Electronic Supplementary Material (ESI) for ChemComm.

SnAP reagents for the synthesis of Selenomorpholines and 1,4-Selenazepanes and their biological evaluation

Supporting Information

Contents

1. General Information

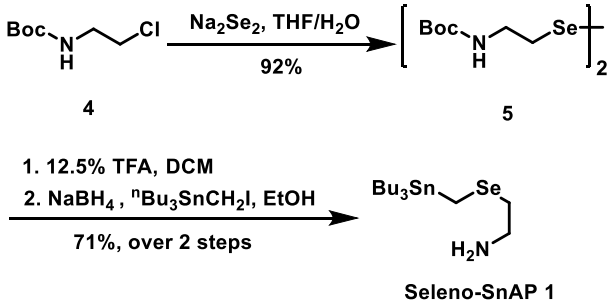
All the air-sensitive and moisture-sensitive reactions were carried out under N_2 atmosphere in oven-dried glassware. TLC plates were stained using potassium permanganate or ninhydrin solutions. Flash column chromatography was performed with silica gel (200-300 mesh) and anhydrous KF was used as a precolumn (ca. 3 cm) on top of the silica gel for the purification of selenium-containing N-heterocyclic products. Petroleum ether (PE, b.p. 60-90 °C) and ethyl acetate (EA) are used for column purification. All the selenium-containing N-heterocyclic compounds were purified with column chromatography with appropriate eluents with 0.1% triethylamine (TEA) v/v.

Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane (DCM) and tetrahydrofuran (THF) were dried and purified by passing through a neutral alumina column under N_2 (solvent purification system). Hexafluoroisopropanol (HFIP) was distilled from molecular sieves 4 Å. $Cu(OTf)_2$ purchased from Strem Chemicals was dried at 110 °C under high vacuum for 2 h and stored in desiccator.

^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker Avance spectrometers (400 MHz for ^1H NMR and 101 MHz for ^{13}C NMR). ^1H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CDCl_3$ peak at 7.26 ppm used as a standard). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CDCl_3$ at 77.16 ppm used as a standard). NMR coupling constants (*J*) are reported in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, doublet of doublet; ddd, double of doublet of doublet; dt, doublet of triplet; t, triplet; q, quartet; quint, quintet; sext, sextet; m, multiplet.

2. Synthesis of Seleno-SnAP reagents

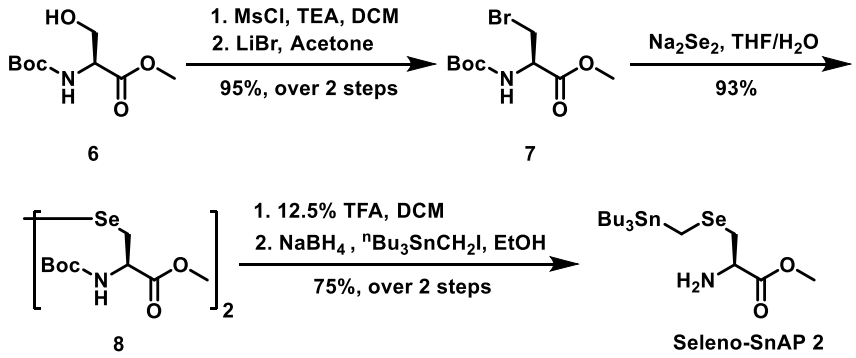
Synthesis of Seleno-SnAP 1



Di-*tert*-butyl (diselanediylbis(ethane-2,1-diyl))dicarbamate (5). To an ice-cooled solution of Na_2Se_2[1] (1 *N*, 18 mL, 18 mmol, 0.6 equiv) was added **4** (5.39 g, 30 mmol, 1.0 equiv) in THF (40 mL) dropwise. Then the reaction was stirred at room temperature overnight. The reaction was removed to a separating funnel and extracted with EA. The organic layer was then dried over Na_2SO_4. The solvent was evaporated in vacuo and purification of the crude compound by column chromatography (PE/EA, 4:1) to yield **5** as yellow solid (6.16 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (br s, 2H), 3.47 (q, *J* = 6.1 Hz, 4H), 2.99 (t, *J* = 6.6 Hz, 4H), 1.44 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 79.7, 41.1, 29.6, 28.5. ESI-HRMS calcd for $C_{14}H_{28}N_2NaO_4Se_2$ [M + Na] 477.0272, found 477.0279.

2-(((Tributylstannyl)methyl)selanyl)ethan-1-amine (Seleno-SnAP 1). To an ice-cooled solution of diselenide **5** (4.46 g, 10 mmol, 1.0 equiv) in DCM (36 mL) was slowly added a mixture of DCM/TFA (3:1, v/v, 36 mL) and then the reaction was stirred for 4 h at room temperature. After the reaction was completed, the solvent was evaporated under vacuum and most TFA was removed. Then deprotected diselenide was dissolved in EtOH (80 mL) and triethylamine was used to neutralize the remaining TFA. The yellow solution was degassed for 5 min and then cooled to 0 °C. $NaBH_4$ (0.84 g, 22 mmol, 2.2 equiv) was added under N_2 in one portion. The mixture was stirred at 0 °C for 15 min and tributyl(iodomethyl)stannane[2] (9.48 g, 22 mmol, 2.2 equiv) was added. After 30 min, the solvent was evaporated in vacuo. The resulting mixture was purified by column chromatography (PE/EA, 2:1) to give Seleno-SnAP **1** as light yellow oil (6.06 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92 (t, *J* = 6.4 Hz, 2H), 2.63 (t, *J* = 6.5 Hz, 2H), 1.82 (s, 2H), 1.58 – 1.44 (m, 6H), 1.40 (br s, 2H), 1.35 – 1.25 (m, 6H), 0.96 – 0.85 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 41.0, 33.7, 29.2, 27.4, 13.8, 9.8, -2.5. ESI-HRMS calcd for $C_{15}H_{36}NSeSn$ [M + H] 430.1030, found 430.1022.

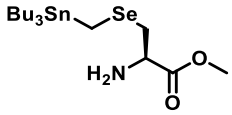
Synthesis of Seleno-SnAP 2



Methyl (*R*)-3-bromo-2-((*tert*-butoxycarbonyl)amino)propanoate (7). To a solution of **6** (13.15 g, 60 mmol, 1.0 equiv) in DCM (300 mL) was added methanesulfonyl chloride (5.1 mL, 66 mmol, 1.1 equiv) dropwise at 0 °C in an ice bath and then triethylamine (10.0 mL, 72 mmol, 1.2 equiv) was added. The resulting solution was stirred for 8 h, lithium bromide (52.11 g, 600 mmol, 10.0 equiv) and acetone (250 mL) were added to the solution at 0 °C and then left to stir at room temperature for 14 h. The solvents were removed and the residue was dissolved in EA and poured into a separation funnel. The organic layer was washed with H_2O, saturated $NaHCO_3$ and brine. The organic layer was then dried over Na_2SO_4. The solvent was evaporated in vacuo and purification of the crude compound by column chromatography (PE/EA, 5:1) to yield **7** as white solid (16.08 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (br d, *J* = 7.0 Hz, 1H), 4.75 (dt, *J* = 7.1, 3.1 Hz, 1H), 3.84 – 3.77 (m, 4H), 3.70 (dd, *J* = 10.4, 3.5 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 155.1, 80.6, 54.0, 53.1, 34.2, 28.4. Spectral data matches with the literature data.[3]

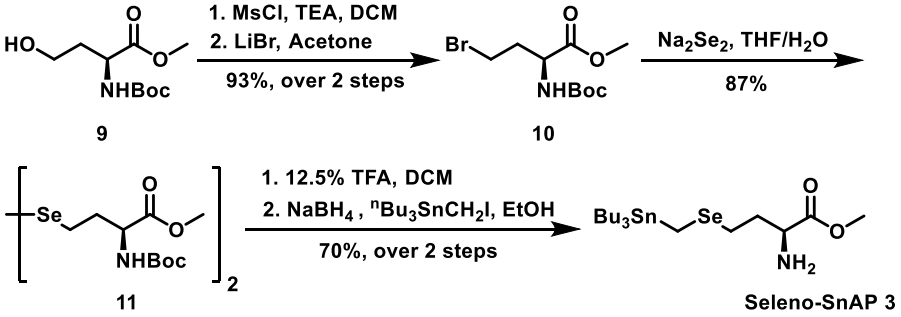
Dimethyl 3,3'-diselanediyl(2*R*,2'*R*)-bis(2-((*tert*-butoxycarbonyl)amino)propanoate) (8). To an ice-cooled solution of Na_2Se_2 (1 *N*, 24 mL, 24 mmol, 0.6 equiv) was added bromide **7** (11.29 g, 40 mmol, 1.0 equiv) in THF (50 mL) dropwise. Then the reaction was stirred at room temperature overnight. The reaction was removed to a separating funnel and extracted with EA. The organic layer was then dried over Na_2SO_4. The solvent was evaporated in vacuo and purification of the crude compound by column chromatography (PE/EA, 4:1) to yield **8** as yellow solid (10.46 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (d, *J* = 8.4 Hz, 2H), 4.67 – 4.49 (m, 2H), 3.74 (s, 6H), 3.43 – 3.27 (m, 4H), 1.43 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 155.1, 80.4, 53.8, 52.7, 32.5, 28.4. ESI-HRMS calcd for $C_{18}H_{32}N_2NaO_8Se_2$ [M + Na] 587.0382, found 587.0391.

Methyl (*R*)-2-amino-3-(((tributylstannyl)methyl)selanyl)propanoate (Seleno-SnAP 2). To an ice-cooled solution of diselenide **8** (8.44 g, 15 mmol, 1.0 equiv) in

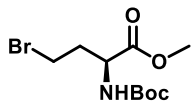


DCM (64 mL) was slowly added a mixture of DCM/TFA (3:1, v/v, 64 mL) and then the reaction was stirred at room temperature for 4 h. After the reaction was completed, the solvent was evaporated under vacuum and most TFA was removed. Then deprotected diselenide was dissolved in EtOH (120 mL), triethylamine was used to neutralize the remaining TFA. The yellow solution was degassed for 5 min and then cooled to 0 °C. $NaBH_4$ (1.25 g, 33 mmol, 2.2 equiv) was added under N_2 slowly. The mixture was stirred at 0 °C for 15 min and tributyl(iodomethyl)stannane (14.22 g, 33 mmol, 2.2 equiv) was added. After 30 min, the solvent was evaporated in vacuo. The resulting mixture was purified by column chromatography (PE/EA, 4:1) to give Seleno-SnAP **2** as light yellow oil (10.92 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 – 3.68 (m, 4H), 2.91 (dd, *J* = 12.5, 4.7 Hz, 1H), 2.80 (dd, *J* = 12.5, 7.7 Hz, 1H), 1.92 – 1.82 (m, 4H), 1.55 – 1.44 (m, 6H), 1.34 – 1.25 (m, 6H), 0.95 – 0.84 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 53.9, 52.3, 34.2, 29.2, 27.4, 13.8, 9.8, -1.1. ESI-HRMS calcd for $C_{17}H_{38}NO_2SeSn$ [M + H] 488.1085, found 488.1075.

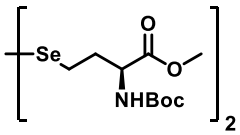
Synthesis of Seleno-SnAP 3



Methyl (*S*)-4-bromo-2-[(*tert*-butoxycarbonyl)amino] butanoate (10). To a solution



of **9** (6.0 g, 25.6 mmol, 1.0 equiv) in DCM (80 mL) was added methanesulfonyl chloride (2.2 mL, 28.2 mmol, 1.1 equiv) dropwise at 0 °C in an ice bath and then triethylamine (4.3 mL, 30.7 mmol, 1.2 equiv) was added. The resulting solution was stirred for 6 h, lithium bromide (22.23 g, 256.0 mmol, 10.0 equiv) and acetone (60 mL) were added to the solution at 0 °C and then left to stir at room temperature for 14 h. The solvents were removed and the residue was dissolved in EA and poured into a separation funnel. The organic layer was washed with H_2O, saturated $NaHCO_3$ and brine. The organic layer was then dried over Na_2SO_4. The solvent was evaporated in vacuo and purification of the crude compound by column chromatography (PE/EA, 5:1) to yield **10** as pale yellow oil (7.05 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (br d, *J* = 6.5 Hz, 1H), 4.46 – 4.34 (m, 1H), 3.73 (s, 3H), 3.41 (t, *J* = 7.0 Hz, 2H), 2.44 – 2.30 (m, 1H), 2.25 – 2.10 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 155.4, 80.3, 52.7, 52.5, 35.9, 28.4, 28.4. Spectral data matches with the literature data.[4]

Dimethyl 4,4'-diselanediyl(2*S*,2'*S*)-bis(2-((*tert*-butoxycarbonyl)amino)butanoate) (11).  To an ice-cooled solution of Na_2Se_2 (1 *N*, 12 mL, 12 mmol, 0.6 equiv) was added bromide **10** (5.93 g, 20 mmol, 1.0 equiv) in THF (25 mL) dropwise. Then the reaction was stirred at room temperature overnight. The reaction was removed to a separating funnel and extracted with EA. The organic layer was then dried over Na_2SO_4. The solvent was evaporated in vacuo and purification of the crude compound by column chromatography (PE/EA, 3:1) to yield **11** as yellow solid (5.49 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (d, *J* = 7.9 Hz, 2H), 4.42 – 4.30 (m, 2H), 3.71 (s, 6H), 2.87 (t, *J* = 7.6 Hz, 4H), 2.29 – 2.16 (m, 2H), 2.06 – 1.96 (m, 2H), 1.39 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 155.4, 80.1, 53.3, 52.5, 34.4, 28.3, 25.0. ESI-HRMS calcd for $C_{20}H_{36}N_2NaO_8Se_2$ [M + Na] 615.0695, found 615.0687.

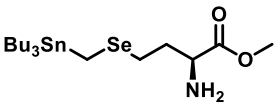
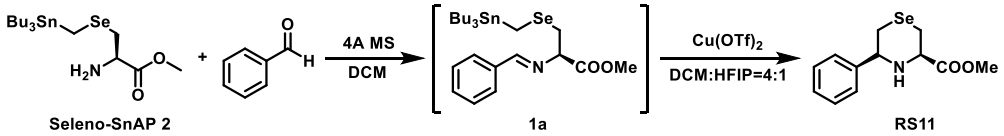
Methyl (*S*)-2-amino-4-(((tributylstannyl)methyl)selanyl)butanoate (Seleno-SnAP 3).  To an ice-cooled solution of diselenide **11** (2.95 g, 5 mmol, 1.0 equiv) in DCM (24 mL) was slowly added a mixture of DCM/TFA (3:1, v/v, 24 mL) and then the reaction was stirred at room temperature for 4 h. After the reaction was completed, the solvent was evaporated under vacuum and most TFA was removed. Then deprotected diselenide was dissolved in EtOH (40 mL) and triethylamine was used to neutralize the remaining TFA. The yellow solution was degassed for 5 min and then cooled to 0 °C. $NaBH_4$ (0.42 g, 11.0 mmol, 2.2 equiv) was added under N_2 in one portion. The mixture was stirred at 0 °C for 15 min and tributyl(iodomethyl)stannane (4.74 g, 11.0 mmol, 2.2 equiv) was added. After 30 min, the solvent was evaporated in vacuo. The resulting mixture was purified by column chromatography (PE/EA, 4:1) to give Seleno-SnAP **3** as light yellow oil (3.49 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.58 (dd, *J* = 8.2, 4.9 Hz, 1H), 2.67 – 2.58 (m, 2H), 2.16 – 2.06 (m, 1H), 1.93 – 1.78 (m, 3H), 1.58 – 1.44 (m, 8H), 1.35 – 1.25 (m, 6H), 0.95 – 0.86 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 54.5, 52.2, 34.8, 29.2, 27.4, 24.5, 13.8, 9.8, -2.1. ESI-HRMS calcd for $C_{18}H_{40}NO_2SeSn$ [M + H] 502.1241, found 502.1233.

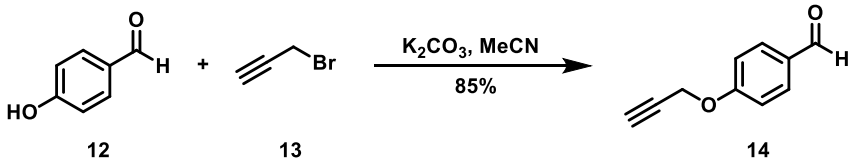
Table S1: Optimization of reaction conditions.



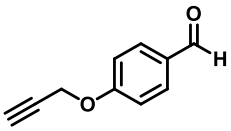
Entry[a]	Additive	Temp.	Yield[b] (%)
1	2,6-Lutidine (1.0 equiv)	RT	51 (40)[c]
2	Pyridine (1.0 equiv)	RT	trace
3	2,6-Dibromopyridine (1.0 equiv)	RT	trace
4	1,10-Phenanthroline (1.0 equiv)	RT	trace
5	2,6-Di-^{t}butyl pyridine (1.0 equiv)	RT	51
6	Collidine (1.0 equiv)	RT	30
7	DMEDA (1.0 equiv)	RT	0
8	2,6-Lutidine (1.0 equiv) 2,2'-Dipyridine (0.1 equiv)[e]	RT	40
9	2,6-Lutidine (1.0 equiv) 2,6-Di-^{t}butyl pyridine (0.1 equiv)[e]	RT	50
10	2,6-Lutidine (1.0 equiv) 5,5'-Dimethyl-2,2'-bipyridine (0.1 equiv)[e]	RT	45
11	2,6-Lutidine (1.0 equiv) 2-Methyl-6-phenylpyridine (0.1 equiv)[e]	RT	38
12	2,6-Lutidine (1.0 equiv) 2-Phenylpyridine (0.1 equiv)[e]	RT	40
13	2,6-Lutidine (1.0 equiv) 2-Phenoxypyridine (0.1 equiv)[e]	RT	25
14	**2,6-Lutidine (2.0 equiv)**	**RT**	**62 (52)[c]**
15[d]	2,6-Lutidine (1.0 equiv)	60	42
	Deviation from the standard condition 14		
16	$CuCl_2$ instead of $Cu(OTf)_2$	RT	11%
17	CuI instead of $Cu(OTf)_2$	RT	trace
18	Cu(OAc)2 instead of $Cu(OTf)_2$	RT	no reaction
19	Cu(I) thiophene-2-carboxylate instead of $Cu(OTf)_2$	RT	no reaction
20	$CuSO_4$. xH_2O	RT	10%
21	THF instead of DCM:HFIP	RT	~10%
22	1,4-dioxane instead of DCM:HFIP	RT	~10%
23	MeOH instead of DCM:HFIP	RT	trace
24	*t*BuOH instead of DCM:HFIP	RT	trace
25	Toluene instead of DCM:HFIP	RT	trace
26	CH_3CN instead of DCM:HFIP	RT	trace

[a] All reactions were performed on a 0.1 mmol scale. [b] Yield determined by ^{1}H NMR spectroscopy with benzyl methyl ether as an internal standard. [c] Isolated yield after purification by silica gel column chromatography. [d] Reaction performed at 60 °C for 2 h. [e] Ligand. DMEDA=*N*,*N*'-dimethylethylenediamine, HFIP=hexafluoroisopropyl alcohol.

Synthesis of aldehyde 14



4-(Prop-2-yn-1-yloxy)benzaldehyde (14). To a solution of 4-hydroxybenzaldehyde (0.25 g, 2 mmol, 1.0 equiv) and anhydrous K_2CO_3 (0.28 g, 2 mmol, 1.0 equiv) in 10 mL acetone was added propargyl bromide (0.36 g, 3 mmol, 1.5 equiv). The resulting mixture was heated under reflux for 6 h, then the remaining solution was filtered and washed with acetone. After concentration, the residue was purified by column chromatography (PE/EA, 5:1) to give **14** as a white solid (0.27 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.90 – 7.83 (m, 2H), 7.12 – 7.06 (m, 2H), 4.78 (d, *J* = 2.4 Hz, 2H), 2.57 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9, 162.5, 132.0, 130.7, 115.3, 77.7, 76.5, 56.1. Spectral data matches with the literature data.[5]



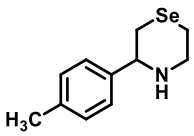
3. Synthesis of Selenomorpholines and 1,4-selenazepanes

General procedure:

To a 10 mL oven-dried tube were added the amino tributylstannane – SnAP reagent (0.25 mmol, 1.00 equiv), the corresponding aldehyde (0.25 mmol, 1.00 equiv) and MS 4Å (ca. 100 mg/mmol). The tube was sealed with rubber stopper, exchanged the gas using N_2 for 3 **times** and then dry DCM (1.5 mL) was added. The reaction mixture was stirred at room temperature for 2-12 h and filtered through a short layer of Celite (DCM rinse). The filtrate was concentrated under reduced pressure to afford the imine.

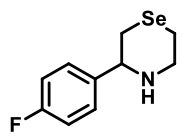
Separately, to a 20 mL oven-dried tube equipped with $Cu(OTf)_2$ (0.25 mmol, 1.00 equiv) were added HFIP (1.0 mL) and 2,6-lutidine (0.5 mmol, 2.00 equiv) under N_2. The mixture was stirred at room temperature for 1 h, during which a dark green homogeneous suspension was formed. A solution of the imine (0.25 mmol, 1.00 equiv) in DCM (4.0 mL) was added in one portion and the resulting mixture was stirred at room temperature for 12 h. The reaction was quenched with a mixture of sat aq. $NaHCO_3$ (2.5 mL) and 10% aq. NH_4OH (1.5 mL), and stirred vigorously for 15 min. The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography afforded the corresponding N-heterocycle.

3-(*p*-Tolyl)selenomorpholine (RS1). Purification by flash column chromatography (PE/EA, 2:1) afforded **RS1** (37 mg, 62% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 3.97 (dd, *J* = 10.9, 2.0 Hz, 1H), 3.61 (dt, *J* = 12.6, 3.0 Hz,

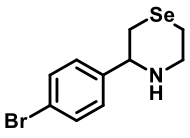


1H), 3.26 (td, *J* = 12.3, 2.2 Hz, 1H), 3.03 – 2.94 (m, 2H), 2.42 (ddd, *J* = 11.8, 8.1, 4.1 Hz, 2H), 2.33 (s, 3H), 1.77 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 137.5, 129.4, 126.4, 63.4, 50.3, 25.0, 21.2, 18.3. ESI-HRMS calcd for $C_{11}H_{16}NSe$ [M + H] 242.0443, found 242.0447.

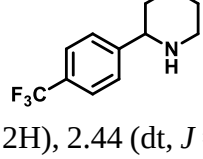
3-(4-Fluorophenyl)selenomorpholine (RS2). Purification by flash column chromatography (PE/EA, 2:1) afforded **RS2** (44 mg, 72% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (ddd, *J* = 8.4, 5.3, 2.5 Hz, 2H), 7.04 – 6.97 (m, 2H), 3.99 (dd, *J* = 10.9, 2.0 Hz, 1H), 3.61 (dt, *J* = 12.0, 3.2 Hz, 1H), 3.26 (td, *J* = 12.3, 2.2 Hz, 1H), 3.02 – 2.89 (m, 2H), 2.48 – 2.35 (m, 2H), 1.75 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (d, J_{CF} = 245.8 Hz), 141.0 (d, J_{CF} = 3.0 Hz), 128.1 (d, J_{CF} = 8.0 Hz), 115.5 (d, J_{CF} = 21.1 Hz), 62.9, 50.2, 25.0, 18.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.7. ESI-HRMS calcd for $C_{10}H_{13}FNSe$ [M + H] 246.0192, found 246.0190.



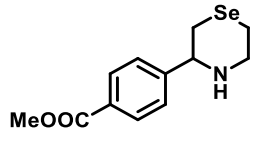
3-(4-Bromophenyl)selenomorpholine (RS3). Purification by flash column chromatography (PE/EA, 2:1) afforded **RS3** (53 mg, 69% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 7.25 – 7.21 (m, 2H), 3.97 (dd, *J* = 10.9, 2.0 Hz, 1H), 3.60 (dt, *J* = 12.7, 3.1 Hz, 1H), 3.25 (td, *J* = 12.3, 2.2 Hz, 1H), 3.02 – 2.86 (m, 2H), 2.47 – 2.35 (m, 2H), 1.74 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 131.9, 128.3, 121.5, 63.0, 50.1, 24.8, 18.3. ESI-HRMS calcd for $C_{10}H_{13}BrNSe$ [M + H] 305.9391, found 305.9396.



3-(4-(Trifluoromethyl)phenyl)selenomorpholine (RS4). Purification by flash column chromatography (PE/EA, 2:1) afforded **RS4** (54 mg, 73% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 4.08 (dd, *J* = 11.0, 2.1 Hz, 1H), 3.66 – 3.59 (m, 1H), 3.27 (td, *J* = 12.4, 2.2 Hz, 1H), 3.05 – 2.88 (m, 2H), 2.44 (dt, *J* = 12.4, 1.9 Hz, 2H), 1.76 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 130.0 (q, J_{CF} = 32.4 Hz), 126.9, 125.8 (q, J_{CF} = 3.7 Hz), 124.2 (q, J_{CF} = 272.0 Hz), 63.2, 50.0, 24.7, 18.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5. ESI-HRMS calcd for $C_{11}H_{13}F_3NSe$ [M + H] 296.0160, found 296.0163.



Methyl 4-(selenomorpholin-3-yl)benzoate (RS5). Purification by flash column chromatography (PE/EA, 3:1) afforded **RS5** (42 mg, 59% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 4.07 (dd, *J* = 10.9, 1.9 Hz, 1H), 3.90 (s, 3H), 3.62 (dt, *J* = 12.7, 3.1 Hz, 1H), 3.26 (td, *J* = 12.3, 2.2 Hz, 1H), 3.03 – 2.89 (m, 2H), 2.44 (d, *J* = 12.6 Hz, 2H), 1.79 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 150.0, 130.1, 129.6, 126.6, 63.3, 52.2, 49.9, 24.6, 18.3. ESI-HRMS calcd for $C_{12}H_{16}NO_2Se$ [M + H] 286.0341, found 286.0343.



3-(4-(Trifluoromethoxy)phenyl)selenomorpholine (RS6). Purification by flash column chromatography (PE/EA, 2:1) afforded **RS6** (40 mg, 51% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.03 (dd, *J* = 10.9, 1.7 Hz, 1H), 3.62 (dt, *J* = 12.7, 3.0 Hz, 1H), 3.27 (td, *J* = 12.4, 2.0 Hz, 1H), 3.03 – 2.89 (m, 2H), 2.43 (d, *J* = 12.5 Hz, 2H), 1.73 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6 (q, J_{CF} = 2.0 Hz), 143.9, 128.0, 121.3, 120.6 (q, J_{CF} = 257.0 Hz), 62.9, 50.1, 24.8, 18.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.9. ESI-HRMS calcd for $C_{11}H_{13}F_3NOSe$ [M + H] 312.0109, found 312.0104.

3-(4-(Methylthio)phenyl)selenomorpholine (RS7). Purification by flash column chromatography (PE/EA, 2:1) afforded **RS7** (38 mg, 56% yield) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 9.4 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 3.97 (dd, *J* = 10.9, 2.1 Hz, 1H), 3.61 (dt, *J* = 12.6, 3.0 Hz, 1H), 3.26 (td, *J* = 12.4, 2.1 Hz, 1H), 2.96 (ddd, *J* = 17.2, 13.3, 10.2 Hz, 2H), 2.52 – 2.38 (m, 5H), 1.68 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2, 137.8, 127.1, 127.0, 63.2, 50.2, 24.9, 18.3, 16.1. ESI-HRMS calcd for $C_{11}H_{16}NSSe$ [M + H] 274.0163, found 274.0166.

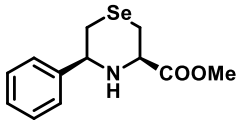
3-(3-Chlorophenyl)selenomorpholine (RS8). Purification by flash column chromatography (PE/EA, 2:1) afforded **RS8** (44 mg, 68% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.26 – 7.20 (m, 3H), 3.99 (dd, *J* = 10.9, 2.0 Hz, 1H), 3.61 (dt, *J* = 12.7, 3.0 Hz, 1H), 3.25 (td, *J* = 12.3, 2.2 Hz, 1H), 3.02 – 2.88 (m, 2H), 2.49 – 2.37 (m, 2H), 1.75 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 134.6, 130.0, 127.9, 126.7, 124.8, 63.1, 50.0, 24.7, 18.3. ESI-HRMS calcd for $C_{10}H_{13}ClNSe$ [M + H] 261.9896, found 261.9902.

3-(Pyren-1-yl)selenomorpholine (RS9). Purification by flash column chromatography (PE/EA, 3:1) afforded **RS9** (27 mg, 31% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 9.4 Hz, 1H), 8.25 – 8.12 (m, 5H), 8.08 – 7.98 (m, 3H), 5.11 (dd, *J* = 10.8, 2.2 Hz, 1H), 3.79 (dt, *J* = 12.5, 3.1 Hz, 1H), 3.51 (td, *J* = 12.3, 2.3 Hz, 1H), 3.26 (dd, *J* = 12.0, 10.9 Hz, 1H), 3.17 (td, *J* = 12.1, 3.2 Hz, 1H), 2.72 (d, *J* = 12.1 Hz, 1H), 2.57 (dt, *J* = 12.4, 3.3 Hz, 1H), 1.91 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 131.5, 130.8, 130.8, 128.0, 127.7, 127.6, 127.4, 126.1, 125.4, 125.4, 125.2, 125.1, 123.5, 122.5, 59.9, 50.8, 24.8, 18.7. ESI-HRMS calcd for $C_{20}H_{18}NSe$ [M + H] 352.0599, found 352.0592.

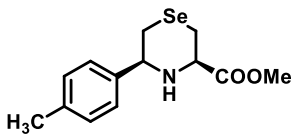
3-(Thiophen-3-yl)selenomorpholine (RS10). Purification by flash column chromatography (PE/EA, 3:1) afforded **RS10** (30 mg, 52% yield) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.07 (dd, *J* = 5.0, 1.1 Hz, 1H), 4.15 (dd, *J* = 10.9, 2.2 Hz, 1H), 3.61 (dt, *J* = 12.7, 3.2 Hz, 1H), 3.25 (td, *J* = 12.4, 2.3 Hz, 1H),

3.01 – 2.88 (m, 2H), 2.53 (d, *J* = 12.0 Hz, 1H), 2.42 (d, *J* = 12.1 Hz, 1H), 1.76 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2, 126.1, 126.0, 120.5, 58.9, 50.0, 24.5, 18.3. ESI-HRMS calcd for $C_8H_{12}NSSe$ [M + H] 233.9850, found 233.9855.

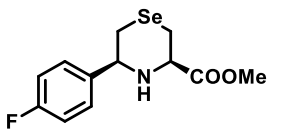
Methyl (*3R,5S*)-5-phenylselenomorpholine-3-carboxylate (RS11). Purification by flash column chromatography (PE/EA, 20:1) afforded **RS11** (37 mg, 52% yield, d.r. > 20:1) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 4.07 (d, *J* = 11.0 Hz, 1H), 3.90 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.75 (s, 3H), 2.96 – 2.82 (m, 3H), 2.50 (s, 1H), 2.46 (d, *J* = 12.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 144.3, 128.9, 128.1, 126.7, 64.5, 61.8, 52.6, 24.8, 18.9. ESI-HRMS calcd for $C_{12}H_{16}NO_2Se$ [M + H] 286.0341, found 286.0347.



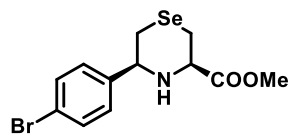
Methyl (*3R,5S*)-5-(*p*-tolyl)selenomorpholine-3-carboxylate (RS12). Purification by flash column chromatography (PE/EA, 20:1) afforded **RS12** (41 mg, 55% yield, d.r. > 20:1) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.03 (d, *J* = 10.9 Hz, 1H), 3.89 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.74 (s, 3H), 2.94 – 2.81 (m, 3H), 2.48 (s, 1H), 2.43 (d, *J* = 12.0 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171. 8, 141.5, 137.7, 129.5, 126.5, 64.2, 61.8, 52.5, 24.8, 21.2, 18.8. ESI-HRMS calcd for $C_{13}H_{18}NO_2Se$ [M + H] 300.0497, found 300.0493.



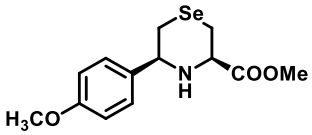
Methyl (*3R,5S*)-5-(4-fluorophenyl)selenomorpholine-3-carboxylate (RS13). Purification by flash column chromatography (PE/EA, 20:1) afforded **RS13** (48 mg, 63% yield, d.r. > 20:1) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 7.05 – 6.98 (m, 2H), 4.05 (d, *J* = 10.9 Hz, 1H), 3.88 (dd, *J* = 8.8, 4.6 Hz, 1H), 3.75 (s, 3H), 2.91 – 2.81 (m, 3H), 2.47 – 2.38 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 162.4 (d, J_{CF} = 246.2 Hz), 140.2 (d, J_{CF} = 3.2 Hz), 128.2 (d, J_{CF} = 8.0 Hz), 115.6 (d, J_{CF} = 21.3 Hz), 63.7, 61.8, 52.6, 24.8, 18.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.3. ESI-HRMS calcd for $C_{12}H_{15}FNO_2Se$ [M + H] 304.0247, found 304.0250.



Methyl (*3R,5S*)-5-(4-bromophenyl)selenomorpholine-3-carboxylate (RS14). Purification by flash column chromatography (PE/EA, 20:1) afforded **RS14** (46 mg, 51% yield, d.r. > 20:1) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.45 (m, 2H), 7.29 – 7.25 (m, 2H), 4.04 (d, *J* = 10.9 Hz, 1H), 3.91 – 3.85 (m, 1H), 3.75 (s, 3H), 2.90 – 2.81 (m, 3H), 2.45 (s, 1H), 2.41 (d, *J* = 12.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 143.3, 132.0, 128.4, 121.8, 63.8, 61.7, 52.6, 24.6, 18.8. ESI-HRMS calcd for $C_{12}H_{15}BrNO_2Se$ [M + H] 363.9446, found 363.9443.

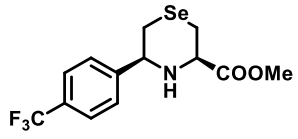


Methyl (*3R,5S*)-5-(4-methoxyphenyl)selenomorpholine-3-carboxylate (RS15).



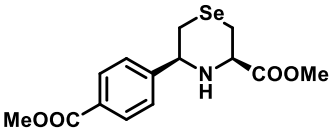
Purification by flash column chromatography (PE/EA, 20:1) afforded **RS15** (42 mg, 53% yield, d.r. > 20:1) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.01 (d, *J* = 10.9 Hz, 1H), 3.89 (dd, *J* = 10.2, 2.9 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 2.93 – 2.81 (m, 3H), 2.48 – 2.39 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 159.4, 136.7, 127.8, 114.2, 63.9, 62.0, 55.5, 52.6, 24.9, 18.8. ESI-HRMS calcd for $C_{13}H_{18}NO_3Se$ [M + H] 316.0446, found 316.0452.

Methyl (*3R,5S*)-5-(4-(trifluoromethyl)phenyl)selenomorpholine-3-carboxylate (RS16).



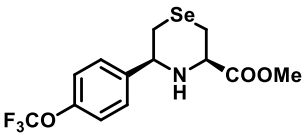
Purification by flash column chromatography (PE/EA, 20:1) afforded **RS16** (51 mg, 58% yield, d.r. > 20:1) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 4.15 (d, *J* = 10.9 Hz, 1H), 3.90 (dd, *J* = 8.2, 4.1 Hz, 1H), 3.76 (s, 3H), 2.93 – 2.83 (m, 3H), 2.49 (s, 1H), 2.44 (d, *J* = 12.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 148.1, 130.3 (q, J_{CF} = 32.5 Hz), 127.1, 125.9 (q, J_{CF} = 3.8 Hz), 124.2 (q, J_{CF} = 272.1 Hz), 64.0, 61.6, 52.7, 24.6, 18.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5. ESI-HRMS calcd for $C_{13}H_{15}F_3NO_2Se$ [M + H] 354.0215, found 354.0218.

Methyl (*3R,5S*)-5-(4-(methoxycarbonyl)phenyl)selenomorpholine-3-carboxylate (RS17).



