Supplementary Information

Synthesis and Biological Evaluation of Lipophilic Nucleoside Analogues as Inhibitors of Aminoacyl-tRNA Synthetases

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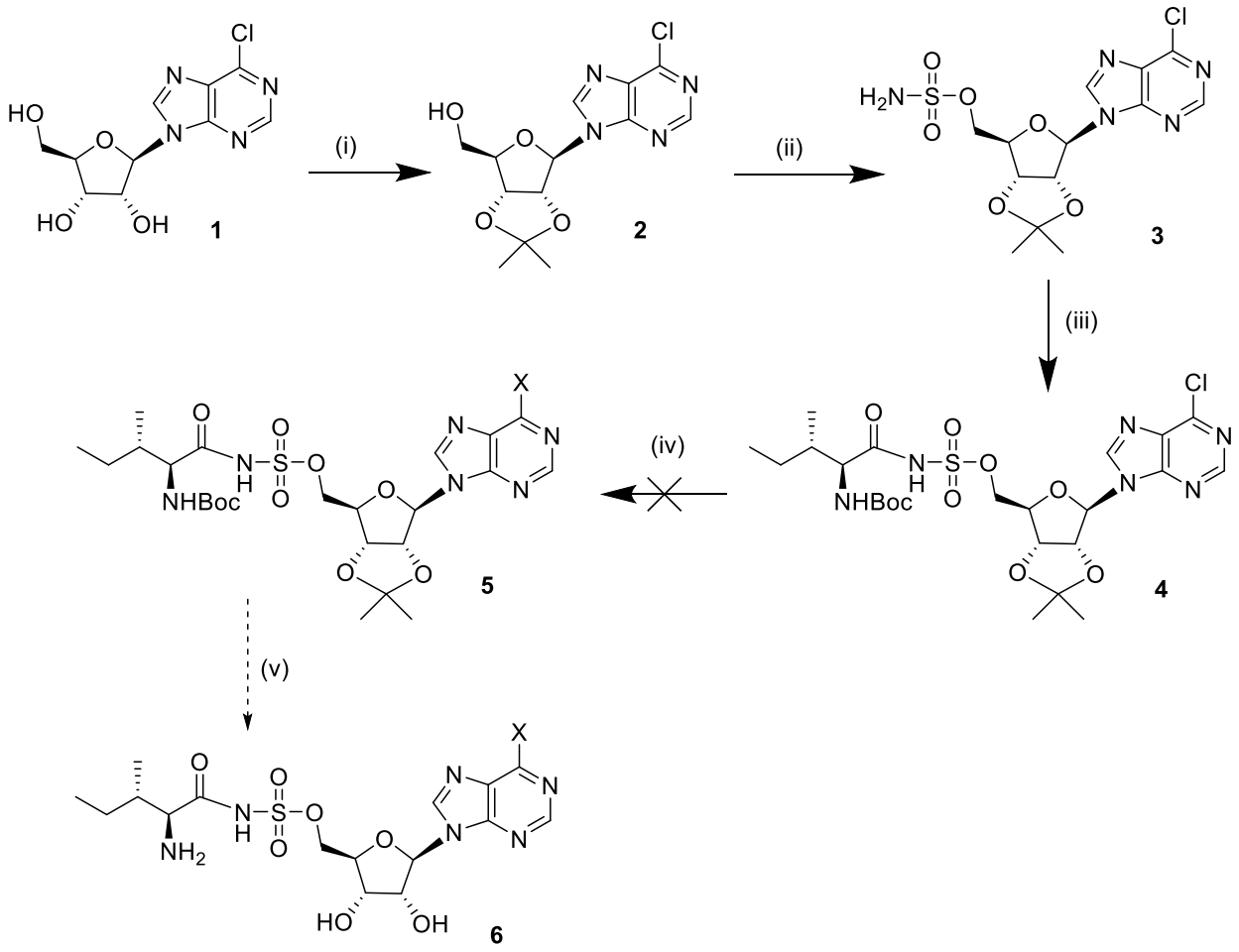
Contents

Supplementary reaction scheme S1.

Following **reaction scheme 1**, the plan was to make a general scaffold (**5**) where various substitutions could be introduced using **reaction (iv)**. This reaction scheme proved to be useful for the introduction of N-substituted aliphatic sidechains, albeit with low yields due to degradation of the scaffold (due to the cumulative negative effect of base and high temperature). Unfortunately,

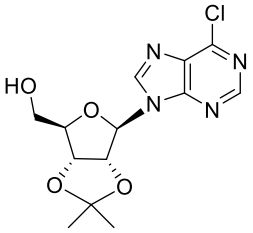
nucleophilic substitution did not work out for the less nucleophilic anilines. Different base catalysts substituting for potassium carbonate like DIPEA and DMAP were also tried combined with heating but to no avail.

Initially proposed plan for the synthesis of alkylated compounds: -



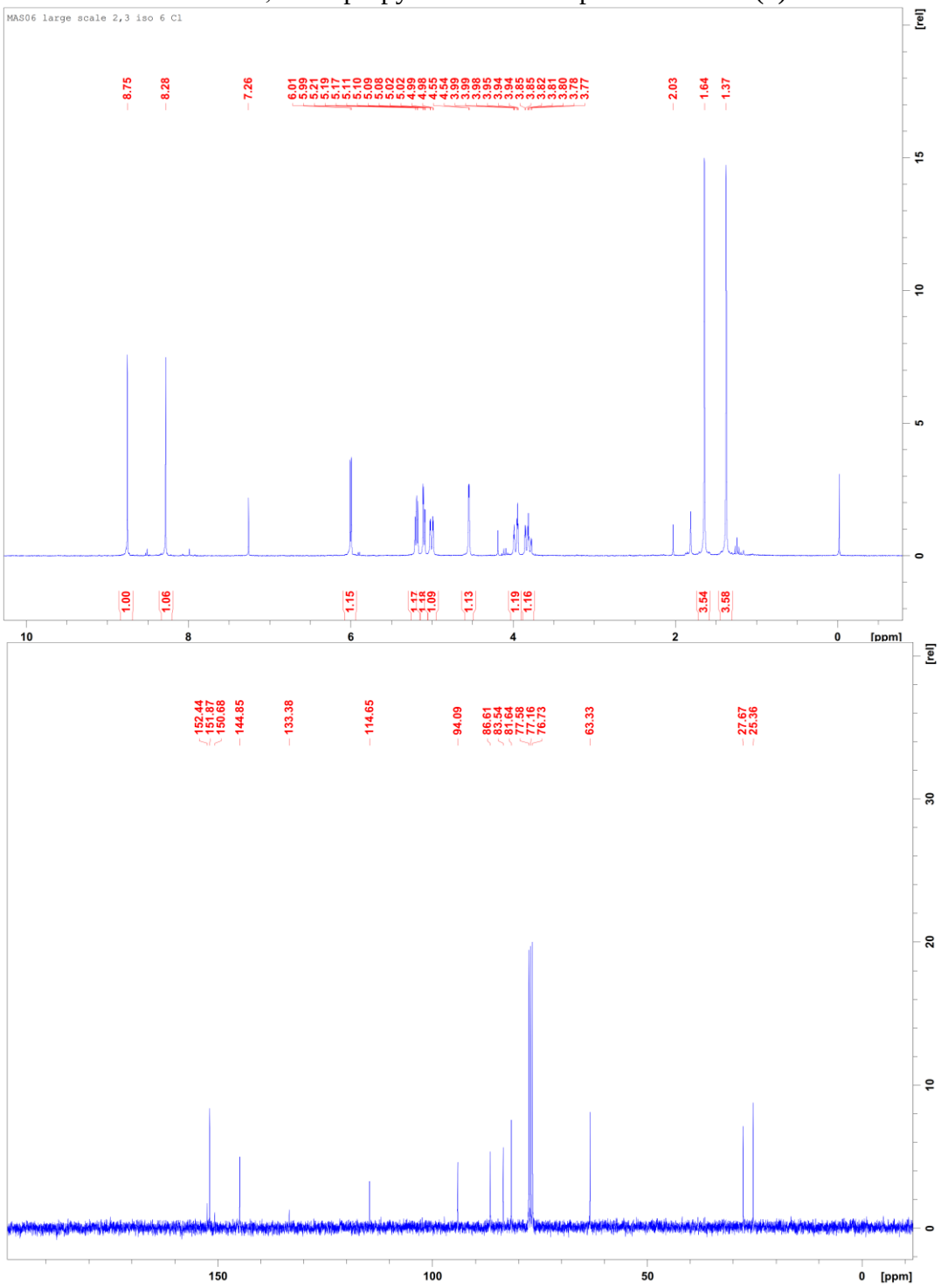
Supplementary reaction scheme S1. **Reagents and conditions:** (i) Acetone, DMP, PTSA, RT, overnight, rt; (ii) (a) CSI, HCOOH, 0 °C, 15 min; (b) ACN, 4-6h, rt; (c) DMA, overnight, rt; (iii) DBU, Boc-Ile-Osu, DMF, overnight, rt; (iv) K_2CO_3, R-NH_2, DMF, 80 °C, overnight; (v) TFA/H_2O (1:1 v/v), 3 hours, RT.

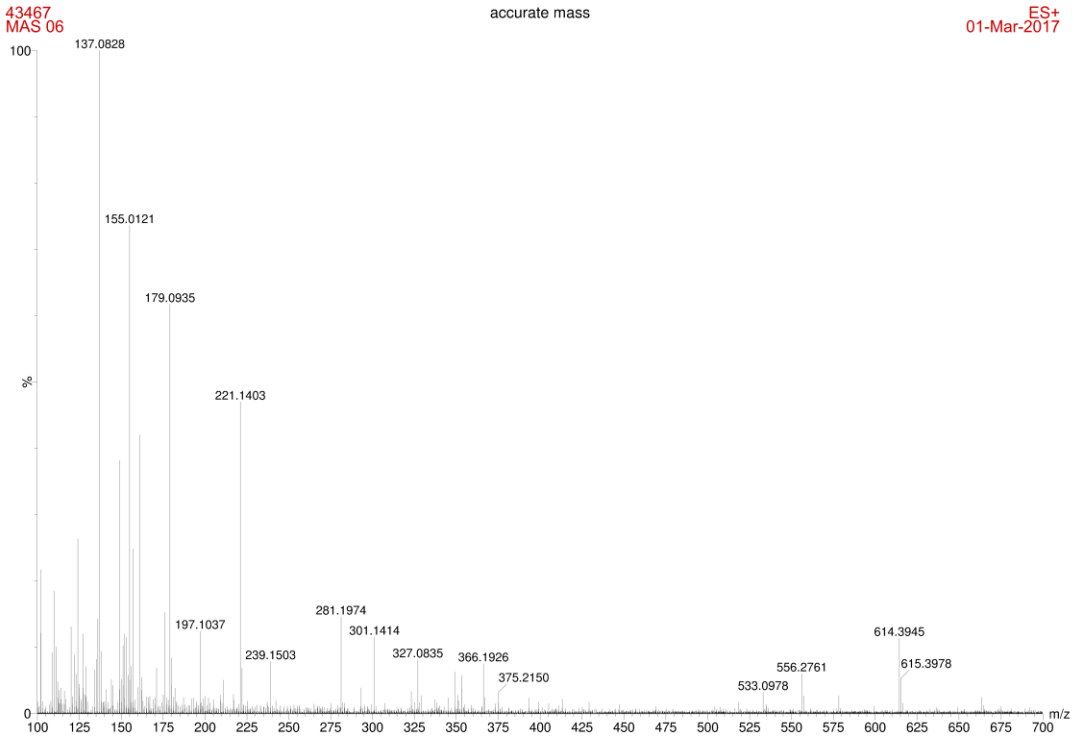
C6 purine derivatives - intermediate & final compounds - NMR & MS

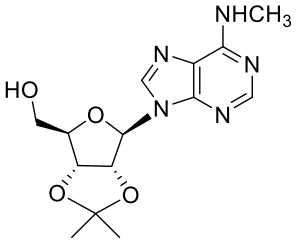


Exact Mass: 326.0782

2, 3’-isopropylidene 6-chloropurine riboside (2)







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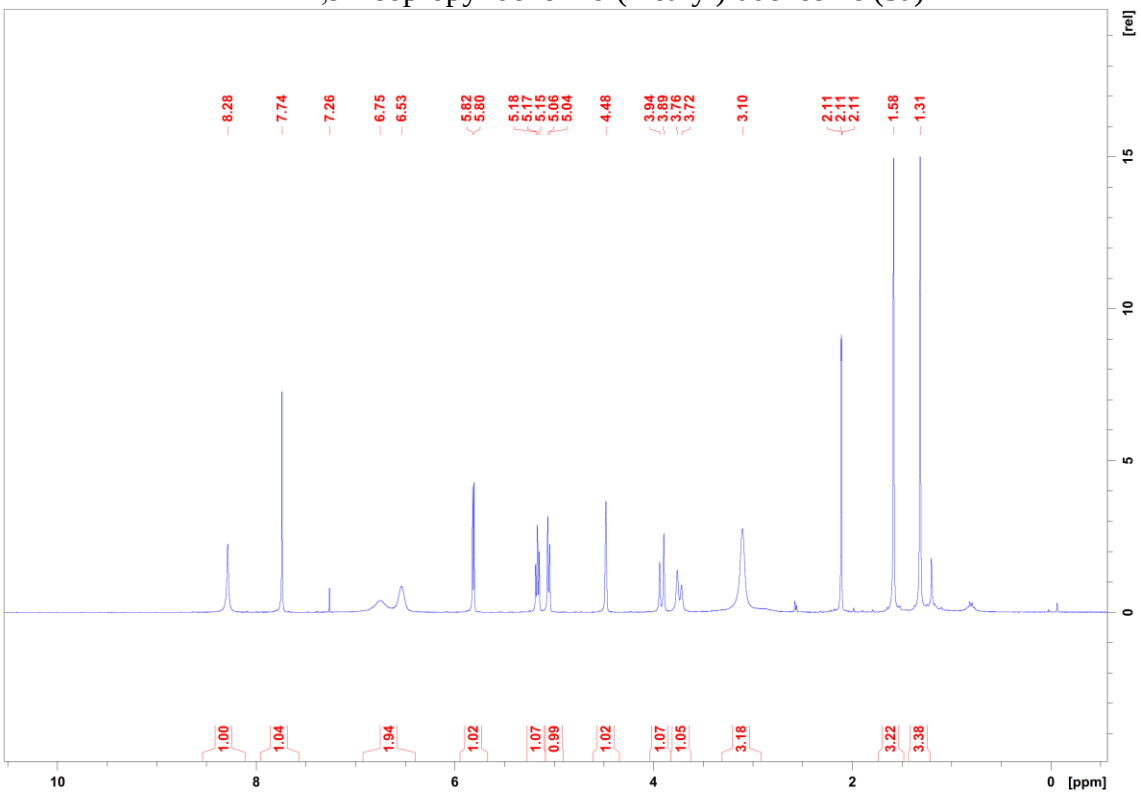

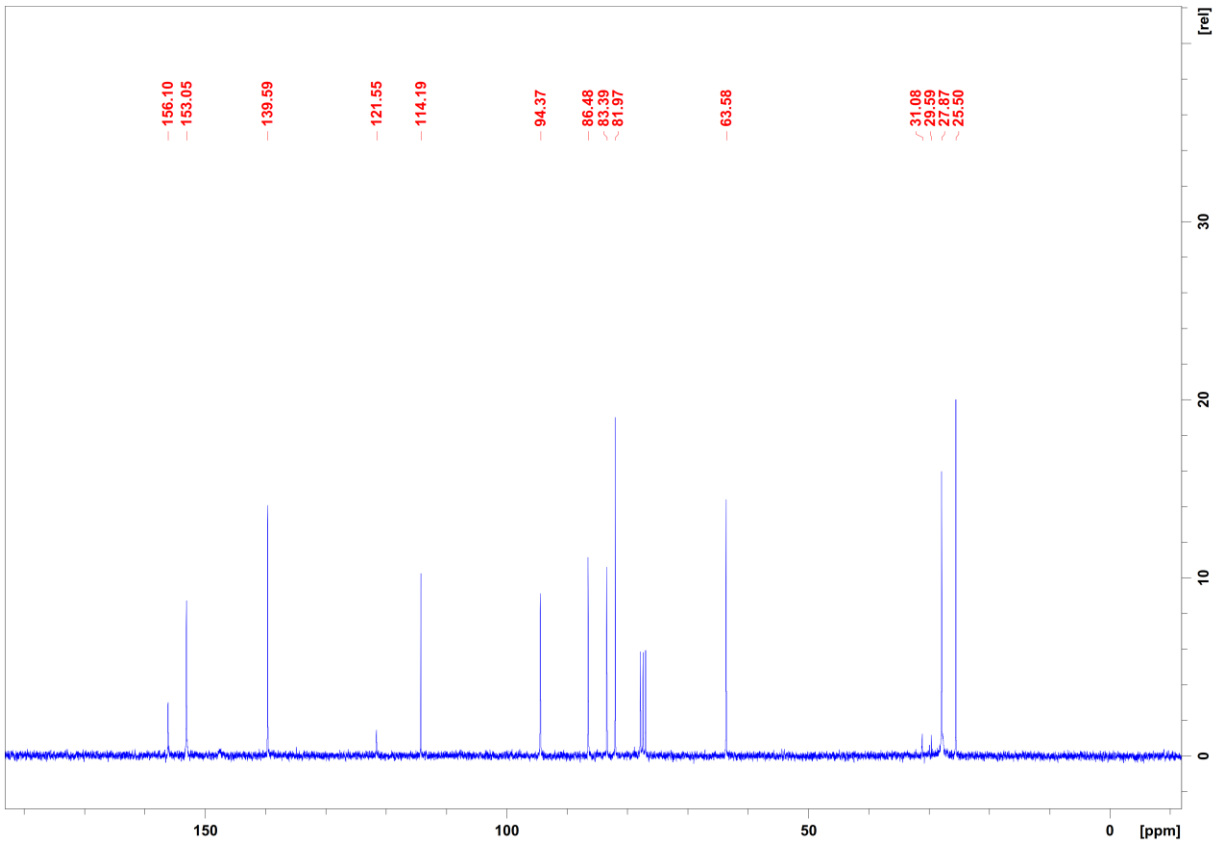
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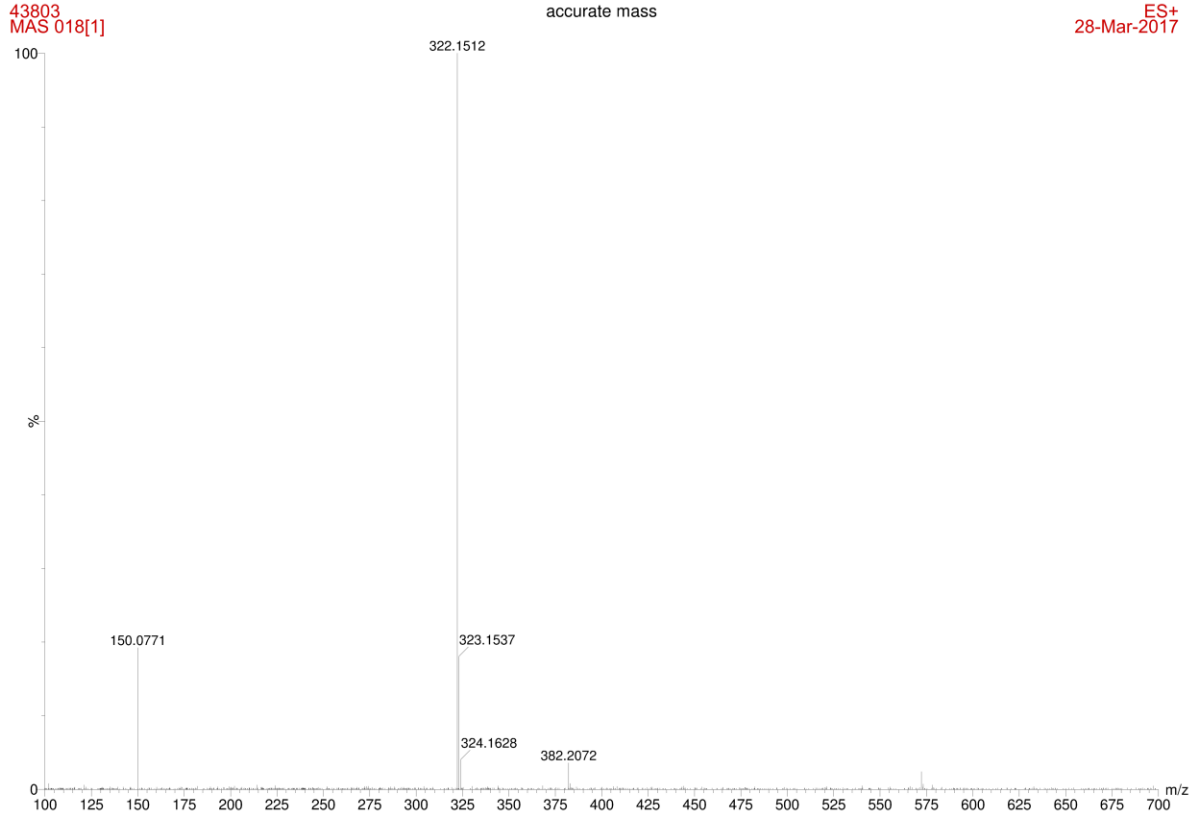
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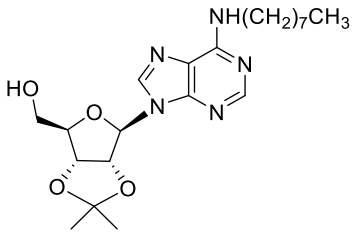

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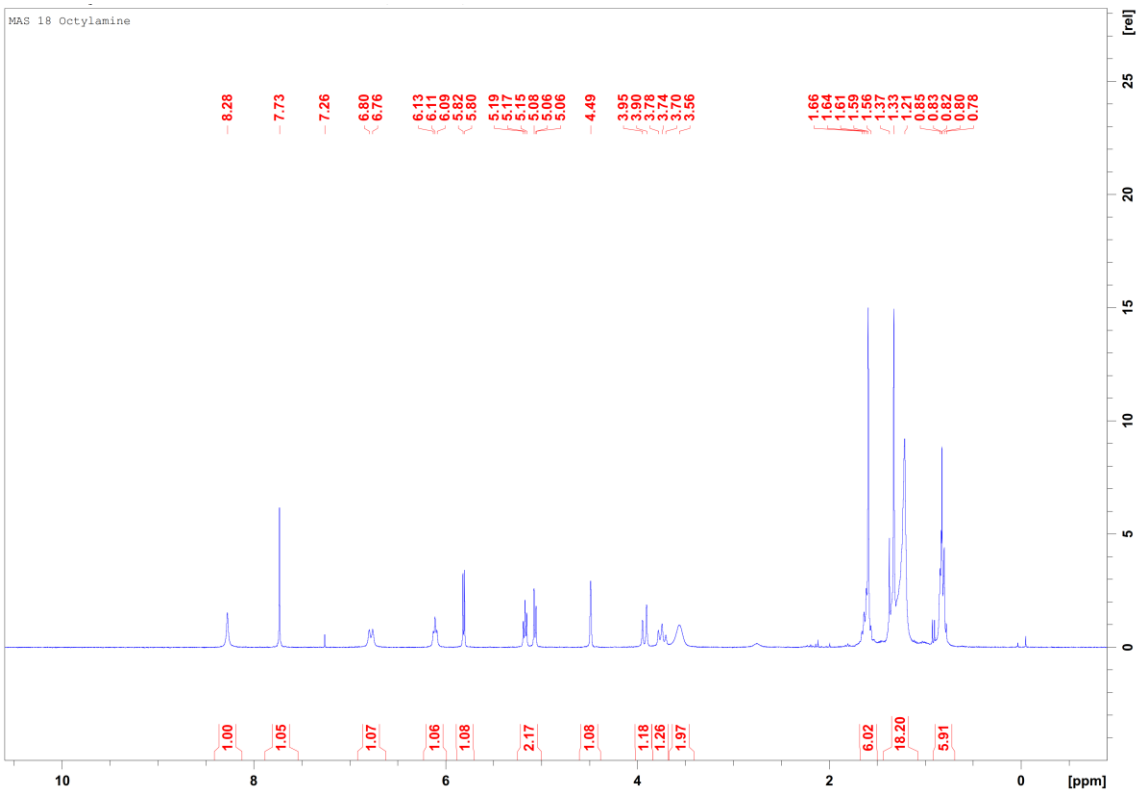

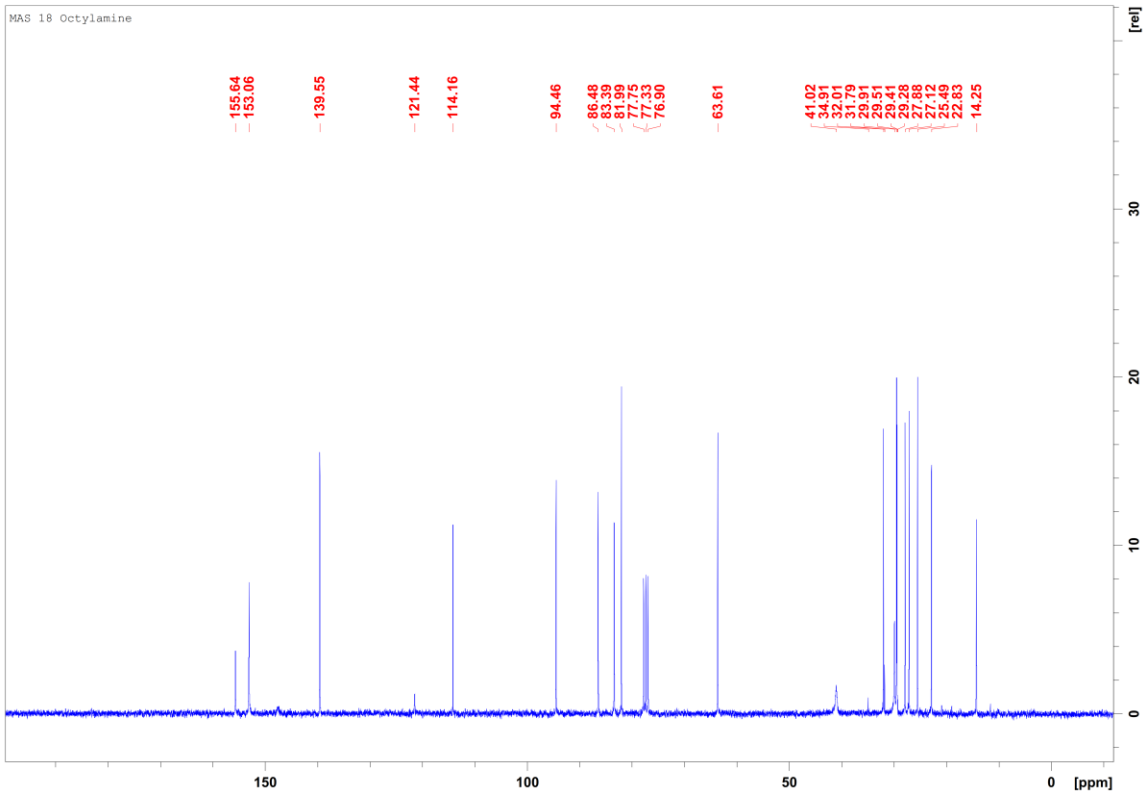

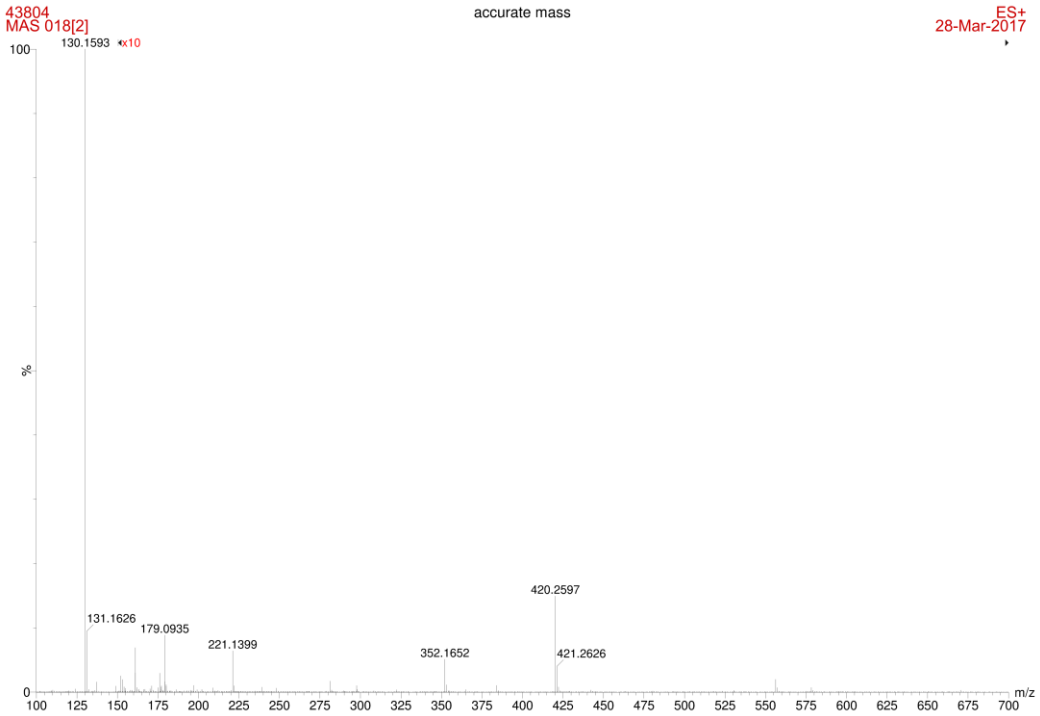

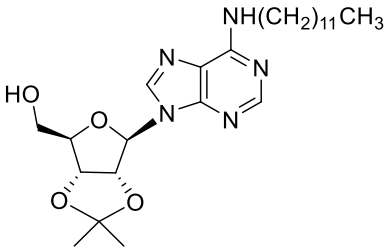

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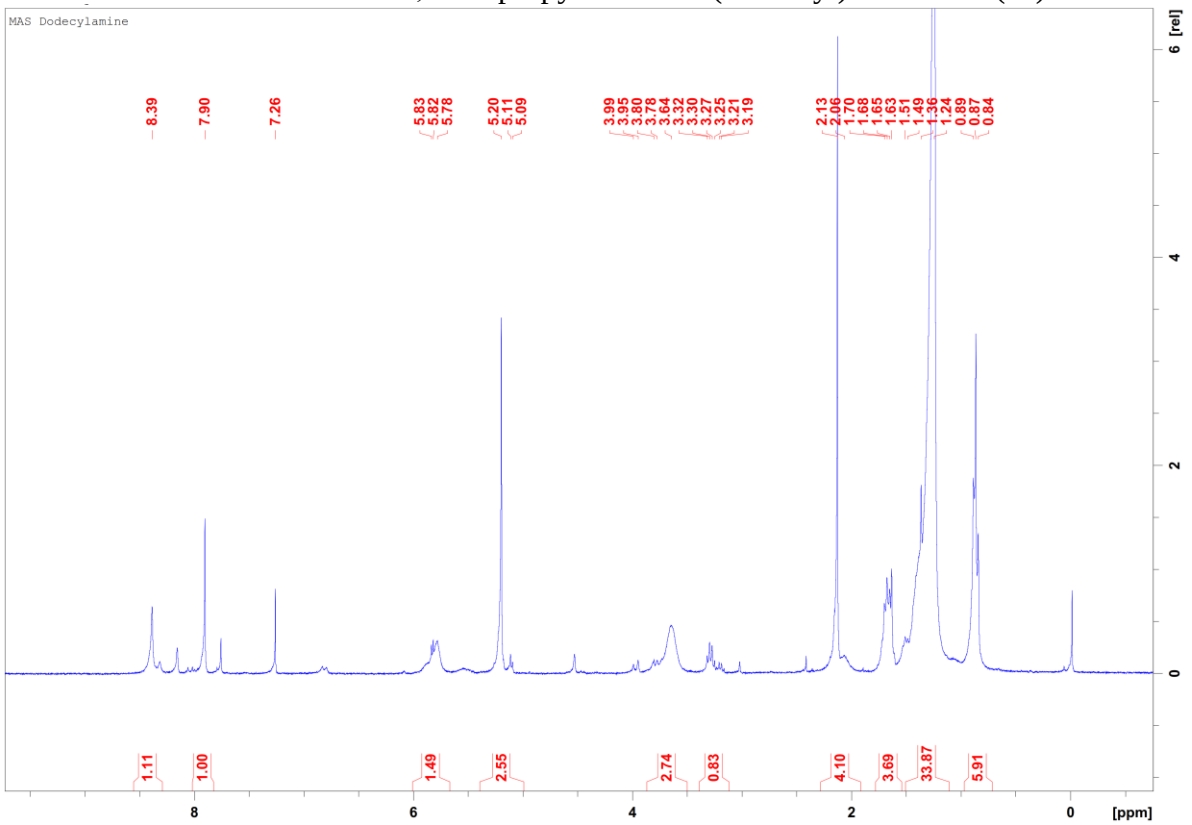

