Supplementary Information

Stereoselective Michael additions on α-aminoacrylates as the key step to an *L*-Oic analogue bearing a quaternary stereocenter

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1. General Information

Dry solvents were purchased and stored under nitrogen over molecular sieves (bottles with crown caps). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F254 pre- coated glass plates (0.25 mm thickness) and visualized by UV light and a $KMnO_4$ solution. Flash chromatography was carried out on silica gel (230-400 mesh). Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Fourier 300). Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). 13C NMR spectra were recorded on 300 MHz spectrometers (Bruker Fourier 300) operating at 75 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). 19F NMR spectra were recorded on 300 MHz spectrometers (Bruker AMX 300) operating at 282 MHz. Fluorine chemical shifts are reported in ppm (δ) relative to CF_3Cl. Enantiomeric excess determinations were performed under below reported conditions with Agilent 1200 series HPLC. Mass spectra (MS) were performed at CIGA (Centro Interdipartimentale Grandi Apparecchiature), with mass spectrometer APEX II & Xmass software (Bruker Daltonics). Optical rotations were obtained on a polarimeter at 589 nm using 5 mL or 1 mL cell with a length of 1 dm.

2. Preparation of acrylates

2.1 Preparation of methyl 2-(2,2,2-trifluoroacetamido)acrylate (**2b**)[1]

To a solution of serine methyl ester hydrochloride (11.2 mmol, 1.742 g) in anhydrous dichloromethane (20 mL), triethylamine (44.90 mmol, 4 eq, 6.3 mL) and trifluoroacetic anhydride (28 mmol, 2.5 eq, 3.9 mL) were added, dropwise, at 0°C. The reaction became dark and after stirring for 24 hours, water was added to eliminate triethylamonium chloride. The phases were separated and the organic layer was washed with saturated $NaHCO_3$ (2 x 10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by a short silica gel flash column chromatography, eluting with hexane:ethyl acetate 4:1. The pure product (1.912 g) was isolated as an yellow oil in 87% yield. The spectroscopic data are in agreement with literature values.[1] **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 3.87 (s, 3H), 6.10 (s, 1H), 6.69 (s, 1H), 8.67 (s, 1H).

2.2 Preparation of benzyl 2-(2,2,2-trifluoroacetamido)acrylate (**2c**)

To a solution of serine benzyl ester hydrochloride (8 mmol, 1.853 g) in anhydrous dichloromethane (18 mL), triethylamine (32 mmol, 4 eq, 4.5 mL) and trifluoroacetic anhydride (20 mmol, 2.5 eq, 2.8 mL) were added, dropwise, at 0°C. The reaction became dark and after stirring for 24 hours, water was added to eliminate triethylamonium chloride. The phases were separated and the organic layer was washed with saturated $NaHCO_3$ (2 x 10 ml) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by a short silica gel flash column chromatography, eluting with hexane:ethyl acetate 4:1. The pure product (1.749 g) was isolated as an oil in 80% yield. The spectroscopic data are in agreement with literature values.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.31 (s, 3H), 6.17 (s, 1H), 6.20 (s, 1H), 7.39 (s, 5H), 8.55 (s broad, 1H).

2.3 Preparation of methyl 2-benzamidoacrylate (**2a**)[3]

To a solution of serine methyl ester hydrochloride (12 mmol, 1.866 g) in anhydrous dichloromethane (15 mL), triethylamine (40 mmol, 3.3 eq, 5.6 mL) and benzoylchloride (24 mmol, 2.0 eq, 2.8 mL) were added, dropwise, at 0°C under inert atmosphere. The reaction was stirred overnight at room temperature, then, water was added. The phases were separated and the organic layer was washed with saturated $NaHCO_3$ (2 x 10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the quantitative crude methyl 2-amino-3-hydroxypropanoate without purification was used for the following step.

To a solution of the product (12 mmol, 3.115 g) in anhydrous dichloromethane (12 mL) at 0°C, under inert atmosphere, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (14 mmol, 1.16 eq, 2.1 mL) was added. Stirring was continued at 0° C for 9 hours. Water was added, the phases were separated and the organic layer was washed with saturated $NaHCO_3$ (2 x 10 ml) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude acrylate was purified over a short silica gel flash chromatography column using *n*-hexane/ethyl acetate 4:1 as eluent. The acrylate (2.390 g) was recovered in 97% chemical yield. The spectroscopic data are in agreement with literature values. **^{1}H NMR** (300 MHz, CDCl3) δ: 3.88 (s, 3H), 5,98 (s, 1H), 6,79 (s, 1H),7.43-7.57 (m, 3H), 7.81-7.85 (m, 2H), 8.54 (s broad, 1H).

3 General procedure for the preparation of chiral ketimines.

5 Å Molecular sieves were activated by heating for 30 minutes at reduced pressure at 200 °C. After cooling, anhydrous toluene (8 mL), 2-substituted cyclanone (8 mmol) and (*R*)- or (*S*)-phenylethylamine (PEA) (8 mmol, 1 mL) were added under inert atmosphere. The mixture was stirred under reflux for 24-30 hours in order to obtain a high PEA conversion (75-94%). The conversions were monitored by ^{1}H-NMR ($CDCl_3$) of the reaction mixture, comparing the quartet at δ 4.11 of PEA with the signal of the same proton of the ketimine which shifts on the left of the spectrum. Ketimines were used for the following step without any purification.

Ketimine (δ, q)	Conversion (%)
1a, 4.81	90%
1b, 4.76	84%
1c, 4.56	88%
1d, 4.43	86%
1e, 4.91	84%
1f, 4.80	84%
1g, 4.60	94%
1h, 4.58	75%
1i, 4.87	80%
1j, 4.88	80%

4 General procedure for the Michael additions

4.1 General procedure for the Michael addition of ketimines ((***R***)-**1f-j**) with acrylate **2b** and ketamine (***S***)-**1a** with acrylate **2c**.

To a anhydrous toluene solution (6 mL) of crude ketimines (**1f-j**) (7.2 mmol), **2b** (3.6 mmol, 0.5 eq, 710 mg) and hydroquinone (5 mg) were added (ketimine **1a** reacted in the same condition with **2c**). After stirring at room temperature for 30 hours, the crude was filtered to remove the molecular sieves and 20% aqueous acetic acid (3 mL) was added. The mixture was stirred for 1 hour, then extracted with ethyl acetate (10 mL x 3). The collected organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography column over silica gel, eluting firstly with hexane:ethyl acetate 9:1 and then with hexane:ethyl acetate 8:2.

4.2 General procedure for the Michael addition of chiral ketimines ((***S***)-**1a-e**) with acrylates **2a**.

To an anhydrous THF solution (6 mL) of crude ketimine (**1a-e**) (7.2 mmol), **2a** (3.6 mmol, 0.5 eq, 739 mg) and hydroquinone (5 mg) were added. After stirring under reflux for 3 day, 20% aqueous acetic acid (3 mL) was added. The mixture was stirred for 1 hour, then extracted with ethyl acetate (10 mL x 3). The collected organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography column over silica gel, eluting with hexane:ethyl acetate 7:3.

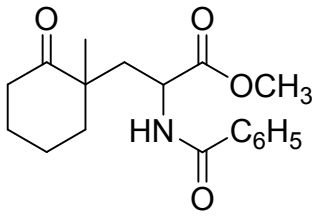
5. Domino deprotection/cyclization and hydrogenation reaction of 3f.

To a solution of **3f** (0.81 mmol, 251 mg) in 1.3 mL of methanol, *p*-toluenesulfonic acid (0.81 mmol, 1 eq, 0.113 mL) was added. The reaction mixture was heated to 65 °C under stirring until TLC showed complete reaction (about 24-30 hours). The crude mixture was diluted with MeOH to 15 ml and Pd/C (10% w/w, 250 mg) was added. The reaction mixture was placed in a glass Parr reaction bottle and shaken under 12 atm of hydrogen. The catalytic hydrogenation was carried out for 24 hours at 40°C. The catalyst was removed by filtration on a celite cake, and the filtrate was concentrated in vacuo. Ethyl acetate was added to the crude product in order to induce precipitation. After filtration, white crystals of 2*R*,3a*S*,7a*S*)-2-(methoxycarbonyl)-3a-methyloctahydro-1H-indol-1-ium 4-methylbenzenesulfonate (**5**) (135 mg) were obtained in 45% yield.

6 Synthesis of (2*R*,3a*S*,7a*S*)-methyl 1-((2-bromophenyl)sulfonyl)-3a-methyloctahydro-1H-indole-2-carboxylate (6).

TEA (0.43 mmol, 1.1 eq, 0.060 mL) was added to a solution of **5** (0.39 mmol, 143 mg) in anhydrous THF (8 mL) under nitrogen atmosphere at rt. After 1h under stirring, TEA (0.43 mmol, 1.1 eq, 0.060 mL), 2-bromobenzenesulfonylchloride (0.39 mmol, 1 eq, 100 mg) and DMAP (0.08 mmol, 0.2 eq, 10 mg) were added. The reaction mixture was stirred at rt for 24 hours, quenched with 1M HCl (2 mL), extracted with ethyl acetate (5 mL x 4), dried with Na_2SO_4 and concentrated in vacuo. The crude residue was purified by silica gel flash chromatography (starting with hexane/ethyl acetate 9:1 to hexane/ethyl acetate 8:2) to yield 85 mg of **6** as a colorless solid (53% chemical yield).

Methyl 2-benzamido-3-(1-ethyl-2-oxocyclohexyl)propanoate (Table 1, compound 3a)



3a

Yield 90% (3.24 mmol, 1.03 g)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.20 (s, 3H), 1.40-1.90 (m, 7H), 2.20-2.55 (m, 3H), 3.71 (s, 3H), 4.79 (ddd, J = 7.8, 4.8, 4.0 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H), 7.25-7.55 (m, 3H), 7.75 (d, J = 10.1 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.96, 25.60, 26.79, 36.45, 38.55, 38.82, 48.08, 50.25, 52.57, 127.24, 128.78, 131.91, 133.74, 166.92, 173.22, 217.02.

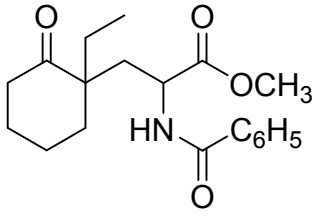
IR (KBr) cm^{-1} 3292 (NH), 2983-2845 (CH), 1749 (C=O ester), 1700 (C=O ketone), 1631 (C=O amide), 1535 (C-N), 1218 (C-O).

MS Mass (ESI) m/z calc. for C18H23NO4Na1+: 340.2, found: 340.2 [M + Na].

$[\alpha]^{20}_D$ = - 72.7 (*c* 0.994, CH_2Cl_2).

e.e. 96% determined by HPLC on Daicel Chiralpak AD column; mobile phase: 85:15 Hexane/Ethanol; flow rate: 0,8 mL/min; pressure: 70 bar; detection wavelength 210 nm; t_R 15.385 min (minor), t_R 19.602 min (major).

Methyl 2-benzamido-3-(1-ethyl-2-oxocyclohexyl)propanoate (Table 1, compound 3b)



3b

Yield 90% (3.24 mmol, 1.074 g)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.80 (t, 3H), 1.40-2.00 (m, 9H), 2.25-2.50 (m, 2H), 2.65 (dd, J = 14.5, 12.1 Hz, 1 H), 3.74 (s, 3H), 4.71 (ddd, J = 7.8 ,4.0, 3.7 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 7.45-7.55 (m, 3H), 7.78 (d, J = 9.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.86, 20.64, 26.68, 30.93, 33.71, 34.67, 39.27, 50.19, 51.43, 52.54, 127.24, 128.77, 131.87, 133.74, 166.87, 173.40, 216.94.

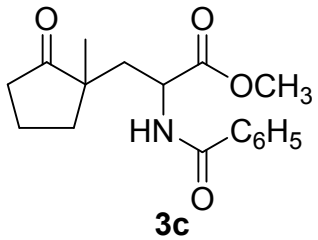
IR (NaCl) cm^{-1} 3346 (NH), 3030- 2867 (CH), 1746 (C=O ester), 1697 (C=O ketone), 1661 (C=O amide), 1531 (C-N), 1224 (C-O).

MS Mass (ESI+) m/z calc. for C19H25NO4H1+: 332.1, found: 332.1 [M + H]; m/z calc. for C19H25NO4Na1+: 354.2, found: 354.2 [M + Na]

$[\alpha]^{20}_D$ = - 65.9 (*c* 0.720, CH_2Cl_2)

e.e. > 98 % determined by HPLC on Daicel Chiralpak AD column; mobile phase: 80:20 Hexane/Ethanol; flow rate: 0,8 mL/min; pressure: 70 bar; detection wavelength 210 nm; t_R 14.492 min (minor), t_R 18.706 min (major).

Methyl 2-benzamido-3-(1-methyl-2-oxocyclopentyl)propanoate (Table 1, compound 3c)



3c

Yield 95% (3.42 mmol, 1.037 g)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06 (s, 3H), 1.70-2.31(m, 8H), 3.73 (s,3H), 4.92 (ddd, J = 9.2, 4.7, 3.6 Hz, 1H), 6.32 (d, J = 9.3 Hz, 1H), 7.40-7.60 (m, 3H), 7.74 (d, J = 6.8 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.69, 23.91, 33.49, 37.55, 38.50, 47.81, 49.99, 52.73, 116.21, 127.21, 128.76, 128.90, 132.17, 133.46, 167.26, 173.00.

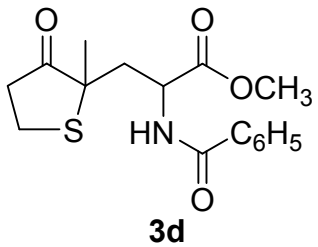
IR (NaCl) cm^{-1} 3344 (NH), 3031- 2861 (CH), 1737 (C=O ester), 1658 (C=O ketone), 1650 (C=O amide), 1533 (C-N), 1212 (C-O).

MS Mass: (ESI+) m/z calc. for C17H21NO4H1+: 304.1, found: 304.1 [M + H].

$[\alpha]^{20}_D$ = - 4 (*c* 1.04, CH_2Cl_2)

e.e. > 98 determined by HPLC on Daicel Chiralpak IB column; mobile phase: 85:15 Hexane/Ethanol; flow rate: 0,8 mL/min; pressure: 70 bar; detection wavelength 210 nm; t_R 7.56 min (major), t_R 7.88 min (minor).

Methyl 2-benzamido-3-(2-methyl-3-oxotetrahydrothiophen-2-yl)propanoate (Table 1, compound 3d)



3d

Yield 93% (3.35 mmol, 1.076 g)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.46 (s, 3H), 2.34 (dd, J = 10.3, 5.1 Hz, 2H), 2.41-2.53 (m,1H), 2.56-2.68 (m, 1H), 2.90 (dd, J = 13.2, 6.6 Hz, 2H), 3.78 (s, 3H), 5.19 (ddd, J = 9.2, 5.0, 4.6 Hz, 1H), 6.36 (d, J = 9.2 Hz, 1H), 7.40-7.60 (m, 3H), 7.80 (d, J = 6.0 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.32, 27.43, 39.28, 41.04, 50.79, 52.81, 55.54, 127.30, 128.92, 132.21, 133.57, 167.39, 172.70, 217.28.

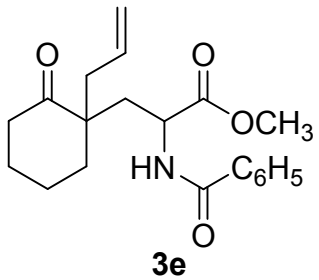
IR 3301 (NH), 3027-2840 (CH), 1760 (C=O ester), 1724 (C=O ketone), 1645 (C=O amide), 1532 (C-N), 1218 (C-O), 661 (C-S).

MS Mass: (ESI+) m/z calc. for C16H19NO4S1Na1+: 344.1, found: 344.1 [M + Na].

$[\alpha]^{20}_D$ = + 10.8 (*c* 0.991, CH_2Cl_2).

e.e. 98 determined by HPLC on Daicel Chiralpak AD column; mobile phase: 85:15 Hexane/2-Propanol; flow rate: 0,8 mL/min; pressure: 70 bar; detection wavelength 210 nm; t_R 10.77 min (minor), t_R 14.26 min (major).

Methyl 3-(1-allyl-2-oxocyclohexyl)-2-benzamidopropanoate (Table 1, compound 3e)



3e

Yield 80% (2.88 mmol, 0.989 g)

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.40-2.50 (m, 12H), 3.74 (s, 3H), 4.75 (ddd, J = 7.4, 5.1, 3.5 Hz, 1H), 4.90-5.20 (m, 2H), 5.50-5.70 (m, 1H), 6.85 (d, J = 7.4 Hz, 1H), 7.42-7.51 (m, 3H), 7.80 (dd, J = 8.0, 1.0 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.60, 26.58, 29.90, 33.38, 35.27, 39.31, 42.27, 50.18, 51.38, 52.69, 116.25, 127.36, 128.83, 132.00, 133.52, 166.95, 173.30, 216.38.

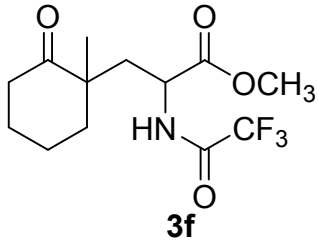
IR (NaCl) cm^{-1} 3355 (NH), 3030- 2865 (CH), 1746 (C=O ester), 1699 (C=O ketone), 1661 (C=O amide), 1529 (C-N), 1216 (C-O).

MS Mass: (ESI+) m/z calc. for C20H23NO4H+: 344.3, found 344.3 [M + H].

$[\alpha]^{20}_D$ = - 87.5 (*c* 1.30, CH_2Cl_2)

e.e. 96% determined by HPLC on Daicel Chiralpak AD column; mobile phase: 85:15 Hexane/Ethanol; flow rate: 0,8 mL/min; pressure: 70 bar; detection wavelength 210 nm; t_R 14.68 min (minor), t_R 18.48 min (major).

Methyl 3-(1-methyl-2-oxocyclohexyl)-2-(2,2,2-trifluoroacetamido)propanoate (Table 2, compound 3f)



3f

Yield 80% (2.88 mmol, 0.891 g)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H), 1.50-1.92 (m, 7H), 1.97-2.10 (m, 1H), 2.28-2.64 (m, 3H), 3.77 (s, 3H), 4.58 (ddd, J = 10.5, 7.9, 4.1 Hz, 1 H), 7.25 (bs, 1H).

^{13}C NMR (75, $CDCl_3$) δ: 20.65, 24.94, 26.80, 36.40, 37.74, 38.40, 44.39, 47.86, 49.88, 109.89-121.32, 156.07-157.57, 171.20, 216.59.

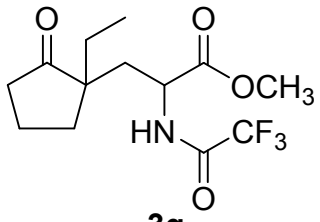
^{19}F NMR (300MHz, $CDCl_3$) δ: -76.17.

HRMS Mass (TOF MS ES+) m/z calc. for C13H18F3NO4Na1+: 332.1078, found: 332.1078 [M + Na].

$[\alpha]^{20}_D$ = - 66,2 (*c* 0.5, CH_2Cl_2).

e.e. 94% determined by HPLC using Phenomenex Lux 3µ cellulose-4 column; mobile phase: 80:20 Hexane/2-Propanol; flow rate: 0,8 mL/min; pressure: 70 bar; detection wavelength 210 nm; t_R 7.65 min (minor), t_R 8.85 min (major).

Methyl 3-(1-ethyl-2-oxocyclopentyl)-2-(2,2,2-trifluoroacetamido)propanoate (Table 2, compound 3g)



3g

Yield 68% (2.448 mmol, 0.757 g)

^{1}H NMR (300MHz, $CDCl_3$) δ: 0.87 (t, J = 7.5 Hz, 3H), 1.42-1.51 (q, 2H), 1.70 (s, 1H), 1.83-2.20 (m, 8H), 2.30-2.44 (m, 1H), 3.79 (s, 3H), 4.67 (td, J = 9.7, 4.3 Hz, 1H), 6.71 (d, J = 8.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.89, 18.14, 28.25, 31.23, 34.65, 36.98, 49.71, 50.84, 52.88, 109.82-121.25, 156.30-157.80, 171.15, 222.85.

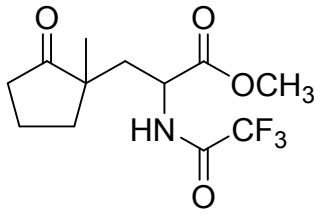
^{19}F NMR (300MHz, $CDCl_3$) δ: -76.11.

HRMS Mass (TOF MS ES+) m/z calc. for C13H18F3NO4Na1+ 332.1076, found: 332.1076 [M + Na].

$[\alpha]^{20}_{D}$ = +24,4 (*c* 0.5, CH_2Cl_2).

e.e. 97% determined by HPLC on Phenomenex Lux 3µ cellulose-4 column; mobile phase: Hexane/2-Propanol 90:10, flow rate: 0,8 mL/min, pressure: 70 bar; detection wavelength 210 nm; t_R 7.81 min (major), t_R 9.94 min (minor).

Methyl 3-(1-methyl-2-oxocyclopentyl)-2-(2,2,2-trifluoroacetamido)propanoate (Table 2, compound 3h).



3h

Yield 52% (1.872 mmol, 0.553 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.07 (s, 3H), 1.77-2.19 (m, 7H), 2.36-2.48 (m, 1H), 3.79 (s, 3H), 4.73 (td, J = 8.6, 5.9 Hz, 1H), 6.95 (bs, 1H).

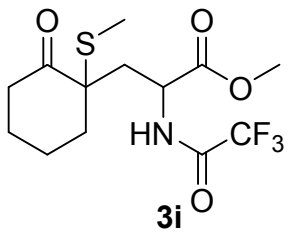
^{13}C NMR (75, $CDCl_3$) δ: 18.33, 22.58, 34.13, 36.66, 37.40, 47.64, 49.75, 52.93, 113.62-117.44, 156.76-157.26, 171.05, 223.11.

^{19}F NMR (300MHz, $CDCl_3$) δ: -76.11.

HRMS Mass (TOF MS ES+) m/z calc. for C12H16F3NO4Na1+ 318.0925, found: 318.0925 [M + Na].

e.e. 94% determined by HPLC on Phenomenex Lux 3µ cellulose-4 column; mobile phase: 90:10 Hexane/2-Propanol; flow rate: 0,8 mL/min; pressure: 70 bar; detection wavelength 210 nm; t_R 7.98 min (major), t_R 8.94 min (minor).

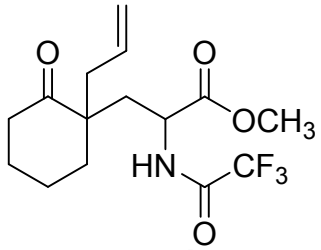
Methyl 3-(1-(methylthio)-2-oxocyclohexyl)-2-(2,2,2-trifluoroacetamido)propanoate (Table 2, compound 3i)



3i

Yield 80% (2.88 mmol, 0.983 g).
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.49-1.80 (m, 3H), 1.87 (s, 3H), 1.98-2.13 (m, 4H), 2.20-2.34 (m, 2H), 2.52 (dd, J = 14.8, 10.7 Hz, 1H), 3.11 (ddd, J = 15.5, 14.1, 6.1 Hz, 1H), 3.80 (s, 3H), 4.78 (ddd, J = 8.4, 5.2, 3.9 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.07, 20.55, 25.99, 34.47, 35.30, 36.68, 49.23, 52.99, 55.18, 109.83-121.26, 156.03-157.53, 171.07, 206.85.
^{19}F NMR (300MHz, $CDCl_3$) δ: -76.12.
HRMS Mass (TOF MS ES+) m/z calc. for C13H18F3NO4SNa1+ 364.0796, found: 364.0796 [M + Na].
$[\alpha]^{20}_{D}$ = + 22,3 (*c* 0.5, CH_2Cl_2).
e.e. 97% determined by HPLC on Phenomenex Lux 3µ cellulose-4 column; mobile phase: Hexane/2-Propanol 90:10; flow rate: 0,8 mL/min; pressure: 70 bar; detection wavelength 210 nm; t_R= 8.48 min (major), t_R= 10.79 min (minor).

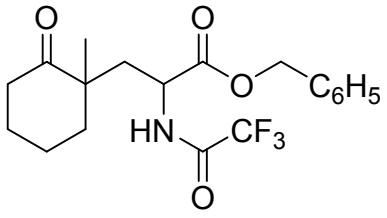
Methyl 3-(1-allyl-2-oxocyclohexyl)-2-(2,2,2-trifluoroacetamido)propanoate (Table 2, compound 3j)



3j

Yield 75% (2.7 mmol, 0.905 g).
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.50-1.93 (m, 7H), 2.01-2.12 (m, 1H), 2.22-2.64 (m, 5H), 3.78 (s, 3H), 4.53 (ddt, J = 11.8, 7.9, 3.7 Hz, 1H), 4.99-5.19 (m, 2H), 5.58 (ddt, J = 11.9, 7.2, 4.3 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.30, 26.60, 33.40, 34.65, 38.85, 41.79, 49.80, 51.10, 53.09, 109.88-121.31, 119.64, 131.25, 156.12-157.61, 171.21, 215.73.
^{19}F NMR (300 MHz, $CDCl_3$) δ: -76.17.
HRMS Mass (TOF MS ES+) m/z calc. for C15H20F3NO4Na1+: 358.1235, found: 358.1235 [M + Na].
$[\alpha]^{20}_{D}$ = + 95,6 (*c* 0.5, CH_2Cl_2).
e.e. 97% determined by HPLC on Phenomenex Lux 3µ cellulose-4 column; mobile phase: Hexane/2-Propanol 90:10; flow rate: 0,8 ml/min; pressure: 70 bar; detection wavelength 210 nm; t_R= 6.41 min (major), t_R= 7.47 min (minor).

Benzyl 3-(1-methyl-2-oxocyclohexyl)-2-(2,2,2-trifluoroacetamido)propanoate (Table 2, compound 3k)



3k

Yield 90% (3.24 mmol, 1.249 g)

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 3H), 1.50-1.83 (m, 7H), 2.23-2.60 (m, 3H), 4.65 (ddd, J = 11.8, 7.5, 3.9 Hz, 1H), 5.17 (s, 2H), 7.34-.7.37 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 20.92, 25.46, 27.02, 36.46, 37.83, 38.68, 48.15, 50.33, 67.91, 118.72, 126.52, 128.57, 135.18, 156.77, 170.80, 216.93.

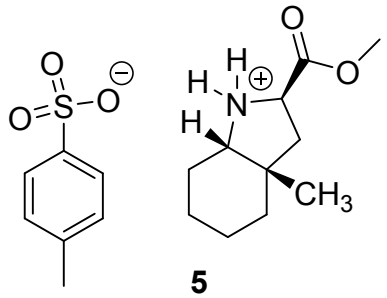
IR: (NaCl) cm^{-1} 3326 (NH), 2872-3068 (CH), 1723 (C=O estere), 1696 (C=O ketone), 1554 (C-N), 1267 (C-O).

MS Mass: (ESI+) m/z calc. for C19H22F3NO4Na1+: 408.2, found: 408.2 [M + Na].

$[\alpha]^{20}_D$ =- 51.3 (*c* 1.11, CH_2Cl_2)

e.e. 96% determined by HPLC on Daicel Chiralpak AD column; mobile phase: 85:15 Hexane/Ethanol; flow rate: 0,8 mL/min; pressure: 70 bar; detection wavelength 210 nm; t_R 6.86 min (major), t_R 8.01 min (minor).

(2*R*,3a*S*,7a*S*)-2-(methoxycarbonyl)-3a-methyloctahydro-1H-indol-1-ium 4-methylbenzenesulfonate (5)



5

Yield 45% (0.365 mmol, 135 mg)

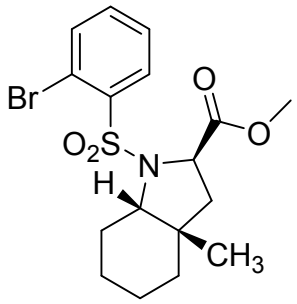
^{1}H NMR (300MHz, CD_3OD) δ: 1.15 (s, 3H), 1.43-1.64 (m, 6H), 1.78-2.01 (m, 3H), 2.39 (s, 3H), 3.42 (t, J = 4.8 Hz, 1H), 3.86 (s, 3H), 4.64 (t, J = 9.0 Hz, 1H), 7.26 (d, J = 7.8 Hz, 2H), 7.72 (d, J = 7.9 Hz, 2H).

^{13}C NMR (75 MHz, CD_3OD) δ: 19.53, 19.96, 20.21, 22.15, 22.64, 31.34, 40.13, 40.83, 52.71, 56.37, 64.46, 125.60, 128.47, 140.37, 142.20, 169.92.

HRMS Mass: (TOF MS ES+) m/z calc. for $C11H20NO2^+$ [M] 198.1498, found 198.1498 [M].

$[\alpha]^{20}_D$ = +13,4 (*c* 0.5, MeOH)

(2R,3aS,7aS)-methyl 1-((2-bromophenyl)sulfonyl)-3a-methyloctahydro-1H-indole-2-carboxylate (6).



6

Yield 53% (0.207 mmol, 86 mg)

^{1}H NMR (300MHz, CD_3OD) δ: 1.12 (s, 3H), 1.25-1.35 (m, 4H), 1.46-1.85 (m, 5H), 2.22 (dd, J = 12.8, 9.4 Hz, 1H), 3.70 (s, 3H), 3.78 (t, J = 4.4 Hz, 1H), 4.75 (dd, J = 9.3, 6.9 Hz, 1H), 7.34-7.45 (m, 2H), 7.74 (dd, J = 7.5, 1.6 Hz, 1H), 8.18 (dd, J = 7.6, 2.0 Hz, 1H).

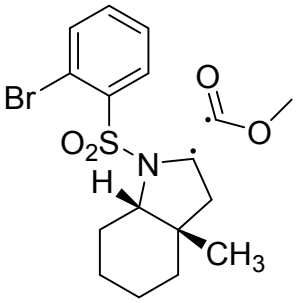
^{13}C NMR (75 MHz, CD_3OD) δ: 20.44, 21.13, 23.95, 24.80, 33.94, 40.71, 42.26, 52.26, 60.70, 66.14, 121.26, 127.35, 131.8, 133.34, 135.17, 141.18, 173.77.

e.e. >98% determined by HPLC on Daicel Chiralpak OD-H column; mobile phase: 80:20 Hexane/2-Propanol; flow rate: 0,8 mL/min; pressure: 70 bar; detection wavelength 210 nm; t_R 11.27 min (major), t_R 13.86 min (minor).

During high resolution EI mass analysis the ester portion is lost:

HRMS (EI): calcd for C15H19BrNO2S•: 356,03199, found: 356,032810

Chemical Formula: $C_{15}H_{19}BrNO_2S^{\bullet}$
Exact Mass: 356,03199



Chemical Formula: $C_2H_3O_2^{\bullet}$
Exact Mass: 59,01330

6

References

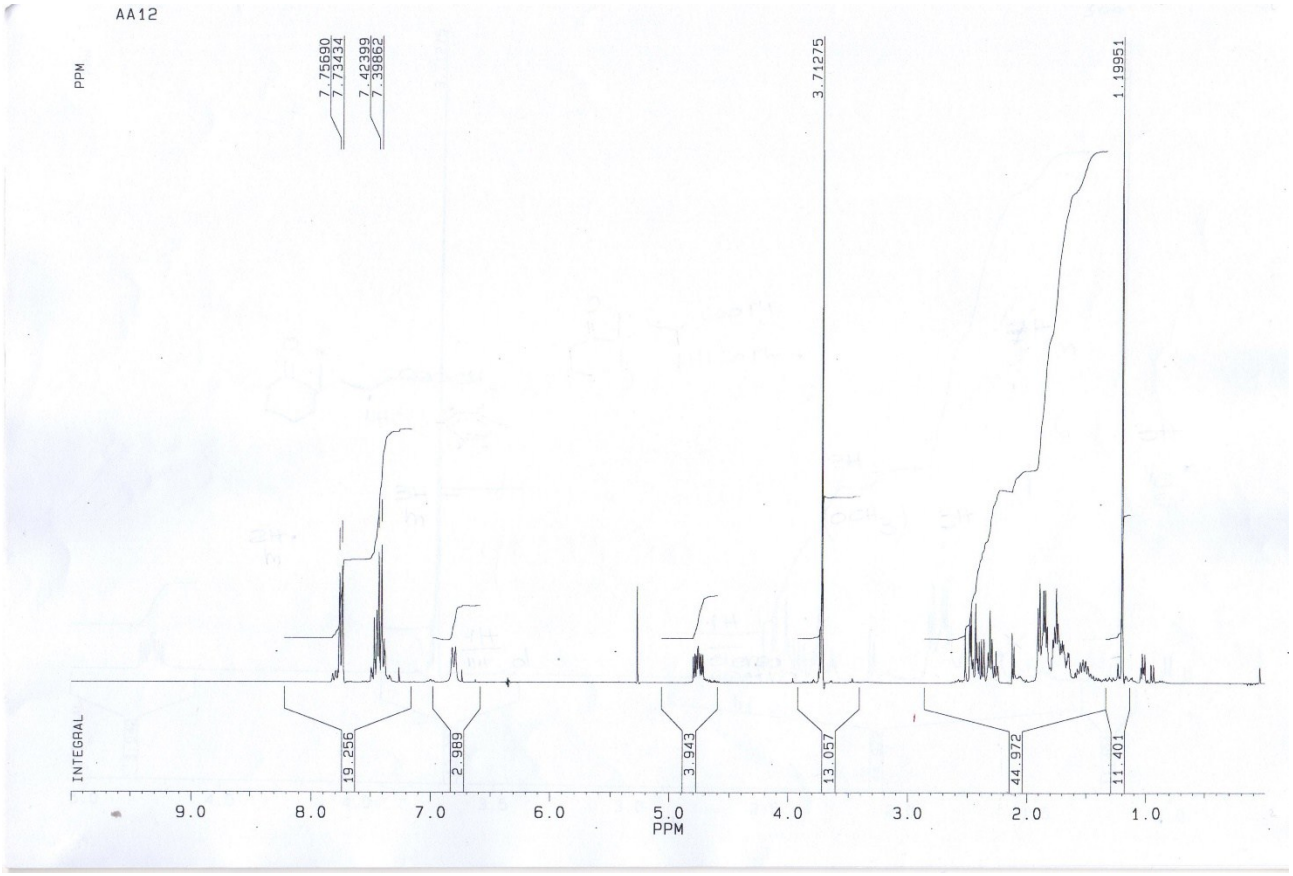
[1]A. Avenoza, J. H. Busto, N. Canal, J. I. Garcia,G. Jimenez-Oses, J. M. Peregrina, M. Perez-Fernandez, *New J. Chem.*, **2007**, *31*, 224-229.

