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Identification of a Novel Class of Autotaxin Inhibitors Through Cross-Screening

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Supporting Information

Contents

1. General

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[1]

1.1 Experimental Details

Reactions were carried out using conventional glassware. Room temperature was generally 18 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.

1.2 Purification of Products

Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analysed under 254 nm UV light or developed using potassium permanganate solution. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 µm silica gel.

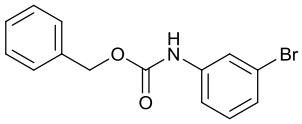
1.3 Analysis of Products

Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{1}H and ^{13}C, NMR spectra were obtained on a Bruker AV 400 at 400 MHz and 125 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^{1}H) and 77.1 ppm (^{13}C) and methanol-d4 referenced at 3.31 (^{1}H) and 49.0 ppm (^{13}C). High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University

2. General Procedures

General Procedure A: Acylation Reaction

For example, for the preparation of benzyl(3-bromophenyl)carbamate, **11**.



A mixture of 3-bromoaniline (6.3 mL, 58.1 mmol) and K_2CO_3 (8.82 g, 63.9 mmol) in 2-MeTHF (175 mL) was cooled to 0 °C before dropwise addition of benzyl chloroformate (10 mL, 70 mmol) over a period of 10 min. The reaction mixture was allowed to warm to room temperature and left to stir for 24 h. The reaction mixture was then quenched using ice water (50 mL) and saturated $NaHCO_3$ (2 mL) and extracted using EtOAc with 2% MeOH (2 x 100 mL). The organics were then collected, dried (hydrophobic frit), and concentrated under vacuum to a residue that was purified by silica chromatography (10-40% EtOAc in petroleum ether) to afford the desired product as a white solid (16.9 g, 95%).

υ_{max} (neat): 1703, 1591, 1529, 1421 cm^{-1}.

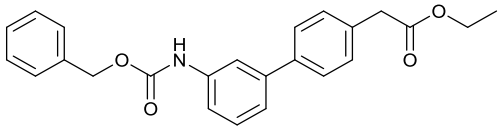
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.45 – 7.11 (m, 8H), 6.71 (s, 1H), 5.20 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.6, 138.6, 135.3, 129.8, 128.2, 128.0, 127.9, 126.0, 122.3, 121.0, 116.6, 66.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{13}BrNO_2$) $[M+H]^+$ requires *m/z* 306.0124, 308.0104 found *m/z* 306.0126, 308.0103.

General Procedure B: Suzuki-Miyaura Cross-Coupling

For example, for the preparation of ethyl 2-(3'-(((benzyloxy)carbonyl)amino)-[1,1'-biphenyl]-4-yl)acetate, **14**.



To a microwave vial ethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (650 mg, 2.24 mmol), 2'-(dimethylamino)-2-biphenylyl-palladium(II)chloride dinorbornylphosphine complex (10 mol%, 28.3 mg, 0.05 mmol), K_3PO_4 (630 mg, 3.00 mmol), and benzyl (3-bromophenyl)carbamate (300 mg, 1.00 mmol) was added. The vial was then capped and purged with N_2 before adding 1,4-dioxane (2.4 mL) and H_2O (0.6 mL). The reaction mixture was then heated to 130 °C for 30 min under microwave irradiation. The reaction mixture was allowed to return to room temperature and concentrated under vacuum to a residue that was filtered through a silica plug (EtOAc). The filtrate was collected, concentrated under vacuum to a residue that was purified using silica chromatography (40-60% EtOAc in petroleum ether) to afford the desired product as a yellow oil (358 mg, 92%).

υ_{max} (neat): 3327, 1729, 1717, 1608, 1594, 1545 cm^{-1}.

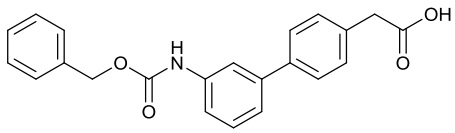
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.54 (dd, *J* = 8.2, 2.5 Hz 4H), 7.46–7.25 (m, 8H), 6.77 (s, 1H), 5.22 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.65 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6, 153.3, 141.8, 139.5, 138.2, 136.0, 133.5, 133.2, 129.7, 129.4, 128.6, 128.4, 128.3, 127.3, 127.2, 122.3, 67.1, 60.9, 41.1, 14.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{24}H_{24}NO_4$) requires *m/z* 390.1701, found *m/z* 390.1700.

General Procedure C: Hydrolysis

For example, for the preparation of 2-(3'-(3-phenylpropanamido)-[1,1'-biphenyl]-4-yl)acetic acid, **7**.



To a round-bottomed flask was added ethyl 2-(3'-(3-phenylpropanamido)-[1,1'-biphenyl]-4-yl)acetate (50 mg, 0.13 mmol), NaOH (1 M, 0.5 mL), and THF (0.5 mL). The reaction was then stirred at room temperature for 16 h. The reaction mixture was quenched using saturated NH_3Cl (2 mL), acidified with 2 M HCl, and extracted with EtOAc (2 x 10 mL). The organics were combined, dried (hydrophobic frit), and concentrated under vacuum to afford the desired product as a white solid (39 mg, 92%).

υ_{max} (neat): 3270, 3034, 1694, 1591, 1543, 1519 cm^{-1}.

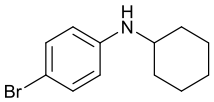
^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.27 (m, 10H), 6.76 (s, 1H), 5.23 (s, 2H), 3.71 (s, 2H). OH not observed.

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.3, 141.7, 139.8, 138.2, 136.0, 132.6, 129.8, 129.5, 128.7, 128.4, (2C) 127.4, 122.4, 67.2, 40.5. 3xC not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{20}NO_4$) requires *m/z* 362.1392, found *m/z* 362.1390.

General Procedure D: Reductive Amination

For example, for the preparation of 4-bromo-*N*-cyclohexyaniline, **19**.



To a round-bottomed flask was added 4-bromoaniline (1.0 g, 5.81 mmol), cyclohexanone (0.8 mL, 7.56 mmol), AcOH (0.5 mL), and 2-MeTHF (25 mL). $NaBH(OAc)_3$ (1.83 g, 8.72 mmol) was then added and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with Na_2HCO_3 (20 mL) and extracted with $CHCl_3$ (3 x 20 mL). The organics were collected, washed with brine (50 mL), dried (Na_2SO_4), and concentrated under vacuum to give a residue that was purified by silica chromatography (15-30% EtOAc in petroleum ether) to afford the desired product as a white solid (1.5 g, 93%).

υ_{max} (neat): 3450, 2926, 2850, 1591, 1494, 1351 cm^{-1}.

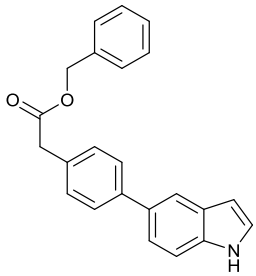
^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 8.7 Hz, 2H), 3.19 (tt, *J* = 10.2, 3.7 Hz, 1H), 2.03 (m, 2H), 1.80 – 1.71 (m, 2H), 1.69 – 1.61 (m, 1H), 1.54 (s, 1H), 1.42 – 1.08 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.9, 131.4, 114.1, 107.6, 51.3, 32.8, 25.4, 24.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{17}BrN$) requires *m/z* 254.0542, 256.0518 found *m/z* 256.0518, 256.0518.

General Procedure E: Indole Acylation

For example, for the preparation of benzyl 5-bromo-1*H*-indole-1-carboxylate, **8**.



To a round-bottomed flask was added 2-(4-(1*H*-indol-6-yl)phenyl)acetic acid (260 mg, 1.0 mmol) and DMF (3 mL) and cooled to 0 °C. NaH (49 mg, 2.0 mmol) was then added portion wise and the mixture was stirred for 1 hr at 0 °C. *N*-(Benzyloxycarbonyloxy)succinimide (373.8 mg, 1.5 mmol) was then added and allowed to warm to room temperature and stirred for 16 h. The reaction was quenched with ice H_2O (10 mL) and saturated $NaHCO_3$ (10 mL) and extracted using EtOAc (2 x 100 mL). The organics were collected, dried (hydrophobic frit) and concentrated under vacuum to a residue that was purified using silica chromatography (5-20% EtOAc in petroleum ether) to afford the desired product as a red solid (59 mg, 17%).

υ_{max} (neat): 2922, 1734, 1716 cm^{-1}.

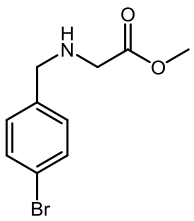
^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.87 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.47 (s, 2H), 7.41 – 7.33 (m, 6H), 7.27 (dd, *J* = 3.1, 2.5 Hz, 1H), 6.65 – 6.62 (m, 1H), 5.19 (s, 2H), 3.75 (s, 2H). NH not observed.

^{13}C NMR (101 MHz, DMSO): δ 171.1, 140.5, 136.1, 135.5, 132.1, 131.0, 129.8, 128.4, 128.2, 128.9, 127.9 (2C), 126.6, 126.0, 120.2, 118.0, 111.7, 101.5, 65.8.

HRMS: exact mass calculated for $[M-H]^+$ ($C_{18}H_{18}NO_2$) requires *m/z* 340.1343, found *m/z* 340.1334.

General Procedure F: Reductive Amination

For example, for the preparation of methyl (4-bromobenzyl)glycinate **34**.



To a round-bottomed flask was added 4-bromobenzaldehyde (0.5 g, 2.7 mmol), glycine methyl ester hydrochloride (0.34 g, 2.7 mmol), EtOH (7.5 mL), NEt_3 (0.726 mL, 78.3 mmol) under N_2 and stirred at 50 °C for 1h. EtOH was removed and the residue was redissolved in MeOH (7.5 mL) and cooled to 0° C. $NaBH_4$ (0.112 g, 2.97 mmol) was added portion wise and the reaction stirred at room temperature for 2 h. The reaction was concentrated to dryness and H_2O (20 mL) added. The suspension was extracted using CH_2Cl_2 (2 x 25 mL). The organics were then collected, washed with brine (15 mL), dried (hydrophobic frit), and concentrated under vacuum to give a residue that was purified by silica chromatography to afford the desired product as a clear yellow oil (0.456 g, 66%).

υ_{max} (neat): 3230, 2017, 1057 cm^{-1}.

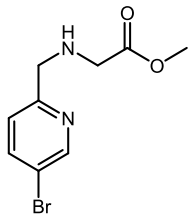
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 2H), 3.72 (s, 3H), 3.39 (s, 2H), 1.96 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2, 138.0, 131.2, 129.3, 120.3, 51.9, 51.2, 49.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{10}H_{13}BrNO_2$) requires *m/z* 258.0124, 260.0104, found *m/z* 258.0127, 260.0103.

General Procedure G: Reductive Amination

For example, for the preparation of methyl 2-(((5-bromopyridin-2-yl) methyl) amino) acetate, **43**.



To a round-bottomed flask was added glycine methyl ester hydrochloride (1.23 g, 9.8 mmol) and MeOH (10 mL). NEt_3 (1.16 mL, 8.3 mmol) was added with stirring. The resulting solution was added drop wise to a solution of 5-bromopicolinaldehyde (0.91 g, 4.9 mmol) in MeOH (15 mL) under N_2. After 30 min $NaBH(OAc)_3$ (2.49 g, 11.7 mmol) was added portion wise. The reaction mixture was stirred at room temperature for 16 h and then quenched using saturated $NaHCO_3$ (40 mL). The suspension was extracted using CH_2Cl_2 (2 x 25 mL). The organics were then collected, washed with brine (25 mL), dried (hydrophobic frit), and

concentrated under vacuum to give a residue that was purified by silica chromatography to afford the desired product as a clear yellow oil (1.09 g, 85 %).

υ_{max} (neat): 1735, 1207, 729 cm^{-1}.

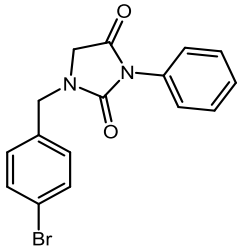
^{1}H NMR (400 MHz, $CDCl_3$):δ 8.62 (d, J = 2.2 Hz, 1H), 7.78 (dd, J = 8.3, 2.4 Hz, 1H), 7.27 (d, J = 9.0 Hz, 1H), 3.92 (s, 2H), 3.74 (s, 3H), 3.48 (s, 2H).NH not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7, 156.4, 150.4, 139.3, 123.9, 119.4, 53.3, 52.1, 49.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_9H_{12}BrN_2O_2$) requires *m/z* 259.0077, found *m/z* 259.0078.

General Procedure H – Hydantoin Synthesis

For example, for the preparation of 1-(4-bromobenzyl)-3-phenylimidazolidine-2,4-dione, **35.**



To a round-bottomed flask was added methyl 2-((4-bromobenzyl) amino) acetate (0.4 g, 1.55 mmol), CH_2Cl_2 (38 mL) and phenyl isocyanate (0.3 mL, 3.08 mmol). The clear solution was stirred at room temperature for 16 h. The reaction mixture was concentrated and azeotroped three times with CH_2Cl_2 (10 mL). The mixture was redissolved in CH_2Cl_2 (15 mL). CF_3CO_2H (3.16 mL, 41.0 mmol) was added and the solution stirred for 2 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (20 mL) and extracted using CH_2Cl_2 (3x 20 mL). The organics were collected, dried (hydrophobic frit) and concentrated under vacuum to a residue that was purified using silica chromatography (30% EtOAc in petroleum ether) to afford the desired product as a yellow solid (0.34 g, 60 %).

υ_{max} (neat): 1647, 1228, 696 cm^{-1}.

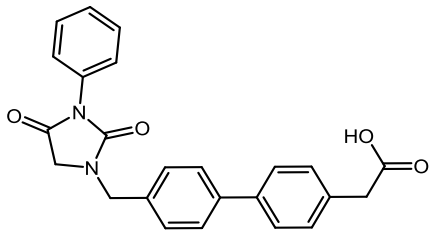
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 – 7.50 (m, 2H), 7.50 – 7.34 (m, 5H), 7.23 – 7.18 (m, 2H), 4.60 (s, 2H), 3.90 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5, 155.8, 134.4, 132.4, 131.7, 130.1, 129.2, 128.3, 126.2, 122.5, 49.1, 46.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{14}BrN_2O_2$) requires *m/z* 345.0233, 347.0213 found *m/z* 345.0239, 347.0216.

General Procedure I – Suzuki-Miyaura and Hydrolysis

For example, for the preparation of 2-(4'-((2, 4-dioxo-3-phenylimidazolidin-1-yl)methyl)-[1,1'-biphenyl]-4-yl)acetic acid, **9**.



To a round-bottomed flask was added 1-(4-bromobenzyl)-3-phenylimidazolidine-2,4-dione (0.18 g, 0.52 mmol), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (0.16 g, 0.57 mmol), $Pd_2(dba)_3$ (1 mol %, 5 mg, 0.005 mmol), K_3PO_4 (0.19 g, 0.89 mmol) and PCy_3 (2.4 mol %, 4 mg, 0.01 mmol). The flask was purged N_2 before adding before adding 1,4-dioxane (4 mL) and H_2O (1.3 mL).The reaction mixture was heated to 100 °C 16 h. The reaction mixture was allowed to return to room temperature and concentrated under vacuum to a residue that was filtered through a silica plug (EtOAc). The filtrate and washings were collected, concentrated under vacuum to a residue that was purified using silica chromatography (50 % EtOAc in petroleum ether) to afford methyl 2-(4'-((2,4-dioxo-3-phenylimidazolidin-1-yl)methyl)-[1,1'-biphenyl]-4-yl)acetate (41 mg, 19 %) as a white solid. Methyl 2-(4'-((2,4-dioxo-3-phenylimidazolidin-1-yl)methyl)-[1,1'-biphenyl]-4-yl)acetate (41 mg, 0.1 mmol) was dissolved in THF:H_2O (3:1, 3 mL), LiOH (8 mg, 0.2 mmol) was added and the reaction stirred at room temperature for 3 h. The solution was acidified using HCl (1M, 2 mL) and extracted using EtOAc (2 x 15 mL), and washed with brine (10 mL). The organics were collected, dried (hydrophobic frit) and concentrated under vacuum to afford the desired product as a white powder (25 mg, 12 %).

υ_{max} (neat): 2922, 1716, 1684, 1463 cm^{-1}.

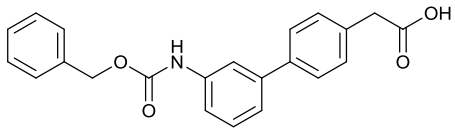
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.33 (m, 13H), 4.69 (s, 2H), 3.96 (s, 2H), 3.73 (s, 2H), 1.71 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.8, 155.7, 141.0, 139.6, 134.3, 131.9, 130.0, 129.2, 128.9, 128.3, 127.9, 127.4, 126.2, 49.2, 46.8, 15.3. 2xC coincident.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{24}H_{21}N_2O_4$) requires *m/z* 401.1501, found *m/z* 401.1499.

3. Characterisation Data

Compound 7: 2-(3'-(3-phenylpropanamido)-[1,1'-biphenyl]-4-yl)acetic acid.



Prepared according to general procedure C using ethyl 2-(3'-(3-phenylpropanamido)-[1,1'-biphenyl]-4-yl)acetate (50 mg, 0.13 mmol), NaOH (1 M, 0.5 mL) and THF (0.5 mL) to afford the desired product (39 mg, 92%) as a white solid.

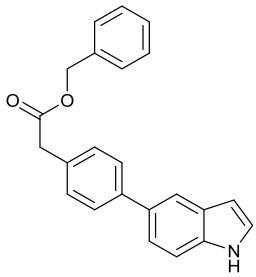
υ_{max} (neat): 3270, 3034, 1694, 1591, 1543, 1519 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.27 (m, 10H), 6.76 (s, 1H), 5.23 (s, 2H), 3.71 (s, 2H). OH not observed.

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.3, 141.7, 139.8, 138.2, 136.0, 132.6, 129.8, 129.5, 128.7, 128.4 (2C) 127.4, 122.4, 67.2, 40.5. 3xC not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{20}NO_4$) requires *m/z* 362.1392, found *m/z* 362.1390.

Compound 8: Benzyl 5-bromo-1*H*-indole-1-carboxylate.



Prepared according to general procedure E using 2-(4-(1H-indol-6-yl)phenyl)acetic acid (150 mg, 0.60 mmol), DMF (5 mL), NaH 60% w/w (48 mg, 2.0 mmol), and N-(benzyloxycarbonyloxy)succinimide (223.1 mg, 0.90 mmol) to give the desired product (147.8 mg, 72%) as a red solid.

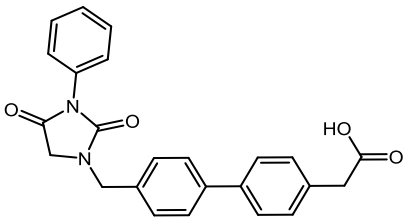
υ_{max} (neat): 2922, 1734, 1716 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.87 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.47 (s, 2H), 7.41 – 7.33 (m, 6H), 7.27 (dd, *J* = 2.5, 3.1Hz, 1H), 6.65 – 6.62 (m, 1H), 5.19 (s, 2H), 3.75 (s, 2H). NH not observed.

^{13}C NMR (101 MHz, DMSO): δ 171.1, 140.5, 136.1, 135.5, 132.1, 131.0, 129.8, 128.4, 128.2, 128.9, 127.9 (2C), 126.6, 126.0, 120.2, 118.0, 111.7, 101.5, 65.8.

HRMS: exact mass calculated for $[M-H]^+$ ($C_{18}H_{18}NO_2$) requires *m/z* 340.1343, found *m/z* 340.1334.

Compound 9: 2-(4'-((2, 4-dioxo-3-phenylimidazolidin-1-yl)methyl)-[1,1'-biphenyl]-4-yl)acetic acid



Prepared according to general procedure H using 1-(4-bromobenzyl)-3-phenylimidazolidine-2,4-dione (0.18 g, 0.52 mmol), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (0.16 g, 0.57 mmol), $Pd_2(dba)_3$ (1 mol %, 5 mg, 0.005 mmol), K_3PO_4 (0.19 g, 0.89 mmol), PCy_3 (2.4 mol %, 4 mg, 0.01 mmol), 1,4-dioxane (1.3 mL) H_2O (0.7 mL), and LiOH (8 mg, 0.2 mmol) to afford the desired product as a white powder (25 mg, 12%).

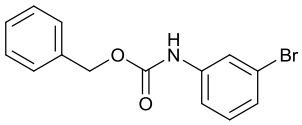
υ_{max} (neat): 3415 (broad), 1600, 1485 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.33 (m, 13H), 4.69 (s, 2H), 3.96 (s, 2H), 3.73 (s, 2H), 1.71 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.8, 155.7, 141.0, 139.6, 134.3, 131.9, 130.0, 129.2, 128.9, 128.3, 127.9, 127.4, 126.2, 49.2, 46.8, 15.3. 2xC coincident.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{24}H_{21}N_2O_4$) requires *m/z* 401.1496, found *m/z* 401.1499.

Compound 11: Benzyl(3-bromophenyl)carbamate.



Prepared according to general procedure A using 3-bromoaniline (6.3 mL, 58.1 mmol), K_2CO_3 (8.82 g, 63.9 mmol), 2-MeTHF (175 mL), and benzyl chloroformate (10 mL, 70 mmol) to afford the desired product as a white solid (16.9 g, 95%).

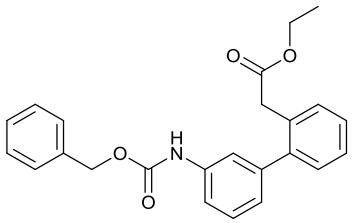
υ_{max} (neat): 1703, 1591, 1529, 1421 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.45 – 7.11 (m, 8H), 6.71 (s, 1H), 5.20 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.6, 138.6, 135.3, 129.8, 128.2, 128.0, 127.9, 126.0, 122.3, 121.0, 116.6, 66.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{13}BrNO_2$) requires *m/z* 306.0124, 308.0104 found *m/z* 306.0126, 308.0103.

Compound 12: Ethyl 2-(3'-(((benzyloxy)carbonyl)amino)-[1,1'-biphenyl]-2-yl)acetate.



Prepared according to general procedure B using ethyl 2-(3-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolane-2-yl)phenyl)acetate (547.2 mg, 1.88 mmol), benzyl-(3-bromophenyl)acetate (305.7 mg, 1.00 mmol), K_3PO_4 (686.0 mg, 3.23 mmol), 2'-(dimethylamino)-2-biphenylyl-palladium(II)chloride dinorbornylphosphine complex (10 mol%, 56.1 mg, 0.01 mmol), 1,4-dioxane (2.4 mL), and H_2O (0.6 mL) to afford the desired product as a yellow oil (212.4 mg, 55%).

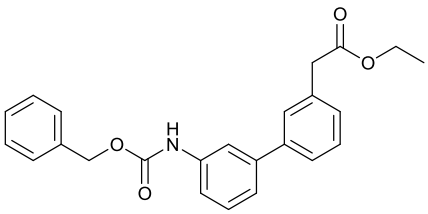
υ_{max} (neat): 1732, 1712, 1589, 1544, 1539 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.28 (m, 12H), 7.04 – 7.00 (m, 1H), 6.68 (s, 1H), 5.20 (s, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.58 (s, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.6, 171.4, 141.6, 141.4, 131.5, 131.4, 129.8, 129.6, 128.4, 128.1, 127.9, 127.8, 127.2, 126.6, 124.0, 124.0, 66.6, 60.2, 38.4, 13.6. 2xC coincident.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{24}H_{24}NO_4$) requires *m/z* 390.1701, found *m/z* 390.1700.

Compound 13: Ethyl 2-(3'-(((benzyloxy)carbonyl)amino)-[1,1'-biphenyl]-3-yl)acetate.



Prepared according to general procedure B using ethyl 2-(3-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolane-2-yl)phenyl)acetate (646.2 mg, 2.23 mmol), benzyl-(3-bromophenyl)acetate (307 mg, 1.00 mmol), K_3PO_4 (637 mg, 3.00 mmol), 2'(dimethylamino)-2-biphenylyl-palladium(II)chloride dinorbornylphosphine complex (10 mol%, 0.01 mmol, 56.7 mg), 1,4-dioxane (2.4 mL), and H_2O (0.6 mL) to afford the desired product as a yellow oil (357.8 mg, 92%).

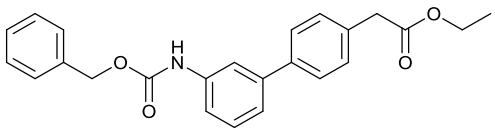
υ_{max} (neat): 1732, 1604, 1546, 1496, 1408 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.51 – 7.26 (m 11H), 6.78 (s, 1H), 5.23 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 2H), 1.27 (t, 3H). NH not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 152.9, 141.5, 140.5, 137.7, 135.6, 134.1, 128.9, 128.5, 128.1, 127.9, 127.8, 127.7 (2C), 125.5, 122.0, 117.2, 117.1, 66.6, 60.4, 41.0, 13.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{24}H_{24}NO_4$) requires *m/z* 390.1701, found *m/z* 390.1700.

Compound 14: Ethyl 2-(3'-(((benzyloxy)carbonyl)amino)-[1,1'-biphenyl]-4-yl)acetate.



Prepared according to general procedure B using ethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (650 mg, 2.24 mmol), 2'-(dimethylamino)-2-biphenylyl-palladium(II)chloride dinorbornylphosphine complex (10 mol%, 28.3 mg, 0.05 mmol), K_3PO_4 (630 mg, 3.00 mmol), and benzyl (3-bromophenyl)carbamate (300 mg, 1.00 mmol), 1,4-dioxane (2.4 mL) and H_2O (0.6 mL) to afford the desired product as a yellow oil (358 mg, 92%).

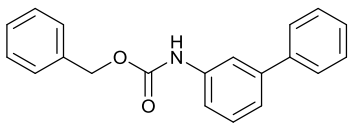
υ_{max} (neat): 3327, 1729, 1717, 1608, 1594, 1545 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.54 (dd, *J* = 8.2, 2.5 Hz, 4H), 7.46 – 7.25 (m, 8H), 6.77 (s, 1H), 5.22 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.65 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6, 153.3, 141.8, 139.5, 138.2, 136.0, 133.5, 133.2, 129.7, 129.4, 128.6, 128.4, 128.3, 127.3, 127.2, 122.3, 67.1, 60.9, 41.1, 14.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{24}H_{24}NO_4$) requires *m/z* 390.1701, found *m/z* 390.1700.

Compound 15: Benzyl [1,1'-biphenyl]-3-ylcarbamate.



Prepared according to general procedure B using phenylboronic acid (365.6 mg, 3.00 mmol), benzyl-(3-bromophenyl)acetate (306.2 mg, 1.00 mmol), K_3PO_4 (636.5 mg, 3.00 mmol), 2'(dimethylamino)-2-biphenylyl-palladium(II)chloride dinorbornylphosphine complex (10 mol%, 55.6 mg, 0.01 mmol), 1,4-dioxane (2.4 mL), and H_2O (0.6 mL) to afford the desired product as a yellow oil (220.2 mg, 73%).

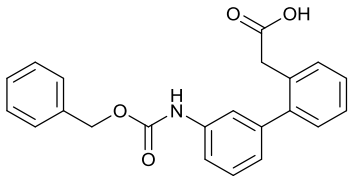
υ_{max} (neat): 1708, 1597, 1539, 1496 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.47 – 7.28 (m, 11H), 6.73 (s, 1H), 5.23 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.0, 141.8, 140.2, 137.7, 135.5, 128.9, 128.2 (2C), 127.9, 127.8, 127.0, 126.7, 121.9, 117.1, 117.0, 66.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{18}NO_2$) requires *m/z* 304.1335, found *m/z* 304.1332.

Compound 16: 2-(3'-(((benzyloxy)carbonyl)amino)-[1,1'-biphenyl]-2-yl)acetic acid



Prepared according to general procedure C using ethyl 2-(3'-(((benzyloxy)carbonyl)amino)-[1,1'-biphenyl]-2-yl)acetate (46.1 mg 0.18 mmol), NaOH (0.5 mL), and THF (0.5 mL) to afford the desired product (39.3 mg, 92 %) as a brown solid.

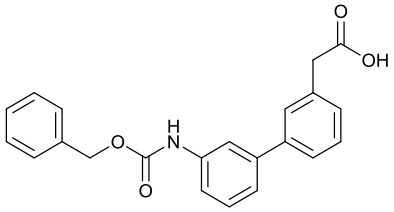
υ_{max} (neat): 1701, 1535, 1408 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.28 (m, 12H), 7.02 – 6.98 (m, 1H), 5.17 (s, 2H), 3.61 (s, 2H). NH and OH not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.0, 141.6, 141.3, 137.3, 135.5, 130.8, 130.0, 129.7, 128.5, 128.1, 127.9, 127.9, 127.3, 126.9, 124.0, 66.7, 38.1. 3xC not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{20}NO_4$) requires *m/z* 360.1241, found *m/z* 360.1240.

Compound 17: 2-(3'-(((benzyloxy)carbonyl)amino)-[1,1'-biphenyl]-3-yl)acetic acid.



Prepared according to general procedure C using ethyl 2-(3'-(((benzyloxy)carbonyl)amino)-[1,1'-biphenyl]-3-yl)acetate (48.1 mg, 1.24 mmol), NaOH (0.5 mL), and THF (0.5 mL) to afford the desired product as an off white solid (34.5 mg, 77%).

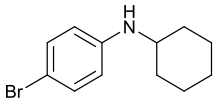
υ_{max} (neat): 1697, 1604, 1531, 1508 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.50 (s, 2H), 7.45 – 7.28 (m, 11H), 6.76 (s, 1H), 5.23 (s, 2H), 3.73 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.7, 141.8, 141.1, 138.2, 136.0, 133.9, 129.5, 129.0, 128.7, 128.5, 128.4, 128.3 (2C), 126.2, 122.5, 67.2, 41.0. 3xC not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{20}NO_4$) requires *m/z* 360.1241, found *m/z* 360.1240.

Compound 19: 4-bromo-*N*-cyclohexyaniline.



Prepared according to general procedure D using 4-bromoaniline (1.0 g, 5.81 mmol), cyclohexanone (0.8 mL, 7.56 mmol), AcOH (0.5 mL), 2-MeTHF (25 mL), and NaBH-$(OAc)_3$ (1.83 g, 8.72 mmol) to afford the desired product as a white solid (1.5 g, 93%).

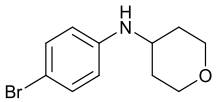
υ_{max} (neat): 3450, 2926, 2850, 1591, 1494, 1351 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 8.7 Hz, 2H), 3.23 – 3.16 (m, 1H), 2.03 (m, 2H), 1.80 – 1.71 (m, 2H), 1.69 –1.61 (m, 1H), 1.54 (s, 1H), 1.42 – 1.08 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.9, 131.4, 114.1, 107.6, 51.3, 32.8, 25.4, 24.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{17}BrN$) requires *m/z* 254.0542, 256.0518 found *m/z* 256.0518, 256.0518.

Compound 20: *N*-(4-bromophenyl)tetrahydro-2*H*-pyran-4-amine.



Prepared according to general procedure D using 4-bromoaniline (1.0 g, 5.81 mmol), tetrahydro-4*H*-pyran-one (0.7 mL, 7.56 mmol), AcOH (0.5 mL), and $NaBH(OAc)_3$ (1.83 g, 8.72 mmol) to afford the desired product as an off white solid (1.5 g, 98%).

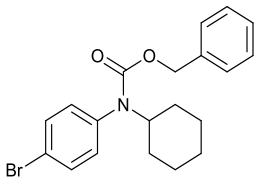
υ_{max} (neat): 3336, 2927, 2833, 1716, 1591, 1512, 1485 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.9 Hz, 2H), 6.48 (d, *J* = 8.8 Hz, 2H), 4.03 – 3.94 (m, 2H), 3.54 – 3.39 (m, 4H), 2.00 (d, *J* = 11.5 Hz, 2H), 1.40-1.50 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.2, 131.5, 114.4, 108.4, 66.3, 48.7, 32.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{11}H_{15}BrNO$) requires *m/z* 256.0332, 258.0311 found *m/z* 256.0335, 258.0310.

Compound 21: Benzyl(4-bromophenyl)(cyclohexyl)carbamate.



Prepared according to general procedure A using 4-bromo-*N*-cyclohexylaniline (504.1 mg, 1.97 mmol), K_2CO_3 (301.4 mg, 2.16 mmol), DMC (9 mL), H_2O (0.05 mL), and benzyl chloroformate (0.3 mL, 2.16 mmol) to afford the desired product as a white solid (223.5 mg, 30%).

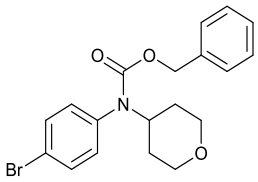
υ_{max} (neat): 1597, 1489, 1452, 1396 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 3H), 7.18 (s, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 5.09 (s, 2H), 4.22 – 4.10 (m, 1H), 1.85 (dd, *J* = 12.8, 1.6 Hz, 2H), 1.73 (dd, *J* = 12.3, 1.6 Hz, 2H), 1.57 (m, 1H), 1.33 (pent, *J* = 13.0 Hz, 2H), 1.14 – 1.05 (m, 2H), 0.97 – 0.86 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7, 137.2, 136.3, 131.4, 131.3, 127.9, 127.3, 126.8, 120.9, 66.4, 56.4, 31.5, 25.3, 24.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{23}BrNO_2$) requires *m/z* 388.0907, 390.0886 found *m/z* 388.0904, 390.0879.

Compound 22: Benzyl(4-bromophenyl)(tetrahydro-2*H*-pyran-4-yl)carbamate.



Prepared according to general procedure D using 4-bromophenyl)(tetrahydro-2*H*-pyran-4-amine (510 mg, 1.97 mmol), K_2CO_3 (290 mg, 2.14 mmol), DCE (9 mL), H_2O (0.05 mL), and benzyl chloroformate (0.3 mL, 2.15 mmol) to afford the desired product as an orange solid (448.0 mg, 60%).

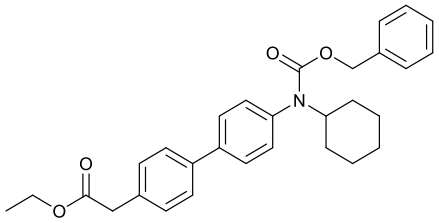
υ_{max} (neat): 2970, 1732, 1502, 1473, 1413 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 6.6 Hz, 2H), 7.38 – 7.28 (m, 3H), 7.17 (s, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 5.09 (s, 2H), 4.40 (m, 1H), 3.94 (dd, *J* = 11.5, 4.6 Hz, 2H), 3.44 (t, *J* = 12.7 Hz, 2H), 1.77 – 1.73 (m, 2H), 1.51–1.42 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 136.7, 136.1, 131.6, 131.2, 127.9, 127.4, 126.9, 121.3, 66.8, 66.7, 53.6, 31.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{21}BrNO_3$) requires *m/z* 390.0699, 392.0679 found *m/z* 390.0699, 392.0677.

Compound 23: Ethyl 2-(4'-(((benzyloxy)carbonyl)(cyclohexyl)amino)-[1,1'-biphenyl]-4-yl)acetate].



Prepared according to general procedure B using ethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (300 mg, 1.03 mmol), benzyl(4-bromophenyl)(cyclohexyl)carbamate (200 mg, 0.51 mmol), K_3PO_4 (330 mg, 1.55 mmol), 2'(dimethylamino)-2-biphenylyl-palladium(II)chloride dinorbornylphosphine complex (10 mol%, 28.9 mg, 0.01 mmol), 1,4-dioxane (2.4 mL), and H_2O (0.6 mL) to afford the desired product as a yellow oil (170 mg, 70%).

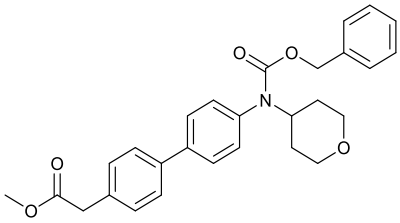
υ_{max} (neat): 1733, 1695, 1497, 1398, 1301 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.53 (m, 5H), 7.39 – 7.30 (m, 4H), 7.22 – 7.16 (m, 4H), 5.14 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 2H), 1.93 (d, *J* = 11.1 Hz, 2H), 1.77 (d, *J* = 13.3 Hz, 2H), 1.45 – 1.15 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 154.9, 139.4, 138.7, 136.6, 132.9, 129.8, 129.2, 129.2, 127.8, 127.1, 126.8, 126.7, 66.3, 60.4, 56.6, 40.6, 31.5, 25.4, 24.8, 24.4, 13.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{30}H_{34}NO_4$) $[M+H]^+$ requires *m/z* 472.2482, found *m/z* 472.2474.

Compound 24: Methyl 2-(4'-(((benzyloxy)carbonyl)(tetrahydro-2*H*-pyran-4-yl)amino)-[1,1'-biphenyl]-4-yl)acetate



Prepared according to general procedure B using benzyl (4-bromophenyl)(tetrahydro-2*H*-pyran-4-yl)carbamate (250 mg, 0.64 mmol), K_3PO_4 (408.2 mg, 1.92 mmol), 2'(dimethylamino)-2-biphenylyl-palladium(II)chloride dinorbornylphosphine complex (10 mol %, 18 mg, 0.03 mmol), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (212 mg, 0.77 mmol), 1,4-dioxane (2.4 mL) and water

(0.4 mL). After 72 h, the reaction mixture was subjected to the purification outlined in general procedure D to afford the desired product as white solid (160 mg 54 %).

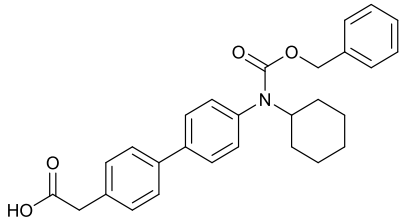
υ_{max} (neat): 1732, 1699, 1498, 1404, 1381 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.54 (m, 4H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.25 (m, 3H), 7.20 (d, *J* = 5.5 Hz, 2H), 7.17 – 7.12 (m, 2H), 5.14 (s, 2H), 4.50 – 4.44 (m, 1H), 3.96 (dd, *J* = 11.4, 4.4 Hz, 2H), 3.73 (s, 3H), 3.69 (s, 2H), 3.45 – 3.44 (m, 2H), 1.81 (dd, *J* = 12.3, 2.2 Hz, 2H), 1.55-1.65 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4, 155.0, 139.8, 138.7, 136.8, 136.3, 132.9, 129.8, 129.3, 127.9, 127.3, 127.0, 126.8, 66.9, 66.5, 53.7, 51.6, 40.3, 31.4. 1xC coincident.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{29}H_{30}NO_5$) requires *m/z* 460.2112, found *m/z* 460.2118.

Compound 25: 2-(4'-(((benzyloxy)carbonyl)(cyclohexyl)amino-[1,1'biphenyl]-4-yl)acetic acid.



Prepared according to general procedure C ethyl 2-(4'-(((benzyloxy)carbonyl)(cyclohexyl)amino)-[1,1'-biphenyl]-4-yl)acetate] (50 mg, 1.06 mmol), NaOH (0.5 mL), and THF (0.5 mL) to afford the desired product as a yellow oil (40.4 mg, 86%).

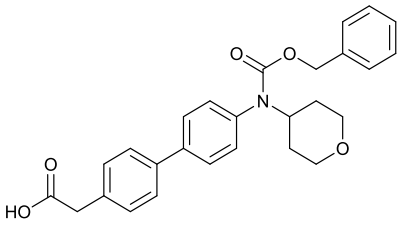
υ_{max} (neat): 2930, 1699, 1550, 1403, 1313 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (dt, *J* = 17.8, 8.7 Hz, 4H), 7.48 – 7.09 (m, 9H), 5.15 (s, 2H), 4.22 (t, *J* = 11.9 Hz, 1H), 3.71 (d, *J* = 16.0 Hz, 2H), 1.94 (d, *J* = 11.1 Hz, 2H), 1.78 (d, *J* = 13.1 Hz, 2H), 1.60 (d, *J* = 12.9 Hz, 1H), 1.50 – 1.09 (m, 5H). OH not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.4, 155.1, 139.3, 139.0, 137.4, 136.5, 132.1, 129.8, 129.4, 127.8, 127.1, 126.9, 126.8, 115.1, 66.4, 56.7, 40.2, 31.5, 25.4, 24.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{28}H_{30}NO_4$) requires *m/z* 444.2175, found *m/z* 444.2168.

Compound 26: 2-(4'-(((benzyloxy)carbonyl)(tetrahydro-2*H*-pyran-4-yl)amino)-[1,1'-biphenyl]-4-yl)acetic acid



Prepared according to general procedure C using methyl 2-(4'-(((benzyloxy)carbonyl)(tetrahydro-2*H*-pyran-4-yl)amino)-[1,1'-biphenyl]-4-yl)acetate (160 mg, 0.35 mmol), NaOH (1.6 mL), THF (1.6 mL) to afford the desired product as a brown oil (139.9 mg, 90%).

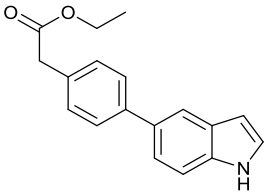
υ_{max} (neat): 1700, 1693, 1494, 1375 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 – 7.53 (m, 4H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 3H), 7.16 (t, *J* = 12.3 Hz, 4H), 5.14 (s, 2H), 4.47 (t, *J* = 11.8 Hz, 1H), 3.97 (dd, *J* = 11.3, 4.3 Hz, 2H), 3.71 (s, 2H), 3.45 – 3.50 (m, 2H), 1.81 (dd, *J* = 12.3, 2.2 Hz, 2H), 1.54-1.64 (m, 2H). OH not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.3, 155.0, 139.8, 138.9, 136.7, 136.3, 132.3, 129.8, 129.4, 127.9, 127.3, 127.0, 126.9, 126.8, 66.9, 66.6, 53.6, 40.1, 31.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{27}H_{28}NO_5$) *m/z* requires 446.1962, found *m/z* 446.1956.

Compound 28: Ethyl 2-(4-(1*H*-indol-5-yl)phenyl)acetate.



Prepared according to general procedure G using 6-bromoindole (390 mg, 2.0 mmol), ethyl 2-(4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolane-2-yl)phenyl)acetate (1.15 g, 3.96 mmol), K_3PO_4 (1.27 g, 6.01 mmol), 2'(dimethylamino)-2-biphenylyl-palladium(II)chloride dinorbornylphosphine complex, (10 mol%, 0.11 g, 0.01 mmol), 1,4-dioxane (2.4 mL), and H_2O (0.6 mL) to afford the desired product as a red solid (441.4 mg, 79%).

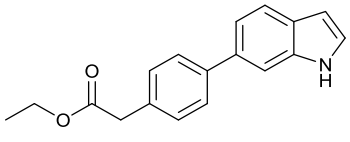
υ_{max} (neat): 3403, 1721, 1621, 1516, 1470 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.85 (d, *J* = 0.8 Hz, 1H), 7.66 – 7.59 (m, 2H), 7.44 (d, *J* = 1.1 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.24 (dd, *J* = 3.1, 2.5 Hz, 1H), 6.61 (dd, *J* = 3.1, 2.1 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, MeOD): δ 173.8, 143.0, 133.4, 133.3, 130.6, 128.2, 126.3, 121.8, 119.5, 112.4, 102.8, 102.8, 62.0, 41.7, 25.2, 14.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{18}NO_2$) *m/z* requires 280.1333, found *m/z* 280.1332.

Compound 29: Ethyl 2-(4-(1*H*-indol-6-yl)phenyl)acetate.



Prepared according to general procedure G using 5-bromoindole (100 mg, 0.5 mmol), ethyl 2-(4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolane-2-yl)phenyl)acetate (260 mg, 0.91 mmol), K_3PO_4 (320 mg, 1.5 mmol), 2'(dimethylamino)-2-biphenylyl-palladium(II)chloride dinorbornylphosphine complex (10 mol%, 29 mg, 0.01 mmol), 1,4-dioxane (2.4 mL), and H_2O (0.6 mL) to afford the desired product as a red solid (253.7 mg, 65%).

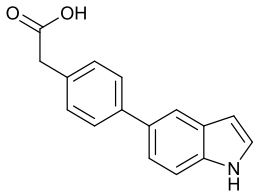
υ_{max} (neat): 3383, 2929, 1733, 1495, 1453, 1337 cm^{-1}.

^1H NMR (400 MHz, DMSO): δ 11.15 (s, 1H), 7.64 – 7.59 (m, 4H), 7.39 – 7.36 (m, 1H), 7.35 (s, 1H), 7.33 (s, 1H), 7.29 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.44 (m, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 2H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 141.2, 136.5, 134.9, 132.4, 129.7, 127.6, 127.3, 125.1, 120.9, 119.60, 109.6, 102.3, 61.1, 41.1, 14.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{18}NO_2$) requires *m/z* 280.1337, found *m/z* 280.1335.

Compound 30: 2-(4-(1*H*-indol-5-yl)phenyl)acetic acid.



Prepared according to general procedure E using ethyl 2-(4-(1*H*-indol-5-yl)phenyl)acetate (100 mg, 0.34 mmol), NaOH (1 mL), and THF (2 mL) to give the desired product as a red solid (141.9 mg, 77%).

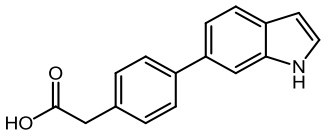
υ_{max} (neat): 3380, 2922, 1688, 1454, 1406, 1355 cm^{-1}.

^1H NMR (400 MHz, MeOD): δ 10.46 (s, 1H), 7.60 (dd, *J* = 4.7, 10.9 Hz, 4H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 1.6 Hz, 1H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.26 – 7.23 (m, 1H), 6.45 (s, 1H), 3.64 (s, 2H).

^{13}C NMR (101 MHz, MeOD): δ 173.8, 173.7 140.7, 133.6, 132.2, 128.8, 127.0, 126.2, 124.4, 119.5, 117.8, 108.5, 100.3, 39.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{14}NO_2$) requires *m/z* 250.0875, found *m/z* 250.0874.

Compound 31: 2-(4-(1*H*-indol-6-yl)phenyl)acetic acid.



Prepared according to general procedure E using ethyl 2-(4-(1*H*-indol-6-yl)phenyl)acetate (50 mg, 0.18 mmol), NaOH (1 mL), and THF (2 mL) to give the desired product as a red solid (34.3 mg, 78%).

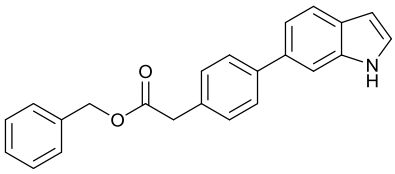
υ_{max} (neat): 3381, 2518, 1689, cm^{-1}.

^1H NMR (400 MHz, MeOD): δ 7.64 (dd, *J* = 11.0, 4.7 Hz, 5H), 7.39 (s, 1H), 7.37 (s, 1H), 7.33 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.29 (s, 1H), 6.48 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.68 (s, 2H). OH not observed.

^{13}C NMR (101 MHz, MeOD): δ 192.2, 173.8, 145.9, 140.7, 136.4, 133.6, 132.2, 128.8, 126.2, 124.3, 117.7, 108.5, 100.3, 39.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{14}NO_2$) requires *m/z* 252.1019, found *m/z* 252.1019.

Compound 32: 2-(4-(1-((benzyloxy)carbonyl)-1*H*-indol-6-yl)phenyl)acetic acid



Prepared according to general procedure G using 2-(4-(1*H*-indol-6-yl)phenyl)acetic acid (260 mg, 1.0 mmol,), NaH 60% w/w (49 mg, 2.0 mmol), *N*-(benzyloxycarbonyloxy)succinimide (373.8 mg, 1.5 mmol), and DMF (3 mL) to afford the desired product as a red solid (59 mg, 17%).

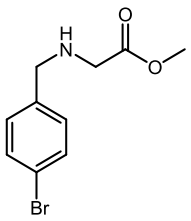
υ_{max} (neat): 3382, 1728, 1526, 1492, 1454 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.63 – 7.58 (m, 3H), 7.40 – 7.31 (m, 9H), 7.24 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.59 – 6.56 (m, 1H), 5.17 (s, 2H), 3.73 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.6, 141.3, 136.4, 135.9, 135.1, 132.2, 129.7, 128.6, 128.3, 128.2, 127.6, 127.3, 124.9, 120.9, 119.7, 109.5, 102.5, 66.7, 41.0.

HRMS: exact mass calculated for $[M-H]^+$ ($C_{24}H_{19}NO_4$) requires *m/z* 340.1343, found *m/z* 340.1335.

Compound 34: Methyl 2-((4-bromobenzyl) amino) acetate



Prepared according to general procedure F using 4-bromobenzaldehyde (0.5 g, 2.7 mmol), glycine methyl ester hydrochloride (0.34 g, 2.7 mmol), EtOH (7.5 mL), NEt_3 (0.73 mL, 78.3 mmol) was stirred at 50 °C for 1 h. MeOH (7.5 mL), and $NaBH_4$ (0.11 g, 2.97 mmol) to afford the desired product as clear yellow oil (0.46 g, 66%).

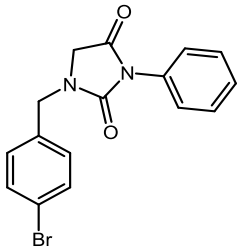
υ_{max} (neat): 3230, 2017, 1057 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 2H), 3.72 (s, 3H), 3.39 (s, 2H), 1.96 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2, 138.0, 131.2, 129.3, 120.3, 51.9, 51.2, 49.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{10}H_{13}BrNO_2$) requires *m/z* 258.0124, 260.0104, found *m/z* 258.0127, 260.0103.

Compound 35: 1-(4-bromobenzyl)-3-phenylimidazolidine-2,4-dione



Prepared according to general procedure H using methyl 2-((4-bromobenzyl) amino) acetate (0.4 g, 1.55 mmol), CH_2Cl_2 (38 mL), phenyl isocyanate (0.3 mL, 3.08 mmol), and CF_3CO_2H (3.16 mL, 41.0 mmol) to afford the desired product as a yellow solid (0.34 g, 60%).

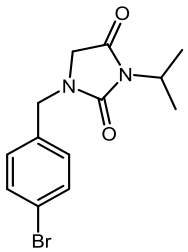
υ_{max} (neat): 1647, 1228, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.55 – 7.50 (m, 2H), 7.50 – 7.34 (m, 5H), 7.23 – 7.18 (m, 2H), 4.60 (s, 2H), 3.90 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5, 155.8, 134.4, 132.4, 131.7, 130.1, 129.2, 128.3, 126.2, 122.5, 49.1, 46.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{14}BrN_2O_2$) requires *m/z* 345.0233, 347.0213 found *m/z* 345.0239, 347.0216.

Compound 36: 1-(4-bromobenzyl)-3-isopropylimidazolidine-2, 4-dione



Prepared according to general procedure H using methyl 2-((4-bromobenzyl) amino) acetate (0.38 g, 1.47 mmol), CH_2Cl_2 (35 mL), isopropyl isocyanate (0.29 mL, 2.93 mmol), and CF_3CO_2H (2.71 mL, 33.81 mmol) to afford the desired product as a yellow solid (0.3 g, 65%).

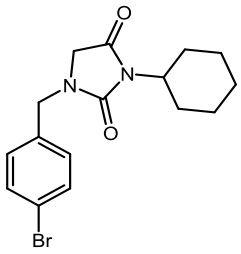
υ_{max} (neat): 1697, 1180 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 4.48 (s, 2H), 4.34 (dt, *J* = 13.9, 6.9 Hz, 1H), 3.65 (s, 2H), 1.43 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 156.9, 134.5, 132.3, 130.0, 122.4, 49.0, 46.3, 44.5, 19.7.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{13}H_{15}BrN_2O_2Na$) requires *m/z* 333.0209, 335.0189 found *m/z* 333.0209, 335.0186.

Compound 37: 1-(4-bromobenzyl)-3-cyclohexylimidazolidine-2,4-dione



Prepared according to general procedure H using methyl 2-((4-bromobenzyl) amino) acetate (0.4 g, 1.55 mmol), CH_2Cl_2 (35 mL), cyclohexyl isocyanate (0.39 mL, 3.08 mmol), and CF_3CO_2H (2.75 mL, 35.7 mmol) to afford the desired product as a yellow solid (0.24 g, 44 %).

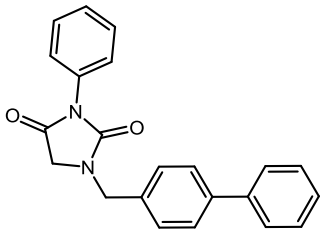
υ_{max} (neat): 2937, 1761, 1691 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 4.48 (s, 2H), 3.92 (tt, *J* = 12.4, 4.0 Hz, 1H), 3.65 (s, 2H), 2.14 (qd, *J* = 12.3, 3.0 Hz, 2H), 1.84 (d, *J* = 13.5 Hz, 2H), 1.69 (d, *J* = 10.5 Hz, 2H), 1.28 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 157.0, 134.8, 132.3, 130.0, 122.4, 52.1, 48.9, 46.3, 29.5, 26.0, 25.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}BrN_3O_2$) requires *m/z* 351.0703,353.0682 found *m/z* 351.0706, 353.0685.

Compound 38: 1-([1,1'-biphenyl]-4-ylmethyl)-3-phenylimidazolidine-2,4-dione



Prepared according to general procedure I using 1-(4-bromobenzyl)-3-phenylimidazolidine-2,4-dione (0.18 g, 0.52 mmol), (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (0.12 g, 0.57 mmol), $Pd_2(dba)_3$ (1 mol %, 5 mg, 0.005 mmol), K_3PO_4 (0.19 g, 0.89 mmol) PCy_3 (2.4 mol %, 4 mg, 0.012 mmol), 1,4-dioxane (1.3 mL), and H_2O (0.7 mL) to afford the desired product as a white powder (84 mg, 47 %).

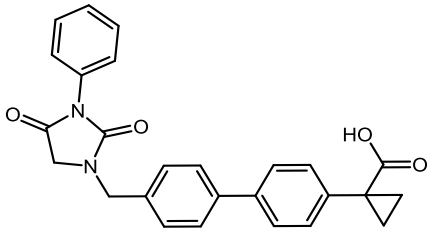
υ_{max} (neat): 1213, 744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 – 7.57 (m, 4H), 7.50 – 7.35 (m, 10H), 4.69 (s, 2H), 3.96 (s, 2H).

^{13}C NMR (101 MHz, CDCl3) δ 168.8, 155.8, 141.6, 140.6, 134.3, 131.9, 129.2, 129.0, 129.0, 128.3, 128.0, 127.7, 127.3, 126.2, 49.2, 46.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{19}N_2O_2$) requires *m/z* 343.1441, found *m/z* 343.1440.

Compound 39: 1-(4'-((2,4-dioxo-3-phenylimidazolidin-1-yl)methyl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid



Prepared according to general procedure I using 1-(4-bromobenzyl)-3-phenylimidazolidine-2,4-dione (0.20 mg, 0.57 mmol), methyl 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-

carboxylate (0.19 g, 0.68 mmol), $Pd_2(dba)_3$ (1 mol %, 5 mg, 0.005 mmol) , K_3PO_4 (0.22 g, 1.04 mmol) and PCy_3 (2.4 mol %, 4 mg, 0.013 mmol), 1,4-dioxane (1.3 mL), H_2O (0.7 mL), and LiOH (19 mg, 0.45 mmol) to afford the desired product as a white powder (70 mg, 29 %).

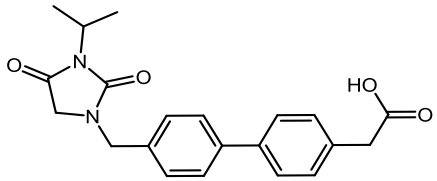
υ_{max} (neat): 3143, 1712,1452,1172 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.50 – 7.36 (m, 9H), 4.68 (s, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 2H), 1.64 (q, *J* = 3.9 Hz, 2H), 1.25 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 168.7, 141.1, 139.2, 134.2, 131.9, 131.0, 129.2, 128.9, 128.2, 127.8, 126.9, 126.1, 61.1, 49.2, 46.8, 28.9, 24.9, 16.6, 14.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{26}H_{23}N_2O_4$) requires m/z 427.1652, found *m/z* 427.1650.

Compound 40: 2-(4'-((3-isopropyl-2,4-dioxoimidazolidin-1-yl)methyl)-[1,1'-biphenyl]-4-yl)acetic acid



Prepared according to general procedure I using 1-(4-bromobenzyl)-3-phenylimidazolidine-2,4-dione (0.25 g, 0.8 mmol), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (0.24 g, 0.09 mmol), $Pd_2(dba)_3$ (1 mol %, 8 mg, 0.008 mmol) , K_3PO_4 (0.29 g, 1.37 mmol) and PCy_3 (2.4 mol %, 5 mg, 0.19 mmol), 1,4-dioxane (1.3 mL) H_2O (0.7 mL), and LiOH (44 mg, 1.05 mmol) to afford the desired product as a white powder (67 mg, 23 %).

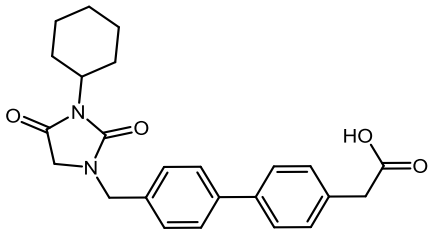
υ_{max} (neat): 1730, 1672, 796 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (t, *J* = 8.5 Hz, 4H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 4.57 (s, 2H), 4.36 (sept, *J* = 7.0 Hz, 1H), 3.70 (d, *J* = 3.2 Hz, 4H), 1.44 (d, *J* = 7.0 Hz, 6H). OH proton not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 156.8, 140.7, 139.4, 134.7, 130.0, 128.7, 127.7, 127.3, 49.0, 46.4, 44.2, 19.8. 3xC coincident.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{23}N_2O_4$) *m/z* 367.1652, found *m/z* 367.1654.

Compound 41: 2-(4'-((3-cyclohexyl-2, 4-dioxoimidazolidin-1-yl)methyl)-[1,1'-biphenyl]-4-yl)acetic acid:



Prepared according to general procedure I using 1-(4-bromobenzyl)-3-cyclohexylimidazolidine-2,4-dione (0.35 g, 1.0 mmol), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (0.30 g, 1.1 mmol), $Pd_2(dba)_3$ (1 mol %, 9 mg, 0.01 mmol), K_3PO_4 (0.36 g, 1.7 mmol) and PCy_3 (2.4 mol %, 7 mg, 0.024 mmol), 1,4-dioxane (1.3 mL), H_2O (0.7 mL), and LiOH (22 mg, 0.52 mmol) to afford the desired product as a white powder (63 mg, 15 %).

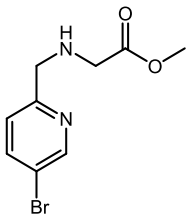
υ_{max} (neat): 1685, 796 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 9.7, 8.2 Hz, 4H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.57 (s, 2H), 3.94 (tt, *J* = 11.0, 3.2 Hz, 1H), 3.71 (d, *J* = 3.7 Hz, 4H), 2.16 (ddd, *J* = 15.9, 12.4, 2.9 Hz, 2H), 1.84 (d, *J* = 13.3 Hz, 2H), 1.70 (d, *J* = 13.7 Hz, 3H), 1.38 – 1.20 (m, 3H). OH not observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.0, 157.0, 140.7, 139.6, 134.7, 132.9, 130.0, 128.7, 127.7, 127.4, 65.9, 52.0, 49.0, 46.5, 29.5, 26.0, 25.1, 15.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{24}H_{27}N_2O_4$) requires *m/z* 407.1971, found *m/z* 407.1970.

Compound 43: Methyl 2-(((5-bromopyridin-2-yl) methyl) amino) acetate



Prepared according to general procedure G using glycine methyl ester hydrochloride (1.23 g, 9.8 mmol), methanol (10 mL), Et_3N (1.16 mL, 8.3 mmol), 5-bromopicolinaldehyde (0.91 g, 4.9 mmol), MeOH (15 mL), and $NaBH(OAc)_3$ (2.49 g, 11.7 mmol) to afford the desired product as clear yellow oil (1.09 g, 85 %).

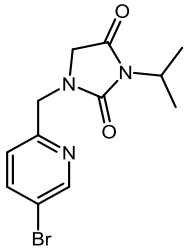
υ_{max} (neat): 1735, 1207 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$):δ 8.62 (d, J = 2.2 Hz, 1H), 7.78 (dd, J = 8.3, 2.4 Hz, 1H), 7.27 (d, J = 9.0 Hz, 1H), 3.92 (s, 2H), 3.74 (s, 3H), 3.48 (s, 2H).NH not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7, 156.4, 150.4, 139.3, 123.9, 119.4, 53.3, 52.1, 49.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_9H_{12}BrN_2O_2$) requires *m/z* 259.0077, found *m/z* 259.0078

Compound 44: 1-((5-bromopyridin-2-yl) methyl)-3-isopropylimidazolidine-2,4-dione



Prepared according to general procedure H using methyl 2-(((5-bromopyridin-2-yl) methyl) amino) acetate (0.4 g, 1.54 mmol), CH_2Cl_2 (15 mL), isopropyl isocyanate (0.30 mL, 3.07 mmol) and TFA (2.73 mL, 35.42 mmol) to afford the desired product as a yellow solid (0.28 g, 58 %).

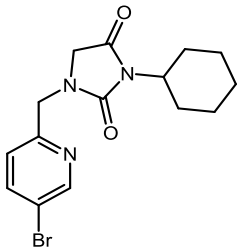
υ_{max} (neat): 1703, 906 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 1.9 Hz, 1H), 7.81 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 4.60 (s, 2H), 4.33 (sept, *J* = 6.9 Hz, 1H), 3.89 (s, 2H), 1.42 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 157.2, 154.4, 150.8, 139.9, 123.7, 120.1, 50.0, 47.5, 44.3, 19.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{15}BrN_3O_2$) requires *m/z* 312.0342, 314.0322, found *m/z* 312.0345, 314.0322.

Compound 45:1-((5-bromopyridin-2-yl)methyl)-3-cyclohexylimidazolidine-2,4-dione:



Prepared according to general procedure H using methyl 2-(((5-bromopyridin-2-yl) methyl) amino) acetate (0.4 g, 1.54 mmol), CH_2Cl_2 (15 mL), cyclohexyl isocyanate (0.39 mL, 3.07 mmol) and TFA (2.73 mL, 35.42 mmol) was added and the solution stirred for 2 h to afford the desired product as a yellow solid (0.40 g, 74%).

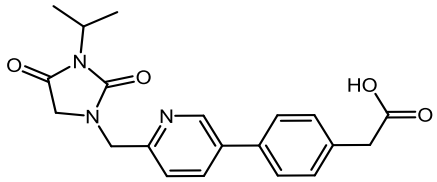
υ_{max} (neat): 2927, 1751, 1618, 1539 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, *J* = 2.3 Hz, 1H), 7.82 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.27 (d, *J* = 9.5 Hz, 1H), 4.45 (s, 2H), 4.11 (s, 2H), 3.70 – 3.56 (m, 1H), 1.89 – 1.84 (m, 2H), 1.69 – 1.62 (m, 2H), 1.59 – 1.53 (m, 1H), 1.41 – 1.29 (m, 2H), 1.21 – 1.13 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 158.0, 156.2, 150.3, 139.8, 124.1, 119.9, 54.1, 52.1, 49.5, 33.5, 25.8, 24.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{19}BrN_3O_2$) requires *m/z* 352.0655, 354.0635, found *m/z* 352.0650, 354.0628.

Compound 46: 2-(4-(6-((3-isopropyl-2,4-dioxoimidazolidin-1-yl)methyl)pyridin-3-yl)phenyl)acetic acid



Prepared according to general procedure I using 1,1-((5-bromopyridin-2-yl)methyl)-3-isopropylimidazolidine-2,4-dione (0.20 g, 0.64 mmol), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (0.21 g, 0.77 mmol), 2'(dimethylamino)-2-biphenylyl-palladium(II)chloride dinorbornylphosphine complex (5 mol %, 18 mg, 0.03 mmol), K_3PO_4 (0.41 g, 1.93 mmol), 1,4-dioxane (4 mL), H_2O (1 mL), and LiOH (18 mg, 0.44 mmol) to afford the desired product as a white powder (28 mg, 12 %).

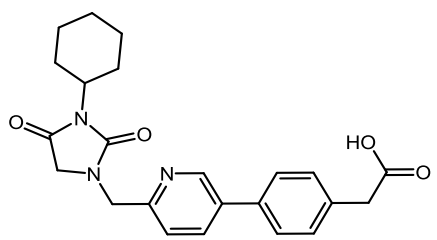
υ_{max} (neat): 1701, 1174, 1134 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.02 (d, *J* = 1.7 Hz, 1H), 8.35 (dd, *J* = 8.2, 2.0 Hz, 1H), 8.06 (br.s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 4.96 (s, 2H), 4.35 (sept, *J* = 7.0 Hz ,1H), 3.99 (s, 2H), 3.73 (s, 2H), 1.43 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.9, 169.5, 157.5, 151.1, 142.2, 141.4, 138.8, 135.9, 133.1, 131.0, 127.5, 125.8, 50.3, 44.8, 44.6, 40.5, 19.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{22}N_3O_4$) requires *m/z* 368.1605, found *m/z* 368.1594.

Compound 47: 2-(4-(6-((3-cyclohexyl-2,4-dioxoimidazolidin-1-yl)methyl)pyridin-3-yl)phenyl)acetic acid



Prepared according to general procedure I using 1-((5-bromopyridin-2-yl)methyl)-3-cyclohexylimidazolidine-2,4-dione (0.20 g, 0.57 mmol), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate

(0.19 g, 0.68 mmol), 2'(dimethylamino)-2-biphenylyl-palladium(II)chloride dinorbornylphosphine complex (5 mol %, 16 mg, 0.03 mmol), K_3PO_4 (0.36 g, 1.71 mmol) , 1,4-dioxane (4 mL), H_2O (1 mL), and LiOH (14 mg, 0.36 mmol) to afford the desired product as a white powder (56 mg, 24 %).

υ_{max} (neat): 3360, 1699, 1114 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.34 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.04 (br.s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 4.96 (s, 2H), 3.99 (s, 2H), 3.92 (tt, *J* = 12.3, 3.8 Hz, 1H), 3.72 (s, 2H), 2.11 (qd, *J* = 12.5, 3.2 Hz, 2H), 1.83 (d, *J* = 13.5 Hz, 2H), 1.67 (t, *J* = 14.1 Hz, 3H), 1.37 – 1.15 (m, 3H).

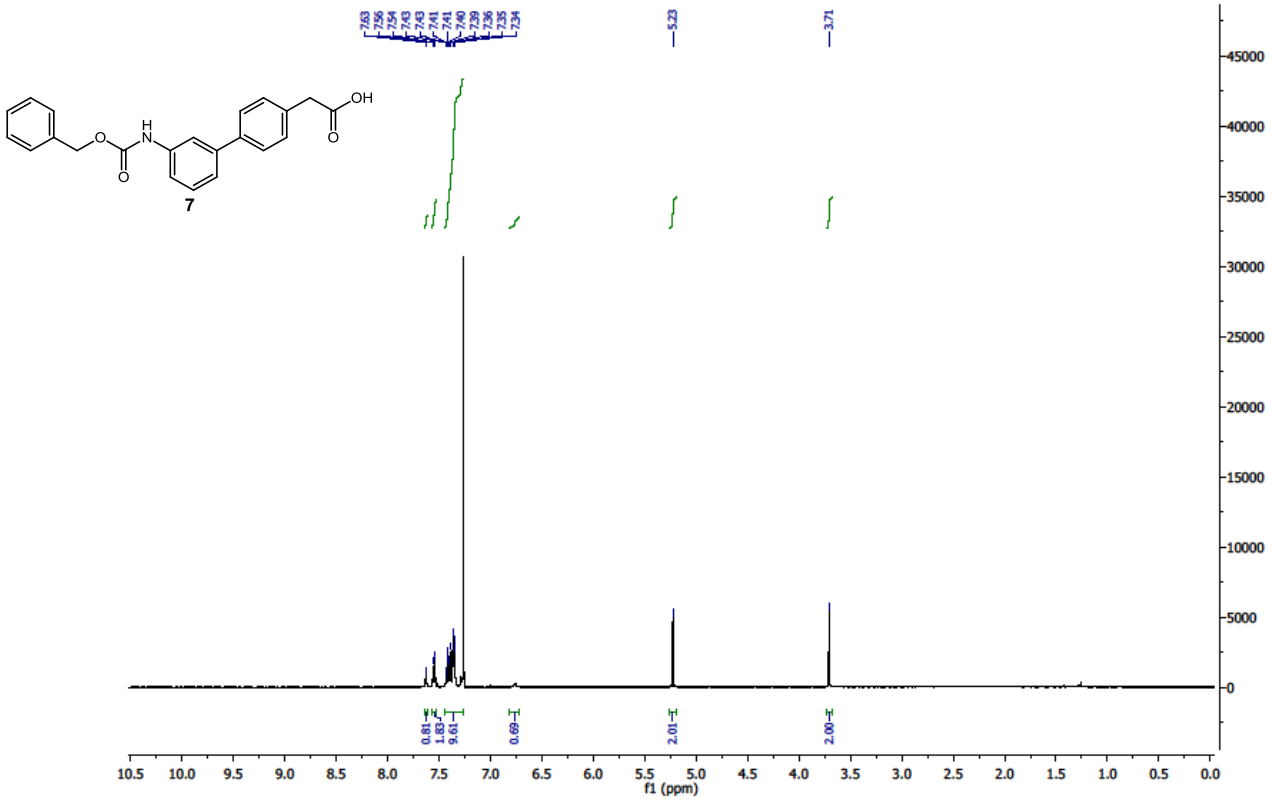
^{13}C NMR (101 MHz, $CDCl_3$): δ 175.1, 169.6, 157.6, 151.0, 142.1, 141.4, 138.8, 136.0, 133.0, 131.0, 127.5, 125.9, 52.4, 50.3, 44.8, 40.5, 29.4, 26.0, 25.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{23}H_{26}N_3O_4$) requires *m/z* 408.1923, found *m/z* 408.1917.

