Supplementary Material

An Expedient Synthesis of CMF-019: (*S*)-5-Methyl-3-{1-(pentan-3-yl)-2-(thiophen-2-ylmethyl)-1*H*-benzo[d]imidazole-5-carboxamido}hexanoic Acid, a Potent Apelin Receptor (APJ) Agonist

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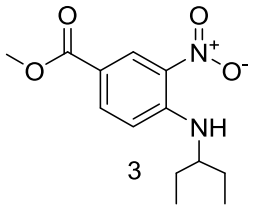
Contents

1. NMR spectra images

1H-NMR (400MHz, CDCl3)



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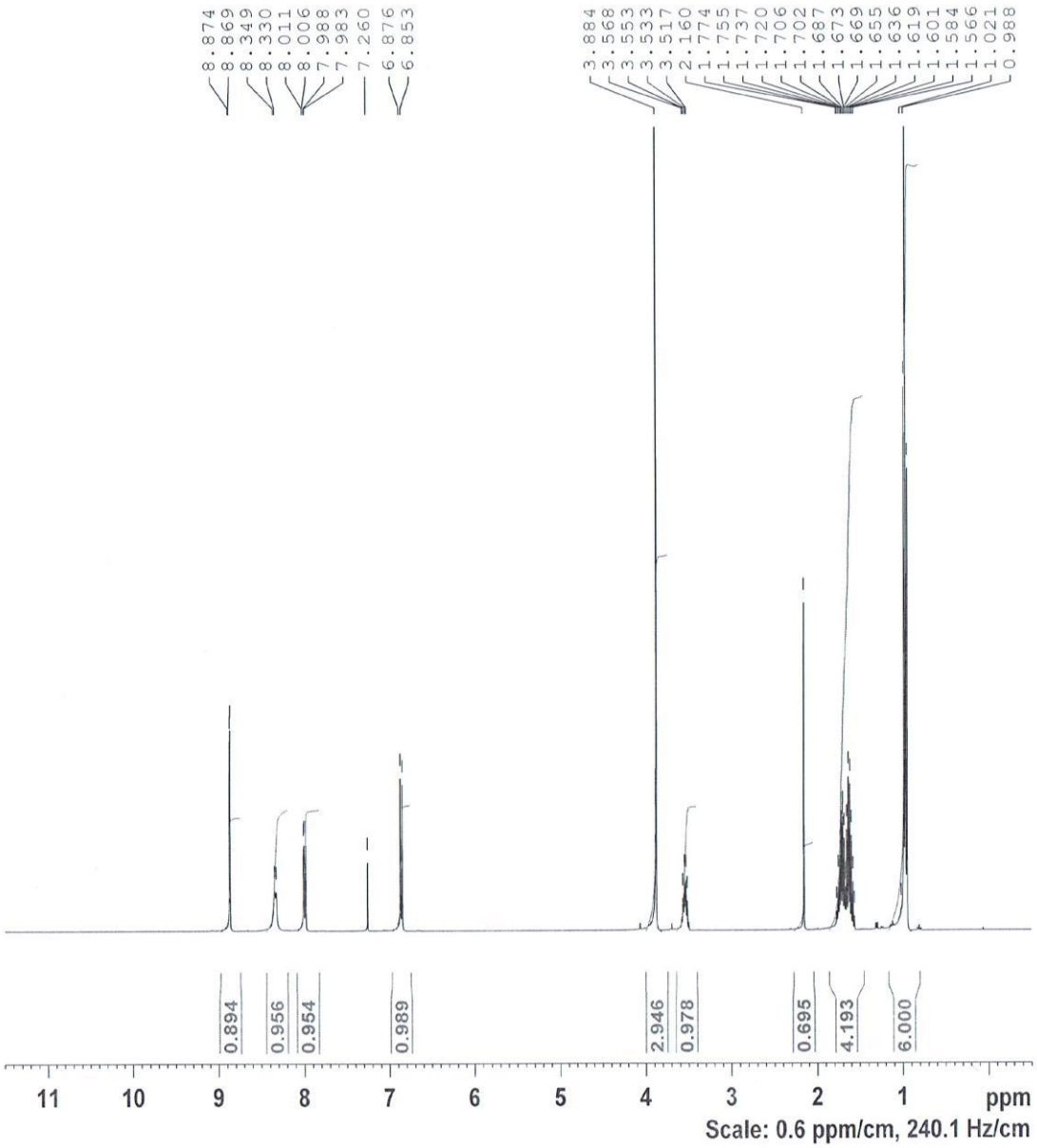
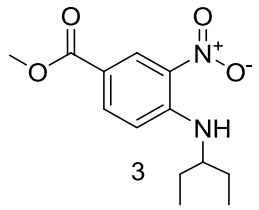


13C-NMR (100MHz, CDCl3)



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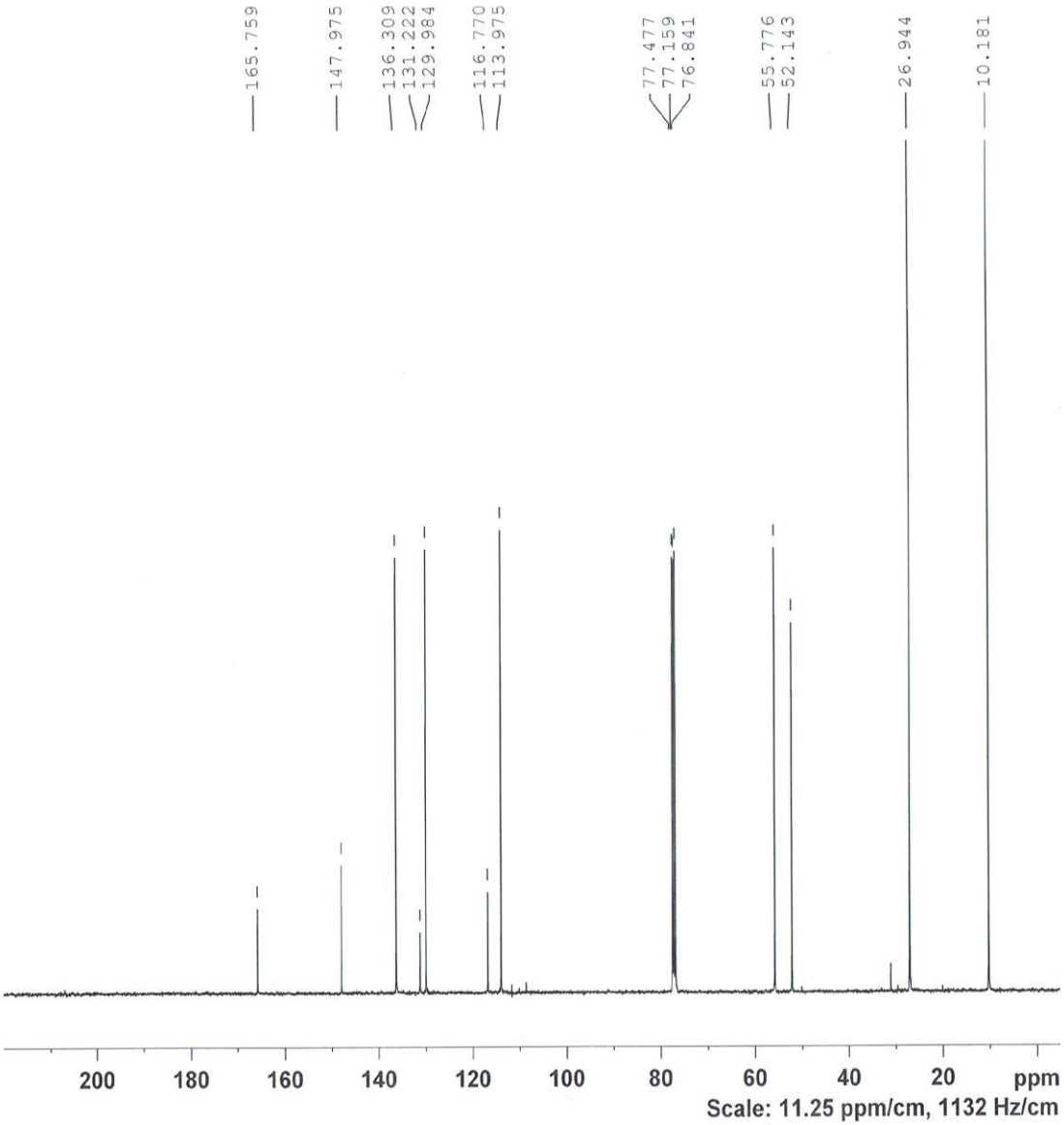
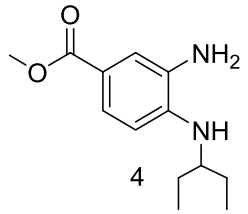


1H-NMR (400MHz, CDCl3)



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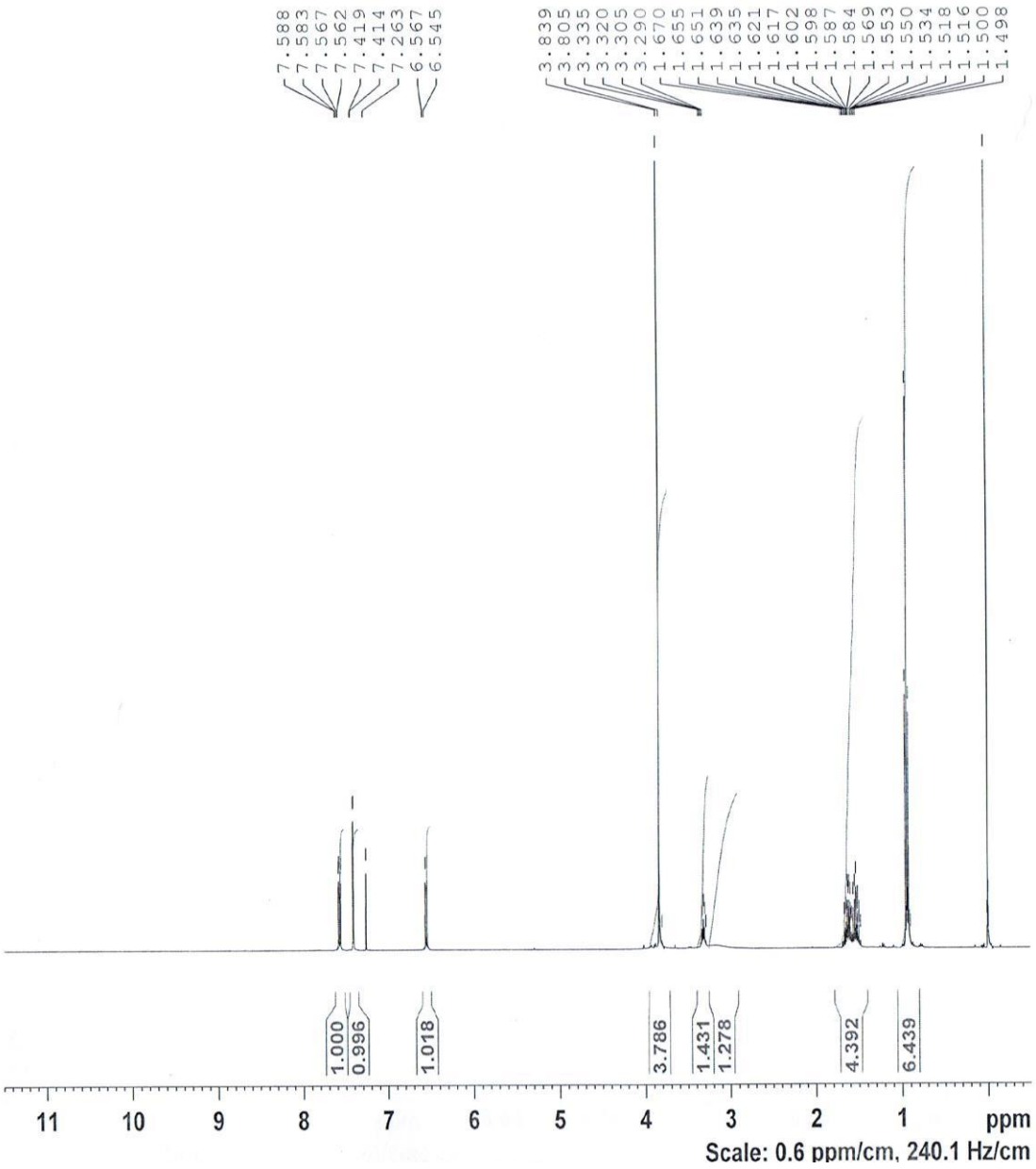
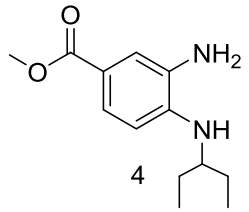


