

Catalytic enantioselective addition of Isocyanoacetate esters to 4-Nitro-5-styrylisoxazoles under phase transfer catalysis conditions.

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1. General Experimental :

General Methods. ^1H , ^{13}C , NMR spectra were recorded on a Varian AS 300, Bruker 400 and 600 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^1H and ^{13}C NMR (^1H NMR: 7.26 ppm for CDCl_3 ; ^{13}C NMR: 77.0 ppm for CDCl_3 . ^{13}C NMR spectra were acquired with ^1H broad band decoupled mode. DMSO- d_6 (referenced to 2.52 and 3.35 ppm for ^1H and 40.0 for ^{13}C). Coupling constants (J) are in Hz. Multiplicities are reported as follows: s, singlet, d, doublet, dd, doublets of doublets, t, triplet, q, quartet, m, multiplet, c, complex, and br, broad. Melting points were determined using a Stuart scientific melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded as KBr disc using a Bruker Tensor27 FT-IR instrument. Absorption maximum (ν_{max}) was reported in wave numbers (cm^{-1}) and only selected peaks are reported. High resolution mass spectra were obtained on a Waters Micro mass LCT and low resolution mass spectra were recorded on Waters Micro mass Quattro LC-MS spectrometers at 70 eV. Tetrahydrofuran was freshly distilled over sodium benzophenone prior to use according to standard procedure. All other reagents and solvents were used as purchased from Aldrich. Reactions were checked for completion by TLC (EM Science, silica gel 60 F254). Flash chromatography was performed using silica gel 60 (0.040-0.063 mm, 230-400 mesh).

The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD, Daicel Chiralpak AD-H Chiracel OJ, Chiracel OD, Chiralpak AS columns), using a UV detector operating at 254 nm. Retention factors (Rf) are reported to ± 0.05 .

Racemic samples were prepared using tetra-*N*-butylammonium bromide as a catalyst at room temperature overnight. 3-Methyl-4-nitro-styrylisoxazoles were prepared through the Knoevenagel condensation between 3,5-dimethyl-4-nitroisoxazole and the appropriate aromatic or heteroaromatic aldehyde (piperidine 0.1 equiv., EtOH, 65 °C, 2-3 hours).¹

2. General procedure for the organocatalytic, enantioselective preparation of compounds **3a-m** (Table 2).

To a test tube equipped with a magnetic stirring bar were sequentially added the 5-styrylisoxazole **1a-m** (0.1 mmol), catalyst **6l** or **6m** (0.01 mmol, 10 mol% loading), ethylisocyanoacetate (0.5 mmol, 5 equiv.) and toluene (0.5 mL). The test tube was placed at -20°C, then finely ground K₂CO₃ (0.5 mmol) was added in one portion. The mixture was then vigorously stirred at the same temperature, with no precautions to exclude moisture or air. After the stated reaction time, the reaction was filtered on a short plug of silica gel to remove the catalyst, the solvent and un-reacted ethyl isocyanoacetate evaporated in vacuo and the residue purified by flash chromatography to give compounds **3a-m** as a 1:1 mixture of diastereoisomers.

3. Analytical data for compounds **3a-m**

(3R)-ethyl 2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenylbutanoate (3a). Following the general procedure using catalyst **6l** (6 mg, 0.010 mmol, 10 mol%) for 78h at -20° C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) dried and the title compound was obtained in 88% yield (dr 1:1) as yellow oil. IR 2985, 2148, 1754, 1520; ¹H NMR (CDCl₃, 300 MHz) δ 7.35-7.27 (m,10H), 4.64 (d, J= 4.5, 1H), 4.52 (t, J= 2.4, 1H), 4.26-

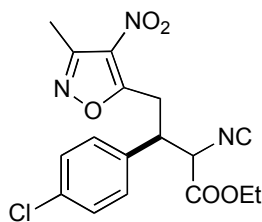
¹ M. F. A. Adamo, E. F. Duffy, V. R. Konda,; F. Murphy, *Heterocycles* **2007**, *71*, 1173.

4.19 (dq, J= 7.2, J= 14.4, 2H), 4.17-4.10 (dq, J= 6.9, J= 14.1, 2H), 4.02-3.90 (m, 4H), 3.78-3.65 (m, 2H), 2.52 (s, 3H), 2.48 (s, 3H), 1.24 (t, J= 7.2, 3H), 1.51 (t, J=7.2, 3H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 171.3, 171.2, 164.9, 164.6, 163.6, 163.2, 155.8, 155.6, 135.9, 134.8, 129.2, 129.0, 128.9, 128.9, 128.1, 127.7, 63.3, 63.0, 61.8, 61.0, 44.8, 44.1, 30.2, 28.6, 14.0, 13.9, 11.6, 11.6. HRMS found: [M-H]⁻ 342.1082, C₁₇H₁₆N₃O₅, requires: 342.1090; *m/z*: 342 (100%, [M-H]⁻).

(3*R*)-ethyl 2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)-3-*p*-tolylbutanoate (3b).

Following the general procedure using catalyst **6l** (6.0 mg, 0.010 mmol, 10 mol%) for 52 h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 91% yield (dr 1:1) as yellow oil. IR 2974, 2136, 1744, 1510; ¹H NMR (CDCl₃, 400 MHz) δ 7.10 (d, J= 8, 4H), 7.05 (d, J=7.6, 4H), 4.52 (d, J= 4.4, 1H), 4.40 (d, J= 3.2, 1H), 4.40-4.09 (m, 2H), 4.06 (dq, J= 7.2, J= 14.4, 2H), 3.90-3.81 (m, 4H), 3.65-3.57 (m, 2H), 2.44 (s, 3H), 2.40 (s, 3H), 2.24 (s, 6H), 1.17 (t, J= 7.2, 3H), 1.09 (t, J= 7.2, 3H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 171.44, 171.3, 165.0, 164.6, 155.7, 155.6, 138.8, 138.7, 132.7, 131.6, 129.8, 129.6, 127.9, 127.5, 63.3, 63.0, 62.0, 61.0, 44.4, 43.8, 30.3, 28.6, 21.1, 21.1, 13.9, 11.6. HRMS found: [M-H]⁻ 356.1251, C₁₈H₁₈N₃O₅, requires: 356.1246; *m/z*: 356 (100%, [M-H]⁻).

(3*R*)-ethyl 3-(4-chlorophenyl)-2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)butanoate (3c).



Following the general procedure using ethylisocyanoacetate and catalyst **6m** (5.76 mg, 0.010 mmol, 10 mol%) for 58h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 85% yield (dr 1:1) as yellow oil. IR 2982, 2136 1746, 1518; ¹H NMR (CDCl₃, 300 MHz) δ 7.26-7.7.23 (m, 4H), 7.22-7.17 (m, 4H), 4.54 (d, J= 4.4, 1H), 4.42 (d, J= 4.8, 1H), 4.17 (dq, J= 6.8, J= 0.8, 2H), 4.07 (q, J= 6.8, 2H), 3.92-3.80 (m, 4H), 3.65-3.60 (m, 2H), 2.45 (s, 3H), 2.41 (s, 3H), 1.20 (t, J= 7.2, 3H), 1.10 (t, J=7.2, 3H); ¹³C NMR (CDCl₃, 400 MHz) δ 170.9, 170.7, 164.7, 164.3, 155.8, 155.7, 137.1, 135.1, 134.9, 134.3, 133.2, 132.9, 129.5, 129.4, 129.2, 129.1, 63.5, 63.2, 44.0, 43.5, 30.2, 28.4, 13.9, 11.6; HRMS found: [M-H]⁻ 376.0710, C₁₇H₁₅ClN₃O₅, requires: 376.0700; *m/z*: 376 (100%, [M-H]⁻).

(3R)-ethyl 2-isocyano-3-(2-methoxyphenyl)-4-(3-methyl-4-nitroisoxazol-5-yl) butanoate (3d).

Following the general procedure using catalyst **6m** (5.76 mg, 0.010 mmol, 10 mol%) for 120h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 83% yield (dr 2:1) as yellow oil. IR 2999, 2153, 1737, 1510; ¹H NMR (CDCl₃, 400 MHz) δ 7.02-7.163 (m, 4H), 7.10-7.07 (dd, J= 1.2, 2H), 6.83-6.76 (m, 6H), 4.75 (d, J=6.8, 3H), 4.18-4.09 (m, 5H), 4.08-4.03 (q, J= 4.4, J=11.2, 4H), 3.96 (dd, J= 10.4, J= 14.8, 2H), 3.85 (dd, J= 9.8, J= 14.9, 1H), 3.78 (s, 6H), 3.75 (s, 3H), 3.60 (dd, J= 4.8, J= 14.8, 3H), 2.41 (s, 3H), 2.39 (s, 6H), 1.16 (t, J= 7.2, 3H), 1.08 (t, J= 7.2, 6H); ¹³C (CDCl₃, 100.6 MHz) δ 171.9, 171.8, 165.3, 165.3, 162.0, 161.8, 157.0, 157.0, 155.5, 155.5, 129.9,129.9, 129.3, 129.2, 123.4, 123.3, 121.0, 120.9, 110.9, 62.9, 62.8, 59.7, 59.2, 55.4, 55.4, 41.0, 40.3, 28.8, 27.4, 13.9, 13.8, 11.6; HRMS found:[M-H]⁻ 372.1200, C₁₈H₁₈N₃O₆, requires: 372.1196; *m/z*: 372 (100%, [M-H]⁻).

(3R)-ethyl 3-(4-fluorophenyl)-2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)butanoate (3e).

Following the general procedure using catalyst **6m** (5.76 mg, 0.010 mmol, 10 mol%) for 26h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 93% yield (dr 1:1) as yellow oil. IR 2972, 2155, 1746, 1518; ¹H NMR (CDCl₃, 400 MHz) δ 7.24-7.20 (m, 4H), 6.98-6.93 (m, 4H), 4.55 (d, J= 4.4, 1H), 4.41 (d, J= 4.8, 1H), 4.16 (dq, J= 1.2, J= 7.2, 2H), 4.07 (dq, J= 1.2, J= 7.2, 2H), 3.93-3.80 (m, 4H), 3.65-3.61 (m, 2H), 2.45 (s, 3H), 2.41 (s, 3H), 1.19 (t, J=7.2, 3H), 1.09 (t, J=7.2, 3H); ¹³C (CDCl₃, 100.6 MHz) δ 171.0, 170.9, 164.8, 164.4, 155.8, 155.7, 130.0, 129.9, 129.6, 129.5, 116.3, 116.1, 115.9, 63.4, 63.1, 44.0, 43.4, 30.4, 28.7, 13.9, 11.5; HRMS found:[M-H]⁻ 360.0989, C₁₇H₁₅FN₃O₅, requires: 360.0996; *m/z*: 360 (100%, [M-H]⁻).

(3S)-ethyl 3-(furan-2-yl)-2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)butanoate (3f).

Following the general procedure using catalyst **6l** (6 mg, 0.010 mmol, 10 mol%) for 183h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 91% yield (dr 1:1) as yellow oil. IR 2994, 2158, 1745, 1533; ¹H NMR (CDCl₃, 400 MHz) δ 7.3-7.29 (m, 2H), 6.25 (t, J= 1.6, 4H), 4.6 (d, J= 4.8, 1H), 4.51 (d, J= 4.4, 1H), 4.25-4.16 (m, 4H), 4.03-4.00 (m, 2H), 3.85-3.73 (m, 2H), 3.63-3.54 (m, 2H), 2.48 (s, 3H), 2.46 (s, 3H), 1.25 (t, J= 7.2, 3H), 1.20 (t, J= 7.2, 3H); ¹³C (CDCl₃, 100.6 MHz) δ 170.9, 170.7, 164.6, 164.4, 163.5, 163.3, 155.8, 155.7, 149.0, 148.3, 143.2, 143.2, 110.7, 110.6, 109.2, 108.9, 63.5, 63.3, 59.7, 59.5, 39.0, 38.9, 29.7, 28.6, 27.2, 13.9, 11.6; HRMS found:[M-H]⁻ 332.0891, C₁₅H₁₄N₃O₆, requires: 332.0883; *m/z*: 332 (100%, [M-H]⁻).

(3R)-ethyl-2-isocyano-3-(4-methoxyphenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)butanoate (3g).

Following the general procedure using catalyst **6m** (7.56 mg, 0.010 mmol, 10 mol%) for 48h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 85% yield (dr 1:1) as yellow oil. IR 2994, 2156, 1753, 1520; ¹H NMR (CDCl₃, 400 MHz) δ 7.15-7.13 (m, 4H), 6.78-6.75 (m, 4H), 4.51 (d, J= 4, 1H), 4.39 (d, J= 3.2, 1H), 4.39-4.12 (m, 2H), 4.09-4.04 (m, 2H), 3.86-3.83 (m, 4H), 3.71 (s, 3H), 3.70 (s, 3H), 3.61-3.56 (m, 2H), 2.44 (s, 3H), 2.40 (s, 3H), 1.81 (t, J= 7.2, 3H), 1.10 (t, J= 7.2, 3H); ¹³C NMR(CDCl₃, 100.6 MHz) δ 171.4, 171.3, 165.0, 164.6, 163.4, 163.0, 159.9, 159.8, 155.7, 155.6, 129.2, 128.9, 127.6, 126.5, 114.5, 114.3, 63.2, 63.0, 62.0, 61.1, 55.3, 55.2, 44.1, 43.5, 30.4, 29.7, 28.7, 13.9, 13.9, 11.6, 11.6; HRMS found:[M-H]⁻ 372.1201, C₁₈H₁₈N₃O₆, requires: 372.1196; *m/z*: 372 (100%, [M-H]⁻).

(3R)-ethyl 2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)-3-*m*-tolylbutanoate (3h).

Following the general procedure using catalyst **6l** (6.00 mg, 0.010 mmol, 10% mol) for 22h at -20° C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 87% yield (dr 1:1) as yellow oil. IR 2992, 2155, 1753, 1520; ¹H NMR (CDCl₃, 400 MHz) δ 7.16-7.11 (m, 2H), 7.04-7.01 (m, 6H), 4.52 (d, J= 4.4, 1H), 4.42 (d, J= 4.4, 1H), 4.15 (dq, J= 7.2, J= 0.8, 2H), 4.10-4.04 (m, 2H), 3.86-3.83 (m, 4H), 3.64-3.58 (m, 2H), 2.45 (s, 3H), 2.41 (s, 3H), 2.25 (s, 6H), 1.17 (t, J= 6.8, 3H), 1.08 (t, J= 7.2, 3H).¹³C NMR (CDCl₃, 100.6 MHz) δ 171.4, 171.2, 165.0, 164.6, 155.8, 155.6, 138.9, 138.6, 135.8, 134.7, 129.7, 129.6, 129.0, 128.8, 128.4, 125.1, 124.7, 63.3, 63.0, 44.7, 44.1, 30.2, 28.55, 21.4, 21.39,

13.9, 11.6; HRMS found:[M-H]⁻ 356.1237, C₁₈H₁₈N₃O₅, requires: 356.1246; *m/z*: 356 (100%, [M-H]⁻).

(3*R*)-ethyl 2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)-3-(4-nitrophenyl)butanoate (3i).

Following the general procedure using catalyst **6l** (6.0 mg, 0.010 mmol, 10 mol%) for 46h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 92% yield (dr 1:1) as yellow oil. IR 2981, 2158, 1739, 1530, ¹H NMR (CDCl₃, 400 MHz) δ 8.25 (d, *J*= 8.8, 1H), 8.17- 8.14 (m, 3H), 7.75 (d, *J*= 8.8, 1H), 7.48-7.45 (m, 3H), 4.61 (d, *J*= 4.8, 1H), 4.46 (d, *J*= 4.8, 1H), 4.22 (dq, *J*= 7.2, *J*= 1.6, 2H), 4.10 (q, *J*= 7.2, 2H), 4.06-4.02 (m, 2H), 3.92-3.85 (m, 2H), 3.73- 3.64 (m, 2H), 2.46 (s, 3H), 2.42 (s, 3H), 1.23 (t, *J*= 7.2, 3H), 1.12 (t, *J*= 7.2, 3H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 170.2, 170.1, 164.8, 164.5, 164.3, 164.0, 155.9, 155.8, 148.3, 148.2, 143.0, 141.9, 139.6, 129.4, 129.0, 128.9, 124.4, 124.4, 124.1, 114.7, 63.8, 63.5, 44.2, 43.6, 30.07, 28.2, 13.9, 11.6, 11.5; HRMS found:[M-H]⁻ 387.0931, C₁₇H₁₅N₄O₇, requires: 387.0941; *m/z*: 387 (100%, [M-H]⁻).

(3*R*)-ethyl 3-(2,3-dichlorophenyl)-2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl) butanoate (3j).

Following the general procedure using catalyst **6m** (5.76 mg, 0.010 mmol, 10 mol%) for 48h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 91% yield (dr 1:0.4) as yellow oil. IR 2964, 2145, 1740, 1522, ¹H NMR (CDCl₃, 400 MHz) δ 7.38 (dt, *J*= 0.8, *J*= 8.0, 2.4H), 7.23-7.19 (m, 1.8H), 4.55 (m, 0.4H), 4.53 (d, *J*= 3.6, 1H), 4.27 (q, *J*= 6.8, 2H), 4.15-4.03 (m, 1.2H), 3.85 (dd, *J*=10.4, *J*= 15.2, 1H), 3.74 (t, *J*= 9.6, 0.8H), 3.57 (dd, *J*= 4.8, *J*= 15.2, 1H), 2.46 (s, 1.2H), 2.43 (s, 3H), 1.28 (t, *J*= 7.2,

3H), 1.10 (t, J= 7.2, 1.2H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 170.5, 170.3, 164.6, 164.1, 163.6, 155.8, 155.8, 135.7, 135.4, 134.0, 132.3, 130.9, 130.9, 127.9, 126.6, 63.7, 63.3, 60.2, 59.4, 40.6, 29.4, 26.9, 14.0, 13.7, 11.6; HRMS found:[M-H]⁻ 410.0309, C₁₇H₁₄Cl₂N₃O₅, requires: 410.0311; *m/z*: 410 (100%, [M-H]⁻).

(3R)-2-Isocyano-4-(3-methyl-4-nitro-isoxazol-5-yl)-3-naphthalen-2-yl-butyric acid ethyl ester (3k).

Following the general procedure using catalyst **6m** (5.76 mg, 0.010 mmol, 10 mol%) for 65h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 86% yield (dr 1:1) as yellow oil. IR 2970, 2145, 1735, 1533, ¹H NMR (CDCl₃, 400 MHz) δ 7.76-7.72 (m, 6H), 7.68-7.67 (m, 2H), 7.43-7.40 (m, 4H), 7.36 (dt, J= 1.6, J= 8.8, 2H), 4.62 (d, J= 4.8, 1H), 4.52 (d, J= 4.8, 1H), 4.16-3.97 (m, 8H), 3.74-3.65 (m, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 1.12 (t, J= 7.2, 3H), 1.01 (t, J= 7.2, 3H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 171.2, 171.1, 164.9, 164.6, 163.8, 163.4, 155.8, 155.6, 133.3, 133.2, 133.2, 133.1, 130.7, 129.2, 128.9, 128.1, 127.9, 127.7, 127.3, 126.7, 126.7, 126.6, 125.2, 124.9, 63.4, 63.1, 44.9, 44.3, 30.9, 30.3, 29.7, 28.5, 14.0, 13.9, 11.6, 11.5; HRMS found:[M-H]⁻ 392.1238, C₂₁H₁₈N₃O₅, requires: 392.1249; *m/z*: 392 (100%, [M-H]⁻).

(3R)-3-(4-Cyano-phenyl)-2-isocyano-4-(3-methyl-4-nitro-isoxazol-5-yl)-butyric acid ethyl ester (3l).

Following the general procedure using catalyst **6m** (5.76 mg, 0.010 mmol, 10 mol%) for 48 h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title

compound was obtained in 86% yield (dr 1:1) as yellow oil. IR 2976, 2143, 1740, 1531. ¹H NMR (CDCl₃, 400 MHz) δ 7.60-7.57 (m, 4H), 7.41-7.38 (m, 4H), 4.59 (d, J= 4.4, 1H), 4.44 (d, J= 4.8, 1H), 4.20 (q, J= 2, J= 7.2, 2H), 4.08 (q, J= 7.2, J= 14.4, 2H), 4.00-3.96 (m, 2H), 3.85 (m, 2H), 3.66 (m, 2H), 2.46 (s, 3H), 2.42 (s, 3H), 1.22 (t, J= 7.2, 3H), 1.10 (t, J= 7.2, 3H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 170.4, 170.2, 164.6, 164.4, 164.3, 155.9, 155.8, 141.2, 140.0, 133.0, 132.7, 129.1, 128.7, 118.0, 117.9, 113.2, 113.1, 63.7, 63.4, 61.1, 60.3, 44.4, 43.9, 30.0, 29.7, 28.1, 14.1, 13.9, 11.6, 11.5; HRMS found:[M-H]⁻ 367.1038, C₁₈H₁₅N₄O₅, requires: 367.1042; *m/z*: 367 (100%, [M-H]⁻).

(3*S*)-ethyl 2-isocyano-5-methyl-3-((3-methyl-4-nitroisoxazol-5-yl)methyl)hexanoate (3m).

Following the general procedure using catalyst **6l** (5.76 mg, 0.010 mmol, 10 mol%) for 48h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 88% yield (dr 1:1) as yellow oil. IR 2988, 2150, 1746, 1525. ¹H NMR (CDCl₃, 400 MHz) δ 4.35 (d, J= 2.8, 1H), 4.25-4.18 (m, 5H), 3.41 (dd, J= 0.8, 1H), 3.26-3.13 (m, 3H), 2.69-2.67 (m, 2H), 2.69 (s, 3H), 2.67 (m, 3H), 1.58-1.50 (m, 3H), 1.42-1.25 (m, 6H), 1.25-1.15 (m, 3H), 0.89-0.87 (m, 6H), 0.84-0.81 (m, 6H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 172.2, 172.1, 165.7, 165.3, 162.4, 162.3, 156.0, 155.9, 63.3, 63.1, 60.0, 58.9, 40.3, 38.9, 37.2, 36.7, 29.1, 28.3, 25.0, 25.0, 23.3, 23.0, 21.6, 21.6, 14.1, 14.0, 11.7; HRMS found:[M-H]⁻ 322.1478, C₁₈H₁₅N₄O₅, requires: 322.1481; *m/z*: 322 (100%, [M-H]⁻).

4. General procedure for the preparation of product 4a-m (Table 2)

To a solution of **3a-m** (0.1 mmol) in THF (1.0 mL) at 35°C DIPEA (0.2 mmol) was added. The solution was stirred until the starting was consumed (typically 3-8 hours). The solvents was removed under reduce pressure and purified by silica gel to afford desired **4a-m**.

5. Analytical data for compounds 4a-m

(2*S*,3*S*)-ethyl-4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4a)

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 93% yield as yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 18.2 min, t_{min} = 26.7 min, 99% *ee*). mp 54°C; $[\alpha]_{\text{D}}^{20}$ = + 54 (c = 0.84 in CHCl₃); IR 2976, 1736, 1545. ¹H NMR (CDCl₃, 300 MHz) δ 8.76 (dd, J= 0.6, J=3.6, 1H), 7.33-7.31 (m, 2H), 7.30-7.22 (m, 3H), 5.69 (s, 1H), 4.81 (d, J=3.9, 1H), 4.40 (d, J=3.9, 1H), 4.39-4.25 (m, 2H), 2.46 (s, 3H), 1.36 (t, J=7.2, 3H); ¹³C NMR (CDCl₃, 75.4 0MHz) δ 171.5, 166.2, 156.5, 151.4, 142.6, 129.2, 127.8, 127.1, 102.7, 68.8, 62.6, 50.8, 14.4, 12.6; HRMS found:[M-H]⁻ 342.1081, C₁₇H₁₆N₃O₅, requires: 342.1090; *m/z*: 342 (100%, [M-H]⁻).

(2*S*,3*S*)-ethyl-4-(3-methyl-4-nitroisoxazol-5-yl)-3-*p*-tolyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4b).

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 96% yield as yellow oil. The *ee* of the product

was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, $t_{\text{maj}} = 19.5$ min, $t_{\text{min}} = 26.9$ min, 93% *ee*). $[\alpha]_{\text{D}}^{20} = + 86$ ($c = 0.54$ in CHCl_3); IR 2988, 1742, 1550. ^1H NMR (CDCl_3 , 400 MHz) δ 8.6 (d, $J = 3.2$, 1H), 7.13 (d, $J = 8$, 2H), 7.04 (d, $J = 8$, 2H), 5.52 (s, 1H), 4.69 (d, $J = 3.6$, 1H), 4.31 (d, $J = 4$, 1H), 4.27-4.18 (m sistema ABX, 2H), 2.38 (s, 3H), 2.23 (s, 3H), 1.28 (t, $J = 7.2$, 3H); ^{13}C (CDCl_3 , 100.6 MHz) δ 171.4, 150.9, 139.5, 137.2, 129.6, 126.8, 102.8, 68.7, 62.3, 50.2, 21.0, 14.2, 12.3; HRMS found: $[\text{M}-\text{H}]^-$ 356.1237, $\text{C}_{18}\text{H}_{18}\text{N}_3\text{O}_5$, requires: 356.1246; m/z : 356 (100%, $[\text{M}-\text{H}]^-$).

(2*S*,3*S*)-ethyl 3-(4-chlorophenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4c).

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 92% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, $t_{\text{maj}} = 19.8$ min, $t_{\text{min}} = 27.4$ min, 96% *ee*). $[\alpha]_{\text{D}}^{20} = + 71$ ($c = 0.72$ in CHCl_3); IR 2980, 1740, 1547. ^1H NMR (CDCl_3 , 300 MHz) δ 8.73 (d, $J = 2.7$, 1H), 7.31-7.24 (m, 4H), 5.66 (s, 1H), 4.79 (d, $J = 4.2$, 1H), 4.39-4.23 (m, 3H), 4.6 (s, 3H), 1.36 (t, $J = 7.2$, 3H); ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 171.2, 166.0, 156.6, 151.2, 141.1, 133.6, 129.4, 128.5, 102.4, 68.6, 62.7, 50.2, 14.4, 12.6; HRMS found: $[\text{M}-\text{H}]^-$ 376.0711, $\text{C}_{17}\text{H}_{15}\text{ClN}_3\text{O}_5$, requires: 376.0700; m/z : 376 (100%, $[\text{M}-\text{H}]^-$).

(2*S*,3*S*)-ethyl 3-(2-methoxyphenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4d).

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 96% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, $t_{\text{maj}} = 25.3$ min, $t_{\text{min}} = 33.7$ min, 96% *ee*). $[\alpha]_{\text{D}}^{20} = + 54$ ($c = 0.52$ in CHCl_3); IR 2997, 1736, 1557. ^1H NMR (CDCl_3 , 300 MHz) δ 8.80 (dd, $J = 0.6$, $J = 3.6$, 1H), 7.26-7.20 (m, 1H), 7.07 (dd, $J = 1.8$, $J = 7.8$, 1H), 6.94-6.84 (m, 2H), 5.62 (s, 1H), 5.19 (d, $J = 3.6$, 1H), 4.37-4.19 (m, 3H), 3.89 (s, 3H), 2.47 (s, 3H), 1.36 (t, $J = 7.2$, 3H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 171.4, 166.2, 156.9, 156.2, 151.8, 129.6, 128.6, 127.5, 124.7, 120.8, 111.0, 101.1, 67.8, 62.0, 55.3, 44.5, 14.2, 12.4. HRMS found: $[\text{M}-\text{H}]^-$ 372.1206, $\text{C}_{18}\text{H}_{18}\text{BrN}_3\text{O}_6$, requires: 372.1196; m/z : 372 (100%, $[\text{M}-\text{H}]^-$).

(2*S*,3*S*)-ethyl 3-(4-fluorophenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4e).

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 91% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, $t_{\text{maj}} = 18.6$ min, $t_{\text{min}} = 29.6$ min, 88% *ee*). $[\alpha]_{\text{D}}^{20} = + 79$ ($c = 0.77$ in CHCl_3); IR 2988, 1741, 1542. ^1H NMR (CDCl_3 , 400 MHz) δ 8.65 (s, 1H), 7.23-7.20 (m, 2H), 6.95-6.91 (m, 2H), 5.54 (s, 1H), 4.72 (d, $J = 3.6$, 1H), 4.28 (d, $J = 3.6$, 1H), 4.27-4.19 (m, 2H), 2.39 (s, 3H), 1.29 (t, $J = 6.8$, 3H); ^{13}C NMR (CDCl_3 , 100.6MHz) δ 171.2, 156.4, 150.9, 138.3, 128.6, 128.5, 116.0, 115.8, 102.5, 68.6, 62.4, 49.9, 29.7, 14.2, 12.3; HRMS found: $[\text{M}-\text{H}]^-$ 360.1003, $\text{C}_{17}\text{H}_{15}\text{FN}_3\text{O}_5$, requires: 360.0996; m/z : 360 (100%, $[\text{M}-\text{H}]^-$).

(2*S*,3*S*)-ethyl 3-(furan-2-yl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4f).

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 88% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, $t_{\text{maj}} = 21.3$ min, $t_{\text{min}} = 23.5$ min, 90% *ee*). $[\alpha]_{\text{D}}^{20} = + 65$ ($c = 1.22$ in CHCl_3); IR 2980, 1737, 1550. ^1H NMR (CDCl_3 , 400 MHz) δ 8.59 (s, 1H), 7.26 (dd, $J = 1.6$, $J = 0.8$, 1H), 6.22 (dd, $J = 3.2$, $J = 1.6$, 1H), 6.10 (d, $J = 3.2$, 1H), 5.57 (s, 1H), 4.90 (d, $J = 3.6$, 1H), 4.52 (d, $J = 4.0$, 1H), 4.27-4.19 (m, 2H), 2.43 (s, 3H), 1.28 (t, 7.2, 3H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 170.9, 165.9, 156.4, 153.5, 151.1, 142.1, 110.6, 106.7, 99.4, 65.4, 62.5, 44.0, 29.7, 14.2, 12.4, HRMS found: $[\text{M}-\text{H}]^-$ 372.1203, $\text{C}_{18}\text{H}_{18}\text{N}_3\text{O}_6$, requires: 372.1196; m/z : 372 (100%, $[\text{M}-\text{H}]^-$).

(2*S*,3*S*)-ethyl 3-(4-methoxyphenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4g).

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 89% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, $t_{\text{maj}} = 23.4$ min, $t_{\text{min}} = 33.4$ min, 89% *ee*). $[\alpha]_{\text{D}}^{20} = + 93$ ($c = 0.47$ in CHCl_3); IR 2997, 1743, 1546. ^1H NMR (CDCl_3 , 300 MHz) δ 8.71 (d, $J = 3.3$, 1H), 7.25-7.23 (m, $J = 3.0$, $J = 2.1$, 1H), 7.21 (m, $J = 2.1$, $J = 3.0$, 1H), 6.85-6.84 (m, $J = 3.0$, $J = 2.1$, 1H), 6.82-6.81 (m, $J = 3.0$, $J = 2.1$, 1H), 5.60 (d, $J = 2.7$, 1H), 4.36 (d, $J = 3.9$, 1H), 4.33-4.23 (m, 2H), 3.77 (s, 3H), 2.45 (s, 3H), 1.34 (t,

$J=7.2$, 3H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 171.4, 166.1, 158.9, 156.3, 150.8, 134.6, 114.3, 102.9, 68.7, 62.3, 55.3, 49.9, 14.2, 12.4. HRMS found: $[\text{M}-\text{H}]^-$ 372.1206, $\text{C}_{18}\text{H}_{18}\text{N}_3\text{O}_6$, requires: 372.1196; m/z : 372 (100%, $:[\text{M}-\text{H}]^-$).

(2*S*,3*S*)-ethyl 4-(3-methyl-4-nitroisoxazol-5-yl)-3-*m*-tolyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4h)

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 84% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, $t_{\text{maj}} = 17.6$ min, $t_{\text{min}} = 30.9$ min, 94% *ee*). $[\alpha]_{\text{D}}^{20} = + 78$ ($c = 0.71$ in CHCl_3); IR 2990, 1742, 1551. ^1H NMR (CDCl_3 , 400 MHz) δ 8.67 (s, 1H), 7.14-7.10 (m, 1H), 7.04-7.03 (m, 2H), 6.98 (d, $J = 7.6$, 1H), 5.32 (s, 1H), 4.68 (d, $J = 3.6$, 1H), 4.31 (d, $J = 4.0$, 1H), 4.27-4.18 (m, 2H), 2.39 (s, 3H), 2.25 (s, 3H), 1.28 (t, $J = 7.2$, 3H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 151.0, 128.9, 128.3, 127.5, 123.9, 68.7, 65.9, 62.3, 50.5, 29.7, 22.4, 21.5, 15.3, 14.2, 14.1, 12.4. HRMS found: $[\text{M}-\text{H}]^-$ 356.1253, $\text{C}_{18}\text{H}_{18}\text{N}_3\text{O}_5$, requires: 356.1246; m/z : 356 (100%, $[\text{M}-\text{H}]^-$).

(2*S*,3*S*)-ethyl 4-(3-methyl-4-nitroisoxazol-5-yl)-3-(4-nitrophenyl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4i).

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) the title compound was obtained in 79% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, $t_{\text{maj}} = 39.3$ min, $t_{\text{min}} = 45.9$ min, 88% *ee*). $[\alpha]_{\text{D}}^{20} = + 87$ ($c = 0.75$ in CHCl_3); IR 2994,

1742, 1545. ¹H NMR (CDCl₃, 300 MHz) δ 8.74 (s, 1H), 8.20 (t, J=2.4, J=1.8, 2H), 8.17 (t, J=2.1, J=2.4, 2H), 5.68 (s, 1H), 4.92 (d, J=4.2, 1H), 4.37 (d, J=4.2, 1H), 4.38-4.27 (m, 2H), 2.46 (s, 3H), 1.368 (t, J=6.9, 3H); ¹³C NMR (CDCl₃, 75.4 MHz) δ 170.7, 165.7, 156.7, 151.3, 149.7, 147.6, 128.2, 124.6, 101.7, 68.2, 63.0, 50.5, 14.4, 12.5. HRMS found:[M-H]⁻ 387.0938, C₁₇H₁₅N₄O₇, requires: 387.0941; m/z: 387 (100%, [M-H]⁻).

(2*S*,3*R*)-3-(2,3-Dichloro-phenyl)-4-(3-methyl-4-nitro-isoxazol-5-yl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid ethyl ester (4j).

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 91% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, *t*_{maj} = 18.7 min, *t*_{min} = 20.7 min, 88% *ee*). [α]_D²⁰ = + 34 (c = 0.25 in CHCl₃); IR 2992, 1738, 1541. ¹H NMR (CDCl₃, 400 MHz) δ 8.72 (d, J= 2.4, 1H), 7.31 (dd, J= 8, J= 1.6, 1H), 7.06 (t, J= 7.6, 1H), 6.99-6.96 (m, 1H), 5.55 (s, 1H), 4.24 (m, 4H), 2.40 (s, 3H), 1.29 (t, J= 7.2, 3H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 170.6, 165.6, 151.7, 129.7, 127.7, 62.5, 53.4, 29.7, 14.1, 12.3; HRMS found:[M-H]⁻ 410.0308, C₁₇H₁₄Cl₂N₃O₅, requires: 410.0311; m/z: 410 (100%, [M-H]⁻).

(2*S*,3*S*)-4-(3-Methyl-4-nitro-isoxazol-5-yl)-3-naphthalen-2-yl-2,3-dihydro-1H-pyrrole-2-carboxylic acid ethyl ester (4k).

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 93% yield as yellow oil. The *ee* of the product

was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, $t_{\text{maj}} = 22.8$ min, $t_{\text{min}} = 33.8$ min, 86% *ee*). $[\alpha]_{\text{D}}^{20} = + 47$ ($c = 0.95$ in CHCl_3); IR 2986, 1732, 1549. ^1H NMR (CDCl_3 , 300 MHz) δ 8.73 (s, 1H), 7.75-7.68 (m, 4H), 7.41-7.36 (m, 3H), 5.62 (s, 1H), 4.90 (d, $J=4$, 1H), 4.39 (d, $J=4$, 1H), 4.32-4.19 (m, $J=7.2$, 2H), 2.36 (s, 3H), 1.30 (t, $J=7.2$, 3H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 171.5, 166.2, 156.5, 151.4, 139.6, 133.5, 132.8, 129.0, 127.9, 127.6, 126.3, 126.0, 125.7, 124.9, 102.7, 68.8, 62.6, 50.8, 29.7, 14.4, 12.6; HRMS found: $[\text{M-H}]^-$ 392.1239, $\text{C}_{21}\text{H}_{18}\text{N}_3\text{O}_5$, requires: 392.1249; m/z : 392 (100%, $[\text{M-H}]^-$).

(2*S*,3*S*)-ethyl 3-(4-cyanophenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4l).

