Supporting Information

A Straightforward Microwave Method for Rapid Synthesis of

N-1, C-6 Functionalized 3,5-Dichloro-2(1*H*)-Pyrazinones

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General Section

All reactions were performed in reaction vials dedicated for microwave processing. The microwave experiments were carried out using a Smith Synthesizer™ or Emrys Initiator™ single mode cavity, equipped with magnetic stirring and producing controlled irradiation at 2450 MHz. The temperature of the reaction mixture was measured using a built-in, on-line infrared temperature sensor. To avoid over pressurizations or explosions, sealed reactions should always be performed in dedicated equipment. For flash chromatography commercially available silica gel 60 (particle size: 0.040-0.063 mm) was used. Analytical thin-layer chromatography was performed on silica gel 60 F-254 plates (E. Merck) and visualized with UV light. ^{1}H NMR spectra were recorded at 399.9 MHz and ^{13}C NMR spectra at 100.5 MHz. The chemical shifts for ^{1}H NMR and ^{13}C NMR are referenced to TMS via residual solvent signals (^{1}H, $CDCl_3$ at 7.26 ppm, CD_3OD at 3.31 ppm; ^{13}C, $CDCl_3$ at 77.16 ppm, CD_3OD at 49.0 ppm). Optical rotations were obtained on a Perkin-Elmer 241 polarimeter and the concentration (*c*) is given as g/100 mL in the specified solvent. Analytical RPLC-MS analysis of reaction mixtures and pure products were performed using a Gilson HPLC system with a Chromolith SpeedROD RP-18e column (50×4.6 mm) and a Finning AQA quadropole mass spectrometer using a 4 mL/min CH_3CN/H_2O gradient (0.05% aqueous HCOOH) and detection by UV (DAD) or ELSD and MS (ESI+). Preparative RP-HPLC was performed using a Zorbax SB-C8 column (5 μm, 21.2 × 150 mm) with gradients of $MeCN/H_2O$ (0.1% TFA) at a flow rate of 5 mL/min and UV detection at 230 nm. The purity of pseudo peptides **7a** and **7b** were determined on an ACE 5 C18 column (5 μm, 4.6 × 50 mm) using the same buffer system at a flow rate of 2 mL/min and with UV detection at 220 nm. Analytische Laboratorien, Lindlar, Germany performed elemental analyses. Compounds **3a** and **3e** were purchased from Acros. Compounds **3e***,[1-3] **3i**,[4] **3k**,[5] **4f**,[6] **4g**,[7] **4i**,[8] **4p**,[9] **4q**,[4] **4r**,[10] **4s**,[10] (1*R*,2*S*)-

ethyl 1-amino-2-vinylcyclopropanecarboxylate hydrochloride are all known compounds. Spectral data were in agreement with the proposed structures.

Biochemical evaluation: Compounds **7a** and **7b** were evaluated against the hepatitis C virus NS3 protease in vitro, using the full-length NS3 protein, the central part of the co-factor NS4A and an internally quenched fluorescent peptide substrate as described elsewhere.[11]

General One-Pot, Two-Step Procedure for Preparation of 2(1*H*)-Pyrazinones 4a-n. Method I.

A 2.0-5.0 mL Smith microwave vial was charged with amine (**1a-h,** 1.0 mmol) and was dissolved in 3.0 mL DME. The aldehyde (**2a-e**, 1.2 mmol) was added and the mixture was stirred for 30 s before adding trimethylsilyl cyanide (1.1 mmol, 138 µL). The vial was sealed and irradiated with microwaves for 10 min at stated temperatures (step 1, Table 1). The solvent was removed under a stream of nitrogen gas and the residue was dissolved in 5.0 mL diethylether. HCl gas was bubbled through the reaction mixture for 5 min followed by evaporation under a stream of nitrogen gas. DME (3.0 mL) and oxalyl chloride (2.5 mmol, 214 µL) were added and the vial was sealed. After 30 s of stirring, the overpressure was released with a needle before irradiation with microwaves for 10 min at 170 °C (creating a pressure of 10-17 bar). Purification by flash chromatography yielded pure products **4a-n** (>95% by LC-ELSD).

One-Pot, Two-Step Procedure for Preparation of Benzyl 2-(3,5-dichloro-6-methyl-2-oxopyrazin-1(2*H*)-yl)-3-methylbutanoate 4j. Method II.

The title compound was prepared following method I with amine **1f** (2.04 mmol, 0.423 g), acetaldehyde **1a** (2.46 mmol, 0.137 mL), trimethylsilyl cyanide (2.25 mmol, 0.282 mL),

oxalyl chloride (5.11 mmol, 0.438 mL), using 10 min of microwave heating at 80 °C in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 5:95 to 15:85, yielded pure product **4j** as colorless oil, 0.397 g (53%).

5 mmol, One-Pot, Two-Step Procedure for Preparation of Ethyl 2-(3,5-dichloro-6-methyl-2-oxopyrazin-1(2*H*)-yl)-3-phenylpropanoate 4m. Method III.

A 10.0-20.0 mL Smith microwave vial was charged with amine **1h** (5.0 mmol, 0.965 g) and 10.0 mL DME. Acetaldehyde **2a** (6.0 mmol, 0.335 mL) was added and the mixture was stirred for 30 s before adding trimethylsilyl cyanide (5.5 mmol, 0.710 mL). The vial was sealed and irradiated with microwaves at 80 °C for 10 min (step 1). The solvent was removed under a stream of nitrogen gas and the residue was dissolved in 15 mL diethylether. HCl gas was bubbled through the reaction mixture for 5 min followed by evaporation under a stream of nitrogen gas. DME (10.0 mL) and oxalyl chloride (12.5 mmol, 1.09 mL) were added and the vial was sealed. After 30 s stirring the overpressure was released with a needle before irradiation with microwaves for 25 min at 145 °C (creating a pressure of 20 bar). Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 10:90 to 20:80, yielded pure product **4m** as pale yellow solid, 0.973 g (55%).

General Procedure for Preparation of α-Aminonitrile 3e*,i-k. Method IV.

A 2.0-5.0 mL Smith microwave vial was charged with 1 equiv amine **1e,i-j** and 3.0 mL DME. (Diisopropylamine (1.2 equiv) was added if the amine was a HCl salt). Addition of 1.2 equiv aldehyde **2a,b** or phenylacetaldehyde (**2f**) followed by 30 s stirring before addition of 1.1 equiv trimethylsilyl cyanide. The vial was sealed and irradiated with microwaves for 10

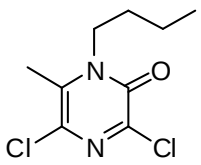
minutes at stated temperatures. The solvent was evaporated in vacuum and the crude residue purified by flash chromatography yielding pure products **3e*,i-k**.

General Procedure for Preparation of 2(1*H*)-Pyrazinones 4i,o-s from Pure α-Aminonitriles. Method V.

A 2.0-5.0 mL Smith microwave vial was loaded with 1 mmol α-aminonitrile **3a,e*,e,i-k** and 5.0 mL diethylether. HCl gas was bubbled through the reaction mixture for 5 min followed by removal of the diethylether under a stream of nitrogen gas. DME (3.0 mL) and oxalyl chloride (2.5 mmol, 214 µL) were added and the vial was sealed. After 30 s stirring the overpressure was released and the reaction irradiated by microwaves for 10 min at 170 °C. Purification by flash chromatography yielded pure products **4i,o-s**.

General Procedure for Determination of Diasteriomeric Ratio of compounds 4j-n. Method VI.

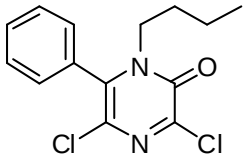
A 0.5-2.0 mL Smith microwave vial was loaded with 2(1*H*)-pyrazinones **4j-n** (0.05-0.15 mmol), (1*S*,2*R*)-*cis*-1-amino-2-indanol (3 equiv.) and acetonitrile (2.0 mL). The reaction was then irradiated with microwaves: **4j** at 150 °C for 1.5 h; **4k** at 140 °C for 2 h; **4l** at 140 °C for 0.5 h; **4m** at 160 °C for 2 h; **4n** at 160 °C for 1.5 h. The diasteriomeric ratios were determined by ^{1}H-NMR or by HPLC separation with ELSD and ESI-MS detection.

1-Butyl-3,5-dichloro-6-methylpyrazin-2(1*H*)-one (4a) 

The compound was prepared according to method I, using 60 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 10:90 to 20:80. Pale

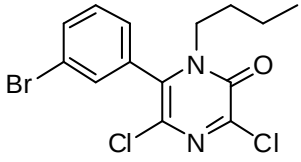
yellow oil, 72% yield. ^{1}H NMR ($CDCl_3$) δ 4.06 (m, 2H), 2.49 (s, 3H), 1.66 (m, 2H), 1.43 (qm, *J*=7.4 Hz, 2H), 0.97 (t, *J*=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 152.7, 143.5, 135.6, 123.8, 47.4, 29.9, 20.2, 16.6, 13.7. ESI-MS (*m/z)* 235 (M + H^+), 471 (2M + H^+). Anal. Calcd for $C_9H_{12}Cl_2N_2O$: C, 45.98; H, 5.14; N, 11.91. Found: C, 46.14; H, 5.25; N, 12.04.

1-Butyl-3,5-dichloro-6-phenylpyrazin-2(1*H*)-one (4b)



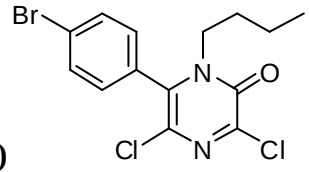
The compound was prepared according to method I, using 60 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 5:95 to 15:85. Pale yellow oil, 58% yield. ^{1}H NMR ($CDCl_3$) δ 7.49-7.44 (m, 3H), 7.22 (m, 2H), 3.66 (m, 2H), 1.43 (m, 2H), 1.03 (qm, *J* = 7.4 Hz, 2H), 0.62 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 152.4, 145.9, 138.6, 130.7, 130.5, 129.4, 129.1, 124.1, 48.6, 30.0, 19.9, 13.4. ESI-MS (*m/z)* 297 (M + H^+), 595 (2M + H^+). Anal. Calcd for $C_{14}H_{14}Cl_2N_2O$: C, 56.58; H, 4.75; N, 9.43. Found: C, 56.68; H, 4.82; N, 9.35.

6-(3-Bromophenyl)-1-butyl-3,5-dichloropyrazin-2(1*H*)-one (4c)



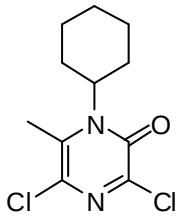
The compound was prepared according to method I, using 60 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 5:95 to 15:85. Colourless oil, 57% yield. ^{1}H NMR ($CDCl_3$) δ 7.71 (dm, *J*=8.1 Hz, 1H), 7.49 (m, 1H), 7.45 (ddm, *J* =8.8, 8.1 Hz, 1H), 7.27 (dm, *J*=8.8 Hz, 1H), 3.75 (m, 2H), 1.54 (m, 2H), 1.17 (qm, *J*=7.3 Hz, 2H), 0.76 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 151.2, 145.6, 135.9, 132.9, 131.3, 131.1, 130.0, 126.9, 123.1, 122.4, 47.7, 29.1, 18.9, 12.4. ESI-MS (*m/z)* 377 (M + H^+), 753

(2M + H^+). Anal. Calcd for $C_{14}H_{13}BrCl_2N_2O$: C, 44.71; H, 3.48; N, 7.45. Found: C, 44.84; H, 3.61; N, 7.40.



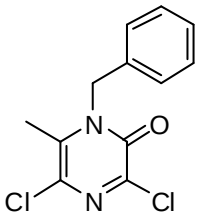
6-(4-Bromophenyl)-1-butyl-3,5-dichloropyrazin-2(1*H*)-one (4d)

The compound was prepared according to method I, using 80 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 5:95 to 15:85. White solid, 43% yield. ^{1}H NMR ($CDCl_3$) δ 7.70 (m, 2H), 7.20 (m, 2H), 3.75 (m, 2H), 1.51 (m, 2H), 1.15 (qm, *J*=7.3 Hz, 2H), 0.76 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 152.2, 146.3, 137.4, 132.8, 130.8, 129.3, 125.3, 124.1, 48.6, 30.1, 20.0, 13.4. ESI-MS (*m/z)* 377 (M + H^+), 753 (2M + H^+). Anal. Calcd for $C_{14}H_{13}BrCl_2N_2O$: C, 44.71; H, 3.48; N, 7.45. Found: C, 44.88; H, 3.63; N, 7.44.

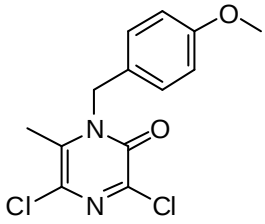


3,5-Dichloro-1-cyclohexyl-6-methylpyrazin-2(1*H*)-one (4e)

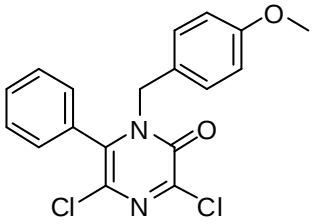
The compound was prepared according to method I, using 60 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 5:95 to 15:85. White solid, 79% yield. ^{1}H NMR ($CDCl_3$) δ 4.00 (m, 1H), 2.64 (m, 2H), 2.46 (s, 3H), 1.85 (m, 2H), 1.67-1.54 (m, 3H), 1.33-1.16 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 152.6, 145.1, 135.4, 123.9, 63.5, 27.2, 26.0, 24.8, 17.3. ESI-MS (*m/z)* 261 (M + H^+), 523 (2M + H^+). Anal. Calcd for $C_{11}H_{14}Cl_2N_2O$: C, 50.59; H, 5.40; N, 10.73. Found: C, 50.62; H, 5.49; N, 10.59.

1-Benzyl-3,5-dichloro-6-methylpyrazin-2(1*H*)-one (4f)[6] 

The compound was prepared according to method I, using 60 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 10:90 to 20:80. Colourless oil, 67% yield.

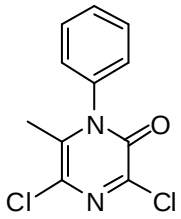
3,5-Dichloro-1-(4-methoxybenzyl)-6-methylpyrazin-2(1*H*)-one (4g)[7] 

The compound was prepared according to method I, using 80 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 10:90 to 25:75. Colourless oil, 55% yield.

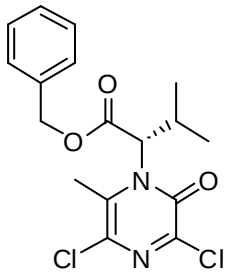
3,5-Dichloro-1-(4-methoxybenzyl)-6-phenylpyrazin-2(1*H*)-one (4h) 

The compound was prepared according to method I, using 80 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 10:90 to 20:80. Pale yellow oil, 38% yield. ^{1}H NMR ($CDCl_3$) δ 7.57-7.44 (m, 3H), 7.12 (m, 2H), 6.79-6.68 (m, 4H), 5.03 (br s, 2H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.7, 153.0, 146.3, 138.6, 130.7, 130.4, 129.7, 129.6, 129.3, 127.0, 124.5, 114.0, 55.4, 50.9. ESI-MS (*m/z)* 361 ($M + H^+$), 723 ($2M + H^+$). Anal. Calcd for $C_{18}H_{14}Cl_2N_2O_2$: C, 59.85; H, 3.91; N, 7.76. Found: C, 59.80; H, 3.92; N, 7.65.

3,5-Dichloro-6-methyl-1-phenylpyrazin-2(1*H*)-one (4i)[8]

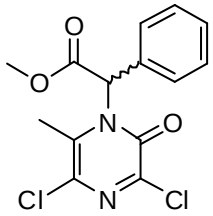


The compound was prepared according to method I using 100 °C temperature in step 1 or from **3i** utilizing method V. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 10:90 to 20:80. White solid, 29% yield utilizing method I, 70% yield utilizing method V. ^{13}C NMR ($CDCl_3$) δ 152.9, 144.7, 137.2, 136.0, 130.5, 130.3, 127.0, 123.5, 18.3.



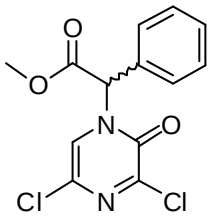
Benzyl 2-(3,5-dichloro-6-methyl-2-oxopyrazin-1(2*H*)-yl)-3-methylbutanoate (4j)

The compound was prepared according to method I, using 100 °C temperature in step 1 or by method II, using 80 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 5:95 to 15:85. Colourless oil, 51% yield from method I, 53% yield from method II. The product **4j** was isolated in >98:2 diastereomeric ratio according to ^{1}H-NMR using method VI. ^{1}H NMR (CD_3OD at 50 °C) δ 7.34-7.21 (m, 5H), 5.22 (d, *J*=12.2 Hz, 1H), 5.06 (d, *J*=12.2 Hz, 1H), 4.90 (m, 1H), 2.88 (m, 1H), 2.45 (s, 3H), 1.28 (d, *J*=6.5 Hz, 3H), 0.71 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (CD_3OD at 50 °C) δ 168.8, 154.0, 144.2, 138.2, 136.7, 129.6, 129.4, 129.3, 125.4, 68.5, 68.0, 28.4, 22.0, 19.2, 17.7. ESI-MS (*m/z)* 369 ($M + H^+$), 739 ($2M + H^+$). $[\alpha]^{21}_D$ -53.5 ° (*c* 0.95, CH_2Cl_2).Anal. Calcd for $C_{17}H_{18}Cl_2N_2O_3$: C, 55.30; H, 4.91; N, 7.59. Found: C, 55.46; H, 5.01; N, 7.50.



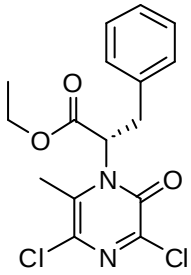
Methyl 2-(3,5-dichloro-6-methyl-2-oxopyrazin-1(2*H*)-yl)-2-phenylacetate (4k)

The compound was prepared according to method I, using 80 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 15:85 to 25:75. Pale yellow solid, 44% yield. The product **4k** was isolated in a 47:54 diastereomeric ratio according to HPLC separation with ELSD and ESI-MS detection using method VI. ^{1}H NMR (CD_3OD) δ 7.43-7.35 (m, 5H), 6.47 (br s, 1H), 3.77 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (CD_3OD) δ 168.7, 154.4, 144.7, 138.2, 133.7, 129.9, 129.72, 129.69, 125.7, 65.4, 53.5, 17.5. EIS-MS (*m/z)* 327 ($M + H^+$), 655 ($2M + H^+$). $[\alpha]^{21}_D$ -57.5 ° (*c* 0.92, CH_2Cl_2). Anal. Calcd for $C_{14}H_{12}Cl_2N_2O_3$: C, 51.40; H, 3.70; N, 8.56. Found: C, 51.13; H, 3.64; N, 8.46.



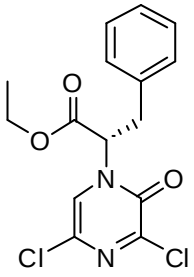
Methyl 2-(3,5-dichloro-2-oxopyrazin-1(2*H*)-yl)-2-phenylacetate (4l)

The compound was prepared according to method I, using 170 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 15:85. White semi solid, 38% yield. The product **4l** was isolated in a 44:56 diastereomeric ratio according to HPLC separation with ELSD and ESI-MS detection using method VI. ^{1}H NMR ($CDCl_3$) δ 7.54-7.48 (m, 3H), 7.31 (m, 2H), 6.94 (s, 1H), 6.51 (br s, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.1, 152.0, 146.8, 130.9, 130.8, 130.2, 129.5, 124.5, 124.3, 63.4, 53.6. ESI-MS (*m/z)* 313 ($M + H^+$), 627 ($2M + H^+$). $[\alpha]^{24}_D$ -0.3 ° (*c* 1.05, CH_2Cl_2). Anal. Calcd for $C_{13}H_{10}Cl_2N_2O_3$: C, 49.86; H, 3.22; N, 8.95. Found: C, 49.46; H, 3.30; N, 8.72.



Ethyl 2-(3,5-dichloro-6-methyl-2-oxopyrazin-1(2*H*)-yl)-3-phenylpropanoate (4m)

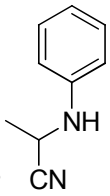
The compound was prepared according to method I, using 100 °C temperature in step 1 or by method III, using 80 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 10:90 to 20:80. Pale yellow solid; 63% yield from method I, 55% yield from method III. The product **4m** was isolated in a 97:3 diastereomeric ratio according to HPLC separation with ELSD and ESI-MS detection using method VI. ^{1}H NMR (CD_3OD at 50 °C) δ 7.28-7.21 (m, 3H), 7.05 (m, 2H), 5.36 (ddm, *J*=10.4, 4.5 Hz, 1H), 4.25 (qm, *J*=7.1 Hz, 2H), 3.59 (dd, *J*=14.1, 4.5 Hz, 1H), 3.49 (dd, , *J*=14.1, 10.4 Hz, 1H), 1.97 (s, 3H), 1.25 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (CD_3OD at 50 °C) δ 168.8, 153.8, 144.0, 138.5, 137.8, 130.3, 129.9, 128.5, 125.0, 64.7, 63.2, 34.1, 17.1, 14.3. ESI-MS (*m/z)* 355 ($M + H^+$), 711 ($2M + H^+$). $[\alpha]^{21}_D$ -328.0 ° (*c* 0.99, CH_2Cl_2). Anal. Calcd for $C_{16}H_{16}Cl_2N_2O_3$: C, 54.10; H, 4.54; N, 7.89. Found: C, 54.28; H, 4.96; N, 7.92.



Ethyl 2-(3,5-dichloro-2-oxopyrazin-1(2*H*)-yl)-3-phenylpropanoate (4n)

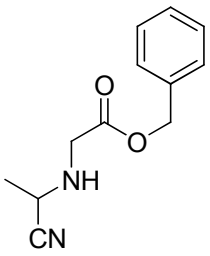
The compound was prepared according to method I, using 170 °C temperature in step 1. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 10:90 to 20:80. White solid, 54% yield. The product **4n** was isolated in >98:2 diastereomeric ratio according to ^{1}H-NMR using method VI. ^{1}H NMR (CD_3OD) δ 7.56 (s, 1H), 7.29-7.18 (m, 3H), 7.12 (m, 2H), 5.43 (dd, *J*=10.8, 5.5 Hz, 1H), 4.25 (q, *J*=7.2 Hz, 2H), 3.57 (dd, *J*=14.4, 5.5 Hz, 1H), 3.39 (dd,

J=14.4, 10.8 Hz, 1H), 1.25 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (CD_3OD) δ 167.7, 151.4, 146.9, 134.3, 129.1, 128.8, 127.8, 125.4, 123.7, 62.7, 61.7, 36.3, 14.1. ESI-MS (*m/z)* 341 ($M + H^+$), 683 ($2M + H^+$). HRMS calcd for $C_{15}H_{14}Cl_2N_2O_3$ ($M + H^+$) 341.0460; found: 341.0447. $[\alpha]^{21}_D$ -25.8 ° (*c* 1.05, CH_2Cl_2).



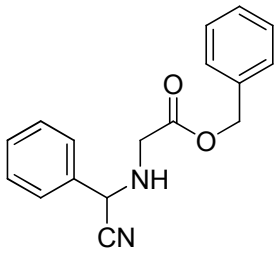
2-(Phenylamino)propanenitrile (3e*) [1-3]

The compound was prepared according to method IV, using aniline **1e** (2.6 mmol, 0.239 g), acetaldehyde **2a** (3.1 mmol, 172 µL), trimethylsilyl cyanide (2.8 mmol, 354 µL) and a temperature of 100 °C. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 10:90 to 15:85. White solid, 42% yield. ^{1}H NMR (CD_3OD) δ 7.19 (m, 2H), 6.80-6.73 (m, 3H), 4.42 (m, 1H), 1.60 (m, 3H); ^{13}C NMR (CD_3OD) δ 147.5, 130.2, 122.0, 120.0, 115.0, 41.7, 19.4. ESI-MS (*m/z)* 147 ($M + H^+$).



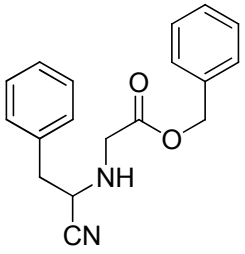
Benzyl 2-(1-cyanoethylamino)acetate (3i)[4]

The compound was prepared according to method IV, using HCl×HGlyOBn (2.0 mmol, 0.402 g), diisopropylamine (2.3 mmol, 400 µL), acetaldehyde **2a** (2.5 mmol, 140 µL), trimethylsilyl cyanide (2.2 mmol, 280 µL) and a temperature of 100 °C. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 30:70 to 75:25. Colorless oil, 68% yield. ^{13}C-NMR (CD_3OD) δ 172.5, 137.3, 129.7, 129.5 (two peaks), 121.7, 67.8, 49.2, 45.8, 19.6.



Benzyl 2-(cyano(phenyl)methylamino)acetate (3j)

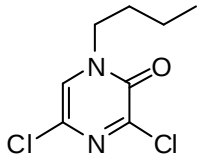
The compound was prepared according to method IV, using HCl×HGlyOBn (2.0 mmol, 0.403 g), diisopropylamine (2.4 mmol, 400 µL), benzaldehyde **2b** (2.5 mmol, 250 µL), trimethylsilyl cyanide (2.2 mmol, 280 µL) and a temperature of 100 °C. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 30:70 to 75:25. Colorless oil, 83% yield. ^{1}H-NMR (CD_3OD) δ 7.52-7.49 (m, 2H), 7.42-7.28 (m, 8H), 5.19 (d, *J*=12.3 Hz, 1H), 5.15 (d, *J*=12.3 Hz, 1H), 5.05 (s, 1H), 3.58 (d, *J*=17.5 Hz, 1H), 3.51 (d, *J*=17.5 Hz, 1H). ^{13}C-NMR (CD_3OD) δ 172.5, 137.2, 136.1, 130.2, 130.1, 129.7, 129.5 (two peaks), 128.8, 67.8, 54.3, 48.7. ESI-MS (*m/z)* 281 ($M + H^+$), 561 ($2M + H^+$).. Anal. calcd for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 10.00. Found: C, 72.63; H, 5.86; N, 9.83.



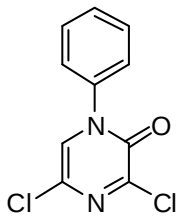
Benzyl 2-(1-cyano-2-phenylethylamino)acetate (3k)[5]

The compound was prepared according to method IV, using HCl×HGlyOBn (2.0 mmol, 0.402 g), diisopropylamine (2.4 mmol, 400 µL), 2-phenylacetaldehyde (2.5 mmol, 310 µL), trimethylsilyl cyanide (2.2 mmol, 280 µL) and a temperature of 100 °C. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 30:70 to 75:25. Colorless oil, 88% yield. ^{1}H-NMR (CD_3OD) δ 7.37-7.28 (m, 10H), 5.19 (d, *J*=12.3 Hz, 1H), 5.16 (d, *J*=12.3 Hz, 1H), 4.01 (dd, *J*=8.7, 5.9 Hz, 1H), 3.62 (d, *J*=17.4 Hz, 1H), 3.54 (d, *J*=17.4 Hz, 1H), 3.09 (dd, *J*=13.5, 5.9 Hz, 1H), 2.99 (dd, *J*=13.5, 8.7 Hz, 1H). ^{13}C-NMR (CD_3OD) δ 172.5, 137.3, 137.1, 130.6,

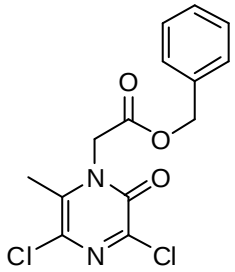
129.8, 129.7, 129.5 (two peaks), 128.5, 67.8, 52.8, 49.3, 40.2. ESI-MS (*m/z)* 295 ($M + H^+$), 589 ($2M + H^+$).

1-Butyl-3,5-dichloropyrazin-2(1H)-one (4o) 

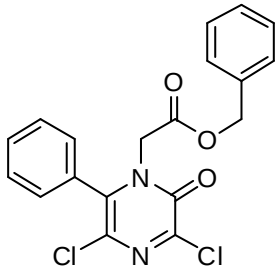
The compound was prepared according to method V. The α-aminonitrile **3a** was bought. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 10:90 to 20:80. White solid, 64% yield. ^{1}H NMR ($CDCl_3$) δ 7.21 (s, 1H), 3.93 (m, 2H), 1.75 (m, 2H), 1.38 (qm, *J*=7.3 Hz, 2H), 0.96 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 151.9, 147.5, 126.9, 123.9, 51.3, 30.7, 19.9, 13.6. ESI-MS (*m/z)* 221 ($M + H^+$), 443 ($2M + H^+$). Anal. Calcd for $C_8H_{10}Cl_2N_2O$: C, 43.46; H, 4.56; N, 12.67. Found: C, 43.51; H, 4.58; N, 12.63.

3,5-Dichloro-1-phenylpyrazin-2(1*H*)-one (4p)[9] 

The compound was prepared according to method V. The α-aminonitrile **3e** was bought. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 10:90 to 20:80. White solid, 80% yield.

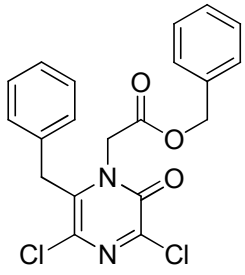
Benzyl 2-(3,5-dichloro-6-methyl-2-oxopyrazin-1(2*H*)-yl)acetate (4q)[4] 

The compound was prepared according to method V. Purification by flash chromatography, eluent ethyl acetate:iso-hexane 20:80 to 35:65. Pale yellow solid, 86% yield. ^{13}C-NMR ($CDCl_3$) δ 166.1, 152.7, 143.8, 135.2, 134.6, 129.1, 129.0, 128.7, 124.0, 68.4, 47.6, 16.9. ESI-MS (*m/z)* 327 ($M + H^+$), 655 ($2M + H^+$).



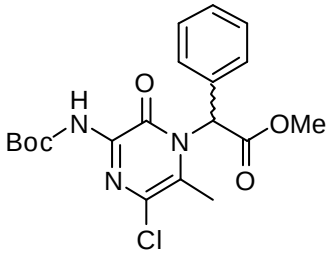
Benzyl 2-(3,5-dichloro-2-oxo-6-phenylpyrazin-1(2*H*)-yl)acetate (4r)[10]

The compound was prepared according to method V. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 20:80 to 35:65. Pale yellow solid, 65% yield. ^{1}H-NMR (CD_3OD) δ 7.54 (m, 1H), 7.47 (m, 2H), 7.35 (m, 3H), 7.30-7.26 (m, 4H), 5.15 (s, 2H), 4.54 (s, 2H). ^{13}C-NMR (CD_3OD) δ 168.1, 154.0, 146.3, 140.2, 136.7, 132.1, 131.5, 130.7, 130.3, 129.8 (two peaks), 129.7, 125.3, 68.9, 50.7. ESI-MS (*m/z)* 389 ($M + H^+$), 779 ($2M + H^+$).



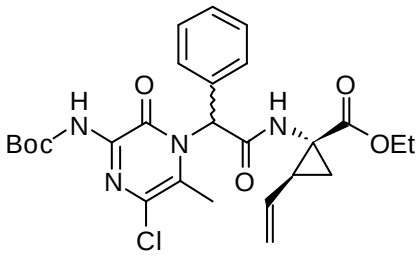
Benzyl 2-(6-benzyl-3,5-dichloro-2-oxopyrazin-1(2*H*)-yl)acetate (4s)[10]

The compound was prepared according to method V. Purification by flash chromatography, eluent ethyl acetate:*iso*-hexane 20:80 to 35:65. Pale yellow solid, 56% yield. ^{1}H-NMR (CD_3OD) δ 7.38-7.25 (m, 8H), 7.17 (m, 2H), 4.96 (s, 2H), 4.82 (s, 2H), 4.25 (s, 2H). ^{13}C-NMR (CD_3OD) δ 167.3, 154.6, 145.3, 139.3, 136.8, 135.4, 130.4, 129.8, 129.7, 129.4 (two peaks), 128.8, 126.3, 68.8, 49.5, 36.5. ESI-MS (*m/z)* 403 ($M + H^+$), 807 ($2M + H^+$).



Methyl 2-(3-(tert-butoxycarbonylamino)-5-chloro-6-methyl-2-oxopyrazin-1(2H)-yl)-2-phenylacetate (5)

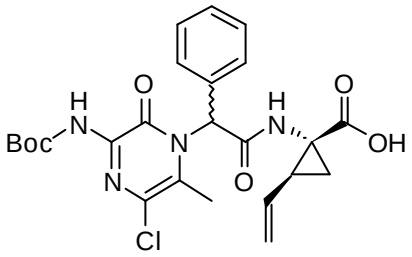
A 2.0-5.0 mL Smith microwave vial was charged with **4k** (0.196 g, 0.601 mmol), *tert*-butyl carbamate (0.353 g, 3.01 mmol), $Pd(OAc)_2$ (0.007 g, 0.052 mmol), Xantphos (0.028 g, 0.048 mmol) and Cs_2CO_3 (0.392 g, 1.20 mmol). The vial was sealed and irradiated with microwaves for 30 min at 100 °C. The solvent was removed and the residue purified by flash chromatography, eluent DCM:ethyl acetate 100:2 to 100:4 yielding the sought product **5** in 51% yield, 0.090 g as a white solid. ^{1}H NMR ($CDCl_3$ with two drops of D_2O) δ 7.41-7.29 (m, 5H), 6.25 (br s, 1H), 3.81 (s, 3H), 2.33 (s, 3H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 167.4, 151.2, 149.5, 143.3, 132.5, 129.1, 129.0, 128.3, 126.5, 126.0, 82.4, 62.7, 53.4, 28.3, 17.0. ESI-MS (*m/z)* 408 ($M + H^+$), 815 ($2M + H^+$). $[\alpha]^{21}_D$ -0.2 ° (*c* 1.09, CH_2Cl_2). Anal. Calcd for $C_{19}H_{22}ClN_3O_5x0.25H_2O$: C, 55.34; H, 5.50; N, 10.19. Found: C, 55.48; H, 5.26; N, 10.14.



(1*R*,2*S*)-Ethyl 1-(2-(3-(*tert*-butoxycarbonylamino)-5-chloro-6-methyl-2-oxopyrazin-1(2*H*)-yl)-2-phenylacetamido)-2-vinylcyclopropanecarboxylate (6)

Compound **5** (0.37 mmol, 0.150 g) was dissolved in THF (7.0 mL). A solution of LiOH (3.8 mmol, 0.092 g,) and H_2O (4.0 mL) was added and the reaction was stirred at room temperature for 7 h. Water (20 mL) was added and the THF was removed in vacuo. The pH

was adjusted to ≈2 using 1 M HCl (aq). The aqueous phase was extracted twice with ethyl acetate, the organic phases were combined and the solvent was removed in vacuo. The corresponding acid was used in the subsequent coupling reaction without further purification. The crude acid (0.051 g), (1*R*,2*S*)-ethyl 1-amino-2-vinylcyclopropanecarboxylate hydrochloride (0.20 mmol, 0.039 g), HATU (0.16 mmol, 0.061 g) and DIEA (1.2 mmol, 0.20 mL) was dissolved in DMF (1.3 mL). The pH of the solution was controlled and found to be >10. The reaction was stirred at room temperature over night, after which another portion of (1*R*,2*S*)-ethyl 1-amino-2-vinylcyclopropanecarboxylate hydrochloride (0.13 mmol, 0.025 g), HATU (0.16 mmol, 0.062 g) and DIEA (0.6 mmol, 100 µL) were added. The pH was stable >10. Stirring was continued for a total of five days. Ethyl acetate (10 mL) was added, and the solution was washed with 0.1 M $NaHSO_4$ (3×5 mL) and $NaHCO_3$ (sat) (2×5 mL) and the solvent was removed in vacuo. The crude product **6** was purified by column chromatography (DCM:methanol 95:5) to give (0.057 g, 29% over two steps) as a diastereomeric mixture (approximately 1:1 as determined by NMR). ^{1}H-NMR ($CDCl_3$) δ 8.16 (s, 1H), 8.15 (s, 1H), 7.41 (m, 10 H), 6.65 (s, 1H), 6.56 (s, 1H), 6.36 (s, 1H), 6.14 (s, 1H), 5.74 (m, 2H), 5.28 (m, 2H), 5.12 (m, 2H), 4.16 (m, 4H), 2.37 (s, 3H), 2.34 (s, 3H), 2.24 (m, 1H), 2.10 (m, 1H), 1.90 (dd, *J*=8.2, 5.5 Hz, 1H), 1.85 (dd, *J*=8.2, 5.5 Hz, 1H), 1.67 (dd, *J*=9.7, 5.5 Hz, 1H), 1.54 (dd, *J*=9.7, 5.5 Hz, 1H), 1.52 (s, 18 H), 1.26 (t, *J*=7.1 Hz, 3H), 1.26 (t, *J*=7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 169.8 (two peaks), 167.0 (two peaks), 151.5, 151.4, 149.6, 149.5, 143.4, 143.3, 133.3, (two peaks), 133.1, 132.9, 129.7, 129.6 (two peaks), 129.4, 128.4, 128.3, 127.4, 127.3, 126.2 (broad signal), 118.5, 118.4, 82.3 (two peaks), 65.4, 64.7, 61.8 (two peaks), 40.5, 40.4, 34.2, 34.1, 28.3, 23.0 (two peaks), 17.5, 17.2, 14.4. Anal. Calcd for $C_{26}H_{31}ClN_4O_6$: C, 58.81; H, 5.88; N, 10.55. Found: C, 58.92; H, 5.80; N, 10.49.



