Electronic supplementary materials *Mendeleev Commun.*, 2022, **32**, 769–770

Synthesis of 5-methylidene-2-thio- and 2-selenohydantoins from isothiocyanates or isoselenocyanates and L-serine

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EXPERIMENTAL SECTION

All common reagents were purchased from commercial suppliers and used as received. The melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (400MHz for^{1}H, 100MHz for ^{13}C) in DMSO-d_6. Chemical shifts are reported in parts per million relative to TMS. High resolution mass spectra (HRMS) were recorded on an Orbitrap Elite (Thermo Scientific) mass spectrometer with electrospray ionization (ESI) and orbital trap. To inject solutions with a concentration of 0.1 to 9 mg ml^{-1} (in 1% formic acid in acetonitrile), direct injection into the ion source using a syringe pump (5 ml min^{-1}) was used. The spray voltage was ±3.5 kV, the temperature of the capillary was 275 °C.

Synthesis of 5-hydroxymethyl-3-phenyl-2-thioxoimidazolidin-4-one 2a.

L-Serine ethyl ester hydrochloride **1'** (1 g, 5.9 mmol) was suspended in chloroform (25 ml), then triethylamine (0.9 ml, 6.49 mmol) was added, and suspension was stirred at room temperature for 30 min. Then phenyl isothiocyanate (0.8 g, 5.9 mmol) was added, and resulting mixture was stirred at room temperature for 3 days. After that mixture was washed with water (25 ml), chloroform was evaporated under reduced pressure, and product **2a** was isolated as white solid by column chromatography (MeOH:$CHCl_3$ = 1:15, R_f=0.43). Yield 0.7 g, 53%. **^{1}H NMR** (400 MHz, DMSO-d6): δ 10.47 (s, 1H), 7.51-7.39 (m, 3H), 7.25-7.21 (m, 2H), 5.34 (t, J=5.3 Hz, 1H), 4.44 (t, J=2.5 Hz, 1H), 3.86-3.79 (m, 1H), 3.77-3.70 (m, 1H).

General Procedure for the synthesis of methylidenethio- and selenohydantoins 3.

*5-Methylidene-3-phenyl-2-thioxoimidazolidin-4-one (**3a**).* L-Serine (0.5 g, 4.76 mmol) was dissolved in a pyridine-water mixture (7 + 7 ml), and 1 M NaOH was added until pH reached 9-10. The solution was heated to 40°C. Phenyl isothiocyanate (0.71 g, 5.23 mmol) was added, and the mixture was stirred at 40°C for 25 min with dropwised addition of 1 M NaOH to maintain the required pH 9-10. Then pyridine and excess of isothiocyanate were removed by extraction with toluene (3×10 ml). The aqueous phase was diluted with water (100 ml), acidified with concentrated hydrochloric acid to pH ~ 2, and the resulting mixture was stirred at rt for 2 days. The resulting suspension was filtered to obtain pale yellow solid **3a**, 0.57 g. Additional stirring of the filtrate for 2 days allowed obtaining more 0.19 g of **3a**. Overall yield 0.76 g, 78%. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 12.50 (s, 1H), 7.53-7.42 (m, 3H), 7.38-7.32 (m, 2H), 5.35 (d, J=1.7 Hz, 1H), 5.17 (d, J=1.8 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 178.1, 162.4, 135.3, 133.0, 128.8, 128.8, 97.7. **HRMS** (ESI) m/z calcd. for ($C_{10}H_8N_2OS$, M+H): 205.0436, found: (M+H): 205.0431.

*5-Methylidene-3-(4-methylphenyl)-2-thioxoimidazolidin-4-one (**3b**) and 5-hydroxymethyl-3-(4-methylphenyl)-2-thioxoimidazolidin-4-one (**2b**).* From L-serine **1** (0.13 g, 1.22 mmol) and 4-methylphenyl isothiocyanate (0.2 g, 1.34 mmol) (with 30 ml of added water before acidification with HCl) after 2 days, a mixture of **2b** (0.18 g, 63%) and **3b** (0.007 g, 3%) was obtained. A sample of 0.1 g of this mixture was suspended in water (50 ml), conc. HCl (10 drops) was added, the mixture was stirred for 5 days and filtered to obtain 0.07 g of pale yellow solid **3b**. Overall yield 44%. (**2b**): **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.42 (s, 1H), 7.27 (d, J=8.1 Hz, 2H), 7.09 (d, J=8.2 Hz, 2H), 5.31 (t, J=5.2 Hz, 1H), 4.43-4.40 (m,

1H), 3.85-3.77 (m, 1H), 3.76-3.69 (m, 1H), 2.35 (s, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 183.2, 173.1, 138.0, 131.0, 129.2, 128.5, 62.1, 59.7, 20.8. (**3b**): **^{1}H NMR** (400 MHz, DMSO-d_6): δ 12.46 (s, 1H), 7.29 (d, J=8.1 Hz, 2H), 7.21 (d, J=8.2 Hz, 2H), 5.34 (d, J=1.5 Hz, 1H), 5.15 (d, J=1.6 Hz, 1H), 2.36 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 178.3, 162.5, 138.4, 135.3, 130.4, 129.3, 128.5, 97.6, 20.8. **HRMS** (ESI) m/z calcd. for ($C_{11}H_{10}N_2OS$, M+H): 219.0587, found: (M+H): 219.0582.

*5-Methylidene-3-(3-methylphenyl)-2-thioxoimidazolidin-4-one (**3c**) and 5-hydroxymethyl-3-(3-methylphenyl)-2-thioxoimidazolidin-4-one (**2c**).* From L-serine **1** (0.13 g, 1.22 mmol) and 3-methylphenyl isothiocyanate (0.2 g, 1.34 mmol) (with 30 ml of added water before acidification with HCl) after 2 days, a mixture of **2c** (0.16 g, 54%) and **3c** (0.02 g, 8%) was obtained. 0.1 g of this mixture was suspended in 100 ml of water, 10 drops of concentrated HCl was added and mixture was stirred for 5 days, then filtered to obtain 0.08 g of pale yellow solid **3c**. Overall yield 48%. (**2c**): **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.43 (s, 1H), 7.39-7.33 (m, 1H), 7.26-7.21 (m, 1H), 7.04-6.99 (m, 2H), 5.32 (bs, 1H), 4.44-4.40 (m, 1H), 3.82 (d, J=11.3 Hz, 1H), 3.73 (d, J=11.3 Hz, 1H), 2.34 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 183.1, 173.1, 138.1, 133.5, 129.2, 129.1, 128.5, 125.9, 62.2, 59.7, 20.8. (**3c**): **^{1}H NMR** (400 MHz, DMSO-d_6): δ 12.48 (bs, 1H), 7.38 (t, J=7.7 Hz, 1H), 7.27 (d, J=7.6 Hz, 1H), 7.17-7.11 (m, 2H), 5.34 (d, J=1.4 Hz, 1H), 5.16 (d, J=1.5 Hz, 1H), 2.34 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 178.2, 162.4, 138.3, 135.3, 132.9, 129.5, 129.1, 128.6, 125.8, 97.7, 20.8. **HRMS** (ESI) m/z calcd. for ($C_{11}H_{10}N_2OS$, M+H): 219.0587, found: (M+H): 219.0584.

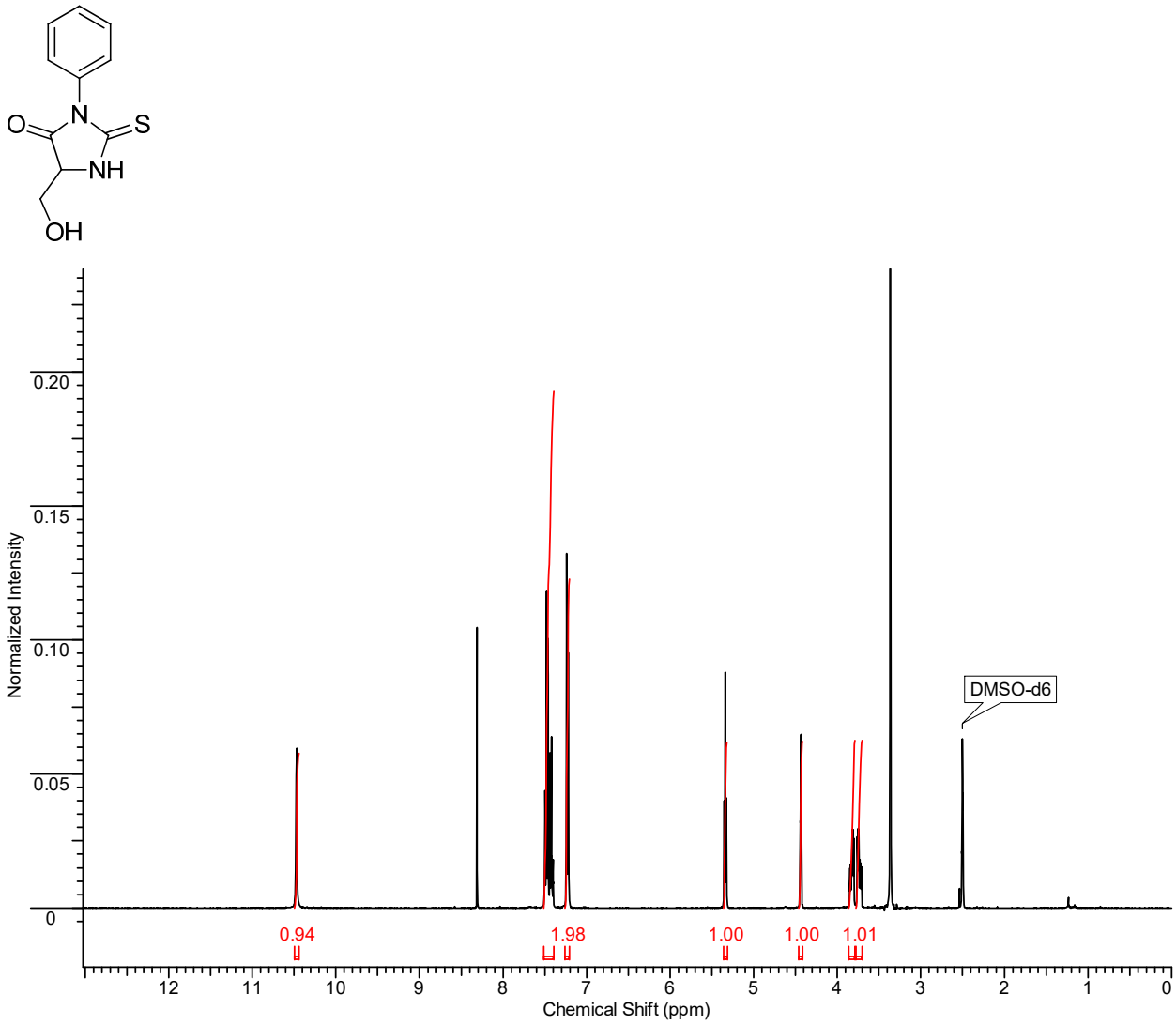
*3-(4-chlorophenyl)-5-methylidene-2-thioxoimidazolidin-4-one (**3d**) and 3-(4-chlorophenyl)-5-hydroxymethyl-2-thioxoimidazolidin-4-one (**2d**).* From L-serine (0.11 g, 1.07 mmol) and 4-chlorophenyl isothiocyanate (0.2 g, 1.18 mmol) (with 60ml of added water before acidification with HCl) after 4 days mixture of **2d** (0.19 g, 71%) and **3d** (0.02 g, 7%) was obtained. A 0.1 g sample of this mixture was suspended in water (150 ml), concentrated HCl (15 drops) was added, and the mixture was stirred for 10 days, filtered to obtain 0.08 g of pale yellow solid **3d**. Overall yield 60%. (**2d**): **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.54 (s, 1H), 7.56 (d, J=8.6 Hz, 2H), 7.28 (d, J=8.7 Hz, 2H), 5.34 (t, J=5.3 Hz, 1H), 4.46-4.42 (m, 1H), 3.86-3.78 (m, 1H), 3.76-3.69 (m, 1H). (**3d**): **^{1}H NMR** (400 MHz, DMSO-d_6): δ 12.54 (s, 1H), 7.58 (d, J=8.5 Hz, 2H), 7.41 (d, J=8.5 Hz, 2H), 5.38-5.33 (m, 1H), 5.19-5.14 (m, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 177.8, 162.2, 135.3, 133.5, 131.9, 130.7, 128.9, 97.9. **HRMS** (ESI) m/z calcd. for ($C_{10}H_7ClN_2OS$, M+H): 239.0040, found: (M+H): 239.0037.

