

Supporting information for:

An Enantioselective Hydrogenation of an Alkenoic Acid as a Key Step in the Synthesis of AZD2716

*Staffan Karlsson^{*a}, Henrik Sörensen^a, Sören M. Andersen^a, Angele Cruz^a and Per Ryberg^b*

^a CVMD iMed, Medicinal Chemistry, AstraZeneca R & D Mölndal, SE-431 83 Mölndal, Sweden.

^b SP Process Development, Box 36, SE-151 21 Södertälje, Sweden.

staffan.po.karlsson@astrazeneca.com

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P 7-8: HPLC analysis of compound **4**

P 9: ¹H NMR for compound **6** (salt with 1*R*-1-phenylethylamine)

P 10: ¹H NMR for compound **7**

P 11: ¹H NMR for compound **AZD2716**

P 12: ¹³C NMR for compound **AZD2716**

P 13-20: HPLC analysis, HRMS, ee-determination for compound **AZD2716**

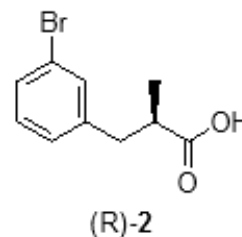
P 21-22: Extended hydrogenation screen of compound **8**

EnantioBase

Analysis Report

Sample Information

| Sample ID | Compound name | Project name |
|--------------|---------------|--------------|
| SN1033302520 | AZ13468845 | sPLA2x |

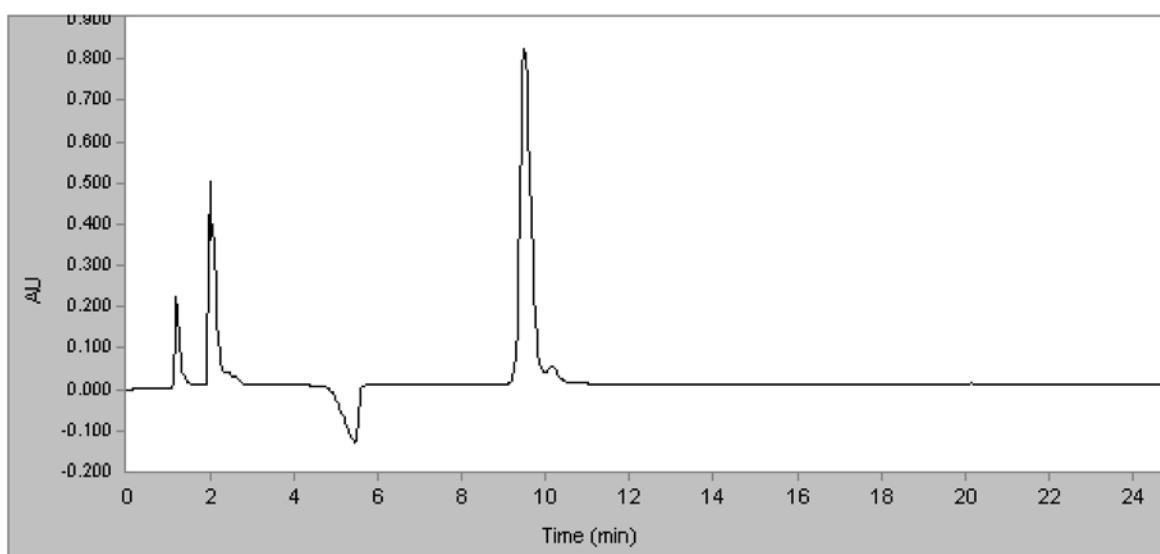


Analytical Conditions

| Column | Dimensions (mm) | Particle Size (µm) |
|------------------------|-----------------|--------------------|
| t-Bu CQN | 4.6 * 250 mm | 10 |
| Mobile Phase | | |
| ACN/IPA/HOAc 90/10/0.3 | | |
| Flow (ml/min) | Detection (nm) | Temperature (C) |
| 1 ml/min | PDA 230.0 nm | RT |
| Comment | | |
| | | |

Analytical Result

UV Chromatogram



| Retention Time | Area | Area % | K' | N | USP Resolution |
|----------------|----------|--------|-------|---|----------------|
| 1.100 | 0 | | 0.000 | | |
| 9.493 | 14413823 | | 7.630 | | |
| 10.152 | 740154 | | 8.229 | | |

ee: 90%

Chemist Signature

Print Date

2010-11-12

Openlynx Report walk-up LC/MS

JobCode (batch):kssf06134
 UserName:kssf061
 Vial:1:44
 Method:C:\MassLynx\OA_2min_sur_HSSC18.olg

Sample: 1
 Sample ID:SN1031506451
 Instrument:ACQ-SQD#F08SQD296W
 pH: 3

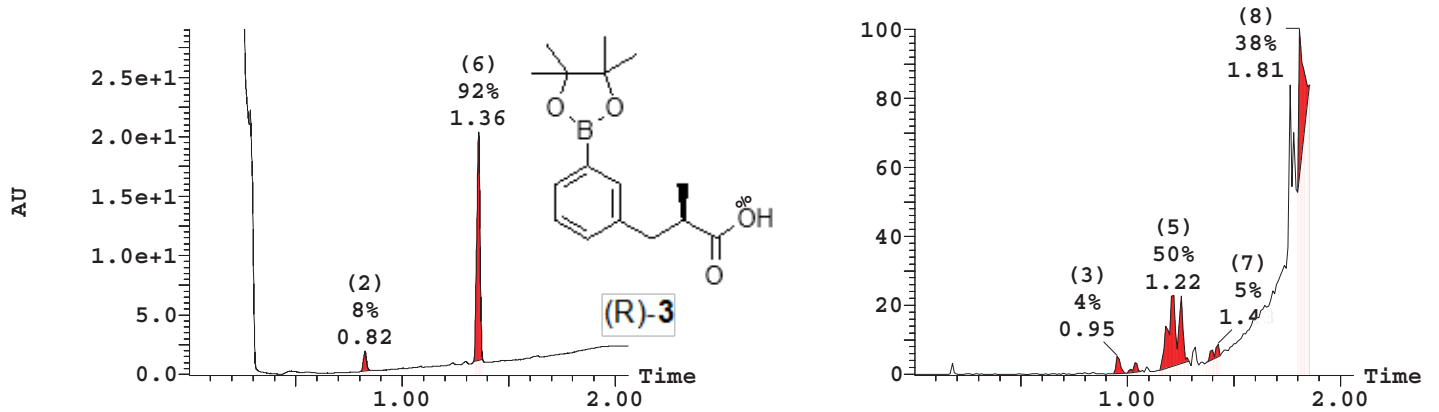
Date:16-Nov-2010
 Description:IPC 1_Rxn 19h
 Location: KJ205
 Column: HSS C18 1.8µ 2.1x50 mm

Printed: Tue Nov 16 08:29:39 2010

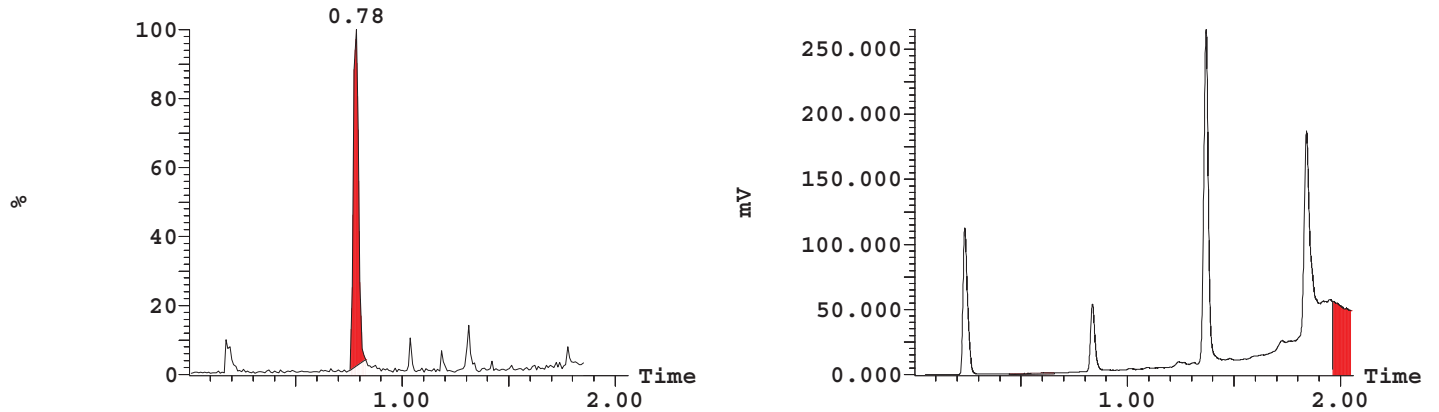
Sample Report:

Sample ID SN1031506451 Description IPC 1_Rxn 19h

3: UV Detector: TIC 2.903e+1 1: MS ES+ :BPI 1.1e+008
 Range: 2.903e+1

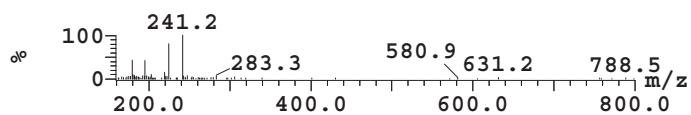


2: MS ES- :BPI 6.7e+005 (2) Corona CAD Smooth (Mn, 2x2) 265.200
 Range: 265.197



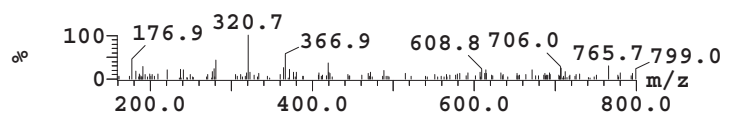
Peak ID 1 Time 0.52 Mass Found

1:MS ES+
6.3e+004



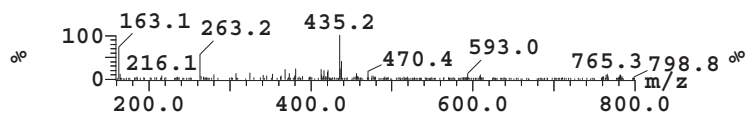
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2:MS ES-
2.0e+003