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 94% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, $t_{\text{maj}} = 36.4$ min, $t_{\text{min}} = 46.1$ min, 86% *ee*). $[\alpha]_{\text{D}}^{20} = + 75$ ($c = 0.38$ in CHCl_3); IR 2990, 1742, 1540. ^1H NMR (CDCl_3 , 400 MHz) δ 8.67 (s, 1H), 7.56 (d, $J= 8.0$, 2H), 7.37 (d, $J=8.4$, 2H), 5.69 (s, 1H), 4.79 (d, $J= 4$, 1H), 4.28 (d, $J= 4.4$, 1H), 4.24 (m, 2H), 2.39 (s, 3H), 1.29 (t, $J= 7.2$, 3H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 170.6, 165.6, 156.5, 151.3, 147.6, 132.94, 127.9, 111.6, 101.4, 68.1, 62.7, 50.5, 29.7, 14.2, 12.3; HRMS found: $[\text{M-H}]^-$ 367.1040, $\text{C}_{18}\text{H}_{15}\text{N}_4\text{O}_5$, requires: 367.1042; m/z : 367 (100%, $[\text{M-H}]^-$).

(2*S*,3*S*)-ethyl 3-isobutyl-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4m)

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 89 % yield as yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, $t_{\text{maj}} = 13.1$ min, $t_{\text{min}} = 13.8$ min, 77% *ee*). $[\alpha]_{\text{D}}^{20} = + 59$ (c = 0.38 in CHCl₃); IR 2997, 1742, 1545. ¹H NMR (CDCl₃, 400 MHz) δ 8.52 (s, 1H), 4.20-4.16 (m, 3H), 3.71-3.63 (m, 2H), 2.50-2.48(m, 1H), 2.47 (s, 3H), 1.82-1.78 (m, 2H), 1.26 (t, J= 7.3, 3H), 1.02 (d, J= 6.8, 3H), 0.91 (d, J= 6.4, 3H); ¹³C (CDCl₃, 100.6 MHz) δ 172.1, 166.1, 156.5, 151.0, 103.2, 64.7, 62.1, 43.9, 43.0, 25.4, 23.8, 20.9, 14.1, 12.5 ; HRMS found:[M-H]⁻ 322.1475, C₁₈H₁₅N₄O₅, requires: 322.1481; *m/z*: 322 (100%, [M-H]⁻).

6. Preparation of catalysts 6l and 6m

N-(3,5-bis(trifluoromethyl)benzyl) cinchonidinium bromide (6l).

Following the procedure used for 6l, the title compound was obtained as a brown solid in 70% yield. Spectral data were consistent with the literature.¹

N-3,5-Bis(*tert*-butylbenzyl)cinchonidinium bromide (6m)

To a stirred suspension of cinchonidine (1.0 mmol) in THF (3.0 mL), 3,5-bis(trifluoromethyl)benzyl bromide (1.3 mmol) was added. The resulting mixture was then heated at 60°C, and stirred for 36h at the same temperature. After cooling to rt, the precipitate was collected by Büchner filtration and washed several times with Et₂O, affording the title compound as a white solid in 80% yield. $[\alpha]_D^{25} = -105.5$ (c = 0.80, CHCl₃)¹H NMR (CDCl₃, 400 MHz) δ 8.86 (d, J= 4.4, 1H), 8.12-8.10 (m, 1H), 7.98 (d, J= 8, 1H), 7.82-7.81 (m, 1H), 7.69 (d, J= 1.6, 2H), 7.66-7.58 (m, 2H), 7.51 (s, 1H), 6.76-6.68 (m, 2H), 5.90-5.87 (m, 1H), 5.60-5.52 (m, 1H), 5.13-5.09 (m, 2H), 5.02 (d, J= 10.4, 1H), 4.92-4.88 (b, 1H), 3.79 (t, J= 8.4, 1H), 3.68-3.62 (m, 1H), 3.49-3.43 (b, 1H), 3.33-3.31 (b, 1H), 2.63 (b, 1H), 2.17-2.12 (b, 2H), 1.99 (s, 1H), 1.67 (b, 1H), 1.33 (s, 18H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 152.2, 149.5, 147.2, 145.9, 136.5, 129.8, 129.6, 128.3, 127.9, 126.3, 124.8, 124.4, 123.0, 120.2, 117.9, 68.5, 64.6, 63.8, 61.3, 51.6, 38.0, 35.1, 31.47, 26.7, 24.9, 21.7.

7. Preparation of pyrrolidines 7-9

Preparation of (2*S*,3*R*)-ethyl 4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenylpyrrolidine-2-carboxylate (7).

To a solution of 4a (34 mg, 0.1 mmol) in TFA (950 μ L), Et₃SiH (199 μ L, 1.25 mmol) was added. The solution was stirred for 45 min and a solution of NaHCO₃ sat. (3 mL) was added at -78°C. The solution was extracted with EtOAc (3 X 3 mL) and under reduced pressure. Water was added to the yellow oil and extracted with CH₂Cl₂ (5 X 2 mL). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent petroleum ether:EtOAc 10:8) to give 7 as yellow oil in 73% yield. R_f 0.36 in petroleum ether:EtOAc 1:1; IR 2975, 1763, 1522; ¹H NMR (CDCl₃, 400 MHz) δ 7.27-7.17 (m, 5H), 4.47 (q, J= 8.4, 1H), 4.19-4.11 (m, 1H), 4.10-4.02 (m, 1H), 3.96 (d, J= 8, 1H), 3.81 (t, J= 8.8, 1H), 3.67 (t, J= 10, 1H), 3.35 (t, J= 8.8, 1H), 2.81 (s, 1H), 2.43 (s, 3H), 1.105 (t, J= 7.2, 3H); ¹³C (CDCl₃, 100.6 MHz) δ 173.0, 172.8, 156.0, 138.8, 128.9, 127.7, 127.5, 68.0, 61.5, 54.2, 51.7, 47.1, 29.7, 14.1, 11.6; HRMS found:[M-H]⁻ 344.1251, C₁₇H₁₉N₃O₅, requires: 344.1246; *m/z*: 344 (100%, [M-H]⁻).

Preparation of (2*R*,3*R*)-4-(3-Methyl-4-nitro-isoxazol-5-yl)-3-phenyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (8).

To a solution of 7 (60mg, 0.17mmol) in DCM (1mL) were subsequently added DMAP (12.2mg, 0.10mmol), TEA (140 μ L, 0.10mmol) and (Boc)₂O (43.7mg, 0.20mmol) at 0°C. The solution was taken to room temperature and stirred for 90 minutes. The mixture was quenched with NH₄Cl

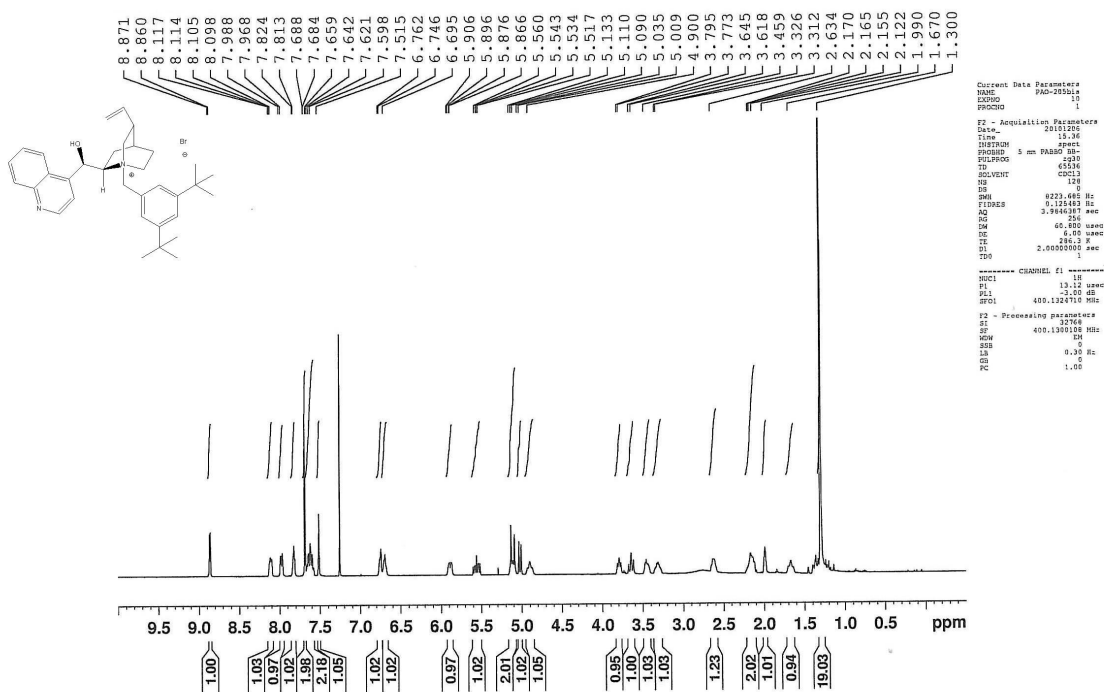
saturated solution and extracted with DCM (3x2mL). The organic layer was concentrated under reduced pressure. The crude was purified by flash chromatography (eluent system petroleum ether: diethyl ether 7:3) to give **16** as a light yellow oil in 70% yield. R_f 0.6 in petroleum ether: diethyl ether 1:1; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm) 7.32-7.20 (m, 5H), 4.62-4.58 (m, 1H), 4.46-4.29 (m, 2H), 4.28-4.19 (m, 1H), 4.15-4.04 (m, 1H), 3.99-3.92 (m, 1H), 3.75 (t, $J= 10.4$, 1H), 2.48 (s, 3H), 1, 49-1.43 (m, 9H), 1.25-1.12 (m, 3H). ^{13}C NMR (CDCl_3 , 400 MHz) δ (ppm) 171.7, 156.3, 153.3, 136.5, 129.4, 129.2, 128.7, 127.8, 127.4, 127.1, 81.5, 66.5, 61.7, 54.0, 50.3, 41.7, 28.7, 27.8, 14.5, 11.8. EI/HRMS: $[\text{M}^+]$ calcd for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_7\text{Na}$ 468.1747 found 468.1754.

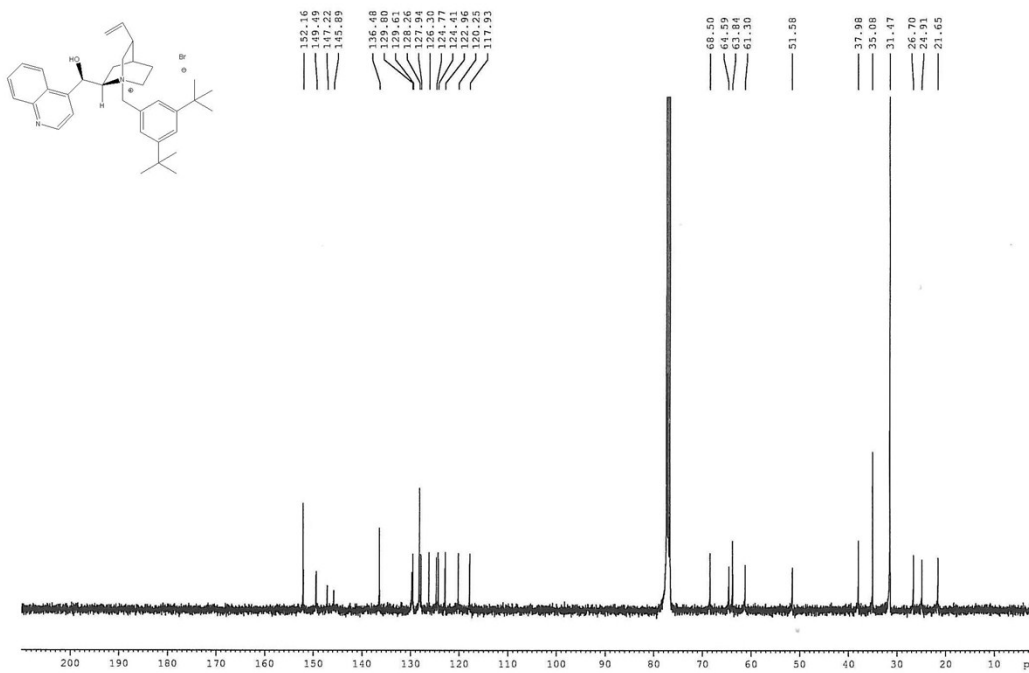
Preparation (2R,3R)-3-Phenyl-pyrrolidine-1,2,4-tricarboxylic acid 1-tert-butyl ester 2-ethyl ester (9).

To a solution of **8** (43.3 mg, 0.1mmol) in THF (1mL) at r.t., a solution of KMnO_4 dissolved in (H_2O /dioxane, 3.5:1) was added drop wise over 30 minutes. The reaction was left stirring for 60 minutes at room temperature. After this time, a saturated solution of Na_2SO_3 was added and HCl 6N solution until clearance. The mixture was extracted with EtOAc (3x2mL). The organic layer was concentrated under reduced pressure. The crude was purified by flash chromatography (eluent system DCM:MeOH 99:1) to give **5** as a yellow solid in 87% yield. R_f 0.22 in DCM:MeOH, 98:2; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm) 7.33-7.22 (m, 5H), 4.36-4.14 (m, 2H), 4.12-3.98 (m, 2H), 3.78-3.72 (m, 2H), 3.36 (q, $J= 8.4$, 1H), 1.50-1.38 (m, 9H), 1.18-1.11 (m, 3H) ^{13}C NMR (CDCl_3 , 400 MHz) δ (ppm) 176.3, 172.0, 153.7, 139.0, 128.2, 127.7, 81.3, 66.6, 61.5, 52.8, 49.2, 28.7, 14.5. EI/HRMS: $[\text{M}^+]$ calculated for $\text{C}_{19}\text{H}_{25}\text{N}\text{O}_6\text{Na}$. 386.1580 found 386.1572.

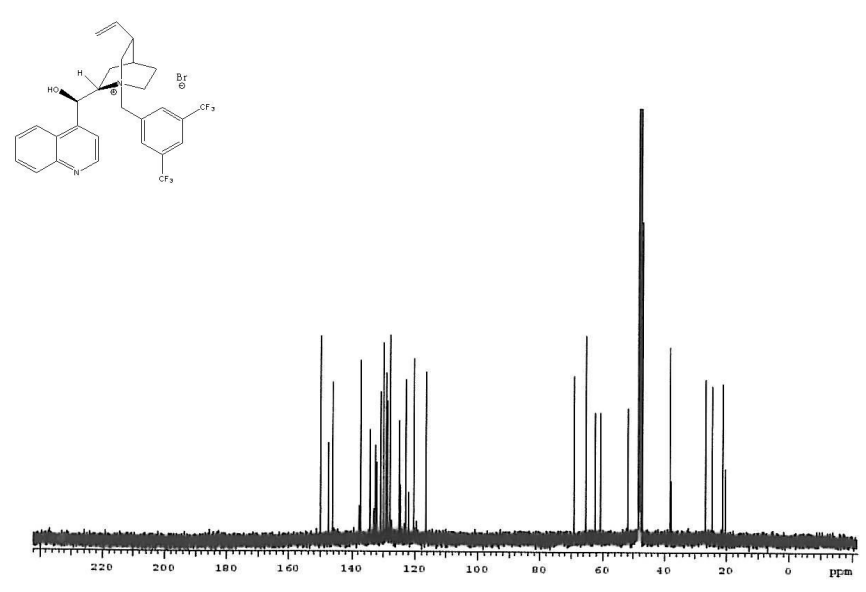
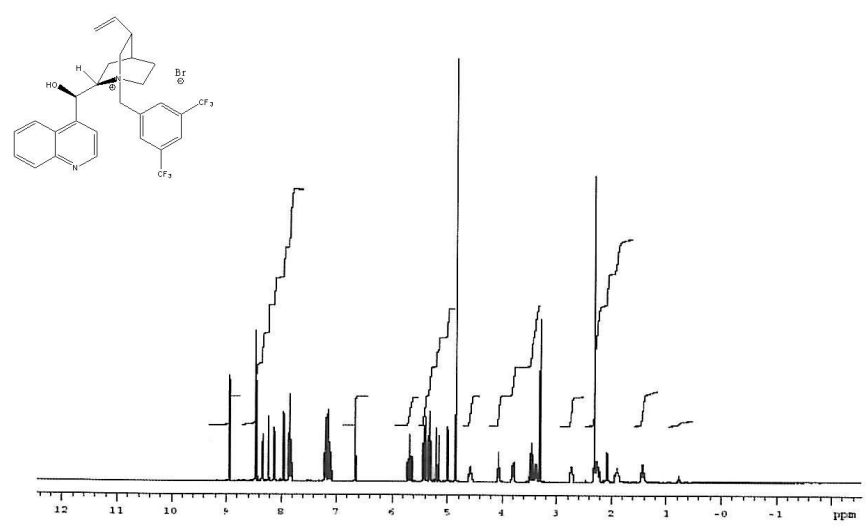
8. Spectra and HPLC of compounds 3a-m, 4a-m and 7-9

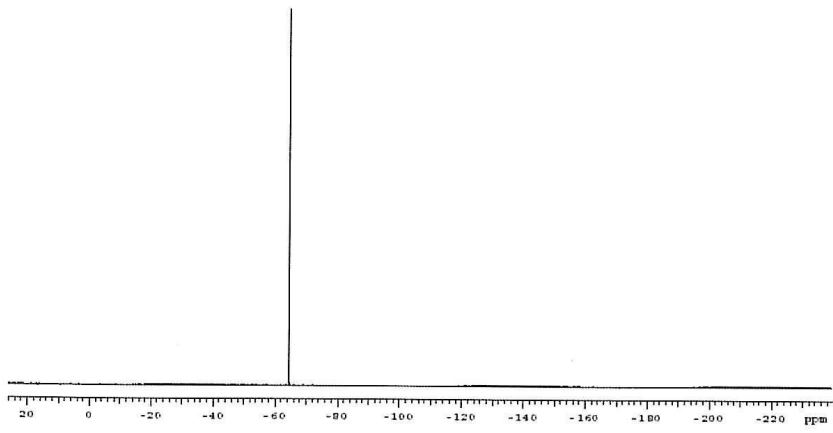
Catalyst 6m



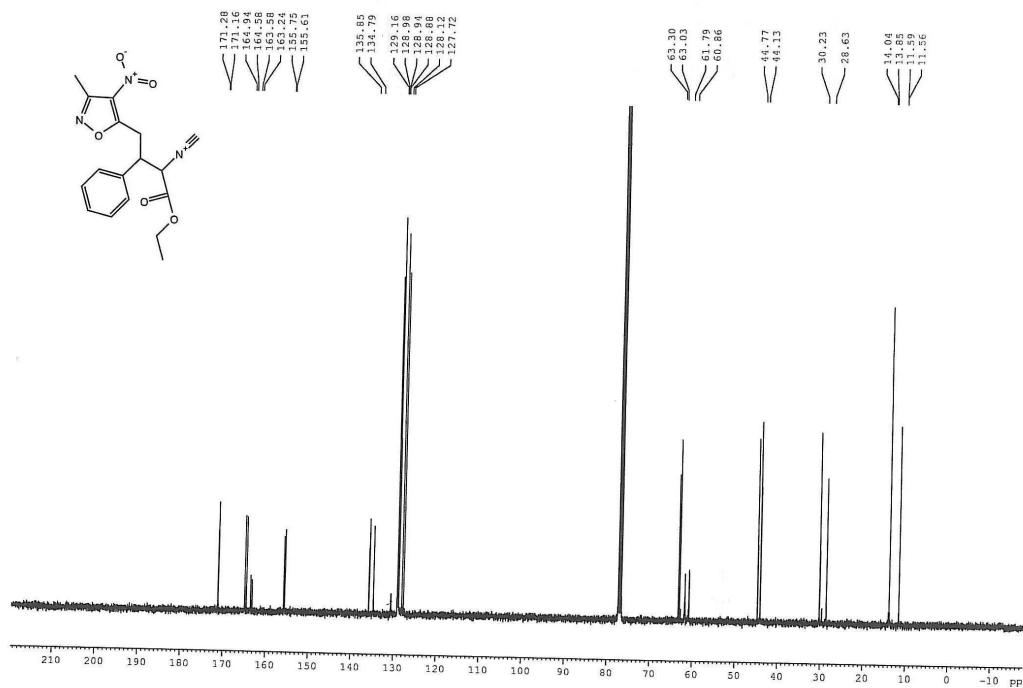
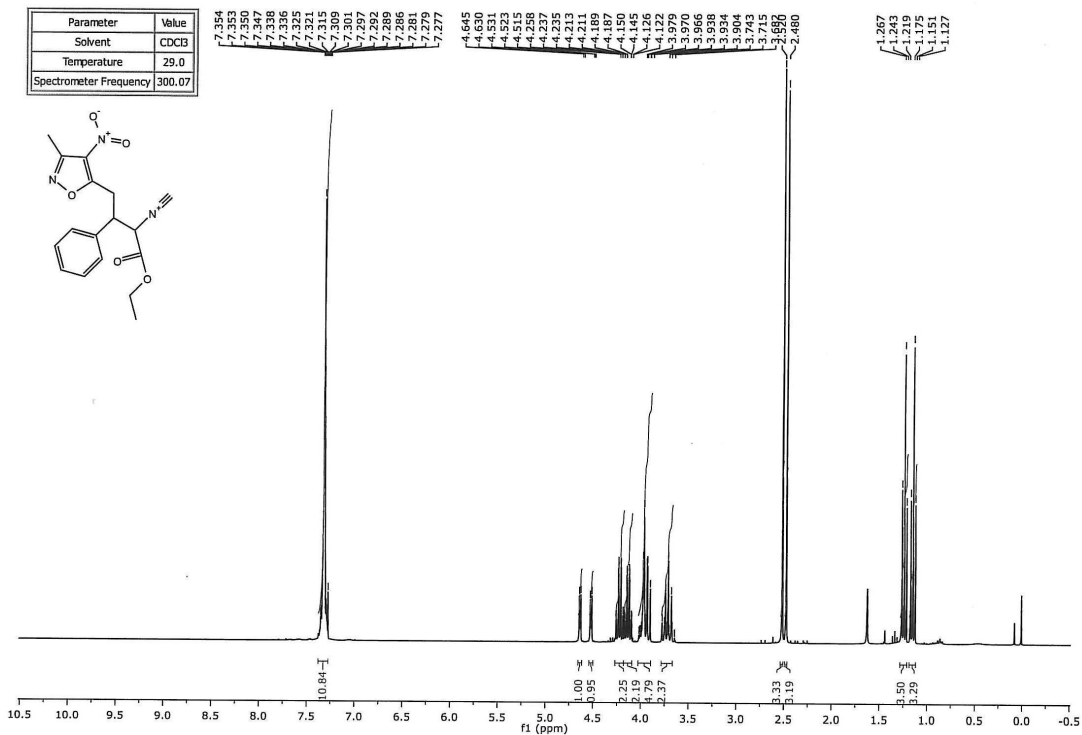


Catalyst 6I



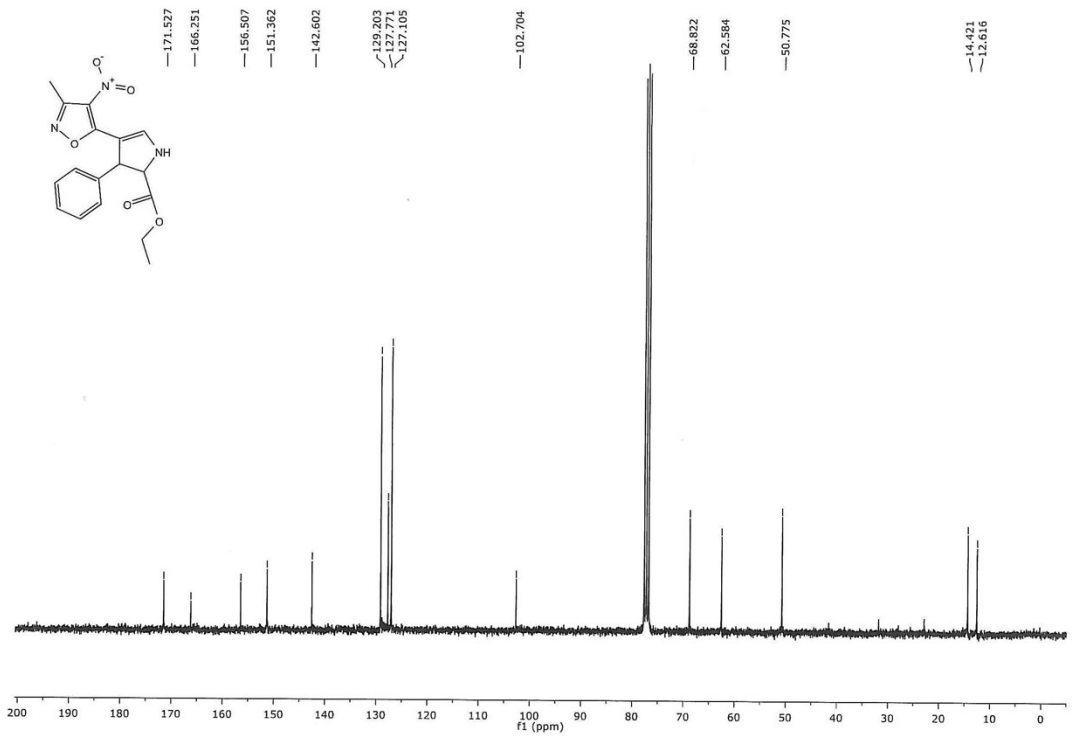
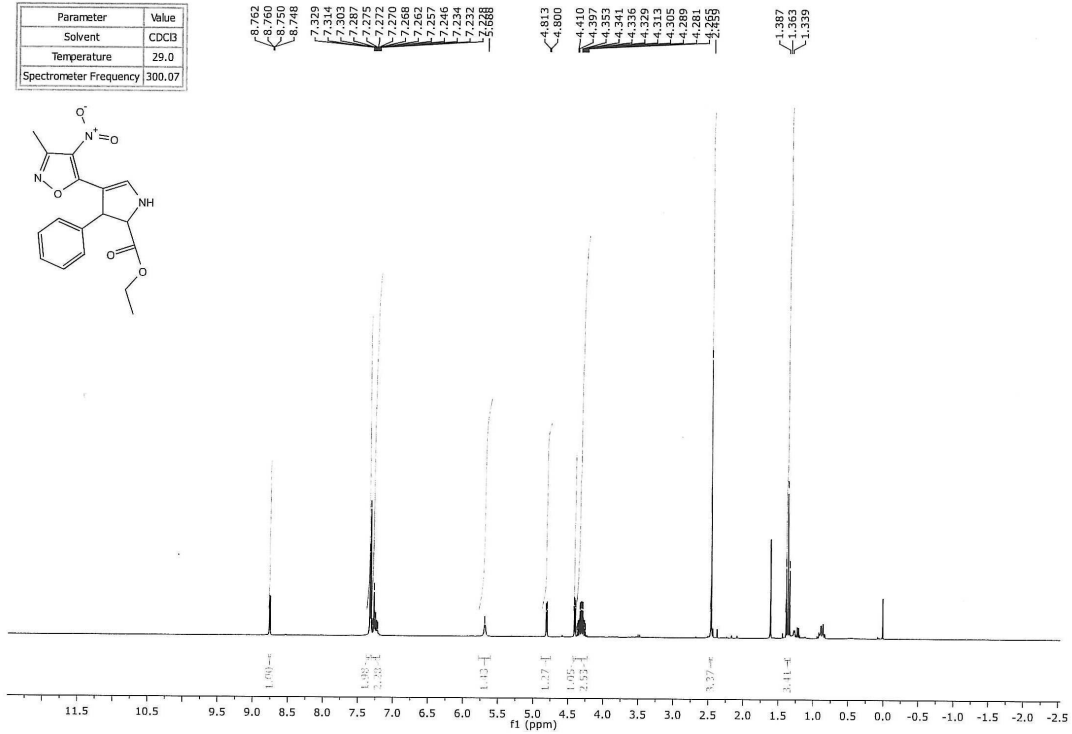
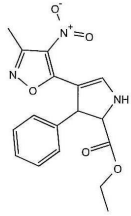


Compound 3a



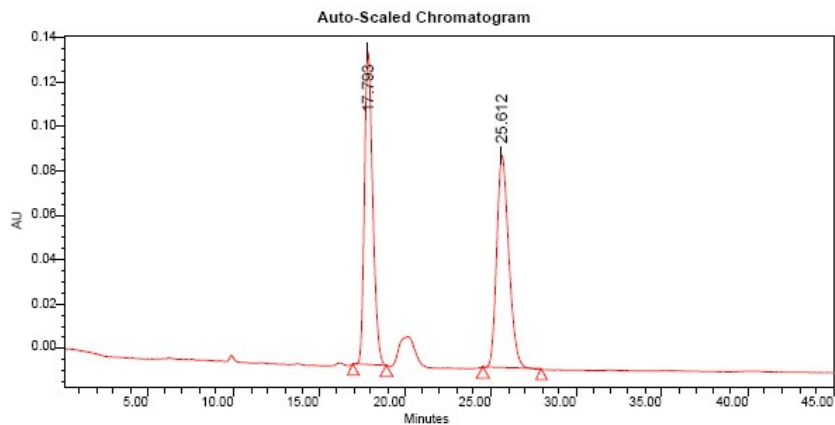
Compound 4a

Parameter	Value
Solvent	CDCl ₃
Temperature	29.0
Spectrometer Frequency	300.07



SAMPLE INFORMATION

Sample Name: PAO-racemo Sample Type: Unknown Vial: 1 Injection #: 1 Injection Volume: 10.00 ul Run Time: 45.0 Minutes Sample Set Name:	Acquired By: System Date Acquired: 6/23/10 12:07:48 PM Acq. Method Set: Chiralmiscela Date Processed: 6/23/10 1:19:02 PM Processing Method: HPLC Channel Name: PDA Single 254.0 nm Proc. Chnl. Descr.: PDA 254.0 nm
--	---



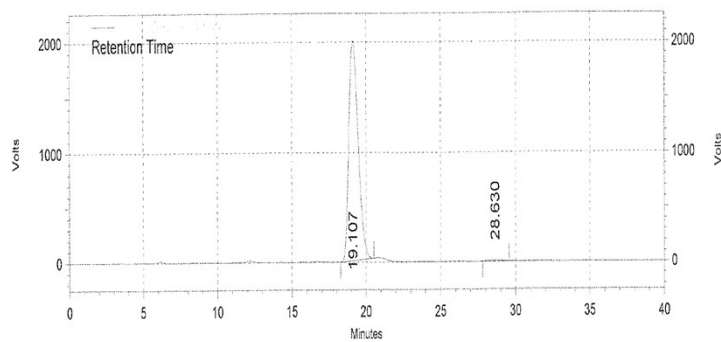
Unknown Peak Results

Peak Type	RT	Area	% Area	Height
1 Unknown	17.793	4752780	50.19	141051
2 Unknown	25.612	4716972	49.81	95737

Compound 4a

Area % Report

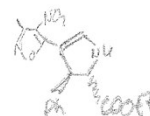
Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\DS209.PAO2-7-2012 1-34-15 PM\System.dat
 Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\untitled.met
 Acquired: 2/7/2012 1:35:36 PM
 Printed: 2/7/2012 3:18:29 PM



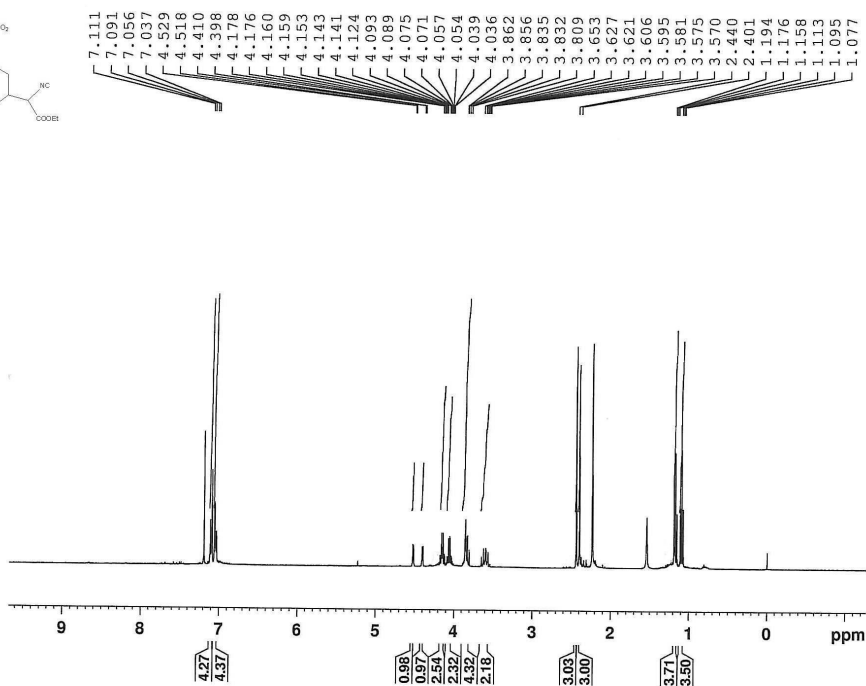
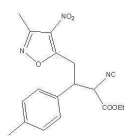
VWD: Signal A,
 210 nm Results

Retention Time	Area	Area %	Height	Height %
19.107	1466779202	99.26	33442472	99.42
28.630	10876711	0.74	195753	0.58

Totals	1477655913	100.00	33638225	100.00
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Compound 3b

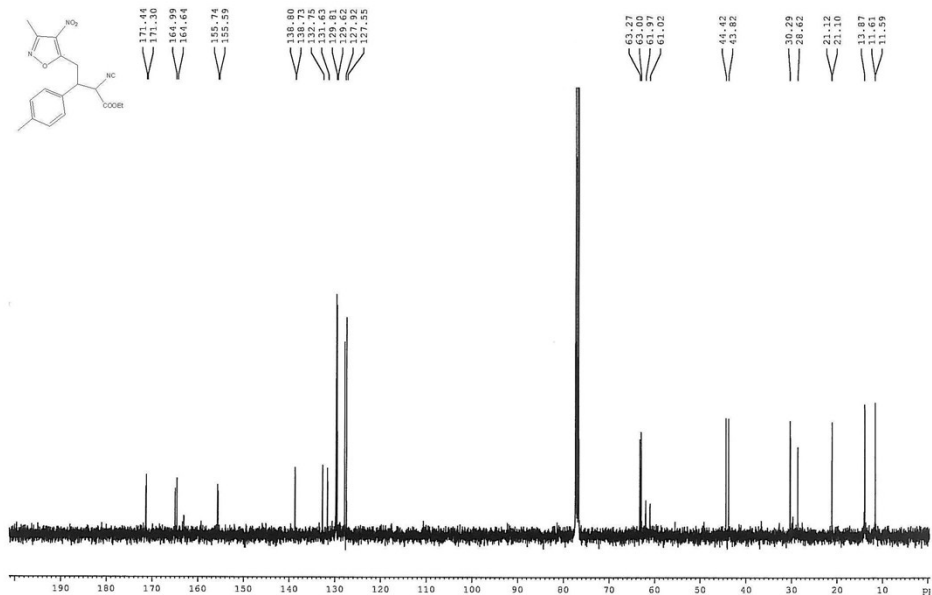


Current Data Parameters
 NAME Aug21-2018
 PRONO 70
 PROCNO 1

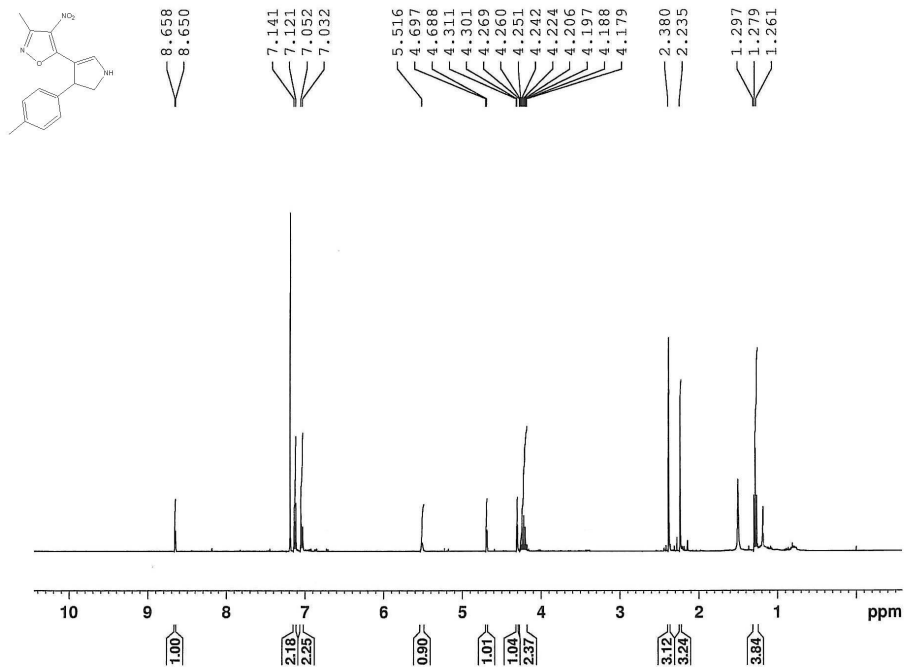
F2 - Acquisition Parameters
 Date_ 20100921
 Time 16:16
 INSTRUM spect
 PROBNM 5 mm PABBO QNP
 PULPROG zgpg30
 TD 65534
 SOLVENT CDCl3
 NS 16
 DS 4
 RB 8223.685 Hz
 FIDRES 0.126480 Hz
 AQ 3.848627 sec
 RU 32
 DW 60.800 usec
 DE 19.00 usec
 TE 295.1 K
 D1 1.0000000 sec
 TDS

----- CHANNEL f1 -----
 NUC1 13
 P1 13.12 usec
 PL1 -3.20 dB
 SFO1 400.1324710 MHz