*3-(4-Methoxylphenyl)-5-methylidene-2-thioxoimidazolidin-4-one (**3e**) and 5-hydroxymethyl-3-(4-methoxyphenyl)-2-thioxoimidazolidin-4-one (**2e**).* From L-serine **1** (0.12 g, 1.1 mmol) and 4-methoxyphenyl isothiocyanate (0.2 g, 1.21 mmol) (with 30 ml of added water before acidification with HCl) after 3 days a mixture of **2e** (0.11 g, 39%) and **3e** (0.03 g, 11%) was obtained. A 0.1 g sample of this mixture was suspended in water (100 ml), conc. HCl (10 drops) was added, and the mixture was stirred for 7 days and then filtered to obtain 0.08 g of pale yellow solid **3e**. Overall yield 34%. (**2e**): **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.41 (s, 1H), 7.12 (d, J=8.9 Hz, 2H), 7.01 (d, J=8.9 Hz, 2H), 5.34-5.26 (m, 1H), 4.42-4.38 (m, 1H), 3.84-3.77 (m, 4H), 3.72 (dd, J_1=2.2 Hz, J_2=11.4 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 183.4, 173.2, 159.1, 129.9, 126.1, 113.9, 62.1, 59.7, 55.4. (**3e**): **^{1}H NMR** (400 MHz, DMSO-d_6): δ 12.45 (s, 1H), 7.25 (d, J=8.8 Hz, 2H), 7.03 (d, J=8.9 Hz, 2H), 5.33 (d, J=1.3 Hz, 1H), 5.14 (d, J=1.5 Hz, 1H), 3.80 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d6): δ 178.5, 162.6, 159.3, 135.3, 129.9, 125.5, 114.0, 97.6, 55.4. **HRMS** (ESI) m/z calcd. for ($C_{11}H_{10}N_2O_2S$, M+H): 235.0536, found: (M+H): 235.0536.

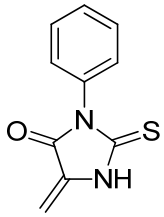
*5-Methylidene-3-(4-methylphenyl)-2-selenoxoimidazolidin-4-one (**3f**)*

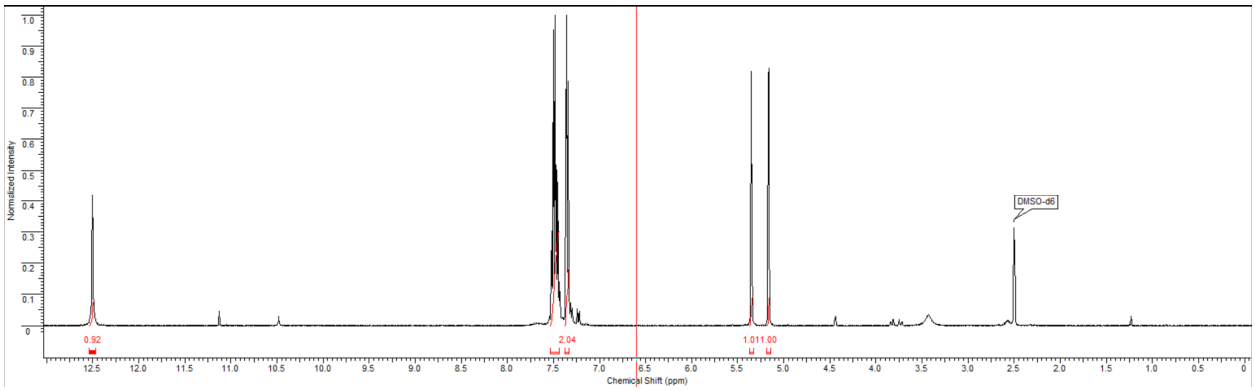
From L-serine **1** (0.15 g, 1.39 mmol) and 4-methylphenyl isoselenocyanate (0.3 g, 1.53 mmol) (with 80 ml of added water before acidification with HCl) after 2 days, 0.16 mg of **3f** was obtained as orange solid. Yield 42%. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 13.01 (s, 1H), 7.29 (d, J=8.2 Hz, 2H), 7.22 (d, J=8.3 Hz, 2H), 5.46 (d, J=1.8 Hz, 1H), 5.40 (d, J=1.9 Hz, 1H), 2.36 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 179.0, 162.0, 138.5, 135.9, 131.2, 129.3, 128.7, 99.0, 20.8. **HRMS** (ESI) m/z calcd. for ($C_{11}H_{10}N_2OSe$, M+H): 267.0031, found: (M+H): 267.0029.

Compound **2a**


O
N
S
NH
OH
Normalized Intensity
0.20
0.15
0.10
0.05
0
0.94
1.98
1.00
1.00
1.01
DMSO-d6
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

Compound **3a**


O
N
S
NH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DMSO-d6
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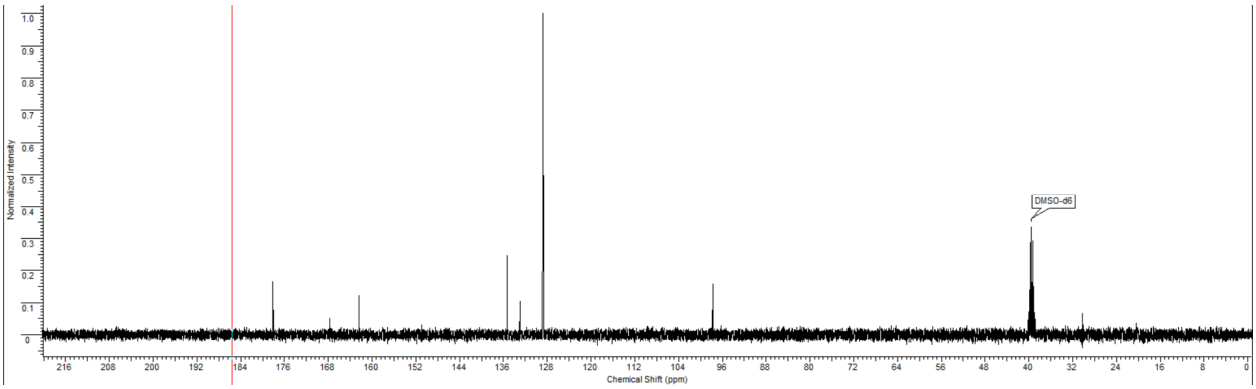
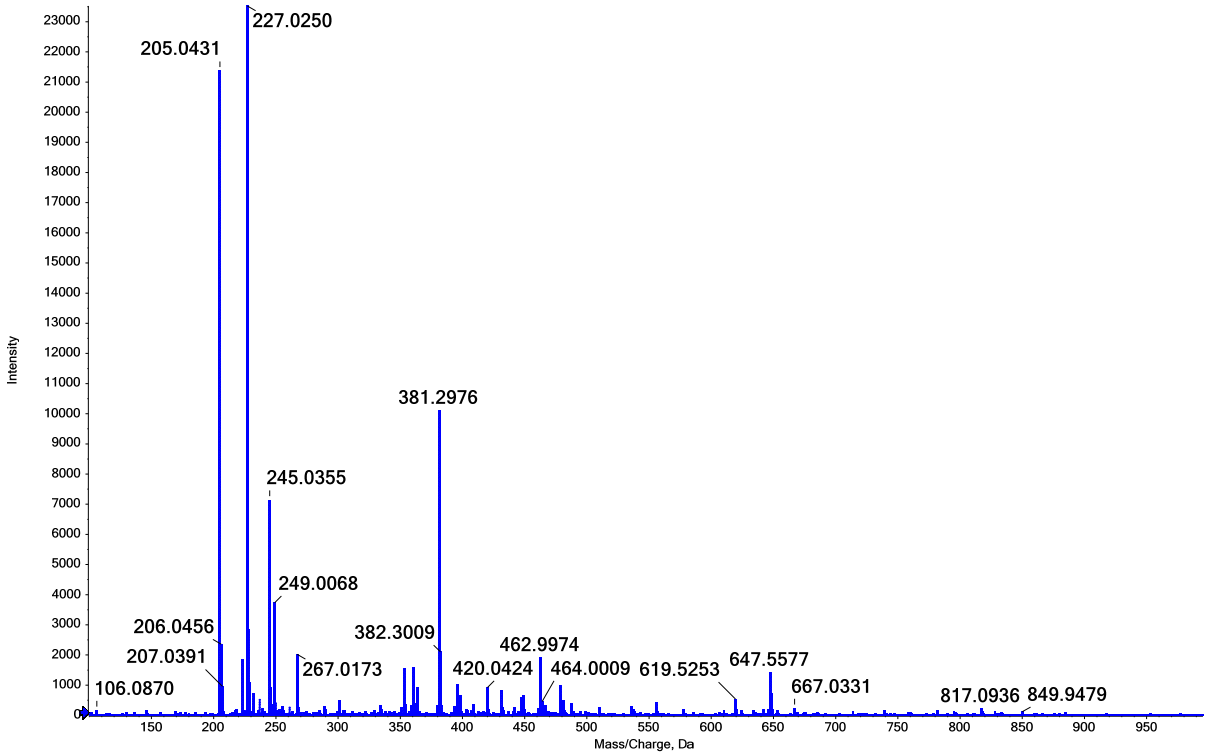
2.04
1.011.00
Chemical Shift (ppm)


