Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information for

Photoluminescent Selenospirocyclic and Selenotetracyclic Derivatives by Domino Reactions of Amines and Imine

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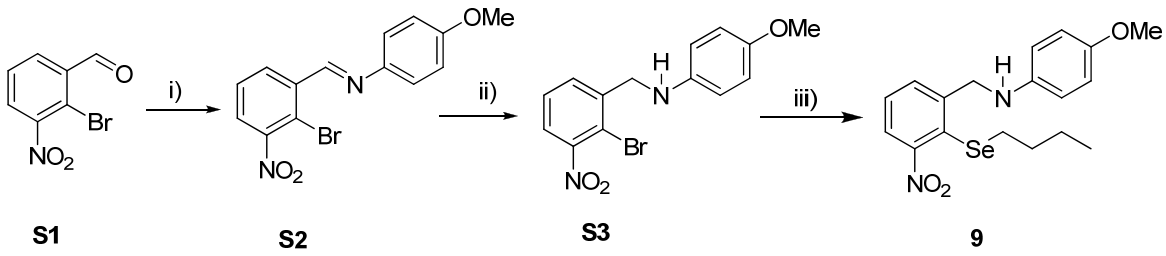
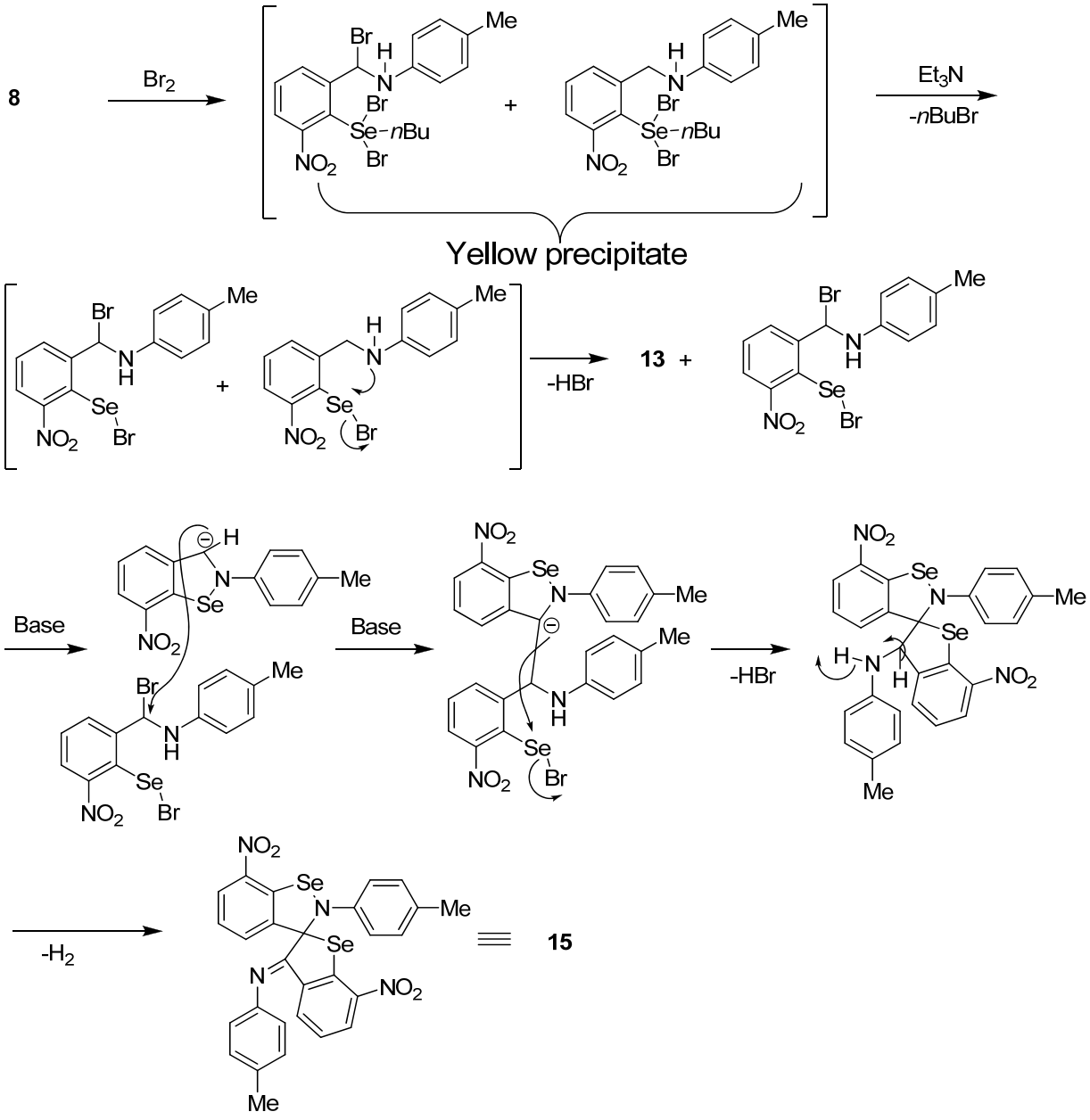
General experimental procedure

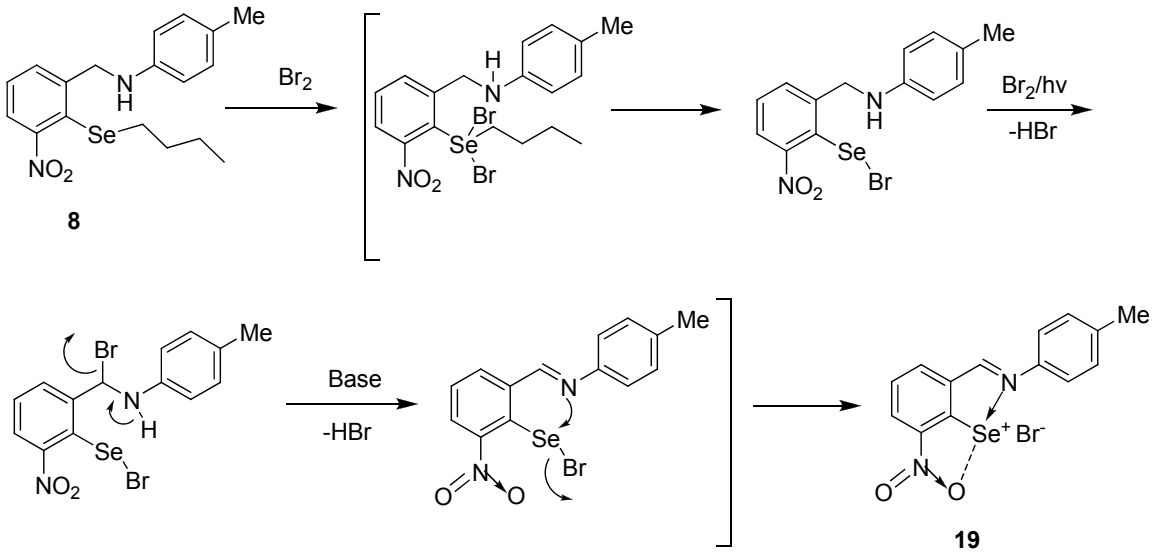
2-Bromo-3-nitrobenzaldehyde (**S1**)[1] was prepared by the reported procedures. Selenium powder and 3-nitrophthalic acid used were purchased from Sigma Aldrich. All the reactions were performed under nitrogen or argon atmosphere by modified Schlenk techniques and monitored by using thin layer chromatography (TLC) from time to time. Solvents were purified by standard techniques.[2] Melting points were recorded on a VEEGO melting point (VMP-1) apparatus and are uncorrected. ^{1}H (399.88 MHz) & ^{1}H (299.95 MHz), ^{13}C (100.6 MHz) and ^{77}Se (57.26 MHz) and ^{77}Se (76.31 MHz) NMR spectra were recorded on a Varian NMR-Mercury plus 400 MHz & Bruker Avance^{III} 400 MHz spectrometer and Varian NMR-Mercury plus 300 MHz for ^{77}Se NMR at the indicated frequencies. Chemicals shifts (δ) are shown with respect to $SiMe_4$ (TMS) as internal standard for nuclei ^{1}H & ^{13}C and Me_2Se for nuclei ^{77}Se as the external standard; s = singlet, d = doublet, t = triplet, dd = doublet of doublets. The high resolution mass spectra (HRMS) were recorded at room temperature on a Micro mass Q–TOF (YA 107) mass spectrometer. FT-IR spectra were recorded in the range 4000-450 cm^{-1} using KBr for solid samples and neat for liquid samples between CsI plates on a Perkin Elmer precisely spectrum one FT–IR spectrometer. The UV-Visible and emission spectra in solution were recorded using Varian Cary 100 Bio UV-Visible Spectrophotometer and Varian Cary Eclipse Fluorescence Spectrophotometer.



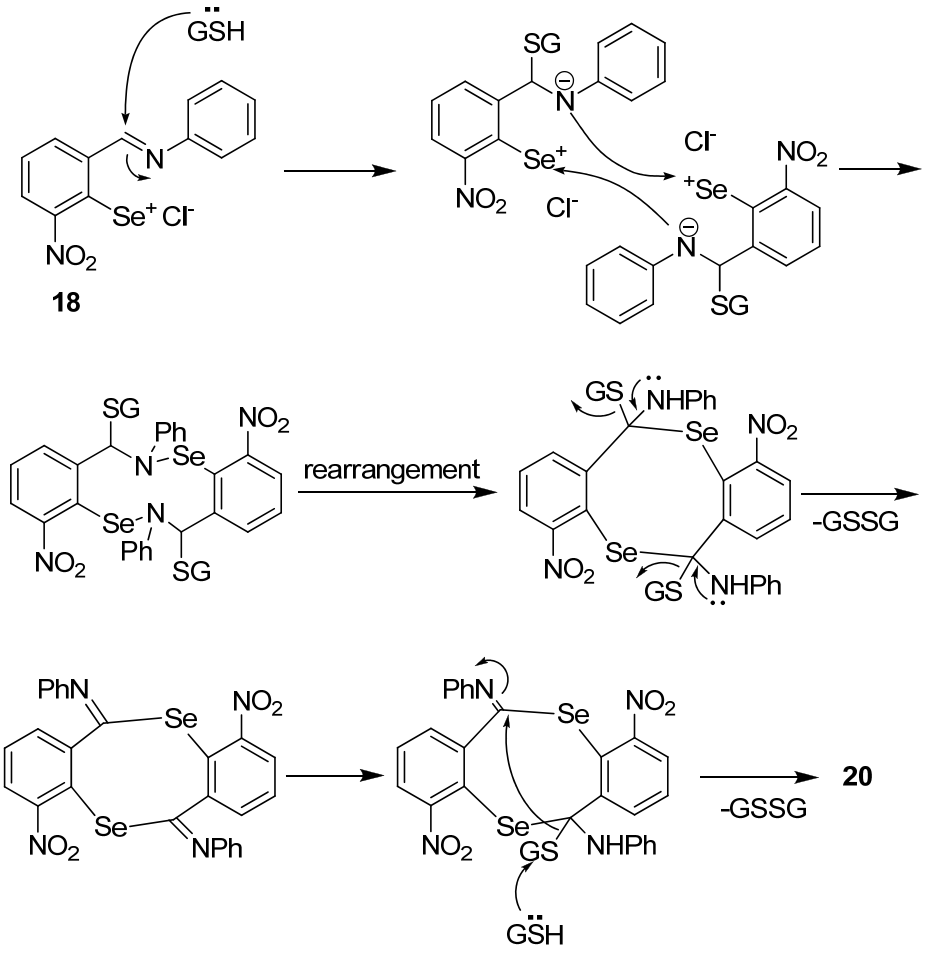
Scheme S1. i) i. *p*-Anisidine in (glac.) AcOH; ii) $NaBH_4$, C_2H_5OH, r.t.; iii) *n*-BuSeNa, C_2H_5OH, 0 °C.



Scheme S2



Scheme S3



Scheme S4

Synthesis and characterization data

Synthesis of Compound S2: To a solution of 2-bromo-3-nitrobenzaldehyde (**S1**) (13.04 mmol, 3.0 g) in glacial acetic acid (10 mL) was added *p*-anisidine (13.04 mmol, 1.60 g) with continuous stirring at room temperature. A yellow precipitate was formed. To complete the precipitation, the reaction mixture was cooled with ice, then filtered and washed with ice-cooled ethanol. Recrystallization from hot ethanol afforded a light yellow solid. Yield: 2.8 g (64 %); M.p 132-135 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 3H, OCH_3), (d, J = 9.2 Hz, 2H), (d, J = 9.2 Hz, 2H), 7.51-7.55 (td, J = 0.6, 7.9 Hz, 1H), 7.76-7.79 (dd, J = 1.5, 7.9 Hz, 1H), 8.42-8.44 (dd, J = 1.5, 7.9 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 55.7, 114.7, 116.6, 123.0, 126.6, 128.2, 131.9, 137.5, 143.6, 151.6, 154.9, 159.5; IR (KBr): 2965, 1615, 1595, 1528, 1504, 1355, 836 cm^{-1}; HRMS (TOF MS ES^{+}) *m/z* calcd for $C_{14}H_{11}N_2O_3Br$ [*M*+H]$^{+}$: 335.0031; found: 335.0034.

Synthesis of Compound S3: To a solution of compound **S2** (6.86 mmol, 2.30 g) in deoxygenated ethanol (10 ml) was added $NaBH_4$ (27.45 mmol, 1.04 g) at room temperature under inert atmosphere. The stirring was continued for 6 h at room temperature. The solvent was evaporated to give a semi-solid of reddish color. The precipitate was dissolved in water and extracted with chloroform. The extracted organic layer was again washed 2-3 times with water. The separated organic layer was dried over anhydrous sodium sulphate and concentrated to yield an orange liquid and which was solidified by keeping in deep freeze to give a crystalline solid. Yield: 1.90 g (82 %); M.p 74-76 ^{o}C. ^{1}H NMR ($CDCl_3$): δ 3.74 (s, 3H, OCH_3), 4.09 (s, NH), 4.44 (s, 2H, CH_2), 6.51-6.53(dd, J = 7.9 Hz, 2H), 6.76-6.78 (dd, J = 8.9 Hz, 2H), 7.51-7.557.36-7.39 (t, J = 7.9 Hz, 1H), 7.60-7.64 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 49.6, 55.8, 114.0, 114.1, 115.0, 123.5, 128.1, 131.7, 141.2, 142.0, 151.2, 152.6; IR (KBr): 3411, 2928, 1531, 1514, 1362, 1236, 1034, 821 cm^{-1}; HRMS (TOF MS ES^{+}) *m/z* calcd for $C_{14}H_{13}N_2O_3Br$ [*M*+H]$^{+}$: 337.0199; found: 337.0188.

Synthesis of Compound 9: To a solution of di-*n*-butyl diselenide (2.85 mmol, 0.77 g) in deoxygenated ethanol (20 mL) was added $NaBH_4$ (5.69 mmol, 0.22 g) at 0 ^oC. The reaction mixture was stirred for 30 min at the room temperature. Compound **S3** (4.75 mmol, 1.60 g) was added at 0 ^oC to *in situ* prepared *n*-BuSeNa. The reaction was stirred for 4 h at room temperature. The excess of the solvent was removed under vacuum. The residue was dissolved in $CHCl_3$ and washed with water. The organic layer and the $CHCl_3$ extract from the aqueous layer were combined and dried over anhydrous Na_2SO_4. Removal of solvent and purification of the residue by silica gel column chromatography (elution with 5 % ethyl acetate/petroleum ether) afforded an orange liquid. Yield: 1.25 g (69 %). ^1H NMR ($CDCl_3$): δ 0.86-0.89 (t, J = 7.3 Hz, 3H), 1.32-1.41 (m, 2H), 1.55-1.61 (m, 2H), 2.84-2.87 (t, J = 7.6 Hz, 2H), 3.73 (s, 3H, OCH_3), 4.58 (s, 2H, CH_2), 4.77 (br s, 1H, NH), 6.53-6.55 (dd, J = 1.1, 6.7 Hz, 2H), 6.75-6.78 (dd, J = 1.1, 6.7 Hz, 2H), 7.37-7.41 (t, J = 7.6 Hz, 1H), 7.47-7.49 (dd, J = 1.5, 7.9 Hz, 1H), 7.64-7.66 (dd, J = 1.5, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.6, 22.9, 30.3, 32.5, 50.0, 55.8, 114.3, 115.1, 121.4, 121.8, 129.4, 130.8, 141.6, 146.4, 152.5, 156.8; ^{77}Se NMR ($CDCl_3$): δ 204; IR (neat): 3419 (NH), 2957, 2931, 1515, 1372, 1235, 1037, 820, 796, 736 cm^{-1}; HRMS (TOF MS ES^+) *m/z* calcd for $C_{18}H_{22}N_2O_3Se$ $[M+H]^+$: 395.0874; found: 395.0859.

Synthesis of Compound 15: To a solution of selenide **8** (0.56 mmol, 0.21 g) was added Br_2 (0.56 mmol, 0.16 g, 0.03 mL) in $CHCl_3$ (1 mL) 0 ^oC with continuous stirring under an inert atmosphere to yield an yellow precipitate. The obtained precipitate was filtered and taken in dry $CHCl_3$ (1 mL) as suspension. To this Et_3N (0.56 mmol, 0.06 g, 0.08 mL) was added. The solution turned to dark-black colored solution. Additionally, the reaction mixture was stirred at room temperature for 3 h. The mixture was extracted with $CHCl_3$ by adding water (10 mL). The separated organic layers were combined and dried over anhydrous Na_2SO_4. Removal of solvent and purification of the residue by silica gel column chromatography (eluted with 20 % ethyl acetate/petroleum ether mixture) afforded compound **15**. Yield: 0.03 g (17 %); M.p 188-192 ^oC. ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 5.81-5.83 (d, J = 8.3 Hz, 2H), 6.49-6.51 (d, J = 8.3 Hz, 2H), 6.65-6.67 (d, J = 8.2 Hz, 2H), 6.97-6.99 (d, J = 8.2 Hz, 2H),

7.35-7.43 (m, 2H), 7.54-7.58 (t, J = 7.9 Hz, 1H), 8.21-8.23 (d, J = 8.3 Hz, 1H), 8.37-8.39 (d J = 8.3 Hz, 1H), 8.59-8.61 (d J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.6, 20.9, 29.9, 117.3, 118.3, 124.1, 126.7, 127.8, 128.2, 128.3, 129.8, 129.9, 130.6, 132.9, 133.2, 134.9, 138.9, 139.8, 140.7, 141.7, 145.5, 145.9, 146.7, 165.2; ^{77}Se NMR ($CDCl_3$): δ 666, 970; IR (KBr): 2922, 2854, 1590, 1506, 1300, 1147, 1041, 984, 791, 732 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z* calcd for $C_{28}H_{20}N_4O_4Se_2$ $[M+H]^+$: 636.9839; found: 636.9922.

Synthesis of Compound 16: Compound **16** was synthesized from selenide **9** (1.01 mmol, 0.40 g) in $CHCl_3$ (2 mL), Br_2 (1.01 mmol, 0.16 g, 0.05 mL) in $CHCl_3$ (1 mL) at 0 ^{o}C and Et_3N (1.01 mmol, 0.10 g, 0.14 mL) according to the procedure described for the preparation of compound 1**5**. Removal of solvent and purification of the residue by silica gel column chromatography (eluted with 20 % ethyl acetate/petroleum ether mixture) afforded compound **16**. Recrystallization from chloroform/petroleum ether (1:1) afforded dark-black crystals. Yield: 0.09 g (26 %); M.p 215 ^{o}C. ^{1}H NMR ($CDCl_3$): δ 3.67 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 6.22-6.24 (d, J = 8.8 Hz, H), 6.47-6.49 (d, J = 8.8 Hz, H), 6.68-6.75 (m, H), 7.28-7.37 (m, H), 7.47-7.51 (t, J = 7.6 Hz, H), 8.17-8.20 (dd, J = 1.2, 7.9 Hz, 1H), 8.28-8.30 (dd, J = 1.2, 7.3 Hz, 1H), 8.50-8.52 (dd, J = 8.3, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 55.4, 55.5, 92.6, 113.2, 114.5, 120.3, 121.5, 123.9, 126.4, 127.7, 127.9, 129.2, 132.5, 135.5, 136.1, 139.0, 140.2, 141.5, 142.0, 145.2, 145.4, 155.4, 156.5, 163.7; ^{77}Se NMR ($CDCl_3$): δ 665, 971; IR (KBr): 2924, 1594, 1505, 1297, 1247, 1029, 849, 737 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z* calcd for $C_{28}H_{20}N_4O_6Se_2$ $[M+H]^+$: 668.9792; found: 668.9808.

Synthesis of Selenenium Cation 18: To a solution of compound **6** (3.25 mmol, 1.0 g) in the presence of Et_3N (3.25 mmol, 0.45 mL) at 0 ^{o}C in $CHCl_3$ (5 mL) was added SO_2Cl_2 (3.25 mmol, 0.26 mL) in $CHCl_3$ (2 mL) with continuous stirring under an inert atmosphere. Additionally, the reaction mixture was stirred at room temperature for 1.5 h minutes. The resulting greenish-yellow precipitates was filtered off and dried under vacuum. Yield: 0.60 g (54 %); M.p 181-184 ^{o}C. ^{1}H NMR (CD_3OD): δ = 7.75-7.77 (m, 3H; ArH), 7.98-8.02 (m, 2H; ArH), 8.21-8.24 (t, J = 8.1 Hz, 1H; ArH), 8.98-9.00 (dd, J = 0.8, 8.1 Hz, 1H; ArH), 9.08-9.10 (dd, J = 0.7, 7.9 Hz, 1H; ArH), 10.63 (s, 1H); ^{13}C NMR (CD_3OD): δ =124.2, 124.7,

130.4, 131.3, 131.4, 131.9, 132.1, 133.1, 140.1, 140.8, 163.5; ^{77}Se NMR (CD_3OD): δ 1180; IR (KBr): 1614, 1520, 1312, 766 cm^{-1}; HRMS (TOF MS ES^+) *m/z* calcd for $C_{13}H_9N_2O_2SeCl$ $[M\text{-}Cl]^+$: 304.9834; found: 304.9829.

Synthesis of Selenenium Cation 19: To a solution of selenide **8** (0.90 mmol, 0.34 g) in $CHCl_3$ (2 mL) and triethylamine (0.90 mmol, 0.09 g, 0.124 mL) was added Br_2 (1.35 mmol, 0.22 g, 0.07 mL) in $CHCl_3$ (1 mL) at 0 ^oC with continuous stirring under an inert atmosphere. After the complete addition of Br_2, the reaction mixture was further stirred at the room temperature for 1 h. The yellow precipitate was filtered off and dried under vacuum afforded **19**. Recrystallization from methanol/dichloromethane [1:1] afforded light yellow needle-like crystals. Yield: 0.095 g (27 %); M.p 245-247 ^oC. ^{1}H NMR (CD_3OD): δ 2.51 (s, 3H, CH_3), 7.55-7.57 (d, J = 7.3 Hz, 2H), 7.86-7.89 (d, J = 8.3 Hz, 2H), 8.19-8.23 (t, J = 7.9 Hz, 1H), 8.97-8.99 (d, J = 7.5 Hz, 1H), 9.05-9.07 (d, J = 7.9 Hz, 1H), 10.58 (s, 1H); ^{13}C NMR (CD_3OD): δ 21.4, 124.4, 131.1, 131.8, 132.4, 135.5, 138.5, 139.8, 144.7, 146.6 162.5; ^{77}Se NMR (CD_3OD): δ 1182; IR (KBr): 2989, 1615 (C=N), 1529 (NO_2), 1360, 1311, 809 cm^{-1}; HRMS (TOF MS ES^+) *m/z* calcd for $C_{14}H_{11}N_2O_2SeBr$ $[M\text{-}Br]^+$: 318.9986; found: 318.9993.

Synthesis of Compound 20: To a solution of **18** (0.30 mmol, 0.10 g) in methanol (1 mL) and water (1 mL) was added GSH (0.60 mmol, 0.18 g) at room temperature. The reaction mixture was stirred for 2 h with continuous stirring. The color of the reaction mixture turned into black. The mixture was submitted to column with silica gel and eluted by 10 % ethyl acetate/petroleum ether mixture afforded orange product alongwith black-colored intractable mixture (0.024 g). Recrystallization from $CHCl_3$/petroleum ether gave orange needle like crystals of **20**. Yield: 0.03 g (34 %); M.p 218-220 ^oC. ^{1}H NMR ($CDCl_3$): δ 4.69 (s, NH, 2H), 6.05-6.07 (d, J = 7.8 Hz, 4H), 6.54-6.58 (t, J = 7.3 Hz, 2H), 6.78-6.82 (t, J = 7.3 Hz, 4H), 7.38-7.42 (t, J = 7.9 Hz, 2H), 7.62-7.64 (dd, J = 1.2, 7.6 Hz, 2H), 8.29-8.31 (dd, J = 0.9, 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 85.9, 115.7, 119.2, 125.1, 127.8, 128.6, 132.2, 134.2, 144.2, 144.3, 144.5; ^{77}Se NMR ($CDCl_3$): δ 707; IR (KBr): 3395, 2924, 2853, 1595, 1506, 1310, 1124, 802, 737, 690 cm^{-1}; HRMS (TOF MS ES^+) *m/z* calcd for $C_{26}H_{18}N_4O_4Se_2$ $[M+H]^+$: 610.9737; found: 610.9716.

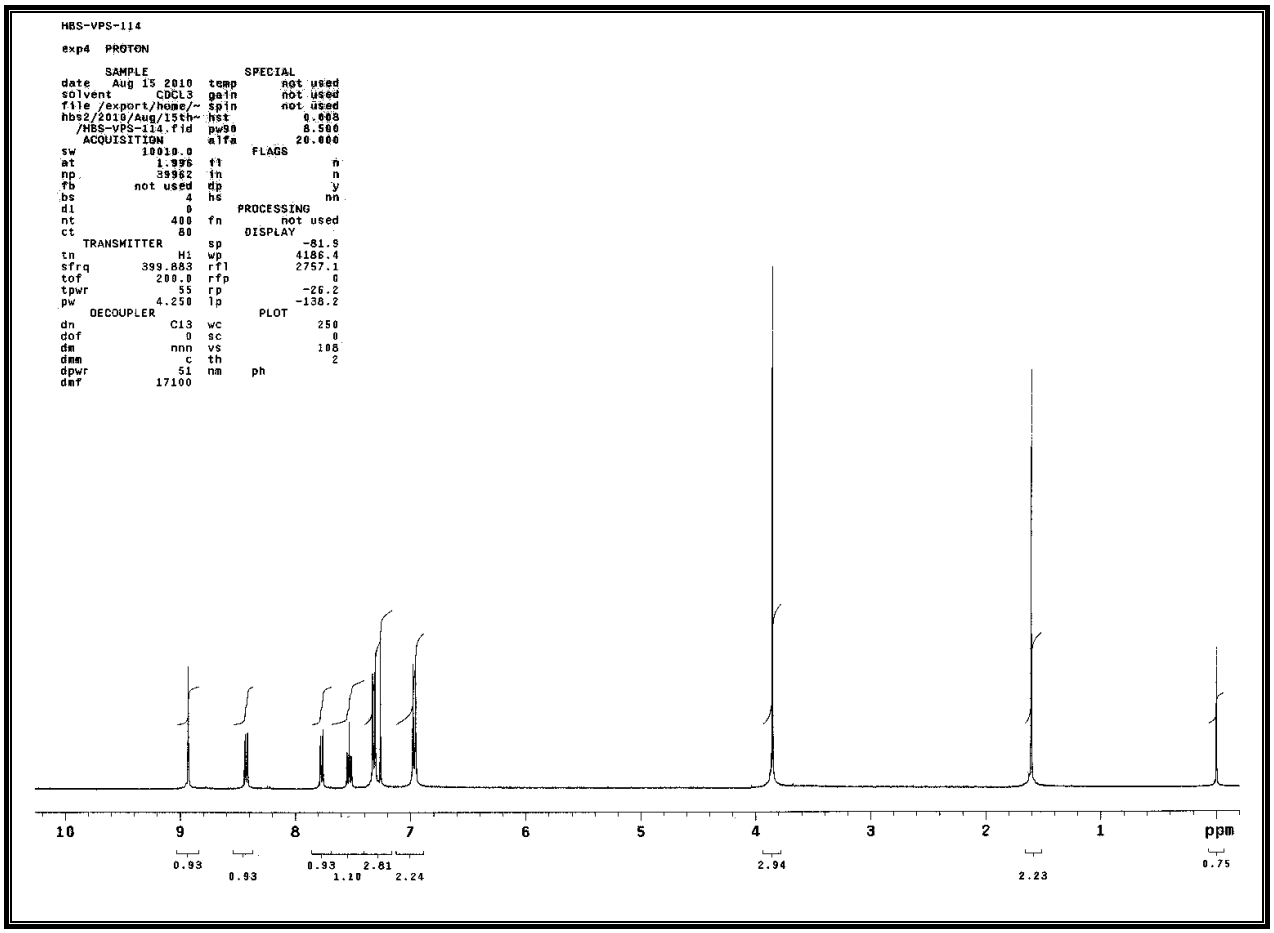


Figure S1. ^{1}H NMR spectrum of compound **S2**

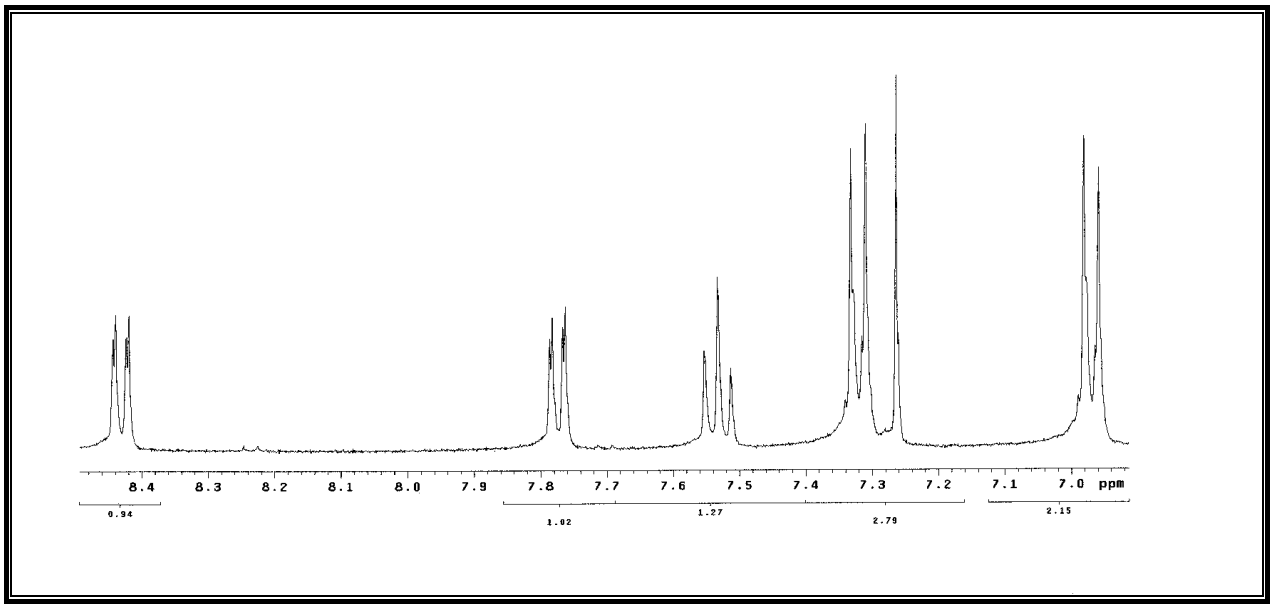


Figure S2. Expanded version of a part of the ^{1}H NMR spectrum of compound **S2**

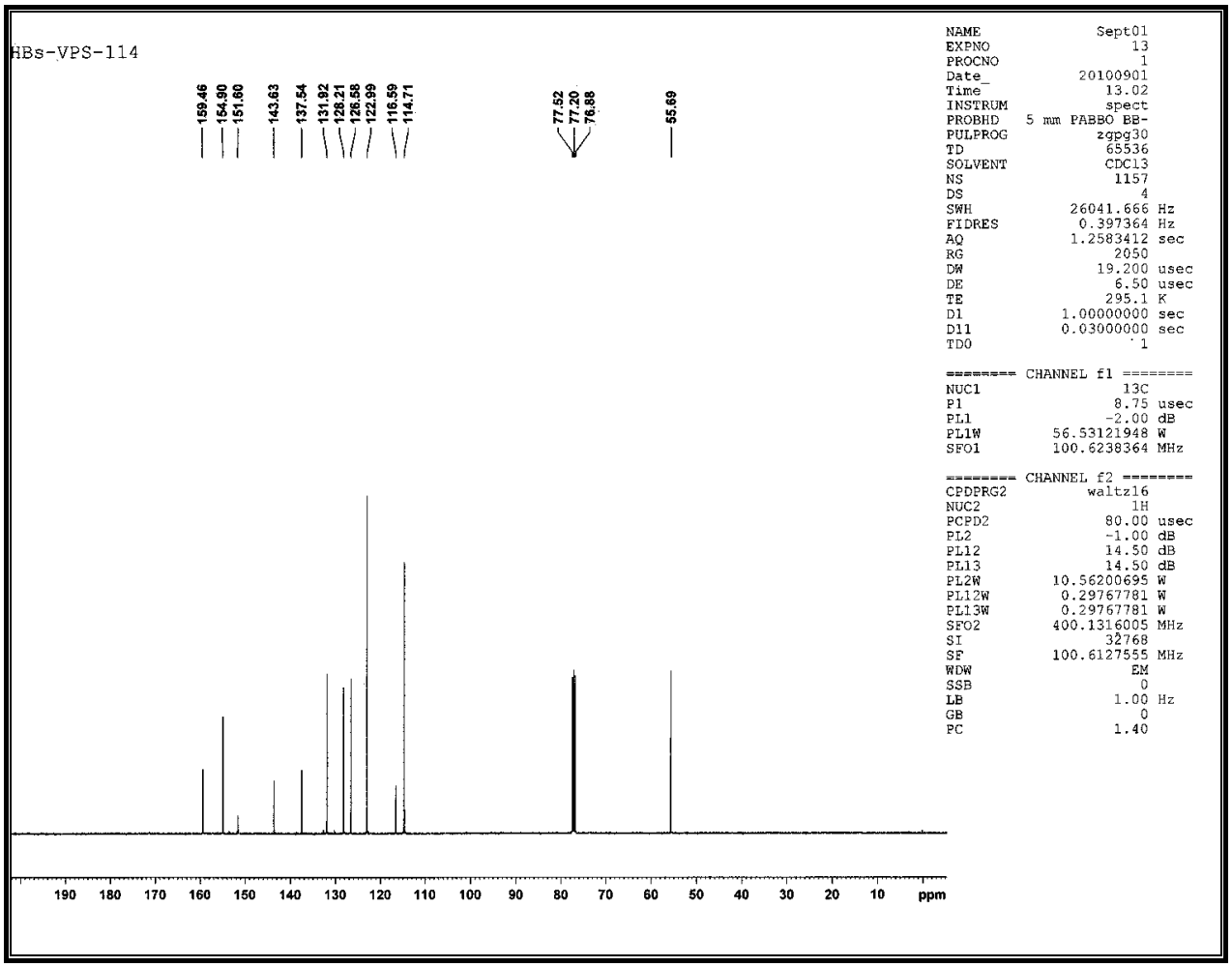


Figure S3. ^{13}C NMR spectrum of compound **S2**.

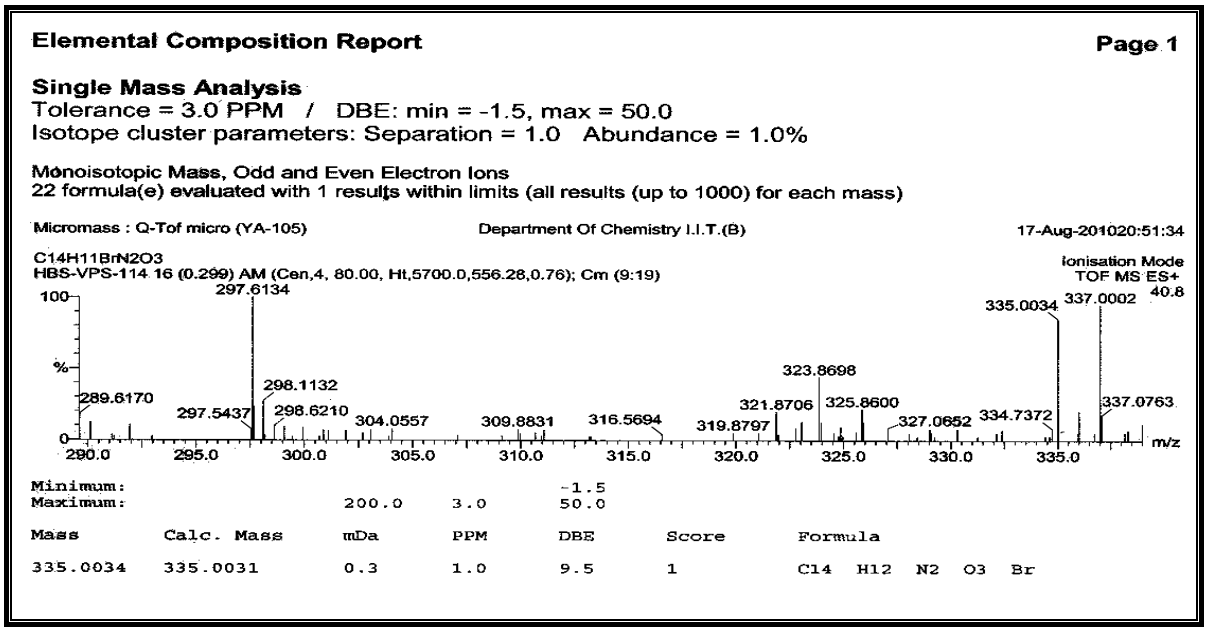


Figure S4. HRMS spectrum of compound **S2**.

