Supporting Information

Process Research and Impurity Control Strategy of Esketamine

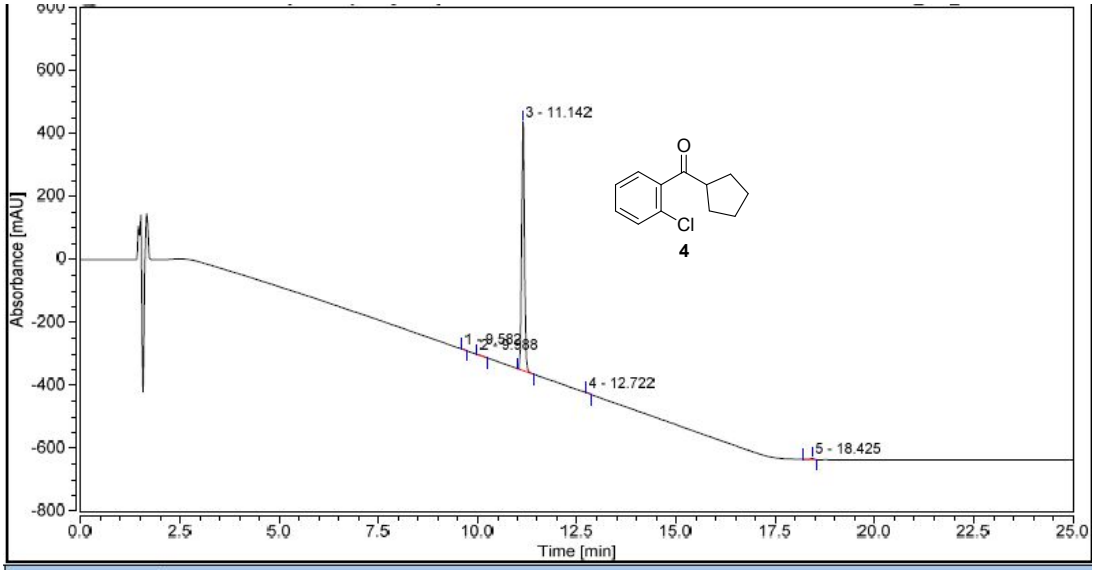
Shenghua Gao,† Xuezhi Gao,† Zhezhou Yang,,† and Fuli Zhang*,†*

†Shanghai Institute of Pharmaceutical Industry, China State Institute of Pharmaceutical Industry, 285 Gebaini Road, Pudong District, Shanghai 201203, China

Table of Contents

1.1 HPLC data, HRMS, and NMR of Compound 4

1.1.1 HPLC data after vacuum distillation

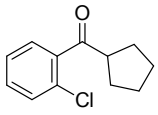


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
n.a.	MF	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
1		9.582	0.063	0.000	0.10	0.00	n.a.
2		9.988	0.178	0.000	0.28	0.00	n.a.
3		11.142	63.323	792.191	98.74	99.47	n.a.
4		12.722	0.117	0.000	0.18	0.00	n.a.
n.a.	KDY	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
5		18.425	0.448	4.219	0.70	0.53	n.a.
Total:			**64.129**	**796.410**	**100.00**	**100.00**	

1.1.2 HRMS

Elemental Composition Report **Page 1**

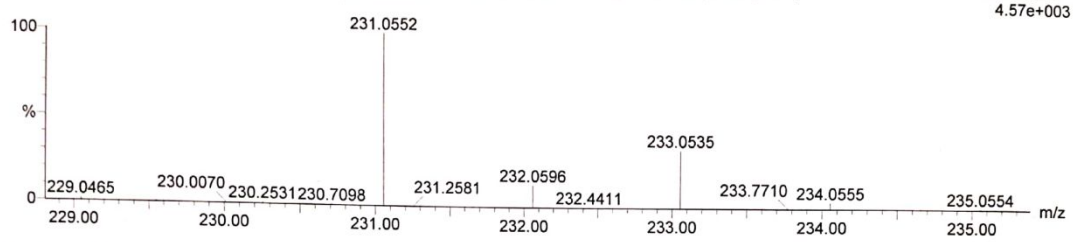


Exact Mass: 208.07

Multiple Mass Analysis: 3 mass(es) processed
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

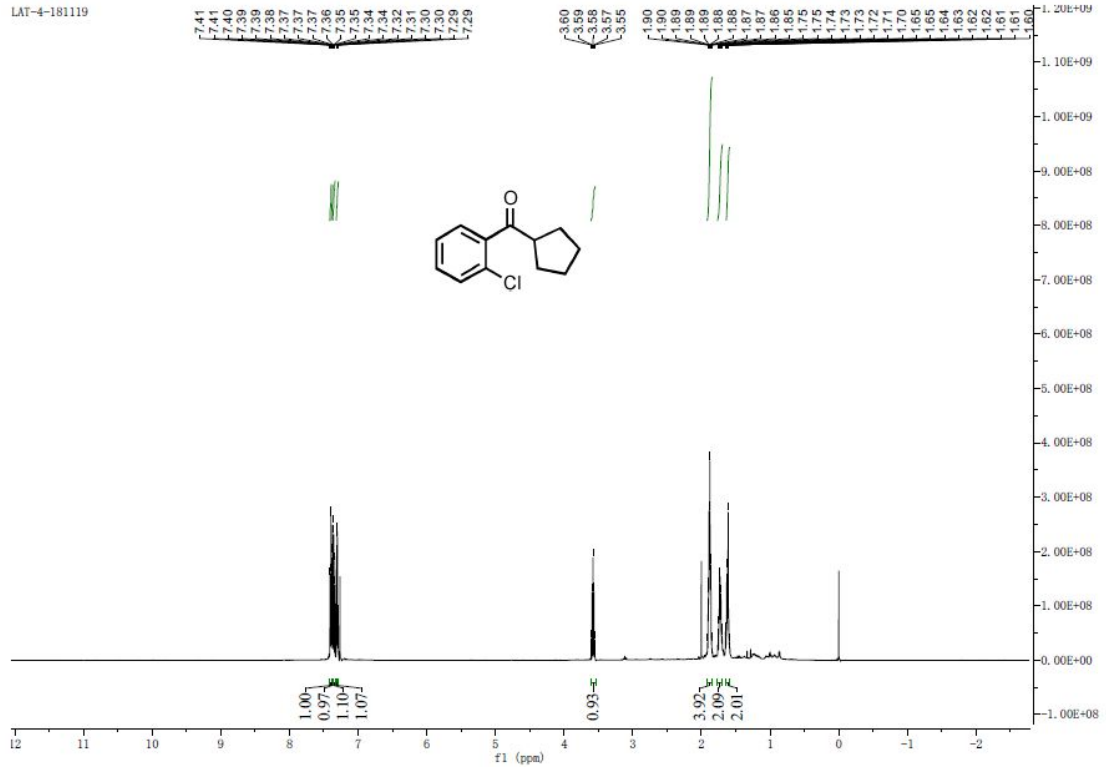
Monoisotopic Mass, Even Electron Ions
175 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-30 O: 0-1 Na: 1-1 35Cl: 0-3 37Cl: 0-3

SIPI
4-190910
Q-Tof micro
YA019
15:04:16,17-Oct-2019
Q19-1426HR 19 (0.352) AM (Cen,2, 80.00, Ar,5000.0,255.10,2.00); Sm (Mn, 2x3.00); Sb (1,5.00); Cm (18:23)
TOF MS ES+
4.57e+003

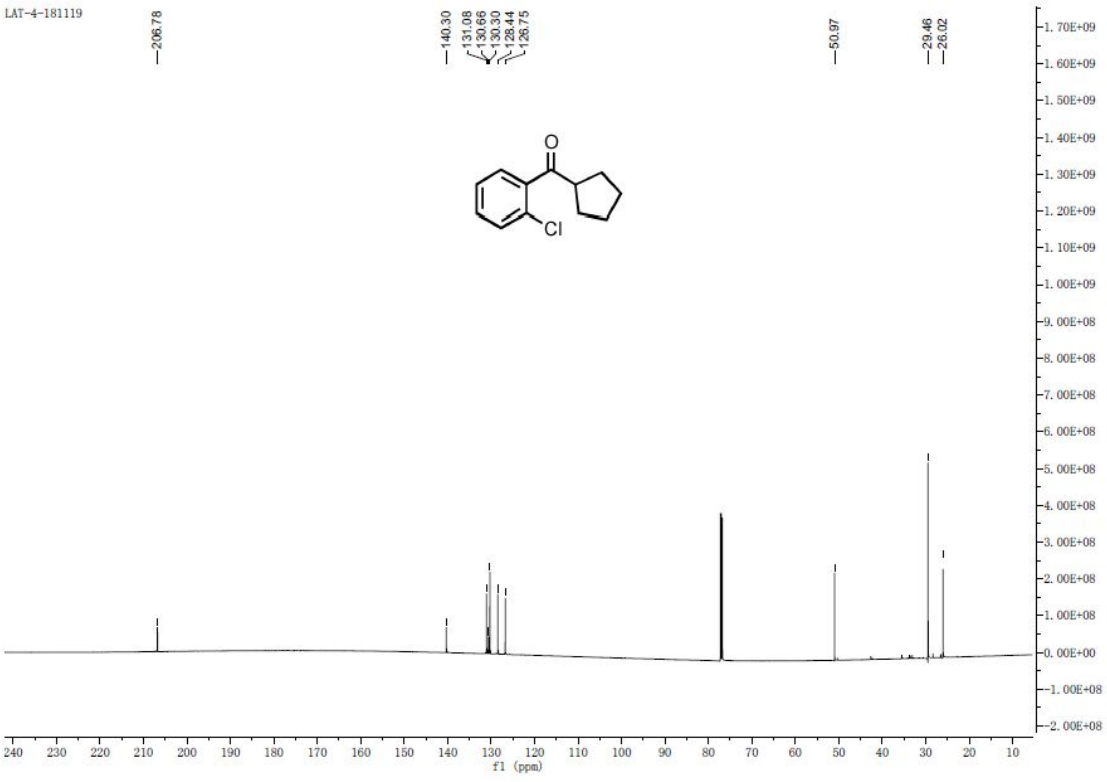


Minimum:	5.00				-1.5		
Maximum:	100.00		5.0	10.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
231.0552	100.00	231.0553	-0.1	-0.4	5.5	719.3	C12 H13 O Na 35Cl
232.0596	12.71	---					
233.0535	33.23	233.0523	1.2	5.1	5.5	6.2	C12 H13 O Na 37Cl

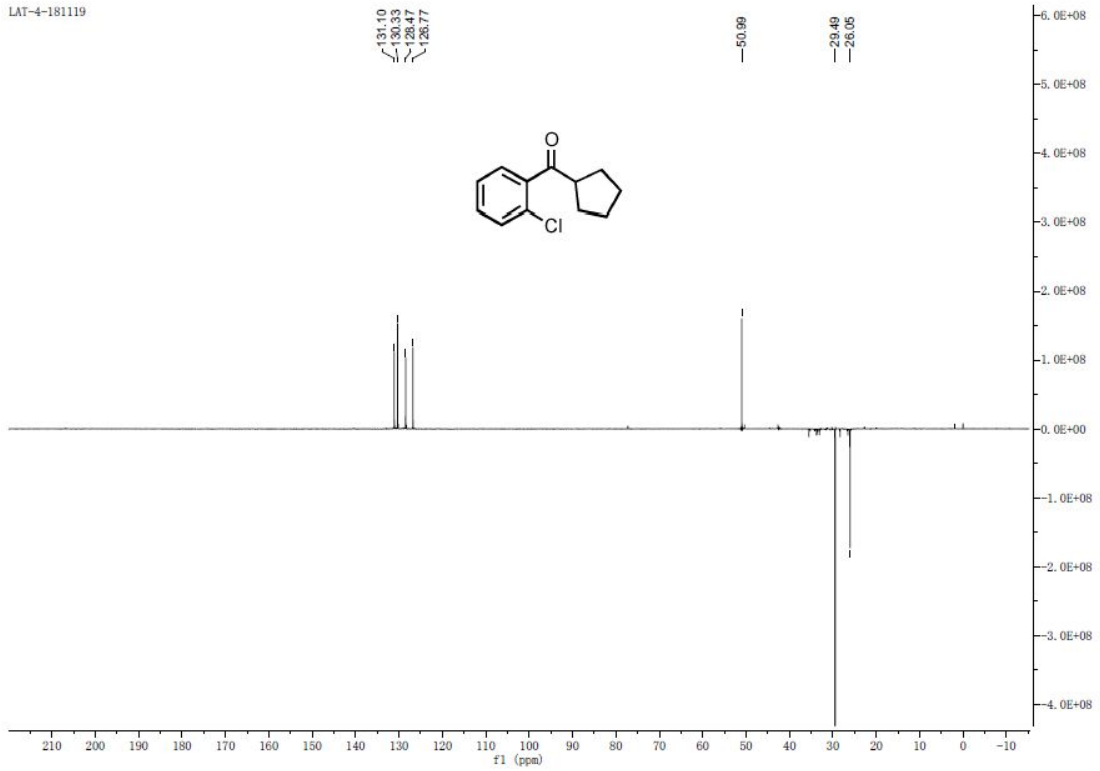
1.1.3 ^{1}H NMR ($CDCl_3$)



1.1.4 ^{13}C NMR ($CDCl_3$)

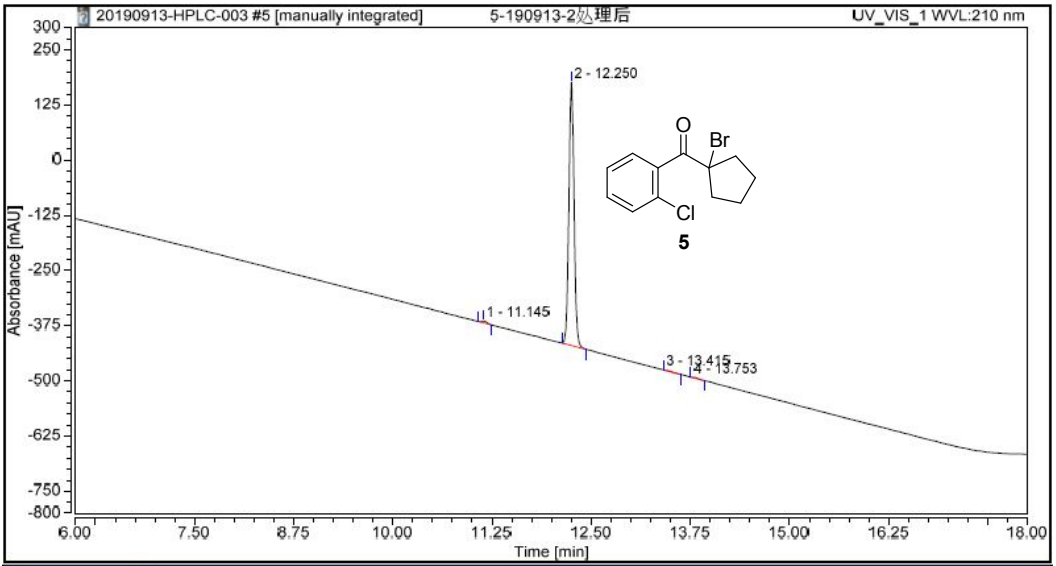


1.1.5 DEPT ($CDCl_3$)



1.2 HPLC, HRMS, and NMR spectra of Compound 5

1.2.1 HPLC

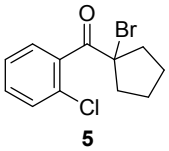


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
n.a.	MF	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
1		11.145	0.335	4.695	0.74	0.78	n.a.
2		12.250	45.031	597.145	98.93	99.22	n.a.
3		13.415	0.059	0.000	0.13	0.00	n.a.
4		13.753	0.095	0.000	0.21	0.00	n.a.
n.a.	KDY	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total:			**45.520**	**601.840**	**100.00**	**100.00**	

1.2.2 HRMS

Elemental Composition Report



5

Multiple Mass Analysis: 5 mass(es) processed
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Molecular Weight: 287.58

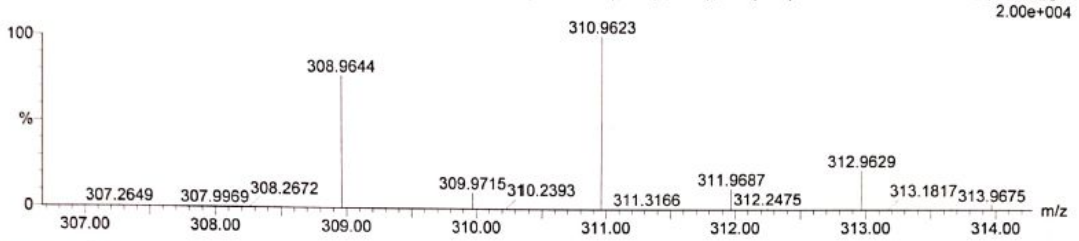
Monoisotopic Mass, Even Electron Ions
380 formula(e) evaluated with 7 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-30 O: 0-1 Na: 1-1 35Cl: 0-1 37Cl: 0-1 79Br: 0-1 81Br: 0-1

SIPI
5-190913
Q19-1430HR 11 (0.204) AM (Cen,2, 80.00, Ar,5000.0,319.05,2.00); Sm (Mn, 2x3.00); Sb (1,5.00); Cm (8:14)

Q-Tof micro
YA019

09:40:28,18-Oct-2019

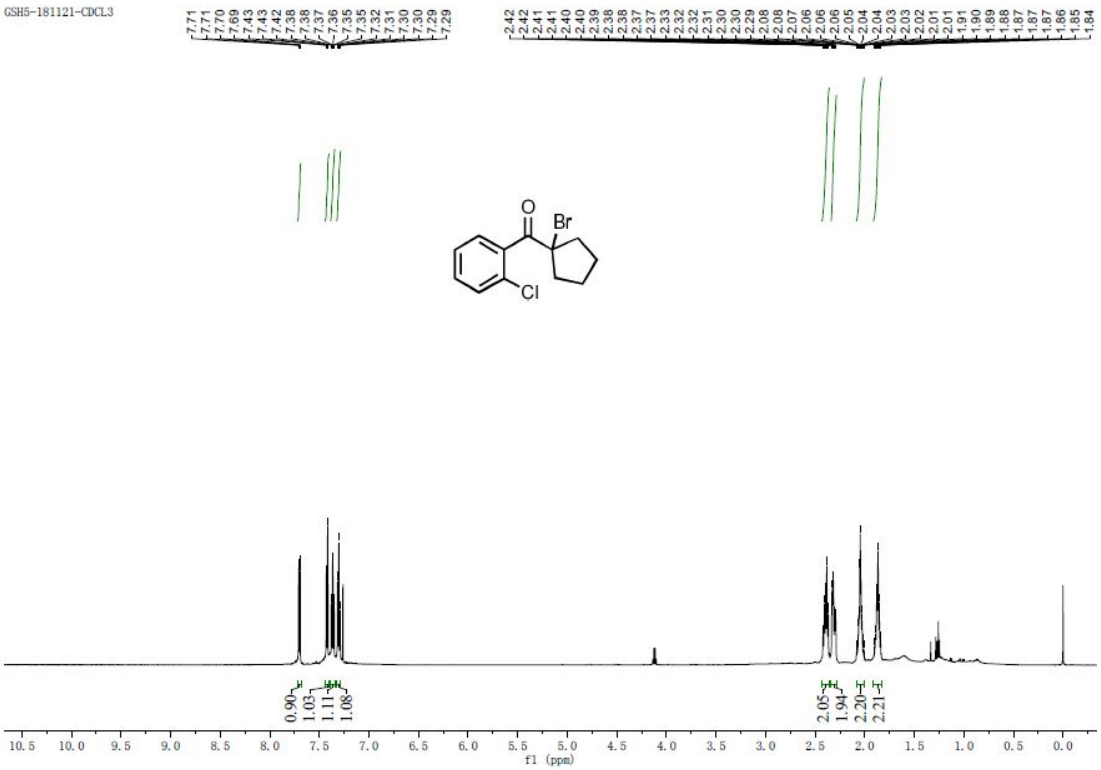
TOF MS ES+
2.00e+004



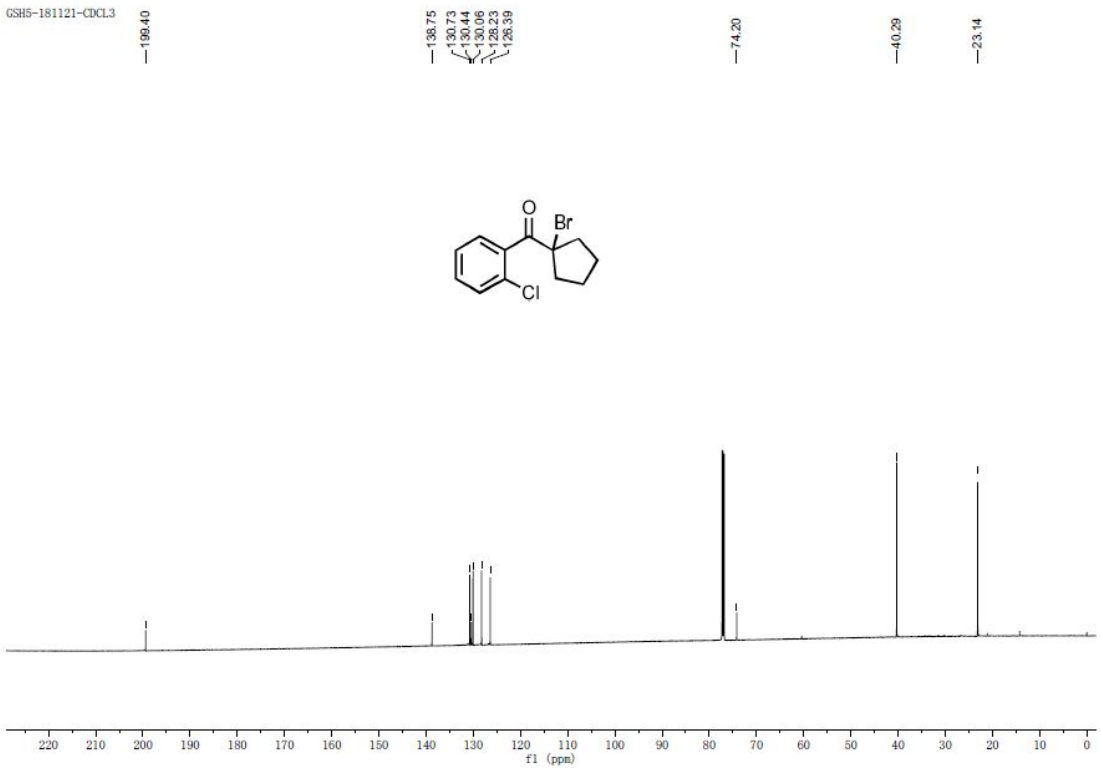
Minimum:	5.00				-1.5	
Maximum:	100.00		5.0	5.0	50.0	

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
308.9644	76.29	308.9652	-0.8	-2.6	-0.5	9975.6	C9 H18 Na 79Br 81Br
		308.9658	-1.4	-4.5	5.5	9886.9	C12 H12 O Na 35Cl 79Br ✓
		308.9659	-1.5	-4.9	6.5	9927.5	C13 H12 Na 37Cl 81Br
309.9715	9.18	---					
310.9623	100.00	310.9628	-0.5	-1.6	5.5	2071.9	C12 H12 O Na 37Cl 79Br ✓
		310.9637	-1.4	-4.5	5.5	2074.2	C12 H12 O Na 35Cl 81Br
311.9687	11.82	---					
312.9629	22.51	312.9629	0.0	0.0	13.5	n/a	C17 H7 Na 79Br
		312.9635	-0.6	-1.9	20.5	n/a	C21 H Na 37Cl

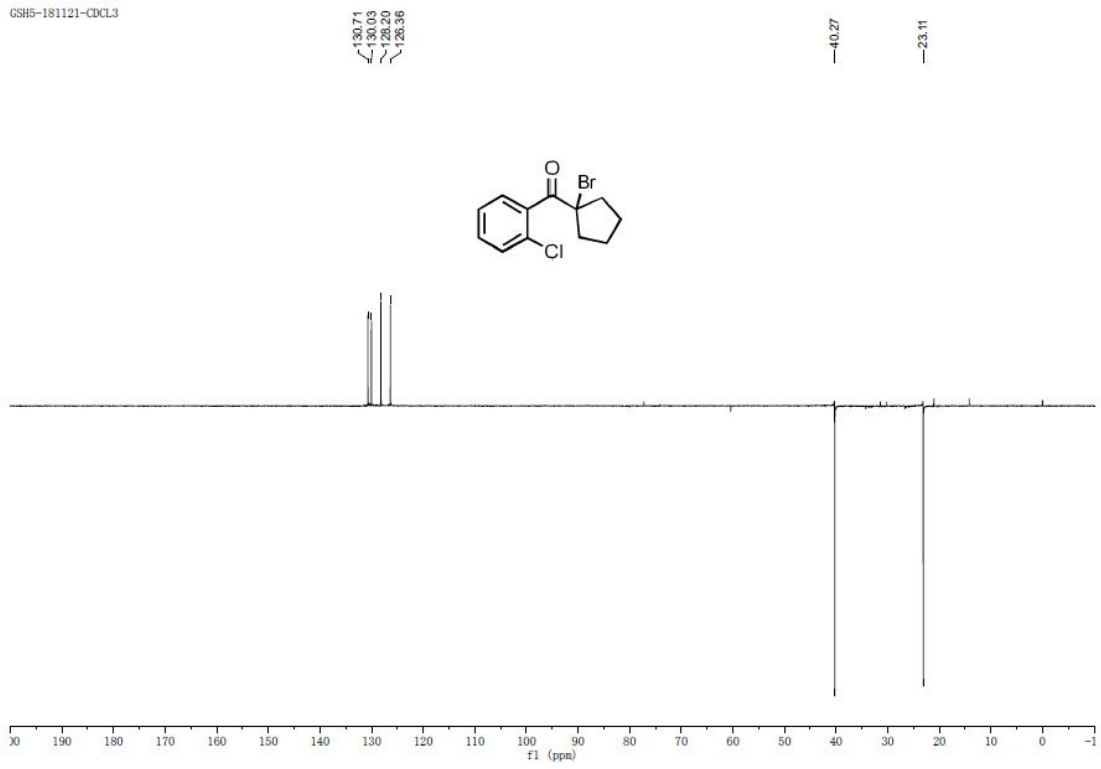
1.2.3 ^{1}H NMR ($CDCl_3$)



1.2.4 ^{13}C NMR ($CDCl_3$)

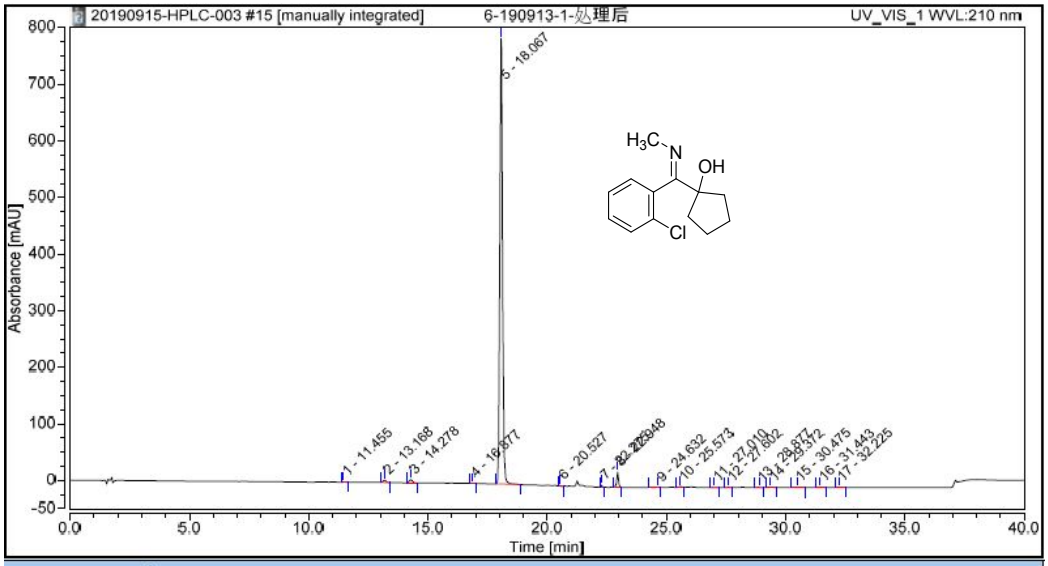


1.2.5 DEPT ($CDCl_3$)



1.3 HPLC data, HRMS, and NMR of Compound 6

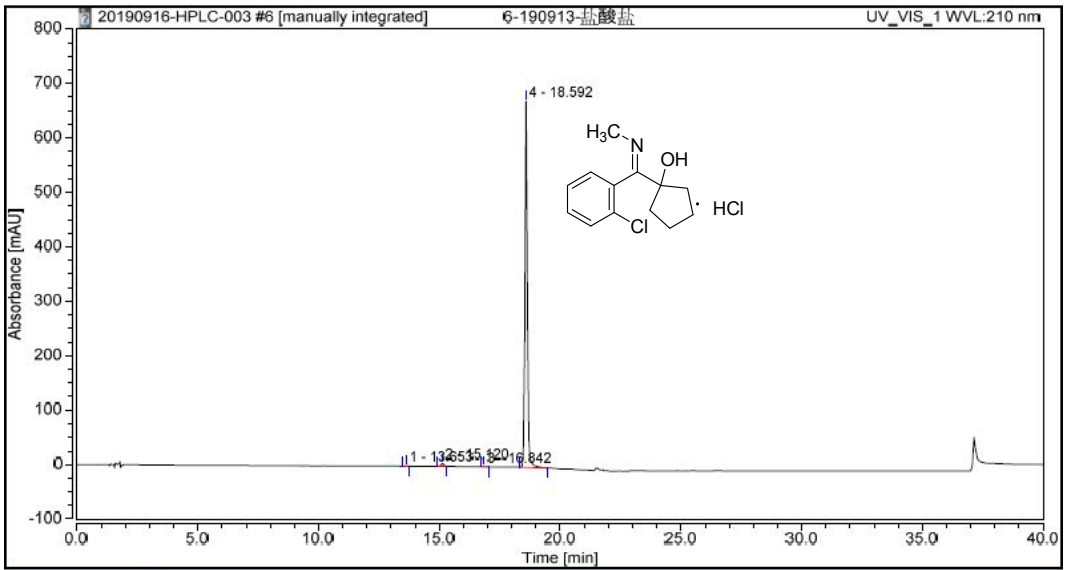
1.3.1.1 HPLC (Base)



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
n.a.	MF	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
1		11.455	0.028	0.260	0.03	0.03	n.a.
2		13.168	0.521	4.116	0.50	0.49	n.a.
3		14.278	0.834	6.075	0.79	0.73	n.a.
4		16.877	0.036	0.359	0.03	0.04	n.a.
5		18.067	100.534	787.013	95.65	94.30	n.a.