F2 - Processing parameters
 SI 32768
 SF 400.1300361 MHz
 DS 4
 SWH 4000.000000 MHz
 GB 0.30 Hz
 RB 45.82 Hz
 PC 3.00

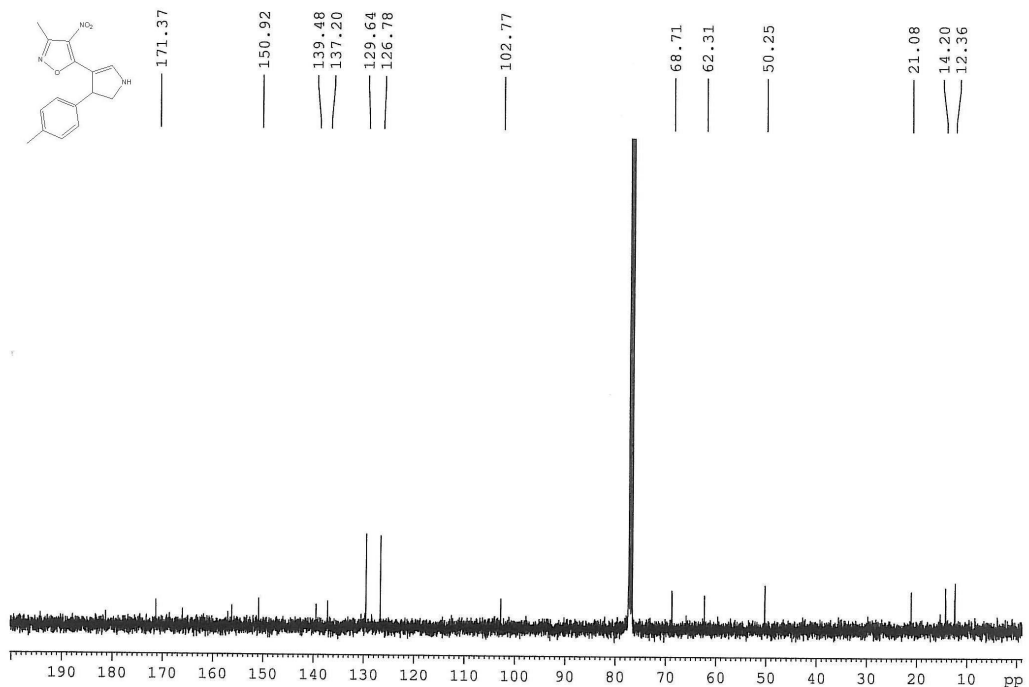


Compound 4b



```

Current Data Parameters
NAME      Jul04-2010
EXPNO    2
PROCNO   1
F2 - Acquisition Parameters
Date_    20100704
Time     14.28
INSTRUM  spect
PROBHD   5 mm PABBO DQ-
PULPROG  zgpg30
TD        65536
SOLVENT  CDCl3
NS        16
DS        2
SWH       8233.645 Hz
FIDRES    0.1221683 Hz
AQ         3.9844367 sec
RG         640
DM         60.800 uM
DE         1.00 uM
TE         295.0 K
D1         1.0000000 sec
TDD        1
----- CHANNEL f1 -----
NUC1       13
P1         13.12 uM
PL1        -1.00 dB
SFO1       400.1324710 MHz
F2 - Processing parameters
SI         32768
SF         400.1350364 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
PC         1.00
    
```

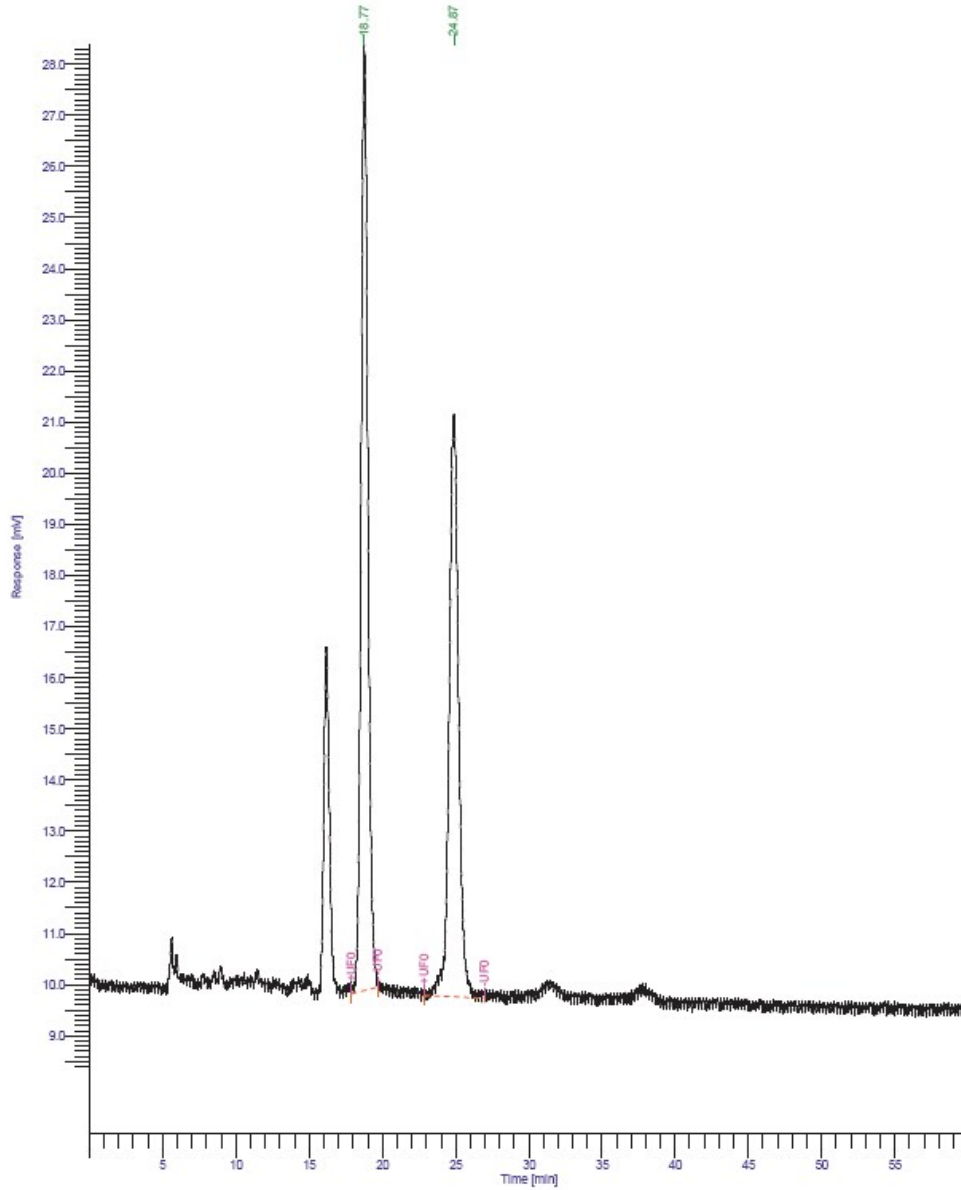


DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		18.773	598529.70	18485.47	53.95	53.95			*MM	0.5985	0.5985
2		24.875	509132.54	11395.26	46.05	46.05			*MM	0.5091	0.5091
			1105662.24	29880.73	100.00	100.00				1.1057	1.1057

Missing Component Report
Component Expected Retention (Calibration File)

All components were found



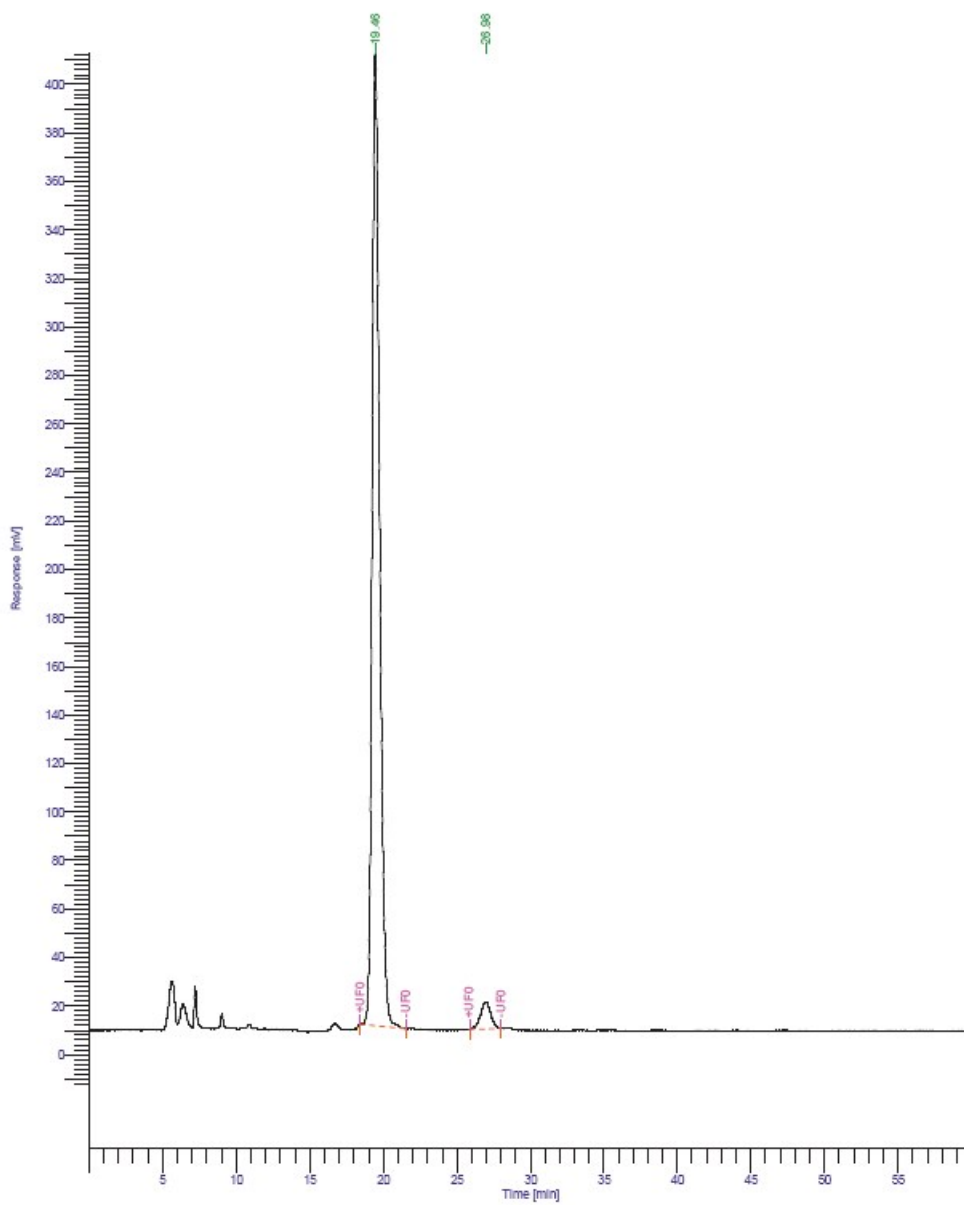
Compound 4b

DEFAULT REPORT

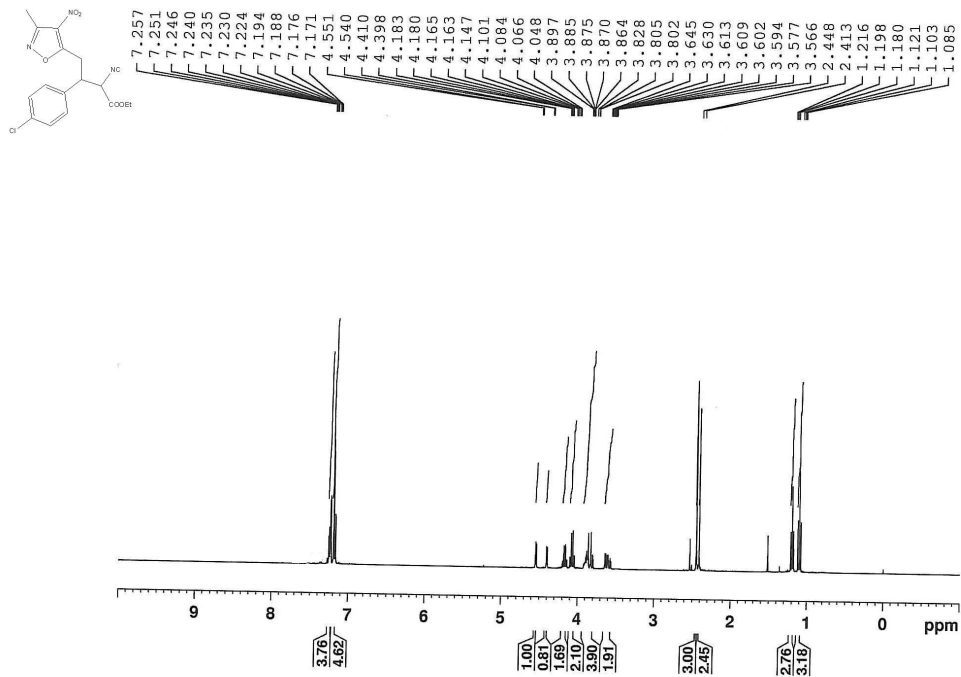
Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		19.463	14140770.84	400803.08	96.34	96.34			*MM	14.1408	14.1408
2		28.979	536478.70	11150.75	3.66	3.66			*MM	0.5365	0.5365
			14677247.54	411953.83	100.00	100.00				14.6772	14.6772

Missing Component Report
Component Expected Retention (Calibration File)

All components were found



Compound 3c

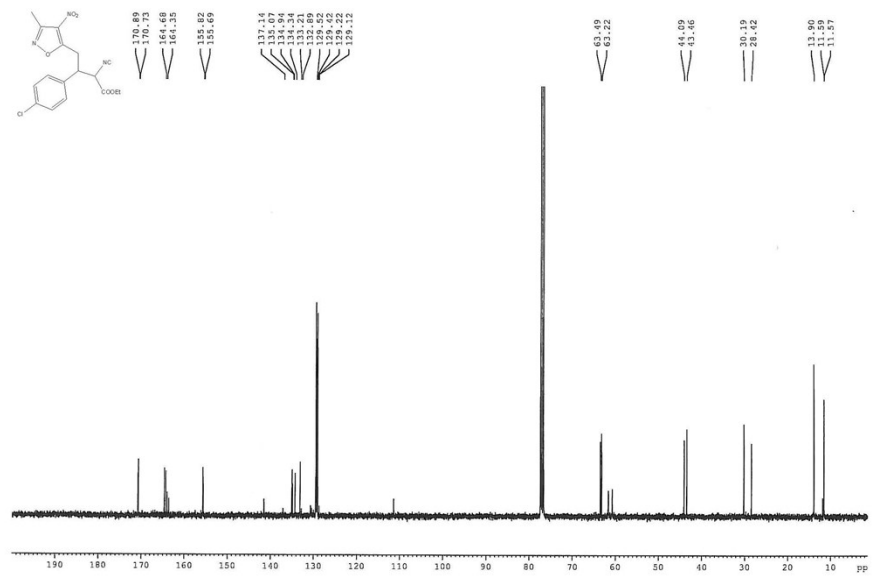


Current Data Parameters
 NAME PAO-261
 EXPNO 12
 PROCNO 12

F2 - Acquisition Parameters
 Date_ 20100901
 Time 22:10
 INSTRUM spect
 PROCNO 5
 PULPROG zgpg30
 ID 6054
 SOLVENT cdcl3
 NS 128
 DS 0
 SWE 8233.458 Hz
 FIDRES 0.103483 Hz
 AQ 1.2846297 sec
 RG 266
 GM 62.800 usec
 DE 6.00 usec
 TE 295.2 K
 DQ 2.0000000 sec
 TD 1

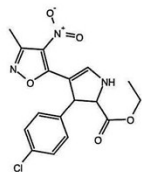
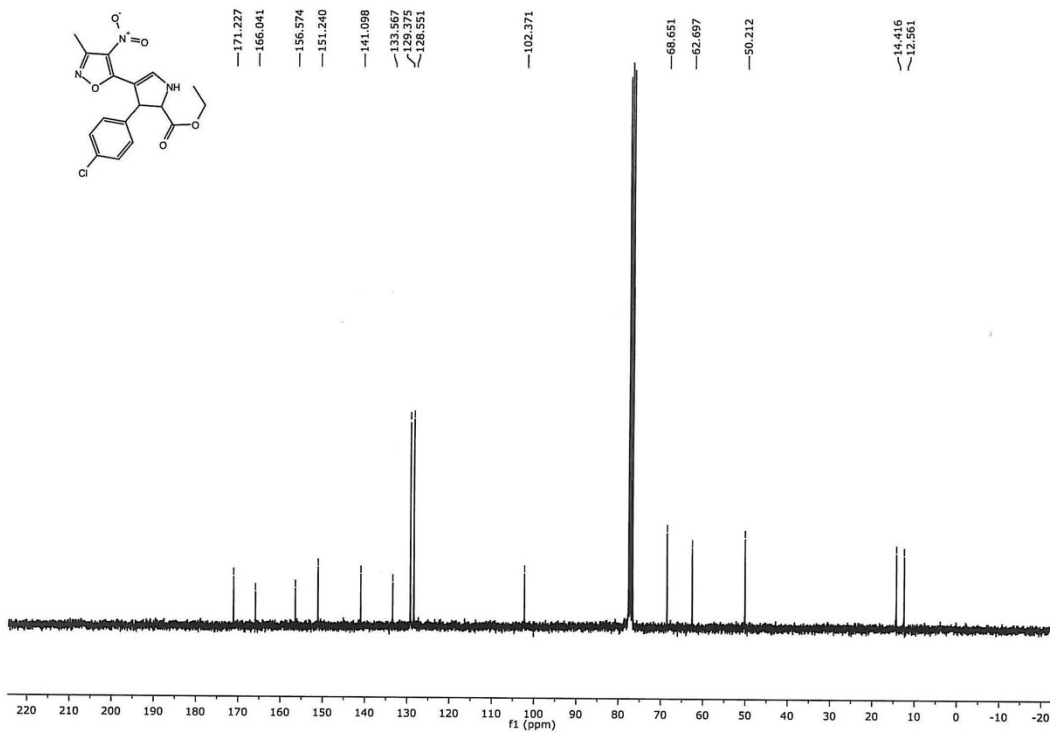
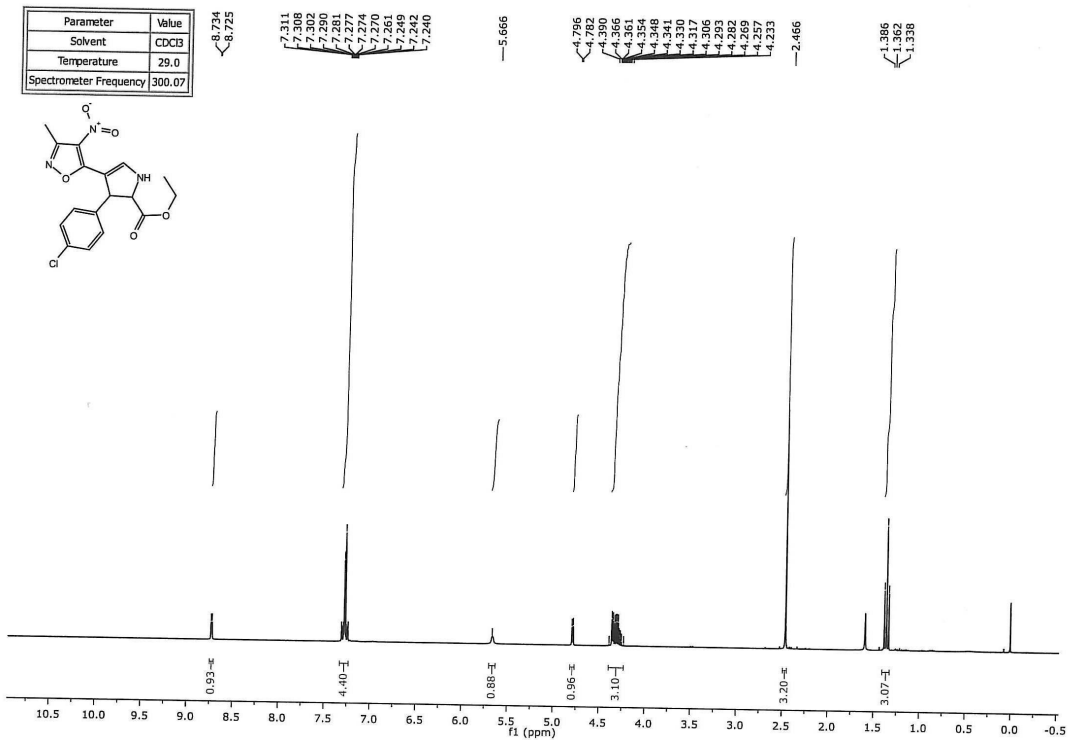
----- CHANNEL f1 -----
 NUC1 1H
 PL 13.12 usec
 FL1 -1.00 dB
 SFO1 400.1324710 MHz

F2 - Processing parameters
 SI 32768
 SF 400.1303357 MHz
 MSB 0
 SSB 0
 LB 0.38 Hz
 GB 0
 PC 1.00



Compound 4c

Parameter	Value
Solvent	CDCl ₃
Temperature	29.0
Spectrometer Frequency	300.07



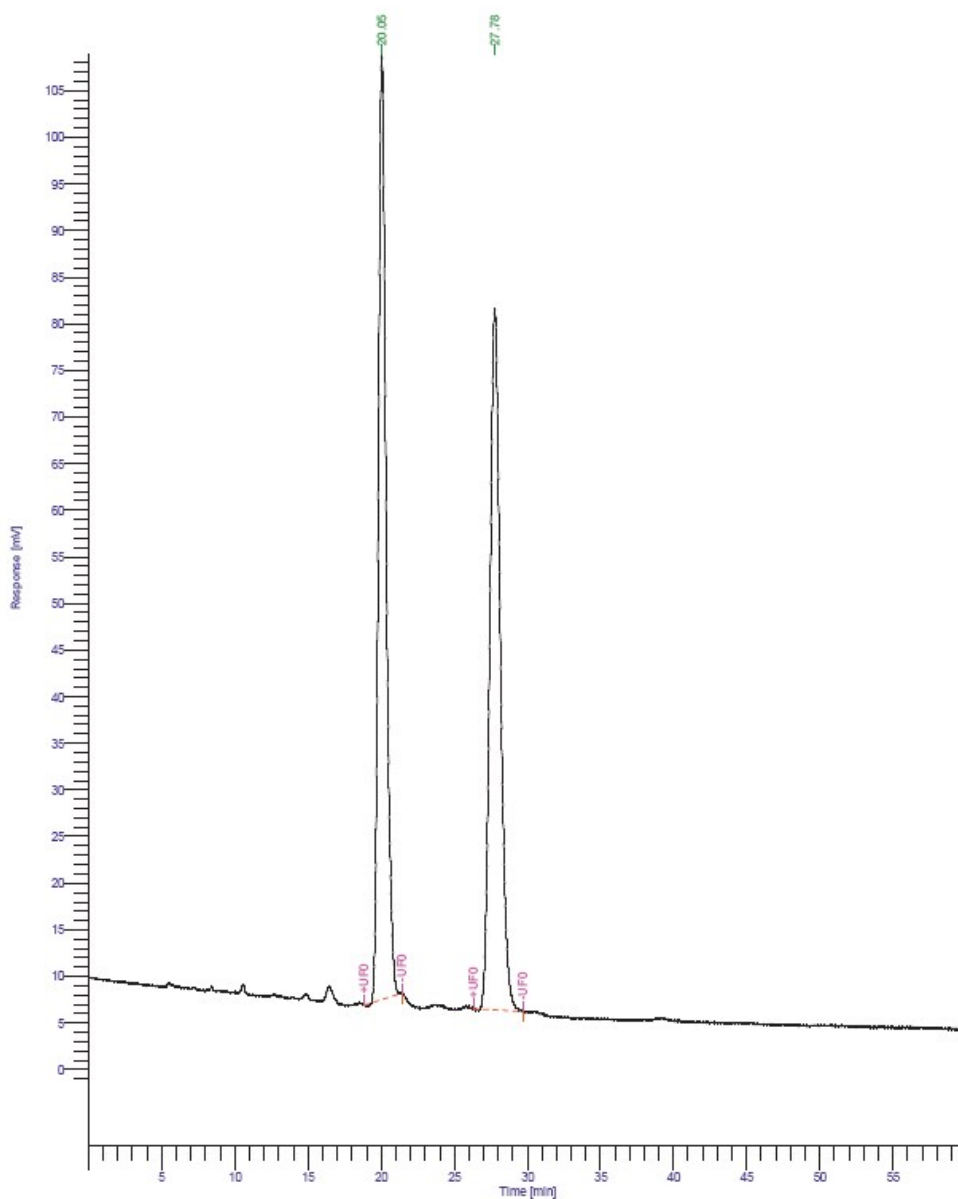
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		20.049	3719948.02	101367.32	49.79	49.79			*MM	3.7199	3.7199
2		27.779	3750705.39	75261.17	50.21	50.21			*MM	3.7507	3.7507
			7470653.41	178628.49	100.00	100.00				7.4707	7.4707

Missing Component Report

Component Expected Retention (Calibration File)

All components were found



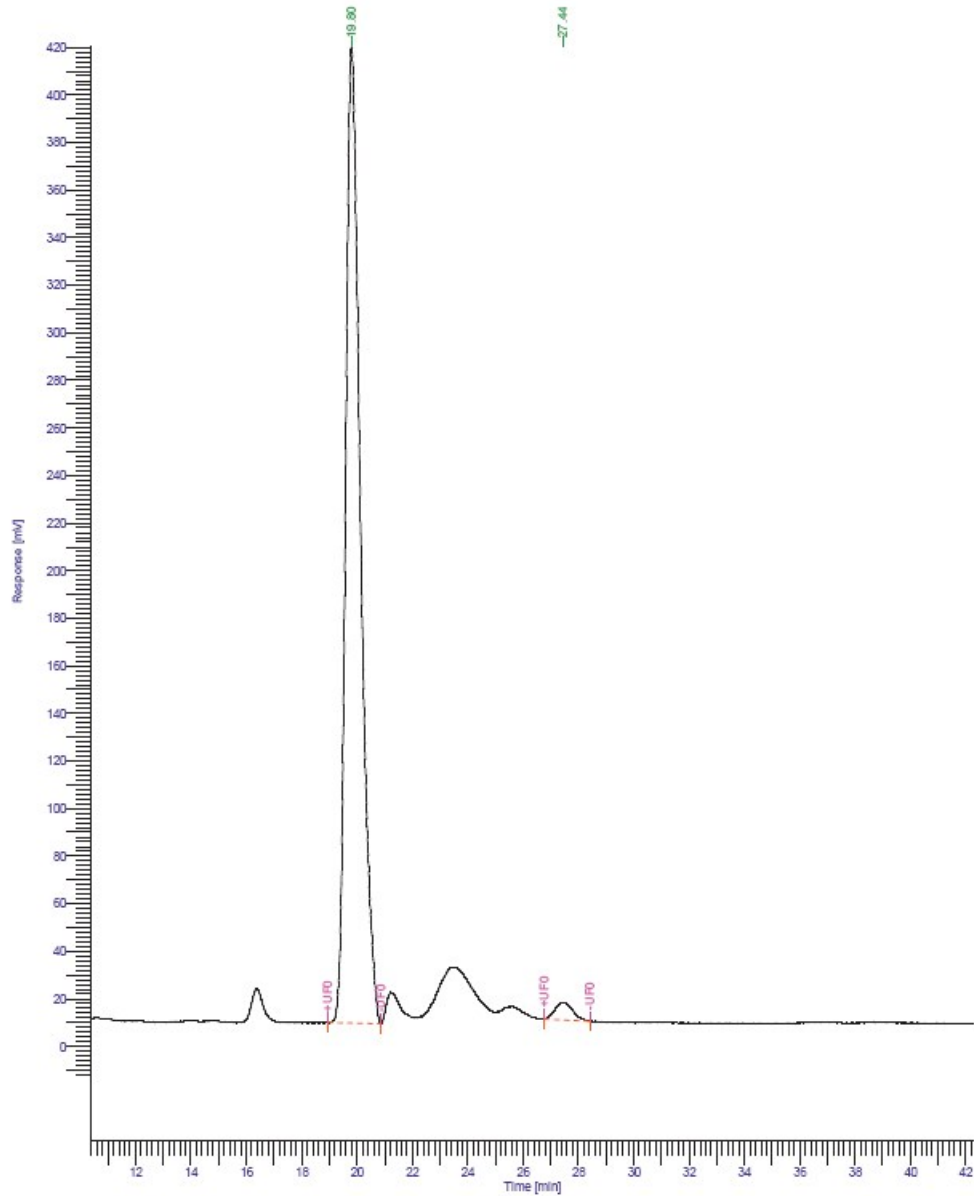
Compound 4c

DEFAULT REPORT

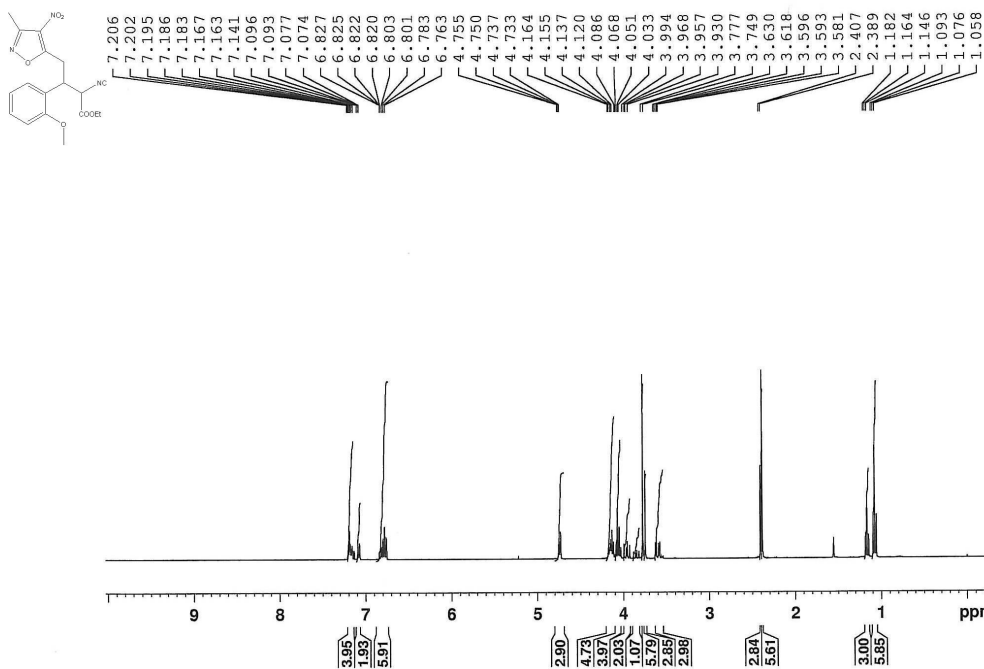
Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		19.800	15270042.41	410522.41	97.94	97.94			*MM	15.2700	15.2700
2		27.441	321314.13	7453.39	2.06	2.06			*MM	0.3213	0.3213
			15591356.55	417975.80	100.00	100.00				15.5914	15.5914

Missing Component Report
Component Expected Retention (Calibration File)

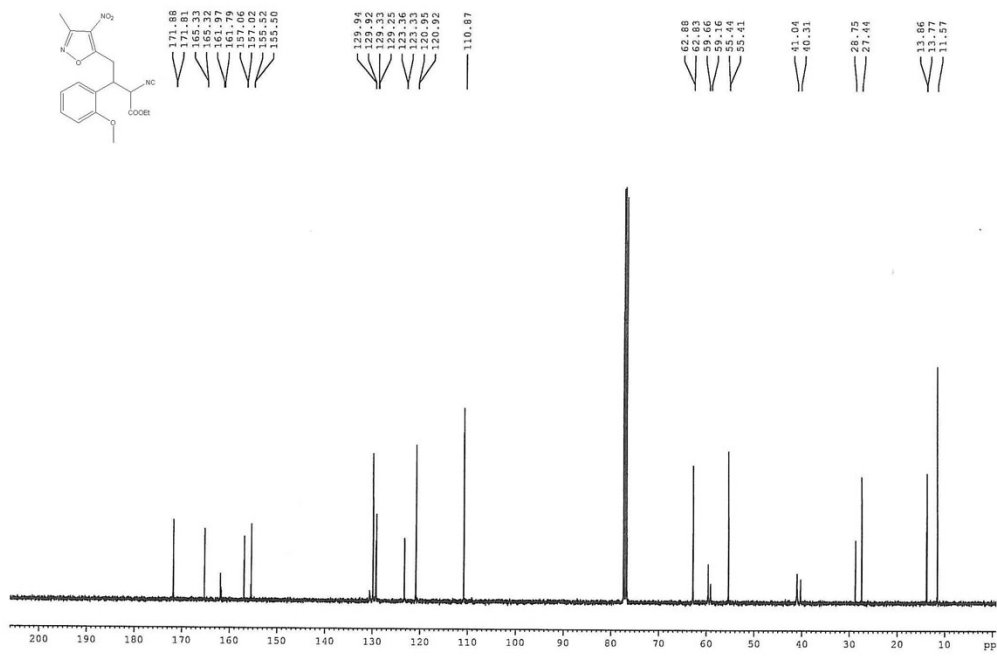
All components were found



Compound 3d

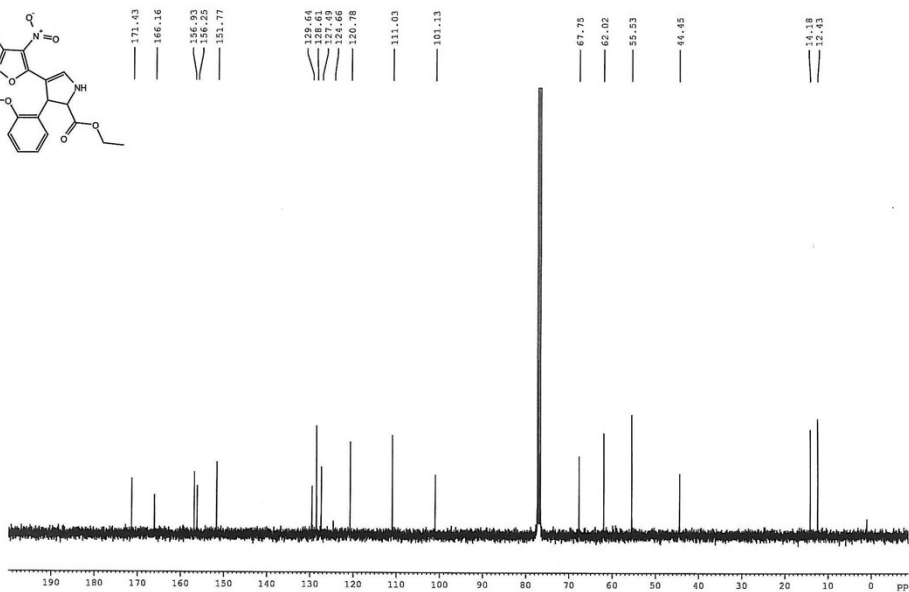
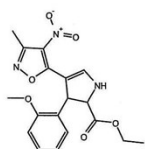
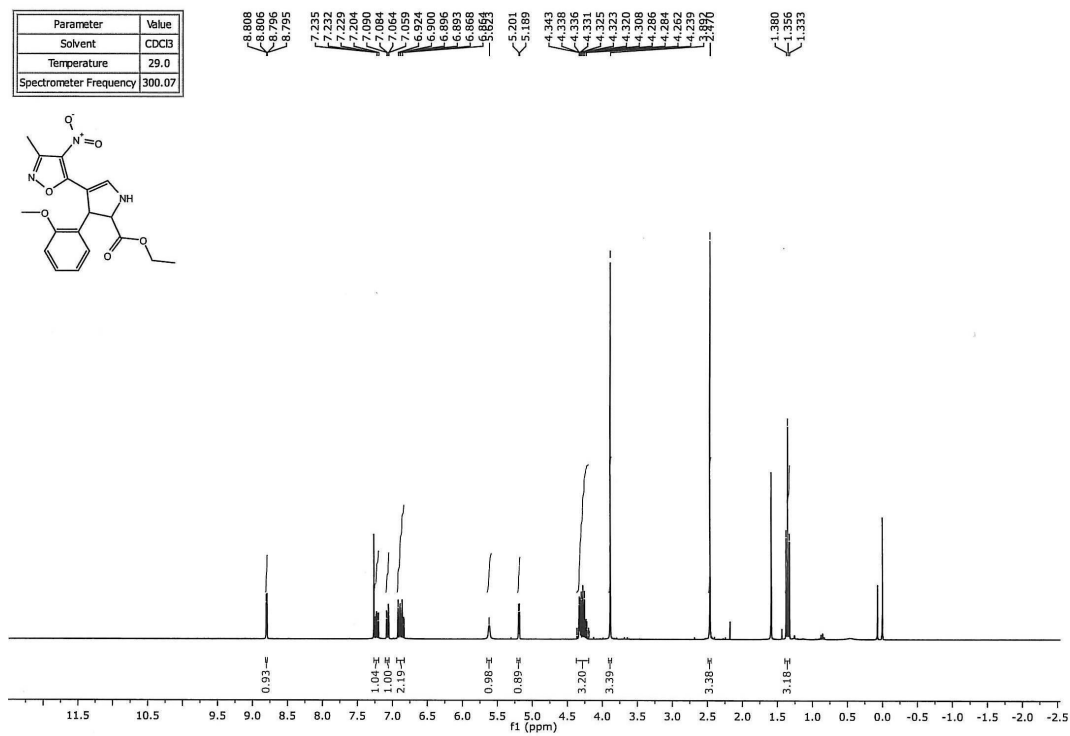
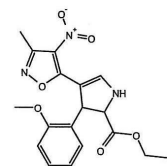


