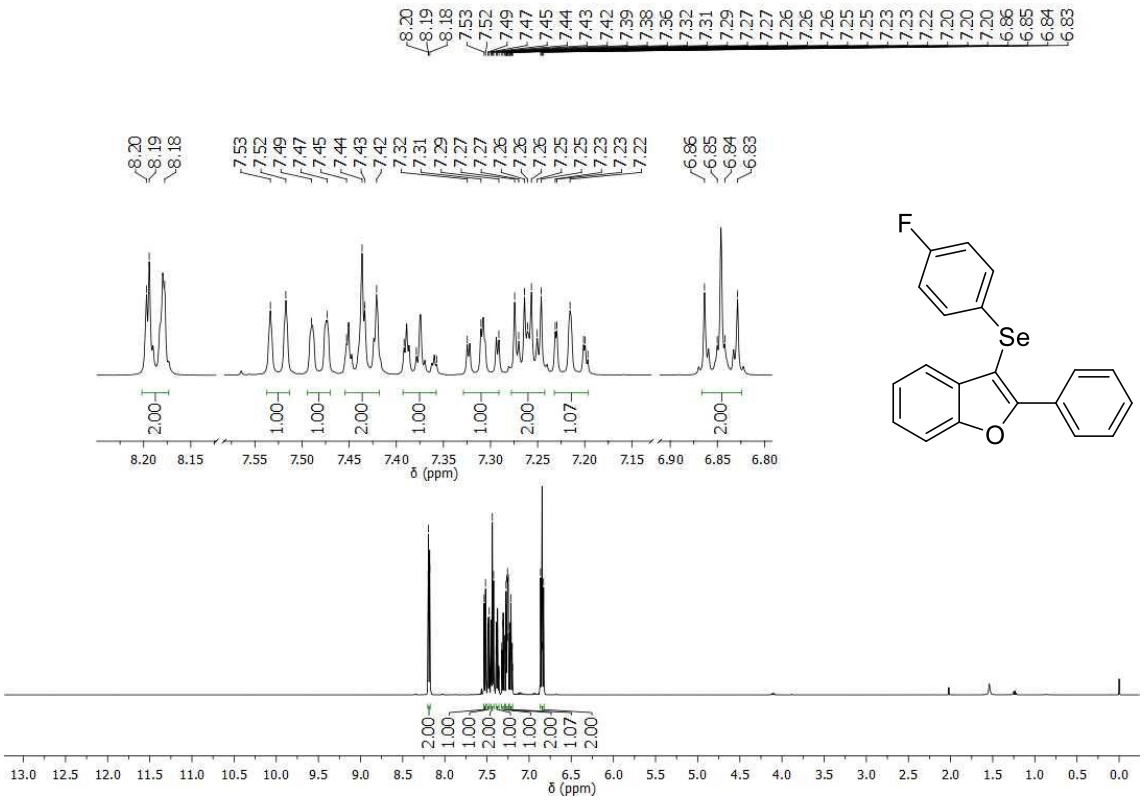


Figure S15: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3h**

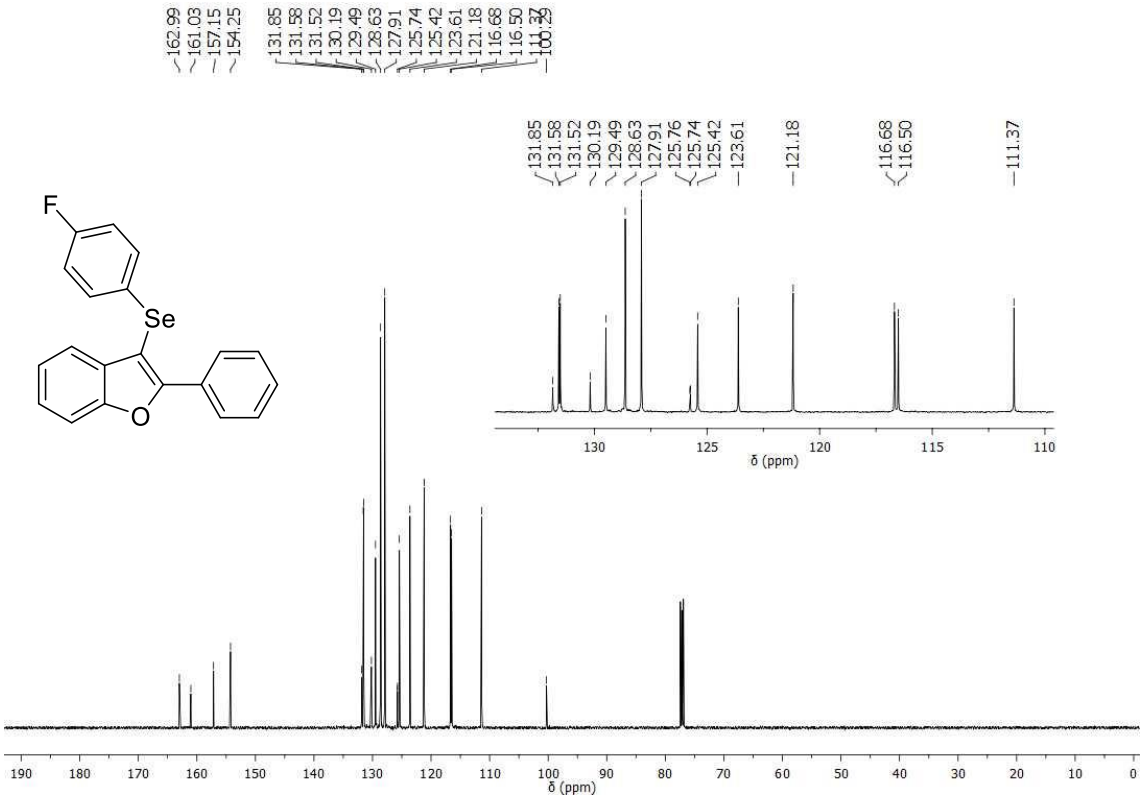


Figure S16: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3h**

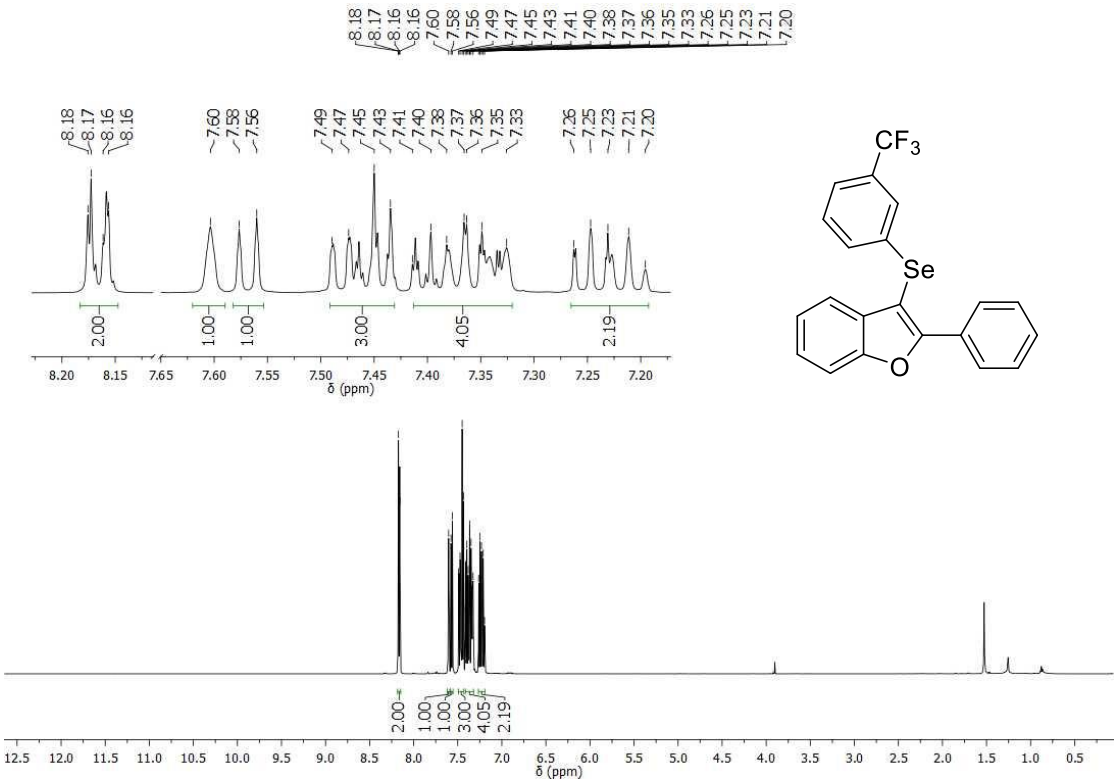


Figure S17: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3i**

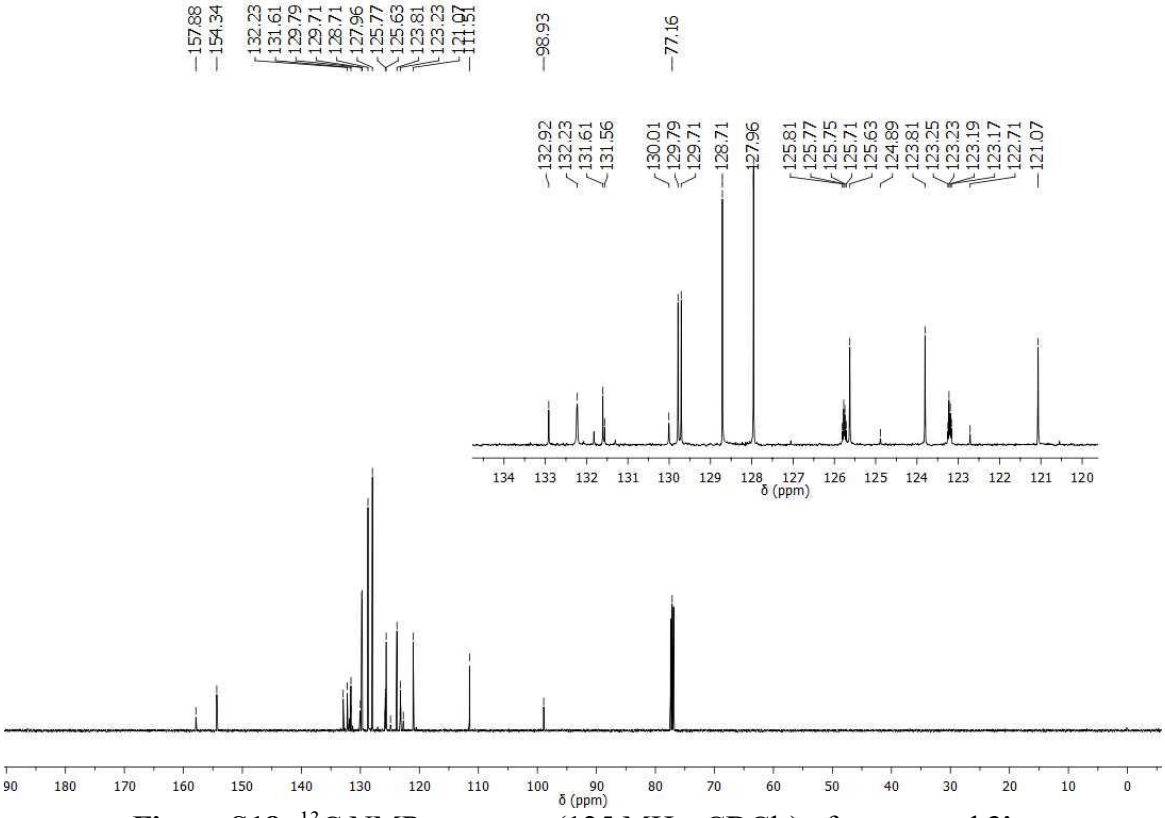


Figure S18: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3i**

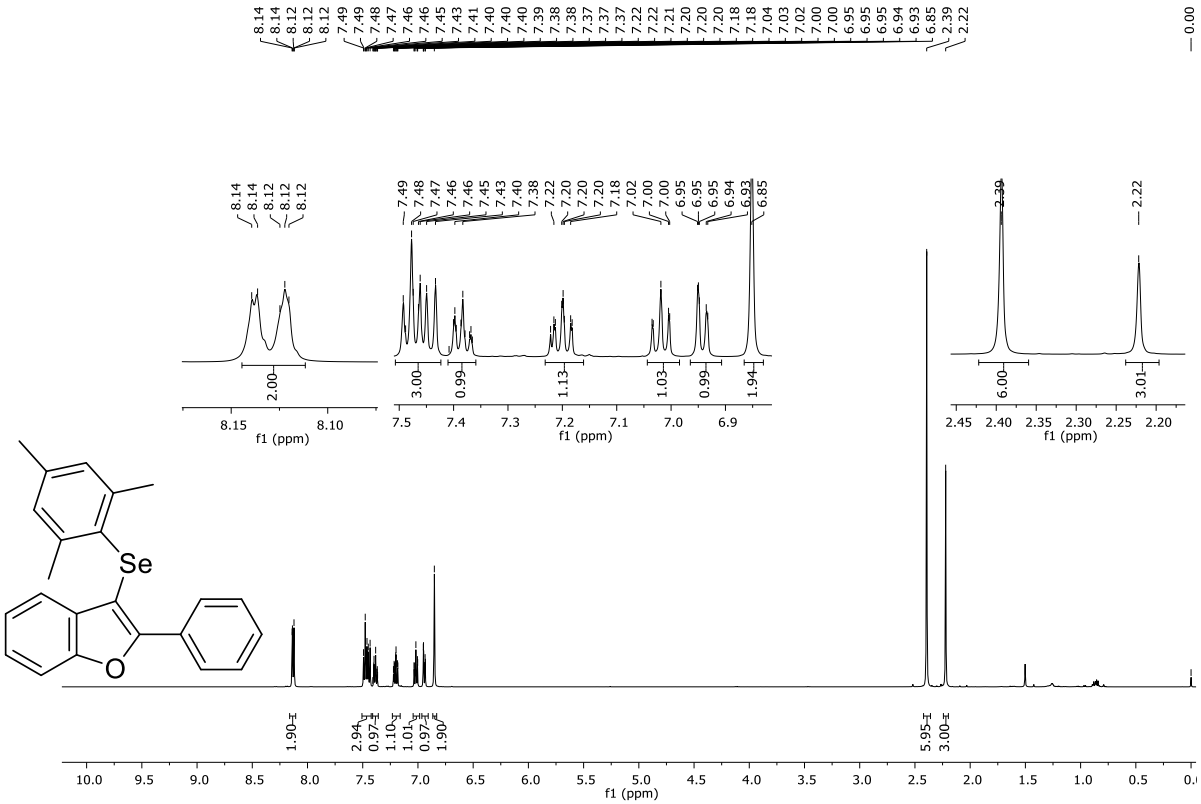


Figure S19: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3j**

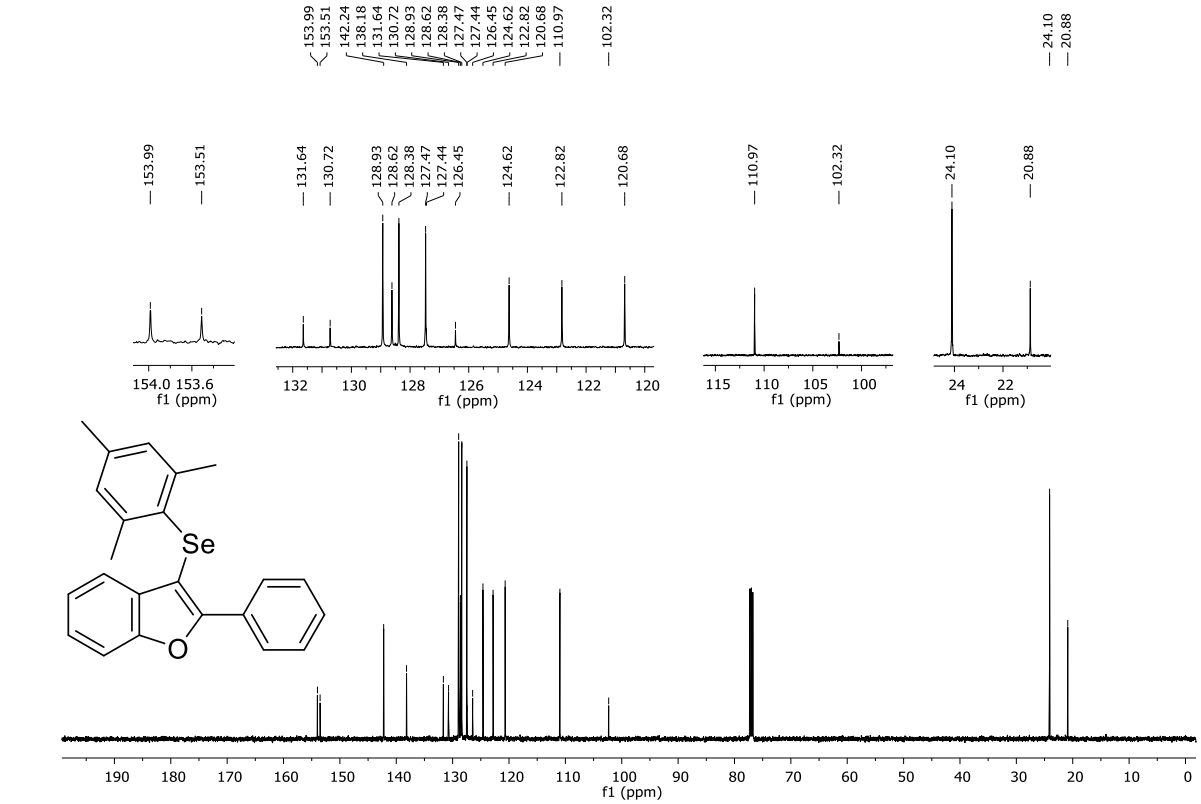


Figure S20: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3j**

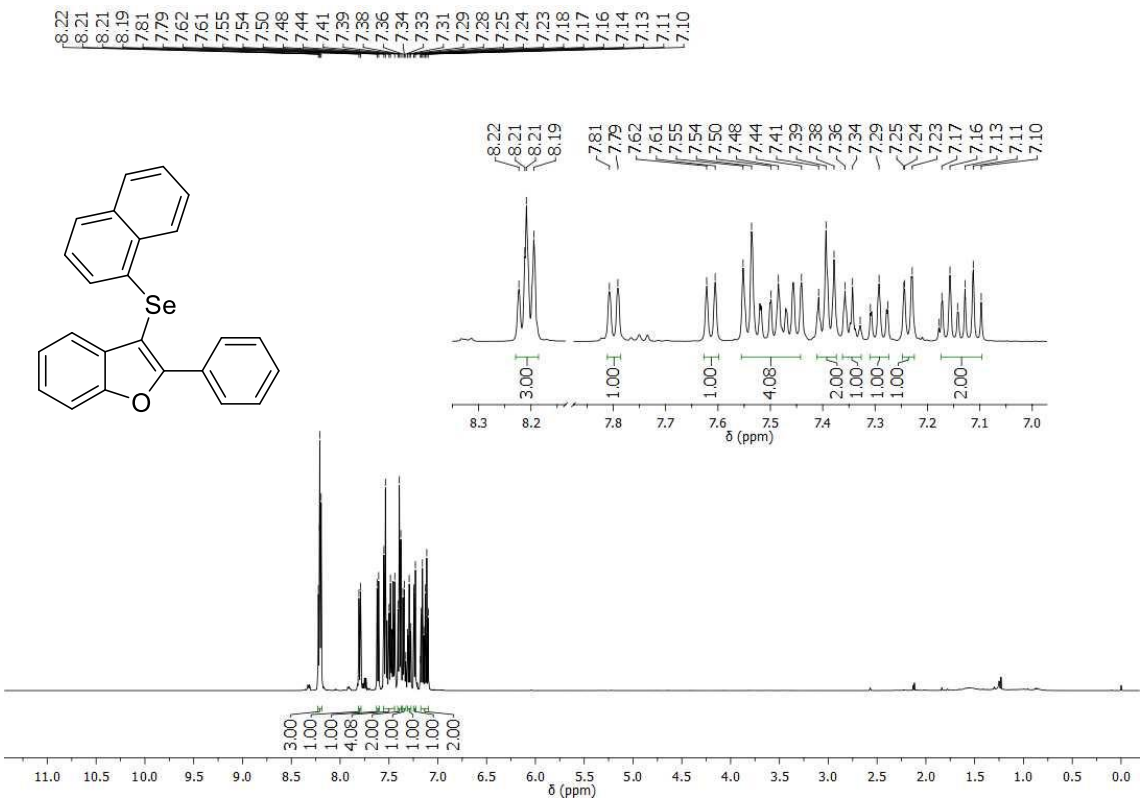


Figure S21: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3k**