1.3.1.1 HPLC (Hydrochloride)

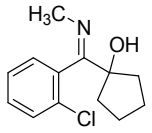


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
n.a.	MF	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
1		13.653	0.063	0.561	0.08	0.08	n.a.
2		15.120	0.722	5.220	0.93	0.77	n.a.
3		16.842	0.029	0.255	0.04	0.04	n.a.
n.a.	KDY	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
4		18.592	76.876	672.483	98.95	99.11	n.a.
Total:			**77.689**	**678.520**	**100.00**	**100.00**	

1.3.2 HRMS

Elemental Composition Report

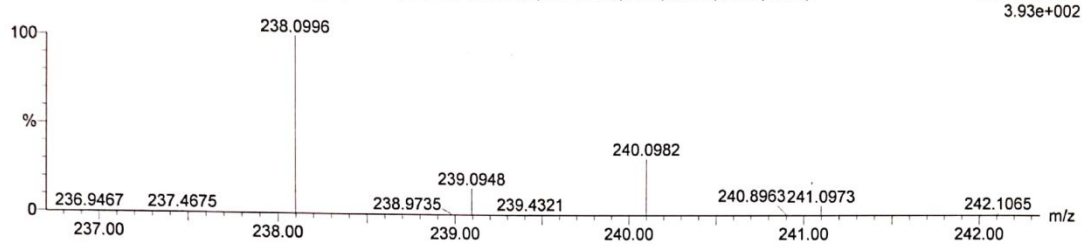


Page 1

Exact Mass: 237.09

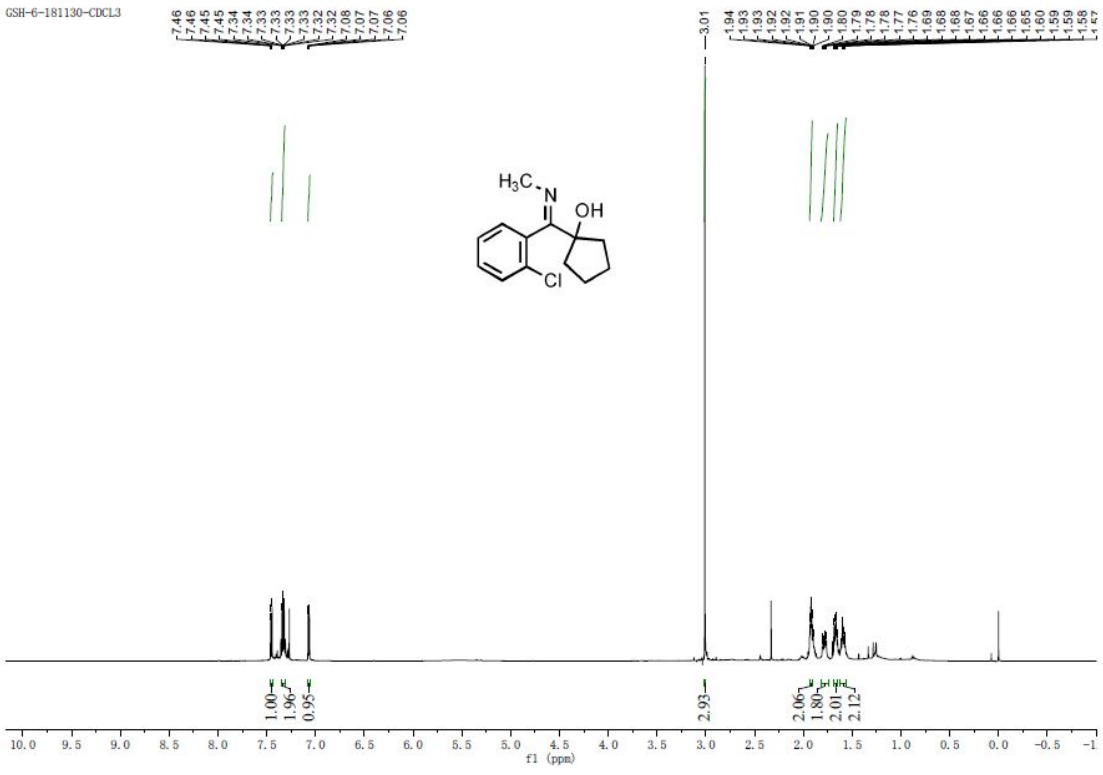
Multiple Mass Analysis: 4 mass(es) processed
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
159 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-30 N: 0-1 O: 0-1 35Cl: 0-1 37Cl: 0-1
SIPI
6-190916
Q-Tof micro
YA019
16:02:25,17-Oct-2019
Q19-1427HR 15 (0.279) AM (Cen,2, 80.00, Ar,5000.0,233.17,2.00); Sm (Mn, 2x3.00); Sb (1,5.00); Cm (15:18)
TOF MS ES+
3.93e+002

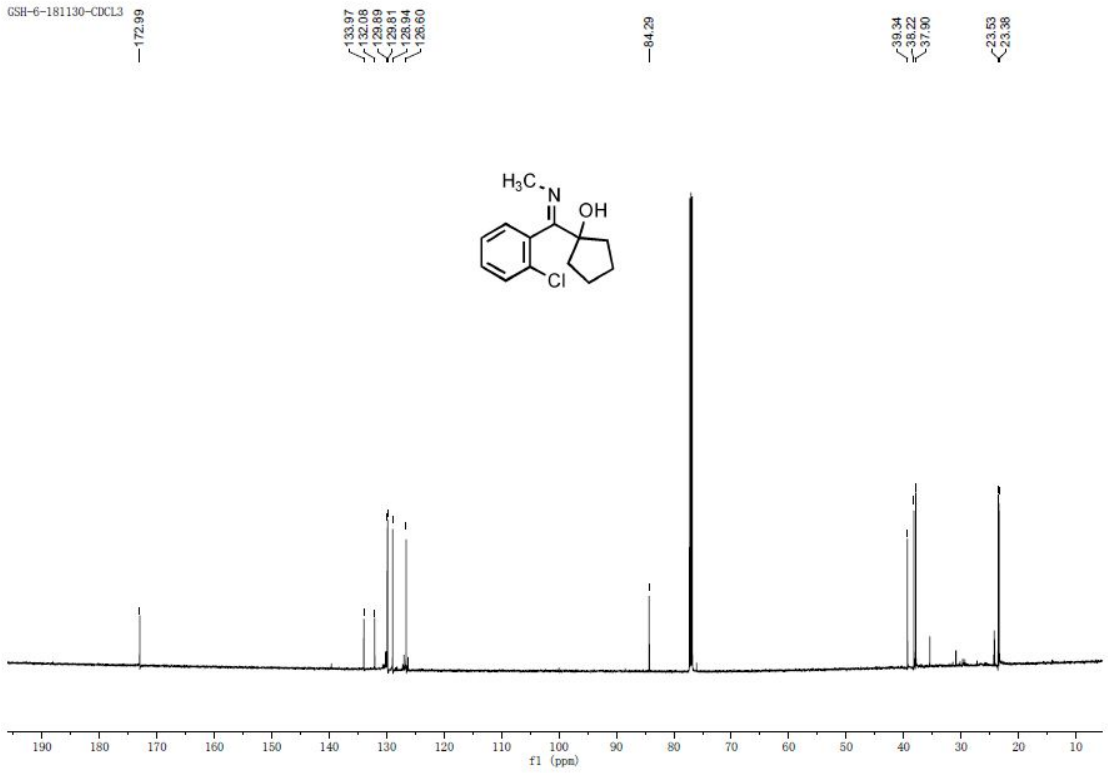


Minimum:	5.00				-1.5		
Maximum:	100.00		5.0	10.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
238.0996	100.00	238.0999	-0.3	-1.3	5.5	58.5	C13 H17 N O 35Cl
239.0948	14.88	---					
240.0982	31.97	240.0969	1.3	5.4	5.5	0.8	C13 H17 N O 37Cl
241.0973	5.15	---					

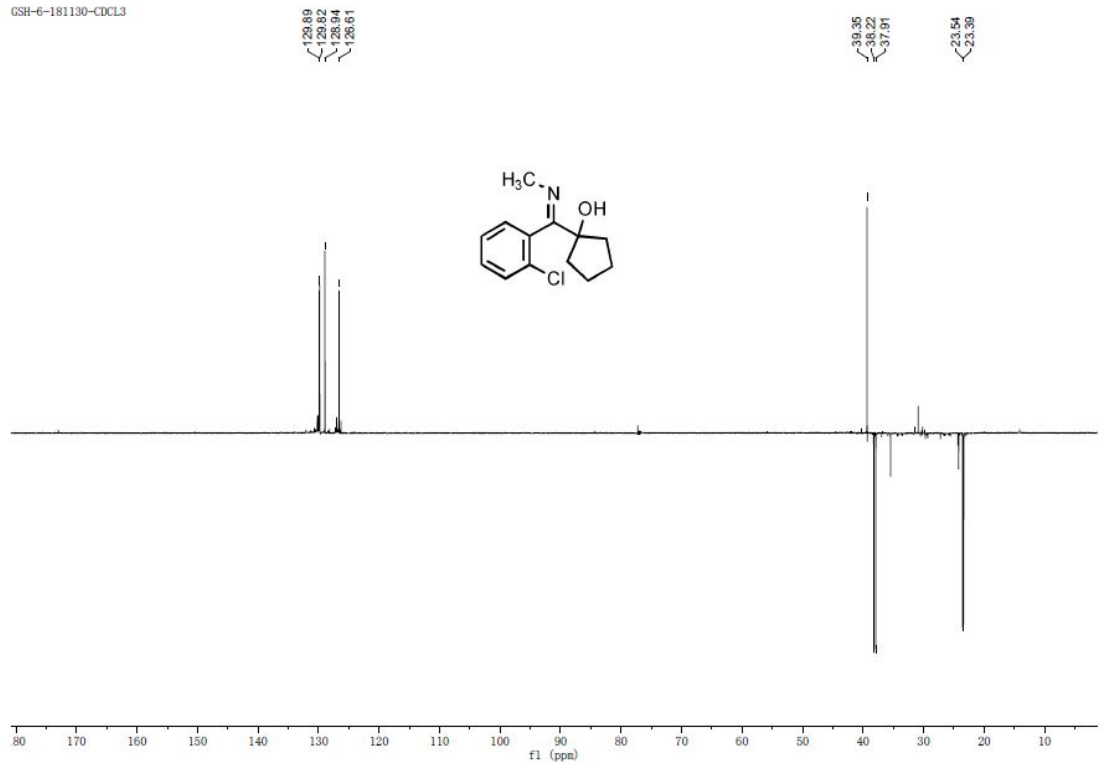
1.3.3 ^{1}H NMR



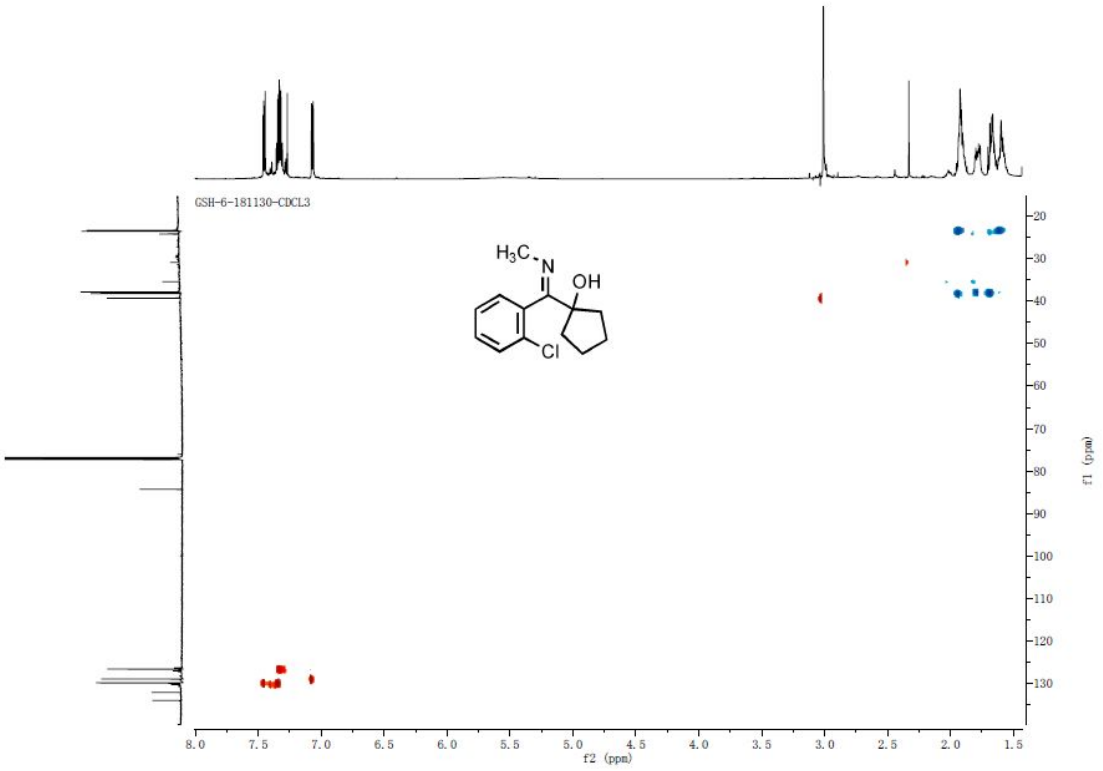
1.3.4 ^{13}C NMR



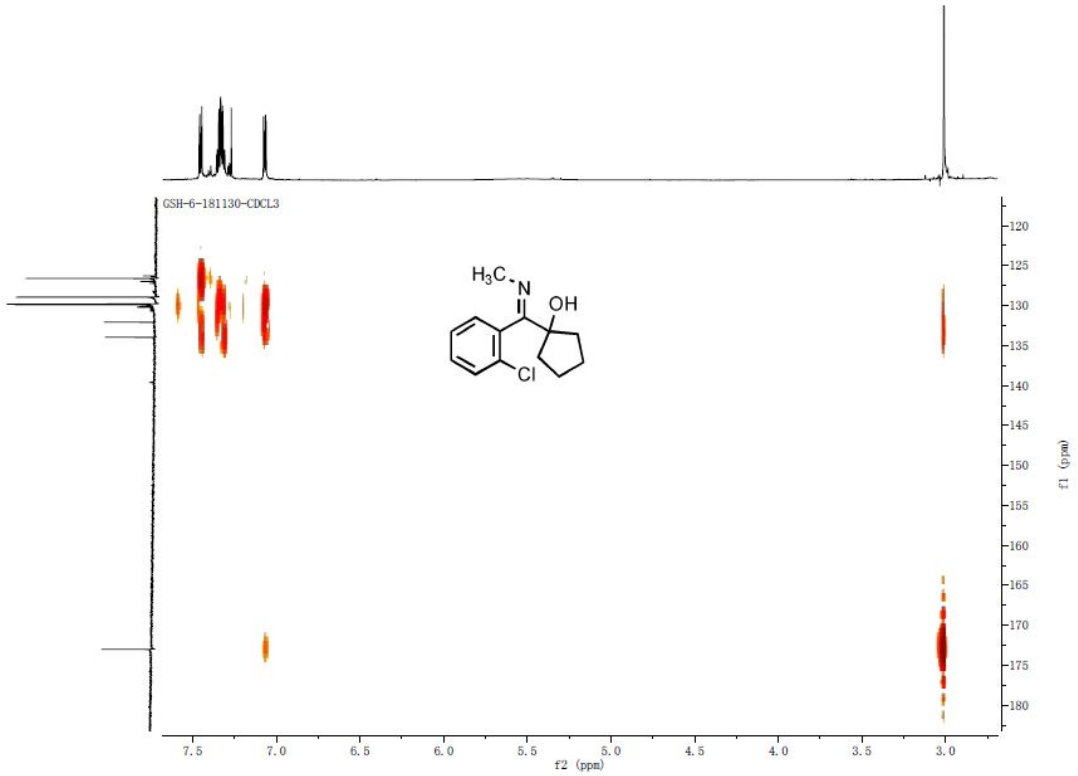
1.3.5 DEPT



1.3.6 HSQC

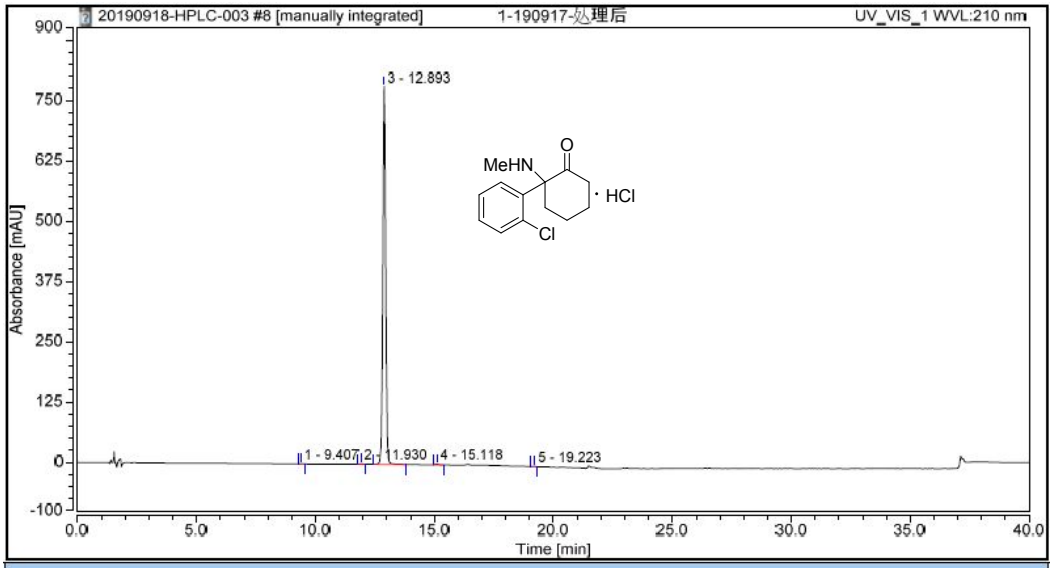


1.3.7 The enlarged view of HMBC



1.4 HPLC, HRMS, NMR, DSC and Elemental analysis spectra of Ketamine

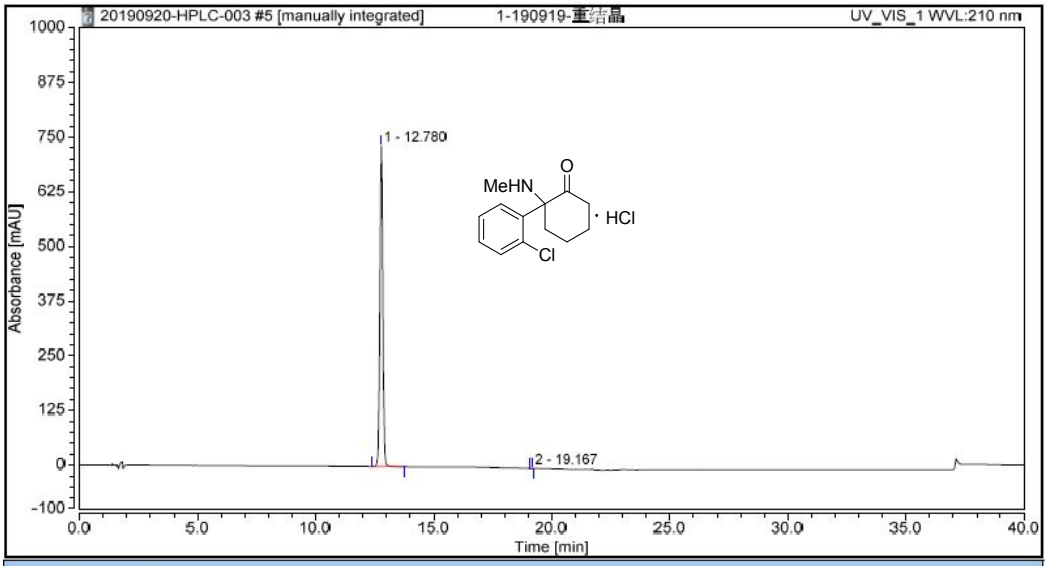
1.4.1.1 HPLC data (Crude product)



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
n.a.	MF	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
1		9.407	0.022	0.229	0.02	0.03	n.a.
2		11.930	0.122	1.004	0.11	0.13	n.a.
3		12.893	108.380	782.618	99.55	99.51	n.a.
4		15.118	0.265	1.732	0.24	0.22	n.a.
n.a.	KDY	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
5		19.223	0.087	0.915	0.08	0.12	n.a.
Total:			**108.875**	**786.498**	**100.00**	**100.00**	

1.4.1.2 HPLC data (Recrystallized product by acetone/H_2O)



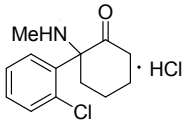
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
n.a.	MF	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
1		12.780	101.983	734.163	99.97	99.95	n.a.
n.a.	KDY	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2		19.167	0.029	0.384	0.03	0.05	n.a.
Total:			**102.011**	**734.547**	**100.00**	**100.00**	

1.4.2 HRMS

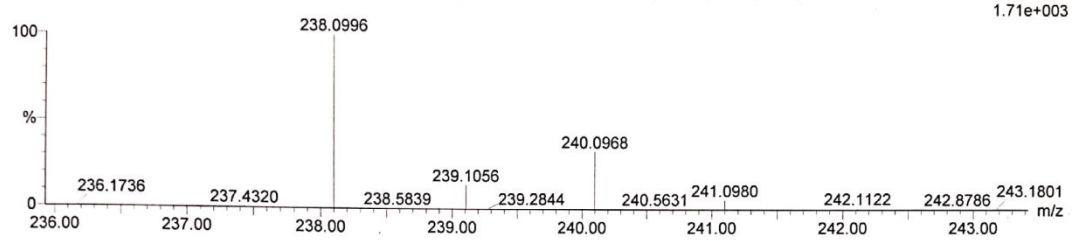
Elemental Composition Report **Page 1**

Multiple Mass Analysis: 4 mass(es) processed
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



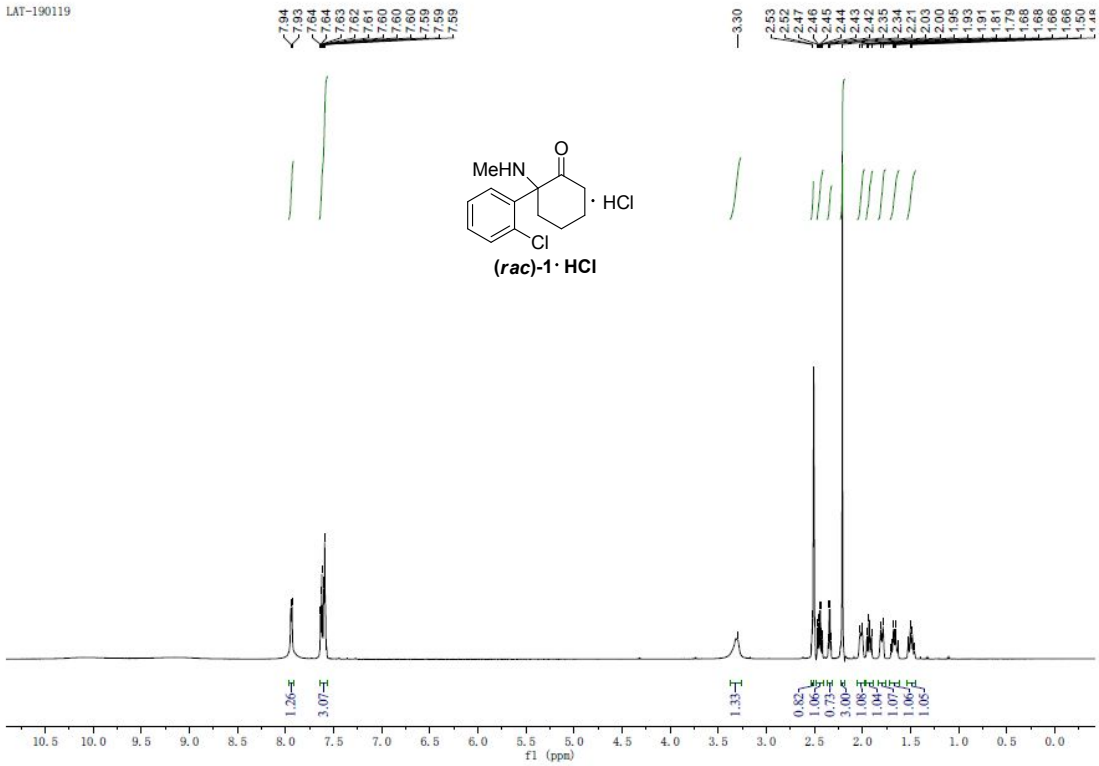
Exact Mass: 237.09

Monoisotopic Mass, Even Electron Ions
159 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-30 N: 0-1 O: 0-1 35Cl: 0-1 37Cl: 0-1
SIPI
LAT-190922
Q19-1428HR 39 (0.724) AM (Cen,2, 80.00, Ar,5000.0,233.17,2.00); Sm (Mn, 2x3.00); Sb (1,5.00); Cm (34:47)
Q-Tof micro
YA019
16:19:16,17-Oct-2019
TOF MS ES+
1.71e+003



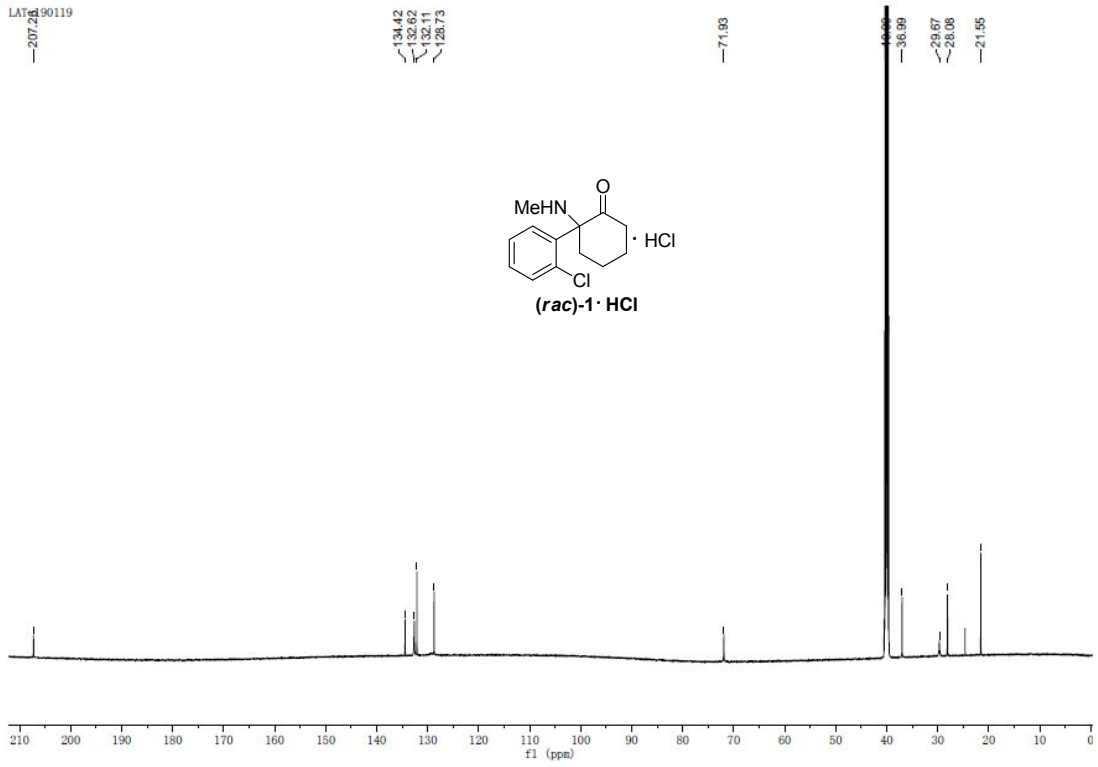
Minimum:	5.00				-1.5		
Maximum:	100.00		5.0	10.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
238.0996	100.00	238.0999	-0.3	-1.3	5.5	266.3	C13 H17 N O 35Cl
239.1056	13.56	---					
240.0968	33.13	240.0969	-0.1	-0.4	5.5	0.6	C13 H17 N O 37Cl
241.0980	5.32	---					

1.4.3 ^{1}H NMR (DMSO)

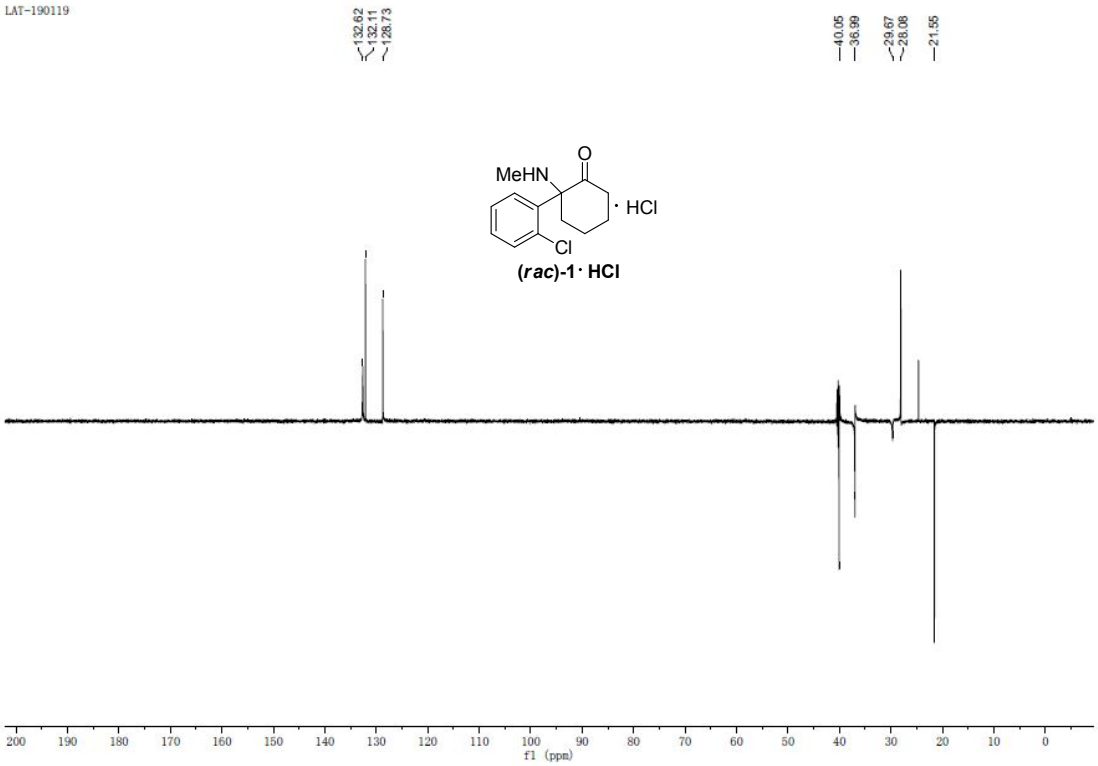


(*rac*)-**1**· **HCl**

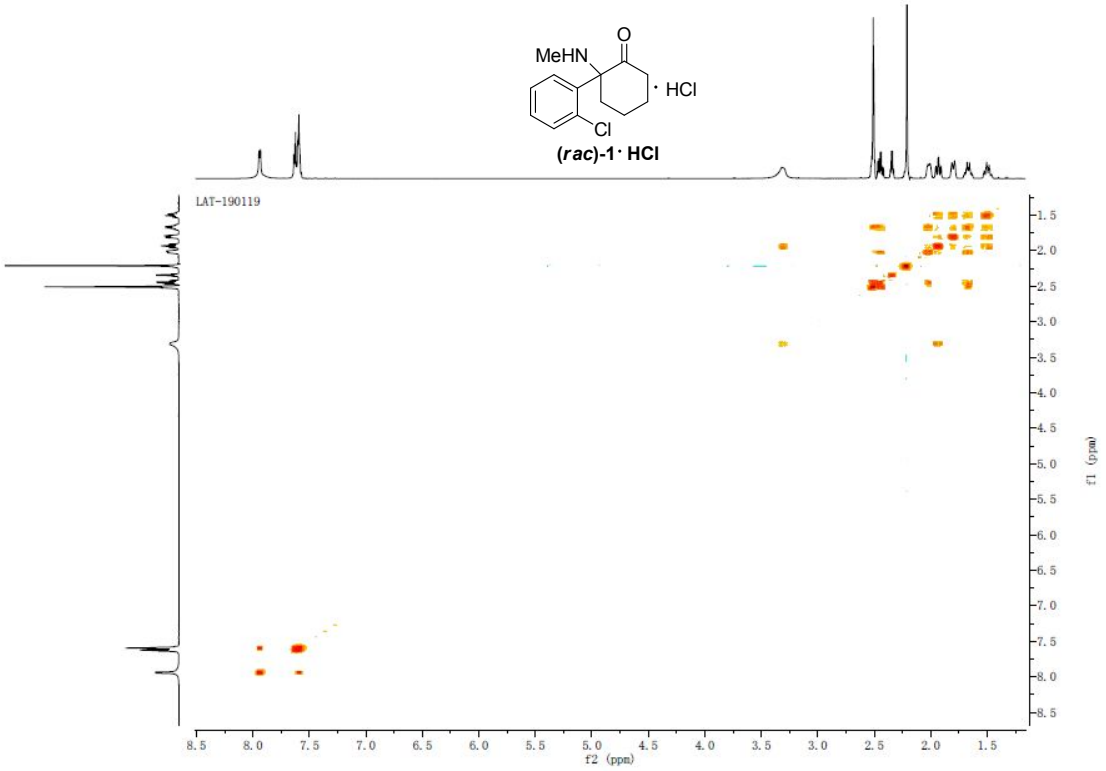
1.4.4 ^{13}C NMR (DMSO)