[2] L. Navarre, R. Martinez, J.-P. Genet, S. Darses, *J. Am. Chem. Soc*., **2008**, *130*, 6159-6169

[3] M. Crossley, A. Stamford, *Aust. J. Chem*., **1994**, *47*, 1695-1711.

[4]S. Wang,Y. Otani, X. Liu, M. Kawahata, K. Yamaguchi, T. Ohwada, *J. Org. Chem.*,**2014**, *79*, 5287-5300.

COMPOUND 3a


AA12
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7.42399
7.39862
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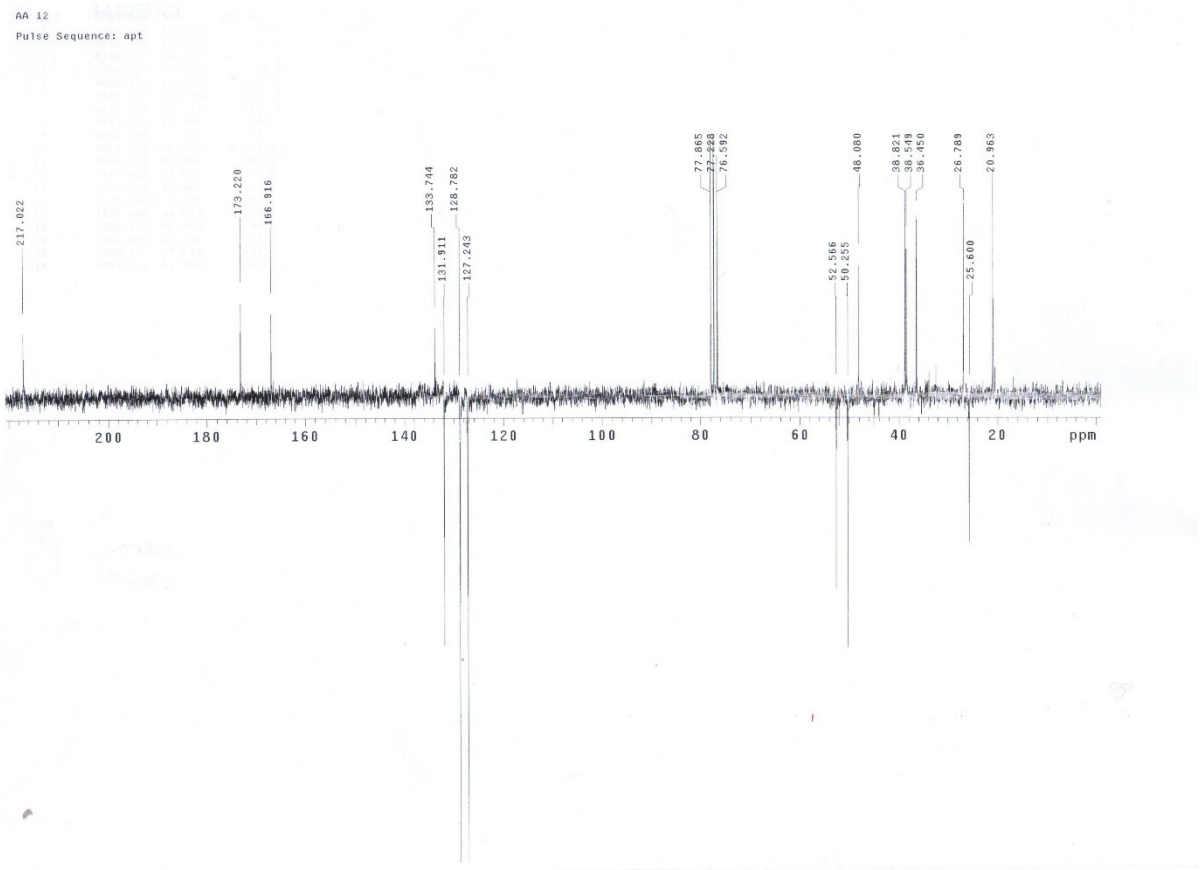
1.19951
INTEGRAL
19.256
2.989
3.943
13.057
44.972
11.401
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM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Pulse Sequence: apt
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166.916
133.744
131.911
128.782
127.243
77.865
77.228
76.592
52.566
50.255
40.080
38.821
38.540
36.450
26.789
25.600
20.963
200
180
160
140
120
100
80
60
40
20
ppm

Data File C:\HPCHEM\1\DATA\NIKIRAC.D Sample Name: nikir ad15etoh

```
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Injection Date  : 20/06/11 15.46.21
Sample Name     : nikir ad15etoh                    Vial :   1
Acq. Operator   : cece
Method          : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 20/06/11 15.47.24  by cece
                  (modified after loading)
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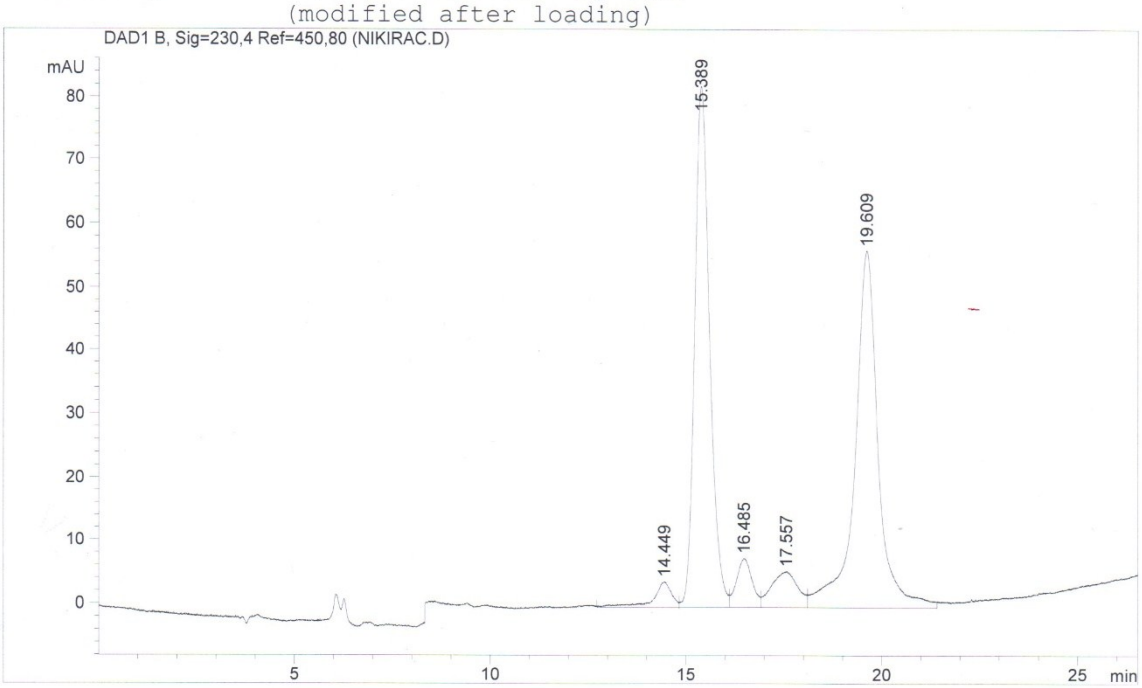


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==========================================================================
                          Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=230,4 Ref=450,80

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
   1  14.449 VV    0.4661  134.54424    3.94323   2.6231
   2  15.389 VV    0.4068 2191.35840   82.26465  42.7238
   3  16.485 VV    0.4166  211.48540    7.60030   4.1232
   4  17.557 VV    0.6222  261.55701    5.54597   5.0994
   5  19.609 VB    0.6068 2330.17847   56.31241  45.4303

Totals :                  5129.12350  155.66657

 Results obtained with enhanced integrator!
==========================================================================
                          *** End of Report ***
```

Instrument 1 20/06/11 16.13.54 cece Page 1 of 1

Data File C:\HPCHEM\1\DATA\NIKI16B.D Sample Name: niki ad15etoh

```
==========================================================================
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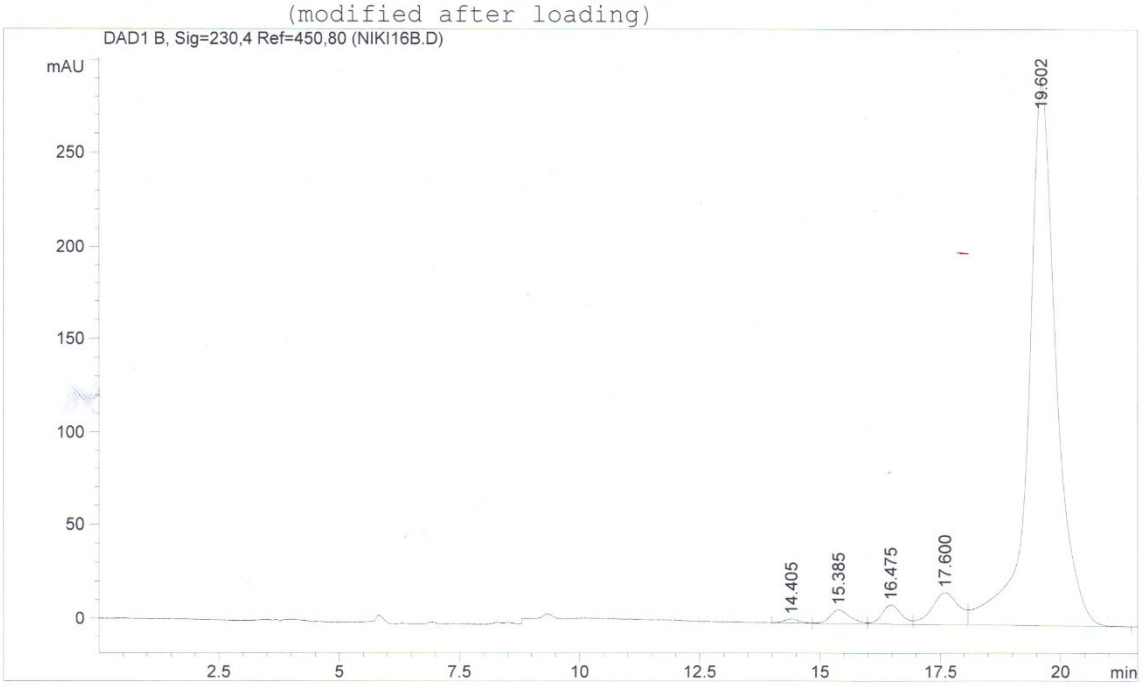
Sample Name     : niki ad15etoh                          Vial :   1
Acq. Operator   : cece
Acq. Method     : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 10/06/11 16.59.35  by cece
Analysis Method : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 20/06/11 15.47.24  by cece
                  (modified after loading)
```

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==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: DAD1 B, Sig=230,4 Ref=450,80

Peak RetTime Type  Width     Area      Height     Area
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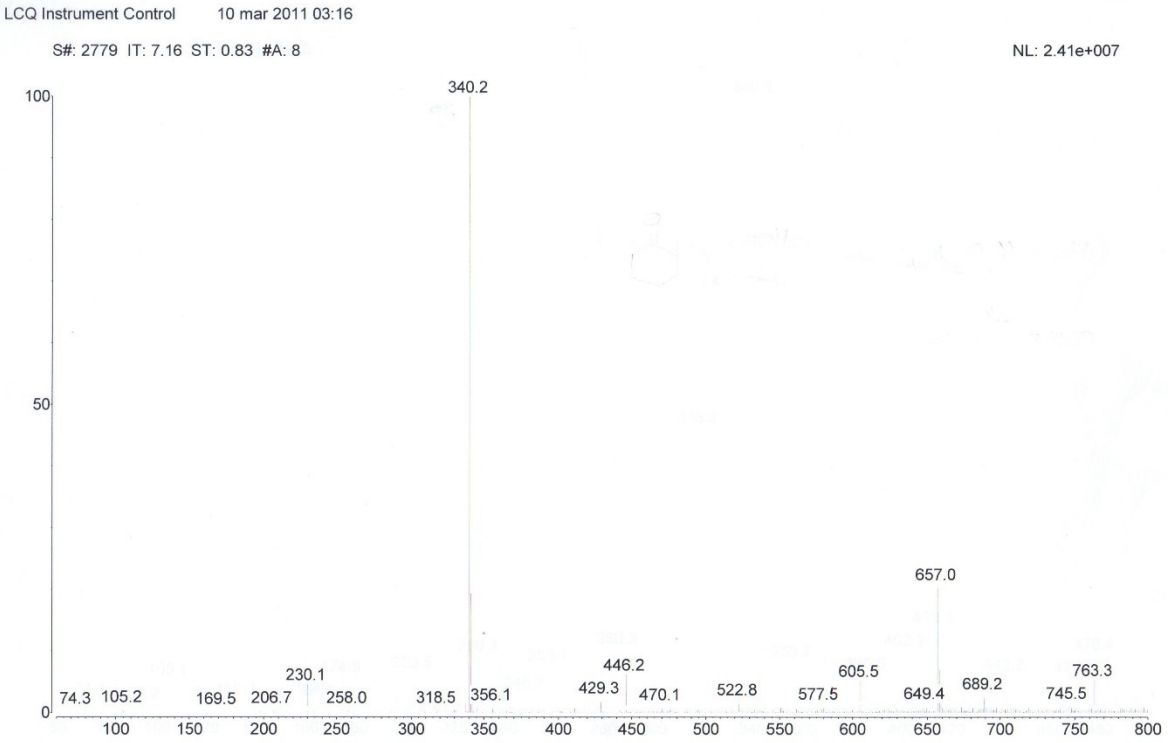
----|-------|----|-------|----------|----------|--------|
   1  14.405 BP    0.3213   44.70756    2.12607   0.3454
   2  15.385 VV    0.4278  214.34973    7.53633   1.6561
   3  16.475 VV    0.4264  291.79514   10.55948   2.2544
   4  17.600 VV    0.5818  690.49756   17.44588   5.3348
   5  19.602 VB    0.5904 1.17020e4   290.22021  90.4094

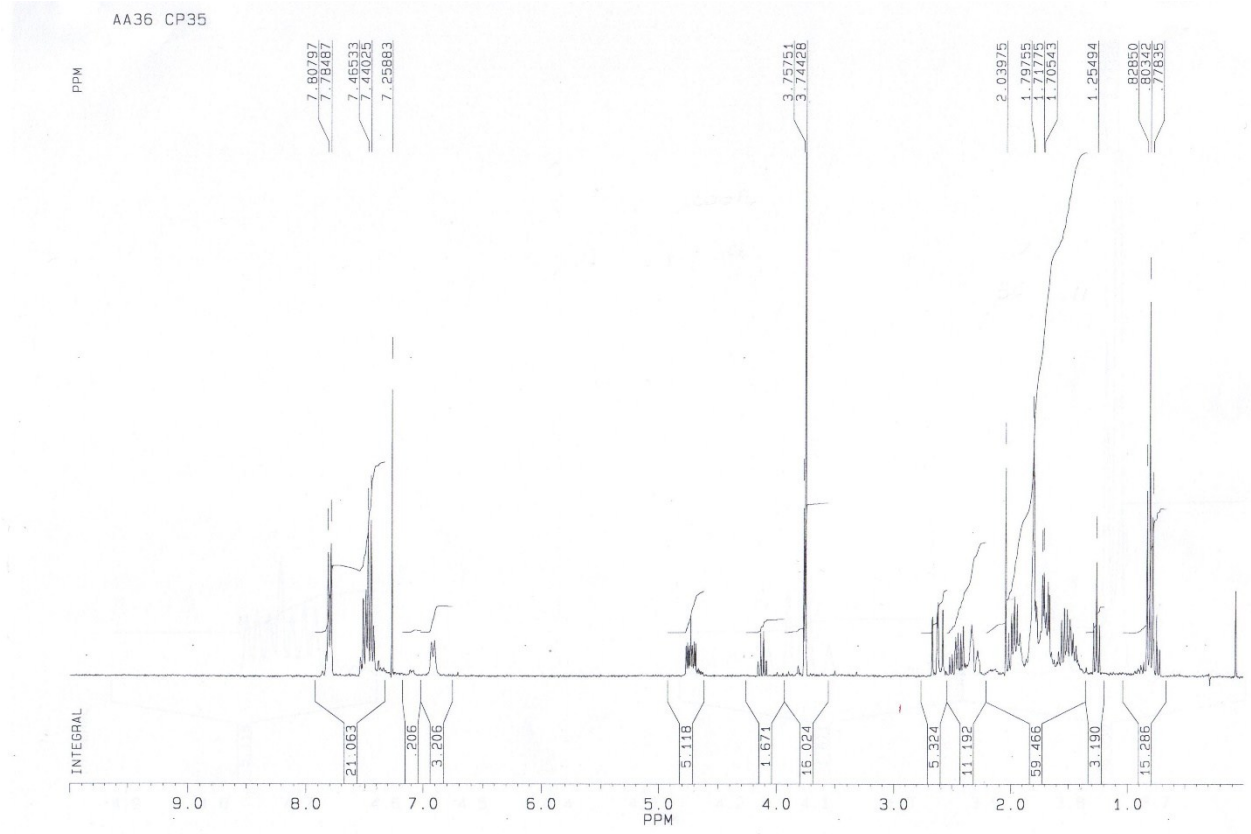
Totals :                  1.29433e4   327.88798

 Results obtained with enhanced integrator!
==========================================================================
                          *** End of Report ***

Instrument 1 20/06/11 15.47.50  cece                    Page 1 of 1
```


LCQ Instrument Control 10 mar 2011 03:16
S#: 2779 IT: 7.16 ST: 0.83 #A: 8
NL: 2.41e+007
100
50
0
340.2
657.0
446.2
230.1
605.5
763.3
689.2
74.3
105.2
169.5
206.7
258.0
318.5
356.1
429.3
470.1
522.8
577.5
649.4
745.5
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800

COMPOUND 3b


AA36 CP35
PPM
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7.78487
7.46533
7.44025
7.25883
3.75751
3.74428
2.03975
1.79755
1.77755
1.70543
1.25494
.82850
.80342
.77835
INTEGRAL
21.063
.206
3.206
5.118
1.671
16.024
5.324
11.192
59.466
3.190
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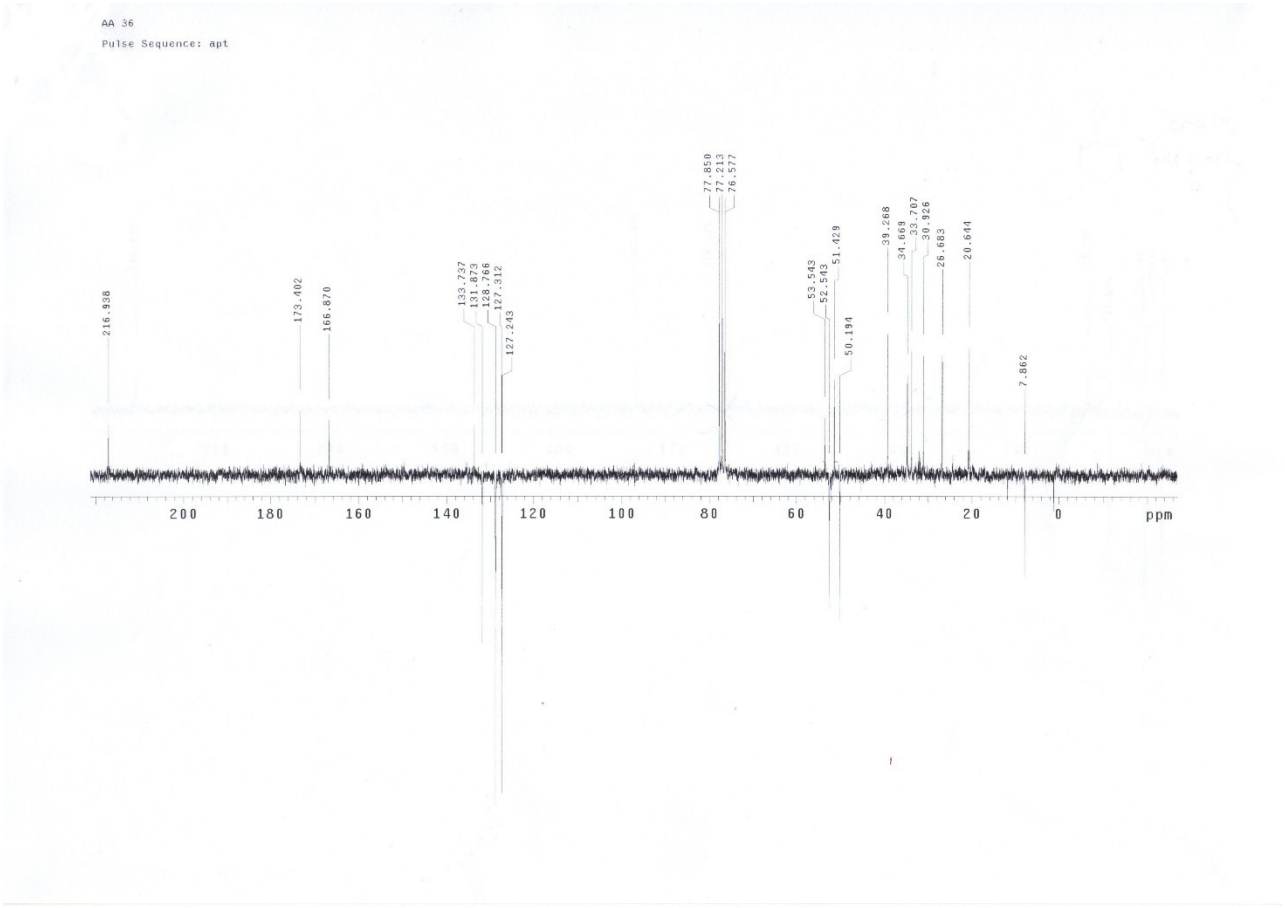
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM


AA 36
Pulse Sequence: apt
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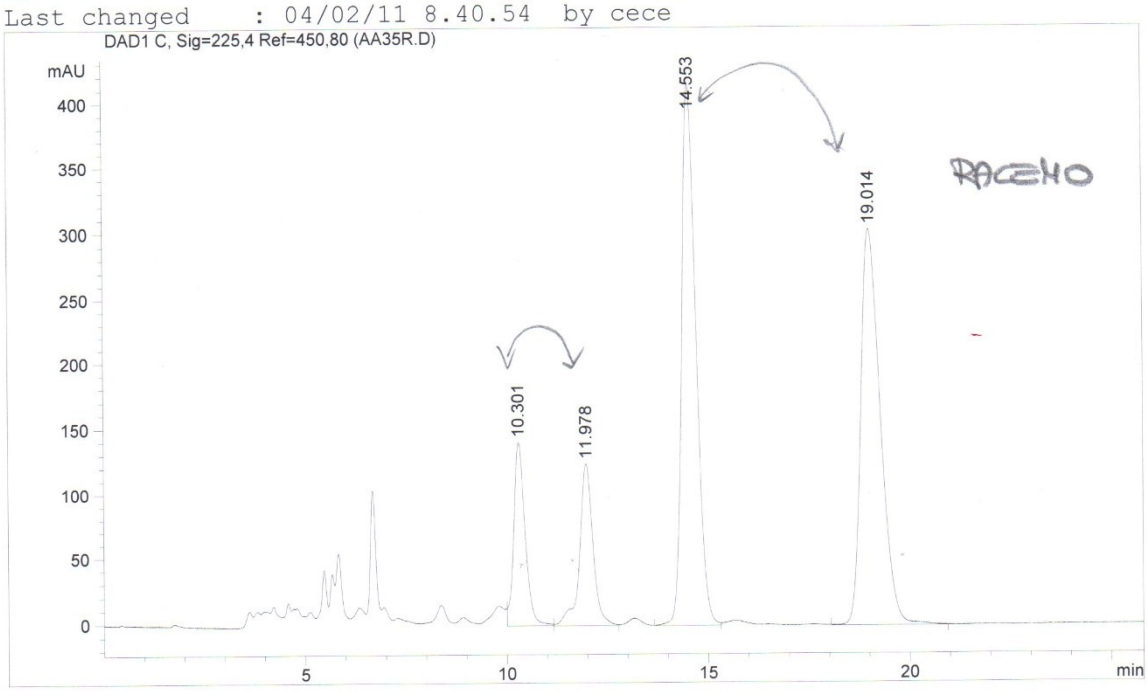
173.402
166.870
130.737
131.873
128.766
127.312
127.243
77.850
77.213
76.577
53.543
52.543
51.429
50.194
39.268
34.669
33.707
30.926
26.683
20.644
7.862
200
180
160
140
120
100
80
60
40
20
0
ppm

Data File C:\HPCHEM\1\DATA\AA35R.D Sample Name: aa35r ad 20ipa

==========

Injection Date : 08/02/11 10.38.36
Sample Name : aa35r ad 20ipa Vial : 1
Acq. Operator : cece
Method : C:\HPCHEM\1\METHODS\CECE.M
Last changed : 04/02/11 8.40.54 by cece



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Area Percent Report

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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 C, Sig=225,4 Ref=450,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.301	BV	0.2940	2755.65234	141.01541	10.5796
2	11.978	VV	0.3480	2881.90210	124.53719	11.0643
3	14.553	VV	0.3818	1.01704e4	415.17941	39.0467
4	19.014	VV	0.5237	1.02389e4	303.42209	39.3094
Totals :				2.60469e4	984.15410	

Results obtained with enhanced integrator!

==========

*** End of Report ***

Instrument 1 08/02/11 11.05.16 cece Page 1 of 1

Data File C:\HPCHEM\1\DATA\AA361.D Sample Name: aa361 ad 20ipa

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==========================================================================
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Sample Name     : aa361 ad 20ipa                        Vial :   1
Acq. Operator   : cece
Acq. Method     : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 04/02/11 8.40.54  by cece
Analysis Method : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 08/02/11 11.33.49  by cece
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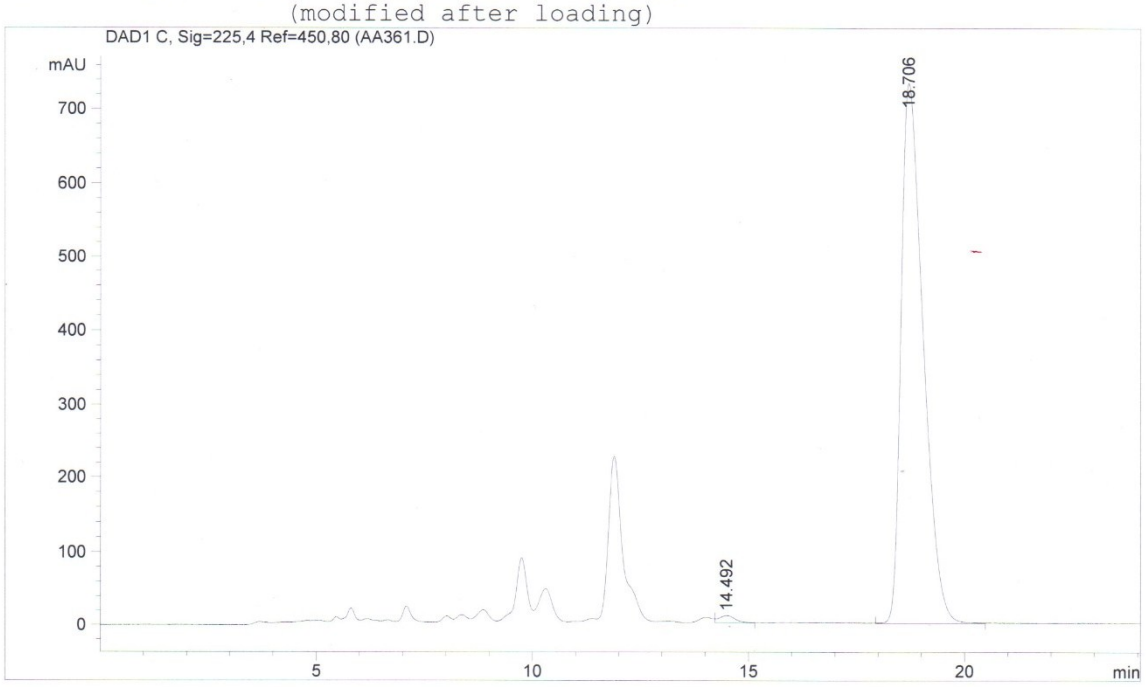


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==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: DAD1 C, Sig=225,4 Ref=450,80

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.492 VV    0.3104  263.11176   10.15164   1.0039
   2  18.706 VV    0.4952 2.59454e4   732.61005  98.9961

Totals :                  2.62085e4   742.76169

 Results obtained with enhanced integrator!
==========================================================================
                          *** End of Report ***
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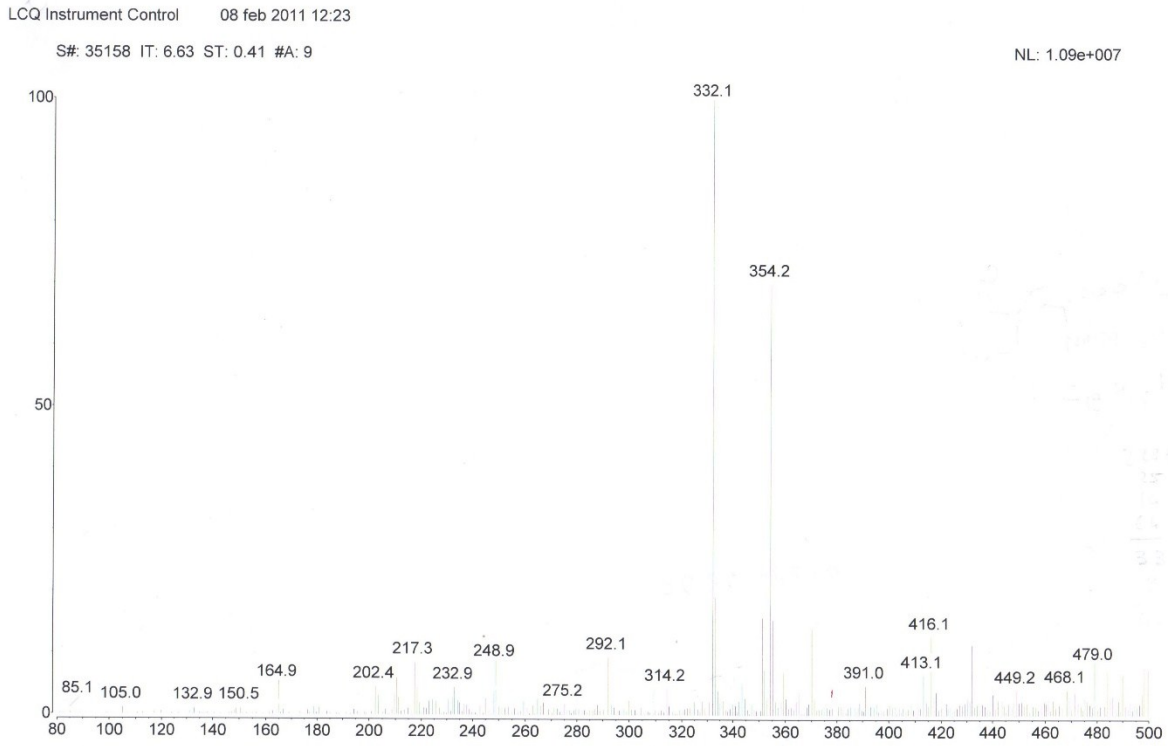
LCQ Instrument Control 08 feb 2011 12:23
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NL: 1.09e+007
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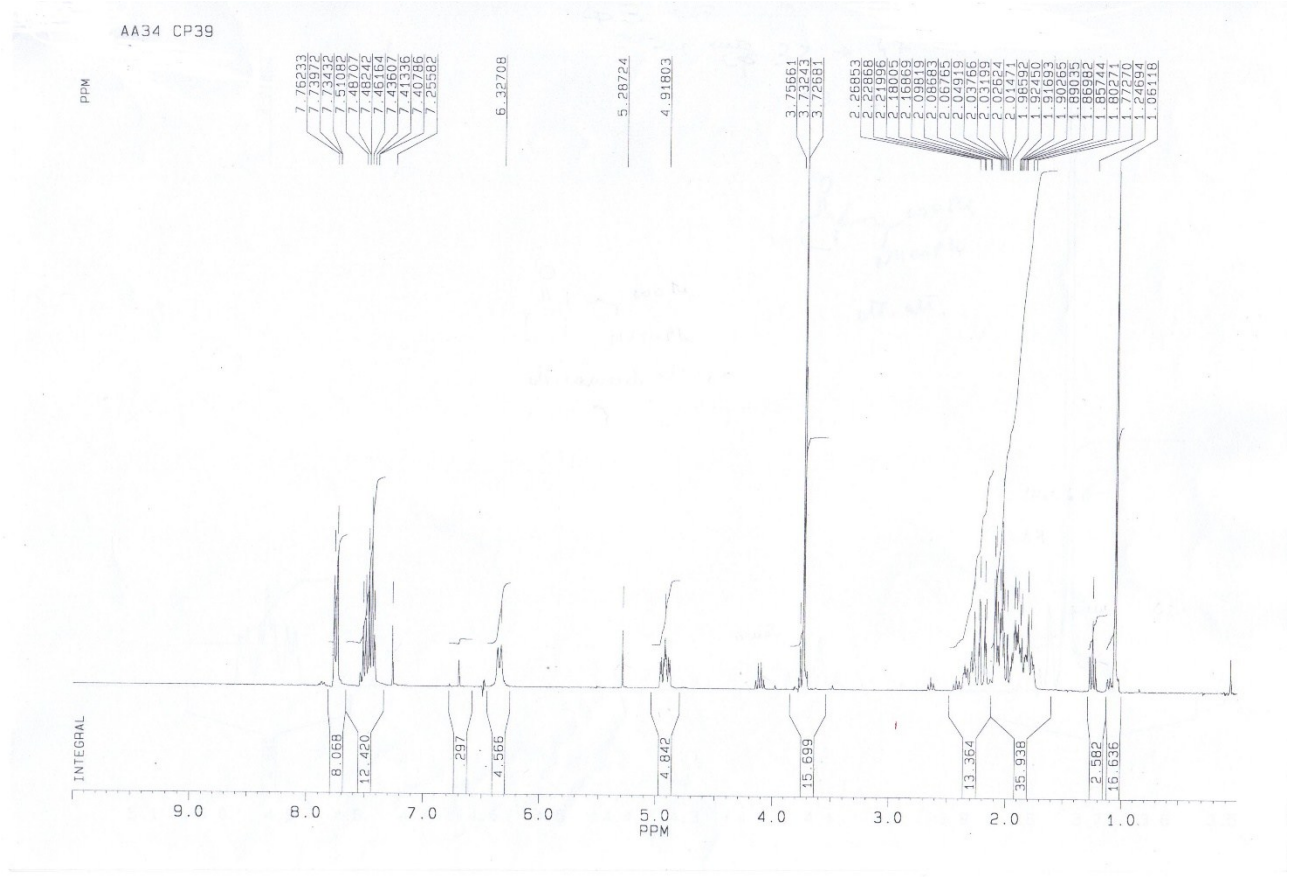
0
332.1
354.2
416.1
413.1
479.0
449.2
468.1
391.0
292.1
314.2
275.2
217.3
248.9
202.4
232.9
164.9
85.1
105.0
132.9
150.5
80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500

COMPOUND 3c


AA34 CP39
PPM
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7.48222
7.46164
7.43607
7.41336
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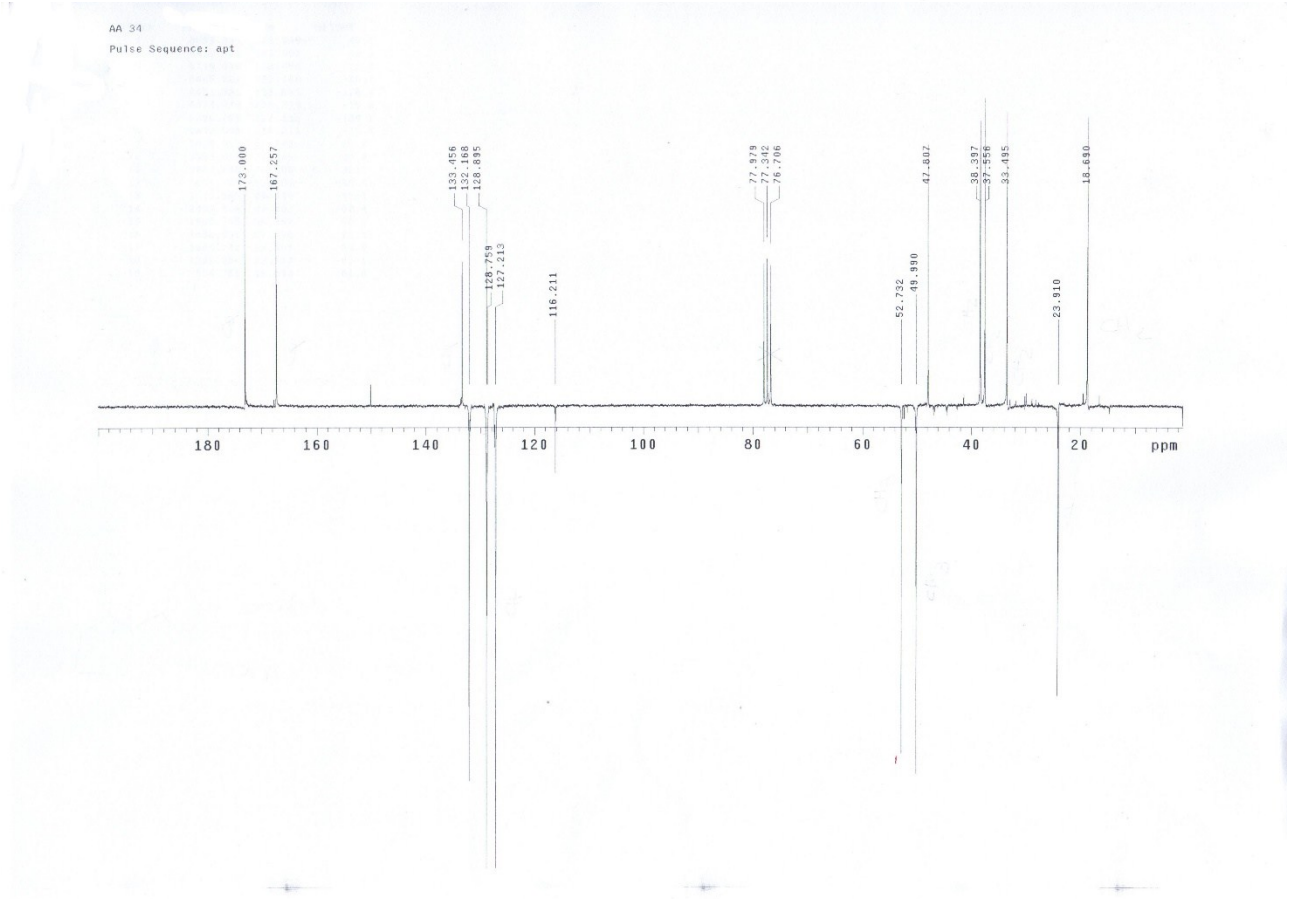
7.25582
6.32708
5.28724
4.91803
3.75661
3.73243
3.72681
2.26853
2.22868
2.21996
2.18005
2.16869
2.09819
2.08683
2.06765
2.04919
2.03766
2.03359
2.01274
1.96592
1.92456
1.91693
1.90265
1.89035
1.86982
1.85744
1.80271
1.77270
1.24694
1.06118
INTEGRAL
8.068
12.420
2.97
4.566
4.842
15.699
13.364
35.938
2.582
16.636
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM


AA 34
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167.257
133.456
132.168
128.895
128.759
127.213
116.211
77.979
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180
160
140
120
100
80
60
40
20
ppm

Data File C:\HPCHEM\1\DATA\AA48PM.D Sample Name: aa48+- ib15etoh

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Analysis Method : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 16/03/11 14.55.40  by cece
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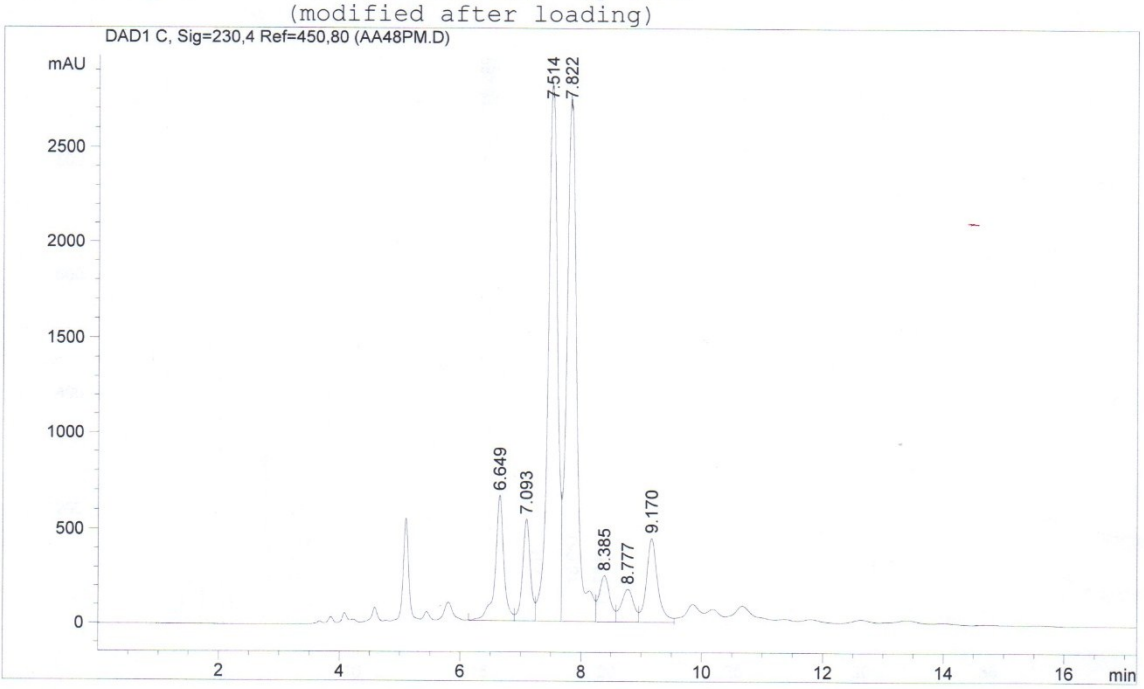