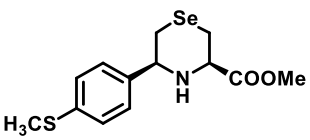
Purification by flash column chromatography (PE/EA, 10:1) afforded **RS17** (56 mg, 65% yield, d.r. > 20:1) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 4.14 (dd, *J* = 10.8, 1.6 Hz, 1H), 3.93-3.87 (m, 4H), 3.76 (s, 3H), 2.88 (td, *J* = 11.7, 8.9 Hz, 3H), 2.50 (s, 1H), 2.45 (dd, *J* = 12.1, 1.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 166.9, 149.1, 130.3, 129.9, 126.7, 64.1, 61.6, 52.7, 52.3, 24.5, 18.9. ESI-HRMS calcd for $C_{14}H_{18}NO_4Se$ [M + H] 344.0396, found 344.0391.

Methyl (*3R,5S*)-5-(4-(trifluoromethoxy)phenyl)selenomorpholine-3-carboxylate (RS18).



Purification by flash column chromatography (PE/EA, 20:1) afforded **RS18** (46 mg, 50% yield, d.r. > 20:1) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 4.09 (d, *J* = 10.9 Hz, 1H), 3.89 (dd, *J* = 9.4, 4.0 Hz, 1H), 3.76 (s, 3H), 2.92 – 2.82 (m, 3H), 2.43 (d, *J* = 13.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 148.8, 143.0, 128.1, 121.4, 120.6 (q, J_{CF} = 257.1 Hz), 63.7, 61.7, 52.6, 24.7, 18.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.9. ESI-HRMS calcd for $C_{13}H_{15}F_3NO_3Se$ [M + H] 370.0164, found 370.0160.

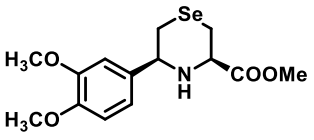
Methyl (*3R,5S*)-5-(4-(methylthio)phenyl)selenomorpholine-3-carboxylate (RS19).



Purification by flash column chromatography (PE/EA, 20:1) afforded **RS19** (45 mg, 55% yield, d.r. > 20:1) as light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.3

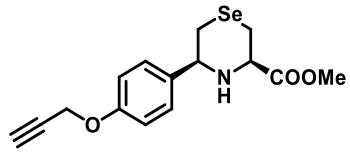
Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 4.03 (d, *J* = 10.8 Hz, 1H), 3.89 (dd, *J* = 9.9, 3.4 Hz, 1H), 3.75 (s, 3H), 2.92 – 2.80 (m, 3H), 2.53 – 2.37 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 141.3, 138.2, 127.2, 127.0, 64.0, 61.8, 52.6, 24.7, 18.8, 16.0. ESI-HRMS calcd for $C_{13}H_{18}NO_2SSe$ [M + H] 332.0218, found 332.0214.

Methyl (*3R,5S*)-5-(3,4-dimethoxyphenyl)selenomorpholine-3-carboxylate (RS20).

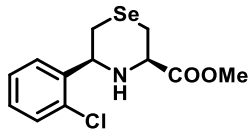


Purification by flash column chromatography (PE/EA, 6:1) afforded **RS20** (37 mg, 43% yield, d.r. > 20:1) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (dd, *J* = 6.2, 2.0 Hz, 2H), 6.85 – 6.81 (m, 1H), 4.01 (dd, *J* = 10.8, 1.7 Hz, 1H), 3.92 – 3.86 (m, 7H), 3.75 (s, 3H), 2.94 – 2.81 (m, 3H), 2.49 (s, 1H), 2.44 (d, *J* = 11.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 149.2, 148.7, 137.2, 118.8, 111.2, 109.6, 64.4, 62.0, 56.1, 56.1, 52.6, 24.9, 18.8. ESI-HRMS calcd for $C_{14}H_{20}NO_4Se$ [M + H] 346.0552, found 346.0556.

Methyl (*3R,5S*)-5-(4-(prop-2-yn-1-yloxy)phenyl)selenomorpholine-3-carboxylate (RS21). Purification by flash column chromatography (PE/EA, 20:1) afforded **RS21** (28 mg, 33% yield, d.r. > 20:1) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.62 (d, *J* = 2.4 Hz, 2H), 3.96 (dd, *J* = 11.2, 2.6 Hz, 1H), 3.84 – 3.80 (m, 1H), 3.68 (s, 3H), 2.86 – 2.74 (m, 3H), 2.46 (t, *J* = 2.4 Hz, 1H), 2.40 – 2.33 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 157.3, 137.6, 127.8, 115.2, 78.6, 75.7, 63.8, 61.9, 56.0, 52.6, 24.8, 18.8. ESI-HRMS calcd for $C_{15}H_{18}NO_3Se$ [M + H] 340.0446, found 340.0441.

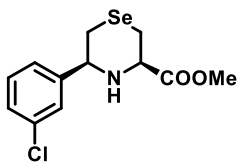


Methyl (*3R,5S*)-5-(2-chlorophenyl)selenomorpholine-3-carboxylate (RS22).



Purification by flash column chromatography (PE/EA, 20:1) afforded **RS22** (39 mg, 49% yield, d.r. > 20:1) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.29 (td, *J* = 7.5, 1.4 Hz, 1H), 7.22 (td, *J* = 7.6, 1.8 Hz, 1H), 4.54 (d, *J* = 10.5 Hz, 1H), 3.94 (dd, *J* = 8.3, 5.2 Hz, 1H), 3.76 (s, 3H), 2.93 – 2.84 (m, 2H), 2.80 – 2.73 (m, 1H), 2.58 (d, *J* = 11.9 Hz, 1H), 2.46 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 141.3, 132.6, 129.7, 128.9, 127.6, 127.4, 61.8, 59.9, 52.6, 23.1, 19.0. ESI-HRMS calcd for $C_{12}H_{15}ClNO_2Se$ [M + H] 319.9951, found 319.9957.

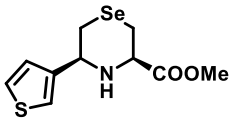
Methyl (*3R,5S*)-5-(3-chlorophenyl)selenomorpholine-3-carboxylate (RS23).



Purification by flash column chromatography (PE/EA, 20:1) afforded **RS23** (47 mg, 59% yield, d.r. > 20:1) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.29 – 7.23 (m, 3H), 4.05 (d, *J* = 10.9 Hz, 1H), 3.88 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.75 (s, 3H), 2.91 – 2.81 (m, 3H), 2.47 (s, 1H), 2.43 (d, *J* = 12.1 Hz, 1H).

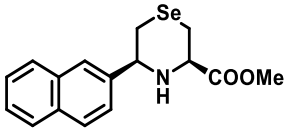
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 146.2, 134.7, 130.1, 128.2, 126.8, 124.9, 63.9, 61.6, 52.6, 24.6, 18.8. ESI-HRMS calcd for $C_{12}H_{15}ClNO_2Se$ [M + H] 319.9951, found 319.9955.

Methyl (*3R,5S*)-5-(thiophen-3-yl)selenomorpholine-3-carboxylate (RS24).



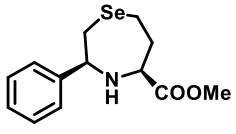
Purification by flash column chromatography (PE/EA, 20:1) afforded **RS24** (31 mg, 43% yield, d.r. > 20:1) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.24 (ddd, *J* = 3.0, 1.3, 0.6 Hz, 1H), 7.10 (dd, *J* = 5.0, 1.3 Hz, 1H), 4.21 (dd, *J* = 11.0, 2.2 Hz, 1H), 3.89 (dd, *J* = 9.9, 3.7 Hz, 1H), 3.75 (s, 3H), 2.91 – 2.81 (m, 3H), 2.51 (ddd, *J* = 12.0, 2.3, 0.9 Hz, 1H), 2.47 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 145.3, 126.2, 126.1, 121.0, 61.7, 59.7, 52.6, 24.4, 18.9. ESI-HRMS calcd for $C_{10}H_{14}NO_2SSe$ [M + H] 291.9905, found 291.9901.

Methyl (*3R,5S*)-5-(naphthalen-2-yl)selenomorpholine-3-carboxylate (RS25).



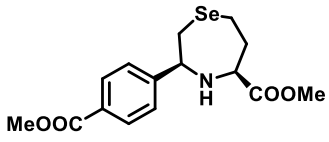
Purification by flash column chromatography (PE/EA, 20:1) afforded **RS25** (38 mg, 45% yield, d.r. > 20:1) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 4H), 7.52 – 7.44 (m, 3H), 4.25 (dd, *J* = 10.9, 2.0 Hz, 1H), 3.97 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.77 (s, 3H), 3.05 – 2.86 (m, 3H), 2.64 (s, 1H), 2.58 – 2.51 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 141.7, 133.6, 133.2, 128.6, 128.1, 127.8, 126.4, 126.1, 125.2, 125.0, 64.5, 61.9, 52.6, 24.8, 18.9. ESI-HRMS calcd for $C_{16}H_{18}NO_2Se$ [M + H] 336.0497, found 336.0493.

Methyl (*5S*)-3-phenyl-1,4-selenazepane-5-carboxylate (RS26). Purification by flash column chromatography (PE/EA, 20:1) afforded **RS26** (28 mg, 37% yield, d.r. = 3:2) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 4H), 7.30 – 7.27 (m, 1H), 4.18 (dd, *J* = 11.4, 4.9 Hz, 1H), 3.94 (dd, *J* = 10.4, 2.9 Hz, 1H), 3.73 (s, 3H), 3.16 – 3.04 (m, 1H), 3.00 – 2.92 (m, 1H), 2.88 (dd, *J* = 12.9, 10.4 Hz, 1H), 2.75 (dd, *J* = 12.9, 2.8 Hz, 1H), 2.60 (s, 1H), 2.33 (ddd, *J* = 18.2, 11.5, 6.4 Hz, 1H), 2.12 – 2.02 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 144.9, 128.9, 127.8, 126.6, 68.7, 61.5, 52.5, 35.5, 35.4, 23.2. ESI-HRMS calcd for $C_{13}H_{18}NO_2Se$ [M + H] 300.0497, found 300.0501.

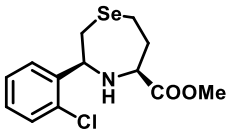


Methyl (*5S*)-3-(4-(trifluoromethyl)phenyl)-1,4-selenazepane-5-carboxylate (RS27). Purification by flash column chromatography (PE/EA, 20:1) afforded **RS27** (42 mg, 46% yield, d.r. = 2:1) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 4.16 (dd, *J* = 11.3, 4.8 Hz, 1H), 4.02 (d, *J* = 10.0 Hz, 1H), 3.74 (s, 3H), 3.12 – 3.03 (m, 1H), 2.99 – 2.92 (m, 1H), 2.84 (dd, *J* = 12.9, 10.0 Hz, 1H), 2.75 (d, *J* = 11.9 Hz, 1H), 2.60 (s, 1H), 2.41 – 2.30 (m, 1H), 2.12 – 2.02 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 148.6, 130.0 (q, J_{CF} = 32.6 Hz), 127.0, 125.8 (q, J_{CF} = 3.7 Hz), 124.2 (d, J_{CF} = 272.0 Hz). 67.8, 61.3, 52.6, 35.5,

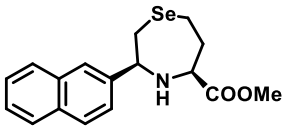
35.2, 23.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5. ESI-HRMS calcd for $C_{14}H_{17}F_3NO_2Se$ [M + H] 368.0371, found 368.0377.

Methyl (*5S*)-3-(4-(methoxycarbonyl)phenyl)-1,4-selenazepane-5-carboxylate (RS28). 

Purification by flash column chromatography (PE/EA, 12:1) afforded **RS28** (47 mg, 53% yield, d.r. = 2:1) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 4.16 (dd, *J* = 11.3, 4.7 Hz, 1H), 4.00 (dd, *J* = 10.1, 3.0 Hz, 1H), 3.91 (s, 3H), 3.73 (s, 3H), 3.13 – 3.03 (m, 1H), 2.99 – 2.92 (m, 1H), 2.84 (dd, *J* = 12.9, 10.2 Hz, 1H), 2.78 – 2.71 (m, 1H), 2.61 (s, 1H), 2.40 – 2.29 (m, 1H), 2.12 – 2.02 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 167.0, 149.7, 130.2, 129.6, 126.6, 68.1, 61.3, 52.6, 52.3, 35.5, 35.2, 23.3. ESI-HRMS calcd for $C_{15}H_{20}NO_4Se$ [M + H] 358.0552, found 358.0559.

Methyl (*5S*)-3-(2-chlorophenyl)-1,4-selenazepane-5-carboxylate (RS29). 

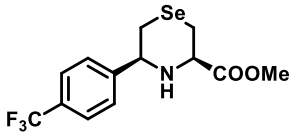
Purification by flash column chromatography (PE/EA, 20:1) afforded **RS29** (36 mg, 43% yield, d.r. = 3:2) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 4.42 (d, *J* = 9.9 Hz, 1H), 4.18 (dd, *J* = 11.3, 4.8 Hz, 1H), 3.74 (s, 3H), 3.11 – 3.02 (m, 1H), 2.95 (dd, *J* = 13.3, 6.3 Hz, 1H), 2.87 (d, *J* = 12.4 Hz, 1H), 2.74 (dd, *J* = 12.8, 10.0 Hz, 1H), 2.56 (s, 1H), 2.41 – 2.30 (m, 1H), 2.13 – 2.03 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 142.1, 132.3, 129.7, 128.6, 127.6, 127.5, 63.4, 61.4, 52.6, 35.6, 33.6, 23.2. ESI-HRMS calcd for $C_{13}H_{17}ClNO_2Se$ [M + H] 334.0108, found 334.0102.

Methyl (*5S*)-3-(naphthalen-2-yl)-1,4-selenazepane-5-carboxylate (RS30). 

Purification by flash column chromatography (PE/EA, 20:1) afforded **RS30** (29 mg, 33% yield, d.r. = 3:2) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 4H), 7.52 – 7.43 (m, 3H), 4.24 (dd, *J* = 11.3, 4.5 Hz, 1H), 4.12 (dd, *J* = 10.4, 2.9 Hz, 1H), 3.73 (s, 3H), 3.20 – 3.09 (m, 1H), 3.04 – 2.93 (m, 2H), 2.83 (dd, *J* = 12.9, 2.5 Hz, 1H), 2.73 (s, 1H), 2.42 – 2.31 (m, 1H), 2.17 – 2.06 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 142.2, 133.6, 133.1, 128.6, 128.1, 127.8, 126.4, 126.0, 125.1, 125.1, 68.7, 61.6, 52.6, 35.5, 35.4, 23.3. ESI-HRMS calcd for $C_{17}H_{20}NO_2Se$ [M + H] 350.0654, found 350.0659.

4. Scale-up reaction for RS16

Procedure for scale-up reaction of **RS16**:



To a 10 mL oven-dried flask were added the SnAP reagent **2** (1.46 g, 3 mmol, 1.00 equiv), 4-(trifluoromethyl)benzaldehyde (0.53 g, 3 mmol, 1.00 equiv) and MS 4Å. The flask was sealed with rubber stopper, exchanged the gas using N_2 for 3 times and then dry DCM (15.0 mL) was added. The reaction mixture was stirred at room temperature for 6 h and filtered through a short layer of Celite (DCM rinse). The filtrate was concentrated under reduced pressure to afford the imine.

Separately, to a 50 mL oven-dried flask equipped with $Cu(OTf)_2$ (1.08 g, 3 mmol, 1.00 equiv) were added HFIP (6.0 mL) and 2,6-lutidine (0.64 g, 6 mmol, 2.00 equiv) under N_2. The mixture was stirred at room temperature for 1 h, during which a dark green homogeneous suspension was formed. A solution of the imine (3 mmol, 1.00 equiv) in DCM (24.0 mL) was added in one portion and the resulting mixture was stirred at room temperature for 12 h. The reaction was quenched with a mixture of sat aq. $NaHCO_3$ and 10% aq. NH_4OH, and stirred vigorously for 15 min. The layers were separated and the aqueous layer was extracted with DCM (2 x 30 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography afforded **RS16** (0.52 g, 49% yield).

5. Biological experimental section:

Determination of minimum inhibitory concentration (MIC): Overnight grown *C. albicans* and *C. parapsilosis* strains cultivated in Sabouraud's dextrose (SD) agar plate and the colonies suspended in SD broth at a starting OD_{600} = ~0.08 in a flat-bottomed microtitre plate. A serial dilution of the organic compounds in the same broth were mixed with the inoculum and adjusted to final concentration range 1.56-800 μM. The antifungal activity was assessed by monitoring the OD_{620} in cycles of 30 minutes and an orbital shaking at 100 rpm using an Infinite M200 microplate reader (Tecan Group Ltd., Switzerland) for 24 h at 30 ˚C. Culture without organic compounds was used as a positive control and broth alone served as negative controls. The minimum concentration required for complete inhibition was assessed by both visible observations as well as by measuring the OD_{620} and taken as the MIC. Each experiment was repeated twice in duplicates and the average MIC values are reported.

Table S2 Antimicrobial properties of selenomorpholines and selenazepanes

Compound	Minimum Inhibitory Concentration (MIC) in μg/mL		
	***P. aeruginosa* ATCC 9027**	***S. aureus ATCC* 29213**	***C. albicans* ATCC 10231**
RS1	400	400	800
RS2	200	200	800
RS3	800	400	800
RS4	>800	>800	800
RS5	>800	>800	>800
RS6	>800	>800	>800
RS7	>800	>800	>800
RS8	400	400	800
RS9	>100	>100	100
RS10	**>800**	**800**	**25**
RS11	>800	>800	100
RS12	400	200	100
RS13	400	200	100
RS14	400	200	50
RS15	200	100	100
RS16	400	200	50
RS17	400	200	100
RS18	>200	>200	100
RS19	>200	>200	100
RS20	>800	>800	100
RS21	>200	100	100
RS22	**>200**	**>200**	**12.5**

RS23	400	200	100
RS24	**>800**	**400**	**25**
RS25	800	400	200
RS26	**>200**	**>200**	**12.5**
RS27	400	100	100
RS28	400	100	100
RS29	**>200**	**200**	**25**
RS30	400	100	100

Time-kill Kinetics Assay: The time-kill kinetics of RS 22 was determined against *C. parapsilosis strains*. Fungal cultures were grown overnight in SD broth and the cell concentration was adjusted to 10^4–10^5 CFU/mL in the same broth. A stock solution of RS 22 dissolved in SD broth was added to fungal inoculum to a final concentration of 1x or 2x MIC values and incubated at 37°C with constant shaking. 100 µL of the suspension was withdrawn at predetermined time points, serially diluted (10^2 or 10^3 fold) and poured into the SDA plate. The plate was incubated for 48 h at 37°C for colony counting. The data were expressed in terms of viable cells in CFU/mL with exposure time.

Determination of cytotoxicity of RS 22 for mammalian cells: Cytotoxicity of RS 22 was determined for primary human dermal fibroblasts (hDFs) and immortalised keratinocytes (HaCaT) cells, following the protocol reported before (ACS Infect Dis. 2019 Aug 9;5(8):1411-1422). Briefly, cells were cultured in cell Dulbecco's Modified Eagle Medium (DMEM) supplemented with fetal bovine serum (10% v/v) and antibiotics (50 U/mL penicillin and 50 µg/mL streptomycin). Cells were seeded in 96-well tissue culture plates (Fisher Scientific Ireland Ltd., Dublin) at a cell density of 2-4×10^3 cells/well, and incubated at 37°C and 5% CO_2 for 24 h. The cells were then treated with varying concentrations of RS 22, ranging from 0 – 20 µM, obtained through serial dilution in the same cell culture medium. The positive control involved the treatment of cells with nocodazole (5 µg/mL), while wells containing untreated cells and media diluted accordingly with sterile water constituted the negative control. After 24 h incubation, MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) solution (20 µL, provided in the assay kit) was added to each well, and incubated at 37°C and 5% CO_2 for 1.5 – 2 h. Absorbance was then measured at 490 nm using a TECAN microplate reader, and the relative cell viability was calculated. All solutions were equilibrated in a 37°C water bath for at least 30 min prior to addition into the cell culture wells. Each treatment was performed in triplicates. Mean and standard deviation were reported in the bar charts plotted with GraphPad Prism 6.0 software.

For high content analysis, formaldehyde (4% final concentration) was added to the treated cells and the resulting plate was incubated at room temperature for 10 – 20 min for fixing. Cells were then washed with 1X phosphate buffered saline (PBS, diluted

from 10X PBS with sterile water) and permeabilized with Triton X-100 (0.3%). The cells were washed with PBS again, and blocked with bovine serum albumin (BSA, 3%). After the BSA was removed, adherent cells were then stained with fluorescent dyes. Anti-α-tubulin antibody and Alexa Fluor 569 phalloidin were used to visualize the cellular morphologies while blue-colored Hoechst dye was used to visualize the nuclei. Plates were scanned (12 randomly selected fields/well) using IN Cell Analyzer 2200, an automated microscope.

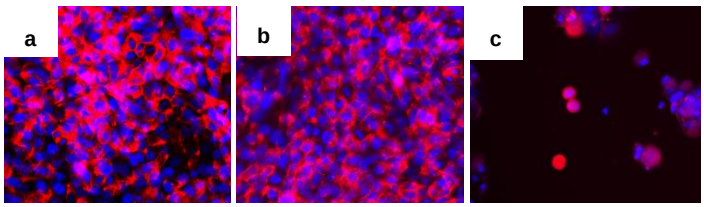


Fig. S1 High content images of HaCaT cells treated with (**a**) RS 22 (20 μM), **b**) Untreated control and **c**) nocodazole 5 (μM). Note that cells treated with RS22 displayed cobblestone morphology with smooth formation of cytosketal components and nuclear morphology similar to that of untreated control cells, suggesting lack of toxicity for mammalian cells. However the anti-neoplastic agent, nocodazole caused substantial damage to the cytoskeletal components and nuclear morphology indicating significant lethality of the drug.

6. References

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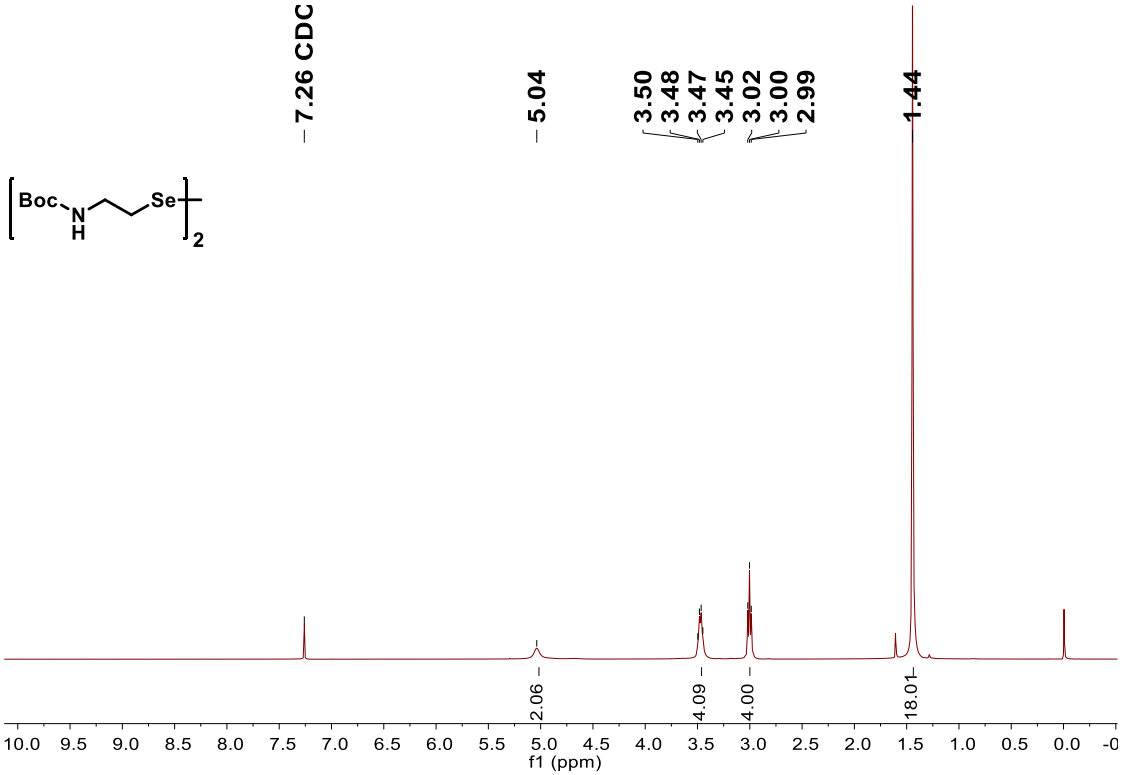
5. S. Wu, S. Y. Tan, C. Y. Ang, K. T. Nguyen, M. Li and Y. Zhao, *Chem. Commun.*, 2015, **51**, 11622-11625.

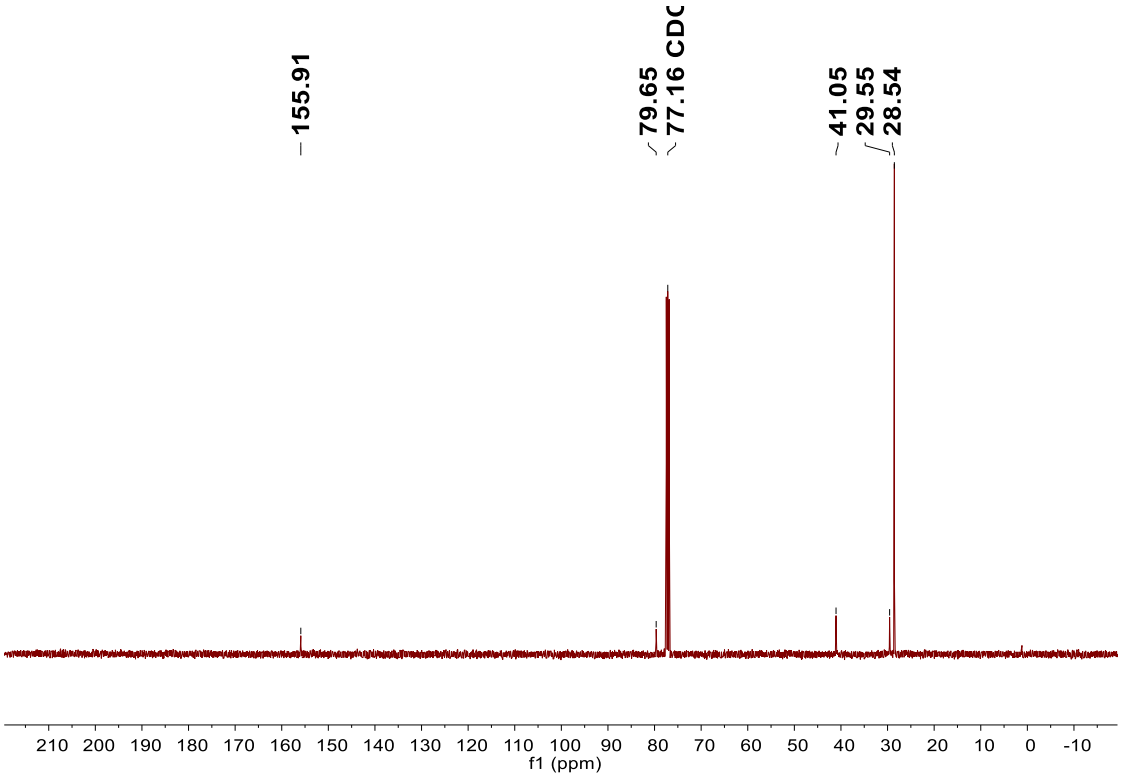
7. NMR Spectra

Compound 5

^{1}H NMR (400 MHz, $CDCl_3$)

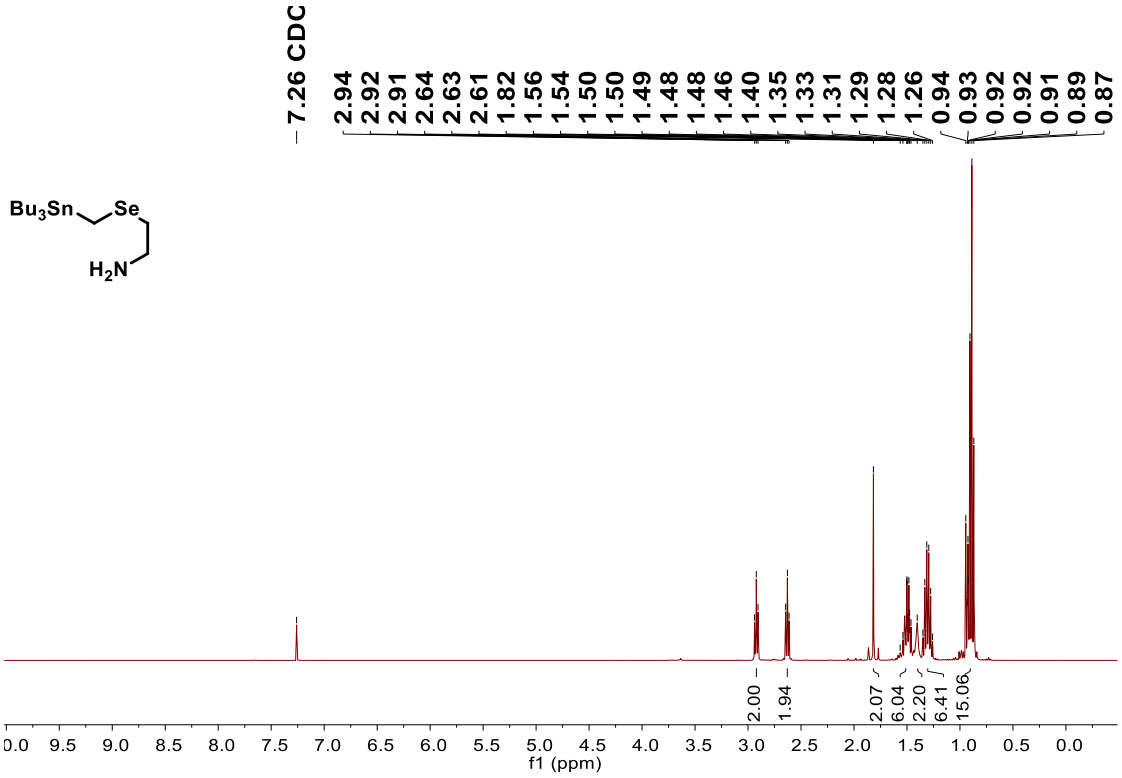


^{13}C NMR (101 MHz, $CDCl_3$)

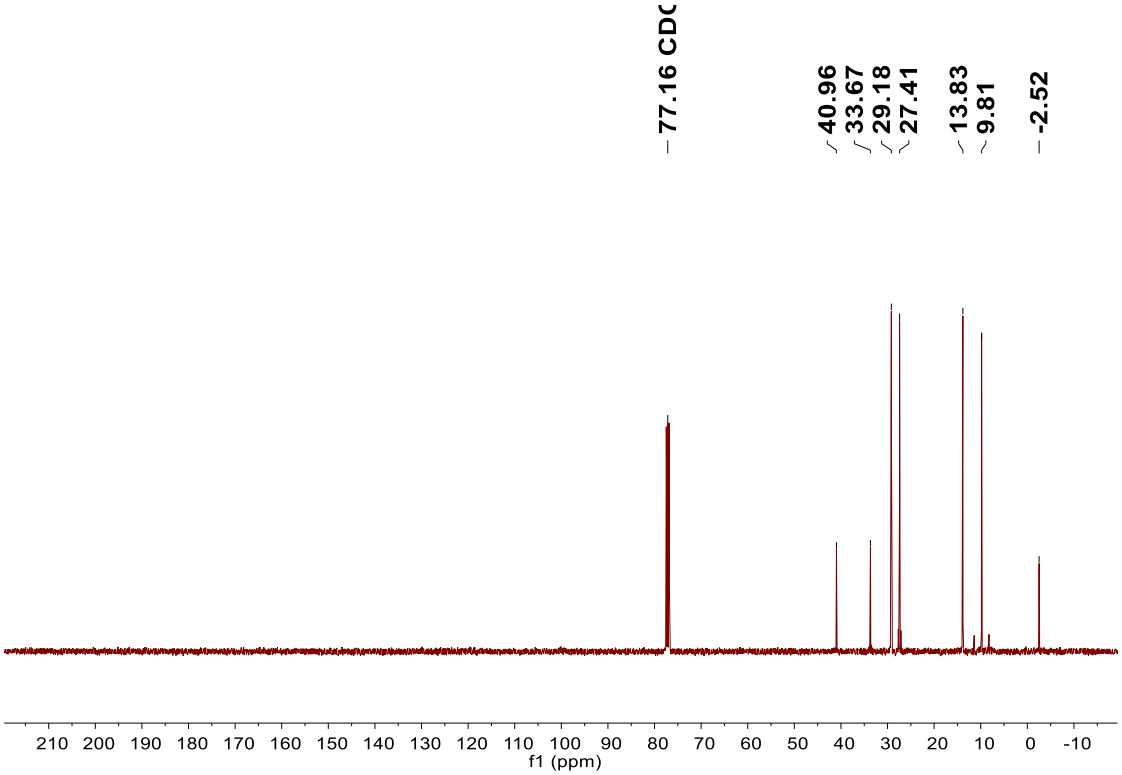


Seleno-SnAP 1

^{1}H NMR (400 MHz, $CDCl_3$)

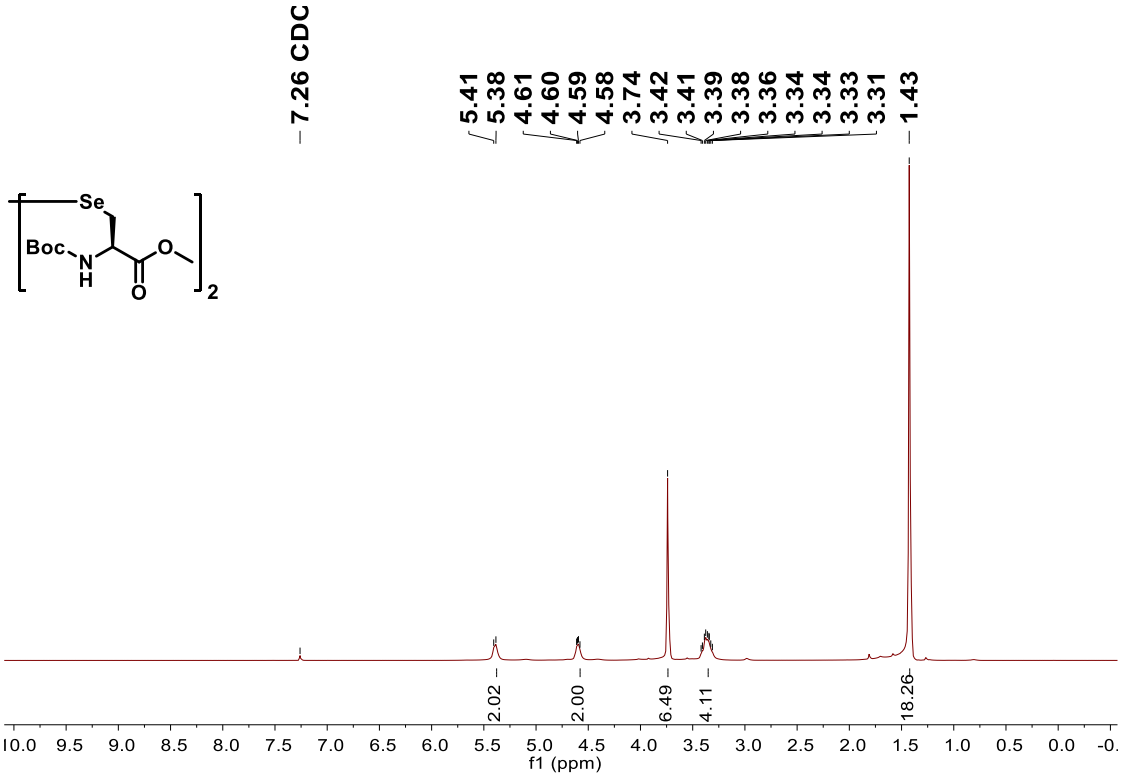


^{13}C NMR (101 MHz, $CDCl_3$)

