Synthesis of amino phosphinodiselenoic acid ester and β-amino diselenides employing P_2Se_5

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Full experimental details

Starting materials used for the following reactions were obtained from Sigma-Aldrich, Spectrochem used as received unless otherwise mentioned. HPLC grade solvents and distilled water were used for reactions. Reactions were done under inert nitrogen atmosphere. Analytical thin layer chromatography was done on TLC silica gel 60 F_{254} obtained from Merck. Spots were visualised by using one of the (or all the) following methods : (1) UV activity (2) treating with iodine. Column chromatography was carried out on Spectrochem silica gel (60-120 mesh or 100-200 mesh). Solvents of laboratory reagent grade were used for column purification. Mass spectra were recorded by using Shimadzu LC 2020. ^{1}H NMR spectra were recorded on a Bruker AV-400 spectrometer with chemical shifts reported as ppm (in DMSO-*d*6/$CDCl_3$ with TMS as internal standard). ^{13}C NMR, ^{77}Se, ^{31}P spectra were recorded on a Bruker AMX 100, 76 and 162 MHz respectively with DMSO-*d*6/$CDCl_3$. High resolution mass spectra (HRMS) were obtained from on Agilent Technologies 6538 UHD Accurate-Mass Q-TOF.

General Experimental Procedures

Procedure for the Preparation of P_2Se_5

Red phosphorus, washed with anhydrous ether and dried (31 mg, 1 mmol) was taken into glass vial and greyish elemental selenium (200 mg, 2.5 mmol) was added. The resulting mixture was heated under electric bunsen till it turned to glassy black-purple solid. It was then cooled to rt and the material was well grounded in to consistent powder.

General procedure of amino phosphinodiselenoic esters 2

Freshly prepared P_2Se_5 (20 mmol) and ethanol (10 mL) were refluxed under nitrogen atmosphere until the evolution of H_2Se ceased. A solution of N^{α}-protected amino alkyl iodide (10 mmol) in EtOH was added to the reaction mixture and refluxed. After complete consumption of alkyl iodide (TLC analysis), the reaction mixture was filtered and the filterate was evaporated and purified through column chromatography (Hexane:EtOAc = 8:2).

General procedure for symmetrical diselenides 3

To the solution of N^{α}-protected amino alkyl iodide/alkyl halide (10 mmol) in polar aprotic solvents (ACN, THF, and DCM) was added freshly prepared powdered blacky purple P_2Se_5 (20 mmol). The reaction mixture was refluxed, subsequently few drops of water were added. After complete consumption of the starting components (TLC analysis) the solvent was evaporated and isolated after column purification (Hexane:EtOAc = 8:2).

Characterization data

N^{α}-protected amino phosphinodiselenoic esters

1. **Fmoc-Leu-CH_2-Se-P(Se)$(OEt)_2$ [2a]:**

Yellow gummy solid, yield = 88%, $[\alpha]^{30}_{D}$ = +21.92 (c 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 7.2 Hz, 1H), 7.82 – 7.25 (m, 8H), 4.88 (d, J = 8.8 Hz, 2H), 4.48 (t, J = 8.0 Hz, 1H), 4.28 – 4.01 (m, 5H), 1.88 – 1.74 (m, 2H), 1.70 – 1.52 (m, 3H), 1.43 – 1.20 (m, 6H), 0.93 (d, J = 4 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.75, 142.88, 140.32, 126.66, 126.05, 124.04, 120.09, 67.35, 59.99, 48.38, 46.31, 43.54, 24.00, 21.94, 21.20, 18.33. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 289.80 (d, $J_{P\text{-}Se}$ = 482 Hz), -88.19 (d, $J_{P=Se}$ = 888 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 86.59 (s + dd satellites). HRMS: m/z Calculated for $C_{25}H_{35}NO_4PSe_2$ $[M + H]^+$ 604.0634; found: 604.0638.

2. **Fmoc-Ile-CH_2-Se-P(Se)$(OEt)_2$ [2b]:**

Yellow gummy solid, yield = 83%, $[\alpha]^{30}_{D}$ = +57.47 (c 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 6.8 Hz, 1H), 7.81 – 7.25 (m, 8H), 5.08 (d, J = 8 Hz, 2H), 4.50 (t, J = 8.0 Hz, 1H), 4.28 – 4.02 (m, 5H), 2.40 – 2.19 (m, 1H), 1.90 – 1.75 (m, 2H), 1.63 – 1.50 (m, 2H), 1.45 – 1.20 (m, 6H), 0.98 – 0.77 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.07, 143.93, 141.37, 127.73, 127.12, 125.13, 120.00, 66.68, 59.56, 51.37, 47.38, 44.03, 25.37, 21.85, 19.13, 18.91, 11.60. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 288.03 (d, $J_{P\text{-}Se}$ = 461 Hz), -86.98 (d, $J_{P=Se}$ = 799 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 82.17 (s + dd satellites).

3. **Cbz-Phe-CH_2-Se-P(Se)$(OEt)_2$ [2c]:**

Yellow gummy solid, yield = 82%, $[\alpha]^{30}_{D}$ = +76.08 (c 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 8.0 Hz, 1H), 7.52 – 7.15 (m, 10H), 4.97 (s, 2H), 4.16 – 3.87 (m, 5H), 3.10 – 2.85 (m, 2H), 1.91 – 1.76 (m, 2H), 1.38 – 1.19 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.45, 138.03, 137.09, 129.04, 128.22, 128.15, 127.61, 127.36, 126.20, 69.11, 61.23, 50.18, 45.47, 23.19, 18.10. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 284.87 (d, $J_{P\text{-}Se}$ = 485 Hz), -89.04 (d, $J_{P=Se}$ = 888 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 85.17 (s + dd satellites).

4. **Fmoc-[Ser-CH_2-Se-P(Se)$(OEt)_2$]-COOMe [2d]:**

Yellow liquid, yield = 79%, $[\alpha]^{26}_{D}$ = +12.77 (c 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (br s, 1H), 7.95 – 7.26 (m, 8H), 4.8 (d, J = 8 Hz, 2H), 4.50 – 4.32 (m, 2H), 4.23 – 4.03 (m, 4H), 3.71 (s, 3H), 2.15 – 1.98 (m, 2H), 1.40 – 1.13 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.70, 156.54, 143.92, 140.67, 127.52, 126.98, 125.07, 120.04, 64.92, 60.35, 52.51, 52.11, 46.68, 20.15, 18.49. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 284.83 (d, $J_{P\text{-}Se}$ = 477 Hz), -89.58 (d, $J_{P=Se}$ = 981 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 85.18 (s + dd satellites).

5. **Fmoc-Ala-CH_2-Se-P(Se)$(OEt)_2$ [2e]:**

Yellow gummy solid, yield = 86%, $[\alpha]^{28}_D$ = -28.80 (c 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, *J* = 8 Hz, 1H), 7.92 – 7.28 (m, 8H), 4.75 (d, *J* = 8 Hz, 2H), 4.51 (t, *J* = 7.8 Hz, 1H), 4.21 = 3.95 (m, 5H), 1.96 – 1.74 (m, 2H), 1.39 – 1.18 (m, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.93, 143.59, 140.69, 127.54, 126.98, 125.07, 120.05, 66.13, 59.51, 46.70, 44.54, 25.84, 24.03, 18.80. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 257.96 (d, $J_{P\text{-}Se}$ = 642 Hz), -87.51 (d, $J_{P=Se}$ = 1074 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 81.68 (s + dd satellites). HRMS: m/z Calculated for $C_{22}H_{29}NO_4PSe_2$ $[M + H]^+$ 562.0165; found: 562.0170.

6. **Fmoc-Phg-CH$_2$-Se-P(Se)(OEt)$_2$ [2f]:**

Yellow gummy solid, yield = 81%, $[\alpha]^{25}_D$ = +47.16 (c 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, *J* = 8 Hz, 1H), 7.92 – 7.20 (m, 13H), 4.96 (t, *J* = 7.2 Hz, 1H), 4.76 (d, *J* = 8 Hz, 2H), 4.52 (t, *J* = 8 Hz, 1H), 4.28 – 4.19 (m, 4H), 2.08 – 1.83 (m, 2H), 1.36 – 1.16 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.43, 143.69, 140.69, 128.51, 127.95, 127.56, 126.97, 126.54, 126.16, 125.04, 120.07, 65.32, 59.32, 55.17, 46.69, 26.11, 18.66. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 278.04 (d, $J_{P\text{-}Se}$ = 508 Hz), -89.22 (d, $J_{P=Se}$ = 855 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 82.31 (s + dd satellites).

7. **Cbz-Val-CH$_2$-Se-P(Se)(OEt)$_2$ [2g]:**

Yellow gummy solid, yield = 84%, $[\alpha]^{26}_D$ = +3.84 (c 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 7.8 Hz, 1H), 7.78 – 7.20 (m, 5H), 5.01 (s, 2H), 4.23 – 3.98 (m, 5H), 2.50 – 2.29 (m, 1H), 2.05 – 1.85 (m, 2H), 1.39 – 1.13 (m, 6H), 0.84 (d, *J* = 7.8 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.86, 137.24, 128.26, 127.67, 127.06, 67.36, 59.30, 54.87, 37.38, 22.02, 20.30, 18.95. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 290.68 (d, $J_{P\text{-}Se}$ = 442 Hz), -90.37 (d, $J_{P=Se}$ = 819 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 81.82 (s + dd satellites).

β-amino diselenides

1. **Boc-Leu-CH_2-Se)$_2$ [3a]:**

Gummy solid, yield = 91%, $[\alpha]^{29}_{D}$ = +20.60 (c 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.71 (d, *J* = 8.8 Hz, 2H), 3.95 – 3.71 (m, 2H), 1.85 – 1.70 (m, 4H), 1.65 – 1.50 (m, 6H), 1.36 (s, 18H), 0.85 (d, *J* = 8.8 Hz, 12 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.15, 80.27, 48.46, 46.03, 28.20, 25.95, 24.51, 23.02. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 282.80. HRMS: m/z Calculated for $C_{22}H_{45}N_2O_4Se_2$ $[M + H]^+$ 561.1710; found: 561.1705.

2. **Boc-Val-CH_2-Se)$_2$ [3b]:**

Gummy solid, yield = 93%, $[\alpha]^{26}_{D}$ = +126.98 (c 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.66 (d, *J* = 12 Hz, 2H), 3.98 – 3.79 (m, 2H), 2.60 – 2.39 (m, 2H), 1.81 – 1.69 (m, 4H), 1.37 (s, 18H), 0.84 (d, *J* = 8Hz, 12H). ^{13}C NMR (100 MHz, DMSO-d_6) δ155.54, 80.20, 52.25, 37.02, 28.22, 23.28, 19.05. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 282.40.

3. **Fmoc-Ile-CH_2-Se)$_2$ [3c]:**

Gummy solid, yield = 95%, $[\alpha]^{26}_{D}$ = +42.89 (c 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 - 7.24 (m, 16H), 6.74 (d, *J* = 7.2 Hz, 2H), 4.84 (d, *J* = 6.4 Hz, 4H), 4.45 (t, *J* = 6.4 Hz, 2H), 3.95 – 3.81 (m, 2H), 2.35 – 2.20 (m, 2H), 1.98 – 1.77 (m, 8H), 0.99 – 0.76 (m, 12H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.02, 143.88, 140.67, 127.53, 126.94, 125.17, 120.03, 65.15, 56.84, 46.77, 44.94, 25.47, 22.92, 17.89, 11.71. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 301.19.

4. **Boc-Gly-CH_2-Se)$_2$ [3d]:**

Gummy solid, yield = 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.51 (d, *J* = 6 Hz, 2H), 3.01 (t, *J* = 6.8 Hz, 4H), 2.06 (t, *J* = 6.8 Hz, 4H), 1.41 (s, 18H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.69, 79.07, 38.23, 28.66, 22.73. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 291.28.

5. **Cbz-Ala-CH_2-Se)$_2$ [3e]:**

Gummy solid, yield = 90%, $[\alpha]^{27}_{D}$ = +84.62 (c 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 - 7.20 (m, 10H), 6.60 (d, *J* = 8 Hz, 2H), 5.01 (s, 4H), 3.92 – 3.75 (m, 2H), 1.96 – 1.79 (m, 4H), 1.33 (d, *J* = 6 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.85, 137.64, 128.81, 128.22, 127.65, 65.66, 47.87, 27.11, 23.43. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 290.37.

6. **Cbz-Phe-CH_2-Se)$_2$ [3f]:**

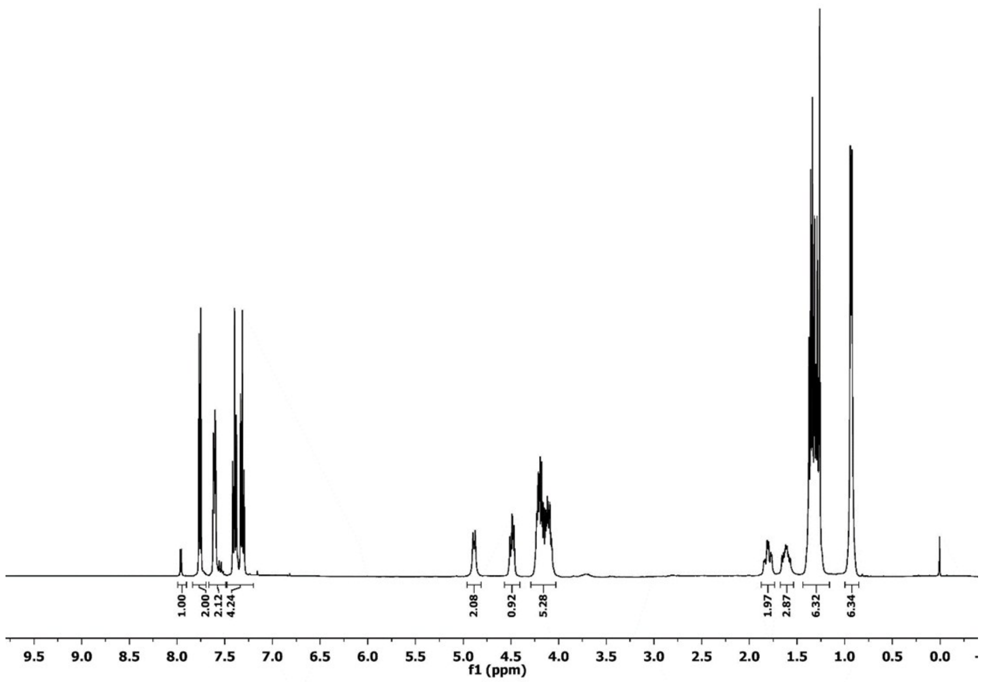
Gummy solid, yield = 96%, $[\alpha]^{28}_{D}$ = +2.40 (c 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 – 7.07 (m, 20H), 6.50 (d, *J* = 7.2 Hz, 2H), 4.97 (s, 4H), 4.08 – 3.86 (m, 2H), 2.97-2.62 (m, 4H), 1.99-1.82 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.04, 138.92, 137.72, 129.59, 128.75, 128.63, 128.11, 127.88, 126.61, 65.46, 53.66, 46.08, 25.62. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 289.07. HRMS: m/z Calculated for $C_{34}H_{37}N_2O_4Se_2$ $[M + H]^+$ 697.1083; found: 697.1085.

7. **Fmoc-Phg-CH_2-Se)$_2$ [3g]:**

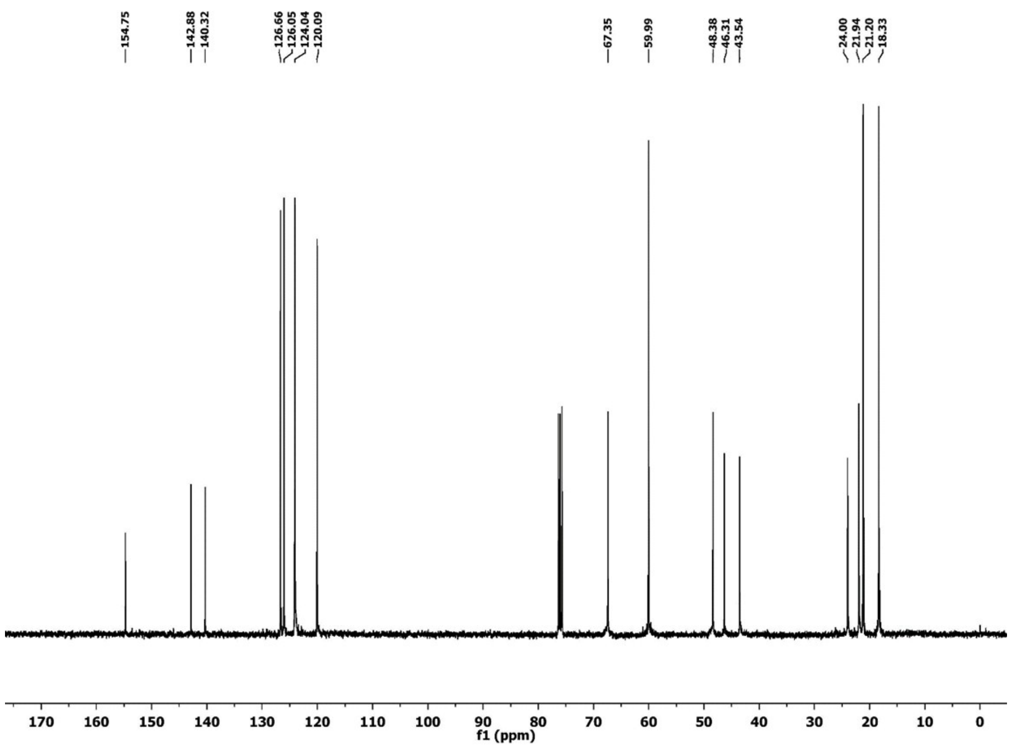
Gummy solid, yield = 92%, $[\alpha]^{28}_{D}$ = +14.45 (c 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.16 (m, 26H), 6.46 (d, *J* = 7.2 Hz, 2H), 4.99 (t, *J* = 6.8 Hz, 2H), 4.76 (d, *J* = 6 Hz, 4H), 4.69 (t, *J* = 6.4 Hz, 2H), 2.10 – 1.85 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.96, 144.29, 141.19, 138.91, 129.62, 128.60, 128.06, 127.49, 126.57, 125.67, 120.56, 65.71, 53.65, 47.21, 28.51. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 307.83.