(1*R*,2*S*)-1-(2-(3-(*Tert*-butoxycarbonylamino)-5-chloro-6-methyl-2-oxopyrazin-1(2*H*)-yl)-2-phenylacetamido)-2-vinylcyclopropanecarboxylic acid (7a and 7b)

Compounds **7a** and **7b** was prepared from diastereomeric mixture of **6** (0.11 mmol, 0.057 g), LiOH (1.2 mmol, 0.028 g), THF (3.0 mL) and H_2O (1.0 mL). After two days stirring at room temperature, the pH was adjusted to 2 using 1 M HCl (aq). The aqueous phase was extracted with ethyl acetate (3×10 mL), the organic phases were combined and the solvent was removed in vacuum. The crude product was purified by RP-HPLC (Sorbax SB-C8 column, MeCN:H_2O gradient with 0.1% TFA) to give the pure diastereomers **7a** (0.0029 g, yield 5.3 %) and **7b** (0.0035 g, yield 6.3%) of the title compound.

7a: ^{1}H-NMR ($CDCl_3$) δ 8.22 (s, 1H), 7.44 (m, 3H), 7.35 (m, 2H), 6.41 (s, 1H), 5.99 (s, 1H), 5.80 (ddd, *J*=17.1, 10.4, 8.4 Hz, 1H), 5.31 (dd, *J*=17.1, 1.9 Hz, 1H), 5.17 (dd, *J*=10.3, 1.9 Hz, 1H), 2.38 (s, 3H), 2.23 (m, 1H), 1.89 (dd, *J*=8.4, 5.7 Hz, 1H), 1.54 (s, 9H), 1.51 (dd, *J*=9.6, 5.7 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ 172.3, 168.2, 151.4, 149.8, 143.5, 133.0, 132.6, 130.2, (two peaks) 128.5, 127.3, 126.8, 119.0, 66.0, 40.4, 35.0, 28.4, 23.9, 17.1. HRMS calcd for $C_{24}H_{27}ClN_4O_6$ ($M+H^+$) 503.1697; found 503.1707. RP-HPLC purity, column A (ACE 5 C8-A3071, MeCN:H_2O linear gradient with 0.1% TFA, UV detection at 220 nm): 97.5%**.**

7b: ^{1}H-NMR ($CDCl_3$) δ 8.18 (s, 1H), 7.46 (m, 3H), 7.37 (m, 2H), 6.38 (brs, 1H), 5.92 (s, 1H), 5.78 (ddd, *J*=17.1, 10.3, 8.7 Hz, 1H), 5.31 (dd, *J*=17.1, 2.0 Hz, 1H), 5.17 (dd, *J*=10.3, 2.0 Hz, 1H), 2.39 (s, 3H), 2.20 (m, 1H), 1.90 (dd, *J*=8.4, 5.6 Hz, 1H), 1.57-1.53 (m, 10H). ^{13}C-NMR ($CDCl_3$) δ 172.3, 168.1, 151.4, 149.8, 143.6, 132.9, 132.2, 130.4, 130.3, 128.5, 127.2, 126.8, 119.1, 82.8, 66.3, 40.4, 35.5, 28.4, 23.7, 17.0. HRMS calcd for $C_{24}H_{27}ClN_4O_6$ ($M+H^+$)

503.1697; found 503.1699. RP-HPLC purity, column A (ACE 5 C8-A3071, MeCN:H_2O linear gradient with 0.1% TFA, UV detection at 220 nm): 98.6%.

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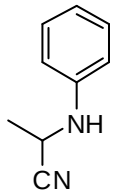
3e*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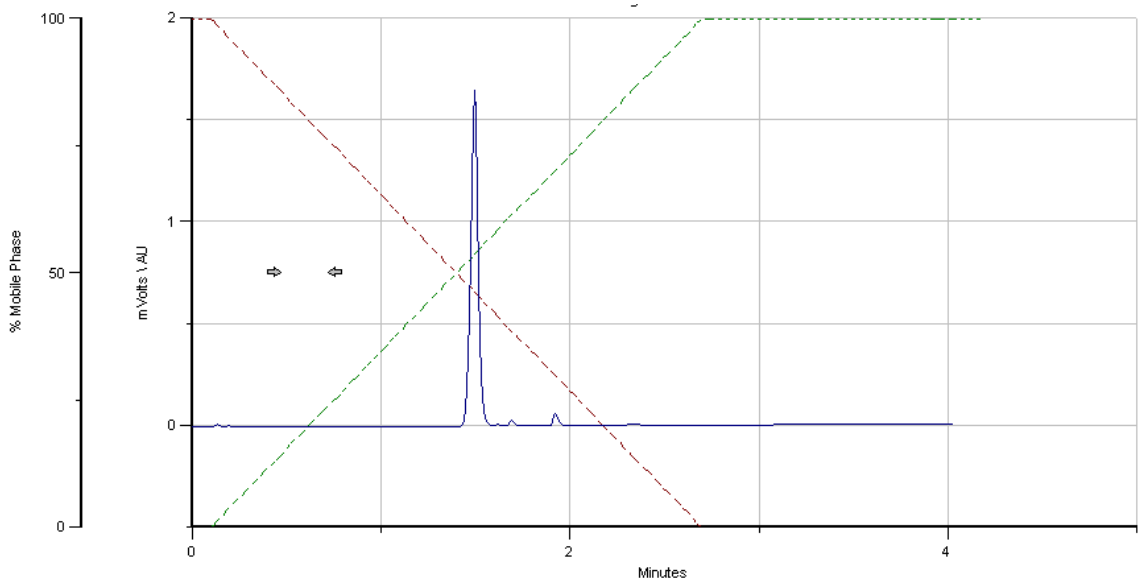
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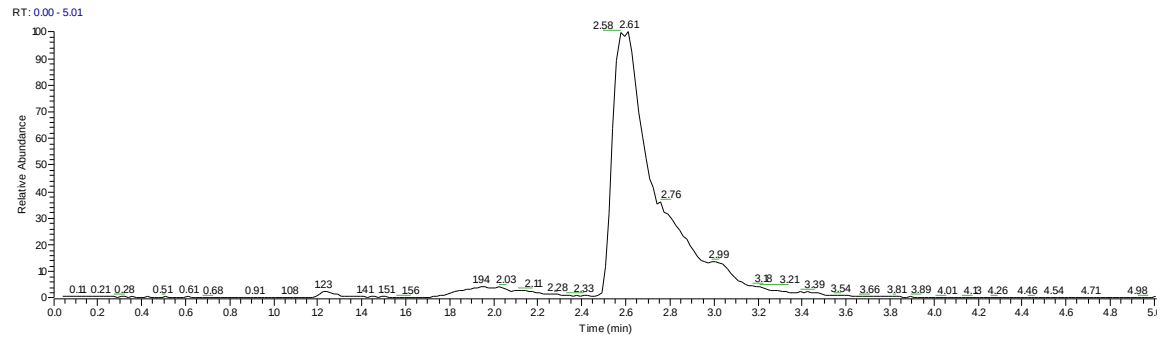
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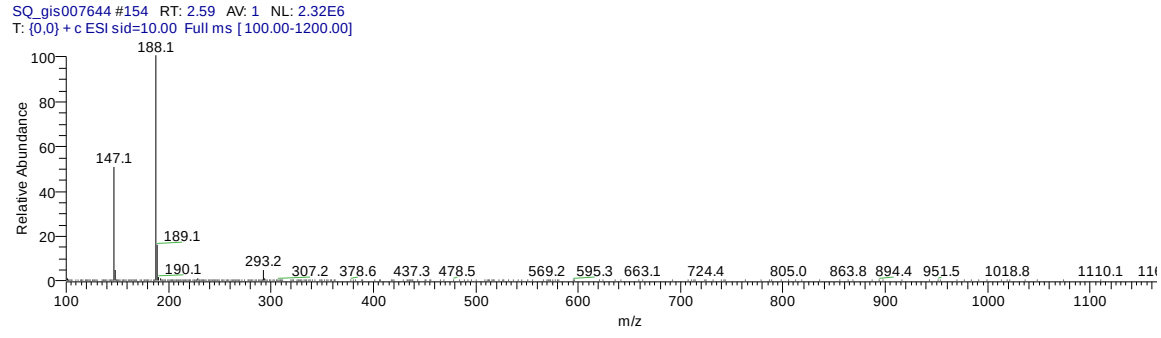
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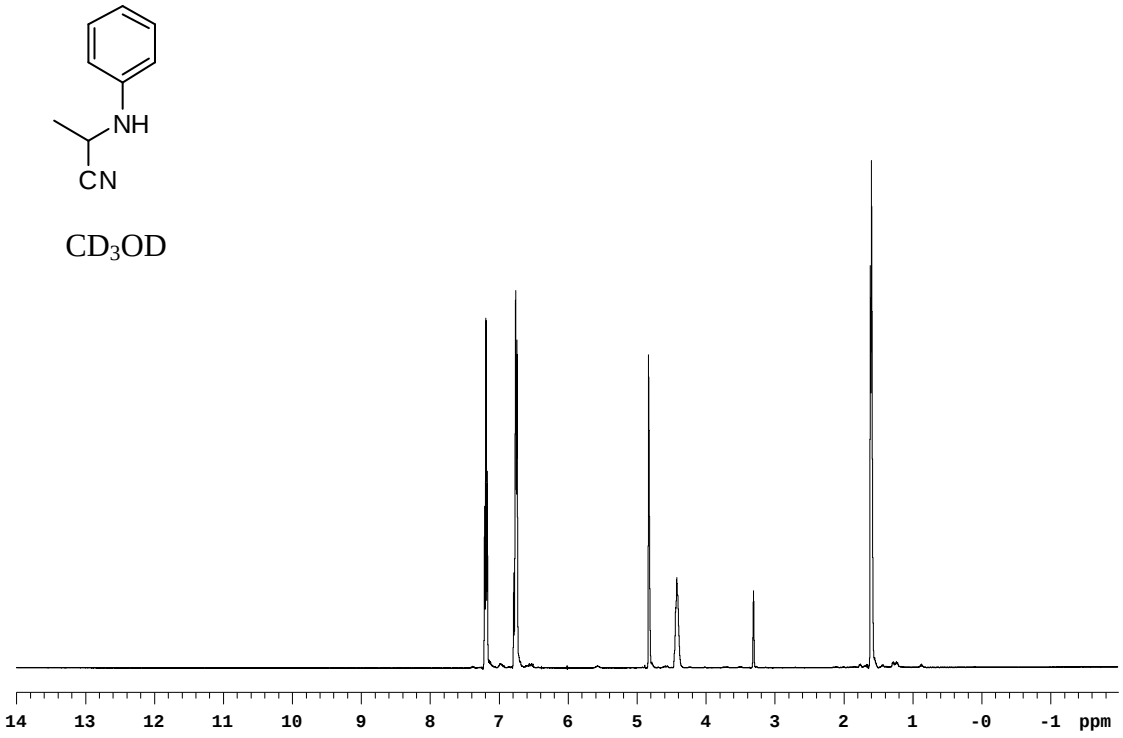
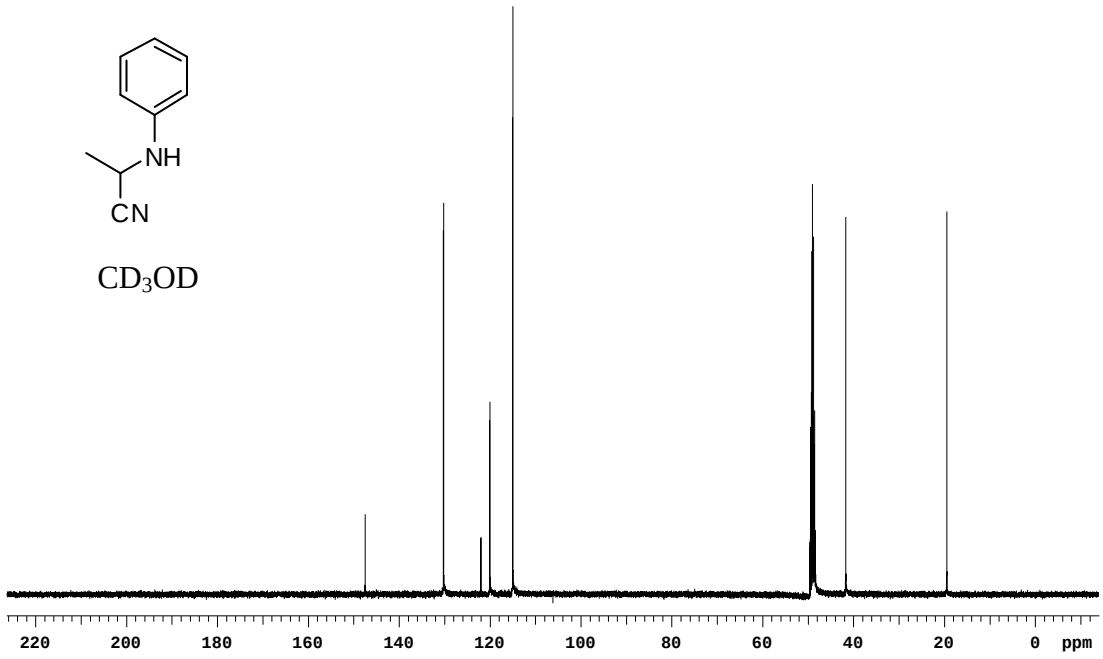
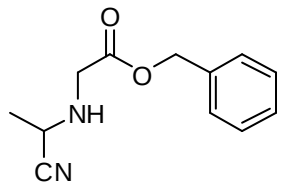
m/z

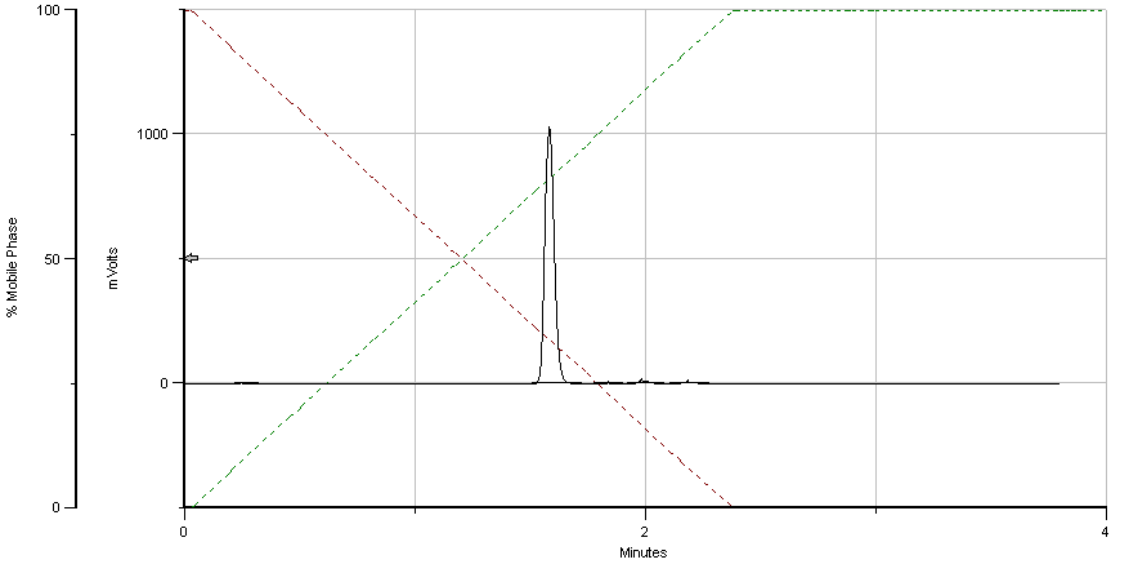
3e*

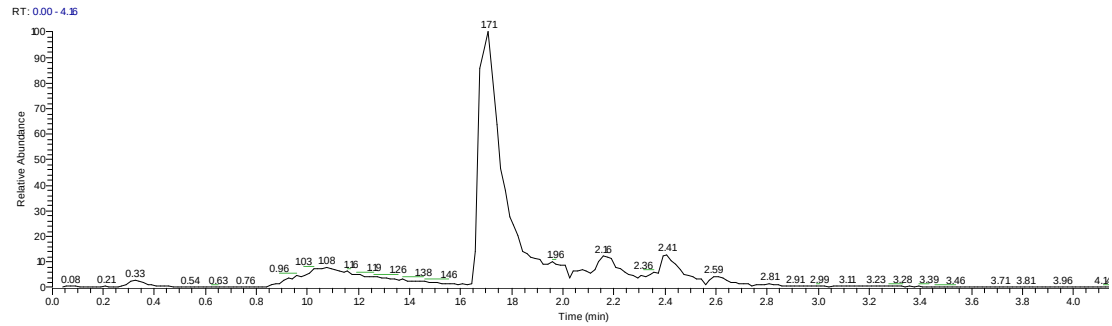

NH
CN
CD3OD
14 13 12 11 10 9 8 7 6 5 4 3 2 1 -0 -1 ppm

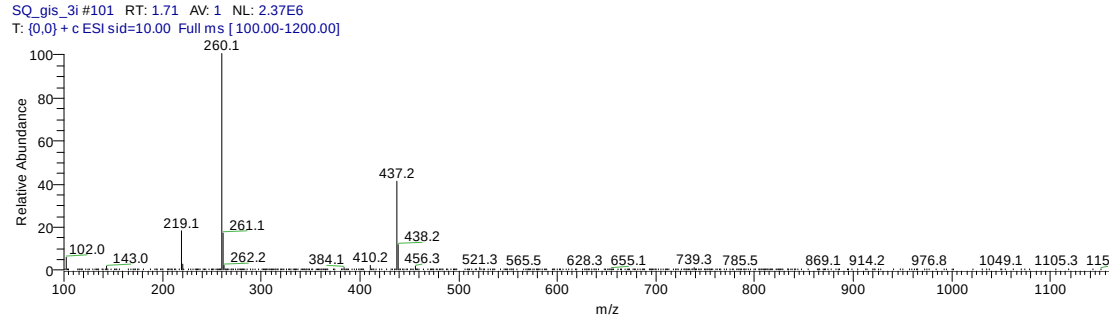

NH
CN
CD3OD
220 200 180 160 140 120 100 80 60 40 20 0 ppm

3i

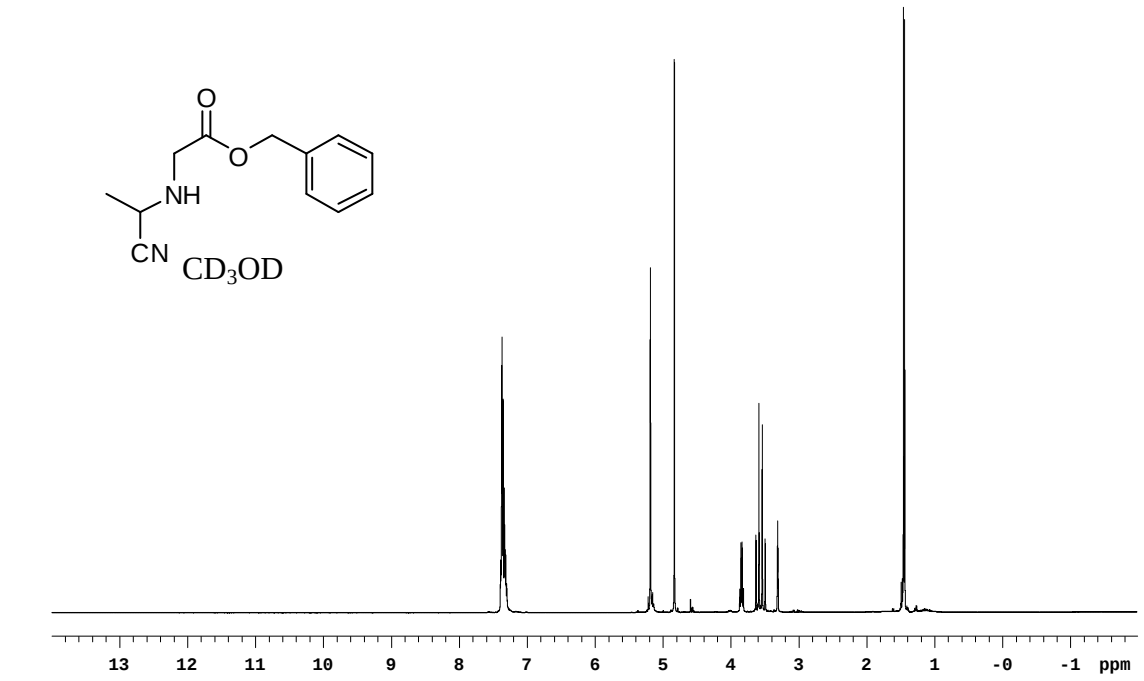

O
O
NH
CN

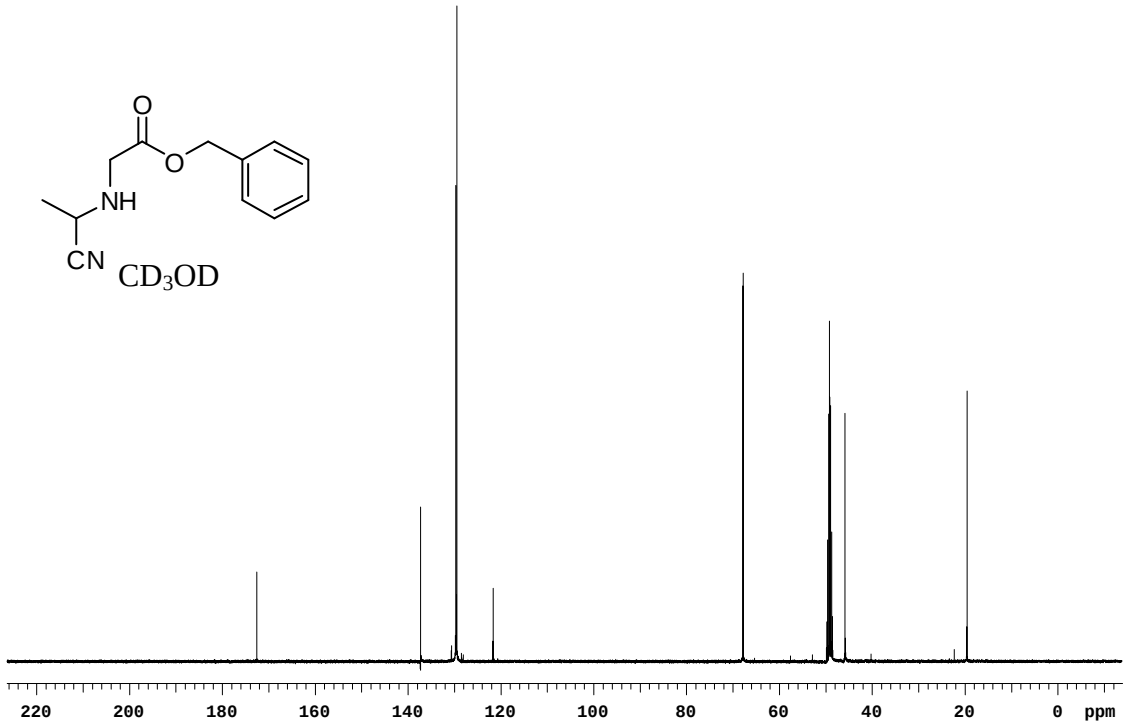

100
50
0
% Mobile Phase
1000
0
m Volts
0
2
4
Minutes


RT: 0.00 - 4.16
Relative Abundance
171
196
2.41
2.59
Time (min)

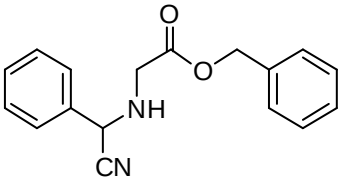

SQ_gis_3i #101 RT: 1.71 AV: 1 NL: 2.37E6
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
260.1
437.2
219.1
261.1
438.2
102.0
143.0
262.2
384.1
410.2
456.3
521.3
565.5
628.3
655.1
739.3
785.5
869.1
914.2
976.8
1049.1
1105.3
m/z

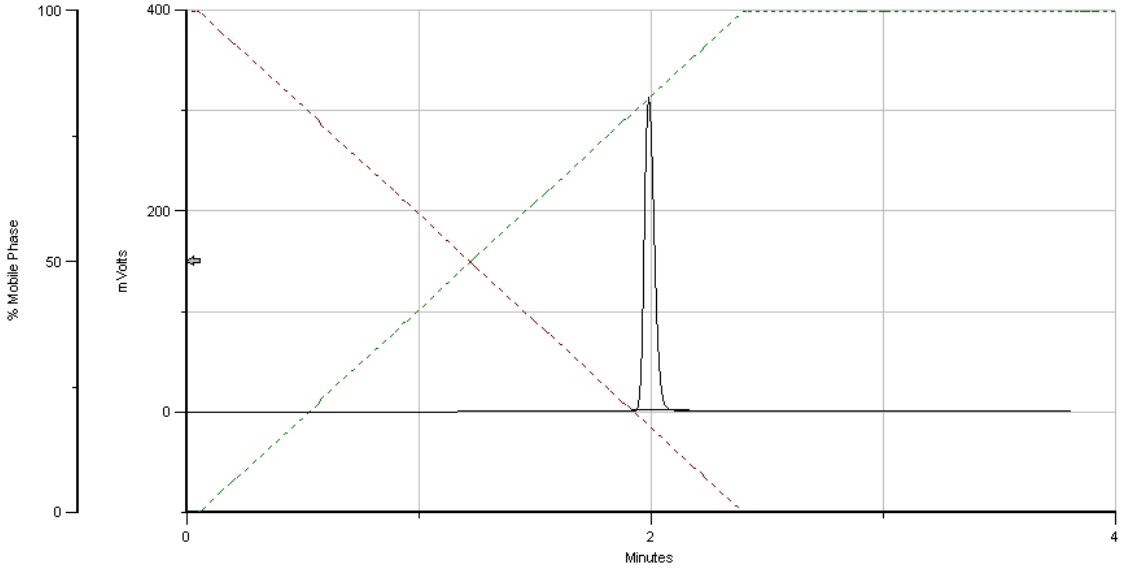
3i

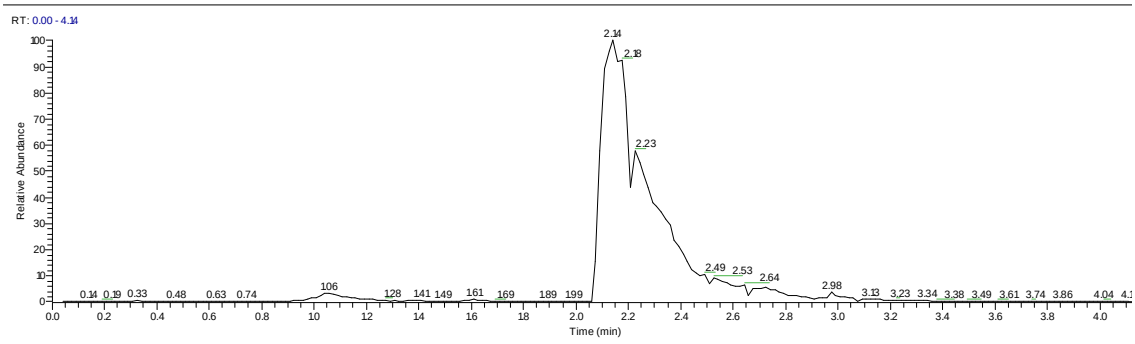

O
O
NH
CN
CD3OD
13 12 11 10 9 8 7 6 5 4 3 2 1 -0 -1 ppm

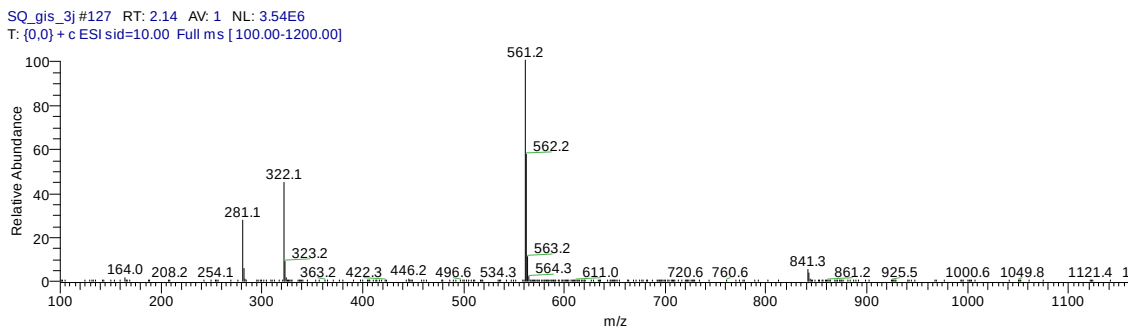

O
O
NH
CN
CD3OD
220 200 180 160 140 120 100 80 60 40 20 0 ppm

3j

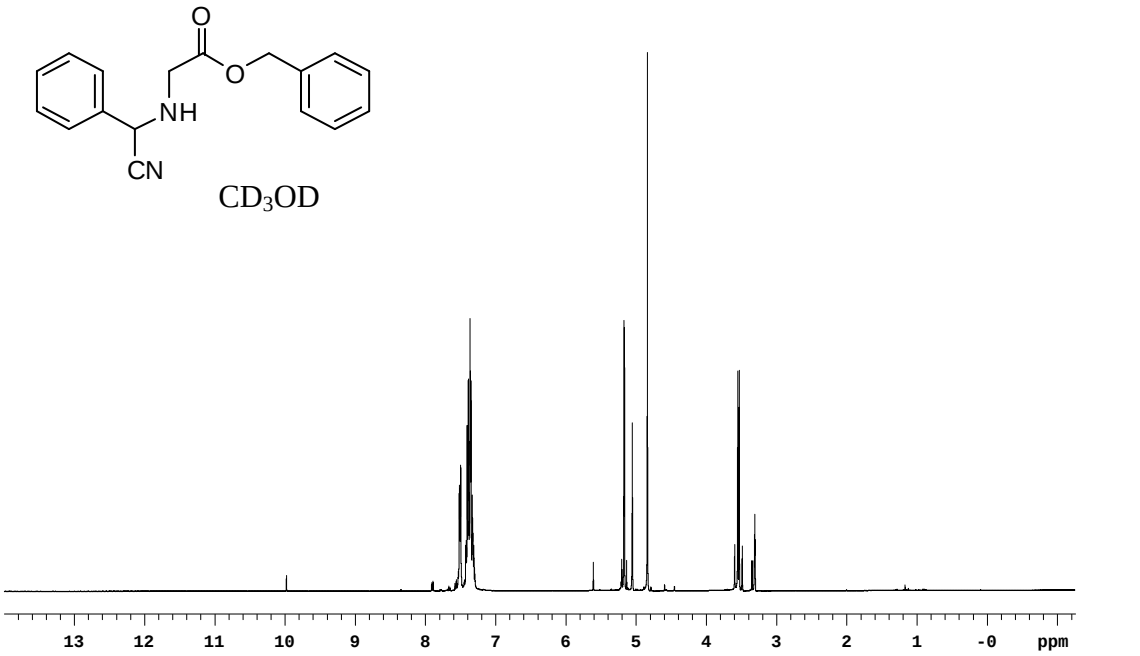

O
O
NH
CN

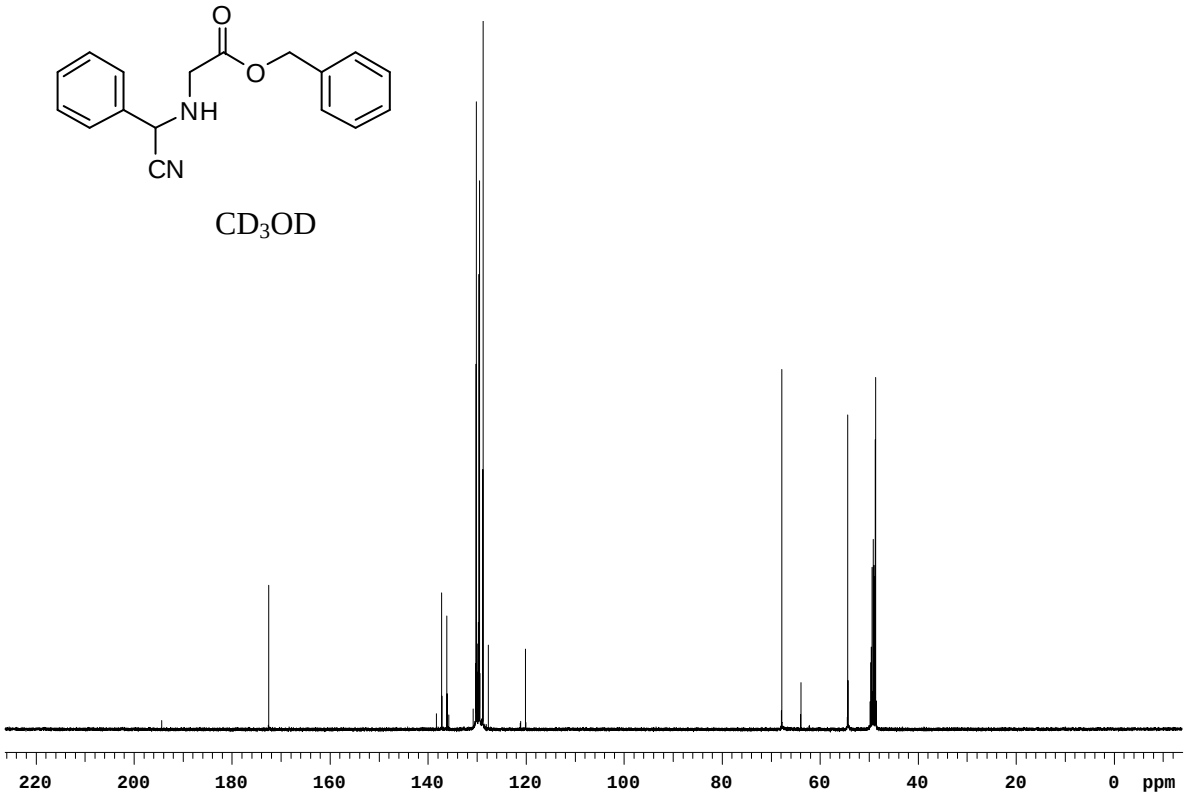

% Mobile Phase
m Volts
Minutes


RT: 0.00 - 4.14
Relative Abundance
Time (min)

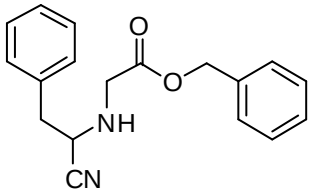

SQ_gis_3j #127 RT: 2.14 AV: 1 NL: 3.54E6
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
m/z