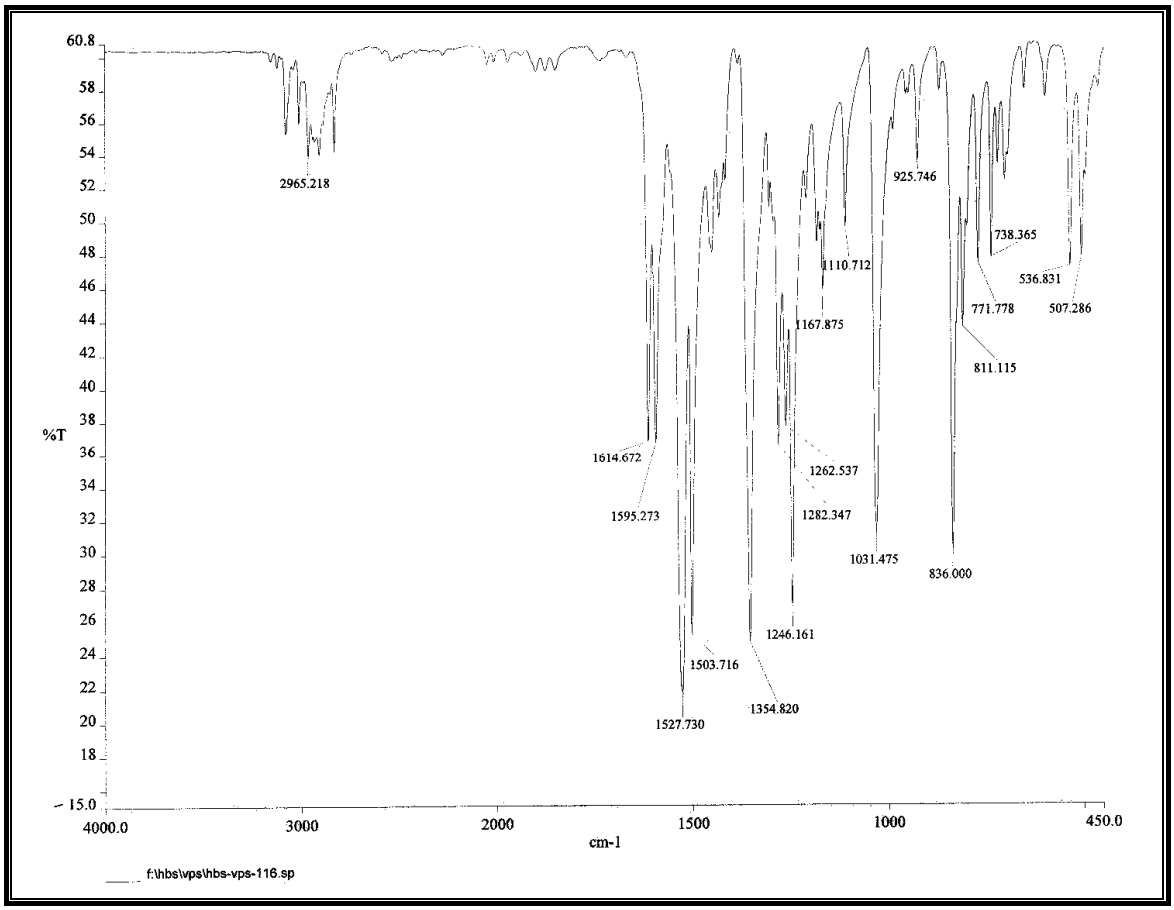


Figure S5. FT-IR spectrum of compound **S2**.

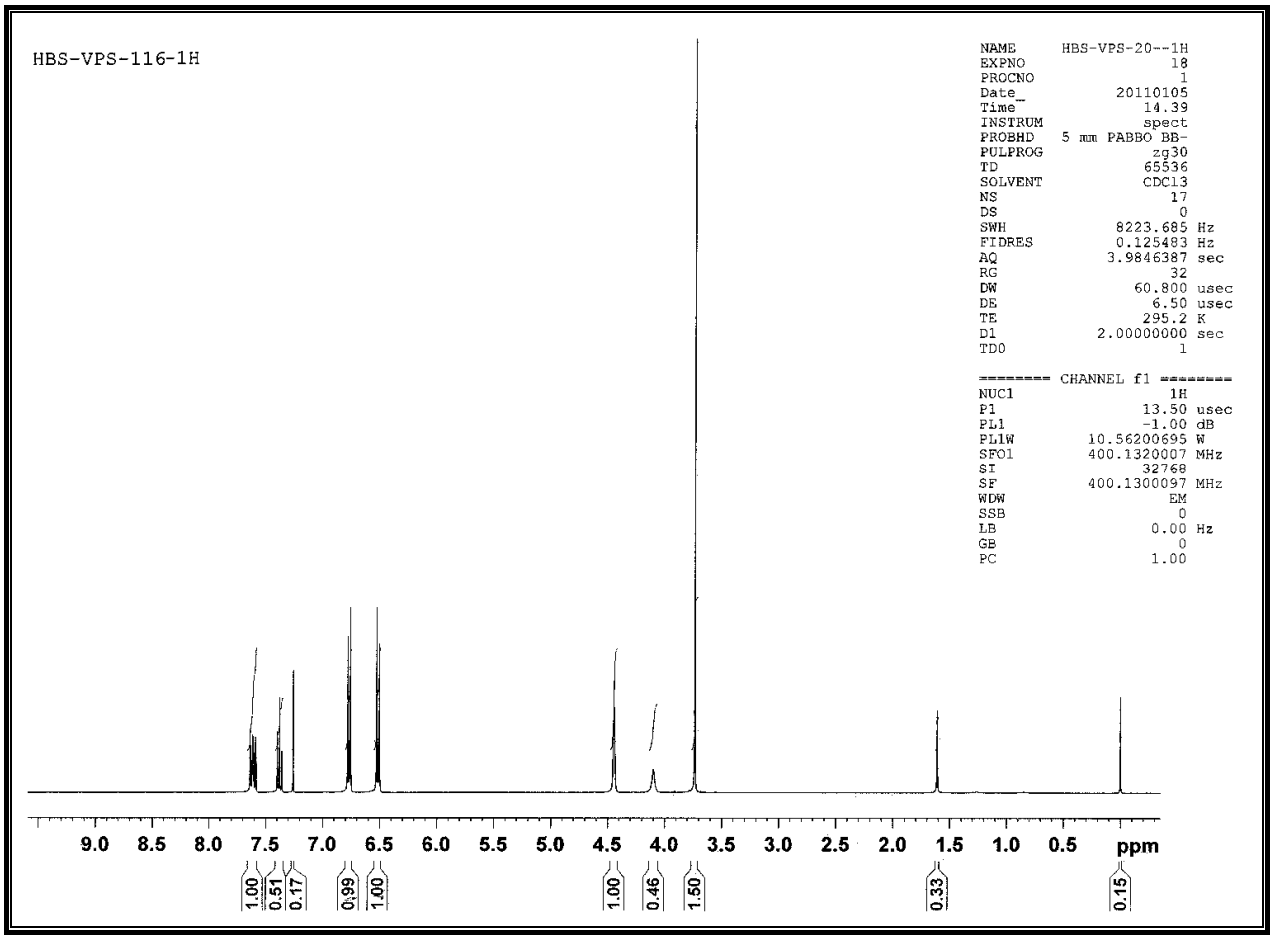


Figure S6. ^{1}H NMR spectrum of compound **S3**.

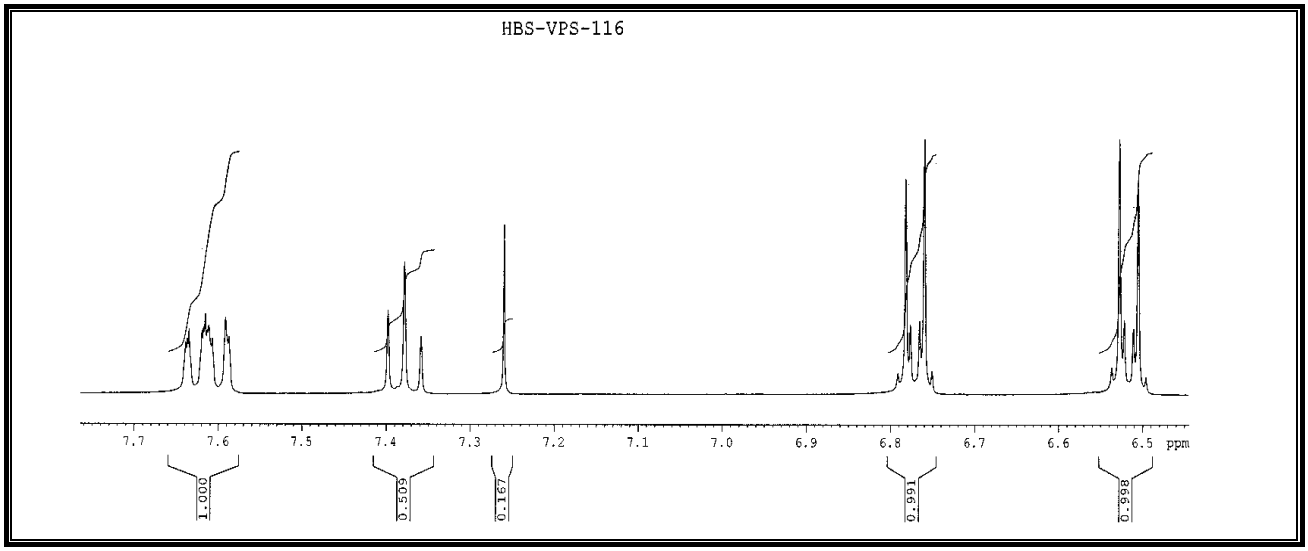


Figure S7. Expanded version of a part of the ^{1}H NMR spectrum of compound **S3**

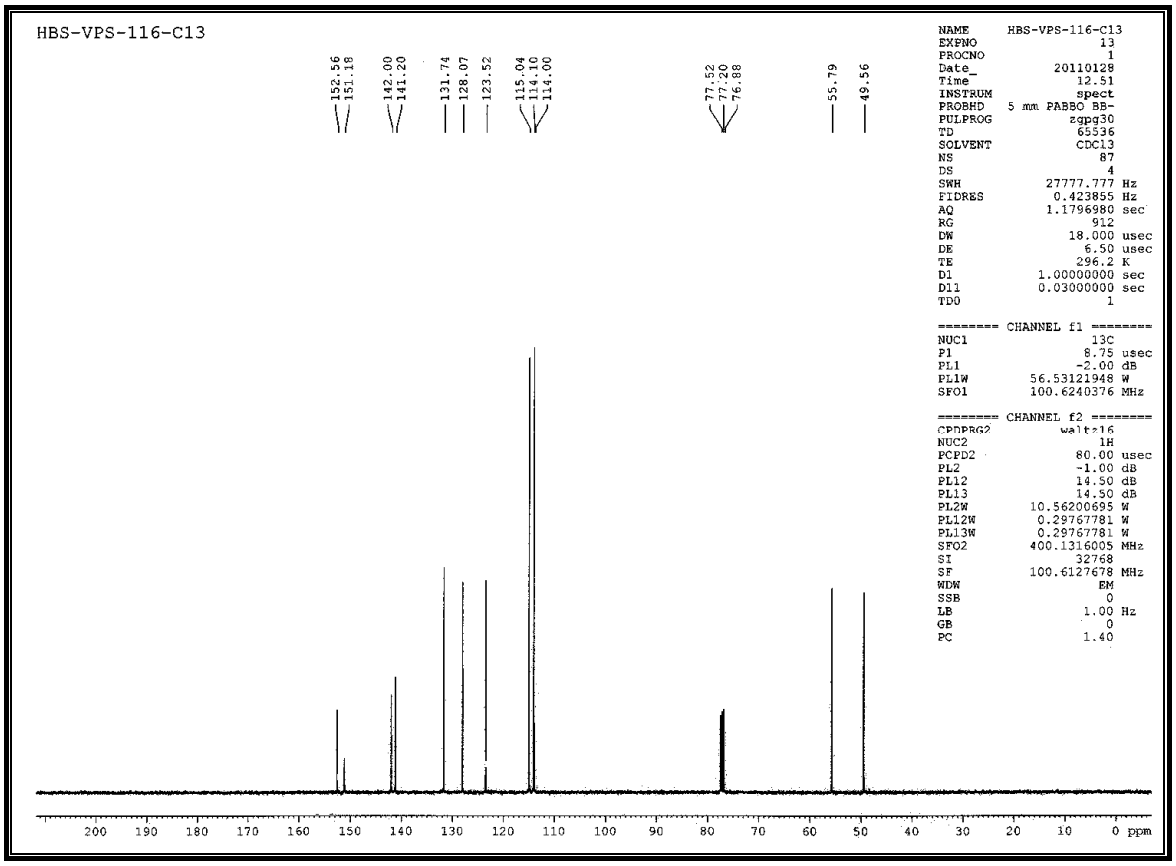


Figure S8. ^{13}C NMR spectrum of compound **S3**.

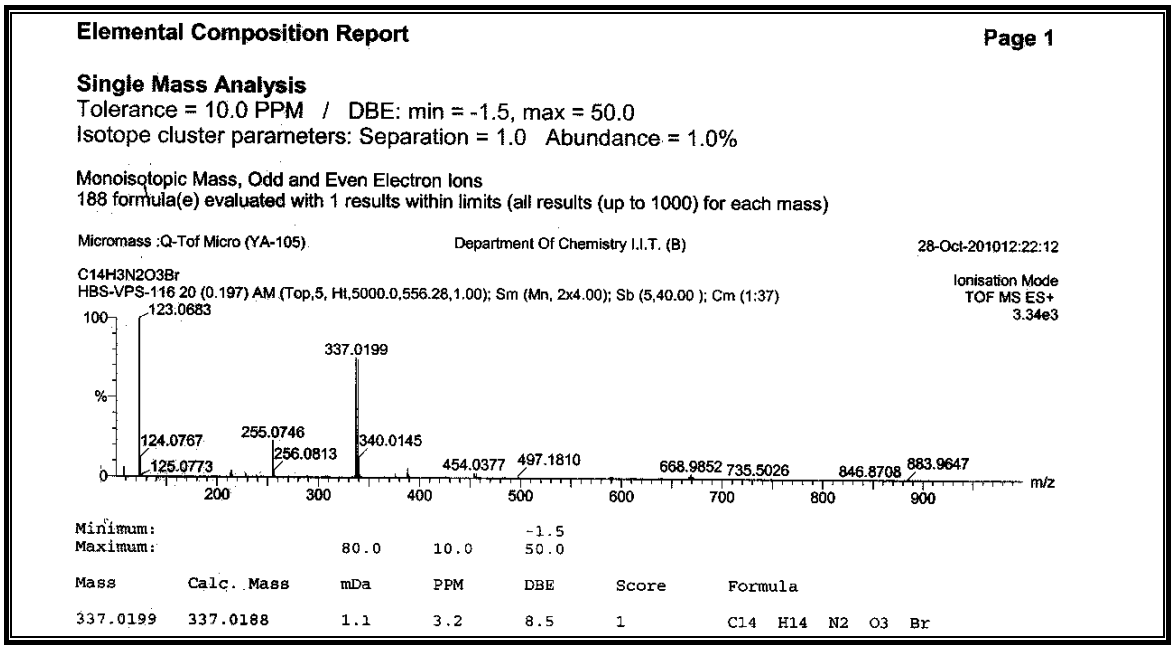


Figure S9. HRMS spectrum of compound **S3**

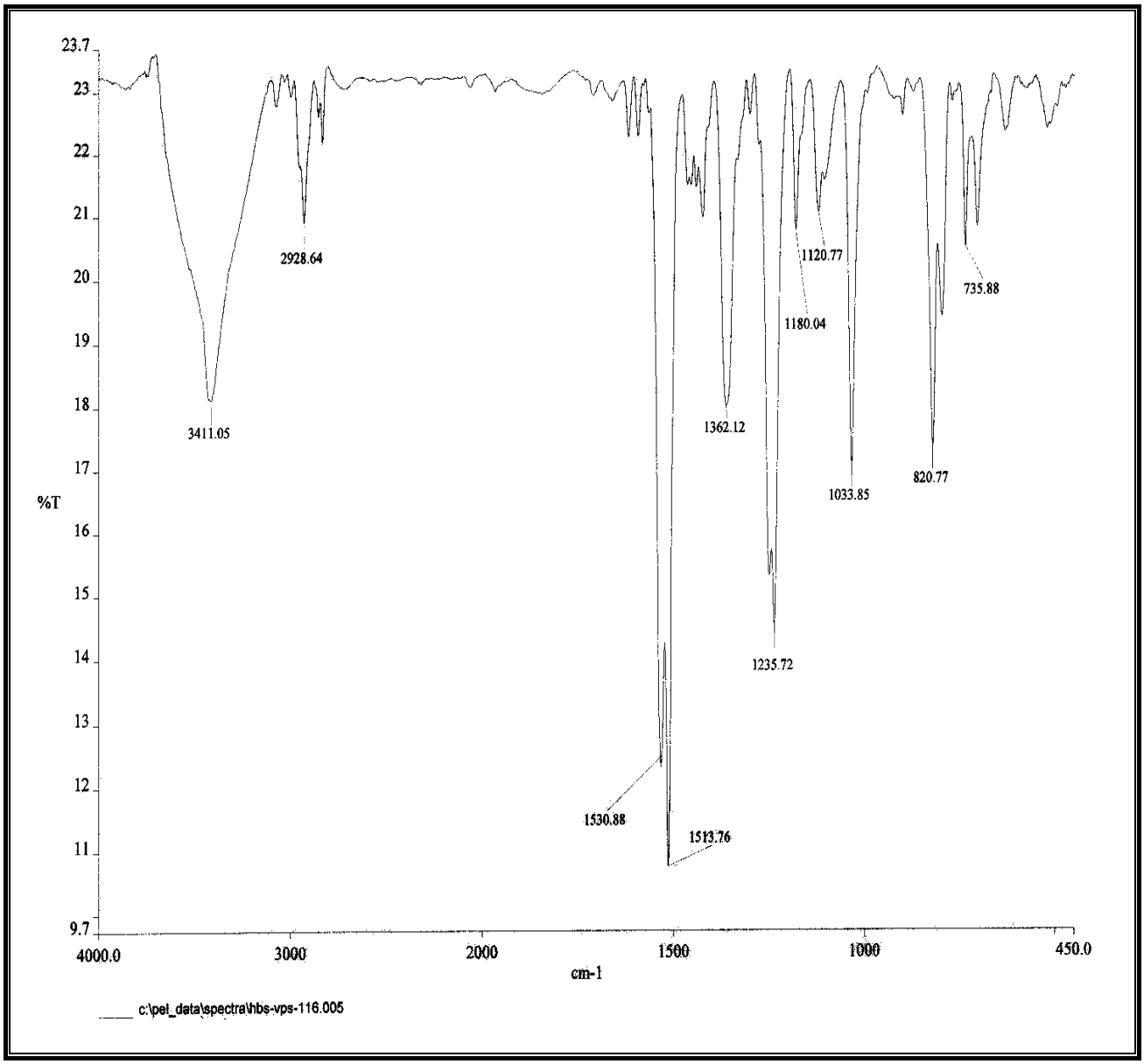


Figure S10. FT-IR spectrum of compound **S3**.

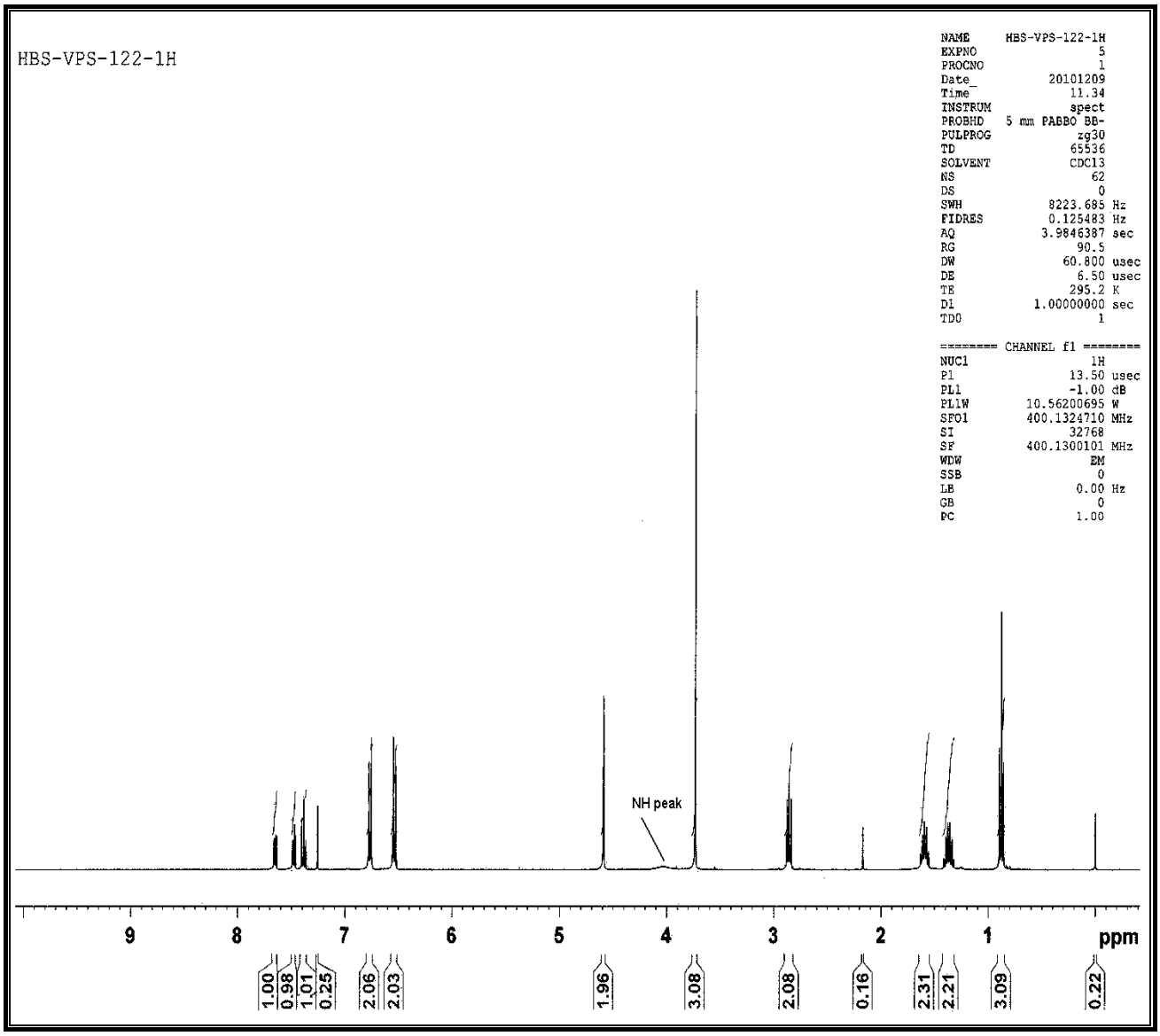


Figure S11. ^{1}H NMR spectrum of compound **9** in $CDCl_3$

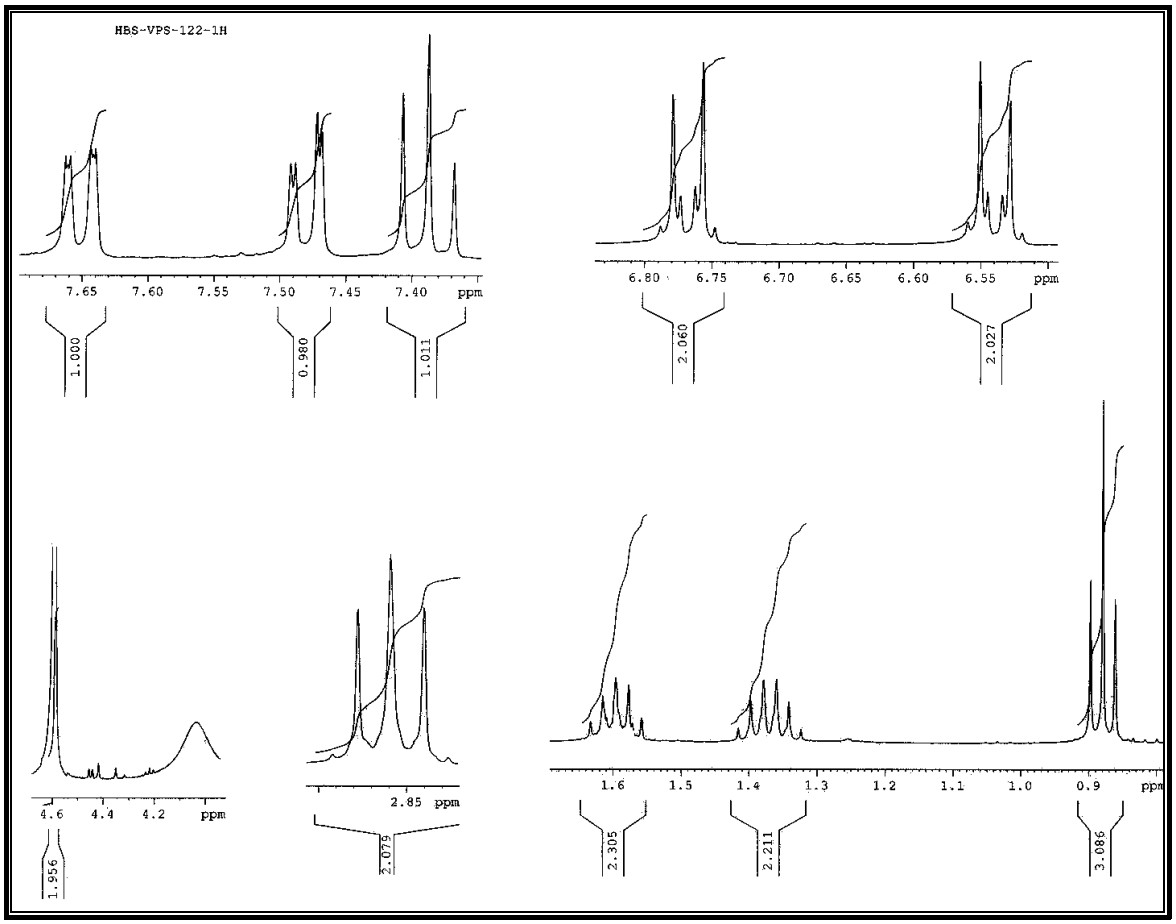


Figure S12. Expanded version of a part of the ^{1}H NMR spectrum of compound **9**

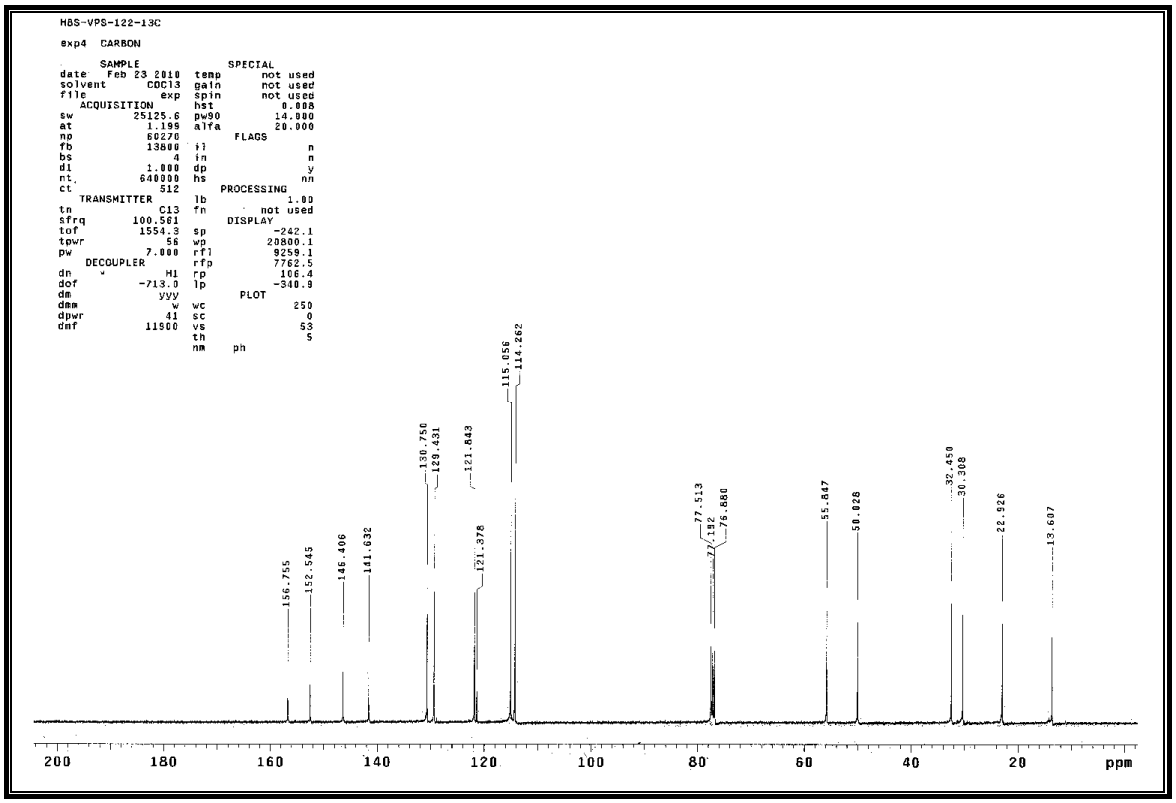


Figure S13. ^{13}C NMR spectrum of compound **9** in $CDCl_3$

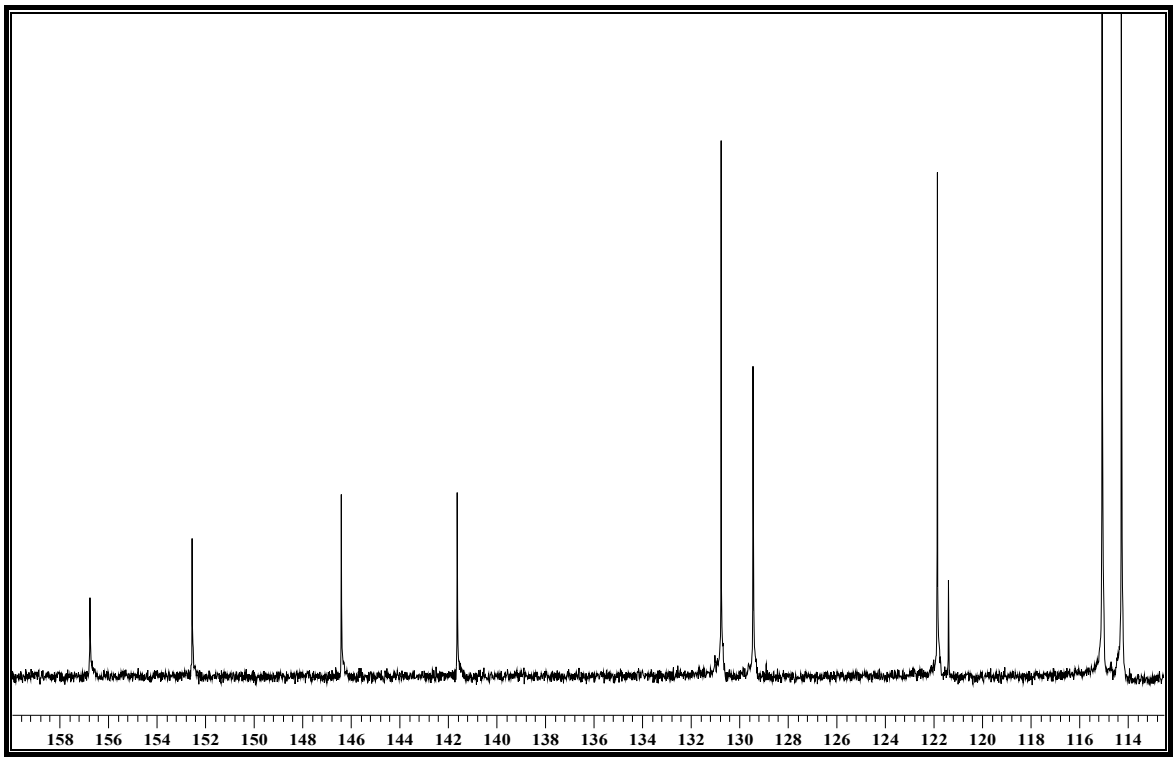


Figure S14. Expanded version of a part of the ^{13}C NMR spectrum of compound **9**.