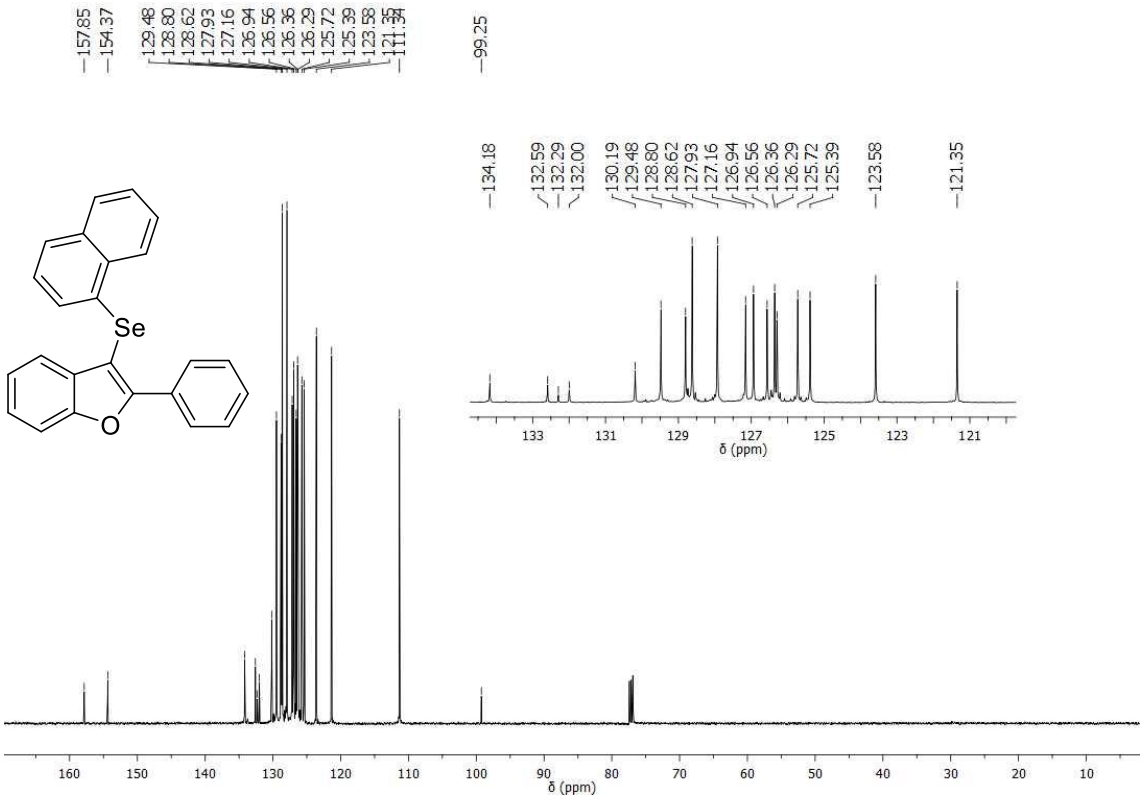


Figure S22: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3k**

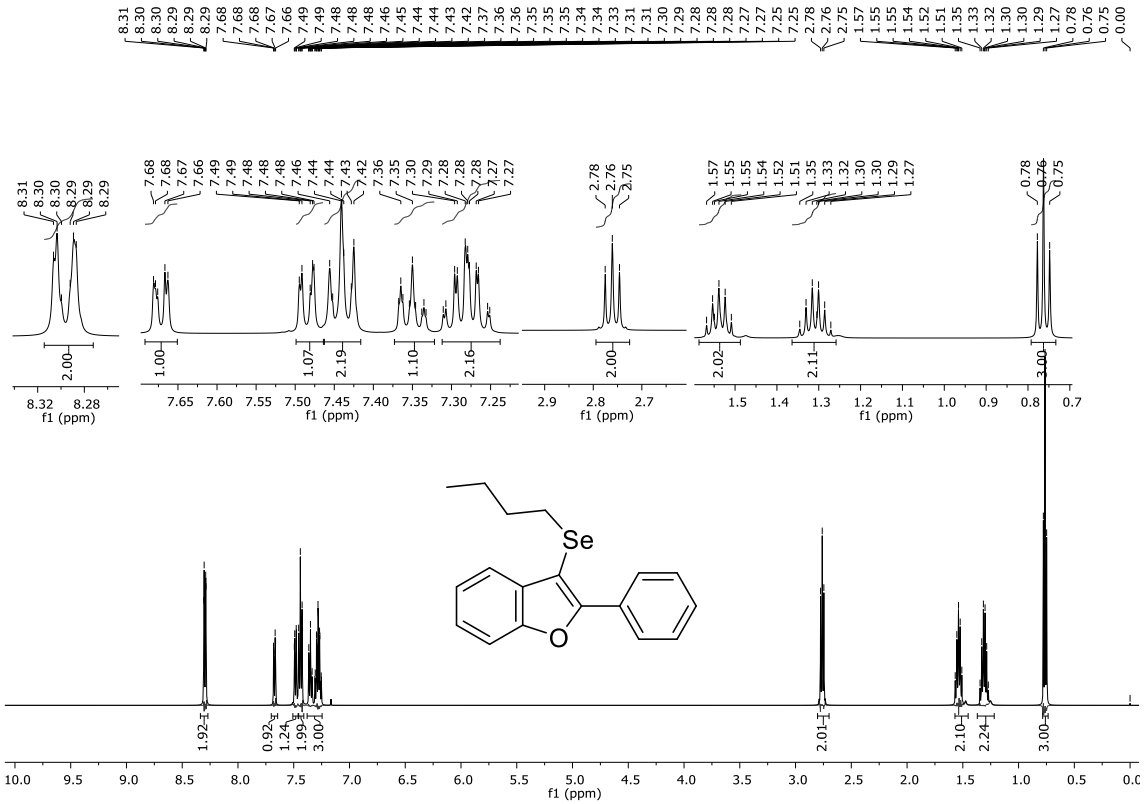


Figure S23: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3l**

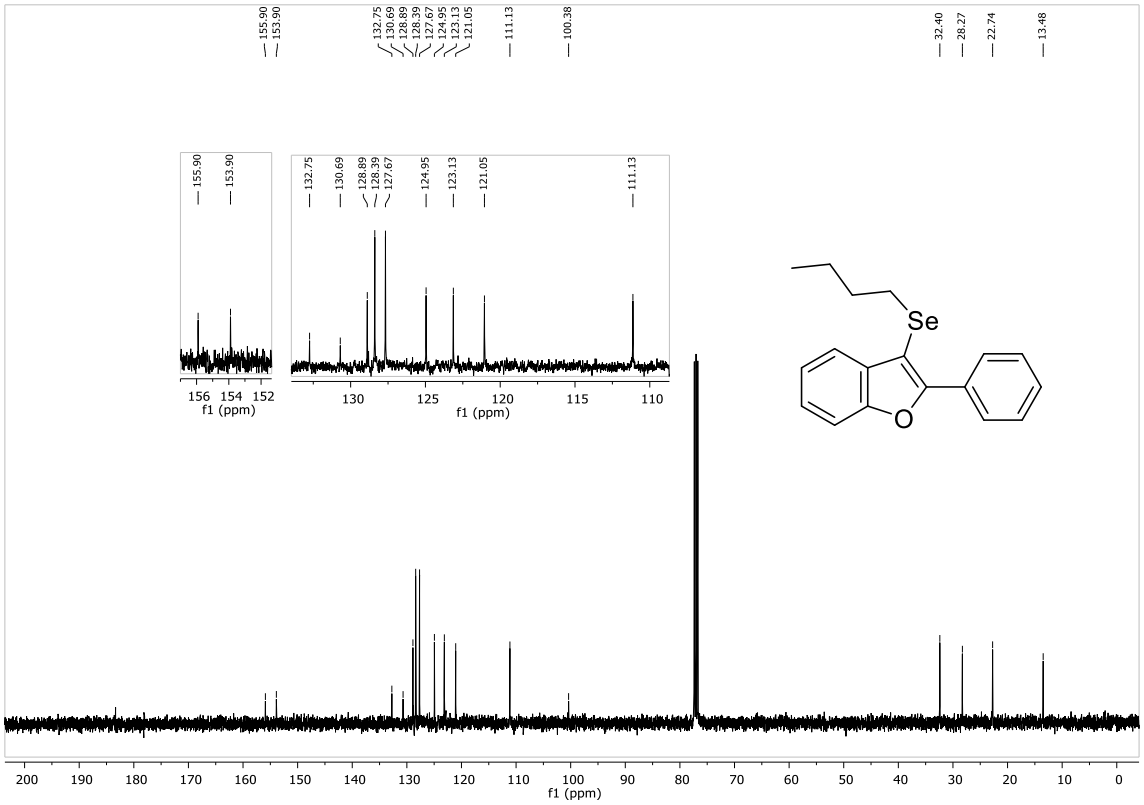


Figure S24: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3l**

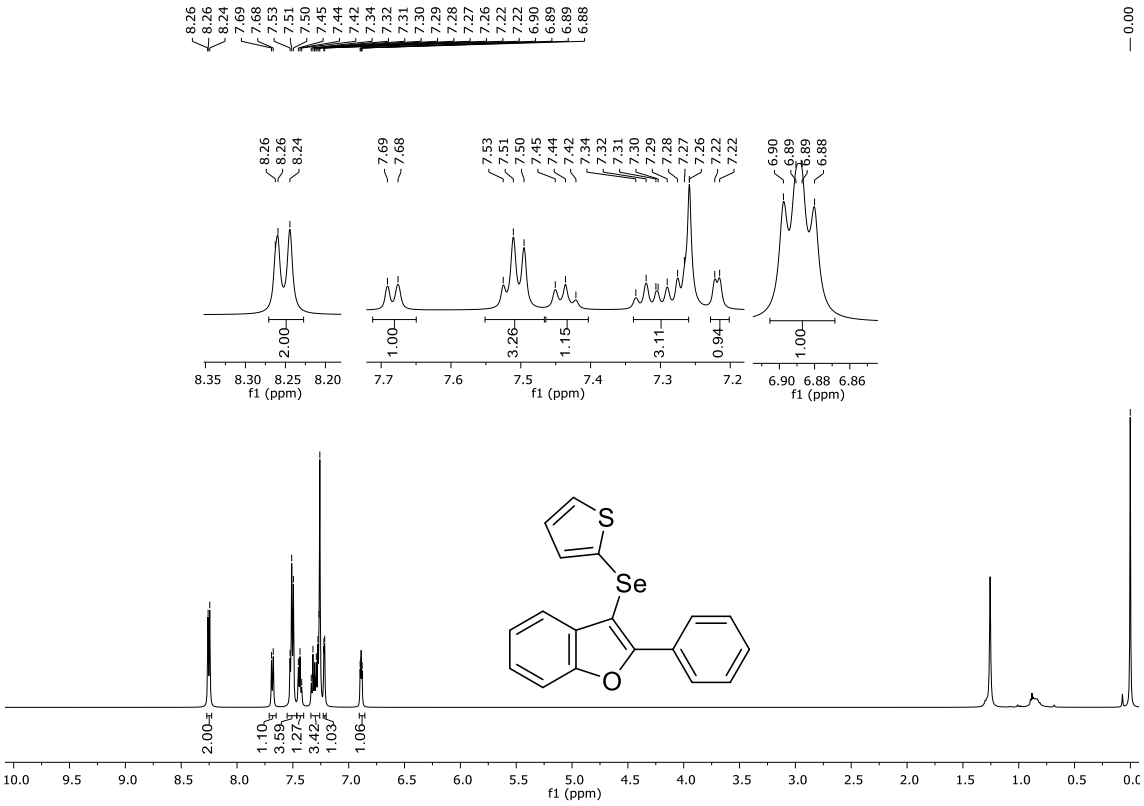


Figure S25: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3m**

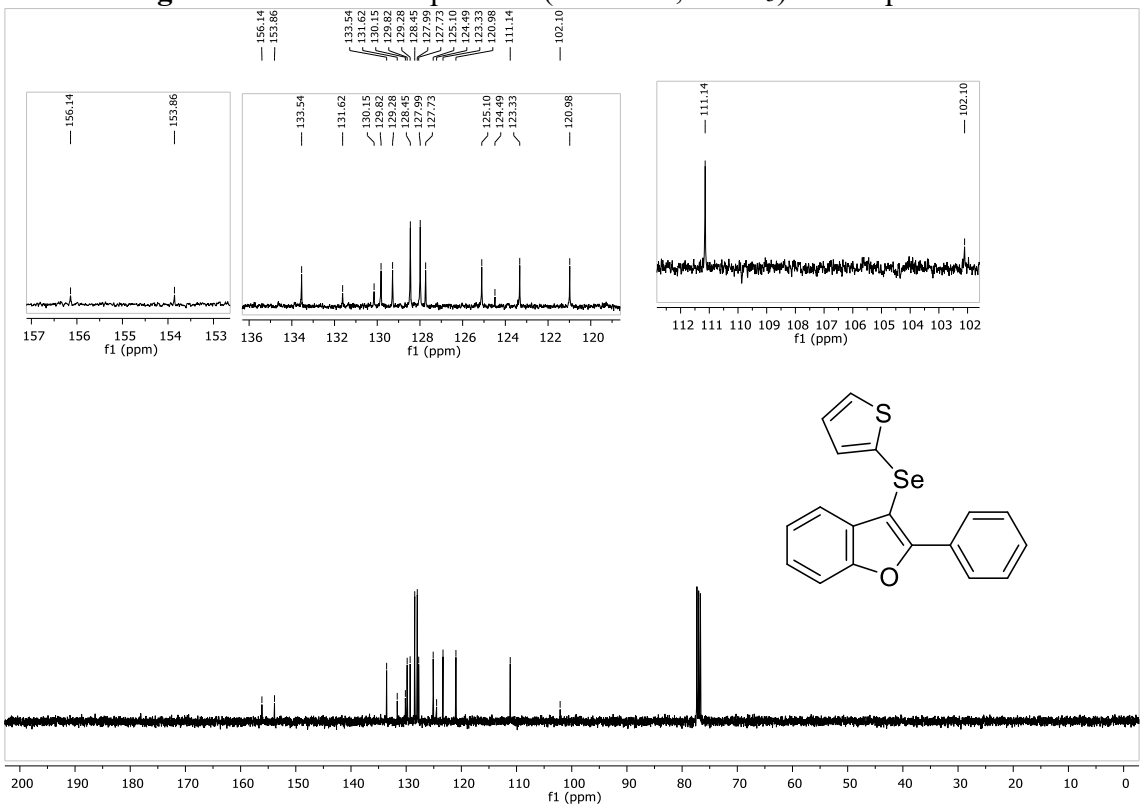


Figure S26: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3m**

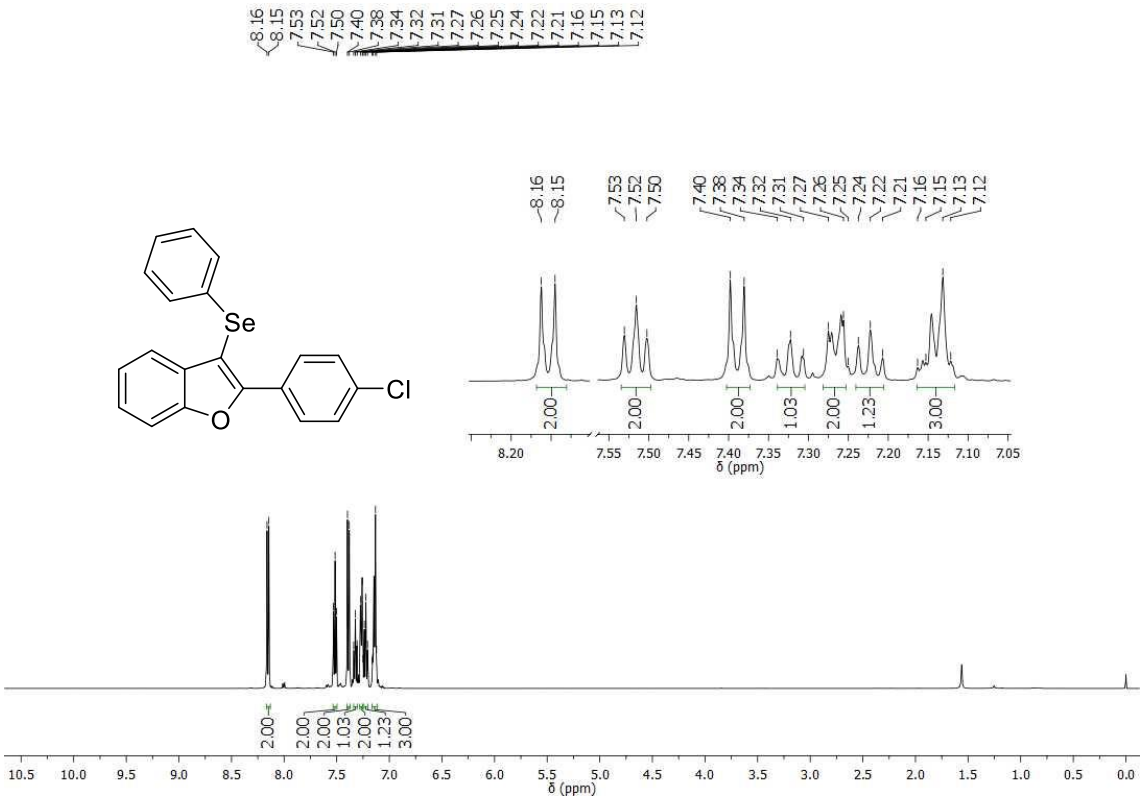


Figure S27: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3n**

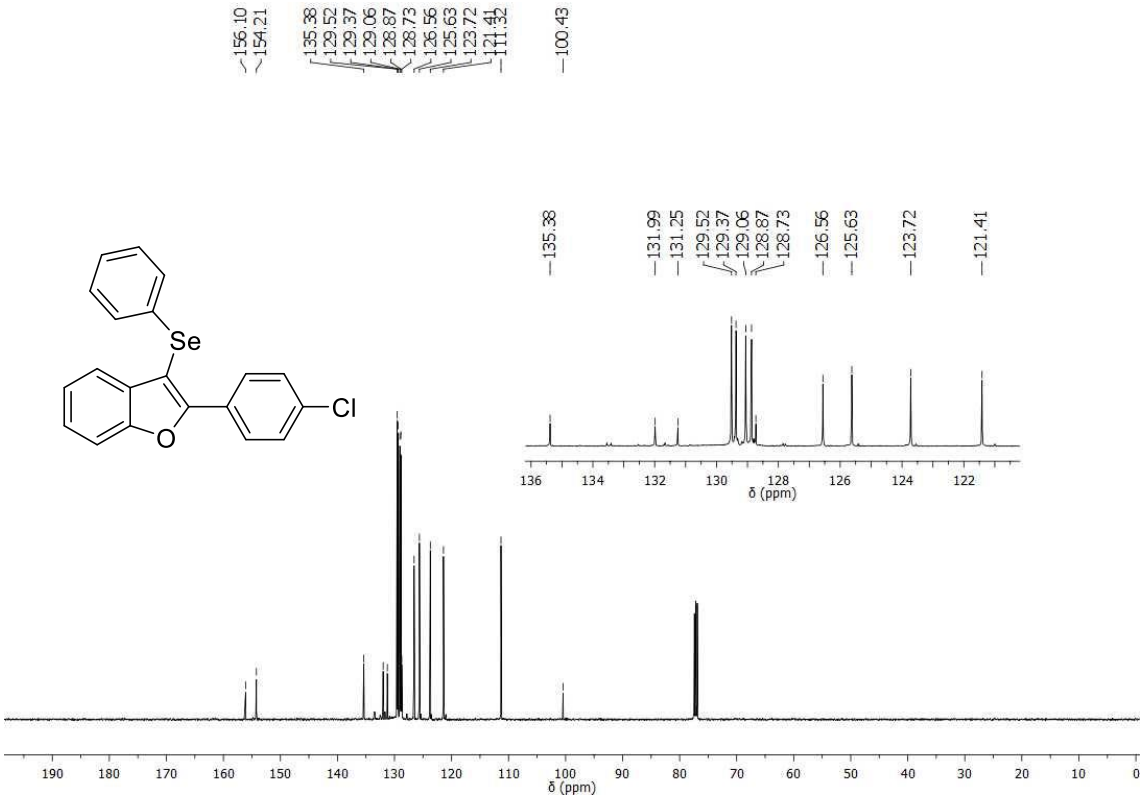


Figure S28: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3n**