Spectral data

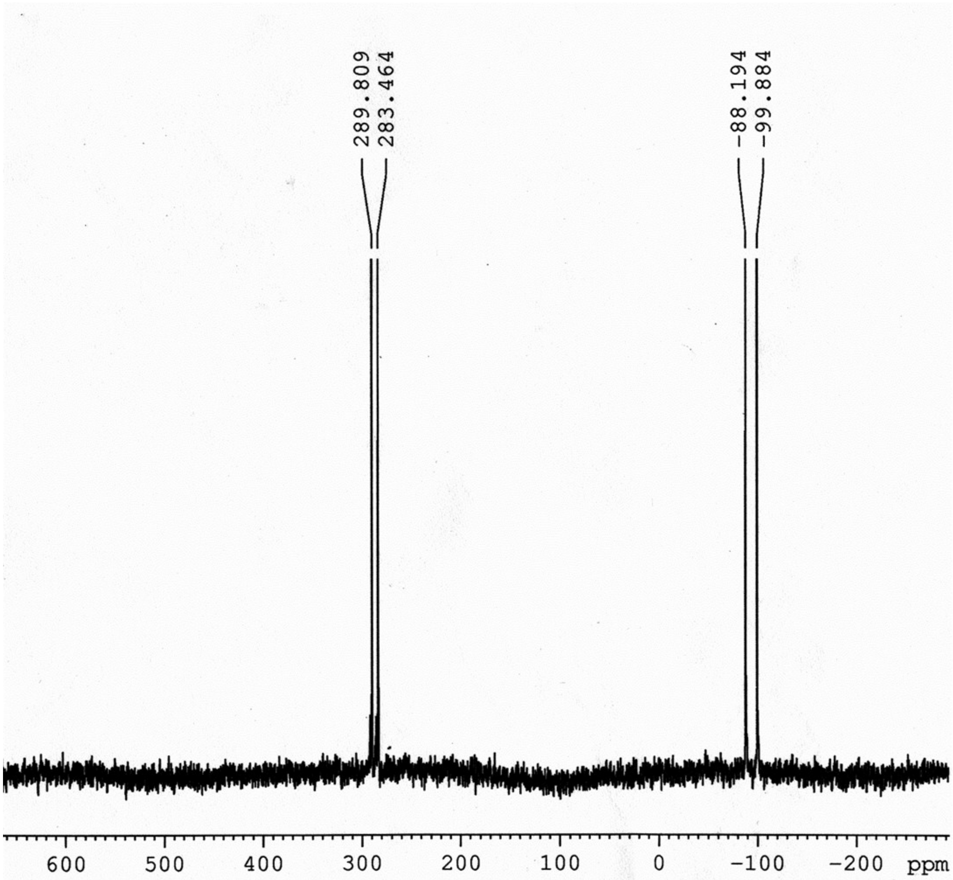
Amino phosphinodiselenoic esters



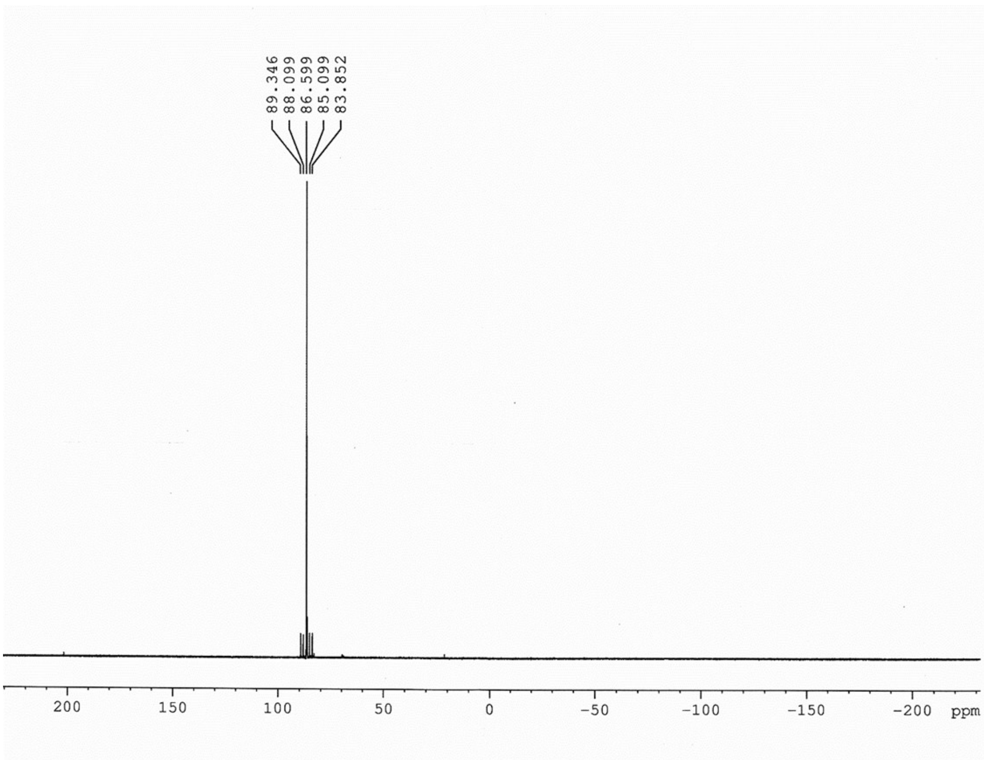
^{1}H NMR spectrum of compound 2a



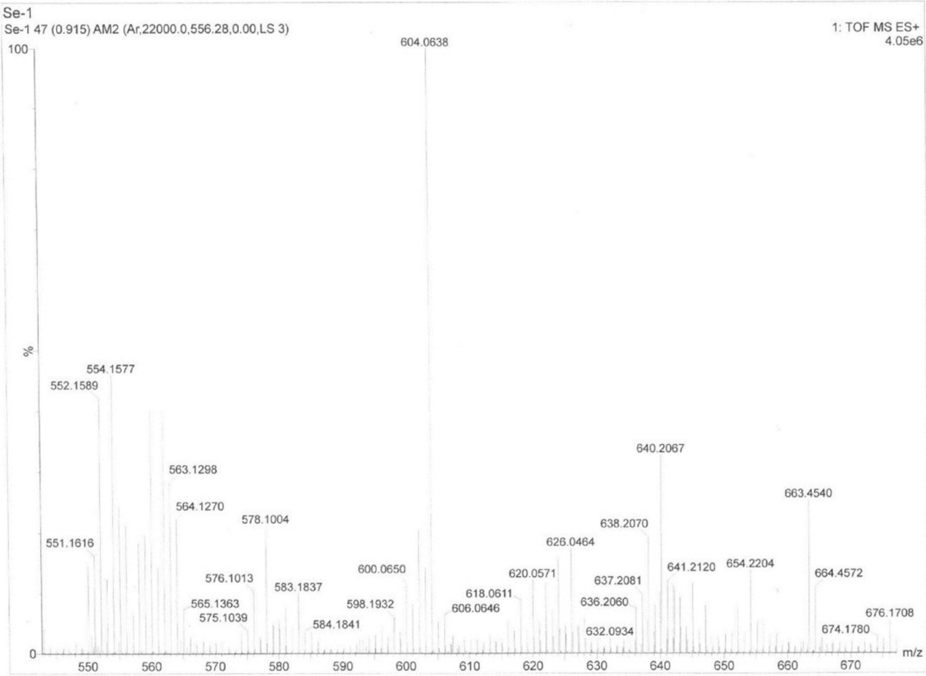
^{13}C NMR spectrum of compound 2a



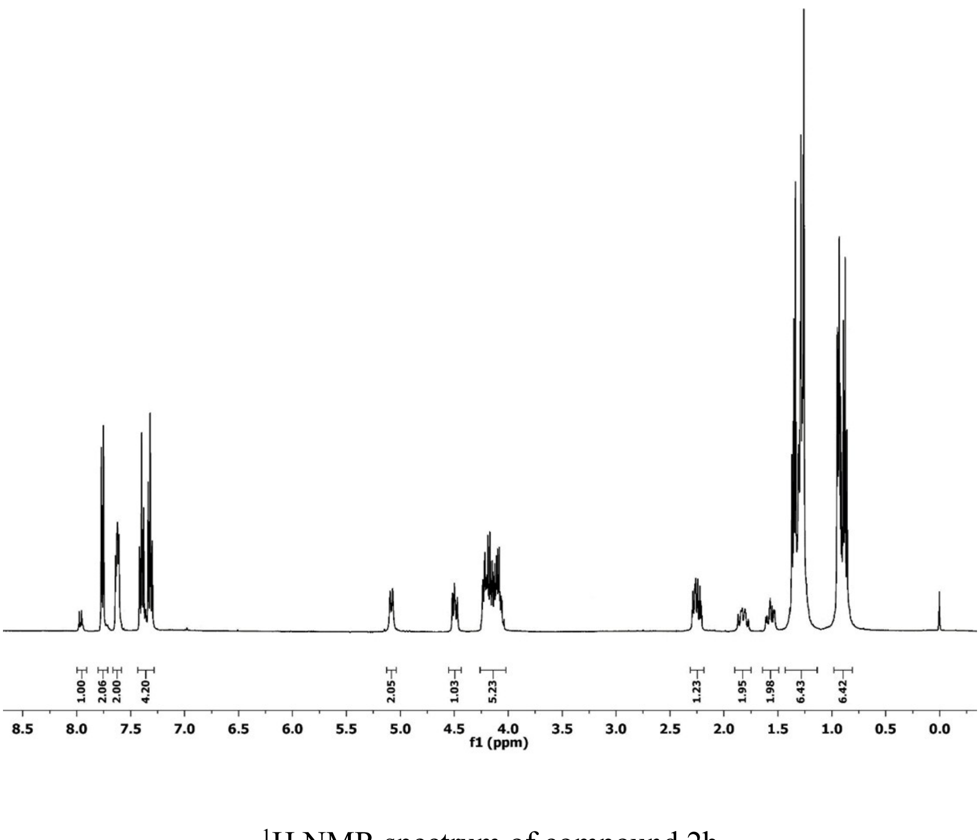
^{77}Se NMR spectrum of compound 2a



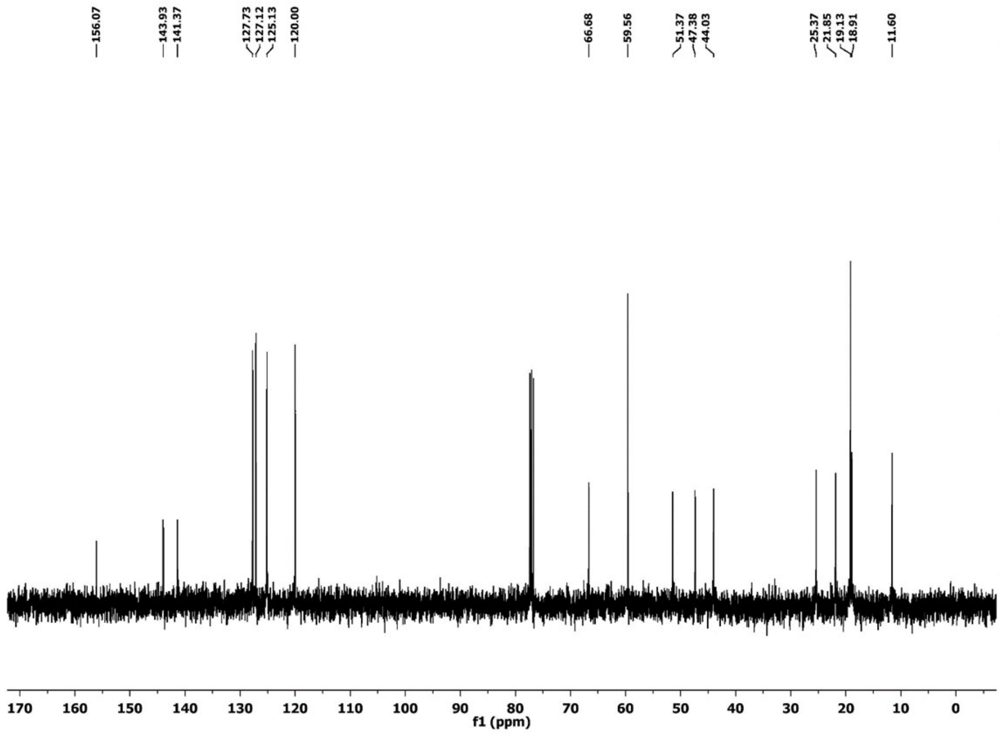
^{31}P NMR spectrum of compound 2a



HRMS of compound 2a



^{1}H NMR spectrum of compound 2b



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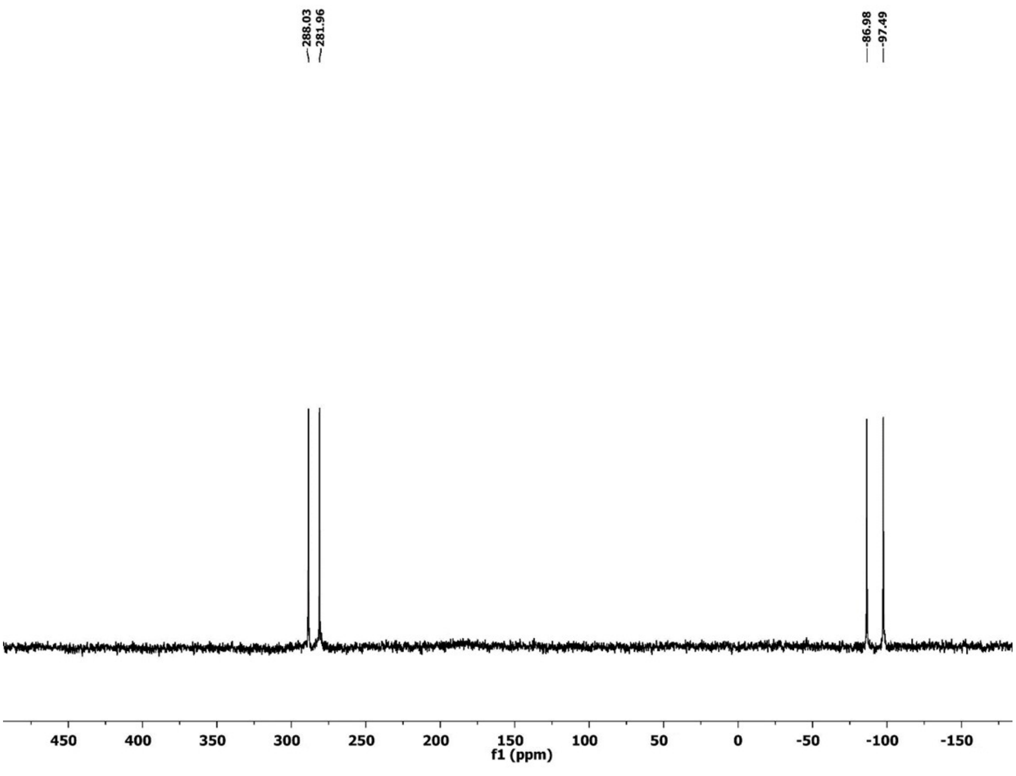

