N-N bond formation in Ugi Processes: from nitric acid to libraries of Nitramines

Valentina Mercalli, Aude Nyadanu, Marie Cordier, Gian Cesare Tron, Laurence Grimaud, and Laurent El Kaim.

EXPERIMENTAL SECTION

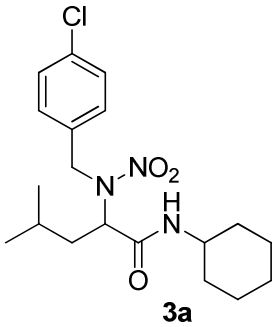
General Methods. Commercially available reagents and solvents were used without further purification. ^{1}H and ^{13}C NMR were recorded on a Bruker Avance 300 and 400 MHz. Chemical shifts (δ) are reported in part per million (ppm) relative to internal TMS. High-Resolution Mass spectra (HRMS) were carried out with JEOL JMSGCmateII spectrometer. IR spectra were performed on a Perkin-Elmer FT 1600 spectrometer with wavelengths in cm^{-1}. Column chromatography was performed on silica gel (70–230 mesh ASTM) using the reported eluents. Thin layer chromatography (TLC) was performed using plates of silica 60 F_{254}.Melting points (mp) were determined on a Stuart SMP3 apparatus and were left uncorrected.

General preparation of ammonium nitrate salt:
The amine (1 equiv) was dissolved in the toluene (1 M) and HNO_3 70% (1 equiv) was added dropwise. The reaction was stirred at room temperature under for 30 minutes. The white solid precipitate was filtrate, washed with Et_2O, and used without further purifications. When the precipate does not form, the salt can be dried by azeotropic removal of water with toluene, followed by evaporation of the solvent under reduced pressure.

General procedure for Ugi reaction:
The ammonium nitrate salt (1 equiv) was dissolved in MeOH (0.3 M), aldehyde (1 equiv) and isocyanide (1 equiv) were added. The reaction was stirred at room temperature under argon overnight. After evaporation of the solvent the crude was purified by column chromatography (usually eluents EP/EtOAc). When necessary the final product was crystallized in MeOH.

Spectroscopic data

2-((4-chlorobenzyl)(nitro)amino)-*N*-cyclohexyl-4-methylpentanamide, 3a

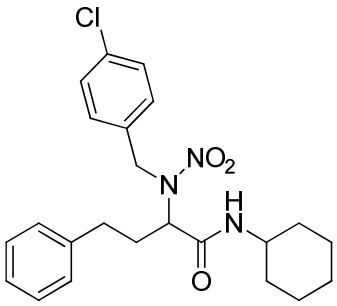


3a

Starting material: ammonium nitrate salt (204 mg, 1.0 mmol, 1.0 equiv), aldehyde (107 µL, 1.0 mmol, 1.0 equiv), and isocyanide (124 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 8:2) to give the product as amorphous solid (342 mg, yield 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32 – 7.26 (m, 4H), 6.18 (d, *J* = 8.0 Hz, 1H), 5.21 (t, *J* = 7.5 Hz, 1H), 5.05 (d, *J* = 16.1 Hz, 1H), 4.88 (d, *J* = 16.1 Hz, 1H), 3.73 – 3.68 (m, 1H), 1.92 – 1.85 (m, 2H), 1.71 – 1.58 (m, 5H), 1.56 – 1.48 (m, 1H), 1.39 – 1.27 (m, 2H), 1.21 – 1.06 (m, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.7, 134.0, 133.7, 129.2, 128.8, 61.8, 51.3, 48.8, 38.1, 32.7, 32.6, 25.4, 25.0, 24.7, 22.4, 22.3. IR (thin film) 3418, 3058, 2858, 1682, 1516, 1371, 1289, 899ν_{max}/cm^{-1}. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{19}H_{28}ClN_3O_3$: 381.1819; calcd for $[M\text{-}NO_2]^{+\bullet}$: 335.189016 Found: 335.1880 $[M\text{-}NO_2]^{+\bullet}$.

2-((4-chlorobenzyl)(nitro)amino)-*N*-cyclohexyl-4-phenylbutanamide, 3b

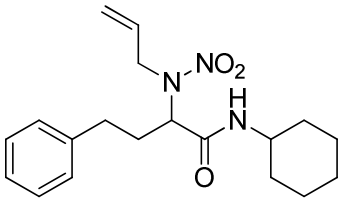


3b

Starting material: ammonium nitrate salt (204 mg, 1.0 mmol, 1.0 equiv), aldehyde (132 µL, 1.0 mmol, 1.0 equiv), and isocyanide (124 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as white solid (367 mg, yield 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.24 – 7.20 (m, 4H), 7.20 – 7.13 (m, 3H), 7.03 – 7.00 (m, 2H), 5.61 (d, *J* = 8.0 Hz, 1H), 4.98 (d, *J* = 16.1 Hz, 1H), 4.89 (t, *J* = 7.5 Hz, 1H), 4.74 (d, *J* = 16.1 Hz, 1H), 3.68 – 3.58 (m, 1H), 2.63 – 2.45 (m, 2H), 2.32 – 2.23 (m, 1H), 2.03 – 1.97 (m, 1H), 1.81 (d, *J* = 9.2 Hz, 1H), 1.70 – 1.52 (m, 4H), 1.29 – 1.22 (m, 2H), 1.12 – 0.93 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.5, 139.7, 134.0, 133.8, 129.4, 129.0, 128.8, 128.4, 126.7, 62.7, 51.7, 48.8, 32.8, 32.7, 32.1, 30.8, 25.4, 24.7.IR (thin film) 3417, 3062, 2858, 1682, 1516, 1351, 1296, 899 ν_{max}/cm^{-1}. MP (crystallized in MeOH) 152.2-153.5 °C. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{23}H_{28}ClN_3O_3$: 429.1819; calcd for $[M\text{-}NO_2]^{+\bullet}$:383.1890 Found: 383.1901$[M\text{-}NO_2]^{+\bullet}$.

2-(allyl(nitro)amino)-*N*-cyclohexyl-4-phenylbutanamide, 3c

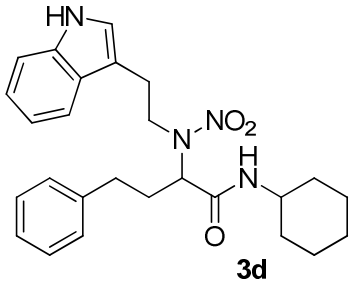


3c

Starting material: ammonium nitrate salt (120 mg, 1.0 mmol, 1.0 equiv), aldehyde (132 µL, 1.0 mmol, 1.0 equiv), and isocyanide (124 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluent: PE/EtOAc 9:1) to give the product as yellow solid (245 mg, yield 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25 – 7.20 (m, 2H), 7.18 – 7.14 (m, 1H), 7.11 – 7.07 (m, 2H), 5.87 – 5.76 (m, 2H), 5.22 (d, *J* = 16.0 Hz, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 4.94 (t, *J* = 7.6 Hz, 1H), 4.34 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.22 (dd, *J* = 16.0, 6.0 Hz, 1H), 3.82 – 3.74 (m, 1H), 2.66 – 2.52 (m, 2H), 2.30 – 2.20 (m, 1H), 2.08 – 1.98 (m, 1H), 1.86 – 1.73 (m, 2H), 1.67 – 1.52 (m, 3H), 1.32 – 1.20 (m, 2H), 1.13 – 0.98 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.6, 140.0, 130.6, 128.7, 128.4, 126.6, 119.7, 62.2, 50.9, 48.8, 32.9, 32.8, 32.2, 30.7, 25.4, 24.8, 24.7. IR (thin film) 3417, 2935, 1679, 1518, 1414, 1351, 1236, 1050 ν_{max}/cm^{-1}. MP130.6-131.8 °C. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{19}H_{27}N_3O_3$: 345.2052; calcd for $[M\text{-}NO_2]^{+\bullet}$:299.2123 Found:299.2122$[M\text{-}NO_2]^{+\bullet}$.

2-((2-(1H-indol-3-yl)ethyl)(nitro)amino)-*N*-cyclohexyl-4-phenylbutanamide, 3d

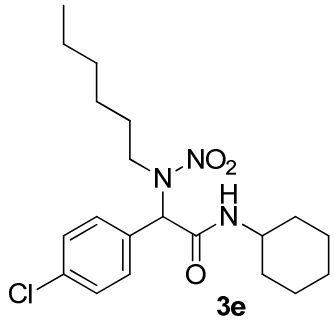


3d

Starting material: ammonium nitrate salt (223 mg, 1.0 mmol, 1.0 equiv), aldehyde (132 µL, 1.0 mmol, 1.0 equiv), and isocyanide (124 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 8:2) to give the product as yellow oil (194 mg, yield 43%).

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm) 8.20 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.43 – 7.40 (m, 1H), 7.36 – 7.31 (m, 2H), 7.30 – 7.25 (m, 2H), 7.22 – 7.18 (m, 1H), 7.16 – 7.12 (m, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 5.81 (br d, *J* = 8.0 Hz, 1H), 4.99 (t, *J* = 7.5 Hz, 1H), 4.12 – 4.00 (m, 2H), 3.83 – 3.73 (m, 1H), 3.31 – 3.16 (m, 2H), 2.75 – 2.59 (m, 2H), 2.40– 2.34 (m, 1H), 2.07 – 1.96 (m, 1H), 1.87 – 1.80 (m, 2H), 1.79 – 1.60 (m, 4H), 1.43 – 1.33 (m, 3H), 1.23 – 1.10 (m, 3H), 1.02 – 0.92 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.6, 140.0, 136.3, 128.7, 128.4, 127.2, 126.5, 122.5, 122.4, 119.8, 118.8, 111.8, 111.3, 62.3, 49.6, 48.8, 32.8, 32.0, 30.4, 25.4, 24.8, 24.7, 23.0. IR (thin film) 3469, 3419, 3046, 1683, 1514, 1352, 1289, 1031 ν_{max}/cm^{-1}.HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{26}H_{32}N_4O_3$: 448.2474 calcd for $[M\text{-}NO_2]^{+\bullet}$: 402.2574 Found: 402.2531 $[M\text{-}NO_2]^{+\bullet}$.

2-(4-chlorophenyl)-*N*-cyclohexyl-2-(hexyl(nitro)amino)acetamide, 3e

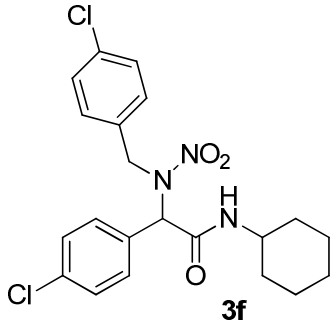


3e

Starting material: ammonium nitrate salt (164 mg, 1.0 mmol, 1.0 equiv), aldehyde (141 mg, 1.0 mmol, 1.0 equiv), and isocyanide (124 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluent: PE/EtOAc 9:1) to give the product as white solid (191 mg, yield 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.97 (s, 1H), 5.39 (br d, *J* = 7.5 Hz, 1H), 3.74 – 3.64 (m, 2H), 3.44 – 3.32 (m, 1H), 1.86 – 1.61 (m, 2H), 1.58 – 1.52 (m, 4H), 1.28 – 1.27 (m, 2H), 1.26 – 1.18 (m, 10H), 0.74 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.9, 135.8, 131.3, 131.1, 129.6, 66.6, 50.1, 49.1, 32.8, 32.7, 31.0, 27.0, 26.2, 25.4, 24.8, 24.7, 22.4, 13.9. IR (thin film) 3417, 3061, 2858, 1688, 1517, 1378, 1292, 891 ν_{max}/cm^{-1}.MP 169.2-171.6 °C. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{20}H_{30}ClN_3O_3$: 395.1976; calcd for $[M\text{-}NO_2]^{+\bullet}$: 349.2047 Found: 349.2061 $[M\text{-}NO_2]^{+\bullet}$.

2-((4-chlorobenzyl)(nitro)amino)-2-(4-chlorophenyl)-*N*-cyclohexylacetamide, 3f

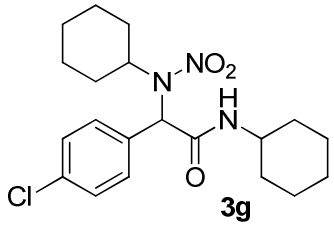


3f

Starting material: ammonium nitrate salt (204 mg, 1.0 mmol, 1.0 equiv), aldehyde (141 mg, 1.0 mmol, 1.0 equiv), and isocyanide (124 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 8:2) to give the product as white solid (301 mg, yield 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.16 (s, 1H), 5.75 (br d, *J* = 4.0 Hz, 1H), 5.17 (d, *J* = 16.2 Hz, 1H), 4.57 (d, *J*= 16.2 Hz, 1H), 3.91 – 3.81 (m, 1H), 1.94 (br s, 2H), 1.73 (br s, 3H), 1.41 – 1.34 (m, 2H), 1.23 – 1.09 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.0, 136.1, 134.1, 133.5, 131.3, 130.9, 129.6, 128.9, 128.6, 66.9, 52.6, 49.2, 32.8, 25.4, 24.8, 24.7. IR (thin film) 3416, 3066, 2937, 1688, 1519, 1317, 1095, 895 ν_{max}/cm^{-1}. MP (crystallized in MeOH) 189.7-191.2 °C. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{21}H_{23}Cl_2N_3O_3$: 435.1116; calcd for $[M\text{-}NO_2]^{+\bullet}$: 389.1187 Found: 389.1197$[M\text{-}NO_2]^{+\bullet}$.

2-(4-chlorophenyl)-*N*-cyclohexyl-2-(cyclohexyl(nitro)amino)acetamide, 3g

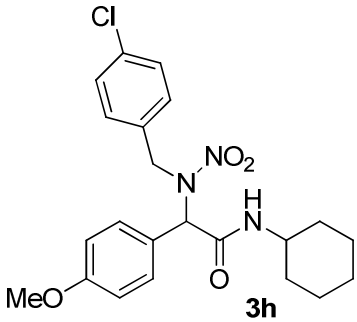


3g

Starting material: ammonium nitrate salt (162 mg, 1.0 mmol, 1.0 equiv), aldehyde (141 mg, 1.0 mmol, 1.0 equiv), and isocyanide (124 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 8:2) to give the product as white solid (81 mg, yield 21%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 – 7.31 (m, 2H), 7.28 – 7.24 (m, 2H), 5.47 (br d, *J* = 8.1 Hz, 1H), 5.29 (s, 1H), 4.38 – 4.32 (m, 1H), 3.76 – 3.66 (m, 1H), 2.10 (br d, 1H), 1.83 – 1.71 (m, 3H), 1.69 – 1.49 (m, 7H), 1.38 – 1.18 (m, 5H), 1.10 – 0.96 (m, 4H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.5, 135.1, 132.8, 129.9, 129.5, 64.9, 61.7, 49.1, 32.7, 32.6, 30.6, 29.1, 25.8, 25.5, 25.4, 25.2, 24.7, 24.6. IR (thin film) 3421, 3046, 2982, 1683, 1512, 1351, 1290, 891 ν_{max}/cm^{-1}. MP (crystallized in MeOH) 203.1-204.5 °C. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{20}H_{28}ClN_3O_3$: 393.1819; calcd for $[M\text{-}NO_2]^{+\bullet}$: 347.1890 Found: 347.1884$[M\text{-}NO_2]^{+\bullet}$.

2-((4-chlorobenzyl)(nitro)amino)-*N*-cyclohexyl-2-(4-methoxyphenyl)acetamide, 3h

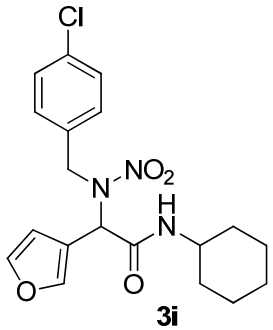


3h

Starting material: ammonium nitrate salt (204 mg, 1.0 mmol, 1.0 equiv), aldehyde (122 µL, 1.0 mmol, 1.0 equiv), and isocyanide (124 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluent: PE/EtOAc 8:2) to give the product as white solid (118 mg, yield 27%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25 – 7.11 (m, 2H), 7.08 – 7.04 (m, 2H), 6.82 – 6.78 (m, 4H), 6.06 (s, 1H), 5.49 (d, *J* = 8.1 Hz, NH), 5.02 (d, *J* = 16.1 Hz, 1H), 4.45 (d, *J* = 16.1 Hz, 1H), 3.79 – 3.76 (m, 1H), 3.74 (s, 3H), 1.89 – 1.79 (m, 2H), 1.66 – 1.50 (m, 3H), 1.34 – 1.22 (m, 2H), 1.10 – 0.97 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.6, 160.7, 134.5, 133.3, 131.5, 129.1, 128.4, 124.1, 114.8, 67.3, 55.5, 52.2, 49.1, 32.8 (2C), 25.4, 24.8, 24.7. IR (thin film) 3416, 3052, 2857, 1685, 1517, 1352, 1268, 990 ν_{max}/cm^{-1}. MP (crystallized in MeOH) 183.1-185.2 °C. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{22}H_{26}ClN_3O_4$: 431.1612; calcd for $[M\text{-}NO_2]^{+\bullet}$: 385.1683 Found: 385.1686 $[M\text{-}NO_2]^{+\bullet}$.

2-((4-chlorobenzyl)(nitro)amino)-*N*-cyclohexyl-2-(furan-3-yl)acetamide, 3i

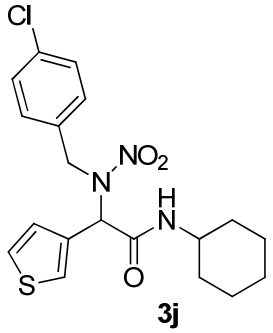


3i

Starting material: ammonium nitrate salt (204 mg, 1.0 mmol, 1.0 equiv), aldehyde (87 µL, 1.0 mmol, 1.0 equiv), and isocyanide (124 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 8:2) to give the product as yellow solid (125 mg, yield 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.51 – 7.48 (m, 1H), 7.36 (d, *J* = 1.7 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.30 (dd, *J* = 1.7, 0.7 Hz, 1H), 5.84 (s, 1H), 5.55 (br d, *J* = 7.8 Hz, 1H), 5.00 (d, *J* = 16.0 Hz, 1H), 4.68 (d, *J* = 16.0 Hz, 1H), 3.77 – 3.67 (m, 1H), 1.88 – 1.77 (m, 2H), 1.63 – 1.53 (m, 3H), 1.34 – 1.24 (m, 2H), 1.12 – 0.94 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.6, 144.4, 143.5, 134.0, 133.7, 129.2, 128.7, 117.7, 110.7, 60.0, 52.9, 49.1, 32.8, 32.7, 25.4, 24.7. IR (thin film) 3417, 3061, 2937, 1688, 1436, 1368, 1246, 875 ν_{max}/cm^{-1}. MP (crystallized in MeOH) 198.8-200.4 °C. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{19}H_{22}ClN_3O_4$: 391.1299; calcd for $[M\text{-}NO_2]^{+\bullet}$: 345.1370 Found:345.1366 $[M\text{-}NO_2]^{+\bullet}$.

2-((4-chlorobenzyl)(nitro)amino)-*N*-cyclohexyl-2-(thiophen-3-yl)acetamide, 3j

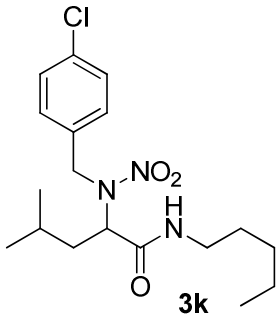


3j

Starting material: ammonium nitrate salt (204 mg, 1.0 mmol, 1.0 equiv), aldehyde (88 µL, 1.0 mmol, 1.0 equiv), and isocyanide (124 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 8:2) to give the product as white solid (172 mg, yield 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 (d, *J* = 3.0 Hz, 1H), 7.27 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.94 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.09 (s, 1H), 5.54 (d, *J* = 7.9 Hz, 1H), 5.05 (d, *J* = 16.1 Hz, 1H), 4.54 (d, *J* = 16.1 Hz, 1H), 3.80 – 3.70 (m, 1H), 1.87 – 1.83 (m, 2H), 1.65 – 1.51 (m, 3H), 1.34 – 1.22 (m, 2H), 1.11 – 1.01(m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.2, 134.3, 133.5, 132.8, 129.1, 128.5, 128.2, 127.6, 127.5, 62.9, 52.7, 49.1, 32.8, 25.4, 24.8, 24.7.IR (thin film) 3416, 3061, 2858, 1688, 1520, 1366, 1289, 845 ν_{max}/cm^{-1}. MP (crystallized in MeOH) 199.5-201.2 °C. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{19}H_{22}ClN_3O_3S$: 407.1070; calcd for $[M\text{-}NO_2]^{+\bullet}$: 361.1141Found:361.1146$[M\text{-}NO_2]^{+\bullet}$.

2-((4-chlorobenzyl)(nitro)amino)-4-methyl-*N*-pentylpentanamide, 3k

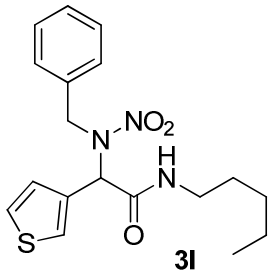


3k

Starting material: ammonium nitrate salt (204 mg, 1.0 mmol, 1.0 equiv), aldehyde (107 µL, 1.0 mmol, 1.0 equiv), and isocyanide (126 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluent: PE/EtOAc 9:1) to give the product as amorphous solid (305 mg, yield 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36 – 7.32 (m, 2H), 7.31 – 7.28 (m, 2H), 6.07 (br s, 1H), 5.24 (t, *J* = 7.5 Hz, 1H), 5.06 (d, *J* = 16.1 Hz, 1H), 4.90 (d, *J* = 16.1 Hz, 1H), 3.28 – 3.20 (m, 2H), 1.95 – 1.86 (m, 1H), 1.69 – 1.67 (m, 1H), 1.56 – 1.45 (m, 3H), 1.39 – 1.24 (m, 4H), 0.98 – 0.91 (m, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.8, 133.9 (2C), 129.3, 128.8, 61.6, 51.4, 39.8, 38.1, 28.9, 25.0, 22.4, 22.3, (2C) 13.4. IR (thin film) 3430, 3046, 2873, 1683, 1517, 1371, 1290, 922 ν_{max}/cm^{-1}. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{18}H_{28}ClN_3O_3$: 369.1819; calcd for $[M\text{-}NO_2]^{+\bullet}$: 323.1890 Found: 323.1886 $[M\text{-}NO_2]^{+\bullet}$.

2-(benzyl(nitro)amino)-*N*-pentyl-2-(thiophen-3-yl)acetamide, 3l

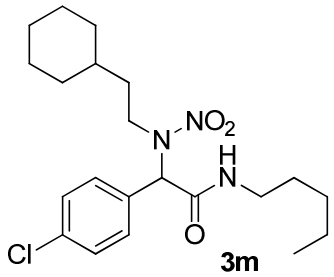


3l

Starting material: ammonium nitrate salt (170 mg, 1.0 mmol, 1.0 equiv), aldehyde (88 µL, 1.0 mmol, 1.0 equiv), and isocyanide (126 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 8:2) to give the product as white solid (143 mg, yield 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 – 7.33 (m, 1H), 7.26 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.17 – 7.14 (m, 3H), 6.95 (dd, *J* = 5.0, 1.9 Hz, 3H), 6.02 (s, 1H), 5.60 (br s, 1H), 5.09 (d, *J* = 15.9 Hz, 1H), 4.66 (d, *J* = 15.9 Hz, 1H), 3.29 – 3.18 (m, 2H), 1.44 – 1.40 (m, 2H), 1.26 – 1.18 (m, 4H), 0.81 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.2, 135.6, 132.8, 128.4, 128.3, 127.7 (2C), 127.6, 127.4, 63.0, 53.6, 40.0, 29.0, 28.9, 22.3, 14.0. IR (thin film) 3427, 3045, 1682, 1524, 1372, 1248, 891 ν_{max}/cm^{-1}. MP 115.3-116.1 °C. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{18}H_{23}N_3O_3S$: 361.1460 Found: 361.1445.

2-(4-chlorophenyl)-2-((2-cyclohexylethyl)(nitro)amino)-*N*-pentylacetamide, 3m

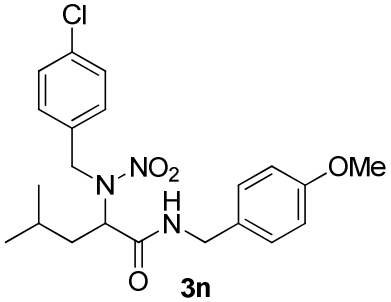


3m

Starting material: ammonium nitrate salt (190 mg, 1.0 mmol, 1.0 equiv), aldehyde (140 mg, 1.0 mmol, 1.0 equiv), and isocyanide (126 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as white solid (191 mg, yield 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38 – 7.33 (m, 2H), 7.30 – 7.26 (m, 2H), 5.99 (s, 1H), 5.76 (s, 1H), 3.77 – 3.68 (m, 1H), 3.45 – 3.37 (m, 1H), 3.24 – 3.18 (m, 2H), 1.57 – 1.32 (m, 9H), 1.29 – 1.12 (m, 5H), 1.00 – 0.98 (m, 5H), 0.81 (t, *J* = 7.0 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.8, 135.9, 131.14 (2C), 129.6, 66.7, 48.4, 40.0, 35.4, 34.3, 32.8, 32.7, 29.0, 28.9, 26.3, 26.1, 26.0, 22.3, 14.0. IR (thin film) 3430, 3047, 2928, 1693, 1519, 1330, 1267, 899 ν_{max}/cm^{-1}. MP116.6-118.1 °C. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{21}H_{32}ClN_3O_3$: 409.2132; calcd for $[M\text{-}NO_2]^{+\bullet}$: 363.2203 Found: 363.2202$[M\text{-}NO_2]^{+\bullet}$.

2-((4-chlorobenzyl)(nitro)amino)-*N*-(4-methoxybenzyl)-4-methylpentanamide, 3n

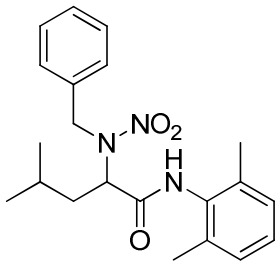


3n

Starting material: ammonium nitrate salt (204 mg, 1.0 mmol, 1.0 equiv), aldehyde (107 µL, 1.0 mmol, 1.0 equiv), and isocyanide (147 mg, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 7:3) to give the product as white solid (326 mg, yield 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.51 (t, *J* = 5.4 Hz, 1H), 5.26 (t, *J* = 7.5 Hz, 1H), 5.06 (d, *J* = 16.1 Hz, 1H), 4.88 (d, *J* = 16.1 Hz, 1H), 4.38 (dd, *J* = 14.5, 7.2 Hz, 1H), 4.33 (dd, *J* = 14.5, 7.2 Hz, 1H), 3.83 (s, 3H), 1.95 – 1.69 (m, 1H), 1.74 – 1.67 (m, 1H), 1.56 – 1.49 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 159.2, 133.8 (2C),129.3, 129.2, 129.1, 128.9, 114.2, 61.7, 55.3, 51.5, 43.3, 38.1, 25.0, 22.4 (2C). IR (thin film) 3425, 3068, 2994, 1682, 1517, 1371, 1292, 901 ν_{max}/cm^{-1}. MP 133.5-134.8 °C. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{21}H_{26}ClN_3O_4$: 419.1612; calcd for $[M\text{-}NO_2]^{+\bullet}$: 373.1683 Found: 373.1672$[M\text{-}NO_2]^{+\bullet}$.

2-(benzyl(nitro)amino)-*N*-(2,6-dimethylphenyl)-4-methylpentanamide, 3o

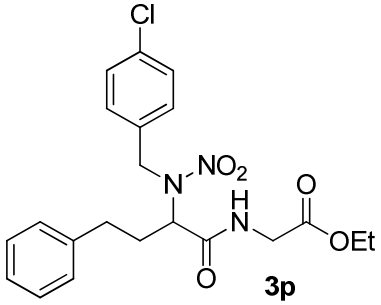


3o

Starting material: ammonium nitrate salt (170 mg, 1.0 mmol, 1.0 equiv), aldehyde (107 µL, 1.0 mmol, 1.0 equiv), and isocyanide (128 mg, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluent: PE/EtOAc 9:1) to give the product as white solid (122 mg, yield 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42 – 7.36 (m, 5H), 7.18 – 7.09 (m, 3H), 5.41 – 5.37 (m, 1H), 5.31 (d, *J* = 16.1 Hz, 1H), 4.92 (d, *J* = 16.1 Hz, 1H), 2.17 (s, 6H), 2.12 – 2.03 (m, 1H), 1.83 – 1.78(m, 1H), 1.71 – 1.64 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.8, 135.4, 135.1, 133.0, 128.9, 128.3, 128.13, 127.8, 127.7, 61.9, 52.8, 38.3, 25.1, 22.6, 22.3, 18.4. IR (thin film) 3399, 3068, 2873, 1695, 1464, 1389, 1294, 942 ν_{max}/cm^{-1}. MP (crystallized in MeOH) 151.7-153.0 °C. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{21}H_{27}N_3O_3$: 369.2052 Found:369.2040.

Ethyl (2-((4-chlorobenzyl)(nitro)amino)-4-phenylbutanoyl)glycinate, 3p

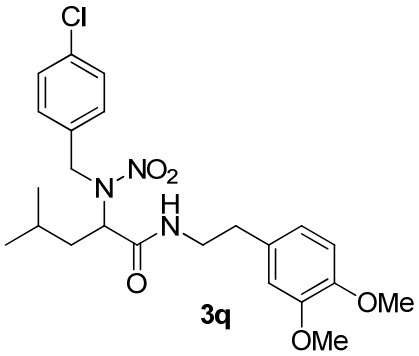


3p

Starting material: ammonium nitrate salt (204 mg, 1.0 mmol, 1.0 equiv), aldehyde (132 µL, 1.0 mmol, 1.0 equiv), and isocyanide (109 µL, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 8:2) to give the product as yellow oil (375 mg, yield 86%).

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm) 7.37 – 7.26 (m, 7H), 7.14 – 7.10 (m, 2H), 6.64 (br t, *J* = 7.5 Hz, 1H), 5.19 – 5.15 (m, 2H), 4.83 (d, *J* = 16.2 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.06 (dd, *J* = 16.0, 5.4 Hz, 1H), 3.99 (dd, *J* = 16.0, 5.4 Hz, 1H), 2.75 – 2.58 (m, 2H), 2.47 – 2.38 (m, 1H), 2.13 – 2.09 (m, 1H), 1.33 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.2, 168.2, 139.7, 134.0, 133.8, 129.3, 129.0, 128.8, 128.4, 126.6, 62.3, 61.8, 52.0, 41.5, 32.1, 31.0, 14.2. IR (thin film) 3420, 3049, 2986, 1744, 1693, 1523, 1377, 1282, 900 ν_{max}/cm^{-1}. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{21}H_{24}ClN_3O_5$: 433.1404; calcd for $[M\text{-}NO_2]^{+\bullet}$: 387.1475 Found:387.1474$[M\text{-}NO_2]^{+\bullet}$.