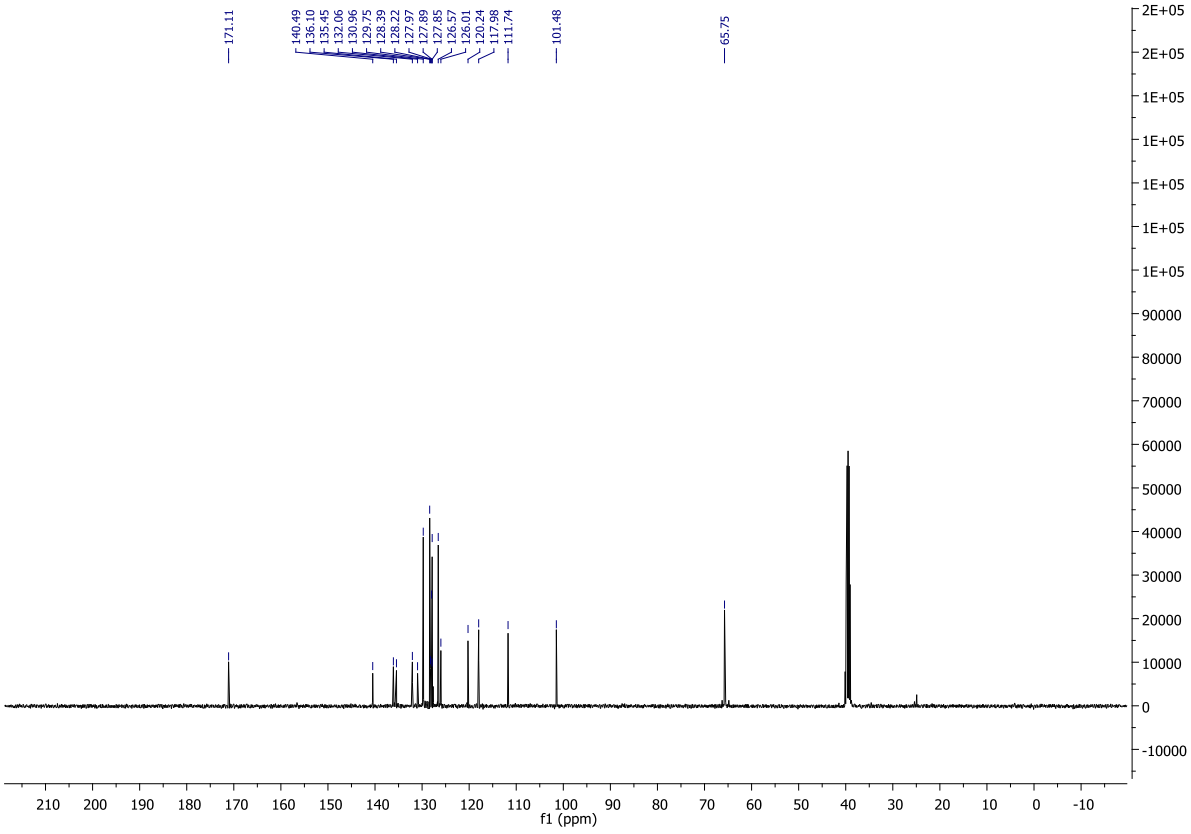
4. ^{1}H, ^{13}C, IR, and HRMS Spectra

Compound 7

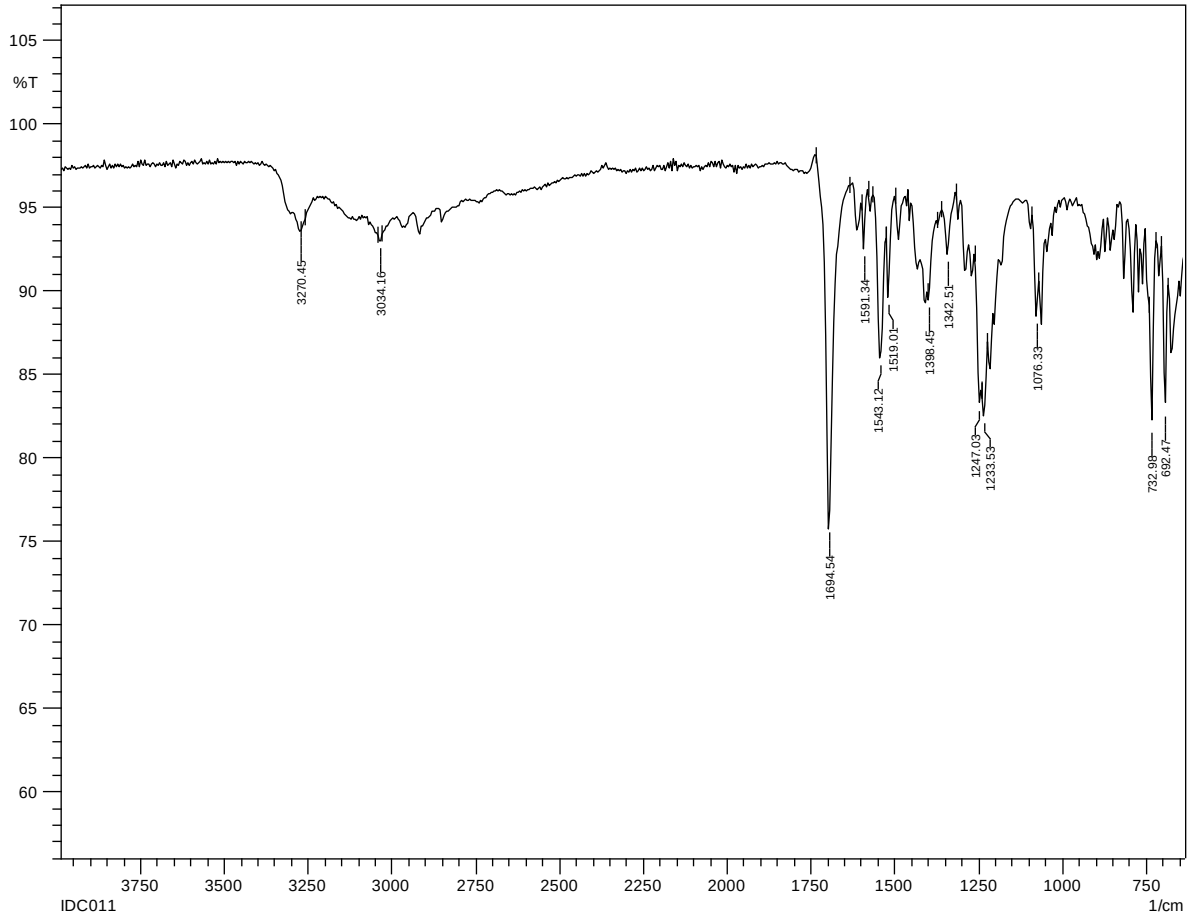
^{1}H NMR



^{13}C NMR



IR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%T
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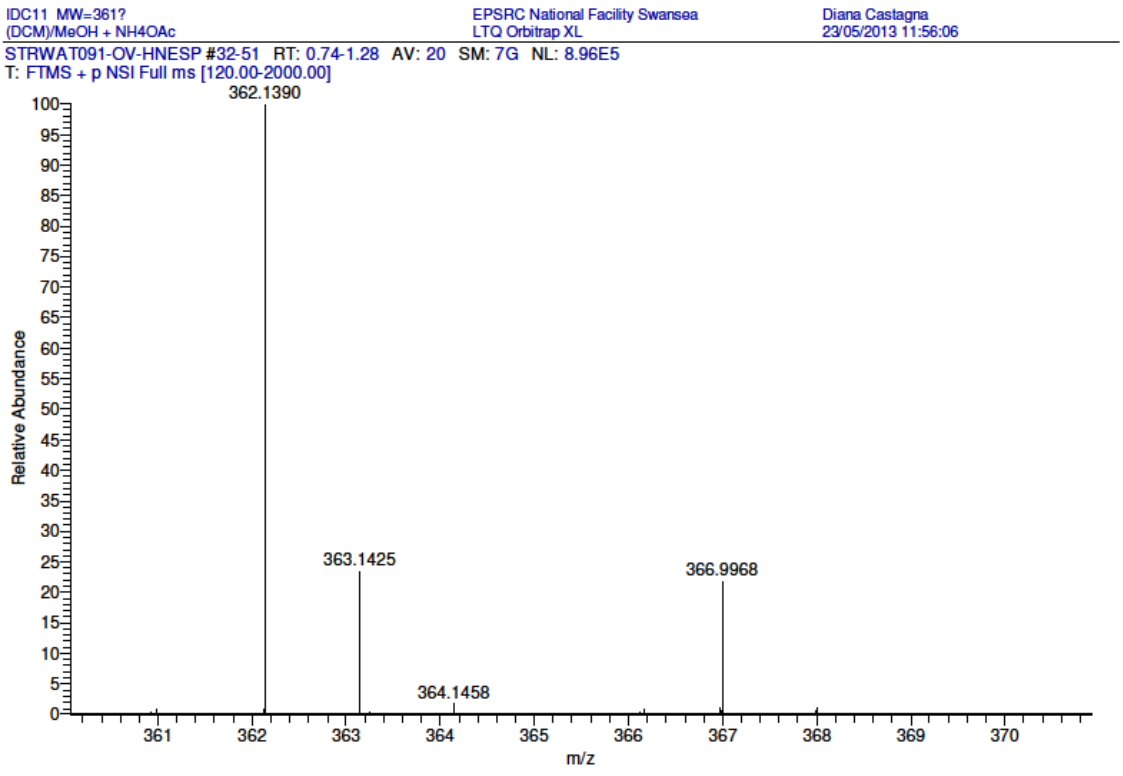
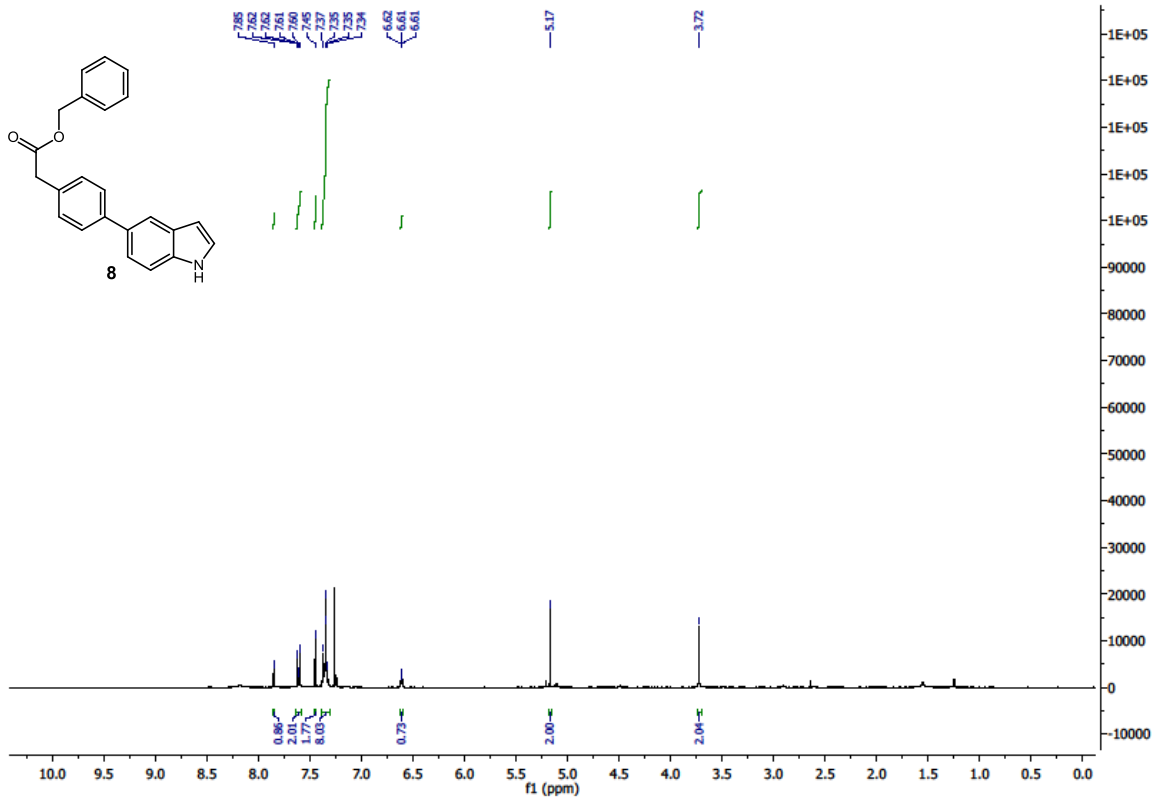
90
85
80
75
70
65
60
3270.45
3034.16
1694.54
1591.34
1543.12
1519.01
1398.45
1342.51
1247.03
1233.53
1076.33
732.98
692.47
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
IDC011
1/cm

HRMS

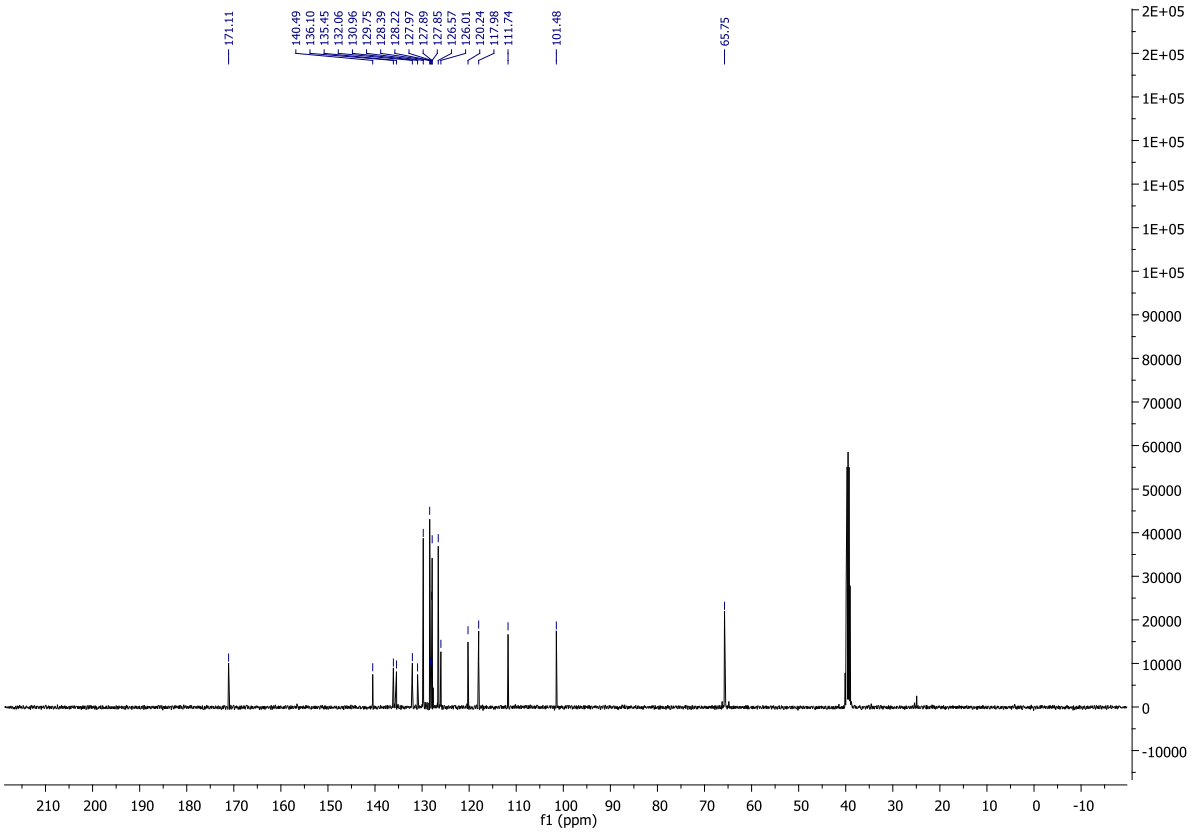

IDC11 MW=361?
(DCM)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
23/05/2013 11:56:06
STRWAT091-OV-HNESP #32-51 RT: 0.74-1.28 AV: 20 SM: 7G NL: 8.96E5
T: FTMS + p NSI Full ms [120.00-2000.00]
362.1390
363.1425
364.1458
366.9968
Relative Abundance
m/z
361
362
363
364
365
366
367
368
369
370

Compound 8

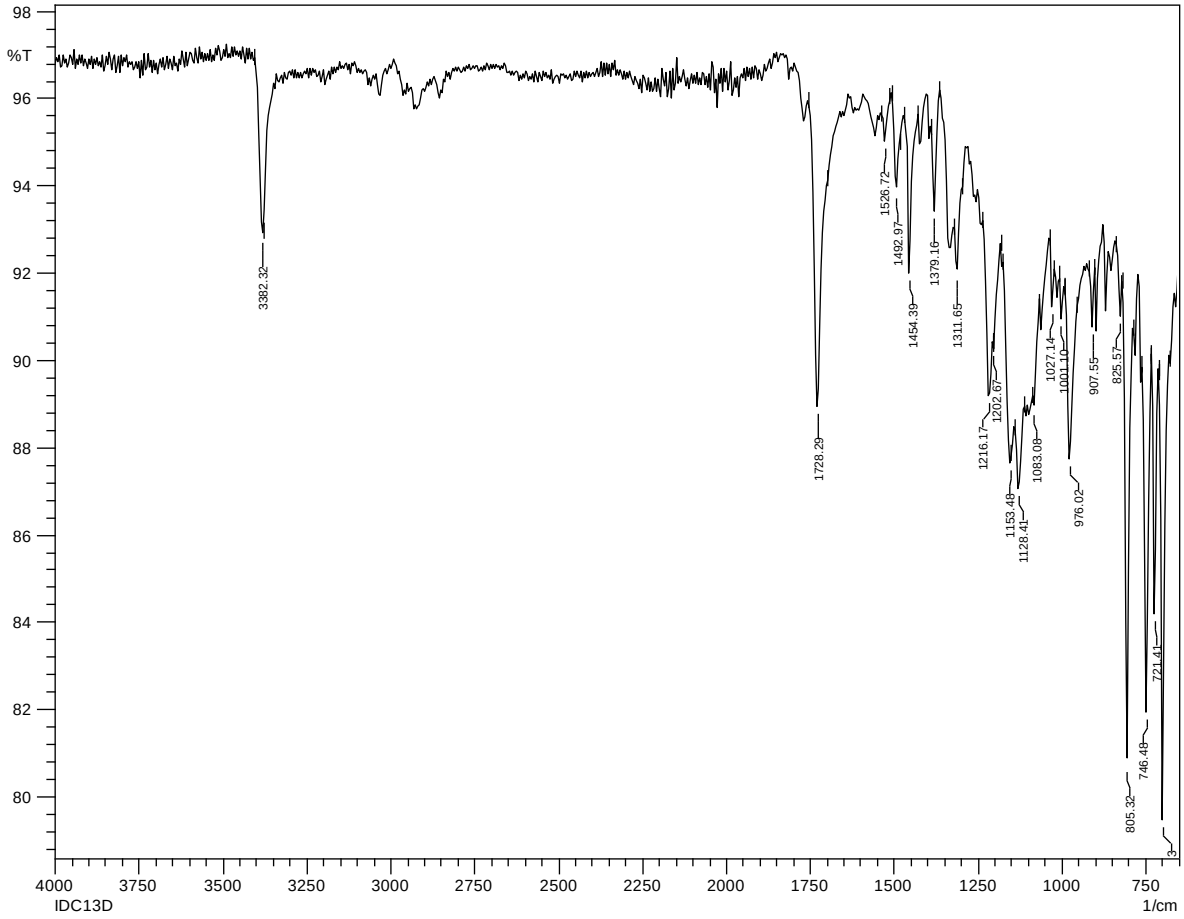
^{1}H NMR



^{13}C NMR



IR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90
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86
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82
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1379.16
1311.65
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1202.67
1153.48
1128.41
1083.08
1027.14
1001.10
976.02
907.55
825.57
805.32
746.48
721.41
4000
3750
3500
3250
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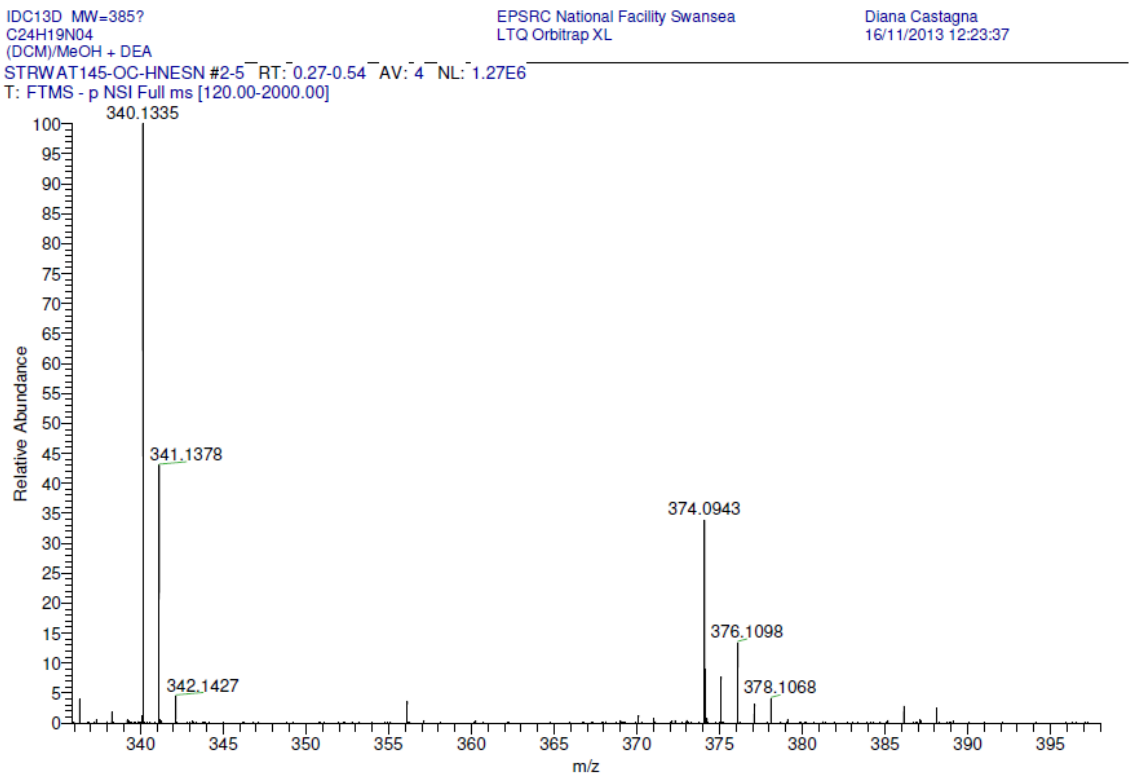
2750
2500
2250
2000
1750
1500
1250
1000
750
IDC13D
1/cm

HRMS


IDC13D MW=385?
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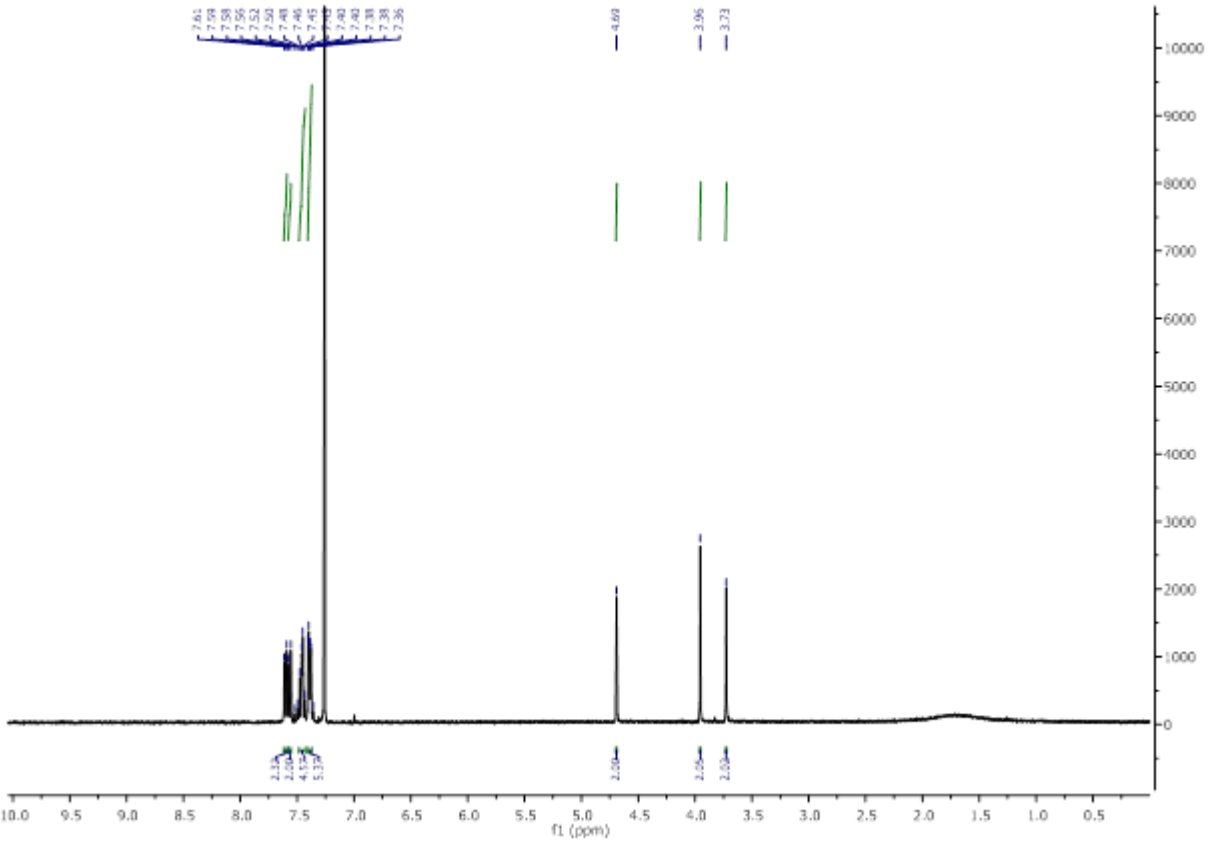
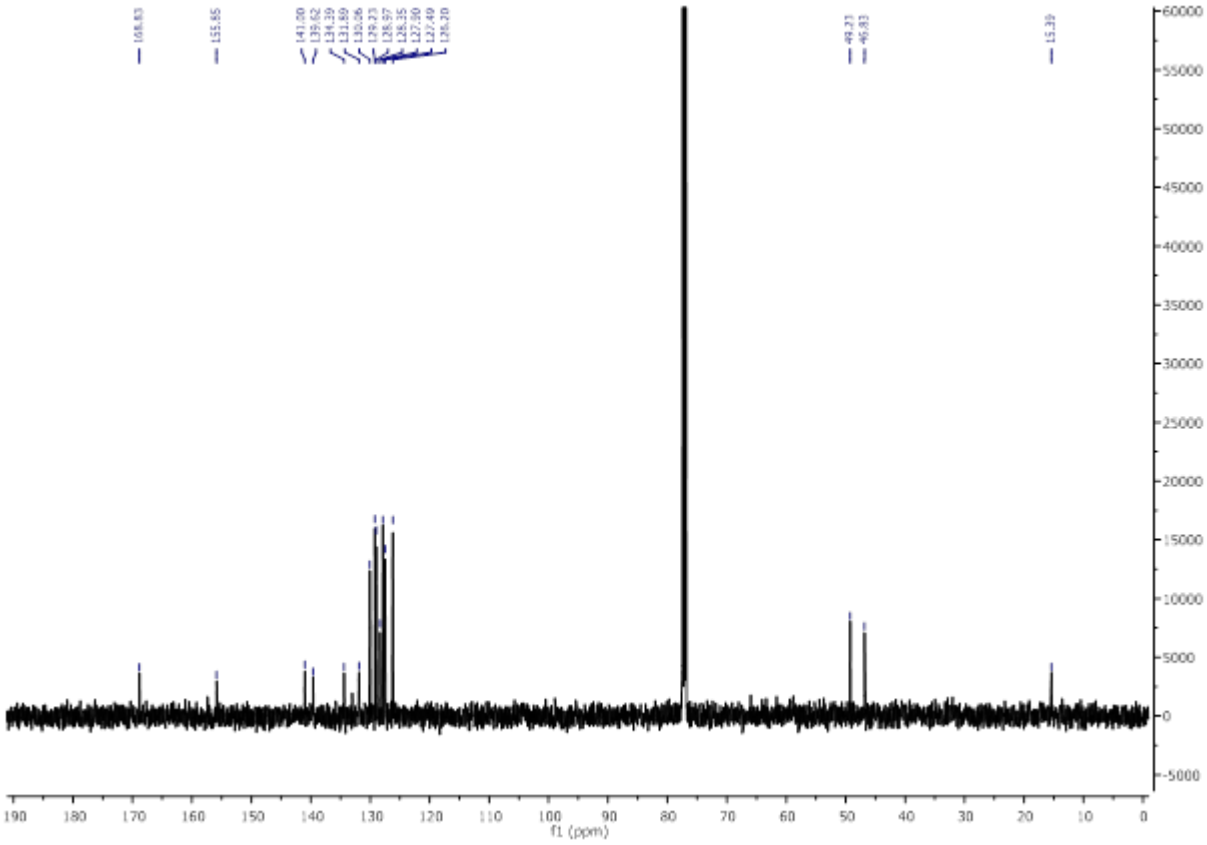
(DCM)/MeOH + DEA
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
16/11/2013 12:23:37
STRWAT145-OC-HNESN #2-5 RT: 0.27-0.54 AV: 4 NL: 1.27E6
T: FTMS - p NSI Full ms [120.00-2000.00]
340.1335
341.1378
342.1427
374.0943
376.1098
378.1068
Relative Abundance
m/z

Compound 9

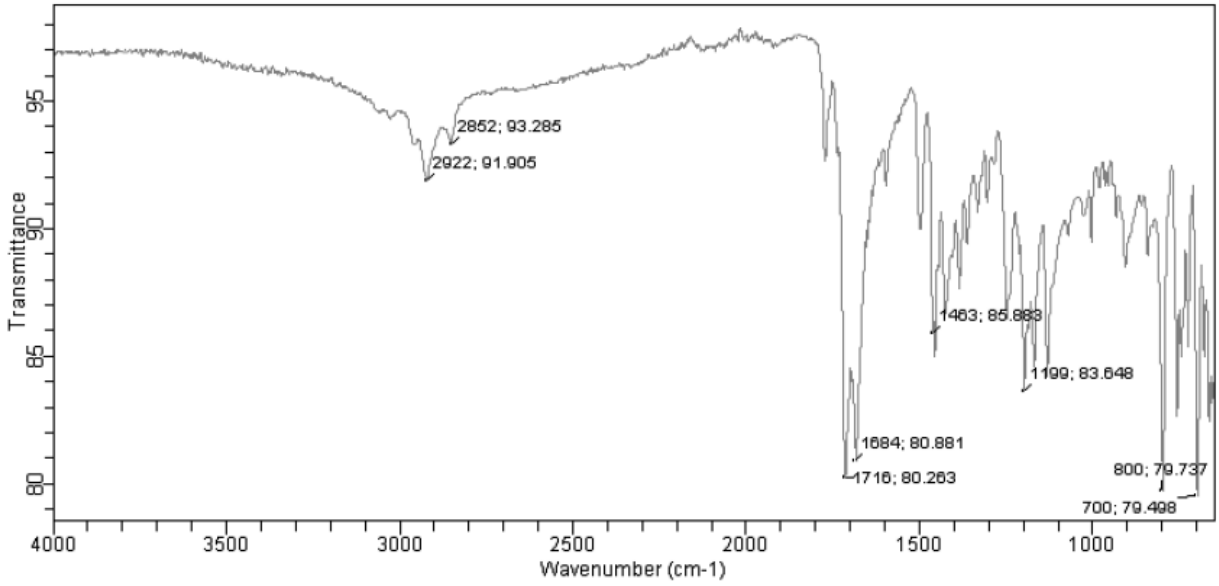
^{1}H NMR



^{13}C NMR



IR


Transmittance
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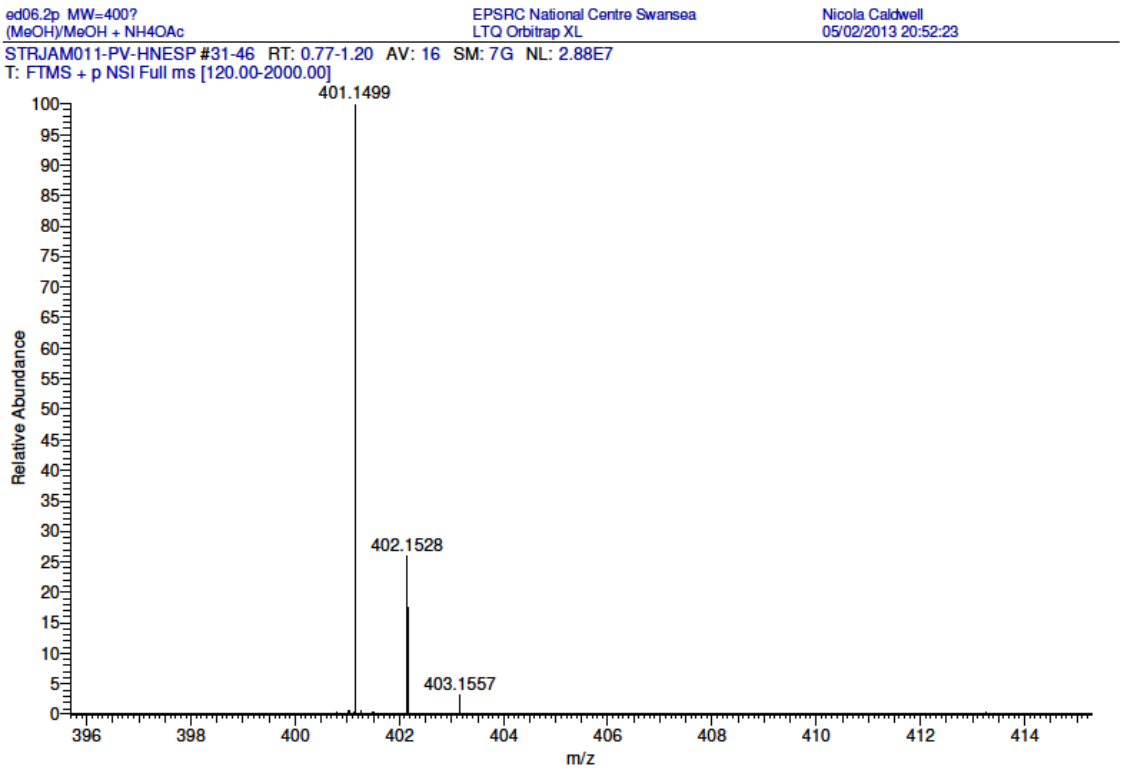
90
85
80
2852; 93.285
2922; 91.905
1463; 85.883
1199; 83.648
1684; 80.881
1716; 80.263
800; 79.737
700; 79.498
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)

HRMS


ed06.2p MW=400?
(MeOH)/MeOH + NH4OAc
EPSRC National Centre Swansea
LTQ Orbitrap XL
Nicola Caldwell
05/02/2013 20:52:23
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T: FTMS + p NSI Full ms [120.00-2000.00]
401.1499
402.1528
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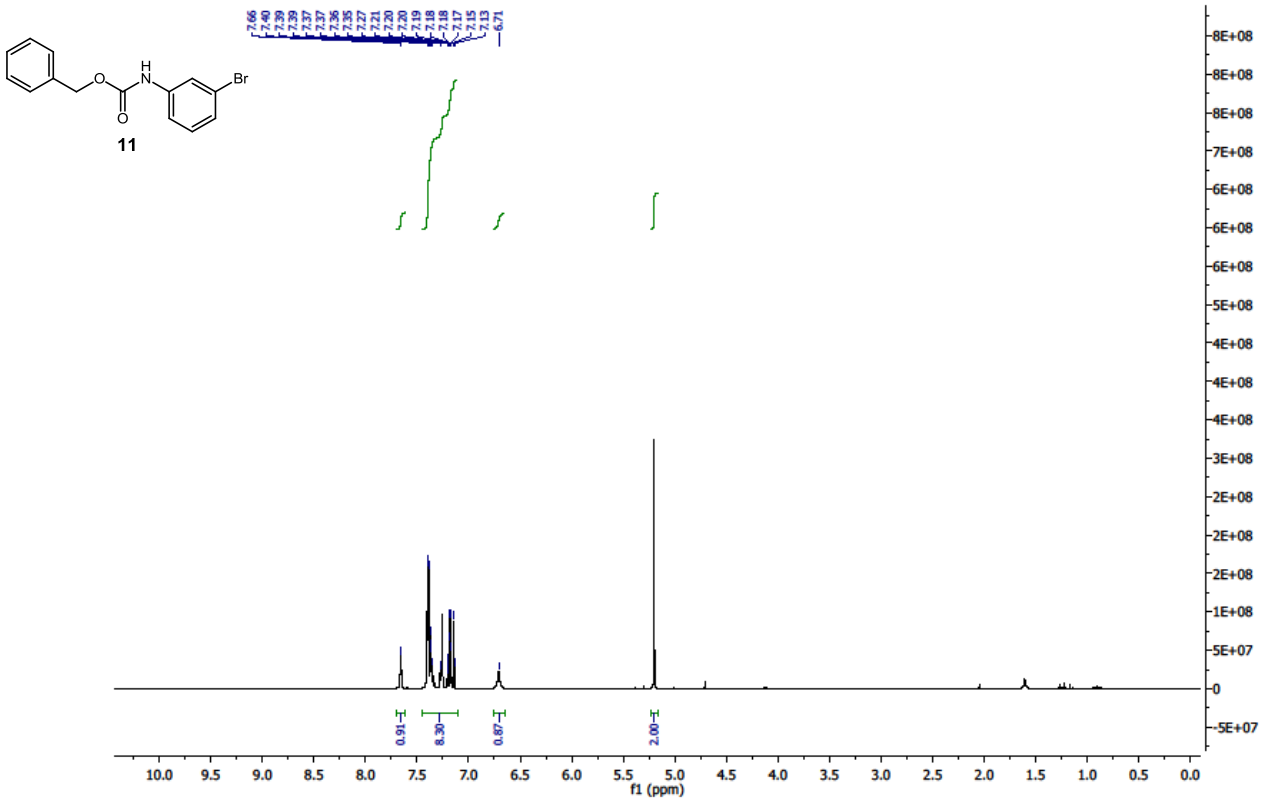
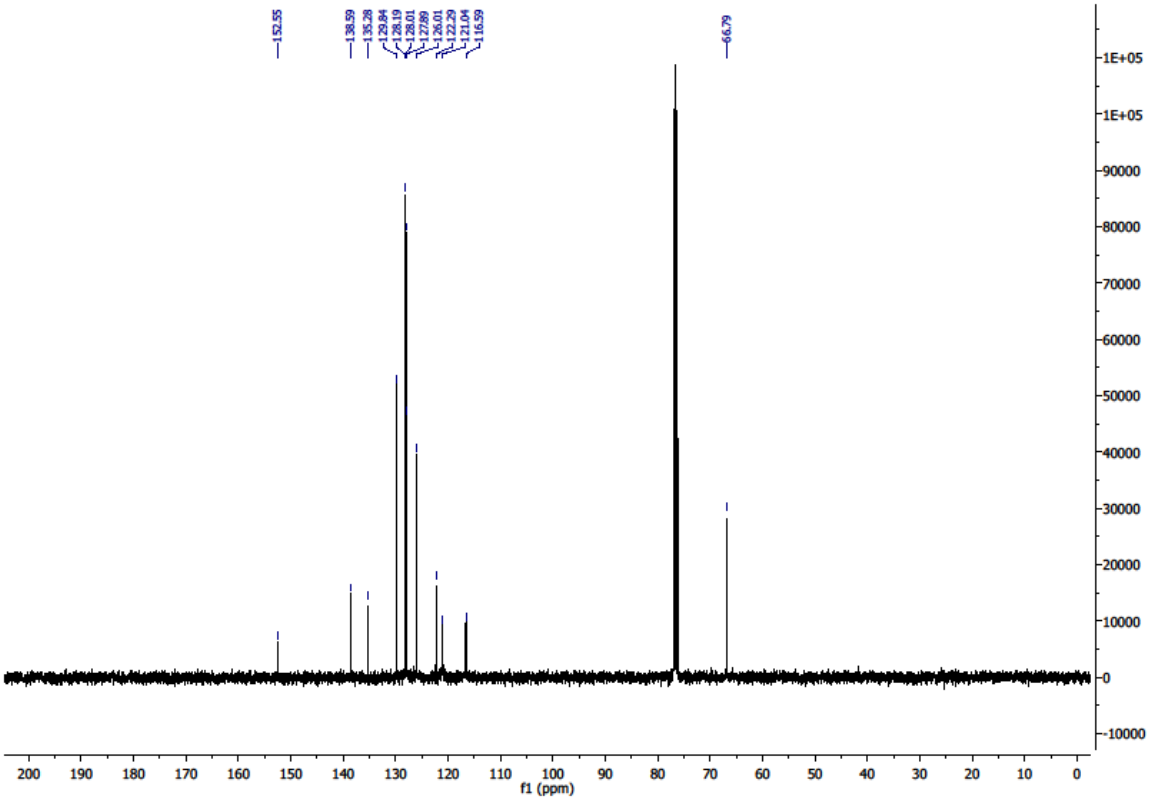
Relative Abundance
m/z
396
398
400
402
404
406
408
410
412
414

Compound 11

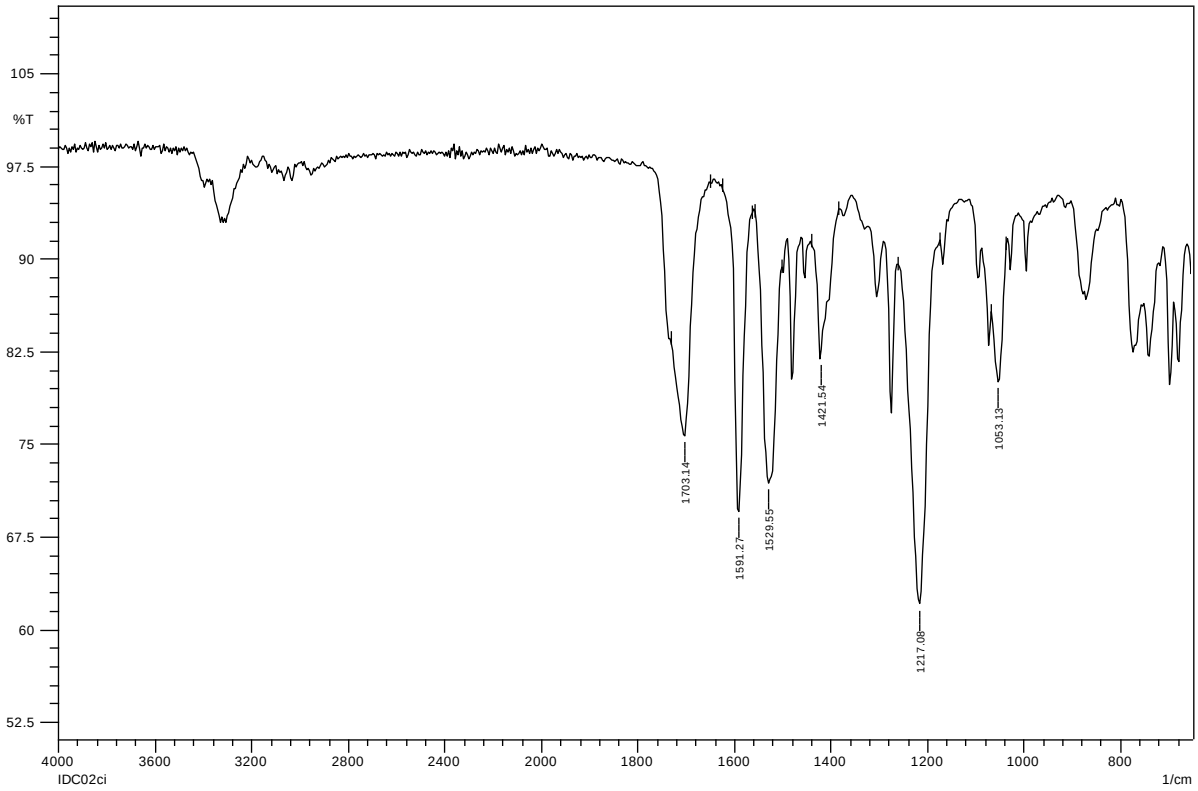
^{1}H NMR



^{13}C NMR



IR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67.5
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1200
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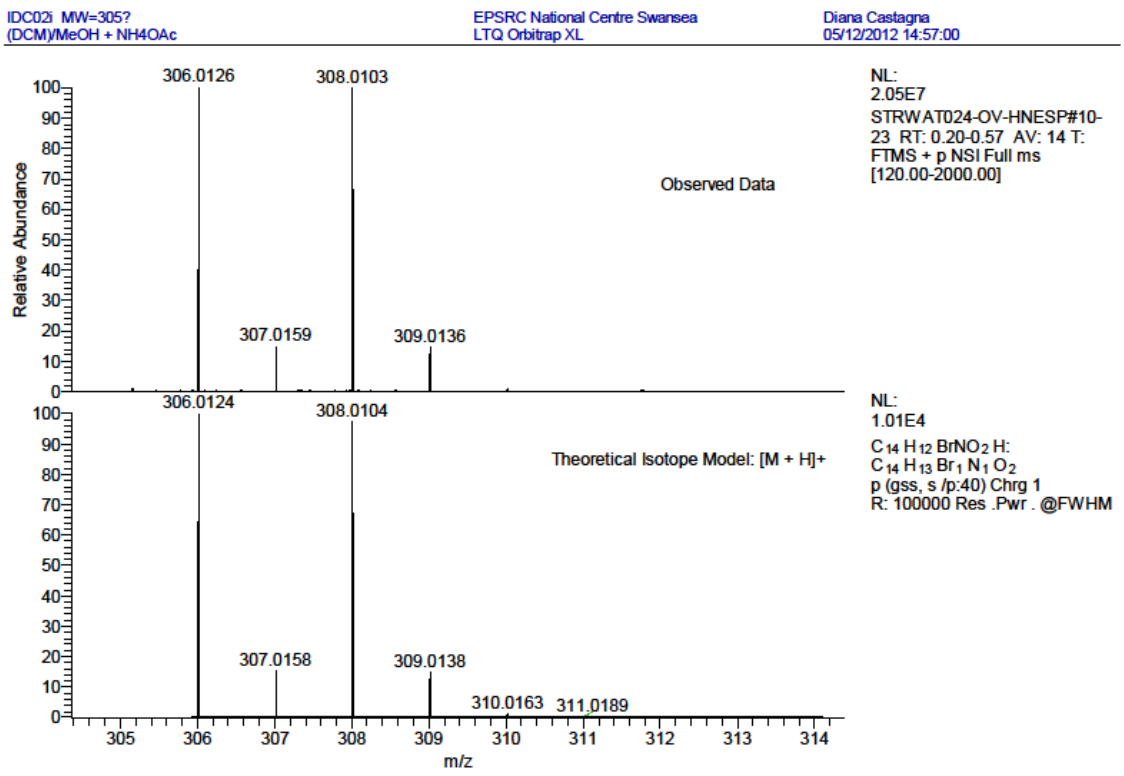
IDC02ci
1/cm

HRMS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EPSRC National Centre Swansea
LTQ Orbitrap XL
Diana Castagna
05/12/2012 14:57:00
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307.0159
309.0136
Observed Data
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308.0104
307.0158
309.0138
310.0163
311.0189
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NL:
1.01E4
C14 H12 BrNO2 H:
C14 H13 Br1 N1 O2
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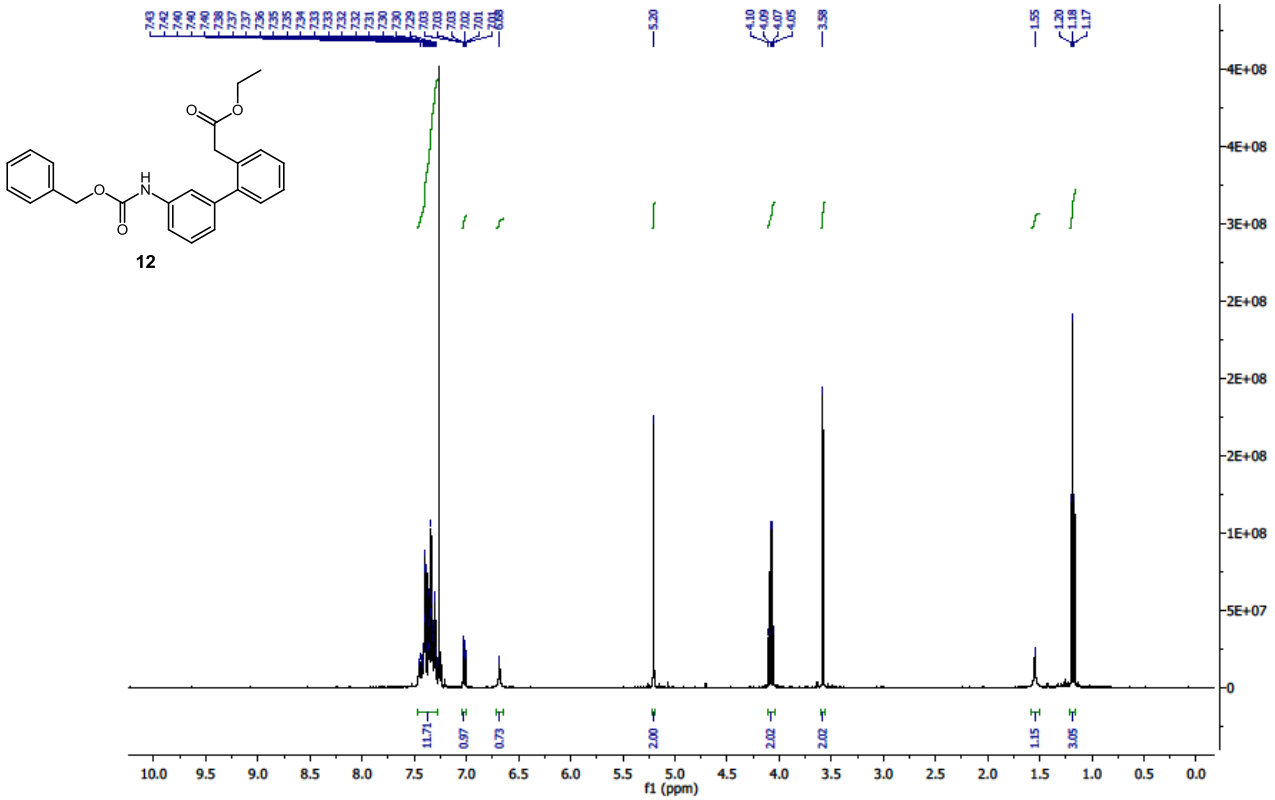
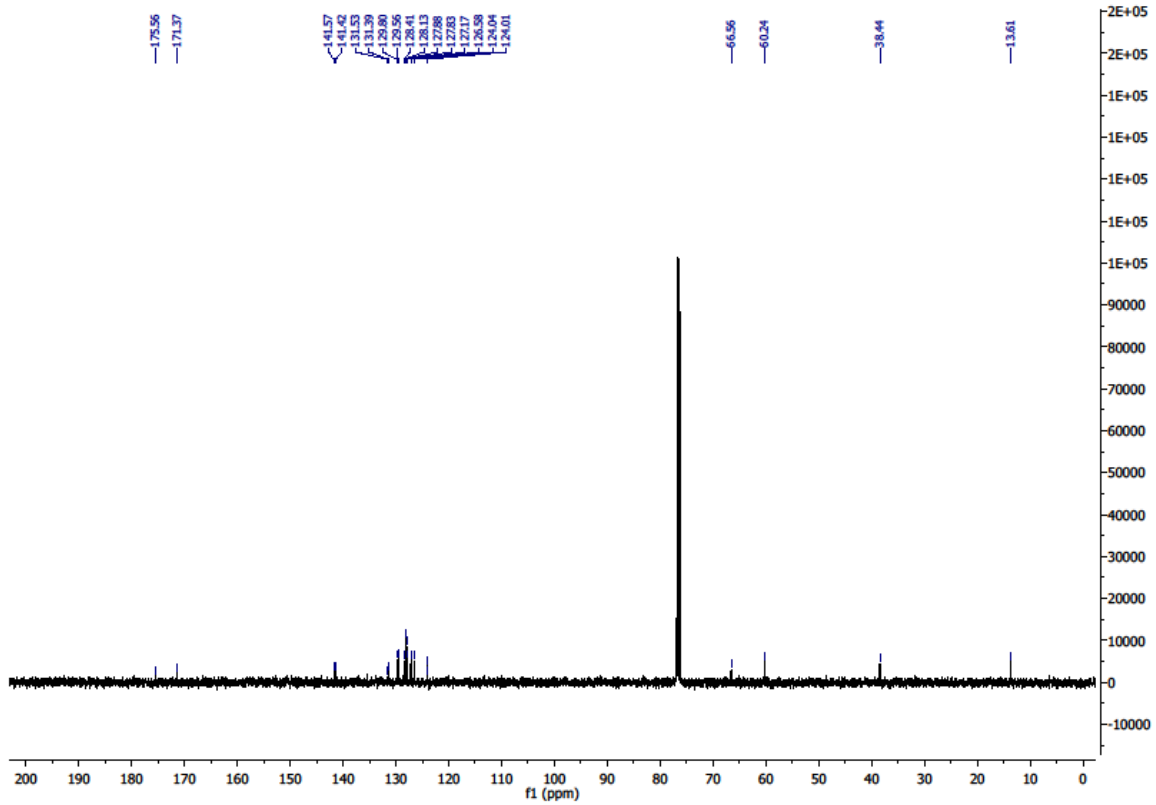
R: 100000 Res .Pwr . @FWHM
Relative Abundance
m/z

Compound 12

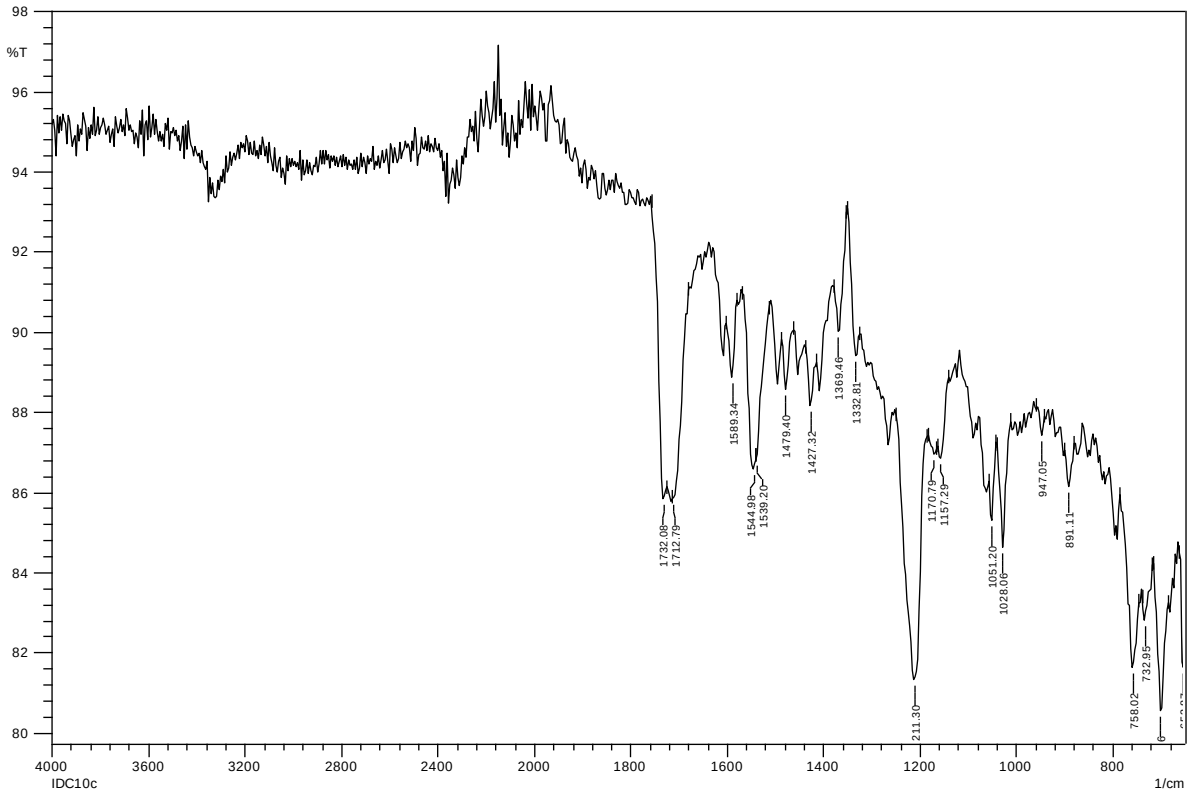
^{1}H NMR



^{13}C NMR



IR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90
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82
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3200
2800
2400
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1800
1600
1400
1200
1000
800
1/cm
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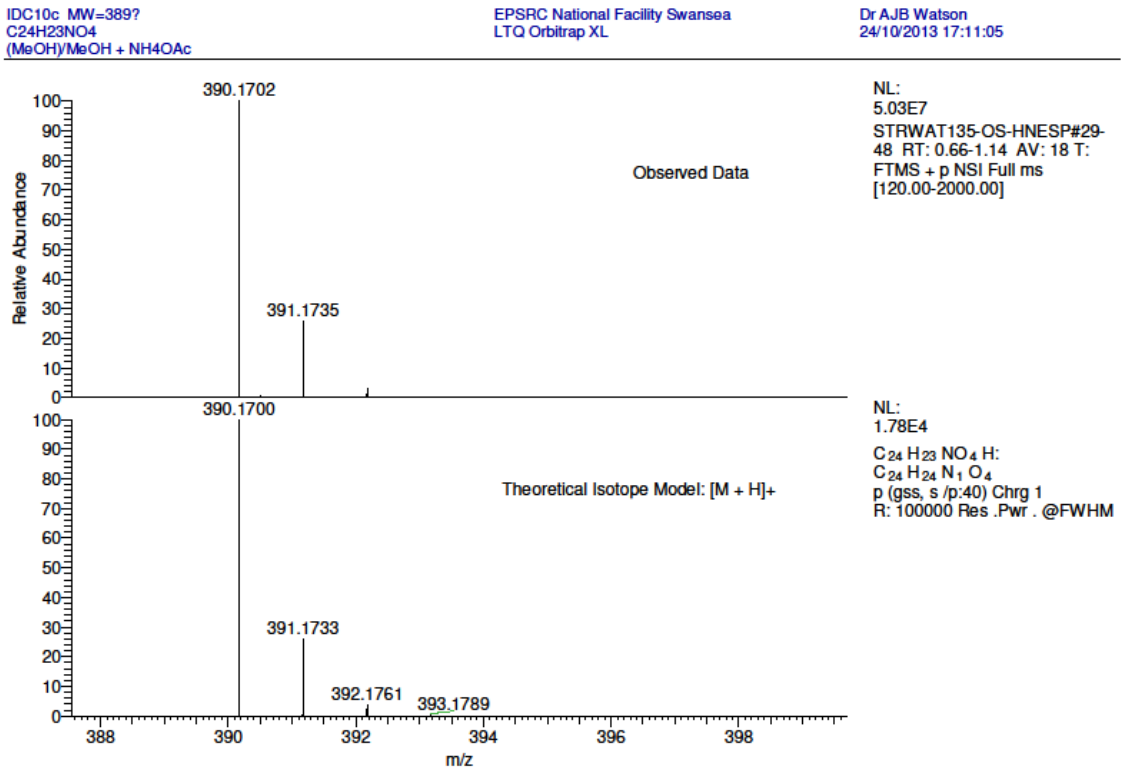
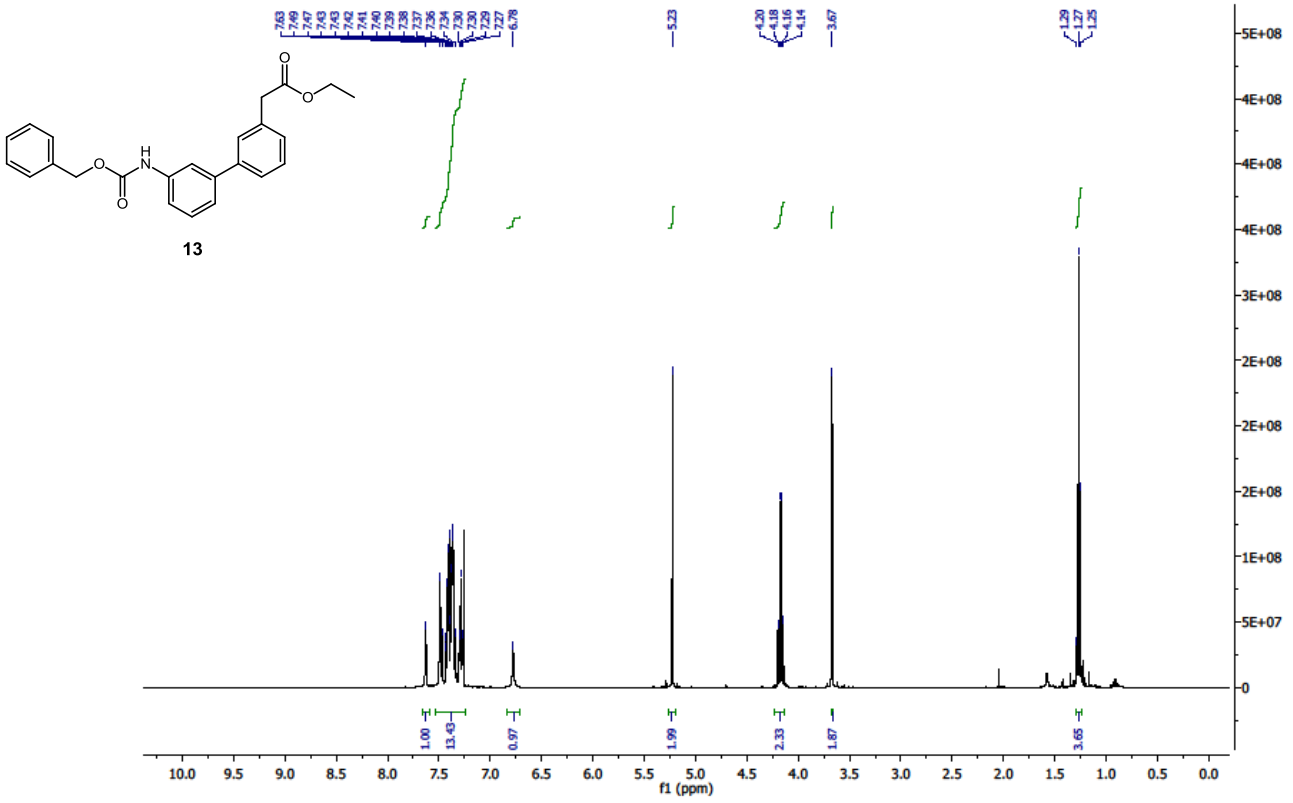
1712.79
1589.34
1544.98
1539.20
1479.40
1427.32
1369.46
1332.81
1170.79
1157.29
1051.20
1028.06
947.05
891.11
758.02
732.95
211.30

HRMS

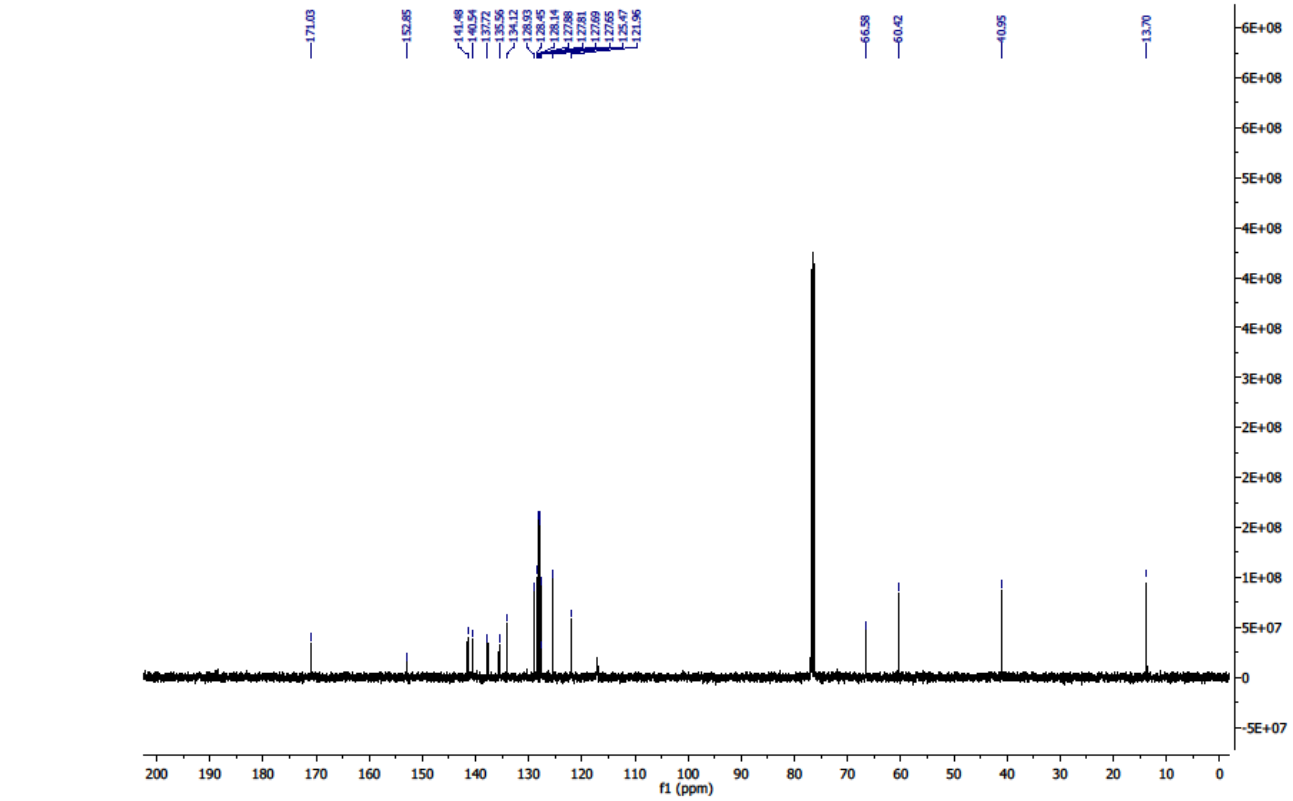

IDC10c MW=389?
C24H23NO4
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Dr AJB Watson
24/10/2013 17:11:05
390.1702
391.1735
Observed Data
NL:
5.03E7
STRWAT135-OS-HNESP#29-48 RT: 0.66-1.14 AV: 18 T: FTMS + p NSI Full ms [120.00-2000.00]
Relative Abundance
390.1700
391.1733
392.1761
393.1789
Theoretical Isotope Model: [M + H]+
NL:
1.78E4
C24 H23 NO4 H:
C24 H24 N1 O4
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
388
390
392
394
396
398
m/z