Normalized Intensity
DMSO-d6
Chemical Shift (ppm)


Intensity
227.0250
205.0431
381.2976
245.0355
249.0068
206.0456
207.0391
106.0870
382.3009
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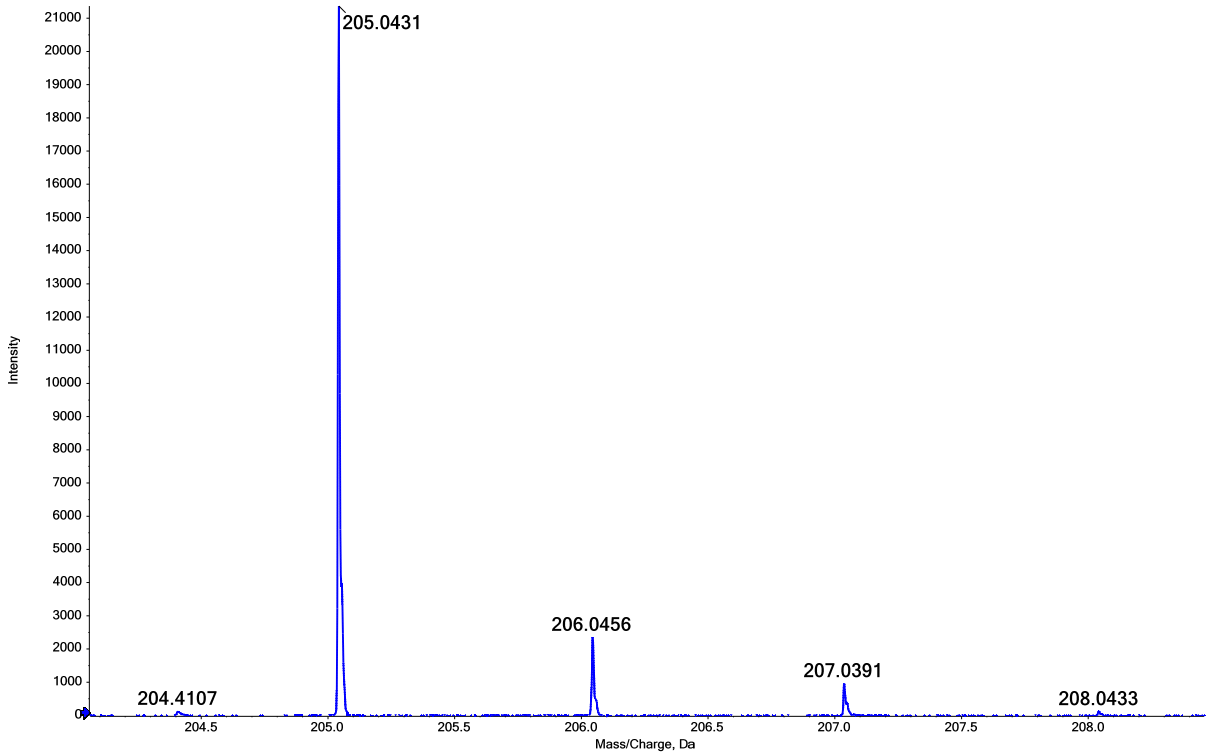
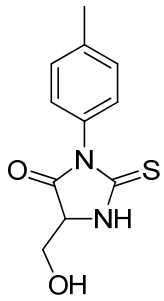
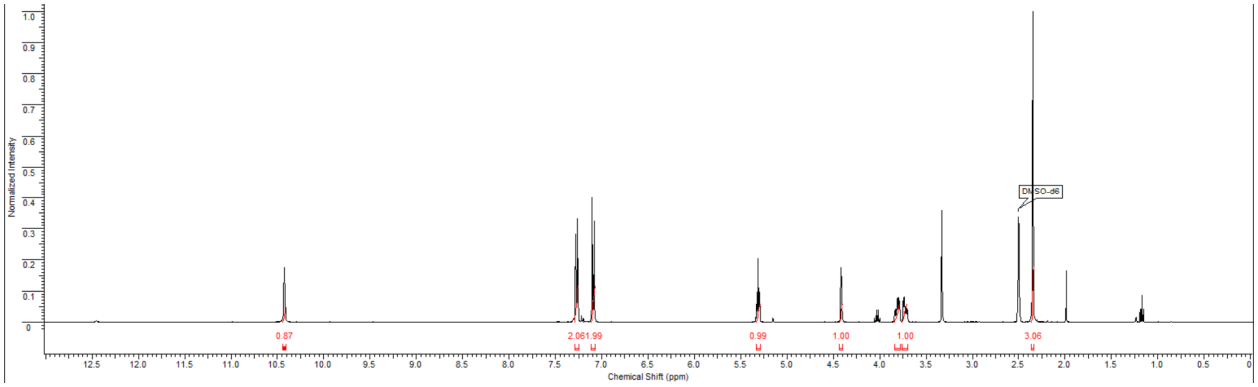
667.0331
817.0936
849.9479
Mass/Charge, Da


205.0431
206.0456
207.0391
204.4107
208.0433
Intensity
Mass/Charge, Da

Compound **2b**


O
N
S
NH
OH


Normalized Intensity
DMSO-d6
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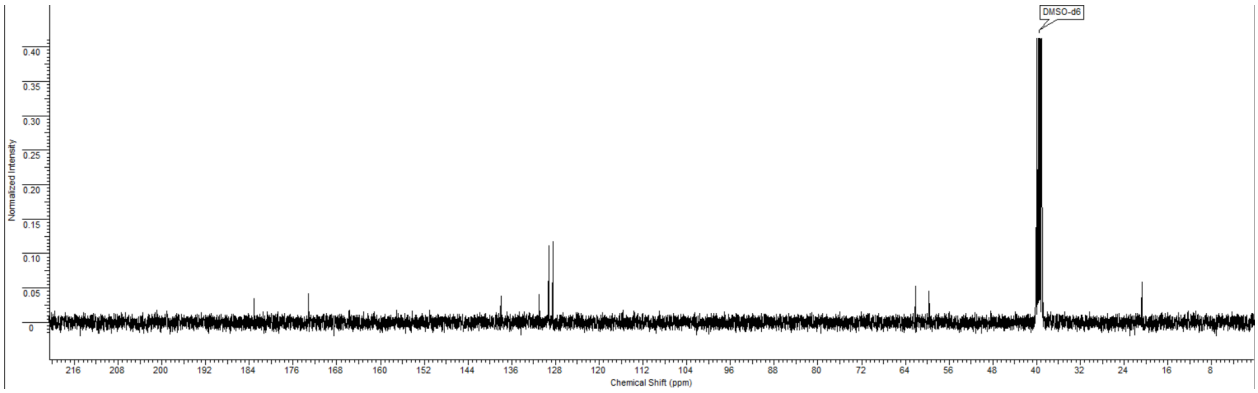
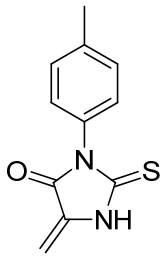
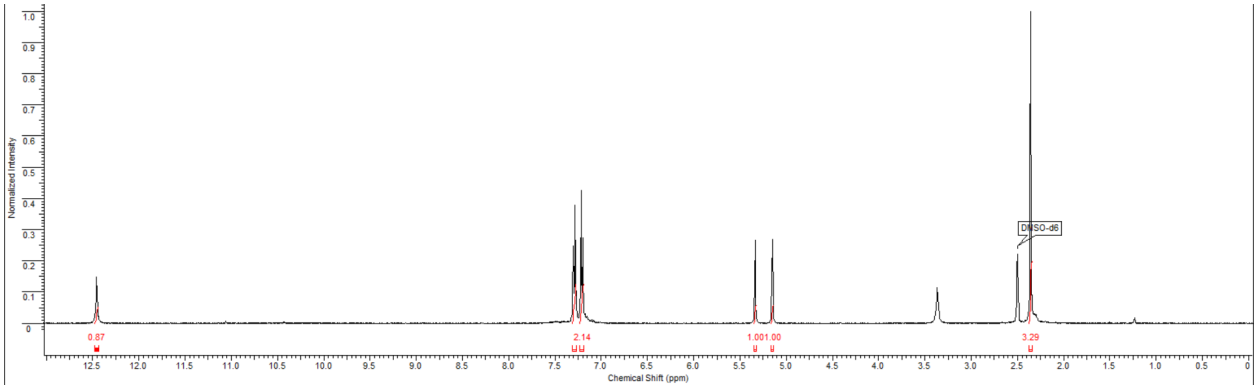
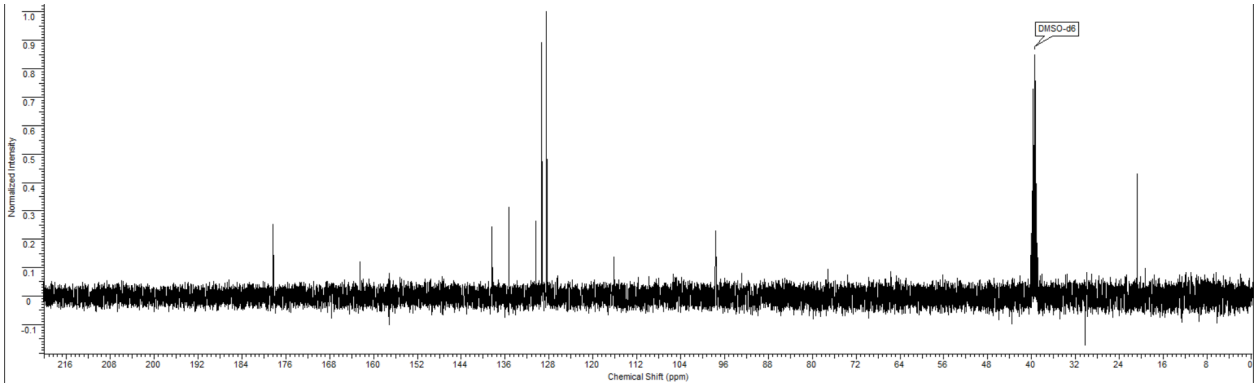
2.06
1.99
0.99
1.00
1.00
3.06
Chemical Shift (ppm)


Normalized Intensity
DMSO-d6
Chemical Shift (ppm)