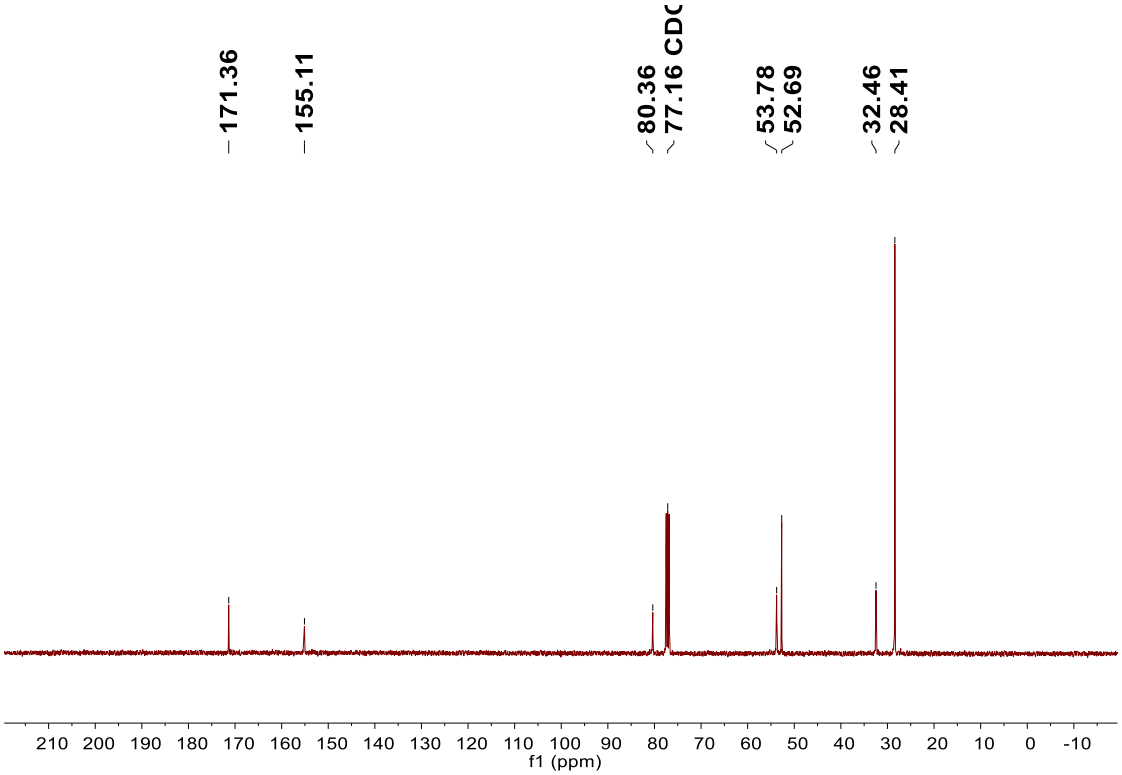


Compound 8

^{1}H NMR (400 MHz, $CDCl_3$)

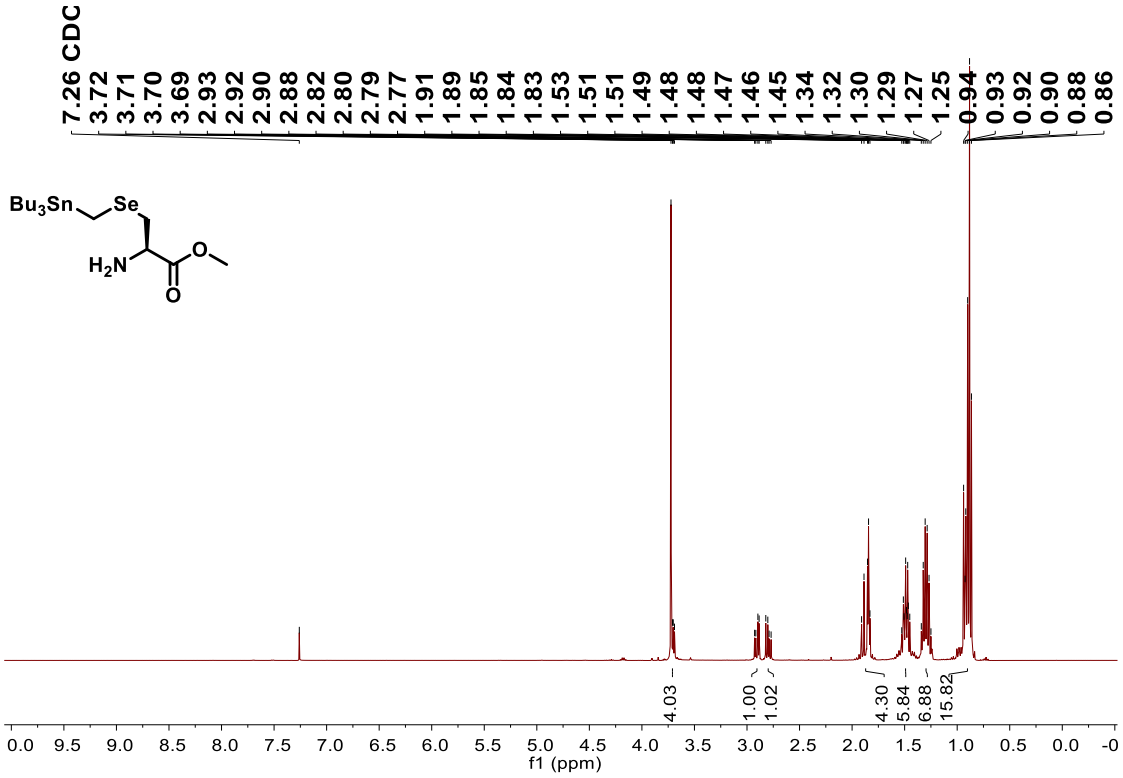


^{13}C NMR (101 MHz, $CDCl_3$)

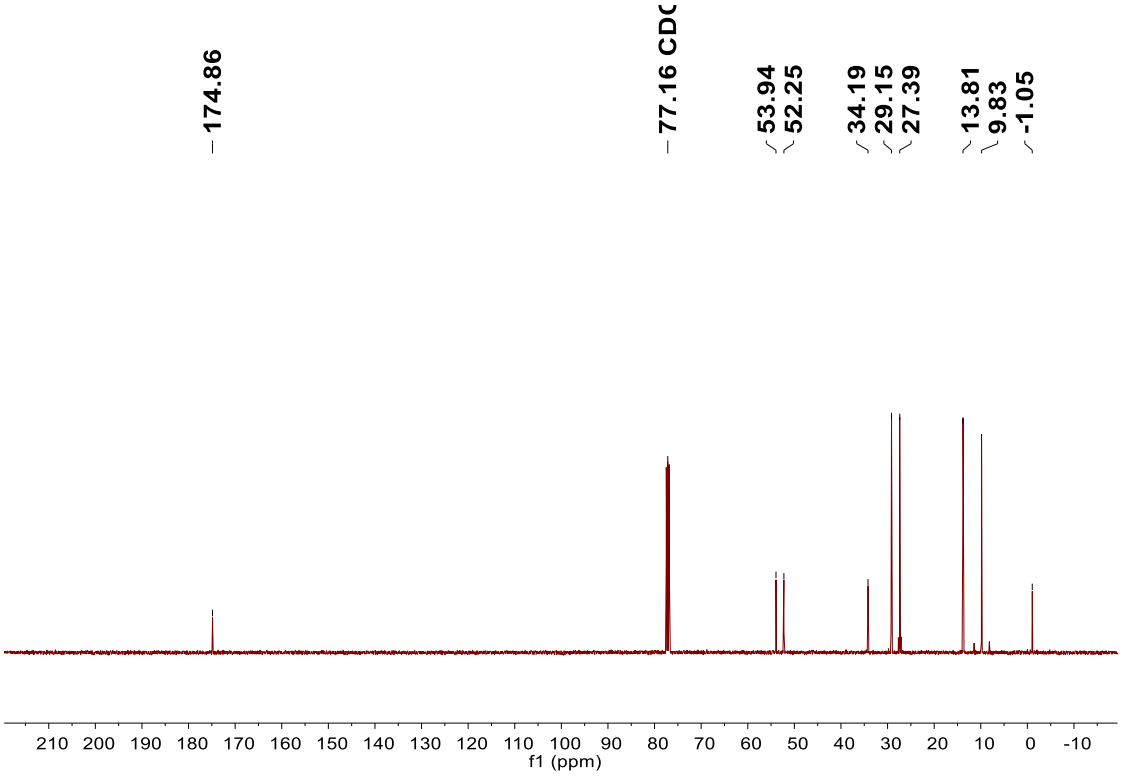


Senelo-SnAP 2

^{1}H NMR (400 MHz, $CDCl_3$)

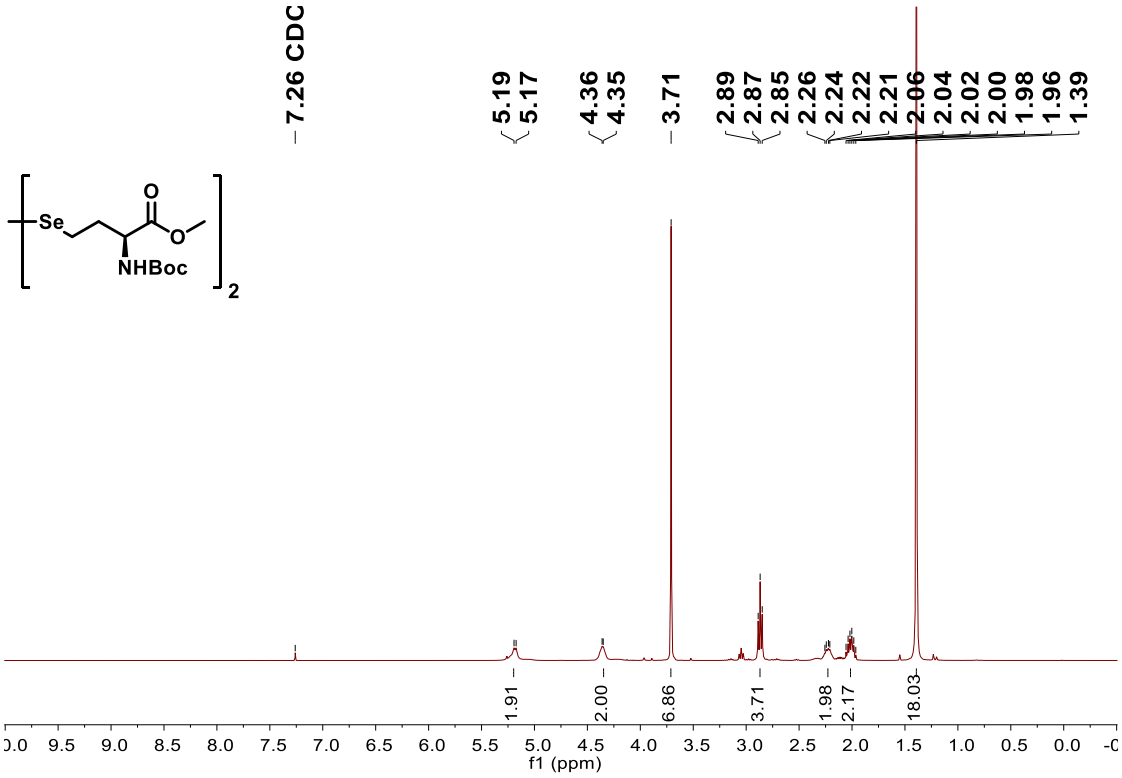


^{13}C NMR (101 MHz, $CDCl_3$)

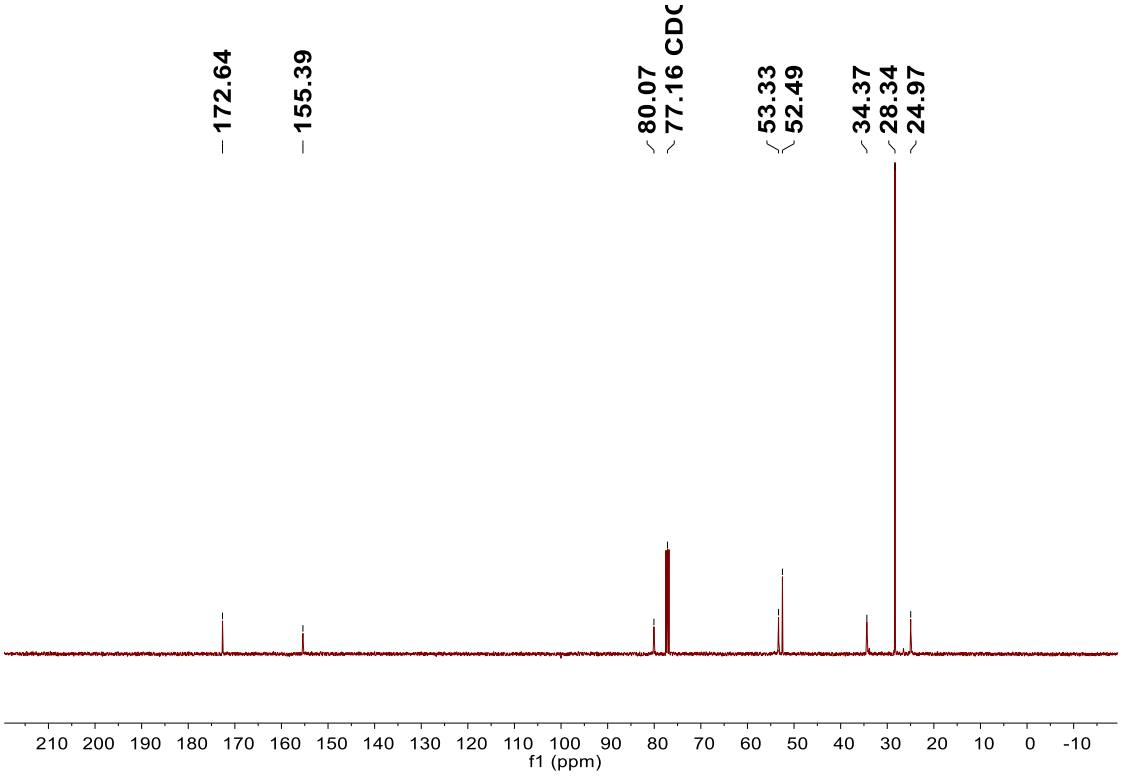


Compound 11

^{1}H NMR (400 MHz, $CDCl_3$)

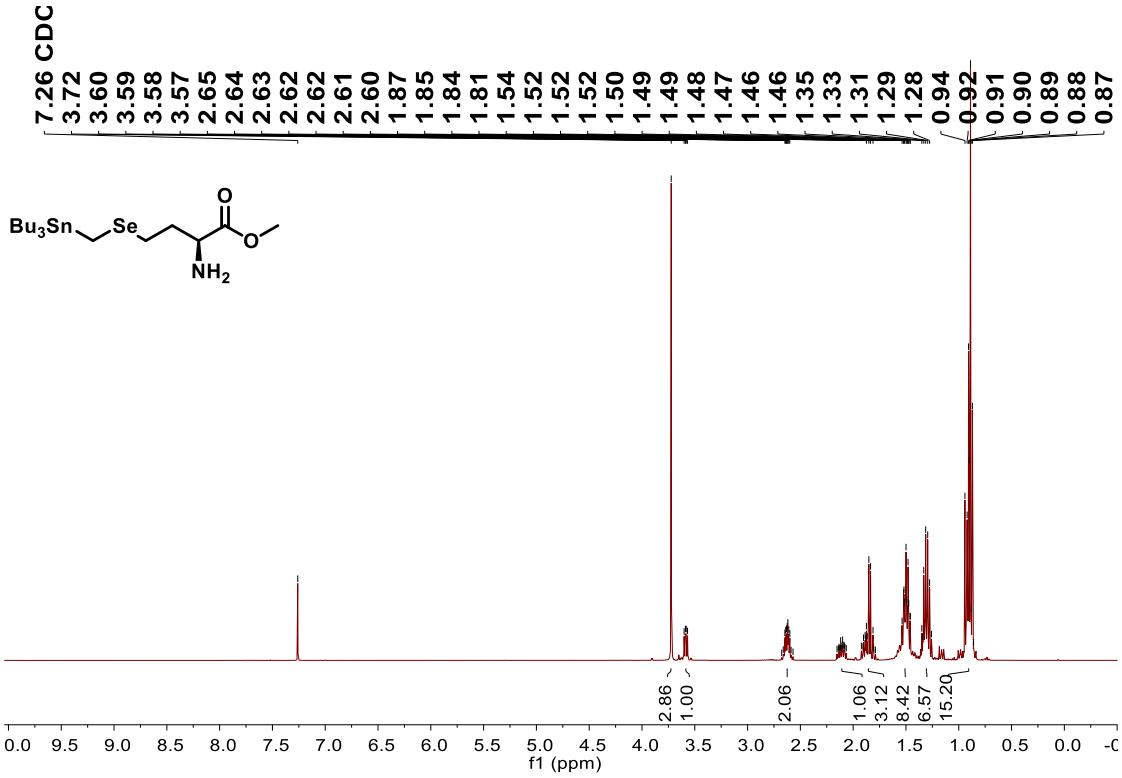


^{13}C NMR (101 MHz, $CDCl_3$)

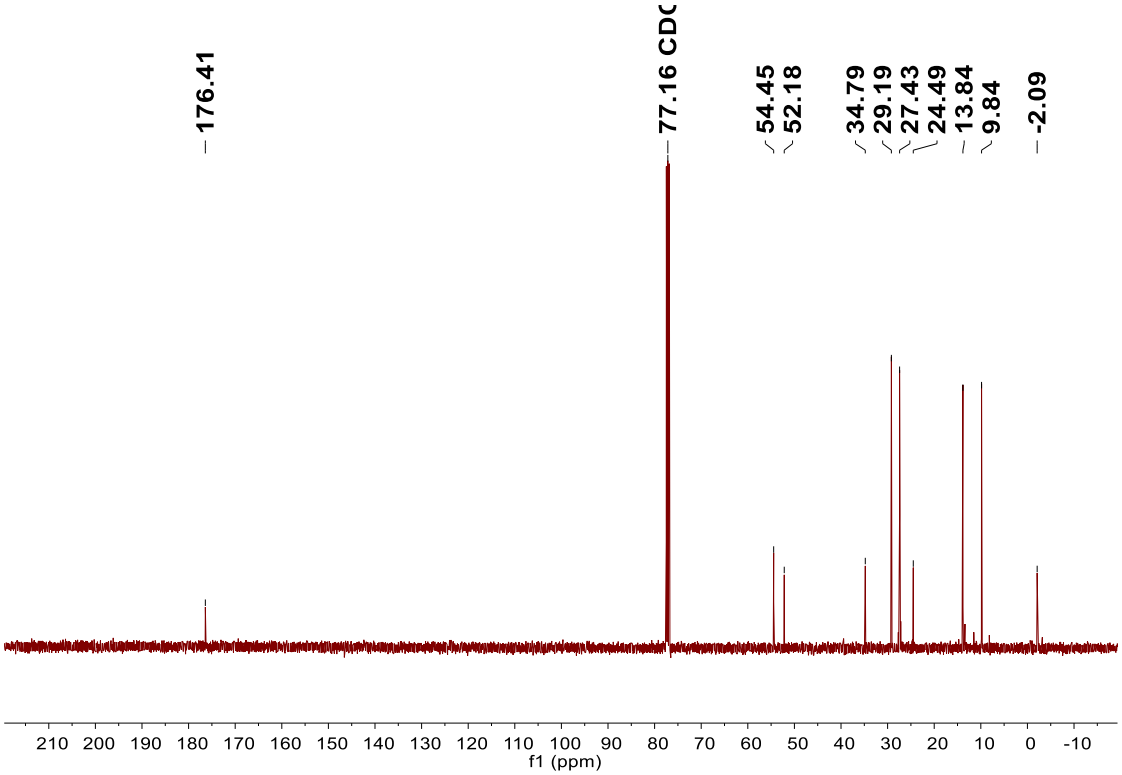


Seno-SnAP 3

^{1}H NMR (400 MHz, $CDCl_3$)

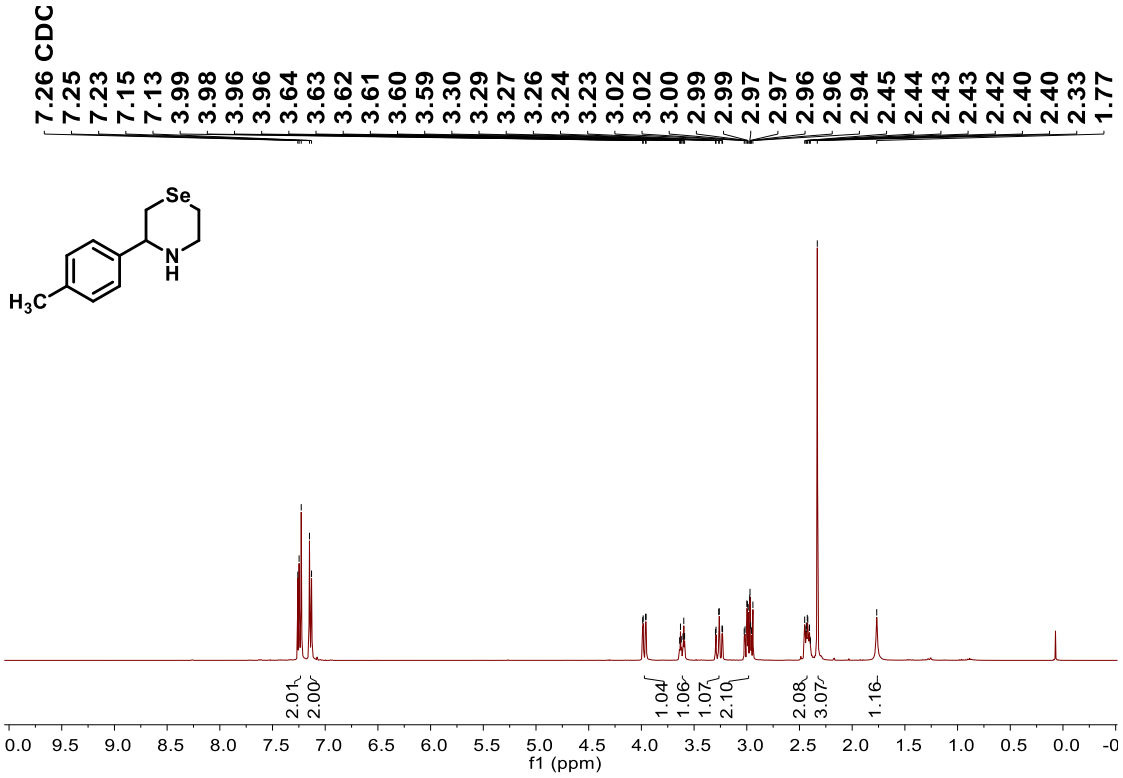


^{13}C NMR (101 MHz, $CDCl_3$)

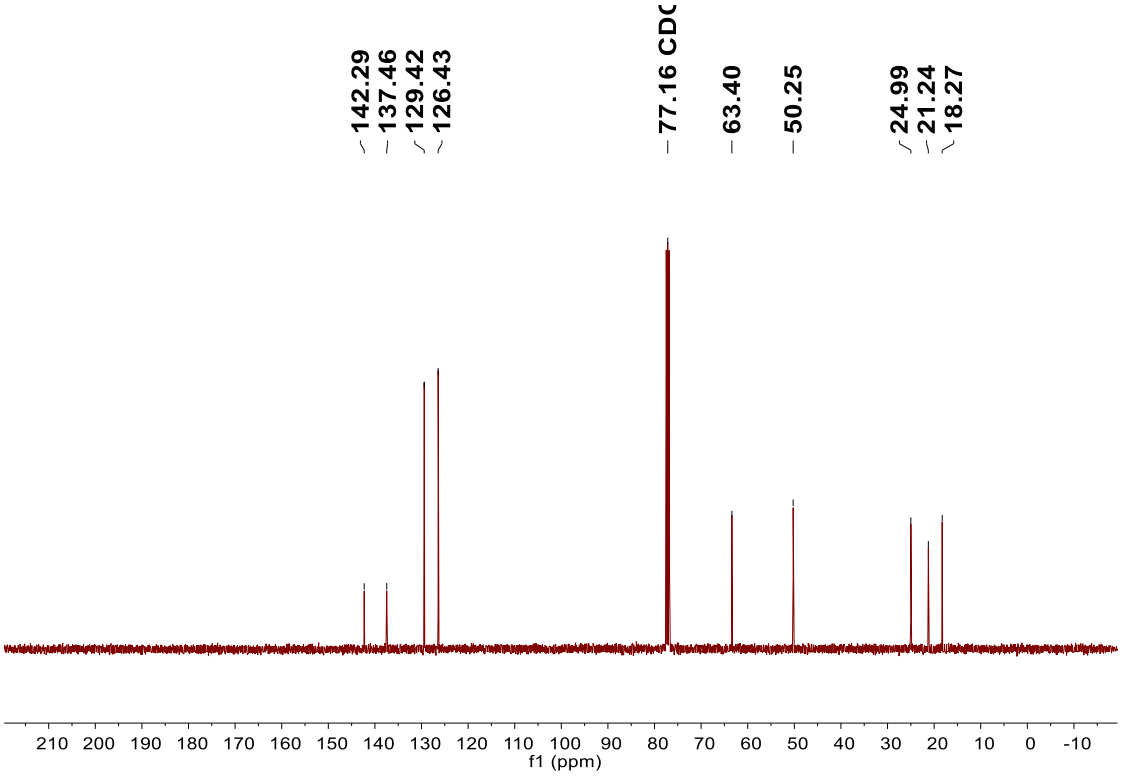


RS1

^{1}H NMR (400 MHz, $CDCl_3$)

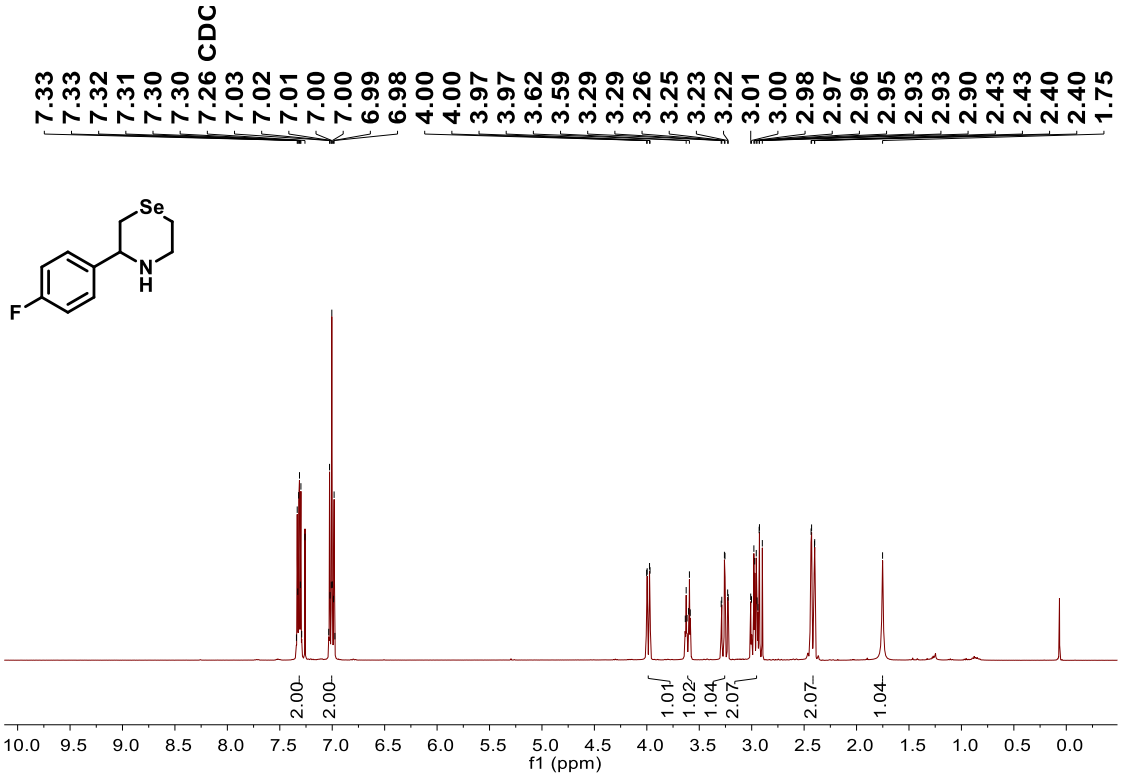


^{13}C NMR (101 MHz, $CDCl_3$)

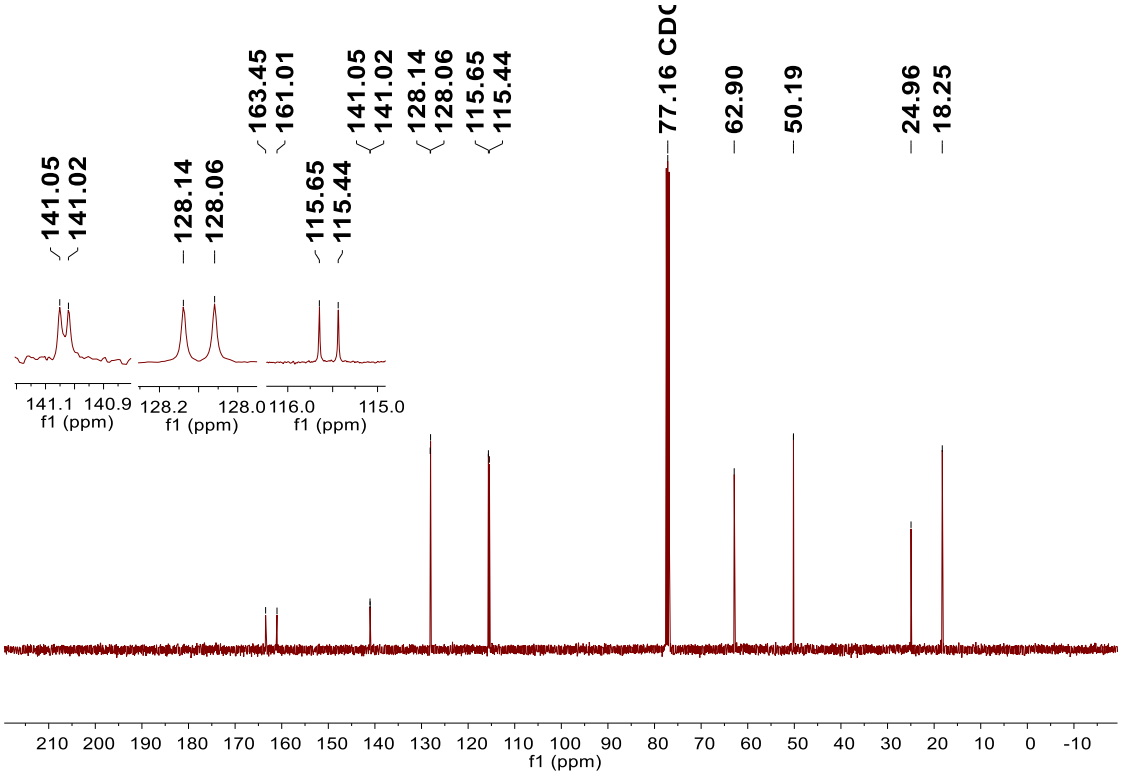


RS2

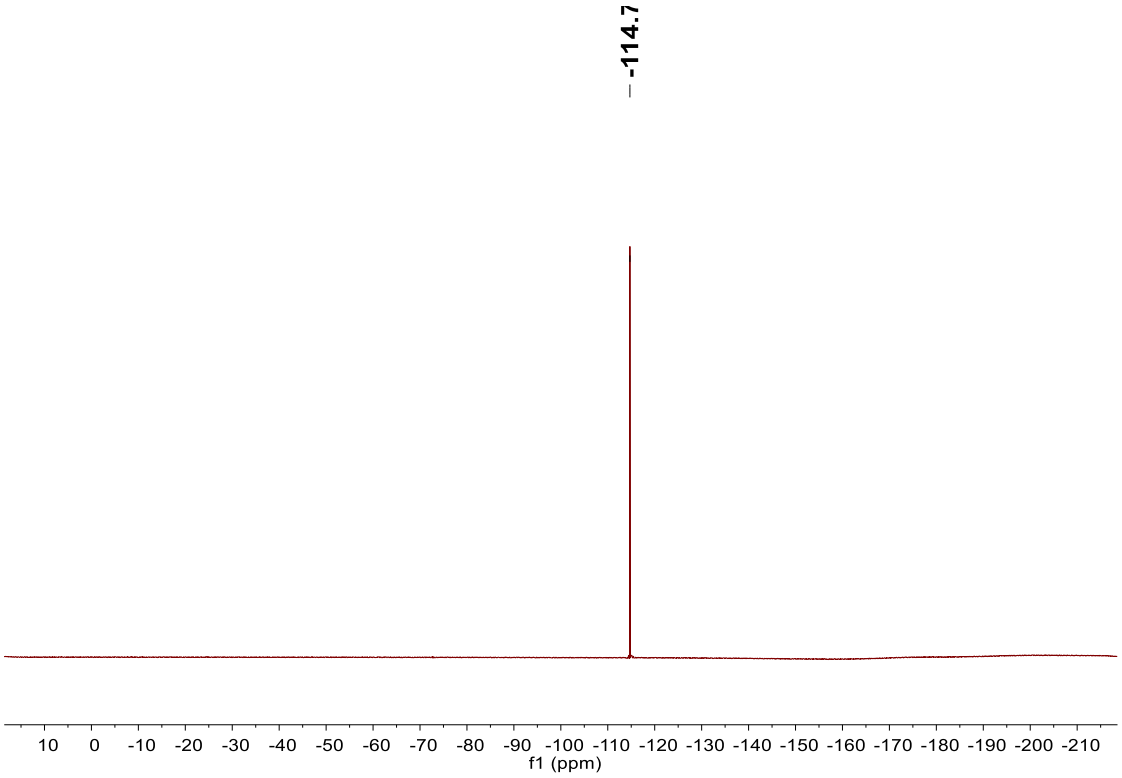
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

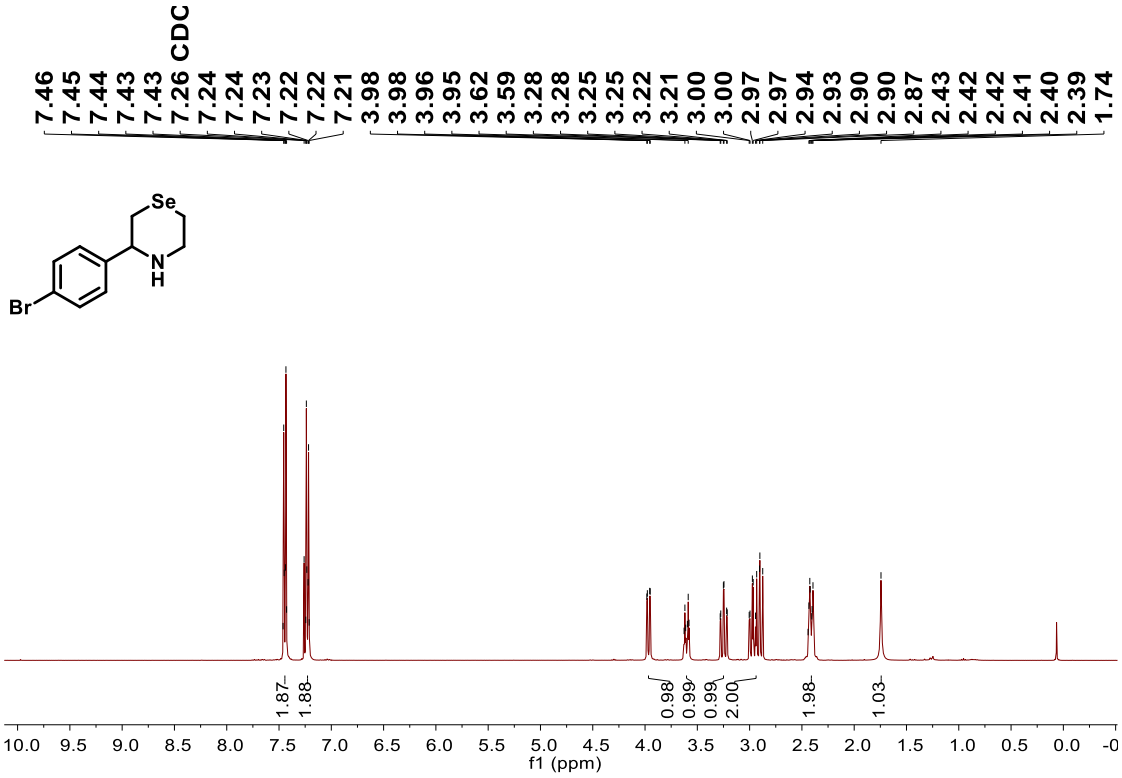


^{19}F NMR (376 MHz, $CDCl_3$)