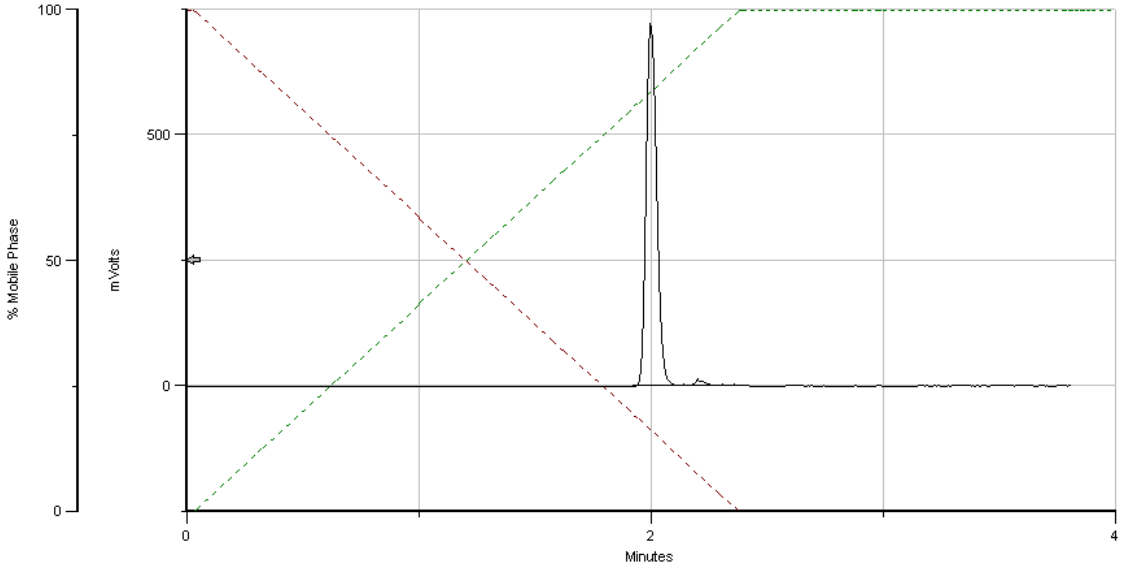
3j

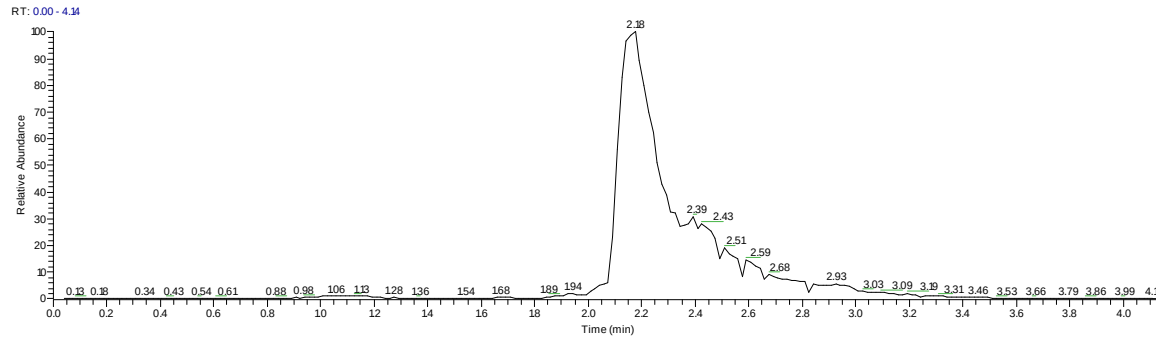

O
O
NH
CN
CD3OD
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

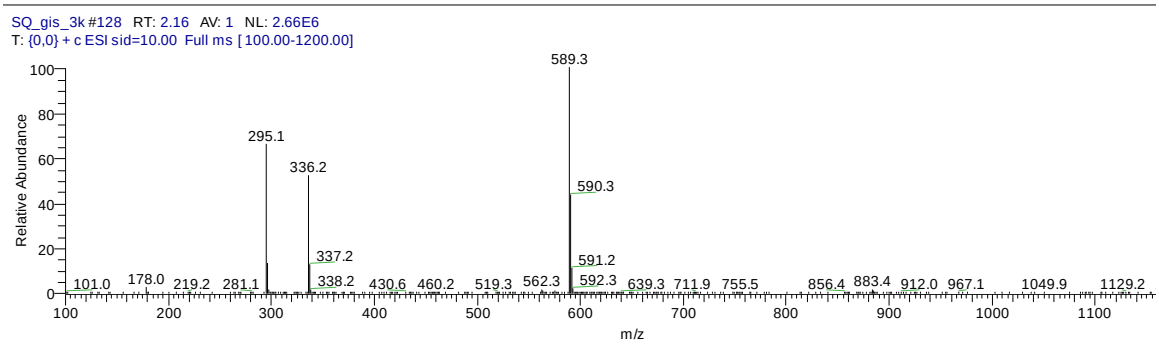

O
O
NH
CN
CD3OD
220
200
180
160
140
120
100
80
60
40
20
0
ppm

3k

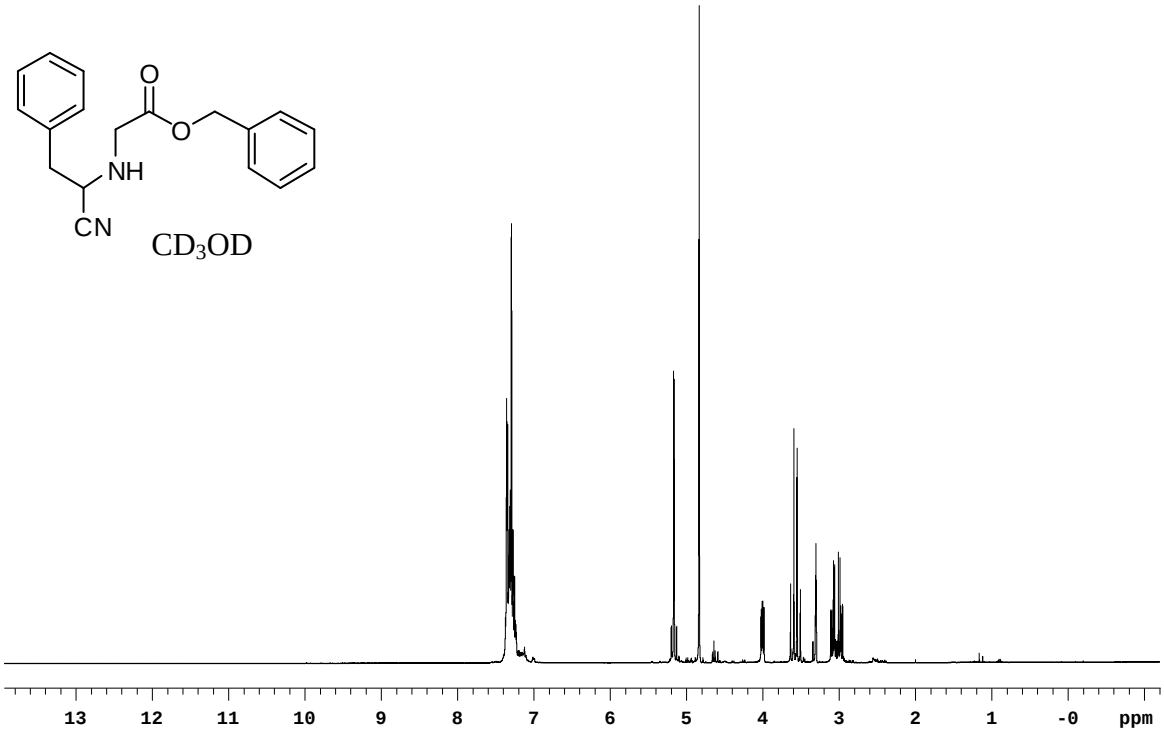

O
O
NH
CN

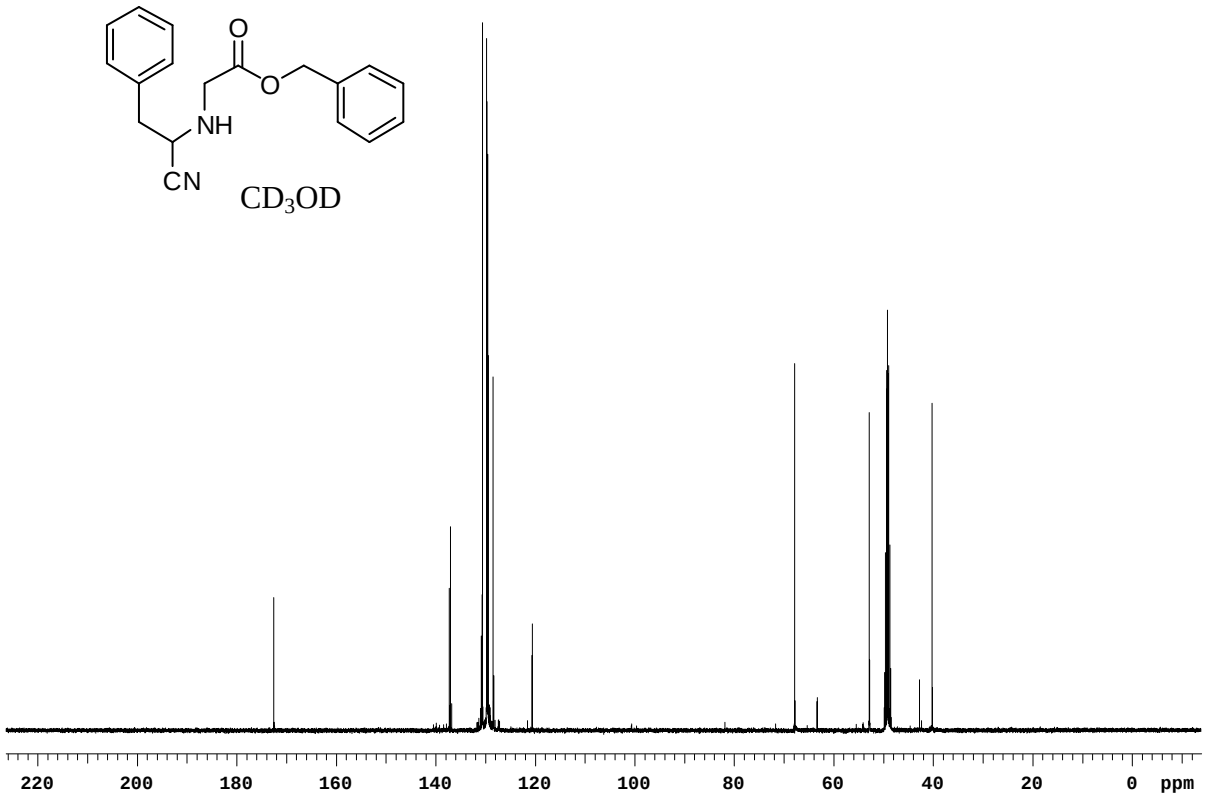

100
50
0
% Mobile Phase
500
0
mVolts
0
2
4
Minutes


RT: 0.00 - 4.14
Relative Abundance
2.18
2.39
2.43
2.51
2.59
2.68
2.93
Time (min)

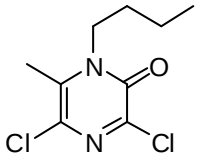

SQ_gis_3k #128 RT: 2.16 AV: 1 NL: 2.66E6
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
589.3
295.1
336.2
590.3
337.2
591.2
338.2
592.3
m/z

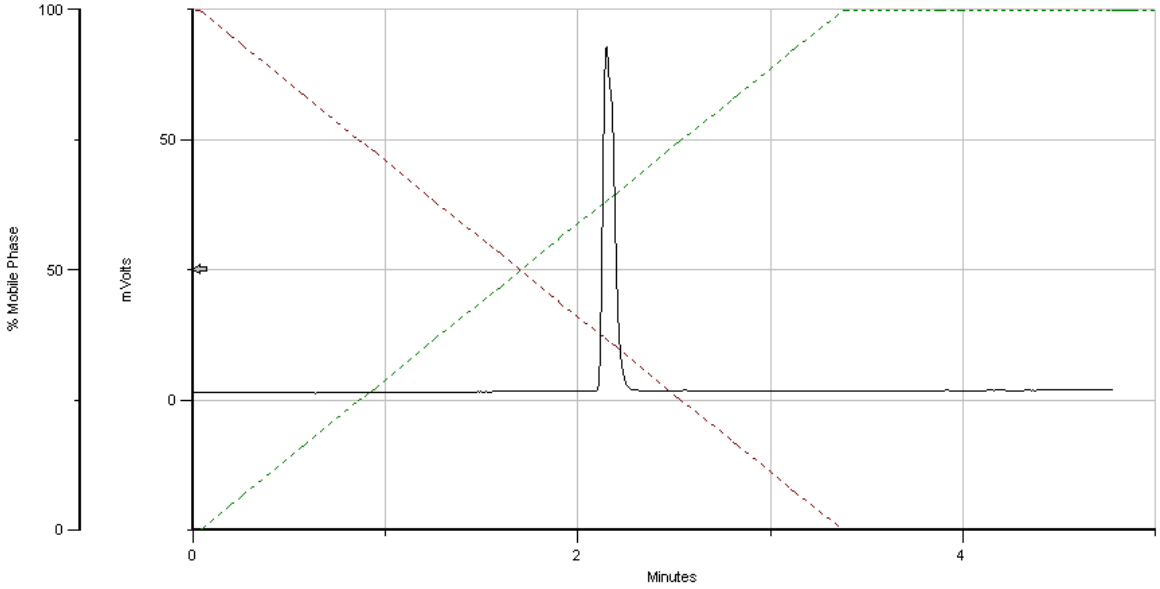
3k

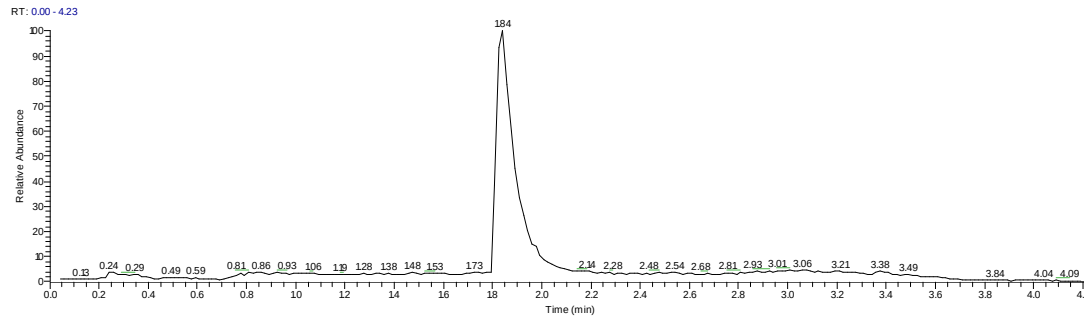

O
O
NH
CN
CD3OD
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

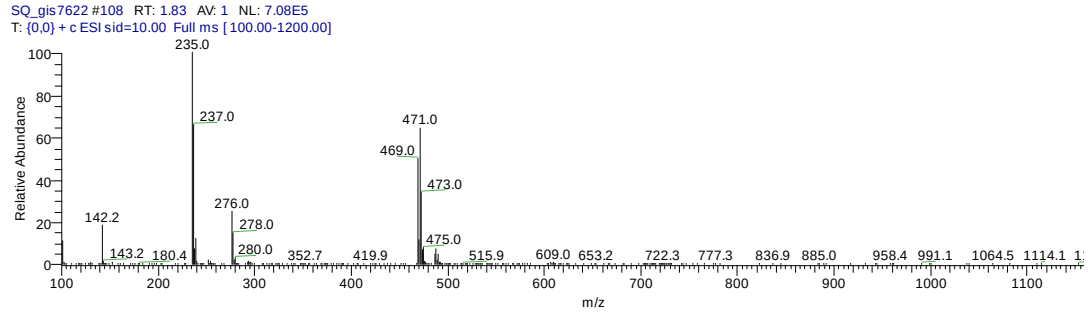

O
O
NH
CN
CD3OD
220
200
180
160
140
120
100
80
60
40
20
0
ppm

4a

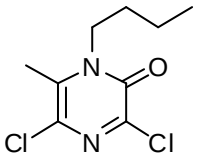

N
O
Cl
N
Cl


100
50
0
% Mobile Phase
mVolts
50
0
0
2
4
Minutes

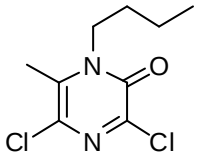

RT: 0.00 - 4.23
Relative Abundance
184
Time (min)


SQ_gis7622 #108 RT: 1.83 AV: 1 NL: 7.08E5
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
235.0
237.0
471.0
469.0
473.0
276.0
278.0
142.2
475.0
280.0
143.2
180.4
352.7
419.9
515.9
609.0
653.2
722.3
777.3
836.9
885.0
958.4
991.1
1064.5
1114.1
m/z

4a

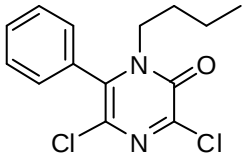


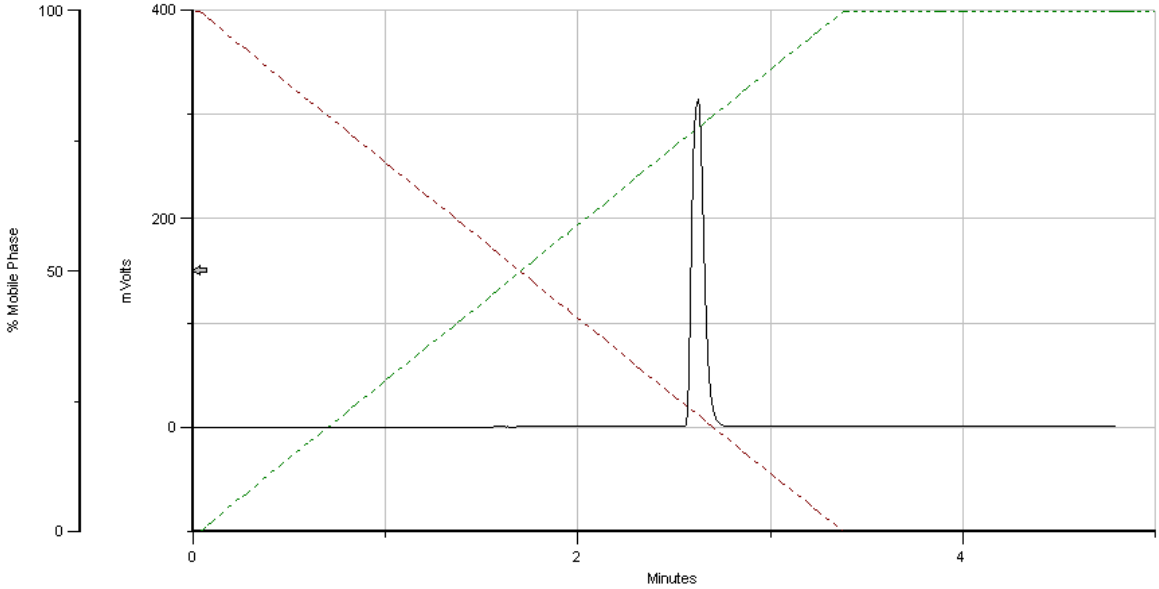
$CDCl_3$

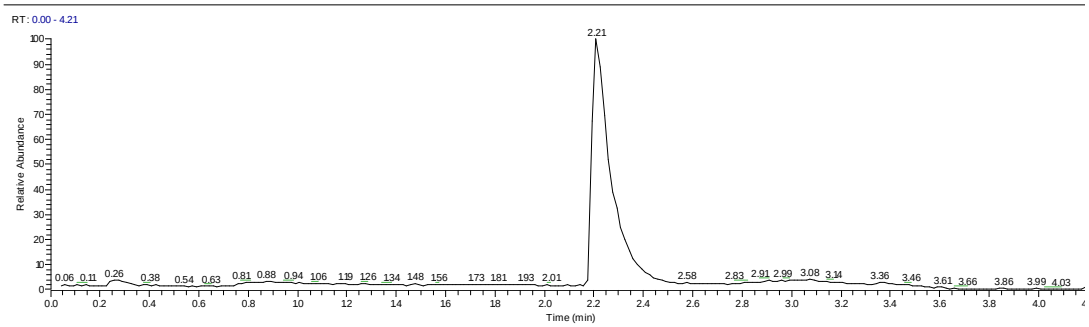


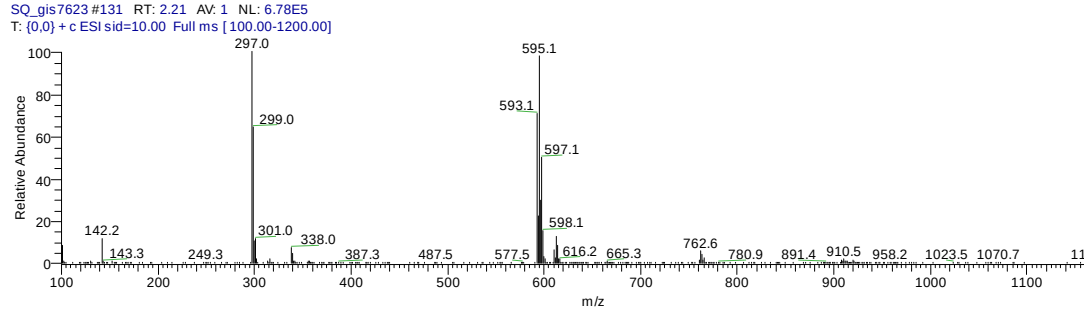
$CDCl_3$

4b

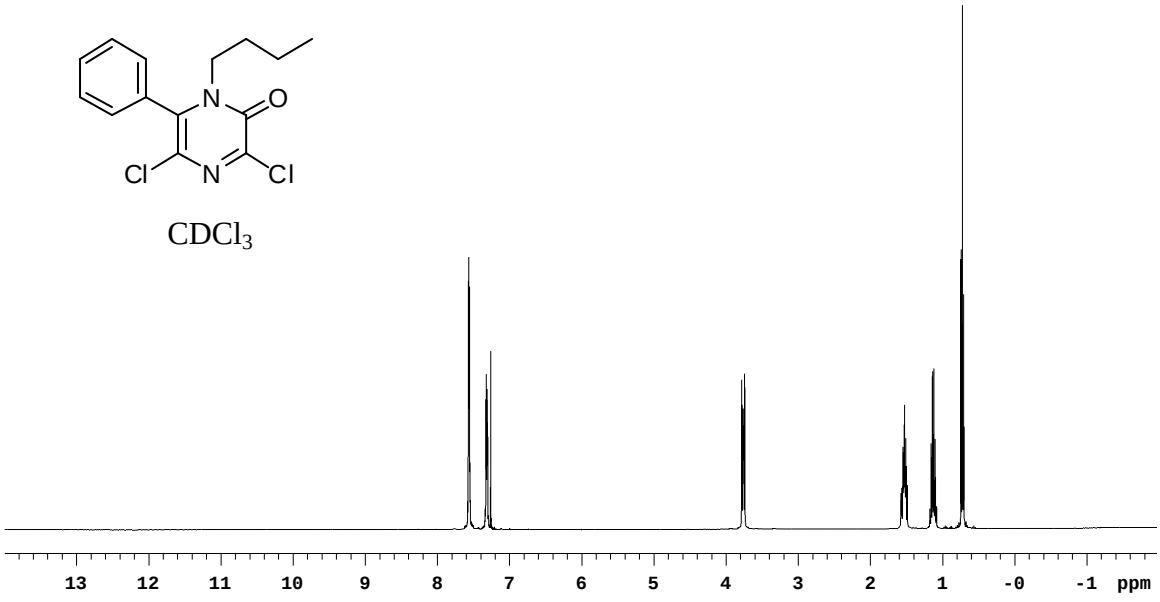

N
O
Cl
N
Cl

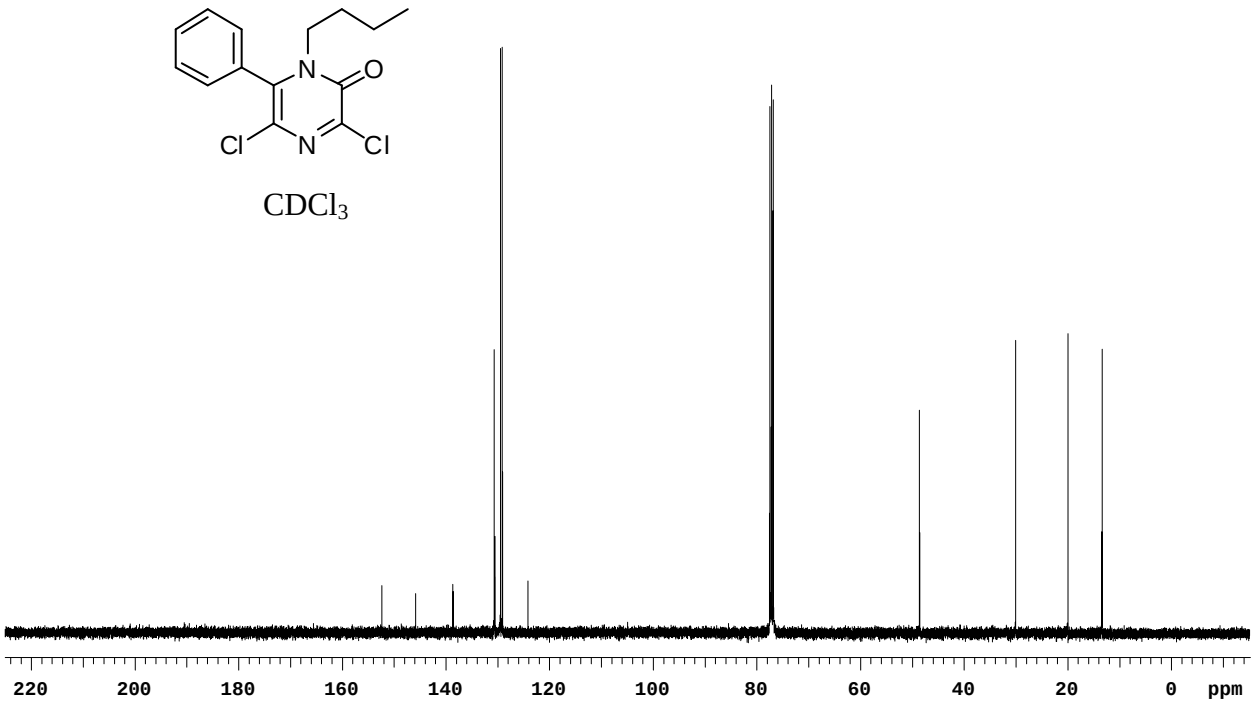

100
50
0
% Mobile Phase
400
200
0
mVolts
0
2
4
Minutes


RT: 0.00 - 4.21
Relative Abundance
2.21
Time (min)

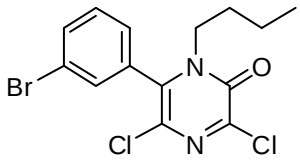

SQ_gis7623 #131 RT: 2.21 AV: 1 NL: 6.78E5
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
297.0
595.1
593.1
299.0
597.1
598.1
142.2
301.0
338.0
m/z

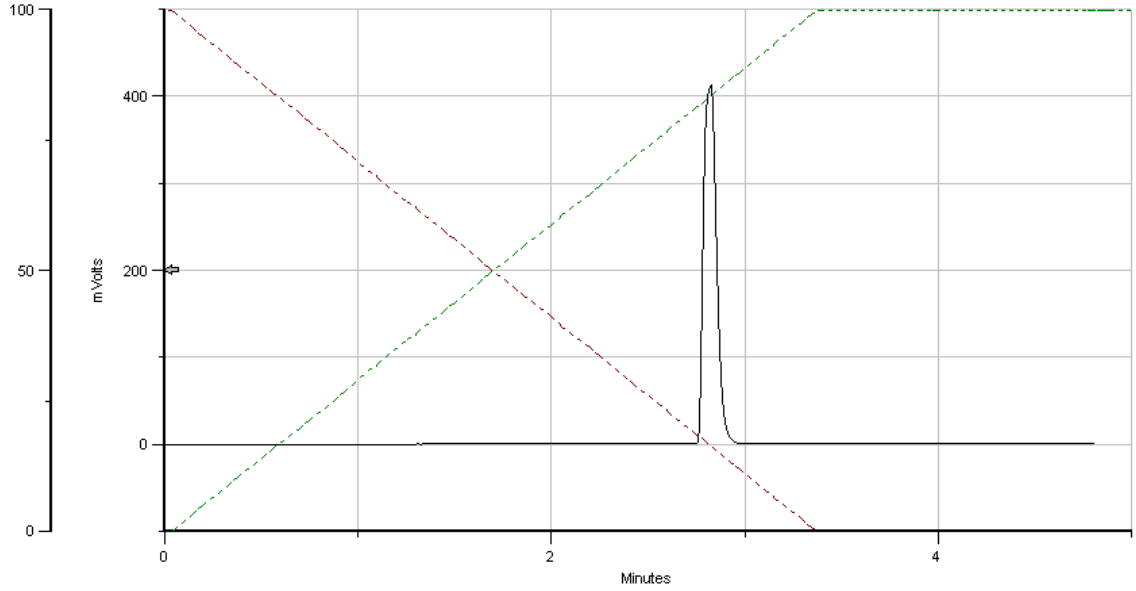
4b

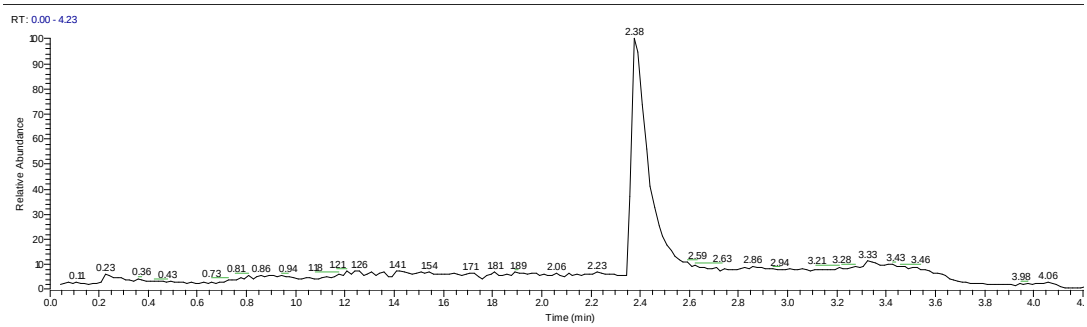

N
O
Cl
N
Cl
CDCl3
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

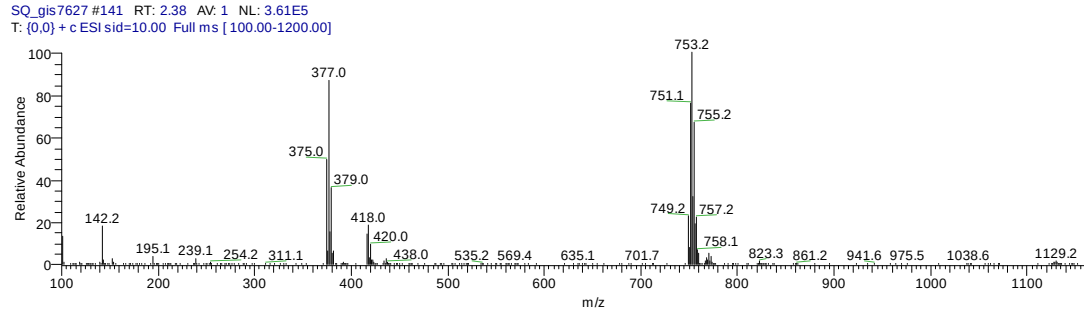

N
O
Cl
N
Cl
CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

4c

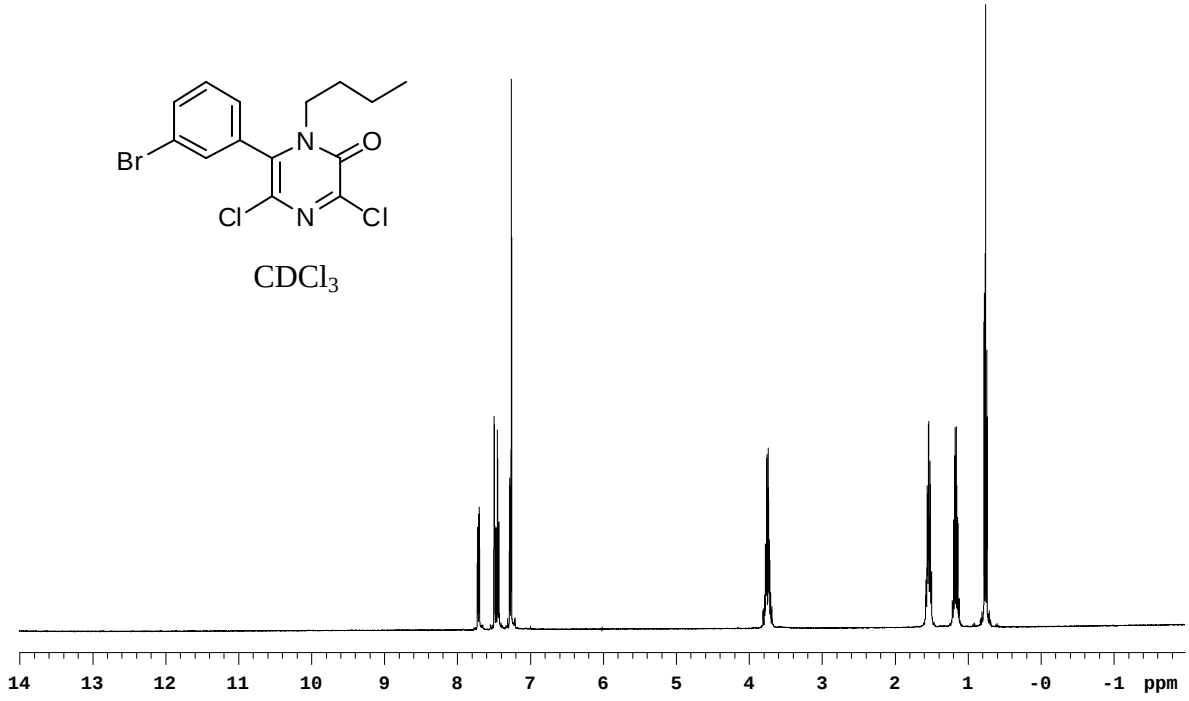

Br
N
O
Cl
N
Cl

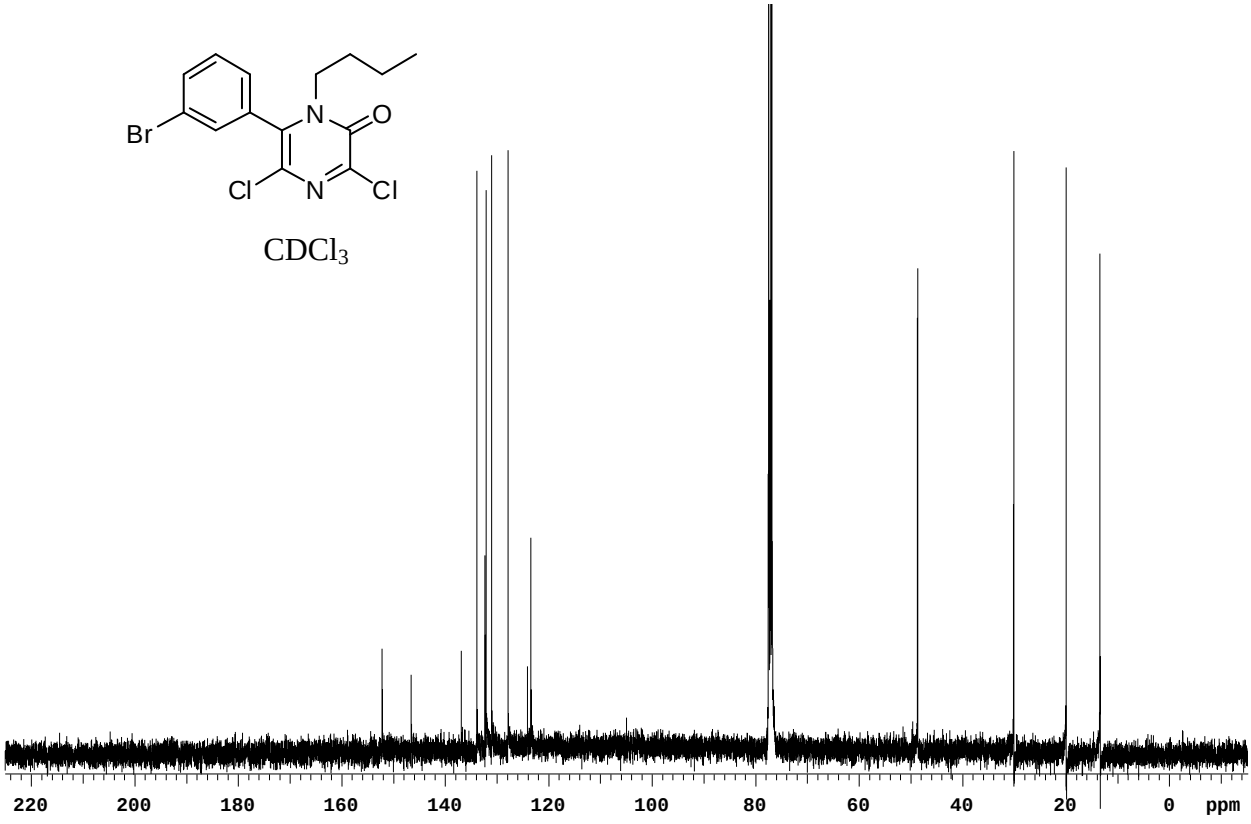

100
50
0
400
200
0
mVolts
0
2
4
Minutes


RT: 0.00 - 4.23
Relative Abundance
Time (min)
2.38

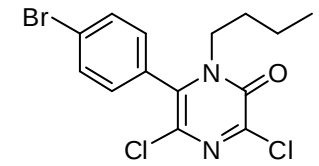

SQ_gis7627 #141 RT: 2.38 AV: 1 NL: 3.61E5
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
m/z
753.2
377.0
751.1
755.2
375.0
379.0
749.2
757.2
418.0
420.0
142.2
758.1