Compound 13

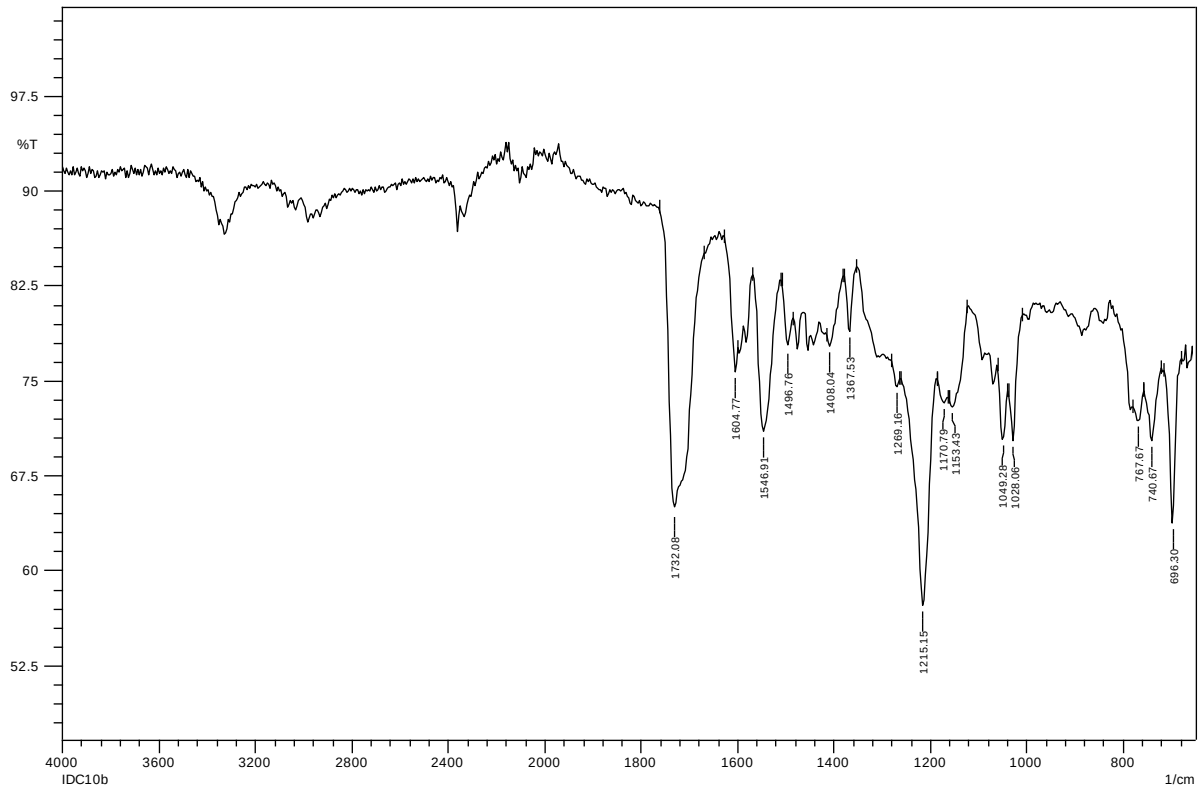
^{1}H NMR



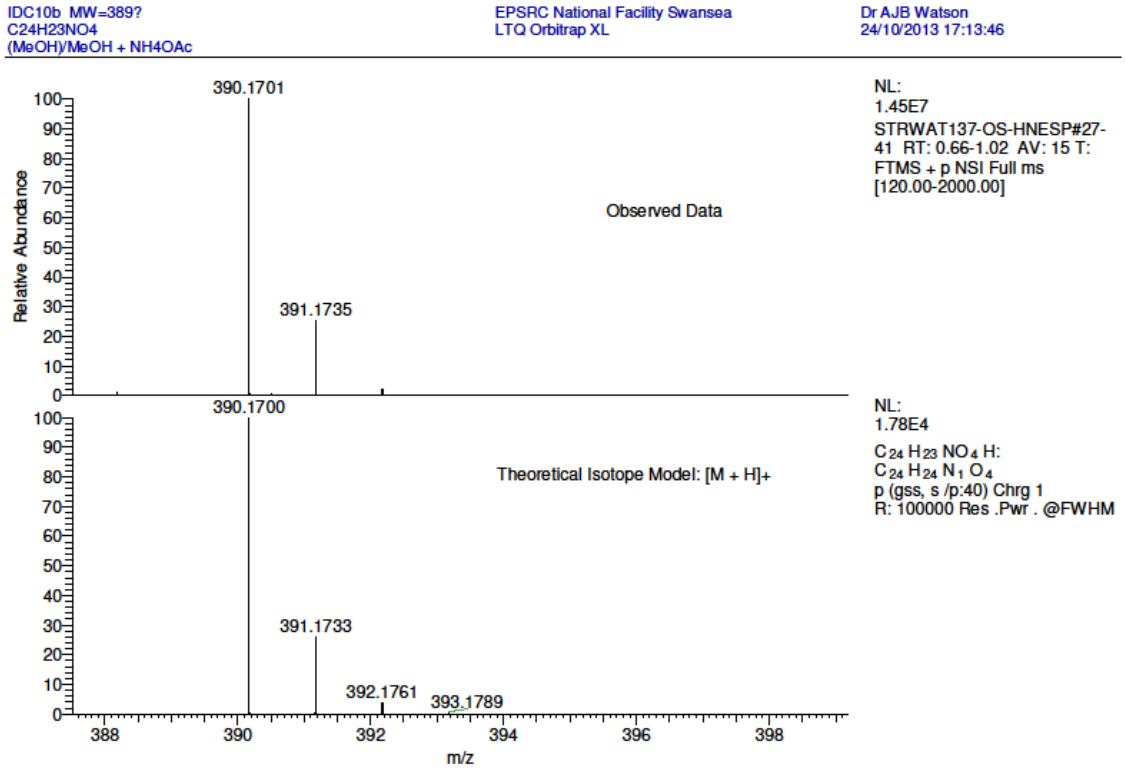
^{13}C NMR



IR

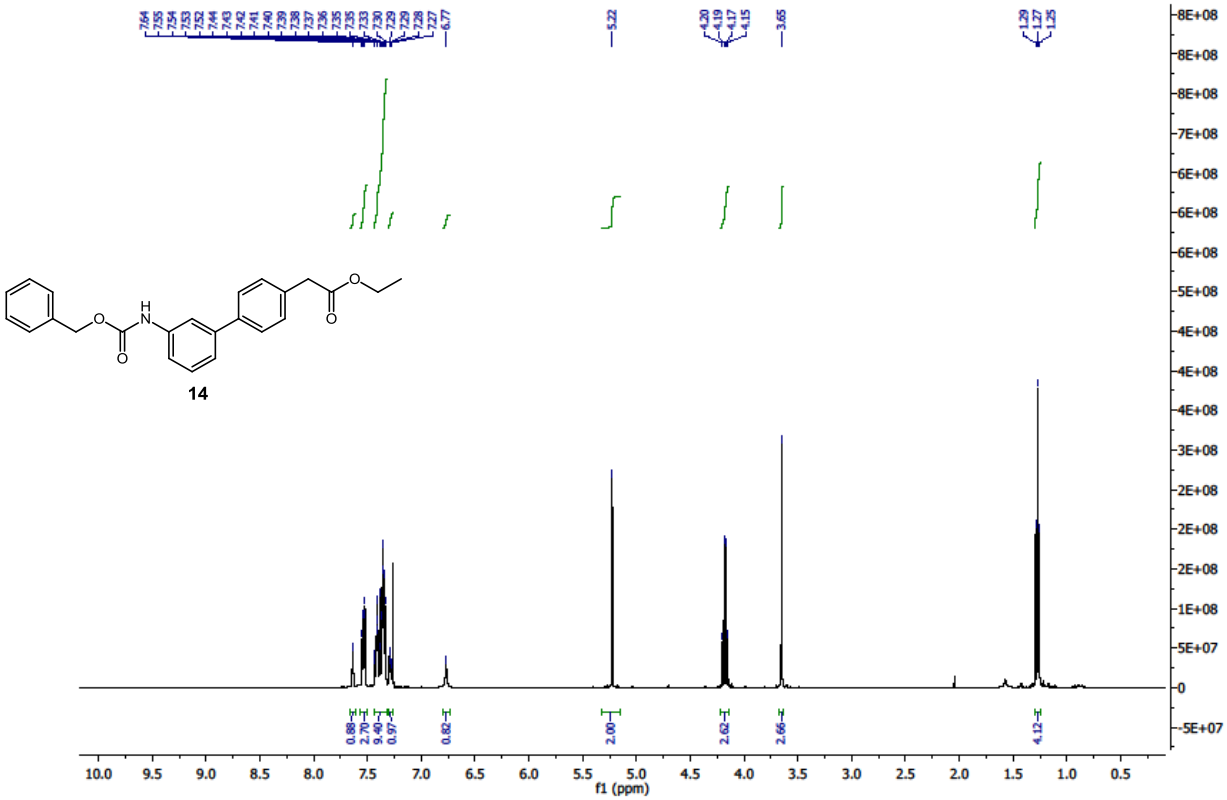

97.5
%T
90
82.5
75
67.5
60
52.5
1732.08
1604.77
1546.91
1496.76
1408.04
1367.53
1269.16
1215.15
1170.79
1153.43
1049.28
1028.06
767.67
740.67
696.30
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
IDC10b
1/cm

HRMS

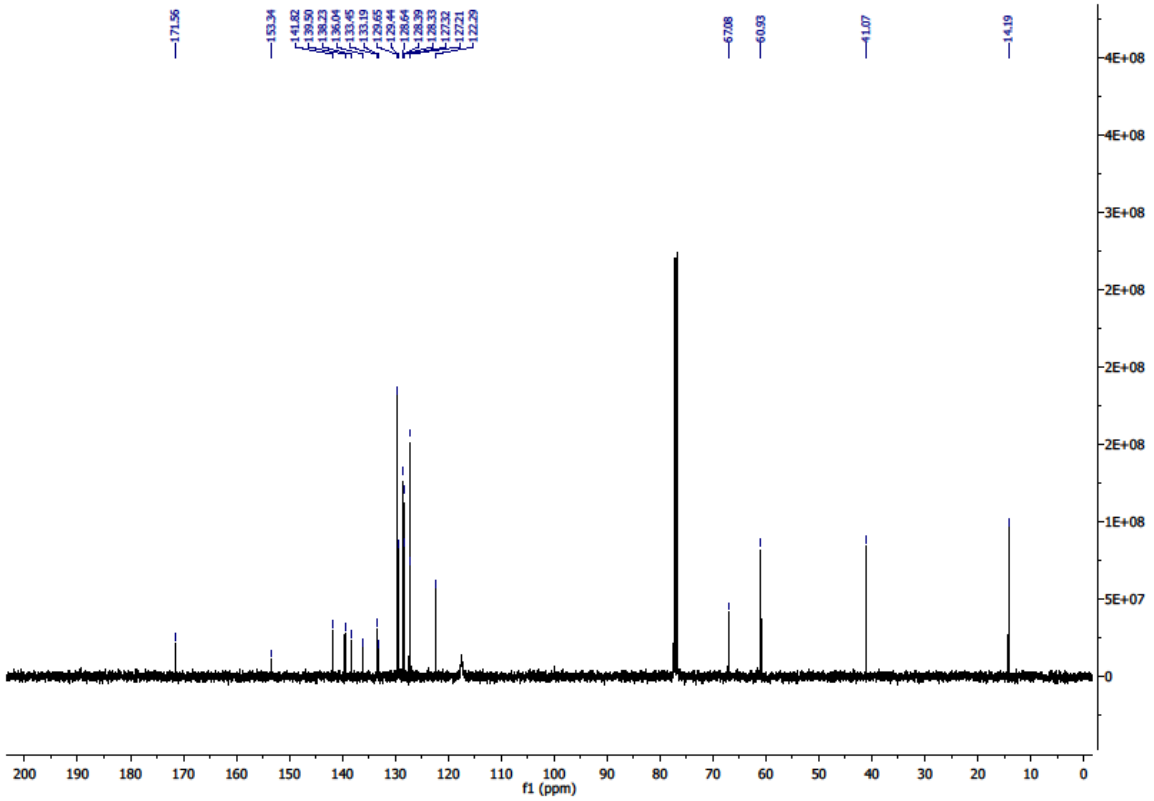

IDC10b MW=389?
C24H23NO4
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Dr AJB Watson
24/10/2013 17:13:46
390.1701
391.1735
Observed Data
NL:
1.45E7
STRWAT137-OS-HNESP#27-41 RT: 0.66-1.02 AV: 15 T: FTMS + p NSI Full ms [120.00-2000.00]
Relative Abundance
390.1700
391.1733
392.1761
393.1789
Theoretical Isotope Model: [M + H]+
NL:
1.78E4
C24 H23 NO4 H:
C24 H24 N1 O4
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
m/z

Compound 14

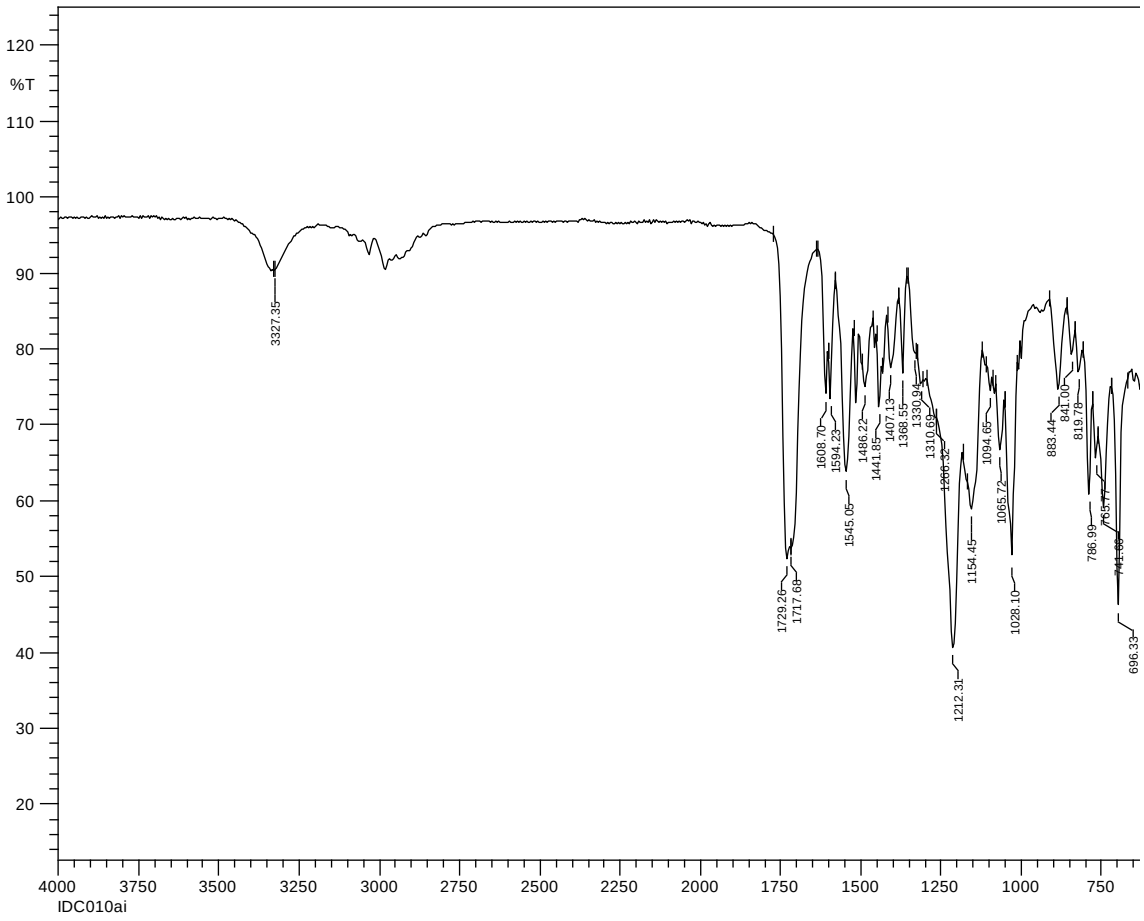
^{1}H NMR



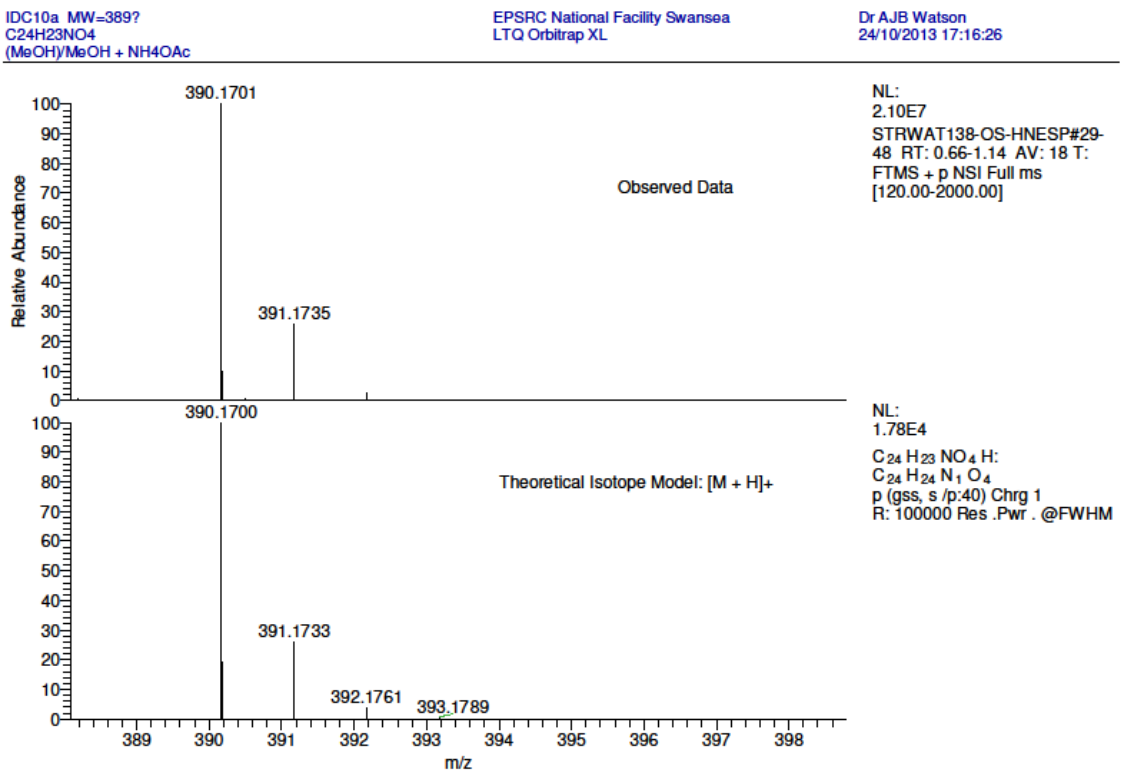
^{13}C NMR



IR

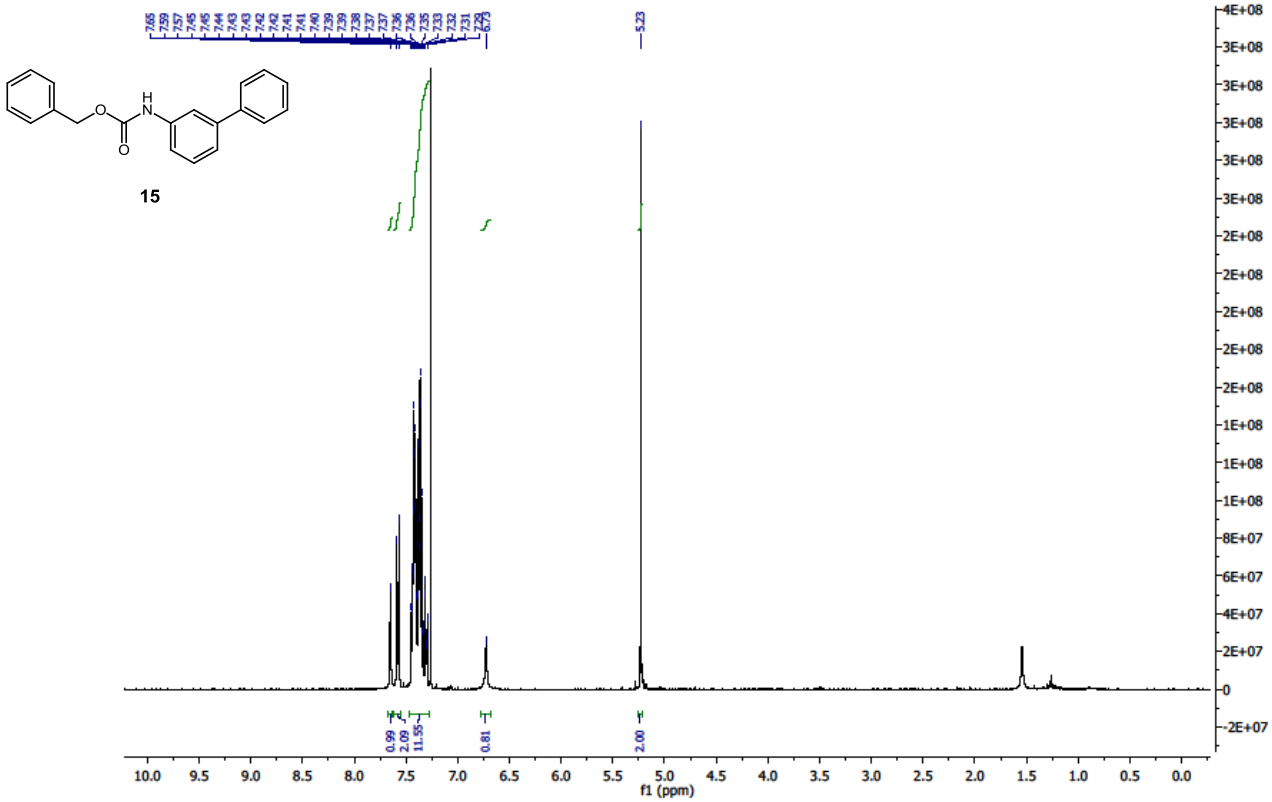

%T
3327.35
1729.26
1717.68
1608.70
1594.23
1545.05
1486.22
1441.85
1407.13
1368.55
1330.04
1310.69
1266.32
1212.31
1154.45
1094.65
1065.72
1028.10
883.44
841.00
819.78
786.99
765.77
741.66
696.33
IDC010ai

HRMS

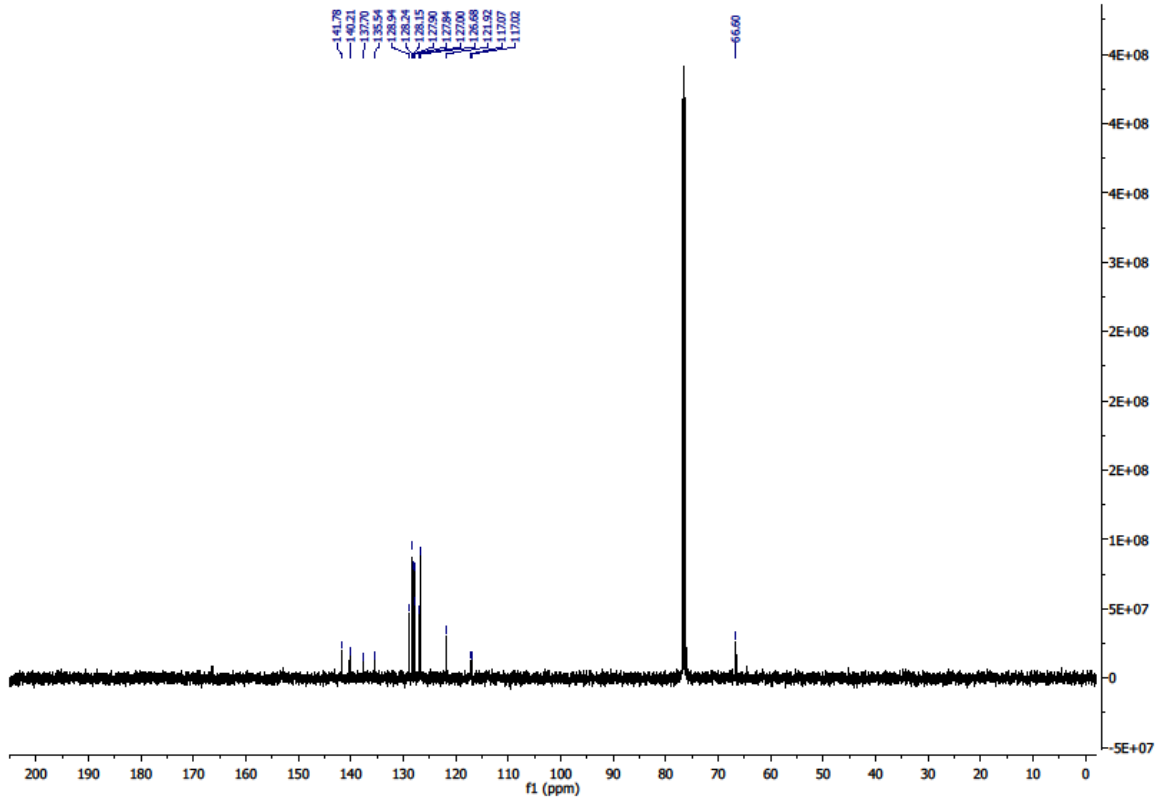

IDC10a MW=389?
C24H23NO4
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Dr AJB Watson
24/10/2013 17:16:26
Relative Abundance
390.1701
391.1735
Observed Data
NL:
2.10E7
STRWAT138-OS-HNESP#29-48 RT: 0.66-1.14 AV: 18 T: FTMS + p NSI Full ms [120.00-2000.00]
390.1700
391.1733
392.1761
393.1789
Theoretical Isotope Model: [M + H]+
NL:
1.78E4
C24 H23 NO4 H:
C24 H24 N1 O4
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
m/z

Compound 15

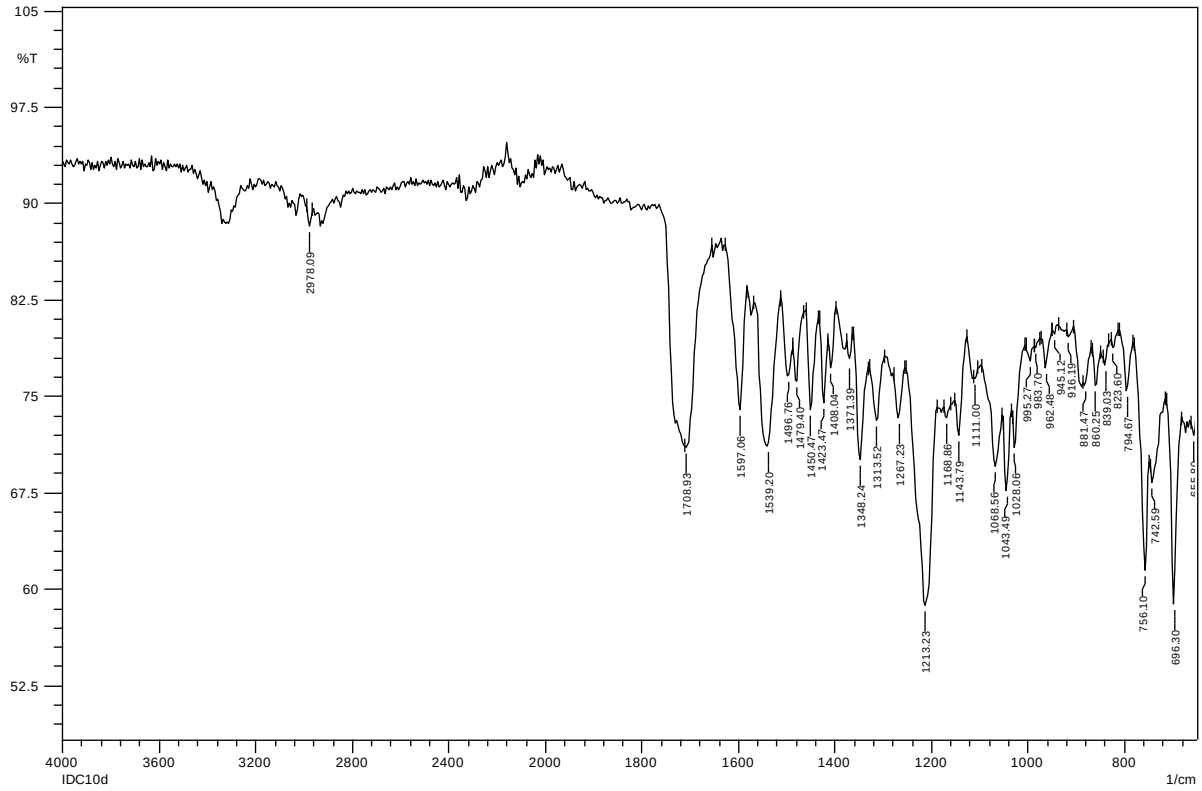
^{1}H NMR



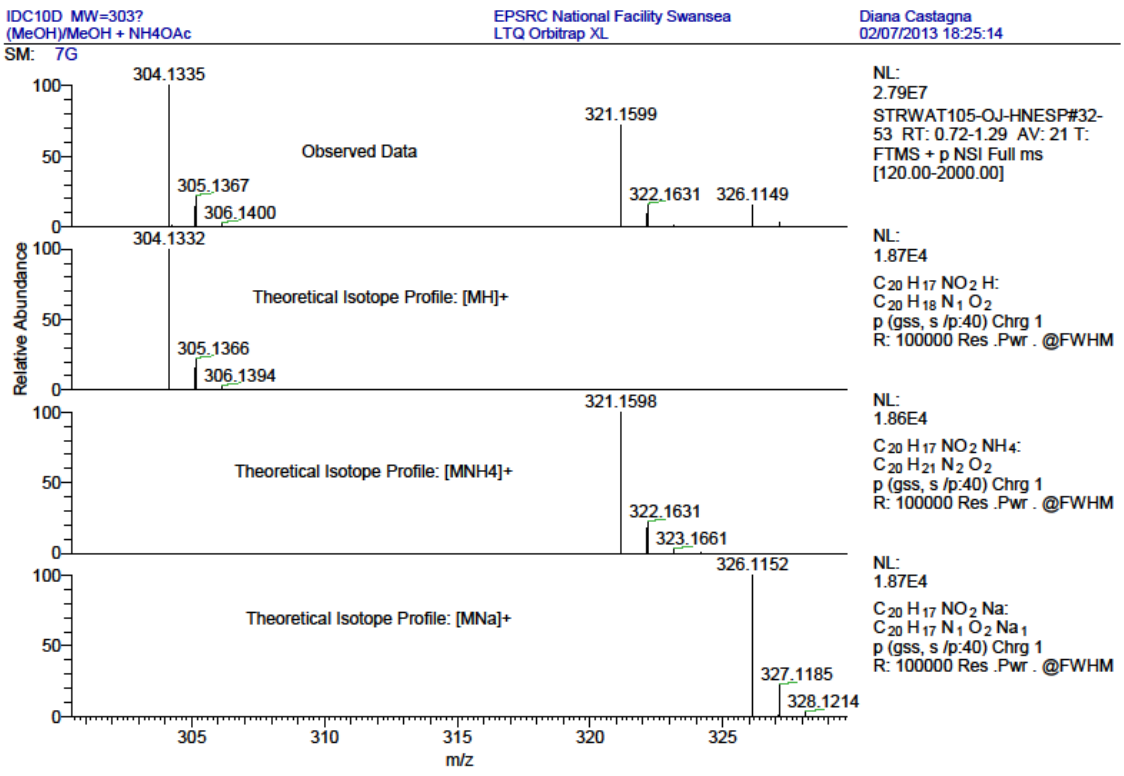
^{13}C NMR



IR

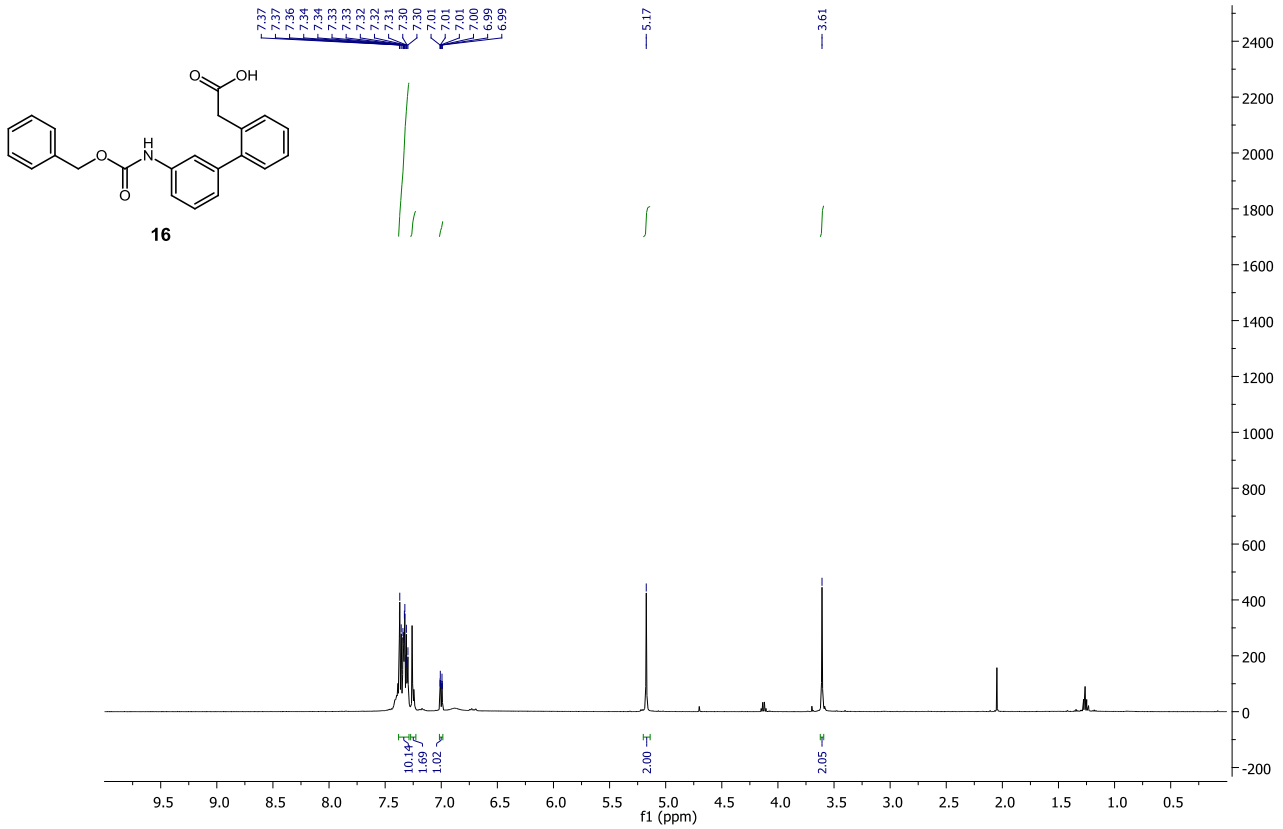

105
%T
97.5
90
82.5
75
67.5
60
52.5
2978.09
1708.93
1597.06
1539.20
1496.76
1479.40
1450.47
1423.47
1408.04
1371.39
1348.24
1313.52
1267.23
1213.23
1168.86
1143.79
1111.00
1068.56
1043.49
1028.06
995.27
983.70
962.48
945.12
916.19
881.47
860.23
839.03
823.60
794.67
756.10
742.59
696.30
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
IDC10d
1/cm

HRMS

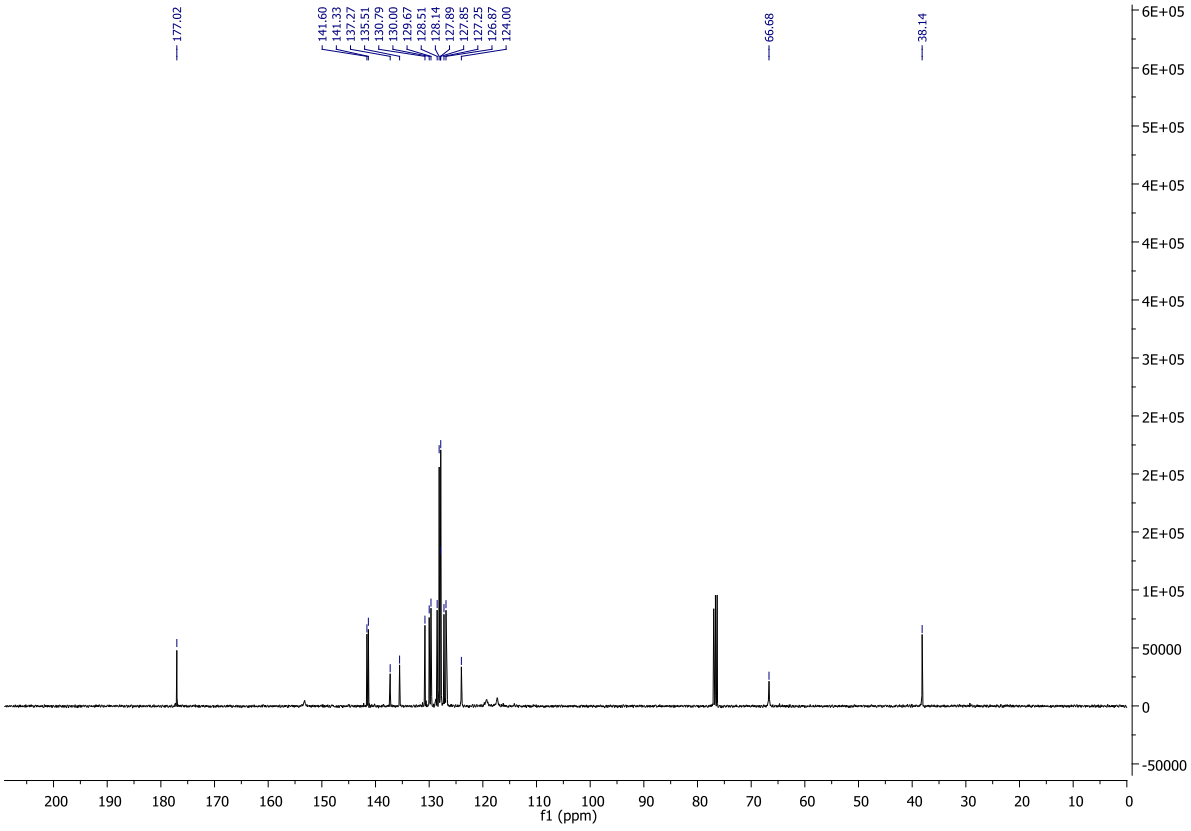

IDC10D MW=303?
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
02/07/2013 18:25:14
SM: 7G
304.1335
321.1599
Observed Data
305.1367
306.1400
322.1631
326.1149
NL:
2.79E7
STRWAT105-OJ-HNESP#32-53 RT: 0.72-1.29 AV: 21 T: FTMS + p NSI Full ms [120.00-2000.00]
304.1332
Theoretical Isotope Profile: [MH]+
305.1366
306.1394
NL:
1.87E4
C20 H17 NO2 H:
C20 H18 N1 O2
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
321.1598
Theoretical Isotope Profile: [MNH4]+
322.1631
323.1661
NL:
1.86E4
C20 H17 NO2 NH4:
C20 H21 N2 O2
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
326.1152
Theoretical Isotope Profile: [MNa]+
327.1185
328.1214
NL:
1.87E4
C20 H17 NO2 Na:
C20 H17 N1 O2 Na1
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
Relative Abundance
100
50
0
305
310
315
320
325
m/z

Compound 16

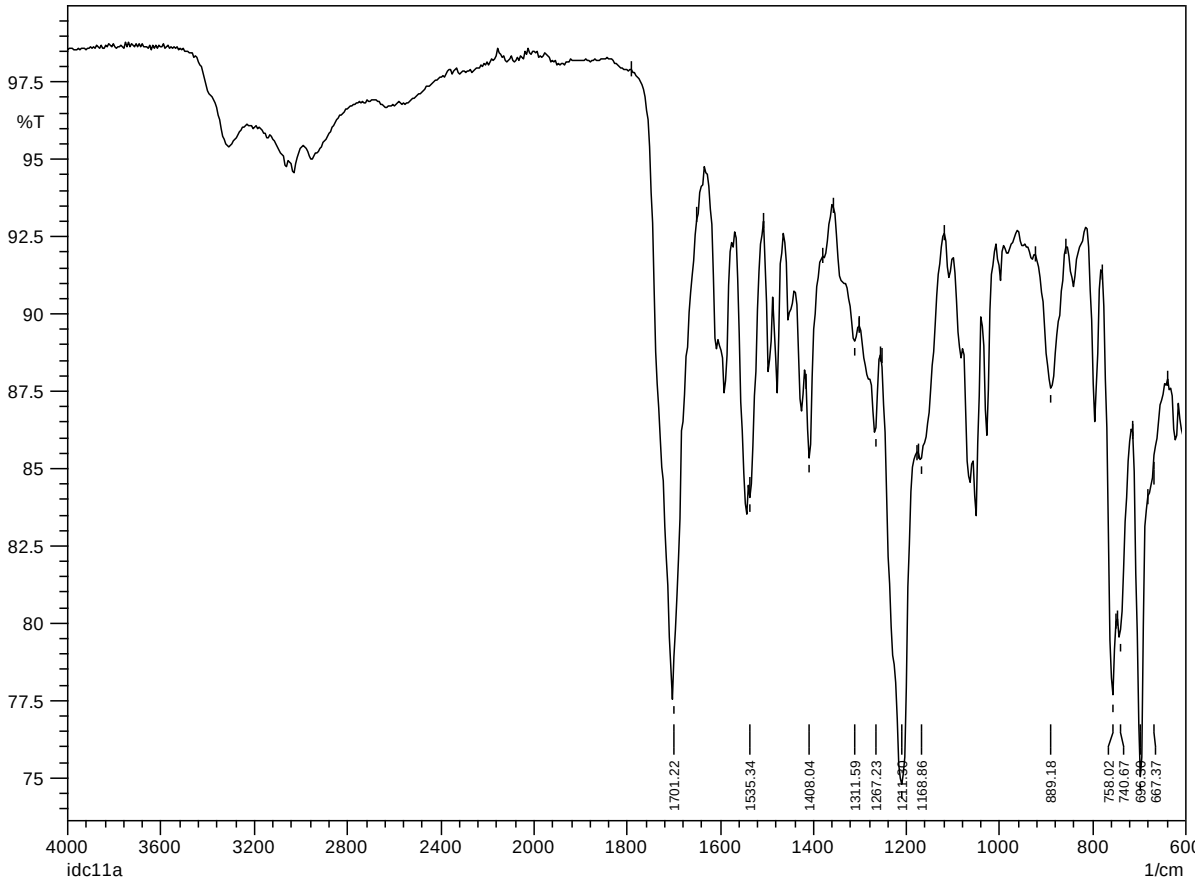
^{1}H NMR



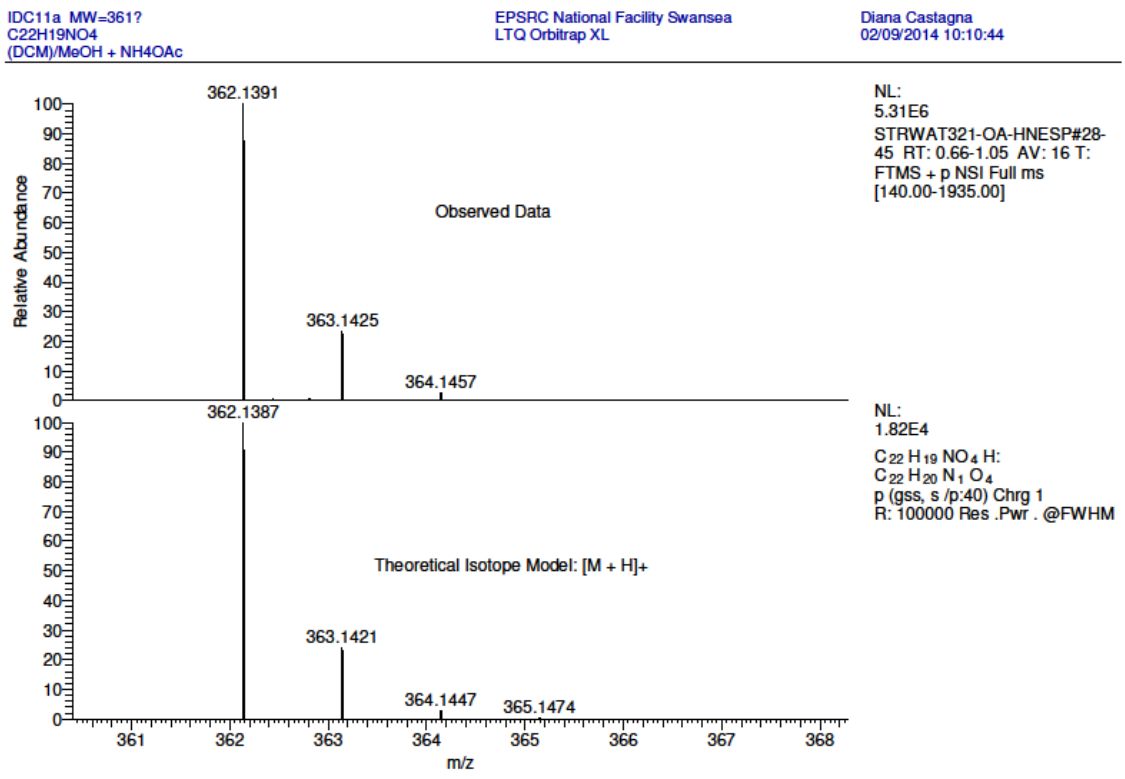
^{13}C NMR



IR

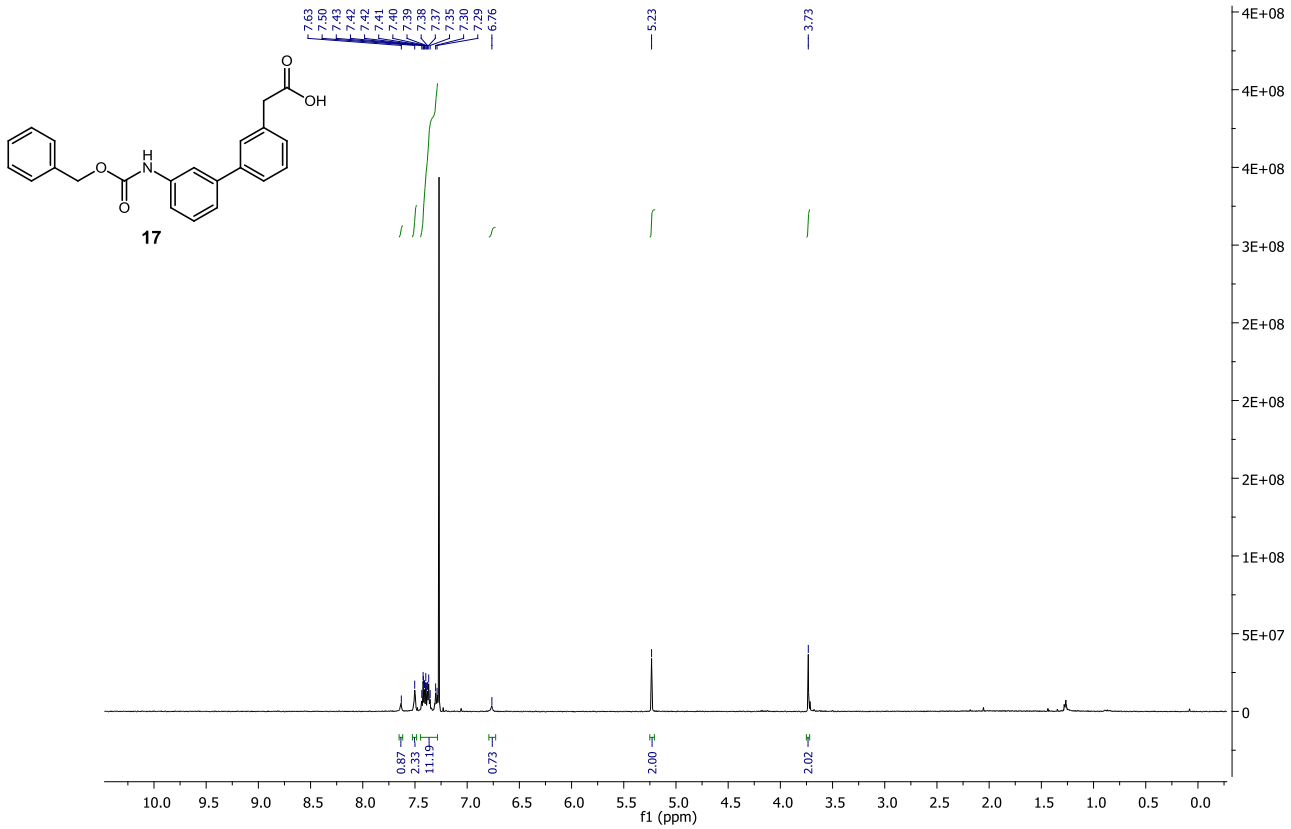

97.5
%T
95
92.5
90
87.5
85
82.5
80
77.5
75
1701.22
1535.34
1408.04
1311.59
1267.23
1168.86
889.18
758.02
740.67
667.37
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
idc11a
1/cm

HRMS

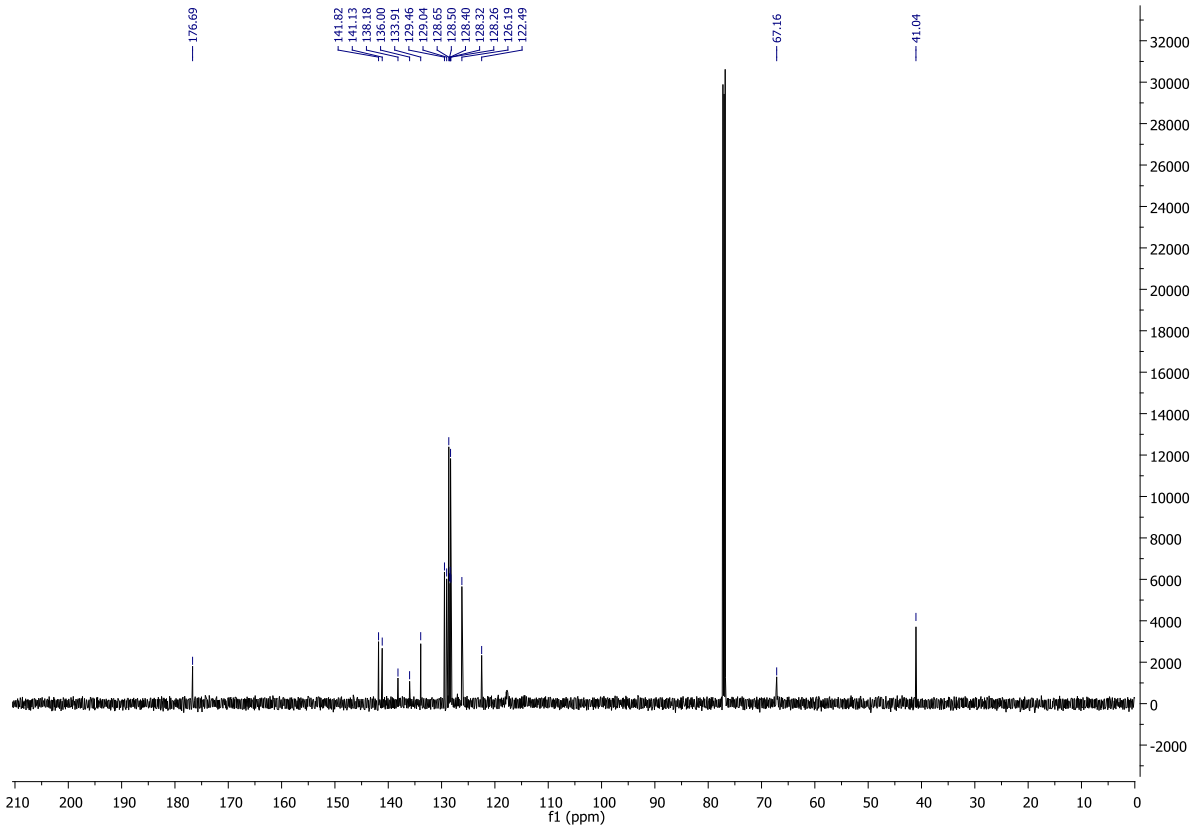

IDC11a MW=361?
C22H19NO4
(DCM)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
02/09/2014 10:10:44
362.1391
363.1425
364.1457
Observed Data
NL:
5.31E6
STRWAT321-OA-HNESP#28-45 RT: 0.66-1.05 AV: 16 T: FTMS + p NSI Full ms [140.00-1935.00]
362.1387
363.1421
364.1447
365.1474
Theoretical Isotope Model: [M + H]+
NL:
1.82E4
C22 H19 NO4 H:
C22 H20 N1 O4
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
Relative Abundance
m/z

Compound 17

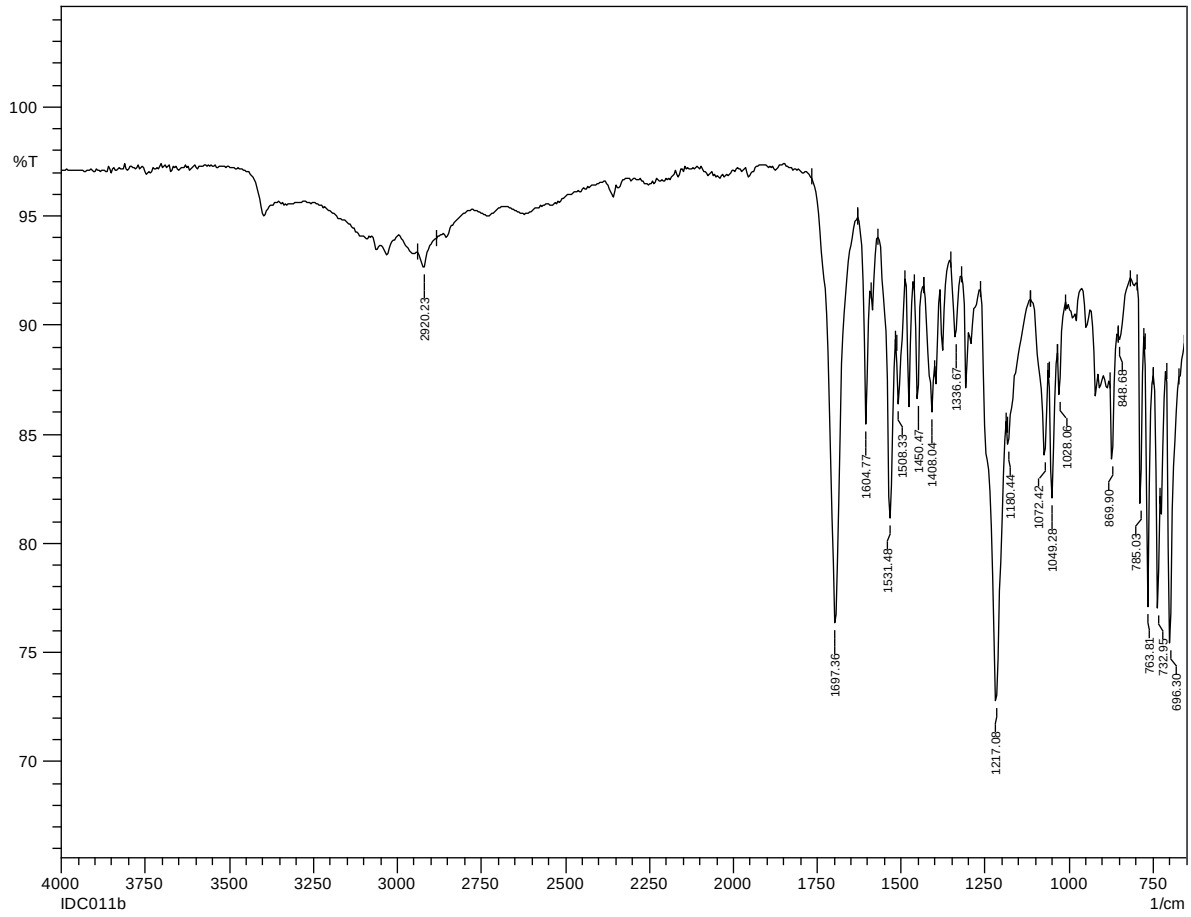
^{1}H NMR



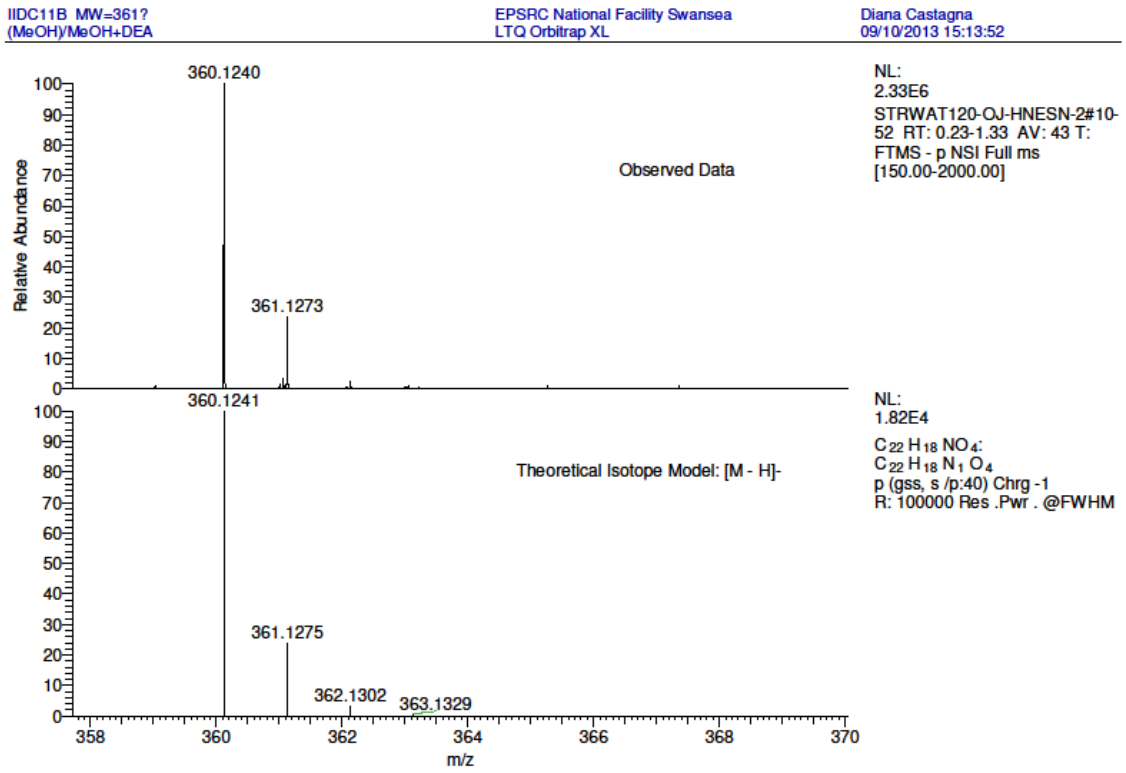
^{13}C NMR



IR

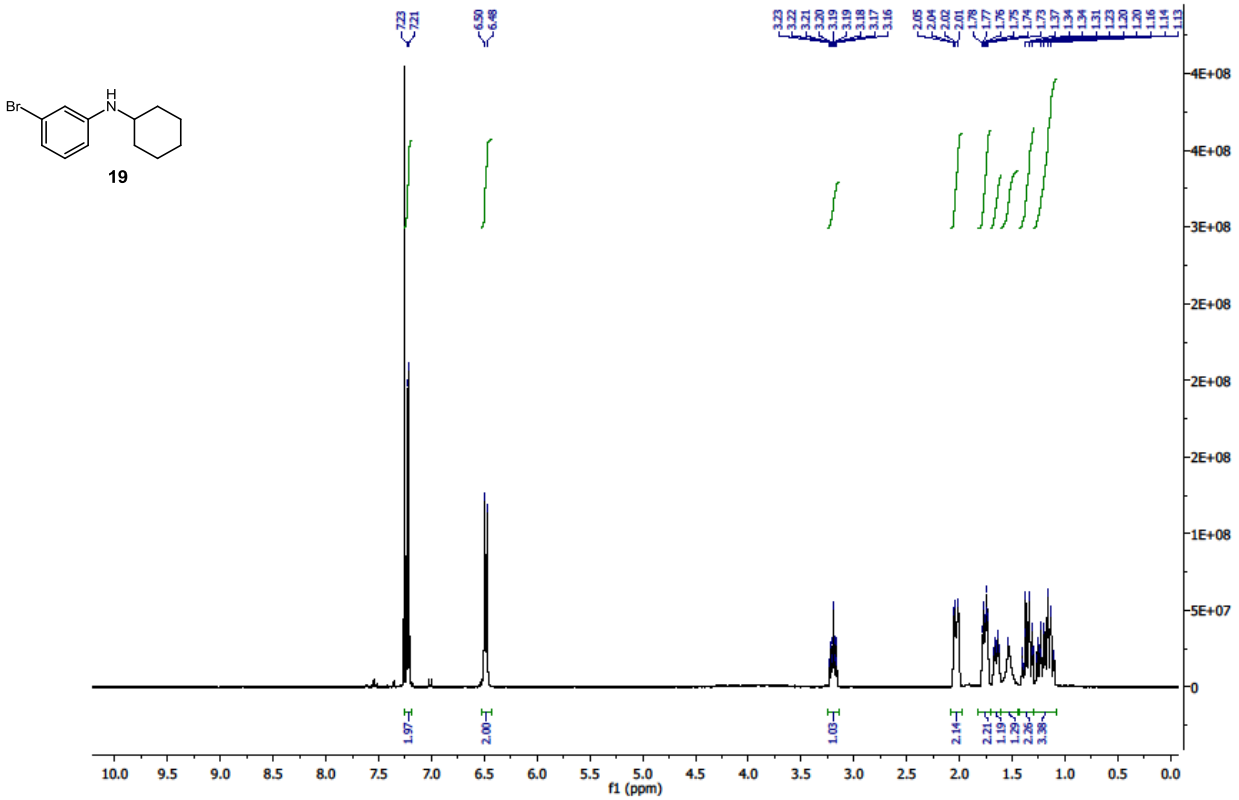

100
%T
95
90
85
80
75
70
2920.23
1697.36
1604.77
1531.48
1508.33
1450.47
1408.04
1336.67
1217.08
1180.44
1072.42
1049.28
1028.06
869.90
848.68
785.03
763.81
732.95
696.30
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
IDC011b
1/cm

HRMS

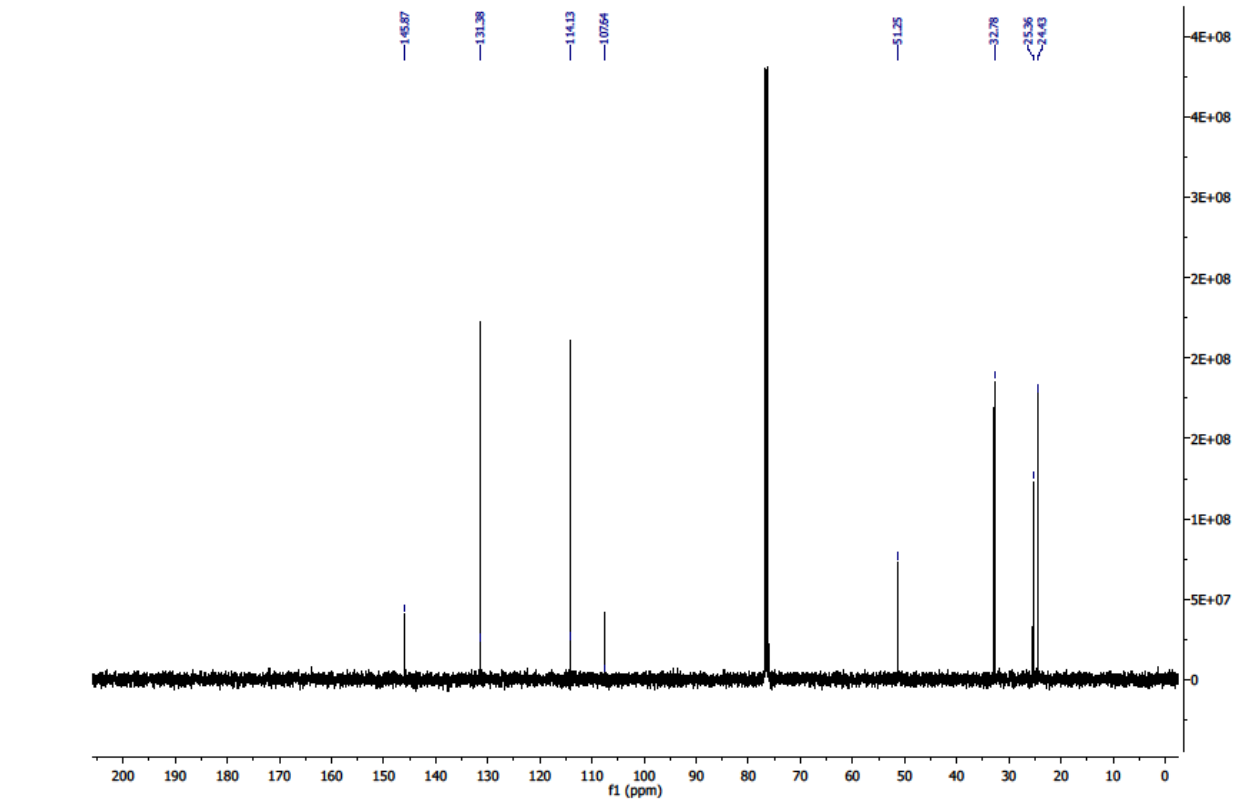

IIDC11B MW=361?
(MeOH)/MeOH+DEA
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
09/10/2013 15:13:52
360.1240
361.1273
Observed Data
NL:
2.33E6
STRWAT120-OJ-HNESN-2#10-52 RT: 0.23-1.33 AV: 43 T: FTMS - p NSI Full ms [150.00-2000.00]
Relative Abundance
360.1241
361.1275
362.1302
363.1329
Theoretical Isotope Model: [M - H]-
NL:
1.82E4
C22 H18 NO4:
C22 H18 N1 O4
p (gss, s /p:40) Chrg -1
R: 100000 Res .Pwr . @FWHM
358
360
362
364
366
368
370
m/z

Compound 19

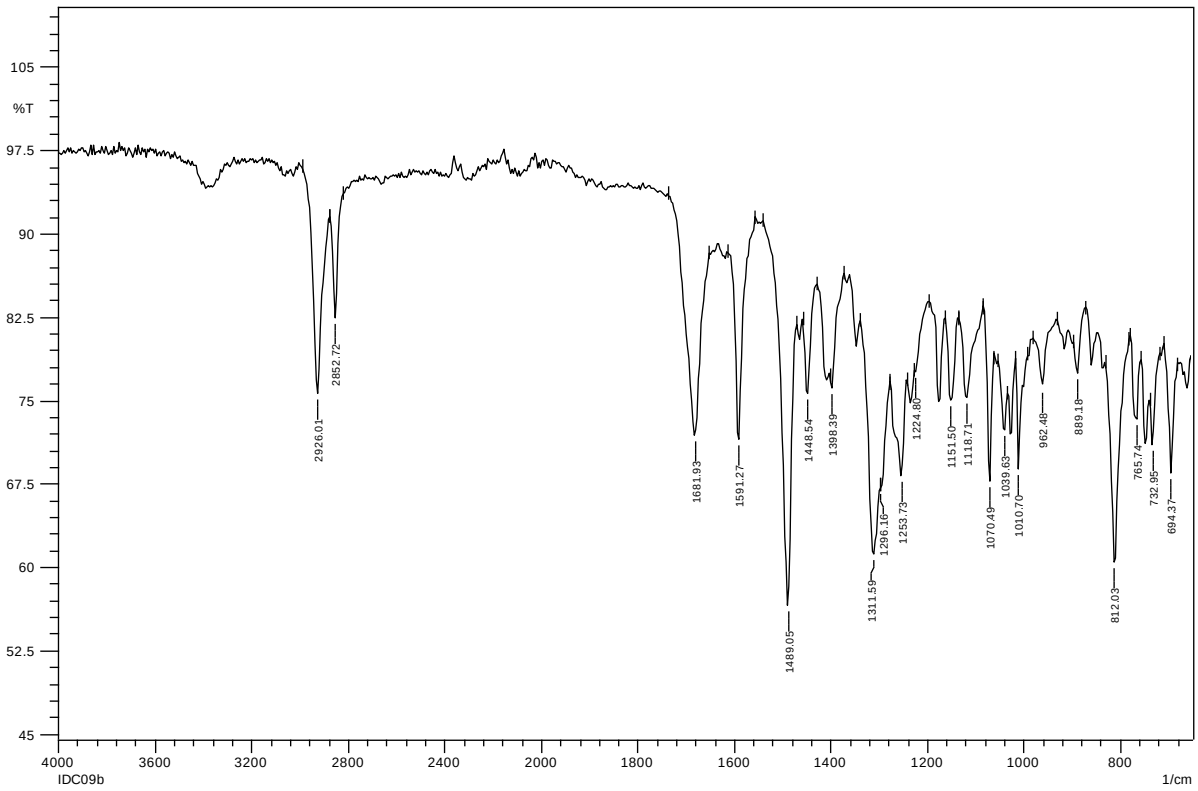
^{1}H NMR



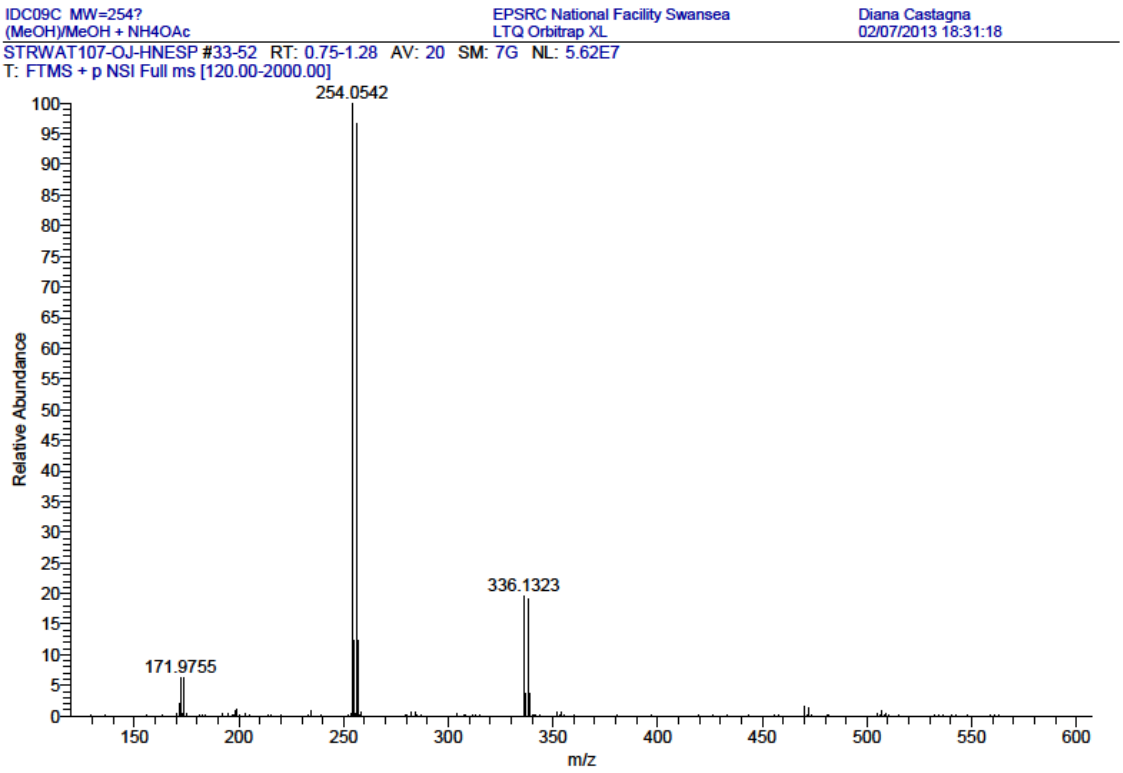
^{13}C NMR



IR

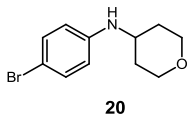

105
%T
97.5
90
82.5
75
67.5
60
52.5
45
2926.01
2852.72
1681.93
1591.27
1489.05
1448.54
1398.39
1311.59
1296.16
1253.73
1224.80
1151.50
1118.71
1070.49
1039.63
1010.70
962.48
889.18
812.03
765.74
732.95
694.37
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
IDC09b
1/cm