2-((4-chlorobenzyl)(nitro)amino)-*N*-(3,4-dimethoxyphenethyl)-4-methylpentanamide, 3q

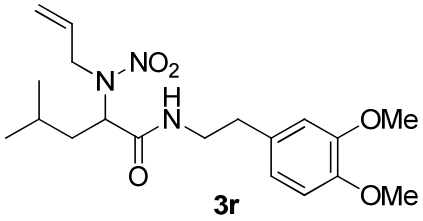


3q

Starting material: ammonium nitrate salt (204 mg, 1.0 mmol, 1.0 equiv), aldehyde (107 µL, 1.0 mmol, 1.0 equiv), and isocyanide (191 mg, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 8:2) to give the product as yellow oil (391 mg, yield 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 2H), 6.09 (br s, 1H), 5.13 (t, *J* = 7.5 Hz, 1H), 4.99 (d, *J* = 16.2 Hz, 1H), 4.80 (d, *J* = 16.2 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.56 – 3.48 (m, 2H), 2.77 – 2.72 (m, 2H), 1.87 – 1.82 (m, 1H), 1.66 – 1.59 (m, 1H), 1.49 – 1.40 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.0, 149.1, 147.8, 133.8 (2C), 130.7, 129.2, 128.9, 120.7, 111.8, 111.4, 61.6, 55.9(2C), 51.5, 40.9, 38.1, 35.1, 24.9, 22.3(2C).IR (thin film) 3427, 3005, 1684, 1517, 1434, 1271, 844 ν_{max}/cm^{-1}.HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{23}H_{30}ClN_3O_5$: 463.1874 Found: 463.1858.

2-(allyl(nitro)amino)-*N*-(3,4-dimethoxyphenethyl)-4-methylpentanamide, 3r



3r

Starting material: ammonium nitrate salt (216 mg, 1.0 mmol, 1.0 equiv), aldehyde (107 µL, 1.0 mmol, 1.0 equiv), and isocyanide (191 mg, 1.0 mmol, 1.0 equiv). The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 7:3) to give the product as colorless oil (196 mg, yield 52%).

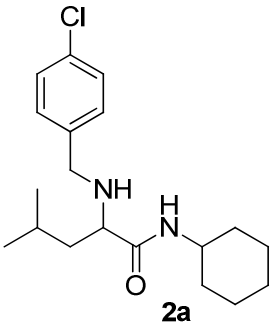
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.87 – 6.84 (m, 1H), 6.76 – 6.72 (m, 2H), 6.04 (br d, 1H), 5.87 – 5.83(m, 1H), 5.31 (d, *J* = 16.0 Hz, 1H), 5.28 (d, *J* =12.0 Hz, 1H), 5.14 (t, *J* = 7.6 Hz, 1H), 4.34 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.27 (dd, *J* = 16.0, 6.0 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.61 – 3.48 (m, 2H), 281 –2.77 (m, 2H), 1.86 – 1.77 (m, 1H), 1.72 –1.67 (m, 1H), 1.60 – 1.50 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H),), 0.94 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.0, 149.1, 147.8, 130.8, 130.6, 120.7, 119.5, 111.8, 111.4, 61.1, 55.9, 55.8 50.9, 40.9, 37.8, 35.1, 24.8, 22.5, 22.2. IR (thin film) 3428, 3057, 2962, 1686, 1516, 1352, 1292, 898 ν_{max}/cm^{-1}. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{19}H_{29}N_3O_5$: 379.2107 Found: 379.2106.

General procedure for the three-component formation of 2:

The amine (1.0 equiv, 1.0 mmol) was dissolved in DCM (0.25 M), aldehyde (1.0 equiv, 1.0 mmol), isocyanide (1.0 equiv, 1.0 mmol) and an aqueous 70% of HNO_3 (1.0 equiv, 1.0 mmol) were added. The reaction was stirred at room temperature under argon overnight. The crude mixture was diluted with a saturated aqueous solution of hydrogenocarbonate and extracted three times with diethyl

ether. The organic layer was then dessicated over magnesium sulfate, filtrated and evaporated under reduced pressure. The crude product was then purified by column chromatography (eluents EP/EtOAc).

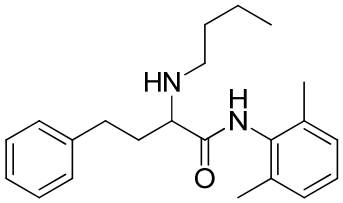
2-((4-chlorobenzyl)amino)-*N*-cyclohexyl-4-methylpentanamide, 2a



2a

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37 – 7.33 (m, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.03 (br d, *J* = 8.4 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.74 (d, *J* = 13.3 Hz, 1H), 3.65 (d, *J* = 13.3 Hz, 1H), 3.16 – 3.12 (m, 1H), 1.96 – 1.87 (m, 2H), 1.76 – 1.59 (m, 6H), 1.47 – 1.37 (m, 3H), 1.28 – 1.14 (m, 3H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.5, 138.2, 133.1, 129.5, 128.7, 61.1, 52.1, 47.4, 43.1, 33.2, 25.6, 25.1, 24.8, 23.3, 21.9. IR (thin film) 3425, 3358, 3053, 1666, 1430, 1245, 900 ν_{max}/cm^{-1}. MP (white solid): 105.1-106.0 °C. HRMS *m/z*: $[M]^{+\bullet}$calcd for $C_{19}H_{29}ClN_2O$: 336.1968 Found: 336.1963.

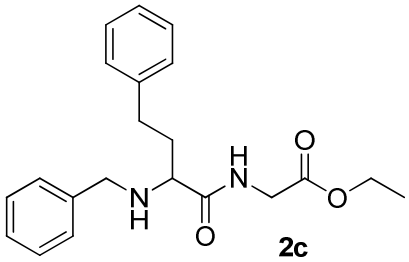
2-(phenethyl)-*N*-2,6-xylyl-2-(butylamino)acetamide 2b



2b

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.35 – 7.22 (m, 3H), 7.21 – 7.11 (m, 3H), 7.08 – 6.96 (m, 3H), 5.18 – 5.13 (m, 1H), 3.73 – 3.62 (m, 2H), 2.75 – 2.64 (m, 2H), 2.51 – 2.33 (m, 1H), 2.20 – 2.03 (m, 7H), 1.82 – 1.66 (m, 1H), 1.65 – 1.46 (m, 1H), 1.28 (hex, *J* = 7.4 Hz, 2H), 0.86 (t, *J* = 7.3 Hz, 3H) . ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.2, 139.8, 134.9 (2C), 132.9, 128.8 (2C), 128.3 (2C), 128.3 (2C), 127.7, 126.6, 62.3, 49.1, 32.3, 30.9, 29.4, 20.1, 18.5 (2C), 13.6 ; HRMS *m/z*: $[M]^{+\bullet}$ calcd for $C_{22}H_{30}N_2O$ 338.2358, found: 337.2402.

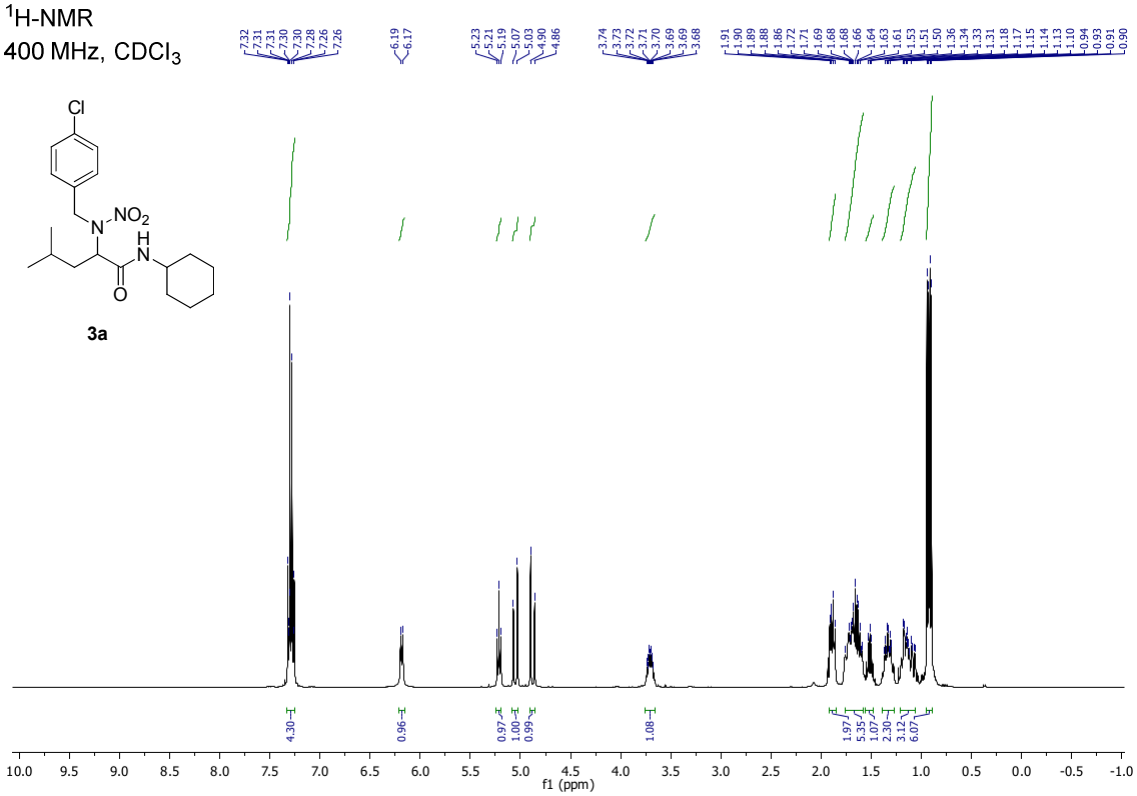
Ethyl (2-(benzylamino)-4-phenylbutanoyl)glycinate 2c



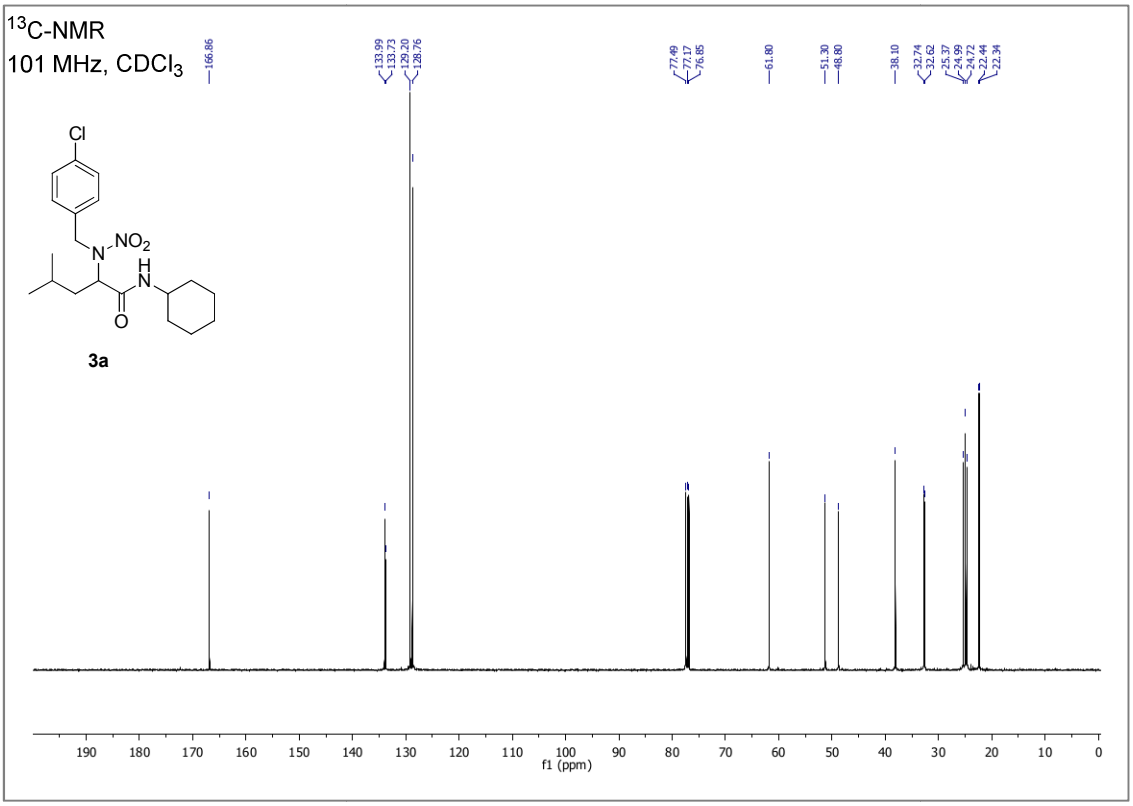
2c

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.53 – 7.14 (m, 9H), 7.14 – 6.96 (m, 2H), 6.44 (br t, *J* = 5.5 Hz, 1H), 5.21 (d, *J* = 16.1 Hz, 1H), 5.06 (t, *J* = 7.4 Hz, 1H), 4.80 (d, *J* = 16.1 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.03 (dd, *J* = 18.0, 6.0 Hz, 1H), 3.90 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.74 – 2.50 (m, 2H), 2.47 – 2.30 (m, 1H), 2.17 – 2.07 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 168.0, 139.8, 135.2, 128.8 (2C), 128.6 (2C), 128.3 (2C), 128.1, 127.8 (2C), 126.4, 62.3, 61.7, 52.8, 41.4, 32.1, 30.7, 14.1 ; HRMS *m*/*z*: $[M]^{+\bullet}$ calcd for $C_{21}H_{26}N_2O_3$ 354.1943, found: 353.1735.

^{1}H-NMR
400 MHz, $CDCl_3$



^{13}C-NMR
101 MHz, $CDCl_3$



Laboratoire de Synthèse Organique

20/06/2016 15:06:09

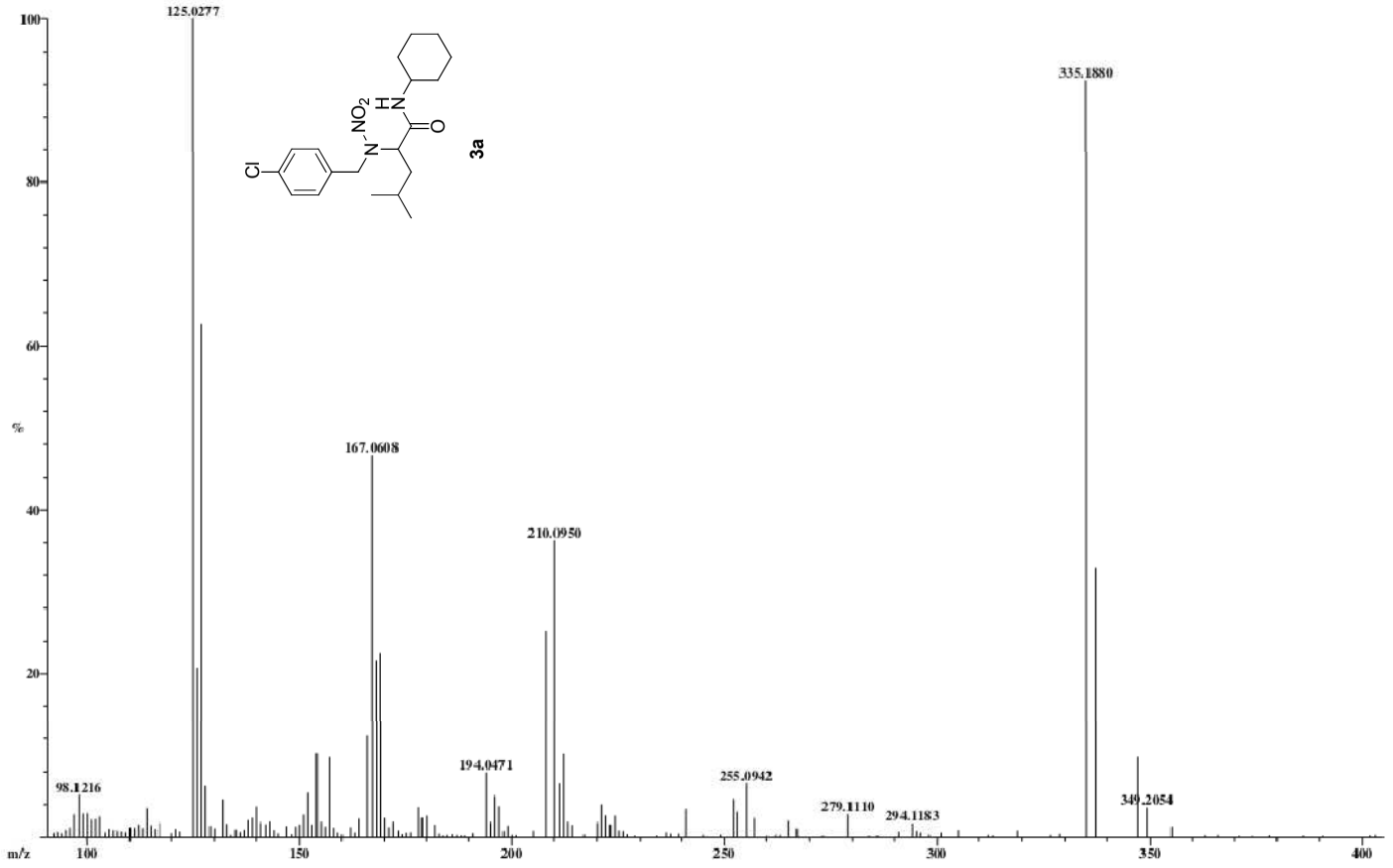
File: MV162
Sample:

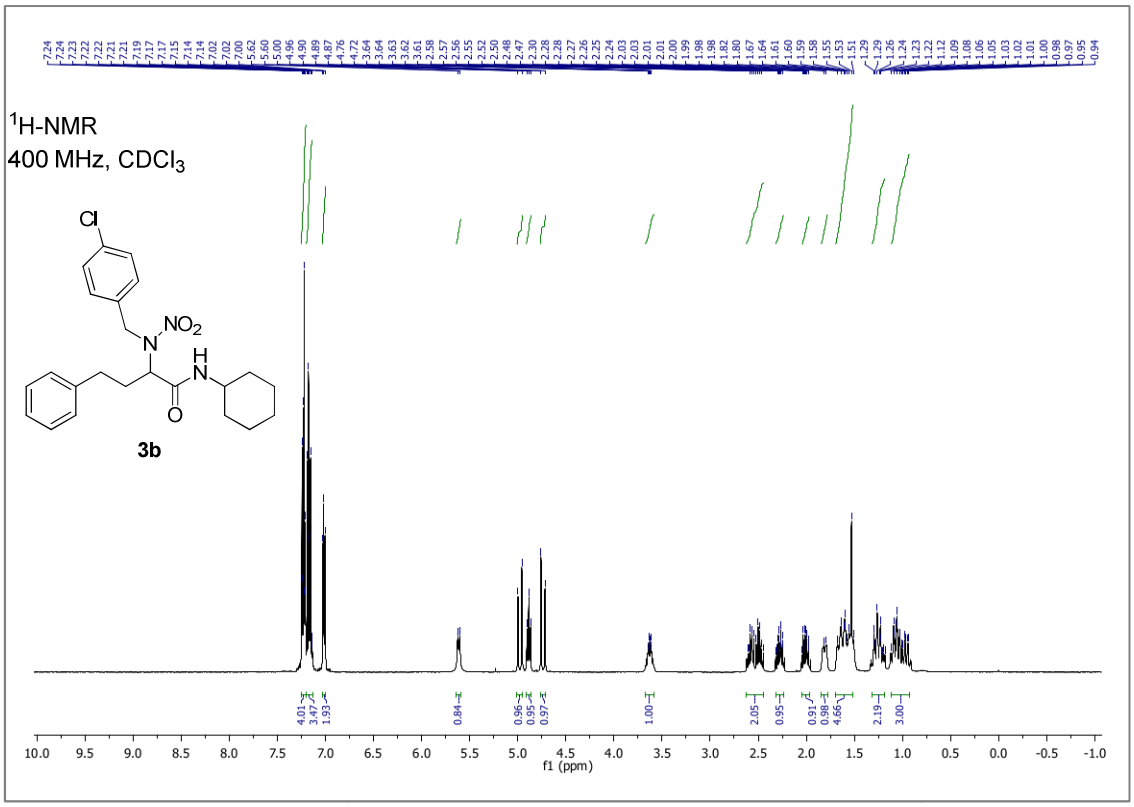
Date Run: 06-20-2016 (Time Run: 14:59:40)
Instrument: JEOL JMSGCmateII

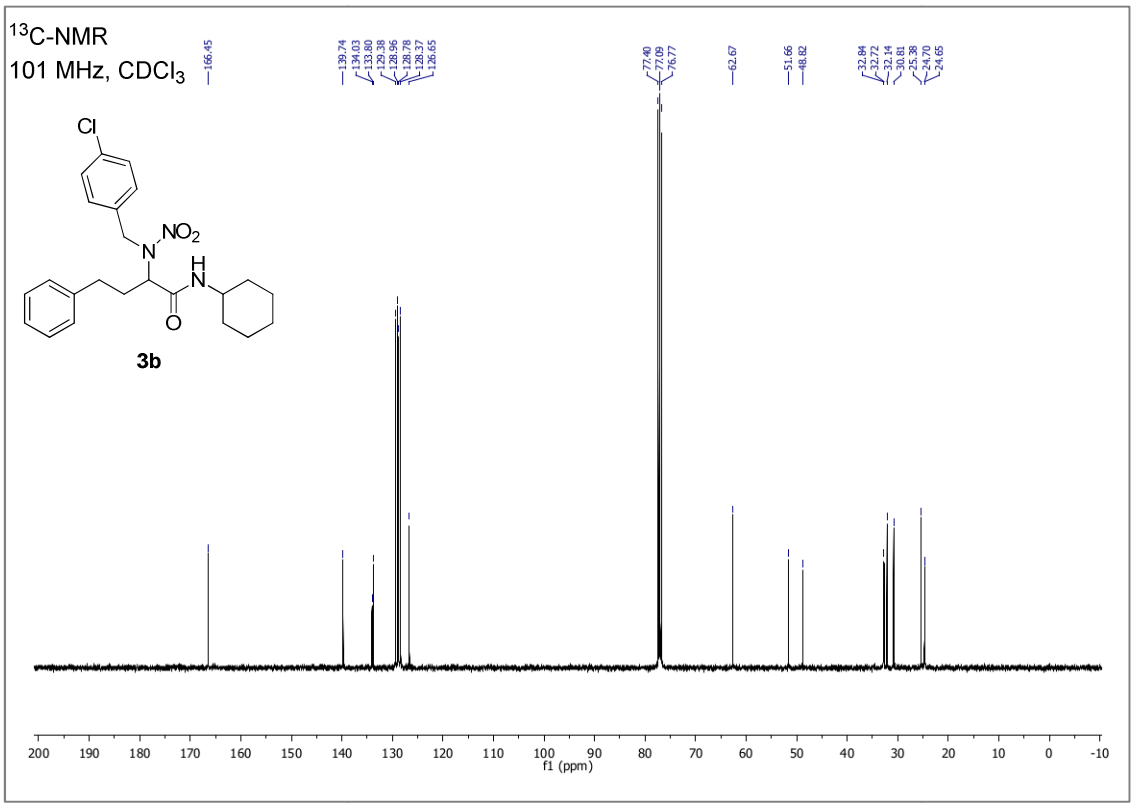
Inlet: Direct Probe

Run By: Vincent Jactel
Ionization mode: EI+

335,1880 : 93 % **Scan: 214** **TIC: 5408736**




1H-NMR
400 MHz, CDCl3
Cl
NO2
N
H
N
O
3b
f1 (ppm)


13C-NMR
101 MHz, CDCl3
Cl
NO2
N
H
N
O
3b
f1 (ppm)

Laboratoire de Synthèse Organique

22/06/2016 11:22:28

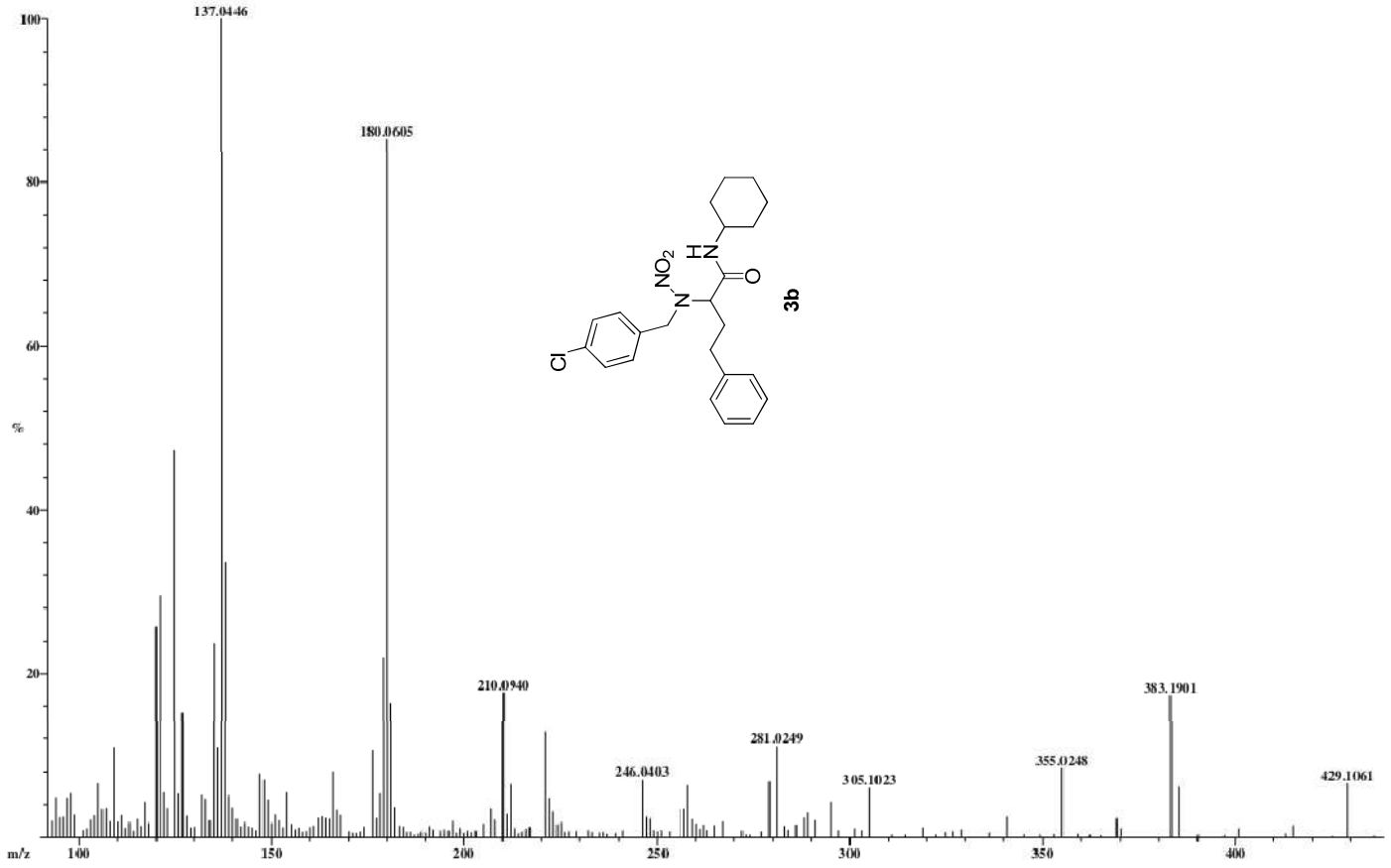
File: MV159
Sample:

Date Run: 06-22-2016 (Time Run: 11:09:41)
Instrument: JEOL JMSGCmateII

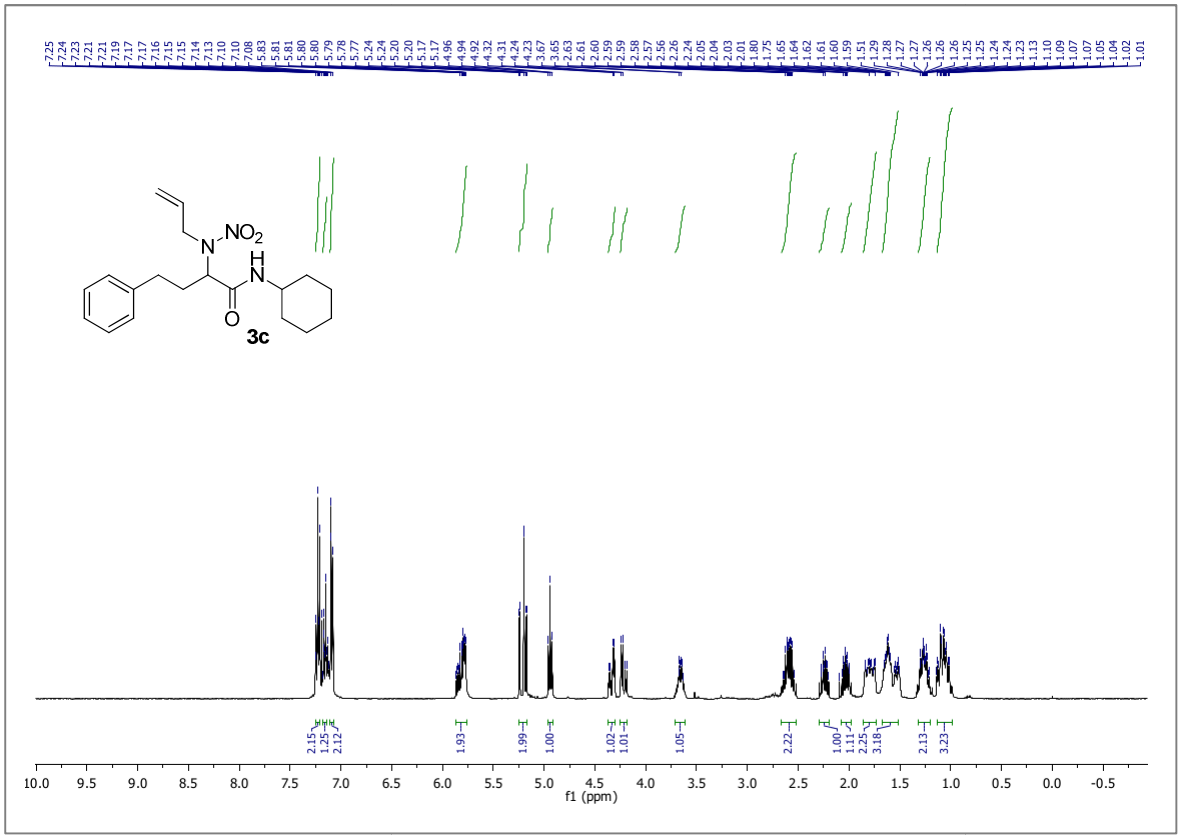
Inlet: Direct Probe

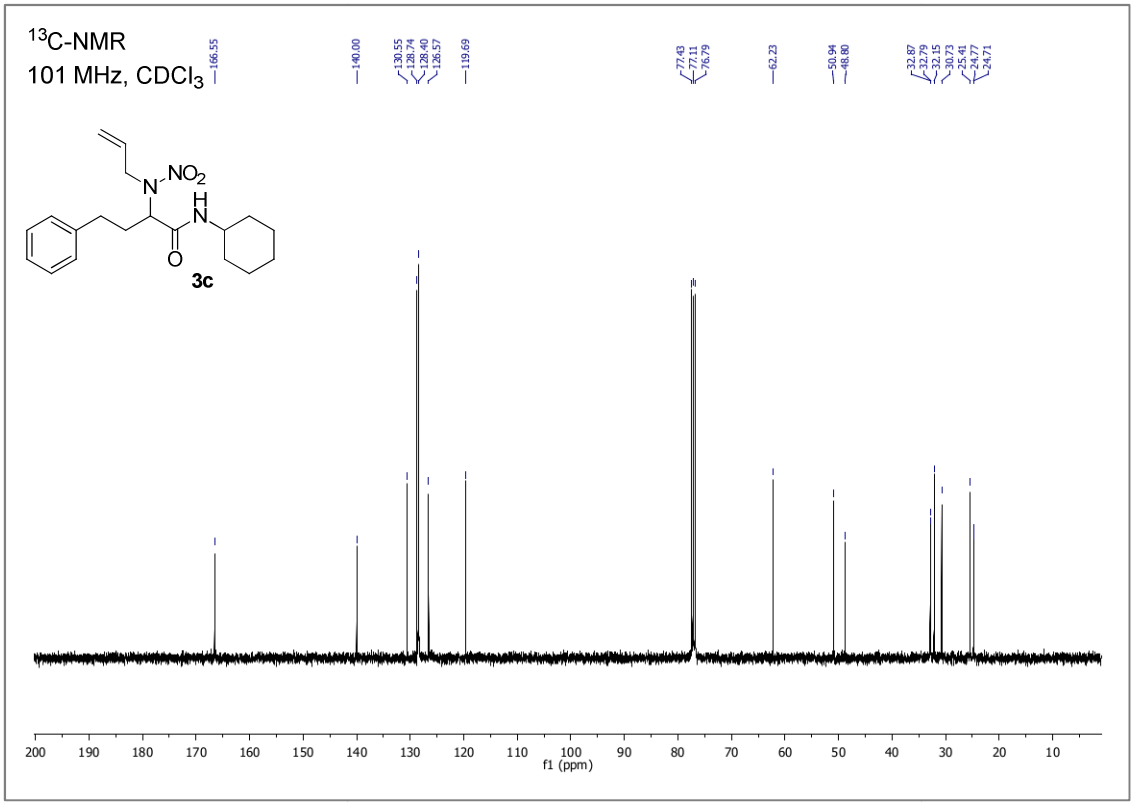
Run By: Vincent Jactel
Ionization mode: EI+

