Supporting Information

Ultrasonic-assisted synthesis of two *t*-butoxycarbonylamino cephalosporin intermediates on SiO_2

Feng Xue[a], Yibin Wei[b], Shengui Ju[a,*] , Weihong Xing[a]

[a] College of Chemical Engineering, Nanjing Tech University, Nanjing, 210009, People's Republic of China

*Corresponding author: Prof. Shengui Ju,

E-mail address: jushengui@njtech.edu.cn

[b] Department of Environmental Sciences, Macquarie University, Sydney, NSW 2109, Australia

Table of Contents

1 General Information…… S2

2 Synthesis of **4a** and **4b**……S2-S4

3 Spectra ……S5-S10

^{1}H-NMR spectrum of **4a**……S5

^{1}H-NMR spectrum of **4b**……S6

^{13}C-NMR spectrum of **4a**……S7

^{13}C-NMR spectrum of **4b**……S8

HRMS (ES) spectrum of **4a**……S9

HRMS (ES) spectrum of **4b**……S10

General information

ACLE.HCl and ACLH.HCl were purchased from Shanghai Arbor Chemical Co., Ltd. The other reagents and solvents were obtained from Sigma-Aldrich and used as received without any further purification. All reactions were monitored by thin layer chromatography (TLC) using commercial silica gel plates. JL-120DTH ultrasonic bath was purchased from Shanghai J & L Science Instrument Co., Ltd. The purity was measured by high performance liquid chromatography (HPLC) on Agilent 1,100 series. The liquid chromatographic system equipped with an ODS-3 C18 column (GL Science Co. Ltd., 180×4.6 mm i.d., 5.0 μm). Melting points were observed on YRT-3 Melting Point Tester and were uncorrected. NMR spectra were determined on Bruker AV300 in DMSO-d_6 with TMS as internal standard for ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz), respectively. HRMS were carried out on an Agilent 6230-LC/TOF MS mass spectrometer.

Synthesis of 4-Methoxyphenyl 7β-*t*-butyl-carbonylamino-3-chloromethyl-3-cephem-4-carboxylate (**4a**):

20.25g (0.05mol) p-Methoxybenzyl 7β-amino-3-chloromethyl-3-cephem4-carboxylate hydrochloride (**5a**, ACLE.HCl) was dissolved into 200 mL dichloromethane in a flask with mechanical stirring under ice cooling at 0-5℃.Then 10.2 g (0.10 mol) triethylamine was introduced into the mixture to neutralize the pH at 7-8 for 15min before adding 10 g SiO_2 and 13.1 g (0.06 mol) Boc_2O into the flask under ultrasonic bath at 0-5℃. The reaction lasted for 30 mins at room temperature. When the raw material (**5a**) completely disappeared and transformed as indicated by

TLC, the mixture was poured into 500 mL water, following by washing with brine water for organic phase. Next, the organic phase was dried with anhydrous sodium sulfate and the solvent was evaporated by vacuum to produce the crude product (**4a**). Finally, the rude products were purified by column chromatography to obtain the pure white amorphous powders (2.27 g, yield 96.0%). HPLC assay confirmed the purity of **4a** was 98.5%. The column oven temperature was set at 295 K. The mobile phase was consisted of methanol and deionized water (75:25, v/v) and flowed through the column in 15 min with the flow rate of 1.0 mL/min. Photodiode array detection was used to detect the Boc-ACLE (or Boc-ACLH） at the wavelength of 254 nm. ^{1}H and ^{13}C NMR refer to table 3 and 4 [1]. ESI-HRMS: calcd. for $C_{21}H_{24}ClN_2O_6S$ ($[M-H]^-$) 467.1049, found 467.1045.

Synthesis of Benzhydryl 7β-*t*-butoxycarbonylamino-3-chloromethyl-3-cephem-4-carboxylate (**4b**):

The **4b** compound was prepared according to a similar manner to that of the **4a** but using the **5b** (ACLH.HCl) as raw material. The weight of purified product was 5.0 g (yield 96.2%). The purity of **4b** was 98.1%. (The HPLC method was similar to the **4a**). m.p.140-142℃ (decomposed). ^{1}H NMR refer to Table 5 [2]. ^{13}C NMR (75 MHz，DMSO-d_6): δ 170.86, 165.01, 161.06, 159.34, 135.70, 130.25, 28.93, 128.16, 126.84, 126.43, 125.29, 124.83, 113.77, 67.28, 59.18, 57.96, 57.86, 55.06, 43.72, 41.55, 40.33, 26.09. ESI-HRMS: calcd. for $C_{26}H_{27}ClN_2O_5NaS$ ($[M+Na]^+$) 537.1221, found 537.1243.