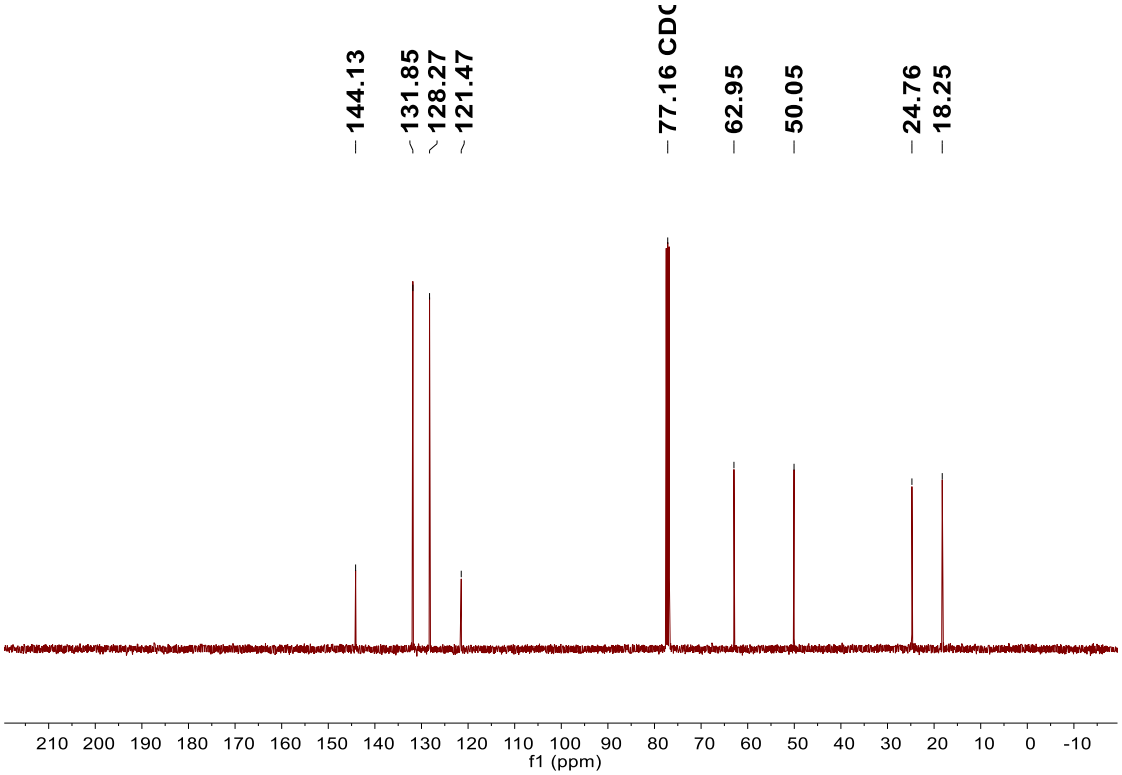


RS3

^{1}H NMR (400 MHz, $CDCl_3$)

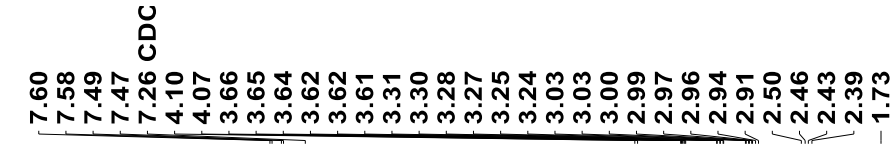


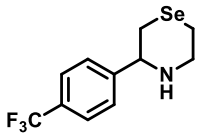
^{13}C NMR (101 MHz, $CDCl_3$)

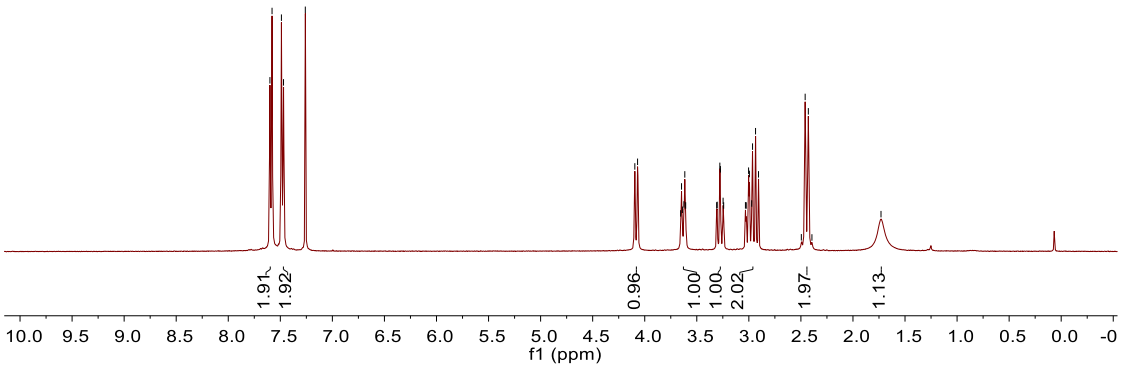


RS4

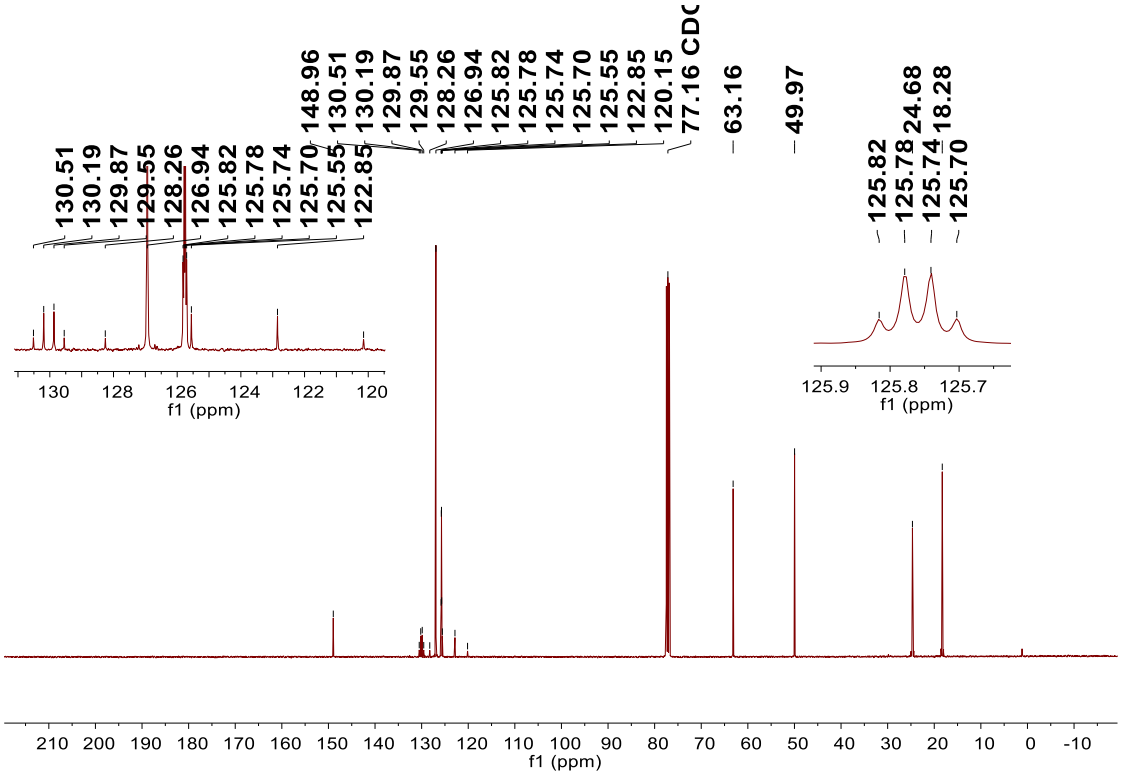
^{1}H NMR (400 MHz, $CDCl_3$)



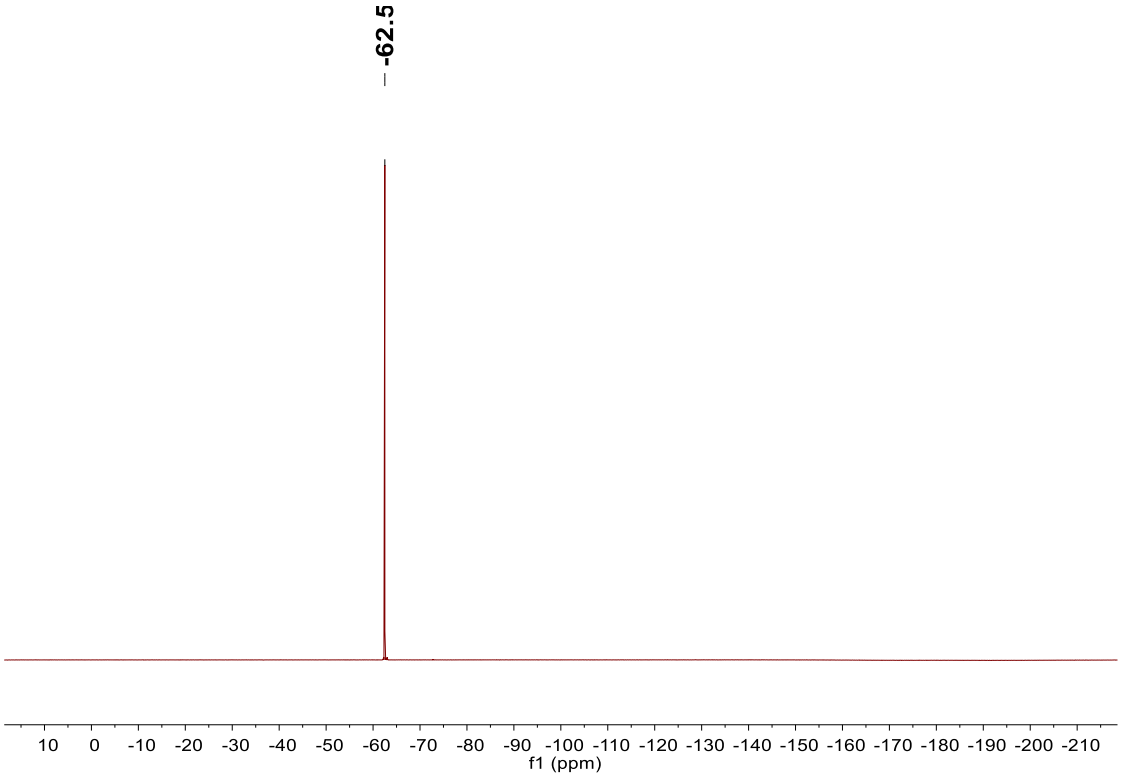




^{13}C NMR (101 MHz, $CDCl_3$)

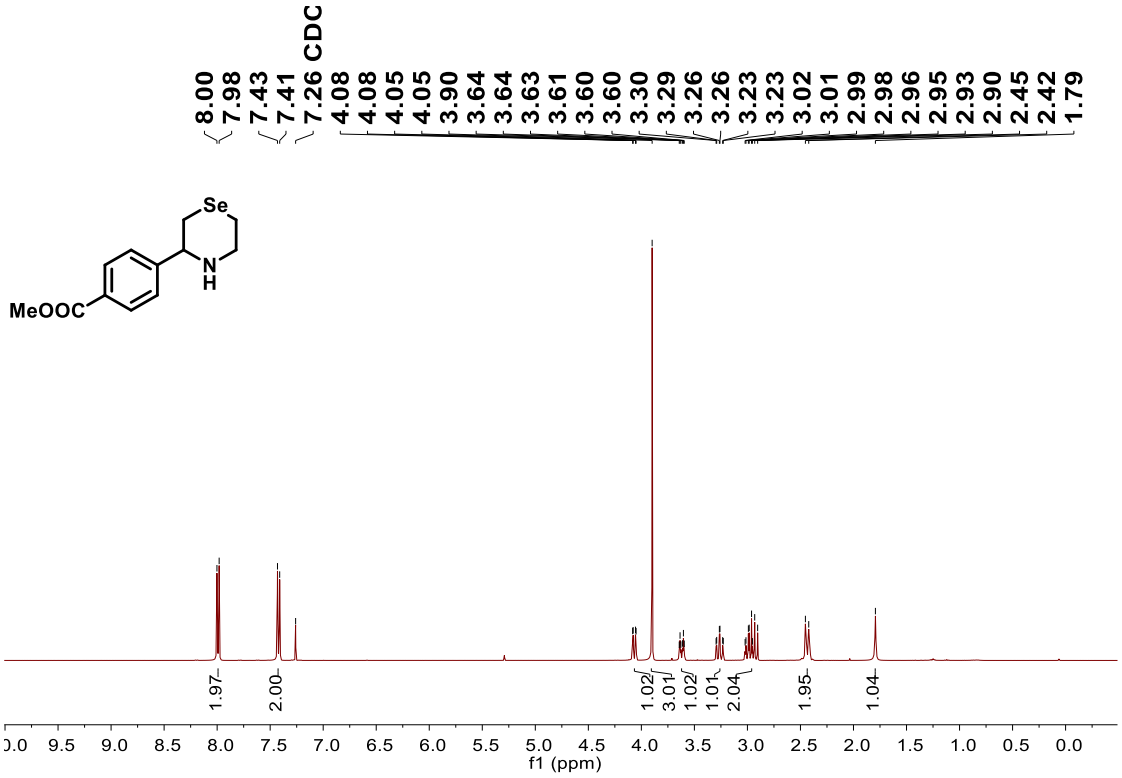


^{19}F NMR (376 MHz, $CDCl_3$)

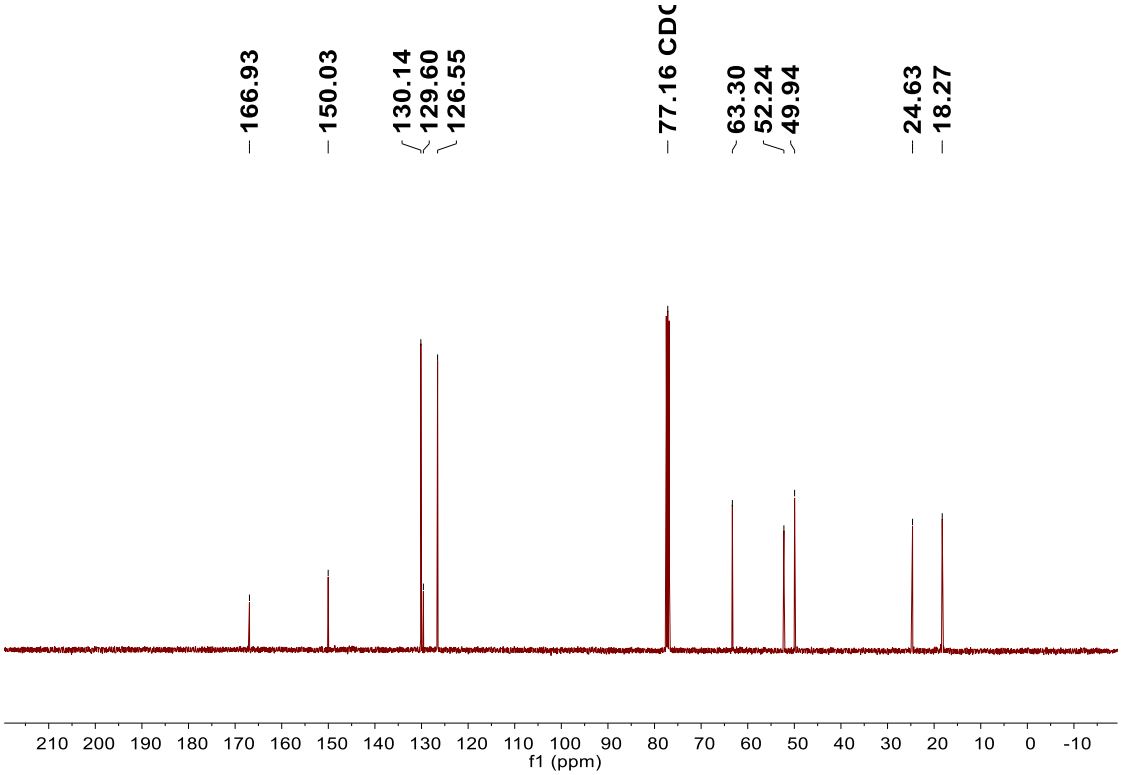


RS5

^{1}H NMR (400 MHz, $CDCl_3$)

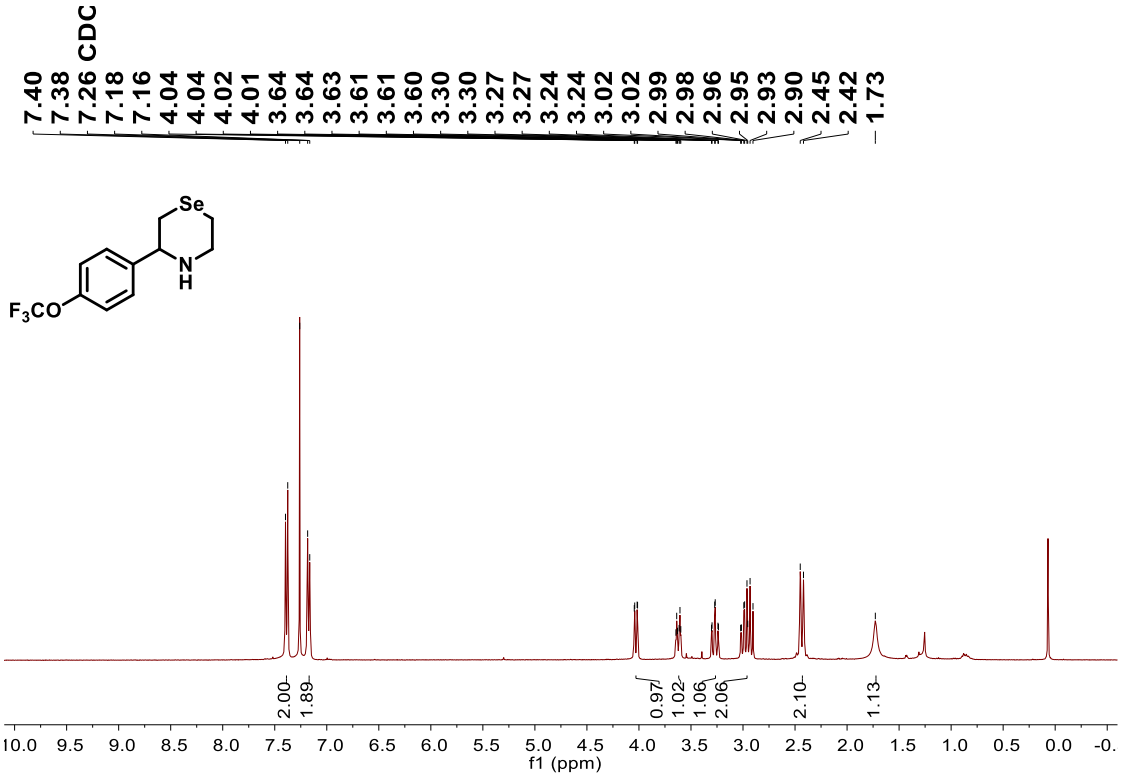


^{13}C NMR (101 MHz, $CDCl_3$)

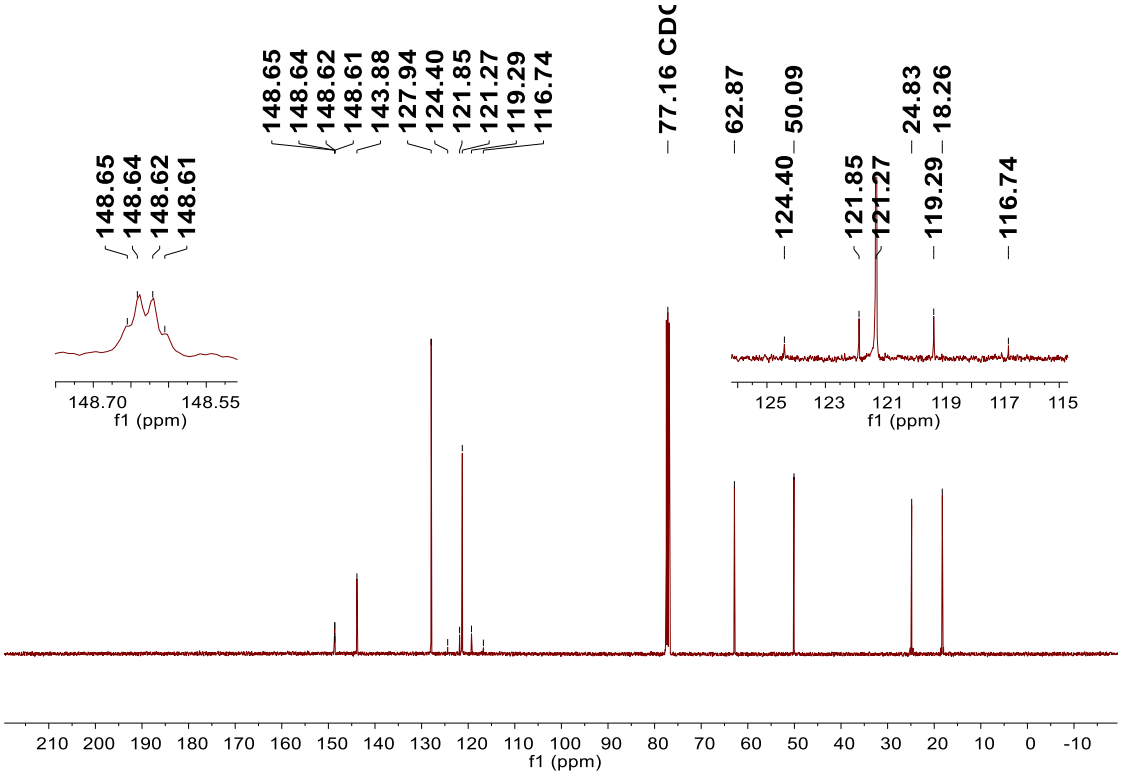


RS6

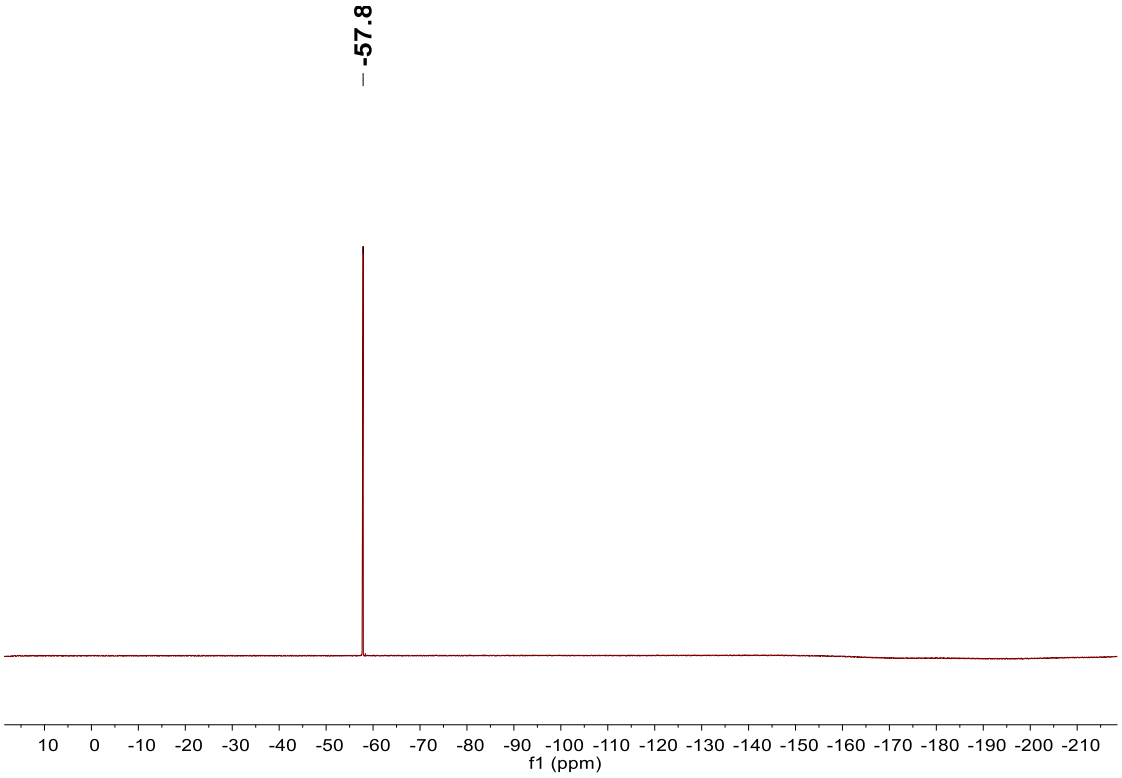
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

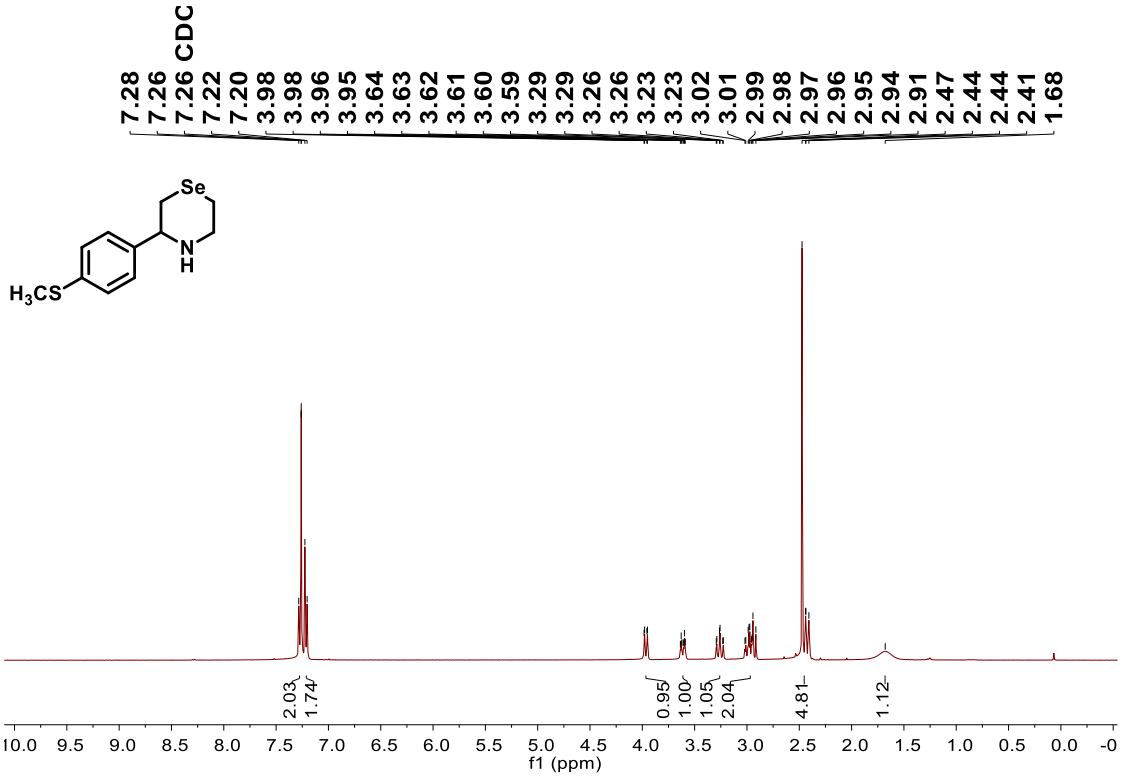


^{19}F NMR (376 MHz, $CDCl_3$)

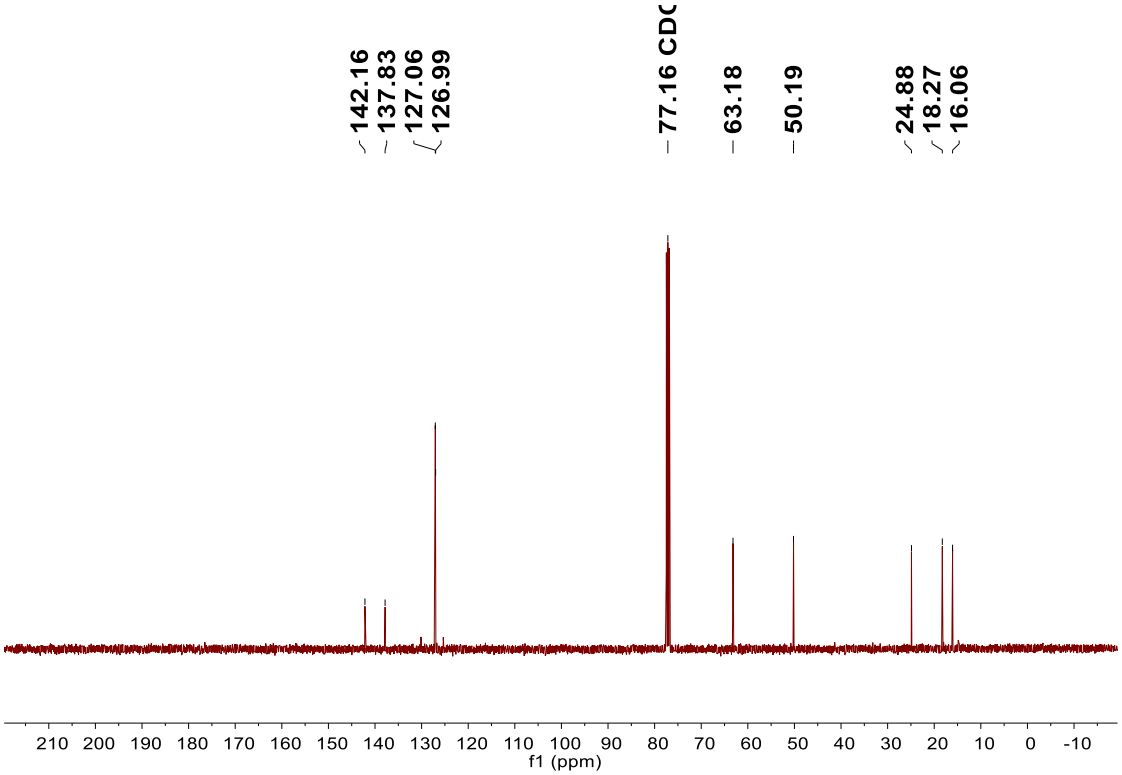


RS7

^{1}H NMR (400 MHz, $CDCl_3$)

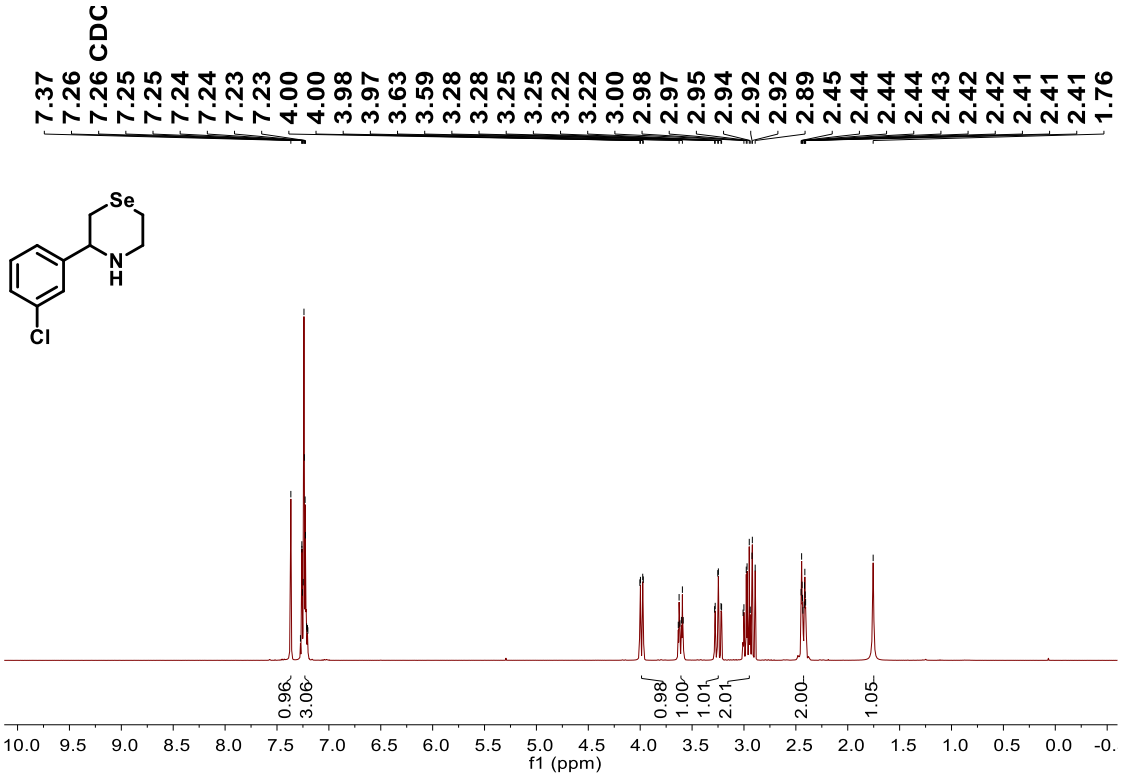


^{13}C NMR (101 MHz, $CDCl_3$)

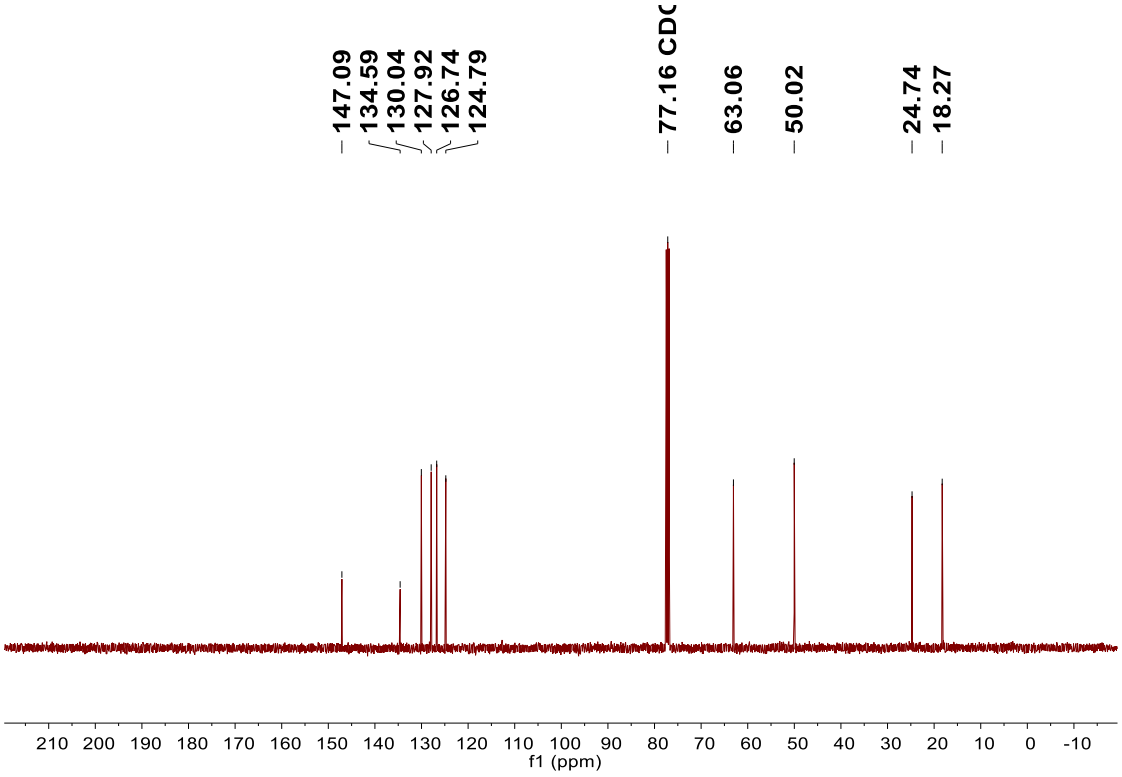


RS8

^{1}H NMR (400 MHz, $CDCl_3$)