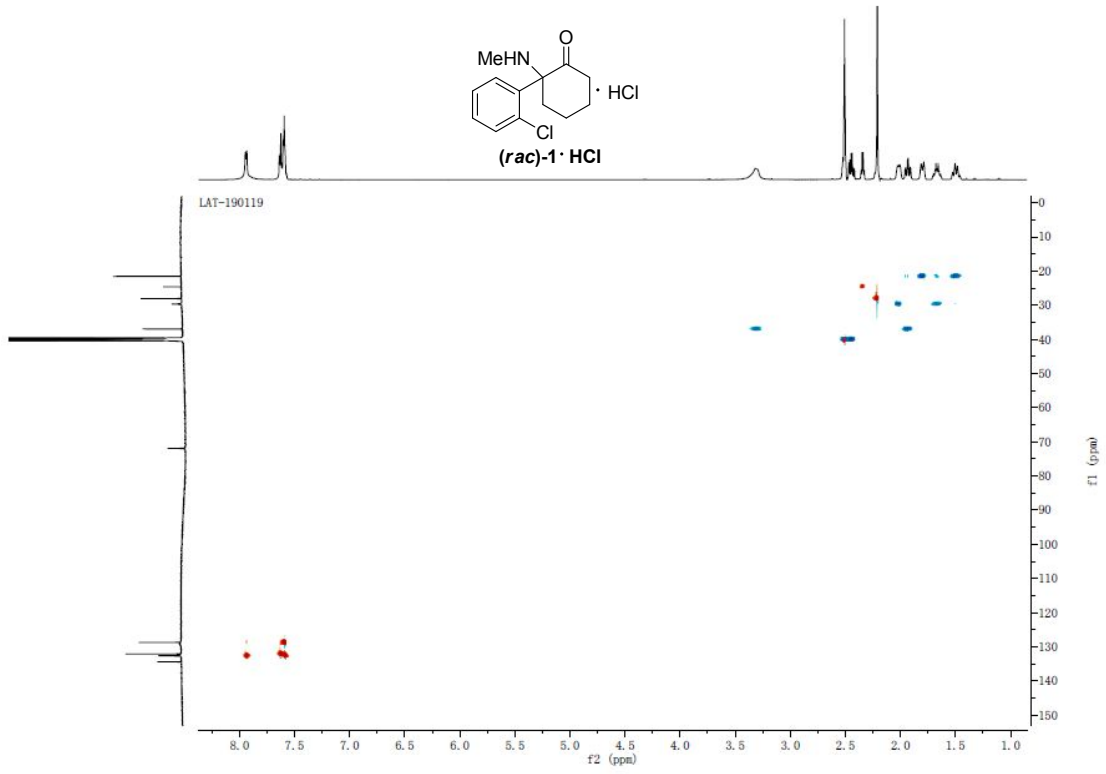
1.4.5 DEPT (DMSO)



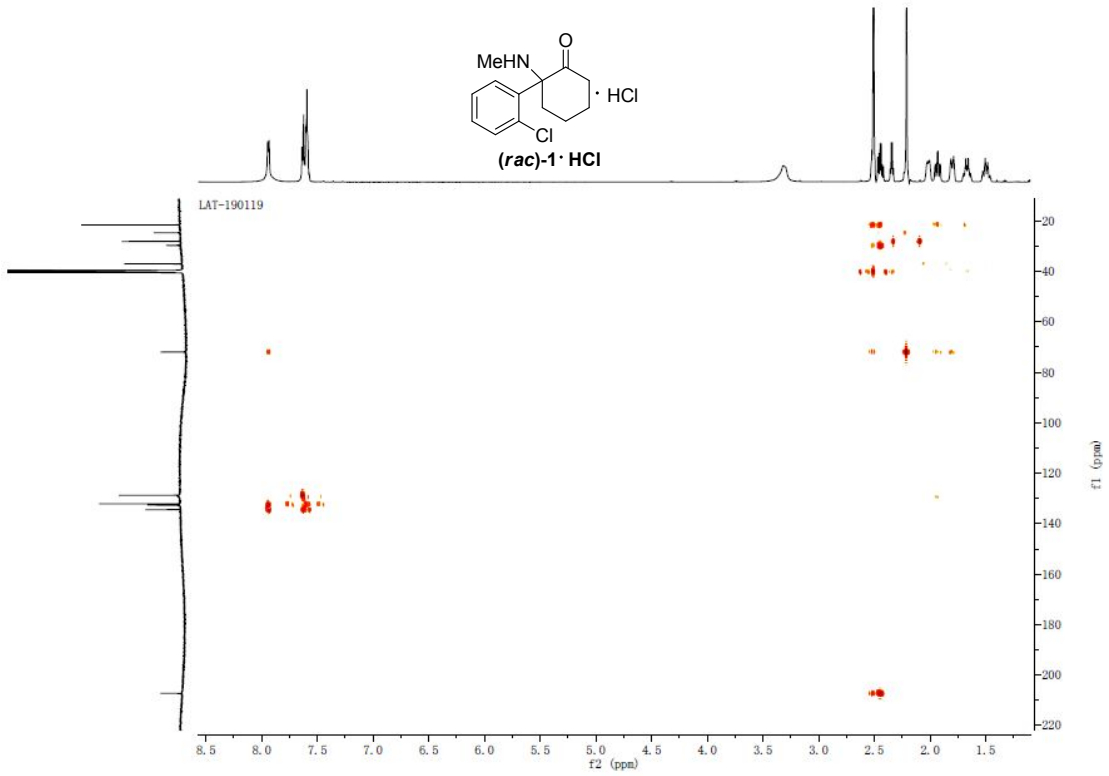
1.4.6 H-H COSY (DMSO)



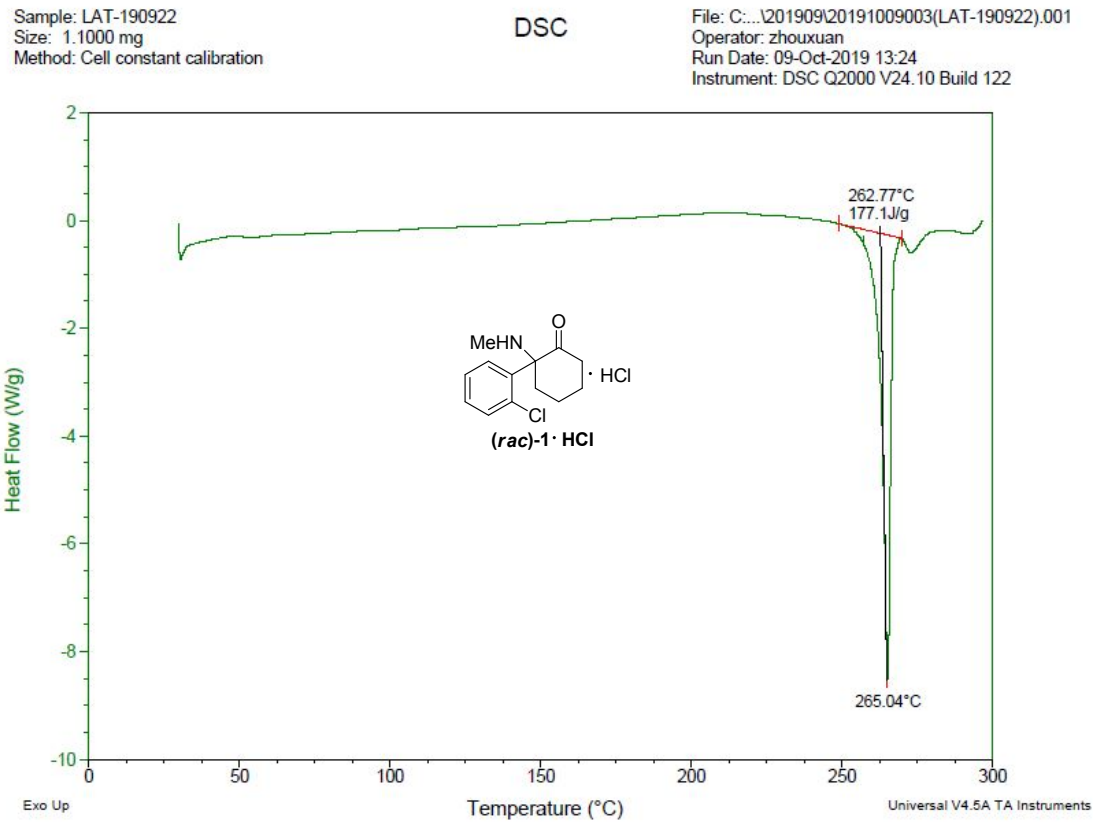
1.4.7 HSQC



1.4.8 HMBC



1.4.9 DSC



1.4.10 Elemental Analysis

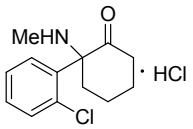
Shanghai Institute of Pharmaceutical Industry

TEST REPORT

Sample Name	LAT-190922	**Batch Number**	190922
Sample Number	20191009003	**Sample Amount**	20 mg
Chemical Formula:	$C_{13}H_{17}Cl_2NO$	**Sample Received**	2019-10-09
Molecular Weight:	274.19	**Test Items**	C、H、N
Reference Methods	JYT017-1996		

Test Items	Specification	Test Results
C	56.95	56.88/56.87
H	6.25	6.27/6.28
N	5.11	5.13/5.12

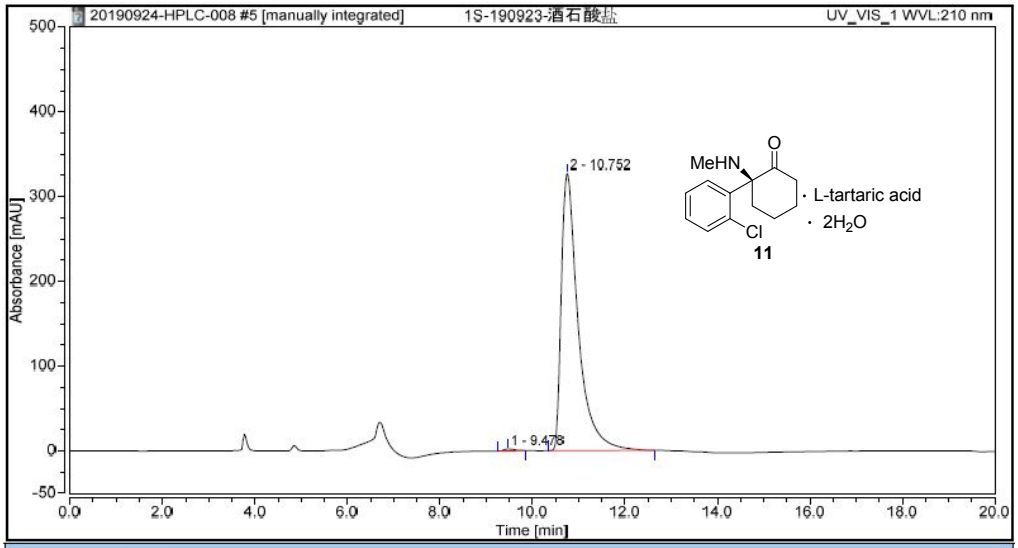
End of Repot



Elemental Analysis: C, 56.95; H, 6.25; N, 5.11

2. Analytical spectrograms and data of Esketamine

2.1.1 Normal phase HPLC (Esketamine tartrate, 11)



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		9.478	0.619	2.332	0.45	0.71	n.a.
2		10.752	137.773	326.710	99.55	99.29	n.a.
Total:			138.392	329.042	100.00	100.00	

2.1.2 SCXRD of Esketamine tartrate (11)

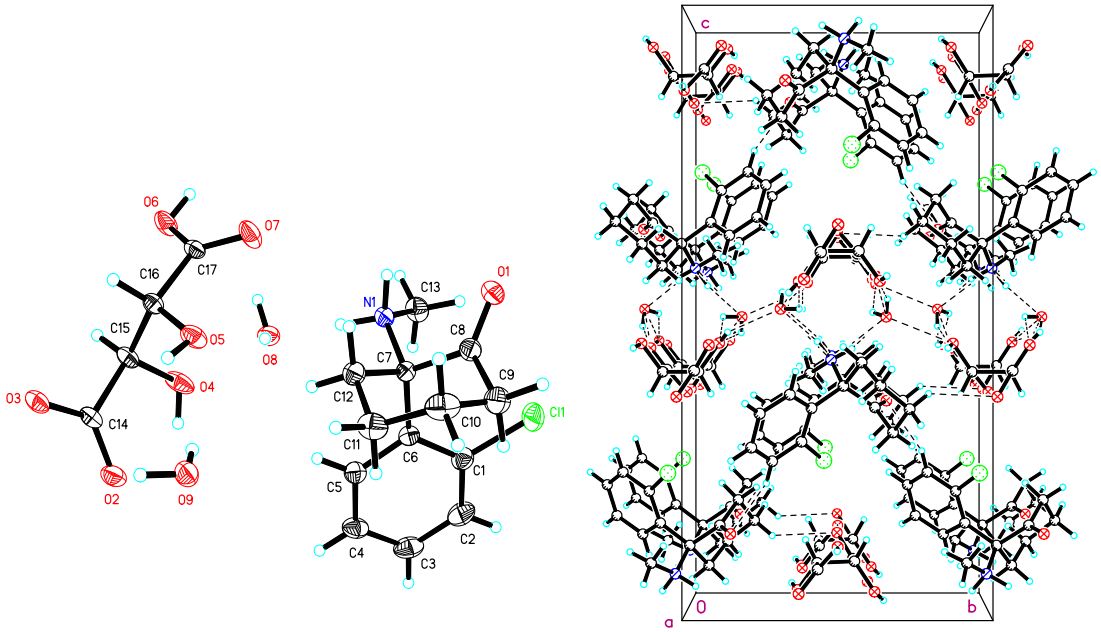
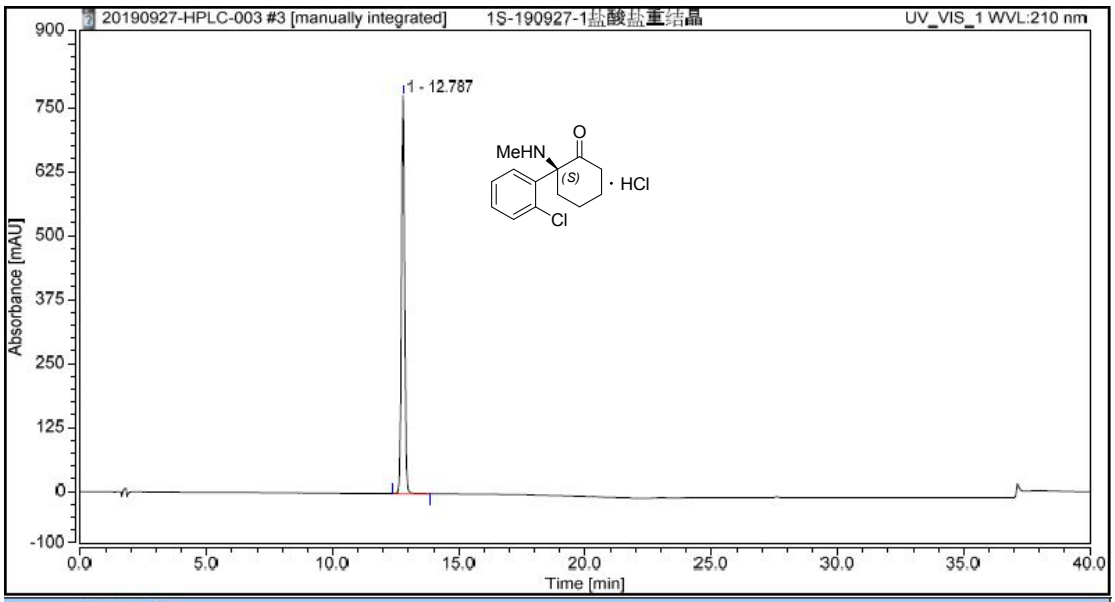


Table S1. Crystal data and structure refinement for mo_d8v19705_0m.

Identification code	mo_d8v19705_0m	
Empirical formula	C17 H26 Cl N O9	
Formula weight	423.84	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.2789(2) Å	α= 90°.
	b = 11.7429(3) Å	β= 90°.
	c = 23.2813(7) Å	γ = 90°.
Volume	1989.98(10) $Å^3$	
Z	4	
Density (calculated)	1.415 Mg/m^3	
Absorption coefficient	0.242 mm^{-1}	
F(000)	896	
Crystal size	0.190 x 0.160 x 0.120 mm^3	
Theta range for data collection	2.464 to 25.996°.	
Index ranges	-8<=h<=8, -14<=k<=14, -28<=l<=26	
Reflections collected	18029	
Independent reflections	3864 [R(int) = 0.0305]	
Completeness to theta = 25.242°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.6688	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3864 / 2 / 283	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R1 = 0.0277, wR2 = 0.0663	
R indices (all data)	R1 = 0.0307, wR2 = 0.0686	
Absolute structure parameter	0.03(2)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.186 and -0.147 $e.Å^{-3}$	

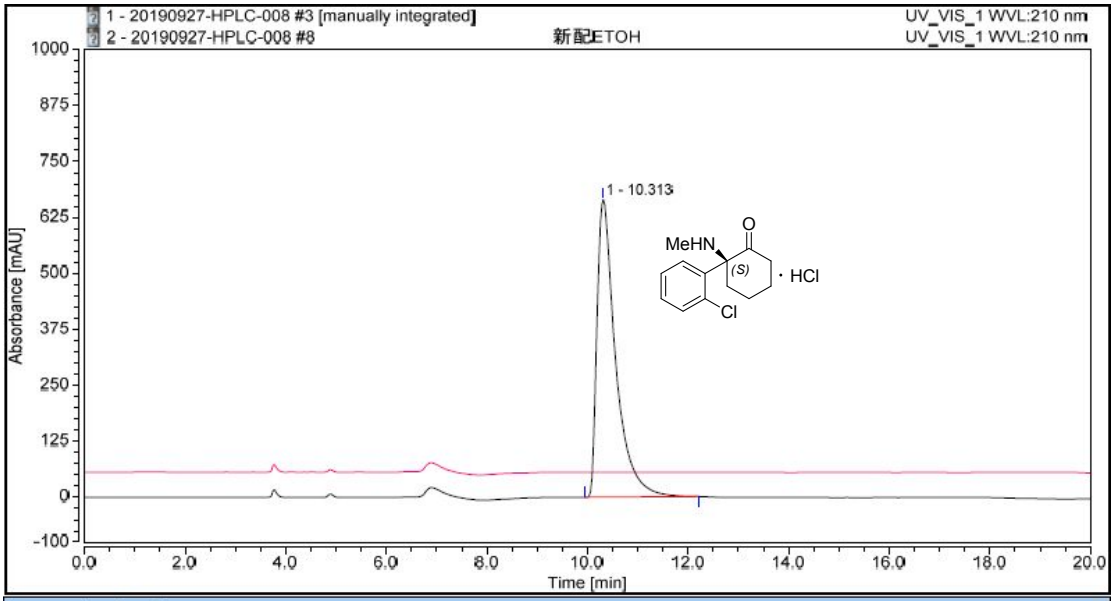
2.2 RP-HPLC (Esketamine hydrochloride after recrystallization)



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
n.a.	MF	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
1		12.787	110.961	777.000	100.00	100.00	n.a.
n.a.	KDY	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total:			**110.961**	**777.000**	**100.00**	**100.00**	

2.3 Normal phase HPLC (Esketamine hydrochloride after recrystallization)



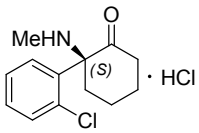
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		10.313	285.850	665.228	100.00	100.00	n.a.
Total:			**285.850**	**665.228**	**100.00**	**100.00**	

2.4 HRMS

Elemental Composition Report **Page 1**

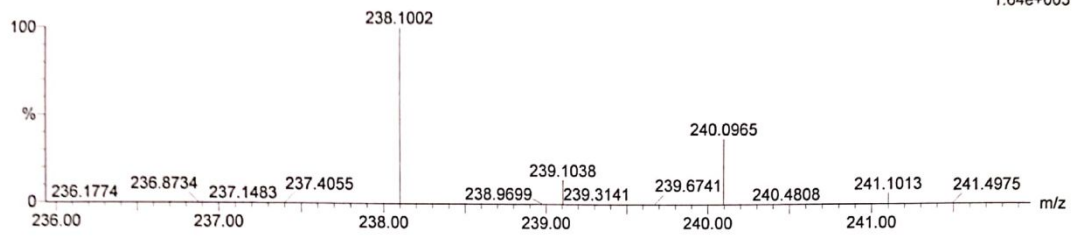
Multiple Mass Analysis: 4 mass(es) processed
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



Exact Mass: 237.09

Monoisotopic Mass, Even Electron Ions
159 formula(e) evaluated with 4 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-30 N: 0-1 O: 0-1 35Cl: 0-1 37Cl: 0-1

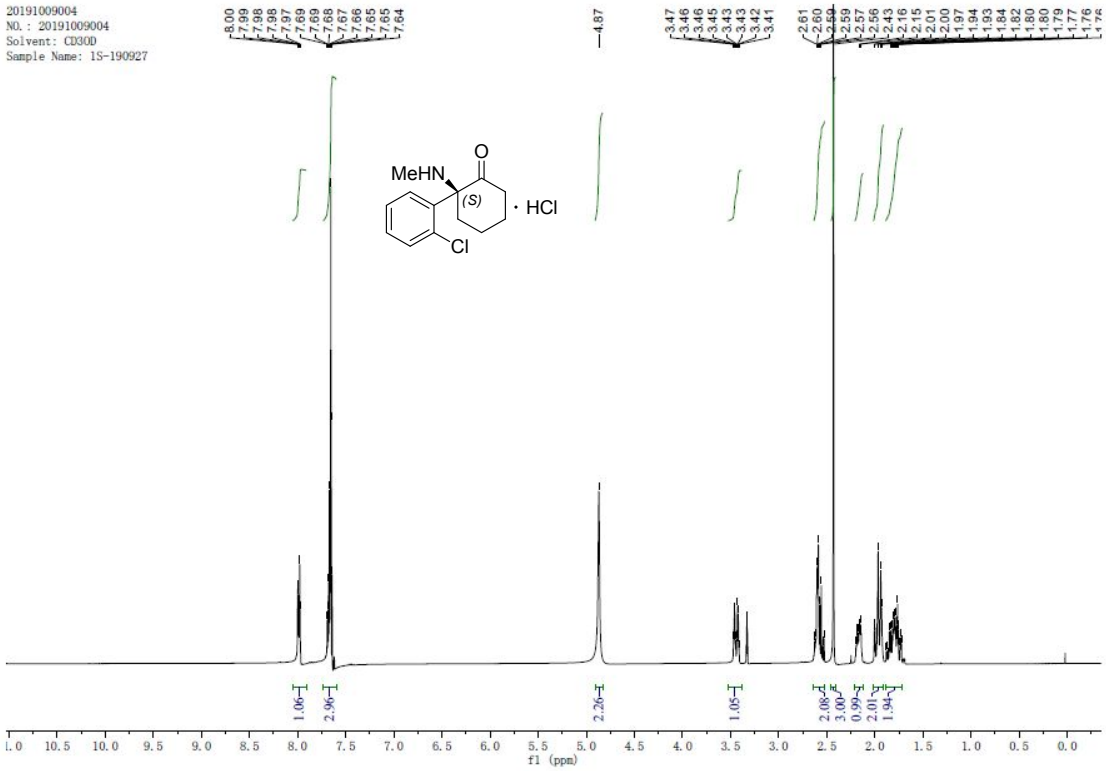
SIPI
IS-190927
Q-Tof micro
YA019
16:25:54,17-Oct-2019
Q19-1429HR 15 (0.278) AM (Cen,2, 80.00, Ar,5000.0,233.17,2.00); Sm (Mn, 2x3.00); Sb (1,5.00); Cm (15:22)
TOF MS ES+
1.64e+003



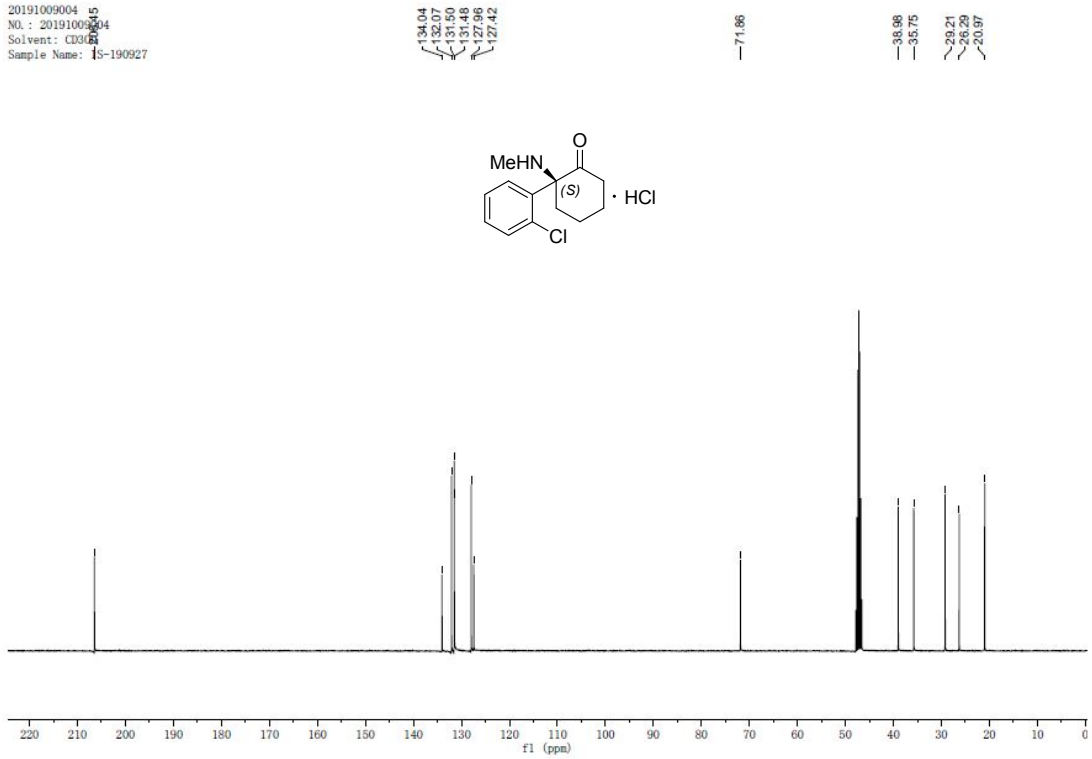
Minimum:	5.00				-1.5			
Maximum:	100.00		5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula	
238.1002	100.00	238.0999	0.3	1.3	5.5	289.7	C13 H17 N O 35Cl	✓
239.1038	13.52	239.1017	2.1	8.8	5.5	315.9	C14 H18 O 37Cl	
240.0965	37.36	240.0969	-0.4	-1.7	5.5	n/a	C13 H17 N O 37Cl	✓
241.1013	5.83	241.1017	-0.4	-1.7	13.5	n/a	C19 H13	

2.5 NMR

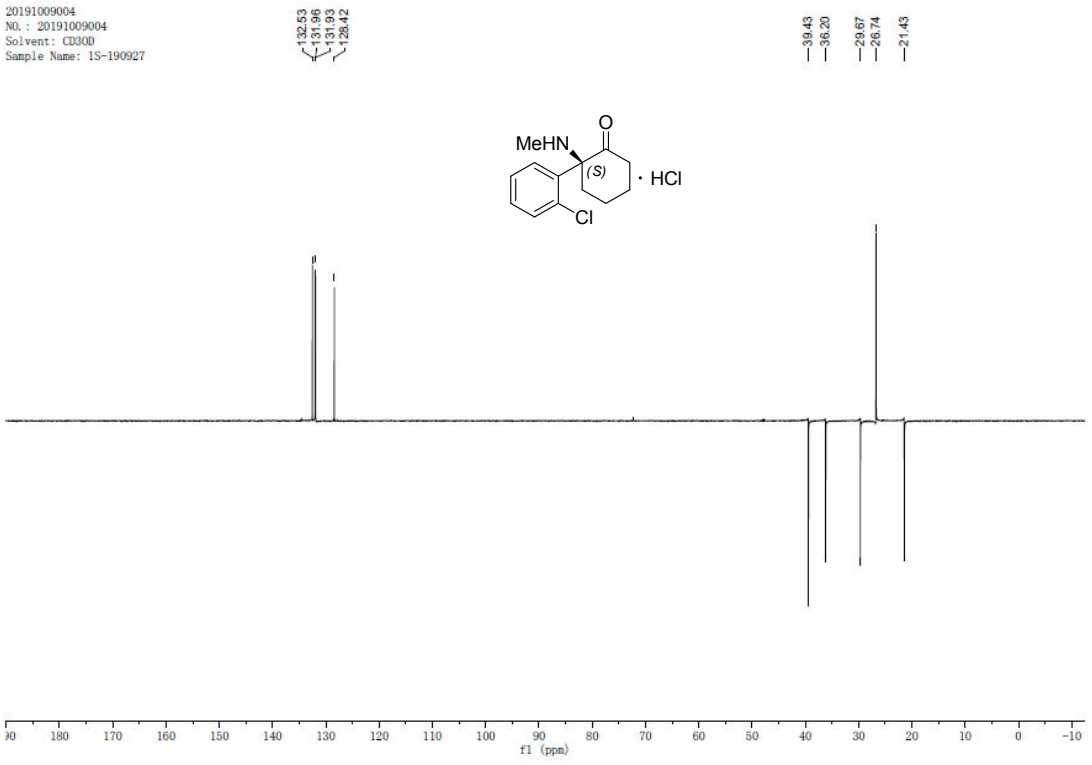
2.5.1 ^{1}H NMR



2.5.2 ^{13}C NMR



2.5.3 DEPT



2.6 SCXRD of Esketamine hydrochloride

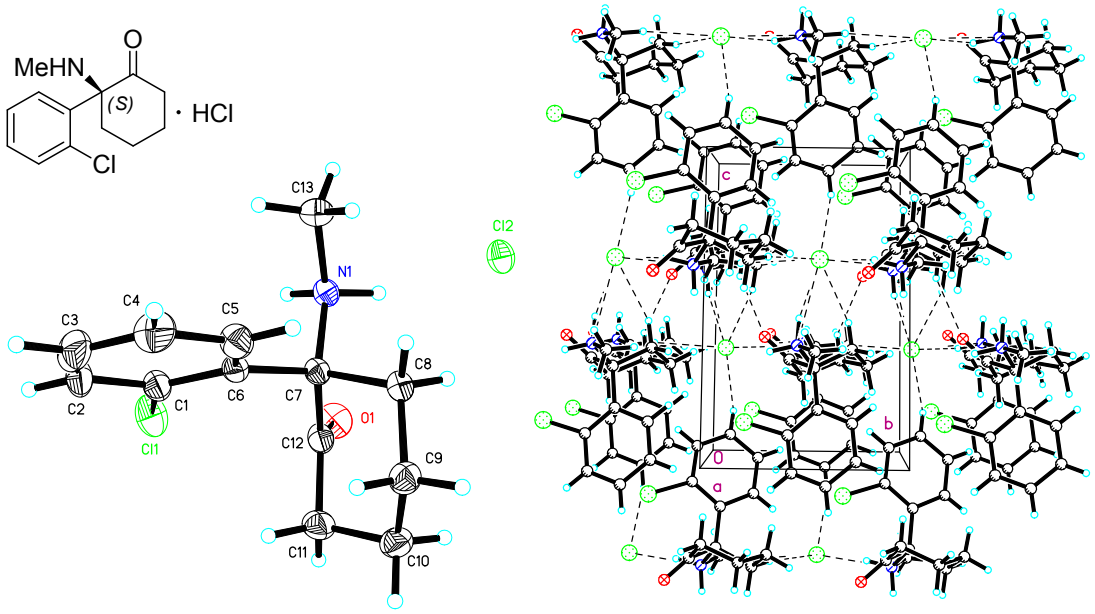


Table S2. Crystal data and structure refinement for mo_d8v19704_0m.

