Supplementary Material

Synthesis of new heterocycle-based selenoamides as potent cytotoxic agents

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1. - Materials and instruments

THF and diethyl ether were distilled from sodium/benzophenone under a nitrogen atmosphere. All reagents and solvents were obtained from commercial suppliers and used without further purification. All compounds were characterized by IR spectra, recorded on a Bruker Tensor 27 spectrophotometer, by KBr or film techniques, and all data are expressed in wave numbers (cm^{-1}). Melting points were obtained on a Melt-Temp II apparatus and are uncorrected. NMR spectra were measured with a JEOL Eclipse +300 and Bruker Avance III 300, using $CDCl_3$ and CD_3CN as solvents. Chemical shifts are in ppm (δ), relative to TMS. The MS-EI were obtained on a JEOL JMS-AX505 HA using 70 eV as ionization energy and for MS-FAB a JEOL JMS-SX 102A using nitrobenzyl alcohol and polyethylene glycol as matrix. All tested compounds synthesized are more than 95 % pure, analyzed using HPLC HP 1100 with diode-array detector.

2. - Synthesis of Fischer ethoxyarylcarbene chromium 0 complexes 1(a-h)

The preparation of Fischer-type carbene complexes was carried out using a slightly modification of the methodology previously described elsewhere.[1] To a solution of the corresponding aryl substrate (8 mmol) in 10 mL of anhydrous THF under argon atmosphere was added at 0°C a solution of *n*BuLi (8.2 mmol). The reaction mixture was stirred at room temperature for 20 to 60 min. and then transferred by canula to a suspension of $Cr(CO)_6$ (1.74 g, 8 mmol) in THF (20 mL). The mixture was then stirred for the time specified in Table 1 of main document, at room temperature. The solvent was removed under vacuum, and then triethyloxonium tetrafluoroborate (2 g, 10 mmol) on ice/water was added. The organic phase was washed with saturated solution of $NaHCO_3$ and then with brine. The organic phase was dried with anhydrous sodium sulfate and the solvent was evaporated under vacuum. The mixture was purified by chromatography on silica gel or alumina using hexane as eluent. Fischer carbene complexes **1a, 1b, 1d, 1e, 1f, 1g** and **1h** are already known and their spectroscopic data match well with literature.[1-3]

[(ethoxy)(benzo[*d*][1,3]dioxol-5-yl)methylidene]pentacarbonyl chromium (0) (1c): Yield: 60 %; mp 66 – 70 (d) °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.36 (d, *J*= 7.2 Hz, 1 H; C_6H_3), 7.03 (s, 1 H; C_6H_3), 6.86 (d, *J*= 7.8 Hz, 1 H; C_6H_3), 6.05 (s, 2 H; OCH_2O), 5.12 (d, 2 H; OCH_2), 1.70 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 339.8 (C=Cr), 223.8 ($CrCO_{ax}$), 216.7 ($CrCO_{eq}$), 150.9 (C, C_6H_3), 147.9 (C, C_6H_3), 147.6 (C, C_6H_3), 124.5 (CH, C_6H_3), 107.6 (CH, C_6H_3), 105.2 (CH, C_6H_3), 101.9 (OCH_2O), 76.6 (OCH_2), 15.2 (CH_3) ppm. IR (KBr) (cm^{-1}): 2057, 1905 (CrCO). MS (EI, 70 eV) *m/z* (%): 370 (8) [M^+], 342 (27) [M^+-CO], 314 (47) [M^+-2CO], 286 (38) [M^+-3CO], 258 (92) [M^+-4CO], 230 (68) [M^+-5CO]. HRMS (FAB^+): *m/z*: calcd. for $C_{15}H_{10}CrO_8$: 369.9781 [M^+]; found: 369.9768.

3. - NMR spectra of 1c

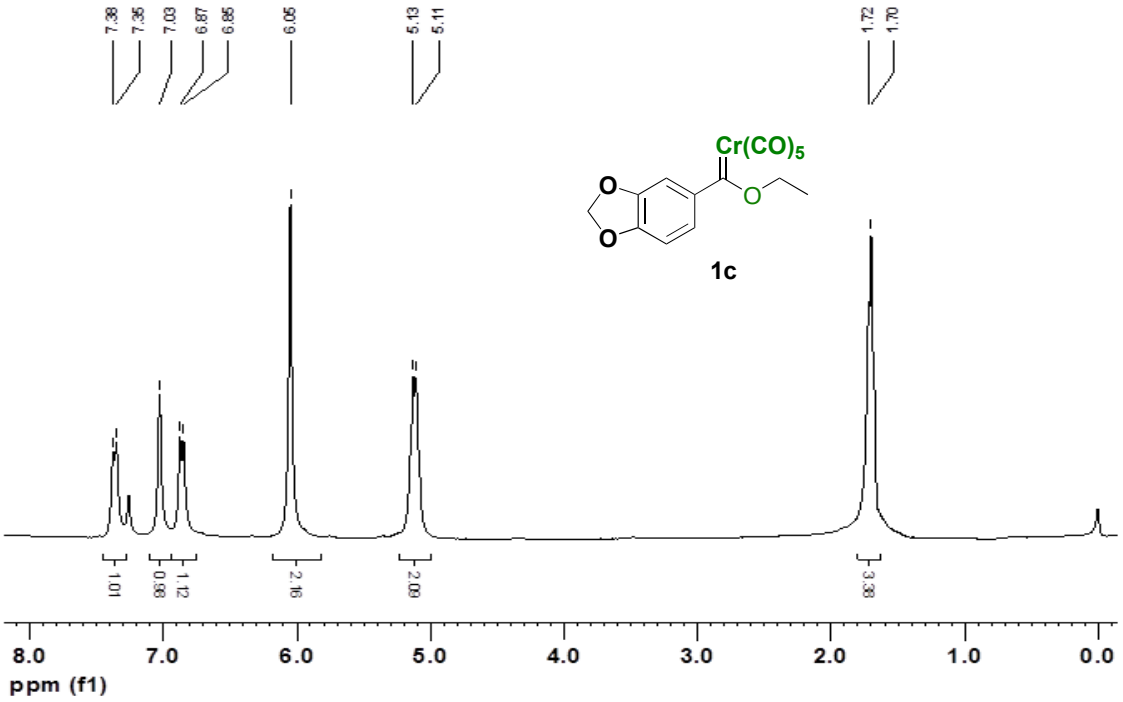

Figure S1. ^{1}H NMR spectrum of **1c**

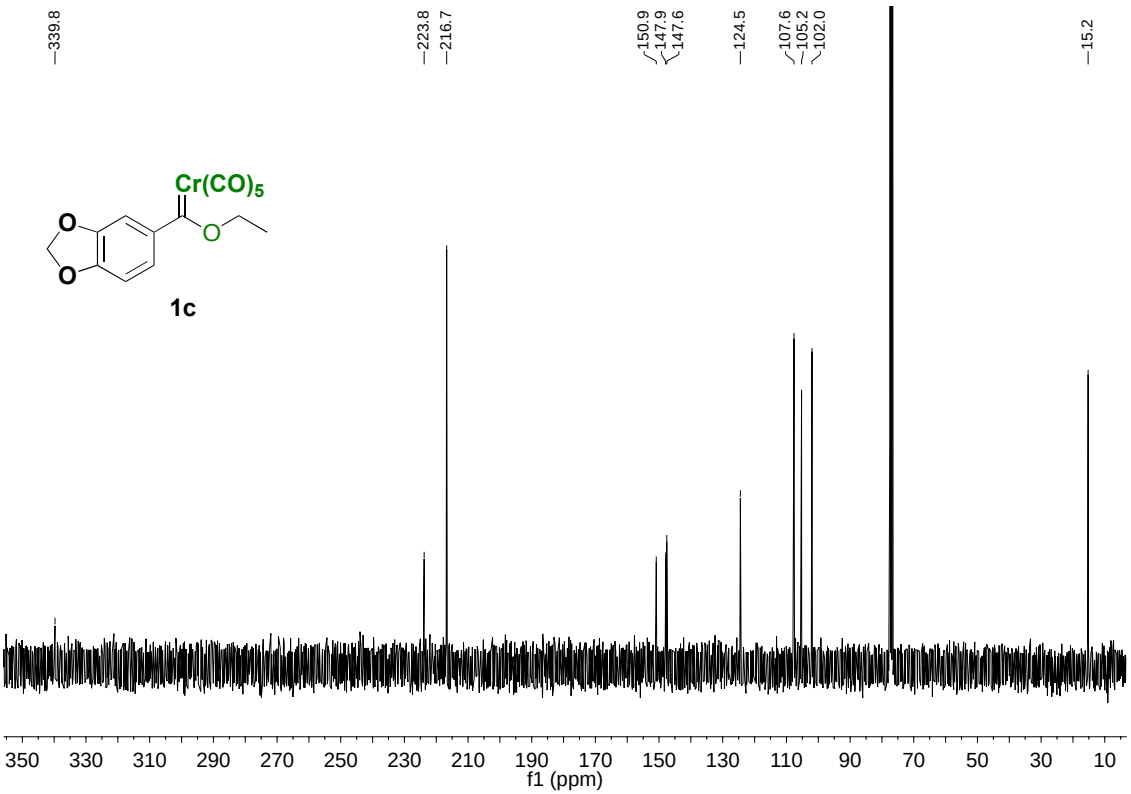

Figure S2. ^{13}C NMR spectrum of **1c**

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[ Elemental Composition ]                                          Page: 1
Data  : Dr-Jose-G-Lopez113         Date :13-Mar-2013   15:42
Sample: 657    OOCrOEt
Note  : Luis-Velasco
Inlet : Direct                     Ion Mode  :    FAB+
RT  : 0.66 min                     Scan#: (1,8)
Elements  : C 30/0, H 49/0, O 9/0, Cr 2/0
Mass Tolerance :    100ppm,   2mmu if m/z >2