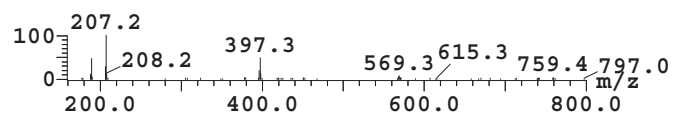
Peak ID 2 Time 0.78 Mass Found

1:MS ES+
1.9e+005



Peak ID 2 Time 0.78 Mass Found

2:MS ES-
2.1e+005



Openlynx Report walk-up LC/MS

Page 2

JobCode (batch):kssf06134

Sample: 1

Date:16-Nov-2010

UserName:kssf061

Sample ID:SN1031506451

Description:IPC 1_Rxn 19h

Vial:1:44

Instrument:ACQ-SQD#F08SQD296W

Location: KJ205

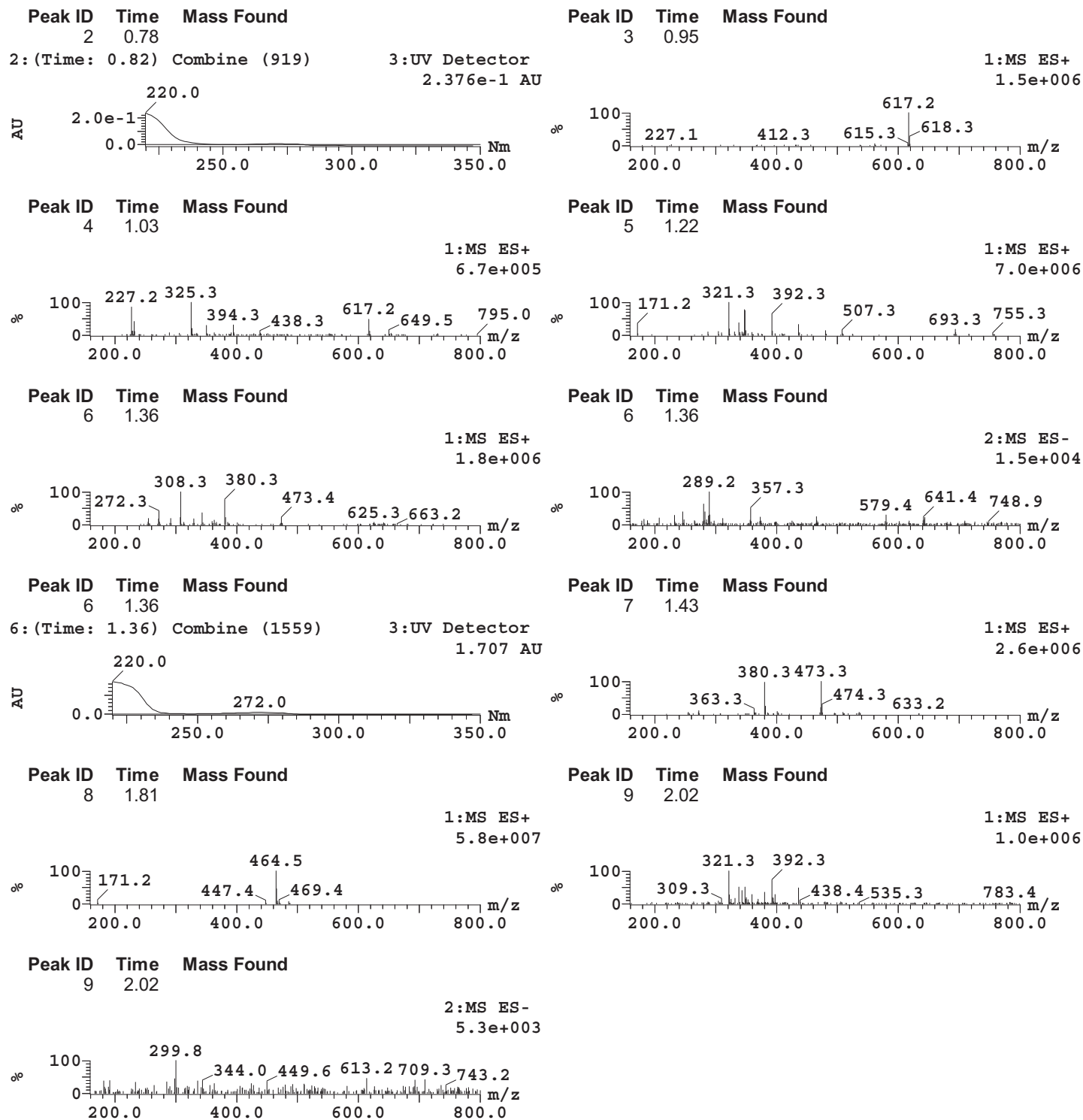
Method:C:\MassLynx\OA_2min_sur_HSSC18.olp

pH: 3

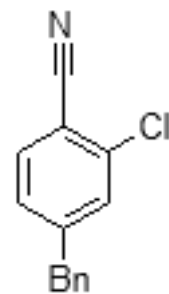
Column: HSS C18 1.8 μ 2.1x50 mm

Printed: Tue Nov 16 08:29:39 2010

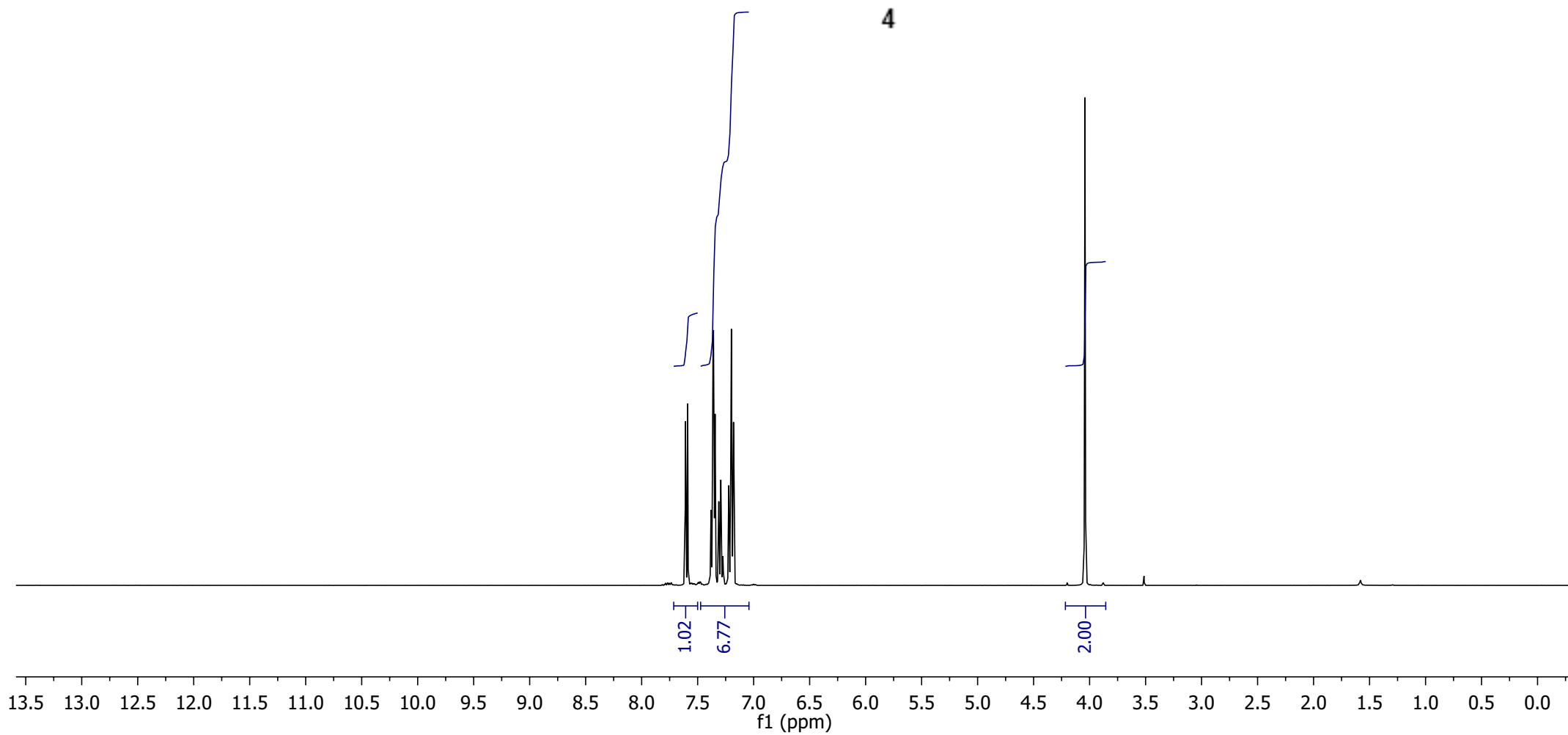
Sample Report (continued):



Analytical Number: SN1029900454
Book Reference: EN04296-82-004
User: Sørensen, Henrik
Prid: kd016
Email: Henrik.Sorensen@astrazeneca.com
Solvent: CDCl₃
Experiment Name: Proton_day
Parameters:
Submission Time: Mon Nov 15 12:10:23 CET 2010
Queue: Day
Extension: 321g



4

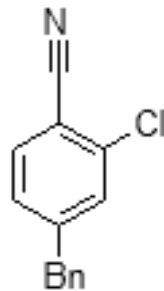


Analytical Number: SN1029900454
Book Reference: EN04296-82-004
User: Sørensen, Henrik
Prid: kd016
Email: Henrik.Sorensen@astrazeneca.com
Solvent: CDCl3
Experiment Name: Carbon_day
Parameters:
Submission Time: Fri Nov 12 08:36:44 CET 2010
Queue: Day
Extension:

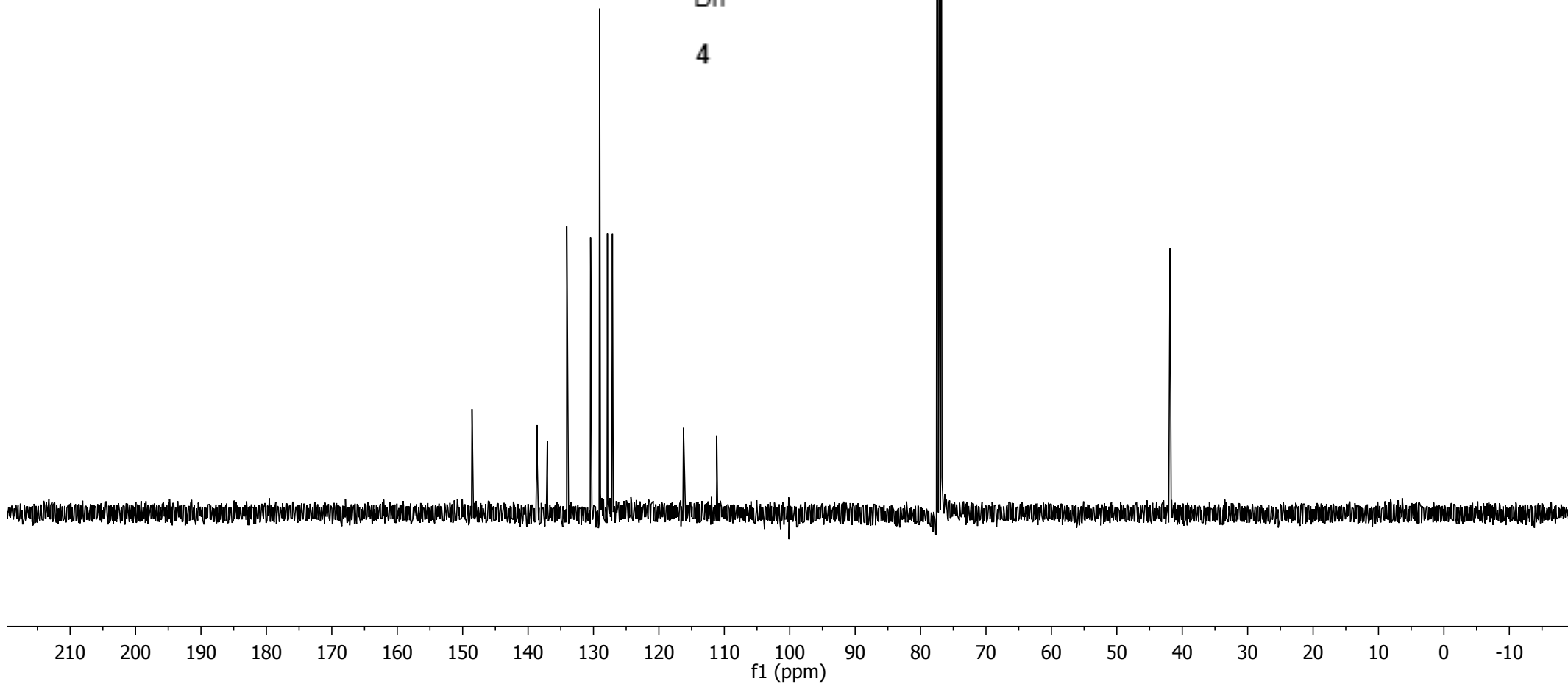
6
—148.57
—138.61
—137.05
—134.08
—130.45
—129.10
—129.06
—127.87
—127.10
—116.24
—111.15

77.48
77.06
76.84

41.85



4



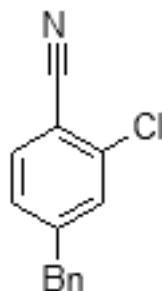
Purity Analysis

Submitter: Henrik Sörensen

Sample ID: SN1029900454

Compound Name: AZ13290640

Project: sPLA2X



4

Results

SN1029900454: Your sample was 99.4% pure (UV 210 nm) at alkaline conditions.

Instrumental setup (Alkaline conditions)

| | |
|-------------------|---|
| Column | Acquity UPLC™ BEH C18 100mm×2.1mm, 1.7µm particles |
| Temperature | 45°C |
| Gradient | 2% ACN to 95% ACN in 6 minutes; 47mM NH ₄ , 6.5mM NH ₄ HCO ₃ , pH 10 |
| Flow | 0.7 mL/min |
| Injection volume | 1 µL |
| Purity | Relative Absorbance at 210 nm |
| Ionization mode | ESI+ |
| Mass spectrometer | Waters Xevo QTOF |
| Lockmass | Leucine Enkephaline C28H37N5O7 |

Signature: _____

Date: 2010-11-16

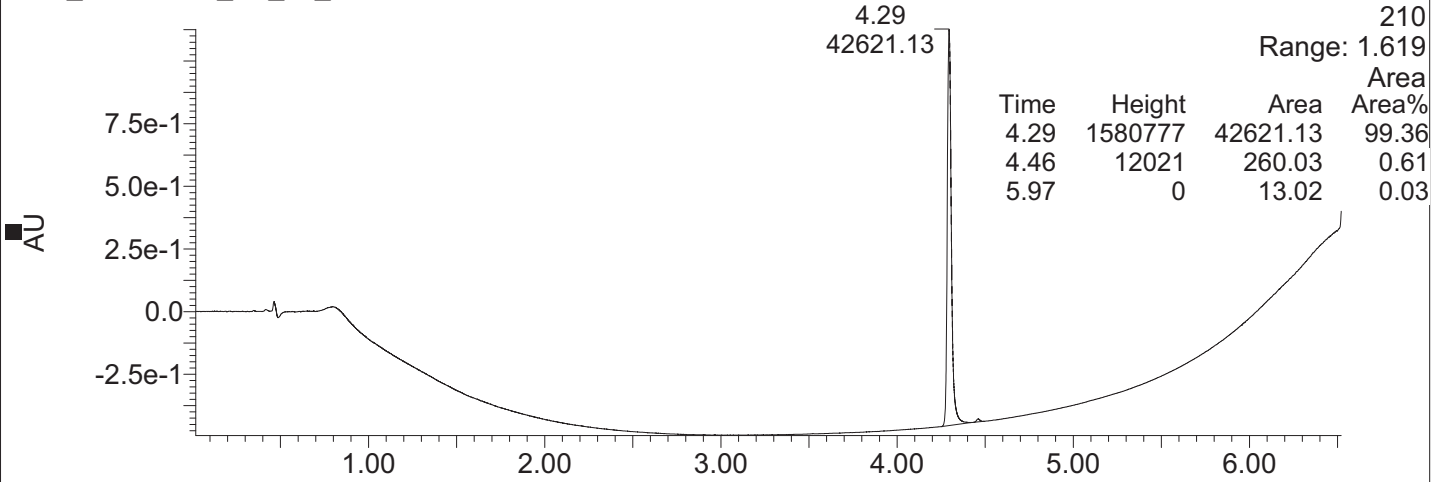
Kristina Öhlén
Medicinal Chemistry
AstraZeneca R&D Mölndal
SE-431 83 Mölndal, Sweden

AZ13290640

SN1029900454

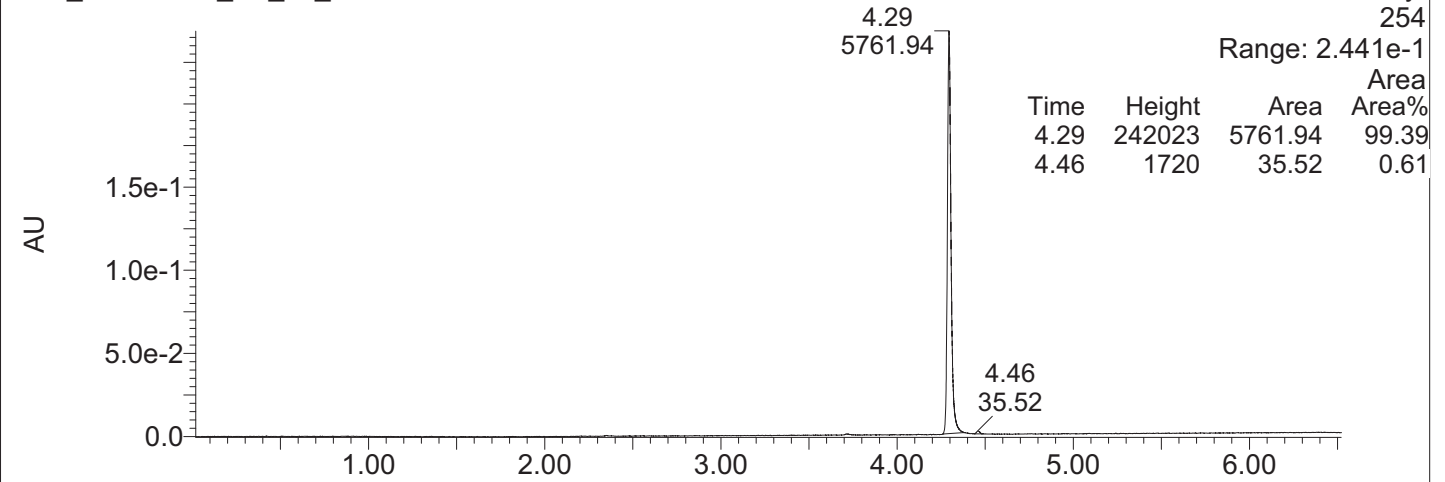
1115_Hsörensens_alk_06_03

3: Diode Array



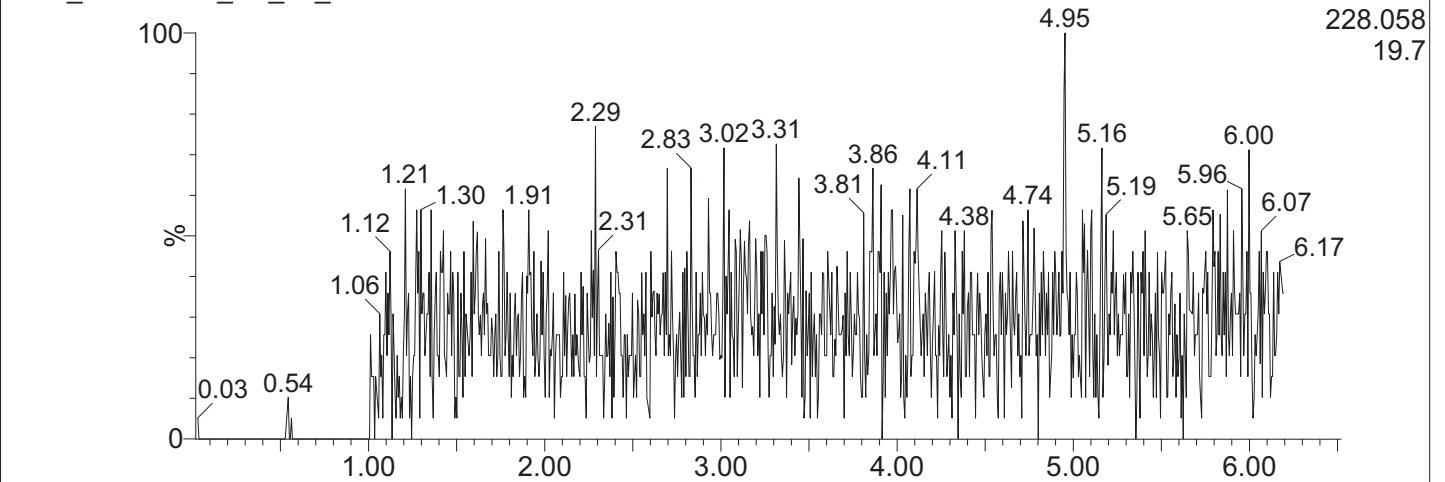
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3: Diode Array