HRMS

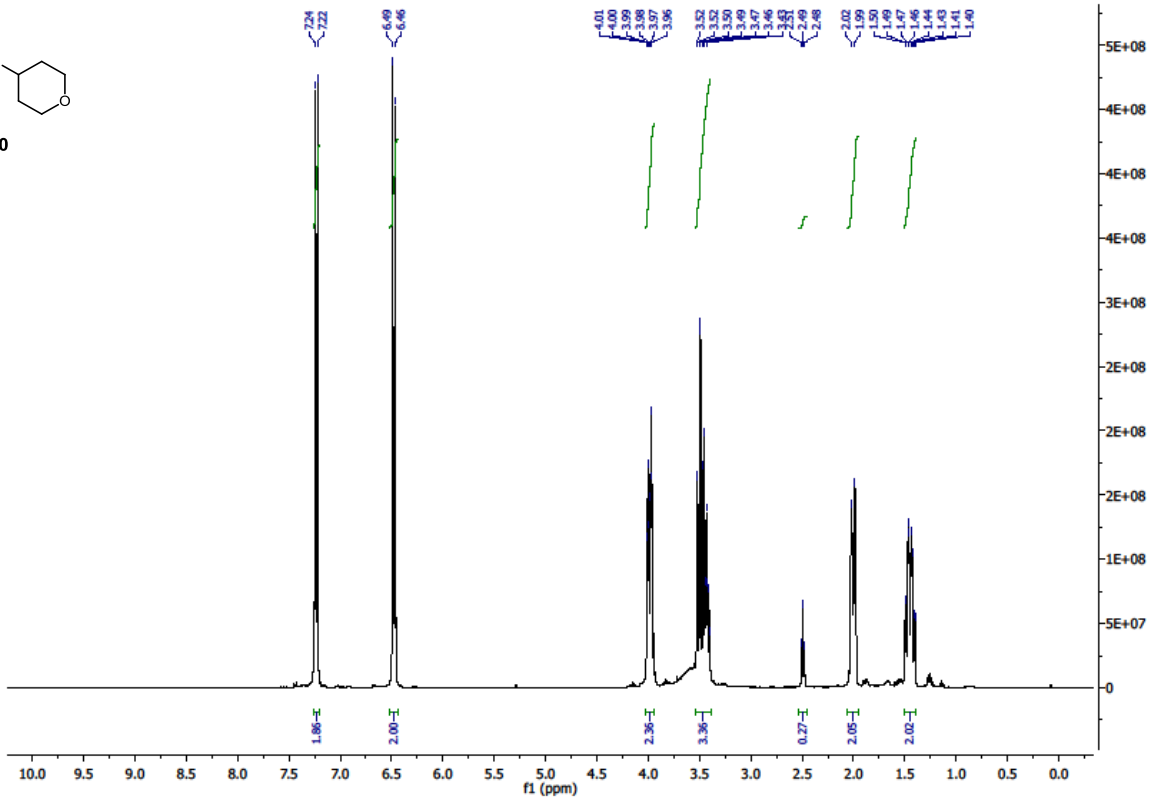

IDC09C MW=254?
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
02/07/2013 18:31:18
STRWAT107-OJ-HNESP #33-52 RT: 0.75-1.28 AV: 20 SM: 7G NL: 5.62E7
T: FTMS + p NSI Full ms [120.00-2000.00]
254.0542
336.1323
171.9755
Relative Abundance
m/z

Compound 20

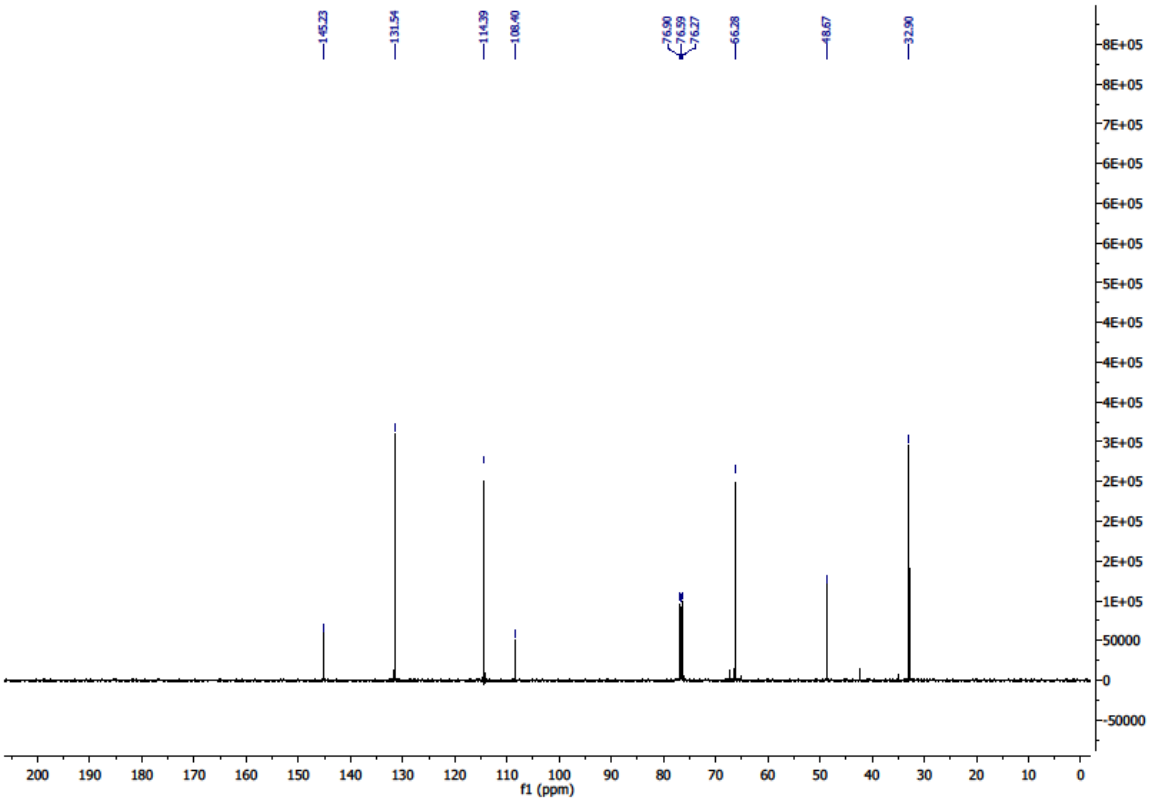
^{1}H NMR



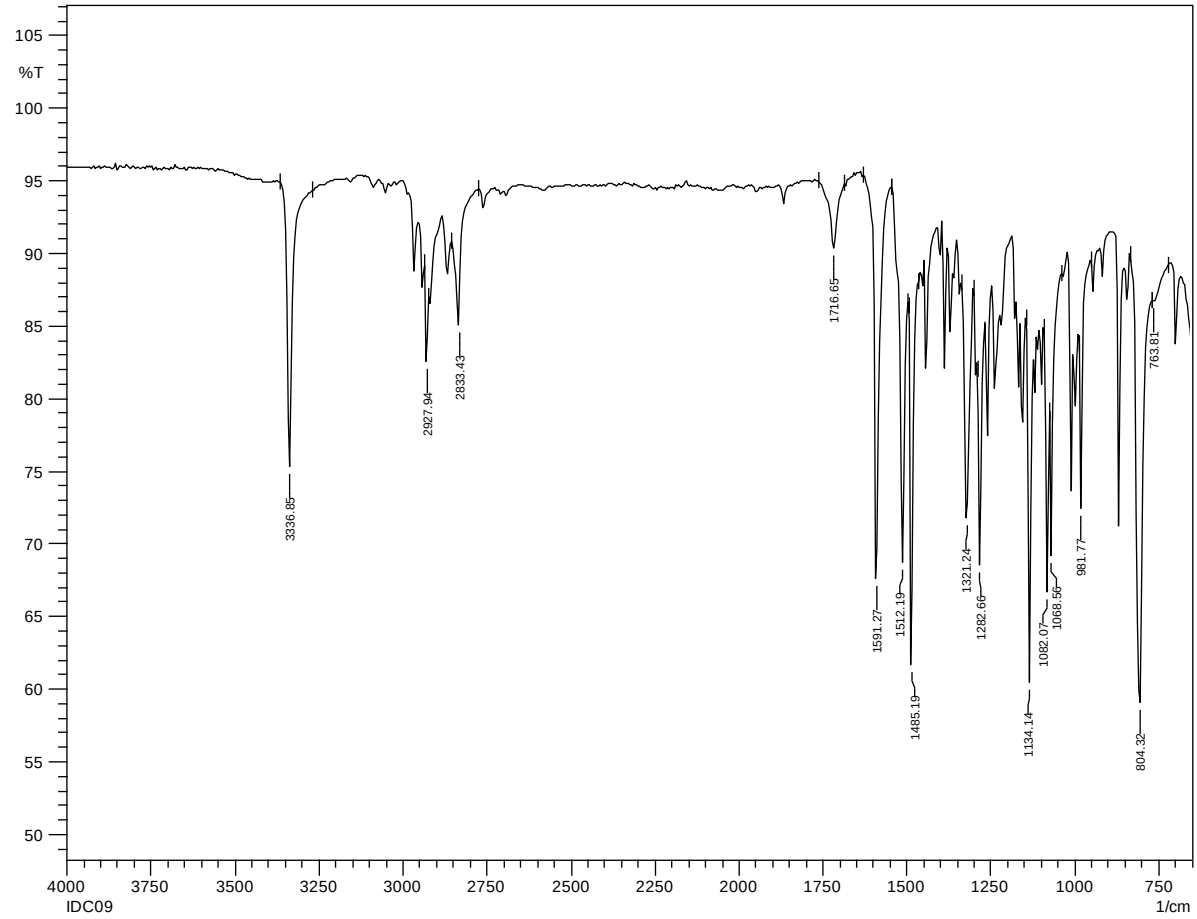
20



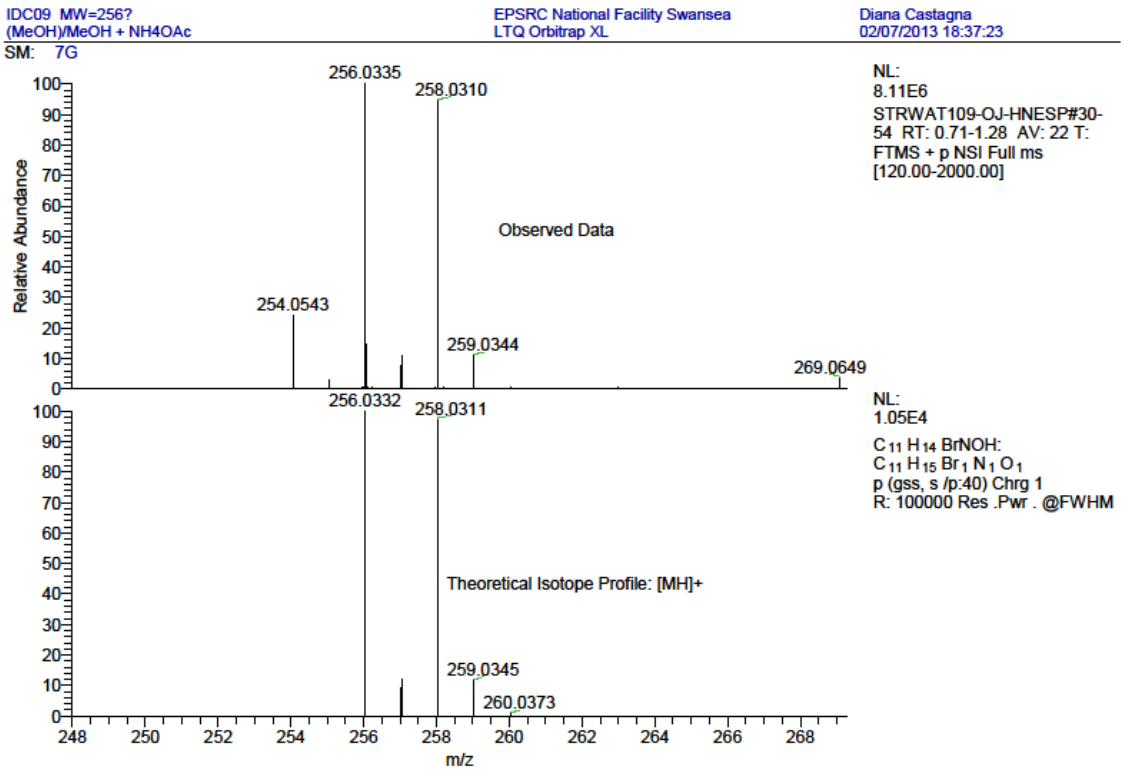
^{13}C NMR



IR

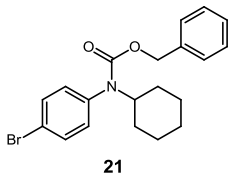

105
%T
100
95
90
85
80
75
70
65
60
55
50
3336.85
2927.94
2833.43
1716.65
1591.27
1512.19
1485.19
1321.24
1282.66
1134.14
1082.07
1068.56
981.77
804.32
763.81
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
IDC09
1/cm

HRMS

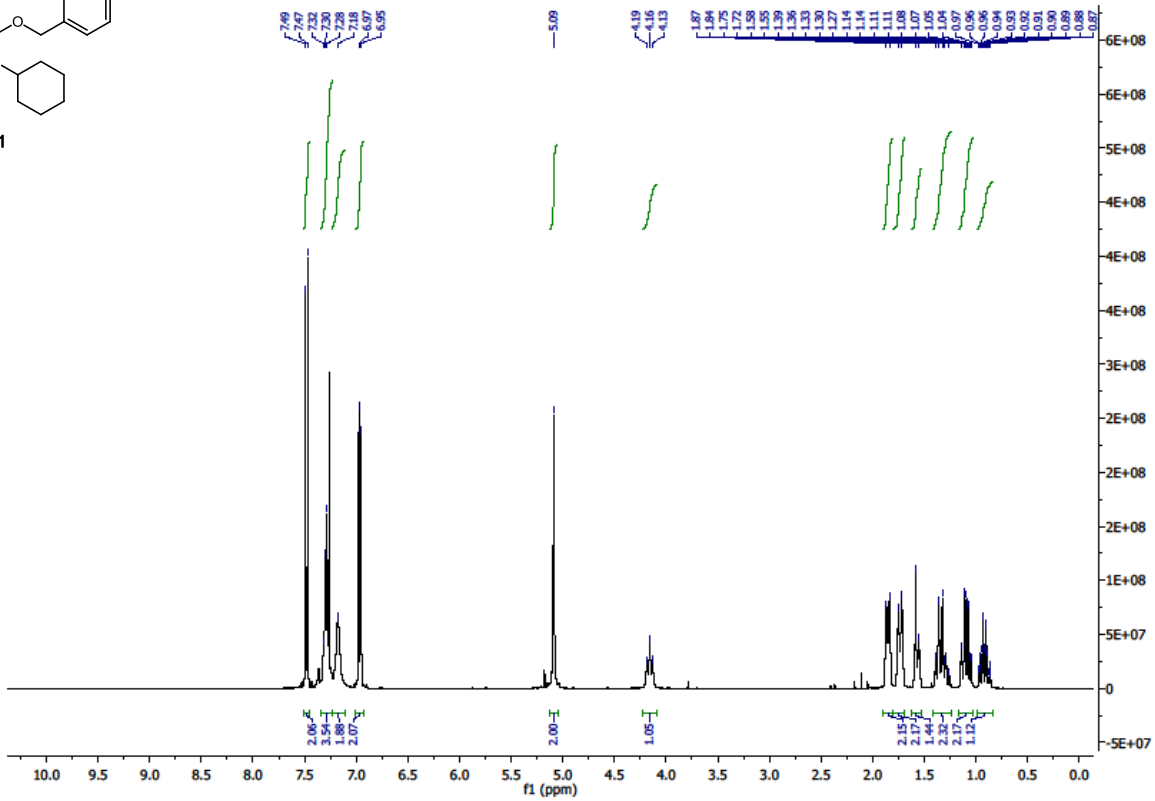

IDC09 MW=256?
(MeOH)/MeOH + NH4OAc
SM: 7G
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
02/07/2013 18:37:23
NL:
8.11E6
STRWAT109-OJ-HNESP#30-54 RT: 0.71-1.28 AV: 22 T: FTMS + p NSI Full ms [120.00-2000.00]
Relative Abundance
256.0335
258.0310
Observed Data
254.0543
259.0344
269.0649
NL:
1.05E4
C11 H14 BrNOH:
C11 H15 Br1 N1 O1
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
256.0332
258.0311
Theoretical Isotope Profile: [MH]+
259.0345
260.0373
m/z

Compound 21

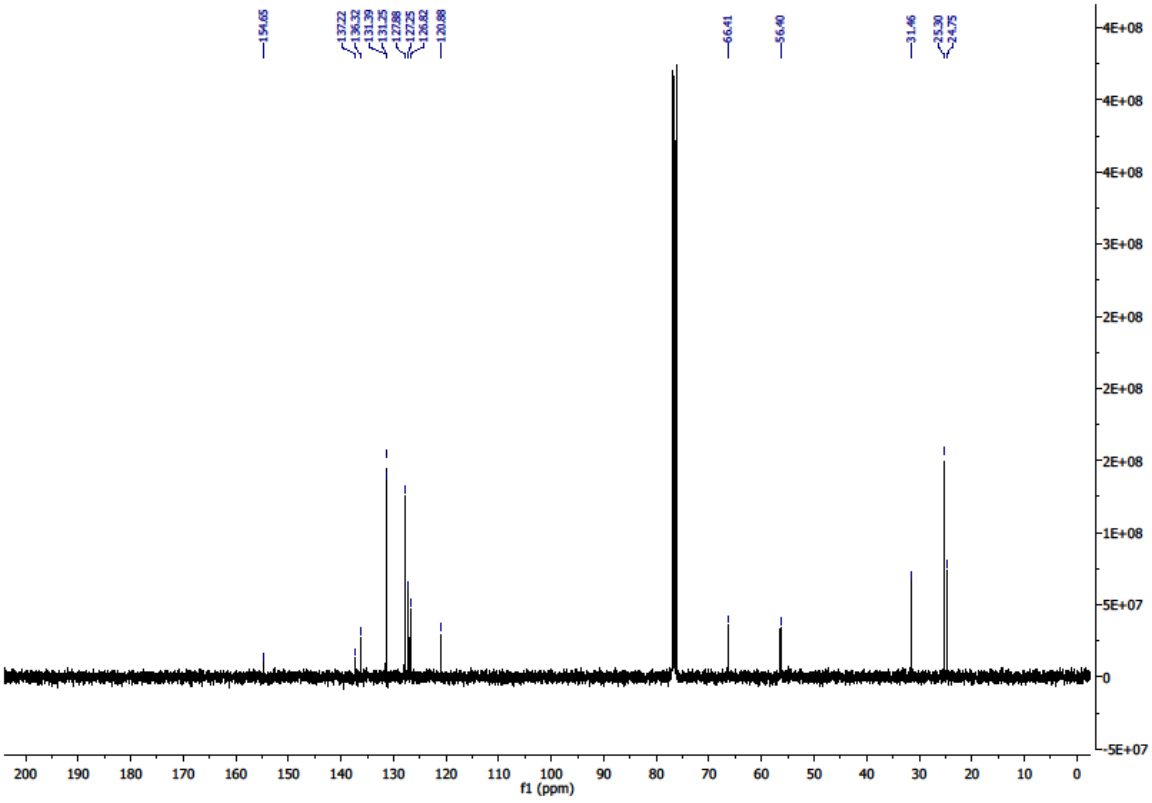
^{1}H NMR



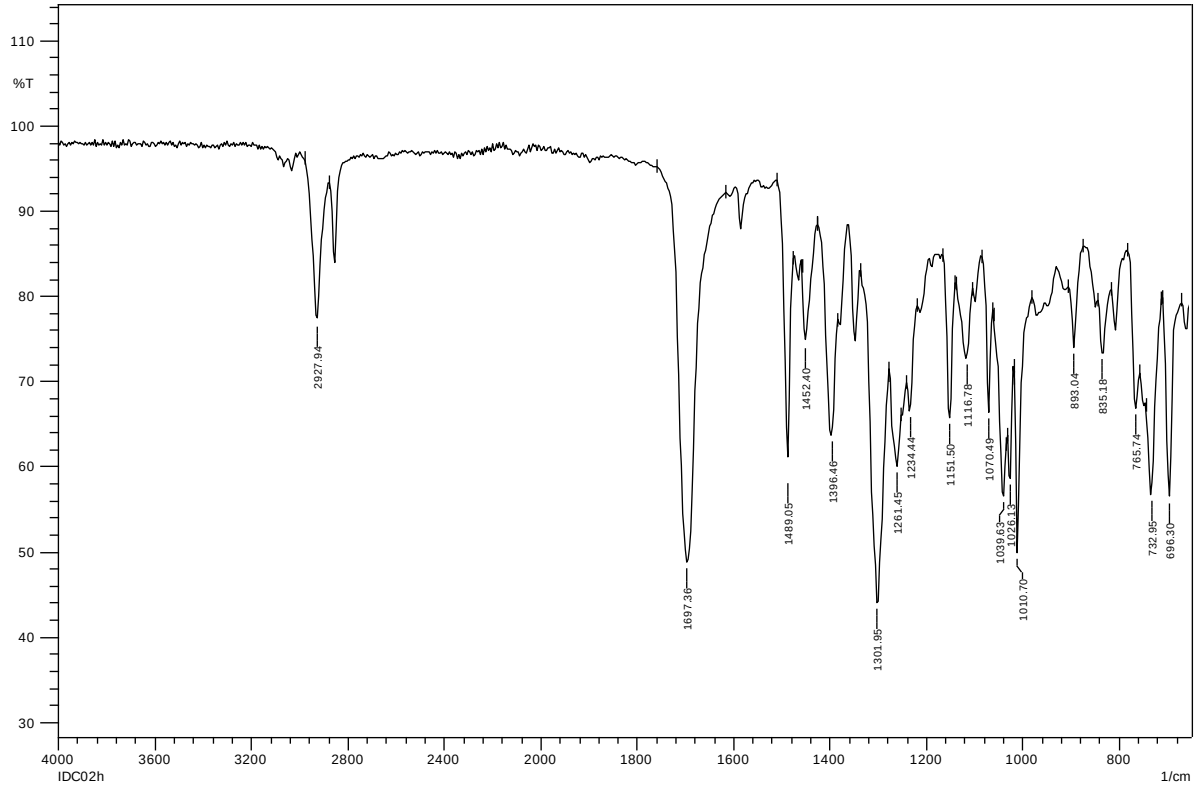
21



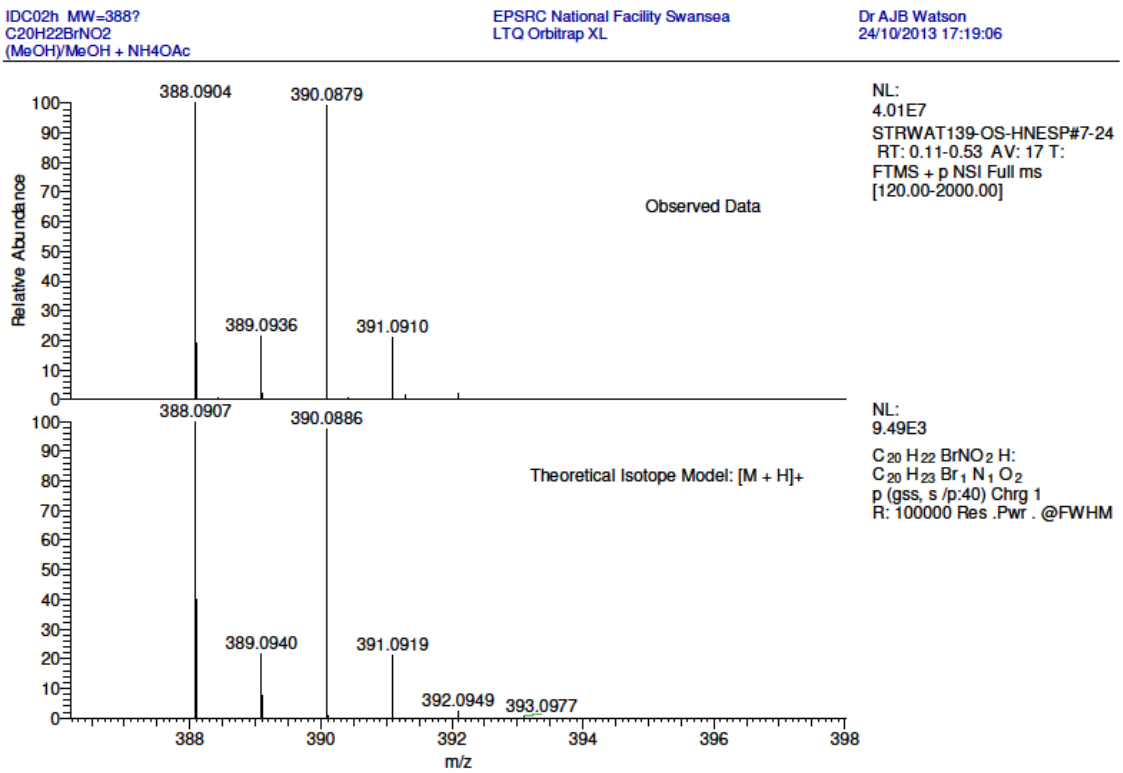
^{13}C NMR



IR

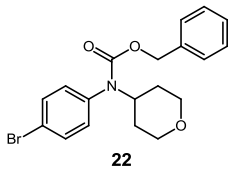

%T
110
100
90
80
70
60
50
40
30
2927.94
1697.36
1489.05
1452.40
1396.46
1301.95
1261.45
1234.44
1151.50
1116.78
1070.49
1039.63
1026.13
1010.70
893.04
835.18
765.74
732.95
696.30
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
IDC02h
1/cm

HRMS

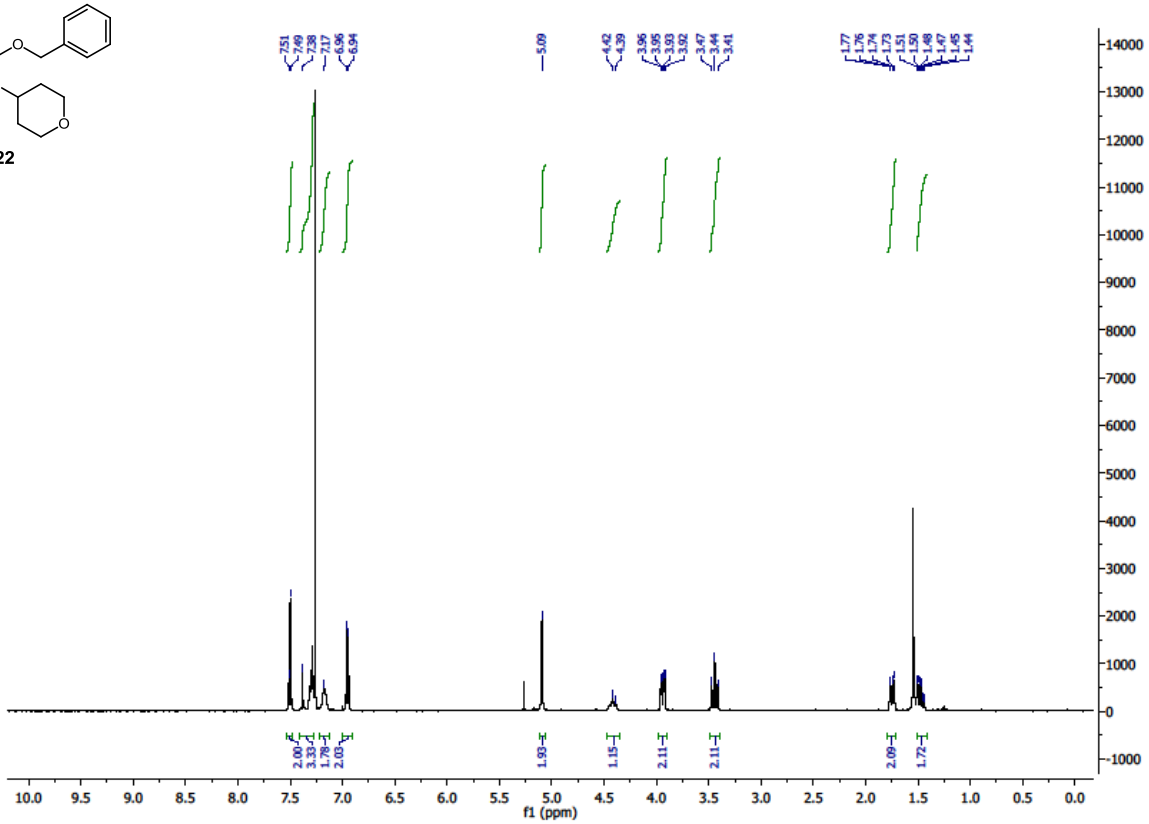

IDC02h MW=388?
C20H22BrNO2
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Dr AJB Watson
24/10/2013 17:19:06
NL:
4.01E7
STRWAT139-OS-HNESP#7-24
RT: 0.11-0.53 AV: 17 T:
FTMS + p NSI Full ms
[120.00-2000.00]
Relative Abundance
388.0904
390.0879
389.0936
391.0910
Observed Data
NL:
9.49E3
C20 H22 BrNO2 H:
C20 H23 Br1 N1 O2
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
388.0907
390.0886
389.0940
391.0919
392.0949
393.0977
Theoretical Isotope Model: [M + H]+
m/z

Compound 22

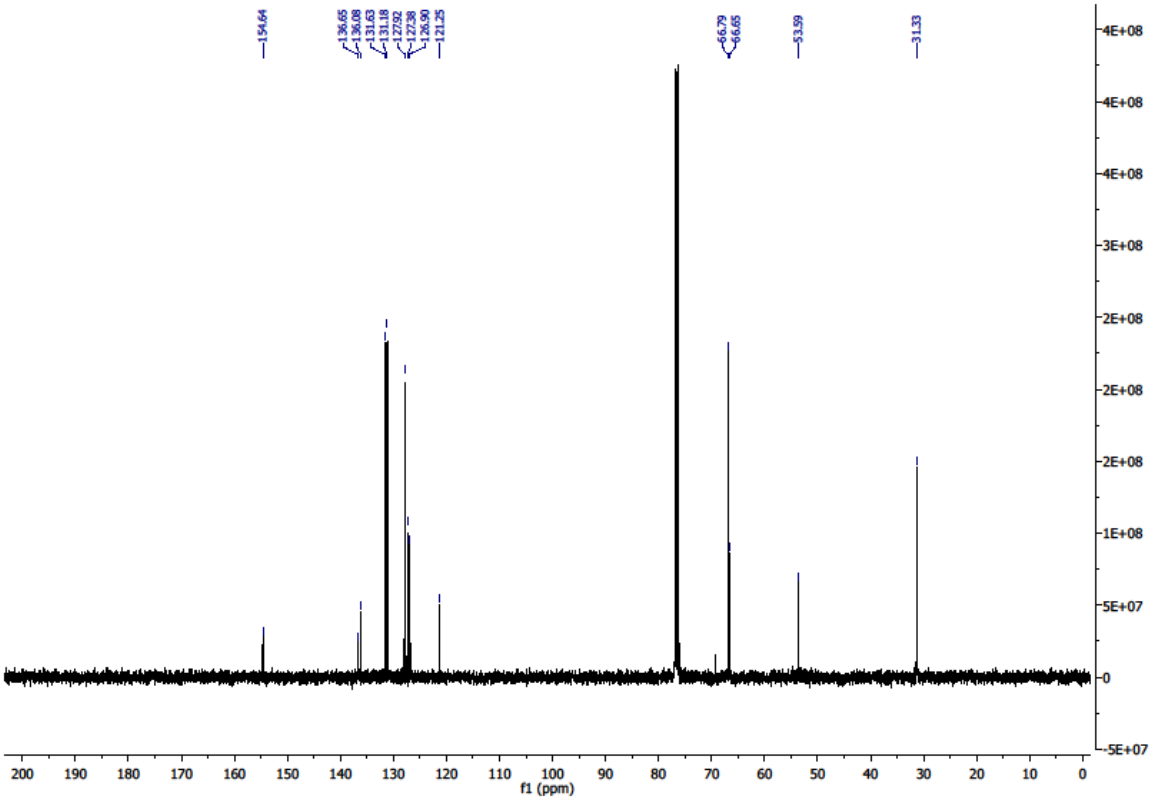
^{1}H NMR



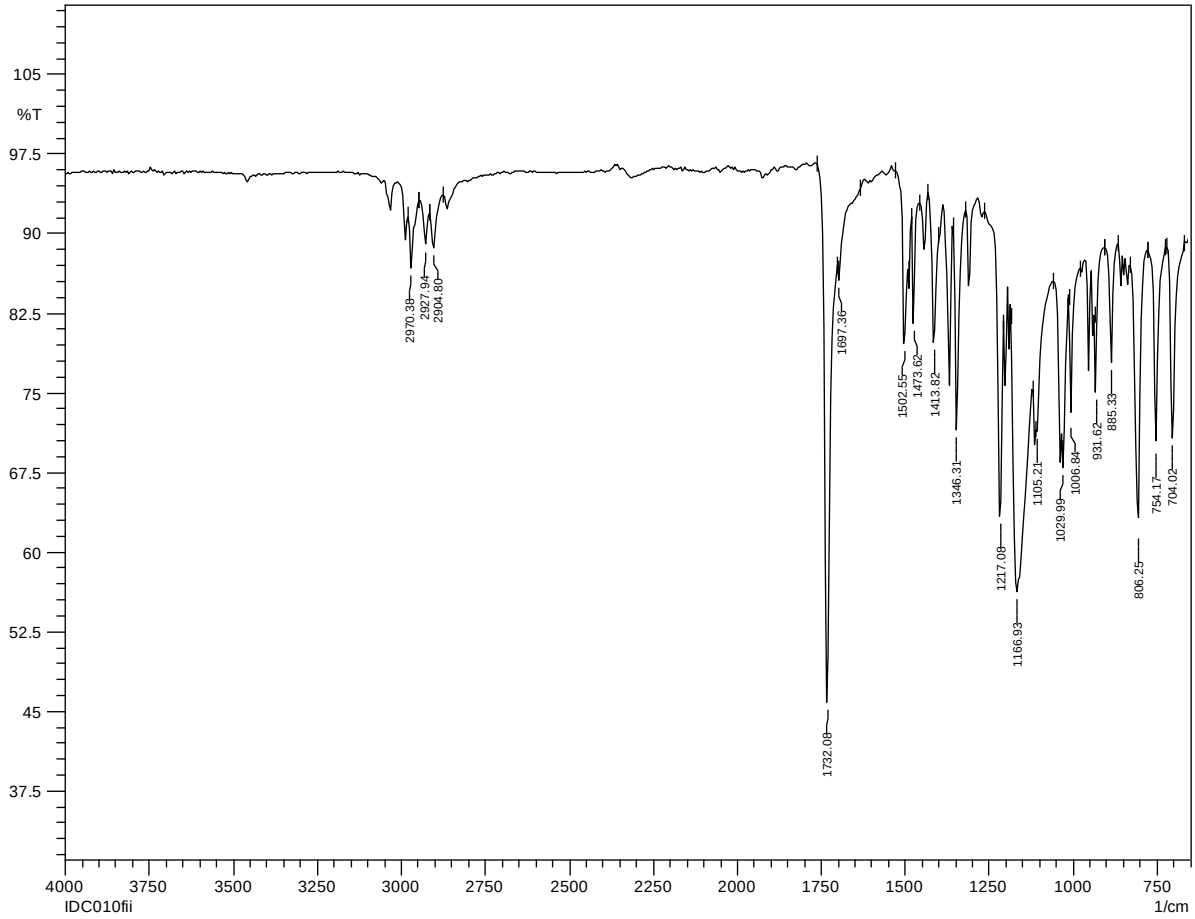
22



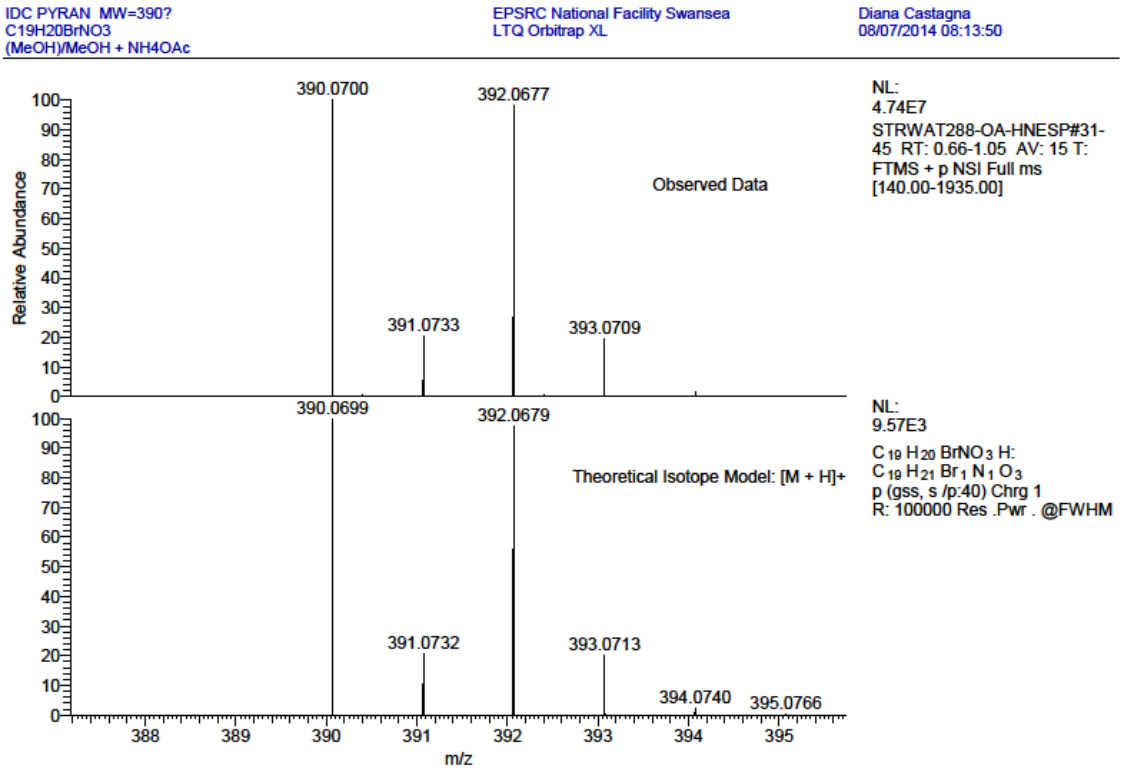
^{13}C NMR



IR

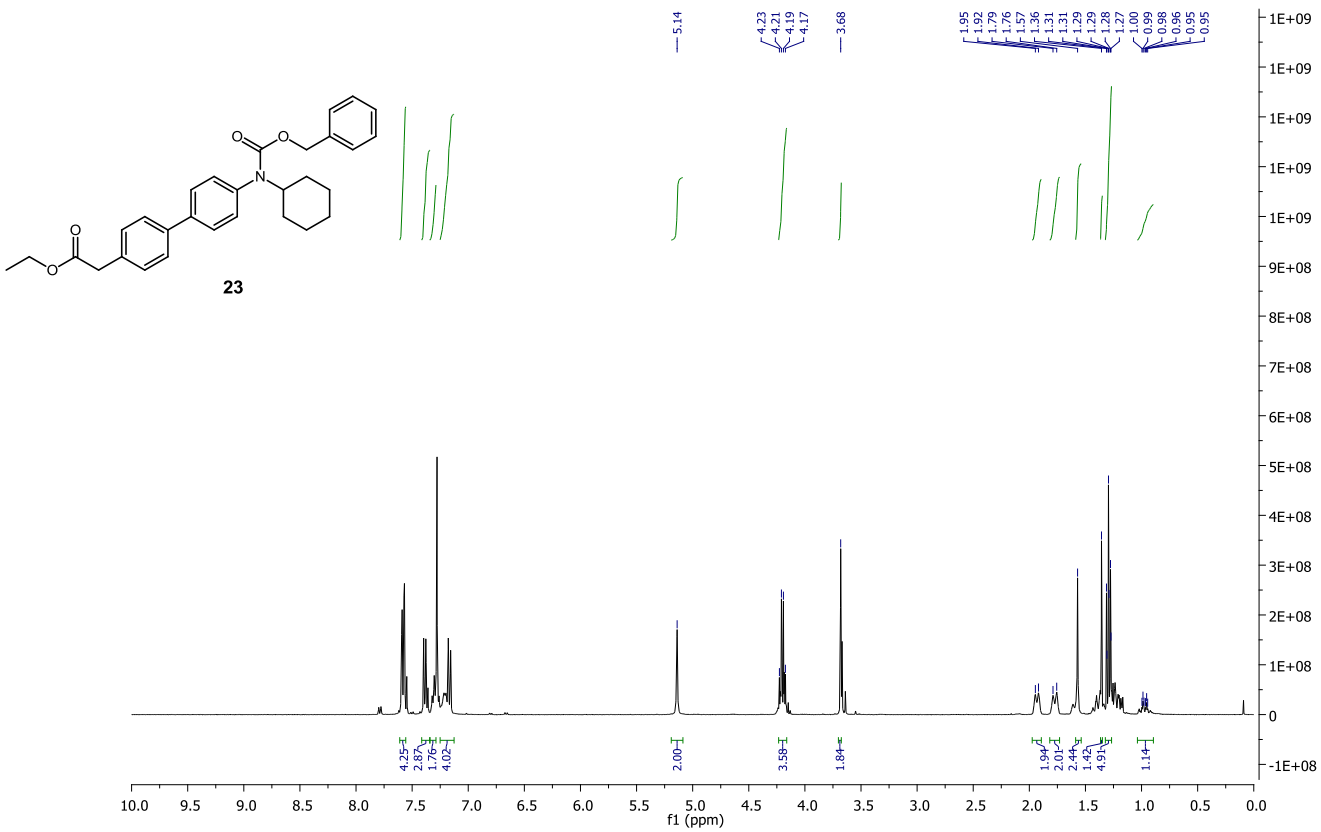

105
%T
97.5
90
82.5
75
67.5
60
52.5
45
37.5
2970.38
2927.94
2904.80
1732.08
1697.36
1502.55
1473.62
1413.82
1346.31
1217.08
1166.93
1105.21
1029.99
1006.84
931.62
885.33
806.25
754.17
704.02
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
IDC010fii
1/cm

HRMS

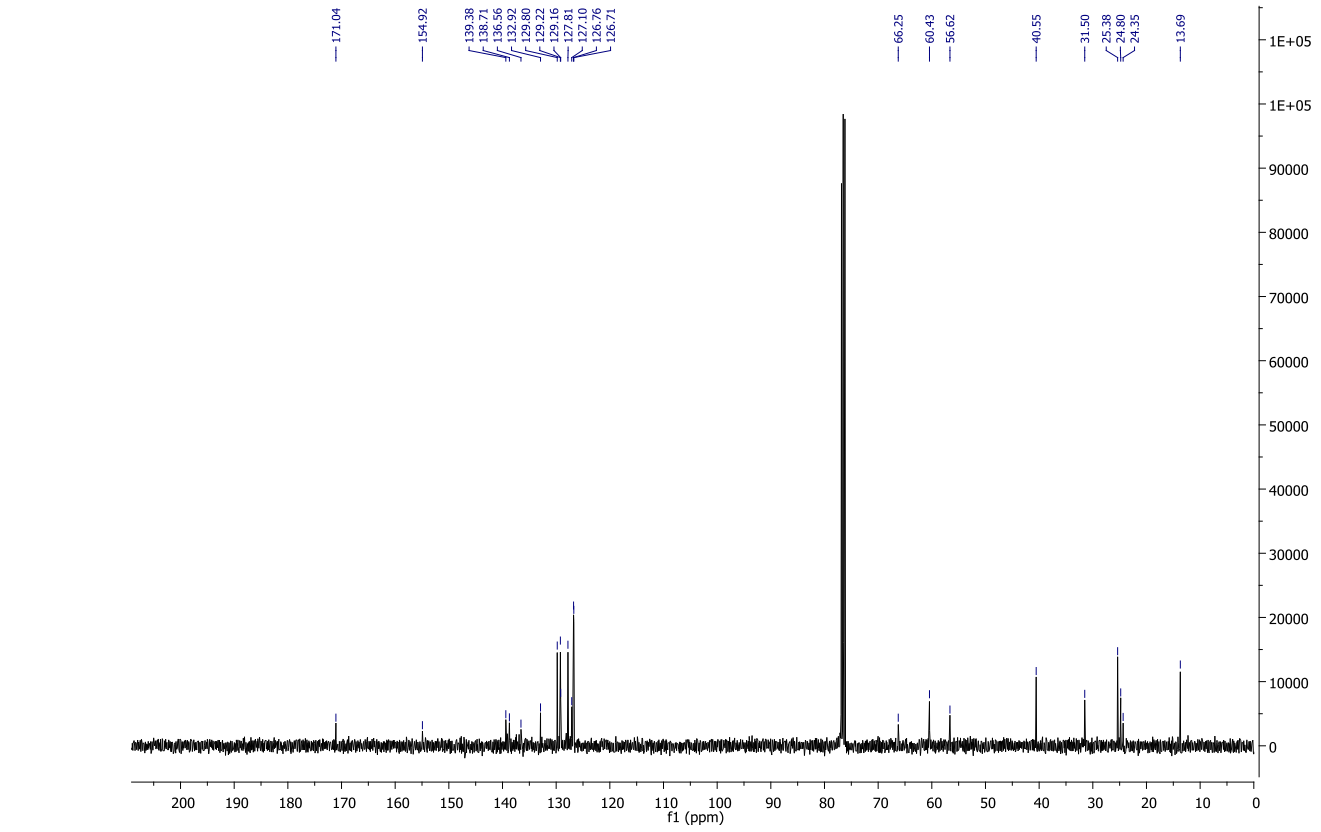

IDC PYRAN MW=390?
C19H20BrNO3
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
08/07/2014 08:13:50
Relative Abundance
390.0700
392.0677
391.0733
393.0709
Observed Data
NL:
4.74E7
STRWAT288-OA-HNESP#31-45 RT: 0.66-1.05 AV: 15 T: FTMS + p NSI Full ms [140.00-1935.00]
390.0699
392.0679
391.0732
393.0713
394.0740
395.0766
Theoretical Isotope Model: [M + H]+
NL:
9.57E3
C19 H20 BrNO3 H:
C19 H21 Br1 N1 O3
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
m/z

Compound 23

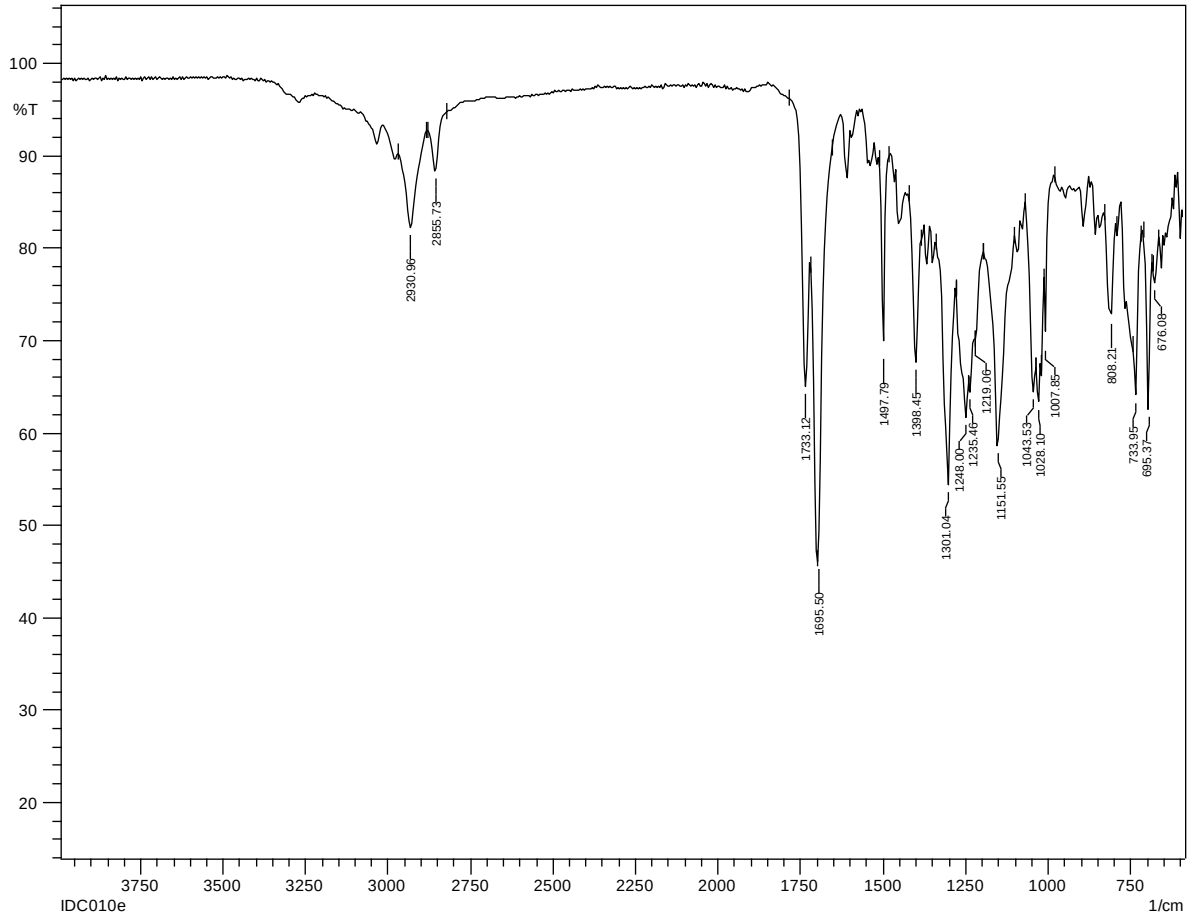
^{1}H NMR



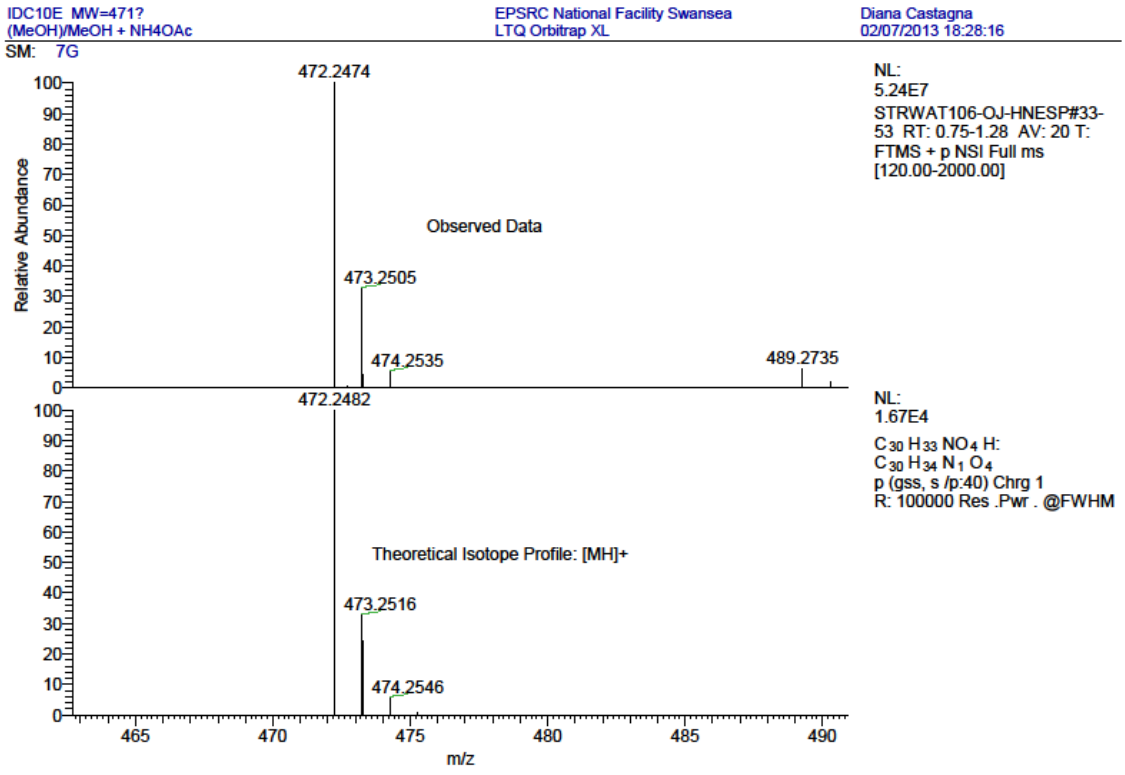
^{13}C NMR



IR

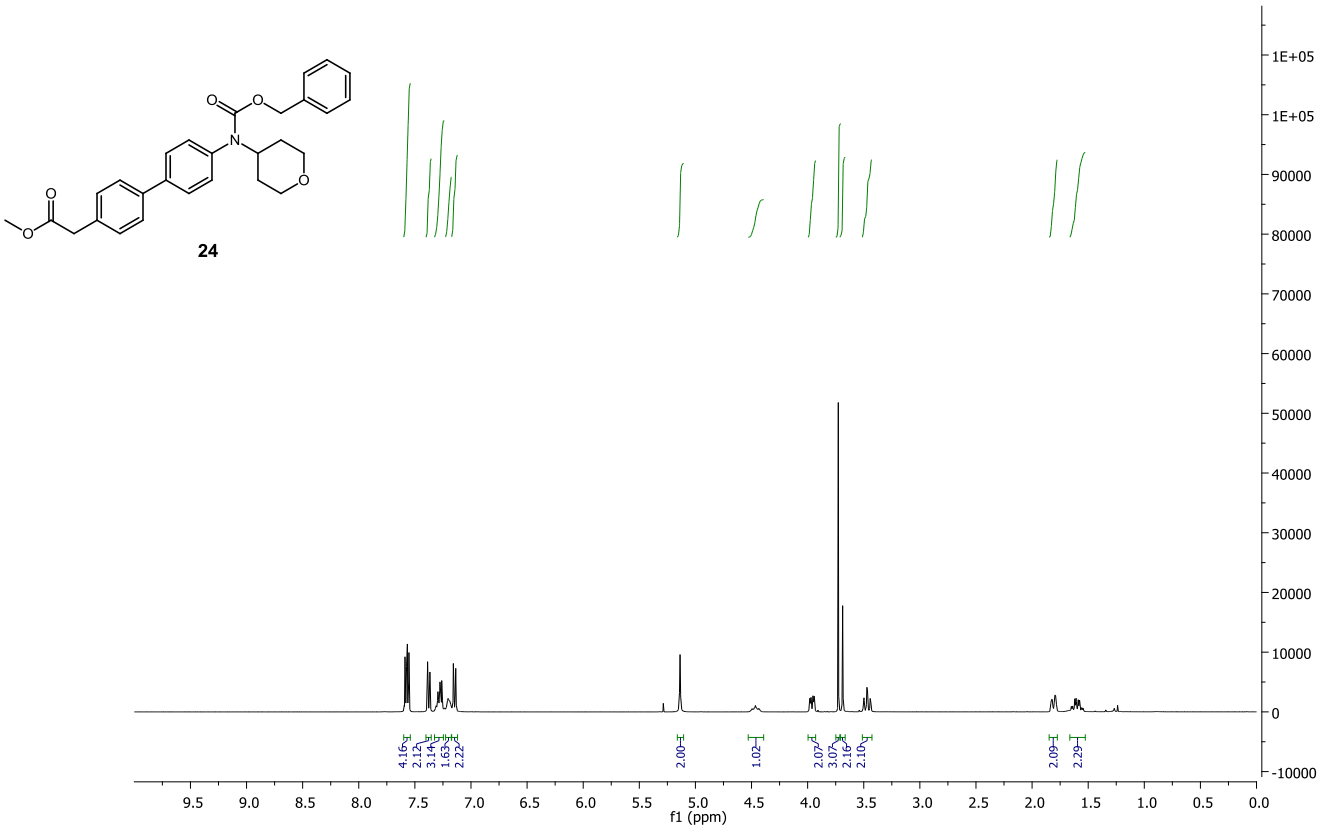

100
%T
90
80
70
60
50
40
30
20
2930.96
2855.73
1733.12
1695.50
1497.79
1398.45
1301.04
1248.00
1235.46
1219.06
1151.55
1043.53
1028.10
1007.85
808.21
733.95
695.37
676.09
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
IDC010e
1/cm

HRMS

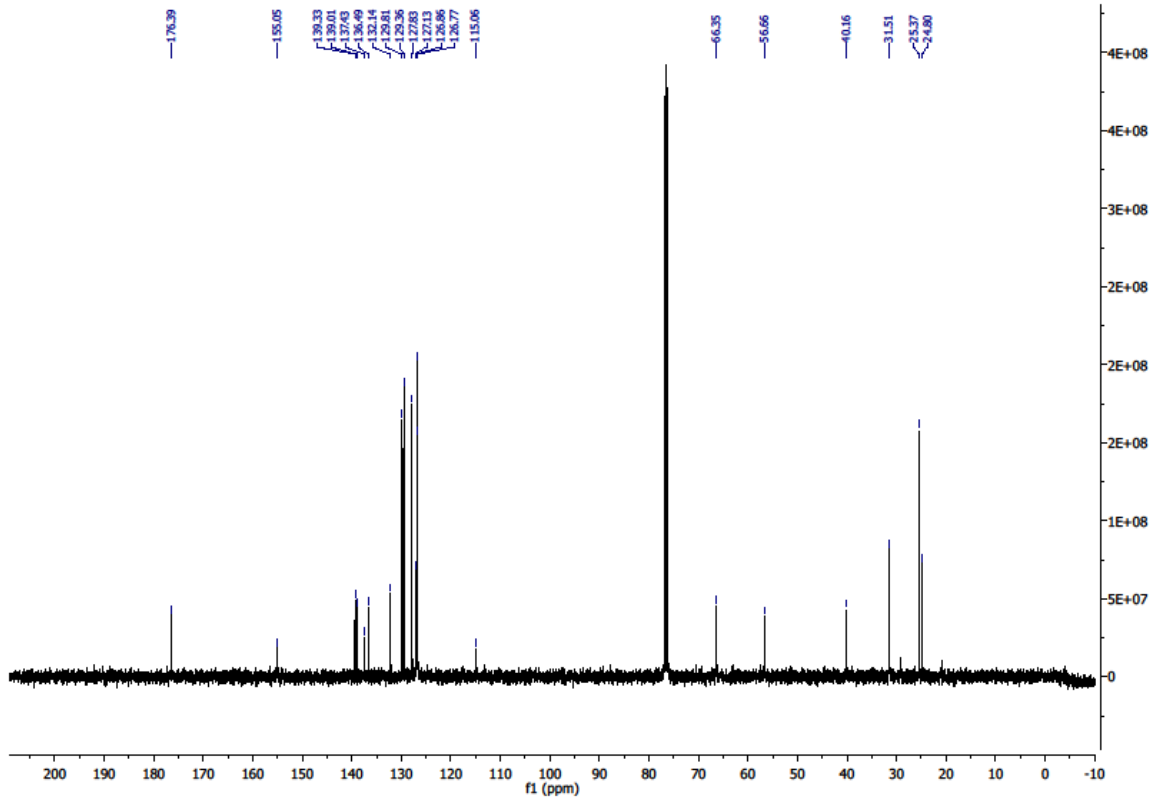

IDC10E MW=471?
(MeOH)/MeOH + NH4OAc
SM: 7G
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
02/07/2013 18:28:16
Relative Abundance
472.2474
Observed Data
473.2505
474.2535
489.2735
NL:
5.24E7
STRWAT106-OJ-HNESP#33-53 RT: 0.75-1.28 AV: 20 T: FTMS + p NSI Full ms [120.00-2000.00]
472.2482
Theoretical Isotope Profile: [MH]+
473.2516
474.2546
NL:
1.67E4
C30 H33 NO4 H:
C30 H34 N1 O4
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
m/z

Compound 24

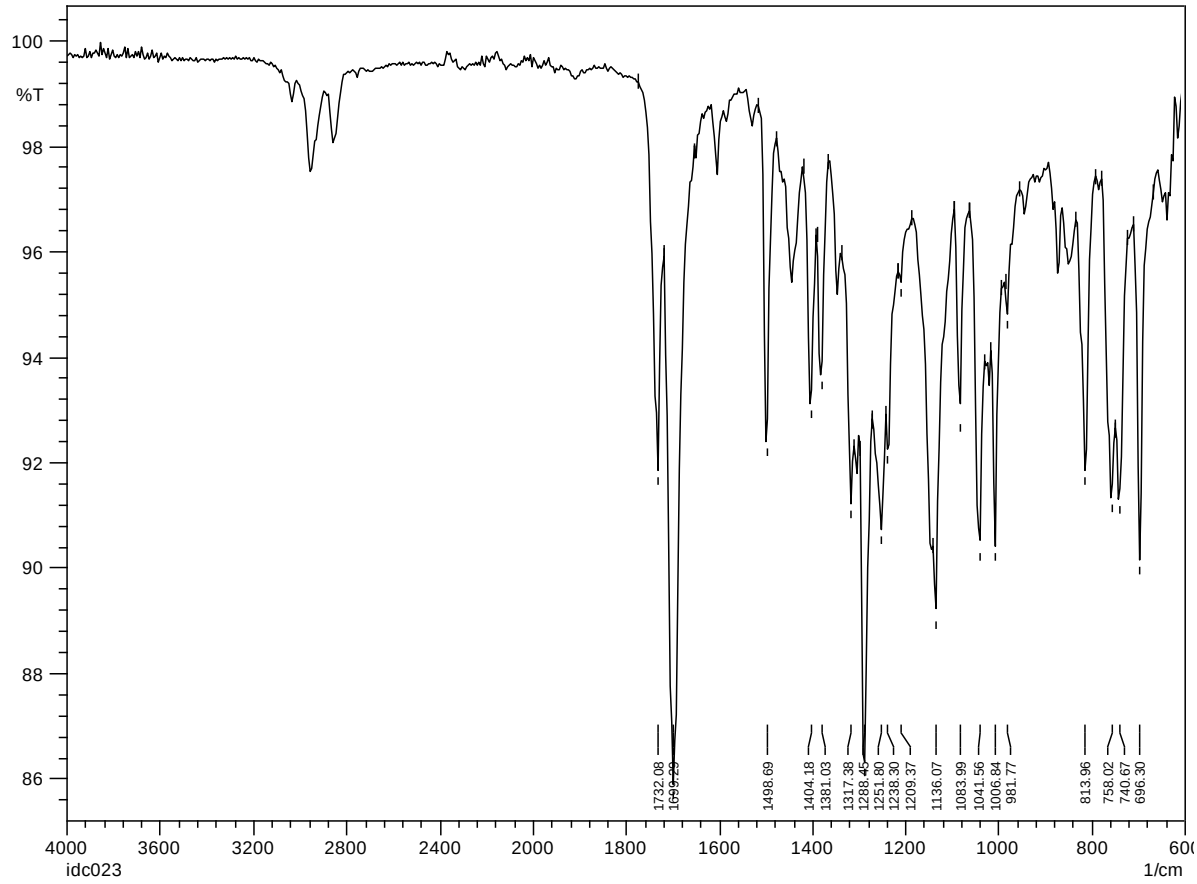
^{1}H NMR



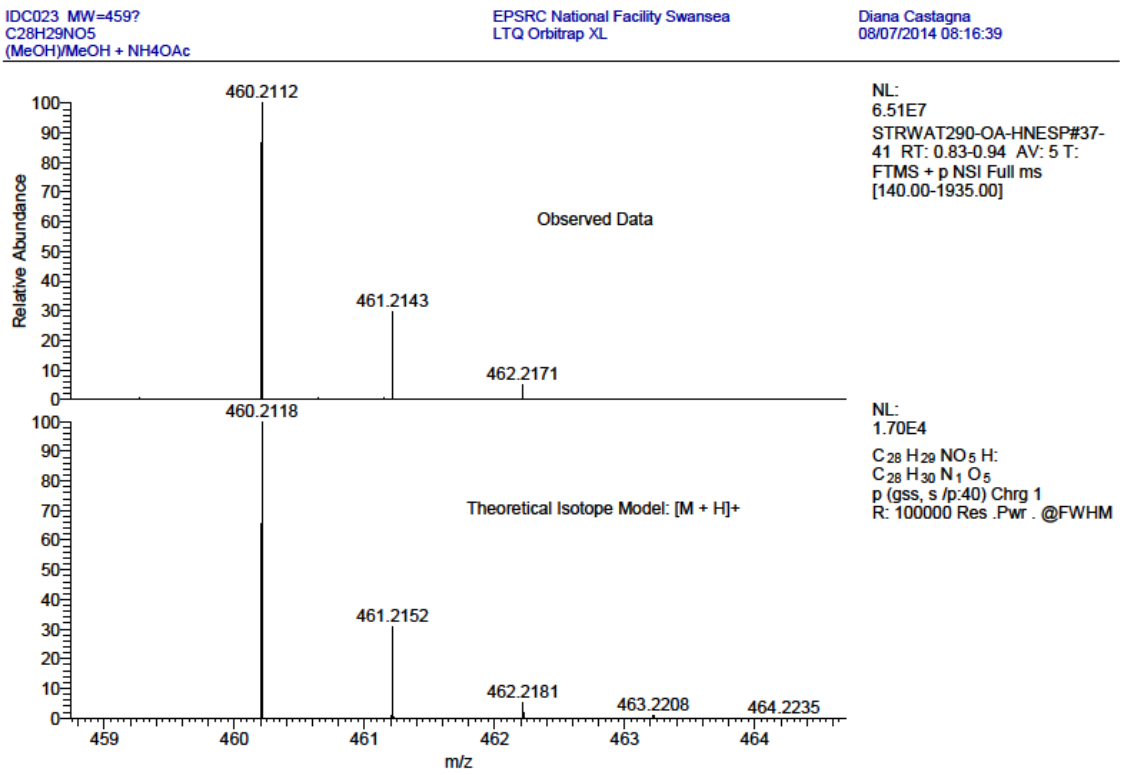
^{13}C NMR



IR

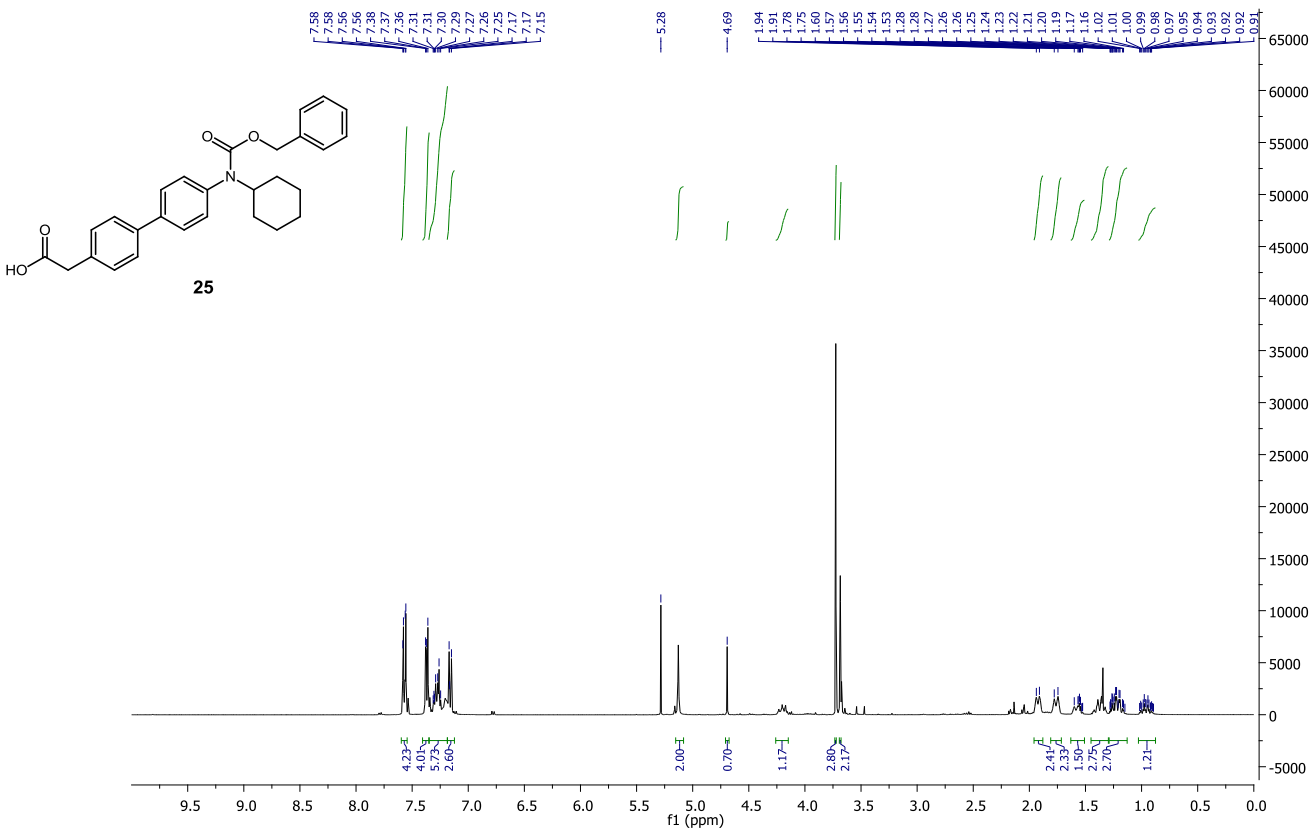

100
%T
98
96
94
92
90
88
86
1732.08
1699.29
1498.69
1404.18
1381.03
1317.38
1288.45
1251.80
1238.30
1209.37
1136.07
1083.99
1041.56
1006.84
981.77
813.96
758.02
740.67
696.30
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
idc023
1/cm