```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

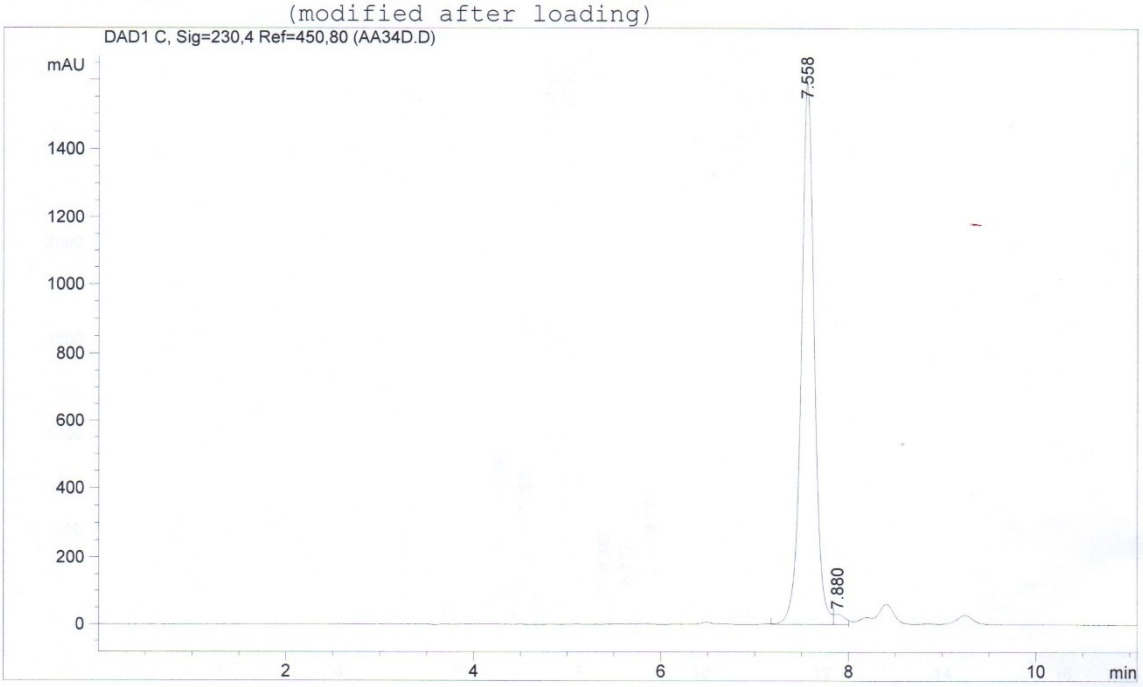
Signal 1: DAD1 C, Sig=230,4 Ref=450,80

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.649 BV    0.1495 6633.15137  658.62531   7.7389
   2   7.093 VV    0.1396 4963.80029  538.39240   5.7912
   3   7.514 VV    0.1674 3.05986e4  2802.65430  35.6993
   4   7.822 VV    0.1766 3.20138e4  2733.74878  37.3504
   5   8.385 VV    0.1932 3170.91260  247.96135   3.6995
   6   8.777 VV    0.2189 2516.69897  175.89311   2.9362
   7   9.170 VV    0.1957 5815.18164  447.21347   6.7845

Totals :                  8.57122e4  7604.48871
```

Data File C:\HPCHEM\1\DATA\AA34D.D Sample Name: aa34- ib15etoh

```
==========================================================================
Injection Date  : 16/03/11 15.21.33
Sample Name     : aa34- ib15etoh                        Vial :   1
Acq. Operator   : cece
Acq. Method     : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 16/03/11 14.55.40  by cece
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 16/03/11 15.37.51  by cece
                  (modified after loading)
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

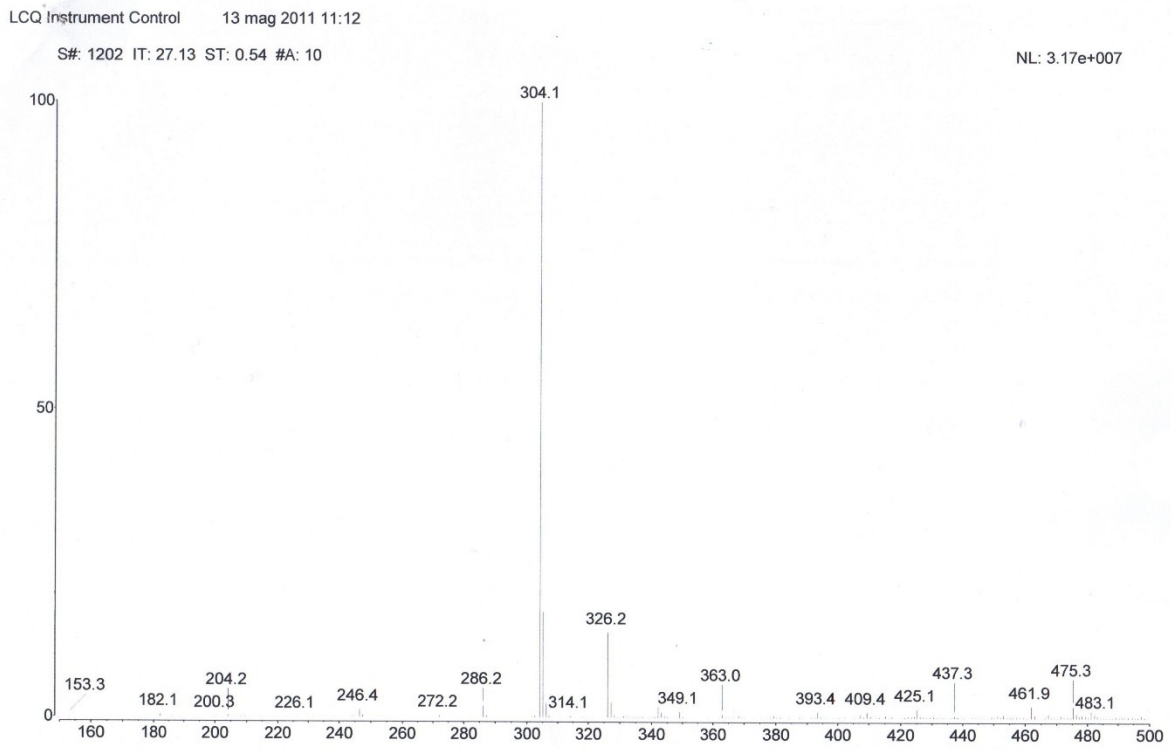

Signal 1: DAD1 C, Sig=230,4 Ref=450,80

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.558 VV    0.1457 1.55012e4  1590.51953  98.4477
   2   7.880 VBA   0.1165  244.41455   31.49755   1.5523

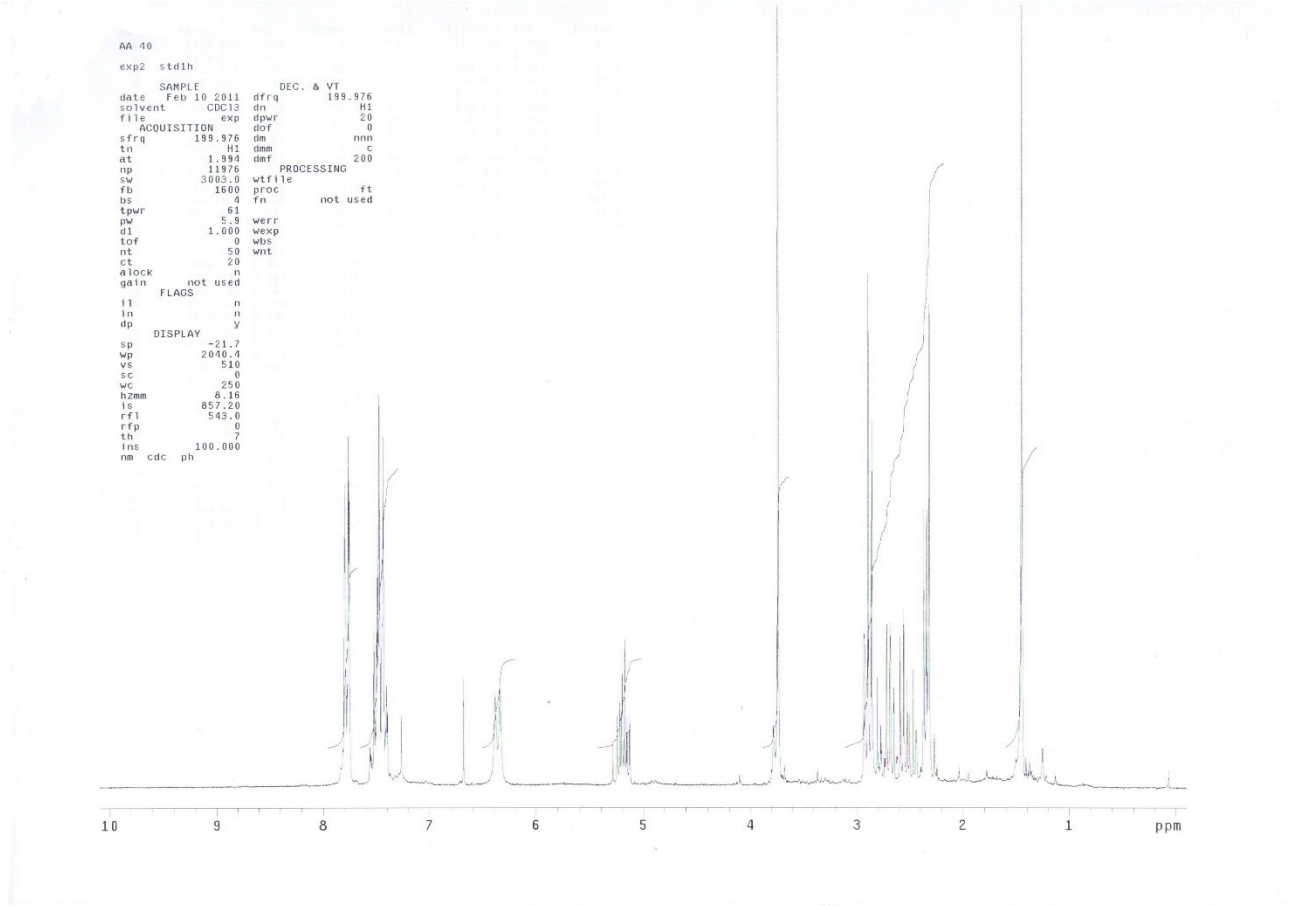
Totals :                  1.57456e4  1622.01708

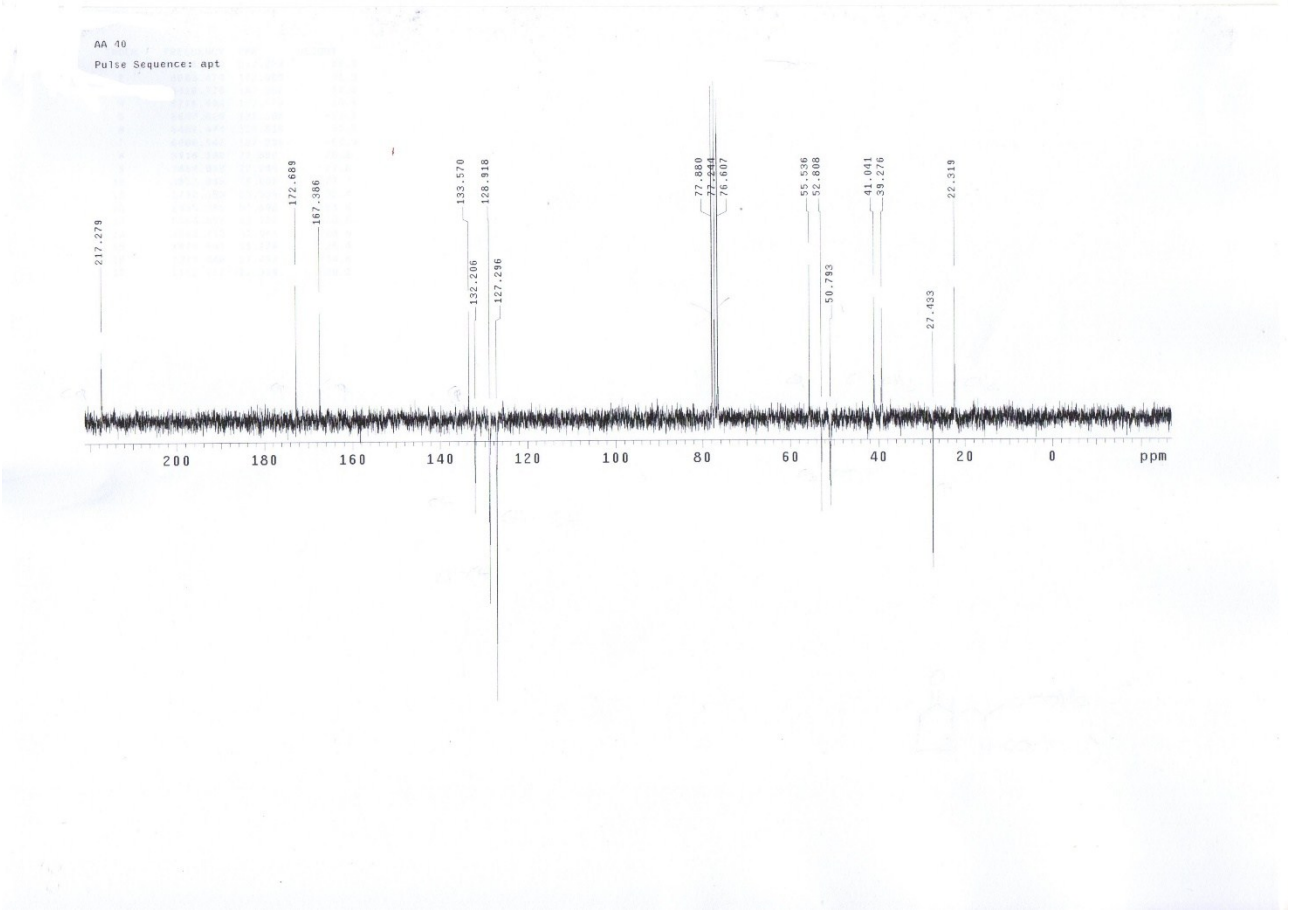
 Results obtained with enhanced integrator!
==========================================================================
                          *** End of Report ***
```

Instrument 1 16/03/11 15.37.54 cece Page 1 of 1


LCQ Instrument Control 13 mag 2011 11:12
S#: 1202 IT: 27.13 ST: 0.54 #A: 10
NL: 3.17e+007
100
50
0
304.1
326.2
153.3
182.1
204.2
200.3
226.1
246.4
272.2
286.2
314.1
349.1
363.0
393.4
409.4
425.1
437.3
461.9
475.3
483.1
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500

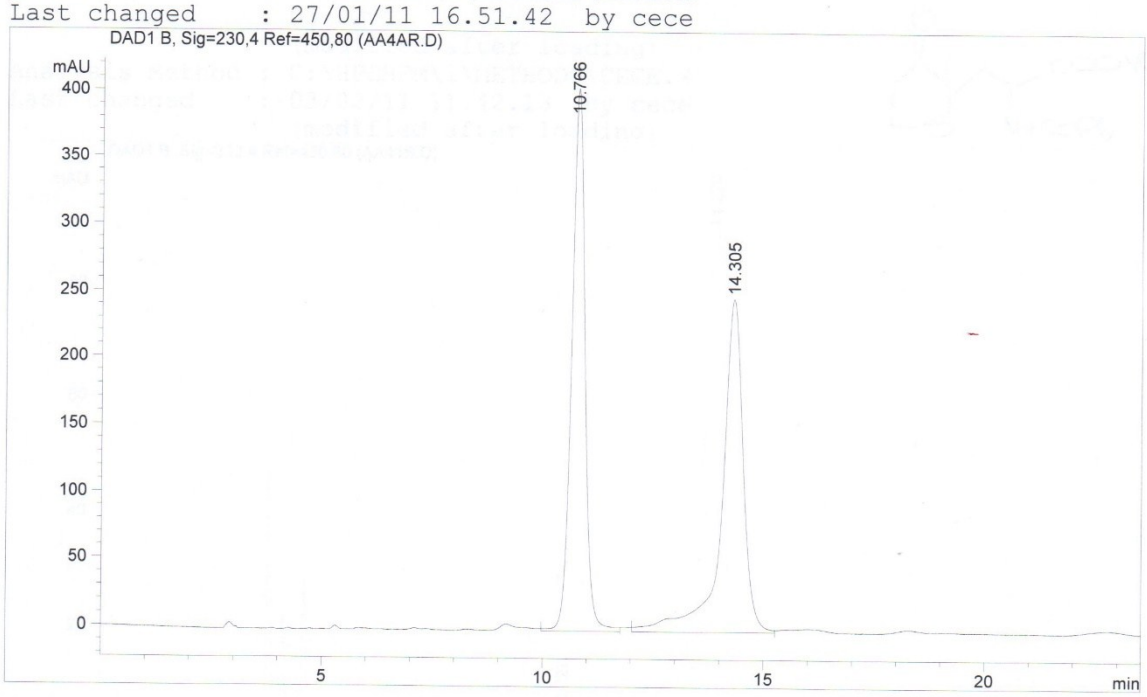
COMPOUND 3d


AA 40
exp2 std1h
SAMPLE
date Feb 10 2011
solvent CDCl3
file exp
ACQUISITION
sfrq 199.976
tn H1
at 1.994
np 11976
sw 3003.0
fb 1600
bs 4
tpwr 61
pw 5.8
d1 1.000
tof 0
nt 50
ct 20
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -21.7
wp 2040.4
vs 510
sc 0
wc 250
hzmm 8.16
is 857.20
rfl 543.0
rfp 0
th 7
ins 100.000
nm cdc ph
DEC. & VT
dfrq 199.876
dn H1
dpwr 20
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
10
9
8
7
6
5
4
3
2
1
ppm


AA 40
Pulse Sequence: apt
217.279
172.689
167.386
133.570
132.206
128.918
127.296
77.880
77.644
76.607
55.536
52.808
50.793
41.041
39.276
27.433
22.319
200
180
160
140
120
100
80
60
40
20
0
ppm

Data File C:\HPCHEM\1\DATA\AA4AR.D Sample Name: aa40r ad15ipa

```
==========================================================================
Injection Date  : 03/02/11 10.14.17
Sample Name     : aa40r ad15ipa                          Vial :   1
Acq. Operator   : cece
Method          : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 27/01/11 16.51.42  by cece
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=230,4 Ref=450,80

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.766 VB    0.3192 8441.41797  404.86581  50.1104
   2  14.305 BV    0.4989 8404.20996  248.28128  49.8896

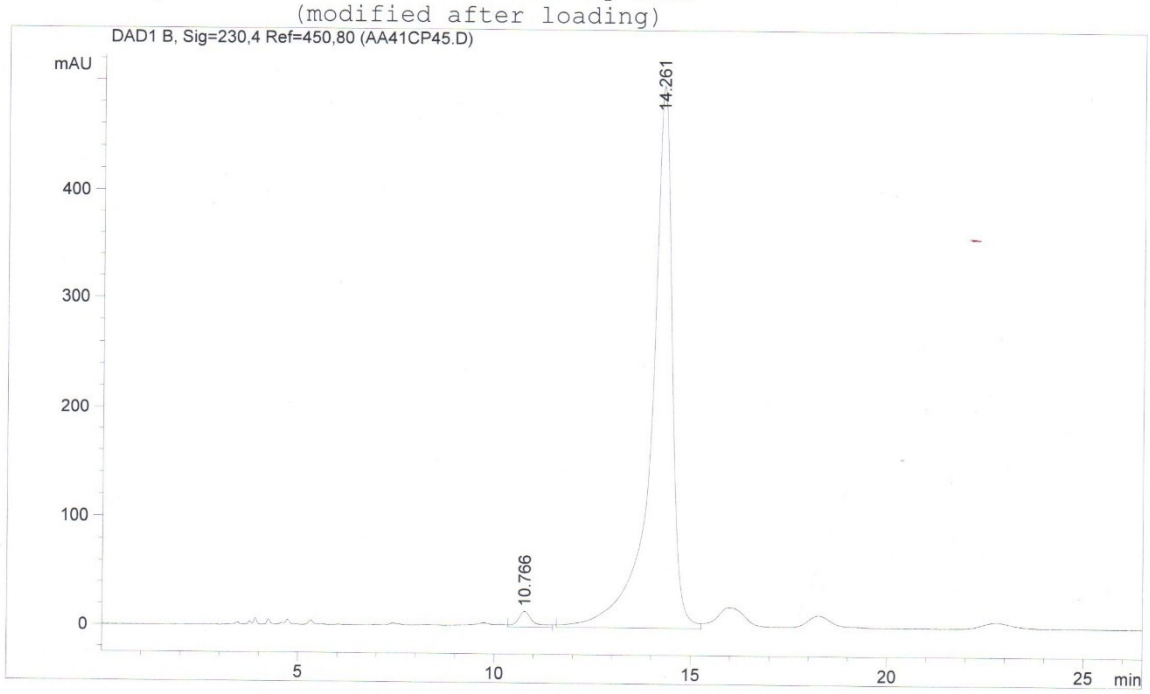
Totals :                  1.68456e4   653.14709

 Results obtained with enhanced integrator!
==========================================================================
                        *** End of Report ***
```

Instrument 1 03/02/11 10.38.49 cece Page 1 of 1

Data File C:\HPCHEM\1\DATA\AA41CP45.D Sample Name: aa41cp45 ad15ipa

```
==========================================================================
Injection Date  : 03/02/11 10.45.06
Sample Name     : aa41cp45 ad15ipa                    Vial :   1
Acq. Operator   : cece
Acq. Method     : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 27/01/11 16.51.42  by cece
Analysis Method : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 03/02/11 11.12.41  by cece
                  (modified after loading)
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

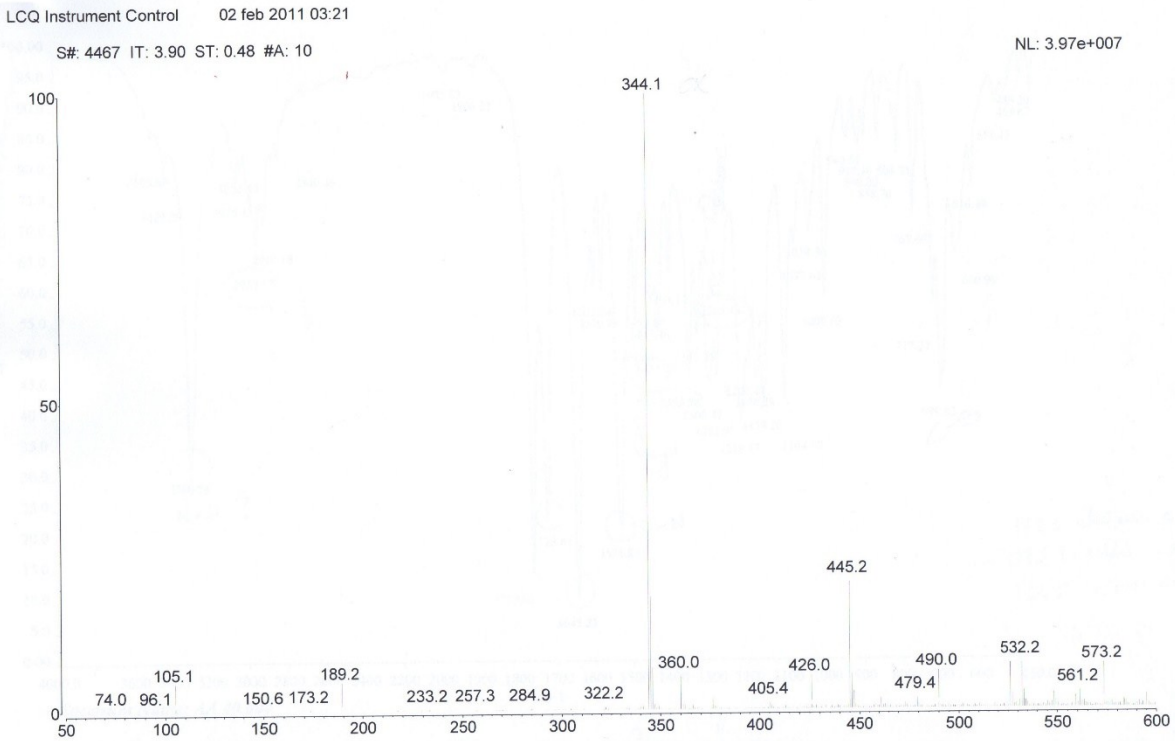
Signal 1: DAD1 B, Sig=230,4 Ref=450,80

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.766 VB    0.3852  389.62689   14.70278   2.1025
   2  14.261 BV    0.5298 1.81421e4   497.12231  97.8975

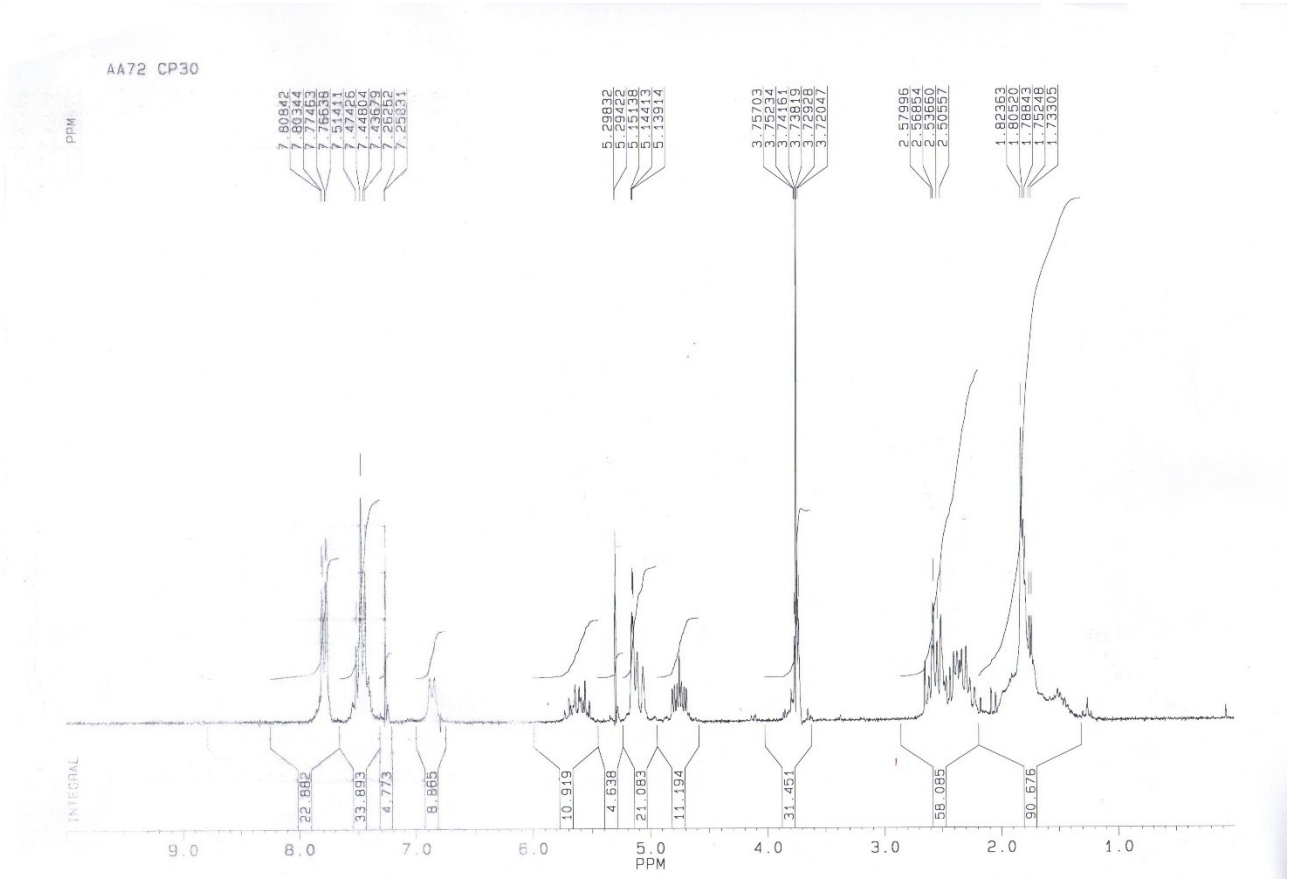
Totals :                  1.85317e4   511.82509

