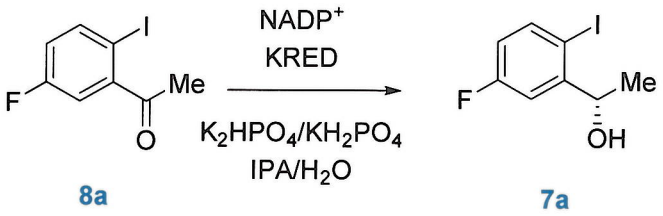
Supporting Information

Developing an Asymmetric Transfer Hydrogenation Process for (S)-5-fluoro-3- methylisobenzofuran-1(3H)-one, a Key Intermediate to Lorlatinib

Shengquan Duan*, Bryan Li, Robert W. Dugger, Brian Conway, Rajesh Kumar, Carlos Martinez, Teresa Makowski, Robert Pearson, Mark Olivier and Roberto Colon-Cruz

Chemical Research and Development and Analytical Research and Development, Pfizer Worldwide Research and Development, Eastern Point Road, Groton, CT 06340

1. Enzyme Screening for Conversion of 8a to 7a

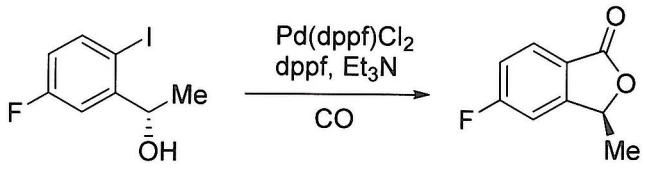


8a 7a

Screening conditions: substrate (1 mg/mL), enzyme (2 mg/mL), NAD(P)+ (0.2 mg/mL), ADH-LB (5% v/v), isopropanol (5% v/v), DMSO (2% v/v), 30 °, 20 hours

KRED Enzyme	% ee S	% Conversion
Codexis KRED-101	-100	24
Codexis KRED-130	100	46
Codexis KRED-P1-B05	97	5
Codexis KRED-P1-C01	98	48
Codexis KRED-P1-H08	99	100
Codexis KRED-P2-D03	99	89
Codexis KRED-P2-D11	99	50
Codexis KRED-P2-D12	100	98
Codexis KRED-P1-D05	99	77
Codexis KRED-P1-G03	97	4
Codexis KRED-P1-G11	98	60
Codexis KRED-P1-H01	99	52
Codexis KRED-P2-E10	99	100
Proteus mirabilis DKGA	100	100
Lactobacillus brevis RADH	100.0	5.5
Saccharomyces cerevisiae Acylglycerone-phosphate reductase (AYR1)	100.0	27.6
Saccharomyces cerevisiae Ydr541c	100.0	11.5
Saccharomyces cerevisiae Putative Reductase 1 YPR1	100.0	24.1
Saccharomyces cerevisiae GCY1	100.0	23.0
Saccharomyces cerevisiae Aldose reductase GRE3	100.0	22.4
Saccharomyces cerevisiae Yjr096w	100.0	66.8
Saccharomyces cerevisiae Ynl274c	100.0	4.6
Candida magnoliae CRS1	100.0	5.1
Candida parapsilosis cpr-C1	100.0	19.7
Leifsonia aquatica LVR	100.0	4.6
Thermoanaerobacter brockii TBAD in pSRF1b	100.0	10.4
Acinetobacter sp. RA3849 phaB	100.0	8.4
Candida albincans SOU1	100.0	4.7
Zoogloea ramigera phbB	100.0	4.3
Acinetobacter baylyi phaB	100.0	2.0

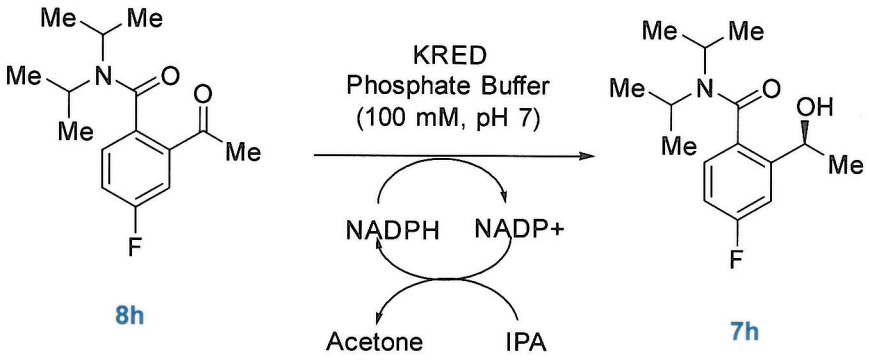
2. Study Results on Solvent and Catalyst loading for the Carbonylation Reaction



7a 6

Solvent	% water	temp	catalyst loading mol%	% conversion	% R-isomer
2-MeTHF	0.1	80	0.15	100	ND
MeOH	0.1	80	0.05	100	1.0%
2-MeTHF	0	80	0.05	100	ND
MeOH	0	80	0.15	100	0.08%
MeOH	0.05	70	0.1	100	1.0%
2-MeTHF	0.05	70	0.1	100	ND
MeOH	0.05	70	0.1	100	1.0%
2-MeTHF	0.05	70	0.1	91	ND
MeOH	0	60	0.05	61	0.29%
2-MeTHF	0.1	60	0.05	60	ND
MeOH	0.1	60	0.15	46	0.31%
2-MeTHF	0	60	0.15	31	ND

3. Enzyme Screening for Conversion of 8h to 7h

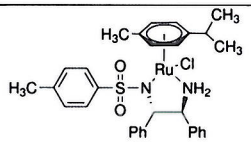


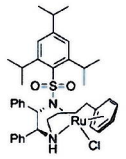
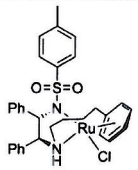
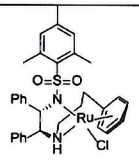
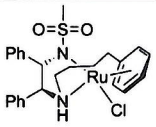
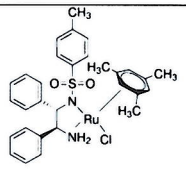
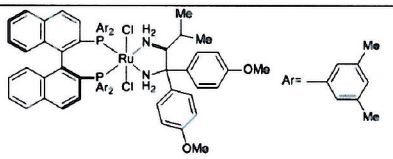
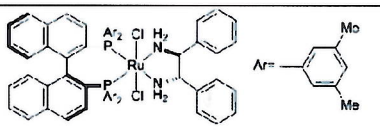
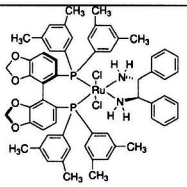
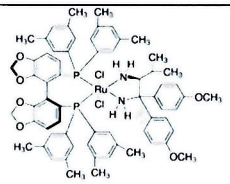
Screening conditions: substrate (2 mg/mL), enzyme (2 mg/mL), NAD(P)+ (0.4 mg/mL), GDH (0.4 mg/mL), Glucose (4 mg/mL), isopropanol (3% v/v), DMSO (2% v/v), 30 °C, 2 hour

KRED Enzyme	% ee S	% Conversion
KRED-P1-B02*	>99	88.94
KRED-P1-B10	>99	93.84
KRED-P1-B12	>99	95.97
KRED-P1-C01	>99	97.26
KRED-P1-H08	>99	94.00
KRED-P2-E10	>99	91.90
KRED-264-55	>99	16.85
SC-AYRI	82.25	12.01
EW-KRED-114	97.03	30.81
EW-KRED-119	96.22	35.88
Evo 1.1.440	98.38	61.60
A661	96.10	27.03
Control no enzyme	0	0.00

* selected for process development due to higher substrate tolerance (25 – 40 g/L)

4. Structure of the Ru- Catalysts for the Asymmetric Hydrogenation Screening

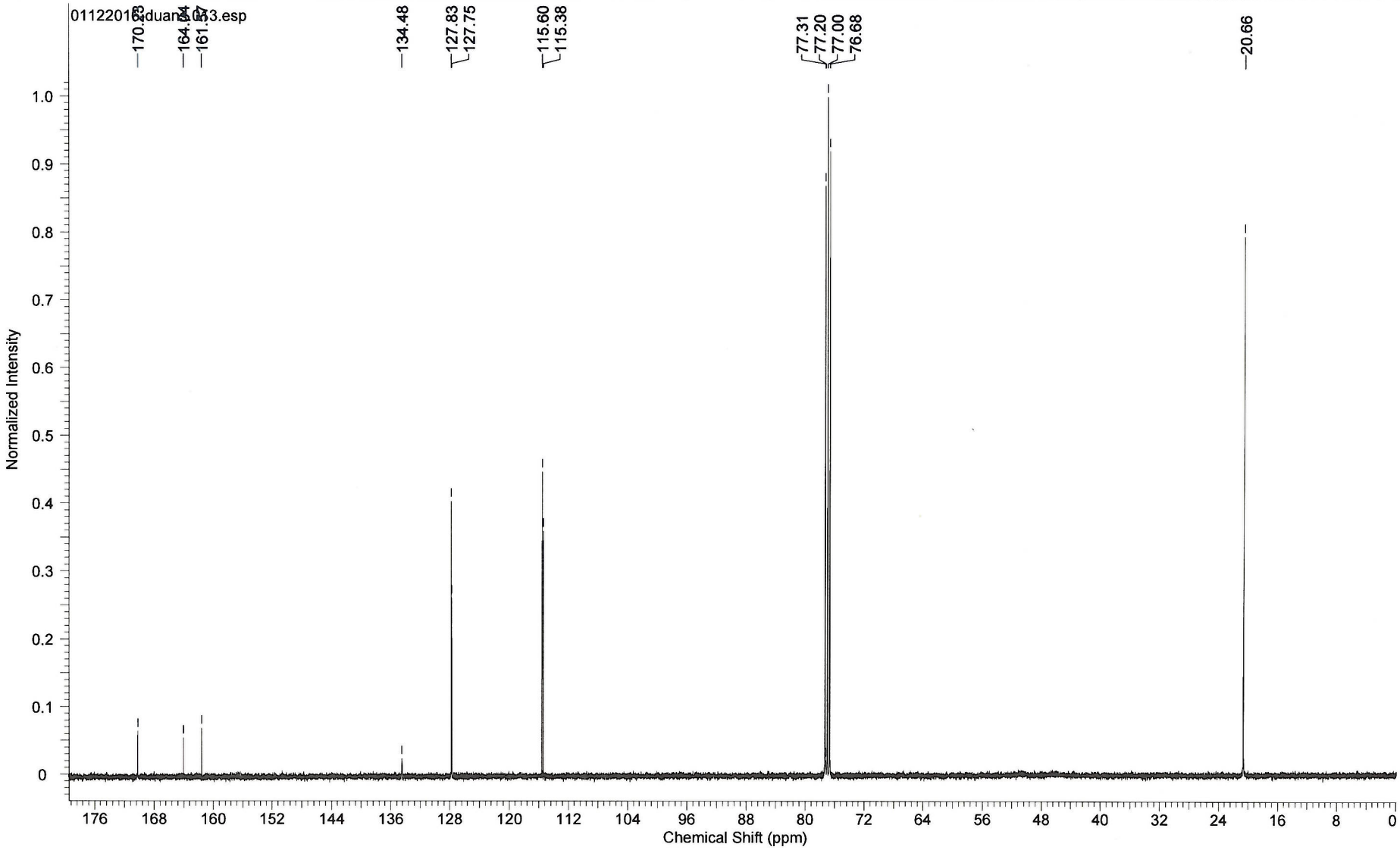
Catalyst	Structure
RuCl[(S,S)-TsDPEN] (p-cymene)	

C4-[(S,S)-teth-TrisDPEN RuCl]	
C4-[(S,S)-teth-TsDPEN RuCl]	
C3-[(S,S)-teth-MtsDPEN RuCl]	
C4-[(S,S)-teth-MsDPEN RuCl]	
RuCl[(S,S)-TsDPEN] (mesitylene)	
$RuCl_2$[(S)-XylBinap](S-Daipen)	
$RuCl_2$[(S)-XylBinap](S,S-Dpen)	
$RuCl_2$[(R)-XylSegphos](R,R-Dpen)	
$RuCl_2$[(S)-XylSegphos](S-Daipen)	

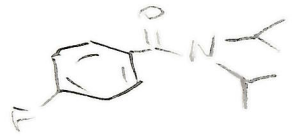
4-fluoro-N,N-diisopropylbenzamide

Number of Nuclei	0 C's

Acquisition Time (sec)	1.3631	Comment	[redacted] C13CPD_night CDCl3 /opt/topspin3.2 duans 51			Date	13 Jan 2016 04:06:08
Date Stamp	13 Jan 2016 04:06:08			File Name	\\SEG7\OAdata\BH091709\data\duans\nmr\01122016-duans\13\fid		
Frequency (MHz)	100.61	Nucleus	13C	Number of Transients	2048	Origin	spect
Original Points Count	32768	Owner	nmr	Points Count	32768	Pulse Sequence	zgpg30
Receiver Gain	203.00	SW(cyclical) (Hz)	24038.46	Solvent	CHLOROFORM-d		
Spectrum Offset (Hz)	10056.1748	Spectrum Type	STANDARD	Sweep Width (Hz)	24037.73	Temperature (degree C)	23.460