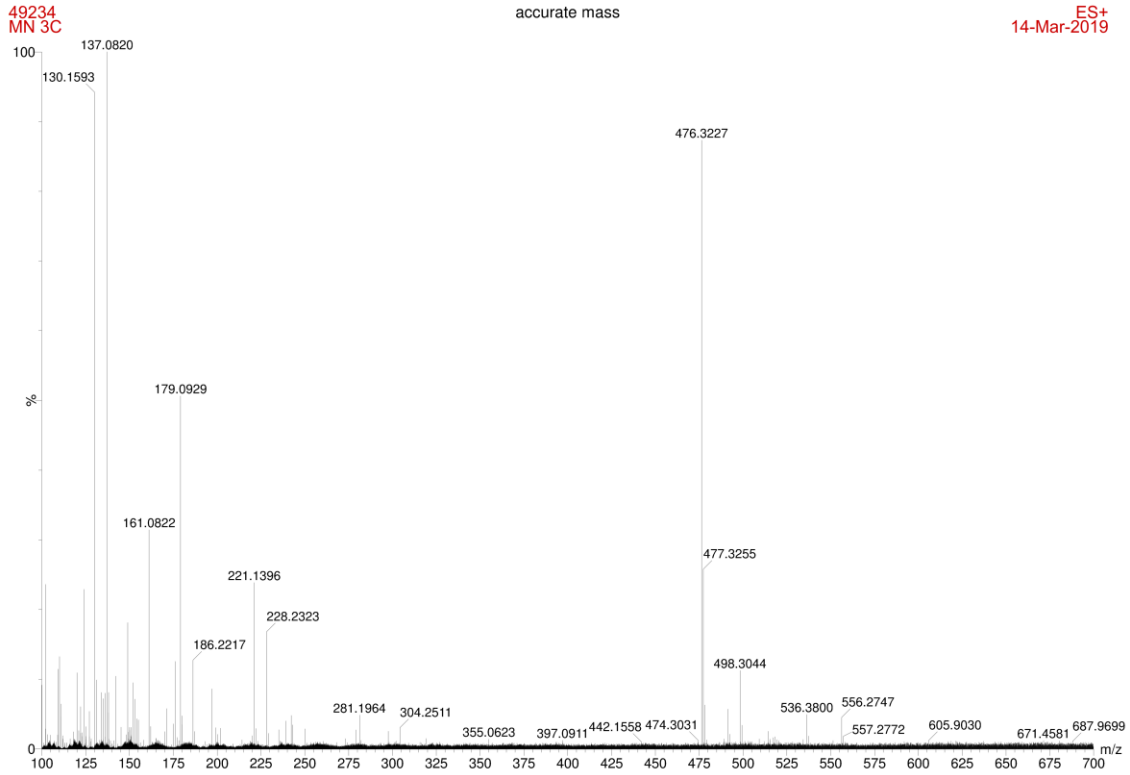

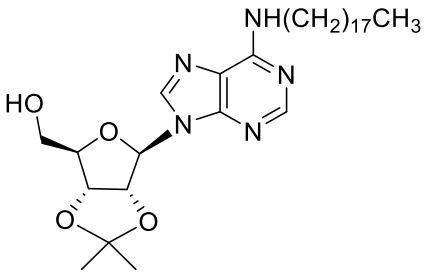

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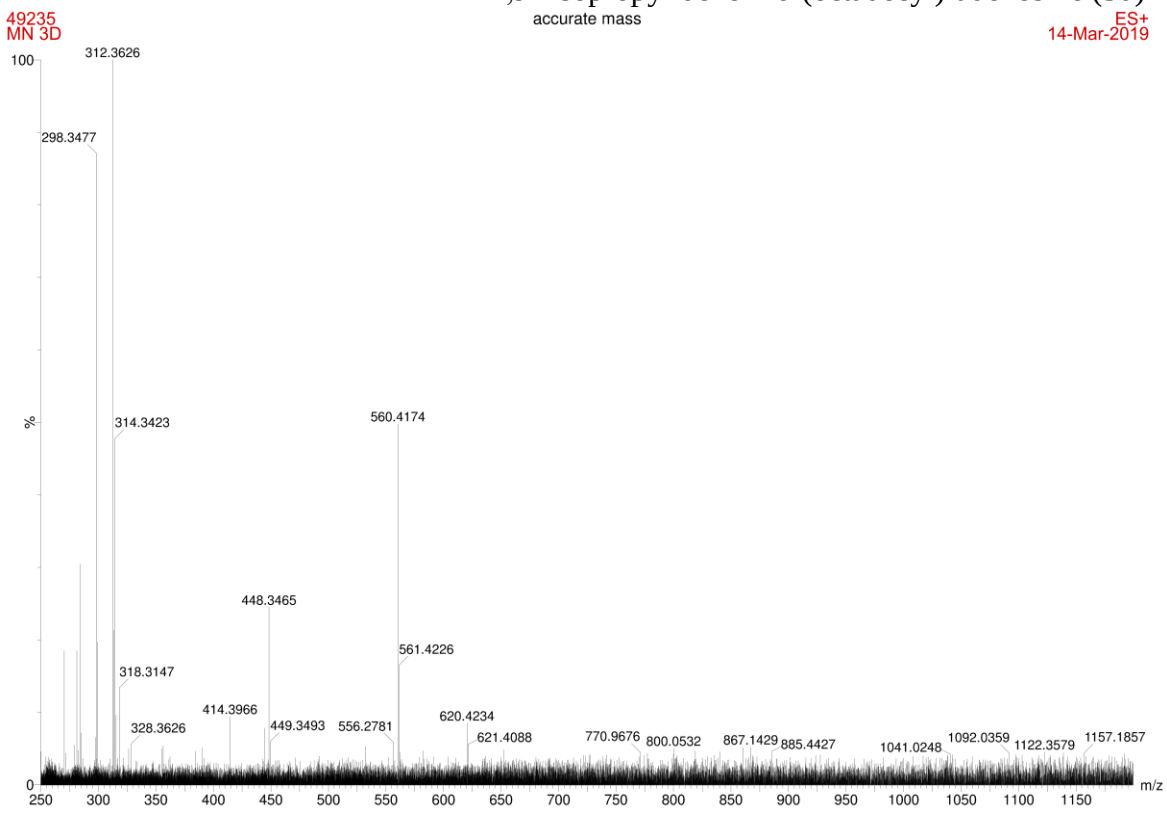

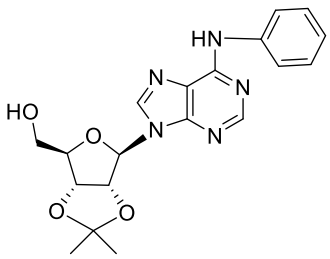

Exact Mass: 383.1594

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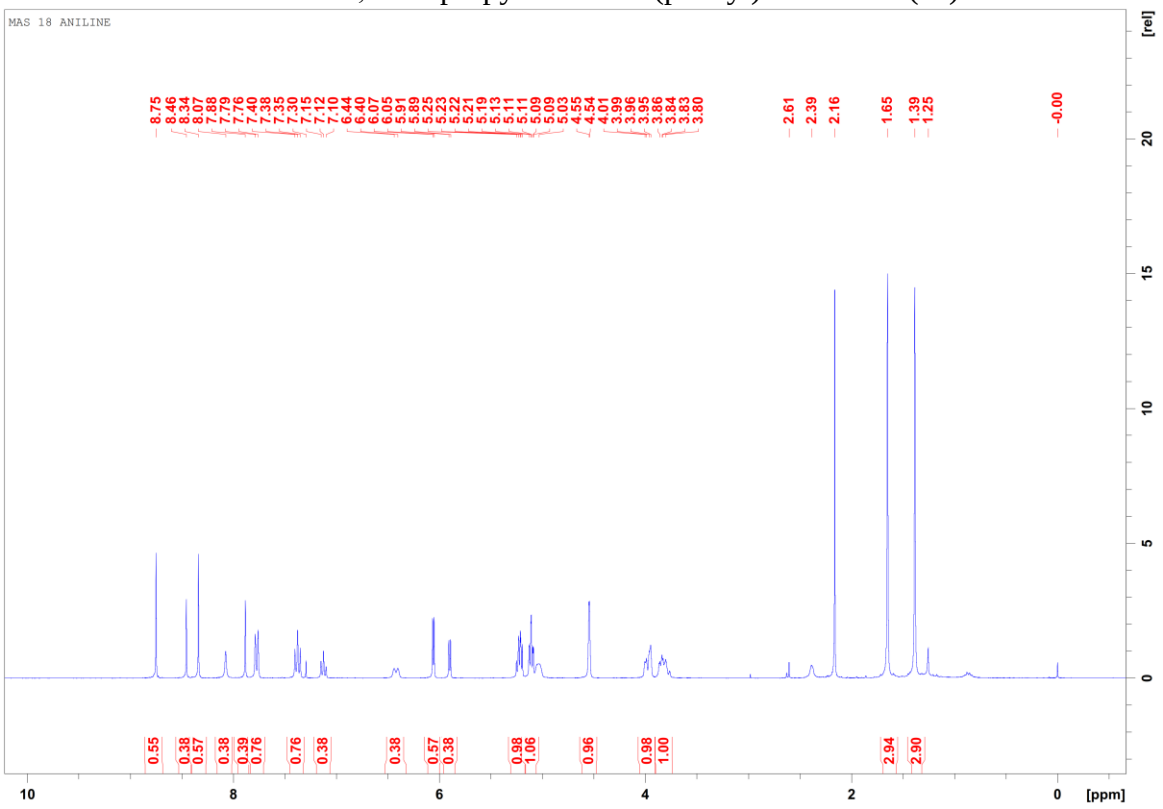

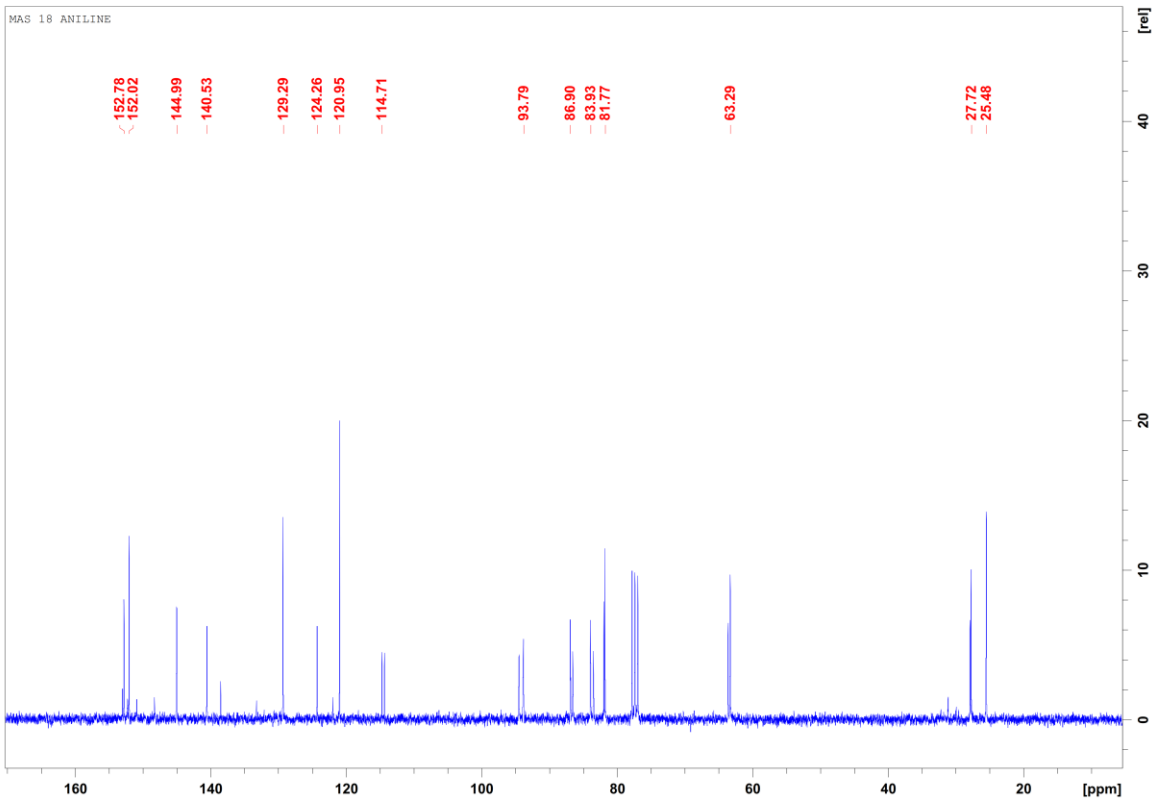

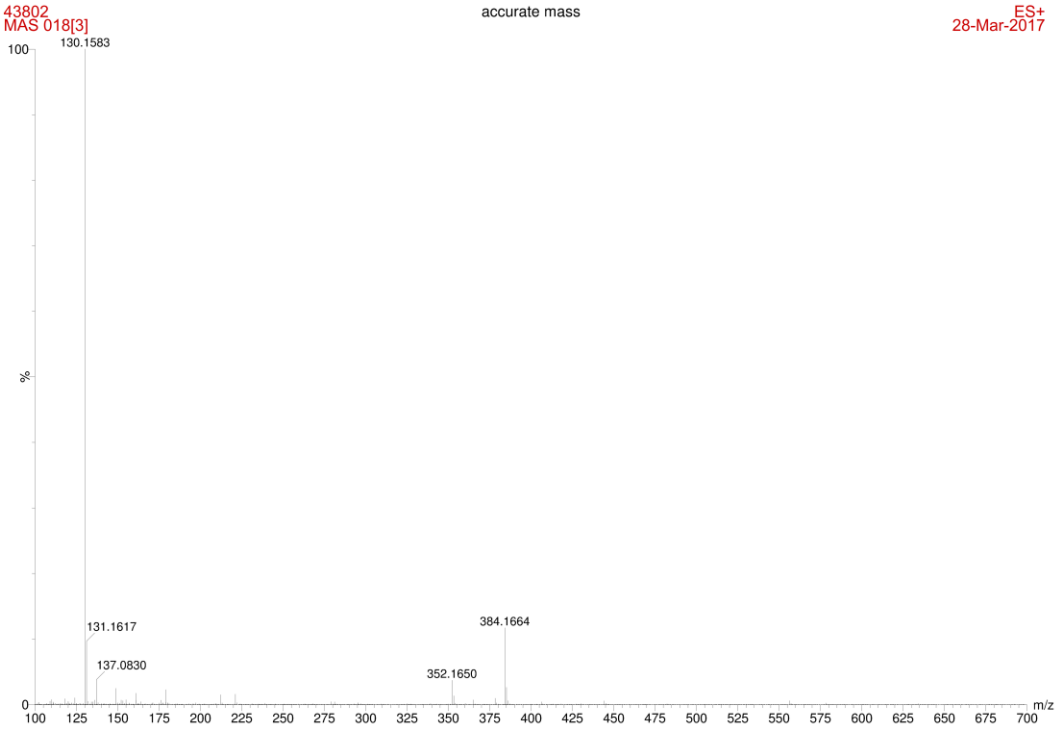

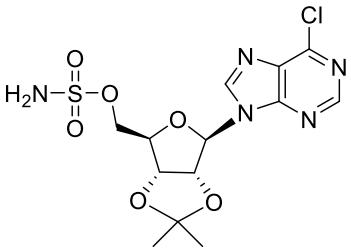

Exact Mass: 405.0510

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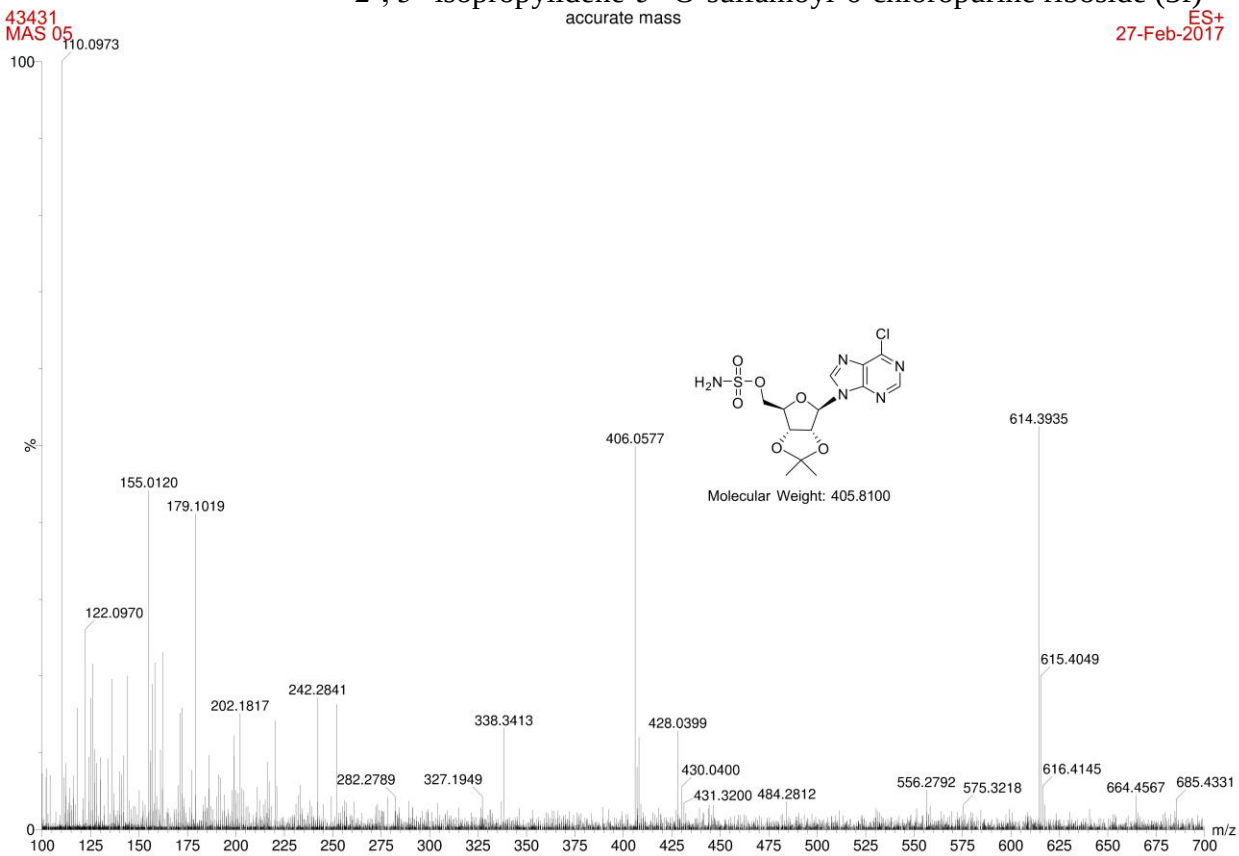

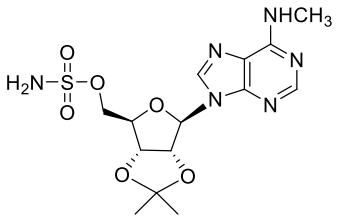

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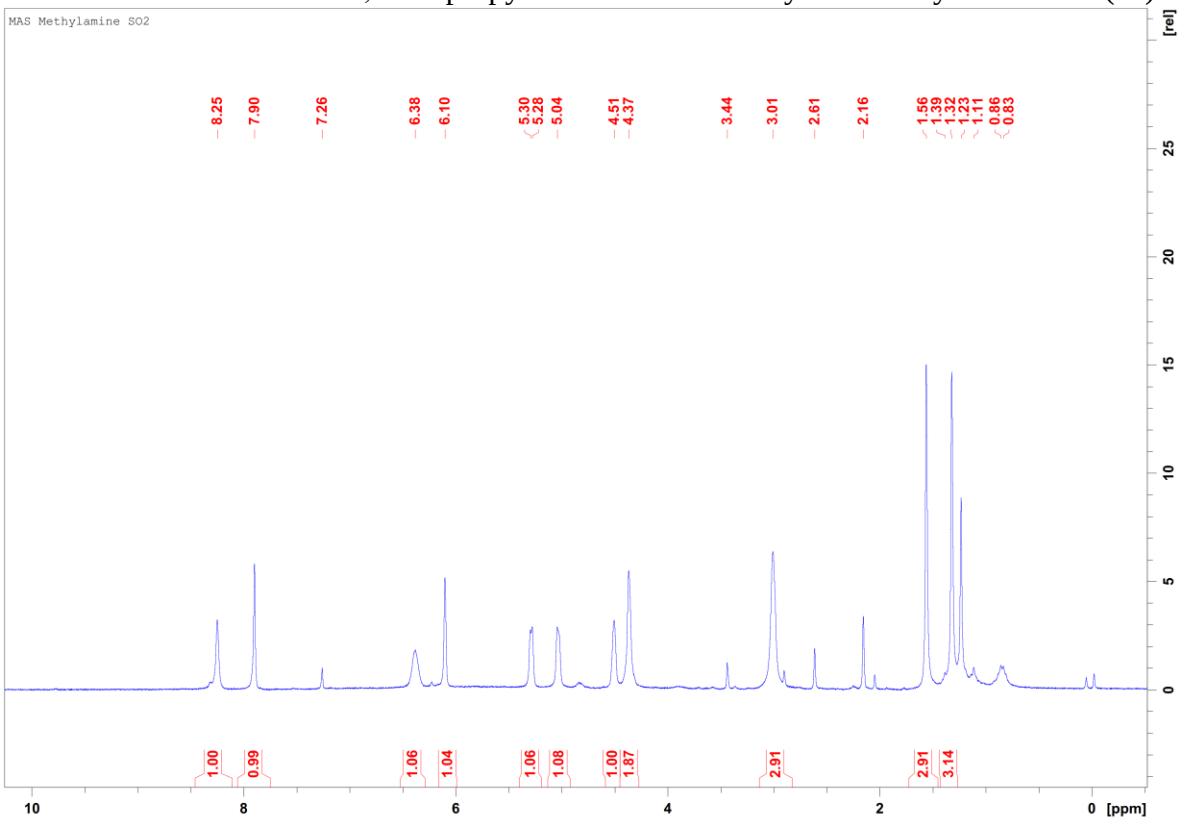

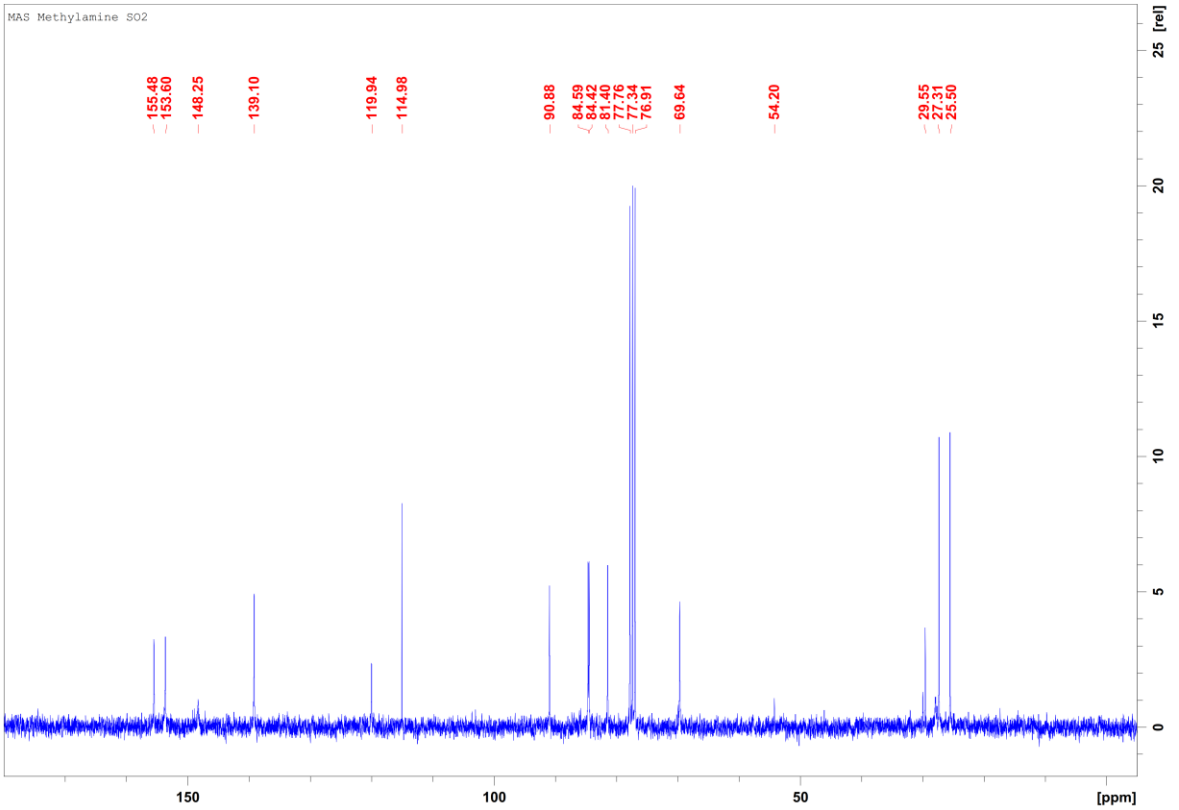

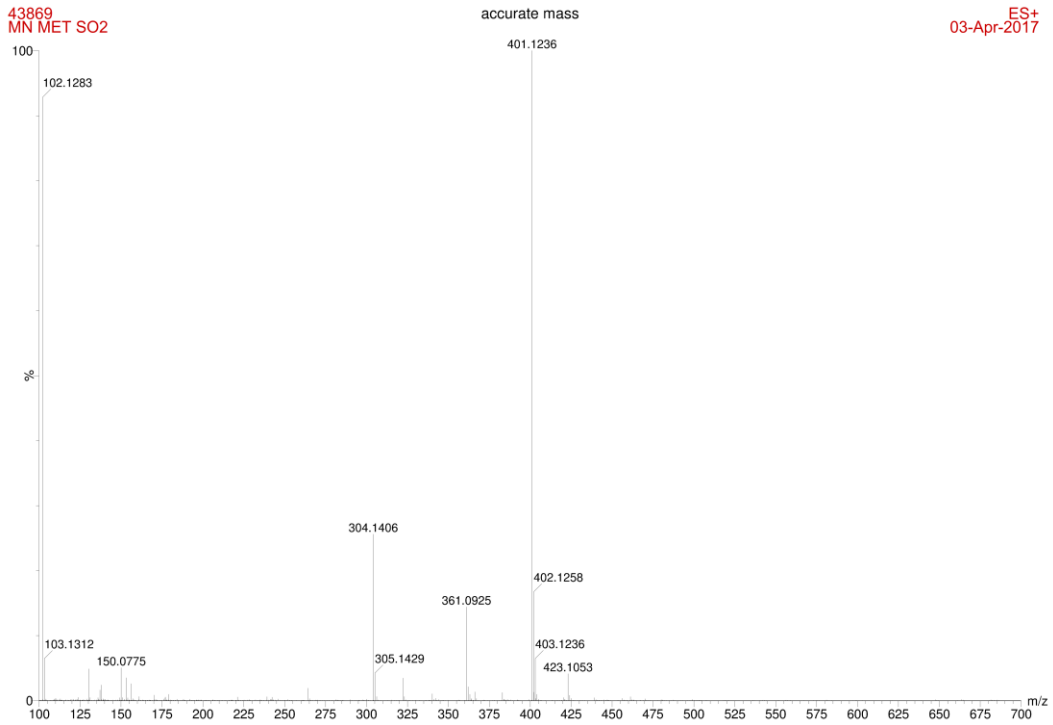

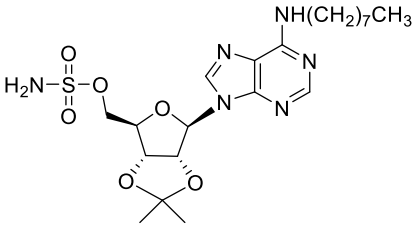

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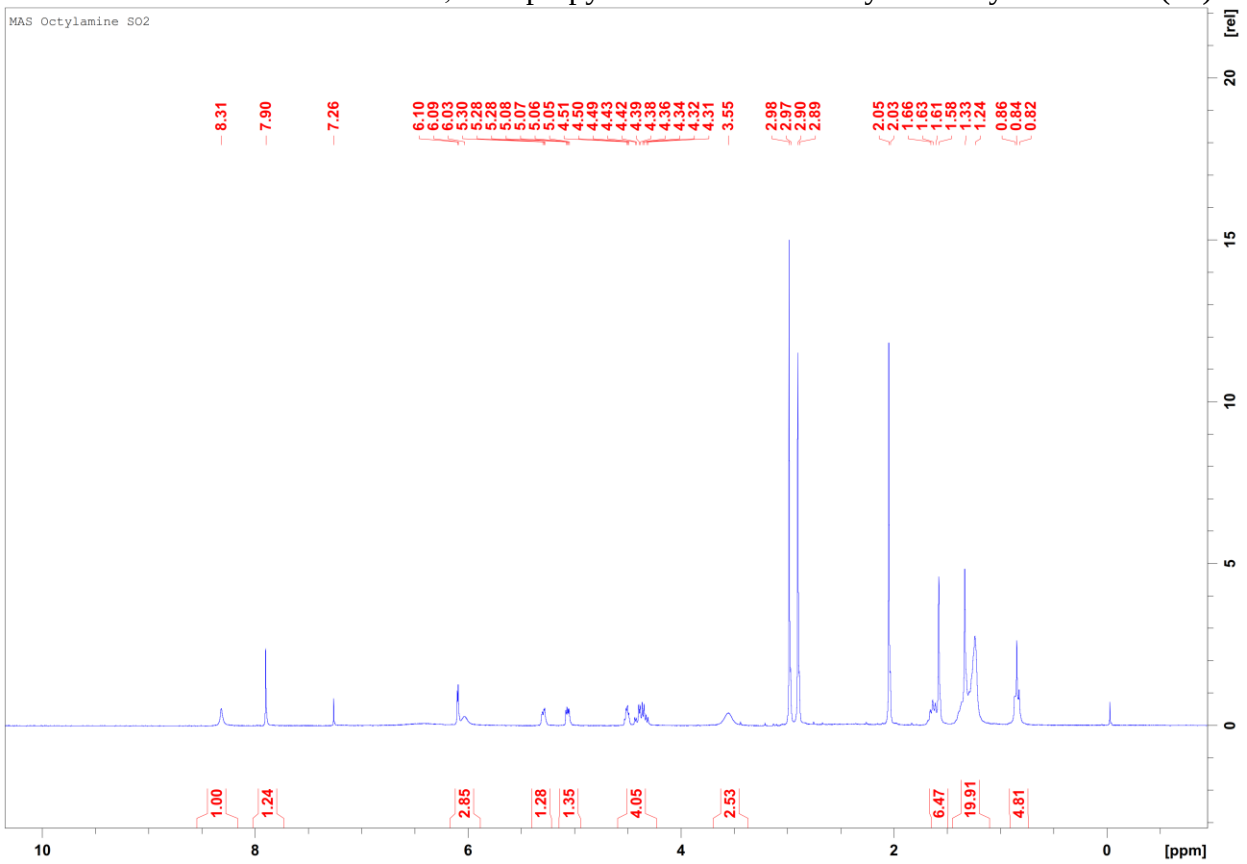