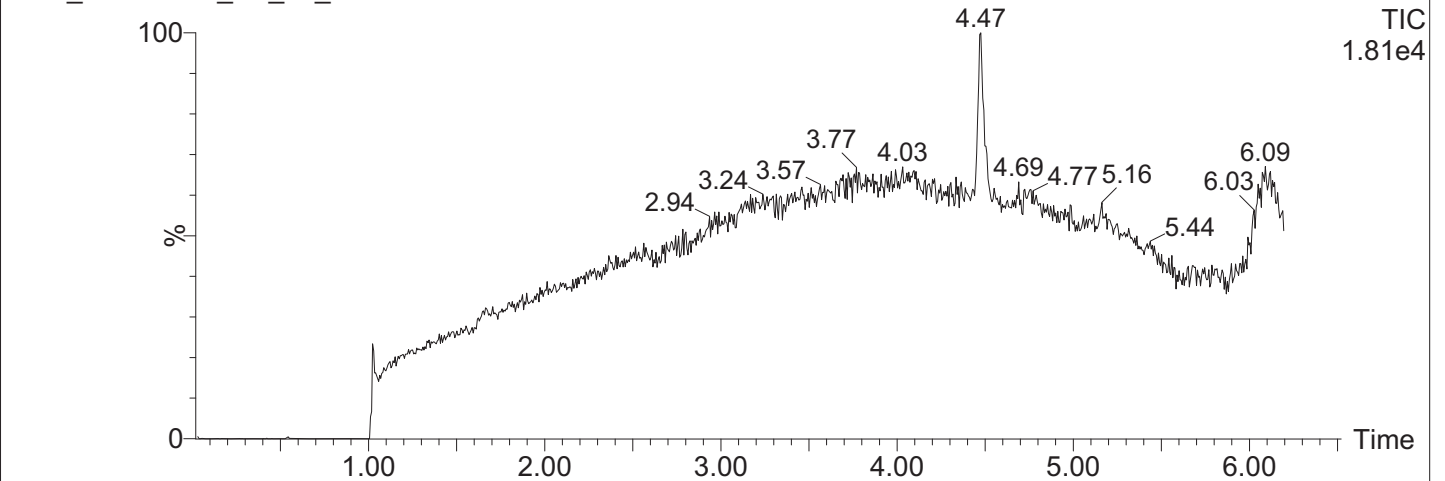
1115_Hsörensens_alk_06_03

1: TOF MS ES+

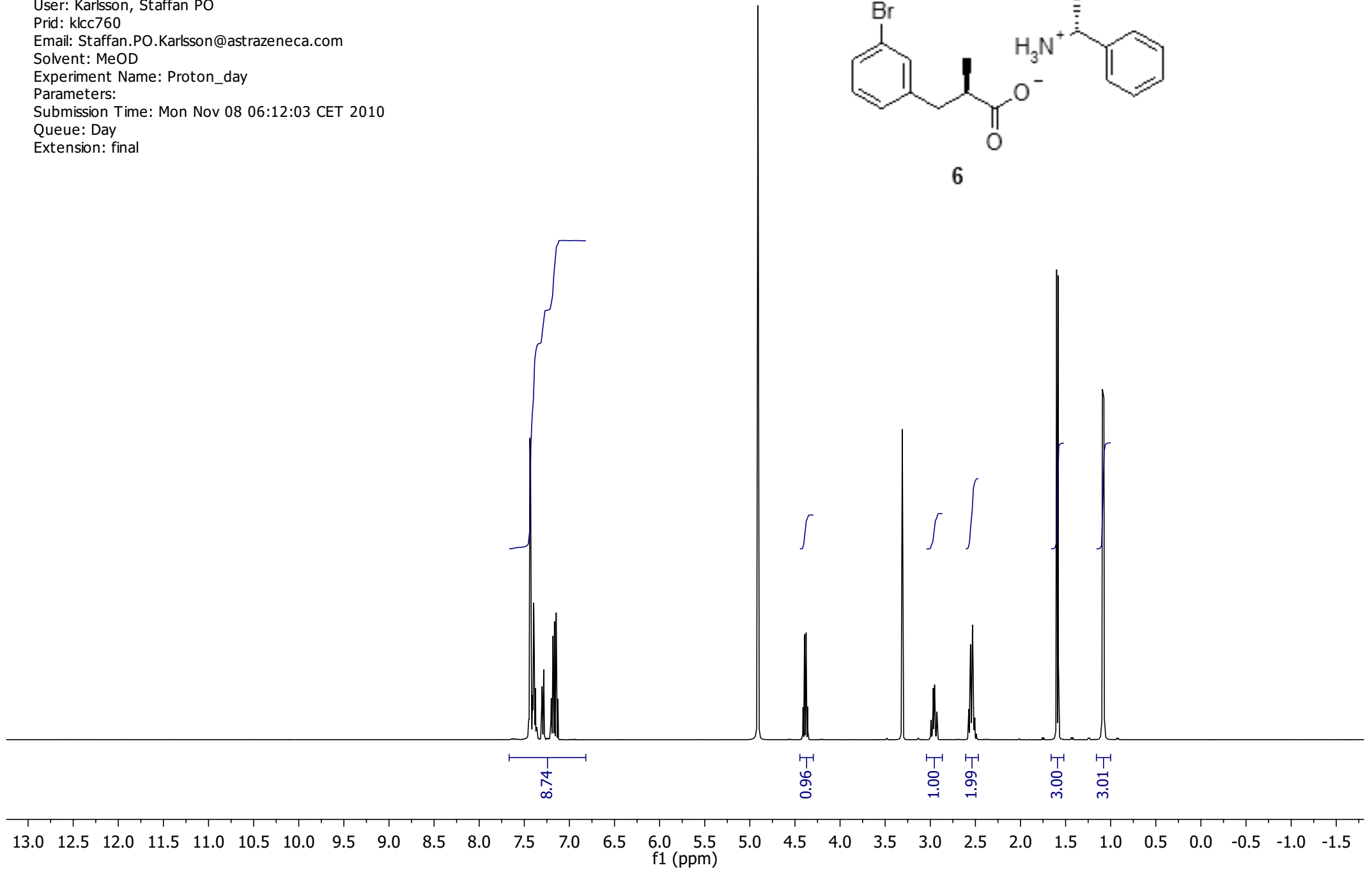
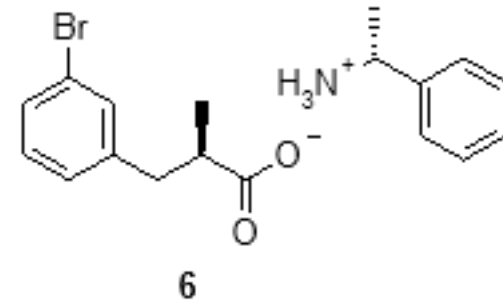


1115_Hsörensens_alk_06_03

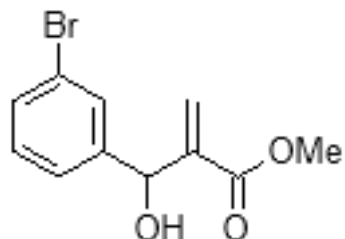
1: TOF MS ES+



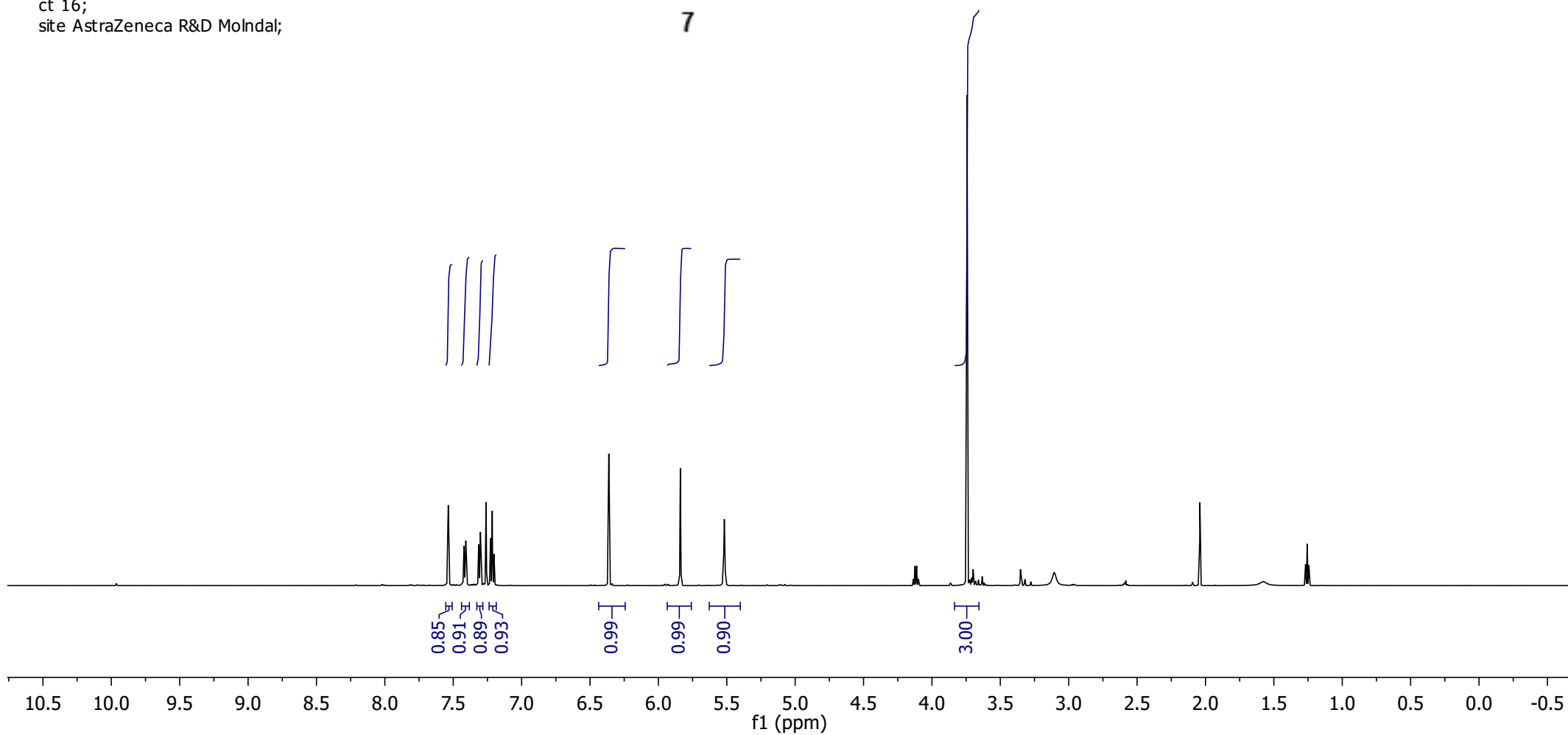
Analytical Number: SN1034112758
Book Reference: EN04556-67-003
User: Karlsson, Staffan PO
Prid: klcc760
Email: Staffan.PO.Karlsson@astrazeneca.com
Solvent: MeOD
Experiment Name: Proton_day
Parameters:
Submission Time: Mon Nov 08 06:12:03 CET 2010
Queue: Day
Extension: final