13C-NMR (100MHz, CDCl3)



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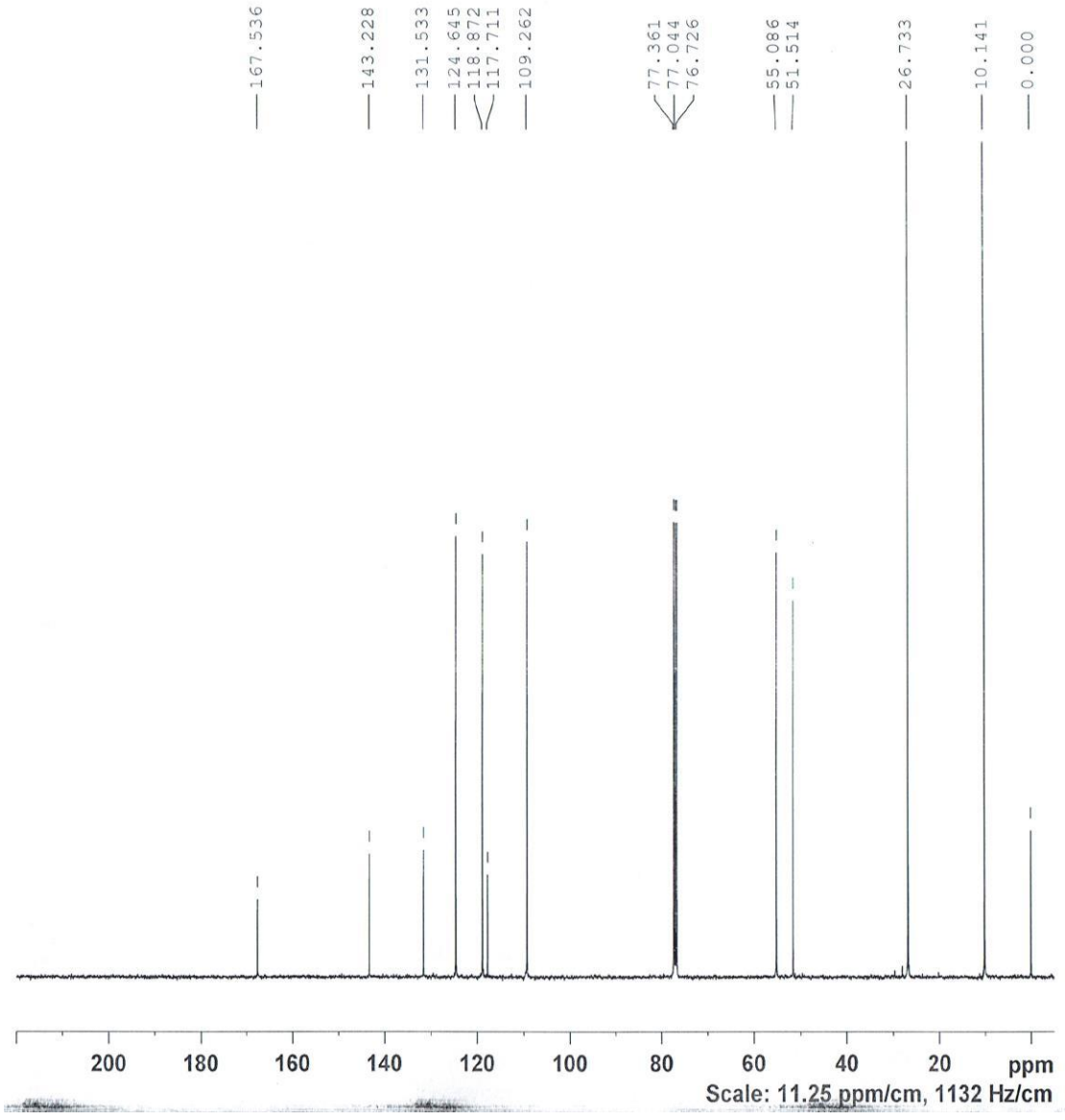

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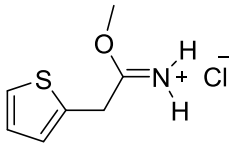

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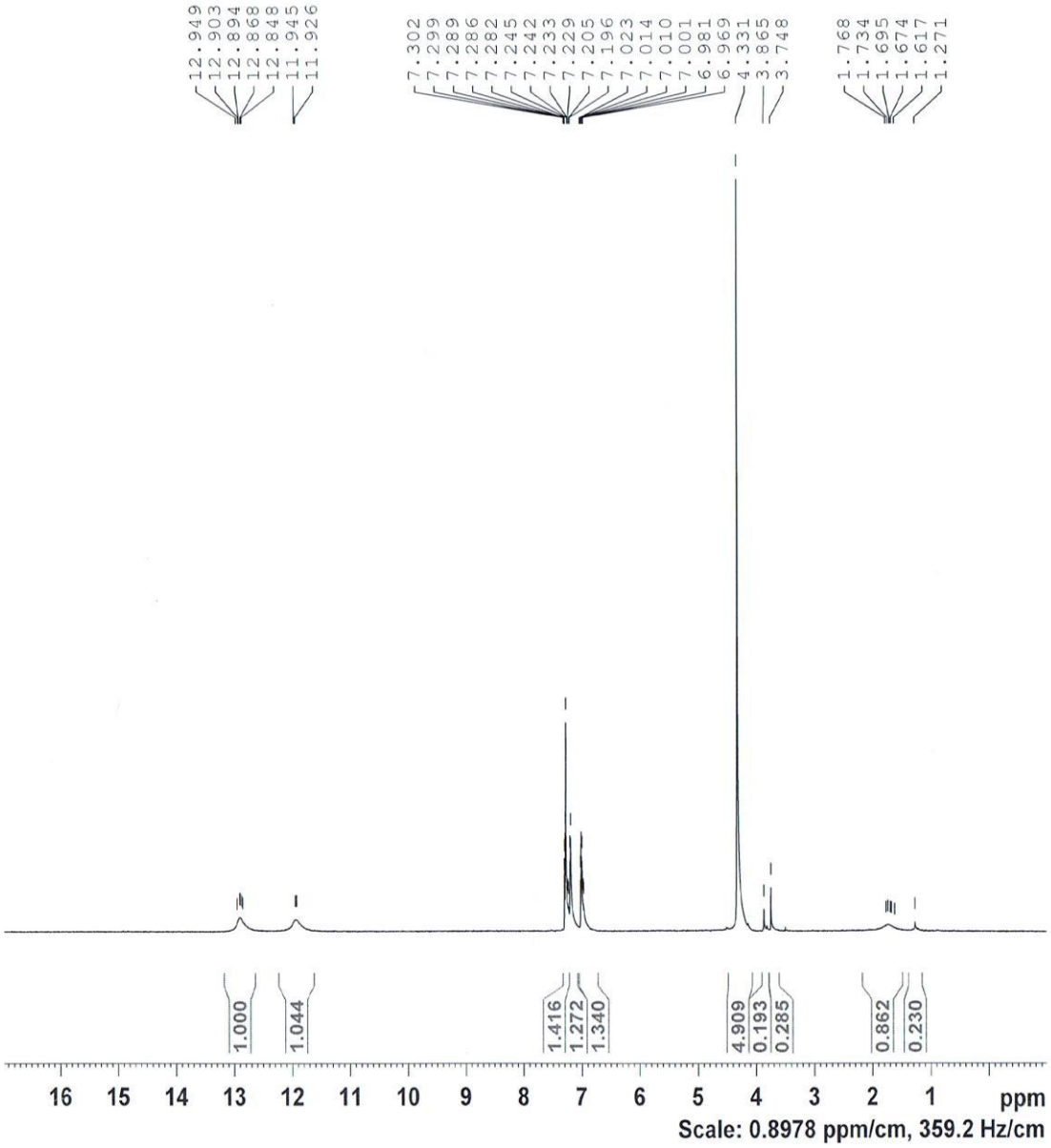
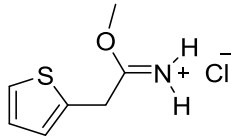


13C-NMR (100MHz, CDCl3)



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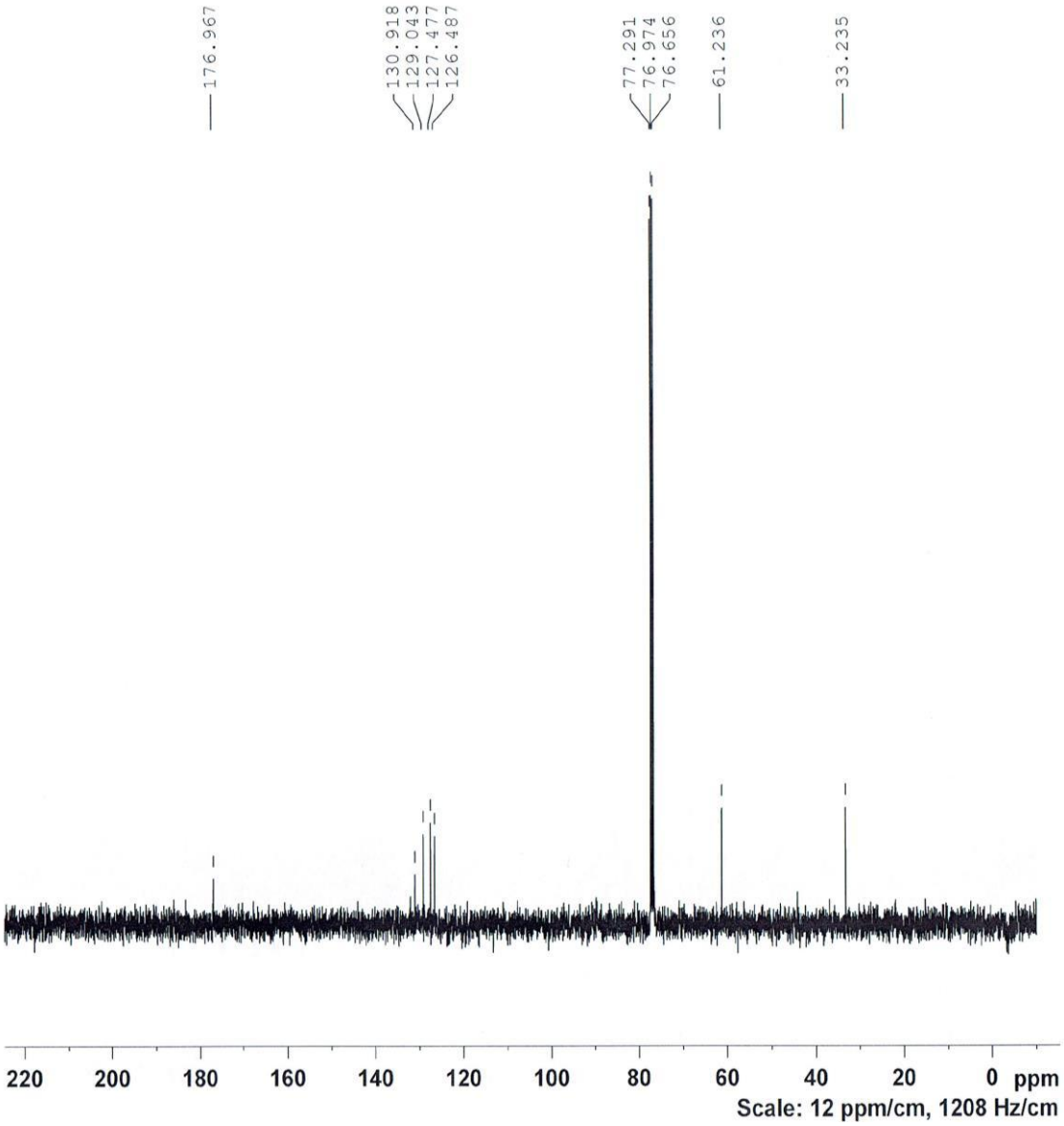