Observed m/z   Int%
    369.9768   12.7
Estimated m/z  Error [ppm]    U.S. C    H    O    Cr
    369.9781   -0.8           13   15   10   8    1
```

Figure S3. HR-MS of compound **1c**

4. - Synthesis of Fischer Aminocarbenes chromium 0 complexes 2(a-h) (Route A)

To a solution of Fischer ethoxycarbene complex (**1**) (2.3 mmol) in 20 mL of anhydrous diethyl ether under nitrogen atmosphere was added 4.9 mmol of ethanolamine. The reaction mixture was stirred at room temperature for 5 to 20 min. and then diluted with 20 mL of water. The organic phase was separated and dried with anhydrous Na_2SO_4, and the solvent was evaporated in vacuum. The crude product was purified by flash column chromatography using alumina and Hexane-AcOEt mixture (95:5) as eluent. Compounds **2a, 2b** and **2h** are known and their spectroscopic data match well with already described in the literature.[1-3]

[(benzo[*d*][1,3]dioxo-5-yl)(2-hydroxyethylamino)methylidene]pentacarbonyl chromium (0) (2c) (Unstable in solution) **:**Yield: 81 %; Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 9.51 (s, 1 H; NH_E), 9.06 (s, 1 H; NH_Z), 6.83 (s, 1 H; C_6H_3), 6.34 – 6.26 (m, 2H; C_6H_3), 5.99 (s, 2H; OCH_2O), 3.76 (s, 2 H; OCH_2), 3.39 (s, 2 H, NCH_2), 1.25 (s, 1 H; OH) ppm. IR (Film), cm^{-1}: 3410 (OH), 3352 (NH), 2054, 1974, 1911 (Cr-CO). MS (FAB$^+$) *m/z* (%): 385 (12) [M^+], 357 (16) [M^+-CO], 329 (15) [M^+-2CO], 301 (21) [M^+-3CO], 273 (28) [M^+-4CO], 245 (72) [M^+-5CO]; HRMS (FAB$^+$) *m/z*: calcd. for $C_{15}H_{11}CrNO_8$: 384.9890 [M^+]; found: 384.9888.

[(*N*-methylpyrrol-2-yl)(2-hydroxyethylamino)methylidene]pentacarbonyl chromium (0) (2d): Yield: 90%; Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 9.40 (s, 1 H; NH_E), 8.62 (s, 1 H; NH_Z), 6.61 and 6.55 (s, 1 H; C_4H_3N), 6.17 (s, H; C_4H_3N), 5.97 (s, H; C_4H_3N), 3.54-3.38 (m, 7 H; OCH_2, NCH_2, NCH_3) 1.25 (s, 1 H; OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 277.2 and 265.4 (CCr, Isomers *E* and *Z*), 223.5 (CO_{ax} Isomer *E*), 217.7 (CO_{eq} Isomers *Z*), 217.2 (CO_{eq} Isomer *E*), 211.5 (CO_{eq} Isomer *Z*), 163.3 (C, C_4H_3N), 145.1 (CH, C_4H_3N), 123.2 (CH, C_4H_3N), 109.0 and 106.1 (CH, C_4H_3N, Isomers *E* and *Z*), 62.9 and 60.9 (OCH_2, Isomers *E* and *Z*), 54.4 and 52.6 (NCH_2, Isomers *E* and *Z*), 52.6 ppm (NCH_3). IR (Film) cm^{-1}: 3609 (OH), 3373 (NH), 1998, 1870 (CrCO). MS (FAB$^+$) *m/z* (%): 345 (80) [M^++1], 317 (12) [M^++1-CO], 289 (65) [M^++1-2CO], 261 (100) [M^++1-3CO], 233 (57) [M^++1-4CO], 204 (14) [M^++1-5CO]; HRMS (FAB$^+$) *m/z*: calcd. for $C_{13}H_{12}CrN_2O_6$: 344.0100 [M^+]; found: 344.0110.

[(*N*-methylindol-2-yl)(2-hydroxyethylamino)methyliden]pentacarbonyl chromium (0) (2e): Yield: 92 %; Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): *δ* = 9.92 (s, 1 H; NH), 7.59 (d, *J*= 7.5 Hz, 1 H; C_8H_5N), 7.33 – 7.12 (m, 3 H; C_8H_5N), 6.18 (s, 1 H; C_8H_5N), 3.72 - 360 (m, 7 H; OCH_2, NCH_2, NCH_3), 3.34 (s, 1 H; OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, TMS): *δ* = 279.0 (CCr), 223.1 ($CrCO_{ax}$), 216.8 ($CrCO_{eq}$), 145.0 (C, C_8H_5N), 137.0 (C, C_8H_5N), 128.1 (C, C_8H_5N), 122.1, (CH, C_8H_5N), 121.0 (CH, C_8H_5N), 120.4 (CH, C_8H_5N), 109.4 (CH, C_8H_5N), 96.0 (CH, C_8H_5N), 60.6 (OCH_2), 50.3 (NCH_2), 30.8 (NCH_3) ppm. IR (Film) cm^{-1}: 3349 (OH) and (NH), 2054, 1976, 1912 (CrCO). MS (FAB$^+$) *m/z* (%): 395

(11) [M^++1], 366 (62) [M^+-CO], 338 (18) [M^+-2CO], 310 (11) [M^+-3CO], 282 (100) [M^+-4CO], 254 (84) [M^+-5CO]. HRMS (FAB$^+$) *m/z*: calcd. for $C_{17}H_{14}CrN_2O_6$: 394.0257 [M^+]; found: 394.0260.

[(thien-2-yl)(2-hydroxyethylamino)methyliden]pentacarbonyl chromium (0) (2f): Yield: 95%; m.p. 105 -107°C (d); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 9.45 (s, 1 H; NH_E), 9.13 (s, 1 H; NH_Z), 7.47 and 7.41 (m, 2 H; C_4H_3S, Isomers *E* and *Z*), 7.11 and 7.06 (m, 2 H; C_4H_3S, Isomers *E* and *Z*), 6.84 (s, 1H; C_4H_3S) 4.27 and 4.09 (d, 4 H; OCH_2, Isomers *E* and *Z*), 3.86 and 3.66 (d, 4 H; NCH_2, Isomers *E* and *Z*), 1.99 (s, 1 H; OH) ppm. ^{13}C NMR (75 MHz, CDC_{l3}, TMS): δ = 272.9 and 261.2 (CCr, Isomers *E* and *Z*), 223.2 (CO_{ax}, Isomers *E* and *Z*), 217.5 and 217.1 (CO_{eq}, Isomers *E* and *Z*), 155.7 and 149.01(C, C_4H_3S, Isomers *E* and *Z*), 129.3 and 128.2 (CH, C_4H_3S, Isomers *E* and *Z*), 127.6 and 127.3 (CH, C_4H_3S, Isomers *E* and *Z*), 126.7 and 122.6 (CH, C_4H_3S, Isomers *E* and *Z*), 61.0 and 60.9 (OCH_2,), 54.6 and 52.3 ppm (NCH_2, Isomers *E* and *Z*) ppm. IR (KBr) cm^{-1}: 3581 (OH), 3308 (NH), 2053, 1869 (Cr-CO). MS (EI, 70 eV) *m/z* (%): 347 (14.96) [M^+], 319 (7.04) [M^+-CO], 291 (8.16) [M^+-2CO], 263 (20.41) [M^+-3CO], 235 (36.73) [M^+-4CO], 207 (13.6) [M^+-5CO]. HRMS (FAB$^+$) *m/z*: calcd for $C_{12}H_9CrNO_6S$: 346.9556 [M^+]; found: 346.9560.

[(furan-2-yl)(2-hydroxyethylamino)methyliden]pentacarbonyl chromium (0) (2g): Yield: 96%; m.p. 85-86 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 9.73 (s, 1 H; NH_E), 8.89 (s, 1 H; NH_Z), 7.67 and 6.48 (s, 2H; C_4H_3O, Isomers *E* and *Z*), 7.19 (s, 1 H; C_4H_3O), 6.61 (s, 2 H; C_4H_3O, , Isomers *E* and *Z*), 4.26 - 3.92 (m, 8 H; OCH_2, NH_2, , Isomers *E* and *Z*), 1.88 (s, 1 H; OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 244.2 (CCr), 222.7 (CO_{ax}), 218.0 and 217.8 (CO_{eq} Isomers *E* and *Z*), 145.8 and 144.2 (C, C_4H_3O, Isomers *E* and *Z*), 125.1 and 123.4 (CH, C_4H_3O, Isomers *E* and *Z*), 113.4 and 112.9 (CH, C_4H_3O, Isomers *E* and *Z*), 61.0 and 60.5 (OCH_2, Isomers *E* and *Z*), 54.1 (NCH_2) ppm. IR (KBr) cm^{-1}: 3581 (OH), 3308 (NH), 2053, 1869 (Cr-CO). MS (EI, 70 eV) *m/z* (%): 331 (15) [M^+], 303 (7) [M^+-CO], 275 (8) [M^+-2CO], 247 (20) [M^+-3CO], 219 (37) [M^+-4CO], 191 (14) [M^+-5CO]. HRMS (FAB+) *m/z*: calcd for $C_{12}H_9CrNO_7$: 330.9784 [M^+]; found: 330.9792.

5. - NMR and HR-MS spectra of 2c-g

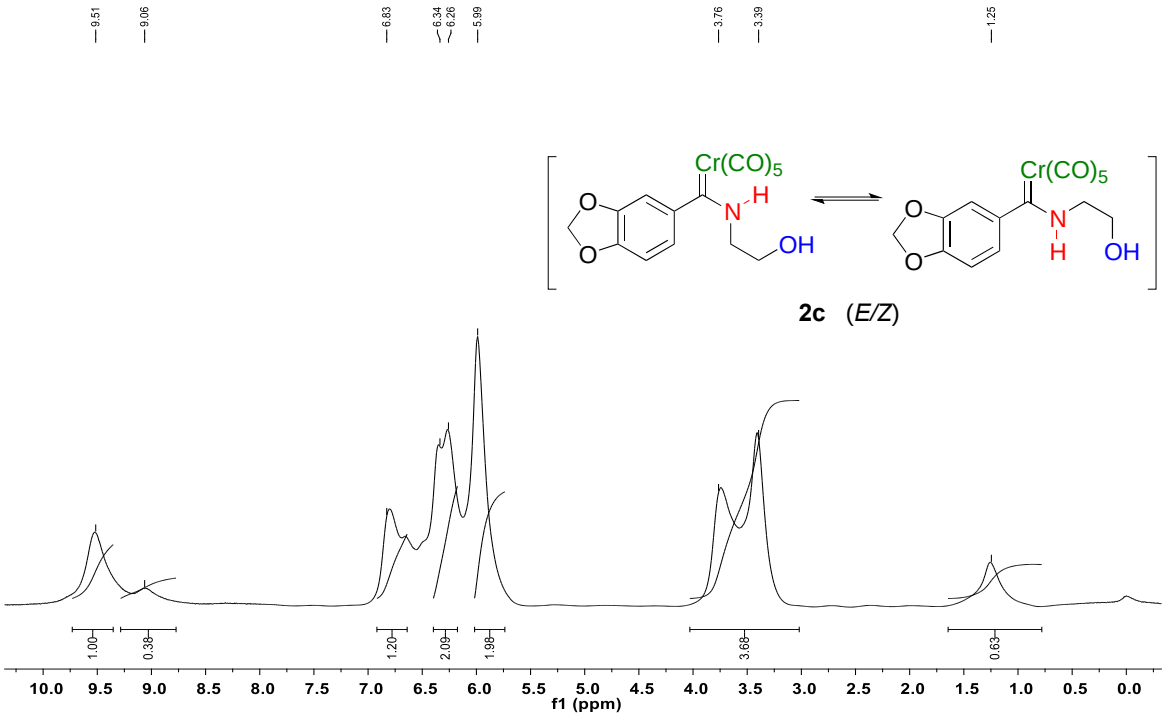

Figure S4. ^{1}H NMR spectrum of **2c** (*E/Z* ratio 72:28)

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[ Elemental Composition ]                                    Page: 1
Data  : Dr-Jose-G-Lopez038          Date :16-Mar-2013   19:28
Sample: 579    OOCrNEtOH
Note  : Luis-Velasco
Inlet : Direct                      Ion Mode  :    FAB+
RT  : 0.62 min                      Scan#: (1,6)
Elements  : C 30/0, H 49/0, O 9/0, N 4/1, Cr 2/0
Mass Tolerance :    100ppm,   2mmu if m/z >2

Observed m/z   Int%
    384.9888   11.2
Estimated m/z  Error [ppm]    U.S. C    H    O    N    Cr
    384.9890   -0.5           13   15   11   8    1    1
```

Figure S5. HR-MS of compound **2c**

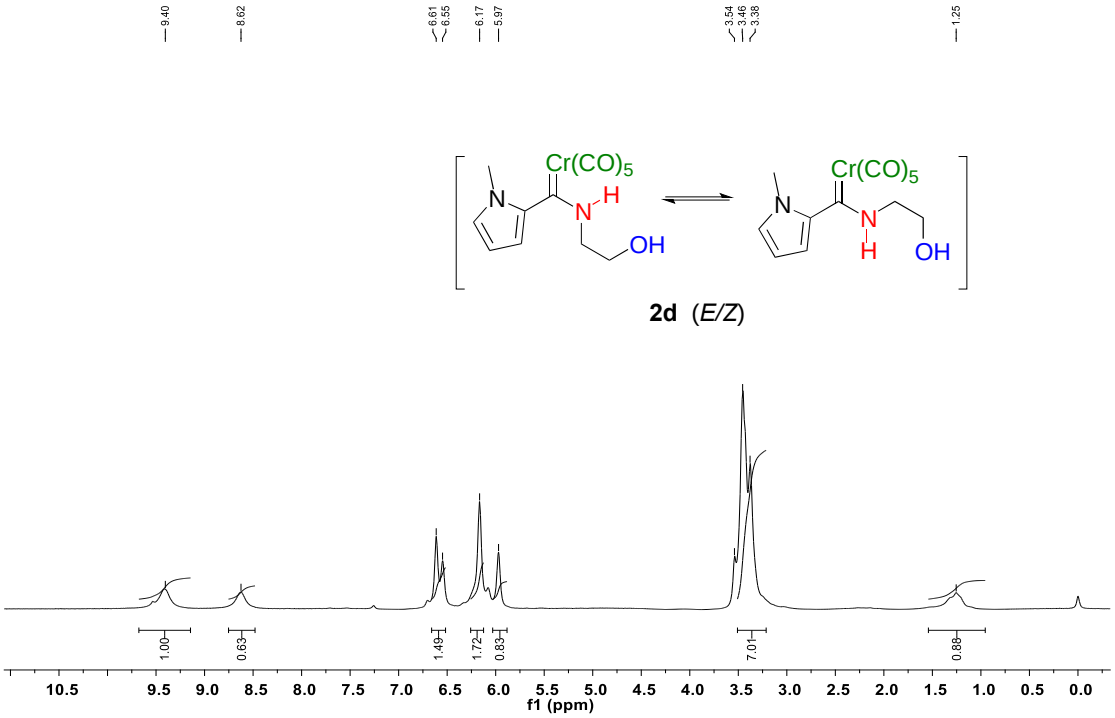

Figure S6. ^{1}H NMR spectrum of **2d** (*E/Z* ratio 61:39)

