

A convenient synthesis of 3-aryl-5-methylidene-2-thiohydantoins

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EXPERIMENTAL SECTION

All common reagents were purchased from commercial suppliers and used as received. The melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (400 MHz for ^1H , 100 MHz 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 $^\circ\text{C}$.

General Procedure for the Synthesis of methylidenethiohydantoins **7** (**7a** as an Example)

5-Methylidene-3-phenyl-2-thioxoimidazolidin-4-one (7a). The β -morpholinoalanine **2a** (2.45 g, 10 mmol) was dissolved in a pyridine-water mixture (20 + 10 ml), then pH of the solution was brought to 9-10 with 3 N NaOH (~7 ml), and the flask contents were heated to 40 $^\circ\text{C}$. Then phenyl isothiocyanate (1.56 g, 10 mmol) and then 3N NaOH (~3 ml) to maintain the required pH was added. The resulting mixture was stirred for 25 min, and pyridine was removed by extraction with toluene (3 \times 20 ml). The aqueous phase was acidified with 10% hydrochloric acid to pH 1-2, the resulting suspension was filtered off and discarded, and the filtrate was refluxed for 1 hour. The mixture was cooled to room temperature, the formed precipitate was filtered off, washed with water and dried in air. An additional portion of the product can be obtained from the mother liquor when it is concentrated to 1/2 volume. The product is a white of pale orange crystalline solid. Yield 1.04 g, 51%. ^1H NMR (400 MHz, DMSO- d_6): δ 12.50 (s, 1H), 7.53-7.44 (m, 3H), 7.37-7.32 (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 178.2, 162.5, 135.4, 133.1, 128.9, 128.8, 128.7, 97.8. HRMS (ESI-) m/z calcd. for ($\text{C}_{10}\text{H}_8\text{N}_2\text{OS}$, M-H): 203.0285, found: (M-H): 203.0289.

3-(2-Fluorophenyl)-5-methylidene-2-thioxoimidazolidin-4-one (7b). From **2a** (2.45 g, 10 mmol) and 2-fluorophenyl isothiocyanate (1.53 g, 10 mmol) compound **7b** (1.65 g, 73%) was obtained as a white of pale orange crystalline solid. ^1H NMR (400 MHz, DMSO- d_6): δ 12.72 (s, 1H), 7.56 (m, 1H), 7.50 (td, $J = 7.7, 1.7$ Hz, 1H), 7.43 (m, 1H), 7.36 (td, $J = 7.7, 1.7$ Hz, 1H), 5.42 (d, $J=2.0$ Hz, 1H), 5.25 (d, $J=2.0$ Hz, 1H). ^{13}C NMR (101 MHz, DMSO- d_6): δ 177.3, 162.0, 157.6 (d, $J_{\text{CF}}=250.1$ Hz, 1C), 135.2, 131.8 (d, $J_{\text{CF}}=8.1$ Hz, 1C), 131.6, 125.0 (d, $J_{\text{CF}}=3.7$ Hz, 1C), 120.5 (d, $J_{\text{CF}}=12.7$ Hz, 1C), 116.3 (d, $J_{\text{CF}}=19.4$ Hz, 1C), 99.0. HRMS (ESI-) m/z calcd. for ($\text{C}_{10}\text{H}_7\text{FN}_2\text{OS}$, M-H): 221.0190, found: (M-H): 221.0190.

3-(3-Fluorophenyl)-5-methylidene-2-thioxoimidazolidin-4-one (7c). From **2a** (2.45 g, 10 mmol) and 3-fluorophenyl isothiocyanate (1.53 g, 10 mmol) compound **7c** (1.56 g, 56%) was obtained

as a white of pale orange crystalline solid. **¹H NMR** (400 MHz, DMSO-*d*₆): δ 12.56 (s, 1H), 7.55 (q, *J*=6.8 Hz, 1H), 7.38-7.29 (m, 2H), 7.23 (d, *J*=7.8 Hz, 1H), 5.36 (s, 1H), 5.18 (s, 1H). **¹³C NMR** (101 MHz, DMSO-*d*₆): δ 177.8, 162.2, 161.7 (d, *J*_{CF}=244.2 Hz, 1C), 135.3, 134.5 (d, *J*_{CF}=10.7 Hz, 1C), 130.4 (d, *J*_{CF}=9.0 Hz, 1C), 125.2 (d, *J*_{CF}=3.0 Hz, 1C), 116.3 (d, *J*_{CF}=23.8 Hz, 1C), 116.0 (d, *J*_{CF}=20.6 Hz, 1C), 98.0. **HRMS** (ESI-) *m/z* calcd. for (C₁₀H₇FN₂OS, M-H): 223.0336, found: (M-H): 221.0182.

3-(4-Fluorophenyl)-5-methylidene-2-thioxoimidazolidin-4-one (7d). From **2a** (2.45 g, 10 mmol) and 4-fluorophenyl isothiocyanate (1.53 g, 10 mmol) compound **7d** (1.51 g, 68%) was obtained as a white of pale orange crystalline solid. **¹H NMR** (400 MHz, DMSO-*d*₆): δ 12.51 (s, 1H), 7.45-7.39 (m, 2H), 7.37-7.31 (m, 2H), 5.35 (d, *J*=1.8 Hz, 1H), 5.16 (d, *J*=1.8 Hz, 1H). **¹³C NMR** (101 MHz, DMSO-*d*₆): δ 178.2, 162.5, 161.9 (d, *J*_{CF}=245.8 Hz, 1C), 135.3, 131.1 (d, *J*_{CF}=9.0 Hz, 1C), 129.3 (d, *J*_{CF}=3.0 Hz, 1C), 115.8 (*J*_{CF}=22.9 Hz, 1C), 97.9. **HRMS** (ESI-) *m/z* calcd. for (C₁₀H₇FN₂OS, M-H): 221.0190, found: (M-H): 221.0189.

3-(2-Chlorophenyl)-5-methylidene-2-thioxoimidazolidin-4-one (7e). From **2a** (2.45 g, 10 mmol) and 2-chlorophenyl isothiocyanate (1.70 g, 10 mmol) compound **7e** (1.56 g, 66%) was obtained as a white of pale orange crystalline solid. **¹H NMR** (400 MHz, DMSO-*d*₆): δ 12.68 (s, 1H), 7.65 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.54-7.46 (m, 3H), 5.40 (d, *J*=1.8 Hz, 1H), 5.23 (d, *J*=2.0 Hz, 1H). **¹³C NMR** (101 MHz, DMSO-*d*₆): δ 177.3, 161.8, 135.2, 132.2, 131.9, 131.1, 130.8, 129.9, 128.1, 98.7. **HRMS** (ESI-) *m/z* calcd. for (C₁₀H₇ClN₂OS, M-H): 236.9895, found: (M-H): 236.9901.

3-(3-Chlorophenyl)-5-methylidene-2-thioxoimidazolidin-4-one (7f). From **2a** (2.45 g, 10 mmol) and 3-chlorophenyl isothiocyanate (1.70 g, 10 mmol) compound **7f** (1.35 g, 57%) was obtained as a white of pale orange crystalline solid. **¹H NMR** (400 MHz, DMSO-*d*₆): δ 12.55 (s, 1H), 7.55-7.52 (m, 3H), 7.37, (m, 1H), 5.36 (d, *J*=1.8 Hz, 1H), 5.23 (d, *J*=1.9 Hz, 1H). **¹³C NMR** (101 MHz, DMSO-*d*₆): δ 177.8, 162.3, 135.3, 134.4, 132.9, 130.5, 129.0, 128.9, 127.8, 98.1. **HRMS** (ESI-) *m/z* calcd. for (C₁₀H₇ClN₂OS, M-H): 236.9895, found: (M-H): 236.9903.

3-(4-Chlorophenyl)-5-methylidene-2-thioxoimidazolidin-4-one (7g). From **2a** (2.45 g, 10 mmol) and 4-chlorophenyl isothiocyanate (1.70 g, 10 mmol) compound **7g** (1.42 g, 60%) was obtained as a white of pale orange crystalline solid. **¹H NMR** (400 MHz, DMSO-*d*₆): δ 12.54 (s, 1H), 7.58 (d, *J*=8.6 Hz, 2H), 7.41 (d, *J*=8.6 Hz, 2H), 5.36 (d, *J*=1.8 Hz, 1H), 5.17 (d, *J*=1.8 Hz, 1H). **¹³C NMR** (101 MHz, DMSO-*d*₆): δ 177.9, 162.3, 135.3, 133.5, 131.9, 130.7, 128.9, 98.0. **HRMS** (ESI-) *m/z* calcd. for (C₁₀H₇ClN₂OS, M-H): 236.9895, found: (M-H): 236.9890.

3-(3-Chloro-4-fluorophenyl)-5-methylidene-2-thioxoimidazolidin-4-one (7h). From **2a** (2.45 g, 10 mmol) and 3-chloro-4-fluorophenyl isothiocyanate (1.88 g, 10 mmol) compound **7h** (1.43 g, 56%) was obtained as a white of pale orange crystalline solid. **¹H NMR** (400 MHz, DMSO-*d*₆): δ 12.59 (s, 1H), 7.73 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.57 (t, *J*=9.0 Hz, 1H), 7.44 (m, 1H), 5.37 (d, *J*=1.7 Hz, 1H), 5.19 (d, *J*=1.8 Hz, 1H). **¹³C NMR** (101 MHz, DMSO-*d*₆): δ 177.8, 162.2, 157.2 (d, *J*_{CF}=248.6 Hz, 1C), 135.3, 131.3, 130.1 (d, *J*_{CF}=7.7 Hz, 1C), 125.39, 119.4 (d, *J*_{CF}=18.8 Hz, 1C), 117.1 (d, *J*_{CF}=22.3 Hz, 1C), 98.1. **HRMS** (ESI-) *m/z* calcd. for (C₁₀H₆ClFN₂OS, M-H): 254.9801, found: (M-H): 254.9807.

3-(3-Methylphenyl)-5-methylidene-2-thioxoimidazolidin-4-one (7i). From **2a** (2.45 g, 10 mmol) and 3-methylphenyl isothiocyanate (1.49 g, 10 mmol) compound **7i** (1.49 g, 68%) was obtained as a white of pale orange crystalline solid. **¹H NMR** (400 MHz, DMSO-*d*₆): δ 12.50 (s, 1H), 7.38 (t, *J*=7.6 Hz, 1H), 7.27 (d, *J*=7.5 Hz, 1H), 7.17-7.09 (m, 2H), 5.35 (d, *J*=1.4 Hz, 1H), 5.17 (d, *J*=1.4 Hz, 1H), 2.34 (s, 3H). **¹³C NMR** (101 MHz, DMSO-*d*₆): δ 178.2, 162.5, 138.4, 135.3,

133.0, 129.5, 129.1, 128.7, 125.9, 97.8, 20.8. **HRMS** (ESI-) m/z calcd. for (C₁₁H₁₀N₂OS, M-H): 217.0441, found: (M-H): 217.0438.

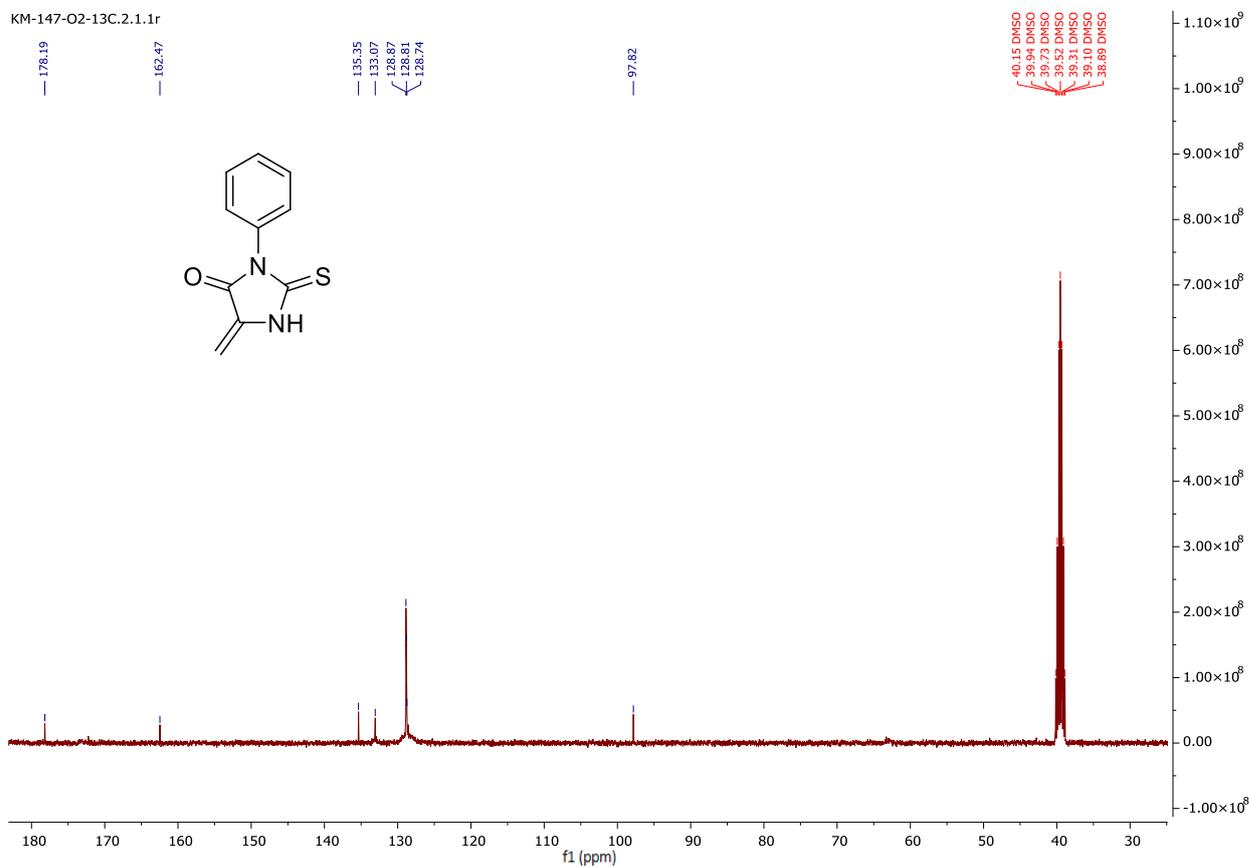
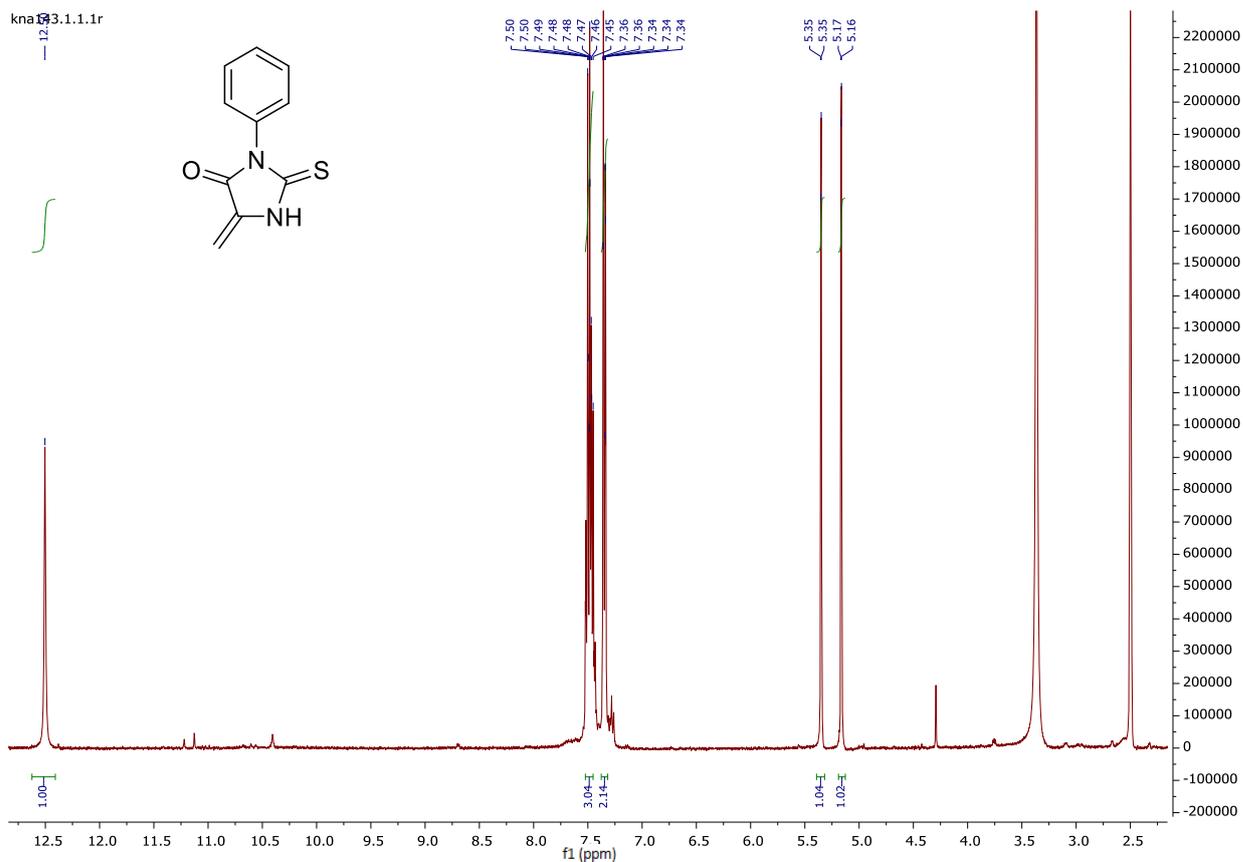
3-(4-Methylphenyl)-5-methylidene-2-thioxoimidazolidin-4-one (7j). From **2a** (2.45 g, 10 mmol) and 4-methylphenyl isothiocyanate (1.49 g, 10 mmol) compound **7j** (1.56 g, 72%) was obtained as a white of pale orange crystalline solid. **¹H NMR** (400 MHz, DMSO-d₆): δ 12.47 (s, 1H), 7.29 (d, J=8.1 Hz, 2H), 7.21 (d, J=8.1 Hz, 2H), 5.37 (s, 1H), 5.19 (s, 1H), 2.36 (s, 3H). **¹³C NMR** (101 MHz, DMSO-d₆): δ 178.3, 162.5, 138.5, 135.3, 130.4, 129.4, 128.5, 97.7, 20.8. **HRMS** (ESI-) m/z calcd. for (C₁₁H₁₀N₂OS, M-H): 217.0441, found: (M-H): 217.0447.