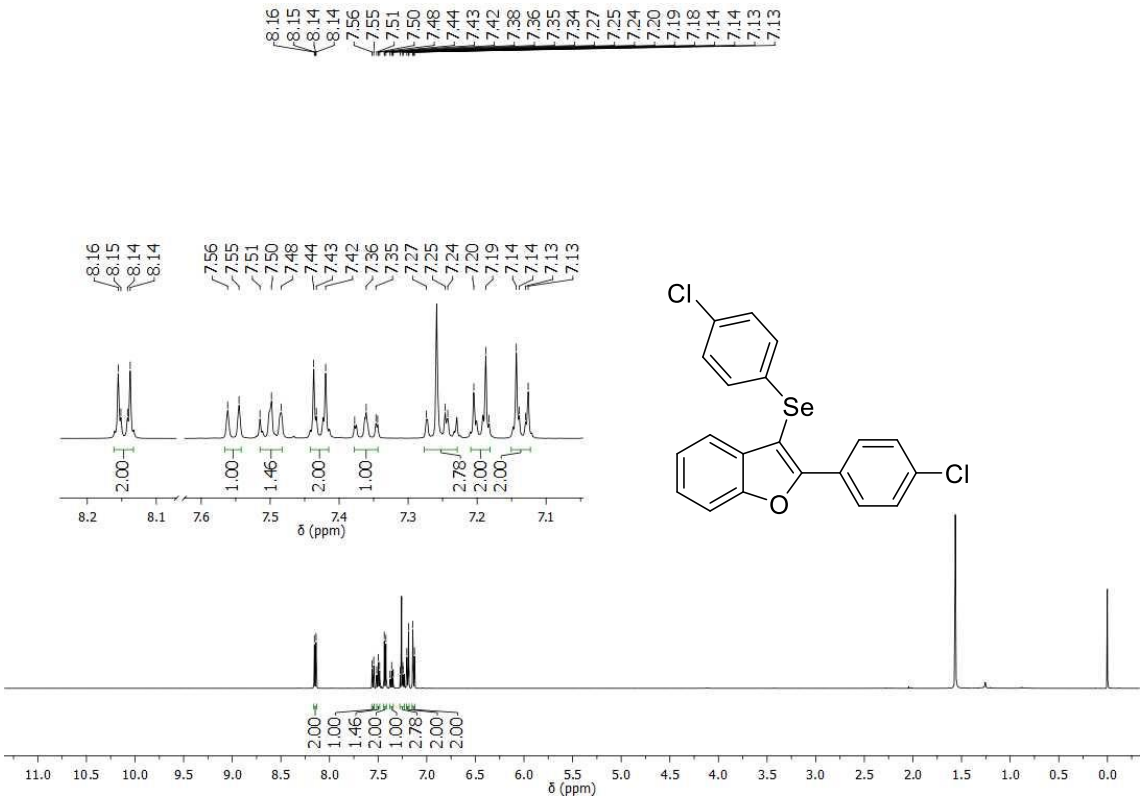


Figure S29: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3p**

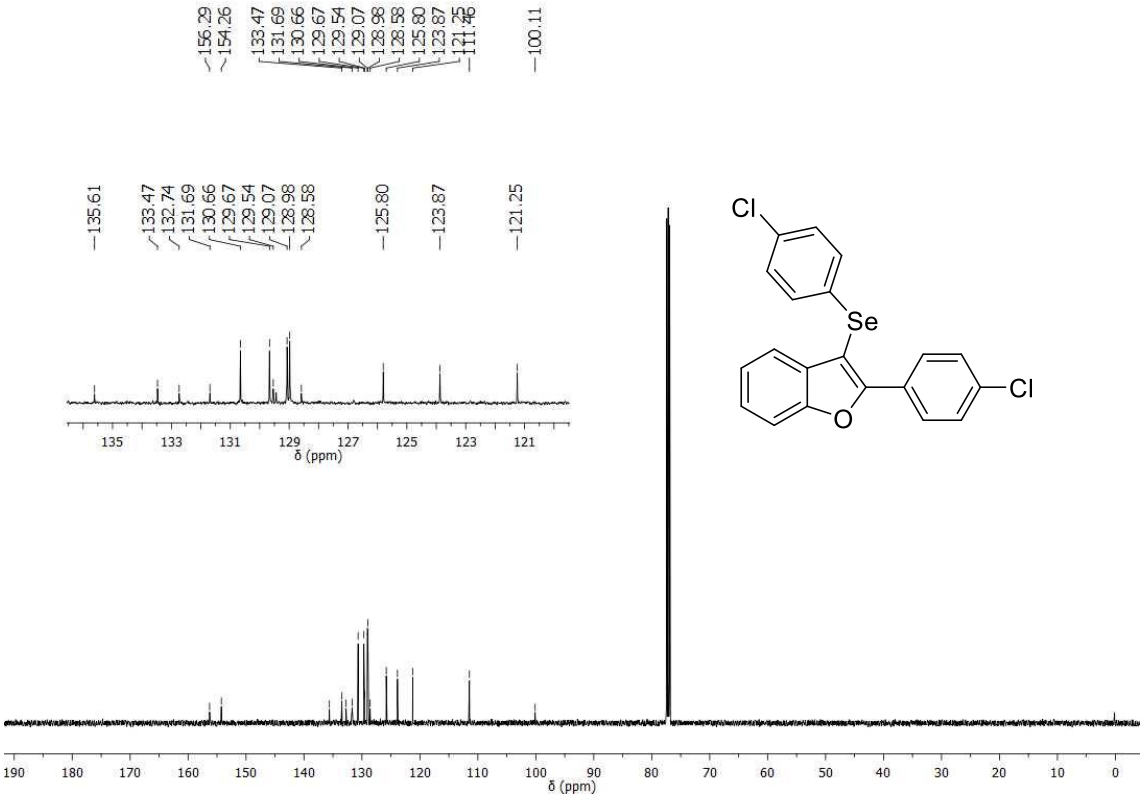


Figure S30: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3p**

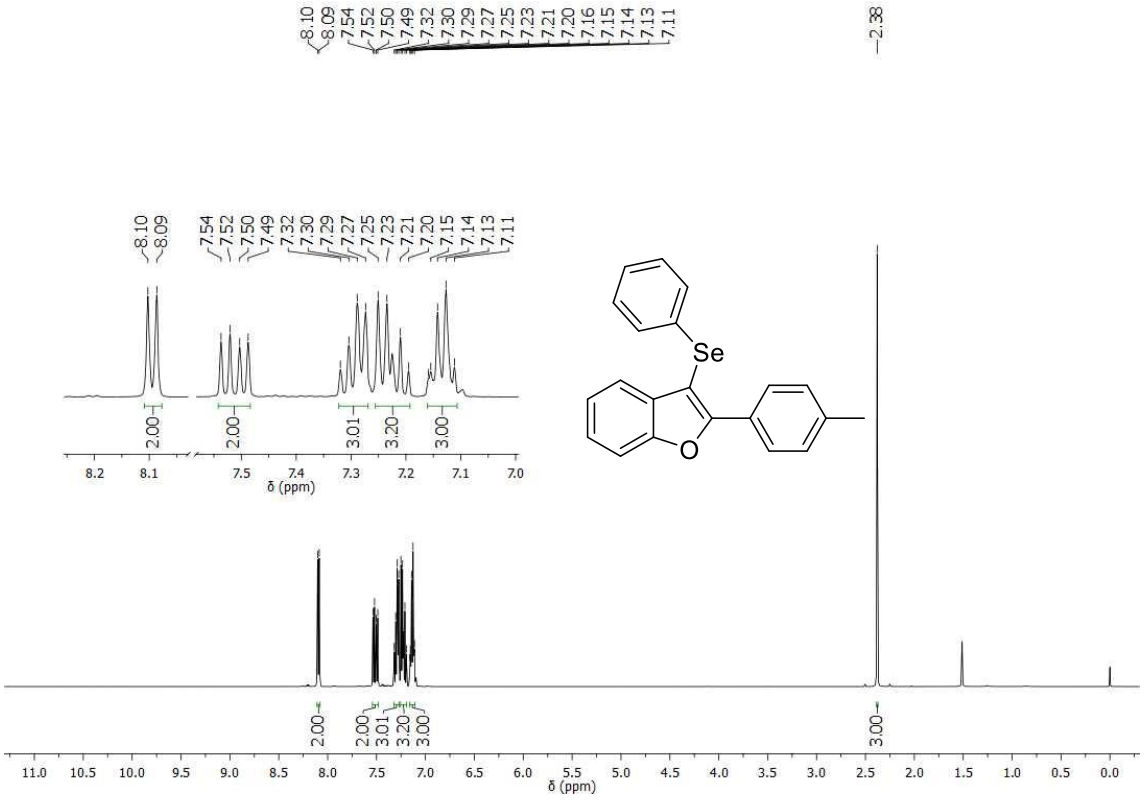


Figure S31: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3q**

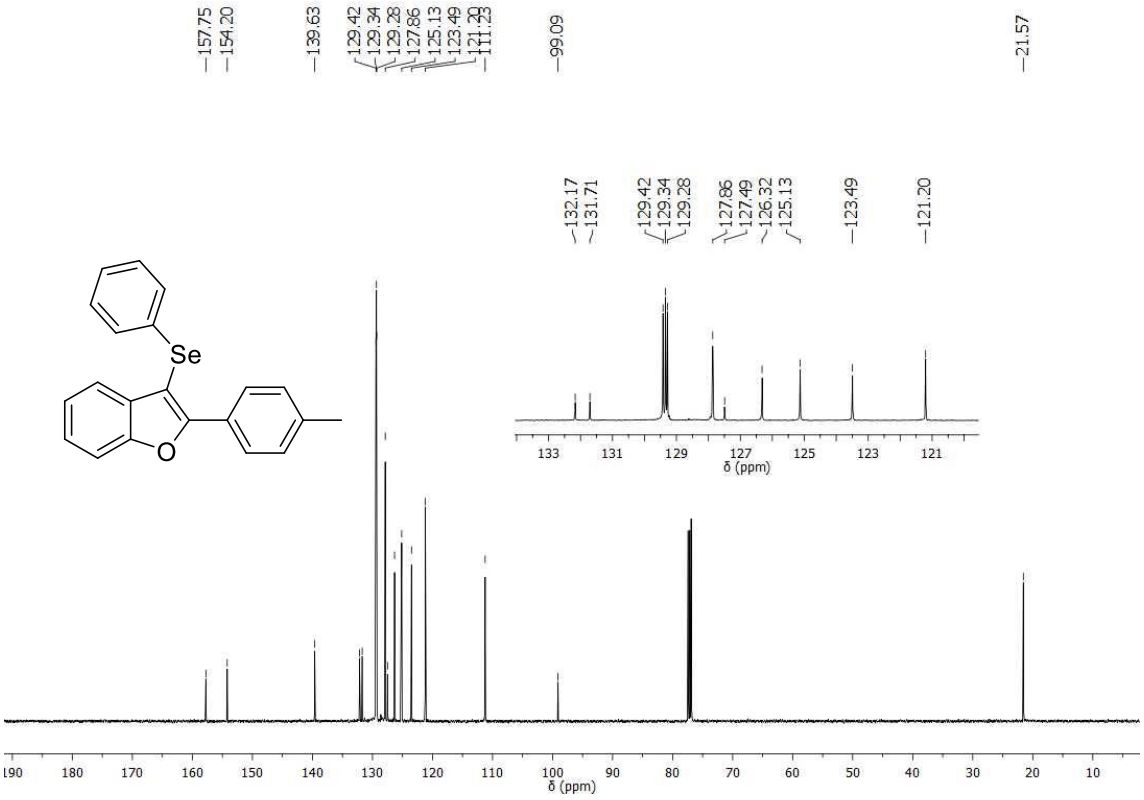


Figure S32: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3q**

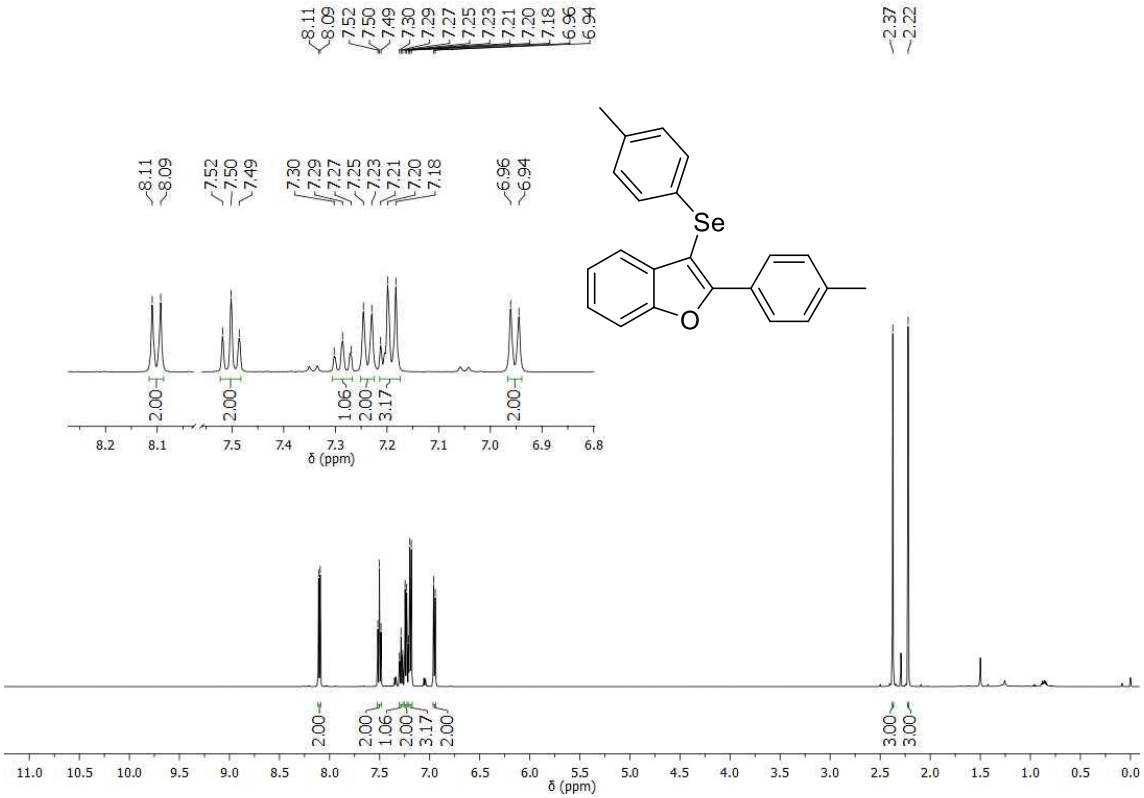


Figure S33: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3r**

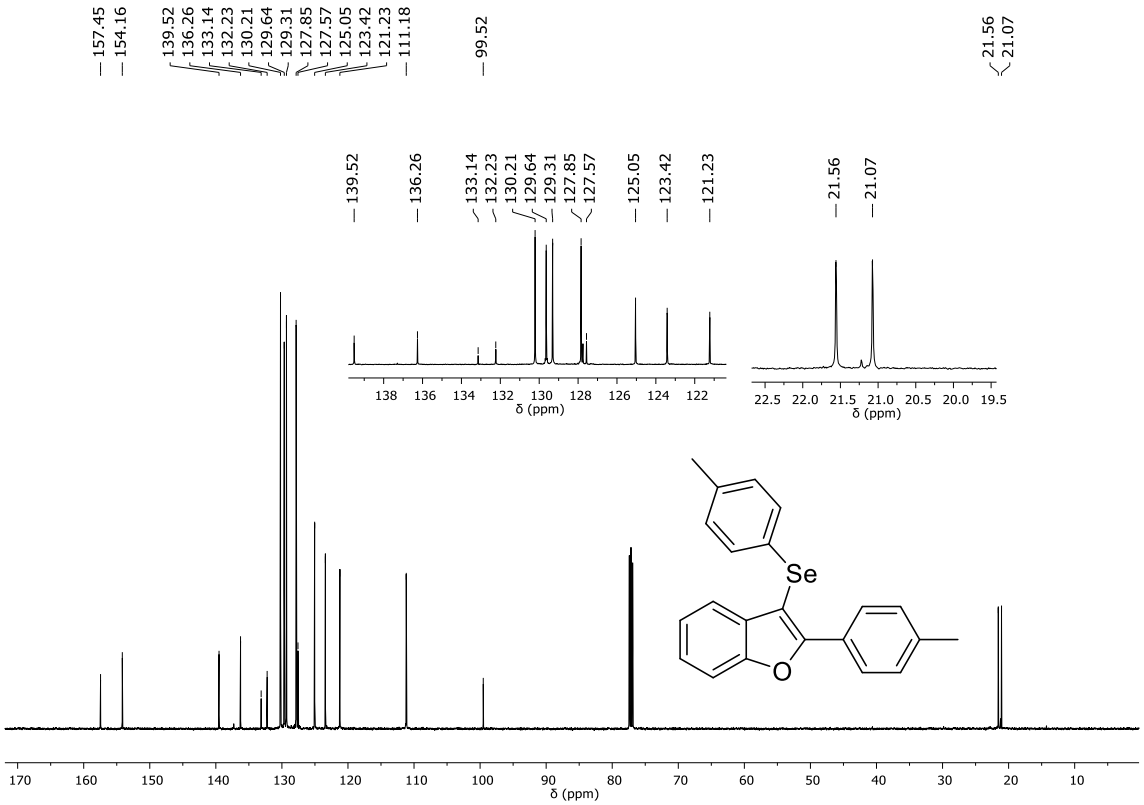


Figure S34: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3r**

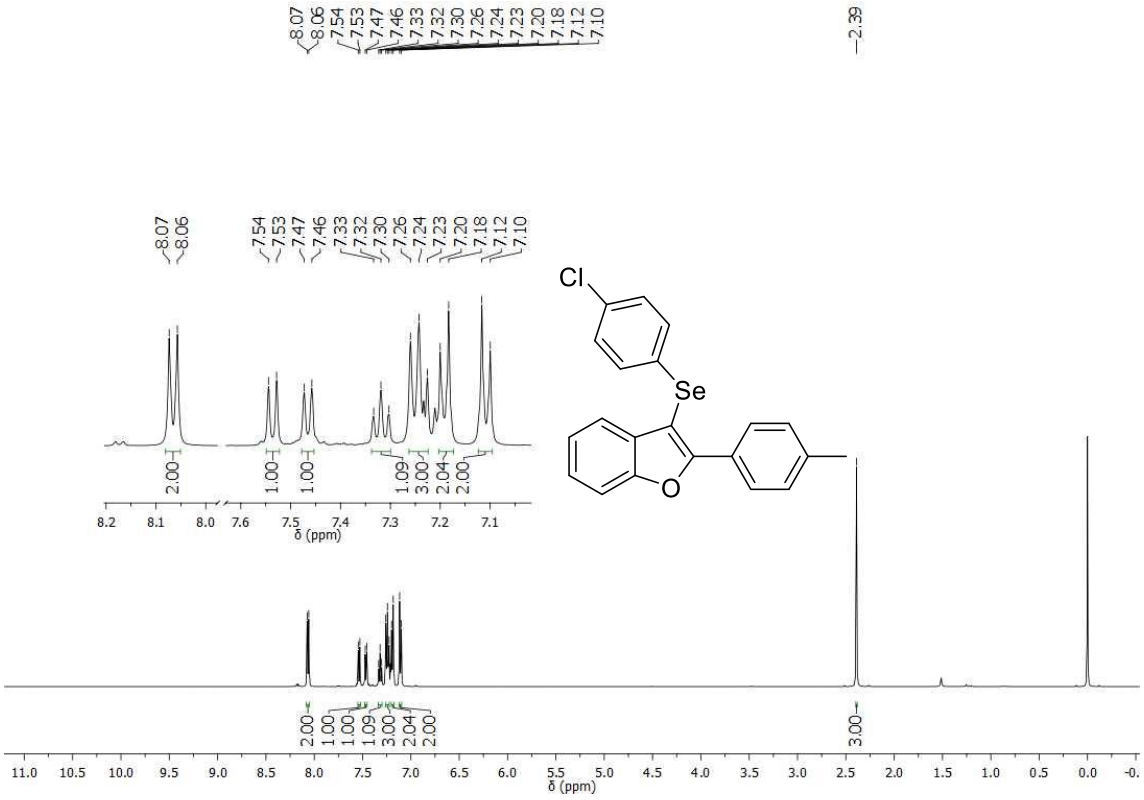


Figure S35: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3s**