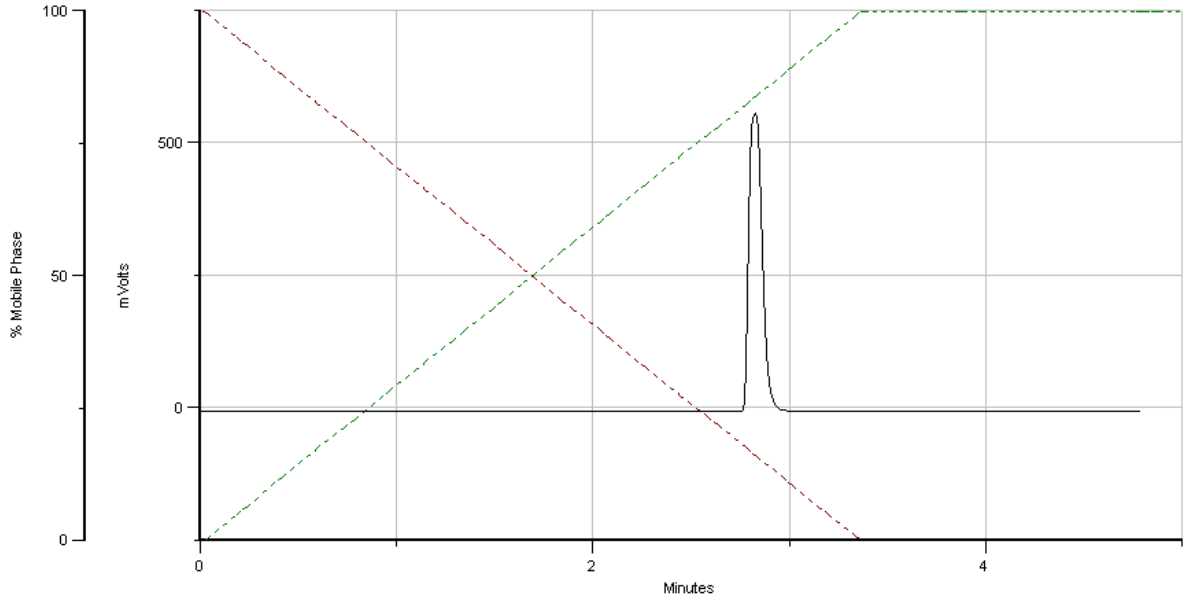
4c

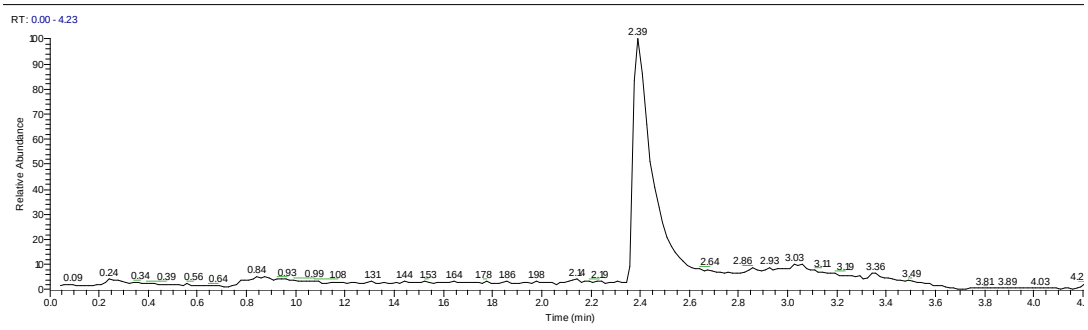

Br
N
O
Cl
N
Cl
CDCl3
14
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

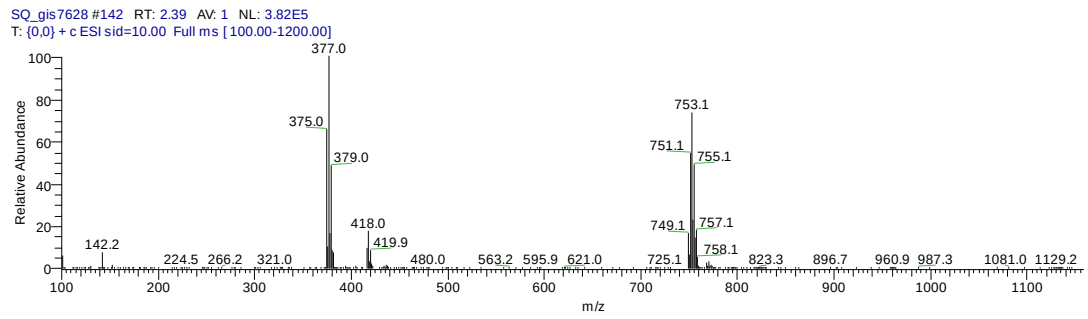

Br
N
O
Cl
N
Cl
CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

4d

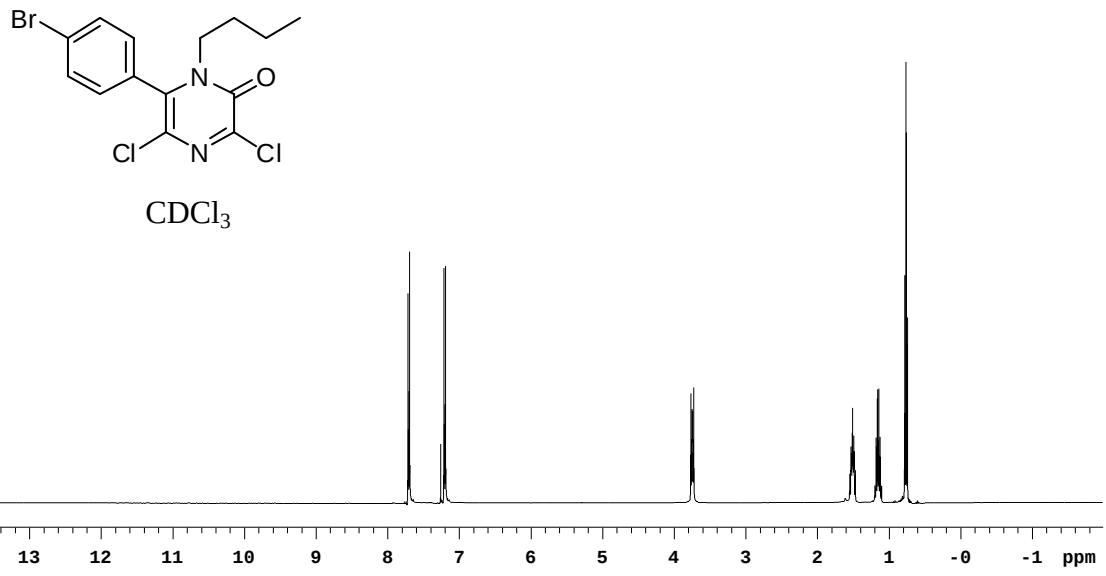

Br
N
O
Cl
N
Cl

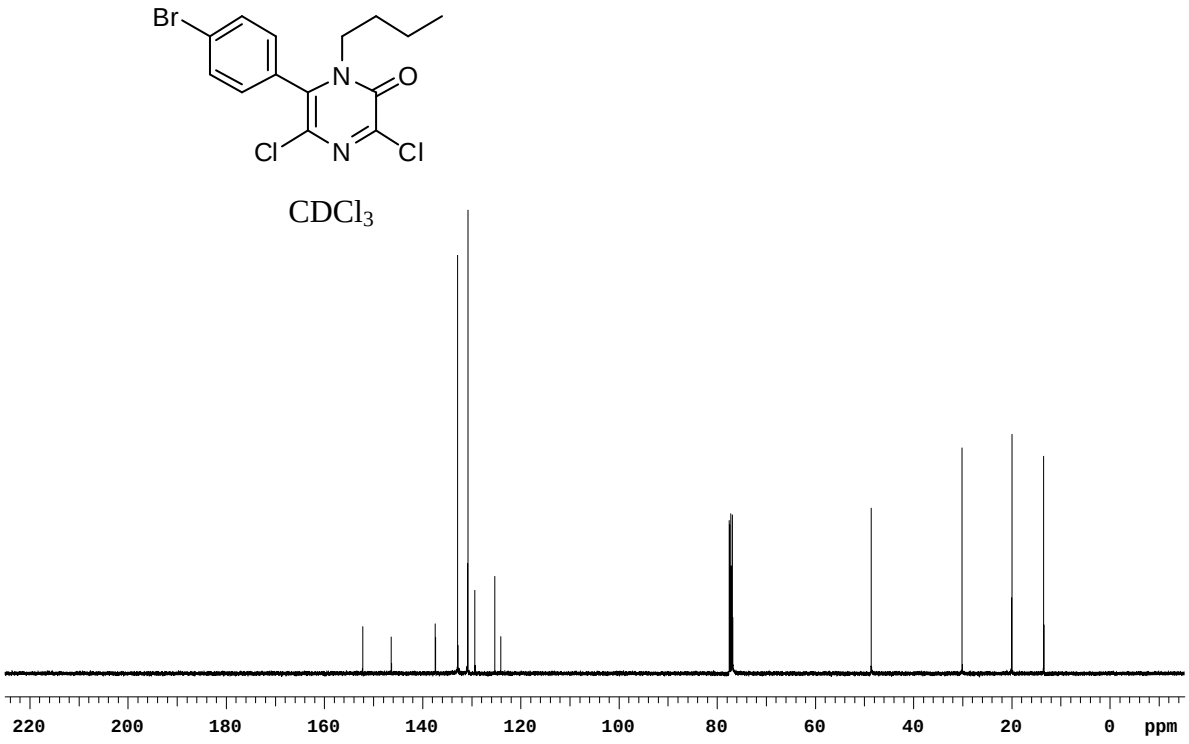

100
50
0
% Mobile Phase
500
0
mVolts
0
2
4
Minutes


RT: 0.00 - 4.23
Relative Abundance
2.39
Time (min)

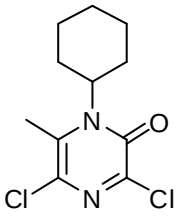

SQ_gis7628 #142 RT: 2.39 AV: 1 NL: 3.82E5
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
377.0
375.0
379.0
418.0
419.9
753.1
751.1
755.1
749.1
757.1
758.1
142.2
224.5
266.2
321.0
480.0
563.2
595.9
621.0
725.1
823.3
896.7
960.9
987.3
1081.0
1129.2
m/z

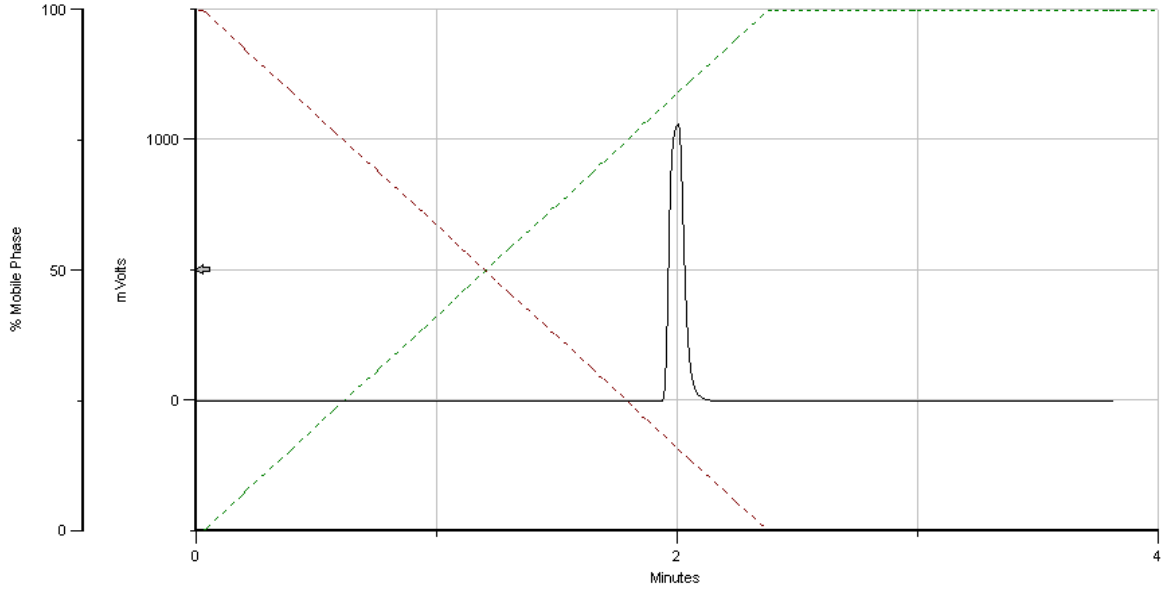
4d

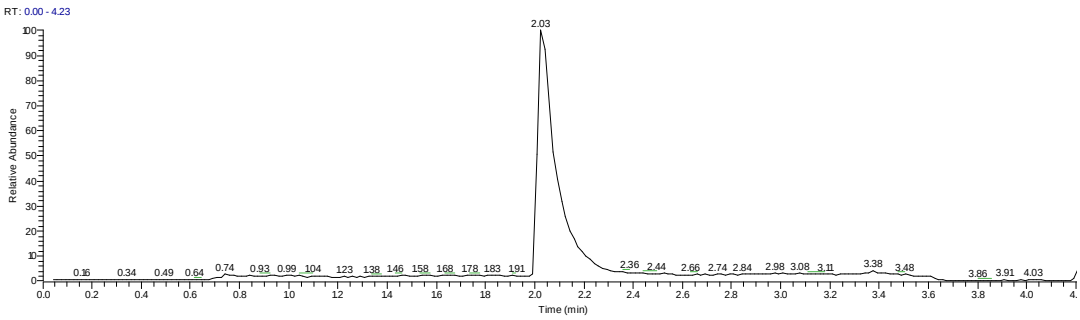

Br
N
O
Cl
N
Cl
CDCl3
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

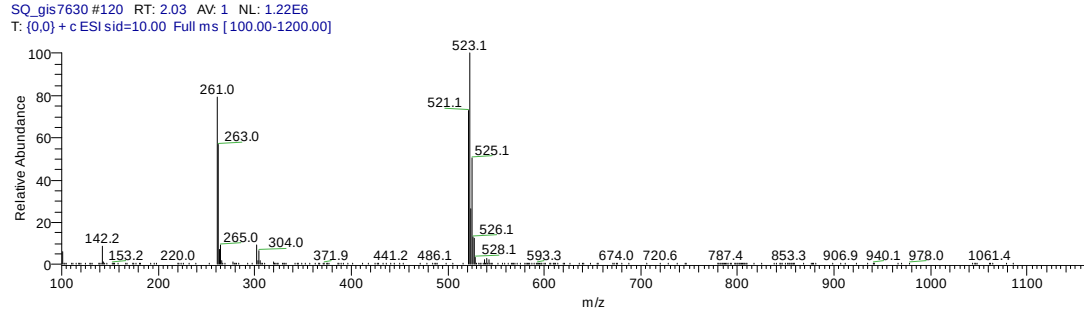

Br
N
O
Cl
N
Cl
CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

4e

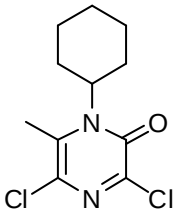

N
O
Cl
N
Cl


100
50
0
% Mobile Phase
1000
0
mVolts
0
2
4
Minutes

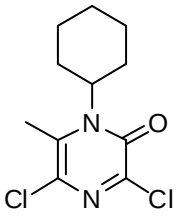

RT: 0.00 - 4.23
Relative Abundance
2.03
Time (min)


SQ_gis7630 #120 RT: 2.03 AV: 1 NL: 1.22E6
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
523.1
261.0
521.1
263.0
525.1
526.1
528.1
142.2
265.0
304.0
m/z

4e

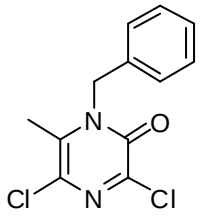


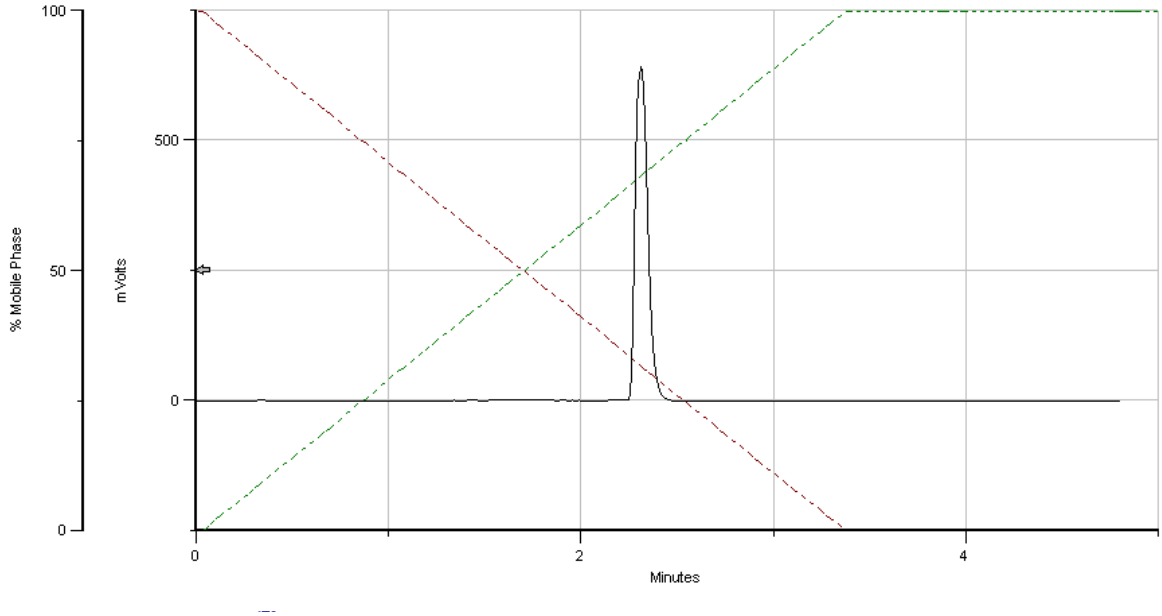
$CDCl_3$

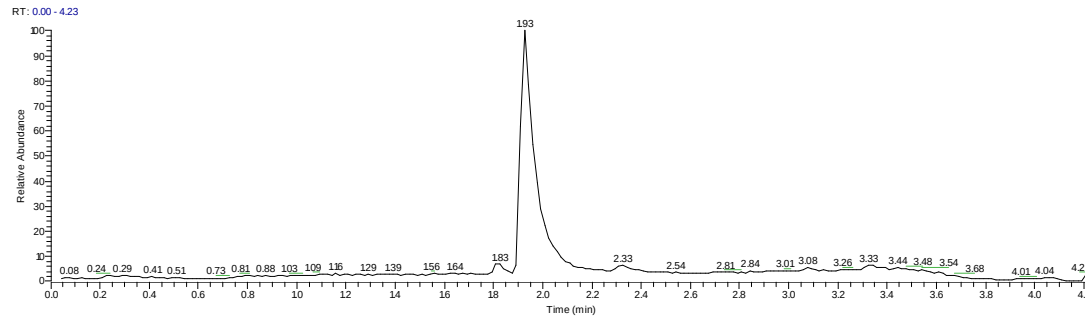


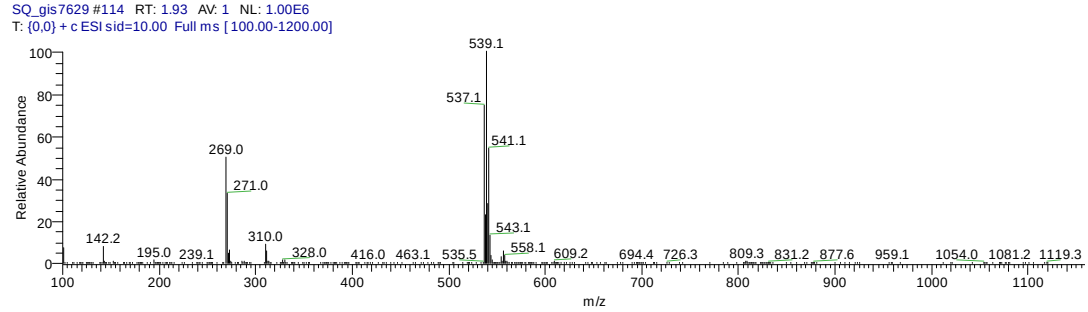
$CDCl_3$

4f

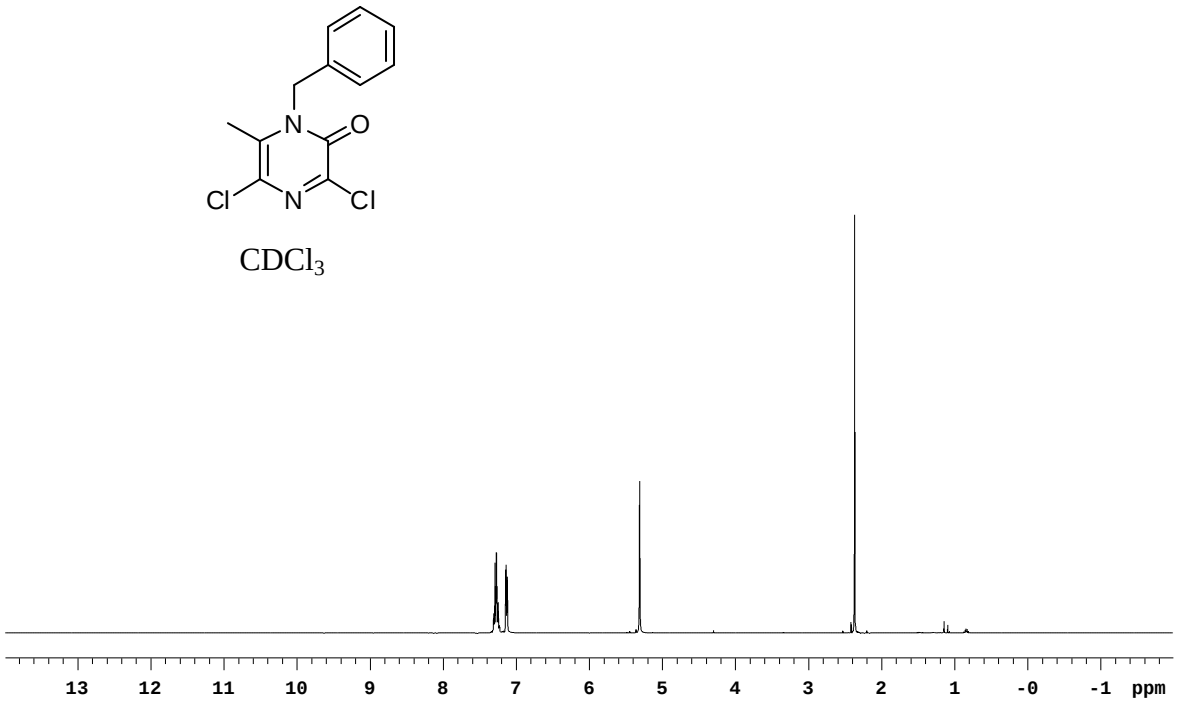

N
O
Cl
N
Cl

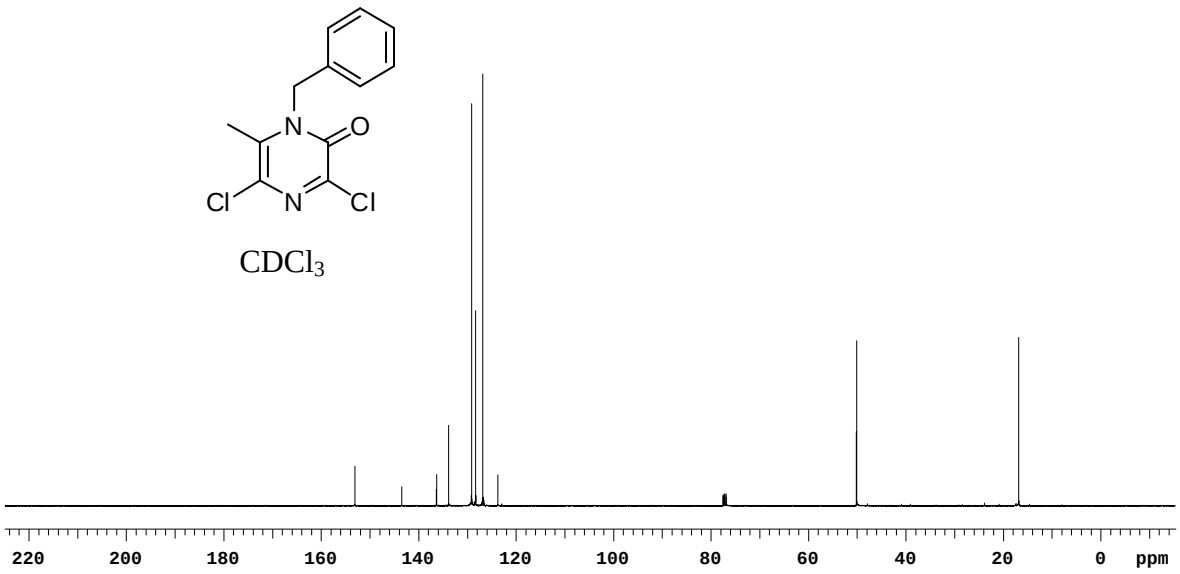

100
50
0
% Mobile Phase
500
0
mVolts
0
2
4
Minutes


RT: 0.00 - 4.23
Relative Abundance
193
183
2.33
Time (min)

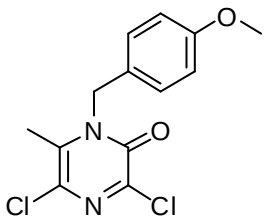

SQ_gis7629 #114 RT: 1.93 AV: 1 NL: 1.00E6
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
539.1
537.1
541.1
269.0
271.0
543.1
142.2
310.0
m/z

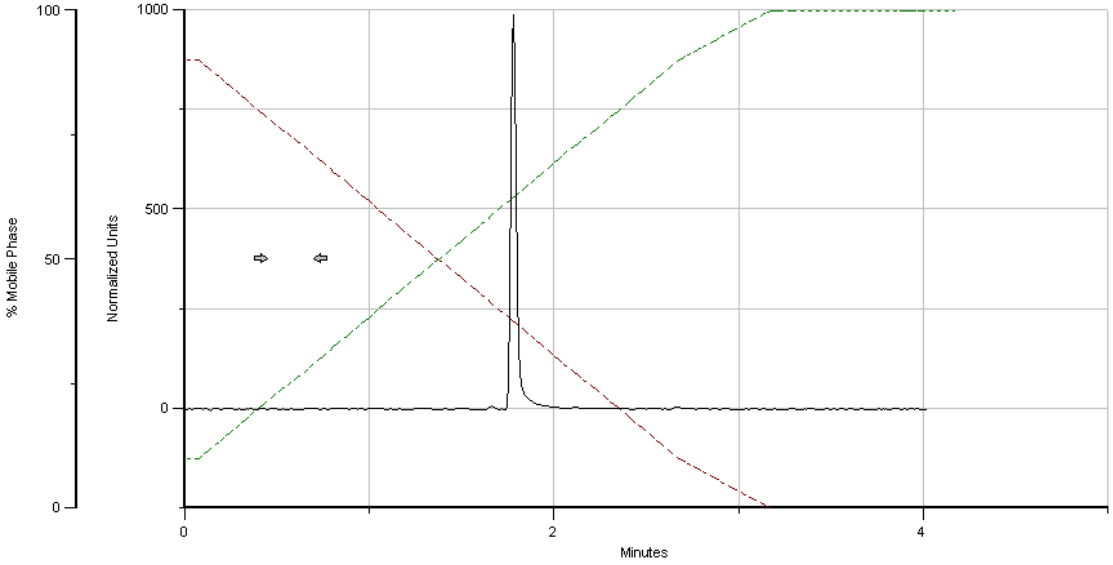
4f

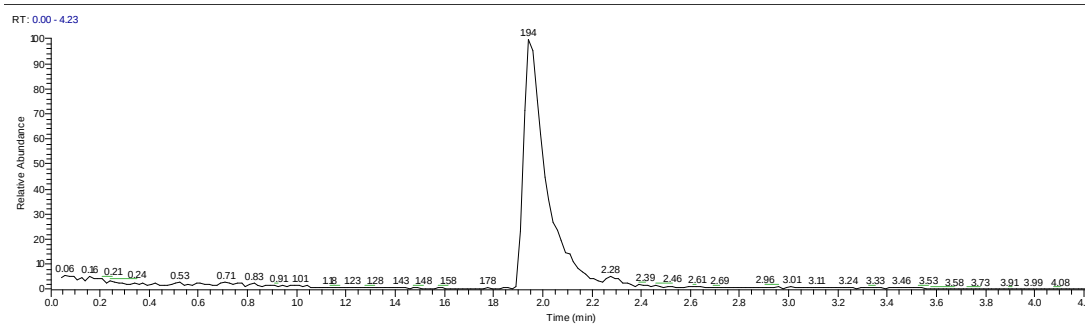

N
O
Cl
N
Cl
CDCl3
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

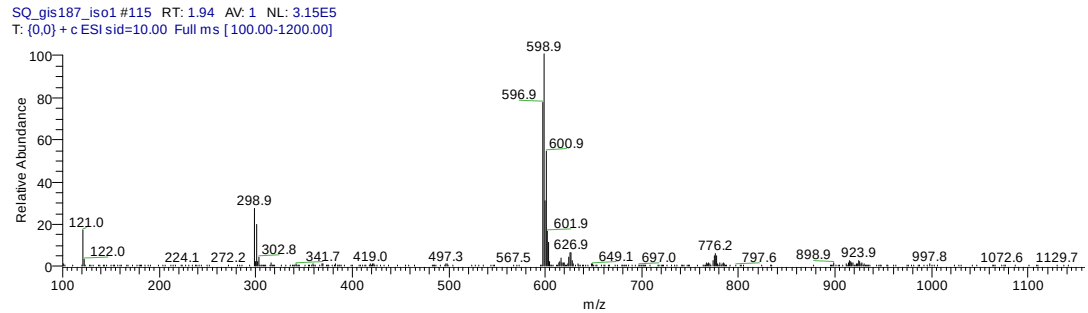

N
O
Cl
N
Cl
CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

4g

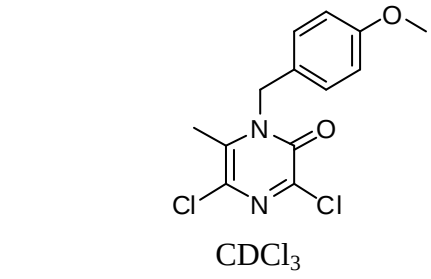

O
N
O
Cl
N
Cl


100
50
0
% Mobile Phase
1000
500
0
Normalized Units
0
2
4
Minutes

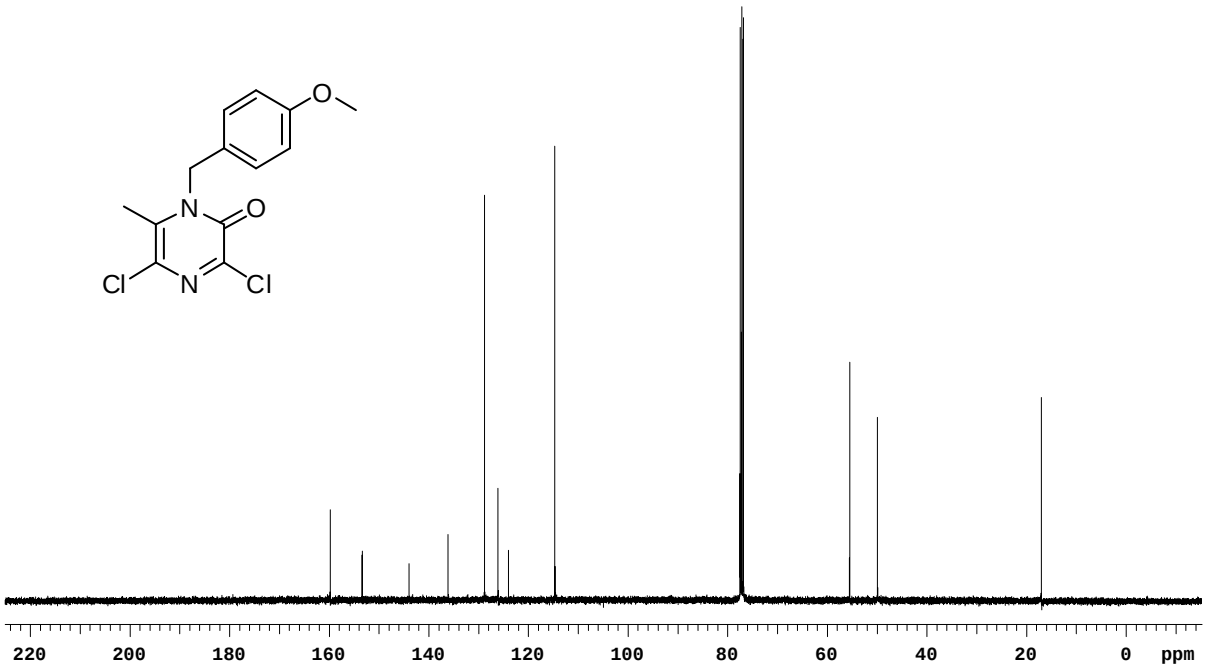

RT: 0.00 - 4.23
Relative Abundance
194
2.28
Time (min)


SQ_gis187_iso1 #115 RT: 1.94 AV: 1 NL: 3.15E5
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
598.9
596.9
600.9
298.9
121.0
601.9
626.9
776.2
m/z

4g


O
N
O
Cl
N
Cl

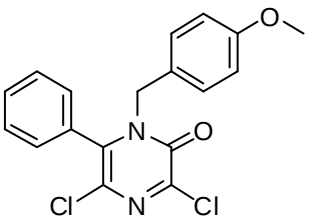
$CDCl_3$

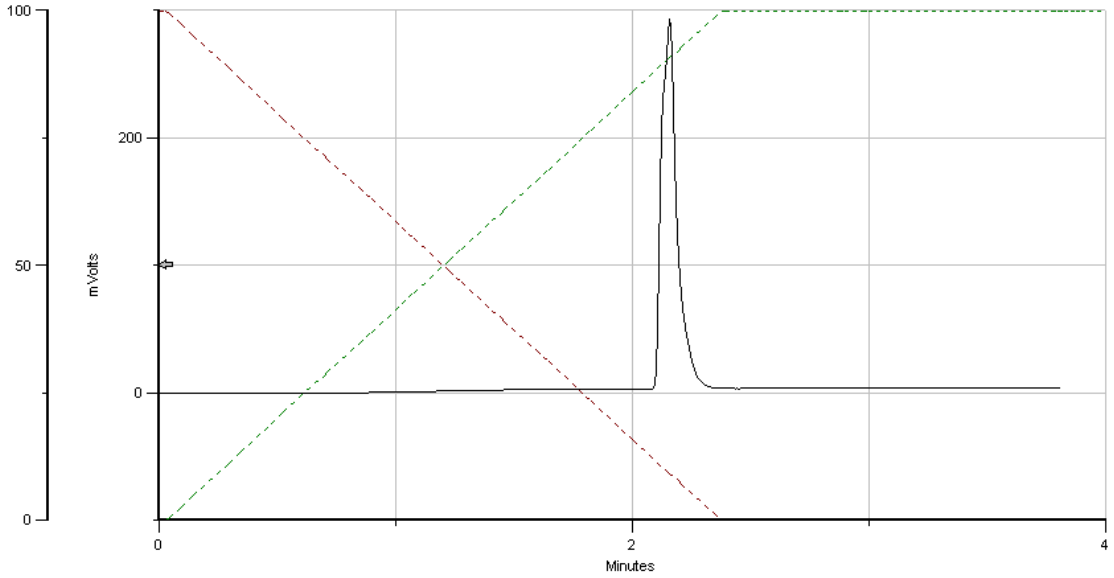

13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

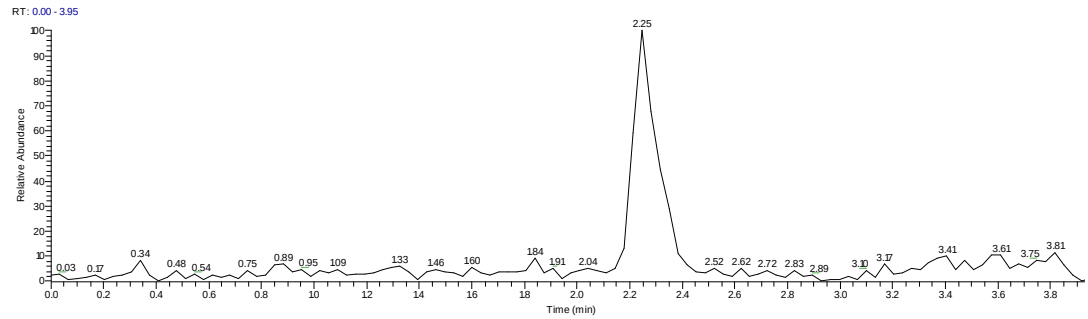
O
N
O
Cl
N
Cl

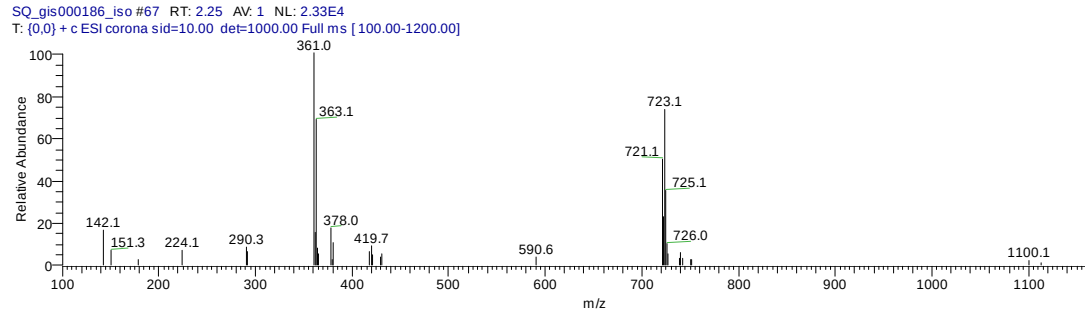
220
200
180
160
140
120
100
80
60
40
20
0
ppm