383,1901 : 17 % **Scan: 109** **TIC: 5254242**



3b


3c
f1 (ppm)


13C-NMR
101 MHz, CDCl3
3c
f1 (ppm)

Laboratoire de Synthèse Organique

21/07/2016 10:53:56

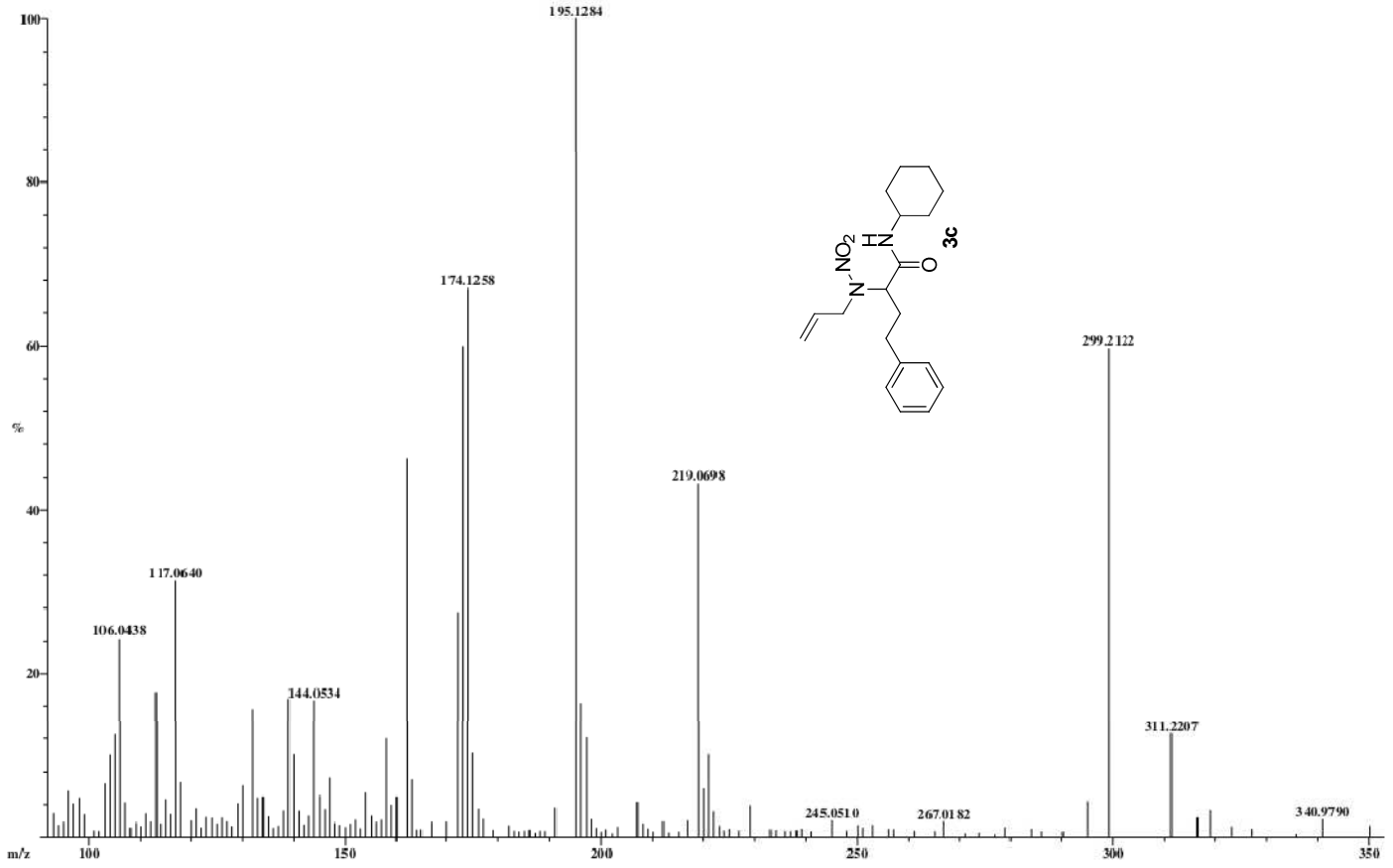
File: MV184
Sample:

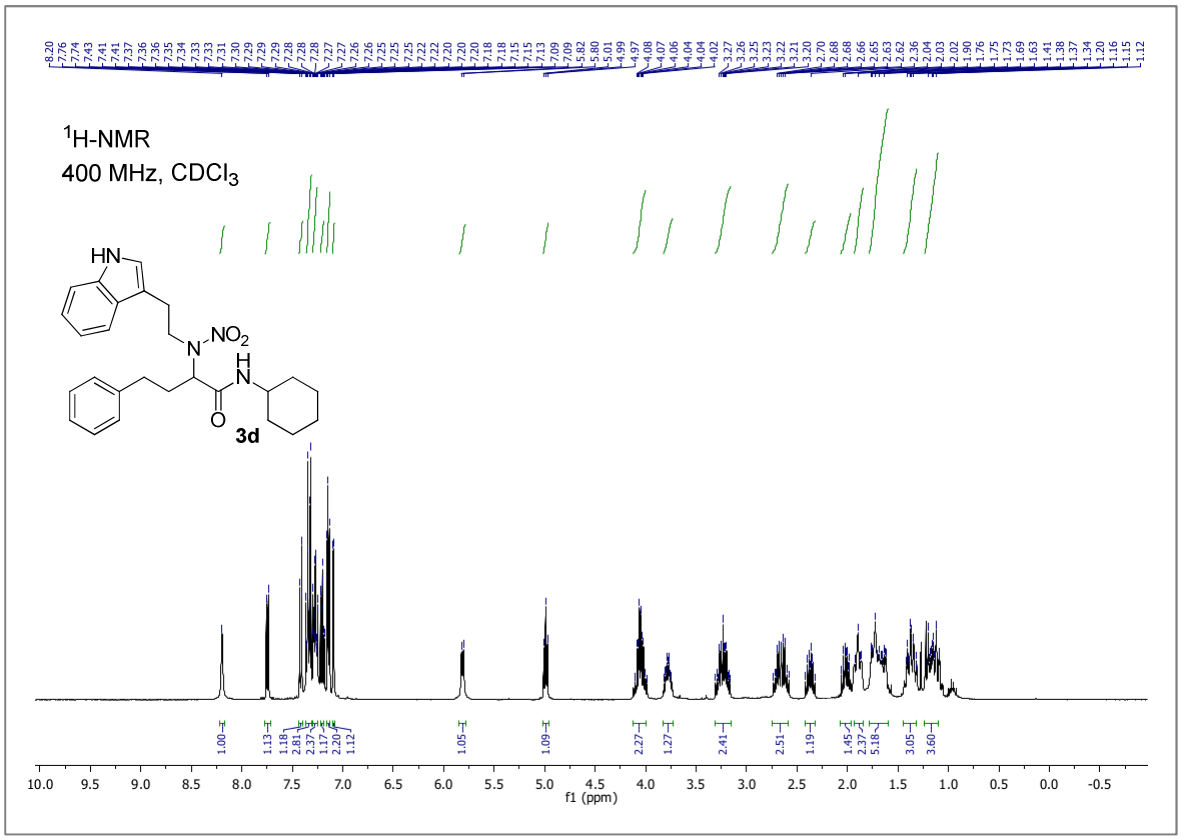
Date Run: 07-21-2016 (Time Run: 10:48:52)
Instrument: JEOL JMSGCmateII

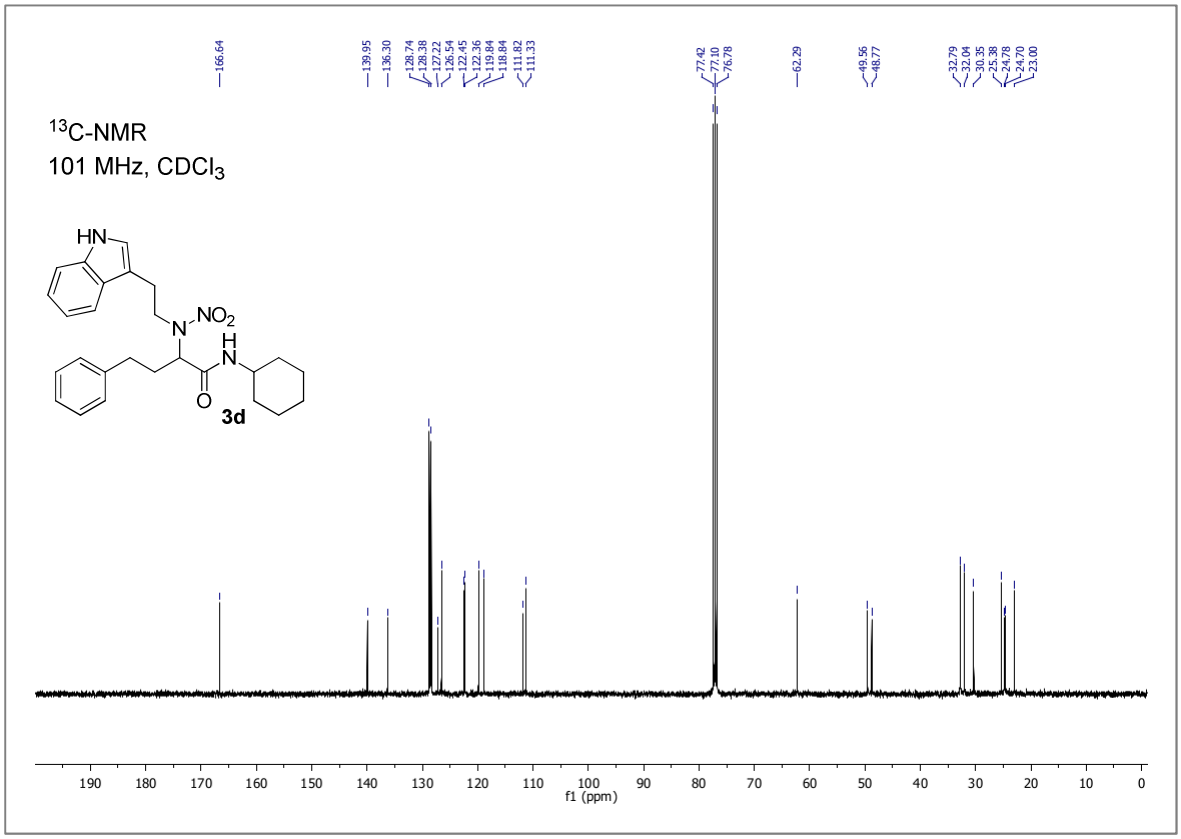
Inlet: Direct Probe

Run By: Vincent Jactel
Ionization mode: EI+

299,2122 : 60 % **Scan: 113** **TIC: 3366232**




^{1}H-NMR
400 MHz, $CDCl_3$
HN
NO_2
N
H
N
O
3d
f1 (ppm)


^{13}C-NMR
101 MHz, $CDCl_3$
HN
NO_2
N
H
N
O
3d
f1 (ppm)

Laboratoire de Synthèse Organique

29/07/2016 10:19:35

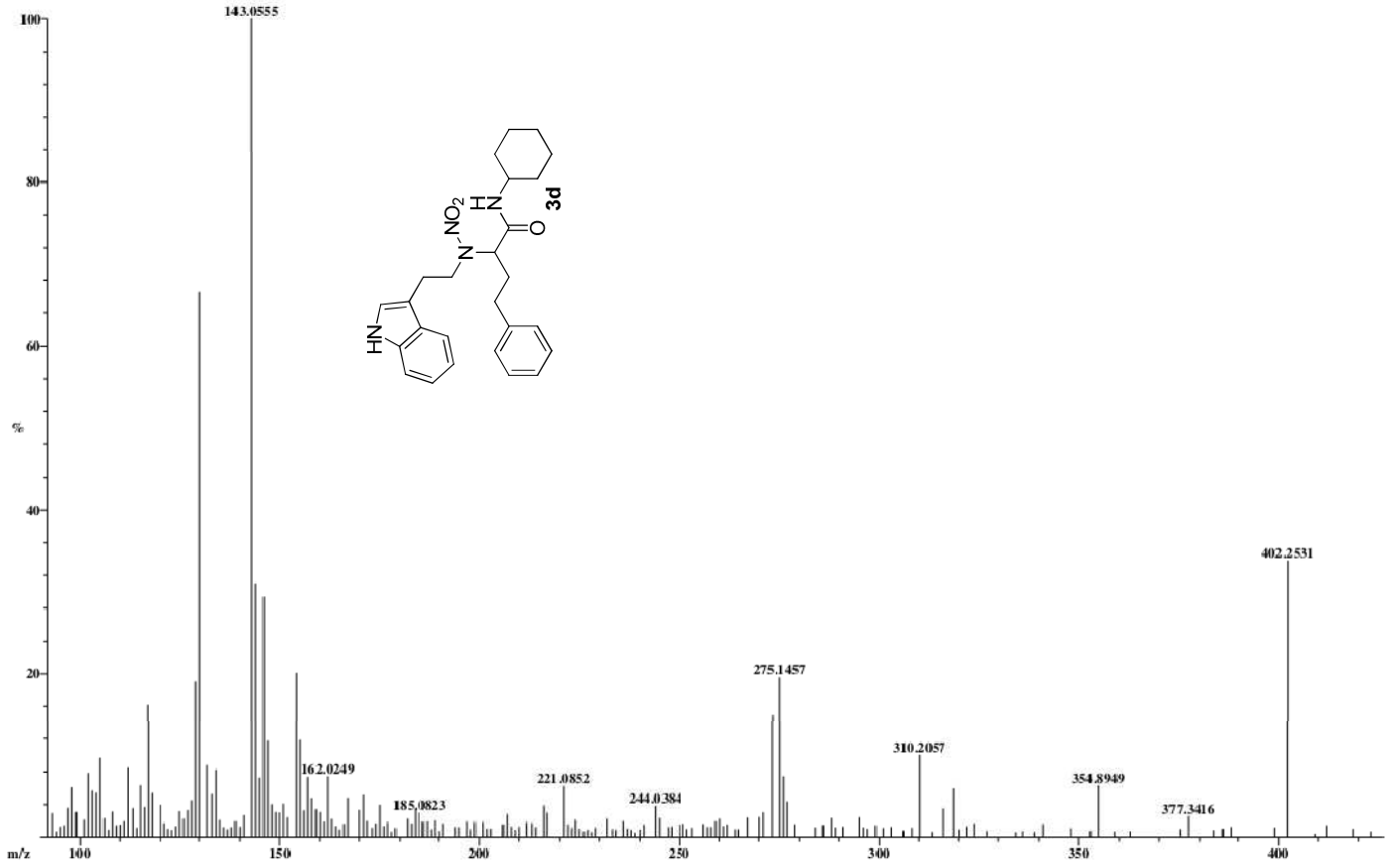
File: MV186
Sample:

Date Run: 07-29-2016 (Time Run: 10:08:45)
Instrument: JEOL JMSGCmateII

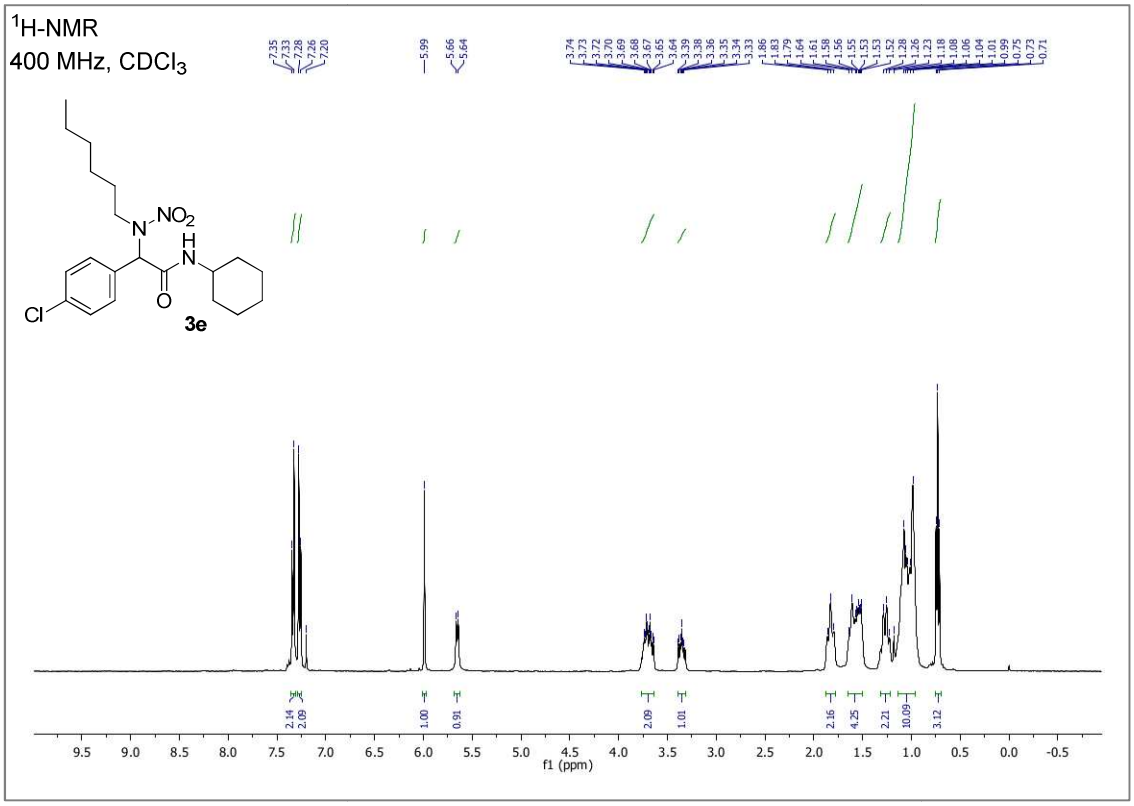
Inlet: Direct Probe

Run By: Vincent Jactel
Ionization mode: EI+

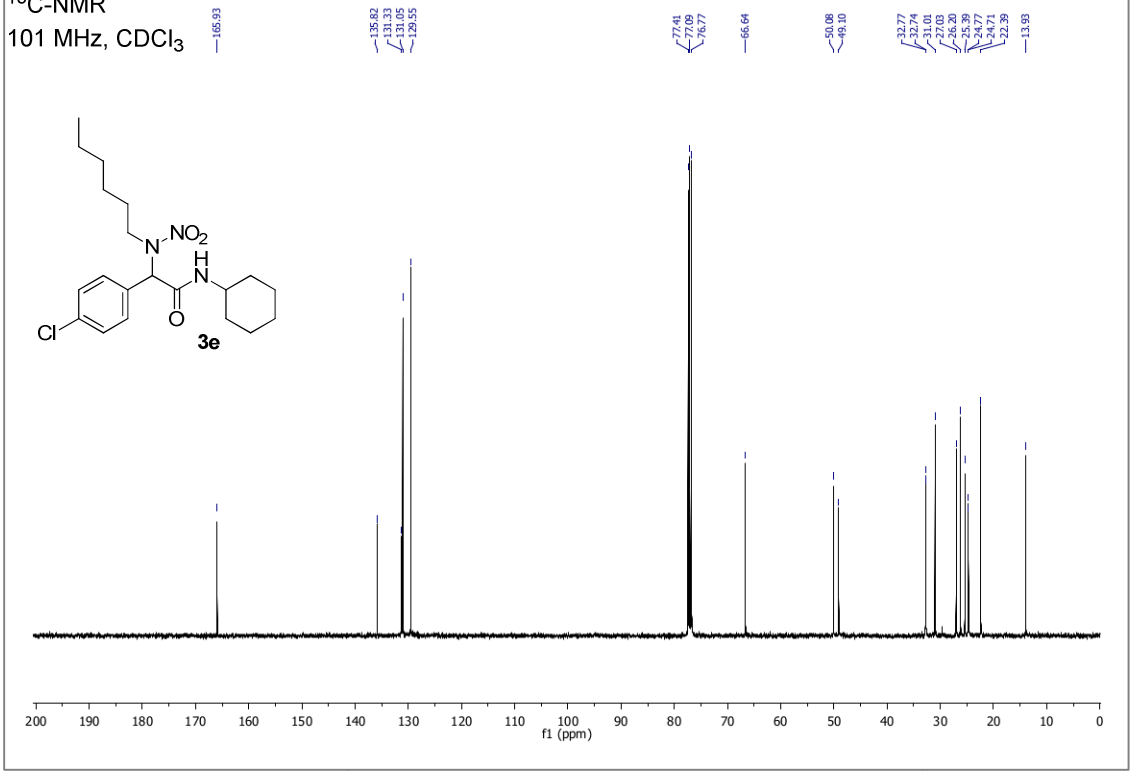
402,2531 : 34 % **Scan: 382** **TIC: 2237154**



^{1}H-NMR
400 MHz, $CDCl_3$



^{13}C-NMR
101 MHz, $CDCl_3$



Laboratoire de Synthèse Organique

01/08/2016 16:53:42

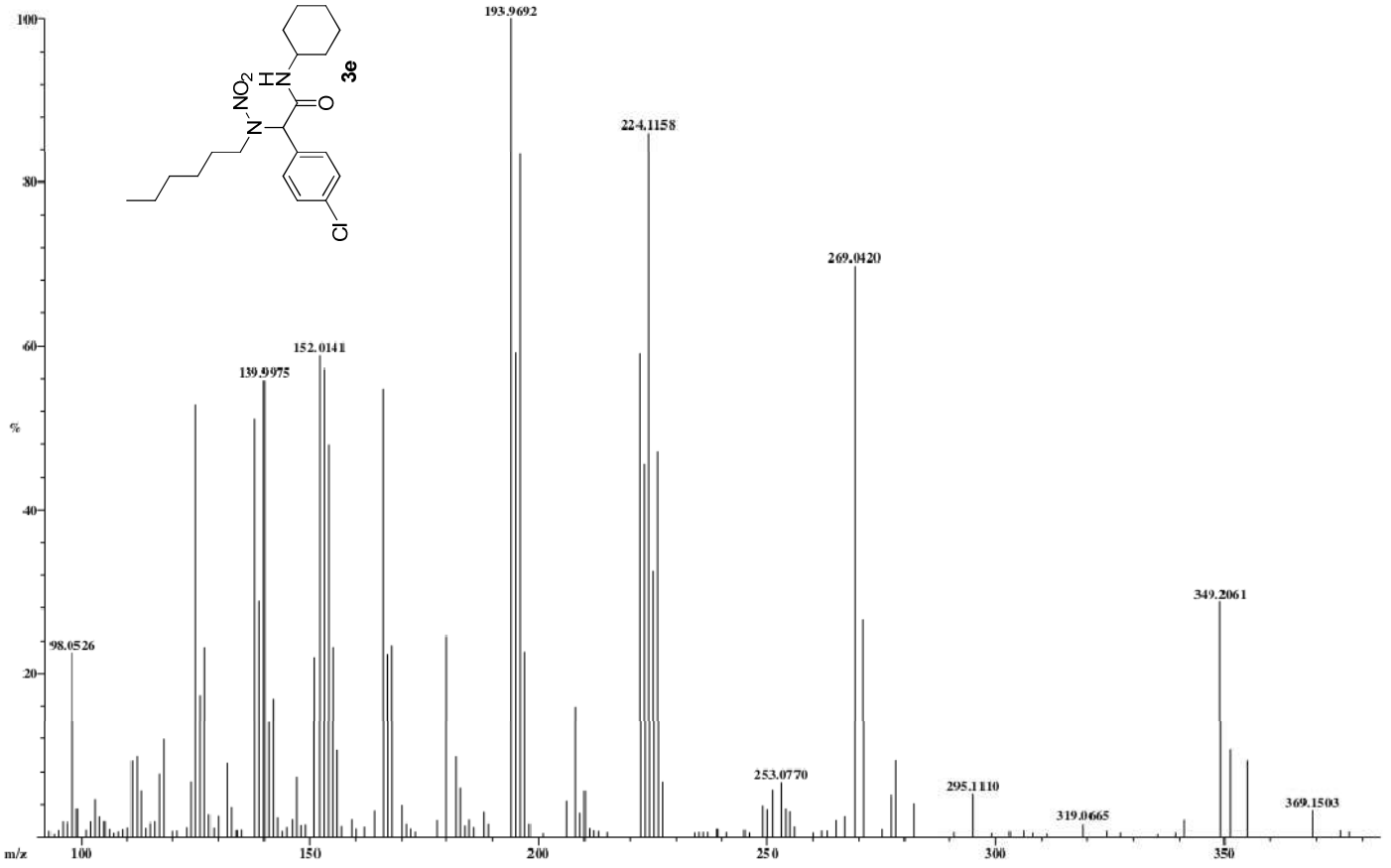
File: MV180 bis
Sample:

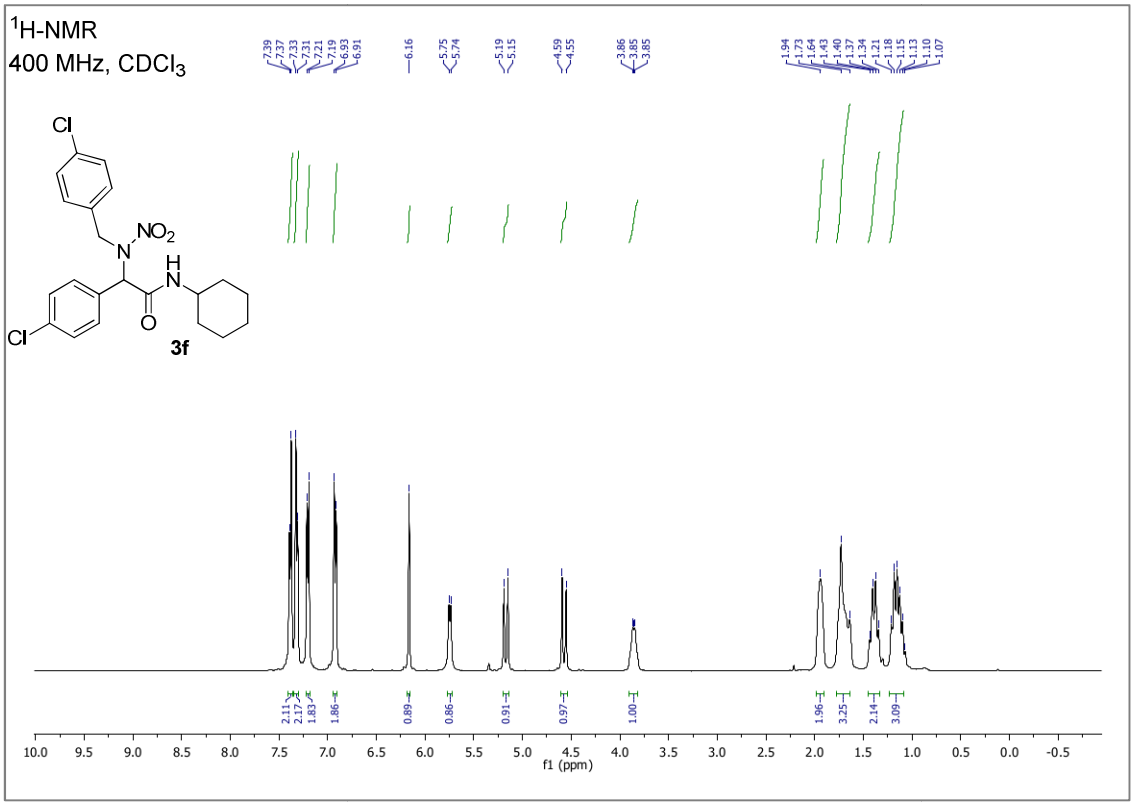
Date Run: 01-08-2016 (Time Run: 16:43:21)
Instrument: JEOL JMSGCmateII

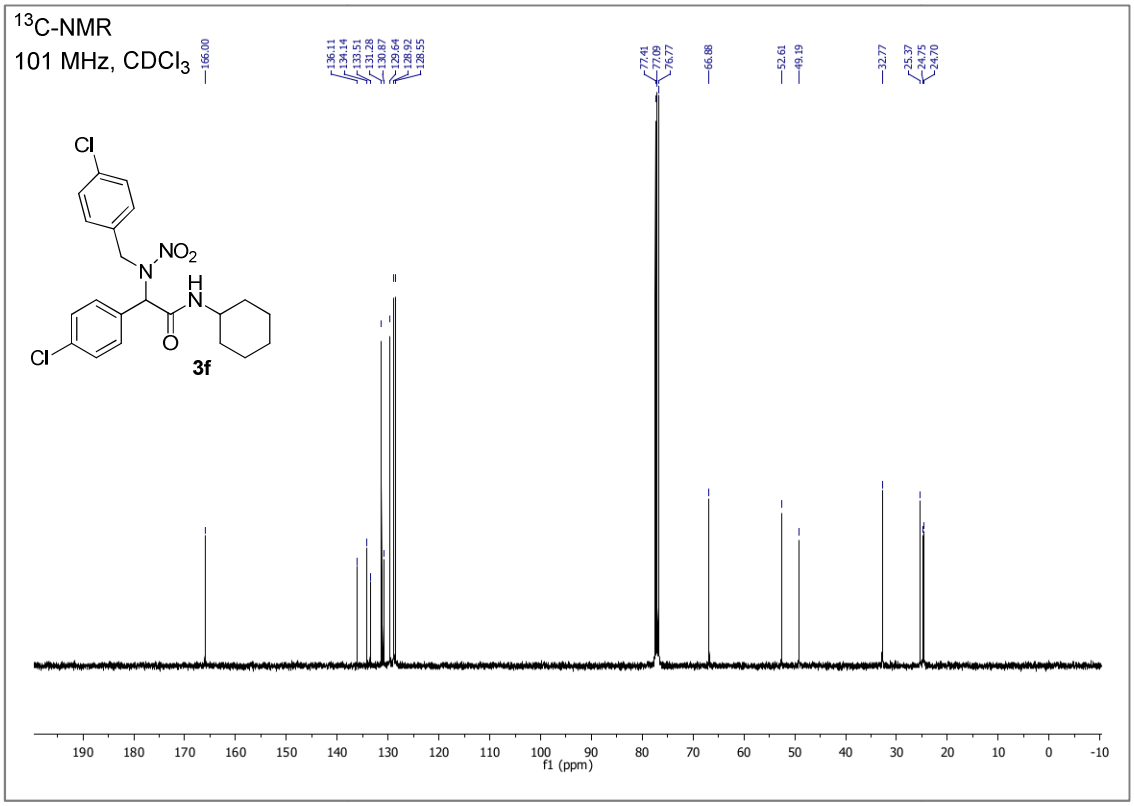
Inlet: Direct Probe

Run By: Vincent Jactel
Ionization mode: EI+

349,2061 : 29 % **Scan: 230** **TIC: 16898716**




1H-NMR
400 MHz, CDCl3
3f
f1 (ppm)