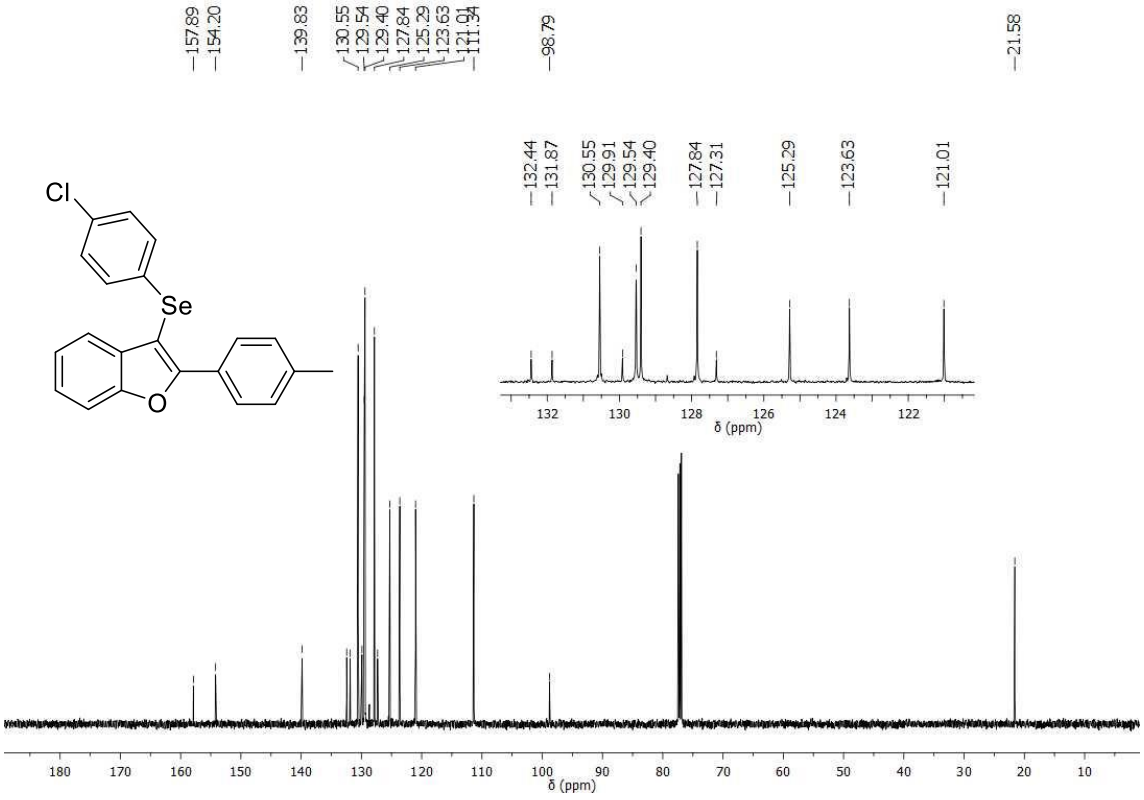


Figure S36: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3s**

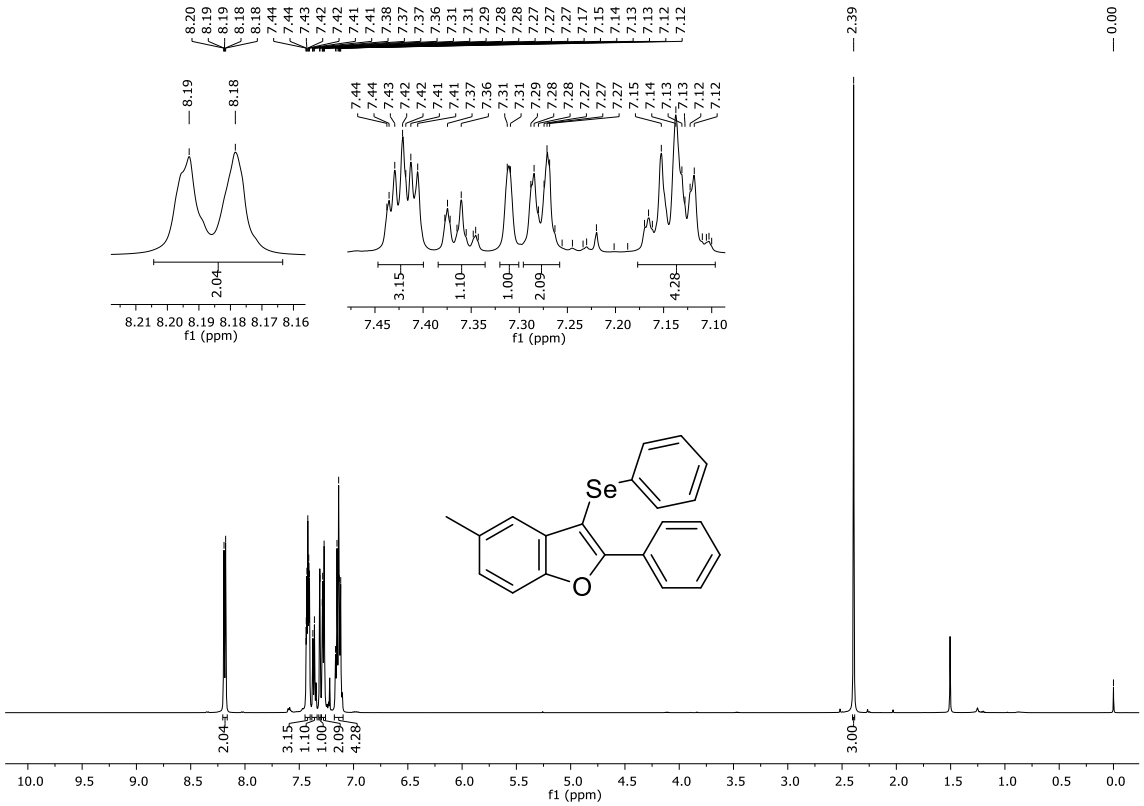


Figure S37: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3t**

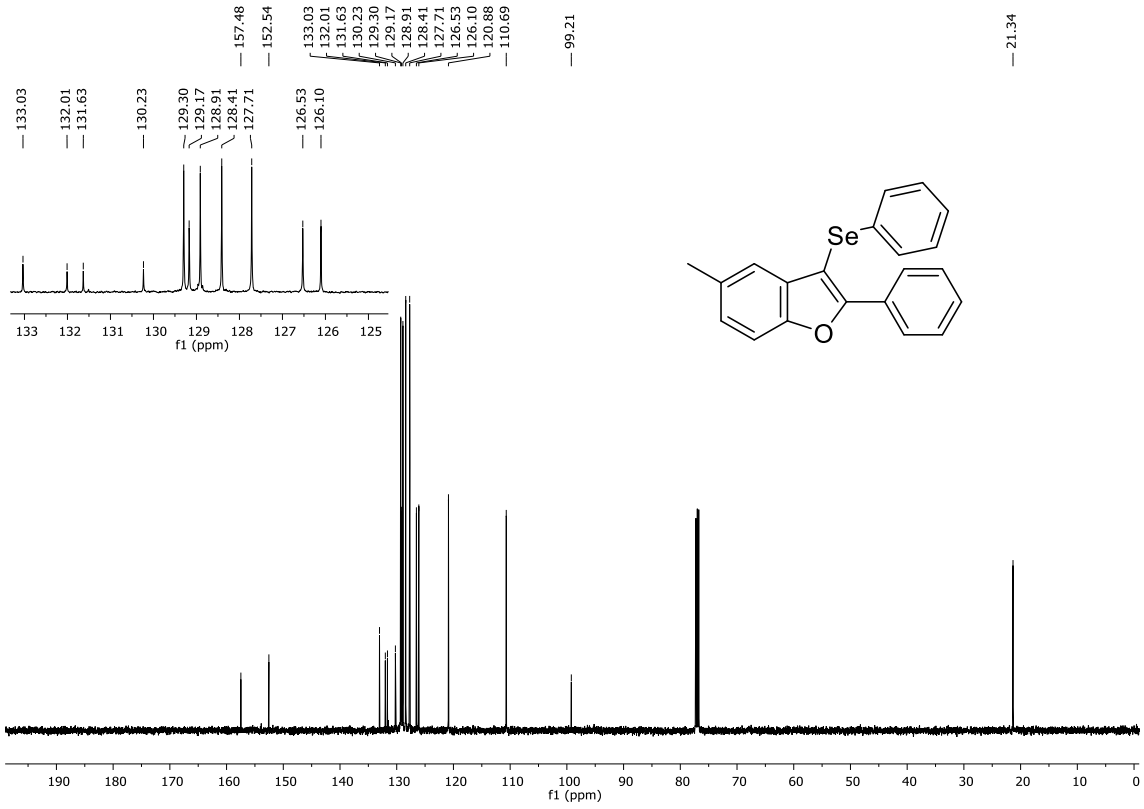


Figure S38: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3t**

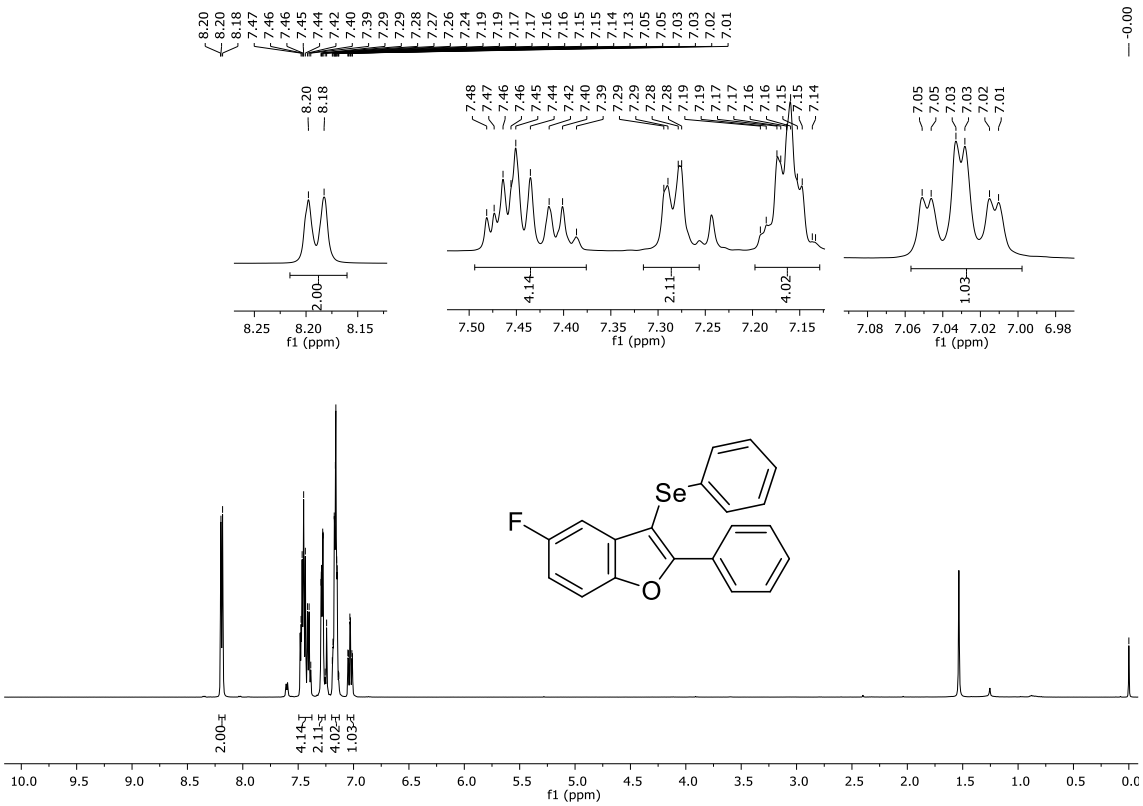


Figure S39: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3u**

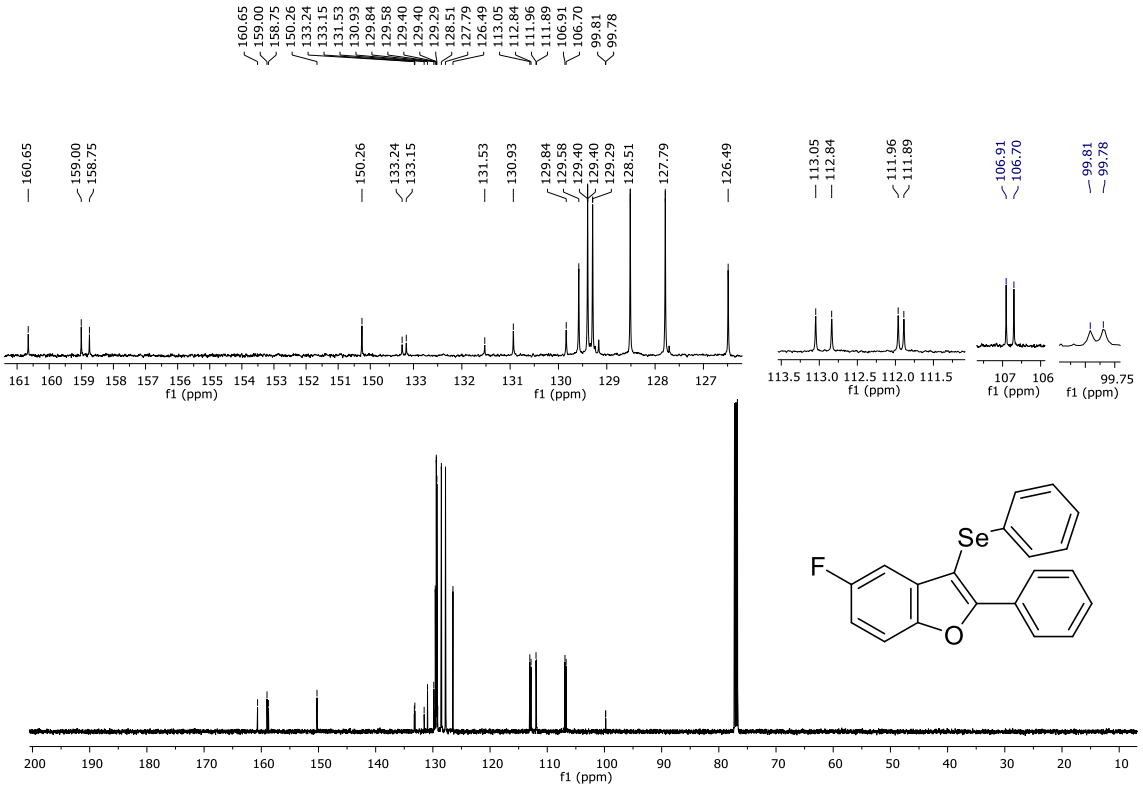


Figure S40: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3u**

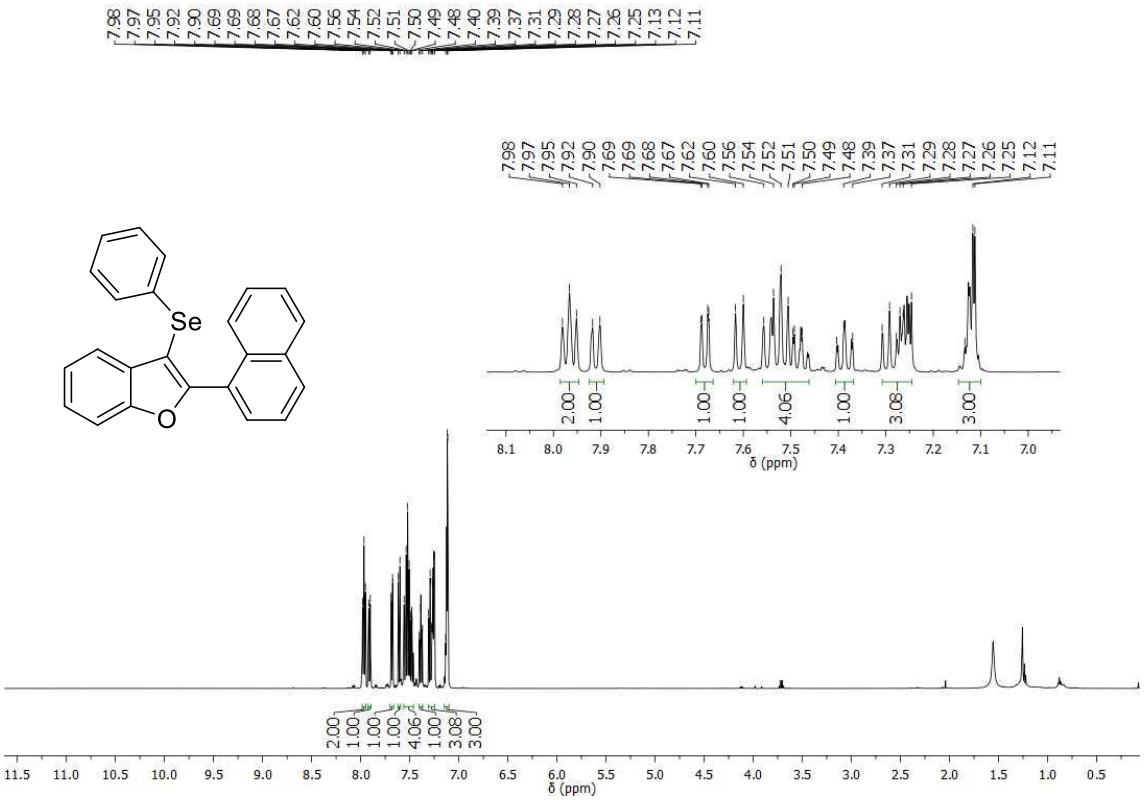


Figure S41: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3v**

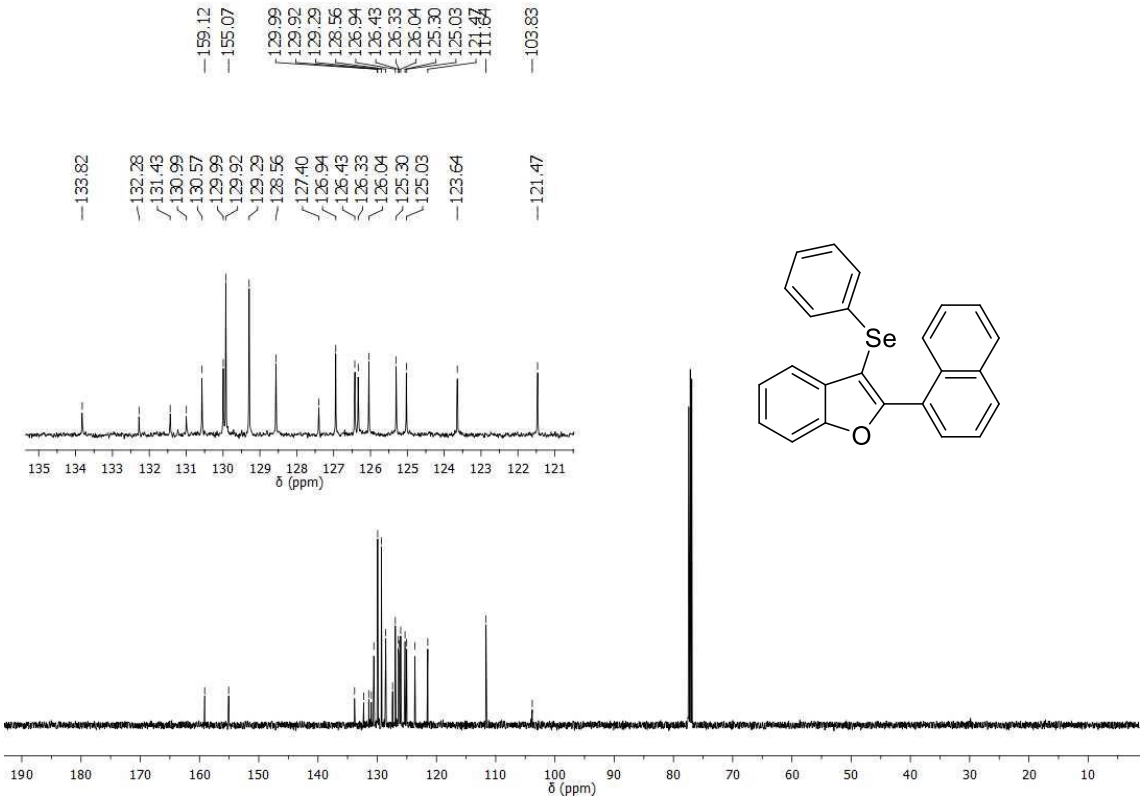


Figure S42: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3v**

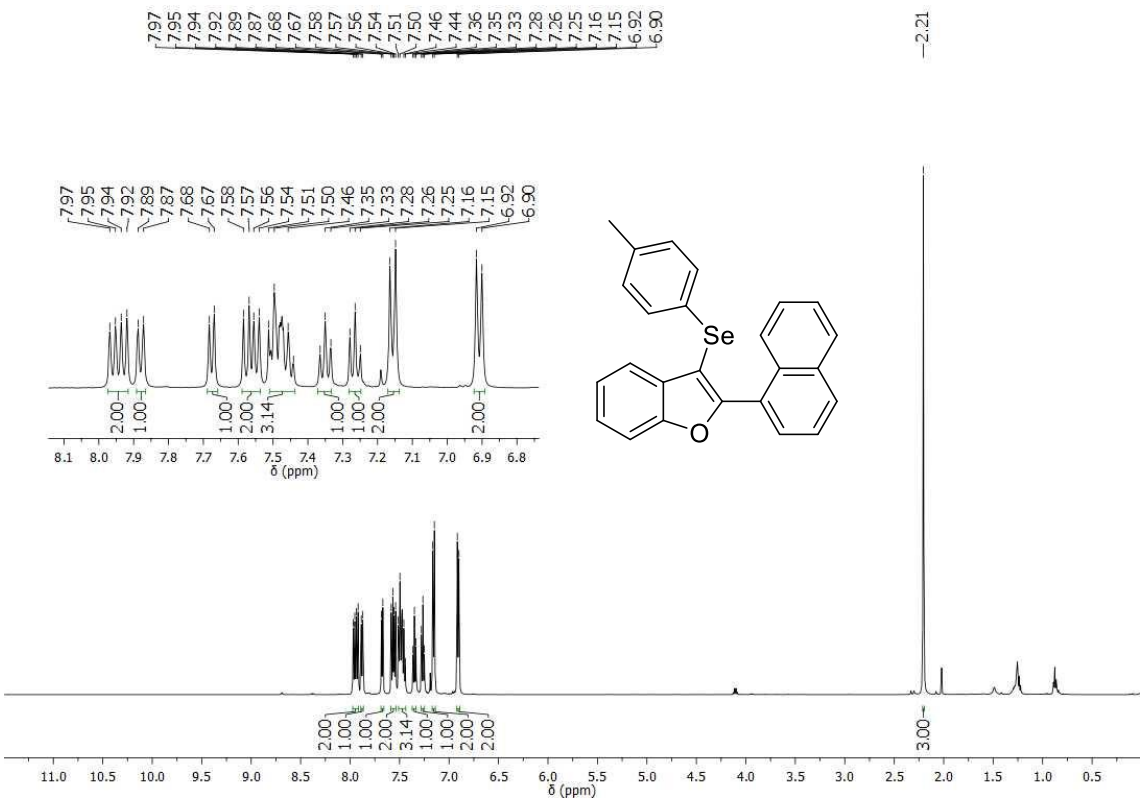