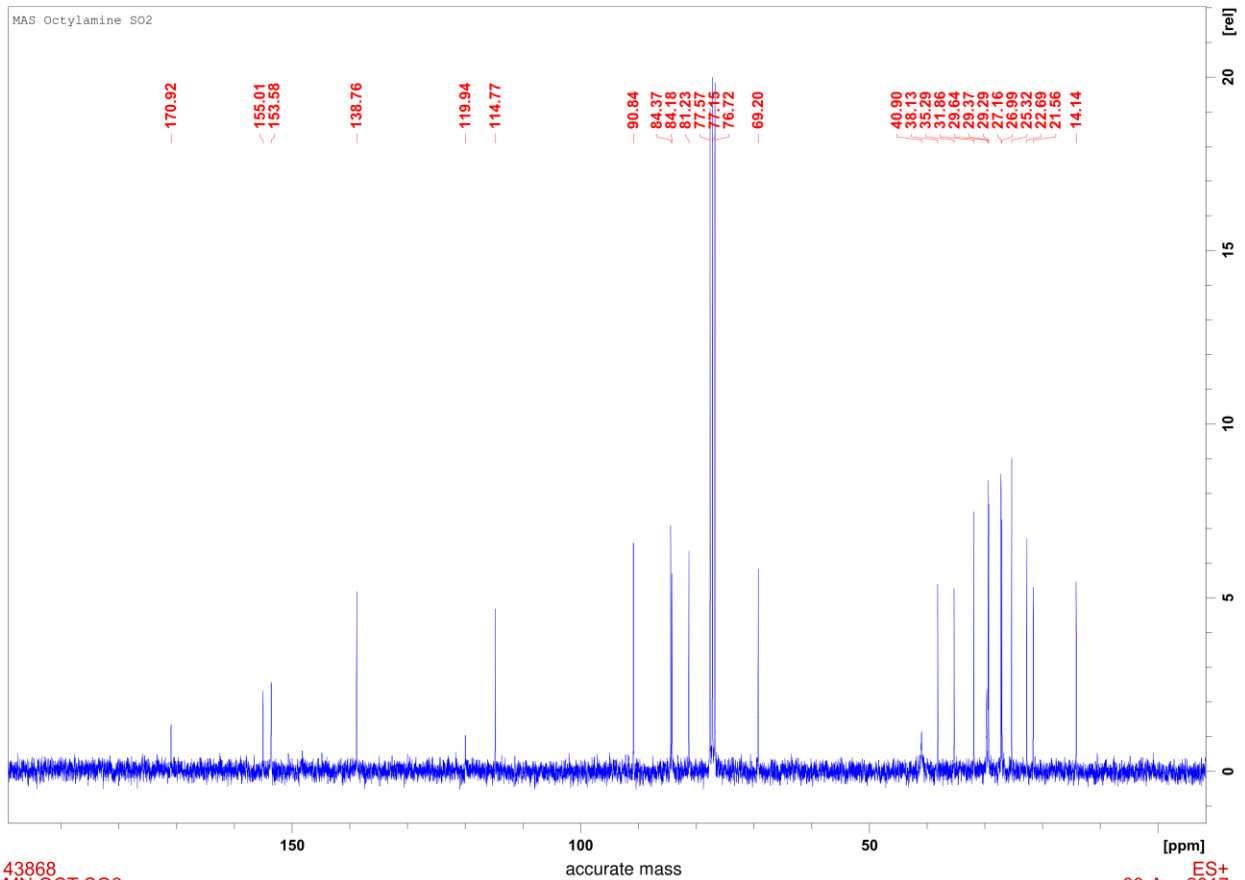
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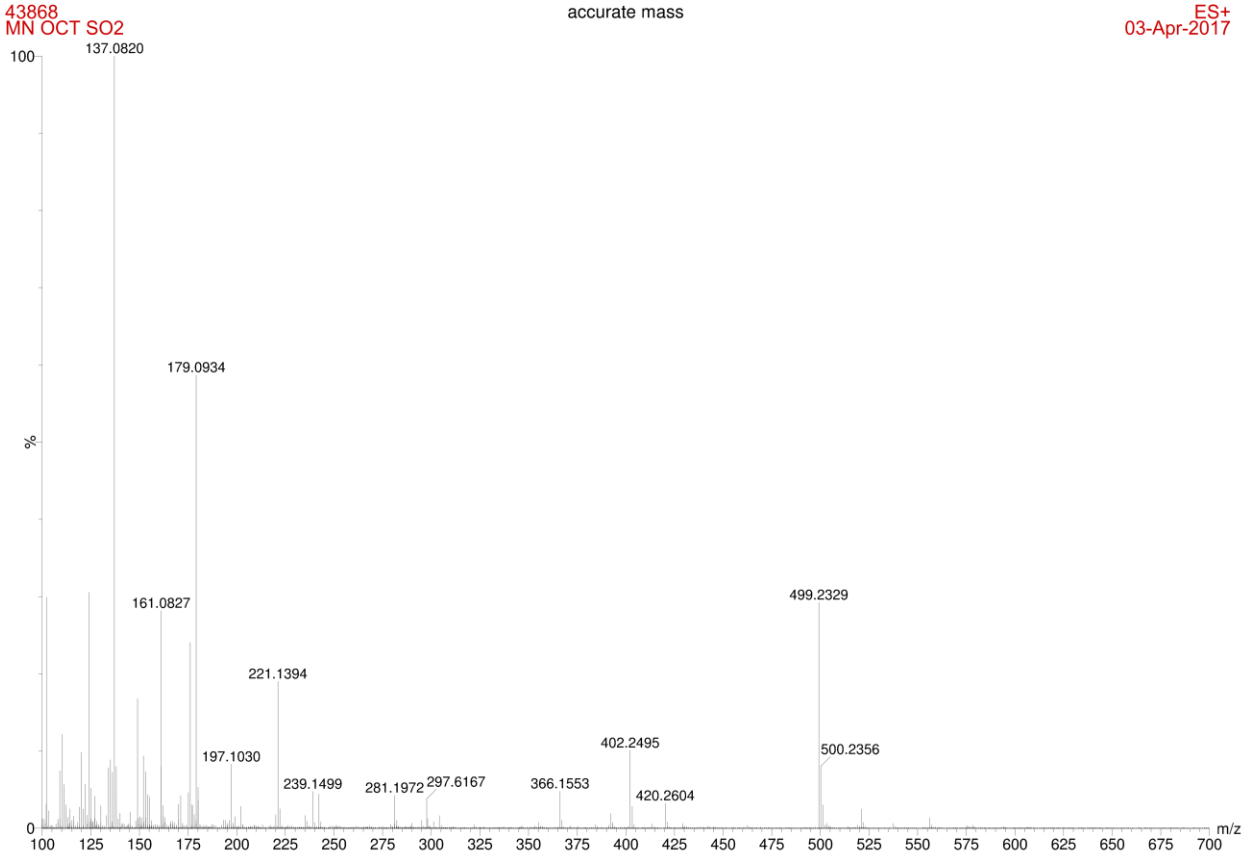
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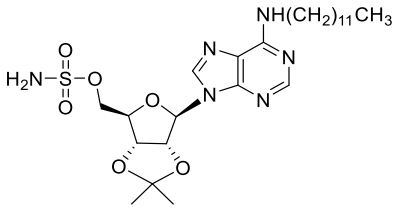

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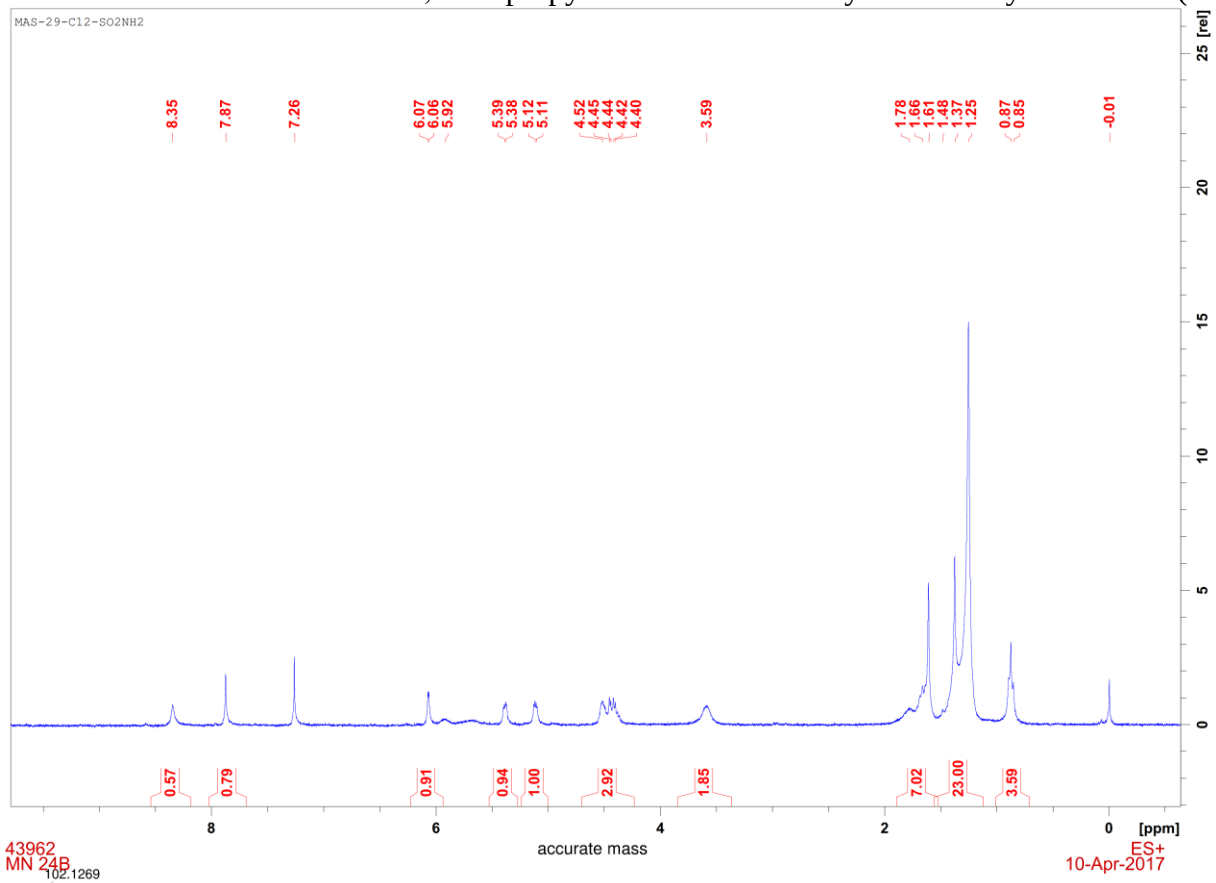

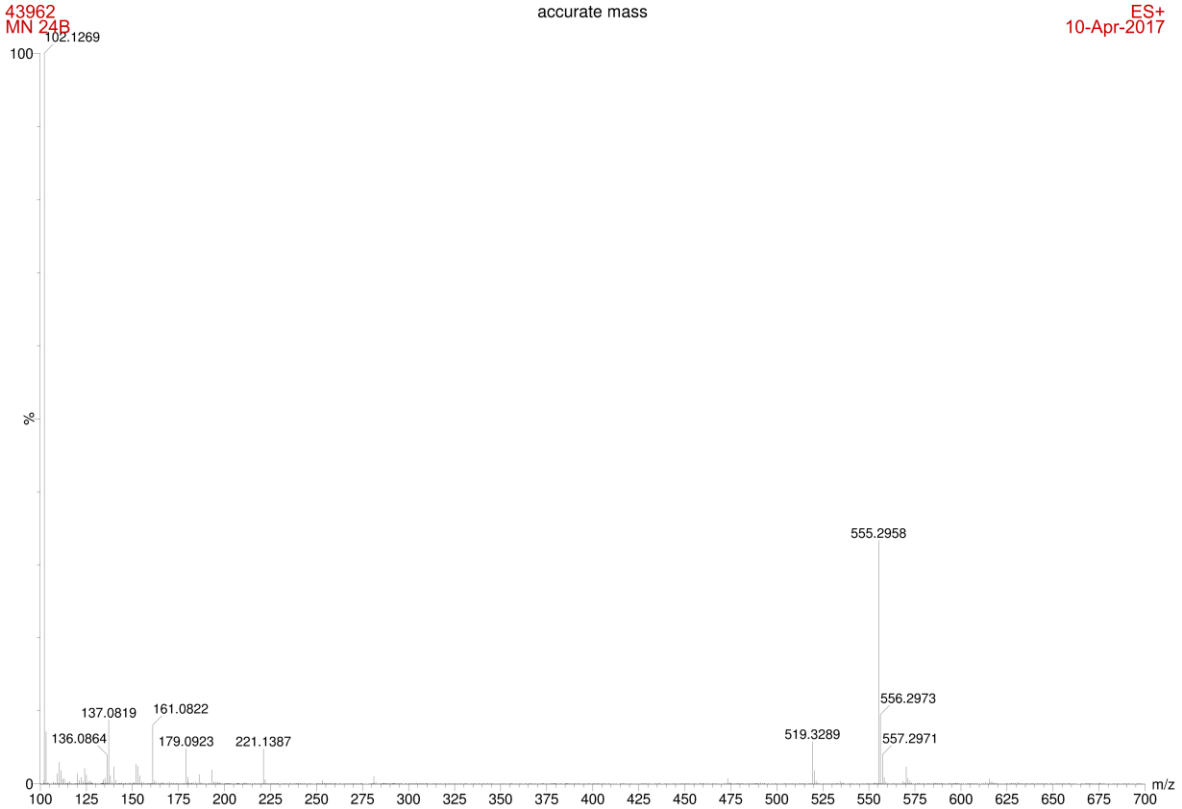

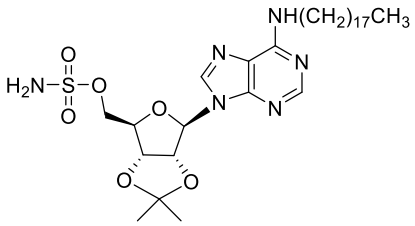

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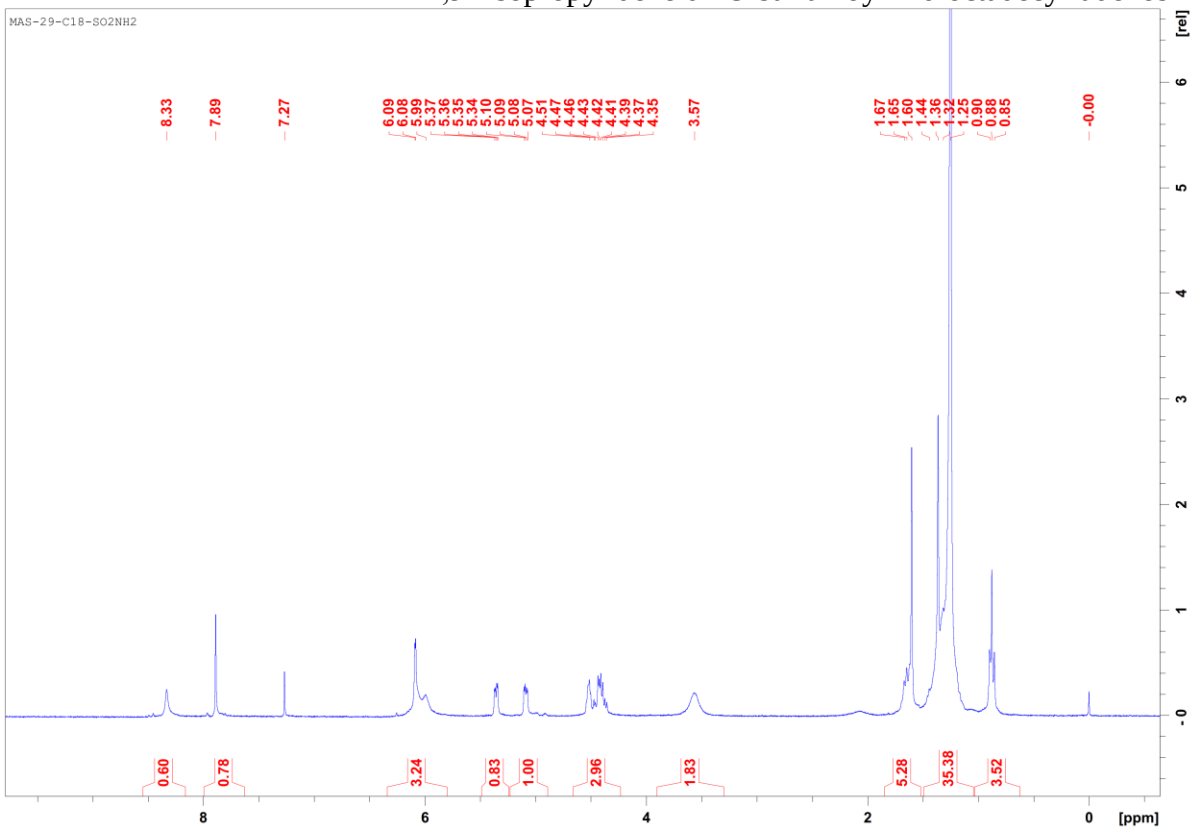

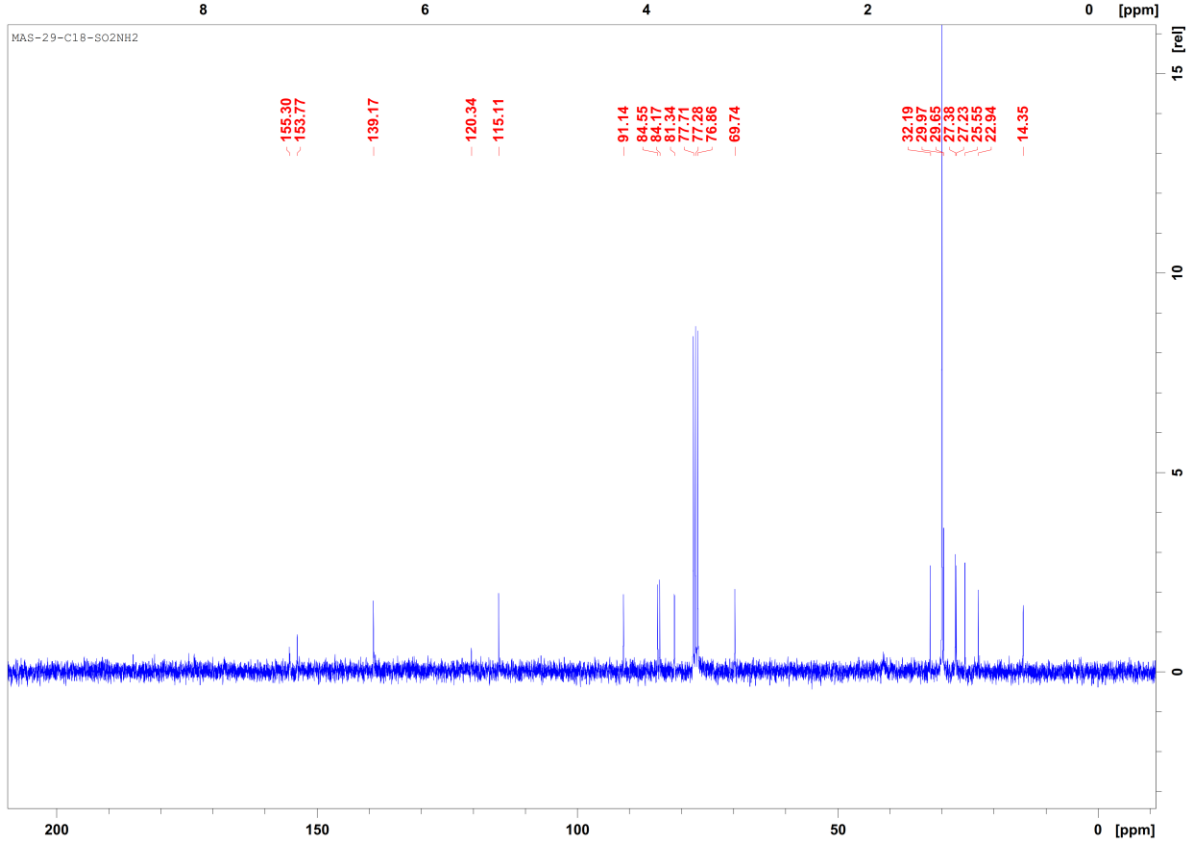

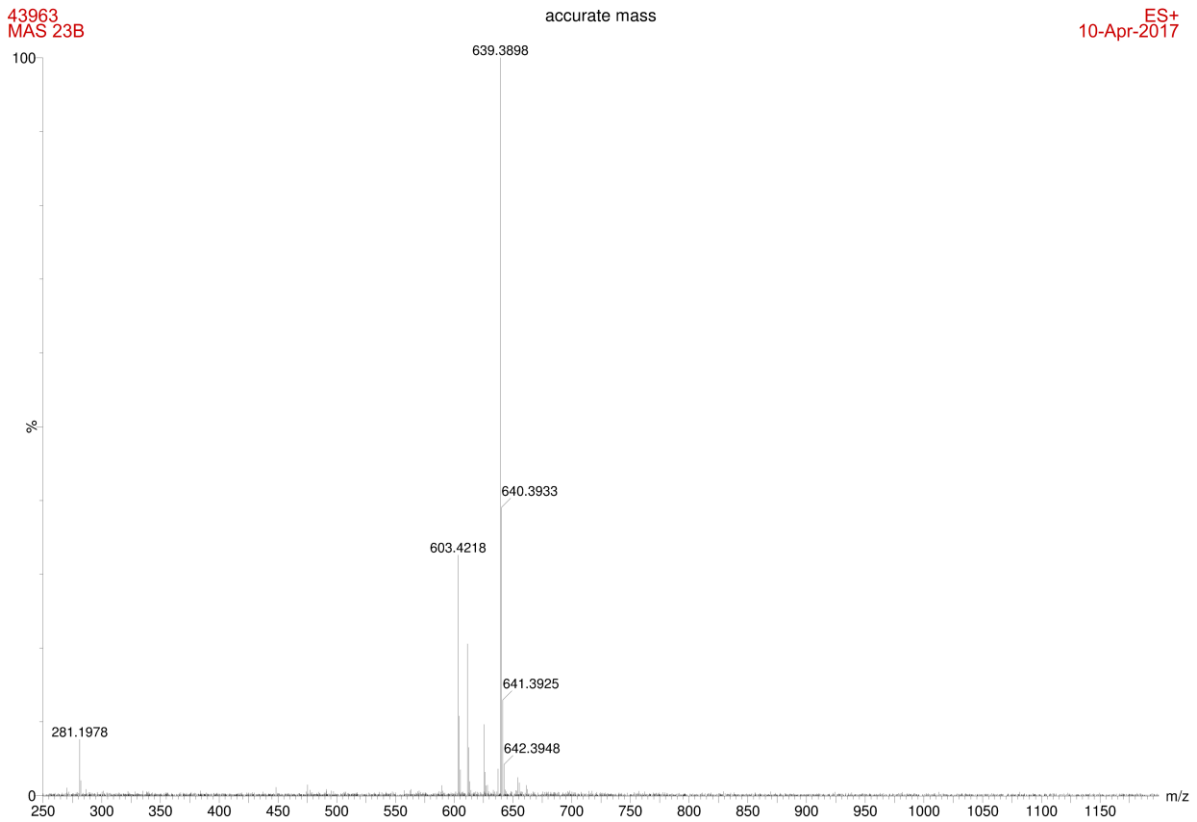

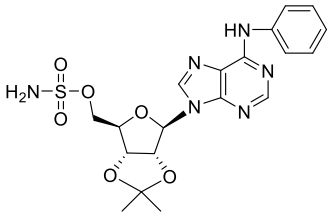

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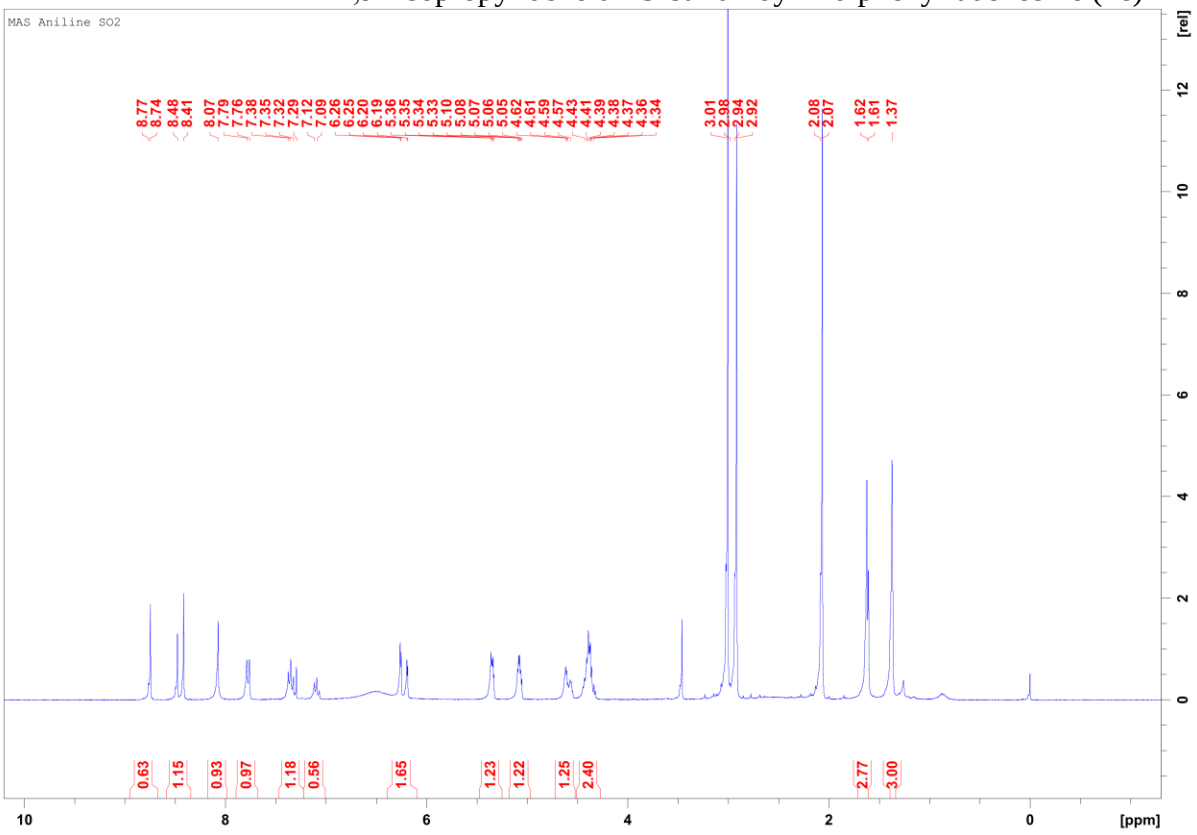