13C-NMR
101 MHz, CDCl3
3f
f1 (ppm)

Laboratoire de Synthèse Organique

22/06/2016 11:04:35

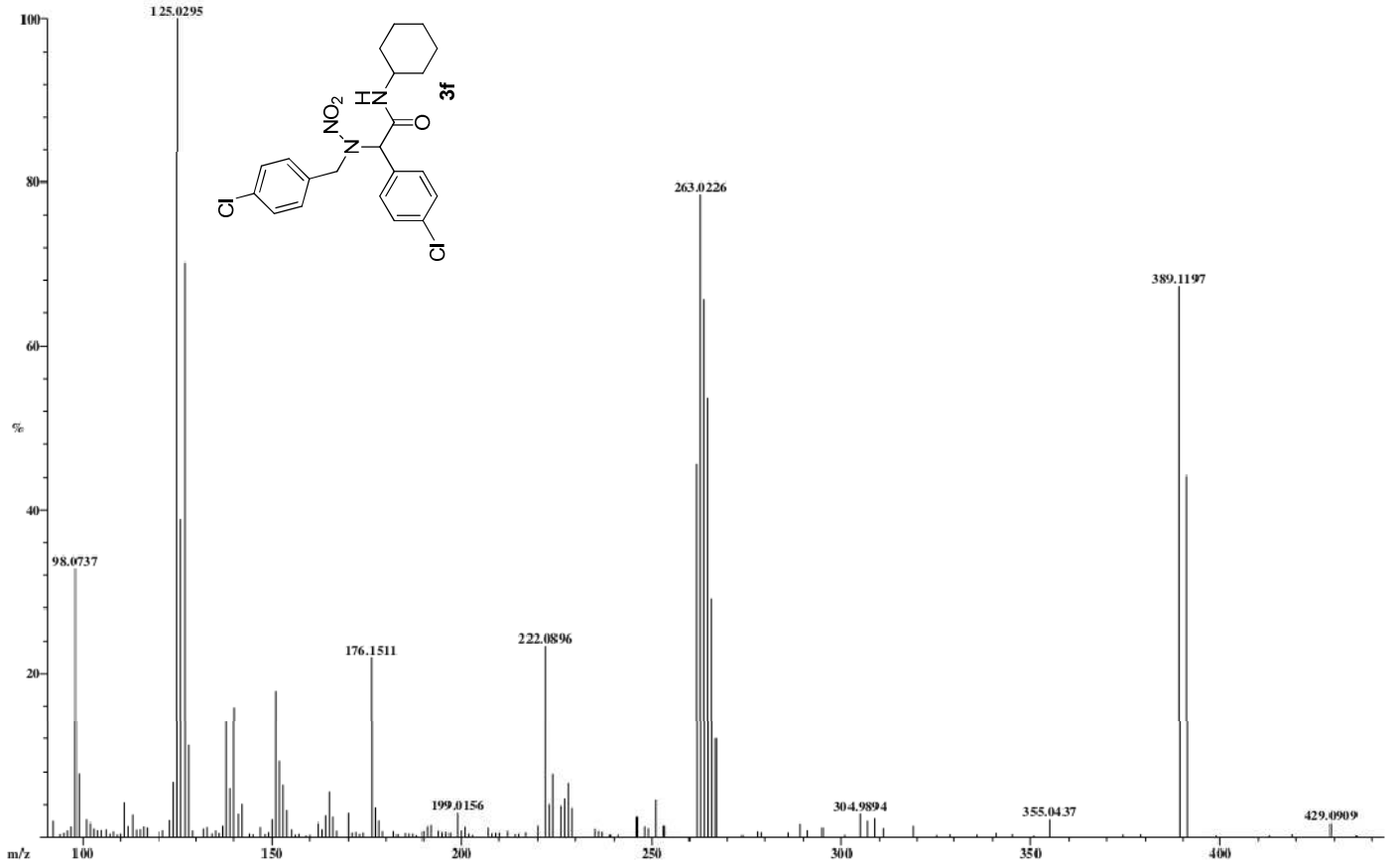
File: MV160
Sample:

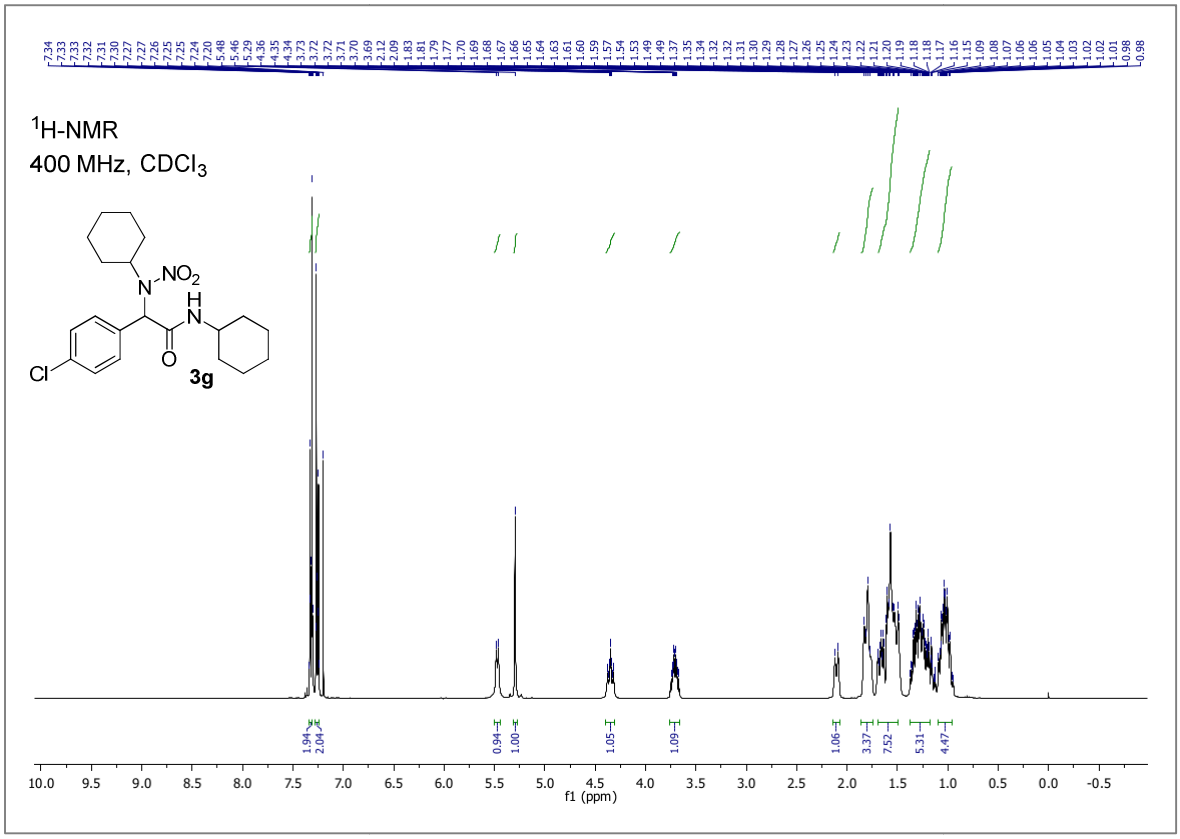
Date Run: 06-22-2016 (Time Run: 10:23:22)
Instrument: JEOL JMSGCmateII

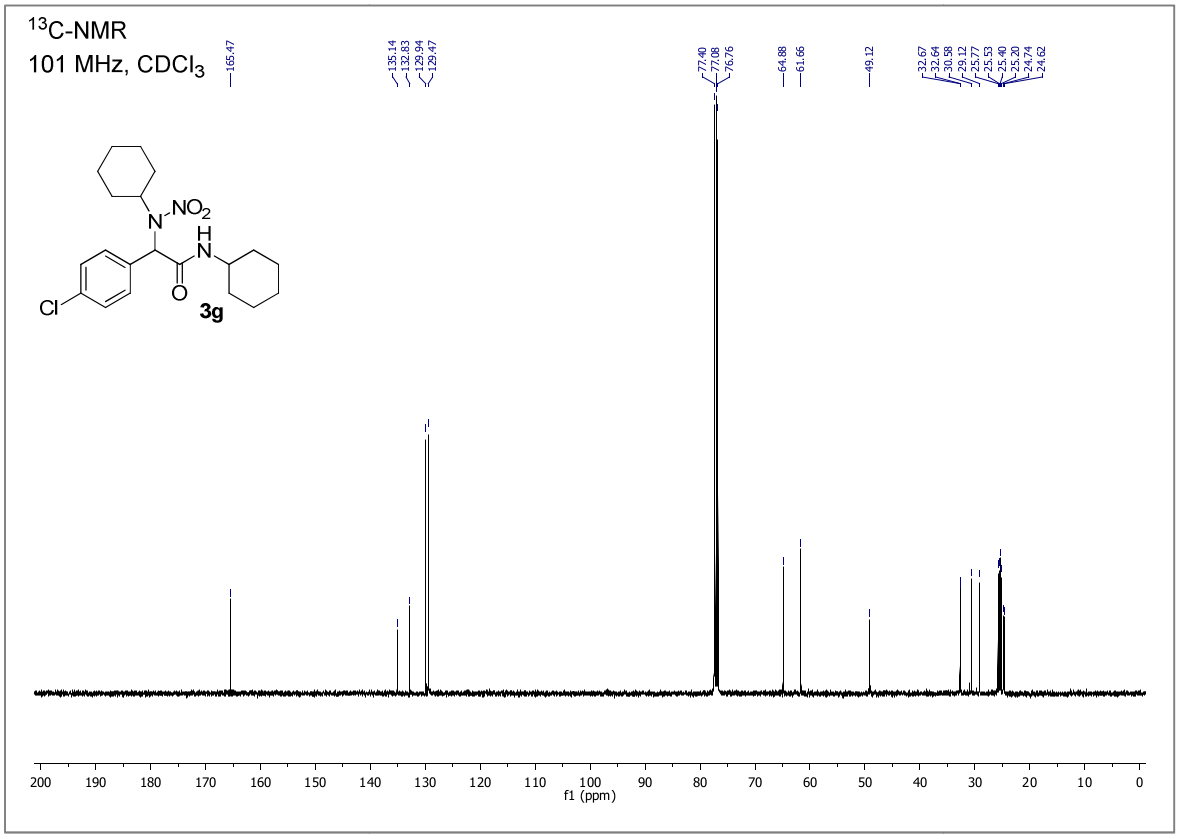
Inlet: Direct Probe

Run By: Vincent Jactel
Ionization mode: EI+

389,1197 : 67 % **Scan: 419** **TIC: 8019248**




1H-NMR
400 MHz, CDCl3
NO2
N
H
N
O
Cl
3g
f1 (ppm)


13C-NMR
101 MHz, CDCl3
NO2
N
H
N
O
Cl
3g
f1 (ppm)

Laboratoire de Synthèse Organique

21/07/2016 18:03:35

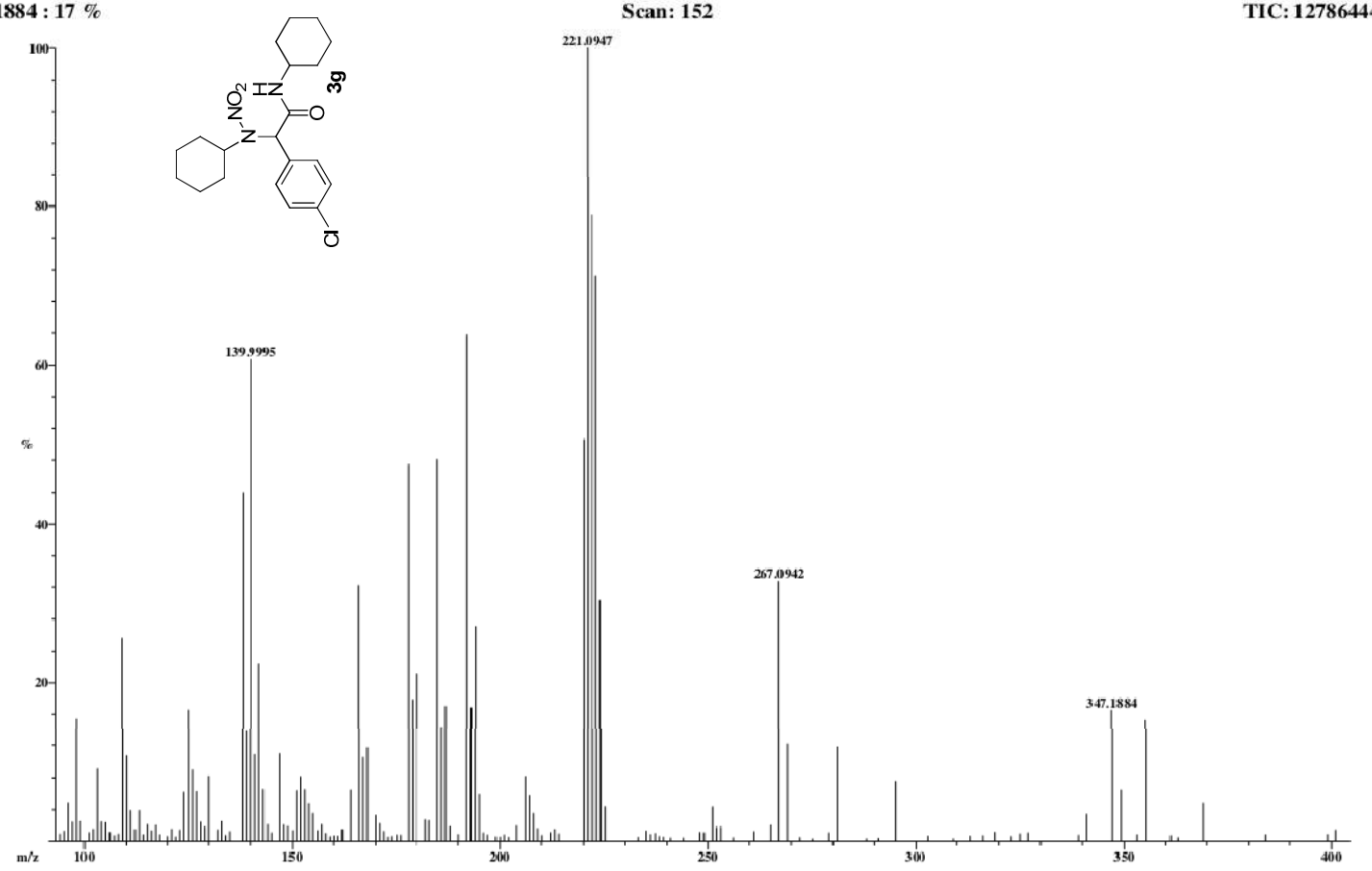
File: MV181
Sample:

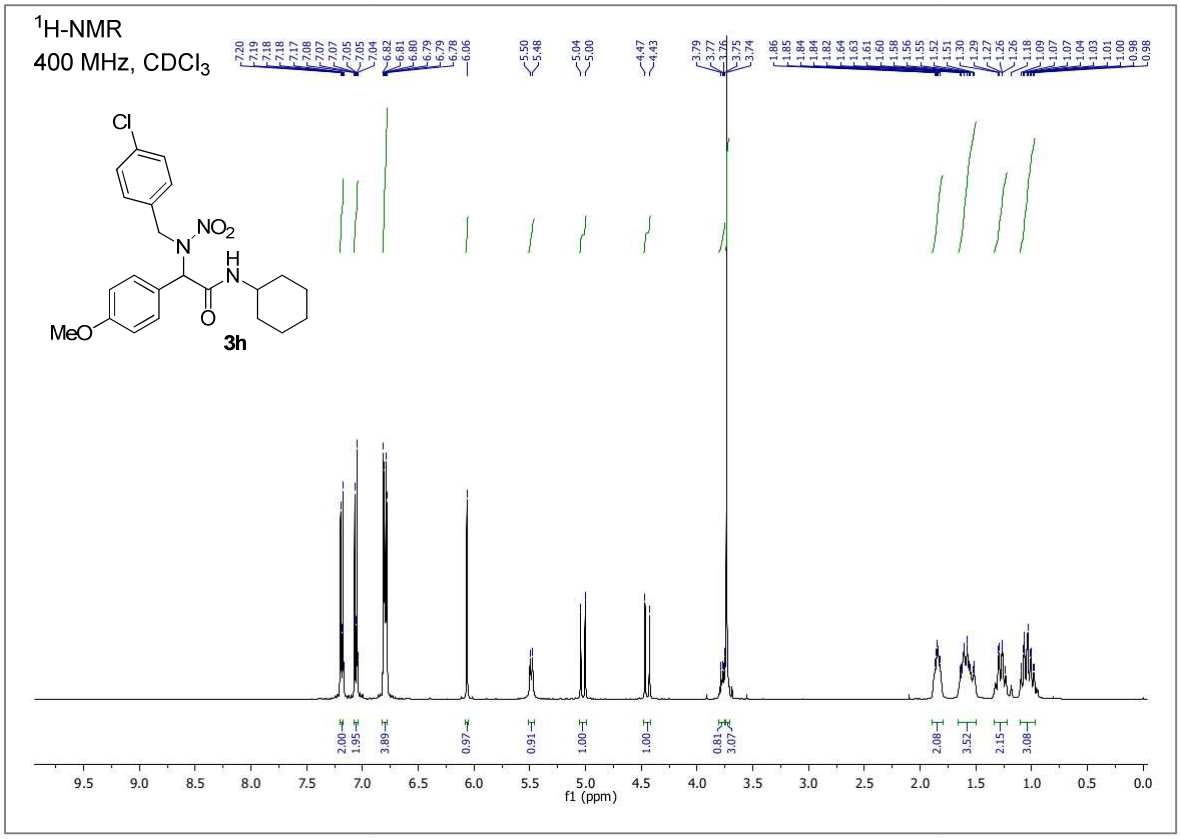
Date Run: 07-21-2016 (Time Run: 17:55:19)
Instrument: JEOL JMSGCmateII

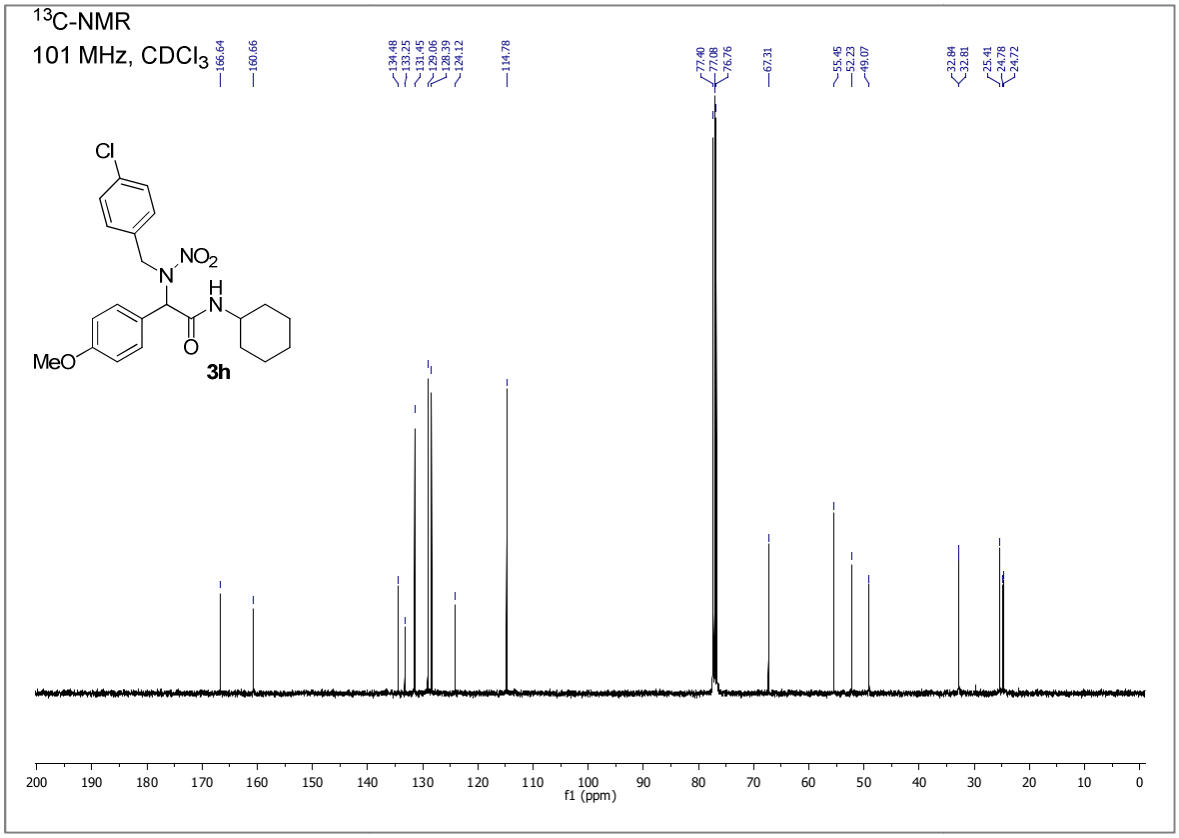
Inlet: Direct Probe

Run By: Vincent Jactel
Ionization mode: EI+

347,1884 : 17 % **Scan: 152** **TIC: 12786444**




1H-NMR
400 MHz, CDCl3
Cl
NO2
N
H
N
O
MeO
3h
f1 (ppm)


13C-NMR
101 MHz, CDCl3
Cl
NO2
N
H
N
O
MeO
3h
f1 (ppm)

Laboratoire de Synthèse Organique, Palaiseau, France

10/08/2016 16:17:32

File: MV169 2
Sample : MV169

Date Run: 07-25-2016 (Time Run: 14:00:02)
Instrument: JEOL JMSGCmateII

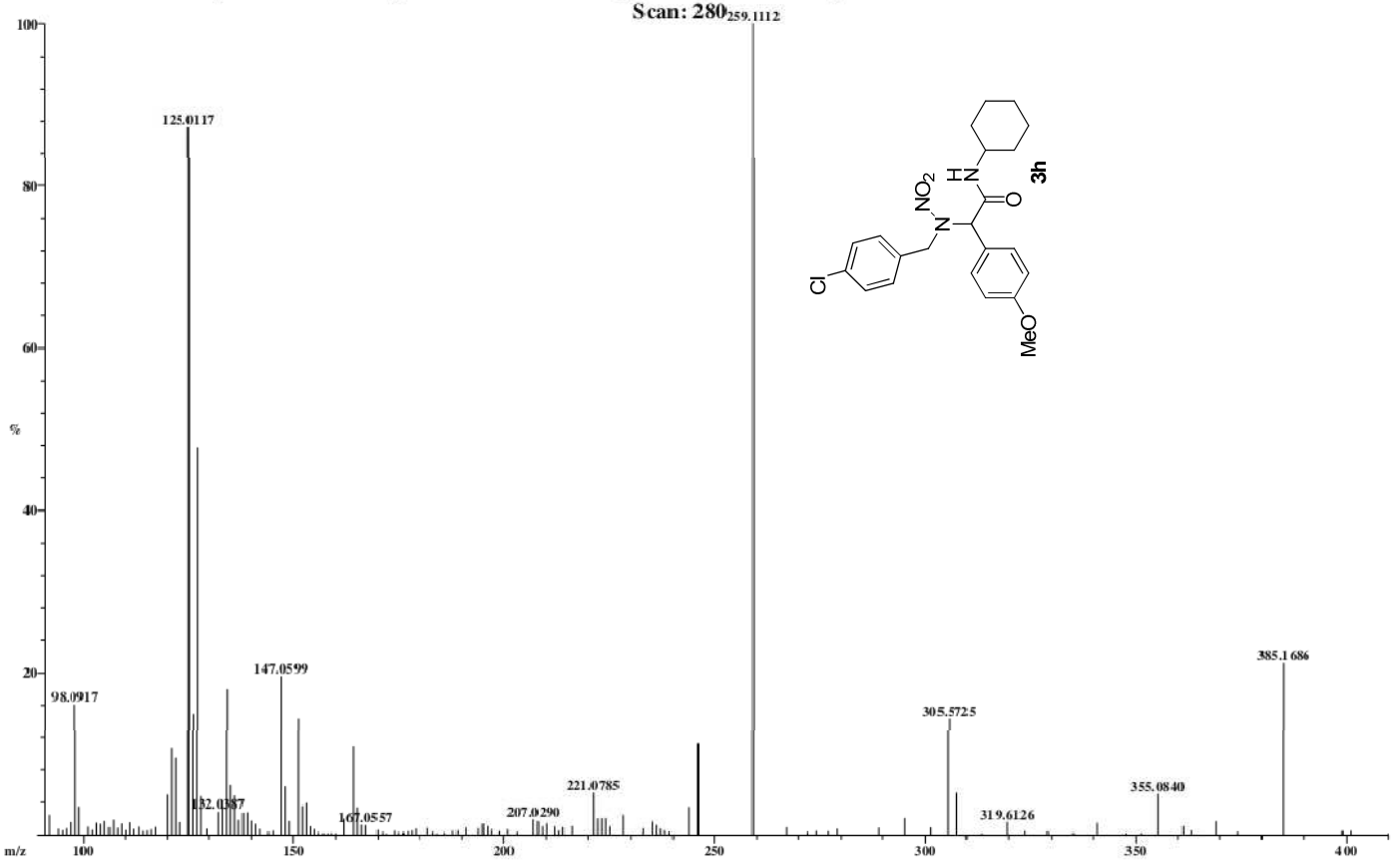
Inlet: Direct Probe

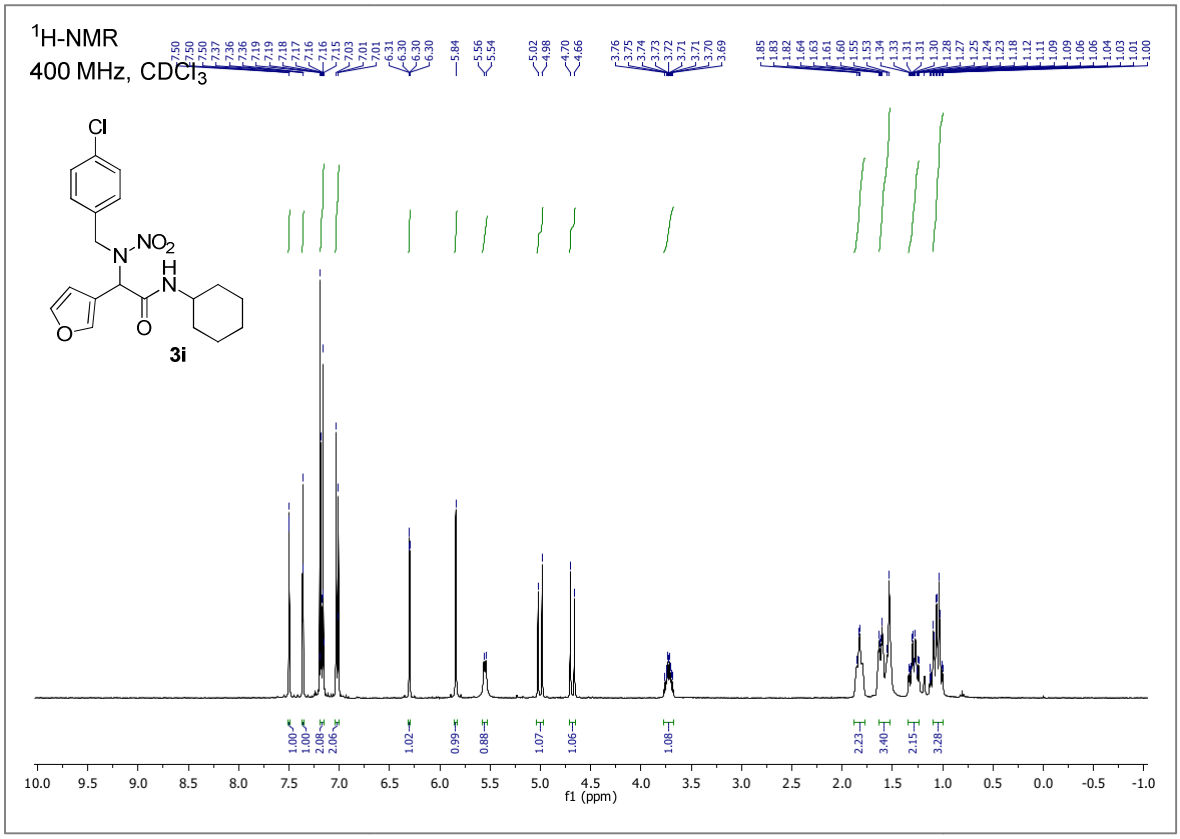
Run By: Vincent Jactel
Ionization mode: EI+

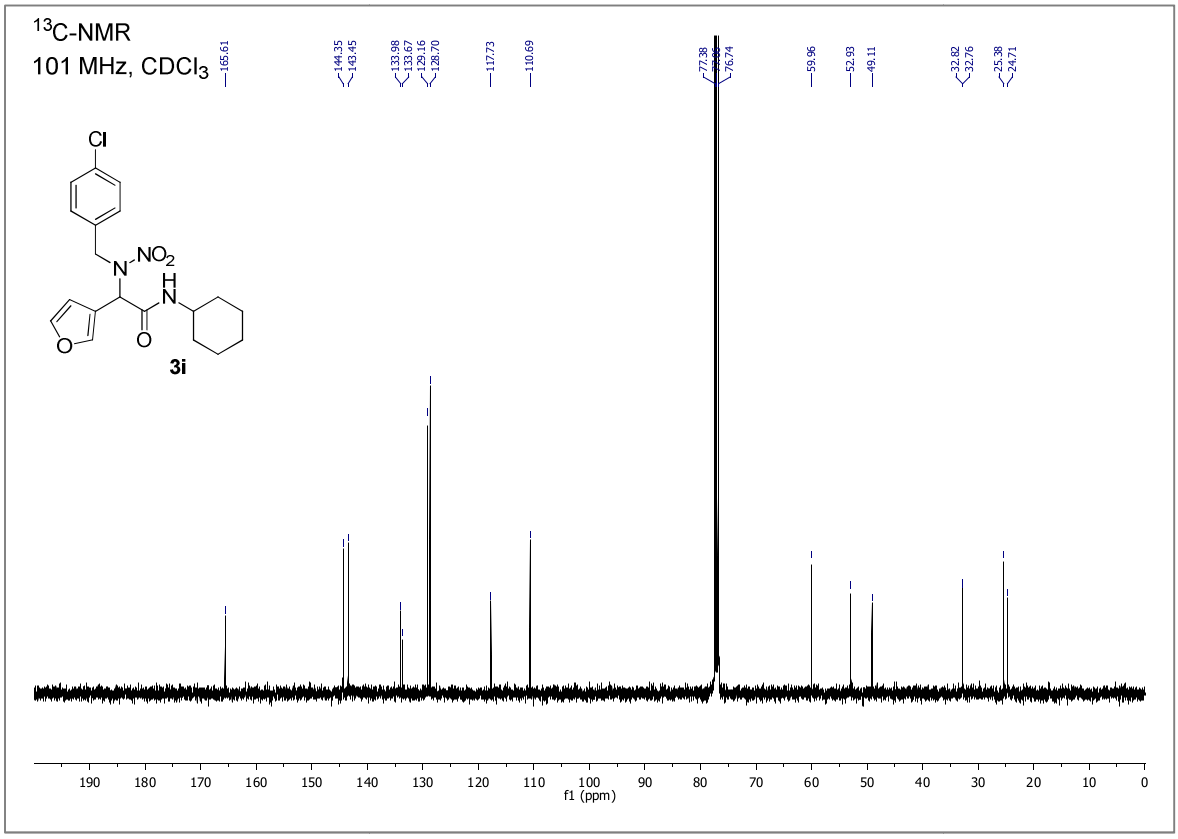
385,1686 : 21 % Absence du pic du second isotope du chlore due à un dysfonctionnement du spectromètre