References

[1] Mijoon L.; Dusan H.; Maxim S.; Wenlin L.; Sergei V.; Shahriar M. *J. Amer. Chem. Soc*. **2003**, *125*, 16322-16326.

[2] Dai X. Y.; Li. L. W.; Guo. P.; Sun C. H. *Chinese J. Pharmaceut*. **2009**, *40*, 16-18.

3. Spectra

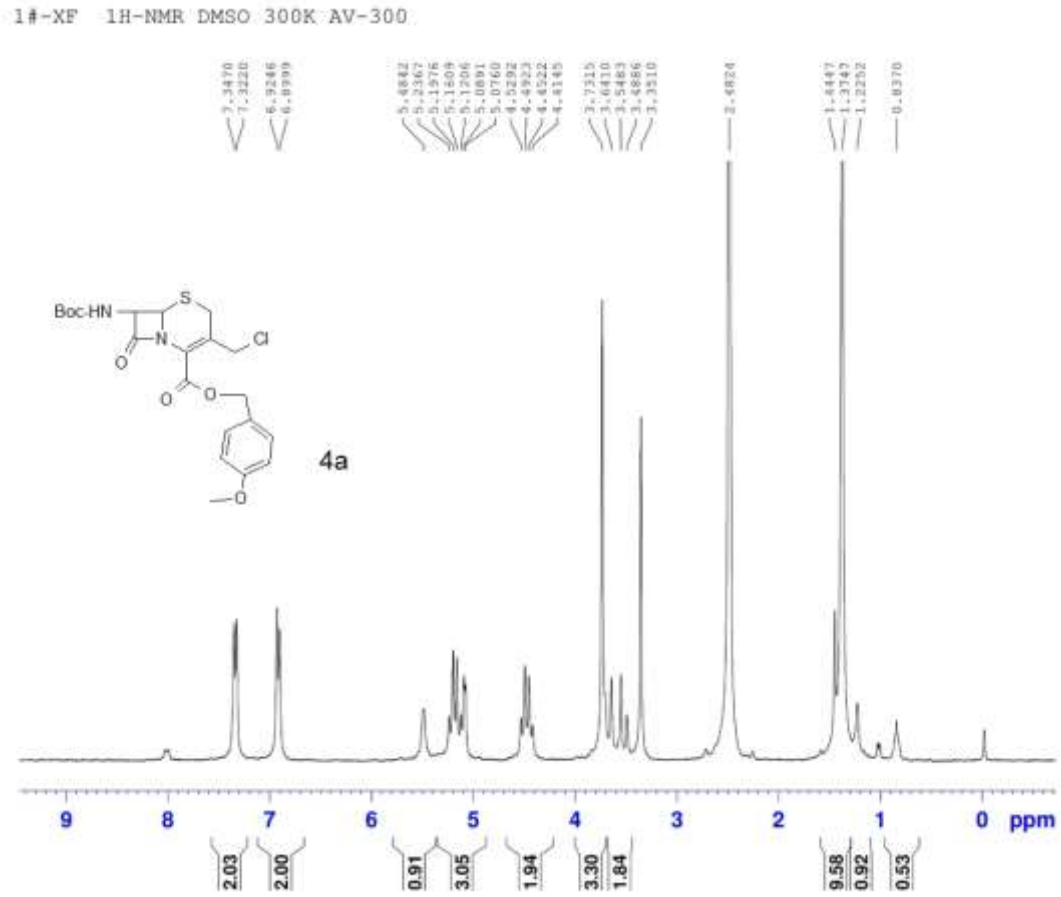