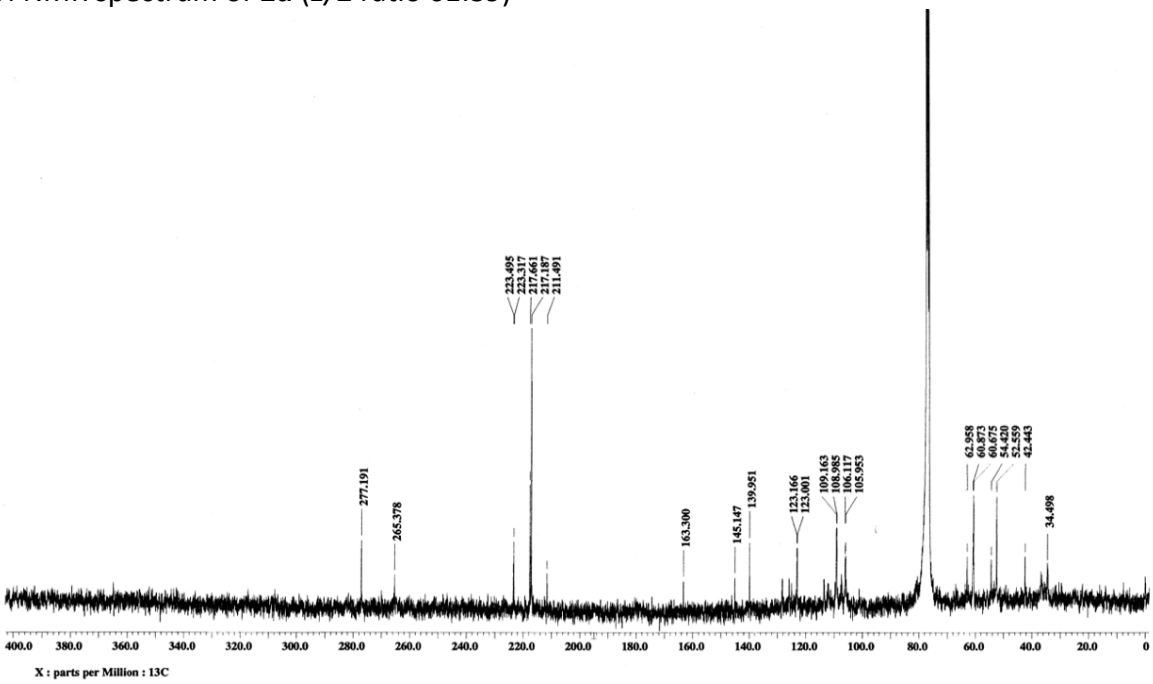

Figure S7. ^{13}C NMR spectrum of **2d**

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[ Elemental Composition ]                                    Page: 1
Data  : Dr-Jose-G-Lopez268          Date :09-Aug-2017   11:37
Sample: 1433   PirrCrN
Note  : Luis-Velasco
Inlet : Direct                      Ion Mode  :    FAB+
RT    : 0.62 min                    Scan#: (1,6)
Elements  : C 30/0, H 49/0, O 9/0, N 4/1, Cr 2/0
Mass Tolerance :    100ppm,   2mmu if m/z >2

Observed m/z   Int%
    344.0110   75.1
Estimated m/z  Error [ppm]    U.S. C    H    O    N    Cr
    344.0100   2.9            11   13   12   6    2    1
```

Figure S8. HR-MS of compound **2d**

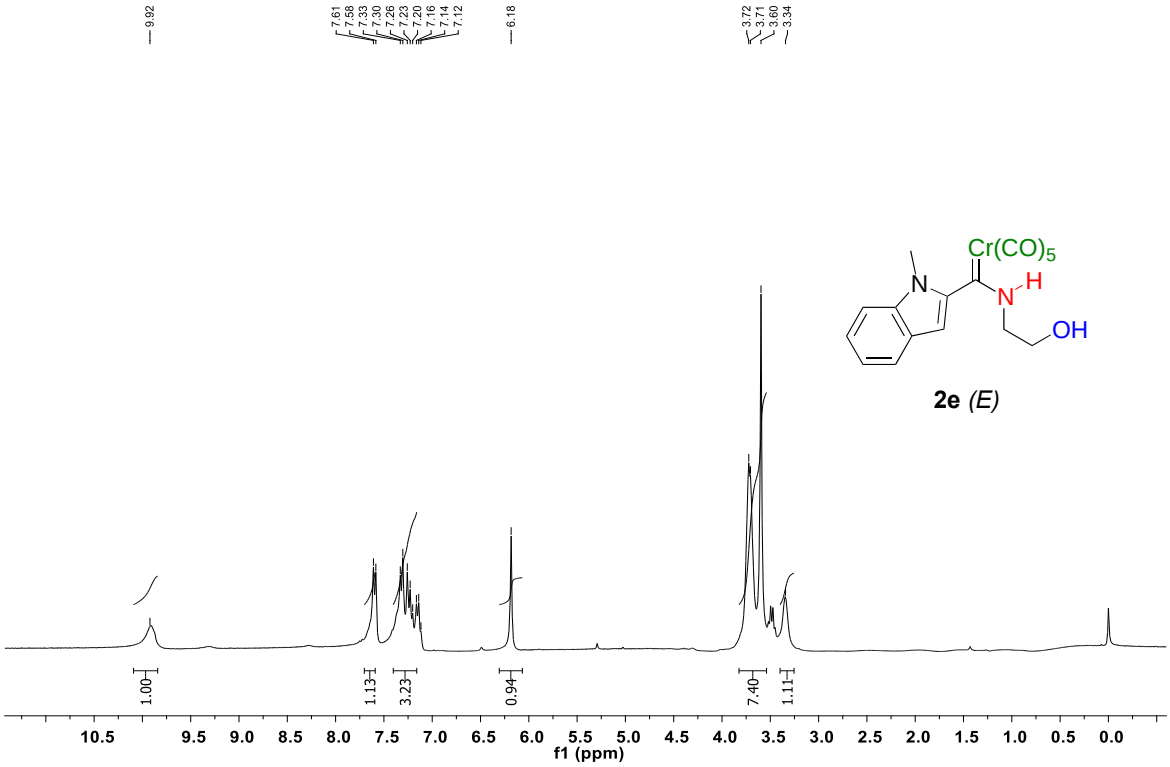

Figure S9. ^{1}H NMR spectrum of **2e**

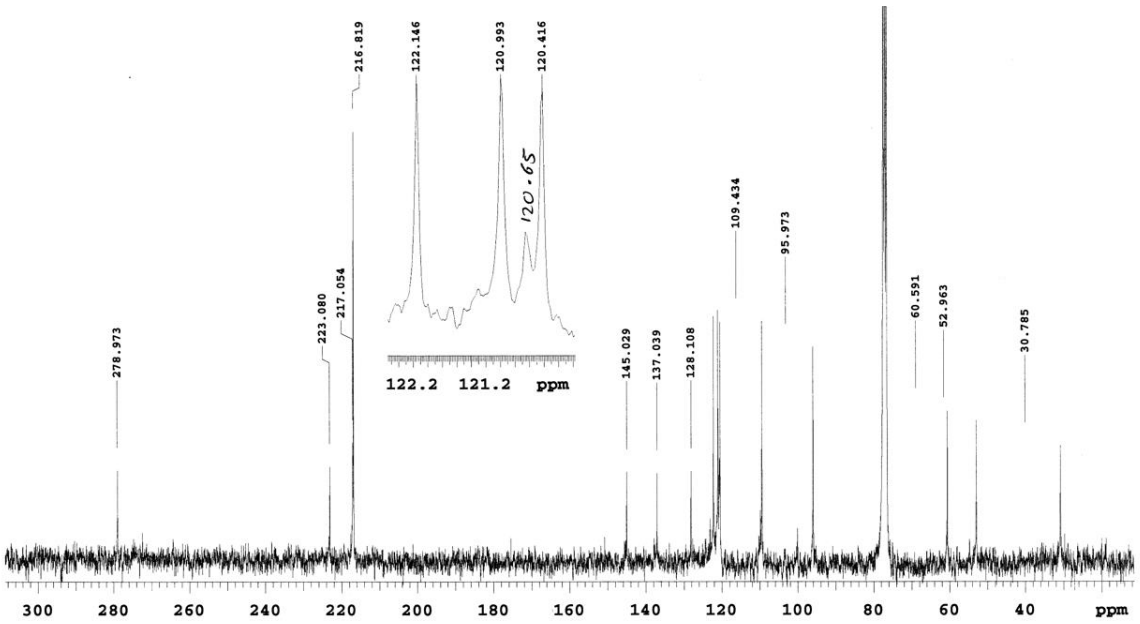

Figure S10. ^{13}C NMR spectrum of **2e**

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[ Elemental Composition ]                                        Page: 1
Data  : Dr-Jose-G-Lopez093          Date :30-Jan-2013   18:31
Sample: 186    MeIndCrNEtOH
Note  : Luis-Velasco
Inlet : Direct                      Ion Mode  :    FAB+
RT  : 0.96 min                      Scan#: (4,8)
Elements  : C 30/0, H 49/0, O 9/0, N 4/1, Cr 2/0
Mass Tolerance :    100ppm,   2mmu if m/z >2

Observed m/z   Int%
    394.0260   58.2
Estimated m/z  Error [ppm]    U.S. C    H    O    N    Cr
    394.0257   -0.7           14   17   14   6    2    1
```

Figure S11. HR-MS of compound **2e**

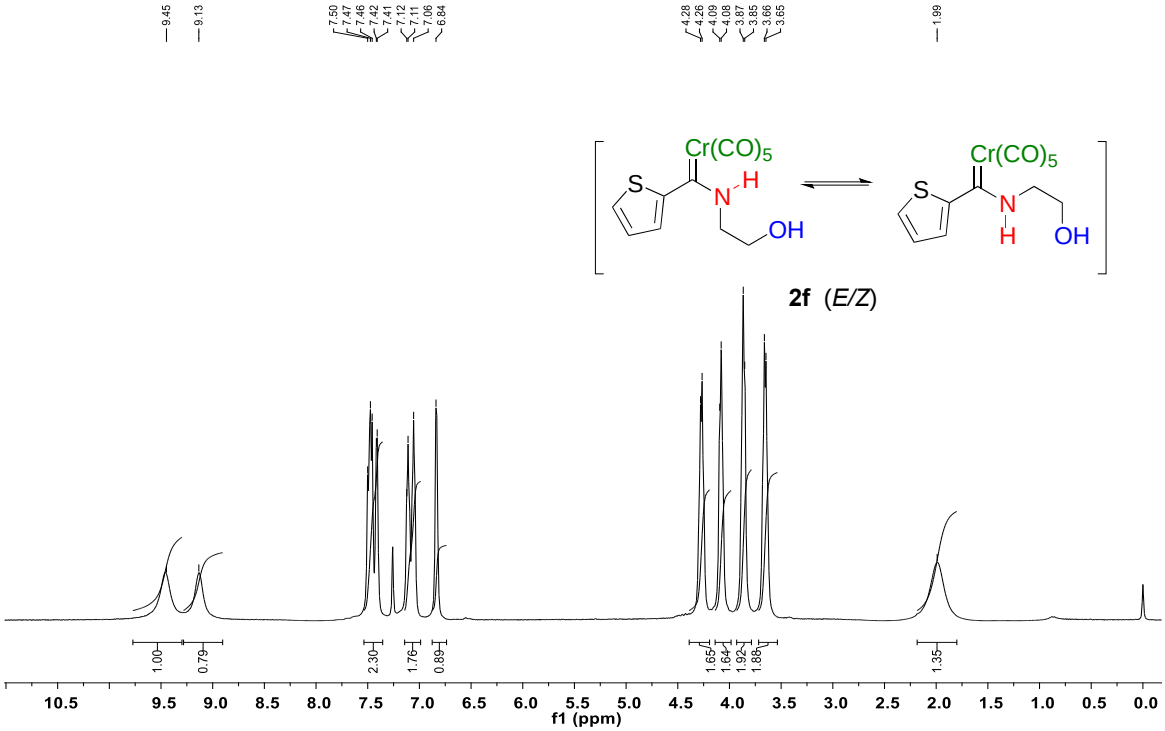

Figure S12. ^{1}H NMR spectrum of **2f** (*E/Z* ratio 56:44)