HRMS

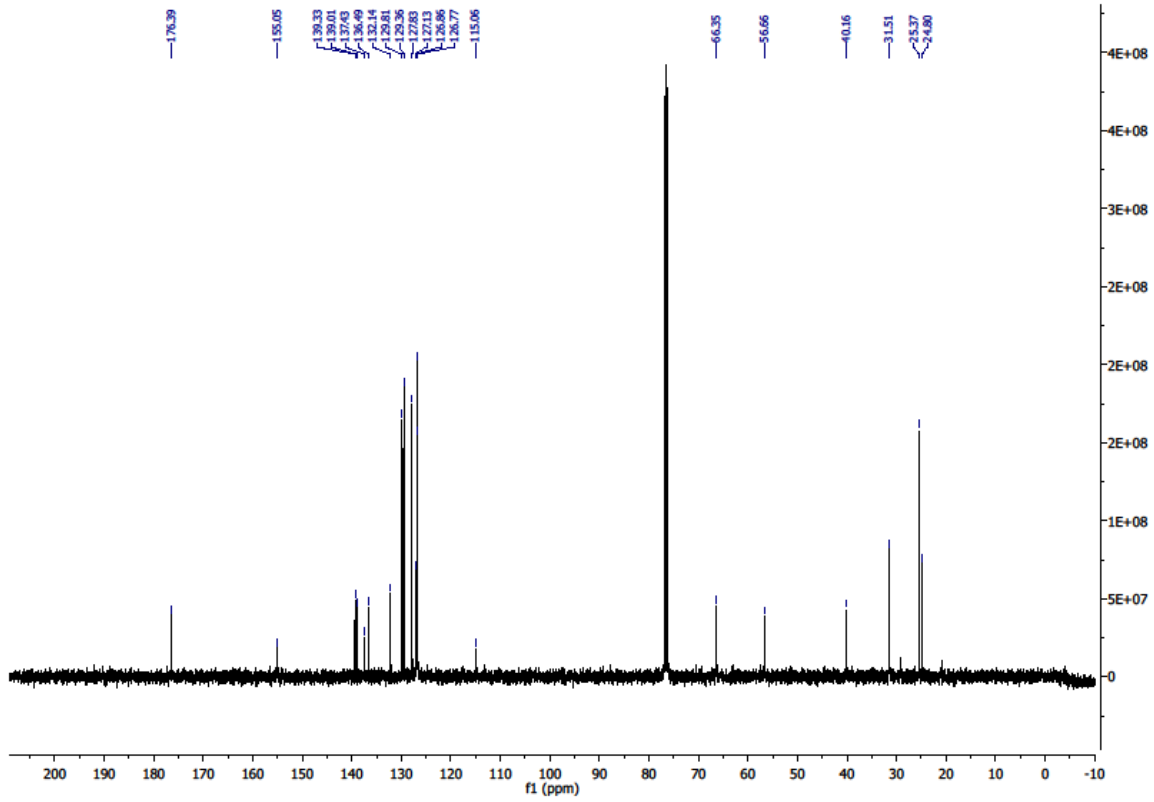

IDC023 MW=459?
C28H29NO5
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
08/07/2014 08:16:39
460.2112
461.2143
462.2171
Observed Data
NL:
6.51E7
STRWAT290-OA-HNESP#37-41 RT: 0.83-0.94 AV: 5 T: FTMS + p NSI Full ms [140.00-1935.00]
Relative Abundance
460.2118
461.2152
462.2181
463.2208
464.2235
Theoretical Isotope Model: [M + H]+
NL:
1.70E4
C28 H29 NO5 H:
C28 H30 N1 O5
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
459
460
461
462
463
464
m/z

Compound 25

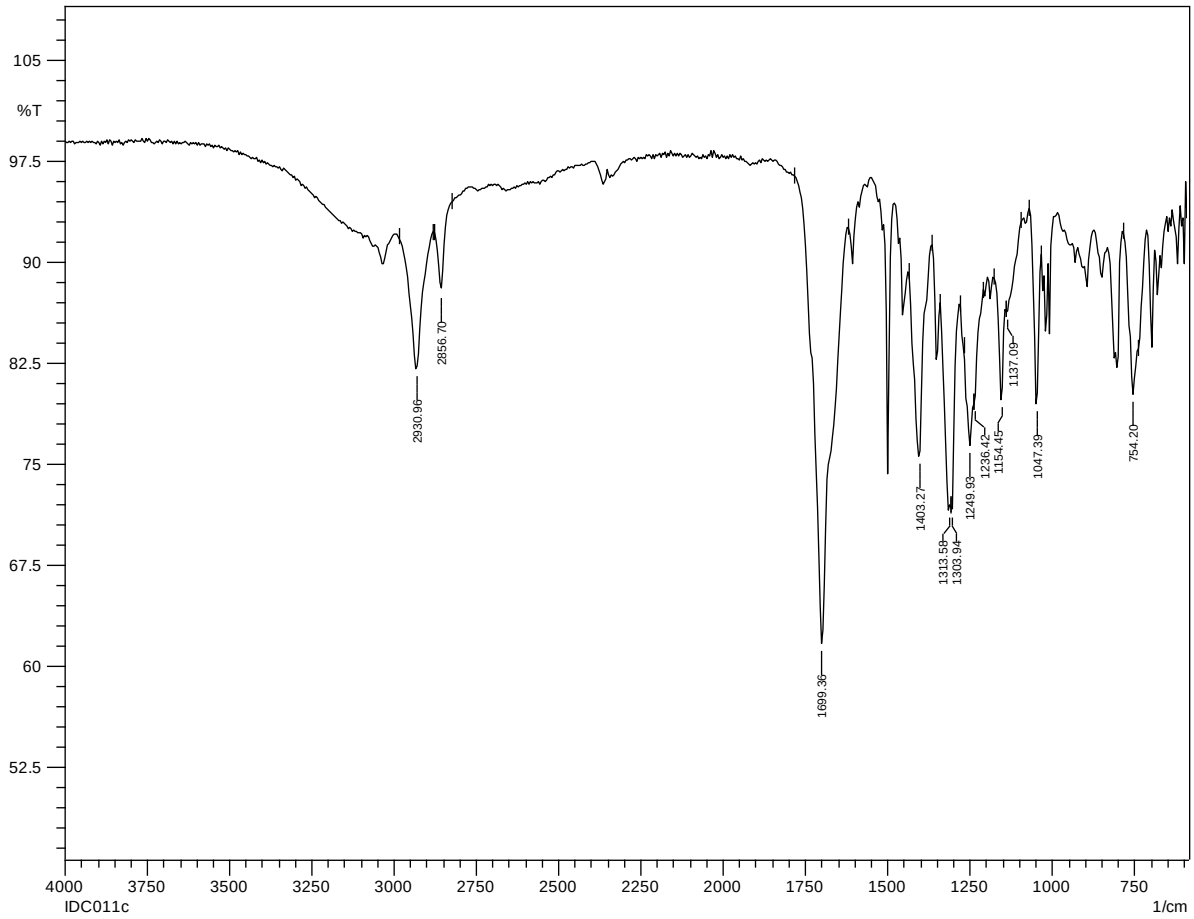
^{1}H NMR



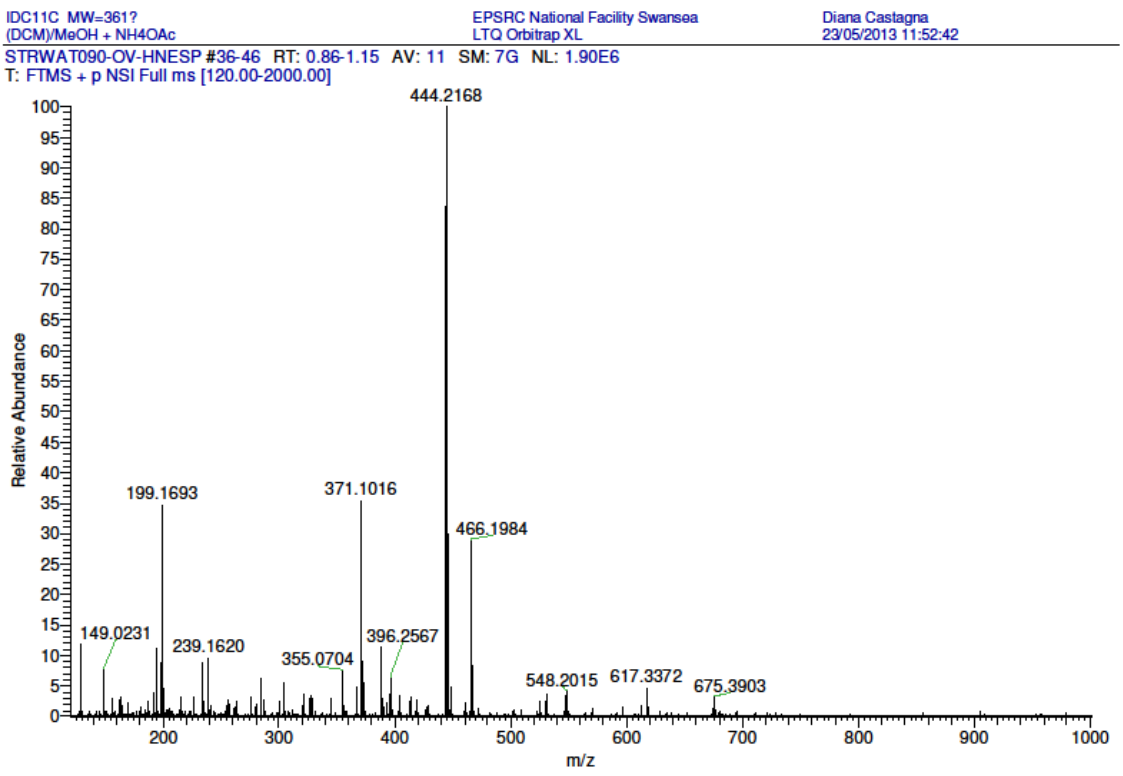
^{13}C NMR



IR

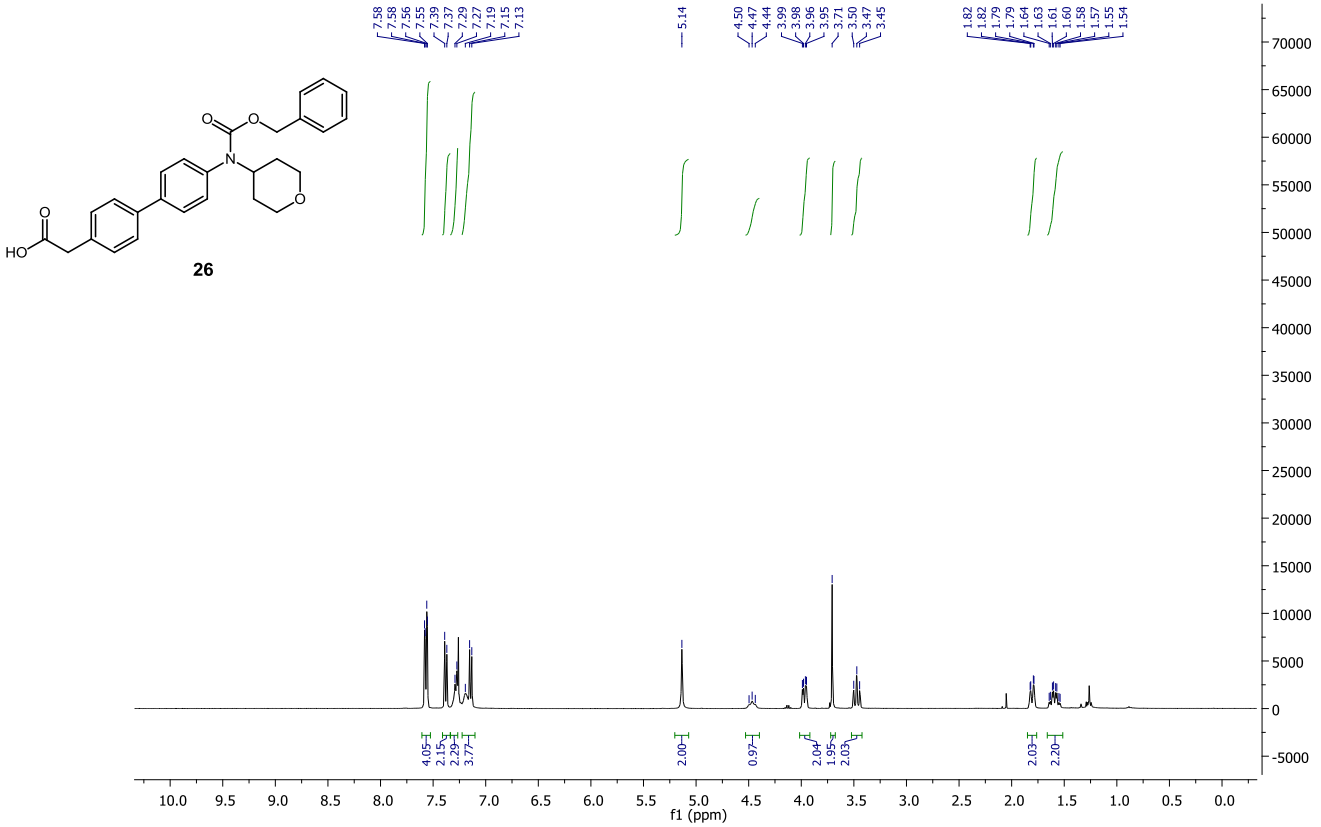

105
%T
97.5
90
82.5
75
67.5
60
52.5
2930.96
2856.70
1699.36
1403.27
1313.58
1303.94
1249.93
1236.42
1154.45
1137.09
1047.39
754.20
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
IDC011c
1/cm

HRMS

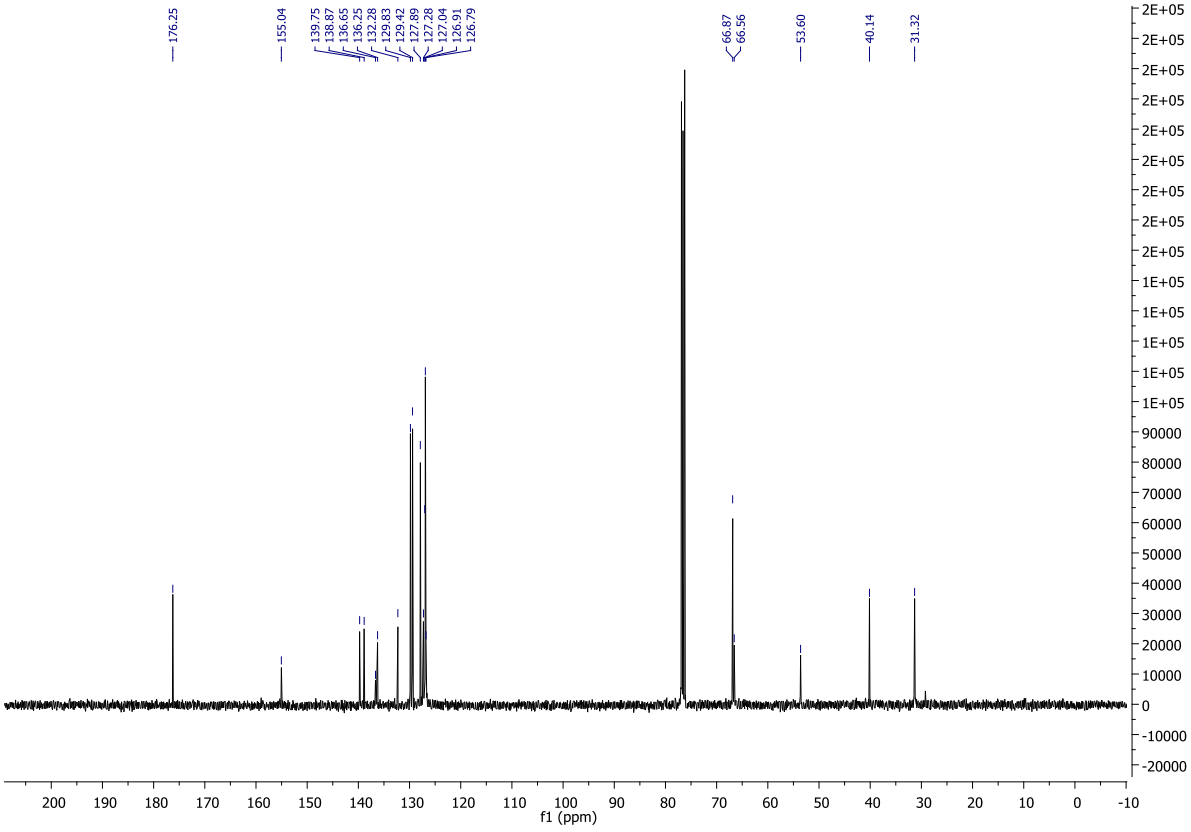

IDC11C MW=361?
(DCM)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
23/05/2013 11:52:42
STRWAT090-OV-HNESP #36-46 RT: 0.86-1.15 AV: 11 SM: 7G NL: 1.90E6
T: FTMS + p NSI Full ms [120.00-2000.00]
444.2168
199.1693
371.1016
466.1984
149.0231
239.1620
355.0704
396.2567
548.2015
617.3372
675.3903
Relative Abundance
m/z

Compound 26

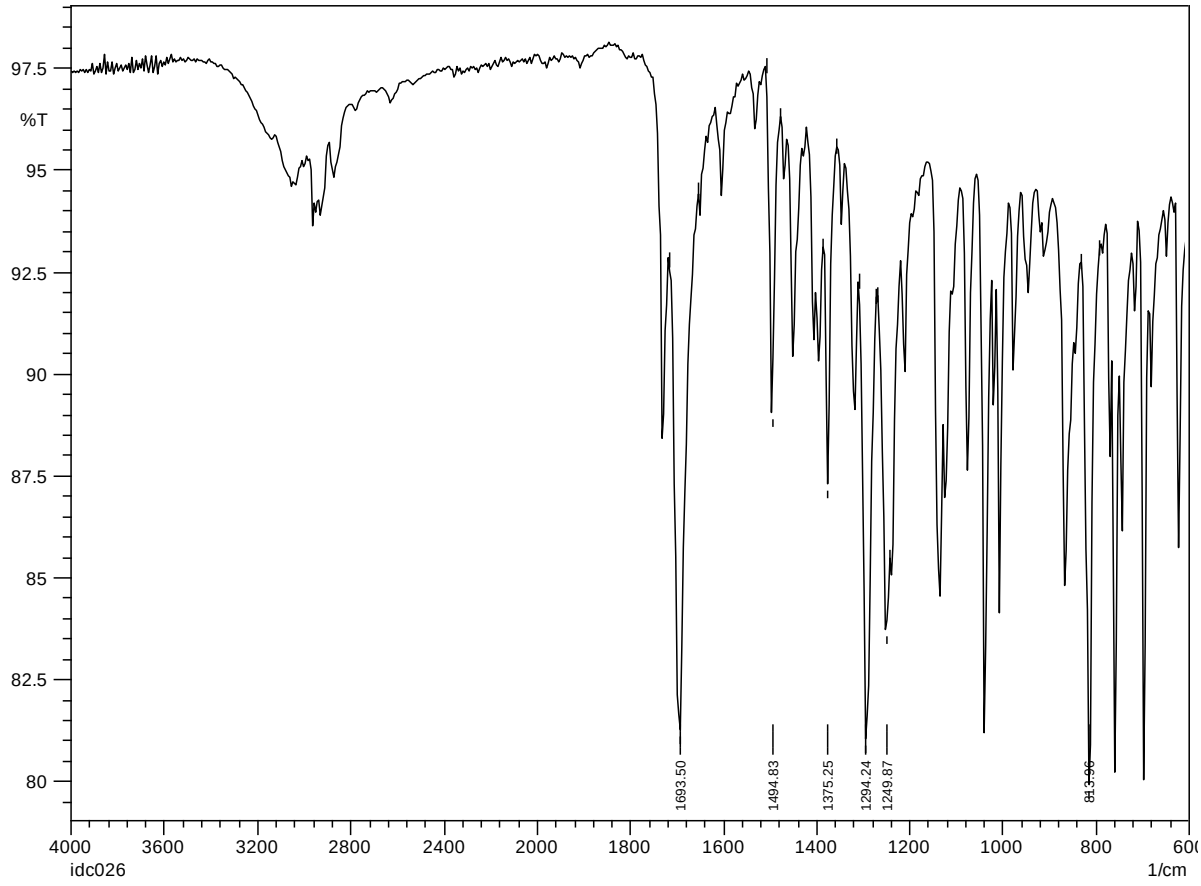
^{1}H NMR



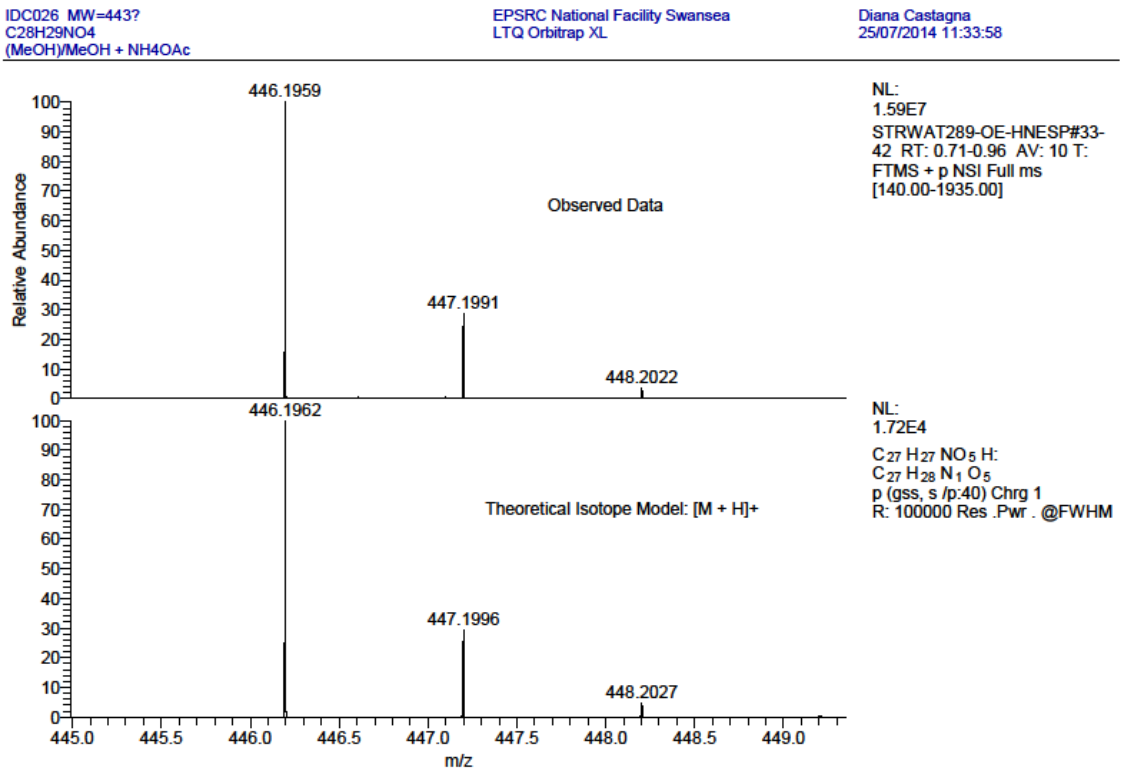
^{13}C NMR



IR

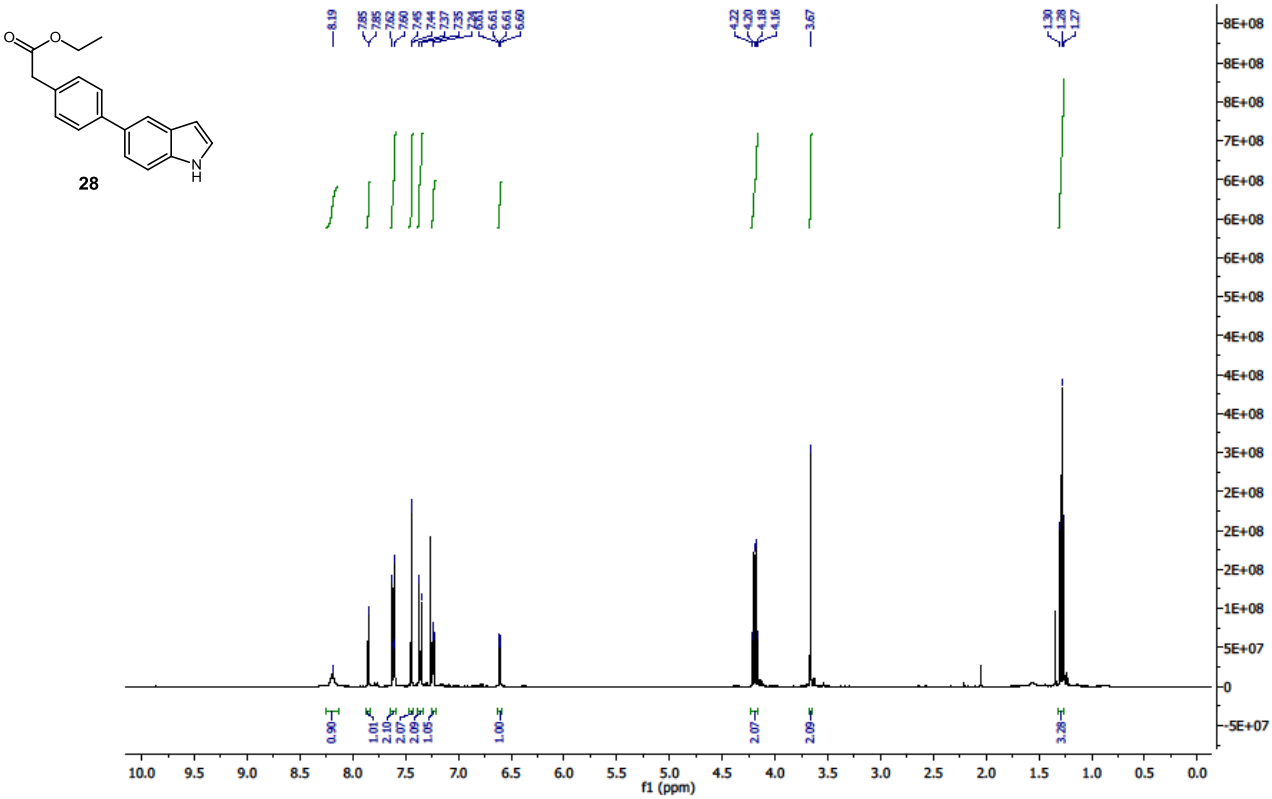

97.5
%T
95
92.5
90
87.5
85
82.5
80
1693.50
1494.83
1375.25
1294.24
1249.87
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
idc026
1/cm

HRMS

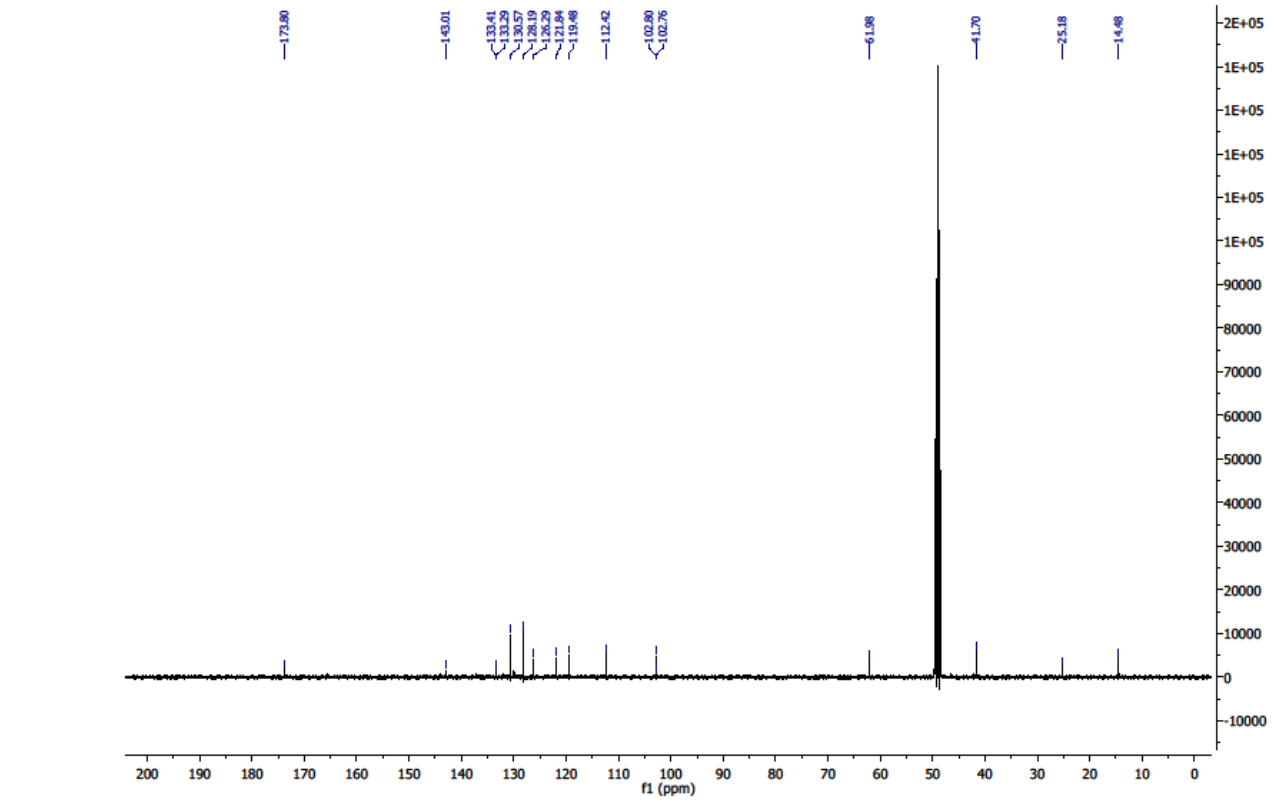

IDC026 MW=443?
C28H29NO4
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
25/07/2014 11:33:58
446.1959
Observed Data
447.1991
448.2022
Relative Abundance
NL:
1.59E7
STRWAT289-OE-HNESP#33-42 RT: 0.71-0.96 AV: 10 T: FTMS + p NSI Full ms [140.00-1935.00]
446.1962
Theoretical Isotope Model: [M + H]+
447.1996
448.2027
NL:
1.72E4
C27 H27 NO5 H:
C27 H28 N1 O5
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
445.0
445.5
446.0
446.5
447.0
447.5
448.0
448.5
449.0
m/z

Compound 28

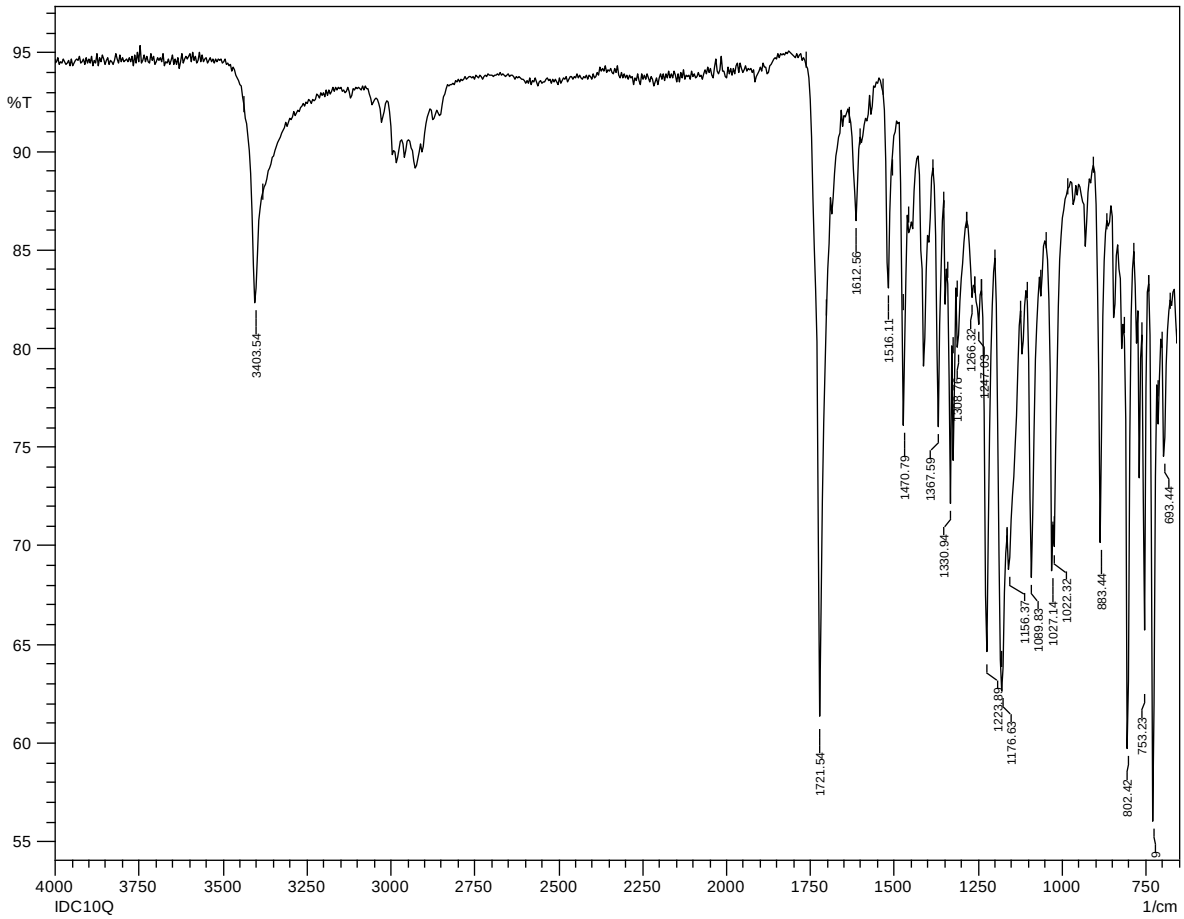
^{1}H NMR



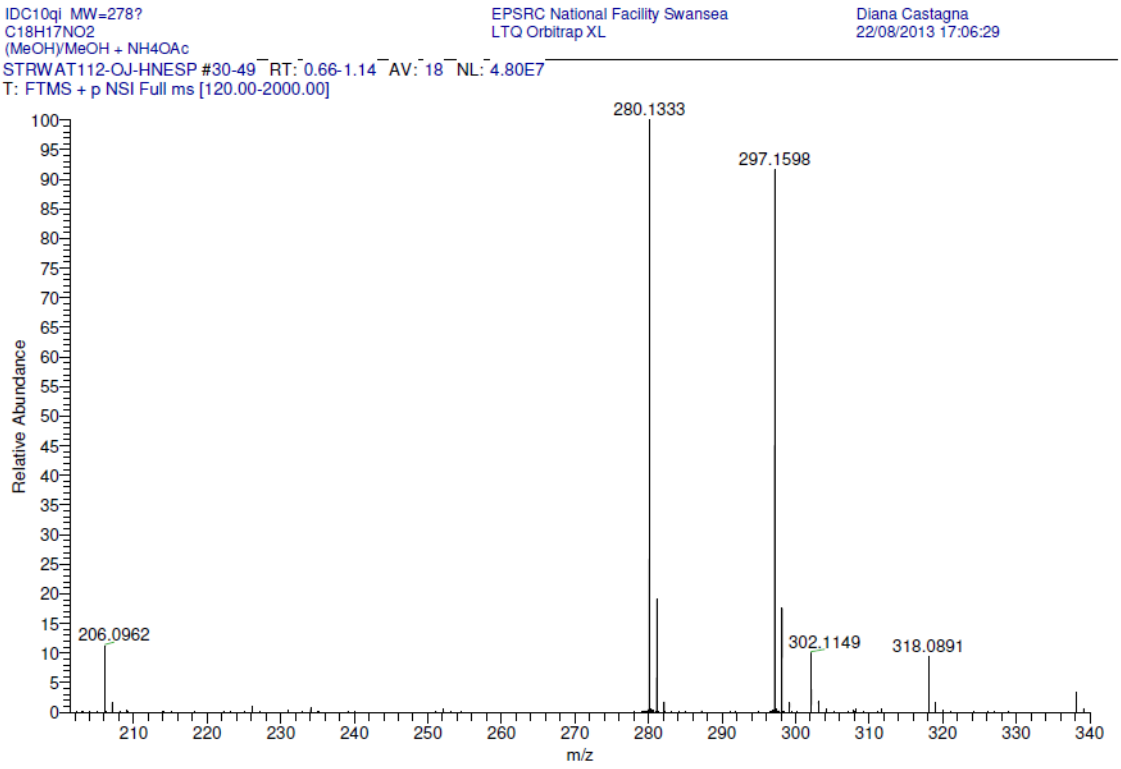
^{13}C NMR



IR

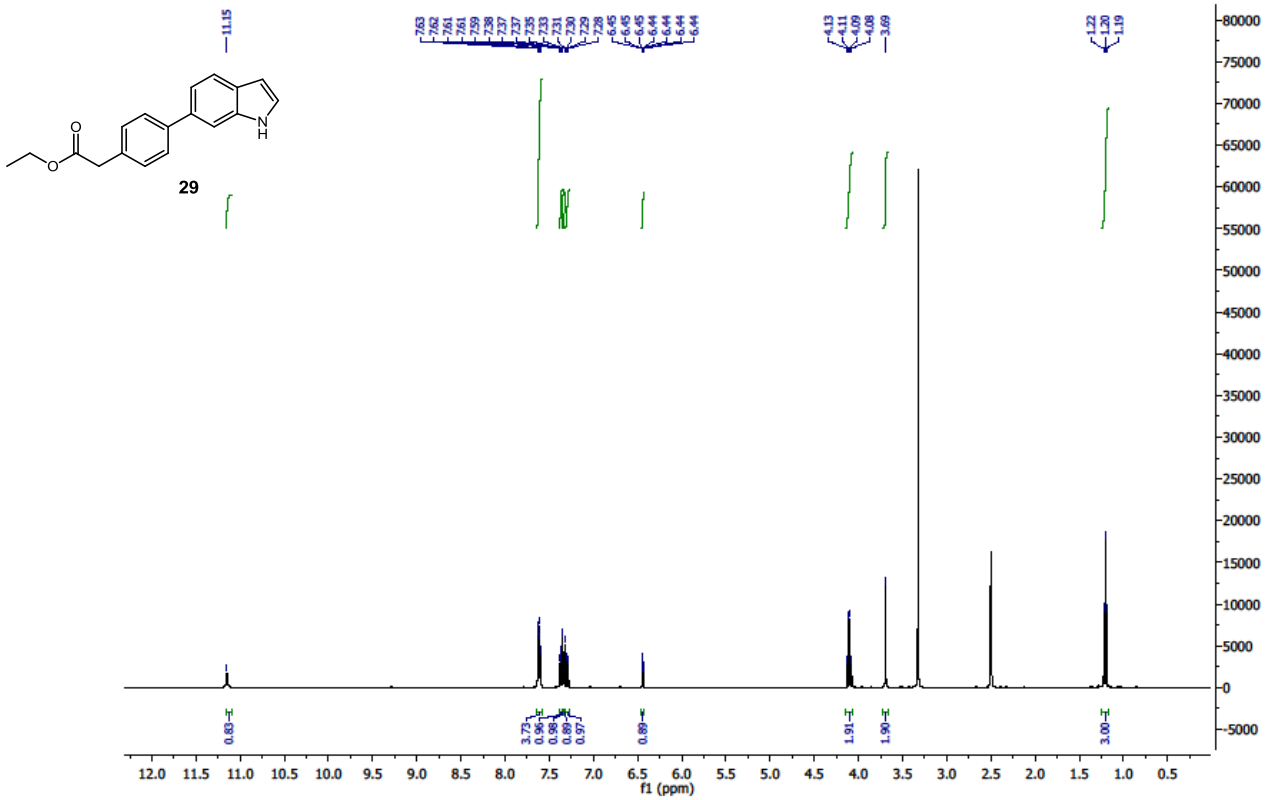

%T
95
90
85
80
75
70
65
60
55
3403.54
1721.54
1612.56
1516.11
1470.79
1367.59
1330.94
1308.76
1266.32
1247.03
1223.80
1176.63
1156.37
1089.83
1027.14
1022.32
883.44
802.42
753.23
693.44
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
IDC10Q
1/cm

HRMS

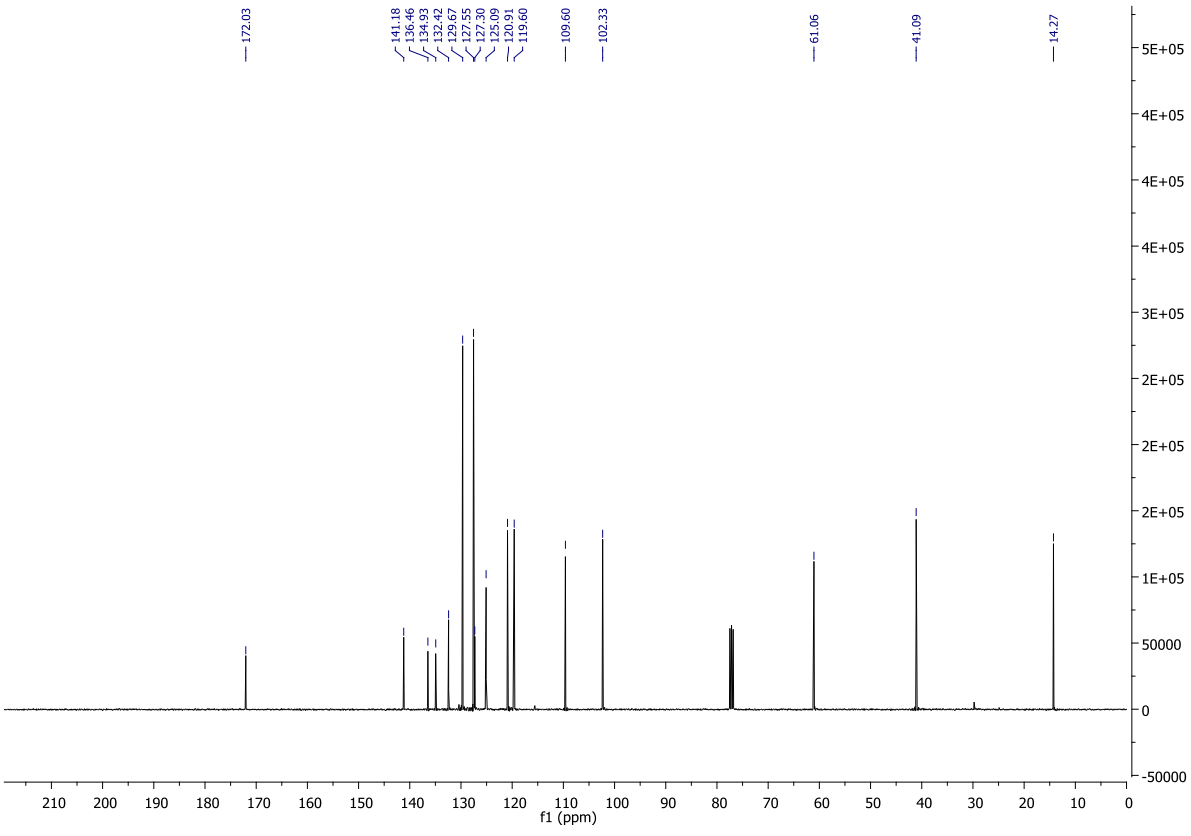

IDC10qi MW=278?
C18H17NO2
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
22/08/2013 17:06:29
STRWAT112-OJ-HNESP #30-49 RT: 0.66-1.14 AV: 18 NL: 4.80E7
T: FTMS + p NSI Full ms [120.00-2000.00]
280.1333
297.1598
206.0962
302.1149
318.0891
Relative Abundance
m/z
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
210
220
230
240
250
260
270
280
290
300
310
320
330
340

Compound 29

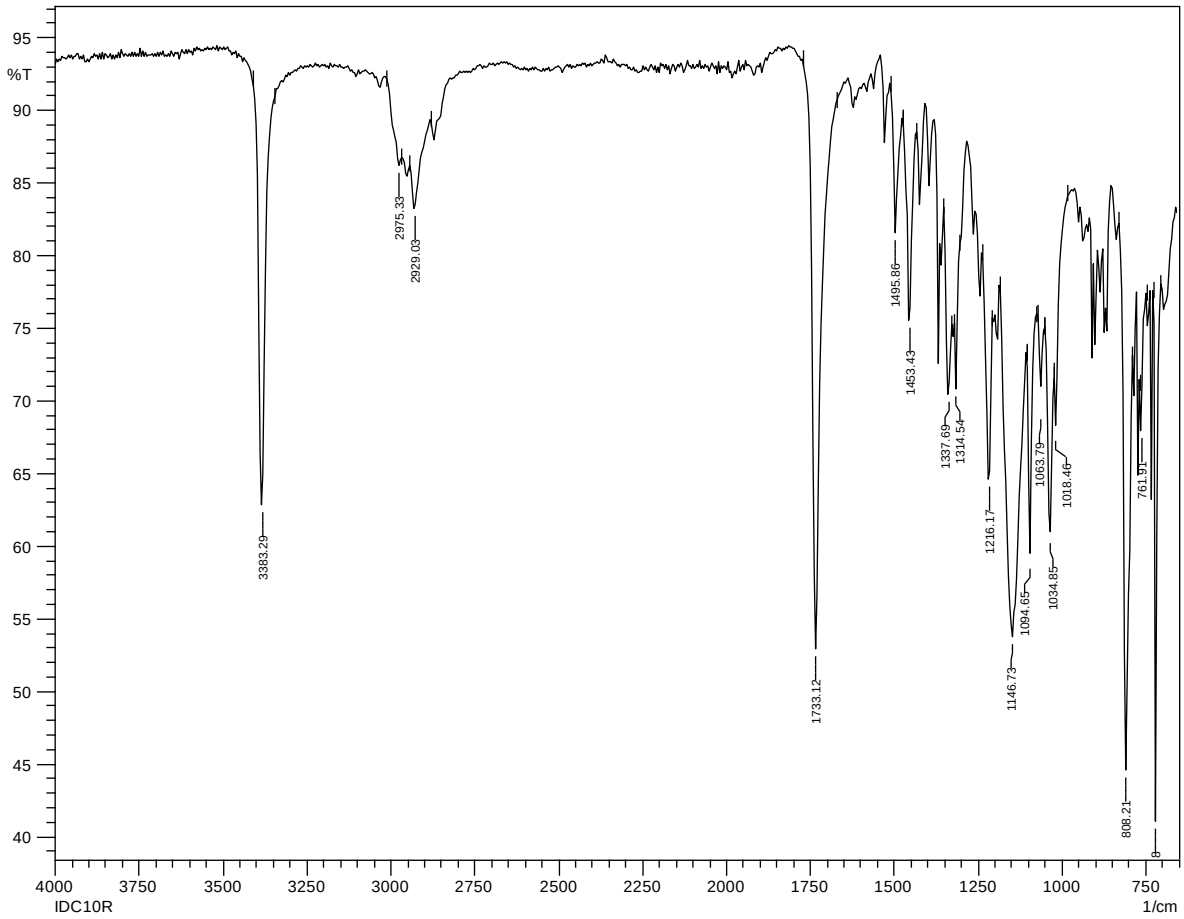
^{1}H NMR



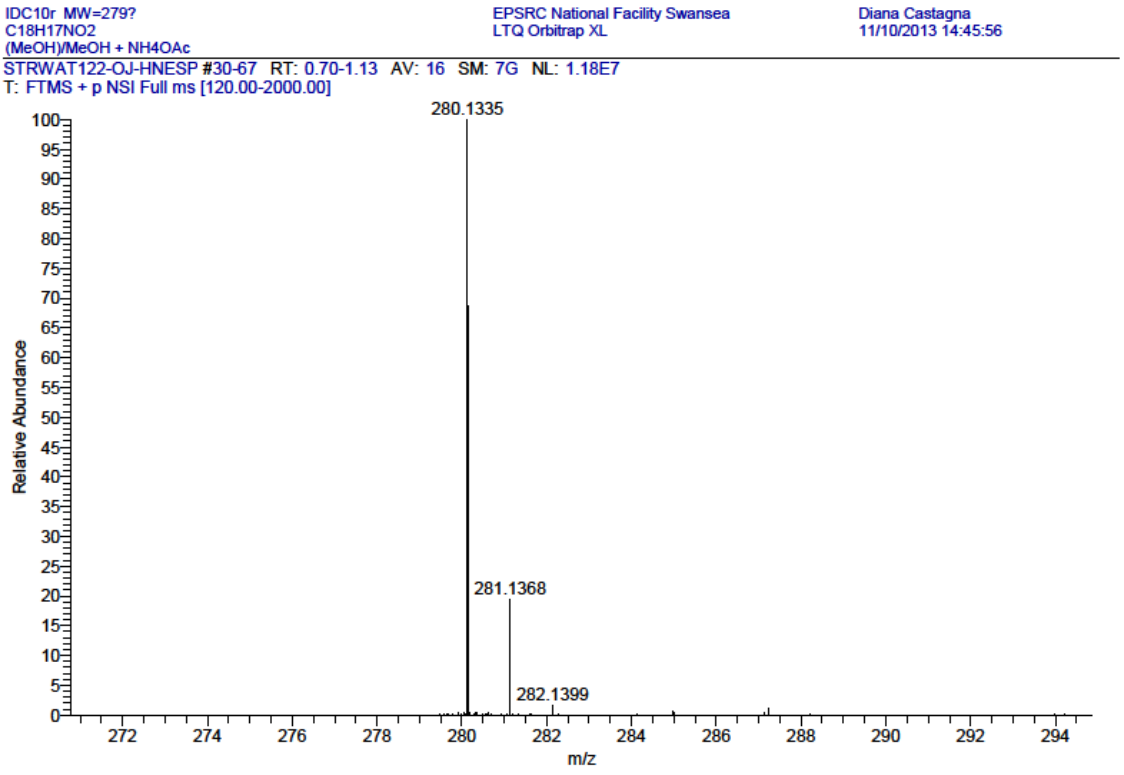
^{13}C NMR



IR

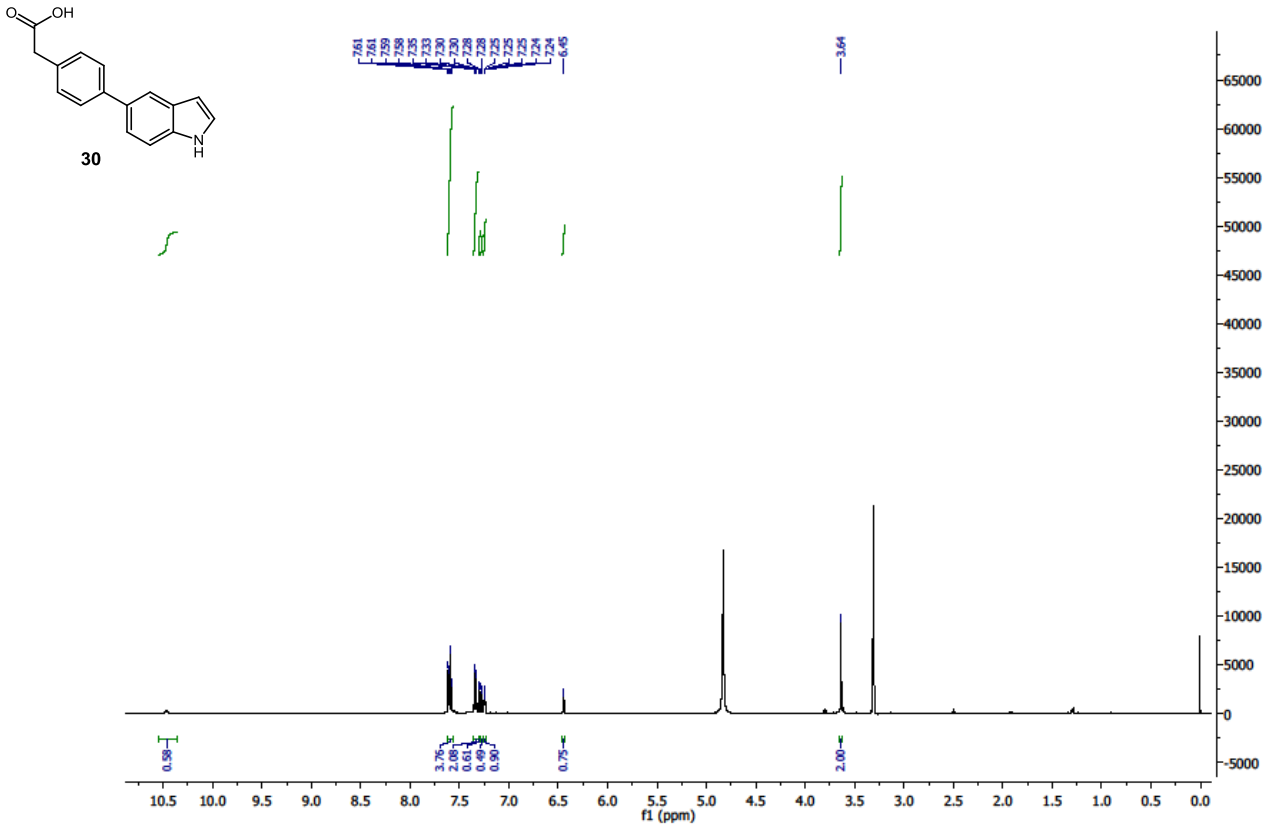

%T
95
90
85
80
75
70
65
60
55
50
45
40
3383.29
2975.33
2929.03
1733.12
1495.86
1453.43
1337.69
1314.54
1216.17
1146.73
1094.65
1063.79
1034.85
1018.40
808.21
761.91
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
IDC10R
1/cm

HRMS

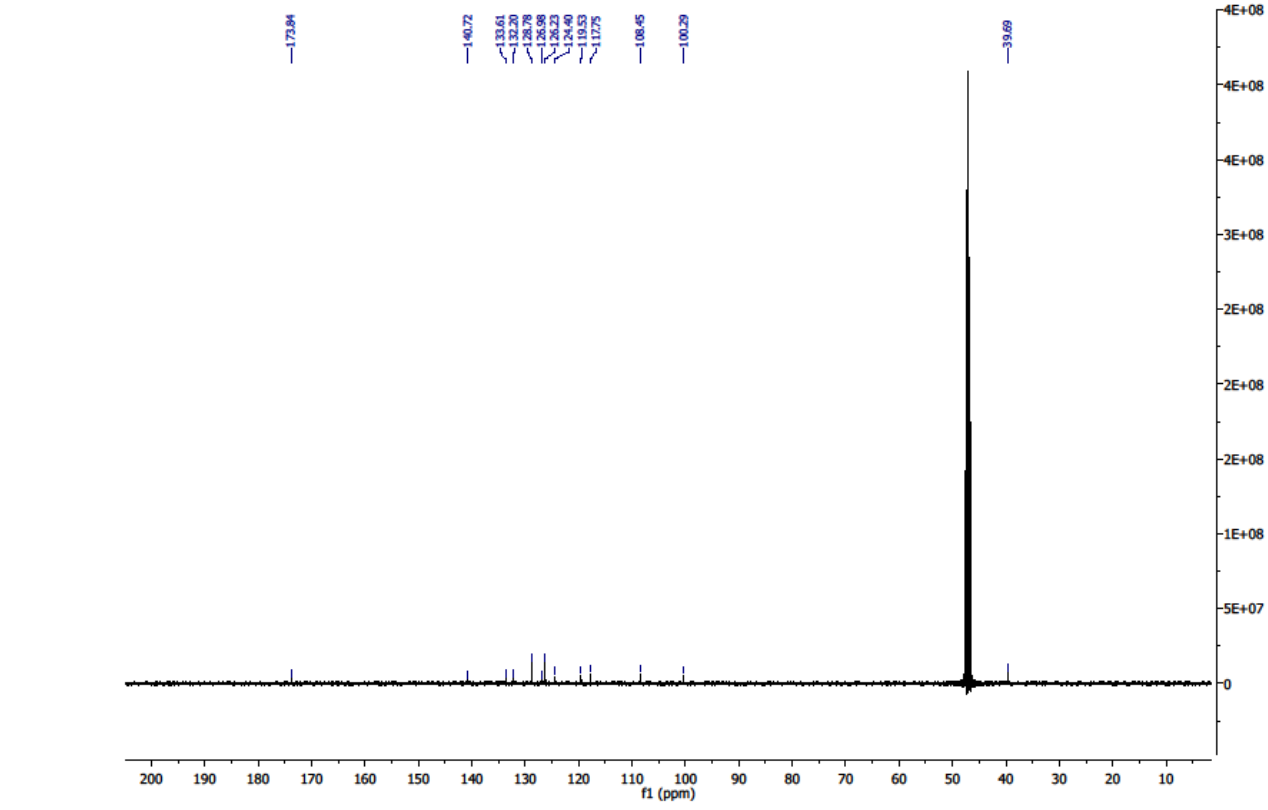

IDC10r MW=279?
C18H17NO2
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
11/10/2013 14:45:56
STRWAT122-OJ-HNESP #30-67 RT: 0.70-1.13 AV: 16 SM: 7G NL: 1.18E7
T: FTMS + p NSI Full ms [120.00-2000.00]
280.1335
281.1368
282.1399
Relative Abundance
m/z
272
274
276
278
280
282
284
286
288
290
292
294

Compound 30

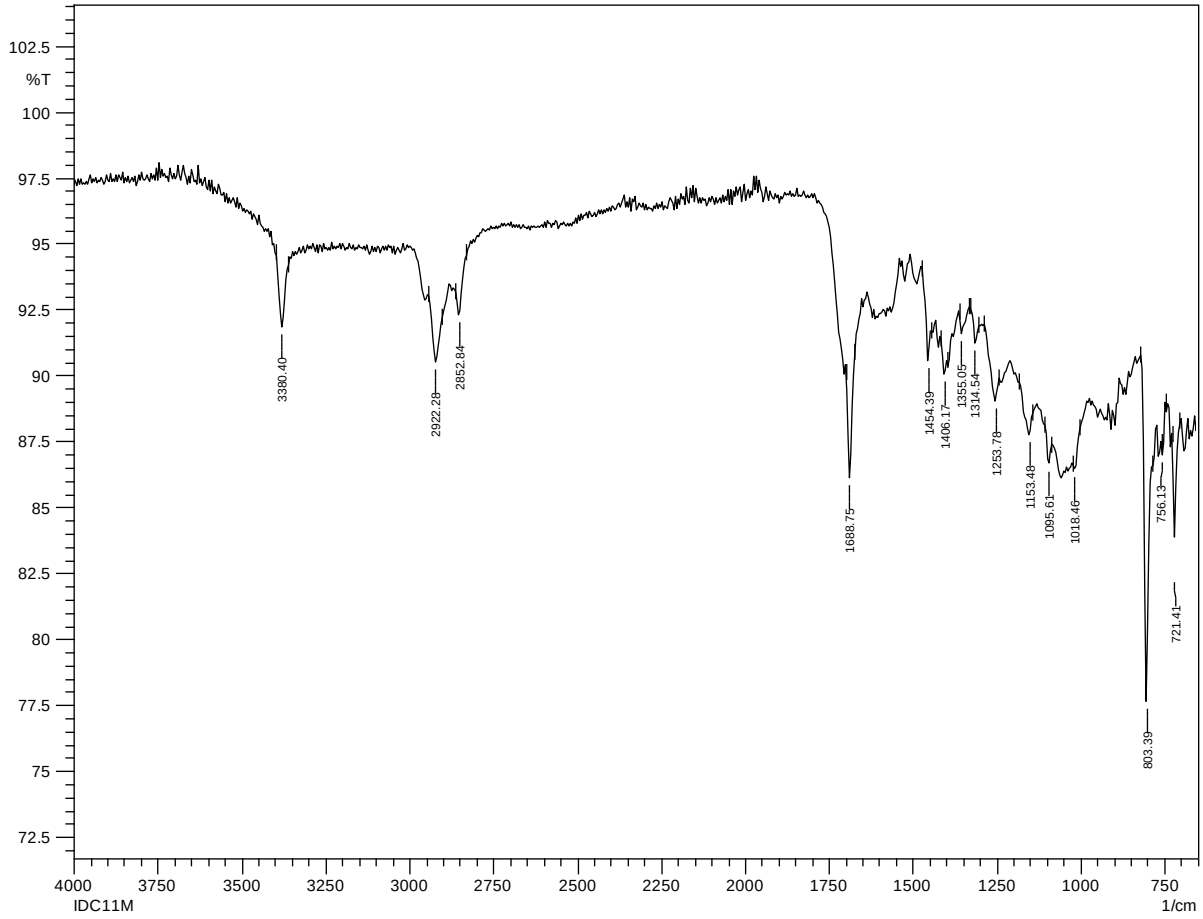
^{1}H NMR



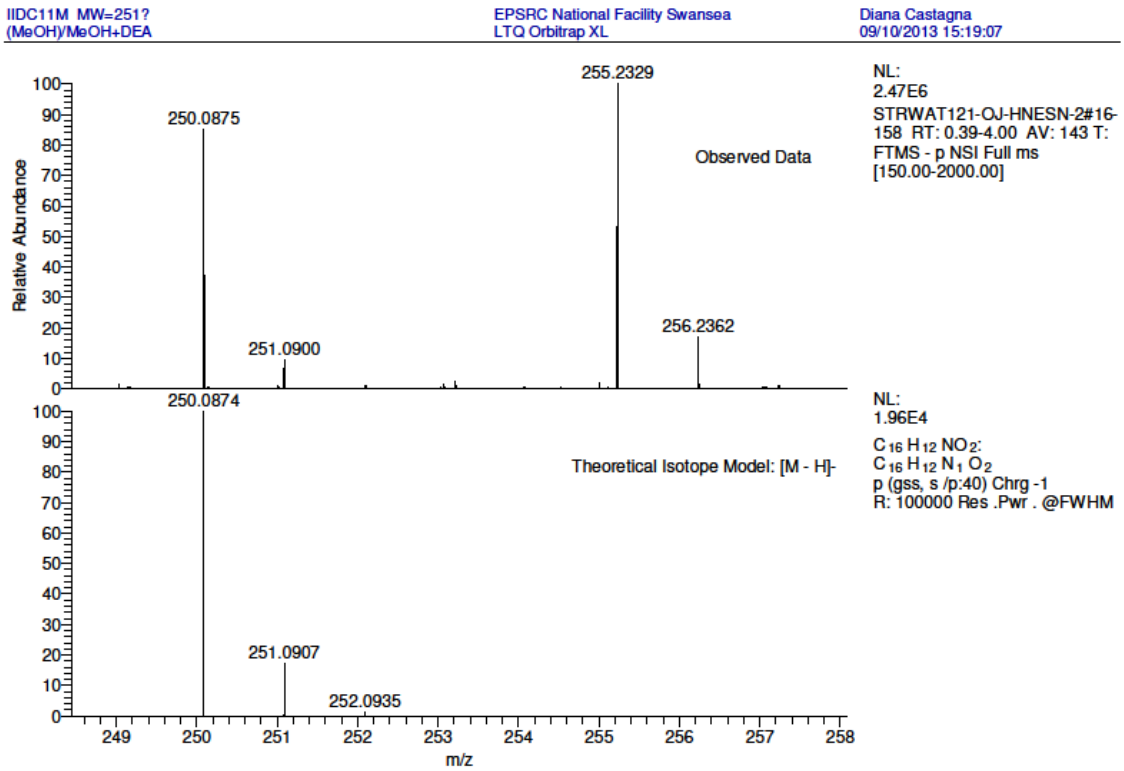
^{13}C NMR



IR

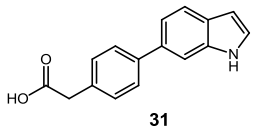

102.5
%T
100
97.5
95
92.5
90
87.5
85
82.5
80
77.5
75
72.5
3380.40
2922.28
2852.84
1688.75
1454.39
1406.17
1355.05
1314.54
1253.78
1153.48
1095.61
1018.46
756.13
721.41
803.39
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
IDC11M
1/cm

HRMS

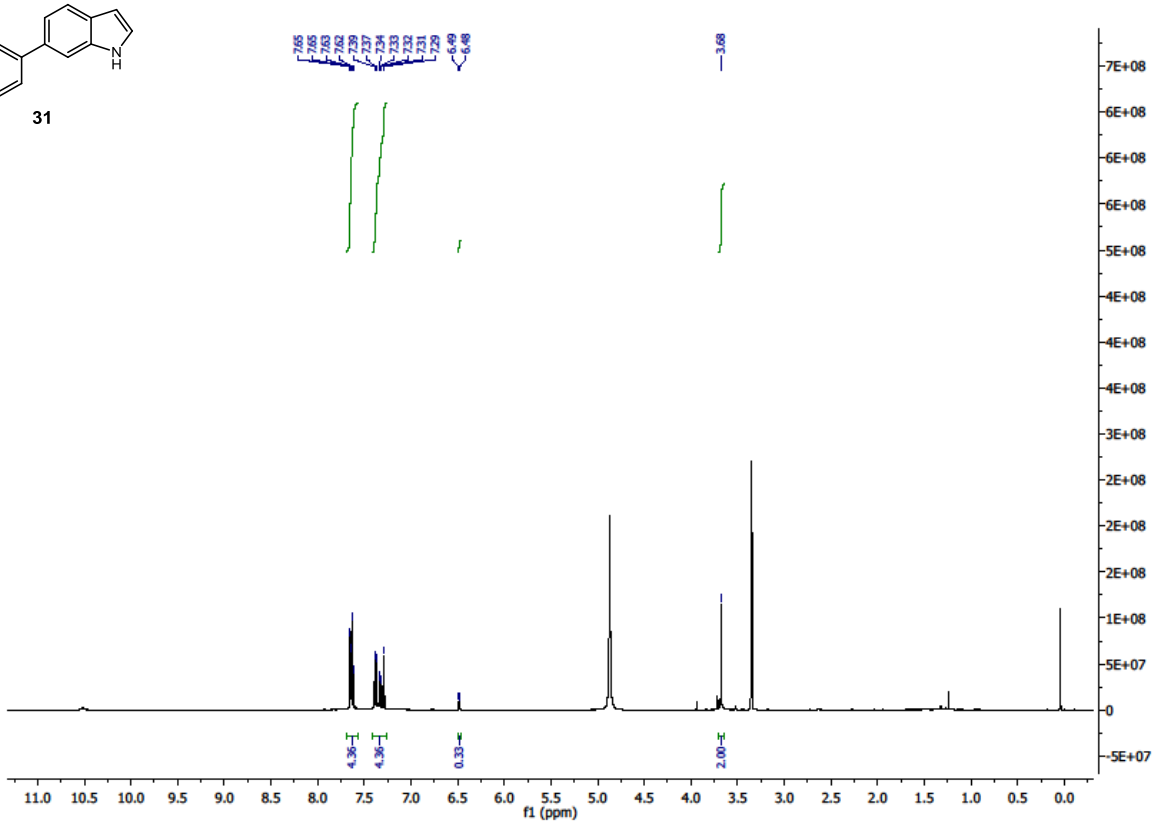

IIDC11M MW=251?
(MeOH)/MeOH+DEA
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
09/10/2013 15:19:07
NL:
2.47E6
STRWAT121-OJ-HNESN-2#16-158 RT: 0.39-4.00 AV: 143 T: FTMS - p NSI Full ms [150.00-2000.00]
255.2329
250.0875
Observed Data
256.2362
251.0900
Relative Abundance
NL:
1.96E4
C16 H12 NO2:
C16 H12 N1 O2
p (gss, s /p:40) Chrg -1
R: 100000 Res .Pwr . @FWHM
250.0874
Theoretical Isotope Model: [M - H]-
251.0907
252.0935
m/z