Figure S1. [1]NMR spectral image of Boc-ACLE

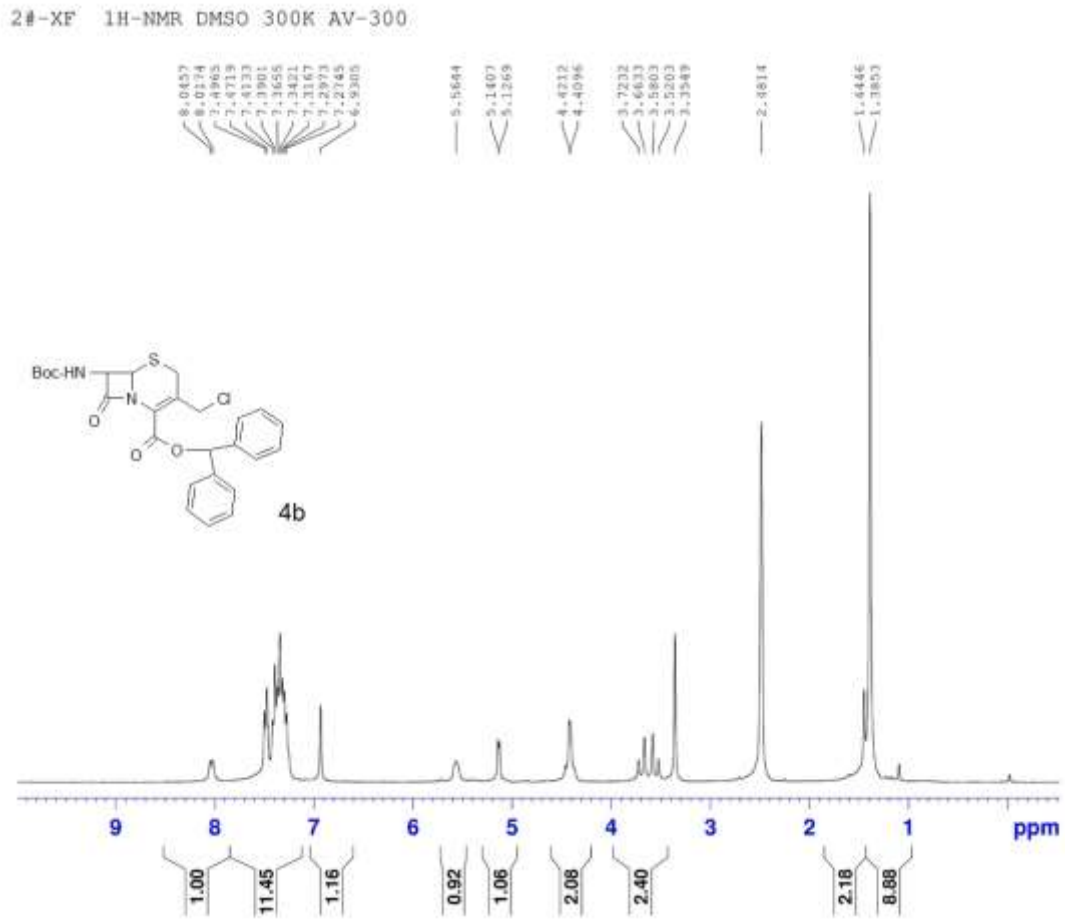
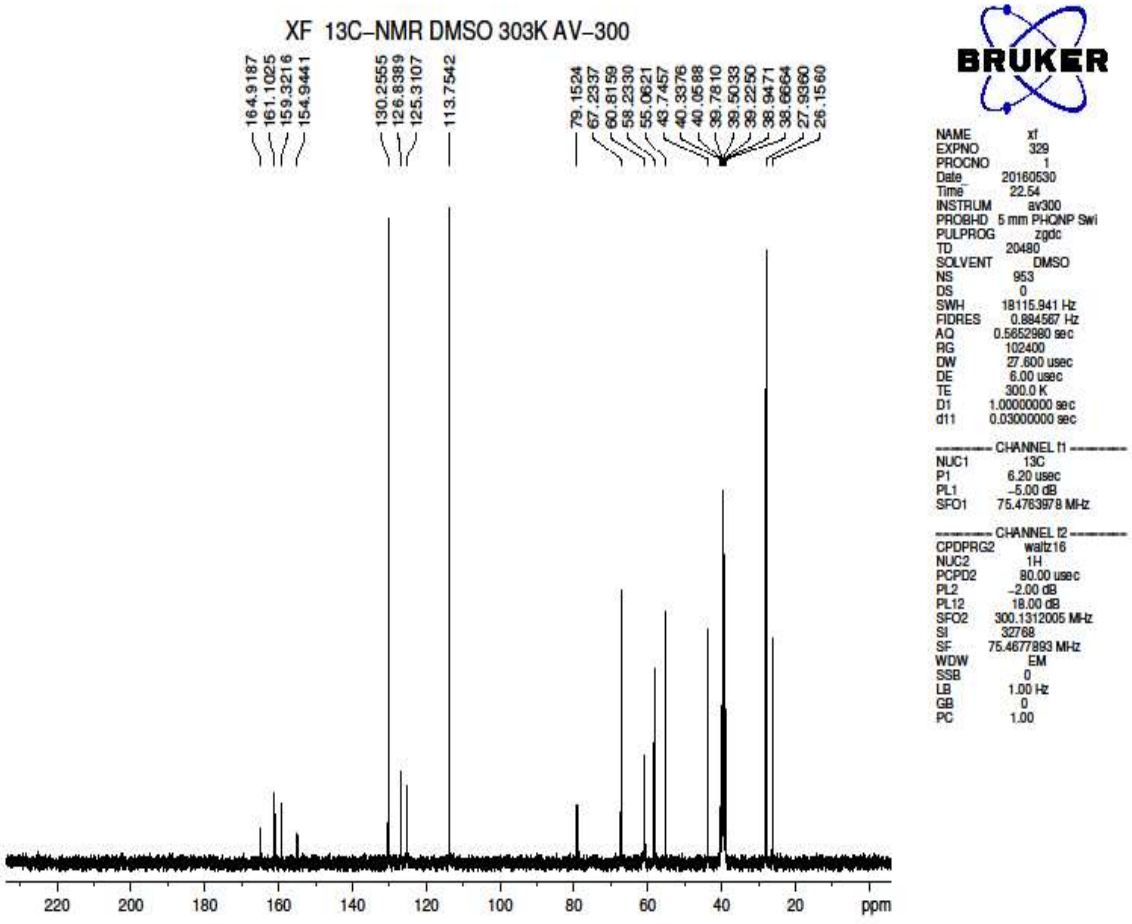
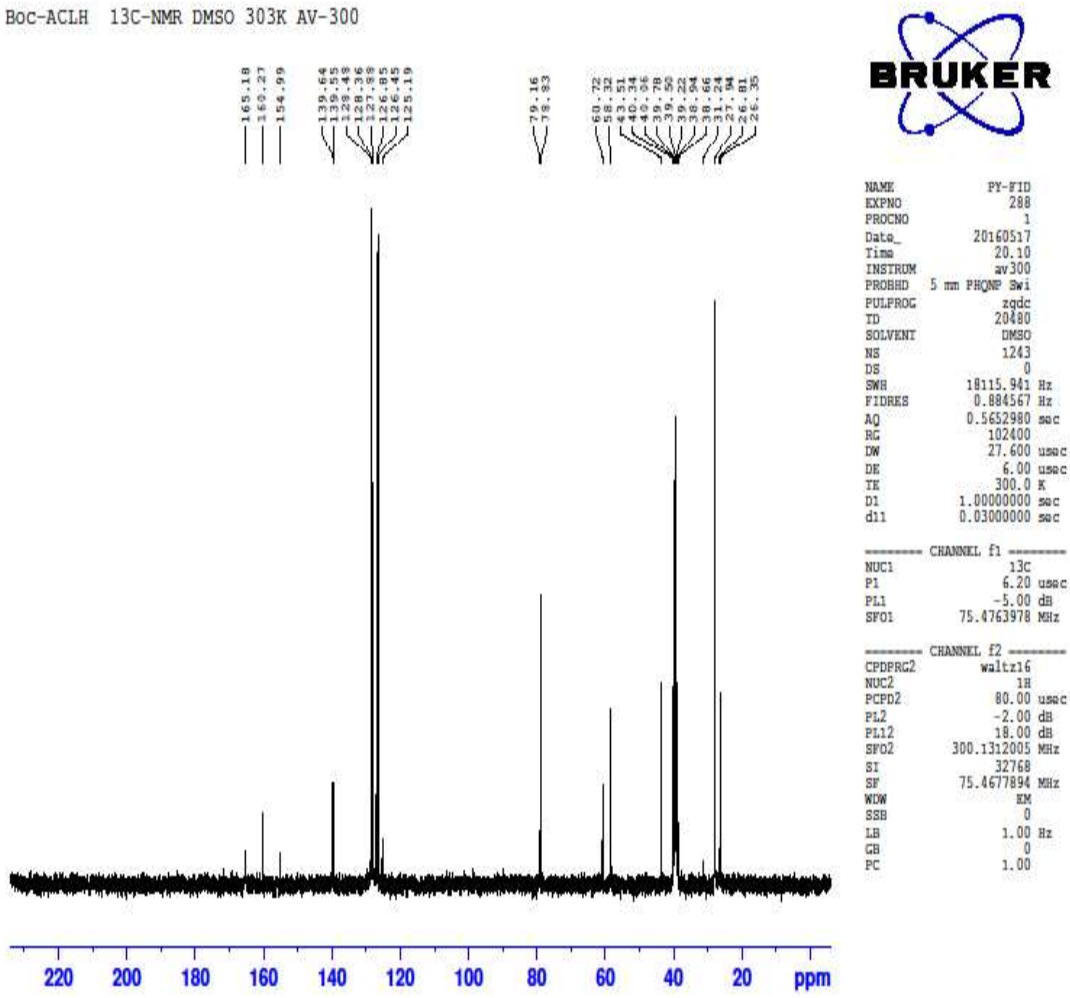