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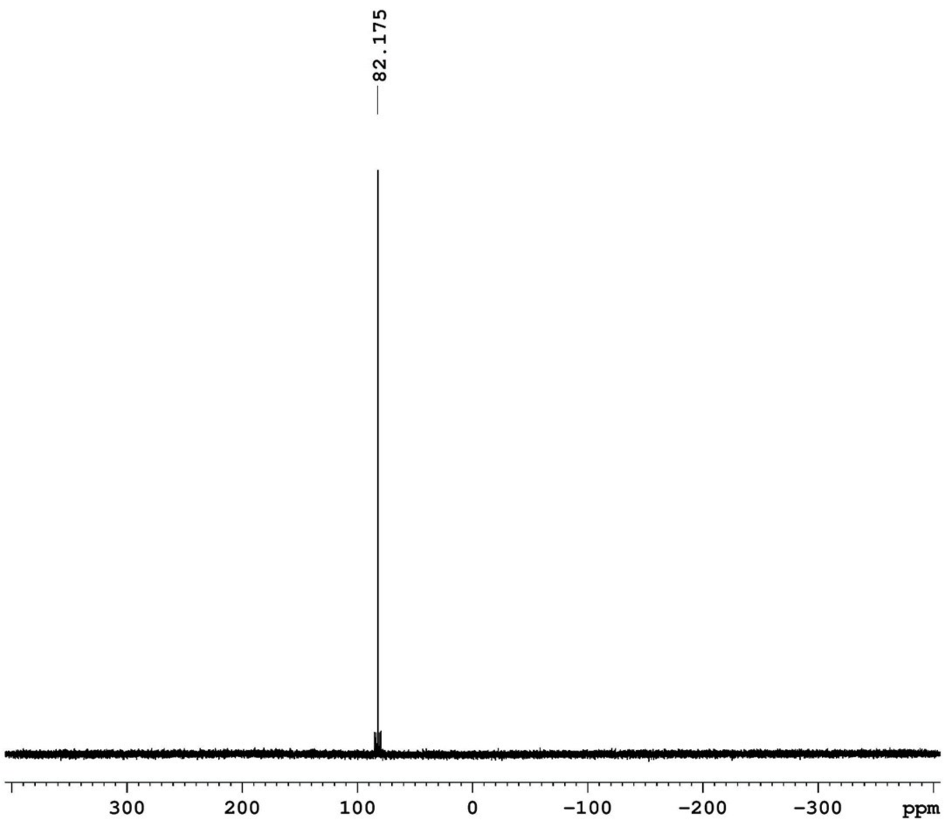
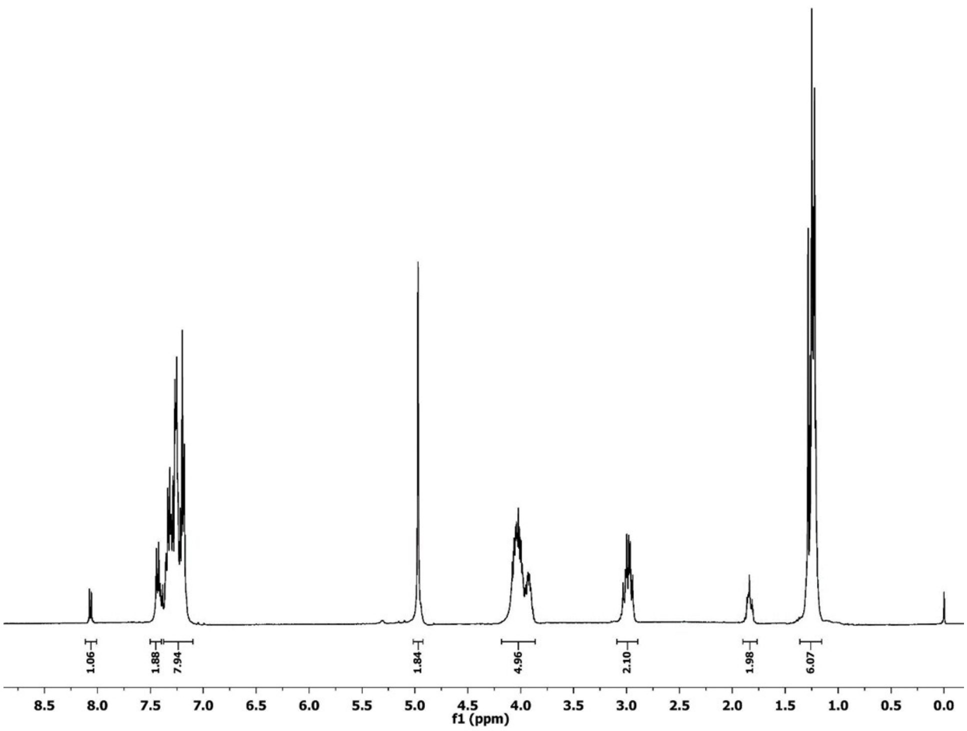
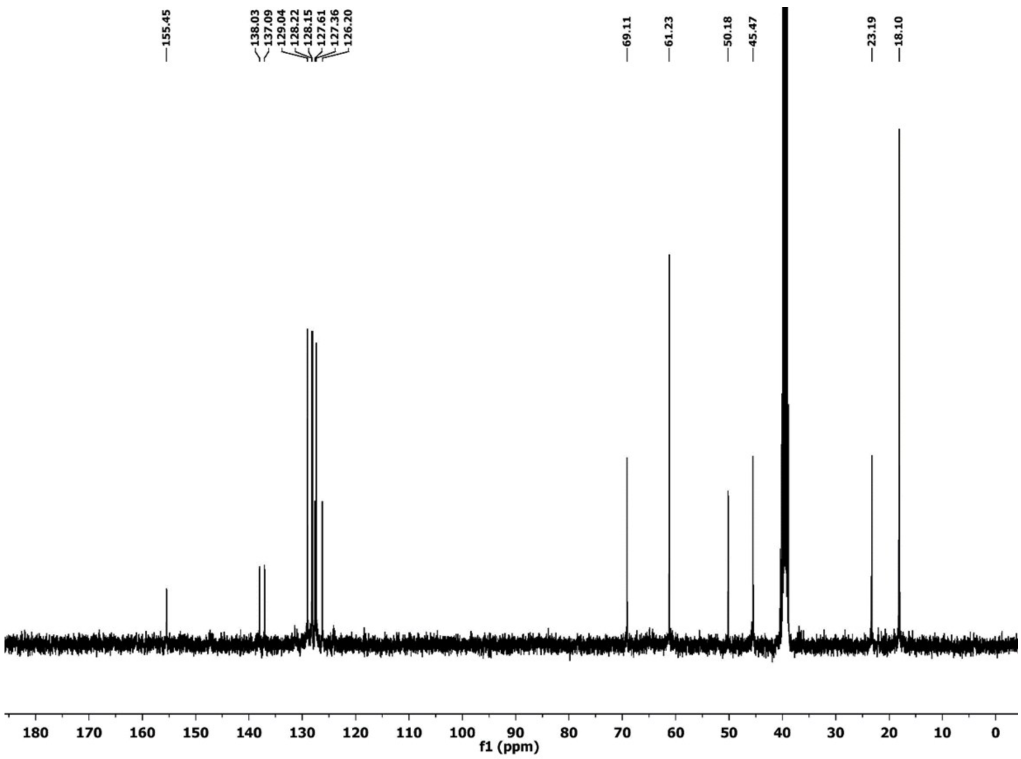


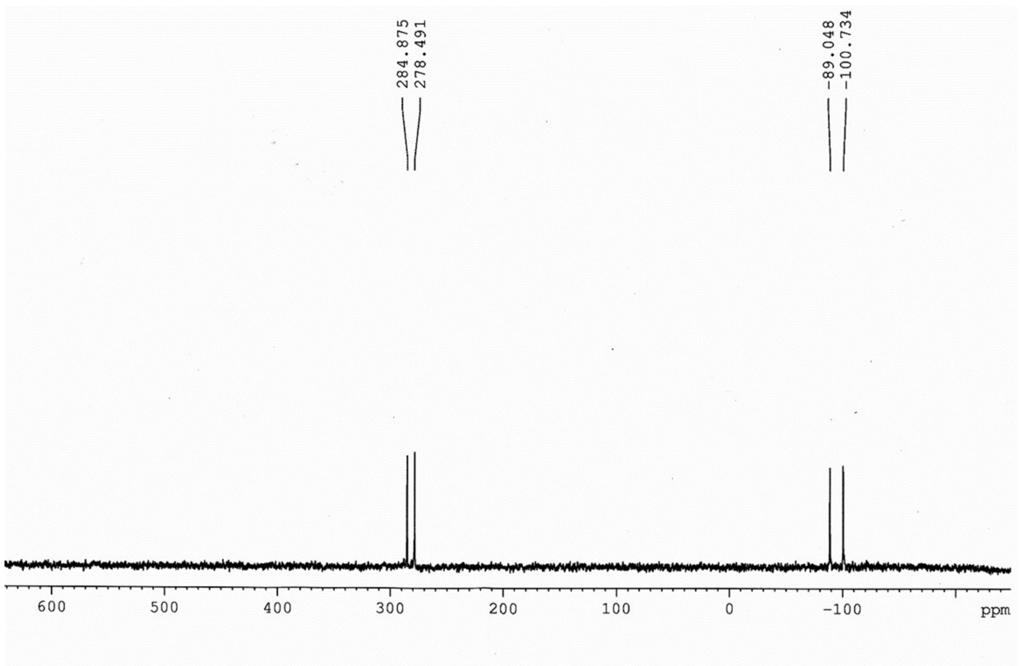
[31]P NMR spectrum of compound 2b



[1]H NMR spectrum of compound 2c



^{13}C NMR spectrum of compound 2c



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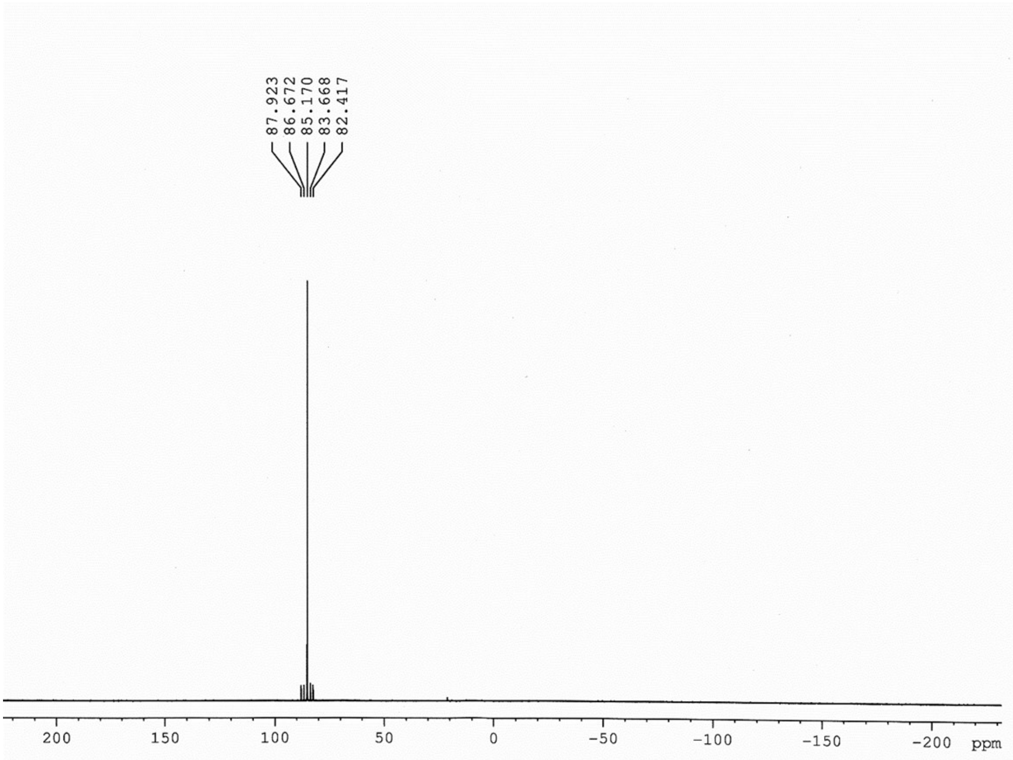

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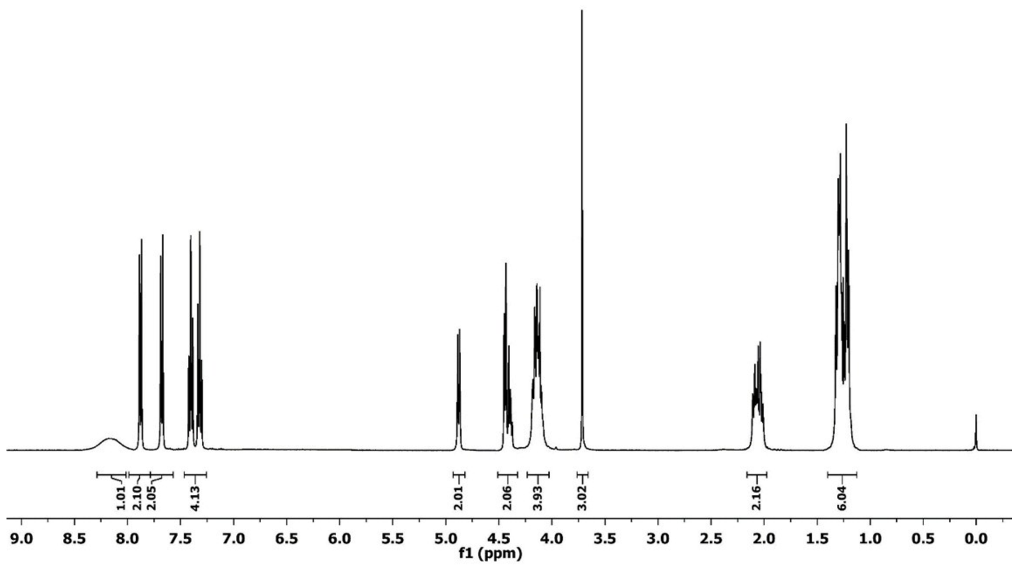
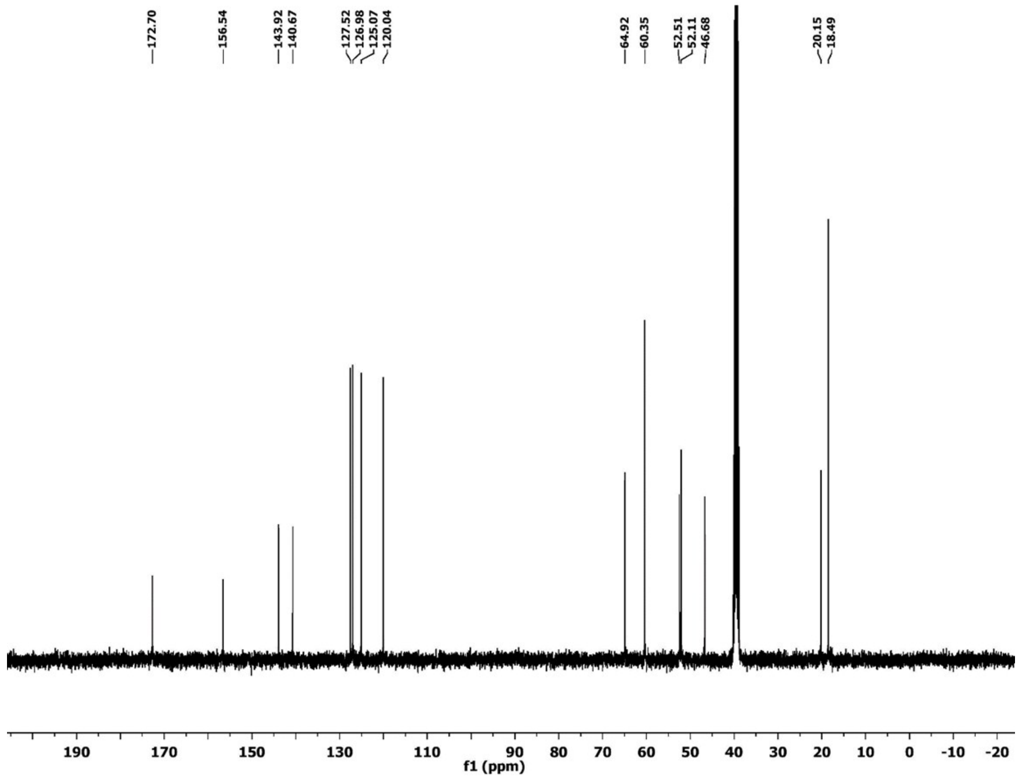


^{1}H NMR spectrum of compound 2d



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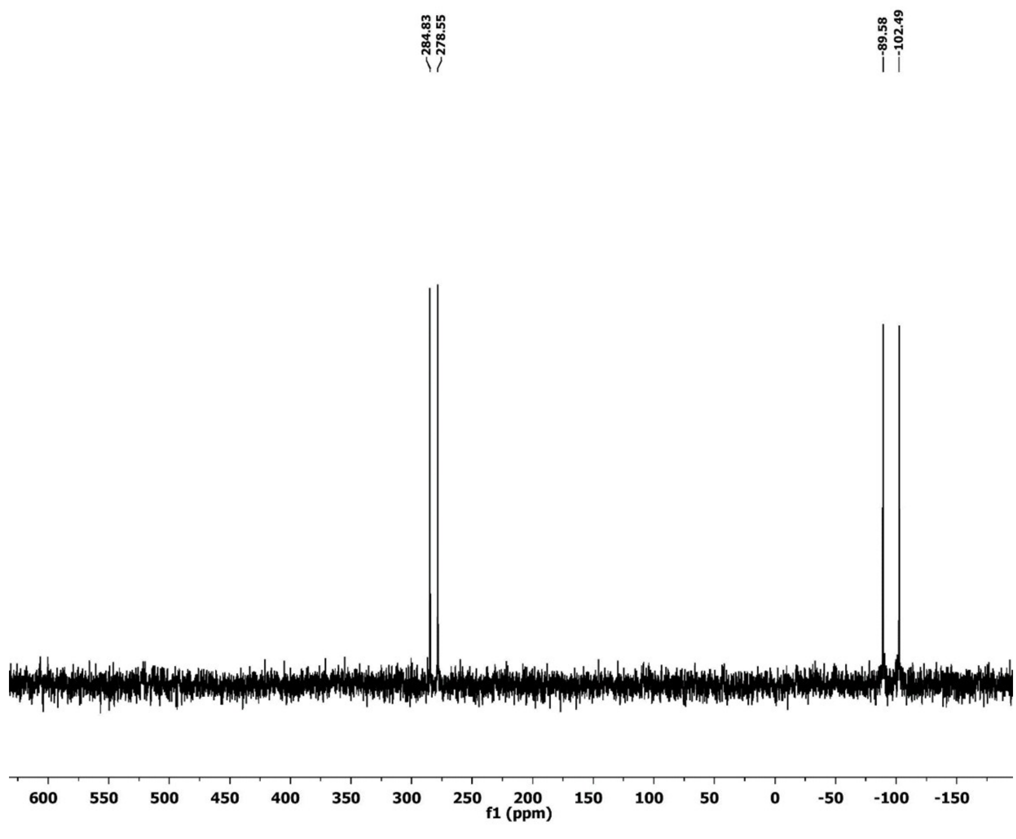