3-(3-Methoxyphenyl)-5-methylidene-2-thioxoimidazolidin-4-one (7k). From **2a** (2.45 g, 10 mmol) and 3-methoxyphenyl isothiocyanate (2.34 g, 10 mmol) compound **7k** (1.61 g, 69%) was obtained as a white of pale orange crystalline solid. **¹H NMR** (400 MHz, DMSO-d₆): δ 12.47 (s, 1H), 7.39 (t, J=8.1 Hz, 1H), 7.02 (dd, J= 8.3, 2.1 Hz, 1H), 6.94 (t, J=2.1 Hz, 1H), 6.90 (m, 1H), 5.33 (d, J=1.6 Hz, 1H), 5.14 (d, J=1.7 Hz, 1H), 3.75 (s, 3H). **¹³C NMR** (101 MHz, DMSO-d₆): δ 178.1, 162.4, 159.5, 135.3, 134.1, 129.6, 121.0, 114.7, 114.5, 97.8, 55.4. **HRMS** (ESI-) m/z calcd. for (C₁₁H₁₀N₂O₂S, M-H): 233.0390, found: (M-H): 233.0387.

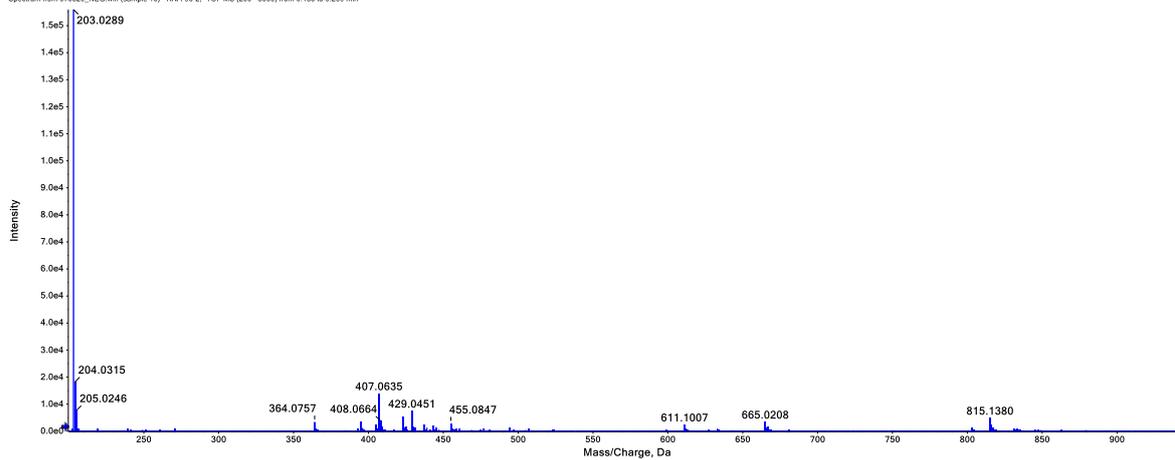
3-(4-Methoxyphenyl)-5-methylidene-2-thioxoimidazolidin-4-one (7l). From **2a** (2.45 g, 10 mmol) and 4-methoxyphenyl isothiocyanate (2.34 g, 10 mmol) compound **7l** (2.11 g, 90%) was obtained as a white of pale orange crystalline solid. **¹H NMR** (400 MHz, DMSO-d₆): δ 12.50 (s, 1H), 7.24 (d, J=8.8 Hz, 2H), 7.01 (d, J=8.9 Hz, 2H), 5.32 (d, J=1.5 Hz, 1H), 5.16 (d, J=1.6 Hz, 1H), 3.78 (s, 3H). **¹³C NMR** (101 MHz, DMSO-d₆): δ 178.5, 162.7, 159.3, 142.9, 135.4, 130.0, 126.8, 125.6, 114.1, 97.7, 55.4. **HRMS** (ESI-) m/z calcd. for (C₁₁H₁₀N₂O₂S, M-H): 233.0390, found: (M-H): 233.0394.

3-(4-Nitrophenyl)-5-methylidene-2-thioxoimidazolidin-4-one (7m). From **2a** (2.45 g, 10 mmol) and 3-fluorophenyl isothiocyanate (1.80 g, 10 mmol) compound **7m** (1.05 g, 42%) was obtained as a white of pale orange crystalline solid. **¹H NMR** (400 MHz, DMSO-d₆): δ 12.67 (s, 1H), 8.36 (d, J= 9.0 Hz, 2H), 7.72 (d, J=9.0 Hz, 2H), 5.40 (d, J=1.9 Hz, 1H), 5.21 (d, J=2.0 Hz, 1H). **¹³C NMR** (101 MHz, DMSO-d₆): δ 177.2, 162.0, 147.2, 138.7, 135.3, 130.2, 124.0, 98.4. **HRMS** (ESI-) m/z calcd. for (C₁₀H₇N₃O₃S, M-H): 248.0135, found: (M-H): 248.0141.

Compound 7a

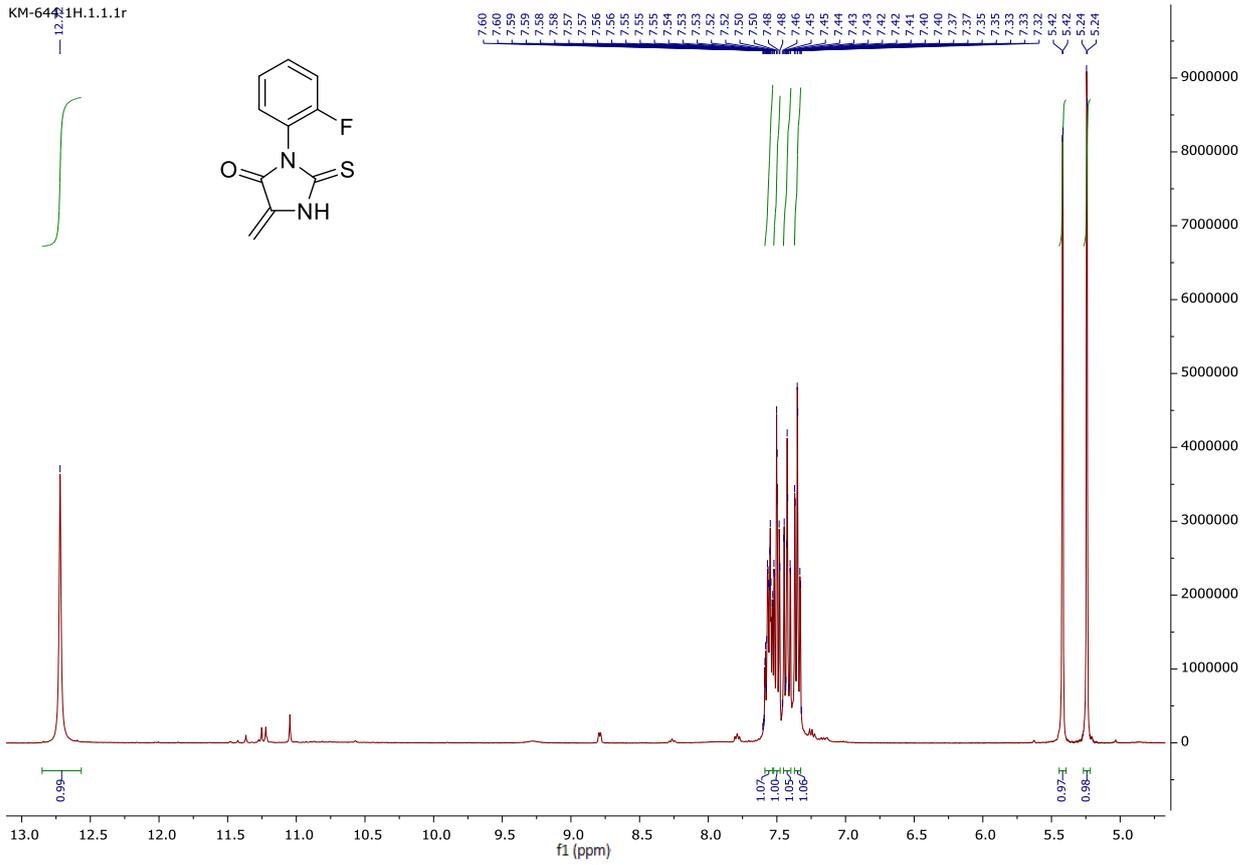


Spectrum from 070320_NEG.wiff (sample 16) - KNA-96-2 - TOF MS (200 - 3000) from 0.135 to 0.209 min