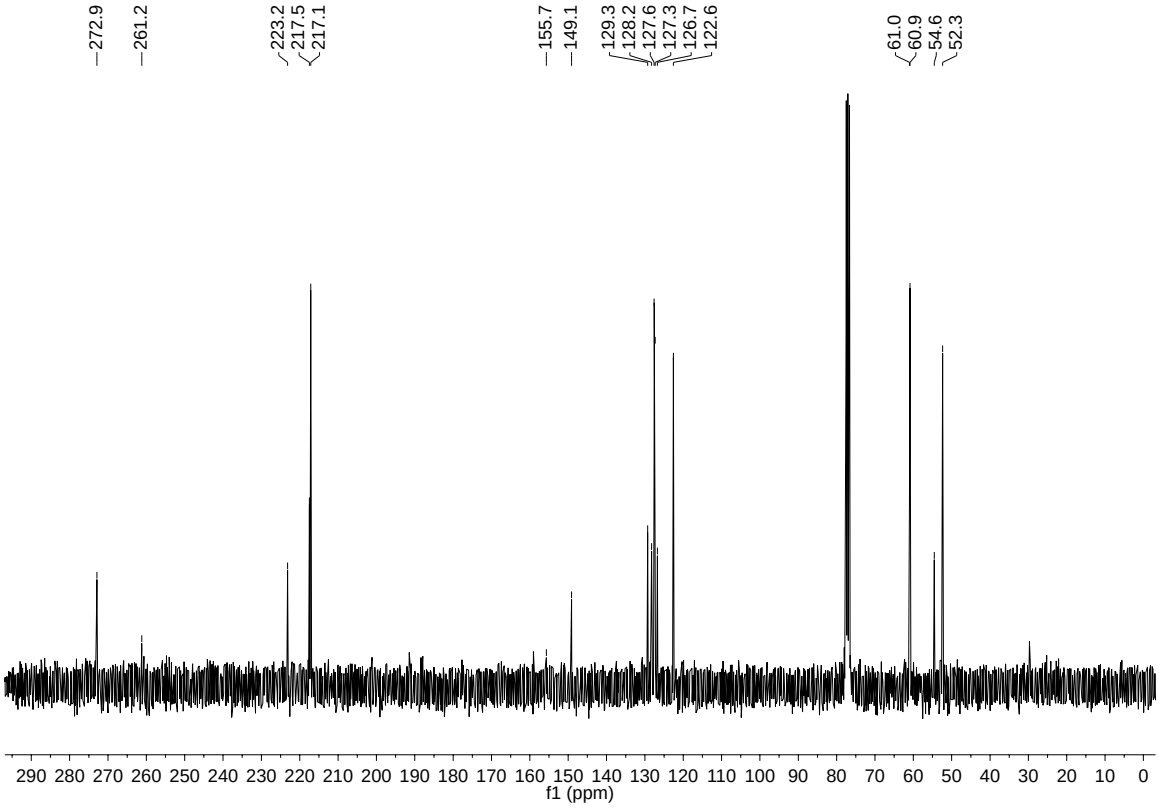

Figure S13. ^{13}C NMR spectrum of **2f**

```
[ Elemental Composition ]                                        Page: 1
Data  : Dr-Jose-G-Lopez093        Date :30-Jan-2013   18:10
Sample: 186    SCrNEtOH
Note  : Luis-Velasco
Inlet : Direct                    Ion Mode  :    FAB+
RT  : 0.85 min                    Scan#: (3,8)
Elements  : C 30/0, H 49/0, O 9/0, N 4/1, S 2/0, Cr 2/0
Mass Tolerance :    100ppm,   2mmu if m/z >2

Observed m/z   Int%
    346.9560   22.5
Estimated m/z  Error [ppm]    U.S. C    H    O    N    S    Cr
    346.9556   1.1            11   12   9    6    1    1    1
```

Figure S14. HR-MS of compound **2f**

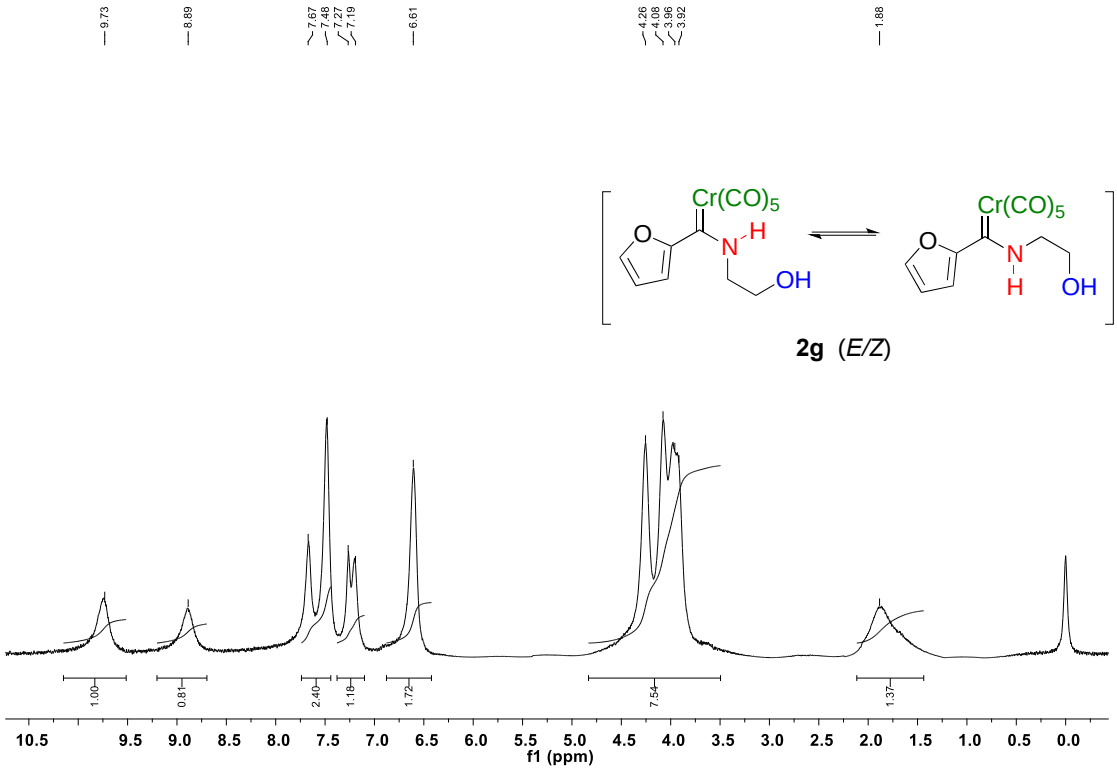

Figure S15. ^{1}H NMR spectrum of **2g** (*E/Z* ratio 55:45)

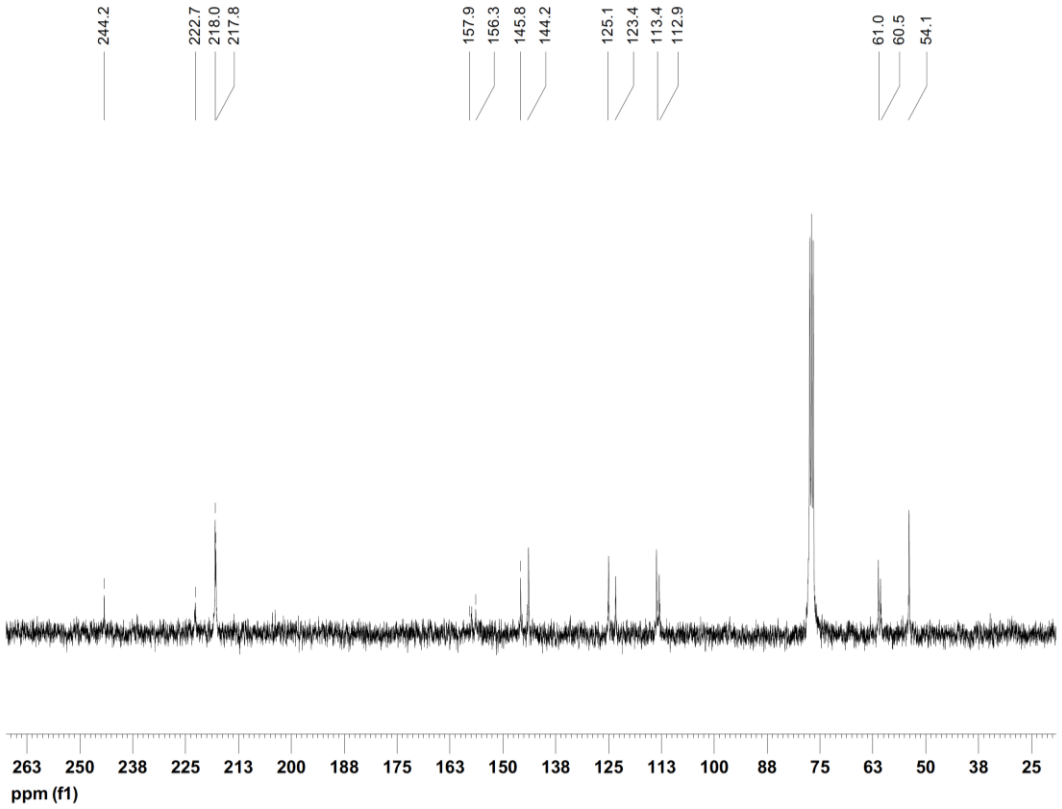

Figure S16. ^{13}C NMR spectrum of **2g**

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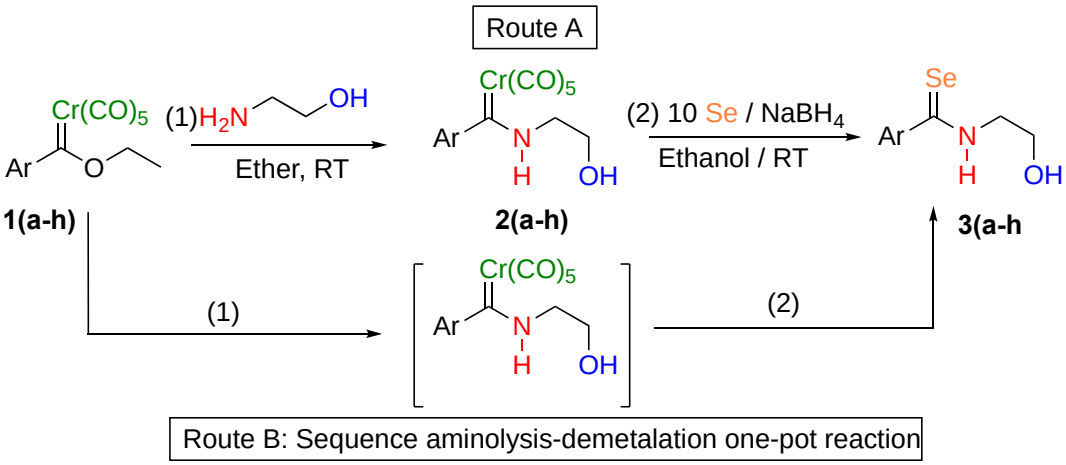
[ Elemental Composition ]                                        Page: 1
Data  : Dr-Jose-G-Lopez103        Date :01-Feb-2013   12:19
Sample: 279    OCrNOH
Note  : Luis-Velasco
Inlet : Direct                    Ion Mode  :    FAB+
RT  : 0.93 min                    Scan#: (2,7)
Elements  : C 30/0, H 49/0, O 9/0, N 4/1, Cr 2/0
Mass Tolerance :    100ppm,   2mmu if m/z >2