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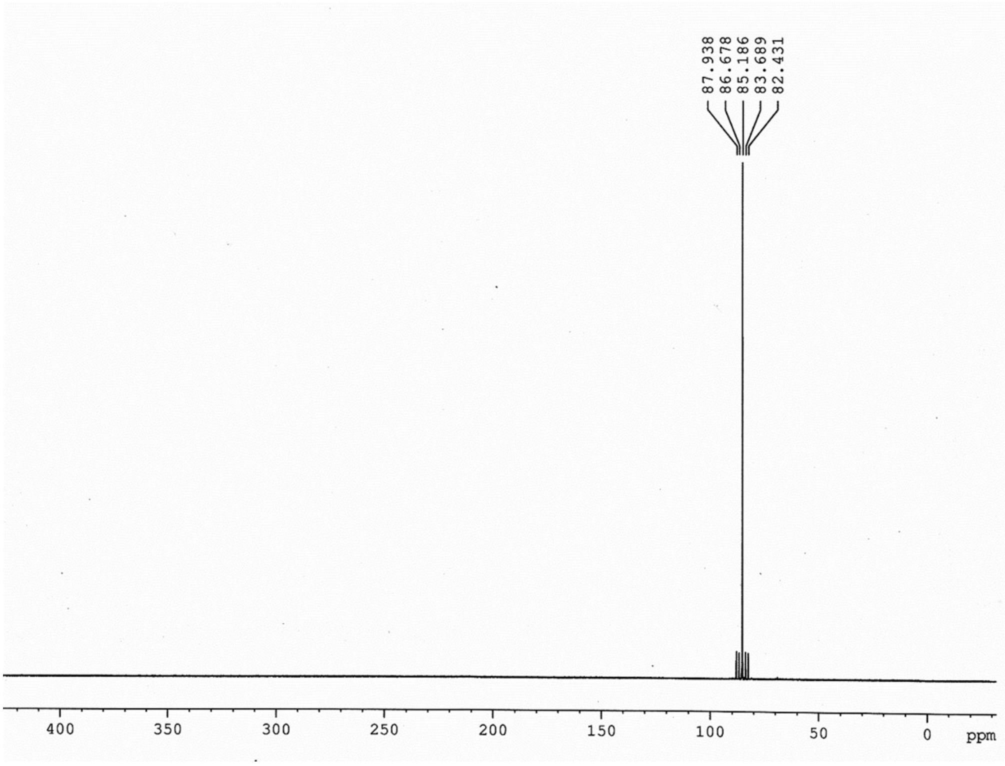

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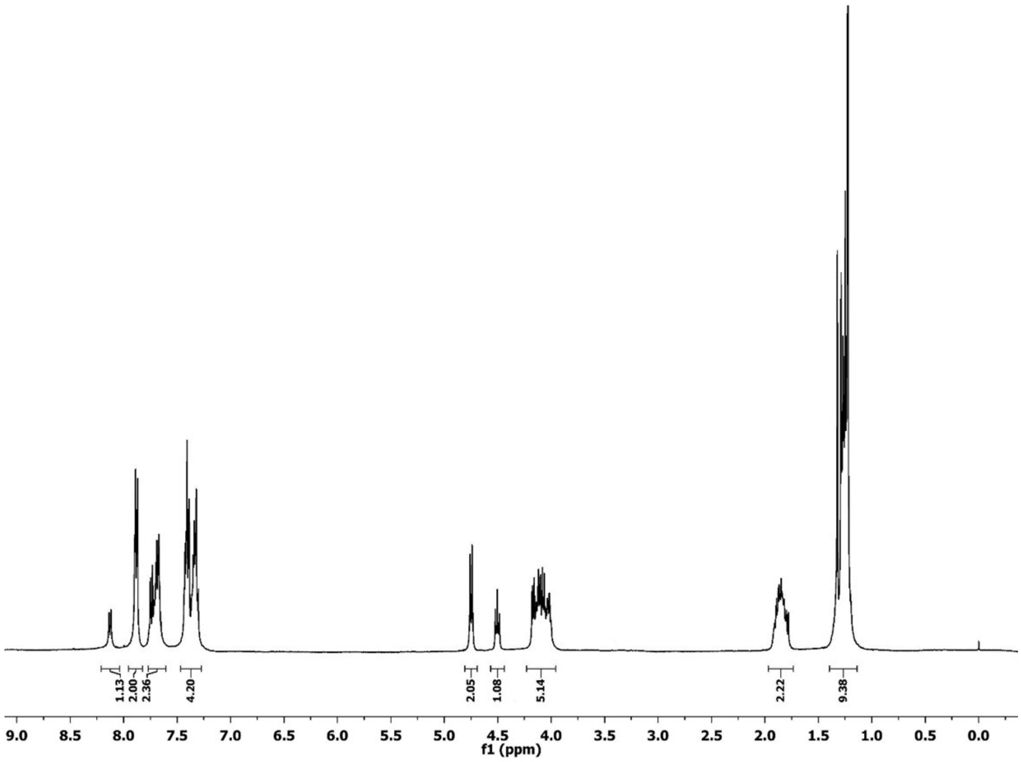

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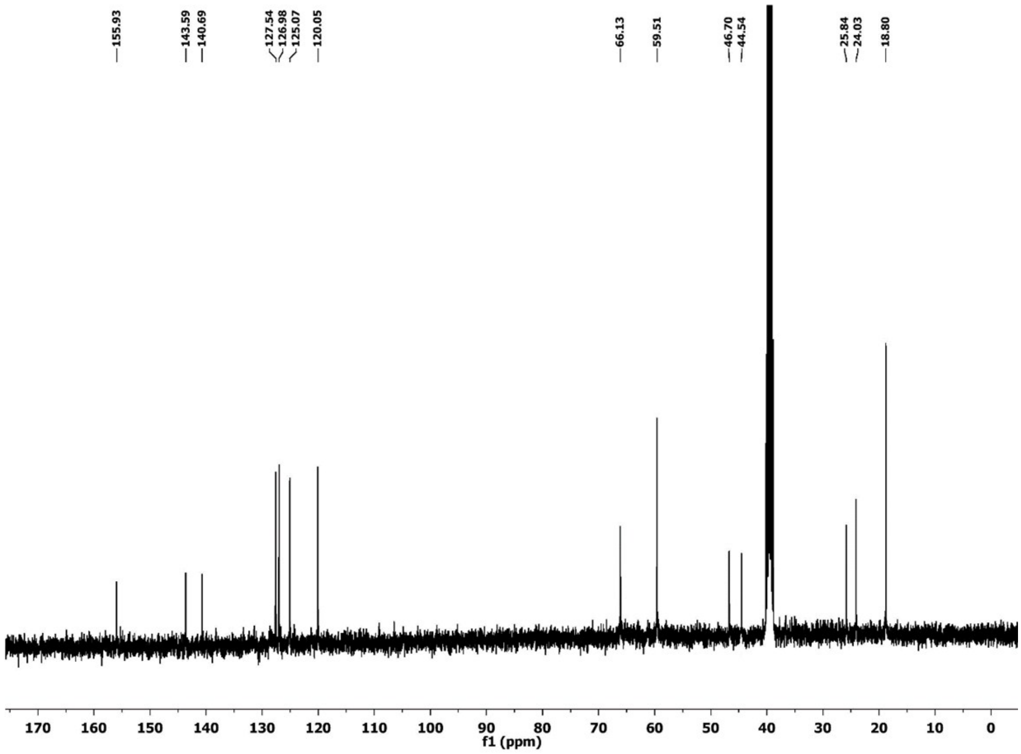

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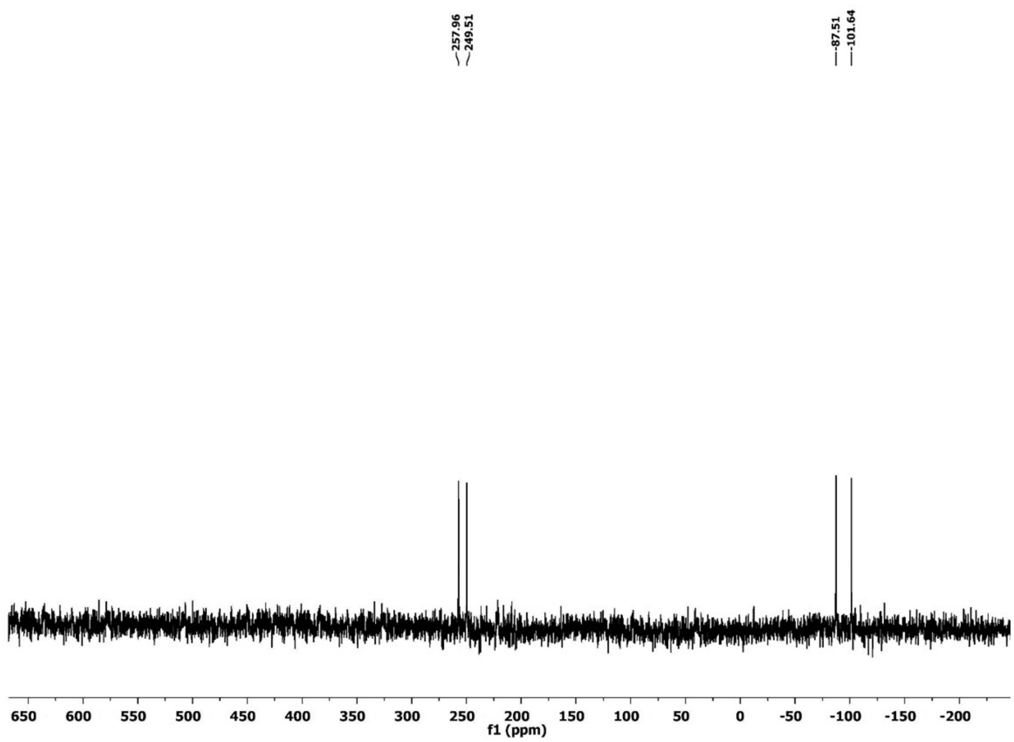

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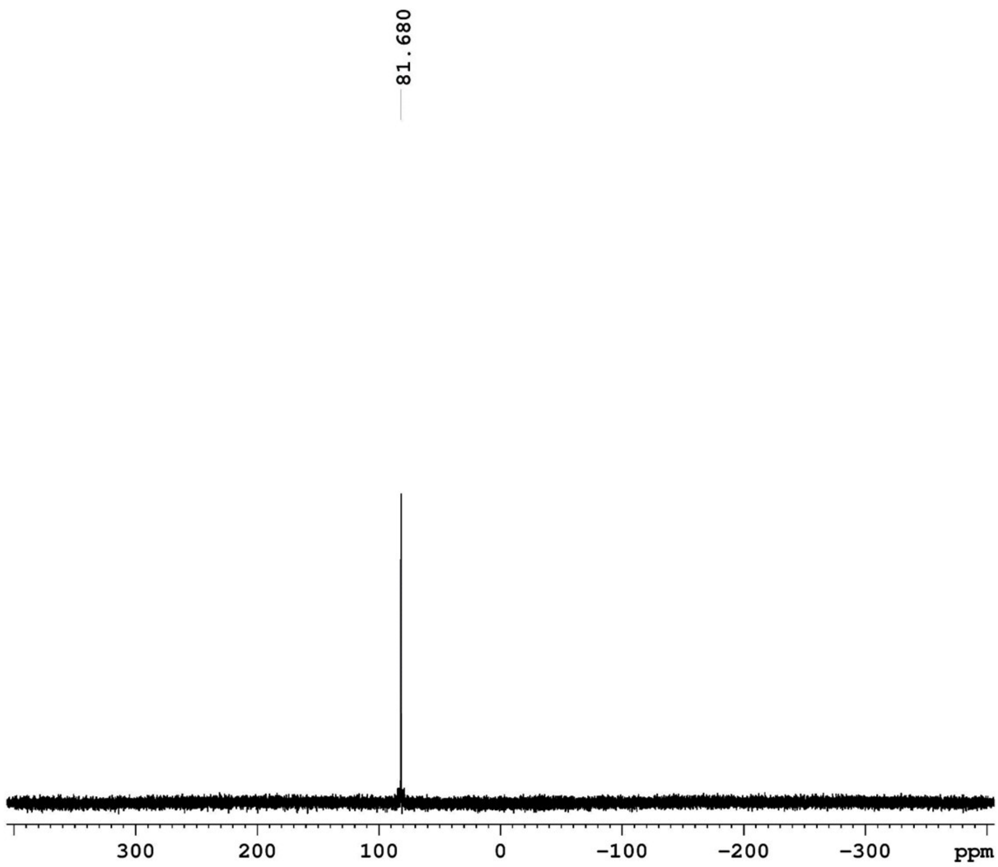
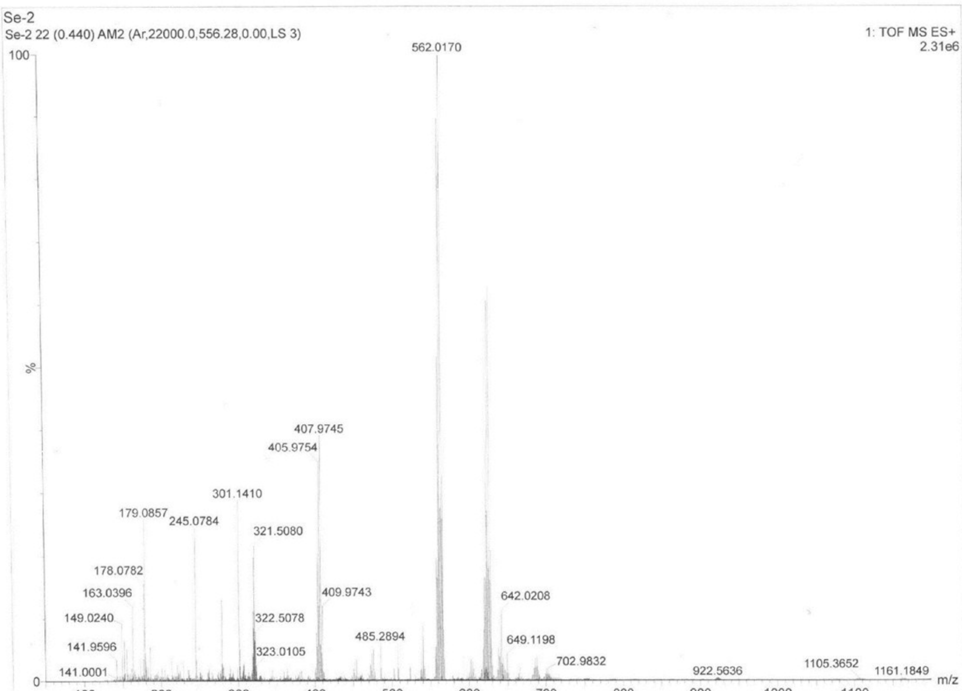
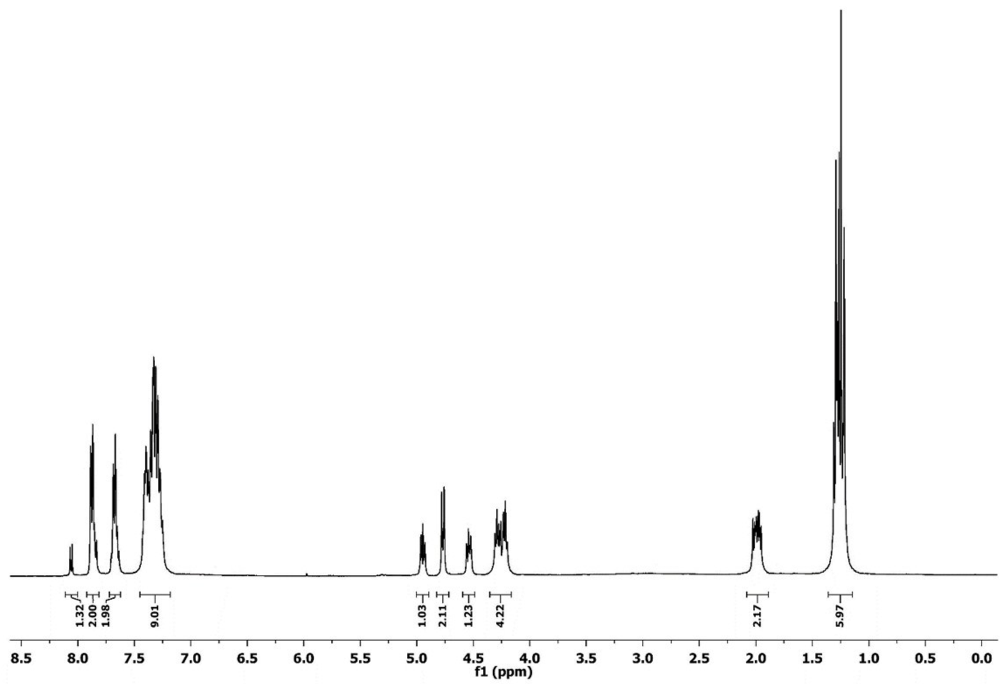