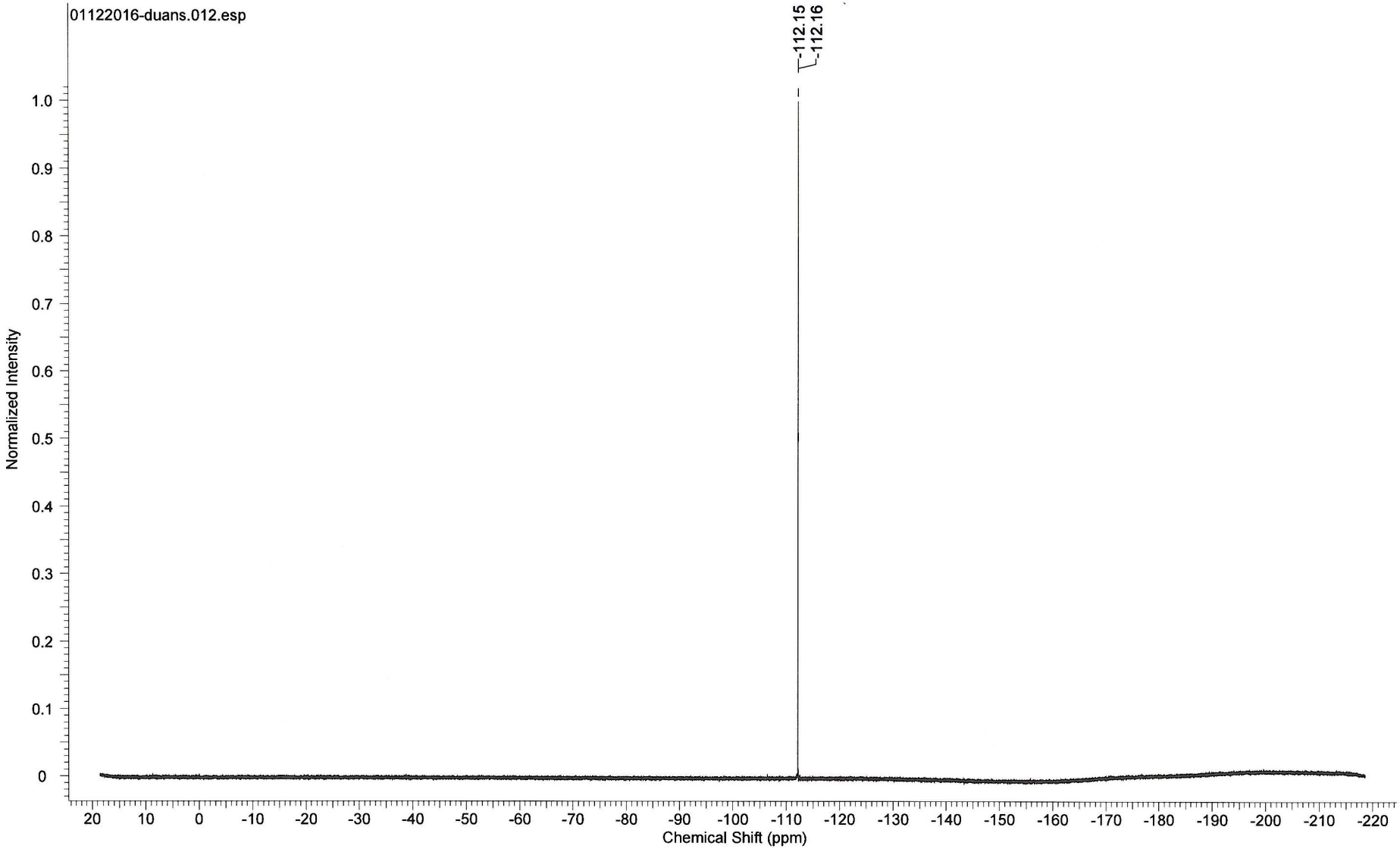


4-fluoro-N,N-diisopropylbenzamide

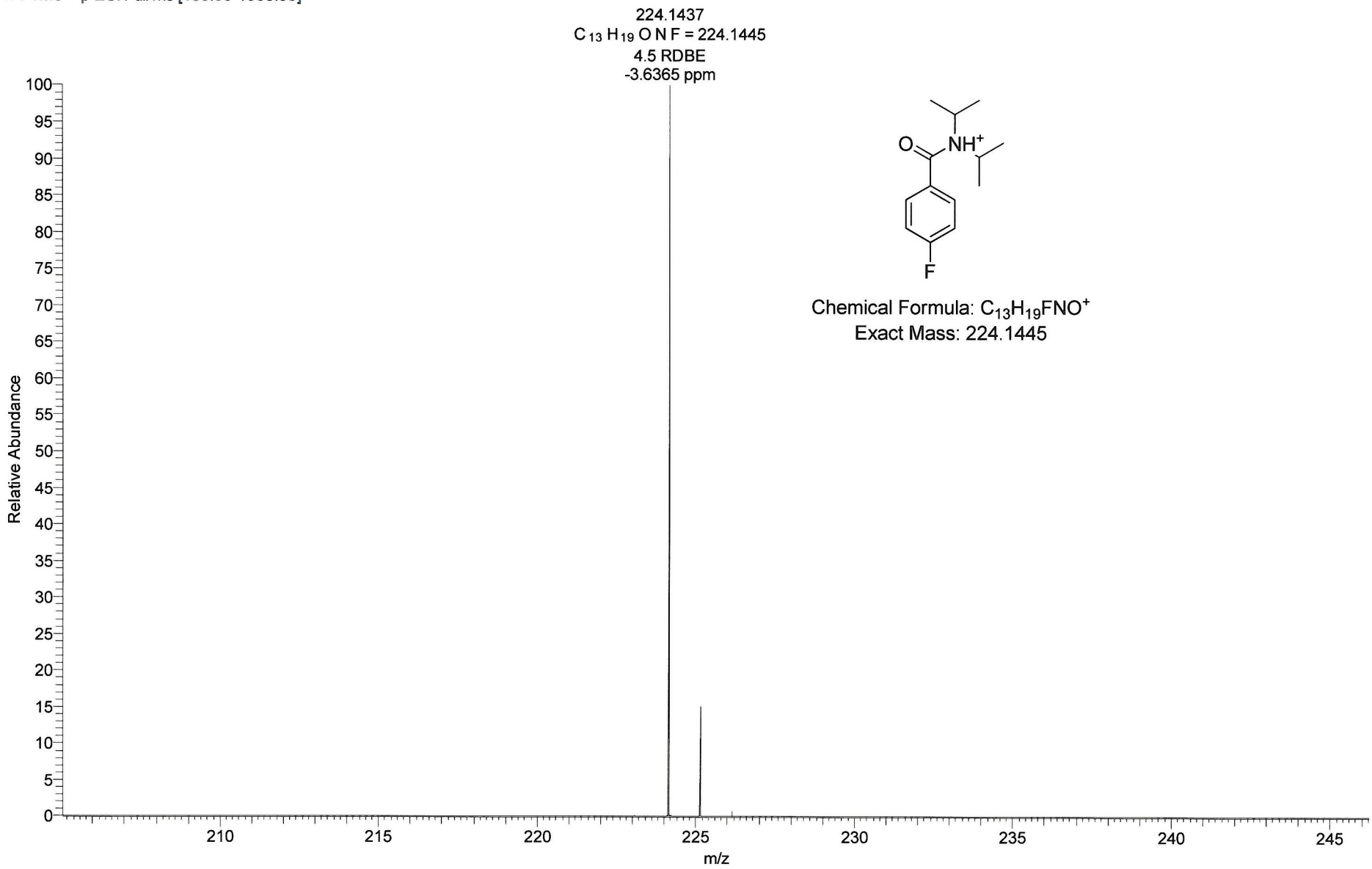


Number of Nuclei	0 F's

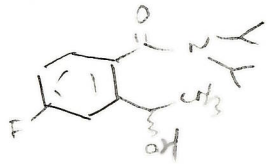
Acquisition Time (sec)	0.7340	Comment	[redacted] F19 CDCl3 /opt/topspin3.2 duans 51			Date	12 Jan 2016 15:50:08
Date Stamp	12 Jan 2016 15:50:08			File Name	\\SEG7\OAdata\BH091709\data\duans\nmr\01122016-duans\12\fid		
Frequency (MHz)	376.50	Nucleus	19F	Number of Transients	16	Origin	spect
Original Points Count	65536	Owner	nmr	Points Count	65536	Pulse Sequence	zgflqn
Receiver Gain	203.00	SW(cyclical) (Hz)	89285.71	Solvent	CHLOROFORM-d		
Spectrum Offset (Hz)	-37649.8359	Spectrum Type	STANDARD	Sweep Width (Hz)	89284.35	Temperature (degree C)	22.560



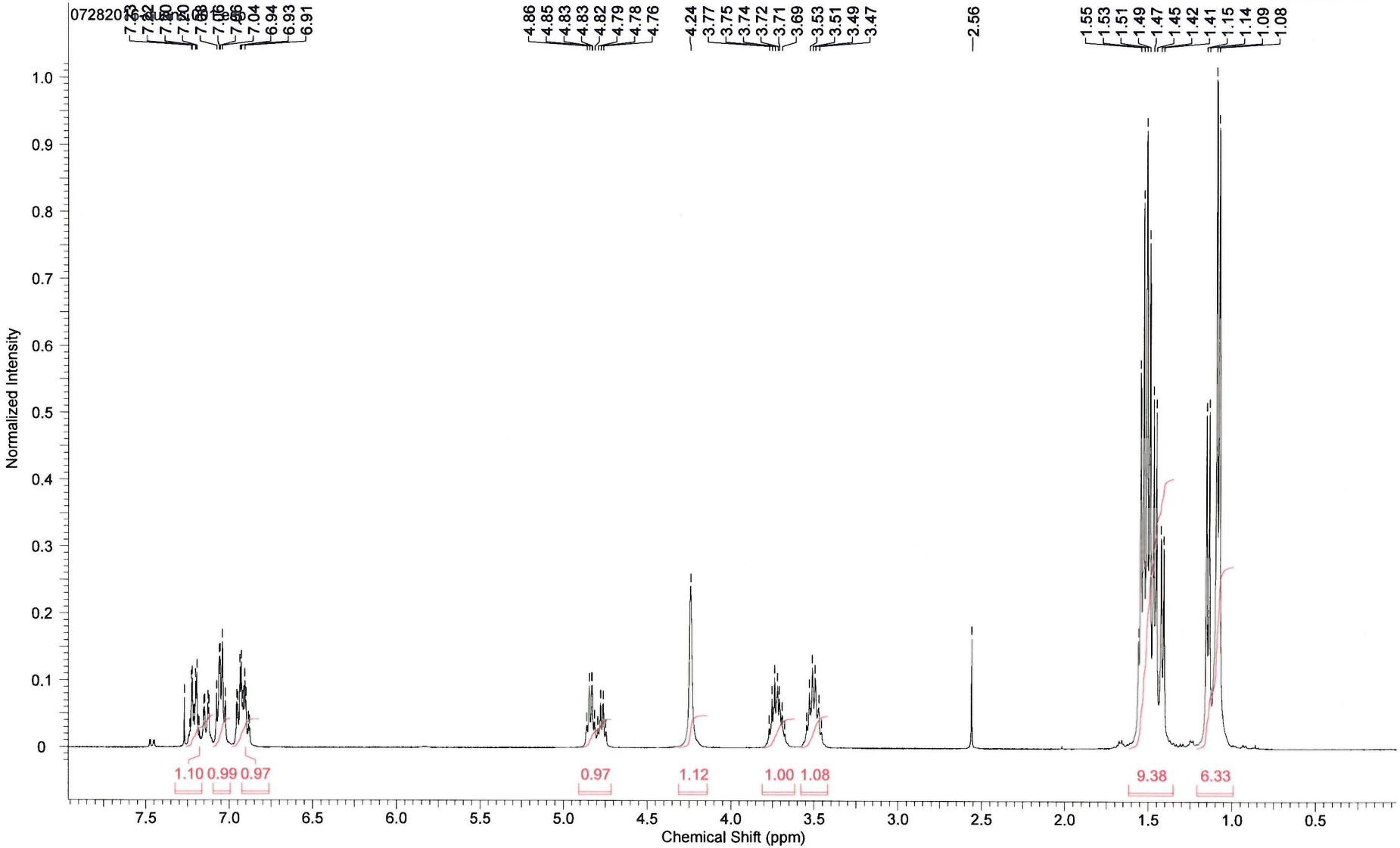
p-BPJ-Shen-[redacted]-Orbi1 #6-8 RT: 0.07-0.09 AV: 3 NL: 1.58E8
T: FTMS + p ESI Full ms [100.00-1000.00]



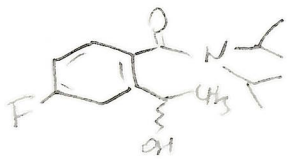
4-fluoro-2-(1-hydroxyethyl)-N,N-diisopropylbenzamide