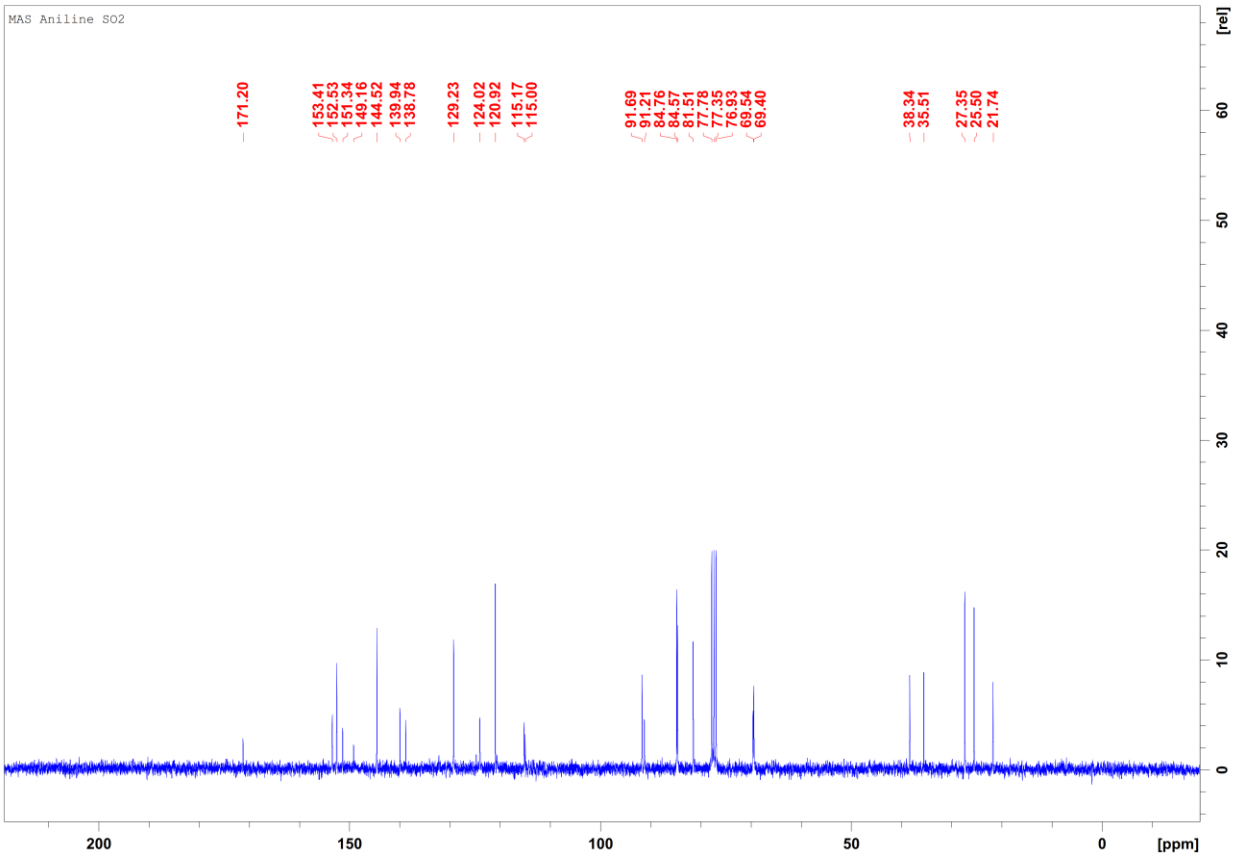
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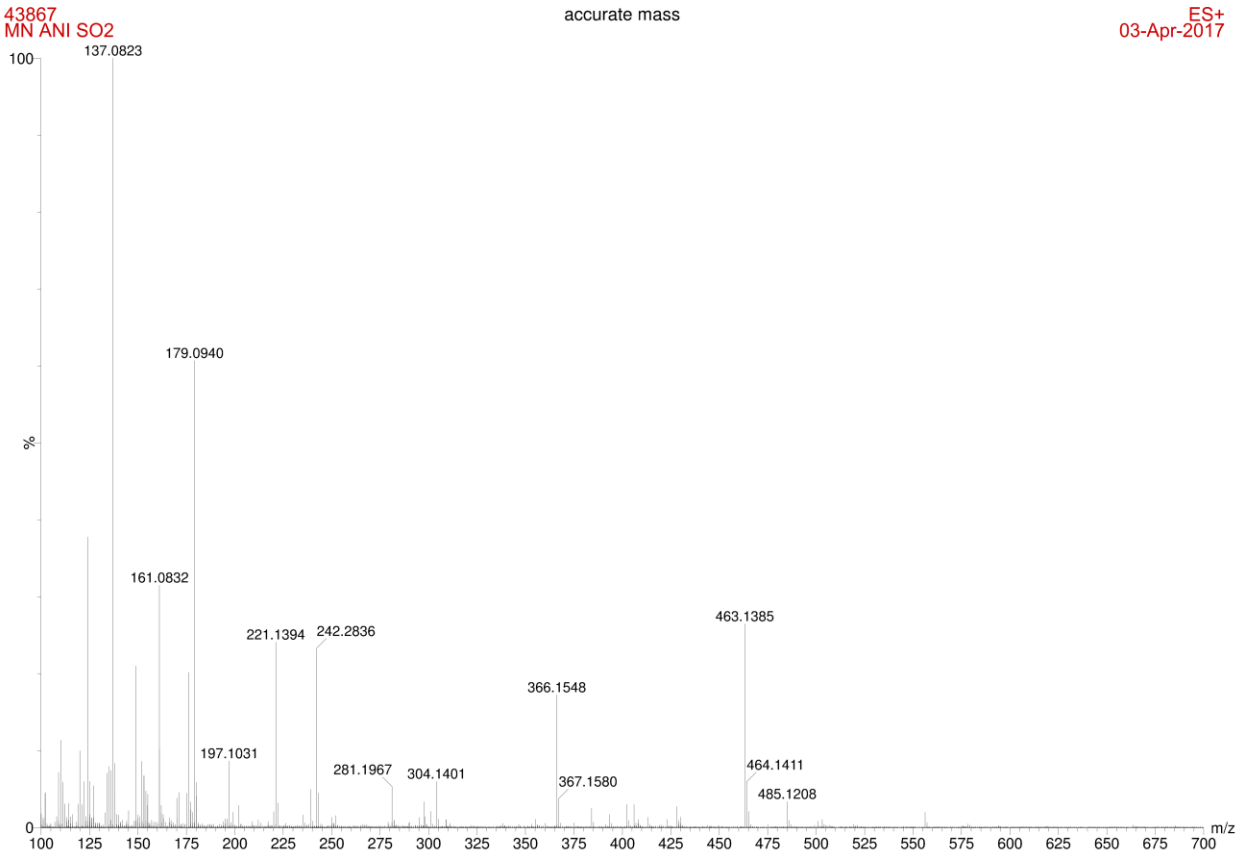
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ES+
03-Apr-2017
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304.1401
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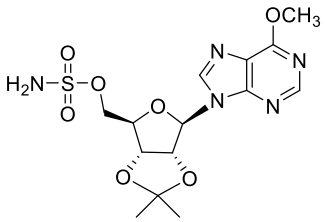
%
m/z



Exact Mass: 401.1005

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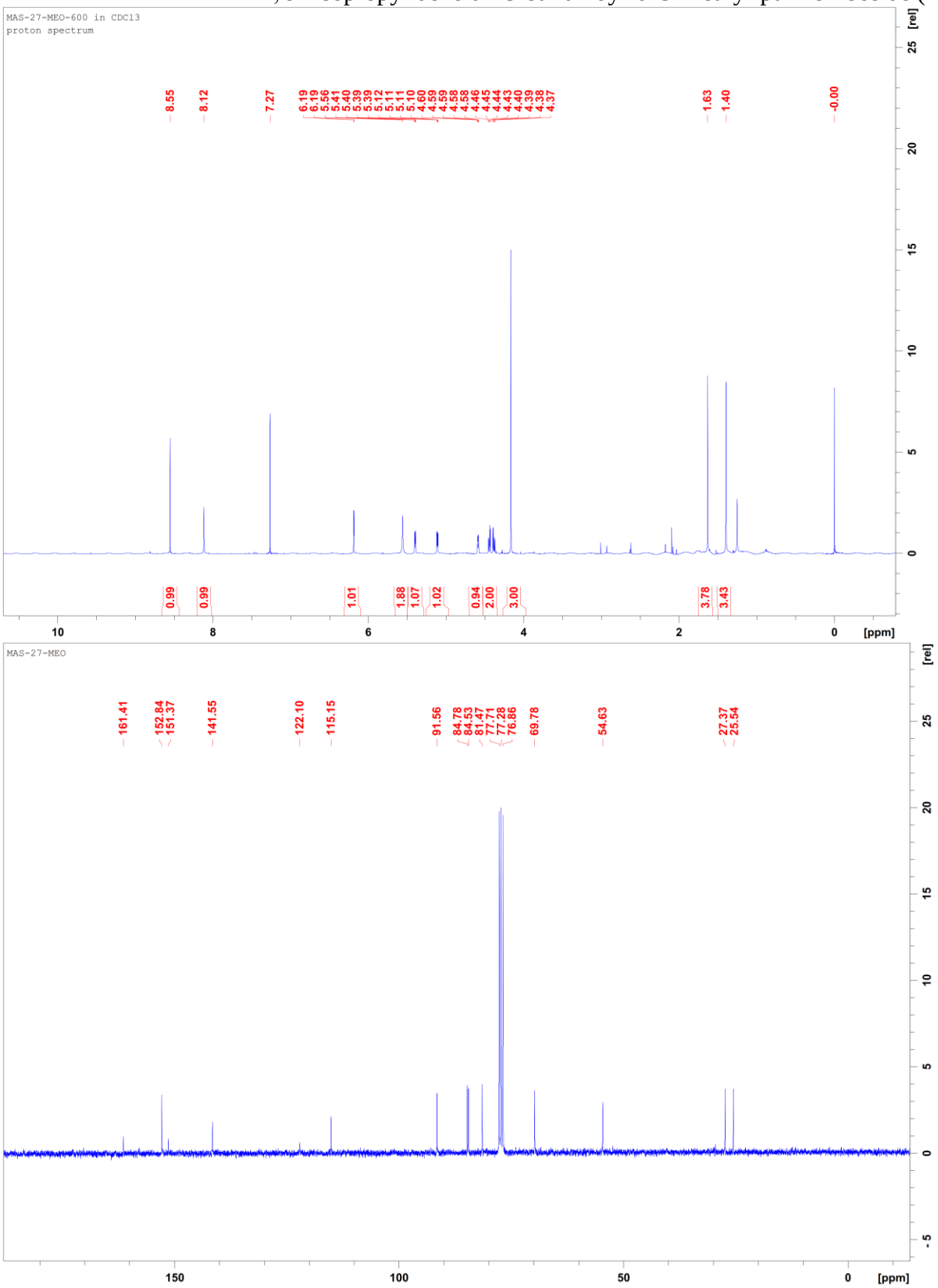

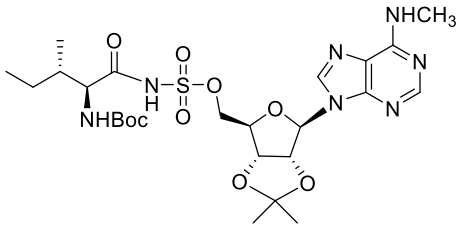

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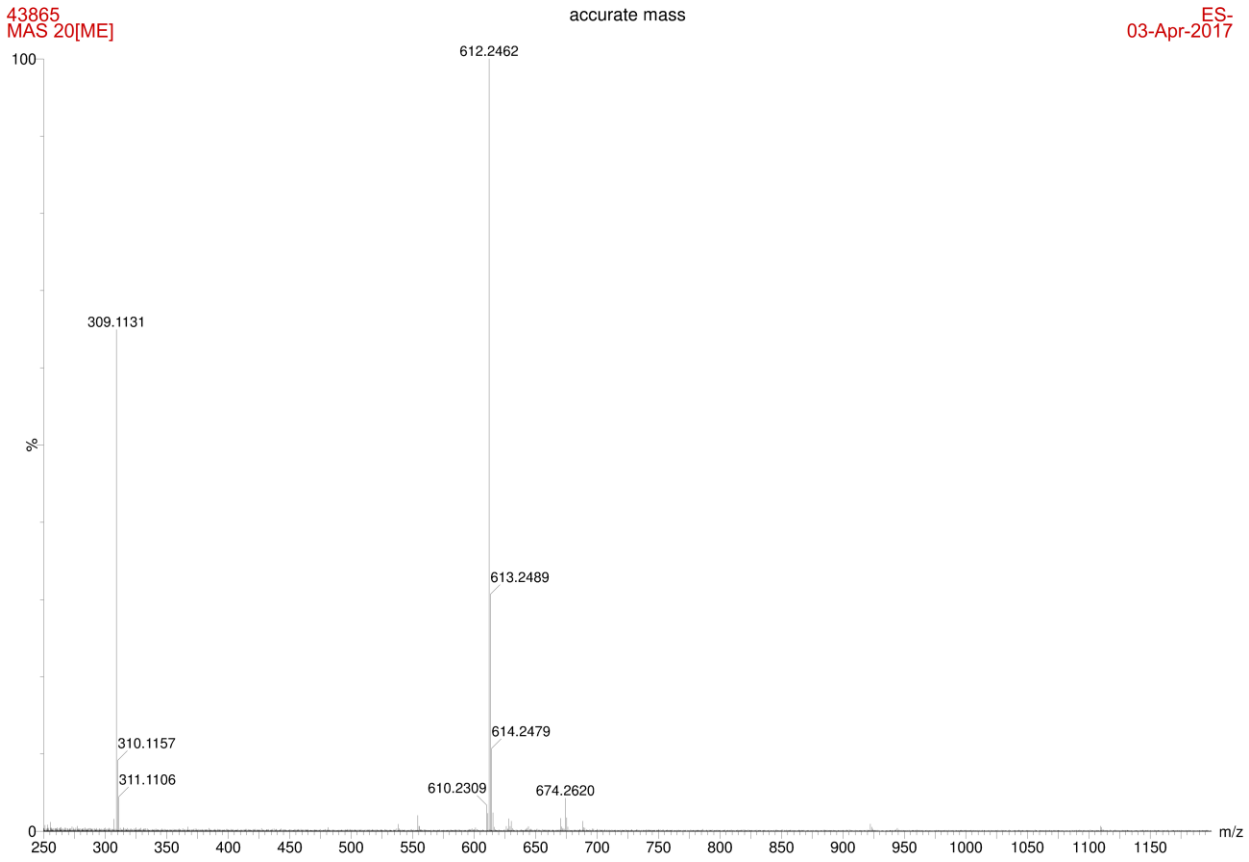
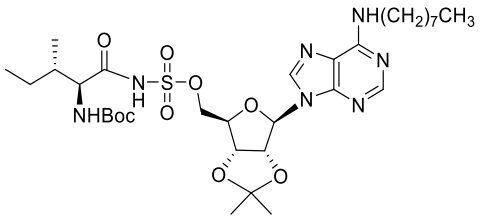
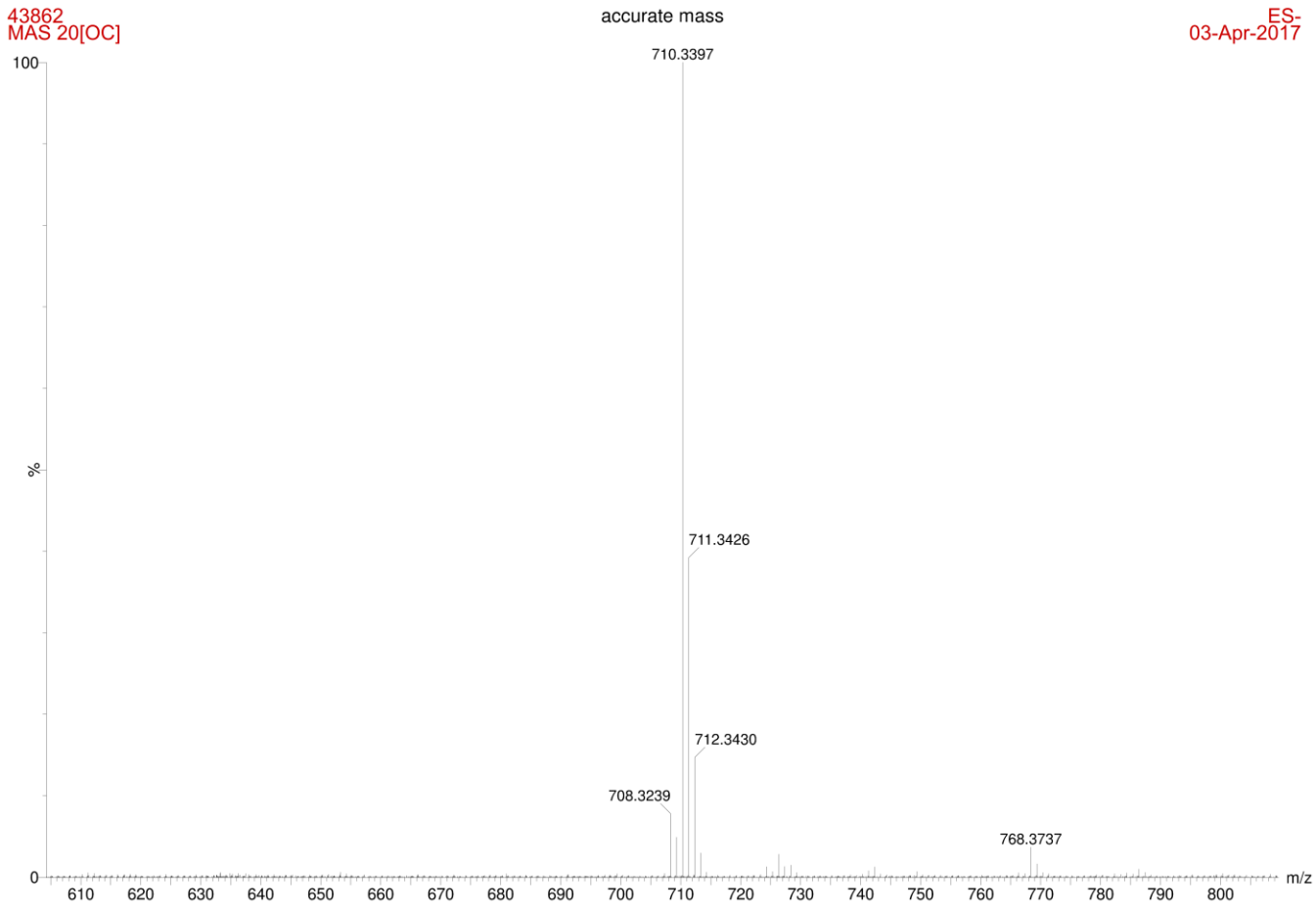
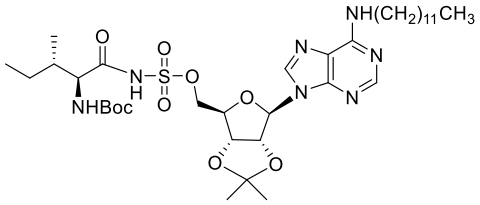




Exact Mass: 711.3625

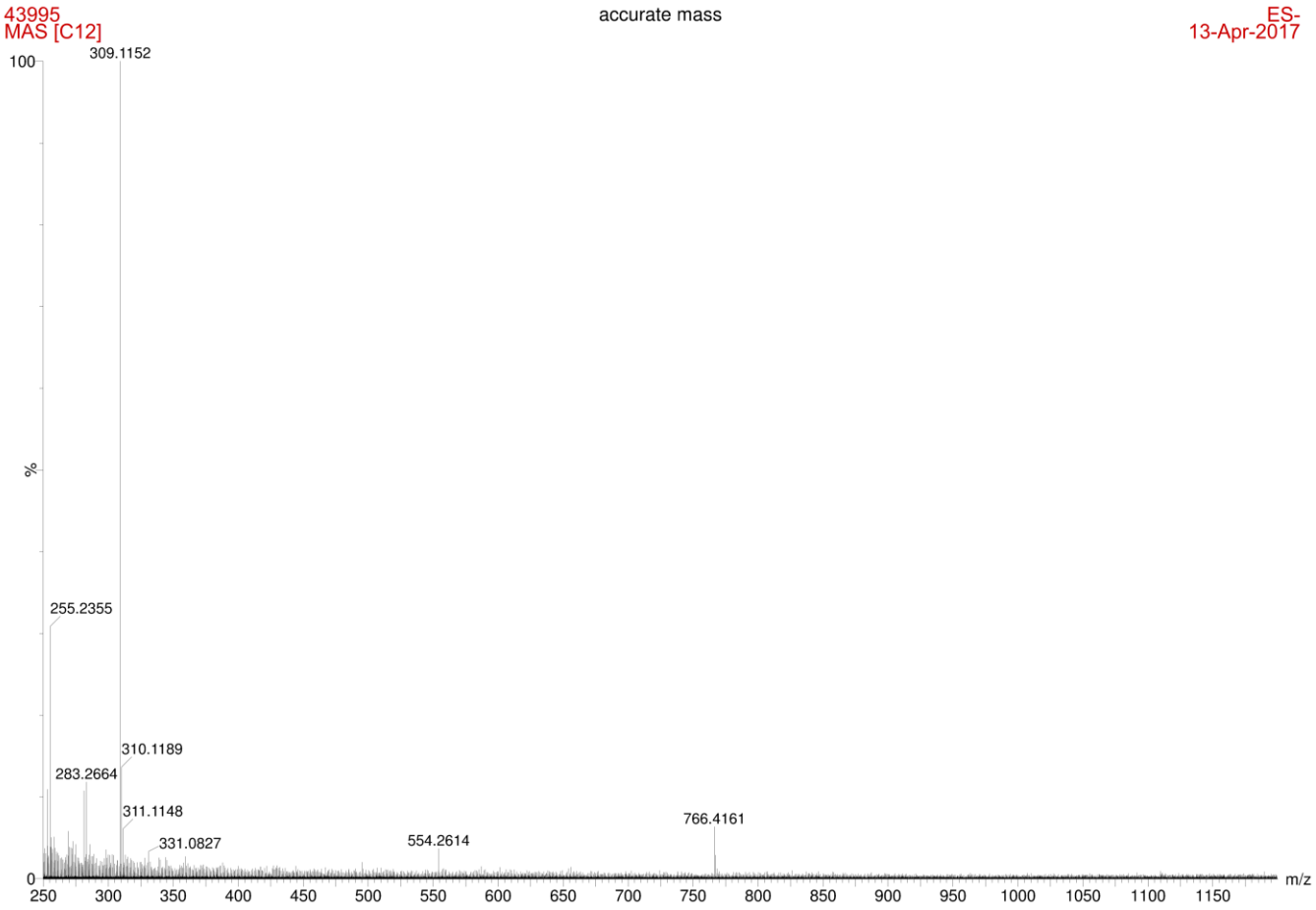
2’,3’-isopropylidene-5’-O-(N-(Nα-Boc-L-isoleucyl))-sulfamoyl-N6-octyl-adenosine (5b)

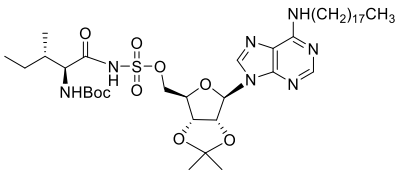




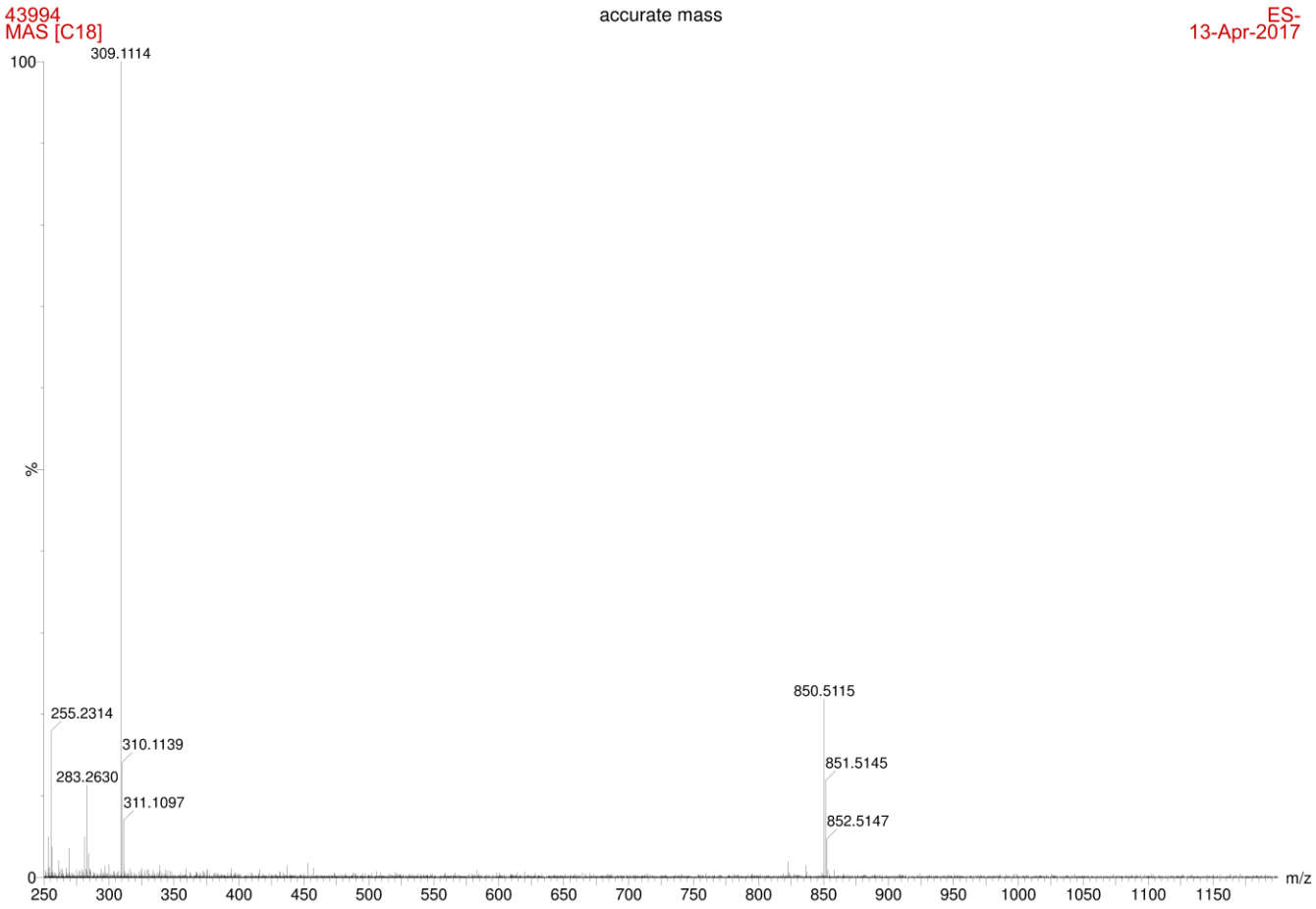
Exact Mass: 767.4251

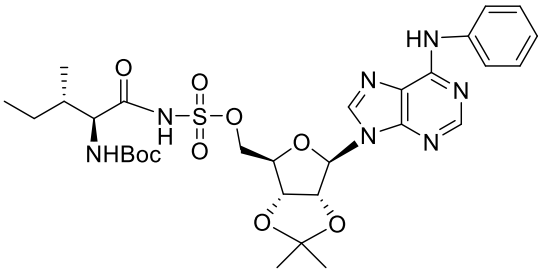
2’,3’-isopropylidene-5’-O-(N-(Nα-Boc-L-isoleucyl))-sulfamoyl-N6-dodecyl-adenosine (5c)