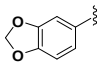
Observed m/z   Int%
    330.9792   17.7
Estimated m/z  Error [ppm]    U.S. C    H    O    N    Cr
    330.9784   2.4            11   12   9    7    1    1
```

Figure S17. HR-MS of compound **2g**

6. - Synthesis of selenoamides 3(a-f) (Route A)

Table S1. Synthesis of arylselenoamides **3(a-f)**



Entry	Ar	Compound	Time (min) Demetalation step	Route A Yield (%)[a]	Route A Global Yield (%)[a]	Route B Yield (%)[b]	Route B Global Yield (%)[b]
1		**3a**	25	94	70	93	74
2		**3b**	20	96	78	95	80
3		**3c**	35	91	44	90	64
4		**3d**	45	83	46	90	64
5		**3e**	45	72	63	80	75
6		**3f**	35	90	60	91	76
7		**3g**	45	90	69	92	74
8	**Fc**	**3h**	15	91	77	95	81

For [a]Route A and [b]Route B, the global yield was determined from the corresponding aryl substrate used as starting material.

Preparation of selenating agent: To a solution of 0.01 mol of $NaBH_4$ in 10 mL of ethanol was added 0.01 mol of powdered selenium, and the mixture was vigorously stirred at room temperature for 30 min under nitrogen atmosphere. The selenating agent was then added to a solution (0.001 mol) of the corresponding aminocarbene complex in 5 mL of ethanol, under nitrogen atmosphere; the reaction was monitored by TLC on silica-gel. After

the reaction was completed, the solvent was evaporated under vacuum, the residual mixture was dissolved in distilled water and the product was extracted with CH_2Cl_2 and then dried with anhydrous Na_2SO_4. After the evaporation of the solvent, the resultant mixture was purified by silica-gel column using a mixture Hexane: CH_2Cl_2 (1:1) as eluent. Selenoamides **3a** and **3f** are known and their spectroscopic data match well with literature.[3]

***N*-(2-hydroxyethyl)-4-methoxybenzenecarboselenoamide (3b).** Yield: 97%; m.p. 68 - 73°C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.51 (s, 1 H; NH), 7.79 (d, *J*= 8.4 Hz, 2 H; C_6H_4), 6.86 (d, *J*= 8.4 Hz, 2 H; C_6H_4), 4.07 – 4.00 (m, 4 H; OCH_2, NCH_2), 3.83 (s, 3 H; OCH_3), 2.17 (s, 1 H; OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 203.0 (C=Se), 162.3 (C, C_6H_4), 137.0 (C, C_6H_4), 128.7 (2 CH, C_6H_4), 113.7 (2CH, C_6H_4), 58.9 (OCH_2), 55.5 (OCH_3), 49.7 (NCH_2) ppm. IR (KBr) cm^{-1}: 3377 (NH), 1607 (C=Se); MS (EI, 70 eV) *m/z* (%): 259 (7) [M^+], 177 (97) [M^+-H_2Se], 134 (15) [$ArCNH^+$]; HRMS (FAB$^+$): *m/z*: calcd. for $C_{10}H_{13}NO_2Se$: 259.0112 [M^+]; found: 259.0100.

***N*-(2-hydroxyethyl)benzo[*d*][1,3]dioxole-5-carboselenoamide (3c).** Yield: 90%; m.p. 254 - 256°C; ^{1}H NMR (300 MHz, CD_3CN, TMS): δ = 9.05 (s, 1 H; NH), 7.33 – 7.31 (m, 2 H; C_6H_3), 6.80 (d, 1 H; C_6H_3), 6.00 (s, 2 H; OCH_2O), 3.88-3.82 (m, 4 H; OCH_2, NCH_2), 3.05 (s, 1 H; OH) ppm. ^{13}C NMR (75 MHz, CD_3CN, TMS): δ = 202.0 (C=Se), 149.8 (C, C_6H_3), 147.3 (C, C_6H_3), 138.6 (C, C_6H_3), 121.2 (CH, C_6H_3), 107.6 (CH, C_6H_3), 107.0 (CH, C_6H_3), 101.9 (CH_2, OCH_2O) 58.4 (OCH_2), 52.0 (NCH_2) ppm. IR (KBr) cm^{-1}: 3357 (NH), 1607 (C=Se). MS (EI, 70 eV) *m/z* (%): 273 (40) [M^+], 191 (14) [M^+-H_2Se], 148 (100) [$ArCNH^+$]; HRMS (FAB$^+$): *m/z*: calcd for $C_{10}H_{12}NO_3Se$: 273.9982 [M^++1]; found: 273.9977.

***N*-(2-hydroxyethyl)-1-methyl-1*H*-pyrrole-2-carboselenoamide (3d).** Yield: 93%; m.p. 79 - 80°C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.86 (s, 1 H; NH), 6.78 (s, 1 H; C_4H_3N), 6.48 – 6.47 (m, 1 H; C_4H_3N), 6.08 – 6.06 (m, 1 H; C_4H_3N), 3.99 (s, 3 H; NCH_3), 3.93 – 3.90 (m, 4 H; NCH_2CH_2), 2.45 (s, 1 H; OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 190.4 (C=Se), 137.2 (C, C_4H_3N), 130.5 (CH, C_4H_3N), 110.2, (CH, C_4H_3N), 107.7 (CH, C_4H_3N), 60.3 (OCH_2), 50.2 (NCH_2), 37.3 (NCH_3) ppm. IR (KBr) cm^{-1}: 3351 (NH), 1652 (C=Se). MS (EI, 70 eV) *m/z* (%): 232 (8) [M^+], 149 (100) [M^+-H_2Se], 107 (24) [M^+- $ArCNH^+$]; HRMS (FAB$^+$): *m/z*: calcd. for $C_8H_{12}N_2OSe$: 232.0115 [M^+]; found: 232.0122.

***N*-(2-hydroxyethyl)-1-methyl-1*H*-indole-2-carboselenoamide (3e).** Yield: 72 %; m.p.70 - 71°C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.63 (s, 1 H; NH), 7.63 (d, 1 H; C_8H_5N), 7.34 (s, 2 H; C_8H_5N), 7.14 (s, 1 H; C_8H_5N), 6.73 (s, 1 H; C_8H_5N), 4.02 – 4.01 (m, 7H; OCH_2, NCH_2, NCH_3) 1.65 ppm (s, 1 H; OH). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 192.5 (C=Se), 143.3 (C, C_8H_5N), 140.3 (C, C_8H_5N), 126.3, (C, C_8H_5N), 124.2 (CH, C_8H_5N), 121.9 (CH, C_8H_5N), 121.0

(CH, C_8H_5N), 110.4 (CH, C_8H_5N), 101.7 (CH, C_8H_5N), 60.4 (OCH_2), 50.6 (NCH_2), 32.4 ppm (NCH_3). IR (KBr): *v* = 3421 (OH), 3150 (NH), 1644 cm^{-1} (C=Se). MS (EI, 70 eV) *m/z* (%): 282 (100) [M^+], 201 (29) [M^+-H_2Se], 157 (79) [$ArCNH^+$]. HRMS (FAB^+) *m/z*: calcd. for $C_{12}H_{14}N_2OSe$: 282.0271 [M^+]; found: 282.0285.

***N*-(2-hydroxyethyl)thiophene-2-carboselenoamide (3f).** Yield: 75%; m.p. 118-120°C; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.42 (s, 1 H; NH), 7.60 (d, *J*= 6.0 Hz, 1 H; C_4H_3S), 7.52 (d, *J*= 3.0 Hz, 1 H; C_4H_3S), 7.13 (d, *J*= 3.0 Hz, 1 H; C_4H_3S), 4.08 - 4.04 (m, 4 H; OCH_2, NCH_2), 1.87 ppm (s, 1 H; OH). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 192.2 (C=Se), 149.8 (C, C_4H_3S), 133.2 (CH, C_6H_4), 128.2 (CH, C_4H_3S), 124.4 (CH, C_4H_3S), 60.4 (OCH_2), 51.2 ppm (NCH_2). IR (KBr): *v* = 3370 (NH), 1658 cm^{-1} (C=Se). MS (EI, 70 eV) *m/z* (%): 235 (100) [M^+], 154 (32) [M^+-H_2Se], 110 (89) [$ArCNH^+$]. HRMS (FAB^+) *m/z*: calcd. for C_7H_9NOSSe: 234.9570 [M^+]; found: 234.9582.

***N*-(2-hydroxyethyl)furan-2-carboselenoamide (3g).** Yield: 97%; m.p. 74-76°C; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.90 (s, 1 H; NH), 7.55 – 7.50 (m, 2 H; C_4H_3O), 6.47 (s, 1 H; C_4H_3O), 4.06 - 3.98 (m, 4 H; OCH_2, NCH_2), 2.51 ppm (s, 1 H; OH). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 185.1 (C=Se), 155.1 (C, C_4H_3O), 144.4 (CH, C_4H_3O), 120.8 (CH, C_4H_3O), 113.7 (CH, C_4H_3O), 60.4 (CH, OCH_2) 50.0 ppm (NCH_2). IR (KBr): ν = 3330 (NH), 1532 cm^{-1} (C=Se). MS (EI, 70 eV) *m/z* (%): 219 (100) [M+], 138 (18) [M+-H2Se], 94 (83) [$ArCNH^+$]. HRMS (FAB+) *m/z*: calcd. for $C_7H_9NO_2Se$: 218.9799 [M+]; found: 218.9785.

7. - NMR and HR-MS spectra of 3b-g

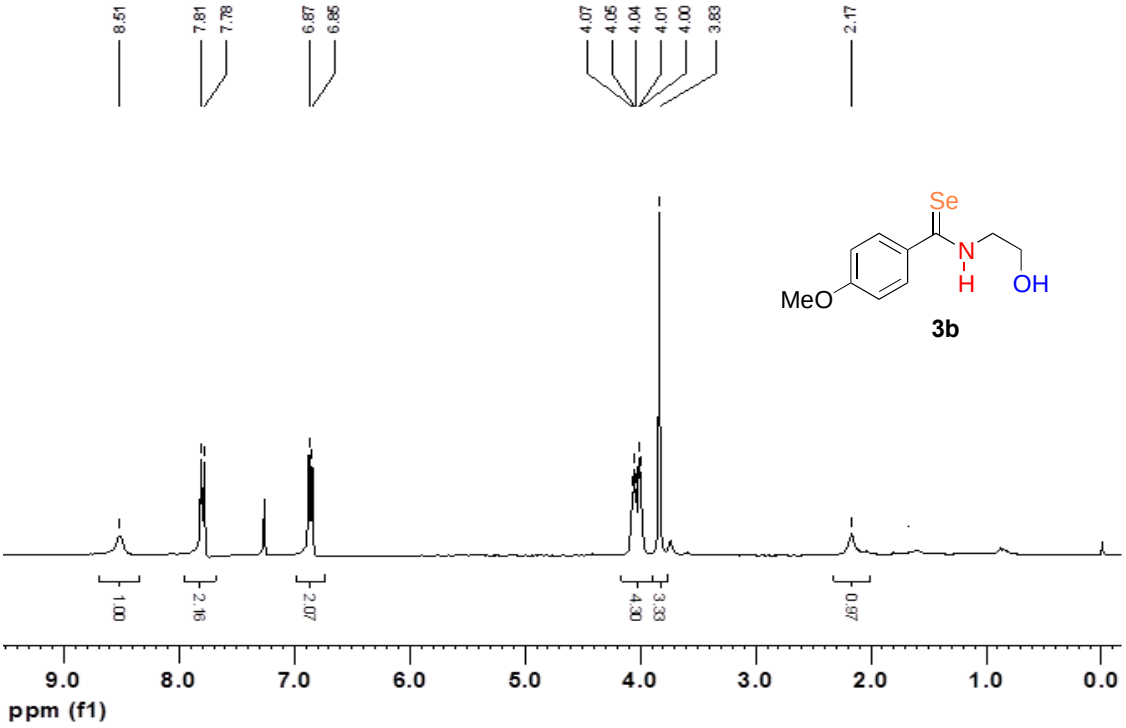


Figure S18. ^{1}H NMR spectrum of **3b**

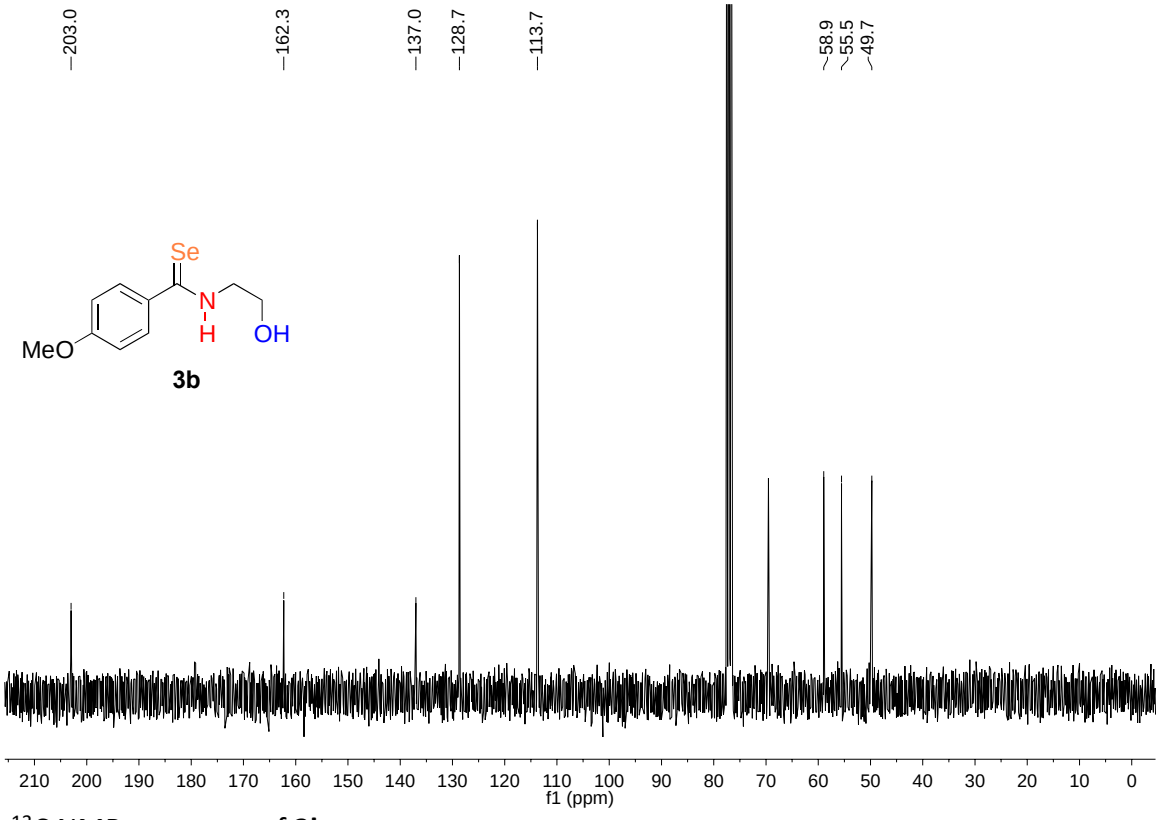


Figure S19. ^{13}C NMR spectrum of **3b**