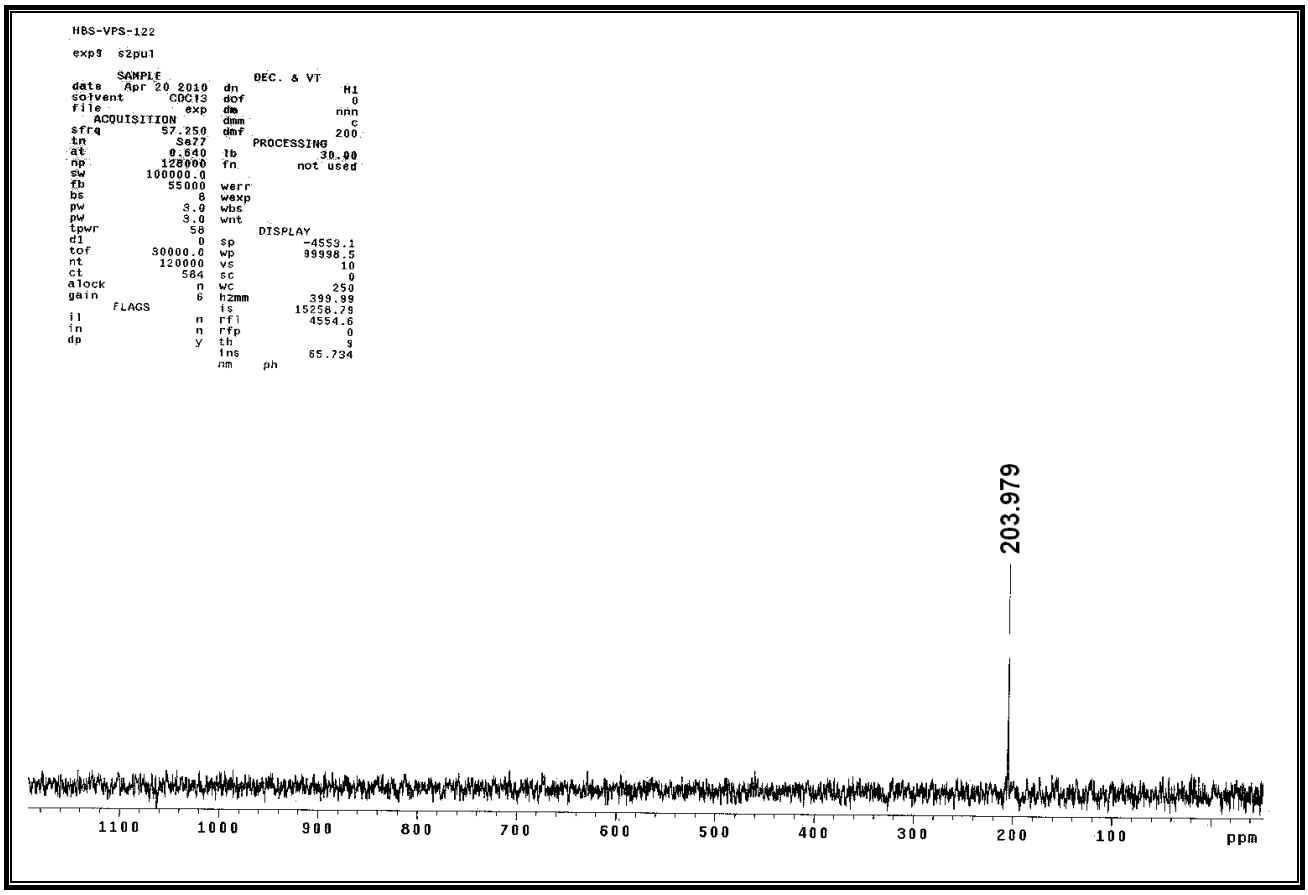


Figure S15. ^{77}Se NMR spectrum of compound **9** in $CDCl_3$

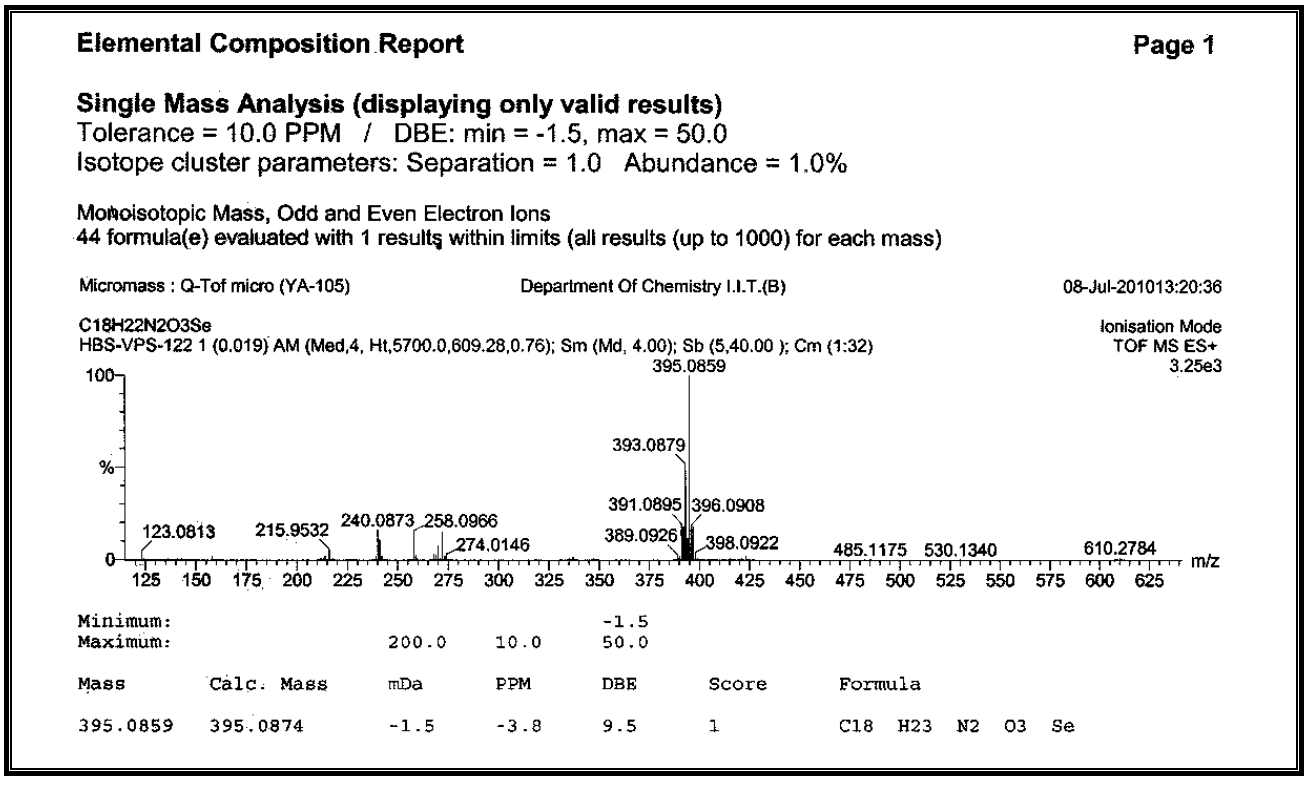


Figure S16. HRMS spectrum of compound **9**

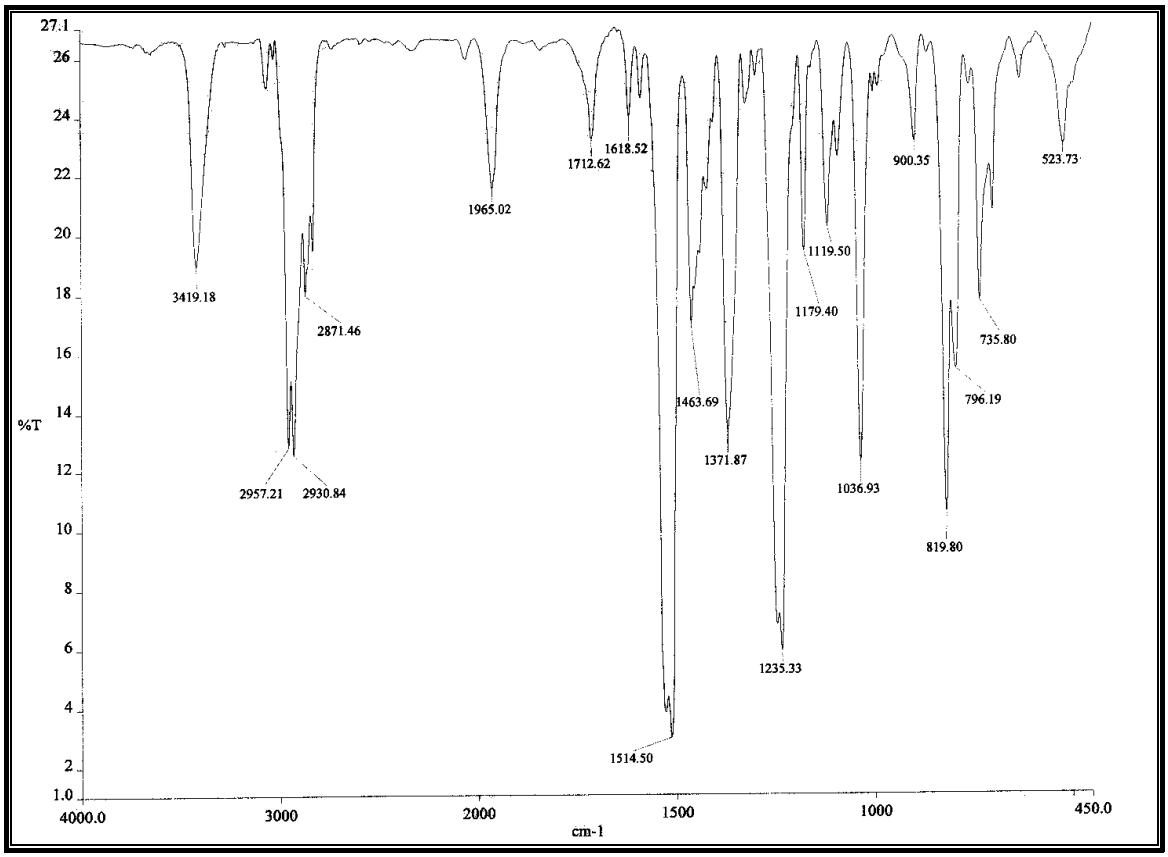


Figure S17. FT-IR spectrum of compound **9**

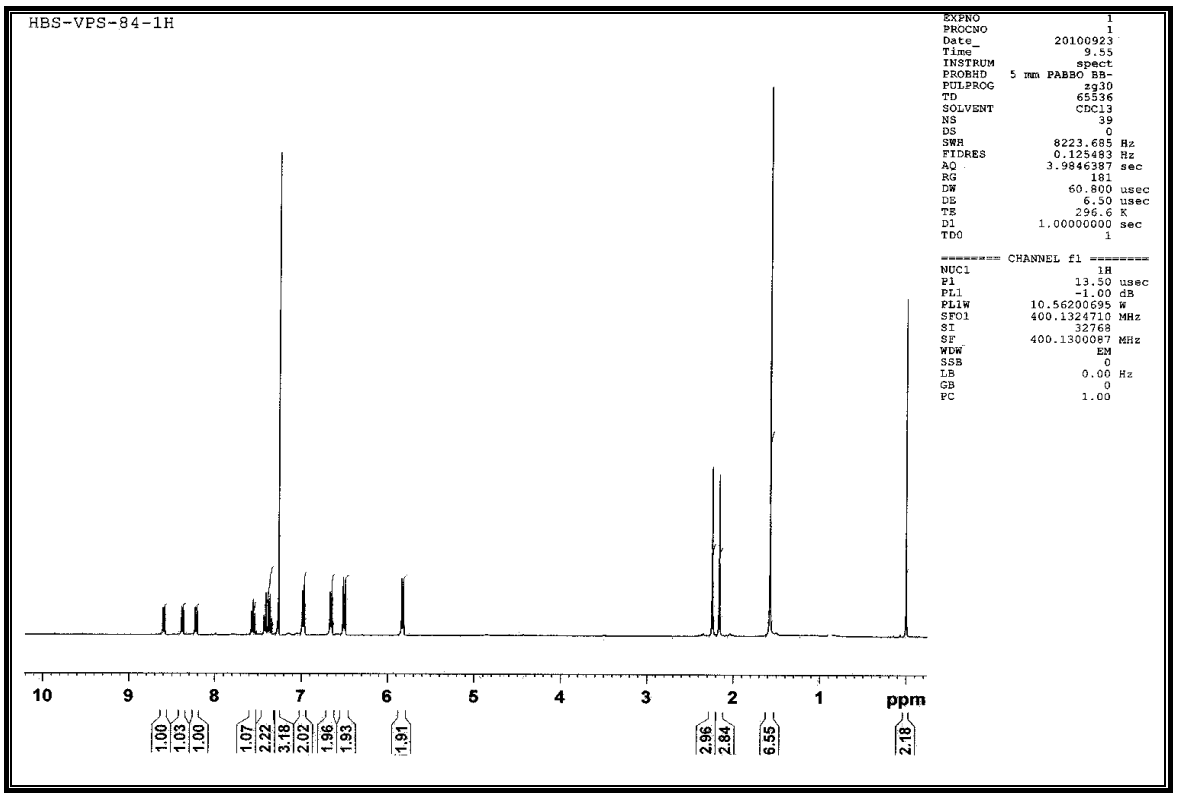


Figure S18. ^{1}H NMR spectrum of compound **15** in $CDCl_3$

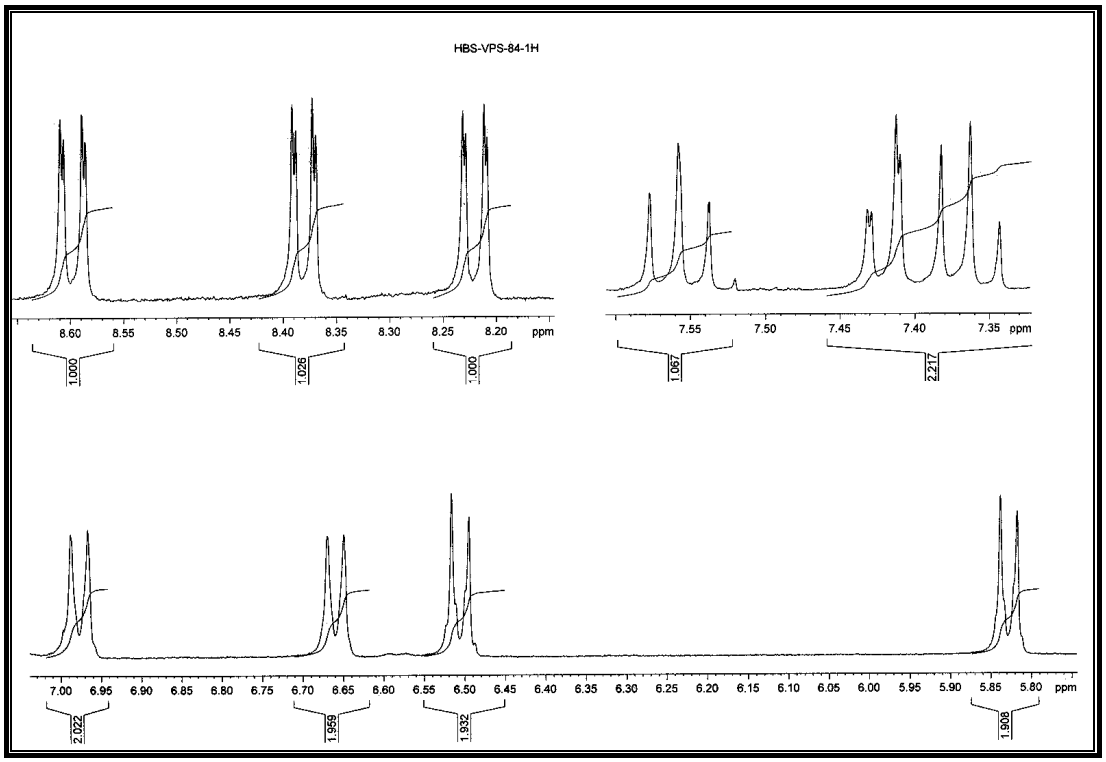


Figure S19. Expanded version of a part of the ^{1}H NMR spectrum of compound **15**

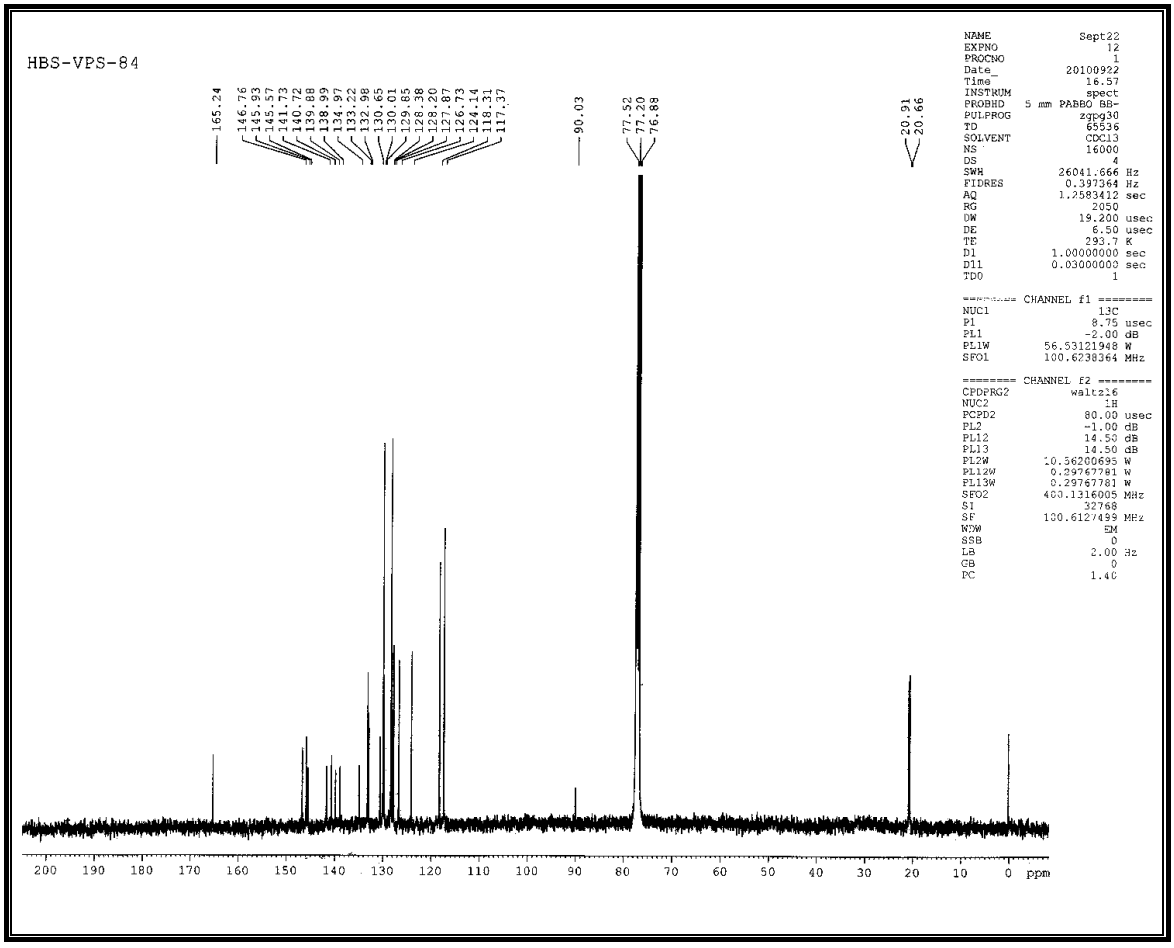


Figure S20. ^{13}C NMR spectrum of compound **15** in $CDCl_3$

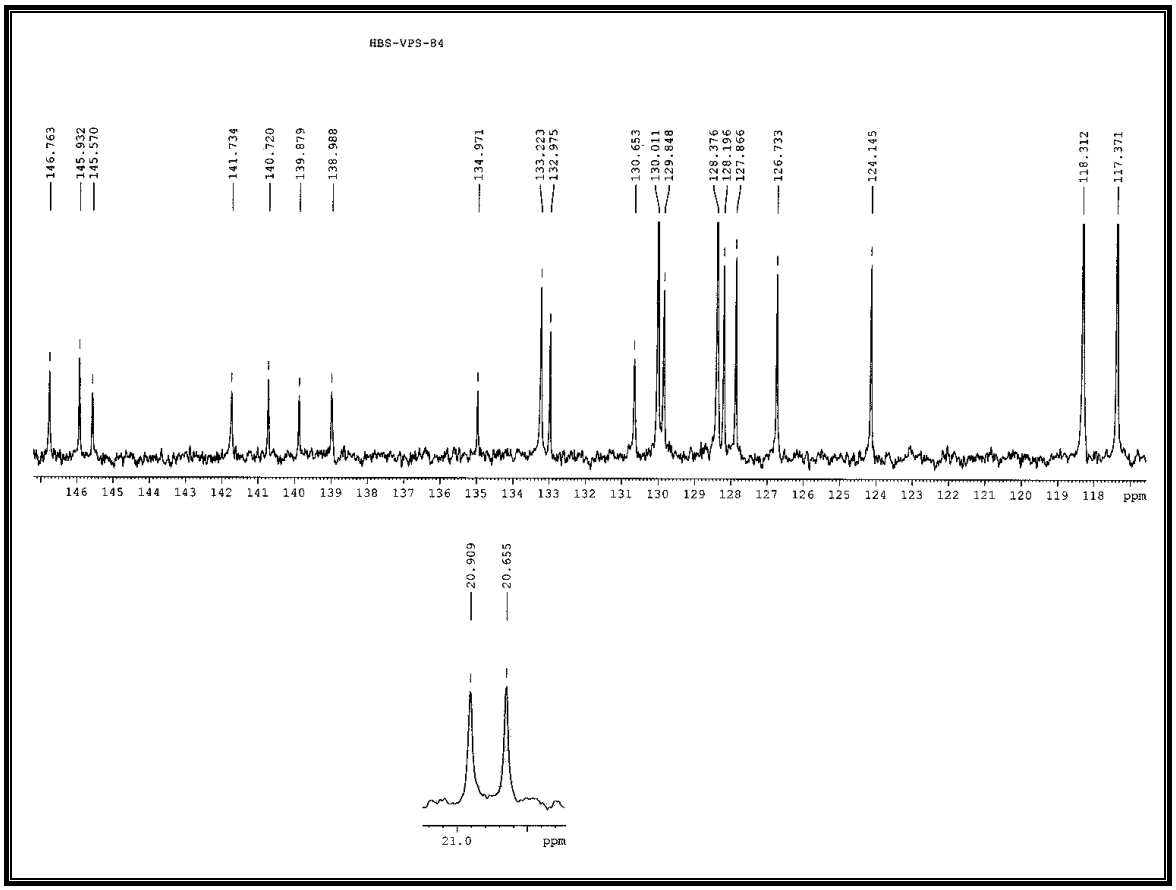


Figure S21. Expanded version of a part of the ^{13}C NMR spectrum of compound **15**

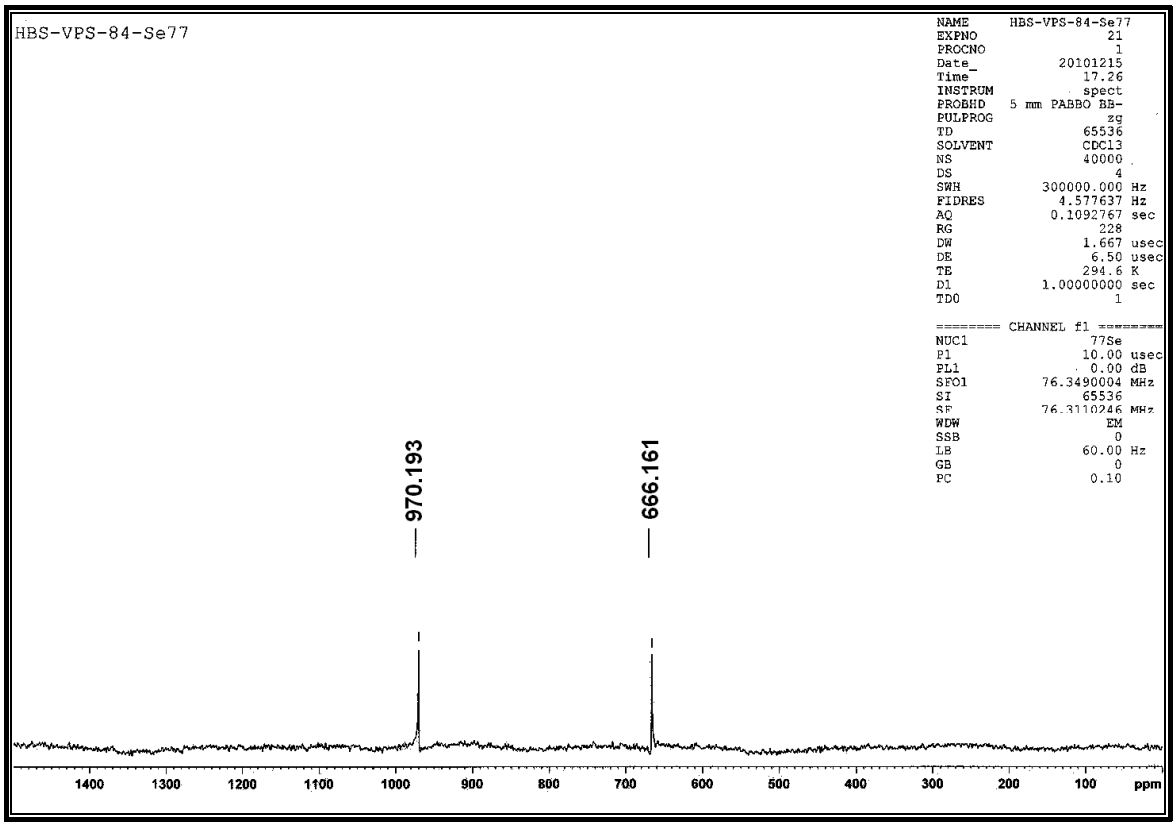


Figure S22. ^{77}Se NMR spectrum of compound **15** in $CDCl_3$

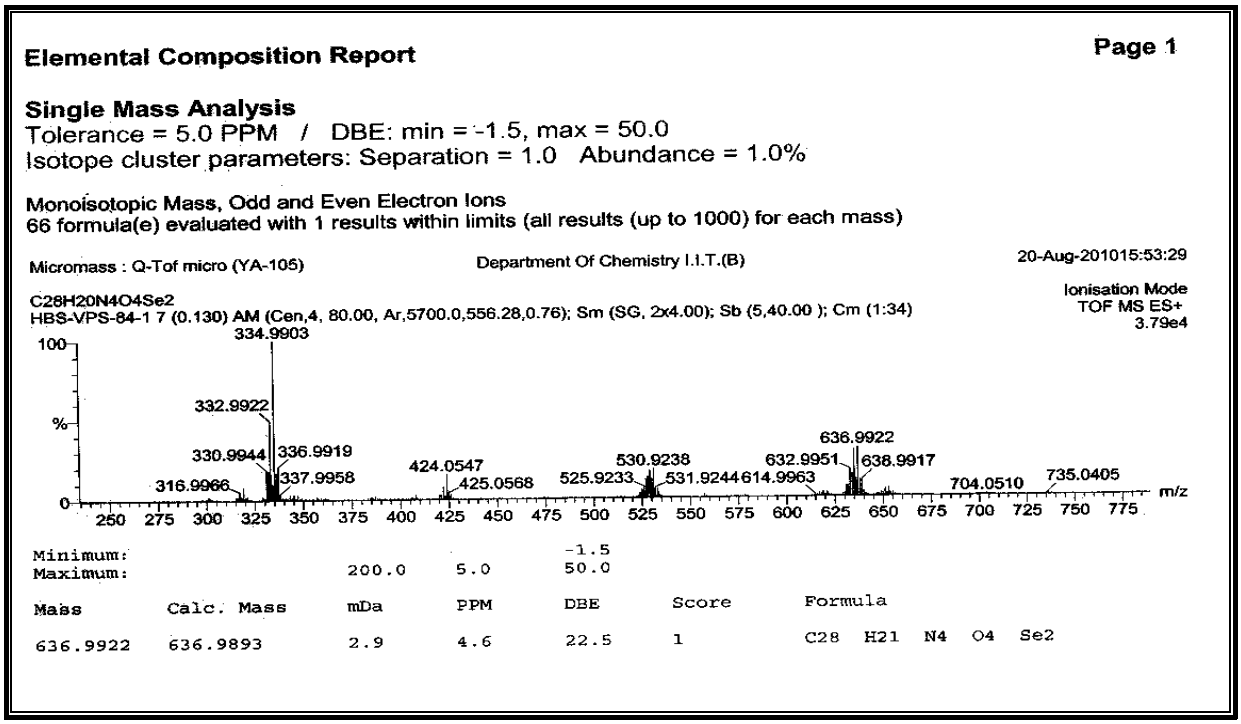


Figure S23. HRMS spectrum of compound **15**

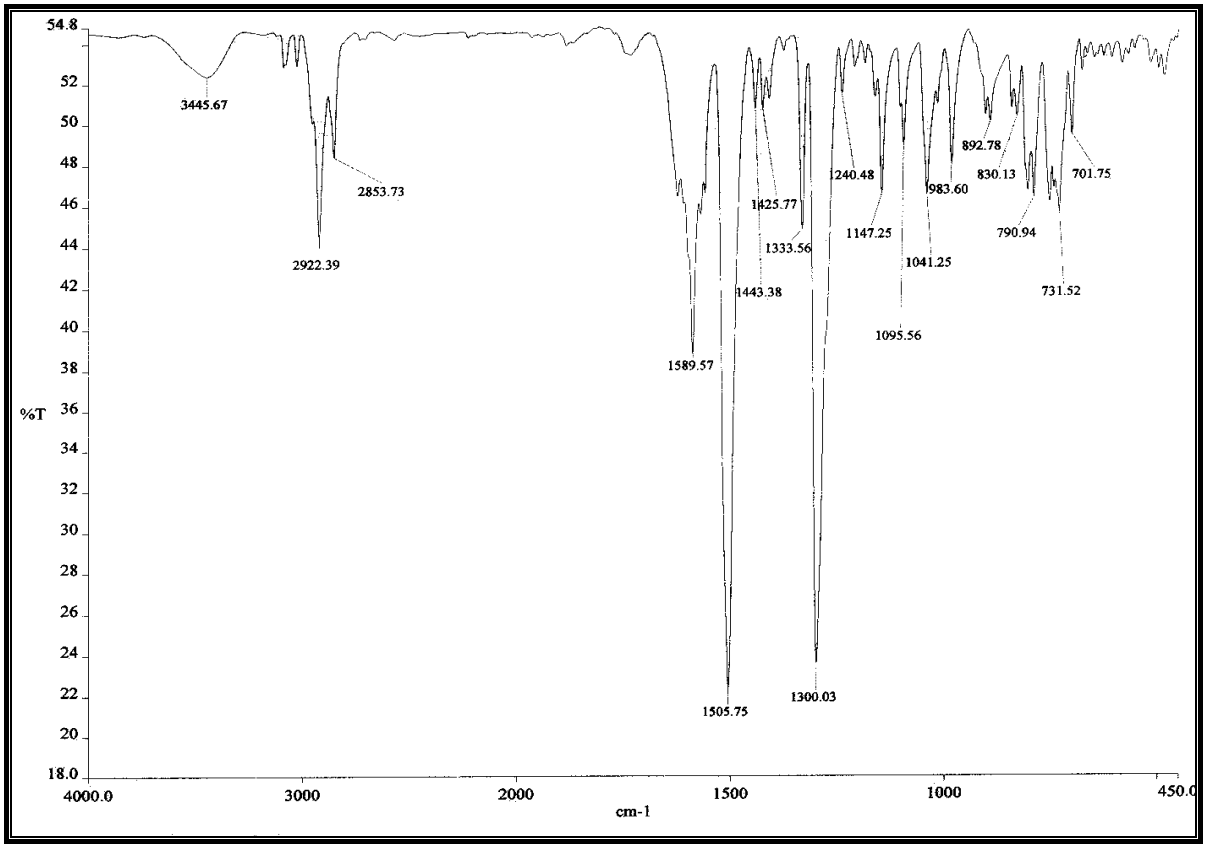


Figure S24. FT-IR spectrum of compound **15**

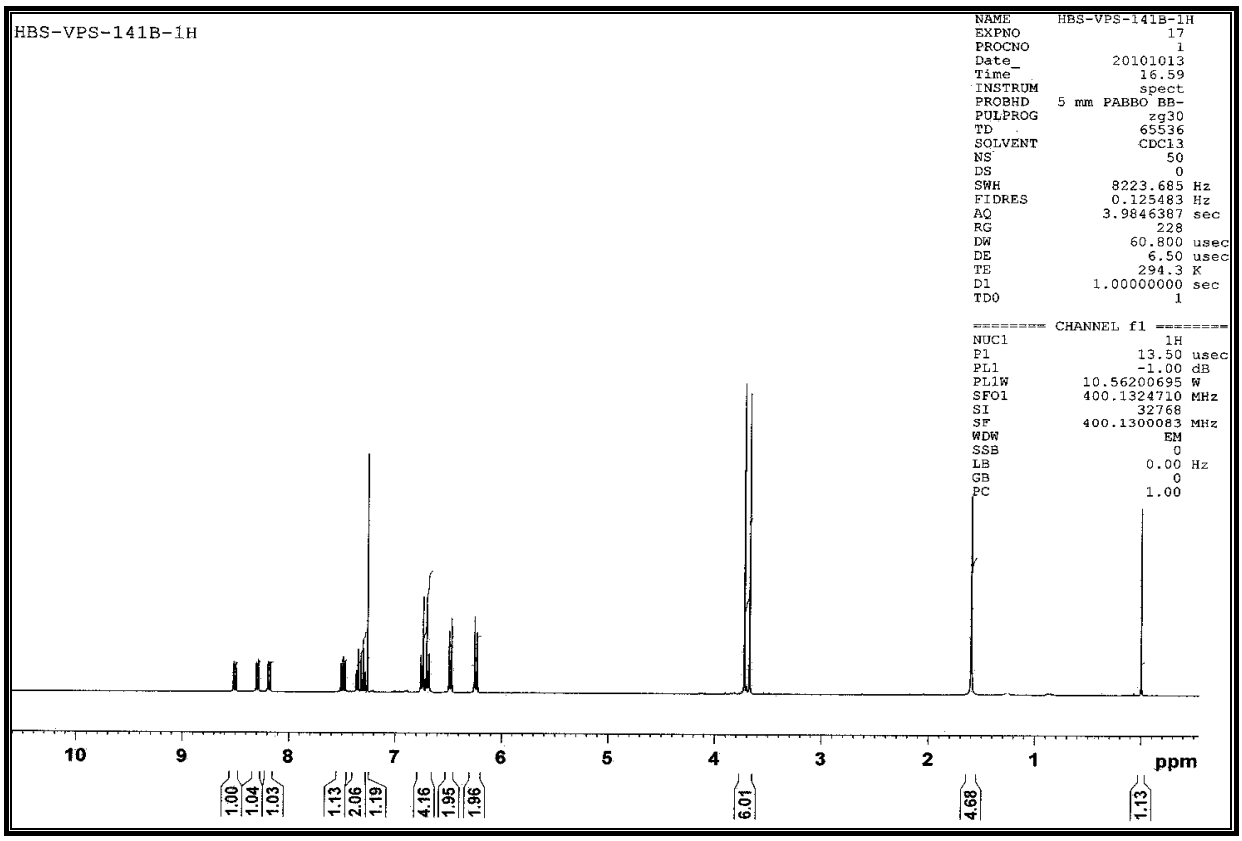


Figure S25. ^{1}H NMR spectrum of compound **16** in $CDCl_3$

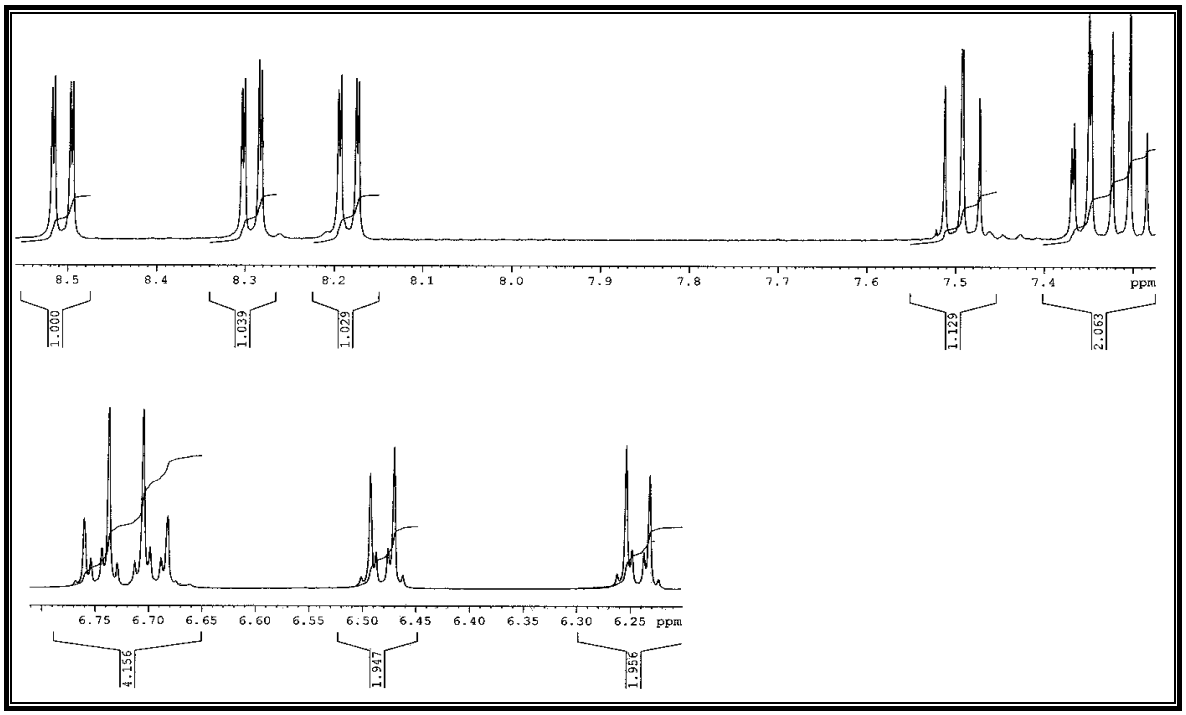


Figure S26. Expanded version of a part of the^{1}H NMR spectrum of compound **16**

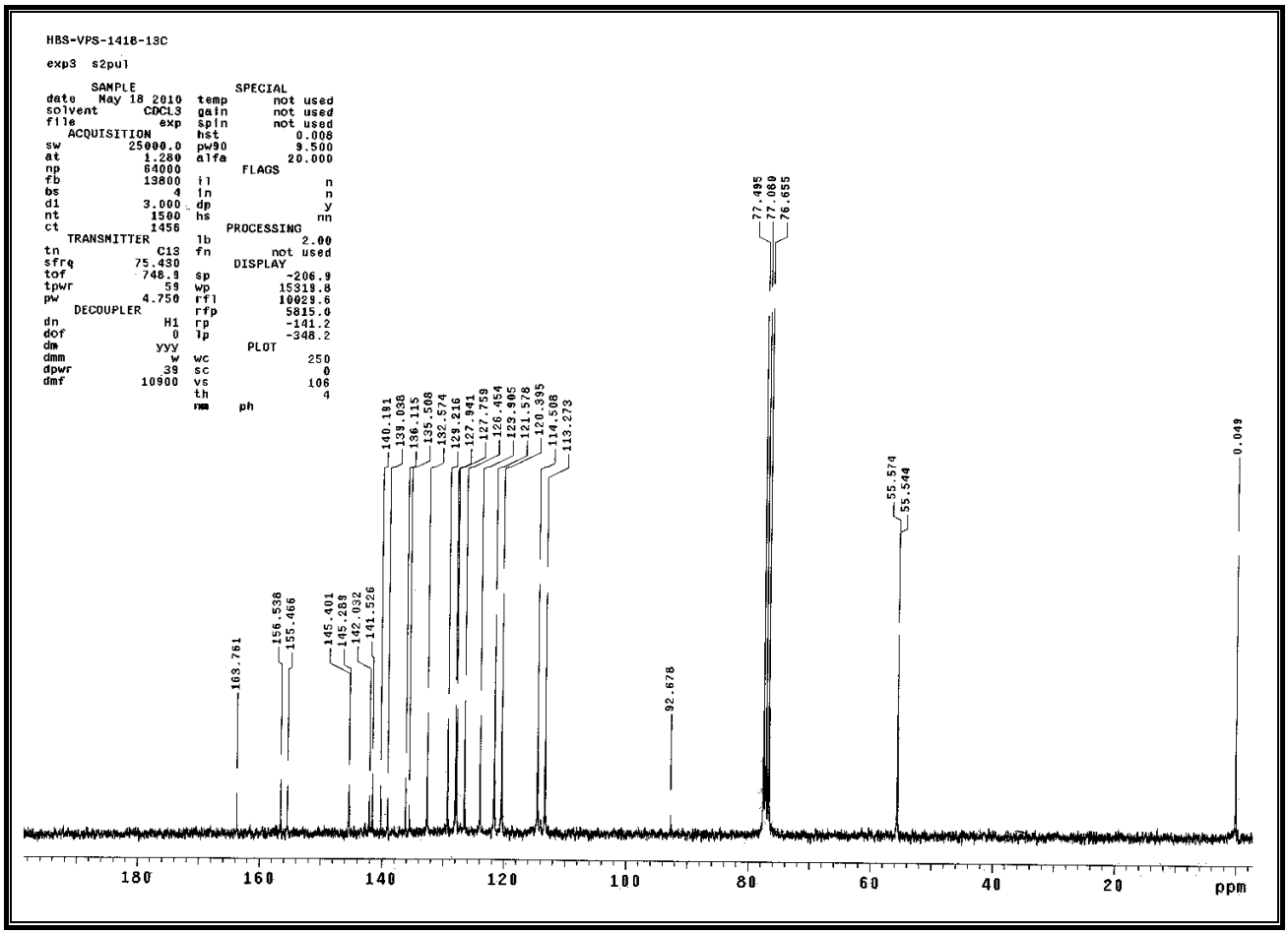


Figure S27. ^{13}C NMR spectrum of compound **16** in $CDCl_3$

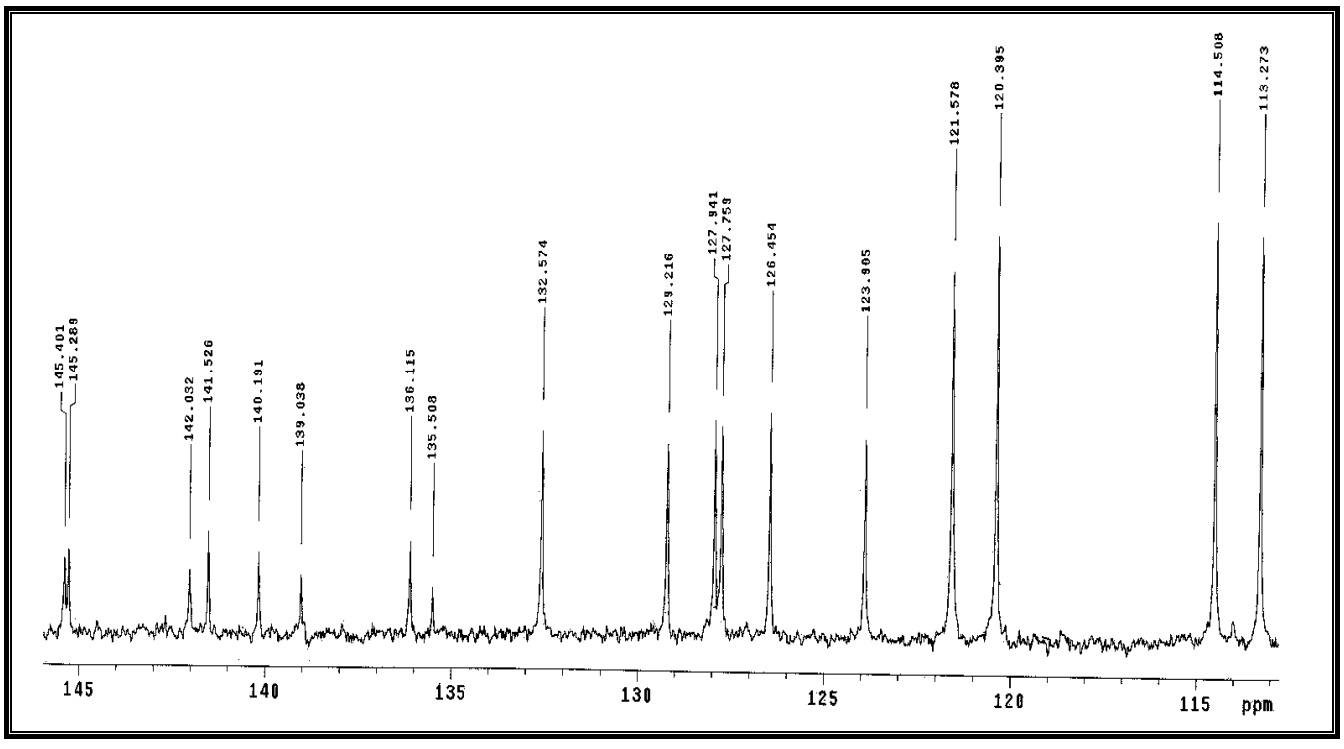


Figure S28. Expanded version of a part of the ^{13}C NMR spectrum of compound **16**