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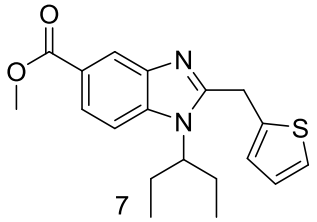
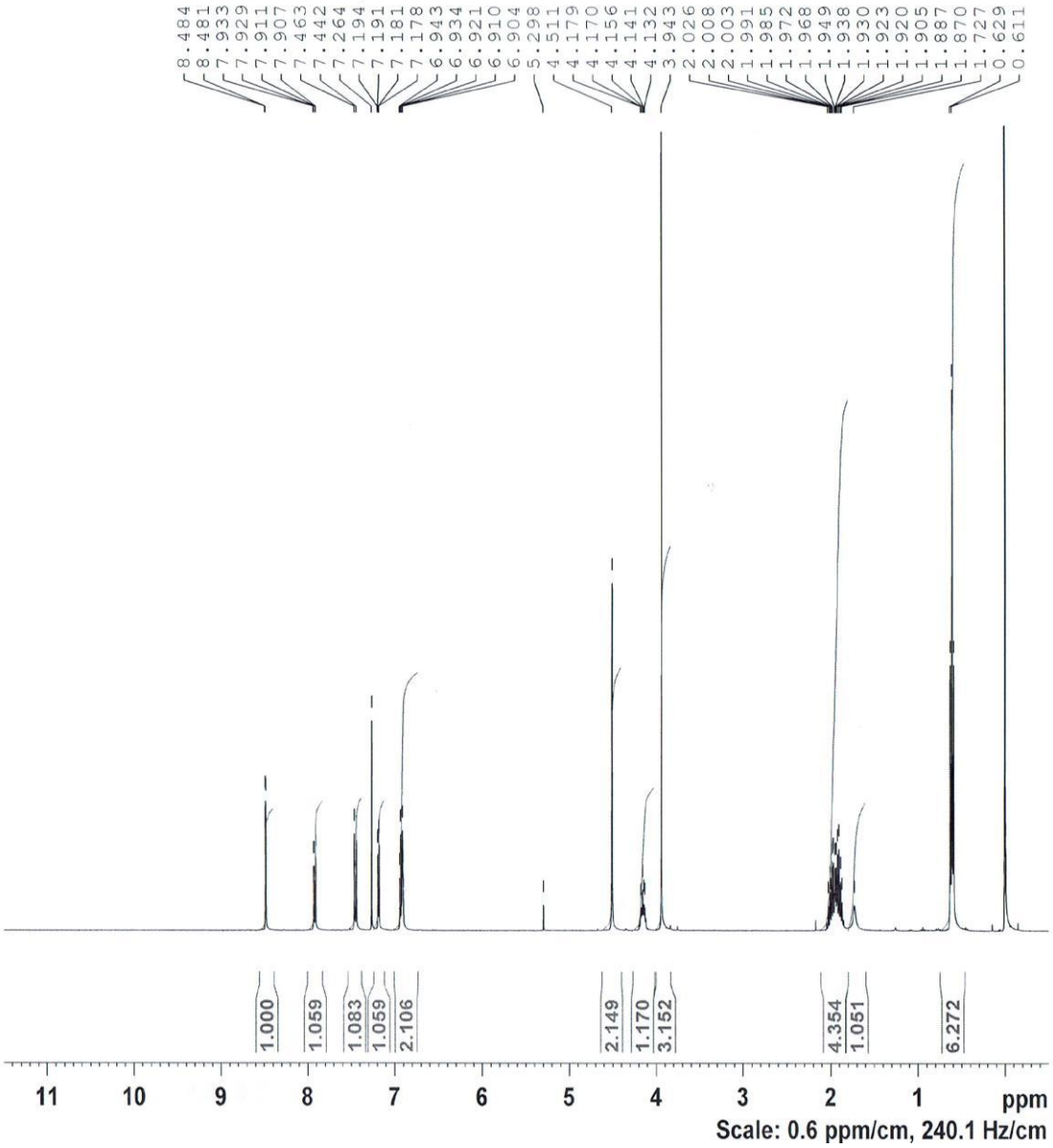
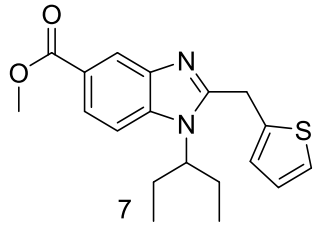




13C-NMR (100MHz, CDCl3)



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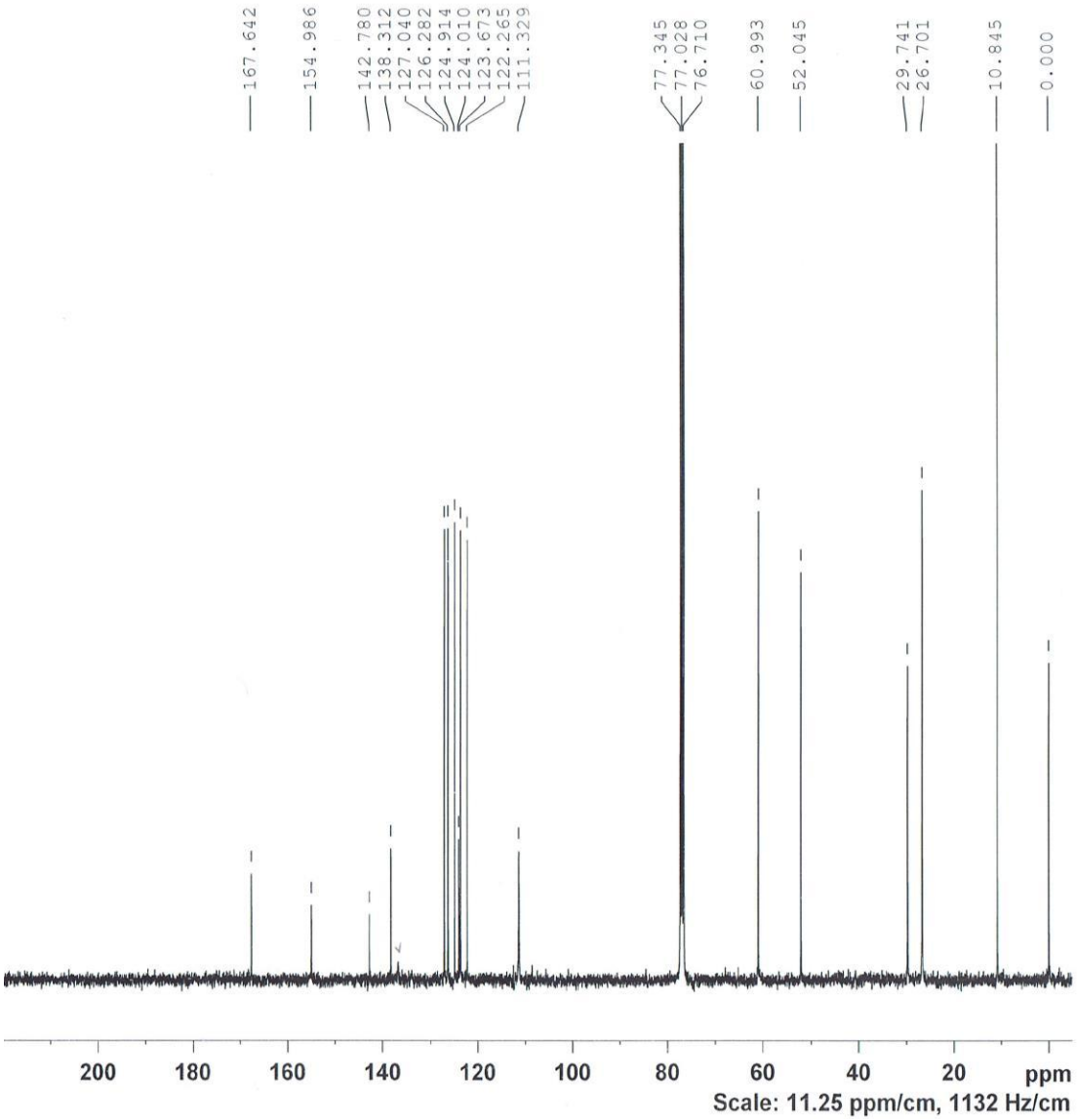

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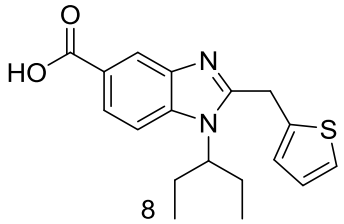