4h

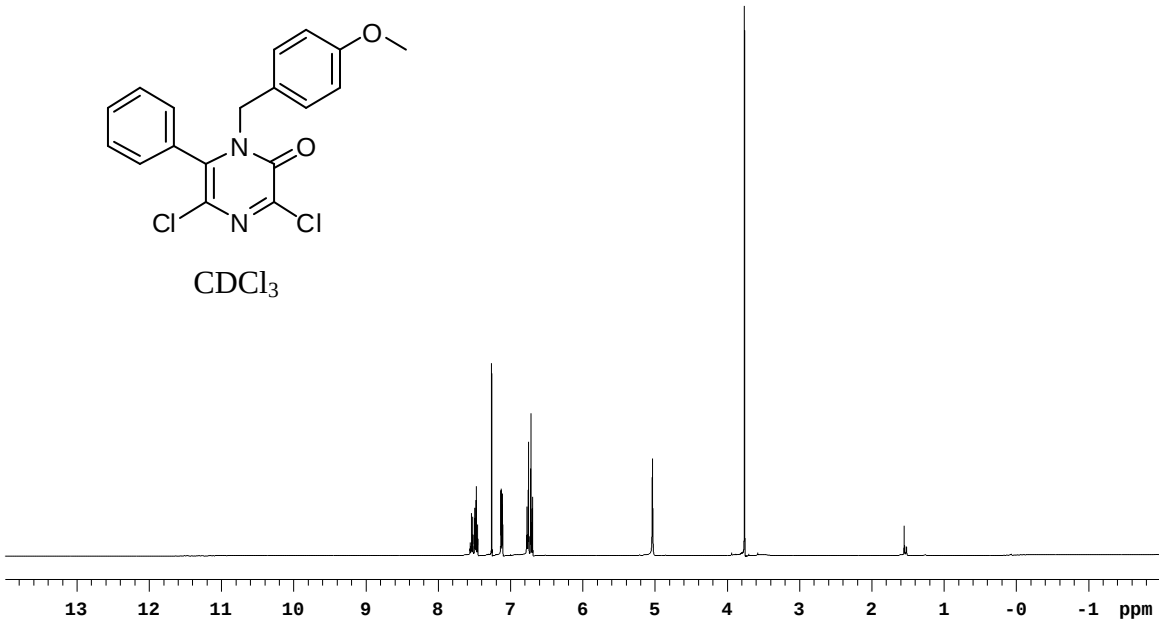

O
N
O
Cl
N
Cl

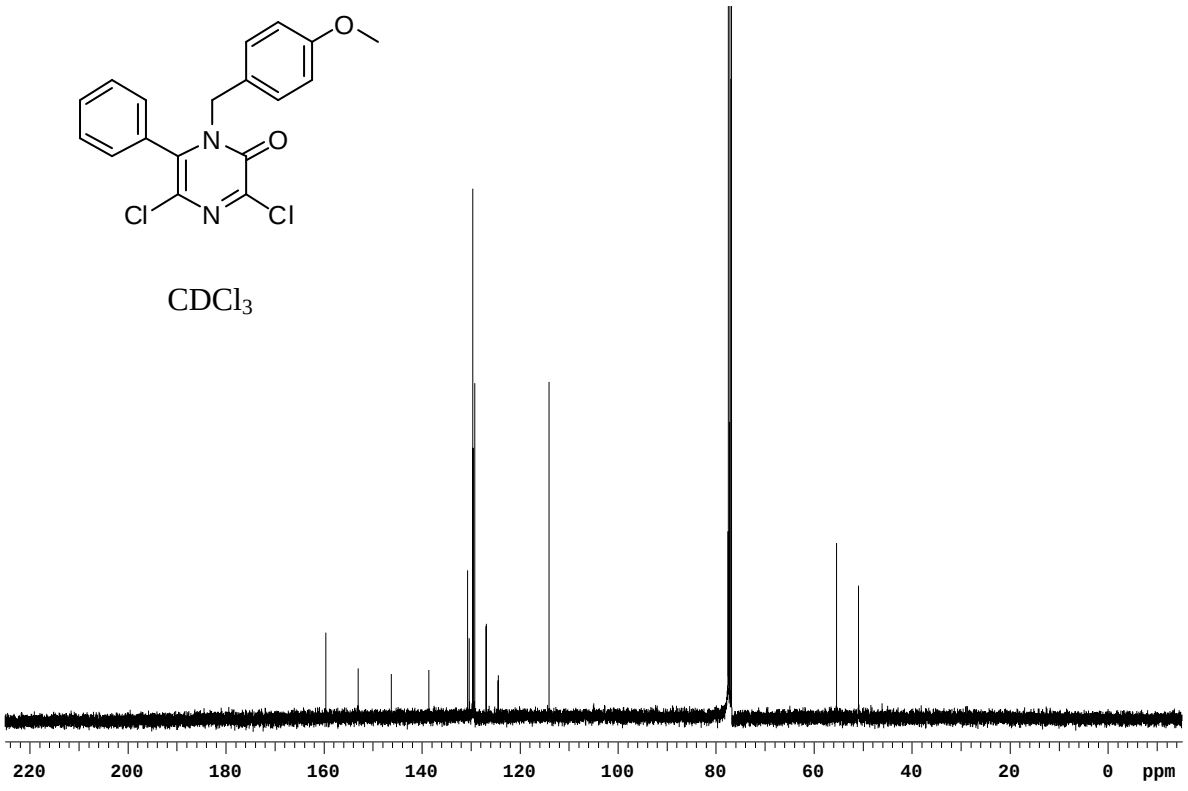

100
50
0
200
0
mVolts
0
2
4
Minutes


RT: 0.00 - 3.95
Relative Abundance
Time (min)
2.25

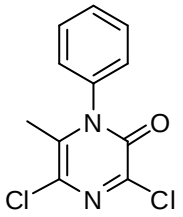

SQ_gis000186_iso #67 RT: 2.25 AV: 1 NL: 2.33E4
T: {0,0} + c ESI corona sid=10.00 det=1000.00 Full ms [100.00-1200.00]
Relative Abundance
m/z
361.0
363.1
723.1
721.1
725.1
726.0
378.0
419.7
142.1
151.3
224.1
290.3
590.6
1100.1

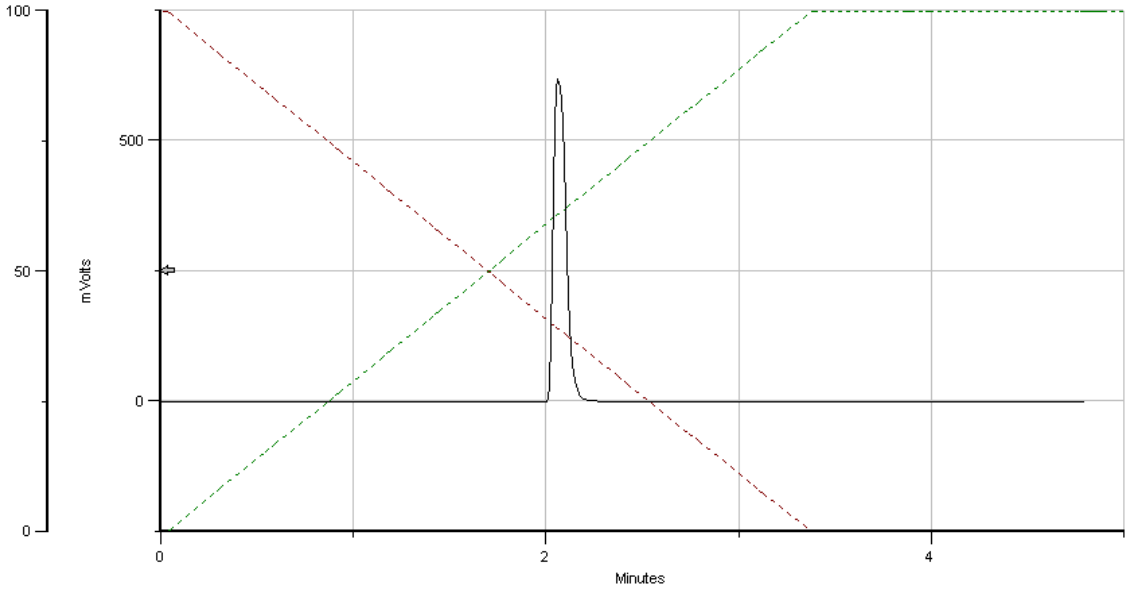
4h

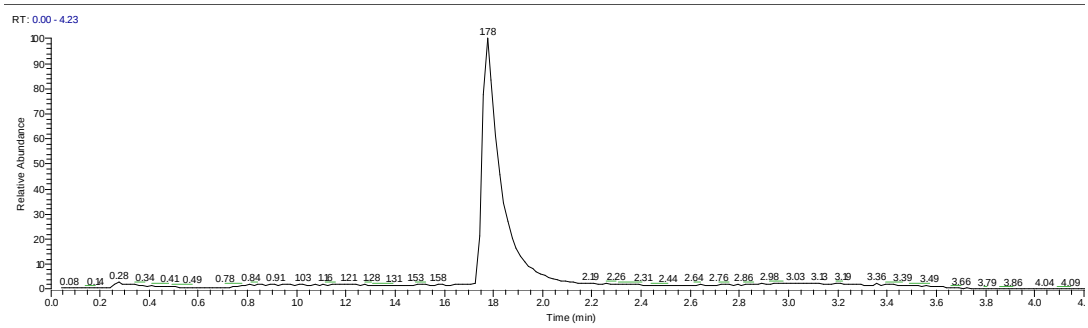

O
N
O
Cl
N
Cl
CDCl3
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

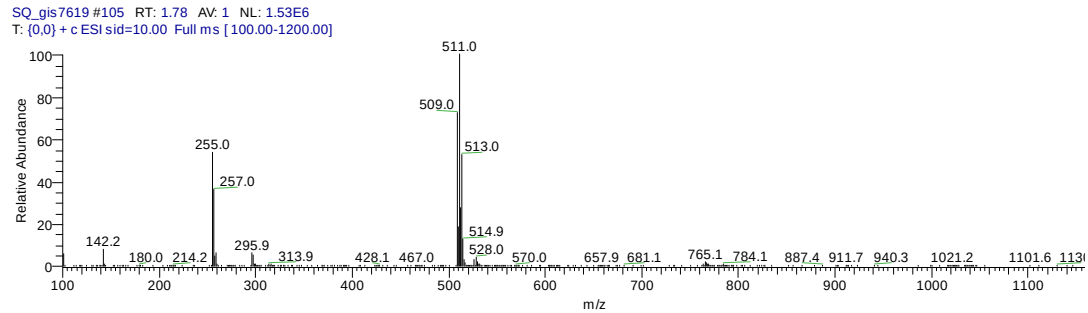

O
N
O
Cl
N
Cl
CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

4i

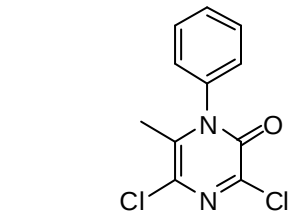

N
O
Cl
N
Cl


100
50
0
500
0
mVolts
0
2
4
Minutes

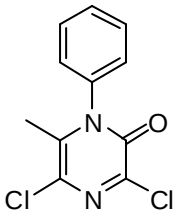

RT: 0.00 - 4.23
Relative Abundance
Time (min)
178


SQ_gis7619 #105 RT: 1.78 AV: 1 NL: 1.53E6
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
m/z
511.0
509.0
513.0
255.0
257.0
514.9
528.0
142.2
295.9

4i

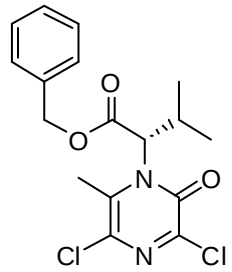


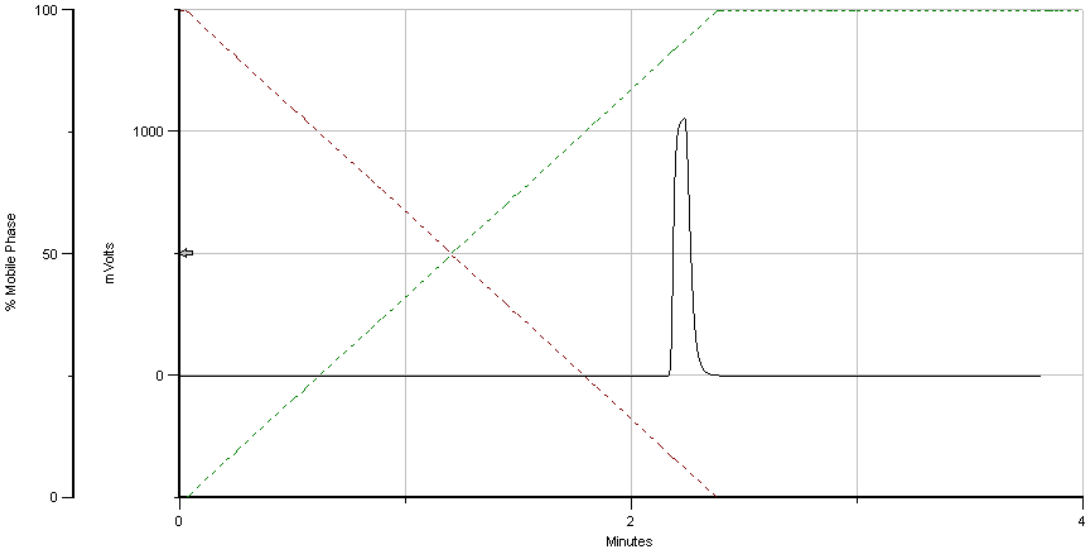
$CDCl_3$

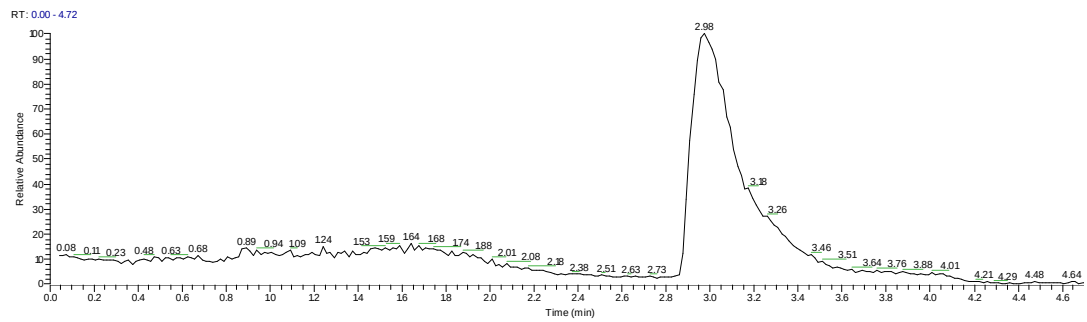


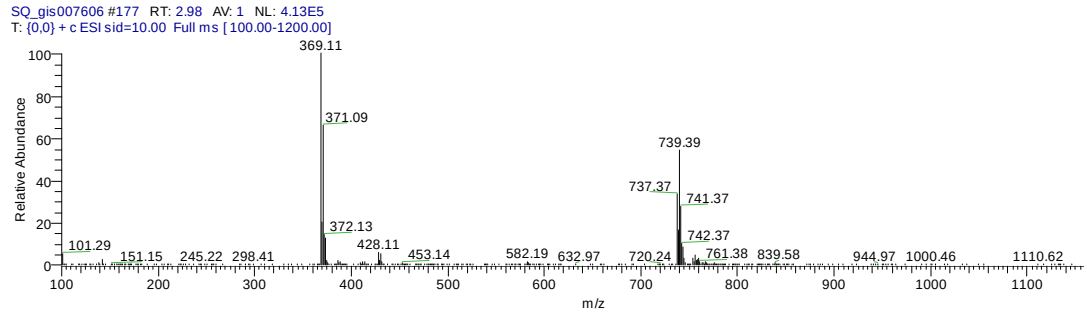
$CDCl_3$

4j

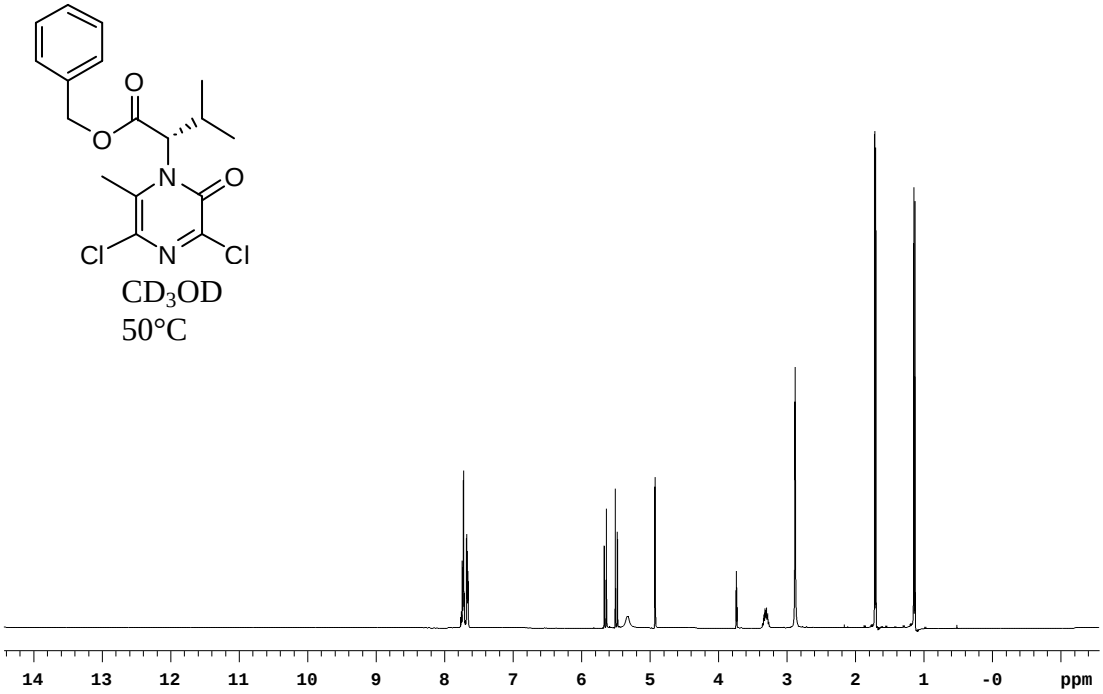

O
O
N
O
Cl
N
Cl

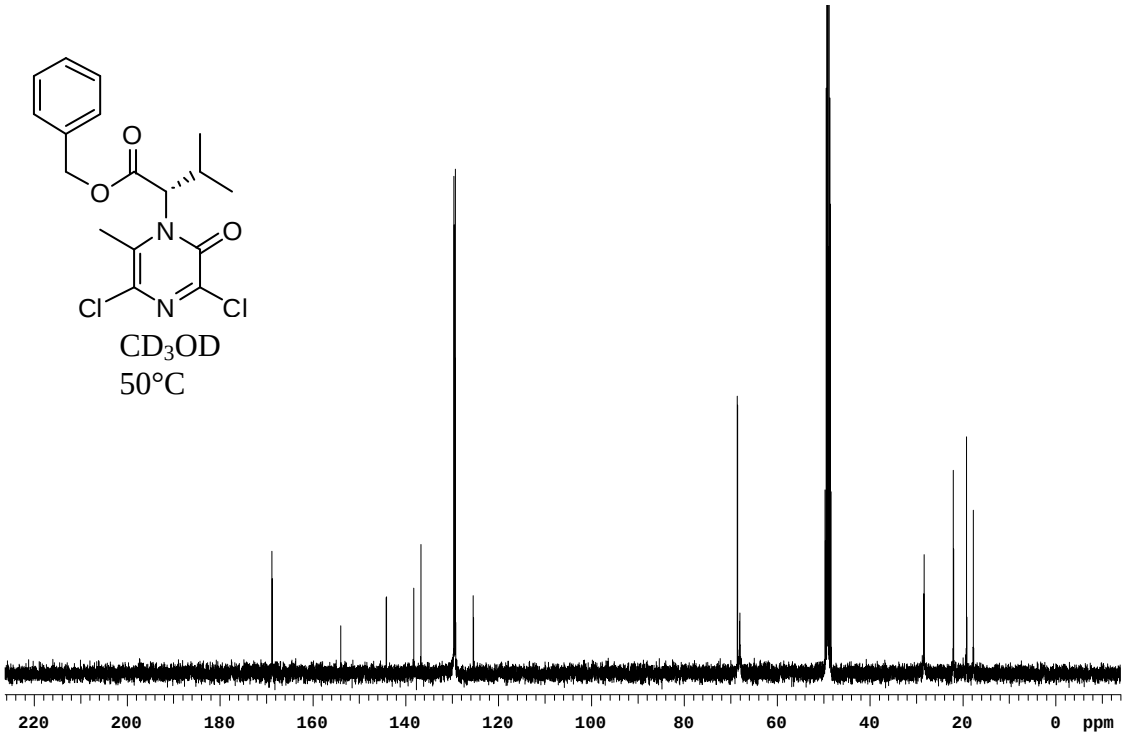

100
50
0
% Mobile Phase
1000
0
mVolts
0
2
4
Minutes


RT: 0.00 - 4.72
Relative Abundance
Time (min)
2.98
3.18
3.26
3.46
3.51
3.64
3.76
3.88
4.01
4.21
4.29
4.48
4.64

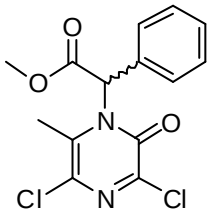

SQ_gis007606 #177 RT: 2.98 AV: 1 NL: 4.13E5
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
m/z
369.11
371.09
739.39
737.37
741.37
742.37
372.13
428.11
101.29
151.15
245.22
298.41
453.14
582.19
632.97
720.24
761.38
839.58
944.97
1000.46
1110.62

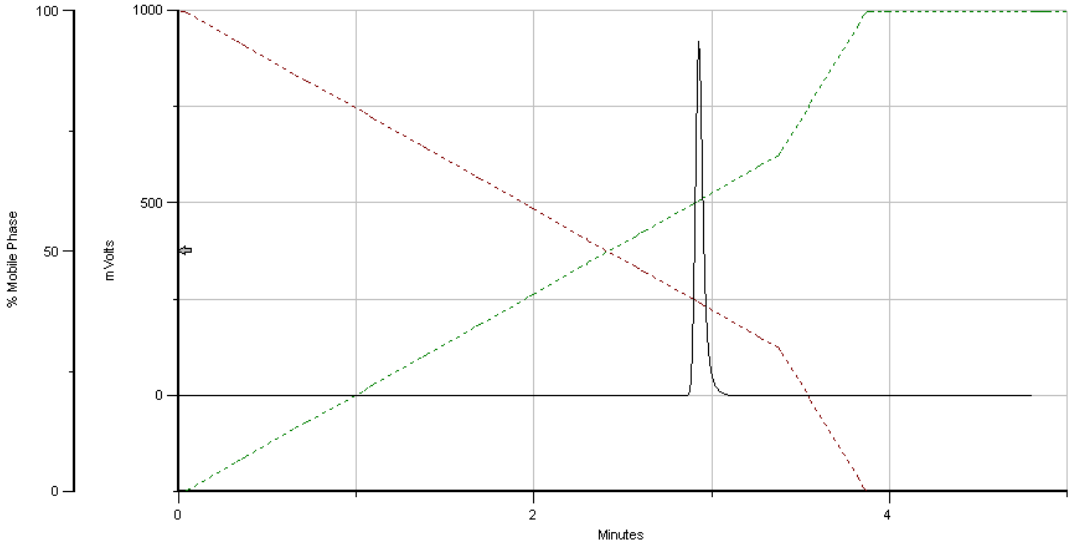
4j

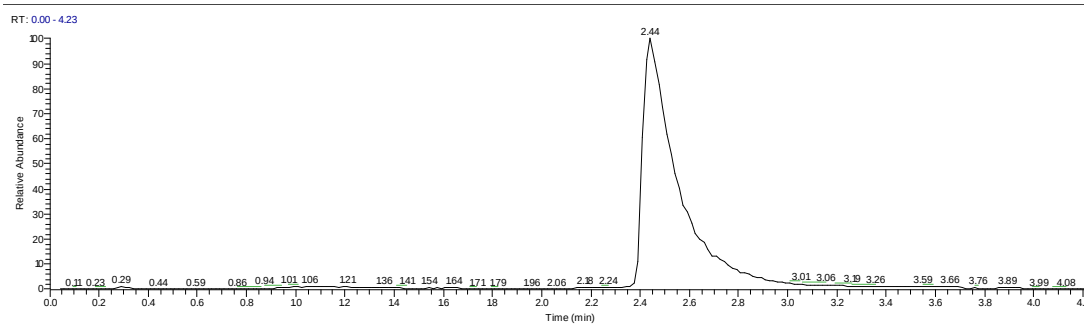

O
O
N
O
Cl
N
Cl
CD3OD
50°C
14
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

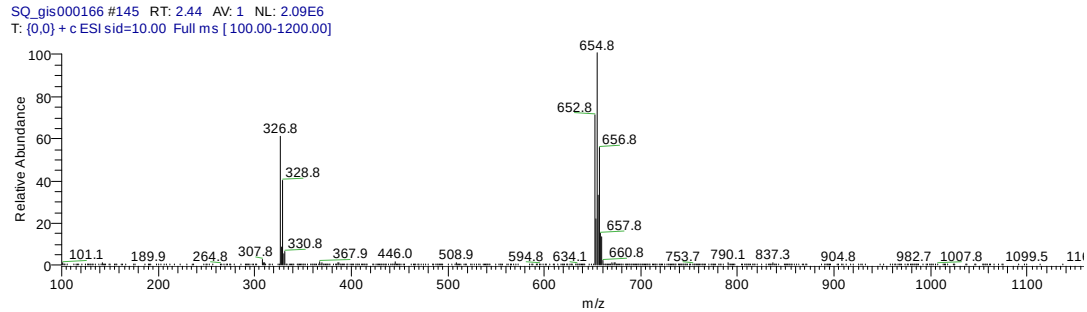

O
O
N
O
Cl
N
Cl
CD3OD
50°C
220
200
180
160
140
120
100
80
60
40
20
0
ppm

4k

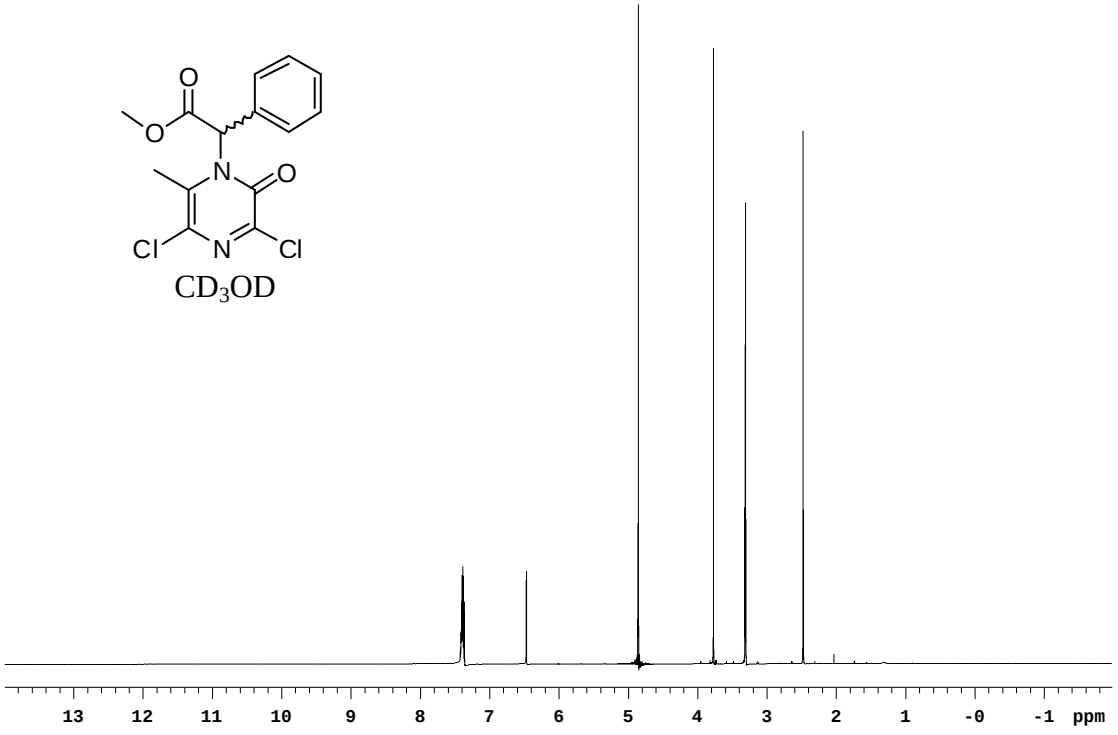

O
O
N
O
Cl
N
Cl

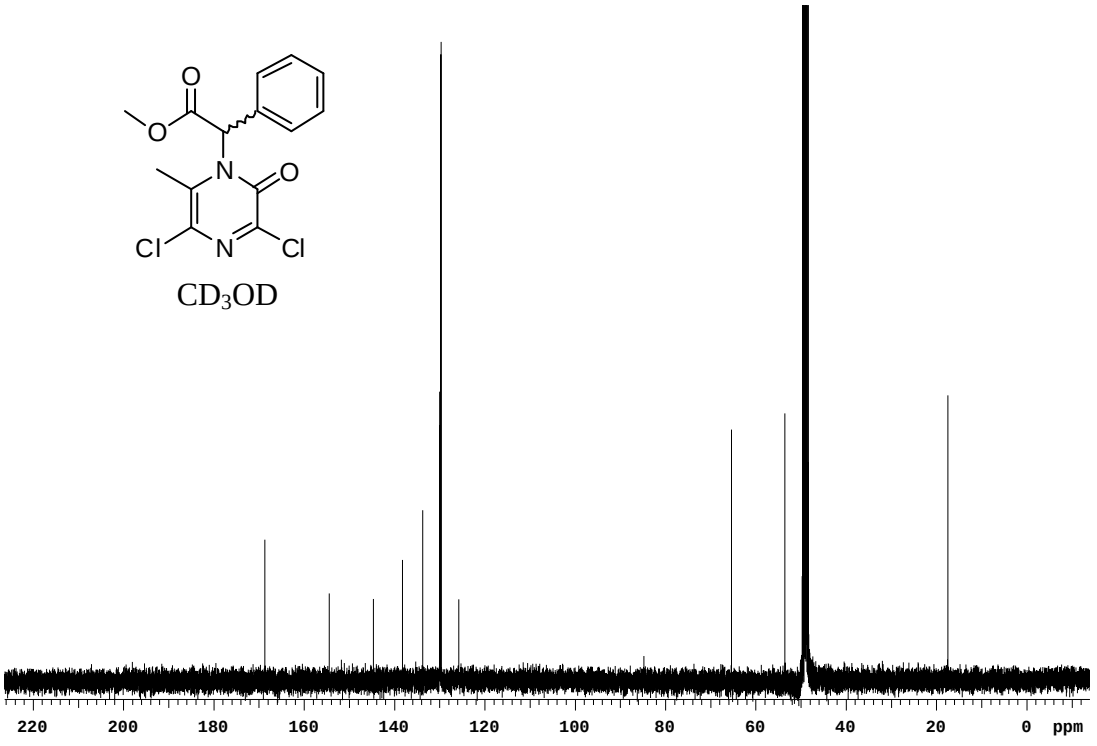

100
50
0
% Mobile Phase
1000
500
0
mVolts
0
2
4
Minutes


RT: 0.00 - 4.23
Relative Abundance
2.44
Time (min)

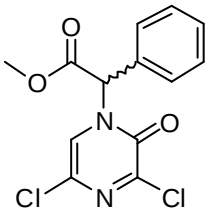

SQ_gis000166 #145 RT: 2.44 AV: 1 NL: 2.09E6
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
654.8
652.8
656.8
326.8
328.8
657.8
330.8
660.8
m/z

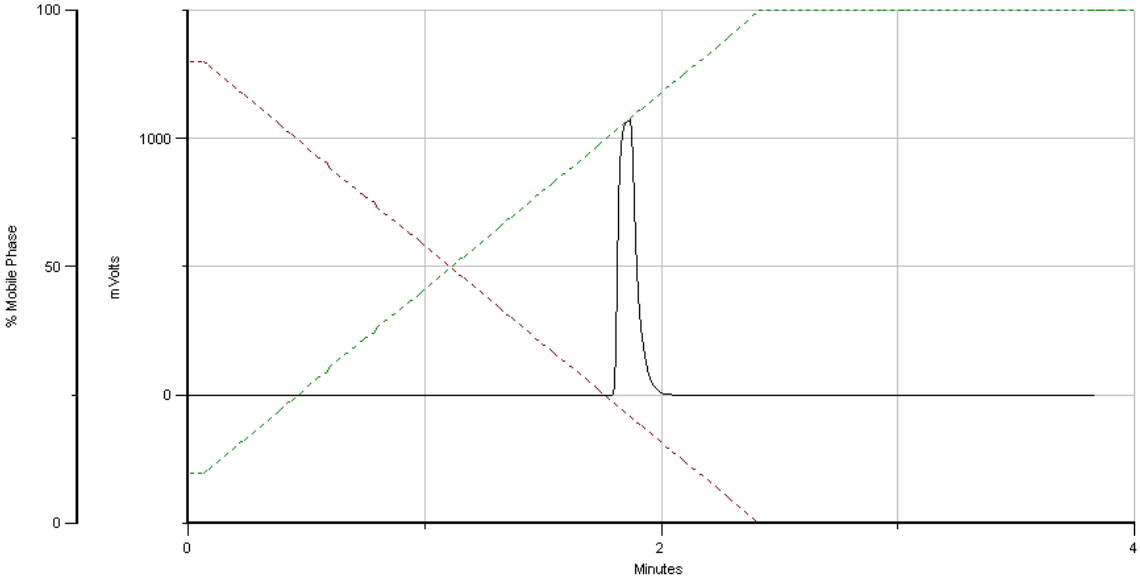
4k

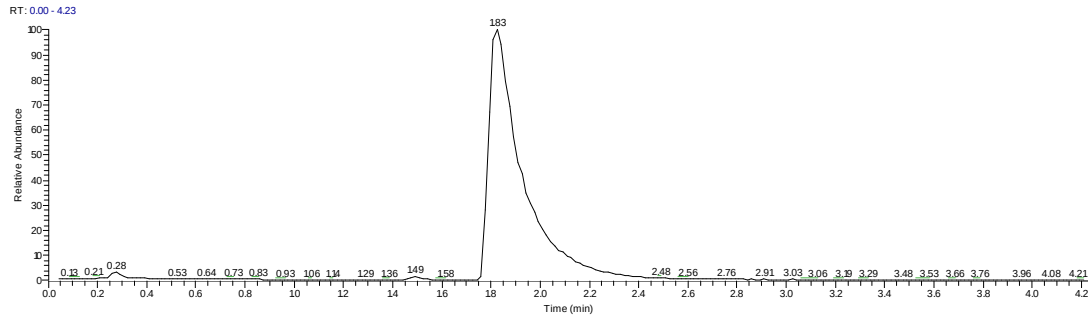

O
O
N
O
Cl
N
Cl
CD3OD
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

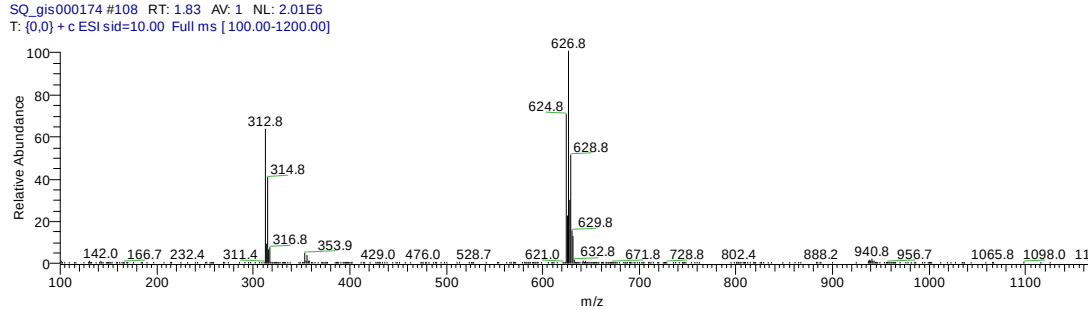

O
O
N
O
Cl
N
Cl
CD3OD
220
200
180
160
140
120
100
80
60
40
20
0
ppm

4l

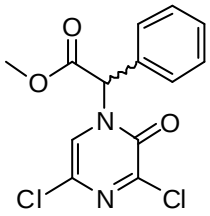

O
O
N
O
Cl
N
Cl


100
50
0
% Mobile Phase
1000
0
mVolts
0
2
4
Minutes

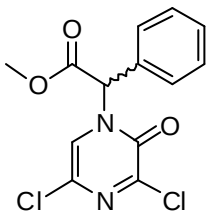

RT: 0.00 - 4.23
Relative Abundance
183
Time (min)