TIC: 5236750

Scan: 280$_{259.1112}$




^{1}H-NMR
400 MHz, $CDCl_3$
Cl
NO_2
N
H
N
O
O
3i
f1 (ppm)


^{13}C-NMR
101 MHz, $CDCl_3$
Cl
NO_2
N
H
N
O
O
3i
f1 (ppm)

Laboratoire de Synthèse Organique

21/07/2016 17:20:52

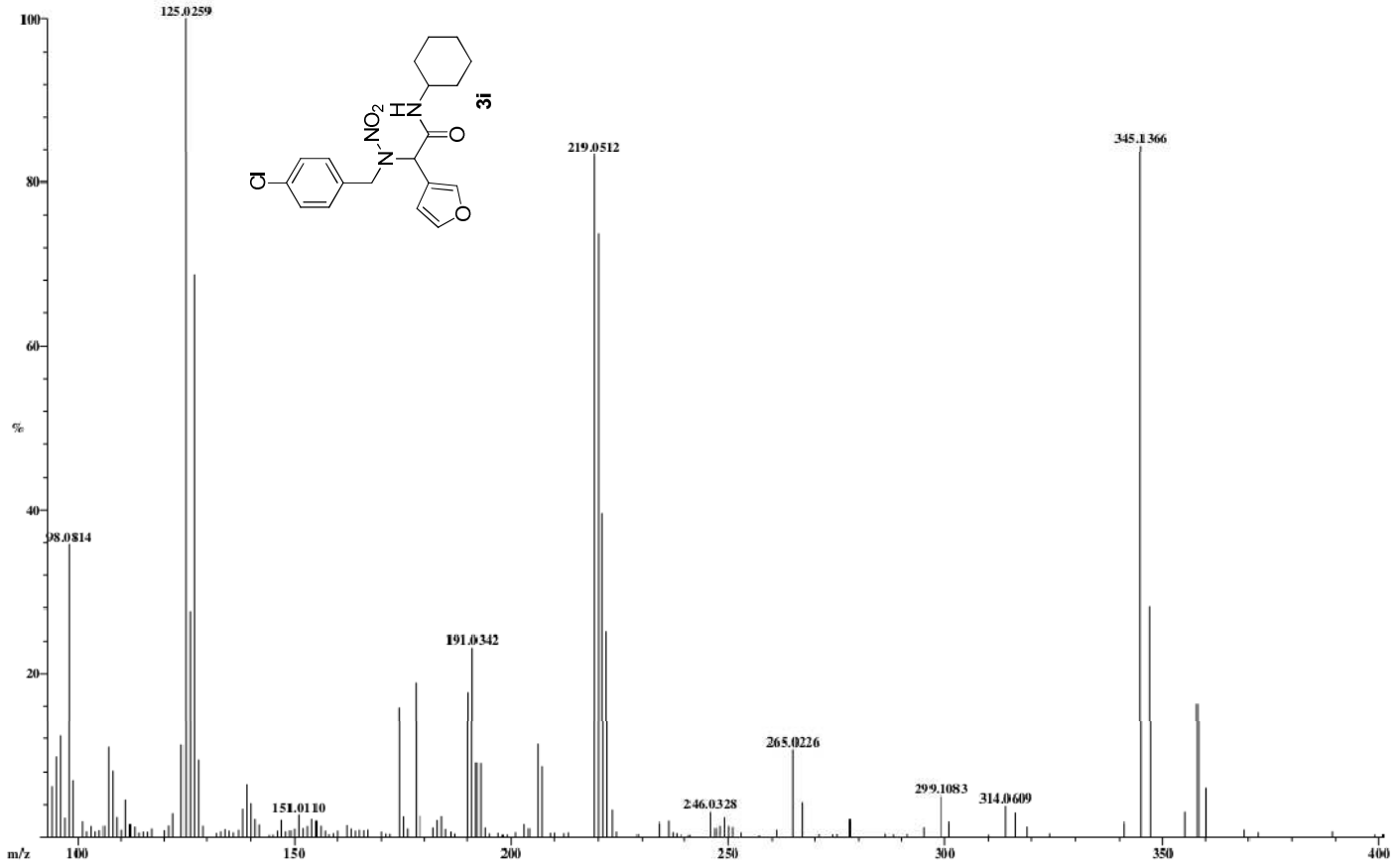
File: MV179
Sample:

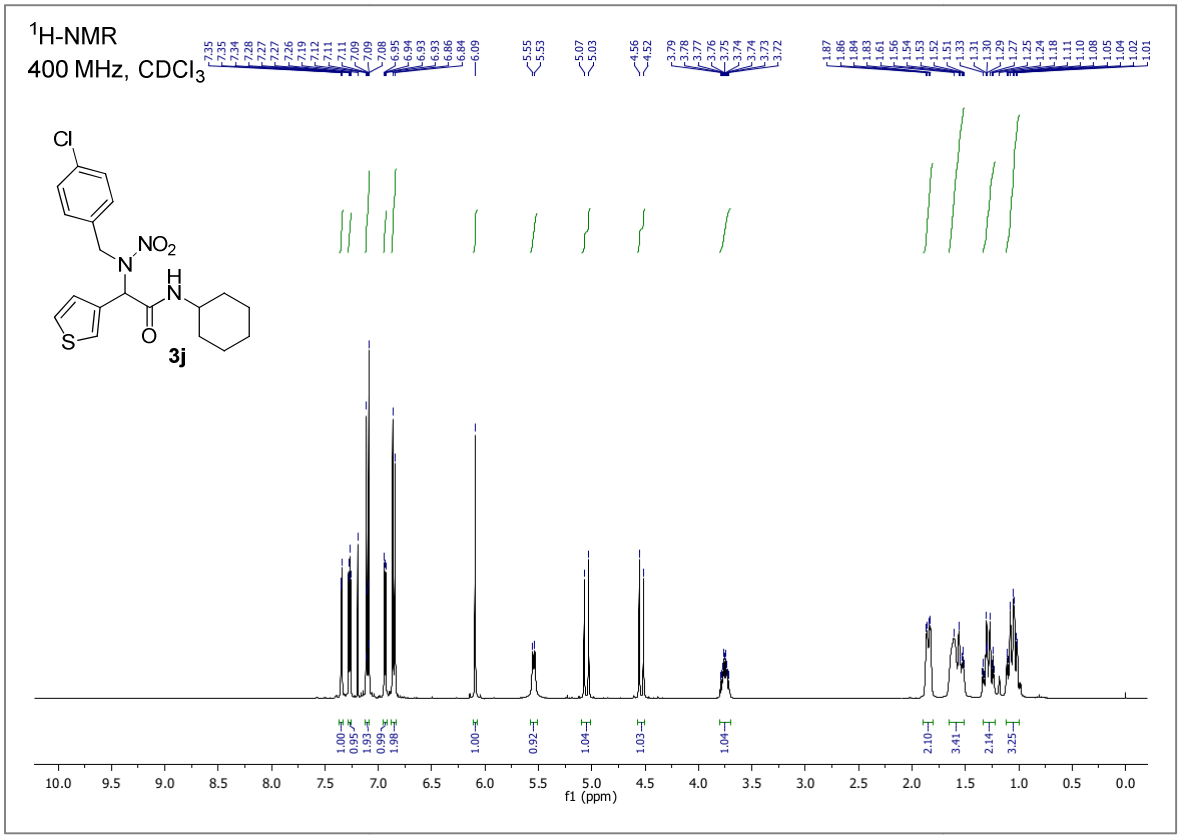
Date Run: 07-21-2016 (Time Run: 17:08:42)
Instrument: JEOL JMSGCmateII

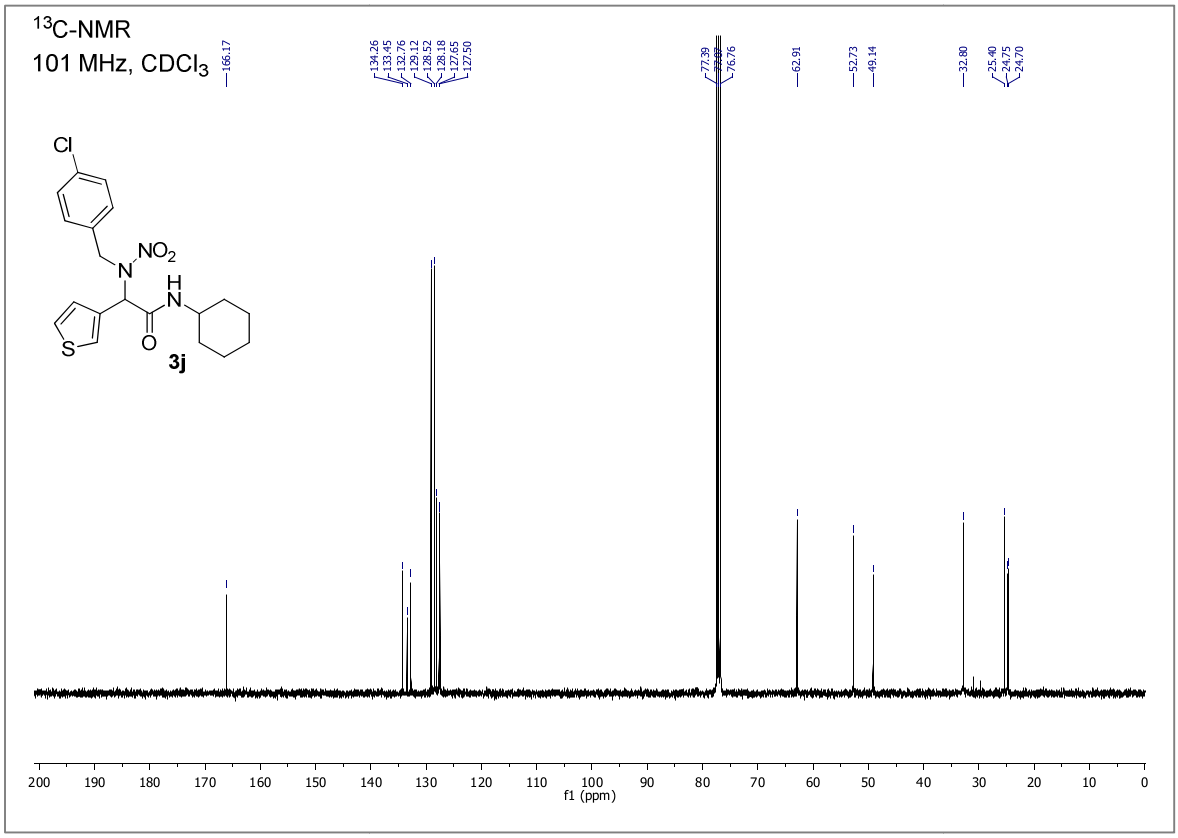
Inlet: Direct Probe

Run By: Vincent Jactel
Ionization mode: EI+

345,1366 : 84 % **Scan: 299** **TIC: 8017296**




^{1}H-NMR
400 MHz, $CDCl_3$
Cl
NO_2
N
H
N
O
S
3j
f1 (ppm)


^{13}C-NMR
101 MHz, $CDCl_3$
Cl
NO_2
N
H
N
O
S
3j
f1 (ppm)

Laboratoire de Synthèse Organique

21/07/2016 13:33:12

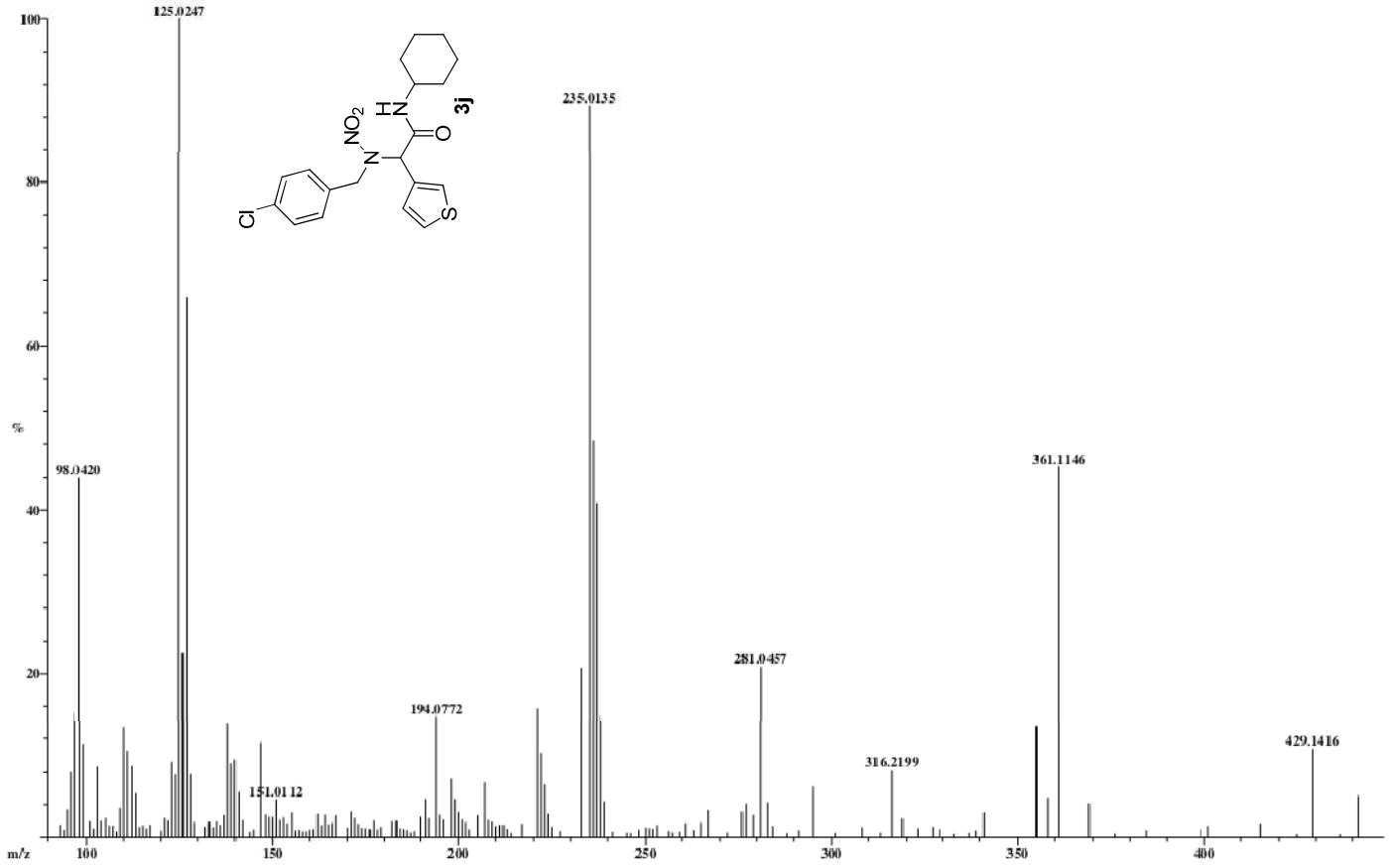
File: MV172 bis
Sample: MV172

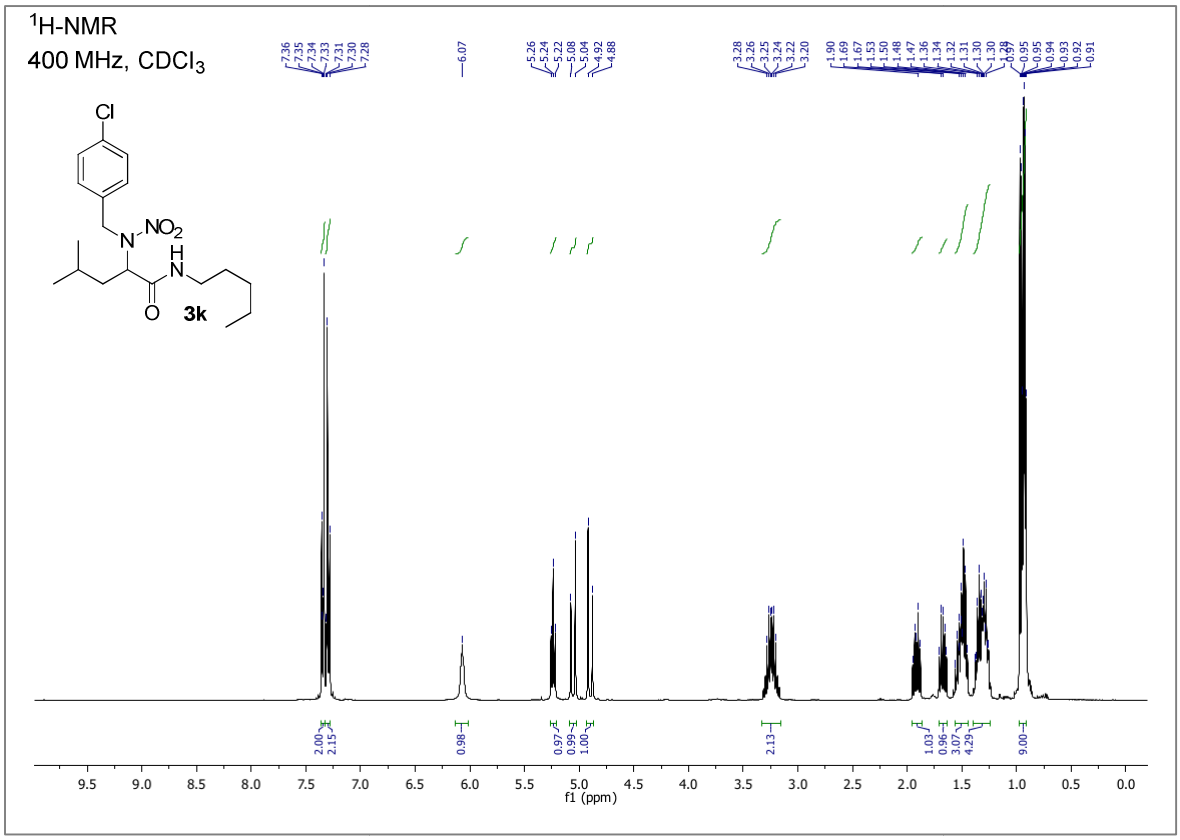
Date Run: 07-21-2016 (Time Run: 13:22:44)
Instrument: JEOL JMSGCmateII

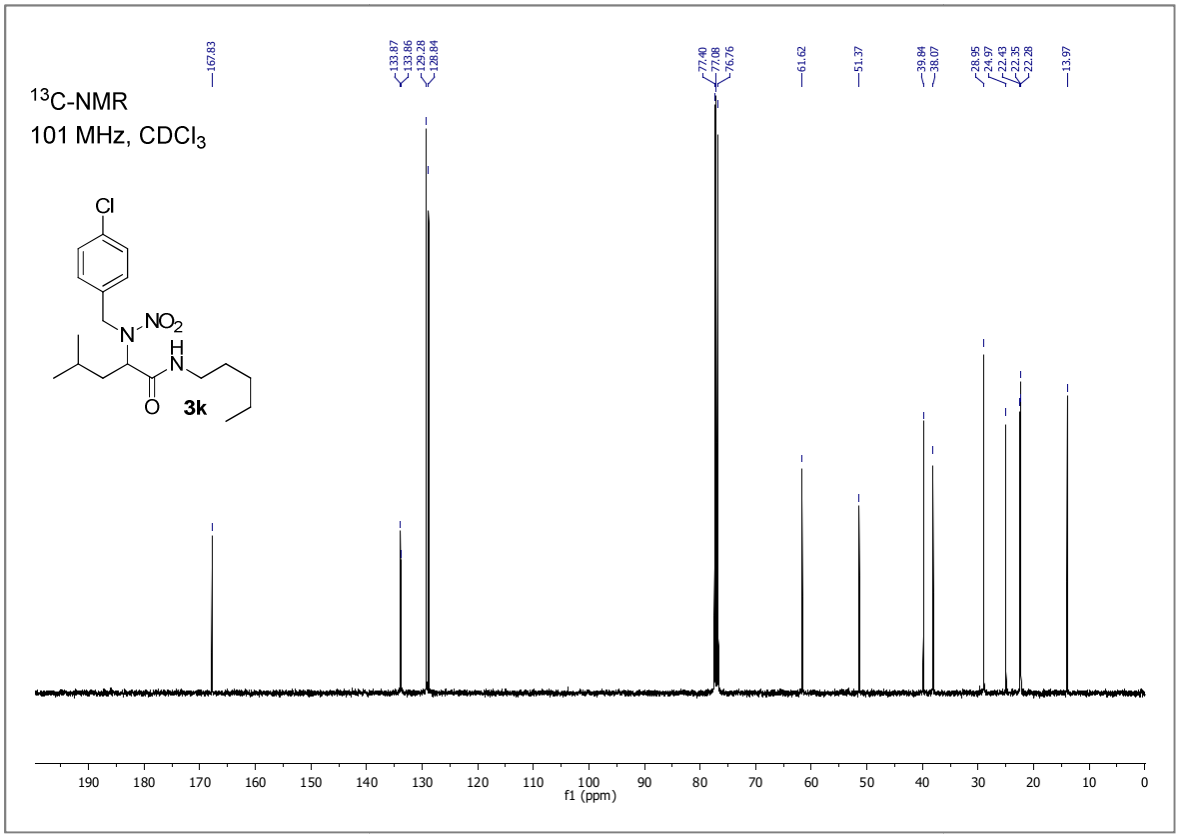
Inlet: Direct Probe

Run By: Vincent Jactel
Ionization mode: EI+

361,1146 : 45 % **Scan: 197** **TIC: 7597708**




^{1}H-NMR
400 MHz, $CDCl_3$
Cl
NO_2
N
H
N
O
3k
7.36
7.35
7.34
7.33
7.31
7.30
7.28
6.07
5.26
5.24
5.22
5.08
5.04
4.92
4.88
3.28
3.26
3.25
3.24
3.22
3.20
1.90
1.69
1.67
1.53
1.50
1.48
1.47
1.36
1.34
1.32
1.31
1.30
0.97
0.95
0.95
0.94
0.93
0.92
0.91
2.00
2.15
0.98
0.97
0.99
1.00
2.13
1.03
0.96
3.07
4.29
9.00
f1 (ppm)


^{13}C-NMR
101 MHz, $CDCl_3$
Cl
NO_2
N
H
N
O
3k
167.83
133.87
133.86
129.28
128.84
77.40
77.08
76.76
61.62
51.37
39.84
38.07
28.95
24.97
22.43
22.35
22.28
13.97
f1 (ppm)

Laboratoire de Synthèse Organique

22/07/2016 14:15:38

File: MV168
Sample:

Date Run: 07-22-2016 (Time Run: 14:01:40)
Instrument: JEOL JMSGCmateII

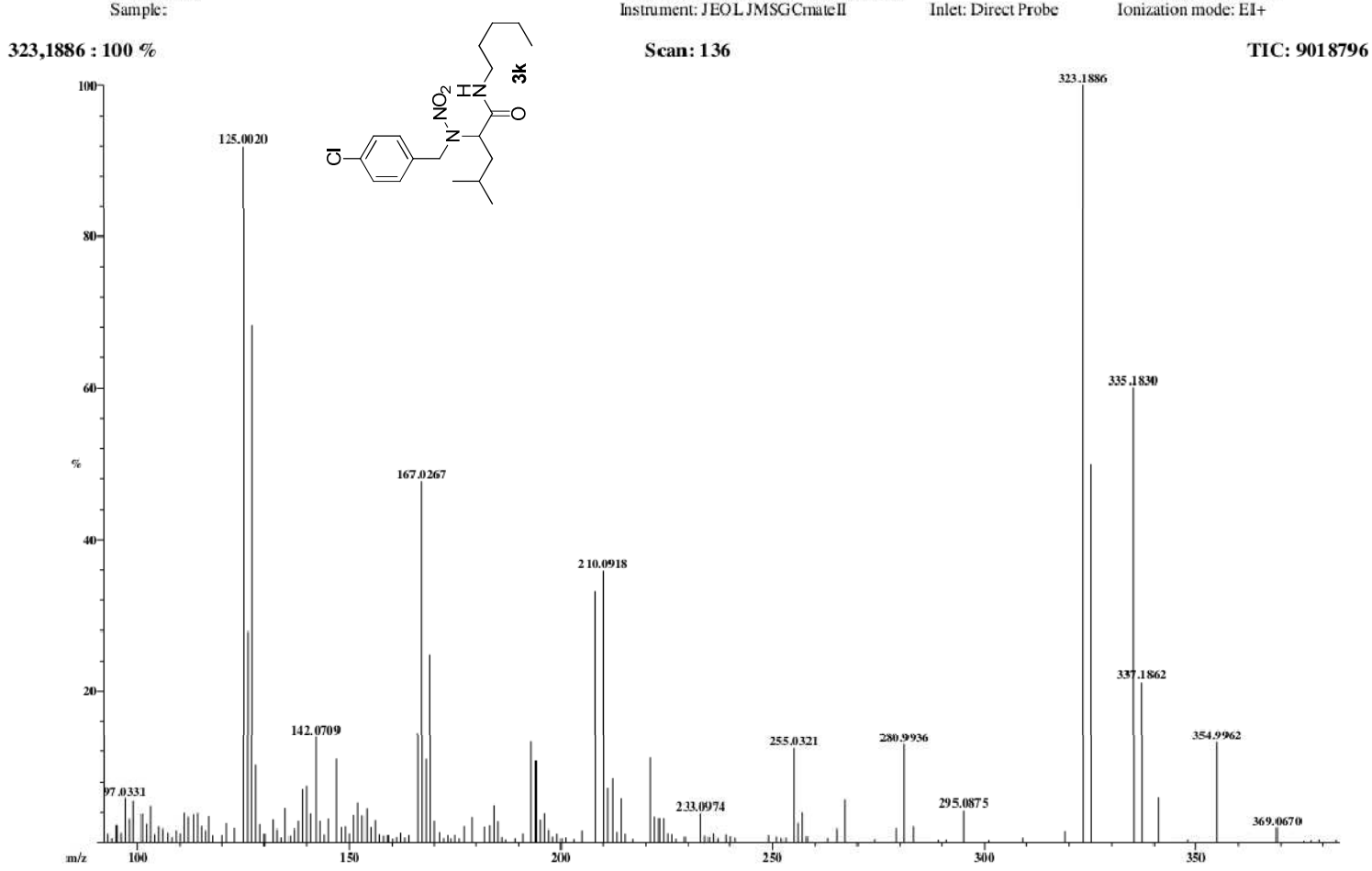
Inlet: Direct Probe

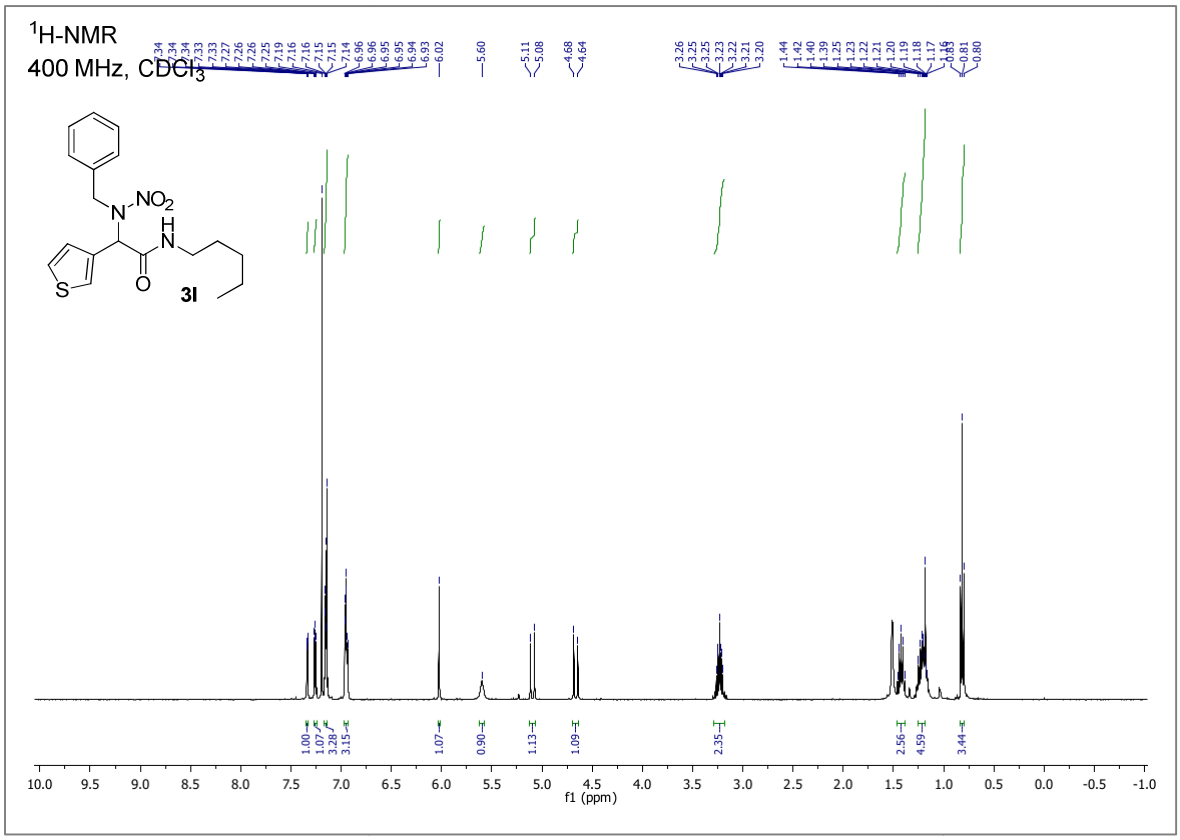
Run By: Vincent Jactel
Ionization mode: EI+