Identification code	mo_d8v19704_0m	
Empirical formula	C13 H17 Cl2 N O	
Formula weight	274.17	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.5612(3) Å	α= 90°.
	b = 7.1443(2) Å	β= 101.2450(10)°.
	c = 11.3370(3) Å	γ = 90°.
Volume	680.10(4) Å^3	
Z	2	
Density (calculated)	1.339 Mg/m^3	
Absorption coefficient	0.461 mm^{-1}	
F(000)	288	
Crystal size	0.180 x 0.150 x 0.120 mm^3	
Theta range for data collection	2.426 to 25.994°.	
Index ranges	-10<=h<=10, -8<=k<=8, -13<=l<=13	
Reflections collected	12148	
Independent reflections	2620 [R(int) = 0.0411]	
Completeness to theta = 25.242°	97.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.6127	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2620 / 1 / 155
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0279, wR2 = 0.0709
R indices (all data)	R1 = 0.0285, wR2 = 0.0714
Absolute structure parameter	-0.01(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.185 and -0.253 e.$Å^{-3}$

2.7 Elemental Analysis

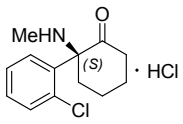
Shanghai Institute of Pharmaceutical Industry

TEST REPORT

Sample Name	LAT-190927	**Batch Number**	190927
Sample Number	20191009004	**Sample Amount**	20 mg
Chemical Formula:	$C_{13}H_{17}Cl_2NO$	**Sample Received**	2019-10-09
Molecular Weight:	274.19	**Test Items**	C、H、N
Reference Methods	JYT017-1996		

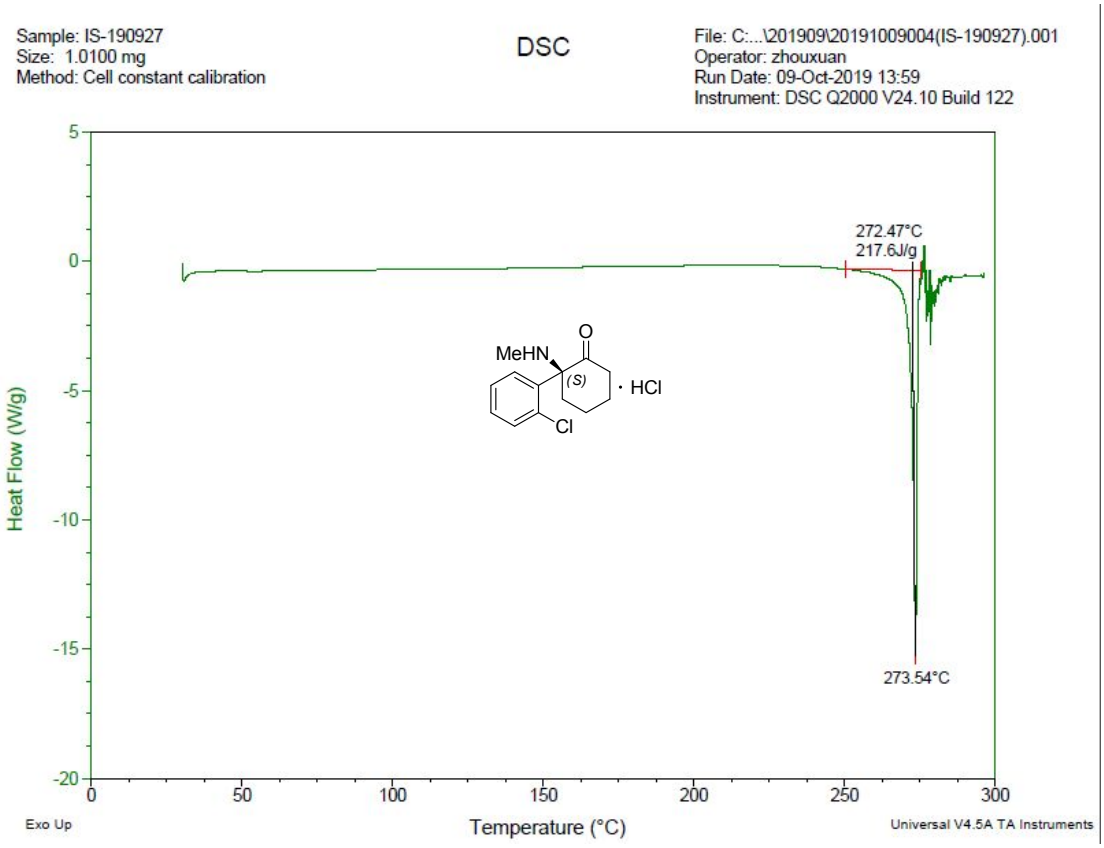
Test Items	Specification	Test Results
C	56.95	56.83/56.82
H	6.25	6.25/6.27
N	5.11	5.09/5.12

End of Repot

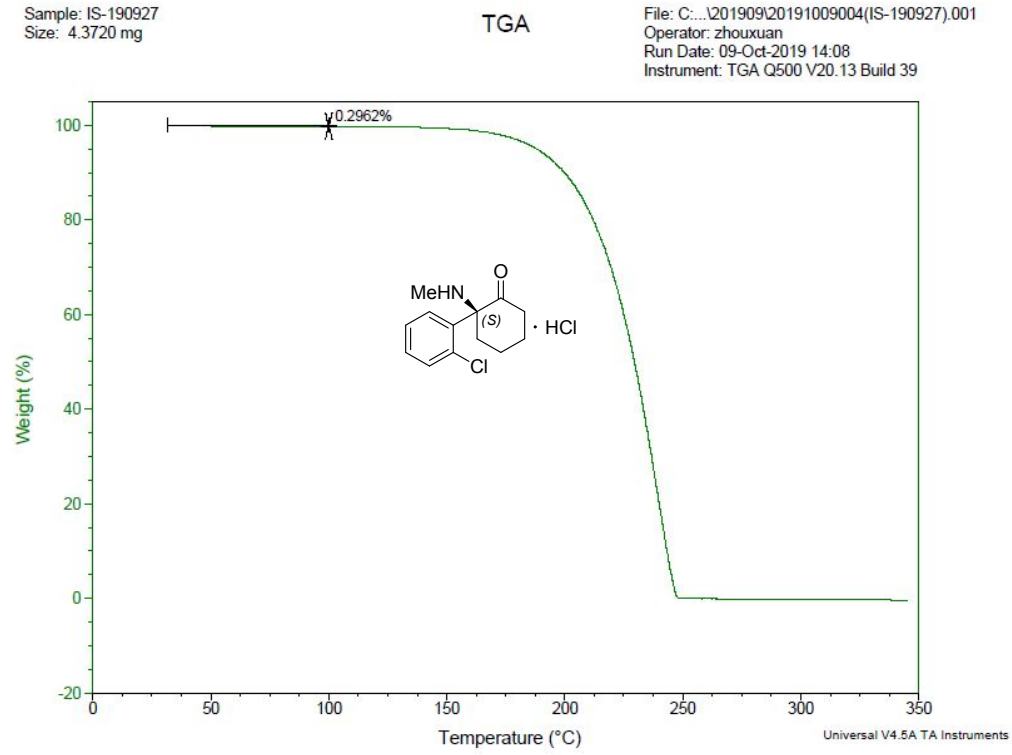


Elemental Analysis: C, 56.95; H, 6.25; N, 5.11

2.8 DSC


Sample: IS-190927
Size: 1.0100 mg
Method: Cell constant calibration
DSC
File: C:...\201909\20191009004(IS-190927).001
Operator: zhouxuan
Run Date: 09-Oct-2019 13:59
Instrument: DSC Q2000 V24.10 Build 122
272.47°C
217.6J/g
273.54°C
MeHN
(S)
· HCl
Cl
Heat Flow (W/g)
Temperature (°C)
Exo Up
Universal V4.5A TA Instruments

2.9 TGA


Sample: IS-190927
Size: 4.3720 mg
TGA
File: C:...\201909\20191009004(IS-190927).001
Operator: zhouxuan
Run Date: 09-Oct-2019 14:08
Instrument: TGA Q500 V20.13 Build 39
0.2962%
MeHN
(S)
· HCl
Cl
Weight (%)
Temperature (°C)
Universal V4.5A TA Instruments

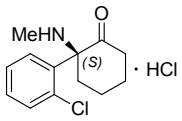
2.10 Optical rotation

Anton Paar MCP 500 - Measurement Results:

Software version: 2.10.53255.92
MCP serial number: 80679479

Sample Information:

- Unique Sample Id: 4743
- Date: 2019-10-12
- Time: 14:16:28
- Method: Specific Rotation
- User: Administrator
- Master Condition: valid
- Sample Name: 1s-190927
- Solvent name : H2O
- Concentration: 0.9883 g/100cm³



Measurement Result:

Sub Measurement Number	Unique Sample Id	Time	Optical Rotation	Sample Cell Temperature	Specific Rotation (calc.)
			[°]	[°C]	[°]
1	4744	14:15:55	0.9042	19.99	91.488
2	4745	14:16:10	0.9049	19.99	91.559
3	4746	14:16:27	0.9045	19.99	91.518
average	4743	14:16:28	0.9045	19.99	91.522
std. dev.			0.000287	0.0000	0.029101

GxP Information (at 589 nm):

- Last Quartz Adjustment: 2019-8-6 11:32:52 by Administrator
- Last Check (80638216): 2019-10-12 14:00:53 by Administrator - Passed

2.11 ICP-MS (Aluminum detection)

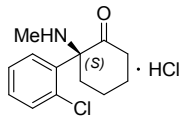
Shanghai Institute of Pharmaceutical Industry

TEST REPORT

Sample Name	1S-190927	Batch Number	190927
Sample Number	20191009004	Sample Amount	1.0 g
Sample State/Package	solid state	Sample Received	2019-10-09
Test Purpose	Request examination	Test Items	Element: **Al**
Reference Methods	2015 Chinese Pharmacopoeia, Four General Rules 0412		

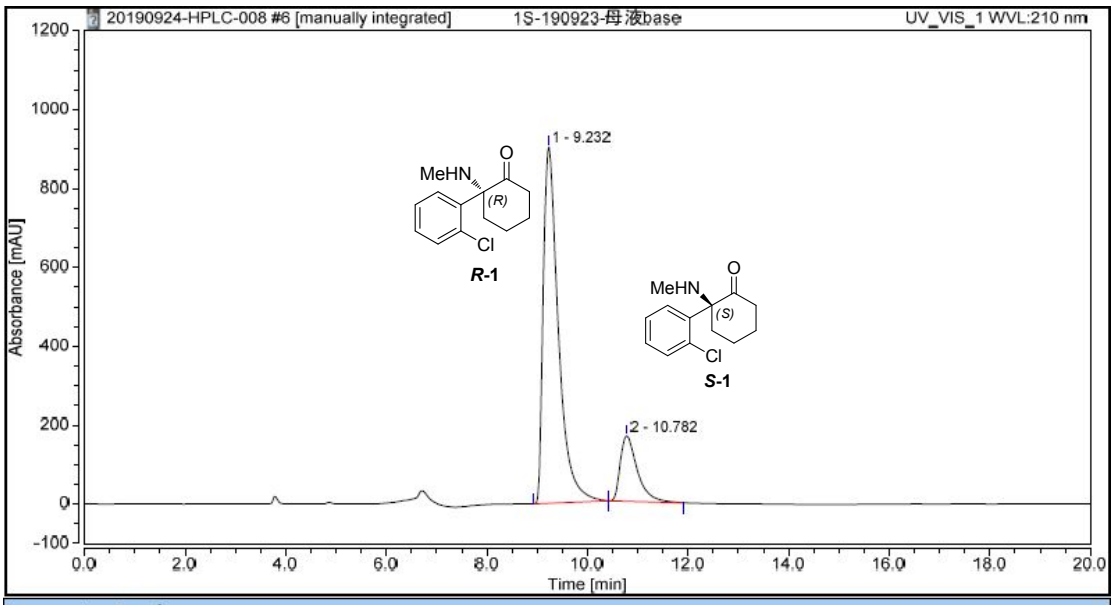
Test Items	Specification	Test Results
Al	/	<2.5 μg/g

End of Repot



3. HPLC and Analytical spectrograms of the racemized Ketamine

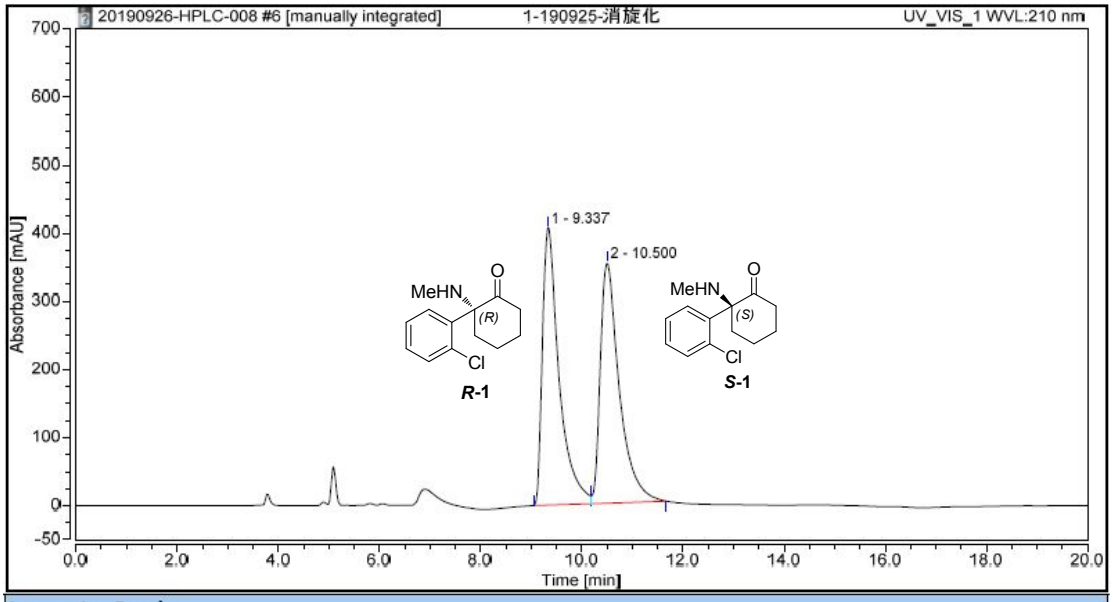
3.1 NP-HPLC spectrogram of the resolution mother liquors enriched (*R*)-1



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		9.232	314.330	902.867	82.87	84.46	n.a.
2		10.782	64.991	166.105	17.13	15.54	n.a.
Total:			**379.322**	**1068.971**	**100.00**	**100.00**	

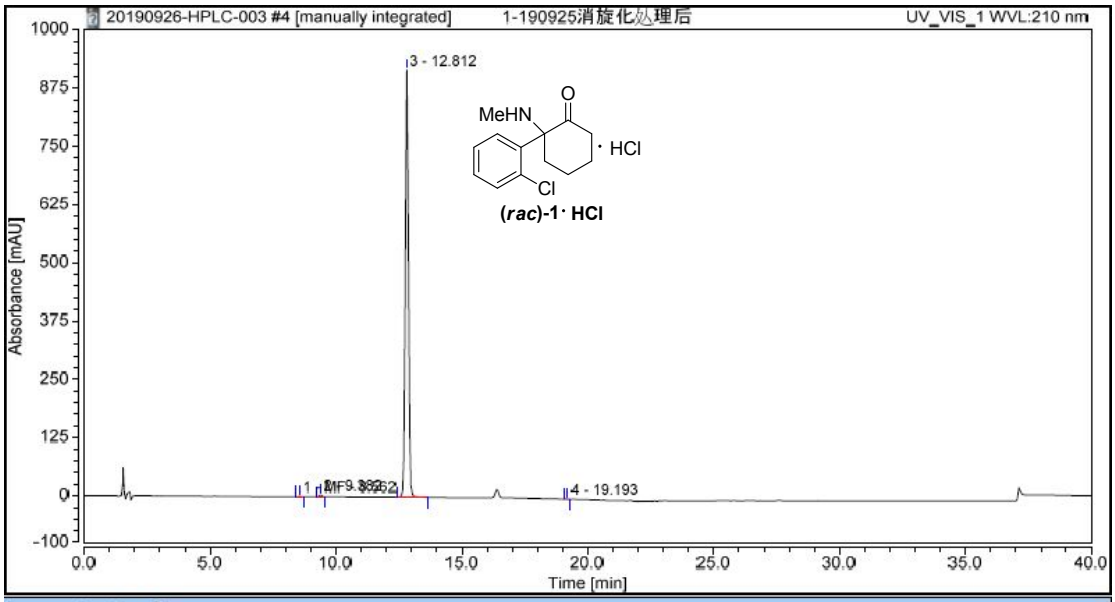
3.2 NP-HPLC spectrogram of the racemized ketamine (0.1 eq $AlCl_3$, 22 h, 150℃)



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		9.337	155.406	407.998	50.31	53.60	n.a.
2		10.500	153.486	353.258	49.69	46.40	n.a.
Total:			**308.892**	**761.256**	**100.00**	**100.00**	

3.1 RP-HPLC spectrogram of the racemized ketamine (0.1 eq $AlCl_3$, 22 h, 150℃)



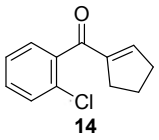
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1	MF	8.562	0.055	0.544	0.04	0.06	n.a.
2		9.382	0.461	4.297	0.35	0.47	n.a.
3		12.812	132.053	916.979	99.58	99.43	n.a.
n.a.	KDY	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
4		19.193	0.047	0.458	0.04	0.05	n.a.
Total:			**132.617**	**922.278**	**100.00**	**100.00**	

4. Analytical spectra of impurities 14, 15, 17, 21, 22 in Intermediate 4

4.1 Analytical spectra of impurity 14

4.1.1 HRMS



14

Exact Mass: 206.05

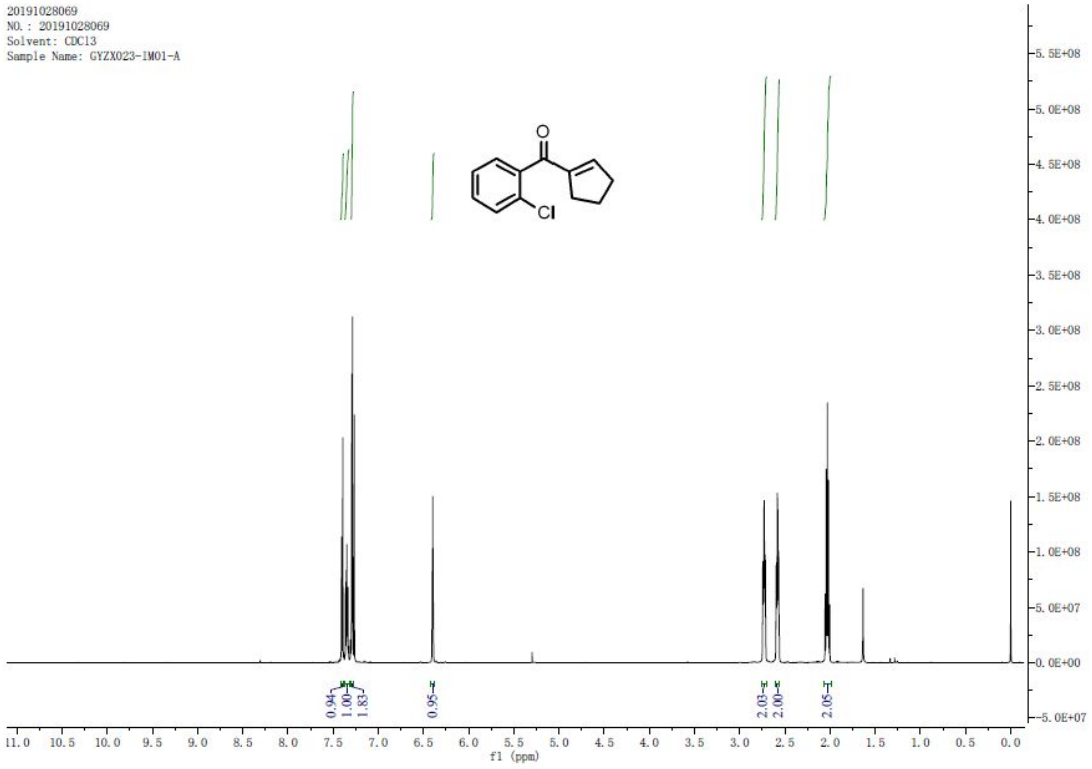
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
13 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-50 O: 0-1 Na: 1-1 Cl: 0-1

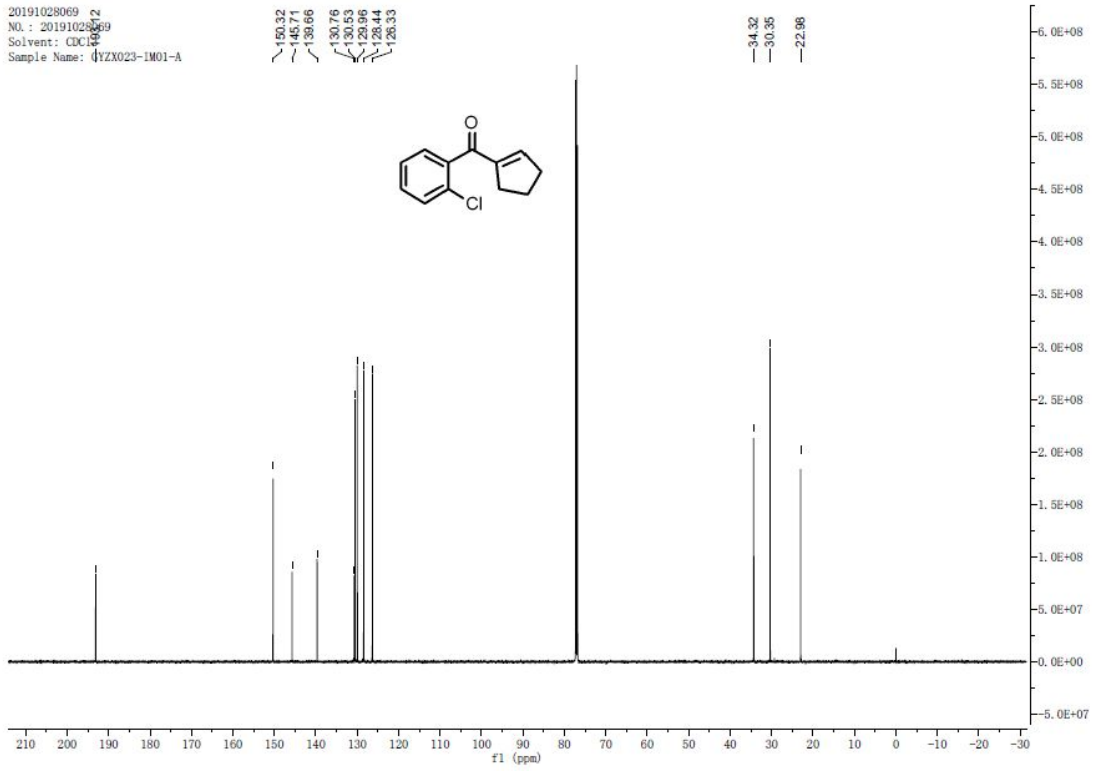
SIPI Q-Tof micro 11:07:23,30-Oct-2019
GYZX023-IM01-A YA019
Q19-1491HR 12 (0.223) AM (Cen,2, 80.00, Ar,5000.0,222.11,2.00); Sm (Mn, 2x3.00); Sb (1,5.00); Cm (4:19) TOF MS ES+ 4.39e+002

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
229.0398	229.0396	0.2	0.9	6.5	n/a	C12 H11 O Na Cl

4.1.2 ^{1}H NMR



4.1.3 ^{13}C NMR

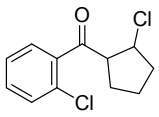


4.1.3 DEPT

4.2 Analytical spectra of impurity 15

4.2.1 HRMS

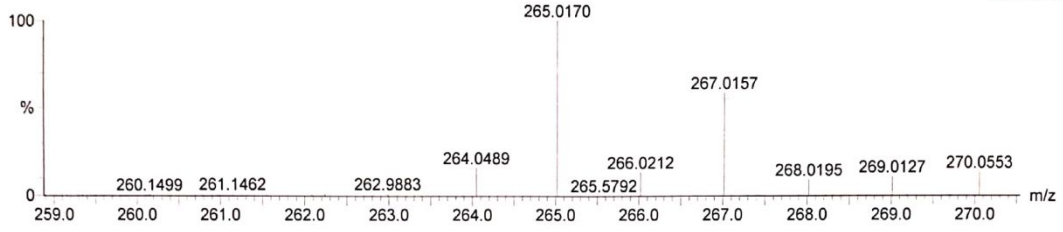
Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



15
Exact Mass: 242.03

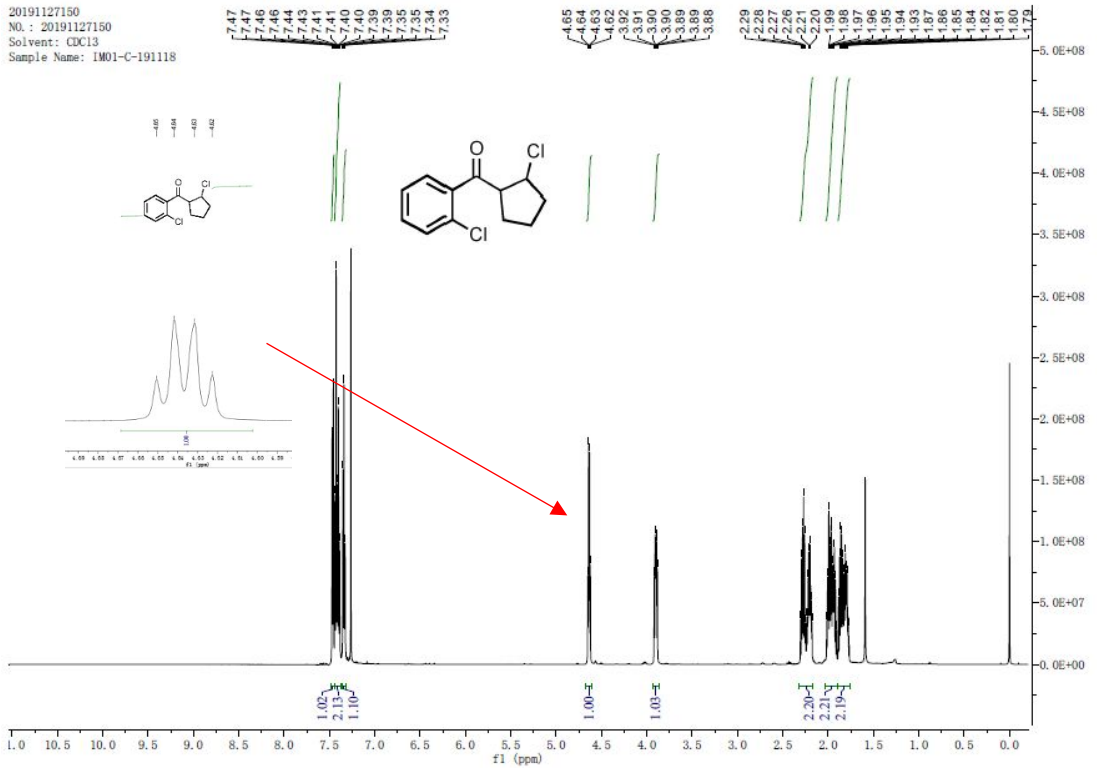
Monoisotopic Mass, Even Electron Ions
20 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-50 O: 0-1 Na: 1-1 Cl: 0-2

SIPI
IM01-C-191118
Q19-1623HR 12 (0.223) AM (Cen,2, 80.00, Ar,5000.0,248.08,2.00); Sm (Mn, 2x3.00); Sb (1,5.00); Cm (12:14)
Q-Tof micro
YA019
10:31:27,09-Dec-2019
TOF MS ES+
1.03e+003

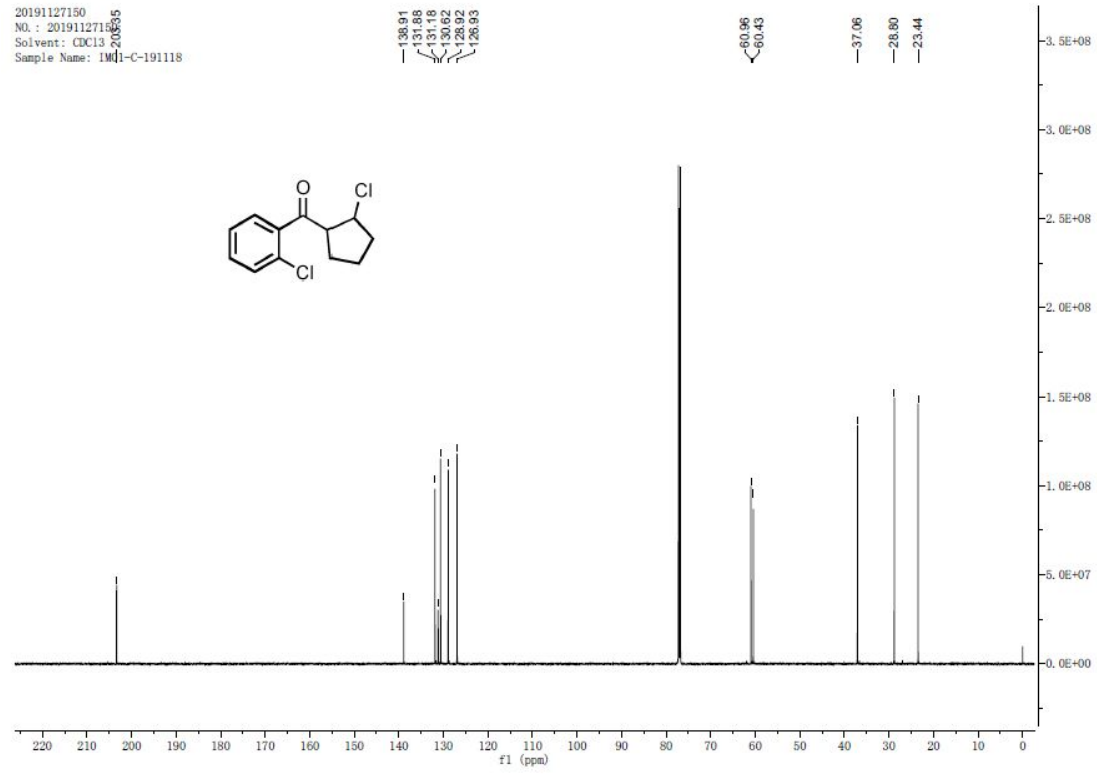


Minimum:				-1.5		
Maximum:		5.0	20.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
265.0170	265.0163	0.7	2.6	5.5	2.3	C12 H12 O Na Cl2