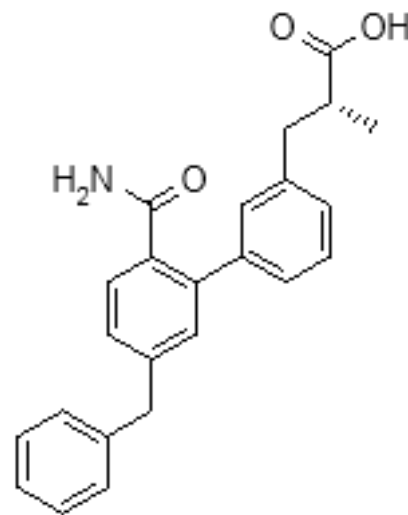
Sample_Id SN1025577332;
EN EN03744-24-001;
filename SN1025577332_upa_h1nmr_1;
experiment h1nmr;
operator Daniel Pettersen;
chemist Daniel Pettersen;
automation SMS;
Sample# 4;
prid kwcj238;
date Feb 5 2010;
solvent cdcl3;
hostname nmr1;
NMR Spectrometer 600 MHz;
probe tr600;
nt 16;
ct 16;
site AstraZeneca R&D Molndal;



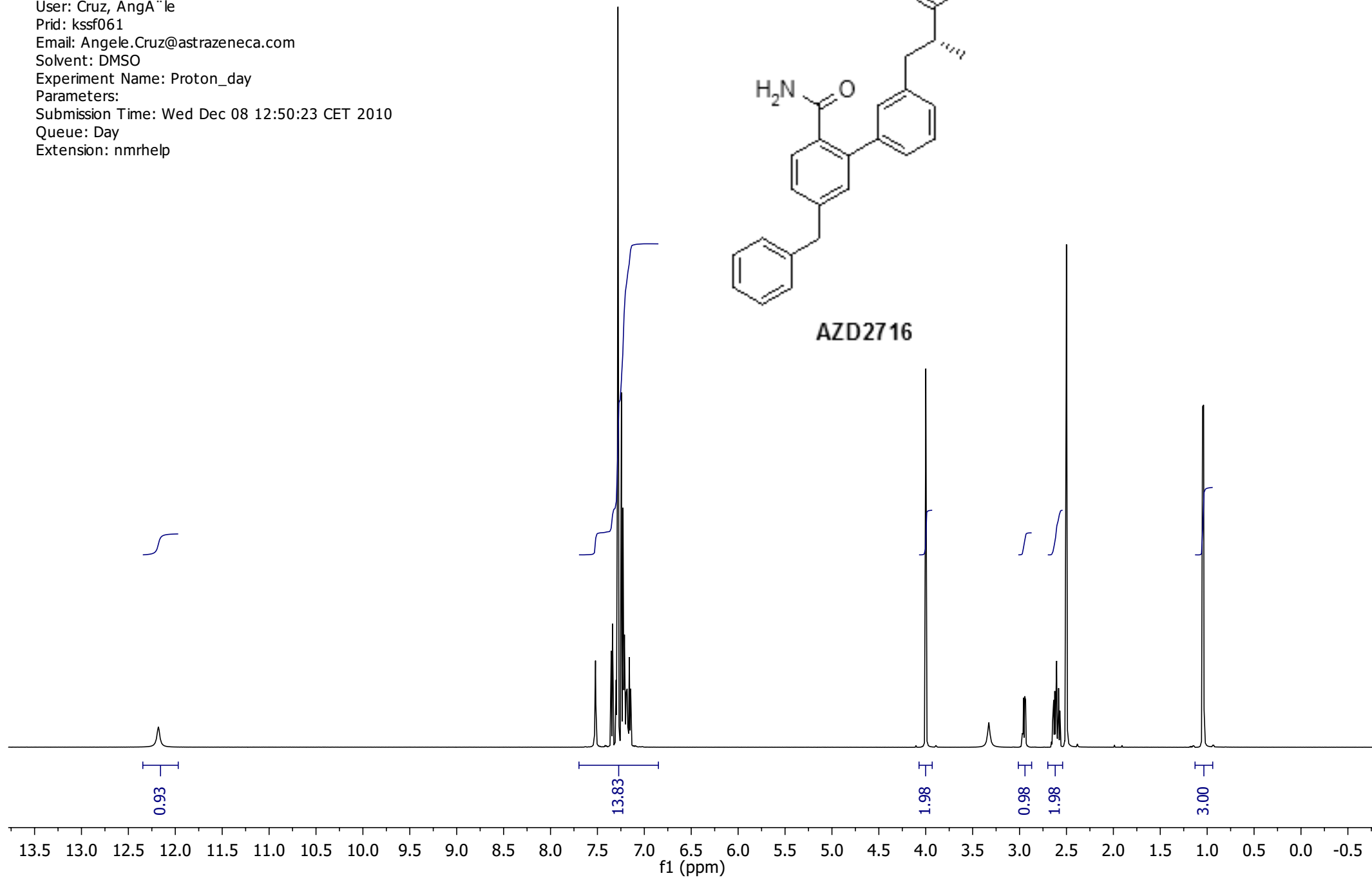
7



Analytical Number: SN1031506602
Book Reference: EN01790-97
User: Cruz, Angelle
Prid: kssf061
Email: Angele.Cruz@astrazeneca.com
Solvent: DMSO
Experiment Name: Proton_day
Parameters:
Submission Time: Wed Dec 08 12:50:23 CET 2010
Queue: Day
Extension: nmrhelp

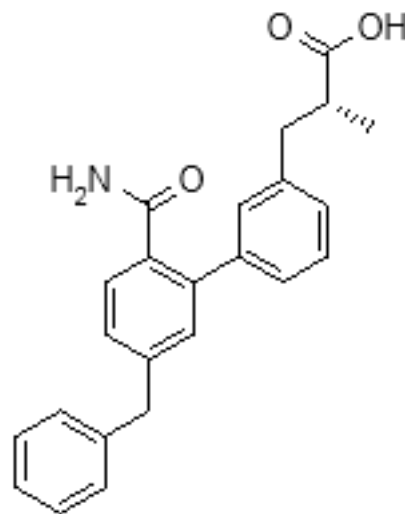


AZD2716



Analytical Number: SN1031506602
Book Reference: EN01790-97
User: Cruz, Angéle
Prid: kssf061
Email: Angele.Cruz@astrazeneca.com
Solvent: DMSO
Experiment Name: Carbon_night
Parameters:
Submission Time: Wed Dec 08 12:50:48 CET 2010
Queue: Night
Extension: nmrhelp