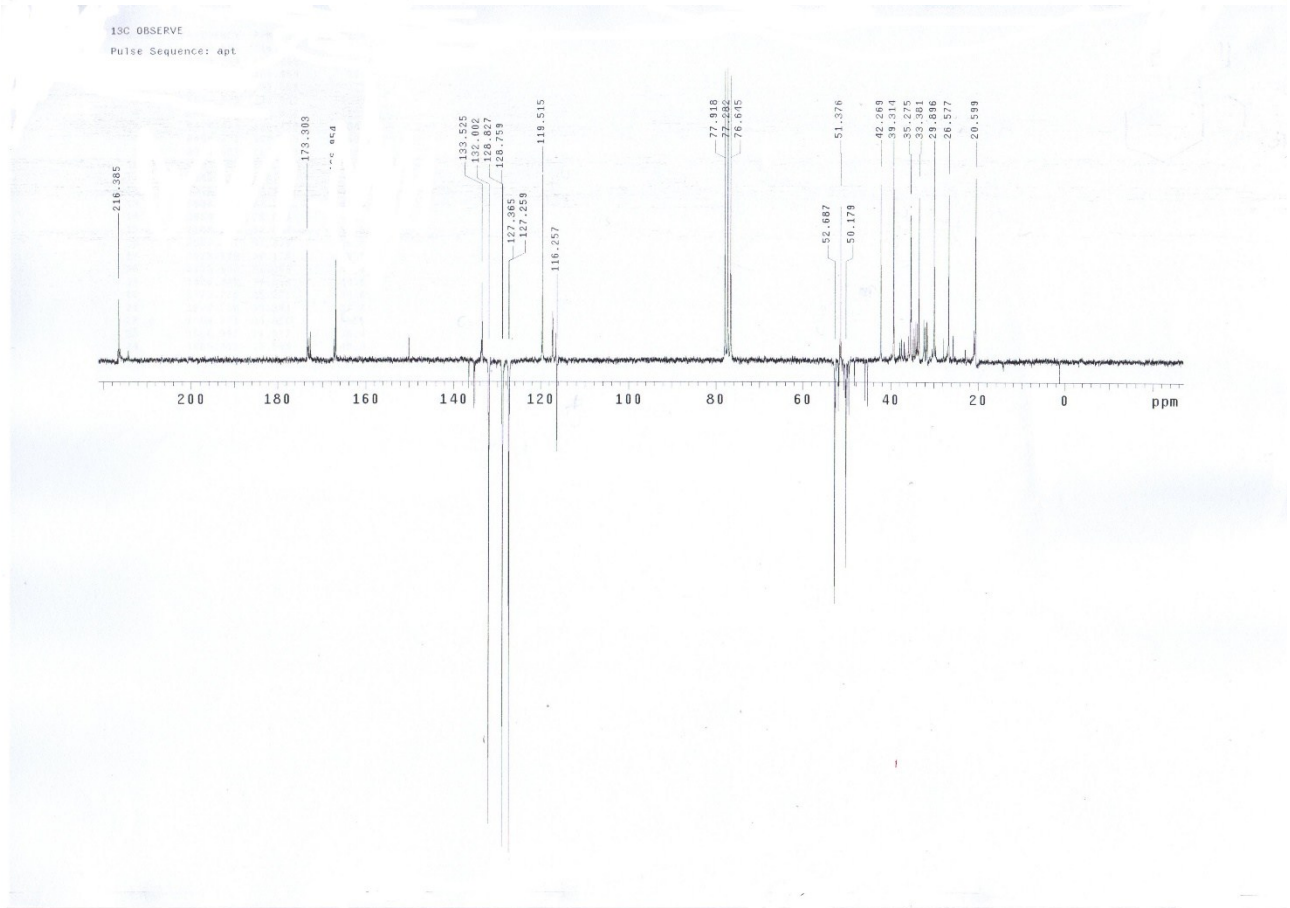
 Results obtained with enhanced integrator!
==========================================================================
                        *** End of Report ***
```

Instrument 1 03/02/11 11.12.46 cece Page 1 of 1


LCQ Instrument Control
02 feb 2011 03:21
S#: 4467 IT: 3.90 ST: 0.48 #A: 10
NL: 3.97e+007
344.1
445.2
105.1
189.2
360.0
426.0
490.0
532.2
573.2
74.0
96.1
150.6
173.2
233.2
257.3
284.9
322.2
405.4
479.4
561.2
100
50
0
50
100
150
200
250
300
350
400
450
500
550
600

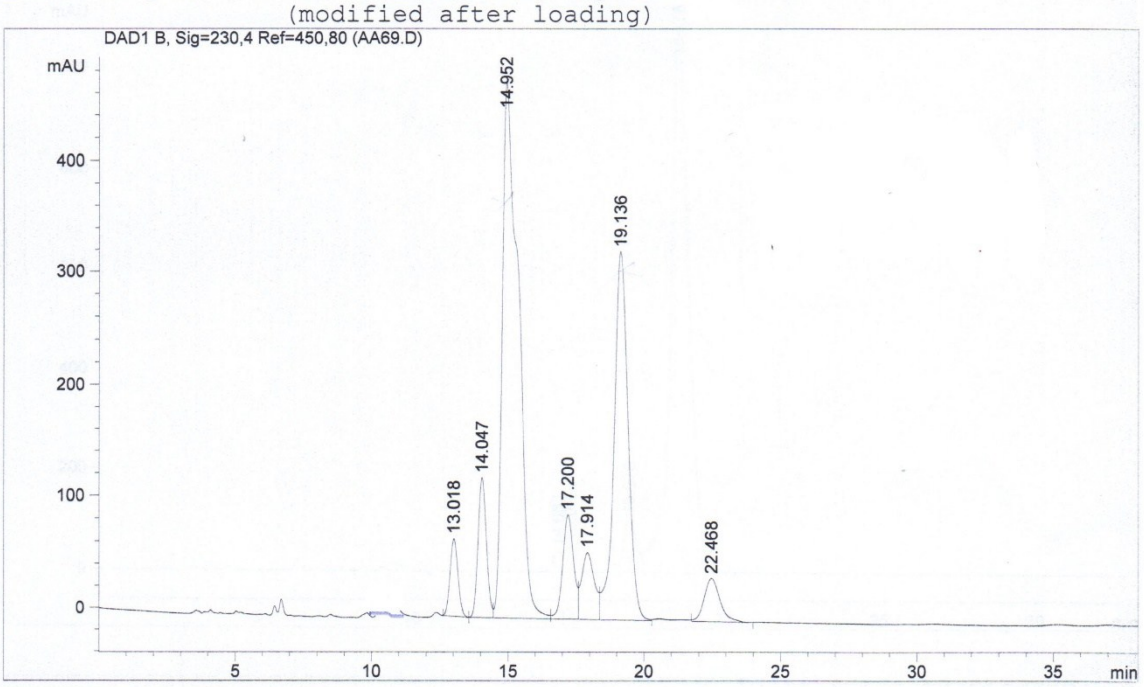
COMPOUND 3e


AA72 CP30
PPM
INTEGRAL
22.882
33.893
4.773
8.865
10.919
4.638
21.083
11.194
31.451
58.085
90.676
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM


13C OBSERVE
Pulse Sequence: apt
216.385
173.303
133.525
132.002
128.827
128.759
127.365
127.259
119.515
116.257
77.918
77.282
76.645
52.687
51.376
50.178
42.269
39.314
35.275
33.381
29.896
26.577
20.599
200
180
160
140
120
100
80
60
40
20
0
ppm

Data File C:\HPCHEM\1\DATA\AA69.D Sample Name: aa69 ad15etoh

```
Injection Date  : 13/05/11 10.26.15
Sample Name     : aa69 ad15etoh                    Vial :   1
Acq. Operator   : cece
Acq. Method     : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 11/05/11 16.26.06  by cece
Analysis Method : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 13/05/11 11.10.38  by cece
                  (modified after loading)
```



Area Percent Report

```
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

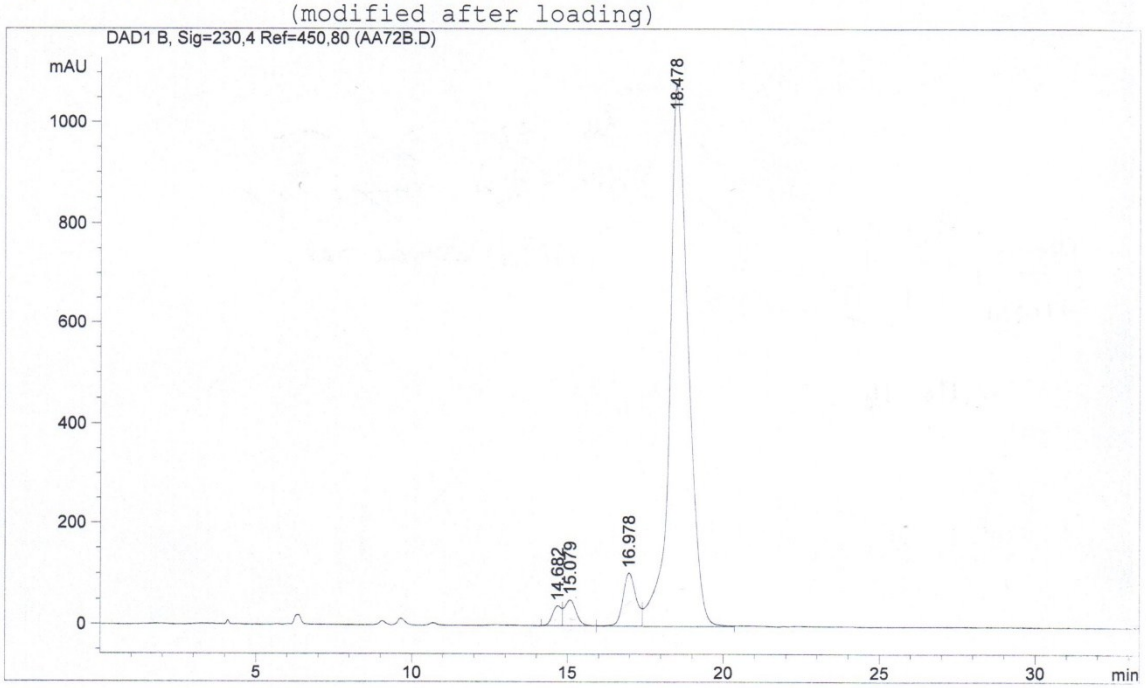
Signal 1: DAD1 B, Sig=230,4 Ref=450,80
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.018	BP	0.3162	1418.03149	70.04366	3.3940
2	14.047	VV	0.3354	2688.58936	124.77391	6.4350
3	14.952	VV	0.5659	1.95807e4	477.96976	46.8654
4	17.200	VV	0.4283	2633.42334	93.57425	6.3030
5	17.914	VV	0.4834	1993.51648	60.66874	4.7714
6	19.136	VV	0.5448	1.18844e4	329.48630	28.4448
7	22.468	BP	0.6240	1581.96912	39.43468	3.7864
Totals :				4.17806e4	1195.95130	

```
 Results obtained with enhanced integrator!
```

Data File C:\HPCHEM\1\DATA\AA72B.D Sample Name: aa72 ad15etoh

```
Injection Date  : 13/05/11 11.43.07
Sample Name     : aa72 ad15etoh                    Vial :   1
Acq. Operator   : cece
Method          : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 13/05/11 11.10.38  by cece
                  (modified after loading)
```



Area Percent Report

```
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=230,4 Ref=450,80

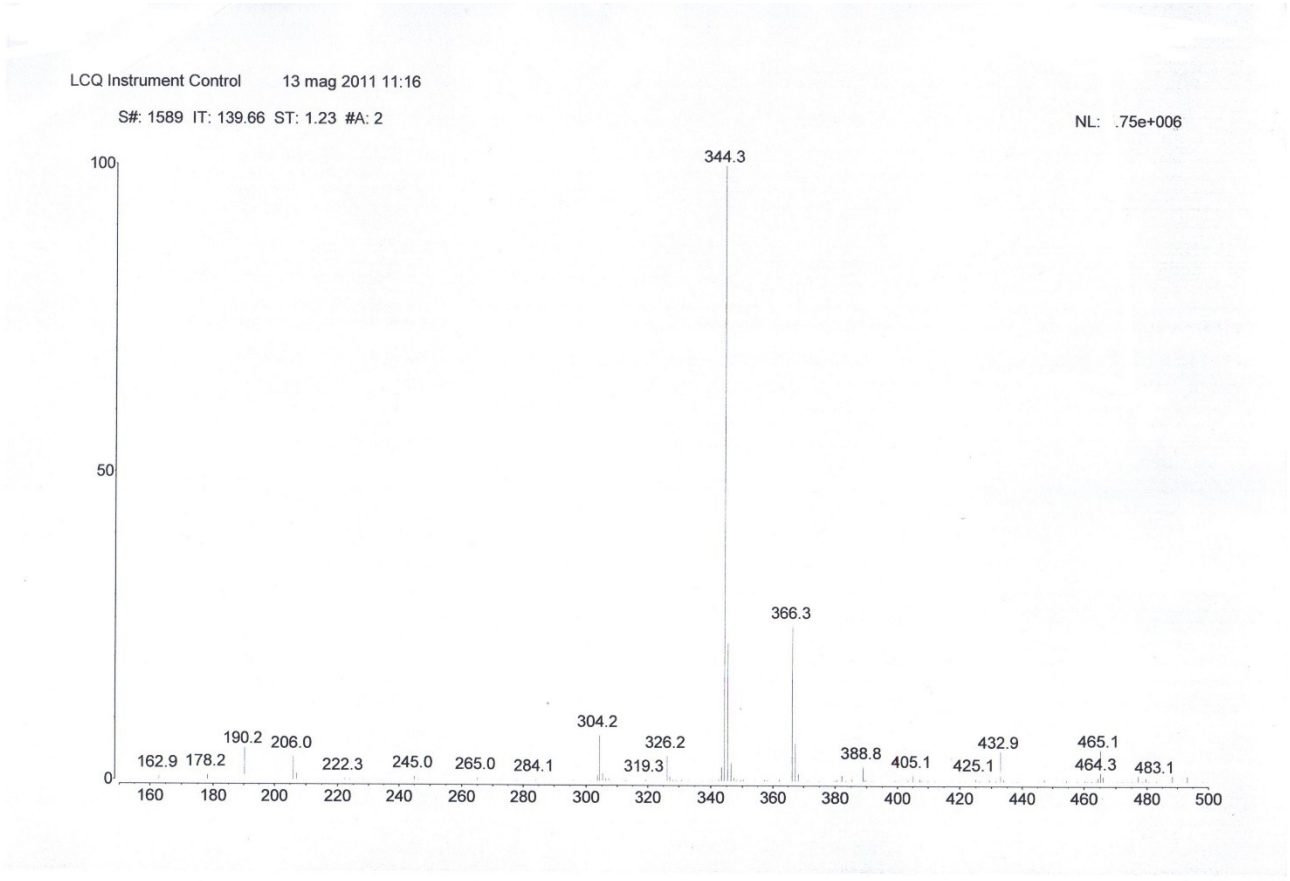
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.682 PV    0.3073  802.52637   39.78873   1.6245
   2  15.079 VV    0.3895 1349.77686   51.54729   2.7323
   3  16.978 VV    0.4443 3080.32568  104.36954   6.2355
   4  18.478 VV    0.6062 4.41675e4  1077.54260  89.4077

Totals :                  4.94001e4  1273.24816

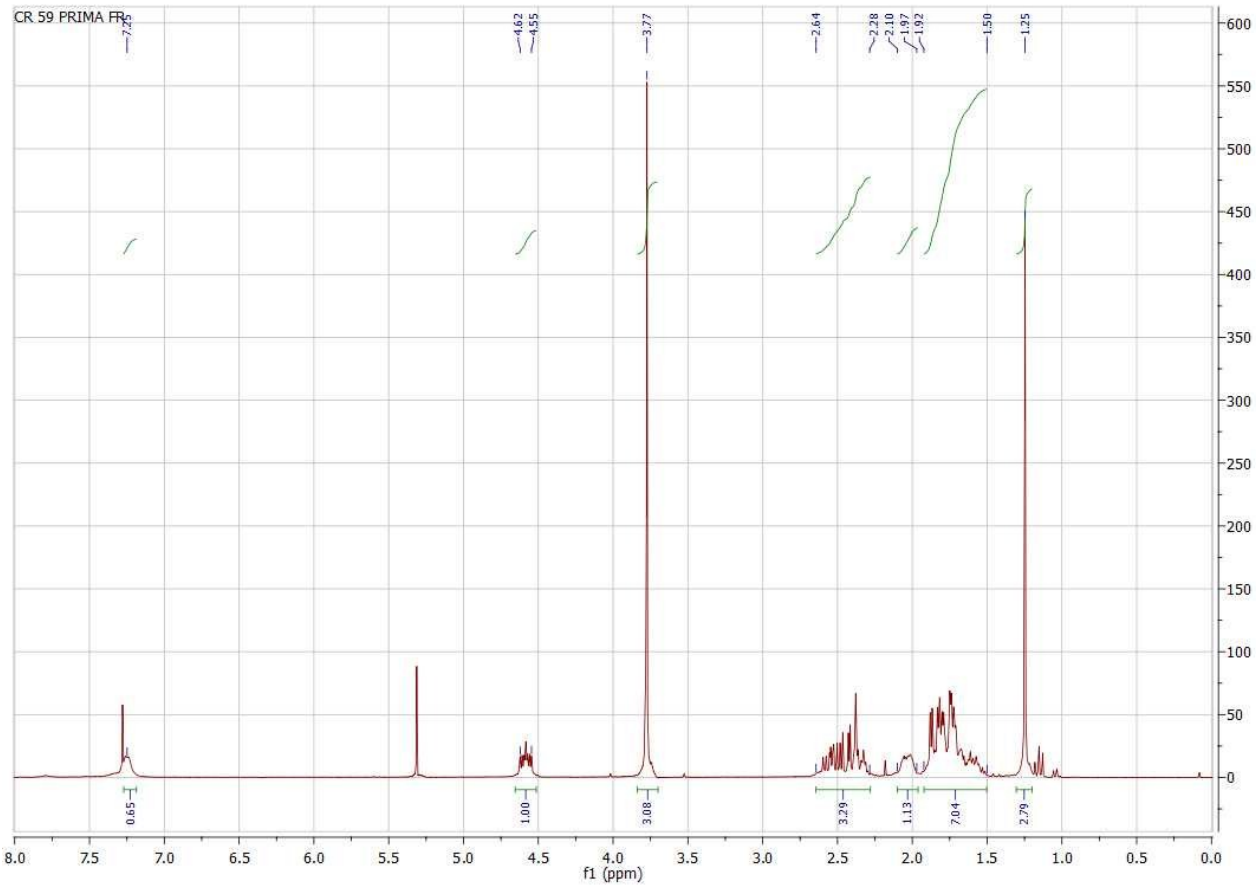
 Results obtained with enhanced integrator!
```

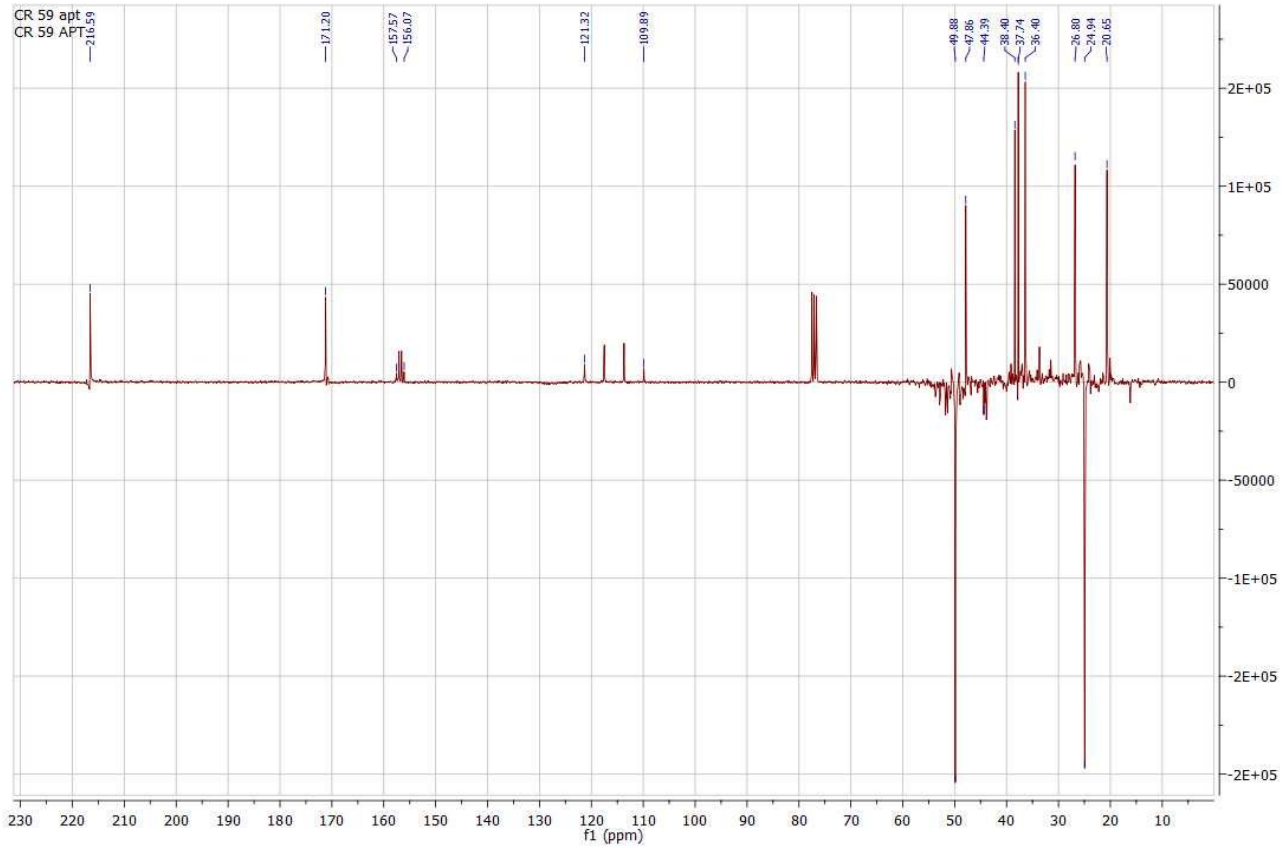
*** End of Report ***

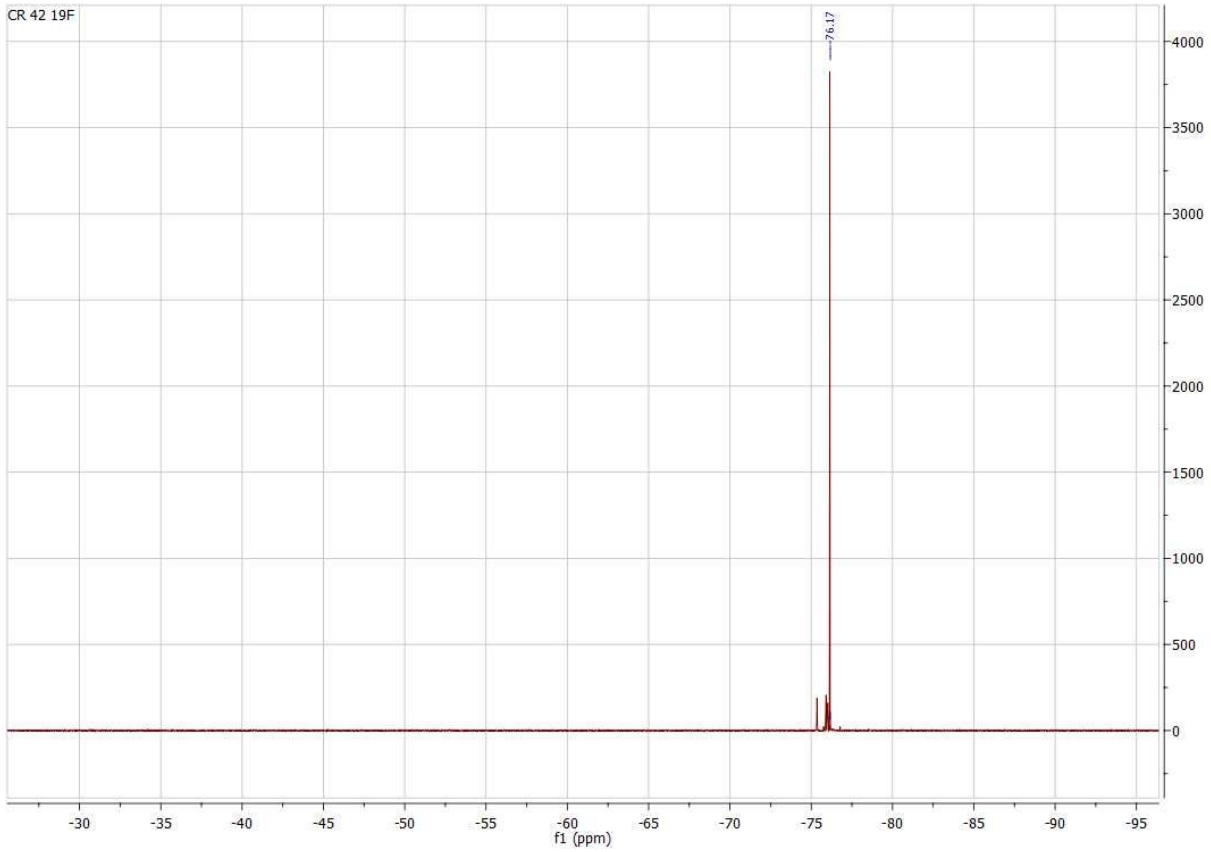
Instrument 1 13/05/11 12.17.10 cece Page 1 of 1

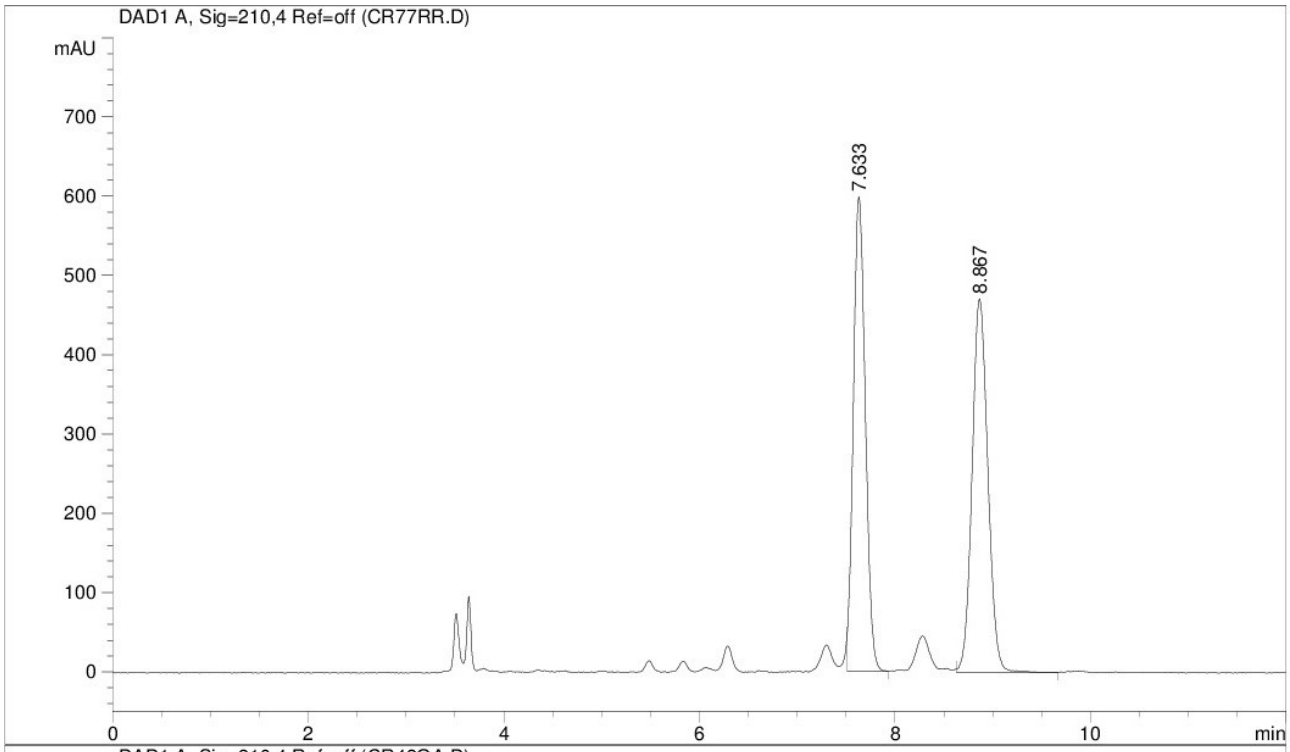

LCQ Instrument Control 13 mag 2011 11:16
S#: 1589 IT: 139.66 ST: 1.23 #A: 2
NL: .75e+006
100
50
0
344.3
366.3
304.2
190.2
206.0
326.2
162.9
178.2
222.3
245.0
265.0
284.1
319.3
388.8
405.1
432.9
425.1
465.1
464.3
483.1
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500

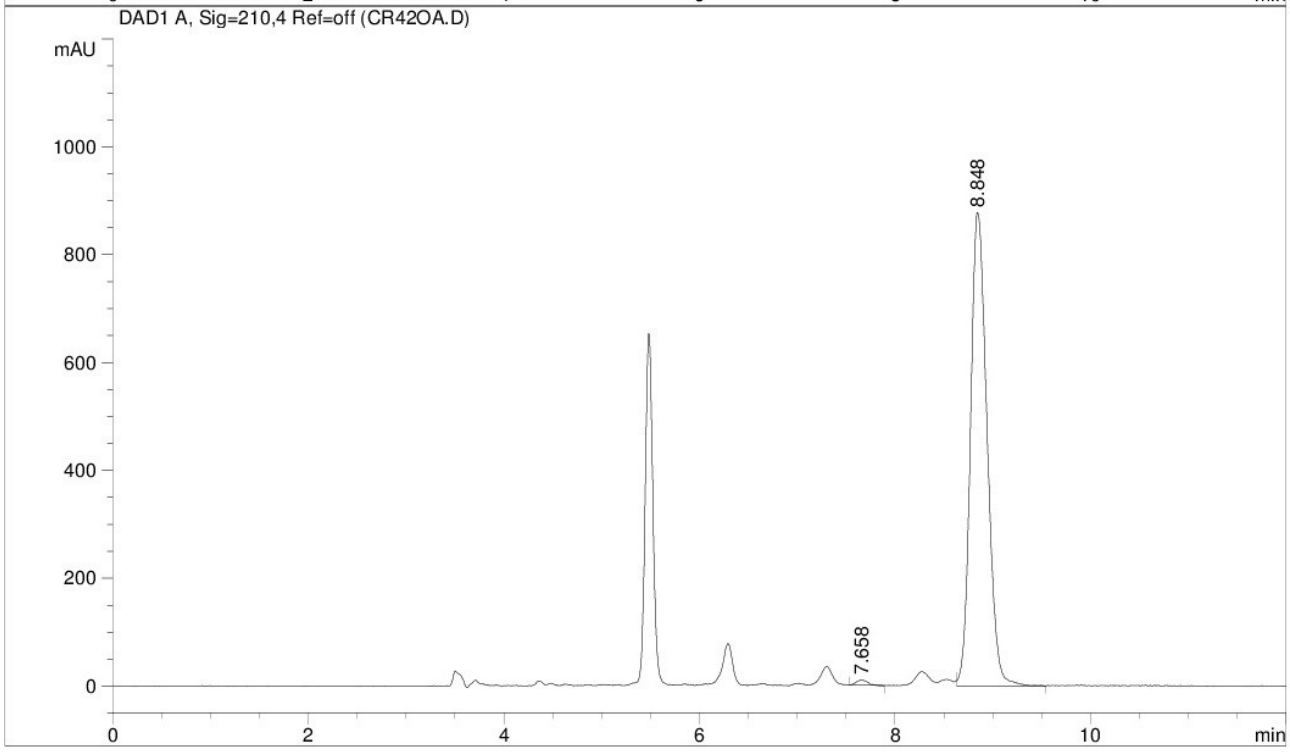
COMPOUND 3f

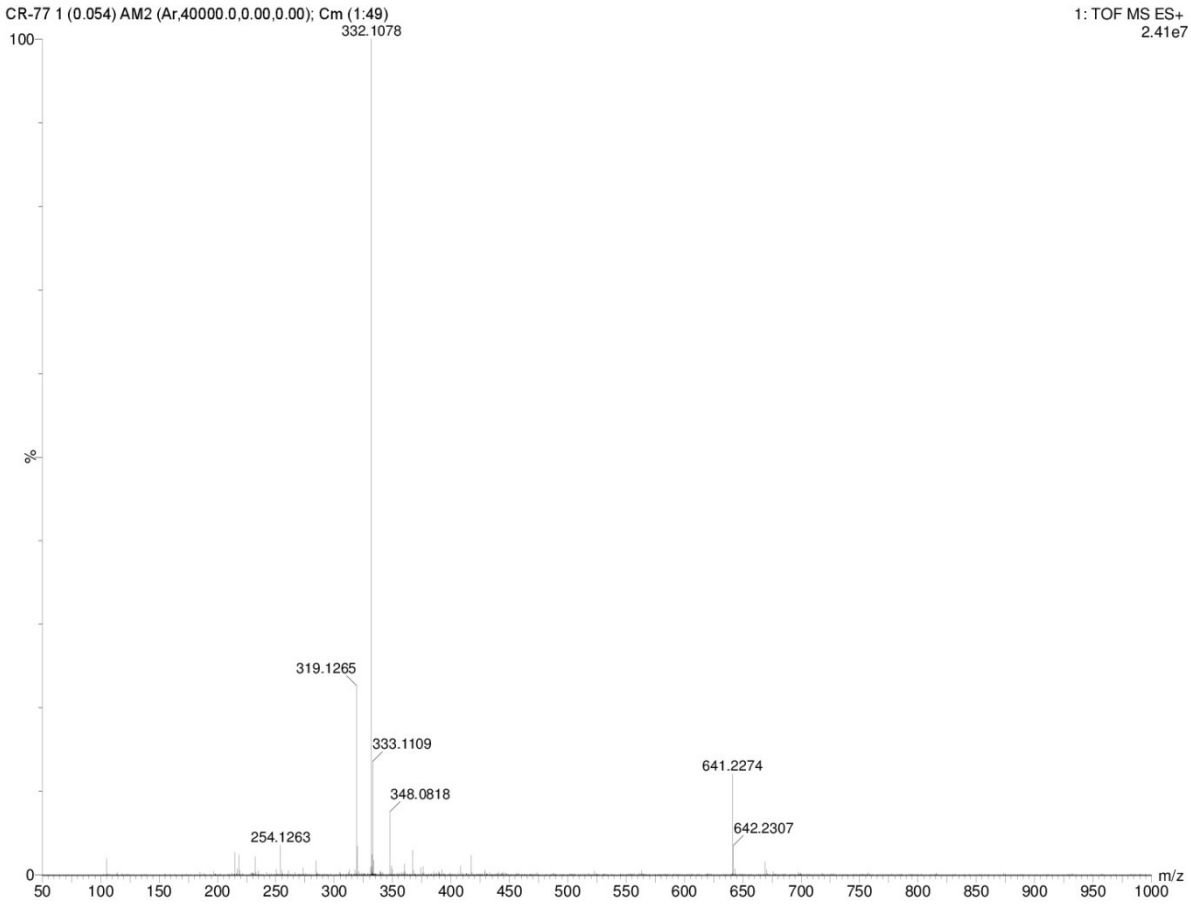

CR 59 PRIMA FR
7.25
4.62
4.55
3.77
2.64
2.28
2.10
1.97
1.92
1.50
1.25
0.65
1.00
3.08
3.29
1.13
7.04
2.79
f1 (ppm)