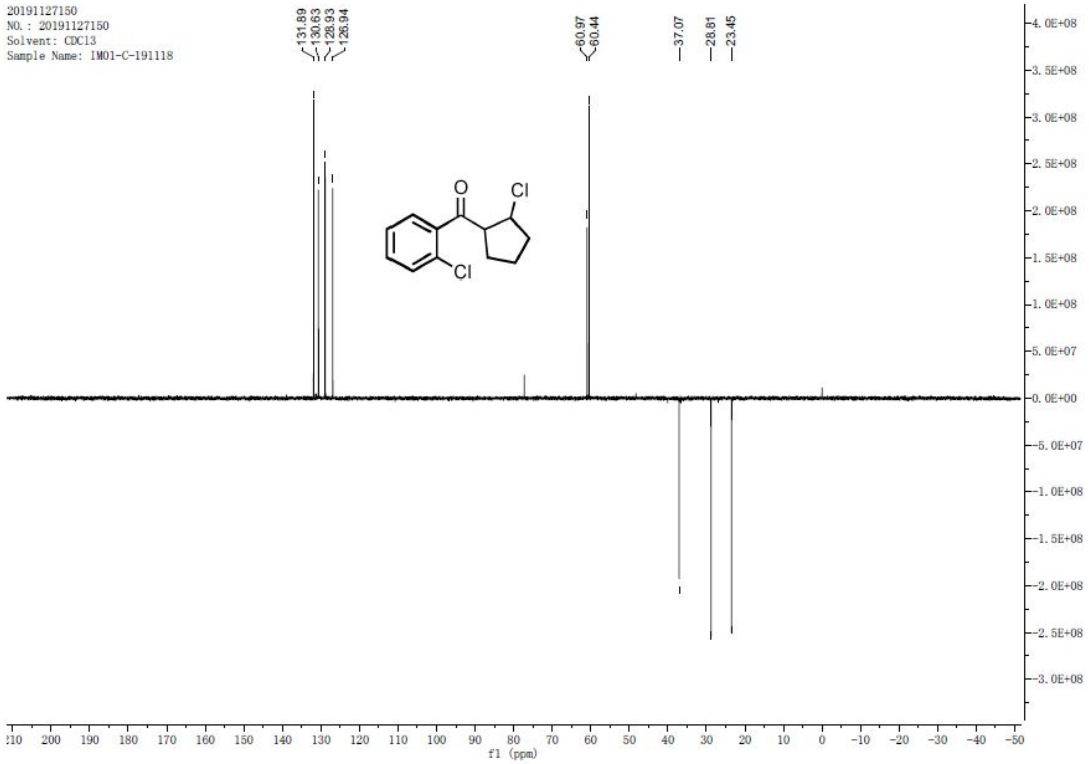
4.2.2 ^{1}H NMR



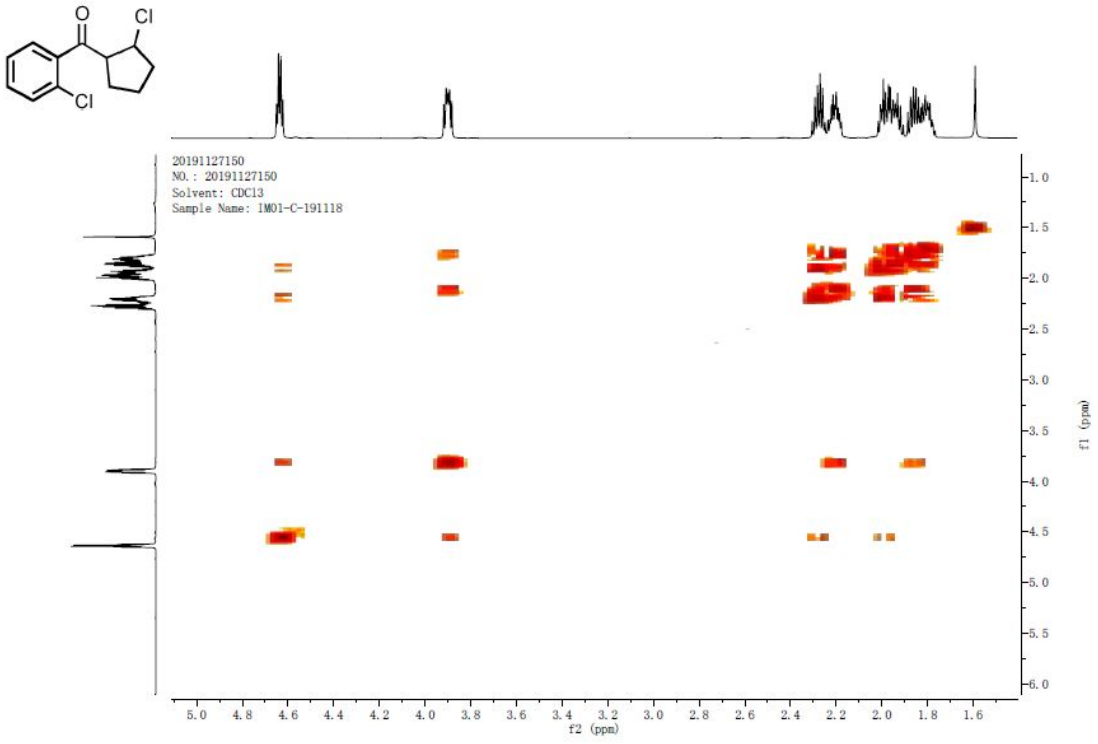
4.2.3 ^{1}H NMR



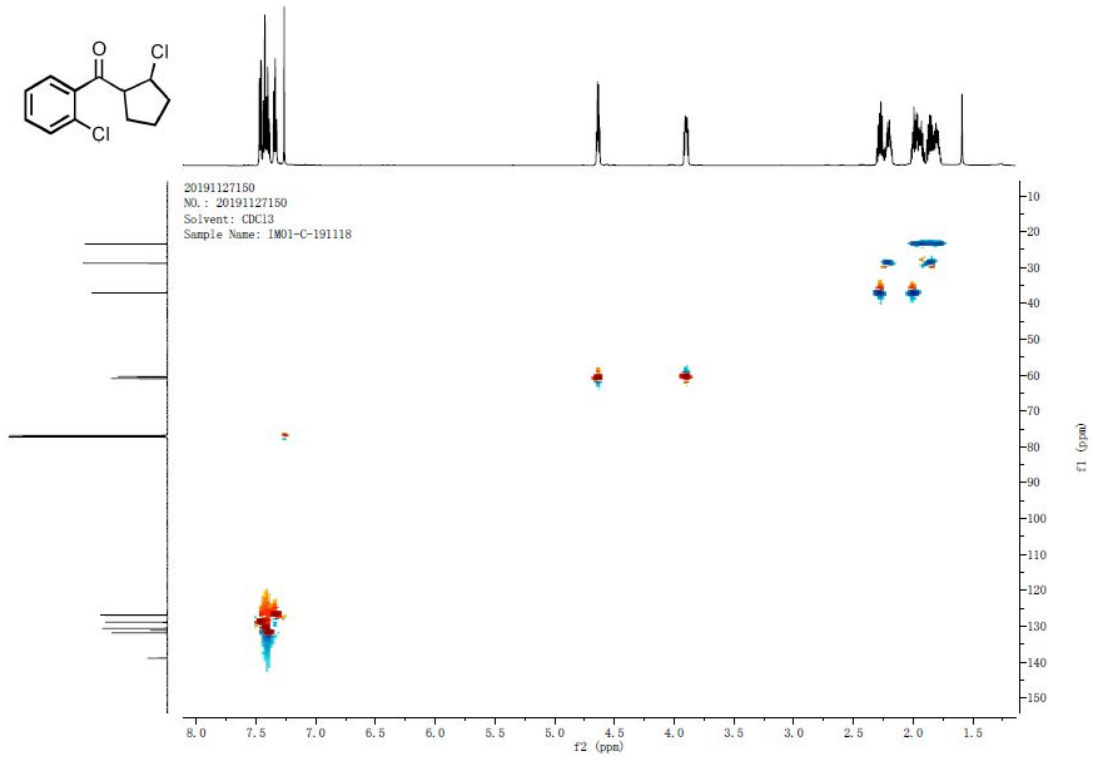
4.2.4 DEPT



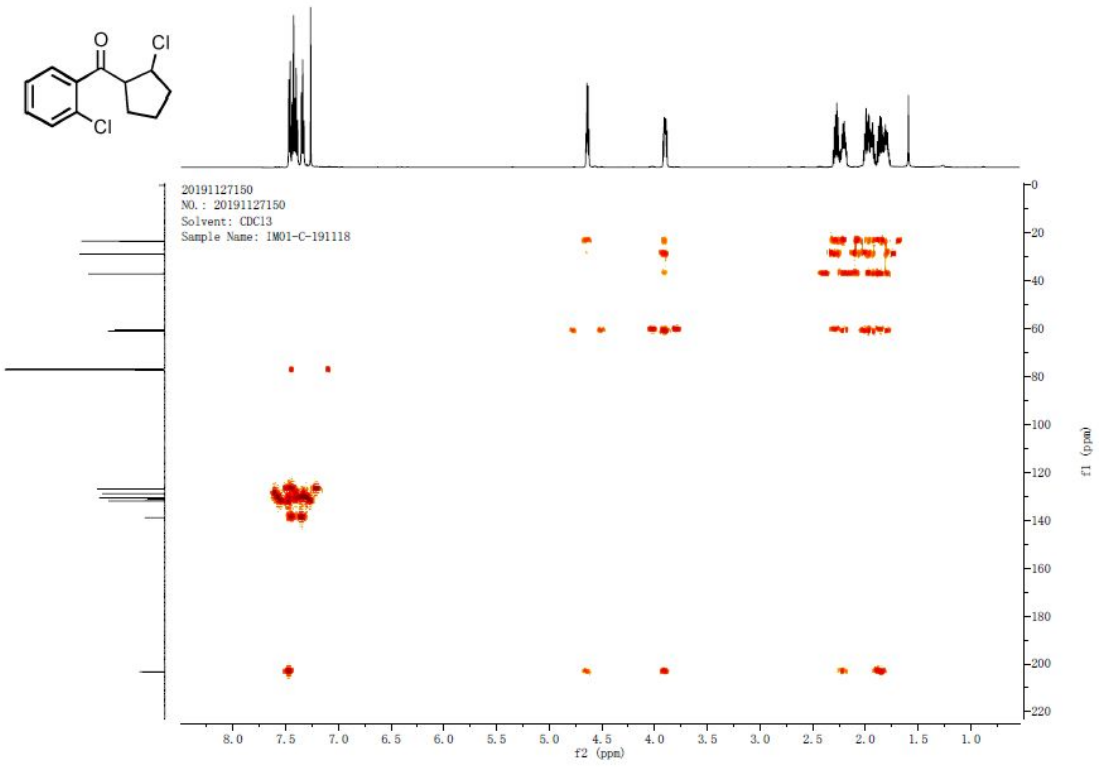
4.2.5 H-H COSY



4.2.6 HSQC

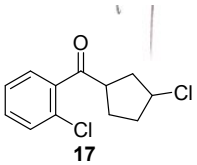


4.2.7 HMBC



4.3 Analytical spectra of impurity 17

4.3.1 HRMS



17

Exact Mass: 242.03

Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

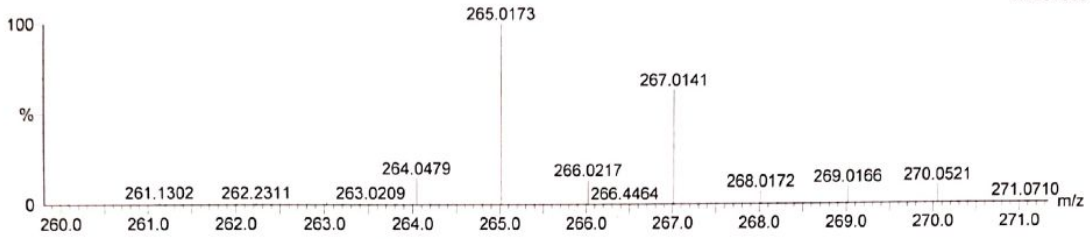
Monoisotopic Mass, Even Electron Ions
20 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-50 O: 0-1 Na: 1-1 Cl: 0-2

SIPI
IM01-D-191118
Q19-1624HR 9 (0.167) AM (Cen,2, 80.00, Ar,5000.0,248.08,2.00); Sm (Mn, 2x3.00); Sb (1,5.00); Cm (6:14)

Q-Tof micro
YA019

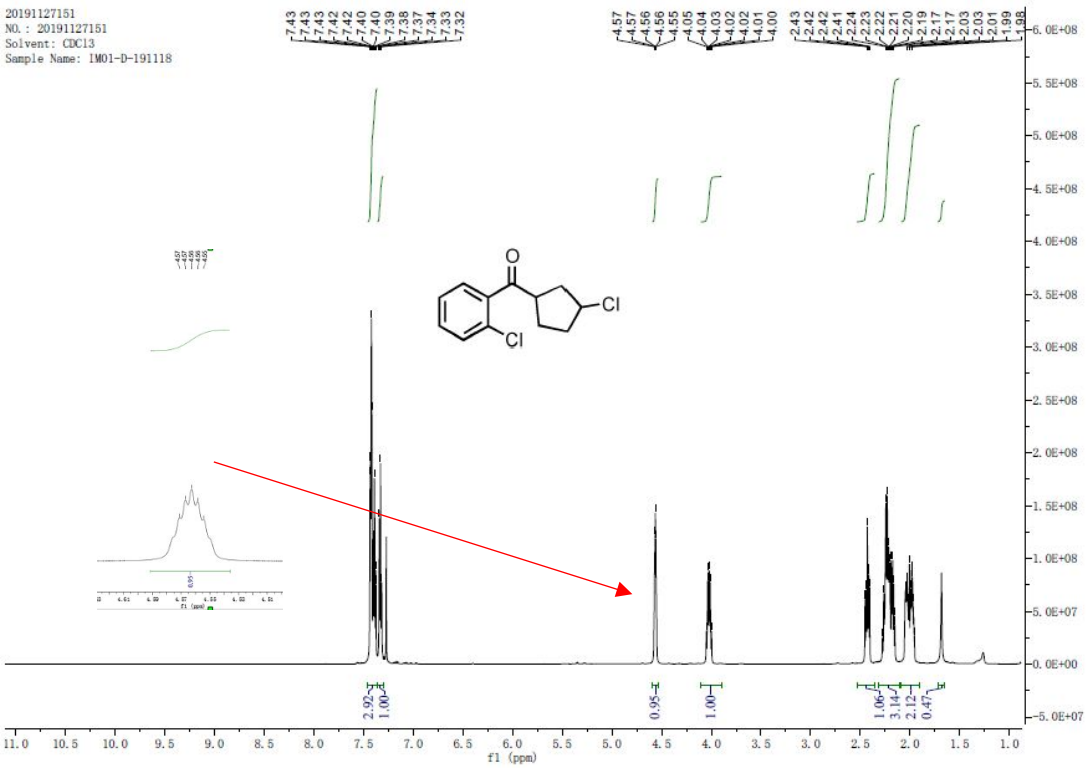
10:38:18,09-Dec-2019

TOF MS ES+
1.42e+003

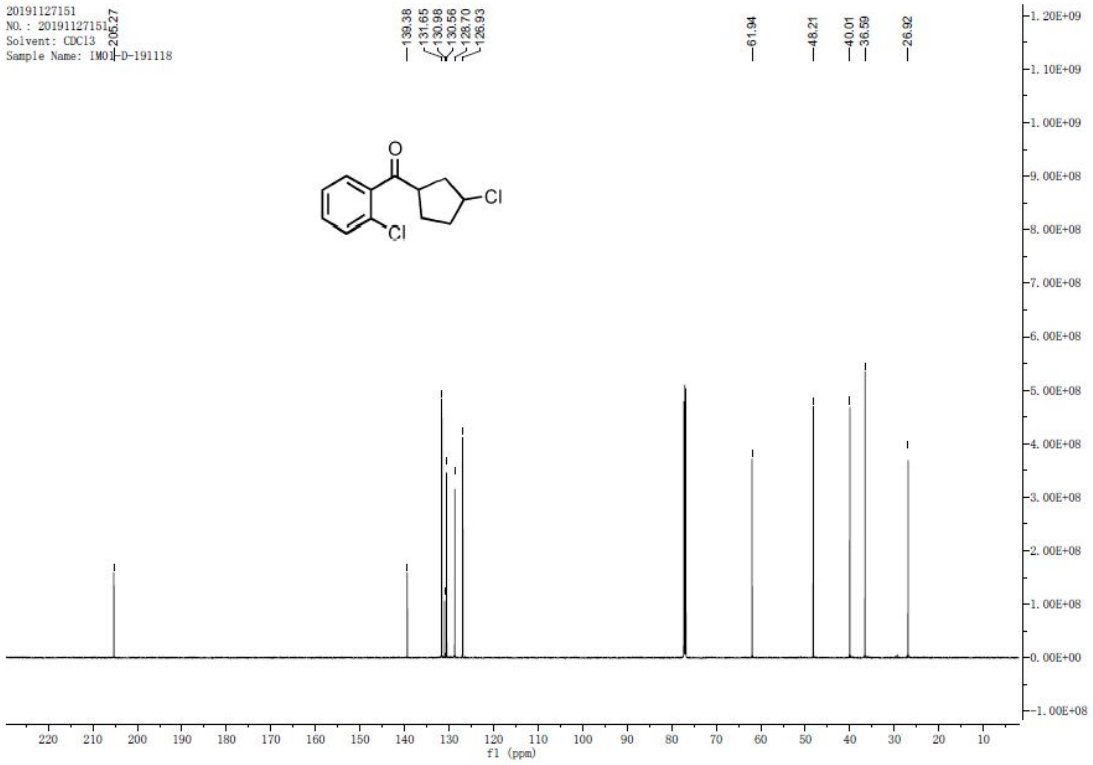


Minimum:				-1.5		
Maximum:		5.0	20.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
265.0173	265.0163	1.0	3.8	5.5	0.3	C12 H12 O Na Cl2

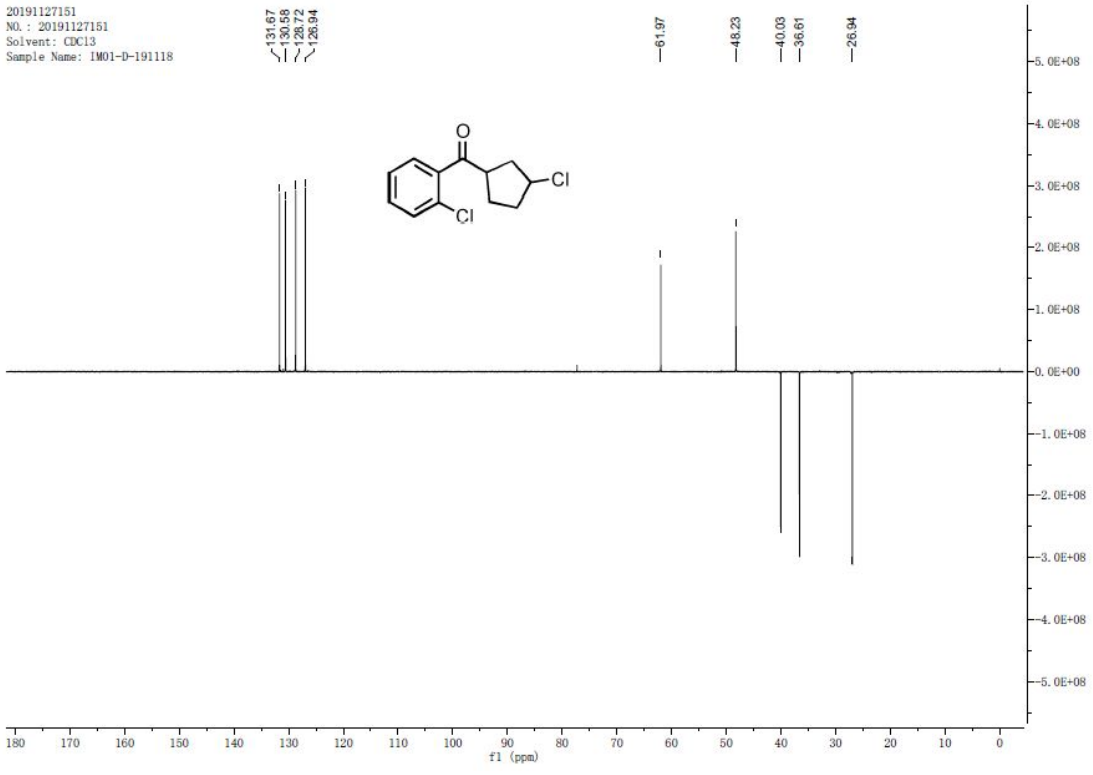
4.3.2 ^{1}H NMR



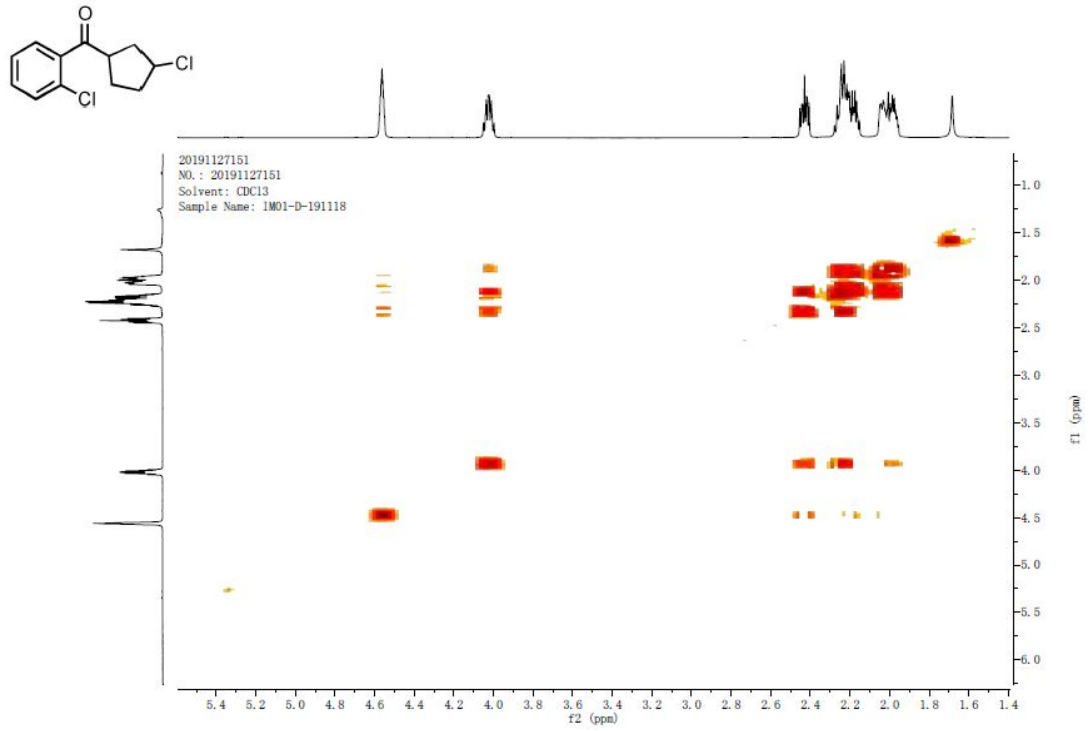
4.3.3 ^{13}C NMR



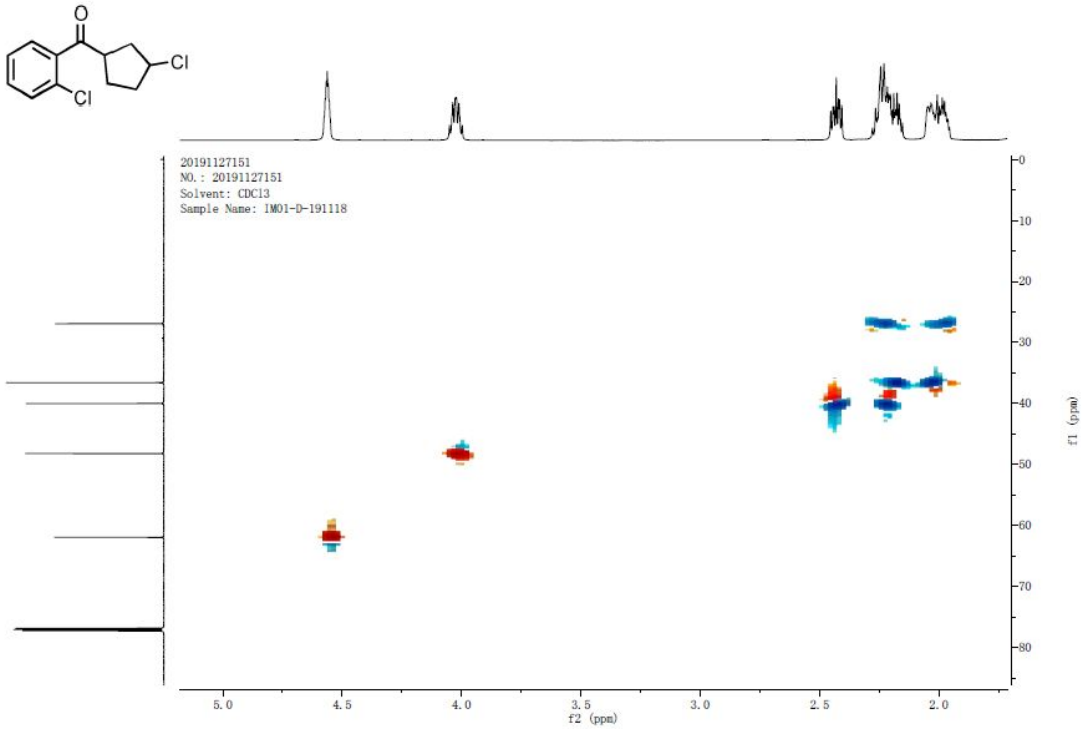
4.3.4 DEPT



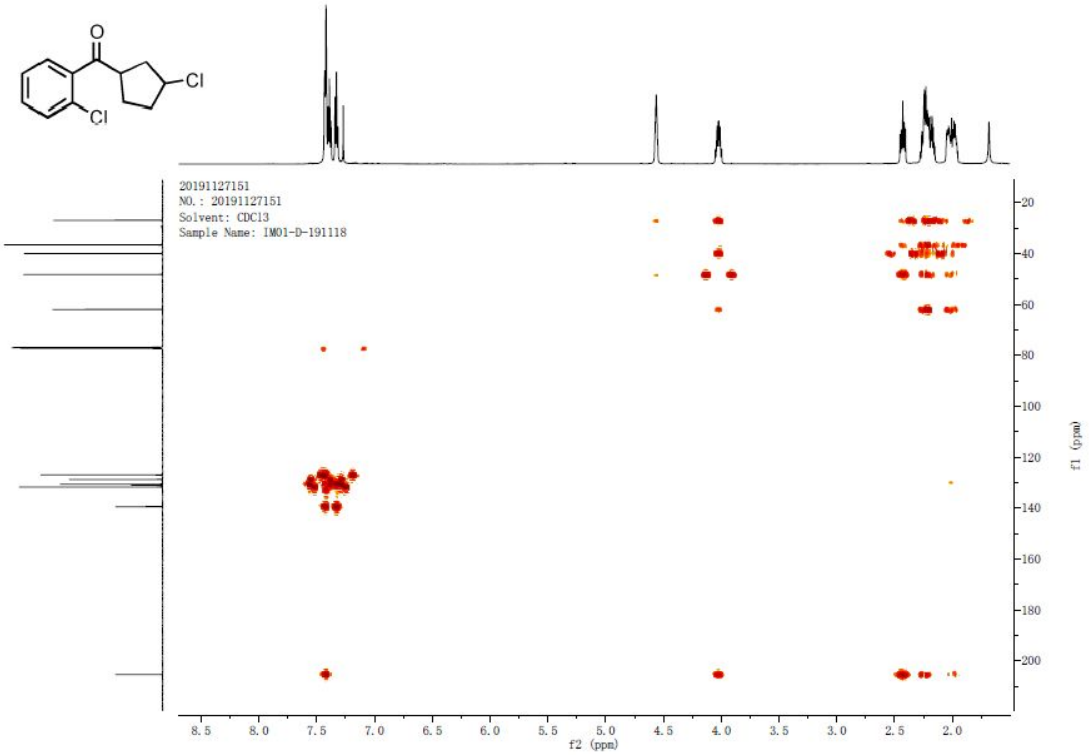
4.3.5 H-H COSY



4.3.6 HSQC

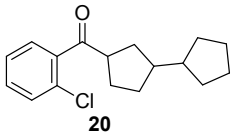


4.3.7 HMBC



4.4 Analytical spectra of impurity 20

4.4.1 HRMS



20

Exact Mass: 276.13

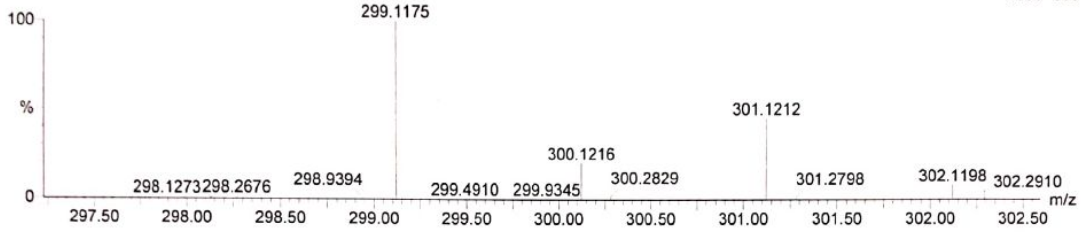
Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
16 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-50 O: 0-1 Na: 1-1 Cl: 0-1

SIPI
IM01-L-191119
Q19-1641HR 29 (0.539) AM (Cen,2, 80.00, Ar,5000.0,248.08,2.00); Sm (Mn, 2x3.00); Sb (1,5.00); Cm (11:29)

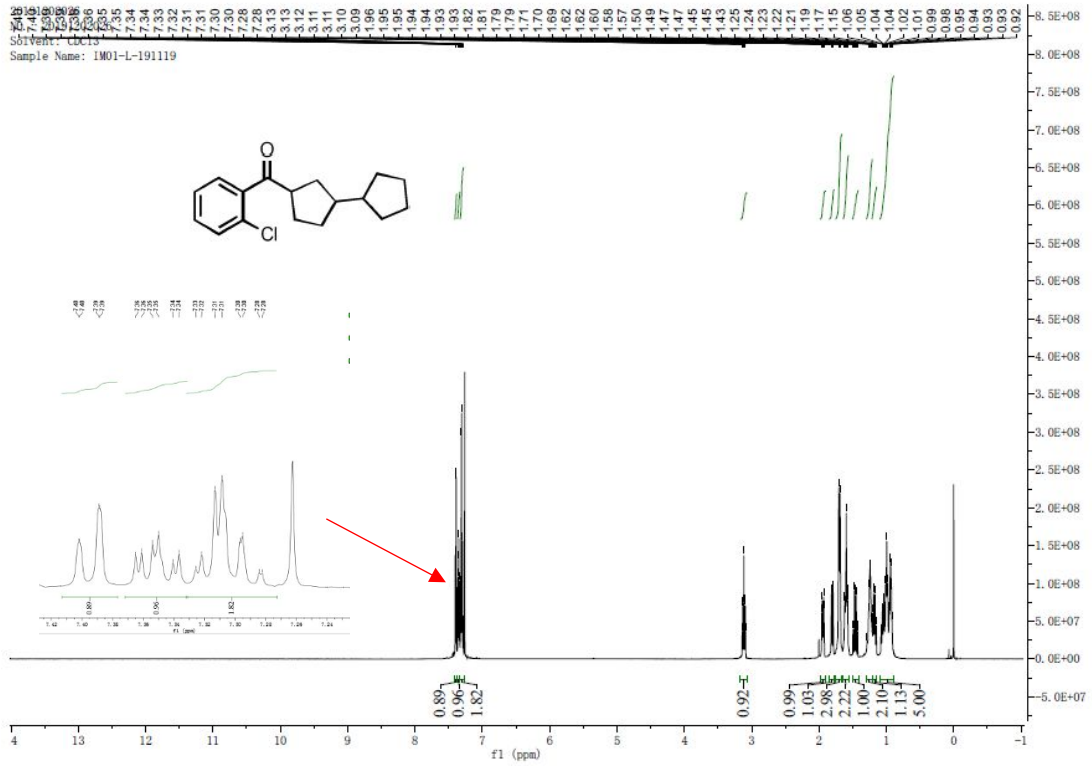
Q-Tof micro
YA019

10:23:45,09-Dec-2019
TOF MS ES+
1.09e+003

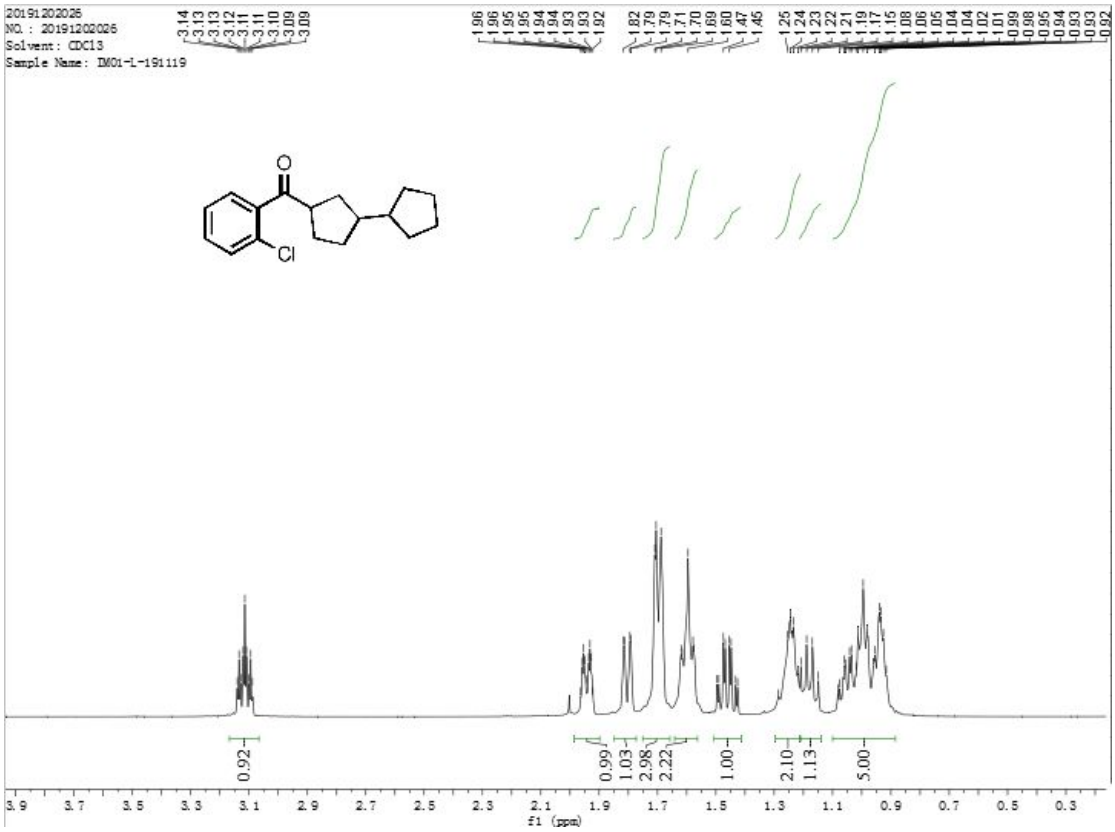


Minimum:				-1.5		
Maximum:		5.0	20.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
299.1175	299.1179	-0.4	-1.3	6.5	13.8	C17 H21 O Na Cl