Figure S43: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3u**

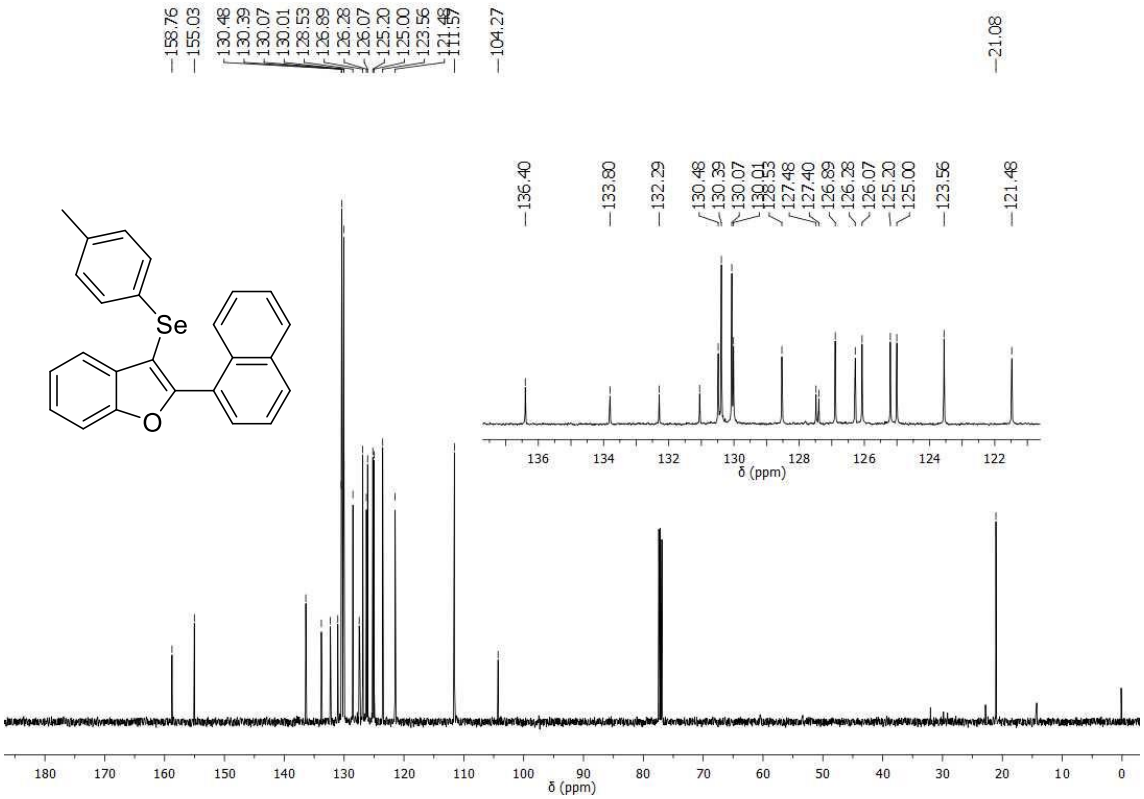


Figure S44: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3u**

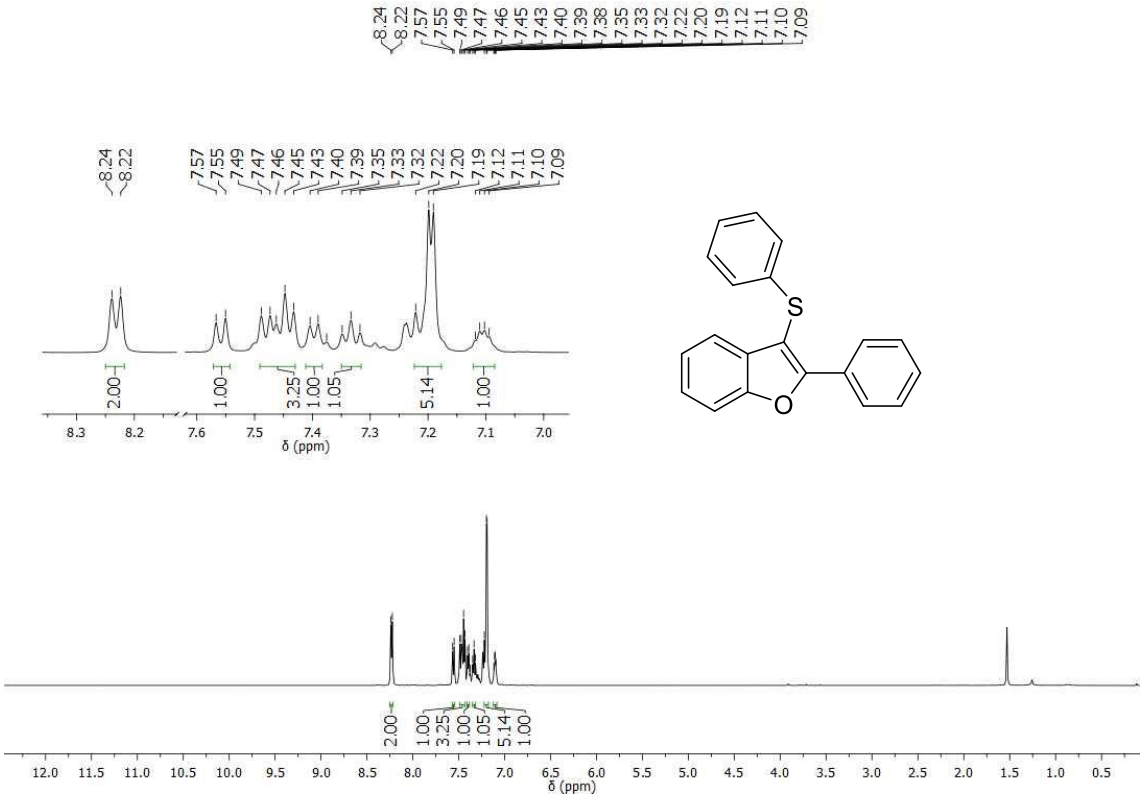


Figure S45: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3z**

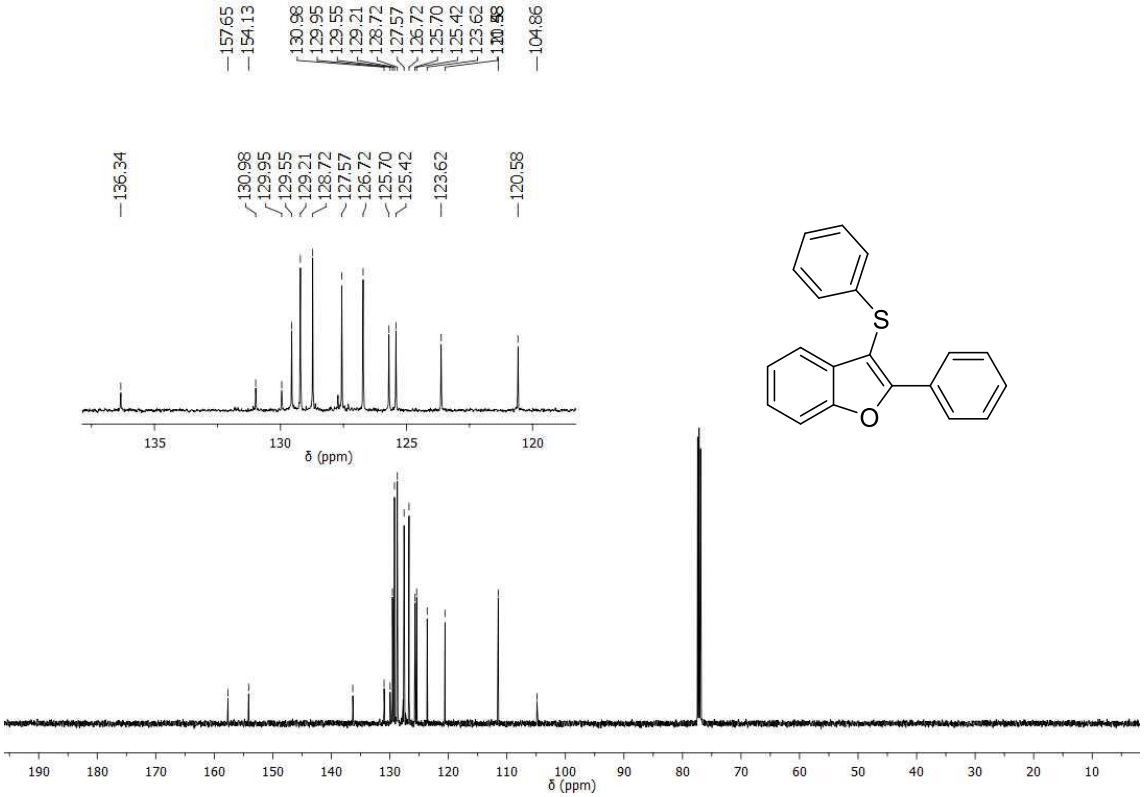


Figure S46: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3z**

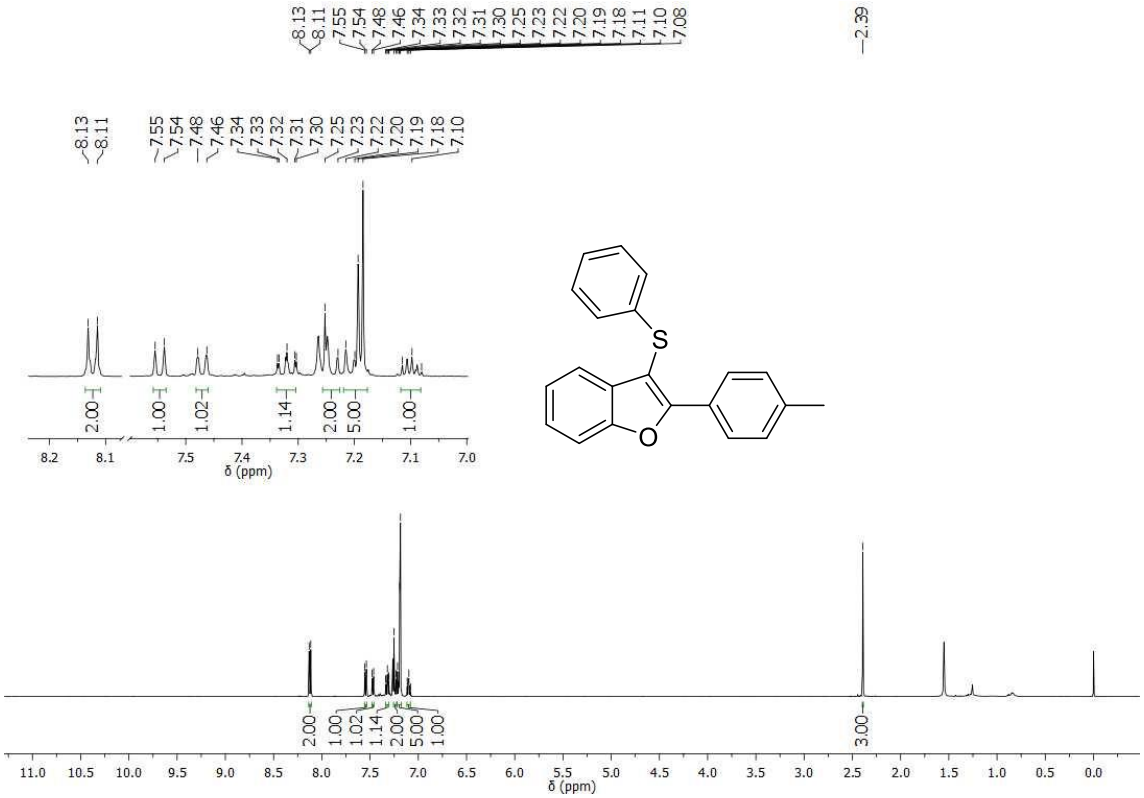


Figure 47: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3aa**

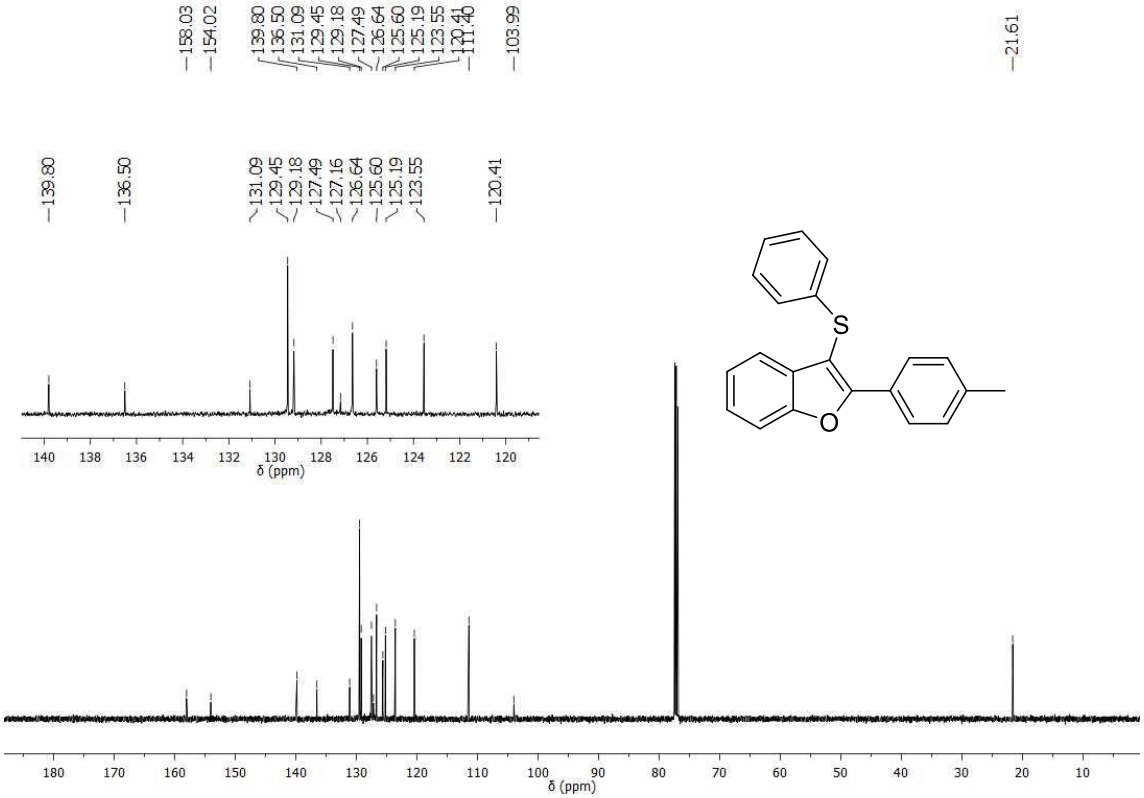


Figure 48: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3aa**

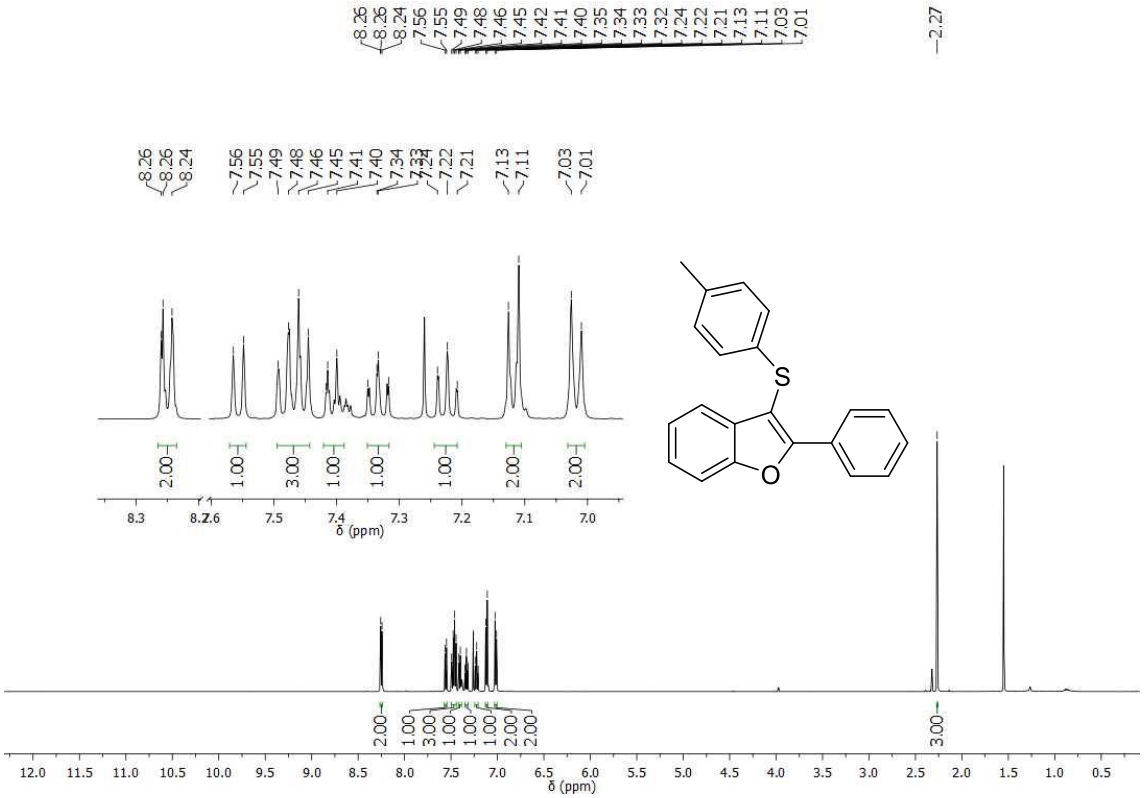


Figure S49: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3ab**

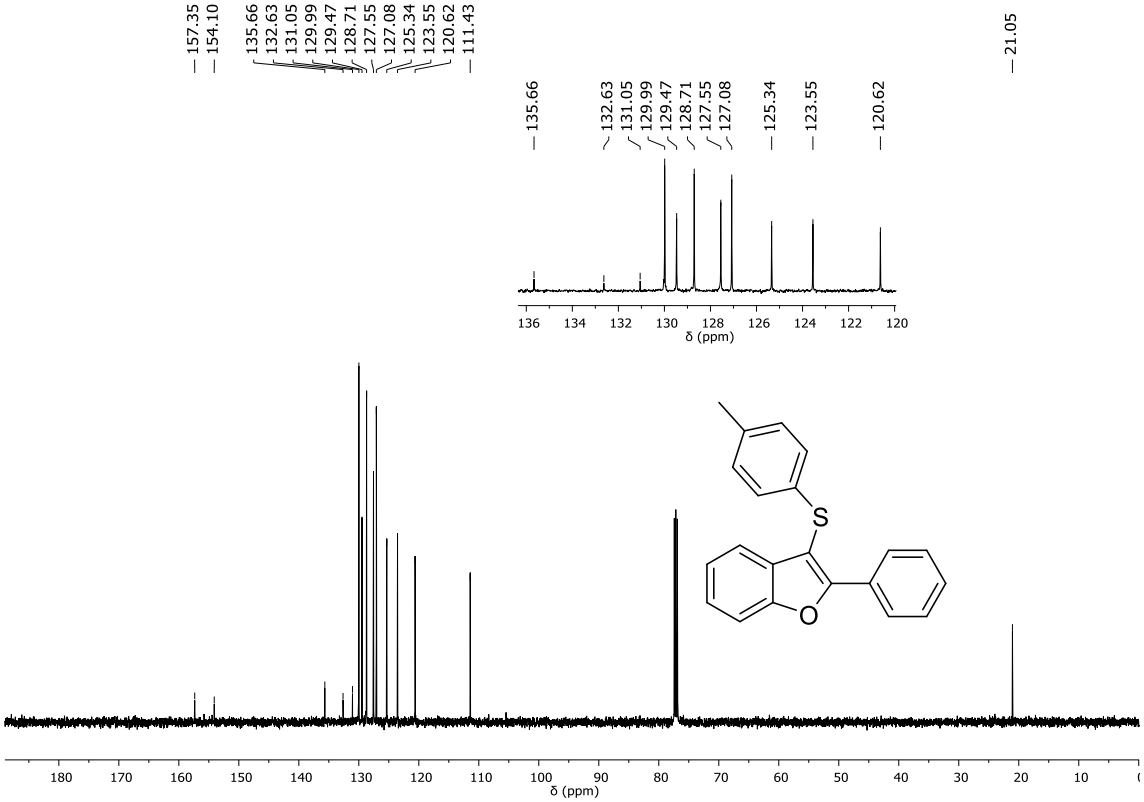