CR 59 apt
CR 59 APT
216.59
171.20
157.57
156.07
121.32
109.89
49.88
47.86
44.39
38.40
37.74
36.40
26.80
24.94
20.65
f1 (ppm)

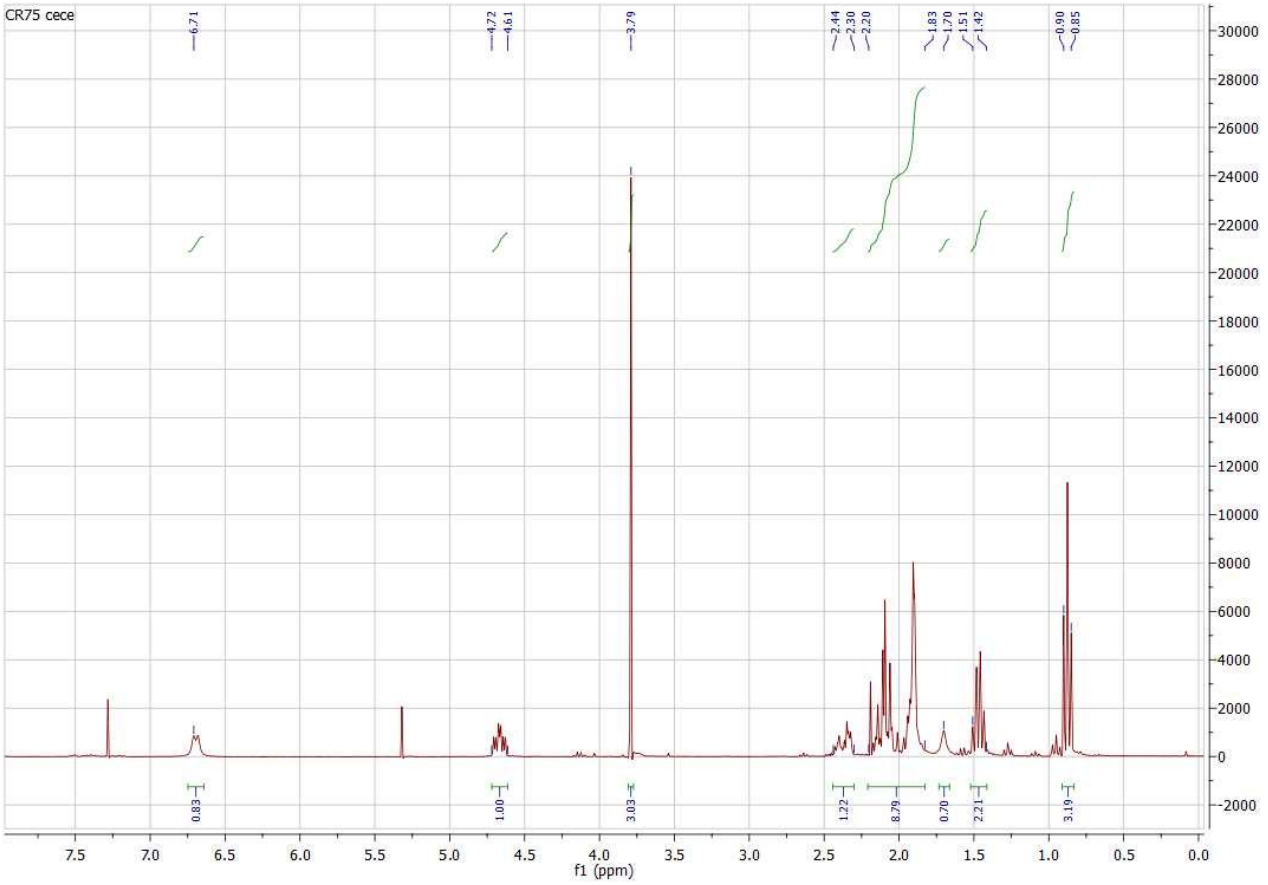

CR 42 19F
-76.17
4000
3500
3000
2500
2000
1500
1000
500
0
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
f1 (ppm)

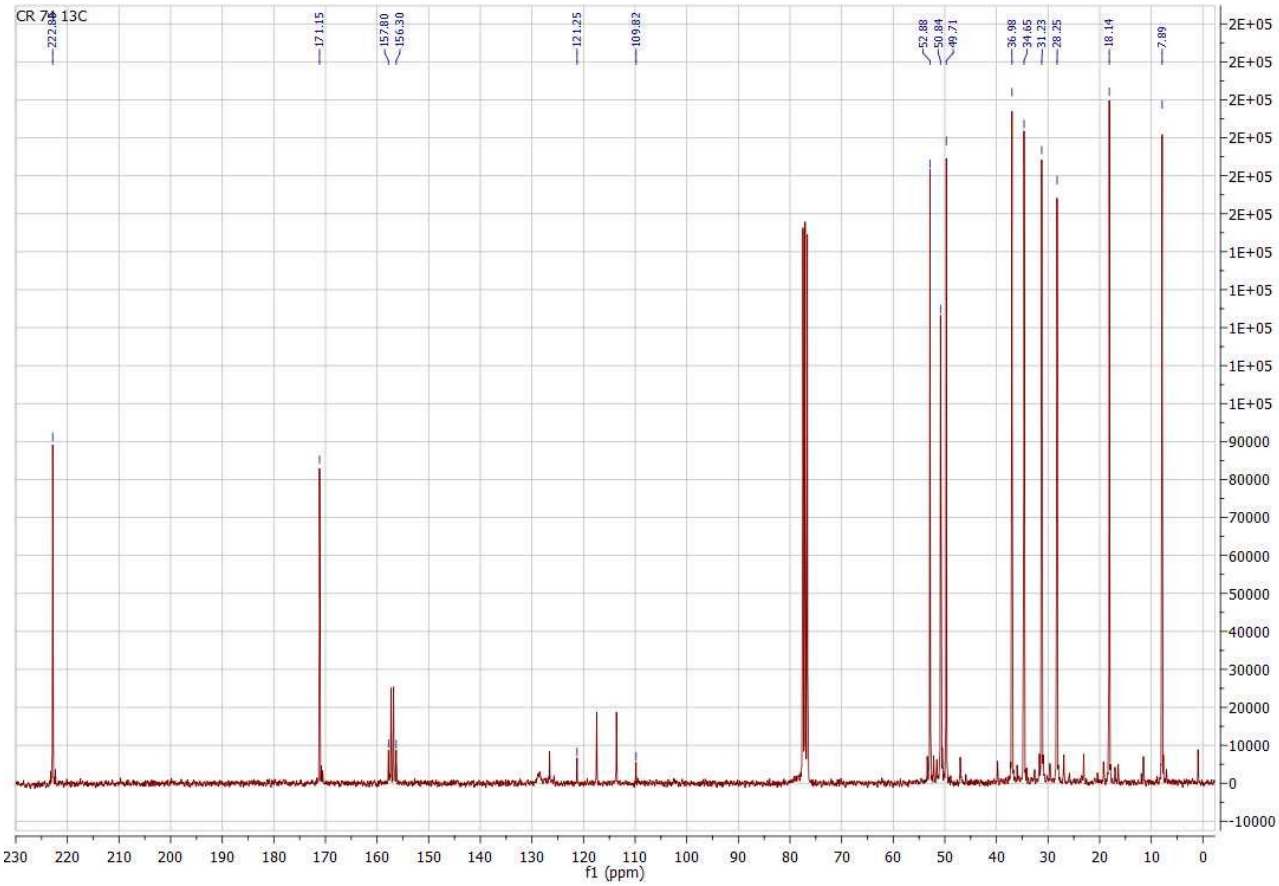

DAD1 A, Sig=210,4 Ref=off (CR77RR.D)
mAU
700
600
500
400
300
200
100
0
7.633
8.867
0
2
4
6
8
10
min

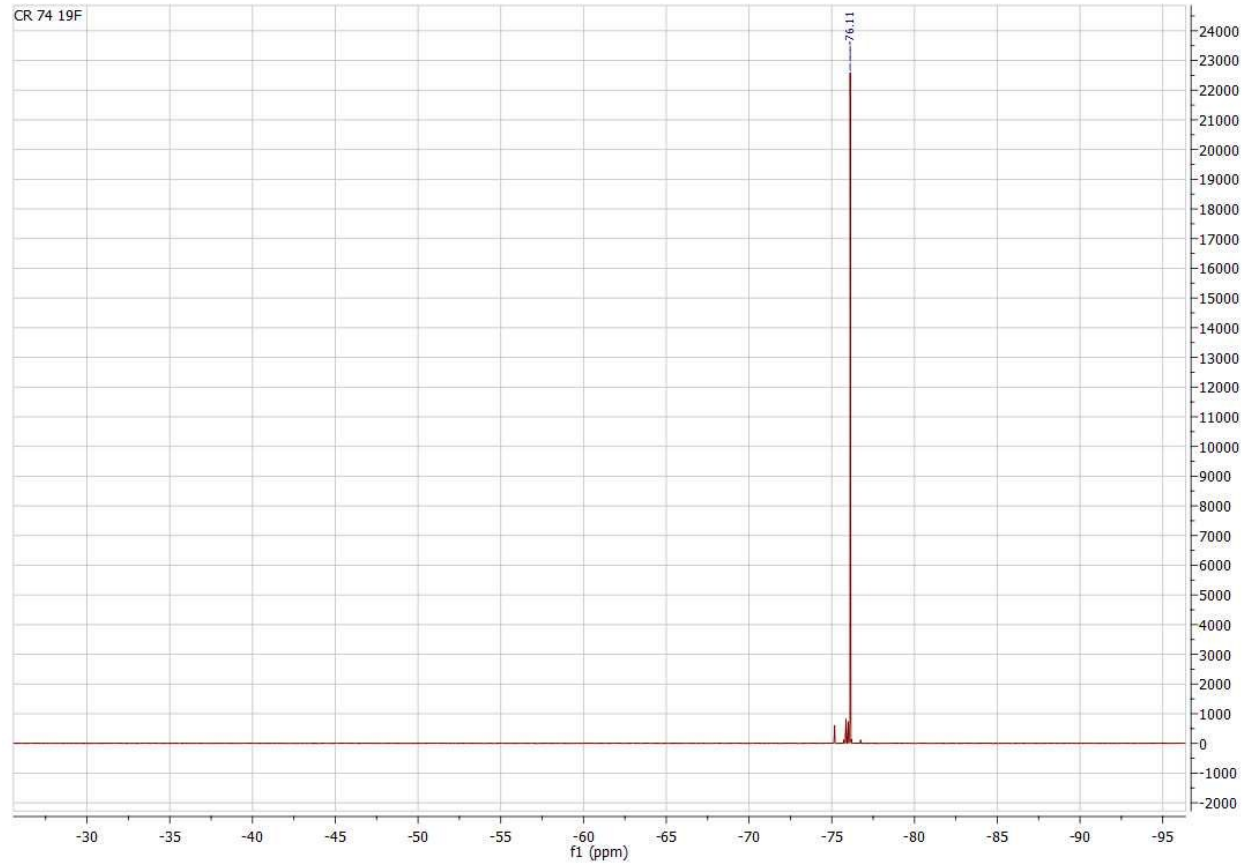

DAD1 A, Sig=210,4 Ref=off (CR42OA.D)
mAU
1000
800
600
400
200
0
8.848
7.658
0
2
4
6
8
10
min

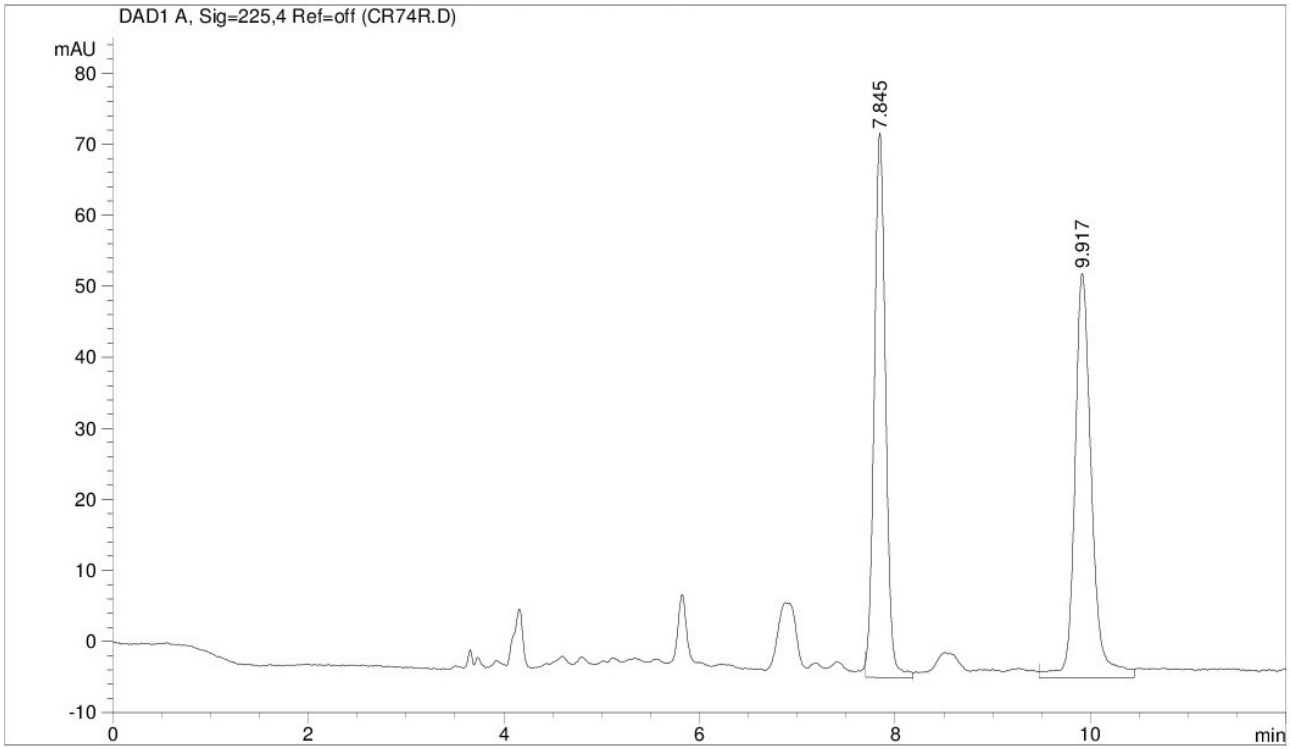

CR-77 1 (0.054) AM2 (Ar,40000.0,0.00,0.00); Cm (1:49)
1: TOF MS ES+
2.41e7
100
%
0
332.1078
319.1265
333.1109
641.2274
348.0818
642.2307
254.1263
m/z
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000

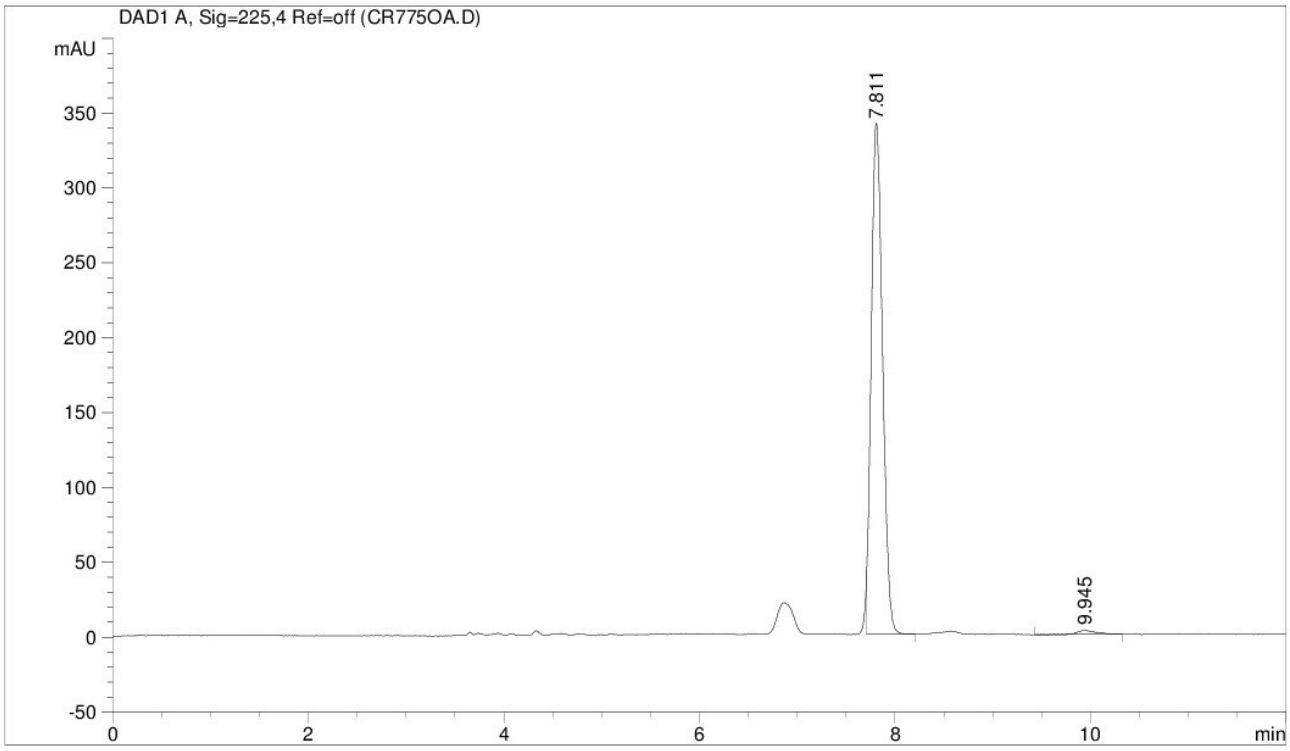
COMPOUND 3g

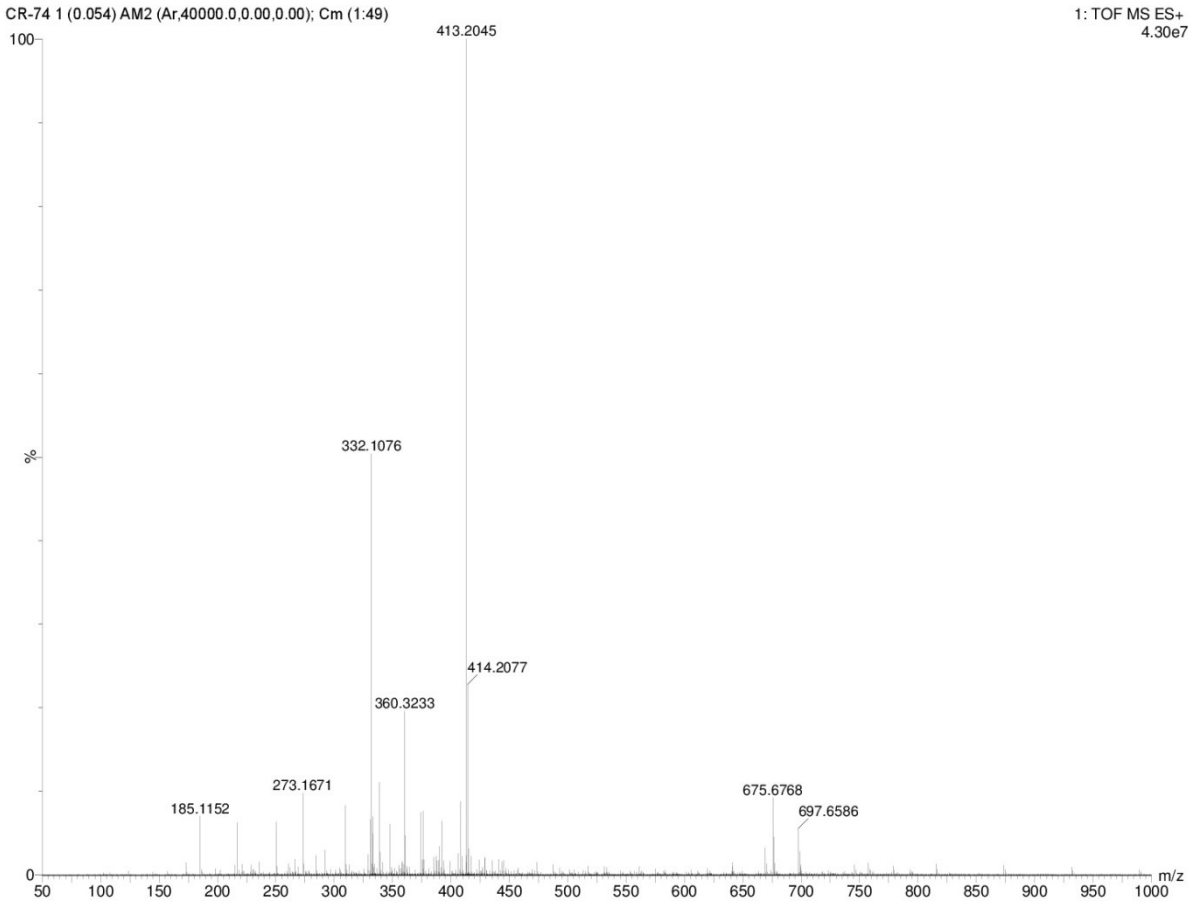

CR75 cece
6.71
4.72
4.61
3.79
2.44
2.30
2.20
1.83
1.70
1.51
1.42
0.90
0.85
0.83
1.00
3.03
1.22
8.79
0.70
2.21
3.19
f1 (ppm)


CR 7a 13C
222.84
171.15
157.80
156.30
121.25
109.82
52.88
50.84
49.71
36.98
34.65
31.23
28.25
18.14
7.89
f1 (ppm)

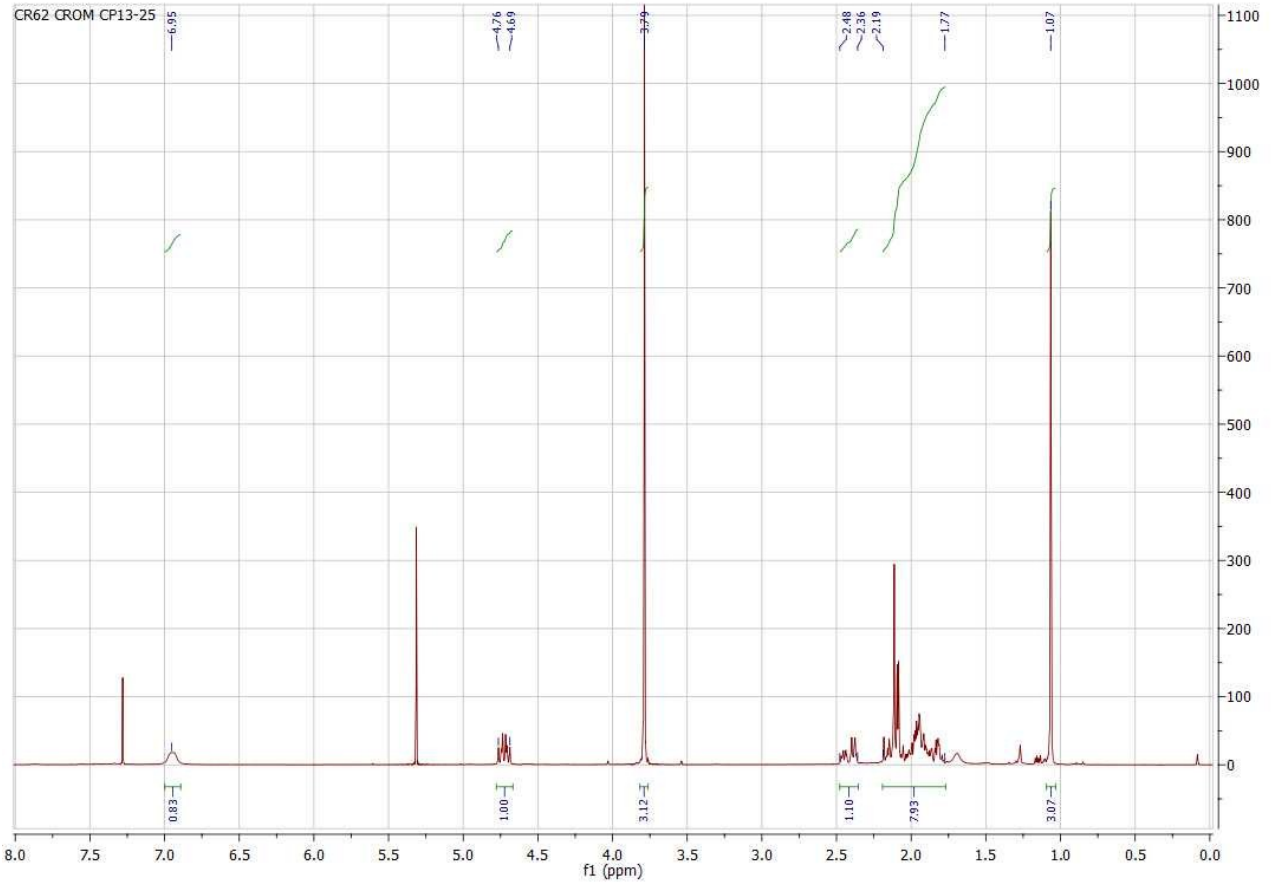

CR 74 19F
-76.11
f1 (ppm)

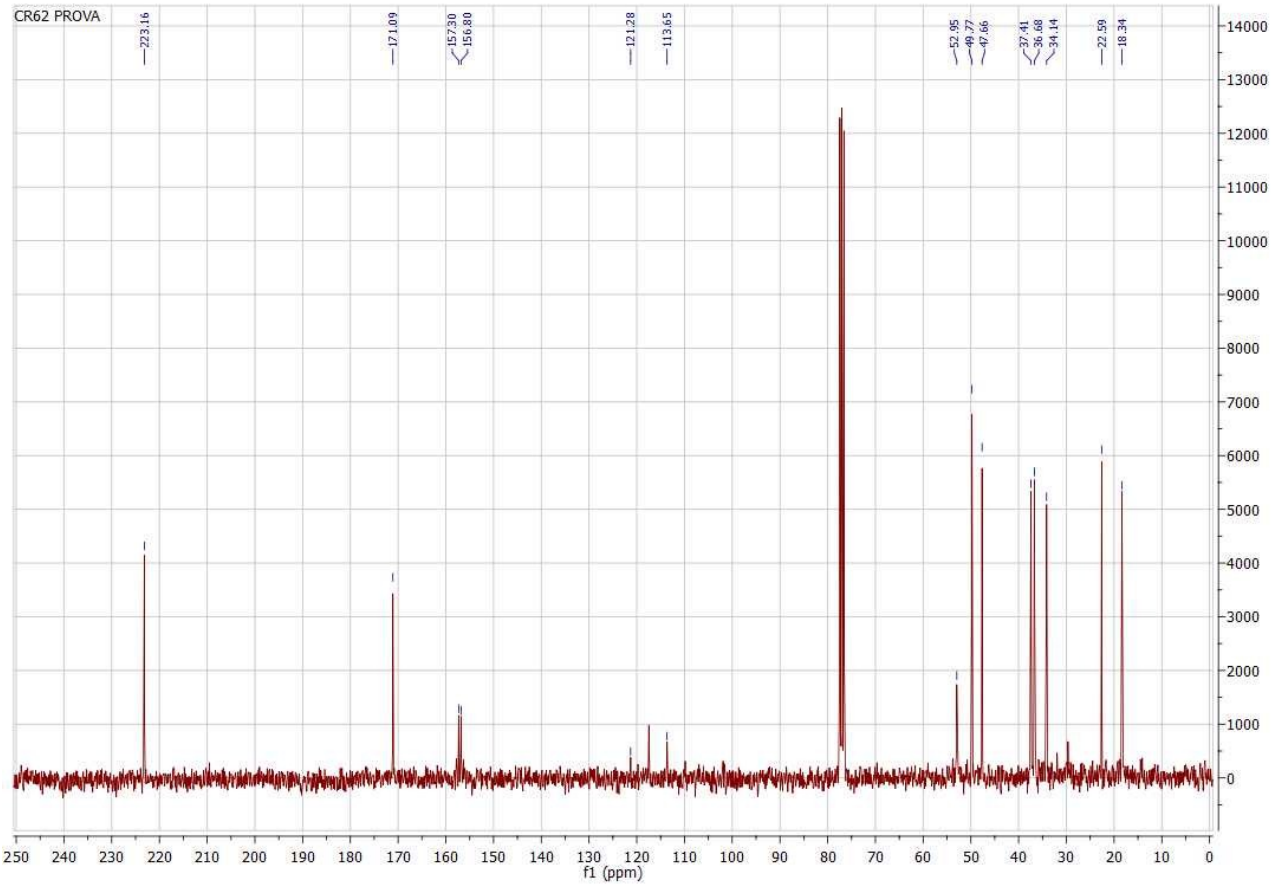

DAD1 A, Sig=225,4 Ref=off (CR74R.D)
mAU
7.845
9.917
min

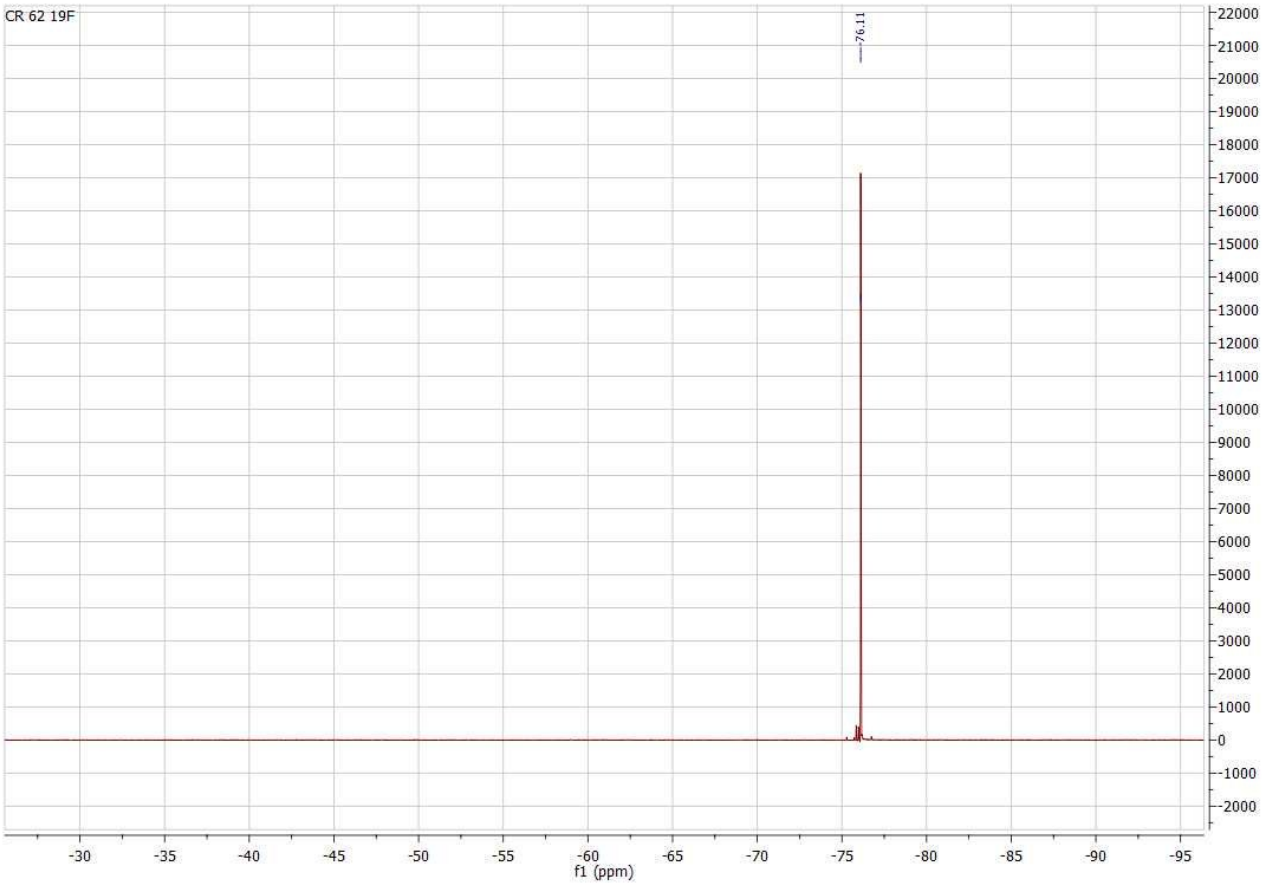

DAD1 A, Sig=225,4 Ref=off (CR775OA.D)
mAU
350
300
250
200
150
100
50
0
-50
7.811
9.945
0
2
4
6
8
10
min