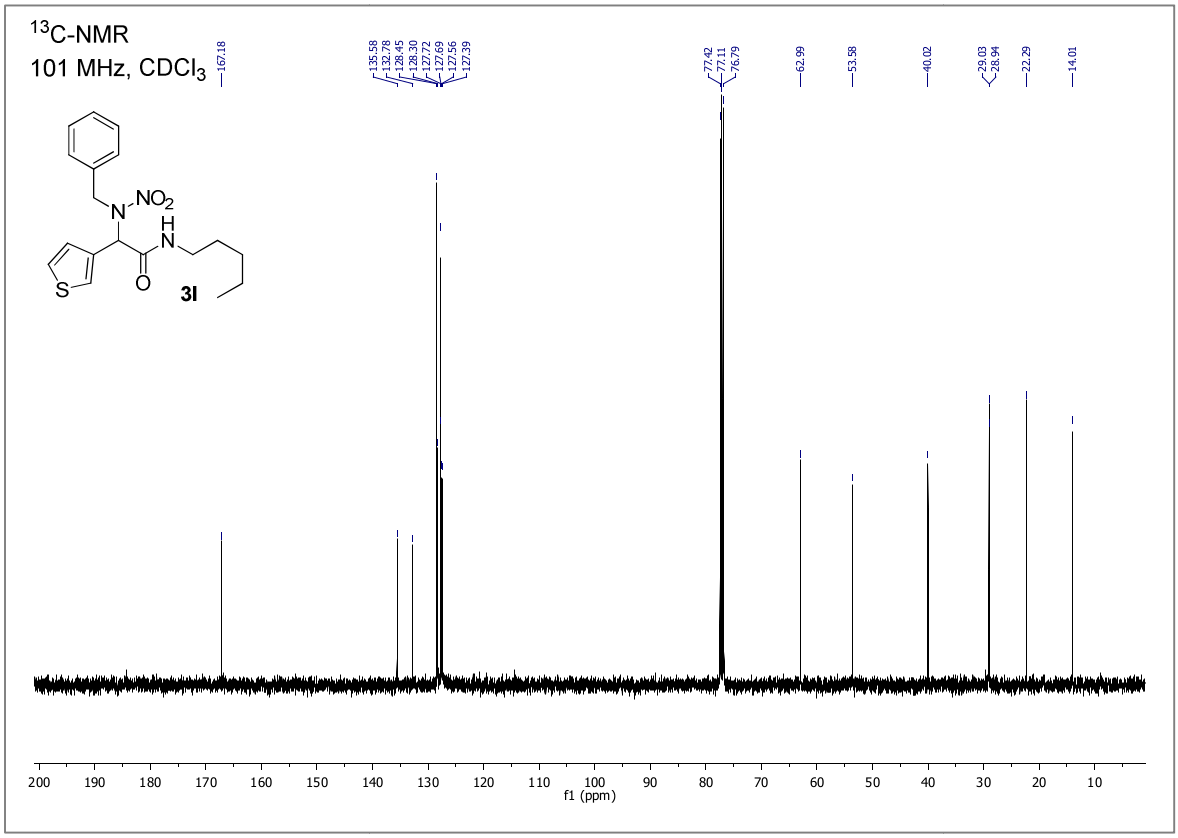
323,1886 : 100 %

Scan: 136

TIC: 9018796




^{1}H-NMR
400 MHz, $CDCl_3$
3l
f1 (ppm)


^{13}C-NMR
101 MHz, $CDCl_3$
3l
f1 (ppm)

Laboratoire de Synthèse Organique

25/07/2016 13:28:24

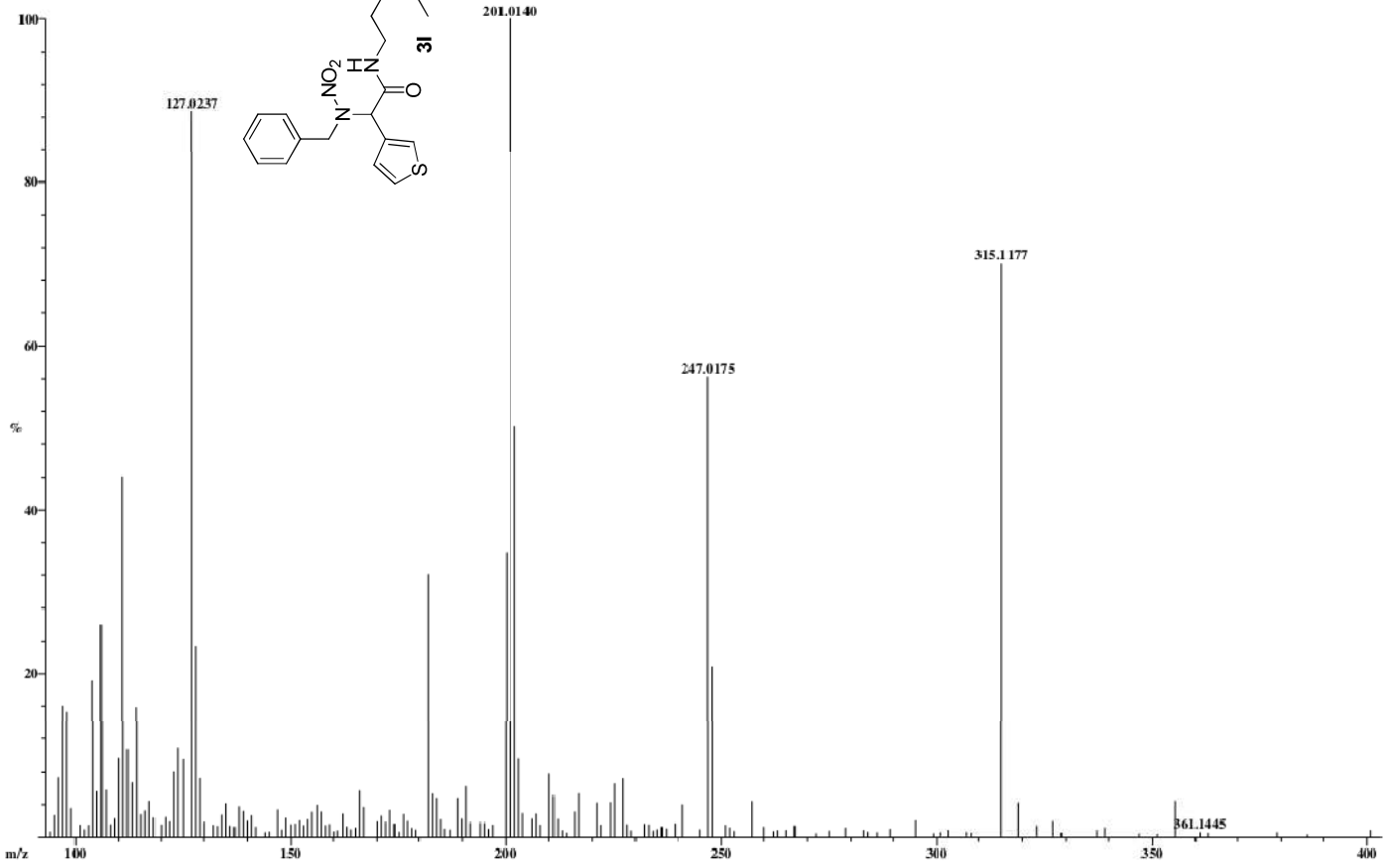
File: MV178
Sample:

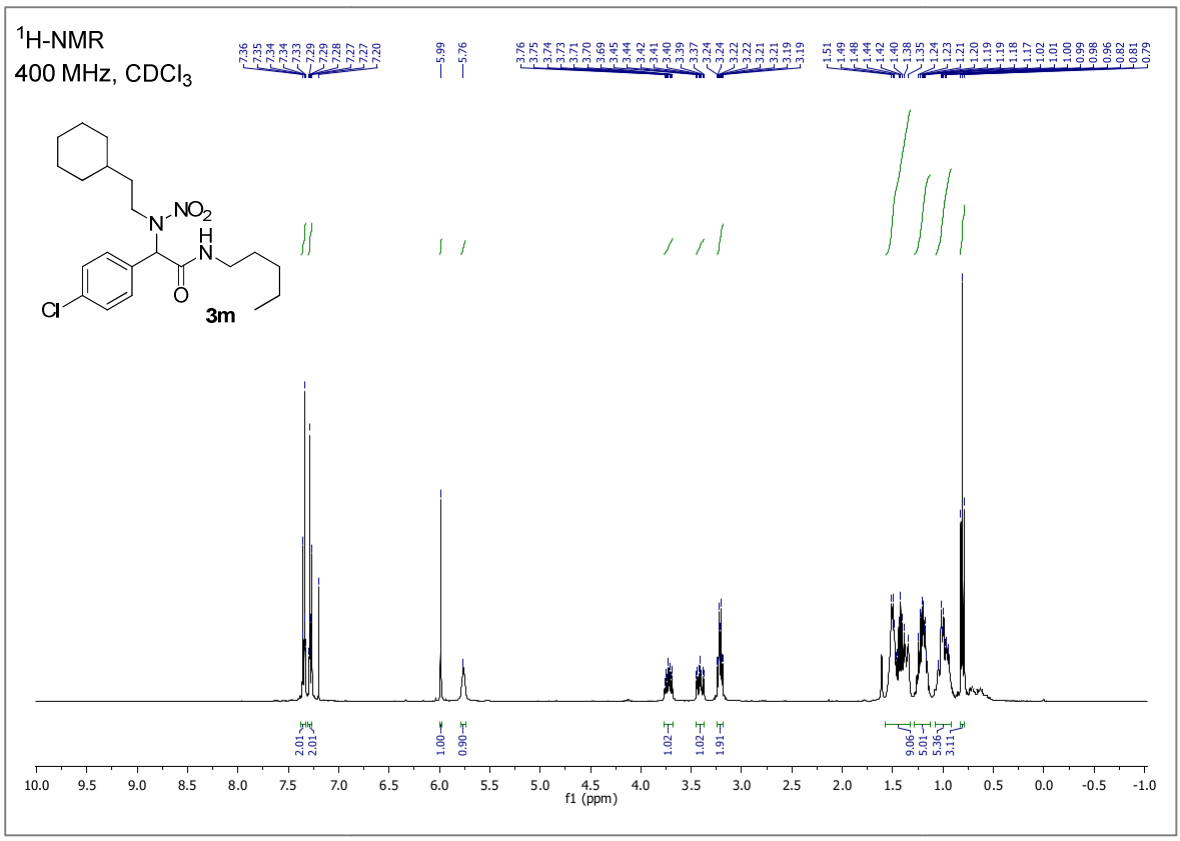
Date Run: 07-25-2016 (Time Run: 13:09:05)
Instrument: JEOL JMSGCmateII

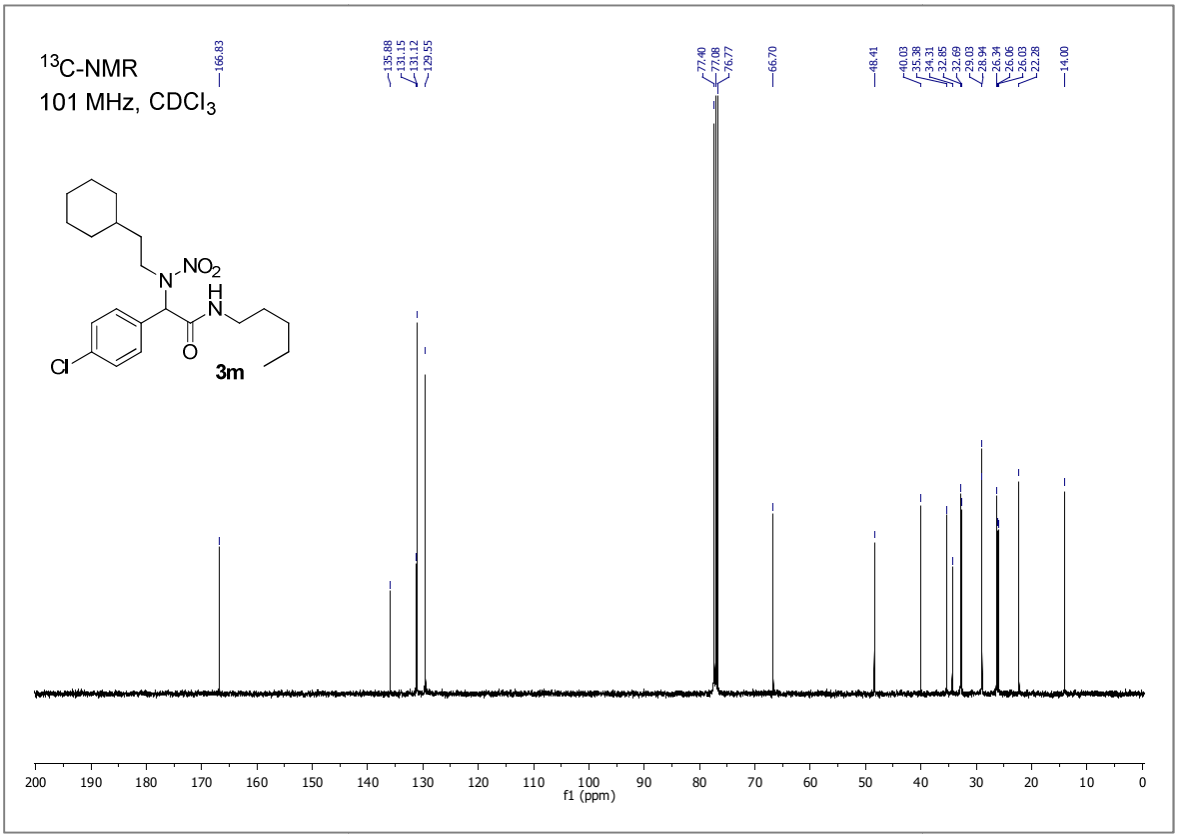
Inlet: Direct Probe

Run By: Vincent Jactel
Ionization mode: EI+

361,1445 : 0,6 % **Scan: 208** **TIC: 4544750**




^{1}H-NMR
400 MHz, $CDCl_3$
3m
f1 (ppm)


^{13}C-NMR
101 MHz, $CDCl_3$
3m
f1 (ppm)

Laboratoire de Synthèse Organique

22/07/2016 11:18:55

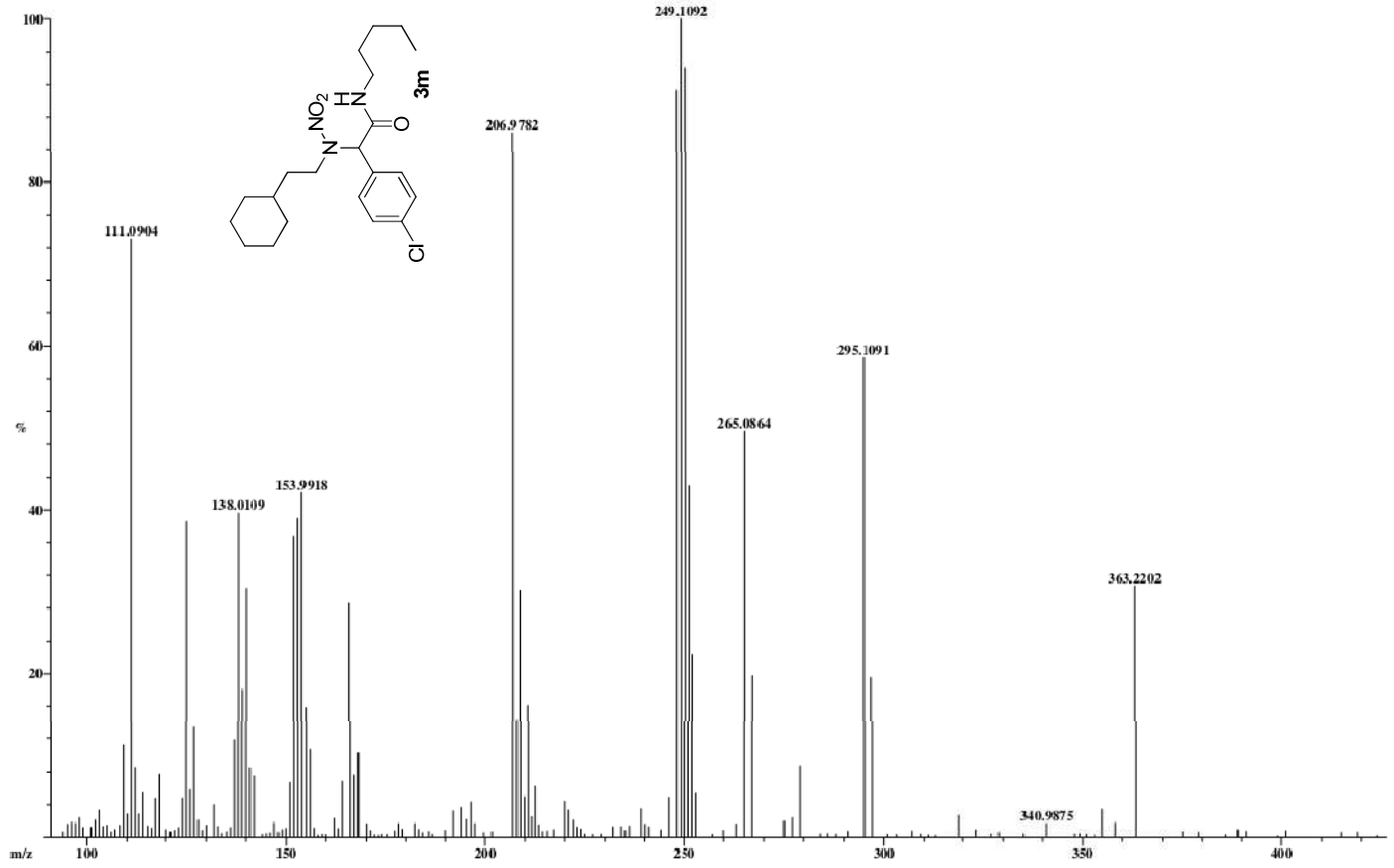
File: MV173
Sample:

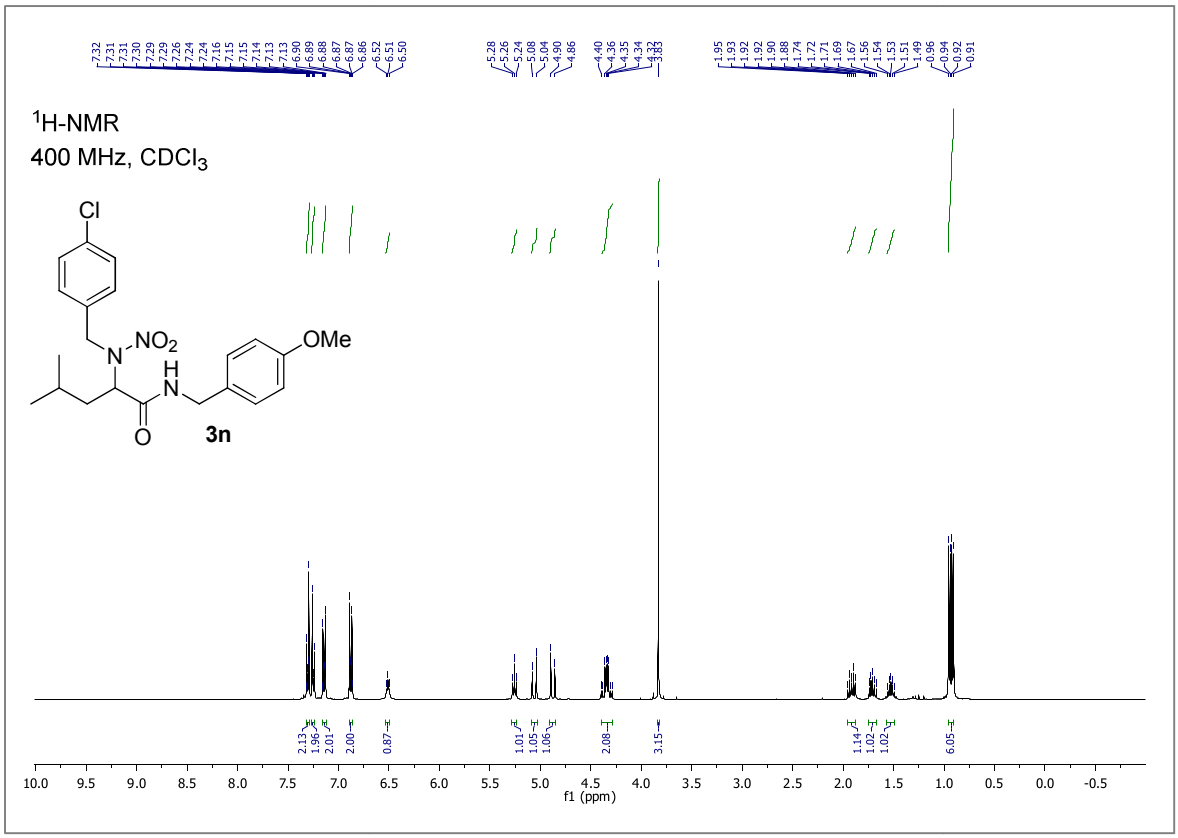
Date Run: 07-22-2016 (Time Run: 11:00:48)
Instrument: JEOL JMSGCmateII

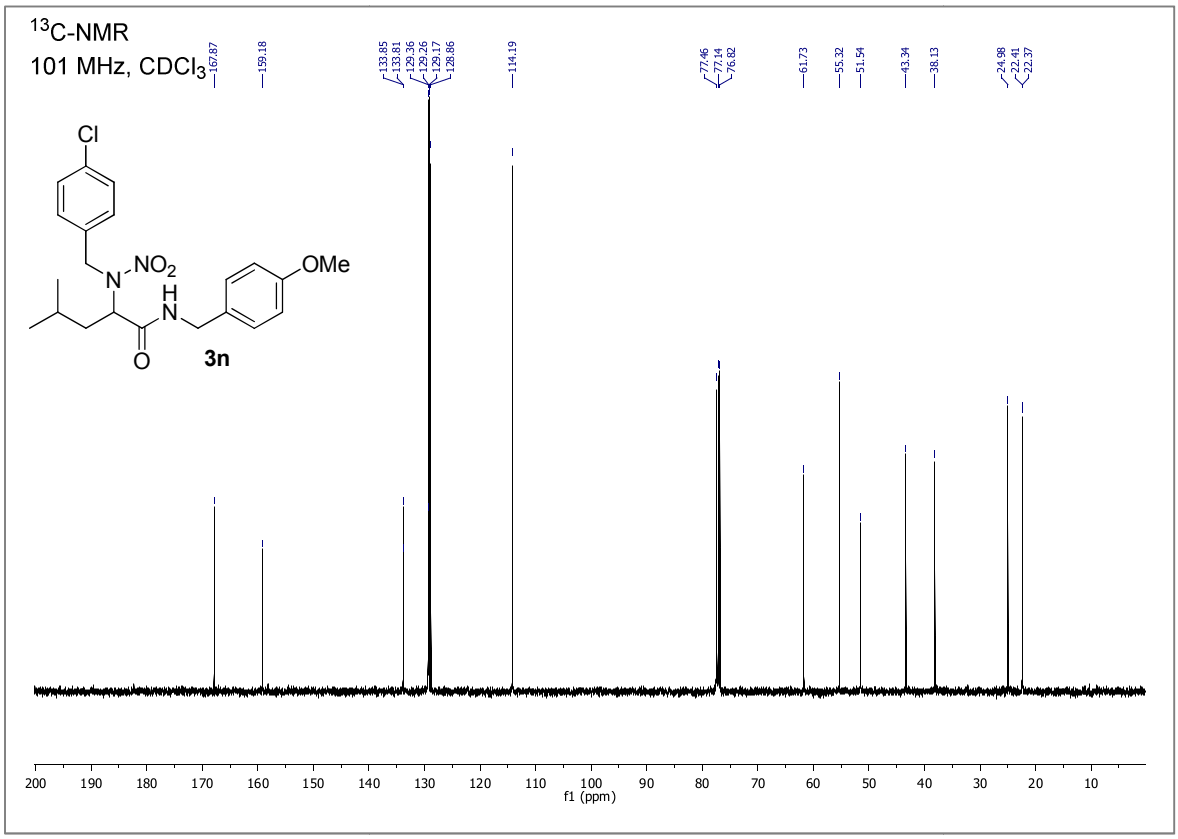
Inlet: Direct Probe

Run By: Vincent Jactel
Ionization mode: EI+

363,2202 : 31 % **Scan: 394** **TIC: 7846250**




1H-NMR
400 MHz, CDCl3
Cl
NO2
N
H
N
OMe
O
3n
f1 (ppm)


13C-NMR
101 MHz, CDCl3
Cl
NO2
N
H
N
OMe
O
3n
f1 (ppm)

Laboratoire de Synthèse Organique

22/07/2016 16:51:28

File: MV164
Sample:

Date Run: 07-22-2016 (Time Run: 16:39:48)
Instrument: JEOL JMSGCmateII

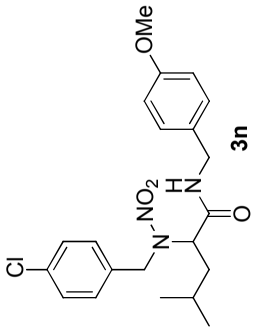
Inlet: Direct Probe

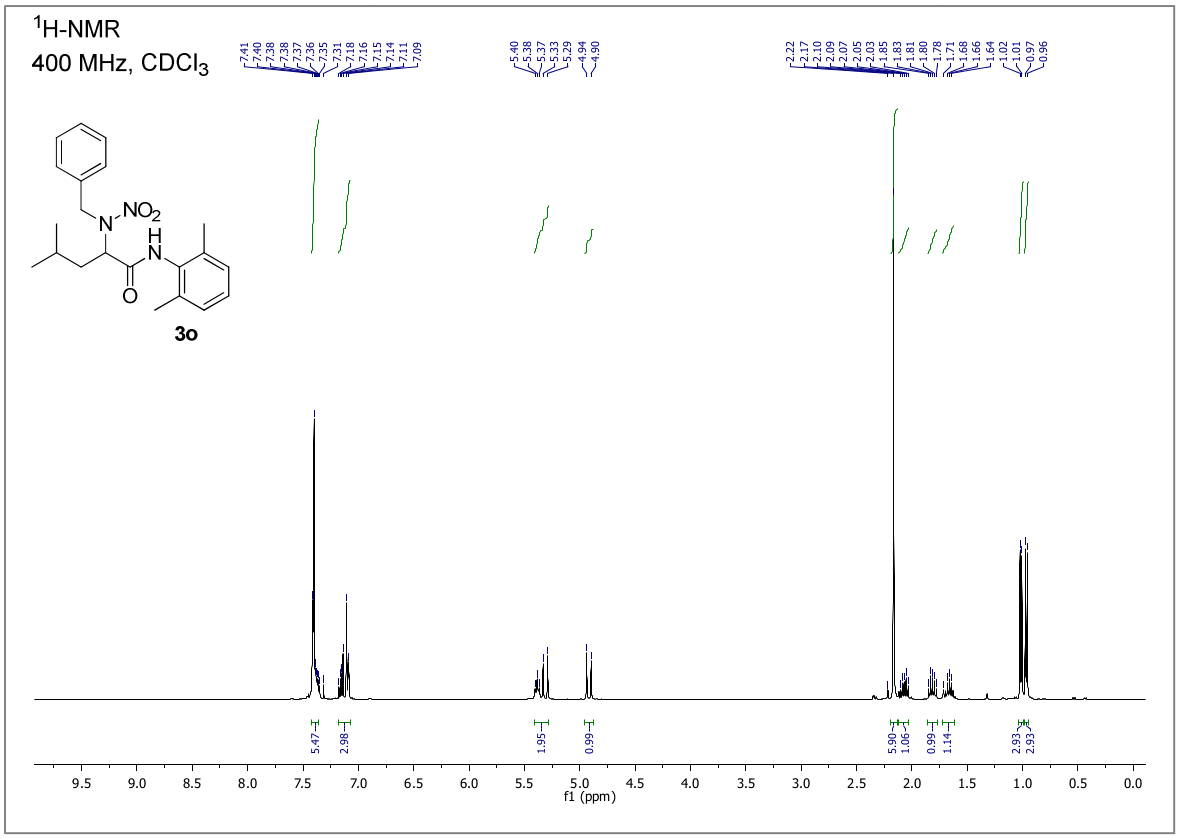
Run By: Vincent Jactel
Ionization mode: EI+

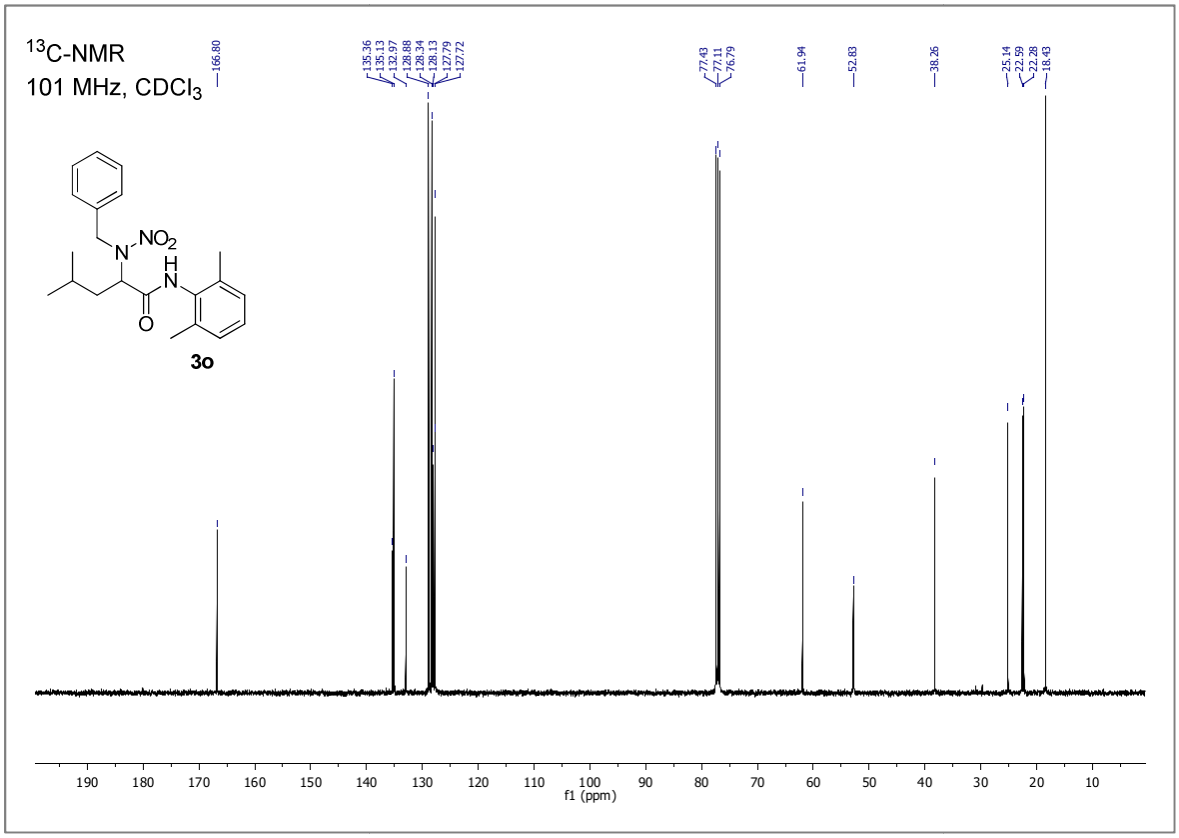
373,1672 : 22 %

Scan: 157

TIC: 3440422




1H-NMR
400 MHz, CDCl3
3o
f1 (ppm)


13C-NMR
101 MHz, CDCl3
3o
f1 (ppm)

Laboratoire de Synthèse Organique

21/07/2016 09:23:36

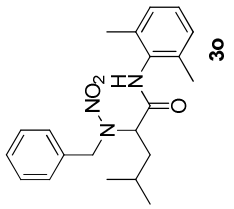
File: MV175
Sample:

Date Run: 07-21-2016 (Time Run: 09:13:57)
Instrument: JEOL JMSGCmateII

Inlet: Direct Probe

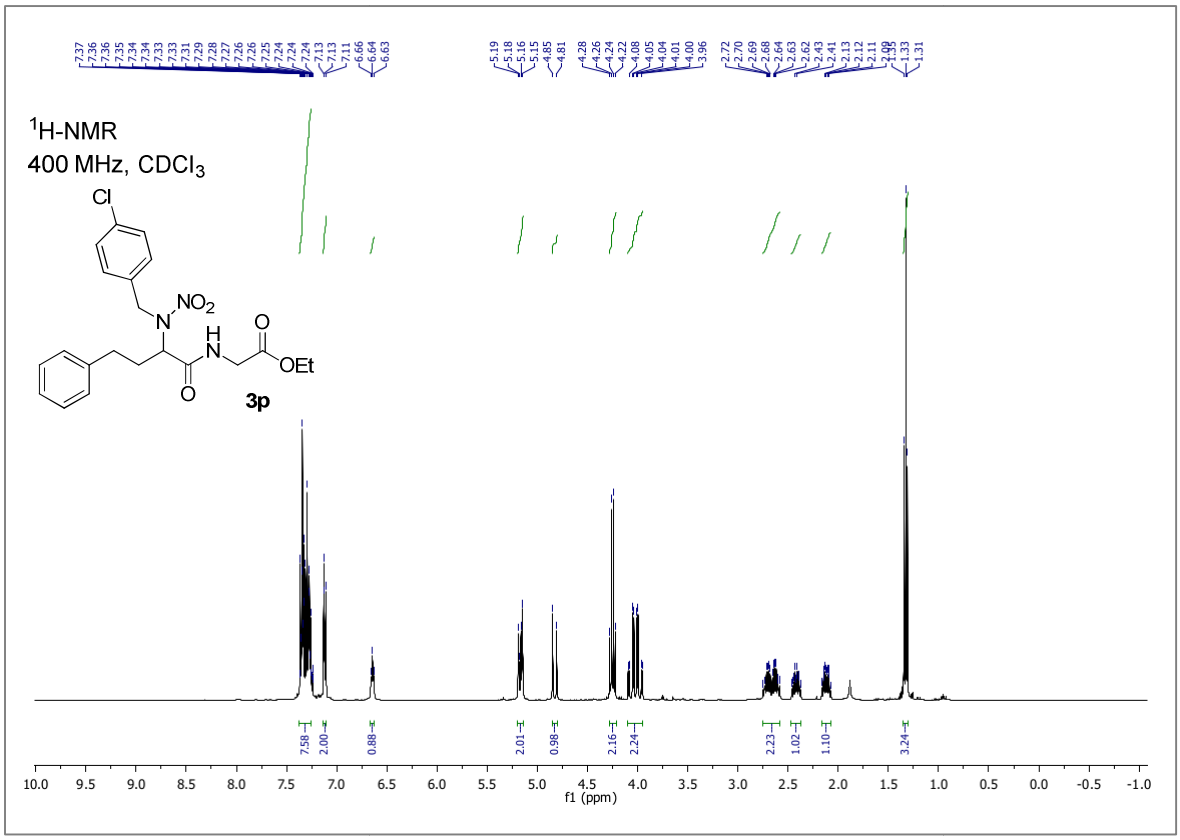
Run By: Vincent Jactel
Ionization mode: EI+

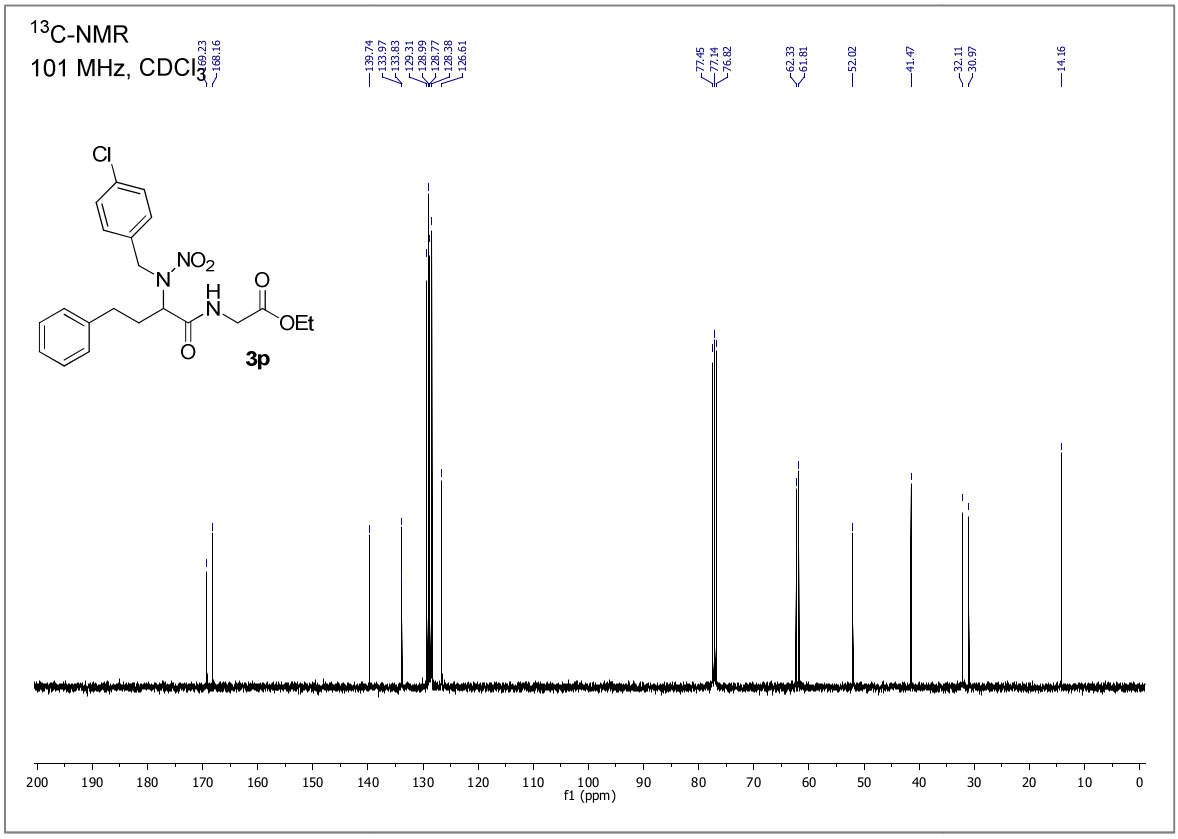
369,2040 : 12 %



Scan: 244

TIC: 6717682


1H-NMR
400 MHz, CDCl3
Cl
NO2
N
H
N
O
O
OEt
O
3p
f1 (ppm)


13C-NMR
101 MHz, CDCl3
Cl
NO2
N
H
N
O
O
OEt
O
3p
f1 (ppm)

Laboratoire de Synthèse Organique

22/07/2016 15:41:59

File: MV188
Sample:

Date Run: 07-22-2016 (Time Run: 15:30:52)
Instrument: JEOL JMSGCmateII

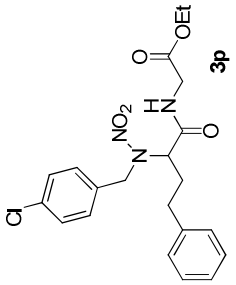
Inlet: Direct Probe

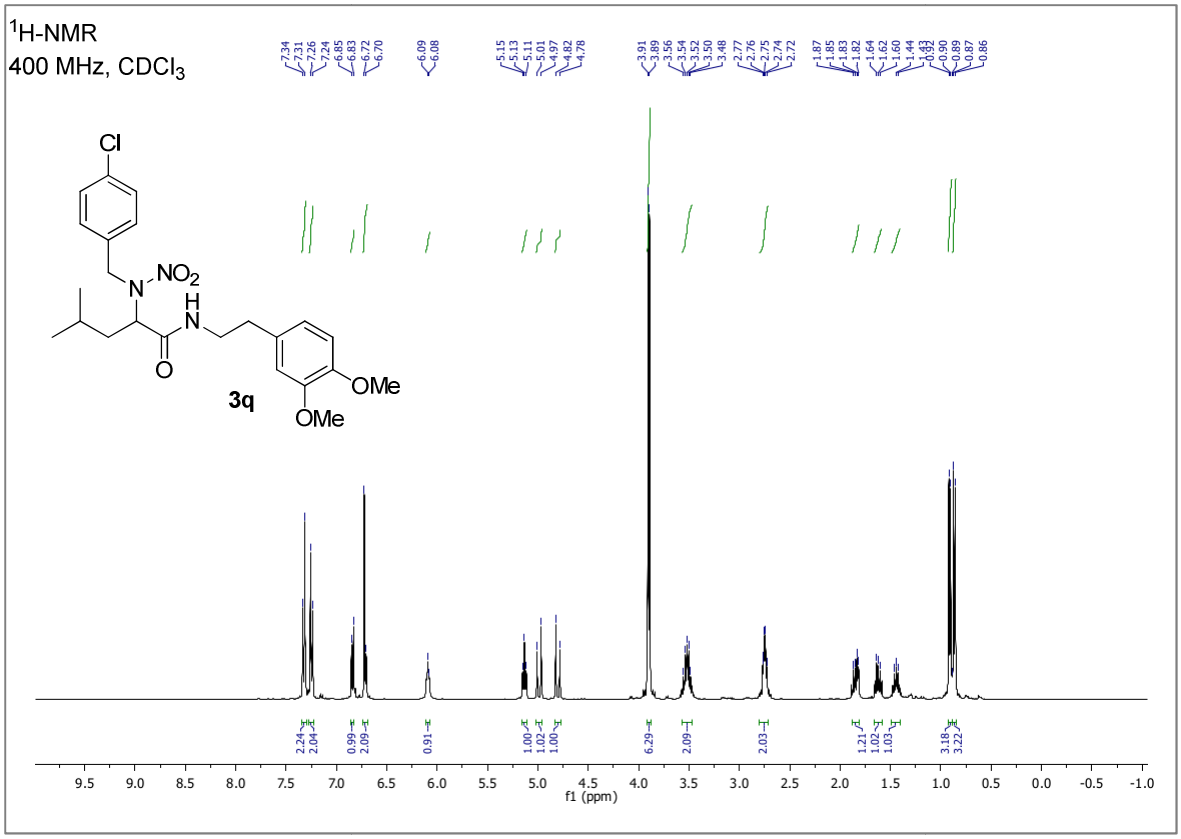
Run By: Vincent Jactel
Ionization mode: EI+

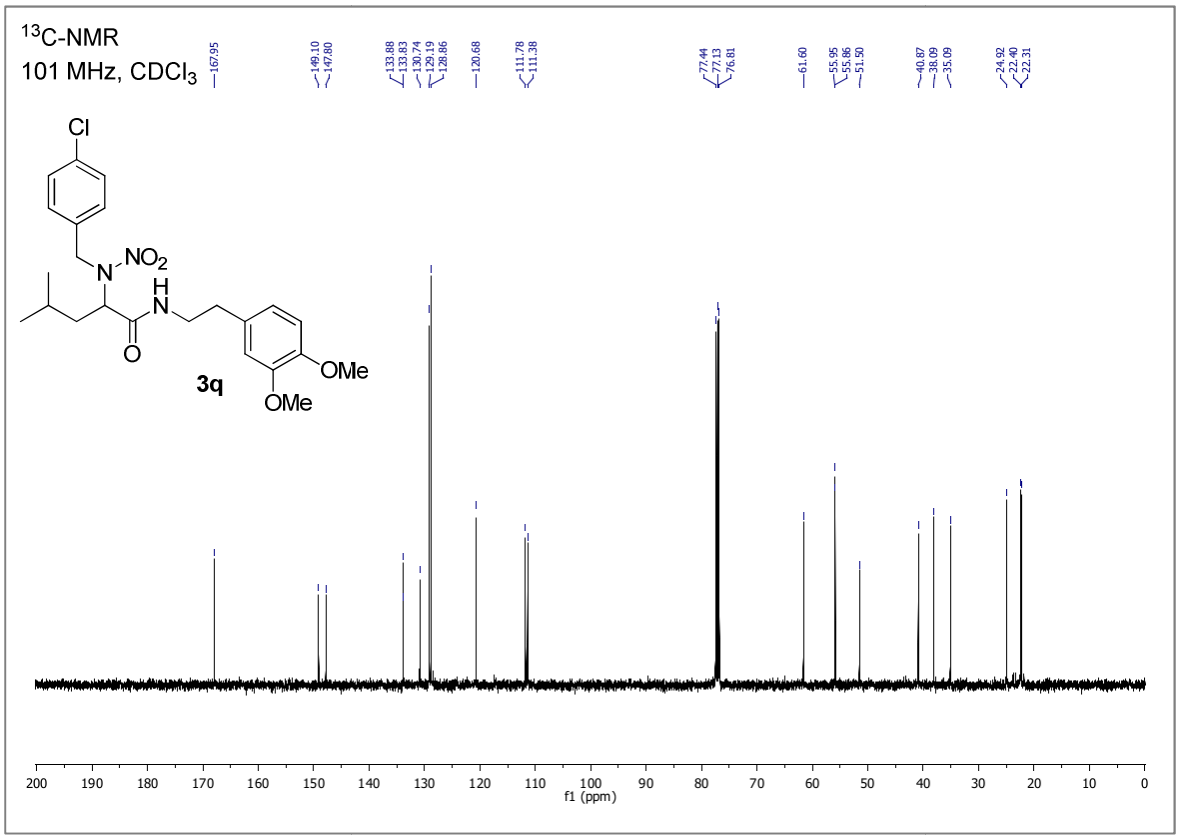
387,1474 : 100 %

Scan: 391

TIC: 6840694




1H-NMR
400 MHz, CDCl3
Cl
NO2
N
H
N
O
OMe
OMe
3q
f1 (ppm)


13C-NMR
101 MHz, CDCl3
Cl
NO2
N
H
N
O
OMe
OMe
3q
f1 (ppm)

Laboratoire de Synthèse Organique

22/06/2016 09:50:05

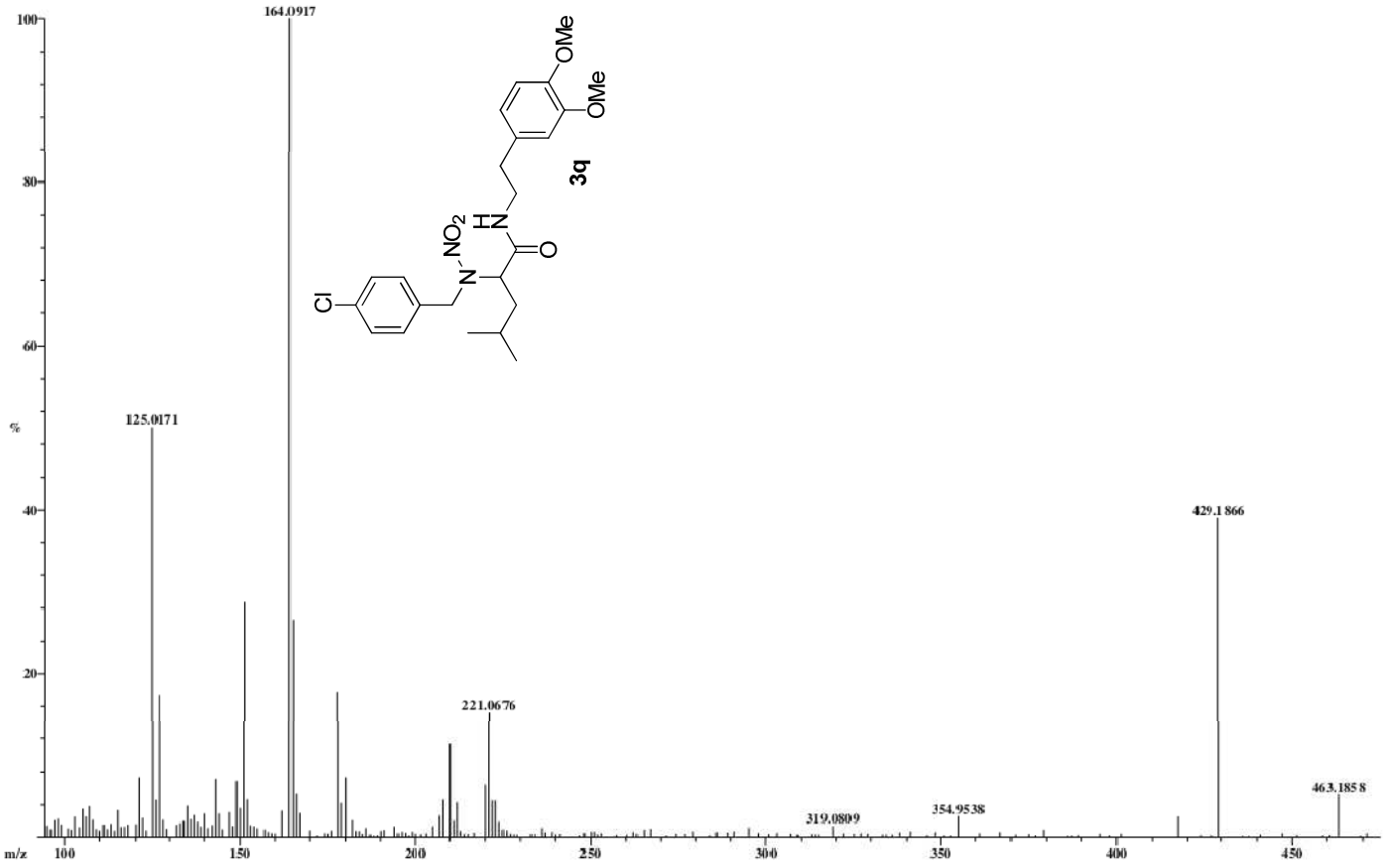
File: MV163
Sample:

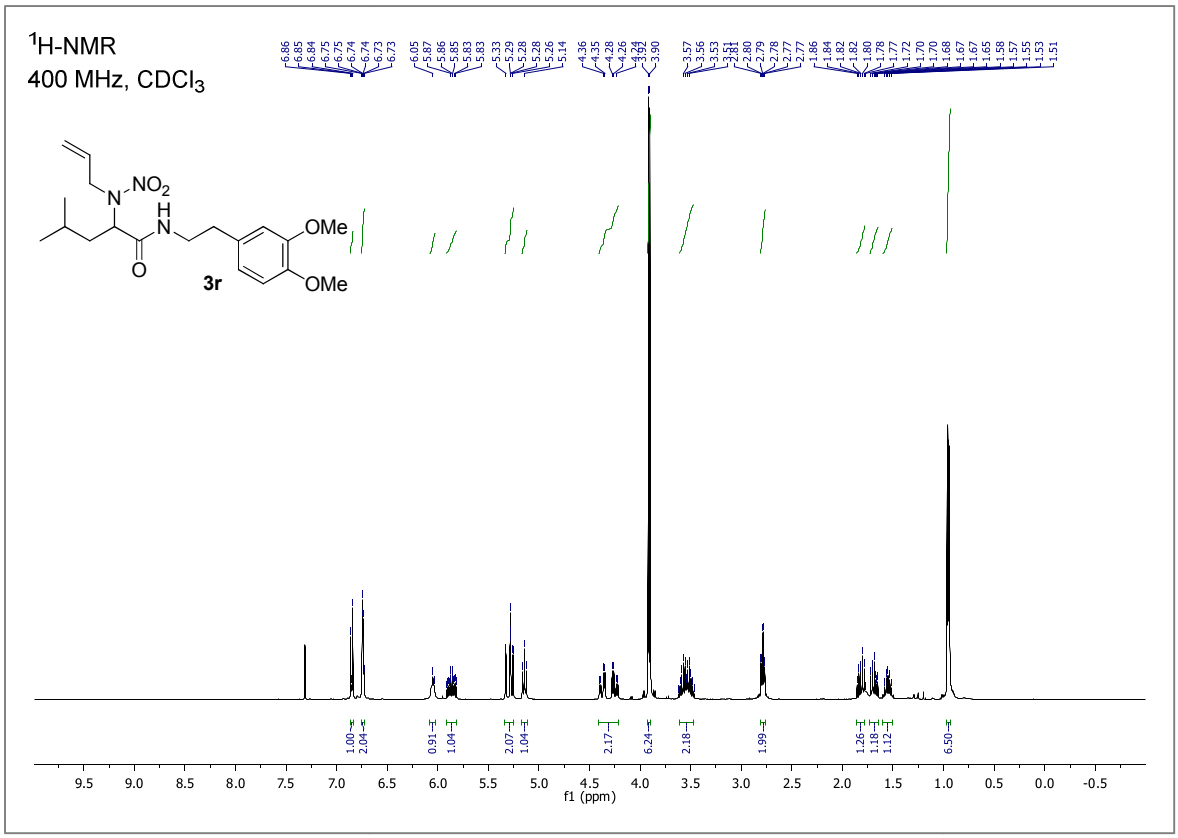
Date Run: 06-20-2016 (Time Run: 13:14:50)
Instrument: JEOL JMSGCmateII

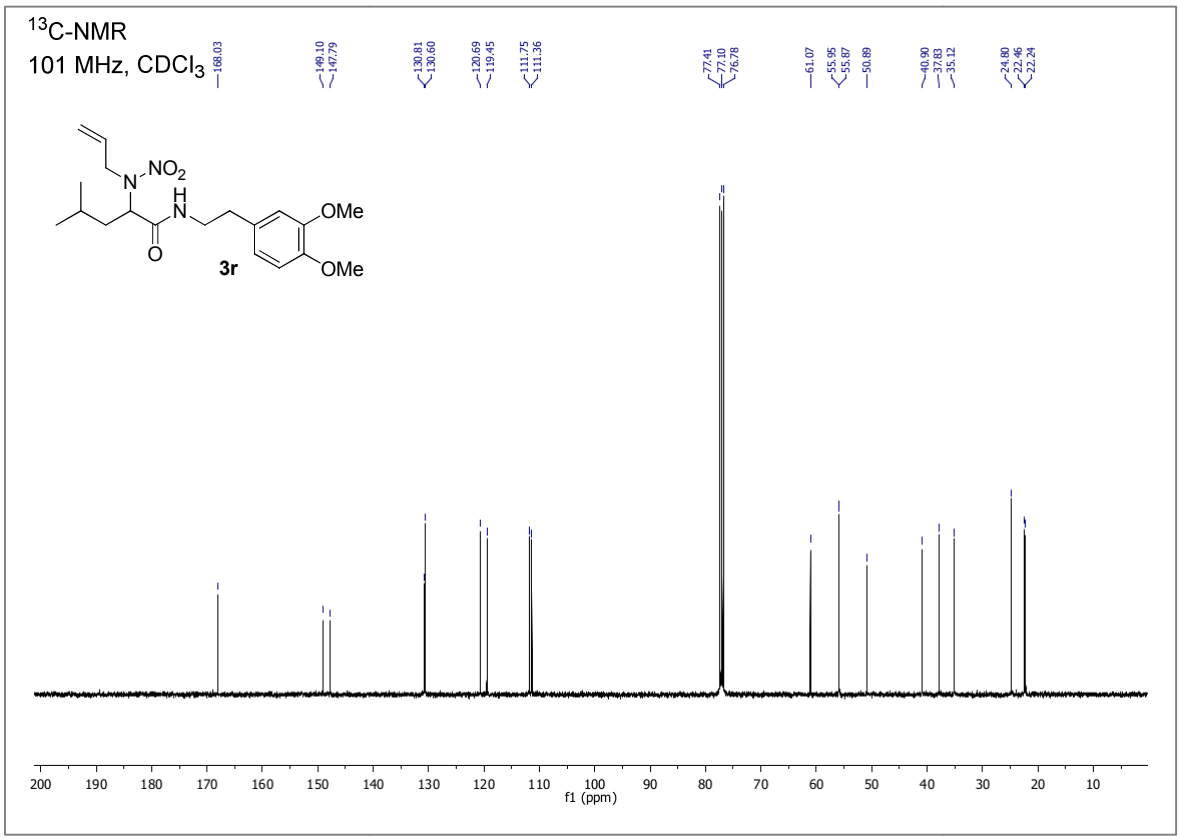
Inlet: Direct Probe

Run By: Vincent Jactel
Ionization mode: EI+

463,1858 : 5% **Scan: 363** **TIC: 2470628**




1H-NMR
400 MHz, CDCl3
NO2
N
H
N
O
OMe
OMe
3r
f1 (ppm)


13C-NMR
101 MHz, CDCl3
NO2
N
H
N
O
OMe
OMe
3r
f1 (ppm)

Laboratoire de Synthèse Organique

22/07/2016 09:49:15

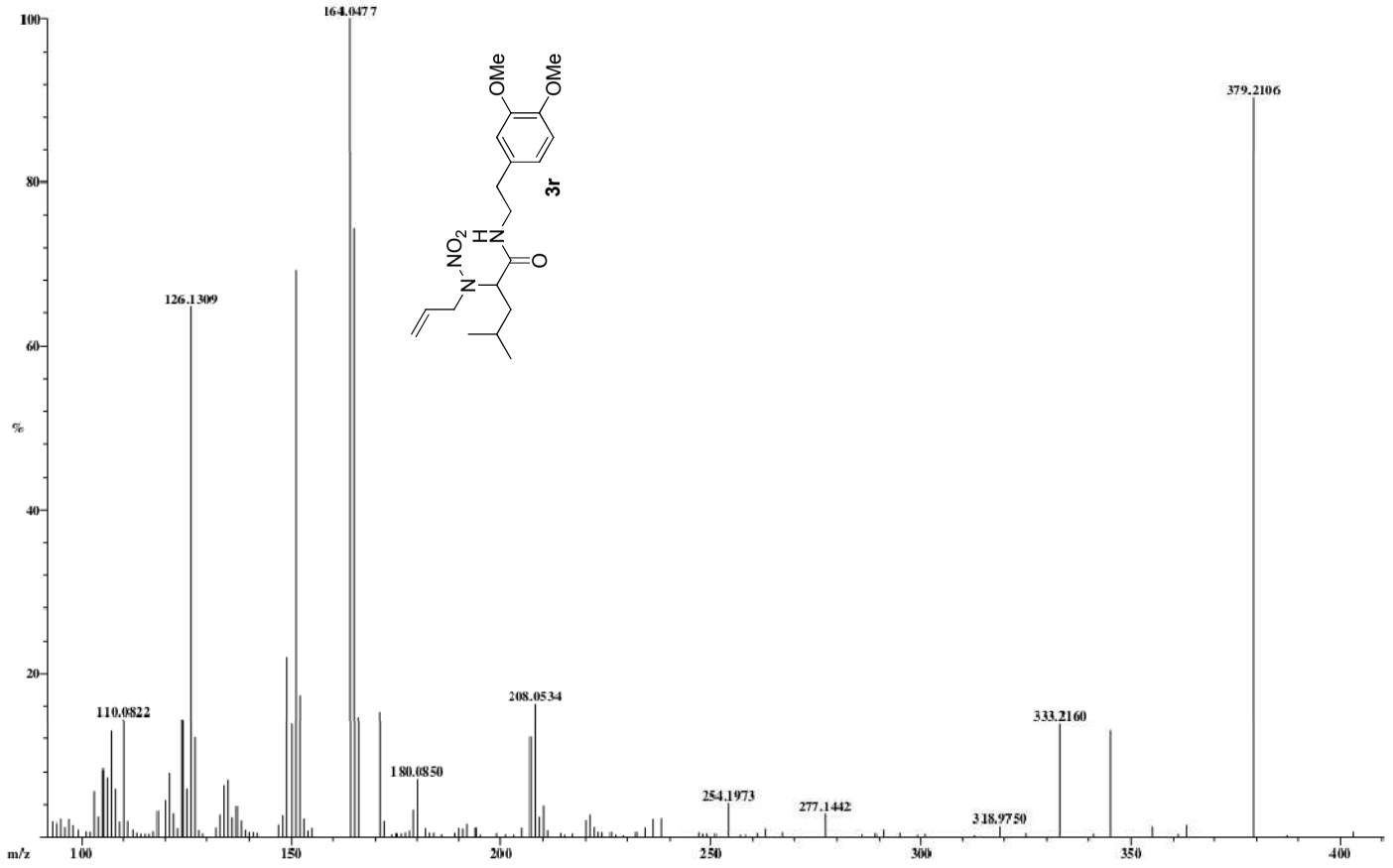
File: MV187
Sample:

Date Run: 07-22-2016 (Time Run: 09:34:50)
Instrument: JEOL JMSGCmateII

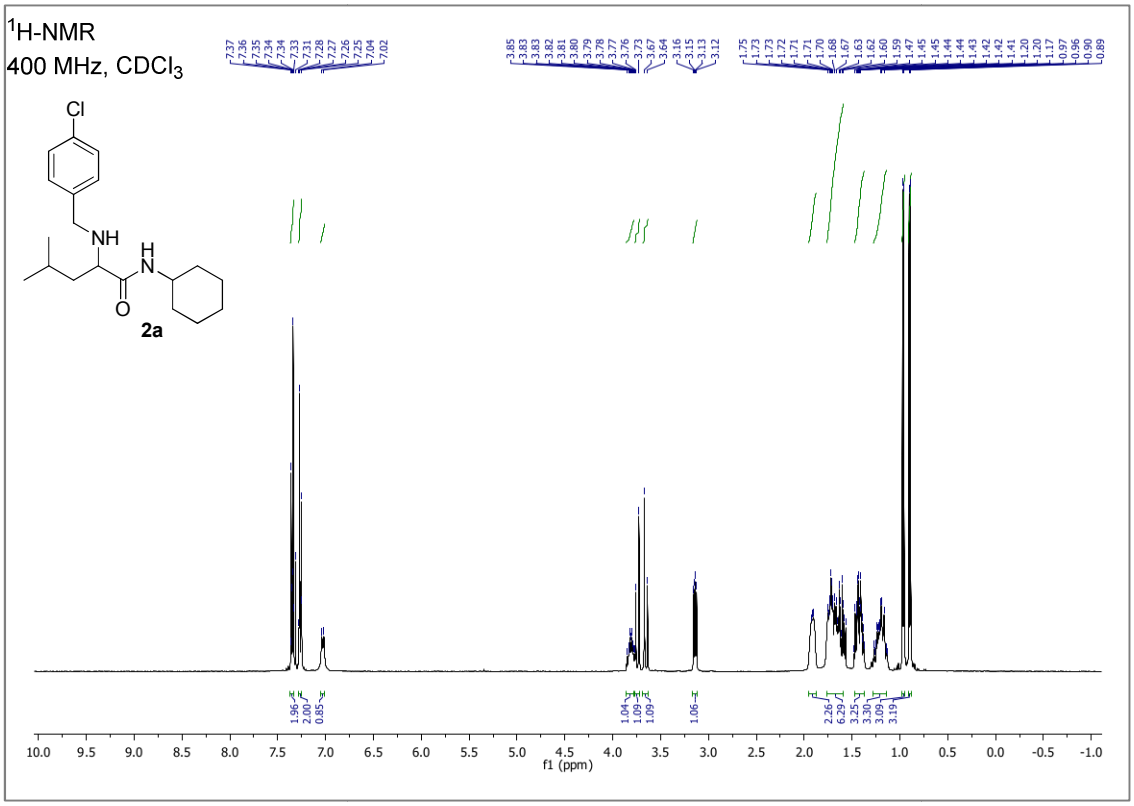
Inlet: Direct Probe

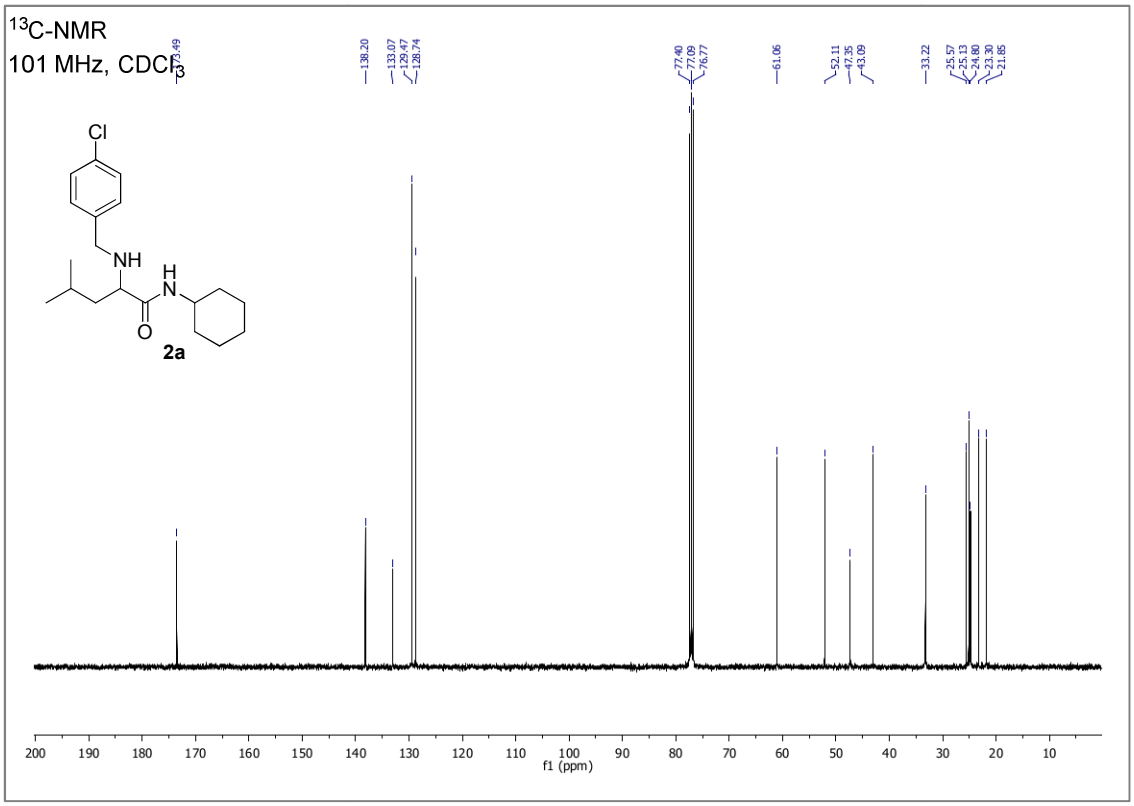
Run By: Vincent Jactel
Ionization mode: EI+