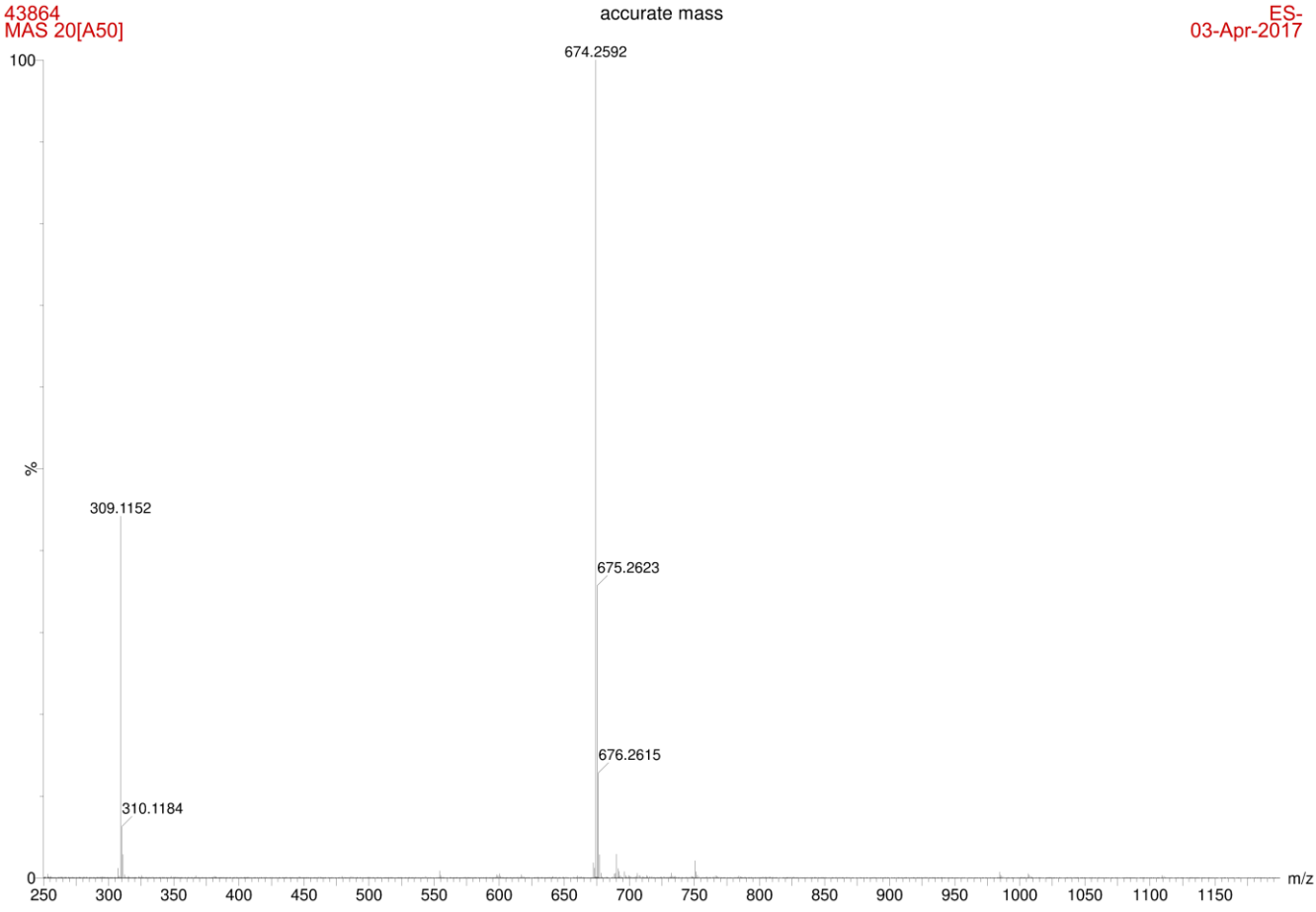
2’,3’-isopropylidene-5’-O-(N-(Nα-Boc-L-isoleucyl))-sulfamoyl-N6-octadecyl-adenosine (5d)

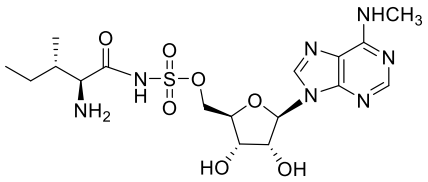




Exact Mass: 675.2686

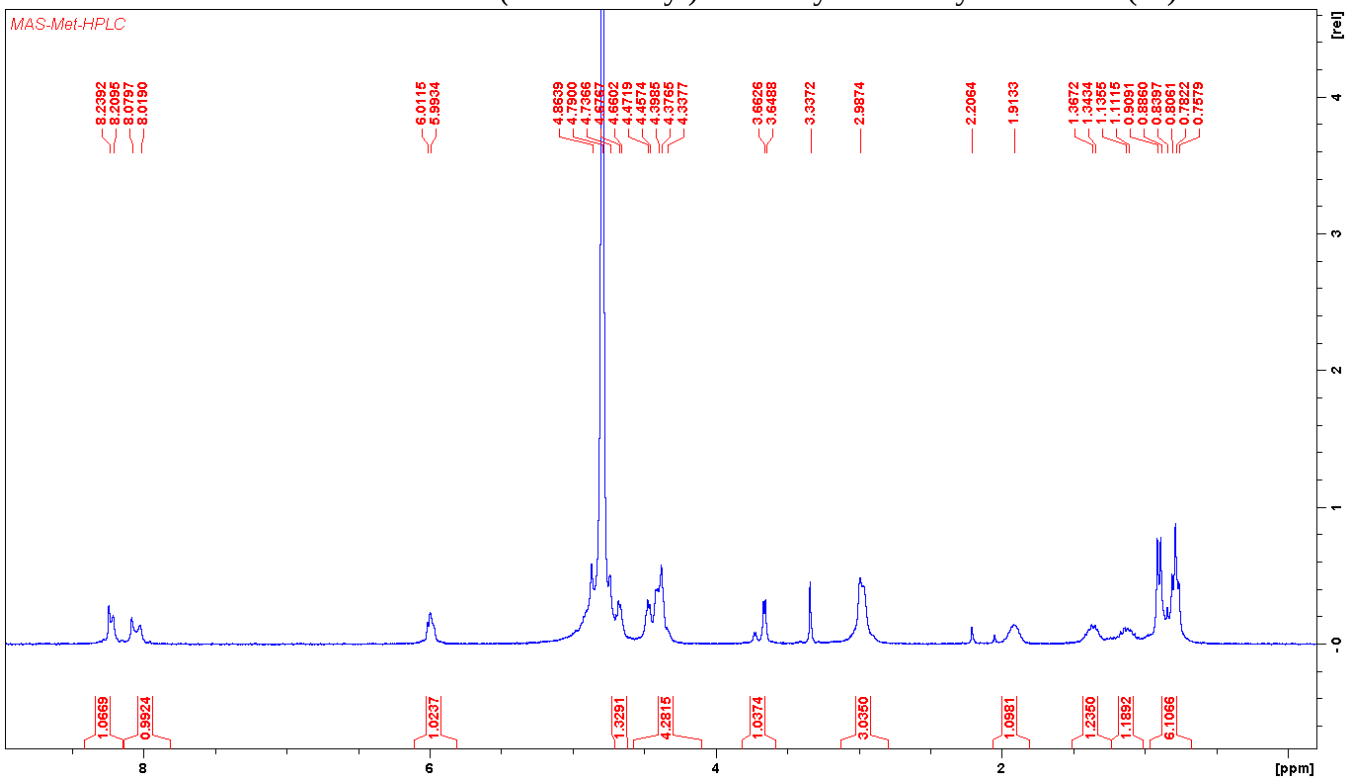
2’,3’-isopropylidene-5’-O-(N-(Nα-Boc-L-isoleucyl))-sulfamoyl-N6-phenyl-adenosine (5e)

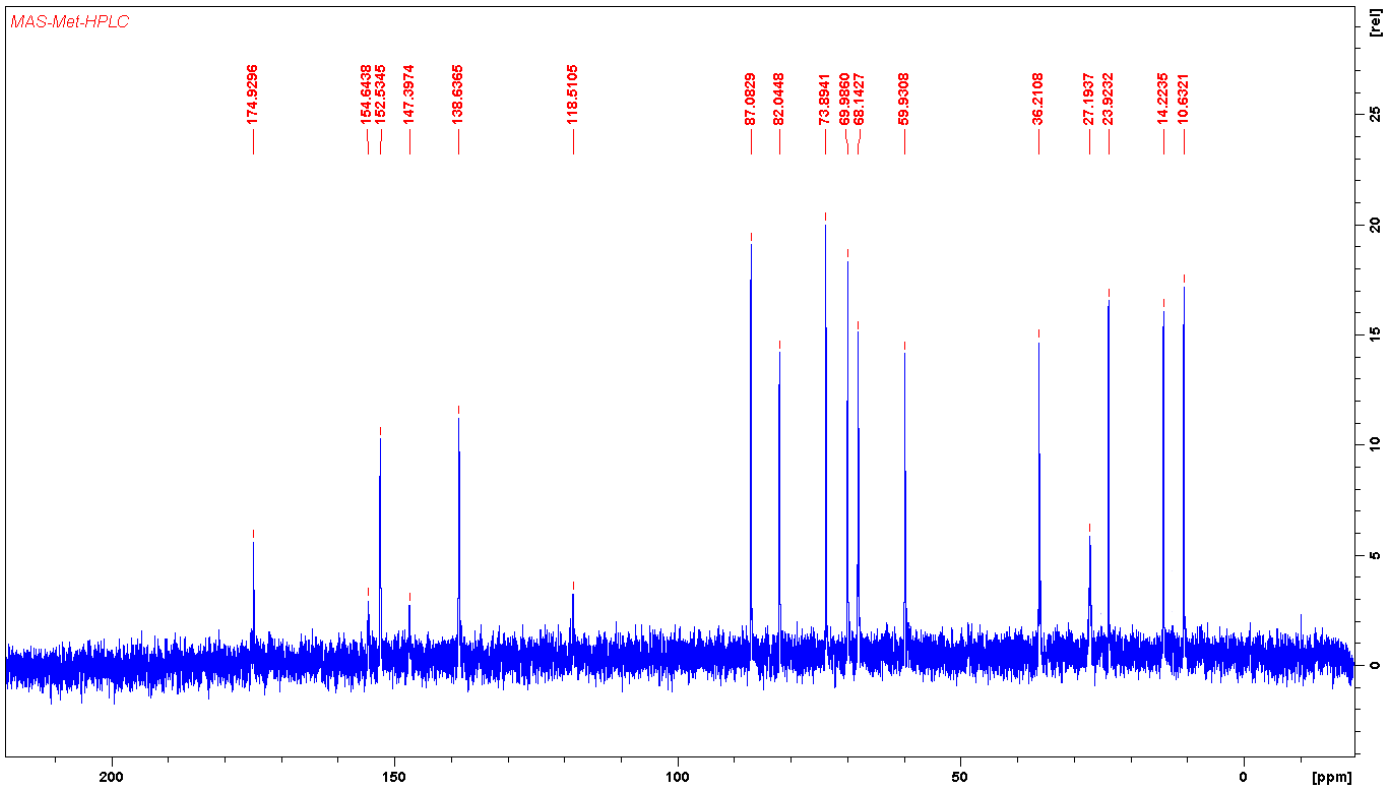


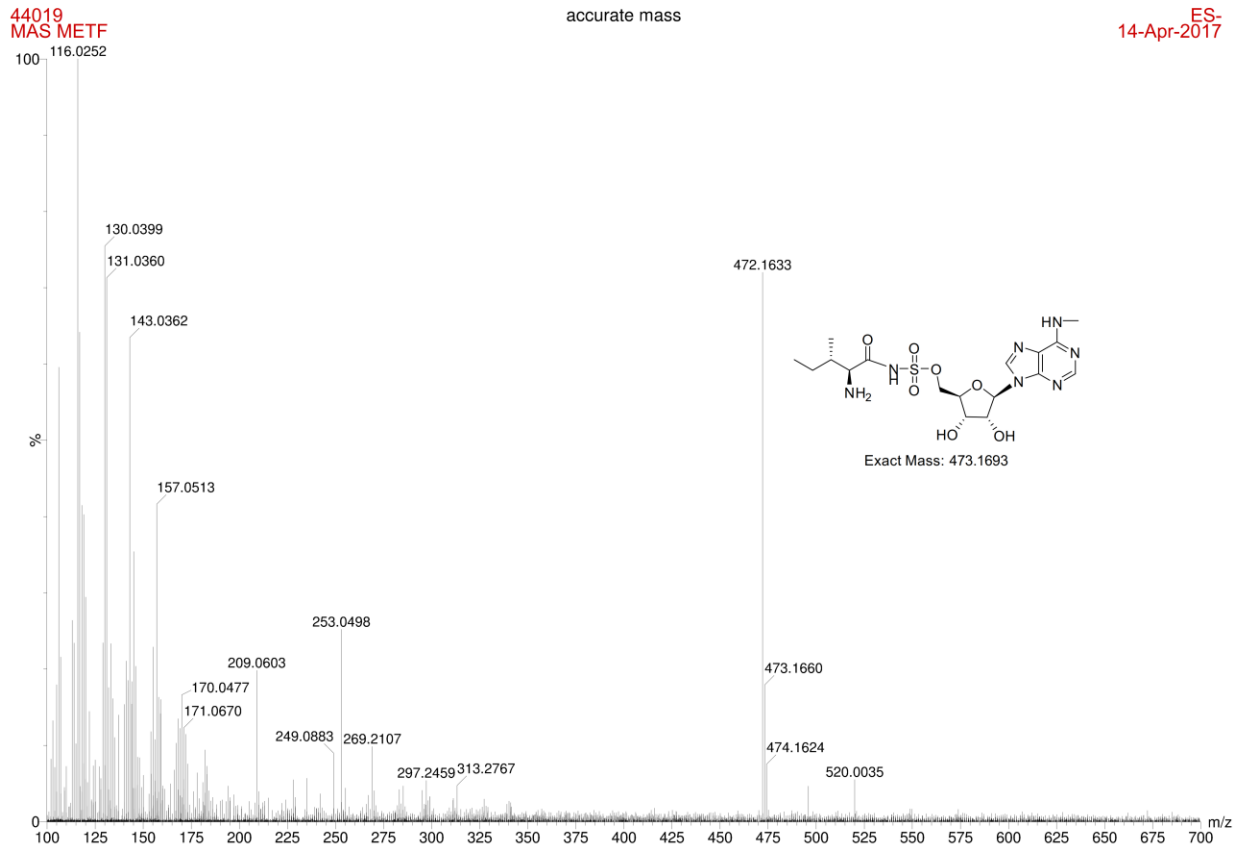


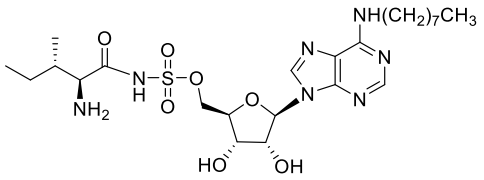
Exact Mass: 473.1693

5’-*O*-(*N*-L-isoleucyl)-sulfamoyl-N^6-methyl-adenosine (6a)

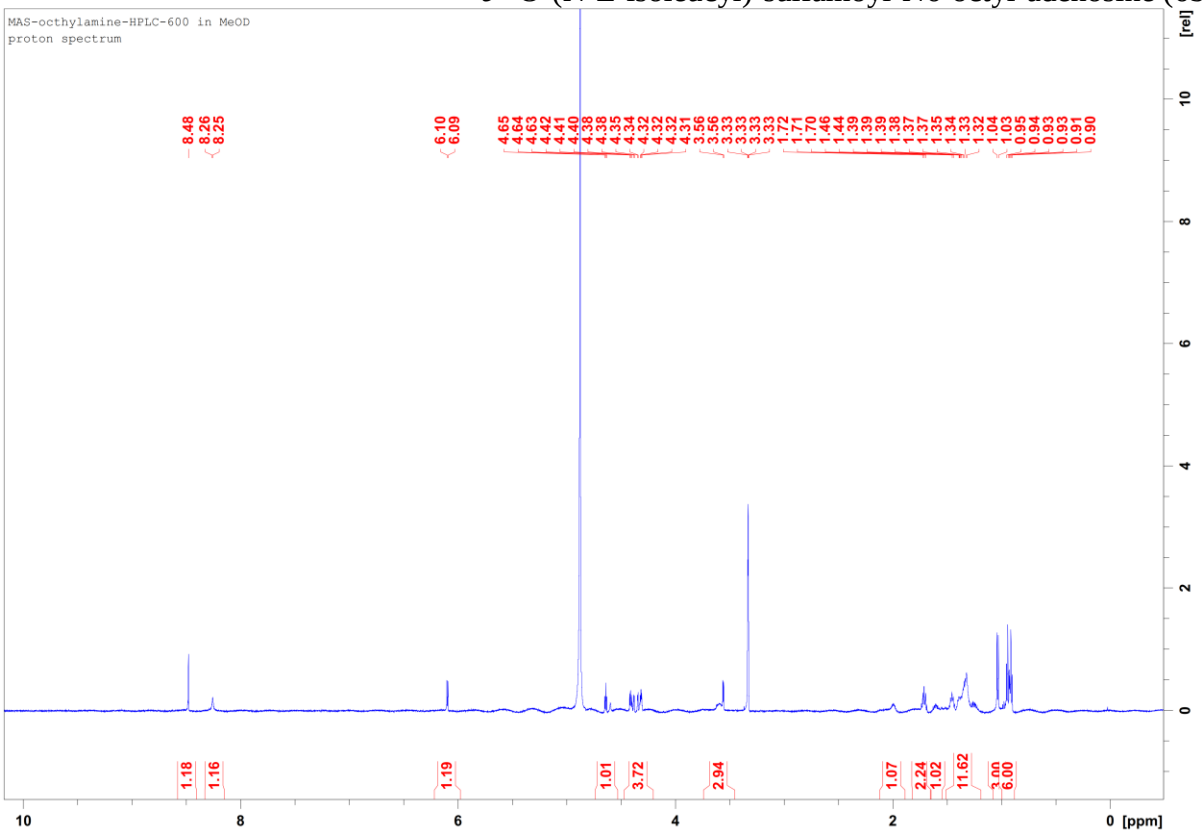


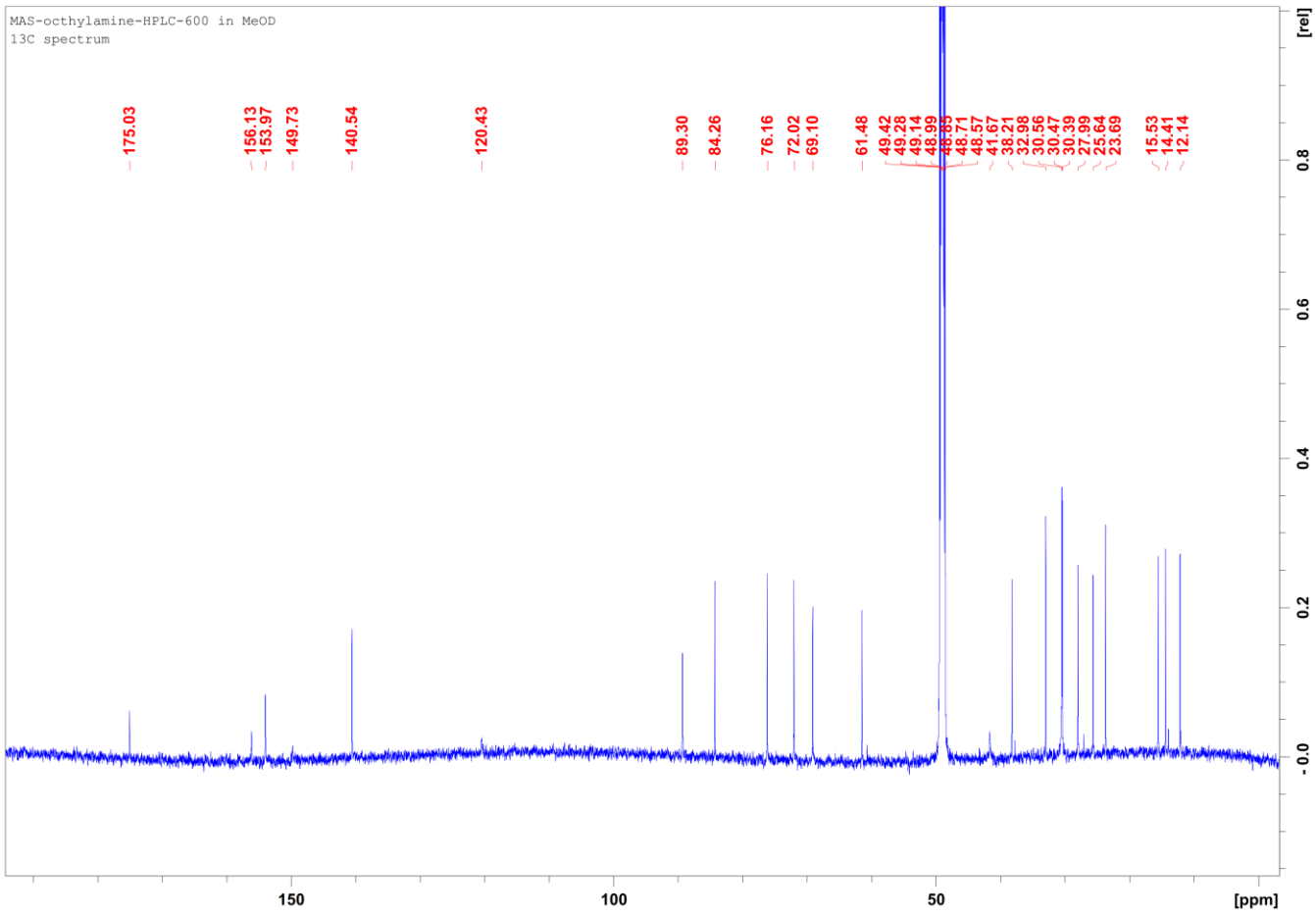






5’-O-(N-L-isoleucyl)-sulfamoyl-N6-octyl-adenosine (6b)




MAS-octhylamine-HPLC-600 in MeOD
13C spectrum
175.03
156.13
153.97
149.73
140.54
120.43
89.30
84.26
76.16
72.02
69.10
61.48
49.42
49.28
49.14
48.99
48.85
48.71
48.57
41.67
38.21
32.98
30.56
30.47
30.39
27.99
25.64
23.69
15.53
14.41
12.14
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0.4
0.2
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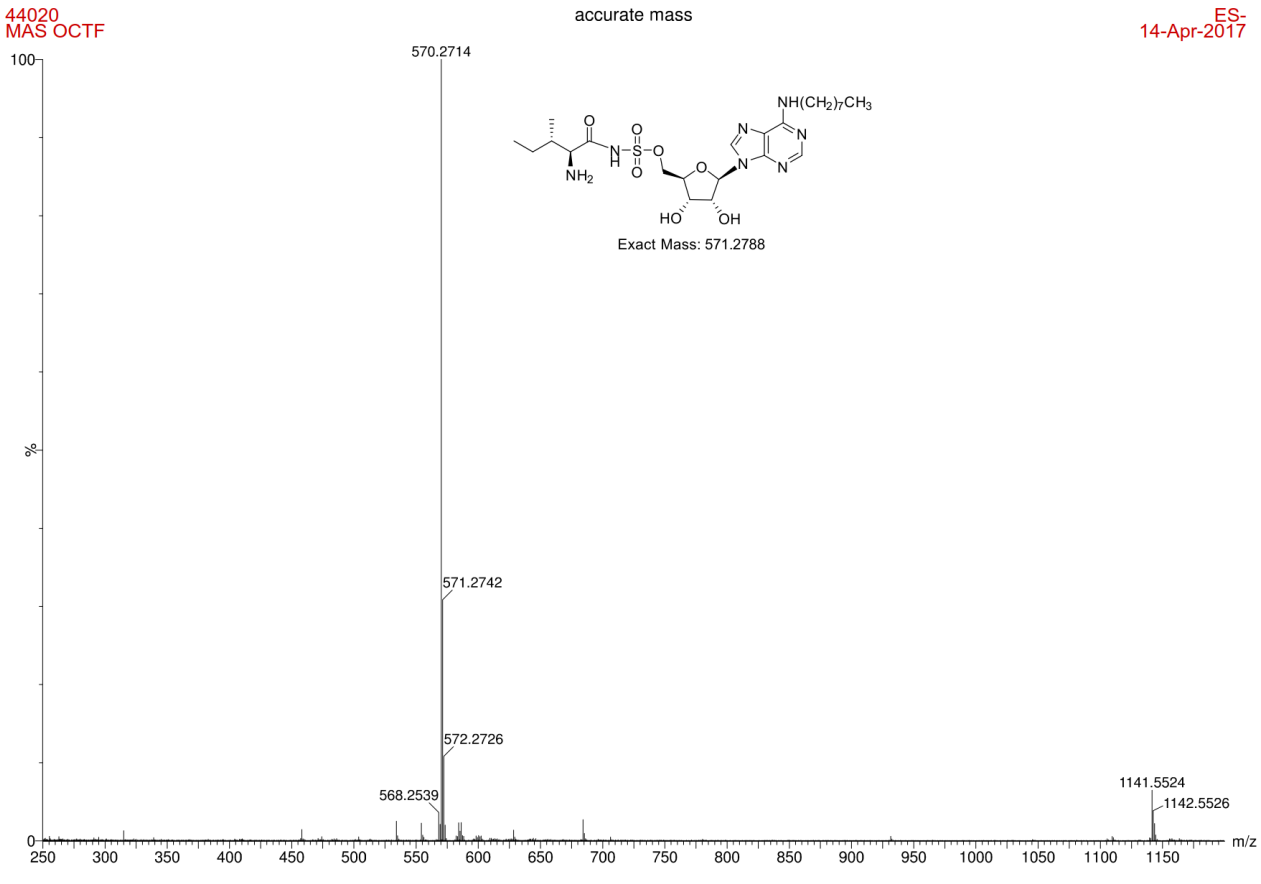
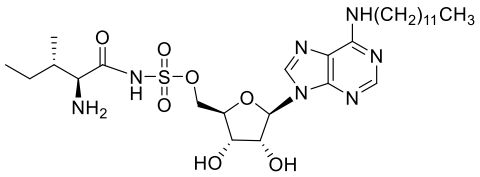
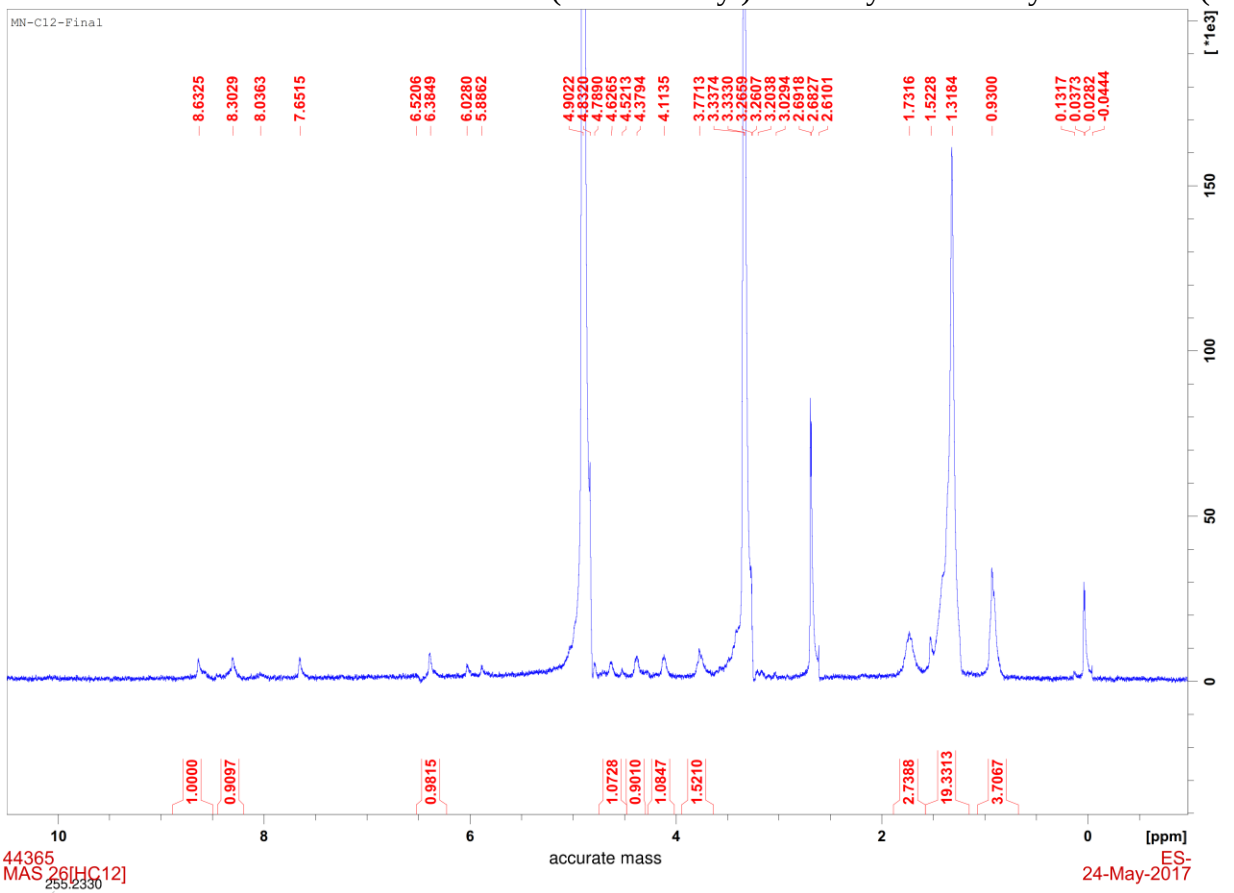
150
100
50
[ppm]