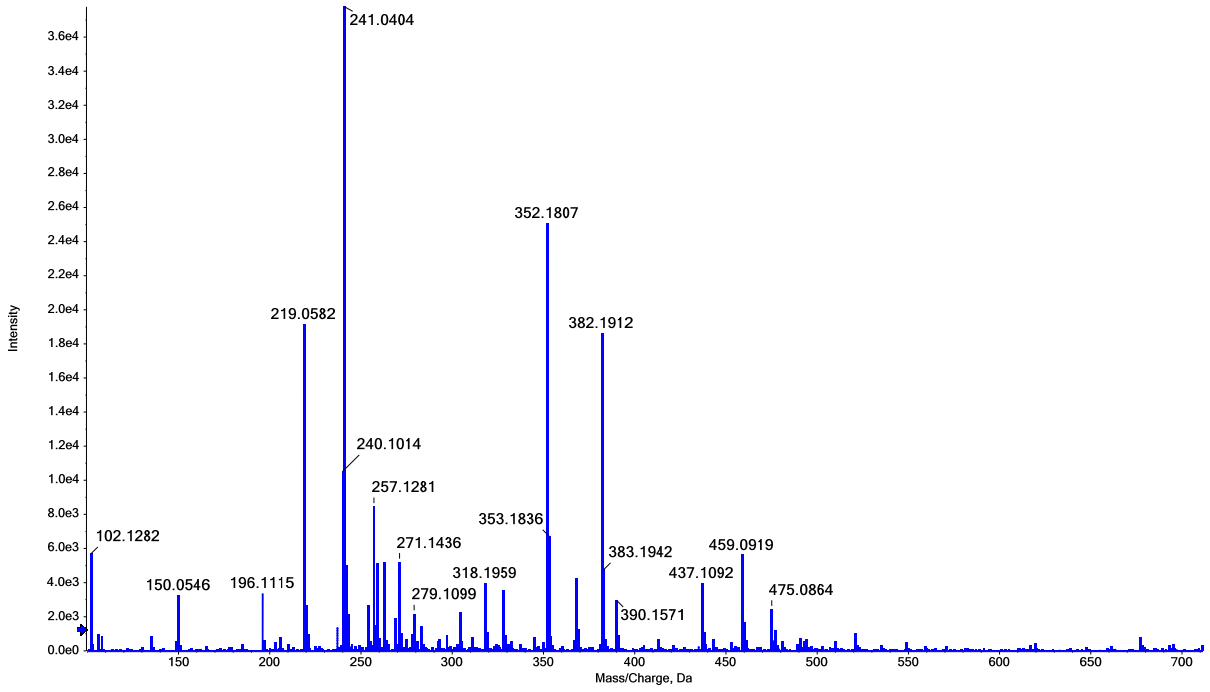
Compound **3b**

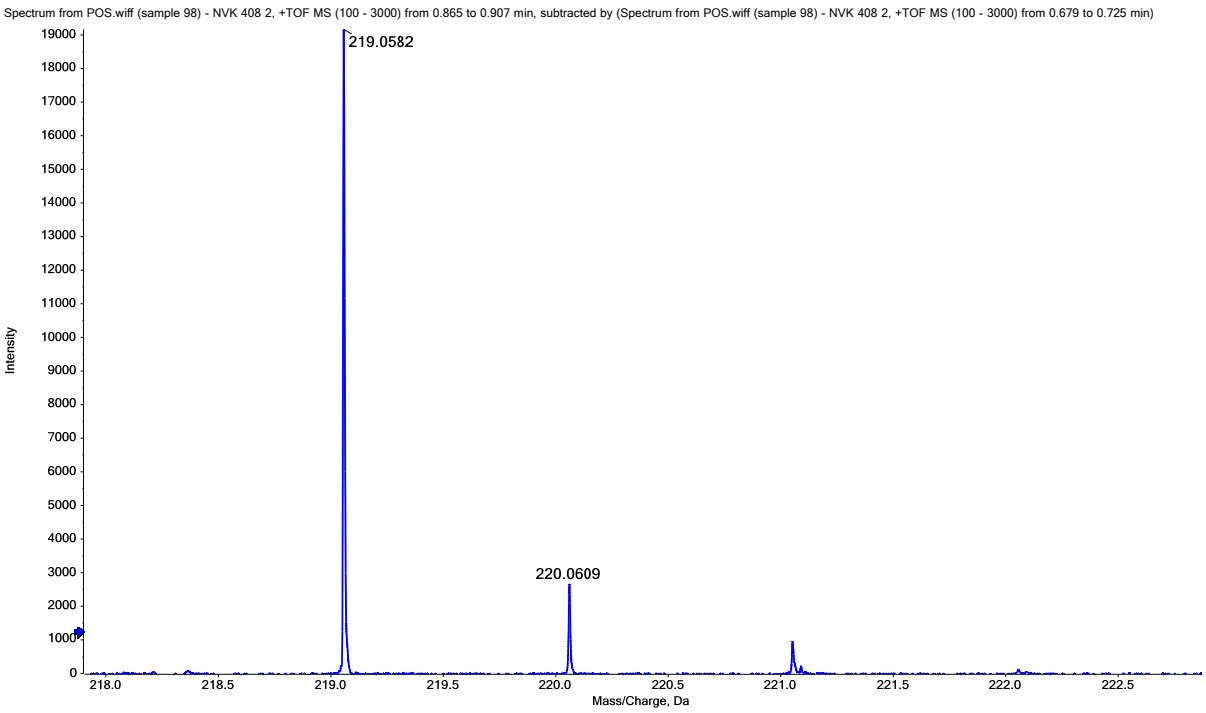




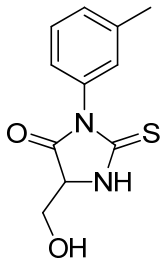


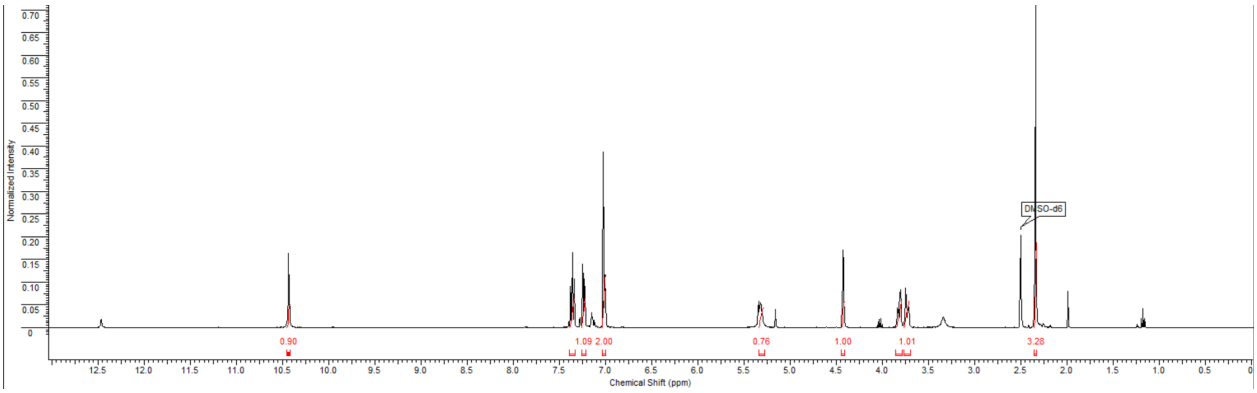
Spectrum from POS.wiff (sample 98) - NVK 408 2, +TOF MS (100 - 3000) from 0.865 to 0.907 min, subtracted by (Spectrum from POS.wiff (sample 98) - NVK 408 2, +TOF MS (100 - 3000) from 0.679 to 0.725 min)

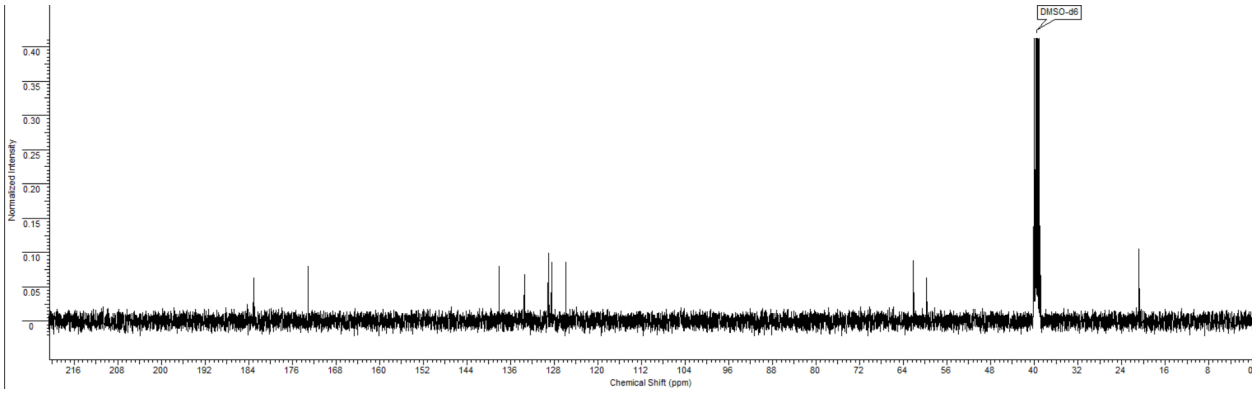



Spectrum from POS.wiff (sample 98) - NVK 408 2, +TOF MS (100 - 3000) from 0.865 to 0.907 min, subtracted by (Spectrum from POS.wiff (sample 98) - NVK 408 2, +TOF MS (100 - 3000) from 0.679 to 0.725 min)
Intensity
Mass/Charge, Da
219.0582
220.0609