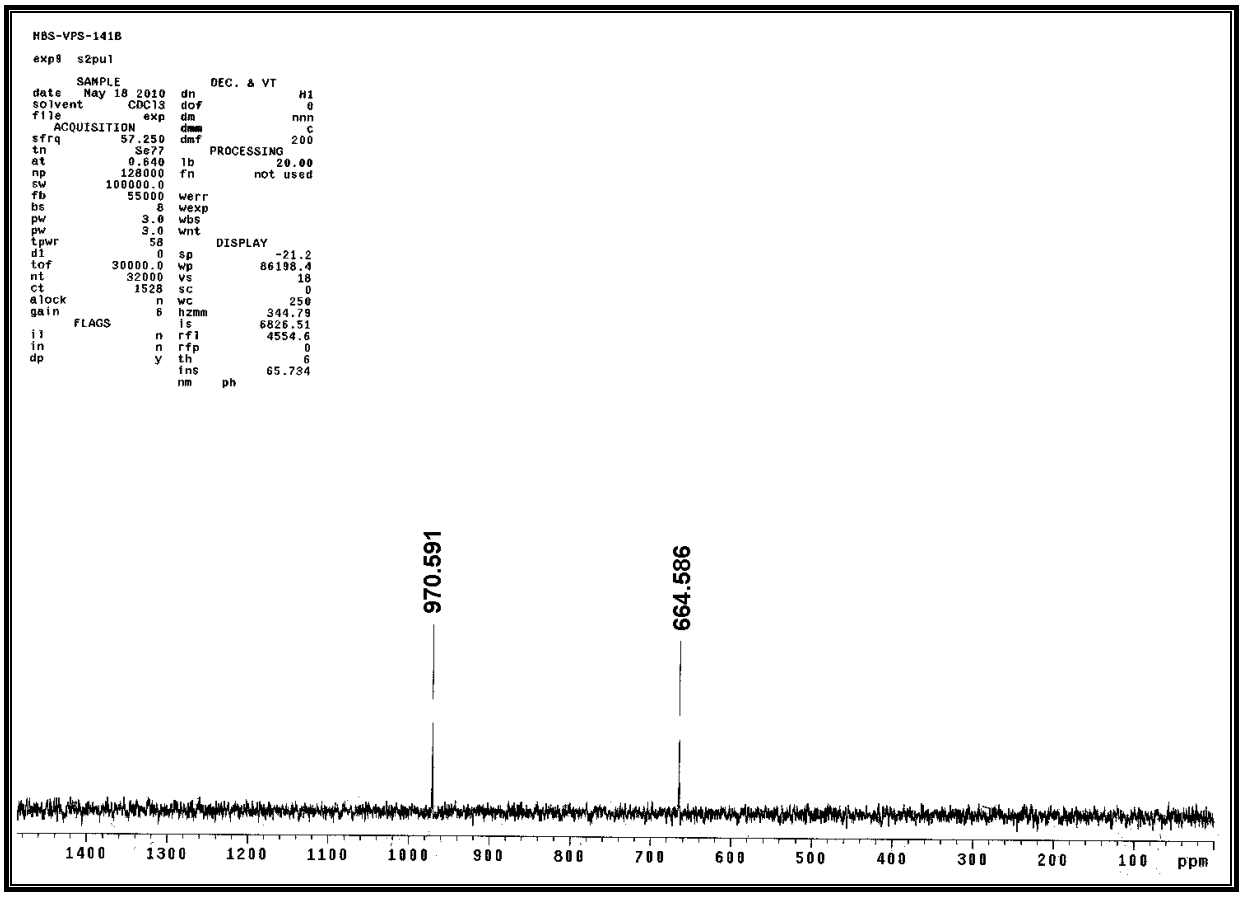


Figure S29. ^{77}Se NMR spectrum of compound **16** in $CDCl_3$

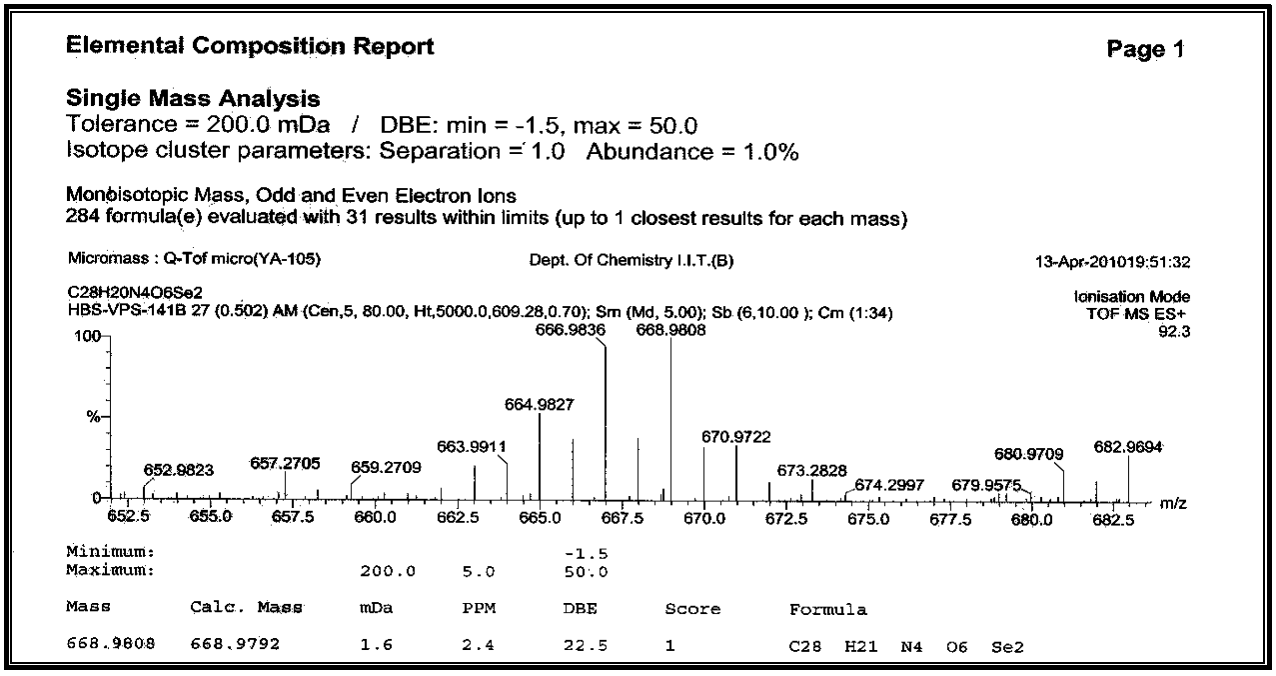


Figure S30. HRMS spectrum of compound **16**

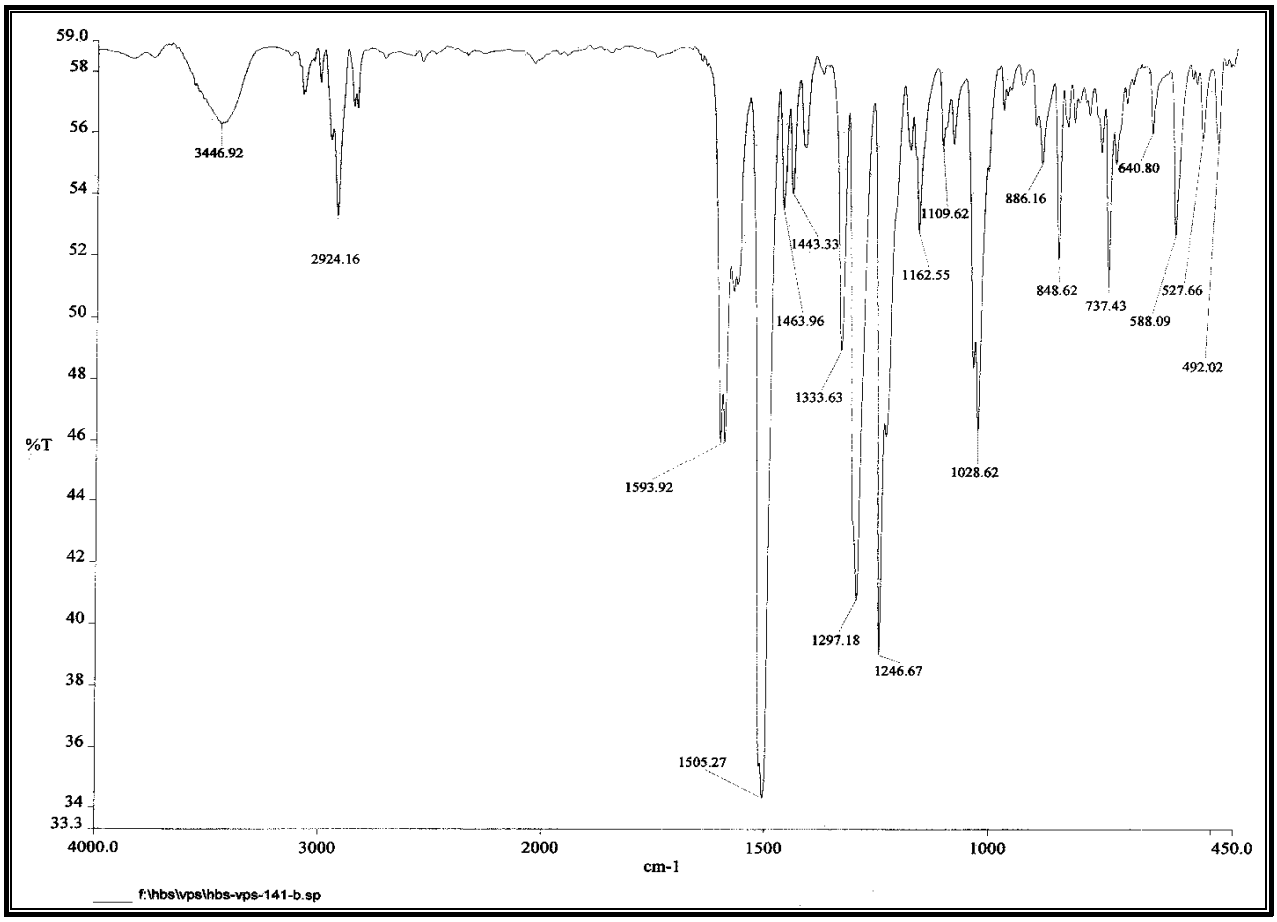


Figure S31. FT-IR spectrum of compound **16**

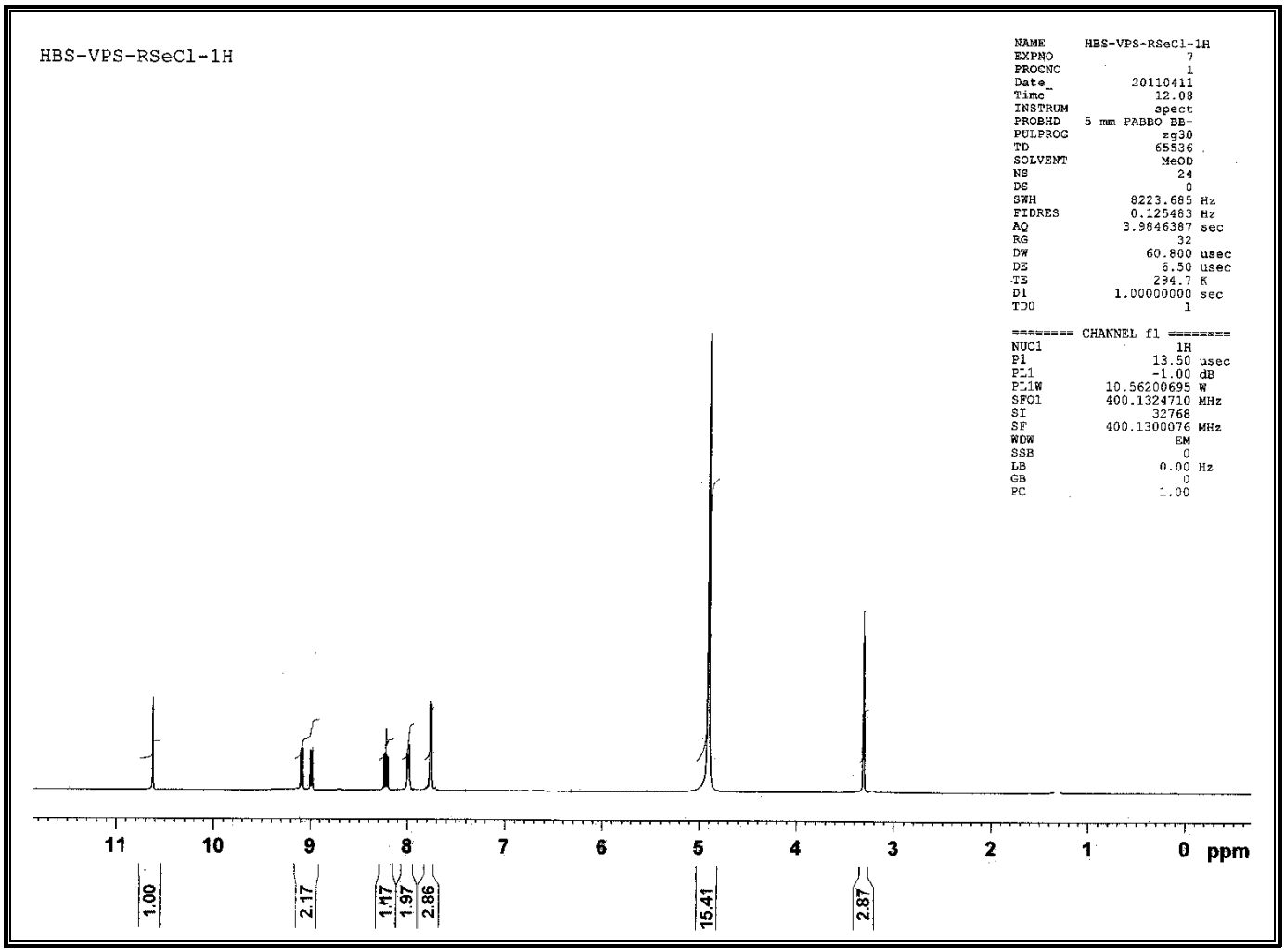


Figure S32. ^{1}H NMR spectrum of compound **18** in CD_3OD.

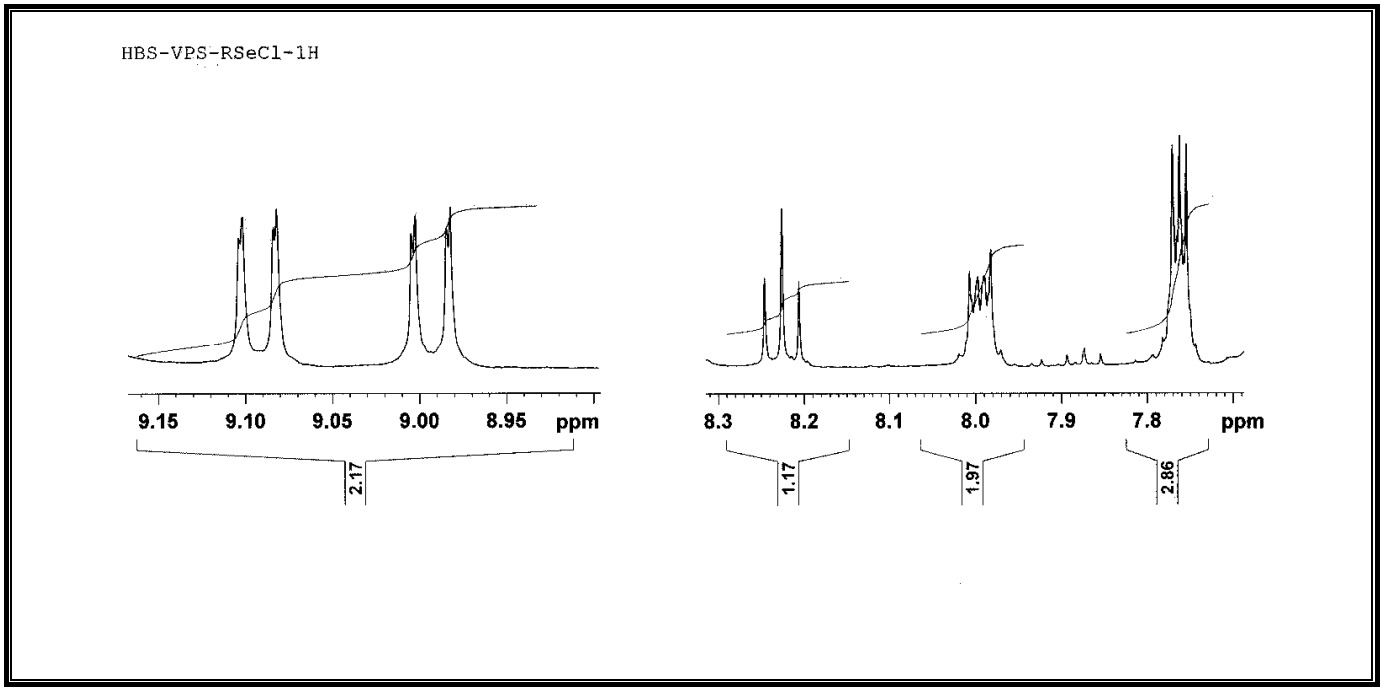


Figure S33. Expanded version of a part of the ^{1}H NMR spectrum of compound **18**

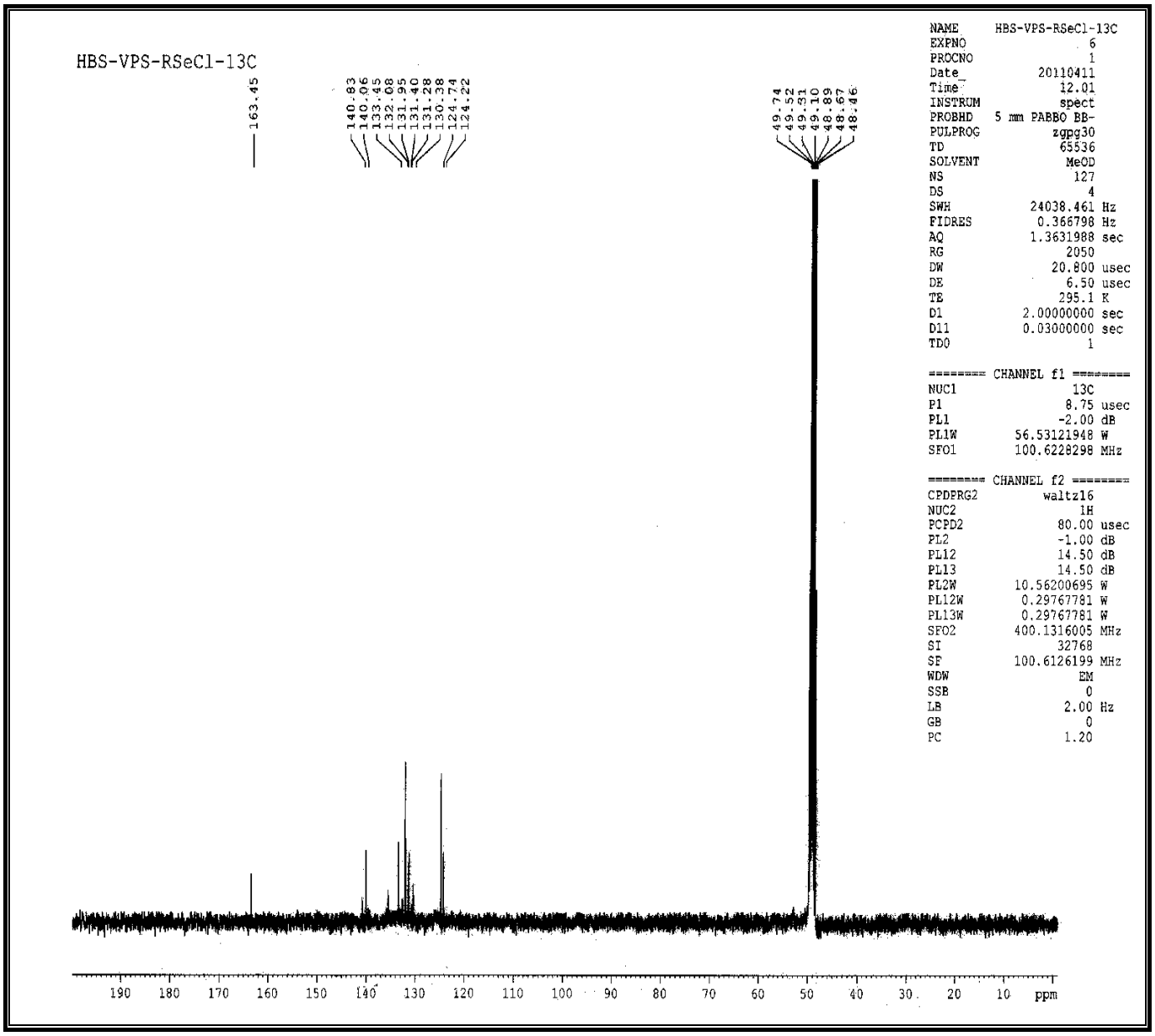


Figure S34. ^{13}C NMR spectrum of compound **18** in CD_3OD.

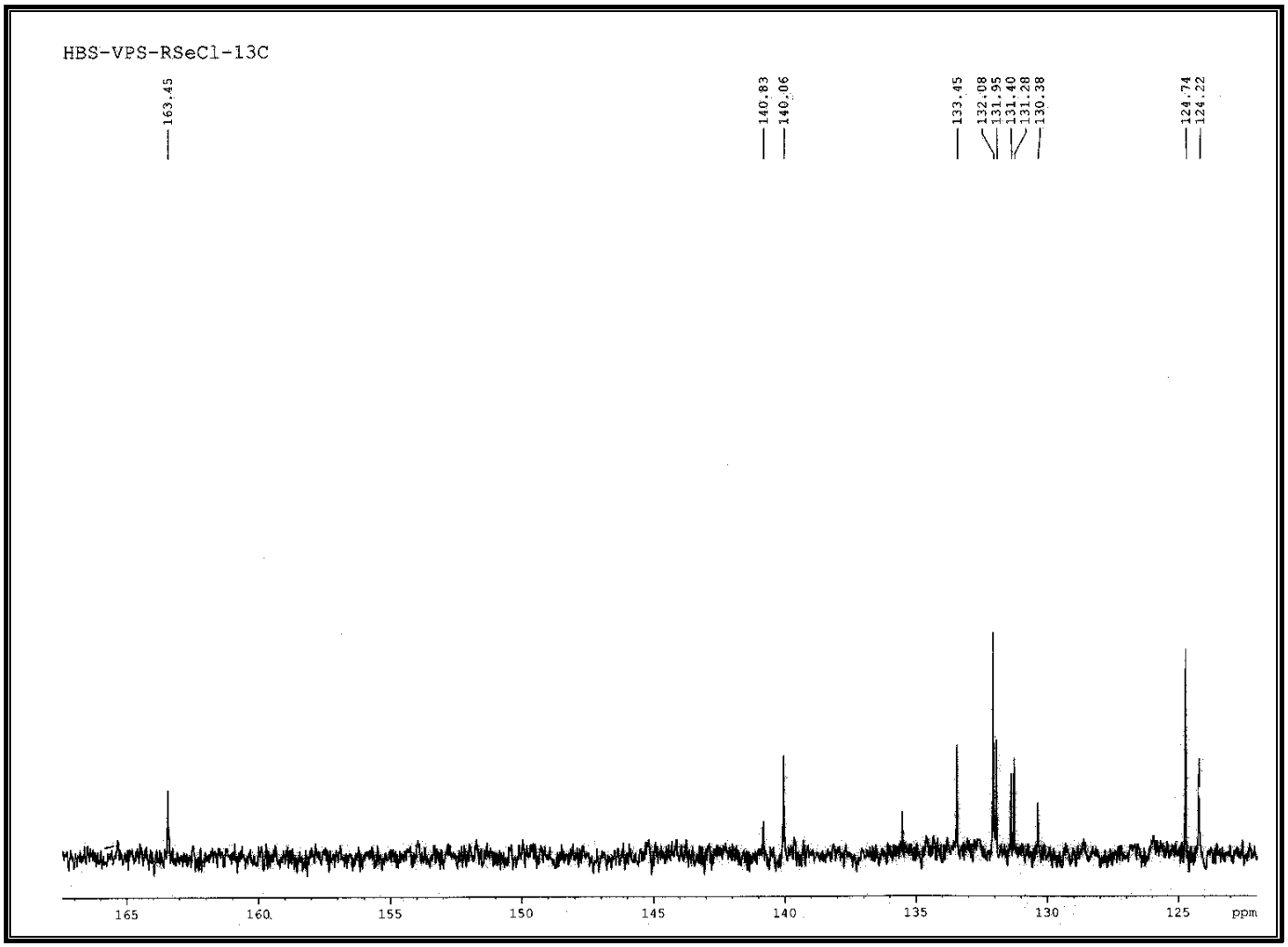


Figure S35. Expanded version of a part of the ^{13}C NMR spectrum of compound **18**

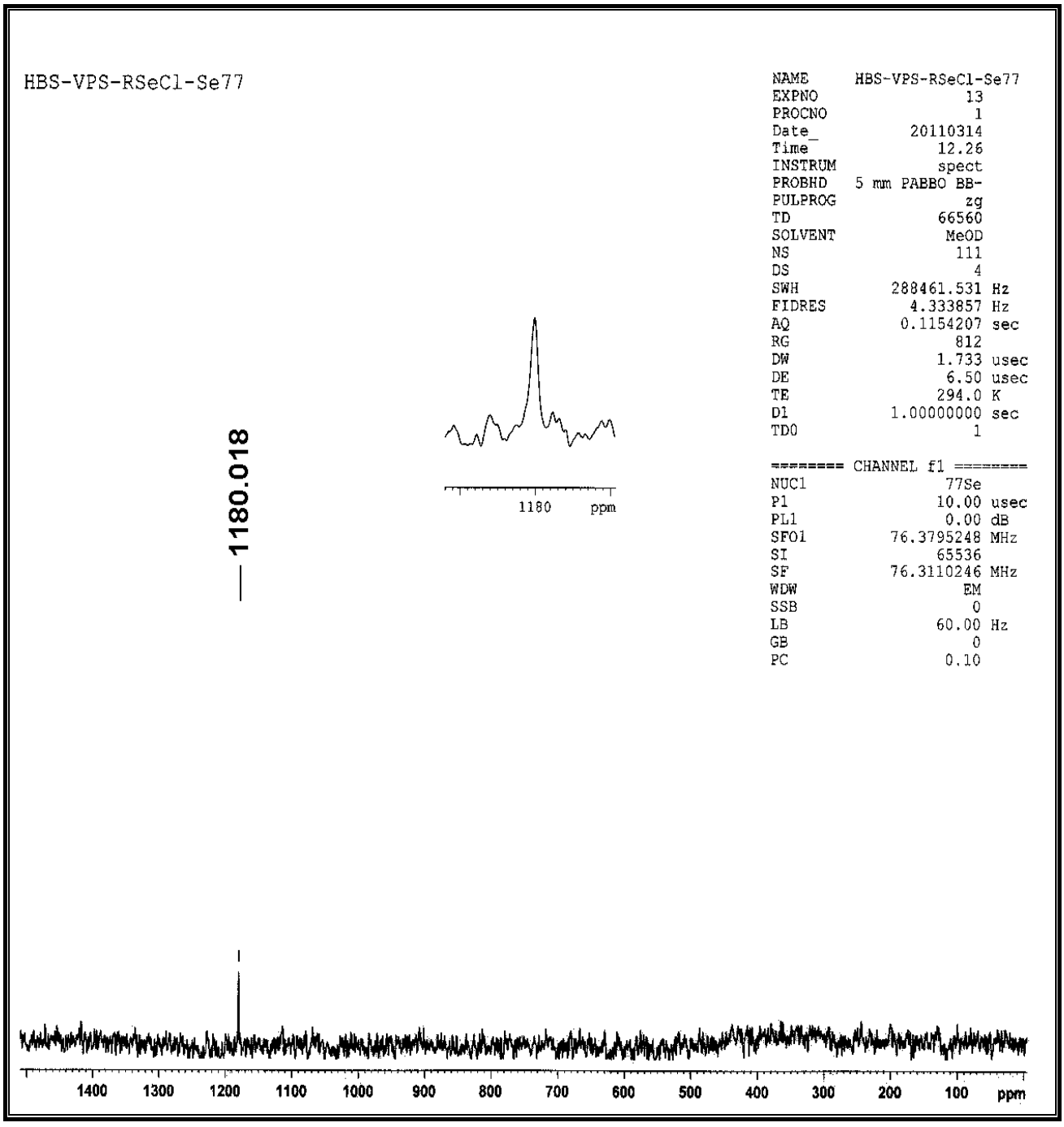


Figure S36. ^{77}Se NMR spectrum of compound **18** in CD_3OD

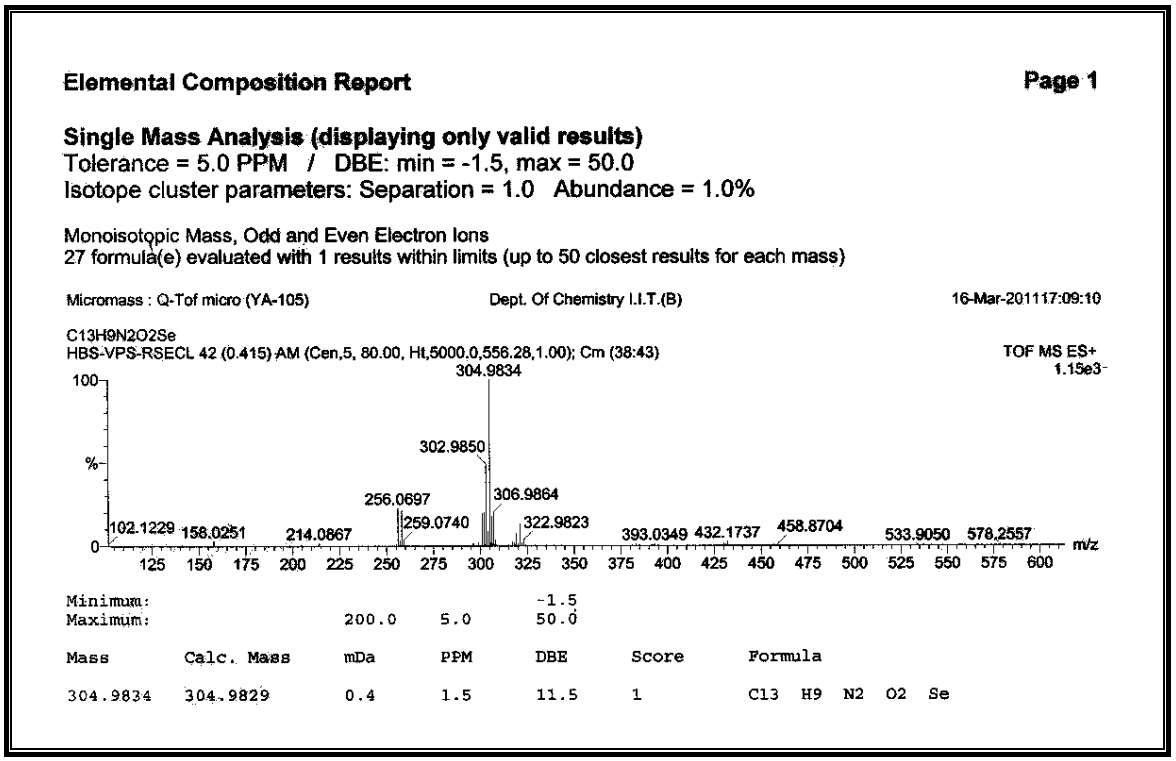


Figure S37. HRMS spectrum of compound **18**

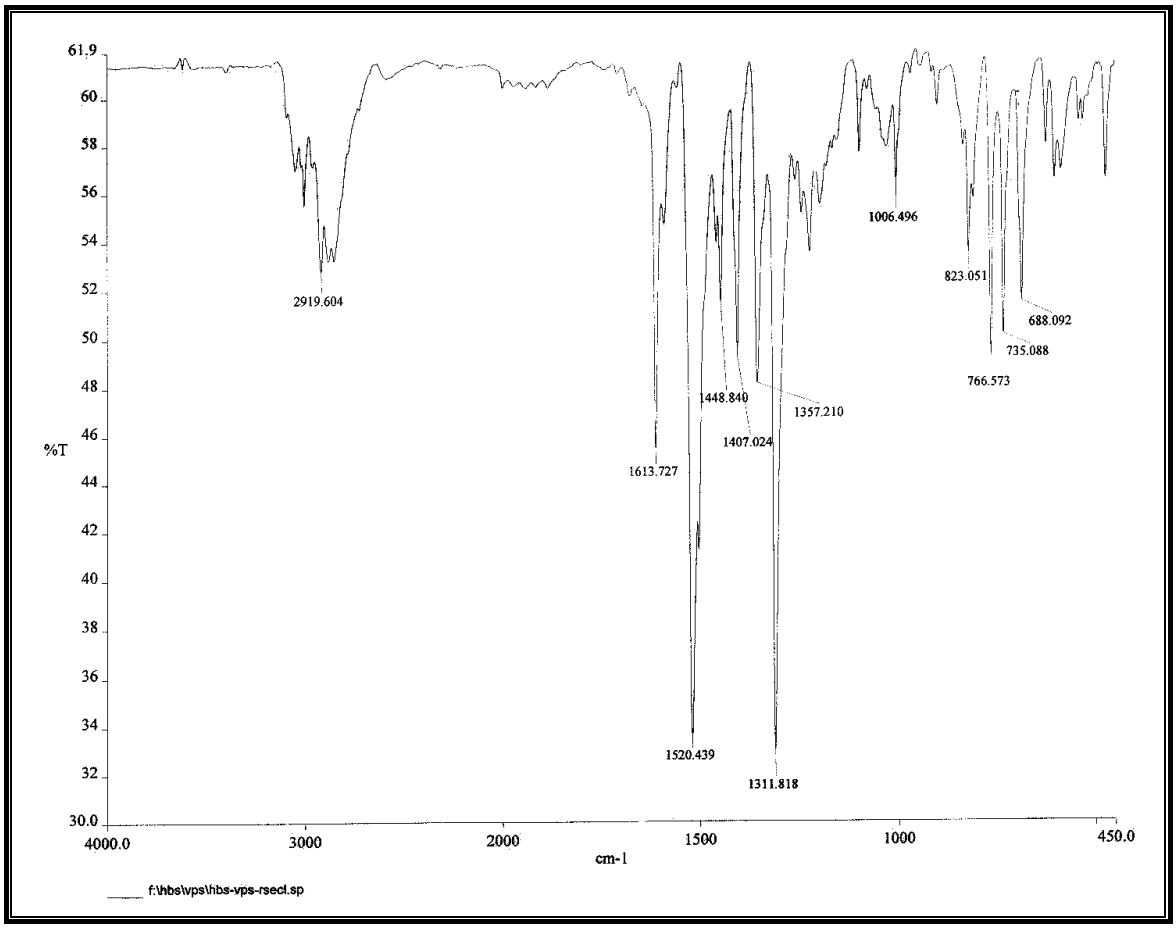


Figure S38. FT-IR spectrum of compound **18**

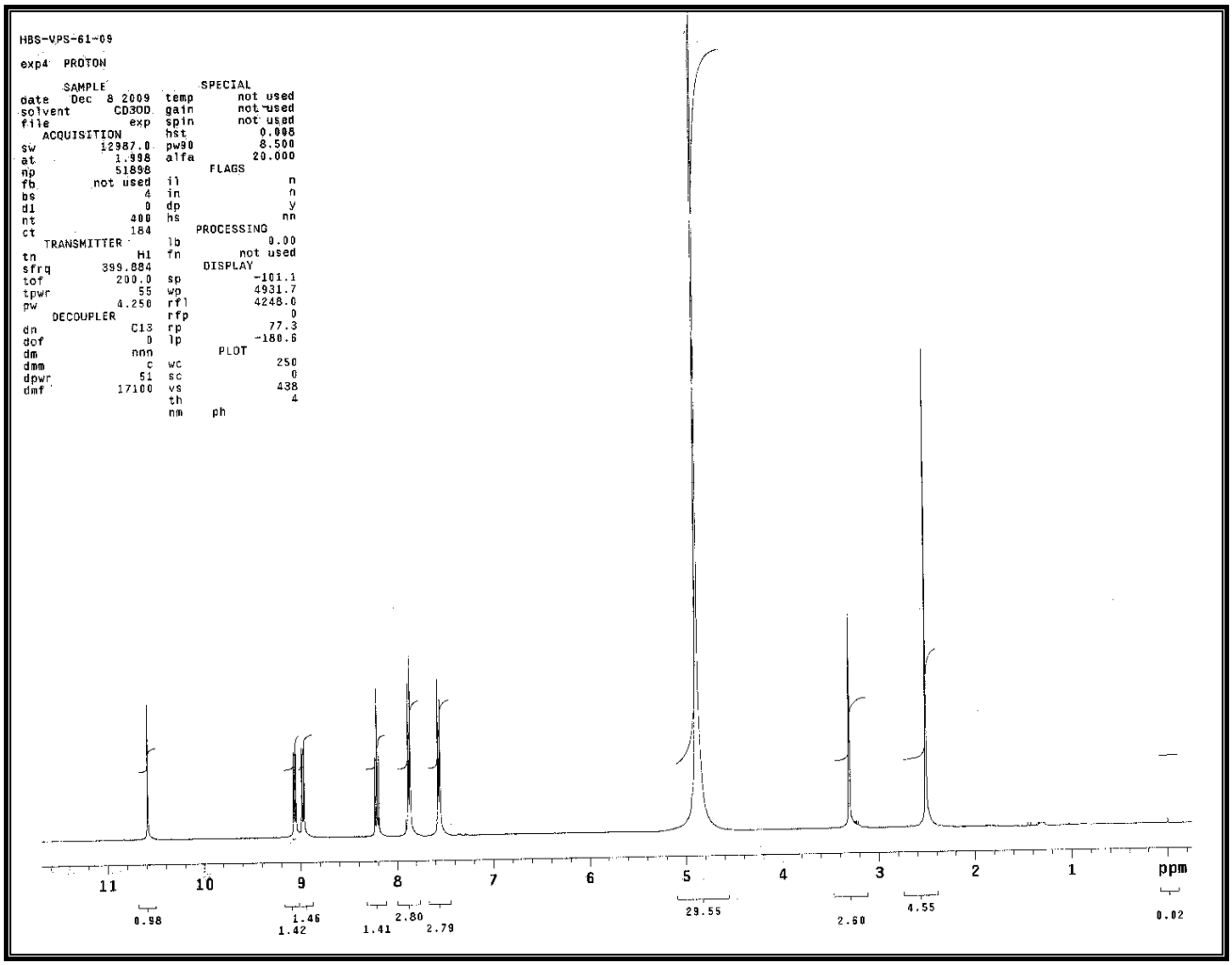


Figure S39. ^{1}H NMR spectrum of compound **19** in CD_3OD.