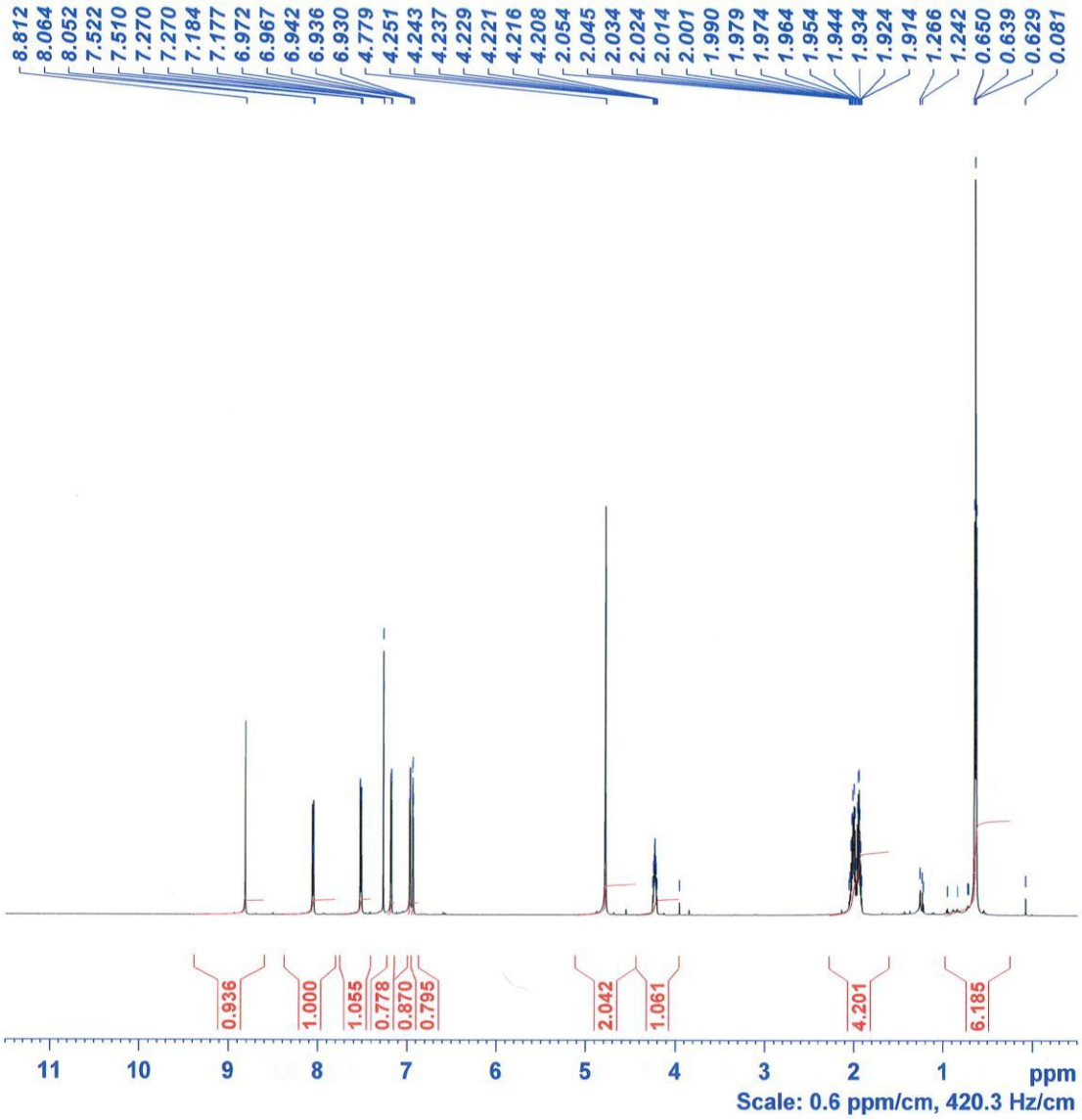

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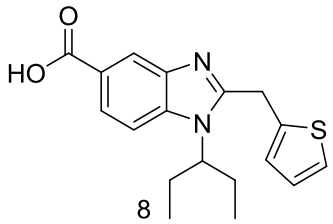
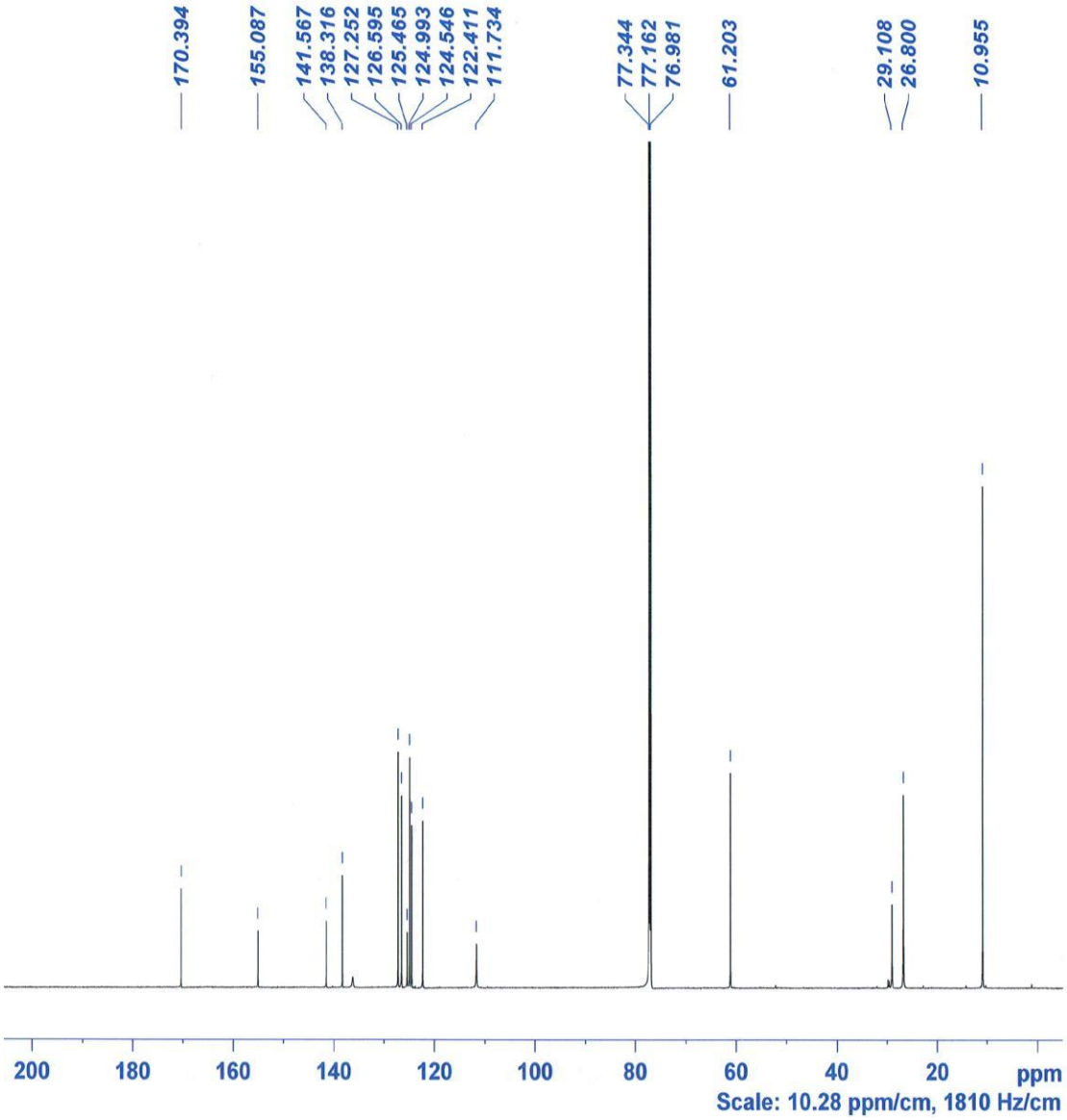
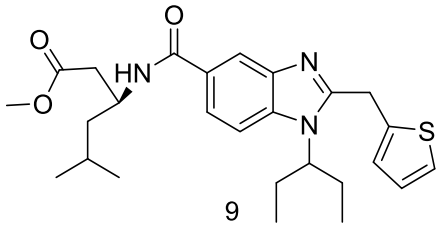




1H-NMR (400MHz, C6D6)



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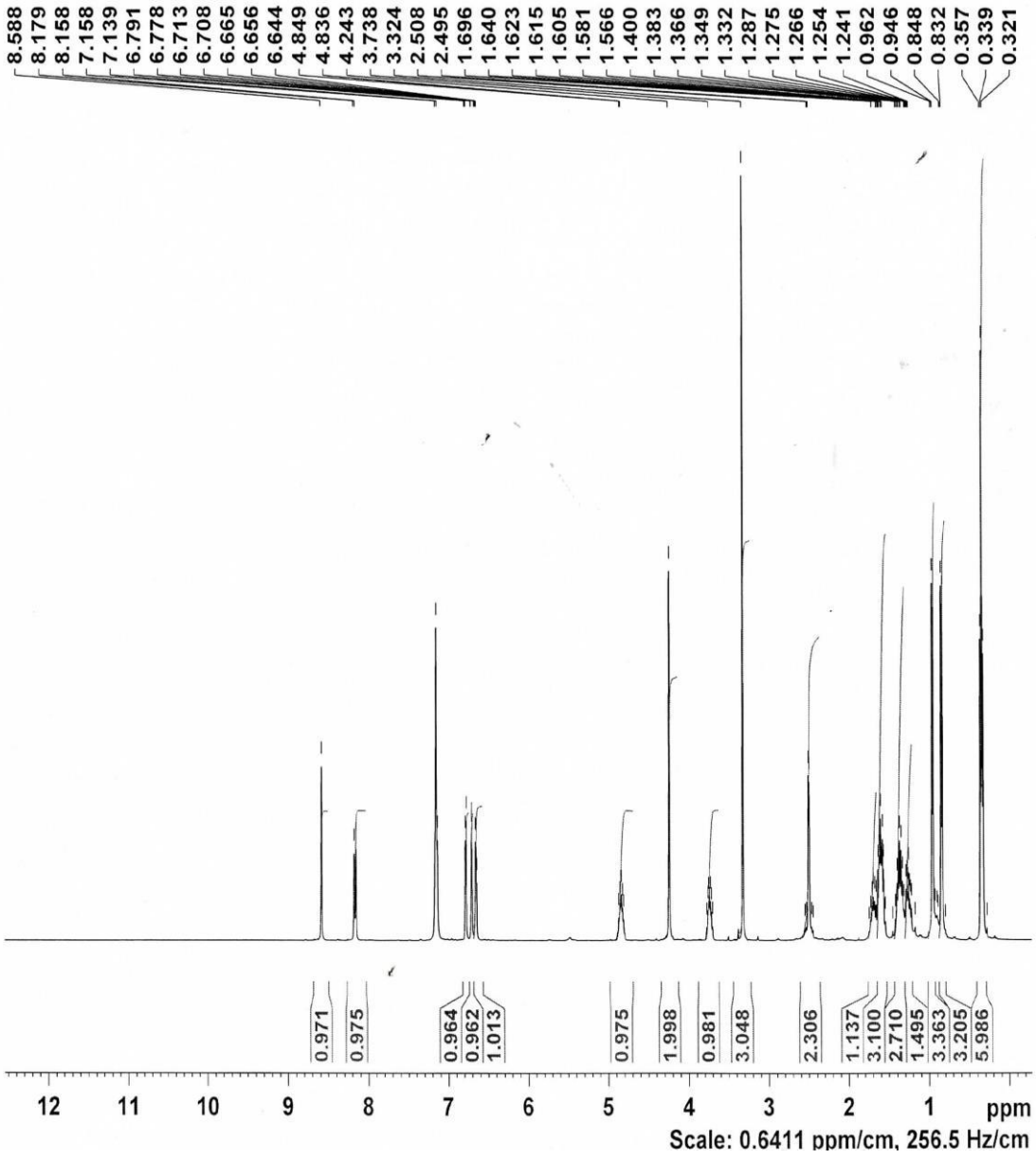
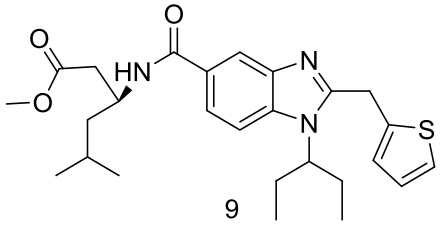


13C-NMR (100MHz, C6D6)



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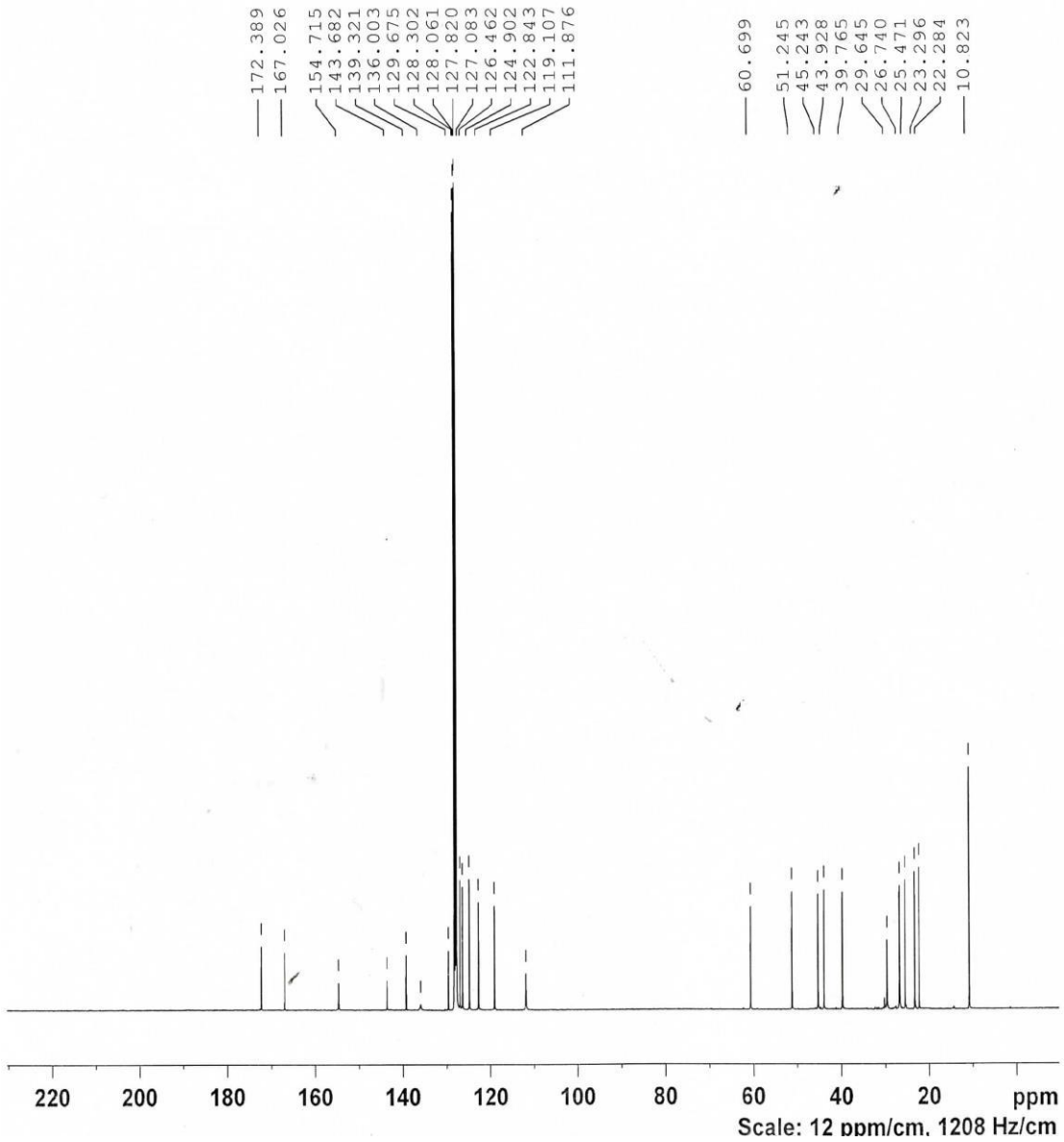
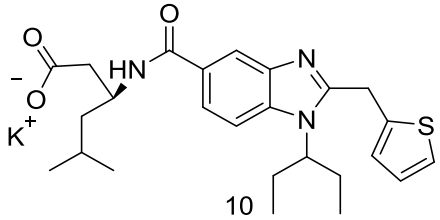