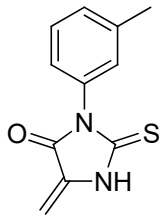
Compound **2c**

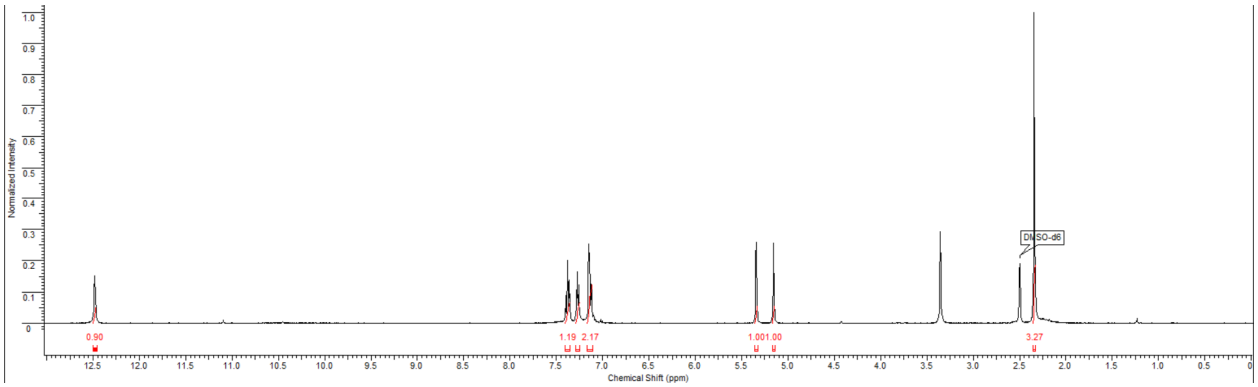

O
N
S
NH
OH

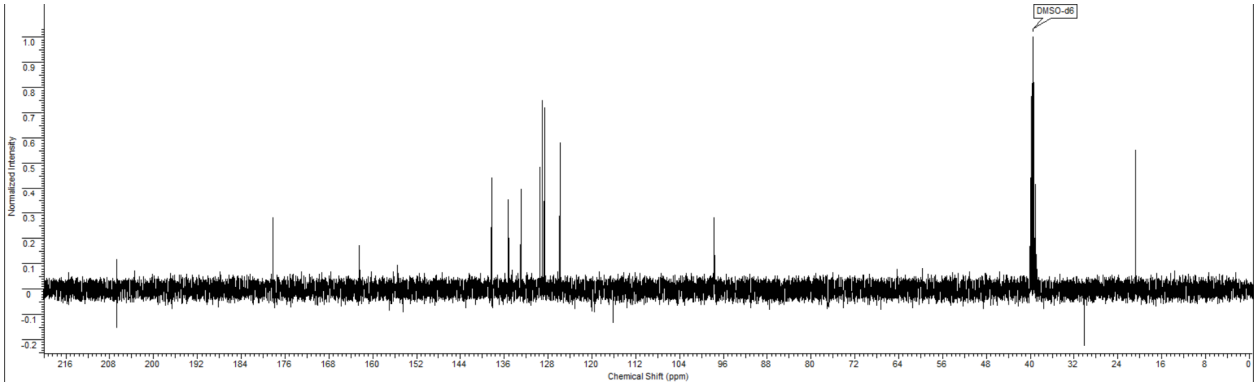

Normalized Intensity
DMSO-d6
0.90
1.09
2.00
0.76
1.00
1.01
3.28
Chemical Shift (ppm)


Normalized Intensity
DMSO-d6
Chemical Shift (ppm)

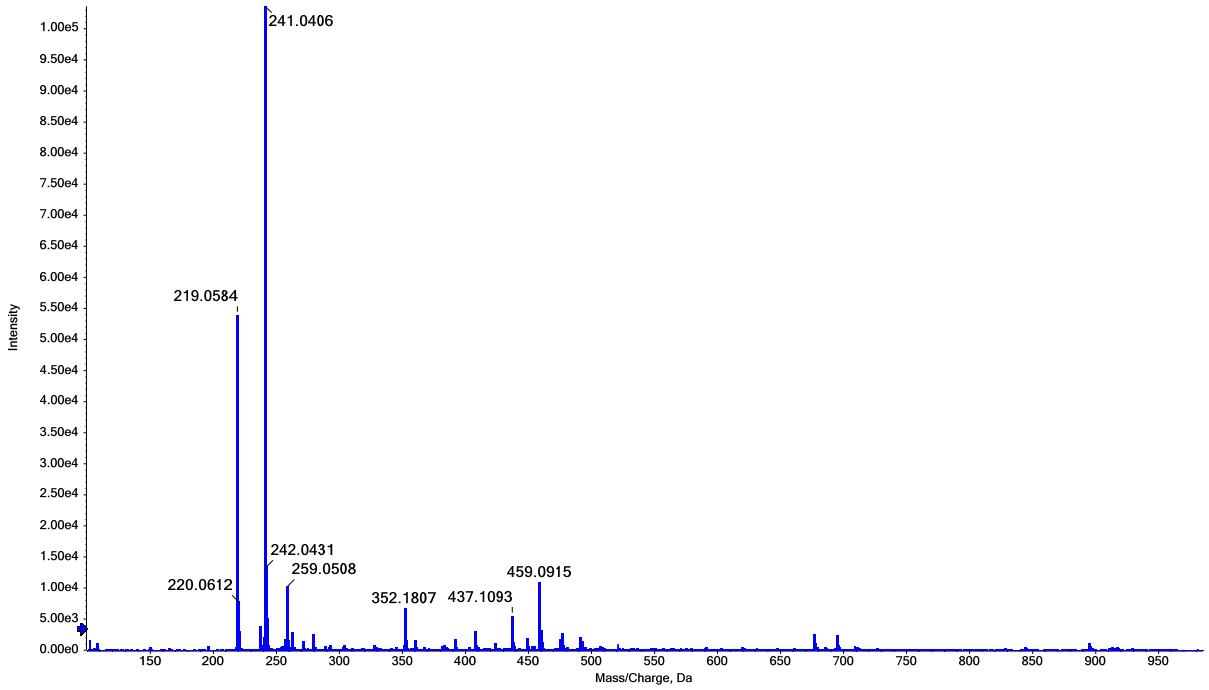
Compound **3c**

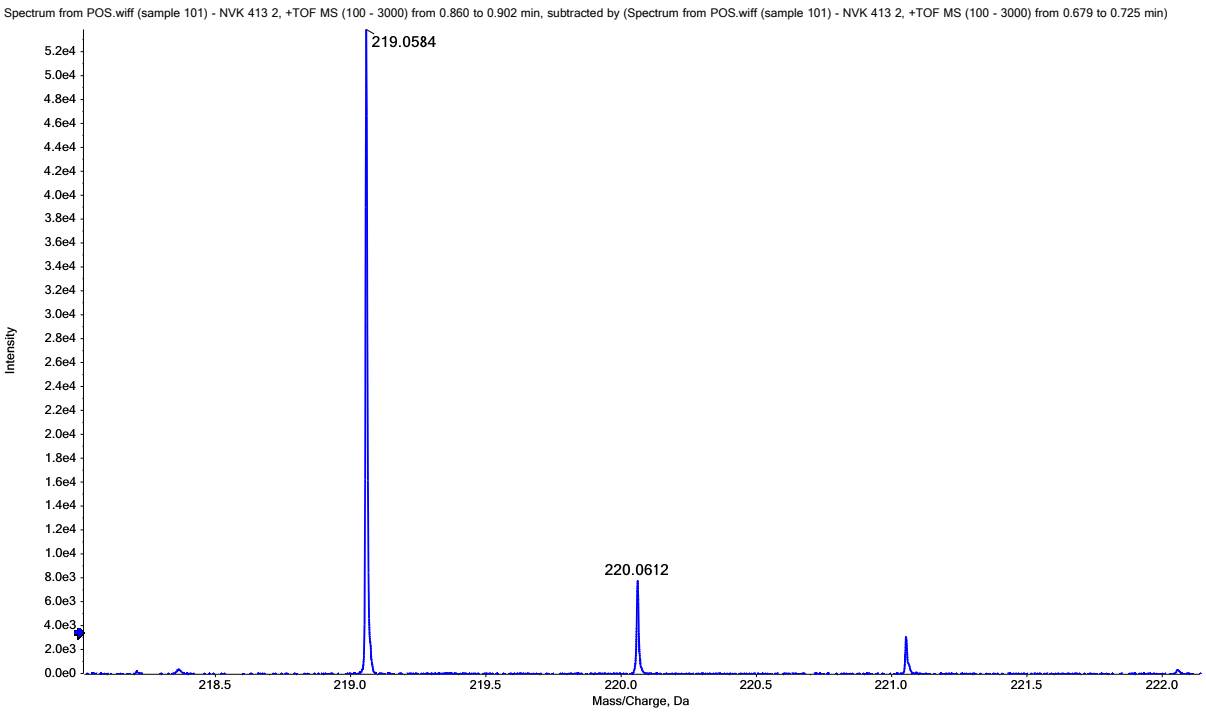




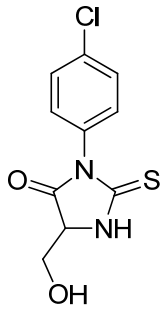


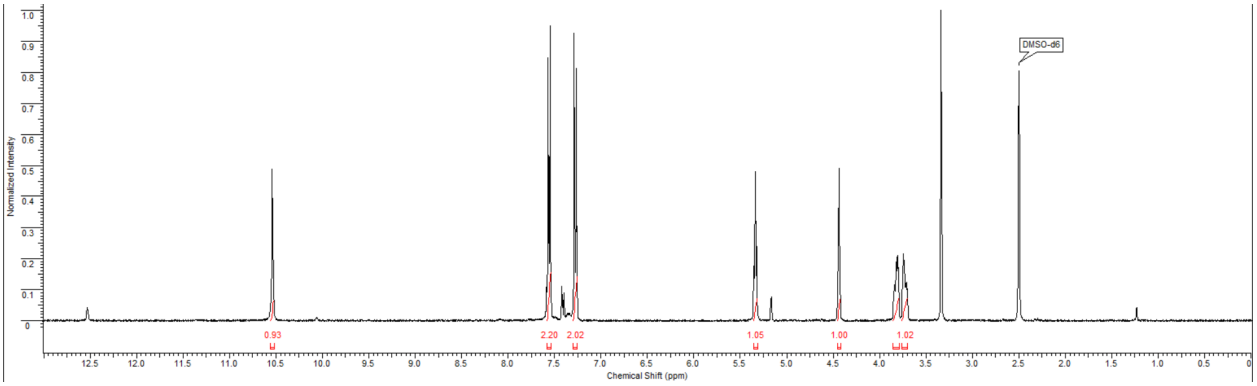
Spectrum from POS.wiff (sample 101) - NVK 413 2, +TOF MS (100 - 3000) from 0.860 to 0.902 min, subtracted by (Spectrum from POS.wiff (sample 101) - NVK 413 2, +TOF MS (100 - 3000) from 0.679 to 0.725 min)



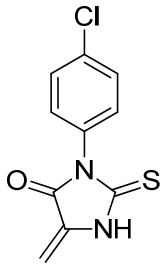

Spectrum from POS.wiff (sample 101) - NVK 413 2, +TOF MS (100 - 3000) from 0.860 to 0.902 min, subtracted by (Spectrum from POS.wiff (sample 101) - NVK 413 2, +TOF MS (100 - 3000) from 0.679 to 0.725 min)
219.0584
220.0612
Intensity
Mass/Charge, Da
5.2e4
5.0e4
4.8e4
4.6e4
4.4e4
4.2e4
4.0e4
3.8e4
3.6e4
3.4e4
3.2e4
3.0e4
2.8e4
2.6e4
2.4e4
2.2e4
2.0e4
1.8e4
1.6e4
1.4e4
1.2e4
1.0e4
8.0e3
6.0e3
4.0e3
2.0e3
0.0e0
218.5
219.0
219.5
220.0
220.5
221.0
221.5
222.0