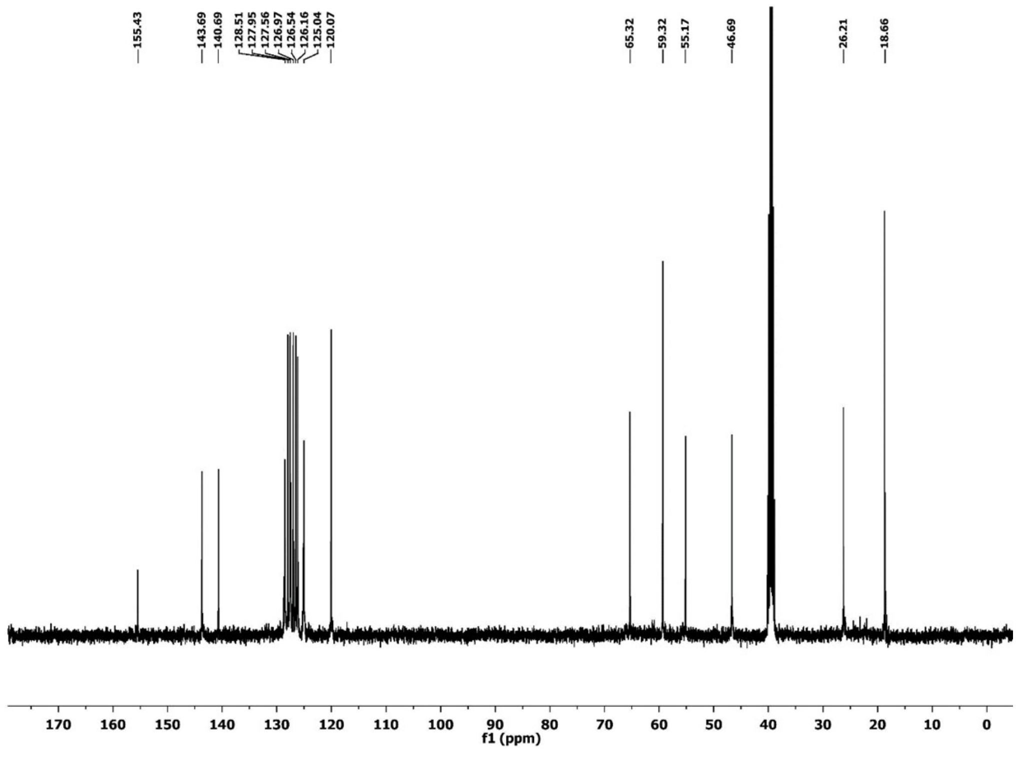
^{31}P NMR spectrum of compound 2e



HRMS of compound 2e



^{1}H NMR spectrum of compound 2f



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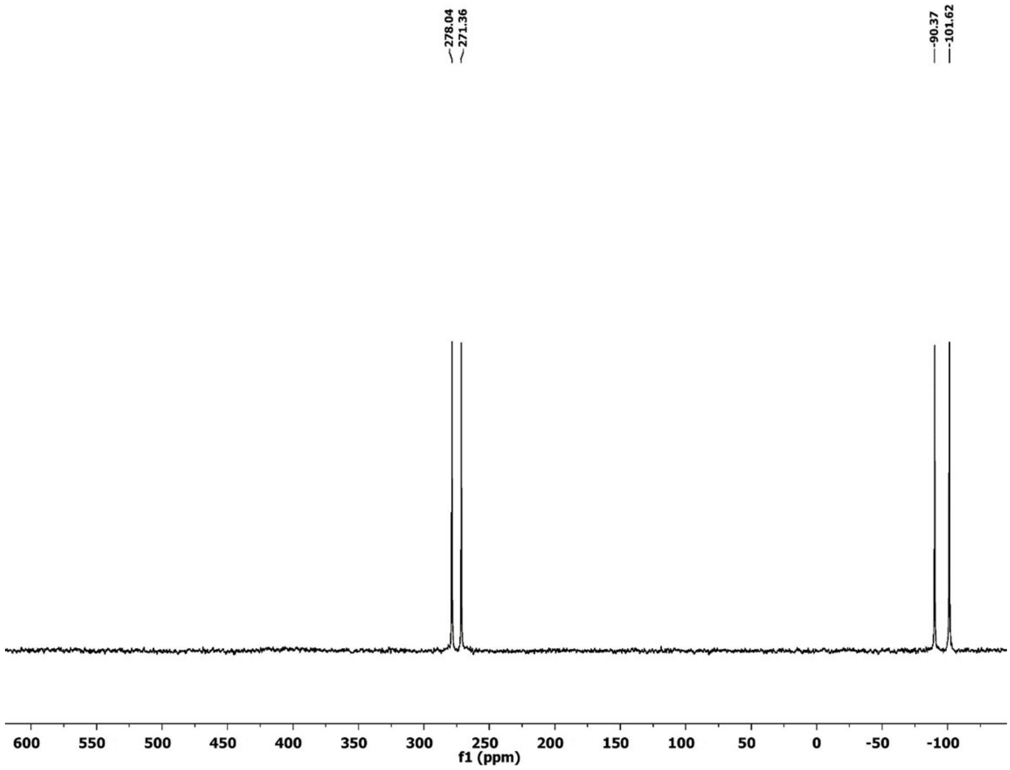
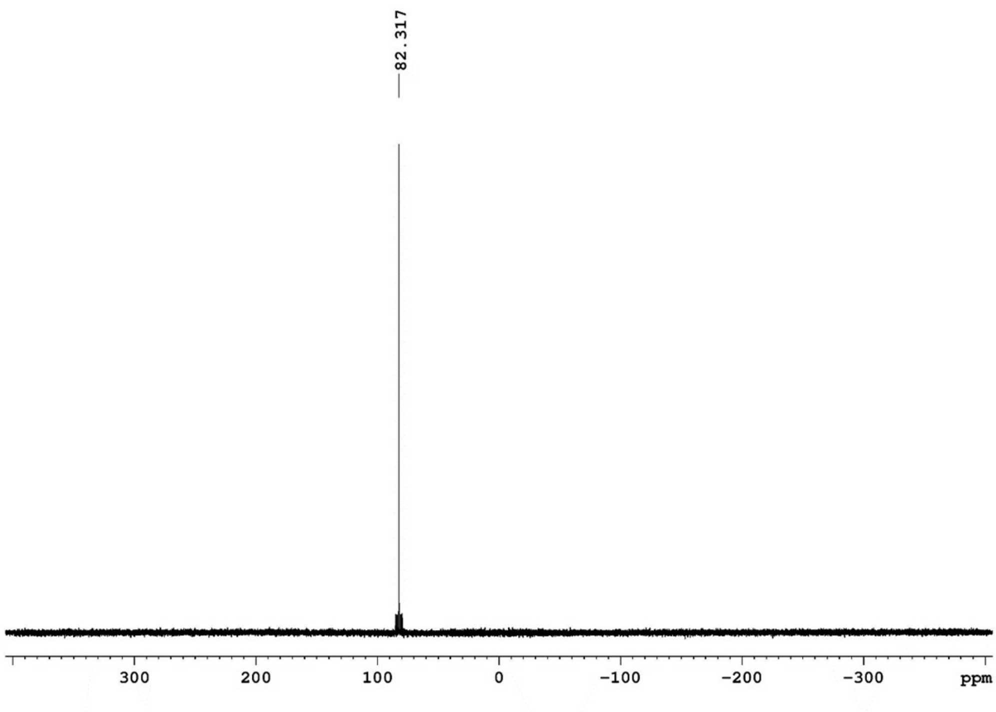
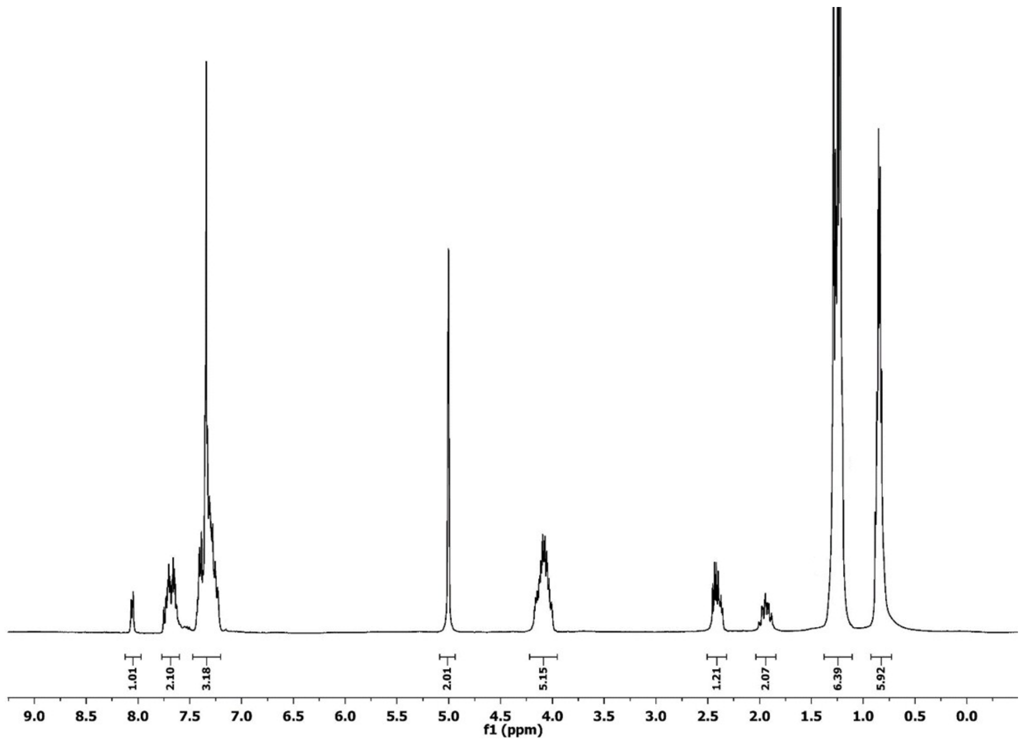