Figure S2. [1]NMR spectral image of Boc-ACLH

(4a)


XF 13C–NMR DMSO 303K AV–300
164.9187
161.1025
159.3216
154.9441
130.2555
126.8389
125.3107
113.7542
79.1524
67.2337
60.8159
58.2330
55.0621
43.7457
40.3376
40.0588
39.7810
39.5033
39.2250
38.9471
38.6664
27.9360
26.1560
220
200
180
160
140
120
100
80
60
40
20
ppm
BRUKER
NAME xf
EXPNO 329
PROCNO 1
Date_ 20160530
Time 22.54
INSTRUM av300
PROBHD 5 mm PHONP Swi
PULPROG zgdc
TD 20480
SOLVENT DMSO
NS 953
DS 0
SWH 18115.941 Hz
FIDRES 0.884567 Hz
AQ 0.5652980 sec
RG 102400
DW 27.600 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
CHANNEL f1
NUC1 13C
P1 6.20 usec
PL1 -5.00 dB
SFO1 75.4763978 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 18.00 dB
SFO2 300.1312005 MHz
SI 32768
SF 75.4677893 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

(4b)


Boc-ACLH 13C-NMR DMSO 303K AV-300
165.18
160.27
154.99
139.64
139.55
129.49
128.36
127.88
126.85
126.45
125.19
79.16
78.83
60.72
58.32
43.51
43.34
40.06
39.78
39.50
39.22
38.94
38.66
31.64
27.81
26.35
BRUKER
NAME PY-FID
EXPNO 288
PROCNO 1
Date_ 20160517
Time 20.10
INSTRUM av300
PROBHD 5 mm PHQNP Swi
PULPROG zqdc
TD 20480
SOLVENT DMSO
NS 1243
DS 0
SWH 18115.941 Hz
FIDRES 0.884567 Hz
AQ 0.5652980 sec
RG 102400
DW 27.600 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
CHANNEL f1
NUC1 13C
P1 6.20 usec
PL1 -5.00 dB
SFO1 75.4763978 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 18.00 dB
SFO2 300.1312005 MHz
SI 32768
SF 75.4677894 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
220
200
180
160
140
120
100
80
60
40
20
ppm

(4a)