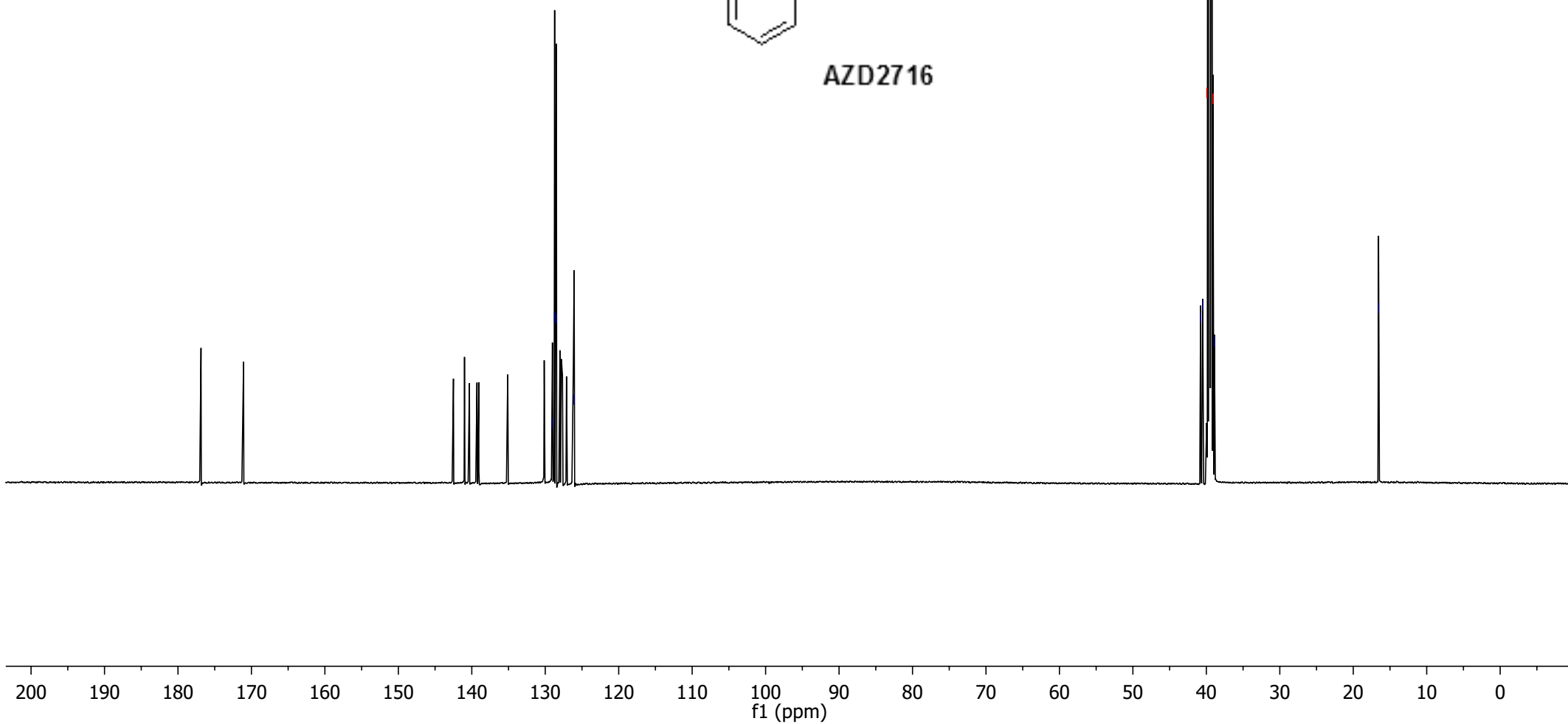
129.03
128.73
128.49
126.08



AZD2716

40.78
40.50
39.93 DMSO
39.80 DMSO
39.66 DMSO
39.52 DMSO
39.38 DMSO
39.24 DMSO
39.10 DMSO
38.91

16.55



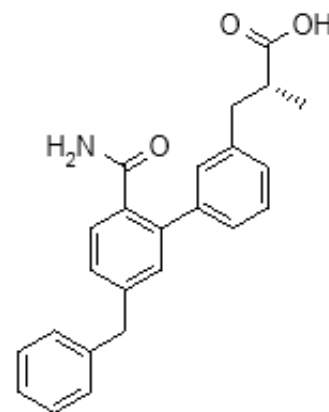
Purity Analysis and Accurate Mass Report

Submitter: Angèle Cruz

Sample ID: SN1031506583

Compound Name: AZ13320735

Project: sPLA2X



AZD2716

Results

The measured mass confirmed the elemental composition (within 5 ppm).

Purity measured at pH3 and UV 230nm was 99.6%.

Purity measured at pH10 and UV 210nm was 99.6%.

No impurity exceeded 0.5%.

Instrumental setup

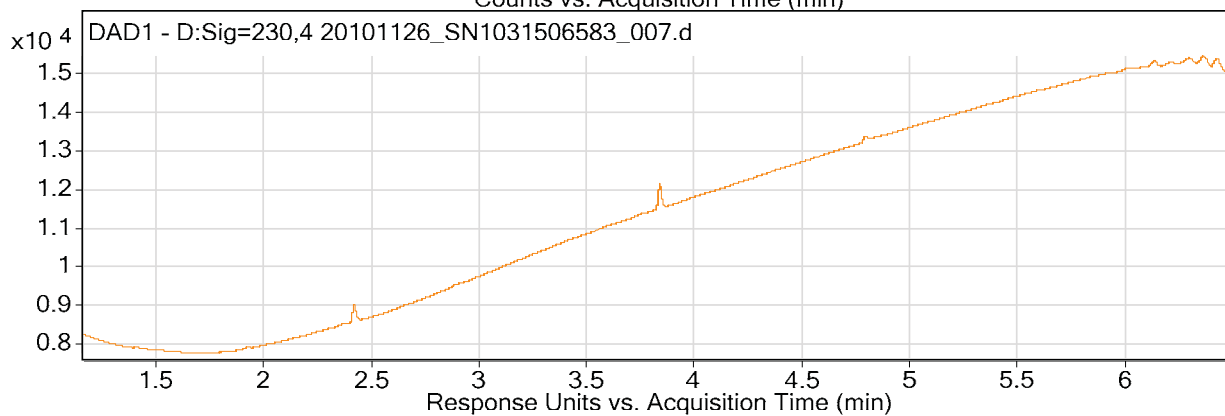
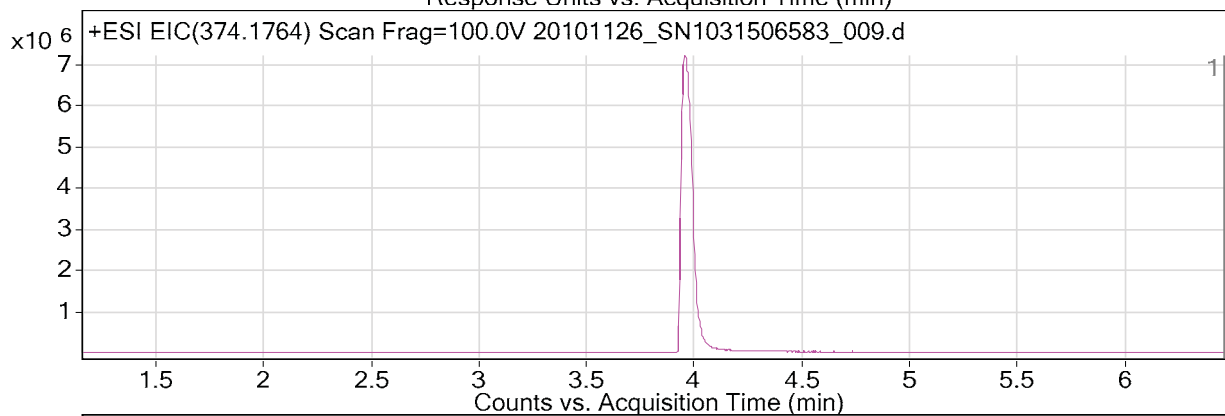
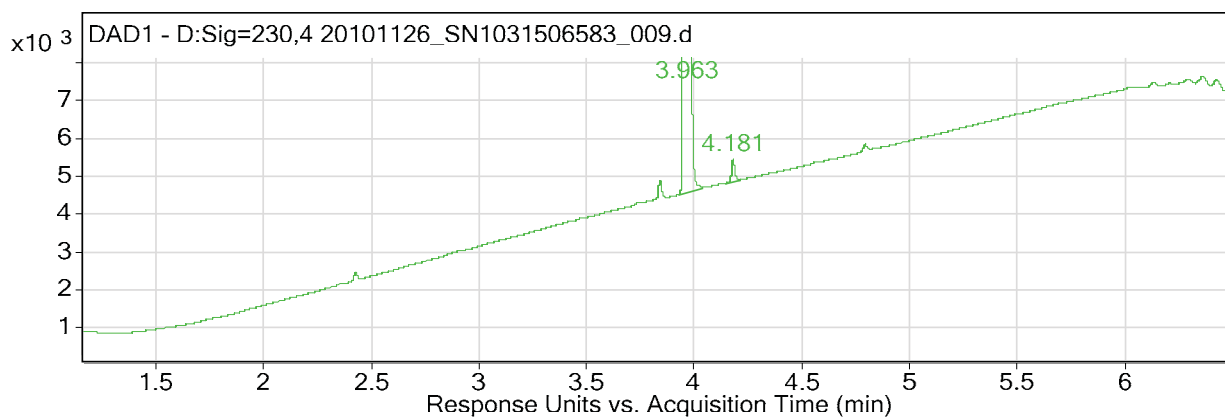
| | |
|-------------------|--|
| Column | pH3: Aquity UPLC HSS C18, 2.1mm×100mm, 1.8µm particles pH10: Aquity UPLC BEH C18, 2.1mm×100mm, 1.7µm particles |
| Temperature | 50°C |
| Gradient | 2% ACN to 95% ACN in 7 minutes. pH3: 10 mM formic acid 1 mM ammonium formate pH10: 40 mM ammonia 6 mM ammonium carbonate |
| Flow | 0.7 ml/min |
| Purity | Relative Absorbance at 210 nm and 230nm |
| Mass spectrometer | QTOF 6530 (Agilent) |