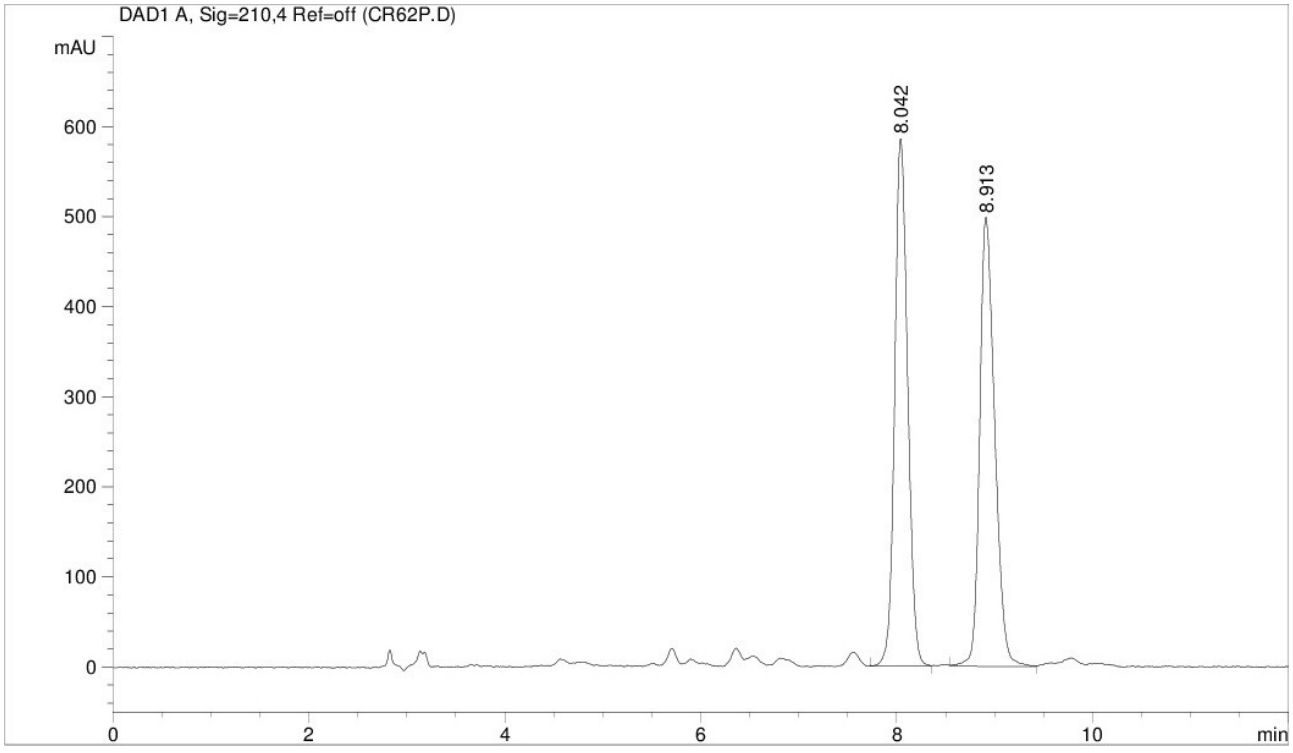

CR-74 1 (0.054) AM2 (Ar,40000.0,0.00,0.00); Cm (1:49)
1: TOF MS ES+
4.30e7
100
%
0
413.2045
332.1076
414.2077
360.3233
273.1671
185.1152
675.6768
697.6586
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
m/z

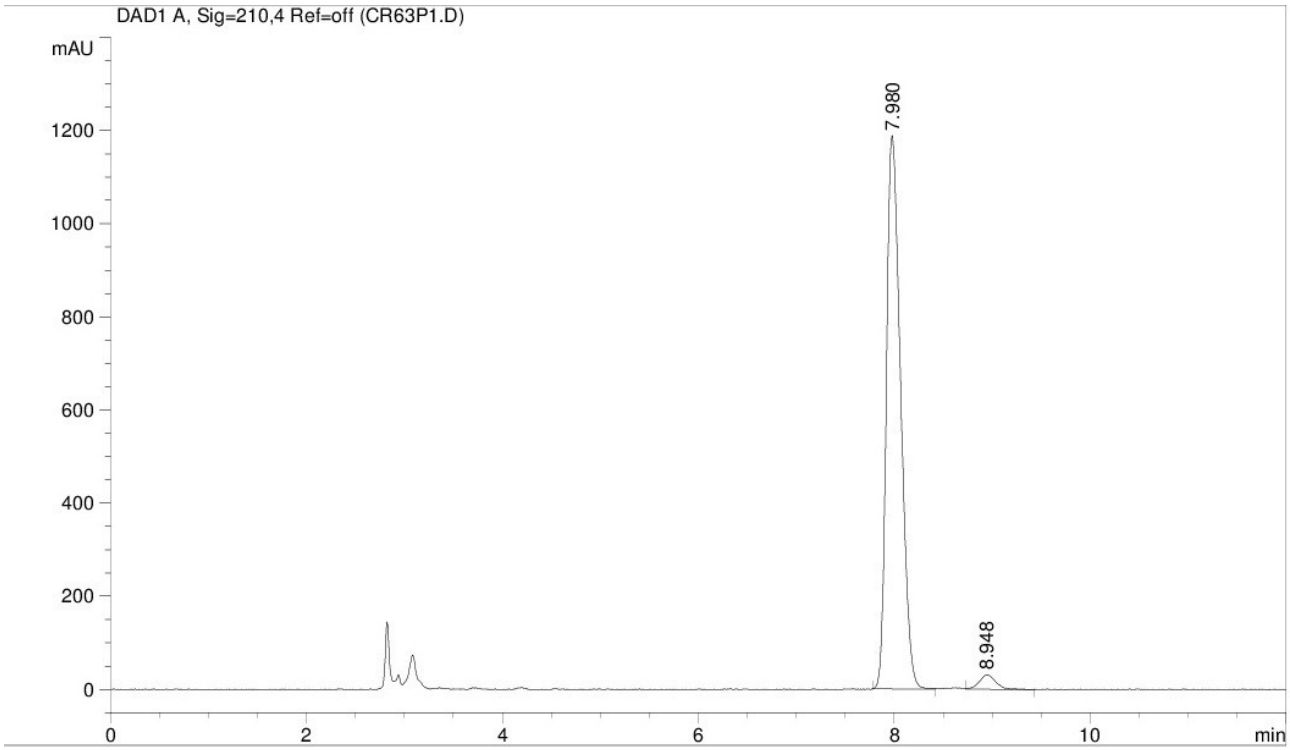
COMPOUND 3h

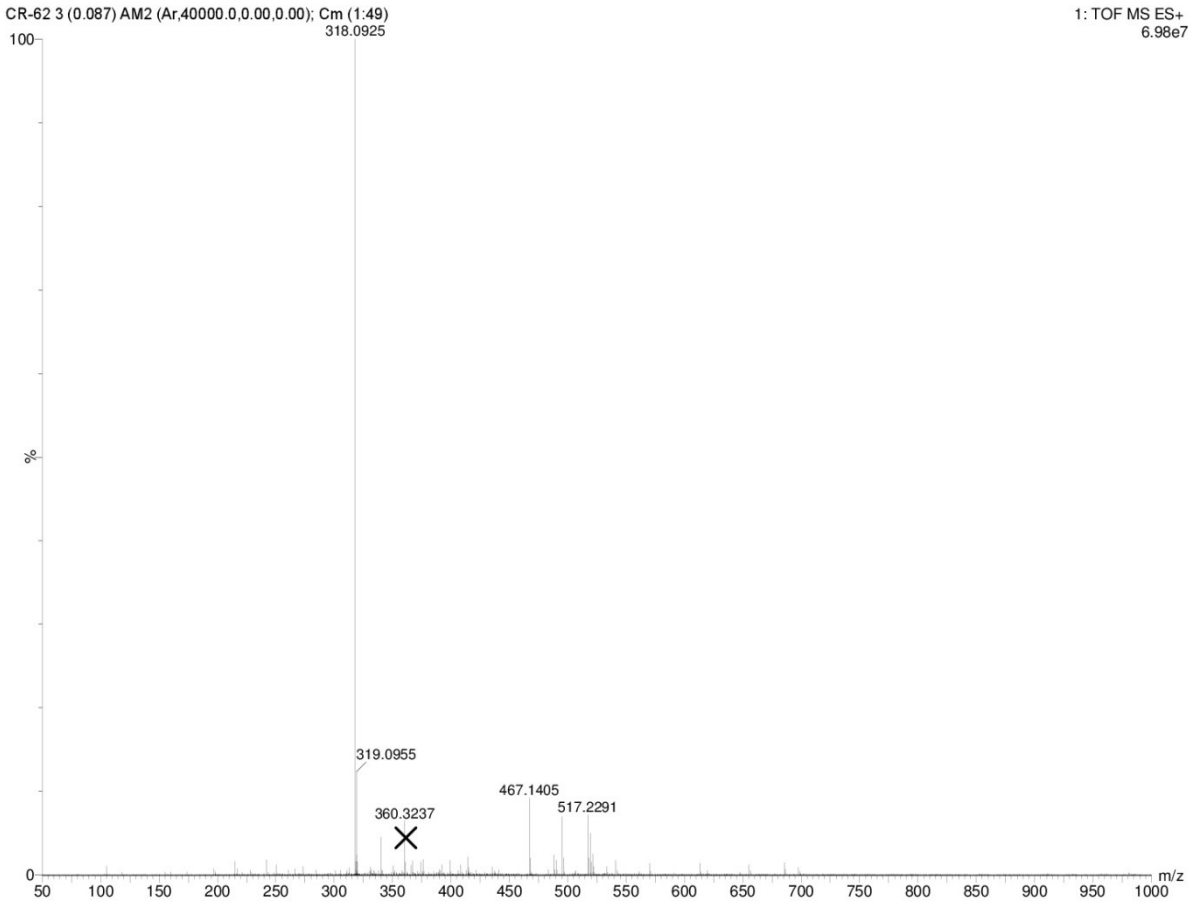

CR62 CROM CP13-25
6.95
4.76
4.69
3.79
2.48
2.36
2.19
1.77
1.07
0.83
1.00
3.12
1.10
7.93
3.07
f1 (ppm)


CR62 PROVA
223.16
171.09
157.30
156.80
121.28
113.65
52.95
49.77
47.66
37.41
36.68
34.14
22.59
18.34
f1 (ppm)

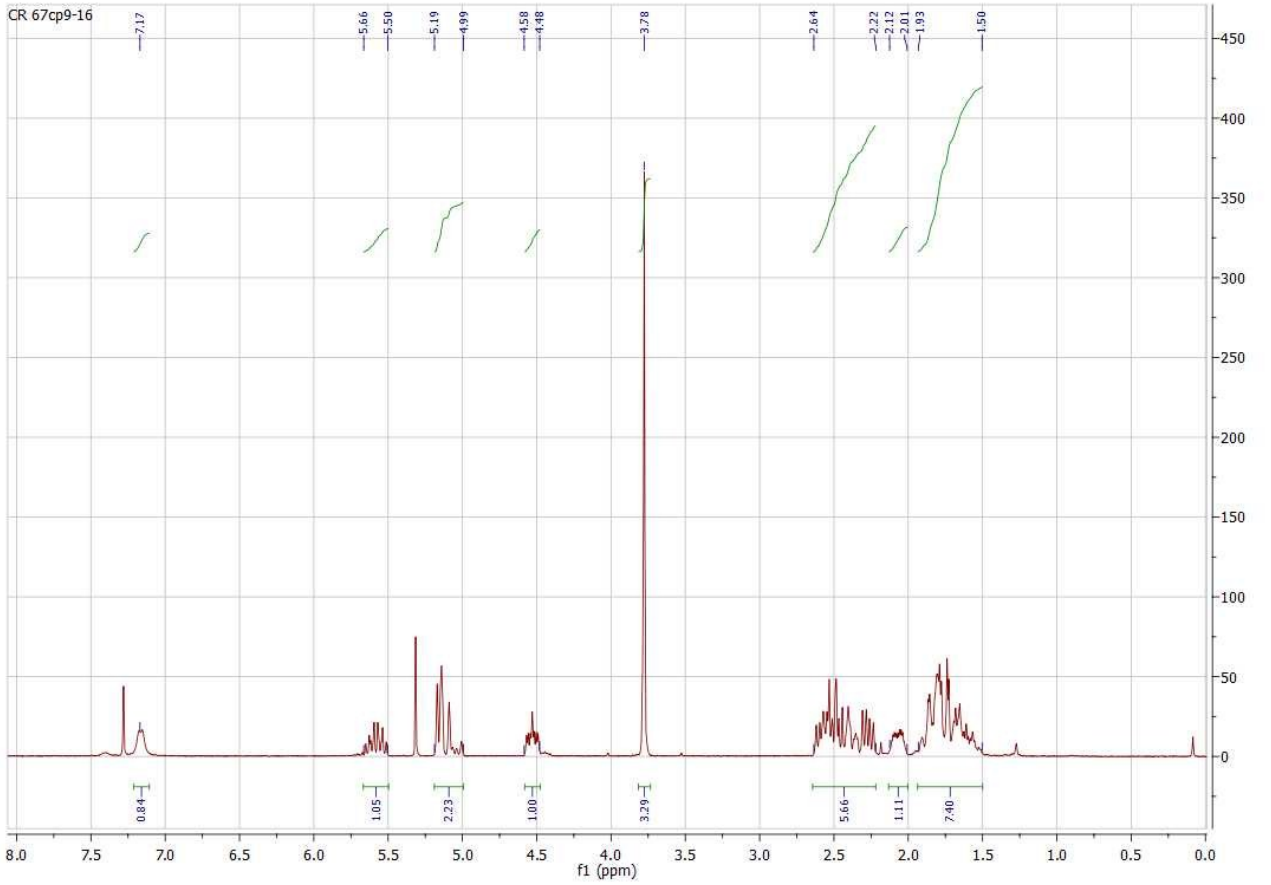

CR 62 19F
-76.11
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
f1 (ppm)

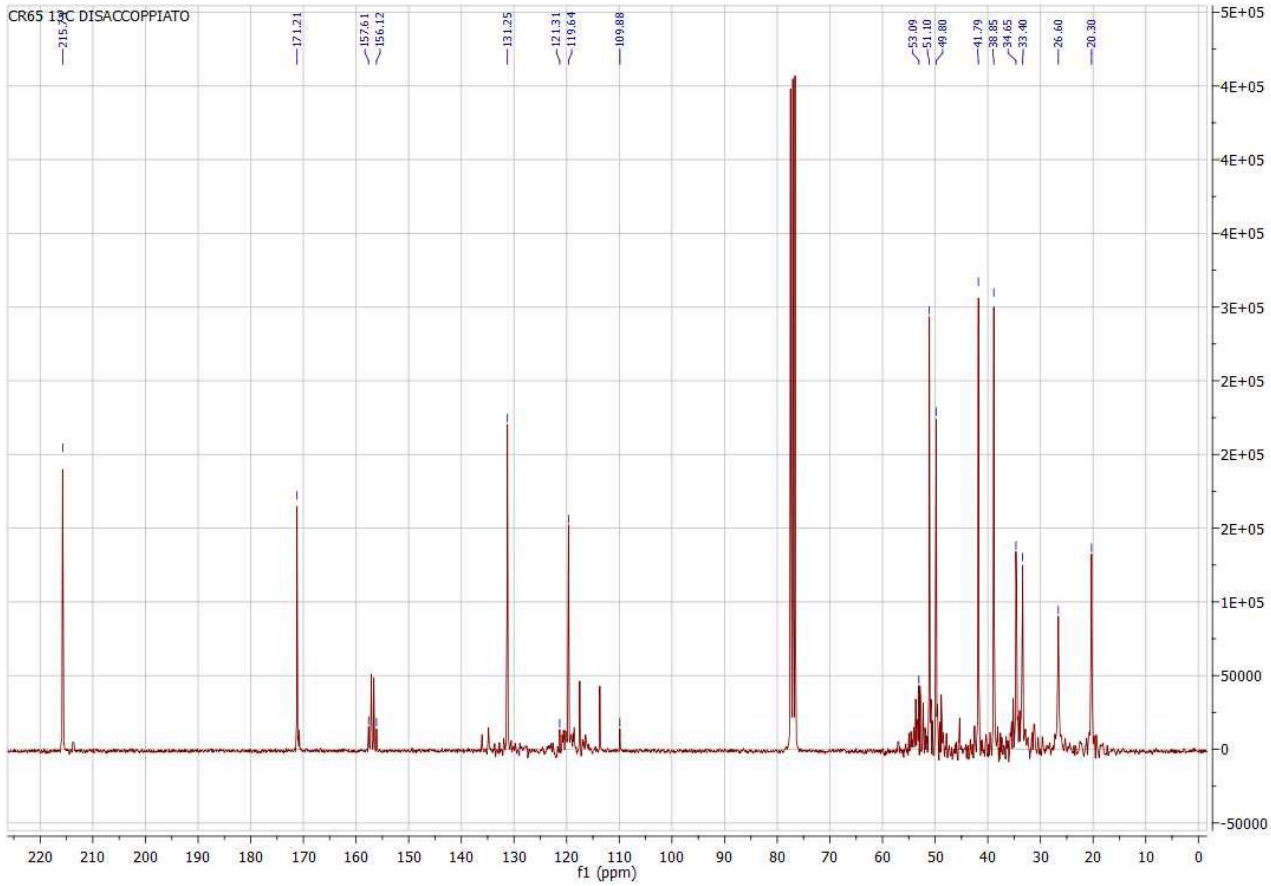

DAD1 A, Sig=210,4 Ref=off (CR62P.D)
mAU
600
500
400
300
200
100
0
8.042
8.913
0
2
4
6
8
10
min

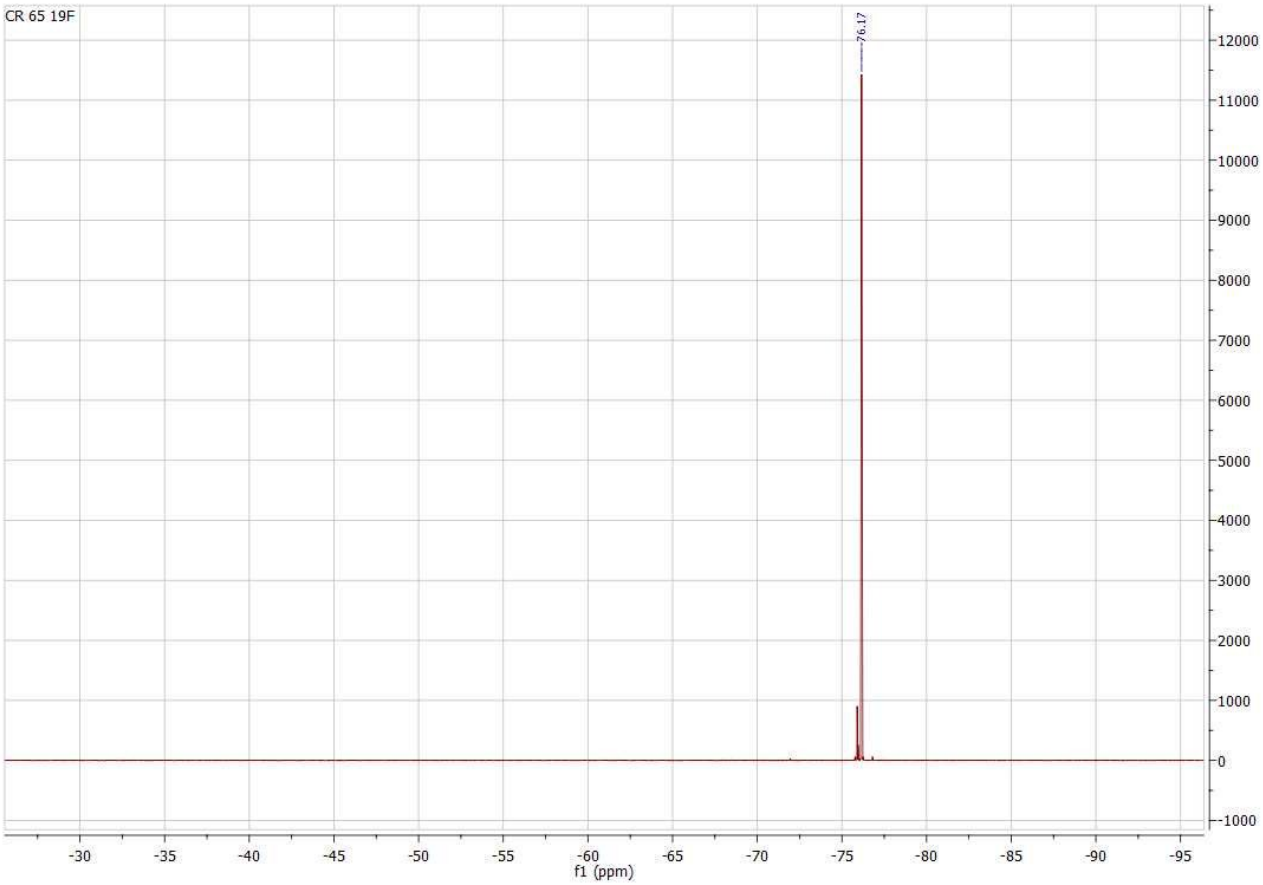

DAD1 A, Sig=210,4 Ref=off (CR63P1.D)
mAU
1200
1000
800
600
400
200
0
7.980
8.948
0
2
4
6
8
10
min

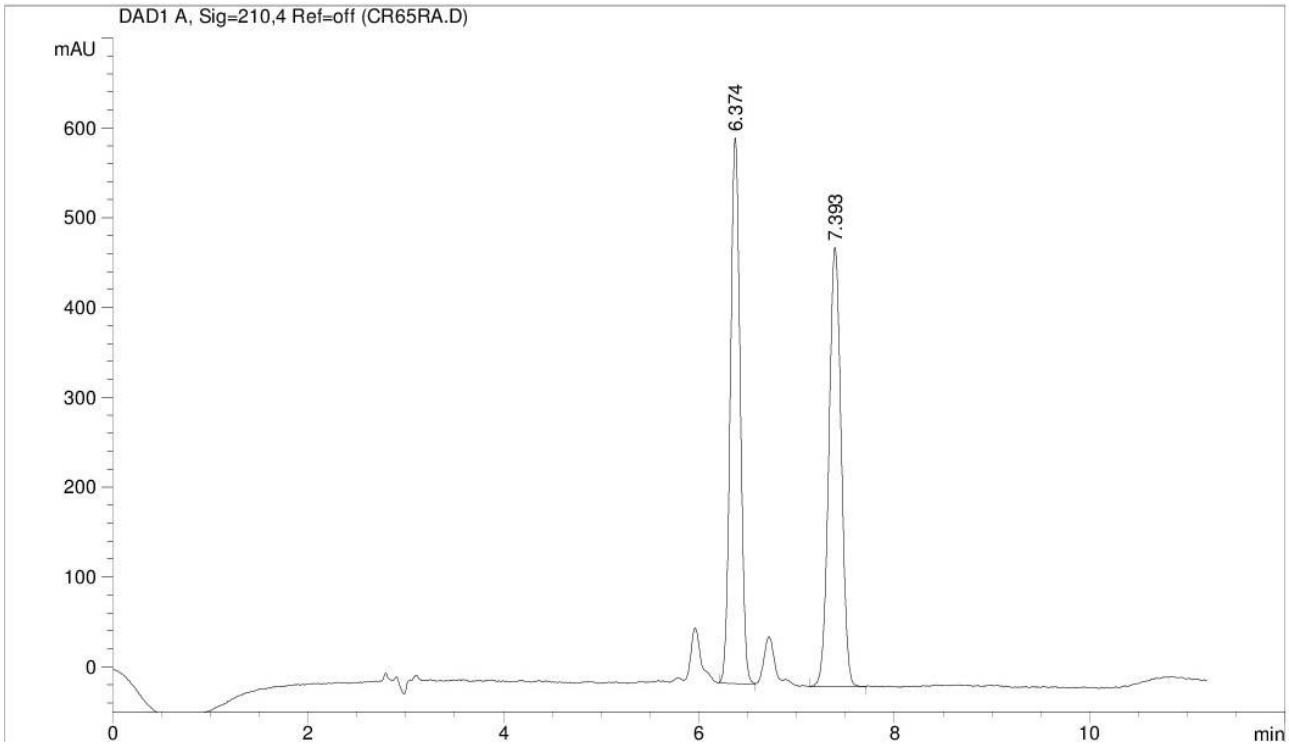

CR-62 3 (0.087) AM2 (Ar,40000.0,0.00,0.00); Cm (1:49)
1: TOF MS ES+
6.98e7
100
%
318.0925
319.0955
467.1405
517.2291
360.3237
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
m/z

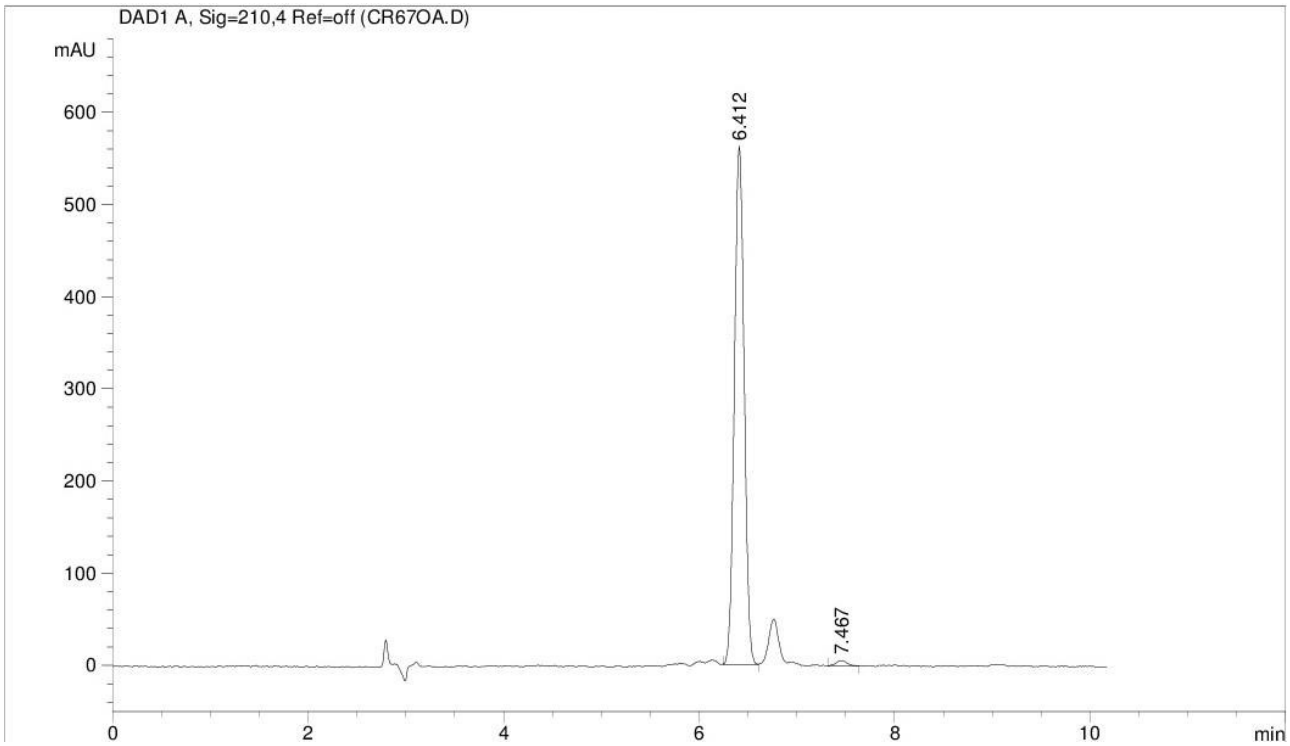
COMPOUND 3j

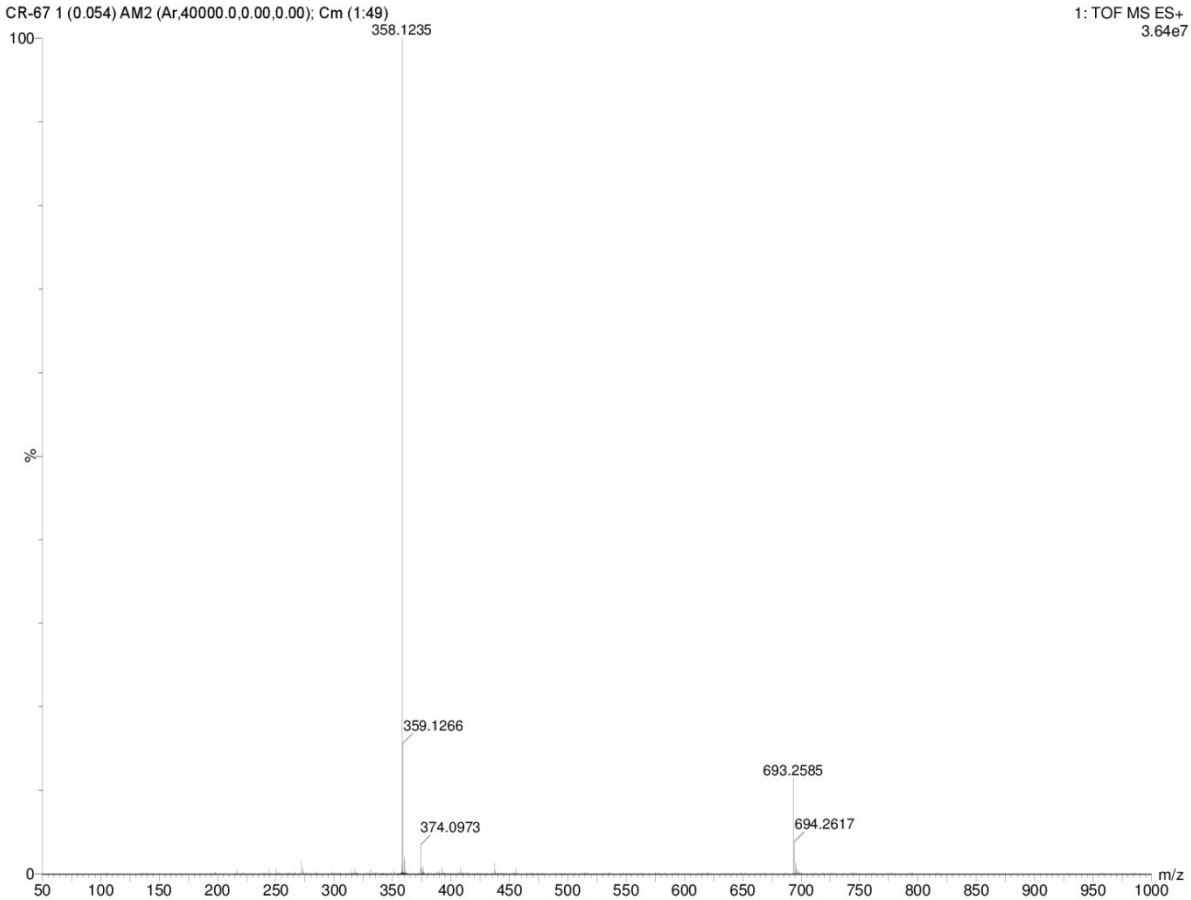

CR 67cp9-16
7.17
5.66
5.50
5.19
4.99
4.58
4.48
3.78
2.64
2.22
2.12
2.01
1.93
1.50
0.84
1.05
2.23
1.00
3.29
5.66
1.11
7.40
f1 (ppm)


CR65 13C DISACCOPPIATO
215.74
171.21
157.61
156.12
131.25
121.31
119.64
109.88
53.09
51.10
49.80
41.79
38.85
34.65
33.40
26.60
20.30
f1 (ppm)

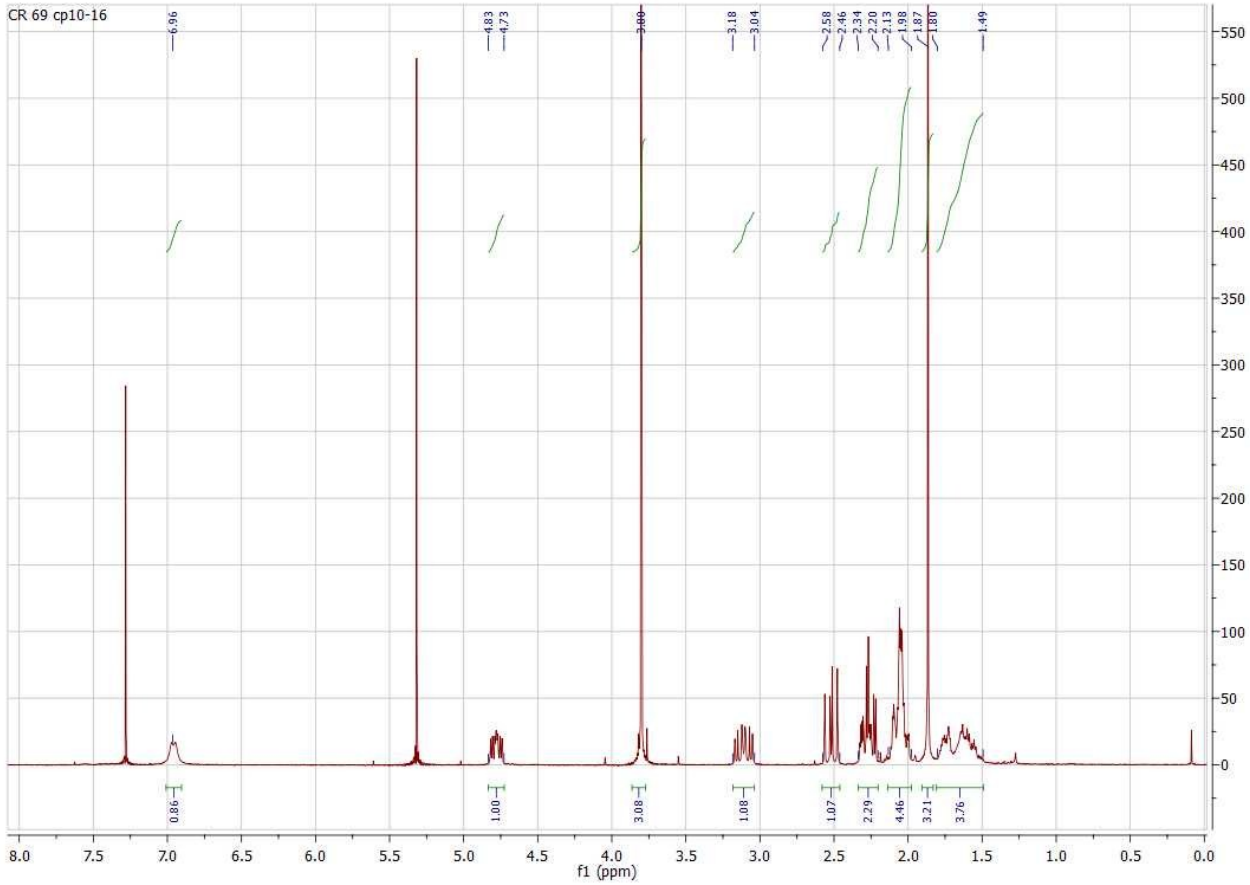

CR 65 19F
-76.17
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
f1 (ppm)