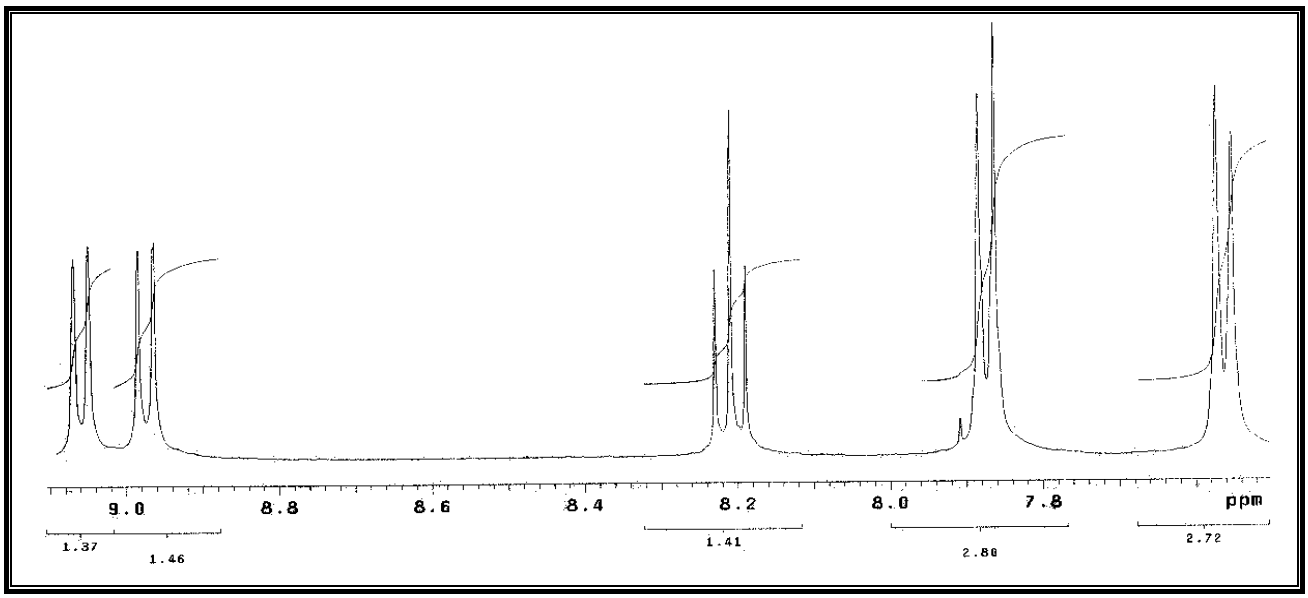


Figure S40. Expanded version of a part of the ^{1}H NMR spectrum of compound **19**

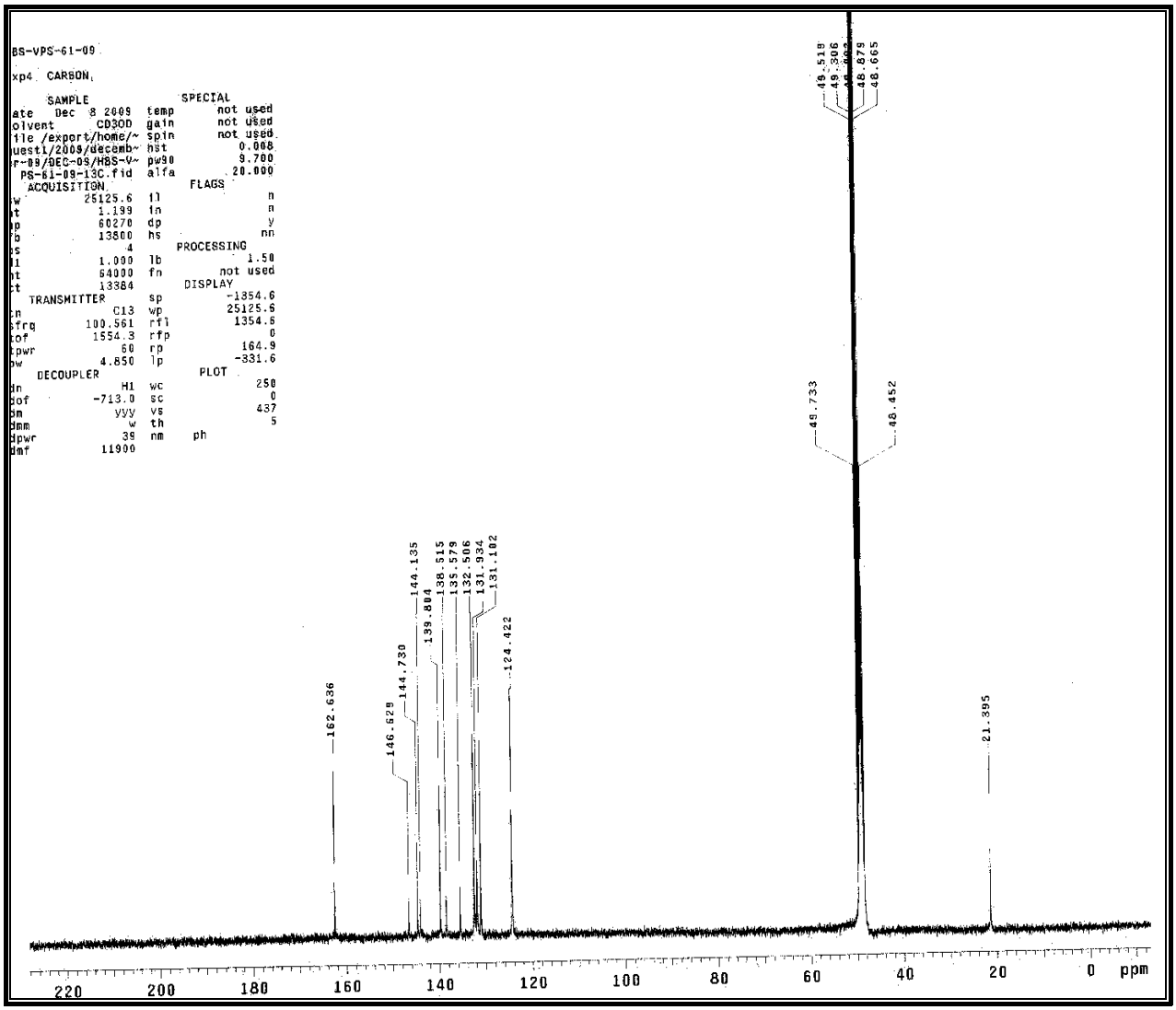


Figure S41. ^{13}C NMR spectrum of compound **19** in CD_3OD

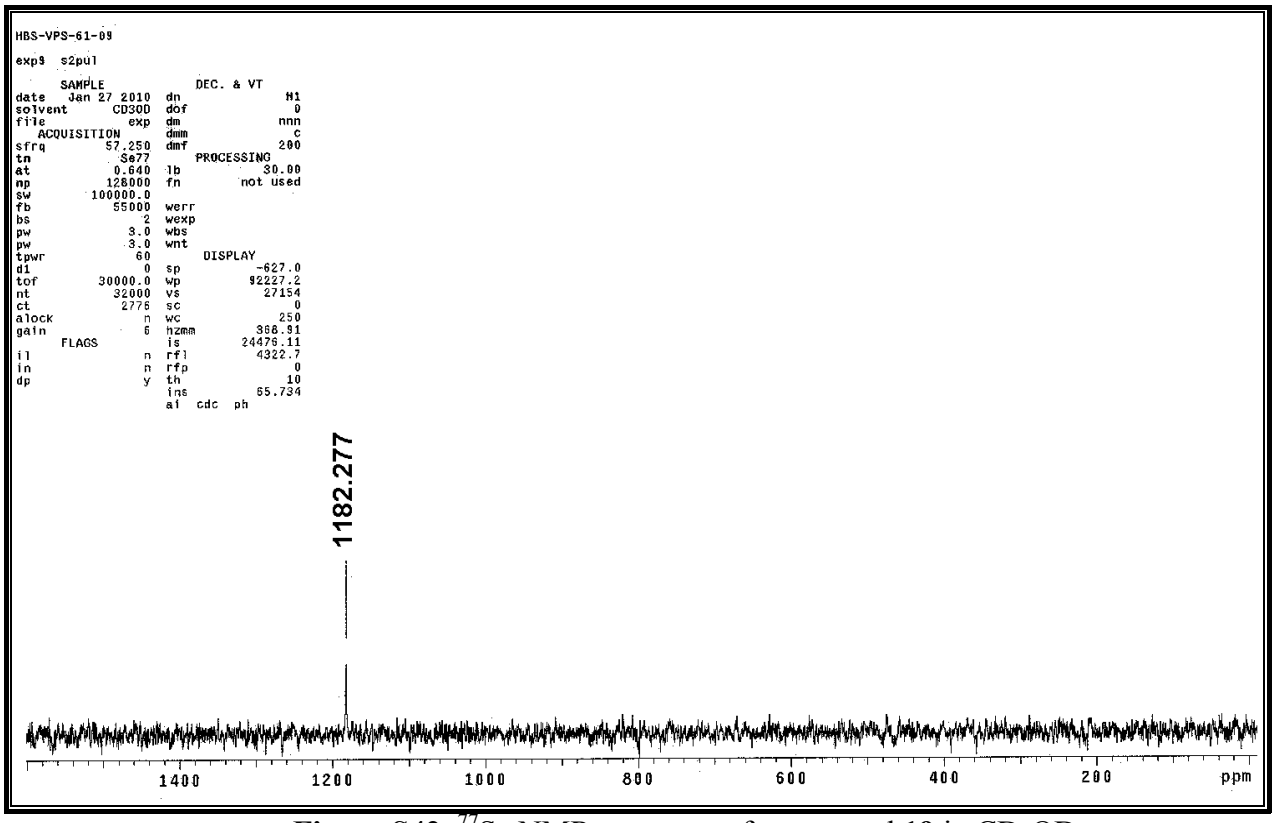


Figure S42. ^{77}Se NMR spectrum of compound **19** in CD_3OD

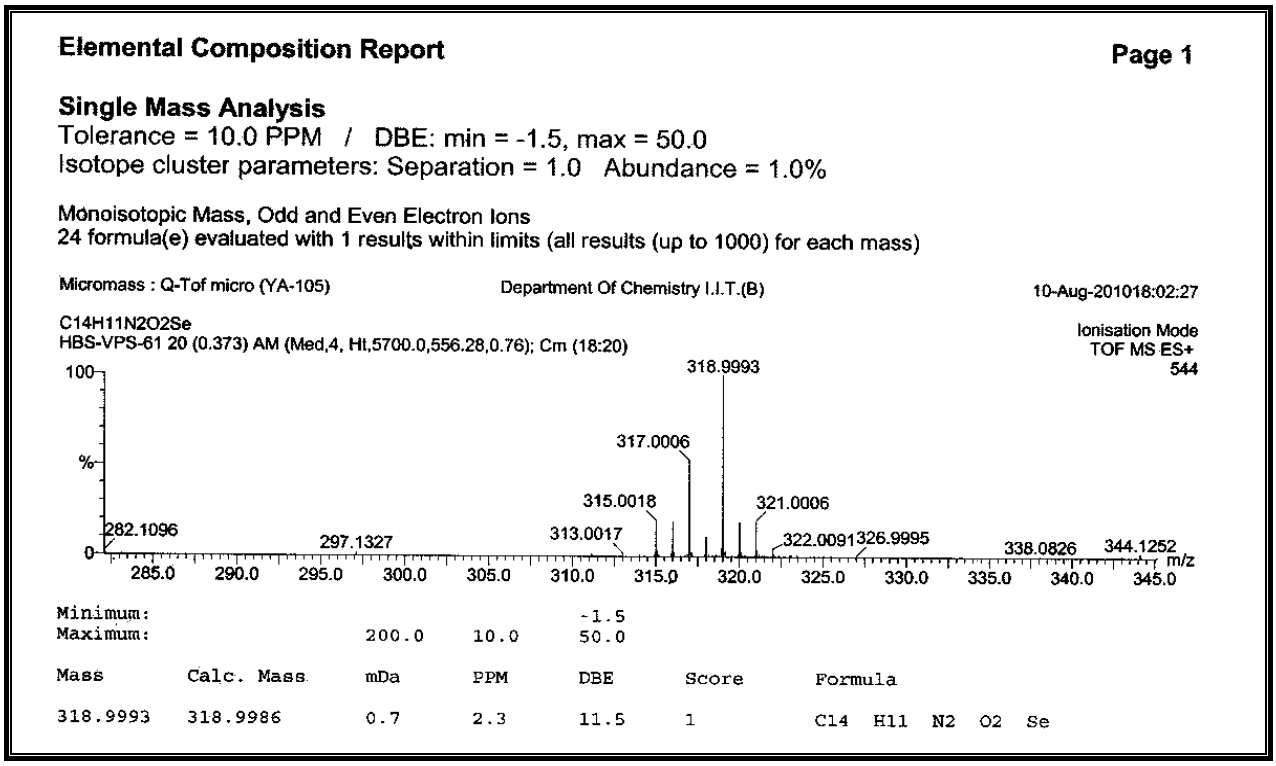


Figure S43. HRMS spectrum of compound **19**

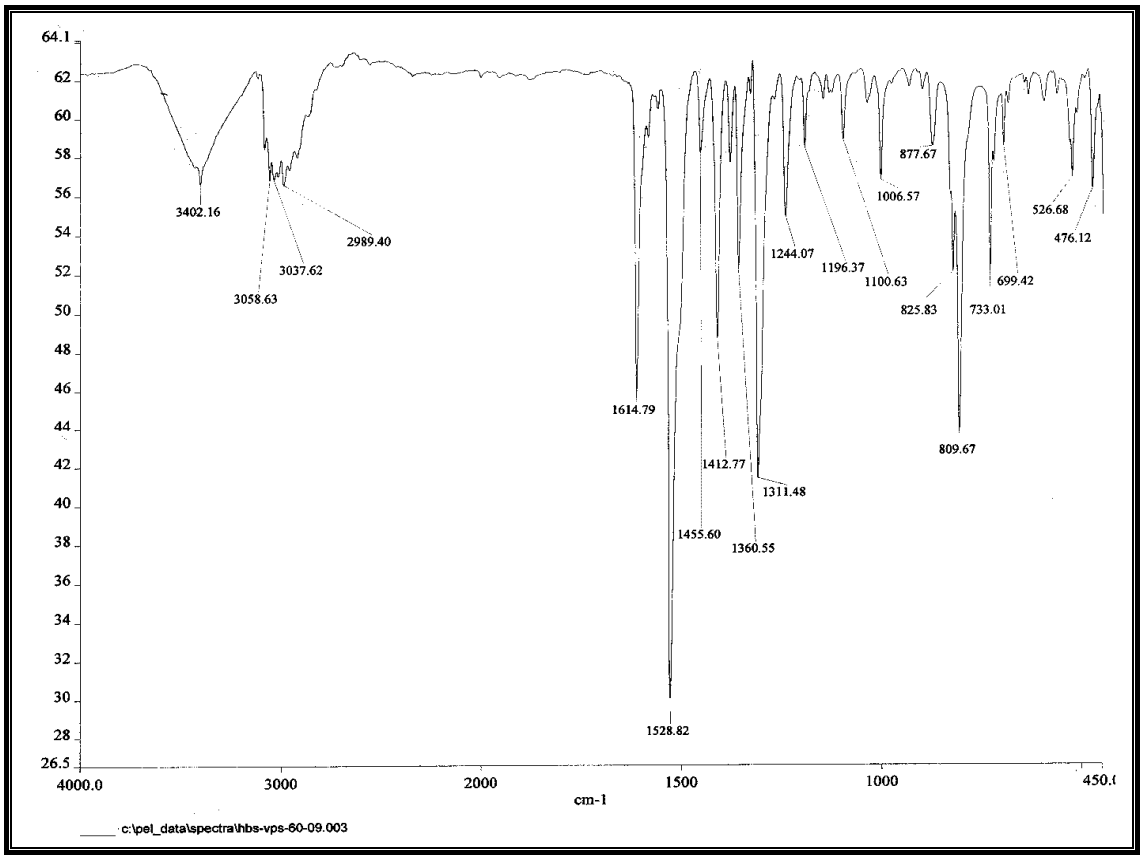


Figure S44. FT-IR spectrum of compound **19**

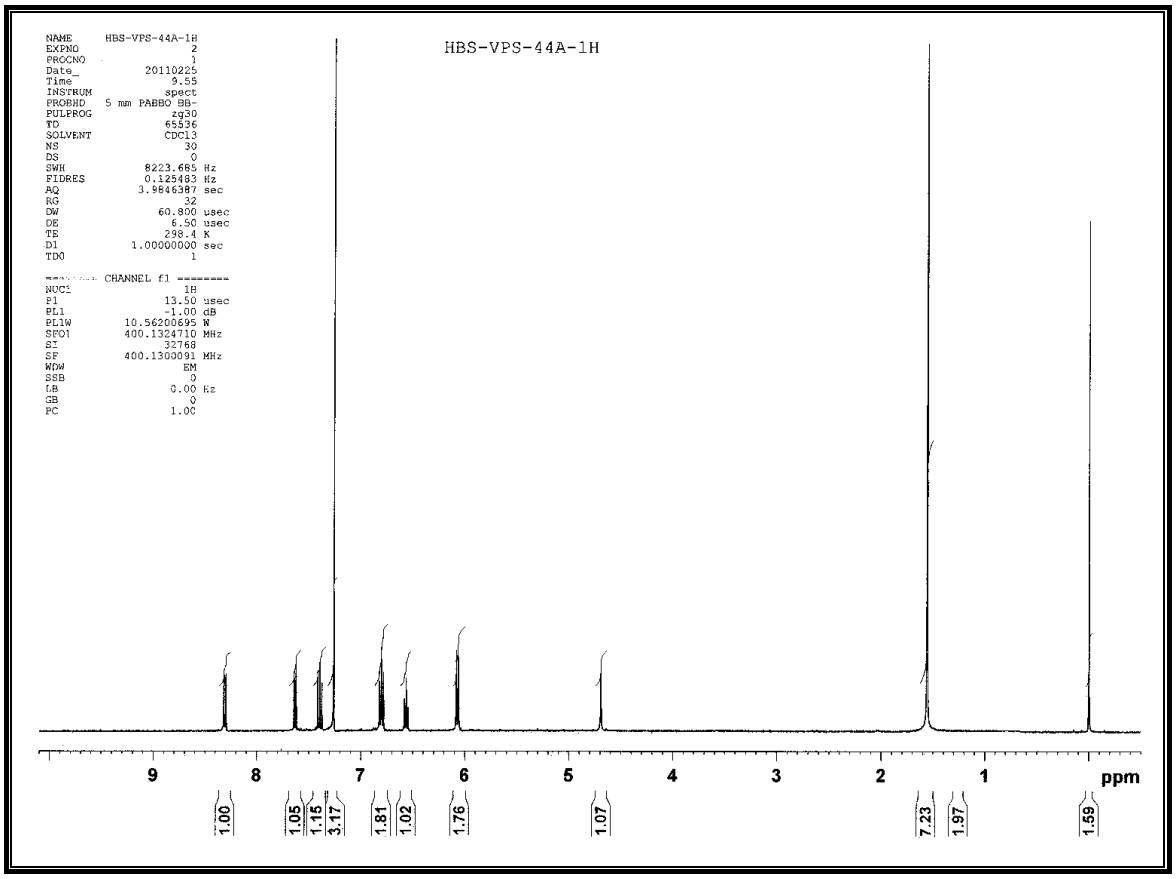


Figure S45. ^{1}H NMR spectrum of compound **20** in $CDCl_3$

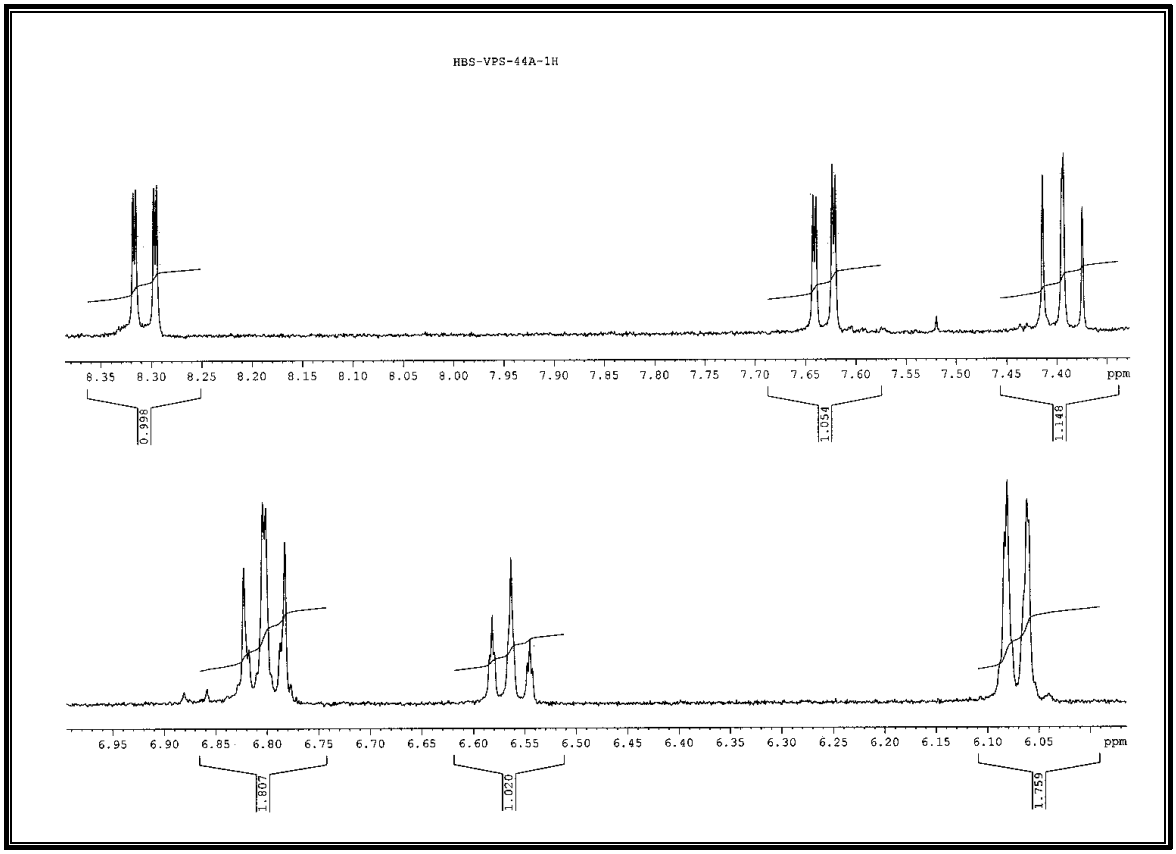


Figure S46. Expanded version of a part of the ^{1}H NMR spectrum of compound **20**

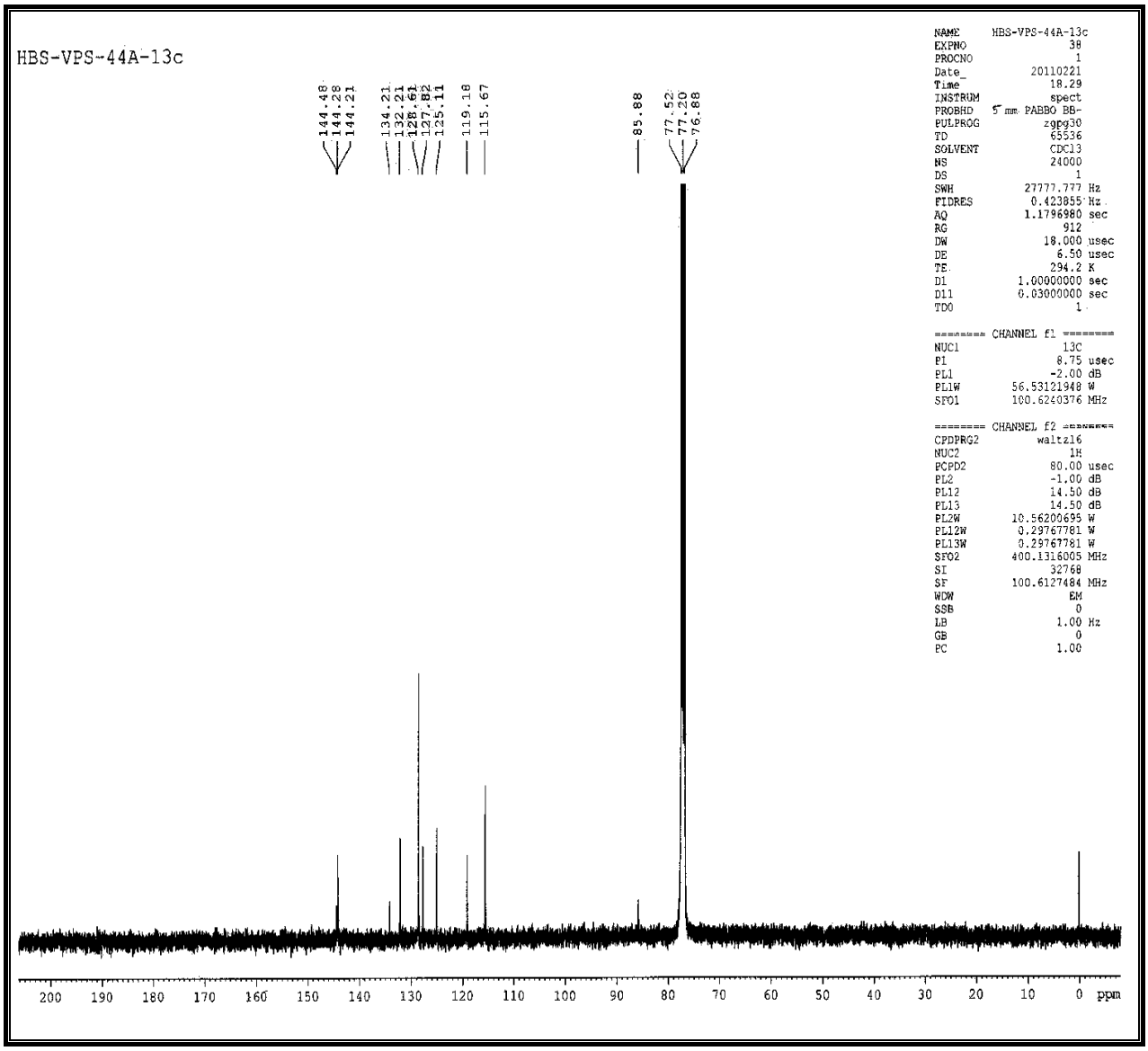


Figure S47. ^{13}C NMR spectrum of compound **20** in $CDCl_3$

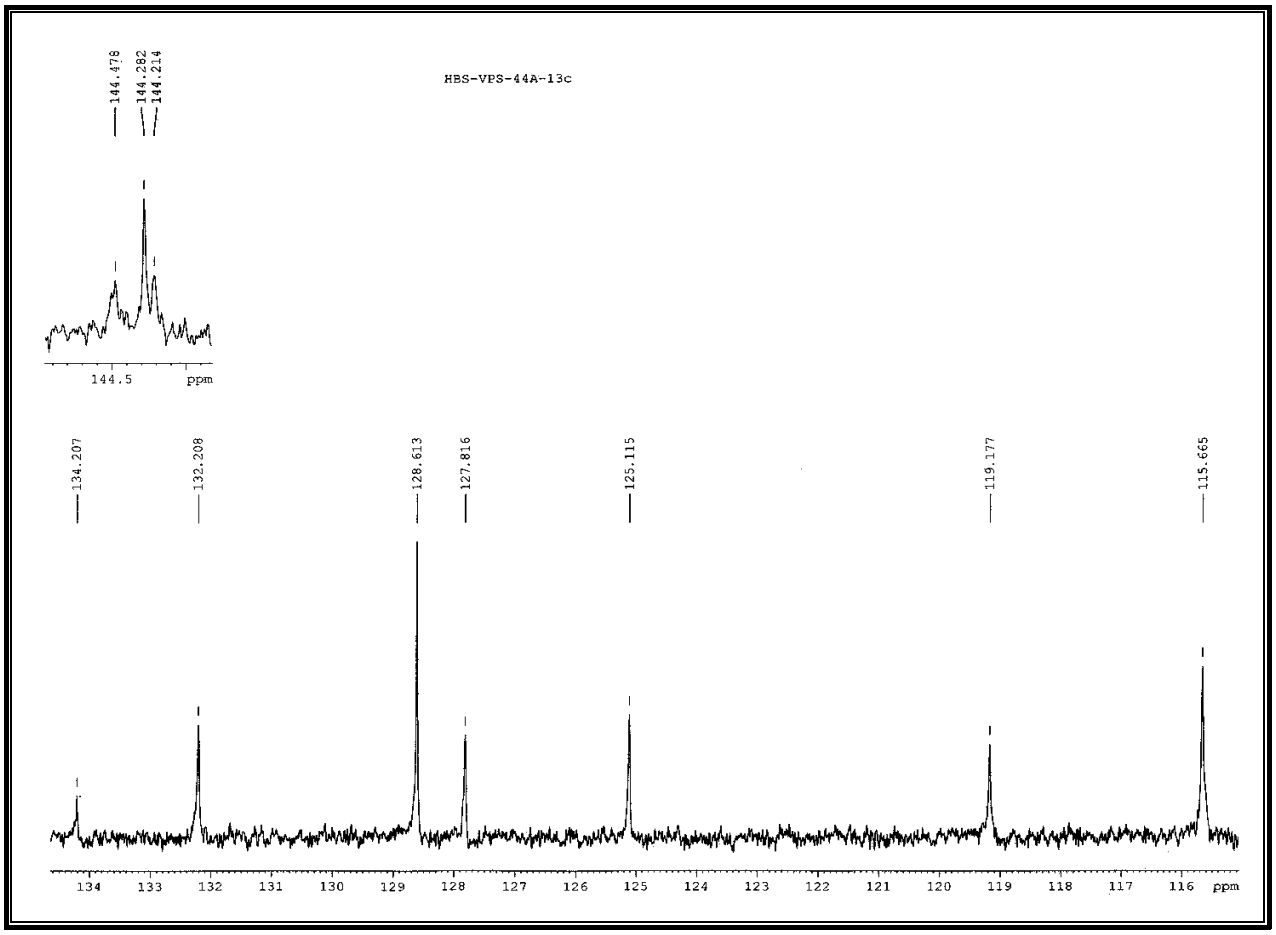


Figure S48. Expanded version of a part of the ^{13}C NMR spectrum of compound **20**