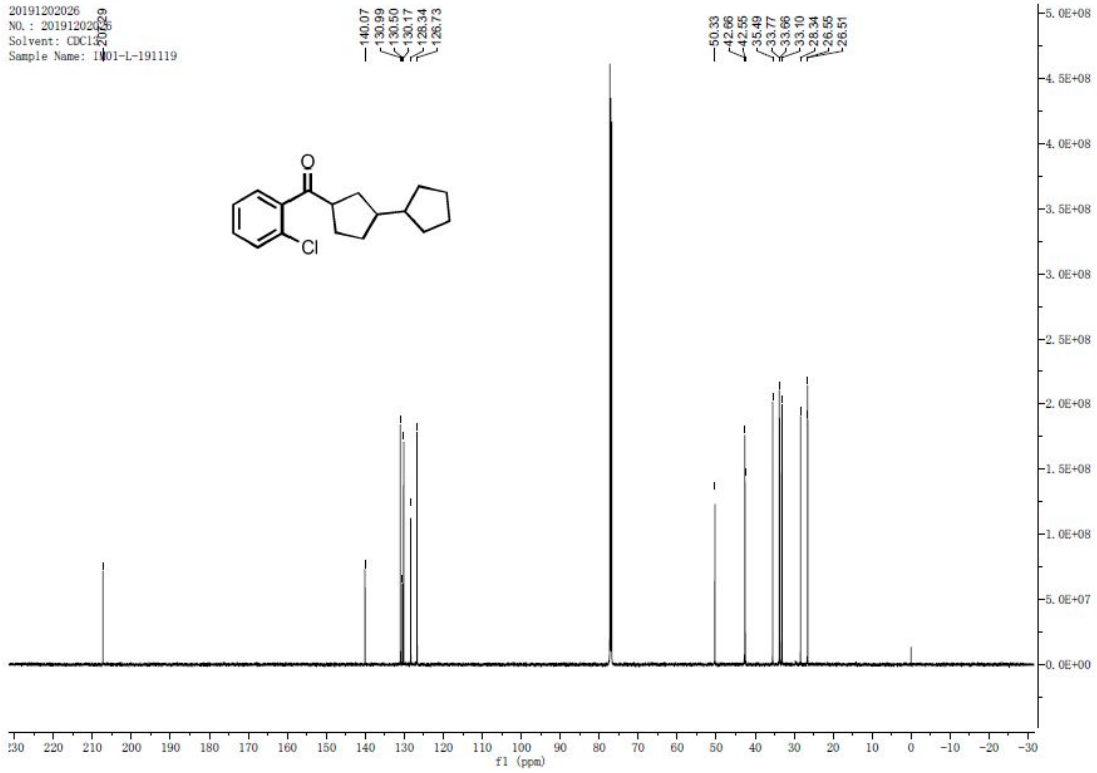
4.4.2 ^{1}H NMR



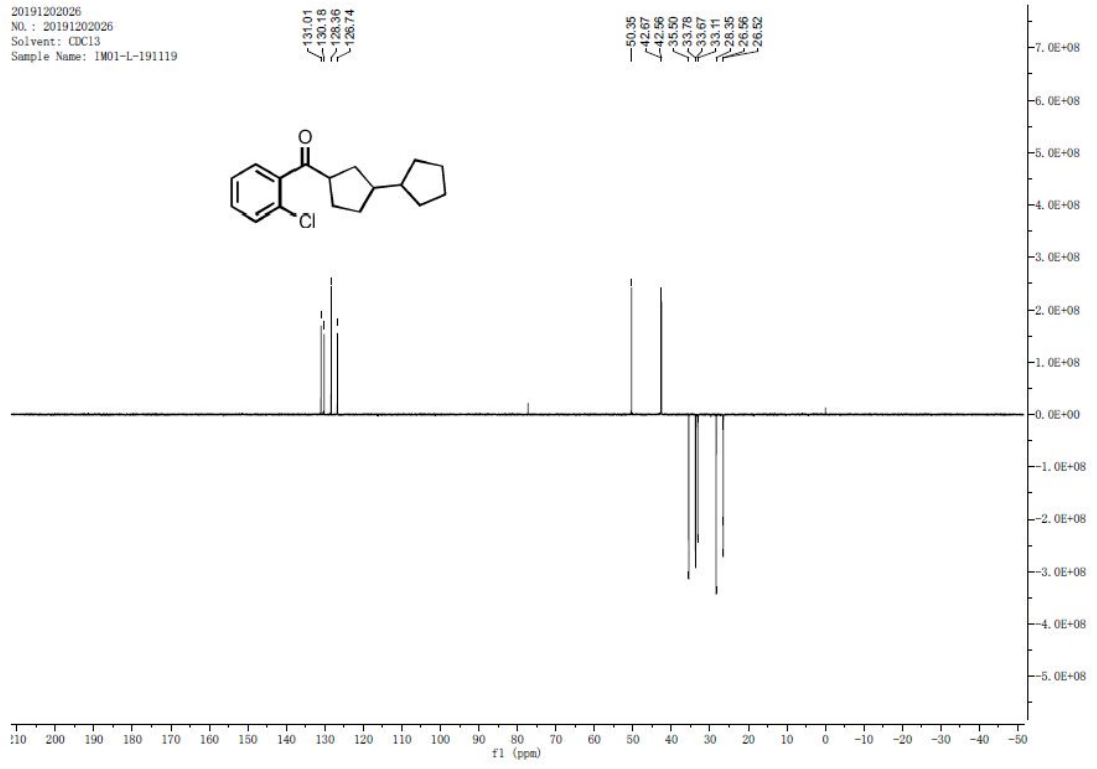
4.4.3 Enlarged view of ^{1}H NMR



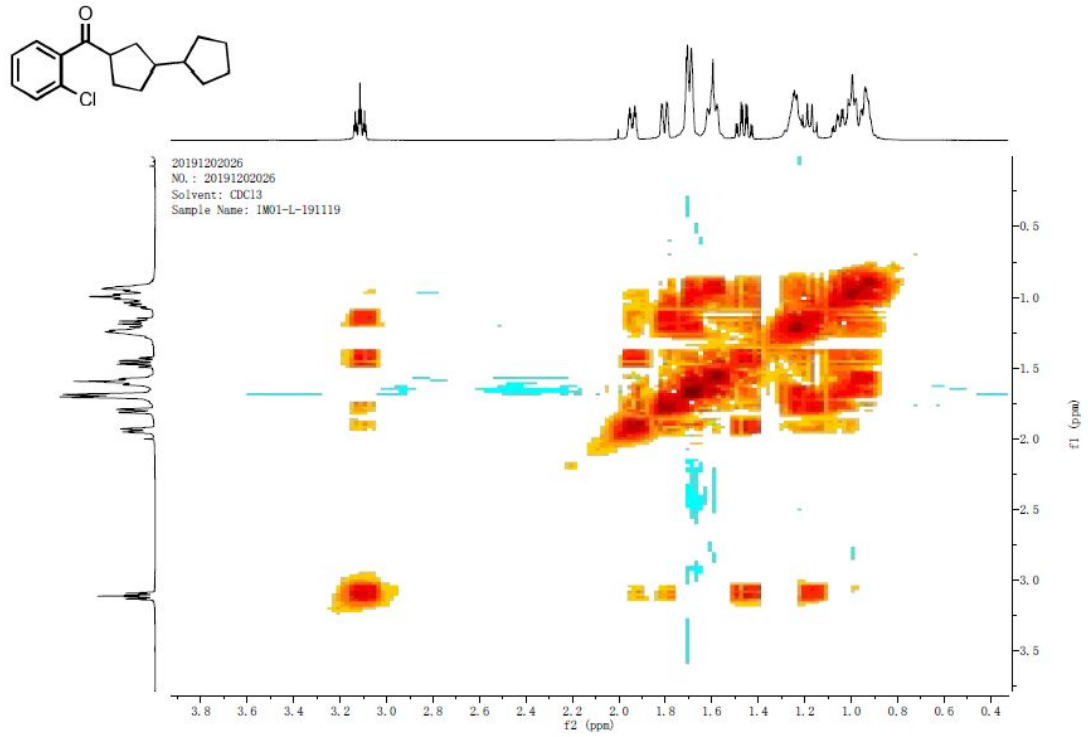
4.4.4 ^{13}C NMR



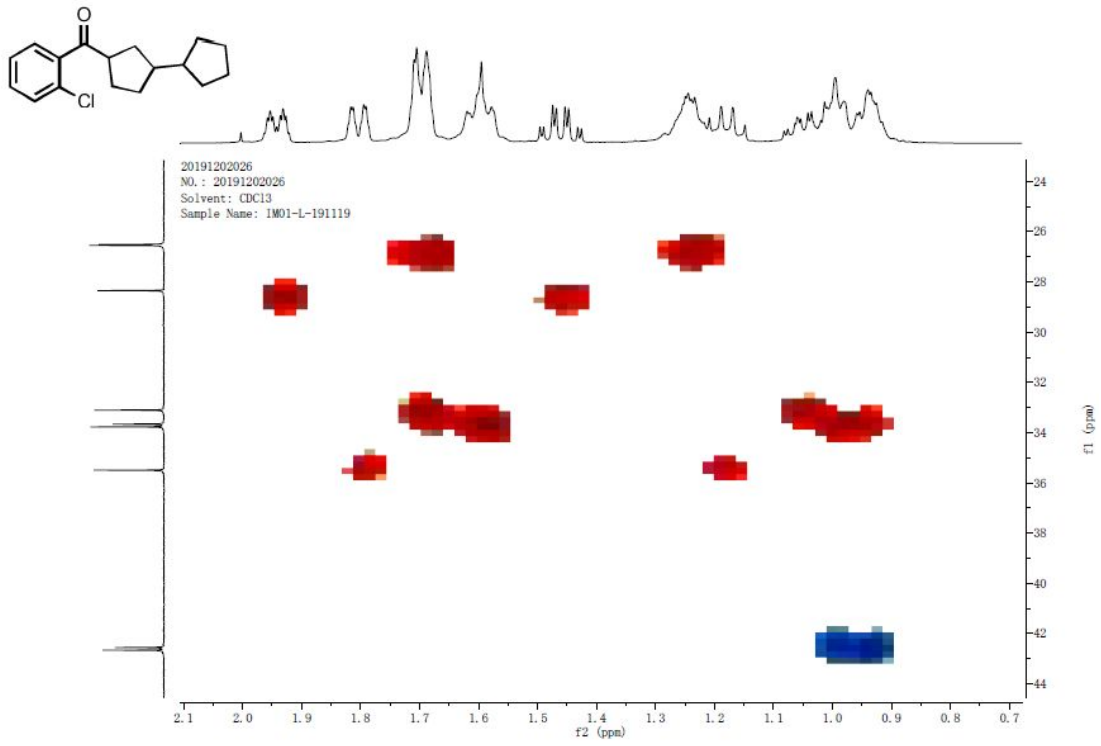
4.4.5 DEPT



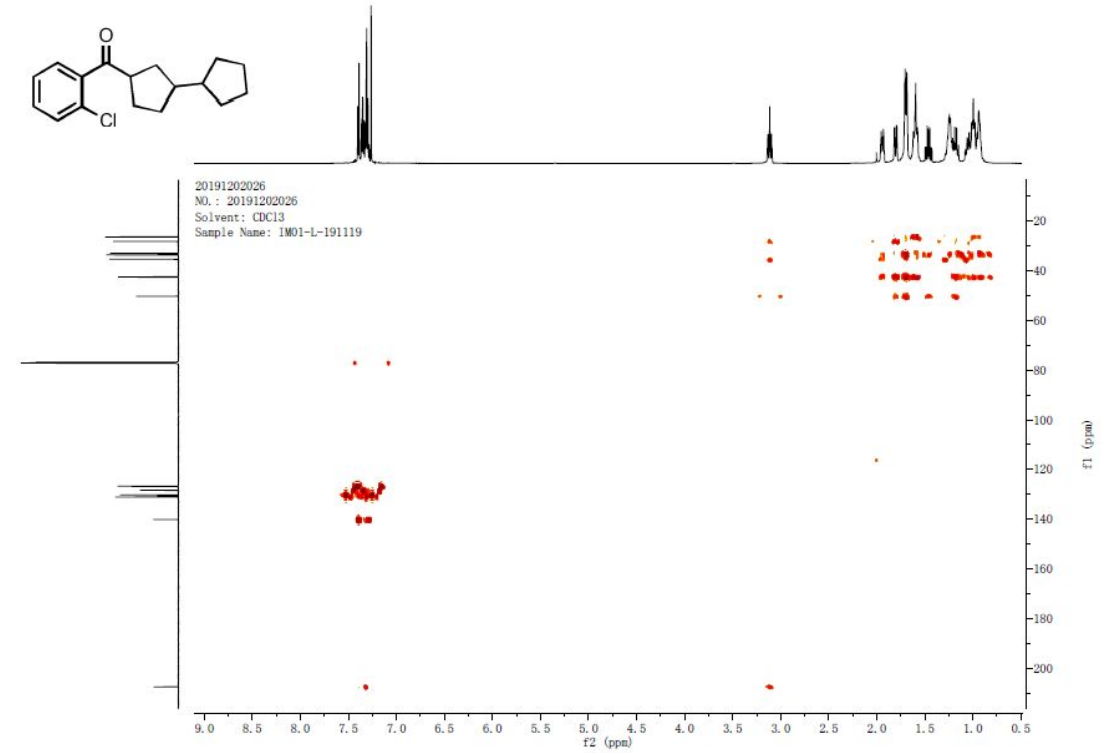
4.4.6 H-H COSY



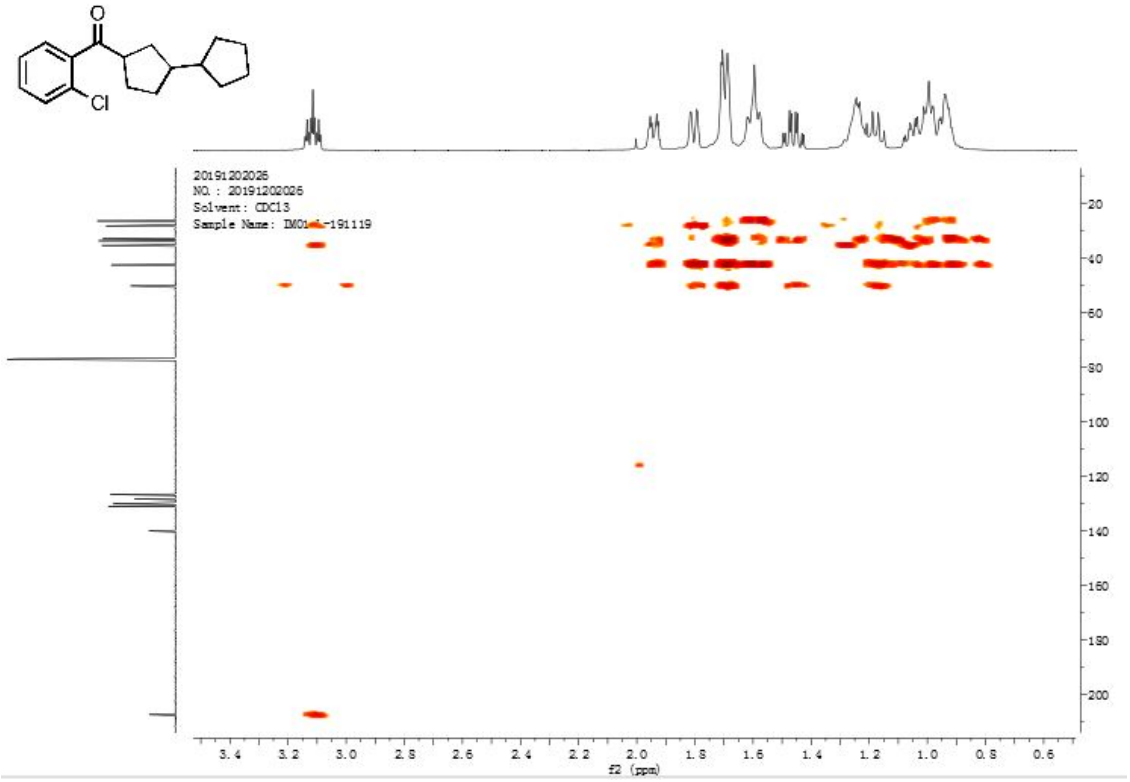
4.4.7 HSQC



4.4.8 HMBC

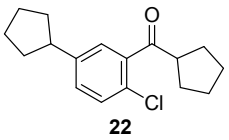


4.4.9 Enlarged view of HMBC



4.5 Analytical spectra of impurity 22

4.5.1 HRMS



22

Exact Mass: 276.13

Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

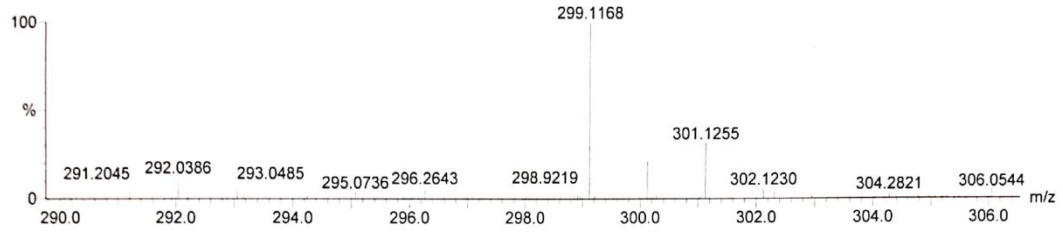
Monoisotopic Mass, Even Electron Ions
22 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-50 O: 0-1 Na: 1-1 Cl: 0-2

SIPI
IM01-G-191119
Q19-1642HR 12 (0.223) AM (Top,2, Ar,5000.0,264.05,2.00); Sm (SG, 2x3.00); Sb (1,5.00); Cm (8:30)

Q-Tof micro
YA019

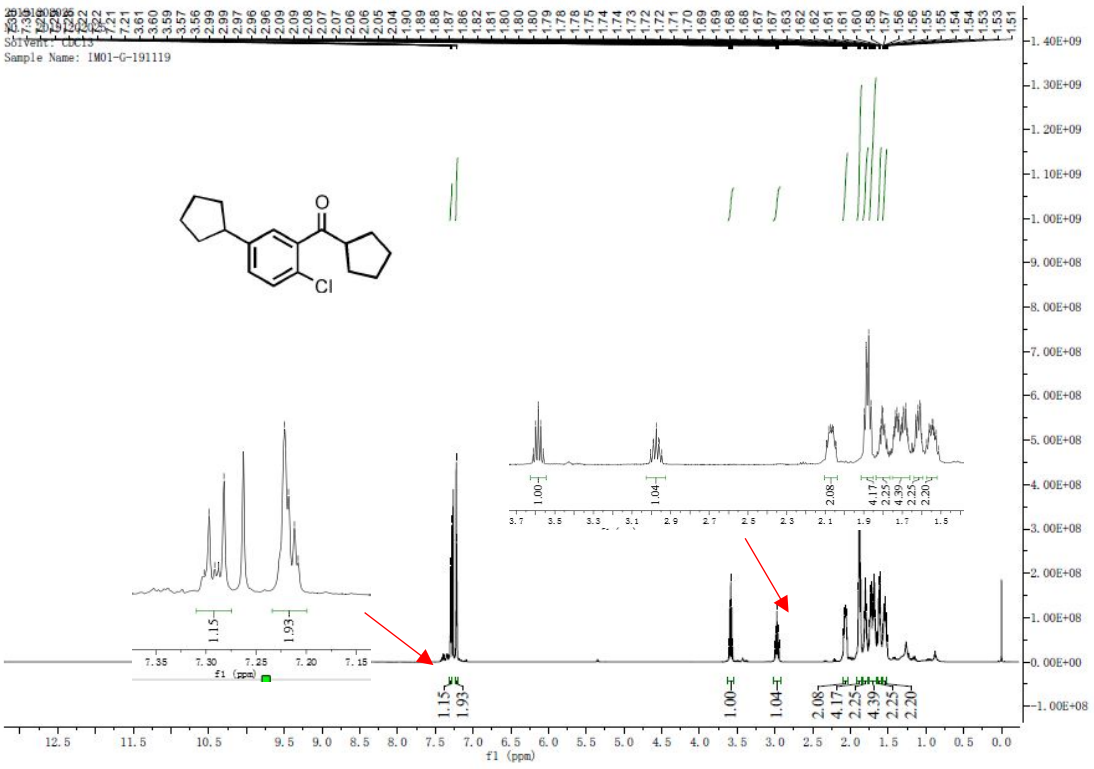
11:15:14,09-Dec-2019

TOF MS ES+
2.04e+002

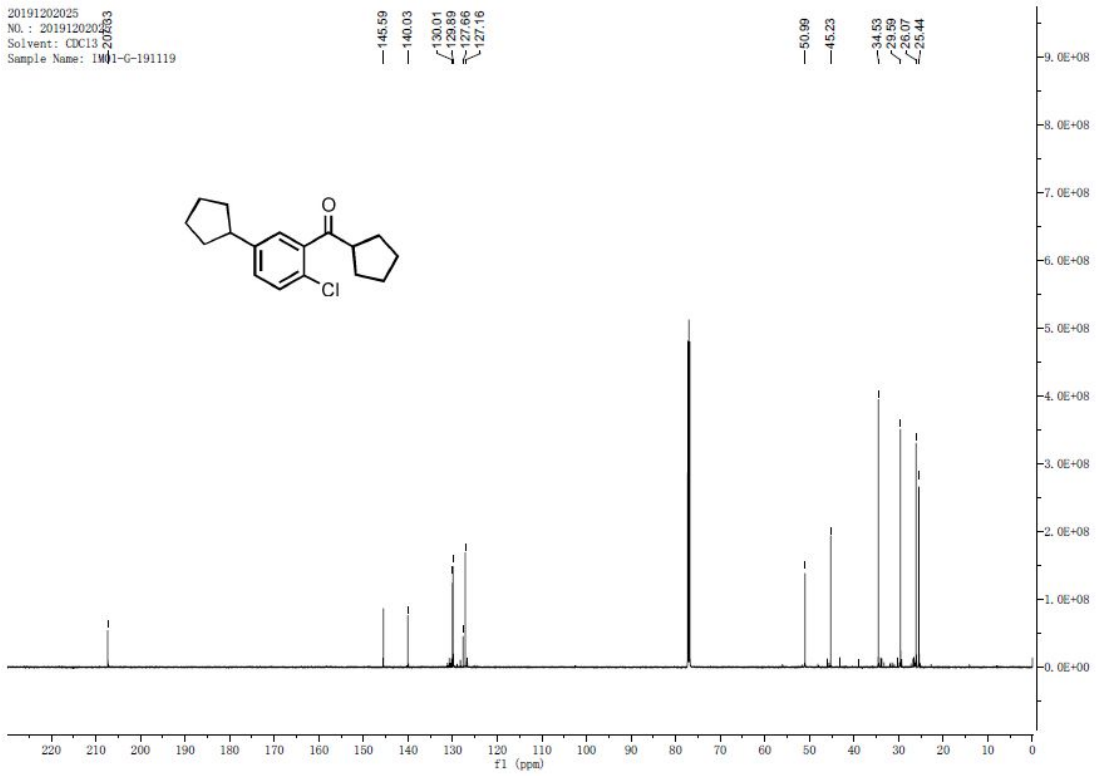


Minimum:				-1.5		
Maximum:		5.0	20.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
299.1168	299.1179	-1.1	-3.7	6.5	0.6	C17 H21 O Na Cl

4.5.2 ^{1}H NMR

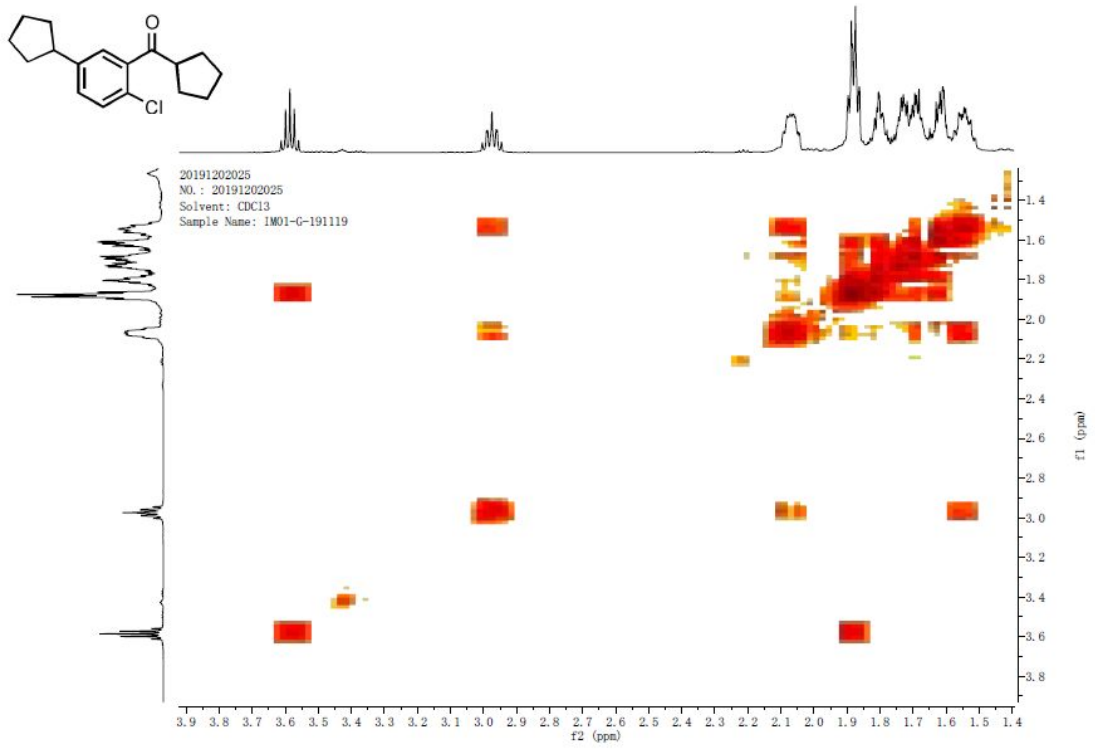


4.5.3 ^{13}C NMR

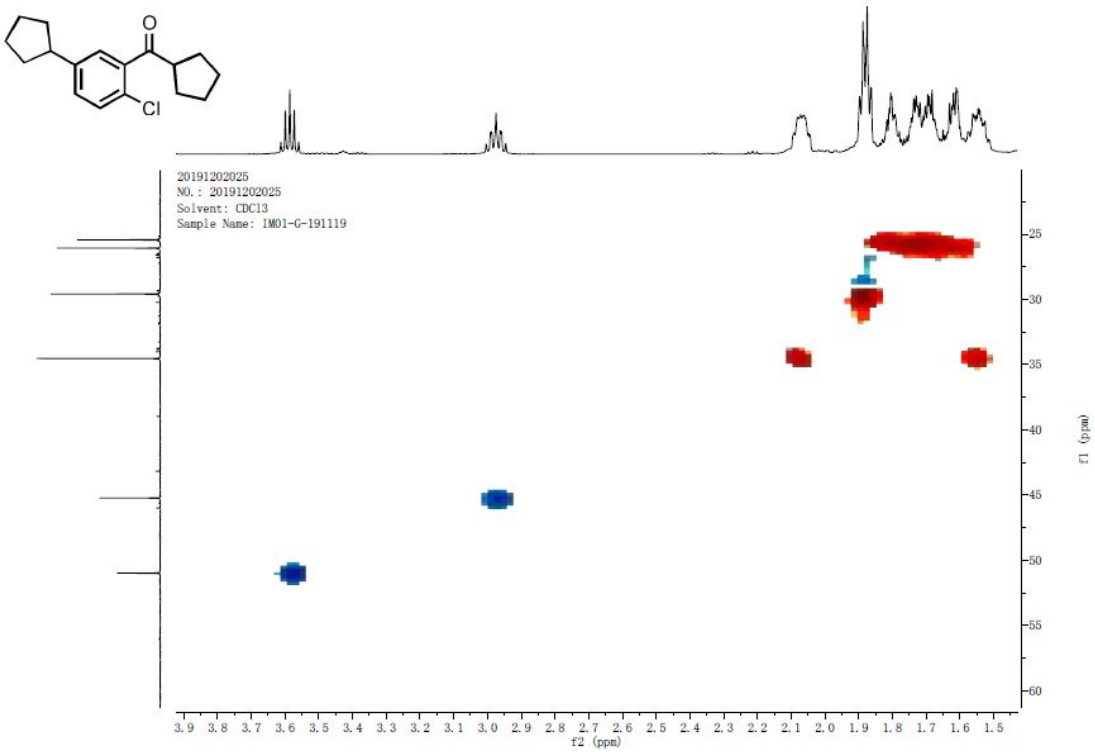


4.5.4 DEPT

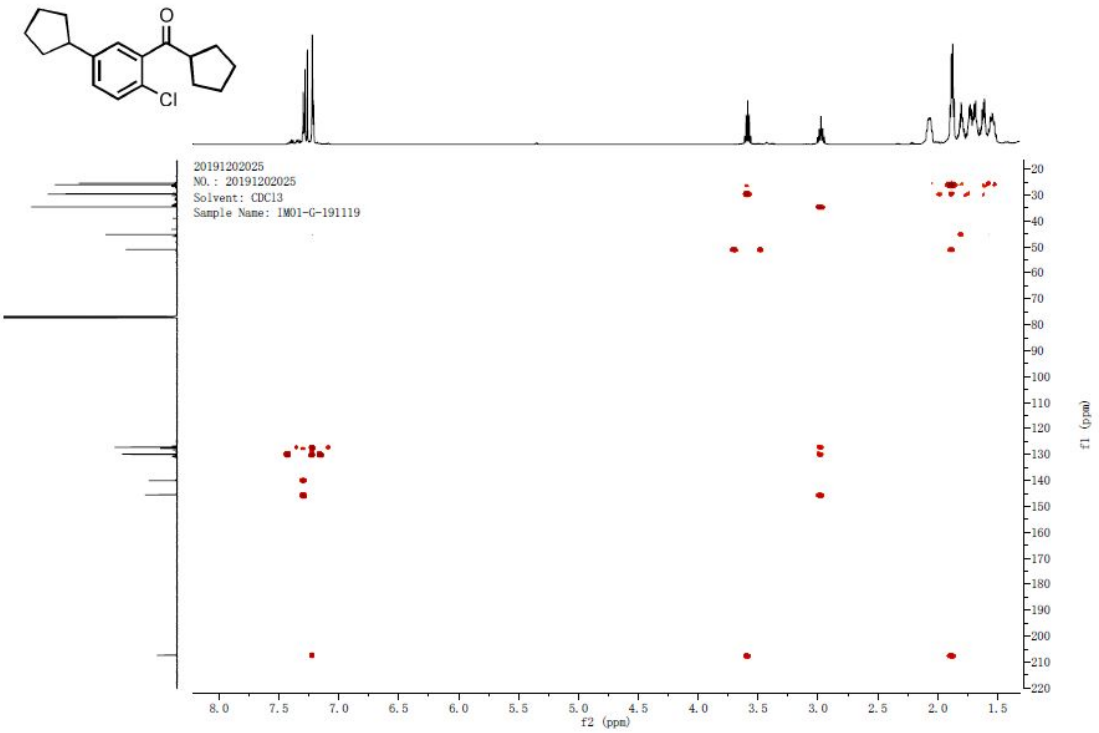
4.5.5 H-H COSY



4.5.6 HSQC



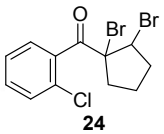
4.5.7 HMBC


O
Cl
20191202025
NO. : 20191202025
Solvent: CDCl3
Sample Name: IM01-G-191119
f2 (ppm)
f1 (ppm)

5. Analytical spectrograms and data of impurities 24, 25, 27, 29

5.1 Analytical spectrograms and data of impurity 24

5.1.1 HRMS



24

Molecular Weight: 366.48

Multiple Mass Analysis: 6 mass(es) processed
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

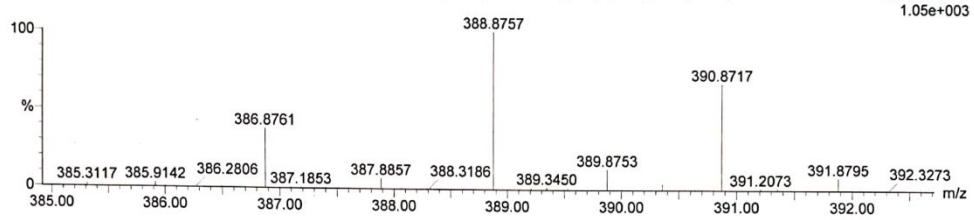
Monoisotopic Mass, Even Electron Ions
1112 formula(e) evaluated with 13 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-50 O: 0-1 Na: 1-1 35Cl: 0-1 37Cl: 0-1 79Br: 0-2 81Br: 0-2

SIPI
GYZX023-IM02-B
Q19-1495HR1 18 (0.333) AM (Cen,2, 80.00, Ar,5000.0,416.16,2.00); Sm (Mn, 2x3.00); Sb (1,5.00); Cm (17:24)