Figure S50: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3ab**

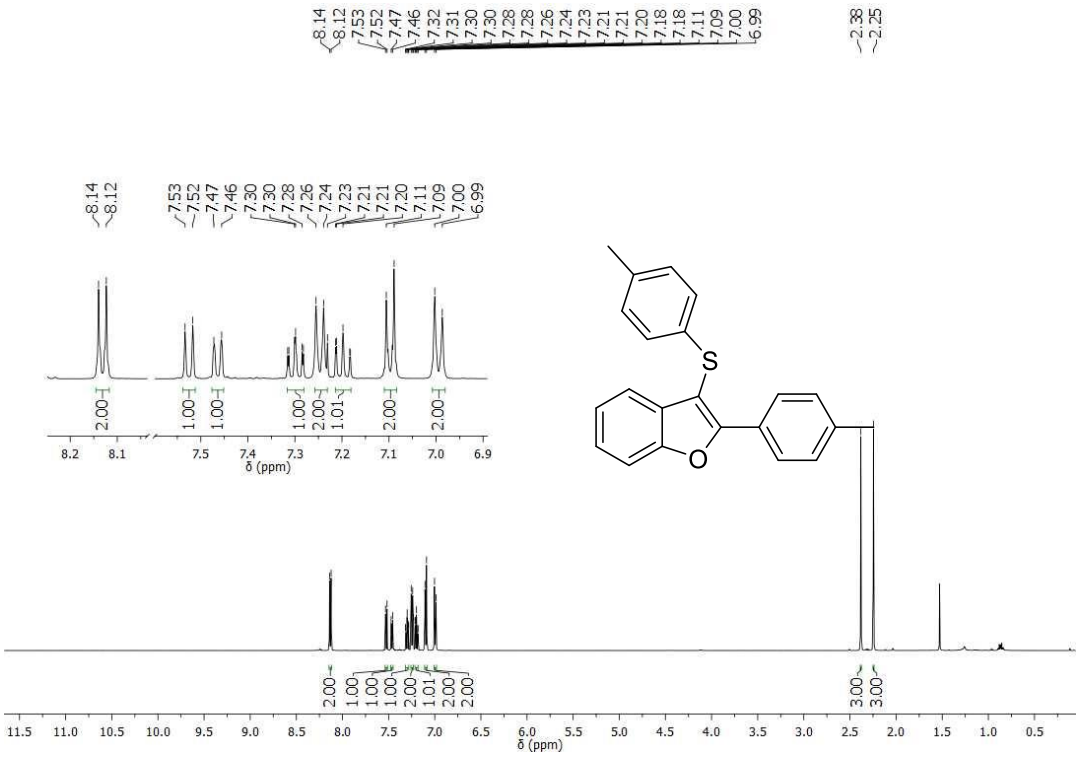


Figure 51: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3ac**

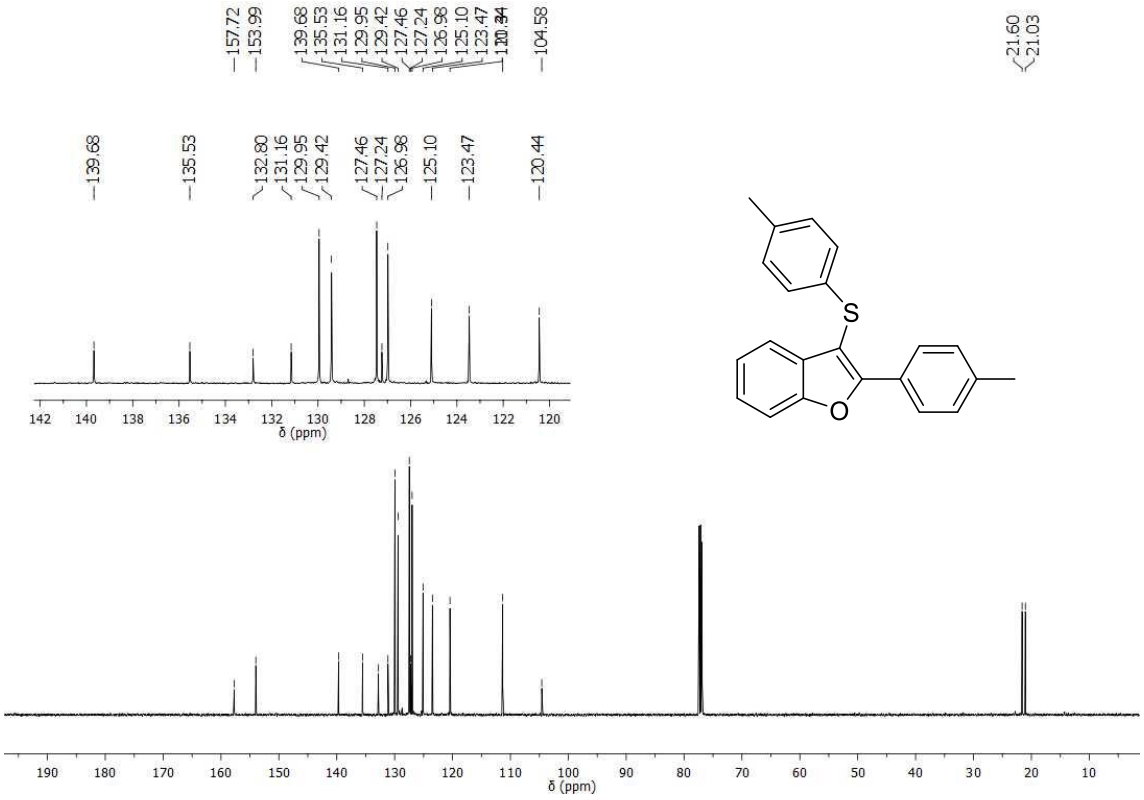


Figure 52: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3ac**

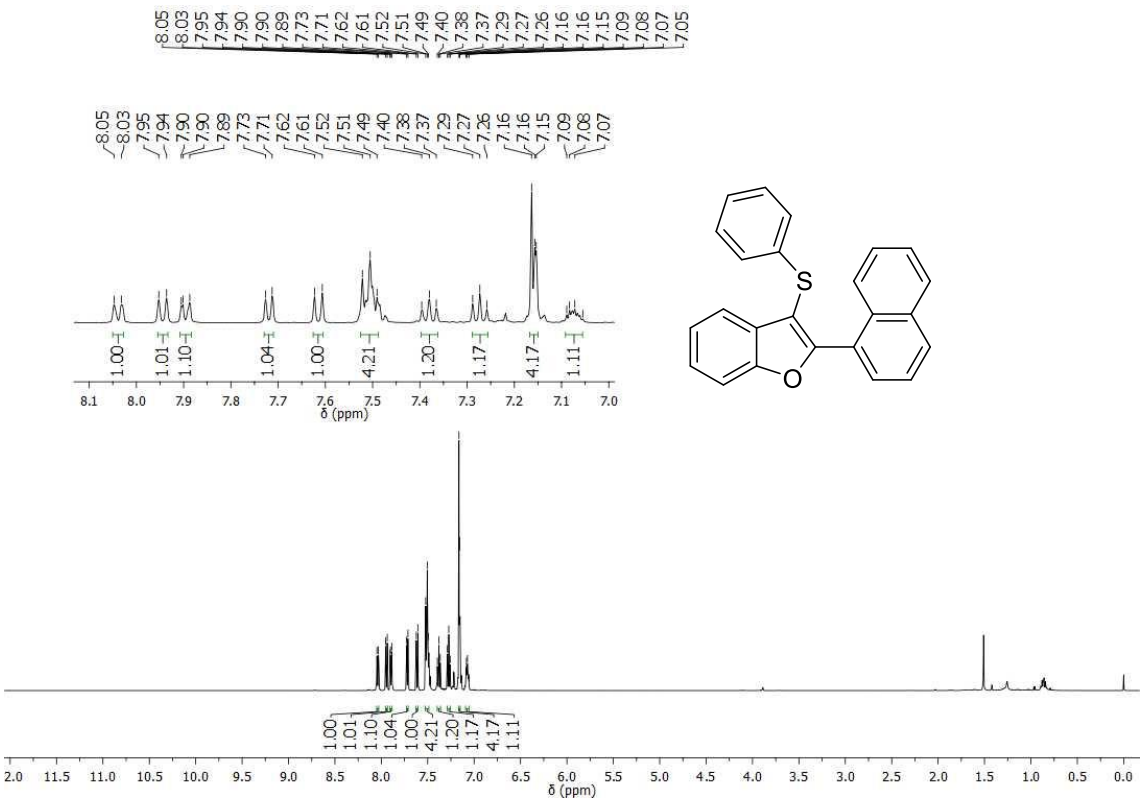


Figure 53: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **3ad**

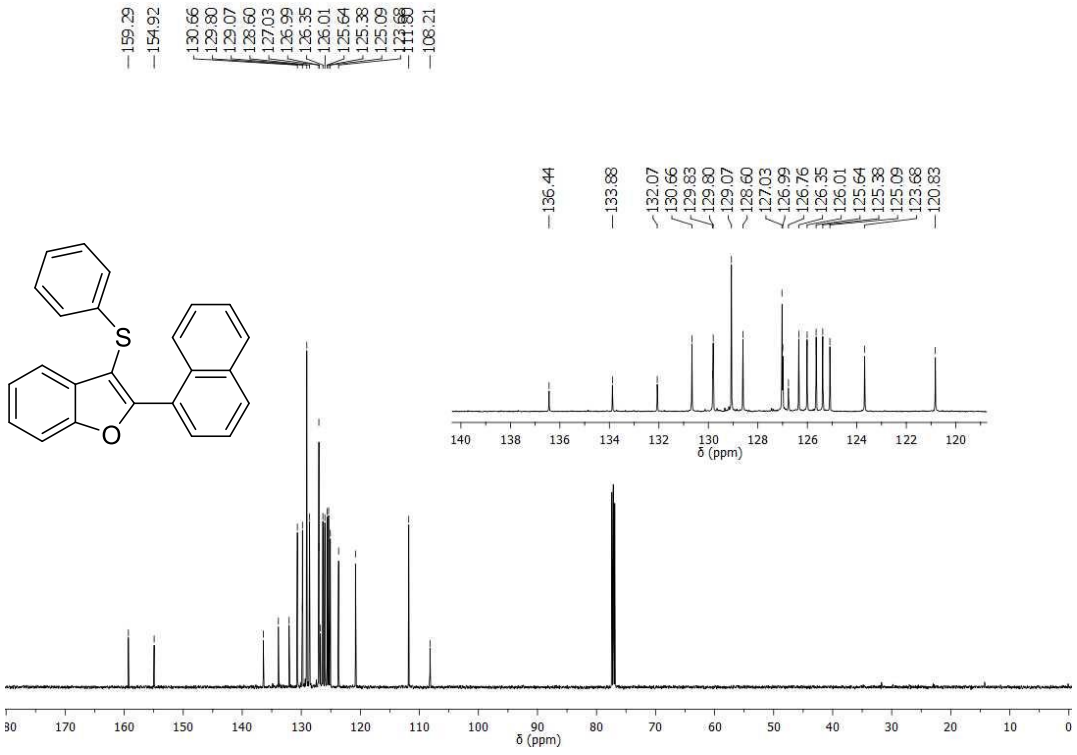


Figure 54: ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **3ad**

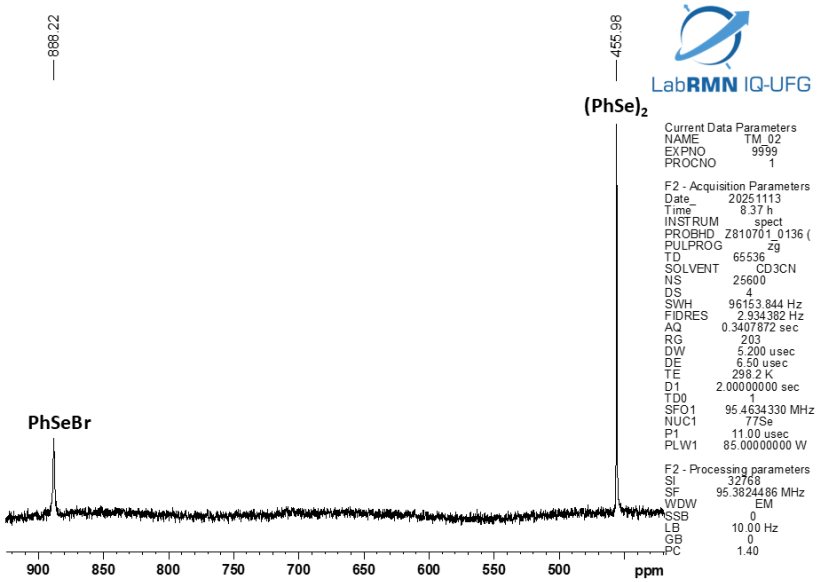


Figure S55: ^{77}Se NMR spectrum (95 MHz, $CDCl_3$) of mixture between **2a** and CBr_4

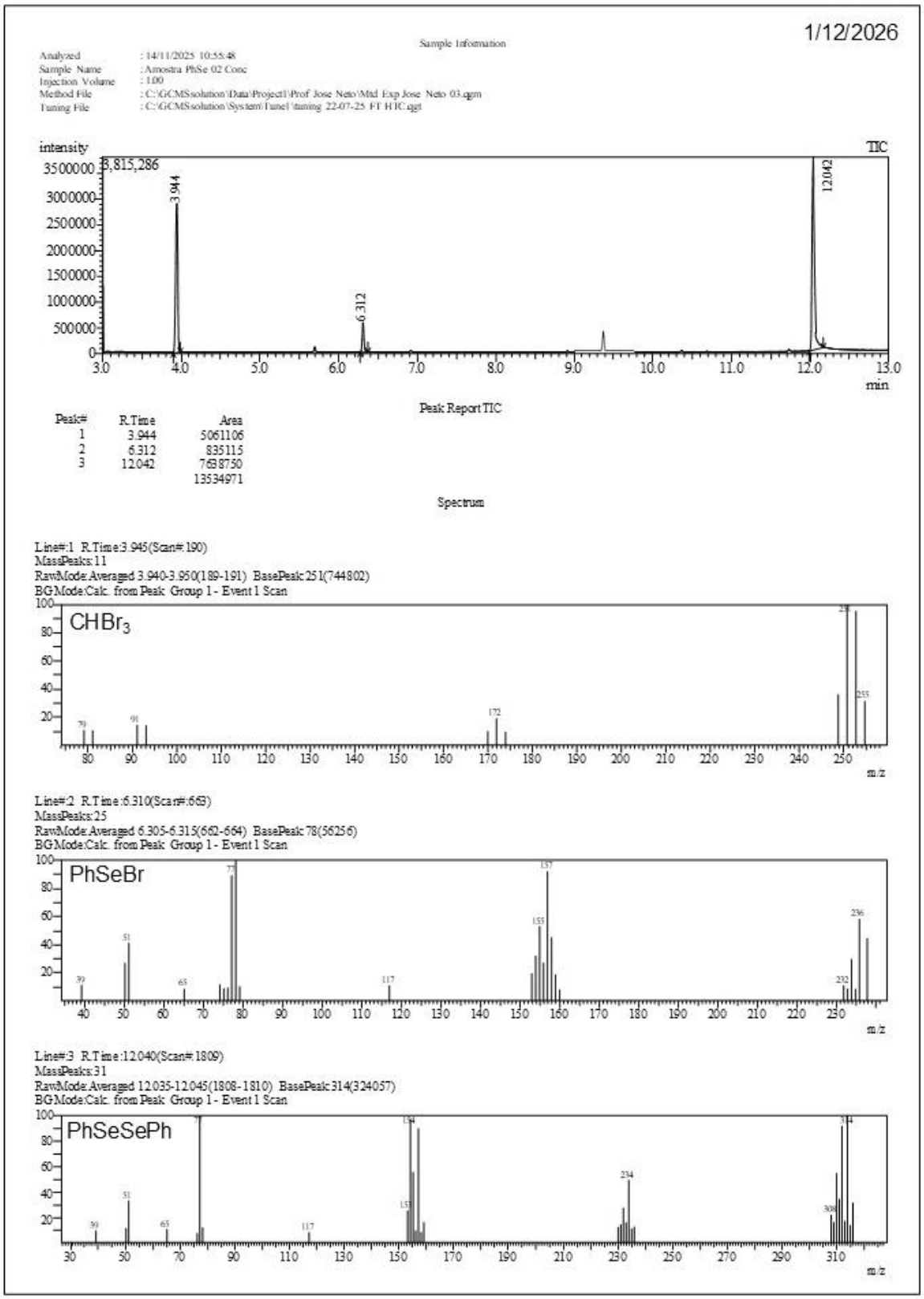


Figure S56: GCMS analysis of the reaction mixture between compound **2a** and CBr_4.