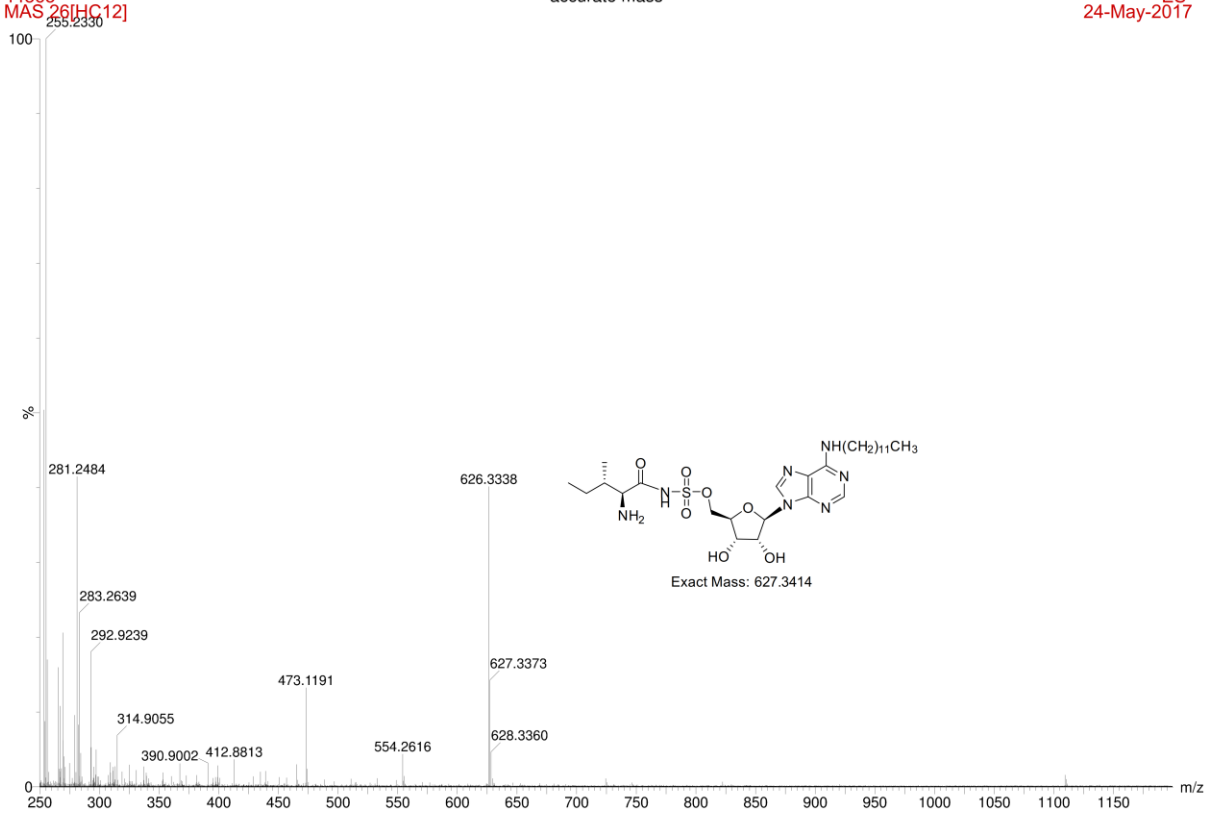

44020
MAS OCTF
accurate mass
ES-
14-Apr-2017
570.2714
571.2742
572.2726
568.2539
1141.5524
1142.5526
100
%
0
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
1050
1100
1150
m/z
NH(CH2)7CH3
NH2
HO
OH
Exact Mass: 571.2788



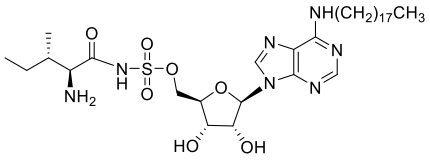
Exact Mass: 627.3414

5’-O-(N-L-isoleucyl)-sulfamoyl-N6-dodecyl-adenosine (6c)



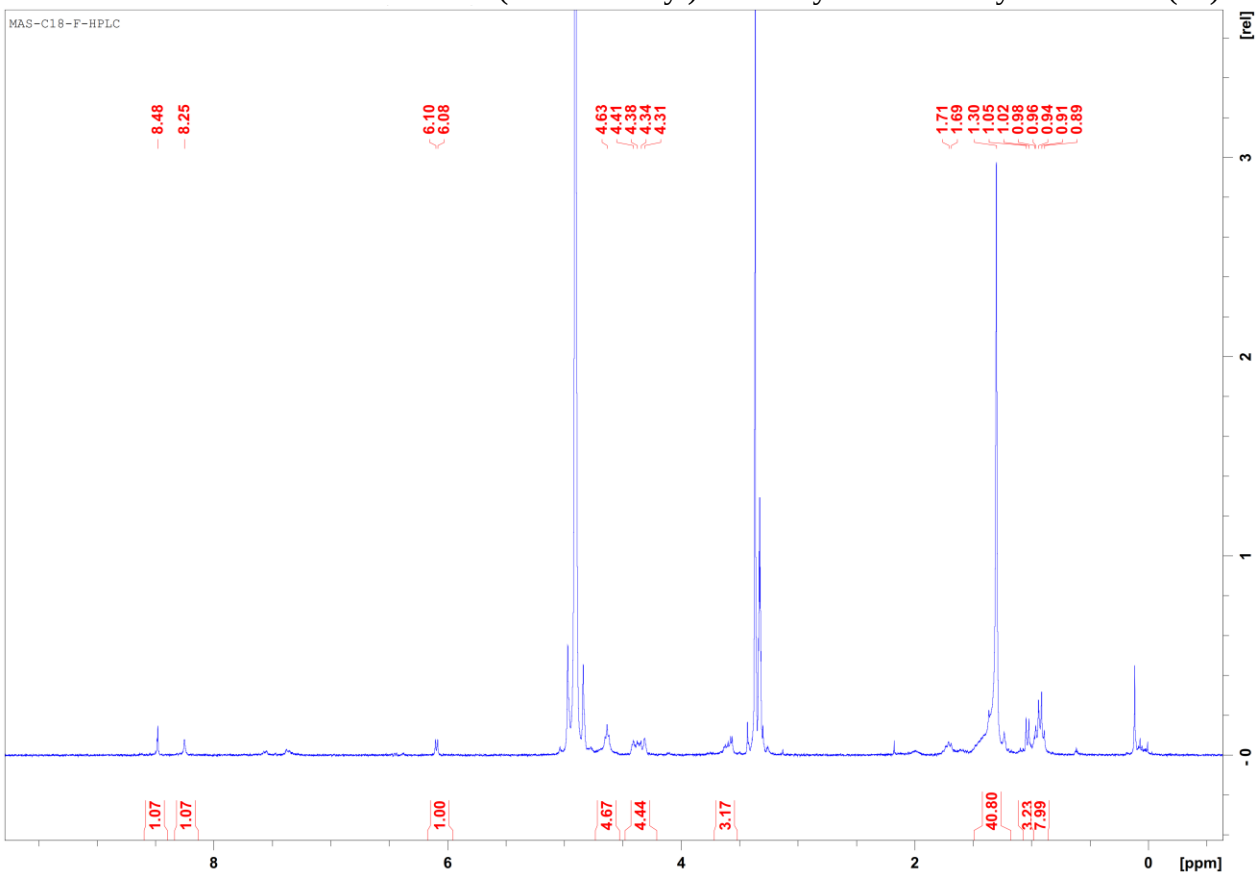


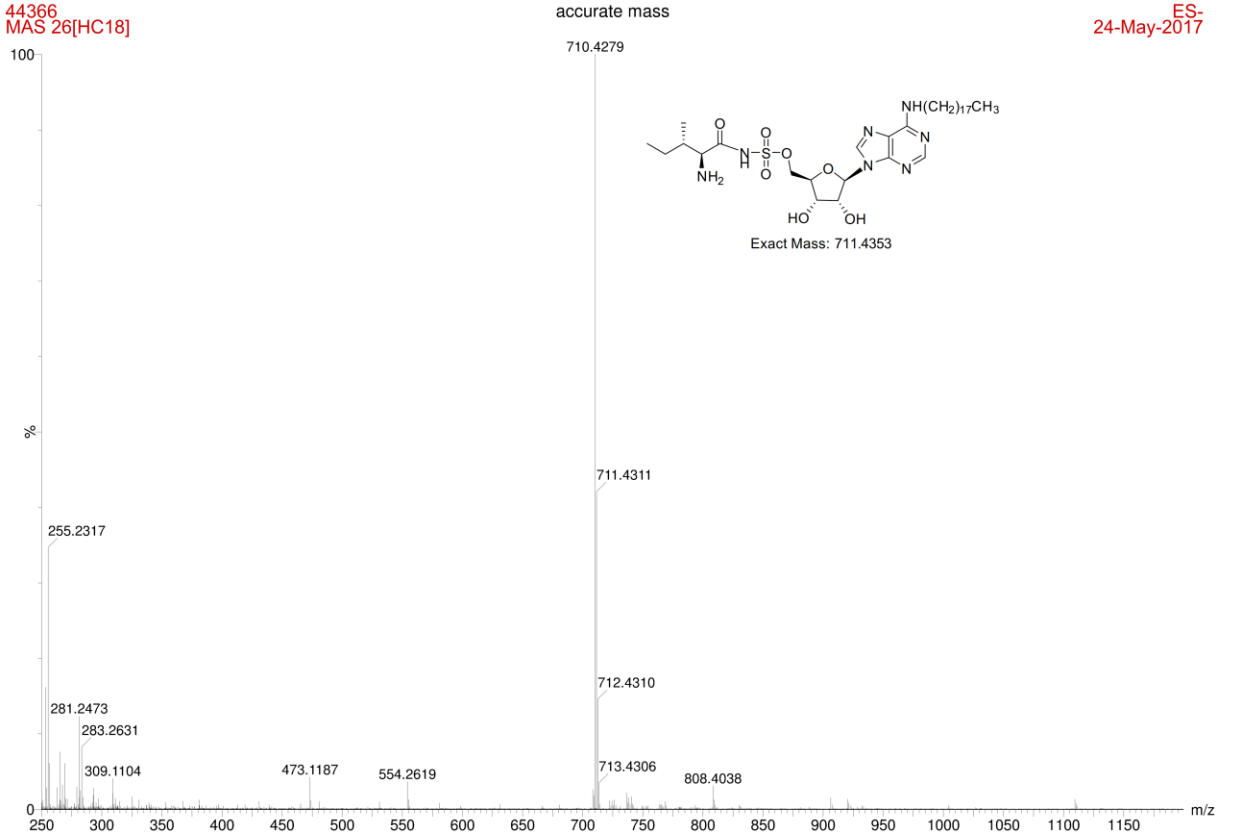
Exact Mass: 627.3414



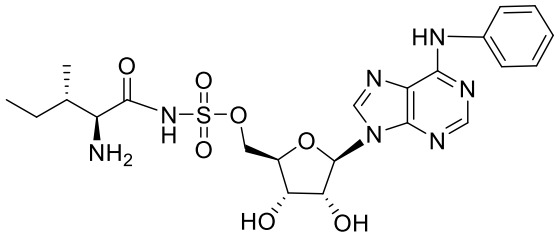
Exact Mass: 711.4353

5’-O-(N-L-isoleucyl)-sulfamoyl-N6-octadecyl-adenosine (6d)



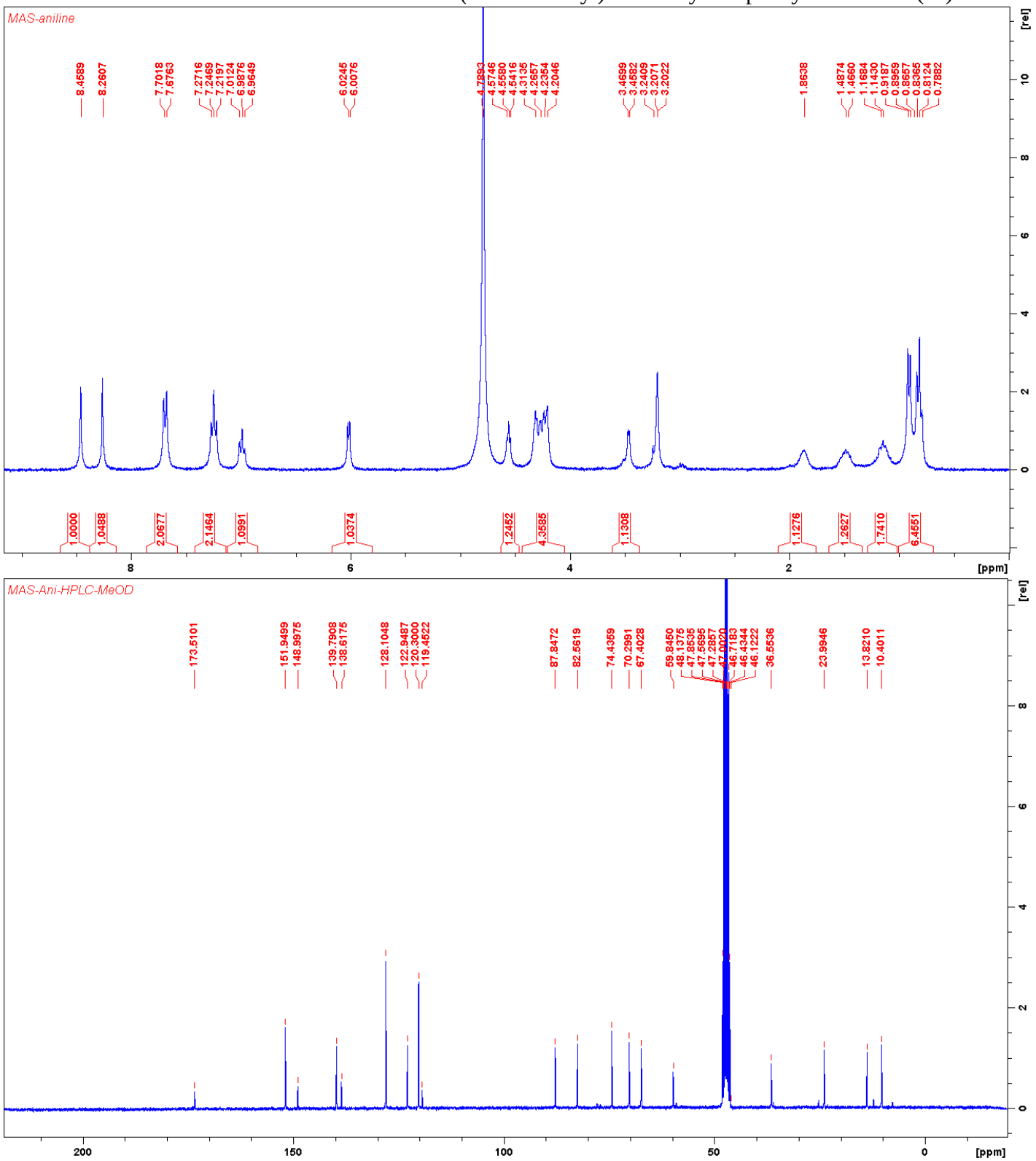


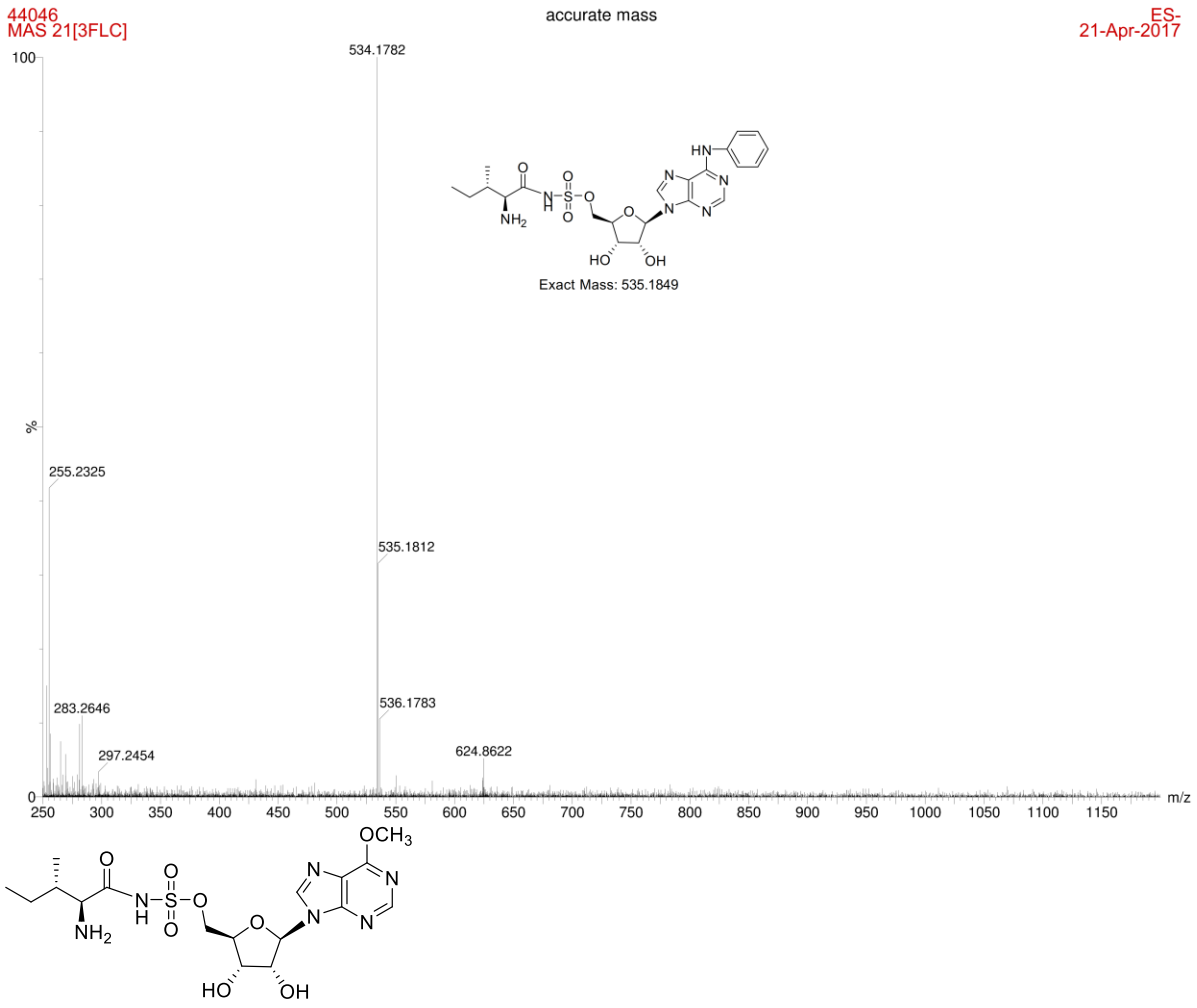
Exact Mass: 711.4353



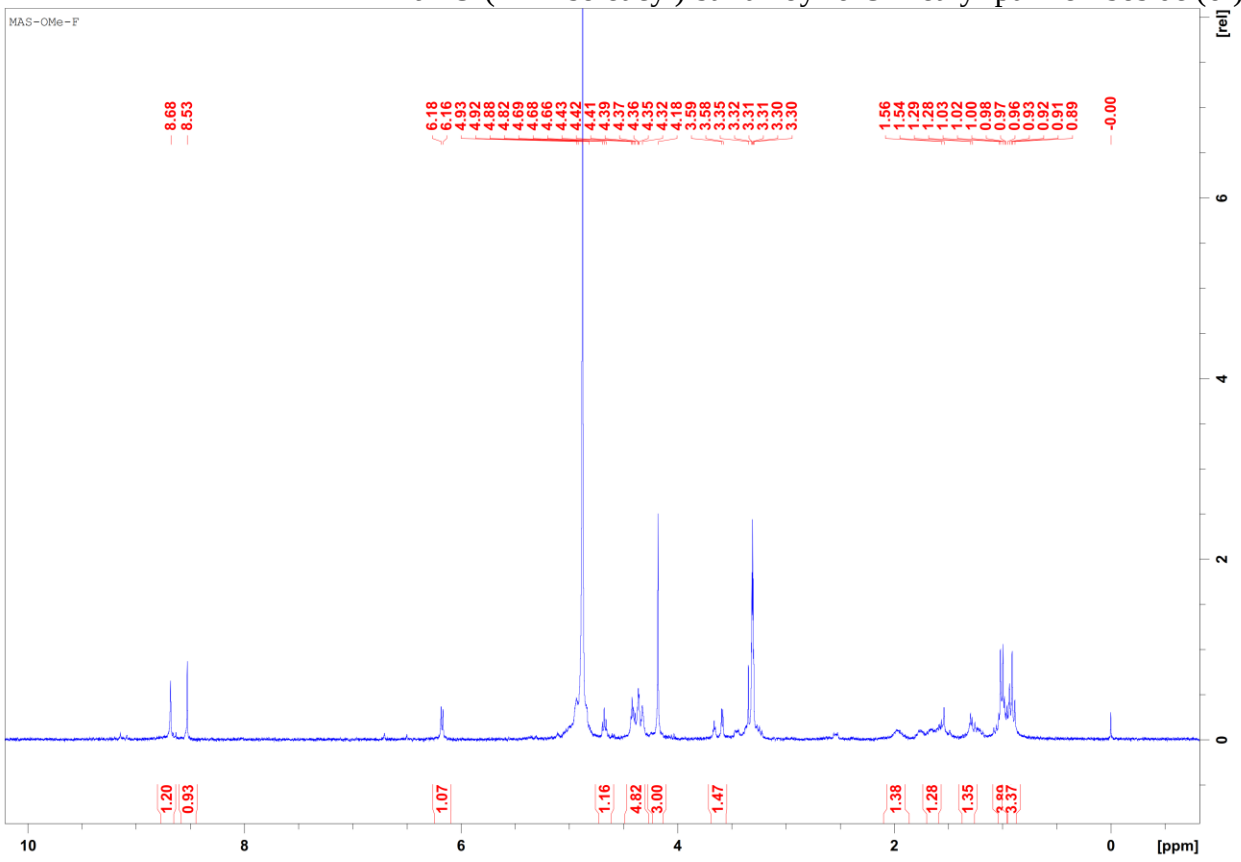
Exact Mass: 535.1849

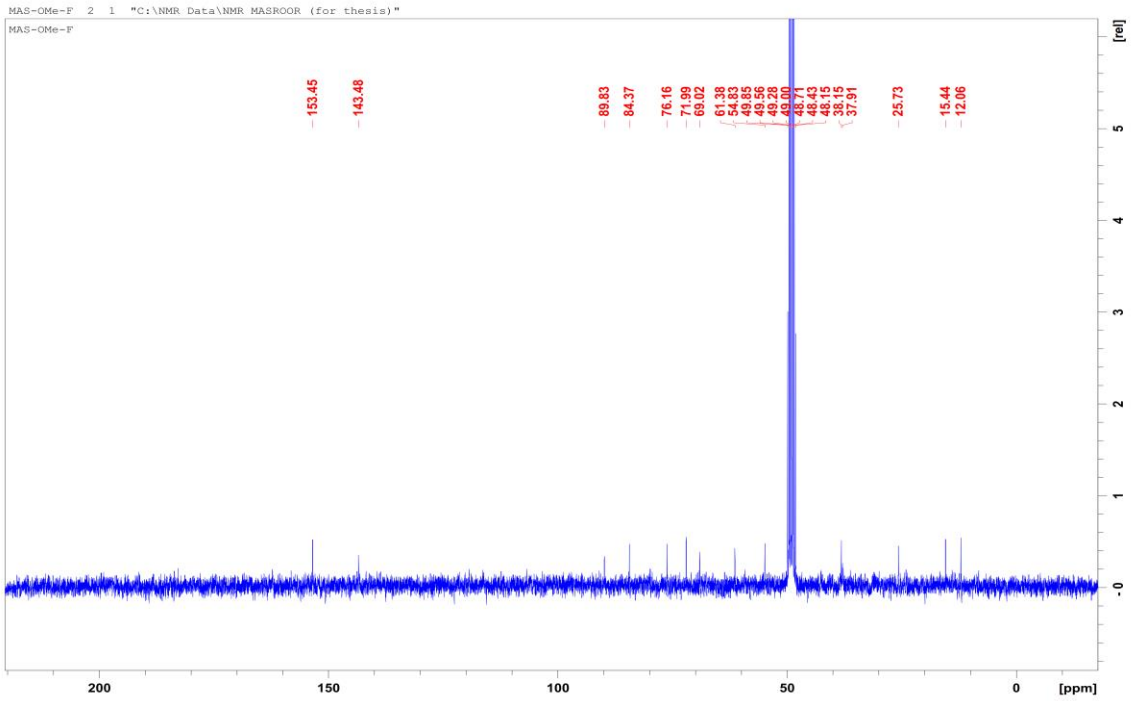
5’-*O*-(*N*-L-isoleucyl)-sulfamoyl-N^6-phenyl-adenosine (6e)

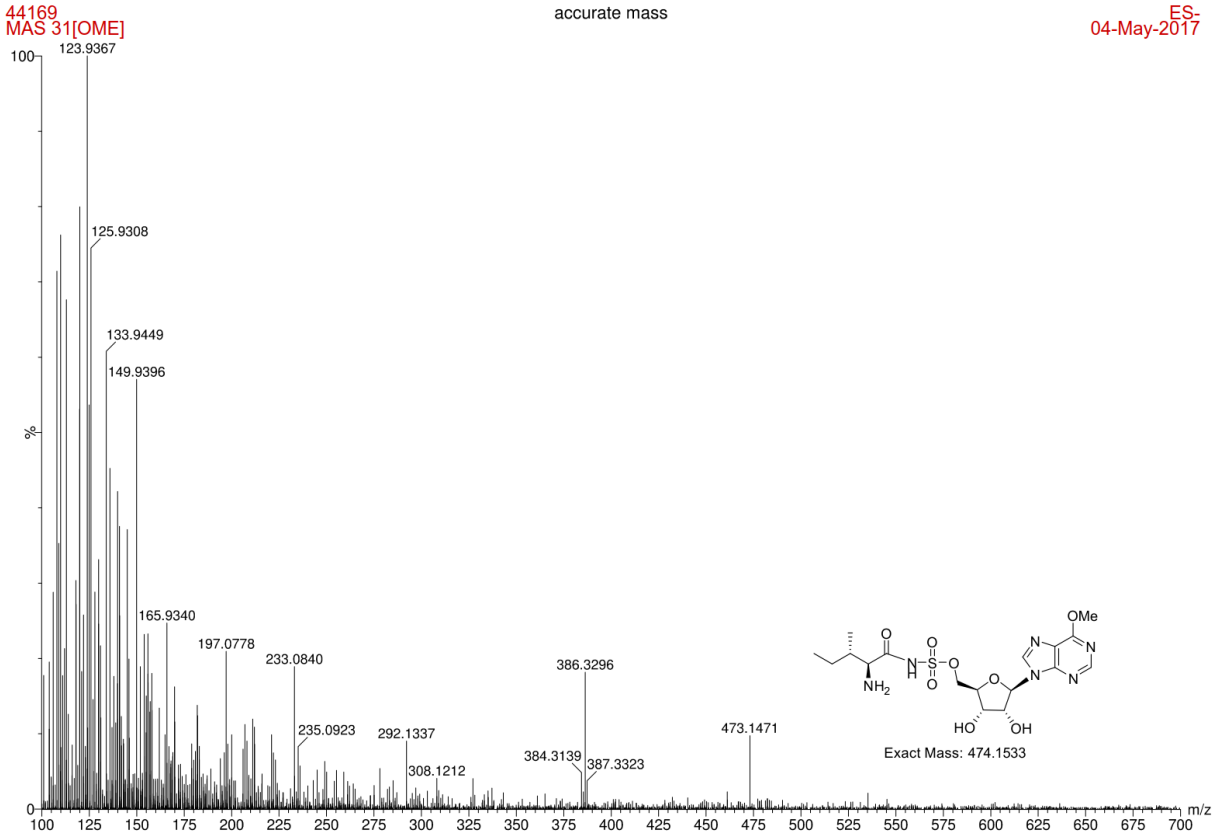




5’-O-(N-L-isoleucyl)-sulfamoyl-6-O-methyl-purine riboside (6f)




MAS-OMe-F 2 1 "C:\NMR Data\NMR MASROOR (for thesis)"
MAS-OMe-F
153.45
143.48
89.83
84.37
76.16
71.99
69.02
61.38
54.83
49.85
49.56
49.28
49.00
48.71
48.43
48.15
38.15
37.91
25.73
15.44
12.06
[rel]
200
150
100
50
0
[ppm]