1H-NMR (400MHz, DMSO)



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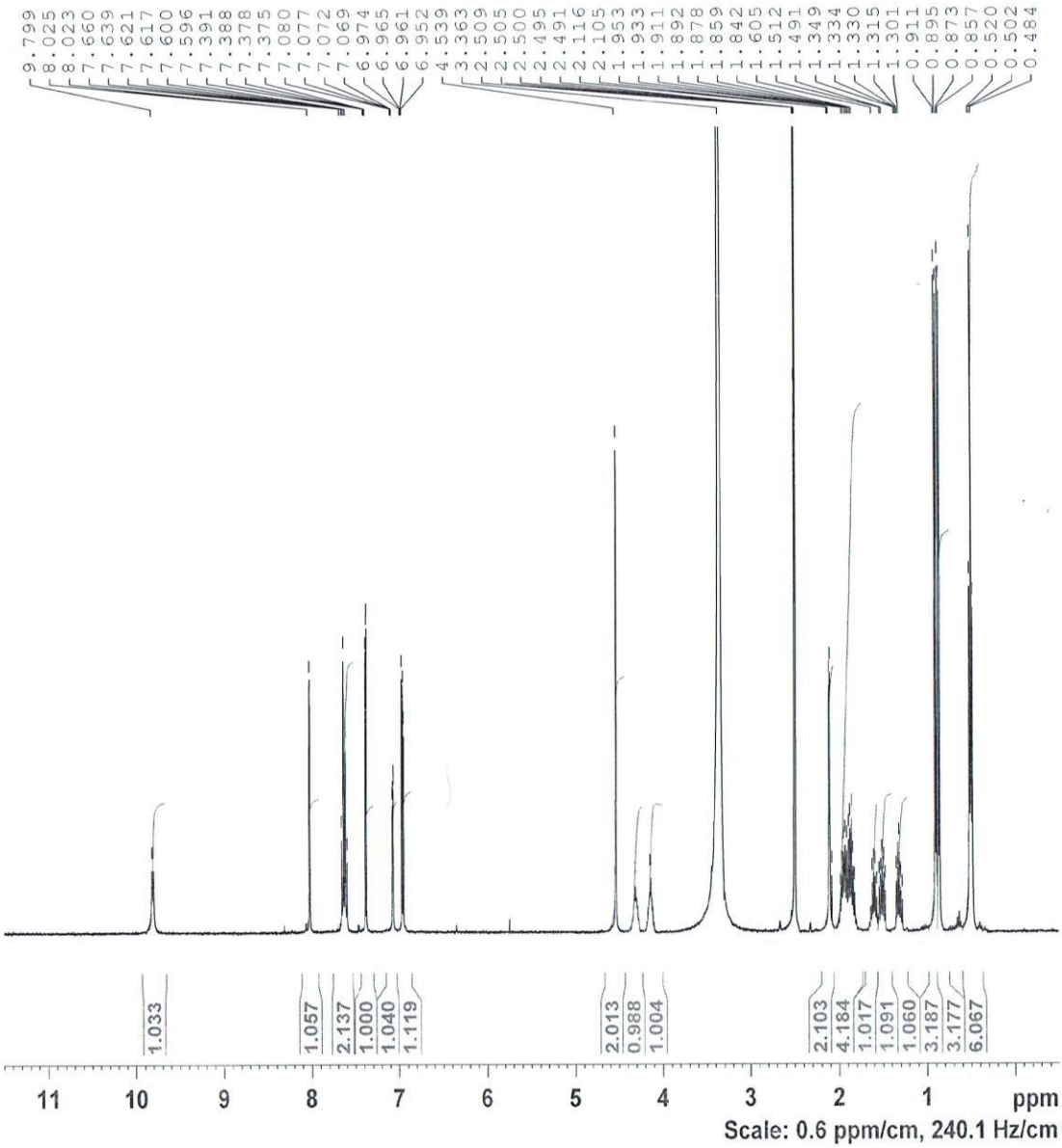
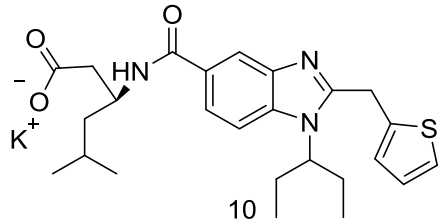


13C-NMR (100MHz, DMSO)



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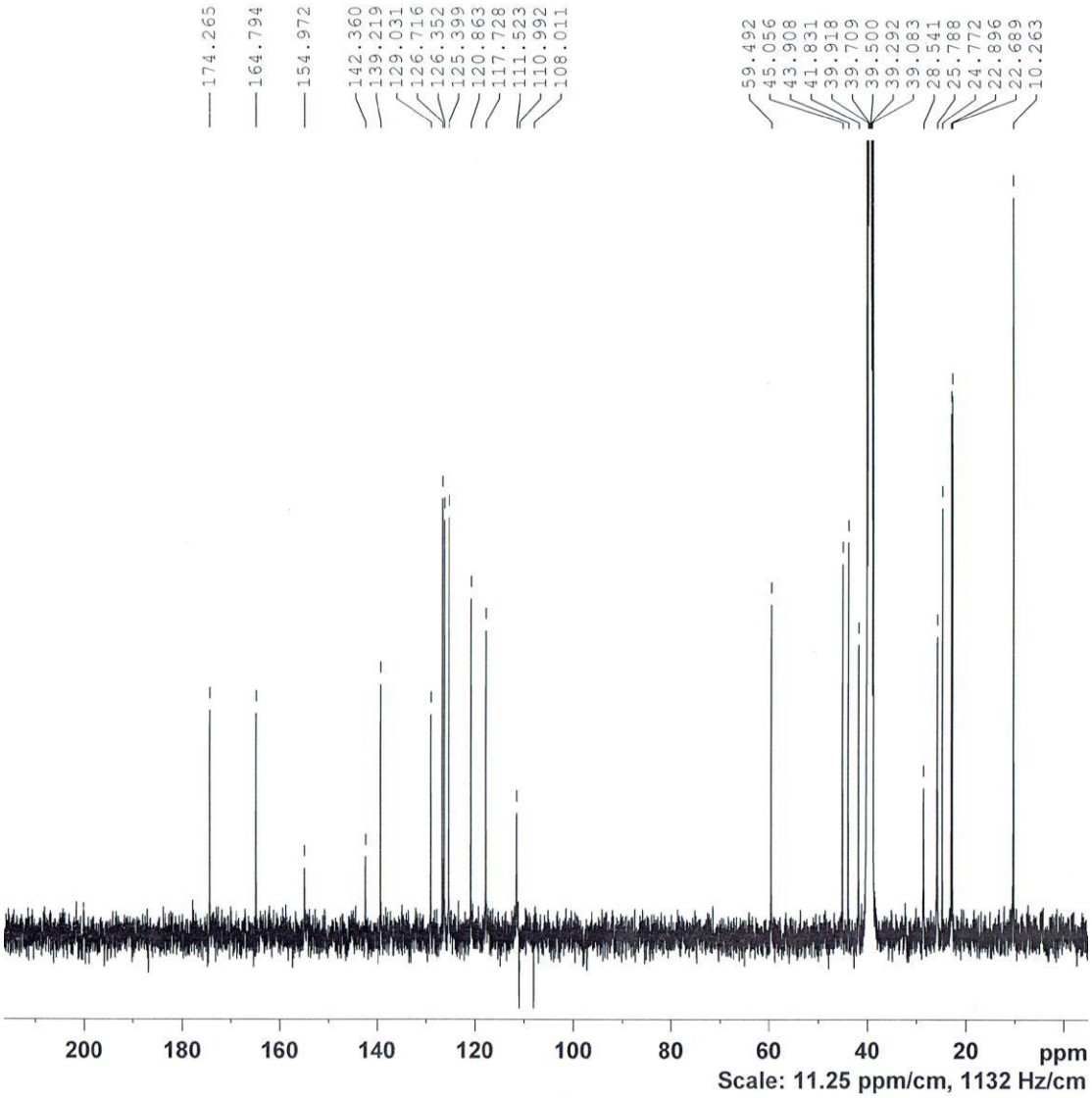
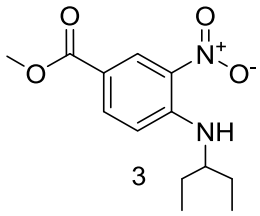


2. Mass Spectroscopy analytical data



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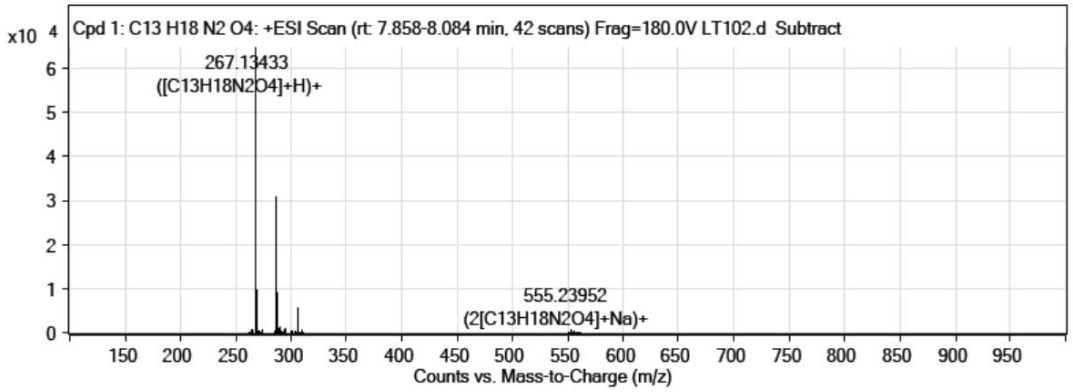
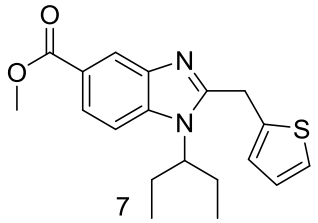
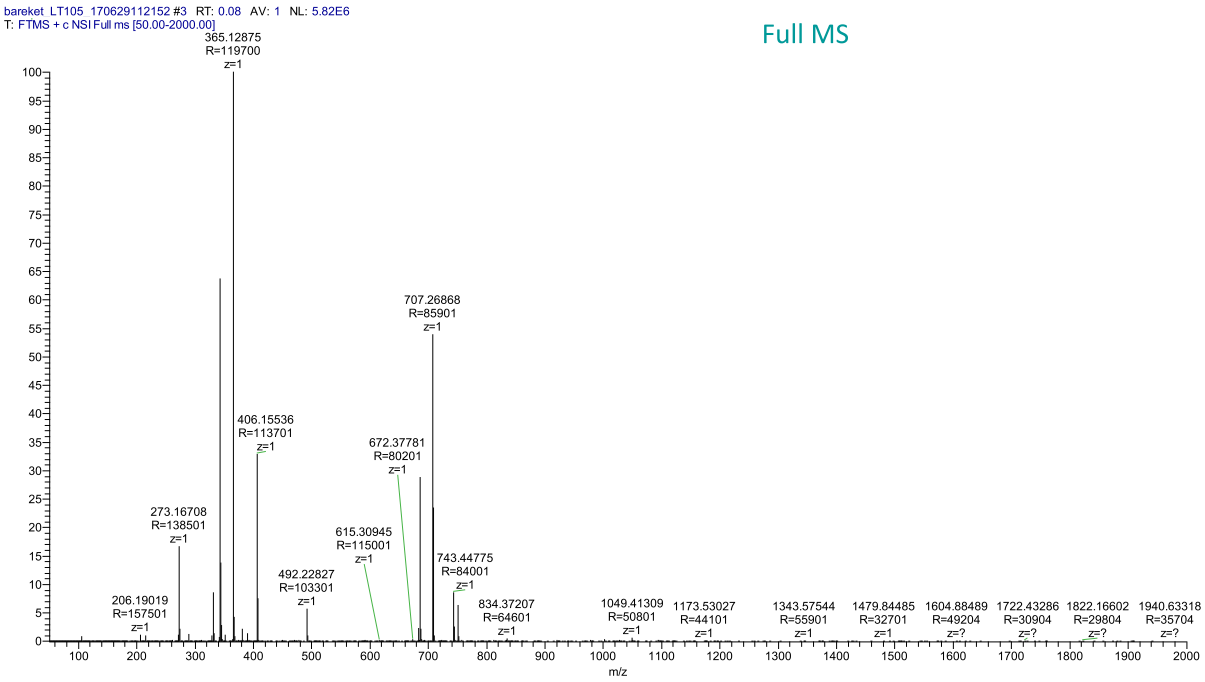
MS Spectrum