Compound 31

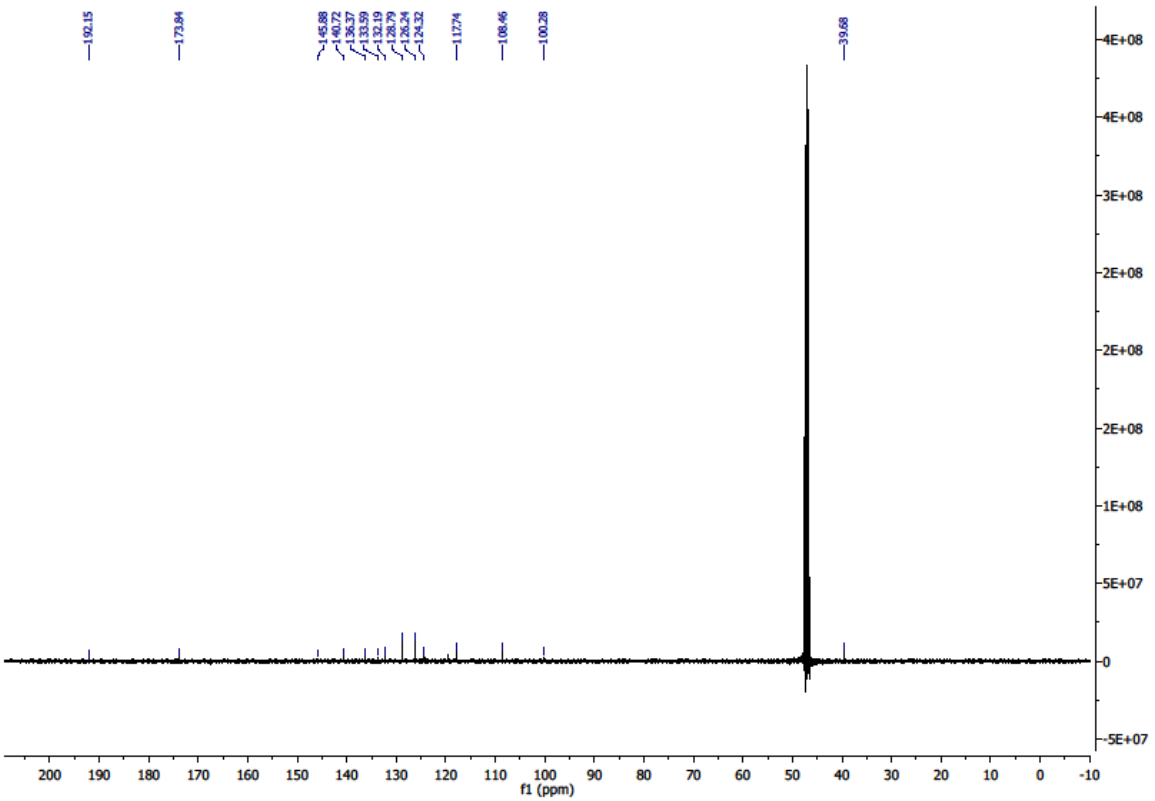
^{1}H NMR



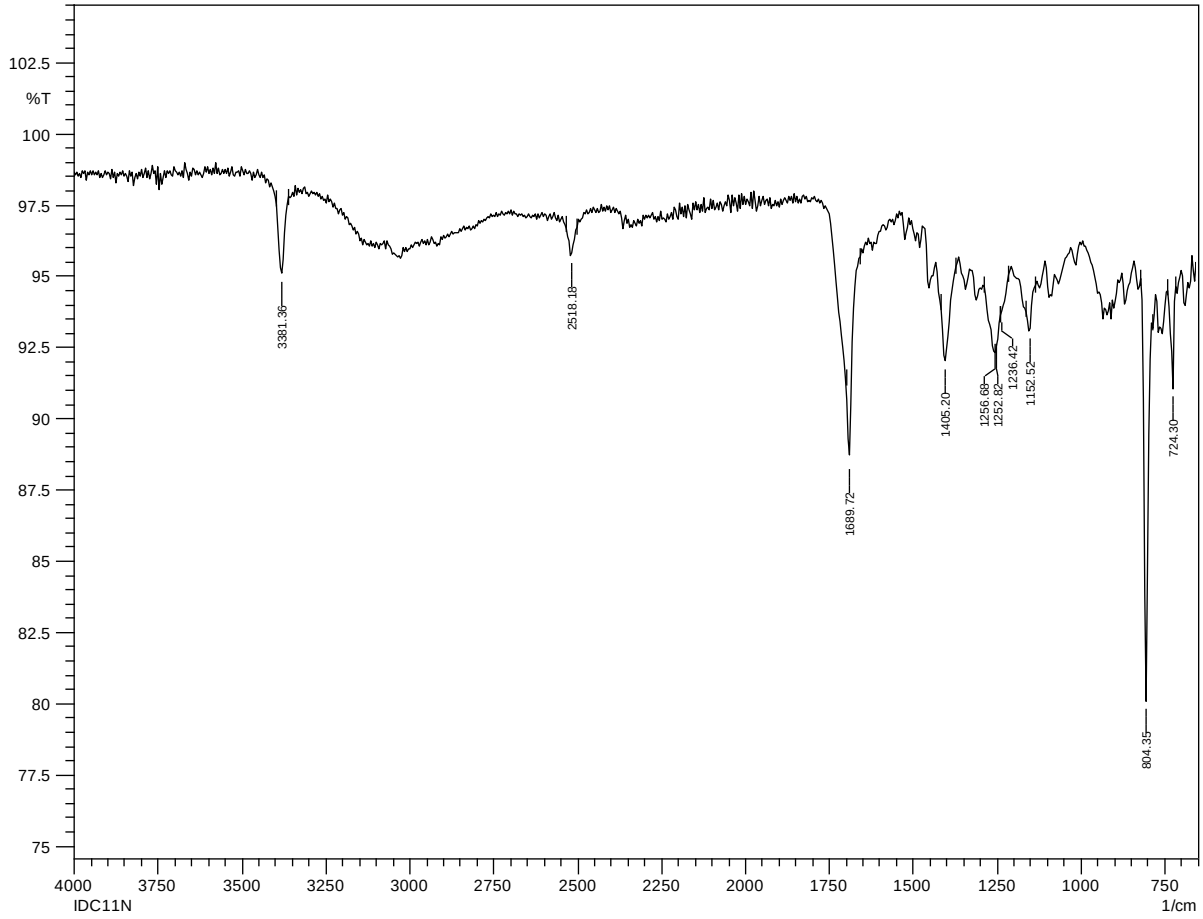
31



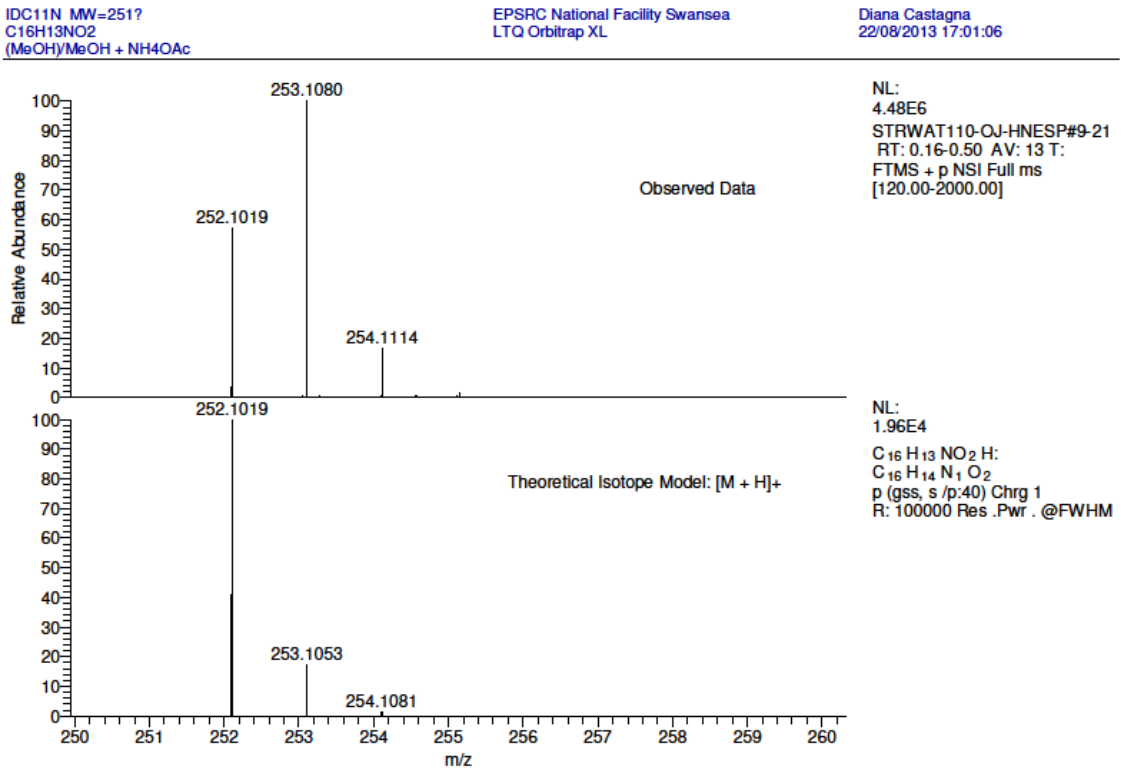
^{13}C NMR



IR

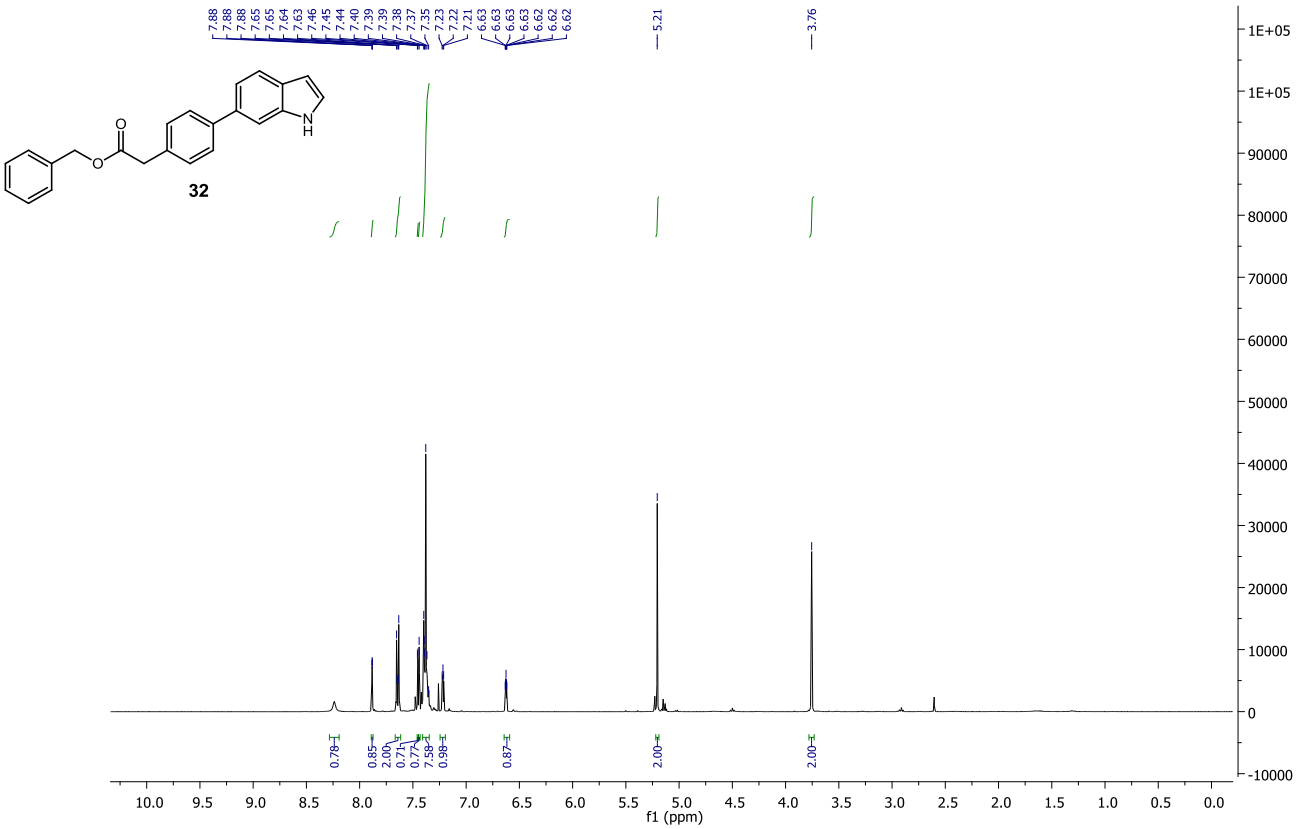

102.5
%T
100
97.5
95
92.5
90
87.5
85
82.5
80
77.5
75
3381.36
2518.18
1689.72
1405.20
1256.68
1252.82
1236.42
1152.52
804.35
724.30
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
IDC11N
1/cm

HRMS

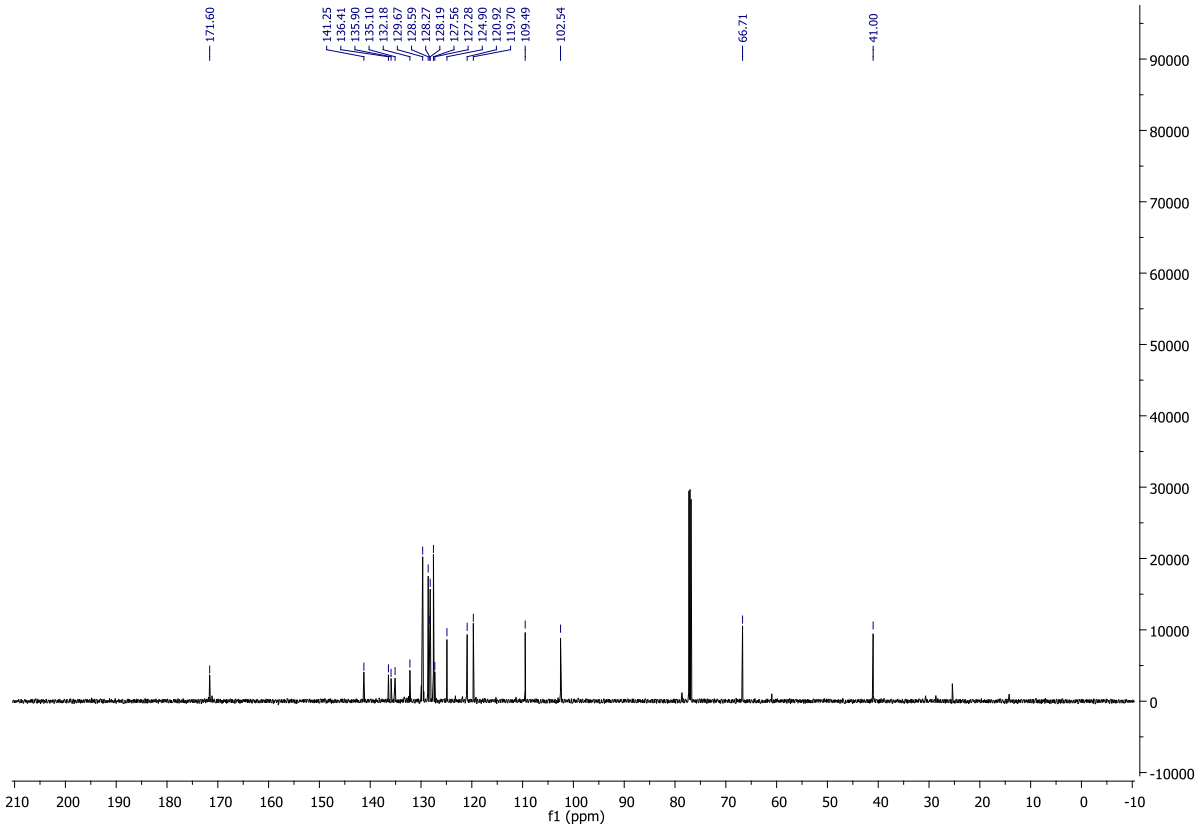

IDC11N MW=251?
C16H13NO2
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
22/08/2013 17:01:06
253.1080
252.1019
254.1114
Observed Data
NL:
4.48E6
STRWAT110-OJ-HNESP#9-21
RT: 0.16-0.50 AV: 13 T:
FTMS + p NSI Full ms
[120.00-2000.00]
Relative Abundance
252.1019
253.1053
254.1081
Theoretical Isotope Model: [M + H]+
NL:
1.96E4
C16 H13 NO2 H:
C16 H14 N1 O2
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
m/z

Compound 32

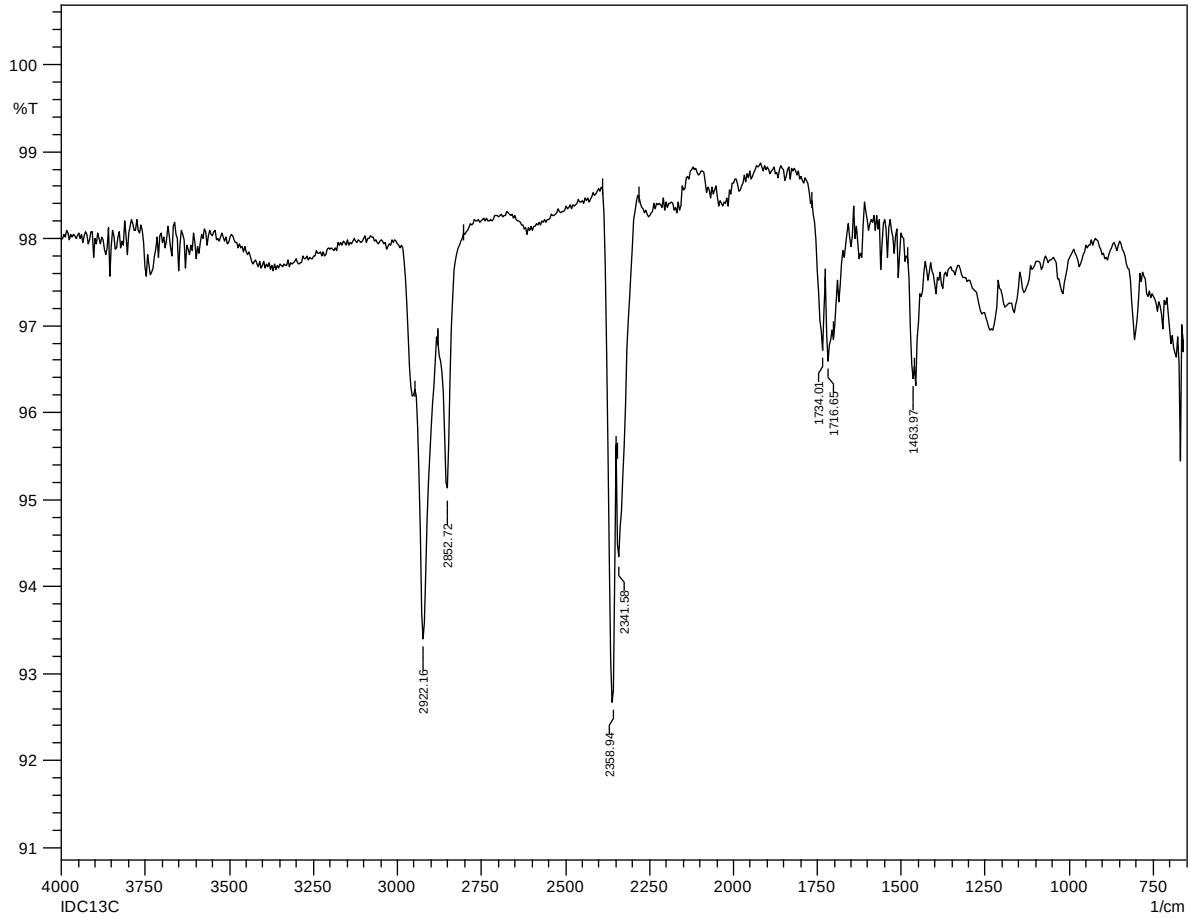
^{1}H NMR



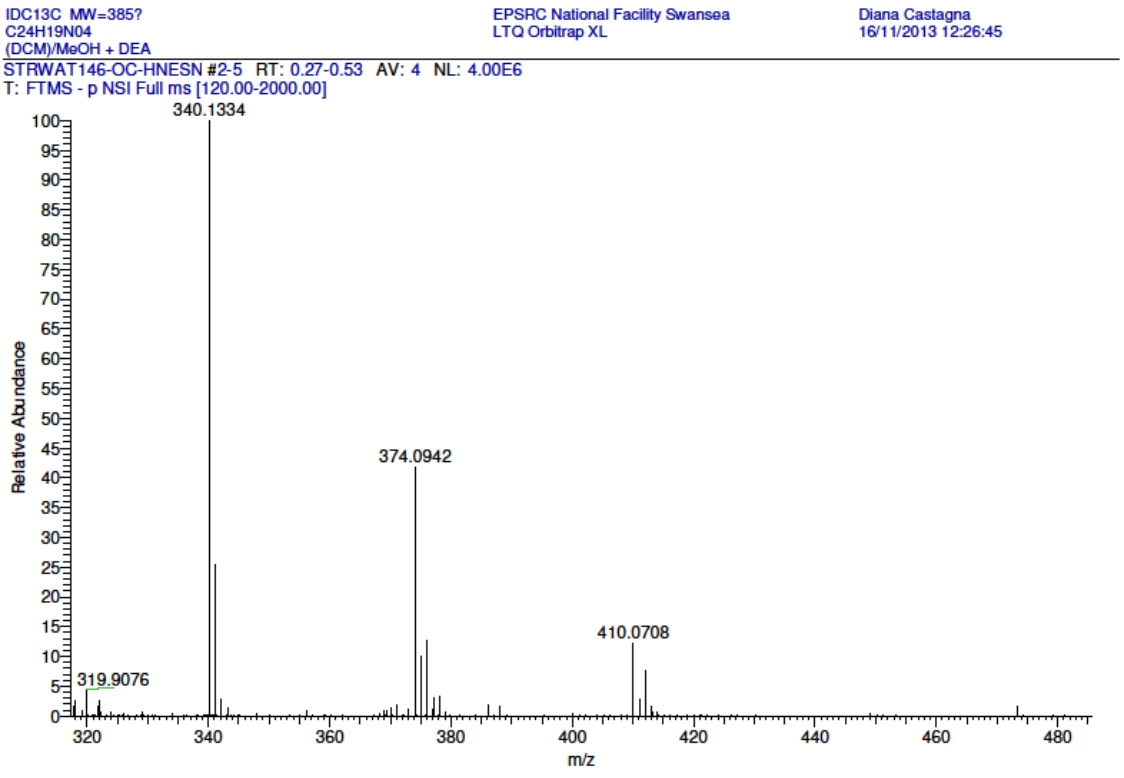
^{13}C NMR



IR

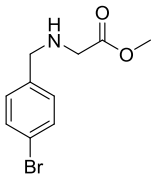

100
%T
99
98
97
96
95
94
93
92
91
2922.16
2852.72
2358.94
2341.58
1734.01
1716.65
1463.97
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
IDC13C
1/cm

HRMS

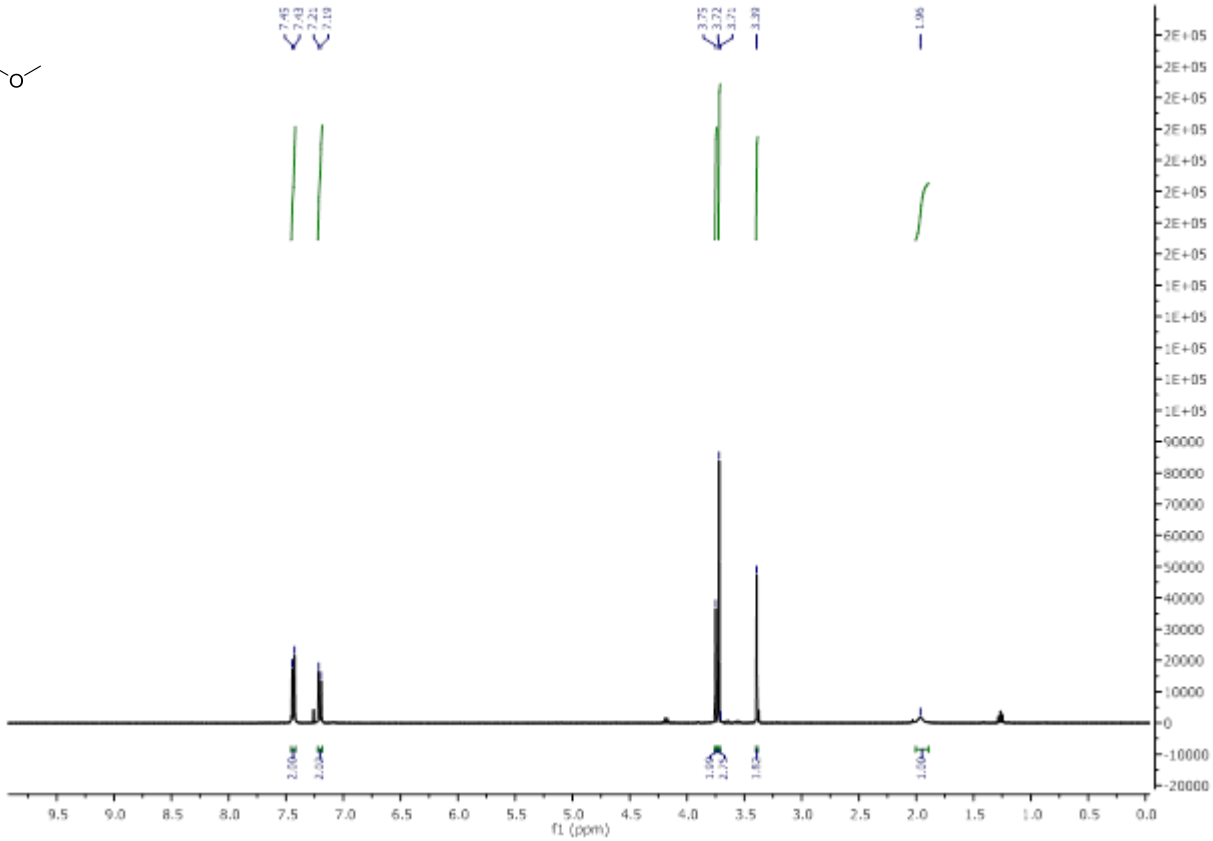

IDC13C MW=385?
C24H19N04
(DCM)/MeOH + DEA
EPSRC National Facility Swansea
LTQ Orbitrap XL
Diana Castagna
16/11/2013 12:26:45
STRWAT146-OC-HNESN #2-5 RT: 0.27-0.53 AV: 4 NL: 4.00E6
T: FTMS - p NSI Full ms [120.00-2000.00]
340.1334
374.0942
410.0708
319.9076
Relative Abundance
m/z
320
340
360
380
400
420
440
460
480

Compound 34

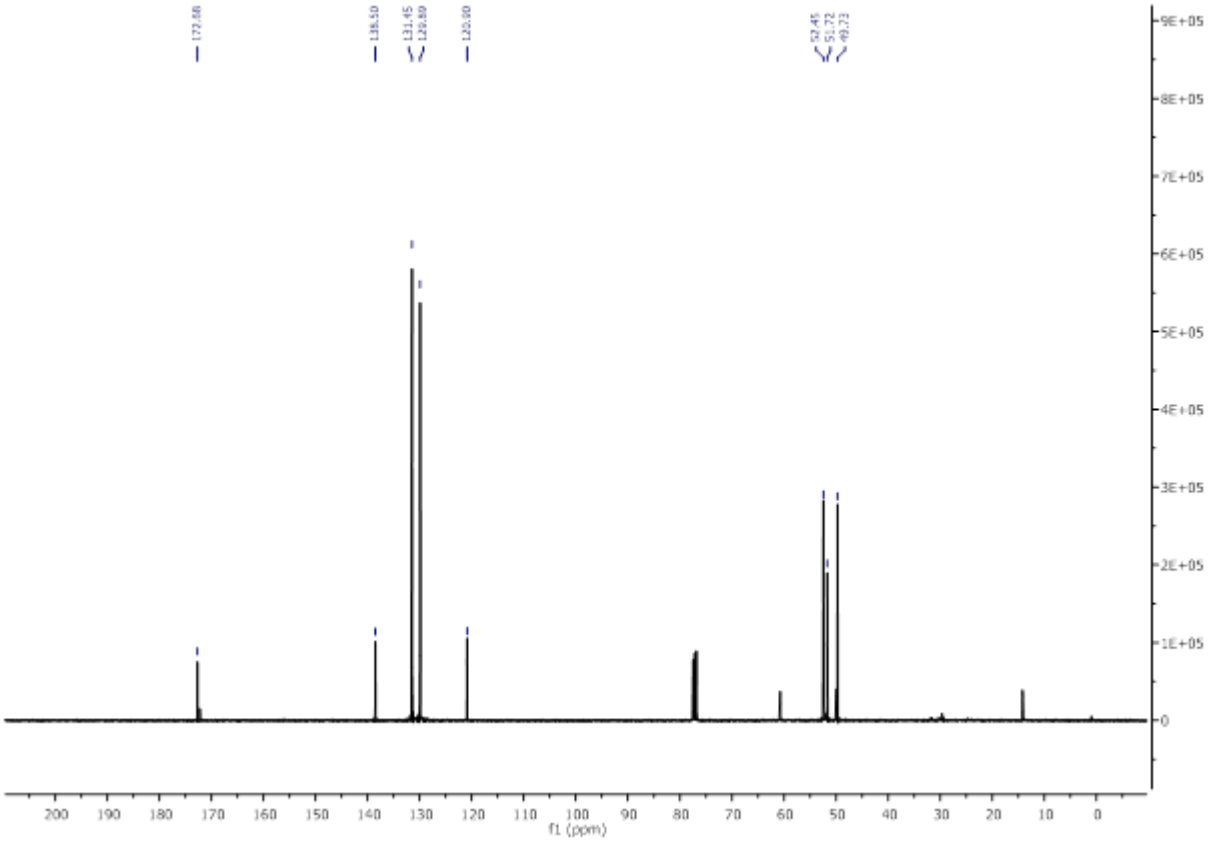
^{1}H NMR



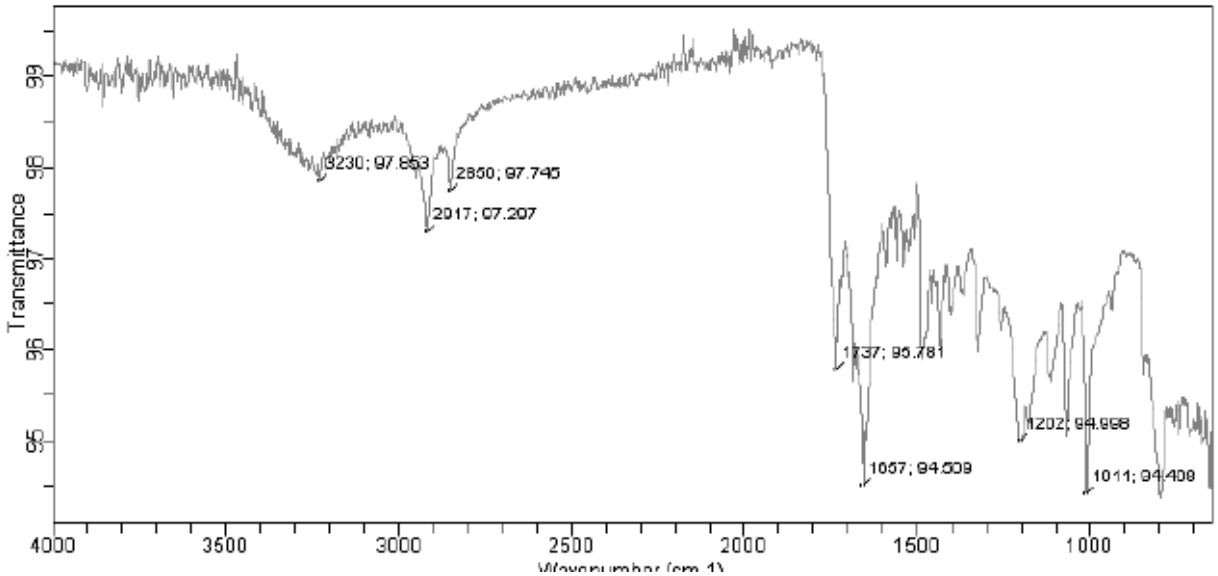
34



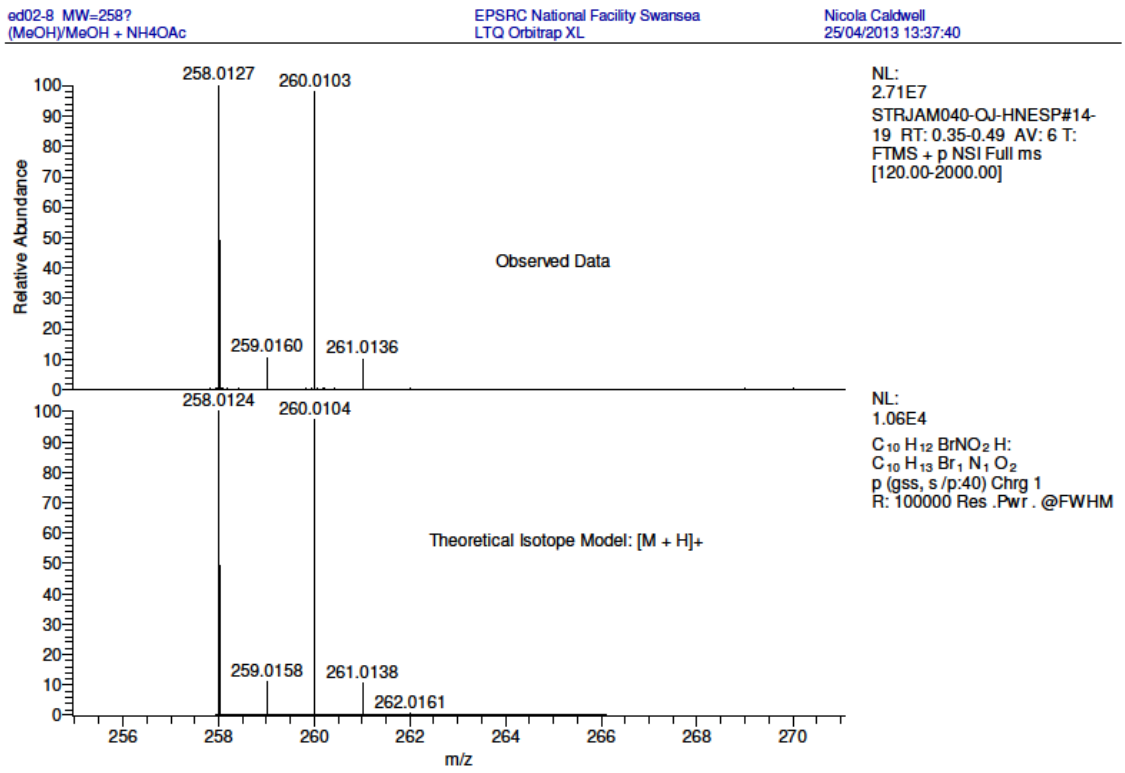
^{13}C NMR



IR

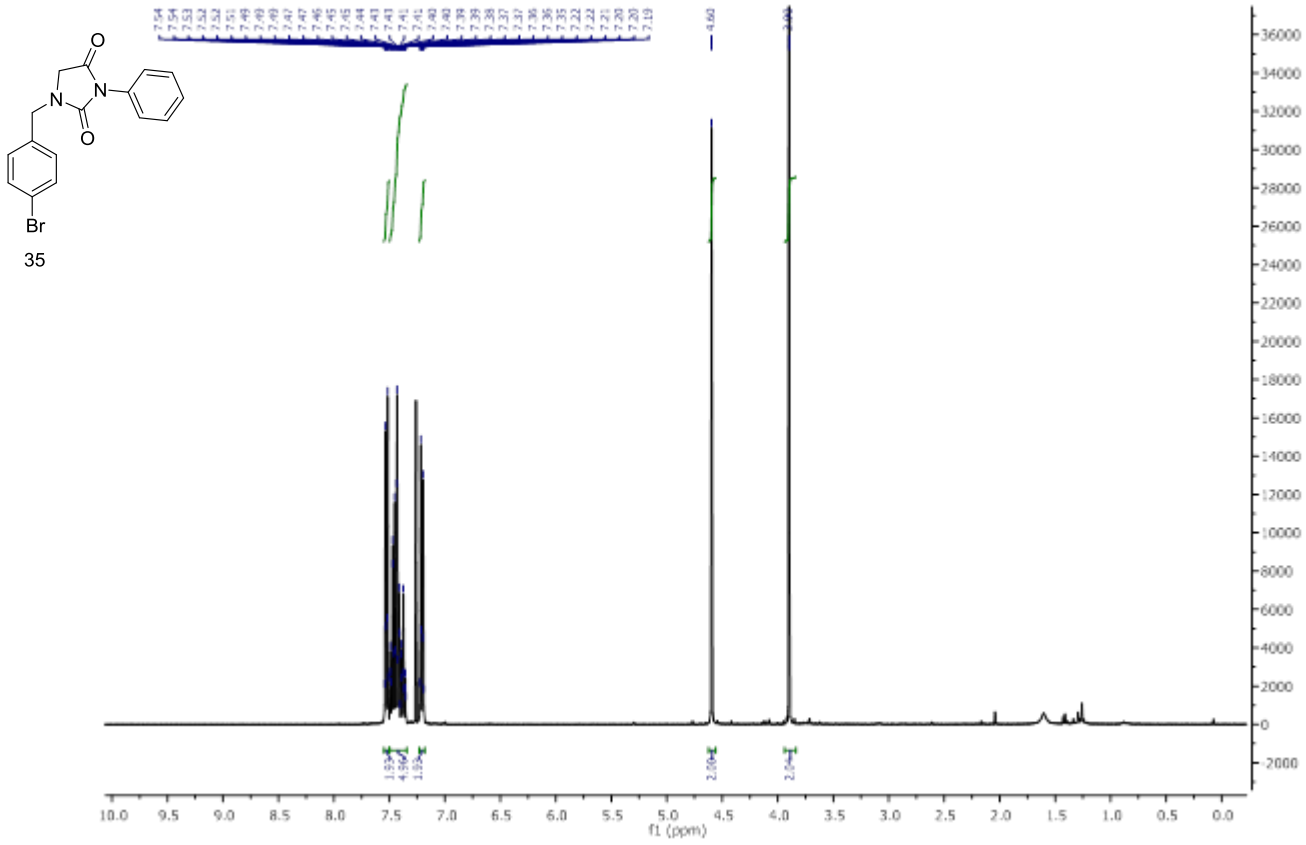

Transmittance
99
98
97
96
95
3230; 97.853
2850; 97.745
2917; 97.207
1737; 95.781
1202; 94.998
1057; 94.509
1011; 94.408
4000
3500
3000
2500
2000
1500
1000

HRMS

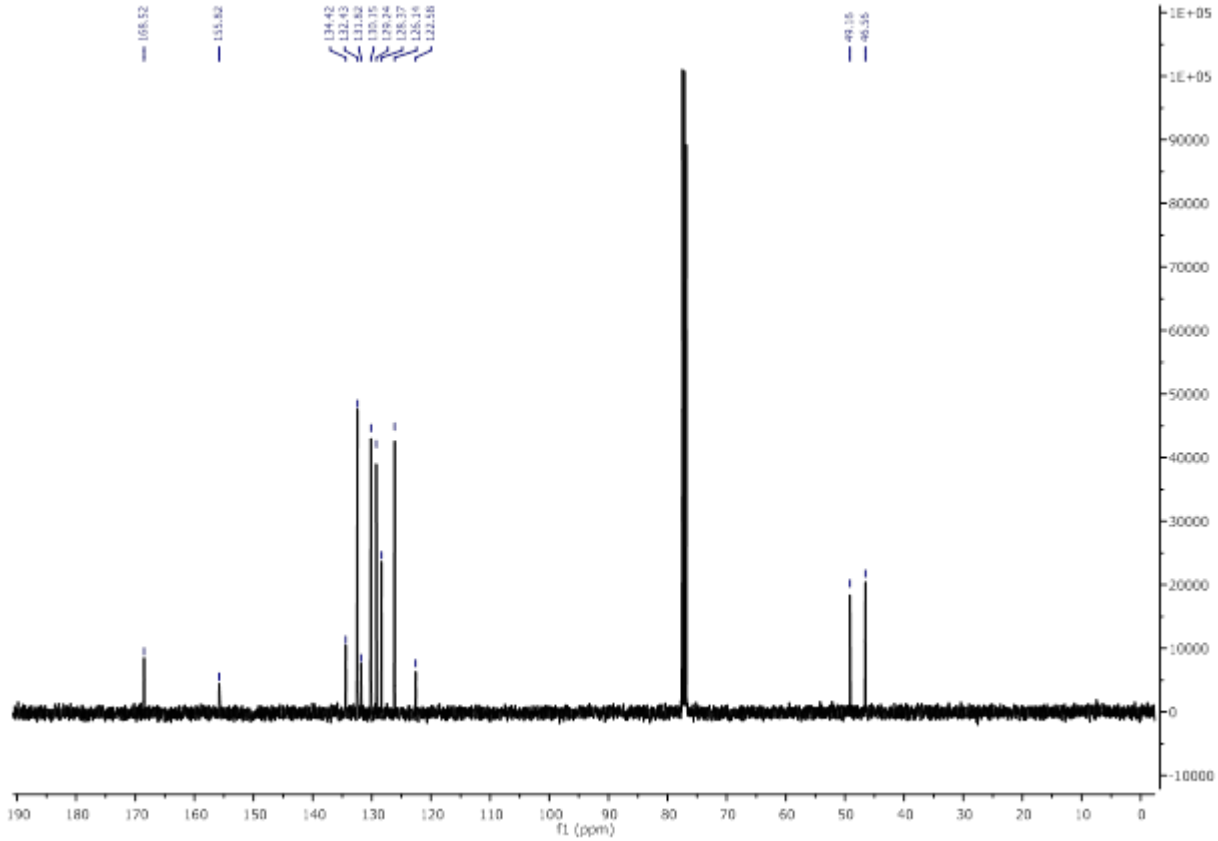

ed02-8 MW=258?
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Nicola Caldwell
25/04/2013 13:37:40
Relative Abundance
258.0127
260.0103
259.0160
261.0136
Observed Data
NL:
2.71E7
STRJAM040-OJ-HNESP#14-19 RT: 0.35-0.49 AV: 6 T: FTMS + p NSI Full ms [120.00-2000.00]
258.0124
260.0104
259.0158
261.0138
262.0161
Theoretical Isotope Model: [M + H]+
NL:
1.06E4
C10 H12 BrNO2 H:
C10 H13 Br1 N1 O2
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
m/z

Compound 35

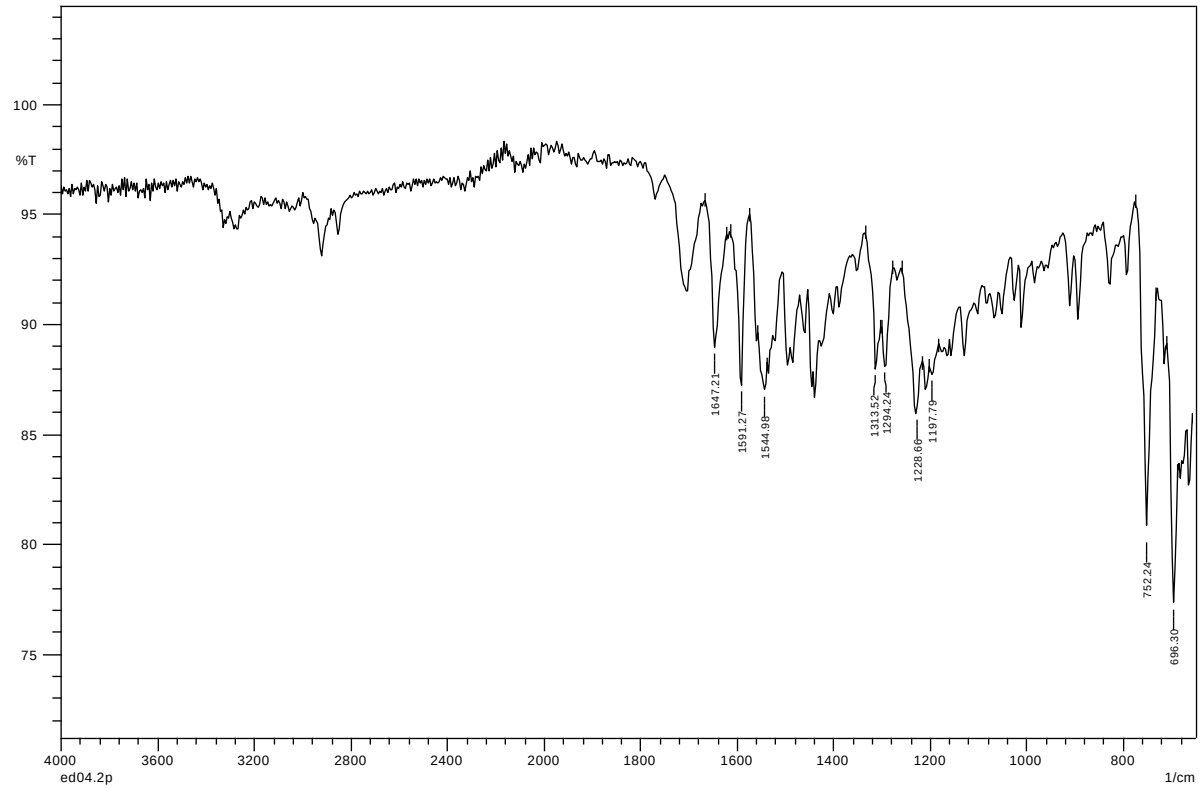
^{1}H NMR



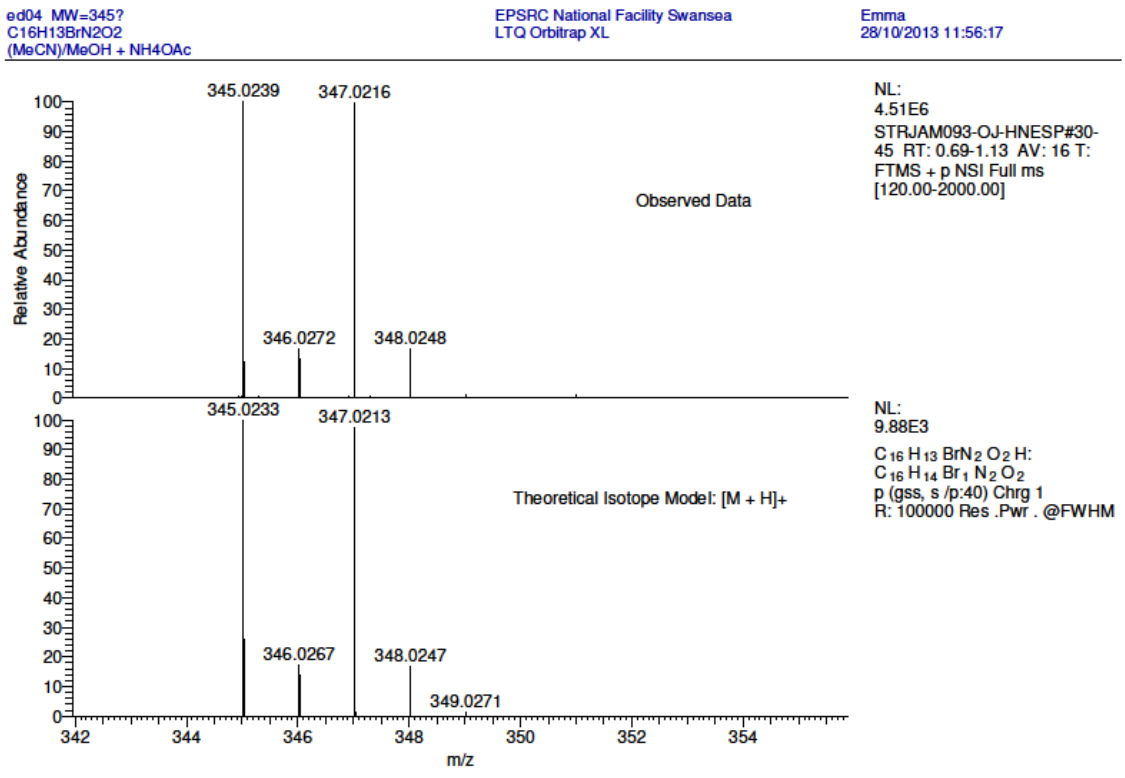
^{13}C NMR



IR

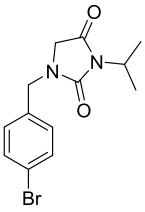

100
%T
95
90
85
80
75
1647.21
1591.27
1544.98
1313.52
1294.24
1228.66
1197.79
752.24
696.30
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
ed04.2p
1/cm

HRMS

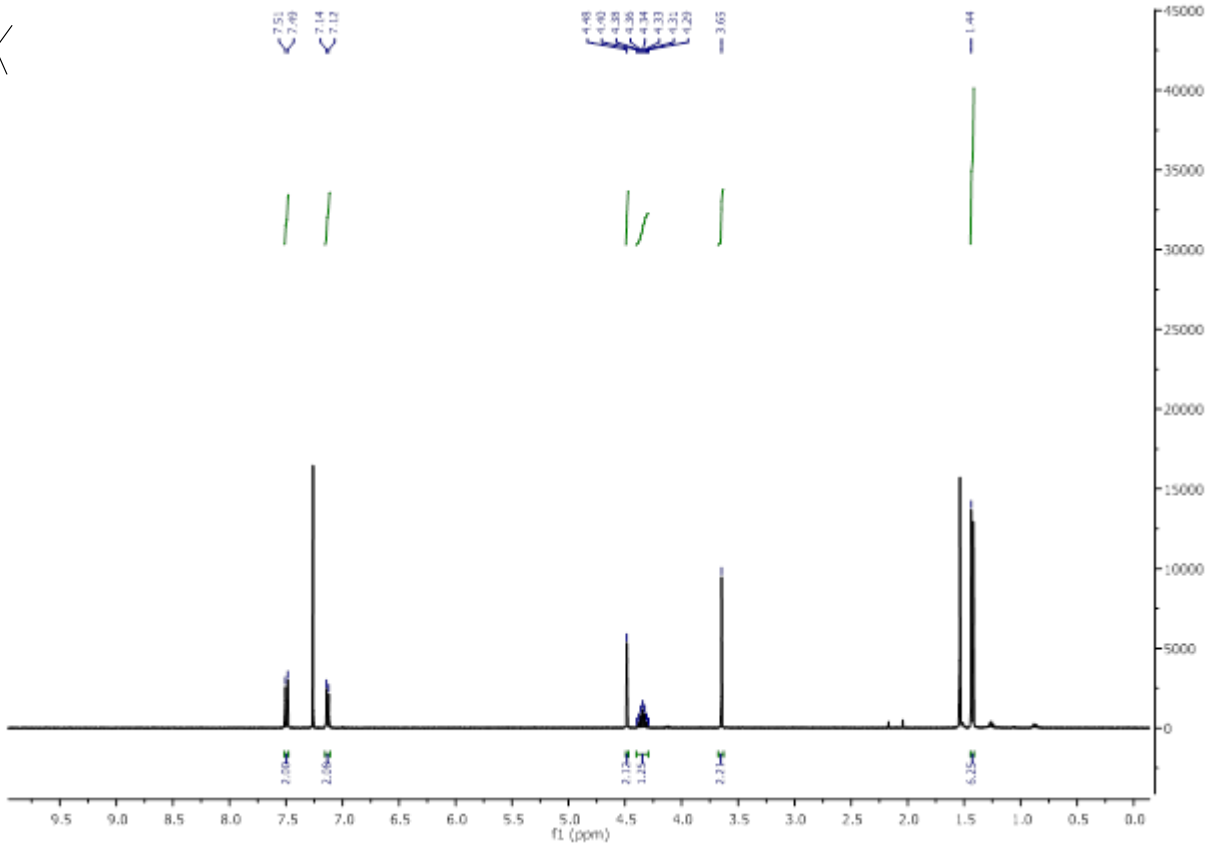

ed04 MW=345?
C16H13BrN2O2
(MeCN)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Emma
28/10/2013 11:56:17
345.0239
347.0216
346.0272
348.0248
Observed Data
NL:
4.51E6
STRJAM093-OJ-HNESP#30-45 RT: 0.69-1.13 AV: 16 T: FTMS + p NSI Full ms [120.00-2000.00]
345.0233
347.0213
346.0267
348.0247
349.0271
Theoretical Isotope Model: [M + H]+
NL:
9.88E3
C16 H13 BrN2 O2 H:
C16 H14 Br1 N2 O2
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
Relative Abundance
m/z

Compound 36

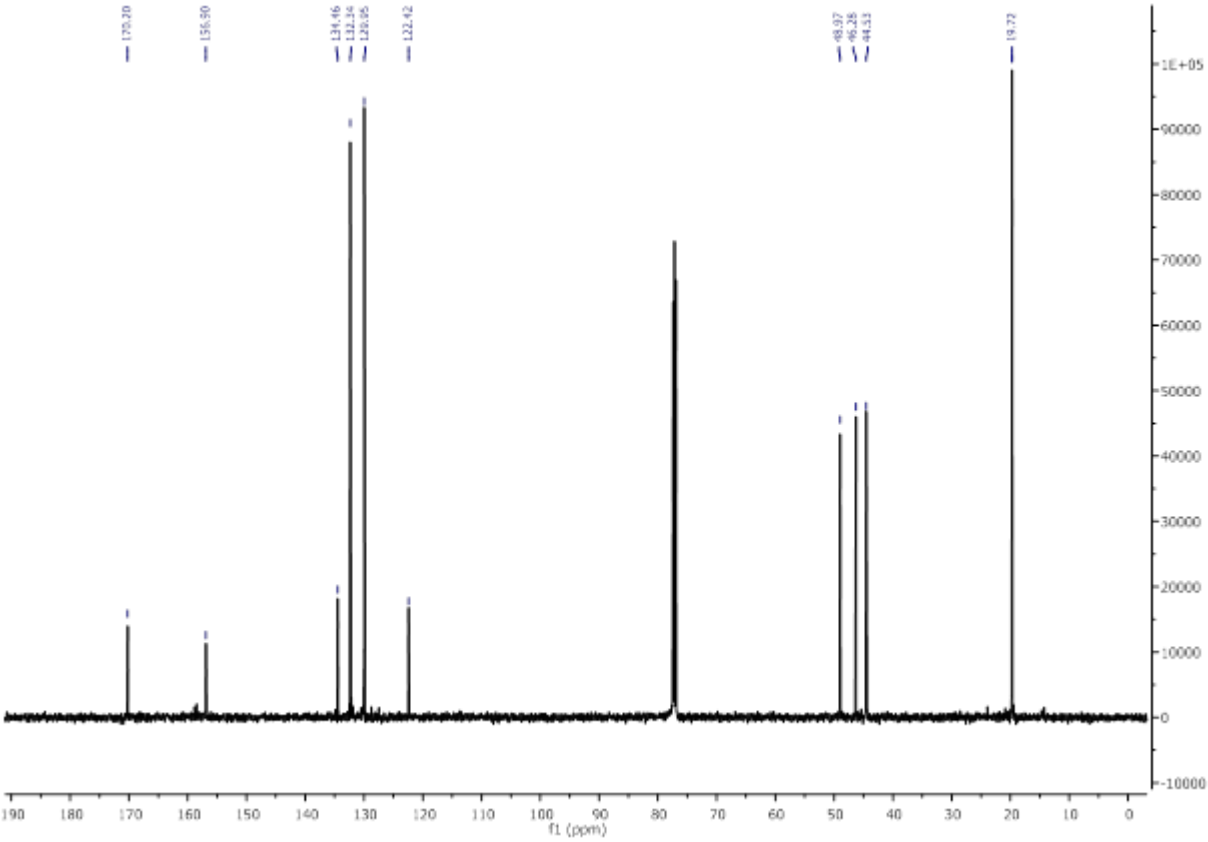
^{1}H NMR



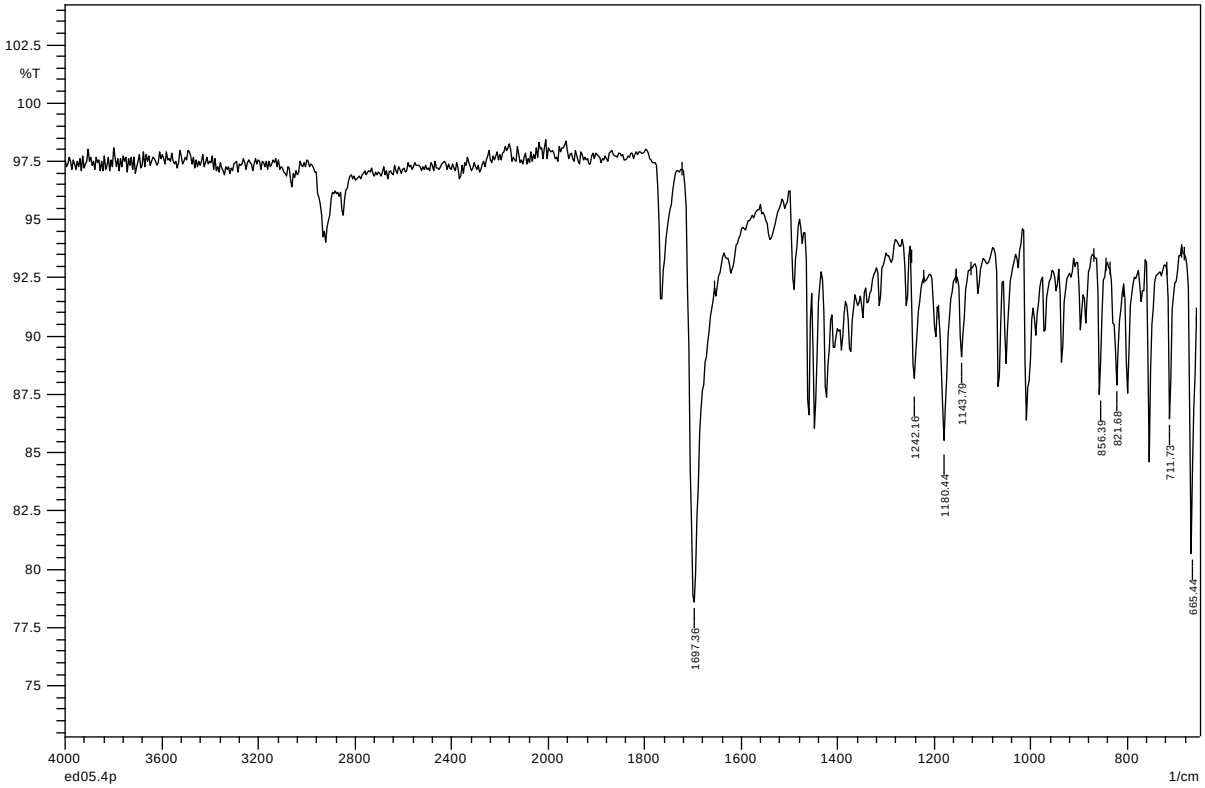
36



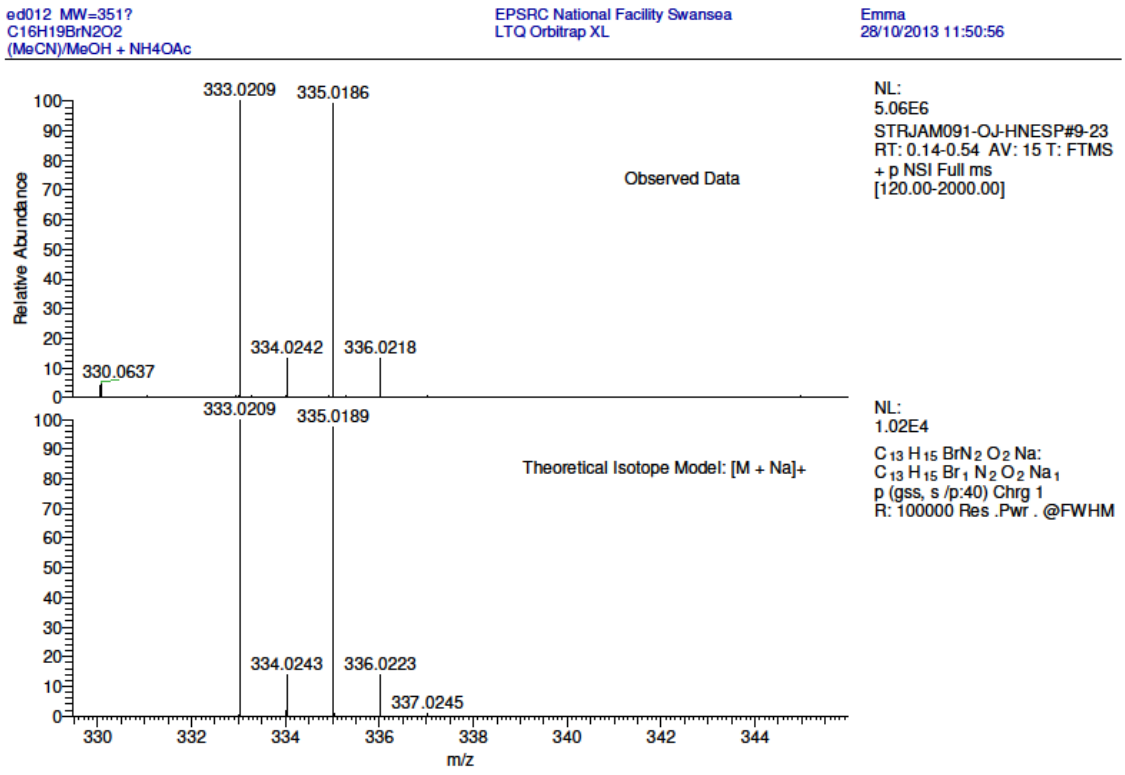
^{13}C NMR



IR

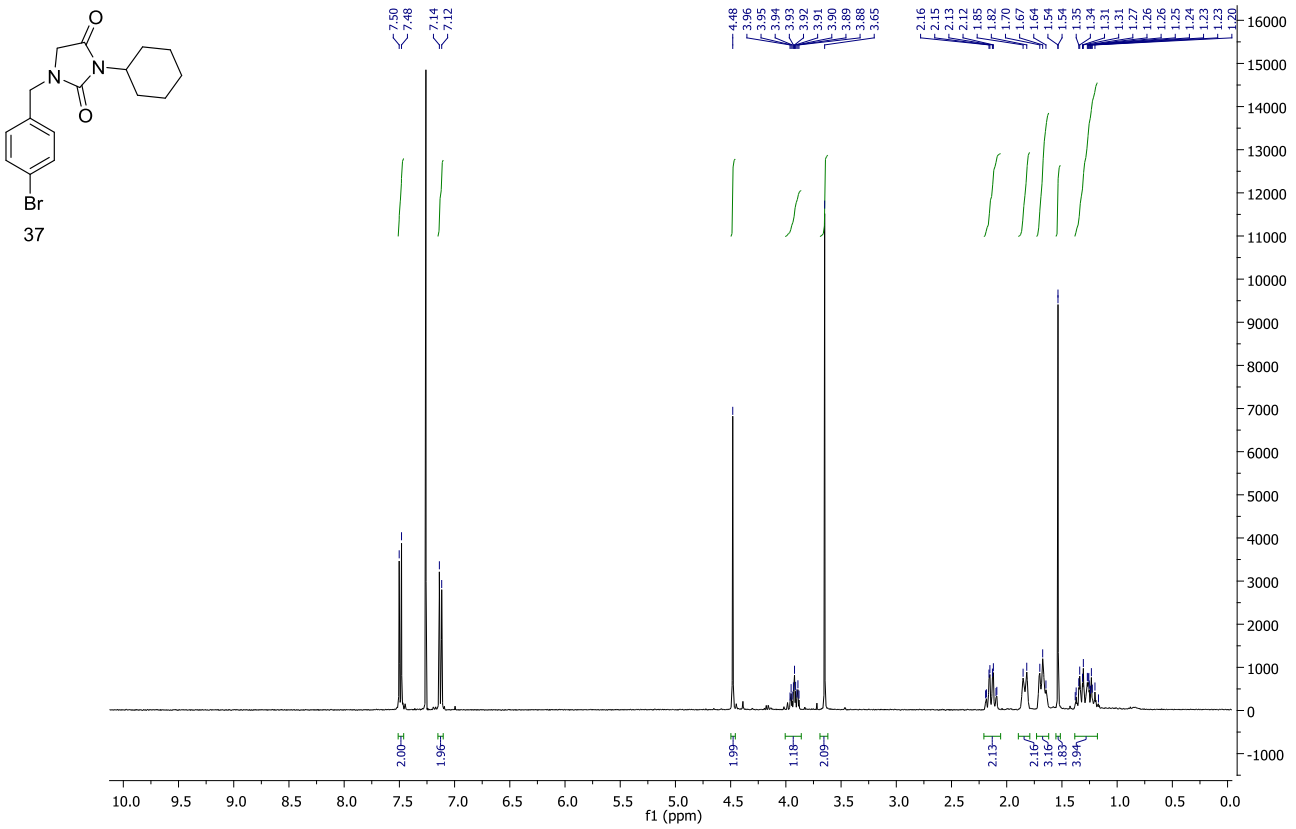

102.5
%T
100
97.5
95
92.5
90
87.5
85
82.5
80
77.5
75
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
1/cm
ed05.4p
1697.36
1242.16
1180.44
1143.79
856.39
821.68
711.73
665.44

HRMS

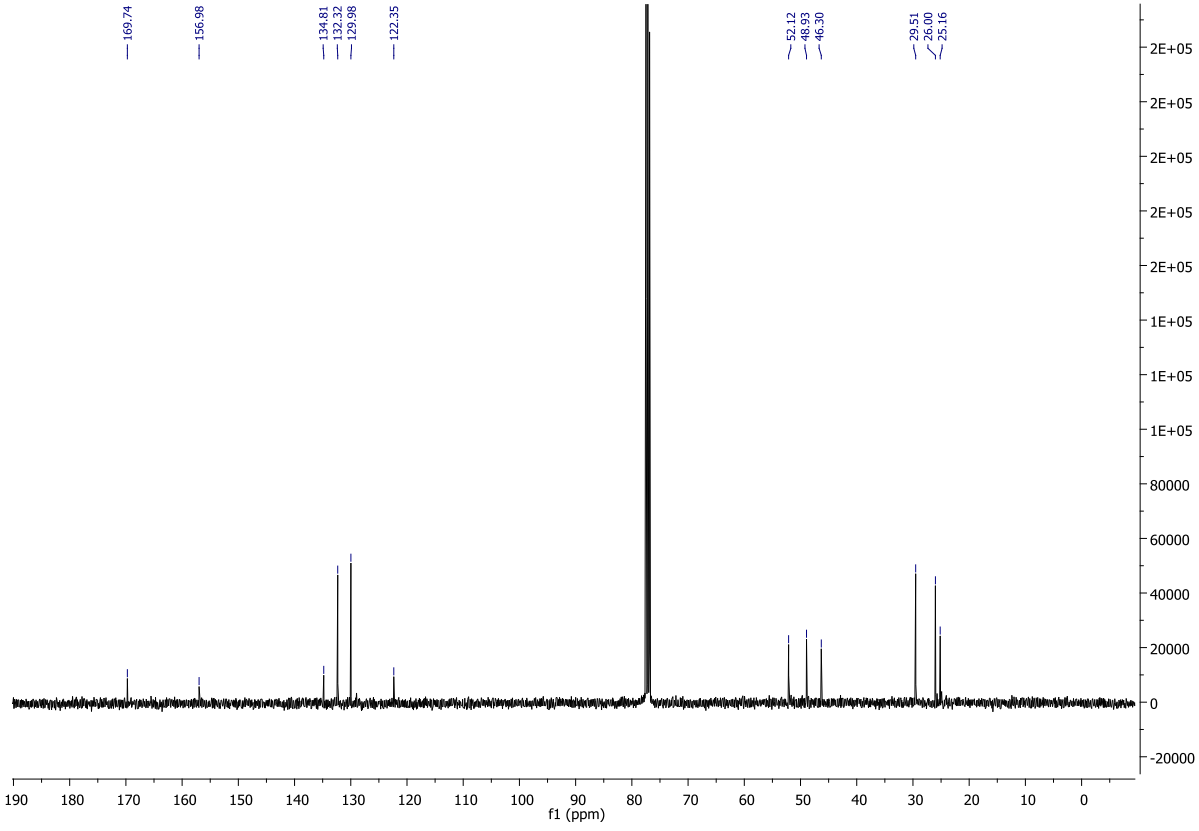

ed012 MW=351?
C16H19BrN2O2
(MeCN)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Emma
28/10/2013 11:50:56
333.0209
335.0186
334.0242
336.0218
330.0637
Observed Data
NL:
5.06E6
STRJAM091-OJ-HNESP#9-23
RT: 0.14-0.54 AV: 15 T: FTMS
+ p NSI Full ms
[120.00-2000.00]
333.0209
335.0189
334.0243
336.0223
337.0245
Theoretical Isotope Model: [M + Na]+
NL:
1.02E4
C13 H15 BrN2 O2 Na:
C13 H15 Br1 N2 O2 Na1
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
Relative Abundance
m/z