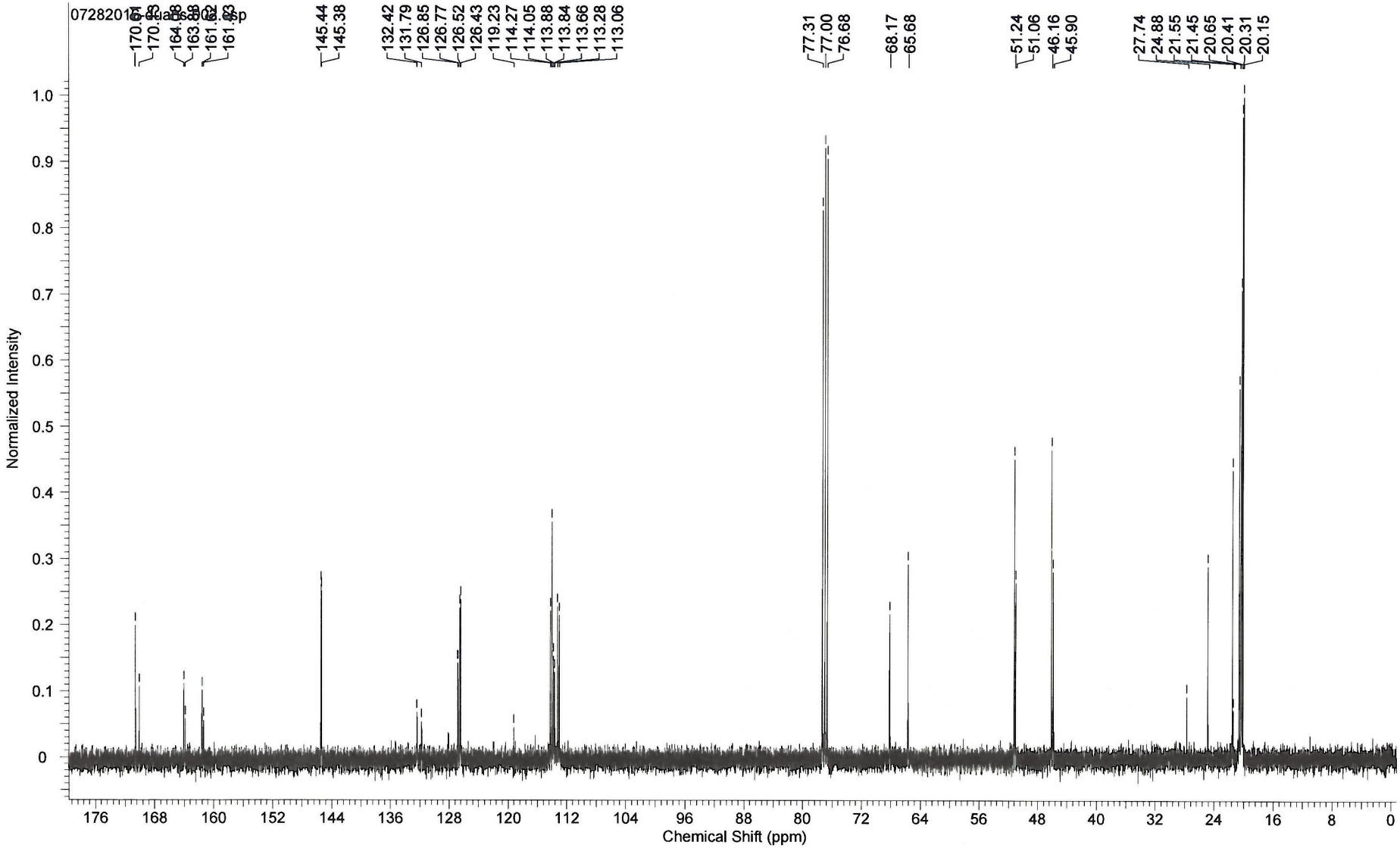
Number of Nuclei	0 H's						
Acquisition Time (sec)	3.9846	***Comment***	racemic alcohol PROTON CDCl3 /opt/topspin3.2 duans 53			***Date***	28 Jul 2016 11:51:28
Date Stamp	28 Jul 2016 11:51:28			***File Name***	\\SEG7\OAdata\BH091709\data\duans\nmr\07282016-duans\1\fid		
Frequency (MHz)	400.13	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	32.00	***SW(cyclical) (Hz)***	8223.68	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2464.6082	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	8223.43	***Temperature (degree C)***	25.260



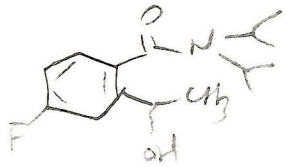
4-fluoro-2-(1-hydroxyethyl)-N,N-diisopropylbenzamide



Number of Nuclei	0 C's						
Acquisition Time (sec)	1.3631	Comment	racemic alcohol C13CPD_day CDCl3 /opt/topspin3.2 duans 53			Date	28 Jul 2016 12:04:16
Date Stamp	28 Jul 2016 12:04:16			File Name	\\SEG7\OAdata\BH091709\data\duans\nmr\07282016-duans\2\fid		
Frequency (MHz)	100.61	Nucleus	13C	Number of Transients	256	Origin	spect
Original Points Count	32768	Owner	nmr	Points Count	32768	Pulse Sequence	zgpg30
Receiver Gain	203.00	SW(cyclical) (Hz)	24038.46	Solvent	CHLOROFORM-d		
Spectrum Offset (Hz)	10051.0400	Spectrum Type	STANDARD	Sweep Width (Hz)	24037.73	Temperature (degree C)	25.160

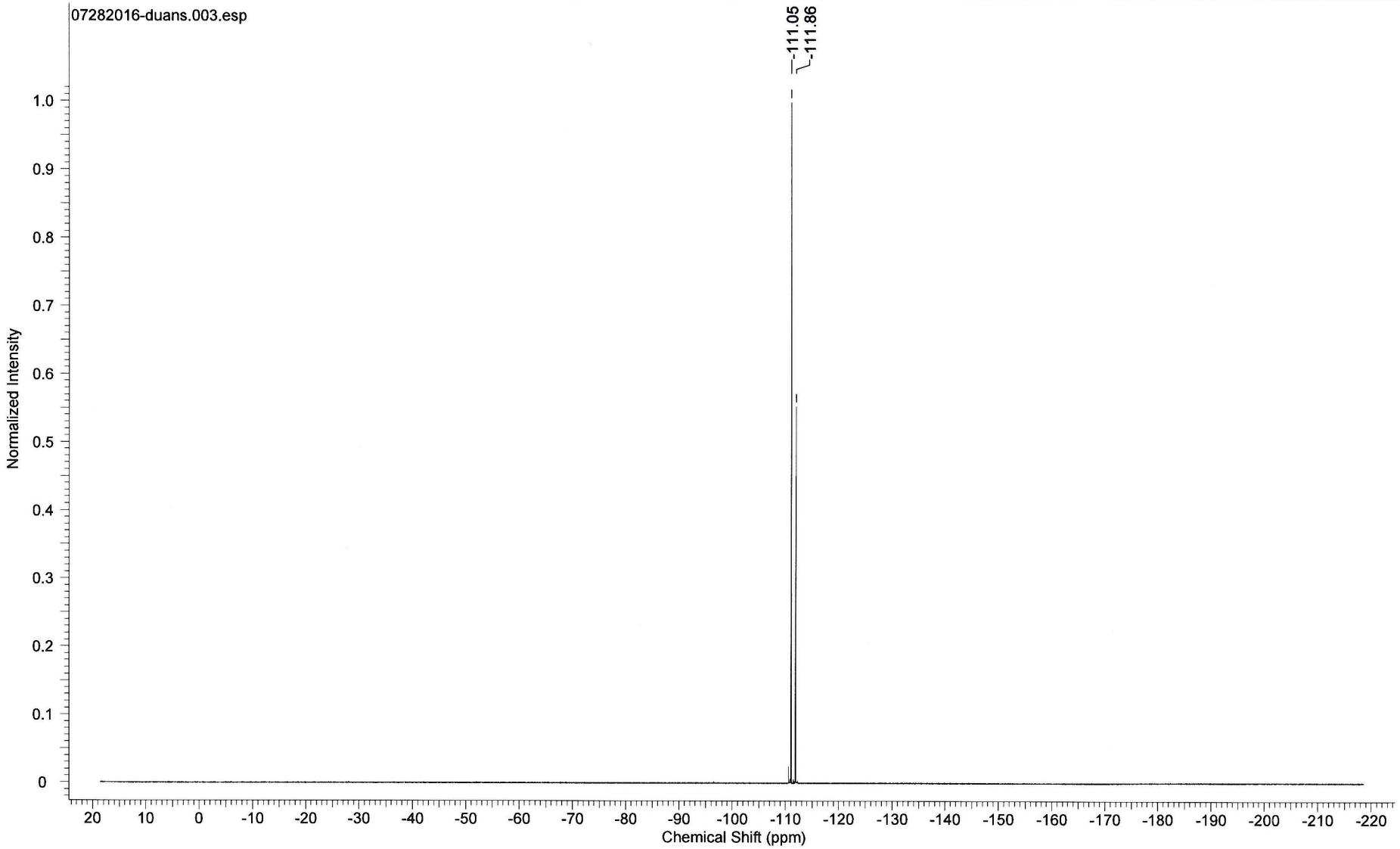


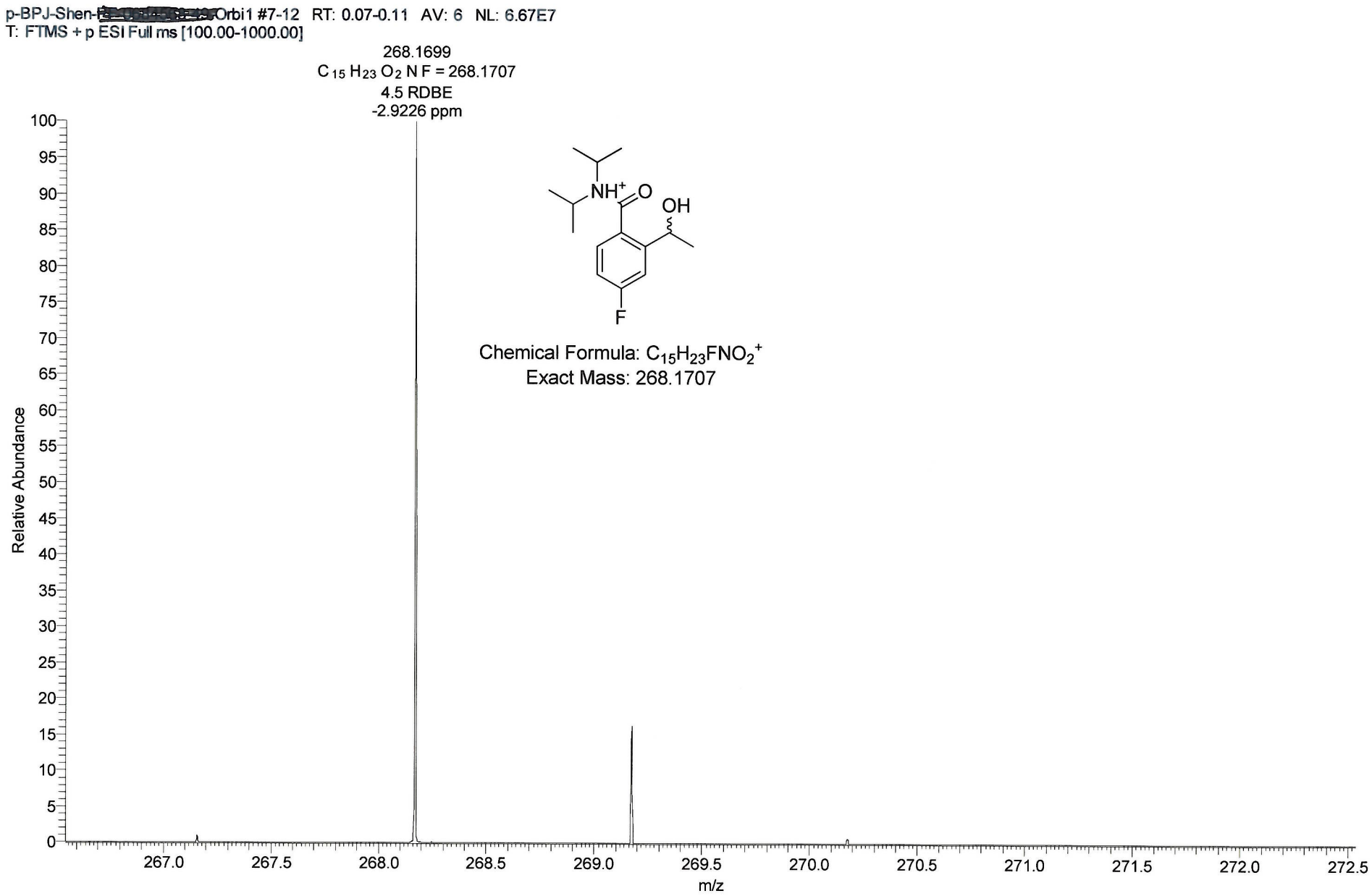
4-fluoro-2-(1-hydroxyethyl)-N,N-diisopropylbenzamide



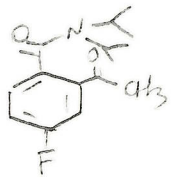
Number of Nuclei 0 F's

Acquisition Time (sec)	0.7340	**Comment**	racemic alcohol F19CPD CDCl3 /opt/topspin3.2 duans 53			**Date**	28 Jul 2016 12:06:24
Date Stamp	28 Jul 2016 12:06:24			**File Name**	\\SEG7\OAdata\BH091709\data\duans\nmr\07282016-duans\3\fid		
Frequency (MHz)	376.50	**Nucleus**	19F	**Number of Transients**	16	**Origin**	spect
Original Points Count	65536	**Owner**	nmr	**Points Count**	65536	**Pulse Sequence**	zgfhigqn.2
Receiver Gain	203.00	**SW(cyclical) (Hz)**	89285.71	**Solvent**	CHLOROFORM-d		
Spectrum Offset (Hz)	-37649.8359	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	89284.35	**Temperature (degree C)**	25.260