8. Supplementary *in silico* data – Molecular docking and ADME/T

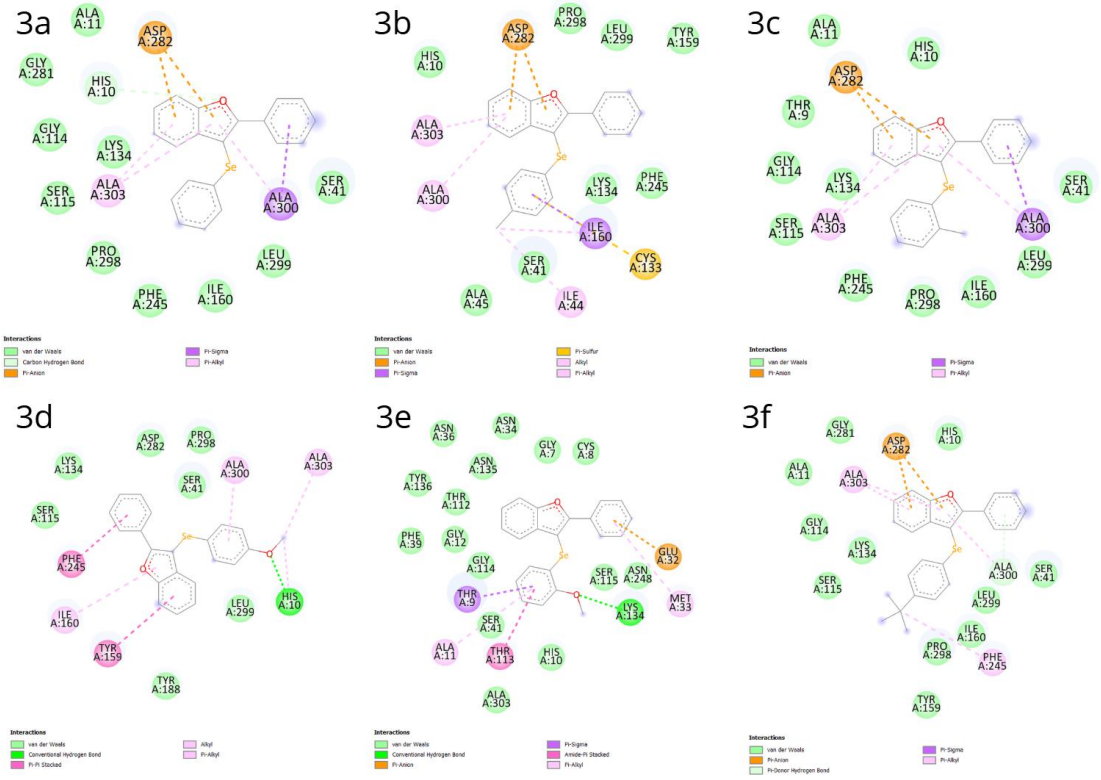
8.1 The molecular docking method. The 2D structures of the compounds were drawn using ChemDraw, converted to 3D, and optimized using Avogadro.[12] Subsequently, charges were assigned, polar hydrogen atoms were added, and rotatable bonds were defined using the AutoDock Tool (ADT), included in the MGLTools package (version 1.5.7).[13] Considering that xanthine oxidase and xanthine dehydrogenase (XDH) has a molybdenum-pterin centers structurally equivalent, the XDH-base structure was employed for the xanthine oxidase docking analyses[14x]. The 3D crystal structures of NADPH oxidase and XDH (equivalent to xanthine oxidase) were obtained from the Protein Data Bank (PDB) (PDB ID: 2CDU)[15] and (PDB ID: 1N5X).[16] After downloading, the structures were organized, and possible duplicate chains or residues were cleaned using PyMOL 3.0.0.[17] To ensure the complete removal of residues, Chimera 1.17.3 was employed.[18] Water molecules were removed, and polar hydrogens and charges were added using ADT, which was also used to define the grid box parameters for these structures. The grid box for NADPH oxidase was centered at 10.151, 0.699, and 6.106 Å (for x, y, and z) with dimensions of 30 × 30 × 30 points. For xanthine oxidase, the grid box was centered at 115.63, 49.857, and 23.254 Å (for x, y, and z), also with dimensions of 30 × 30 × 30 points. Docking was performed using AutoDock Vina 1.1.1,[16] and the docking scores were reported as binding affinities (kcal/mol). The interactions between the ligands and proteins were analyzed using Discovery Studio version 24.1.0.23298.[19]

8.2 ADME/T prediction method. The SMILES codes of the structures were used, obtained through the JSME Test Page software (https://jsme-

[12] M. D. Hanwell, D. E. Curtis, D. C. Lonie, T. Vandermeersch, E. Zurek, G. R. Hutchison, J. Cheminform. 2012, 4, 17.
[13] G. M. Morris, R. Huey, W. Lindstrom, M. F. Sanner, R. K. Belew, D. S. Goodsell, A. J. Olson, J. Comput. Chem. 2009, 30, 2785-2791.
[14] Gao J, Zhang Z, Zhang B, Mao Q, Dai X, Zou Q, Lei Y, Feng Y, Wang S. Bioorg Chem. 2020, 95, 103564.
[15] A. Farouk, M. Mohsen, H. Ali, H. Shaaban, N. Albaridi, Molecules 2021, 26, 4145.
[16] X. J. Wang, Z. J. Lin, B. Zhang, C. S. Zhu, H. J. Niu, Y. Zhou, A. Z. Nie, Y. Wang, Zhongguo Zhong Yao Za Zhi 2015, 40, 3818–3825.
[17] The PyMOL Molecular Graphics System, Version 1.2r3pre, Schrödinger, LLC.
[18] E. F. Pettersen, T. D. Goddard, C. C. Huang, G. S. Couch, D. M. Greenblatt, E. C. Meng, T. E. Ferrin, J. Comput. Chem. 2004, 25, 1605-1612.
[19] Dassault Systèmes BIOVIA, 2024. BIOVIA Discovery Studio, 24.1.0.23298, San Diego: Dassault Systèmes, 2024.

editor.github.io/dist/JSME_test.html). The predictions were performed on the pkCSM website,[20] evaluating aspects related to Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADME/T) for each compound. Among the parameters generated by the program, the most relevant for the research were selected: for the pharmacokinetic property of absorption, Caco-2 permeability and human intestinal absorption were highlighted; for distribution, blood-brain barrier permeability and central nervous system permeability were analyzed. For metabolism, interactions with cytochrome P450 isoforms were evaluated, considering both the potential of the compounds to act as substrates and inhibitors. For the excretion property, total clearance was selected, while for the toxicity parameter, AMES toxicity and hepatotoxicity were considered.

8.3 Molecular docking results



[20] D. E. Pires, T. L. Blundell, D. B. Ascher, J. Med. Chem. 2015, 58, 4066-4072.

Figure S57. 2D interaction diagrams of compounds **3a**, **3b**, **3c**, **3d**, **3e** and **3f** bound to NADPH oxidase active site.

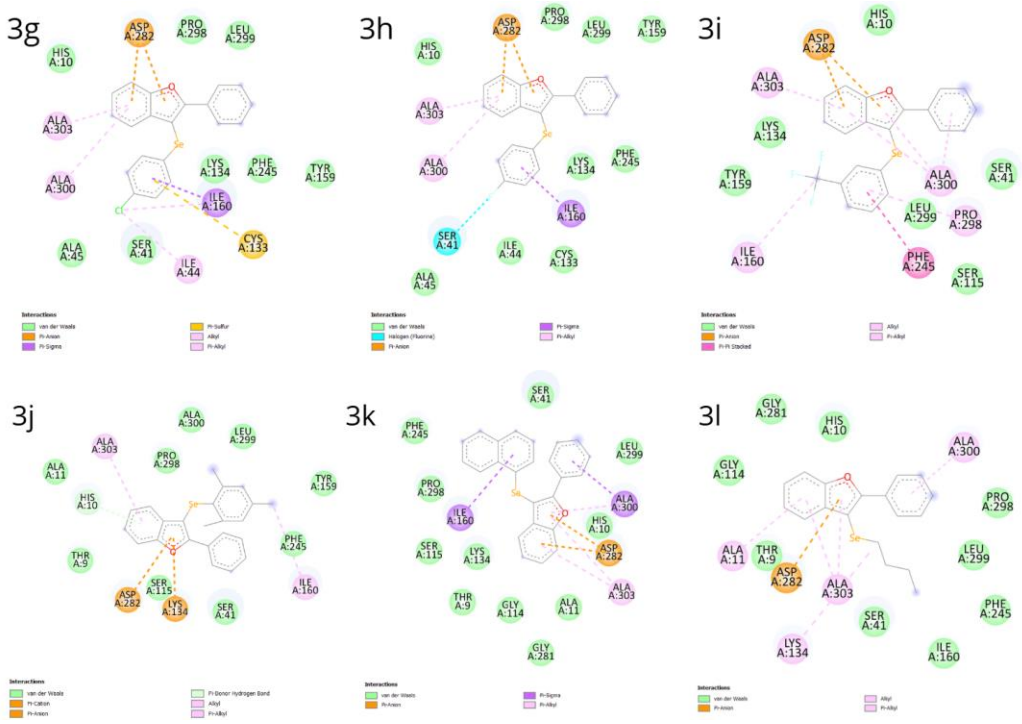


Figure S58. 2D interaction diagrams of compounds **3g**, **3h**, **3i**, **3j**, **3k**, and **3l** bound to NADPH oxidase active site.

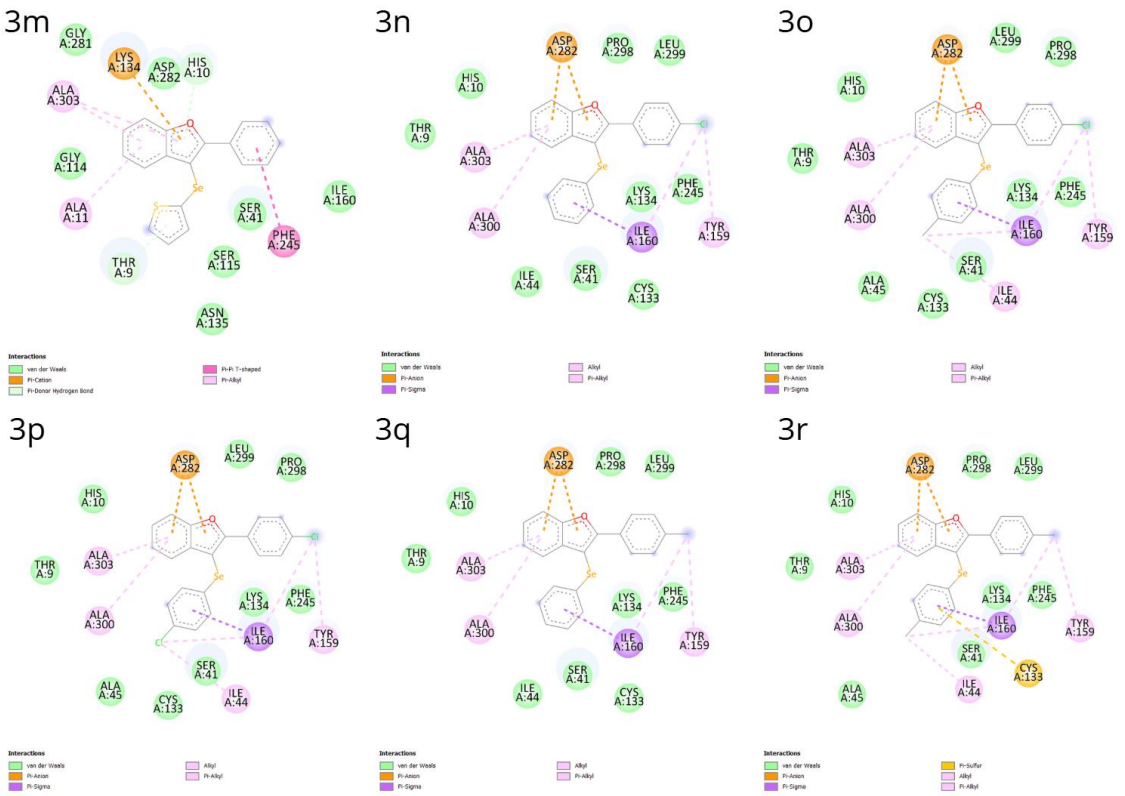


Figure S59. 2D interaction diagrams of compounds **3m**, **3n**, **3o**, **3p**, **3q** and **3r** bound to NADPH oxidase active site.

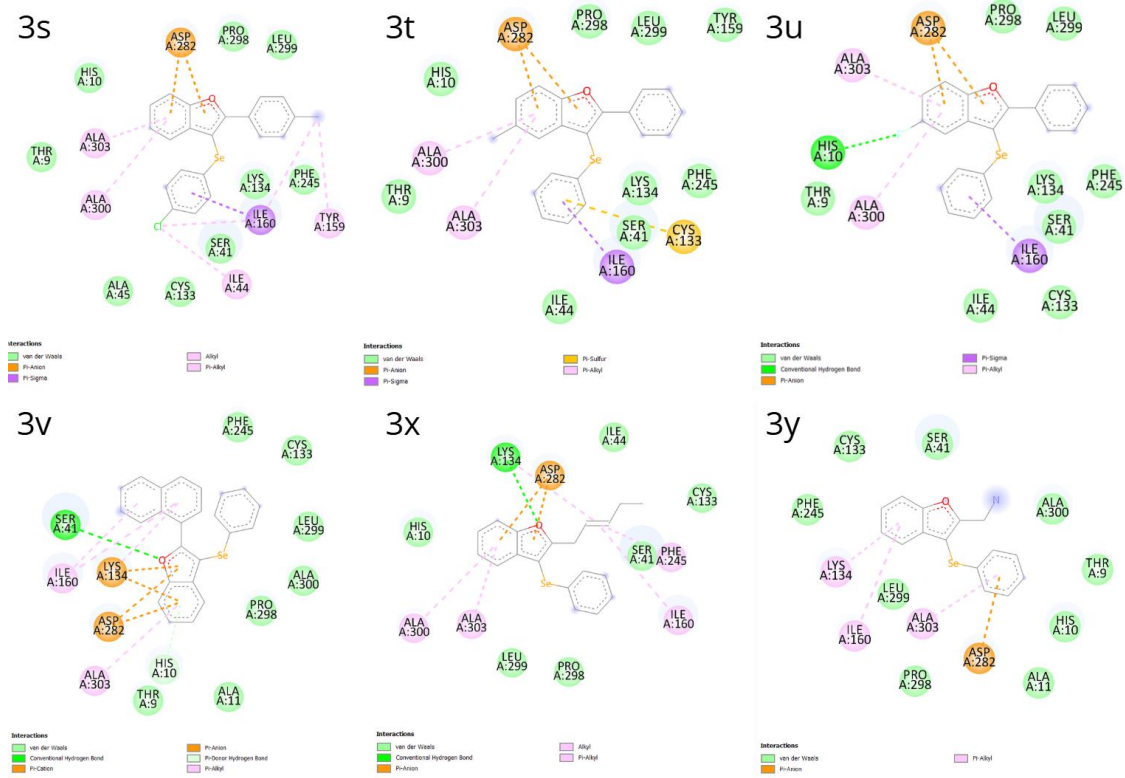


Figure S60. 2D interaction diagrams of compounds **3s**, **3t**, **3u, 3v**, **3x** and **3y** bound to NADPH oxidase active site.

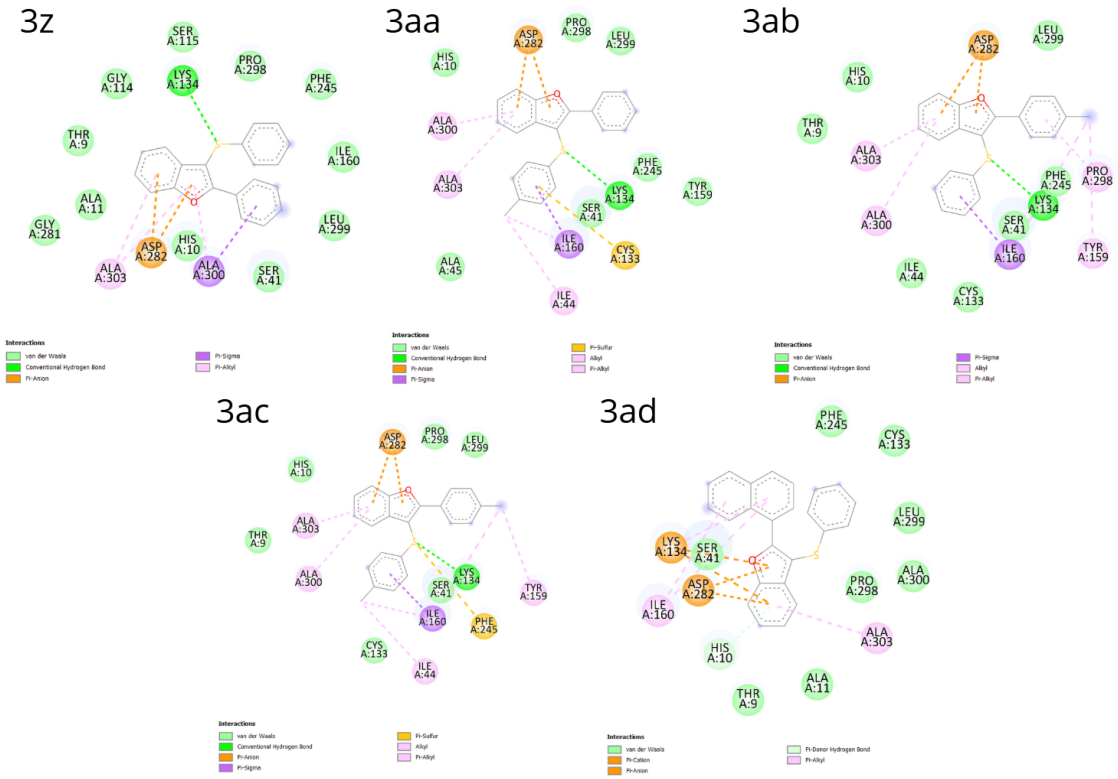


Figure S61. 2D interaction diagrams of compounds **3z**, **3aa**, **3ab**, **3ac** and **3ad** bound to NADPH oxidase active site.