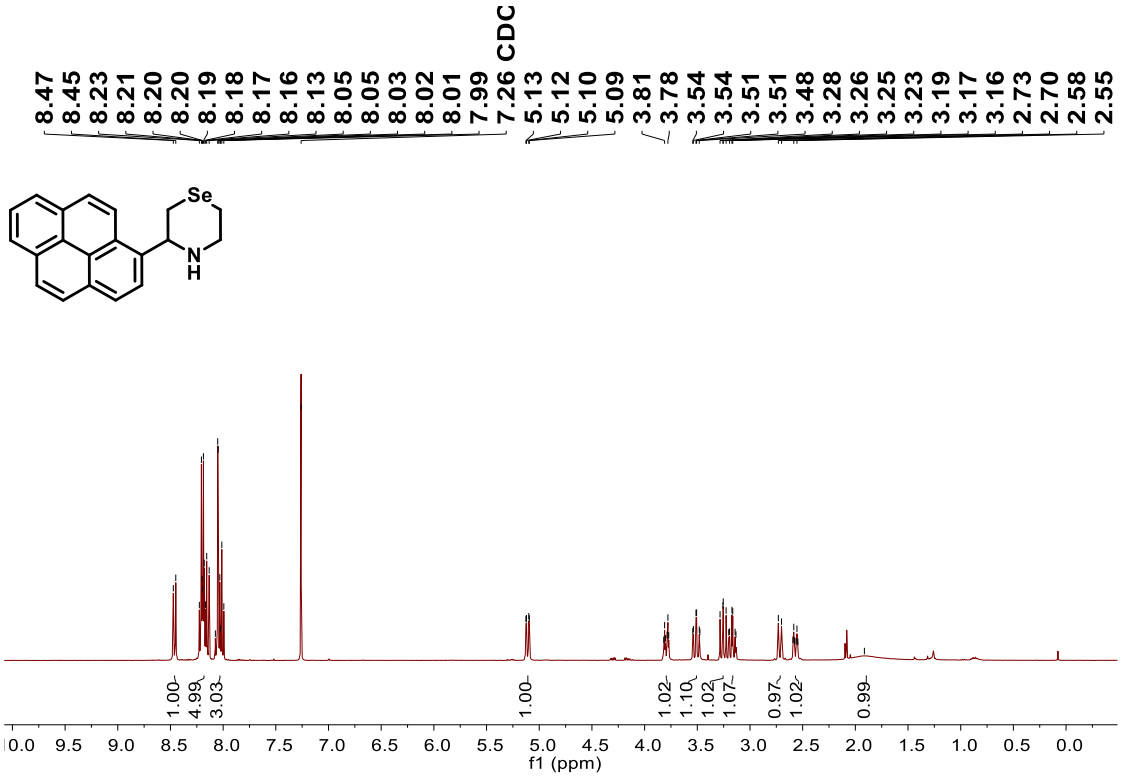


^{13}C NMR (101 MHz, $CDCl_3$)

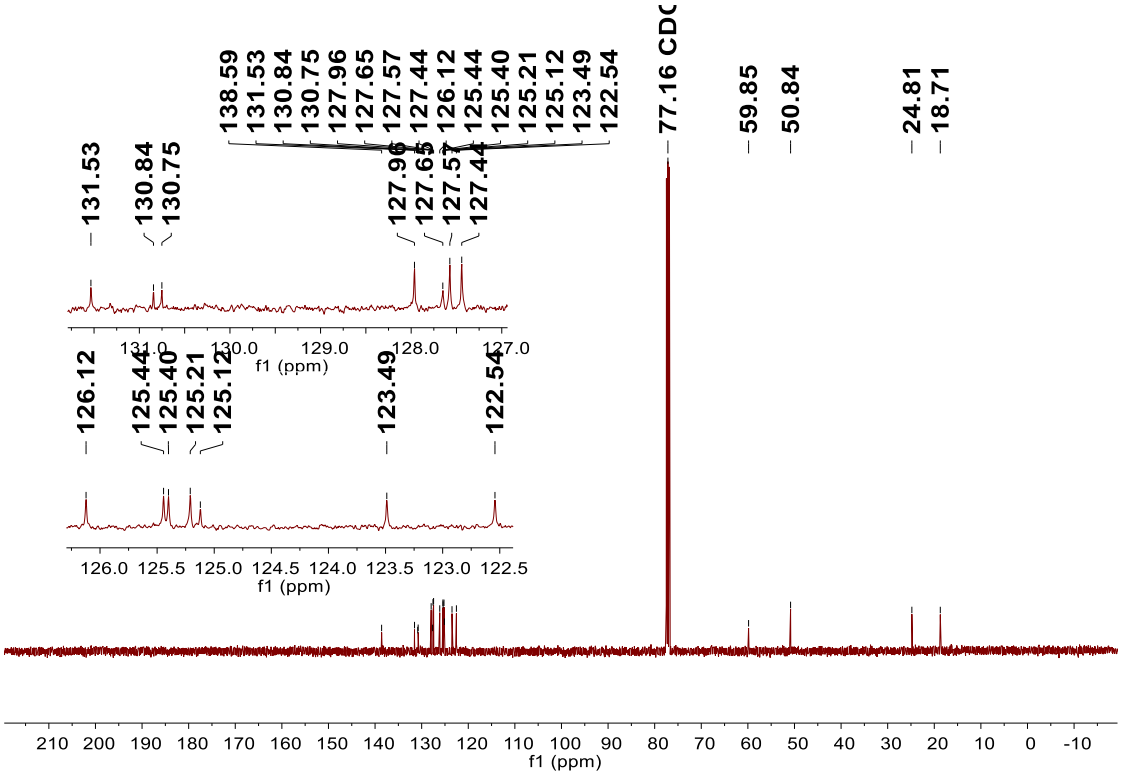


RS9

^{1}H NMR (400 MHz, $CDCl_3$)

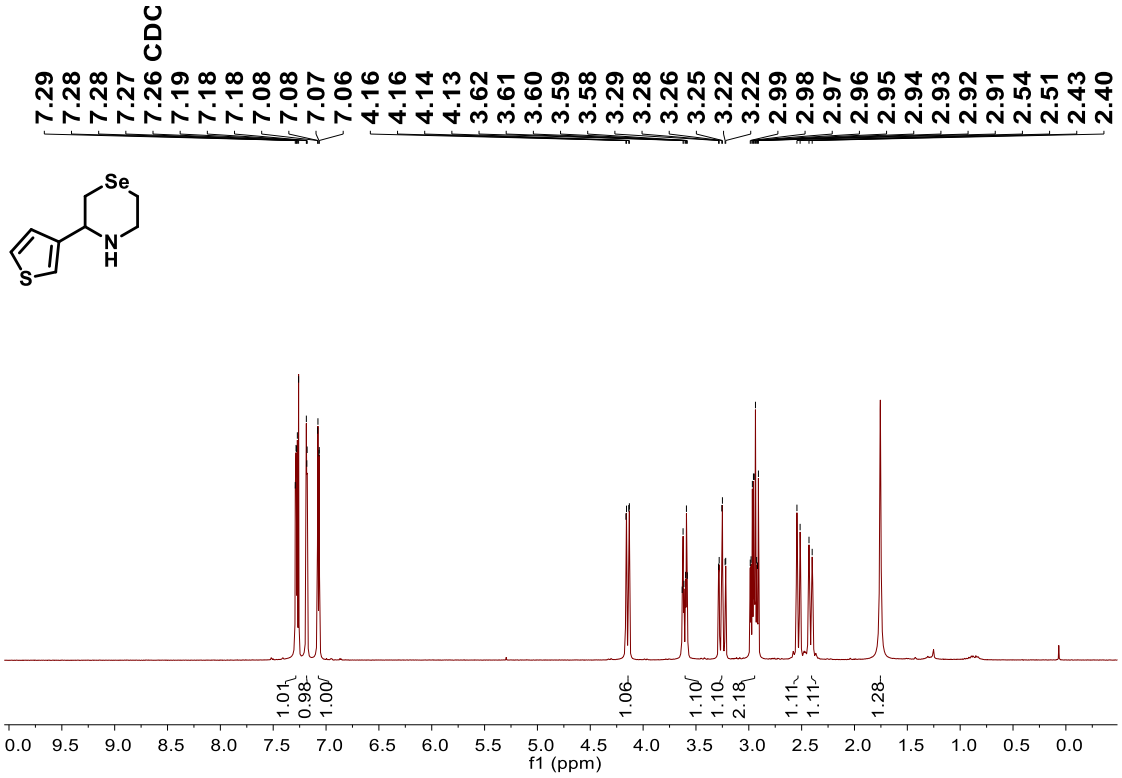


^{13}C NMR (101 MHz, $CDCl_3$)

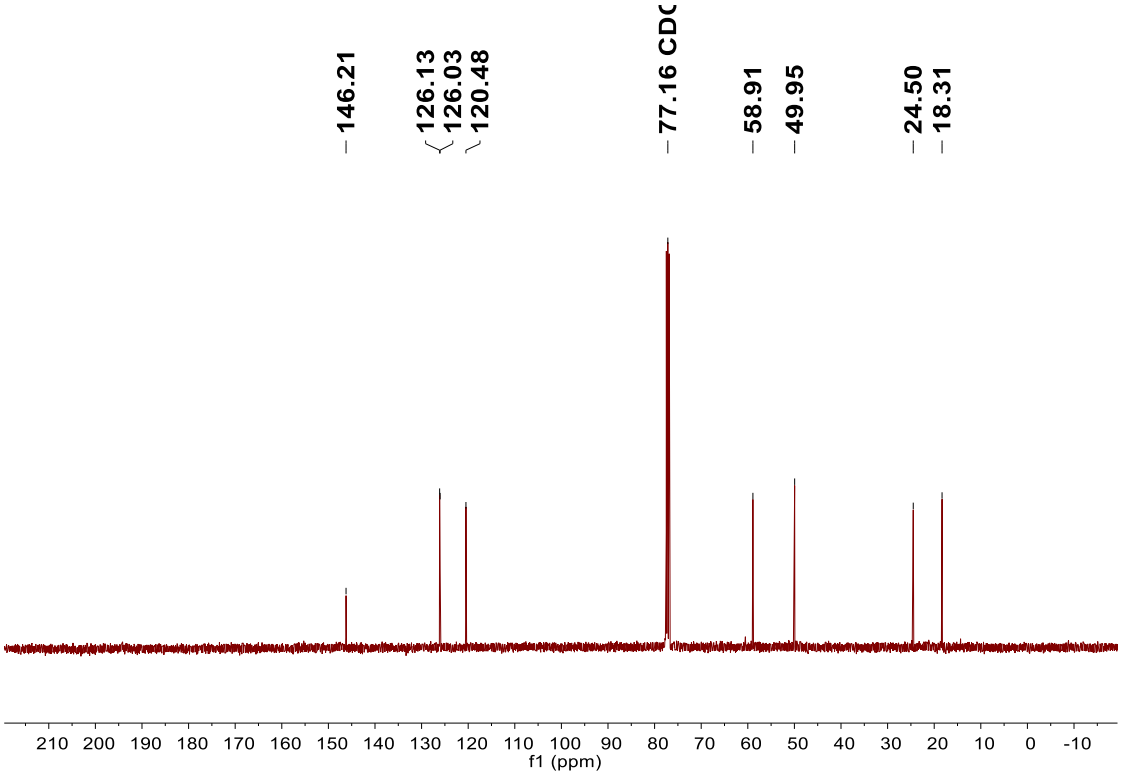


RS10

^{1}H NMR (400 MHz, $CDCl_3$)

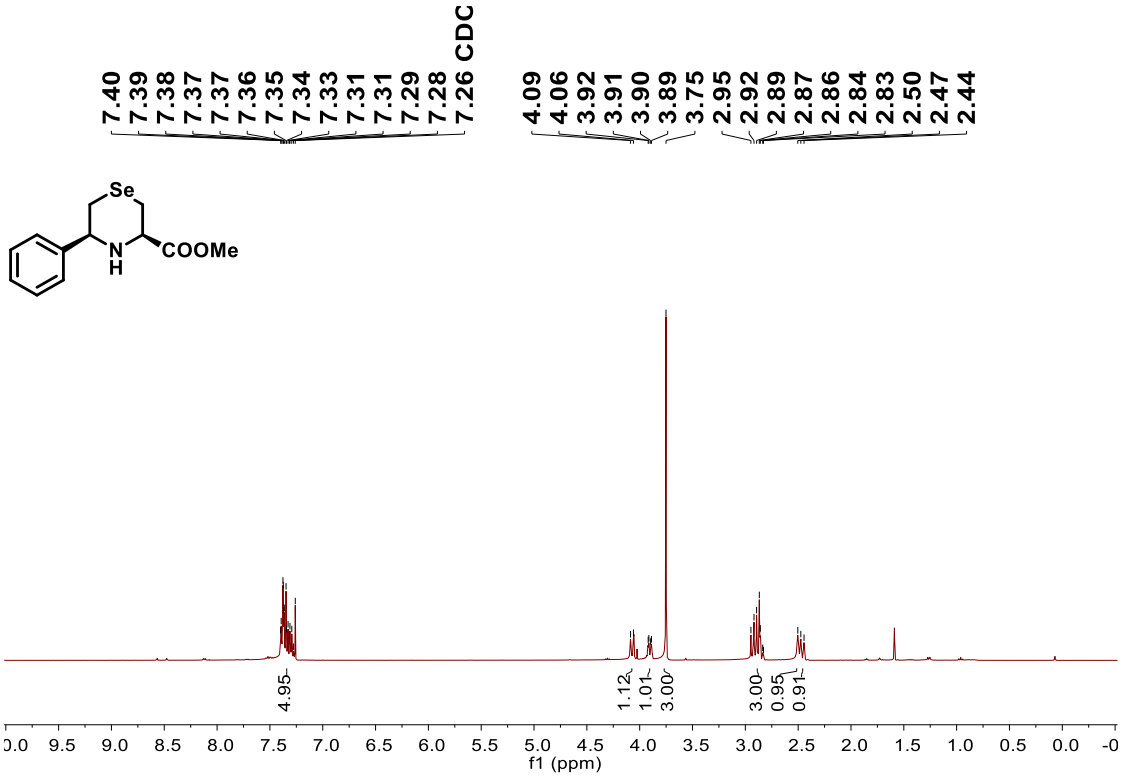


^{13}C NMR (101 MHz, $CDCl_3$)

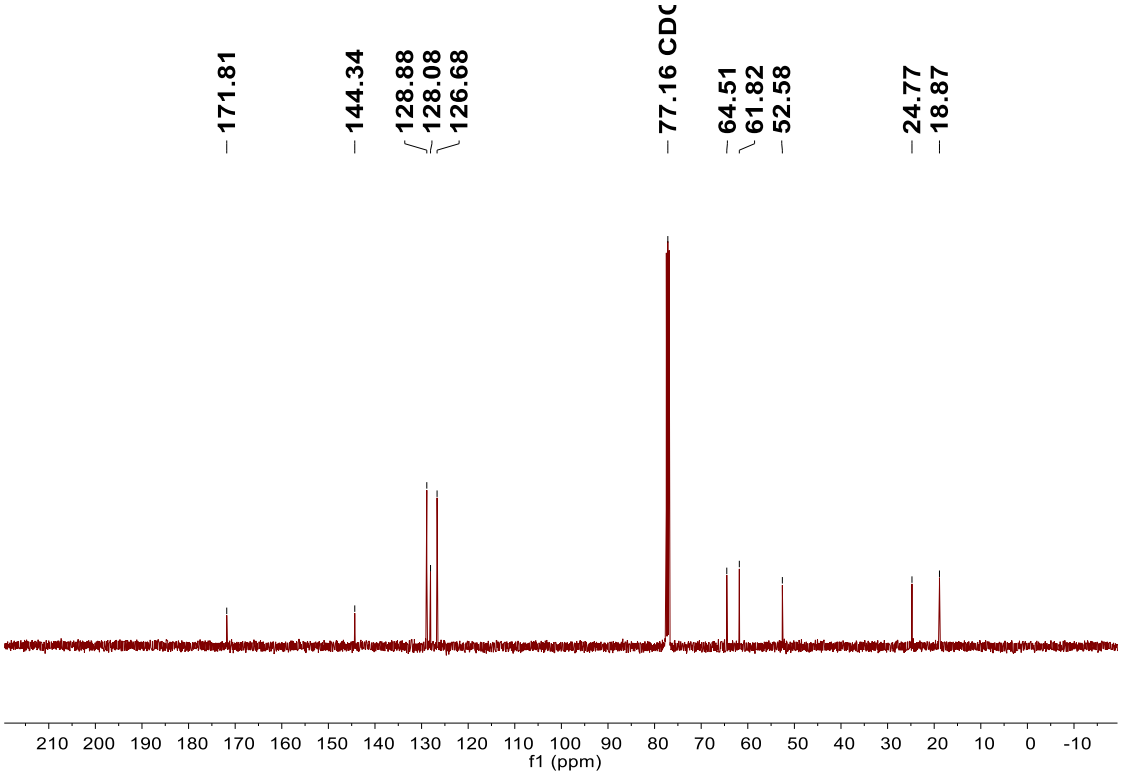


RS11

^{1}H NMR (400 MHz, $CDCl_3$)

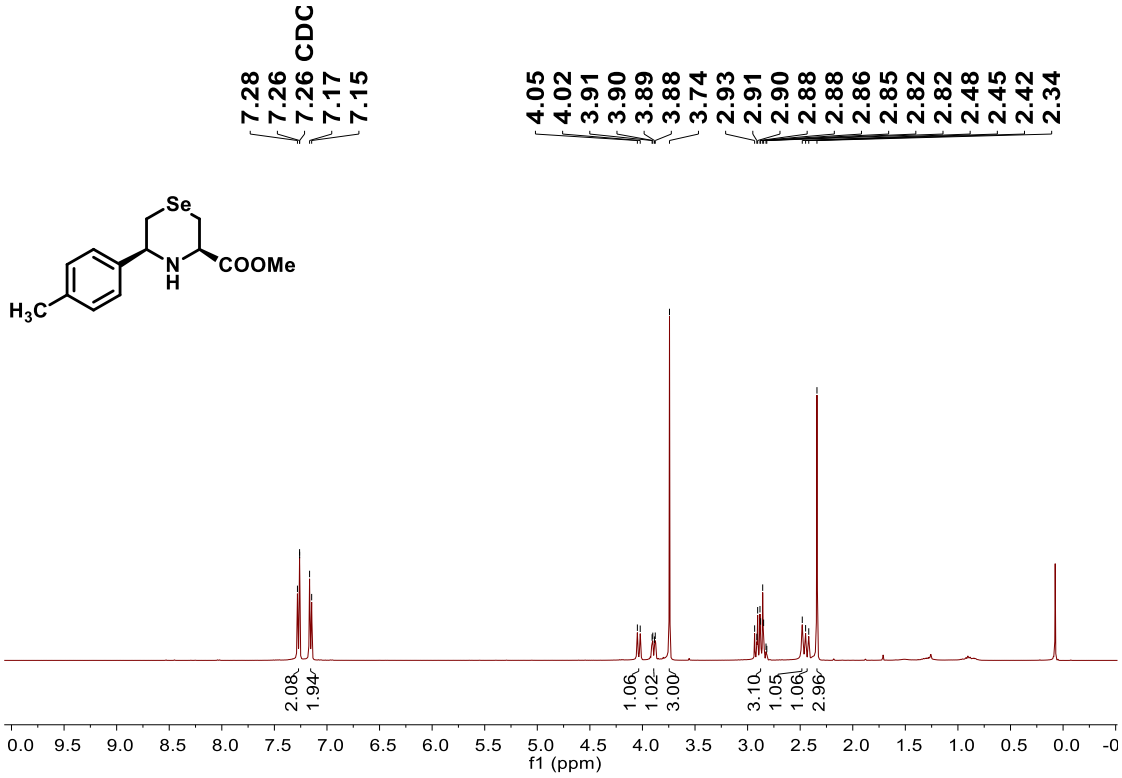


^{13}C NMR (101 MHz, $CDCl_3$)

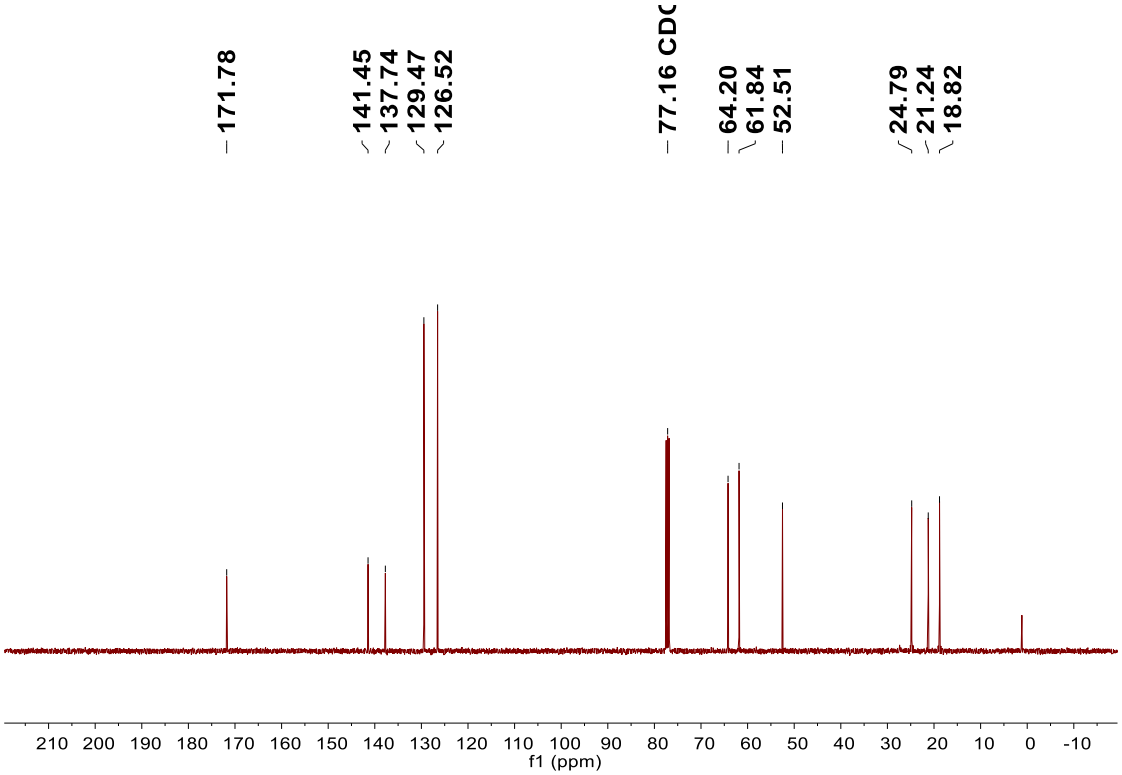


RS12

^{1}H NMR (400 MHz, $CDCl_3$)

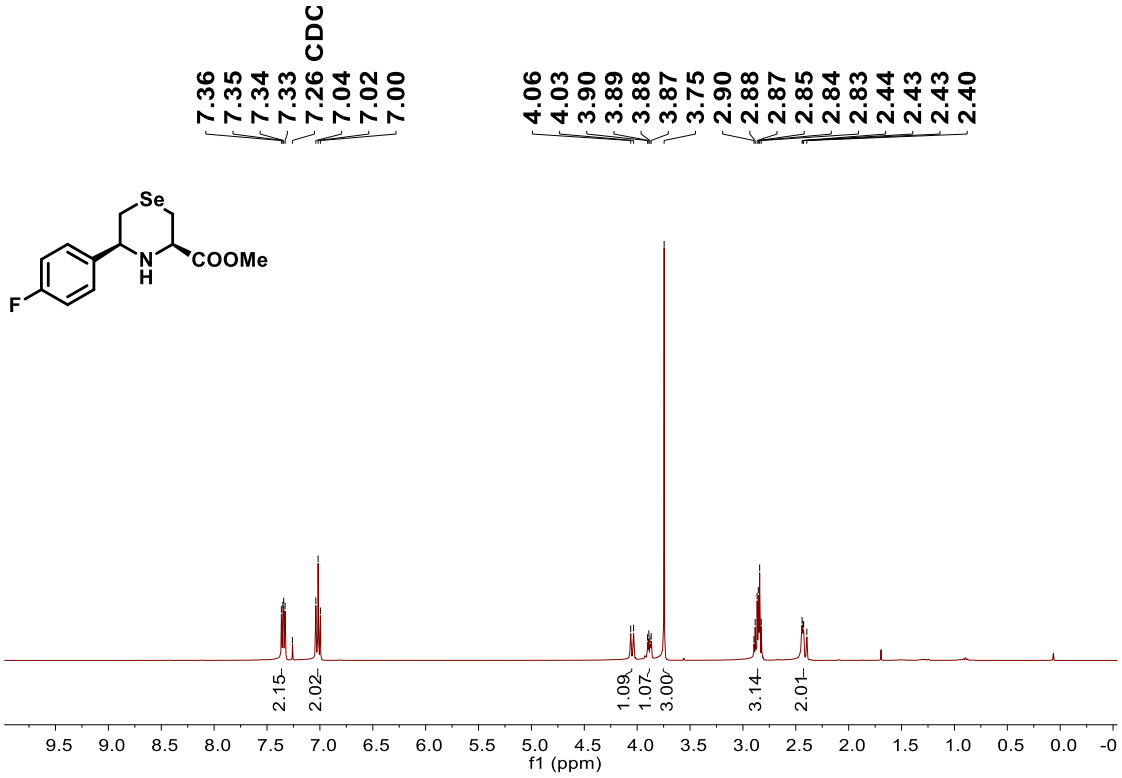


^{13}C NMR (101 MHz, $CDCl_3$)

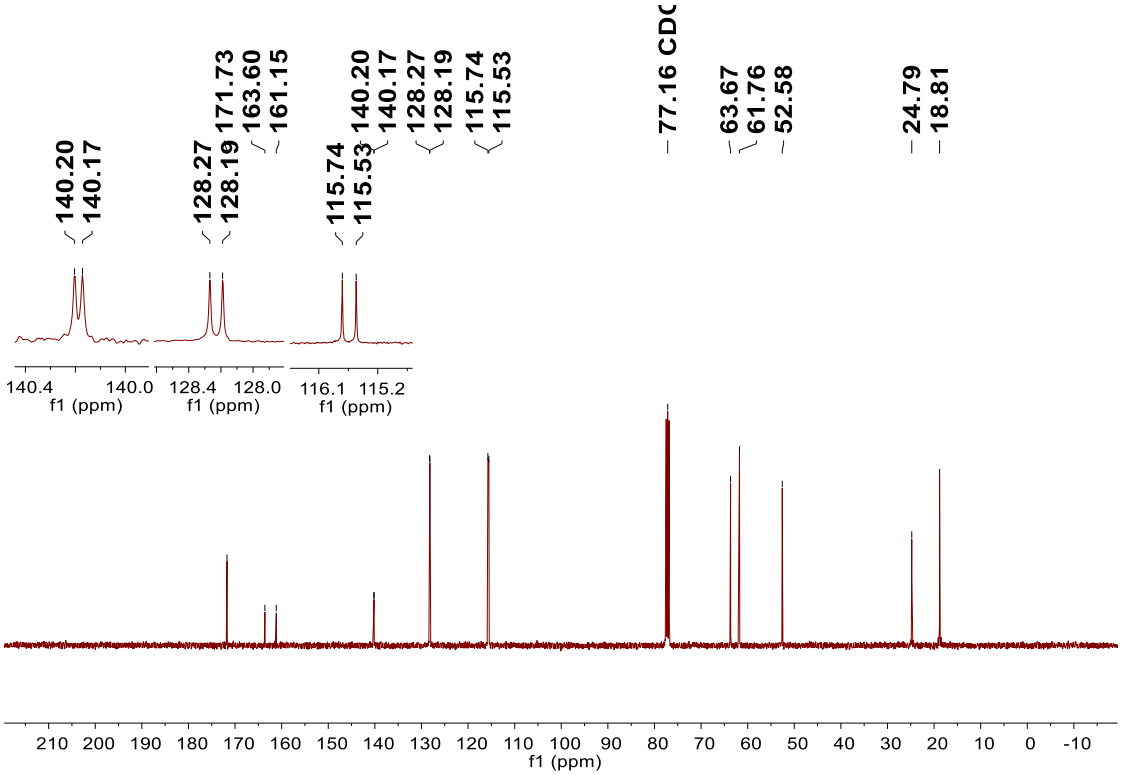


RS13

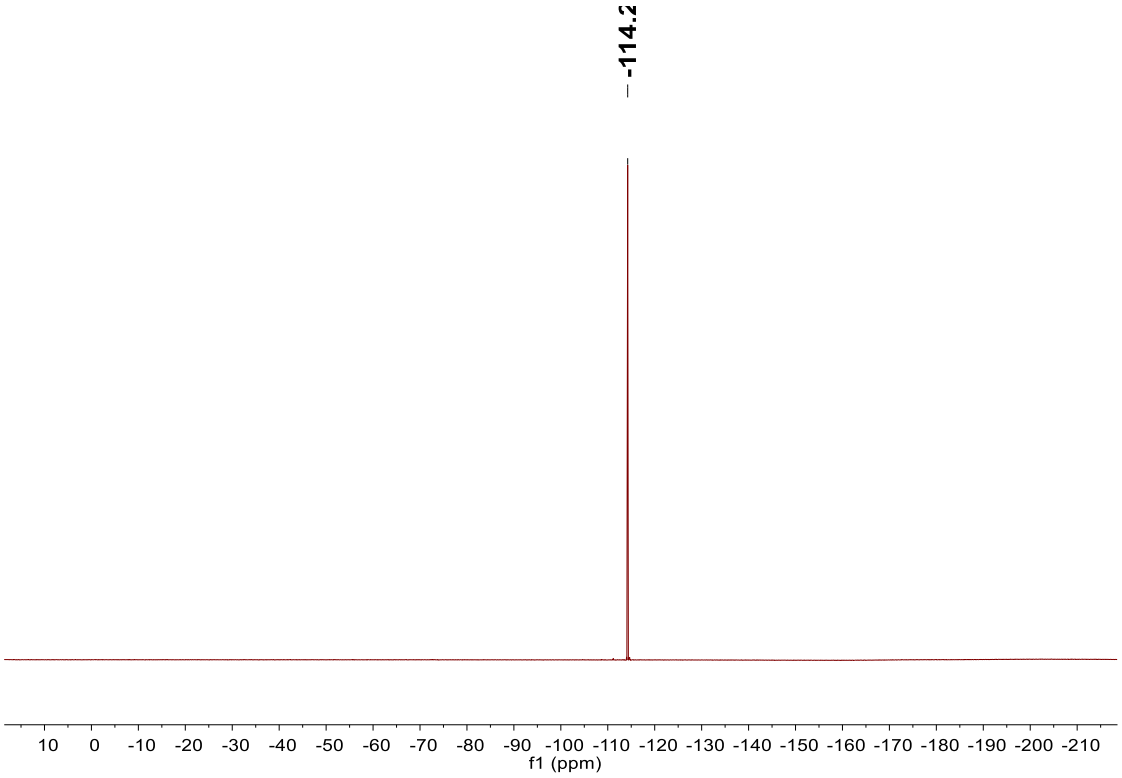
^{1}H NMR (400 MHz, $CDCl_3$)



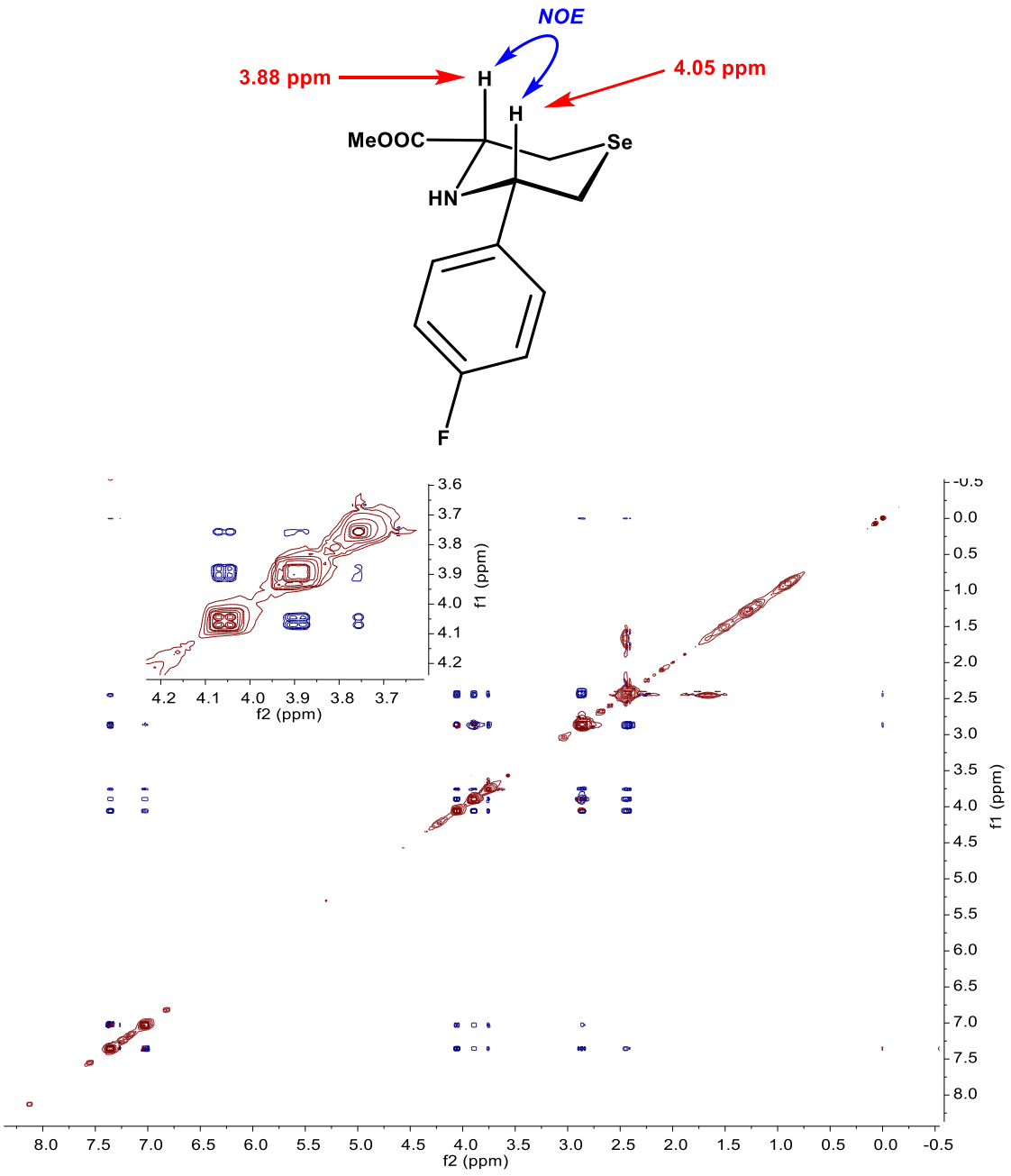
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