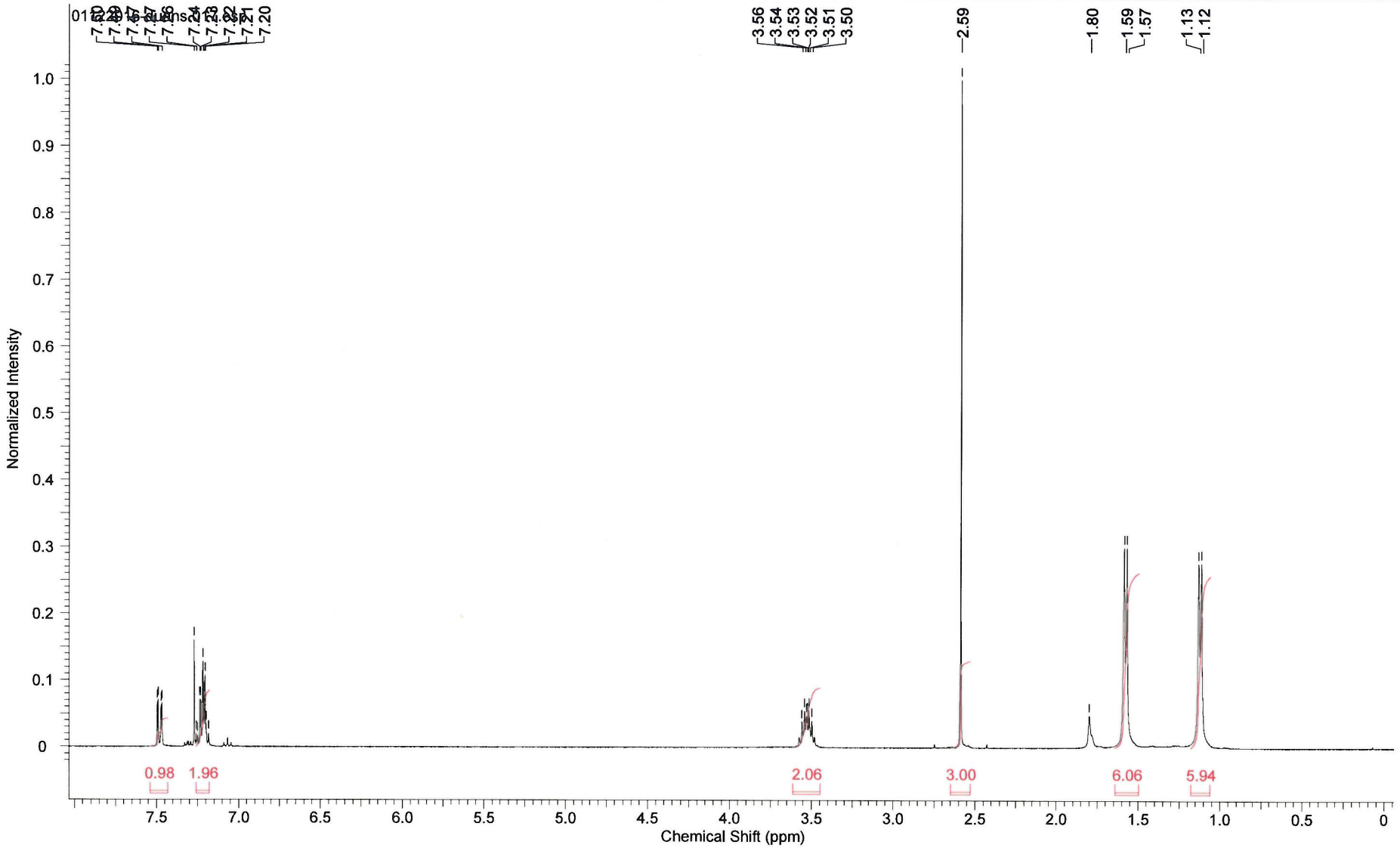

p-BPJ-Shen-[redacted]Orbi1 #7-12 RT: 0.07-0.11 AV: 6 NL: 6.67E7
T: FTMS + p ESI Full ms [100.00-1000.00]
268.1699
C 15 H23 O2 N F = 268.1707
4.5 RDBE
-2.9226 ppm
NH+
O
OH
F
Chemical Formula: C15H23FNO2+
Exact Mass: 268.1707
Relative Abundance
m/z
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
267.0
267.5
268.0
268.5
269.0
269.5
270.0
270.5
271.0
271.5
272.0
272.5

2-acetyl-4-fluoro-N,N-diisopropylbenzamide.

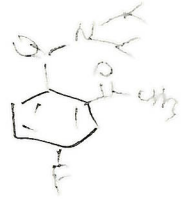


Number of Nuclei 0 H's

Acquisition Time (sec)	3.9846	**Comment**	[redacted] PROTON CDCl3 /opt/topspin3.2 duans 53			**Date**	12 Jan 2016 16:05:04
Date Stamp	12 Jan 2016 16:05:04			**File Name**	\\SEG7\OAdata\BH091709\data\duans\nmr\01122016-duans\17\fid		
Frequency (MHz)	400.13	**Nucleus**	1H	**Number of Transients**	16	**Origin**	spect
Original Points Count	32768	**Owner**	nmr	**Points Count**	32768	**Pulse Sequence**	zg30
Receiver Gain	181.00	**SW(cyclical) (Hz)**	8223.68	**Solvent**	CHLOROFORM-d		
Spectrum Offset (Hz)	2466.1143	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	8223.43	**Temperature (degree C)**	22.360

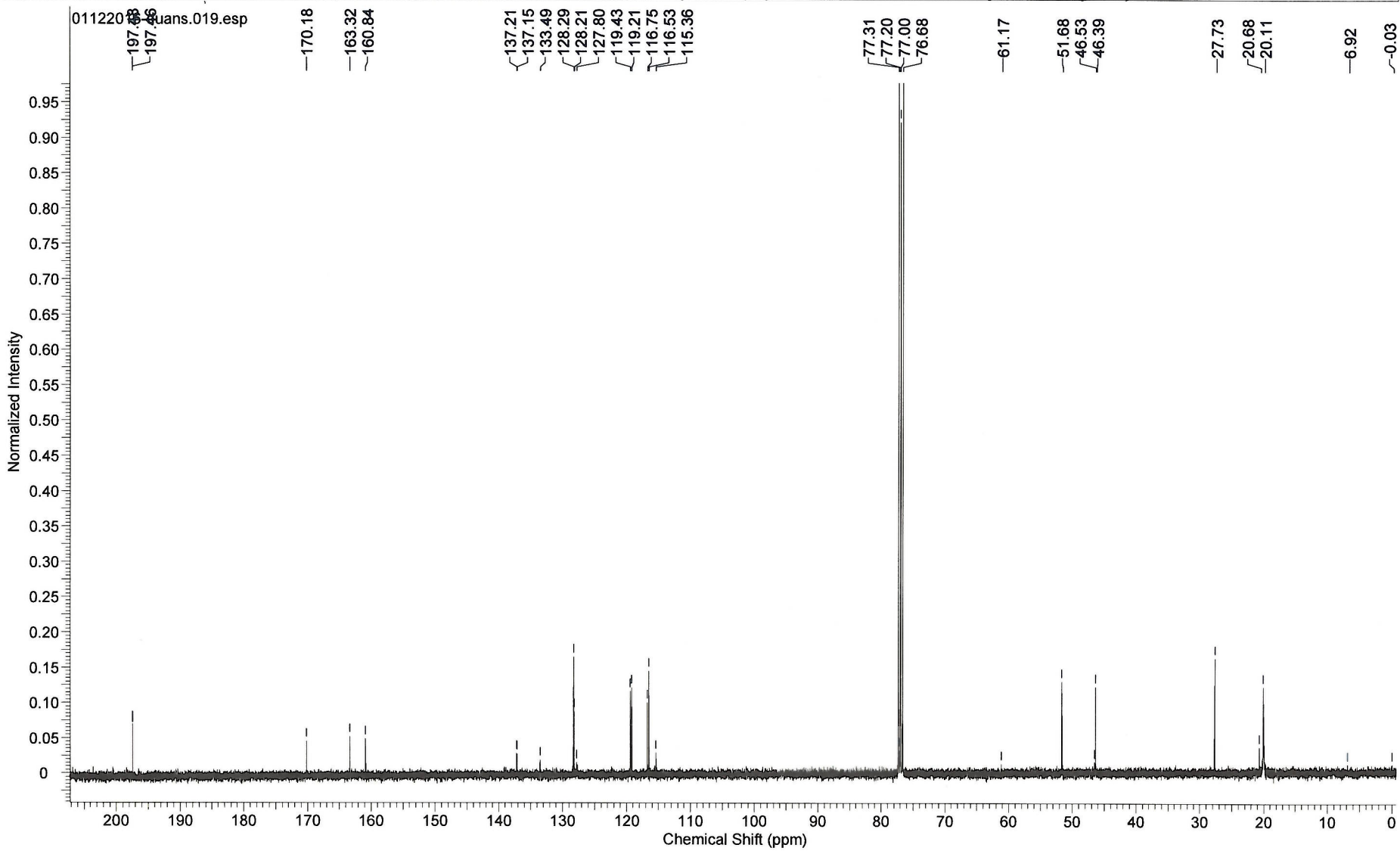


2-acetyl-4-fluoro-N,N-diisopropylbenzamide.



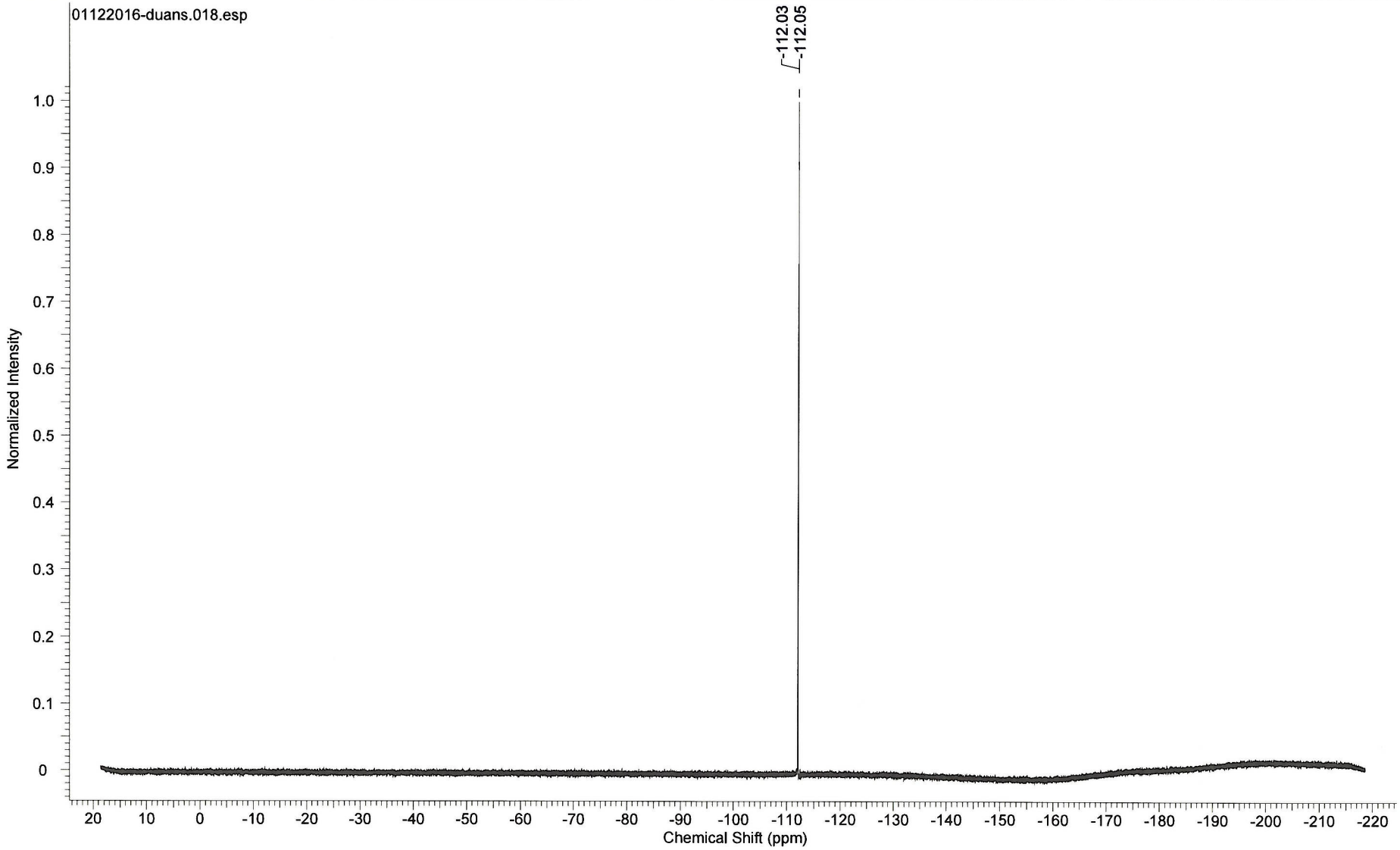
Number of Nuclei 0 C's

Acquisition Time (sec)	1.3631	**Comment**	[redacted] C13CPD_night CDCl3 /opt/topspin3.2 duans 53			**Date**	13 Jan 2016 19:27:44
Date Stamp	13 Jan 2016 19:27:44			**File Name**	\\SEG7\OAdata\BH091709\data\duans\nmr\01122016-duans\19\fid		
Frequency (MHz)	100.61	**Nucleus**	13C	**Number of Transients**	2048	**Origin**	spect
Original Points Count	32768	**Owner**	nmr	**Points Count**	32768	**Pulse Sequence**	zgpg30
Receiver Gain	203.00	**SW(cyclical) (Hz)**	24038.46	**Solvent**	CHLOROFORM-d		
Spectrum Offset (Hz)	10056.1748	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	24037.73	**Temperature (degree C)**	23.160