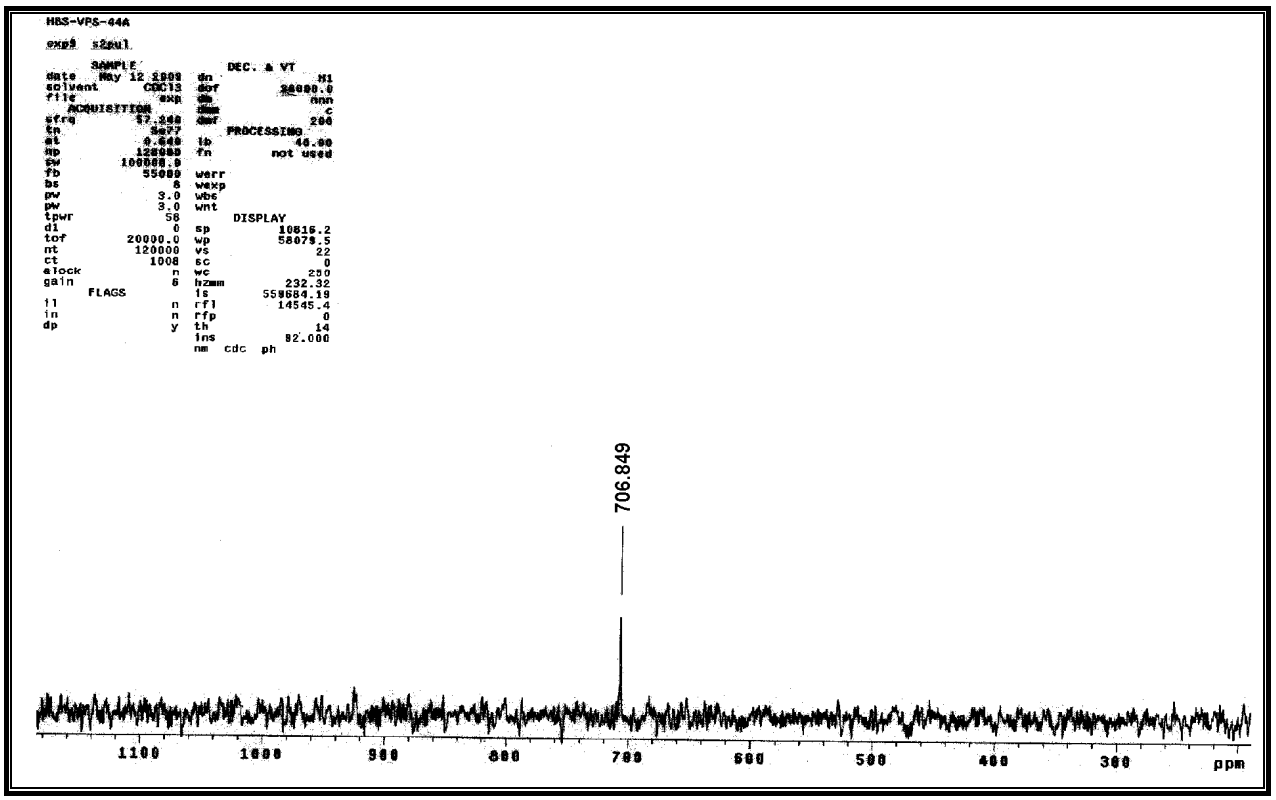


Figure S49. ^{77}Se NMR spectrum of compound **20**

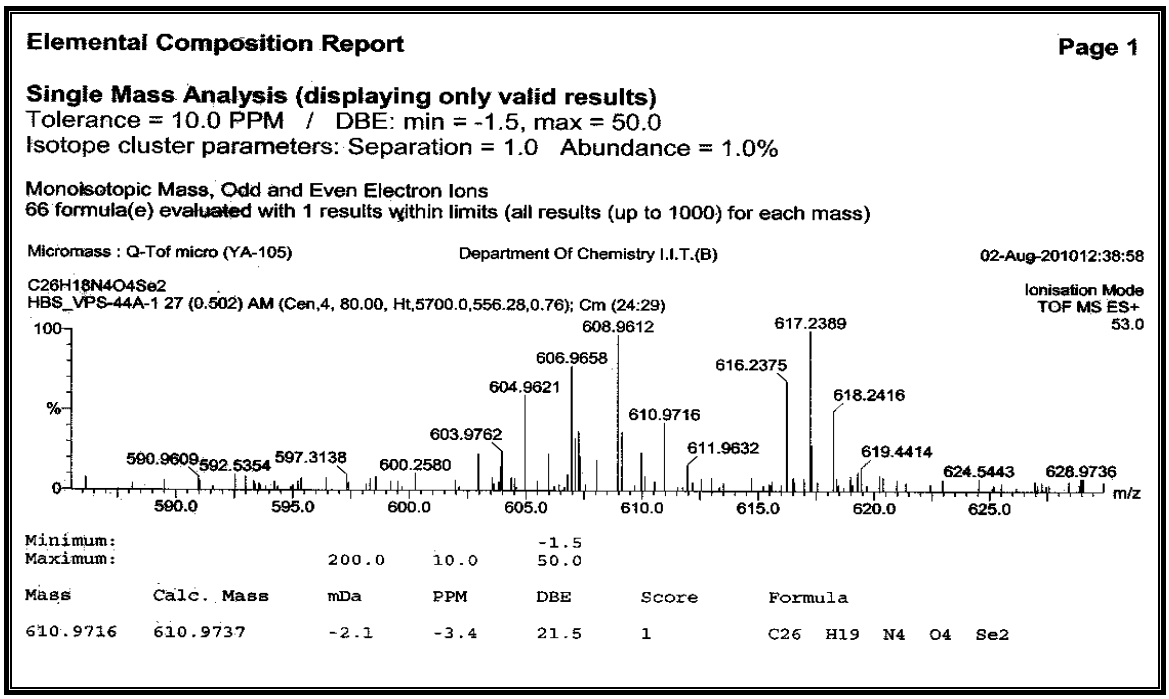


Figure S50. HRMS spectrum of compound **20**

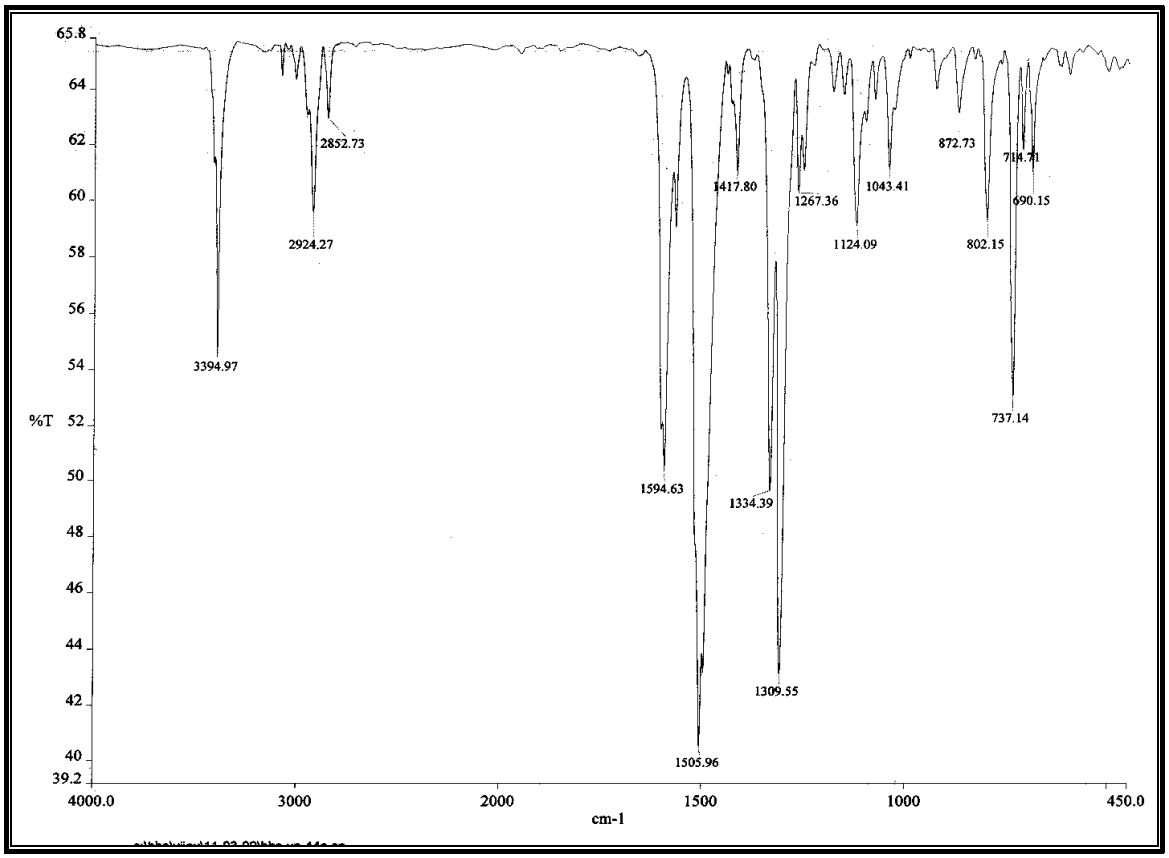


Figure S51. FT-IR spectrum of compound **20**

X-ray Crystallographic Analysis: X-ray crystallographic studies were carried out for compounds **15**, **19** and **20** on a Oxford Diffraction Gemini diffractometer using graphite-monochromatized Mo Kα radiation λ = 1.54184 Å. The diffraction measurements were performed at 295(2) K. The structures were solved by direct method and refined by a full-matrix least-squares procedure on F^2 for all reflections in SHELXL-97 software.[3] Hydrogen atoms were localized by geometrical means. A riding model was chosen for refinement. The isotropic thermal parameters of hydrogen atoms were fixed at 1.5 times for (CH_3 groups) or 1.2 times *U*(eq) (Ar-H) of the corresponding carbon atoms. CCDC-808889 (**19**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Molecular Structure of 19

The molecular structure of **19** is shown in Figure S51. Compound **19** was crystallized as a solvate with two water molecules during crystallization. The geometry around the selenium atom is T-shaped with a O1···Se─N2 angle of 157.00(11)°. The Se─N2 distance [1.919(3) Å] is slightly greater than the sum of the Pauling covalent radii (1.87 Å) of these two atoms.[4] The Se─N distance is nearly same as reported for the selenenium cations with bromide (1.895(0) Å) and tribromide (1.899(2) Å) as counteranions.[5] The Se···O1 distance [2.486(3) Å] is slightly smaller than that reported for the selenenium cations with bromide (2.544(2) Å) and tribromide (2.521(3) Å) as counteranions significantly. The Se─Br distance [3.608 (0) Å] is also greater than the sum of single bond covalent radii of Se─Br [2.31 Å].

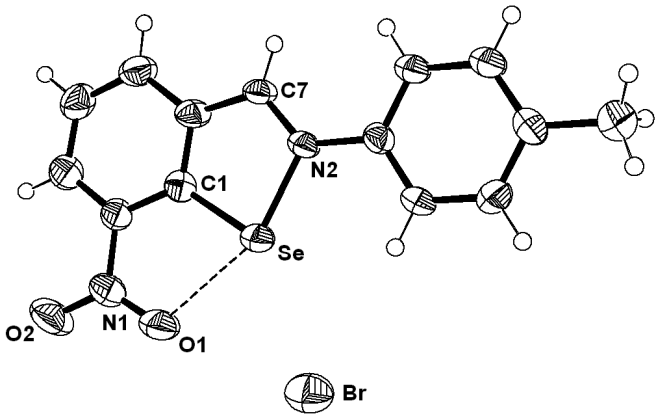


Figure S52. Molecular structure of **19**. Water molecules are omitted for clarity. Thermal ellipsoids are set at 50 % probability. Significant bond lengths [Å] and angles [°]: Se···O1 2.486(3); Se─N2 1.919(3); Se─C1 1.845(4); Se─Br 3.608(0); O1···Se─N2 157.00(11); C1─Se─N2 84.25(15); C7─N2─Se 112.8(3); O1···Se─C1 72.76(14).

Table S1. Crystal Data and Structure Refinement for **19**

Compound	**19**
Empirical formula	$C_{14}H_{15}BrN_2O_4Se$
Formula weight	434.15
Crystal system	Monoclinic
Space group	*C* 1 2 / *c* 1
a(Å)	27.179(2)
b(Å)	7.5043(5)
c(Å)	17.8594(15)
α(deg)	90
β(deg)	119.584(11)
γ(deg)	90
V(Å^3)	3167.7(4)
Z	8
D(calcd)(Mg/m^3)	1.821
Abs coeff(mm^{-1})	4.912
Obsd reflens [I<2σ]	9545
Final R(F) [I<2σ(I)][a]	0.0429
wR(F^2) indices[I<2σ(I)]	0.0822
Data/restrain/parameters	3225 / 6 / 203
Goodness of fit on F^2	0.845

[a]Definitions: $R(F_o) = ||F_o| - |F_c||/|F_o|$ and $wR(F_o^2) = \{\Sigma[w(F_o^2 - F_c^2)^2]/ [w(F_c^2)^2]\}^{1/2}$.

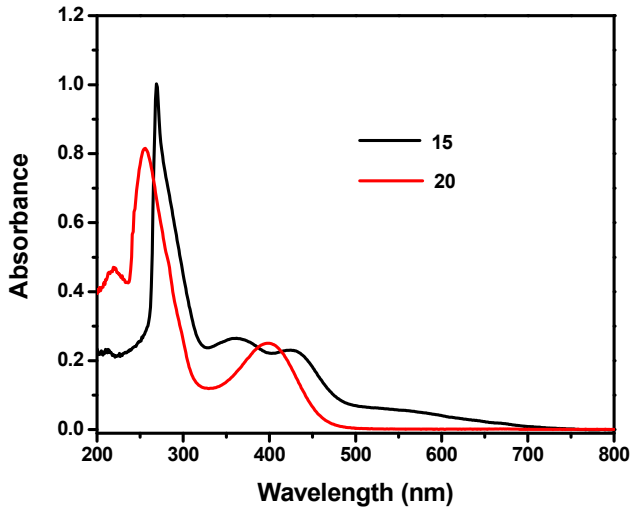


Figure S53. Absorption spectra of **15** and **20** in dilute $CHCl_3$ solution (10^{-5} M).

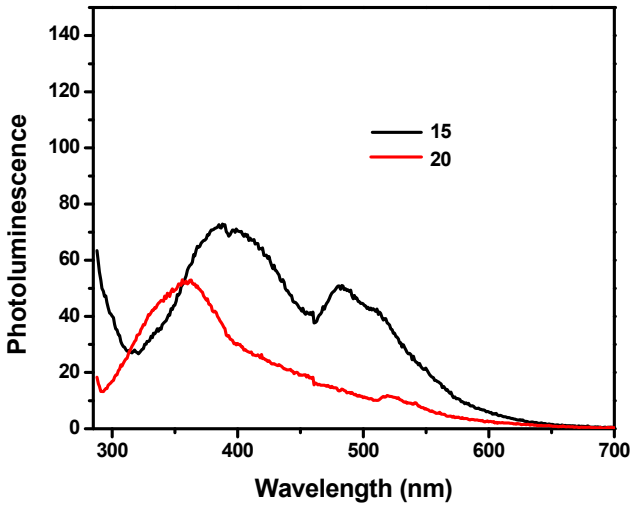


Figure S54. Photoluminescence spectra of **15** and **20** in dilute $CHCl_3$ solution (10^{-5} M) excited at 270 nm.

Table S2. UV-Vis and emission data for compounds **15**, **16** and **20**.

	λ_{abs} Absorption (nm)	λ_{exc} ε ($M^{-1}cm^{-1}$)	Excitation (nm)	Φ
15	270	99930	270	0.006
	360	26040		
	427	23020		
16	270	99360	270	0.02
	360	38730		
	427	28590		
20	257	81610	270	0.002
	400	24780		

λ_{abs} = Wavelength of absorption, λ_{exc} = Wavelength of excitation, ε = Molar extinction coefficient, Φ = Quantum yield calculated using 9-hydroxymethylanthracene as a standard.

References

1. L. K. A. Rahman and R. M. Scrowston, *J. Chem. Soc. Perkin. Trans. I*, **1984,** 385-390.

2. D. D. Perrin and W. L. F. Armarego, "Purification of Laboratory Chemicals", Pergamon Press, 4th Edition, 1996.

3. G. M. Sheldrick, *SHELXL-97,* Program for Crystal Structure Determination, University of Göttingen, Germany, 1997.

4. L. Pauling, in *The Nature of the Chemical Bond*, 3rd edn., Cornell University Press, Ithaca, New York, **1960**.

CheckCIF/PLATON report for compound 15

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Please wait while processing .... Interpreting this report

Datablock: 15

Bond precision: C-C = 0.0066 A Wavelength=1.54184

Cell: a=10.5321(8) b=10.6562(7) c=14.6081(11)
alpha=99.386(6) beta=94.285(6) gamma=111.122(7)

Temperature: 295 K

	Calculated	Reported
Volume	1492.9(2)	1492.92(19)
Space group	P -1	P -1
Hall group	-P 1	?
Moiety formula	C28 H20 N4 O4 Se2, 0.56(C H Cl3), 0.44(C Cl3), 0.44(H)	?
Sum formula	C29 H21 Cl3 N4 O4 Se2	C29 H21 Cl3 N4 O4 Se2
Mr	753.89	753.77
Dx,g cm-3	1.677	1.677
Z	2	2
Mu (mm-1)	5.930	5.928
F000	748.0	748.0
F000'	748.74	
h,k,lmax	13,13,18	13,13,18
Nref	6315	6196
Tmin,Tmax	0.124,0.202	0.502,1.000
Tmin'	0.044	

Correction method= MULTI-SCAN

Data completeness= 0.981 Theta(max)= 77.080

R(reflections)= 0.0592(5563) wR2(reflections)= 0.1673(6196)

S = 1.045 Npar= 395

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

PLAT327_ALERT_2_B Check for Possibly Missing H on sp3? Carbon .... <C2S

Alert level C

PLAT341_ALERT_3_C Low Bond Precision on C-C Bonds (x 1000) Ang .. 7

Alert level G

PLAT002_ALERT_2_G Number of Distance or Angle Restraints on AtSite 8
PLAT003_ALERT_2_G Number of Uiso or Uij Restrained Atom Sites 3
PLAT244_ALERT_4_G Low 'Solvent' Ueq as Compared to Neighbors of C1S
PLAT244_ALERT_4_G Low 'Solvent' Ueq as Compared to Neighbors of C2S
PLAT302_ALERT_4_G Note: Anion/Solvent Disorder ..... 100 Perc.
PLAT432_ALERT_2_G Short Inter X...Y Contact Cl1S .. C5B .. 3.04 Ang.
PLAT432_ALERT_2_G Short Inter X...Y Contact O2B .. C1S .. 3.00 Ang.
PLAT720_ALERT_4_G Number of Unusual/Non-Standard Labels 10
PLAT790_ALERT_4_G Centre of Gravity not Within Unit Cell: Resd. # 2
C H Cl3

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PLAT790_ALERT_4_G Centre of Gravity not Within Unit Cell: Resd.  #          3
               C Cl3
PLAT790_ALERT_4_G Centre of Gravity not Within Unit Cell: Resd.  #          4
               H
PLAT793_ALERT_4_G The Model has Chirality at C7A     (Verify) ....          R
PLAT860_ALERT_3_G Note: Number of Least-Squares Restraints .......         30
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   1 ALERT level B = A potentially serious problem, consider carefully
   1 ALERT level C = Check. Ensure it is not caused by an omission or oversight
  13 ALERT level G = General information/check it is not something unexpected

   0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   5 ALERT type 2 Indicator that the structure model may be wrong or deficient
   2 ALERT type 3 Indicator that the structure quality may be low
   8 ALERT type 4 Improvement, methodology, query or suggestion
   0 ALERT type 5 Informative message, check
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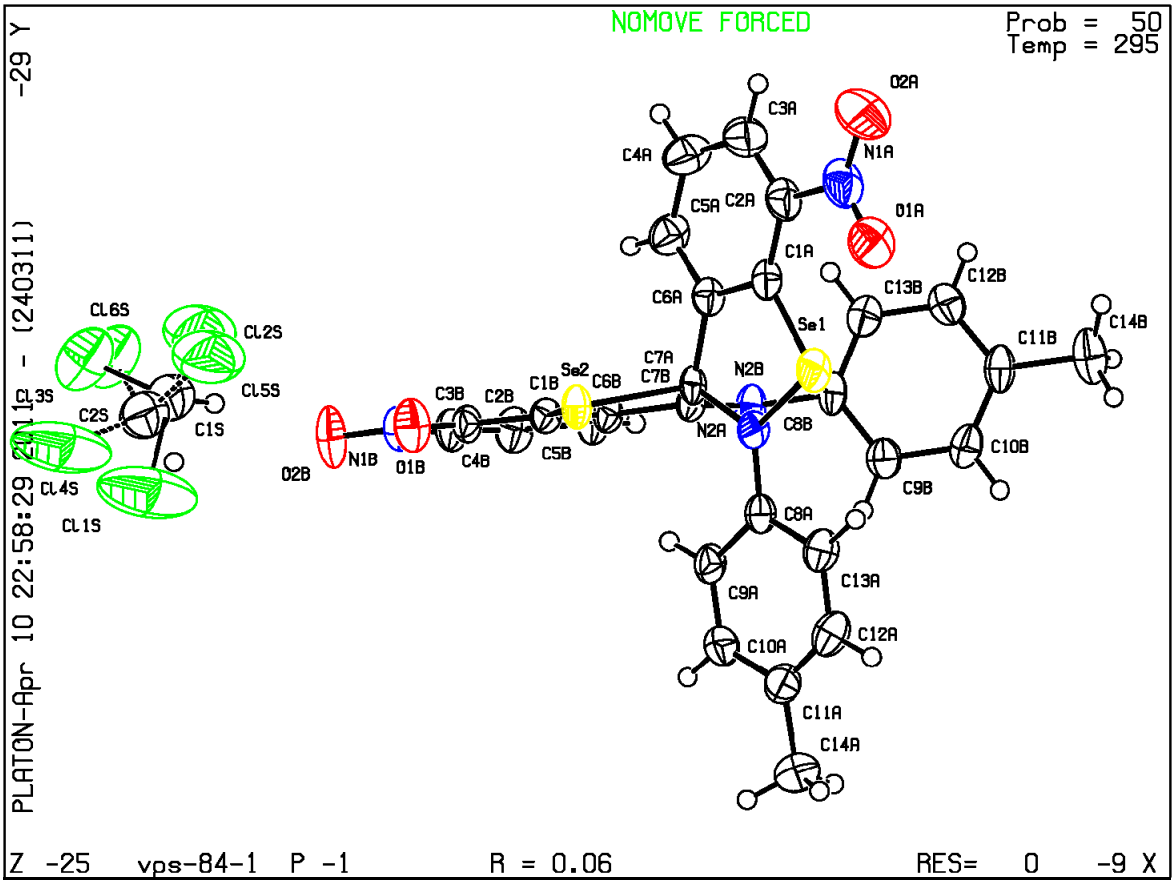

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CheckCIF/PLATON report for compound 19

No syntax errors found. CIF dictionary
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Datablock: 19

Bond precision: C-C = 0.0069 A Wavelength=0.71073
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alpha=90 beta=119.584(11) gamma=90
Temperature: 295 K

	Calculated	Reported
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Hall group	-C 2yc	?
Moiety formula	C14 H11 N2 O2 Se, 2(H2 O), Br	C14 H11 N2 O2 Se, 2(H2 O), Br
Sum formula	C14 H15 Br N2 O4 Se	C14 H15 Br N2 O4 Se
Mr	434.14	434.15
Dx,g cm-3	1.821	1.821
Z	8	8
Mu (mm-1)	4.912	4.912
F000	1712.0	1712.0
F000'	1709.82	
h,k,lmax	33,9,22	33,9,22
Nref	3247	3225
Tmin,Tmax	0.284,0.782	0.531,1.000
Tmin'	0.210	

Correction method= MULTI-SCAN
Data completeness= 0.993 Theta(max)= 26.370
R(reflections)= 0.0429(1758) wR2(reflections)= 0.0902(3225)
S = 0.845 Npar= 203

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

PLAT417_ALERT_2_B Short Inter D-H..H-D H1W2 .. H2W2 .. 1.84 Ang.

Alert level C

PLAT341_ALERT_3_C Low Bond Precision on C-C Bonds (x 1000) Ang .. 7

Alert level G

PLAT002_ALERT_2_G Number of Distance or Angle Restraints on AtSite 6
PLAT720_ALERT_4_G Number of Unusual/Non-Standard Labels 4
PLAT790_ALERT_4_G Centre of Gravity not Within Unit Cell: Resd. # 2
H2 O
PLAT860_ALERT_3_G Note: Number of Least-Squares Restraints 6

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1 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
4 **ALERT level G** = General information/check it is not something unexpected

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
2 ALERT type 2 Indicator that the structure model may be wrong or deficient
2 ALERT type 3 Indicator that the structure quality may be low