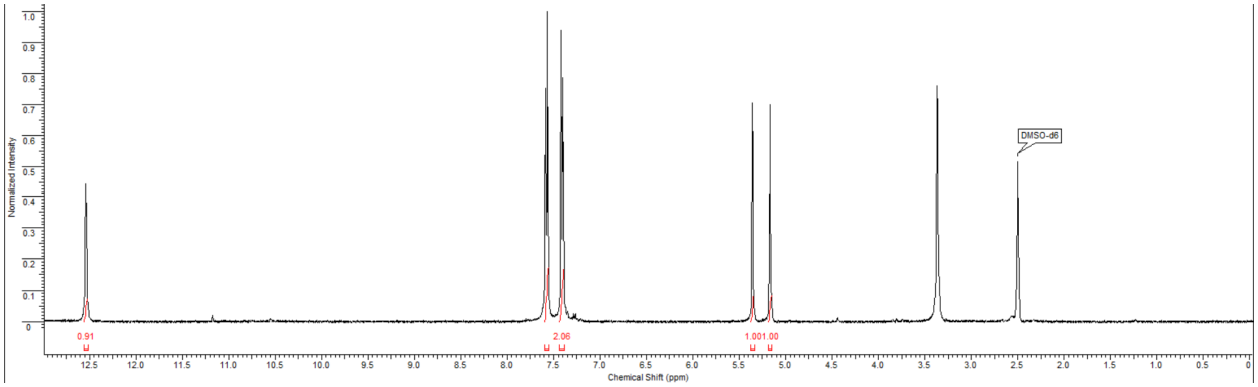
Compound **2d**

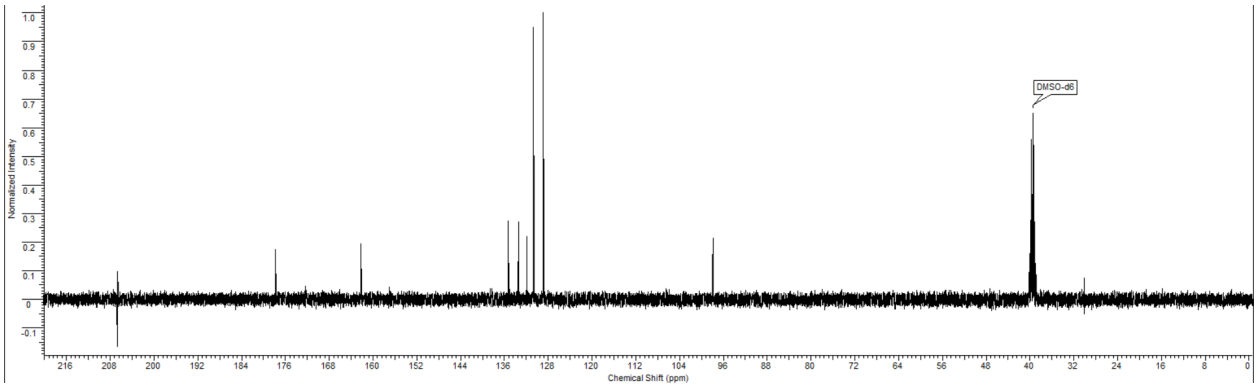

Cl
O
N
S
NH
OH


DMSO-d6
Normalized Intensity
Chemical Shift (ppm)
0.93
2.20
2.02
1.05
1.00
1.02

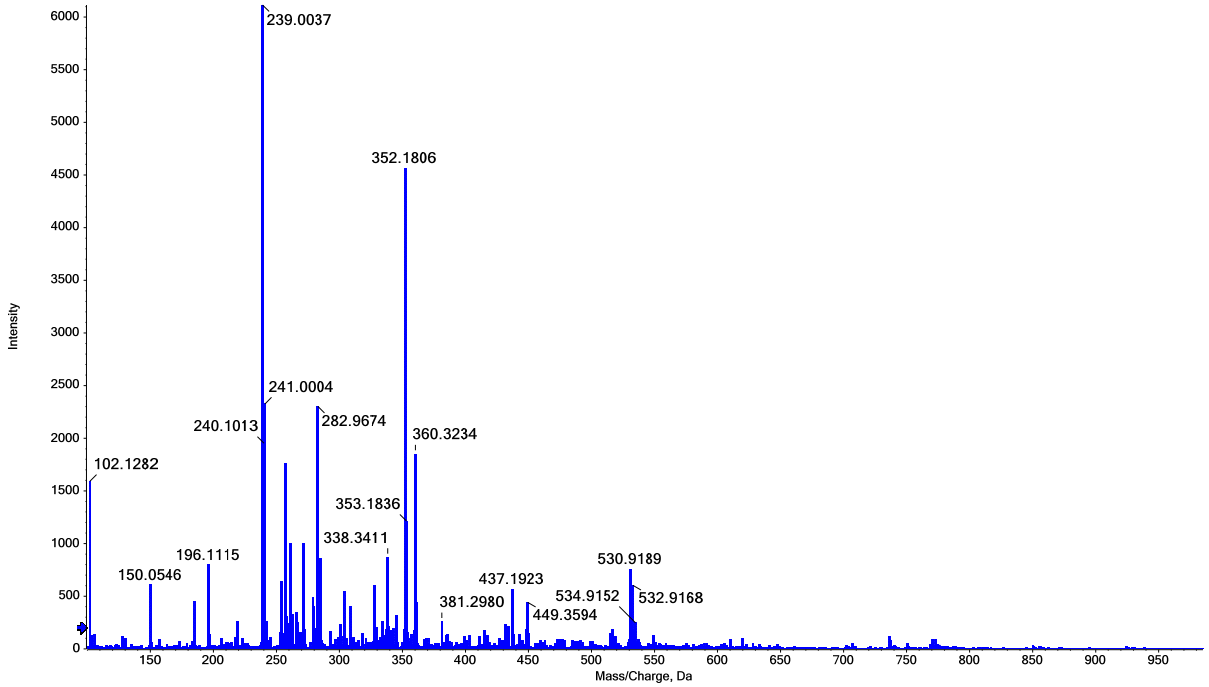
Compound **3d**

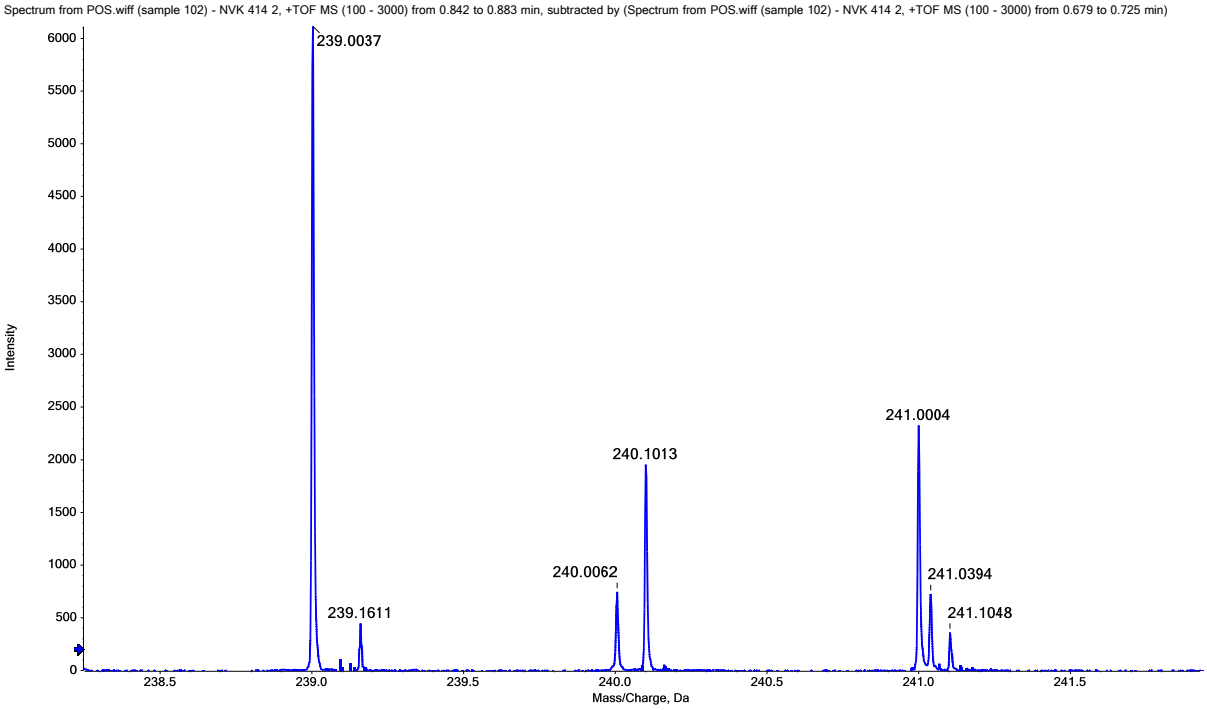




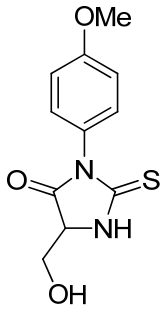


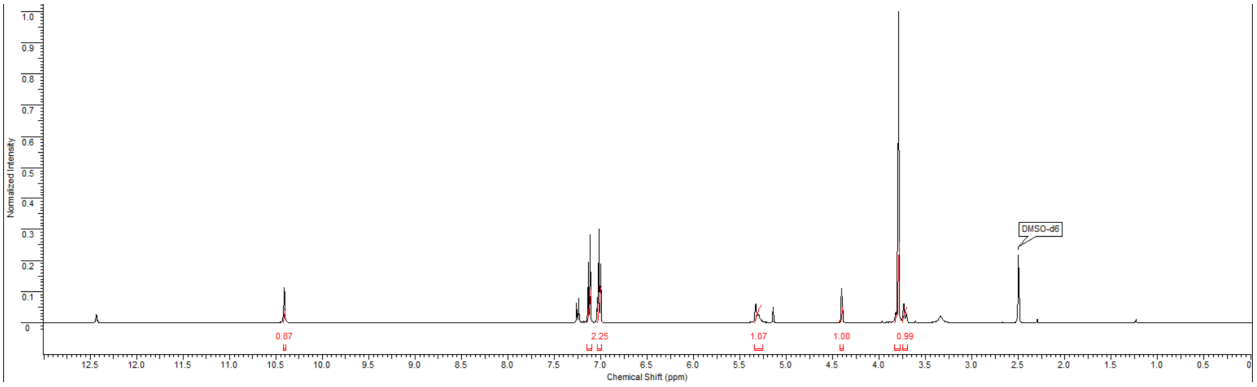
Spectrum from POS.wiff (sample 102) - NVK 414 2, +TOF MS (100 - 3000) from 0.842 to 0.883 min, subtracted by (Spectrum from POS.wiff (sample 102) - NVK 414 2, +TOF MS (100 - 3000) from 0.679 to 0.725 min)