MS Spectrum Peak List

m/z	Calc m/z	Diff(ppm)	z	Abund	Formula	Ion
267.13433	267.13393	-1.5	1	64685.58	C13H18N2O4	(M+H)+
268.1375	268.13703	-1.74	1	9782.74	C13H18N2O4	(M+H)+
269.13861	269.13927	2.47	1	936.54	C13H18N2O4	(M+H)+
289.11546	289.11588	1.43	1	1426.28	C13H18N2O4	(M+Na)+
290.12323	290.11898	-14.64	1	172.7	C13H18N2O4	(M+Na)+
305.08121	305.08982	28.19	1	5746.02	C13H18N2O4	(M+K)+
306.08348	306.09291	30.82	1	869.02	C13H18N2O4	(M+K)+
555.23952	555.24254	5.43	1	267.42	C13H18N2O4	(2M+Na)+
556.23884	556.24563	12.22	1	44.17	C13H18N2O4	(2M+Na)+


O
O
N
N
S
7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406.15536 R=113701 z=1
672.37781 R=80201 z=1
273.16708 R=138501 z=1
615.30945 R=115001 z=1
743.44775 R=84001 z=1
492.22827 R=103301 z=1
206.19019 R=157501 z=1
834.37207 R=64601 z=1
1049.41309 R=50801 z=1
1173.53027 R=44101 z=1
1343.57544 R=55901 z=1
1479.84485 R=32701 z=1
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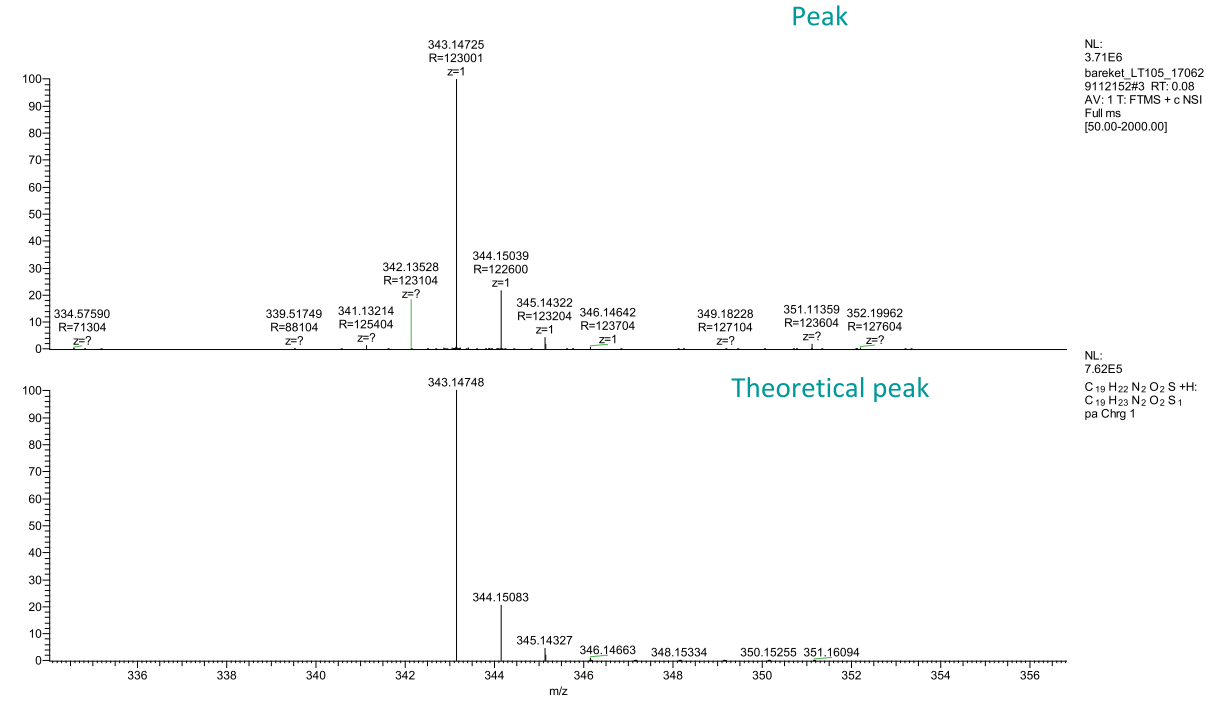
1722.43286 R=30904 z=?
1822.16602 R=29804 z=?
1940.63318 R=35704 z=?
m/z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NL: 3.71E6 bareket_LT105_17062 9112152#3 RT: 0.08 AV: 1 T: FTMS + c NSI Full ms [50.00-2000.00]
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346.14642 R=123704 z=1
334.57590 R=71304 z=?
339.51749 R=88104 z=?
341.13214 R=125404 z=?
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351.11359 R=123604 z=?
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NL: 7.62E5
Theoretical peak
C19 H22 N2 O2 S +H: C19 H23 N2 O2 S1 pa Chrg 1
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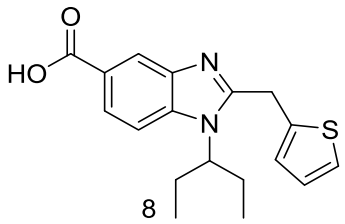
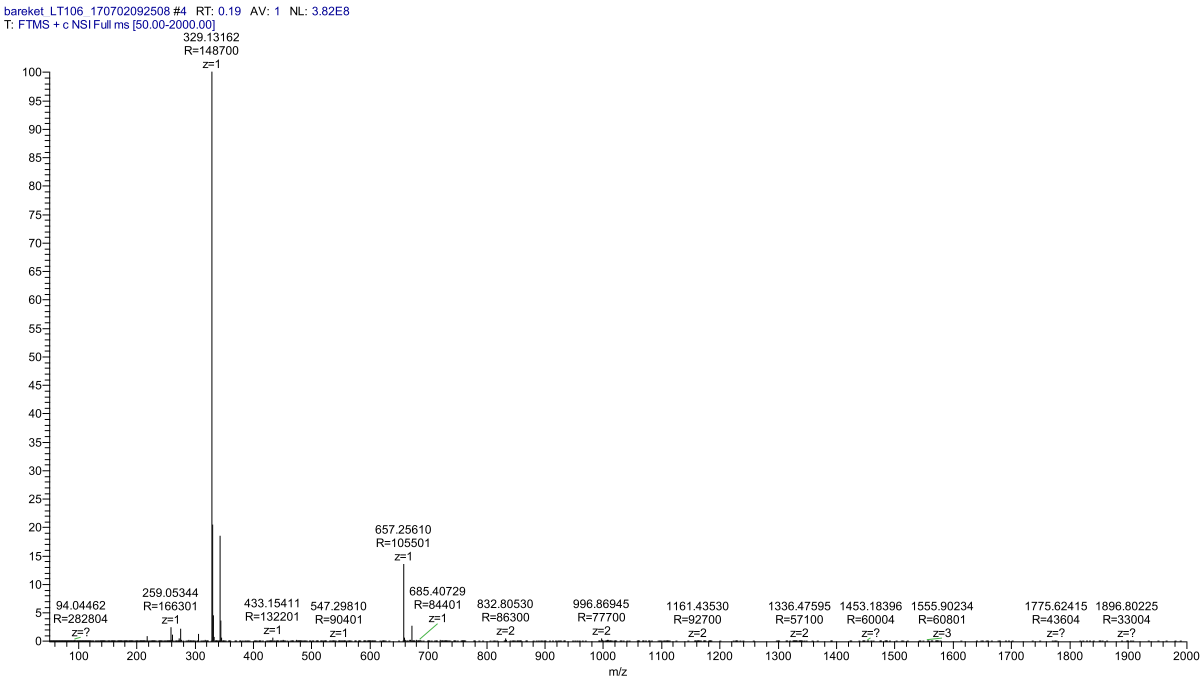
346.14663
348.15334
350.15255
351.16094
m/z