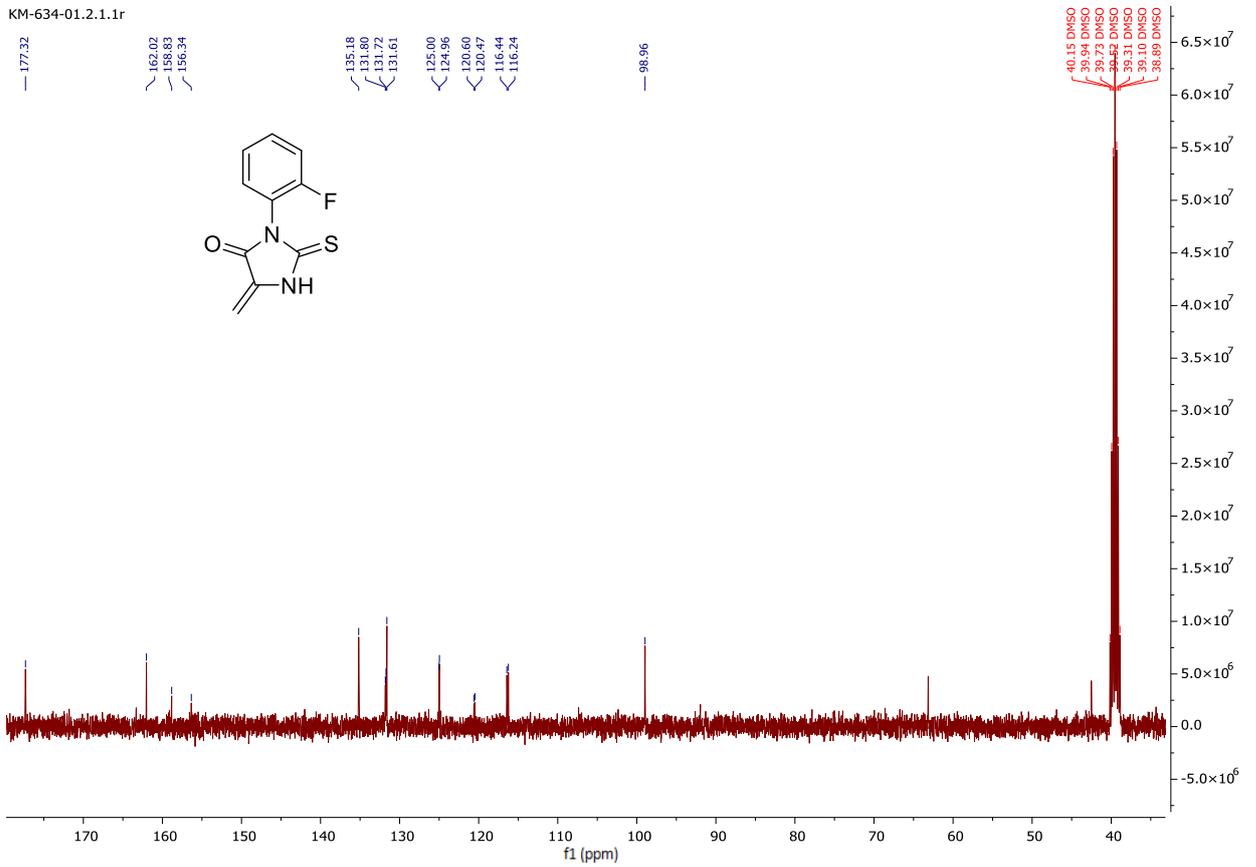


Compound 7b

KM-634-1H.1.1.1r

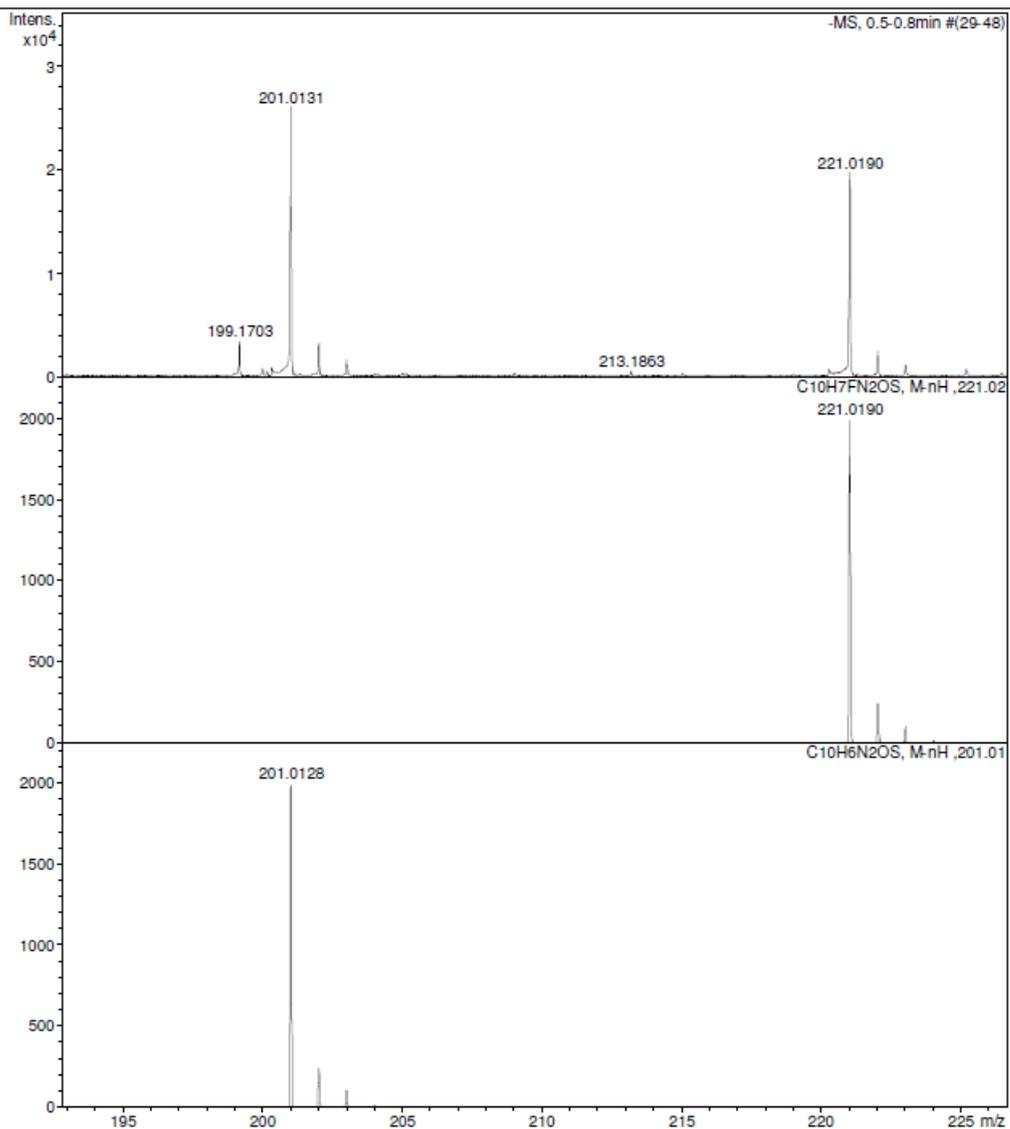


KM-634-01.2.1.1r

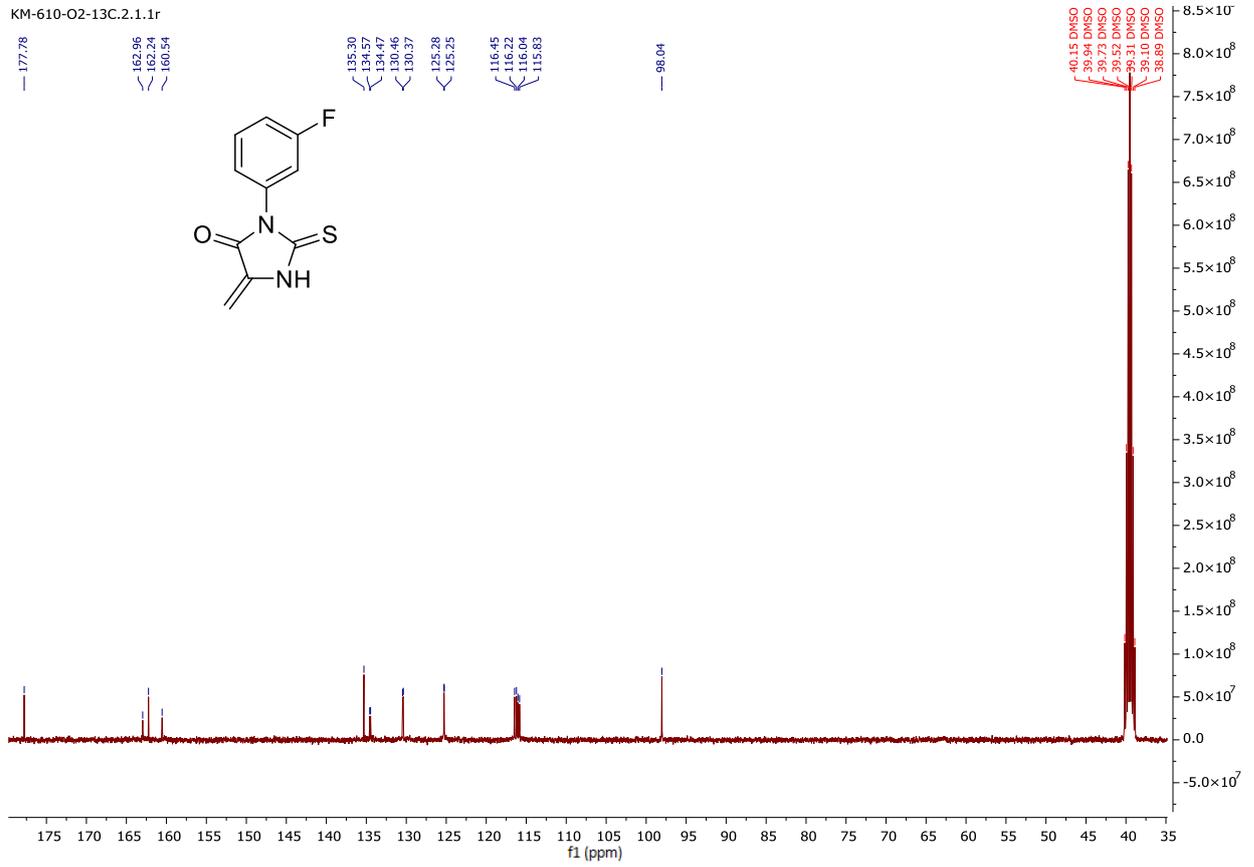
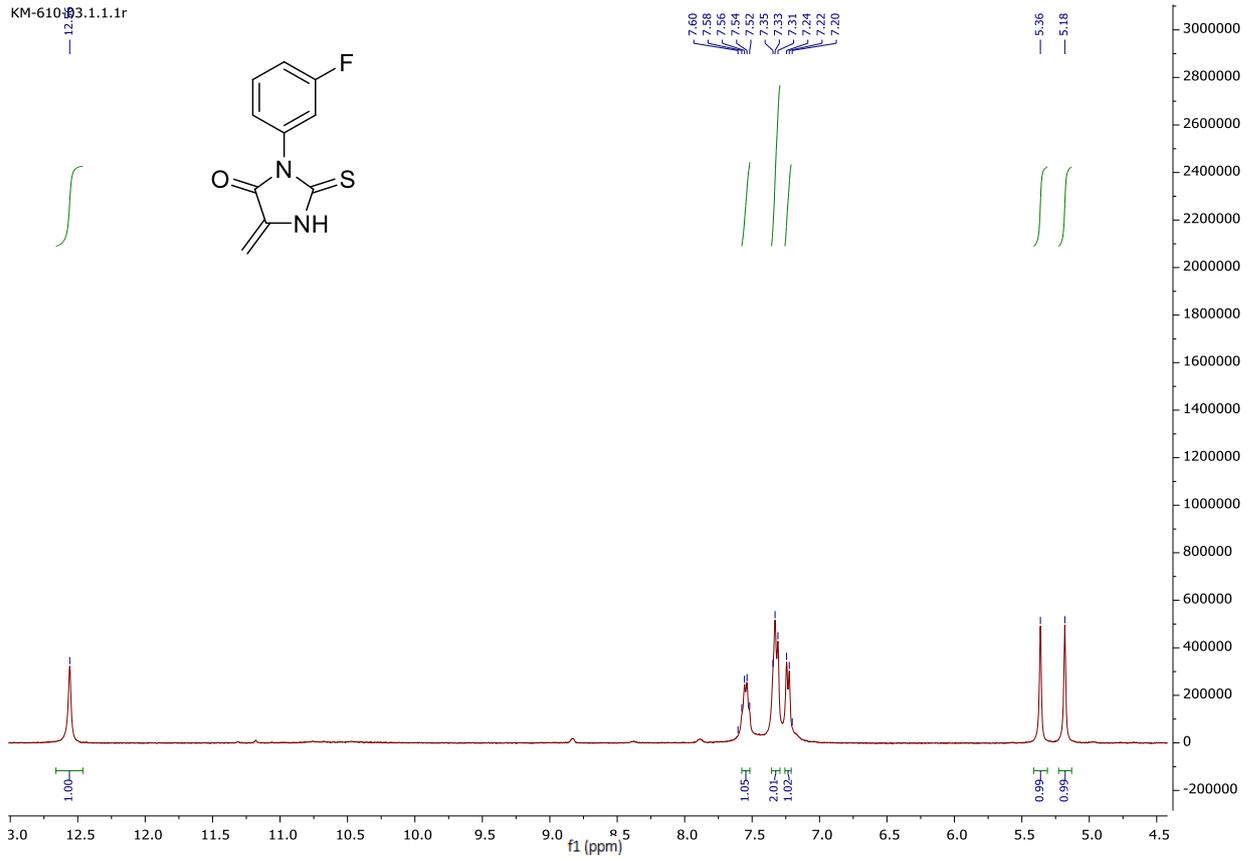


Acquisition Parameter

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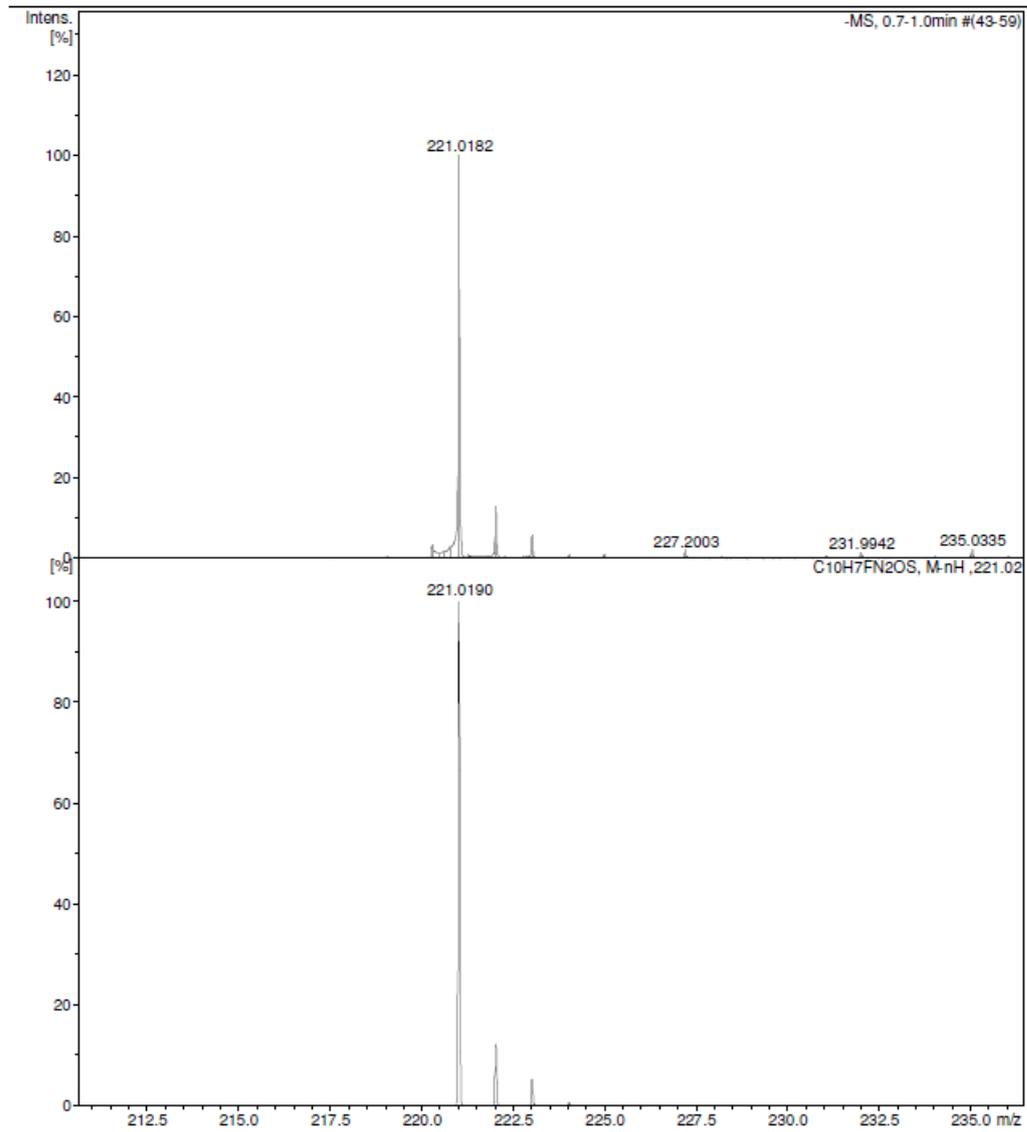


Compound 7c

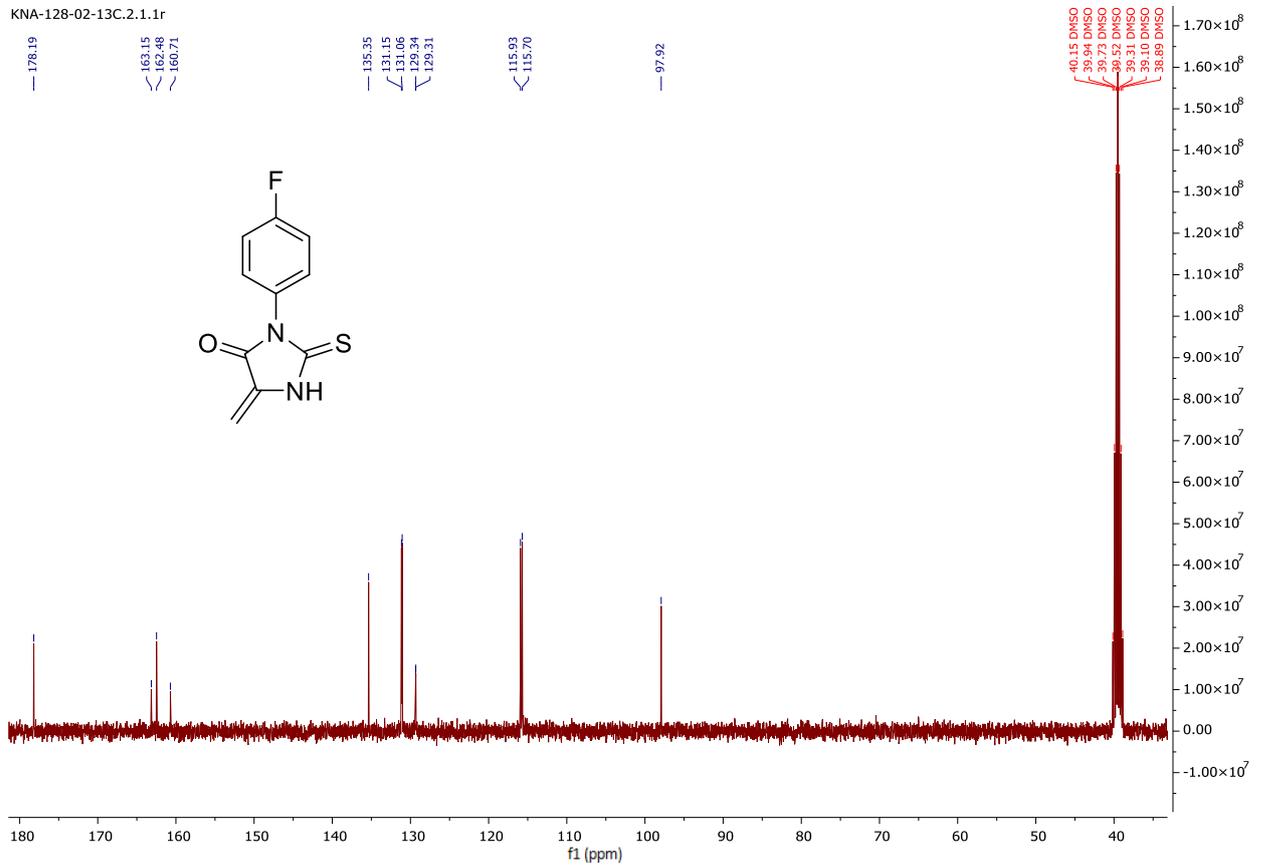
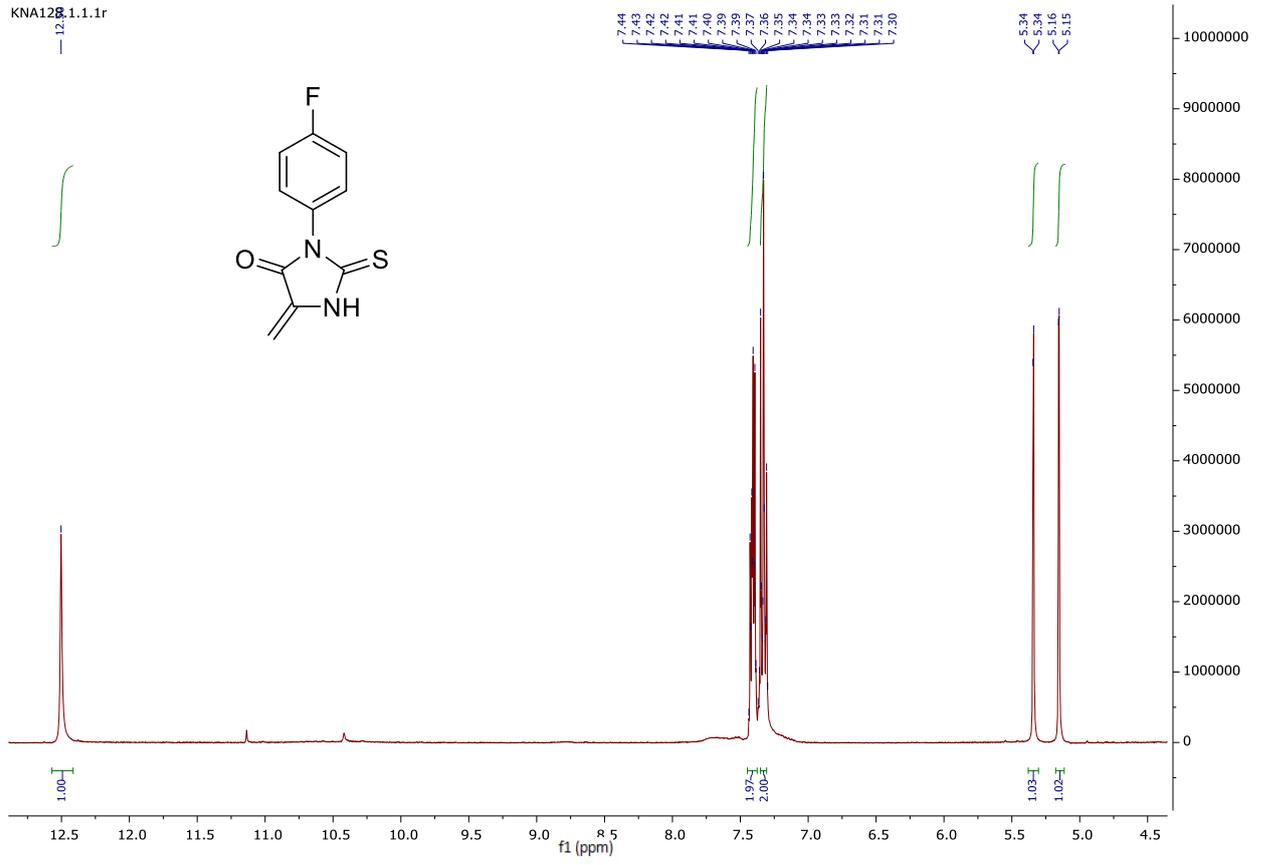


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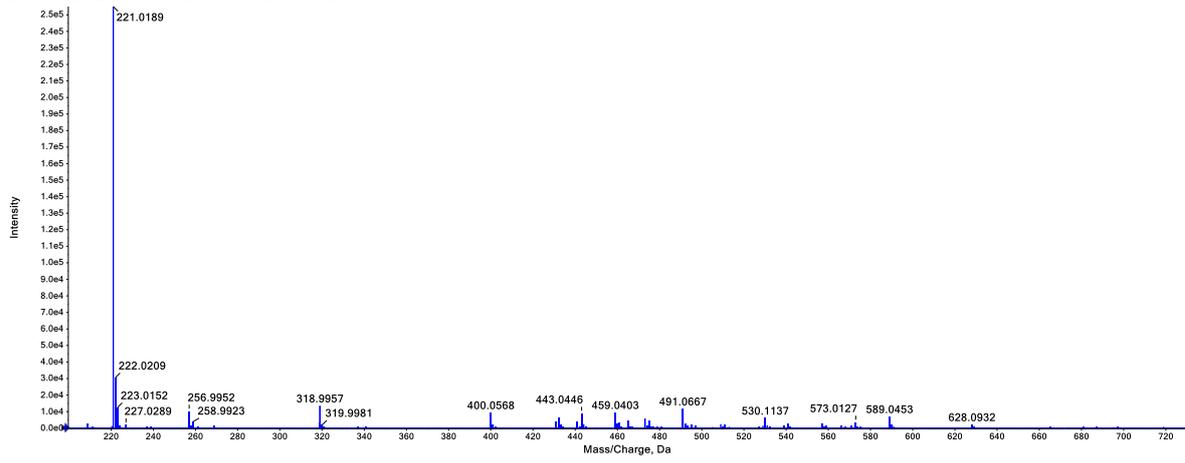
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Compound **7d**