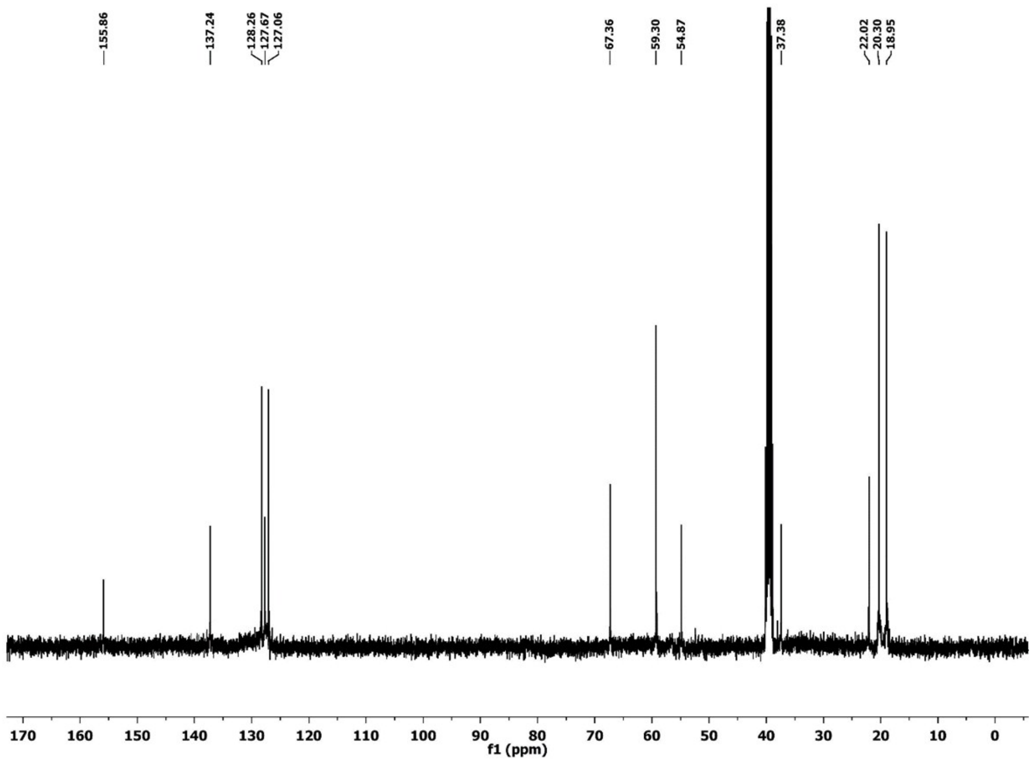
^{77}Se NMR spectrum of compound 2f



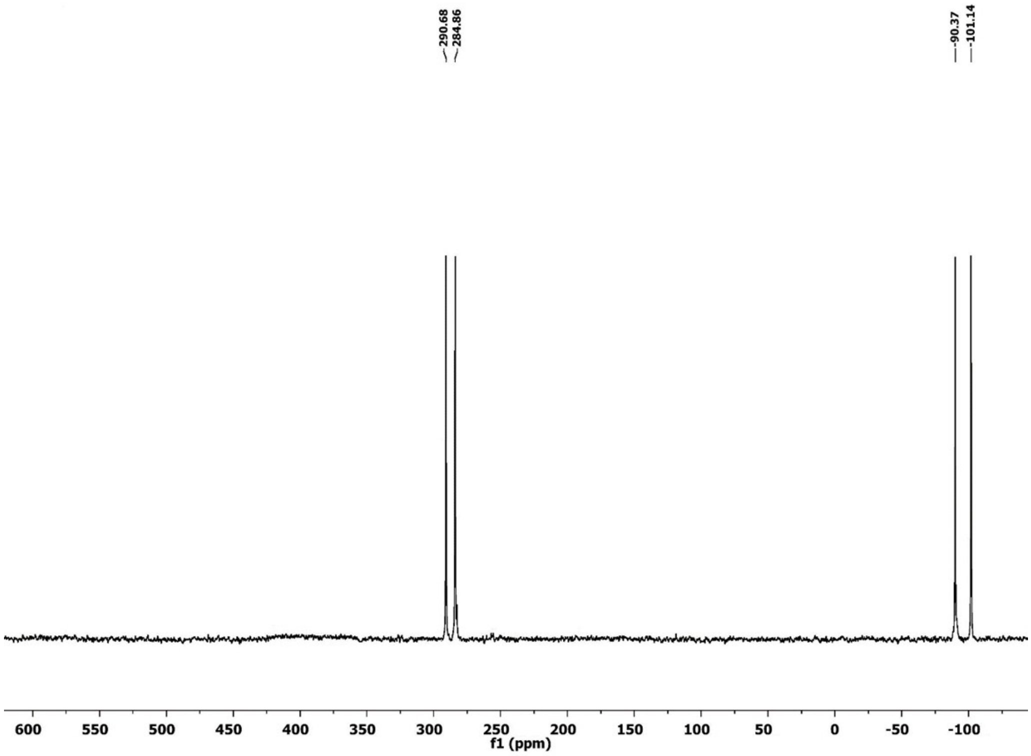
^{31}P NMR spectrum of compound 2f



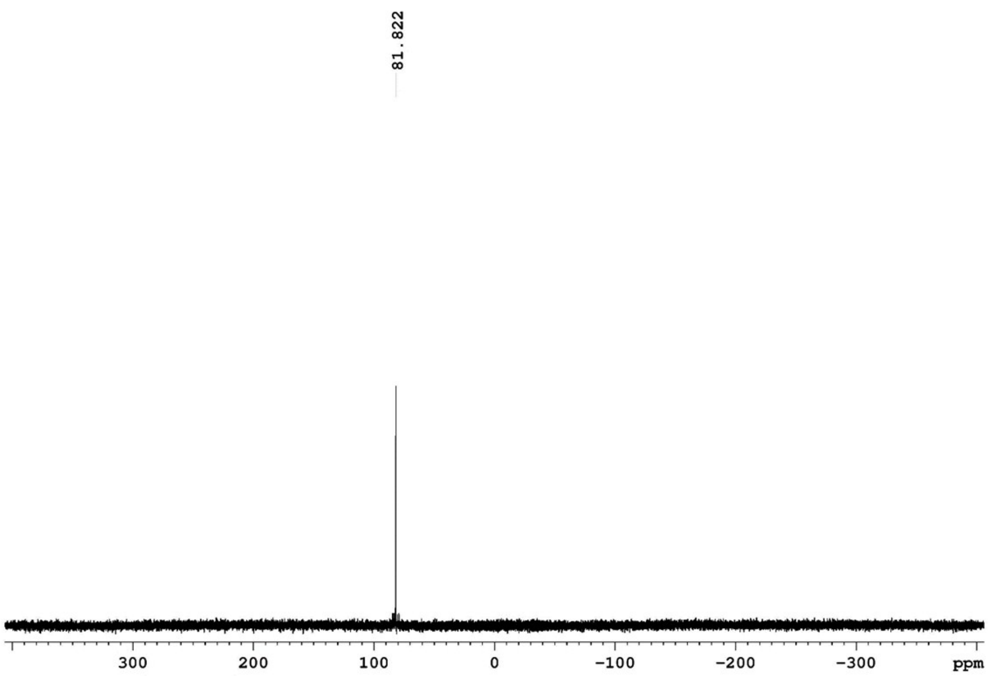
[1]H NMR spectrum of compound 2g



[13]C NMR spectrum of compound 2g

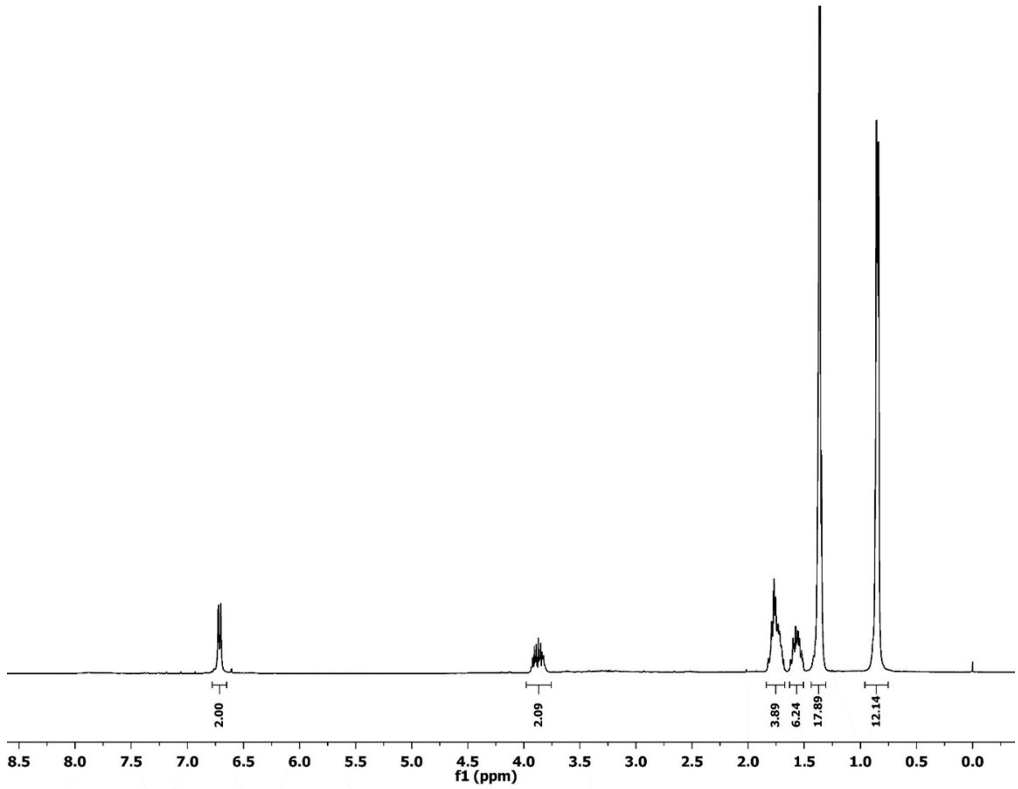


^{77}Se NMR spectrum of compound 2g

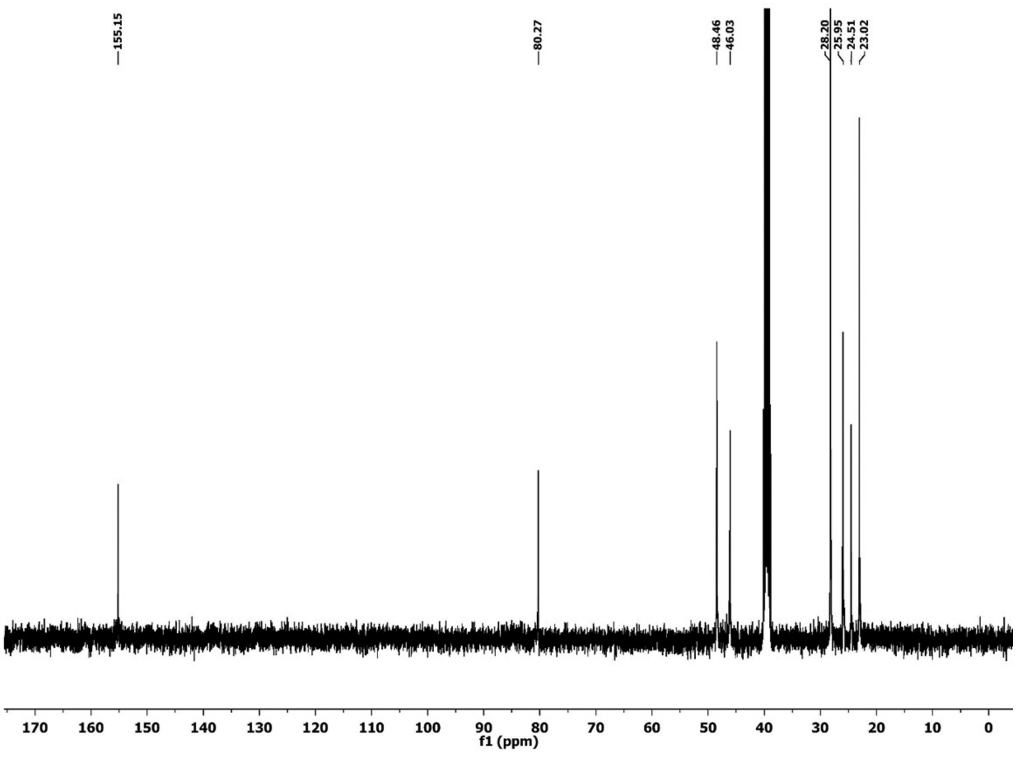


^{31}P NMR spectrum of compound 2g

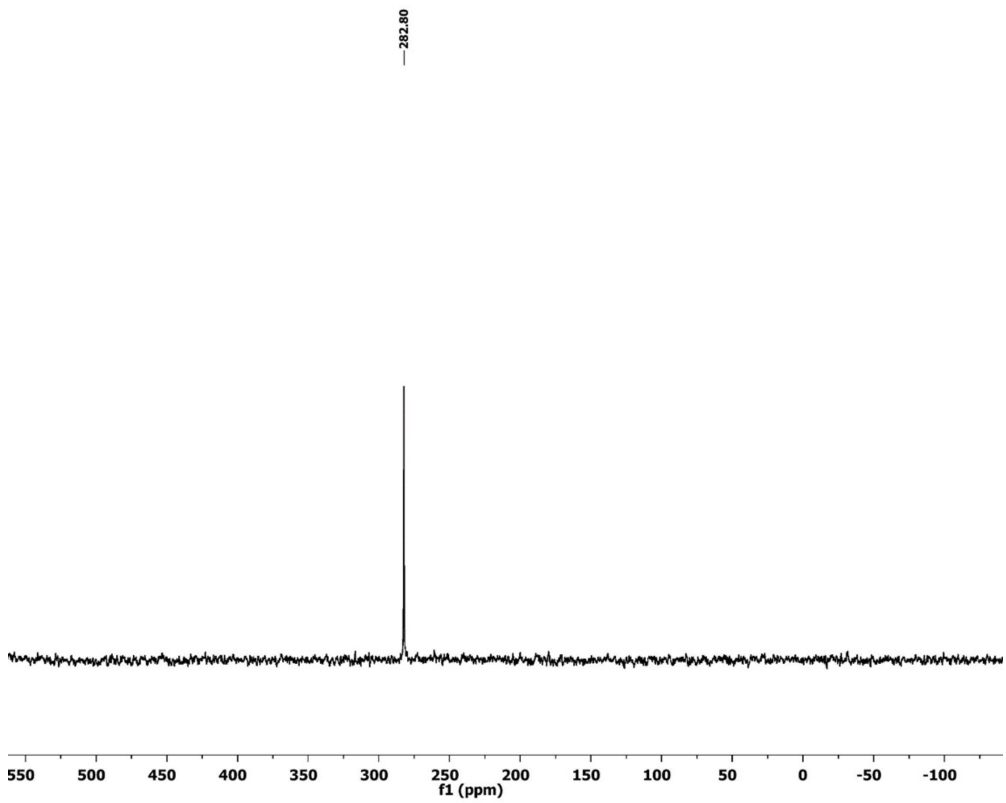
β-amino diselenides



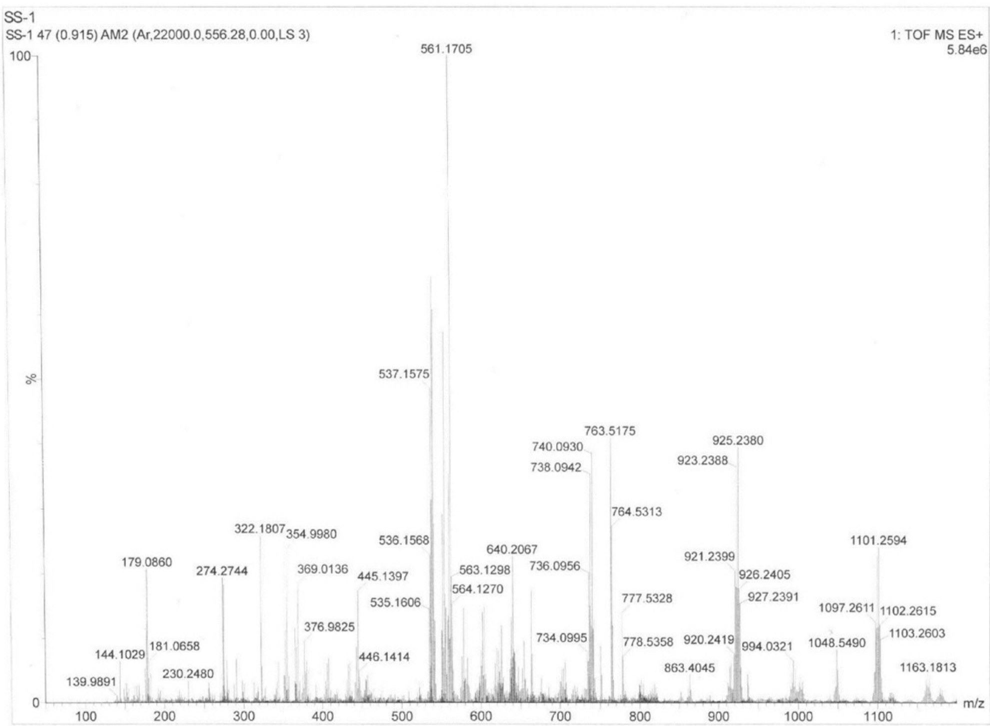
^1H NMR spectrum of compound 3a



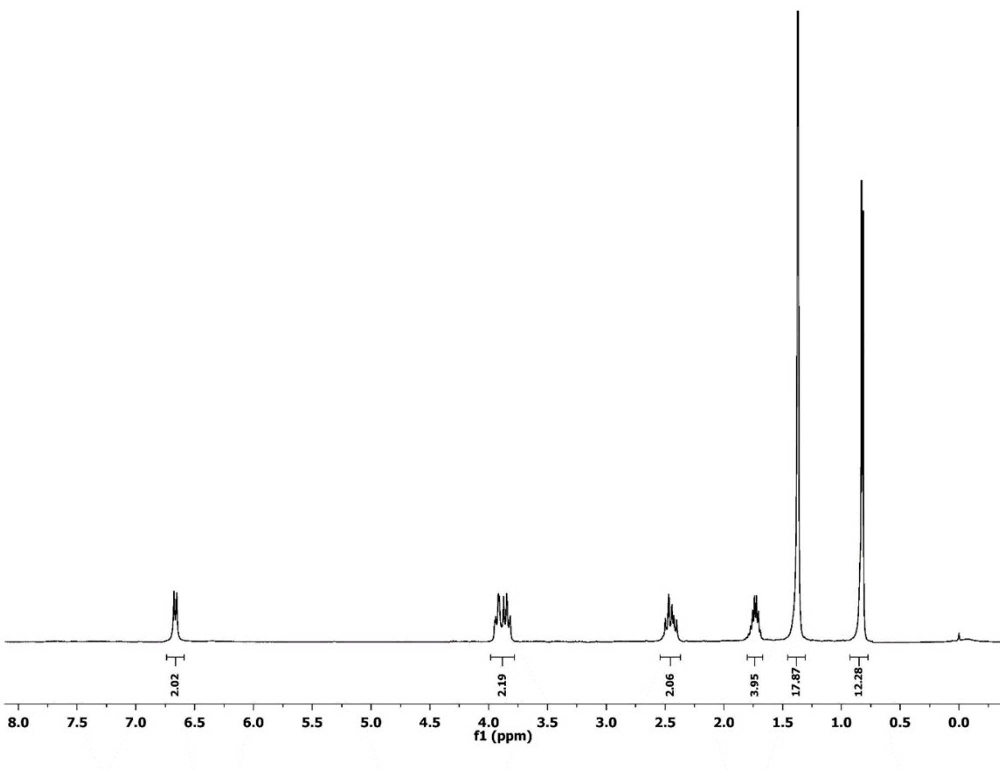
^{13}C NMR spectrum of compound 3a



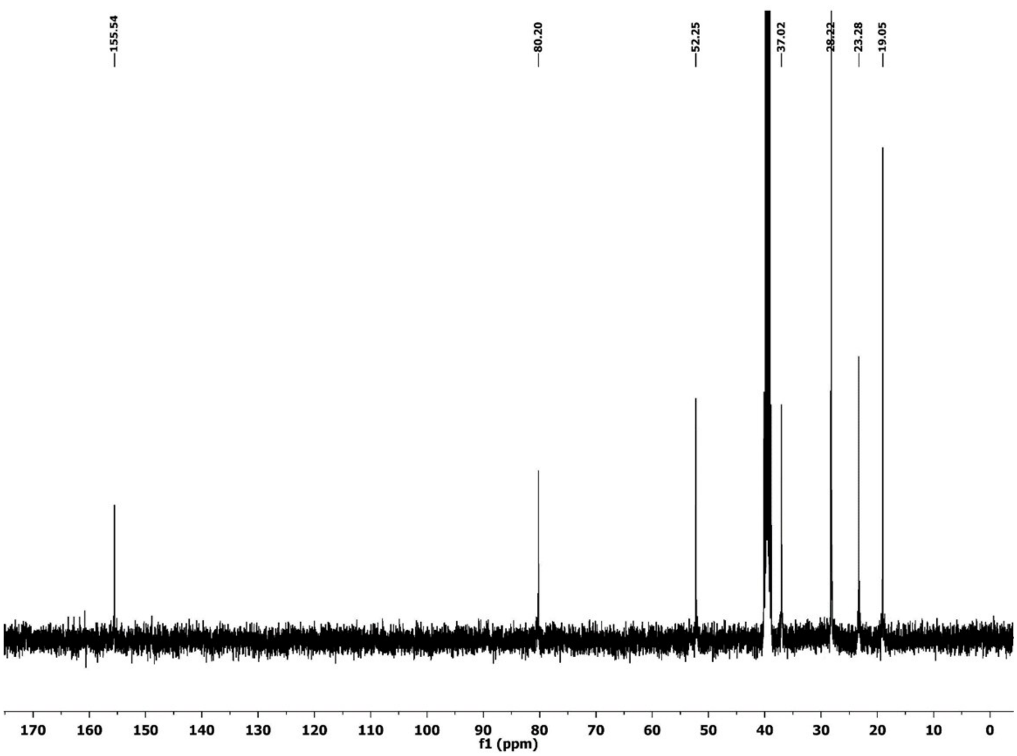
[77]Se NMR spectrum of compound 3a