O
HO
N
N
S

8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z=1
259.05344
R=166301
z=1
94.04462
R=282804
z=?
433.15411
R=132201
z=1
547.29810
R=90401
z=1
832.80530
R=86300
z=2
996.86945
R=77700
z=2
1161.43530
R=92700
z=2
1336.47595
R=57100
z=2
1453.18396
R=60004
z=?
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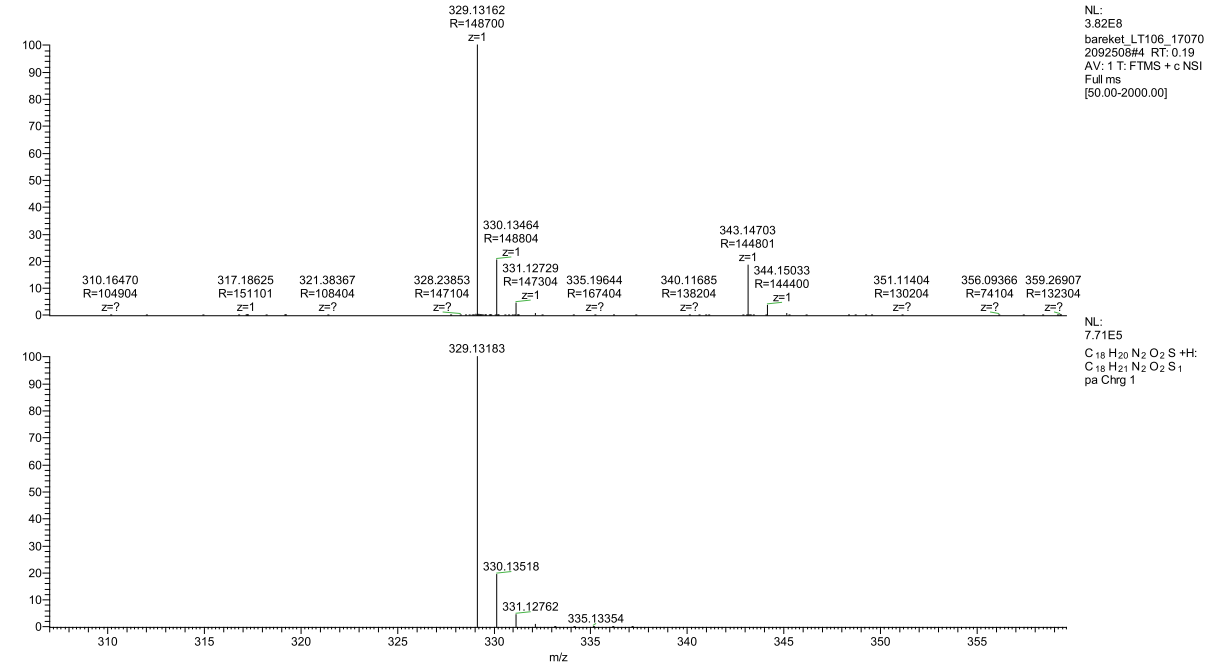
m/z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Full ms
[50.00-2000.00]
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344.15033
R=144400
z=1
310.16470
R=104904
z=?
317.18625
R=151101
z=1
321.38367
R=108404
z=?
328.23853
R=147104
z=?
335.19644
R=167404
z=?
340.11685
R=138204
z=?
351.11404
R=130204
z=?
356.09366
R=74104
z=?
359.26907
R=132304
z=?
NL:
7.71E5
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C 18 H 21 N 2 O 2 S 1
pa Chrg 1
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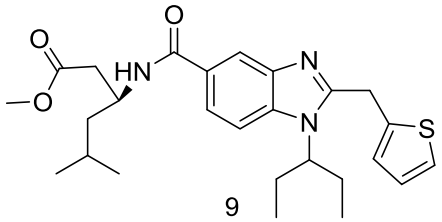
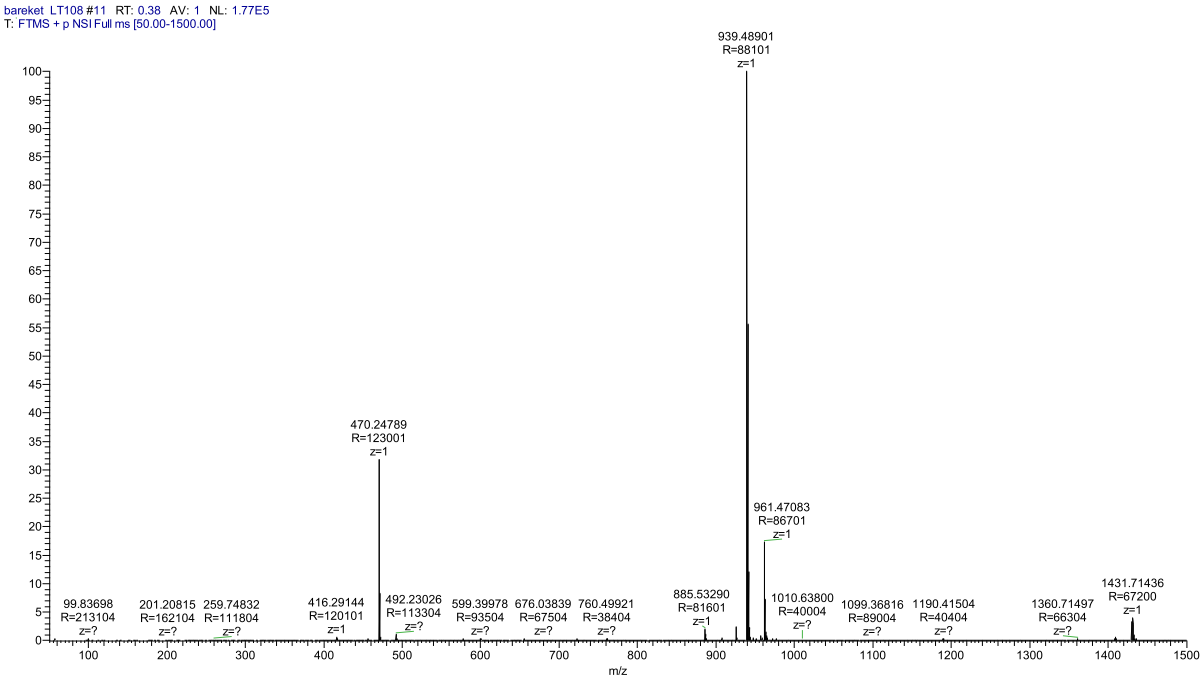
330.13518
331.12762
335.13354
m/z


O
HN
O
O
N
N
S

9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z=1
961.47083
R=86701
z=1
99.83698
R=213104
z=?
201.20815
R=162104
z=?
259.74832
R=111804
z=?
416.29144
R=120101
z=1
492.23026
R=113304
z=?
599.39978
R=93504
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R=38404
z=?
885.53290
R=81601
z=1
1010.63800
R=40004
z=?
1099.36816
R=89004
z=?
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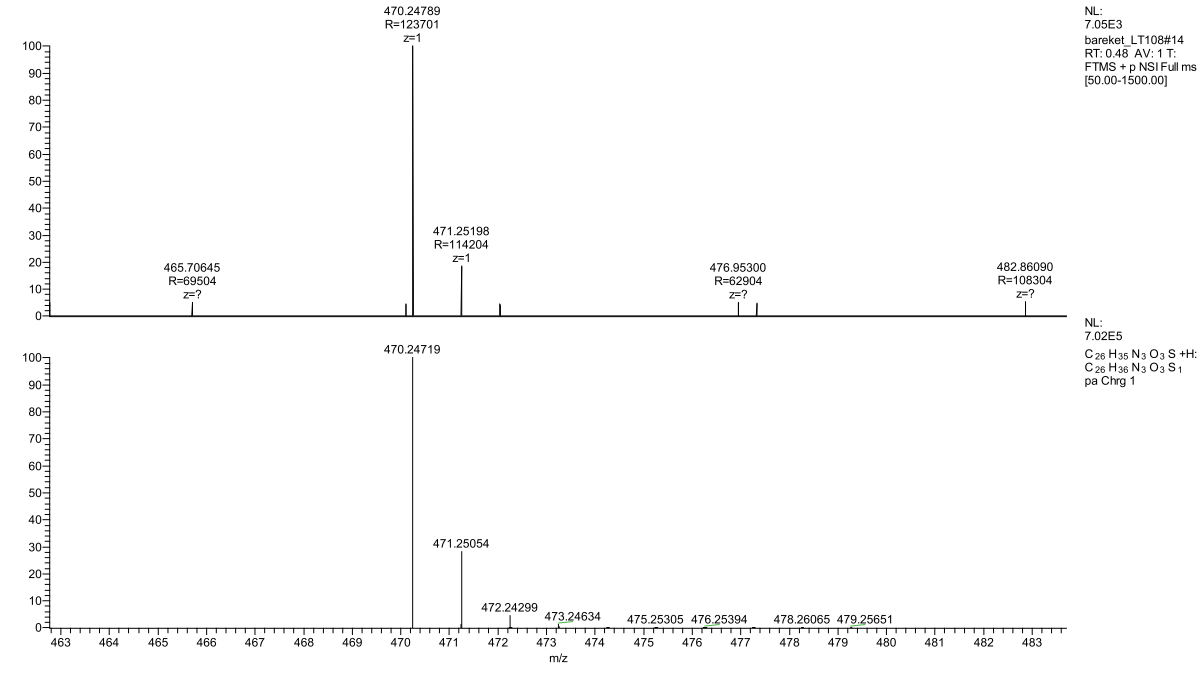
z=?
1431.71436
R=67200
z=1
m/z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z=1
NL:
7.05E3
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RT: 0.48 AV: 1 T:
FTMS + p NSI Full ms
[50.00-1500.00]
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z=1
465.70645
R=69504
z=?
476.95300
R=62904
z=?
482.86090
R=108304
z=?
NL:
7.02E5
C26 H35 N3 O3 S +H:
C26 H36 N3 O3 S1
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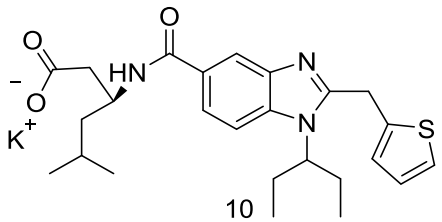
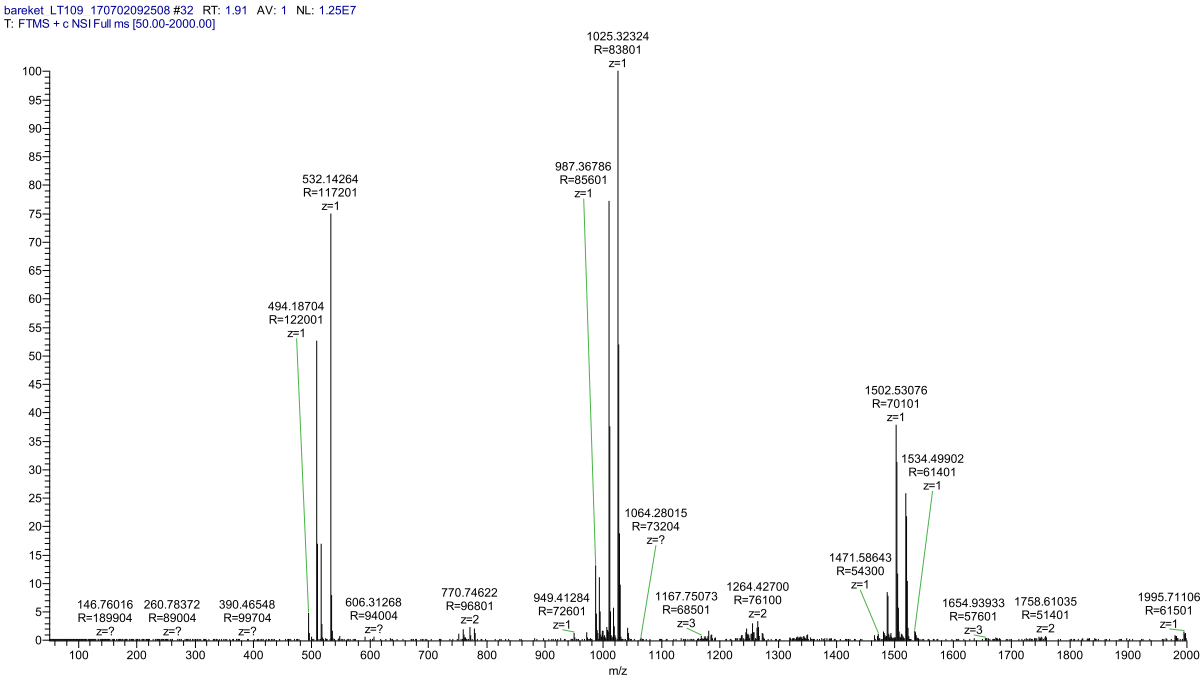