Q-Tof micro
YA019

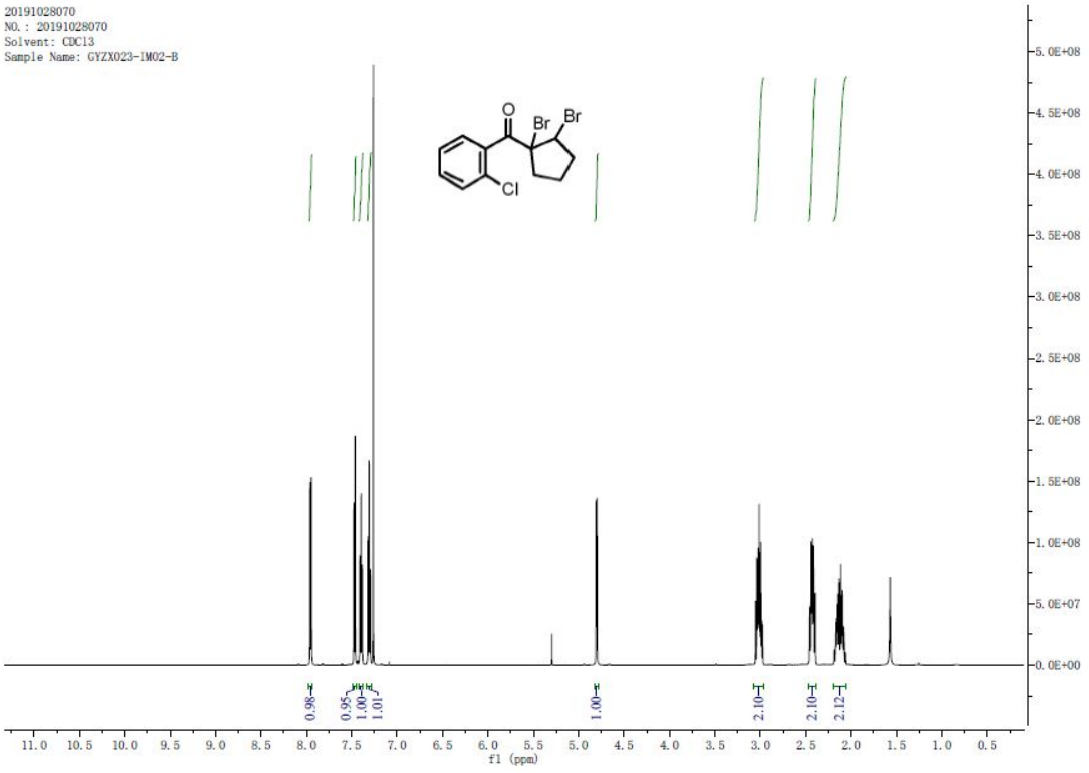
11:43:44,30-Oct-2019

TOF MS ES+
1.05e+003

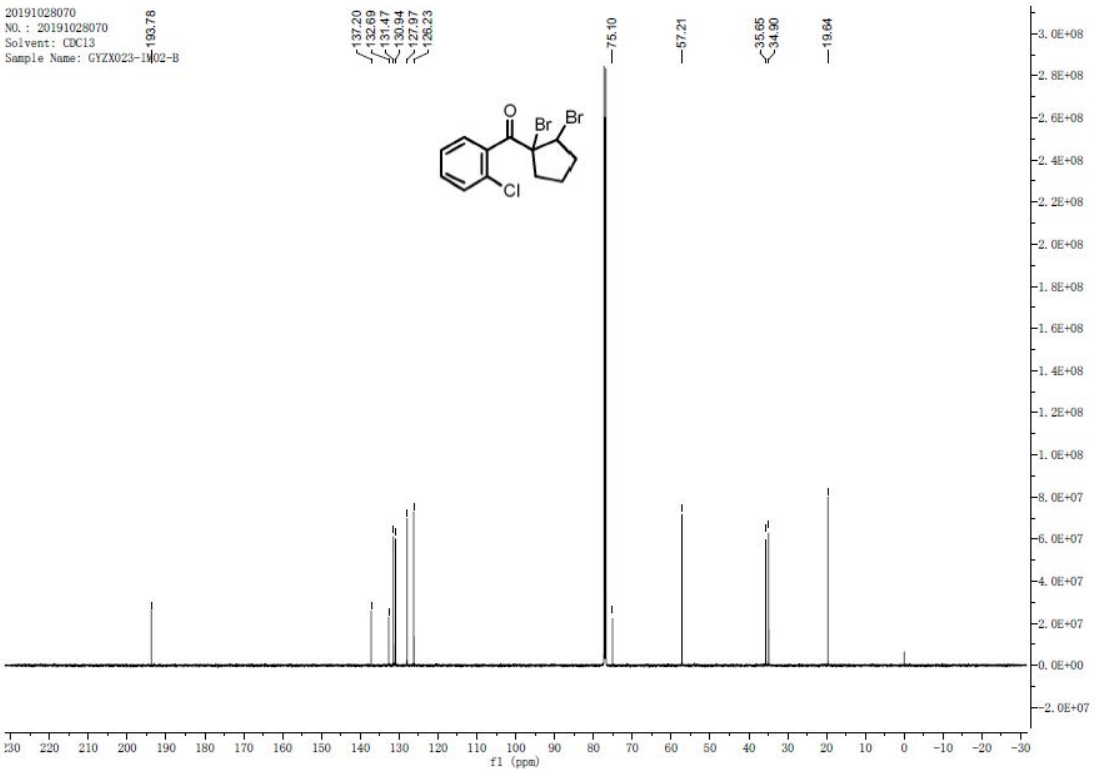


Minimum:	5.00				-1.5		
Maximum:	100.00		5.0	5.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
386.8761	37.71	386.8763	-0.2	-0.5	5.5	520.8	C12 H11 O Na 35Cl 79Br2 ✓
		386.8758	0.3	0.8	-0.5	527.1	C9 H17 Na 79Br2 81Br
		386.8764	-0.3	-0.8	6.5	520.5	C13 H11 Na 37Cl 79Br 81Br
		386.8769	-0.8	-2.1	12.5	517.0	C16 H5 O Na 35Cl 37Cl 79Br
		386.8773	-1.2	-3.1	6.5	520.8	C13 H11 Na 35Cl 81Br2
387.8857	6.62	---					
388.8757	100.00	388.8749	0.8	2.1	12.5	345.9	C16 H5 O Na 35Cl 37Cl 81Br
		388.8770	-1.3	-3.3	20.5	362.6	C21 Na 35Cl 79Br
		388.8743	1.4	3.6	6.5	345.6	C13 H11 Na 37Cl 81Br2
		388.8742	1.5	3.9	5.5	344.0	C12 H11 O Na 35Cl 79Br 81Br ✓
389.8753	13.00	---					
390.8717	67.68	390.8713	0.4	1.0	5.5	n/a	C12 H11 O Na 37Cl 79Br 81Br ✓
		390.8722	-0.5	-1.3	5.5	n/a	C12 H11 O Na 35Cl 81Br2
		390.8707	1.0	2.6	-1.5	n/a	C8 H17 O Na 79Br2 81Br
		390.8734	-1.7	-4.3	13.5	n/a	C17 H6 Na 79Br2

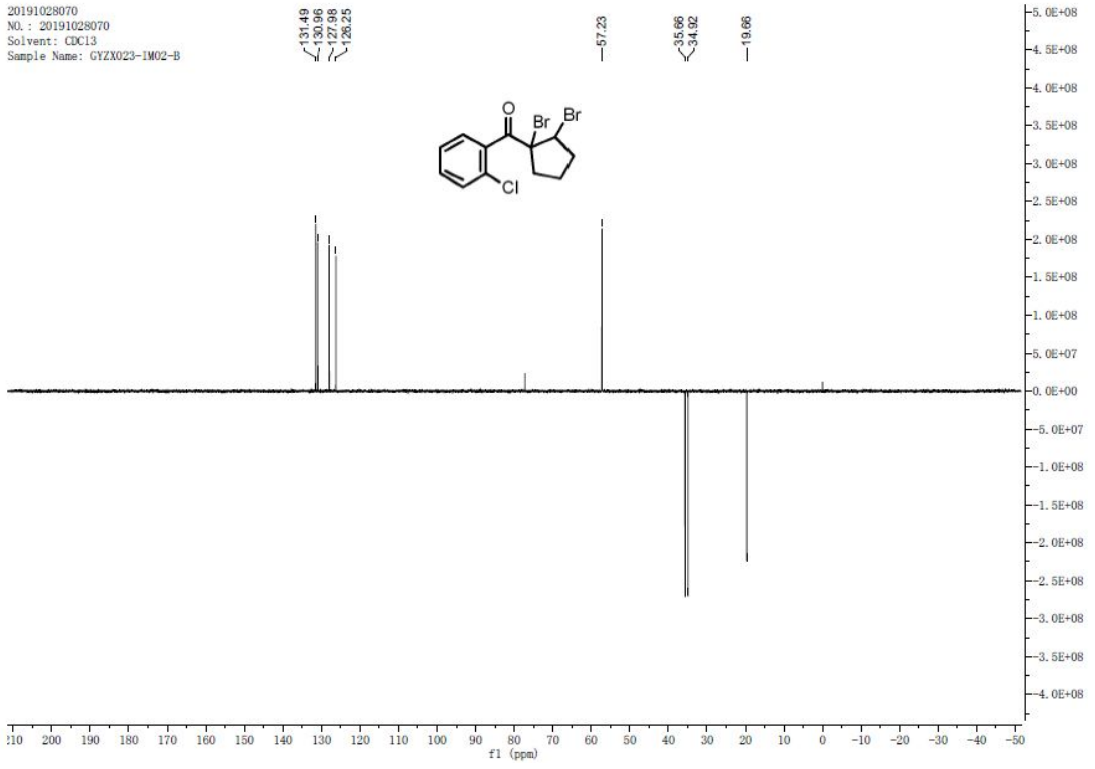
5.1.2 ^{1}H NMR



5.1.3 ^{13}C NMR

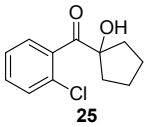


5.1.4 DEPT



5.2 Analytical spectrograms and data of impurity 25

5.2.1 HRMS



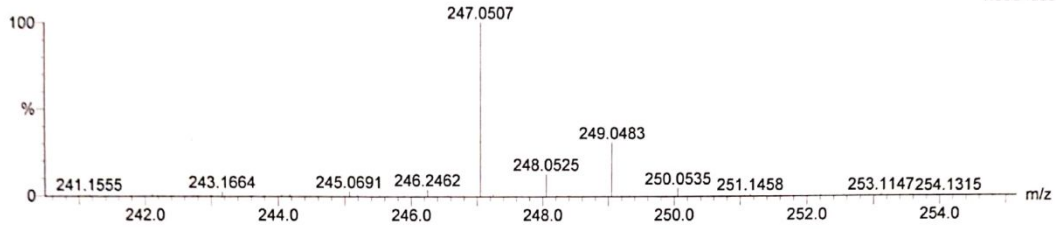
25

Exact Mass: 224.06

Multiple Mass Analysis: 3 mass(es) processed
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

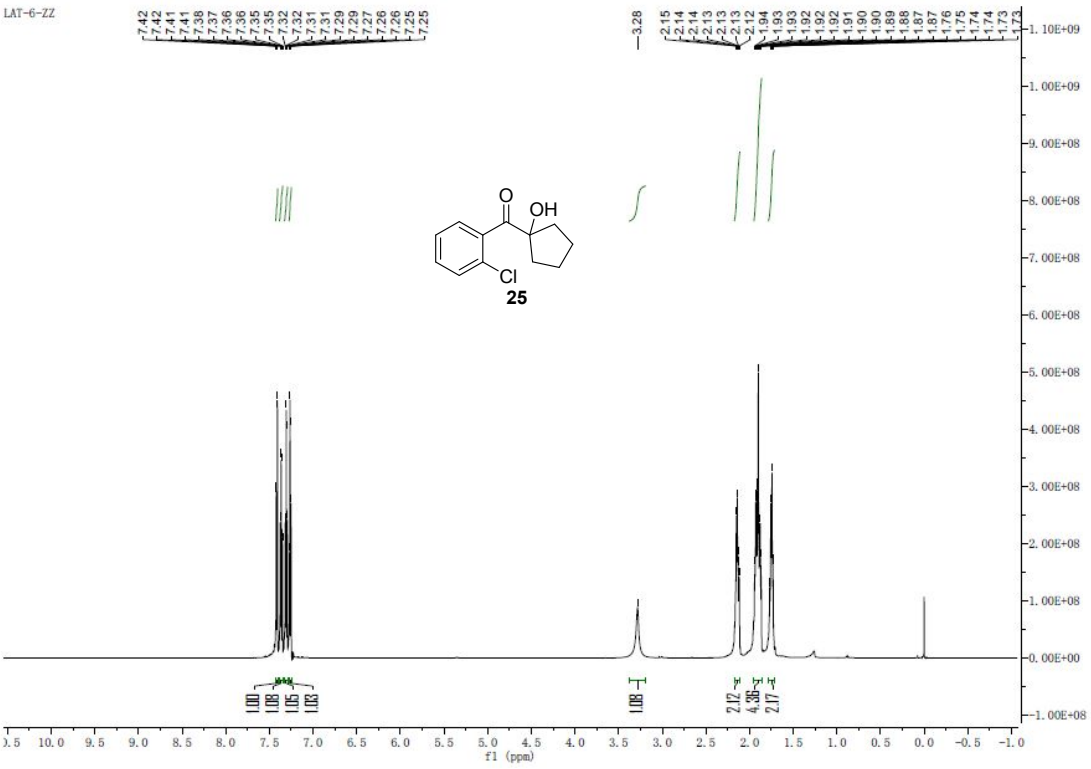
Monoisotopic Mass, Even Electron Ions
104 formula(e) evaluated with 3 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-50 O: 0-2 Na: 1-1 35Cl: 0-1 37Cl: 0-1

SIPI Q-Tof micro 10:47:02,30-Oct-2019
Impurity-C YA019
Q19-1492HR 16 (0.296) AM (Cen,2, 80.00, Ar,5000.0,260.10,2.00); Sm (Mn, 2x3.00); Sb (1,5.00); Cm (13:16) TOF MS ES+
1.99e+003

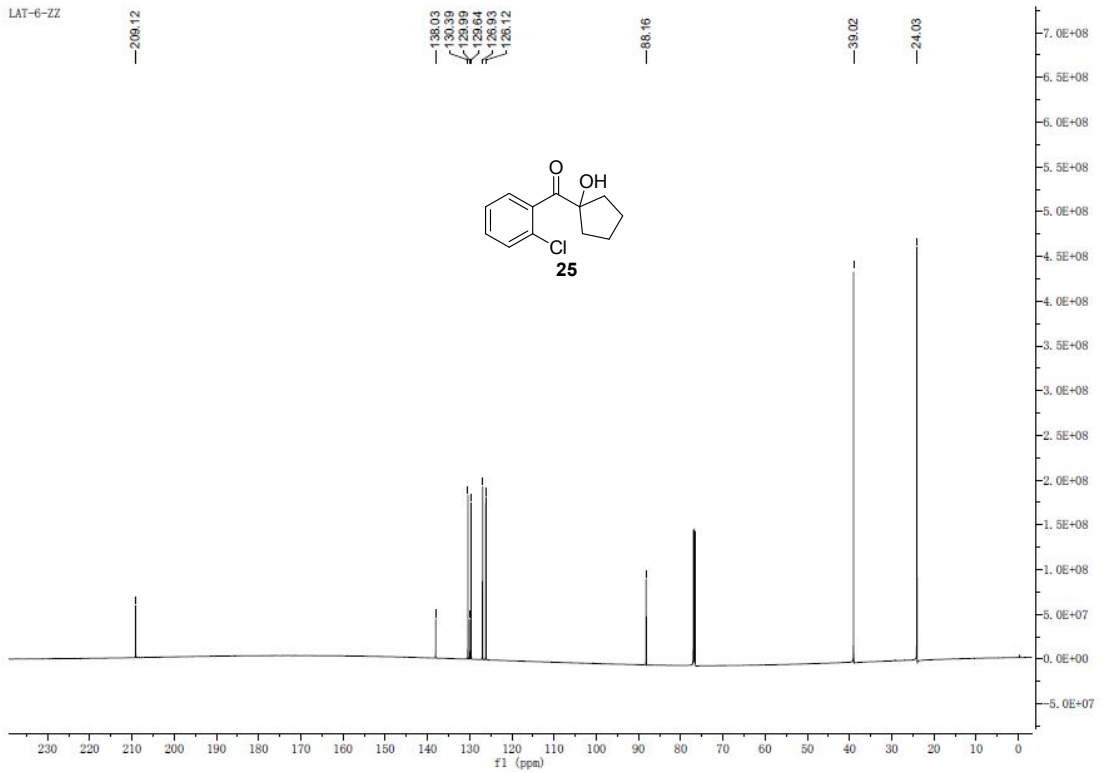


Minimum:	5.00				-1.5		
Maximum:	100.00		5.0	10.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
247.0507	100.00	247.0502	0.5	2.0	5.5	284.7	C12 H13 O2 Na 35Cl
		247.0524	-1.7	-6.9	14.5	309.0	C18 H8 Na
248.0525	12.72	---					
249.0483	30.79	249.0472	1.1	4.4	5.5	3.1	C12 H13 O2 Na 37Cl

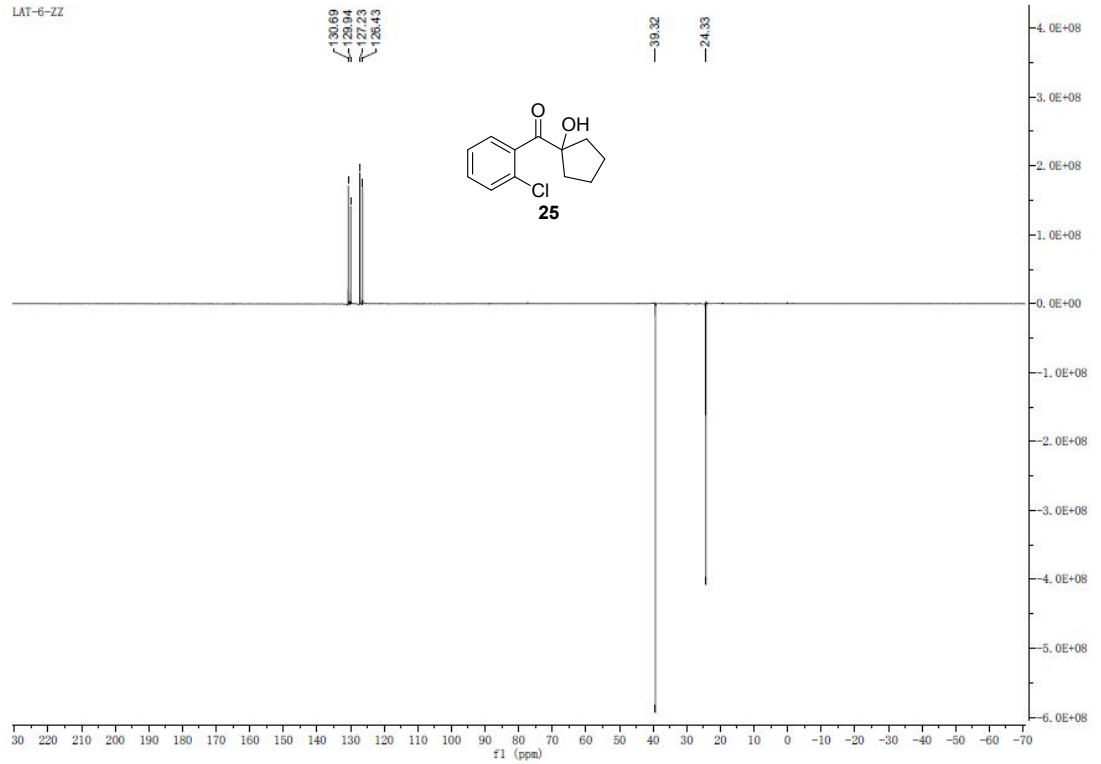
5.2.2 ^{1}H NMR



5.2.3 ^{13}C NMR



5.2.4 DEPT



5.3 Analytical spectrograms and data of impurity 27

5.3.1 HRMS

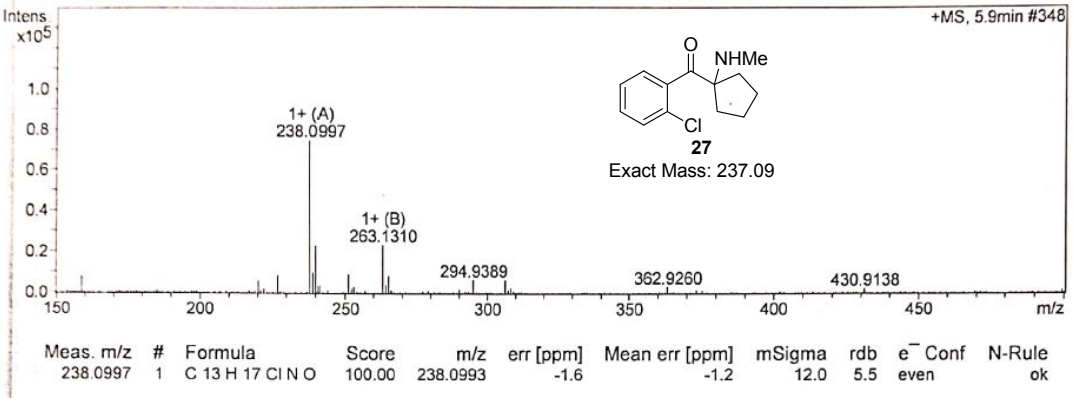
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\SHUJVFENXI\ZHANGFL-group\6-IMP-A_BA2_01_15202.d	Acquisition Date	1/21/2019 10:45:32 PM
Method	20150915.m	Operator	BDAL@DE
Sample Name	6-IMP-A	Instrument / Ser#	maXis 4G 21240
Comment			

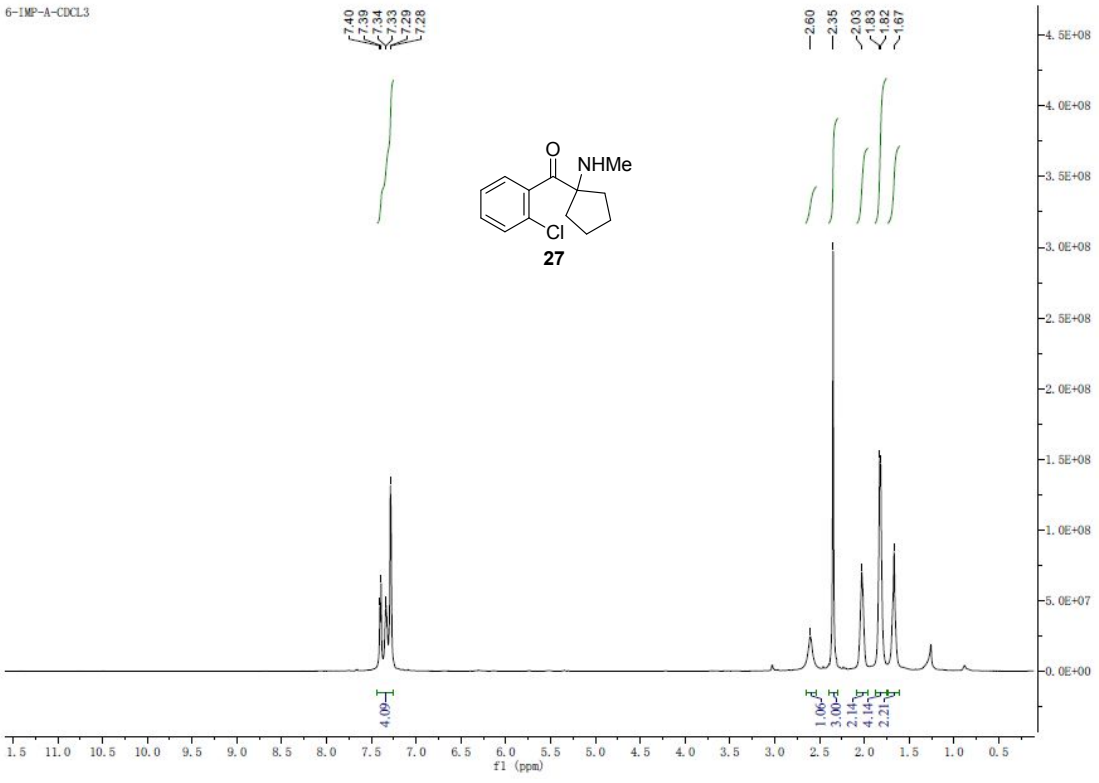
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	1.0 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	6.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	600.0 Vpp	Set Divert Valve	Waste

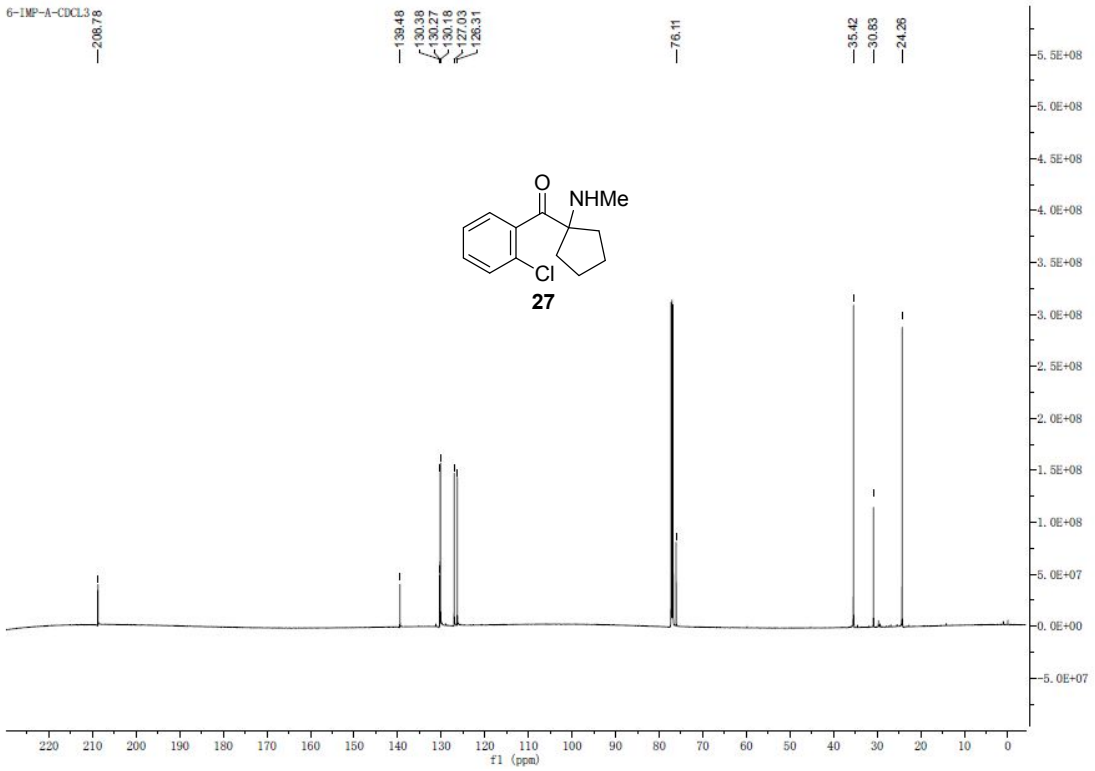


Meas. m/z	#	Formula	Score	m/z	err [ppm]	Mean err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
238.0997	1	C 13 H 17 Cl N O	100.00	238.0993	-1.6	-1.2	12.0	5.5	even	ok

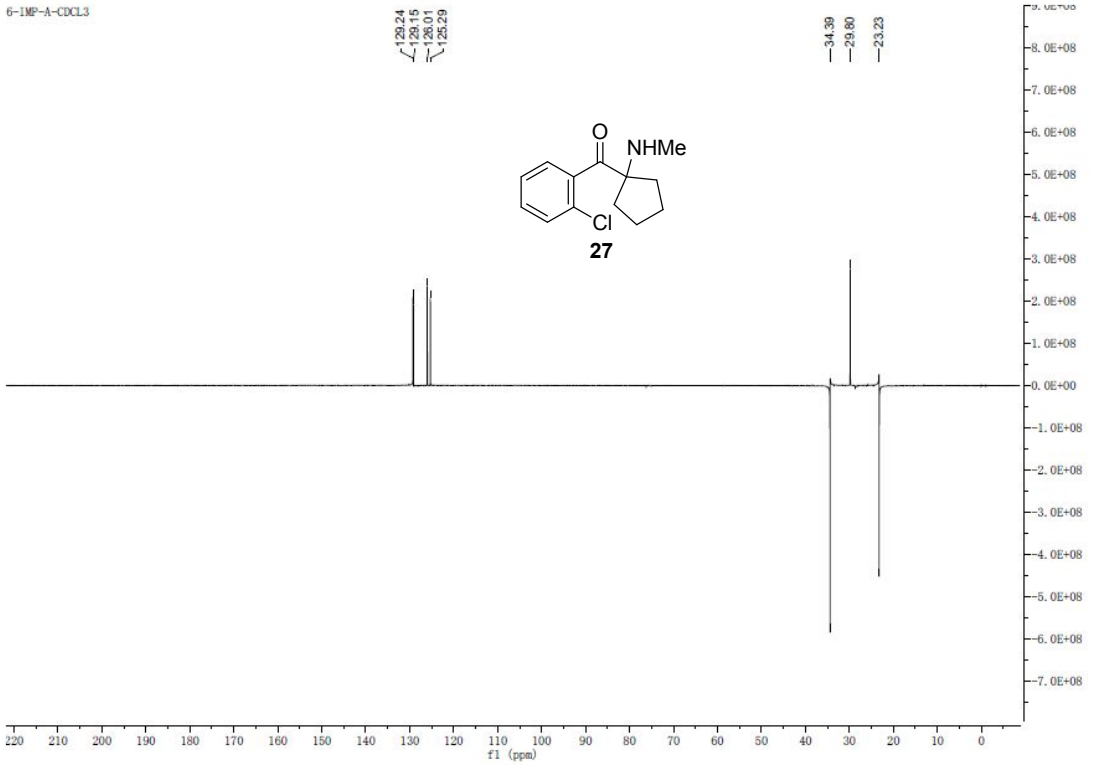
5.3.2 ^{1}H NMR ($CDCl_3$)



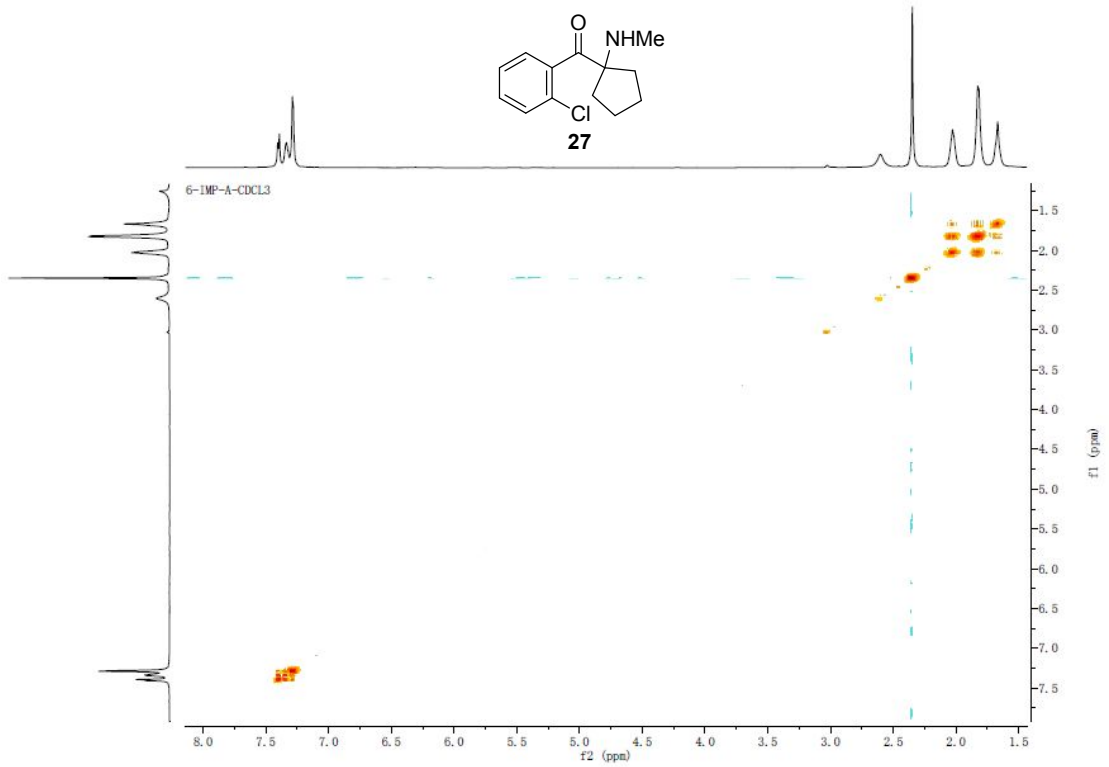
5.3.3 ^{13}C NMR ($CDCl_3$)



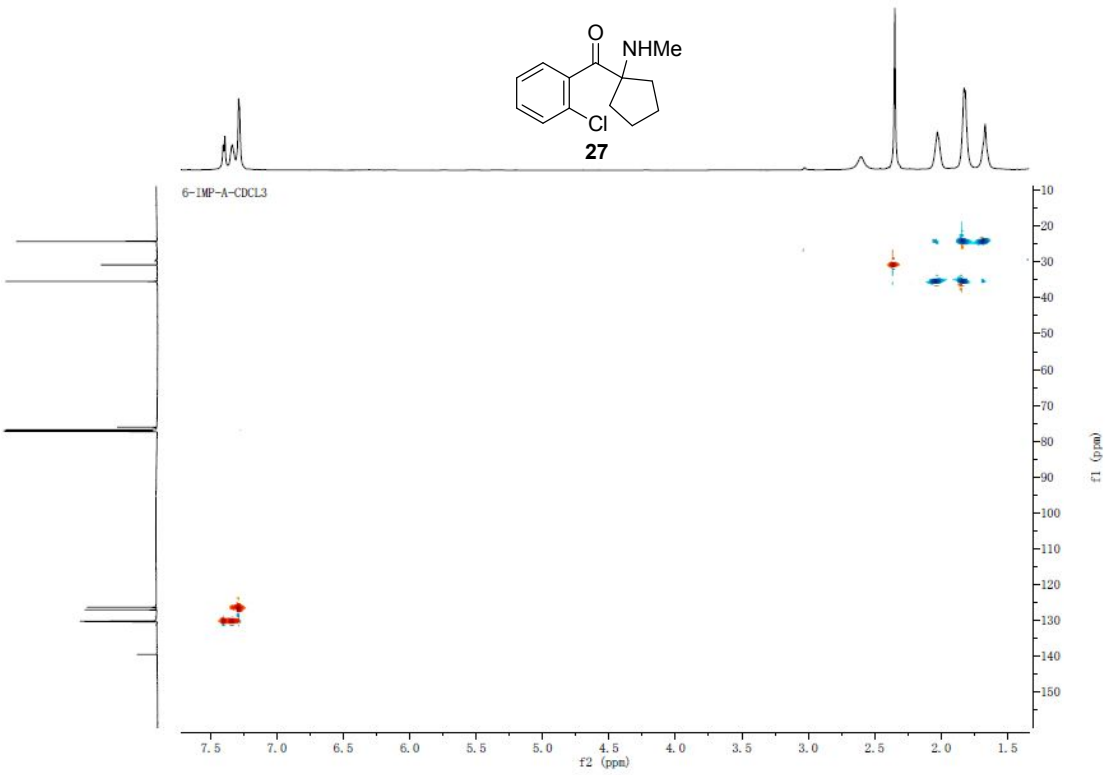
5.3.4 DEPT ($CDCl_3$)