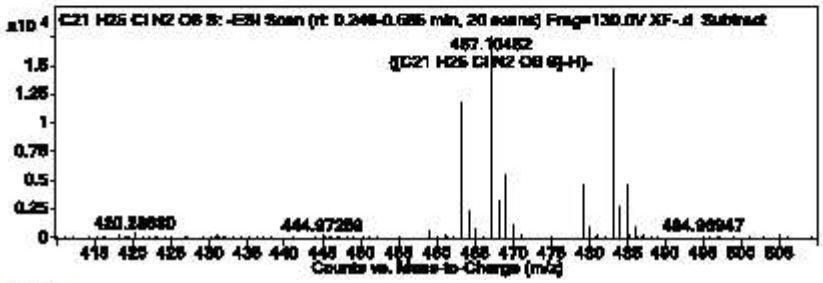
Qualitative Analysis Report

Data Filename	XF-.d	**Sample Name**	XF
Sample Type	Sample	**Position**	Vial 23
Instrument Name	Instrument 1	**User Name**	
Acq Method	0601.m	**Acquired Time**	6/1/2016 8:58:02 PM
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

Sample Group		**Info.**	
Stream Name	LC 1	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.06.01 (B6157)

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
130	0	ESI



Peak List

m/z	z	Abund	Formula	Ion
197.06833		3391.76		
255.23315	1	5148.69		
283.26442	1	4150.53		
407.0916	1	10089.36		
463.15409	1	11837.37		
467.10452	1	17586.93	C21 H25 Cl N2 O6 S	(M-H)-
469.10223	1	5540.29	C21 H25 Cl N2 O6 S	(M-H)-
479.14878	1	4564.1		
483.09924	1	14709.62		
485.0973	1	4643.71		

Formula Calculator Element Limits

Element	Min	Max
C	15	25
H	20	30
O	5	7
Cl	0	2
S	0	2
N	1	3

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Calculated Mz
C21 H25 Cl N2 O6 S	TRUE	468.1118	468.1122	0.82	C21 H24 Cl N2 O6 S	467.10491
C24 H21 Cl N2 O6	FALSE	468.1116	468.1088	-6.03	C24 H20 Cl N2 O6	467.10154
C21 H24 Cl2 N3 O5	FALSE	468.1119	468.1093	-5.49	C21 H23 Cl2 N3 O5	467.10202

--- End Of Report ---

(4b)

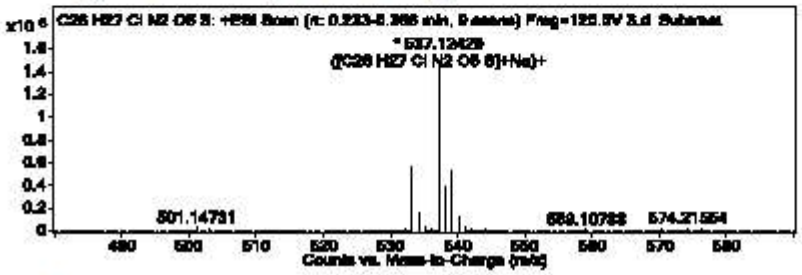
Qualitative Analysis Report

Data Filename	3.d	**Sample Name**	3
Sample Type	Sample	**Position**	Vial 2
Instrument Name	Instrument 1	**User Name**	
Acq Method	0519-1.m	**Acquired Time**	5/21/2016 3:32:27 PM
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

Sample Group		**Info.**	
Stream Name	LC 1	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.06.01 (B6157)

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
120	0	ESI



Peak List

m/z	z	Abund	Formula	Ion
475.32744	1	398230.19		
533.17359	1	560162.5		
537.12429	1	1480055.13	C26 H27 Cl N2 O5 S	(M+Na)+
538.12737	1	385627.34	C26 H27 Cl N2 O5 S	(M+Na)+
539.12226	1	538139	C26 H27 Cl N2 O5 S	(M+Na)+

Formula Calculator Element Limits

Element	Min	Max
C	20	30
H	20	30
O	4	8
N	0	4
Cl	0	3
S	0	3

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	CalculatedMz
C26 H27 Cl N2 O5 S	TRUE	514.135	514.1329	-4.11	C26 H27 Cl N2 Na O5 S	537.12214
C23 H30 Cl2 N3 O4 S	FALSE	514.1353	514.1334	-3.61	C23 H30 Cl2 N3 Na O4 S	537.12263

— End Of Report —