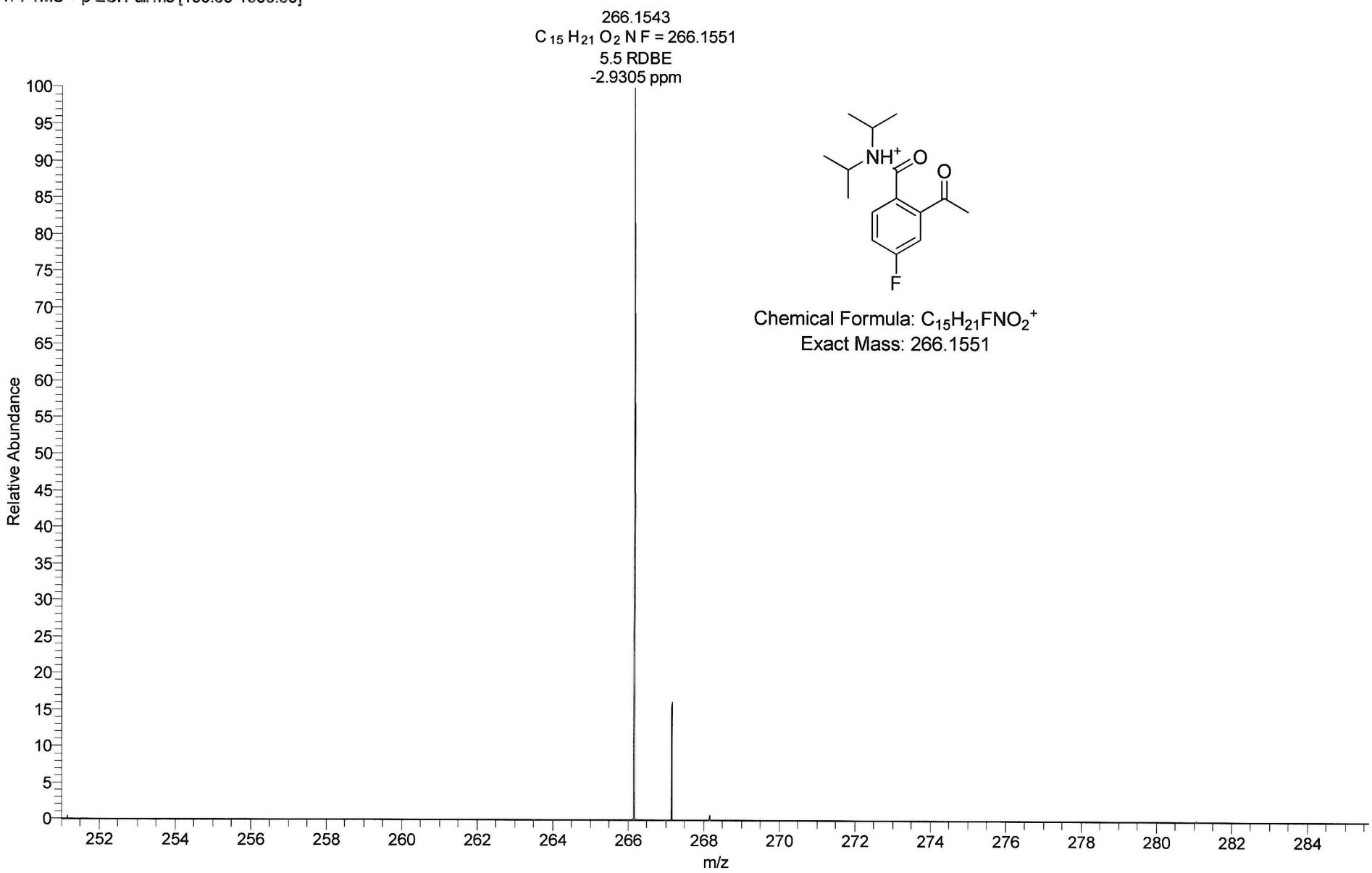


2-acetyl-4-fluoro-N,N-diisopropylbenzamide

Number of Nuclei	0 F's						
Acquisition Time (sec)	0.7340	**Comment**	[redacted] F19 CDCl3 /opt/topspin3.2 duans 53			**Date**	12 Jan 2016 16:07:12
Date Stamp	12 Jan 2016 16:07:12			**File Name**	\\SEG7\OAdata\BH091709\data\duans\nmr\01122016-duans\18\fid		
Frequency (MHz)	376.50	**Nucleus**	19F	**Number of Transients**	16	**Origin**	spect
Original Points Count	65536	**Owner**	nmr	**Points Count**	65536	**Pulse Sequence**	zgflqn
Receiver Gain	203.00	**SW(cyclical) (Hz)**	89285.71	**Solvent**	CHLOROFORM-d		
Spectrum Offset (Hz)	-37649.8359	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	89284.35	**Temperature (degree C)**	22.360

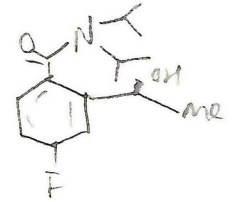


p-BPJ-Shen[redacted]-Orbi1 #7-9 RT: 0.08-0.09 AV: 3 NL: 4.36E7
T: FTMS + p ESI Full ms [100.00-1000.00]



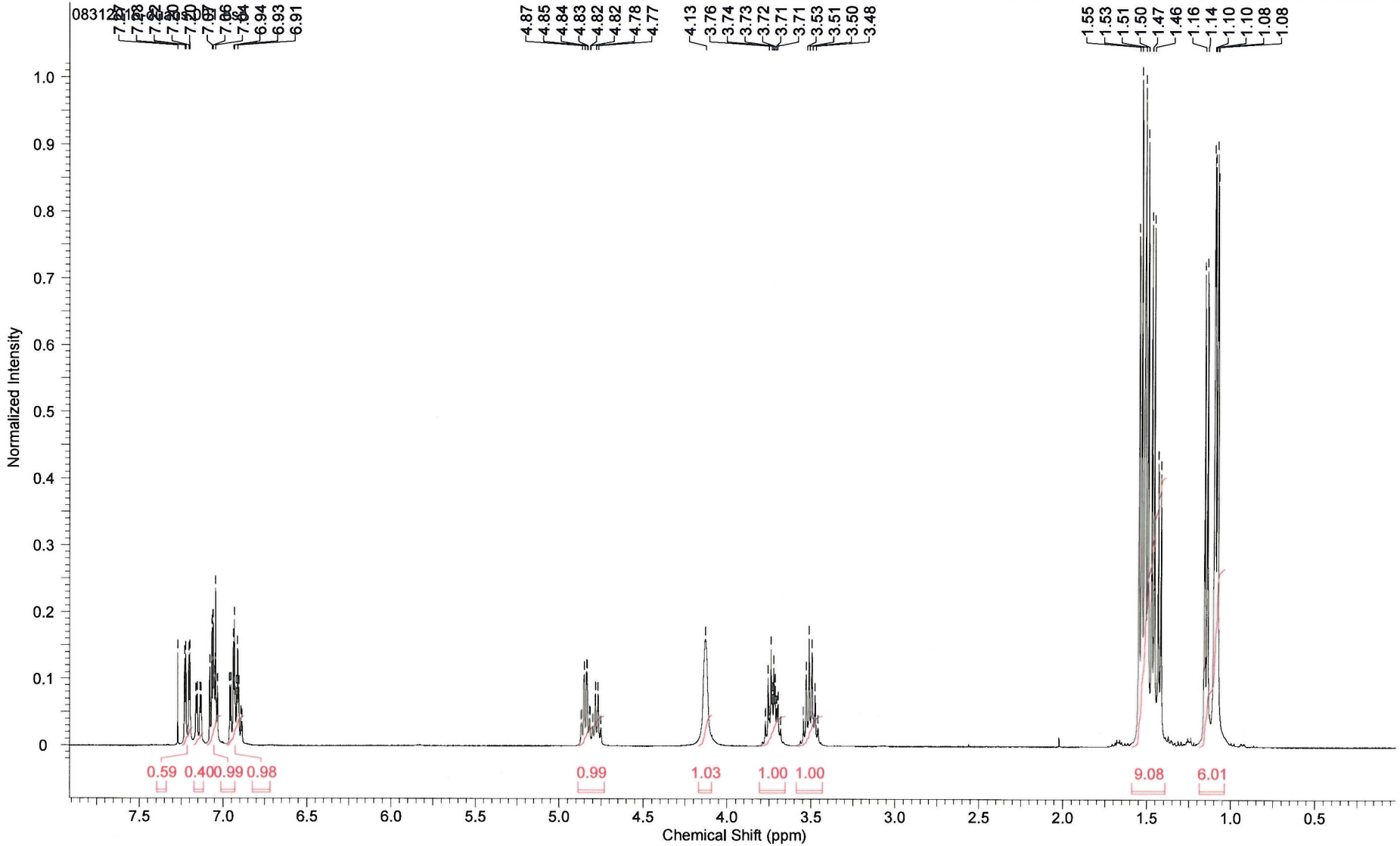
Chemical Formula: $C_{15}H_{21}FNO_2^+$
Exact Mass: 266.1551

(S)-4-fluoro-2-(1-hydroxyethyl)-N,N-diisopropylbenzamide

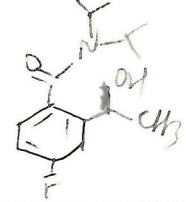


Number of Nuclei 0 H's

Acquisition Time (sec)	3.9846	**Comment**	[redacted]-PROTON CDCl3 /opt/topspin3.2 duans 36			**Date**	31 Aug 2016 12:04:16
Date Stamp	31 Aug 2016 12:04:16			**File Name**	\\SEG7\OAdata\BH091709\data\duans\nmr\08312016-duans\1\fid		
Frequency (MHz)	400.13	**Nucleus**	1H	**Number of Transients**	16	**Origin**	spect
Original Points Count	32768	**Owner**	nmr	**Points Count**	32768	**Pulse Sequence**	zg30
Receiver Gain	36.00	**SW(cyclical) (Hz)**	8223.68	**Solvent**	CHLOROFORM-d		
Spectrum Offset (Hz)	2464.1062	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	8223.43	**Temperature (degree C)**	25.160