Current Data Parameters
 NAME: 8062-2010
 DATE: 10
 PROCNO: 1
 F2 - Acquisition Parameters
 DATE_: 20100921
 TIME: 14.05
 INSTRUM: spect
 PROBPID: 5 mm PABBO QNP
 NUC1: 13C
 NUC2: 1H
 SOLVENT: CDCl3
 NS: 16
 DS: 8221.445 Hz
 SFO: 0.128463 Hz
 AQ: 3.384637 sec
 RG: 10
 SM: 60.800 uM
 SW: 4.00 uM
 FID: 285.1 K
 SFO: 1.0000000 sec
 TDO: ***** CHANNEL f1 *****
 NUC1: 13C
 P1: 13.10 uM
 PL1: -1.00 dB
 SFO1: 400.130110 MHz
 F2 - Processing parameters
 SI: 3274
 SF: 400.130110 MHz
 NDM: 0
 SFR: 0
 LB: 0.30 Hz
 GB: 0
 PC: 1.00



Compound 4d

Parameter	Value
Solvent	CDCl ₃
Temperature	29.0
Spectrometer Frequency	300.07

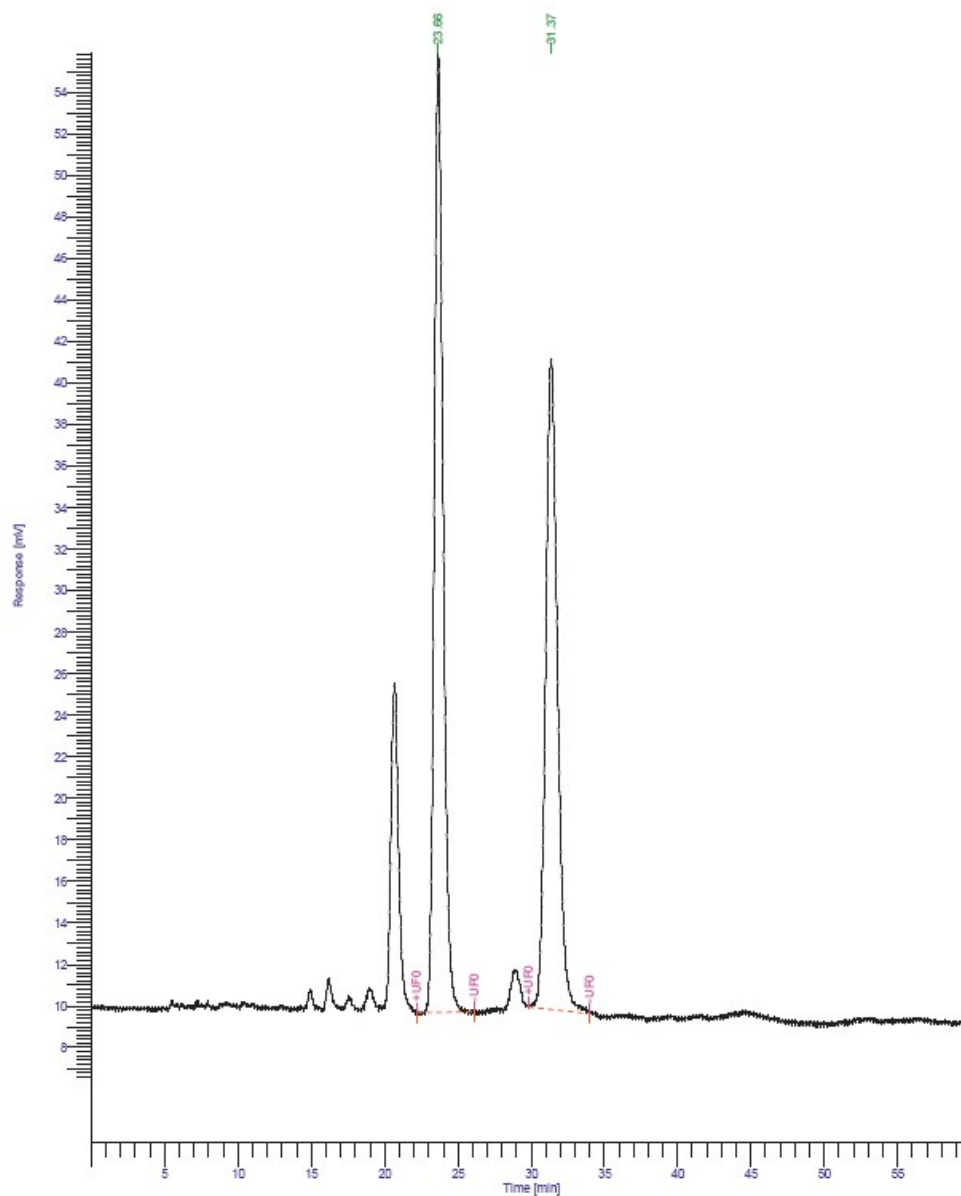


DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		23.865	1950059.90	46182.65	52.45	52.45			*MM	1.9501	1.9501
2		31.372	1767607.12	31337.73	47.55	47.55			*MM	1.7676	1.7676
			3717687.02	77520.38	100.00	100.00				3.7177	3.7177

Missing Component Report
Component Expected Retention (Calibration File)

All components were found



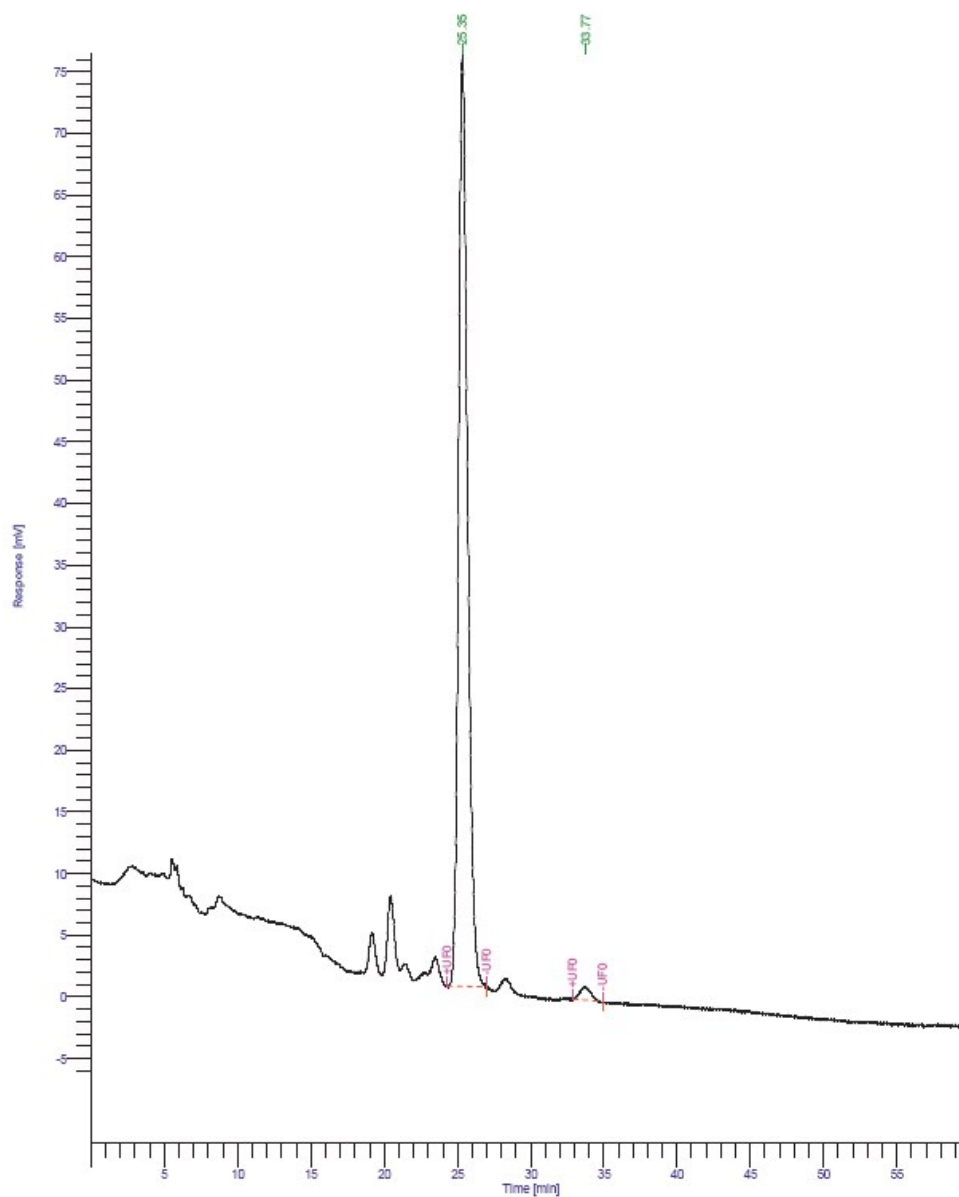
Compound 4d

DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		25.351	3254637.03	75587.79	98.35	98.35			*MM	3.2546	3.2546
2		33.770	54658.29	1153.18	1.65	1.65			*MM	0.0547	0.0547
			3309295.33	76740.98	100.00	100.00				3.3093	3.3093

Missing Component Report
Component Expected Retention (Calibration File)

All components were found



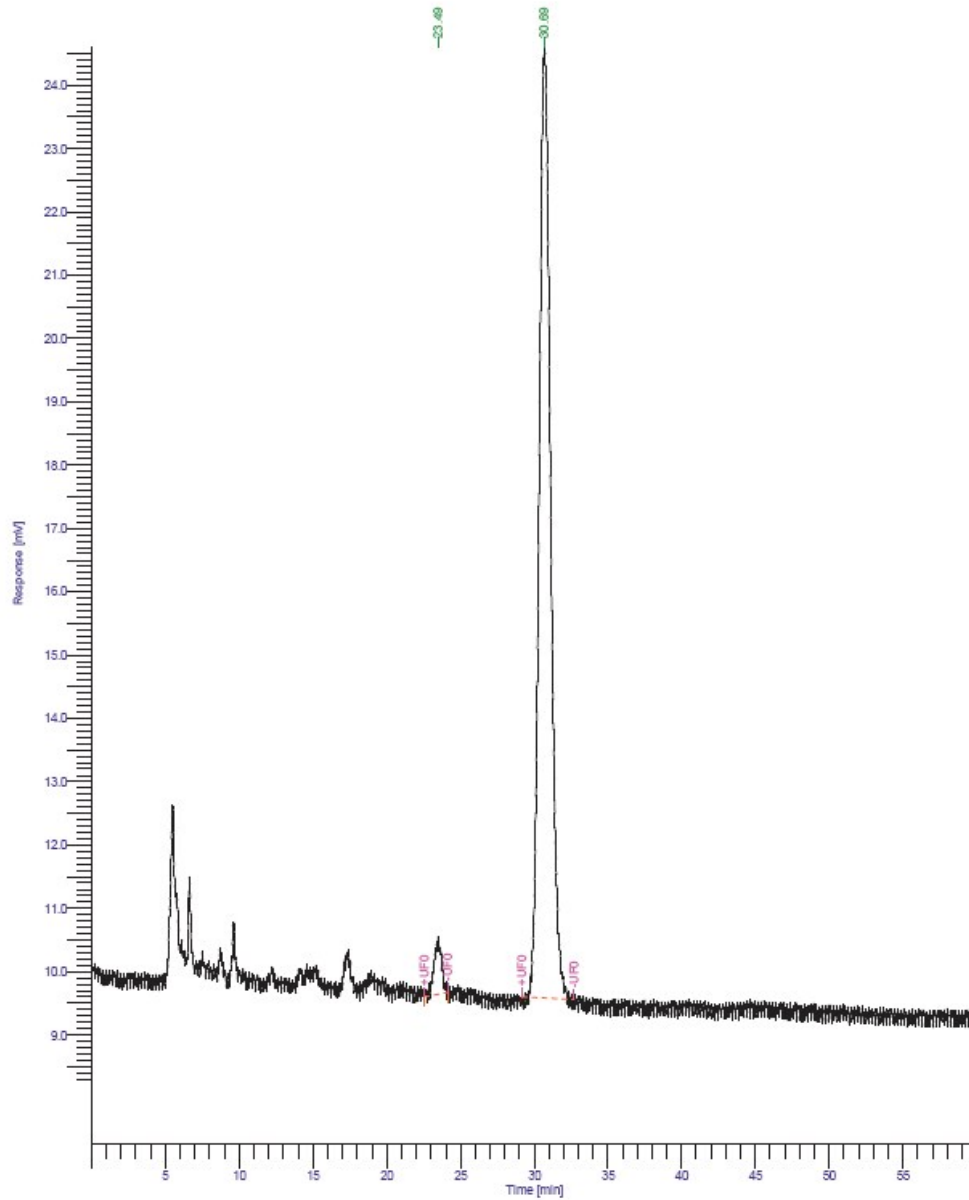
Compound *ent-4d*

DEFAULT REPORT

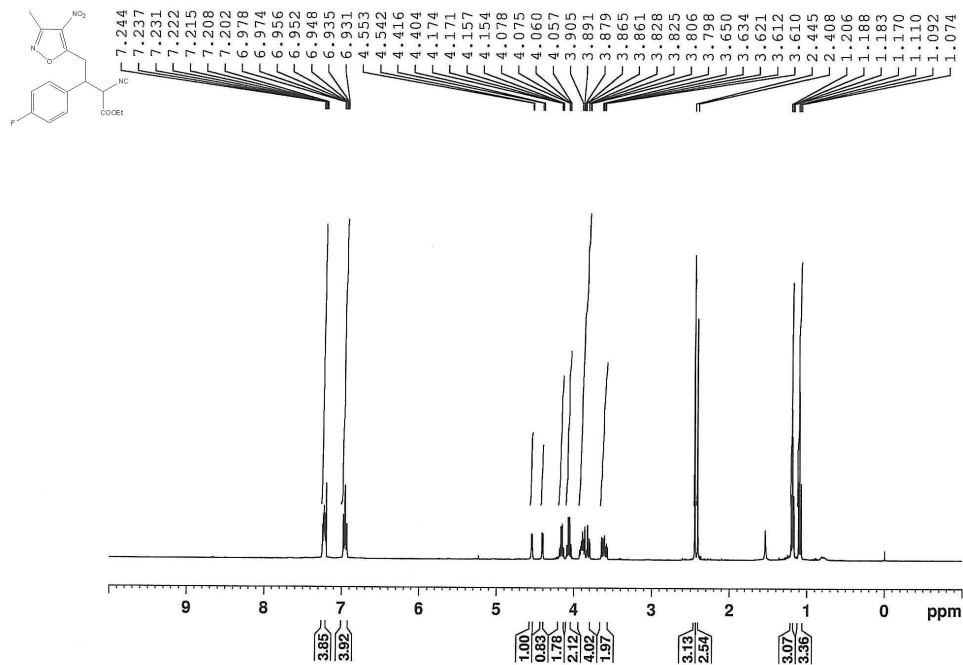
Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount	
1		23.489	31747.92	907.57	3.79	3.79				*MM	0.0317	0.0317
2		30.690	806789.51	15012.95	96.21	96.21				*MM	0.8068	0.8068
			838537.43	15920.51	100.00	100.00					0.8385	0.8385

Missing Component Report
Component Expected Retention (Calibration File)

All components were found



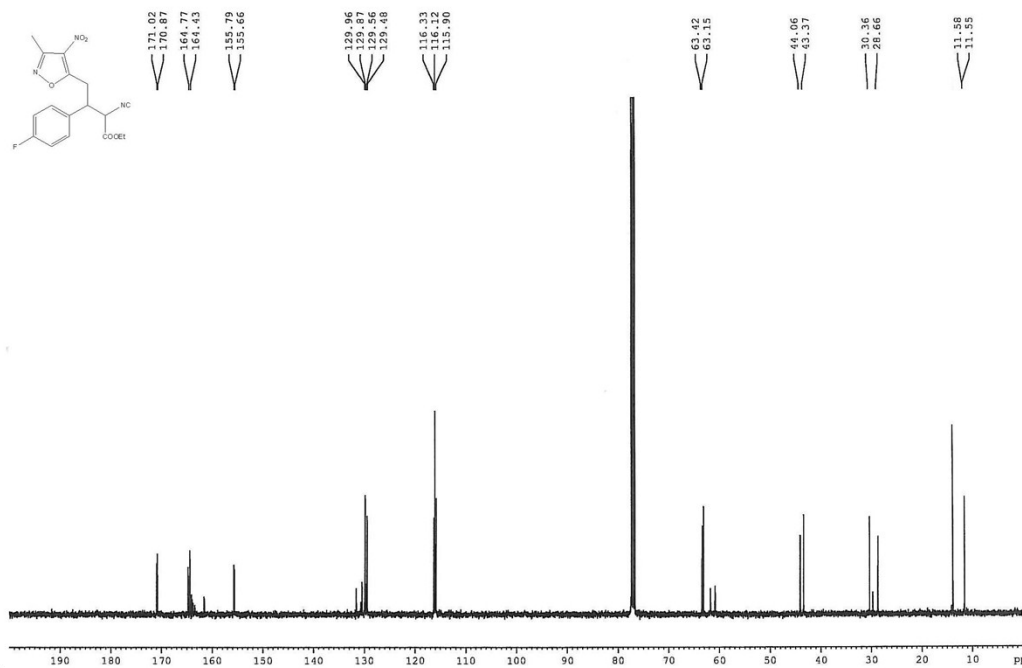
Compound 3e



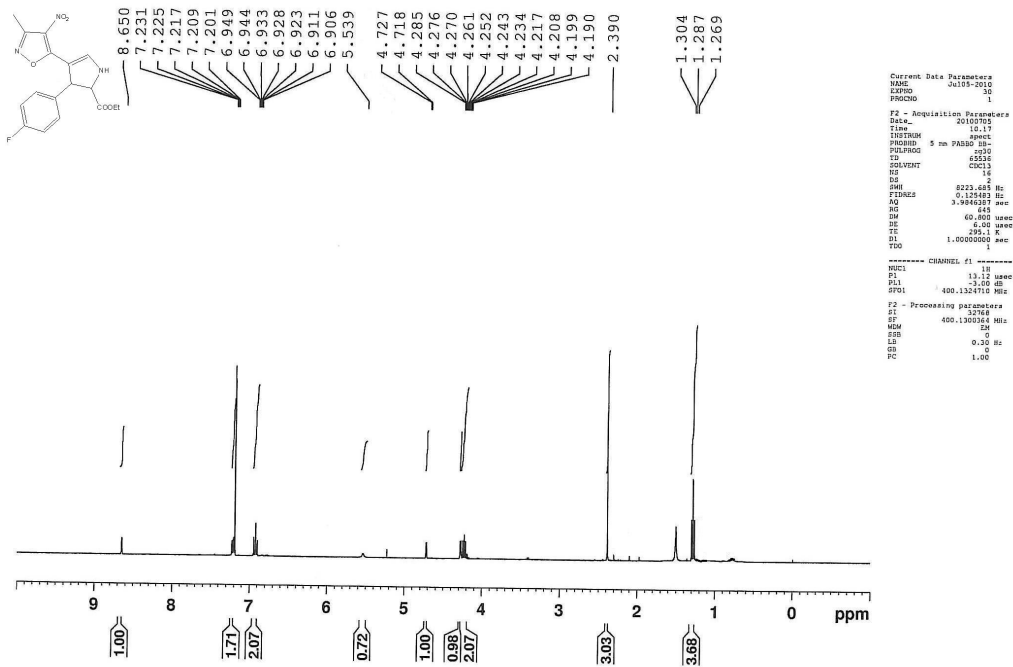
Current Data Parameters
 NAME Aug3-2019
 EXPNO 4
 F2 - Acquisition Parameters
 Date_ 20180823
 Time 20:28
 INSTRUM spect
 PULPROG zgpg30
 PROCNO 5
 TD 65536
 SOLVENT CDCl3
 NS 128
 DS 8
 SWH 4023.685 Hz
 FIDRES 0.129483 Hz
 AQ 3.9846287 sec
 RG 228
 DM 60.800 usec
 DE 6.00 usec
 TE 300.2 K
 D1 2.0000000 sec
 TBO 1

----- CHANNEL f1 -----
 NUC1 13
 P1 13.12 usec
 PL1 -1.00 dB
 SFO1 100.626109 MHz

F2 - Processing parameters
 SI 32768
 SF 100.626109 MHz
 MSW 0
 EN 0
 LB 0.30 Hz
 GB 0
 PC 1.00



Compound 4e



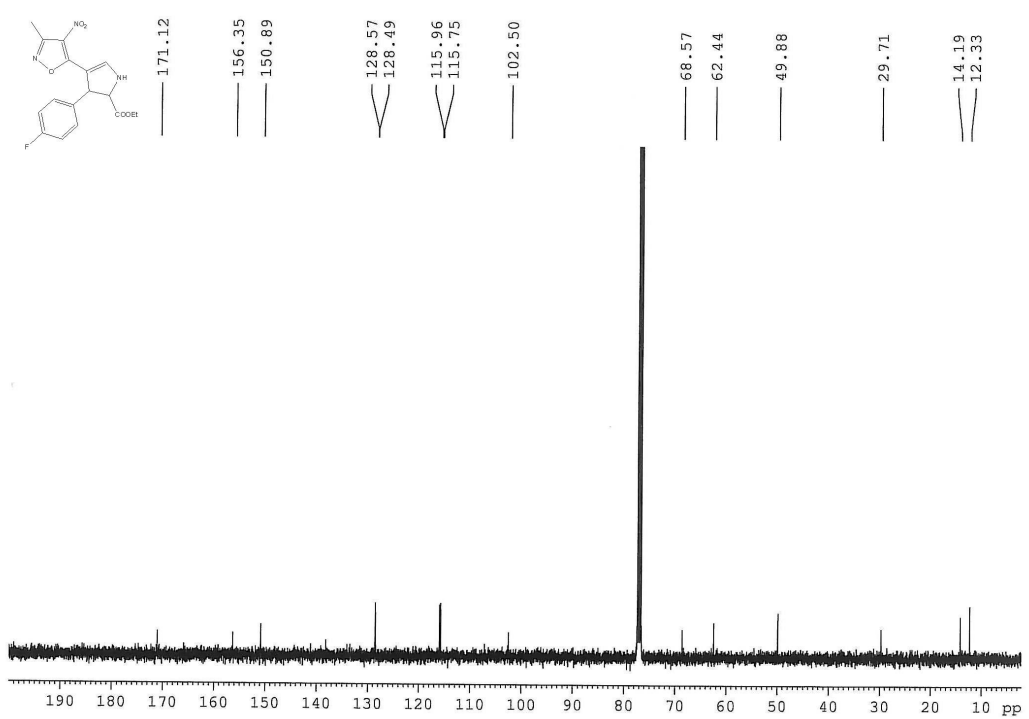
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Current Data Parameters
NAME      Jul15-2010
EXPNO    30
PROCNO   1

F2 - Acquisition Parameters
Date_    20100715
Time     15.17
INSTRUM  spect
PROBHD   5 mm PABBO
PULPROG  zgpg
TE       300K
SOLVENT  CDCl3
NS       16
DS       2
SWH      8223.487 Hz
FIDRES   0.125489 Hz
AQ       3.5862827 sec
RG       645
SFO      400.1324710 MHz
NUC1      13C
NUC2      13C
PC       1.00

----- CHANNEL f1 -----
NUC1      13C
P1        13.12 usec
PL1       -1.00 dB
SFO1      400.1324710 MHz

F2 - Processing parameters
SI        32768
SF        400.1303184 MHz
MSW      2M
SSB      EM
LB        0.30 Hz
GB
PC       1.00
    
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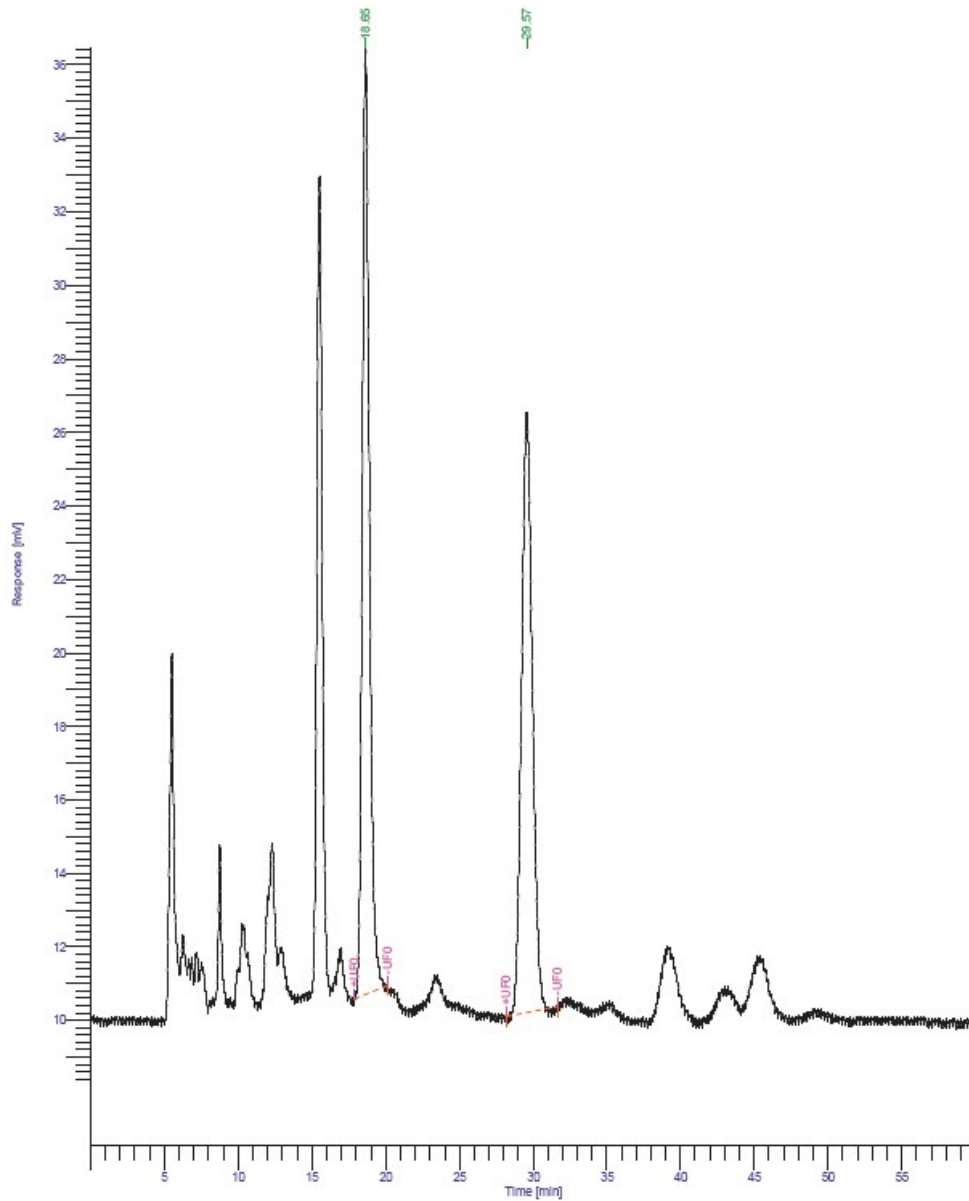


DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		18.649	859178.47	25737.59	50.85	50.85			*MM	0.8592	0.8592
2		29.568	830290.64	16330.19	49.15	49.15			*MM	0.8303	0.8303
			1689469.10	42067.78	100.00	100.00				1.6895	1.6895

Missing Component Report
Component Expected Retention (Calibration File)

All components were found

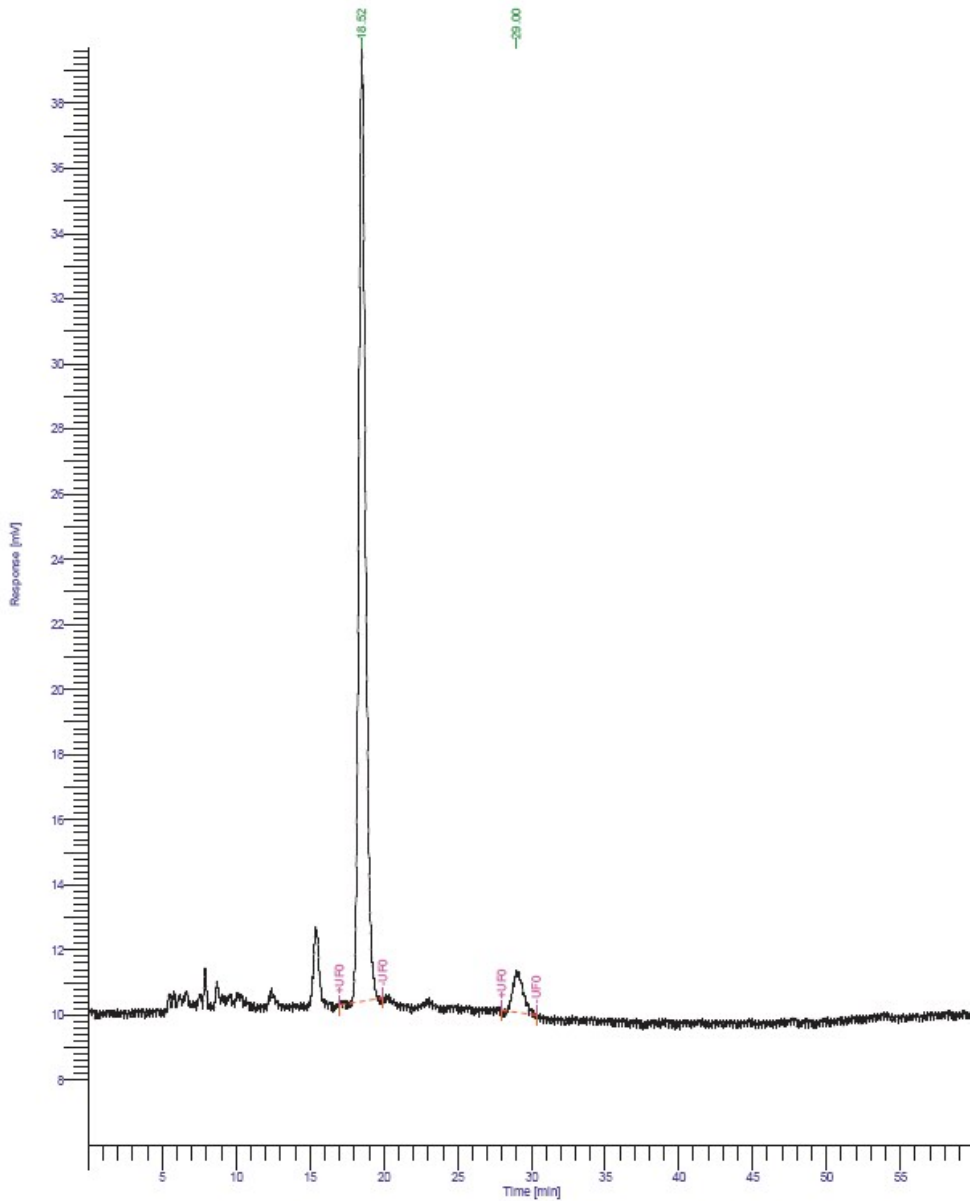


DEFAULT REPORT

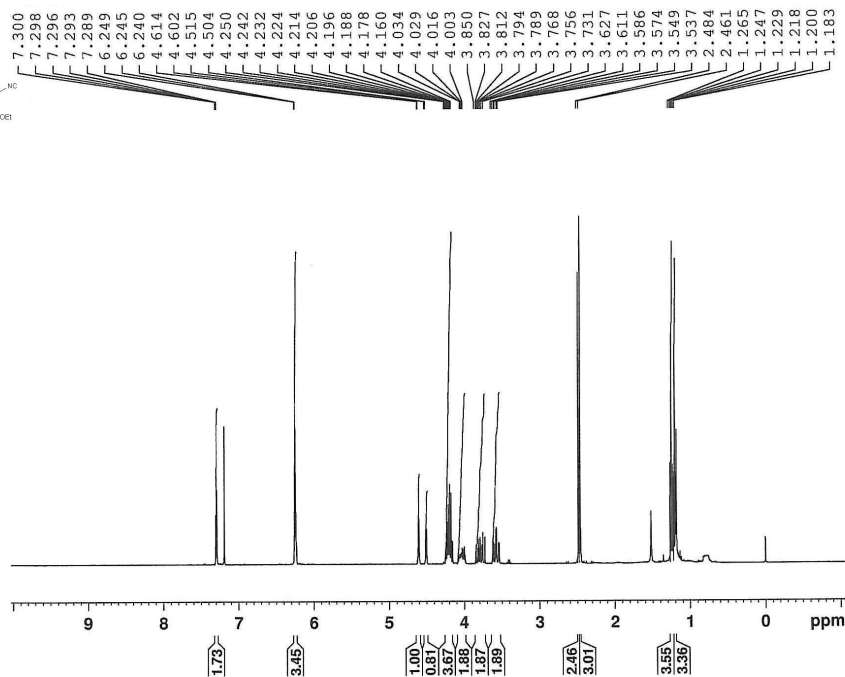
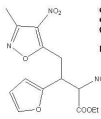
Peak #	Component Name	Time [min]	Area [$\mu\text{V}^2\text{sec}$]	Height [μV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		18.524	938629.53	29258.88	93.93	93.93			*MM	0.9386	0.9386
2		29.003	60691.81	1293.06	6.07	6.07			*MM	0.0607	0.0607
			999321.34	30541.95	100.00	100.00				0.9993	0.9993

Missing Component Report
Component Expected Retention (Calibration File)

All components were found

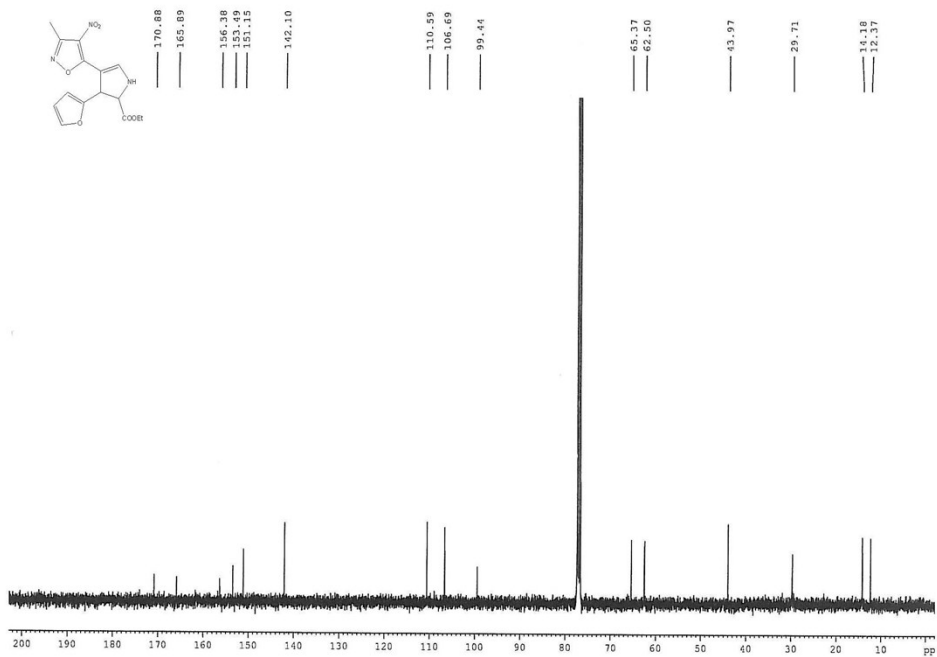


Compound 3f

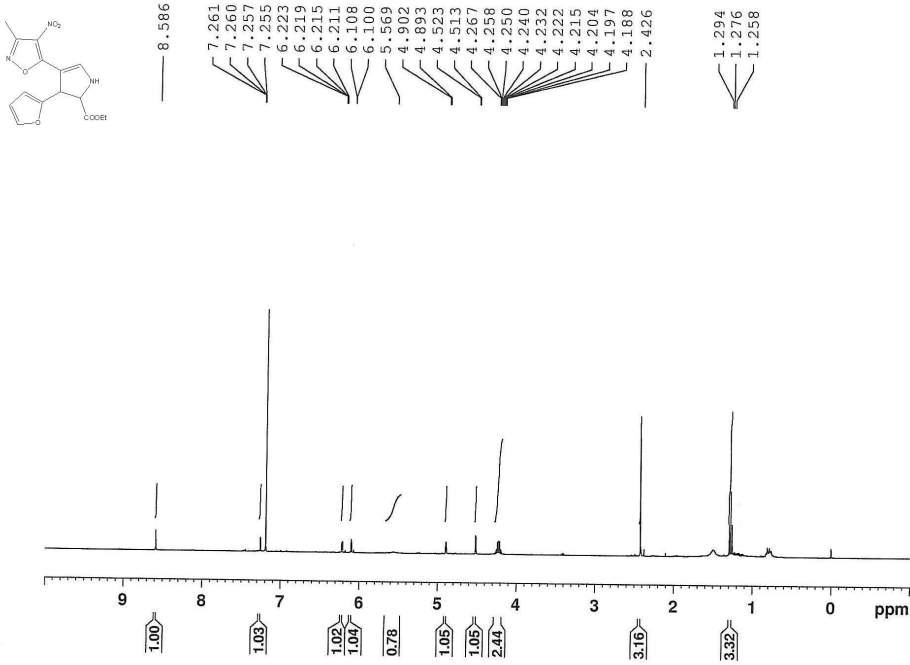


```

Current Data Parameters
NAME: F40-286-11a
EXPNO: 10
PROCNO: 10
F2 - Acquisition Parameters
Date_: 20100908
Time: 17.23
INSTRUM: spect
PROBHD: 5 mm PABBO HS
PULPROG: zg30
TD: 65536
SOLVENT: CDCl3
NS: 16
DS: 4
SWH: 8233.465 Hz
FIDRES: 0.125481 Hz
AQ: 3.3846387 sec
RG: 287
IN: 60.808 usec
PC: 6.00 usec
DT: 234.76 nsec
DQ: 1.00000000 sec
TD0: 1
----- CHANNEL f1 -----
NUC1: 13
P1: 13.12 usec
PL1: -1.00 dB
SFO1: 400.1324711 MHz
F2 - Processing Parameters
SI: 32768
SF: 400.1320314 MHz
WDW: EM
SSB: 0
LB: 0.30 Hz
GB: 0
PC: 1.00
    
```