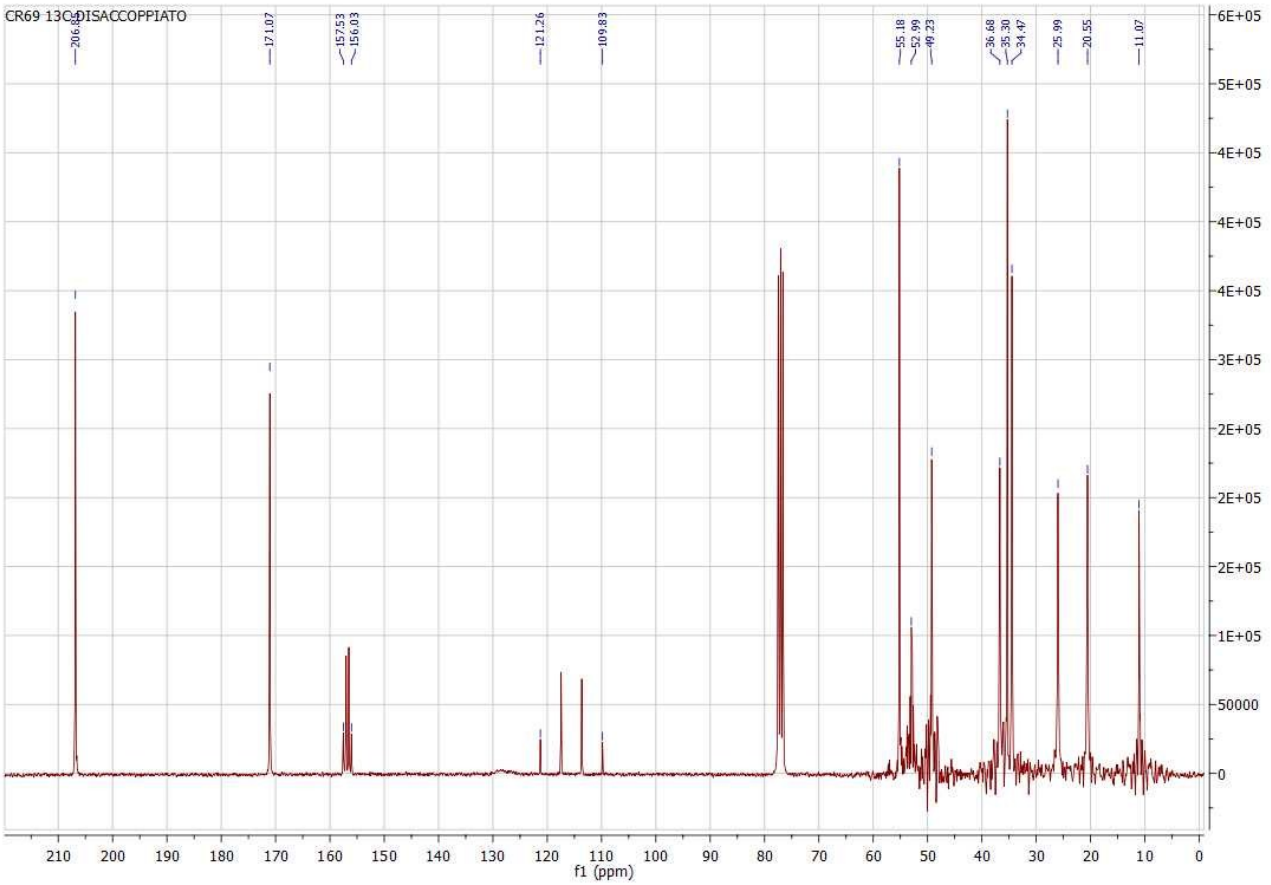

DAD1 A, Sig=210,4 Ref=off (CR65RA.D)
mAU
600
500
400
300
200
100
0
6.374
7.393
0
2
4
6
8
10
min

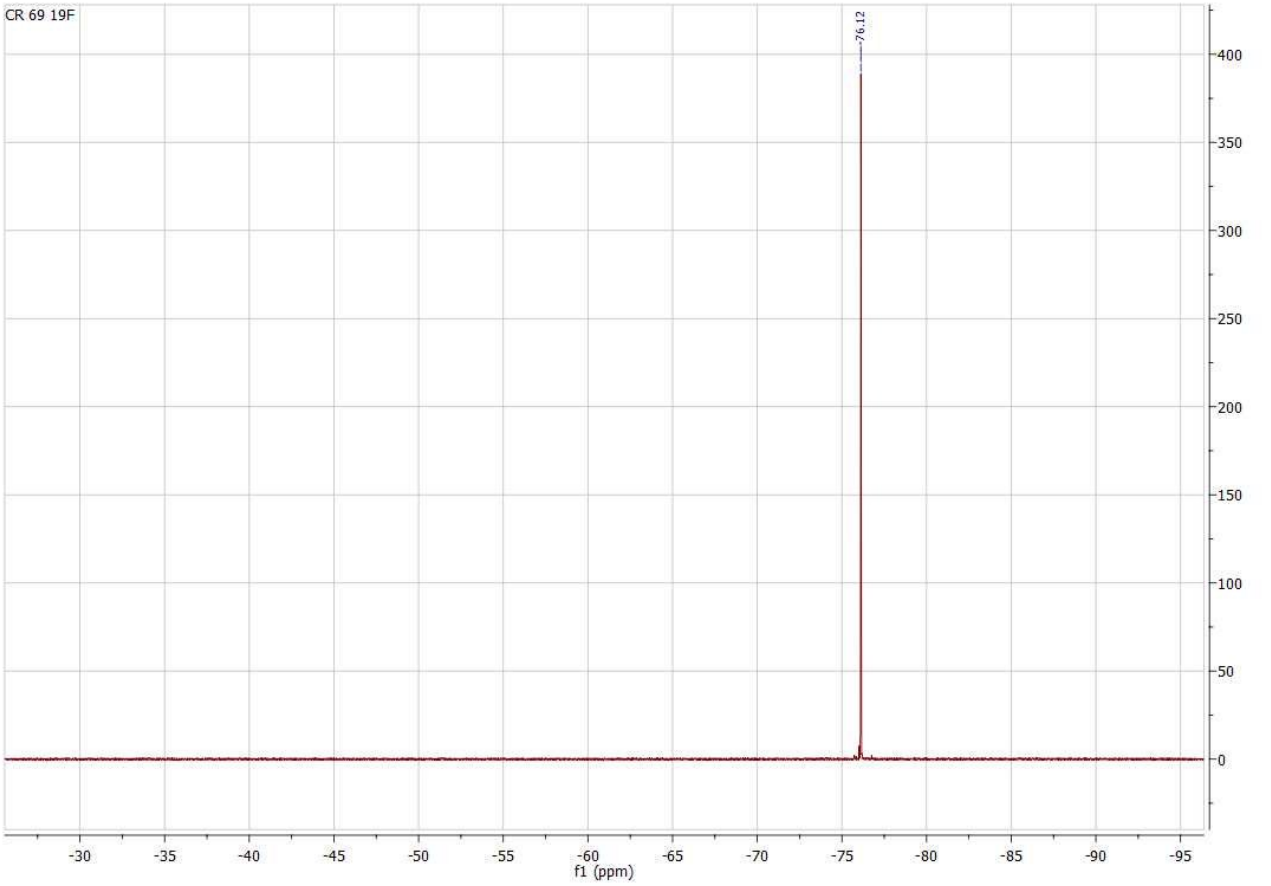

DAD1 A, Sig=210,4 Ref=off (CR67OA.D)
mAU
600
500
400
300
200
100
0
6.412
7.467
0
2
4
6
8
10
min

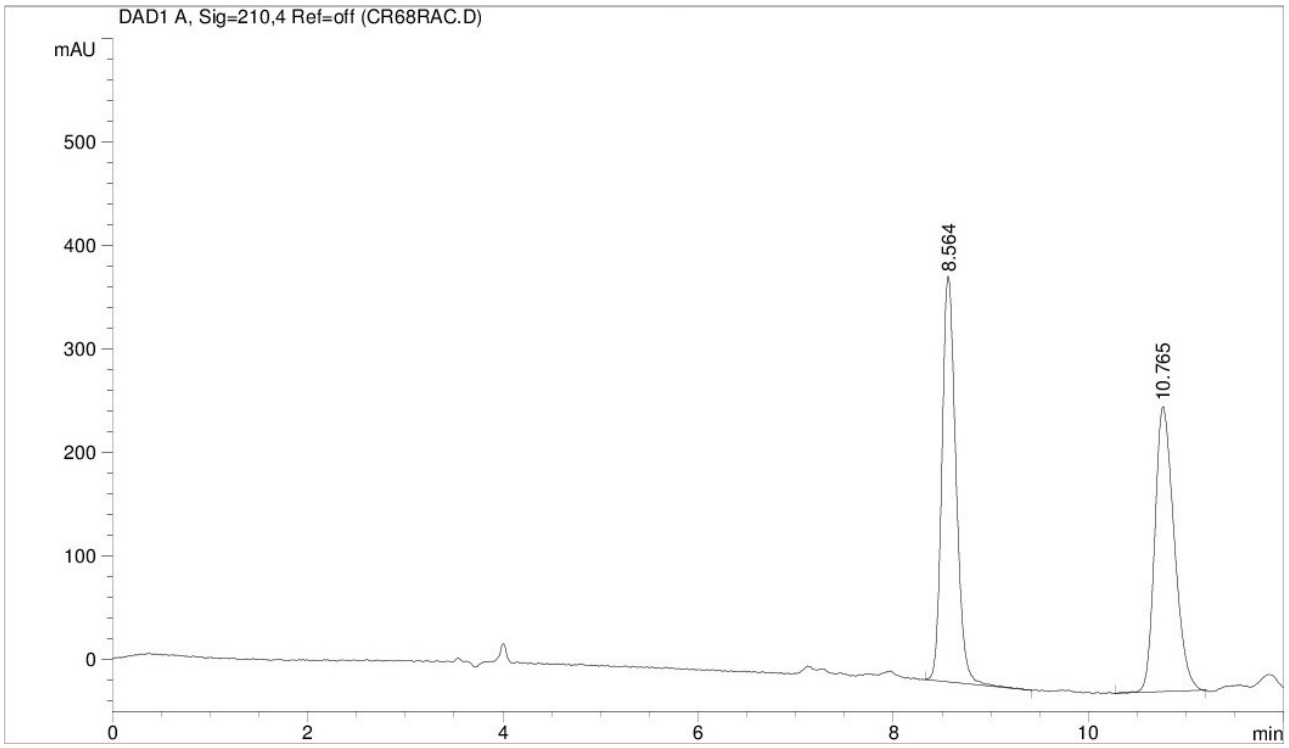

CR-67 1 (0.054) AM2 (Ar,40000.0,0.00,0.00); Cm (1:49)
1: TOF MS ES+
3.64e7
100
%
0
358.1235
359.1266
374.0973
693.2585
694.2617
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
m/z

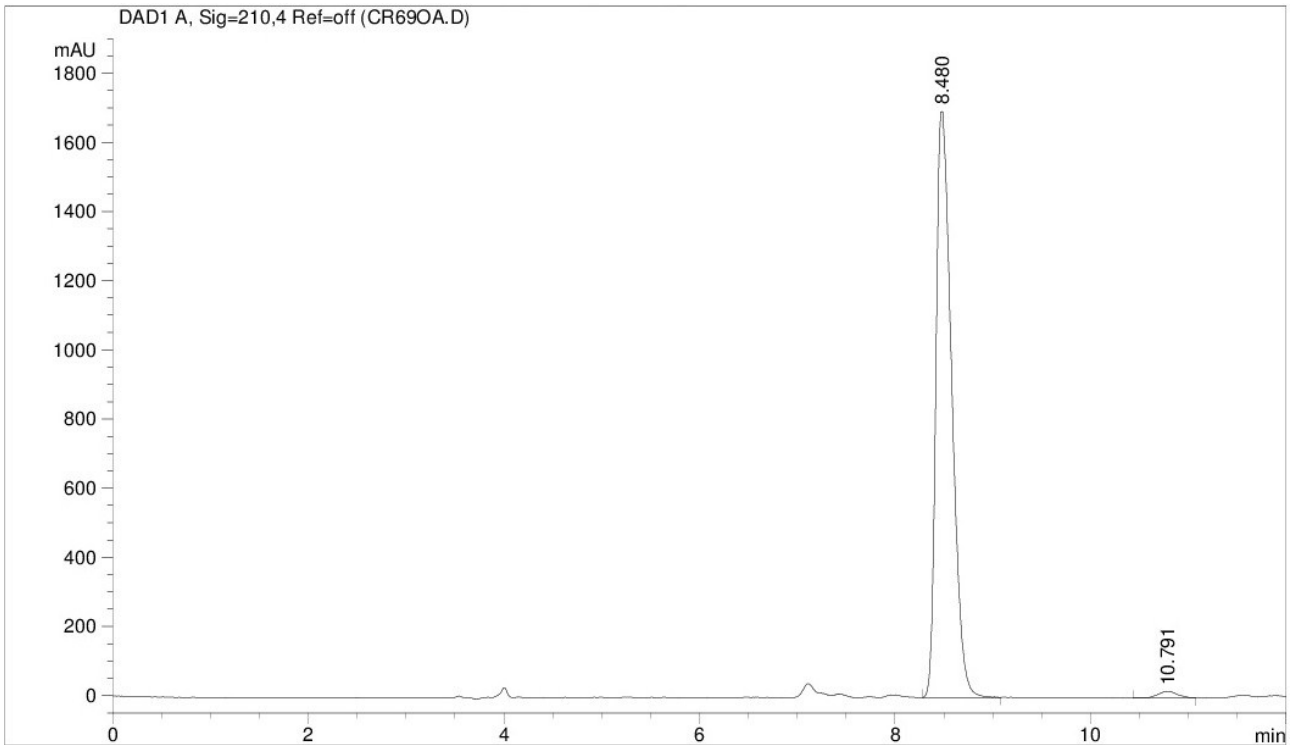
COMPOUND 3i

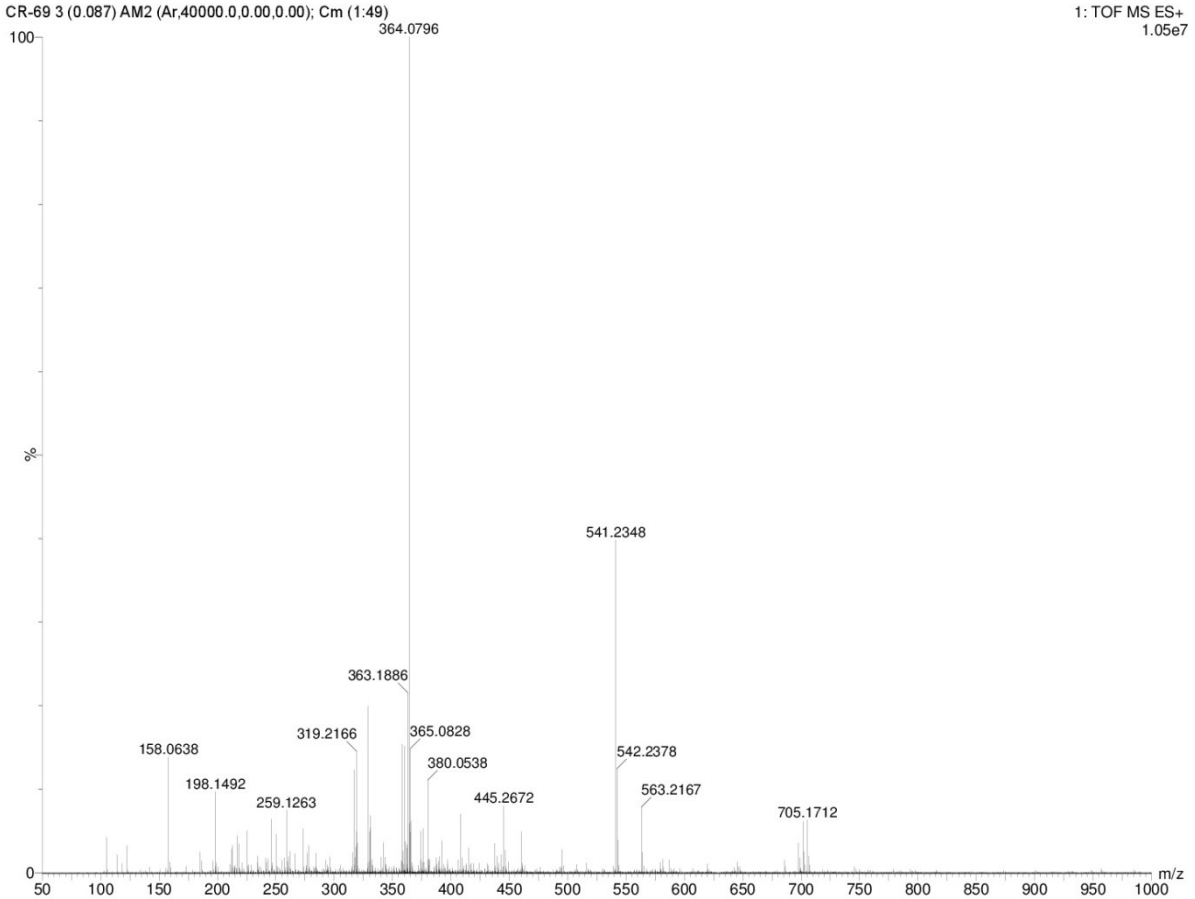

CR 69 cp10-16
6.96
4.83
4.73
3.00
3.18
3.04
2.58
2.46
2.34
2.20
2.13
1.98
1.87
1.80
1.49
0.86
1.00
3.08
1.08
1.07
2.29
4.46
3.21
3.76
f1 (ppm)


CR69 13C-DISACCOPPIATO
206.88
171.07
157.53
156.03
121.26
109.83
55.18
52.99
49.23
36.68
35.30
34.47
25.99
20.55
11.07
f1 (ppm)

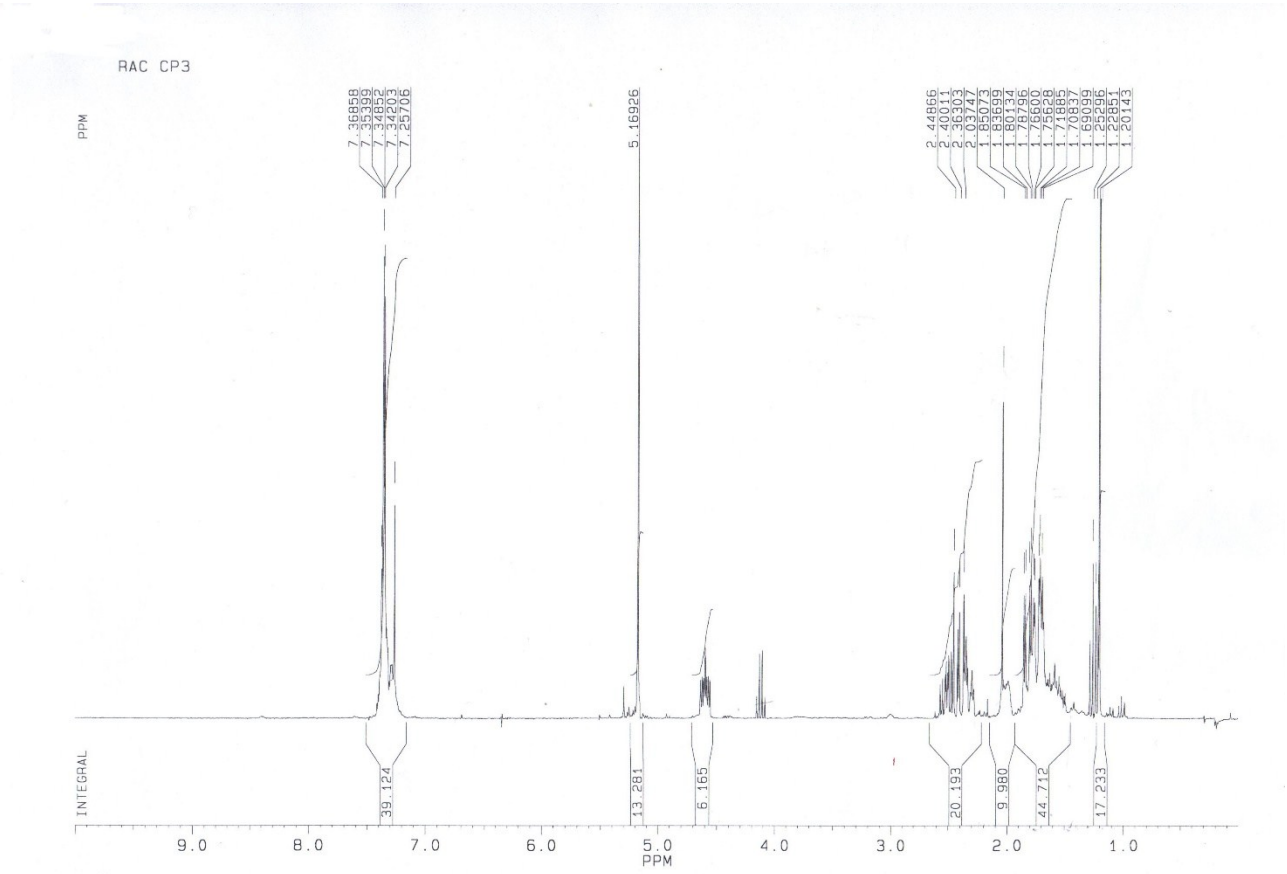

CR 69 19F
-76.12
f1 (ppm)

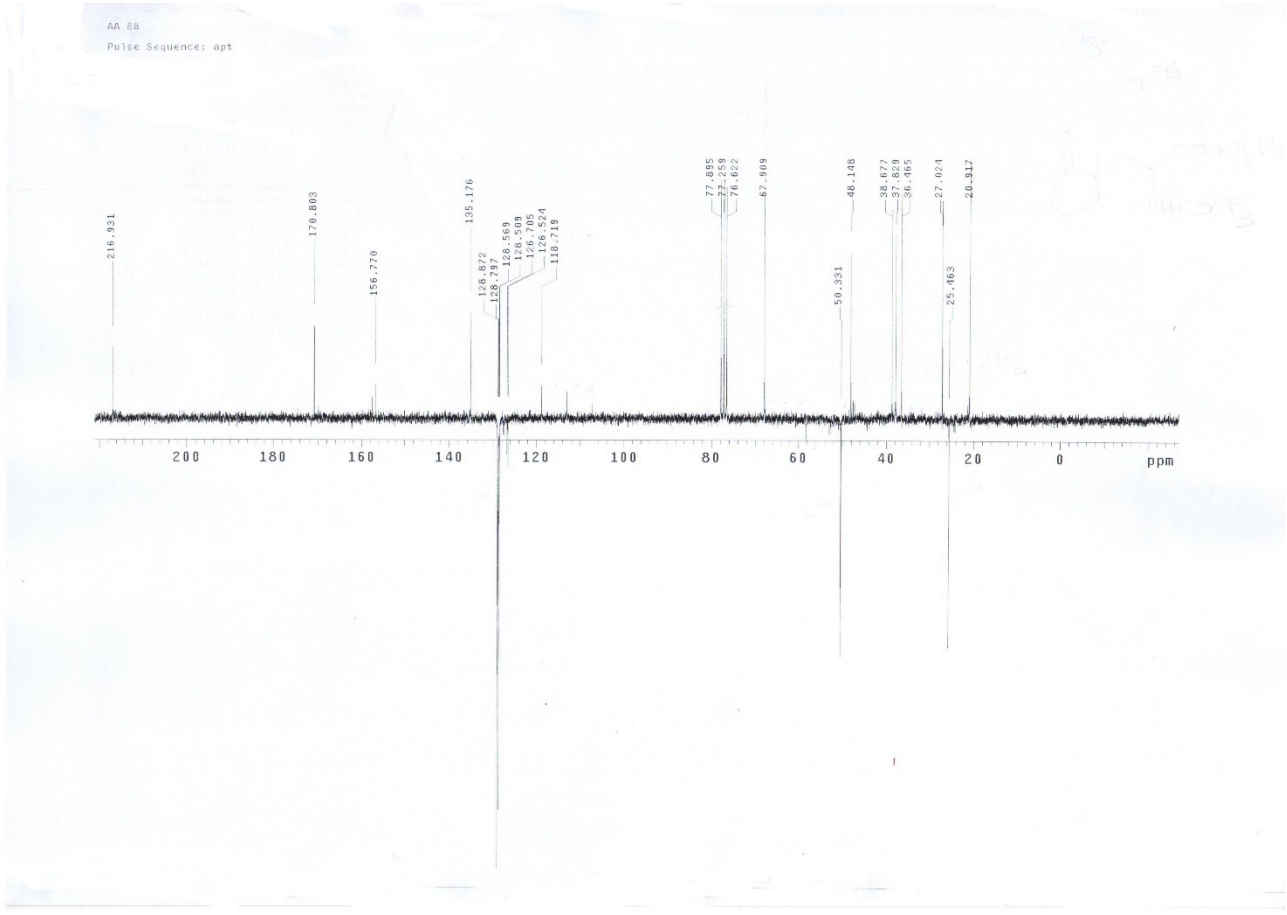

DAD1 A, Sig=210,4 Ref=off (CR68RAC.D)
mAU
500
400
300
200
100
0
8.564
10.765
0
2
4
6
8
10
min


DAD1 A, Sig=210,4 Ref=off (CR69OA.D)
mAU
1800
1600
1400
1200
1000
800
600
400
200
0
8.480
10.791
0
2
4
6
8
10
min


CR-69 3 (0.087) AM2 (Ar,40000.0,0.00,0.00); Cm (1:49)
1: TOF MS ES+
1.05e7
100
%
0
364.0796
541.2348
363.1886
319.2166
365.0828
158.0638
380.0538
542.2378
198.1492
259.1263
445.2672
563.2167
705.1712
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
m/z

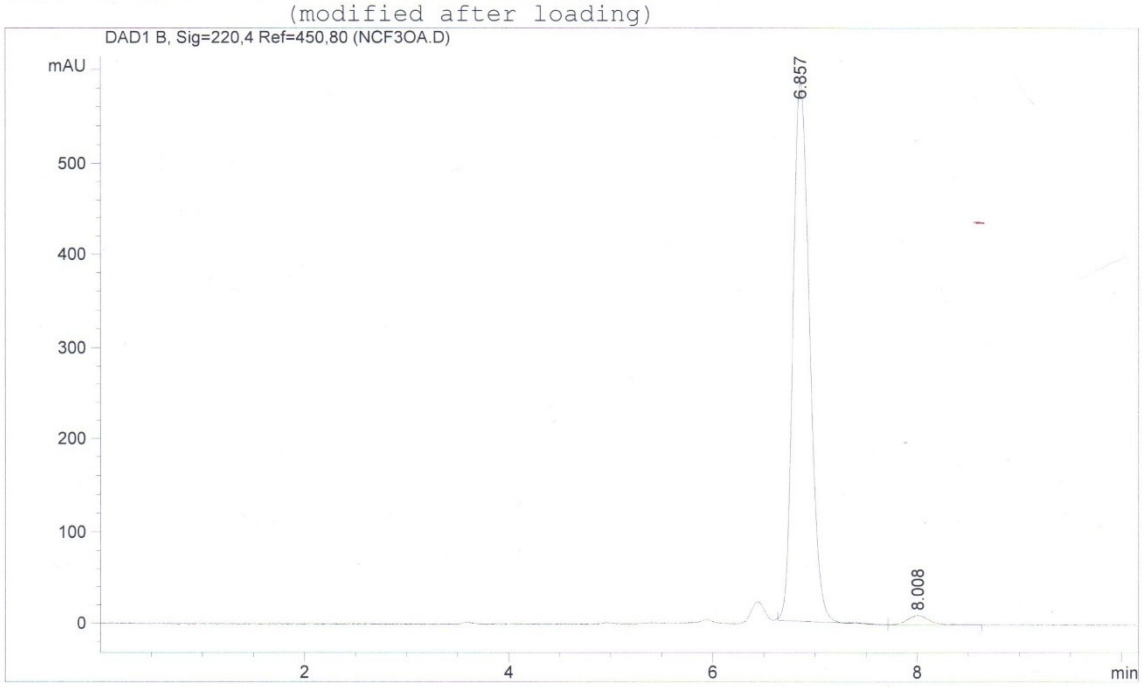
COMPOUND 3k


RAC CP3
PPM
7.36558
7.35339
7.34552
7.34003
7.25706
5.16926
2.44866
2.40011
2.36303
2.03147
1.85073
1.83599
1.79104
1.76600
1.75228
1.71885
1.70837
1.69099
1.25296
1.22851
1.20143
INTEGRAL
39.124
13.281
6.165
20.193
9.980
44.712
17.233
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM


AA 88
Pulse Sequence: apt
216.931
170.803
156.770
135.176
128.672
128.737
128.560
128.508
126.705
126.524
118.719
77.895
77.259
76.622
67.909
48.148
38.677
37.829
36.465
27.024
20.917
50.331
25.463
200
180
160
140
120
100
80
60
40
20
0
ppm

Data File C:\HPCHEM\1\DATA\NCF3OA.D Sample Name: cf3oa ad15etoh

```
Injection Date  : 01/07/11 9.06.05
Sample Name     : cf3oa ad15etoh                    Vial :   1
Acq. Operator   : cece
Acq. Method     : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 01/07/11 8.48.24  by cece
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 01/07/11 9.17.31  by cece
                  (modified after loading)
```



Area Percent Report

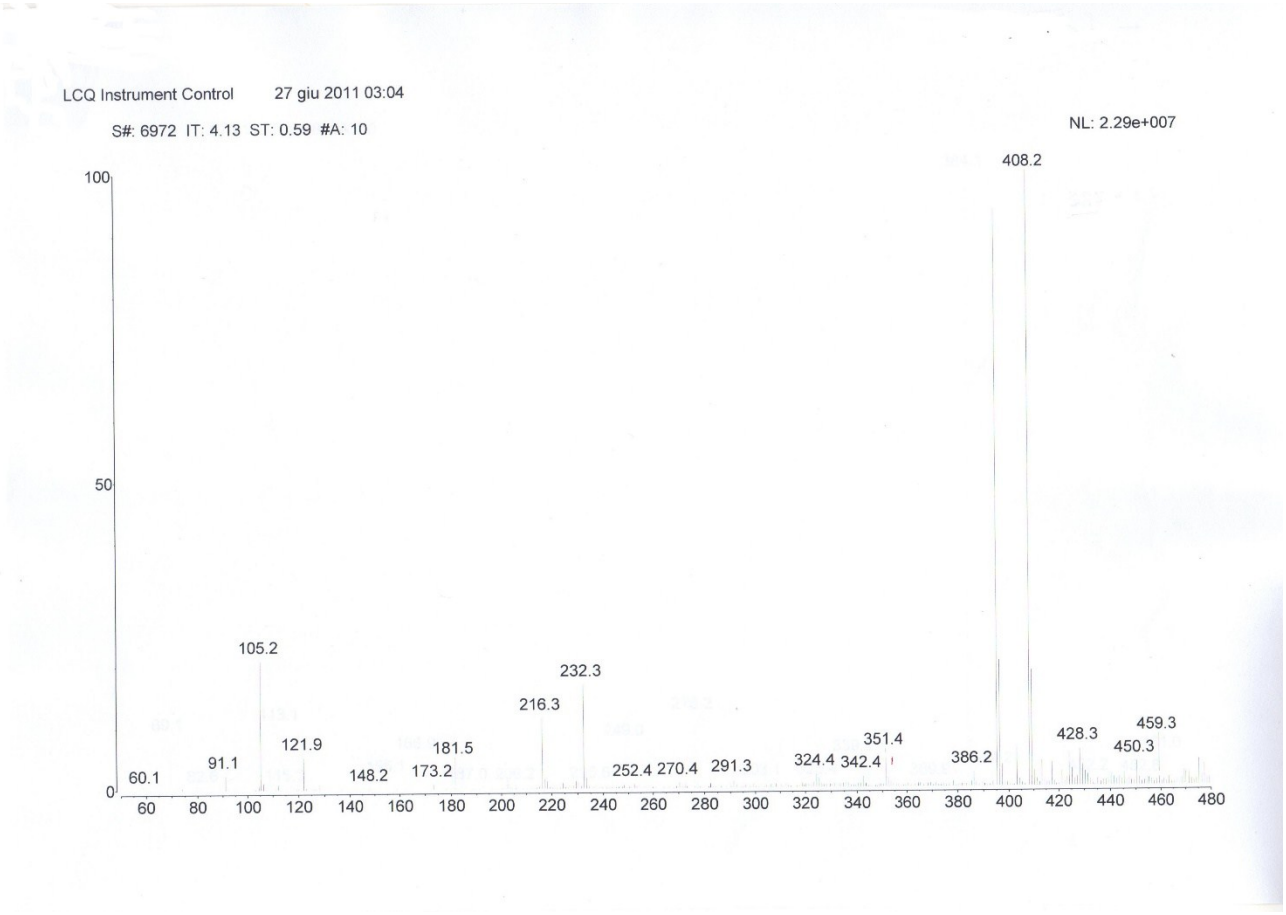
```
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=220,4 Ref=450,80
```