SQ_gis000174 #108 RT: 1.83 AV: 1 NL: 2.01E6
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
626.8
624.8
312.8
628.8
314.8
629.8
316.8
353.9
m/z

4l

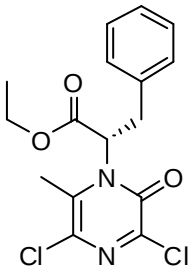


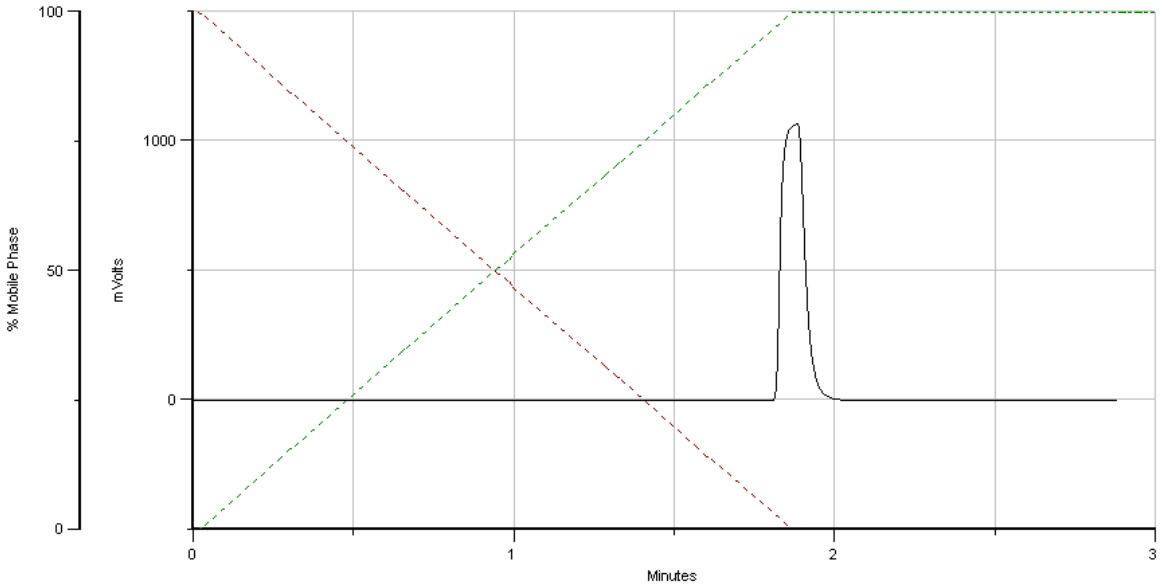
$CDCl_3$

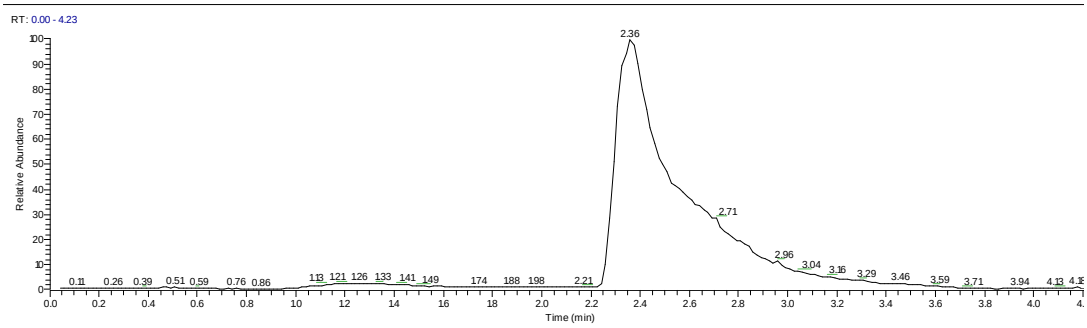


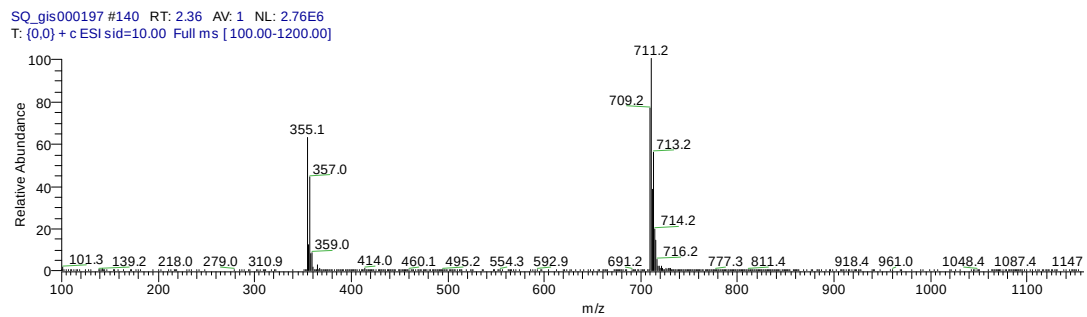
$CDCl_3$

4m

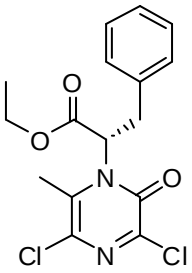

O
O
N
O
Cl
N
Cl


100
50
0
% Mobile Phase
1000
0
mVolts
0
1
2
3
Minutes

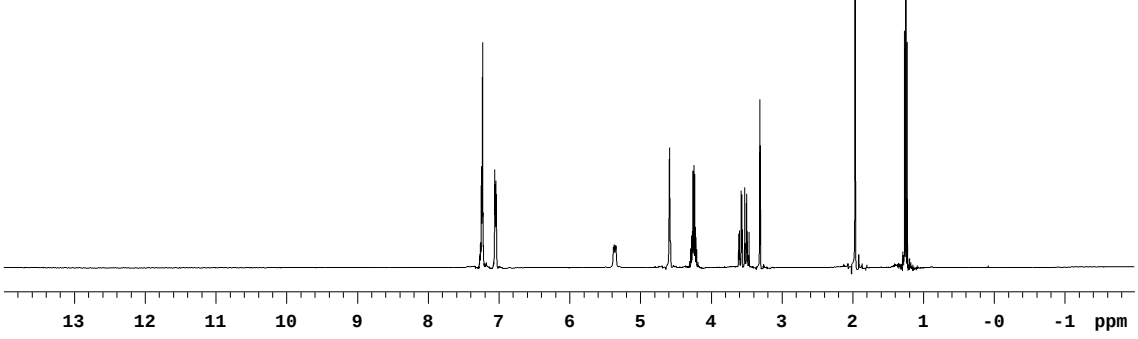

RT: 0.00 - 4.23
Relative Abundance
2.36
2.71
2.96
3.04
3.16
3.29
3.46
3.59
3.71
3.94
Time (min)

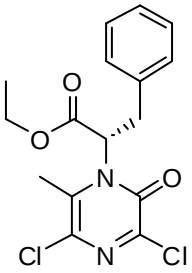

SQ_gis000197 #140 RT: 2.36 AV: 1 NL: 2.76E6
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
711.2
709.2
355.1
713.2
357.0
714.2
359.0
716.2
m/z

4m



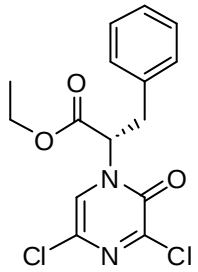
CD_3OD
50°C

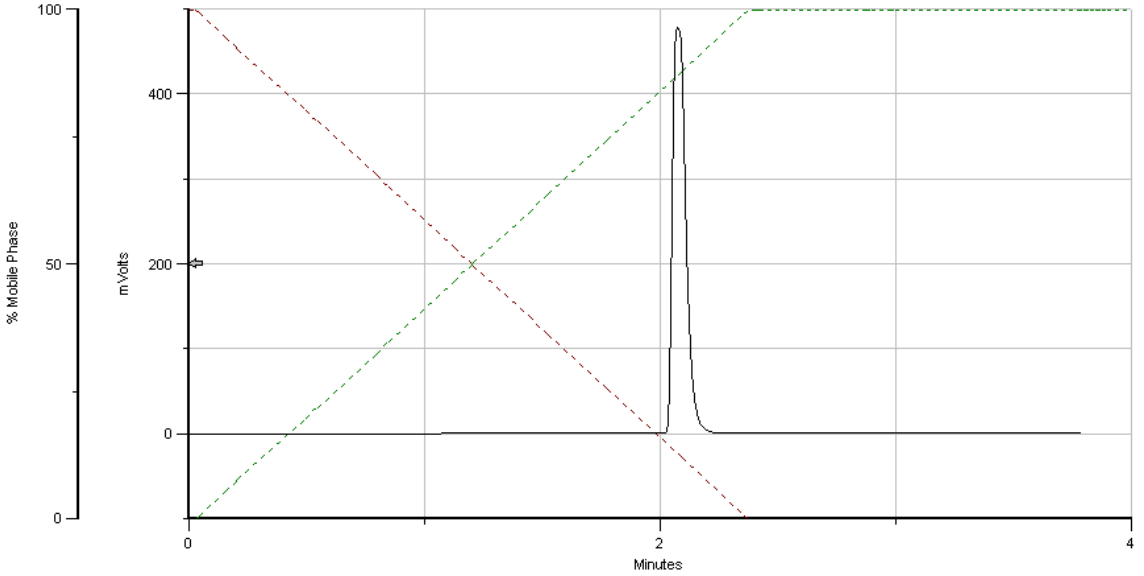


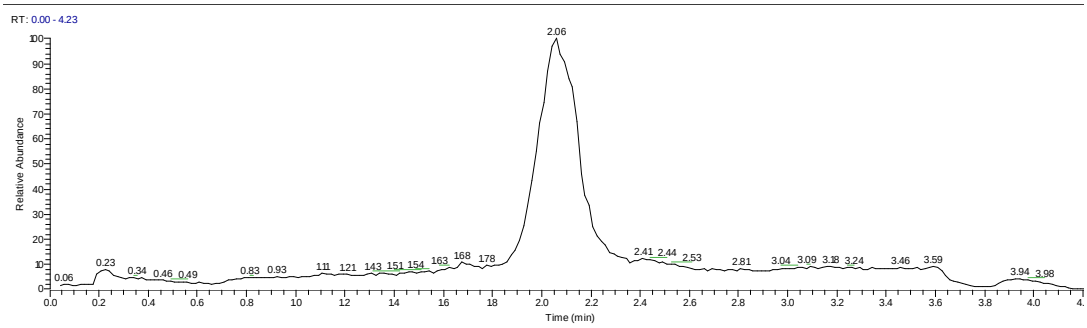


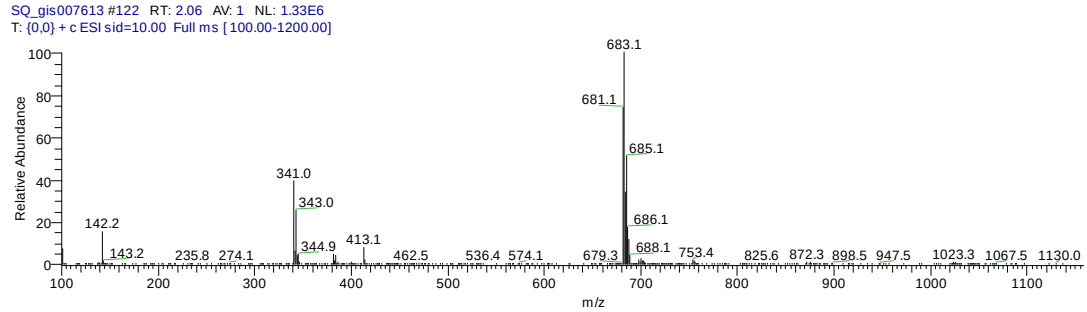
CD_3OD
50°C

4n

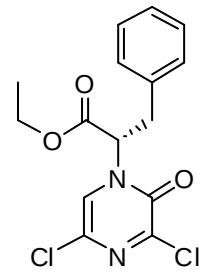

O
O
N
O
Cl
N
Cl


100
50
0
% Mobile Phase
400
200
0
mVolts
0
2
4
Minutes

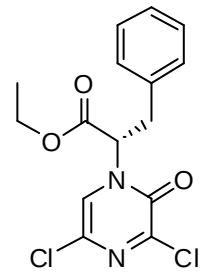

RT: 0.00 - 4.23
Relative Abundance
2.06
0.06
0.23
0.34
0.46
0.49
0.83
0.93
1.11
1.21
1.43
1.51
1.54
1.63
1.68
1.78
2.41
2.44
2.53
2.81
3.04
3.09
3.24
3.46
3.59
3.94
3.98
Time (min)


SQ_gis007613 #122 RT: 2.06 AV: 1 NL: 1.33E6
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
683.1
681.1
685.1
341.0
343.0
686.1
142.2
143.2
344.9
413.1
688.1
m/z

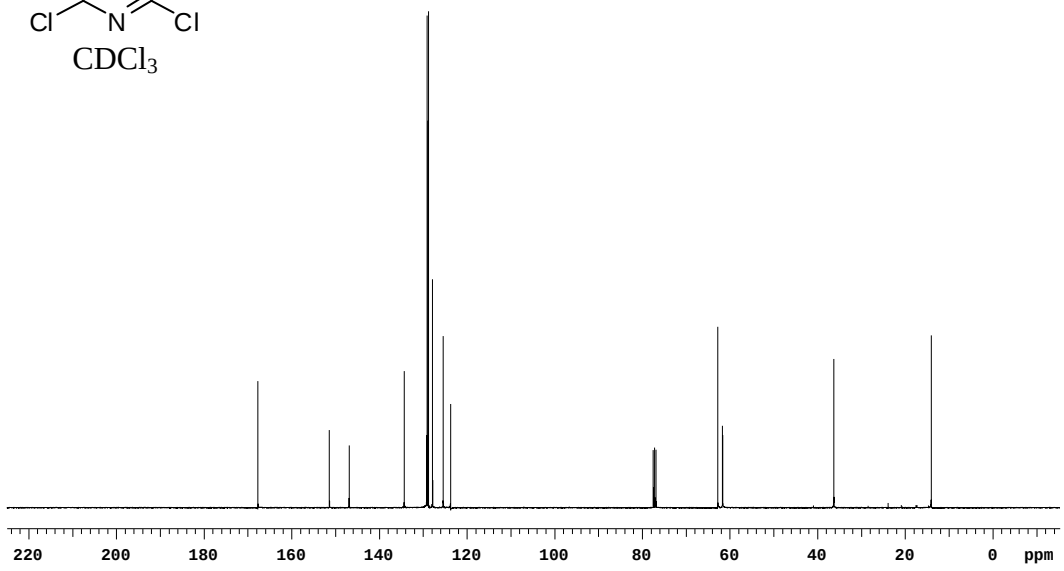
4n



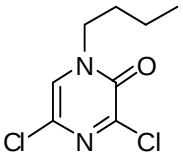
CD_3OD

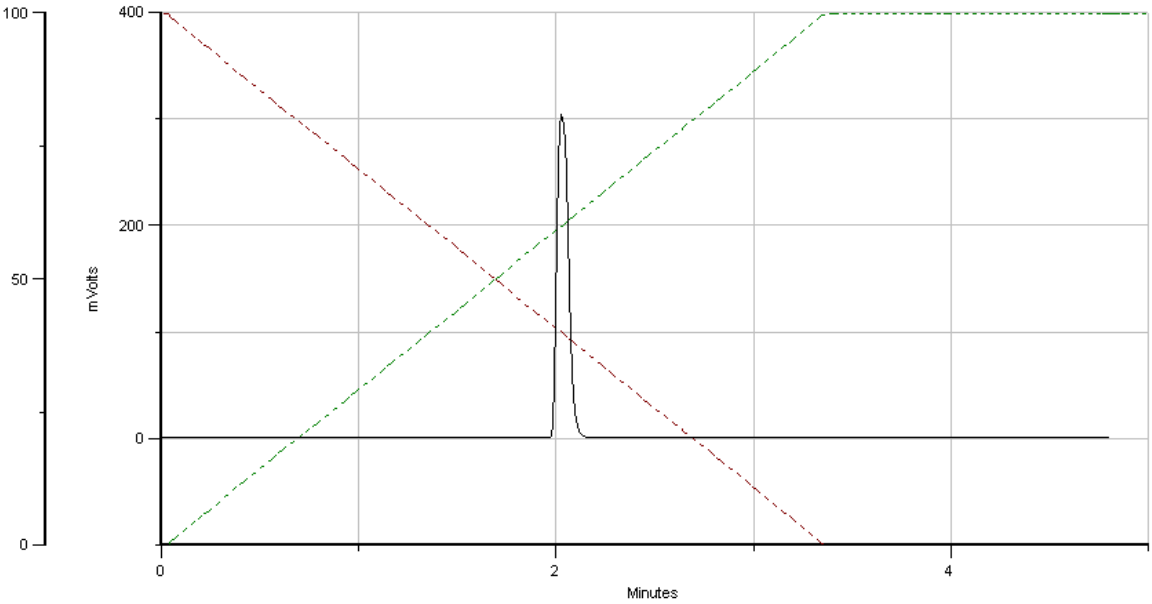


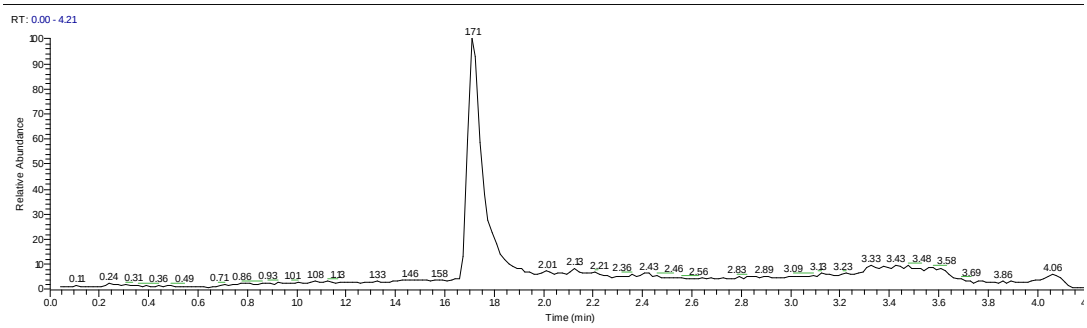
$CDCl_3$

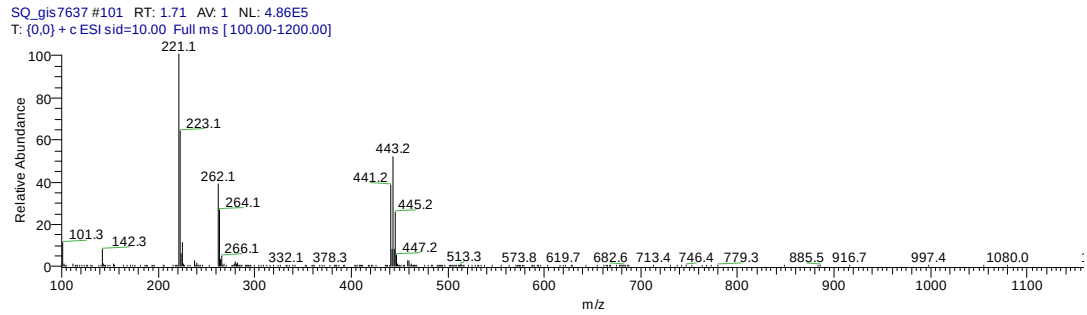


4o

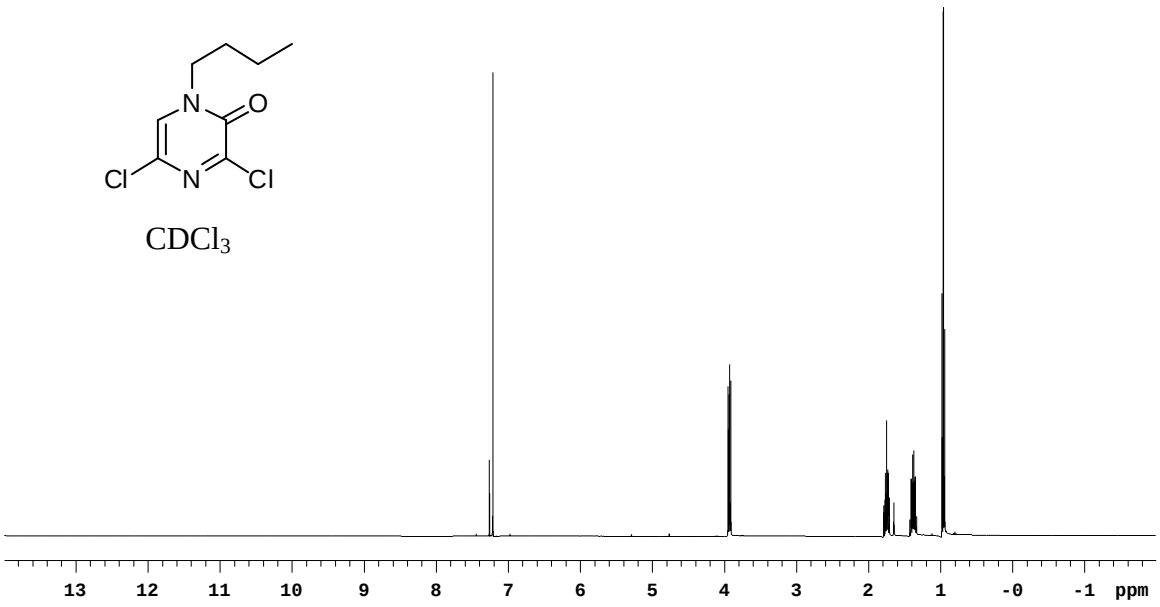

N
O
Cl
N
Cl

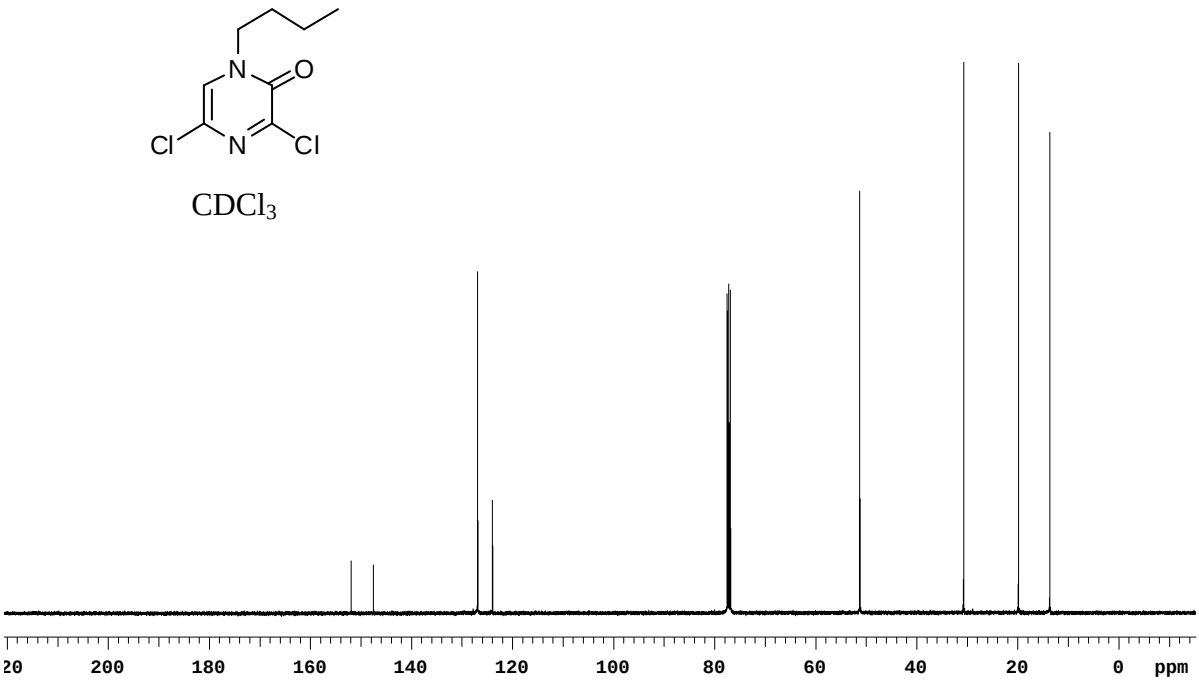

100
50
0
400
200
0
mVolts
0
2
4
Minutes


RT: 0.00 - 4.21
Relative Abundance
Time (min)
171

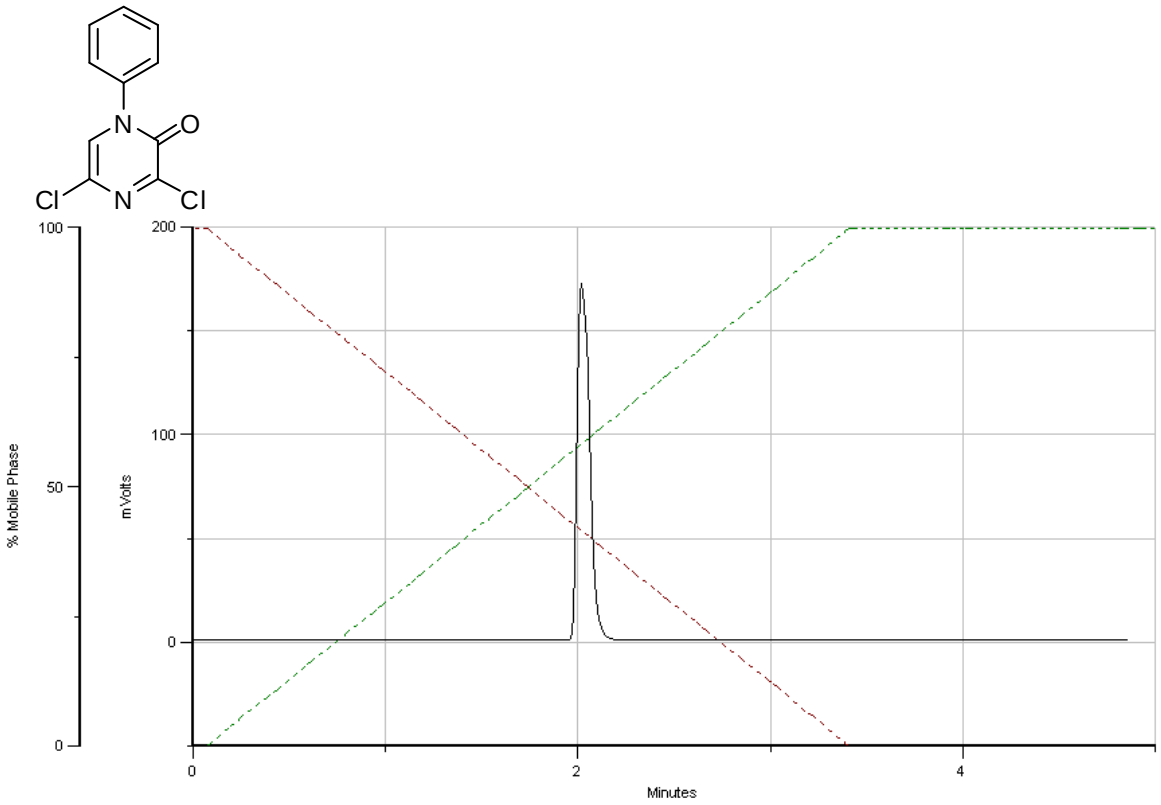

SQ_gis7637 #101 RT: 1.71 AV: 1 NL: 4.86E5
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
m/z
221.1
223.1
443.2
262.1
441.2
264.1
445.2
101.3
142.3
266.1
447.2

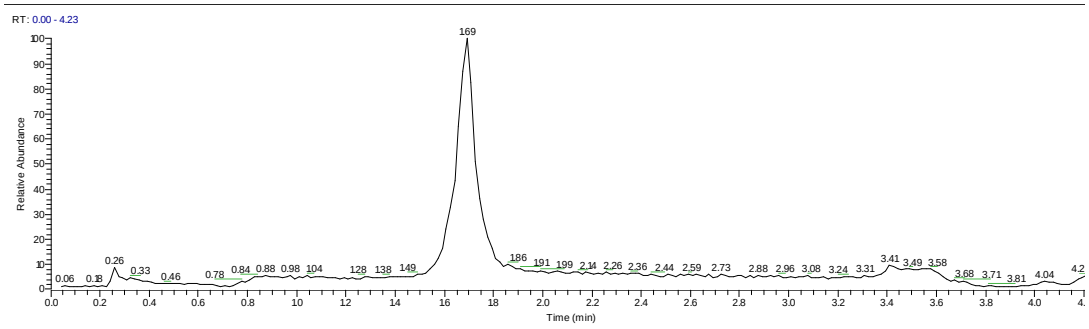
4o

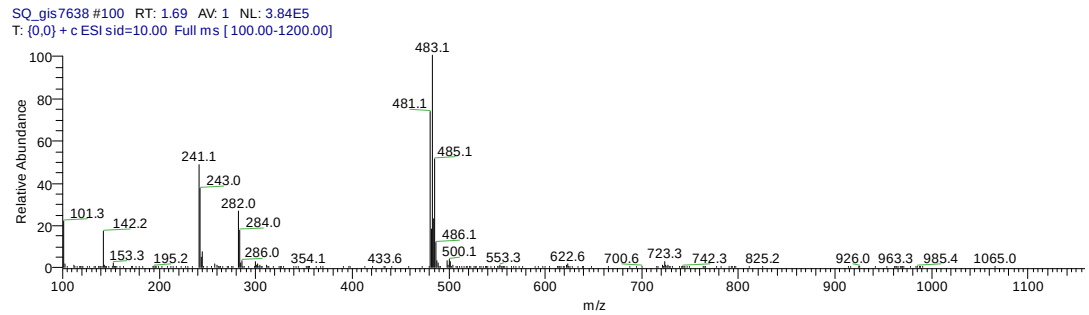

N
O
Cl
N
Cl
CDCl3
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm


N
O
Cl
N
Cl
CDCl3
20
200
180
160
140
120
100
80
60
40
20
0
ppm

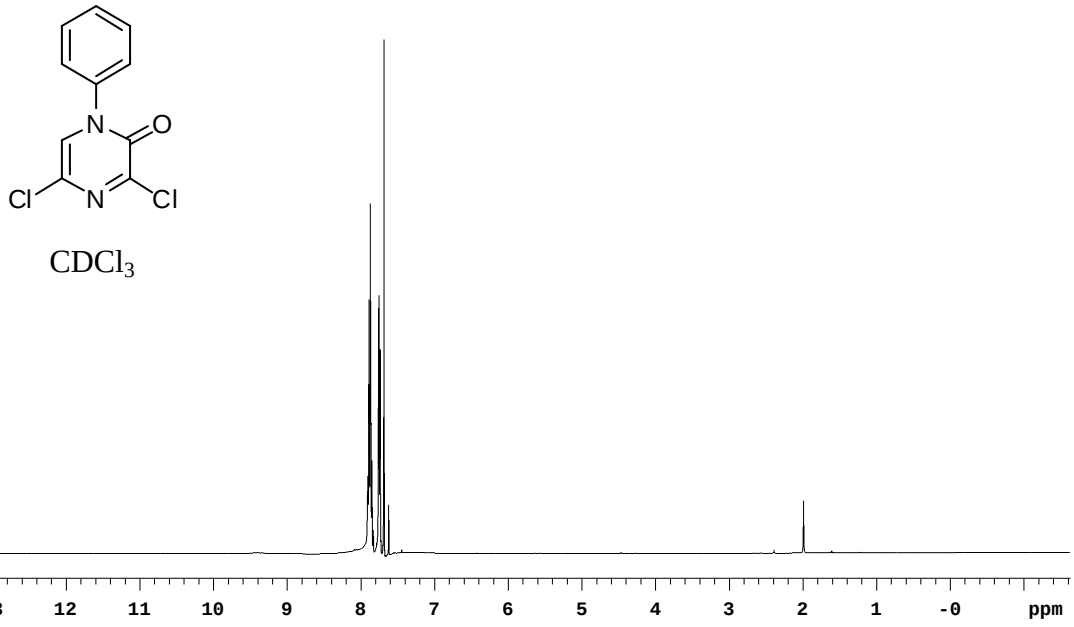
4p

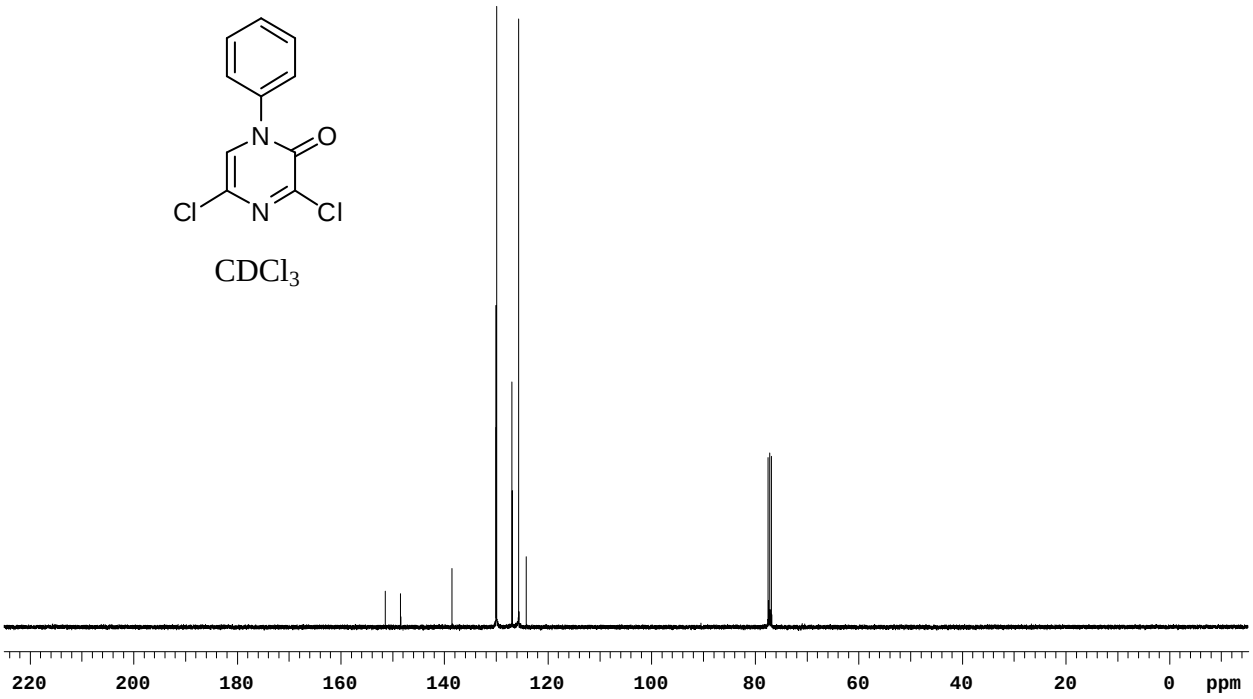

N
O
Cl
N
Cl
100
50
0
% Mobile Phase
200
100
0
mVolts
0
2
4
Minutes


RT: 0.00 - 4.23
Relative Abundance
Time (min)
169
186
0.26
0.33
0.46
0.78
0.84
0.88
0.98
1.04
1.28
1.38
1.49
1.91
1.99
2.14
2.26
2.36
2.44
2.59
2.73
2.88
2.96
3.08
3.24
3.31
3.41
3.49
3.58
3.68
3.71
3.81
4.04