Compound 4f



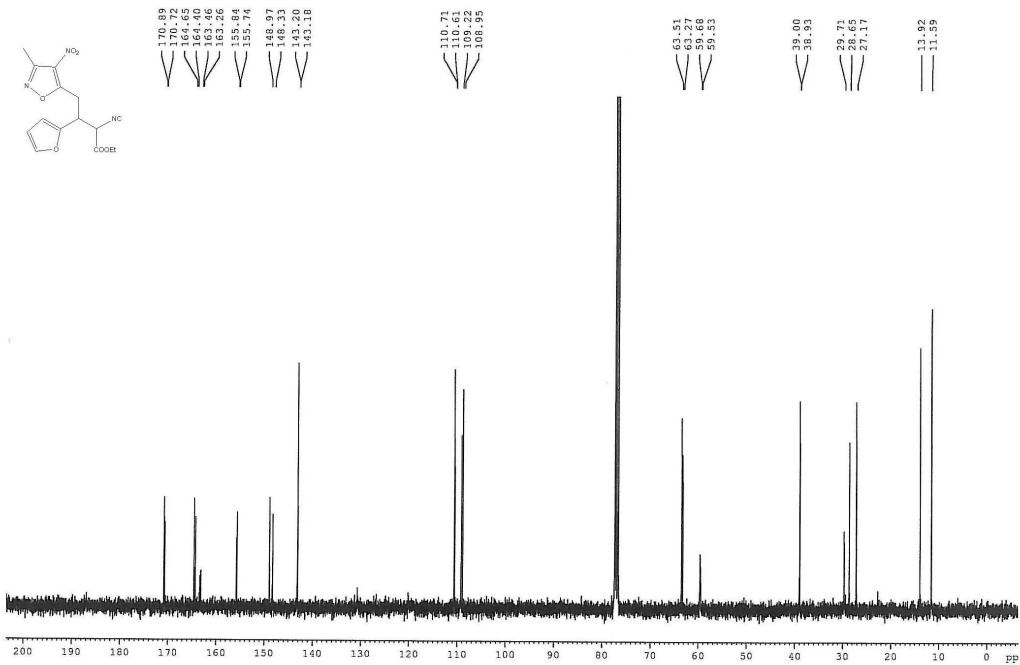
```

Current Data Parameters
NAME      F40-2504a
EXPNO    20
PROCNO   1

F2 - Acquisition Parameters
Date_    20100910
Time     21.58
INSTRUM  spect
PROBHD   5 mm PABBO QNP
PULPROG  zg30
TD        65536
SOLVENT  CDCl3
DS        128
SWH       8233.685 Hz
FIDRES   0.122480 Hz
AQ        1.3846281 sec
RG        641
SFO1     400.1324110 MHz
WDW       EM
SSB       0
GB        0
PC        2.0000000 sec

----- CHANNEL f1 -----
NUC1      13
P1        13.12 usec
PL1       -0.00 dB
SFO1     400.1324110 MHz

F2 - Processing parameters
SI        32768
SF        400.1300365 MHz
WDW       EM
SSB       0
GB        0
PC        2.00
  
```



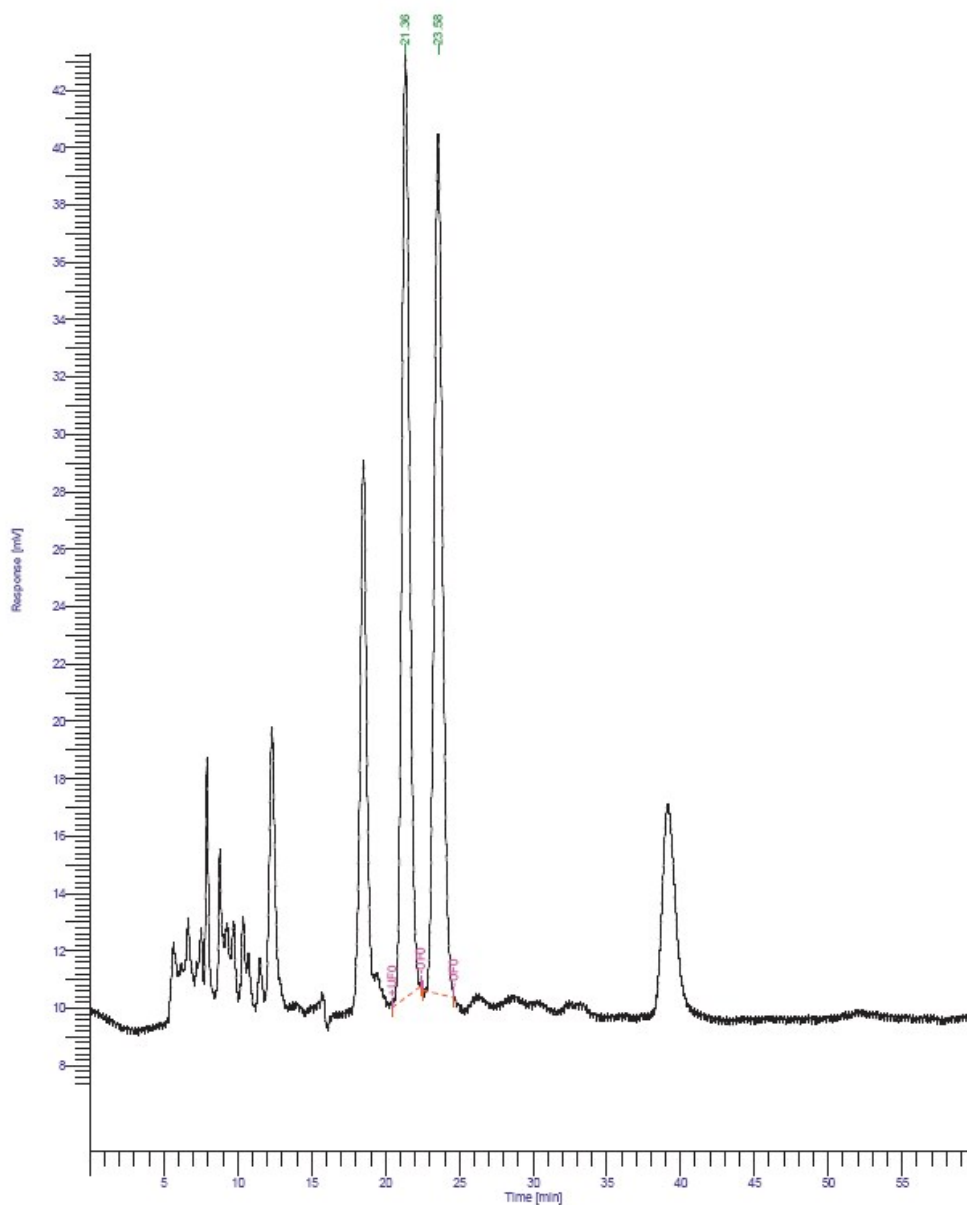
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		21.362	1203330.75	32873.89	50.25	50.25			*MM	1.2033	1.2033
2		23.577	1191576.34	29951.41	49.75	49.75			*MM	1.1916	1.1916
			2394907.09	62825.31	100.00	100.00				2.3949	2.3949

Missing Component Report

Component Expected Retention (Calibration File)

All components were found



Compound 4f

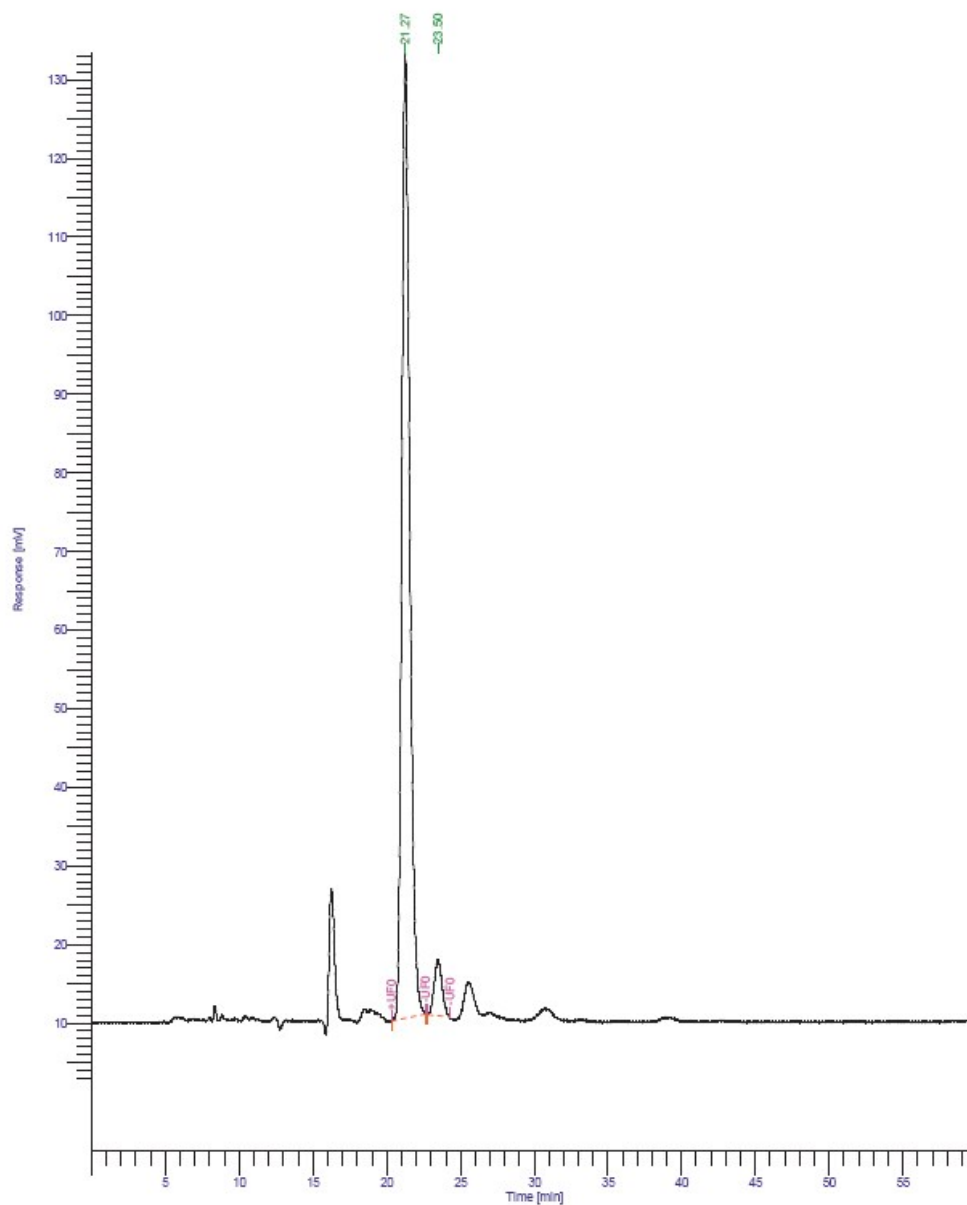
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		21.267	4687933.09	122703.77	94.61	94.61			*MM	4.5879	4.5879
2		23.498	261452.20	7111.11	5.39	5.39			*MM	0.2615	0.2615
			4849385.29	129814.88	100.00	100.00				4.8494	4.8494

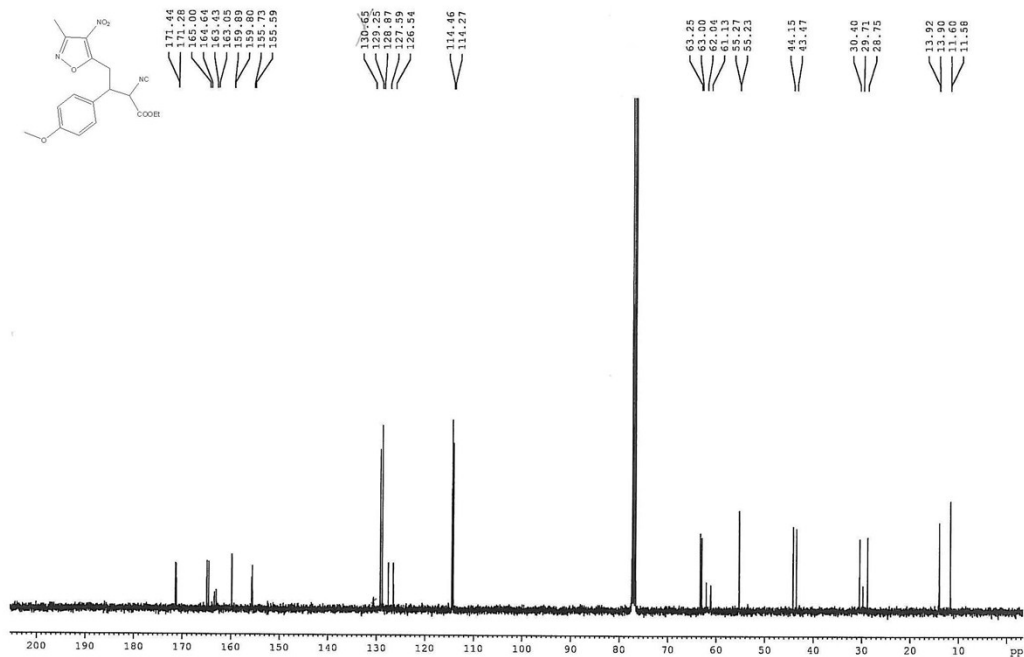
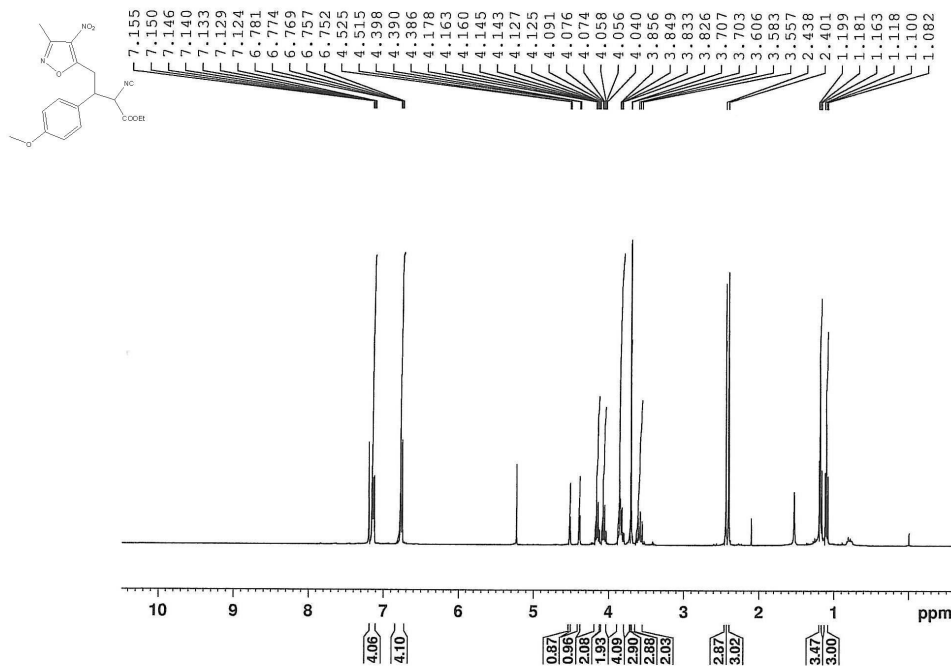
Missing Component Report

Component Expected Retention (Calibration File)

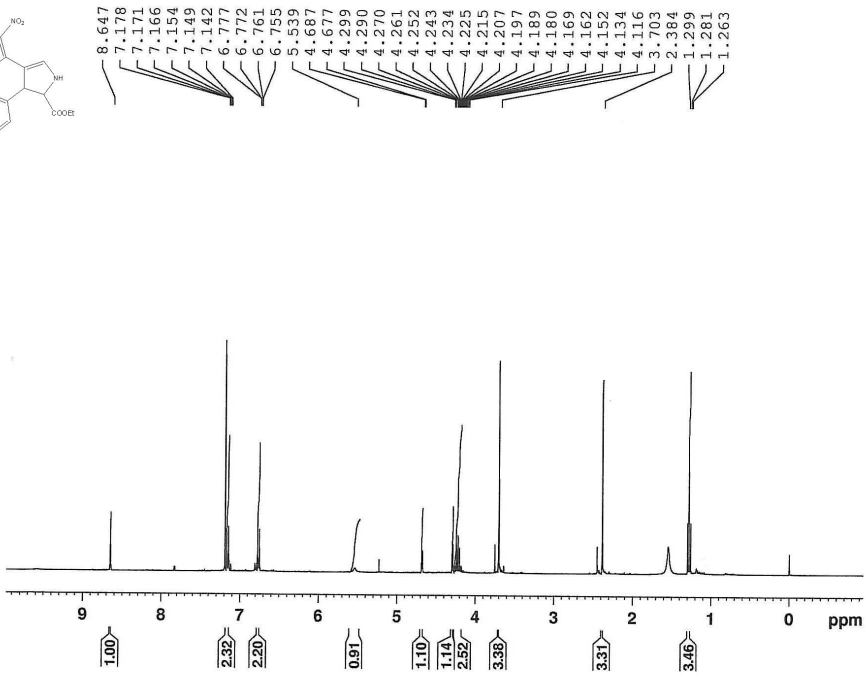
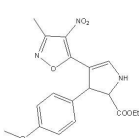
All components were found



Compound 3g



Compound 4g



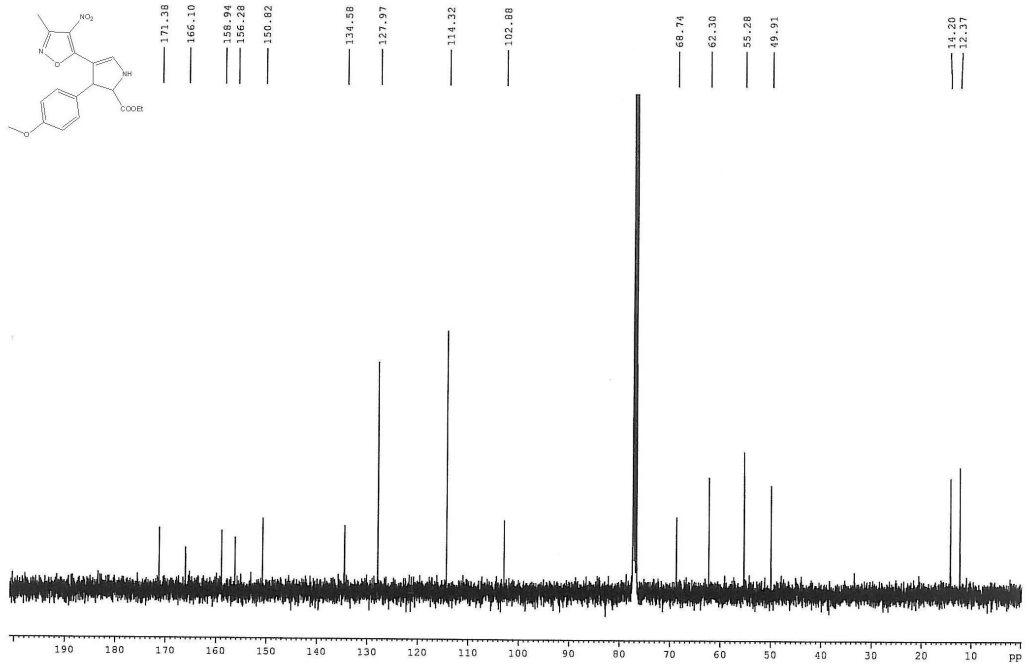
```

Current Data Parameters
NAME      Aug22-2010
EXPNO    10
PROCNO   1

F2 - Acquisition Parameter
Date_    20100822
Time     12.40
INSTRUM  spect
PROBHD   5 mm PABBO BH-
PULPROG  zg30
TE       300.2
SOLVENT  CDCl3
NS       128
DS       0
SWH      8223.685 Hz
FIDRES   0.125483 Hz
AQ       3.9846397 se
RG       512
DM       60.800 um
DE       6.00 um
TE       294.3 K
SI       2.00000000 se
TD0      1

===== CHANNEL f1 =====
NUC1      1H
P1       13.12 us
PL1      -3.00 dB
SFO1     400.1324710 MHz

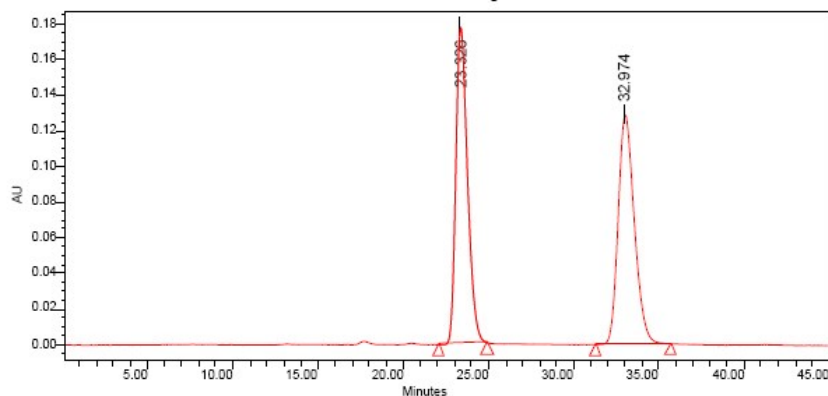
F2 - Processing parameters
SI       32768
SF       400.1300002 MHz
WDW      EM
SSB      0
LB       0.30 Hz
GB       0
PC       1.00
  
```



SAMPLE INFORMATION

Sample Name: PAO-216-high	Acquired By: System	Date Acquired: 6/21/10 12:35:40 PM
Sample Type: Unknown	Acq. Method Set: Chiralmiscela	Date Processed: 6/21/10 1:47:49 PM
Vial: 1	Processing Method: HPLC	Channel Name: PDA Single 421.0 nm
Injection #: 1	Proc. Chnl. Descr.: PDA 254.0 nm	
Injection Volume: 10.00 ul		
Run Time: 45.0 Minutes		
Sample Set Name:		

Auto-Scaled Chromatogram



Unknown Peak Results

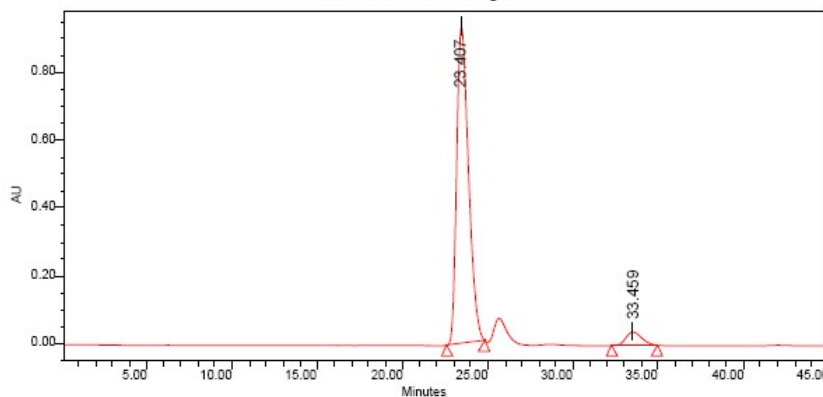
Peak Type	RT	Area	% Area	Height
1 Unknown	23.326	8432062	49.80	177506
2 Unknown	32.974	8480219	50.20	128609

Compound 4g

SAMPLE INFORMATION

Sample Name: PAO-239-2	Acquired By: System	Date Acquired: 6/21/10 11:48:37 AM
Sample Type: Unknown	Acq. Method Set: Chiralmiscela	Date Processed: 6/21/10 1:52:35 PM
Vial: 3	Processing Method: HPLC	Channel Name: PDA Single 421.0 nm
Injection #: 1	Proc. Chnl. Descr.: PDA 254.0 nm	
Injection Volume: 10.00 ul		
Run Time: 45.0 Minutes		
Sample Set Name: PPDD		

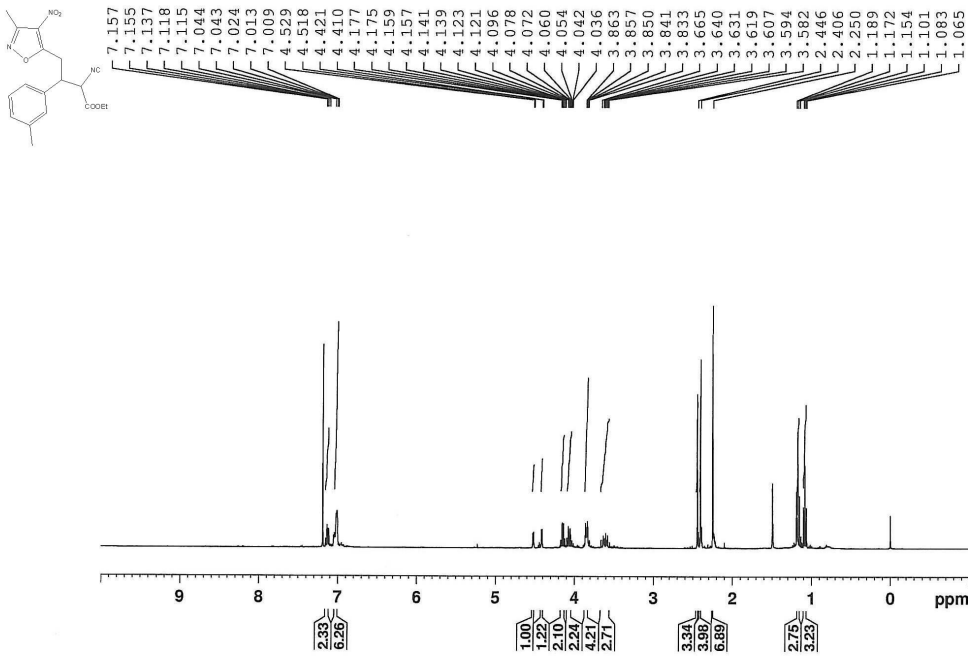
Auto-Scaled Chromatogram



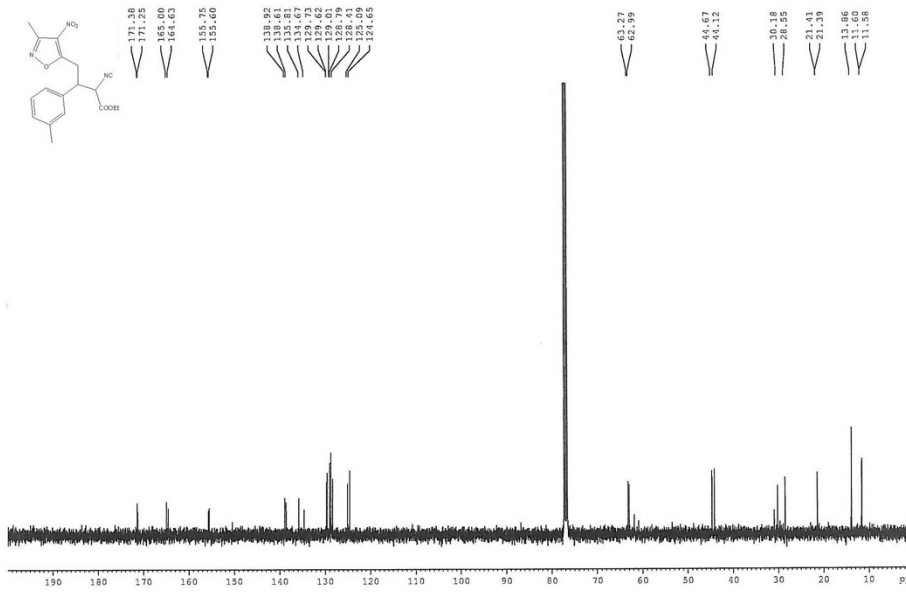
Unknown Peak Results

Peak Type	RT	Area	% Area	Height
1 Unknown	23.407	45178895	94.57	931115
2 Unknown	33.459	2592919	5.43	39981

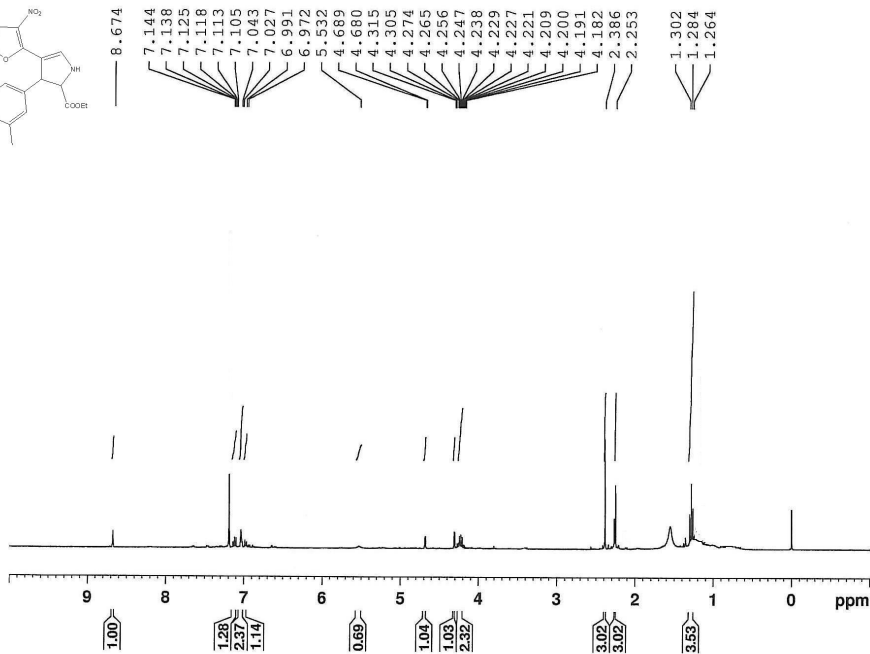
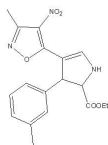
Compound 3h



Current Data Parameters
 NAME P00-218
 EXPNO 1
 PROCNO 1
 F2 - Acquisition Parameters
 Date_ 20100921
 Time 10.29
 INSTRUM spect
 PROBHD 5 mm PABBO BB-
 PULPROG zgpg
 TD 65536
 SOLVENT DMSO-d6
 NS 16
 DS 2
 SWH 8223.645 Hz
 FIDRES 0.133463 Hz
 AQ 3.9946187 sec
 RG 625
 IN 60.000000 sec
 DE 6.000000 sec
 TE 294.2 K
 D1 1.00000000 sec
 TDS 1
 ===== CHANNEL f1 =====
 NUC1 13
 P1 13.12 usec
 PL1 -3.00 dB
 SFO1 400.130470 MHz
 F2 - Processing parameters
 SI 32768
 SF 400.130355 MHz
 SWH 8223.645
 FSN 0
 LB 0.30 Hz
 GB 0
 CB 1.00



Compound 4h



```

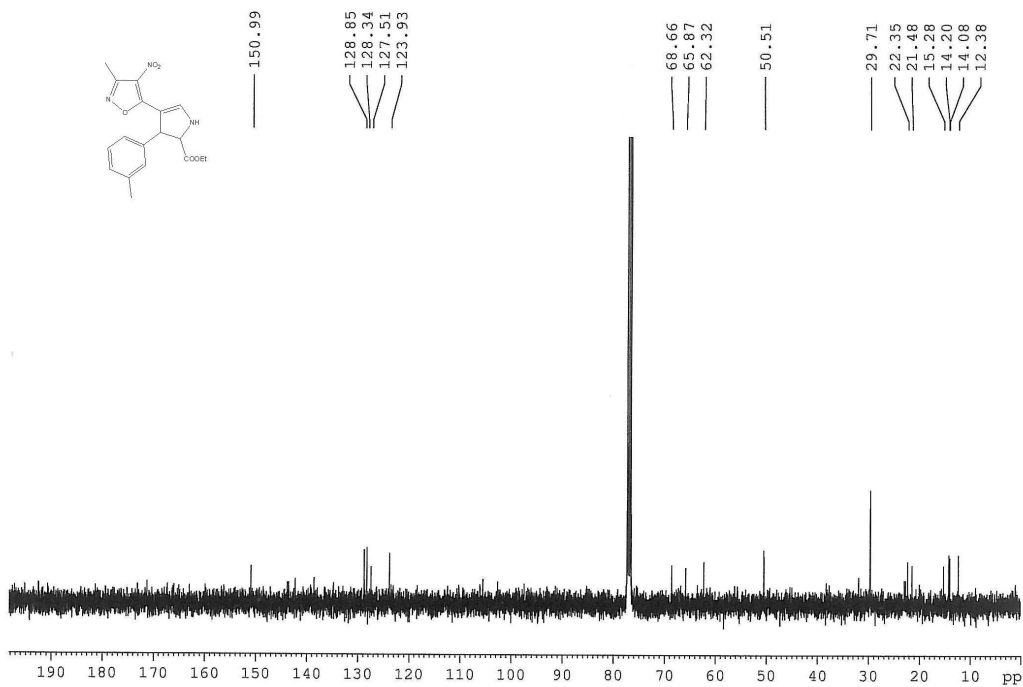
Current Data Parameters
NAME: 800-07041
EXPNO: 10
PROCNO: 1

F2 - Acquisition Parameters
Date_: 20100908
Time: 17:32
INSTRUM: spect
PROBHD: 5 mm PABBO BH-
PULPROG: zgpg30
TD: 65536
SOLVENT: CDCl3
NS: 14
DS: 2
SWH: 8023.685 Hz
FIDRES: 0.12583 Hz
AQ: 5.984637 sec
RG: 456
DSB: 40.800 usec
DE: 6.00 usec
TE: 294.9 K
D1: 1.00000000 sec
TD0: 1

----- CHANNEL f1 -----
NUC1: 13
P1: 12.00 usec
PL1: -3.00 dB
SFO1: 400.132410 MHz

F2 - Processing parameters
SI: 32768
SF: 400.130385 MHz
WDW: EM
SSB: 0
LB: 0.30 Hz
GB: 0
CB: 1.00

```



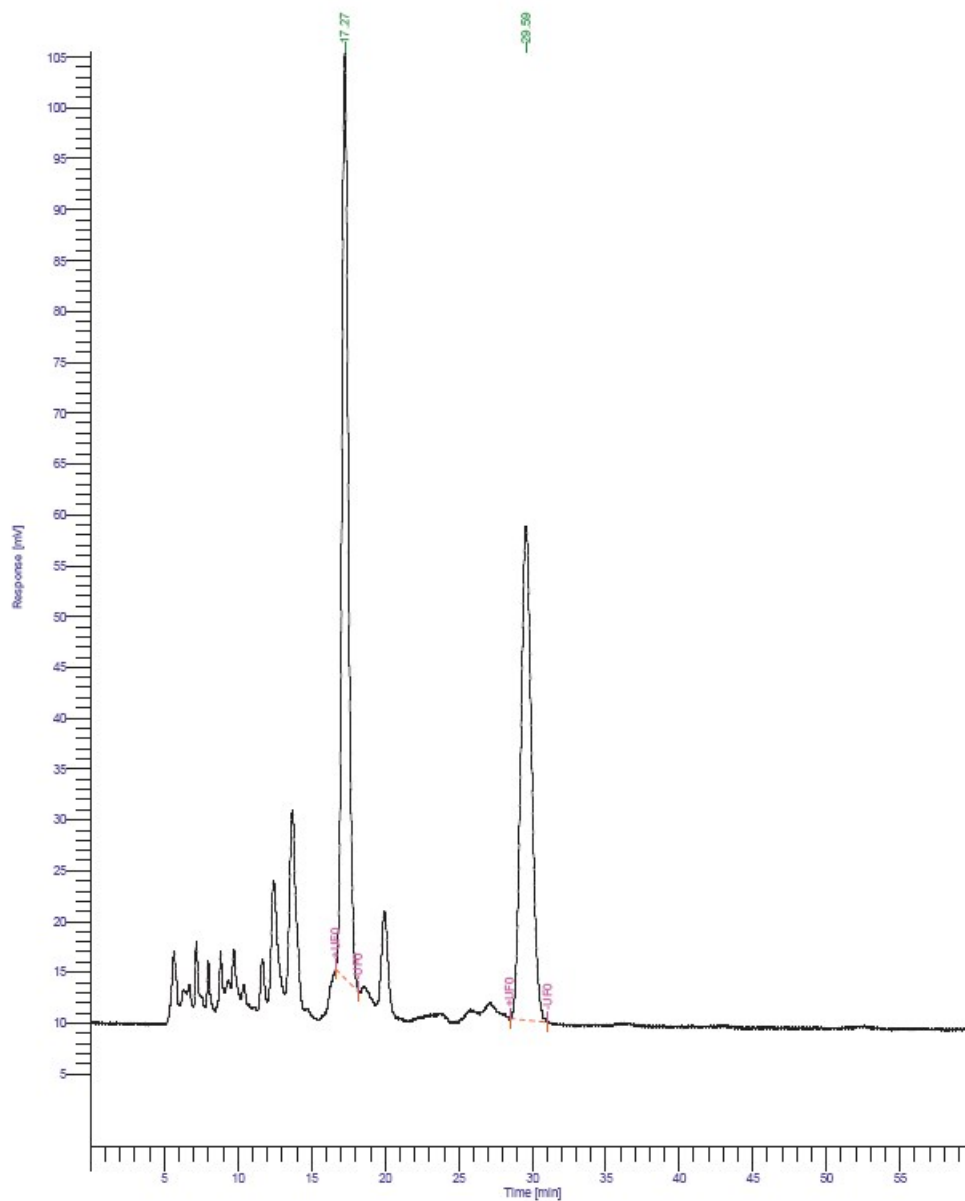
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		17.270	2752821.05	91034.11	52.80	52.80			*MM	2.7528	2.7528
2		29.590	2480912.88	48624.82	47.20	47.20			*MM	2.4809	2.4809
			5213733.93	139658.93	100.00	100.00				5.2137	5.2137

Missing Component Report

Component Expected Retention (Calibration File)

All components were found



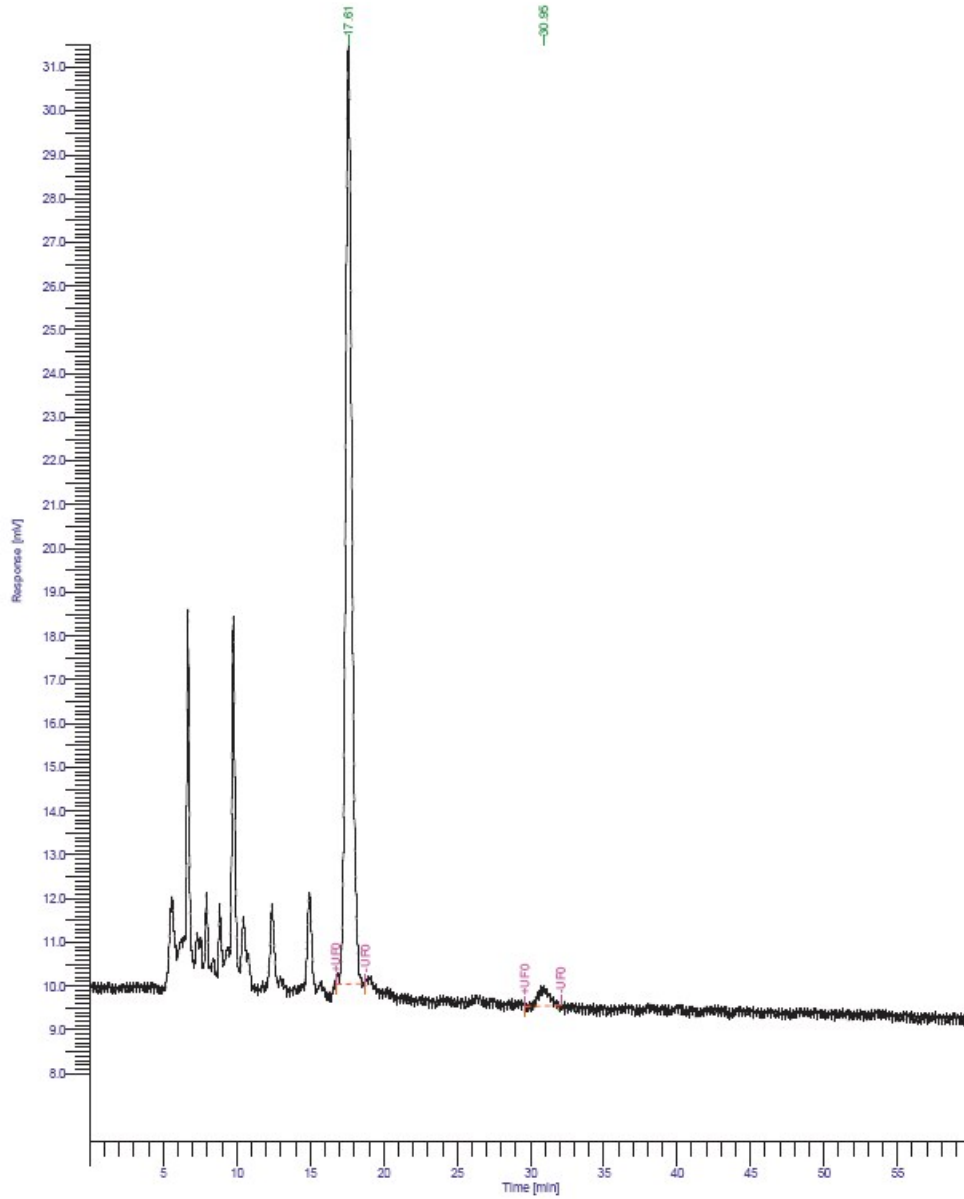
Compound 4h

DEFAULT REPORT

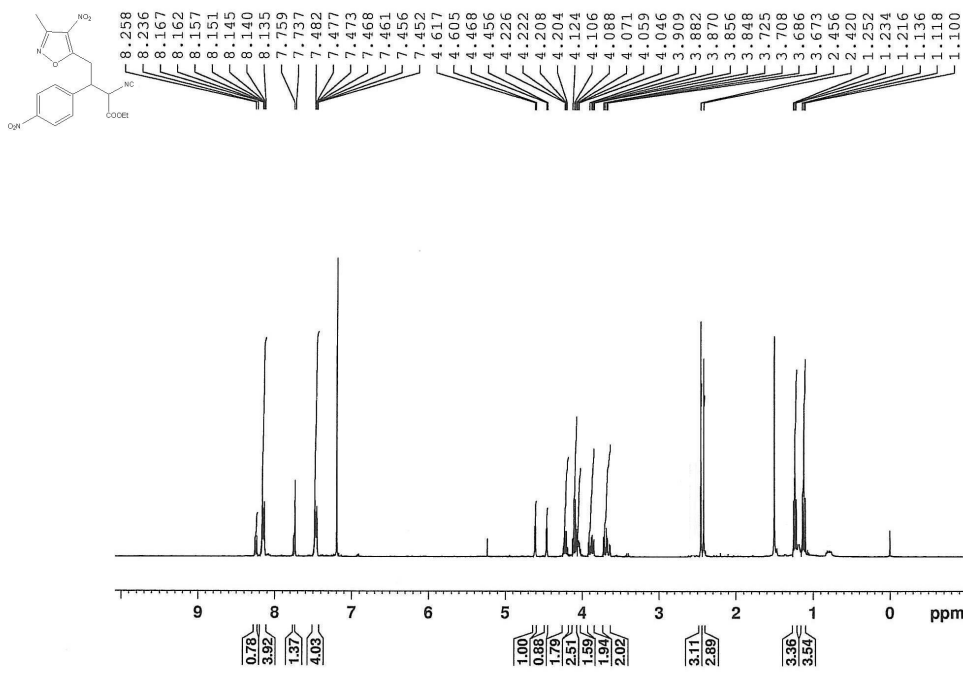
Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		17.815	649869.84	21453.19	96.79	96.79			*MM	0.6499	0.6499
2		30.947	21519.22	457.76	3.21	3.21			*MM	0.0215	0.0215
			671389.06	21910.95	100.00	100.00				0.6714	0.6714

Missing Component Report
Component Expected Retention (Calibration File)

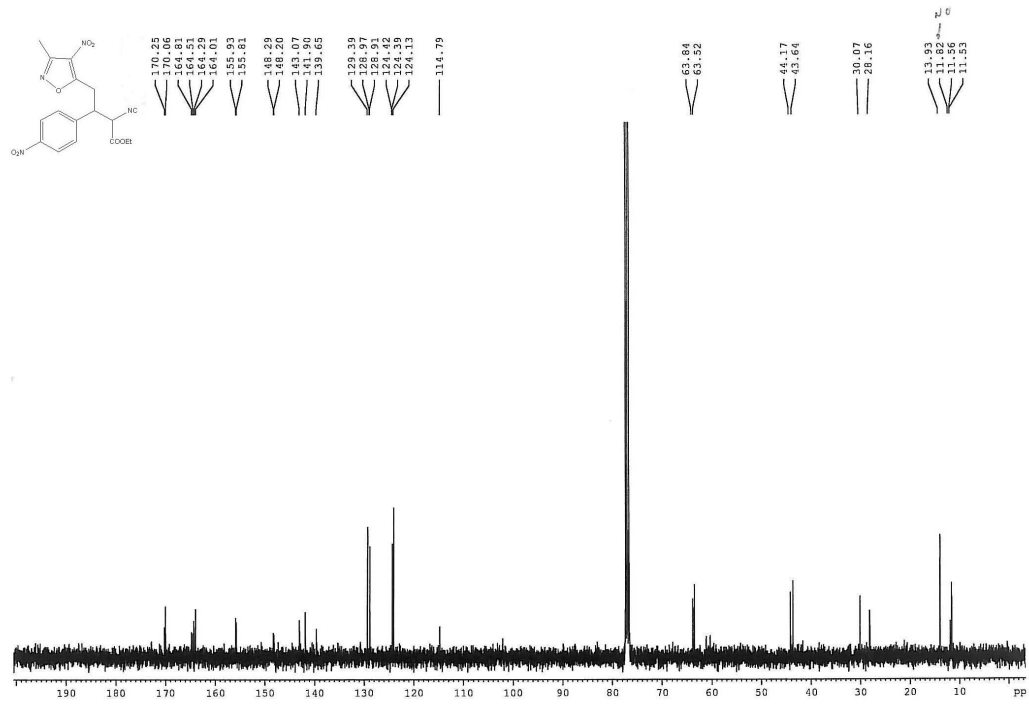
All components were found



Compound 3i

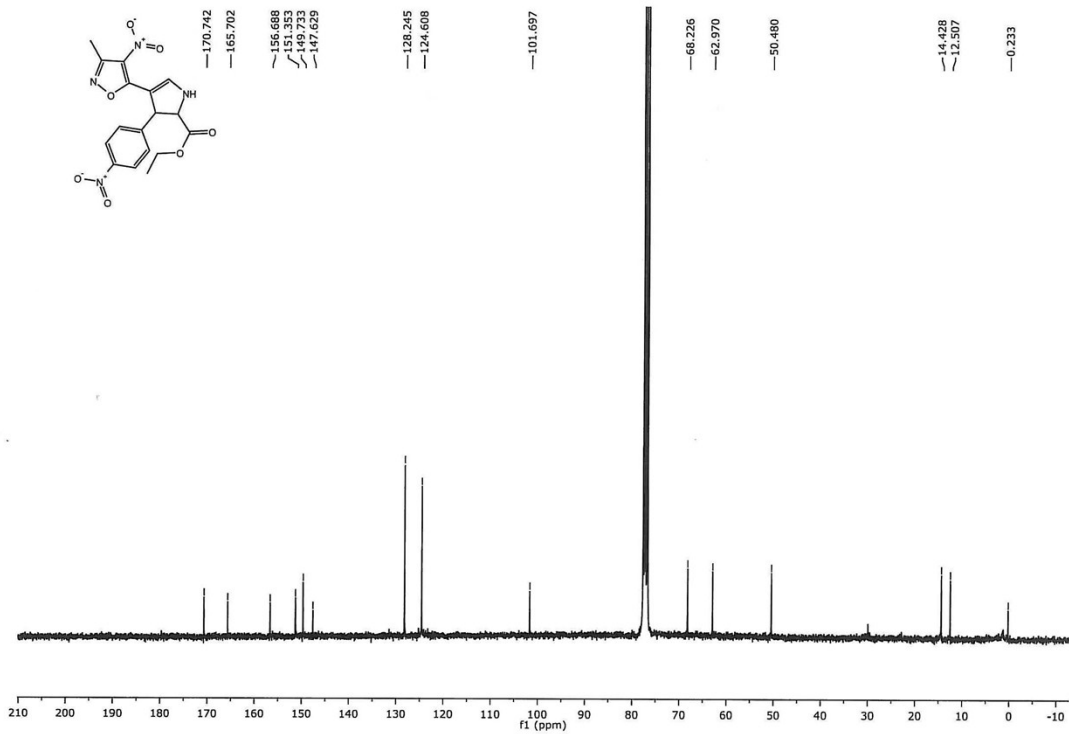
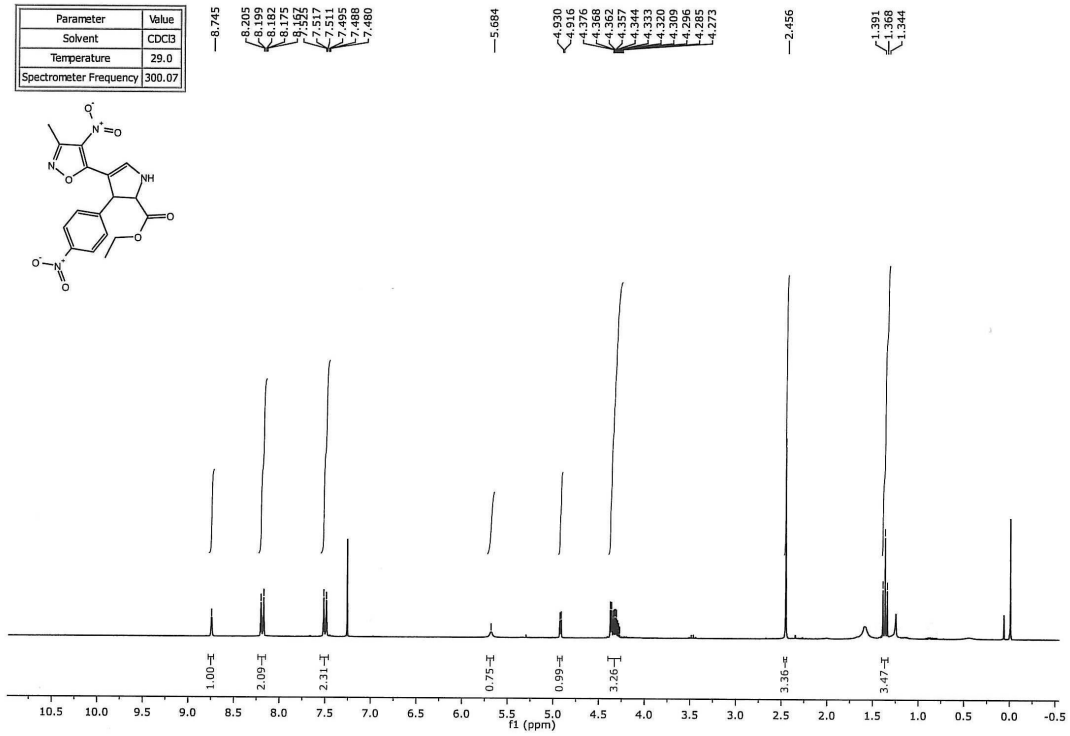


Current Data Parameters
 NAME Aug23-2010
 EXPNO 11
 PROCNO 1
 F2 - Acquisition Parameters
 Date_ 20100926
 Time 4.15
 INSTRUM spect
 PULPROG zgpg30
 PCPRGMR 5 mm PABBO v0
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 128
 DS 4
 SWH 8233.800 Hz
 FIDRES 0.120483 Hz
 AQ 3.9846187 sec
 RG 512
 IN 60.800 usec
 DE 6.00 usec
 TE 295.1 K
 D1 2.00000000 sec
 D2 1
 D3 1
 ----- CHANNEL f1 -----
 NUC1 13
 P1 13.12 usec
 PL1 -3.00 dB
 SFO1 400.124710 MHz
 F2 - Processing parameters
 SI 32768
 SF 400.1305360 MHz
 WF 10
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00



Compound 4i

Parameter	Value
Solvent	CDCl ₃
Temperature	29.0
Spectrometer Frequency	300.07

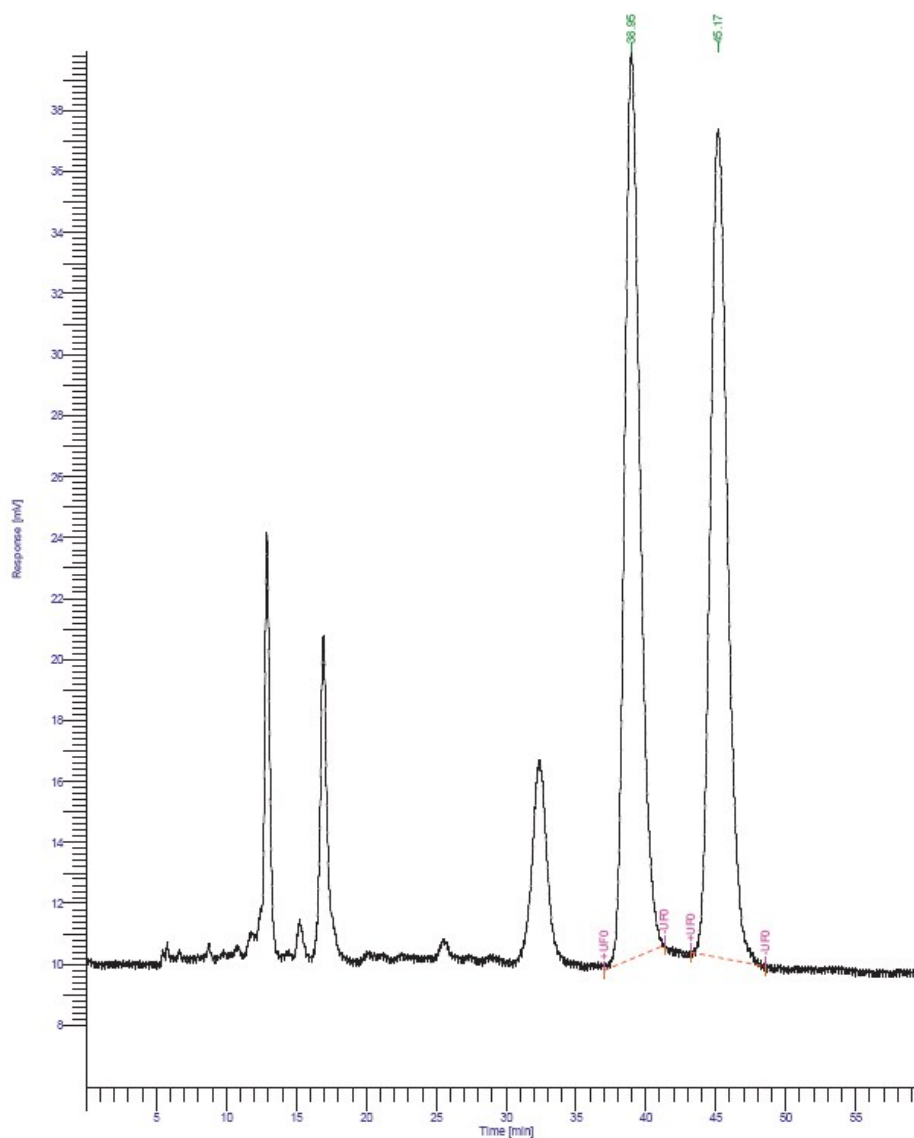


DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		38.955	2298795.81	29737.88	49.79	49.79			*MM	2.2988	2.2988
2		45.166	2318266.75	27173.20	50.21	50.21			*MM	2.3183	2.3183
			4617062.56	56910.89	100.00	100.00				4.6171	4.6171

Missing Component Report
Component Expected Retention (Calibration File)

All components were found



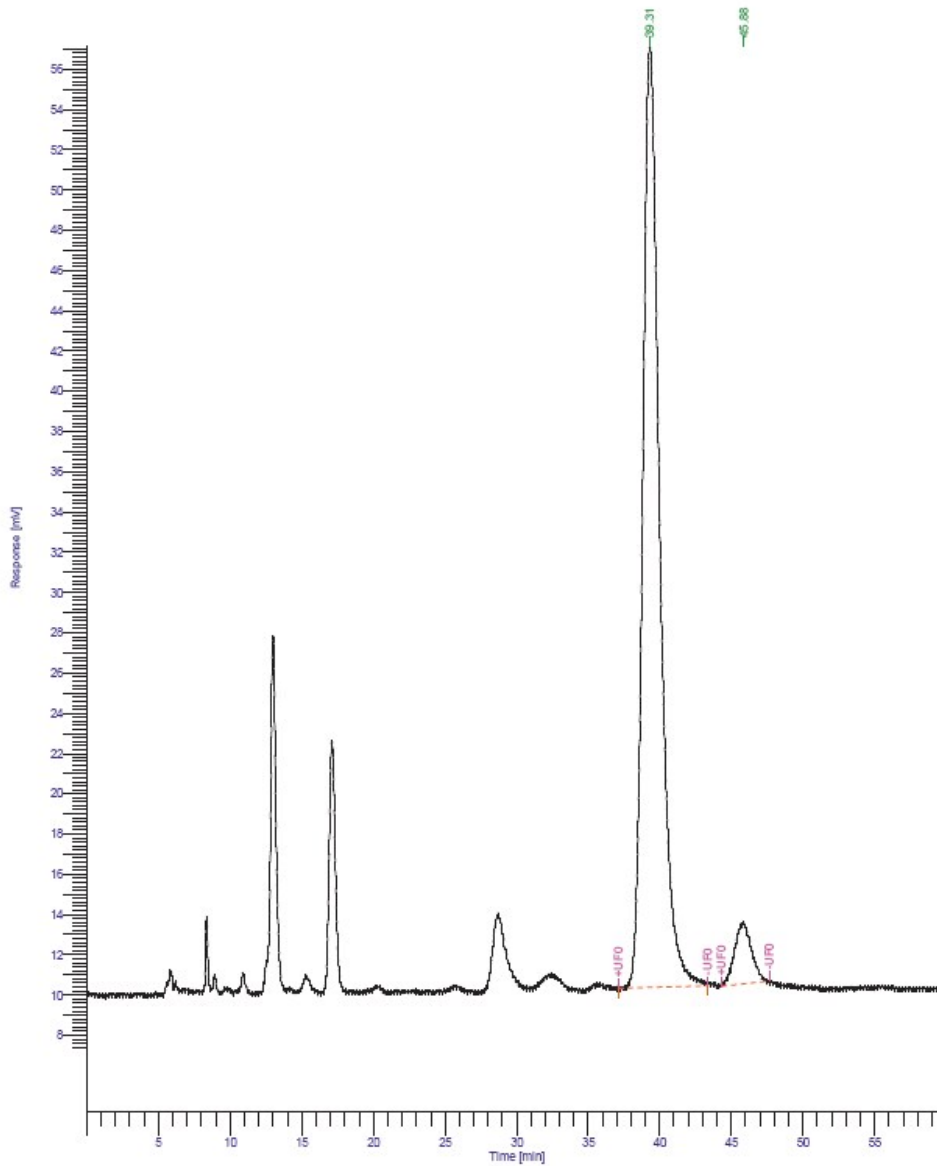
Compound 4i

DEFAULT REPORT

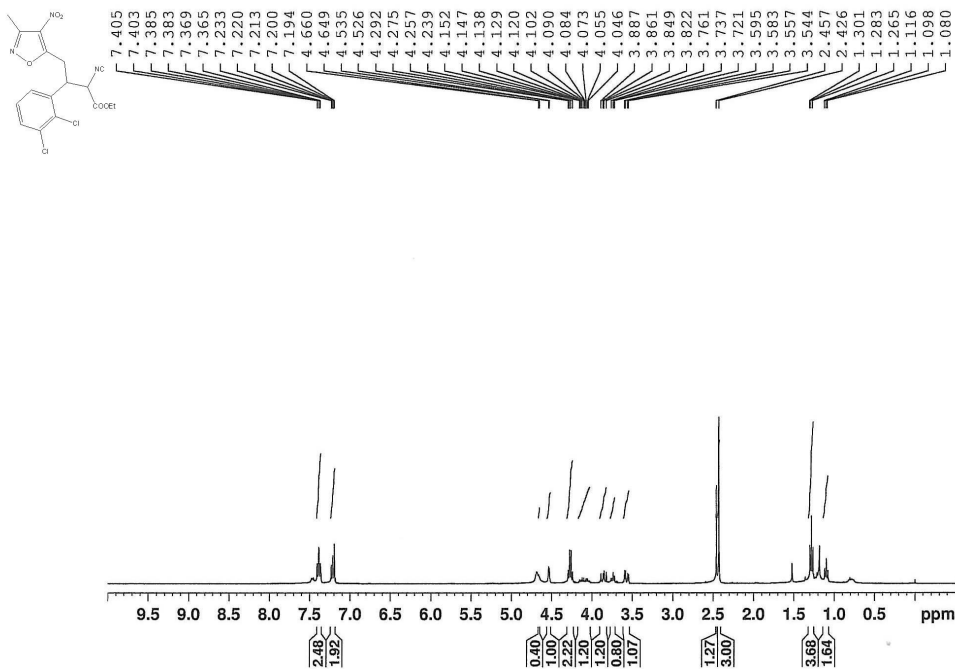
Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		39.314	3818233.72	46749.54	93.89	93.89			*MM	3.8182	3.8182
2		45.877	248593.85	3066.21	6.11	6.11			*MM	0.2486	0.2486
			4086827.57	49815.75	100.00	100.00				4.0668	4.0668

Missing Component Report
Component Expected Retention (Calibration File)

All components were found

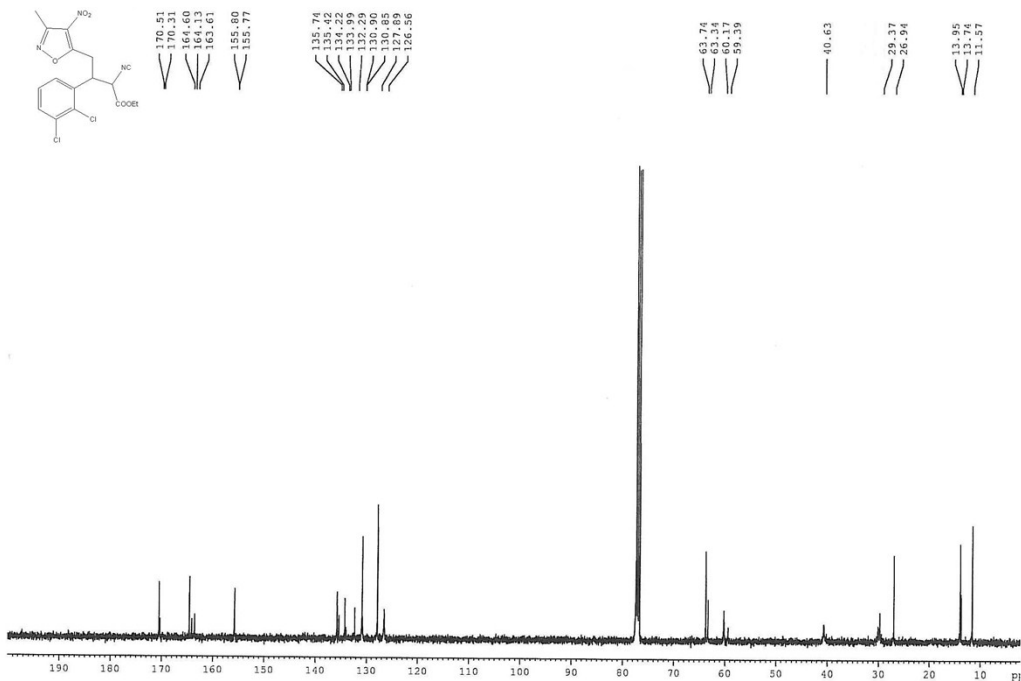


Compound 3j

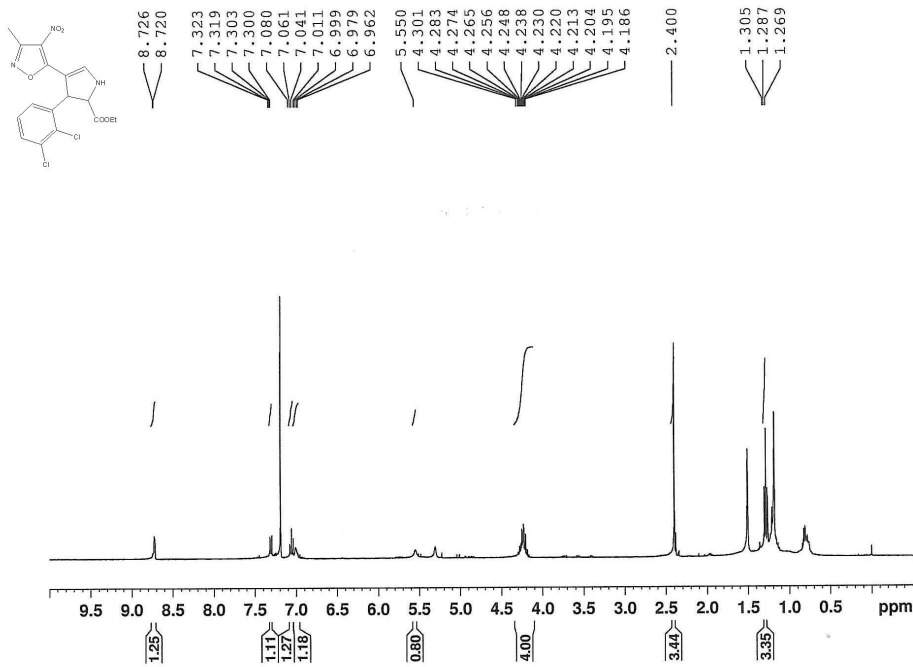


Current Data Parameters
 NAME P50-337
 EXPNO 1
 PROCNO 1
 F2 - Acquisition Parameters
 Date_ 20161016
 Time 21.15
 INSTRUM spect
 PULPROG 5 mm WALTZ16
 TD 65536
 SOLVENT CDCl3
 NS 16
 DS 4
 FWHZ 8221.660 Hz
 AQ 0.115483 Hz
 GC 3.884628 sec
 RG 256
 RW 60.820 sec
 SM 0.00 sec
 TE 295.2 K
 SI 1.0000000 sec
 LDO

===== CHANNEL f1 =====
 NUC1 13C
 P1 19.12 usec
 PL1 -1.00 dB
 PR1 456.1324110 MHz
 F2 - Processing parameters
 SI 12768
 SF 456.1302110 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00



Compound 4j



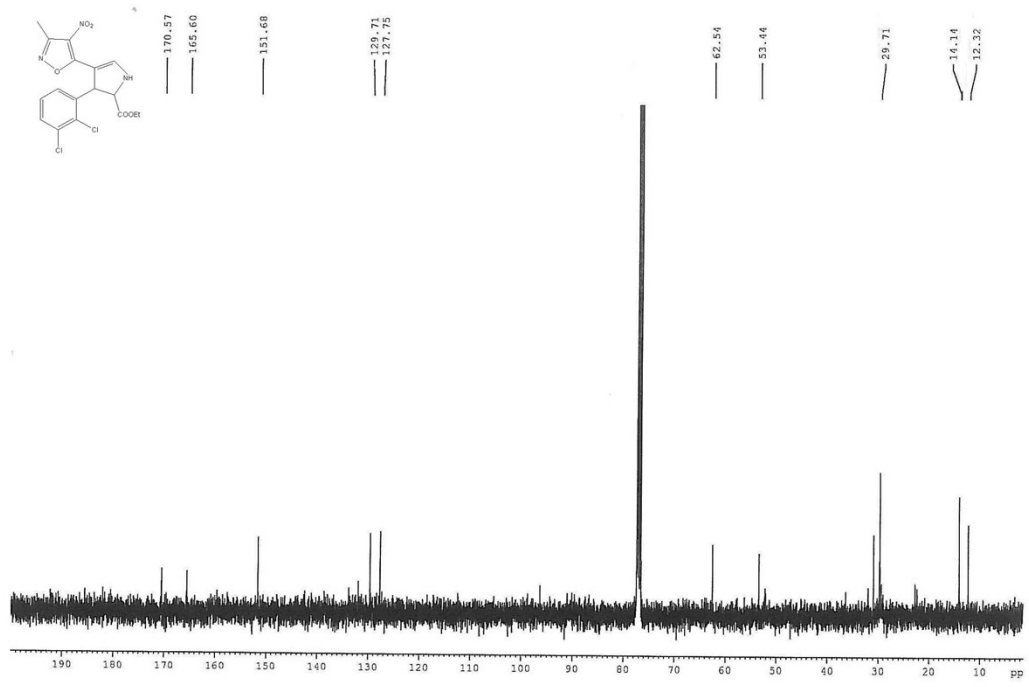
```

Current Data Parameters
NAME      PAO-3376a
EXPNO    1
PROCNO   1

F2 - Acquisition Parameters
Date_    20101018
Time     9.19
INSTRUM  spect
PROBHD   5 mm HARP003
PULPROG  zg30
TD        65536
SOLVENT  CDCl3
SI        16
DS        4
SHE       9223.680 Hz
FIDRES   0.123493 Hz
AQ        3.8466371 sec
RG         511
SFO        400.130365 MHz
RG         60.800 usec
DE         6.00 usec
TE        295.2 K
SI        1.00000000 sec
TD         1

===== CHANNEL f1 =====
NUC1      13
P1        13.12 usec
PL        -2.00 dB
SFO1     400.130365 MHz

F2 - Processing parameters
SI        32768
SF        400.130365 MHz
WDW       EM
SSB       0
LB        0.30 Hz
GB        0
PC        1.00
    
```

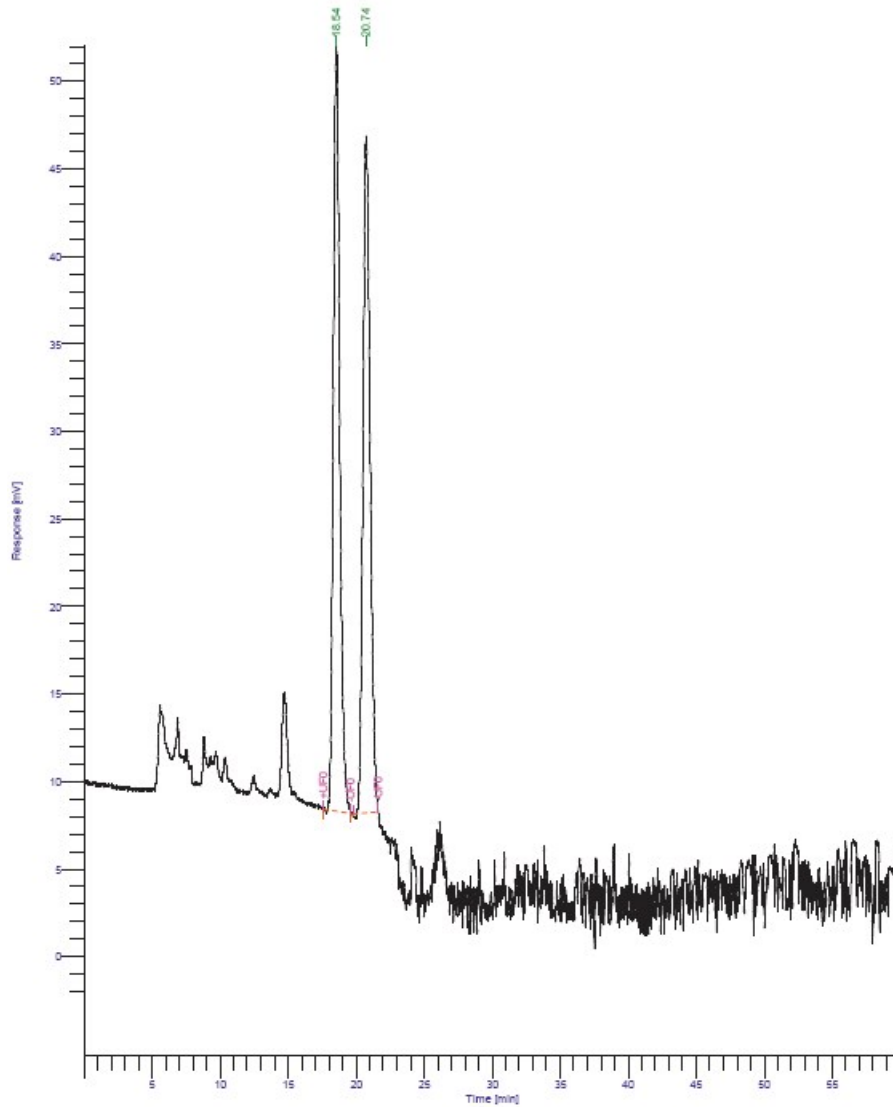


DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		18.539	1430627.11	43764.08	50.59	50.59			*MM	1.4306	1.4306
2		20.739	1397103.17	38675.48	49.41	49.41			*MM	1.3971	1.3971
			2827730.27	82439.56	100.00	100.00				2.8277	2.8277

Missing Component Report
Component Expected Retention (Calibration File)

All components were found



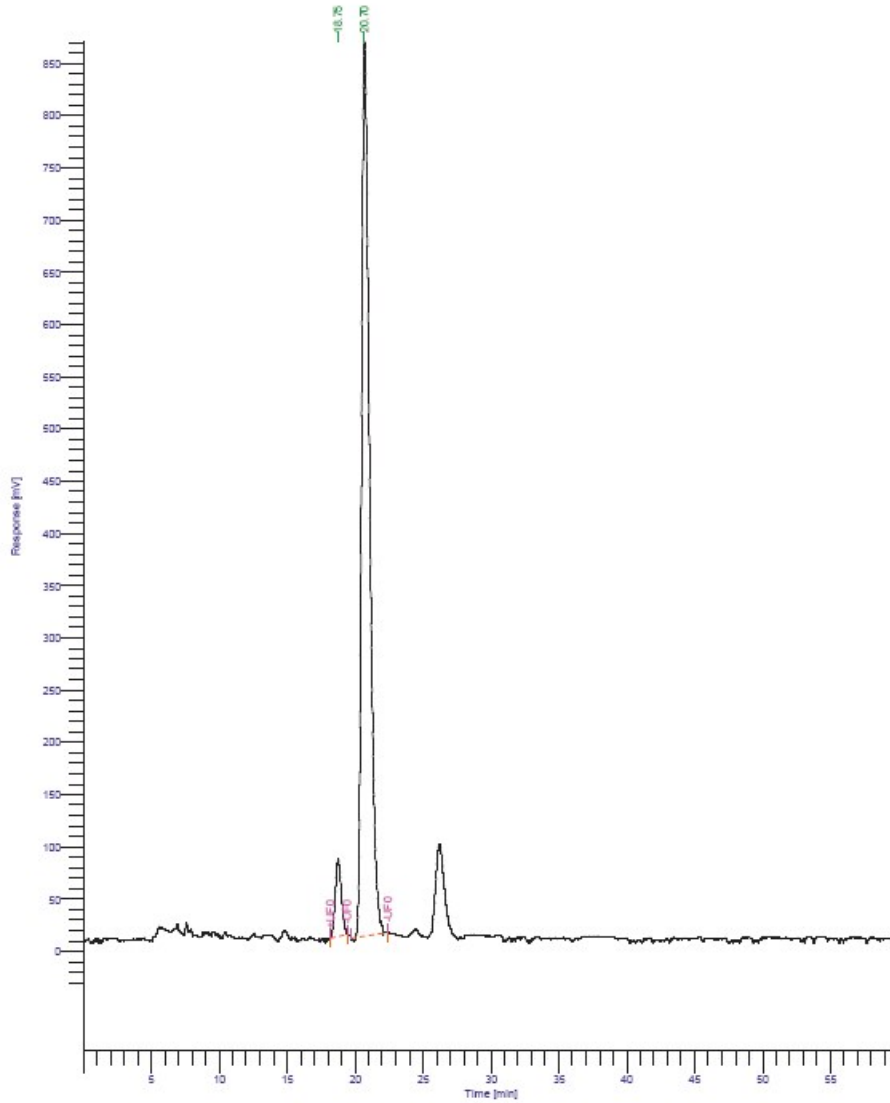
Compound 4j

DEFAULT REPORT

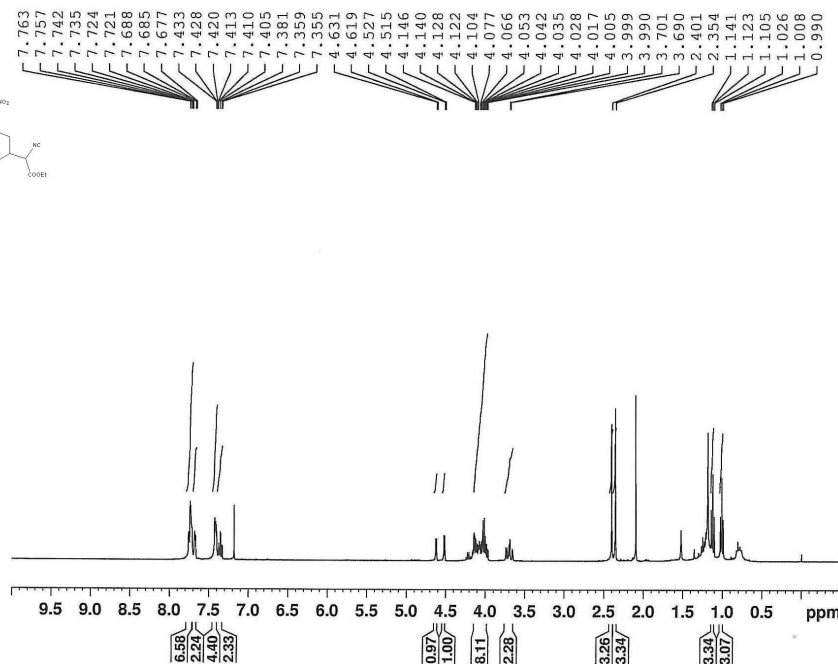
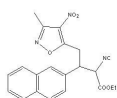
Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		18.751	2301634.58	74000.52	6.22	6.22			*MM	2.3016	2.3016
2		20.702	34872464.36	856521.29	93.78	93.78			*MM	34.8725	34.8725
			36974098.94	930521.80	100.00	100.00				36.9741	36.9741

Missing Component Report
Component Expected Retention (Calibration File)

All components were found



Compound 3k



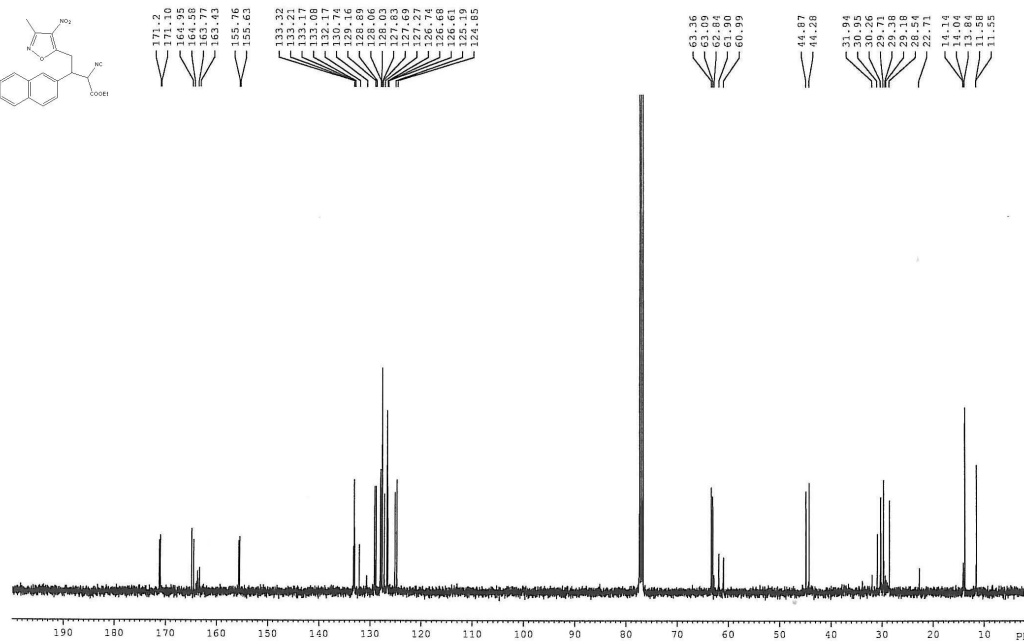
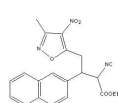
```

===== Data Parameters =====
NAME      P40-333
EXPNO    1
PROCNO   1

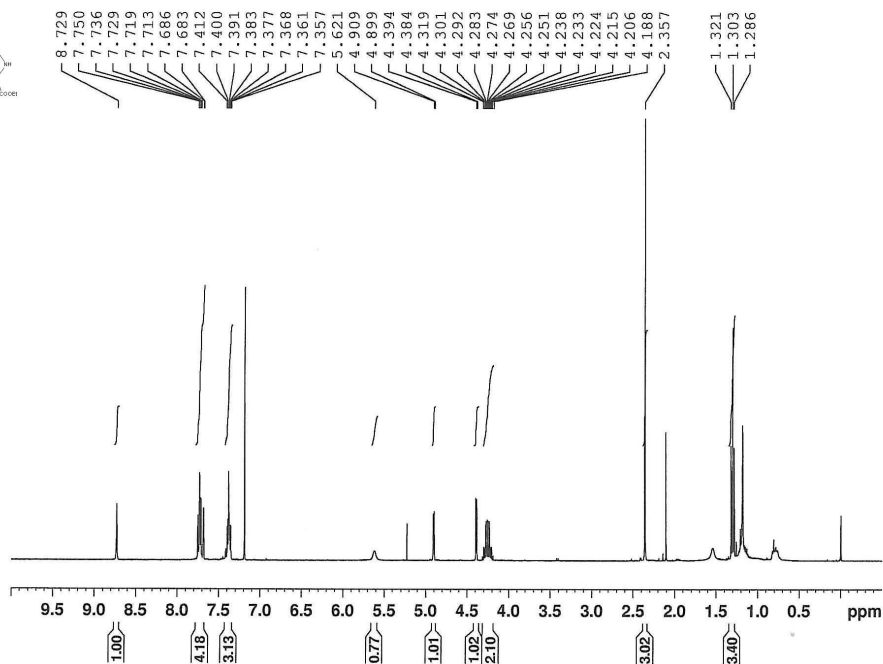
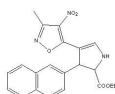
===== Acquisition Parameters =====
DATE_    20101016
TIME     20.06
INSTRUM  spect
PROBHD   5 mm PABBO BB
PULPROG  zgpg30
TD        65536
SOLVENT  CDCl3
NS        16
DS        4
SWH       8223.668 Hz
FIDRES    0.129493 Hz
AQ         3.2846817 sec
RG         328
WDW        EM
SSB        0
LB         60.800 Hz
GB         0
TE         295.2 K
DQ         1.00000000 sec
TD0

===== CHANNEL f1 =====
NUC1      1H
P1         13.12 usec
PL1       -1.90 dB
SFO1      400.1324110 MHz

===== Processing parameters =====
SI         32768
SF         400.1300199 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
TE         1.00
  
```

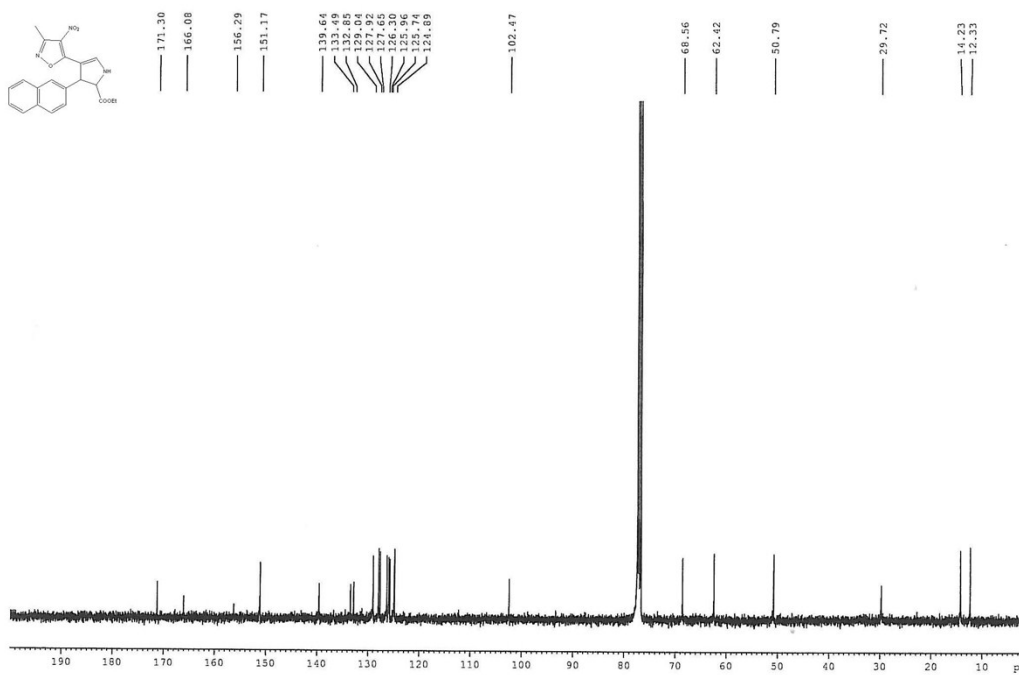


Compound 4k



```

Current Data Parameters
NAME:  P40-3331a2
EXPNO:  1
PROCNO:  1
F2 - Acquisition Parameters
Date_   :  20101002
Time    :  17.25
INSTRUM :  spect
PROBHD  :  5 mm PABBO BBO
PULPROG :  zgpg30
SOLVENT :  CDCl3
NS      :  654
DS      :  4
SWH     :  8231.683 Hz
FIDRES  :  0.125883 Hz
AQ      :  3.1864287 sec
RG      :  600
EM      :  6.00
DE      :  0.300 sec
TE      :  300.2 K
SI      :  1.00000000 sec
TD      :  1
===== CHANNEL f1 =====
NUC1    :  13C
P1      :  13.00 usec
PL1     :  0.00 dB
SFO1    :  400.1324710 MHz
F2 - Processing parameters
SI      :  32768
SF      :  400.1300377 MHz
WDW     :  EM
SSB     :  0
LB      :  0.30 Hz
GB      :  0
PC      :  1.00
    
```

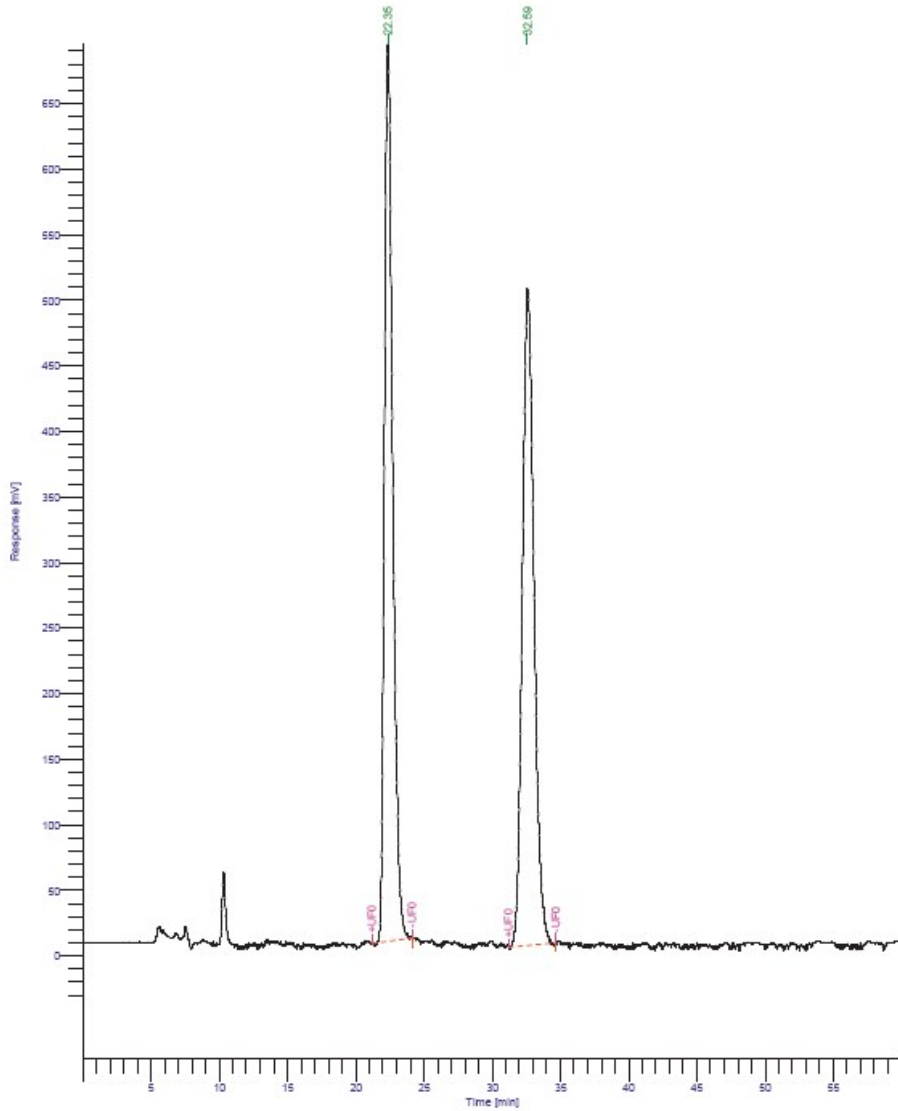


DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [$\mu\text{V}\cdot\text{sec}$]	Height [μV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		22.352	29048951.17	684614.50	49.48	49.48			*MM	29.0490	29.0490
2		32.589	29664832.13	500481.09	50.52	50.52			*MM	29.6648	29.6648
			58713783.30	1.19e+06	100.00	100.00				58.7138	58.7138

Missing Component Report
 Component Expected Retention (Calibration File)

All components were found



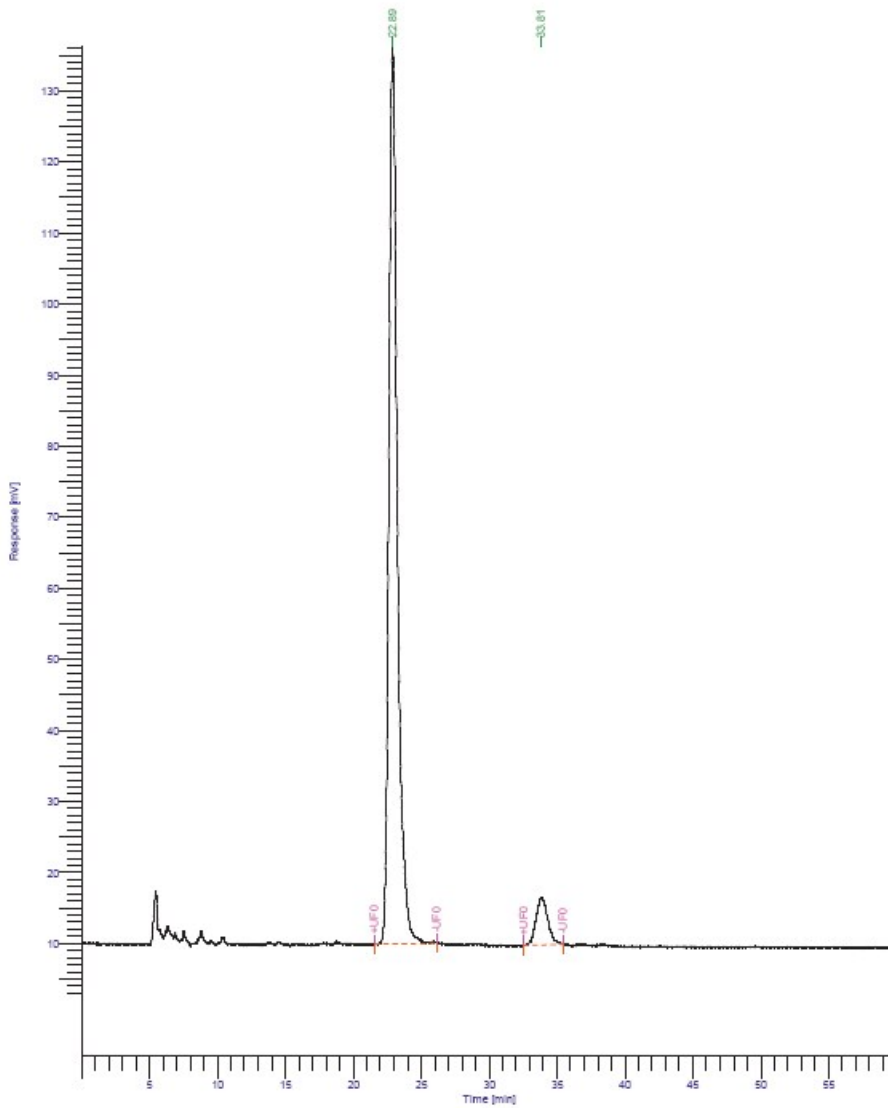
Compound 4k

DEFAULT REPORT

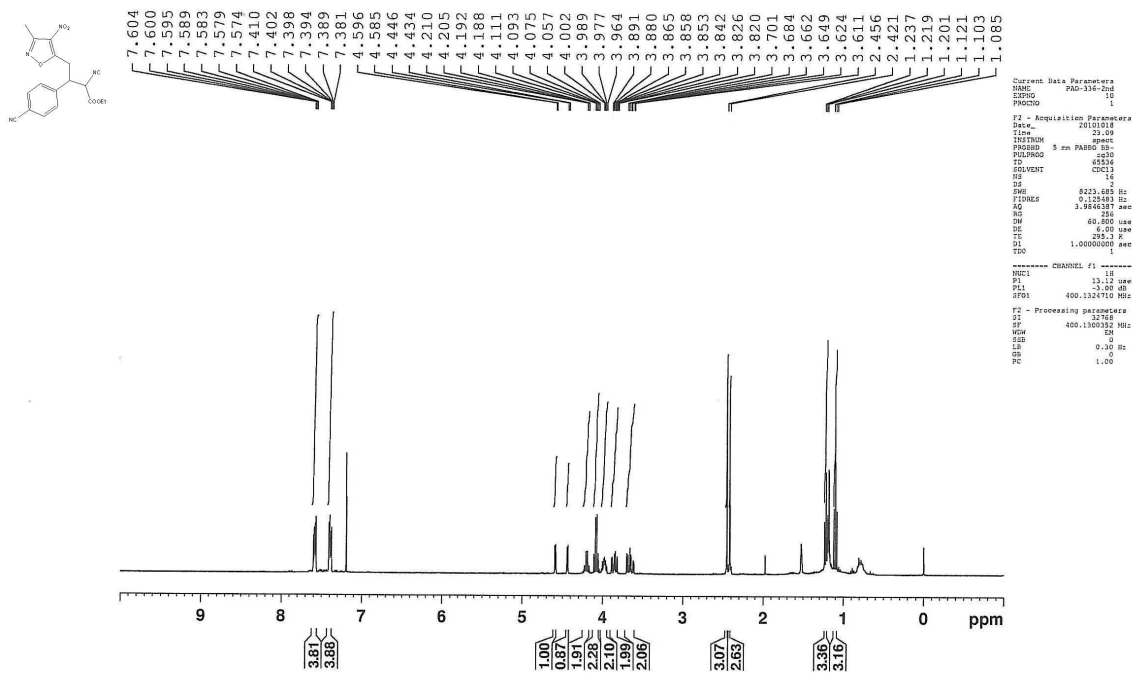
Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		22.896	5504830.35	126372.33	93.23	93.23			*MM	5.5048	5.5048
2		33.807	399618.22	6647.49	6.77	6.77			*MM	0.3996	0.3996
			5904448.57	133019.82	100.00	100.00				5.9044	5.9044

Missing Component Report
Component Expected Retention (Calibration File)

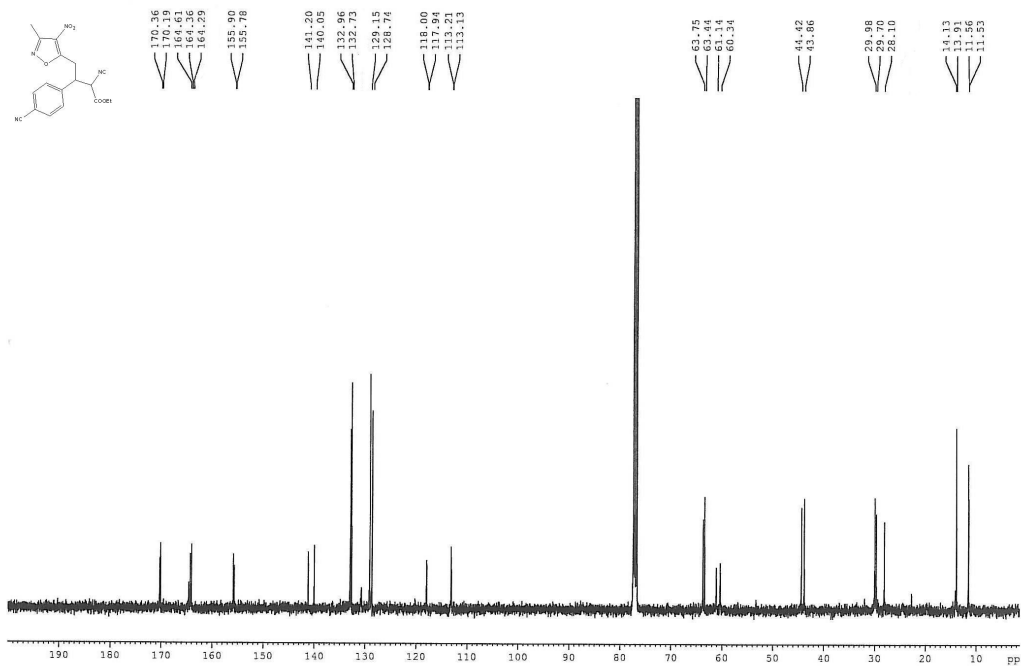
All components were found



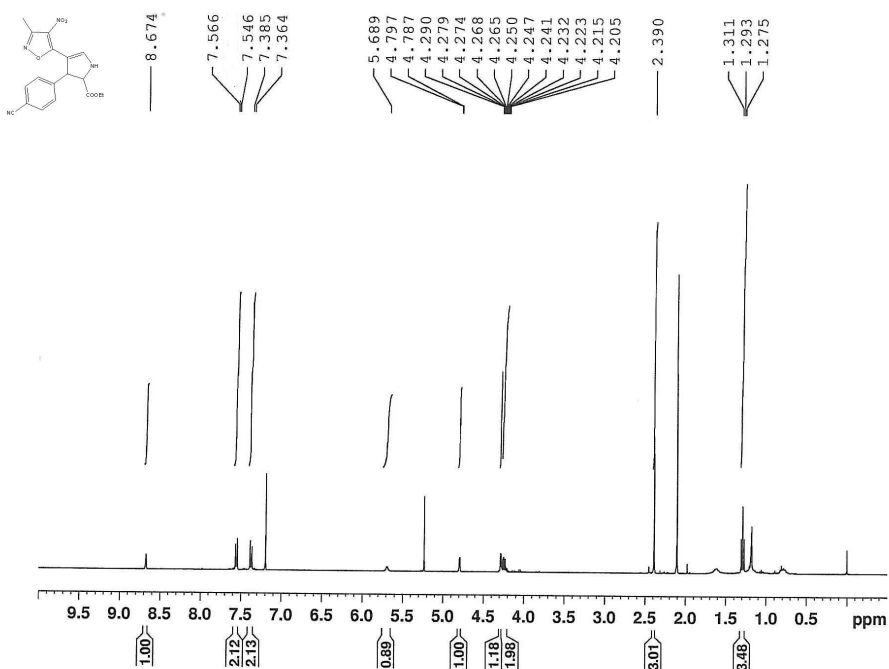
Compound 3l



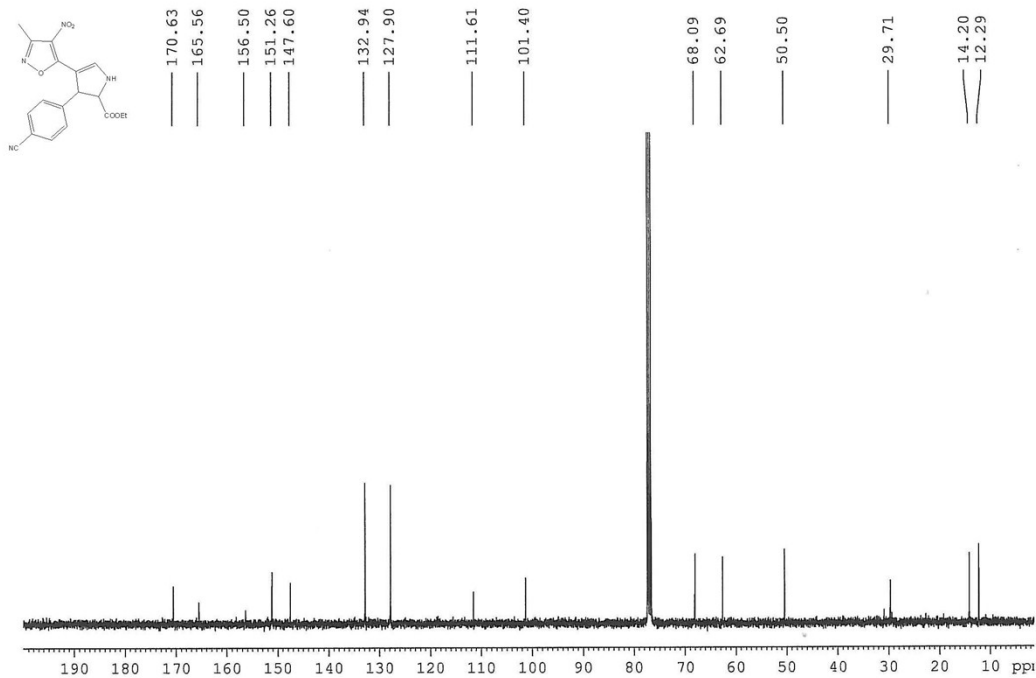
Current Data Parameters
 NAME: P80-316-10d
 EXPNO: 10
 PROCNO: 1
 F2 - Acquisition Parameters
 Date_: 20101018
 Time: 23.00
 INSTRUM: spect
 PROBHD: 3 mm PARAB
 PULPROG: zgpg30
 TD: 65536
 SOLVENT: CDCl3
 NS: 16
 DS: 4
 SWH: 8223.485 Hz
 FIDRES: 0.129483 Hz
 AQ: 3.9846387 sec
 RG: 356
 DM: 60.000 umm
 HF: 6.000 umm
 TC: 285.3 K
 D1: 1.00000000 sec
 TDC: 1
 ----- CHANNEL f1 -----
 NUC1: 13
 P1: 13.12 umm
 PL1: -3.00 dB
 SFO1: 400.132710 MHz
 F2 - Processing parameters
 DT: 33768
 SF: 400.130332 MHz
 WHW: EN
 LB: 0.30 Hz
 GB: 0
 PC: 1.00



Compound 4l



Current Data Parameters
 NAME P40-33612
 EXPNO 10
 PROCNO 1
 F2 - Acquisition Parameters
 Date_ 20101026
 Time 10.11
 INSTRUM spect
 PROBHD 5 mm P400 SP-
 PULPROG zgpg30
 TD 65536
 SFO 400.132710
 SOLVENT cdcl3
 NS 14
 DS 3
 SWH 8233.685 Hz
 FWHM 0.122503 Hz
 AQ 3.9846387 sec
 RG 382
 DW 60.800 usec
 DE 4.00 usec
 TE 298.0 K
 D1 1.0000000 sec
 TDO 1
 ----- CHANNEL F1 -----
 NUC1 1H
 P1 18
 PL1 13.00 usec
 SFO1 400.132710 MHz
 F2 - Processing parameters
 SI 32768
 SF 400.130354 MHz
 DS 4
 MDW 64
 SFO 400.130354 MHz
 GB 0
 GBW 0.30 Hz
 GBG 0
 GBV 1.00

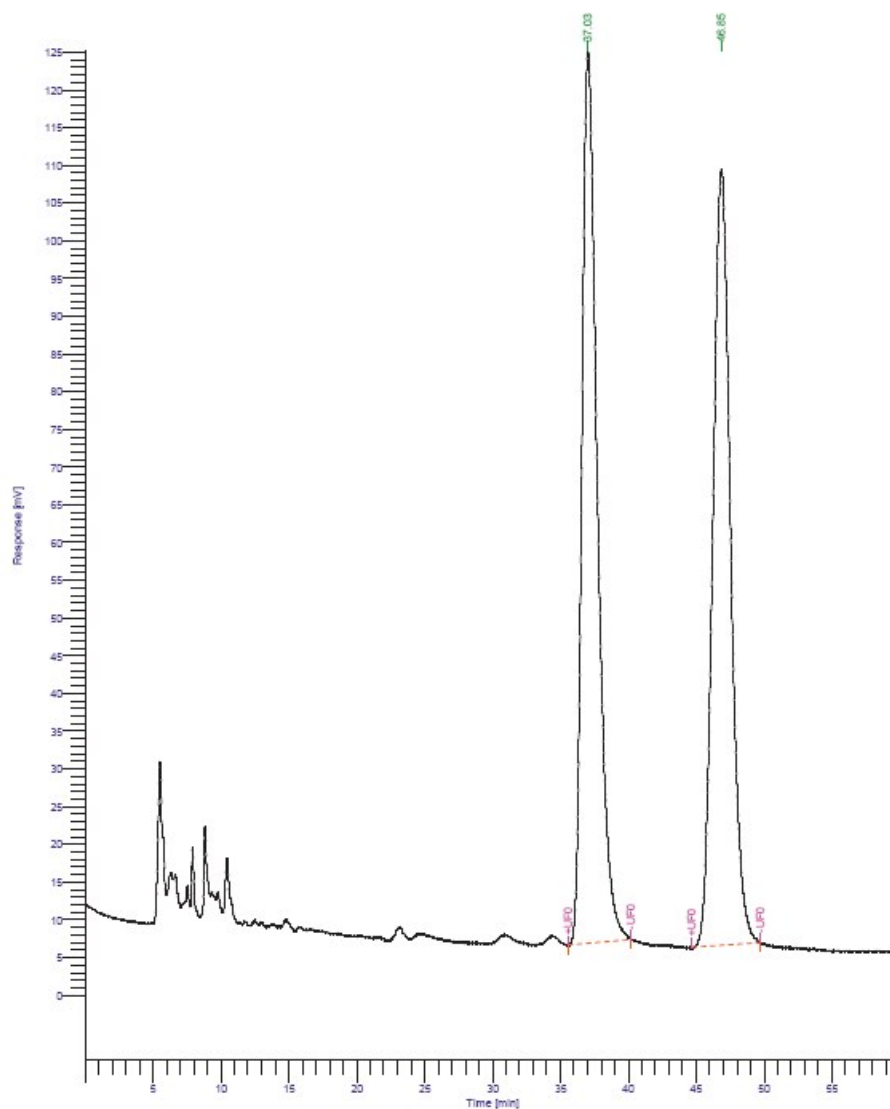


DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		37.033	9320890.18	118329.75	50.03	50.03			*MM	9.3209	9.3209
2		46.845	9311256.89	102801.55	49.97	49.97			*MM	9.3113	9.3113
			18632147.07	221131.31	100.00	100.00				18.6321	18.6321

Missing Component Report
 Component Expected Retention (Calibration File)

All components were found



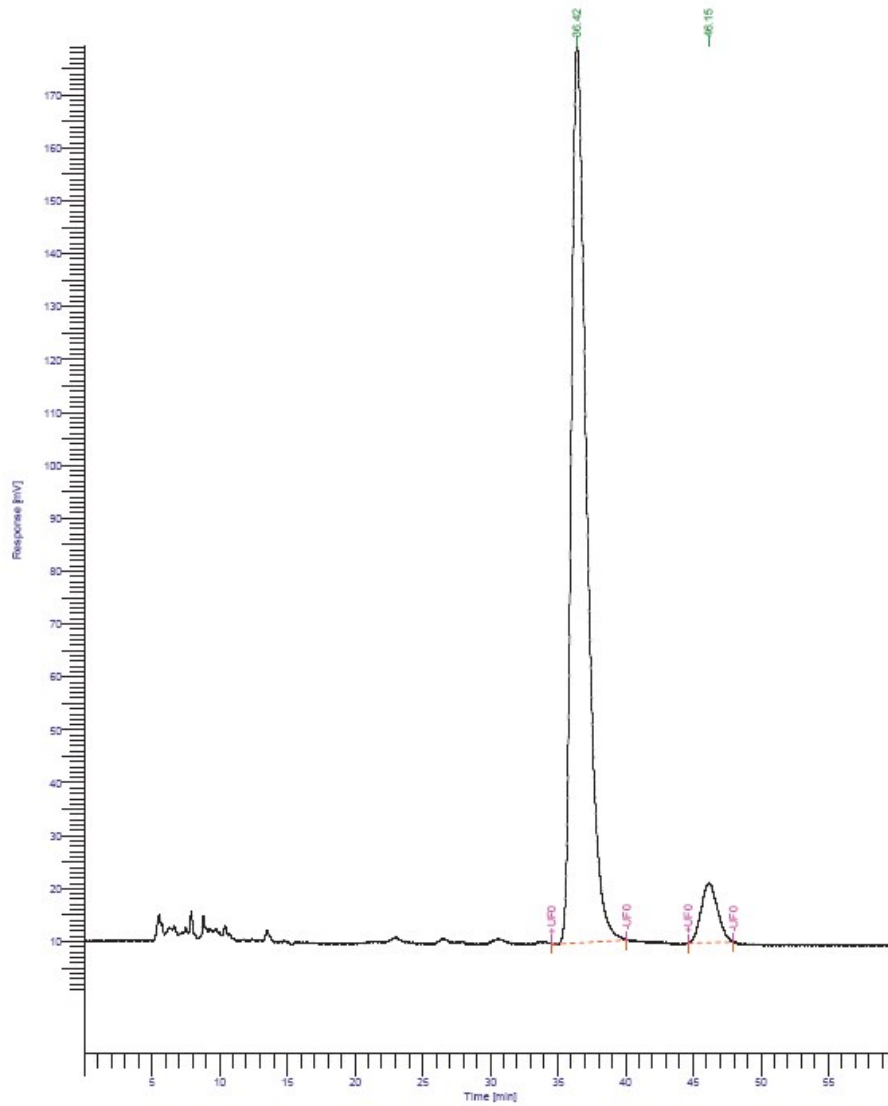
Compound 4I

DEFAULT REPORT

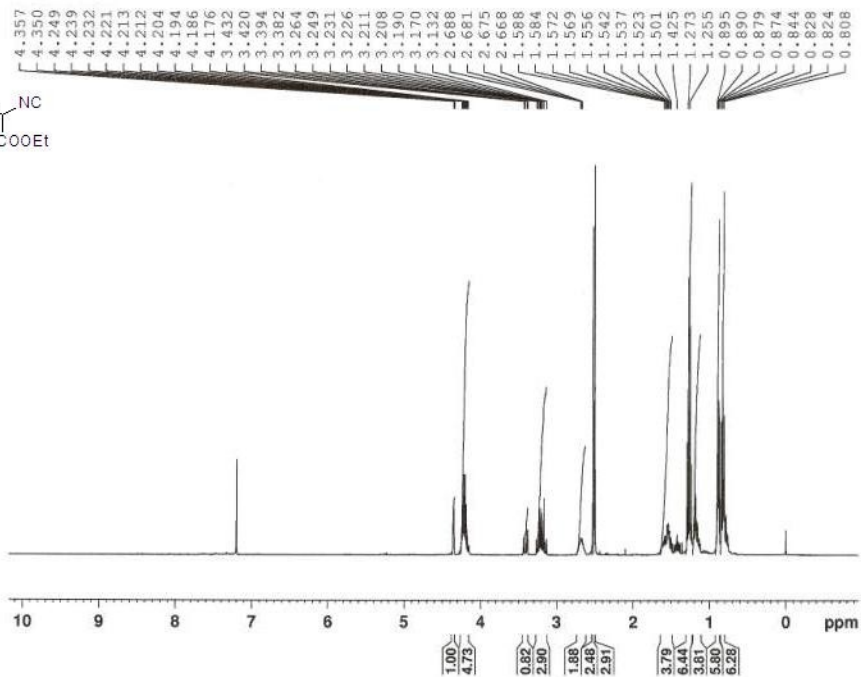
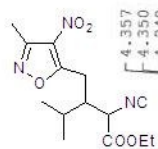
Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		36.417	13374824.13	169607.58	93.35	93.35			*MM	13.3748	13.3748
2		46.149	952769.30	11303.15	6.65	6.65			*MM	0.9528	0.9528
			14327593.43	180910.73	100.00	100.00				14.3276	14.3276

Missing Component Report
Component Expected Retention (Calibration File)

All components were found

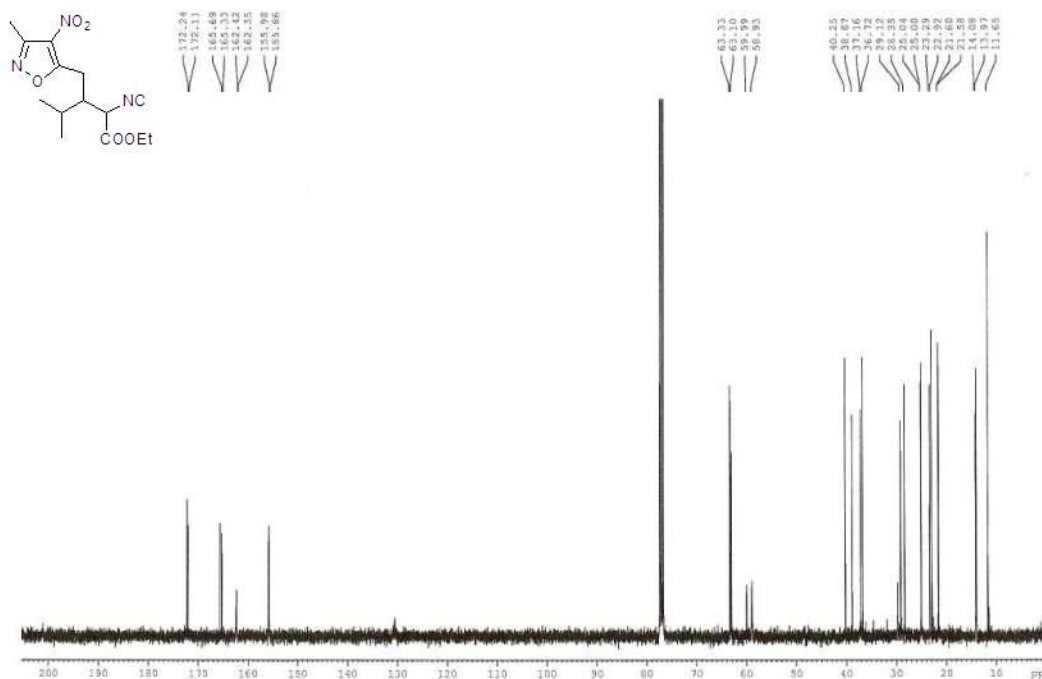


Compound 3m

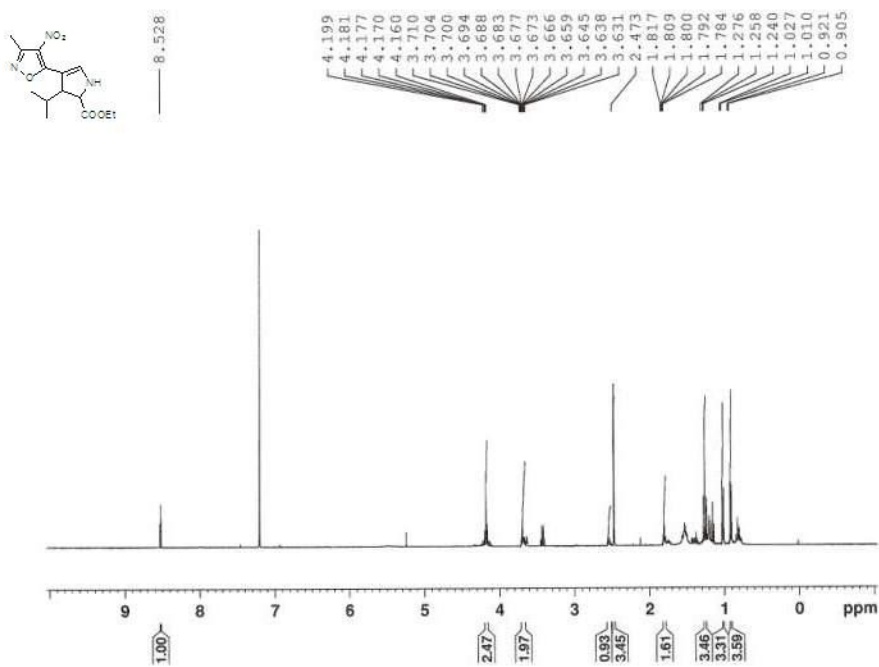


Acquisition Parameters
 NAME: 100-34001
 PROCNO: 1
 Date_: 20100917
 Time: 15.54
 INSTRUM: spect
 F2PROC1: 0 sec F2AQD 90-
 SOLVENT: CDCl3
 ID: 45524
 SOLVENT: CDCl3
 NS: 128
 DS: 4
 SWH: 4001.040 MHz
 FREQ1: 101.625400 MHz
 NU1: 121
 AQ: 3.9946307 sec
 RG: 327
 SW: 40.000 MHz
 FIDRES: 0.160000 MHz
 TD: 65536
 SFO: 2.0000000 MHz
 C4H: 1

CHANNEL f1
 NUC1: 13C
 PULPROG: zgpg30
 SFO1: 101.625400 MHz
 EQ2: 100.625400 MHz
 F2 - Processing parameters
 SI: 32768
 SF: 400.1470000 MHz
 WDW: EM
 SSB: 0
 LB: 0.30 Hz
 GB: 0
 PC: 1.00

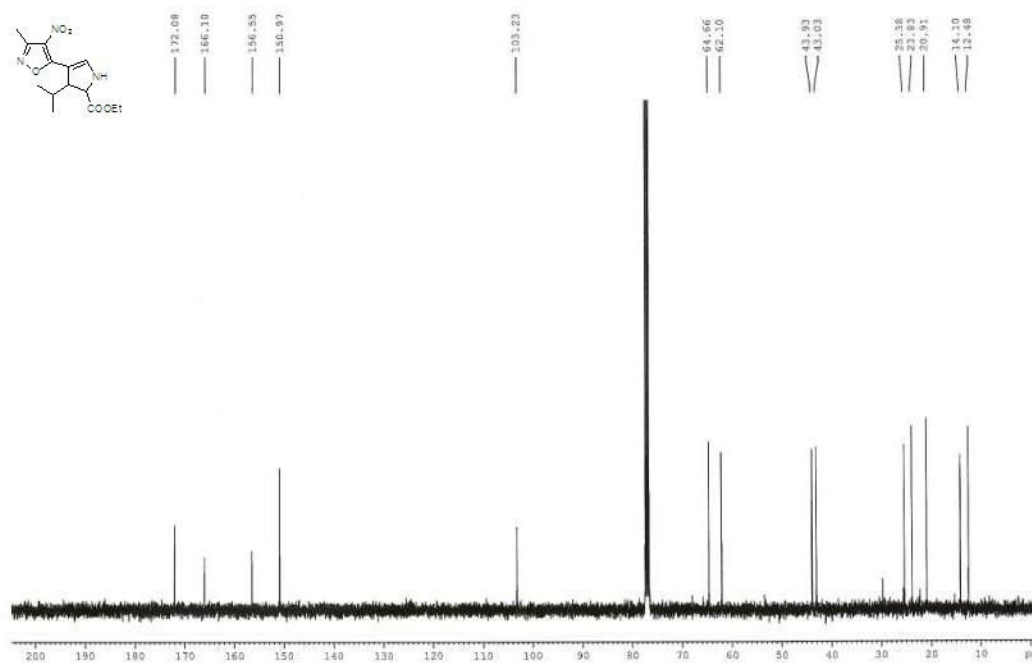


Compound 4m



```

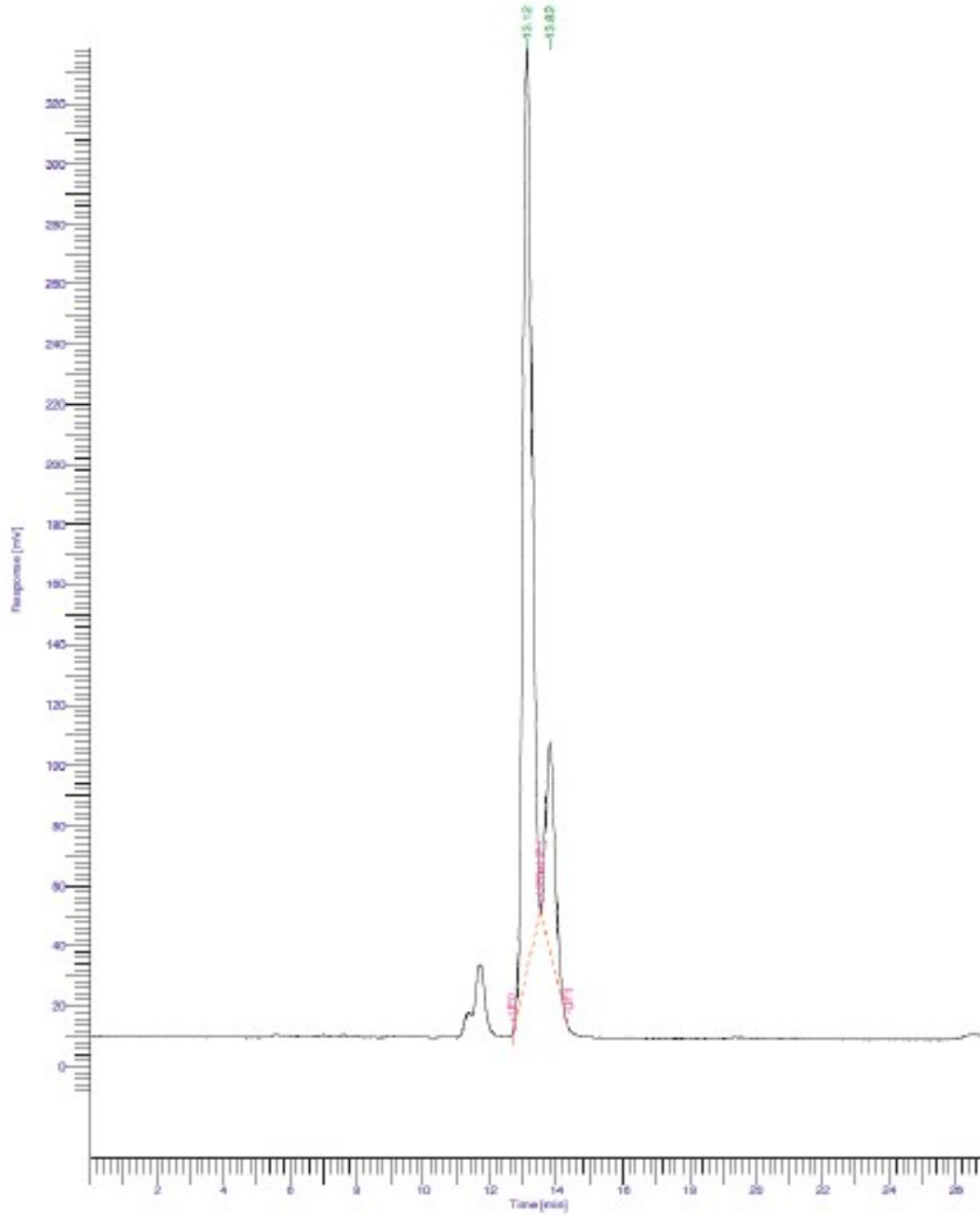
Current Date Parameters
NAME          860-2041a
EXPNO         10
PROCNO        1
F2 - Acquisition Parameters
Date_         01/09/18
Time         11:48
INSTRUM       spect
PROBHD        5 mm PABBO MM
PULPROG       zgpg30
SI            65536
AQ            0.021
RG            320
SOLVENT       CDCl3
NS            512
DS            4
SWH            8223.400 Hz
FIDRES        0.14188 Hz
AQRES         3.3846333 sec
RG            3776
SFO            60.132500 MHz
PC            4.00 sec
DE            280.3 Hz
TE            300.2 K
DQ            1.00000000 sec
CFO           1
===== CHANNEL f1 =====
NUC1           13
P1            12.00 usec
PL1           -1.50 dB
SFO1          400.1464713 MHz
F2 - Processing parameters
SI            65536
AQ            0.021
RG            320
SOLVENT       CDCl3
NS            512
DS            4
SWH            8223.400 MHz
PC            1.00
    
```



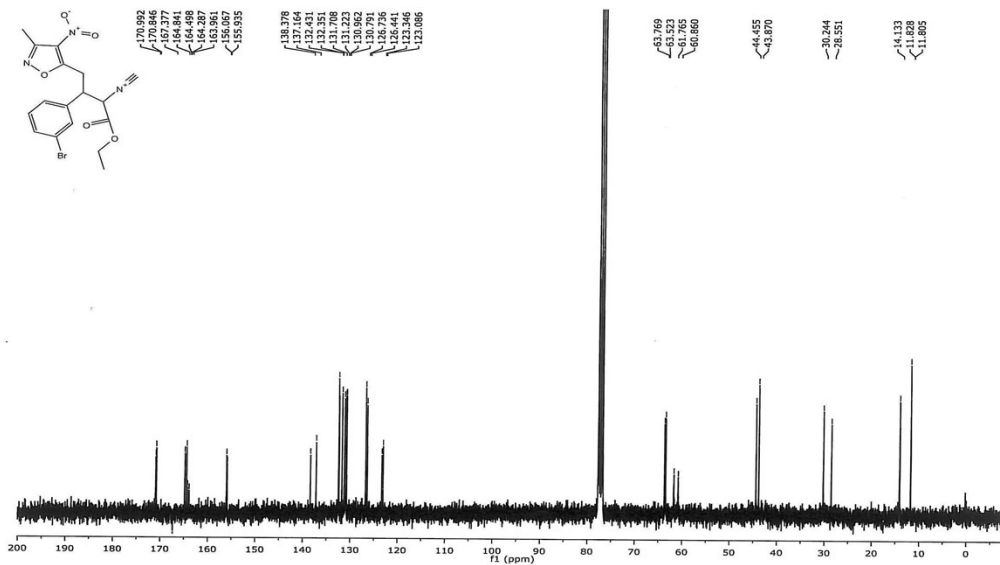
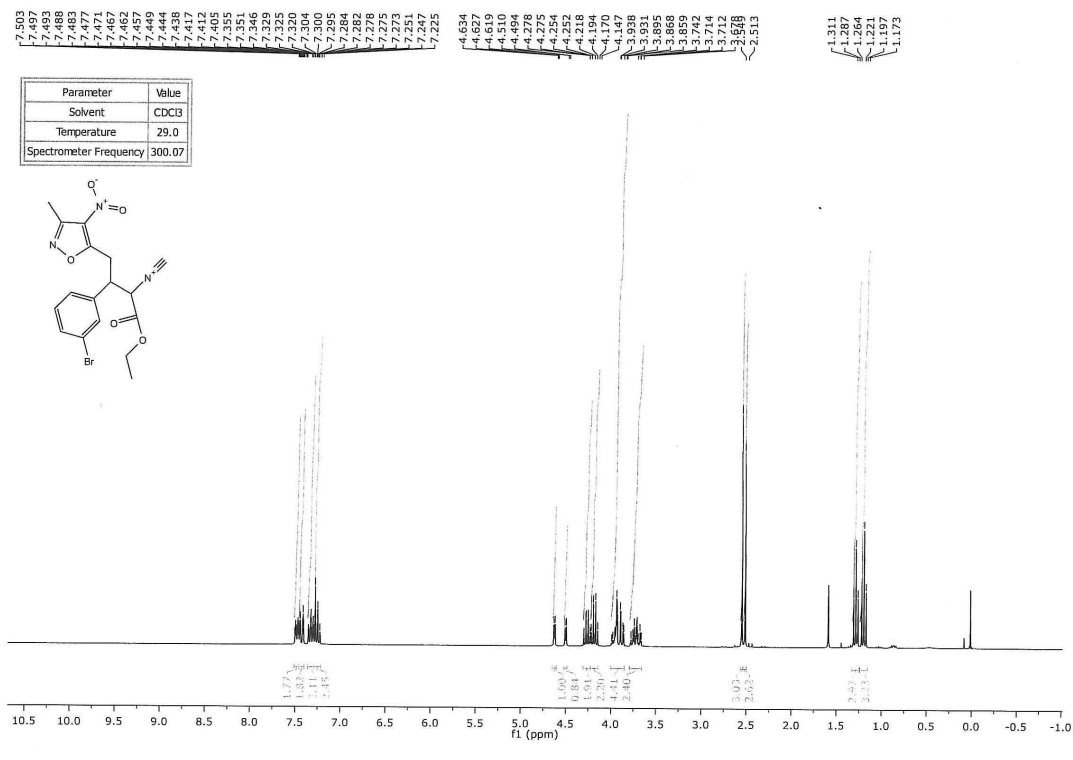
Compound 4m

Compound 2.20n

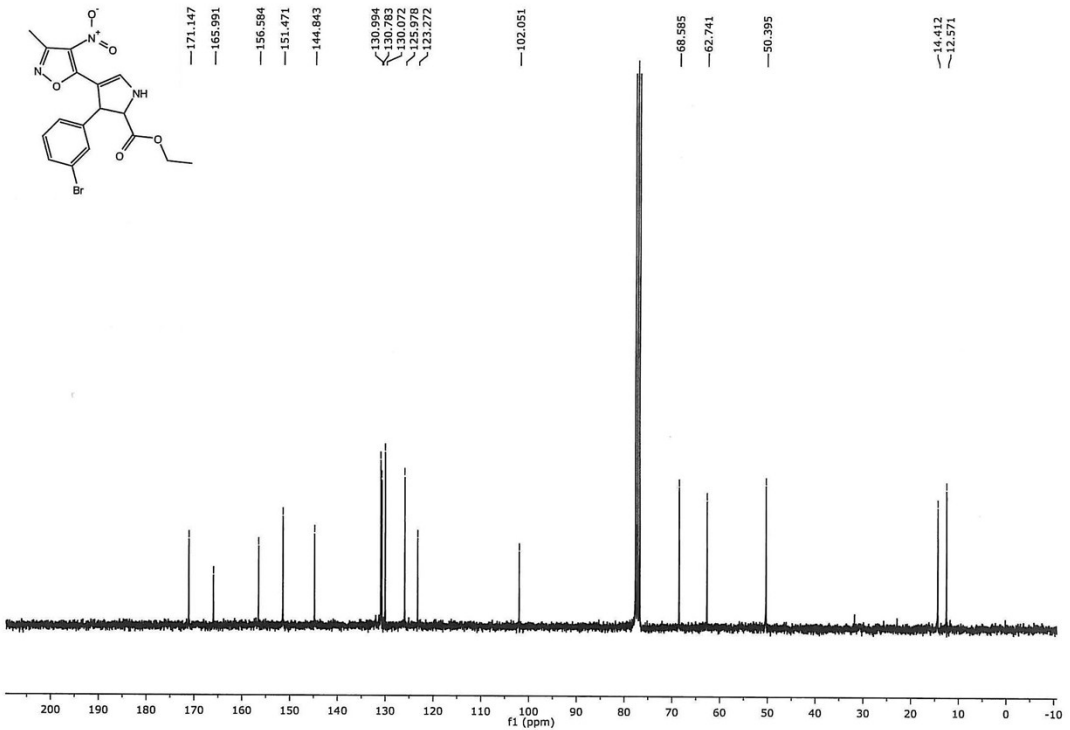
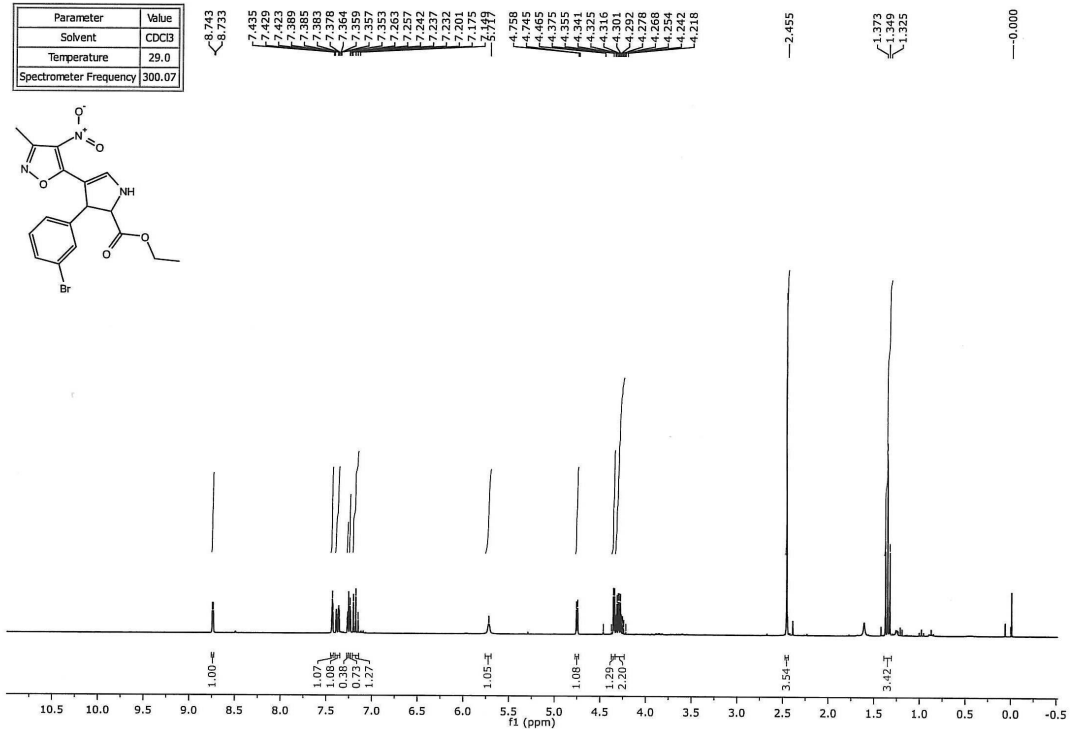
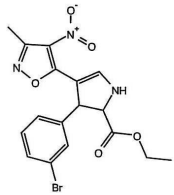
Sample Name : PVO-304 Sample #: Page 1 of 1
FileName : C:\TOTALCHROM DATA\Results\Pvo\PVO-304\PAD-304\PVO-304.ad.B207v.0.0ml.B.001.raw
Date : 15/03/2011 14:39:24
Method : Time of Injection: 15/09/2010 14:58:07
Start Time : 0.00 min End Time : 25.91 min Low Point : -6.57 mAU High Point : 338.46 mAU
Plot Offset: -6.67 mAU Plot Scale: 247.1 mAU

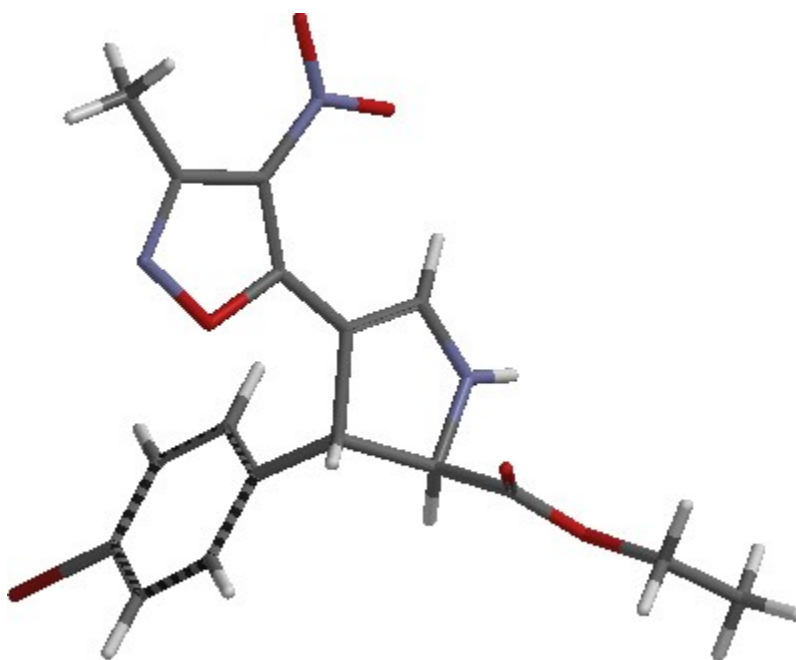


We also reported the analytical data for the compound (2S,3S)-ethyl 3-(3-bromophenyl)-4-nitroisoxazol-5-yl)-2,3-dihydro-1-H-pyrrole-2 carboxylate which have been crystallized for the absolute configuration CCDC1009050.

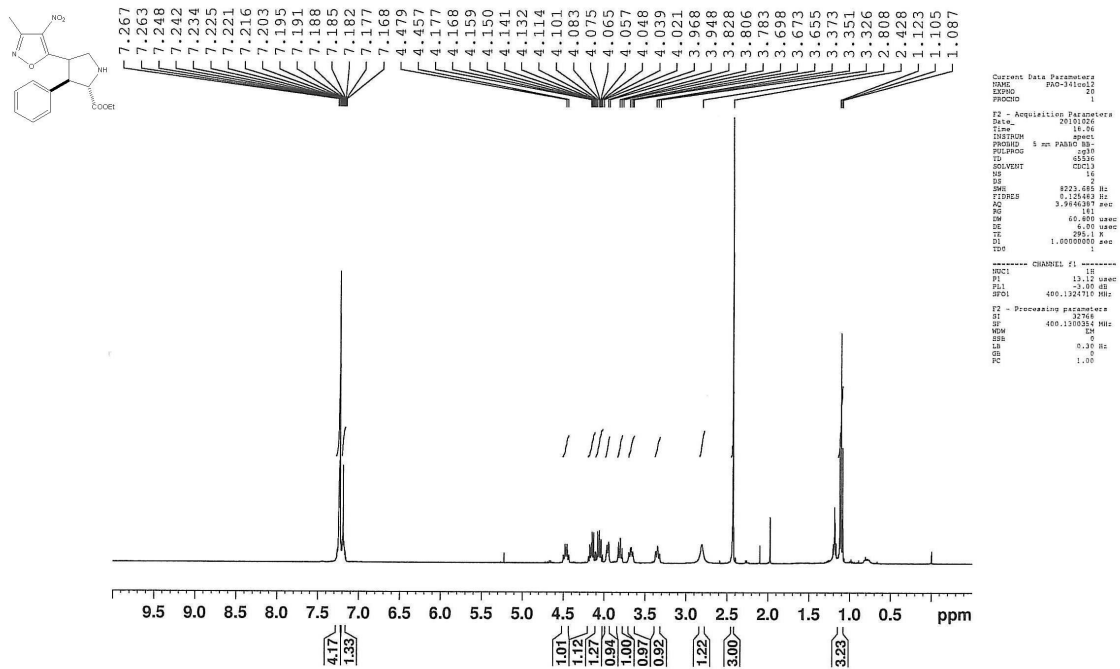


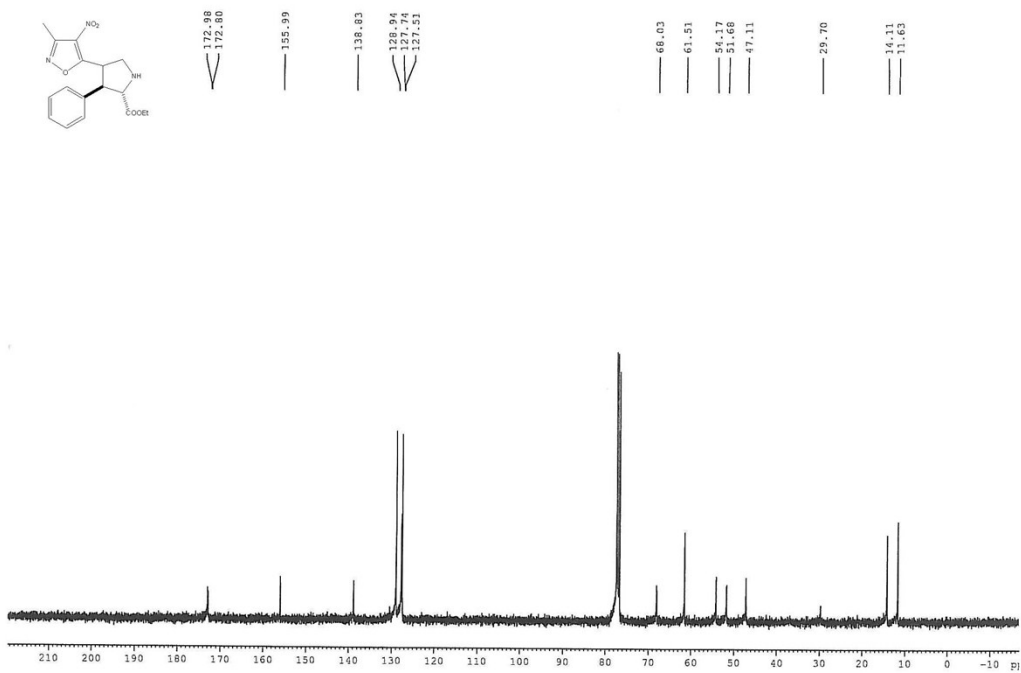
Parameter	Value
Solvent	CDCl ₃
Temperature	29.0
Spectrometer Frequency	300.07



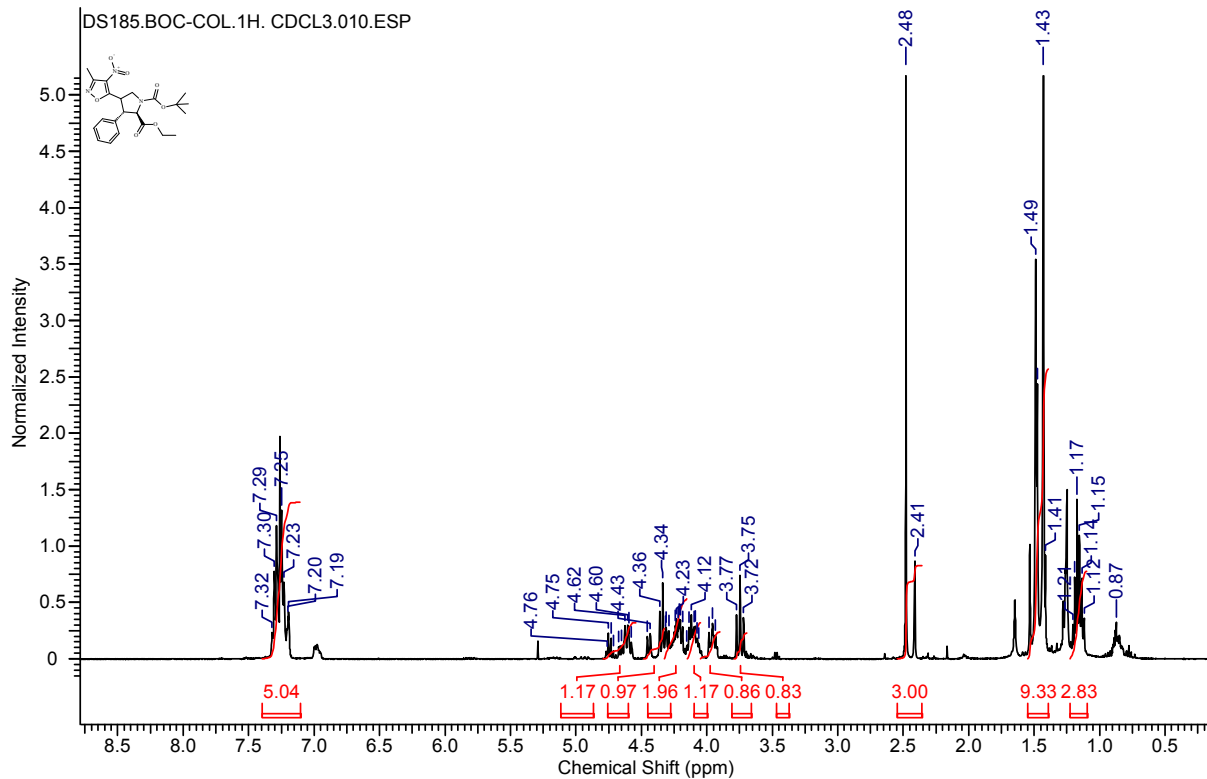


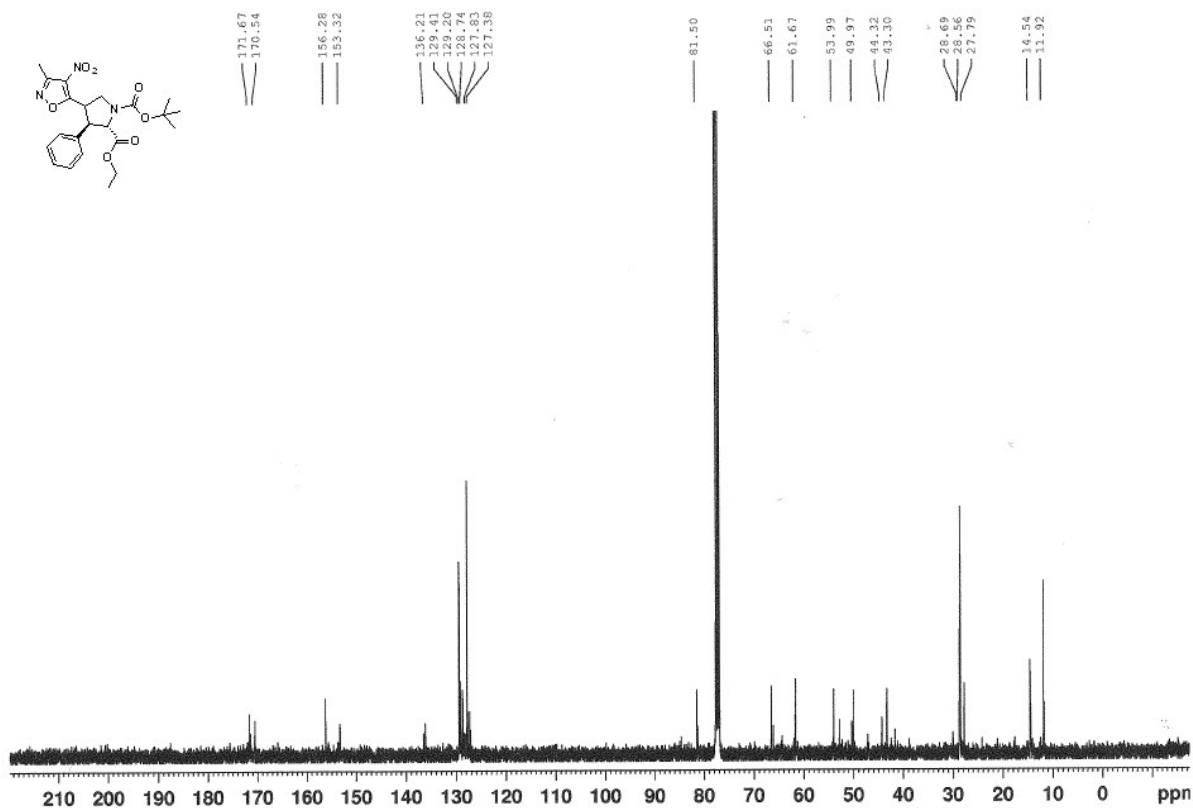
Compound 7





Compound 8





Compound 9