Gustaf Hulthe

Medicinal Chemistry
AstraZeneca R&D Mölndal
SE-431 83 Mölndal, Sweden

Date: 2010-11-26

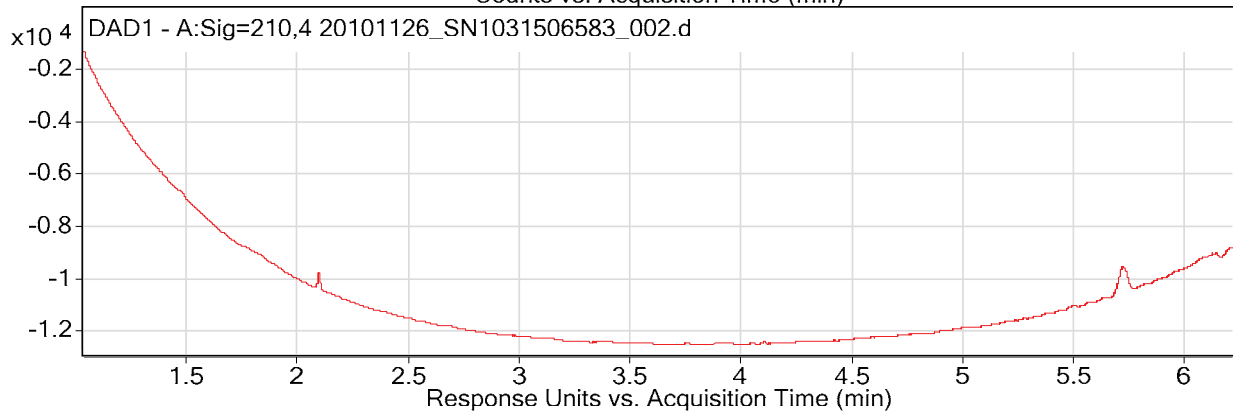
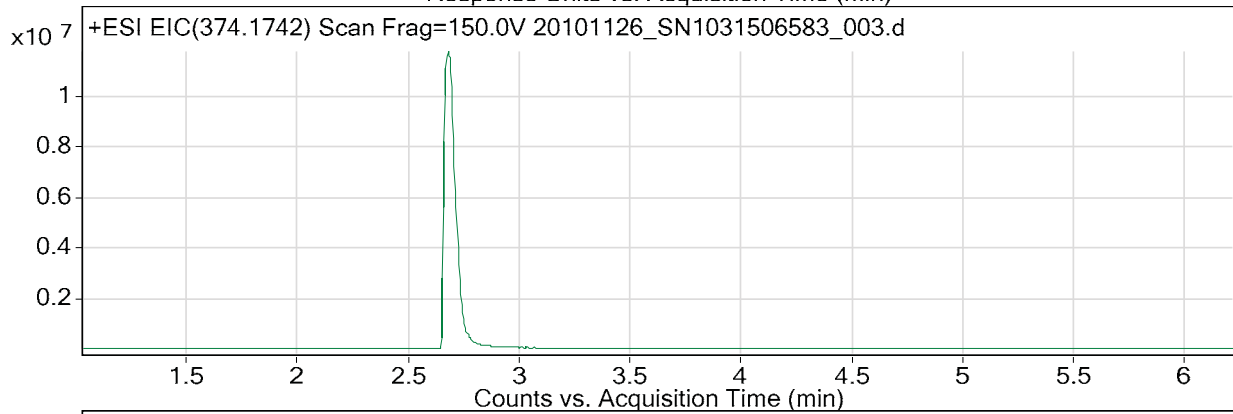
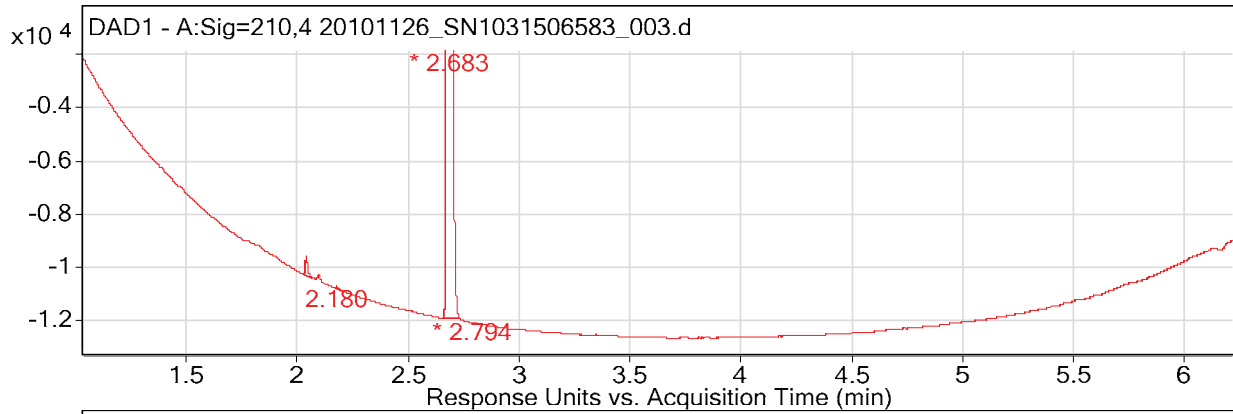
Qualitative Plot Window Report



Peaks: DAD1 - D:Sig=230,4 (20101126_SN1031506583_009.d)

| RT | Area Sum% |
|-------|-----------|
| 3.963 | 99.65 |
| 4.181 | 0.35 |

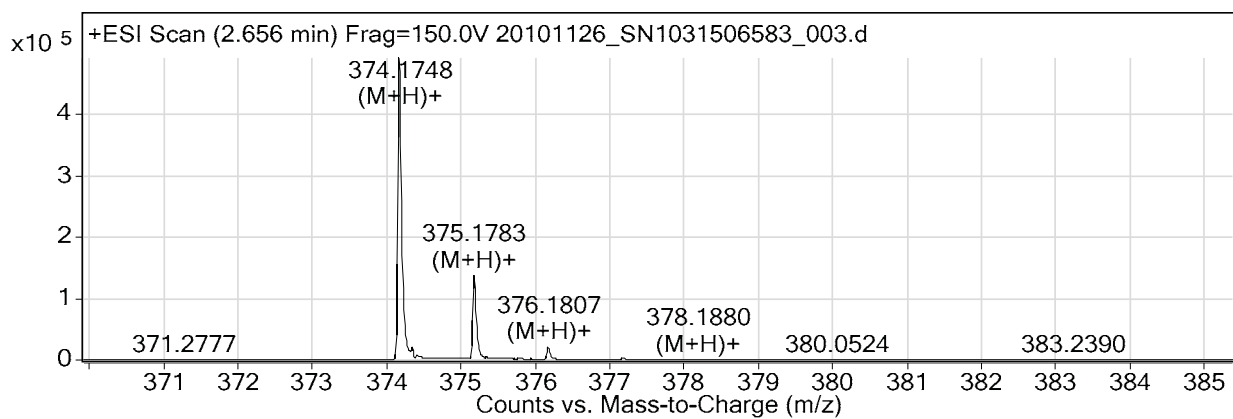
Qualitative Plot Window Report



Peaks: DAD1 - A:Sig=210,4 (20101126_SN1031506583_003.d)

| RT | Area Sum% |
|-------|-----------|
| 2.043 | 0.33 |
| 2.18 | 0.05 |
| 2.683 | 99.63 |
| 2.794 | 0 |

Qualitative Plot Window Report



MS Formula Results: + Scan (2.656 min) (20101126_SN1031506583_003.d)

| m/z | Ion | Formula | Abundance | | | | | | |
|-------------------------------------|--------------------|------------------------|--------------|--------------------|-------------------|-------------------|-------------------|--------------------|----------------------|
| 374.1748 | (M+H) ⁺ | C24 H24 N O3 | 500424.3 | | | | | | |
| Best | Formula (M) | Ion Formula | Score | Cross Score | Calc m/z | Diff (ppm) | Mass Match | Abund Match | Spacing Match |
| <input checked="" type="checkbox"/> | C24 H23 N O3 | C24 H24 N O3 | 99.6 | | 374.1751 | 0.81 | 99.46 | 99.71 | 99.77 |
| Isotope | Abund Sum% | Calc Abund Sum% | m/z | Calc m/z | Diff (ppm) | | | | |
| 1 | 75.85 | 76.22 | 374.1748 | 374.1751 | 0.82 | | | | |
| 2 | 20.75 | 20.36 | 375.1783 | 375.1784 | 0.28 | | | | |
| 3 | 3.01 | 3.08 | 376.1807 | 376.1813 | 1.6 | | | | |
| 4 | 0.39 | 0.34 | 377.1829 | 377.1841 | 3.21 | | | | |
| Best | Formula (M) | Ion Formula | Score | Cross Score | Calc m/z | Diff (ppm) | Mass Match | Abund Match | Spacing Match |
| <input type="checkbox"/> | C20 H19 N7 O | C20 H20 N7 O | 84.01 | | 374.1724 | -6.42 | 71.05 | 94.8 | 97.01 |
| <input type="checkbox"/> | C19 H23 N3 O5 | C19 H24 N3 O5 | 68.23 | | 374.171 | -9.98 | 43.73 | 83.32 | 99.11 |
| <input type="checkbox"/> | C13 H23 N7 O6 | C13 H24 N7 O6 | 59.04 | | 374.1783 | 9.31 | 48.7 | 46.74 | 94.49 |

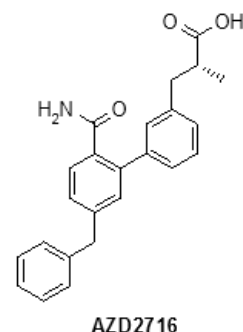
Analysis Report

Sample Information

| Sample ID | Compound name | Project name |
|--------------|---------------|--------------|
| SN1031506583 | AZ13320735 | sPLA2x |

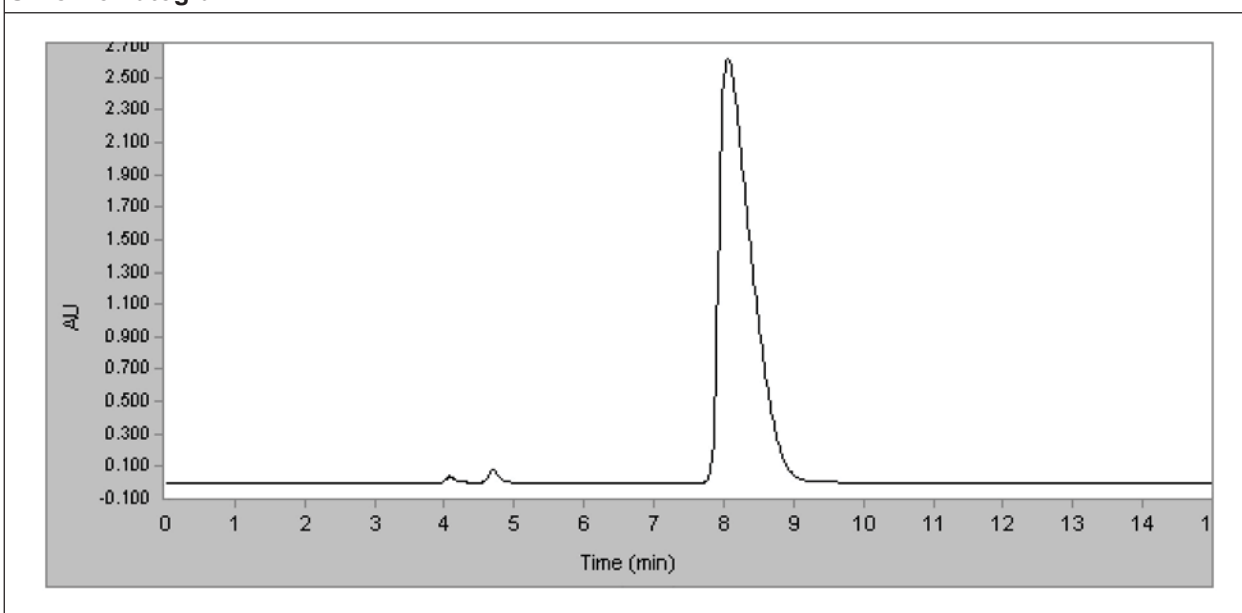
Analytical Conditions

| Column | Dimensions (mm) | Particle Size (μm) |
|--------------------------|-----------------------|---------------------------------|
| Chiralcel OJ | 250 * 4.6 | 5 |
| Mobile Phase | | |
| Heptan/EtOH/FA 10/90/0.1 | | |
| Flow (ml/min) | | |
| 1 ml/min | Detection (nm) | Temperature (C) |
| | PDA 254.0 nm | 40 |
| Comment | | |
| | | |