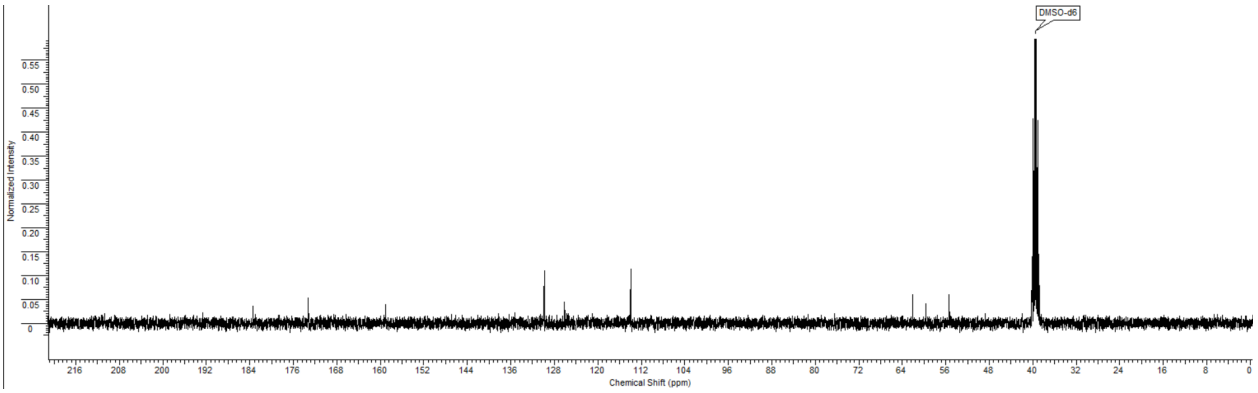



Spectrum from POS.wiff (sample 102) - NVK 414 2, +TOF MS (100 - 3000) from 0.842 to 0.883 min, subtracted by (Spectrum from POS.wiff (sample 102) - NVK 414 2, +TOF MS (100 - 3000) from 0.679 to 0.725 min)
Intensity
Mass/Charge, Da
239.0037
239.1611
240.0062
240.1013
241.0004
241.0394
241.1048

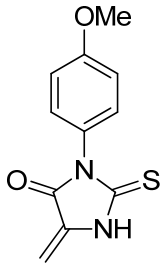
Compound **2e**

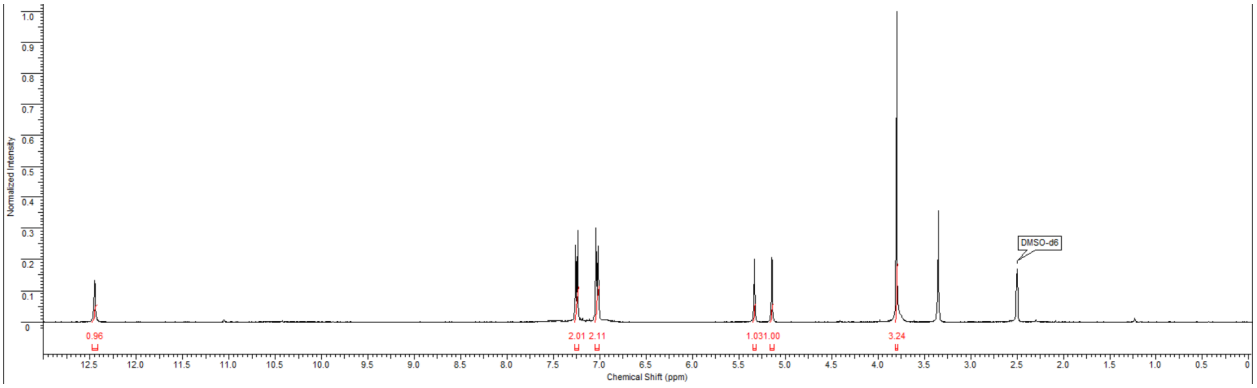

OMe
O
N
S
NH
OH

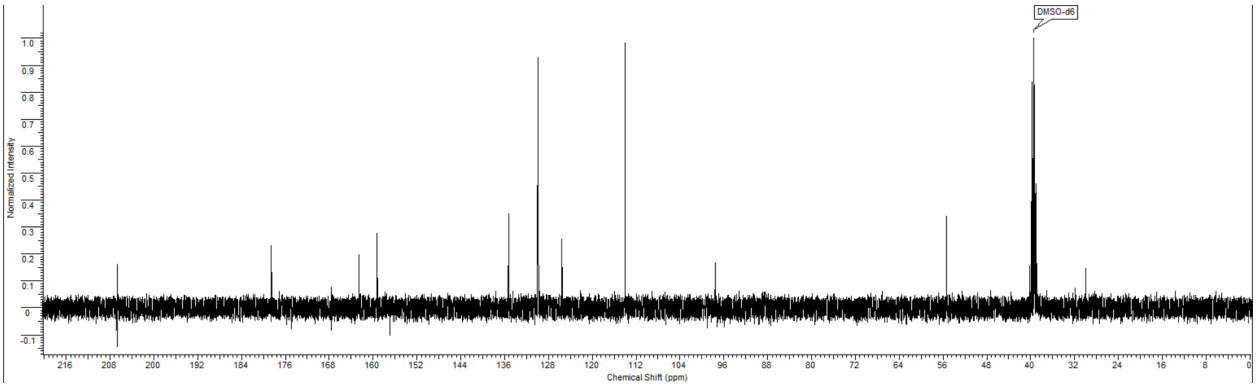

Normalized Intensity
DMSO-d6
0.87
2.25
1.07
1.00
0.99
Chemical Shift (ppm)


Normalized Intensity
DMSO-d6
Chemical Shift (ppm)