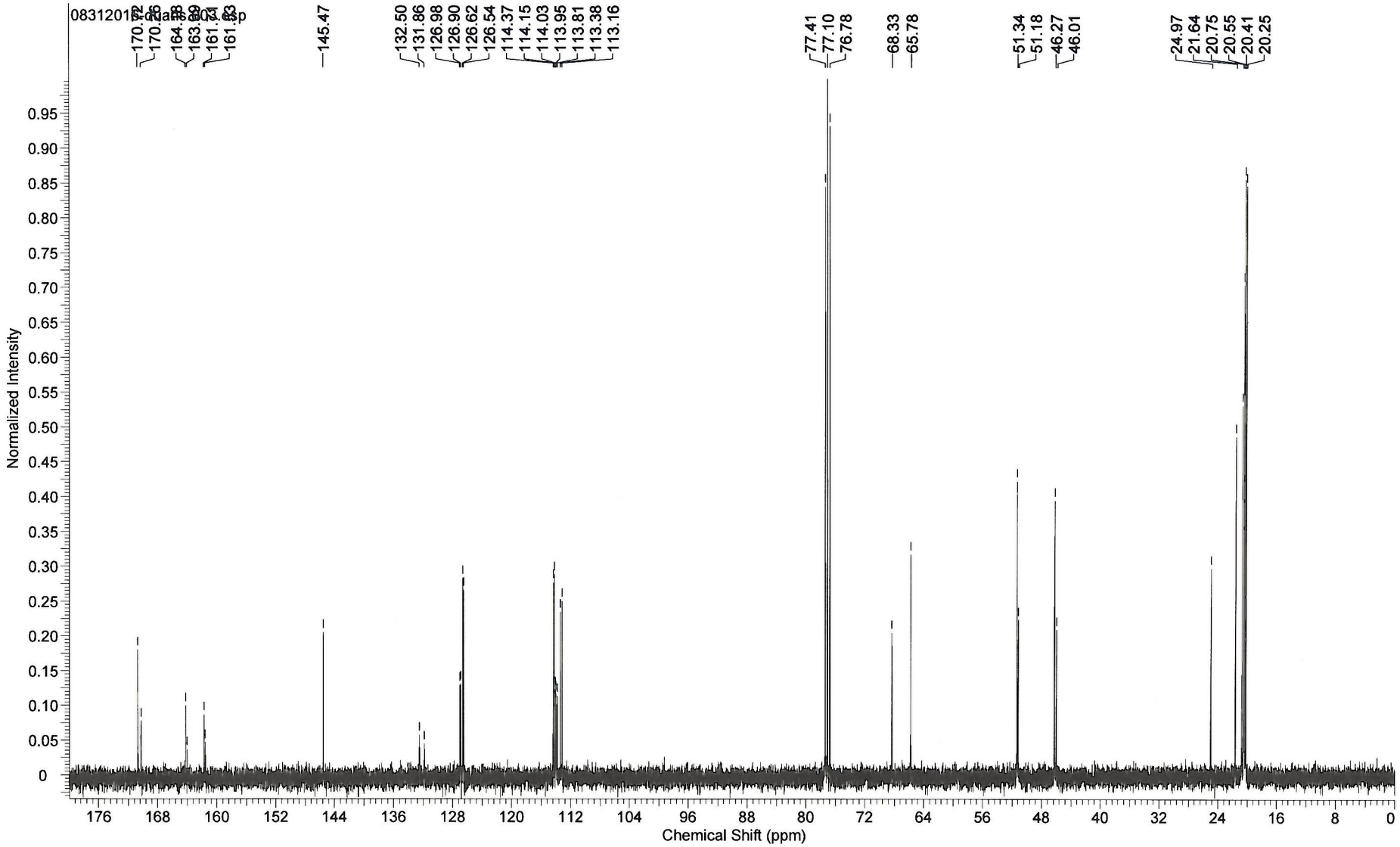


(S)-4-fluoro-2-(1-hydroxyethyl)-N,N-diisopropylbenzamide

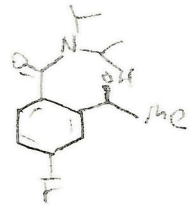


Number of Nuclei 0 C's

Acquisition Time (sec)	1.3631	**Comment**	[redacted] C13CPD_day CDCl3 /opt/topspin3.2 duans 36			**Date**	31 Aug 2016 12:21:20
Date Stamp	31 Aug 2016 12:21:20			**File Name**	\\SEG7\OAdata\BH091709\data\duans\nmr\08312016-duans\3\fid		
Frequency (MHz)	100.61	**Nucleus**	13C	**Number of Transients**	256	**Origin**	spect
Original Points Count	32768	**Owner**	nmr	**Points Count**	32768	**Pulse Sequence**	zgpg30
Receiver Gain	203.00	**SW(cyclical) (Hz)**	24038.46	**Solvent**	CHLOROFORM-d		
Spectrum Offset (Hz)	10060.8047	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	24037.73	**Temperature (degree C)**	25.160

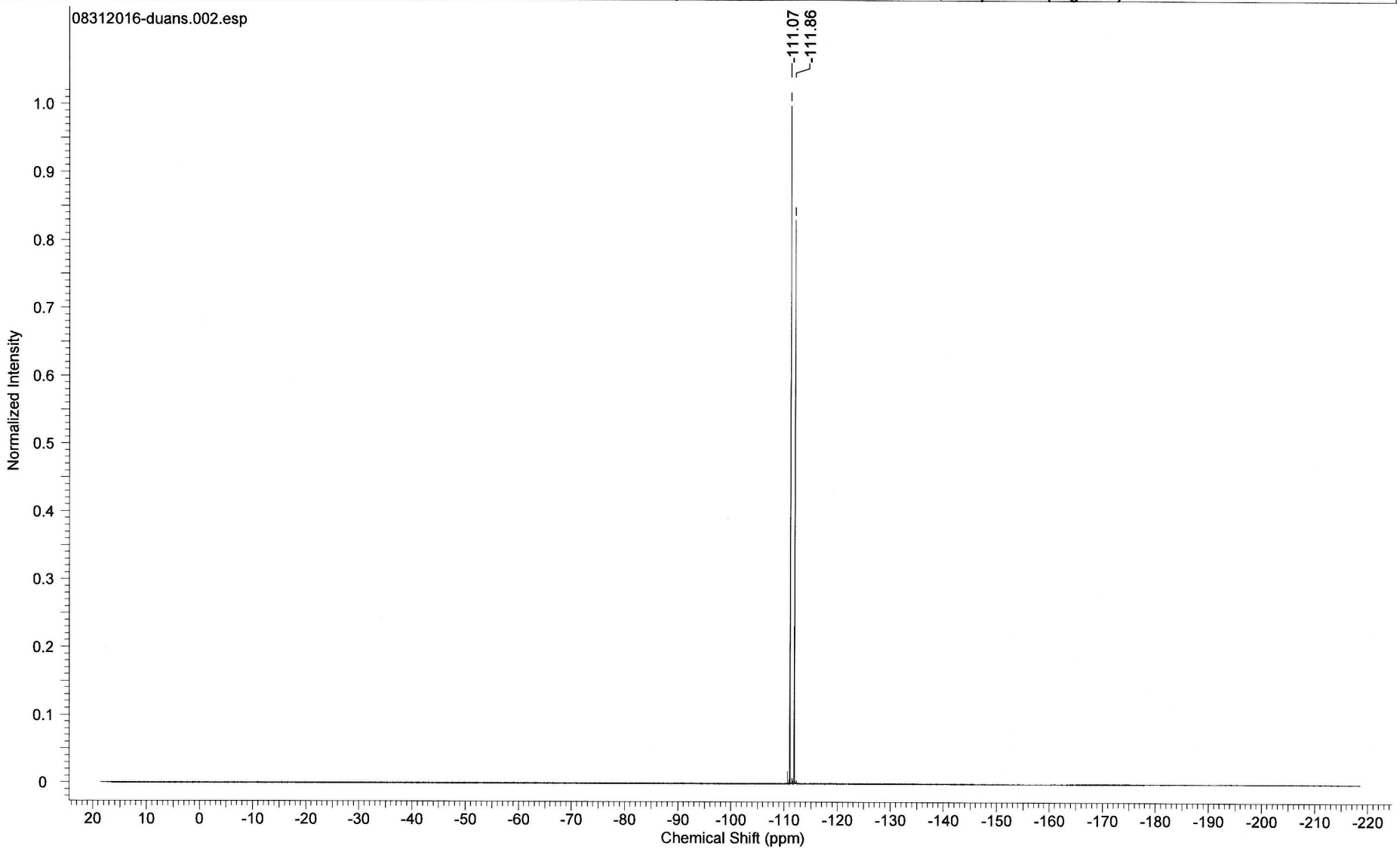


(S)-4-fluoro-2-(1-hydroxyethyl)-N,N-diisopropylbenzamide

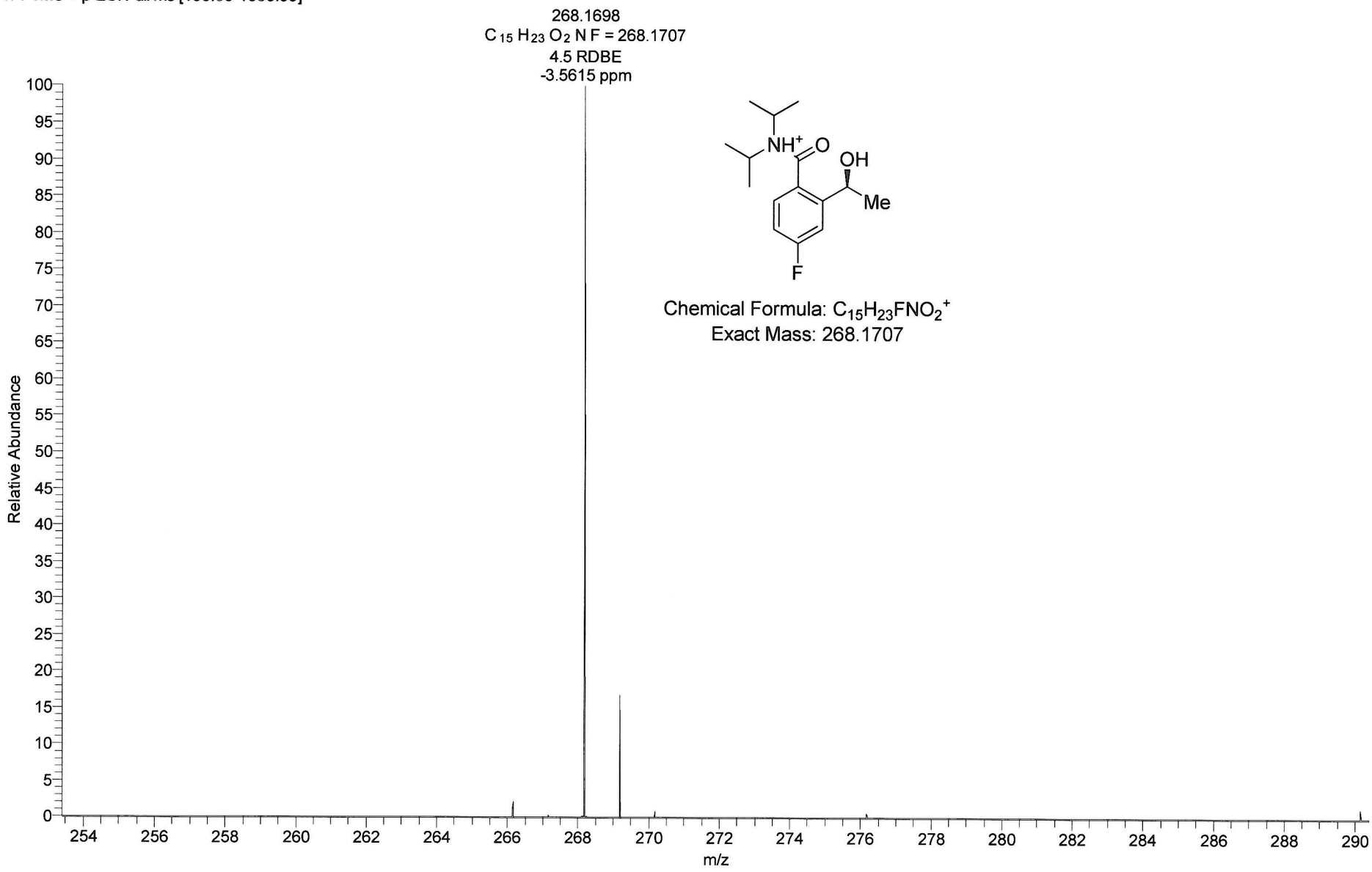


Number of Nuclei 0 F's

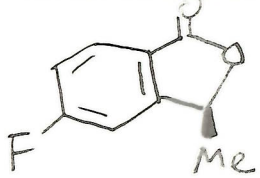
Acquisition Time (sec)	0.7340	**Comment**	[redacted] F19CPD CDCl3 /opt/topspin3.2 duans 36			**Date**	31 Aug 2016 12:08:32
Date Stamp	31 Aug 2016 12:08:32			**File Name**	\\SEG7\OAdata\BH091709\data\duans\nmr\08312016-duans\2\fid		
Frequency (MHz)	376.50	**Nucleus**	19F	**Number of Transients**	16	**Origin**	spect
Original Points Count	65536	**Owner**	nmr	**Points Count**	65536	**Pulse Sequence**	zgfhigqn.2
Receiver Gain	203.00	**SW(cyclical) (Hz)**	89285.71	**Solvent**	CHLOROFORM-d		
Spectrum Offset (Hz)	-37649.8359	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	89284.35	**Temperature (degree C)**	25.260



p-BPJ-Shen[redacted]-Orbi1 #7-10 RT: 0.08-0.10 AV: 4 NL: 2.20E8
T: FTMS + p ESI Full ms [100.00-1000.00]