Analytical Result

UV Chromatogram



| Retention Time | Area | Area % | K' | N | USP Resolution |
|----------------|----------|--------|-------|---|----------------|
| 4.701 | 754444 | | 0.000 | | |
| 8.059 | 83858107 | | 0.714 | | 5.844538e+000 |

ee: 98.2%

Chemist Signature

Print Date

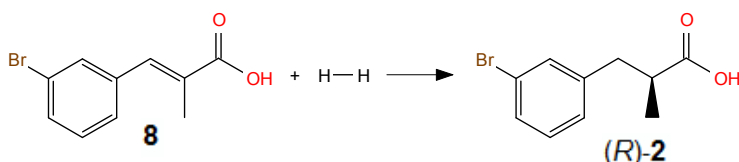
2010-11-26

| | | |
|---|-----------------------|---|
| Per Ryberg SPLA2 05-khhv201-18 SPLA2 hydrogenation 3 AstraZeneca Process R&D, Astrazeneca | Notebook Entry | Notebook Name: 05-khhv201 Creation Date: 09 November 2010 Modify Date: 22 November 2011 |
|---|-----------------------|---|

Investigation of the effect of solvents and acid/base additives.

Strong effect of solvent on activity: MeOH and iPrOH much better than Toluene or THF.

No clear effect of additives



| Materials | | | Planned Amounts | | | | Actual Amounts |
|-----------|--|------------|-----------------|------|--------|--------|----------------|
| | | | Equiv | Mass | Volume | Moles | Equiv |
| Class | Name | Lot Number | equiv | mg | μL | μmoles | equiv |
| Reactants | SPLA2 alken [LR] | | 1.00 | 15.0 | n/a | 62.2 | n/a |
| | hydrogen | | n/a | n/a | n/a | n/a | n/a |
| Chemicals | 20-a SL-J505-1 (R-S) | | n/a | 4.3 | n/a | 7.5 | n/a |
| | Bis(1,5-cyclooctadiene)rhodium (I) Tetrafluoroborate | | n/a | 2.8 | n/a | 6.8 | n/a |
| | Methanol | | n/a | n/a | n/a | n/a | n/a |
| | Isopropyl Alcohol | | n/a | n/a | n/a | n/a | n/a |
| | Toluene | | n/a | n/a | n/a | n/a | n/a |
| | Tetrahydrofuran | | n/a | n/a | n/a | n/a | n/a |
| | Trifluoroacetic Acid | | n/a | 30.2 | 20.0 | 264.5 | n/a |
| | Triethylamine | | n/a | 14.5 | 20.0 | 143.5 | n/a |
| Products | 2-Propanamine, 2-Methyl- | | n/a | 13.9 | 20.0 | 189.7 | n/a |
| | SPLA2 product | | 1.00 | 15.1 | n/a | 62.2 | n/a |

| Materials | | | Actual Amounts | | | Properties | | |
|-----------|--|------------|----------------|--------|--------|---------------|---------|--------|
| | | | Mass | Volume | Moles | Strength | Density | MW |
| Class | Name | Lot Number | mg | μL | μmoles | n/a | g/mL | n/a |
| Reactants | SPLA2 alken [LR] | | n/a | n/a | n/a | 100.00 wt/wt% | 1.00 | 241.08 |
| | hydrogen | | n/a | n/a | n/a | 100.00 wt/wt% | 1.00 | 2.02 |
| Chemicals | 20-a SL-J505-1 (R-S) | | n/a | n/a | n/a | 100.00 wt/wt% | 1.00 | 570.52 |
| | Bis(1,5-cyclooctadiene)rhodium (I) Tetrafluoroborate | | n/a | n/a | n/a | 100.00 wt/wt% | 1.00 | 406.70 |
| | Methanol | | n/a | n/a | n/a | 24.71 M | 0.79 | 32.04 |
| | Isopropyl Alcohol | | n/a | n/a | n/a | 13.08 M | 0.79 | 60.10 |
| | Toluene | | n/a | n/a | n/a | 9.46 M | 0.87 | 92.14 |
| | Tetrahydrofuran | | n/a | n/a | n/a | 12.29 M | 0.89 | 72.11 |
| | Trifluoroacetic Acid | | n/a | n/a | n/a | 13.23 M | 1.51 | 114.02 |
| | Triethylamine | | n/a | n/a | n/a | 7.17 M | 0.73 | 101.19 |
| Products | 2-Propanamine, 2-Methyl- | | n/a | n/a | n/a | 9.49 M | 0.69 | 73.14 |
| | SPLA2 product | | n/a | n/a | n/a | 100.00 wt/wt% | 1.00 | 243.10 |

| Identity | Theoretical Yield (corrected for product strength) | Actual Yield | Process Mass Intensity Review | Meta Data |
|---|---|--|---|-----------|
| SPLA2 product, C ₁₀ H ₁₁ BrO ₂ , 243.10 (calculated) | 1.00 equiv; 62.22 μmoles; 15.13 mg (Based on Planned) n/a (Based on Actuals) | 0.00% 0.00 equiv; 0.00 μmoles; 0.00 mg (Based on Actuals) | 5.33 (Based on Theoretical) n/a (Based on Actuals) | |

2010-11-08

To each of 4 LC vials labelled 1-4 was added 20-a SL-J505-1 (R-S) (0.12 moles/mol-pure-LR; 7.5 μmoles; 4.3 mg; [Planned]) and Bis(1,5-cyclooctadiene)rhodium (I) Tetrafluoroborate (0.11 moles/mol-pure-LR; 6.8 μmoles; 2.8 mg; [Planned]) Then 1mL of MeOH (vial 1), iPrOH (vial 2), Toluene (vial 3) and THF (vial 3) was added respectively to the vials. The vials were heated gently to dissolve the Rh and ligand (difficult to get complete dissolution in toluene).

Then 200mg of starting material was weighed into each of 4 new vials. 3mL of solvent (MeOH, iPrOH, toluene and THF was added to the vials.

Trifluoroacetic Acid (20 μL; 264.5 μmoles; 20.0 μL; 30.2 mg; [Planned]) was added to each of the wells b1,b2,b3,b4,c1,c2,c3,c4
2-Propanamine, 2-Methyl- (20 μL; 189.7 μmoles; 20.0 μL; 13.9 mg; [Planned]) was added to each of the wells g9,g10,g11,g12,h9,h10,h11,h12
Triethylamine (20 μL; 143.5 μmoles; 20.0 μL; 14.5 mg; [Planned]) was added to each of the wells b9, b10,b11,b12,c9,c10,c11,c12

Then 200μL of the starting material stocksolutions were added to all the wells, so that the solvent distribution was according to the table below.

Finally 100 μ L and 50 μ L of the catalyst solutions were added to give 1% and 0.5% cat loadings according to the table below.

The reaction plate was inserted into the autoclave and hydrogen 7 bar was added and the the reactions were agitated at 20°C for 12 hours and then sampled.

| | | H | G | | C | B |
|----|-------|-----|------|--|-----|------|
| | | 1% | 0.5% | | 1% | 0.5% |
| 1 | THF | h1 | g1 | | c1 | b1 |
| 2 | Tol | h2 | g2 | | c2 | b2 |
| 3 | iPrOH | h3 | g3 | | c3 | b3 |
| 4 | MeOH | h4 | g4 | | c4 | b4 |
| | | | | | | |
| 9 | THF | h9 | g9 | | c9 | b9 |
| 10 | Tol | h10 | g10 | | 10 | 10 |
| 11 | iPrOH | h11 | g11 | | c11 | b11 |
| 12 | MeOH | h12 | g12 | | c12 | b12 |

| solvent | sample name | e1 | e2 | sm | Conversion | e1:e2 | ee(%) | |
|--------------|-------------|----|--------|---------|------------|-------|-------|------|
| THF | BH1 | | 3,597 | 45,534 | 571,591 | 7,9 | 92,7 | 85,4 |
| Tol | BH2 | | 3,175 | 18,549 | 821,342 | 2,6 | 85,4 | 70,8 |
| iPrOH | BH3 | | 15,17 | 207,75 | 27,938 | 88,9 | 93,2 | 86,4 |
| MeOH | BH4 | | 13,899 | 187,113 | 0,1 | 100,0 | 93,1 | 86,2 |
| THF tBuNH2 | BH9 | | 6,761 | 78,858 | 472,983 | 15,3 | 92,1 | 84,2 |
| Tol tBuNH2 | BH10 | | 2,332 | 22,54 | 915,721 | 2,6 | 90,6 | 81,2 |
| iPrOH tBuNH2 | BH11 | | 10,877 | 215,929 | 24,048 | 90,4 | 95,2 | 90,4 |
| MeOH tBuNH2 | BH12 | | 9,031 | 156,539 | 0,1 | 99,9 | 94,5 | 89,1 |
| THF TFA | BC1 | | 1,297 | 12,673 | 385,003 | 3,5 | 90,7 | 81,4 |
| Tol TFA | BC2 | | 2,407 | 13,214 | 738,681 | 2,1 | 84,6 | 69,2 |
| iPrOH TFA | BC3 | | 7,224 | 87,418 | 372,645 | 20,3 | 92,4 | 84,7 |
| MeOH TFA | BC4 | | 5,789 | 110,534 | 0,1 | 99,9 | 95,0 | 90,0 |
| THF Et3N | BC9 | | 4,294 | 45,258 | 443,164 | 10,1 | 91,3 | 82,7 |
| Tol Et3N | BC10 | | 2,442 | 26,478 | 794,257 | 3,5 | 91,6 | 83,1 |
| iPrOH Et3N | BC11 | | 10,232 | 194,44 | 43,979 | 82,3 | 95,0 | 90,0 |
| MeOH Et3N | BC12 | | 8,343 | 154,372 | 0,1 | 99,9 | 94,9 | 89,7 |