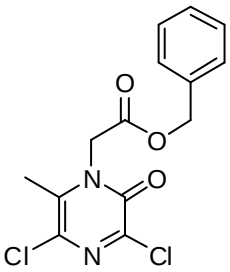

SQ_gis7638 #100 RT: 1.69 AV: 1 NL: 3.84E5
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
m/z
483.1
481.1
485.1
241.1
243.0
282.0
284.0
101.3
142.2
153.3
195.2
286.0
354.1
433.6
486.1
500.1
553.3
622.6
700.6
723.3
742.3
825.2
926.0
963.3
985.4
1065.0

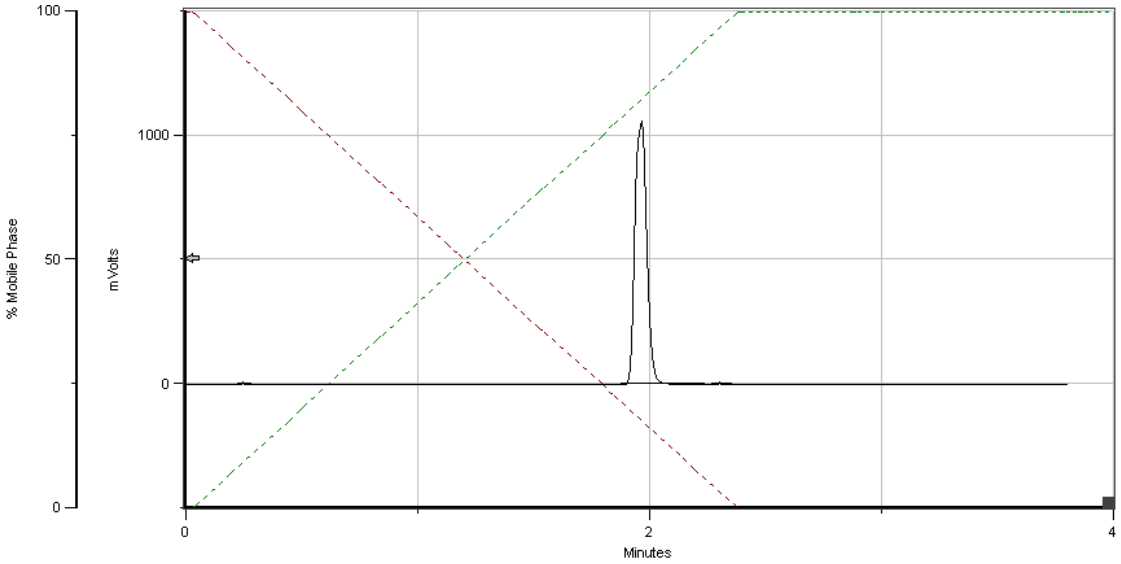
4p

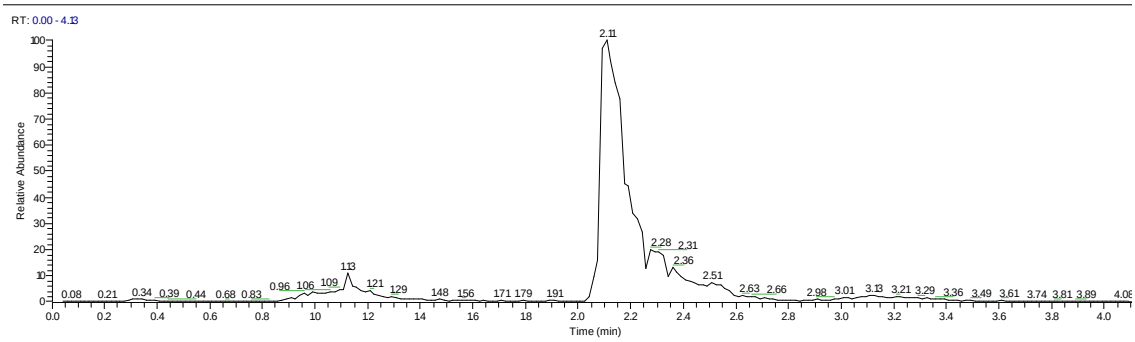

N
O
Cl
N
Cl
CDCl3
14
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

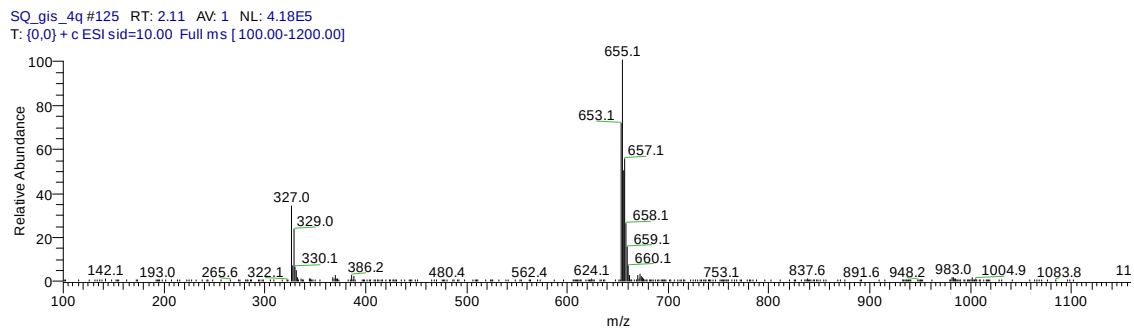

N
O
Cl
N
Cl
CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

4q

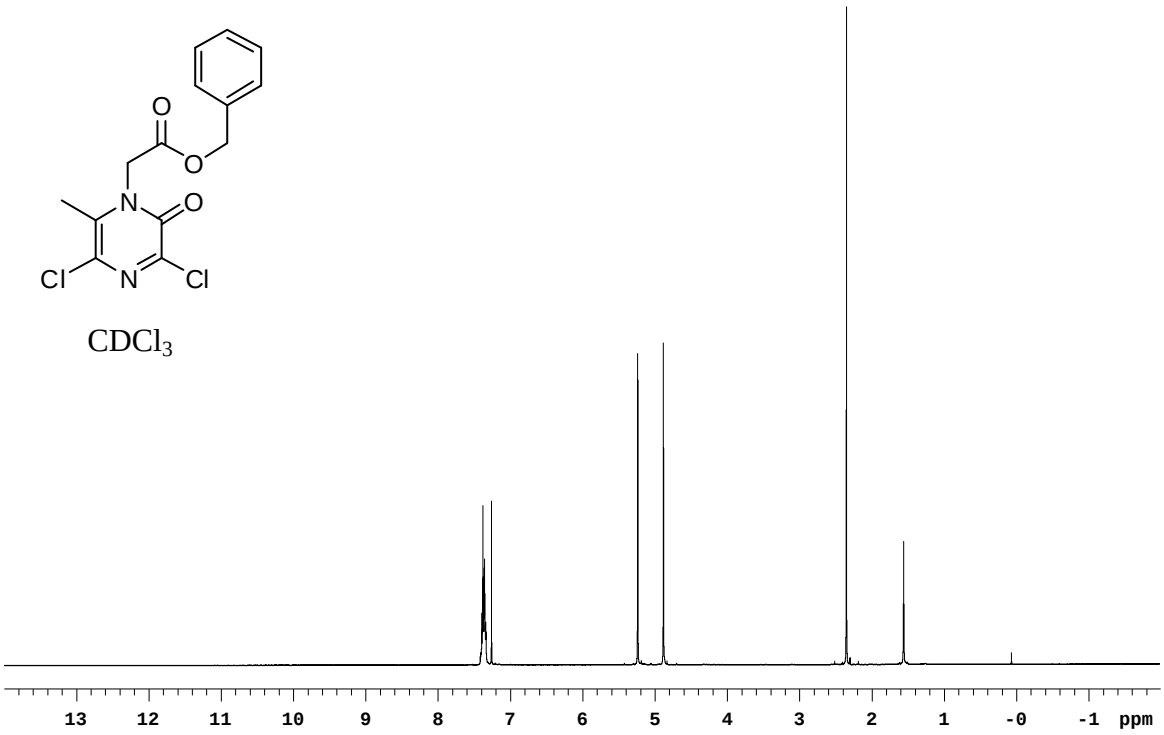

O
O
N
O
Cl
N
Cl

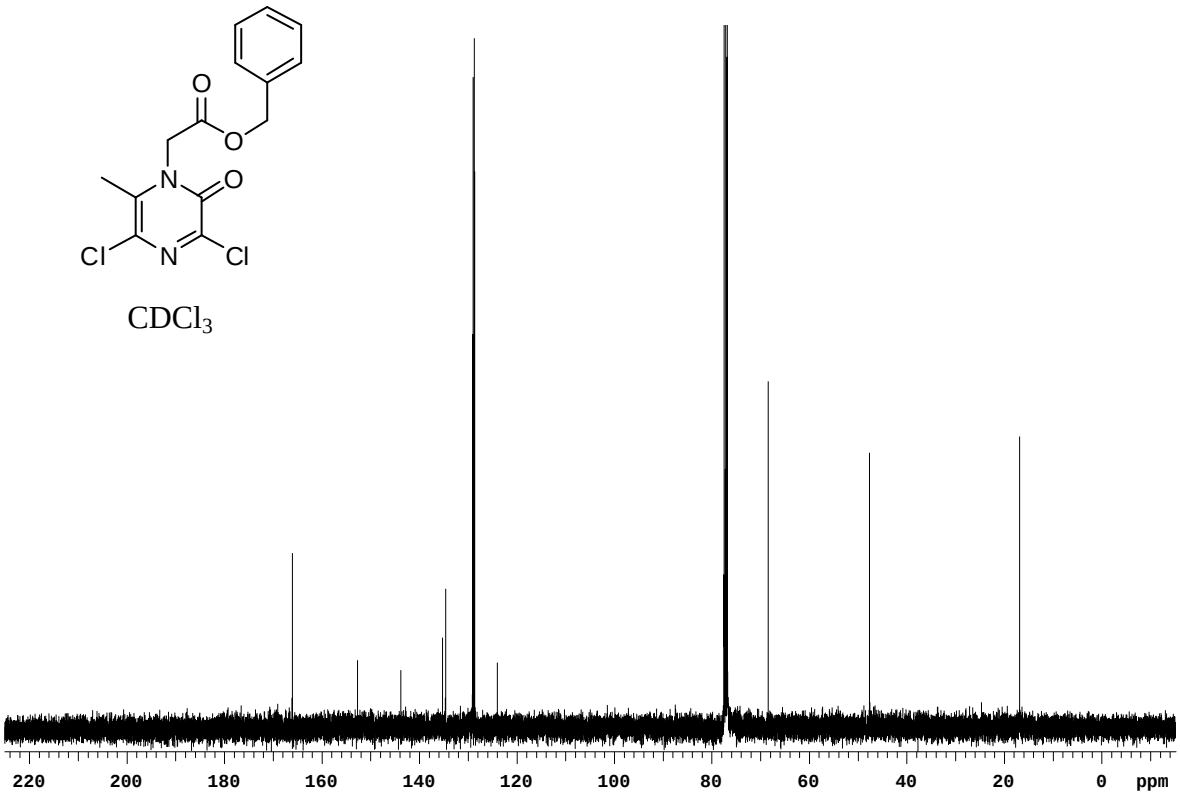

100
50
0
% Mobile Phase
1000
0
mVolts
0
2
4
Minutes


RT: 0.00 - 4.13
Relative Abundance
Time (min)
2.11
2.28
2.31
2.36
2.51
1.13

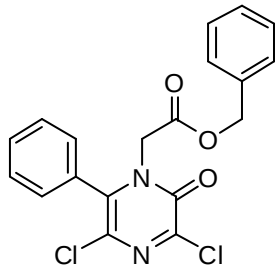

SQ_gis_4q #125 RT: 2.11 AV: 1 NL: 4.18E5
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
m/z
655.1
653.1
657.1
327.0
329.0
658.1
659.1
660.1
330.1
386.2

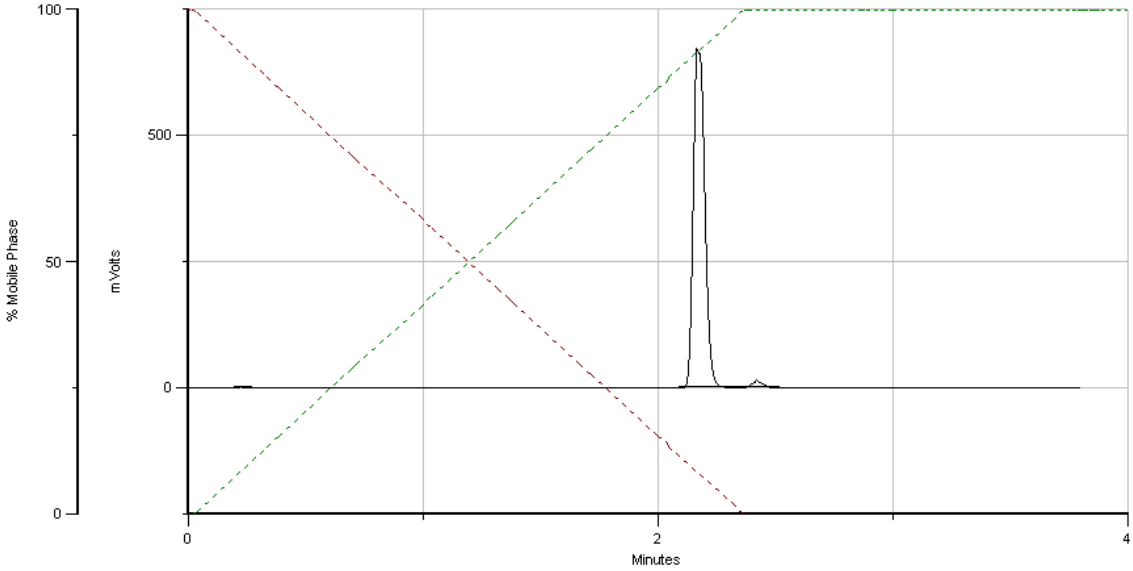
4q

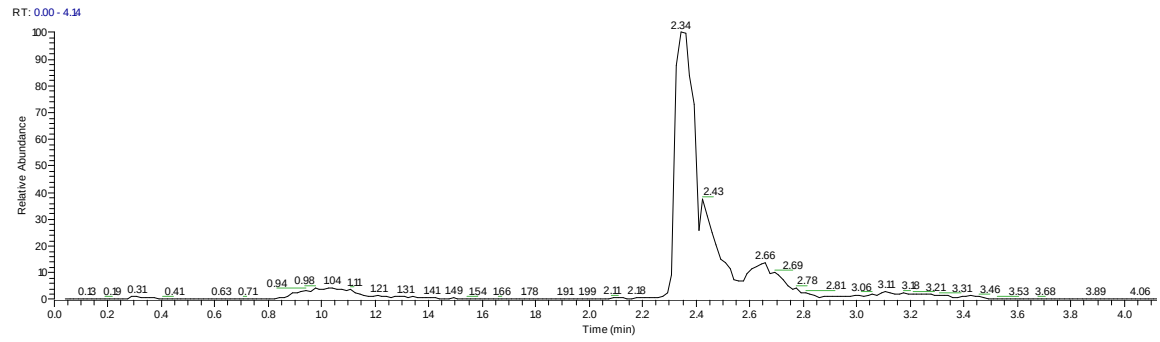

O
O
N
O
Cl
N
Cl
CDCl3
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

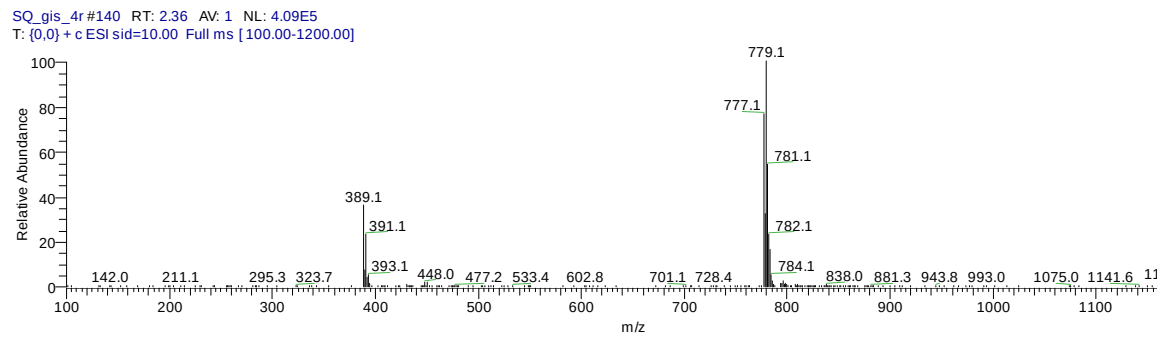

O
O
N
O
Cl
N
Cl
CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

4r

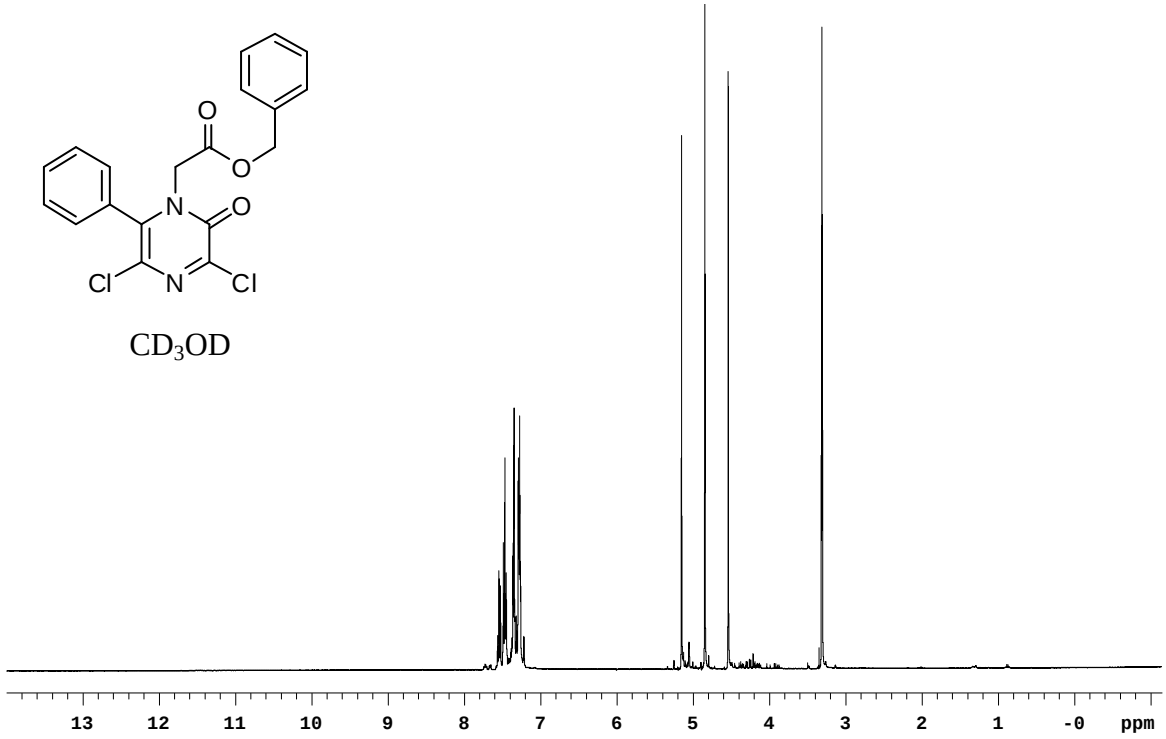

O
O
N
O
Cl
N
Cl

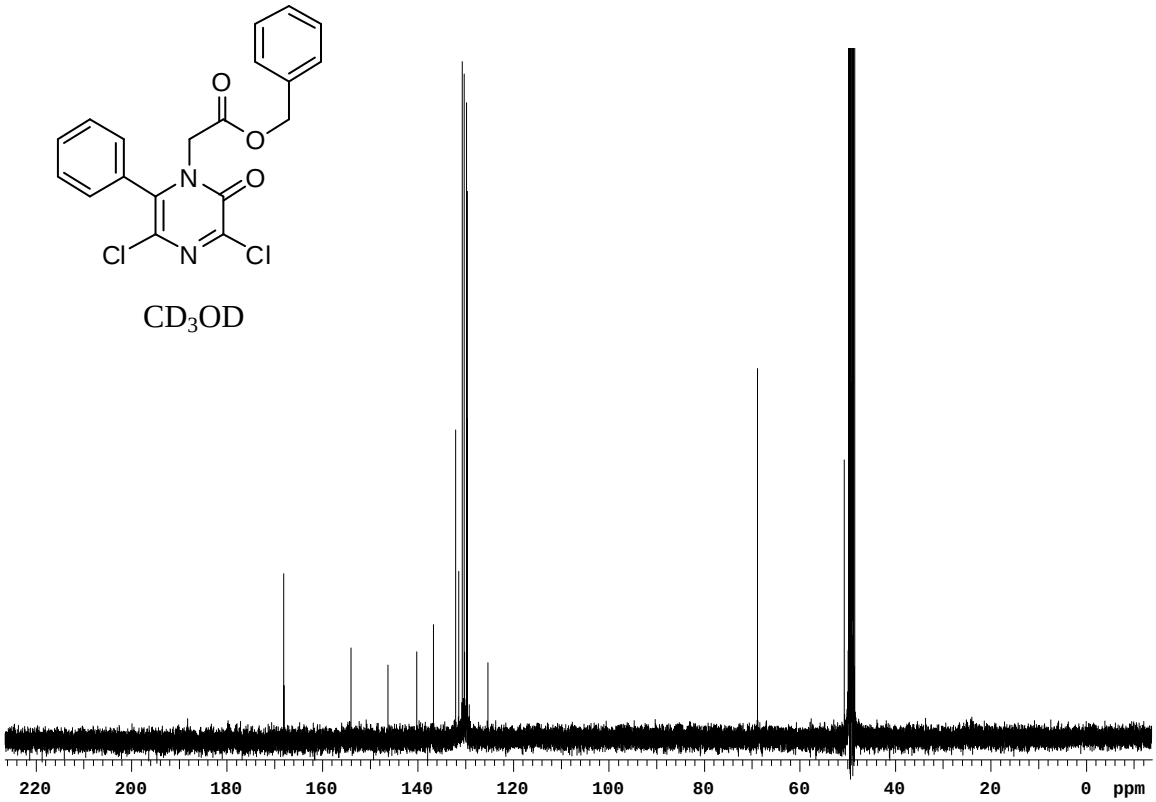

100
50
0
% Mobile Phase
500
0
mVolts
0
2
4
Minutes


RT: 0.00 - 4.14
Relative Abundance
2.34
2.43
2.66
2.69
2.78
Time (min)

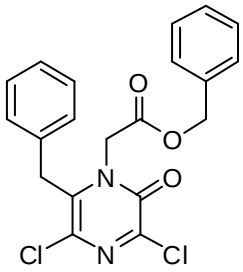

SQ_gis_4r #140 RT: 2.36 AV: 1 NL: 4.09E5
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
779.1
777.1
781.1
389.1
391.1
782.1
393.1
784.1
m/z

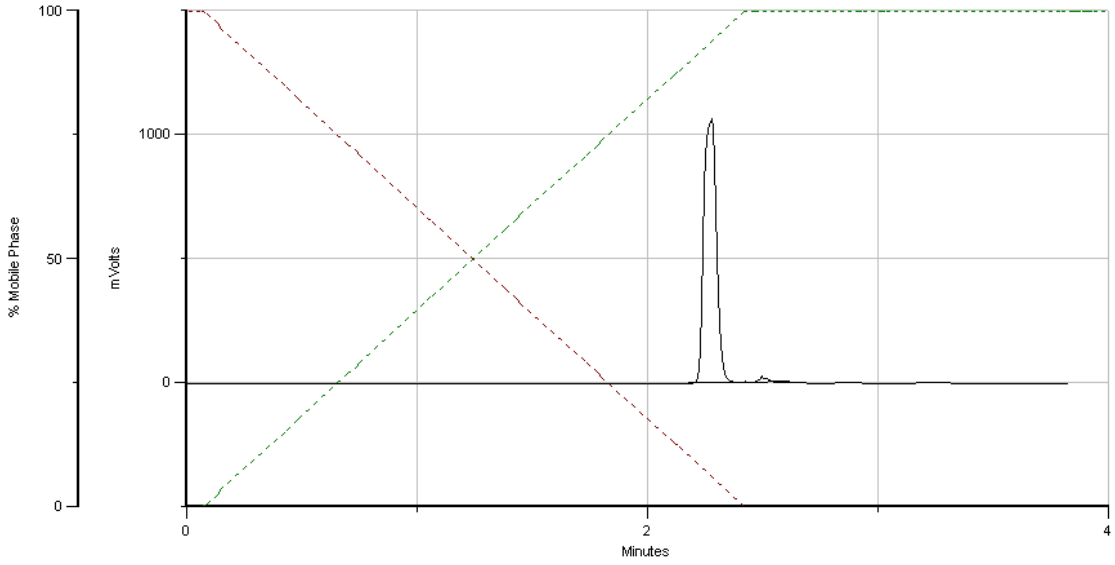
4r

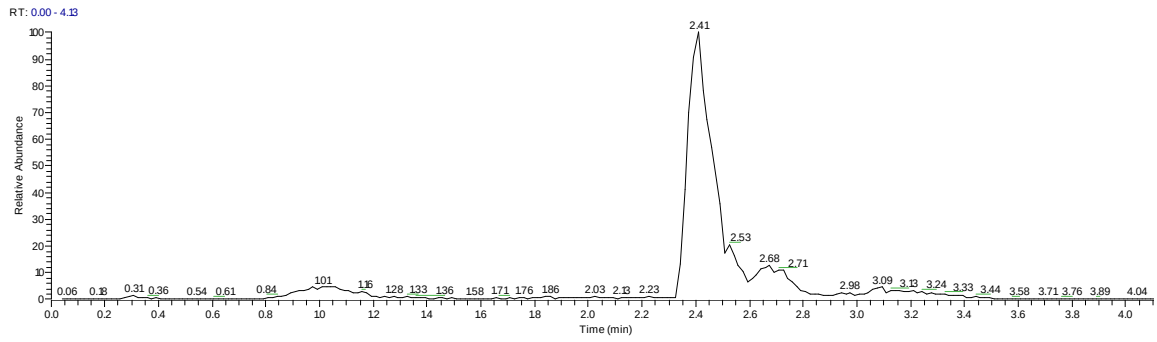

O
O
N
O
Cl
N
Cl
CD3OD
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

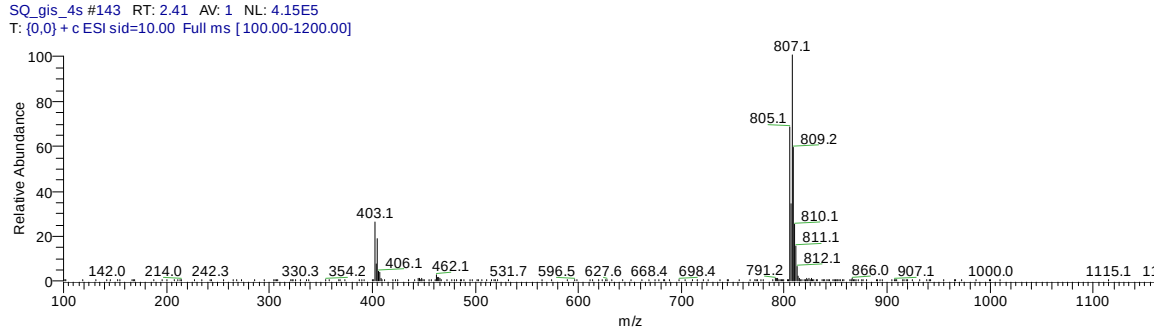

O
O
N
O
Cl
N
Cl
CD3OD
220
200
180
160
140
120
100
80
60
40
20
0
ppm

4s

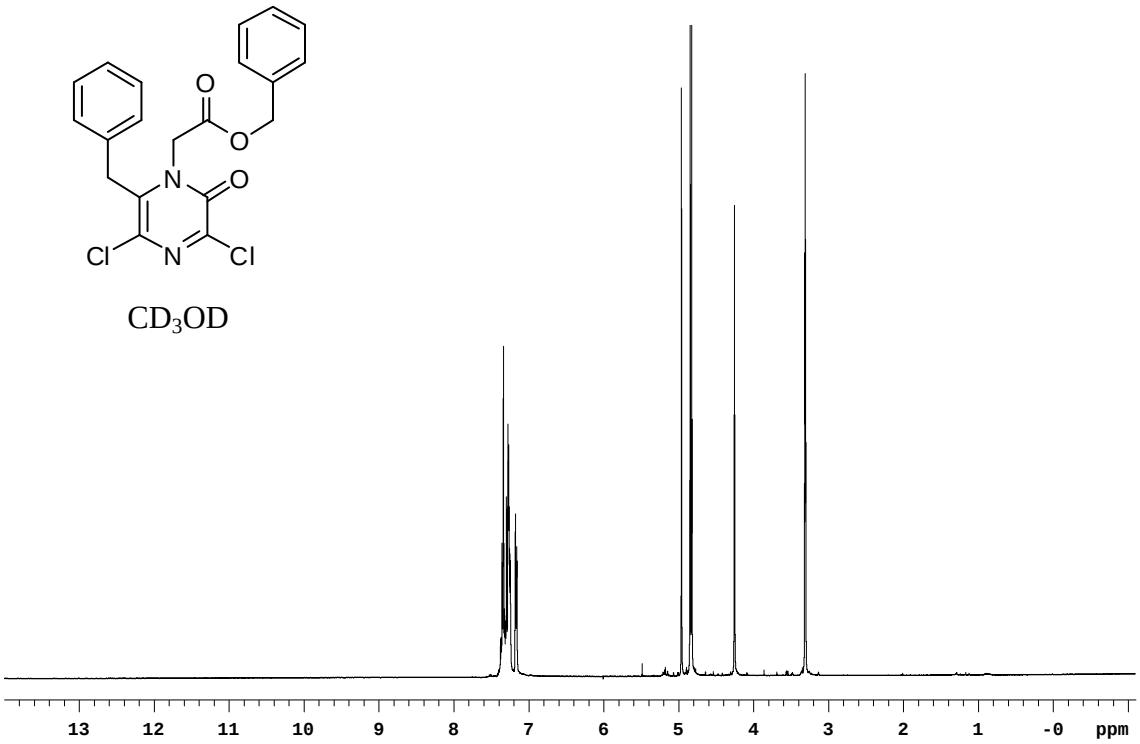

O
O
N
O
Cl
N
Cl

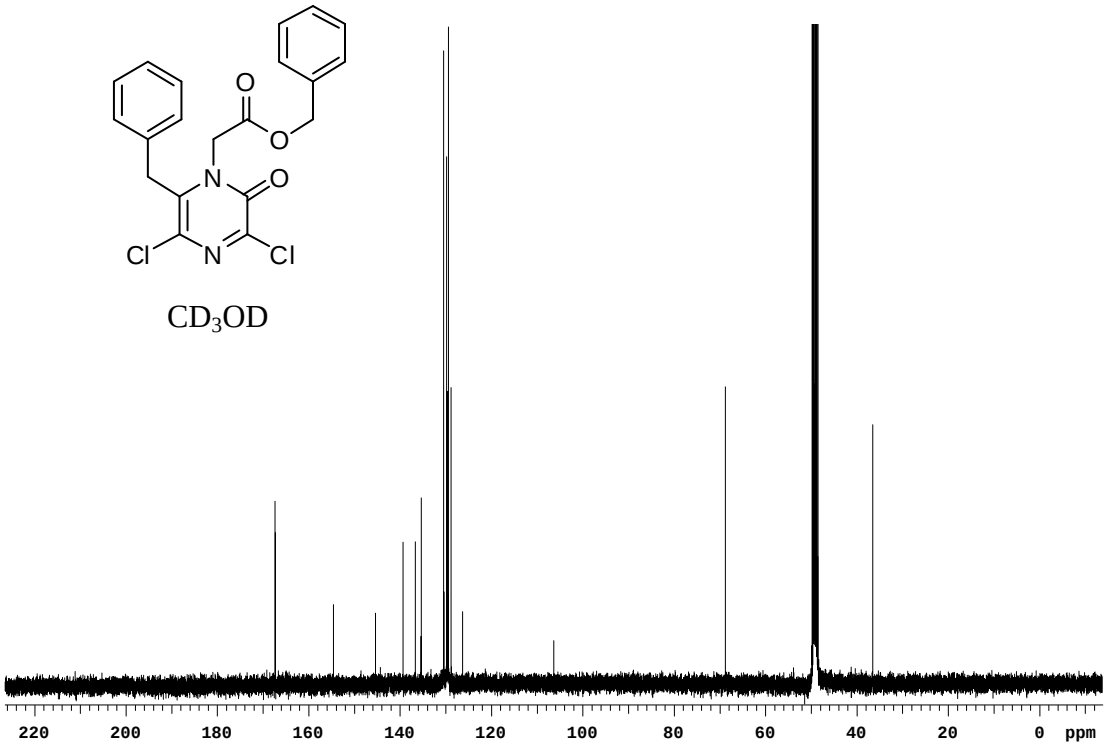

100
50
0
% Mobile Phase
1000
0
mVolts
0
2
4
Minutes


RT: 0.00 - 4.13
Relative Abundance
2.41
2.53
2.68
2.71
Time (min)

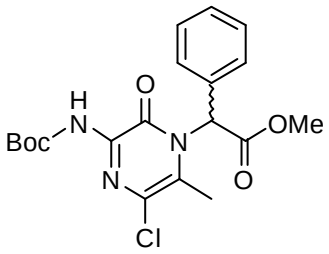

SQ_gis_4s #143 RT: 2.41 AV: 1 NL: 4.15E5
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
807.1
805.1
809.2
403.1
810.1
811.1
812.1
m/z

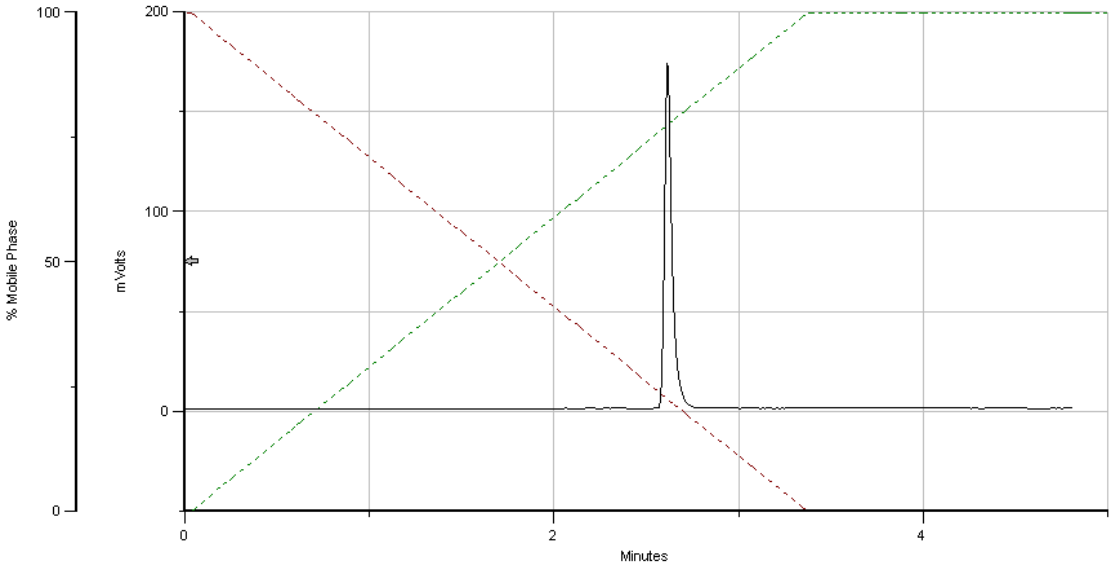
4s

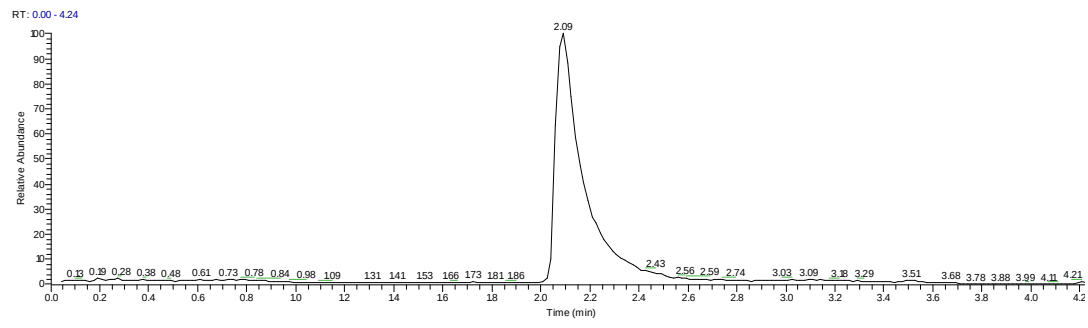

O
O
N
O
Cl
N
Cl
CD3OD
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

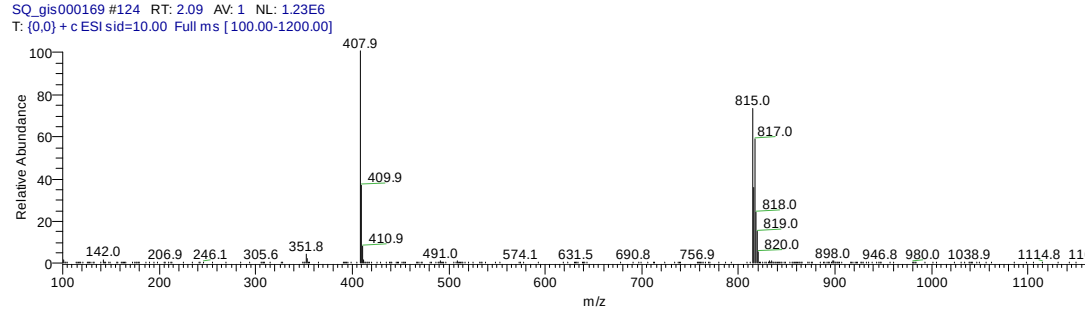

O
O
N
O
Cl
N
Cl
CD3OD
220
200
180
160
140
120
100
80
60
40
20
0
ppm

5

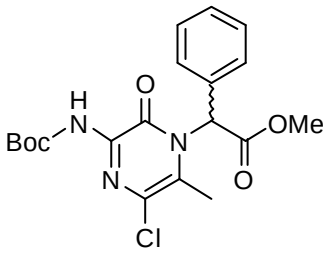

H
N
Boc
O
N
OMe
N
O
Cl


% Mobile Phase
mVolts
Minutes

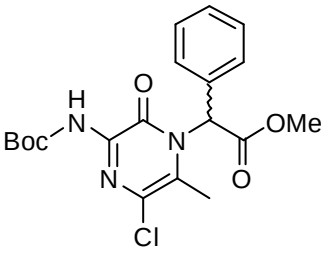

RT: 0.00 - 4.24
Relative Abundance
Time (min)
2.09


SQ_gis000169 #124 RT: 2.09 AV: 1 NL: 1.23E6
T: {0,0} + c ESI sid=10.00 Full ms [100.00-1200.00]
Relative Abundance
m/z
407.9
815.0
817.0
409.9
818.0
819.0
820.0
410.9