44169
MAS 31[OME]
accurate mass
ES-
04-May-2017
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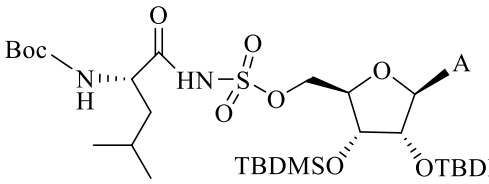
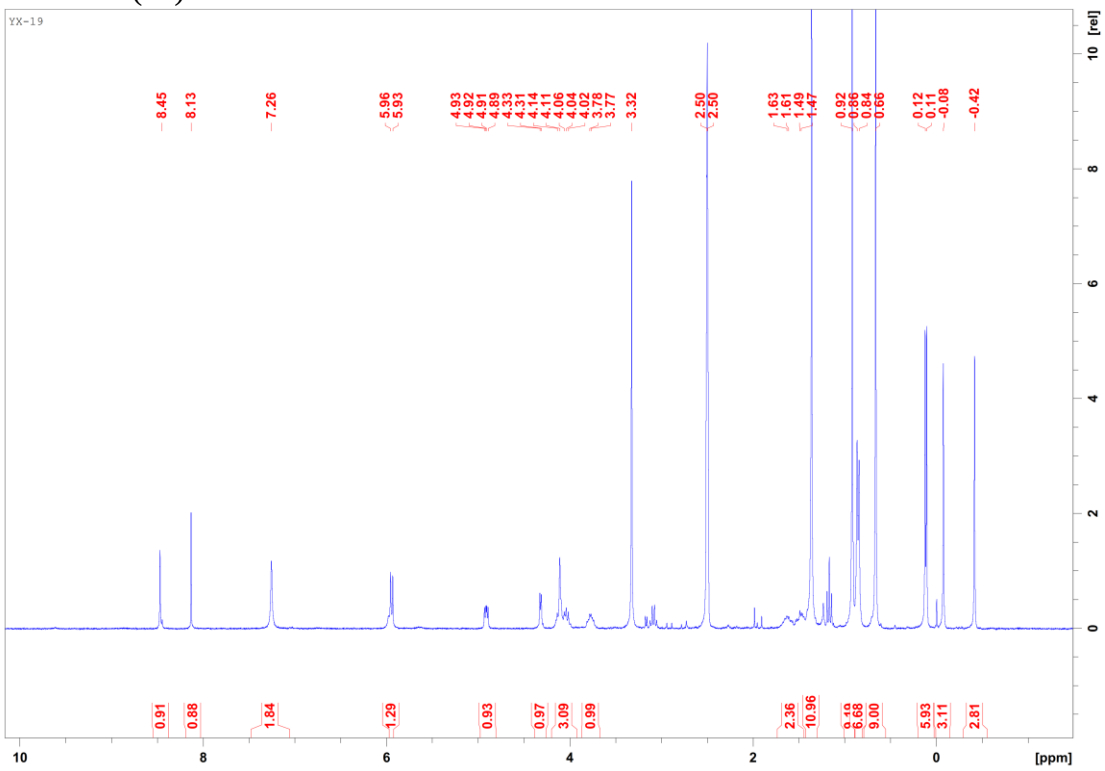
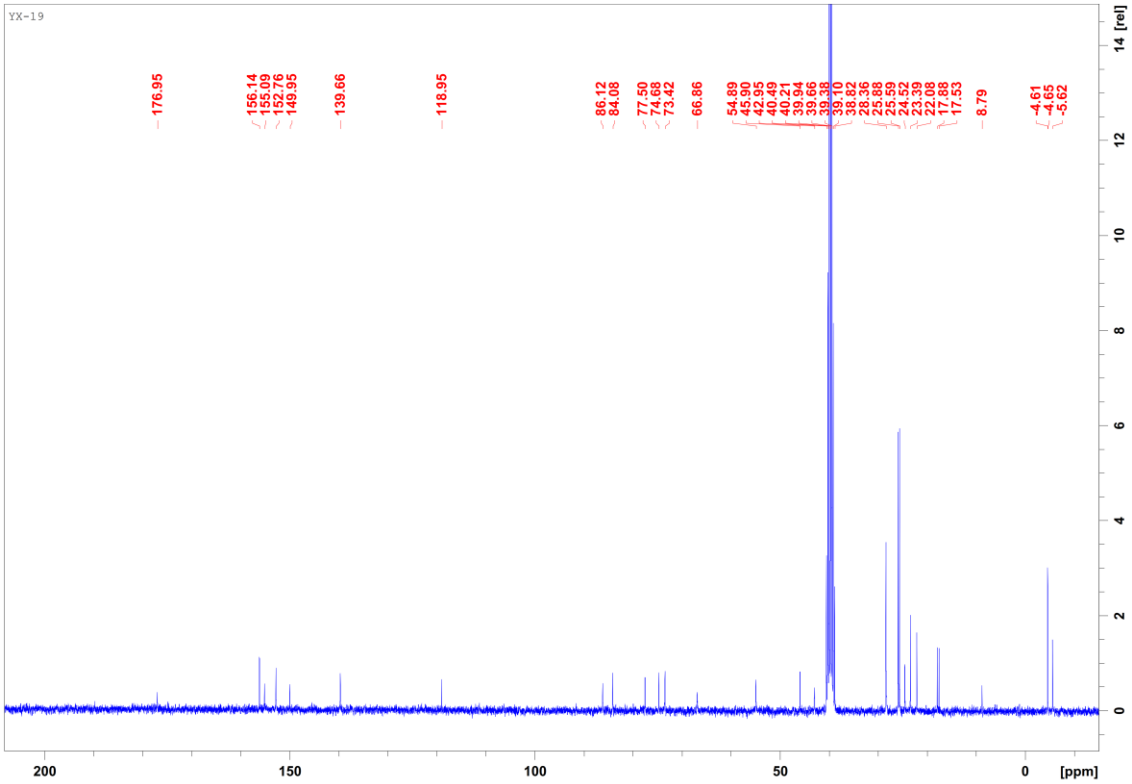
125.9308
133.9449
149.9396
165.9340
197.0778
233.0840
235.0923
292.1337
308.1212
384.3139
386.3296
387.3323
473.1471
%
m/z
Exact Mass: 474.1533

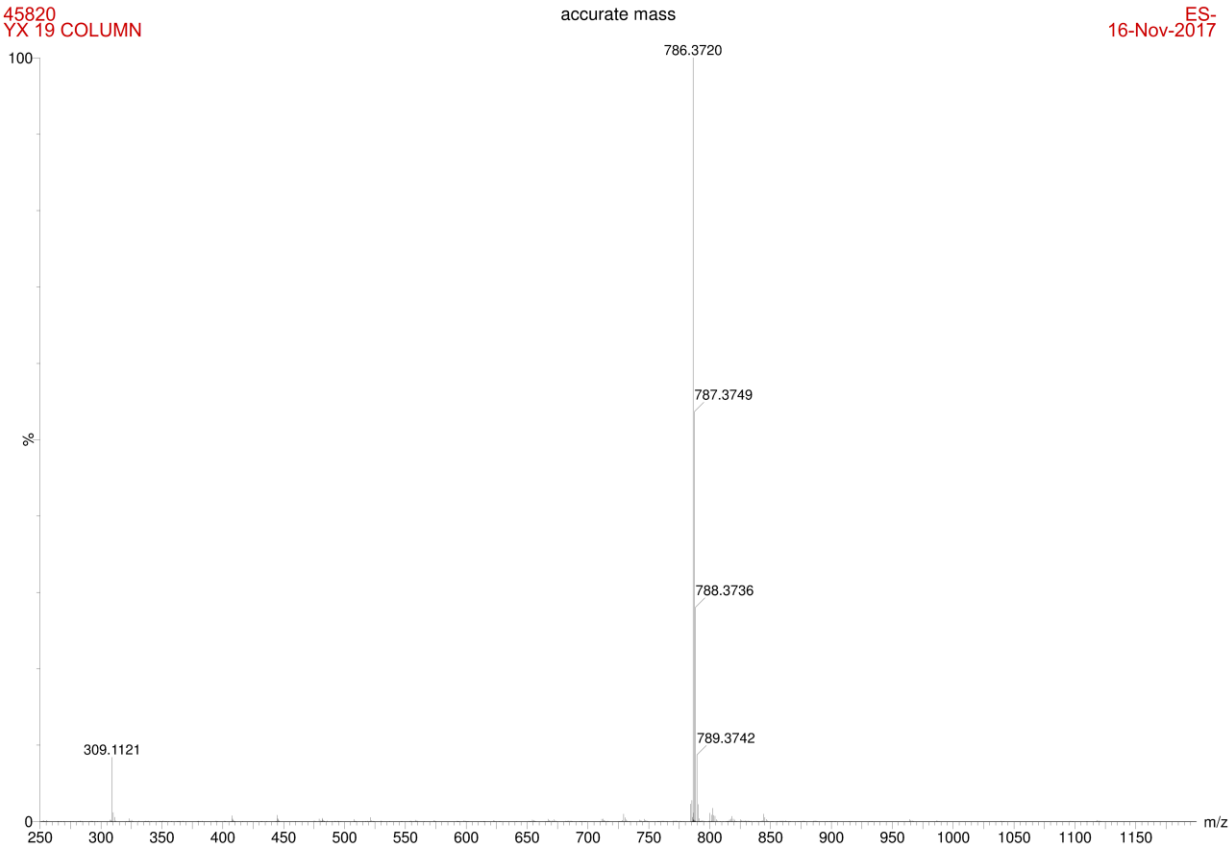
Prodrugs intermediate & final compounds - NMR & MS

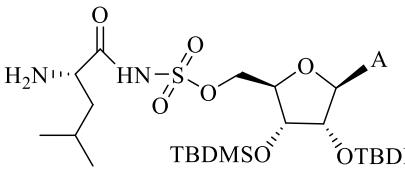


2',3'-di-*O*-TBDMS 5'-*O*-[*N*-(*N*-Boc)leucyl]sulfamoyl adenosine (11)

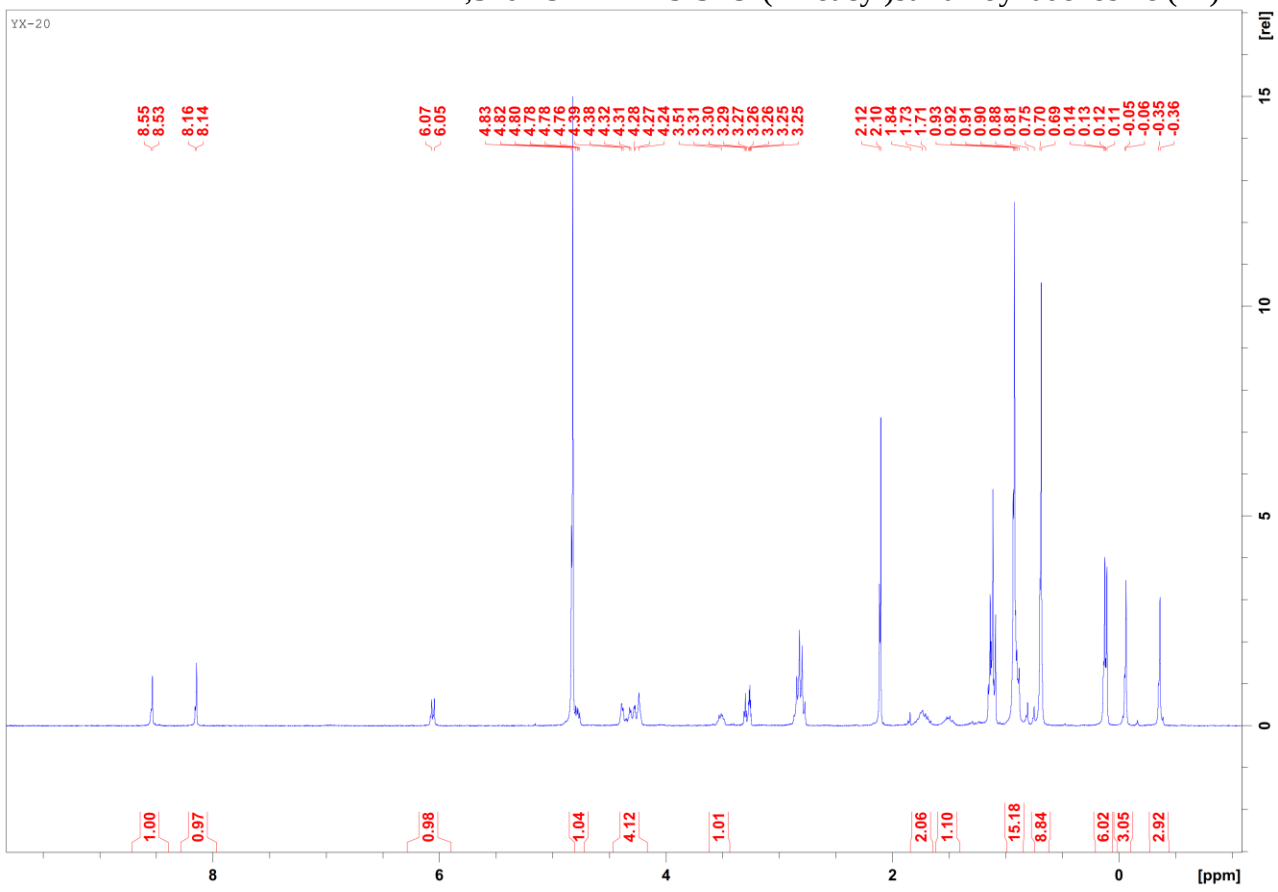


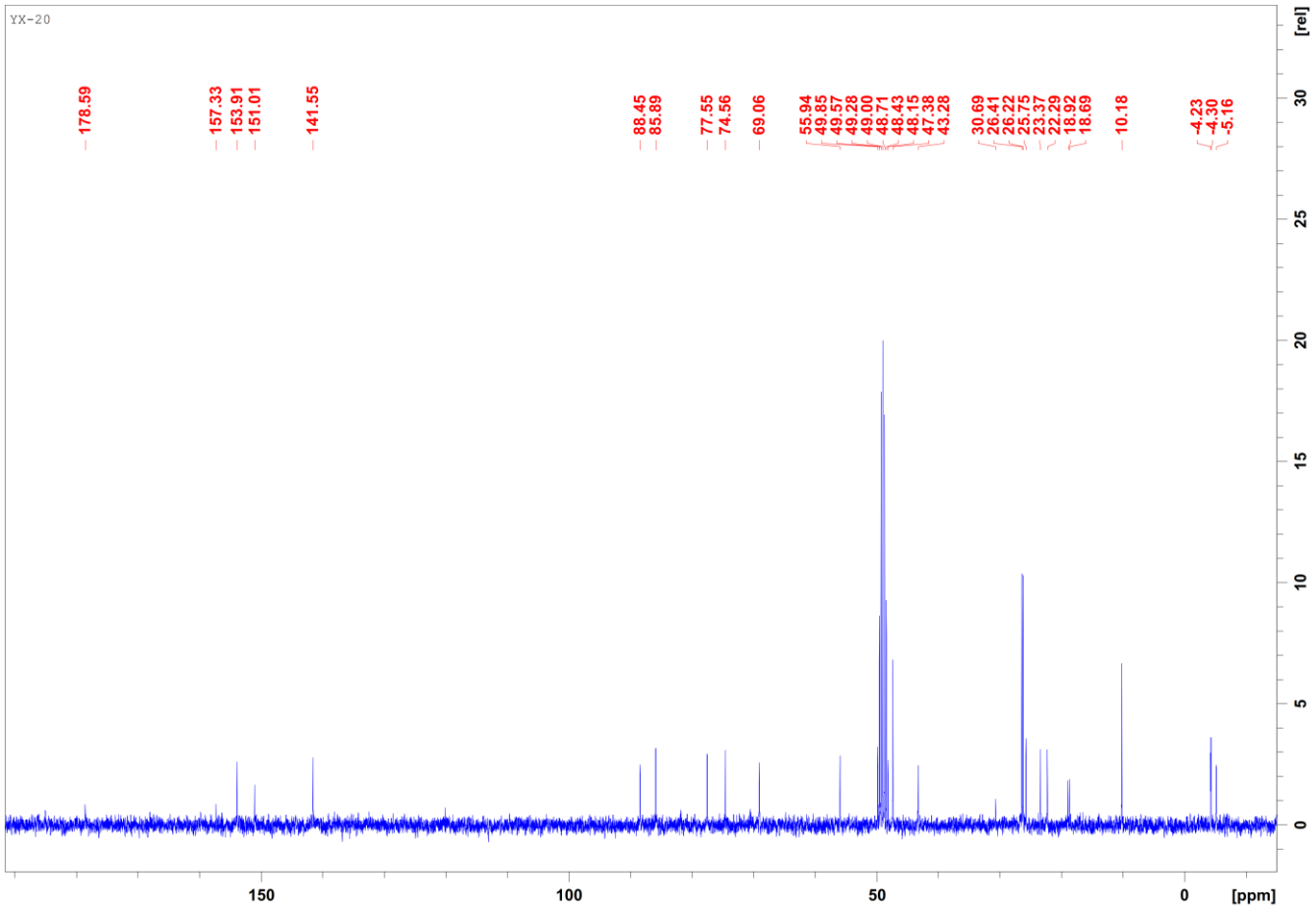






2',3'-di-O-TBDMS-5'-O-(N-leucyl)sulfamoyl adenosine (12)




YX-20
178.59
157.33
153.91
151.01
141.55
88.45
85.89
77.55
74.56
69.06
55.94
49.85
49.57
49.28
49.00
48.71
48.43
48.15
47.38
43.28
30.69
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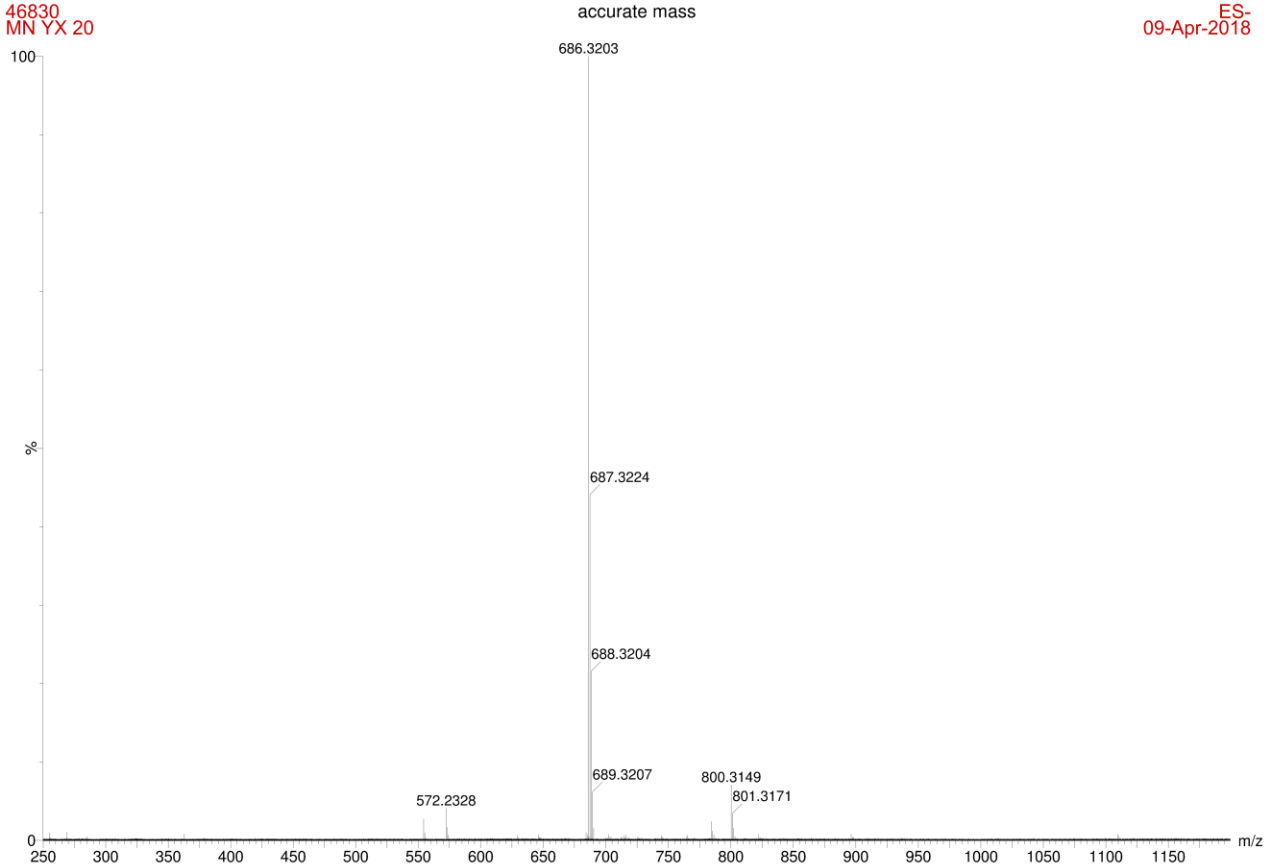
25.75
23.37
22.29
18.92
18.69
10.18
-4.23
-4.30
-5.16
[rel]
150
100
50
0
[ppm]


46830
MN YX 20
accurate mass
ES-
09-Apr-2018
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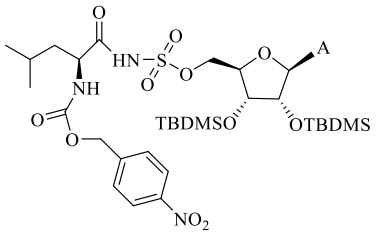
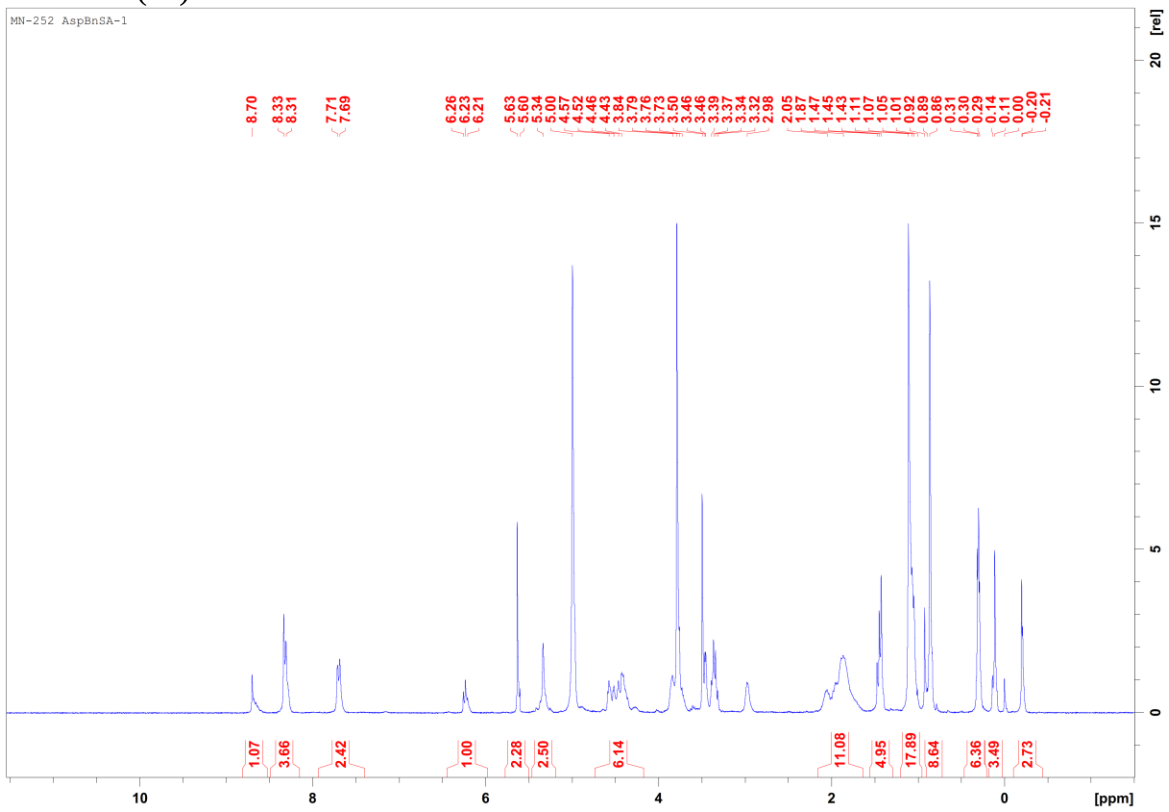
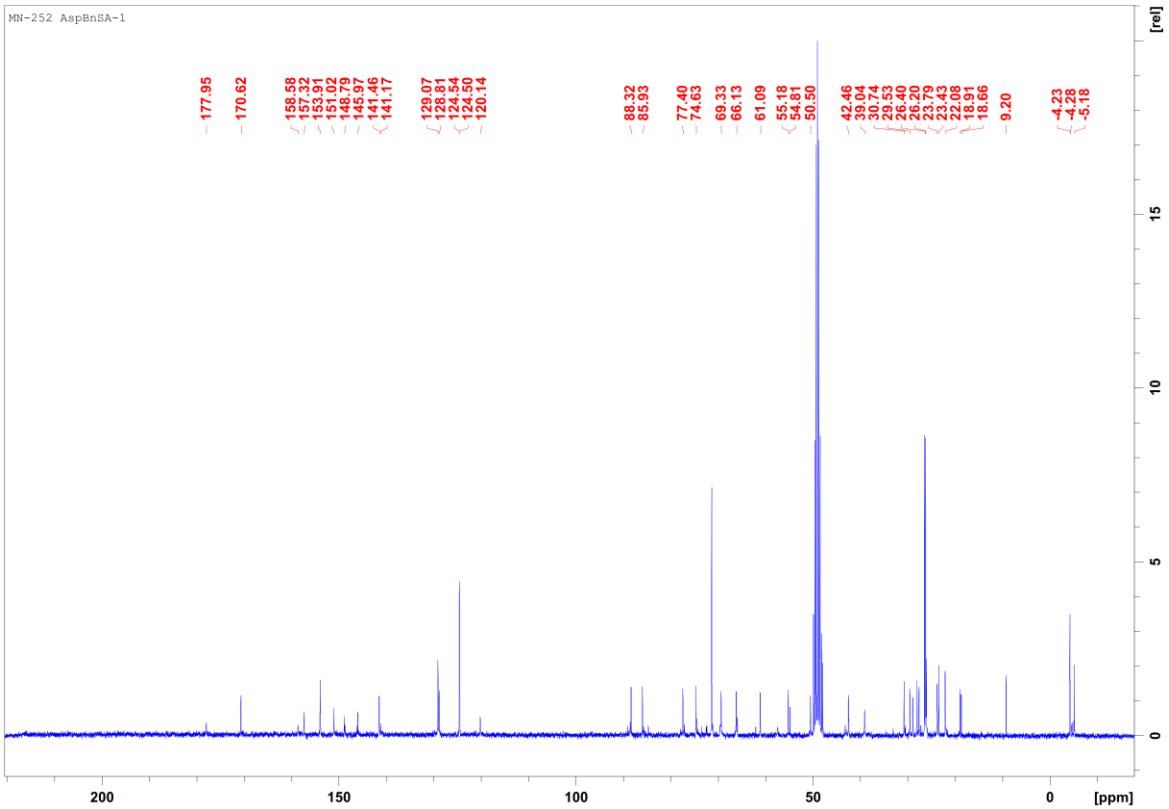
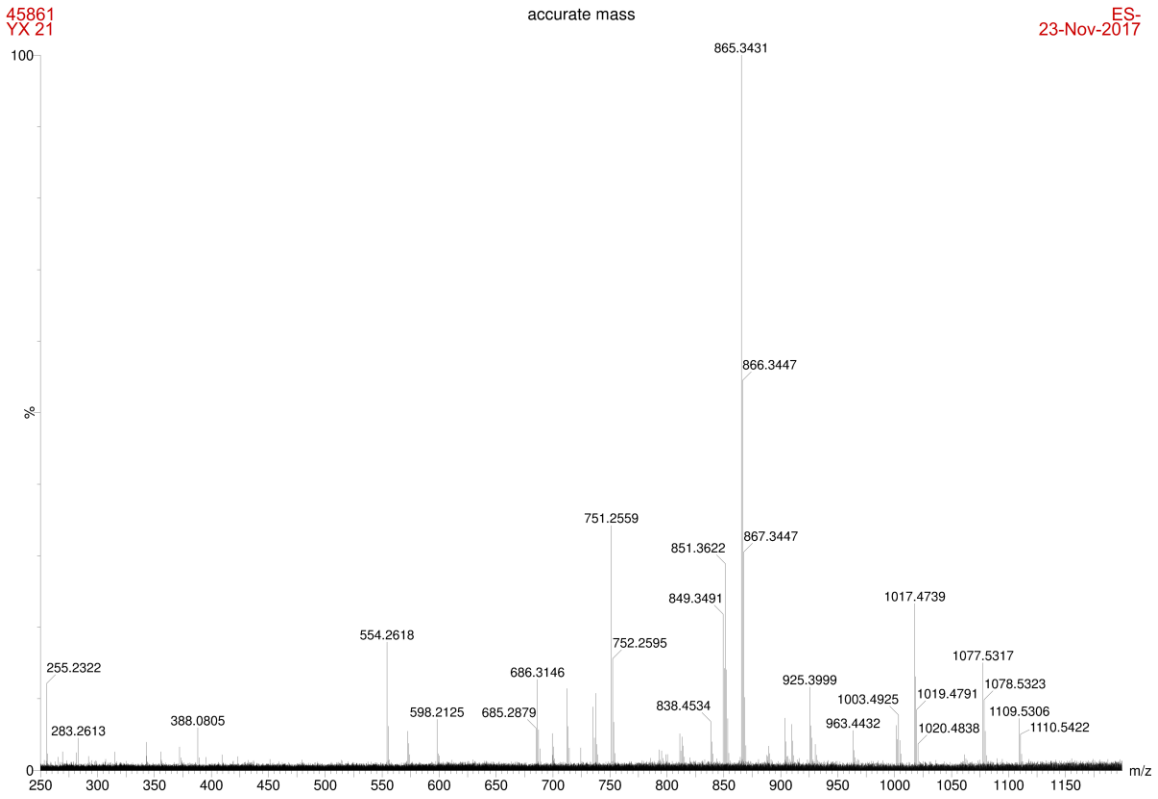
687.3224
688.3204
689.3207
572.2328
800.3149
801.3171
%
m/z

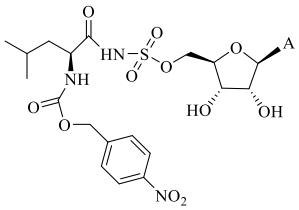


2',3'-di-O-TBDMS-5'-O-[Nα-(p-nitrobenzyloxycarbonyl)leucyl]sulfamoyl adenosine (13)