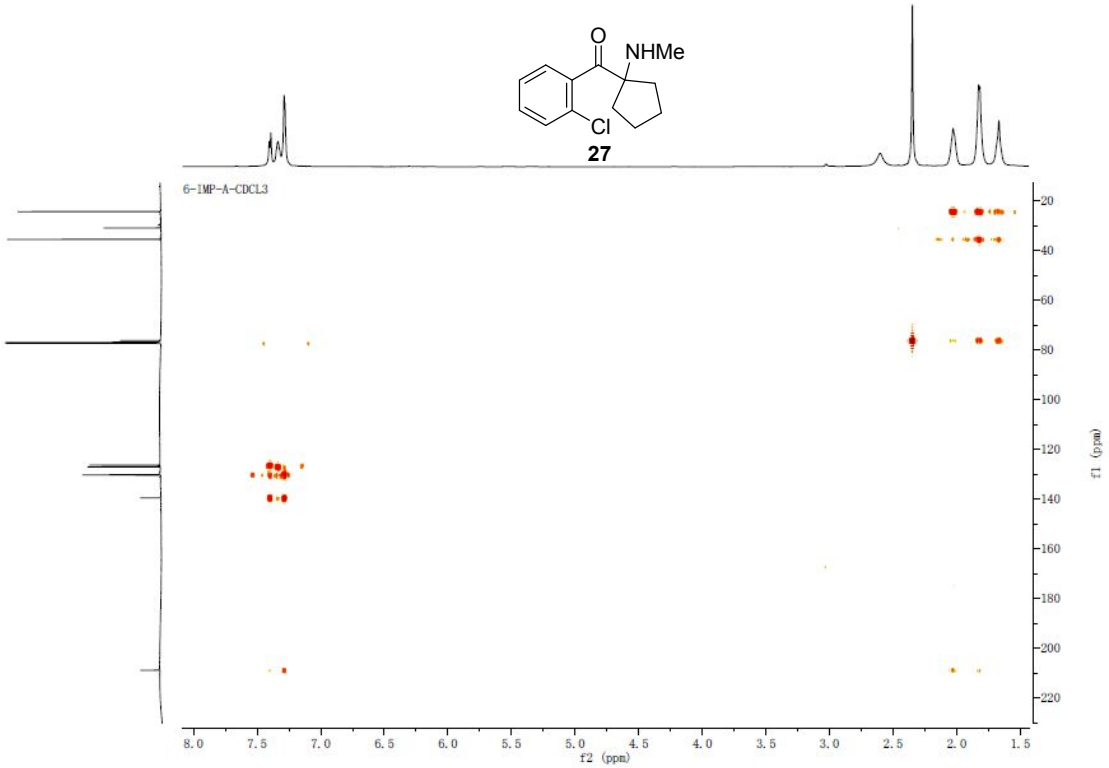
5.3.5 H-H COSY ($CDCl_3$)



5.3.6 HSQC ($CDCl_3$)

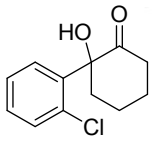


5.3.7 HMBC ($CDCl_3$)



5.4 Analytical spectrograms and data of impurity 29

5.4.1 HRMS



29

Exact Mass: 224.06

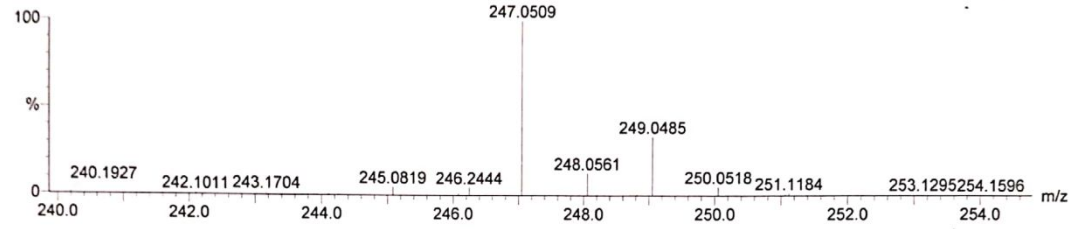
Multiple Mass Analysis: 3 mass(es) processed
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
132 formula(e) evaluated with 3 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-50 O: 0-3 Na: 1-1 35Cl: 0-1 37Cl: 0-1

SIPI
Impurity-D
Q19-1493HR 25 (0.463) AM (Cen,2, 80.00, Ar,5000.0,260.10,2.00); Sm (Mn, 2x3.00); Sb (1,5.00); Cm (22:35)

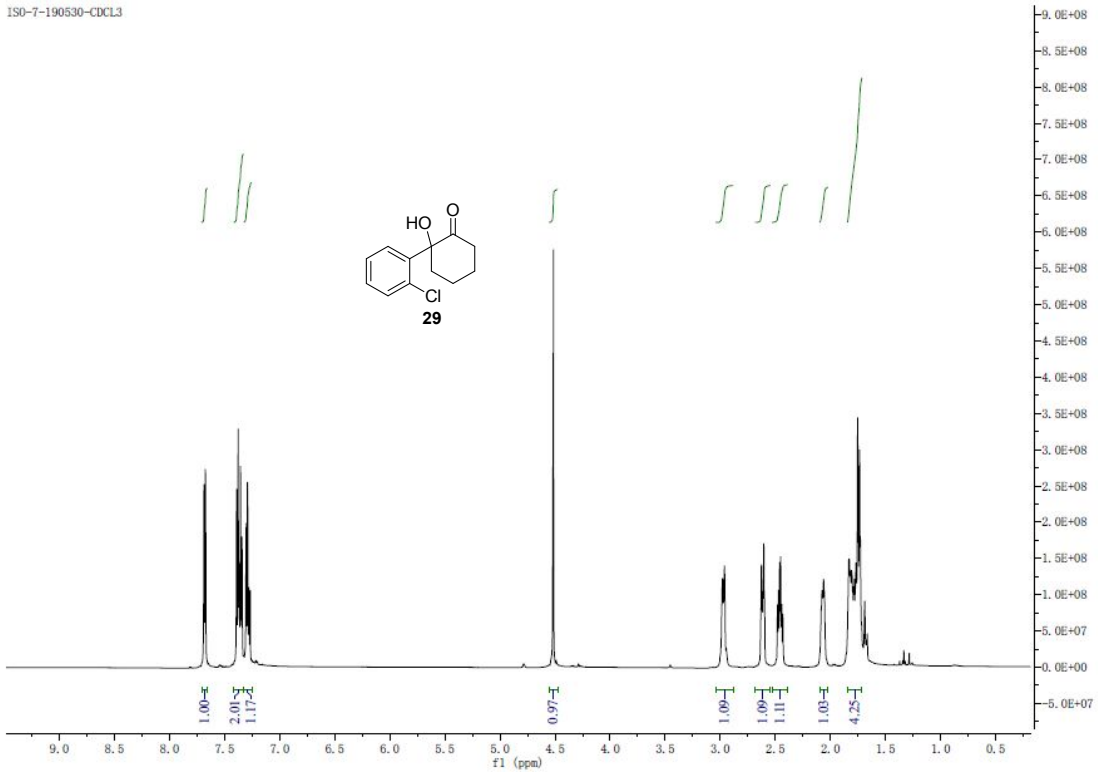
Q-Tof micro
YA019

09:50:43,30-Oct-2019
TOF MS ES+
6.49e+003

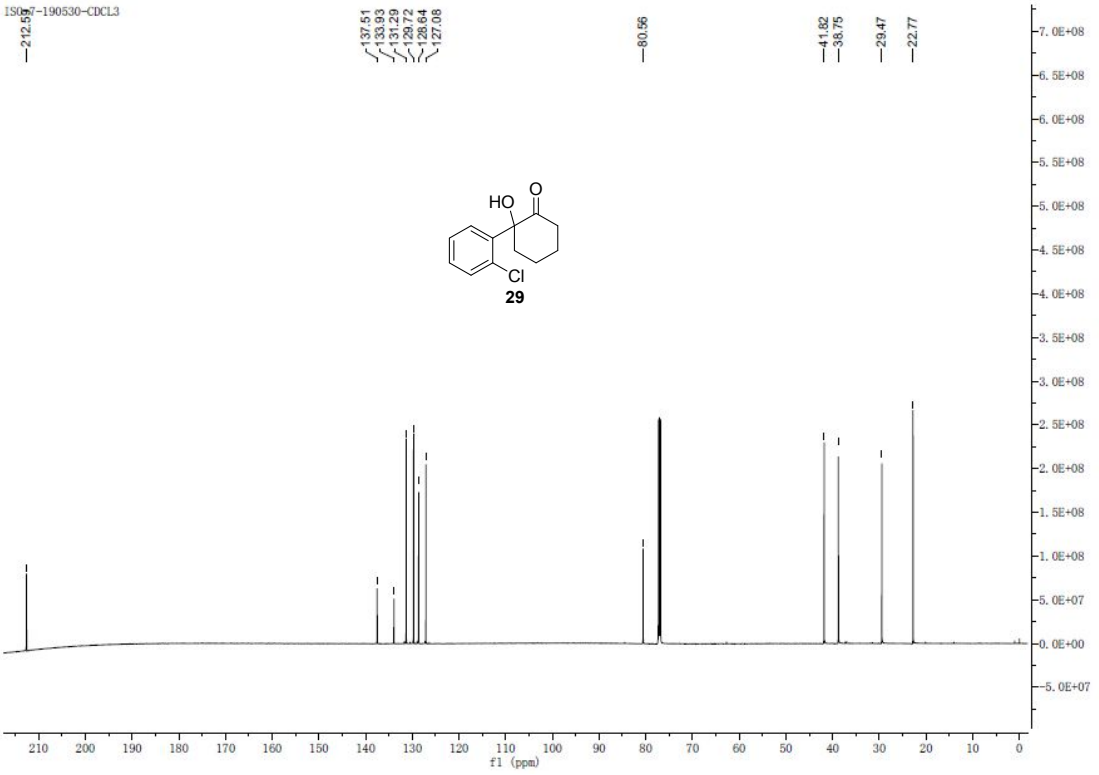


Minimum:	5.00				-1.5		
Maximum:	100.00		5.0	10.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
247.0509	100.00	247.0502	0.7	2.8	5.5	1017.0	C12 H13 O2 Na 35Cl
		247.0524	-1.5	-6.1	14.5	1102.4	C18 H8 Na
248.0561	12.51	---					
249.0485	33.53	249.0472	1.3	5.2	5.5	1.5	C12 H13 O2 Na 37Cl

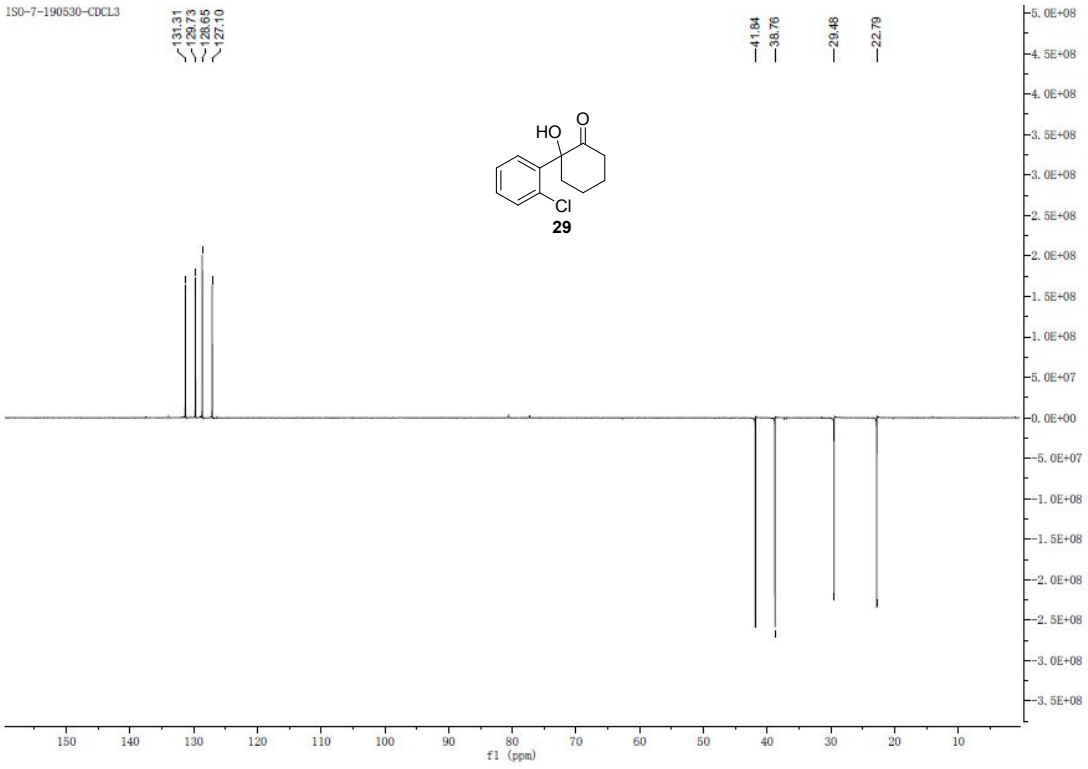
5.4.2 ^{1}H NMR



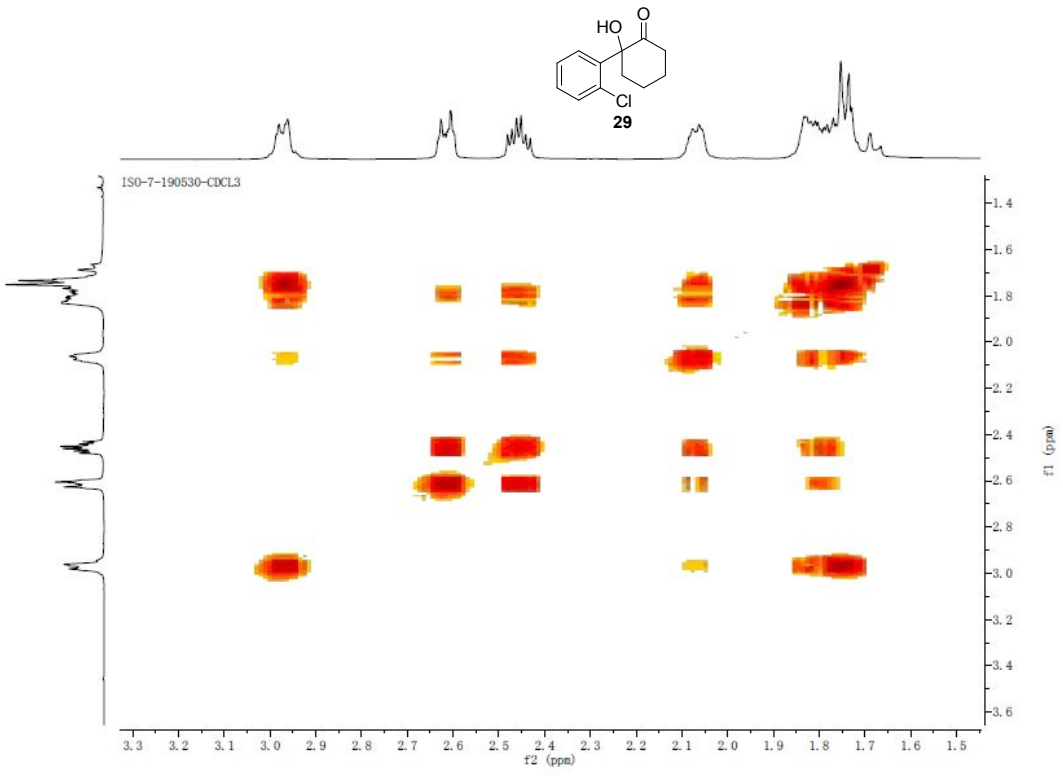
5.4.3 ^{13}C NMR



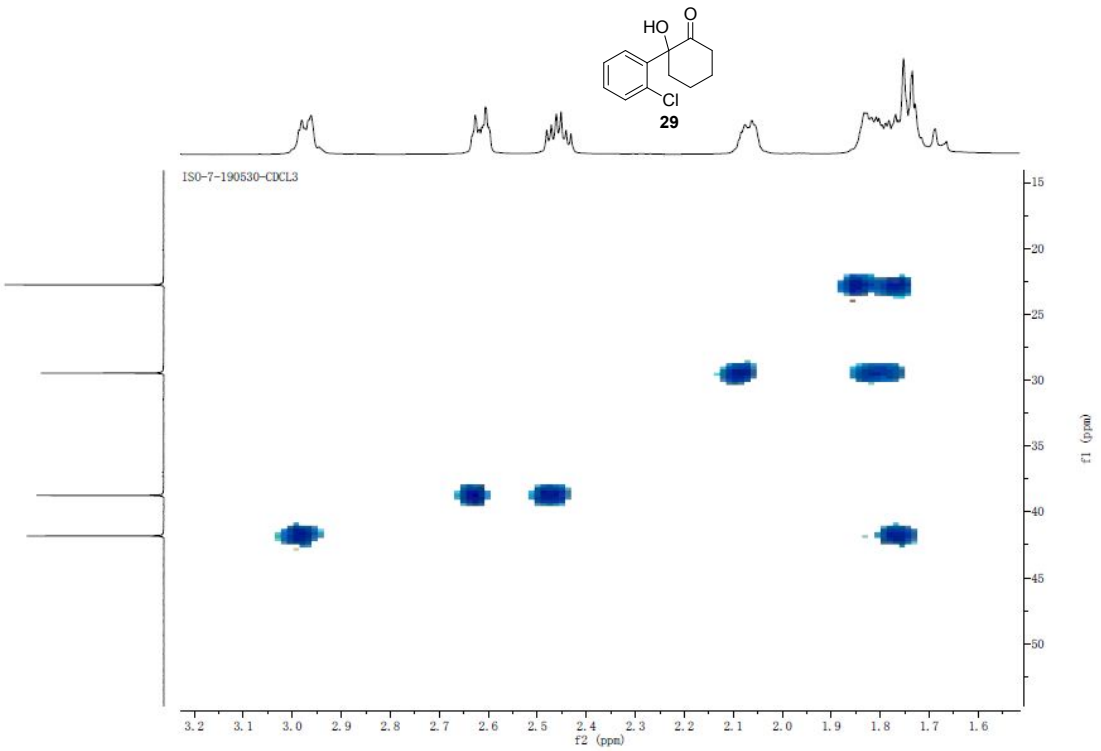
5.4.4 DEPT



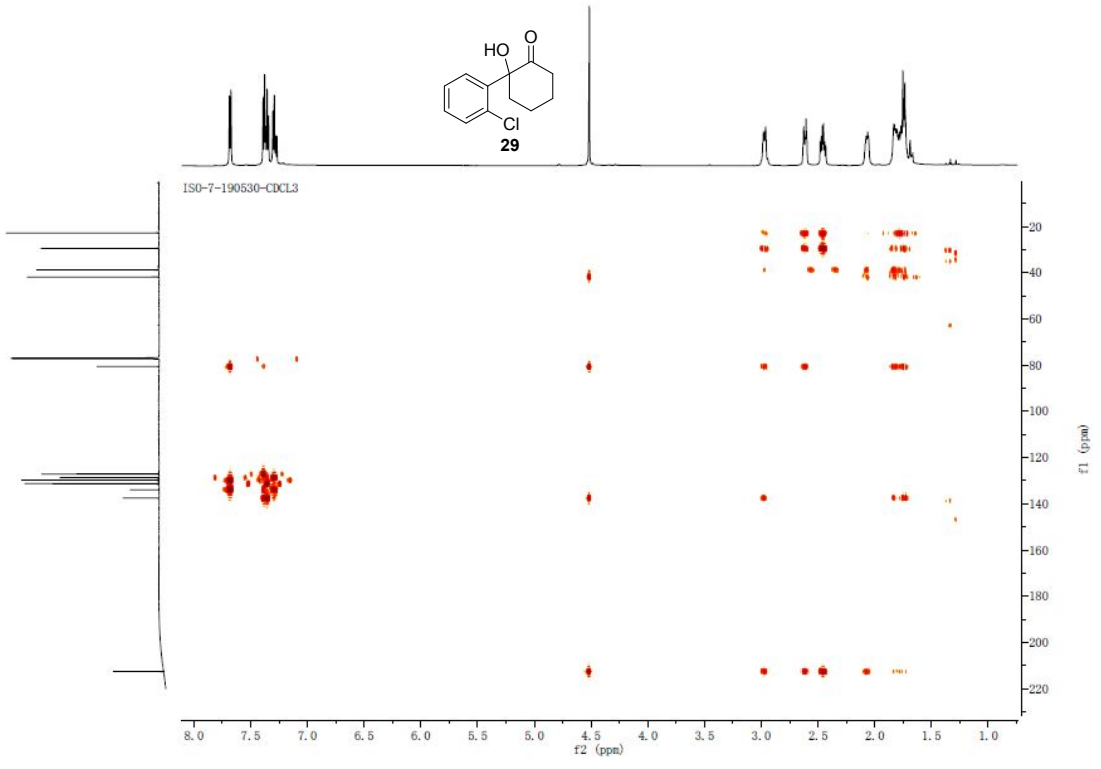
5.4.5 H-H COSY



5.4.6 HSQC



5.4.7 HMBC



8.4.8 SCXRD

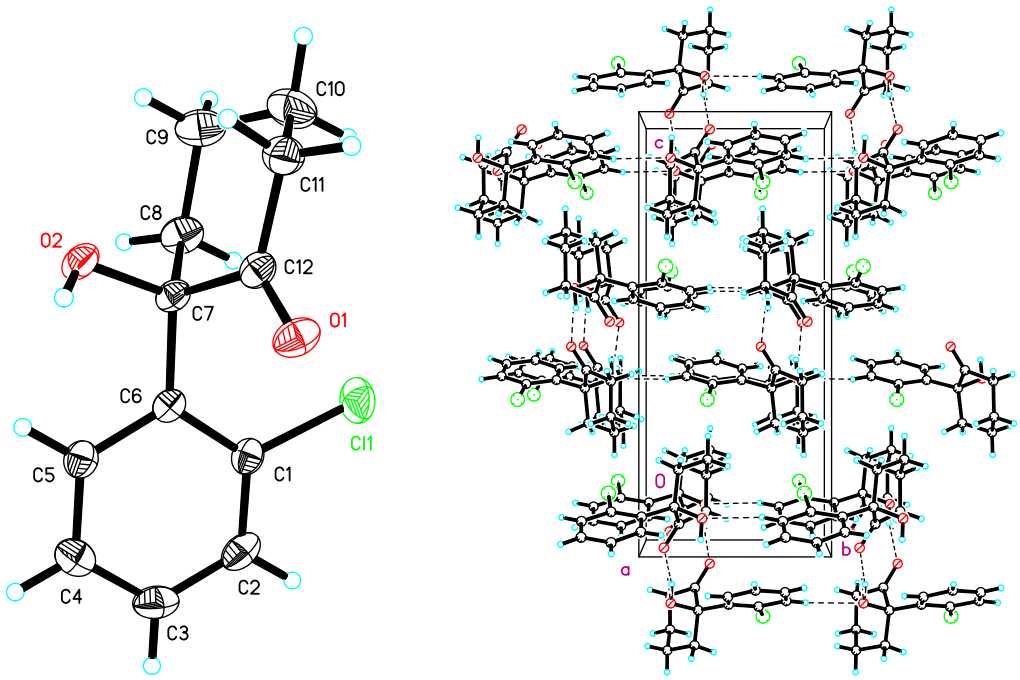


Table S3. Crystal data and structure refinement for mo_d8v19706_0m.

Identification code	mo_d8v19706_0m	
Empirical formula	C12 H13 Cl O2	
Formula weight	224.67	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.2414(8) Å	α= 90°.
	b = 8.1329(8) Å	β= 90°.
	c = 18.752(3) Å	γ = 90°.
Volume	1104.4(2) $Å^3$	
Z	4	
Density (calculated)	1.351 Mg/m^3	
Absorption coefficient	0.322 mm^{-1}	
F(000)	472	
Crystal size	0.200 x 0.160 x 0.130 mm^3	
Theta range for data collection	3.767 to 25.988°.	
Index ranges	-8<=h<=8, -9<=k<=10, -18<=l<=23	
Reflections collected	5396	
Independent reflections	2122 [R(int) = 0.0210]	
Completeness to theta = 25.242°	97.5 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7456 and 0.6427
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2122 / 0 / 140
Goodness-of-fit on F^2	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0279, wR2 = 0.0673
R indices (all data)	R1 = 0.0306, wR2 = 0.0692
Absolute structure parameter	0.02(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.152 and -0.130 e.$Å^{-3}$

6. Complete Reference for Gaussian 09

Gaussian 09, Revision A.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

7. Computational Methods

The DFT calculations conducted in this study were carried out using the Gaussian09 program. DFT method M06 with a standard 6-311++G** basis set was used to calculate the single point energies. The structures were optimized with a SMD continuum solvation model in dichloromethane (ε=8.93). The energies presented in this paper are the M06 calculated Gibbs free energies in dichloromethane solvent.

8. M06 Geometries for carbocation 13, 16 and Transition States

13 E (RM06) = -2622.70458452 Hartree

Sum of electronic and thermal Free Energies= -2622.539992 Hartree

C, 0, 1.2661606358, 2.4649239146, -1.1696273399

C, 0, 1.2938737635, 3.839135386, -0.7733557911

C, 0, 0.2521315342, 3.9956339653, 0.3328092839

C, 0, 0.1693969255, 2.6001326416, 0.9422654429

C, 0, 0.4144898229, 1.704297625, -0.2955659352

H, 0, 1.7926866592, 2.0526045189, -2.0316753773

H, 0, 1.3613968103, 4.5696859722, -1.5839815307

H, 0, 2.3276312443, 3.8367908635, -0.3307444325

H, 0, 0.5223525512, 4.7629637356, 1.0576506494

H, 0, -0.7077565382, 4.2710086855, -0.1188605583

H, 0, 0.9726012808, 2.4221251547, 1.666296224

H, 0,-0.7856086015, 2.3765686396, 1.4211937704

H, 0,-0.5204949269, 1.8246283551, -0.9230705068

C, 0, 0.5895092289, 0.2277928783, -0.0747286145

O, 0, -0.4380029172, -0.4625514519, 0.0474076776

C, 0, 1.906763501, -0.3472870155, 0.0415845309

C, 0, 2.9920188733, 0.5146249514, 0.3010845795

C, 0, 2.175811367, -1.7338256661, -0.0551744208

C, 0, 4.2731533152, 0.039559276, 0.4642632169

H, 0, 2.819080676, 1.5778052774, 0.4427629561

C, 0, 3.4686895785, -2.2045186346, 0.0877405076

C, 0, 4.508849767, -1.3258388693, 0.3523860342

H, 0, 5.0843778339, 0.723438187, 0.6848124386

H, 0, 3.6596463945, -3.2674372726, -0.0111619637

H, 0, 5.5141705682, -1.7167076847, 0.4714465181

Cl, 0, 0.9589583166, -2.9088750865, -0.4250618088

Al, 0, -2.2950646255, -0.4695422195, 0.0793547352

Cl, 0, -2.7502847106, -0.4502087412, 2.1465884097

Cl, 0, -2.854793273, -2.2072723467, -0.9827571165

Cl, 0, -2.891056055, 1.3354309609, -0.9180575791

16 E (RM06) = -2622.71636821 Hartree

Sum of electronic and thermal Free Energies= -2622.551776 Hartree

C, 0, 1.2215614772, 2.7298998825, -0.8674452884

C, 0, 2.4338698653, 2.474517778, -0.1401572759

C, 0, 2.2011095414, 2.3667022366, 1.2758287561

C, 0, 0.7105912113, 2.6369558981, 1.4975050271

C, 0, 0.055047972, 2.4744581128, 0.094192676

H, 0, 1.172444362, 2.3373841272, -1.8867787153

H, 0, 3.4225531514, 2.4793548412, -0.5963632637

H, 0, 2.5303259925, 1.3480691055, 1.5634751239

H, 0, 2.9072859315, 2.9966331986, 1.8367049484

H, 0, 0.2706338452, 1.9782021775, 2.2504264409

H, 0, 0.5612238768, 3.6665055282, 1.8306158504

H, 0, -0.7516634484, 3.1919323451, -0.0369515573

C, 0, -0.4421396212, 1.0654761713, -0.0055823653

O, 0, 0.435220984, 0.1802961609, -0.0004525503

C, 0, -1.8549248093, 0.7490907589, -0.04470482

C, 0, -2.7102317385, 1.6269585752, -0.7344315529

C, 0, -2.410855142, -0.4308371318, 0.4937048337

C, 0, -4.0405566328, 1.318280333, -0.9329074035

H, 0, -2.3082784721, 2.5373657159, -1.1647932742

C, 0, -3.7485175088, -0.7240116972, 0.3191423499

C, 0, -4.5562642869, 0.1412595572, -0.4079879702

H, 0, -4.6754501472, 1.9950322687, -1.4932397854

H, 0, -4.1609364152, -1.6244938497, 0.7609226486

H, 0, -5.6036446096, -0.1057503388, -0.5487987742

Cl, 0, -1.4889528376, -1.5008933126, 1.5081869544

H, 0, 1.3386694517, 3.8344231326, -1.0062513582

Al, 0, 1.476306428, -1.2606560548, -0.4253770641

Cl, 0, 0.3715635799, -2.4742711607, -1.7599796167

Cl, 0, 2.0744230041, -2.127969257, 1.4114789984

Cl, 0, 3.1234225318, -0.253557989, -1.3774754739

TS-Migration E (RM06) = -2622.69983915 Hartree

Sum of electronic and thermal Free Energies= -2622.532462 Hartree

C, 0, 1.3589415006, 2.4907006266, -1.2469527984

C, 0, 1.2362008539, 3.8397979466, -0.9636477224

C, 0, 0.1825767736, 4.065331212, 0.0712921997

C, 0, -0.017458992, 2.6861309793, 0.7014573747

C, 0, 0.3624730989, 1.7240153741, -0.4498829263

H, 0, 2.0142743739, 2.0793179774, -2.0114443899

H, 0, 1.7314147402, 4.6133251155, -1.5442134828

H, 0, 2.2027058609, 3.2098609017, -0.4220078594

H, 0, 0.4356905493, 4.85142291, 0.7829699155

H, 0, -0.7158072594, 4.3864041377, -0.475013774

H, 0, 0.6720017802, 2.5410023372, 1.5415377983

H, 0, -1.0352846069, 2.5219325459, 1.056576974

H, 0, -0.5031744967, 1.6986785404, -1.1427186265

C, 0, 0.5888216834, 0.2879687569, -0.0714785717

O, 0, -0.4180187559, -0.4185245966, 0.1076654365

C, 0, 1.9096602028, -0.2896612156, 0.1034717832

C, 0, 2.9103095782, 0.5006982334, 0.691822993

C, 0, 2.2148639545, -1.6323670056, -0.1998360758

C, 0, 4.1517510066, -0.0203669488, 0.9924064158

H, 0, 2.6879576177, 1.5207061935, 0.9864678701

C, 0, 3.4721762066, -2.1419647624, 0.0688620388

C, 0, 4.4316136674, -1.3428091031, 0.6741811988

H, 0, 4.8974673521, 0.5995820431, 1.4768690005

H, 0, 3.6986180667, -3.1686755278, -0.1970150503

H, 0, 5.4081230145, -1.7622911001, 0.8935419379

Cl, 0, 1.0896558591, -2.6765999653, -1.0111311865

Al, 0, -2.2720347512, -0.532487629, 0.1863972093

Cl, 0, -2.6536307891, -0.3685039334, 2.2661753208

Cl, 0, -2.7312090582, -2.4055492583, -0.6799898663

Cl, 0, -3.0395400315, 1.1167132147, -0.9382601368