```
[ Elemental Composition ]                                    Page: 1
Data  : Dr-Jose-G-Lopez037        Date :28-Jul-2016   11:39
Sample: 951    AIGH-5b
Note  : Luis-Velasco
Inlet : Direct                    Ion Mode  :    FAB+
RT  : 0.32 min                    Scan#: (8,10)
Elements  : C 30/0, H 49/0, O 3/0, N 3/0, Se 1/0
Mass Tolerance :    100ppm,   2mmu if m/z >2

Observed m/z   Int%
    259.0100   70.1
Estimated m/z  Error [ppm]    U.S. C    H    O    N    Se
    259.0112   -4.6           5    10   13   2    1    1
```

Figure S20. HR-MS of compound **3b**

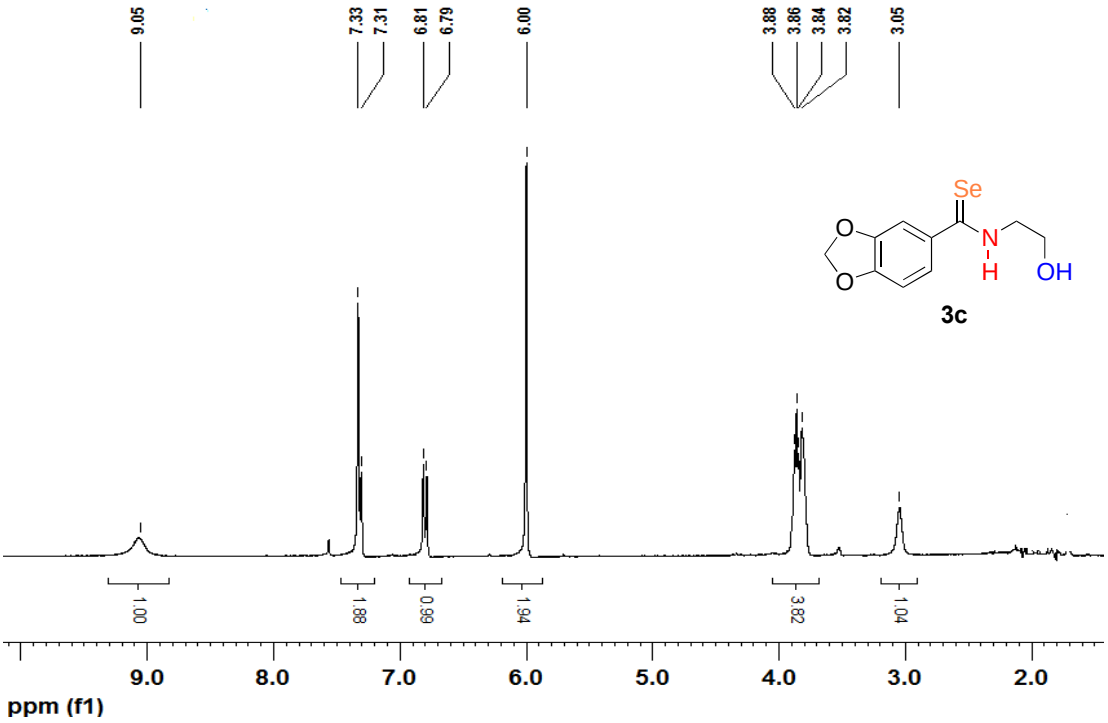


Figure S21. ^{1}H NMR spectrum of **3c**

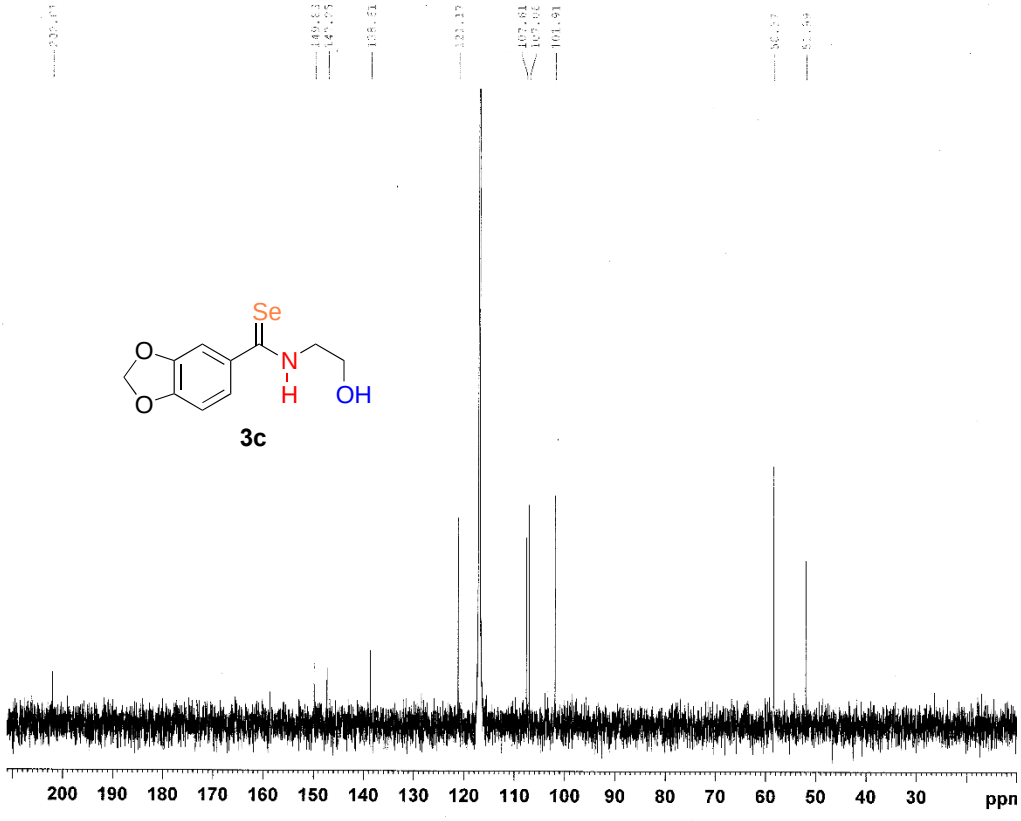


Figure S22. ^{13}C NMR spectrum of **3c**

```
[ Elemental Composition ]                                    Page: 1
Data  : Dr-Jose-G-Lopez015        Date :04-Mar-2013   17:48
Sample: 577    OOSeNEtOH
Note  : Luis-Velasco
Inlet : Direct                    Ion Mode  :    FAB+
RT  : 4.47 min                    Scan#: (11,13)
Elements  : C 40/0, H 49/0, O 3/0, N 3/0, Se 1/0
Mass Tolerance :    100ppm,   2mmu if m/z >2

Observed m/z   Int%
    273.9977   100.0
Estimated m/z  Error [ppm]    U.S. C    H    O    N    Se
    273.9982   -2.1           6.5  10   12   3    1    1
```

Figure S23. HR-MS of compound **3c**

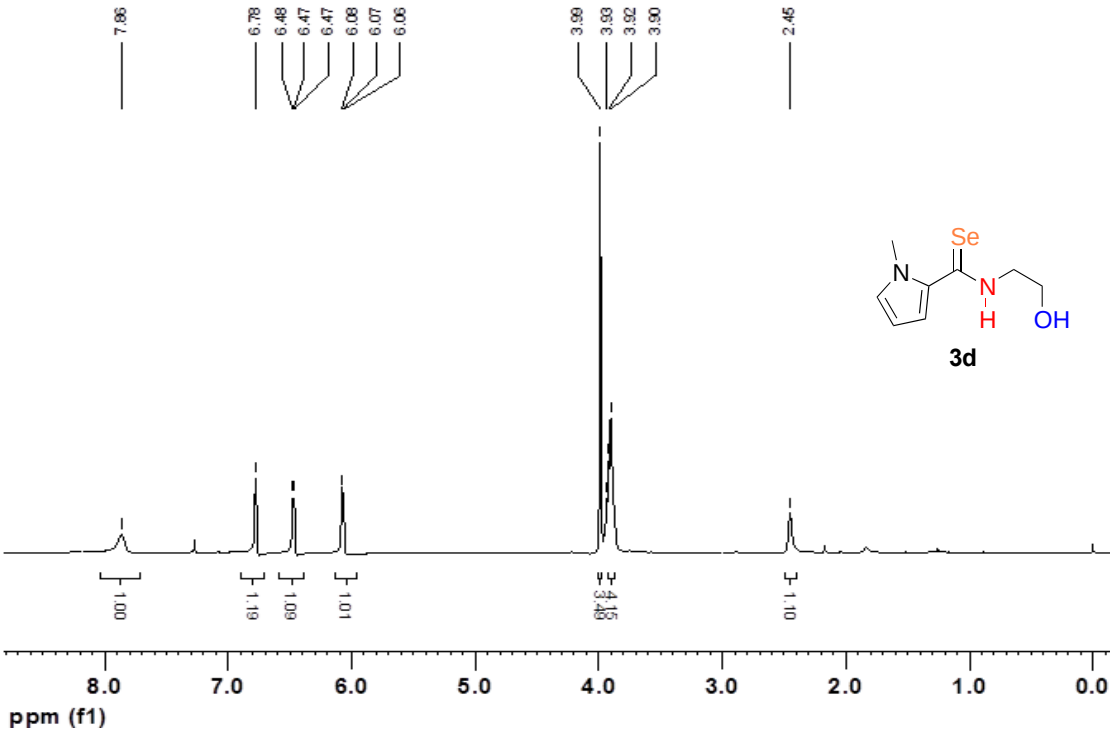


Figure S24. ^{1}H NMR spectrum of **3d**

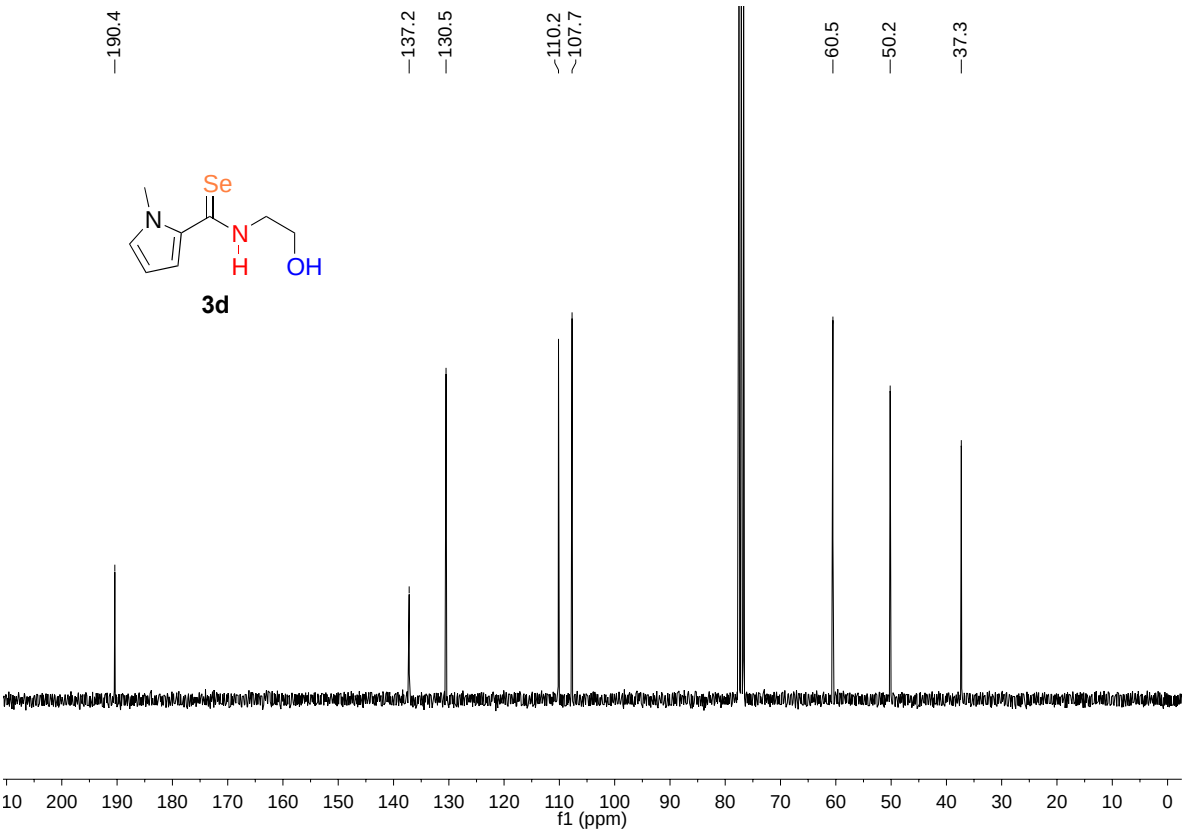


Figure S25. ^{13}C NMR spectrum of **3d.**