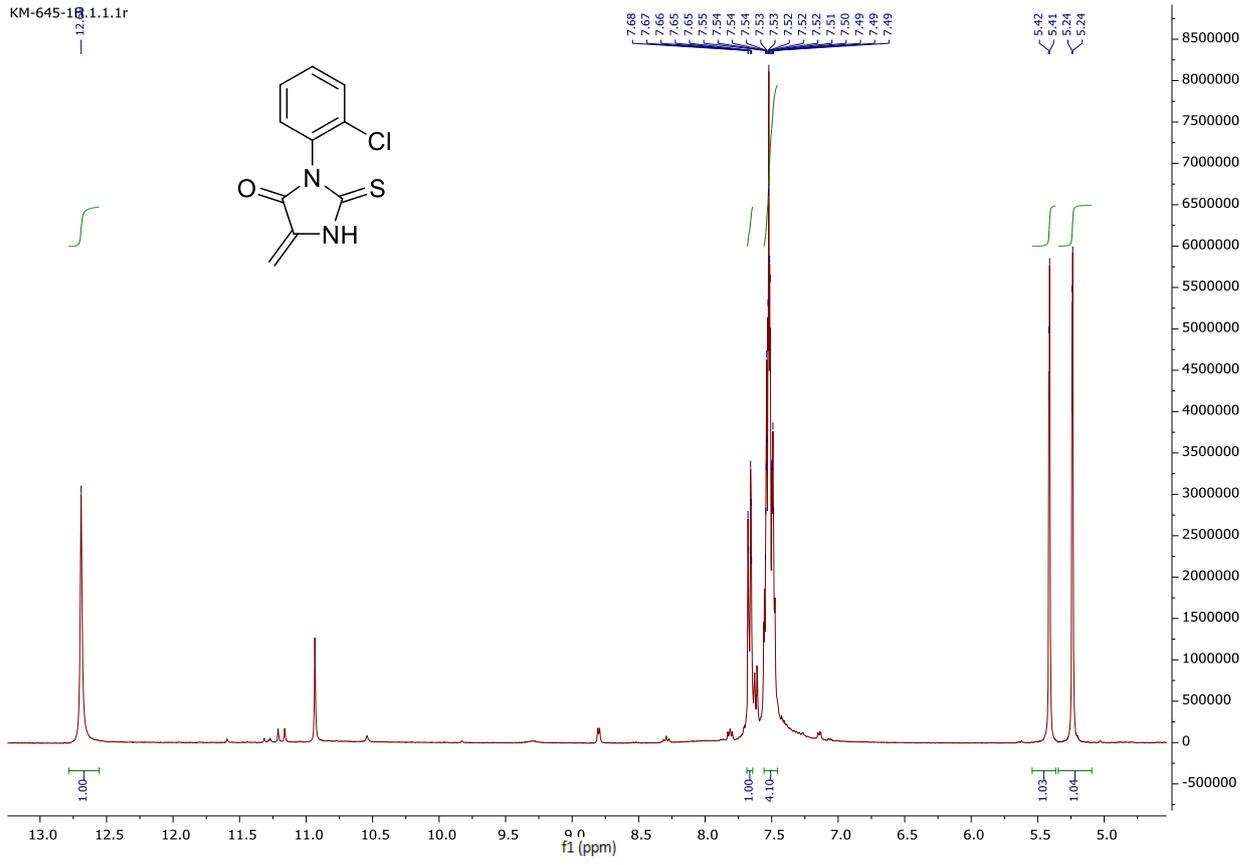


Spectrum from 070320_NEG.wiff (sample 13) - KNA 128 - TOP MS (200 - 3000) from 0.144 to 0.218 min

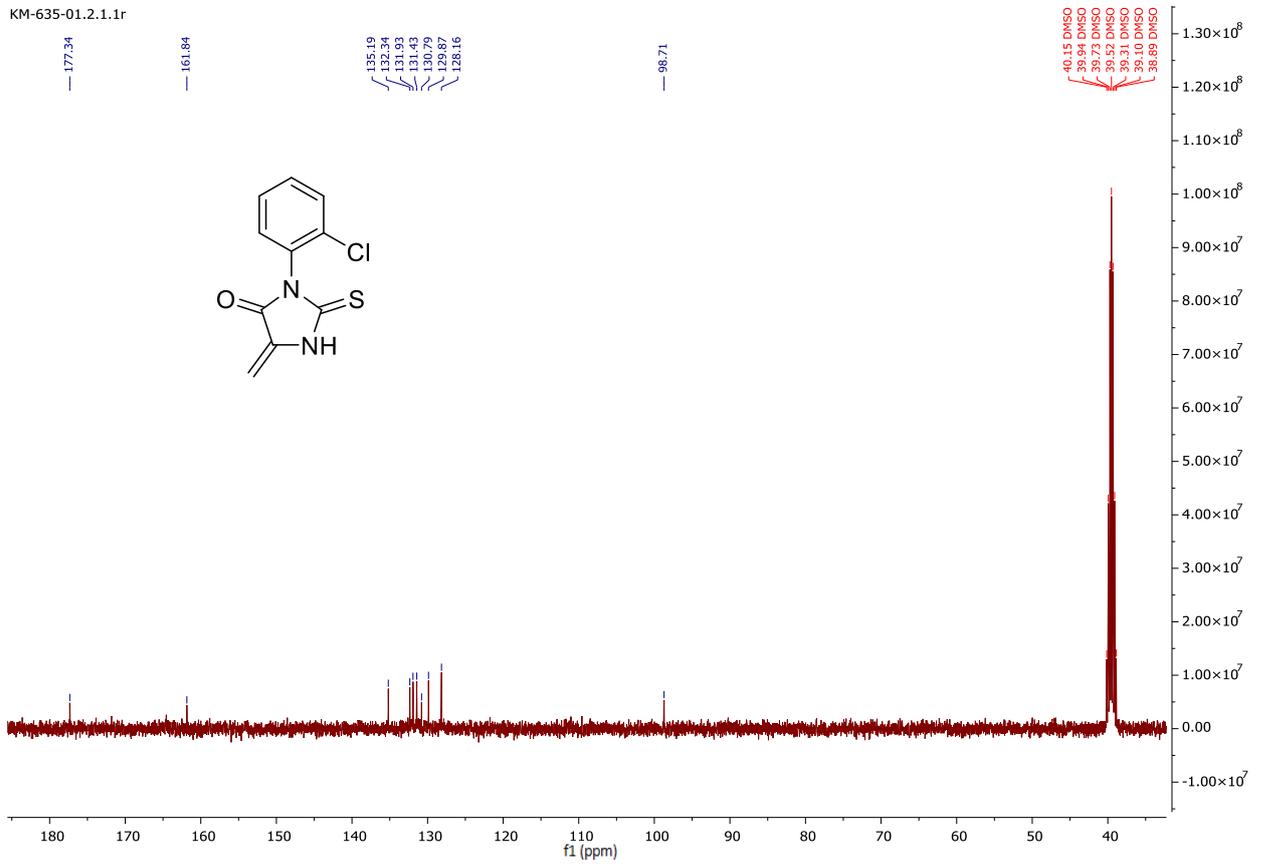


Compound 7e

KM-645-18.1.1.1r

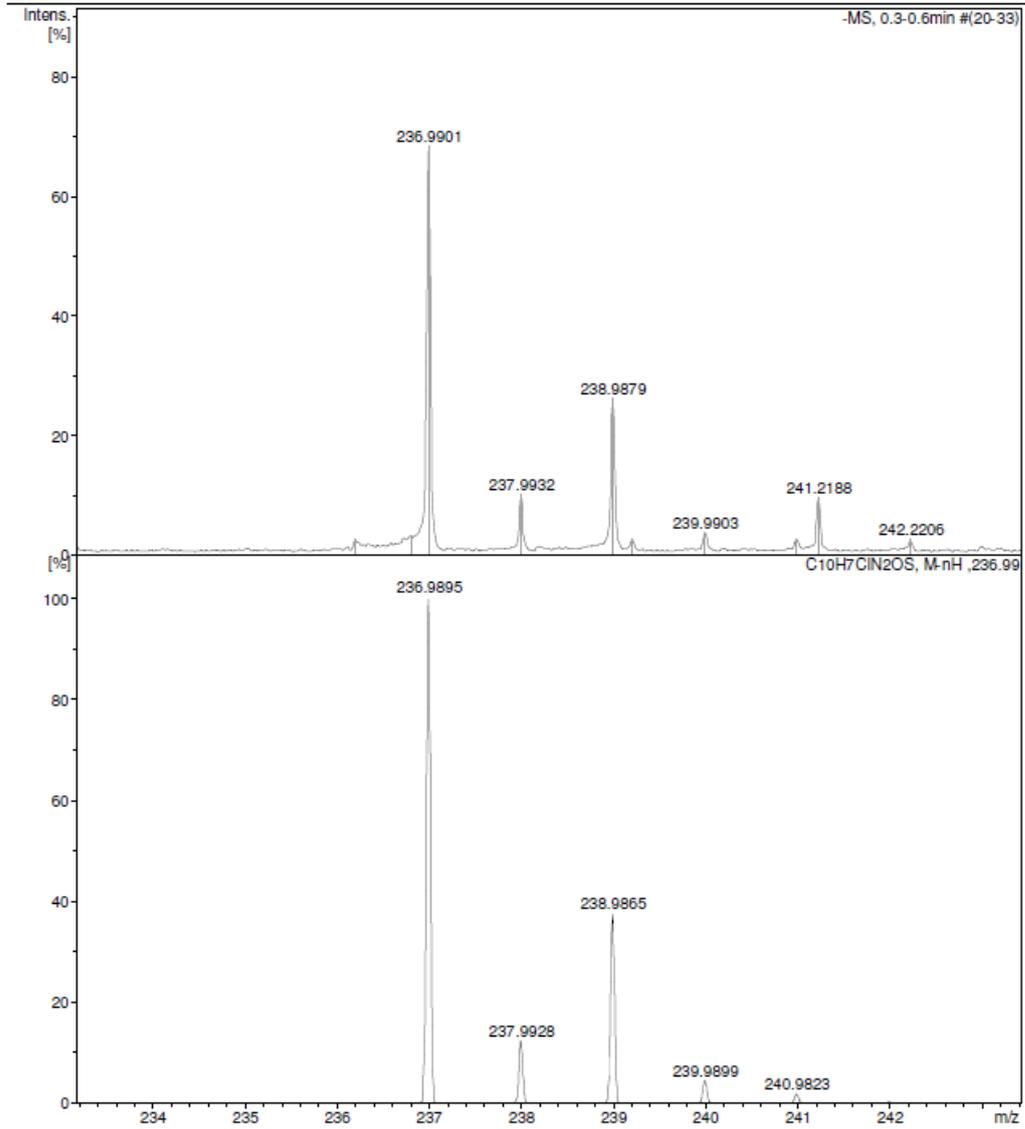


KM-635-01.2.1.1r

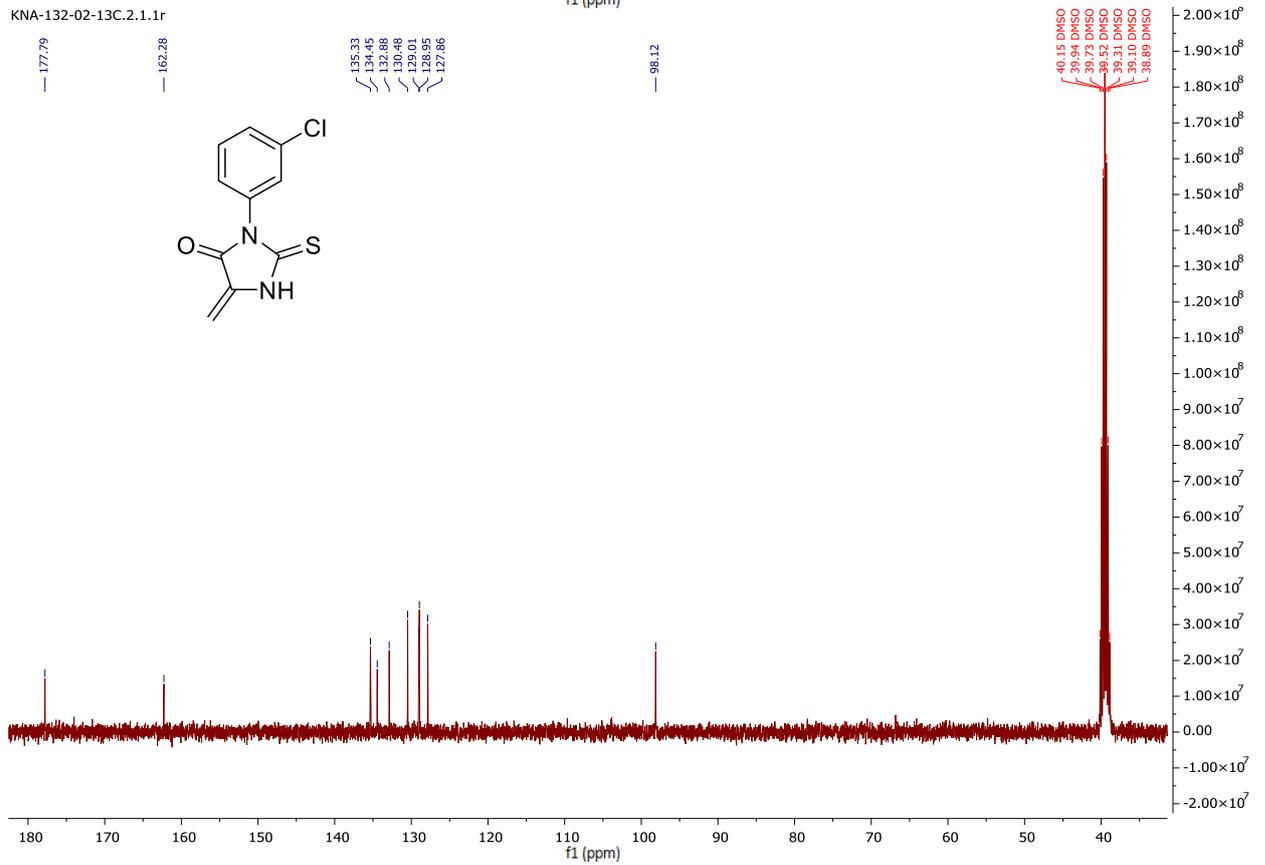
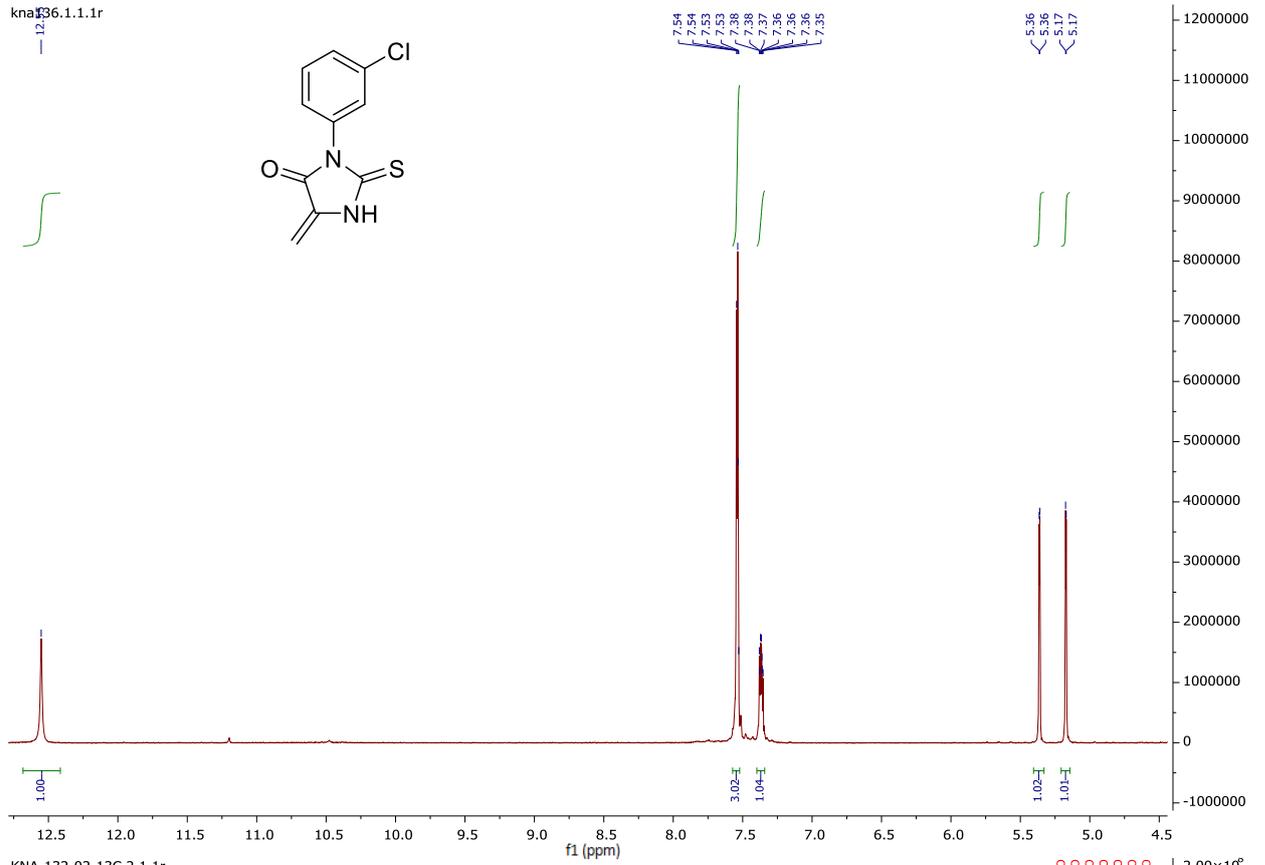