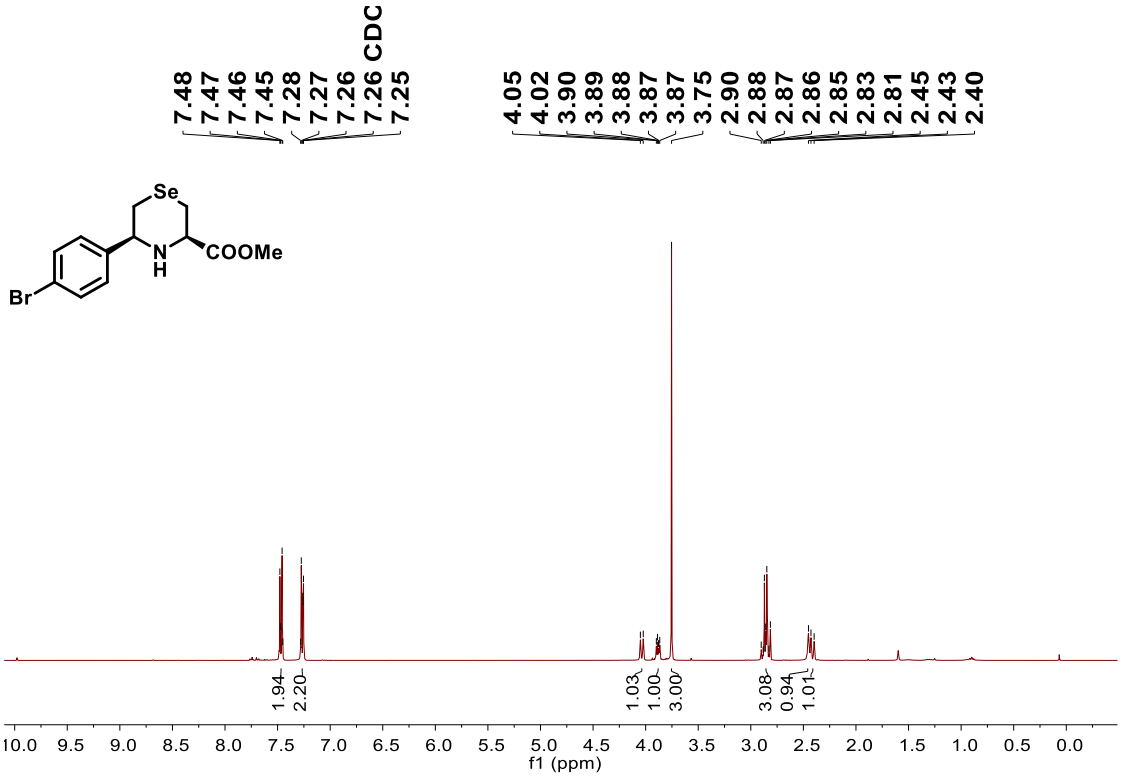


NOESY of **RS13**

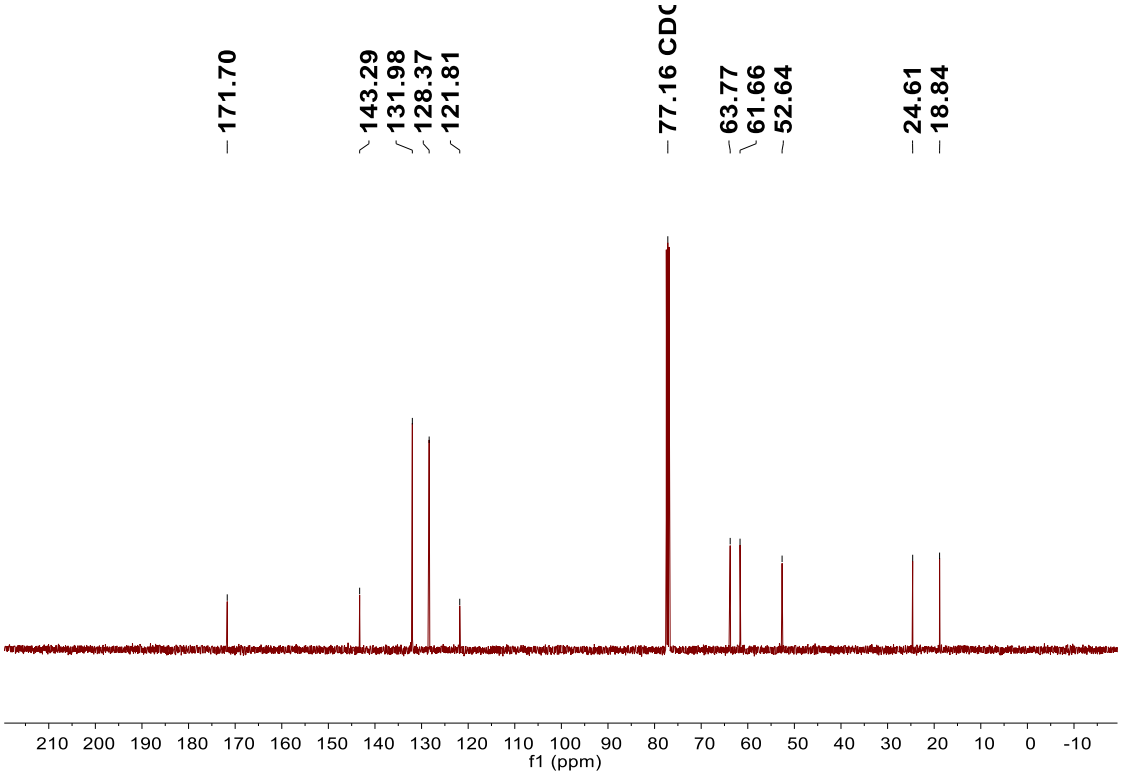


RS14

^{1}H NMR (400 MHz, $CDCl_3$)

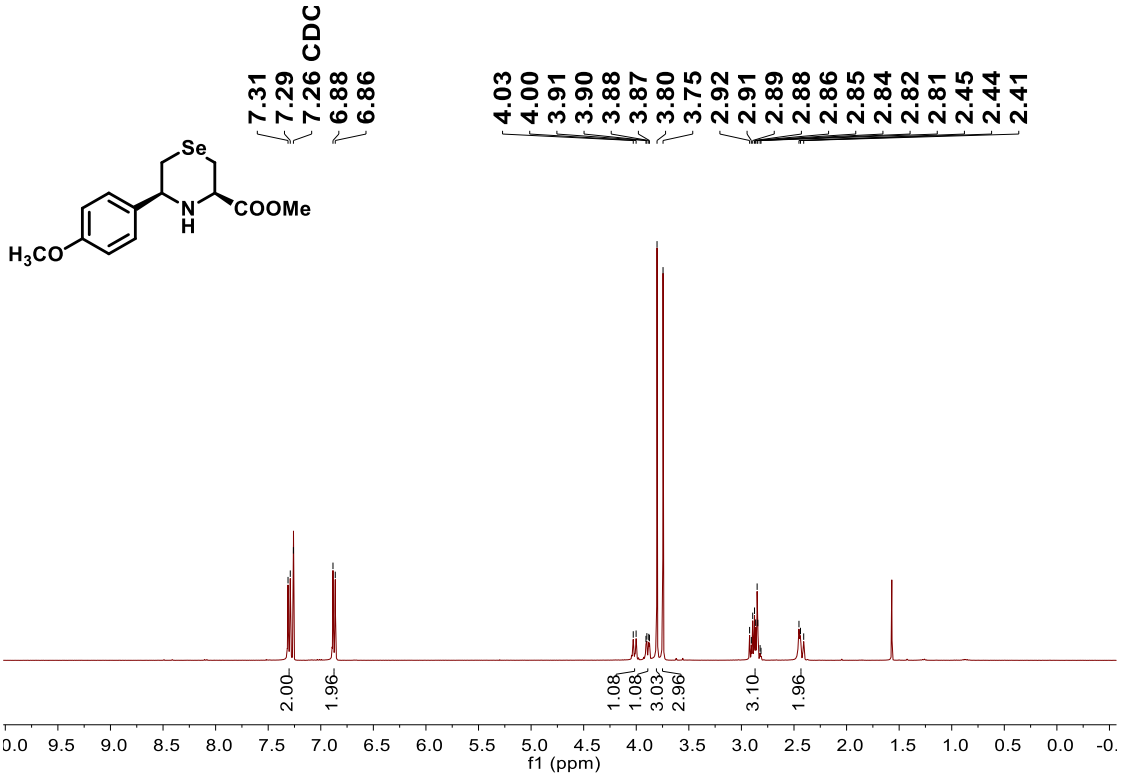


^{13}C NMR (101 MHz, $CDCl_3$)

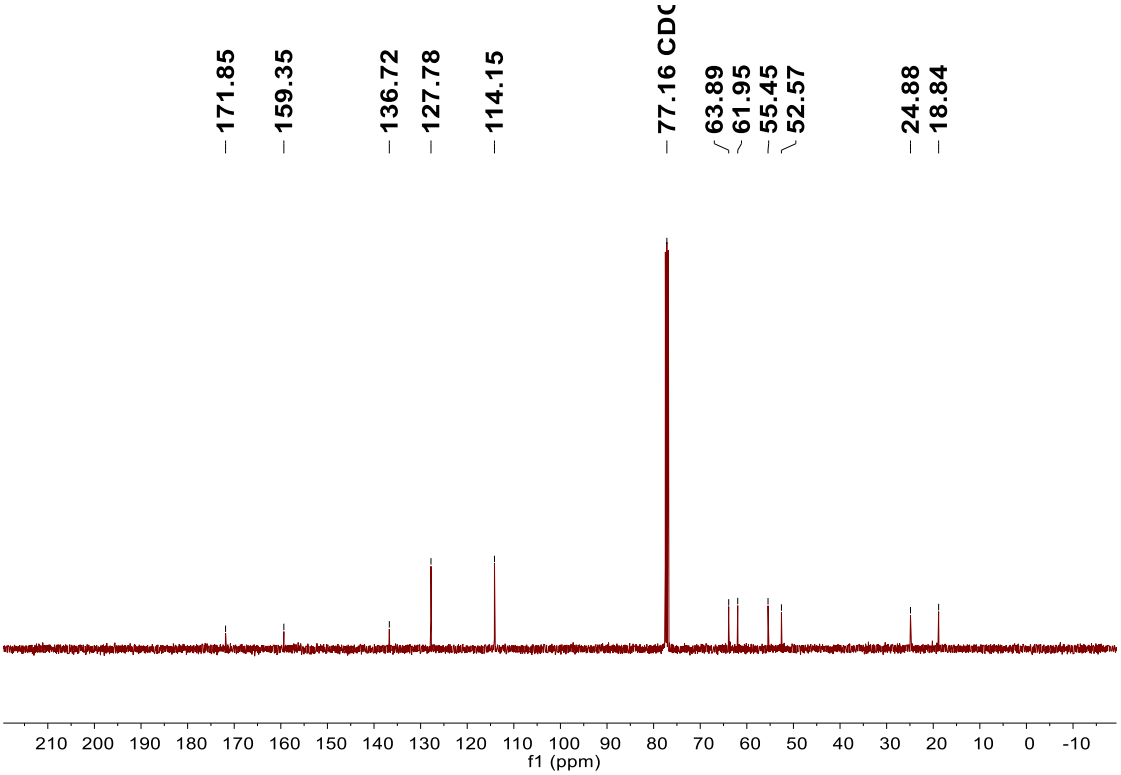


RS15

^{1}H NMR (400 MHz, $CDCl_3$)

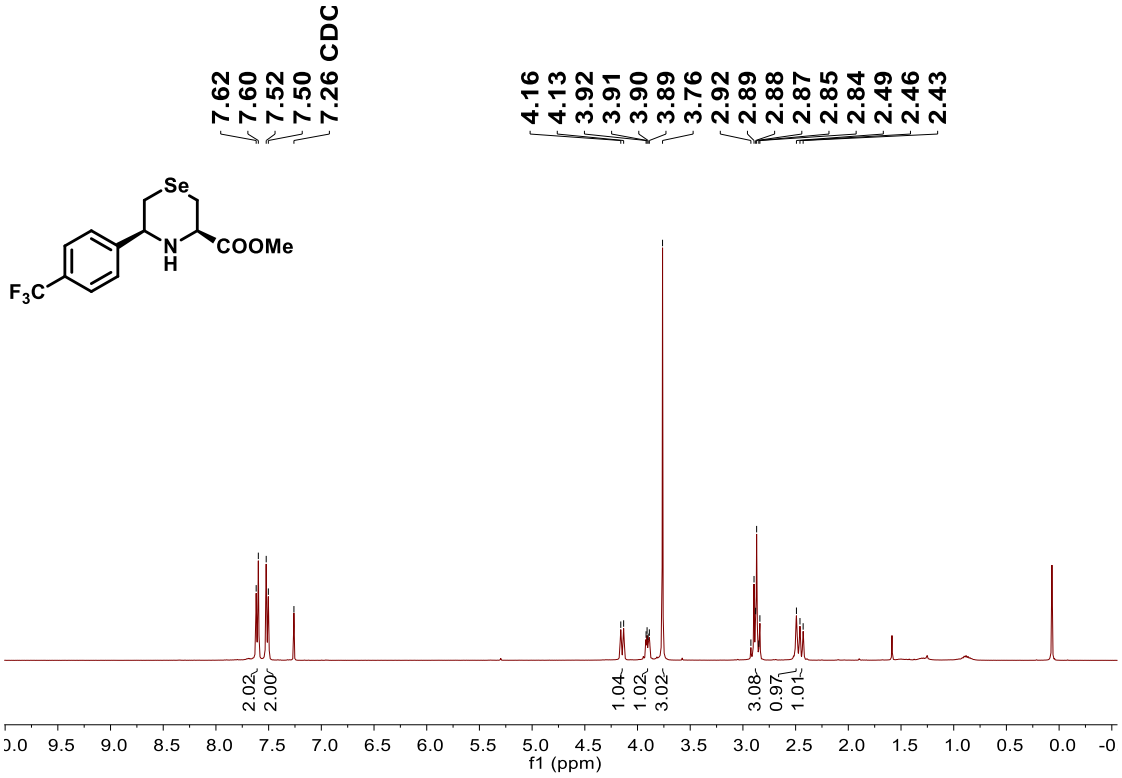


^{13}C NMR (101 MHz, $CDCl_3$)

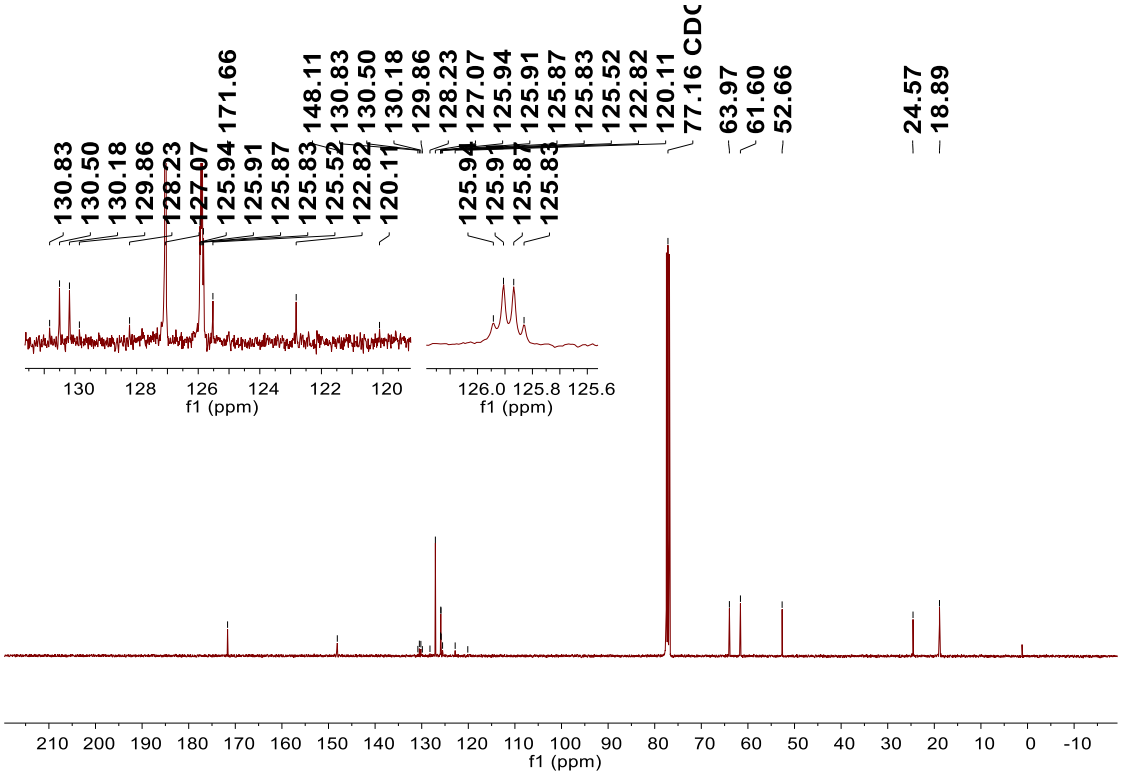


RS16

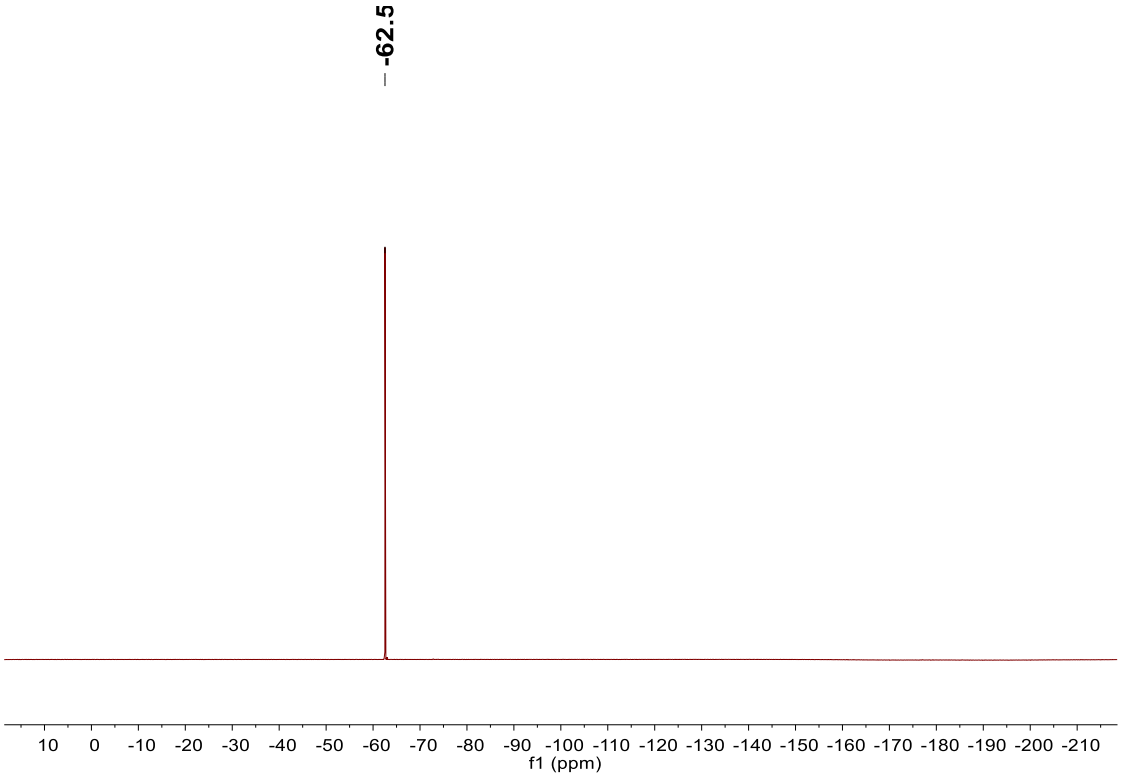
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

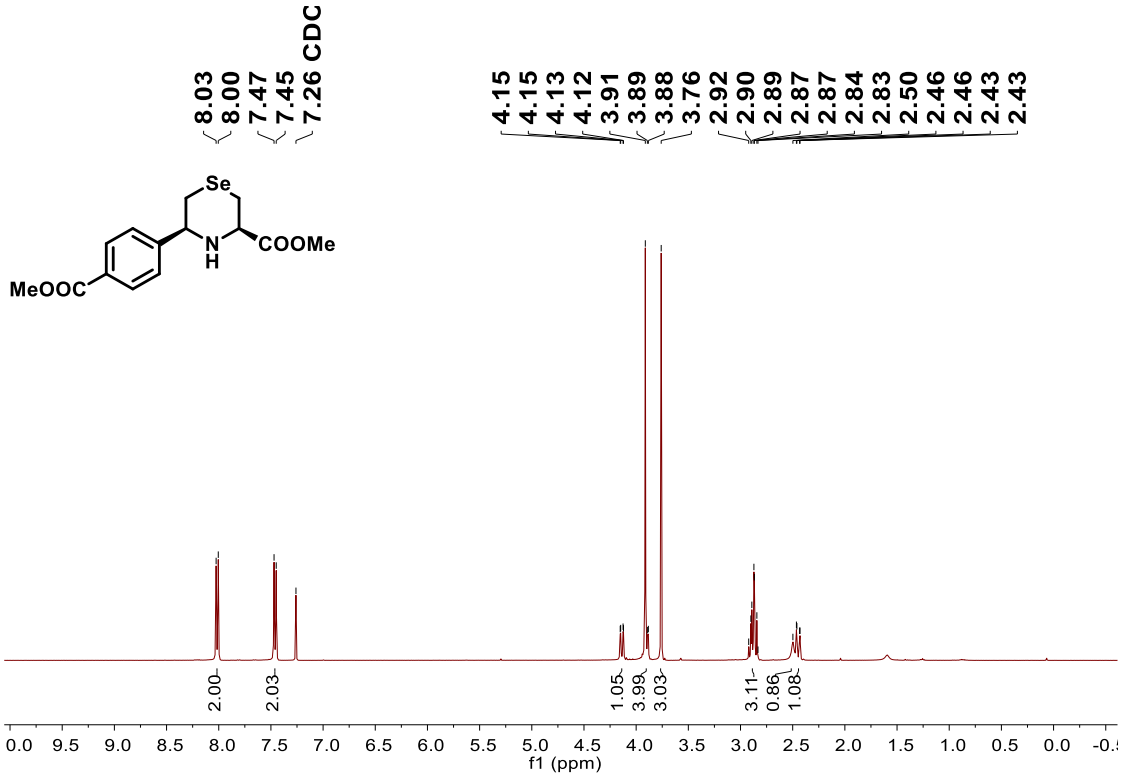


^{19}F NMR (376 MHz, $CDCl_3$)

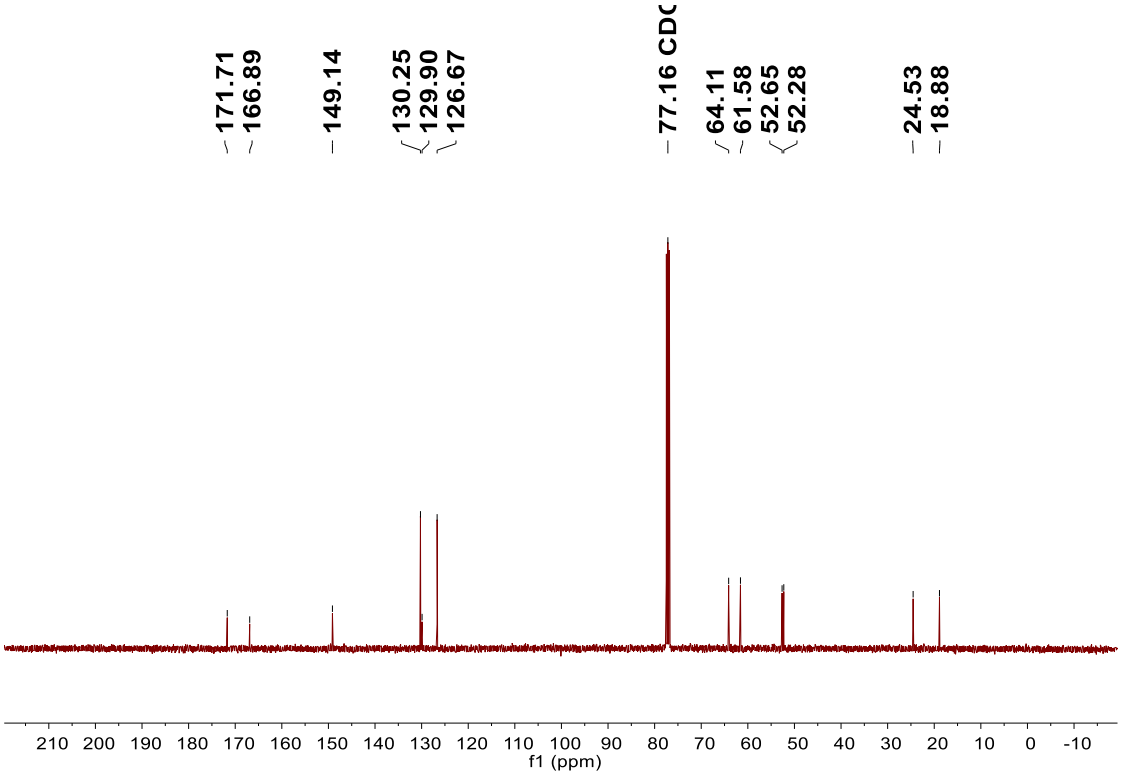


RS17

^{1}H NMR (400 MHz, $CDCl_3$)

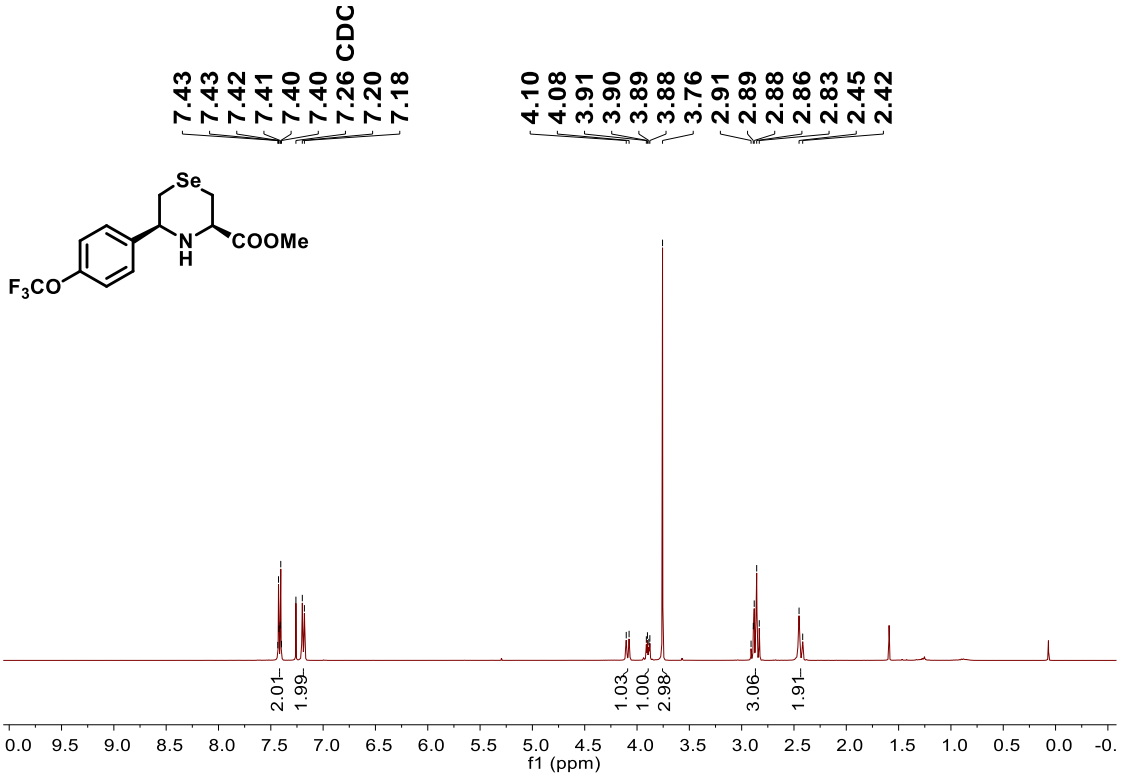


^{13}C NMR (101 MHz, $CDCl_3$)

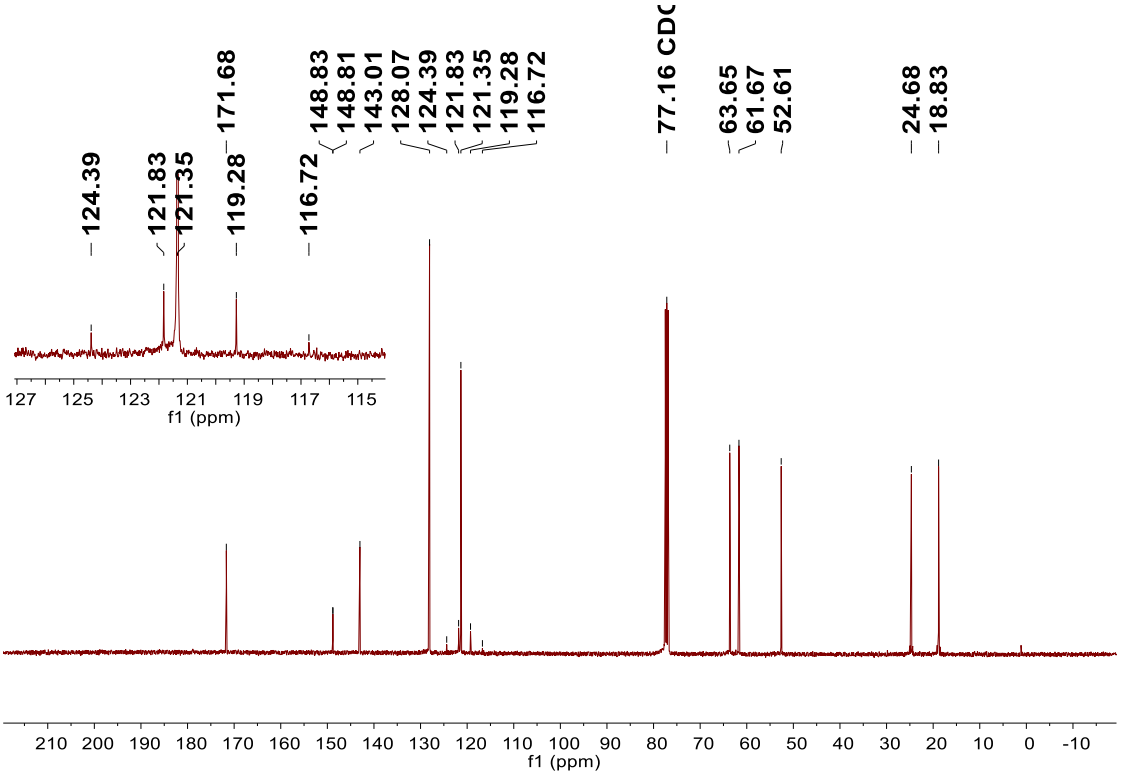


RS18

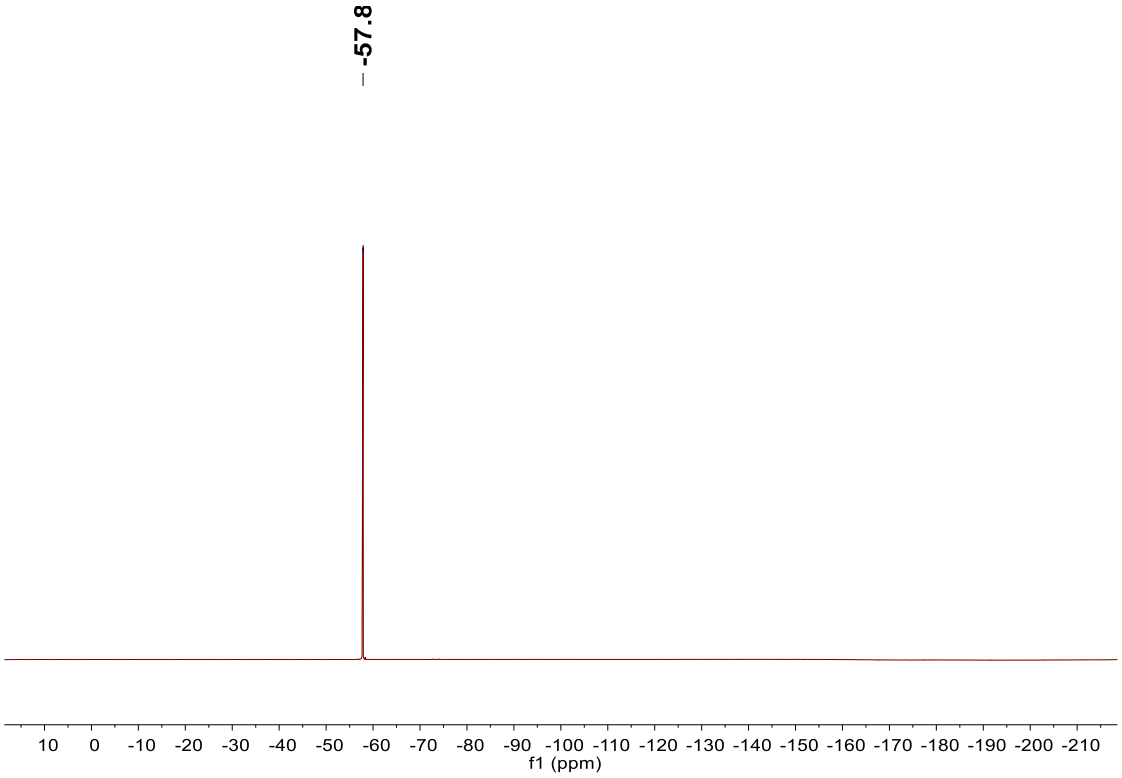
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

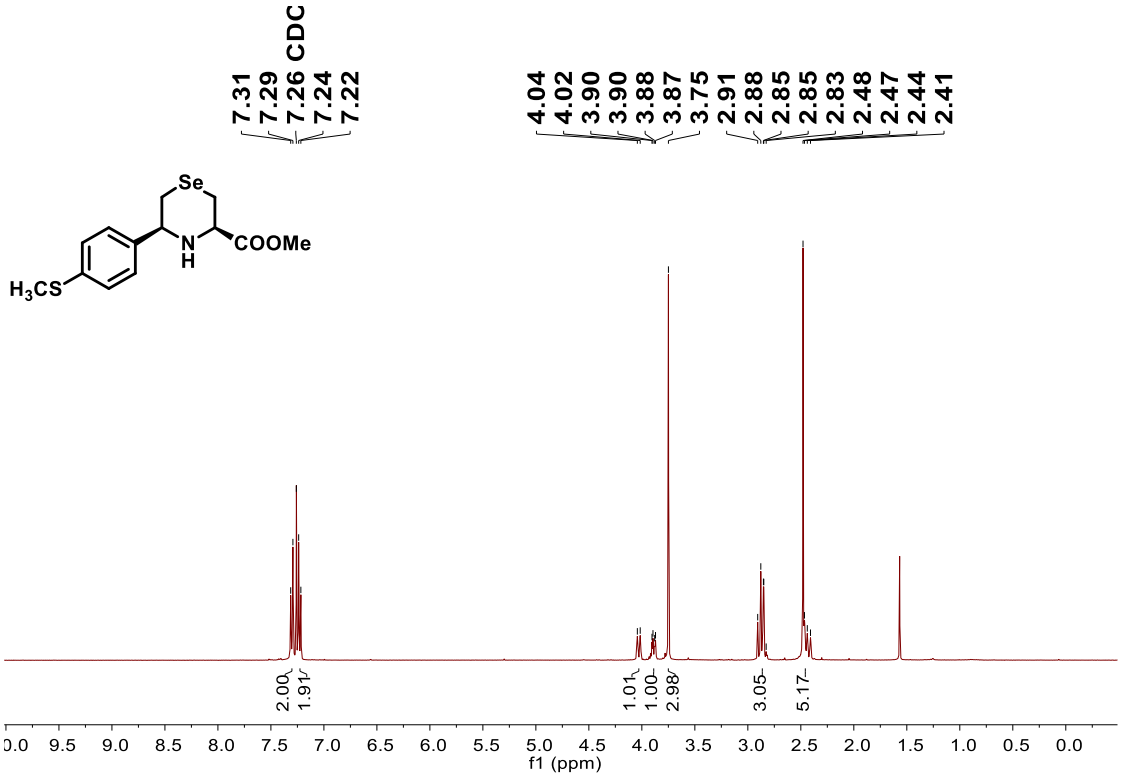


^{19}F NMR (376 MHz, $CDCl_3$)

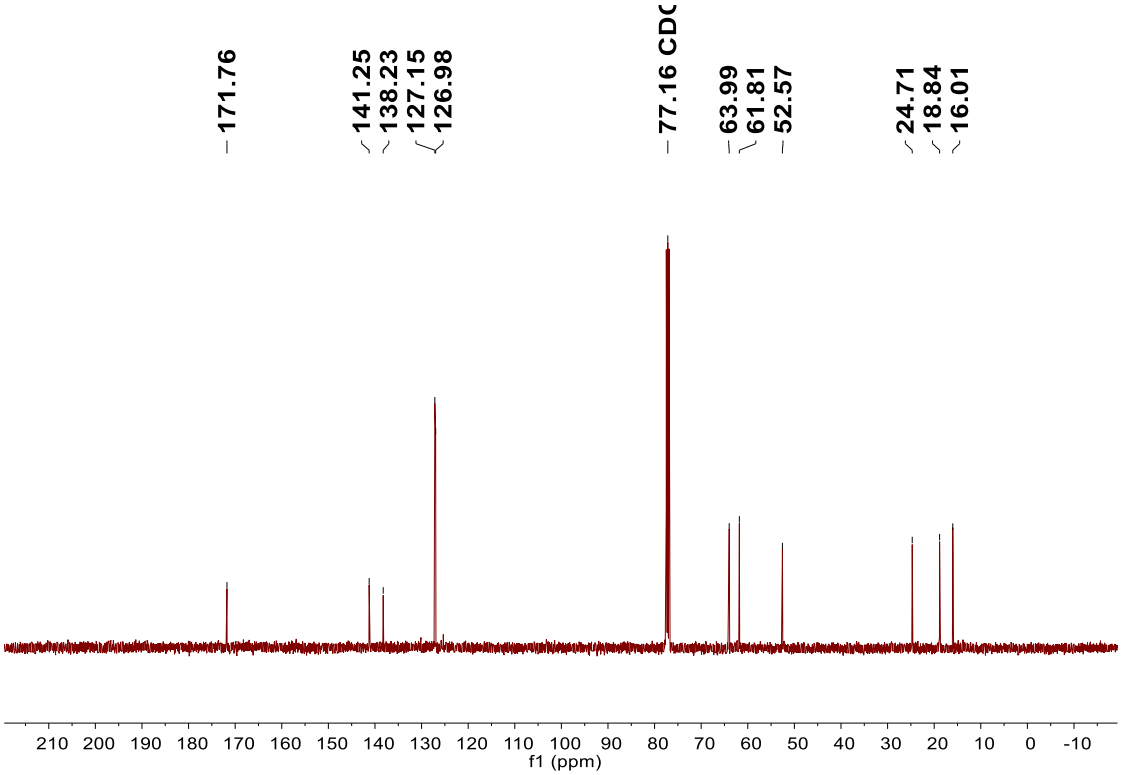


RS19

^{1}H NMR (400 MHz, $CDCl_3$)