```
[ Elemental Composition ]                                    Page: 1
Data  : Dr-Jose-G-Lopez056        Date :23-May-2011   16:17
Sample: 1412   MeP1SeOH2
Note  : Luis-Velasco
Inlet : Direct                    Ion Mode  :    FAB+
RT  : 0.40 min                    Scan#: (6,22)
Elements  : C 40/0, H 49/0, O 3/0, N 3/0, Se 1/0
Mass Tolerance :    100ppm,   2mmu if m/z >2

Observed m/z   Int%
    232.0122   7.1
Estimated m/z  Error [ppm]    U.S. C    H    O    N    Se
    232.0115   3.0            4    8    12   1    2    1
```

Figure S26. HR-MS of compound **3d**

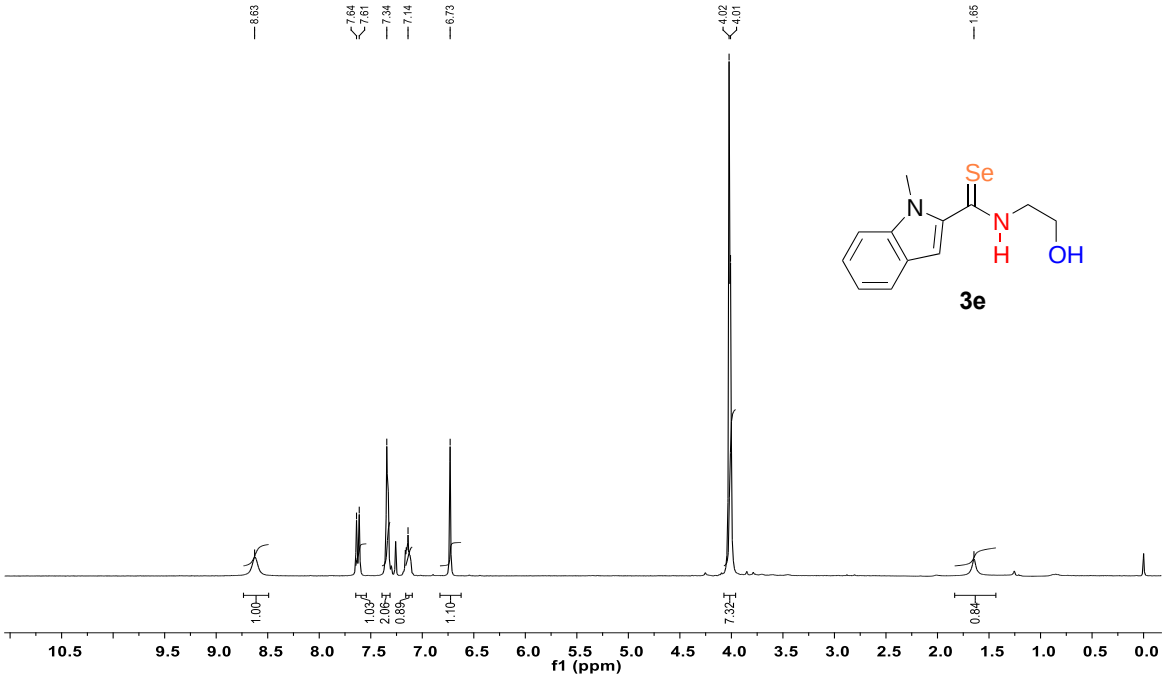


Figure S27. ^{1}H NMR spectrum of **3e**

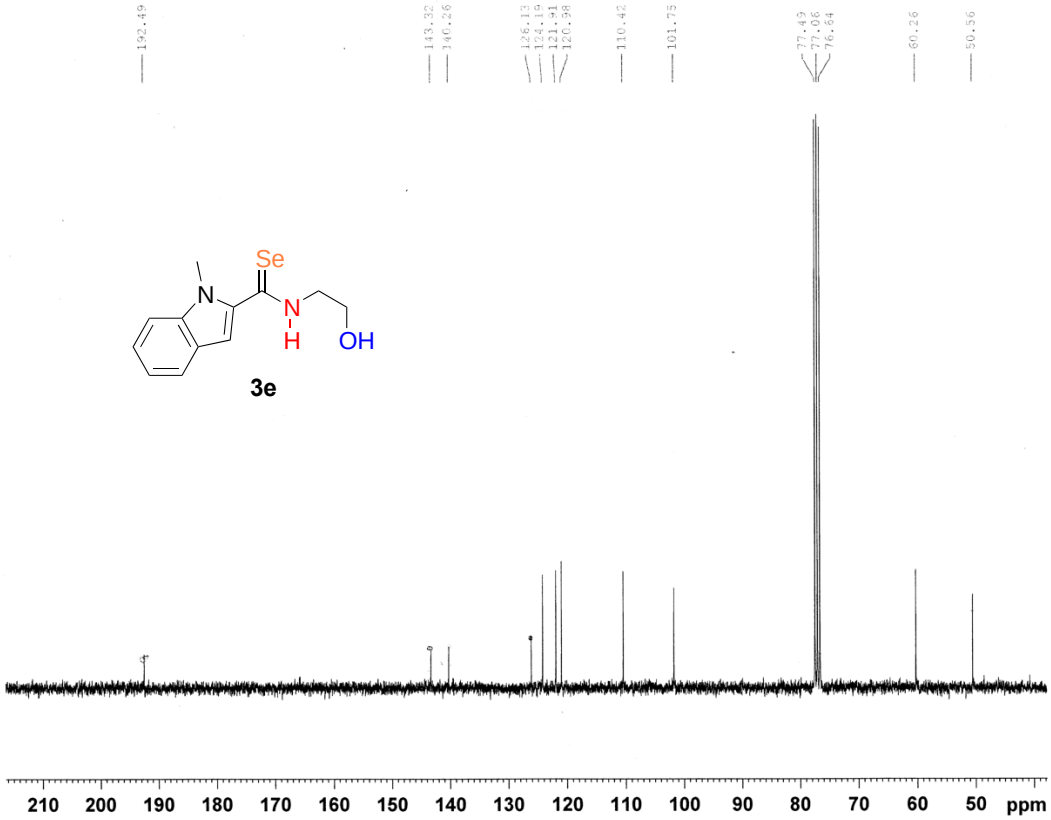


Figure S28. ^{13}C NMR spectrum of **3e**

```
[ Elemental Composition ]                                    Page: 1
Data  : Dr-Jose-G-Lopez016        Date :06-Nov-2012   19:24
Sample: 2772   Caro2
Note  : Luis-Velasco
Inlet : Direct                    Ion Mode  :    FAB+
RT  : 0.31 min                    Scan#: (6,10)
Elements  : C 40/0, H 49/0, O 3/0, N 3/0, Se 1/0
Mass Tolerance :    100ppm,   2mmu if m/z >2

Observed m/z   Int%
    282.0285   100.0
Estimated m/z  Error [ppm]    U.S. C    H    O    N    Se
    282.0271   4.9            7    12   14   1    2    1
```

Figure S29. HR-MS of compound **3e**

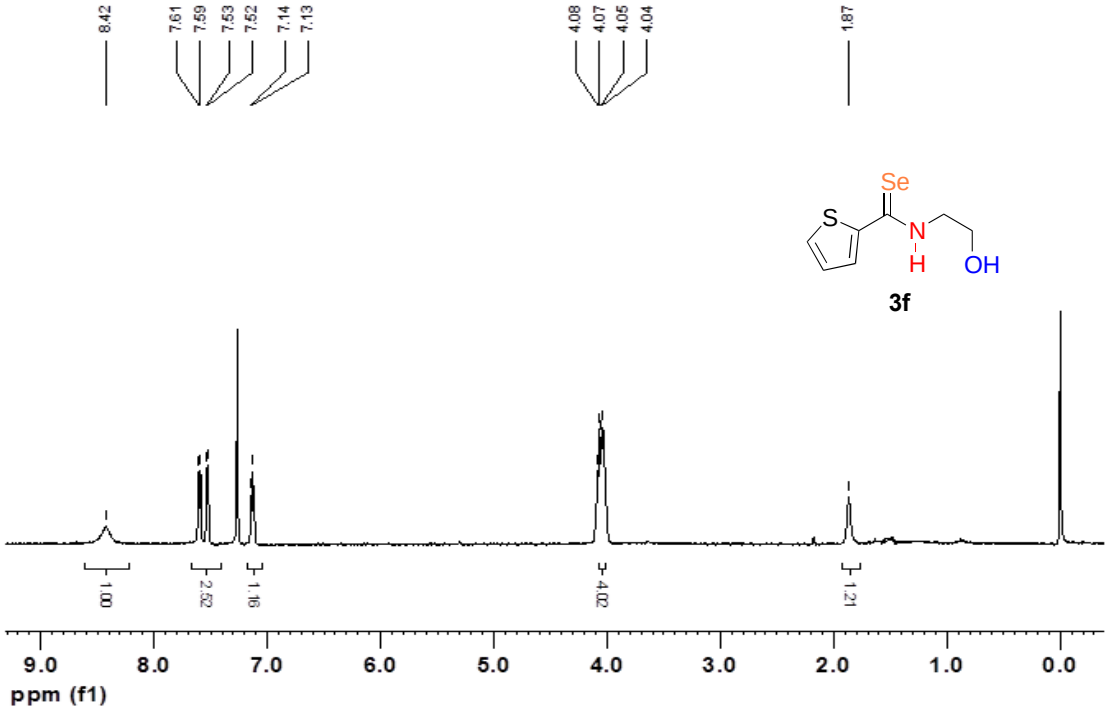


Figure S30. ^{1}H NMR spectrum of **3f**

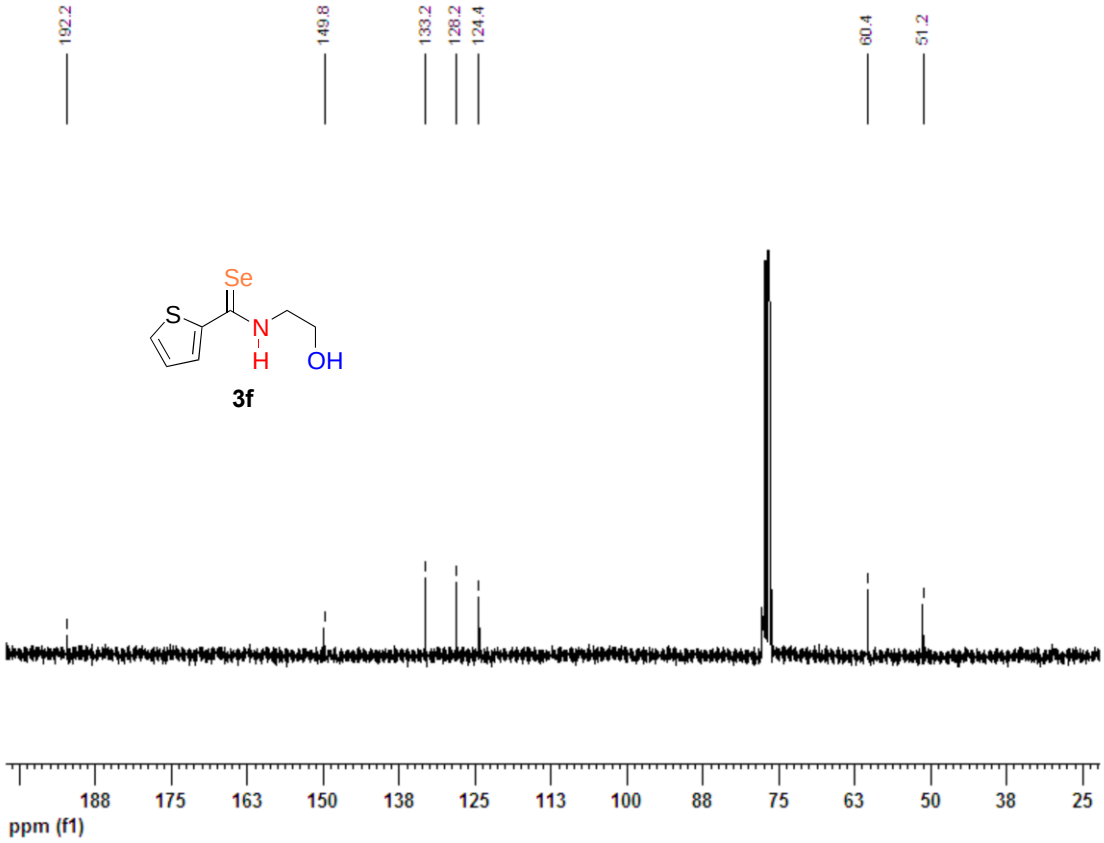


Figure S31. ^{13}C NMR spectrum of **3f**

```
[ Elemental Composition ]                                    Page: 1
Data  : Dr-Jose-G-Lopez009         Date :26-Oct-2012   10:31
Sample: 2731   SSeNOH
Note  : Luis-Velasco
Inlet : Direct                     Ion Mode  :    FAB+
RT  : 1.68 min                     Scan#: (36,43)
Elements  : C 40/0, H 49/0, O 3/0, N 3/0, S 2/0, Se 1/0
Mass Tolerance :    100ppm,   2mmu if m/z >2