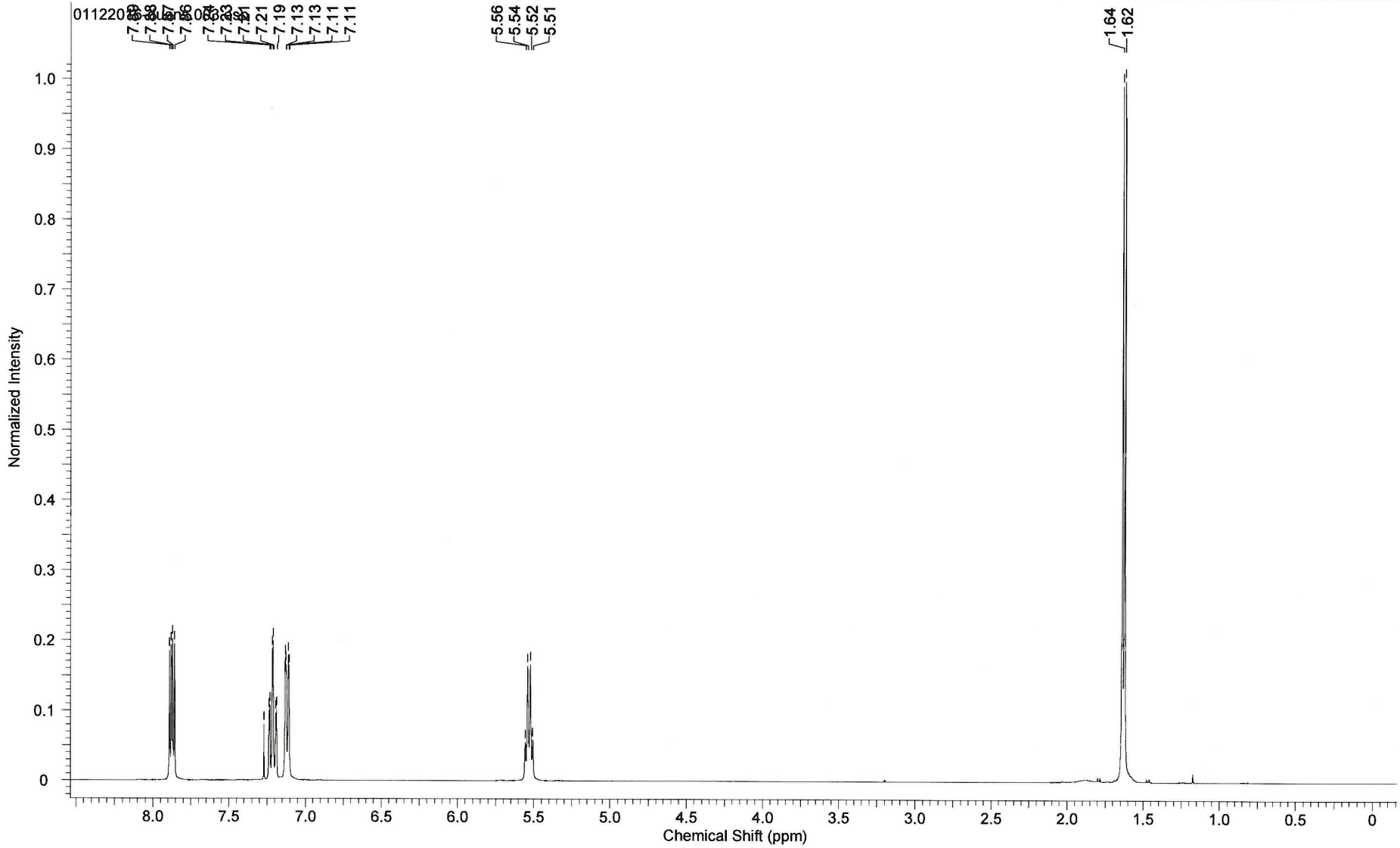


(S)-5-fluoro-3-methylisobenzofuran-1(3H)-one

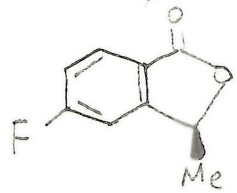


Number of Nuclei 0 H's

Acquisition Time (sec)	3.9846	**Comment**	[redacted] PROTON CDCl3 /opt/topspin3.2 duans 48			**Date**	12 Jan 2016 15:22:24
Date Stamp	12 Jan 2016 15:22:24			**File Name**	\\SEG7\OAdata\BH091709\data\duans\nmr\01122016-duans\3\fid		
Frequency (MHz)	400.13	**Nucleus**	1H	**Number of Transients**	16	**Origin**	spect
Original Points Count	32768	**Owner**	nmr	**Points Count**	32768	**Pulse Sequence**	zg30
Receiver Gain	71.80	**SW(cyclical) (Hz)**	8223.68	**Solvent**	CHLOROFORM-d		
Spectrum Offset (Hz)	2466.1140	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	8223.43	**Temperature (degree C)**	22.460

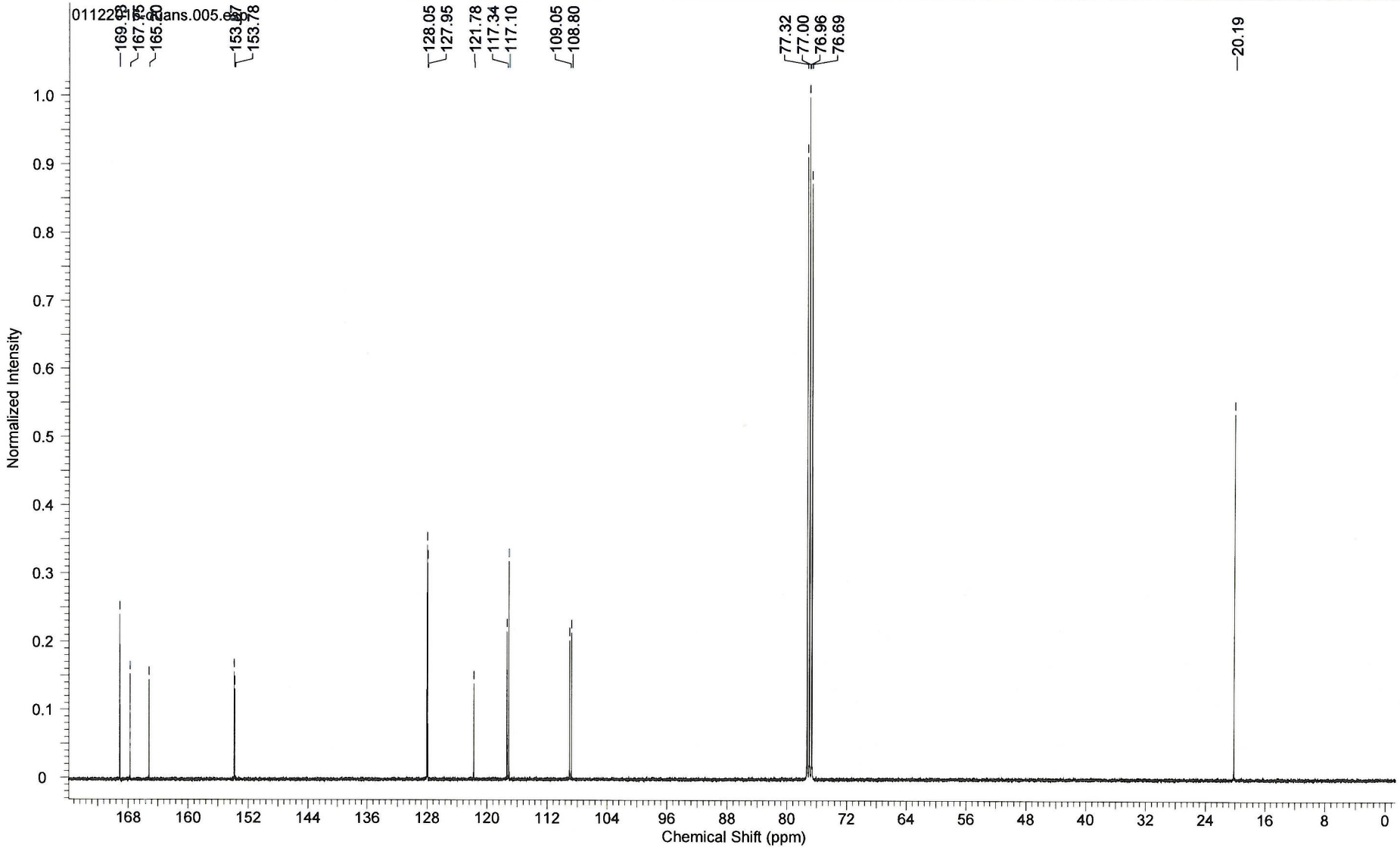


(S)-5-fluoro-3-methylisobenzofuran-1(3H)-one

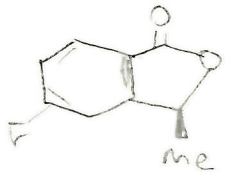


Number of Nuclei 0 C's

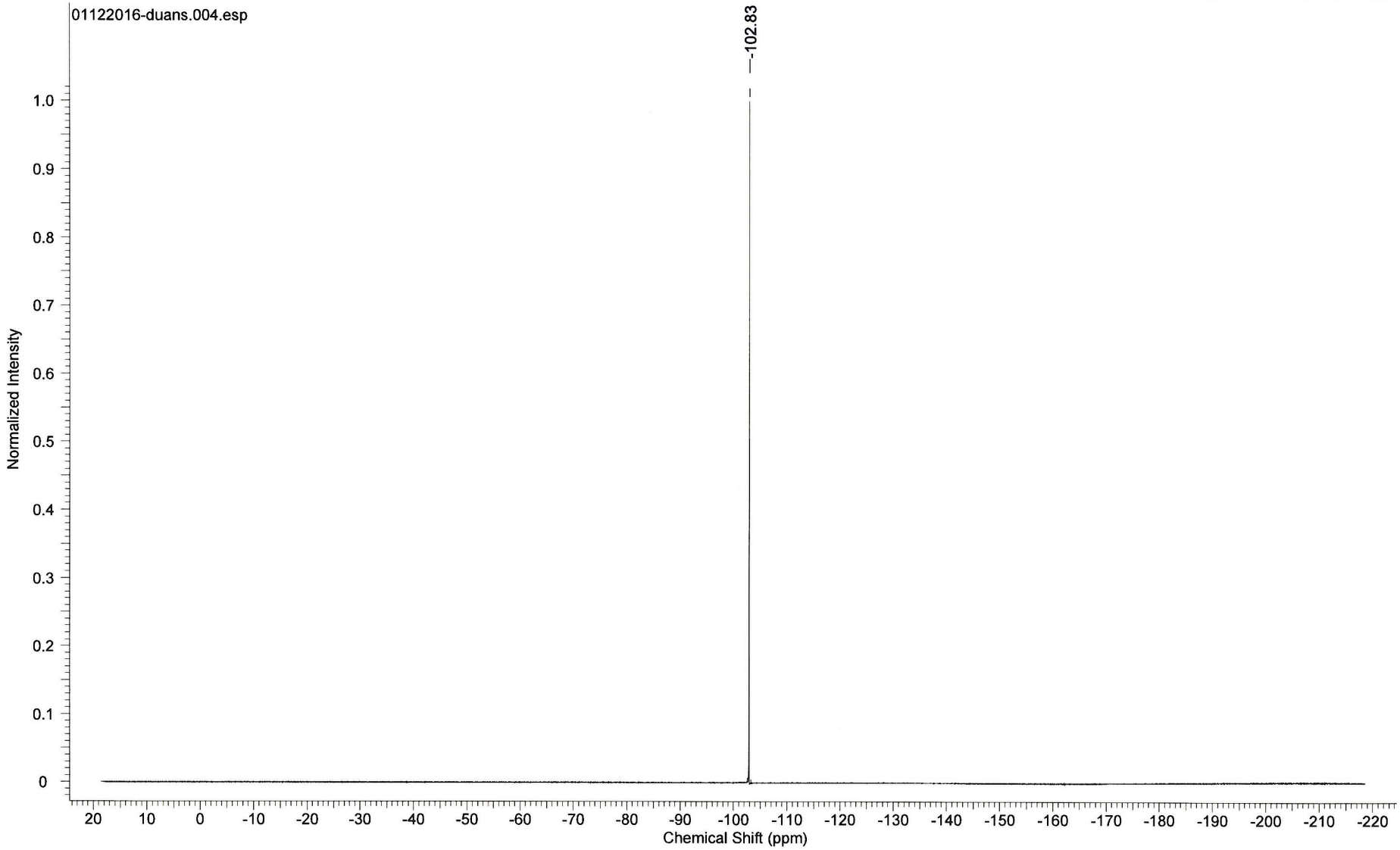
Acquisition Time (sec)	1.3631	**Comment**	[redacted]C13CPD_night CDCl3 /opt/topspin3.2 duans 48			**Date**	12 Jan 2016 23:41:36
Date Stamp	12 Jan 2016 23:41:36			**File Name**	\\SEG7\OAdata\BH091709\data\duans\nmr\01122016-duans\5\fid		
Frequency (MHz)	100.61	**Nucleus**	13C	**Number of Transients**	4096	**Origin**	spect
Original Points Count	32768	**Owner**	nmr	**Points Count**	32768	**Pulse Sequence**	zgpg30
Receiver Gain	203.00	**SW(cyclical) (Hz)**	24038.46	**Solvent**	CHLOROFORM-d		
Spectrum Offset (Hz)	10049.5732	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	24037.73	**Temperature (degree C)**	23.260