Acquisition Parameter

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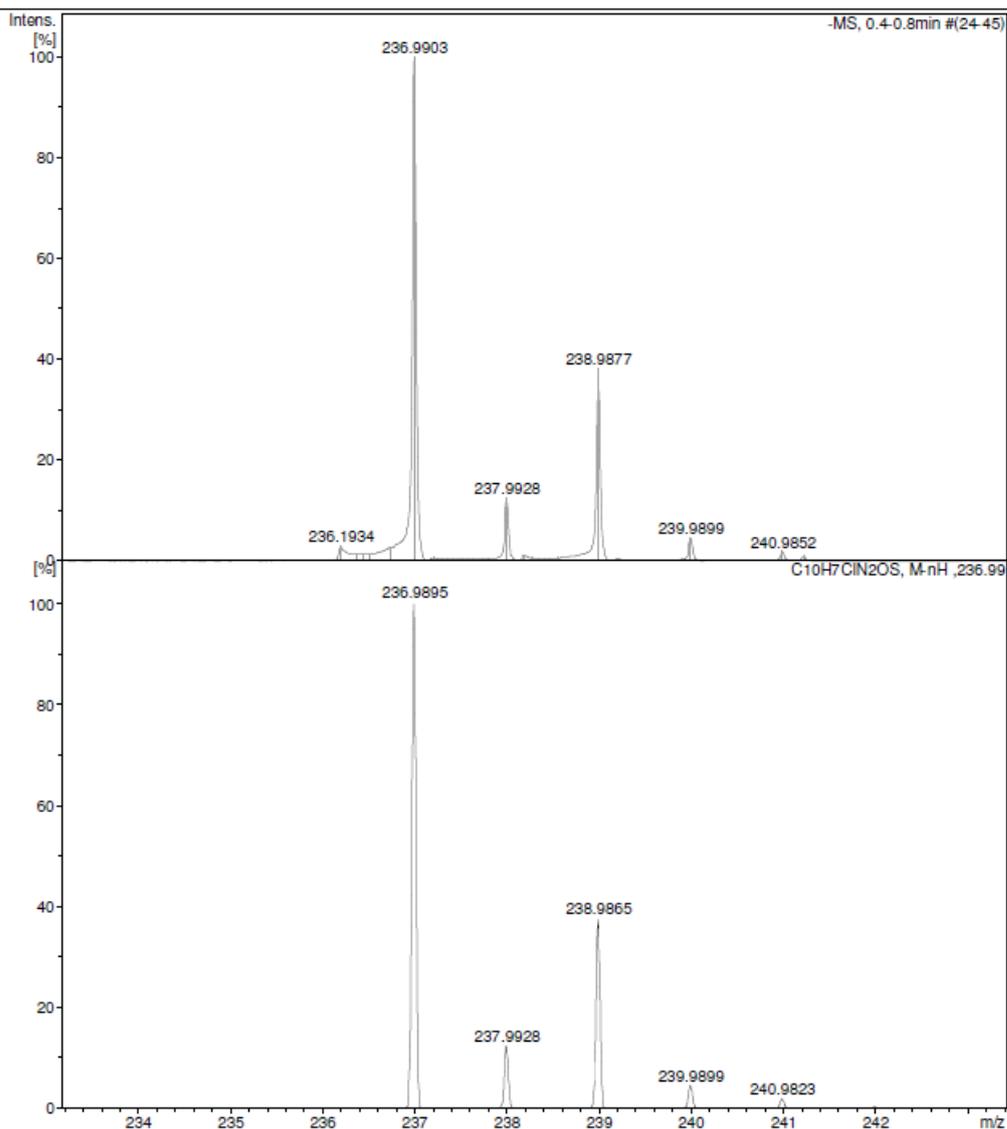


Compound 7f



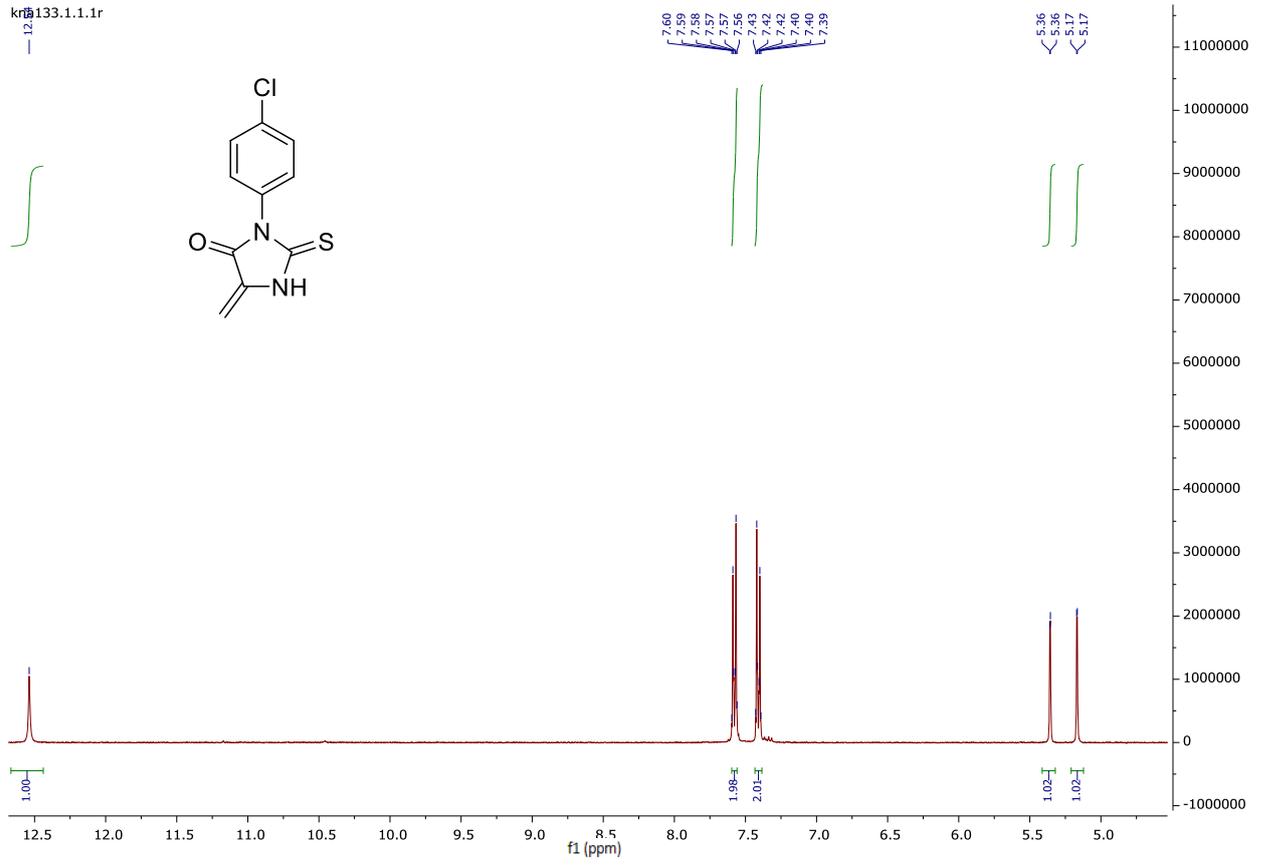
Acquisition Parameter

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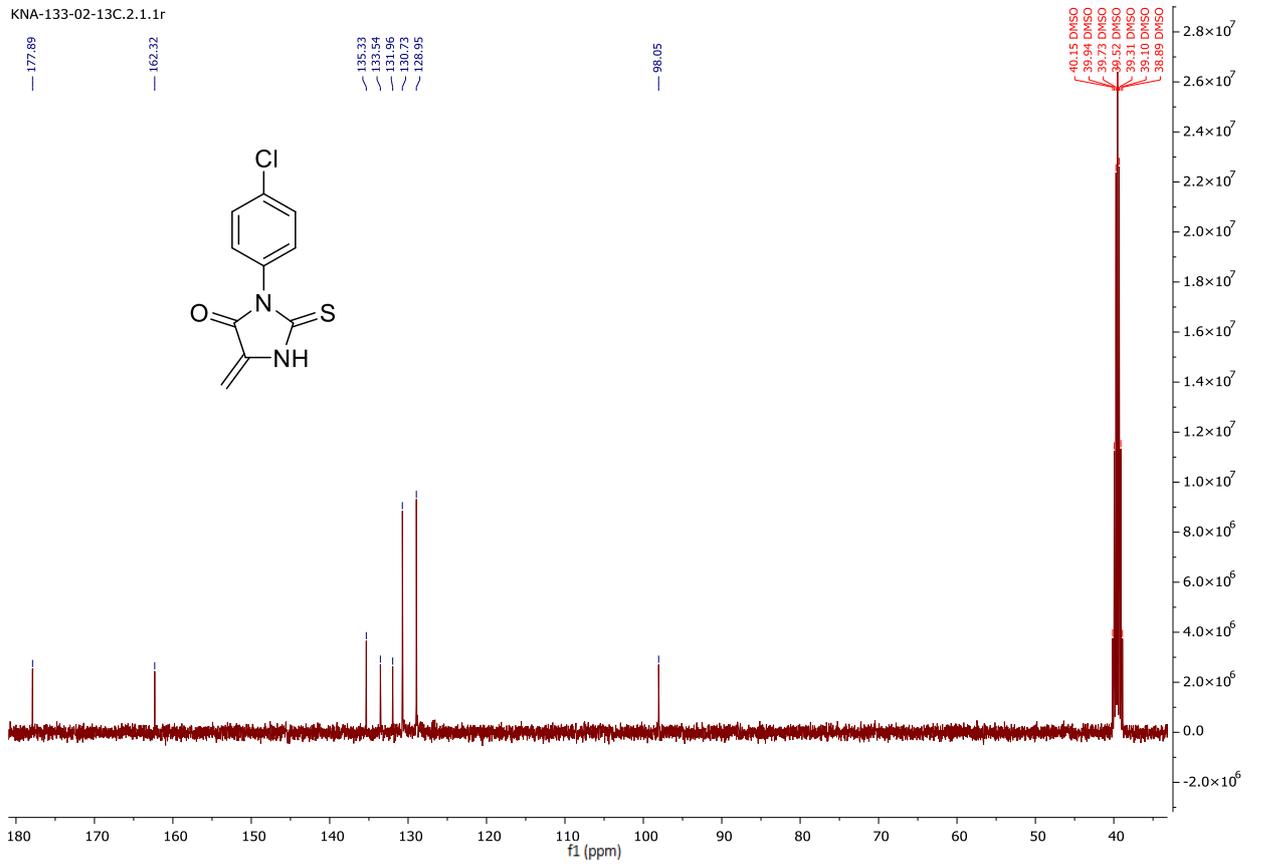


Compound 7g

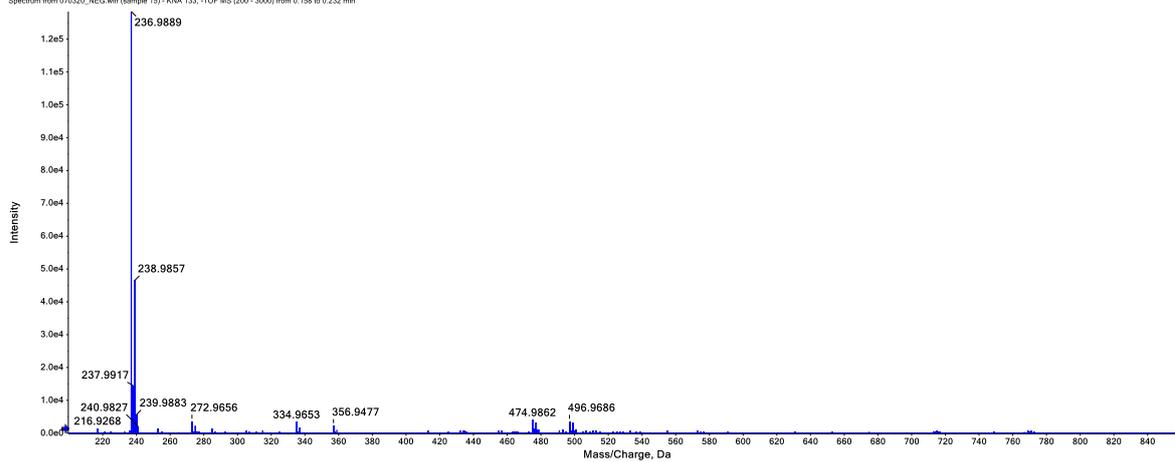
kna133.1.1.1r



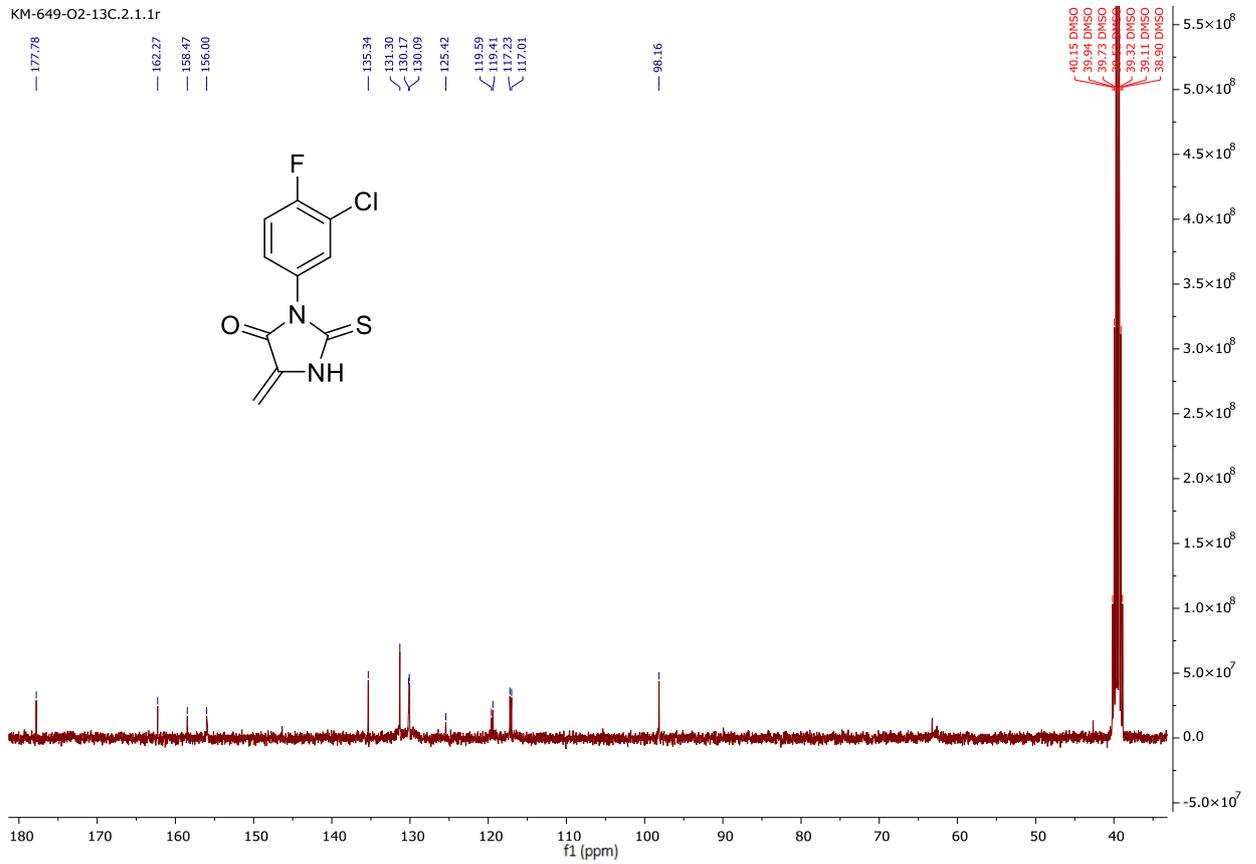
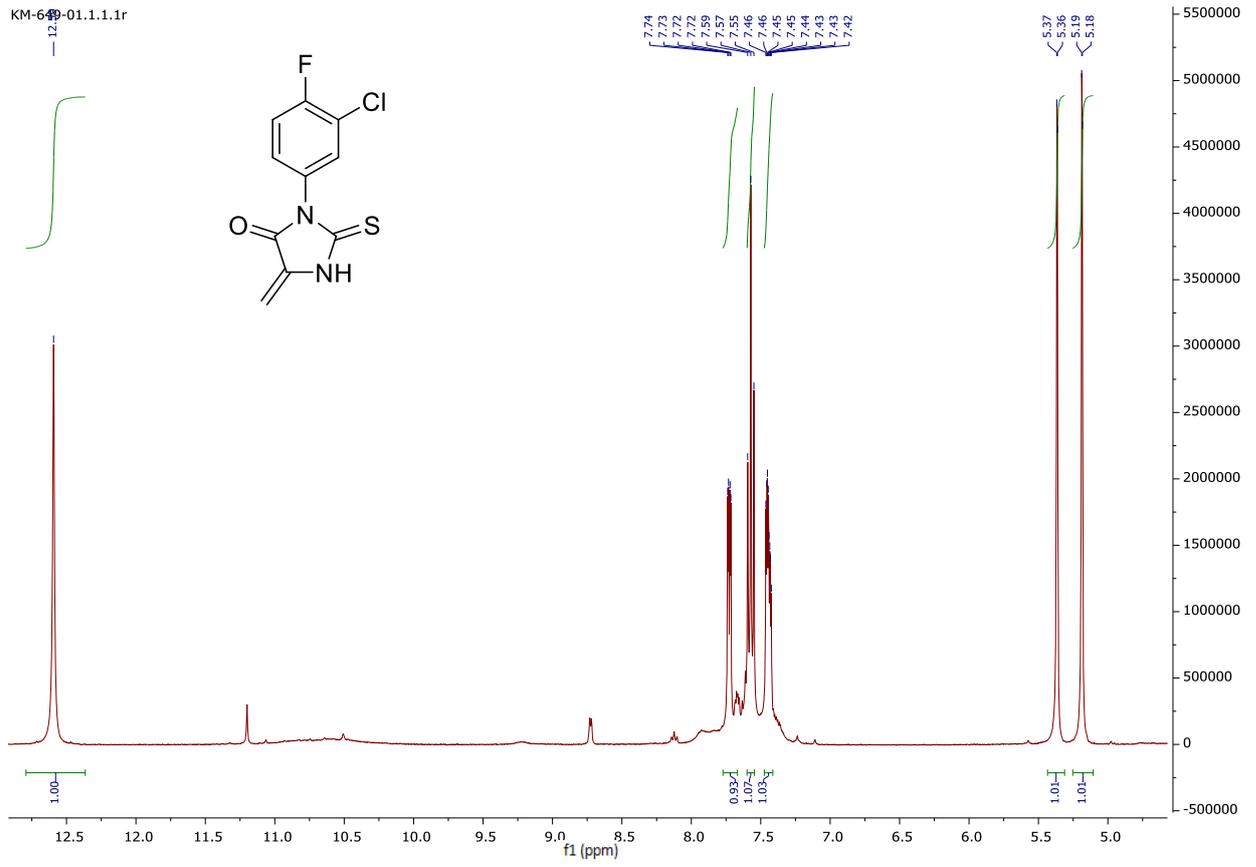
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Spectrum from 070320_NEG.wiff (sample 15) - KNA 133 - TOF MS (200 - 3000) from 0.158 to 0.232 min