5

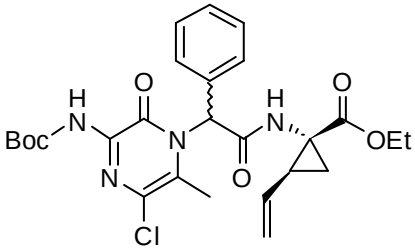


$CDCl_3$

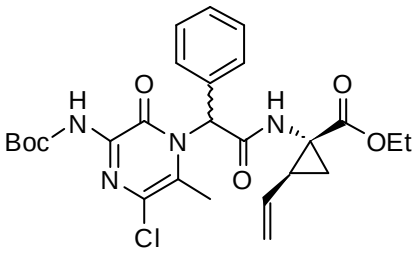


$CDCl_3$

6

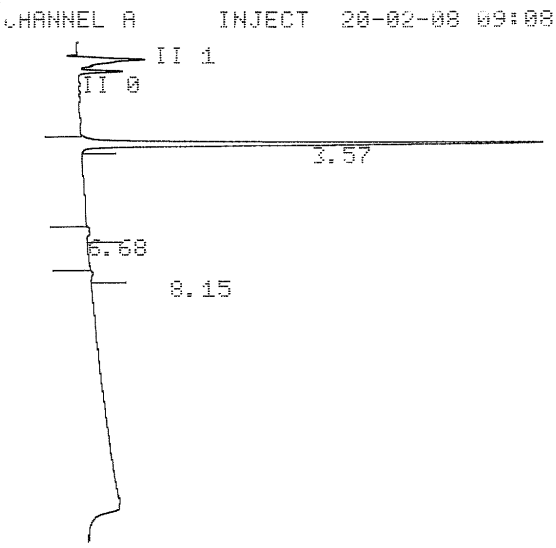


$CDCl_3$



$CDCl_3$

7a

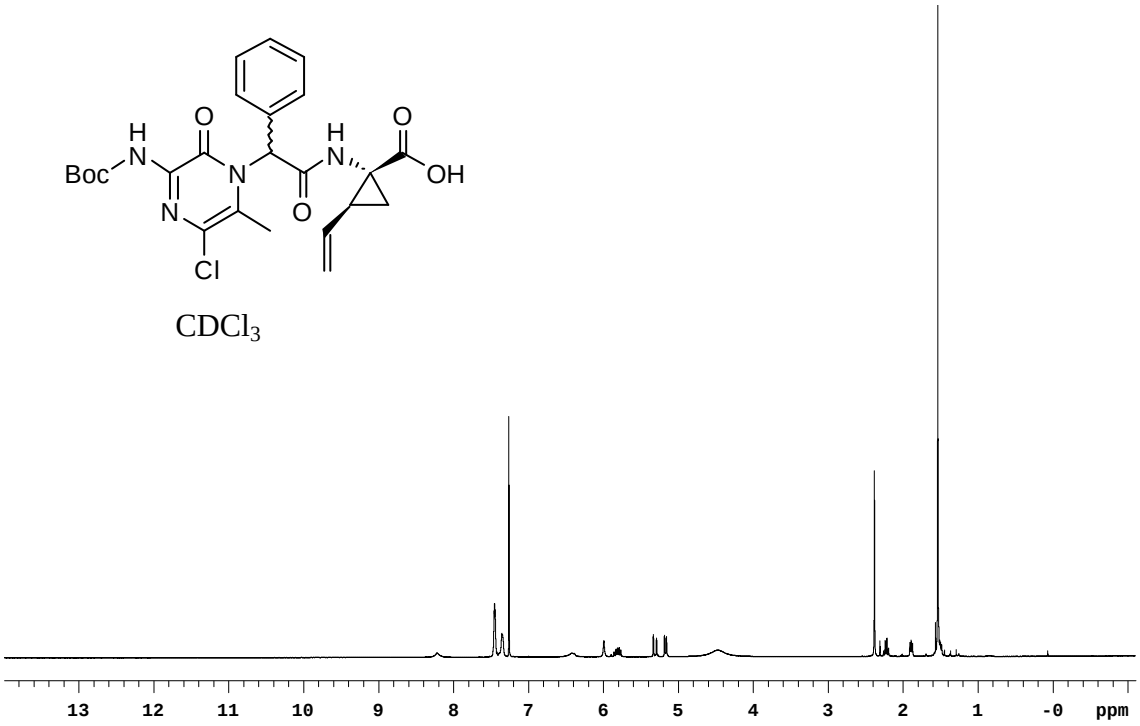


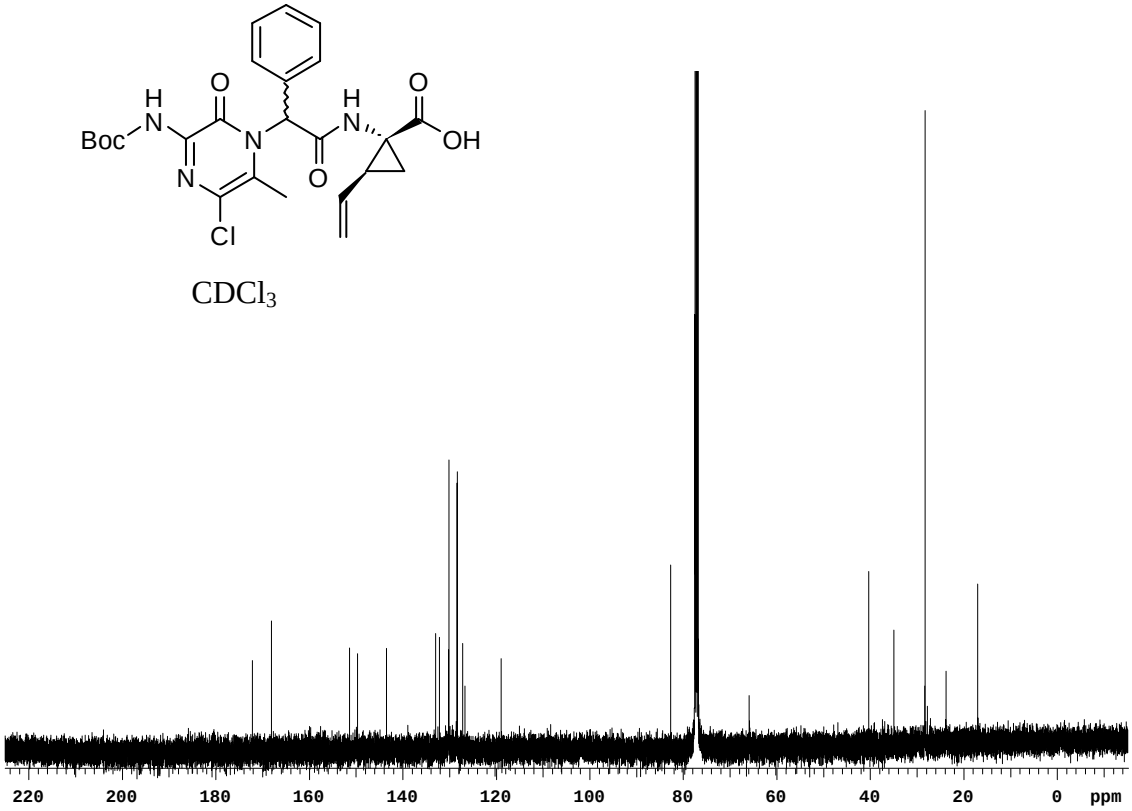
20-02-08 09:08:50 CH= "A" PS= 1.

FILE 1. METHOD 0. RUN 9 INDEX 9

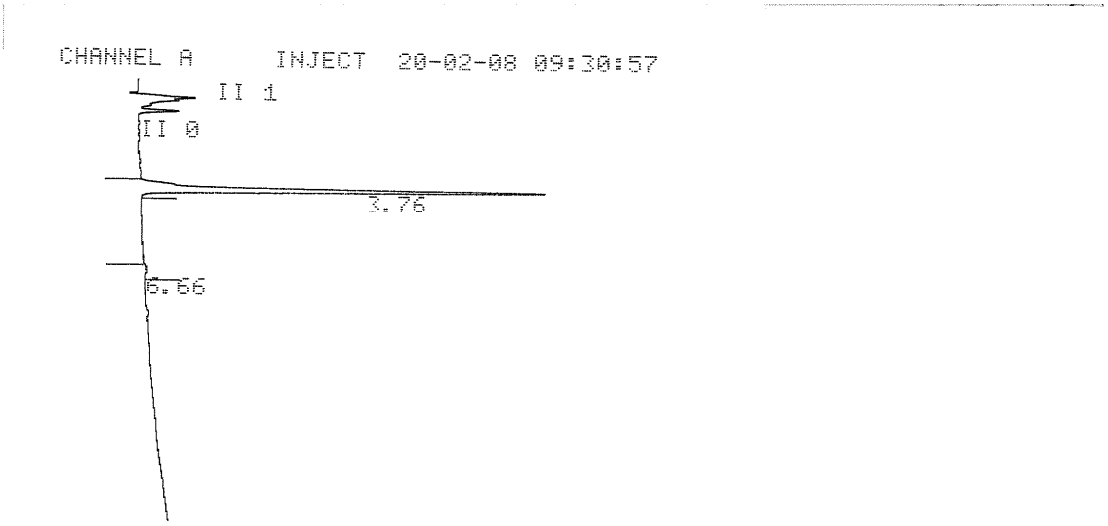
PEAK#	AREA%	RT	AREA	BC
1	97.53	3.57	406563	01
2	1.509	6.68	6289	01
3	0.961	8.15	4007	01
TOTAL	100		416859	

7a


Boc
H
N
O
N
N
Cl
H
N
O
OH
O
CDCl3
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm


Boc
H
N
O
N
N
Cl
H
N
O
OH
O
CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

7b

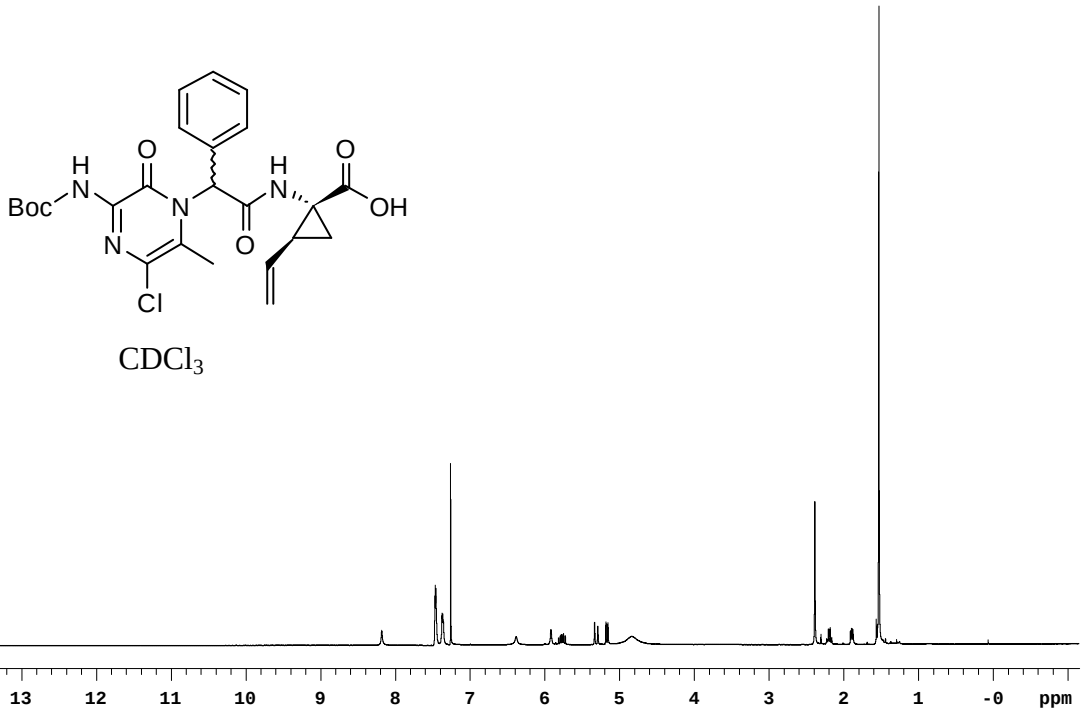


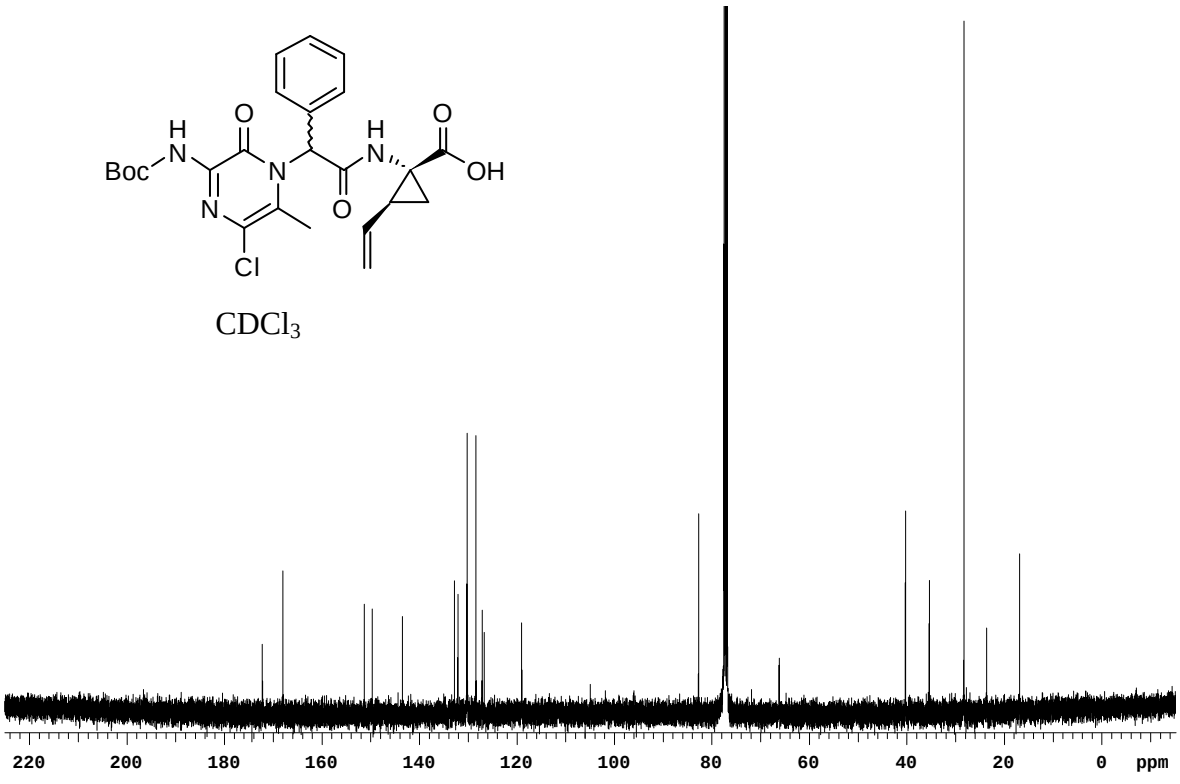
20-02-08 09:30:57 CH= "A" PS= 1.

FILE 1. METHOD 0. RUN 10 INDEX 10

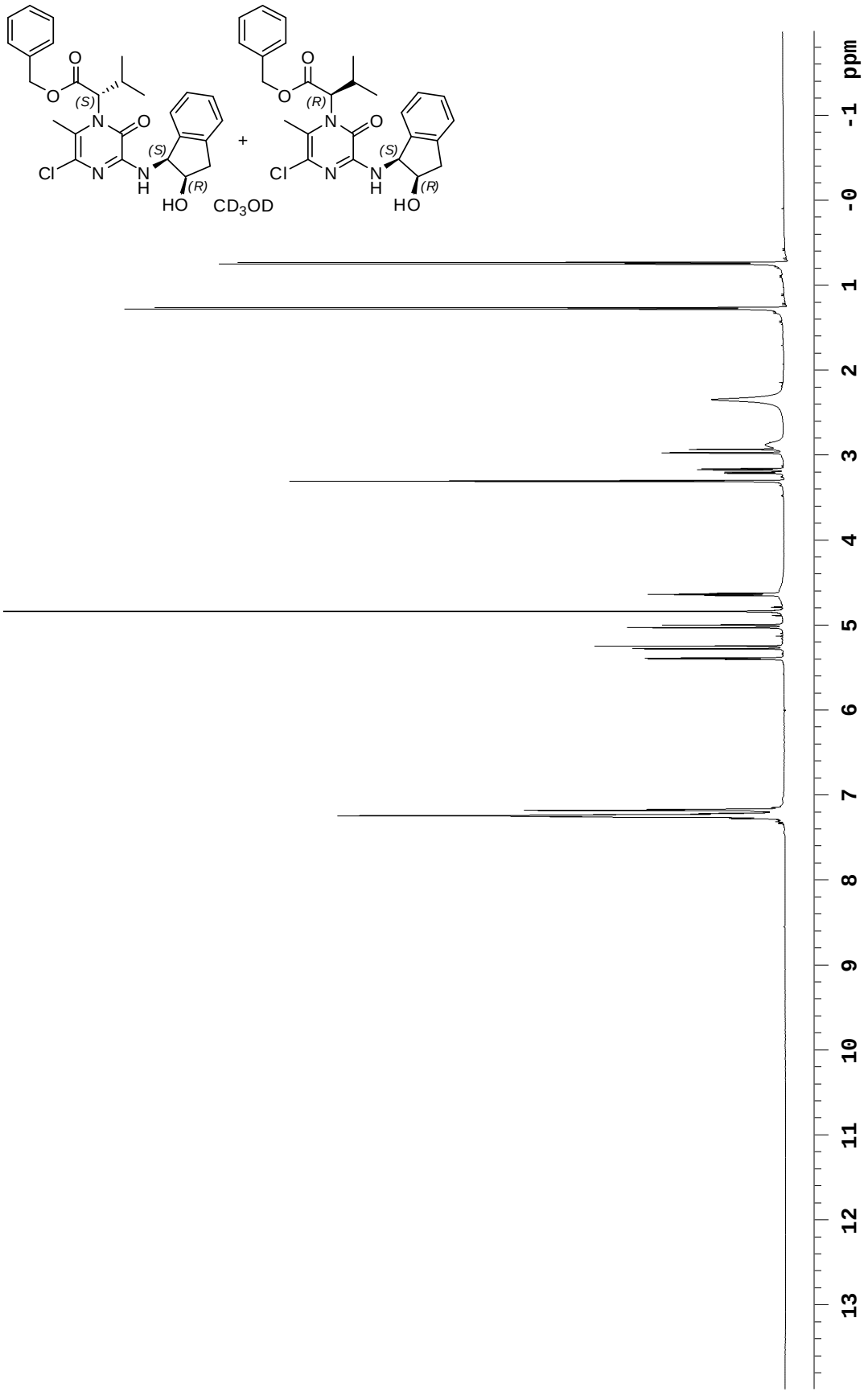
PEAK#	AREA%	RT	AREA	BC
1	98.633	3.76	392885	01
2	1.367	6.66	5444	01
TOTAL	100.		398329	

7b

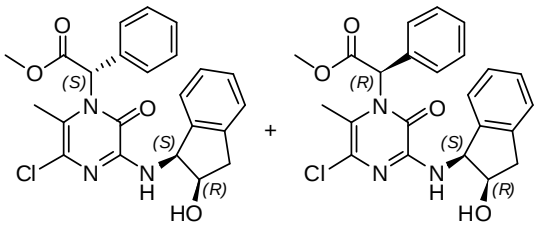

Boc
H
N
O
N
N
Cl
H
N
O
OH
O
CDCl3
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm


Boc
H
N
O
N
N
Cl
H
N
O
OH
O
CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

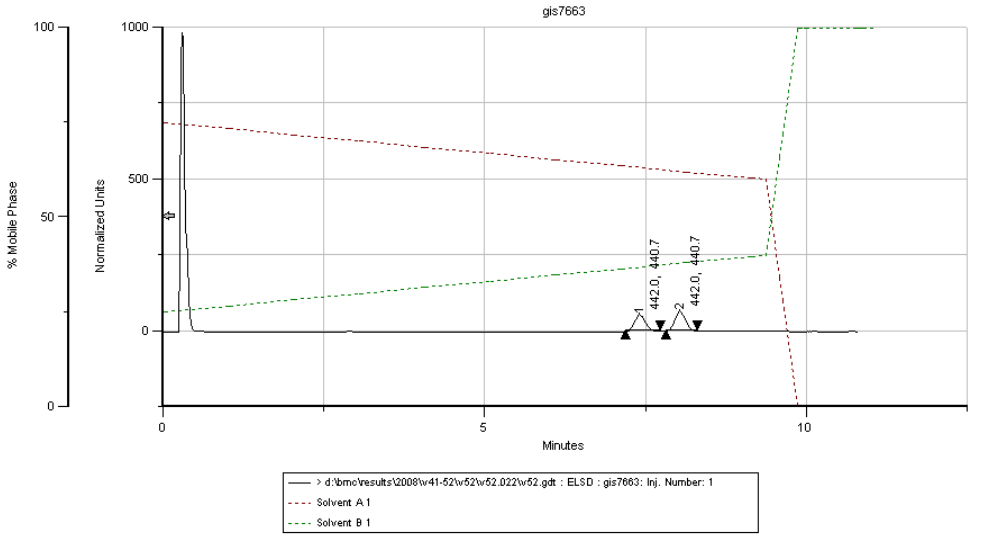
(1*S*,2*R*)-*cis*-1-amino-2-indanol derivitized **4j**

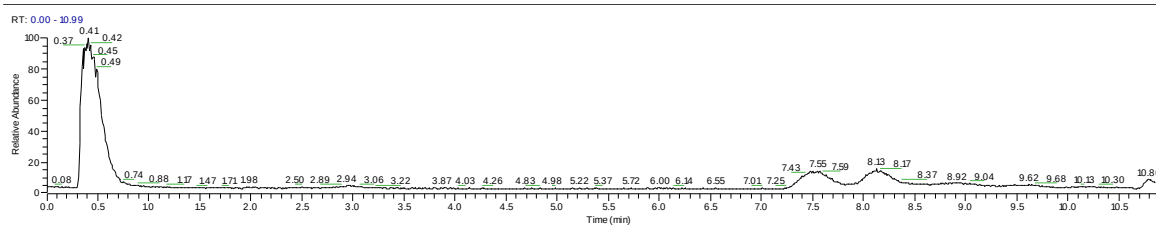


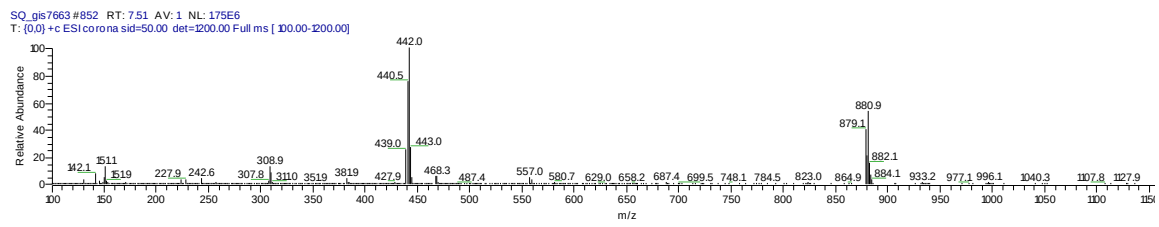
(1*S*,2*R*)-*cis*-1-amino-2-indanol derivitized **4k**

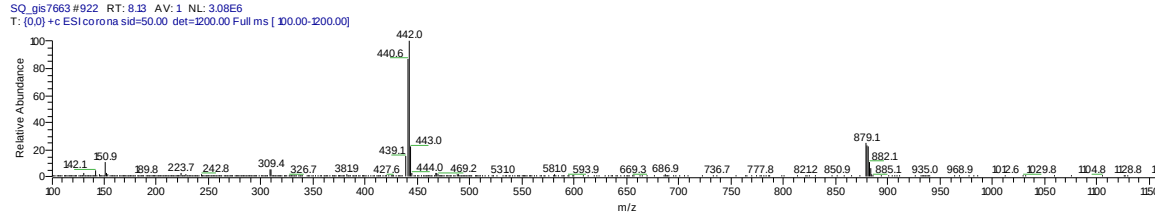


	Sample Descrip.	Peak Name	R. Time	Area %	Area
1	gis7663	*1	7.42	46.50	1149471.00
2	gis7663	2	8.04	53.50	1322533.25

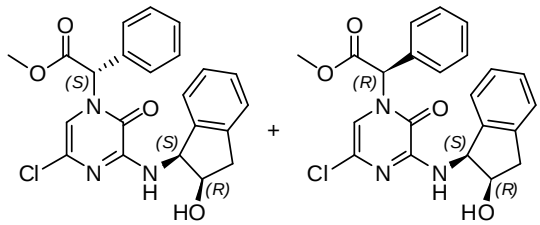




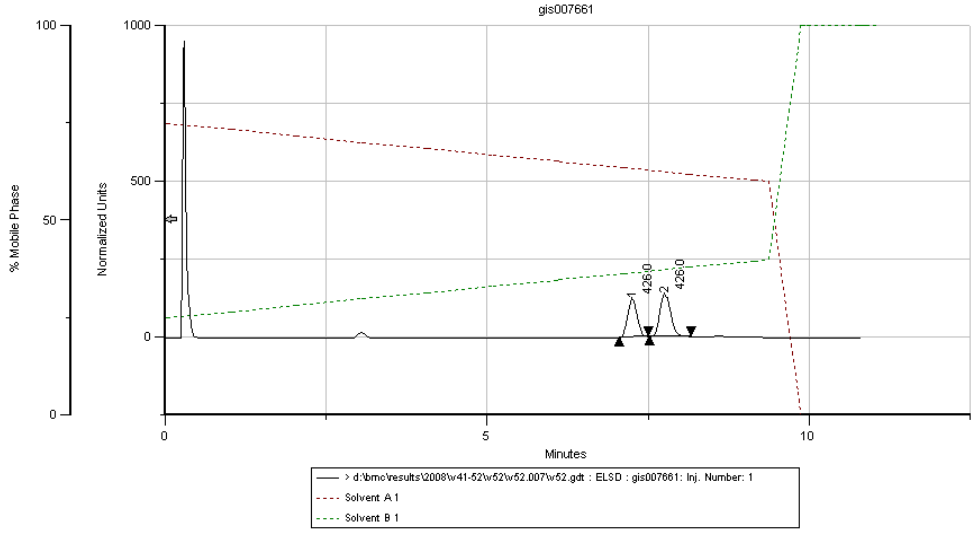


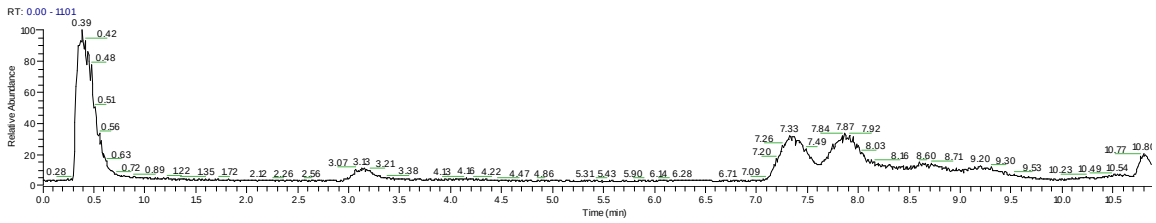


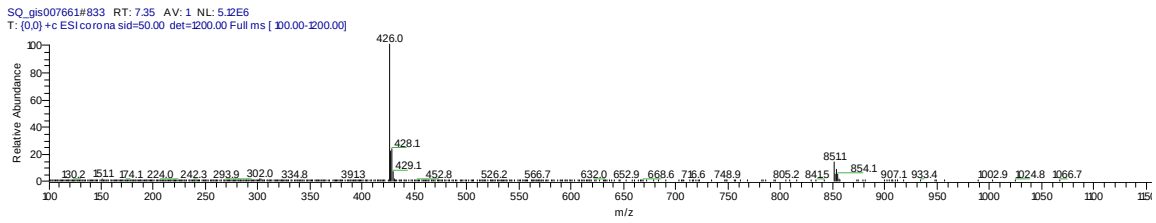
(1*S*,2*R*)-*cis*-1-amino-2-indanol derivitized **4l**

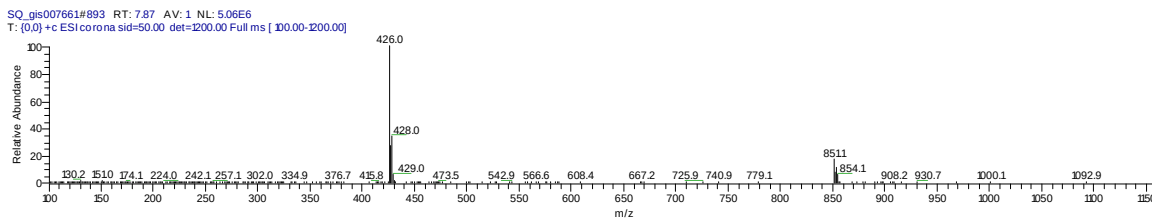


	Sample Descrip.	Peak Name	R. Time	Area %	Area
1	gis007661	*1	7.26	43.92	2162772.00
	gis007661	2	7.76	56.08	2761818.25

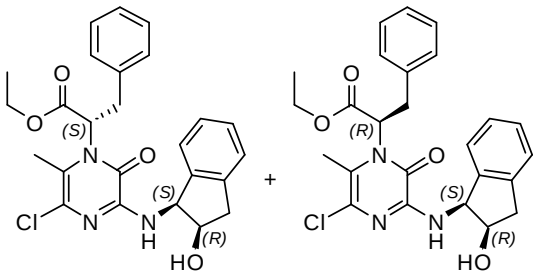




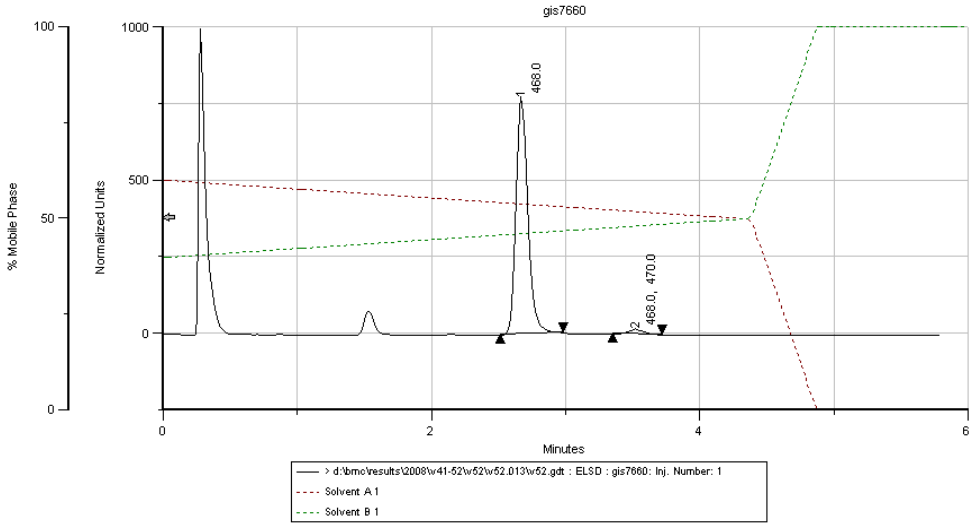


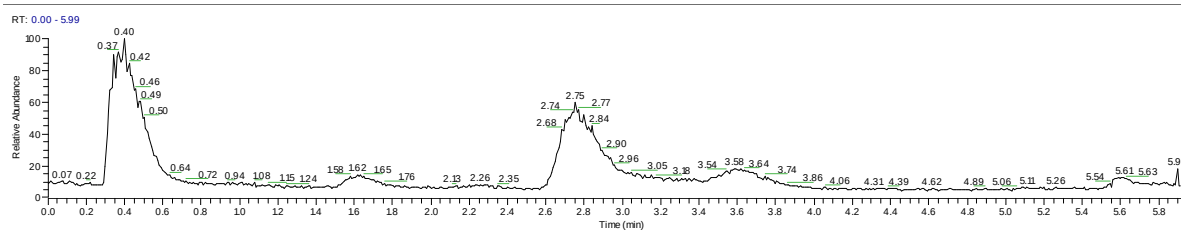


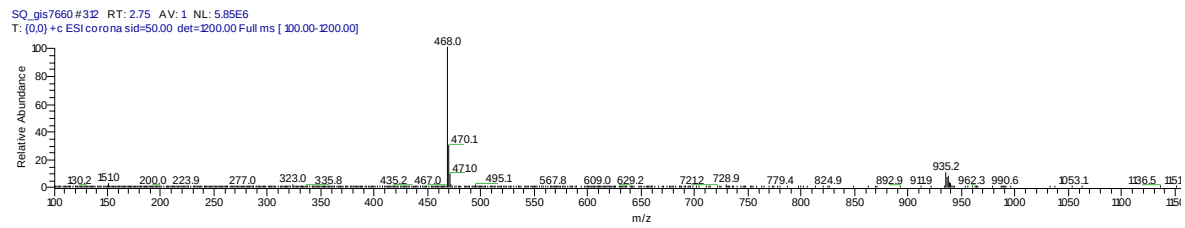
(1*S*,2*R*)-*cis*-1-amino-2-indanol derivitized **4m**

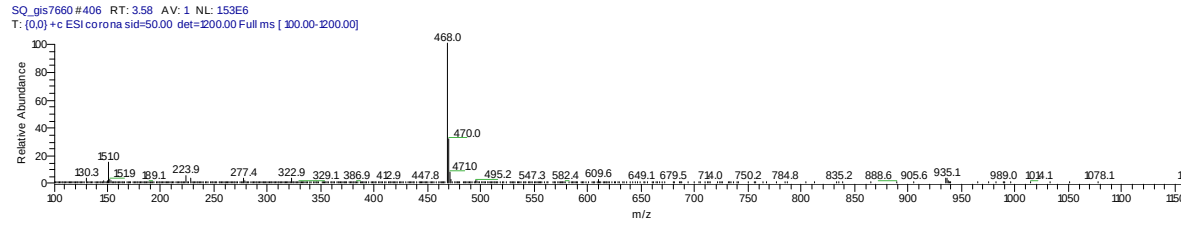


	Sample Descrip.	Peak Name	R. Time	Area %	Area
1	gis7660	*1	2.67	97.10	2307714.75
2	gis7660	*2	3.52	2.90	68963.41









(1*S*,2*R*)-*cis*-1-amino-2-indanol derivitized **4n**