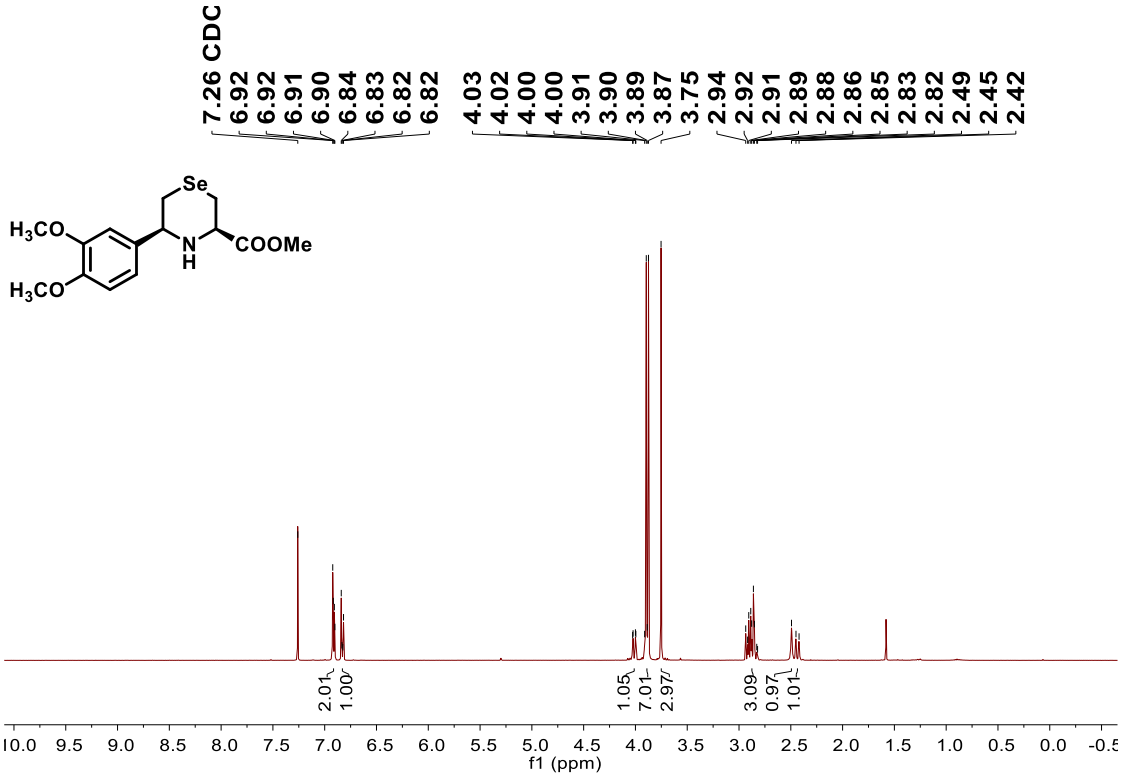


^{13}C NMR (101 MHz, $CDCl_3$)

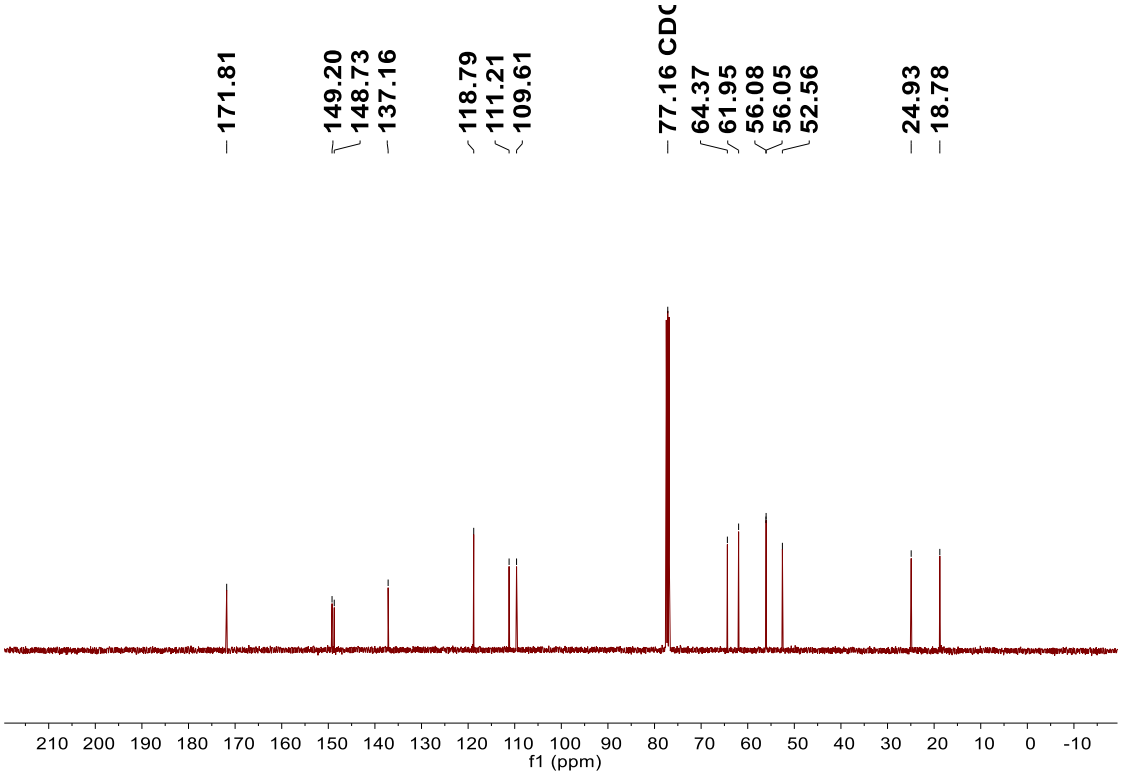


RS20

^{1}H NMR (400 MHz, $CDCl_3$)

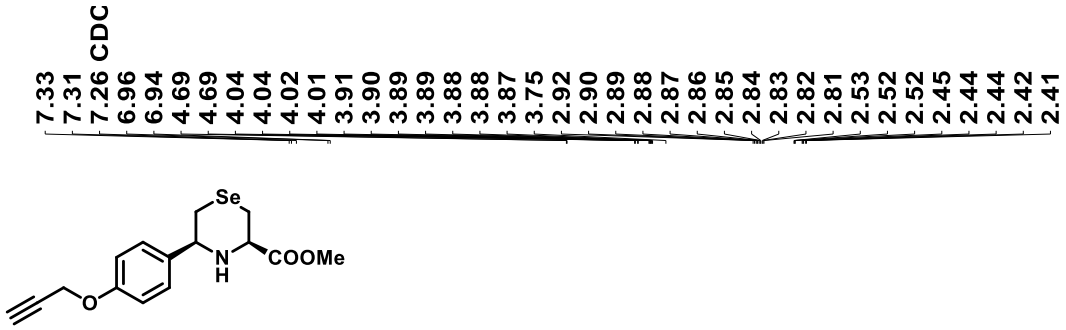


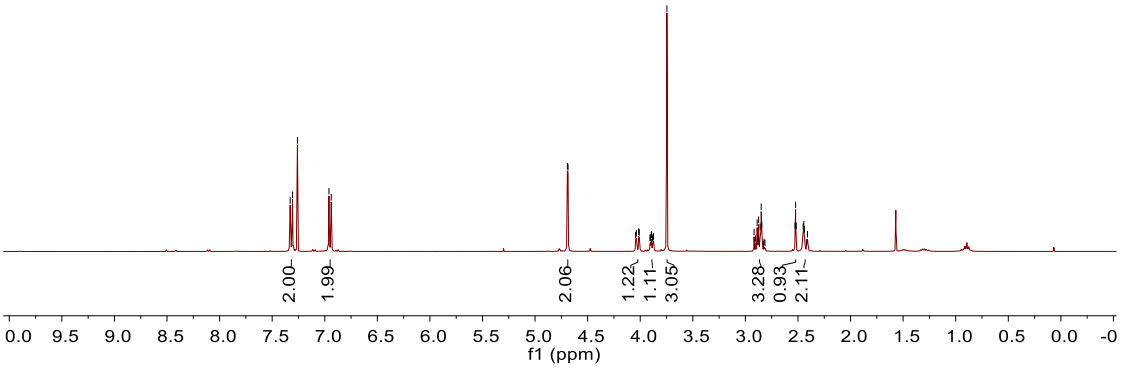
^{13}C NMR (101 MHz, $CDCl_3$)



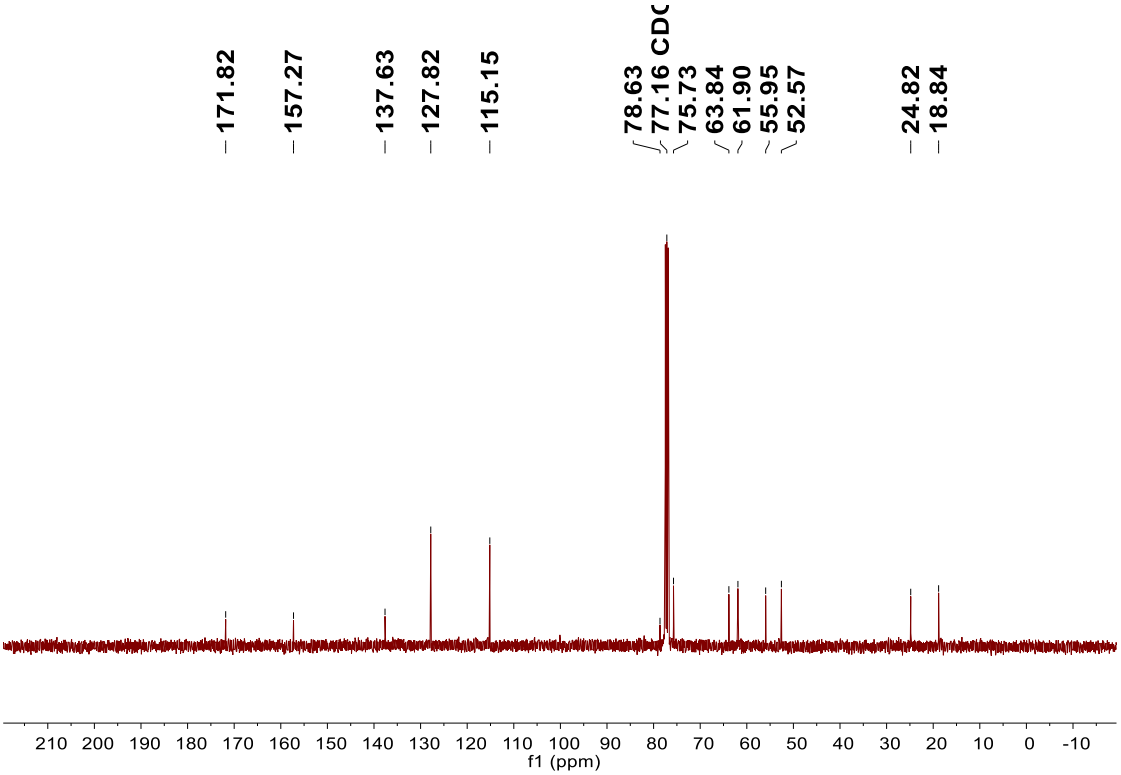
RS21

^{1}H NMR (400 MHz, $CDCl_3$)



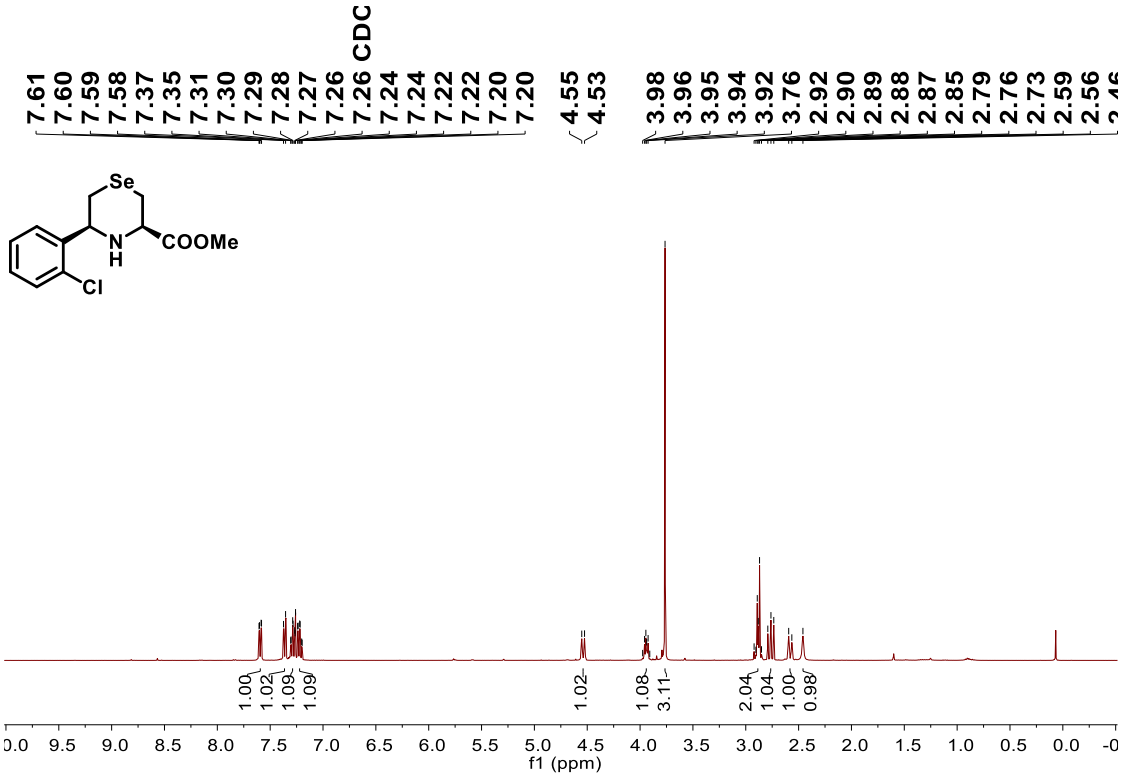


^{13}C NMR (101 MHz, $CDCl_3$)

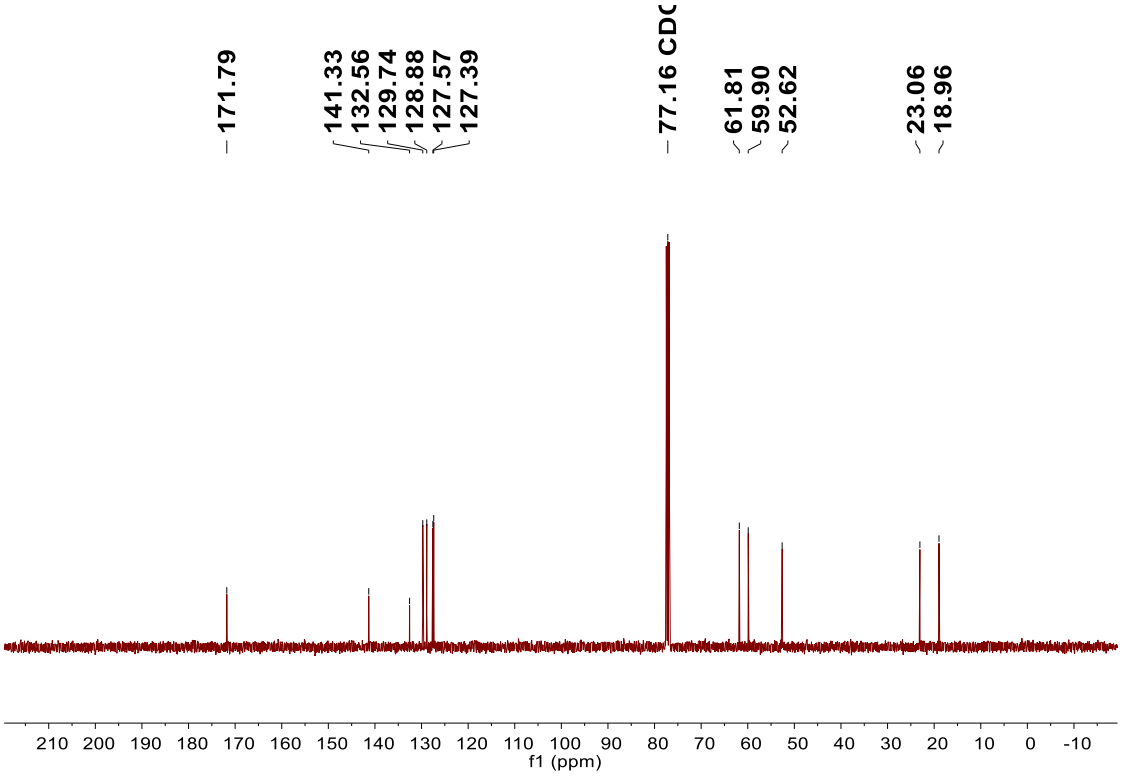


RS22

^{1}H NMR (400 MHz, $CDCl_3$)

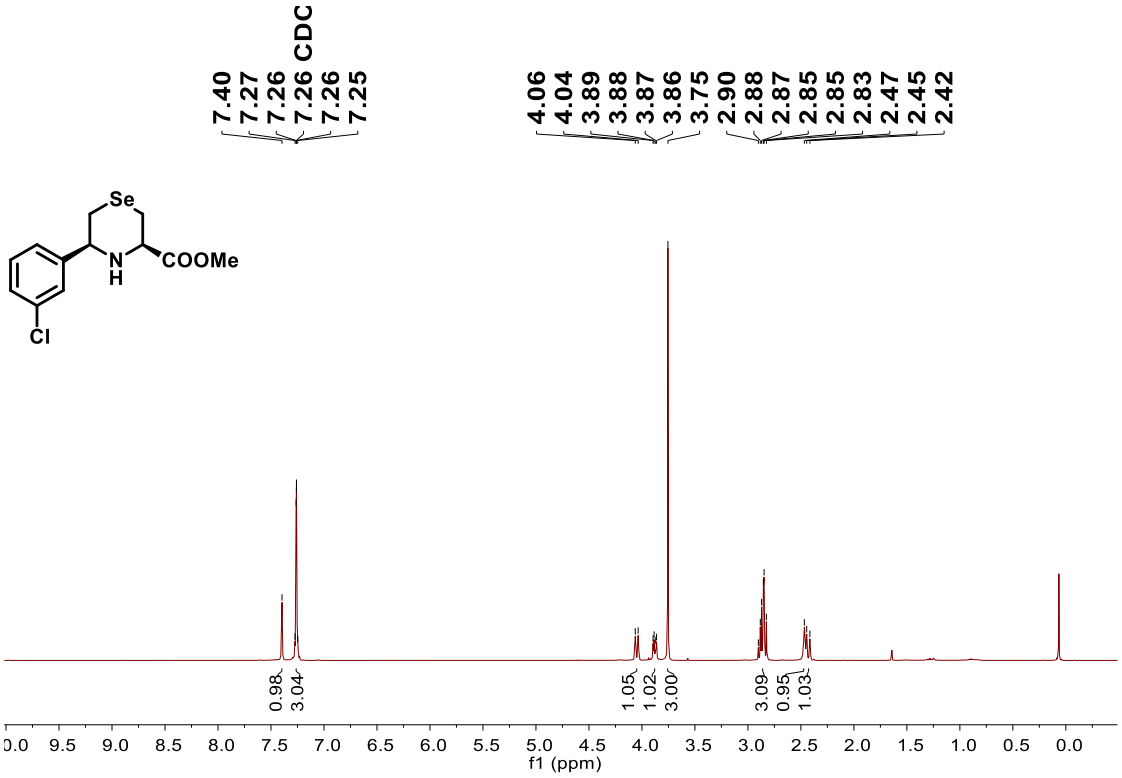


^{13}C NMR (101 MHz, $CDCl_3$)

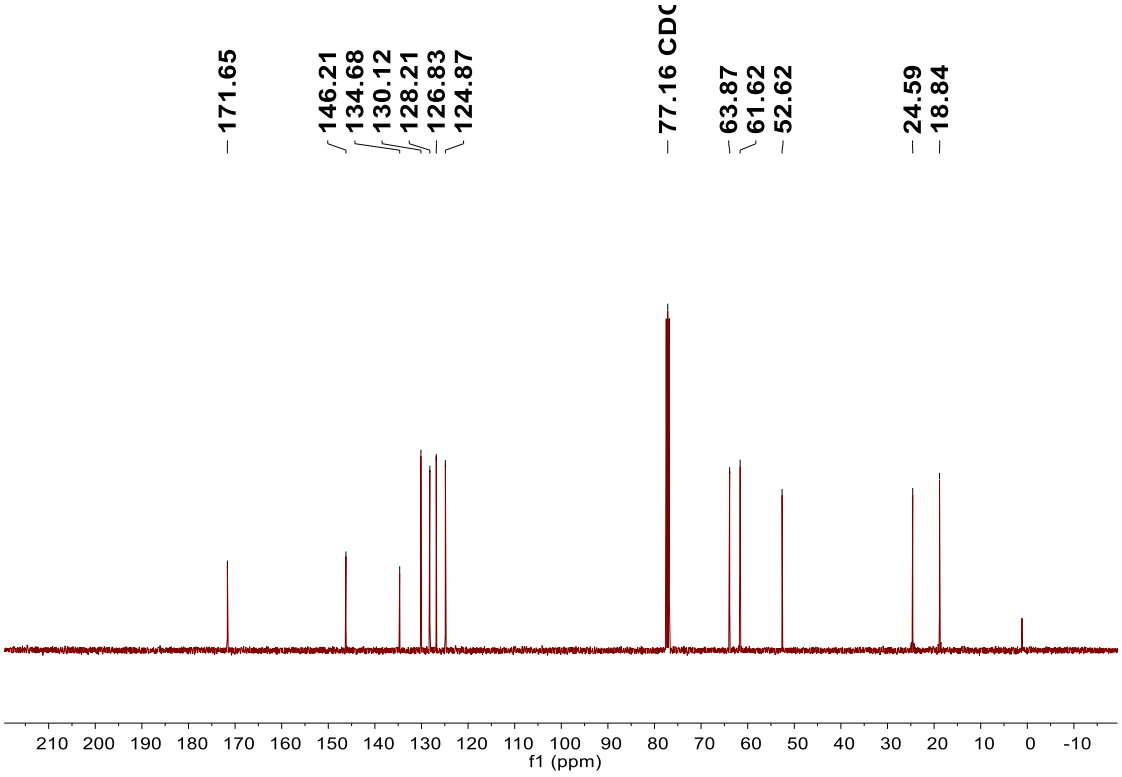


RS23

^{1}H NMR (400 MHz, $CDCl_3$)

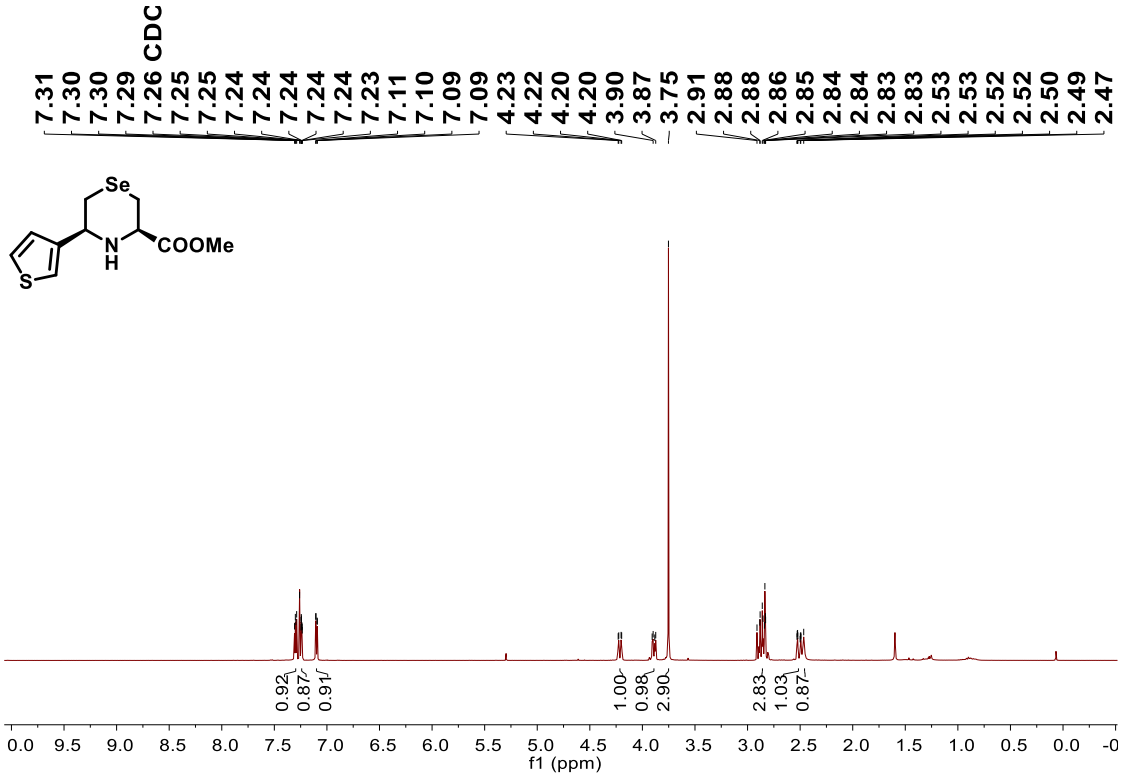


^{13}C NMR (101 MHz, $CDCl_3$)

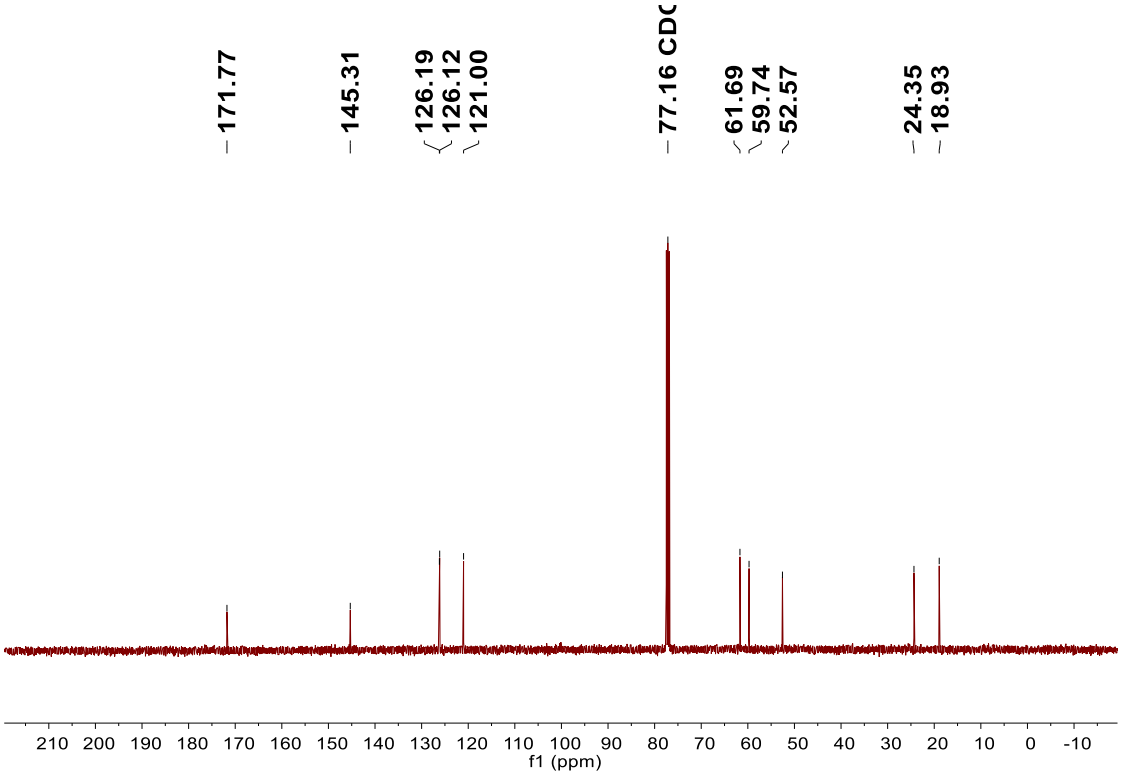


RS24

^{1}H NMR (400 MHz, $CDCl_3$)

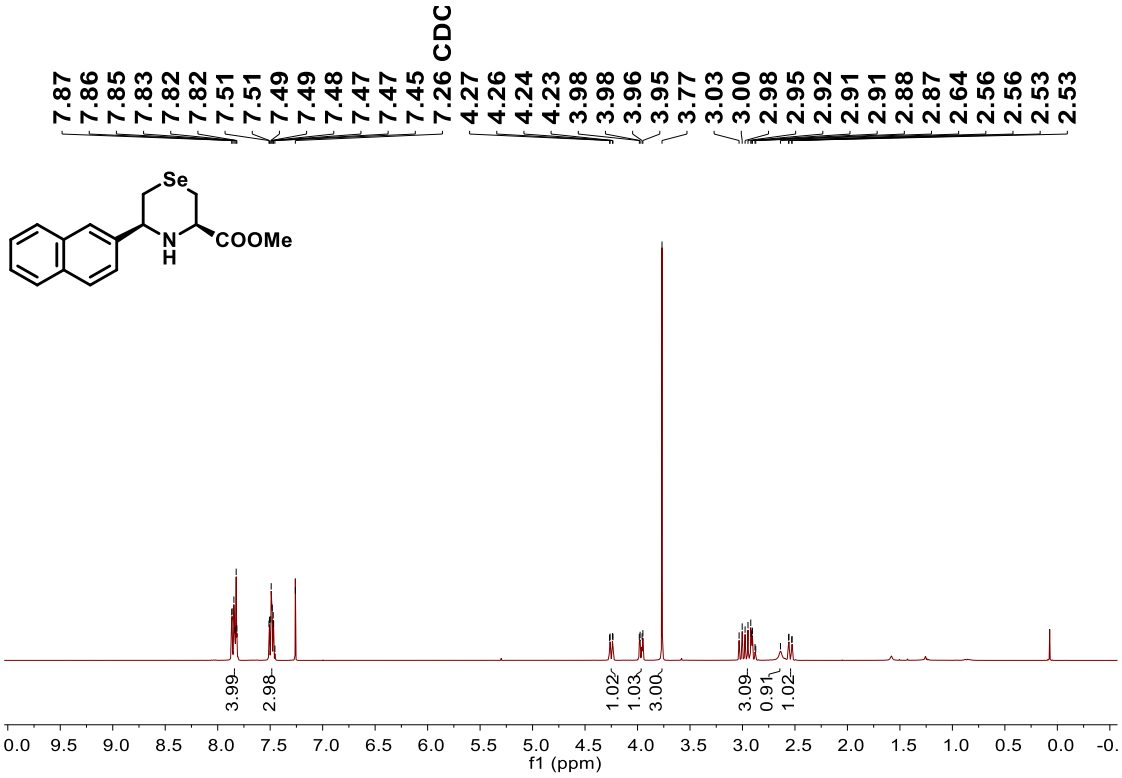


^{13}C NMR (101 MHz, $CDCl_3$)

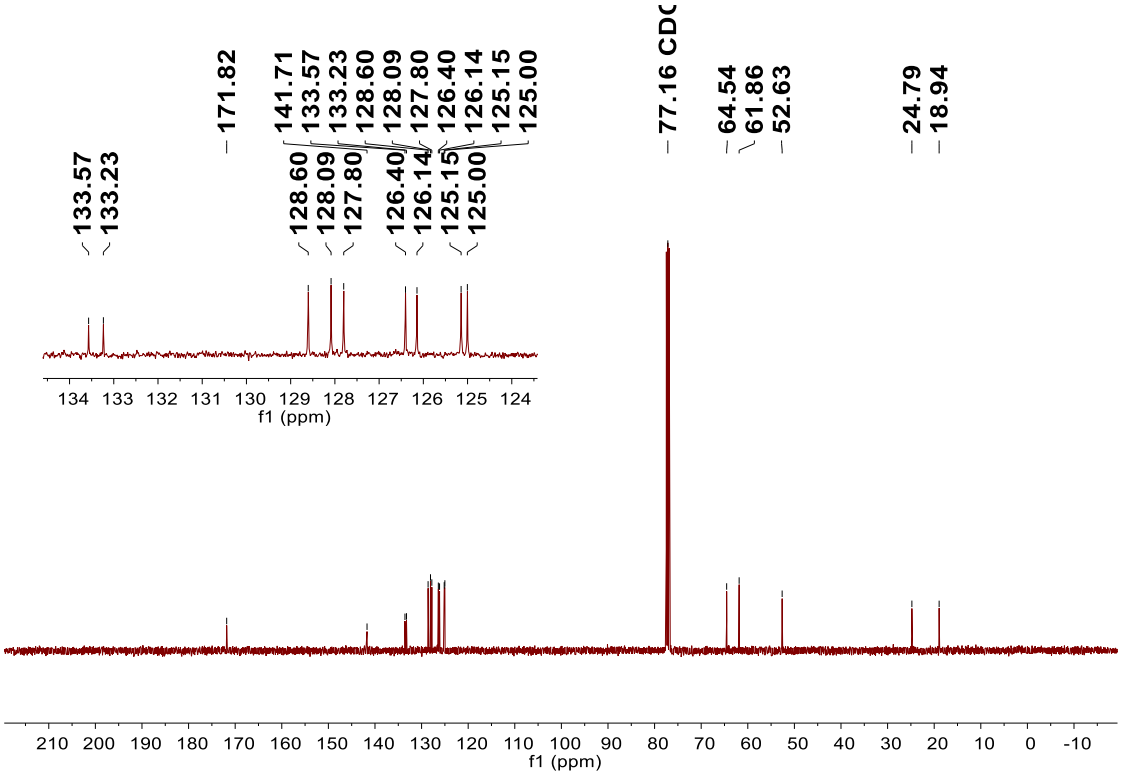


RS25

^{1}H NMR (400 MHz, $CDCl_3$)

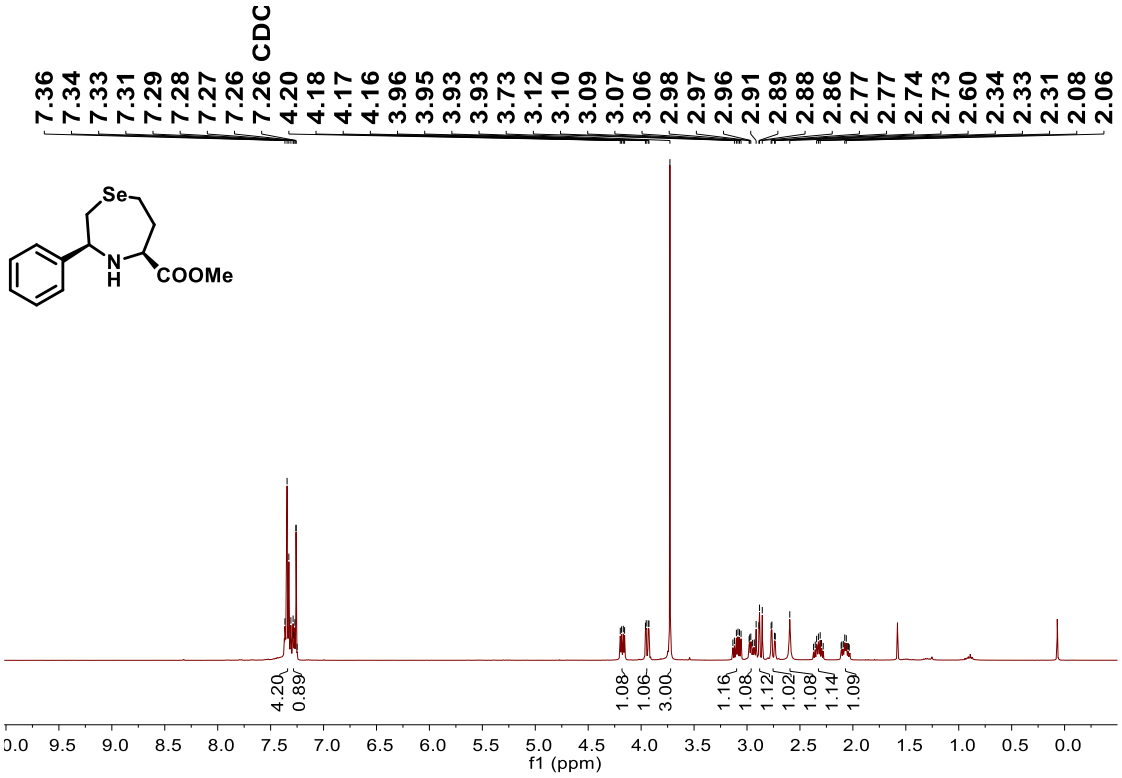


^{13}C NMR (101 MHz, $CDCl_3$)