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2 ALERT type 4 Improvement, methodology, query or suggestion
0 ALERT type 5 Informative message, check
```

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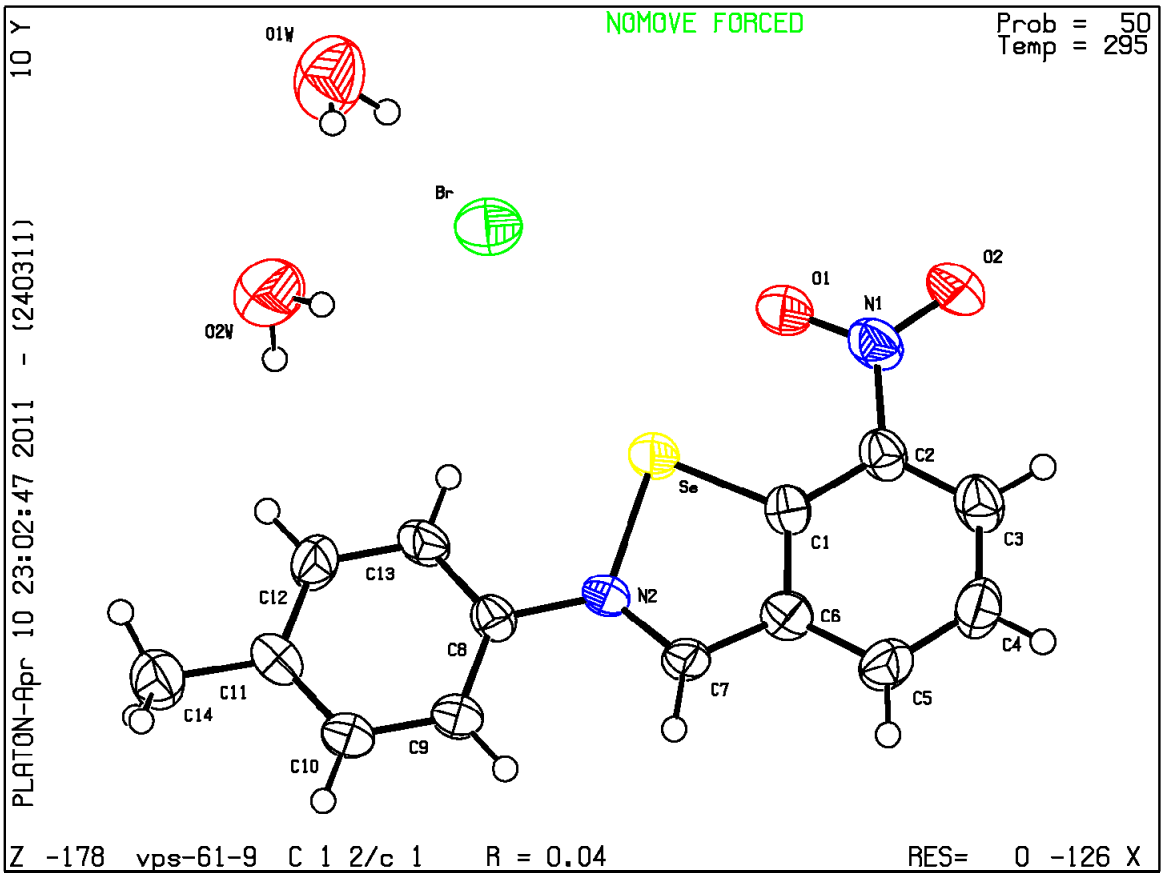

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Datablock: 20

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Temperature: 295 K

	Calculated	Reported
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Hall group	-P 1	?
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Sum formula	C27 H19 Cl3 N4 O4 Se2	C27 H19 Cl3 N4 O4 Se2
Mr	727.73	727.73
Dx,g cm-3	1.694	1.694
Z	4	4
Mu (mm-1)	6.178	6.178
F000	1440.0	1440.0
F000'	1441.11	
h,k,lmax	14,18,23	14,18,23
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Tmin'	0.054	

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Data completeness= 0.982 Theta(max)= 77.620
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S = 1.046 Npar= 734

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

PLAT094_ALERT_2_C Ratio of Maximum / Minimum Residual Density 2.92
PLAT244_ALERT_4_C Low 'Solvent' Ueq as Compared to Neighbors of C1S
PLAT244_ALERT_4_C Low 'Solvent' Ueq as Compared to Neighbors of C2S
PLAT341_ALERT_3_C Low Bond Precision on C-C Bonds (x 1000) Ang .. 8
PLAT732_ALERT_1_C Angle Calc 109.5(2), Rep 109.50(9) ..... 2.22 su-Ra
CL2 -C1S -CL3 1.555 1.555 1.555 # 210

Alert level G

PLAT002_ALERT_2_G Number of Distance or Angle Restraints on AtSite 16
PLAT072_ALERT_2_G SHELXL First Parameter in WGHT Unusually Large. 0.12
PLAT154_ALERT_1_G The su's on the Cell Angles are Equal (x 10000) 300 Deg.
PLAT720_ALERT_4_G Number of Unusual/Non-Standard Labels 18
PLAT793_ALERT_4_G The Model has Chirality at C7A (Verify) .... S
PLAT793_ALERT_4_G The Model has Chirality at C7B (Verify) .... S
PLAT793_ALERT_4_G The Model has Chirality at C7C (Verify) .... S
PLAT793_ALERT_4_G The Model has Chirality at C7D (Verify) .... S
PLAT860_ALERT_3_G Note: Number of Least-Squares Restraints 16

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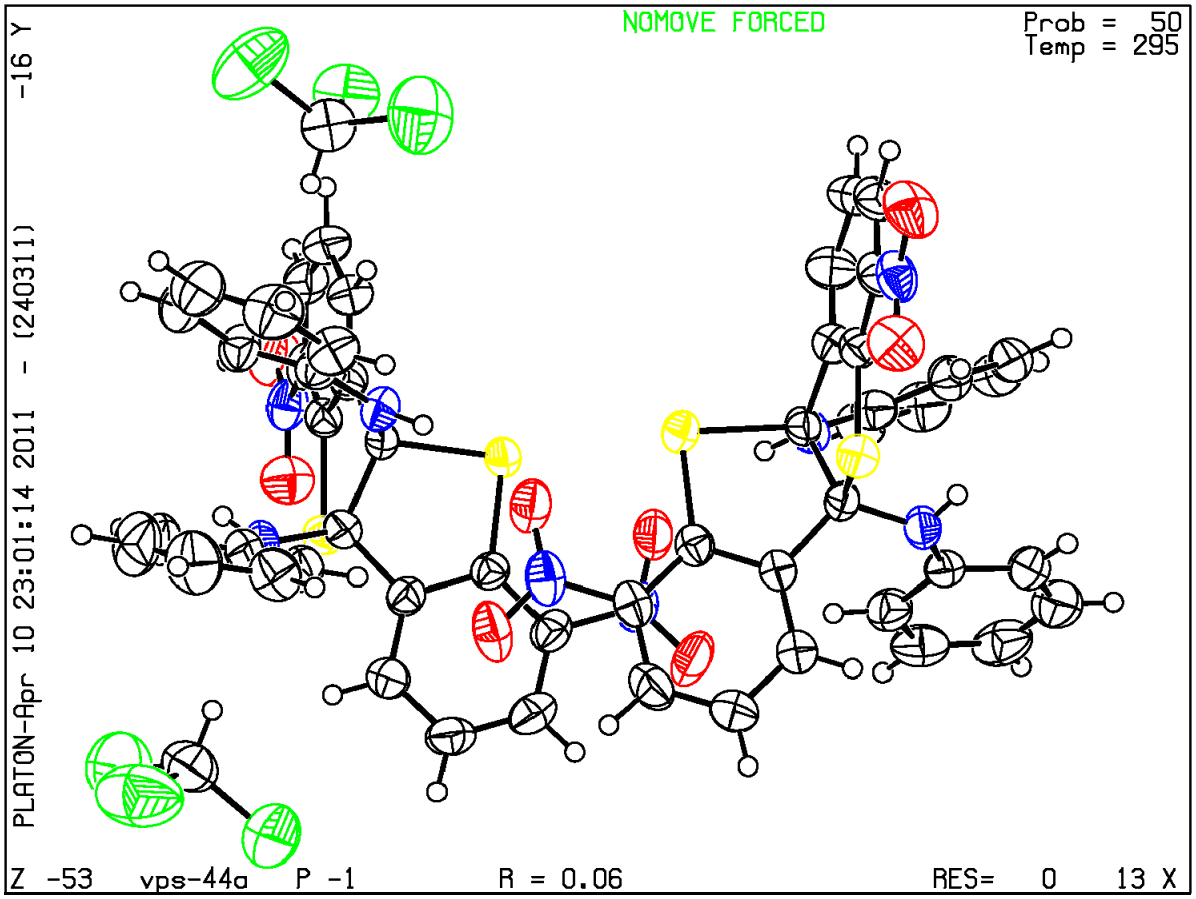
Datablock 20 - ellipsoid plot



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CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.200((will be filled in by the editorial staff))

Synthesis and Glutathione Peroxidase-Like Activities of Selenenamides

Vijay P. Singh,[a] Harkesh B. Singh[a] and Ray J. Butcher[b]*

Dedication ((optional))

Abstract: The aromatic nucleophilic substitution (S_NAr) reactions of *N*-(2-bromo-3- nitrobenzyl)aniline (**18**), *N*-(2-bromo-3-nitrobenzyl)-4-methylaniline (**19**) and *N*-(2-bromo-3-nitrobenzyl)-4-nitroaniline (**20**) with the *in situ* generated selenolate [*n*BuSeNa] afford *N*-(2-(butylselanyl)-3-nitrobenzyl)aniline (**21**), *N*-(2-(butylselanyl)-3-nitrobenzyl)- 4-methylaniline (**22**) and *N*-(2-(butylselanyl)-3-nitrobenzyl)-4-nitroaniline (**23**), respectively. The bromination of **21** results in the formation of cyclic selenenamides; 7-nitro-2-phenyl-2,3-dihydrobenzisoselenazole (**27**) and 2-(4-bromophenyl)-7-nitro-2,3-dihydrobenzisoselenazole (**28**). The bromination of **22** affords selenenamides; 2-(4-methylphenyl)-7-nitro-2,3-dihydrobenzisoselenazole (**29**) and 2-(2-bromo-4-methylphenyl)-7-nitro-2,3-dihydrobenisoselenazole (**30**) alongwith some other products. The bromination reaction of **23**, under identical conditions gave 2-(2-bromo-4-nitrophenyl)-7-nitro-2,3-dihydrobenisoselenazole (**31**). The oxidation reaction of **21**-**22** with H_2O_2 yielded cyclic seleninamides; 7-nitro-2-phenyl-2,3-dihydrobenzisoselenazole selenium-oxide (**33**) and 2-(4-methylphenyl)-7-nitro-2-phenyl-2,3-dihydrobenzisoselenazole selenium-oxide (**34**), respectively. New selenenamides/ seleninamides, stabilized by intramolecular secondary Se···O interaction, have been structurally characterized by single crystal X-ray diffraction studies and computational studies. In addition to the synthesis and characterization, the glutathione peroxidase-like (GPx) activities of selenenamides and seleninamides have been evaluated by the coupled reductase assay.

Keywords: GPx mimics • heterocycles • antioxidants • S_NAr reactions • selenium

Introduction

Ebselen (**1**, PZ 51, 2-phenyl-1,2-benzisoselenzol-3-(*2H*)-one), a heterocyclic compound containing a selenium─nitrogen bond, exhibits both anti-inflammatory activity *in vivo* and glutathione peroxidase (GPx)-like activity *in vitro* (Figure 1).[1] It catalytically reduces the harmful peroxides by reduced glutathione (GSH) or other thiols mimicking the activity of GPx and protects the lipid membranes and other cellular components against oxidative damage.[2] Due to wide applications of ebselen, several methods for its synthesis have been developed.[3,4] In the most direct approach, 2-(chlorocarbonyl)phenyl selenenyl chloride obtained from 2,2'-diselenodibenzoic acid, is treated with aniline to afford ebselen.[4b] The method developed by Engman and co-workers involves *ortho*-lithiation of benzanilide followed by selenium insertion and oxidative cyclization reactions.[4c] A free radical synthesis of ebselen has been reported by intramolecular homolytic substitution with amidyl radicals.[4d,e]

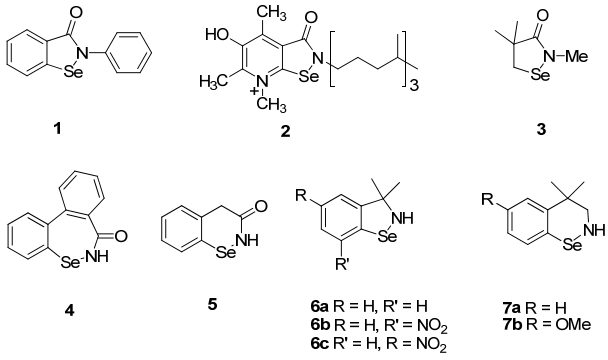

Figure 1. Ebselen **1** and its analogues **2**-**7**.

Very recently, an efficient copper-catalyzed method has been reported for the biologically active ebselen.[5] The reactivity of ebselen could be interpolated by changing the basic structure based on substituent effects and isosteric replacements. To understand the effects of various substituents on the GPx activity of ebselen, several ebselen analogues have been reported.[6b,d,f] Novel pyridine-fused tocopherol, selenium containing antioxidant and anti-inflammatory agent **2** has been reported.[7] Selenenamide **3**, without an aromatic substituent, has also been developed as a model compound for GPx.[8] Another example of selenenamides such as selenenamide **4** containing a Se─N bond in the seven-membered ring has been reported.[9] The internalization of a subsidiary tetrahedral carbon (CR_2) into the heterocycle led to compounds **5**,[10] **6**[11] and **7**[12] as GPx mimics. It is worth mentioning here that the

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introduction of an *ortho*-nitro group in 2-phenyl-7-nitro-1,2-benzisoselenazol-(2H)-3-one (**8**) enhances the GPx-like activity (Figure 2).[13] The synthesis of such ebselen analogues **9**,[14a] **10**[14b] and **11**[14c] has been accomplished by *ortho*-lithiation, selenium insertion followed by oxidation. It has been revealed that the presence of intramolecular secondary Se···O/N interactions enhances the reaction of the Se─N bond towards cleavage by thiols.[14c] The cyclic selenenamides, with CH_2 group as part of the five-membered heterocyclic ring, have not been studied in detail. In contrast to ebselen, the isolation of such cyclic Se─N selenenamides is difficult due to the flexible ─CH_2─NH─ bond with a sp^3 hybridized carbon atom. To date, only a camphor-derived cyclic selenenamide **12**, that showed good GPx-like activity, has been reported by Back and co-workers (Figure 2).[15] Here, the cyclization, probably, is possible due to rigid conformation of the substrate. Furthermore, an attempted cyclization of 2-(bromoseleno)bromomethylbenzene with methylamine did not lead to the formation of expected selenenamide **13**.[6d]

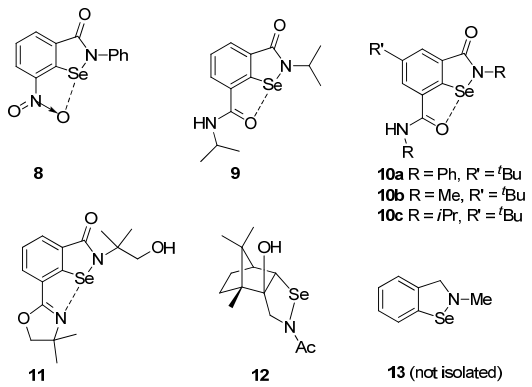
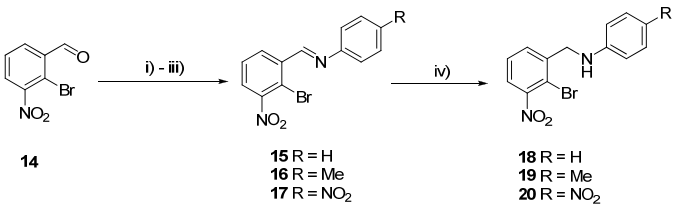


Figure 2. Selenenamides **8**-**12**.

Recently, we have reported the synthesis of related Se─N heterocycles with imine (─CH=N─) and nitro (─NO_2) groups *ortho* to the selenium atom.[16] These heterocycles are closely related with ebselen and exhibit excellent GPx-like activity. Now we have isolated a new range of Se─N heterocycles with CH_2 group present in the five-membered ring. It occured to us that such ebselen analogues might display interesting GPx-like activity due to a weaker Se─N bond. In this paper, we present our findings on the structure-property correlation as well as GPx-like activity of selenenamides/seleninamides with CH_2 group and compare with the analogues having a C=O group.

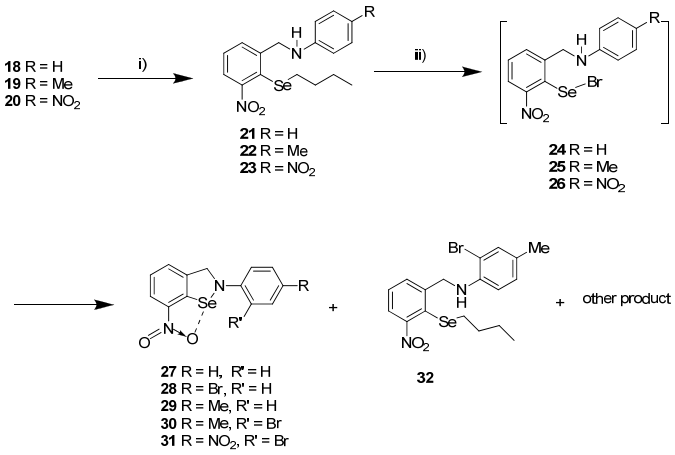
Results and Discussion

Precursor *N*-(2-bromo-3-nitrobenzylimino)benzene (**15**) was prepared from 2-bromo-3- nitrobenzaldehyde (**14**).[16] *N*-(2-Bromo-3-nitrobenzylimino)-4-nitroaniline (**16**) and *N*-(2- bromo-3-nitrobenzylimino)-4-methylaniline (**17**) were synthesized in a similar fashion by treating **14** with *p*-nitroaniline and *p*-toluidine, respectively (Scheme 1). Further treatment of **15**-**17** with $NaBH_4$ in ethanol afforded the expected reduced products **18**-**20** in good yields.



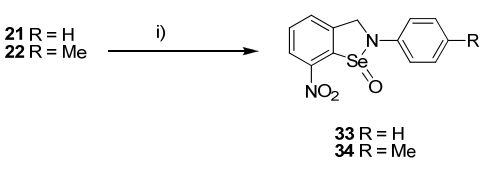
Scheme 1. i) aniline, glacial acetic acid, r. t.; ii) *p*-toluidine, glacial acetic acid, r. t.; iii) *p*- nitroaniline, glacial acetic acid, r. t.; iv) $NaBH_4$, ethanol, reflux, 5 h.

Unsymmetrical selenides **21**-**23**, the required intermediates for the synthesis of selenenamides **27**-**31**, were synthesized by the aromatic nucleophilic substitution (S_NAr) reactions of **18**-**20** with the *in situ* prepared *n*-BuSeNa (Scheme 2). Triethylamine (Et_3N) was added to a $CHCl_3$ solution of **21** after the complete bromination. The progress of the reaction was monitored by thin layer chromatography (TLC). After the usual work-up, selenenamides **27** and **28** were obtained by the silica gel column chromatographic purification with petroleum ether/ethyl acetate. Formation of **28** was accompanied with *N*-phenyl ring bromination at the *para*-position. To prevent the *N*-phenyl ring bromination at the *para*-position and also to see the substituents effect, when selenide **22** was treated with Br_2/Et_3N, the reaction mixture after the work-up and rotary evaporation afforded a black mixture of compounds. The crude mixture was chromatographed on the silca gel to afford selenenamides **29**-**30**, selenide **32** alongwith a selenospirocyclic product,[17] respectively. A similar bromination reaction of **23** afforded selenenamide **31** in very low yield alongwith a yellow precipitate which could not be characterized.



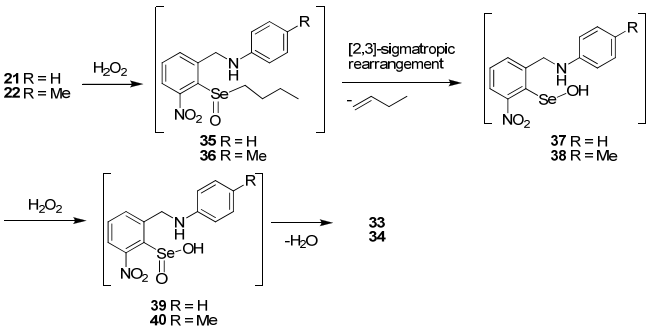
Scheme 2. i) [*n*-BuSeNa], C_2H_5OH, 0 °C, 3 h; ii) $Br_2/CHCl_3$, Et_3N, 0 °C, 2 h.

The oxidation of selenides **21**-**22** with an excess of H_2O_2 afforded cyclic seleninamides **33**-**34** (Scheme 3).



Scheme 3. i) H_2O_2 (6 equiv), $CHCl_3$, at 55-60 °C, 40 min.

The reaction of selenides **21**-**22** with H_2O_2, presumably, leads to selenoxides **35**-**36** which undergo subsequent [2,3]-sigmatropic rearrangement to give selenenic acids **37**-**38** (Scheme 4). Further, oxidation of **37**-**38** to seleninic acids **39**-**40** followed by condensation yields cyclic seleninamides **33**-**34**.



Scheme 4. Plausible mechanism for the formation of seleninamides **33** and **34**.

In order to delineate the structure-GPx-like activity correlations of the newly synthesized cyclic selenenamides **27**-**31**, related ebselen analogue **8** has also been prepared by a modified procedure.[13a] In our modification, 2-(butylselanyl)-3-nitro-*N*-phenylbenzamide (**42**), obtained by the reaction of 2-bromo-3-nitro-*N*-phenylbenzamide (**41**)[18] with the *in situ* generated *n*BuSeNa, has been used instead of 2-(methylselanyl)-3-nitro-*N*-phenylbenzamide (Figure 3).[13a] The reaction of **42** with Br_2/Et_3N in $CHCl_3$ solvent gave **8** in much better yield.

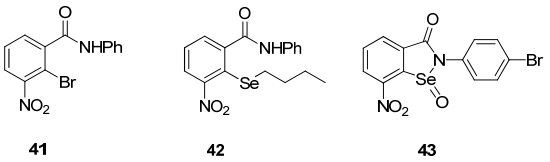


Figure 3. Precursors **41**-**42** and *ortho*-nitro coordinating ebselen analogue **43**.

In summary, a facile synthesis of cyclic selenenamides and seleninamides incorporating a CH_2 group in the five-membered heterocyclic ring have been achieved. The intramolecular coordination of the 6-nitro group to the selenium atom plays a crucial role in the cyclization process.

Spectroscopic Studies

The ^{1}H NMR spectroscopic studies of seleninamides **33** and **34** were performed in DMSO-d_6 (see Figures S92 and S99 of the Supporting Information). Nonequivalent signals for the benzylic protons of **33** {5.19 (d, 1H) and 5.26 (d, 1H) ppm} and **34** {5.16 (d, 1H) and 5.24 (d, 1H) ppm} were observed as two doublets with vicinal coupling (J = 16.0 Hz). The doublets are due the presence of the chiral selenium centres in optically active **33** and **34**.

^{77}Se NMR spectroscopy is a very useful technique for probing the electronic environment around the selenium atom.[6,8a,14-15,19a] The ^{77}Se NMR spectra of selenenamides **27**-**31** exhibit signals at 974, 977, 987, 1060 and 1070 ppm (Table 1). These chemical shifts are slightly downfield as compared to **1** (961 ppm),[6b] **8** (953 ppm),[13a] **3** (819 ppm),[8a] **7a** (693 ppm)[12b] and **12** (885 ppm).[15] As expected for seleninamides **33** and **34** with selenium (IV) showed higher downfield shifted as compared to selenenamides **27**-**31**.

We performed density functional (DFT) calculations for organoselenium compounds to see the effect of CH_2 group in place of CO group in the five-membered heterocycle ring on the ^{77}Se NMR chemical shifts and compare the calculated values with the experimental data. The geometries were fully optimized at the B3LYP/6-31+G(d) basis sets. The NMR calculations were performed at the B3LYP/6-311+G(d,p) level on the B3LYP/6-31+G(d)-level-optimized geometries by using the gauge-including atomic orbital (GIAO) method.[20] As observed from the experimental data, the calculated ^{77}Se NMR chemical shifts for **27**-**31** are downfield shifted as compared to that observed for **1** (Table 1). This difference in the chemical shifts is probably due to the presence of intramolecular secondary Se···O interaction with *ortho*-nitro group. It is well established that the presence of the intramolecular secondary Se···N[6a,19b] and Se···O[6b,e,21,22] interactions leads to a downfield shift of the ^{77}Se NMR chemical shifts. Recently, we have demonstrated that the presence of the Se···O interactions in selenenium cations[16] and selenenate esters[22] leads to downfield shift of the ^{77}Se NMR chemical shifts (*vide infra*).

Table 1. GIAO ^{77}Se NMR chemical shifts calculated in gas phase at the B3LYP/6-311+G(d,p) level on the B3LYP/6-31+G(d)-level-optimized geometries for compounds **1**, **8**, **27**-**31** and **33**-**34** alongwith the experimental values.

Entry	^{77}Se NMR[a] Calcd	^{77}Se NMR[a] Exptl	Solvents
1	960	961[6b]	$CDCl_3$
8	886	953[13a]	$CDCl_3$
27	1045	974	$CDCl_3$
28	1051	977	$CDCl_3$
29	1037	987	$CDCl_3$
30	1025	1060	$CDCl_3$
31	1031	1070	$CDCl_3$
33	1142	1182	DMSO-d_6
34	1139	1174	DMSO-d_6

[a] The values are referenced with respect to Me_2Se (δ = 0 ppm).

X-ray Crystallographic Studies

The molecular structures of **21**, **29**-**30** and **32**-**33** were unambiguously confirmed by single crystal X-ray diffraction studies.

Molecular Structures of 21 and 32

The molecular structure of **21** (Figure 4) indicates a V-shaped geometry around the selenium atom with a bond angle C1─Se1─C14 of 100.00(11)°. The Se···O1 distance [3.295(9) Å] is slightly less than the sum of the van der Waals radii (3.45 Å), indicating a weak secondary Se···O interaction.[23] The geometry of **32** around the selenium atom is quite similar to that observed for **21** with a bond angle C1─Se1─C15A of 100.3(3)° (Figure 5). The Se···O2 distance [3.212(2) Å] is also similar to that observed for **21**.

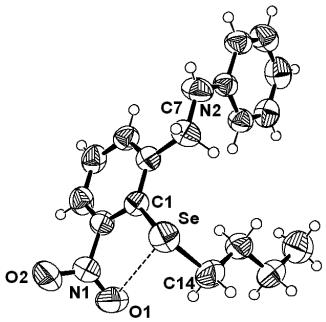


Figure 4. Molecular structure of **21**. Thermal ellipsoids are set at 50 % probability. Significant bond lengths [Å] and angles [°]: Se···O1 3.295(9); Se–C1 1.924(2); Se–C14 1.978(3); O1···Se–C7 115.93(6); C1–Se–C14 100.00(11).

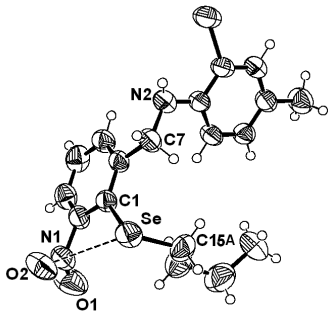


Figure 5. Molecular structure of **32**. Thermal ellipsoids are set at 50 % probability. Significant bond lengths [Å] and angles [°]: Se···O2 3.212(2); Se–C11.926(3); Se–C15B 1.892(10); C1–Se–C14 100.3(3).

Molecular Structures of 29 and 30

The coordination geometry of **29** around the selenium atom is nearly T-shaped with a bond angle O1···Se–N2 of 156.76(11)° (Figure 6). The Se–N2 distance [1.891(3) Å] is found to be similar to that reported for **1** [1.896(3) Å] and **8** [1.896(3)].[24] The Se···O1 distance [2.591(3) Å] is slightly greater than that reported for **8** [2.573(3) Å],[24b] which indicates a weak intramolecular secondary Se···O interaction in **29**. The geometry of **30** around the selenium atom is quite similar to that observed for **29** with a bond angle O1···Se–N2 of 155.61(10)° (Figure 7). The Se–N2 distance [1.905(3) Å] is similar to that observed for **29**. The Se···O1 distance [2.686(3) Å] is slightly greater than that observed for **30**, suggesting a weaker intramolecular secondary Se···O interaction.

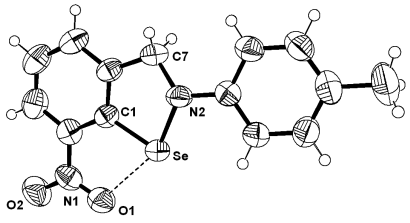


Figure 6. Molecular structure of **29**. Thermal ellipsoids are set at 50 % probability. Significant bond lengths [Å] and angles [°]: Se···O1 2.591(3); Se–N2 1.891(3); Se–C1 1.861(3); O1···Se–N2 156.76(11); C1–Se–N2 85.69(14); C7 –N2–Se 114.0(2).

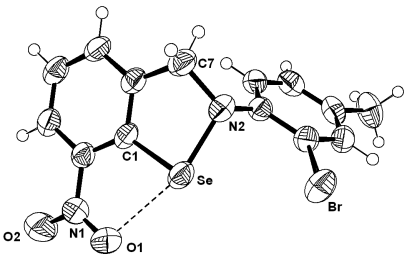


Figure 7. Molecular structure of **30**. Thermal ellipsoids are set at 50 % probability. Significant bond lengths [Å] and angles [°]: Se···O1 2.686(3); Se–N2 1.905(3); Se–C1 1.880(3); O1···Se–N2 155.61(10); C1–Se–N2 88.11(12); C7 –N2–Se 107.00(19).

Molecular Structure of 33

The molecular structure of **33** is shown in Figure 8. The geometry around the selenium shows a "see-saw" type with the bond angle N2–Se···O2 of 152.31(16)°. This angle is quite similar to that reported for 2-(4-bromophenyl)-7-nitro-1,2-benzisoselenazol-(*2H*)-3-one selenium oxide (**43**) [151.74(0)°].[16] The Se–N distance [1.867(4) Å] is slightly smaller than that observed for **43** [1.888(8) Å]. The Se···O2 distance (2.742(5) Å) is close to that observed for **43** (2.749 Å), indicating a weak secondary Se···O interaction.

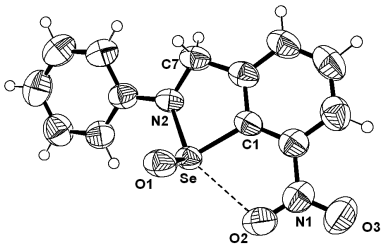


Figure 8. Molecular structure of **33**. Thermal ellipsoids are set at 50 % probability. Significant bond lengths [Å] and angles [°]: Se···O2 2.742(5); Se–O1 1.645(4); Se–N2 1.867(4); Se–C1 1.938(6); N2–Se–C1 84.05(21); N2–Se···O2 152.31(16); N2–Se–O1 106.26(20); C1–Se–O1 104.33(21).

Computational Studies

Effect of CH_2 group in place of CO group in the five-membered heterocycle

The reactivity of the Se–N bond in the ebselen analogues plays a crucial role in the GPx-like activity. The cleavage of the Se–N bond by the thiol leads to the formation of the Se–S bond.[6b,14c,25] Further attack of another thiol on the Se–S bond results in the formation of reactive selenol. The reactivity of the selenosulfide intermediate is tuned by intramolecular secondary Se···O interactions.[6,25] To find out the effect of the incorporation of CH_2 in the place of C=O and intramolecular secondary Se···O interactions on the nature of the Se–N bond in selenenamides **27**-**31** and seleninamides **33**-**34**, DFT calculations have been carried out (for the optimized geometries and coordinates see Tables S1, S3, S5, S7 and S9 of the Supporting Information). The data suggest that incorporation of the CH_2 group

in the place of C=O in compounds **27-31** leads to an increase in the Se─N and Se···O distances (Table 2). In line with this observation, the Se─N distances in **1** (1.880 Å) and **8** (1.908 Å) are shorter when compared with the Se─N distances in **27-31** and **33-34**.

Table 2. The theoretical data for **1**, **8**, **27-31** and **33-34** obtained by DFT calculations at the B3LYP/6-311+G(d,p) level. The NBO analysis and NICS (0) values were calculated at the B3LYP/6-311+G(d,p) level on the B3LYP/6-31+G(d)-level-optimized geometries.

Entry	$r_{Se–N}$ [Å][a]	$r_{Se\cdots O}$ [Å][a]	$E_{Se\cdots O}$ (kcal/mol)	q_{Se}	NICS (0) ppm[b]
1	1.880(1.896)[2a]	----	----	+0.626	-7.14
8	1.908(1.896)[2b]	2.563(2.573)	13.48	+0.771	-5.61
27	1.947	2.603	11.54	+0.706	-2.78
28	1.949	2.585	12.41	+0.709	-2.83
29	1.946(1.891)	2.611(2.591)	11.22	+0.704	-2.88
30	1.948(1.905)	2.598(2.686)	11.68	+0.711	-2.78
31	1.953	2.499	22.72	+0.778	-1.55
33	1.905(1.867)	2.762(2.742)	05.62	+1.576	-1.84
34	1.903	2.65	05.54	+1.575	-1.91

[a] The experimental values are given in parentheses. [b] NICS (0) values are calculated at the centre of the five-membered heterocyclic ring.

Second-order perturbation energy ($E_{Se\cdots O}$) between the selenium and oxygen atoms was calculated at the B3LYP/6-311+G(d,p) level on the B3LYP/6-31+G(d)-level-optimized geometries by using the natural bond orbital (NBO) calculation.[26] The $E_{Se\cdots O}$ due to the $n_O \rightarrow \sigma^*_{Se–N}$ orbital interaction was obtained by the NBO analysis. These studies reveal that the replacement of C=O with CH_2 group in **27-30** and **33-34**, the $E_{Se\cdots O}$ decreased slightly as compared with that of **8** ($E_{Se\cdots O}$ = 13.48 kcal/mol) suggesting a weaker Se···O interaction (Table 2). However, the $E_{Se\cdots O}$ (22.72 kcal/mol) for **31** is found to be higher than **8** and other selenenamides **27-30**. This is due to the presence of $–NO_2$ and –Br groups at the *N*-phenyl ring. Also the interaction energies for **33** ($E_{Se\cdots O}$ = 05.61 kcal/mol) and **34** ($E_{Se\cdots O}$ = 05.50 kcal/mol) are much lower as compared with that of **27-31**, indicating relatively weaker Se···O interactions in **33** and **34**. The NBO analysis further shows that weaker Se···O interactions and the presence of the CH_2 group lead to an elongation of the Se─N bond length.

Further, distinct bond critical point (*bcp*) at the Se···O interaction correlates with the strength of the interacting atoms. The presence of *bcp* was identified in compounds **8**, **27-31** and **33-34** using Bader's theory of atoms in molecules (AIM)[27] with AIM2000 (Table 3).[28] The values of electron density (ρ) obtained are much smaller than a covalent bond (e.g., $\rho_{C\text{-}C}$ = 0.24 ea_0^{-3}) but larger than those for the practical boundary of molecules (ρ = 0.001 ea_0^{-3}).[29] The values of electron density $\rho_{Se\cdots O}$ obtained for the Se···O interaction for compounds **8**, **27-31** and **33-34** range from 0.022 to 0.031 ea_0^{-3} (See Figure S124 for AIM pictures in the Supporting Information). The trend that $\rho_{Se\cdots O}$ decreases from **27-30** to **33-34** is in full accordance with the trend of $E_{Se\cdots O}$ obtained by the NBO analysis and the Se···O distance by quantum chemical calculation (Table 2). The Laplacian ($\nabla^2\rho_{Se\cdots O}$) represents the curvature of the electron density in 3-D space at the *bcp* of the Se···O interaction. The values of $\nabla^2\rho_{Se\cdots O}$ obtained for the Se···O interaction for **8**, **27-31** and **33-34** are all positive, suggesting a dominant electrostatic character. However, the total electron energy density ($H_{Se\cdots O}$) is more reliable to understand the nature of secondary Se···O interactions instead of the $\nabla^2\rho_{Se\cdots O}$. According to the $H_{Se\cdots O}$ values obtained for **27-30** and **33-34** are positive, which strongly suggests that the Se···O interactions are weak. It has been observed that the negative value of $H_{Se\cdots O}$ for **31** indicates increase in the strength of the Se···O interaction. The values obtained for **33-34** are found to be more positive as compared to **8** and **27-30**. It is evident that the values of $H_{Se\cdots O}$ becomes more positive with increase in the Se···O atomic distance (i.e., weakening of the Se···O interaction). A similar observation of the *bcp*, positive values of $\nabla^2\rho_{Se\cdots O}$ and total energy density $H_{Se\cdots O}$ for the Se···O interactions has been obtained by Tomoda and co-workers.[21a]

Table 3. Summary of properties of electron density at the bond critical point (*bcp*).

Entry	$\rho_{Se\cdots O}$[a] (ea_0^{-3})	$\nabla^2\rho_{Se\cdots O}$[b] ($ea_0^{-5}$)	$H_{Se\cdots O}$[c] (ea_0^{-4})
8	0.031	0.091	+0.0002
27	0.028	0.089	+0.0004
28	0.029	0.092	+0.0003
29	0.028	0.088	+0.0004
30	0.029	0.090	+0.0004
31	0.038	0.116	-0.0008
33	0.022	0.068	+0.0008
34	0.022	0.068	+0.0008

[a] The electron density at the *bcp*. [b] The Laplacian of the electron density at the *bcp*. [c] The total energy density at the *bcp*.

The NBO charge calculation shows that the Se···O interaction leads to an increased higher positive charge on the selenium in **8** (+0.771) than ebselen (Table 2). However, there is a slight decrease in the positive charge on the selenium atom of compounds **27** (+0.706), **28** (+0.709), **29** (+0.704) and **30** (+0.711) as compared to that of **8** (+0.771). It should be noted that the high positive charge on selenium in **8** can be due to the delocalization of the carbonyl double bond in the five-membered heterocycle as well as *ortho*-coordinating nitro group. The high positive charge on the selenium atom in compound **31** (+0.778) is due to the presence of the electron withdrawing groups. As expected the NBO charges on the selenium atom in compounds **33** (+1.576) and **34** (+1.575), which contain selenium (IV), are found to be higher as compared to **1**, **8** and **27-31**.

Nucleus-Independent Chemical Shifts (NICS) values for **1** (-7.14 ppm) is more negative than that observed for **8** (-5.61 ppm) (Table 2). This significant loss in the aromatic character in the five-membered ring is due to the presence of the Se···O interaction and the conjugated carbonyl group. The Se···O interaction enhances the electrophilicty at the selenium atom. This decrease in the aromatic character from **27** (-2.78 ppm), **28** (-2.83 ppm), **29** (-2.88 ppm) and **30** (-2.78 ppm), **31** (-1.55 ppm), **33** (-1.84 ppm) and **34** (-1.91 ppm)

is due the absence of carbonyl group (Table 2). The significant decrease in the NICS(0) values of **33**-**34** is mainly due to high positive charge on the selenium atom. Thus, the introduction of CH_2 group in the five-membered heterocycle leads to a decrease the aromaticity. In our earlier report,[22] a similar behaviour for the carbonyl *versus* CH_2 group has been observed in the cases of selenenate esters.

The results obtained by DFT calculations have shown that ^{77}Se NMR chemical shifts are shifted downfield in selenenamides **27**-**31**, with CH_2 group as part of the heterocycle, as compared to that observed for analogues **1** and **8** with C=O. Although the experimental Se─N bond distances in **1**, **8**, **29**, **30** and **33** are in the same range, the calculated distances of **29**, **30** and **33** are much longer (i.e. lengthening of the Se─N bond) than that observed for **1** and **8**. These studies suggest that the introduction of CH_2 group in the place of C=O leads to weakening of the Se─N bond and a decrease in the positive charge on the selenium atom as well as the aromaticity of the heterocycle.

Glutathione Peroxidase-Like Activity

The catalytic reduction of H_2O_2 using reduced glutathione (GSH) as co-substrate in the presence and absence of catalysts; **1**, **8, 27-30** and **33-34** was studied (Table 4). The initial rates (v_0) for the reduction were determined by the coupled reductase assay from a linear fit spanning the first 5-10 % of the reaction by following the oxidation of reduced nicotinamide adenine dinucleotide (NADPH) at 340 nm in phosphate buffer. Interestingly, it was found that compounds **29** (411 ± 1 μM.min^{-1}), **33** (425 ± 1 μM.min^{-1}) and **34** (506 ± 4 μM.min^{-1}) exhibited much higher activities than the carbonyl group based analogues **1** (133 ± 1 μM.min^{-1}) and **8** (221 ± 2 μM.min^{-1}). The GPx-like activity of **1** was found to be lower than **27-30**, which is due the absence of *ortho*-nitro group in **1**. The selenenyl sulfide derived from **1** has been shown to undergo thiol-exchange reactions due to the presence of a strong Se···O interaction.[6] The strong Se···O interactions in selenosulfides hamper the generation of the reactive species selenol. Compound **8** showed nearly two times more activity than **1**. This enhancement in the GPx-like activity of **8** was due to the presence of an *ortho*-nitro group to the selenium.[13b] The GPx-like activity of **28** (204 ± 3 μM.min^{-1}) was found to be higher than **27** (172 ± 5 μM.min^{-1}) due to the presence of *para*-substituent at the *N*-phenyl ring. Similarly, selenenamide **29** showed better activity with *para*-tolyl group at the heterocyclic N-atom than other selenenamides **8**, **27-28** and **30** (255 ± 6 μM.min^{-1}). The activity of **29** decreased to nearly half with additional bromo substituent at the *ortho*-position to the *N*-phenyl ring. The high GPx-like activities of seleninamides **33** and **34** are probably due to weak secondary Se···O interactions, lengthening of the Se─N bond and high positive charge on the selenium atom. Related ebselen analogue **43**[16] also showed good activity (472.7 ± 3.5 μM.min^{-1}). In our earlier report,[22] it has been observed that the seleninate esters exhibited much higher activity than selenenate esters. The present study further suggests that the seleninamides **33-34** are even better catalysts than their corresponding selenenamides **27-30**. Similarly, the *para*-substituted selenamides **28** and **29** are found to be better catalysts.

Table 4. Initial rates, v_0 (μM.min^{-1}) for the reduction of H_2O_2 by glutathione (GSH) in the presence of ebselen **1**, **8, 27-30** and **33**-**34**.

Entry	v_0(μM.min^{-1})[a]	Entry	v_0(μM.min^{-1})[a]
Control[b,c]	31 ± 2	**29**	411 ± 1
1	133 ± 1	**30**	255 ± 6
8	221 ± 2	**33**	425 ± 1
27	172 ± 5	**34**	506 ± 4
28	204 ± 3	**43**	472.7 ± 3.5[d]

[a] Assay conditions: reactions were carried out with phosphate buffer (100 mM), pH 7.5, with ethylenediaminetetraacetate (EDTA): 1 mM; GSH: 2 mM; NADPH: 0.4 mM; glutathione reductase (GR): 1.3 unit/ml; GPx samples: 80 μM; H_2O_2 (1.6 mM). [b] The control values were obtained from the reduction of H_2O_2 by GSH in absence of GPx samples. [c] All these values were triplicated for initial 10 sec and average values were taken with standard deviation. [d] See Ref. [16].

Determination of the Catalytic Parameters

To further understand the catalytic behavior of compounds **29** and **33** with good catalytic activities, detailed kinetic experiments have been carried out. The Lineweaver-Burk (double-reciprocal) plots for **1**, **29** and **33** (see Tables S28-33 and Figures S125-130 of the Supporting Information) were obtained by plotting the reciprocal of initial rate ($1/v_0$) against the reciprocal of substrate concentration (1/[substrate]) and used for the determination of the catalytic parameters. The catalytic parameters, such as maximum velocity (V_{max}), Michaelis constant (K_M), catalytic constant (k_{cat}), and catalytic efficiency (η) were obtained for the reduction of H_2O_2 in the presence of compounds **1**, **29** and **33** (Table 5). It is worth mentioning here that the K_M values for **29** (2.05 mM) and **33** (0.93 mM) were found to be lower than those obtained for ebselen **1** (14.47 mM) when GSH is variable, indicating that the thiol exchange reactions significantly increase the K_M values. The poor catalytic activity of ebselen has been ascribed to the thiol exchange reactions in the selenenyl sulfide due to the presence of strong Se···O interaction.[6a-c] The catalytic efficiencies of **29** and **33** were determined to be 3.83, 3.48 mM^{-1} min^{-1} and 6.74, 8.34 mM^{-1} min^{-1} respectively, whereas the catalytic efficiency of **1** was only 2.21, 0.61 mM^{-1} min^{-1} when both H_2O_2 and GSH variable. The catalytic efficiency of **33** is nearly ~2 times higher than that observed for **29**. Higher catalytic efficiency of **33** as compared with **29** suggests that **33** is found to be more effective GPx mimetic than that of **29**. That may be due to fast reactions in the presence of thiol and peroxide. Moreover, in contrast to H_2O_2, typical saturation kinetics was observed at higher concentrations of GSH.

Table 5. Effect of H_2O_2 and GSH concentrations on the maximum velocity (V_{max}), Michaelis constant (K_M), catalytic constant (k_{cat}), and catalytic efficiency (η) for catalysts **1**, **29** and **33**.

Entry	V_{max}(μM min^{-1})	K_M (mM)	k_{cat} (min^{-1})	η (mM^{-1} min^{-1})
Catalyst **1**				
H_2O_2 (variable)[a]	228.31	1.29	2.85	2.21
GSH (variable)[b]	709.22	14.47	8.86	0.61
Catalyst **29**				
H_2O_2 (variable)[a]	444.44	1.45	5.55	3.83
GSH (variable)[b]	571.43	2.05	7.14	3.48
Catalyst **33**				
H_2O_2 (variable)[a]	609.75	1.13	7.62	6.74
GSH (variable)[b]	621.12	0.93	7.46	8.34

[a] Assay conditions: Phosphate buffer (100 mM), pH 7.5; GSH: 2 mM; NADPH: 0.4 mM; EDTA: 1 mM; GR: 1 unit/ml; H_2O_2 (variable) and test compound: 80 μM. [b] Assay conditions: Phosphate buffer (100 mM), pH 7.5; GSH (variable), NADPH: 0.4 mM; EDTA: 1 mM; GR: 1 unit/ml; H_2O_2: 1.6 mM and test compound: 80 μM. For each value atleast two readings were taken