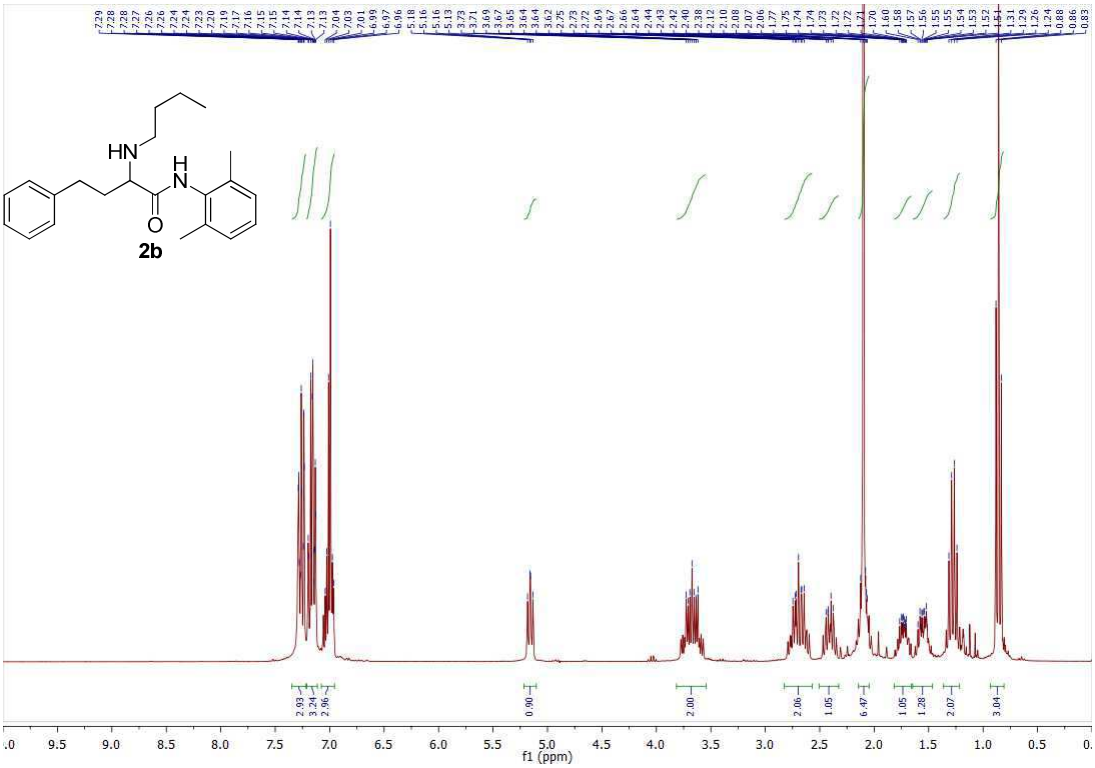
379,2106 : 90 % **Scan: 365** **TIC: 8163578**

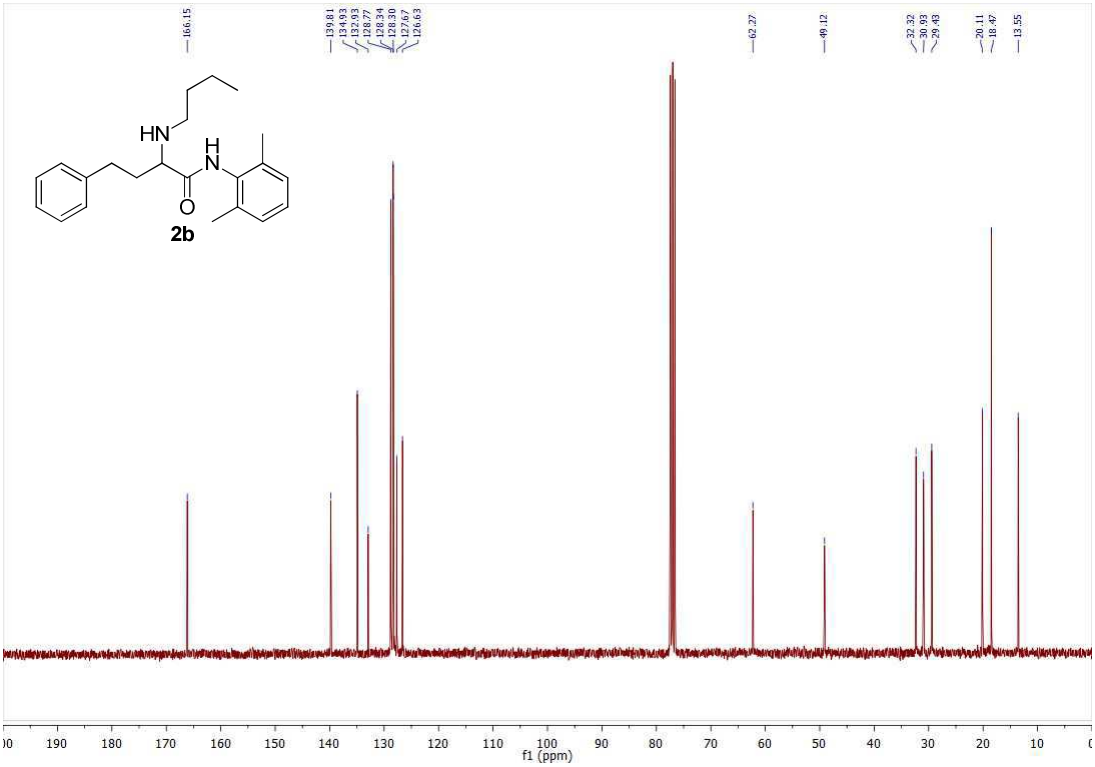


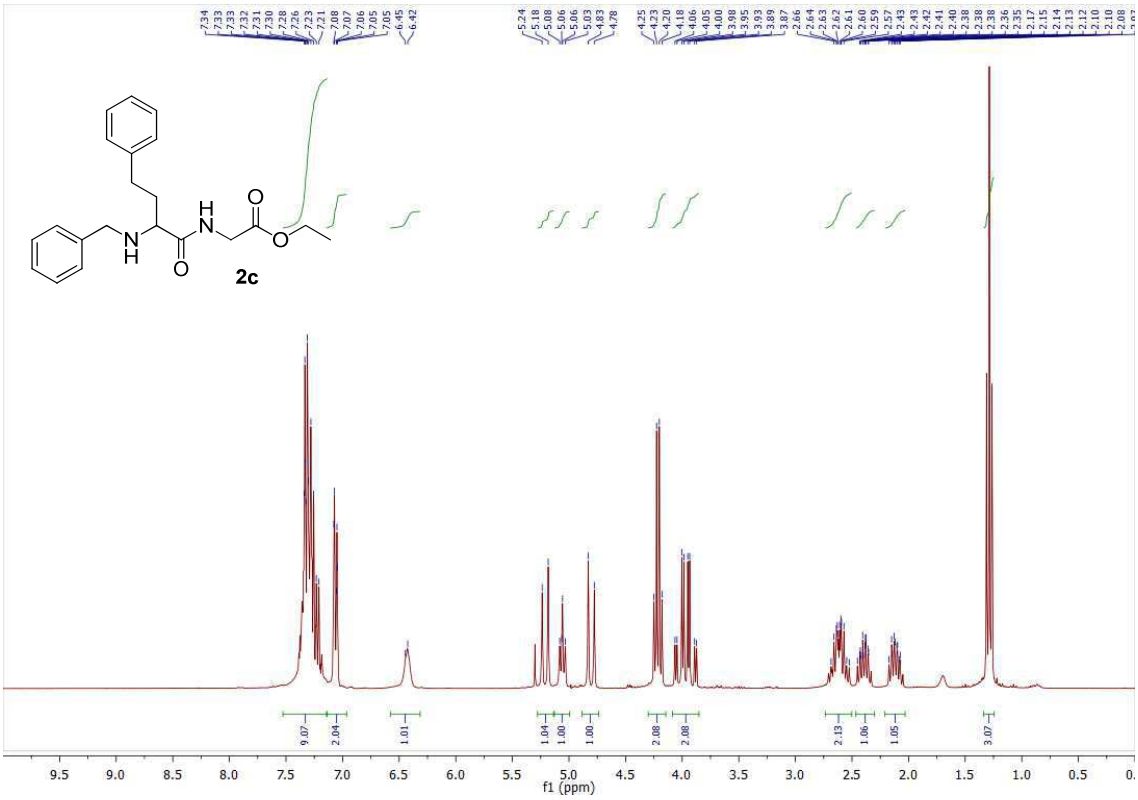
Three-component amine formation:

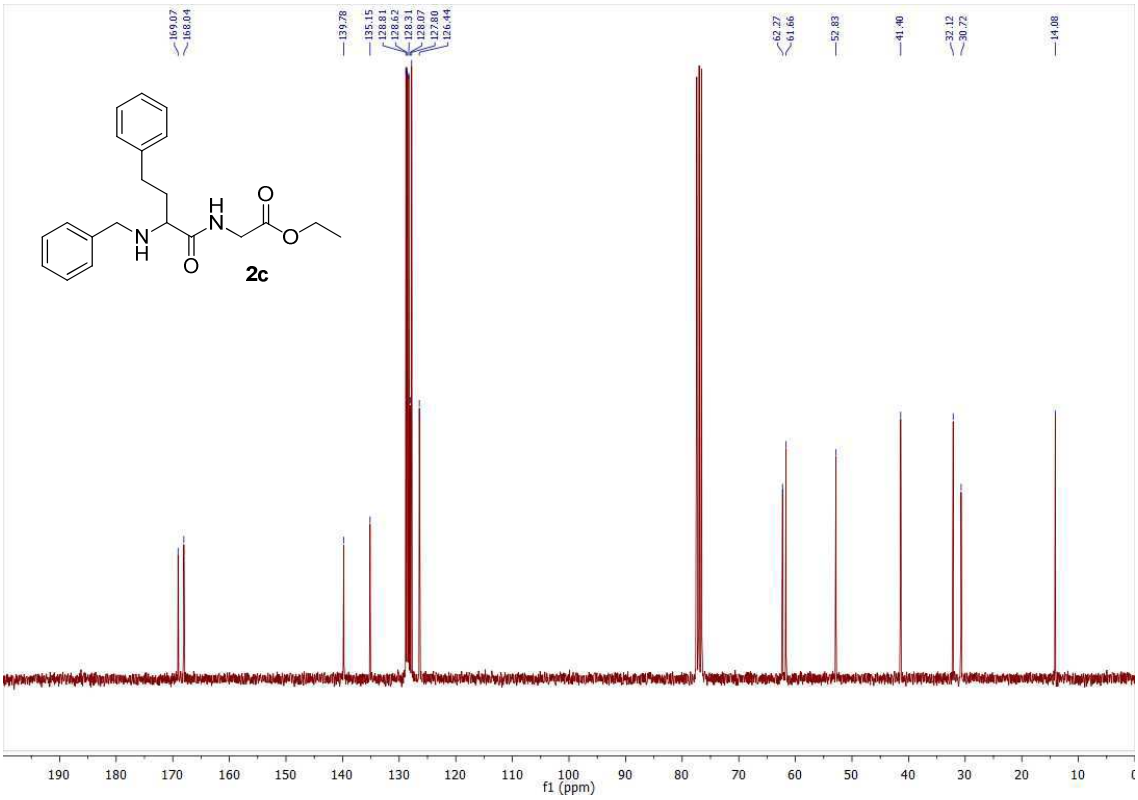





HN
H
N
O
2b
f1 (ppm)


HN
H
N
O
2b
f1 (ppm)


2c
f1 (ppm)


2c
f1 (ppm)

RX Experimental part:

Single crystal of compound **3l** was mounted on a kapton loop using Paratone® oil and cooled to 150 K in a nitrogen stream for X-ray structure determination.
The loop was transferred to a Nonius Kappa CCD diffractometer using Mo Kα (l = 0.71069 Å) X-ray source, a graphite monochromator and a Bruker APEX-II detector. Preliminary orientation matrixes and cell constants were determined by collection of 10 s frames, followed by spot integration and least-squares refinement.

Structure solution:

Data were integrated and corrected for Lorentz and polarization effects. The crystal structure was solved using SHELXT-2014 and refined in SHELXL-2014 by full-matrix least squares using anisotropic thermal displacement parameters for all non-hydrogen atoms.

The structure solution and the refinement were achieved with the PLATON software. The position of the hydrogen atoms was determined using residual electronic densities which are calculated by a Fourier difference.

Finally, ORTEP drawings were produced using Mercury with 50% probability thermal ellipsoids. CCDC 1524126

3l

Experimental data:

Temperature: 150 K

Crystal data:

Empirical Formula	$C_{18}\ H_{23}\ N_3\ O_3\ S$
Formula Weight	361.45
Crystal Color, Habit	colorless block
Crystal Dimensions	0.340x0.180x0.160mm
Crystal System	monoclinic
Lattice Type	P 2_1/c

Lattice Parameters:

a(Å)	9.8097(3)
b(Å)	19.8264(4)
c(Å)	9.5259(3)
α(°)	90
β(°)	95.136(2)
γ(°)	90
V(Å^3)	1845.26(9)
Z	4
d(g-cm^{-3})	1.301
F(000)	768
μ(cm^{-1})	0.197

Intensity measurements:

Diffractometer	Bruker APEX II CCD
Monochromator	graphite
Radiation	MoKα (λ = 0.71069 Å)
Maximum theta	32.218 °
HKL ranges	-13 14; -29 29; -14 14
No. of Reflexions measured	Total: 19633 Unique: 6512 (R_{int} = 0.0386)
Absorption corrections	multi-scan; min = 0.6973 ; max = 0.7464

Structure solution and refinement:

Structure Solution	SHELXT-2014
Refinement	SHELXL-2014
Refinement type	Fsqd
Hydrogen atoms	mixed
Parameters refined	230
Reflections/parameter	22
wR2	0.1288
R1	**4.34 %**
Completeness	**99.7 %**
Weights a, b	0.0657; 0.4231
GoF	1.020
Difference peak / hole (e $Å^{-3}$)	0.420(0.058) / -0.363(0.058)

Structure:

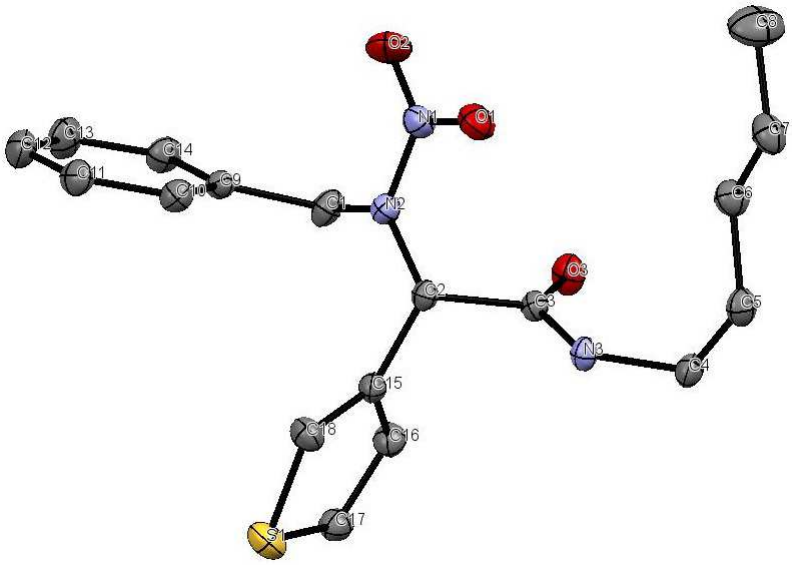


Image 1: ORTEP structure of 3l (hydrogen atoms are omitted for clarity)

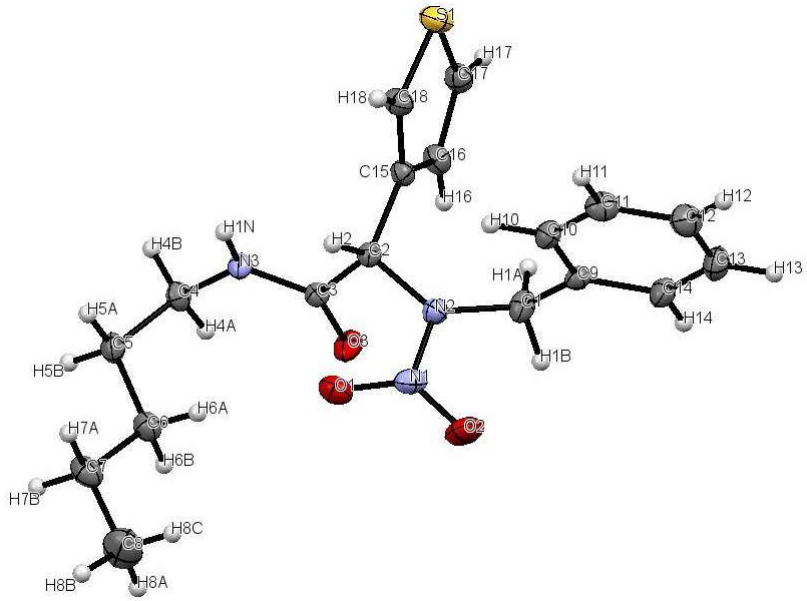


Image 2: ORTEP structure of 3l with the presence of hydrogen atoms

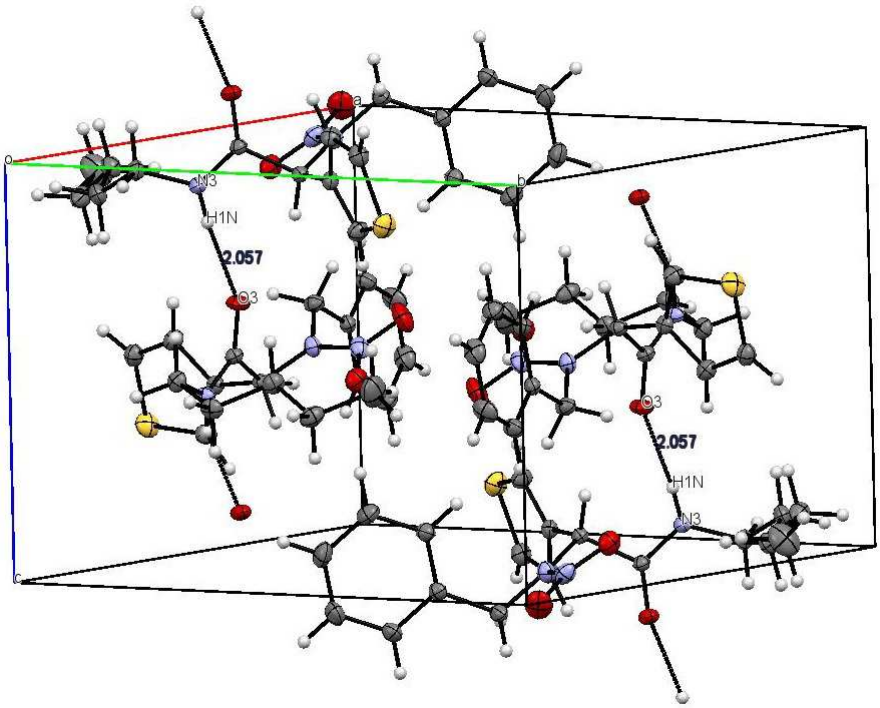


Image 3: ORTEP structure of 3l CCDC 1524126 *showing hydrogen bounding*

Table 2. Atomic Coordinates (A x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for mv178_1_a

atom	x	y	z	U(eq)
S(1)	3693(1)	4856(1)	1751(1)	30(1)
O(1)	5101(1)	1709(1)	704(1)	28(1)
O(2)	6808(1)	1947(1)	-540(1)	39(1)
O(3)	2893(1)	2478(1)	-1403(1)	24(1)
N(1)	5788(1)	2104(1)	55(1)	24(1)
N(2)	5398(1)	2757(1)	1(1)	20(1)
N(3)	1879(1)	2472(1)	656(1)	18(1)
C(1)	6120(1)	3199(1)	-902(1)	22(1)
C(2)	4157(1)	2921(1)	681(1)	16(1)
C(3)	2902(1)	2589(1)	-131(1)	16(1)
C(4)	604(1)	2144(1)	134(1)	21(1)
C(5)	535(1)	1432(1)	738(1)	23(1)
C(6)	1629(1)	963(1)	258(1)	25(1)

C(7)	1728(1)	290(1)	1030(1)	27(1)
C(8)	2842(2)	-159(1)	565(2)	48(1)
C(9)	7460(1)	3467(1)	-214(1)	18(1)
C(10)	7747(1)	3484(1)	1238(1)	20(1)
C(11)	8968(1)	3764(1)	1827(1)	25(1)
C(12)	9903(1)	4031(1)	974(2)	30(1)
C(13)	9615(1)	4015(1)	-475(2)	31(1)
C(14)	8407(1)	3731(1)	-1070(1)	24(1)
C(15)	3926(1)	3670(1)	767(1)	17(1)
C(16)	3358(1)	4077(1)	-373(1)	22(1)
C(17)	3184(1)	4740(1)	9(1)	24(1)
C(18)	4157(1)	4030(1)	1986(1)	23(1)

U(eq) is defined as 1/3 the trace of the Uij tensor.

Table 3. Bond lengths (A) and angles (deg) for mv178_1_a

S(1)-C(17)	1.705(1)	S(1)-C(18)	1.708(1)
O(1)-N(1)	1.235(1)	O(2)-N(1)	1.233(1)
O(3)-C(3)	1.231(1)	N(1)-N(2)	1.350(1)
N(2)-C(1)	1.456(1)	N(2)-C(2)	1.465(1)
N(3)-C(3)	1.325(1)	N(3)-C(4)	1.458(1)
N(3)-H(1N)	0.87(2)	C(1)-C(9)	1.511(2)
C(1)-H(1A)	0.9900	C(1)-H(1B)	0.9900
C(2)-C(15)	1.506(1)	C(2)-C(3)	1.542(1)
C(2)-H(2)	1.0000	C(4)-C(5)	1.528(2)
C(4)-H(4A)	0.9900	C(4)-H(4B)	0.9900
C(5)-C(6)	1.522(2)	C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900	C(6)-C(7)	1.523(2)
C(6)-H(6A)	0.9900	C(6)-H(6B)	0.9900
C(7)-C(8)	1.506(2)	C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900	C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800	C(8)-H(8C)	0.9800
C(9)-C(10)	1.388(2)	C(9)-C(14)	1.392(2)
C(10)-C(11)	1.392(2)	C(10)-H(10)	0.9500
C(11)-C(12)	1.383(2)	C(11)-H(11)	0.9500
C(12)-C(13)	1.384(2)	C(12)-H(12)	0.9500
C(13)-C(14)	1.387(2)	C(13)-H(13)	0.9500
C(14)-H(14)	0.9500	C(15)-C(18)	1.364(2)
C(15)-C(16)	1.426(2)	C(16)-C(17)	1.379(2)
C(16)-H(16)	0.9500	C(17)-H(17)	0.9500
C(18)-H(18)	0.9500		

C(17)-S(1)-C(18)	92.93(6)	O(2)-N(1)-O(1)	124.9(1)
O(2)-N(1)-N(2)	117.6(1)	O(1)-N(1)-N(2)	117.5(1)
N(1)-N(2)-C(1)	116.6(1)	N(1)-N(2)-C(2)	116.1(1)
C(1)-N(2)-C(2)	126.5(1)	C(3)-N(3)-C(4)	123.8(1)
C(3)-N(3)-H(1N)	118(1)	C(4)-N(3)-H(1N)	118(1)
N(2)-C(1)-C(9)	113.9(1)	N(2)-C(1)-H(1A)	108.8
C(9)-C(1)-H(1A)	108.8	N(2)-C(1)-H(1B)	108.8
C(9)-C(1)-H(1B)	108.8	H(1A)-C(1)-H(1B)	107.7
N(2)-C(2)-C(15)	112.25(8)	N(2)-C(2)-C(3)	109.92(8)

C(15)-C(2)-C(3)	109.34(8)	N(2)-C(2)-H(2)	108.4
C(15)-C(2)-H(2)	108.4	C(3)-C(2)-H(2)	108.4
O(3)-C(3)-N(3)	125.9(1)	O(3)-C(3)-C(2)	120.4(1)
N(3)-C(3)-C(2)	113.7(1)	N(3)-C(4)-C(5)	110.5(1)
N(3)-C(4)-H(4A)	109.6	C(5)-C(4)-H(4A)	109.6
N(3)-C(4)-H(4B)	109.6	C(5)-C(4)-H(4B)	109.6
H(4A)-C(4)-H(4B)	108.1	C(6)-C(5)-C(4)	113.3(1)
C(6)-C(5)-H(5A)	108.9	C(4)-C(5)-H(5A)	108.9
C(6)-C(5)-H(5B)	108.9	C(4)-C(5)-H(5B)	108.9
H(5A)-C(5)-H(5B)	107.7	C(5)-C(6)-C(7)	114.0(1)
C(5)-C(6)-H(6A)	108.7	C(7)-C(6)-H(6A)	108.7
C(5)-C(6)-H(6B)	108.7	C(7)-C(6)-H(6B)	108.7
H(6A)-C(6)-H(6B)	107.6	C(8)-C(7)-C(6)	113.1(1)
C(8)-C(7)-H(7A)	109.0	C(6)-C(7)-H(7A)	109.0
C(8)-C(7)-H(7B)	109.0	C(6)-C(7)-H(7B)	109.0
H(7A)-C(7)-H(7B)	107.8	C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5	H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5	H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5	C(10)-C(9)-C(14)	119.2(1)
C(10)-C(9)-C(1)	122.1(1)	C(14)-C(9)-C(1)	118.6(1)
C(9)-C(10)-C(11)	120.1(1)	C(9)-C(10)-H(10)	119.9
C(11)-C(10)-H(10)	119.9	C(12)-C(11)-C(10)	120.5(1)
C(12)-C(11)-H(11)	119.7	C(10)-C(11)-H(11)	119.7
C(11)-C(12)-C(13)	119.3(1)	C(11)-C(12)-H(12)	120.3
C(13)-C(12)-H(12)	120.3	C(12)-C(13)-C(14)	120.5(1)
C(12)-C(13)-H(13)	119.8	C(14)-C(13)-H(13)	119.8
C(13)-C(14)-C(9)	120.3(1)	C(13)-C(14)-H(14)	119.9
C(9)-C(14)-H(14)	119.9	C(18)-C(15)-C(16)	112.1(1)
C(18)-C(15)-C(2)	123.2(1)	C(16)-C(15)-C(2)	124.5(1)
C(17)-C(16)-C(15)	112.8(1)	C(17)-C(16)-H(16)	123.6
C(15)-C(16)-H(16)	123.6	C(16)-C(17)-S(1)	110.6(1)
C(16)-C(17)-H(17)	124.7	S(1)-C(17)-H(17)	124.7
C(15)-C(18)-S(1)	111.5(1)	C(15)-C(18)-H(18)	124.2
S(1)-C(18)-H(18)	124.2		

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for mv178_1_a

atom	U11	U22	U33	U23	U13	U12
S(1)	37(1)	20(1)	33(1)	-5(1)	3(1)	-1(1)
O(1)	33(1)	20(1)	31(1)	0(1)	1(1)	0(1)
O(2)	34(1)	35(1)	49(1)	-13(1)	14(1)	7(1)
O(3)	26(1)	35(1)	13(1)	-3(1)	1(1)	-5(1)
N(1)	24(1)	22(1)	26(1)	-7(1)	-1(1)	2(1)
N(2)	17(1)	19(1)	24(1)	0(1)	3(1)	0(1)
N(3)	17(1)	21(1)	14(1)	-1(1)	1(1)	-3(1)
C(1)	17(1)	32(1)	17(1)	2(1)	1(1)	-2(1)
C(2)	15(1)	18(1)	14(1)	0(1)	0(1)	-1(1)
C(3)	17(1)	16(1)	13(1)	1(1)	0(1)	-1(1)
C(4)	16(1)	23(1)	24(1)	0(1)	0(1)	-3(1)
C(5)	21(1)	24(1)	24(1)	1(1)	5(1)	-6(1)
C(6)	26(1)	22(1)	27(1)	3(1)	4(1)	-2(1)
C(7)	34(1)	22(1)	24(1)	3(1)	-3(1)	-4(1)
C(8)	53(1)	33(1)	60(1)	14(1)	13(1)	12(1)
C(9)	16(1)	19(1)	18(1)	-1(1)	3(1)	2(1)
C(10)	20(1)	24(1)	18(1)	1(1)	2(1)	1(1)
C(11)	24(1)	28(1)	22(1)	-3(1)	-4(1)	2(1)
C(12)	19(1)	33(1)	37(1)	-8(1)	-1(1)	-4(1)
C(13)	23(1)	37(1)	33(1)	-3(1)	10(1)	-8(1)
C(14)	22(1)	29(1)	21(1)	-1(1)	6(1)	-1(1)
C(15)	16(1)	17(1)	19(1)	0(1)	1(1)	-2(1)
C(16)	22(1)	21(1)	22(1)	3(1)	-1(1)	0(1)
C(17)	22(1)	21(1)	28(1)	3(1)	3(1)	1(1)
C(18)	28(1)	20(1)	22(1)	-2(1)	0(1)	-1(1)

The anisotropic displacement factor exponent takes the form

2 pi^2 [h^2a*^2U(11) +...+ 2hka*b*U(12)]

Table 5. Hydrogen Coordinates (A x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for mv178_1_a

atom	x	y	z	U(eq)
H(1N)	2020(20)	2551(7)	1550(20)	21
H(1A)	5520	3585	-1192	26
H(1B)	6302	2948	-1764	26
H(2)	4255	2735	1659	19
H(4A)	543	2121	-908	25
H(4B)	-182	2412	408	25
H(5A)	636	1459	1780	28
H(5B)	-378	1238	452	28
H(6A)	2527	1192	398	30
H(6B)	1434	876	-763	30
H(7A)	1902	374	2055	32
H(7B)	840	52	869	32
H(8A)	2649	-266	-438	72
H(8B)	2878	-577	1116	72
H(8C)	3723	74	713	72
H(10)	7109	3303	1832	25
H(11)	9161	3772	2822	30
H(12)	10733	4224	1379	36
H(13)	10251	4199	-1066	37
H(14)	8224	3717	-2066	28
H(16)	3123	3908	-1297	26
H(17)	2830	5085	-613	28
H(18)	4530	3844	2857	28