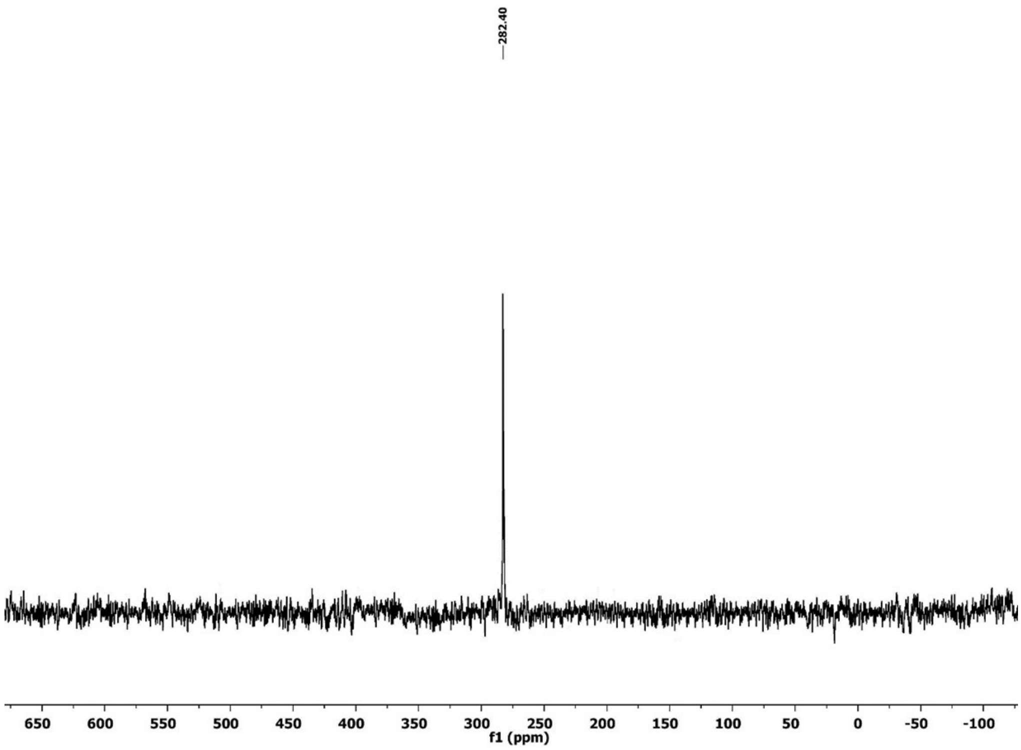
HRMS of compound 3a



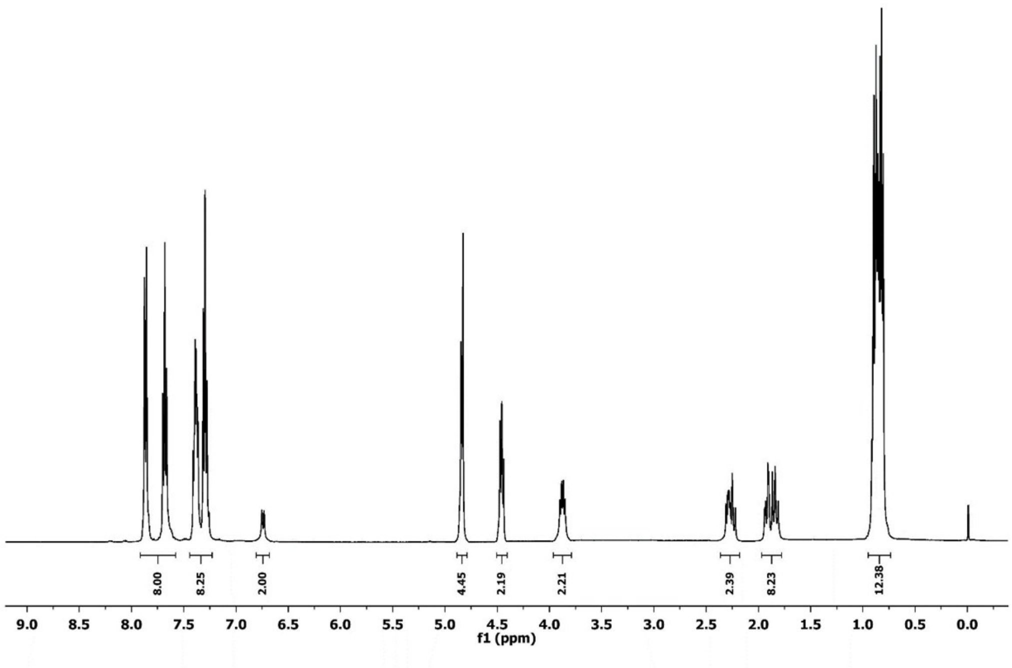
^1H NMR spectrum of compound 3b



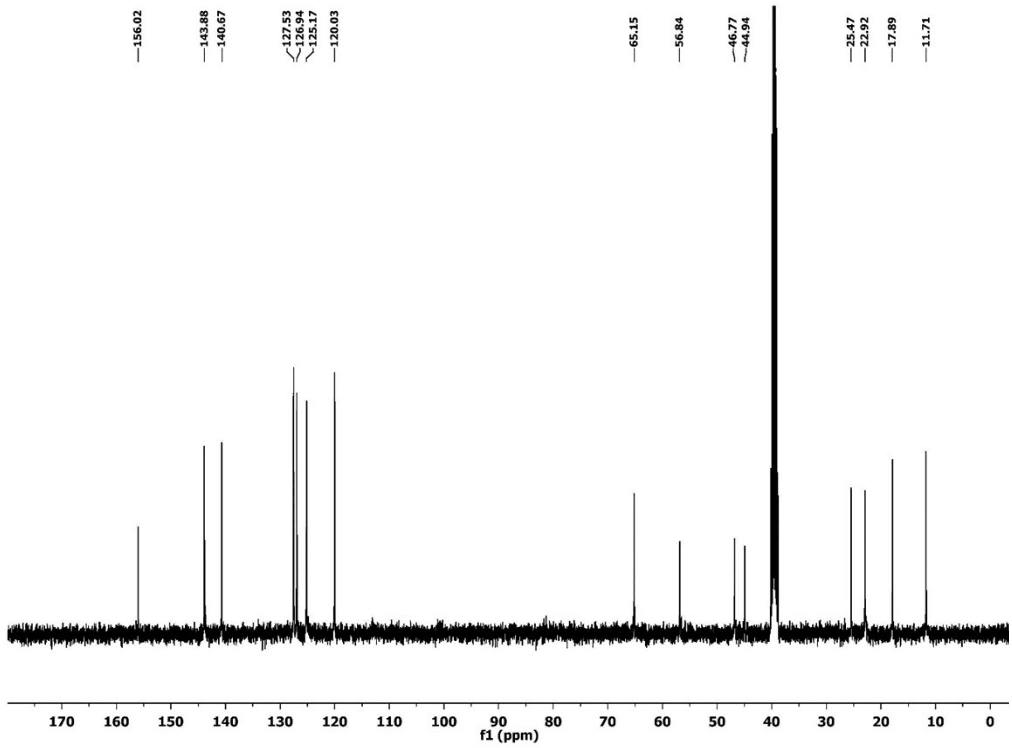
^{13}C NMR spectrum of compound 3b



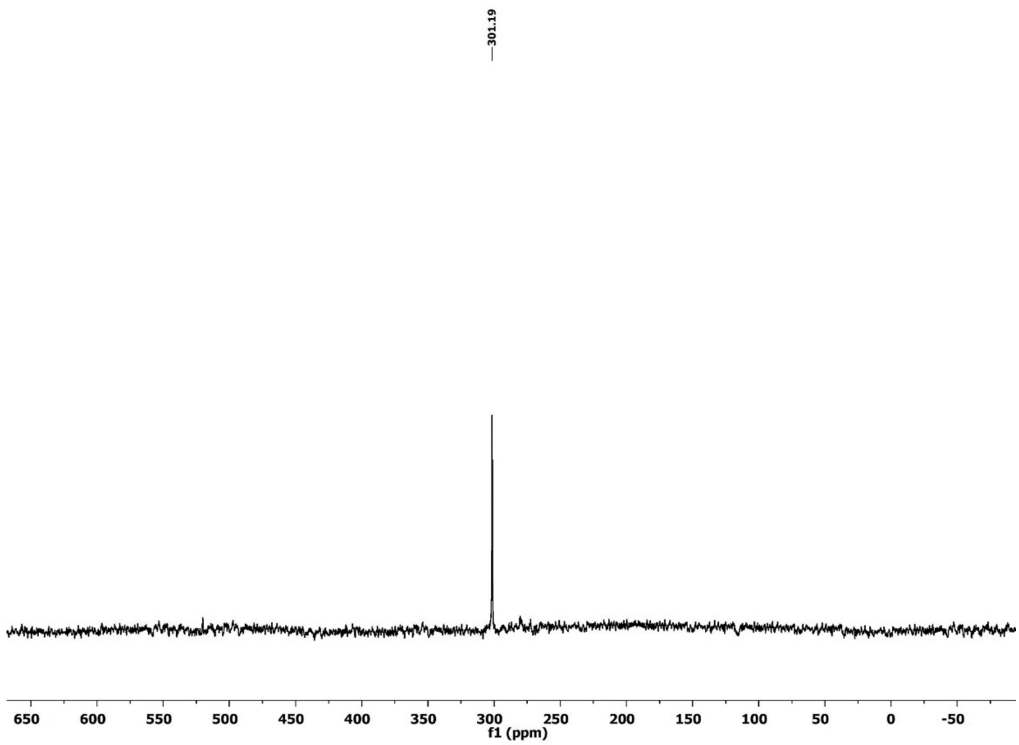
^{77}Se NMR spectrum of compound 3b



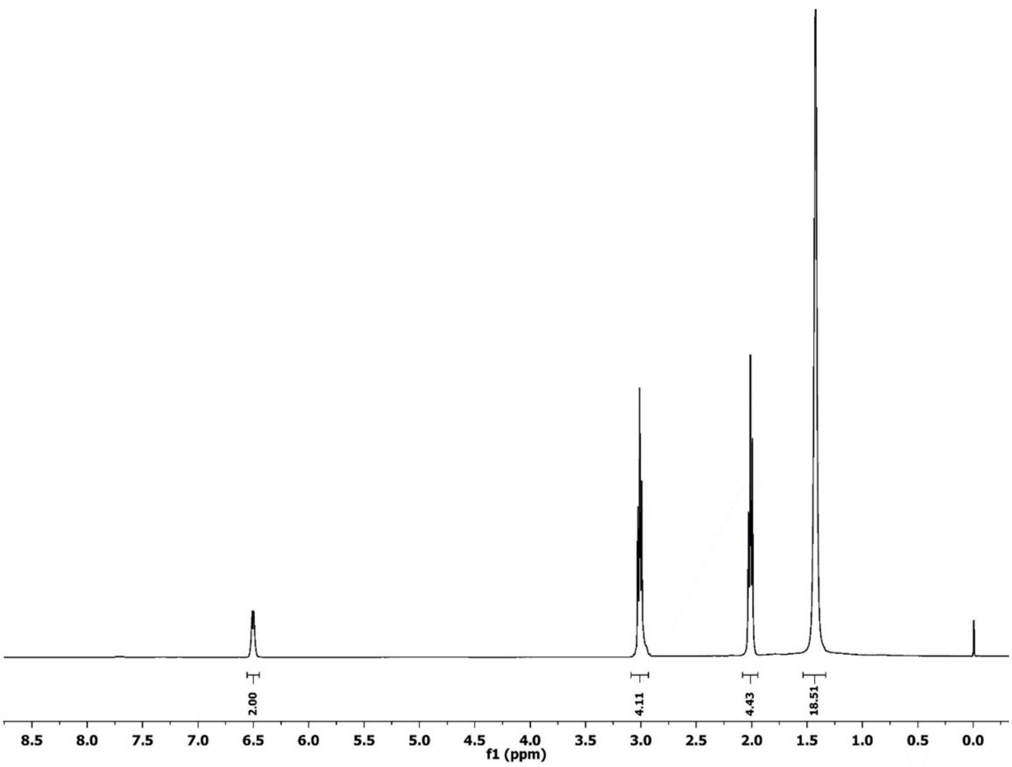
^{1}H NMR spectrum of compound 3c



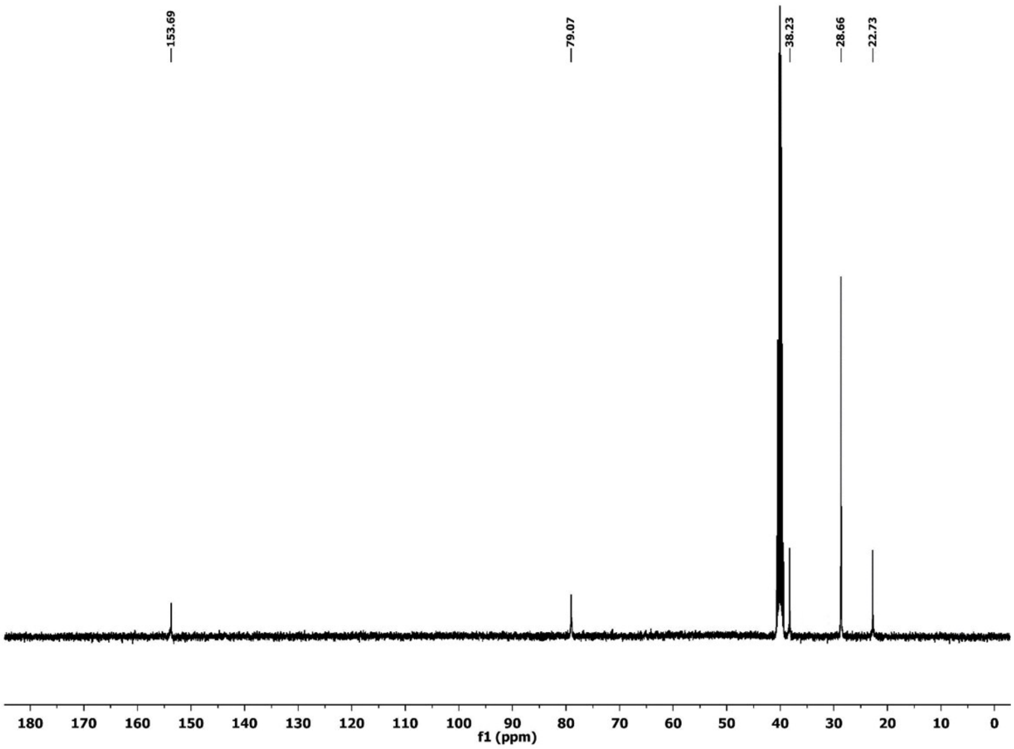
^{13}C NMR spectrum of compound 3c



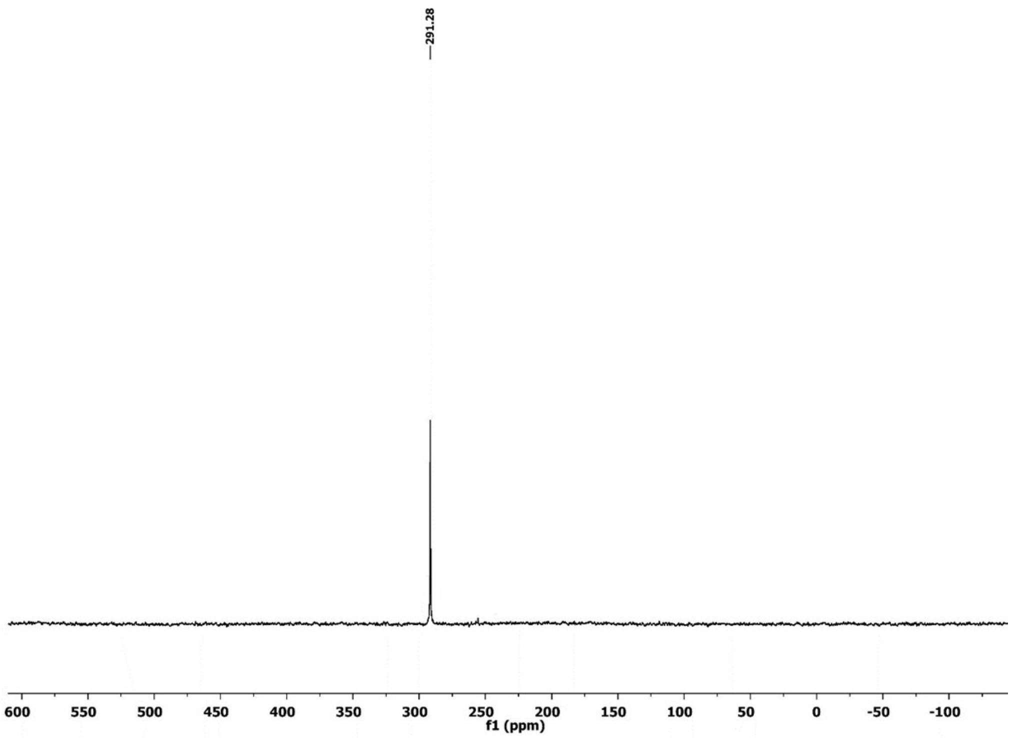
^{77}Se NMR spectrum of compound 3c



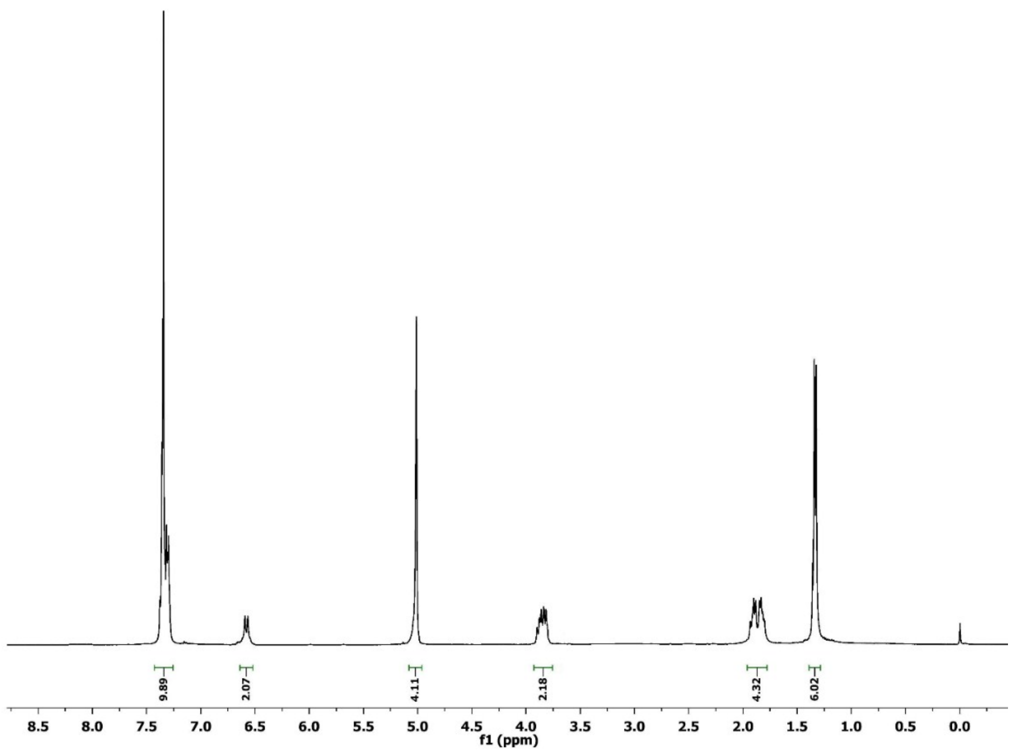
^{1}H NMR spectrum of compound 3d



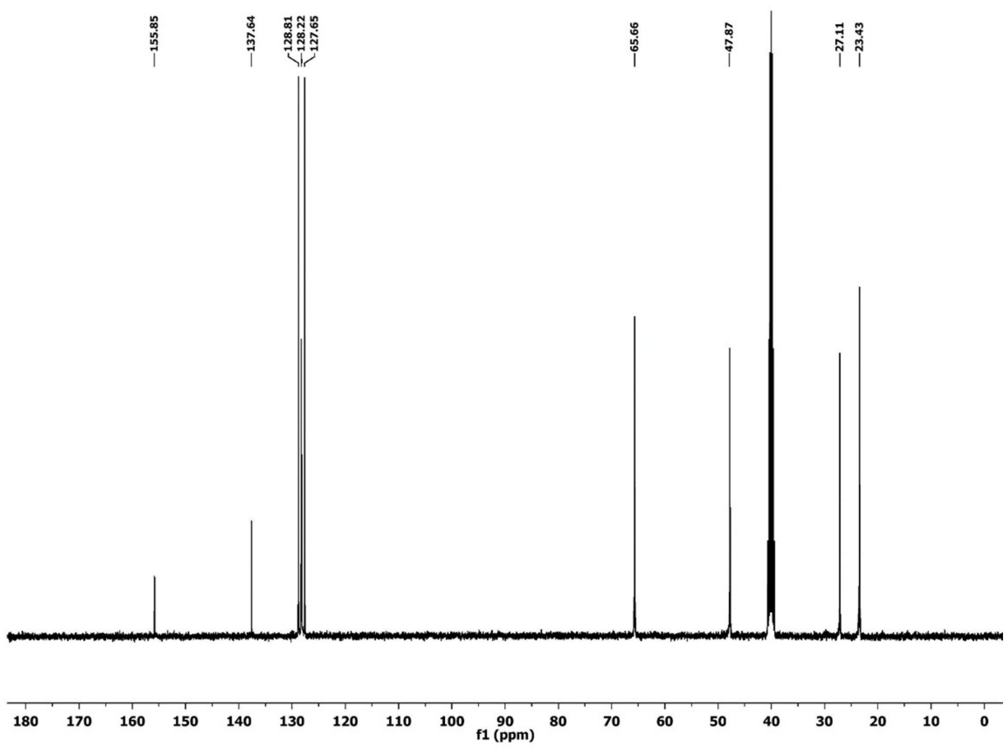
^{13}C NMR spectrum of compound 3d