Consumption of H_2O_2 by GSH in the presence of catalysts 29 and 33

In order to prove that compounds **29** and **33** behaved as catalysts, kinetic reactions were followed for till the completion of the reactions (maximum 10000 sec). Control experiments were carried out in the presence of H_2O_2 and GSH. A combination of catalysts (**29**/**33**), GSH and H_2O_2 was taken in a cuvette [containing 100 mM phosphate buffer pH 7.5, EDTA, NADPH and GR] and the decrease in the absorbance of NADPH was measured. A graph for the consumption for H_2O_2 *versus* time was plotted from the data (obtained from Tables S34-36 of the Supporting Information), upto 65 % and 60 % consumptions of H_2O_2 were observed after 70 min and 166.66 min for catalysts **33** and **29**, respectively (Figure 9). This observation further shows that compound **33** is better catalyst than **29**.

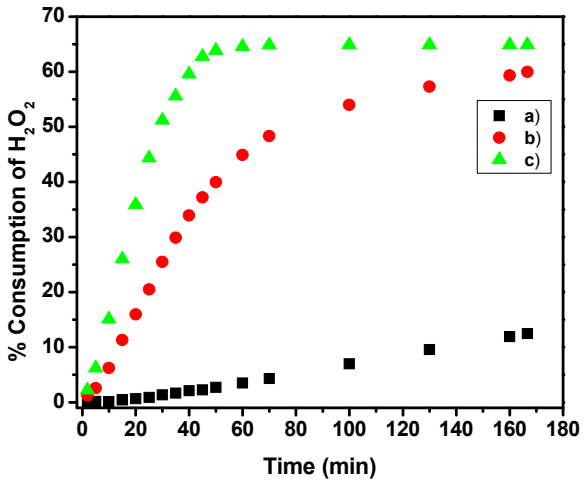
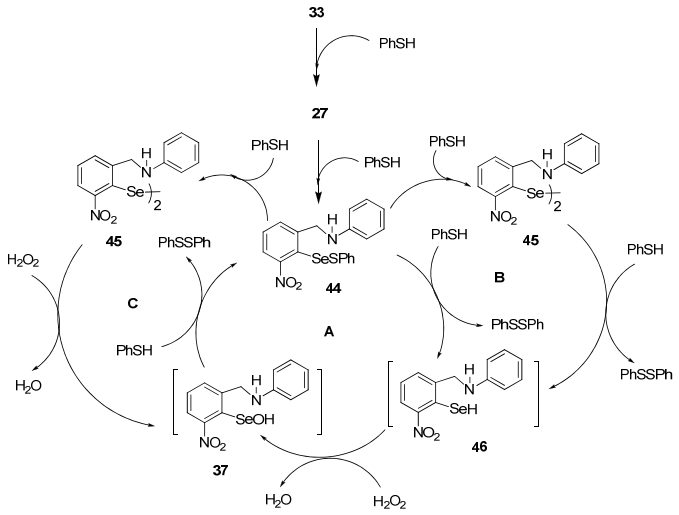


Figure 9. Catalytic reduction of H_2O_2 by GSH in the presence and absence of selenium catalyst. The consumption of H_2O_2 was followed by micromoles of NADPH utilized per min: a) control i.e. in the absence of any catalyst; b) **29**+GSH+H_2O_2; c) **33**+GSH+H_2O_2. Assay conditions: reactions were carried out with phosphate buffer (100 mM), pH 7.5; with EDTA: 1 mM; GSH: 0.25 mM; NADPH: 0.40 mM; GR: 1.3 unit/ml; H_2O_2: 0.20 mM and selenium catalyst: 10 μM.

In summary, a structure-activity correlation reavels that selenenamides **27**-**31** and seleninamides **33**-**34** with CH_2 group are found to be better GPx mimics as compared to **1** and **8** with C=O. It has also been shown that **28** and **29** with para-substituents are nearly 1.5 and 3 times, respectively more active than **1**. On the other hand, as expected seleninamides **33** and **34** are significantly more active than their corresponding selenenamides **27** and **29**. To support the observations based on initial rates for selenenamides **27** and seleninamides **29** with CH_2 group, further detailed kinetic studies using various concentrations of thiol and hydrogen peroxide indicate that compounds **27** and **29** are found to be more efficient catalysts than **1**.

Catalytic mechanism for catalyst 33

To identify the intermediates involved in the catalytic mechanism of seleninamide **33** with promising GPx-like activity, the ^{77}Se NMR spectroscopy was carried out (Scheme 5). When **33** (δ = 1182 ppm) was treated with PhSH (1 equiv) in DMSO-d_6, a new ^{77}Se NMR signal was observed at δ = 973 ppm (see Figures S131-132 of the Supporting Information). The signal observed at δ = 973 ppm can be assigned to selenenamide **27**. The identity of **27** was further established by its independent synthesis and complete characterization (see the experimental section). Upon addition of one more equiv of PhSH to the above mixture, both the signals at 1182 and 973 ppm completely disappeared and new signals were observed at 514 and 424 ppm (see Figures S133-136 of the Supporting Information). The ^{77}Se NMR signals at 514 and 424 ppm can be assigned to the corresponding selenosulfide **44** and diselenide **45**, respectively. The ^{77}Se NMR signals observed at 514 and 424 ppm were further confirmed by the addition of 2 equiv PhSH to a solution of **27** in $CDCl_3$ (see Figure S137 of the Supporting Information). A similar observation has been made by Back and co-workers for the related selenenamide **12** which follows a different catalytic mechanism.[15] In the presence of more thiol, selenosulfide **44** was converted to disulfide (PhSSPh) and selenol **46** (Cycle A). A ^{77}Se NMR signal for **46** was not observed in the catalytic cycle. Compound **46** probably oxidizes to selenenic acid **37**. Selenenic acid **37**, in turn; reacted rapidly with PhSH to regenerate **44** back. In the catalytic cycle, selenosulfide **44** disproportionates to the corresponding diselenide **45**. In excess of thiol, diselenide **45** was converted to **46** (Cycle B). Further oxidation of the diselenide **45** regenerates the selenosulfide **44** followed by thiolysis of **37** (Cycle C). In this catalytic cycle, seleninamide **33** was reduced to **27** which is the procatalyst and rapidly gets depleted in the presence of PhSH to give **44** and **45**. The observation of diselenide **45** is in contrast to the mechanism reported by Back and co-workers for selenenamide **12**.[15]



Scheme 5. Proposed catalytic cycle for the reduction of H_2O_2 by PhSH in the presence of **33**.

Conclusion

In conclusion, an efficient methodology has been developed for the synthesis of new selenenamides incorporating CH_2 moiety in the five-membered heterocyclic ring. The facile synthesis of selenenamides **27-31** and seleninamides **33-34** is due to the presence of *ortho*-nitro group to the selenium atom. Theoretical investigations suggest that the replacement of C=O with CH_2 present in the five-membered heterocycles leads to activate the Se─N bond. It also decreases the positive charge on the selenium atom. It was observed that the selenium centre is more deshielded in the heterocycles with CH_2 group which may be due to weak intramolecular secondary Se···O interaction. Selenenamide **29** and seleninamide **33-34** are exhibited excellent GPx-like activity.

Experimental Section

2-Bromo-3-nitrobenzoic acid[30a] and 2-bromo-3-nitrobenzaldehyde[30b] were prepared by the reported procedures. Selenium powder and 3-nitrophthalic acid used were purchased from Sigma Aldrich. All the reactions were performed under nitrogen or argon atmosphere by modified Schlenk techniques and monitored by using TLC from time to time. Silica gel of 100-200 mesh size was purchaged from merck. Solvents were purified by standard techniques.[31] Melting points were recorded on a VEEGO melting point (VMP-1) apparatus and are uncorrected. ^{1}H (399.88 MHz) & ^{1}H (299.95 MHz), ^{13}C (100.6 MHz) and ^{77}Se (57.26 MHz) NMR spectra were recorded on a Varian NMR-Mercury plus 400 MHz & Bruker Avance^{III} 400 MHz spectrometer and Varian NMR-Mercury plus 300 MHz for ^{77}Se NMR at the indicated frequencies. Chemicals shifts (δ) are shown with respect to $SiMe_4$ (TMS) as internal standard for nuclei ^{1}H & ^{13}C and Me_2Se for nuclei ^{77}Se as the external standard; s = singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets. The high resolution mass spectra (HRMS) were recorded at room temperature on a Micro mass Q–TOF (YA 107) mass spectrometer. FT-IR spectra were recorded in the range 4000-450 cm^{-1} using KBr for solid samples and neat for liquid samples between CsI plates on a Perkin Elmer precisely spectrum one FT–IR spectrometer. The UV–VIS spectra for GPx-like activity in solution were recorded on a JASCO, V-570 spectrometer.

Synthesis of *N*-(2-bromo-3-nitrobenzylimino)-4-methylaniline (16): To a solution of **14** (43.4 mmol, 10.0 g) in glacial acetic acid (10 mL) was added *p*-toluidine (43.4 mmol, 4.64 g) with continuous stirring at room temperature. A curdy yellow precipitate was formed. To complete the precipitation, the reaction mixture was cooled with ice, then filtered and washed with ice-cooled ethanol. Recrystallization from hot ethanol afforded a light yellow solid. Yield: 8.9 g (65 %); mp 110-112 °C. ^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3H, CH_3), 7.19-7.24 (m, ArH), 7.52-7.56 (t, *J* = 7.9 Hz, 1H), 7.77-7.80 (dd, *J* = 1.6, 9.51 Hz, 1H), 8.42-8.45 (dd, *J* = 1.6, 9.5 Hz, 1H), 8.92 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 21.2, 116.7, 121.3, 126.7, 128.2, 130.1, 132.0, 137.3, 137.5, 148.2, 151.5, 156.4 ppm; IR (KBr): ν = 2918, 1616 (C=N), 1534 (NO_2), 1426, 1366, 1029, 829, 818, 713, 529, 487 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{14}H_{11}BrN_2O_2$ [*M*+H]$^+$: 319.0082; found: 319.0088.

Synthesis of *N*-(2-bromo-3-nitrobenzylimino)-4-nitroaniline (17): Compound **17** was synthesized from **14** (8.69 mmol, 2.0 g) in glacial acetic acid (50 mL) and *p*-nitroaniline (8.69 mmol, 1.2 g) according to the procedure described for the preparation **16**. Yield: 1.6 g (53 %); m.p. 195 °C. ^{1}H NMR ($CDCl_3$): δ = 7.30-7.32 (d, *J* = 1.9, 6.73 Hz, 2H), 7.58-7.62 (t, *J* = 7.1 Hz, 1H), 7.62-7.89 (dd, *J* = 1.6, 7.9 Hz, 1H), 8.33-8.34 (d, *J* = 2.8 Hz, 2H), 8.43-8.46 (dd, *J* = 1.6, 7.9 Hz, 2H), 8.91 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 117.5, 121.7, 125.3, 127.9, 128.6, 132.4, 136.4, 146.4, 151.7, 156.6, 160.3 ppm; IR (KBr): ν = 1601, 1582, 1532, 1514, 1341, 1107, 858, 738, 701 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{13}H_8BrN_3O_4$ [*M*+H]$^+$: 349.9776; found: 349.9768.

General procedure for the synthesis of *sec*-amine-based compounds 18-20: To a suspension of compounds **15-17** in ethanol (50 ml) was added $NaBH_4$ (4 equiv) portion-wise. The mixture was stirred for 5 h at room temperature under inert atmosphere. The solvent was reduced to give a semi-solid. The usual work-up using water/chloroform afforded a yellow solution. The solvent was evaporated under reduced pressure to give yellow-colored oil, which was solidified by keeping it in deep freeze to afford a crystalline solid.

Synthesis of *N*-(2-bromo-3-nitrobenzyl)aniline (18): Compound **15** (9.8 mmol, 3.0 g). Yield: 2.4 g (80 %); m.p. 110 °C. ^{1}H NMR ($CDCl_3$): δ = 4.34, (br s, 1H, NH), 4.48-4.49 (d, *J* = 4.9 Hz, 2H, CH_2), 6.54-6.56 (dd, *J* = 1.0, 7.7 Hz, 2H), 6.73-6.77 (td, *J* = 1.0, 7.4 Hz, 1H), 7.16-7.20 (t, *J* = 7.7 Hz, 2H), 7.35-7.39 (t, *J* = 7.7 Hz, 1H), 7.59-7.62 ppm (t, *J* = 6.6 Hz, 2H); ^{1}H NMR (D_2O-exchange): δ = 4.48 (s, 2H, CH_2), 6.54-6.56 (m, 1H), 6.73-6.74 (t, *J* = 7.7 Hz, 1H), 7.16-7.20 (t, *J* = 7.7 Hz, 2H), 7.35-7.39 (t, *J* = 7.7 Hz, 1H), 7.59-7.62 ppm (t, *J* = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 48.9, 112.9, 114.0, 118.4, 123.6, 128.1, 129.5, 131.7, 141.7, 147.0, 151.2 ppm; IR (KBr): ν = 3412 (N-H), 3075, 3046, 3013, 2899, 1601, 1533, 1375, 1270, 755, 699 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{13}H_{11}BrN_2O_2$ [*M*+H]$^+$: 307.0082; found: 307.0087.

Synthesis of *N*-(2-bromo-3-nitrobenzyl)-4-methylaniline (19): Compound **16** (15.7 mmol, 5.0 g). Yield: 3.95 g (78 %); m.p. 99-92 °C. ^{1}H NMR ($CDCl_3$): δ = 2.23 (s, 3H, CH_3), 4.21 (br s, 1H, NH), 4.46 (s, 2H, CH_2), 6.46-6.48 (d, *J* = 8.4 Hz, 2H), 6.98-6.99 (d, *J* = 8.1 Hz, 2H), 7.34-7.38 (t, *J* = 7.8 Hz, 1H), 7.58-7.62 ppm (t, *J* = 7.8 Hz, 2H); ^{1}H NMR (D_2O-exchange): δ = 2.23 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 4.80 (due to H_2O in D_2O), 6.46-6.48 (d, *J* = 8.4 Hz, 2H), 6.98-6.99 (d, *J* = 8.1 Hz, 2H), 7.34-7.38 (t, *J* = 7.8 Hz, 1H), 7.58-7.62 ppm (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 20.5, 49.1, 113.0, 114.0, 123.6, 127.6, 128.1, 130.0, 131.7, 141.9, 144.8, 151.3 ppm; IR (KBr): ν = 3402, 3077, 2919, 1611, 1534, 1522, 1372, 1303, 1271, 825, 810, 797, 789 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{14}H_{13}BrN_2O_2$ [*M*+H]$^+$: 321.0239; found: 321.0224.

Synthesis of *N*-(2-bromo-3-nitrobenzyl)-4-nitroaniline (20): Compound **17** (5.2 mmol, 2.2 g). Yield: 1.35 g (61 %); m.p. 162 °C. ^{1}H NMR ($CDCl_3$): δ = 4.60-4.62 (d, *J* = 6.3 Hz, 2H, CH_2), 5.12-5.14 (t, NH), 6.54-6.57 (d, *J* = 7.9 Hz, 2H), 7.42-7.45 (t, *J* = 7.4 Hz, 1H), 7.50-7.52 (dd, 1H), 7.65-7.67 (dd, 1H), 8.08-8.11 ppm (d, *J* = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 48.3, 111.7, 144.4, 124.3, 126.5, 128.5, 131.2, 139.2, 139.8, 151.6, 152.4 ppm; IR (KBr): ν = 3364, 1601, 1529, 1309, 1284, 1112, 844 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{13}H_{10}BrN_3O_4$ [*M*+H]$^+$: 351.9933; found: 351.9926.

General method for the synthesis of unsymmetrical selenides 21-23: To a solution of the *in situ* prepared *n*-BuSeNa (6.5 mmol) was added *sec*-amine-based compounds **18-20** (6.5 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature under inert atmosphere. The excess of the solvent was removed under reduced pressure to yield a yellow viscous solid, which was dissolved in $CHCl_3$ and then worked up. The combined organic layers were dried over

anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and then purified on silica gel column using ethyl acetate and petroleum ether (4 %) as eluent to give an orange liquid.

Synthesis of *N*-(2-(butylselanyl)-3-nitrobenzyl)aniline (21): The compound was solidified by keeping in open air to afford yellow crystals. Yield 0.85 g (36 %); m.p. 63 °C. ^{1}H NMR ($CDCl_3$): δ = 0.86-0.90 (t, *J* = 7.3 Hz, 3H), 1.33-1.42 (sextet, *J* = 7.3 Hz, 2H), 1.52-1.64 (quintet, *J* = 7.3 Hz, 2H), 2.84-2.88 (t, *J* = 7.3 Hz, 2H), 4.30 (br s, 1H, NH), 4.65 (s, 2H, CH_2), 6.56-6.58 (d, *J* = 8.1 Hz, 2H), 6.72-6.76 (t, *J* = 7.3 Hz, 1H), 7.16-7.20 (t, *J* = 7.3 Hz, 2H), 7.37-7.41 (t, *J* = 7.7 Hz, 1H), 7.48-7.50 (d, *J* = 6.9 Hz, 1H), 7.64-7.66 ppm (d, *J* = 7.3 Hz, 1H); ^{1}H NMR (D_2O-exchange): δ = 0.86-0.90 (t, *J* = 7.3 Hz, 3H), 1.33-1.42 (sextet, *J* = 7.3 Hz, 2H), 1.52-1.64 (quintet, *J* = 7.3 Hz, 2H), 2.84-2.88 (t, *J* = 7.3 Hz, 2H), 4.65 (s, 2H, CH_2), 4.80 (due to H_2O in D_2O), 6.56-6.58 (d, *J* = 8.1 Hz, 2H), 6.72-6.76 (t, *J* = 7.3 Hz, 1H), 7.16-7.20 (t, *J* = 7.3 Hz, 2H), 7.37-7.41 (t, *J* = 7.7 Hz, 1H), 7.48-7.50 (d, *J* = 6.9 Hz, 1H), 7.64-7.66 ppm (d, *J* = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 13.6, 22.9, 30.3, 32.5, 49.2, 112.9, 113.0, 118.1, 121.3, 121.9, 129.5, 130.6, 146.2, 147.4, 156.8 ppm; ^{77}Se NMR ($CDCl_3$): δ = 203 ppm; IR (KBr): v = 3422, 2958, 2930, 1603, 1530, 1370, 1321, 1265, 802, 751 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{17}H_{20}N_2O_2Se$ [*M*+H]$^+$: 365.0768; found: 365.0771.

Synthesis of *N*-(2-(butylselanyl)-3-nitrobenzyl)-4-methylaniline (22): Yield 1.46 g (78 %). ^{1}H NMR ($CDCl_3$): δ = 0.86-0.90 (t, *J* = 0.1 Hz, 3H), 1.34-1.39 (sextet, *J* = 7.3 Hz, 2H), 1.56-1.63 (quintet, *J* = 7.9 Hz, 2H), 2.23 (s, 3H, CH_3), 2.84-2.88 (t, *J* = 7.5 Hz, 2H), 4.17 (br s, 1H, NH), 4.62 (s, 2H, CH_2), 6.48-6.51 (d, *J* = 8.3 Hz, 2H), 6.97-6.99 (d, *J* = 8.3 Hz, 2H), 7.38-7.47 (t, *J* = 6.2 Hz, 1H), 7.46-7.49 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.63-7.65 ppm (d, *J* = 7.5 Hz, 1H); ^{1}H NMR (D_2O-exchange): δ = 0.86-0.90 (t, *J* = 0.1 Hz, 3H), 1.34-1.39 (sextet, *J* = 7.3 Hz, 2H), 1.56-1.63 (quintet, *J* = 7.9 Hz, 2H), 2.23 (s, 3H, CH_3), 2.84-2.88 (t, *J* = 7.5 Hz, 2H), 4.62 (s, 2H, CH_2), 4.80 (due to H_2O in D_2O), 6.48-6.51 (d, *J* = 8.3 Hz, 2H), 6.97-6.99 (d, *J* = 8.3 Hz, 2H), 7.38-7.47 (t, *J* = 6.2 Hz, 1H), 7.46-7.49 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.63-7.65 ppm (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 13.6, 20.5, 22.9, 30.3, 32.5, 49.5, 113.1, 121.2, 121.8, 127.3, 129.4, 129.9, 130.6, 145.1, 146.3, 156.8 ppm; ^{77}Se NMR ($CDCl_3$): δ = 203 ppm; IR (neat): v = 3420 (N-H), 2958, 2929, 2870, 1617, 1523, 1370, 808 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{18}H_{22}N_2O_2Se$ [*M*+H]$^+$: 379.0925; found: 379.0916.

Synthesis of *N*-(2-(butylselanyl)-3-nitrobenzyl)-4-nitroaniline (23): Compound **23** was purified on silica gel column using ethyl acetate and petroleum ether (10 %) as eluent to give an orange liquid. This was solidified by keeping it in open air for a long time to give a dark green solid. Yield: 0.80 g (46 %); m.p. 88 °C. ^{1}H NMR ($CDCl_3$): δ = 0.86-0.90 (t, *J* = 7.3 Hz, 3H), 1.32-1.40 (sextet, *J* = 7.3 Hz, 2H), 1.56-1.64 (quintet, *J* = 7.6 Hz, 2H), 2.85-2.89 (t, *J* = 7.6 Hz, 2H), 4.77 (s, 2H, CH_2), 5.31 (br s, 1H, NH), 6.55-6.57 (d, *J* = 9.2 Hz, 2H), 7.42-7.46 (t, *J* = 7.6 Hz, 1H), 7.52-7.54 (d, *J* = 7.6 Hz, 1H), 7.57-7.59 (d, *J* = 7.6 Hz, 1H), 8.05-8.05 ppm (d, *J* = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 13.6, 22.9, 30.7, 32.5, 48.6, 111.7, 121.7, 122.5, 126.5, 129.9, 130.5, 138.8, 144.7, 152.7, 157.0 ppm; ^{77}Se NMR ($CDCl_3$): δ = 206 ppm; IR (KBr): v = 3354, 2950, 2926, 2868, 1602, 1525, 1300, 1105, 834 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{17}H_{19}N_3O_4Se$ [*M*+H]$^+$: 410.0619; found: 410.0631.

General procedure for the synthesis of 27 and 28: To a solution of compound **21** (2.75 mmol, 1.0 g), in dry $CHCl_3$ (2 mL) was added Br_2 (3.30 mmol, 0.52 g, 0.18 mL, $CHCl_3$ {2 mL}) for 30 min at 0 °C under an inert atmosphere. After the complete bromination, triethylamine (2.75 mmol, 0.27 g, 0.38 mL) was added to the reaction mixture. The reaction was further stirred at room temperature for 2 h. The mixture was extracted with $CHCl_3$ by adding water (10 mL). Separated organic layers were combined and dried over anhydrous Na_2SO_4. Removal of solvent and purification of the residue by silica gel column chromatography (eluted with 2 % ethyl acetate/petroleum ether mixture) afforded **27** and **28**.

Synthesis of 7-nitro-2-phenyl-2,3-dihydrobenzo[*d*][1,2]selenazole (27): Compound **27** was recrystallized from dichloromethane/diethyl ether to give a dark purple colored solid. Yield: 0.06 g (7 %); m.p. 146 °C (decomposed). ^{1}H NMR ($CDCl_3$): δ = 5.04 (s, 2H), 6.70-6.99 (m, 2H), 7.27-7.29 (m, 1H), 7.38-7.42 (t, *J* = 7.9 Hz, 1H), 7.59-7.61 (d, *J* = 7.3 Hz, 1H), 8.19-8.21 ppm (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 60.0, 116.6, 120.2, 123.5, 127.2, 128.3, 129.5, 139.1, 141.7, 143.1, 151.2 ppm; ^{77}Se NMR ($CDCl_3$): δ = 974 ppm; IR (KBr): v = 2925, 1595, 1511, 1293, 733 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z* calcd for $C_{13}H_{10}N_2O_2Se$ [*M*+H]$^+$: 306.9986; found: 306.9977.

Synthesis of 2-(4-bromophenyl)-7-nitro-2,3-dihydrobenzo[*d*][1,2]selenazole (28): Recrystallization from dichloromethane/diethyl ether afforded a dark purple colored compound **28**. Yield: 0.37 g (35 %); m.p. 155 °C (decomposed). ^{1}H NMR ($CDCl_3$): δ = 5.00 (s, 2H, CH_2), 6.67-6.69 (d, *J* = 8.8 Hz, 2H), 7.33-7.36 (d, *J* = 9.2 Hz, 2H), 7.39-7.44 (t, *J* = 7.7 Hz, 1H), 7.58-7.61 (d, *J* = 8.3 Hz, 1H), 8.19-8.21 ppm (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 59.9, 112.3, 117.9, 123.6, 127.4, 128.4, 132.2, 138.6, 141.2, 142.9, 150.0 ppm; ^{77}Se NMR ($CDCl_3$): δ = 977 ppm; IR (KBr): v = 1589, 1570, 1514, 1286, 801 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{13}H_9BrN_2O_2Se$ [*M*+H]$^+$: 384.9091; found: 384.9091.

General procedure for the synthesis of 29-30 and 32: To a solution of selenide **22** (4.29 mmol, 1.62 g), in dry $CHCl_3$ (20 mL) was added bromine (4.29 mmol, 0.68 g, 222 µL) and Et_3N (4.29 mmol, 0.433 g, 594 µL) at 0 °C according to the procedure described for the preparation of **27**. Removal of the solvent and purification of the residue by silica gel column chromatography (eluted with 2-6 % ethyl acetate/petroleum ether) afforded **29-30** and **32**.

Synthesis of 7-nitro-2-*p*-tolyl-2,3-dihydrobenzo[*d*][1,2]selenazole (29): Recrystallization from dichloromethane/ether afforded a dark black colored compound. Yield 0.05 g (3 %); m.p. 140 °C. ^{1}H NMR ($CDCl_3$): δ = 2.27 (s, 3H, CH_3), 4.99 (s, 2H, CH_2), 6.7-6.8 (d, *J* = 8.5 Hz, 2H), 7.05-7.07 (d, *J* = 8.6 Hz, 2H), 7.37-7.41 (t, *J* = 7.9 Hz, 1H), 7.60-7.62 (d, *J* = 7.3 Hz, 1H), 8.17-8.19 ppm (d, *J* = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 20.6, 61.0, 117.3, 123.4, 127.2, 128.2, 129.9, 130.5, 139.3, 142.1, 143.3, 149.7 ppm; ^{77}Se NMR ($CDCl_3$): δ = 987 ppm; IR (KBr): v = 2916, 2855, 1615, 1511, 1287, 799, 730 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{14}H_{13}N_2O_2Se$ [*M*+H]$^+$: 321.0142; found: 321.0145.

Synthesis of 2-(2-bromo-4-methylphenyl)-7-nitro-2,3-dihydrobenzo[*d*][1,2]selenazole (30): Recrystallization from chloroform/ether afforded orange colored crystals. Yield 0.05 g (3 %); m.p. 165 °C. ^{1}H NMR ($CDCl_3$): δ = 2.24 (s, 3H, CH_3), 4.98 (s, 2H, CH_2), 6.79-6.87 (m, 2H), 7.42 (s, 1H), 7.44-7.47 (t, *J* = 7.3 Hz, 1H), 7.69-7.72 (dd, *J* = 1.1, 7.3 Hz, 1H), 8.17-8.19 ppm (d, *J* = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 20.5, 63.3, 119.2, 119.6, 123.6, 127.5, 127.9, 128.7, 134.3, 135.5, 139.8, 143.7, 144.2, 150.8 ppm; ^{77}Se NMR ($CDCl_3$): δ = 1060 ppm; IR (KBr): v = 3082, 2919, 1598, 1508, 1315, 824 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{14}H_{11}BrN_2O_2Se$ [*M*+H]$^+$: 398.9247; found: 398.9232.

Synthesis of 2-bromo-*N*-(2-(butylselanyl)-3-nitrobenzyl)-4-methylaniline (32): Recrystallization from chloroform/ether afforded yellow crystals. Yield 0.35 g (19 %); m.p. 58 °C. ^{1}H NMR ($CDCl_3$): δ = 0.86-0.91 (t, *J* = 7.4 Hz, 3H), 1.32-1.43 (sextet, *J* = 7.2 Hz, 2H), 1.56-1.64 (quintet, *J* = 5.4 Hz, 2H), 2.21 (s, 3H, CH_3), 2.84-2.87 (t, *J* = 7.6 Hz, 2H), 4.68-4.69 (s, 2H, CH_2), 4.82-4.85 (br s, 1H, NH), 6.33-6.35 (d, *J* = 8.2 Hz, 1H), 6.89-6.92 (dd, *J* = 1.5, 8.2 Hz, 1H), 7.28-7.30 (dd, *J* = 0.6, 1.0 Hz, 1H), 7.37-7.41 (t, *J* = 7.9 Hz, 1H), 7.47-7.50 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.57-7.59 ppm (dd, *J* = 0.7, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 13.6, 20.2, 22.9, 30.4, 32.5, 49.2, 109.8, 111.7, 121.4, 122.0, 128.3, 129.2, 129.6, 130.3, 133.0, 141.9, 145.7, 156.9 ppm; ^{77}Se NMR ($CDCl_3$): δ = 203 ppm; IR (KBr): v = 3394 (N-H), 2967, 2925, 1606, 1509, 1365, 803 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{18}H_{21}N_2O_2SeBr$ [*M*+H]$^+$: 457.0030; found: 457.0016.

Synthesis of 2-(2-bromo-4-nitrophenyl)-7-nitro-2,3-dihydrobenzo[*d*][1,2]selenazole (31): To a solution of selenide **23** (1.95 mmol, 0.8 g), in dry $CHCl_3$ (210 mL) was added bromine (1.9 mmol, 0.31 g, 100 µL) and Et_3N (1.95 mmol, 0.19 g, 270 µL) at 0 °C according to the procedure described for the preparation of **27**. It was filtered off and the filtrate was reduced to give dark a red semi-solid, which on column chromatography with silica gel (eluted with 10 % ethyl acetate/petroleum ether) afforded **31** as a brown powder.Yield 0.005 g (0.6 %); m.p. 170-174 °C. ^{1}H NMR ($CDCl_3$): δ = 5.04 (s, 2H, CH_2), 7.00-7.02 (d, *J* = 8.8 Hz, 1H), 7.49-7.53 (t, *J* = 7.6 Hz, 1H), 7.76-7.79 (d, *J* = 7.4 Hz, 1H), 7.98-8.01 (dd, *J* = 2.2, 8.9 Hz, 1H), 8.21-8.23 (d, *J* = 7.9 Hz, 1H), 8.48-8.49 ppm (d, *J* = 2.2 Hz, 1H); ^{77}Se NMR ($CDCl_3$): δ = 1070 ppm; IR (KBr): v = 1591, 1495, 1315, 1112, 735 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{13}H_8BrN_3O_4Se$ [*M*+H]$^+$: 429.8940; found: 429.8942.

Synthesis of 7-nitro-2-phenyl-2,3-dihydrobenzo[*d*][1,2]selenazole selenium-oxide (33): To a solution of selenide **21** (3.30 mmol, 1.20 g) in $CHCl_3$ (5 mL) was added H_2O_2 (30 %) (19.82 mmol, 2.2 mL) at the room temperature. The reaction was stirred for 25 min at room temperature and then heated at 55-60 °C for 40 min. An orange precipitate formed was filtered and dried under vacuum to give orange solid **33**. The product was recrystallized from DMSO/diethyl ether to afford dark red needle-like crystals. Yield: 0.42 g (40 %); m.p. 164 °C. ^{1}H NMR (DMSO-d_6): δ = 5.17-5.22 (d, *J* = 16.0 Hz, 1H), 5.24-5.29 (d, *J* = 16.0 Hz, 1H), 6.98-7.03 (t, *J* = 7.3 Hz, 1H), 7.21-7.24 (d, *J* = 7.7 Hz, 2H), 7.35-7.40 (t, *J* = 7.3 Hz, 2H), 7.93-7.98 (t, *J* = 7.7 Hz, 1H), 8.13-8.15 (d, *J* = 7.7 Hz, 1H), 8.37-8.40 ppm (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ = 55.9, 116.8, 121.3, 123.8, 129.9, 132.1, 133.2, 140.5, 144.0, 144.6, 145.2 ppm; ^{77}Se NMR (DMSO-d_6): δ = 1182 ppm; IR (KBr): v = 3081, 2823, 1594, 1531, 1341, 823, 814, 748 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{14}H_{10}N_2O_3Se$ [*M*+H]$^+$: 322.9935; found: 322.9932.

Synthesis of 7-nitro-2-*p*-tolyl-2,3-dihydrobenzo[*d*][1,2]selenazole selenium-oxide (34): Compound **34** was synthesized from **22** (1.32 mmol, 0.50 g), $CHCl_3$ (2 mL) and H_2O_2 (30 %) (7.96 mmol, 0.90 mL) according to the procedure described for the preparation of **33**. A red colored precipitate obtained was filtered and dried under vacuum. The product was recrystallized from DMSO/diethyl ether to afford dark red crystals. Yield: 0.18 g (38 %); m.p. 156-158 °C. ^{1}H NMR (DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 5.14-5.19 (d, *J* = 16.0 Hz, 1H), 5.22-5.27 (d, *J* = 16.0 Hz, 1H), 7.12-7.15 (d, *J* = 8.7 Hz, 2H), 7.18-7.21 (d, *J* = 8.7 Hz, 2H), 7.95-7.97 (t, *J* = 7.8 Hz, 1H), 8.12-8.15 (d, *J* = 7.8 Hz, 1H), 8.37-8.39 ppm (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ = 20.1, 55.9, 117.2, 123.6, 130.1, 130.4, 131.9, 132.9, 142.8, 141.9, 143.9, 145.3 ppm; ^{77}Se NMR (DMSO-d_6): δ = 1174 ppm; IR (KBr): v = 3091, 2824, 1570, 1530, 1340, 1280, 827, 733 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{14}H_{12}N_2O_3Se$ [*M*+H]$^+$: 337.0091; found: 337.0087.

Preparation of 2-bromo-3-nitro-*N*-phenylbenzamide (41): To a mixture of thionyl chloride (50 mL) and DMF (1 mL) was added 2-bromo-3-nitrobenzoic acid[30a] (40.0 mmol, 10.0 g) and refluxed for 3-4 h. The excess of thiony chloride was removed under vacuum applying a liquid N_2 trap. The brown precipitate was obtained, which was further dissolved in dichloromethane. Aniline (100 mmol, 10 mL) in dry dichloromethane was added dropwise to a suspension of the brown precipitate obtained at room temperature over a period of 2-3 h. Additionally, the reaction was stirred at room temperature for overnight. The mixture was extracted with dichloromethane by adding water (10 mL). The separated layers were combined and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give yellow-colored oil, which was solidified by keeping in deep freeze to give a crystalline solid **41**. Yield: 6.5 g (50 %); m.p. 153-155 °C. ^{1}H NMR ($CDCl_3$): δ = 7.18-7.23 (t, *J* = 7.3 Hz, 1H), 7.36-7.41 (t, *J* = 7.3 Hz, 2H), 7.50-7.55 (t, *J* = 7.8 Hz, 1H), 7.59-7.61 (d, *J* = 7.3 Hz, 2H), 7.68-7.71 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.45-7.78 ppm (dd, *J* = 1.5, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 111.6, 120.4, 125.6, 126.2, 128.9, 129.4, 131.9, 137.2, 141.2, 151.2, 164.4 ppm; IR (KBr): v = 3289 (NH), 1661, 1528, 1369, 1326, 755 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{13}H_9BrN_2O_3$ [*M*+H]$^+$: 320.9875; found: 320.9873.

Synthesis of 2-(butylselanyl)-3-nitro-*N*-phenylbenzamide (42): Compound **42** was synthesized from **41** (6.22 mmol, 2.0 g) with the *in situ* prepared *n*-BuSeNa (6.22 mmol, 0.24 g) in deoxygenated ethanol according to the procedure described for the preparation of **21-23**. Removal of solvent and purification of the residue by silica gel column chromatography (eluted with 10 % ethyl acetate/petroleum ether mixture) afforded a yellow solid **42**. Yield: 1.2 g (53 %); m.p. 98 °C. ^{1}H NMR ($CDCl_3$): δ = 0.74-0.79 (t, *J* = 7.3 Hz, 3H), .1.19-1.31 (sextet, *J* = 7.3 Hz, 2H), 1.45-1.55 (quintet, *J* = 7.3 Hz, 2H), 2.85-2.89 (t, *J* = 7.3 Hz, 2H), 7.18-7.22 (t, *J* = 7.3 Hz, 1H), 7.38-7.43 (t, *J* = 8.3 Hz, 2H), 7.49-7.54 (t, *J* = 7.8 Hz, 1H), 7.64-7.66 (d, *J* = 6.8 Hz, 2H), 7.82-7.87 (dd, *J* = 1.5, 6.8 Hz, 1H), 7.88-7.91 (dd, *J* = 1.5, 6.8 Hz, 1H), 8.35 ppm (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 13.5, 22.7, 31.1, 31.9, 119.9, 122.4, 125.3, 125.6, 128.9, 129.4, 133.3, 137.6, 142.8, 155.0, 165.4 ppm; ^{77}Se NMR ($CDCl_3$): δ = 276 ppm; IR (KBr): v = 3294 (NH), 1658 (CO), 1520, 1436, 1324, 748, 713 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{17}H_{18}N_2O_3$ Se [*M*+H]$^+$: 379.0561; found: 379.0546.

Preparation of `2-phenyl-7-nitro-1,2-benzisoselenazol(*2H*)-3-one (8): To a solution of **42** (0.53 mmol, 0.40 g), in dry $CHCl_3$ (5 mL) was added bromine (0.53 mmol, 0.084 g, 0.027 mL) and triethylamine (0.53 mmol, 0.053 g, 0.072 mL) according to the procedure described for the preparation of **27**. Removal of solvent and purification of the residue by silica gel column chromatography (eluted with 10 % ethyl acetate/petroleum ether mixture) afforded **8.** Yield: 0.31 g (92 %, lit.[13a] 78 %); m.p. 168-170 °C (lit. 160-163 °C). ^{1}H NMR ($CDCl_3$): δ = 7.30-7.35 (t, *J* = 7.3 Hz, 2H), 7.45-7.50 (t, *J* = 8.6 Hz, 2H) 7.63-7.65 (d, *J* = 7.3 Hz, 1H), 7.71-7.76 (t, *J* = 7.8 Hz, 1H), 8.46-8.49 (dd, *J* = 1.0, 7.7 Hz, 1H), 8.57-8.60 ppm (dd, *J* = 1.0, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 125.1, 127.2, 127.7, 127.9, 129.7, 131.5, 135.3, 136.4, 138.5, 142.1, 163.9 ppm; ^{77}Se NMR ($CDCl_3$): δ = 924 ppm; IR (KBr): v = 1650 (CO), 1607, 1518 (NO_2), 1298, 751, 736 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z*: calcd for $C_{13}H_8N_2O_3Se$ [*M*+H]$^+$: 320.9778; found: 320.9769.

Coupled Reductase Assay: GPx-like activity of organoselenium compounds was determined by the spectrophotometric method at 340 nm described by Wilson et al.[32] The test mixture contained GSH (2 mM), EDTA (1 mM), glutathione reductase (1.3 unit/ml), and NADPH (0.4 mM) in 100 mM potassium phosphate buffer, pH 7.5. GPx samples (80 µM) were added to the test mixture at 25 °C and the reaction was started by the addition of H_2O_2 (1.6 mM). The initial reduction rates were calculated from the oxidation rate of NADPH at 340 nm. The initial reduction rate was determined at least 3-4 times and calculated from the first 5-10% of the reaction by using 6.22 mM^{-1}cm^{-1} as the extinction coefficient for NADPH.

X-ray Crystallographic Analysis: X-ray crystallographic studies were carried out for compounds **21**, **29**-**30** and **32**-**33** on a Oxford Diffraction Gemini diffractometer using graphite-monochromatized Mo Kα radiation λ = 1.54184 Å for **21**, **29**-**30** and **32**-**33**. The diffraction measurements were performed at 295(2) K. The structures were solved by direct method and refined by a full-matrix least-squares procedure on F^2 for all reflections in SHELXL-97 software.[33] Hydrogen atoms were localized by geometrical means. A riding model was chosen for refinement. The isotropic thermal parameters of hydrogen atoms were fixed at 1.5 times for (CH_3 groups) or 1.2 times *U* (eq) (Ar-H) of the corresponding carbon atoms. Some details of the refinement is given in Tables 6-7. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publications CCDC-808887 (**21**), CCDC-808888 (**33**), CCDC-808890 (**32**), CCDC-808891 (**29**) and CCDC-808892 (**30**). These data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK or *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 5. Crystal Data and Structure Refinement for **21**, **29** and **30**.

Compound	21	29	30
Empirical formula	$C_{17}H_{20}N_2O_2Se$	$C_{14}H_{12}N_2O_2Se$	$C_{14}H_{11}BrN_2O_2Se$
Formula weight	363.31	319.22	398.12
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	*P* -1	*P* 1 2_1 / *c* 1	*P* 1 2_1 / *c* 1
a(Å)	8.1599(5)	13.6944(6)	13.0789(2)
b(Å)	10.1630(6)	6.3988(3)	7.80369(12)
c(Å)	11.0254(8)	15.6904(8)	13.9947(2)
α(deg)	93.953(6)	90	90
β(deg)	107.286(6)	106.224(5)	98.9459(16)
γ(deg)	99.356(5)	90	90
V(Å^3)	854.71(10)	1320.17(11)	1410.97(4)
Z	2	4	4
D(calcd)(Mg/m^3)	1.412	1.606	1.874
Abs coeff(mm^{-1})	3.041	3.854	6.951
Obsd reflens [I<2σ]	6633	5302	6152
Final R(F) [I<2σ(I)][a]	0.0381	0.0503	0.0325
wR(F^2) indices[I<2σ(I)]	0.1071	0.1404	0.0848
Data/restrain/parameters	3567 / 0 / 204	2736 / 0 / 173	2942 / 0 / 183
Goodness of fit on F^2	1.039	1.060	1.043

[a] Definitions: $R(F_o) = ||F_o| - |F_c||/|F_o|$ and $wR(F_o^2) = \{\Sigma[w(F_o^2 - F_c^2)^2]/[w(F_c^2)^2\}^{1/2}$.

Compound	32	33
Empirical formula	$C_{18}H_{21}BrN_2O_2Se$	$C_{13}H_{10}N_2O_3Se$
Formula weight	456.24	321.19
Crystal system	Monoclinic	Orthorhombic
Space group	*P* 1 2_1 1	*P b c n*
a(Å)	10.9761(5)	13.1780(4)
b(Å)	8.0108(2)	8.4675(3)
c(Å)	11.7412(5)	22.6182(8)
α(deg)	90	90
β(deg)	113.054(5)	90
γ(deg)	90	90
V(Å^3)	949.93(7)	2523.85(15)
Z	2	8
D(calcd)(Mg/m^3)	1.595	1.691
Abs coeff(mm^{-1})	5.240	4.100
Obsd reflens [I<2σ]	6828	21353
Final R(F) [I<2σ(I)][a]	0.0333	0.0635
wR(F^2) indices[I<2σ(I)]	0.0937	0.1407
Data/restrain/parameters	3575 / 1 / 238	2659 / 0 / 172
Goodness of fit on F^2	1.062	1.179

Table 7. Crystal Data and Structure Refinement for **32** and **33**.

[a] Definitions: $R(F_o) = ||F_o| - |F_c||/|F_o|$ and $wR(F_o^2) = \{\Sigma[w(F_o^2 - F_c^2)^2]/[w(F_c^2)^2\}^{1/2}$.

Computational Methods: All theoretical calculations were executed by using Gaussian 03 suite of quantum chemical programs.[34] The hybrid Becke 3-Lee-Yang-Parr (B3LYP) exchange correlation functional was implemented for DFT calculations.[35] The geometry optimizations were carried out at the B3LYP level of DFT by using the 6-31G(d) basis sets. The total energies of the optimized geometries were computed based on with inclusion of zero-point corrections. The ^{77}Se NMR calculations were performed at B3LYP/6-311+G (d,p) level

on B3LYP/6–31G(d)-level-optimized geometries by using the gauge-including atomic orbital (GIAO) method (referenced with respect to the peak of Me_2Se).[20] The quantifications of orbital interaction were done by natural bond orbital (NBO) analysis at B3LYP/6–311+G(d,p) level.[26] Atoms in molecules (AIM)[27-29] calculations have also been used to confirm distinct bond critical point. Nucleus-Independent Chemical Shifts (NICS)[36] have been carried out at B3LYP/6–31G(d)//6-311+G(d,p) level.

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