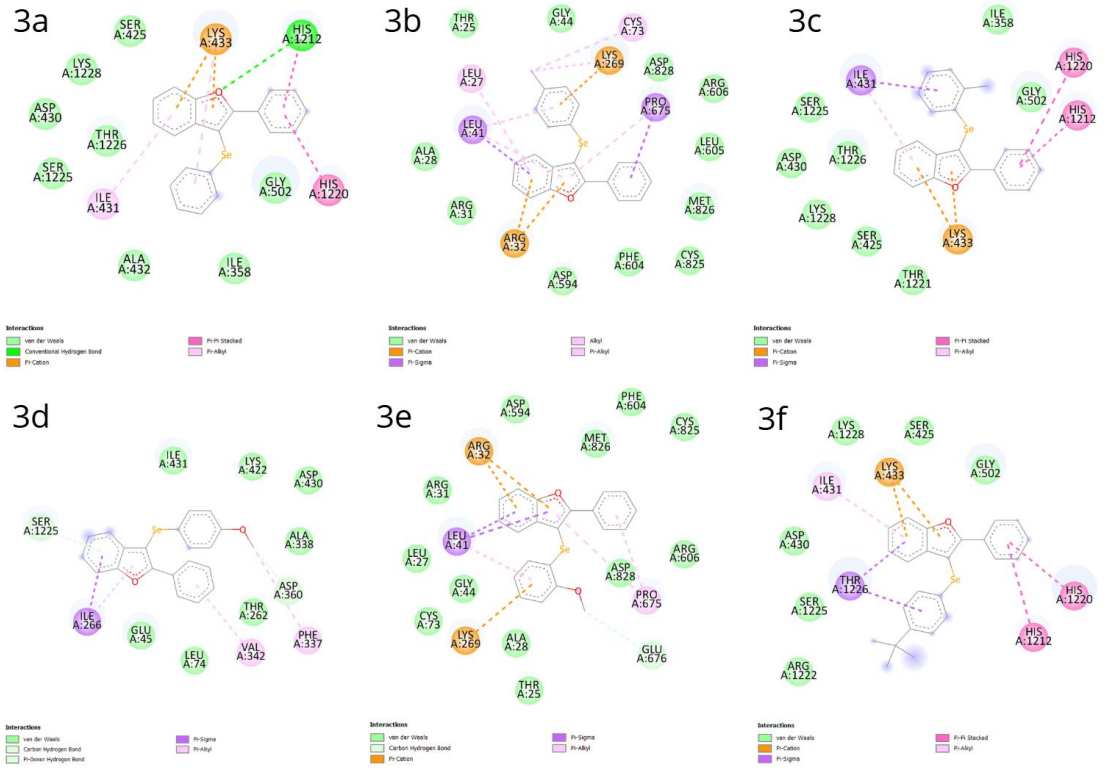


Figure S62. 2D interaction diagrams of compounds **3a**, **3b**, **3c**, **3d**, **3e** and **3f** bound to xanthine oxidase active site.

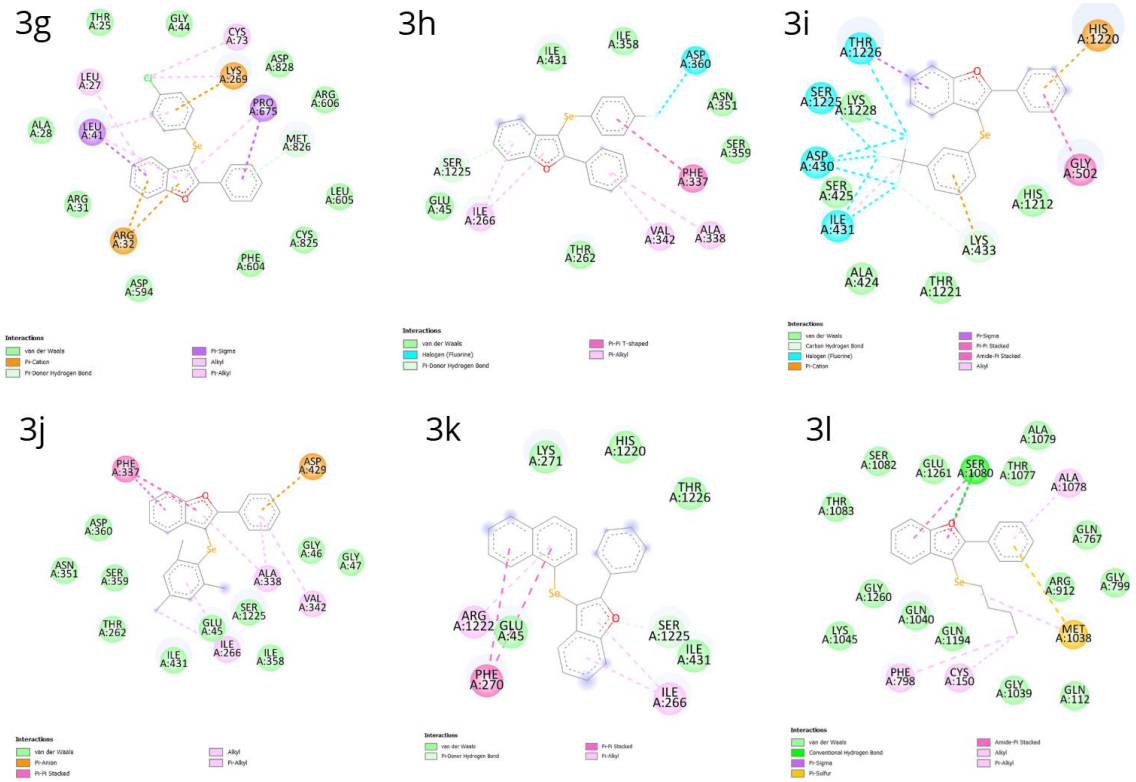


Figure S63. 2D interaction diagrams of compounds **3g**, **3h**, **3i**, **3j**, **3k** and **3l** bound to xanthine oxidase active site.

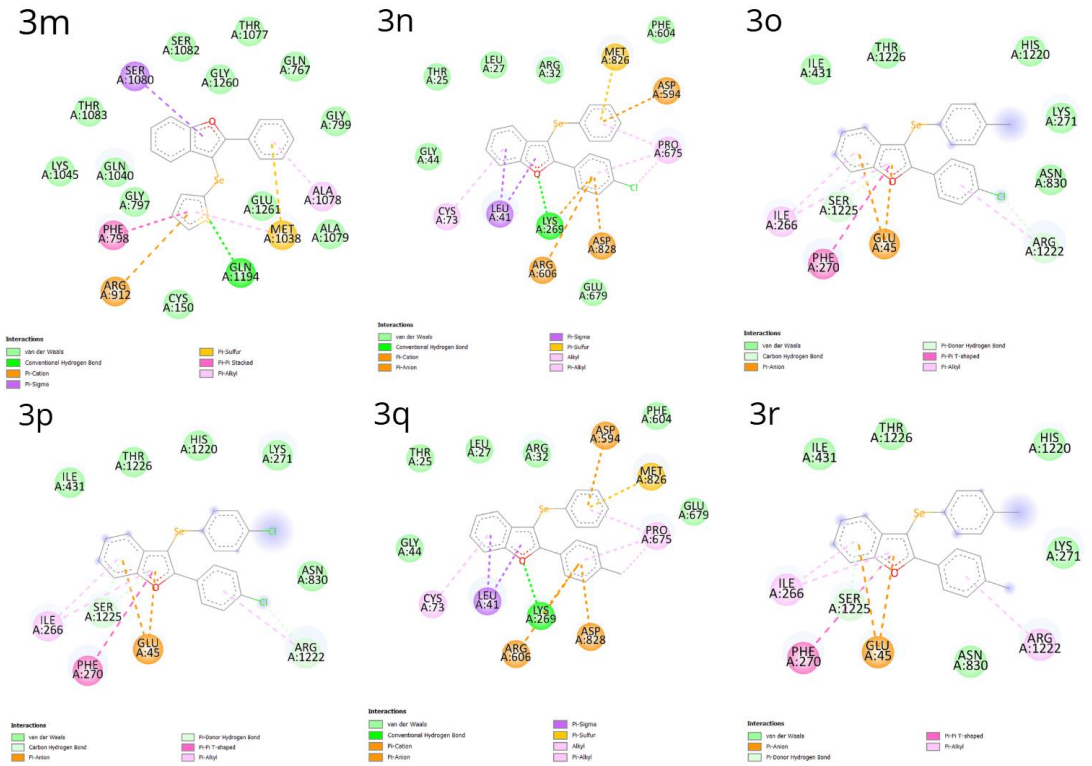


Figure S64. 2D interaction diagrams of compounds **3m**, **3n**, **3o, 3p**, **3q** and **3r** bound to xanthine oxidase active site.

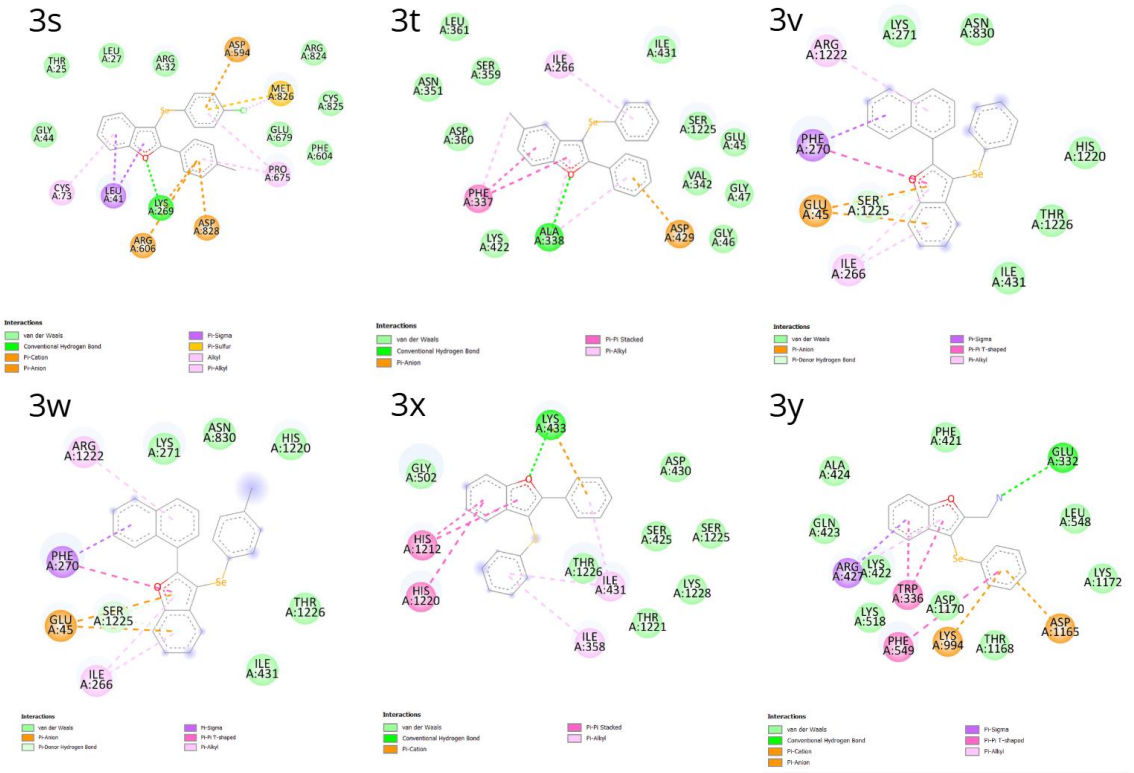


Figure S65. 2D interaction diagrams of compounds **3s**, **3t**, **3v, 3w, 3x** and **3y** bound to xanthine oxidase active site.

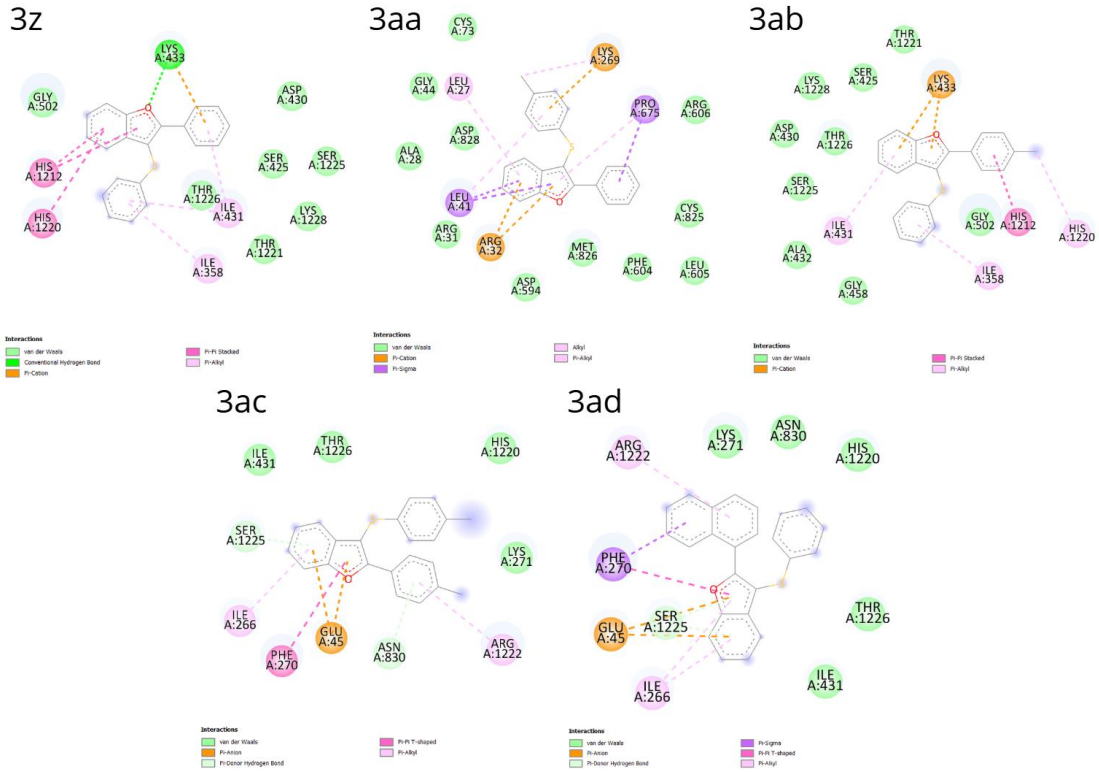


Figure S66. 2D interaction diagrams of compounds **3z**, **3aa, 3ab, 3ac** and **3ad** bound to xanthine oxidase active site.

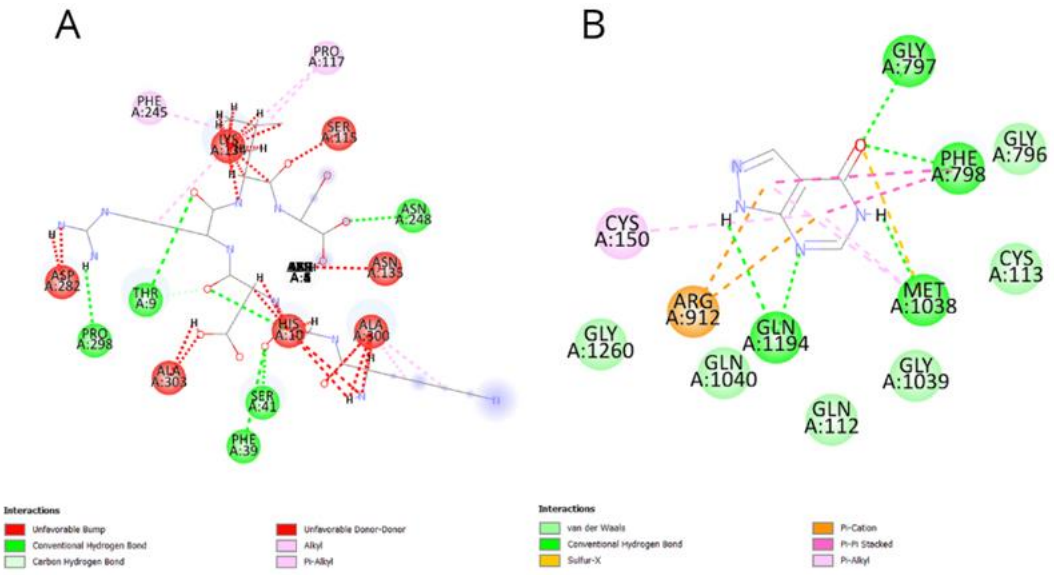


Figure S67. 2D interaction diagrams of the standard control TNF-α with active site of NADPH oxidase (A) and the standard control allopurinol with the active site of xanthine oxidase (B).

8.4 ADME/T results

Table S1. Prediction of the interaction of compounds **3a-3ae** with cytochrome P450 isoforms.

#	CYP2D6 substrate (Yes/No)	CYP3A4 substrate (Yes/No)	CYP2C9 inhibitior (Yes/No)	CYP2D6 inhibitior (Yes/No)	CYP3A4 inhibitior (Yes/No)
3a	No	Yes	No	No	No
3b	No	Yes	Yes	No	No
3c	No	Yes	Yes	No	No
3d	No	Yes	Yes	No	No
3e	No	Yes	Yes	No	Yes
3f	No	Yes	Yes	No	No
3g	No	Yes	Yes	No	Yes
3h	No	Yes	Yes	Yes	No
3i	No	Yes	Yes	Yes	No
3j	No	Yes	Yes	No	No
3k	No	Yes	Yes	No	No
3l	No	Yes	No	No	No
3m	No	Yes	No	No	No
3n	No	Yes	Yes	No	No
3o	No	Yes	Yes	No	Yes
3p	No	Yes	Yes	No	No
3q	No	Yes	Yes	No	No
3r	No	Yes	Yes	No	No
3s	No	Yes	Yes	Yes	Yes
3t	No	Yes	Yes	No	No
3u	No	Yes	Yes	No	No
3v	No	Yes	Yes	Yes	No
3w	No	Yes	No	No	No
3x	No	Yes	No	No	No
3y	No	Yes	No	Yes	No
3z	No	Yes	No	No	No
3aa	No	Yes	Yes	No	No
3ab	No	Yes	Yes	No	No
3ac	No	Yes	Yes	No	No
3ad	No	Yes	Yes	Yes	No

Table S2. Prediction of the pharmacokinetic parameter excretion and toxicological parameters of compounds **3a-3ad**.

#	Total clearance (log ml/min/kg)	AMES toxicity (Yes/No)	Hepatotoxicity (Yes/No)
3a	1.984	No	No
3b	2.041	Yes	Yes
3c	2.043	Yes	Yes
3d	2.109	Yes	Yes
3e	2.113	Yes	Yes
3f	1.869	Yes	No
3g	1.941	No	No
3h	2.165	No	Yes
3i	2.150	No	Yes
3j	2.168	Yes	Yes
3k	0.068	Yes	No
3l	1.961	Yes	Yes
3m	0.072	No	No
3n	2.041	Yes	Yes
3o	0.067	No	Yes
3p	0.034	Yes	No
3q	2.041	Yes	Yes
3r	2.099	Yes	Yes
3s	0.067	No	Yes
3t	2.049	Yes	Yes
3u	1.875	Yes	No
3v	2.169	No	Yes
3w	2.231	No	Yes
3x	2.022	Yes	Yes
3y	1.657	Yes	Yes
3z	0.309	Yes	No
3aa	0.250	Yes	No
3ab	0.251	Yes	No
3ac	0.196	Yes	No
3ad	0.265	No	No