O
HN
O
N
N
S
O
K+

10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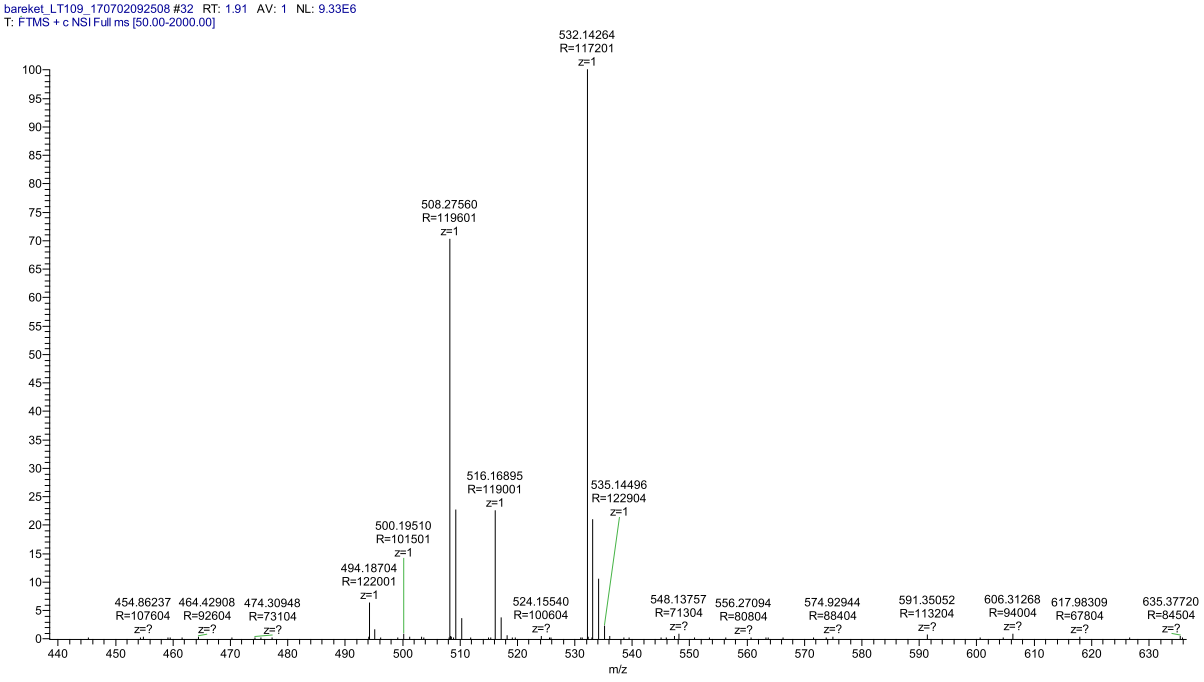
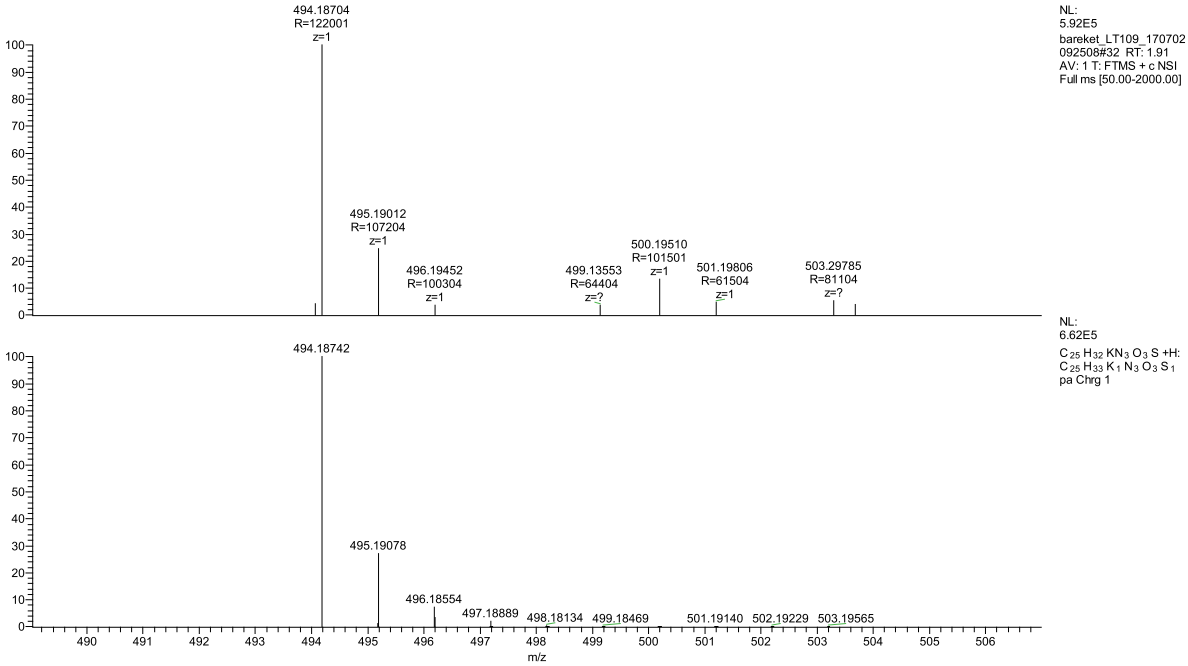
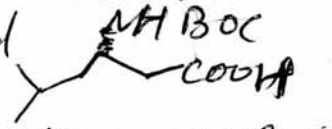
494.18704 R=122001 z=1
1502.53076 R=70101 z=1
1534.49902 R=61401 z=1
1064.28015 R=73204 z=?
1471.58643 R=54300 z=1
1264.42700 R=76100 z=2
1167.75073 R=68501 z=3
770.74622 R=96801 z=2
949.41284 R=72601 z=1
606.31268 R=94004 z=?
146.76016 R=189904 z=?
260.78372 R=89004 z=?
390.46548 R=99704 z=?
1654.93933 R=57601 z=3
1758.61035 R=51401 z=2
1995.71106 R=61501 z=1
m/z


bareket_LT109_170702092508 #32 RT: 1.91 AV: 1 NL: 9.33E6
T: FTMS + c NSI Full ms [50.00-2000.00]
532.14264 R=117201 z=1
508.27560 R=119601 z=1
516.16895 R=119001 z=1
535.14496 R=122904 z=1
500.19510 R=101501 z=1
494.18704 R=122001 z=1
524.15540 R=100604 z=?
454.86237 R=107604 z=?
464.42908 R=92604 z=?
474.30948 R=73104 z=?
548.13757 R=71304 z=?
556.27094 R=80804 z=?
574.92944 R=88404 z=?
591.35052 R=113204 z=?
606.31268 R=94004 z=?
617.98309 R=67804 z=?
635.37720 R=84504 z=?
m/z


494.18704
R=122001
z=1
495.19012
R=107204
z=1
496.19452
R=100304
z=1
499.13553
R=64404
z=?
500.19510
R=101501
z=1
501.19806
R=61504
z=1
503.29785
R=81104
z=?
NL:
5.92E5
bareket_LT109_170702
092508#32 RT: 1.91
AV: 1 T: FTMS + c NSI
Full ms [50.00-2000.00]
494.18742
495.19078
496.18554
497.18889
498.18134
499.18469
501.19140
502.19229
503.19565
NL:
6.62E5
C25 H32 KN3 O3 S +H:
C25 H33 K1 N3 O3 S1
pa Chrg 1
m/z

3. Chiral HPLC report (methyl (S)-3-amino-5-methylhexanoate)

(S)-3-Boc-amino-5-Methyl hexanoic acid (HB108B)
(This is the chiral starting material used for this product.)



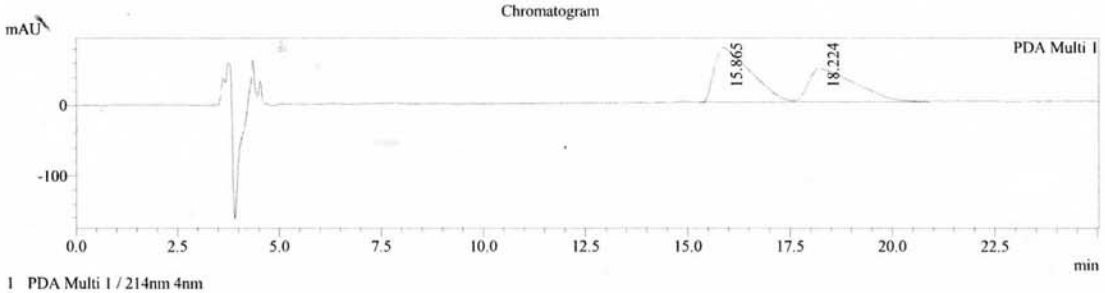
CAS: 132549-43-0

Chiral Hplc Report

Sample Information

Lot Number: HB108B+HB109B
Data File: HB108B+HB109B.lcd
Method File: 20-80-0.5-25-OJ-RH.lcm
Injection Time: 2016-9-21 12:49:21
Report Created: 2016-9-21 13:14:25
Sample Info: Column: CHIRALPAK OJ-RH (150*4.6mm 5um)
Moblie Phase: H2O:ACN:FA=80:20:0.1
Flow:0.5 ml/min
Temperature:25 C
Wavelength: 214nm
Instrument:SHIMADZU 10A
Inj. Volume: 20 ul

Chromatogram



1 PDA Multi 1 / 214nm 4nm

PeakTable

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.865	4715939	76999	56.168	61.729
2	18.224	3680256	47737	43.832	38.271
Total		8396195	124737	100.000	100.000

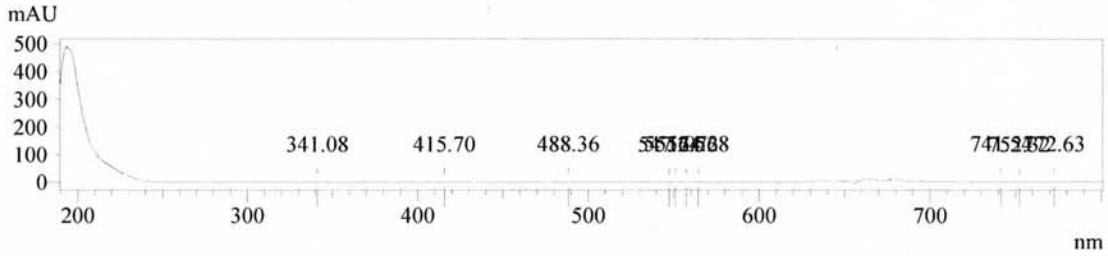
PeakTable

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Resolution	Tailing Factor
1	15.865	0.000	2.327
2	18.224	1.163	2.215
Total			

Spectrum

Peak# : 1
Retention Time : 15.865



HB109B + HB108B (R+S)
(R-) (S-)

The chiral HPLC report for (S)-3-Boc-amino-5-methyl hexanoic acid.

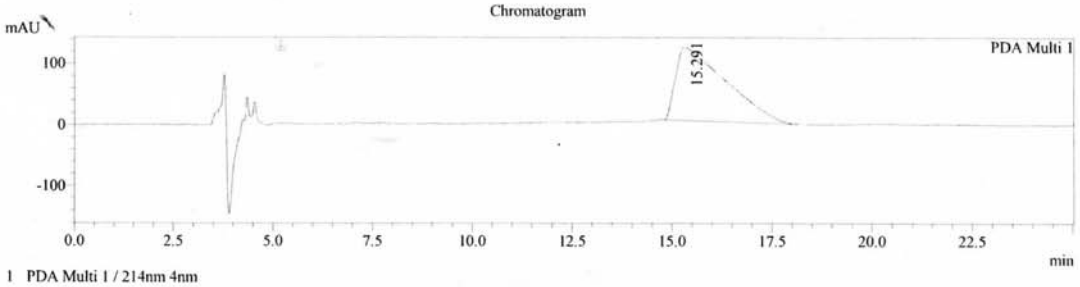
CAS: 132549-43-0

Chiral Hplc Report

Sample Information

Lot Number: HB108B
Data File: HB108B.lcd
Method File: 20-80-0.5-25-OJ-RH.lcm
Injection Time: 2016-9-21 13:15:02
Report Created: 2016-9-21 13:40:13
Sample Info: Column: CHIRALPAK OJ-RH (150*4.6mm 5um)
Moblie Phase: H2O:ACN:FA=80:20:0.1
Flow:0.5 ml/min
Temperature:25 C
Wavelength: 214nm
Instrument:SHIMADZU 10A
Inj. Volume: 20 ul

Chromatogram



1 PDA Multi 1 / 214nm 4nm

PeakTable

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.291	10358966	118676	100.000	100.000
Total		10358966	118676	100.000	100.000

PeakTable

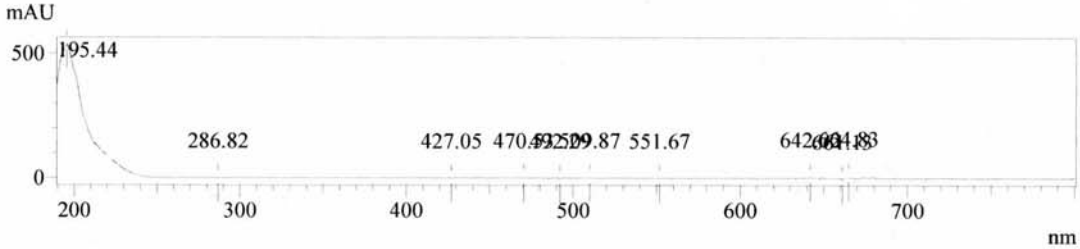
PDA Ch1 214nm 4nm

Peak#	Ret. Time	Resolution	Separation	Tailing Factor
1	15.291	0.000	0.000	3.356
Total				

eoretical Plates/me
3378.736

Spectrum

Peak# : 1
Retention Time : 15.291



Peak# : 2
Retention Time : 18.224