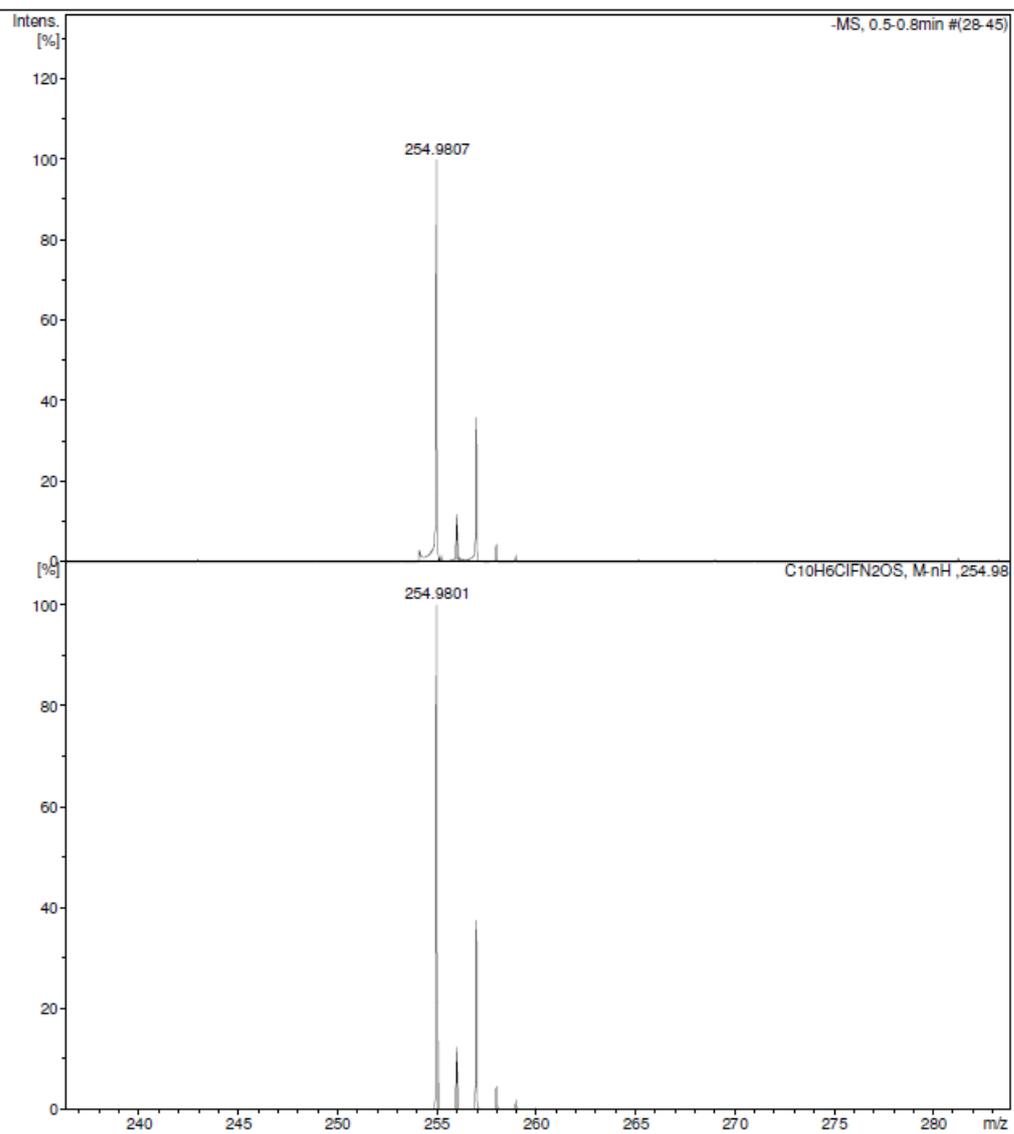


Compound 7h



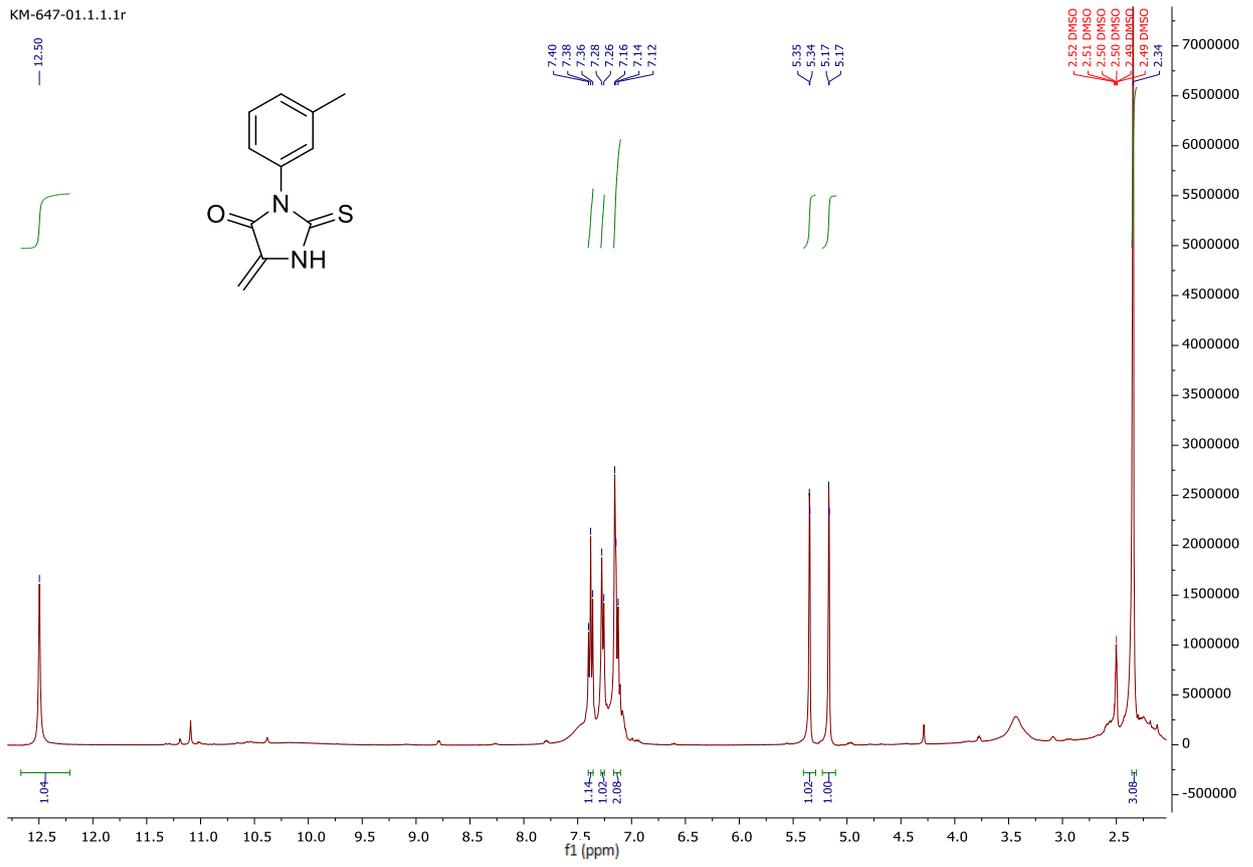
Acquisition Parameter

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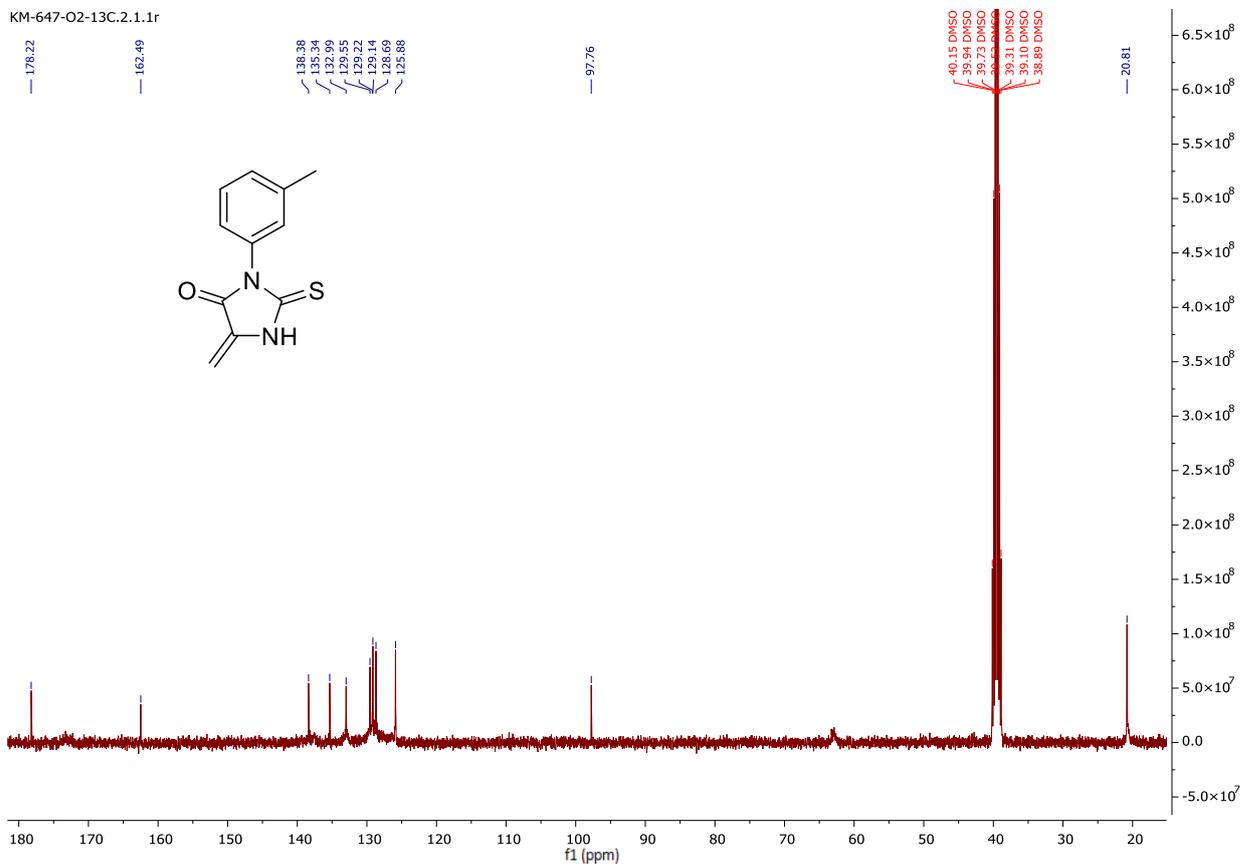


Compound 7i

KM-647-01.1.1.1r

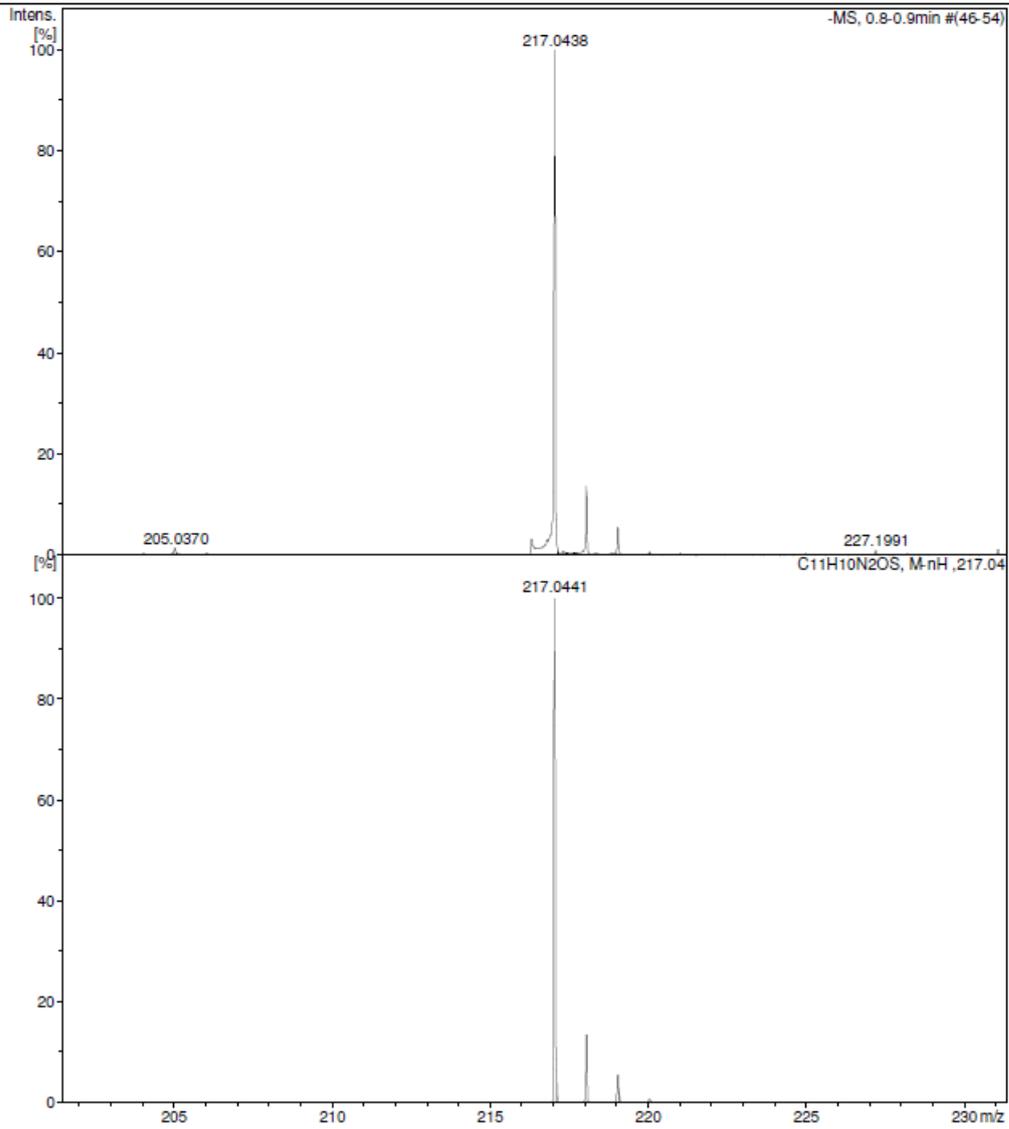


KM-647-O2-13C.2.1.1r



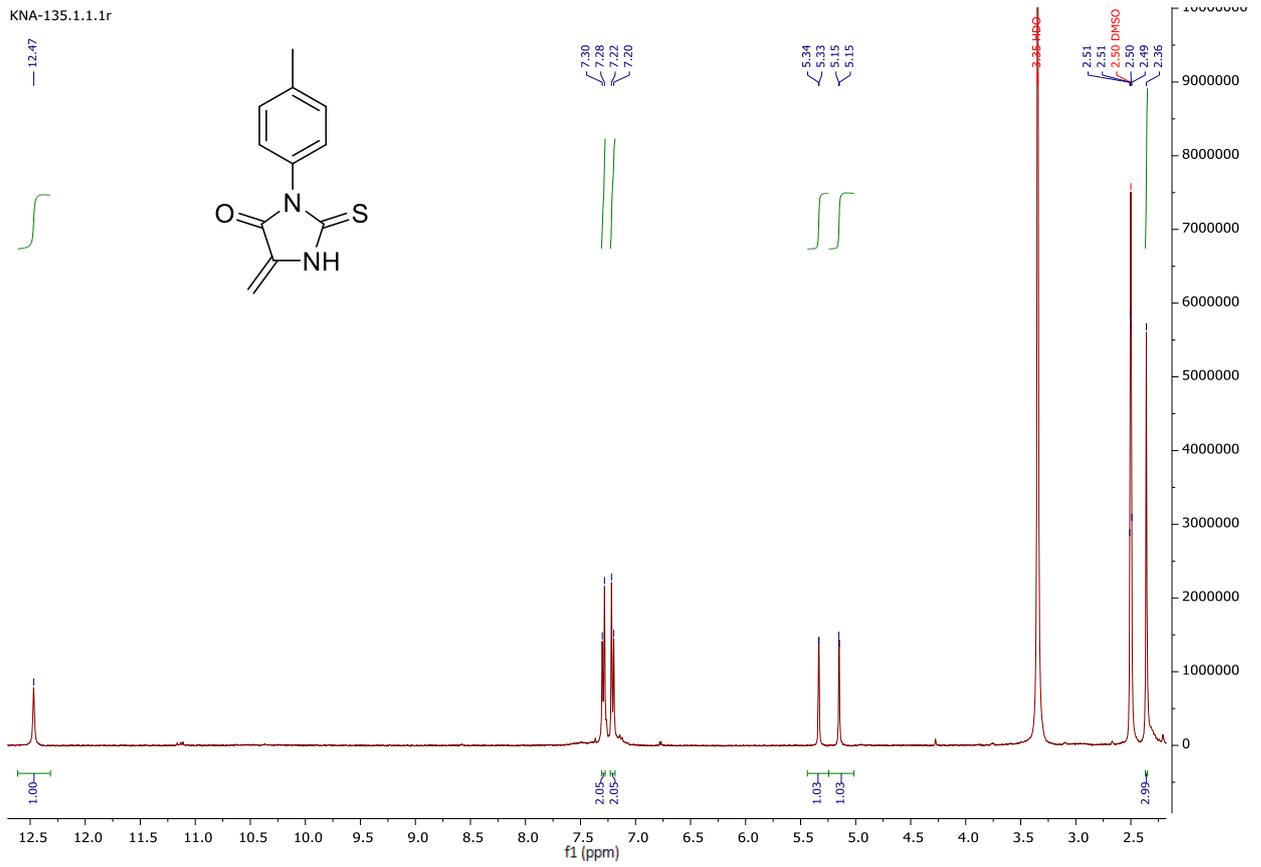
Acquisition Parameter

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Scan Begin	50 m/z	Set Capillary	3200 V	Set Dry Gas	4.0 l/min
Scan End	1650 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste