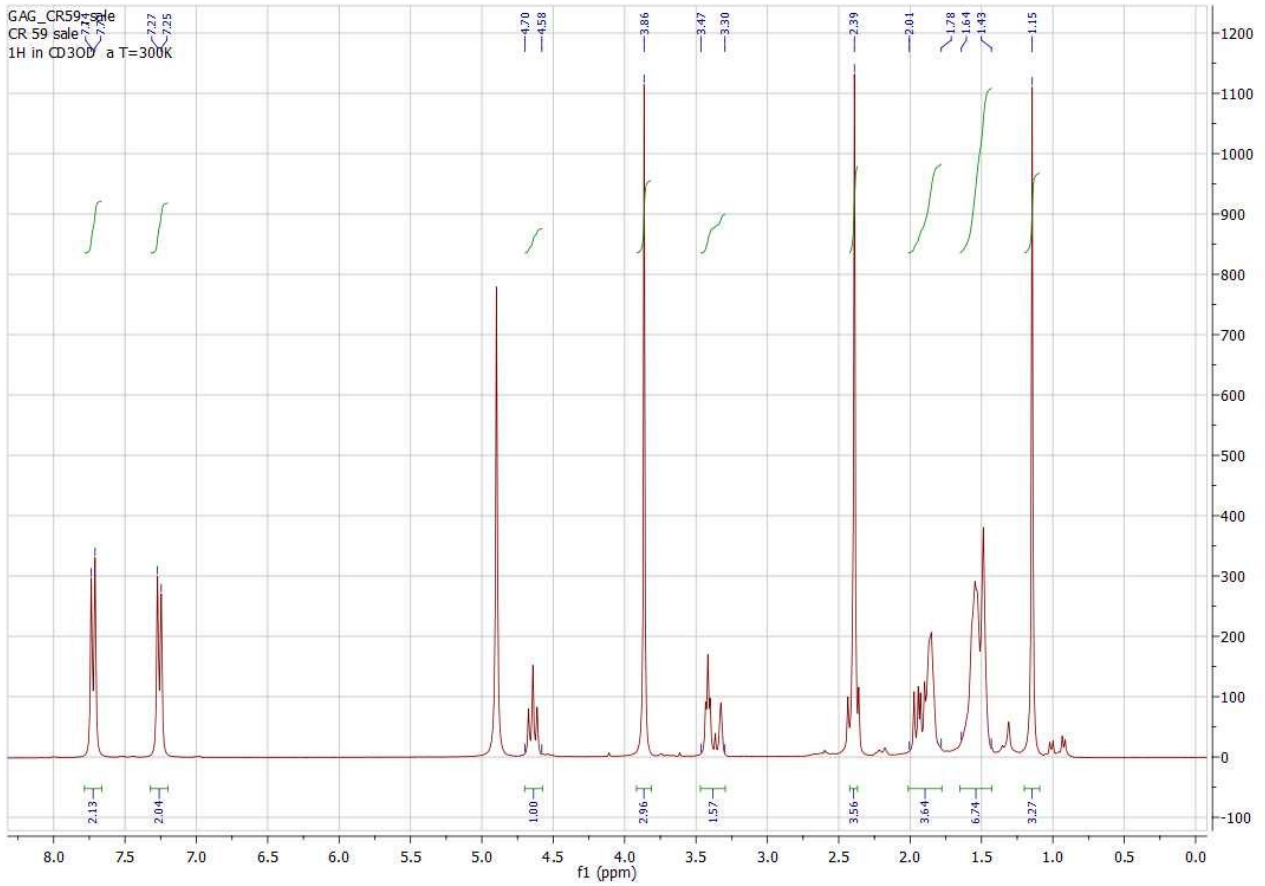
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.857	BP	0.1767	6625.14453	582.27026	97.8840
2	8.008	VB	0.2224	143.21751	10.04056	2.1160
Totals :				6768.36205	592.31082	

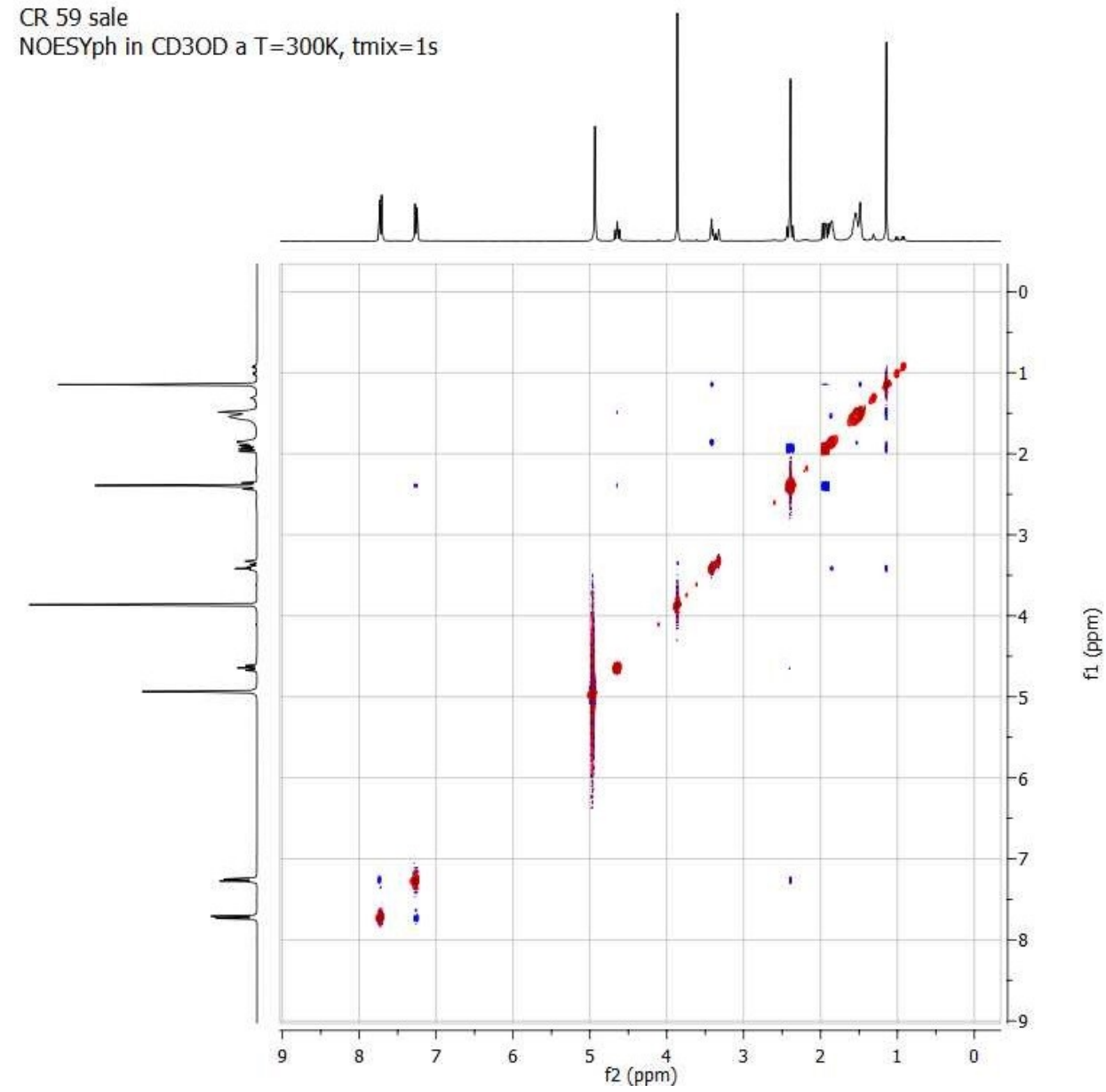
```
 Results obtained with enhanced integrator!
```

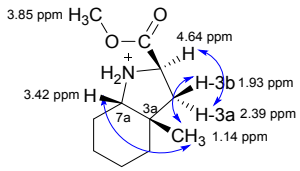
*** End of Report ***


LCQ Instrument Control
27 giu 2011 03:04
S#: 6972 IT: 4.13 ST: 0.59 #A: 10
NL: 2.29e+007
100
50
0
408.2
105.2
232.3
216.3
121.9
181.5
91.1
60.1
148.2
173.2
252.4
270.4
291.3
324.4
342.4
351.4
386.2
428.3
450.3
459.3
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480

COMPOUND **5**

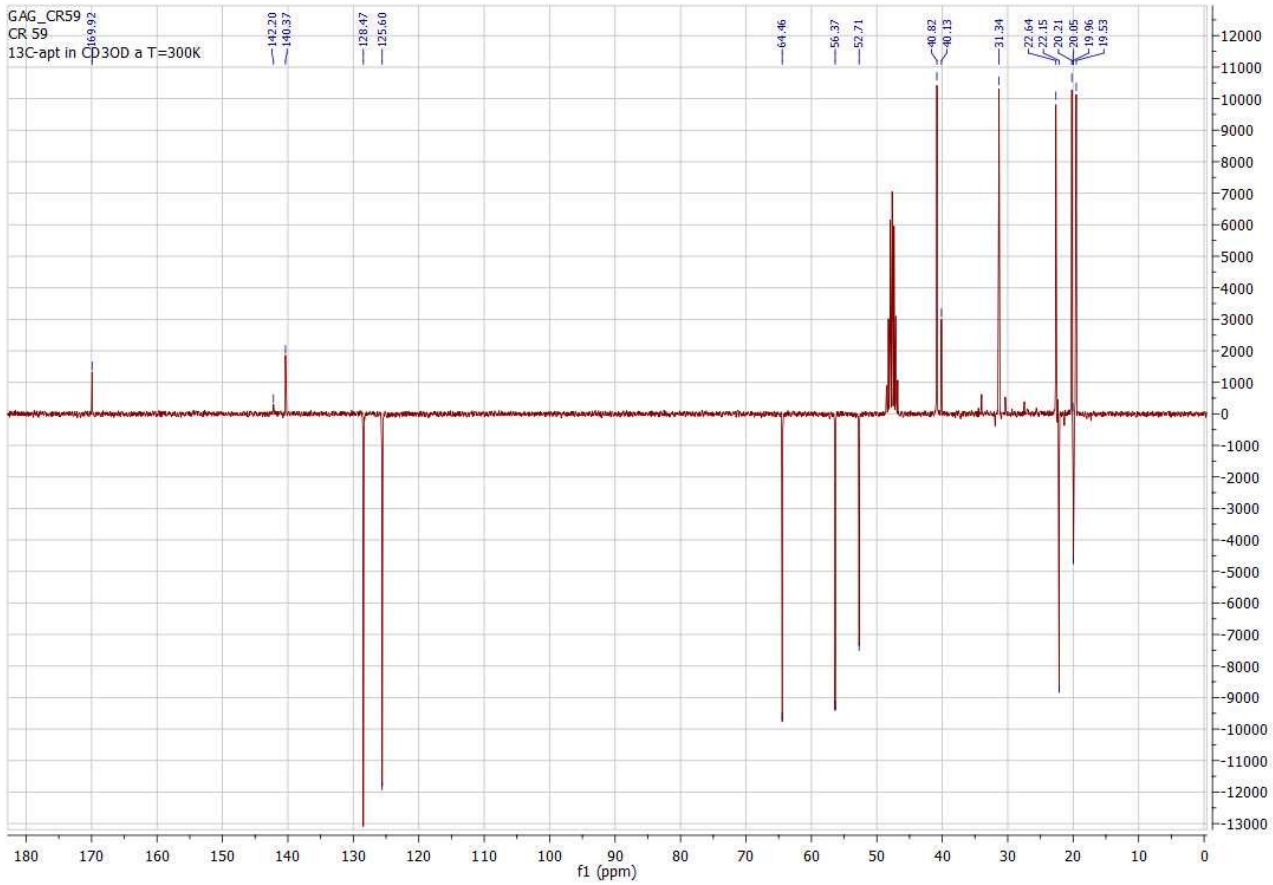

GAG_CR59-sale
CR 59 sale
1H in CD3OD a T=300K
7.74
7.72
7.27
7.25
4.70
4.58
3.86
3.47
3.30
2.39
2.01
1.78
1.64
1.43
1.15
2.13
2.04
1.00
2.96
1.57
3.56
3.64
6.74
3.27
f1 (ppm)

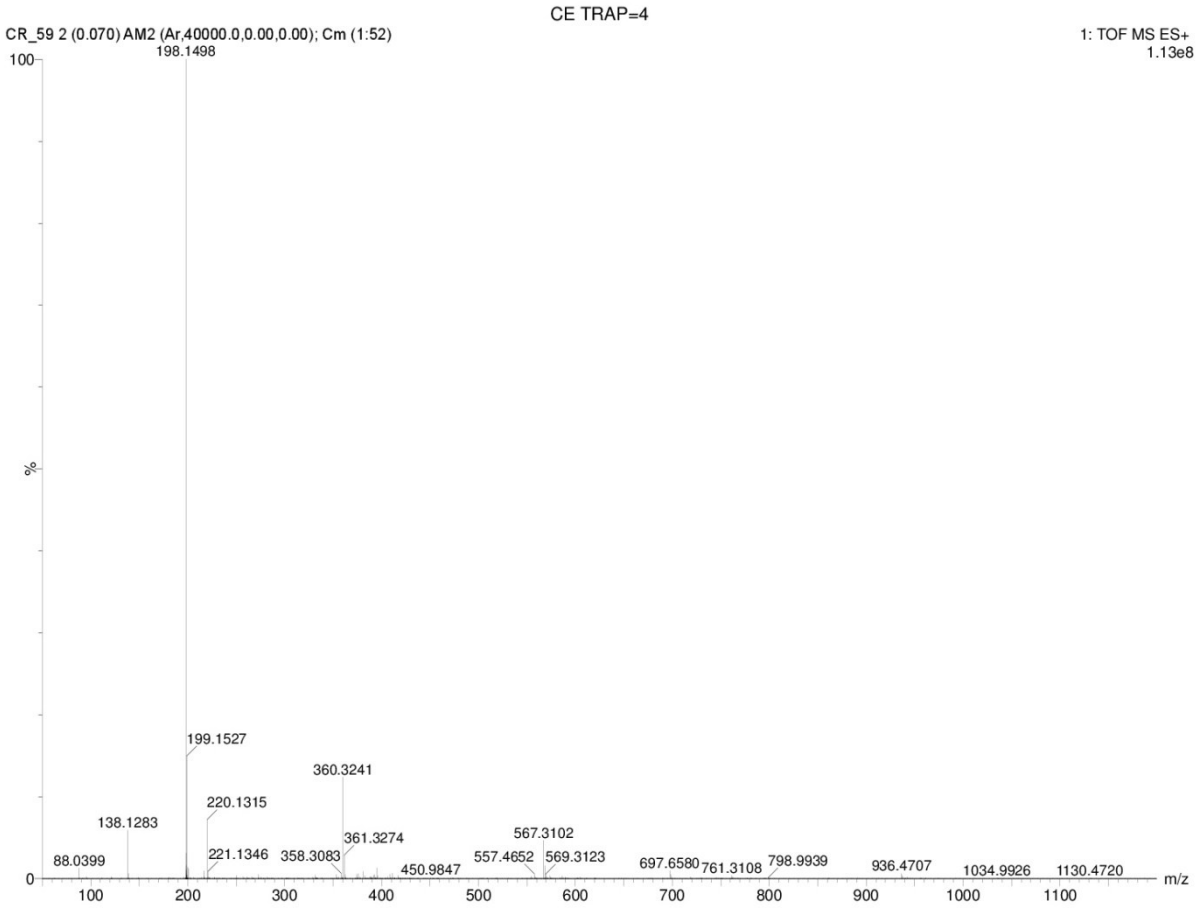




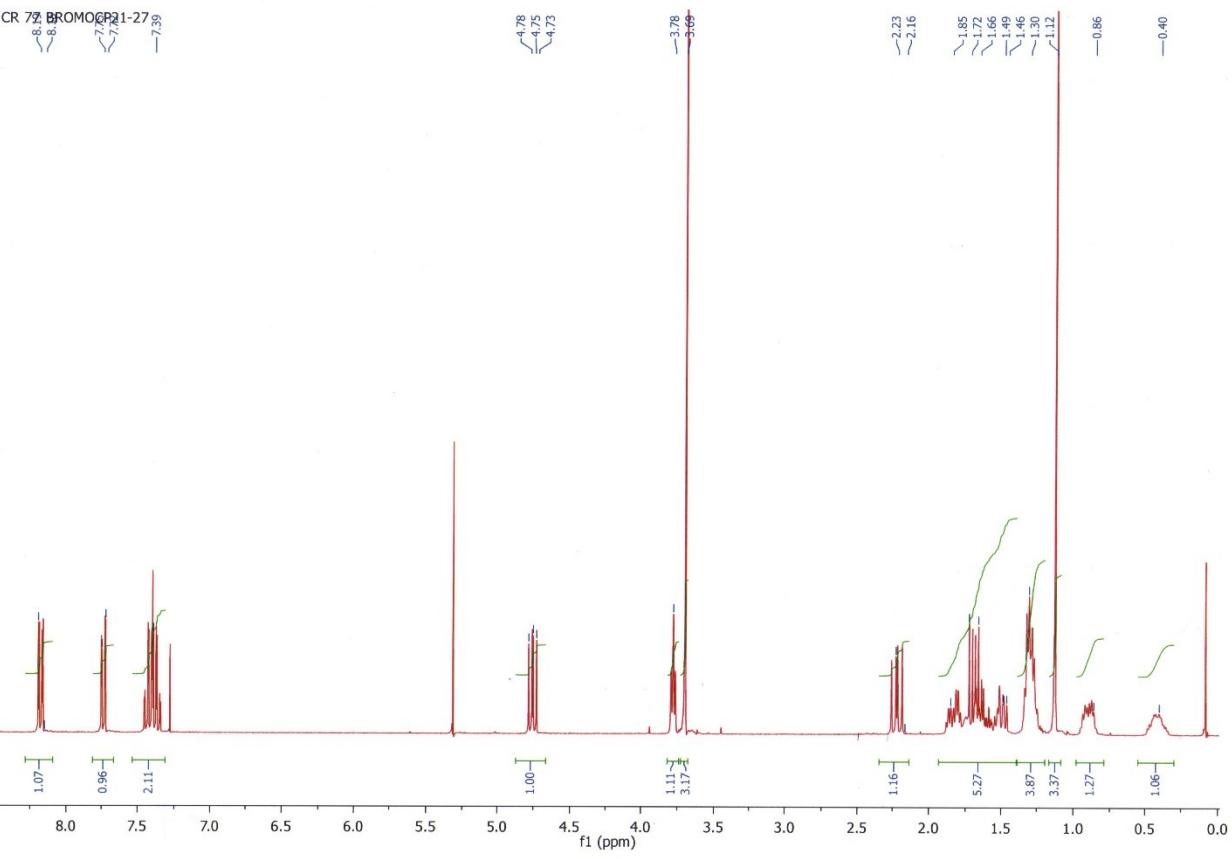
Measurable nOe correlations:

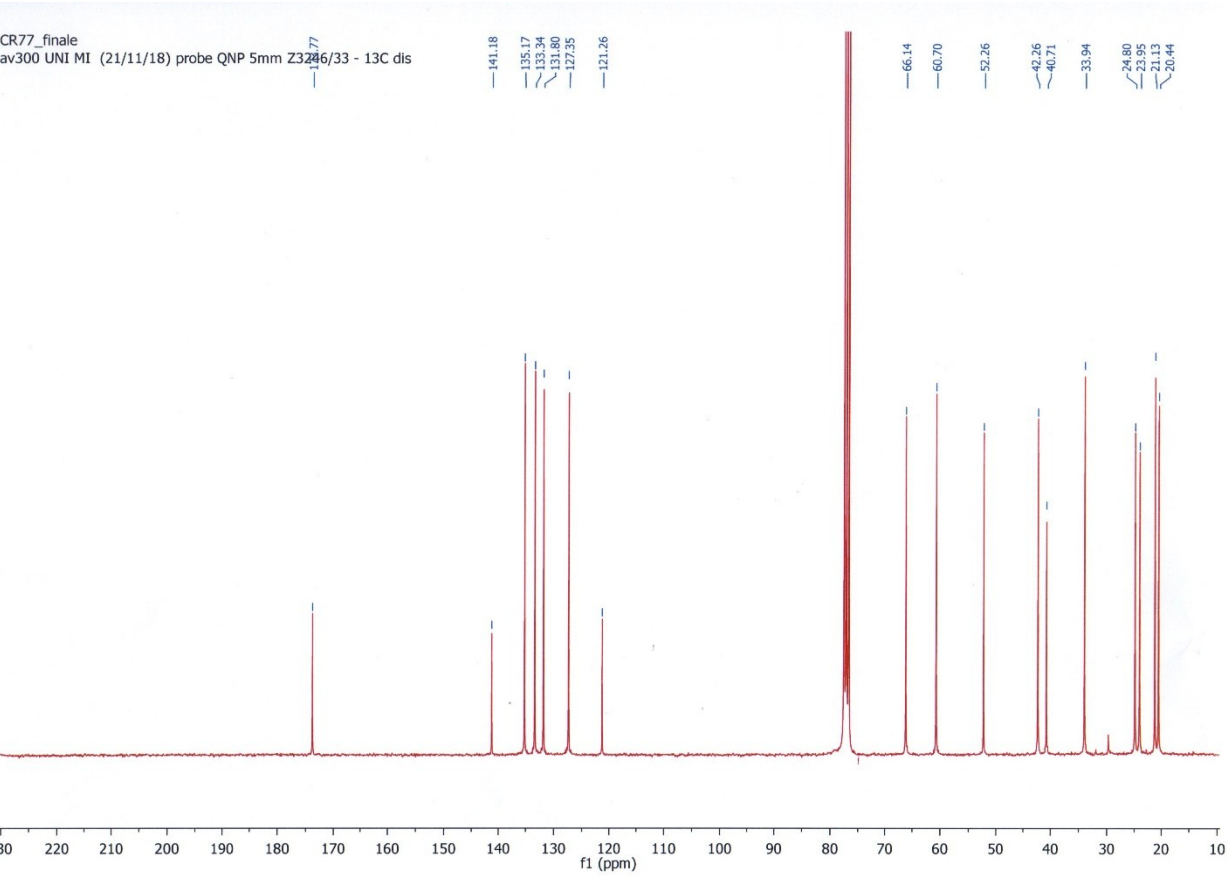
- methyl 3a (1.14 ppm) and H-7a (3.42 ppm)
- methyl 3a (1.14 ppm) and H-3b (1.93 ppm)
- H-2 (4.64 ppm) and H-3a (2.39 ppm)
- H-3b (1.93ppm) and H-7a (3.42 ppm)
- OCH_3 (3.85 ppm) and proton H-3b (1.93 ppm)


GAG_CR59
CR 59
13C-apt in CD3OD a T=300K
169.92
142.20
140.37
128.47
125.60
64.46
56.37
52.71
40.82
40.13
31.34
22.64
22.15
20.21
20.05
19.96
19.53
f1 (ppm)


CE TRAP=4
CR_59 2 (0.070) AM2 (Ar,40000.0,0.00,0.00); Cm (1:52)
1: TOF MS ES+
1.13e8
100
%
0
198.1498
199.1527
360.3241
220.1315
138.1283
361.3274
567.3102
88.0399
221.1346
358.3083
557.4652
569.3123
450.9847
697.6580
761.3108
798.9939
936.4707
1034.9926
1130.4720
100
200
300
400
500
600
700
800
900
1000
1100
m/z

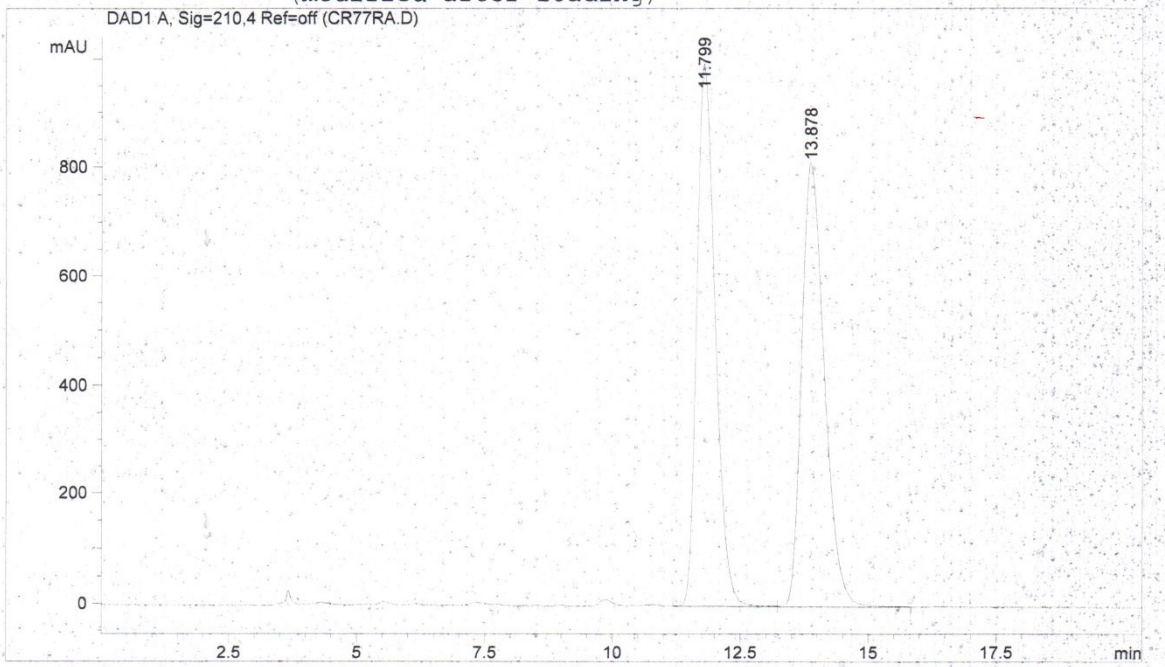
COMPOUND 6


CR 72 BROMOCP21-27
8.24
8.23
7.76
7.75
7.39
4.78
4.75
4.73
3.78
3.69
2.23
2.16
1.85
1.72
1.66
1.49
1.46
1.30
1.12
0.86
0.40
1.07
0.96
2.11
1.00
1.11
3.17
1.16
5.27
3.87
3.37
1.27
1.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


CR77_finale
av300 UNI MI (21/11/18) probe QNP 5mm Z3246/33 - 13C dis
166.77
141.18
135.17
133.34
131.80
127.35
121.26
66.14
60.70
52.26
42.26
40.71
33.94
24.80
23.95
21.13
20.44
f1 (ppm)

Data File C:\HPCHEM\1\DATA\CR77RA.D Sample Name: cr77r odh 20ipa

```
==========================================================================
Injection Date  : 26/02/19 9.16.17
Sample Name     : cr77r odh 20ipa                    Vial :   1
Acq. Operator   : 1
Acq. Method     : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 25/02/19 16.10.33  by 1
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 26/02/19 9.41.00  by 1
                  (modified after loading)
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.799 BV    0.3983 2.49544e4   989.28662  49.8658
   2  13.878 VP    0.4820 2.50887e4   808.47638  50.1342

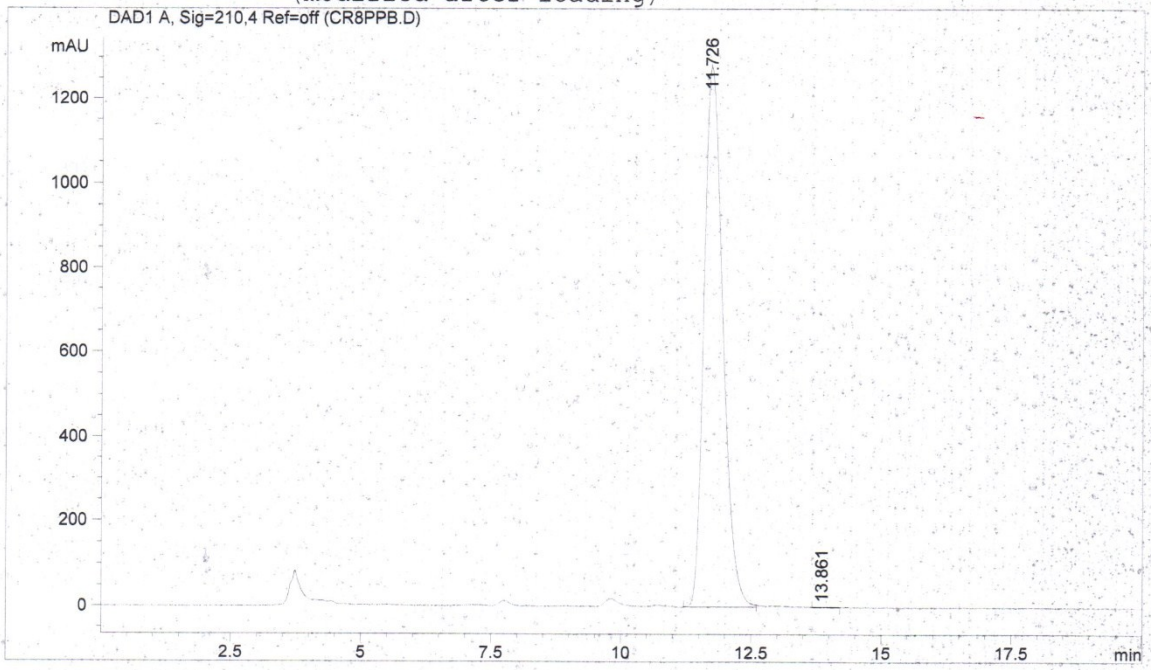
Totals :                  5.00431e4  1797.76300

 Results obtained with enhanced integrator!
==========================================================================

Instrument 1 26/02/19 9.41.09  1                        Page 1 of 1
```

a File C:\HPCHEM\1\DATA\CR8PPB.D Sample Name: cr8pp odh 20ipa

```
==========================================================================
Injection Date  : 26/02/19 9.38.53
Sample Name     : cr8pp odh 20ipa                    Vial :   1
Acq. Operator   : 1
Acq. Method     : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 26/02/19 9.41.00  by 1
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\CECE.M
Last changed    : 26/02/19 10.31.48  by 1
                  (modified after loading)
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

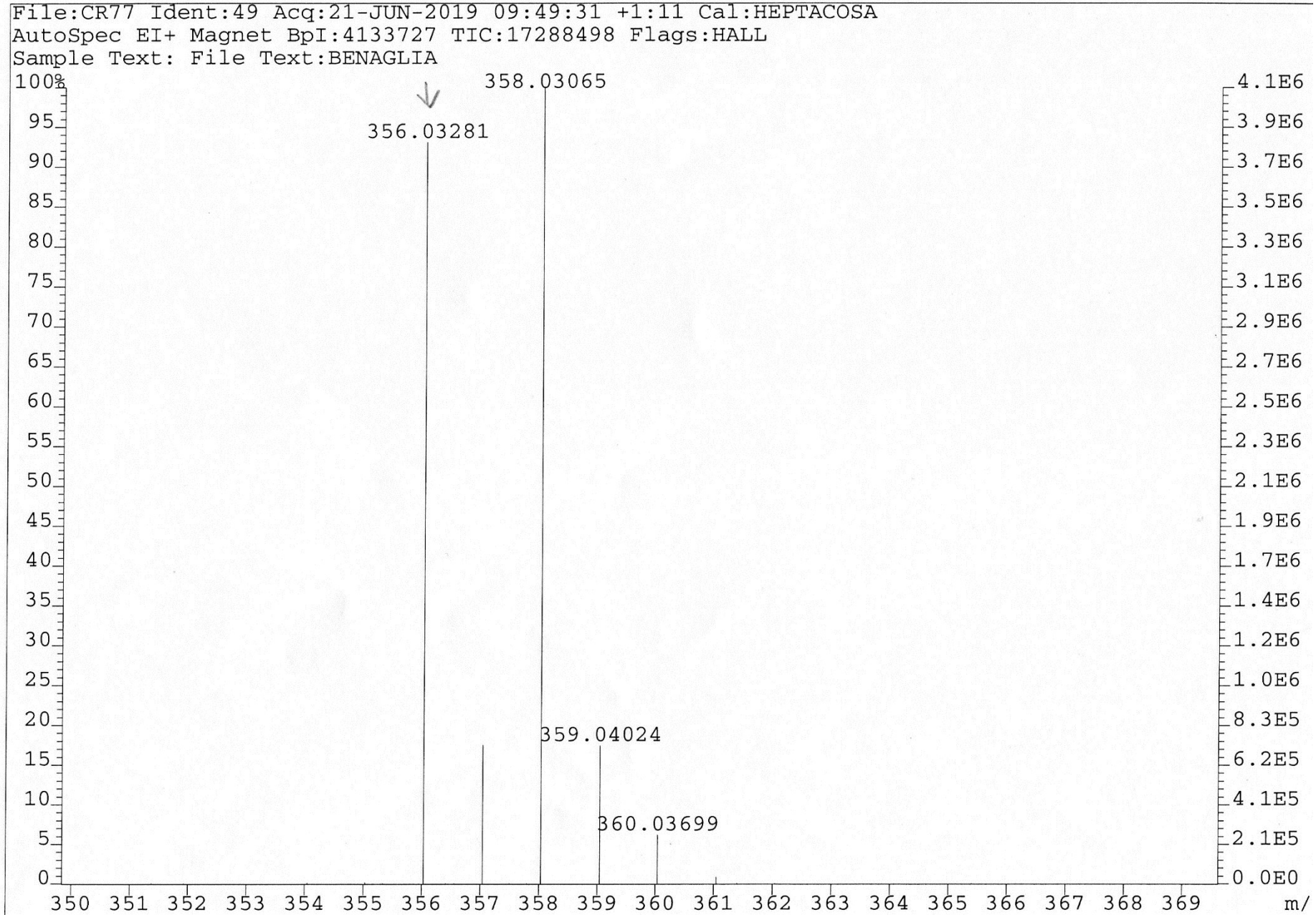
Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.726 PBA   0.3911 3.23234e4  1277.89795  99.9243
   2  13.861 BP    0.1997   24.49681    1.52283   0.0757

Totals :                  3.23479e4  1279.42078

 Results obtained with enhanced integrator!
==========================================================================

Instrument 1 26/02/19 10.31.53  1                        Page 1 of 1
```


File:CR77 Ident:49 Acq:21-JUN-2019 09:49:31 +1:11 Cal:HEPTACOSA
AutoSpec EI+ Magnet BpI:4133727 TIC:17288498 Flags:HALL
Sample Text: File Text:BENAGLIA
100%
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
356.03281
358.03065
359.04024
360.03699
4.1E6
3.9E6
3.7E6
3.5E6
3.3E6
3.1E6
2.9E6
2.7E6
2.5E6
2.3E6
2.1E6
1.9E6
1.7E6
1.4E6
1.2E6
1.0E6
8.3E5
6.2E5
4.1E5
2.1E5
0.0E0
350 351 352 353 354 355 356 357 358 359 360 361 362 363 364 365 366 367 368 369
m/