Compound 37

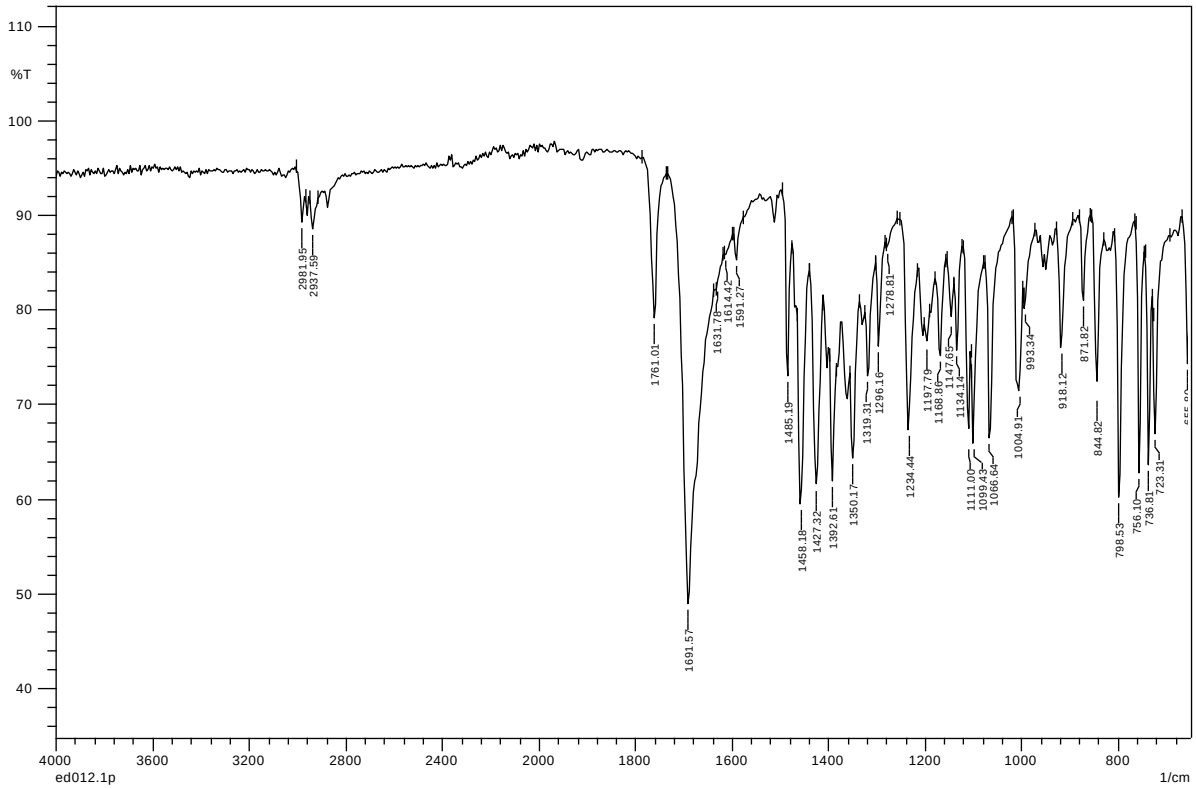
^{1}H NMR



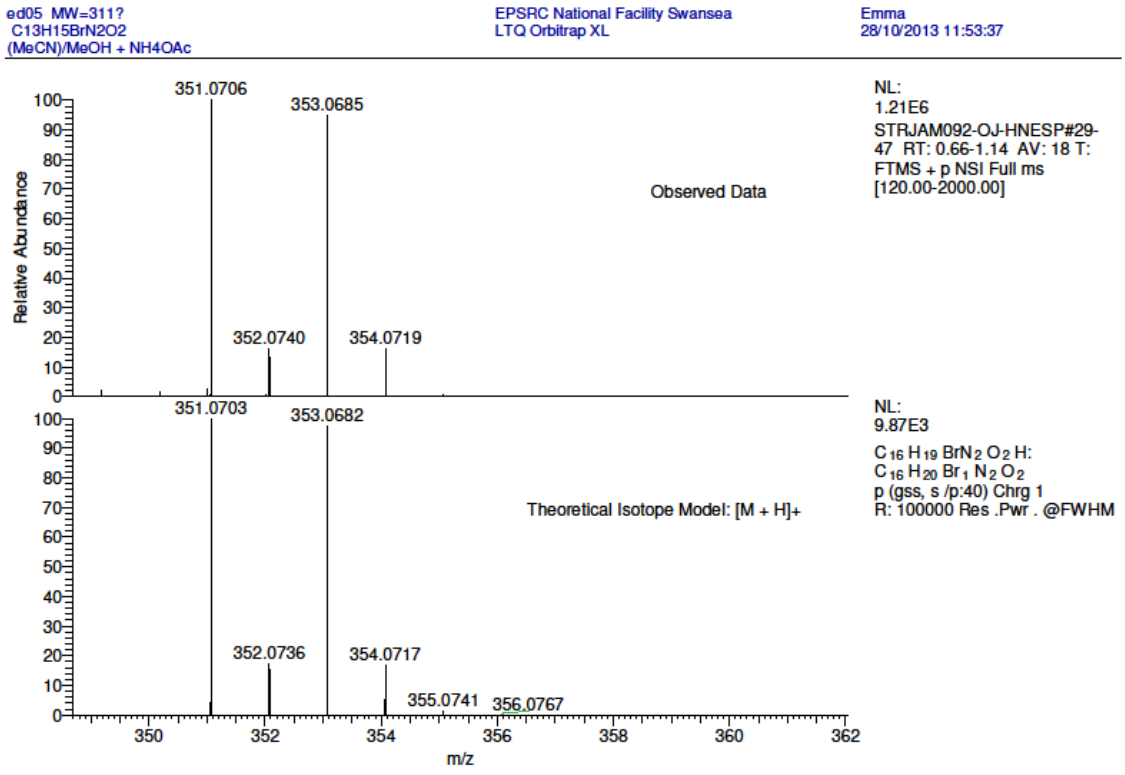
^{13}C NMR



IR

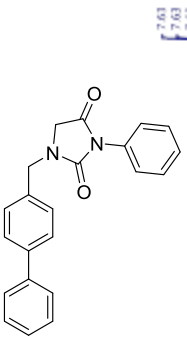

%T
2981.95
2637.58
1761.01
1691.57
1631.78
1614.42
1591.27
1485.19
1458.18
1427.32
1392.61
1350.17
1319.31
1296.16
1278.81
1234.44
1197.79
1168.86
1147.65
1134.14
1111.00
1099.43
1066.64
1004.91
993.34
918.12
871.82
844.82
798.53
756.10
736.81
723.31
ed012.1p
1/cm

HRMS

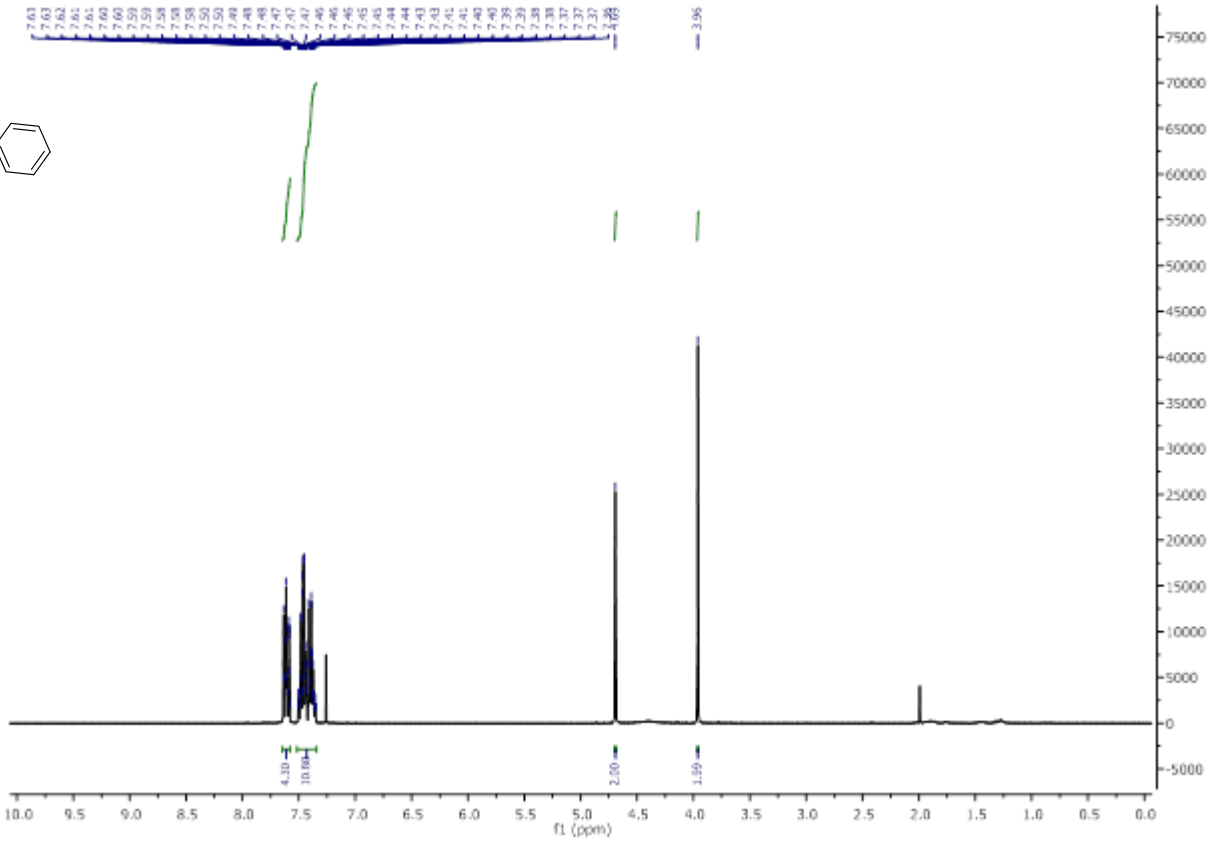

ed05 MW=311?
C13H15BrN2O2
(MeCN)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Emma
28/10/2013 11:53:37
Relative Abundance
351.0706
353.0685
352.0740
354.0719
Observed Data
NL:
1.21E6
STRJAM092-OJ-HNESP#29-47 RT: 0.66-1.14 AV: 18 T: FTMS + p NSI Full ms [120.00-2000.00]
351.0703
353.0682
352.0736
354.0717
355.0741
356.0767
Theoretical Isotope Model: [M + H]+
NL:
9.87E3
C16 H19 BrN2 O2 H:
C16 H20 Br1 N2 O2
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
m/z

Compound 38

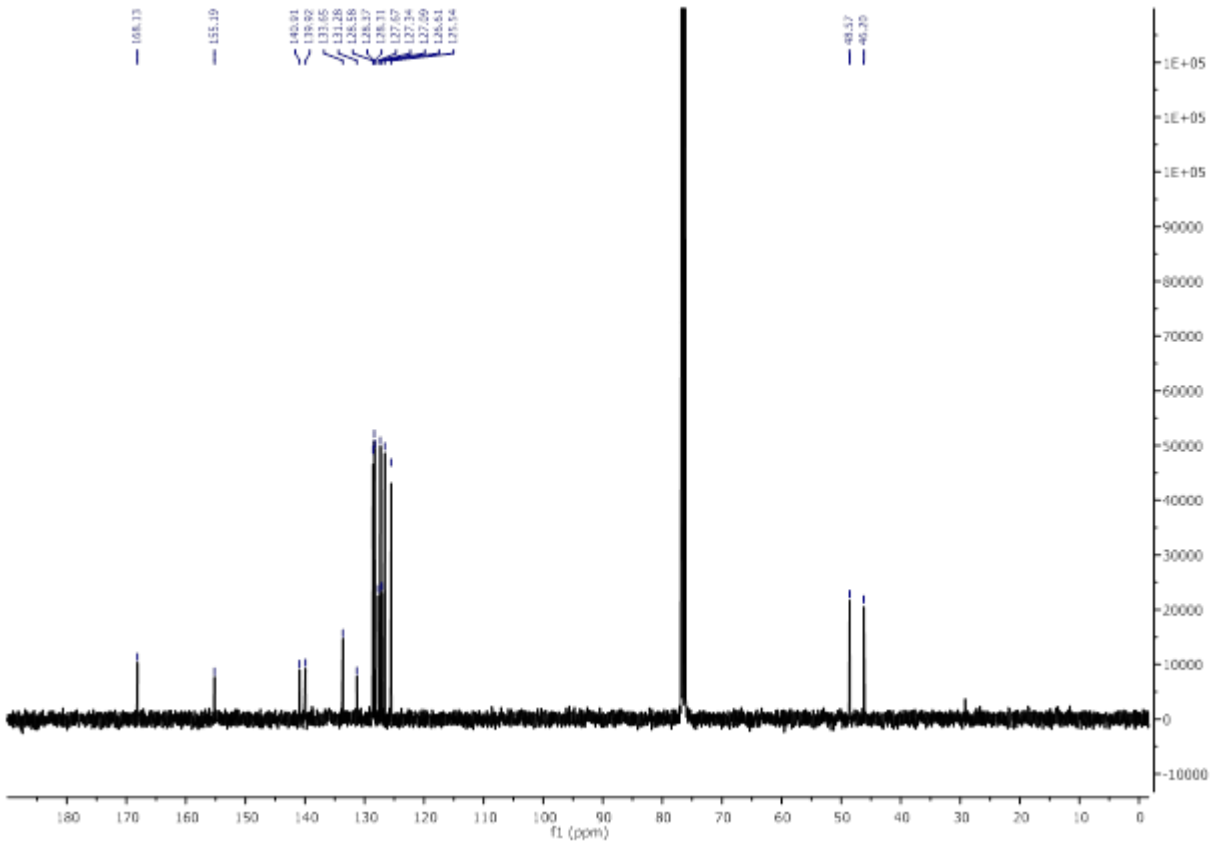
^{1}H NMR



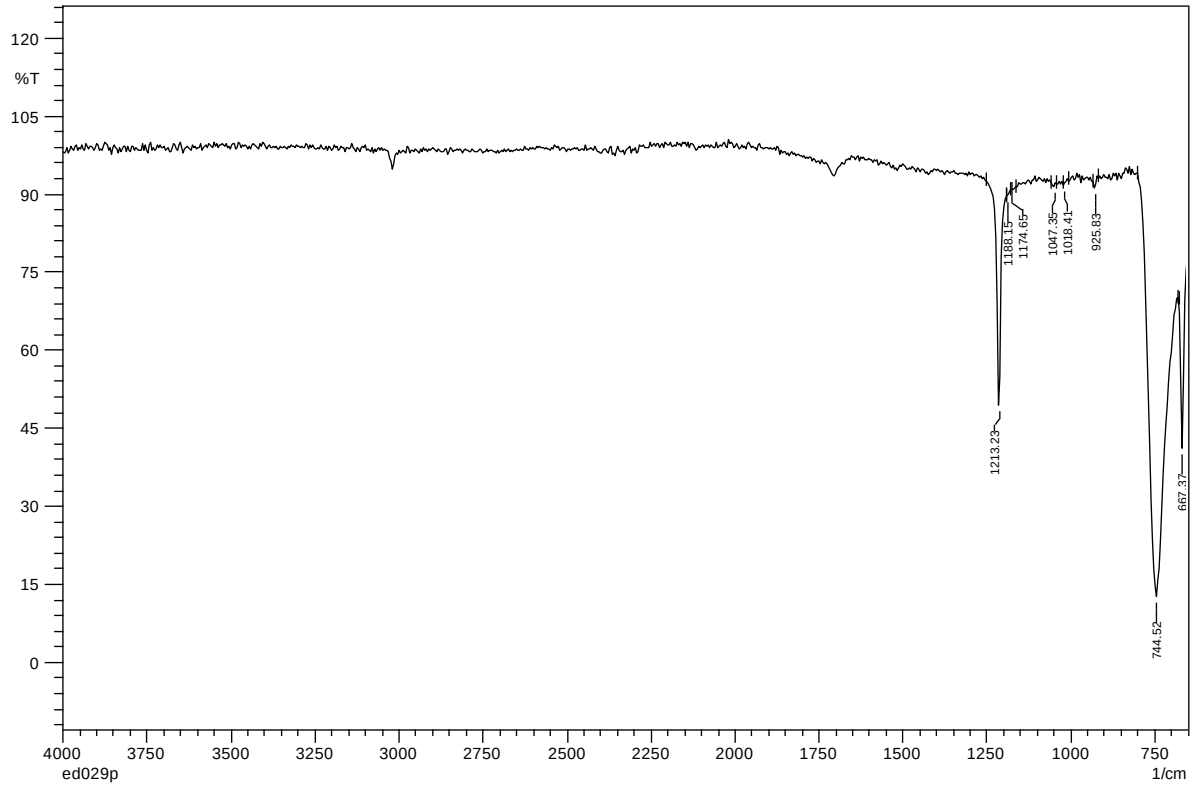
38



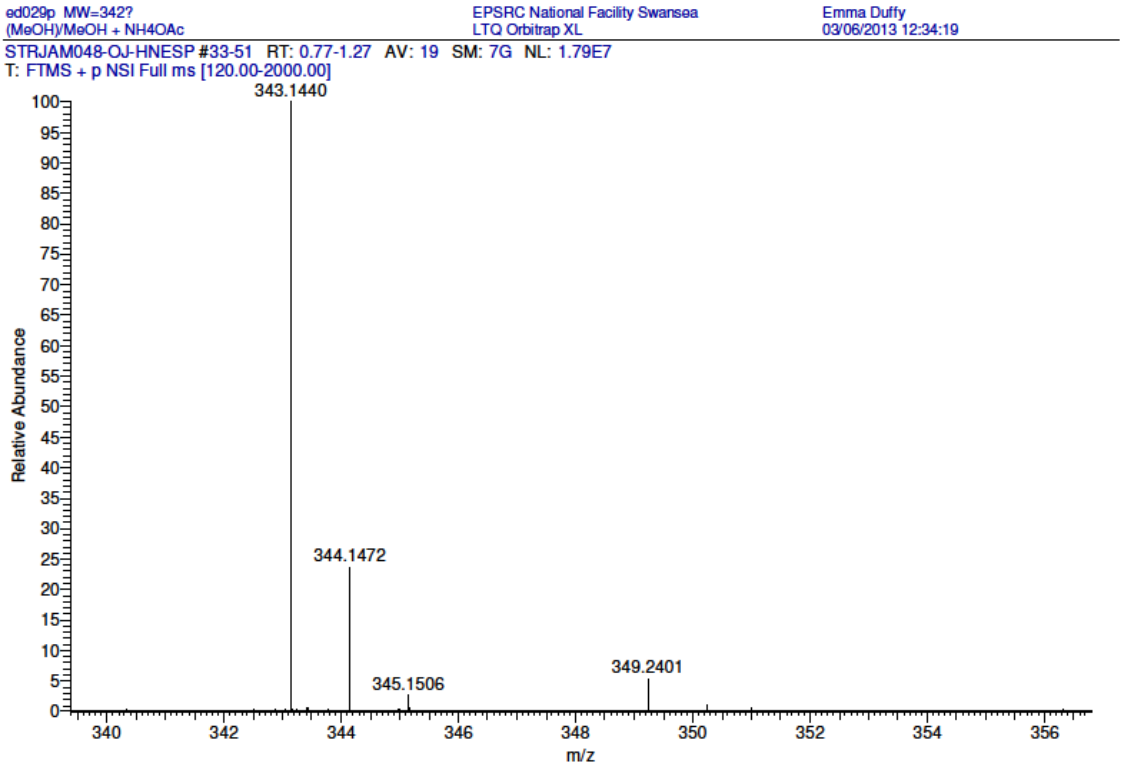
^{13}C NMR



IR

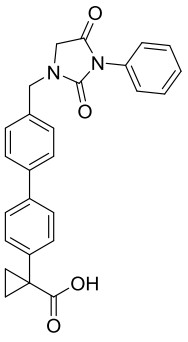

120
%T
105
90
75
60
45
30
15
0
1213.23
1188.15
1174.65
1047.35
1018.41
925.83
744.52
667.37
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
ed029p
1/cm

HRMS

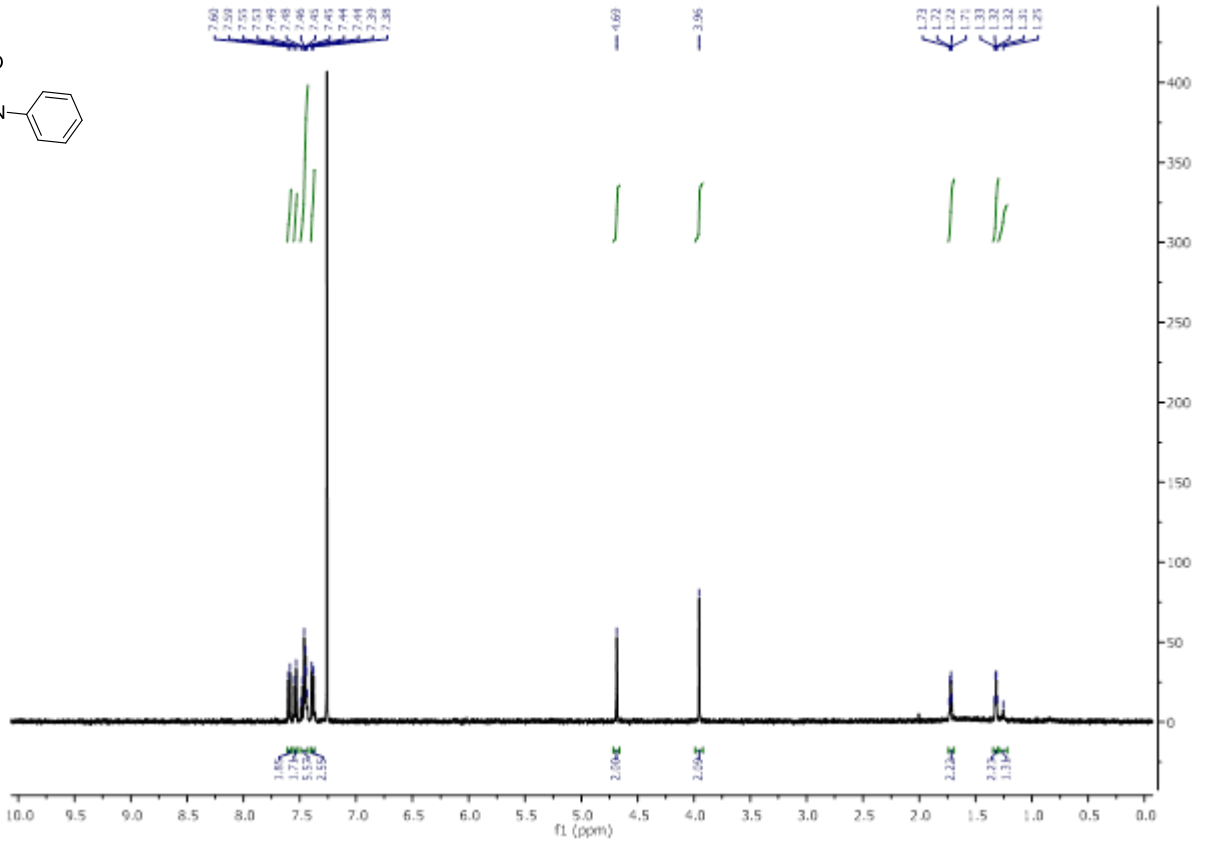

ed029p MW=342?
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Emma Duffy
03/06/2013 12:34:19
STRJAM048-OJ-HNESP #33-51 RT: 0.77-1.27 AV: 19 SM: 7G NL: 1.79E7
T: FTMS + p NSI Full ms [120.00-2000.00]
343.1440
344.1472
345.1506
349.2401
Relative Abundance
m/z
340
342
344
346
348
350
352
354
356

Compound 39

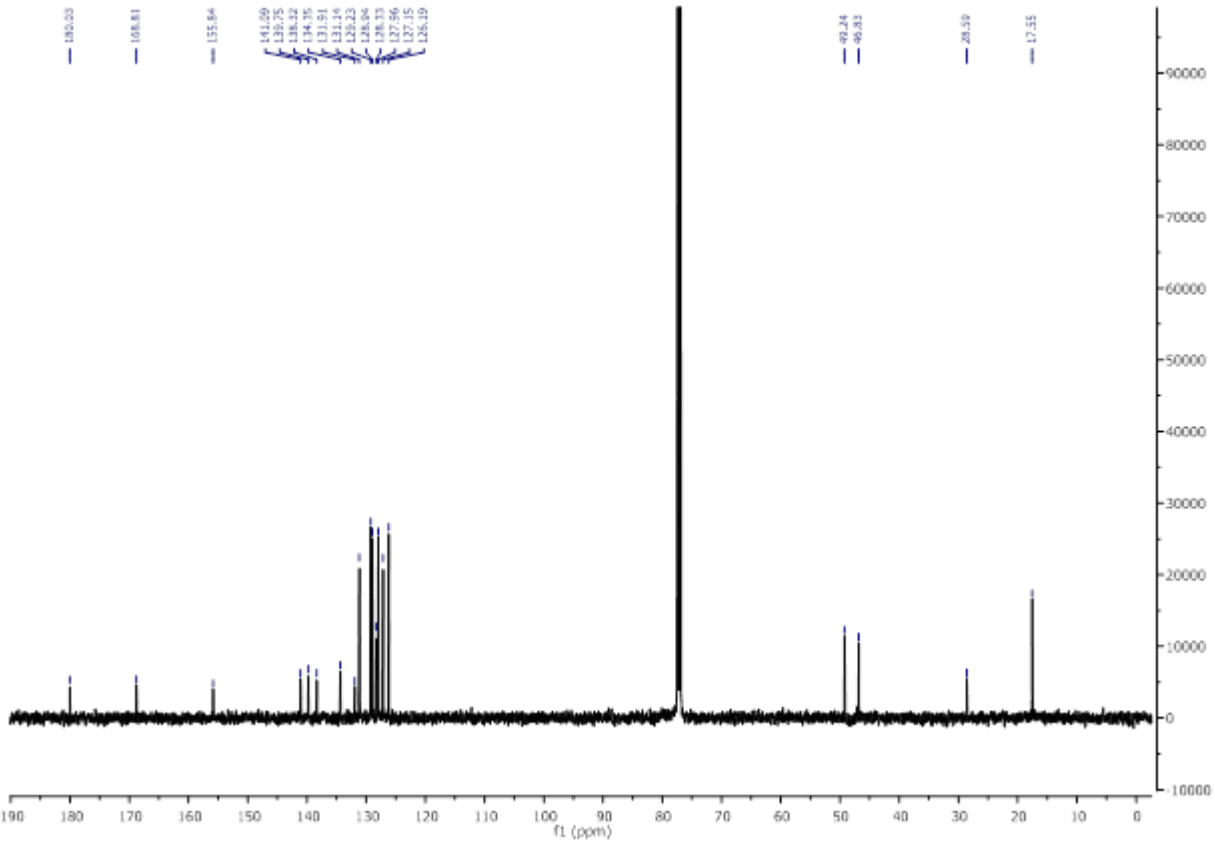
^{1}H NMR



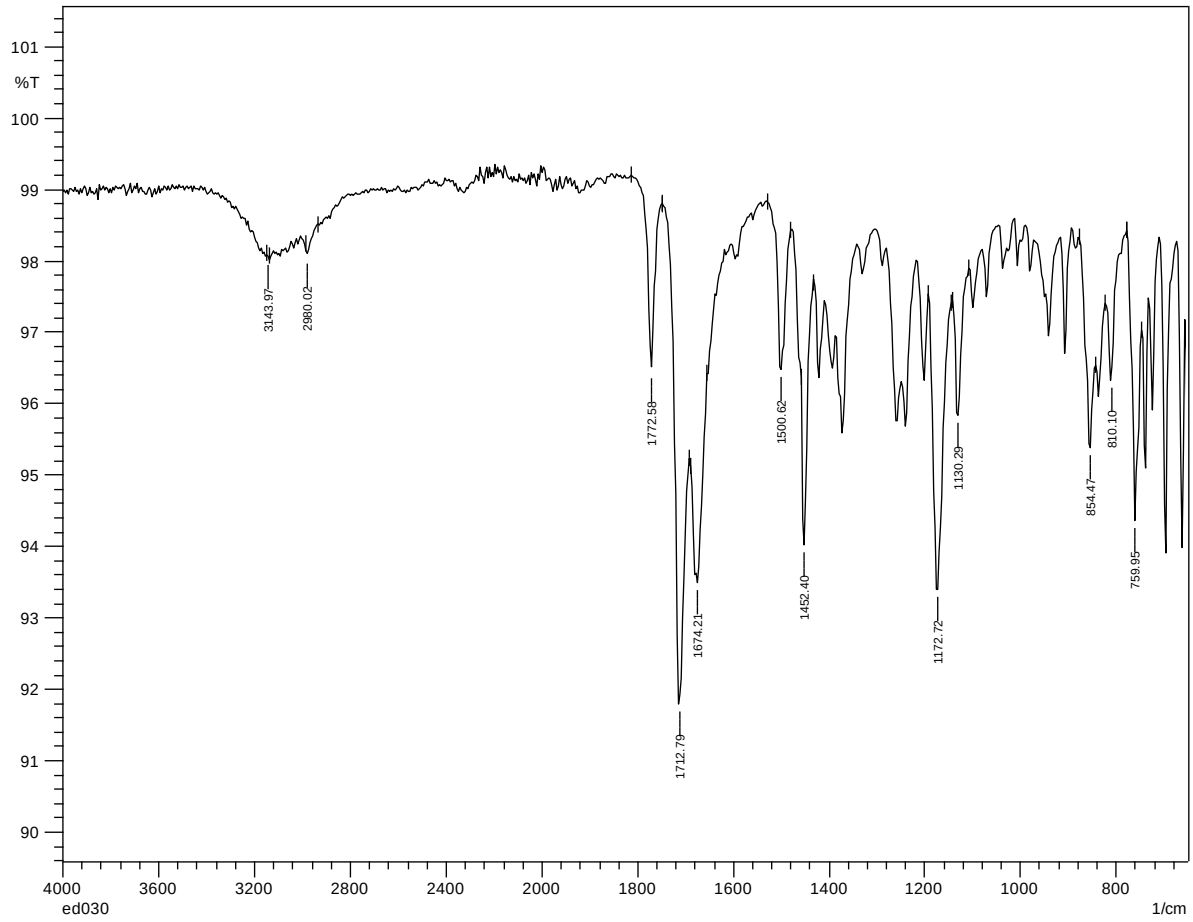
39



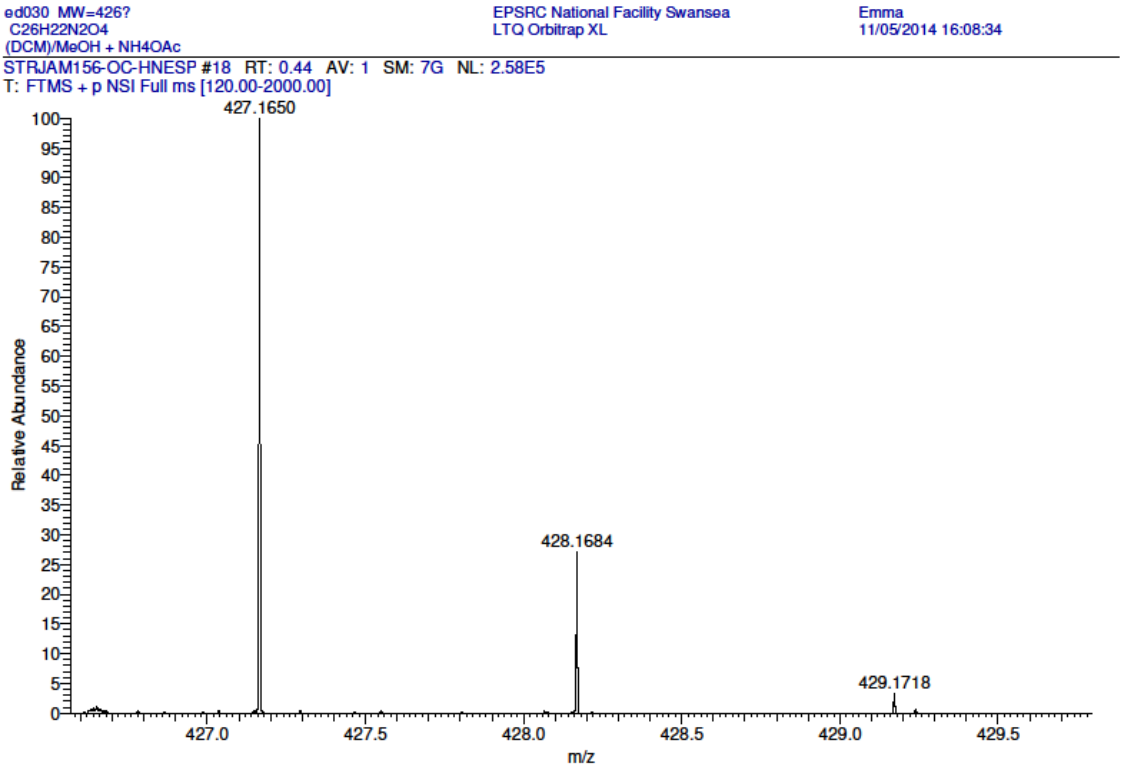
^{13}C NMR



IR

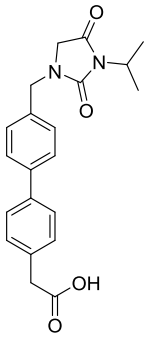

101
%T
100
99
98
97
96
95
94
93
92
91
90
3143.97
2980.02
1772.58
1712.79
1674.21
1500.62
1452.40
1172.72
1130.29
854.47
810.10
759.95
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
ed030
1/cm

HRMS

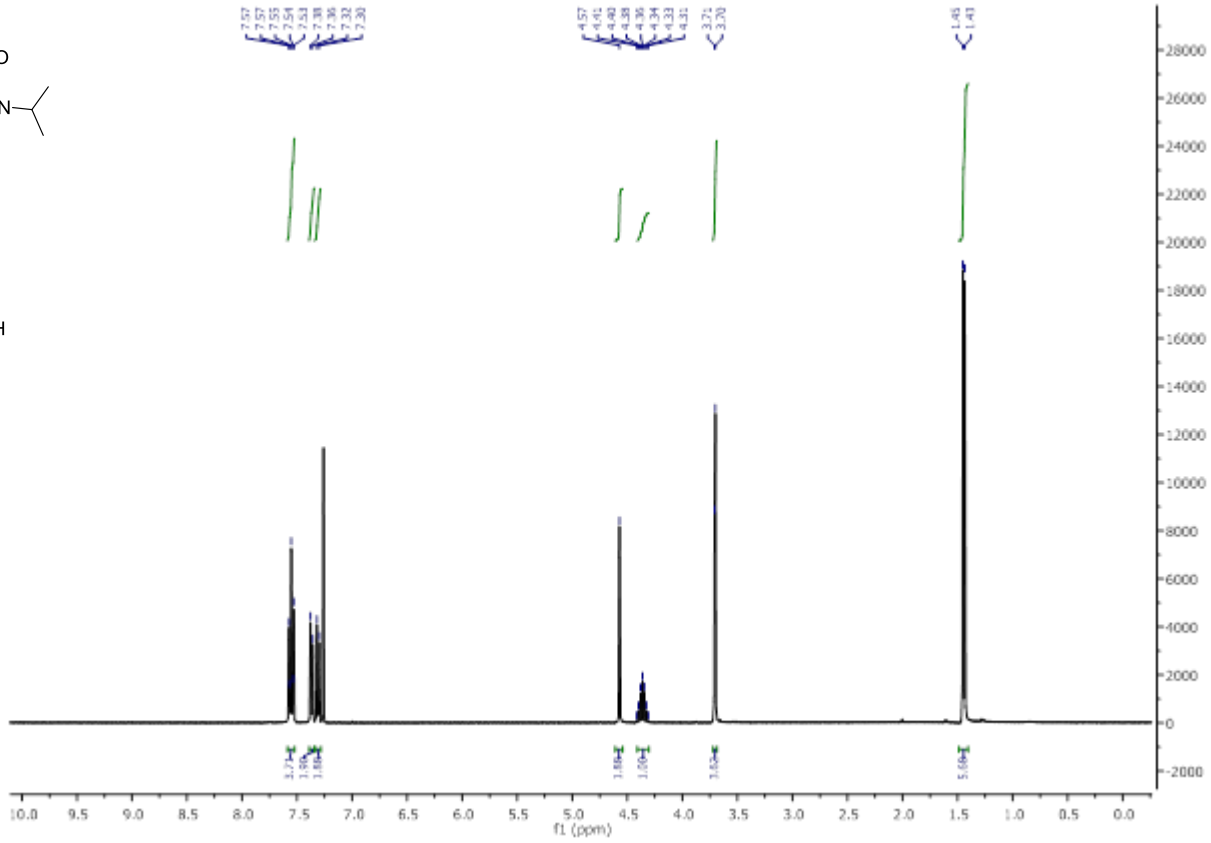

ed030 MW=426?
C26H22N2O4
(DCM)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Emma
11/05/2014 16:08:34
STRJAM156-OC-HNESP #18 RT: 0.44 AV: 1 SM: 7G NL: 2.58E5
T: FTMS + p NSI Full ms [120.00-2000.00]
427.1650
428.1684
429.1718
Relative Abundance
m/z
427.0
427.5
428.0
428.5
429.0
429.5

Compound 40

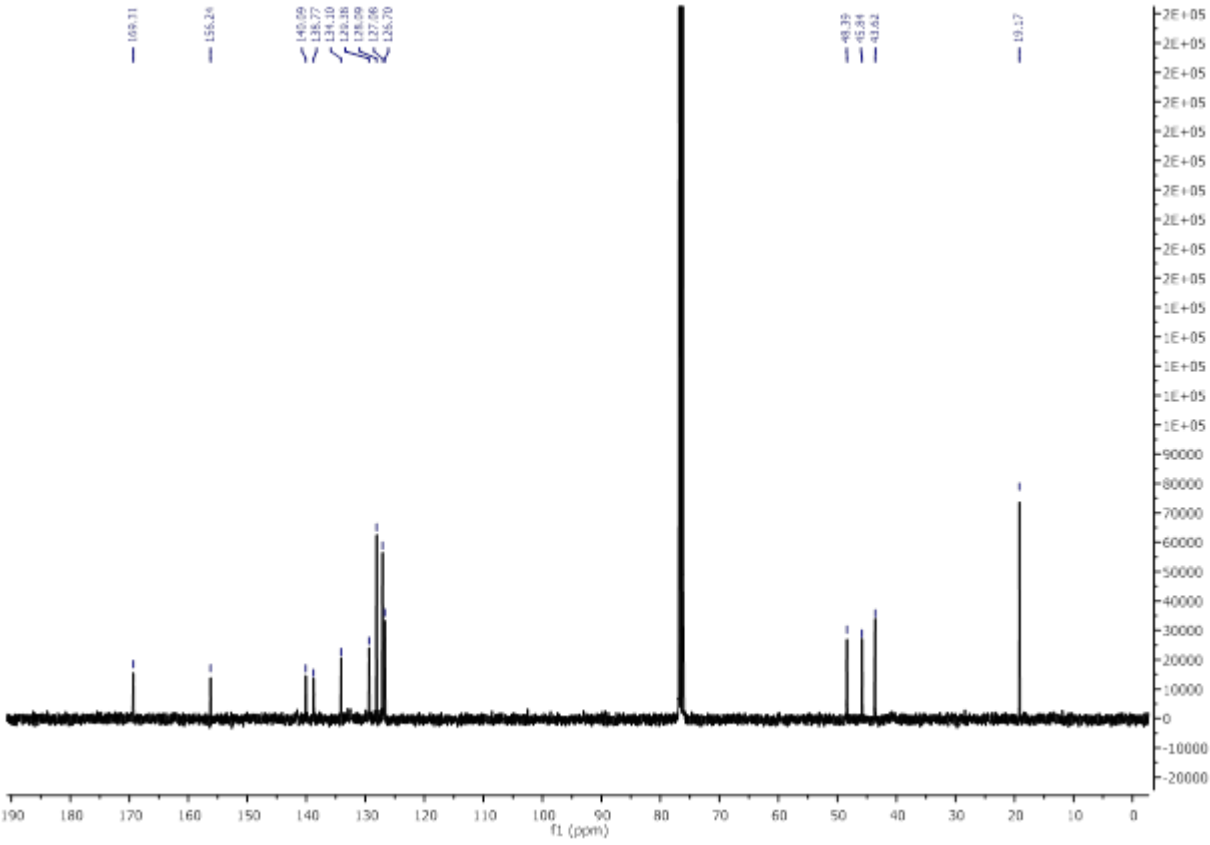
^{1}H NMR



40

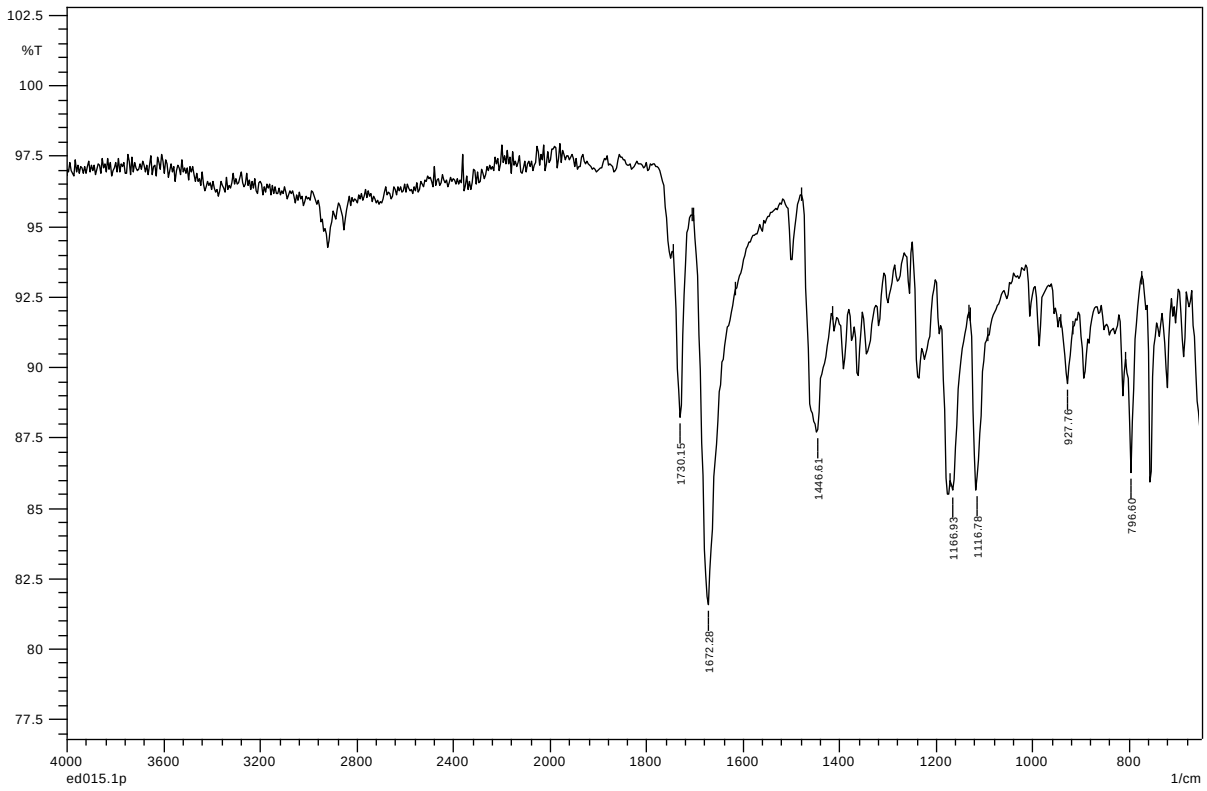


^{13}C NMR

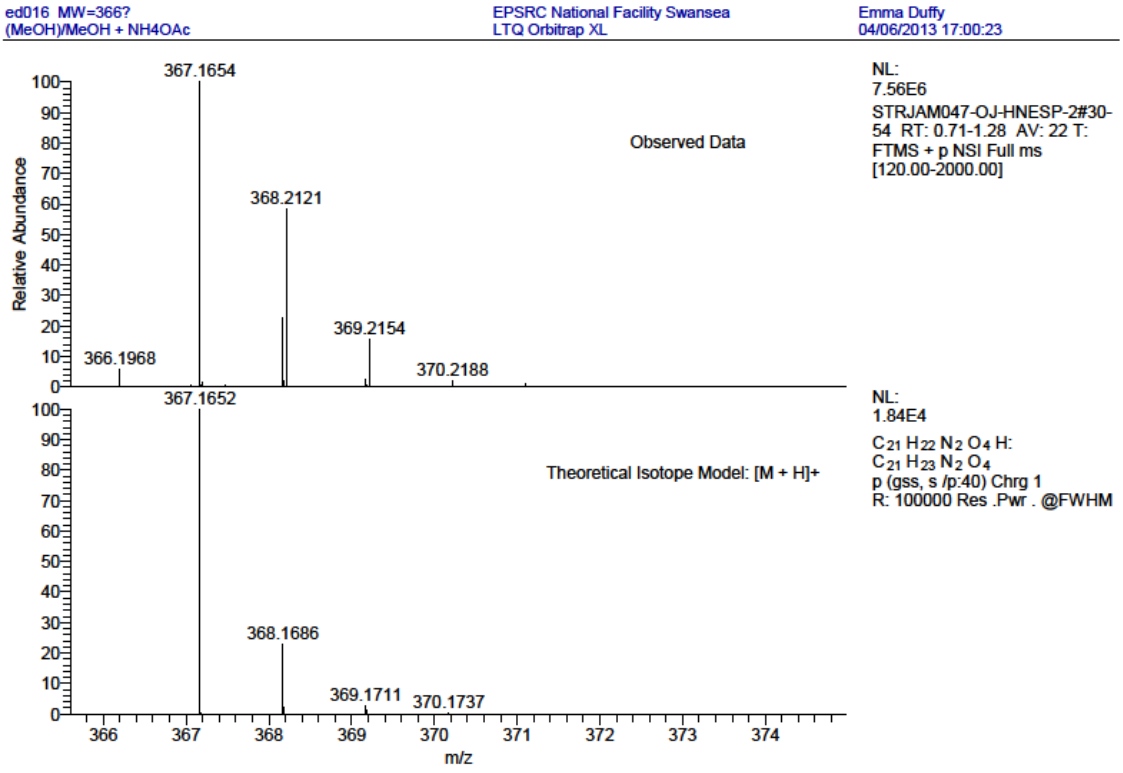


IR

IR

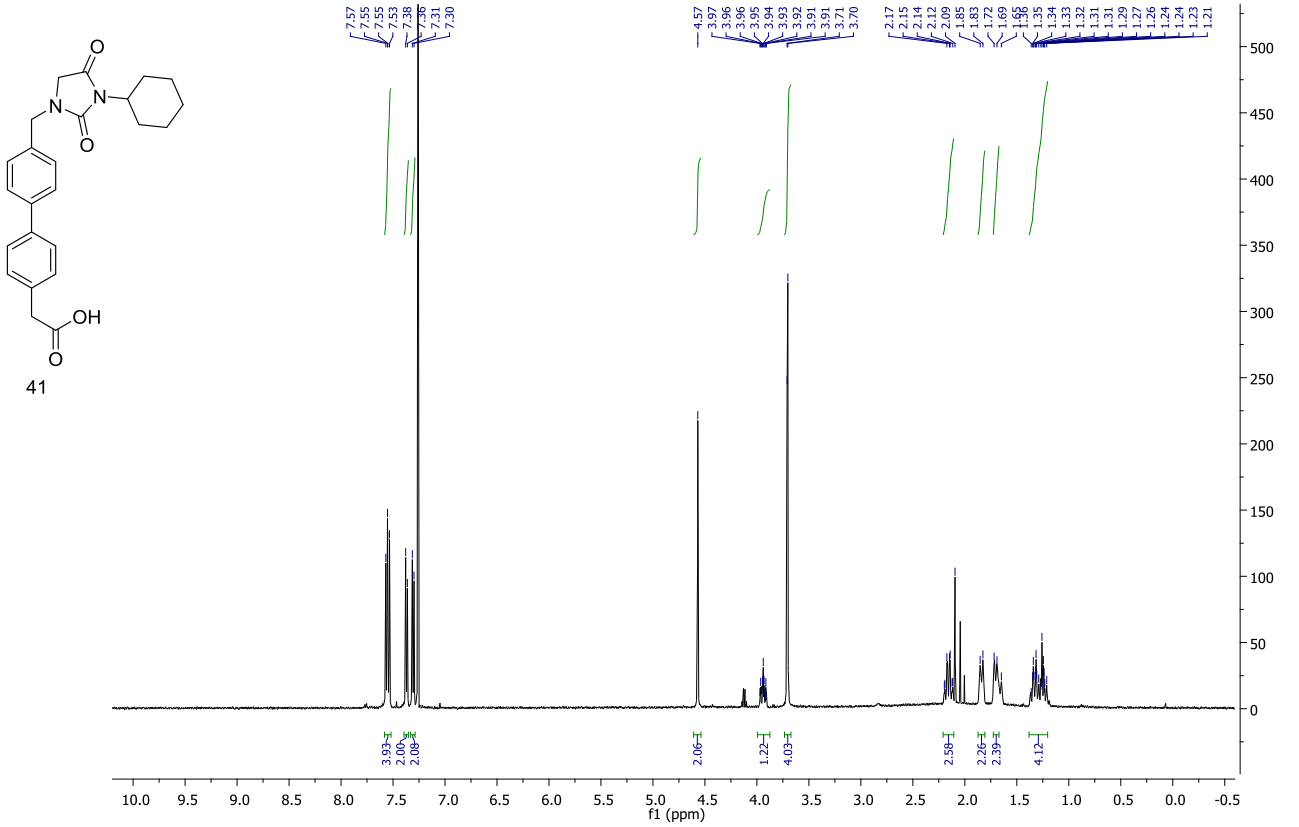

102.5
%T
100
97.5
95
92.5
90
87.5
85
82.5
80
77.5
1730.15
1672.28
1446.61
1166.93
1116.78
927.76
796.60
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
ed015.1p
1/cm

HRMS

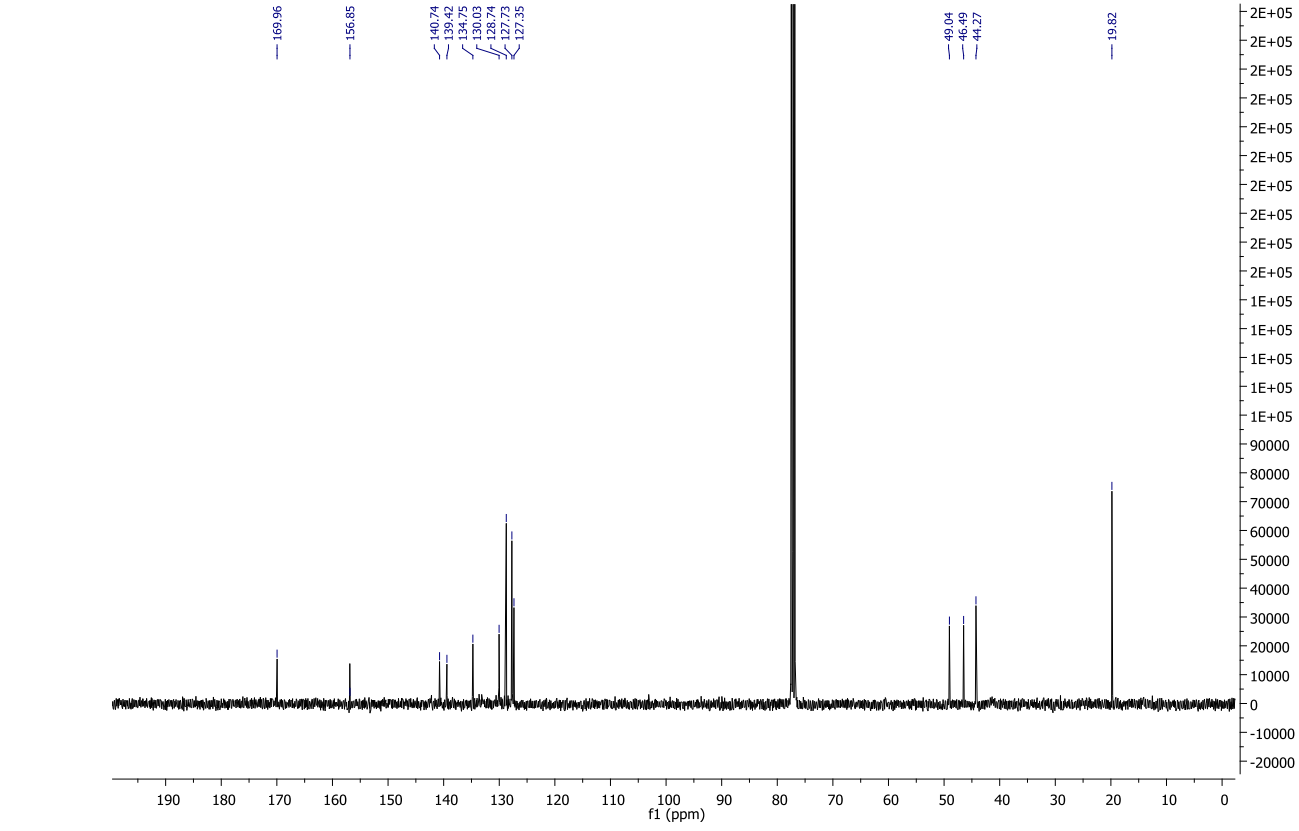

ed016 MW=366?
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Emma Duffy
04/06/2013 17:00:23
Observed Data
NL:
7.56E6
STRJAM047-OJ-HNESP-2#30-54 RT: 0.71-1.28 AV: 22 T: FTMS + p NSI Full ms [120.00-2000.00]
367.1654
368.2121
369.2154
366.1968
370.2188
Relative Abundance
Theoretical Isotope Model: [M + H]+
NL:
1.84E4
C21 H22 N2 O4 H:
C21 H23 N2 O4
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
367.1652
368.1686
369.1711
370.1737
m/z

Compound 41

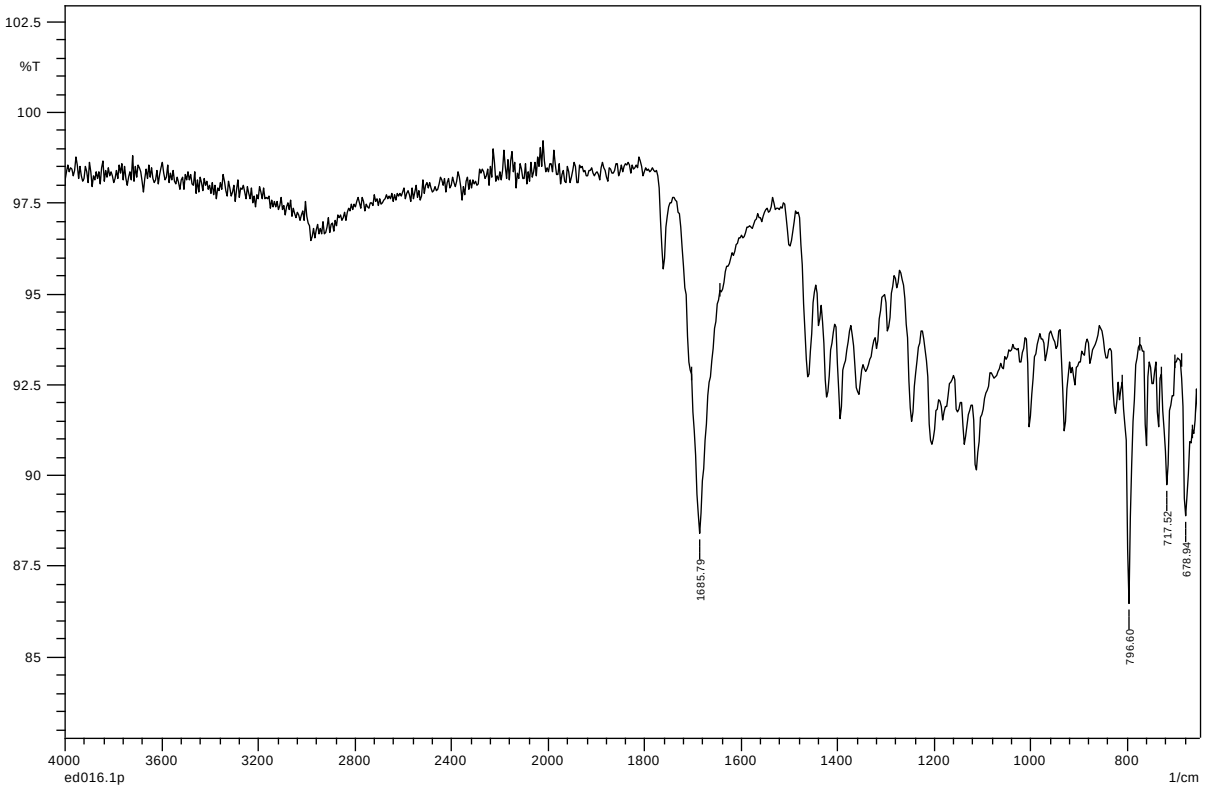
^{1}H NMR



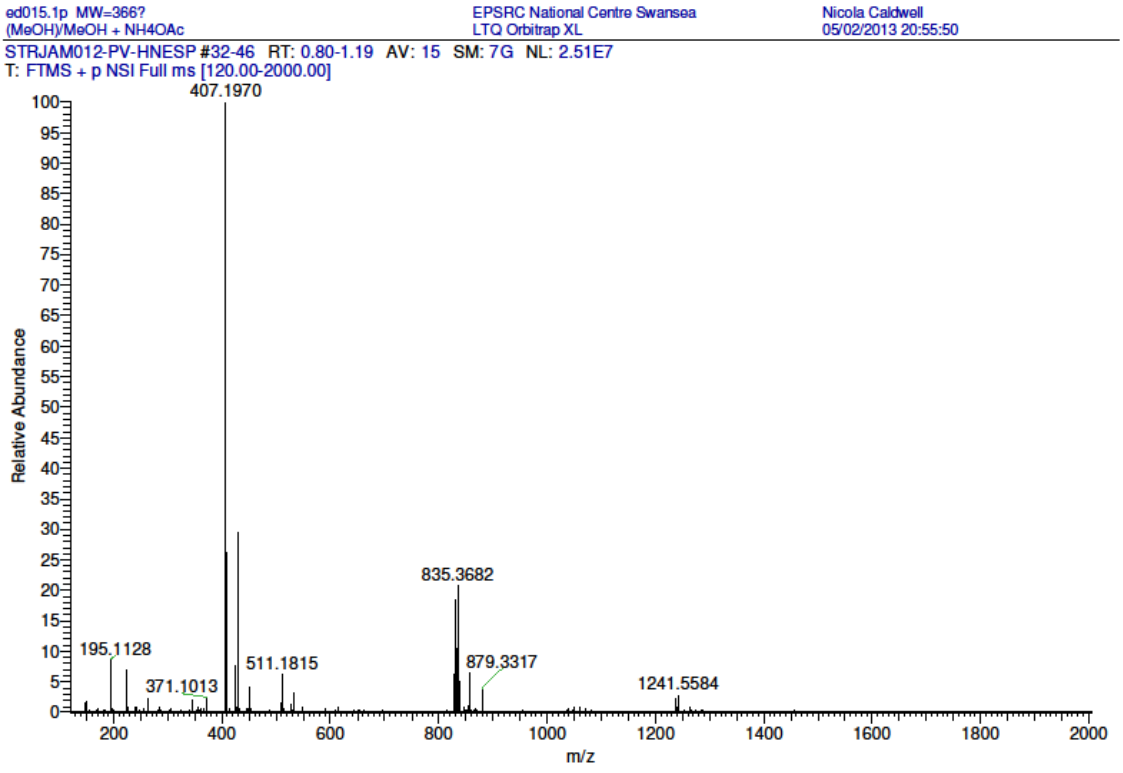
^{13}C NMR



IR

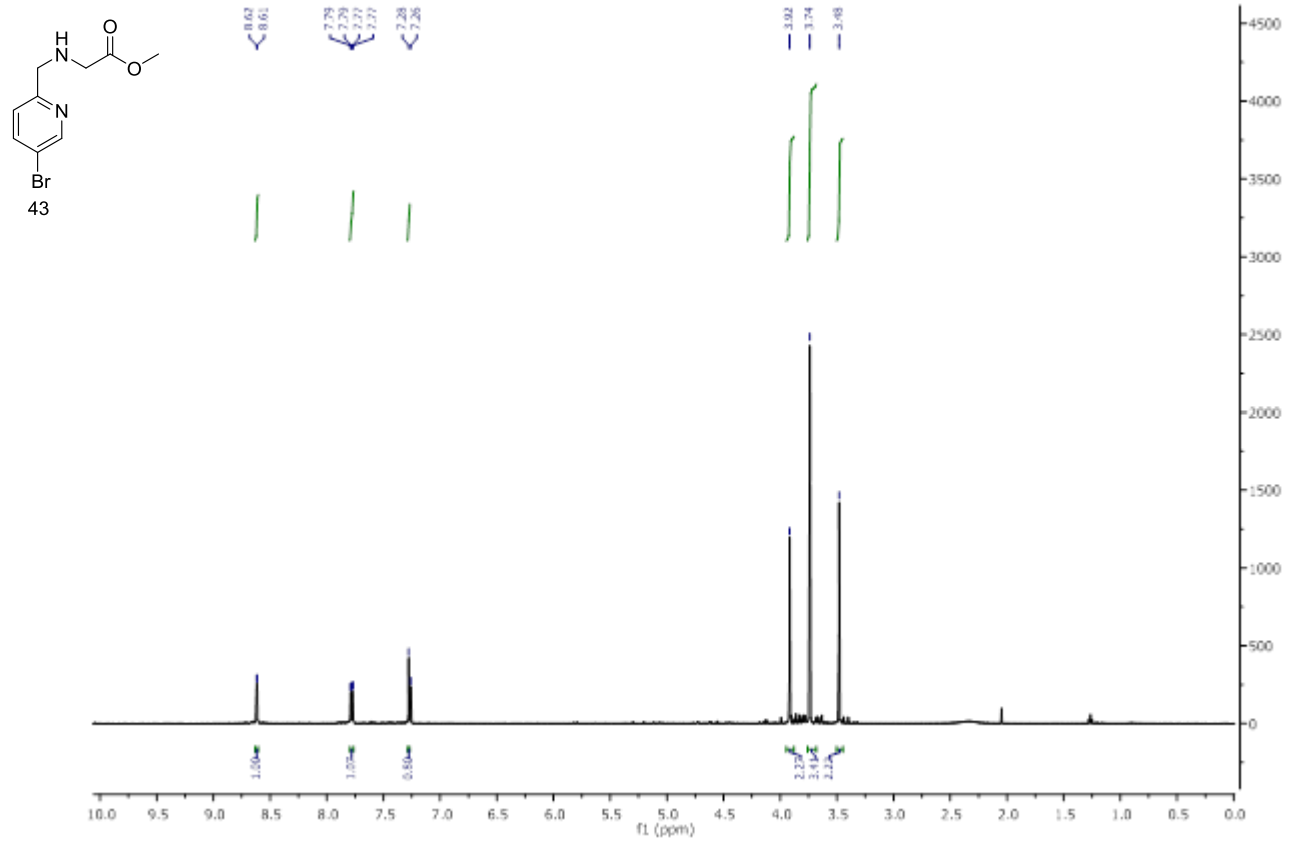

102.5
%T
100
97.5
95
92.5
90
87.5
85
1685.79
796.60
717.52
678.94
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
ed016.1p
1/cm

HRMS

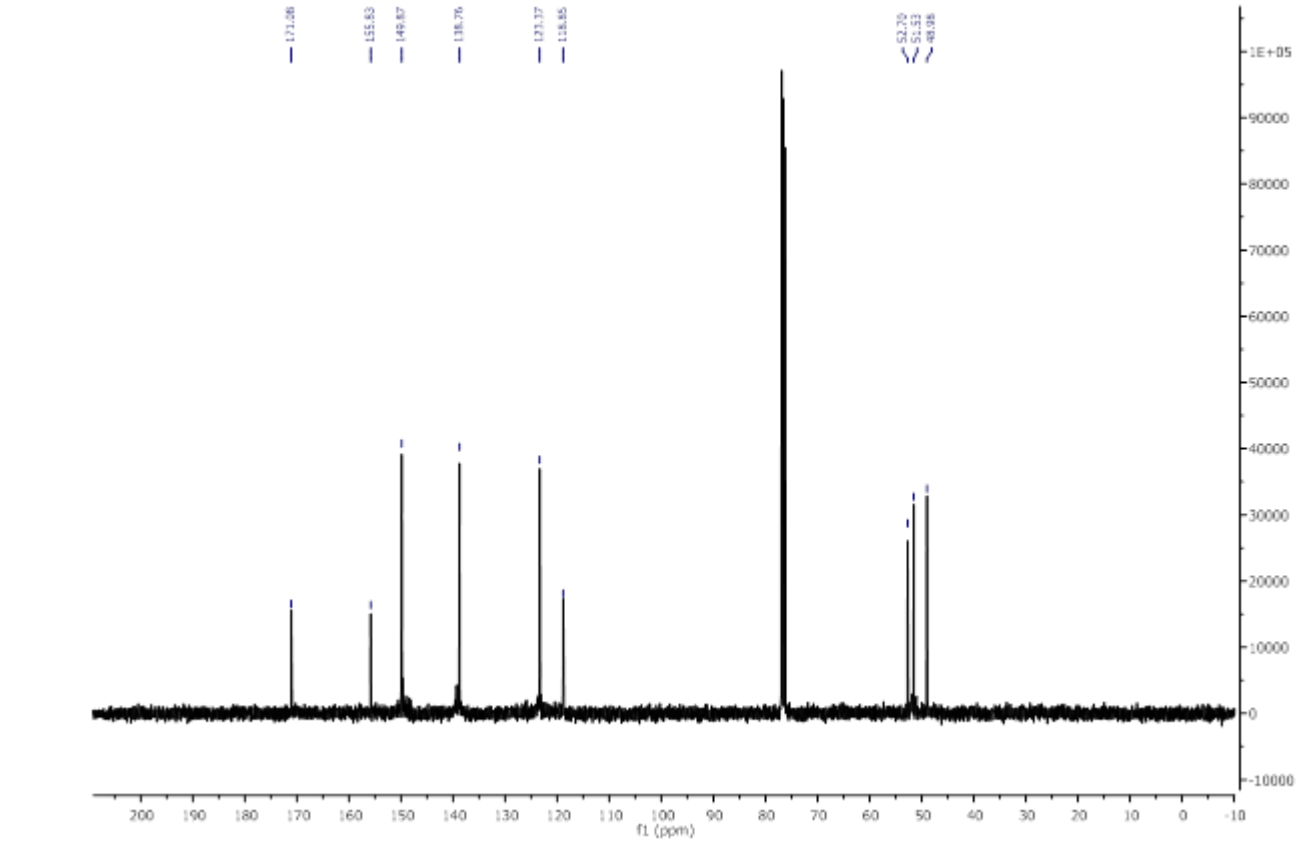

ed015.1p MW=366?
(MeOH)/MeOH + NH4OAc
EPSRC National Centre Swansea
LTQ Orbitrap XL
Nicola Caldwell
05/02/2013 20:55:50
STRJAM012-PV-HNESP #32-46 RT: 0.80-1.19 AV: 15 SM: 7G NL: 2.51E7
T: FTMS + p NSI Full ms [120.00-2000.00]
Relative Abundance
m/z
407.1970
835.3682
195.1128
511.1815
879.3317
371.1013
1241.5584