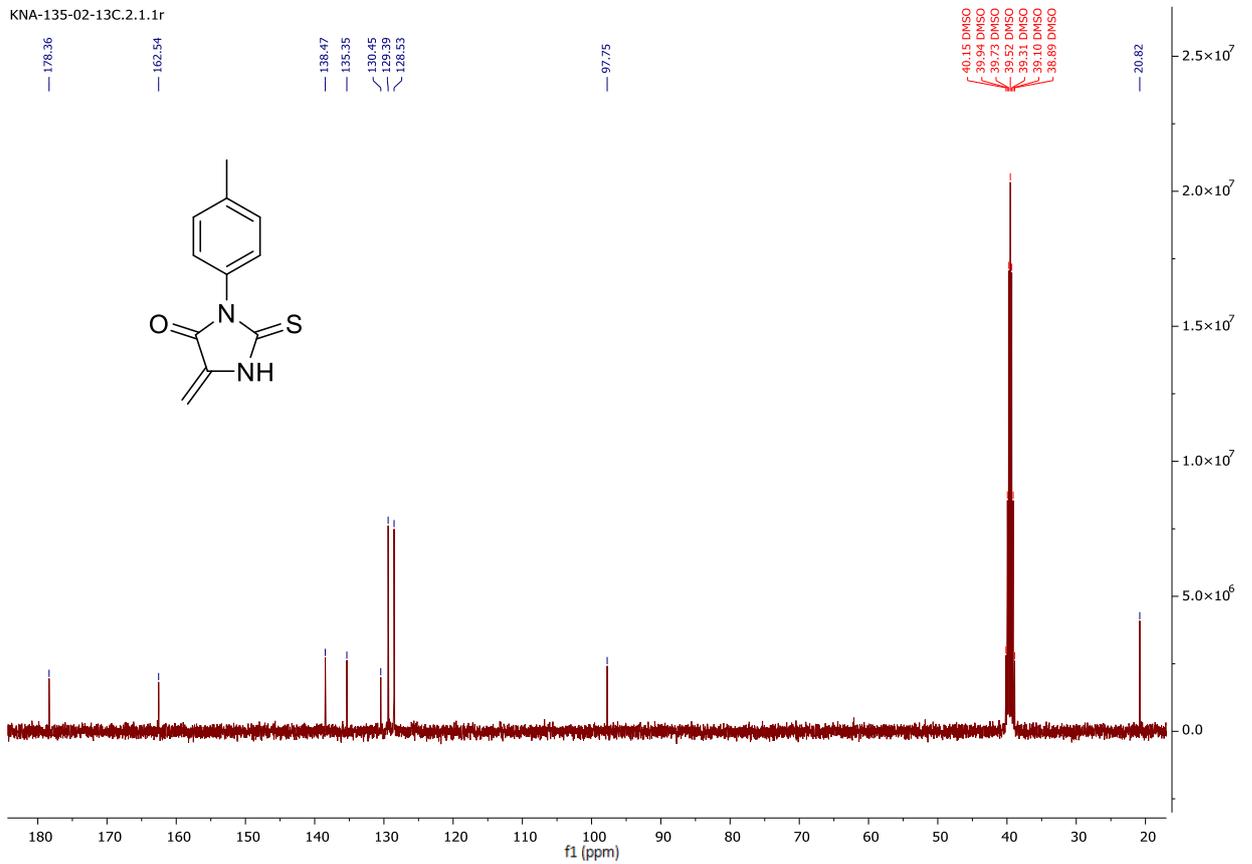


Compound 7j

KNA-135.1.1.1r

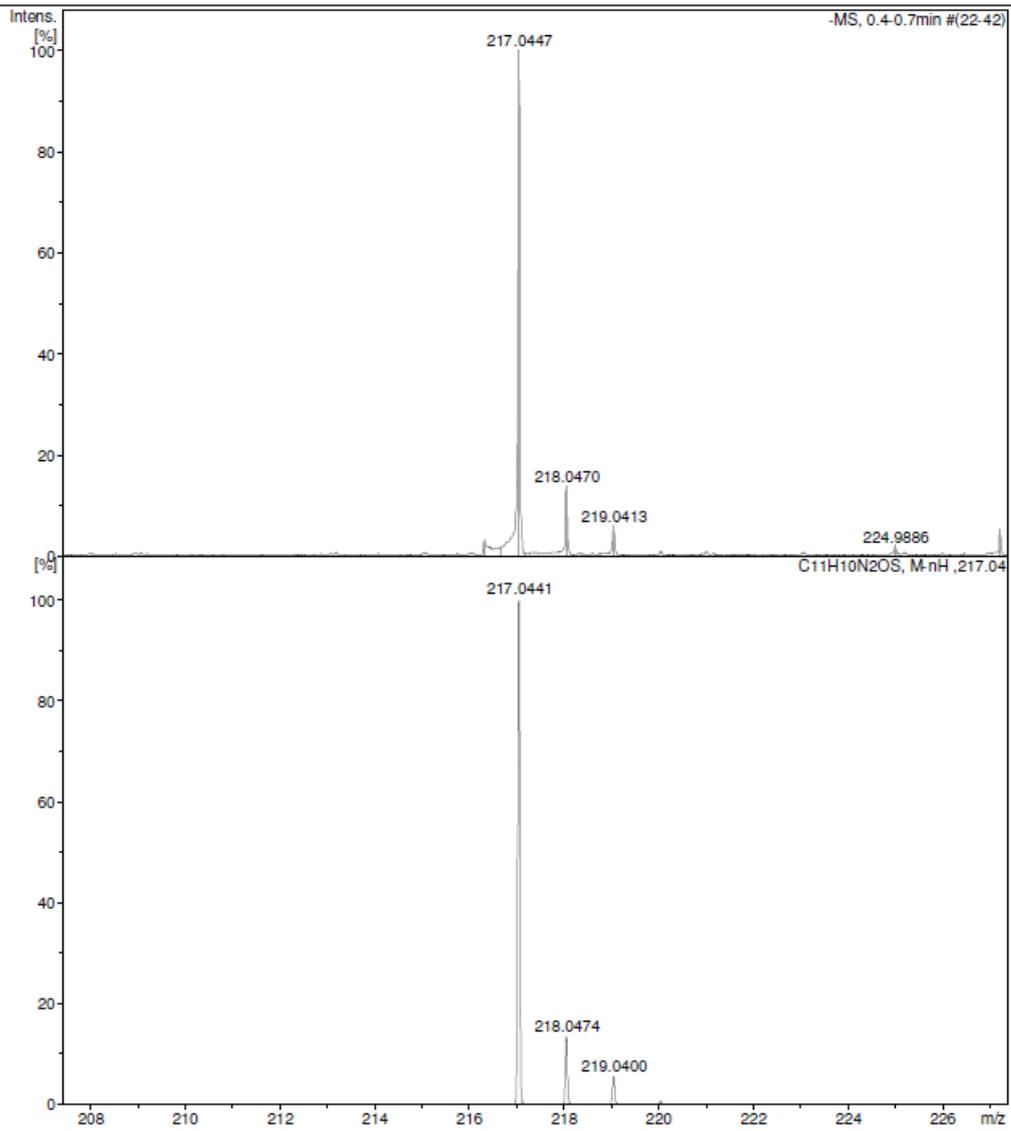


KNA-135-02-13C.2.1.1r

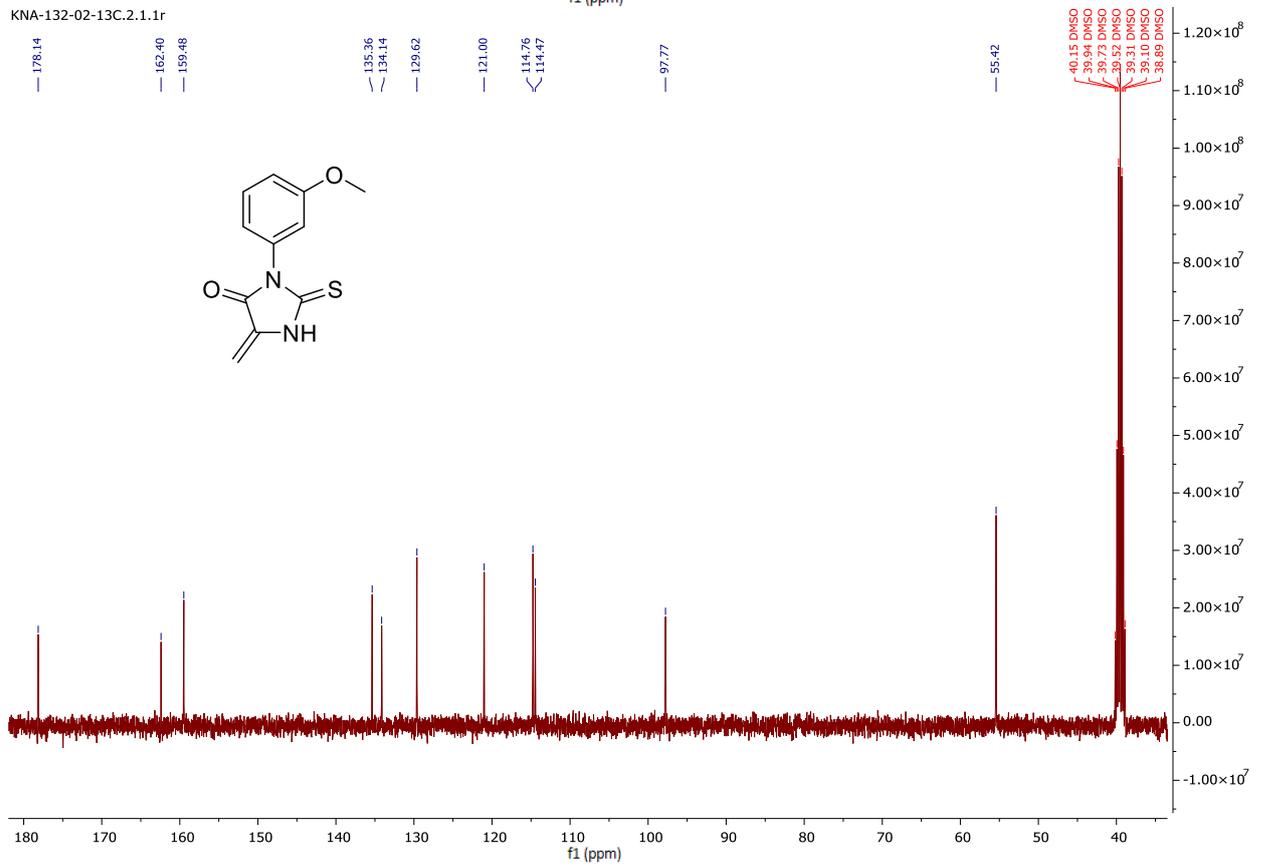
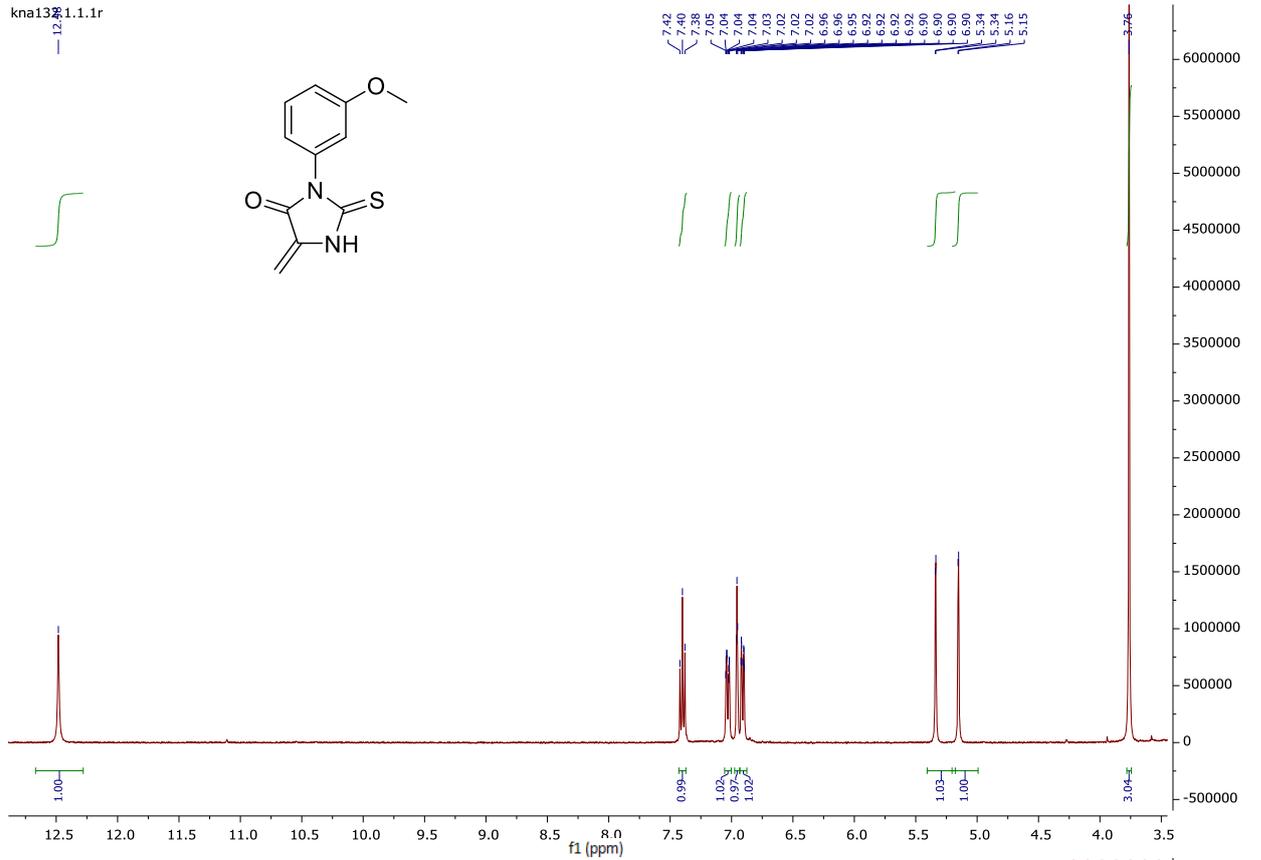


Acquisition Parameter

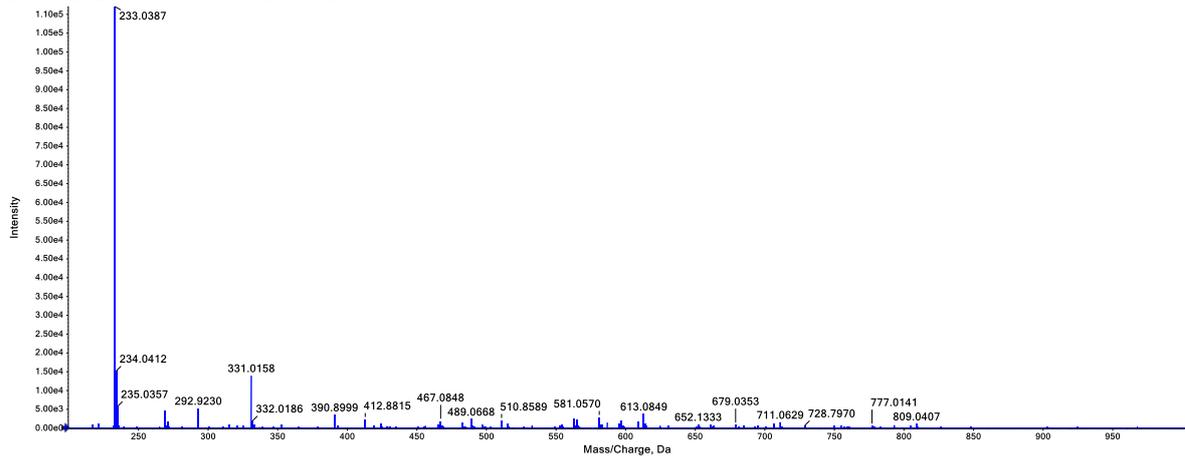
Source Type	ESI	Ion Polarity	Negative	Set Nebulizer	1.0 Bar
Focus	Not active			Set Dry Heater	200 °C
Scan Begin	50 m/z	Set Capillary	3200 V	Set Dry Gas	4.0 l/min
Scan End	1650 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste



Compound 7k

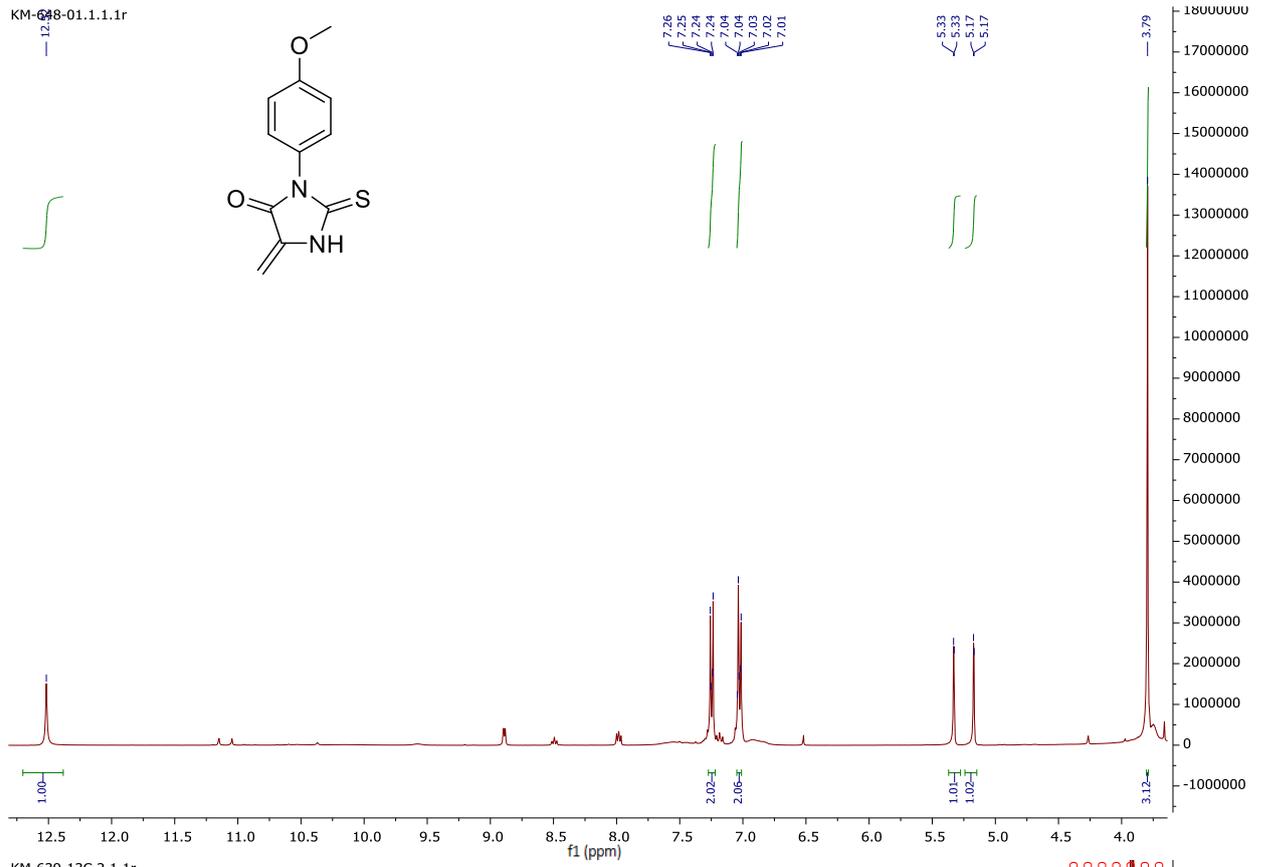


Spectrum from 070320_NEG.wiff (sample 14) - KNA 132 -TOP MS (200 - 3000) from 0.144 to 0.218 min

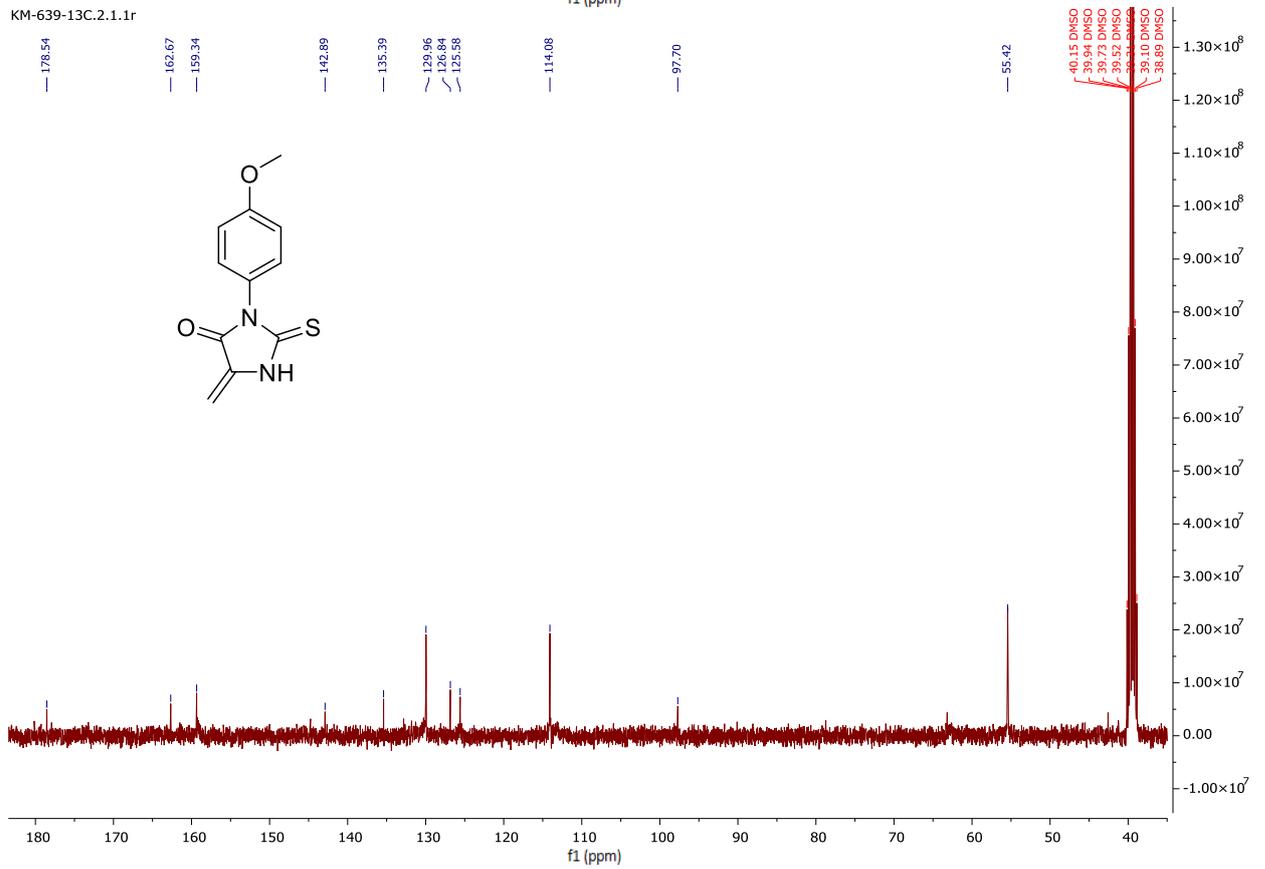


Compound 71

KM-638-01.1.1.1r

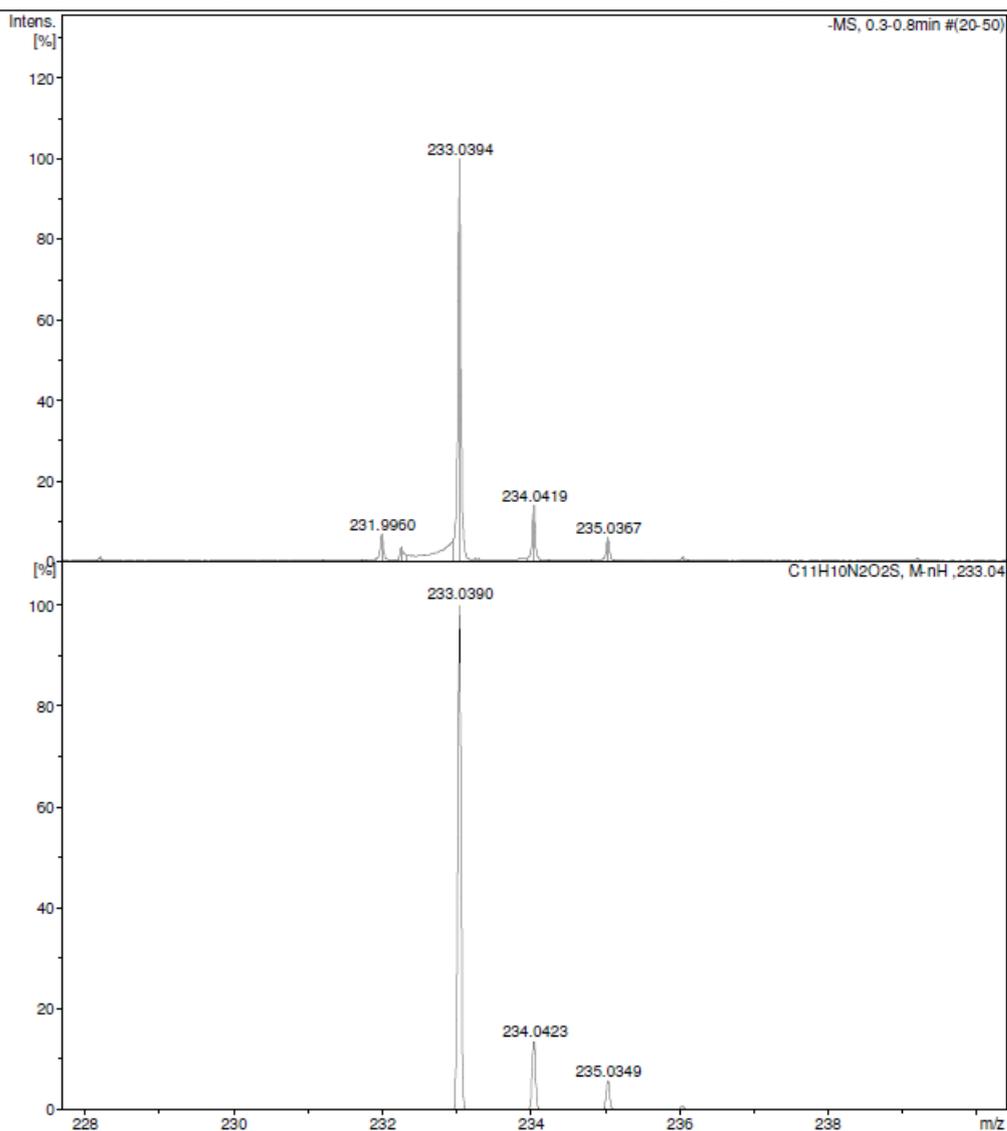


KM-639-13C.2.1.1r



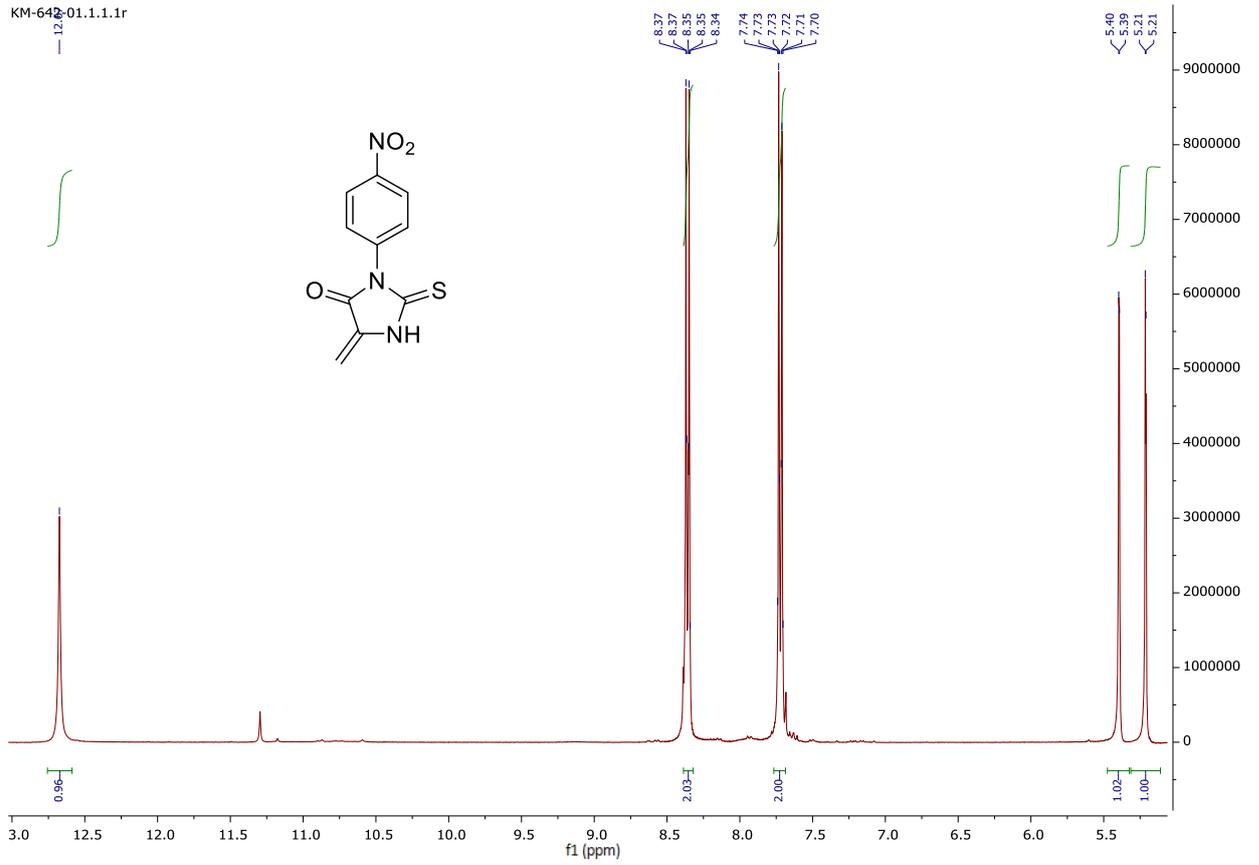
Acquisition Parameter

Source Type	ESI	Ion Polarity	Negative	Set Nebulizer	1.0 Bar
Focus	Not active			Set Dry Heater	200 °C
Scan Begin	50 m/z	Set Capillary	3200 V	Set Dry Gas	4.0 l/min
Scan End	1650 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste

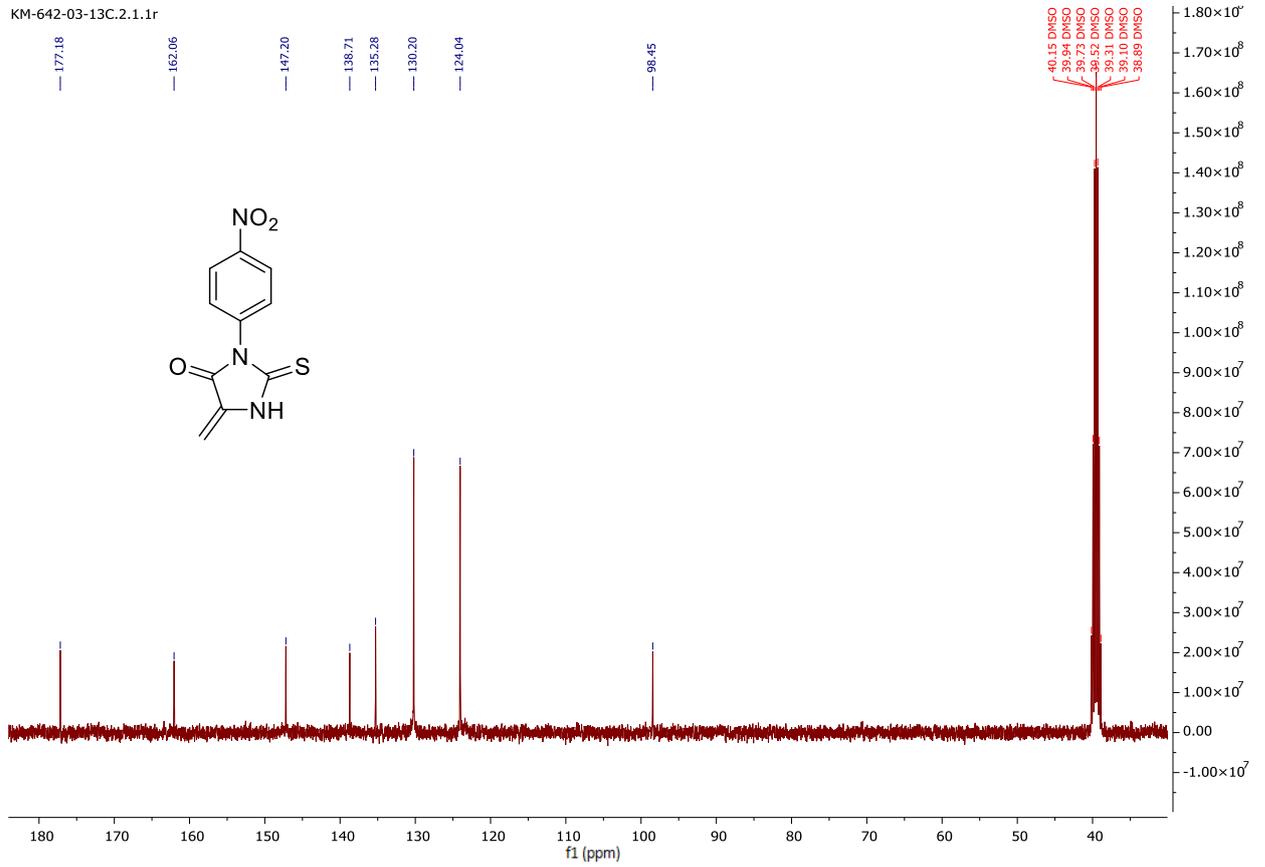


Compound 7m

KM-642-01.1.1.1r



KM-642-03-13C.2.1.1r



Acquisition Parameter

Source Type	ESI	Ion Polarity	Negative	Set Nebulizer	1.0 Bar
Focus	Not active			Set Dry Heater	200 °C
Scan Begin	50 m/z	Set Capillary	3200 V	Set Dry Gas	4.0 l/min
Scan End	1650 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste