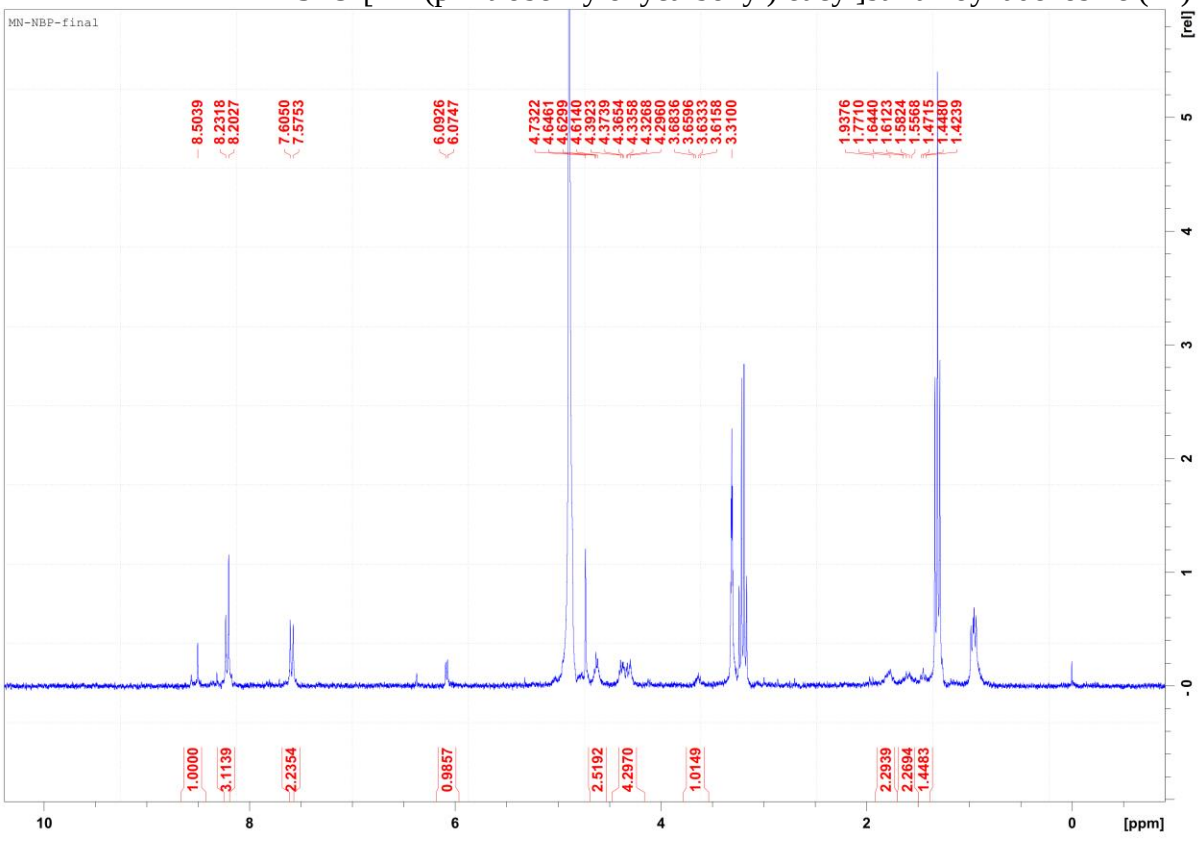


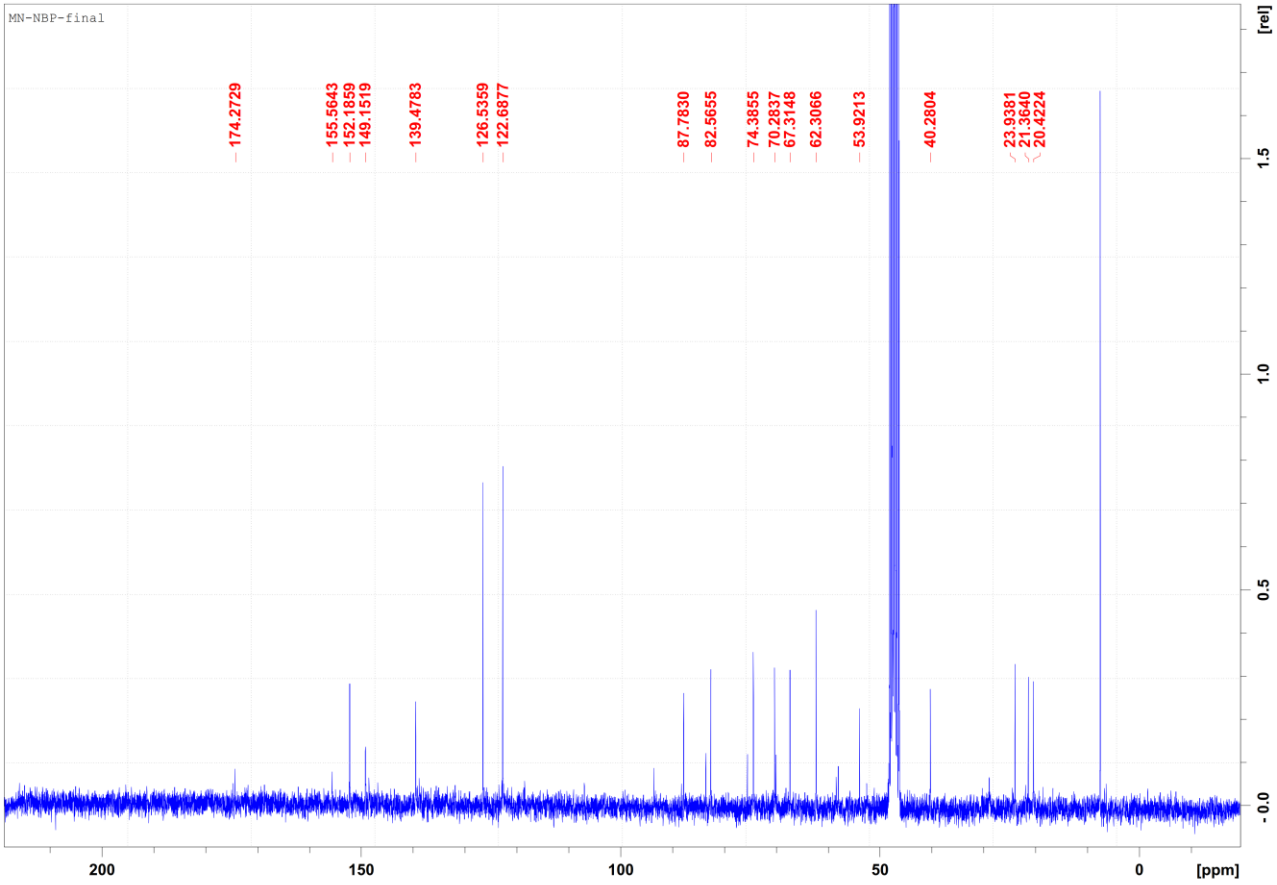






5'-O-[Nα-(p-nitrobenzyloxycarbonyl)leucyl]sulfamoyl adenosine (14)

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152.1859
149.1519
139.4783
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122.6877
87.7830
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67.3148
62.3066
53.9213
40.2804
23.9381
21.3640
20.4224
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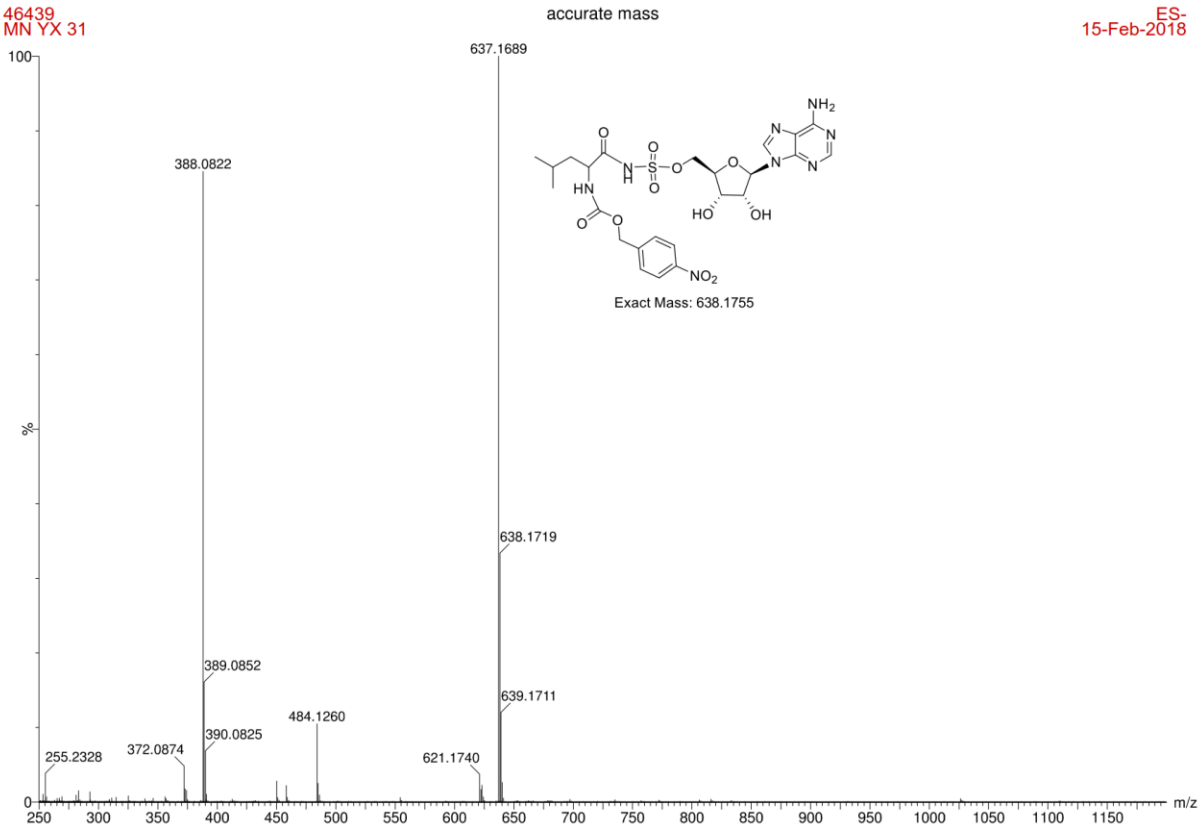
1.0
0.5
-0.0
200
150
100
50
0
[ppm]


46439
MN YX 31
accurate mass
ES-
15-Feb-2018
637.1689
388.0822
638.1719
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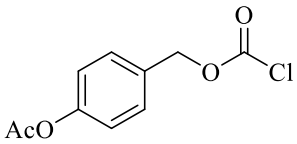
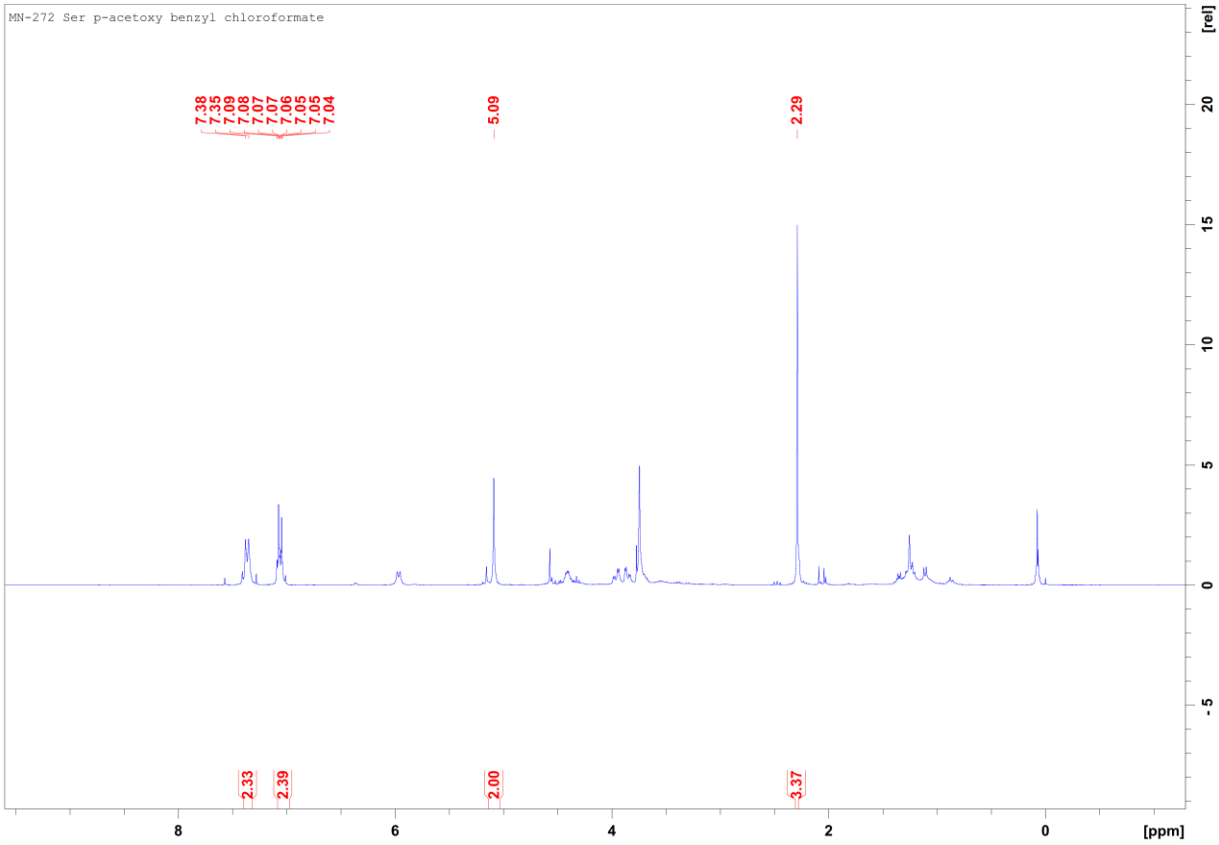
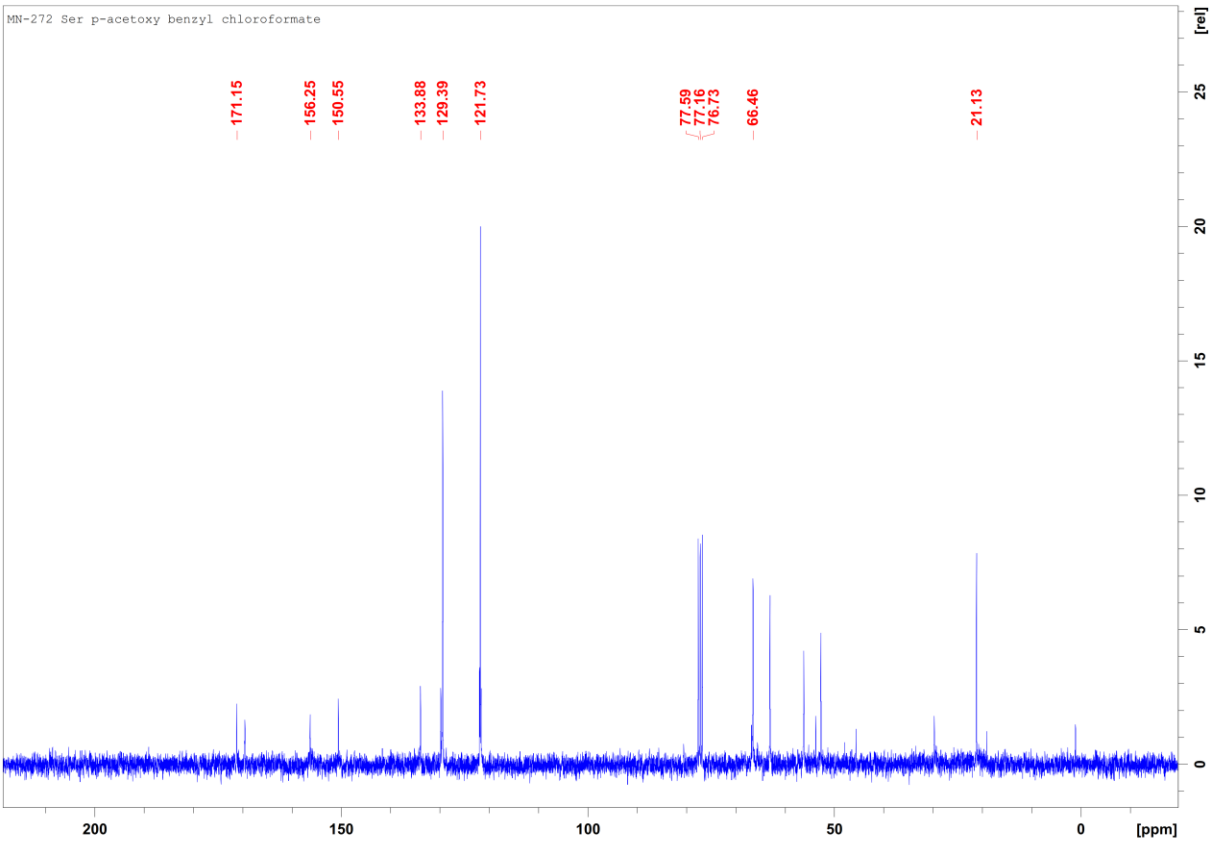
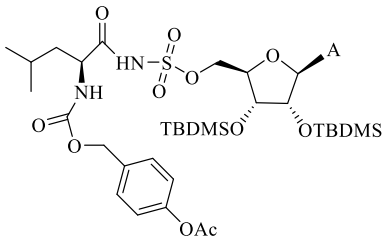
390.0825
255.2328
372.0874
621.1740
%
m/z
Exact Mass: 638.1755



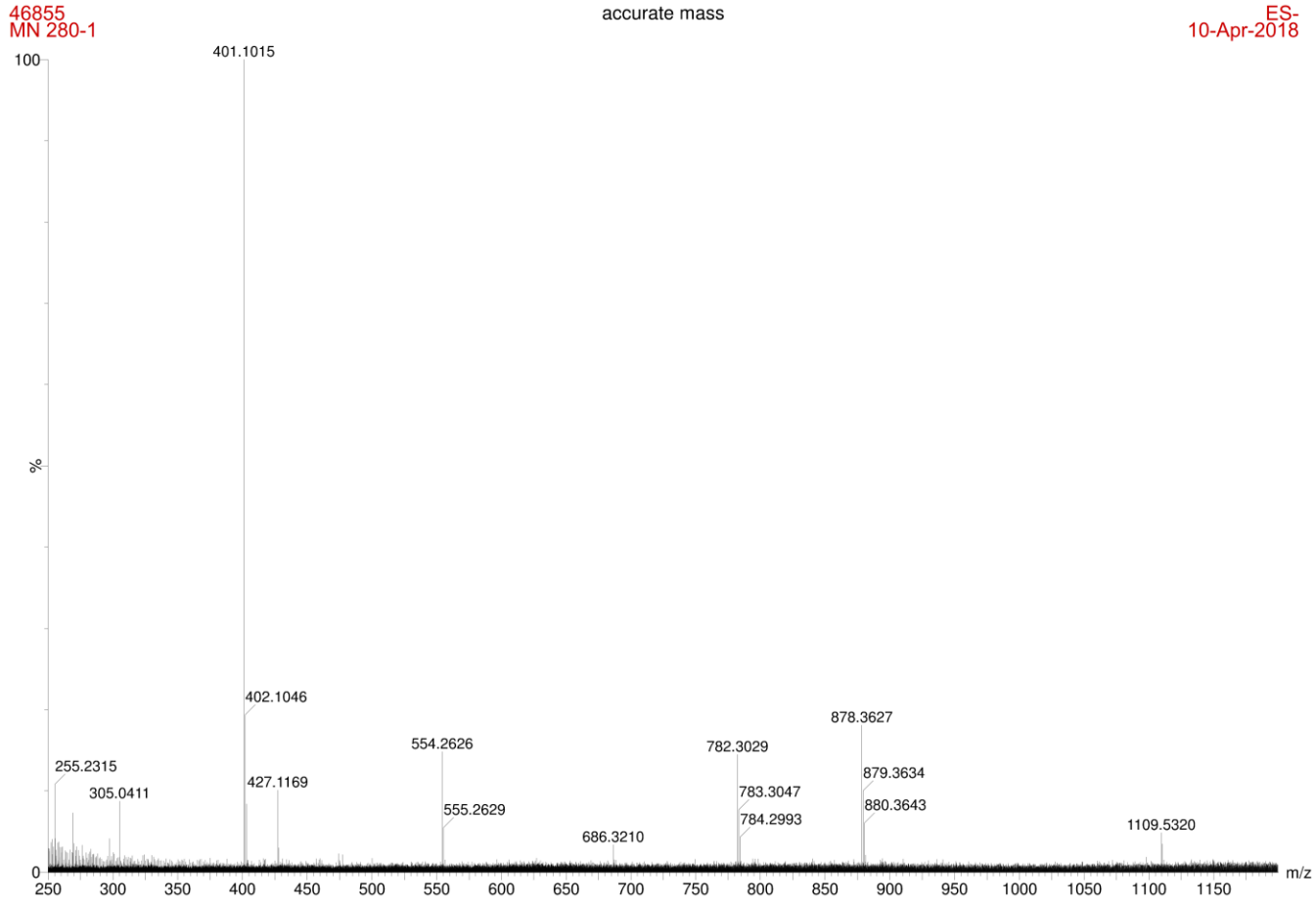
p-acetoxybenzyoxycarbonylchloride (16)

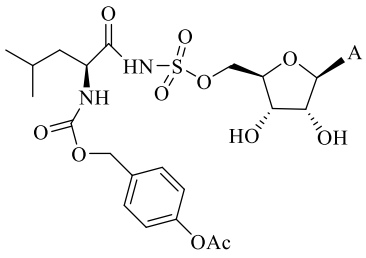




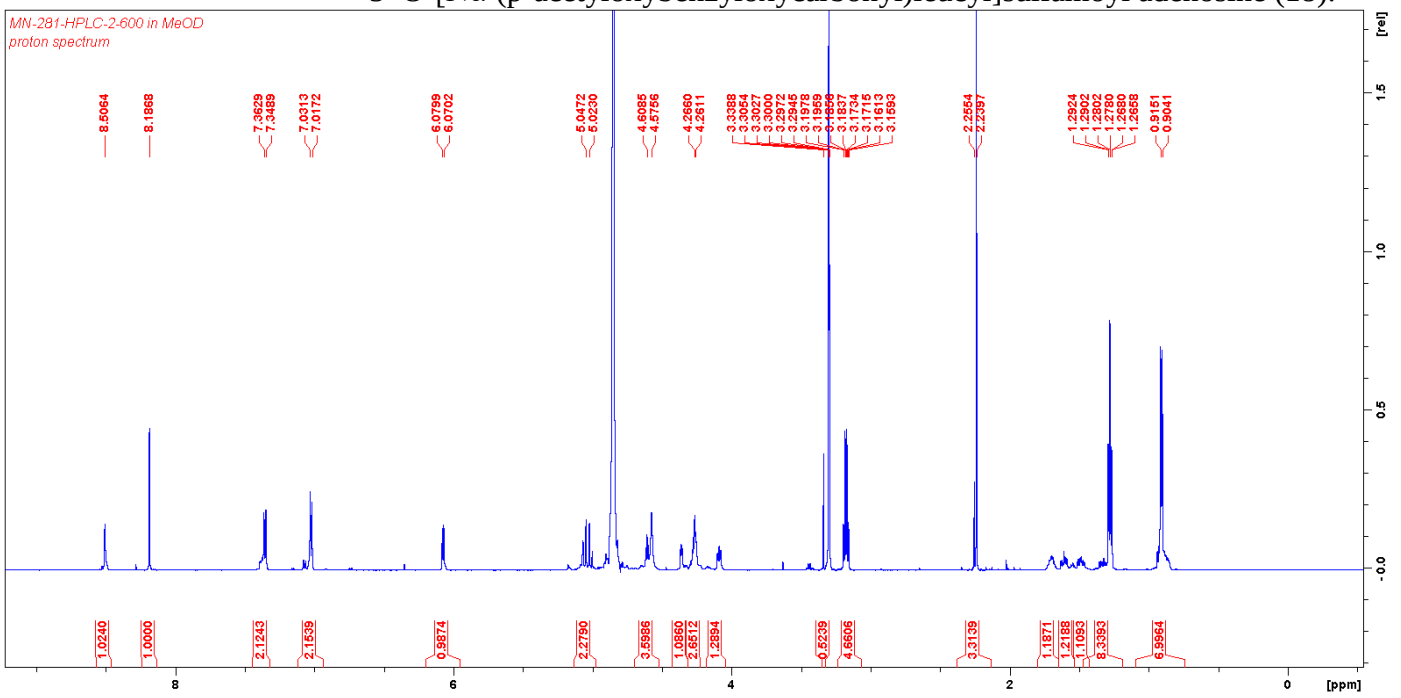


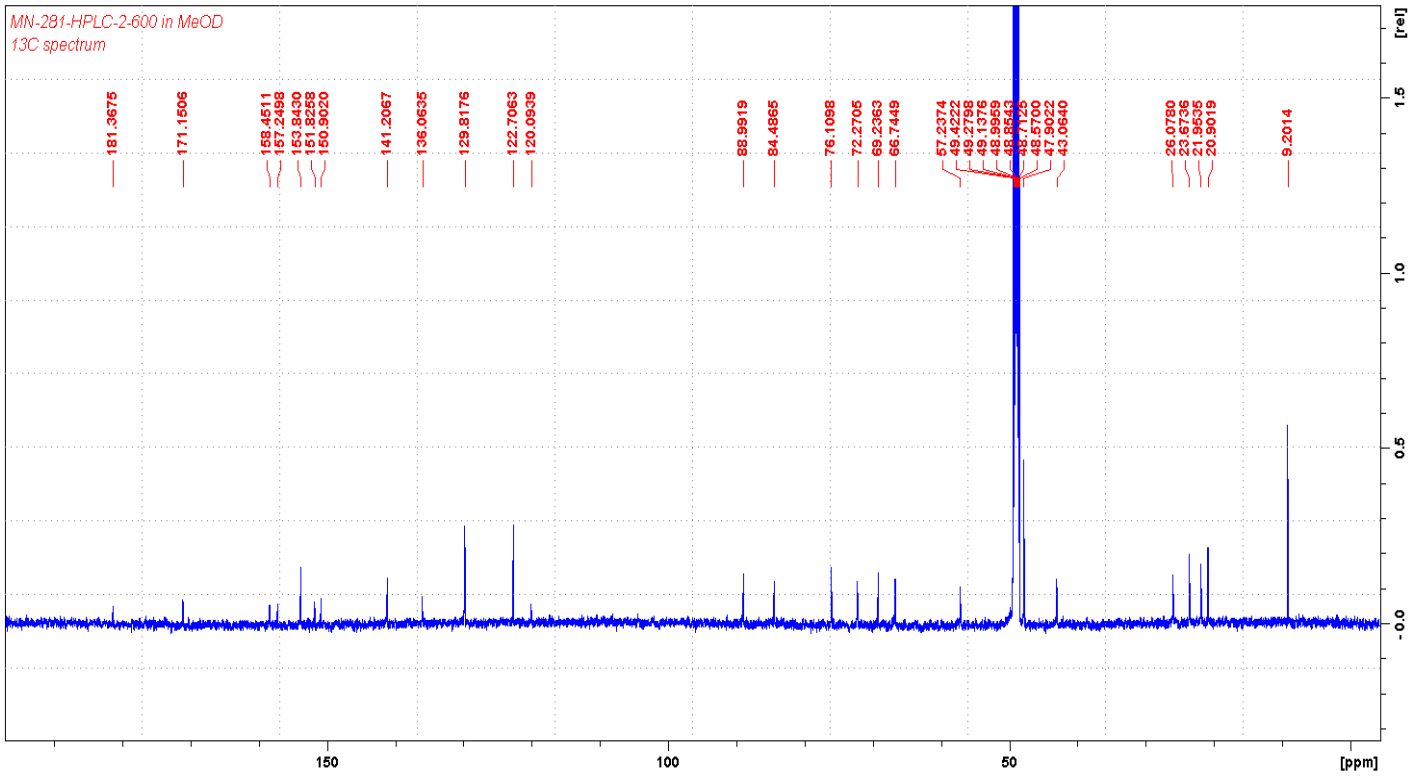
2',3'-di-*O*-TBDMS-5'-*O*-[N^{α}-(*p*-acetoxybenzyloxycarbonyl)leucyl] sulfamoyl adenosine (17)

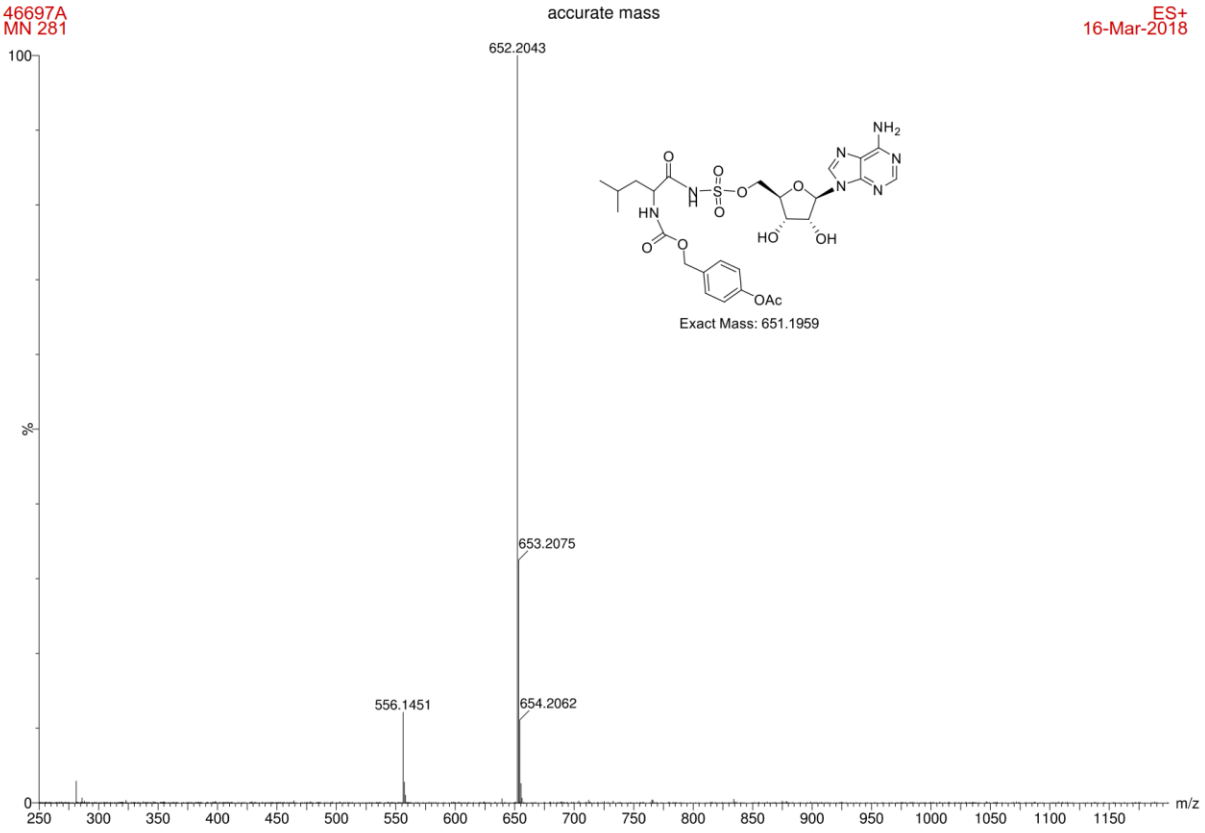




5'-O-[Nα-(p-acetyloxybenzyloxycarbonyl)leucyl]sulfamoyl adenosine (18).



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350
400
450
500
550
600
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m/z
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HN
HO
OH
OAc
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