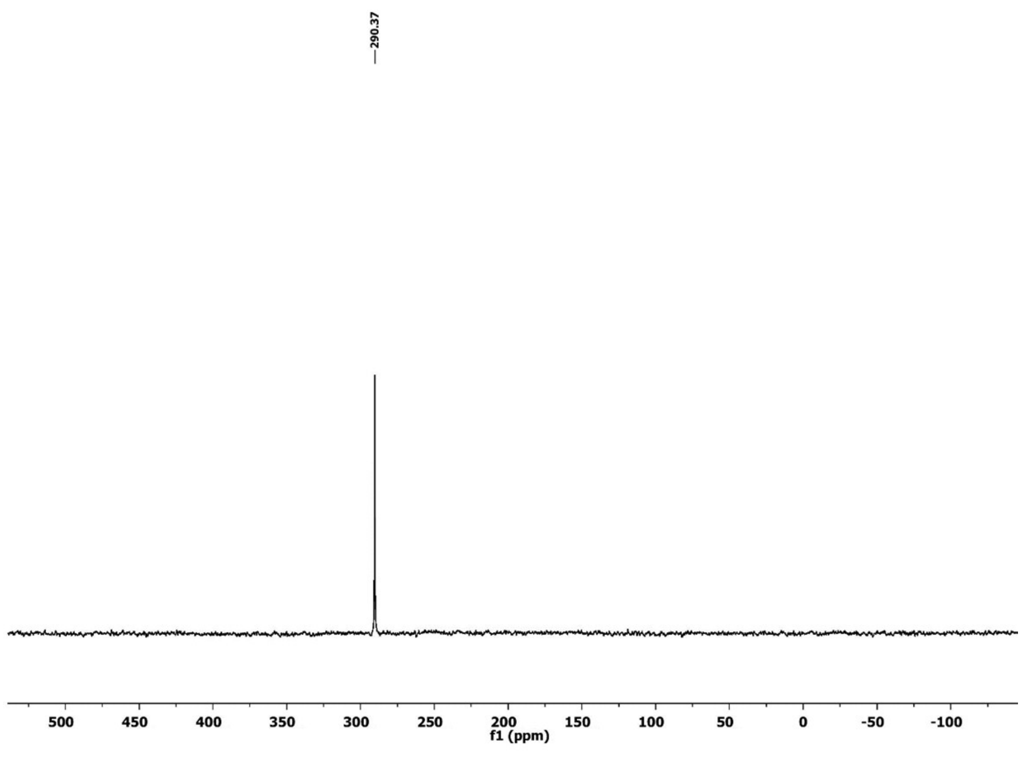
^{77}Se NMR spectrum of compound 3d



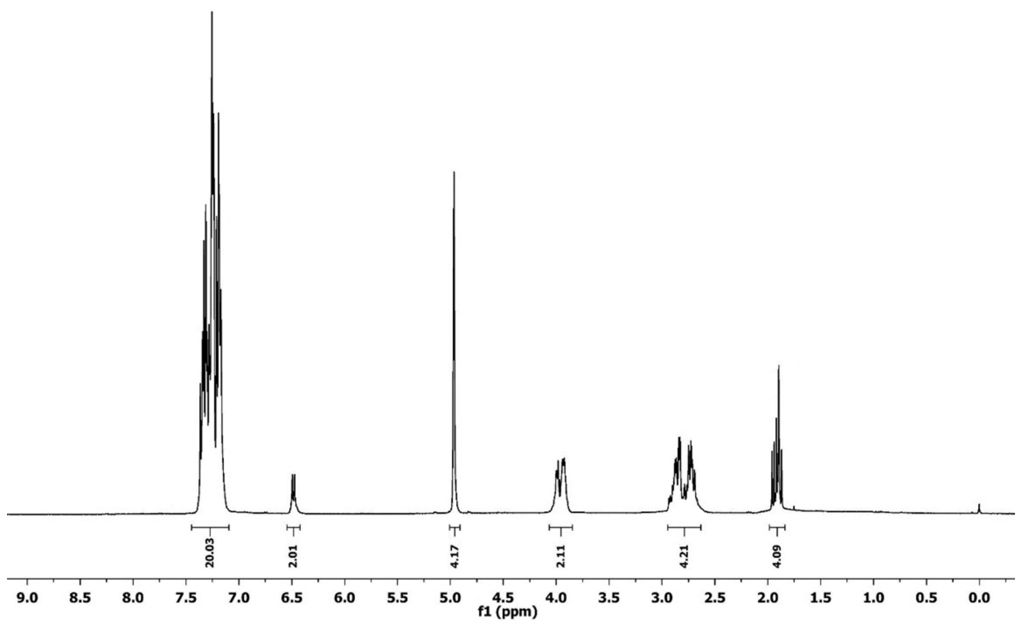
^{1}H NMR spectrum of compound 3e



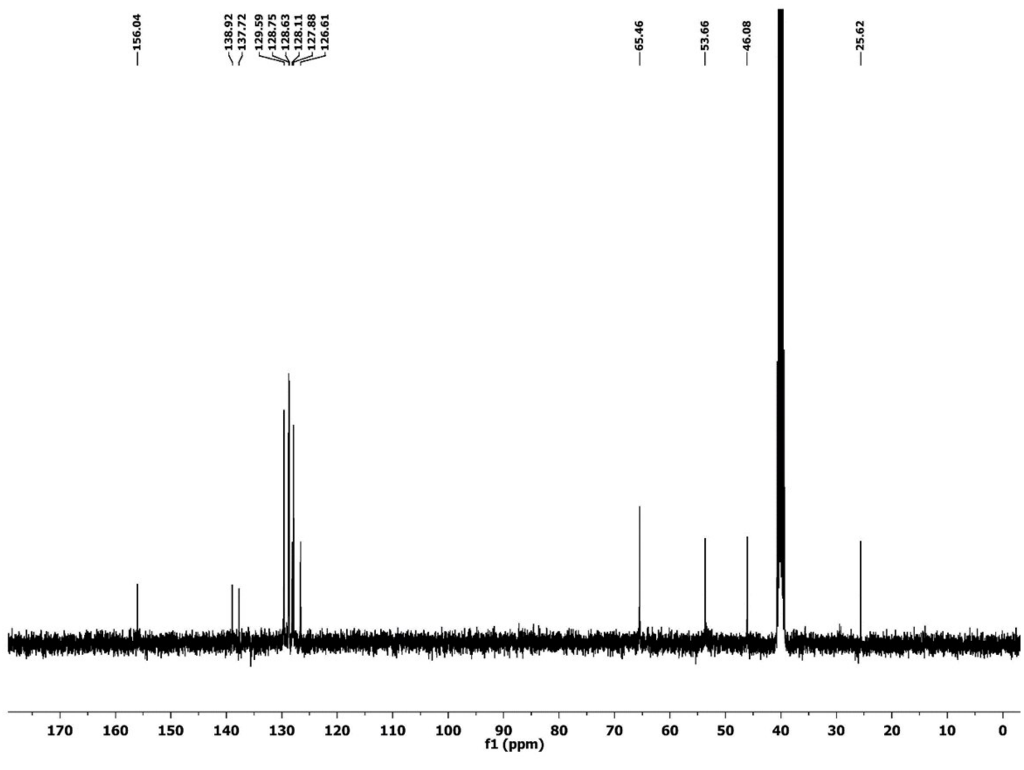
^{13}C NMR spectrum of compound 3e



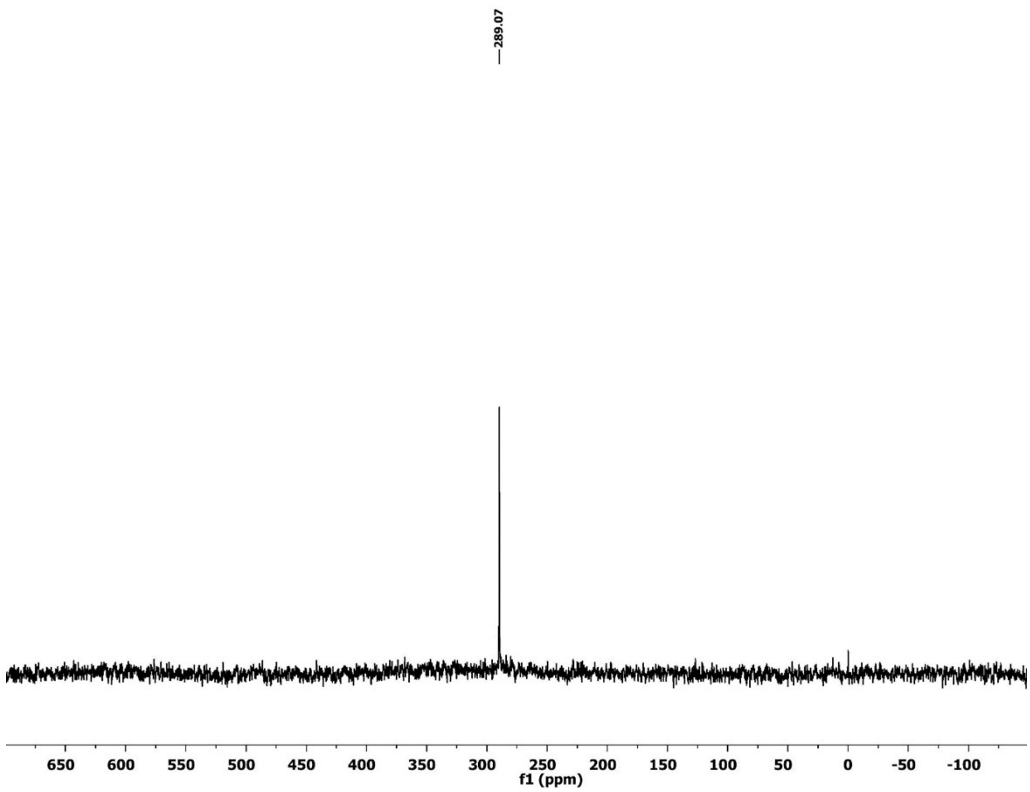
^{77}Se NMR spectrum of compound 3e



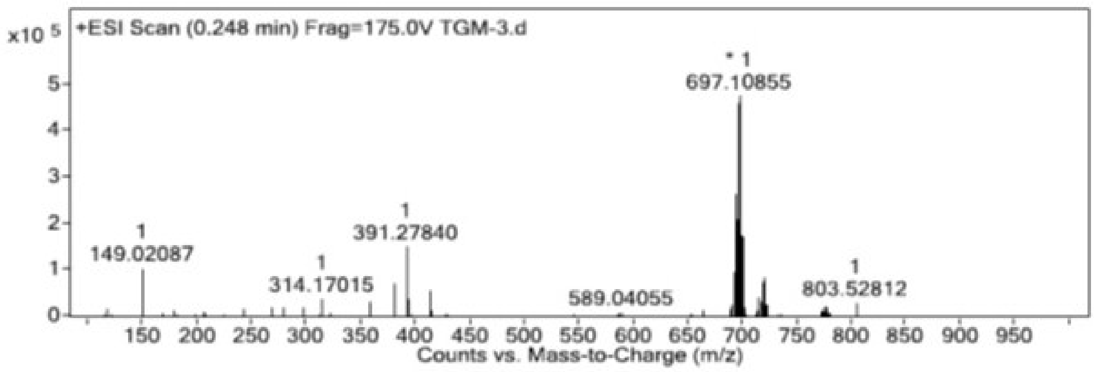
^{1}H NMR spectrum of compound 3f



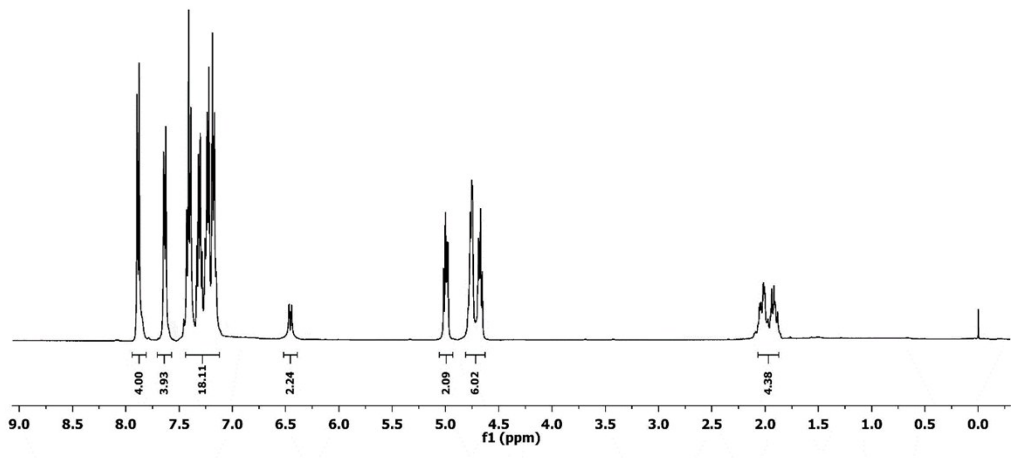
^{13}C NMR spectrum of compound 3f



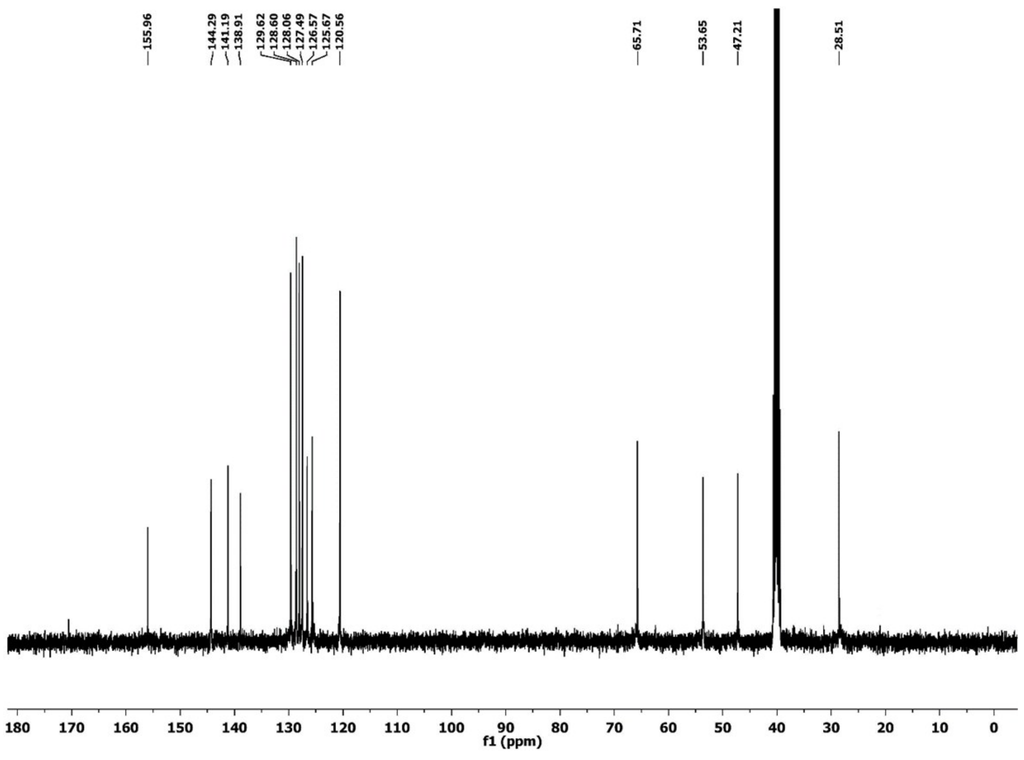
^{77}Se NMR spectrum of compound 3f



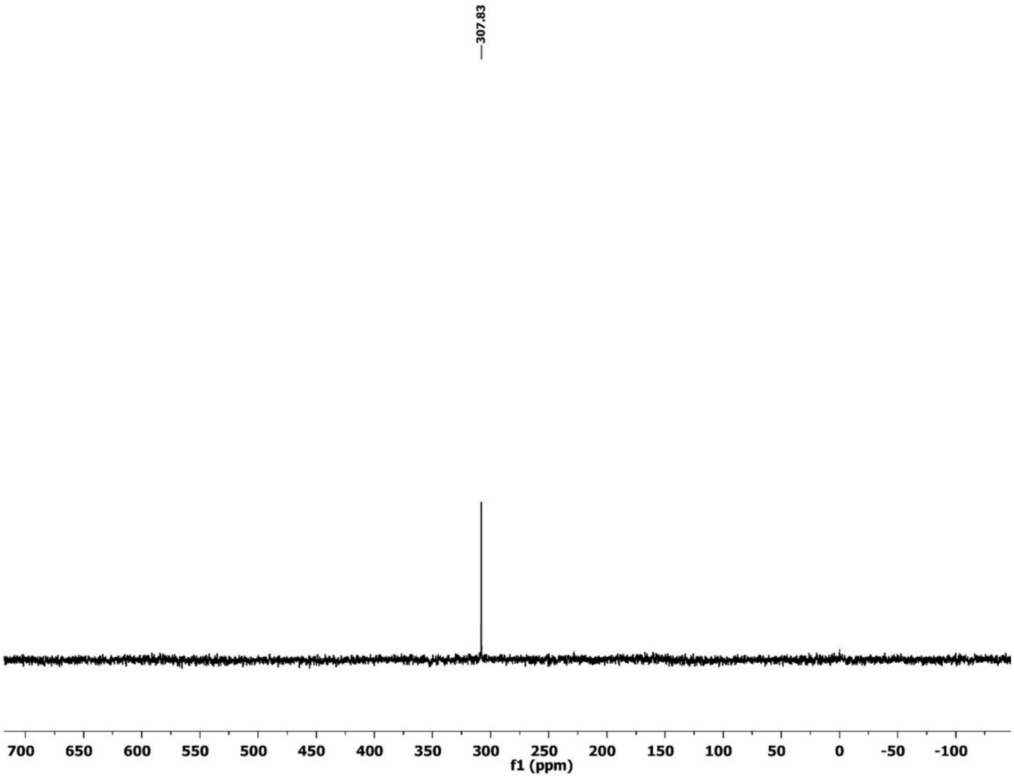
HRMS of compound 3f



^{1}H NMR spectrum of compound 3g



^{13}C NMR spectrum of compound 3g



^{77}Se NMR spectrum of compound 3g