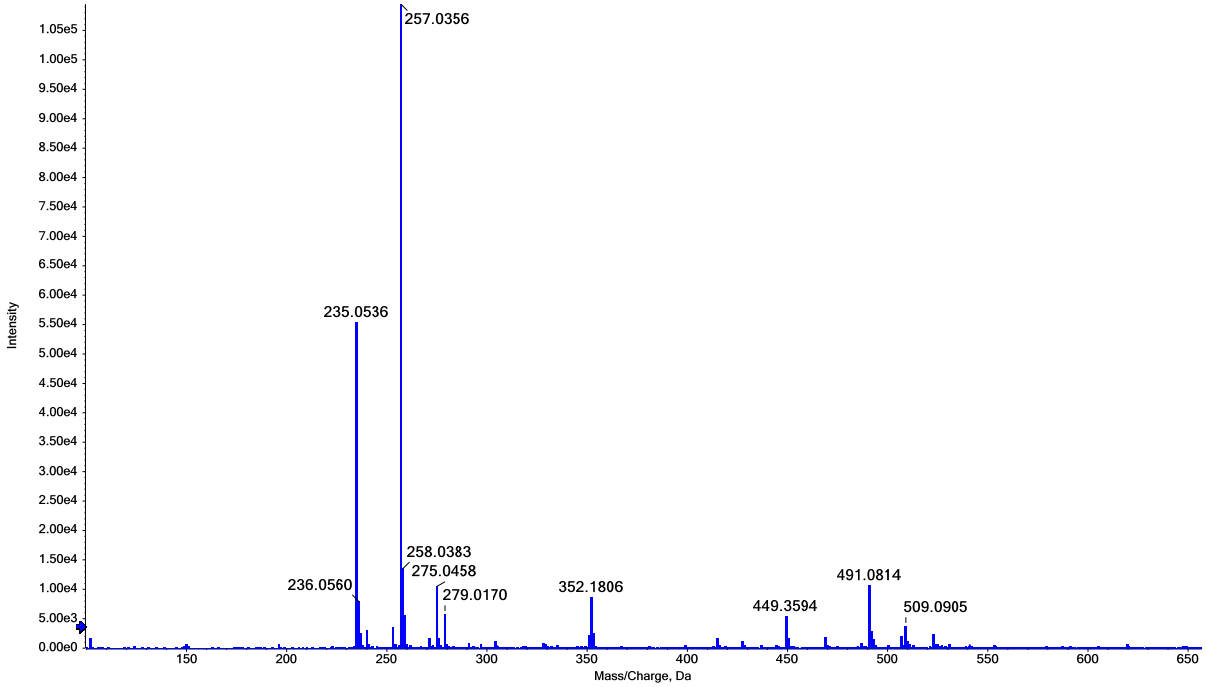
Compound **3e**

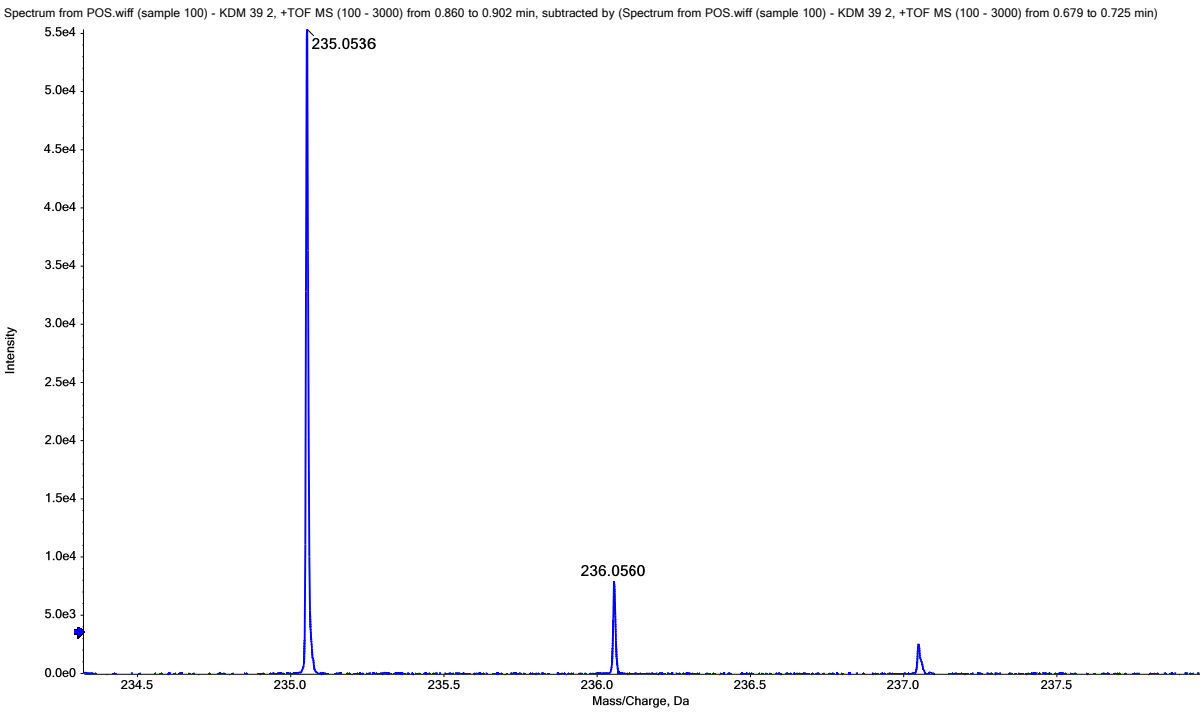




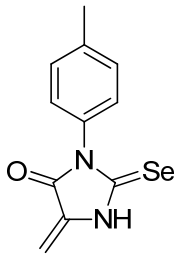


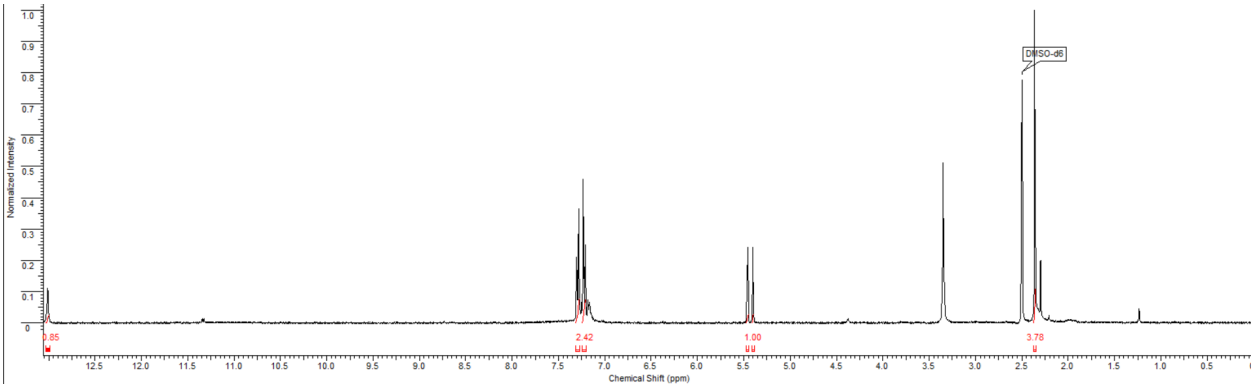
Spectrum from POS.wiff (sample 100) - KDM 39 2, +TOF MS (100 - 3000) from 0.860 to 0.902 min, subtracted by (Spectrum from POS.wiff (sample 100) - KDM 39 2, +TOF MS (100 - 3000) from 0.679 to 0.725 min)

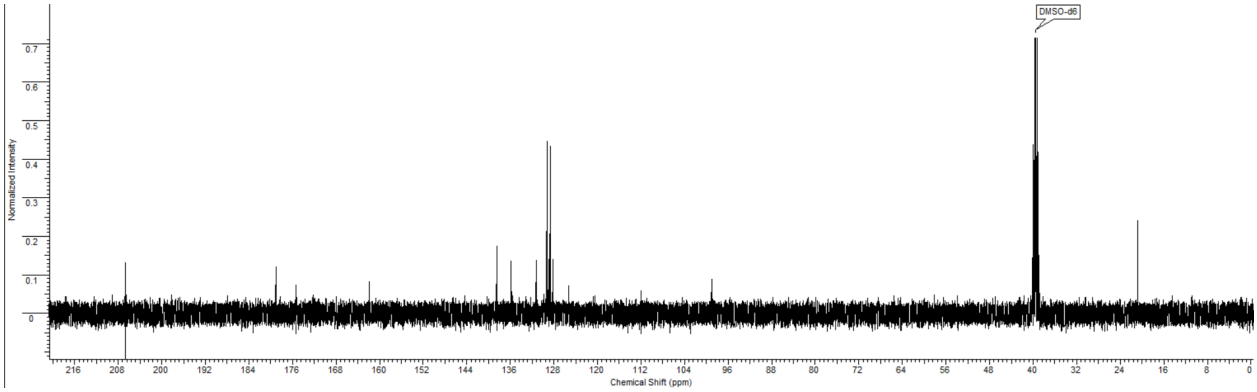



Spectrum from POS.wiff (sample 100) - KDM 39 2, +TOF MS (100 - 3000) from 0.860 to 0.902 min, subtracted by (Spectrum from POS.wiff (sample 100) - KDM 39 2, +TOF MS (100 - 3000) from 0.679 to 0.725 min)
Intensity
5.5e4
5.0e4
4.5e4
4.0e4
3.5e4
3.0e4
2.5e4
2.0e4
1.5e4
1.0e4
5.0e3
0.0e0
235.0536
236.0560
234.5
235.0
235.5
236.0
236.5
237.0
237.5
Mass/Charge, Da

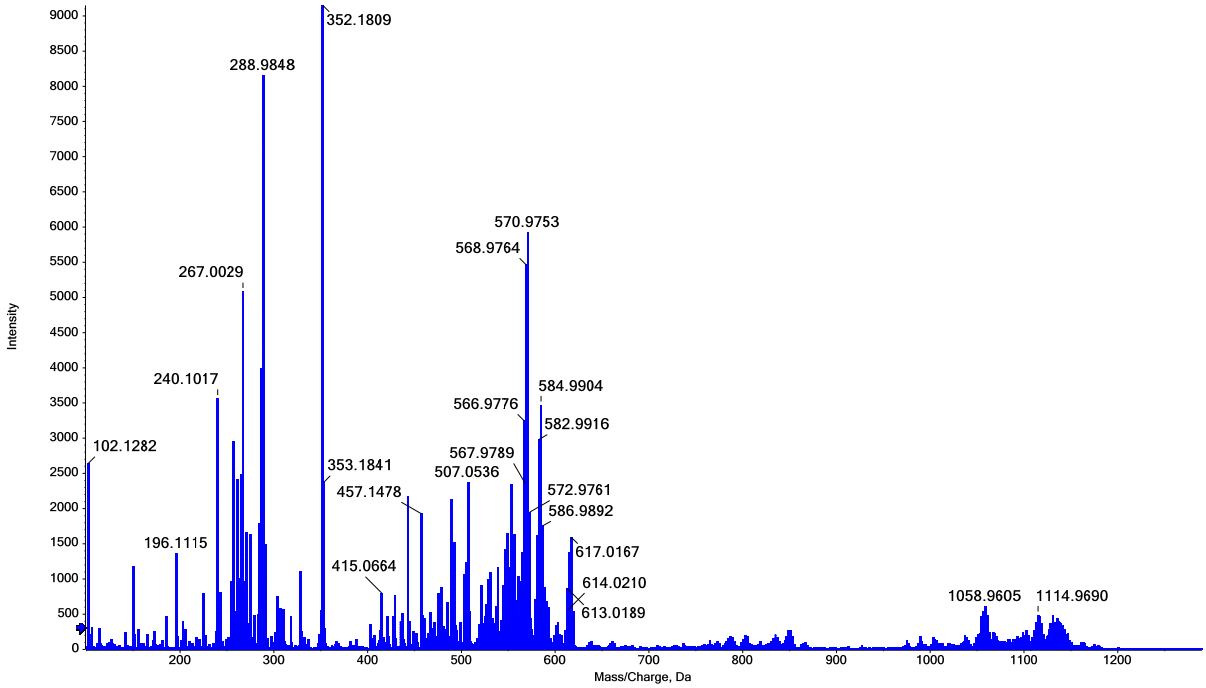
Compound **3f**

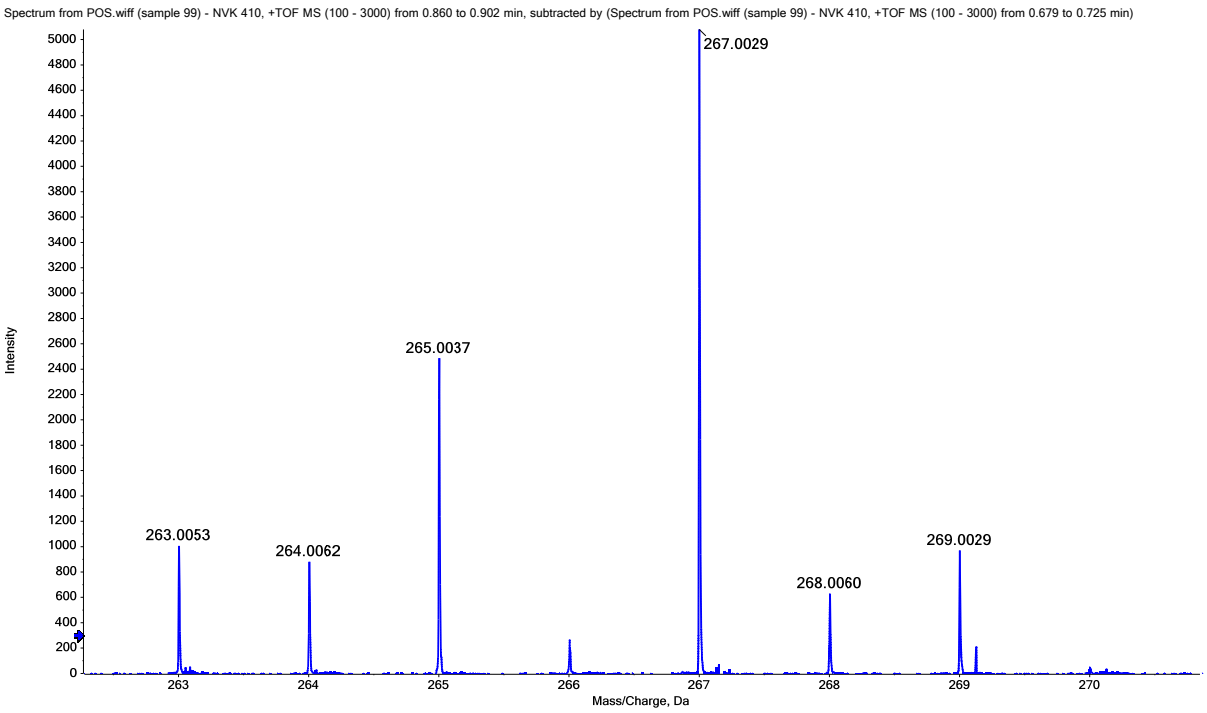






Spectrum from POS.wiff (sample 99) - NVK 410, +TOF MS (100 - 3000) from 0.860 to 0.902 min, subtracted by (Spectrum from POS.wiff (sample 99) - NVK 410, +TOF MS (100 - 3000) from 0.679 to 0.725 min)




Spectrum from POS.wiff (sample 99) - NVK 410, +TOF MS (100 - 3000) from 0.860 to 0.902 min, subtracted by (Spectrum from POS.wiff (sample 99) - NVK 410, +TOF MS (100 - 3000) from 0.679 to 0.725 min)
Intensity
Mass/Charge, Da
263.0053
264.0062
265.0037
267.0029
268.0060
269.0029