Observed m/z   Int%
    234.9582   100.0
Estimated m/z  Error [ppm]    U.S. C    H    O    N    S    Se
    234.9570   4.9            4    7    9    1    1    1
```

Figure S32. HR-MS of compound **3f**

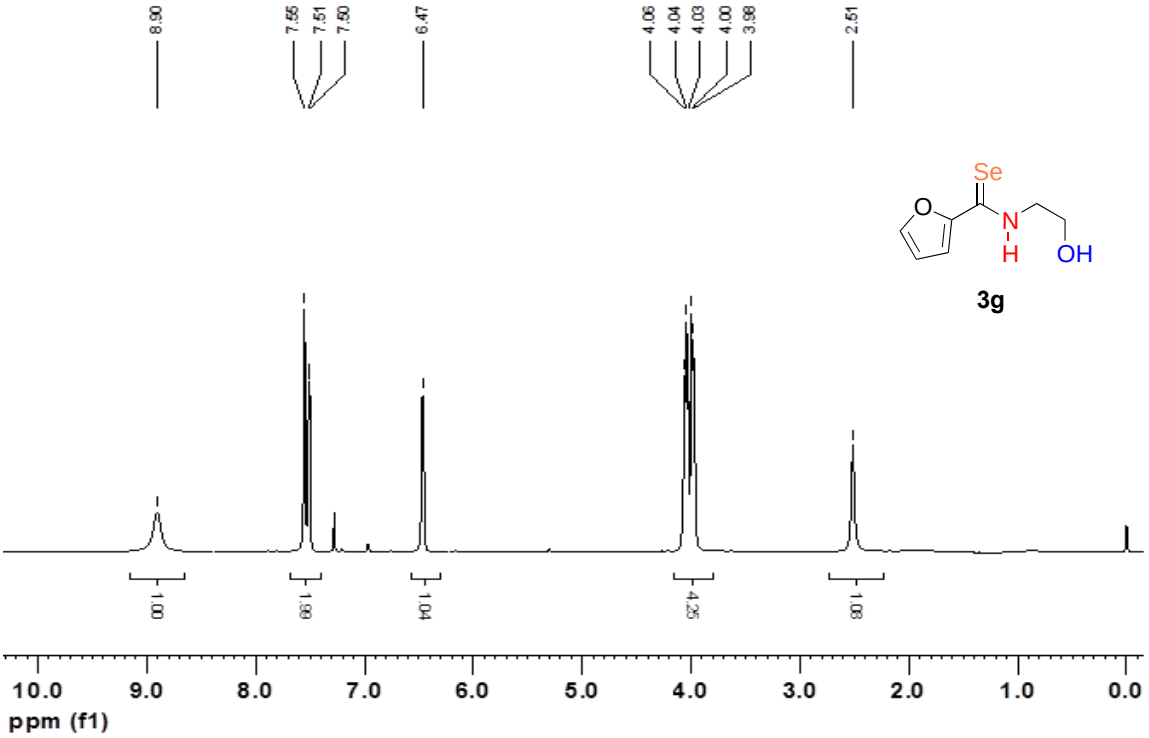


Figure S33. ^{1}H NMR spectrum of **3g**

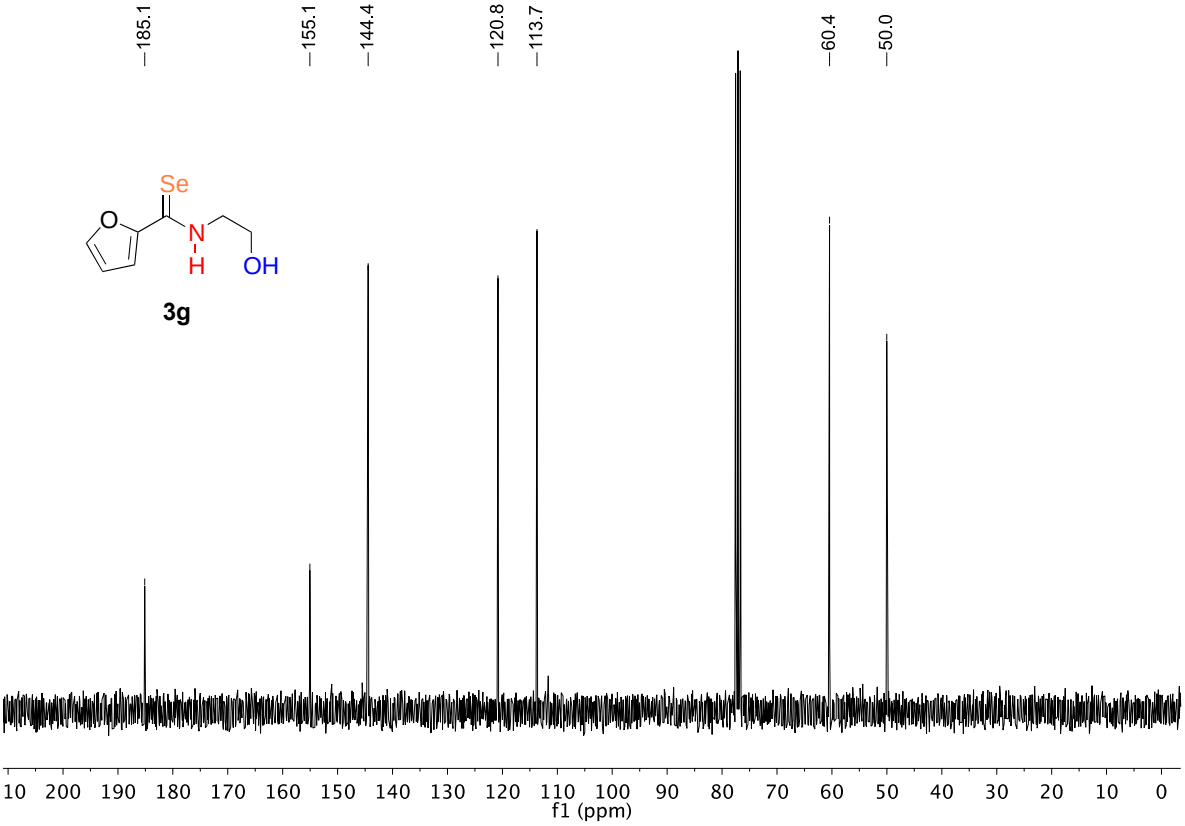


Figure S34. ^{13}C NMR spectrum of **3g**

```
[ Elemental Composition ]                                        Page: 1
Data  : Dr-Jose-G-Lopez008        Date :26-Oct-2012   10:19
Sample: 2729   OSeNOH
Note  : Luis-Velasco
Inlet : Direct                    Ion Mode  :    FAB+
RT  : 1.64 min                    Scan#: (34,42)
Elements  : C 40/0, H 49/0, O 3/0, N 3/0, Se 1/0
Mass Tolerance :    100ppm,   2mmu if m/z >2

Observed m/z   Int%
    218.9785   100.0
Estimated m/z  Error [ppm]    U.S. C    H    O    N    Se
    218.9799   -6.3           4    7    9    2    1    1
```

Figure S35. HR-MS of compound **3g**

8. X-Ray diffraction analyses

Suitable X-ray quality crystals of **3f** were grown by slow evaporation of chloroform at room temperature. A crystal of **3f** was mounted on a glass fiber at room temperature, then placed on a Bruker Smart Apex CCD diffractometer, equipped with Mo KR radiation; decay was negligible in both cases. Details of crystallographic data collected for compound **3f** are provided in Table S2. Systematic absences and intensity statistics were used in space group determination. The structure was solved using direct methods.[4]Anisotropic structure refinements were achieved using full matrix, least-squares technique on all non-hydrogen atoms. All hydrogen atoms were placed in idealized positions, based on hybridization, with isotropic thermal parameters fixed at 1.2 times the value of the attached atom. Structure solutions and refinements were performed using SHELXTL V6.10. [5] CCDC-1015044 (**3f**) 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.ac.uk/data_request/cif.

Table S2. Crystal data and structure refinement for **3f**.

	3f
Empirical Formula	C_7H_9NOSSe
Formula Weight (g mol^{-1})	234.17
Crystal size (mm)	0.28 x 0.22 x 0.07
Color	Orange
Crystal system	Monoclinic
Space Group	$P2_1/c$
a (Å)	8.595(10)
b (Å)	13.301(15)
c (Å)	8.139(9)
α (°)	90
β (°)	107.864(4)
γ (°)	90
V (Å^3)	885.7(17)
Z	4
D_{calc} (g cm^3)	1.756
Number of collected reflections	5879
Number of independent reflections (R_{int})	2026, R_{int}= 0.0202
Absorption correction method	Semi-empirical from equivalents
Maximum and minimum transmission	0.7456 and 0.5658
Data/restraints/parameters	2026/2/1065
Final *R* indices [$I>2\sigma(I)$]	*R* = 0.0292, *wR*2 = 0.0703
R índices (all data)	*R* = 0.0367, *wR*2 = 0.0741
Goodness-of-fit on F^2	1.057

9. Biological studies.

Cell lines culture and culture medium.

The compounds **3(a-h)** were screened in vitro against six tumor cell lines: HCT-15 (human colorectal adenocarcinoma), U251 (human glioblastoma), PC-3 (human prostatic adenocarcinoma), MCF-7 (human mammary adenocarcinoma), K562 (human chronic myelogenous leukemia) and SKLU-1 (human lung adenocarcinoma), and the healthy cell line MT2 (Human T-lymphocyte). These cell lines were supplied by National Cancer Institute (USA). The human tumor cytotoxicity was determined using the protein-binding dye Sulforhodamine B (SRB) in microculture assay to measure cell growth, as described in the protocols established by the NCI.[26] The cell lines were cultured in RPMI-1640 medium (Sigma Chemical Co., Ltd., St. Louis, MO, U.S.A.) supplemented with 10 % fetal bovine serum which was purchased from Invitrogen Corporation, 2 mM L-glutamine, 10,000 units/mL penicillin G sodium, 10,000 μg/mL streptomycin sulfate and 25 μg/mL amphotericin B (Gibco) and 1 % non-essential amino acids (Gibco). They were maintained at 37°C, in a 5 % CO_2 atmosphere with 95% humidity. The viability of the cells used in the experiments exceeds 95 %, which was determined with trypan blue.

Cytotoxicity assays

The cells were removed from the tissue culture flasks by treatment with trypsin, and then diluted with fresh media. Of this cell suspension, 100 μL containing 5000-10,000 cell per well were pipetted into 96 well microtiter plates (Costar) and the material was incubated for 24 h, at 37 °C in a 5% CO_2 atmosphere.

A 20 mM stock solution of each compound was prepared using ethanol as solvent and the solutions of lower concentrations (50 to 1 μM) were prepared by accurate dilution. To determine the inhibition of the growth (%) of human tumor cell lines for **3(a-h)** at 50 μM in EtOH, 100 μL of an ethanolic solution 50 μM of each compound were added to each well (Table S2). The final percentage of ethanol in each well was 0.05%. The cultures were exposed for 48 h. After the incubation period, cells were fixed in situ by the addition of 50 mL of cold 50 % (w/v) trichloroacetic acid. The plates were incubated for 1 h, at 4 °C. The supernatant was discarded, and the plates were washed three times with water and air-dried. Cultures fixed with trichloroacetic-acid were stained for 30 min with 100 μL of 0.4% SRB solution.

Protein-bounded dye was extracted with 10 mM unbuffered tris base and the optical densities were read on a Microplate Reader Synergy HT (Elx 808, BIOTEK Instruments, Inc., U.S.A.), with a test wavelength of 515 nm. Results were expressed as IC_{50} values, they were calculated according to the protocol of Monks,[26] were a dose-response curve was plotted for each compound, and the concentration giving 50% inhibition (IC_{50}) was estimated from non-linear regression equations.

A similar procedure was followed for obtaining the IC_{50} of each compound, which was conducted using the three human cancer cell lines that exhibited the best results. For comparative purposes, the MT2 cell line described above was also used. The solutions of test compounds were prepared at concentrations ranging from 1.0 to 50 μM.

Table S3. Inhibition of the growth (%) of human tumor cell lines for **3(a-h)** at 50 µM in EtOH

Entry	Compound	HCT-15	U251	PC-3	MCF-7	K562	SKLU-1
1	**3a**	62.6	39.9	88.3	59.5	25.4	41.8
2	**3b**	68.7	87.48	100	97.36	46.88	54.3
3	**3c**	67.16	71.96	84.14	62.25	90.74	35.66
4	**3d**	83.92	56.78	74.84	72.15	35.57	21.73
5	**3e**	>100	91.0	>100	>100	99.0	86.1
6	**3f**	>100	97.3	>100	78.9	62.15	48.3
7	**3g**	62.65	60.49	64.19	51.91	44.62	37.54
8	**3h** (Lead)	98.51	98.27	88.64	>100	62.68	95.7

10. - References

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