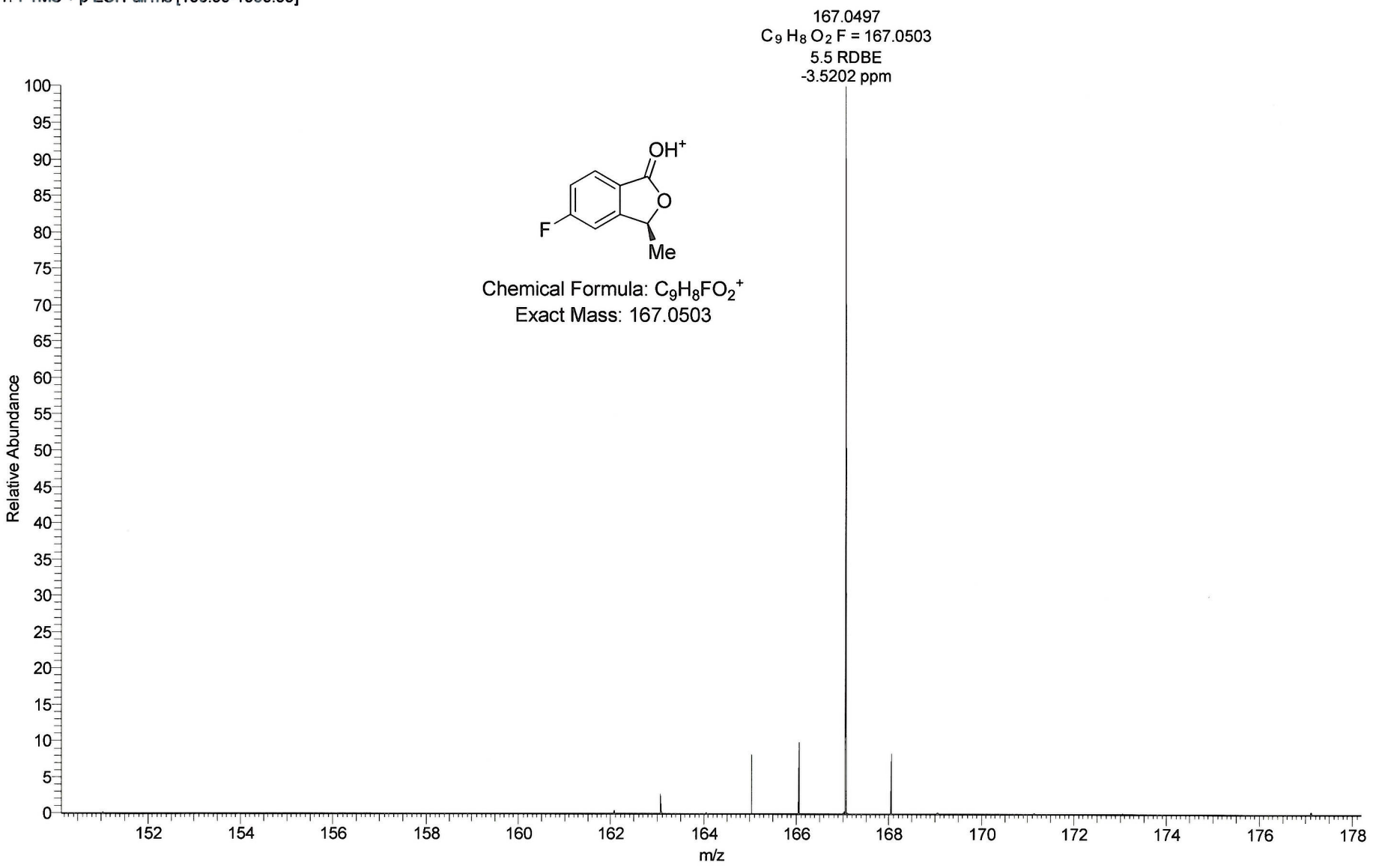
(S)-5-fluoro-3-methylisobenzofuran-1(3H)-one



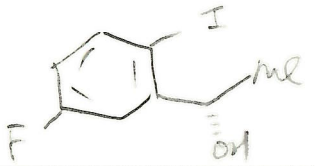
Number of Nuclei	0 F's						
Acquisition Time (sec)	0.7340	***Comment***	[redacted]F19 CDCl3 /opt/topspin3.2 duans 48			***Date***	12 Jan 2016 15:26:40
Date Stamp	12 Jan 2016 15:26:40			***File Name***	\\SEG7\OAdata\BH091709\data\duans\nmr\01122016-duans\4\fid		
Frequency (MHz)	376.50	***Nucleus***	19F	***Number of Transients***	16	***Origin***	spect
Original Points Count	65536	***Owner***	nmr	***Points Count***	65536	***Pulse Sequence***	zgflqn
Receiver Gain	203.00	***SW(cyclical) (Hz)***	89285.71	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	-37649.8359	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	89284.35	***Temperature (degree C)***	22.460



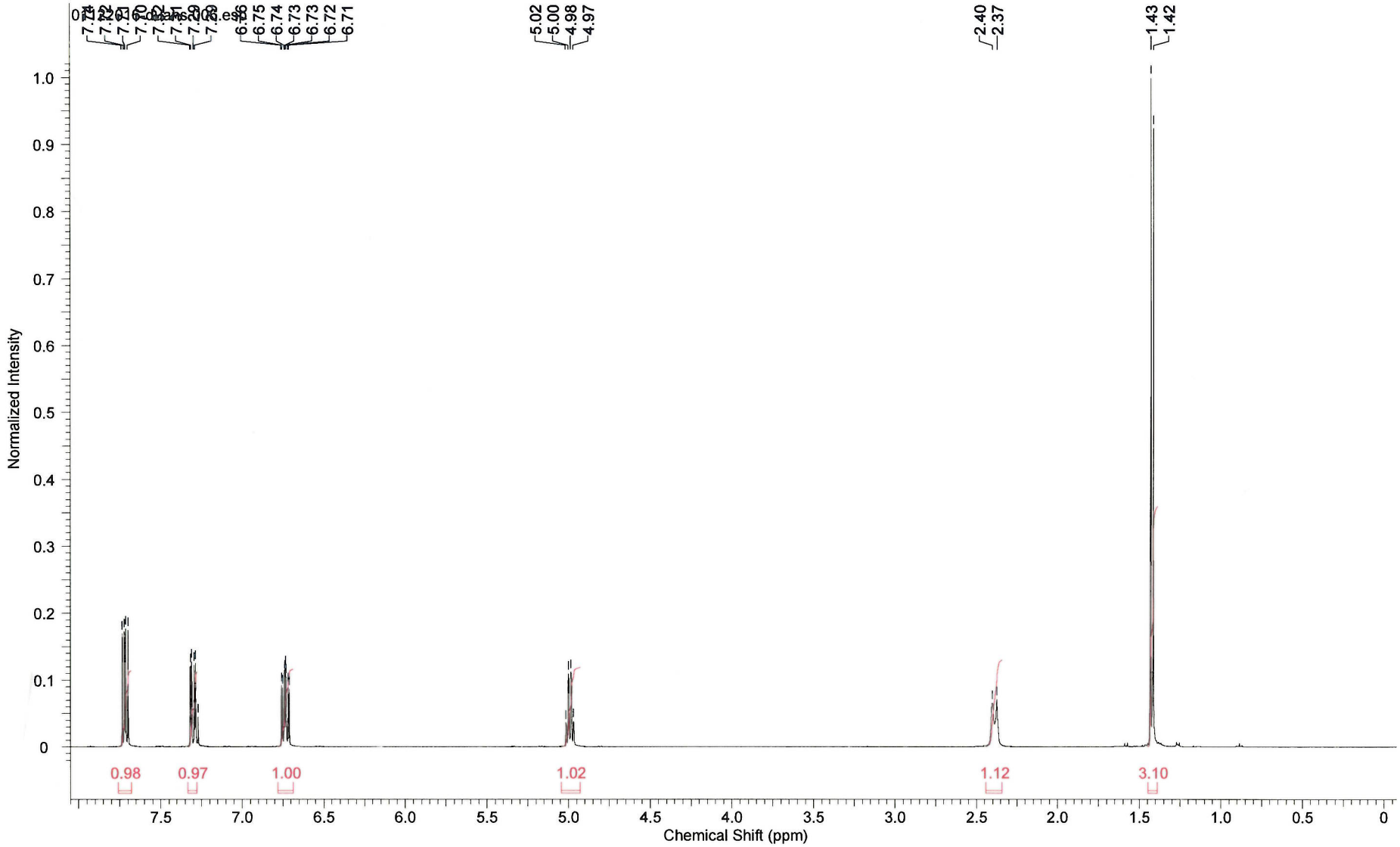
p-BPJ-Shen-[redacted]-Orbi2 #6-9 RT: 0.07-0.09 AV: 4 NL: 1.63E7
T: FTMS + p ESI Full ms [100.00-1000.00]



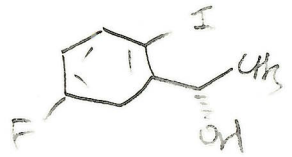
(S)-1-(5-fluoro-2-iodophenyl)ethan-1-ol



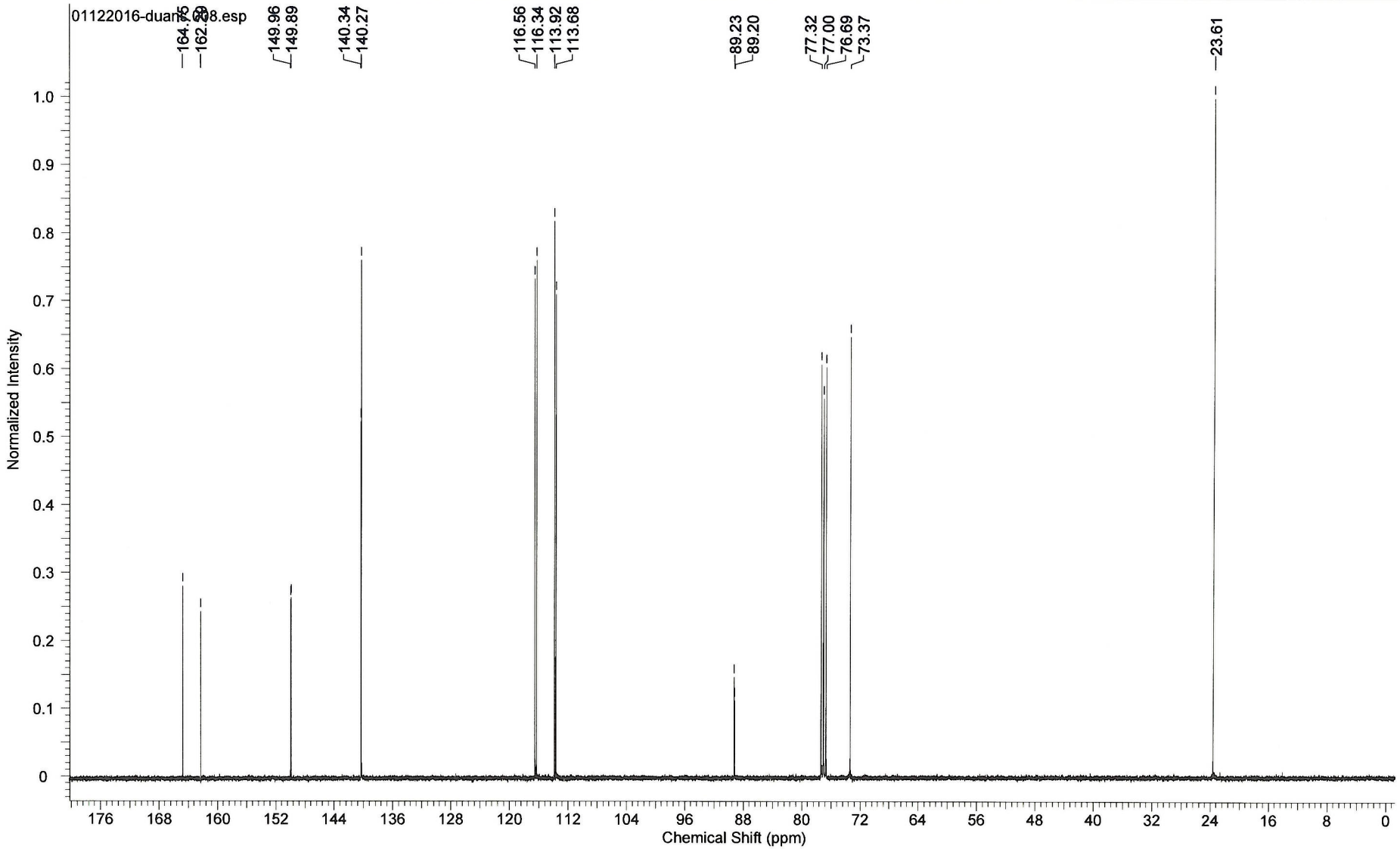
Number of Nuclei	0 H's						
Acquisition Time (sec)	3.9846	***Comment***	[redacted] PROTON CDCl3 /opt/topspin3.2 duans 49			***Date***	12 Jan 2016 15:33:04
Date Stamp	12 Jan 2016 15:33:04			***File Name***	\\SEG7\OAdata\BH091709\data\duans\nmr\01122016-duans\6\fid		
Frequency (MHz)	400.13	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	57.00	***SW(cyclical) (Hz)***	8223.68	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2466.1140	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	8223.43	***Temperature (degree C)***	22.560



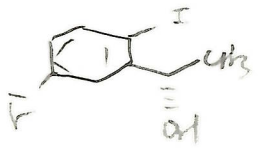
(S)-1-(5-fluoro-2-iodophenyl)ethan-1-ol



Number of Nuclei	0 C's						
Acquisition Time (sec)	1.3631	***Comment***	[redacted] C13CPD_night CDCl3 /opt/topspin3.2 duans 49			***Date***	13 Jan 2016 01:09:04
Date Stamp	13 Jan 2016 01:09:04			***File Name***	\\SEG7\OAdata\BH091709\data\duans\nmr\01122016-duans\8\fid		
Frequency (MHz)	100.61	***Nucleus***	13C	***Number of Transients***	2048	***Origin***	spect
Original Points Count	32768	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	203.00	***SW(cyclical) (Hz)***	24038.46	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10053.2402	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24037.73	***Temperature (degree C)***	23.460



(S)-1-(5-fluoro-2-iodophenyl)ethan-1-ol



Number of Nuclei	0 F's						
Acquisition Time (sec)	0.7340	Comment	[redacted] F19 CDCl3 /opt/topspin3.2 duans 49			Date	12 Jan 2016 15:35:12
Date Stamp	12 Jan 2016 15:35:12			File Name	\\SEG7\OAdata\BH091709\data\duans\nmr\01122016-duans\7\fid		
Frequency (MHz)	376.50	Nucleus	19F	Number of Transients	16	Origin	spect
Original Points Count	65536	Owner	nmr	Points Count	65536	Pulse Sequence	zgflqn
Receiver Gain	203.00	SW(cyclical) (Hz)	89285.71	Solvent	CHLOROFORM-d		
Spectrum Offset (Hz)	-37649.8359	Spectrum Type	STANDARD	Sweep Width (Hz)	89284.35	Temperature (degree C)	22.660