Compound 43

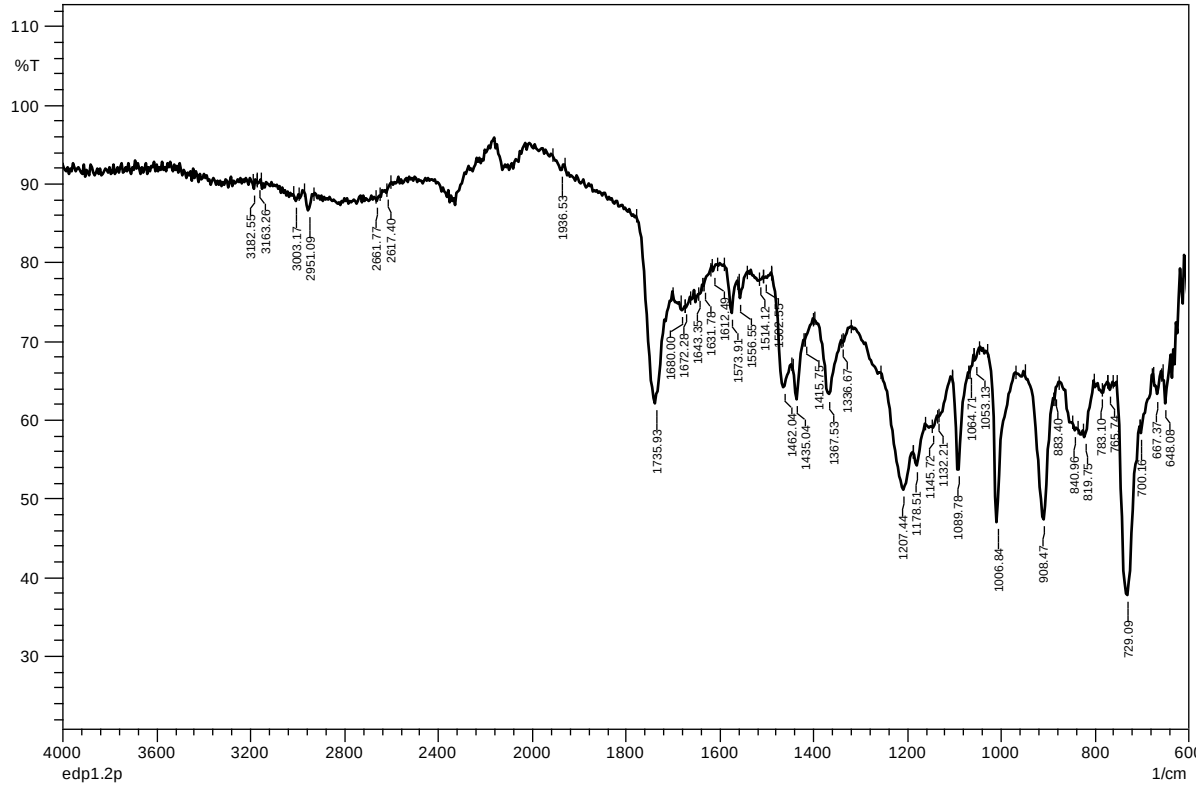
^{1}H NMR



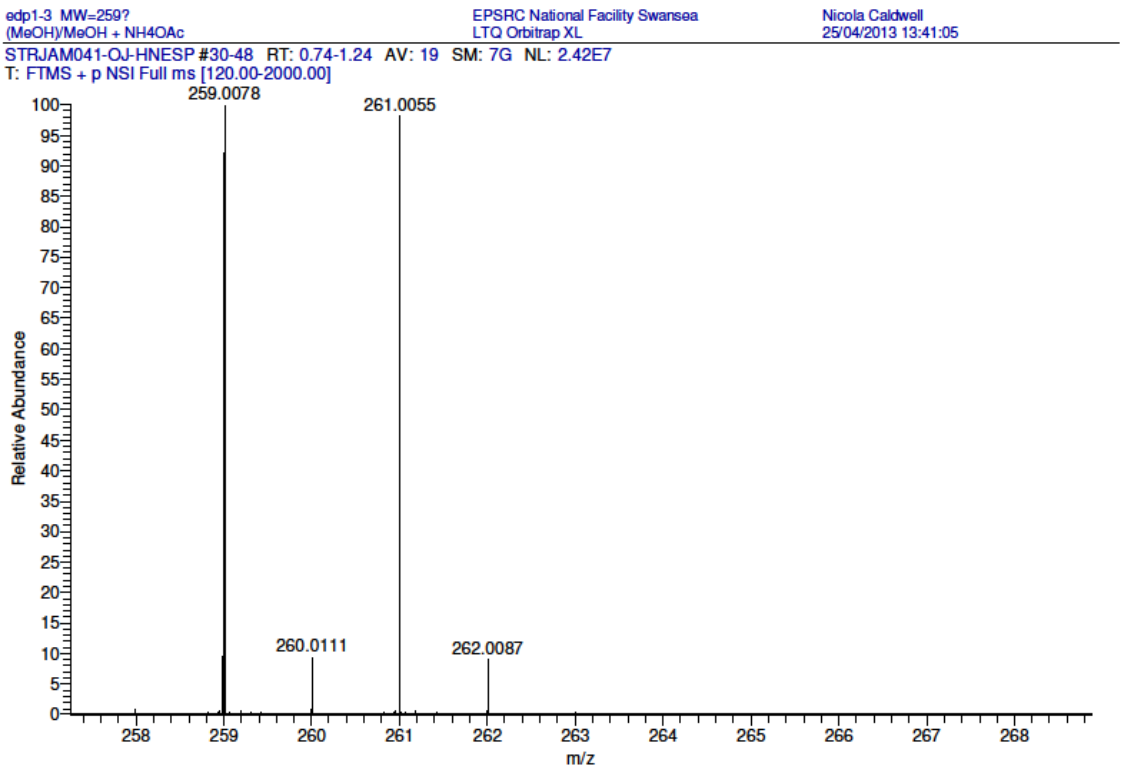
^{1}H NMR



IR

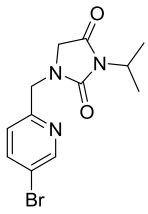

%T
110
100
90
80
70
60
50
40
30
3182.55
3163.26
3003.17
2951.09
2661.77
2617.40
1936.53
1735.93
1680.00
1672.28
1643.35
1631.79
1612.49
1573.91
1556.55
1514.12
1462.04
1435.04
1415.75
1367.53
1336.67
1207.44
1178.51
1145.72
1132.21
1089.78
1064.71
1053.13
1006.84
908.47
883.40
840.96
819.75
783.10
729.09
700.16
667.37
648.08
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
edp1.2p
1/cm

HRMS

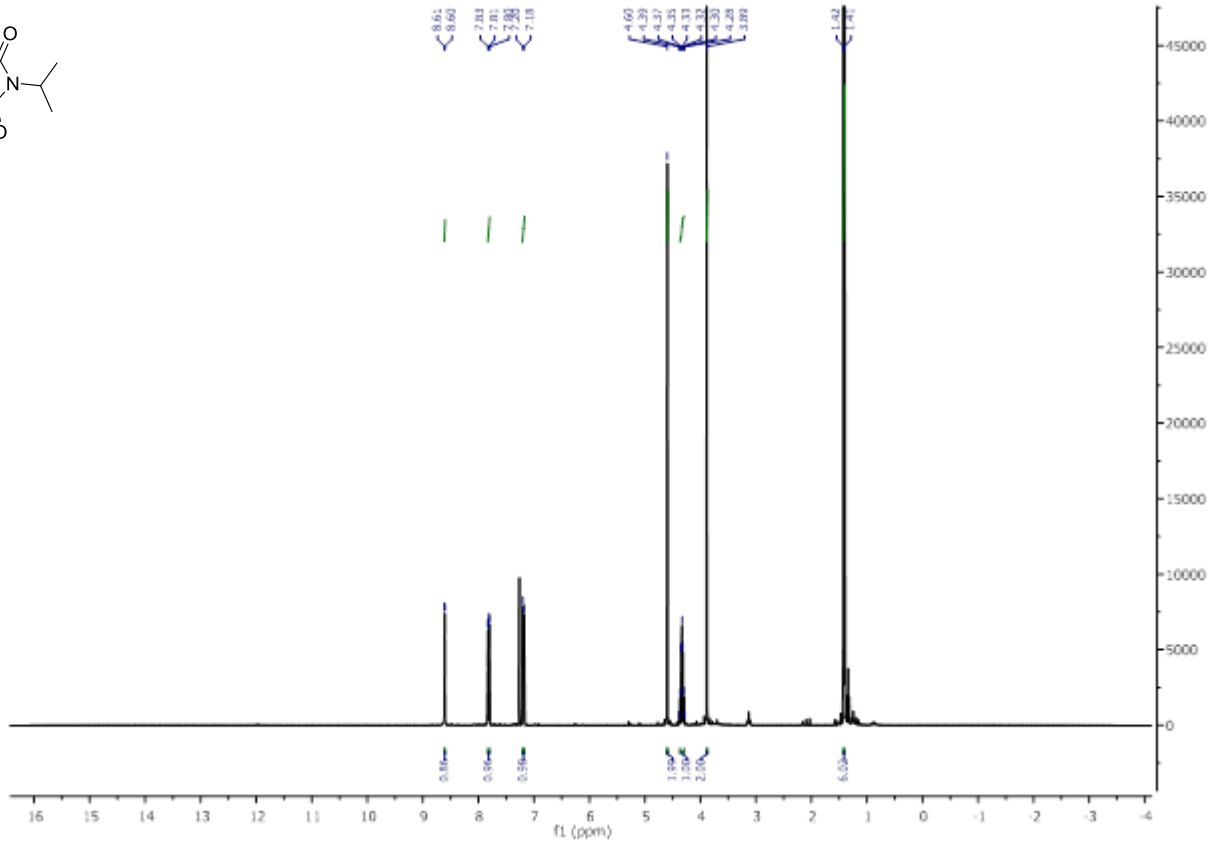

edp1-3 MW=259?
(MeOH)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Nicola Caldwell
25/04/2013 13:41:05
STRJAM041-OJ-HNESP #30-48 RT: 0.74-1.24 AV: 19 SM: 7G NL: 2.42E7
T: FTMS + p NSI Full ms [120.00-2000.00]
259.0078
261.0055
260.0111
262.0087
Relative Abundance
m/z
258
259
260
261
262
263
264
265
266
267
268

Compound 44

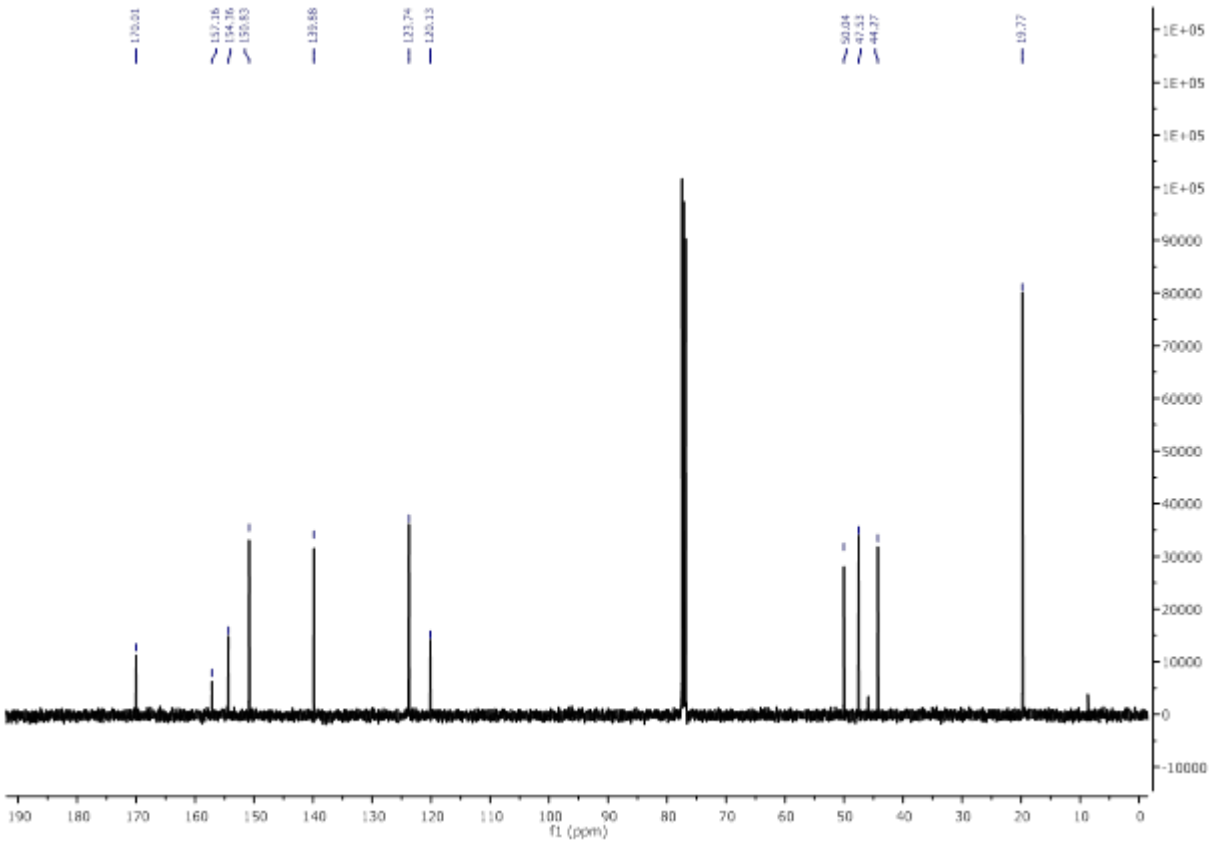
^{1}H NMR



44

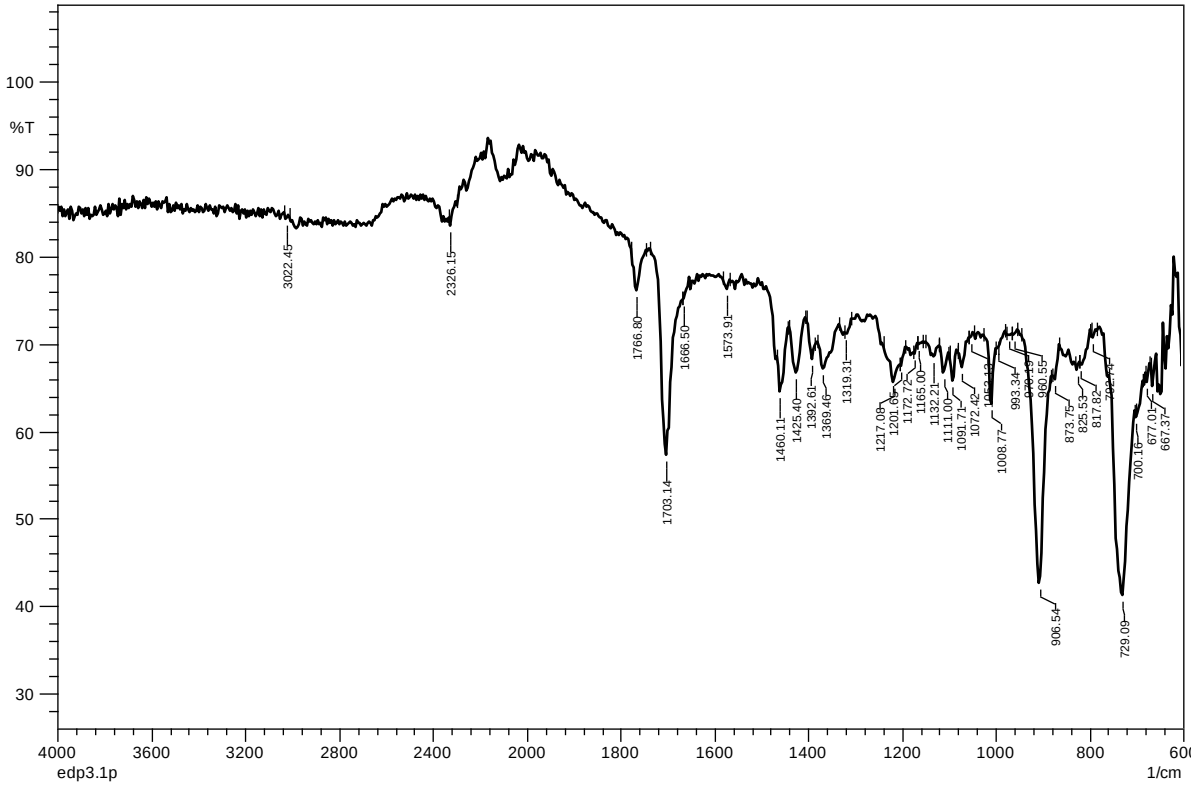


^{13}C NMR

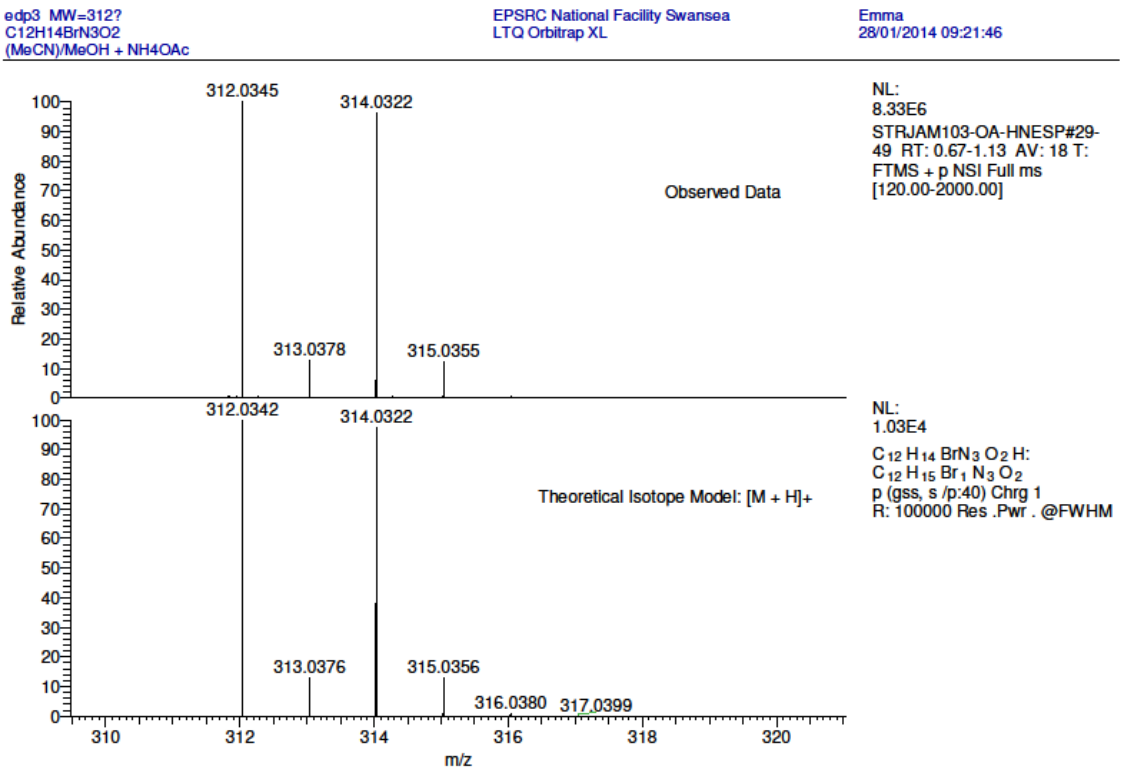


IR

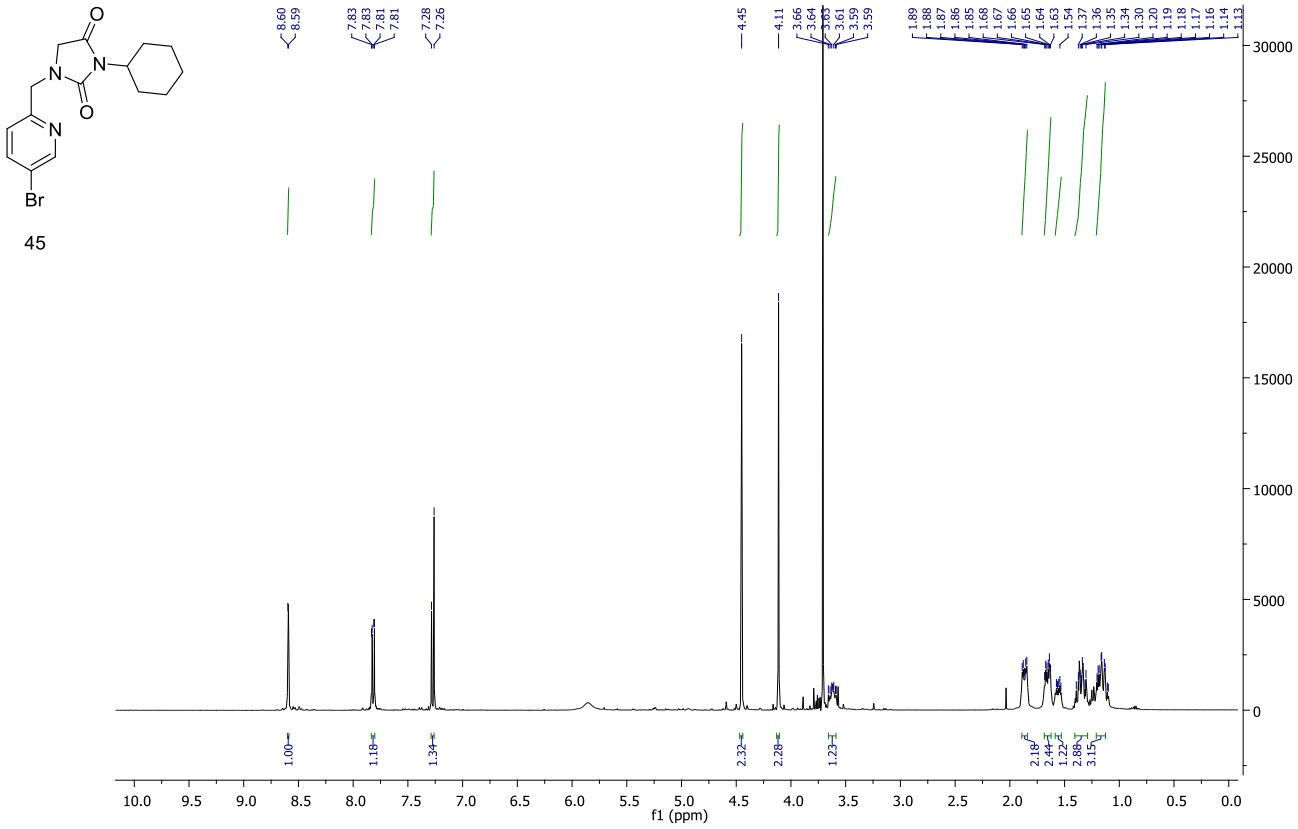
IR


%T
100
90
80
70
60
50
40
30
3022.45
2326.15
1766.80
1703.14
1666.50
1573.91
1460.11
1425.40
1392.61
1369.46
1319.31
1217.08
1201.65
1172.72
1165.00
1132.21
1111.00
1091.71
1072.42
1008.77
993.34
960.55
906.54
873.75
825.53
817.82
729.09
700.16
677.01
667.37
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
edp3.1p
1/cm

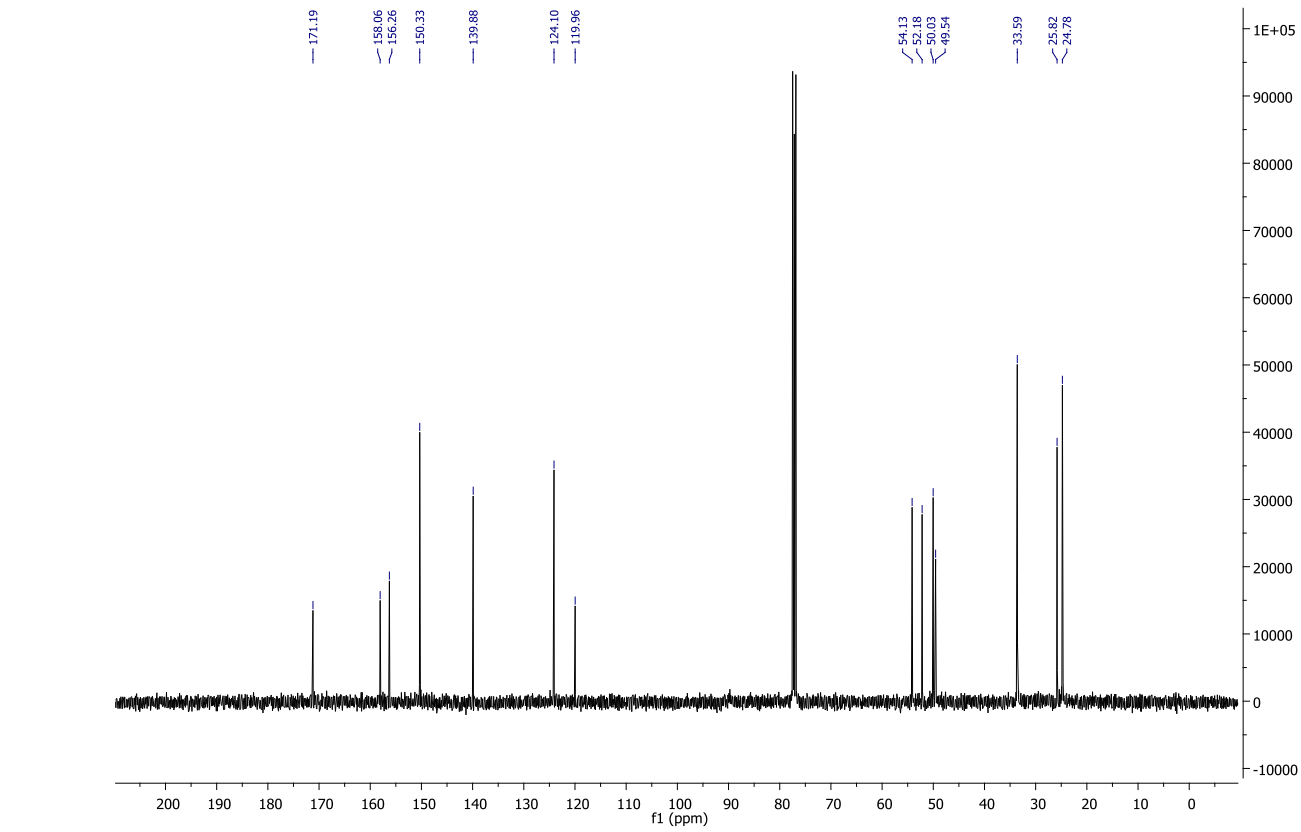
HRMS


edp3 MW=312?
C12H14BrN3O2
(MeCN)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Emma
28/01/2014 09:21:46
Relative Abundance
312.0345
314.0322
313.0378
315.0355
Observed Data
NL:
8.33E6
STRJAM103-OA-HNESP#29-49 RT: 0.67-1.13 AV: 18 T: FTMS + p NSI Full ms [120.00-2000.00]
312.0342
314.0322
313.0376
315.0356
316.0380
317.0399
Theoretical Isotope Model: [M + H]+
NL:
1.03E4
C12 H14 BrN3 O2 H:
C12 H15 Br1 N3 O2
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
310
312
314
316
318
320
m/z

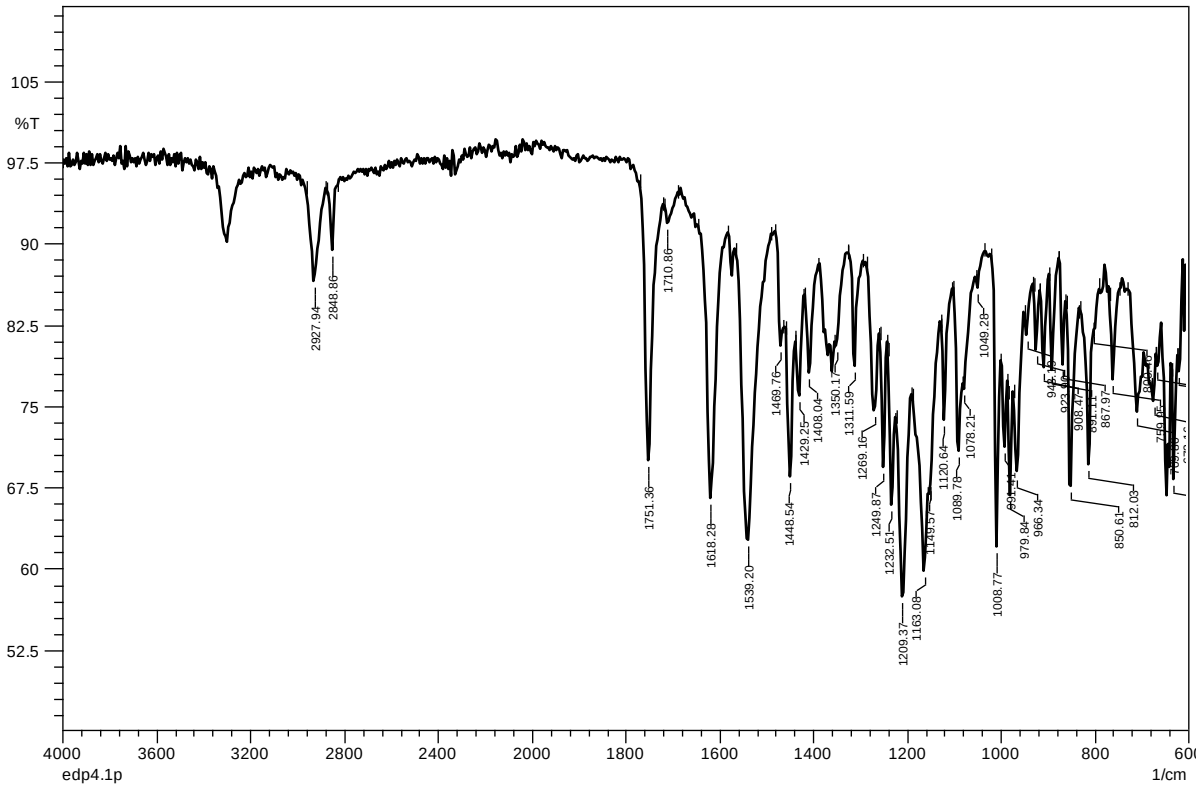
Compound 45
^{1}H NMR



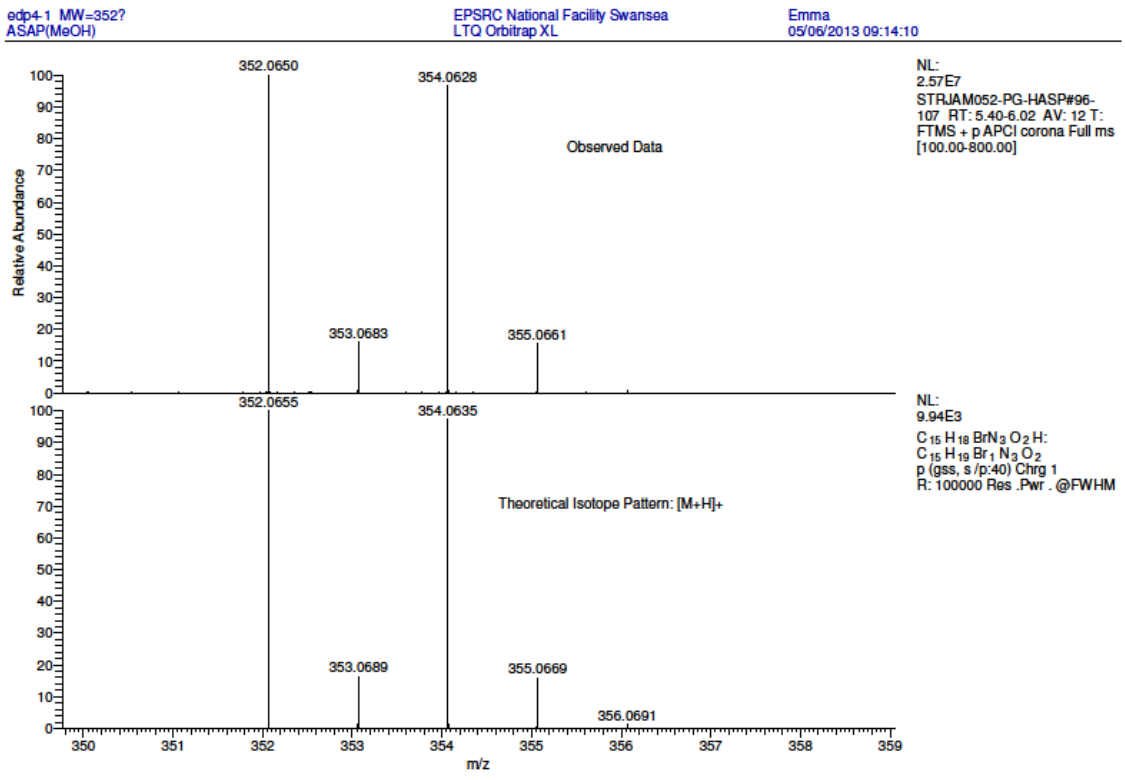
^{13}C NMR



IR

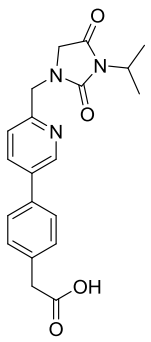

105
%T
97.5
90
82.5
75
67.5
60
52.5
2927.94
2848.86
1751.36
1710.86
1618.28
1539.20
1469.76
1448.54
1429.25
1408.04
1350.17
1311.59
1269.16
1249.87
1232.51
1209.37
1163.08
1120.64
1088.78
1078.21
1049.28
1008.77
979.84
966.34
908.47
891.11
867.97
850.61
812.03
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
edp4.1p
1/cm

HRMS

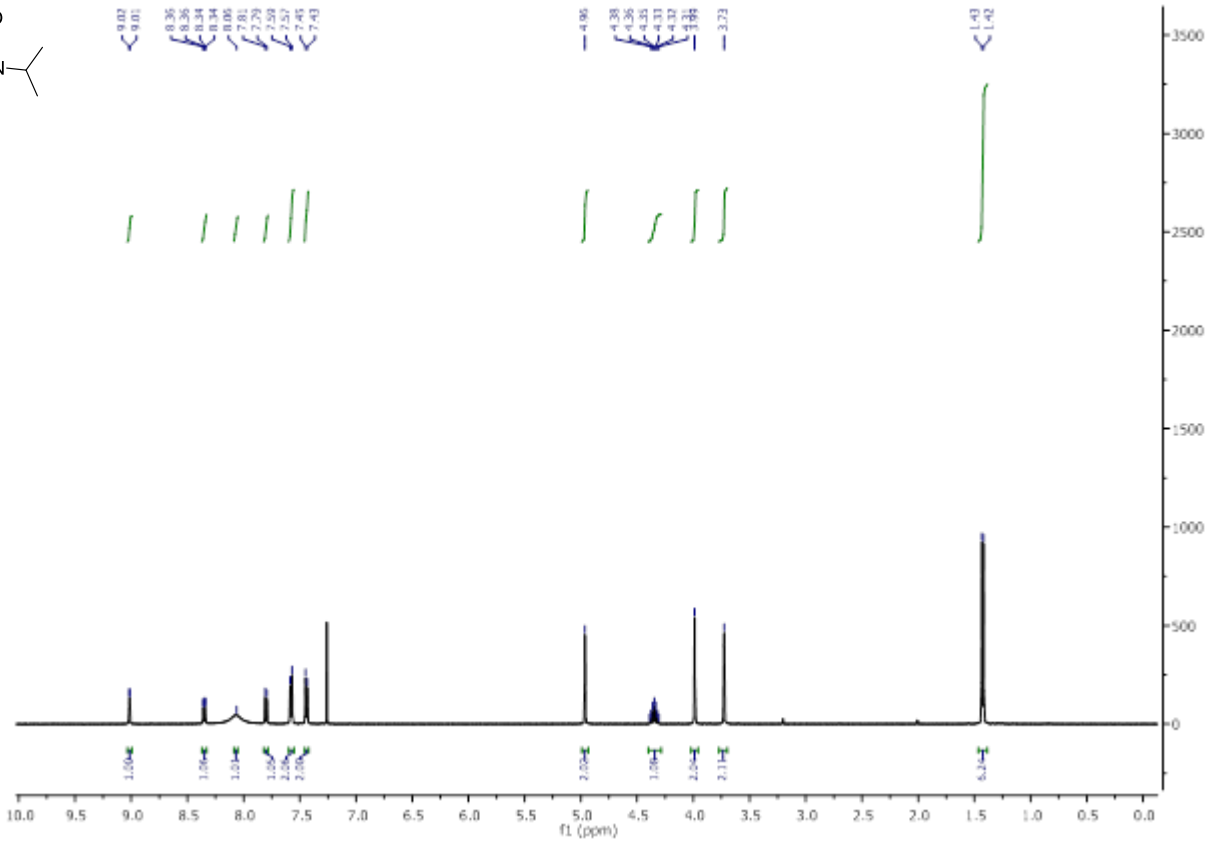

edp4-1 MW=352?
ASAP(MeOH)
EPSRC National Facility Swansea
LTQ Orbitrap XL
Emma
05/06/2013 09:14:10
352.0650
354.0628
353.0683
355.0661
Observed Data
NL:
2.57E7
STRJAM052-PG-HASP#96-107 RT: 5.40-6.02 AV: 12 T: FTMS + p APCI corona Full ms [100.00-800.00]
Relative Abundance
352.0655
354.0635
353.0689
355.0669
356.0691
Theoretical Isotope Pattern: [M+H]+
NL:
9.94E3
C15 H18 BrN3 O2 H:
C15 H19 Br1 N3 O2
p (gss, s /p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
m/z

Compound 46

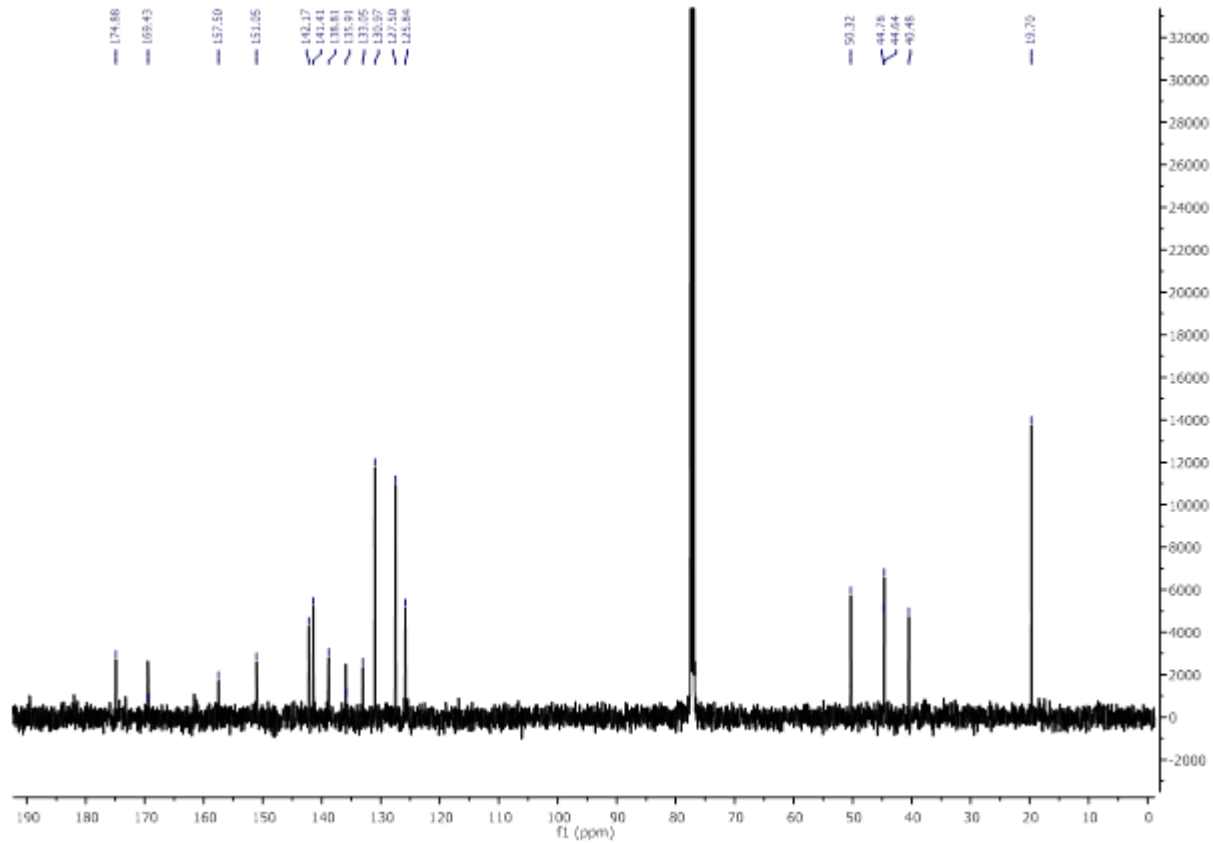
^{1}H NMR



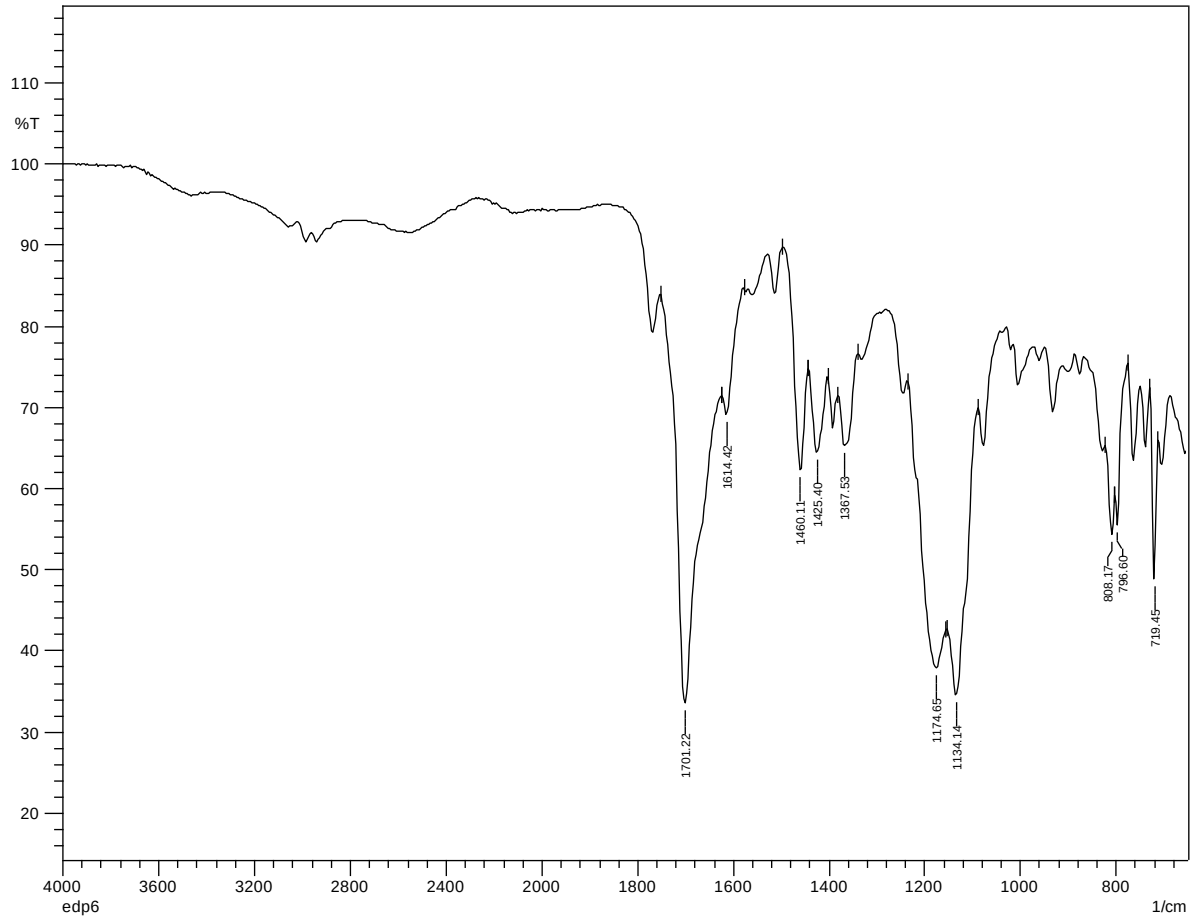
46



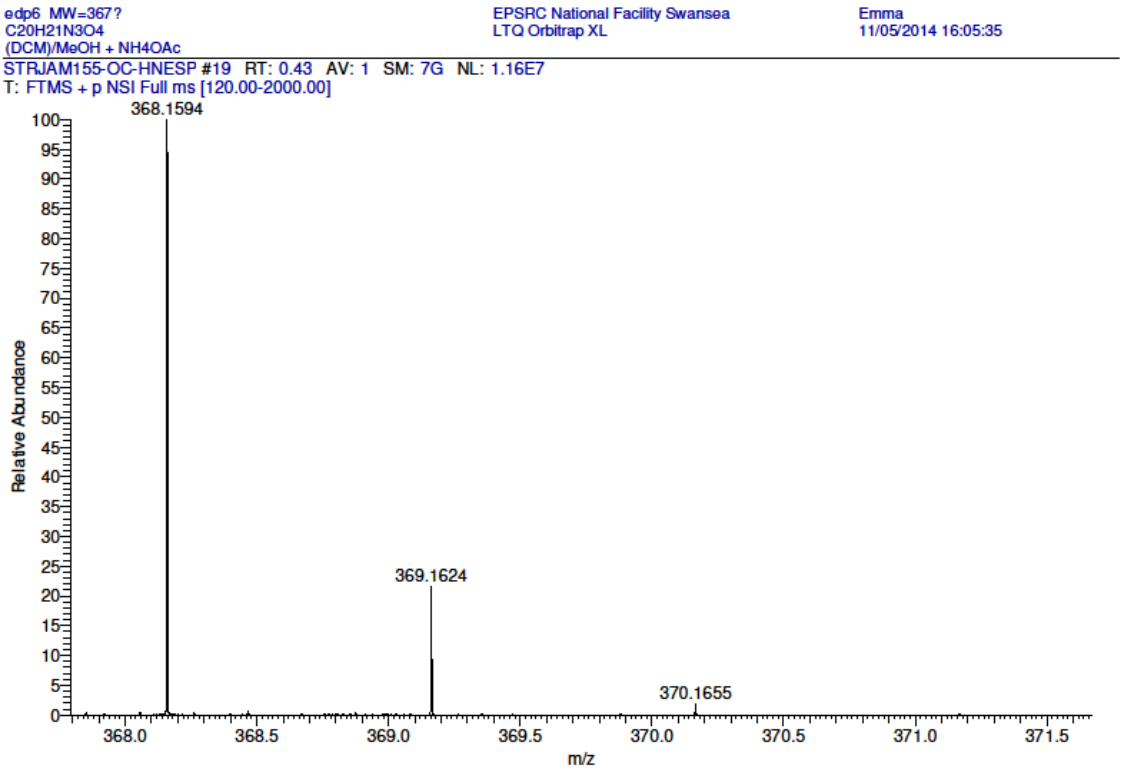
^{1}H NMR



IR

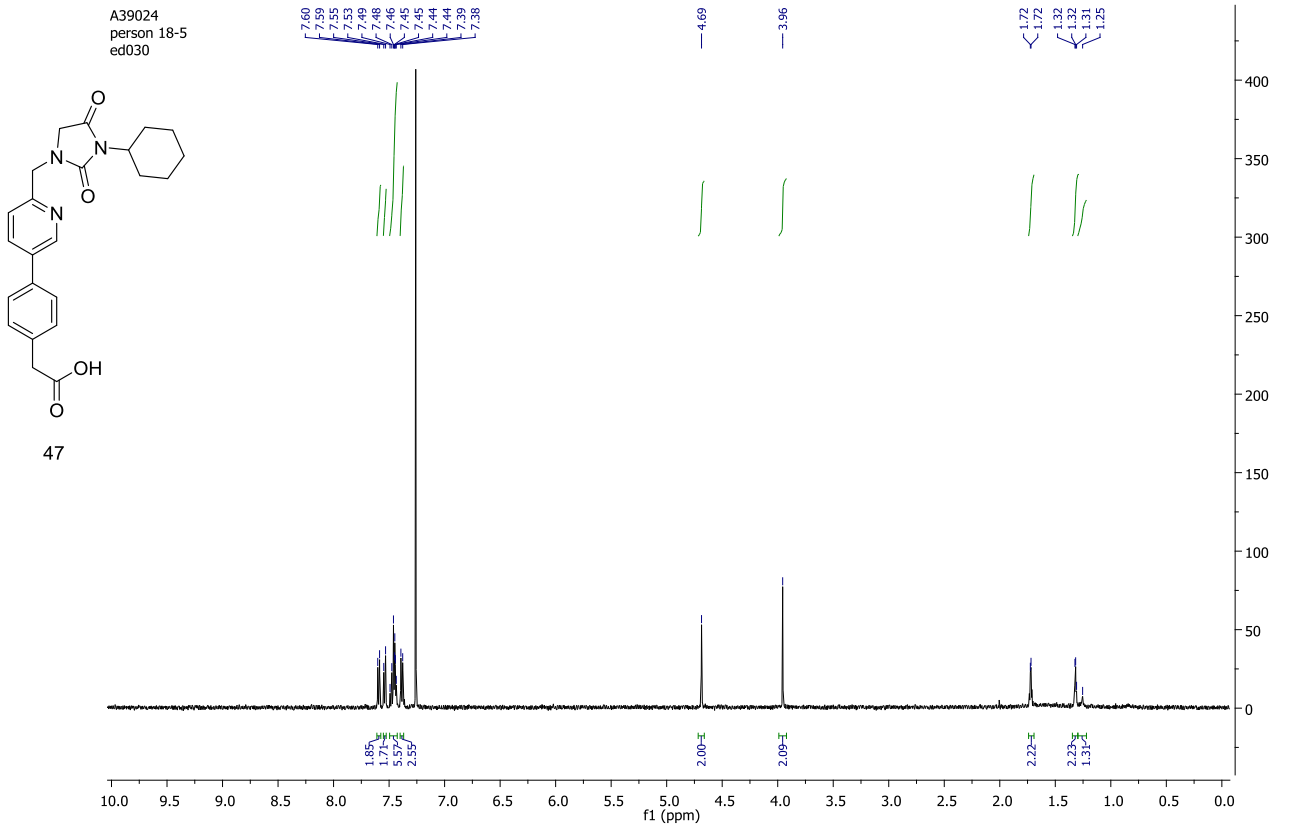

110
%T
100
90
80
70
60
50
40
30
20
1701.22
1614.42
1460.11
1425.40
1367.53
1174.65
1134.14
808.17
796.60
719.45
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
edp6
1/cm

HRMS


edp6 MW=367?
C20H21N3O4
(DCM)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Emma
11/05/2014 16:05:35
STRJAM155-OC-HNESP #19 RT: 0.43 AV: 1 SM: 7G NL: 1.16E7
T: FTMS + p NSI Full ms [120.00-2000.00]
368.1594
369.1624
370.1655
Relative Abundance
m/z
368.0
368.5
369.0
369.5
370.0
370.5
371.0
371.5

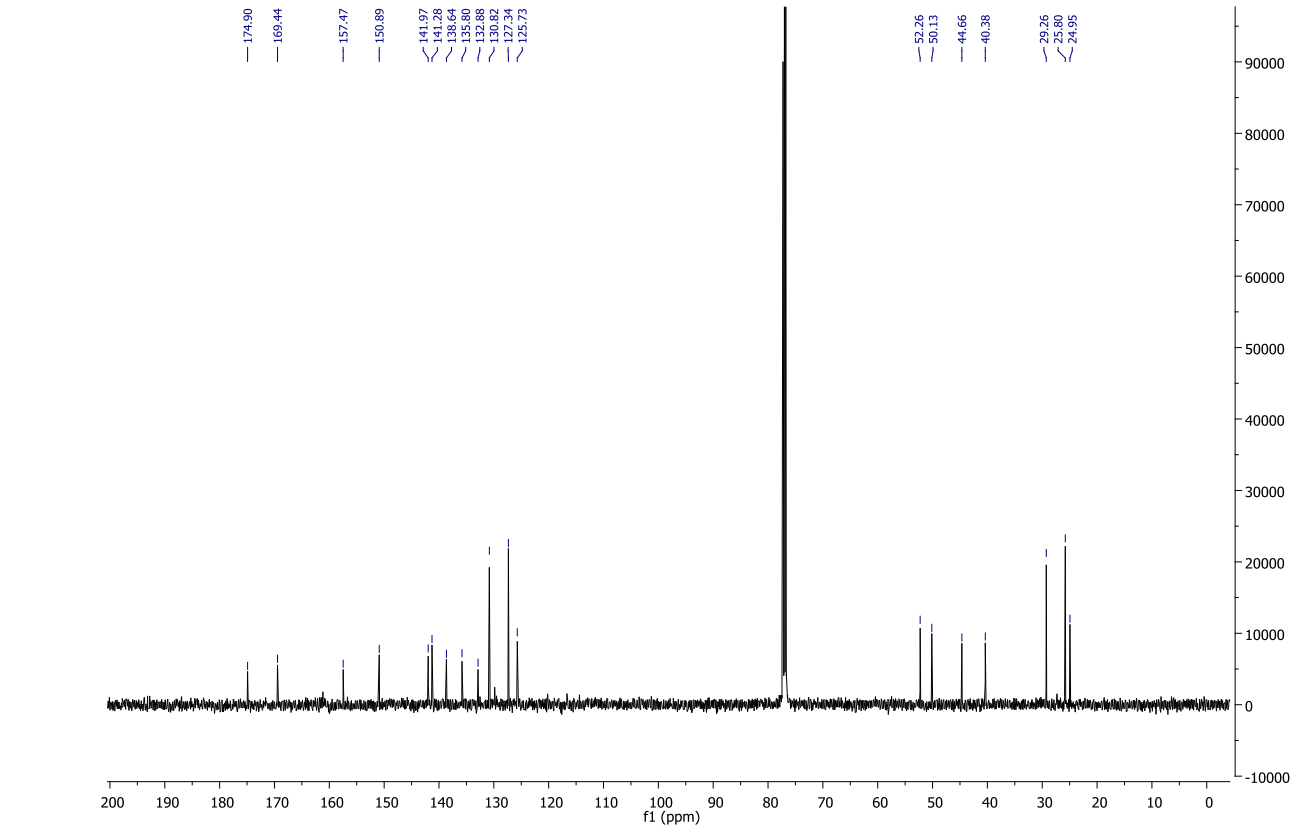
Compound 47

^{1}H NMR

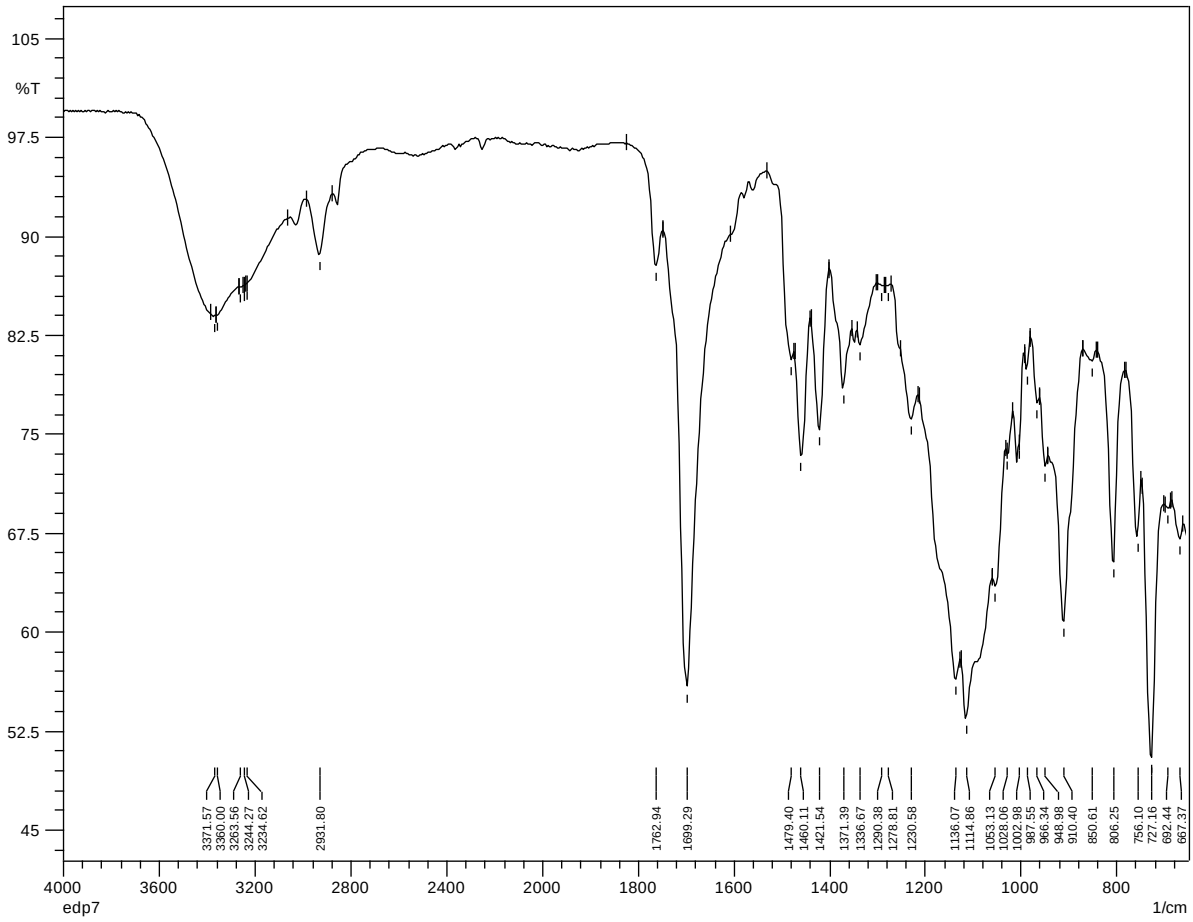


47

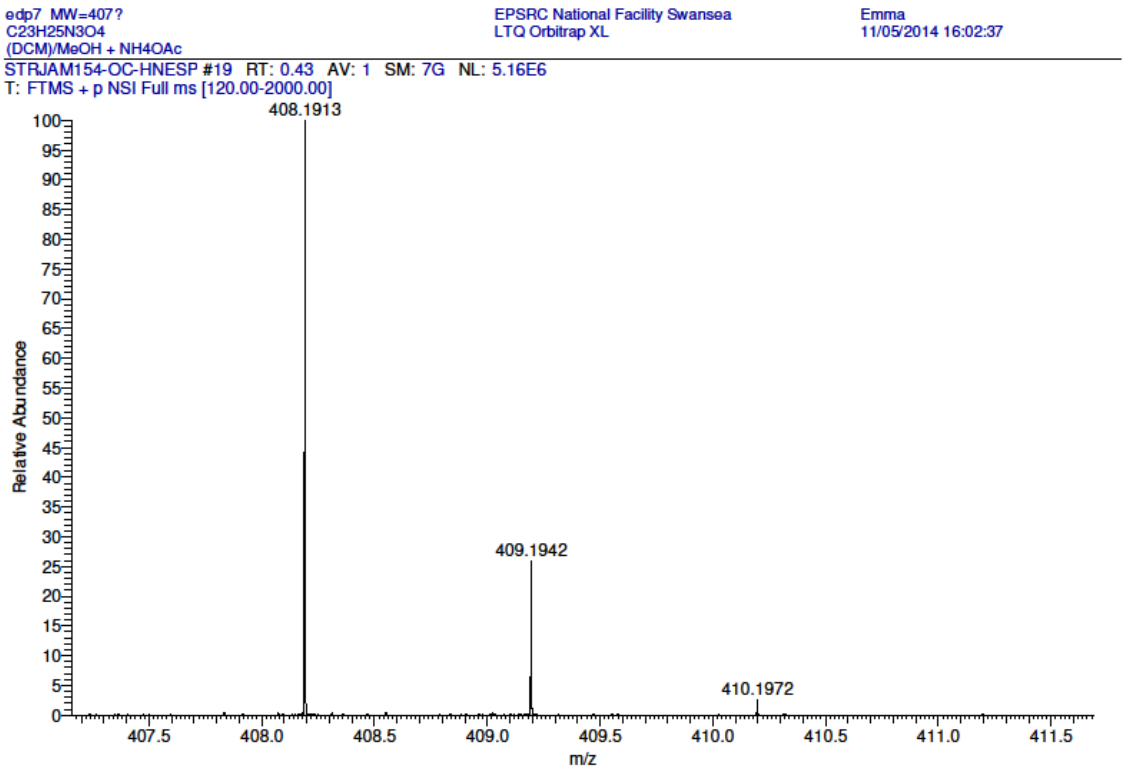
^{13}C NMR



IR


105
%T
97.5
90
82.5
75
67.5
60
52.5
45
3371.57
3360.00
3263.56
3244.27
3234.62
2931.80
1762.94
1699.29
1479.40
1460.11
1421.54
1371.39
1336.67
1290.38
1278.81
1230.58
1136.07
1114.86
1053.13
1028.06
1002.98
987.55
966.34
948.98
910.40
850.61
806.25
756.10
727.16
692.44
667.37
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
edp7
1/cm

HRMS


edp7 MW=407?
C23H25N3O4
(DCM)/MeOH + NH4OAc
EPSRC National Facility Swansea
LTQ Orbitrap XL
Emma
11/05/2014 16:02:37
STRJAM154-OC-HNESP #19 RT: 0.43 AV: 1 SM: 7G NL: 5.16E6
T: FTMS + p NSI Full ms [120.00-2000.00]
408.1913
409.1942
410.1972
Relative Abundance
m/z
407.5
408.0
408.5
409.0
409.5
410.0
410.5
411.0
411.5

5. Biology

5.1 PathHunter® CHO-K1 EDG2 β-Arrestin Compound Screen Study

5.1.2 Agonist Mode Screen

17 compounds were screened against the PathHunter® CHO-K1 EDG2 cell line (DiscoveRx) in agonist mode. The DiscoveRx reference 1-oleoyl-LPA (LPA) specified for the EDG2 cell line was added to the screen. 5000 cells / well were plated in a 384 well assay plate, in 20 µL PathHunter® Cell Plating Reagent 18, and incubated overnight to allow cells to attach and grow. Cells were then exposed to 10 µM compound (four replicates; 1% DMSO) or buffer + 1% DMSO (80 replicates). The stocks of DiscoveRx reference LPA are suspended in Ethanol, rather than DMSO: therefore cells were exposed to 10 µM compound (four replicates; 5% EtOH) or buffer + 5% EtOH (4 replicates). Cells were exposed to compounds for 3 h at room temperature. Following compound incubations, PathHunter® Detection Reagent was added and the assay plates were read on an Envision luminometer.

5.1.3 Antagonist Mode Screen

17 compounds were profiled against the PathHunter® CHO-K1 EDG2 (DiscoveRx) cell line in antagonist mode. The experiment was run concurrently with the agonist mode test. Cells were exposed to 10 µM compound (four replicates; 1% final DMSO) or buffer + 1% DMSO (80 replicates) for 1 h at 37° C, followed by exposure to 500 nM 1-oleoyl-LPA (0.25% final EtOH) for 3 hours at RT. DiscoveRx reference 1-oleoyl-LPA (dissolved in Ethanol) specified for the EDG2 cell line was used as the challenge agonist. Emax control wells (8 replicates) were exposed to 500 nM LPA (@ 0.25% final EtOH) + 1% DMSO. Buffer only (negative) control wells (8 replicates) were exposed to Buffer + 1% DMSO + 0.25% EtOH. The 500 nM agonist challenge dose was based on historical data from the EDG2 cell line. Following compound incubations, PathHunter® Detection Reagent was added and the assay plates were read on an Envision luminometer.

5.2 Autotaxin Inhibition Assay

Molecules were tested for their ability to inhibit autotaxin activity using the Autotaxin Inhibitor Screening Kit (Cayman Chemical) with modifications to the manufacturer's protocol. Briefly, In a 96 well plate 20 ng/mL autotaxin was incubated with 3 mM bis-pNPP at 30 °C for 30 min in 50 mM Tris-HCl buffer (pH8.5) containing 10 mM $CaCl_2$ and 0.02% triton X. Liberated bis-p-nitrophenol was measured using a Wallac Victor2 1420 multilabel counter (Perkin Elmer, Beaconsfield, UK) in absorbance mode at 405nm. The background was determined by incubating bis-pNPP in the absence of enzyme. Activity of the compounds was determined by subtracting the average background OD from all results and expressing the compound activity as a percentage of the enzyme-substrate reaction in the absence of compound. PF-8380 in the

concentration range of 0.1-300 nM in half log units was included as a standard compound in every assay plate. The potential inhibitors were initially tested against autotaxin at a concentration of 30 µM (n=2); samples which showed inhibition of 60% or greater were considered to be active. Dose response curves, in the concentration range of 30 nM to 30 µM in half log units, to calculate Ki values were performed on compounds reaching the designated activity threshold (n=3). Data was expressed as mean ± SEM was plotted using Graph Pad Prism version 6.00 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com

5.3 Methods for [3H]-Thymidine Incorporation Assay

5.3.1 Cell Culture

PC3 (human prostate cancer) cells were kept under conventional cell culture conditions at 37 °C, 5% CO2.

5.3.2 Stimulating Cells

Cells were sub-cultured and grown to 70 % confluence in 24 well plates before quiescing for 24 hours and then treatment with appropriate stimulus or vehicle (DMSO) for 18 hours.

5.3.3 [^{3}H]-Thymidine Incorporation

[^{3}H] thymidine (9.25 kBq diluted in serum free medium) was added to each well 5 h before the expiry of the 18-20 h period. The medium was aspirated to the radioactive sink. 1 mL ice cold 10% (w/v) trichloroacetic acid (TCA) was added to each well and incubated on ice for 6 min x 3. This precipitates the protein and nuclear material remains stuck to the base of the well. The TCA was aspirated to the radioactive sink and 0.25 mL 0.1% (w/v) SDS/0.3 M NaOH was added to each well (at room temperature). This dissolves the nuclear material. The contents of each well were transferred to separate beta vials. 2 mL scintillant was added to each vial, capped and mixed thoroughly. Each vial was counted in scintillation counter (3 min per sample).

5.4 Cytotoxicity

Compounds were tested for any cytotoxic effects against normal fibroblasts (HS27 cells) and an ovarian carcinoma cell line (A2780). The cytotoxicity was evaluated by using the alamarBlue® assay. HS27 cells were incubated in DMEM supplemented with 10% FBS, 2 mM glutamine and 1% penicillin/streptomycin under 5% CO_2 at 37 °C in a humidified incubator. A2780 cells were cultured under the same conditions in RPMI 1640 media with 10% FBS and 1% penicillin-streptomycin. At 70-80% confluency the cells were detached from the culture flasks using Triple® Express and seeded in clear 96-well plates at a concentration of 3750 cells per well (A2780 cells) and 7500 cells per well (HS27 cells). The cells were

allowed to adhere and equilibrate overnight before addition of compound (diluted in the relevant media). After a further 42 h incubation, 10% alamar Blue® was to each well and incubated for 6 h. The resulting fluorescence was measured using a Wallac Victor2 1420 multilabel counter, in fluorescence mode: excitation 560, emission 590. Cells in the absence of compound were considered as 100% viable against which compound treated cells (at a concentration of 30 µM, at least n=2) were compared. 0.1% triton X was used as a negative control. Data was expressed as mean ± SEM and plotted using Graph Pad Prism Software.

6. High Throughput Physchem Measurements

ChromlogD assay (LogD)

The Chromatographic Hydrophobicity Index (CHI) [2] values were measured using reversed phase HPLC column (50 x 2 mm 3 µM Gemini NX C18, Phenomenex, UK) with fast acetonitrile gradient at starting mobile phase of pH = 7.4. CHI values are derived directly from the gradient retention times by using a calibration line obtained for standard compounds. The CHI value approximates to the volume % organic concentration when the compound elutes. CHI is linearly transformed into ChromlogD by the formula: ChromlogD = 0.0857CHI-2.00. The average error of the assay is ±3 CHI unit or ±0.25 ChromlogD.

Chemiluminiescent nitrogen detection (CLND) kinetic aqueous solubility assay (Sol)

GSK in-house kinetic solubility assay: 5 µl of 10 mM DMSO stock solution diluted to 100 ul with pH 7.4 phosphate buffered saline, equilibrated for 1 h at room temperature, filtered through Millipore Multiscreen$_{HTS}$-PCF filter plates (MSSL BPC). The filtrate is quantified by suitably calibrated flow injection Chemi-Luminescent Nitrogen Detection[3]. The standard error of the CLND solubility determination is ±30 µM, the upper limit of the solubility is 500 µM when working from 10 mM DMSO stock solution.

Artificial Membrane Permeability assay (P_{app})

The donor cell contained 2.5 µL of 10mM sample solution in pH 7.40 phosphate buffer. To enhance solubility, 0.5% hydroxypropyl-cyclodextrin (encapsin) has been added to the buffer. The artificial membrane is prepared from 1.8% phosphatydilcholine and 1% cholesterol in decane solution. The sample concentration in both the donor and acceptor compartment is determined by LC-MS after 3 h incubation at room temperature [4]. The permeability ($logP_{app}$) measuring how fast molecules pass through the black lipid membrane is expressed in nm/s. The average standard error of the assay is around ±30 nm/s that can be higher at the low permeability range.

7. References

1. W. L. F. Armarego, C. Chai, *Purification of Laboratory Chemicals, 7th ed.*, Elsevier, Oxford, 2013.
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3. Bhattachar S. N.; Wesley J. A.; Seadeek C. Evaluation of the chemiluminescent nitrogen detector for solubility determinations to support drug discover, J. Pharm. Biomed. Anal. 41, 2006, 152-157.

4. Veber D.F.; Johnson S.R.; Chen H-Y.; Smith B. R.; Ward K. W.; Kopple D. Molecular properties that influence the oral bioavailability of drug candidates, J. Med. Chem. 45, 2002, 2615-2623.