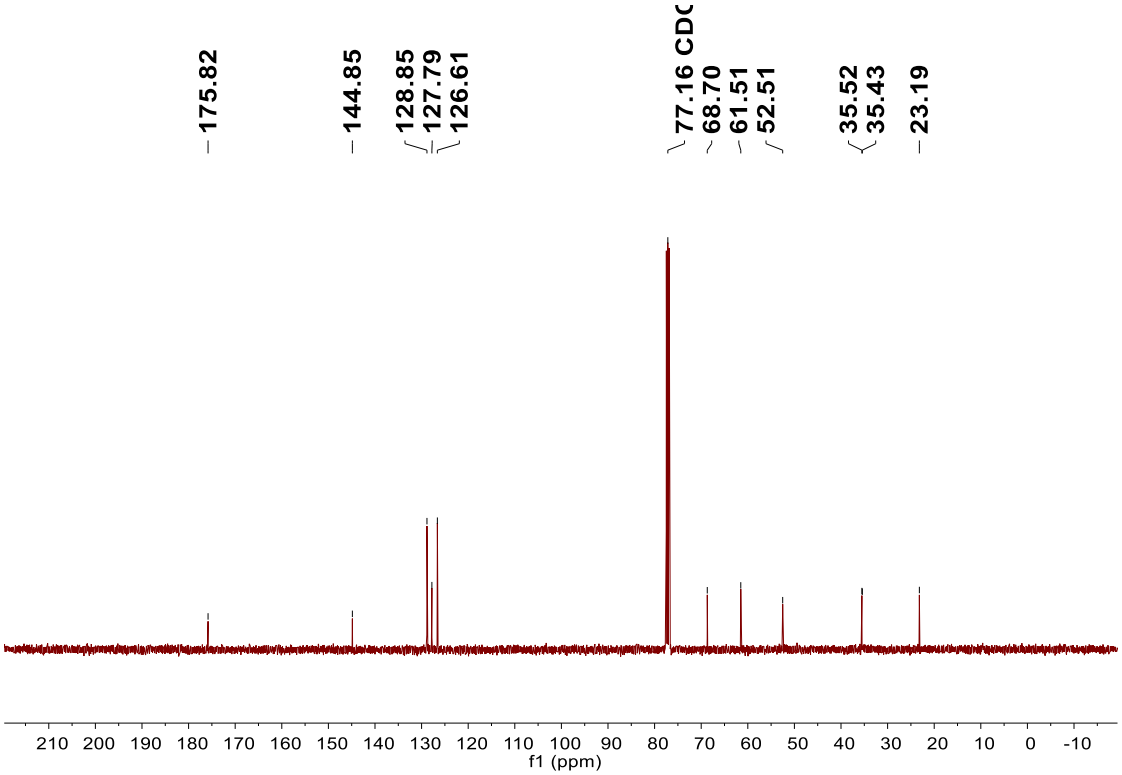


RS26

^{1}H NMR (400 MHz, $CDCl_3$)

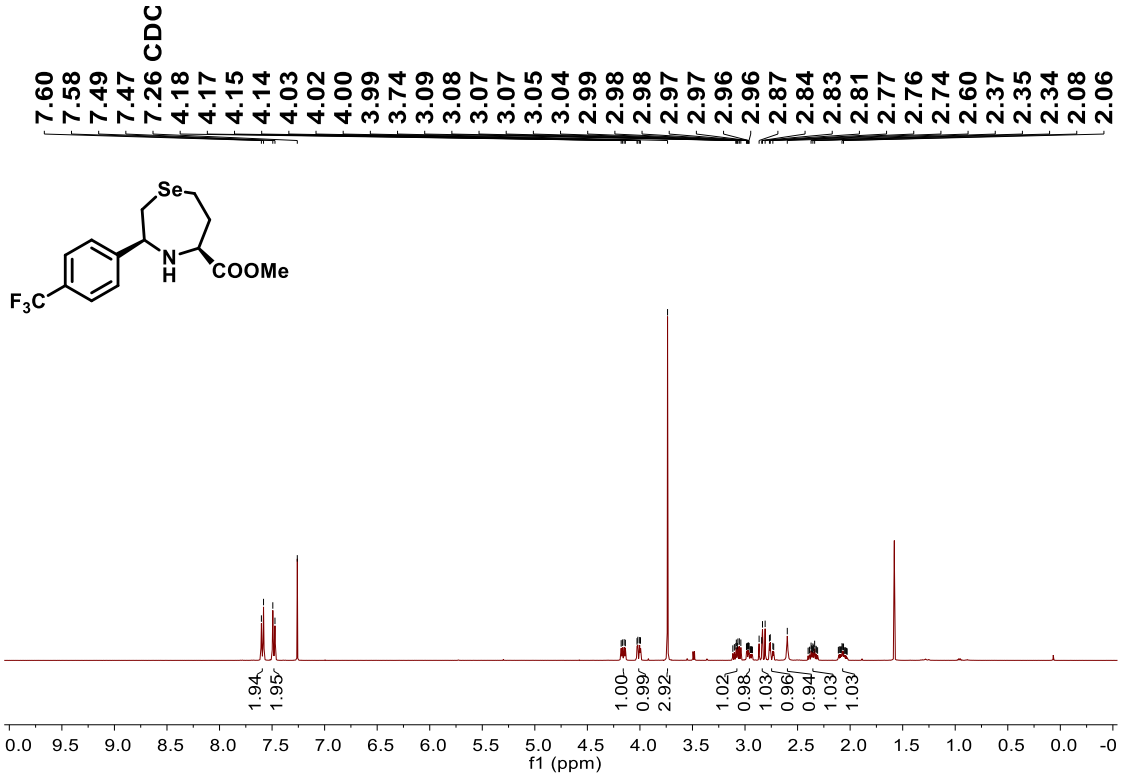


^{13}C NMR (101 MHz, $CDCl_3$)

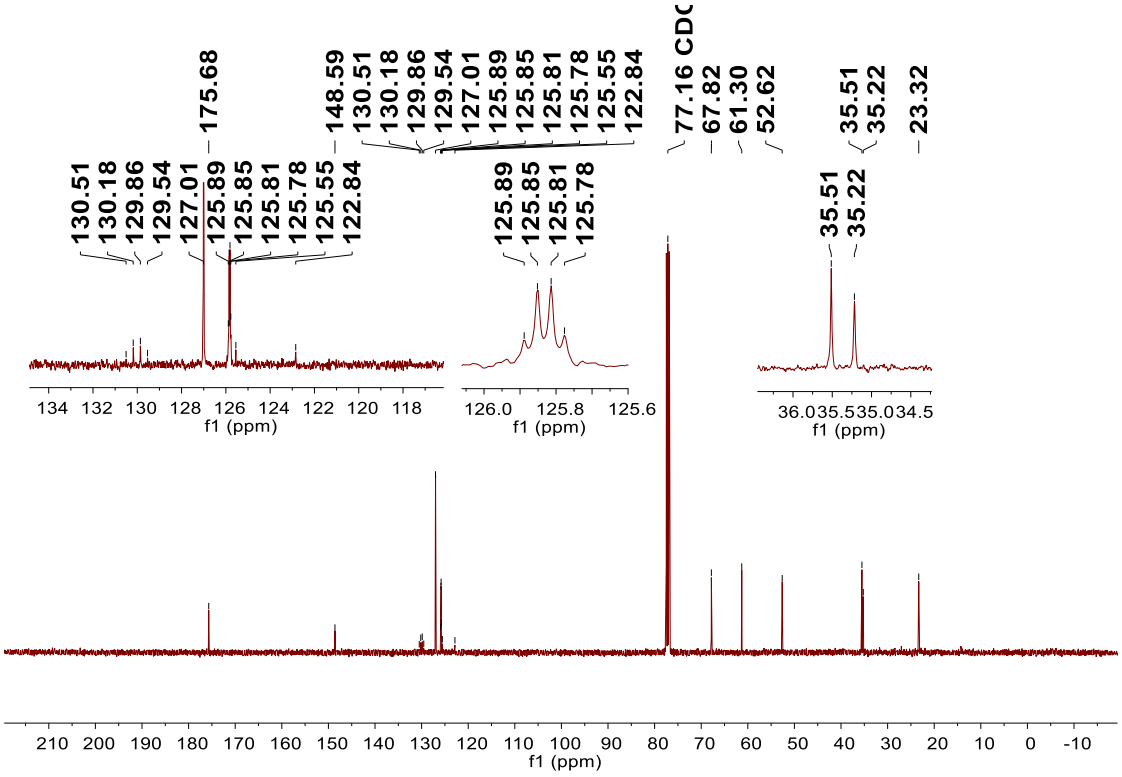


RS27

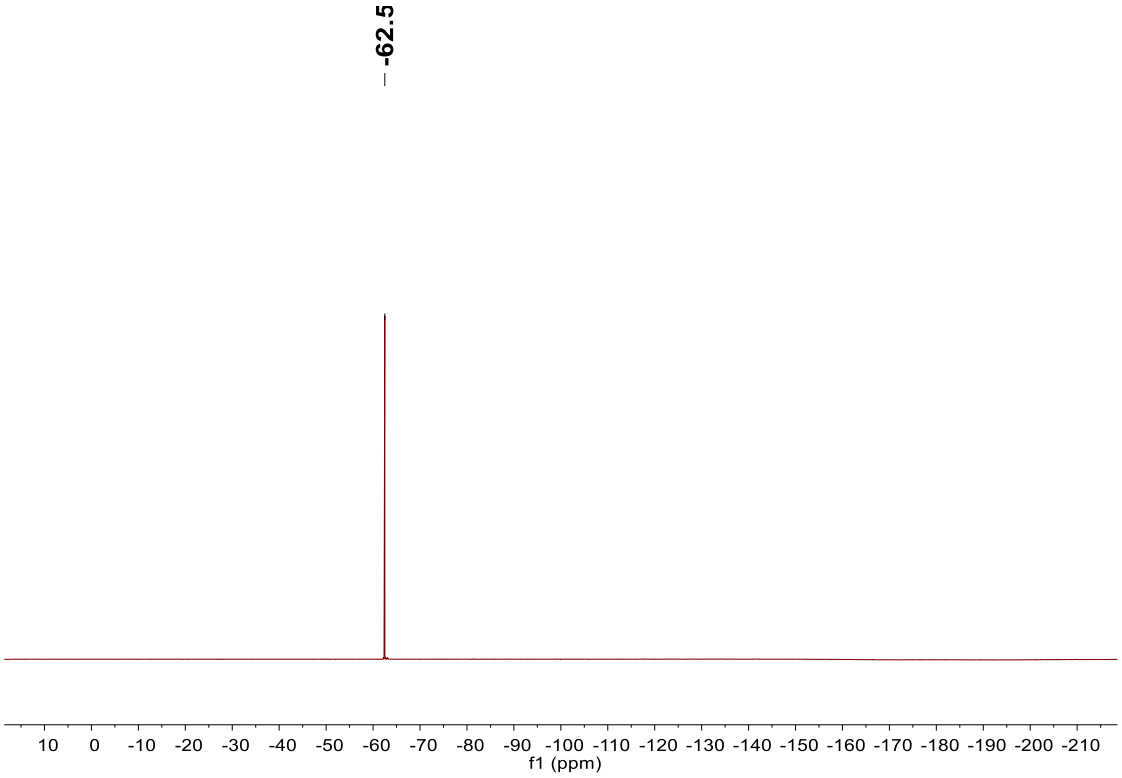
^{1}H NMR (400 MHz, $CDCl_3$)



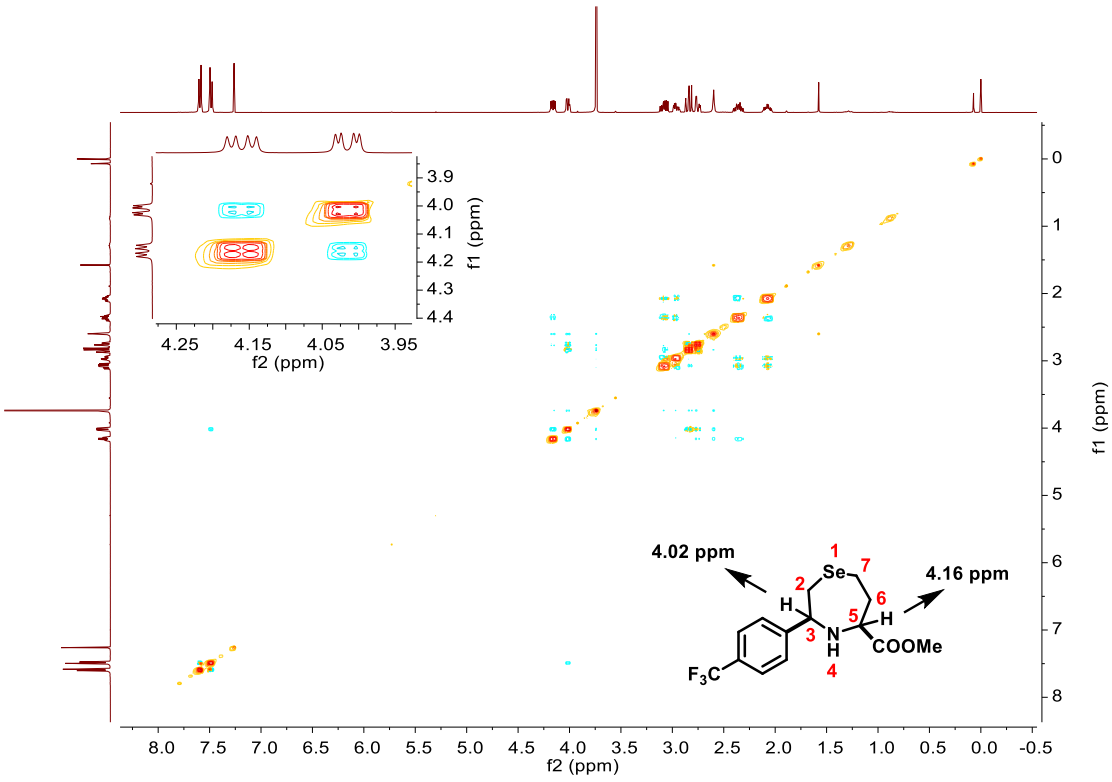
^{13}C NMR (101 MHz, $CDCl_3$)



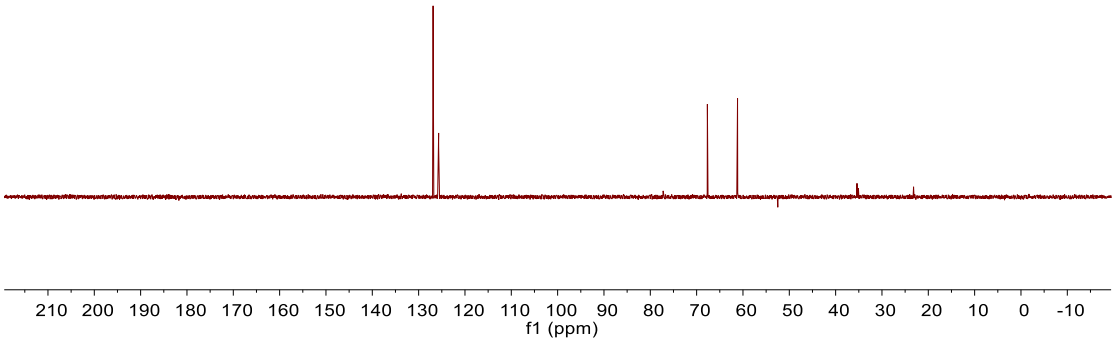
^{19}F NMR (376 MHz, $CDCl_3$)



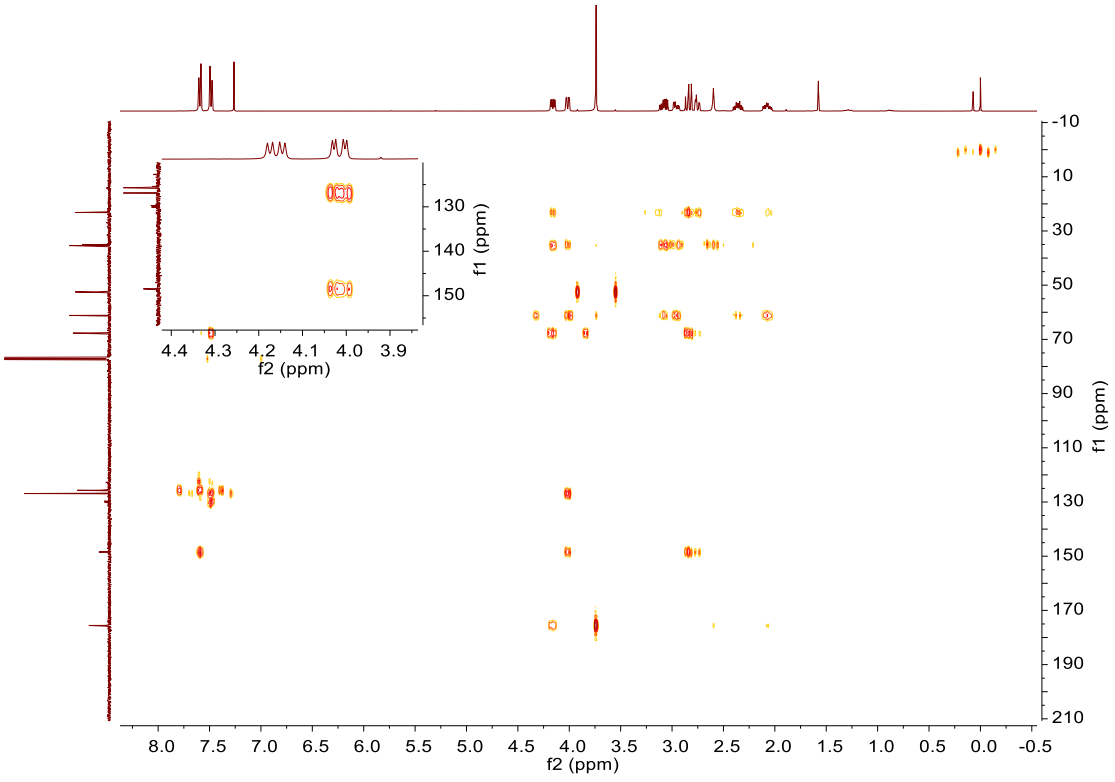
NOESY of RS27



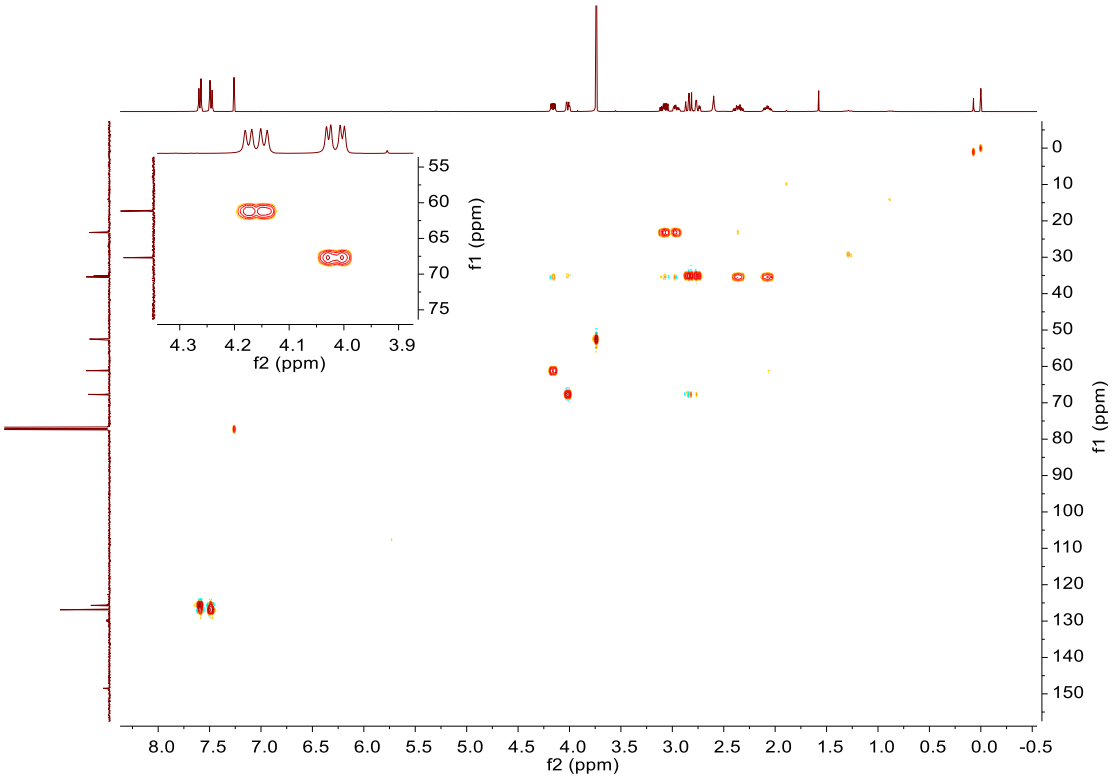
DEPT90 of RS27



HMBC of RS27

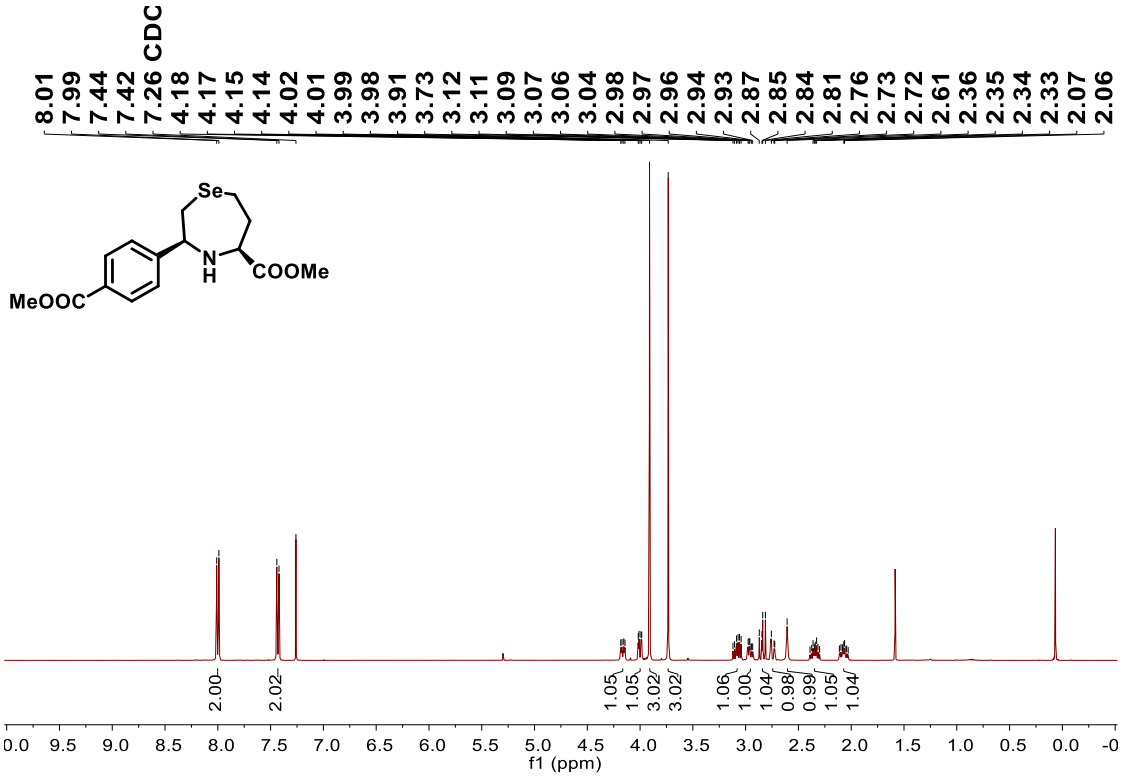


HSQC of RS27

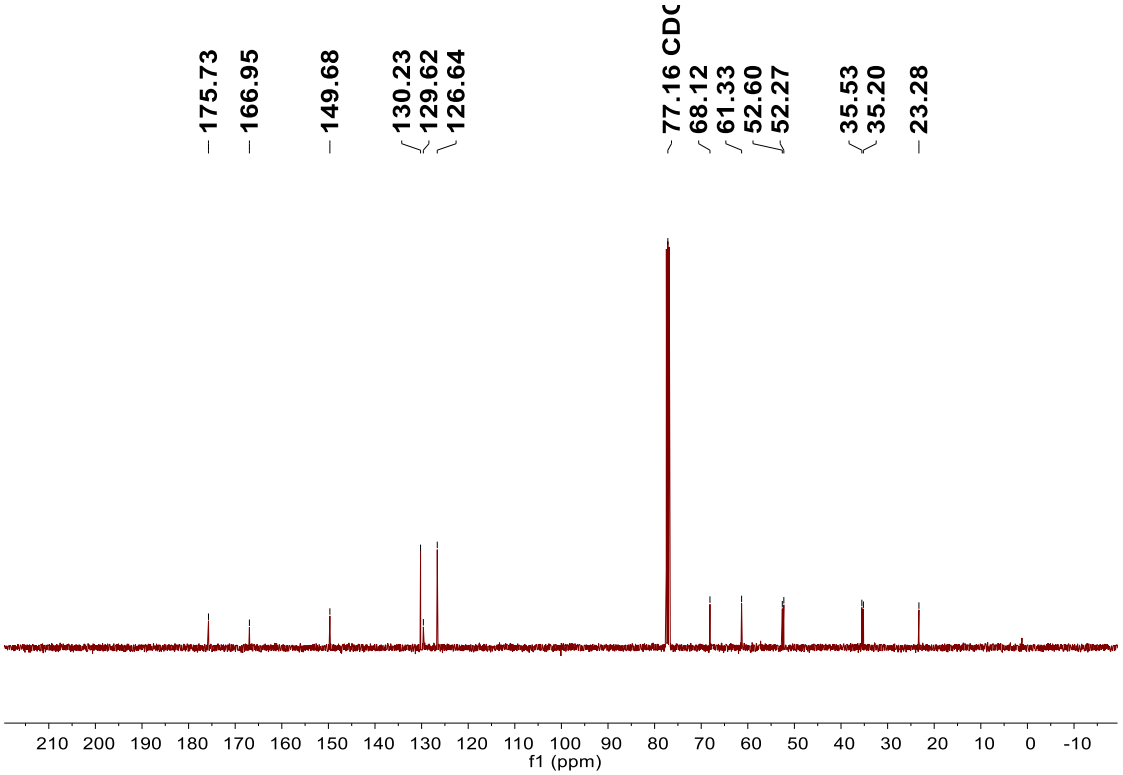

f2 (ppm)
f1 (ppm)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
4.3 4.2 4.1 4.0 3.9
55 60 65 70 75

RS28

^{1}H NMR (400 MHz, $CDCl_3$)

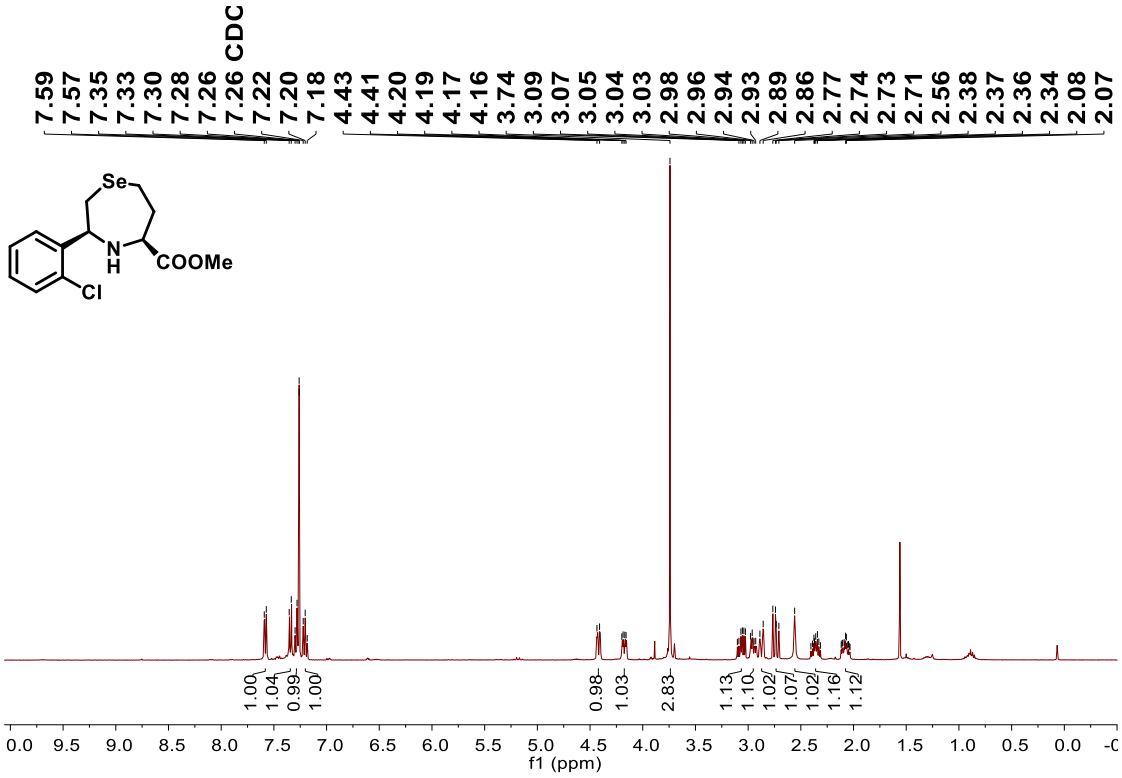


^{13}C NMR (101 MHz, $CDCl_3$)

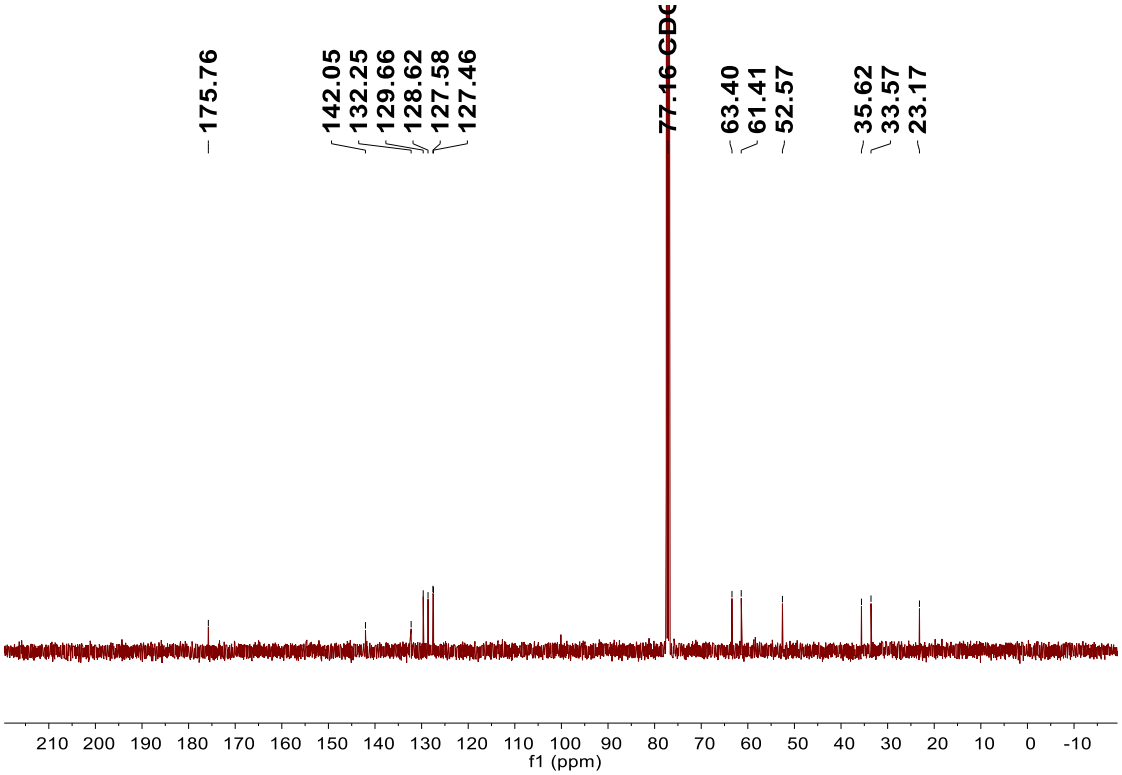


RS29

^{1}H NMR (400 MHz, $CDCl_3$)

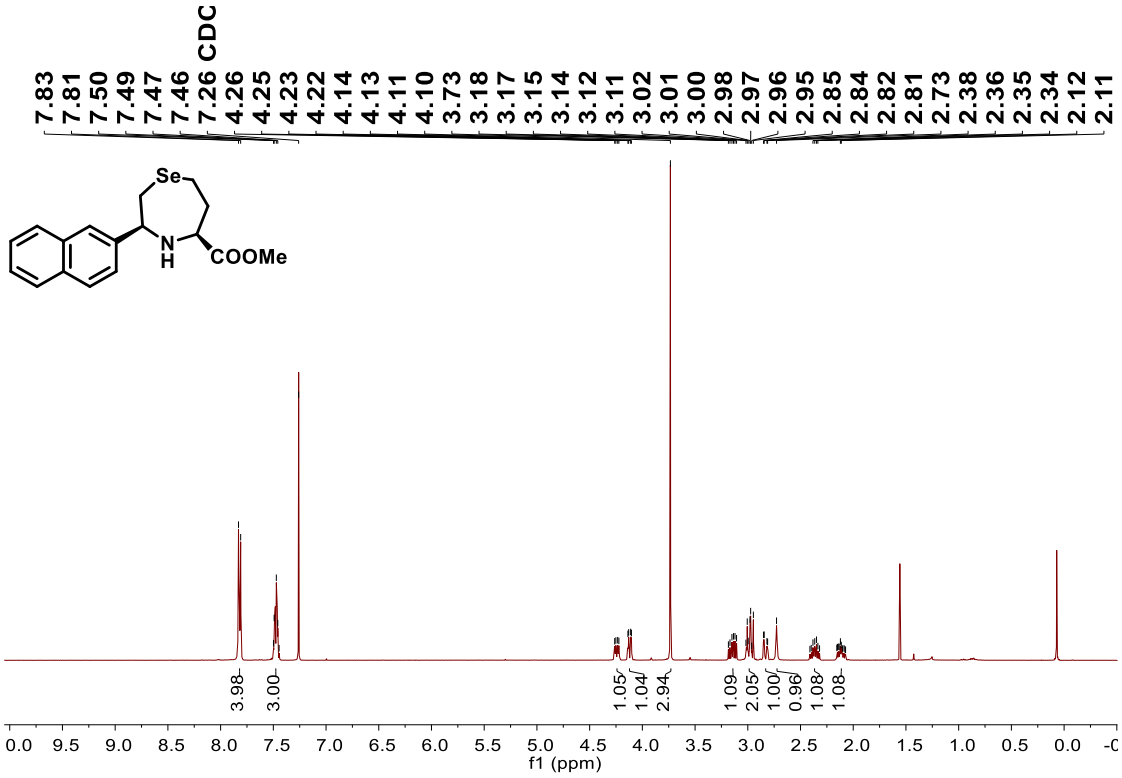


^{13}C NMR (101 MHz, $CDCl_3$)



RS30

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)